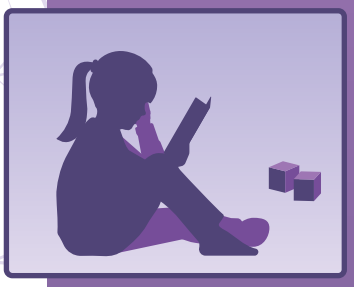

# Center of Excellence in Environmental Toxicology

FOURTEENTH ANNUAL SYMPOSIUM

**Environmental Neuroscience**

## Thursday, May 30, 2019

Henry A. Jordan Medical Education Center
Perelman School of Medicine at the University of Pennsylvania

# Center of Excellence in Environmental Toxicology (CEET)

FOURTEENTH ANNUAL SYMPOSIUM

# Environmental Neuroscience

Henry A. Jordan Medical Education Center
Perelman School of Medicine at the University of Pennsylvania

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Perelman School of Medicine University of Pennsylvania | CEET
CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

NIH National Institute of Environmental Health Sciences

# Contents

Fourteenth Annual CEET Symposium

# Environmental Neuroscience

Monday, May 30, 2019

7:30 – 8:30 A.M. REGISTRATION AND CONTINENTAL BREAKFAST

8:30 – 8:45 A.M. **Welcome & Opening Remarks**
Trevor M. Penning, PhD
The Thelma Brown and Henry Charles Molinoff Professor of Systems Pharmacology & Translational Therapeutics
CEET Director
University of Pennsylvania Perelman School of Medicine

John Dani, PhD
Professor and Chair Neuroscience,
University of Pennsylvania Perelman School of Medicine

Frances Jensen, MD, FACP
Chair of Neurology
University of Pennsylvania Perelman School of Medicine

8:45 – 10:15 A.M. Scientific Session I: Lead and Neurodevelopment

**Moderator**
Sigrid Veasey, MD
Professor of Medicine

Topic 1: **Lead Exposures and Community Engagement**
Marilyn Howarth, MD, FACOEM
Director Community Engagement, CEET
University of Pennsylvania Perelman School of Medicine

Topic 2: **What We Have Learned From the Jintan Child Cohort Study**
Jianghong Liu, PhD, RN, FAAN
Associate Professor School of Nursing
University of Pennsylvania Perelman School of Medicine

Topic 3: **ICP-MS -Heavy Metal Analysis**
Clementina Mesaros, PhD
Technical Director Translational Biomarker Core
University of Pennsylvania Perelman School of Medicine

10:15 – 11:15 A.M. POSTER SESSION WITH COFFEE

11:15 – 12:15 P.M. KEYNOTE

**Moderator**
Trevor M. Penning, PhD
The Thelma Brown and Henry Charles Molinoff Professor
Director CEET

**"Parallels Between the Developmental Neurotoxicity of Ambient Ultrafine Particle Air Pollution and Features of Neurodevelopmental Disorders"**
Deborah Cory-Slechta, PhD
Professor, Environmental Medicine,
Pediatrics and Public Health Sciences
University of Rochester Medical Center

12:15 – 1:30 P.M. LUNCH

1:30 – 3:00 P.M. Scientific Session II: Autism Spectrum Disorders

**Moderator**
Rebecca Simmons, MD
Hallam Hurt Professor in Neonatology
Deputy Director CEET

Topic 1: **Genetic Underpinnings of Autism Spectrum Disorders**
Maja Bucan, PhD
Professor of Genetics
University of Pennsylvania Perelman School of Medicine

Topic 2: **Autism Spectrum Disorder: Is This an Epidemic?**
Jennifer Pinto-Martin, PhD, MPH
Director Center for Public Health Initiatives
Director Center for Autism and Developmental Disabilities Research and Epidemiology
University of Pennsylvania Perelman School of Medicine

Topic 3: **Metabolism, Exposure, and Outcome in Autism Spectrum Disorder Cohort Studies**
Nathaniel Snyder, PhD, MPH
Assistant Professor
A.J. Drexel Autism Institute

