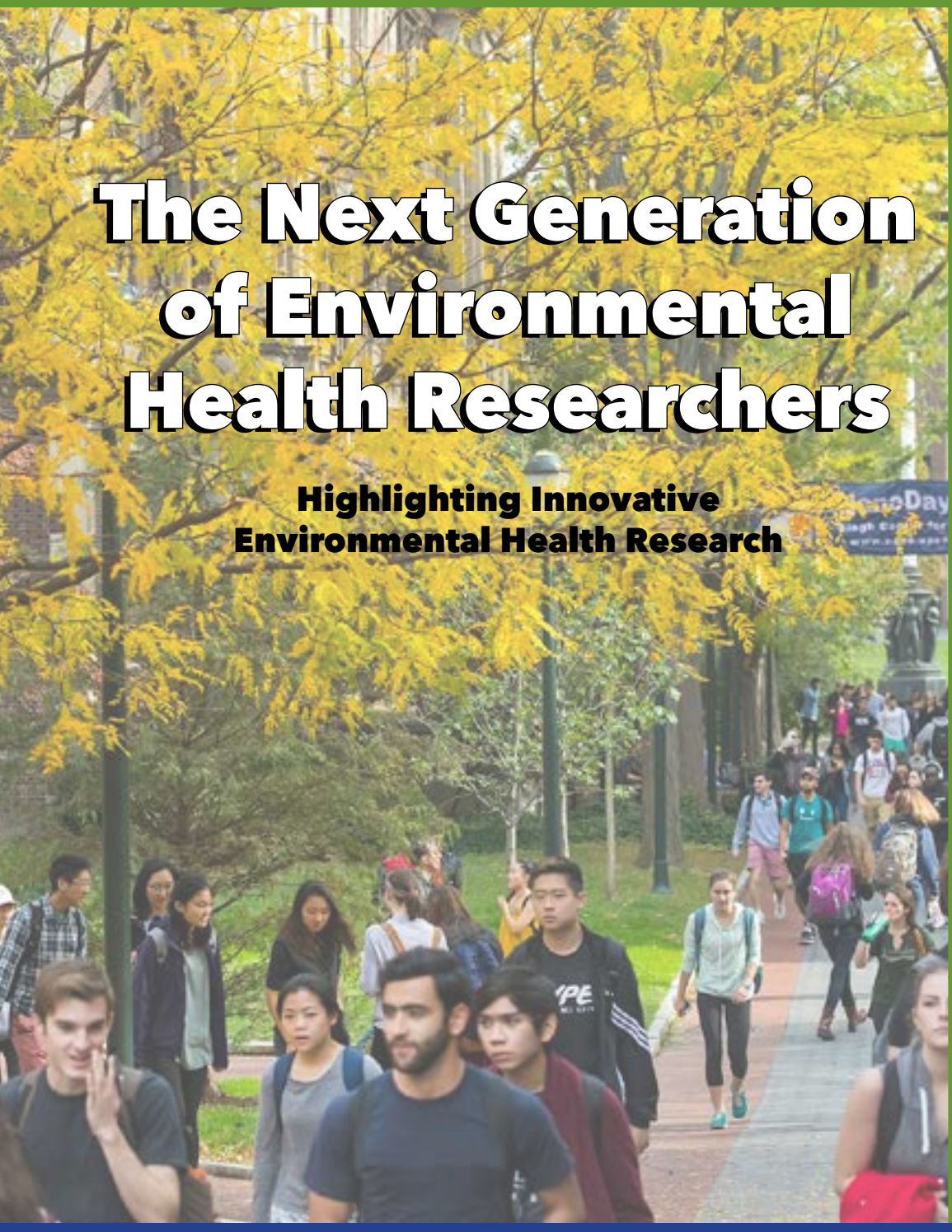
Eighteenth Annual CEET Symposium
Glen Gaulton Auditorium, Biomedical Research Building
Friday, November 10, 2023






The Next Generation of Environmental Health Researchers

Highlighting Innovative Environmental Health Research



Perelman School of Medicine
University of Pennsylvania

CEET
Center of Excellence in Environmental Toxicology

NIH National Institute of Environmental Health Sciences

Center of Excellence in Environmental Toxicology (CEET)

EIGHTEENTH ANNUAL SYMPOSIUM

The Next Generation of Environmental Health Researchers

Glen Gaulton Auditorium & Lobby, Biomedical Research Building
Perelman School of Medicine at the University of Pennsylvania
November 10, 2023

Perelman SCHOOL OF MEDICINE UNIVERSITY of PENNSYLVANIA | CEET CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

NIH National Institute of Environmental Health Sciences

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Eighteenth Annual Symposium

The Next Generation of Environmental Health Researchers

November 10, 2023

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2:15 PM – 2:25 PM WELCOME & OPENING REMARKS

Trevor M. Penning, PhD
The Thelma Brown and Henry Charles Molinoff Professor of Pharmacology
Director, Center of Excellence in Environmental Toxicology (CEET)

Rebecca Simmons, MD
Hallam Hurt Professor in Neonatology
Co-Director, CEET Career Development Program

Blanca Himes, PhD
Associate Professor of Informatics
Co-Director, CEET Career Development Program

2:25 PM – 3:15 PM EARLY CAREER INVESTIGATOR FLASH TALKS

Eva-Maria Collins, PhD
Associate Professor of Biology, Swarthmore College
Rapid multidimensional behavioral screening in planarians to reduce mammalian neurotoxicity testing

Colin Conine, PhD
Assistant Professor of Genetics and Pediatrics (Neonatology)
The transmission of environmentally regulated epigenetically inherited phenotypes by sperm RNAs

Patrick Gleeson, MD, MSCE
Instructor of Medicine (Allergy & Immunology)
Allergy testing utilization in adults with asthma

Thea Golden, PharmD, PhD
Research Assistant Professor of Obstetrics and Gynecology
Circulating extracellular vesicles following EDC exposure

Michael Hart, PhD
Assistant Professor of Genetics
Screening autism genes and small molecule modifiers of behavior in C. elegans

3:15 PM – 3:25 PM BREAK

3:25 PM – 4:15 PM EARLY CAREER INVESTIGATOR FLASH TALKS

Jelte Kelchtermans, MD
Instructor of Pediatrics (Pulmonary and Sleep Medicine)
How gene environment interactions shape the pediatric response to ambient air pollution

Timothy Nelin, MD
Clinical Fellow, Pediatrics (Neonatology)
Associations of environmental exposures with acute respiratory illness among preterm infants with bronchopulmonary dysplasia

Jessica Rice, DO, MHS
Assistant Professor of Pediatrics (Pulmonary and Sleep Medicine)
Indoor environmental study for preterm infants

Joseph Romano, PhD
Assistant Professor of Informatics
Discovering mechanisms of chemical toxicity using interpretable machine learning

Kotaro Sasaki, MD, PhD
Assistant Professor, Biomedical Sciences, School of Veterinary Medicine
Reconstitution of human adrenocortical development and steroidogenesis in vitro

4:15 PM – 5:15 PM POSTER SESSION & RECEPTION

WELCOME MESSAGE

It is with enormous pride that we welcome you to the Eighteenth Annual Symposium of the Center of Excellence in Environmental Toxicology (CEET), the University of Pennsylvania's Environmental Health Sciences Core Center. The annual symposium highlights emerging areas and themes in environmental health sciences.