Topic 4: **Air Pollution and Autism**
Marc G. Weisskopf, PhD, ScD
Cecil K. and Philip Drinker Professor
Environmental Epidemiology and Physiology
Departments of Environmental Health and Epidemiology
Harvard T.H. Chan School of Public Health

3:00 – 4:00 P.M. POSTER SESSION WITH REFRESHMENTS

4:00 – 5:00 P.M. Scientific Session III: Sleep Disturbance and Neurodegeneration

**Moderator**
Park Cho-Park, MD, PhD
Assistant Professor
Systems Pharmacology & Translational Therapeutics

Topic 1: **Neuronal Injury and Sleep Disturbance**
Sigrid Veasey, MD
Professor of Medicine
Center for Sleep and Circadian Neurobiology
University of Pennsylvania Perelman School of Medicine

Topic 2: **Effects of Environmental Noise on Sleep and Health**
Mathias Basner, MD, PhD, MSc
Associate Professor of Sleep and Chronobiology in Psychiatry
University of Pennsylvania Perelman School of Medicine

Topic 3: **Sleep Regulation and Autophagy: A Candidate Link to Neurodegeneration**
Joseph Bedont, PhD
Postdoctoral Researcher, Mentor Amita Sehgal
University of Pennsylvania Perelman School of Medicine

5:00 – 6:00 P.M. RECEPTION

# 14TH ANNUAL SYMPOSIUM

It is with enormous pride that I welcome you to the 14th Annual Symposium of the Center of Excellence in Environmental Toxicology (CEET), the University of Pennsylvania Environmental Health Sciences Core Center. Every year we choose a theme to embrace so that we can learn more about a field and how it might align with current and future directions of the CEET. This year's theme is on our new thematic area "Environmental Neuroscience". This theme originated with our Community Engagement Core who were concerned about lead (Pb) exposure in our communities and the widespread elevated blood levels of Pb in children in Philadelphia and Lancaster County that exceed the CDC level of 5 µg/dL. The behavioral and cognitive effects that ensue have been followed in a longitudinal study in Jintan district in Changzhou in China by Dr. Jianghong Liu. Our keynote speaker is Deborah Cory-Slechta who will speak on air pollution and developmental neurotoxicity and this will lead into a discussion of gene-environment interactions in Autism Spectrum Disorders (ASD). The genetic predisposition to the disease will be described by Maja Bucan and exposures that affect susceptibility will be discussed by Nate Snyder and Marc Weisskopf. Many environmental triggers (e.g. lead, shift work, noise) result in sleep disturbance and emerging work to be discussed by Sigrid Veasey and others will describe work that shows that sleep disturbance can lead to neurodegeneration. Our trainees will also have the opportunity to present their research in environmental health, it what will be an exciting and informative day.

*– Trevor Penning*
Director, CEET

## Keynote Speaker

**Deborah Cory-Slechta, PhD**

Professor, Environmental Medicine,
Pediatrics and Public Health Sciences
University of Rochester
Medical Center

Dr. Deborah Cory-Slechta is a Professor of Environmental Medicine, Pediatrics and Public Health Sciences at the University of Rochester Medical School, and former Chair of its Department of Environmental Medicine and PI of its NIEHS Core Center Grant. She also previously served as Dean for Research at the University of Rochester Medical School, and as Director of the Environmental and Occupational Health Sciences Institute of Rutgers University. Her research includes both animal models and human studies focused largely on the consequences of developmental exposures to environmental chemicals on brain development and behavior. This work has examined the effects of developmental exposures to metals, pesticides and air pollutants in animal models and human cohorts. These efforts have resulted in over 190 peer-reviewed publications. Dr. Cory-Slechta has served on advisory panels of the NIH, the FDA, the Environmental Protection Agency, the National Academy of Sciences, the Institute of Medicine, and the Agency for Toxic Substances and Disease Registry, and on the editorial boards of the journals Environmental Health Perspectives, Neurotoxicology, Toxicology, Toxicological Sciences, Toxicology and Applied Pharmacology and Neurotoxicology and Teratology. She has also served on the U.S. EPA Science Advisory Board and the Board of Scientific Counselors, ATSDR/CDC. In 2017, she was the recipient of the Distinguished Neurotoxicologist Award from the Neurotoxicology Specialty Section of the Society of Toxicology.