This year's symposium showcases the talent of ten early career investigators through a series of vibrant flash talks. Early career investigators are an integral part of our community. The CEET offers dedicated support and guidance through our Career Development Program designed to cultivate the careers of junior faculty—establishing the next generation of environmental health scientists—through mentorship, pilot projects, grant proposal review, workshops, and continuing education opportunities. Our trainees will also have the opportunity to present their research in a poster session.

We look forward to an exciting afternoon of discussion, sharing discoveries, and building collaborations.

Trevor M. Penning, PhD

The Thelma Brown & Henry Charles Molinoff Professor of Pharmacology

Director, CEET

Rebecca Simmons, MD

Hallam Hurt Professor in Neonatology

Co-Director, CEET Career Development Program

Blanca Himes, PhD

Associate Professor of Informatics

Co-Director, CEET Career Development Program

FEATURED EARLY CAREER INVESTIGATORS

Eva-Maria Collins, PhD

Associate Professor
of Biology

Swarthmore College

Dr. Collins is an Associate Professor of Biology at Swarthmore College, an Adjunct Associate Professor of Neuroscience at the Perelman School of Medicine at the University of Pennsylvania, and an Adjunct Associate Professor of Physics at the University of California San Diego. She completed her fellowship at Princeton University. Her research focuses on three major areas: Biomechanics, Neuroethology, and Neurotoxicology. Her lab has pioneered rapid chemical screening in the freshwater planarian Dugesia japonica. By using non-mammalian organisms in their research, Dr. Collins and her team can study the developmental effects of various toxins more efficiently and reduce the use of mammals in research. Her work is currently funded by the NIH/NIEHS, the NSF, the Kaufman Foundation, and the NIH Chemical Countermeasures Research Program.

Colin Conine, PhD

Assistant Professor
of Genetics and Pediatrics
(Neonatology)

University of Pennsylvania &
Children's Hospital
of Philadelphia

Dr. Conine is an Assistant Professor of Genetics and Pediatrics at the University of Pennsylvania Perelman School of Medicine and Division of Neonatology at the Children's Hospital of Philadelphia. He is a faculty member of the Penn Epigenetics Institute, the Institute of Regenerative Medicine, and the Center for Research on Reproduction and Women's Health. Dr. Conine received his BS in Biochemistry from the University of Rochester and PhD from the University of Massachusetts Medical School. His research focuses on how RNAs function in male fertility, inheritance, and development. He was named a 2021 Pew Biomedical Scholar and in 2023 was award an NIH NIGMS Maximizing Investigators Research Award (R35).

FEATURED EARLY CAREER INVESTIGATORS

Dr. Gleeson is an attending physician in the Section of Allergy and Immunology within the Division of Pulmonary, Allergy and Critical Care Medicine at Penn. He did his fellowship in Allergy and Immunology at Penn and then completed a Master of Science in Clinical Epidemiology (MSCE). His research focus is on improving allergy testing implementation in adults with asthma, and he is specifically interested in how allergy test results impact patient care and healthcare utilization. He is currently supported by the CEET T32 training grant.

Patrick Gleeson, MD, MSCE

Instructor of Medicine
(Allergy & Immunology)
University of Pennsylvania

Dr. Golden is a Research Assistant Professor in the Department of Obstetrics and Gynecology at the University of Pennsylvania. She earned her Doctorate of Pharmacy and PhD in Toxicology from Rutgers University and was a postdoctoral fellow with Dr. Rebecca Simmons at the University of Pennsylvania. Her research program focuses on gestational exposure to environmental and pharmaceutical chemicals. She also studies the role of extracellular vesicles in pregnancy complications with the goal of identifying biomarkers and mechanisms of placental dysfunction.

Thea Golden, PharmD, PhD

Research Assistant Professor
of Obstetrics and Gynecology
University of Pennsylvania

FEATURED EARLY CAREER INVESTIGATORS

Michael Hart, PhD

Assistant Professor
of Genetics

University of Pennsylvania

Dr. Hart is an Assistant Professor of Genetics at the University of Pennsylvania Perelman School of Medicine. He received his PhD in Neuroscience at the University of Pennsylvania and completed his post-doctoral degree at Columbia University. Dr. Hart studies the cellular and molecular regulation of circuit plasticity and behavior in the C. elegans nervous system. His ongoing research focuses primarily on the following four goals: 1) identifying conserved autism and schizophrenia genes that contribute to plasticity and behavior; 2) defining the molecular contribution and interactions of these genes in neurons and circuits to further our understanding of disease-associated gene function; 3) testing the functional impact of genetic variants of unknown significance found in patients with neurodevelopmental conditions; and 4) screening for genetic and small molecule modifiers of these genes/variants using behavior as a primary readout.

Jelte Kelchtermans, MD

Instructor of Pediatrics
(Pulmonary and Sleep Medicine)

University of Pennsylvania
& Children's Hospital
of Philadelphia

Dr. Kelchtermans is a pediatric pulmonology attending at the Children's Hospital of Philadelphia (CHOP) where he integrates genomic, environmental, and clinical data to investigate air pollution sensitivity. After obtaining his MD from the KULeuven in Belgium and completing both his pediatric residency and chief resident year at the University of Miami, he joined CHOP for his pediatric pulmonology fellowship. His research is focused on how genetic and clinical variables shape air pollution sensitivity in pediatrics. His most recent work has demonstrated that specific genetic variants are associated with sensitivity to ambient air pollution in pediatric patients with asthma and highlighted the impact of air pollution exposure on bronchopulmonary dysplasia morbidity. He is an active member of the American Thoracic Society and is supported by a Parker B Francis fellowship.

FEATURED EARLY CAREER INVESTIGATORS

Timothy Nelin, MD

Clinical Fellow, Pediatrics (Neonatology)

Children's Hospital of Philadelphia

Dr. Nelin is a Neonatal-Perinatal Medicine fellow at the Children's Hospital of Philadelphia (CHOP). He obtained his medical degree at Ohio State University College of Medicine. He is interested in the impact of the physical environment on preterm birth and long-term outcomes of preterm infants. Specifically, he is interested in exposure to air pollution and exposure to extremes of weather, as a result of climate change, contribute to respiratory health and development of preterm infants.

Jessica Rice, DO, MHS

Assistant Professor of Pediatrics (Pulmonary and Sleep Medicine)

University of Pennsylvania & Children's Hospital of Philadelphia

Dr. Rice is an Assistant Professor of Pediatrics and attending physician with the Division of Pulmonary and Sleep Medicine at the Children's Hospital of Philadelphia (CHOP). After completing her medical degree at Philadelphia College of Osteopathic Medicine and residency at St. Christopher's Hospital for Children, she completed her pediatric pulmonology fellowship at John Hopkin's University School of Medicine. While at Johns Hopkins, Dr. Rice completed a graduate degree in Management Sciences for Health in Clinical Investigation. Her research focuses on the indoor environment as a modifiable risk factor for pediatric lung disease. Her short-term goals are to investigate the health effects of indoor air pollution in the homes of preterm infants. Future work will develop, implement, and evaluate the health impact of an intervention to reduce indoor air pollution in homes of infants and children with chronic lung disease.

FEATURED EARLY CAREER INVESTIGATORS

Joseph Romano, PhD

Assistant Professor
of Informatics

University of Pennsylvania

Dr. Romano is an Assistant Professor of Informatics and Pharmacology at the University of Pennsylvania. He earned a BS degree in Molecular Genetics from the University of Vermont, followed by MA, MPhil, and PhD degrees in Biomedical Informatics from Columbia University. The Romano Lab conducts original research in computational toxicology and translational bioinformatics, with a focus on applying artificial intelligence to predict and explain the clinical outcomes of human exposure to toxic environmental chemicals. Dr. Romano leads the development of several major biomedical knowledge bases, including ComptoxAI, VenomKB, and the Alzheimer's Knowledge Base.

Kotaro Sasaki, MD, PhD

Assistant Professor
of Biomedical Sciences

University of Pennsylvania,
School of Veterinary Medicine

Dr. Kotaro is an Assistant Professor of Biomedical Sciences at the University of Pennsylvania School of Veterinary Medicine. He received his MD from Hokkaido University School of Medicine followed by his PhD from Kyoto University Graduate School of Medicine. He completed post-graduate training in anatomic pathology at the University of Pittsburgh Medical Center and in renal pathology at the University of Washington Medical Center. His research includes deciphering the molecular basis of human germline, gonadal and adrenal development in vivo and their reconstitution in vitro. He is a member of the Institute of Regenerative Medicine and the Center for Research on Reproduction and Women's Health.

MISSION AND VISION STATEMENT

The Center of Excellence in Environmental Toxicology (CEET) is a school-based center housed in the Perelman School of Medicine at the University of Pennsylvania. As the spectrum of environmental health science is broad, ranging from toxicology, chemistry, environmental science, environmental disease, epidemiology, public health, and policy, its more than 80 members come from 7 Schools (21 Departments), the Children's Hospital of Philadelphia and 4 Neighboring Universities. CEET is Penn's designated Environmental Health Science Core Center (EHSCC) funded by the National Institute of Environmental Health Sciences (NIEHS).

The CEET elucidates the mechanistic links between environmental exposures and human disease and translates its findings into action to improve the health of vulnerable individuals, and local, national and global communities.

The CEET mission is achieved by both its community-based research model and by its emphasis in thematic areas. The Community Engagement Core (CEC) identifies community-based environmental health problems that are then framed by our Integrative Health Sciences Facility Core (IHSFC) into research questions that can be answered by CEET investigators. Findings are then translated back to the community using a "community-first communication model." An emerging theme is precision public health in which community exposomes can be used to identify sub-populations most vulnerable to air pollution, lung cancer incidence and lead poisoning. Our flexible thematic areas: Air Pollution and Lung Health; Environmental Exposures and Cancer; Windows-of-Susceptibility; and, Environmental Neuroscience, address immediate concerns that affect our region. Each of these thematic areas embrace exposure assessment, the adverse outcome pathway or network affected and translates these findings to affected communities and human subject-oriented research. In each of these areas, the CEC works with communities impacted by relevant exposures.

The CEET enables its investigators to conduct biomarker work of exposure and effect using its Translational Biomarker Core, which uses sophisticated liquid chromatography mass spectrometry methods. CEET investigators have access to an Exposure Biology Informatics Core so that large siloed data bases in exposomics, genomics, proteomics, metabolomics and chemoinformatics can be merged as predictors of response and disease onset. The Core is also positioned to take these large data sets and use machine learning and AI to predict responses to toxicants. The IHSFC of the CEET provides assistance with a broad range of transdisciplinary services including study design, exposure biology laboratories with access to biospecimens via the Penn Biobank; and biostatistical support.

The CEC works with communities in Pennsylvania to empower them with new knowledge so that they are better informed to influence decision makers about public health policy. To improve the environmental health of these and similar affected communities, the CEET educates health care professionals (Residency Program in Occupational and Environmental Health, Nursing concentration in Occupational and Environmental Health, and Master of Public Health Programs) to improve public health outcomes.

CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

Perelman School of Medicine at the University of Pennsylvania

Center Membership

Director: Trevor Penning, PhD

Deputy Director: Sharon McGrath-Morrow, MBA, MD

Thematic Area I

AIR POLLUTION AND LUNG HEALTH

Leader: Sharon McGrath-Morrow, MBA, MD

Hajera Amatullah, PhD**
Andrea Apter, MD
Michael Beers, MD
Ian Blair, PhD
Jason Christie, MD, MSCE
Olajumoke (Jumy) Fadugba, MD
Reto Gieré, PhD
Patrick Gleeson, MD, MSCE**
Inkyu Han, PhD*
Sarah Henrickson, MD, PhD**
David Hill, MD, PhD
Blanca Himes, PhD
Marilyn Howarth, MD
Dan Dongeun Huh, PhD
Wei-Ting Hwang, PhD
Jelte Kelchtermans, MD**
Despina Kontos, PhD
Beata Kosmider, PhD*
Charles Leonard, PharmD, MSCE**
Krithika Lingappan, MD, MS, PhD
Ming-Lin Liu, MD, PhD
Tara McAlexander, PhD*
Clementina Mesaros, PhD
Edward Morrisey, PhD
Vladimir Muzykantov, MD, PhD
Timothy Nelin, MD**
Trevor Penning, PhD
John Reilly, MD, MSCE
Jessica Rice, DO, MHS**
Carsten Skarke, MD

Thematic Area II

ENVIRONMENTAL EXPOSURES AND CANCER

Leader: Ian Blair, PhD

Steven Albelda, MD
Kara Bernstein, PhD
Donita Brady, PhD
Eric Brown, PhD
Brian Capell, MD, PhD
David Feldser, PhD
Jeffrey Field, PhD
Aime Franco, PhD
Reto Gieré, PhD
Marilyn Howarth, MD
Dan Dongeun Huh, PhD
Wei-Ting Hwang, PhD
Douglas Jerolmack, PhD
Jonathan Katz, MD
Marcelo Kazanietz, PhD
Despina Kontos, PhD
Maayan Levy, PhD
Clementina Mesaros, PhD
Katherine Nathanson, MD
Trevor Penning, PhD
John Seykora, MD, PhD
Andrew Strasser, PhD
Sarah Tishkoff, PhD
Anil Vachani, MD, MSCE

Thematic Area III

WINDOWS-OF-SUSCEPTIBILITY

Leader: Marisa Bartolomei, PhD

Heather Burris, MD
Aimin Chen, MD, PhD
Colin Conine, PhD**
William Gaynor, MD
Thea Golden, PharmD, PhD**
David Hill, MD, PhD
Marilyn Howarth, MD
Dan Dongeun Huh, PhD
A. T. Charlie Johnson, PhD
Yu-Chin Lien, PhD**
Krithika Lingappan, MD, MS, PhD
Clementina Mesaros, PhD
Sunni Mumford, PhD
Timothy Nelin, MD**
Michael Pack, MD
Samuel Parry, MD
Trevor Penning, PhD
Sara Pinney, MD, MSTR
Jessica Rice, DO, MHS**
Kotaro Sasaki, MD, PhD
Enrique Schisterman, PhD
Rebecca Simmons, MD
Nathaniel Snyder, PhD, MPH*
Jerome Strauss, MD, PhD
Aalim Weljie, PhD
Rebecca Wells, MD

CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY
Perelman School of Medicine at the University of Pennsylvania
Center Membership

Thematic Area IV

ENVIRONMENTAL NEUROSCIENCE

Leader: Sigrid Veasey, MD

Ian Blair, PhD
Maja Bućan, PhD
Aimin Chen, MD, PhD
Eva-Maria Collins, PhD*
Arnold Eiser, MD*
Reto Gieré, PhD
Michael Hart, PhD
Elizabeth Heller, PhD
David Jang, MD, MSc
Kelly Jordan-Sciutto, PhD
Erica Korb, PhD
Jianghong Liu, PhD, RN
Guo-Li Ming, MD, PhD
Clementina Mesaros, PhD
Nirmala Nirinjini Naidoo, PhD
Kevin Osterhoudt, MD, MSCE
Jennifer Pinto-Martin, PhD, MPH
David Raizen, MD, PhD
Jay Schneider, PhD*
Rebecca Simmons, MD
Nathaniel Snyder, PhD, MPH*

COMMUNITY ENGAGEMENT CORE

Director: Marilyn Howarth, MD
Program Coordinator: Adrian Wood, MPH
Maria Antonia Andrews, MS
Andrea Apter, MD
Michael Beers, MD
Jeffrey Field, PhD
Aime Franco, PhD
Ira Harkavy, PhD
Blanca Himes, PhD
Marilyn Howarth, MD
Jianghong Liu, PhD, RN
Michael Mann, PhD
Kevin Osterhoudt, MD, MSCE
Trevor Penning, PhD
Jennifer Pinto-Martin, PhD, MPH
Rebecca Simmons, MD

EXPOSURE BIOLOGY INFORMATICS CORE

Director: Blanca Himes, PhD

INTEGRATED HEALTH SCIENCES FACILITY CORE

Director: Anil Vachani, MD, MSCE

Associate Director, Human Studies Design and Performance Services:
Aimin Chen, MD, PhD

Associate Director, Biostatistics:
Wei-Ting Hwang, PhD

TRANSLATIONAL BIOMARKER CORE

Director: Clementina Mesaros, PhD

*Adjunct Member
**Affiliate Member

AP1 Characterizing the Effects of Endothelial *Hif-1*α Deletion on Hyperoxic Lung Injury

Rose Albert, MPH,[1,2,3] Manuel Cantu Gutierrez, PhD,[3] Krithika Lingappan, MD, PhD, MS[2,3]

[1]Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania; [2]Center of Excellence in Environmental Toxicology, Perelman School of Medicine, University of Pennsylvania; [3]Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia

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Preterm birth is one of the leading causes of death during the neonatal period, and extreme heat events induced by the climate crisis can increase risk of preterm birth. Bronchopulmonary dysplasia (BPD) is a chronic lung disease of prematurity that, in the US, develops in more than a third of neonates born at <28 weeks of gestation. BPD is characterized by alveolar simplification, inflammation, and disrupted vascular development. Neonates who develop BPD and survive into adulthood are more vulnerable to respiratory insults such as pollution and morbidities such as asthma and COPD. When preterm neonates receive supplemental oxygen as a lifesaving intervention, the supraphysiological concentrations of oxygen (hyperoxia) contribute to BPD. Additionally, BPD has a known male disadvantage, but the molecular mechanisms underpinning this sex difference are not well understood. Hypoxia inducible factors (HIFs) are oxygen-sensitive transcription factors that regulate genes implicated in lung development and repair. Previous work has shown that *Hif-1*α is regulated in a sex-specific manner after recovery from hyperoxia. We hypothesize that endothelial *Hif-1*α mediates sex differences in respiratory outcomes after hyperoxic lung injury. To test this, we generated a mouse with the Cre/loxP system to induce endothelial specific deletion of *Hif-1*α at birth. Pups were exposed to room air or hyperoxia (95% FiO_2) from postnatal day (PND) 1 to 5 to recapitulate the BPD phenotype. This exposure paradigm parallels the saccular stage of development when neonates may be exposed to supplemental oxygen in the NICU. Preliminary results show alveolar simplification after recovery from hyperoxia at PND 21. Additionally, endothelial deletion of *Hif-1*α at room air shows no detrimental outcomes on alveolar development. Future work will characterize the effects of endothelial *Hif-1*α deletion on pulmonary vascular development, gene expression, and epigenetic regulation after hyperoxic lung injury.