## Invited Outside Speaker

**Marc G. Weisskopf, PhD, ScD**

Cecil K. and Philip Drinker Professor
Environmental Epidemiology
and Physiology
Departments of Environmental Health
and Epidemiology
Harvard T.H. Chan School
of Public Health

Marc G. Weisskopf, Ph.D., Sc.D., is the Cecil K. and Philip Drinker Professor of Environmental Epidemiology and Physiology at the Harvard T.H. Chan School of Public Health in the Departments of Environmental Health and Epidemiology, and the Director of the Harvard T.H. Chan NIEHS Center for Environmental Health. Dr. Weisskopf received his Ph.D. in Neuroscience from the University of California, San Francisco, and his Sc.D. in Epidemiology from the Harvard T.H. Chan School of Public Health. He also spent two years as an Epidemic Intelligence Service Officer with the Centers for Disease Control and Prevention working on environmental health issues in the Wisconsin State Health Department. His neuroscience work focused on molecular and cellular aspects of neural signaling and plasticity. His epidemiological work focuses on the influence of environmental exposures on brain health across the life course. In particular, his research focuses on environmental risk factors for outcomes such as autism spectrum disorders, amyotrophic lateral sclerosis, cognitive function and dementia, and psychiatric conditions. Dr. Weisskopf also explores the use of physiologically-based methods for assessing toxicant effects on the brain, and epidemiological methods issues to improve causal inference from observational environmental health studies.

## 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 70 members come from 18 departments and 5 schools as well as Children's Hospital of Philadelphia. CEET is Penn's designated Environmental Health Sciences Core Center (EHSCC) funded by the National Institute of Environmental Health Sciences (NIEHS). It is one of only twenty-two such Centers in the nation; it is the only one in the Commonwealth of Pennsylvania, and the only one in US EPA Region III (PA, DE, MD, WV, VA and Washington, DC). As such it is a regional and national resource.

**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". Ongoing examples include the fate, transport, remediation and adverse health effects of asbestos exposure in Ambler in SE. Pennsylvania (which is home to one of the largest industrial Superfund Asbestos hazardous waste sites in the country); this work is supported by the Penn Superfund Research and Training Program. An emerging theme is precision public health in which community exposomes can be used to identify sub-populations most vulnerable to air pollution, lead contamination, and endocrine disrupting chemicals.

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, and metabolomics 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 trans-disciplinary services including study design, population exposure services, and exposure biology laboratories with access to biospecimens via the Penn Biobank.

The CEC works with six 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 Masters of Public Health Programs) to improve public health outcomes.

# CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

Perelman School of Medicine at the University of Pennsylvania

ADMINISTRATIVE CORE
Director: Trevor Penning, PhD
Deputy Director: Rebecca Simmons, MD

**Thematic Area I**
AIR POLLUTION & LUNG HEALTH

Leader: Michael Beers, MD

Julian Allen, MD
Andrea Apter, MD
Jason Christie, MD, MSCE
Pete DeCarlo, PhD*
Reto Gieré, PhD
Blanca Himes, PhD
Marilyn Howarth, MD
Dan (Dongeun) Huh, PhD **
Wei-Ting Hwang, PhD
Despina Kontos, PhD
Clementina Mesaros, PhD **
Edward Morrisey, PhD
Trevor Penning, PhD
Mary Porteous, MD, MSCE **
John Reilly, MD, MSCE **
Carsten Skarke, MD **
Douglas Wiebe, PhD

**Thematic Area II**
ENVIRONMENTAL EXPOSURES AND CANCER

Leader: Ian Blair, PhD

Steve Albelda, MD
Frances Barg, PhD
Eric Brown, PhD
Melpo Christofidou-Solomidou, PhD
Pete DeCarlo, PhD *
Edward Emmett, MD, MS
David Feldser, PhD
Jeffrey Field, PhD
Reto Gieré, PhD
Marilyn Howarth, MD
Wei-Ting Hwang, PhD
Douglas Jerolmack, PhD
Marcelo Kazanietz, PhD
Despina Kontos, PhD
Clementina Mesaros, PhD **
Hiroshi Nakagawa, MD, PhD
Trevor Penning, PhD
Ileana Perez-Rodriguez, PhD **
John Seykora, MD, PhD
Andrew Strasser, PhD
Joseph Testa, PhD *
Sarah Tishkoff, PhD
Anil Vachani, MD, MSCE
Douglas Wiebe, PhD