Supported by National Institute of Environmental Health Sciences of the National Institutes of Health under Award Number T32-ES019851.

AP2 Advanced Lung-on-a-Chip: A Tissue-Engineered Microphysiological Model to Investigate Flavored E-Cigarette-Induced Airway Disease

Pouria Fattahi, PhD[1], Mousa Younesi, PhD[1], and Dan Huh, PhD[1,2]

[1]Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, United States; [2]Center of Excellence in Environmental Toxicology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States

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Exposure to nicotine vape, whether through active smoking or passive inhalation, has been linked to a broad spectrum of respiratory health issues and stands as a significant public health concern. Research in inhalation toxicology, particularly concerning the harmful impact of e- cigarette aero-sols on the human respiratory system, is a rapidly evolving field. Traditional cell culture models have served as convenient tools for in vitro studies of e-cigarette aerosol toxicity; however, they fall short in replicating the intricacies of native human lung tissues. In response to this limitation, we introduce a pioneering microengineered biomimetic model designed to faithfully recreate the airway region of the human lung. This model is dedicated to conducting experimental investigations into the respiratory toxicity of e-cigarette aerosols in the distal lung, a pressing question in the field of flavored e-cigarette inhalation toxicology. Our novel model consists of two microfabricated 3D chambers separated by a semipermeable membrane. It allows us to mimic the compartmentalization seen in native airways, offering a platform for long- term co-culture of various cell types, including stem cell-derived airway epithelial cells, primary human pulmonary microvascular endothelial cells, and lung fibroblasts. These cells reside in a 3D microenvironment that closely resembles the physiological conditions of the human lung. This system provides a unique opportunity to engineer fully differentiated airway epithelium directly exposed to air, supported by vascularized, perfusable 3D stromal tissues. It's noteworthy that our preliminary data suggests that the underlying pulmonary vasculature plays a pivotal role in expediting the differentiation and maturation of lung epithelial cells during air-liquid interface culture. Our research approach leverages lung- on-a-chip systems in conjunction with cigarette smoking machines to accurately predict the potential of flavored e-cigarettes to induce acute injury to airway tissues in a dose-dependent manner. We believe that the microengineered systems developed in this study represent a significant advancement in our capacity to model acute respiratory responses to environmental toxins, with a specific focus on e-cigarette aerosols. These systems hold great promise as a robust in vitro platform for studying biochemical threats and advancing the development of medical countermeasures.

Supported by the Center of Excellence in Environmental Toxicology (CEET) - P30-ES013508.

AP3 Investigating the Role of Serum Amyloid A in Mediating T Cell Dysfunction in Pediatric Obese Asthma

Ceire Hay[1,2], Samir Sayed[3], Andrea Mauracher[3,] Peyton Conrey[3,], Jose Campos[1,3], Christopher Pastore[4], Heather Rossi[4], Li-Yun Hung[4], Shaon Sengupta[5], De'Broski R. Herbert[4], Sarah E. Henrickson[1,3,6]

[1]Immunology Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Center of Excellence in Environmental Toxicology, Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; [3]Division of Allergy Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, U.S.A.; [4]Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [5]Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [6]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

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Obese asthma (OA) is a clinically severe, treatment-refractory asthma phenotype characterized by poor control of asthma symptoms and severe exacerbations due to respiratory viral infections. While both asthma and obesity are associated with altered immune status, the mechanisms by which obesity modifies immune function in asthma are not well understood – especially in pediatric populations. Using both clinical samples and murine models, we have demonstrated CD4 T cells from OA subjects are skewed towards a TH2/TH17 phenotype whereas CD8 T cells are skewed towards an exhausted-like phenotype (i.e. increased expression of PD-1, CD39, and TOX) when compared to their healthy weight counterparts. To better understand the mechanisms by which OA alters T cell function, we investigated the immunomodulatory role of Serum Amyloid A (SAA), a multifunctional proinflammatory protein known to be elevated in adults living with OA. Interestingly, in mice SAA has been shown to act as a soluble pattern recognition receptor for house dust mite and to alter cytokine production by CD4 and CD8 T cells *in vitro*. In both pediatric and murine samples, we found SAA levels were elevated in the serum of OA subjects when compared to healthy controls. We are currently developing *in vitro* assays and *in vivo* models to evaluate the role of SAA on T cell function in OA. Together, these data will provide novel insight into the immunopathogenesis of obese asthma.

This work was supported by the Translational Research Training Program in Environmental Health Sciences Pre-Doctoral Fellowship (T32-ES019851) to C.A.H. and K08-AI135091 to S.E.H.

AP4 Analyzing Traffic-Related Air Pollution Exposure in the Philadelphia Area

Irene Woo, University of Pennsylvania, College of Arts and Science, c/o 2026

Faculty Mentor: Blanca Himes, PhD

Email: iewoo@sas.upenn.edu

It is suggested through previous studies that exposure to traffic-related air pollution (TRAP) can increase the risk for the development and persistence of asthma. Particularly, communities of color and those in poverty appear more strongly affected by TRAP exposure near their homes. To further explore a potential connection between air pollution and asthma rates of at-risk groups, my project aimed to determine whether traffic volume was higher in regions of the Greater Philadelphia area with higher proportions of minority groups and/or residents in poverty.

For our data analysis, we utilized demographic variables and census tracts defined by the US Census and American Community Survey (ACS) and downloaded traffic data from the Pennsylvania Department of Transportation. From our data, we estimated the annual average daily traffic (AADT) for local roadways, converted AADT to daily vehicle miles traveled (DVMT), and coded shapefiles for Philadelphia, Bucks, Chester, Delaware, and Montgomery counties. We then overlaid DVMT rasters on county shapefiles to map tract-level DVMT and DVMT/m^2. To find the relationship between demographic variables against tract-level traffic volume, we calculated the regression of DVMT/m^2 versus ACS characteristics by plotting scatter plots with linear models.

Comparing the coefficients of these regression models, we observed that the demography of census tracts with the highest traffic volume in Philadelphia County differs from that in the Five-County Area (FCA) and deviates from our initial expectations. For example, an increased percentage of the White population is associated with a positive change in DVMT/m^2 in Philadelphia but is associated with a negative change in the rest of the FCA. The opposite is true for an increased percentage of the Black population and population below the poverty line. It is possible that this deviation from expectations may be explained by Philadelphia's large Black population and placement of highways near major tourist areas, as opposed to residential neighborhoods like in the other counties. Further steps for this project are planned to investigate the exact difference in the relationship between tract-level ACS variables and traffic volume in Philadelphia and the FCA.

This work was supported through the Penn Undergraduate Research Mentoring Program (PURM).

EEC1 The Effects of NRF2 and 1,8-dinitropyrene on NAD Biogenesis and Macronutrients in Human Lung Cells

Anthony L. Su, PhD, MPH, Jimmy P. Xu, Clementina A. Mesaros, PhD, and Trevor M. Penning, PhD

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The transcription factor nuclear factor erythroid 2–related factor 2 (NRF2) is activated by electrophilic and oxidative stress. Active NRF2 translocates to the nucleus and binds to the antioxidant response element (ARE), which leads to the transcription of genes involved in antioxidant response, intermediary energy metabolism, cofactor cycling, and control of cellular redox state. 1,8-Dinitropyrene (1,8-DNP) is a nitroarene found in diesel exhaust, is metabolically activated by nitroreduction, and may activate NRF2 because its metabolites are electrophilic. Significantly, aldo-keto reductases (AKRs) 1C1-1C3, which are induced by NRF2 activation, catalyze the nitroreduction of 1,8-DNP. As such, 1,8-DNP nitroreduction is dependent on NRF2, and it may play a major role in 1,8-DNP toxicity. Information on how NRF2 may mediate effects on specific energy metabolites, cofactors, and redox state that may impact nitroreduction is unclear. We investigated this gap in knowledge through the use of human lung cells (A549 and HBEC3-KT) in which NRF2 activity is regulated. Cells were exposed to 1,8-DNP and pharmacological modulators of NRF2 for 48 h. *R*-sulforaphane (SFN), 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-imidazolide (CDDO-Im) were used as activators of NRF2, whereas *N*-[4-[2,3-Dihydro-1-(2-methylbenzoyl)-1*H*-indol-5-yl]-5-methyl-2-thiazolyl]-1,3-benzodioxole-5-acetamide (ML385) and all-*trans* retinoic acid (ATRA) were used as inhibitors of NRF2. We found that A549 wild-type cells, which have constitutively active *NFE2L2*/NRF2, have higher levels of NAD, NADH, NADP, and NAM than A549 cells with homozygous knockout of *NFE2L2* by CRISPR/Cas9. By contrast, A549 wild-type cells had equivalent levels of tryptophan compared to A549 cells with homozygous knockout of *NFE2L2*, suggesting that NRF2 mediates NAD biogenesis through the salvage pathway as opposed to the *de novo* synthesis pathway. Effects observed in HBEC3-KT cells, which have inducible NRF2, including treatment with 1,8-DNP or NRF2 pharmacological modulators were more modest. Future directions will elaborate these preliminary data, and more detailed analysis of the metabolome under different treatment conditions will be explored.

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EEC2 RAD51 Paralogs Travel with the Replicative Helicase to Bypass Alkylation-induced DNA Damage

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Accurate DNA replication is essential for genomic stability and cancer prevention. Homologous recombination is important for high-fidelity DNA damage tolerance during replication. The yeast Shu complex, a conserved homologous recombination factor, aids in preventing replication-associated mutagenesis from DNA base damaging agents such as methyl methanesulfonate (MMS). To determine how the Shu complex enables bypass of MMS-induced DNA damage during DNA replication, we examined DNA binding preferences of the Shu complex DNA binding subunit and Rad51 paralog, Csm2, using an unbiased genome-wide chromatin immunoprecipitation sequencing approach. We found that Csm2 is enriched as autonomous replicating sequences, which contain the replication origin. Using evolutionary approaches, we find that the yeast and human Shu complexes are co-evolving with specific replication initiation factors including the origin recognition (ORC) complex and the replicative helicase, the mini chromosome maintenance (MCM) complex. Suggesting that the yeast Shu complex physically interacts with the replication machinery, we find that multiple Shu complex members interact with the ORC and MCM complexes by yeast-2-hybrid and co-immunoprecipitation experiments. We propose that the Shu complex is loaded onto the replication origins through an interaction with the ORC complex in G1 and then travels with the replicative helicase to enable the bypass of fork stalling/blocking lesions. We find that the physical interactions between the Shu complex and replication initiation complexes occur independently of the other HR machinery including the recombinase Rad51 and the canonical Rad51 paralog, Rad55. Together, our results point to a model where the Shu complex travels with the replication machinery to enable error-free bypass of DNA base damage.

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EEC3 Post-translational Modifications of KEAP1 by Nitrated Polycyclic Aromatic Hydrocarbons

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Air pollution has been identified by the International Agency for Research on Cancer as a Group 1 carcinogen and may contribute to lung cancer in both smokers and never smokers. Diesel engine exhaust is a major source of air pollution and is characterized by the emission of nitrated polycyclic aromatic hydrocarbon (NO_2−PAHs) attached to diesel exhaust particles. These particles were found in air ambient and in the lung tissues of exposed individuals, as well as in the lung tissues of non-smokers patients suffering from lung cancer. Therefore, NO_2−PAHs are associated with an increased risk of lung cancer. Among NO_2−PAHs, 1-nitropyrene (1-NP), 1,8-dinitropyrene (1,8-DNP), and 3-nitrobenzanthrone (3-NBA) have been characterized as either Group 2A or 2B carcinogens. To become mutagenic and tumorigenic, these compounds require metabolic activation through a 6electron reduction of the nitro-group catalyzed by cytosolic nitroreductases [including human aldo-keto reductases (AKRs)], producing a nitroso-intermediate. This intermediate is further reduced to the hydroxylamino- and amine-products, which can contribute to DNA adduct formation and possibly protein adducts as well. Importantly, AKRs are robustly induced by NRF2. NRF2 is activated when key cysteine residues in its repressor protein KEAP1 are modified. We sought to determine whether NO_2−PAHs may modify KEAP1. Our preliminary assays show that the nitroso intermediates can bind thiol groups on *N*-acetyl-L-cysteine and glutathione as well as hemoglobin nucleophilic cysteine residues leading to the formation of sulfinamide fully oxidized sulfonamide adducts. Incubations with recombinant KEAP1 protein indicate that 3-nitrosobenzanthrone can bind, to at least, three different cysteine residues, including the ones required for repression of NRF2. These findings suggest that, not only do NO_2−PAHs play a critical role in the *S*-nitrosylation of proteins – a post-translational modification of cysteine residues, involved in the regulation of signaling pathways such as redox regulation and apoptosis, and protein-protein interactions – but they can also be involved in the induction of their own toxicity. To elucidate the contribution of sulfinamide and sulfonamide adducts as products of *S*-nitrosylation, and their role and effects on the development of lung cancer, we are treating human lung cells with NO_2−PAHs, to conduct targeted and untargeted proteomics.

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WS1 Perfluorooctanoic Acid Acts as Specific Competitive Inhibitor to Steroid Hormone Pre-receptor Regulator, Aldo-Keto Reductase Family 1 Member C2

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women during reproductive age. PCOS is characterized by hyperandrogenism, polycystic ovaries, and anovulation. Currently hyperandrogenism is thought to have various organ sources, including white adipose tissue (WAT). Within WAT, metabolic enzymes, aldo-keto reductases (AKRs) regulate androgen production. A screen for inhibitors was performed to detect potential endocrine disrupting chemicals. Perfluorooctanoic acid (PFOA) was identified as an inhibitor. Interestingly, epidemiological data has suggested PCOS patients have higher levels of PFOA compared to non-PCOS individuals. Our data suggests AKR 1 member C2 (AKR1C2), which converts the potent androgen dihydrotestosterone to the less potent androgen 3α-androstanediol, to be potently inhibited by PFOA, yielding an observed IC50 value = 212 nM and tight binding corrected Ki value = 90 nM. This inhibition could lead to potent androgen increase in WAT, contributing to hyperandrogenism in PCOS. The inhibition was specific for AKR1C2, not inhibiting the highly related isoforms AKR1C1 and AKR1C3. The inhibition was computationally modeled to detect residue interactions and steric considerations that lead to inhibitor specificity. This modeling was corroborated by in vitro structure activity relationships. Interestingly, the only residue in the steroid binding cavity that is different from the residues in AKR1C1 is residue 54. To look at this residue, site directed mutagenesis was performed. Mutant AKR1C2 V54L loss the ability to be inhibited by PFOA, while mutant AKR1C1 L54V gained the ability, highlighting the importance.

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WS2 Examining and Communicating the Role of Neighborhood and Diet in the Study of Endocrine Disrupting Chemicals and Child Neurodevelopment: A Pilot Project

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Previous work has suggested associations between prenatal exposure to endocrine disrupting chemicals (EDCs) and autism-related traits in children. Additionally, socioeconomic factors have been associated with exposure to EDCs as well as the diagnosis of and access to autism- related services. Here, we examined the individual and joint effects of neighborhood socioeconomic position, dietary sources of some EDCs, and biomarker-based levels, in association with child autism-related traits. Participants (n=131 mother child dyads) were drawn from the Early Autism Risk Longitudinal Investigation (EARLI), a familial autism cohort study of pregnant participants who previously had a child diagnosed with autism. Concentrations of target EDCs, Bisphenol A (BPA) and summary di(2-ethylhexyl) phthalate (ΣDEHP), were quantified in maternal urine samples. Maternal dietary source of EDCs were ascertained via report on food frequency and source questionnaires, and quantified to develop a novel summary "burden score". Neighborhood deprivation was quantified using the Index of Concentration at the Extremes (ICE) scores based on factors collected during the 1st trimester. Child autism-related traits were collected when children were age ~3 years via caregiver report on the Social Responsiveness Scale (SRS-2). We then evaluated the individual effects of the relationship between neighborhood socioeconomic position with both individual biomarkers (BPA and ΣDEHP) and summary burden scores of dietary sources of EDCs with autism related traits in children. We did not observe a consistent association between terciles of ICE scores that jointly measured extreme conditions of income and race/ethnicity with average urinary concentrations of BPA or ΣDEHP, though EDC summary burden scores were weakly inversely associated with ICE scores. In covariate adjusted models, compared to those in the tercile of highest privilege, those with moderate to higher deprivation had more autism-related traits (β: 3.66; 95% CI: -1.02, 8.35); β: 3.56 (-1.64, 8.76), respectfully). Diet is a source of exposure to some EDCs, and dietary sources of EDC exposure may be higher among those with more neighborhood deprivation, jointly measured by economic and racial/ethnic segregation. Higher levels of neighborhood deprivation during the 1st trimester were also associated with children having more autism-related traits in early childhood.

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EN1 Identifying Potential ASD-Related Pollutants Through Genetics and Protein-Protein Interactions

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Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by deficits in social communication and stereotyped behavior. While ASD has a strong genetic component, there is increasing evidence of a large role for environmental factors, such as in utero exposures to certain compounds. We hypothesize that investigating molecular pathways for compounds may reveal enrichment of ASD risk genes and therefore provide information on susceptibility to ASD. In this study, we utilized the Comparative Toxicogenomics Database (CTD) for the all known interacting genes/proteins for compounds (interactomes) in conjunction with a list of ASD-associated genes to identify compounds that may affect ASD risk. We identified which compounds had a greater fraction of interaction with ASD genes than expected by chance, thus having a greater associated with ASD. Several of the top identified compounds were endocrine disruptors or steroids, such as bisphenol A (BPA), dexamethasone, and bisphenol F, and an estrogen receptor antagonist (fulvestrant).

Interaction networks may provide stronger evidence for relationships between compound interactomes and ASD risk genes at the primary and secondary level, providing key insights into potential targets for further research. To that end, protein-protein interaction (PPI) networks were constructed using the Biological General Repository for Interaction Datasets (BioGRID) and STRING databases. These network connections were then weighted by the mutational burden observed in 20,561 unrelated participants with ASD within the Simons Powering Autism Research (SPARK) consortium, providing valuable insights into genes and sub-networks that are most often burdened with rare, likely deleterious variants. Of these genes and networks, both the ESR1 and ESR2 genes were within the top 10 genes with the highest neighborhood mutation scores. When these scores were then used to rank the compound interactomes, an endocrine disruptor (butylbenzyl phthalate), an estrogen compound (4-hydroxy-equilenin), and a steroid (27-hydroxycholesterol) were identified within the top 10 compound interactomes.

Our work will provide novel insights into the possible link between ASD-risk genes and susceptibility to compounds that may be strongly associated with ASD. Through our unbiased approaches, we have identified steroid hormone pathways, especially estrogen pathways, that appear enriched for mutational burden within ASD. We hope that this integrated approach will provide possible models for more experimental validation of the effects of specific compounds on ASD risk.

This work was supported by the Translational Research Training Program in Environmental Health Sciences Training grant (T32-ES019851) from the National Institute of Environmental Health Sciences.

EN2 Convergent Transcriptional Signatures of Autism Spectrum Disorder Associated Chromatin Modifiers and Toxicant Exposure in Neurons

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Both environmental and genetic factors contribute to neurodevelopmental disorders (NDDs). A disproportionate number of the NDD susceptibility genes, particularly those linked to Autism Spectrum Disorder (ASD), encode epigenetic regulators. Mutations in these proteins may affect chromatin accessibility and gene expression. However, in many cases, these mutations are not fully penetrant. This suggests that other factors such as environmental toxicants may influence the incidence, severity, and development of disorders. Most previous research has focused on the gene of interest or exposure alone, but rarely examined the effects in combination. Thus, the convergent effects contributing to neuronal dysfunction remain largely unknown. To address this, we depleted 10 chromatin modifiers that are closely linked to ASD in a primary mouse neuronal culture system. We examined subsequent changes in gene expression alone as well as after treatment with Bisphenol A (BPA), a pervasive endocrine disruptor linked to NDDs. We found a strong overlap in transcriptomic changes between the partial loss of several of the chromatin regulators and exposure to BPA. A significant number of the differentially expressed genes (DEGs) were shared between individual conditions, with a strong enrichment for those related to synaptic function and cellular metabolism. This enrichment was reinforced when we examined genes that were only significantly dysregulated in the combined treatment. One of the most marked combinatorial effects was observed with Chromodomain Helicase DNA binding protein 8 (Chd8). Interestingly, the ASD patient population with CHD8 mutations exhibit a high degree of heterogeneity. Environmental factors may exacerbate underlying transcriptional disruptions and affect the severity of the disorder. To follow up these experiments in more biologically relevant systems, we will next move into a Chd8 haploinsufficient mouse model and utilize Neuromix: a toxicant solution that better represents normal human chemical exposures.

This work was supported by the Translational Research Training Program in Environmental Health Sciences Training grant (T32-ES019851) from the National Institute of Environmental Health Sciences.

EN3 The Freshwater Planarian Dugesia Japonica is an Alternative Organismal Model for Studying Neurotoxicity and Developmental Neurotoxicity of Organophosphorus Pesticides

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Organophosphorus pesticides (OPs) are a chemically diverse class of insecticides that can cause neurotoxicity in various organisms, including humans. Acetylcholinesterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine, is the primary target of OPs. Many OPs require bioactivation to inhibit AChE and OP toxicity can be mitigated by carboxylesterase (CE) and paraoxonase (PON1) through detoxification reactions. Effective OP inhibition of AChE leads to cholinergic toxicity, ultimately causing paralysis and death. Neuropathy target esterase (NTE) is another target of OPs and >70% inhibition of NTE causes OP-induced delayed neuropathy (OPIDN) in humans, a syndrome characterized by the distal degeneration of axons in central and peripheral nervous systems. Similar degeneration is observed in diseases such as Alzheimer's disease and Parkinson's disease. Here, we show that the freshwater planarian Dugesia japonica is a well-suited invertebrate model for studies of OP neurotoxicity and developmental neurotoxicity because this planarian shares the key enzymatic targets and machinery for OP metabolism with humans. Moreover, its amenability for rapid behavioral screening poses a cost-and-time advantage compared to expensive and time-consuming vertebrate testing. D. japonica can bioactivate OPs during all stages of neurodevelopment/neuroregeneration. It has two cholinesterase (ChE) enzymes that exhibit hybrid AChE and butyrylcholinesterase behavior. In addition, using biochemical assays, we have found that D. japonica has distinct CE and PON1 activities. Finally, we have identified a putative NTE homolog in D. japonica whose protein sequence shares high similarity with that of human NTE. To show that there is NTE activity in D. japonica, we are adapting a colorimetric biochemical assay which involves hydrolysis of phenol valerate. Because only neuropathic OPs can cause OPIDN through an aging reaction upon inhibition, NTE activity is experimentally defined as phenol valerate hydrolase activity that is inhibited by the neuropathic OP mipafox but not by the non-neuropathic OP paraoxon. In parallel, we are characterizing the effects of NTE knockdown using RNA interference on regeneration and behavior to investigate the physiological roles of NTE in planarians. This project will contribute to establishing freshwater planarians as an alternative invertebrate model for OP neurotoxicity and developmental neurotoxicity studies.

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CEC1 Environmental Impacts of Auto shops and Junkyards in Southwest Philadelphia

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The presence of auto shops and junkyards in residential areas pose significant health and environmental hazards to residents. These sites repair, maintain, and dismantle cars, which involves welding, sanding, painting, and using toxic, flammable materials. Southwest Philadelphia is overburdened with auto shops and junkyards. The Center of Excellence in Environmental Toxicology Community Engagement Core has been engaged with the Southwest Community Development Corporation on issues surrounding health and environmental effects of these sites. This summer, the CEC worked with two students from the Short-Term Educational Experiences for Research in Environmental Science for Undergraduates (STEER) to identify and describe the public health risks of auto shops and junkyards, characterize and map these risks to identify hot spots, and identify opportunities for intervention to reduce these risks. Using publicly available data from the City of Philadelphia Licenses and Inspections (L&I), Google maps, historical maps, and drive by photos, we identified auto shops and junkyards in the neighborhoods of Elmwood and Kingsessing and classified them as an air, water, soil, fire, lead, and/or infectious disease hazard. We also collected soil samples in public spaces to analyze for heavy metal contamination. Through this research, we found 65 sites, 56% of the sites had at least one identifiable hazard and 94% of sites with a hazard share a border or are across the street from residences. Nearly a quarter of the sites were identified as a lead hazard. Soil analysis shows elevated zinc but not lead. Improperly stored tires, which lead to an infectious disease risk, were found at 10% of the sites. Identified next steps include additional soil sampling around sites identified as a lead hazard and air monitoring around sites with air hazards. Based on our findings, we recommend L&I enforce existing policies on citations more strictly, require faster remedying of code violations, perform spring inspections of every facility containing tires to ensure they are stored properly to minimize standing water and fire hazards, conduct regular inspections of sites close to schools and playgrounds, consider remediation for elevated heavy metal concentrations in soil. We continue to work with community partners, policymakers, and city officials to address the health and environmental impacts of these sites in Southwest Philadelphia.

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