**Thematic Area III**
WINDOWS OF SUSCEPTIBILITY

Leader: Marisa Bartolomei, PhD

Mary Boland, PhD **
Heather Burris, MD **
William Gaynor, MD
George Gerton, PhD
Marilyn Howarth, MD
Dan (Dongeun) Huh, PhD **
Charlie Johnson, PhD
Kate Nathanson, MD
Sam Parry, MD
Trevor Penning, PhD
Richard Pepino, MS, MSS
Sara Pinney, MD, MS**
Nathaniel Snyder, PhD, MPH *
Rebecca Simmons, MD
Jerome Strauss, MD, PhD
Aalim Weljie, PhD **
Rebecca Wells, PhD

**Thematic Area IV**
ENVIRONMENTAL NEUROSCIENCE

Leader: Sigrid Veasey, MD

Paul Axelsen, MD
Ian Blair, PhD
Maja Bucan, PhD
Park Cho-Park, MD, PhD **
Reto Gieré, PhD
Elizabeth Heller, PhD **
Marilyn Howarth, MD
Harry Ischiropoulos, PhD
Kelly Jordan-Sciutto, PhD
Jianghong Liu, PhD, RN
David Lynch, MD, PhD

*Adjunct Member
**Affiliate Member

# CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

Perelman School of Medicine at the University of Pennsylvania

Guo-Li Ming, MD, PhD
Nirinjini Naidoo, PhD
Kevin Osterhoudt, MD, MSCE
Richard Pepino, MS, MSS
Jennifer Pinto-Martin, PhD, MPH
David Raizen, MD, PhD
Jay Schneider, PhD*
Rebecca Simmons, MD
Nathaniel Snyder, PhD, MPH *
Pouné Saberi, MD
Rebecca Simmons, MD

**EXPOSURE BIOLOGY INFORMATICS CORE**

Director: Jason Moore, PhD
Technical Director: Paul Wang, PhD

**TRANSLATIONAL BIOMARKER CORE**

Director: Ian Blair, PhD
Technical Director: Clementina Mesaros, PhD

**INTEGRATED HEALTH SCIENCES FACILITY CORE**

Director: Anil Vachani, MD, MSCE

Associate Director of Population
Exposure Services: Blanca Himes, PhD

Associate Director Biostatistics:
Wei-Ting Hwang, PhD

Genetics Statistician in Biostatistics:
Mingyao Li, PhD

**COMMUNITY ENGAGEMENT**

Director: Marilyn Howarth, MD
Program Coordinator: Thomas McKeon, MPH

Maria Andrews, MS
Andrea Apter, MD
Fran Barg, PhD
Michael Beers, MD
Edward Emmett, MD, MS
Jeffrey Field, PhD
George Gerton, PhD
Ira Harkavy, PhD
Blanca Himes, PhD
Jianghong Liu, PhD, RN
Judith McKenzie, MD, MPH
Howard Neukrug, PE, BCEE
Kevin Osterhoudt, MD, MSCE
Trevor Penning, PhD
Jennifer Pinto-Martin, PhD, MPH

# Air Pollution and Lung Health

## AP1 Nrf2 Induction of Antioxidant Response Increases Bioactivation of the Mutagenic Air Pollutant 3-Nitrobenzanthrone

*Jessica R. Murray[1], Laureano de la Vega[2], John D. Hayes[2], and Trevor M. Penning[1]*

*[1]Center of Excellence in Environmental Toxicology, Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; [2]Jacqui Wood Cancer Centre, Division of Cellular Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, UK*

*Email: murrayj@pennmedicine.upenn.edu*

3-Nitrobenzanthrone (3-NBA) is a potent mutagen and suspected human carcinogen detected in diesel exhaust particulate and ambient air pollution. It requires metabolic activation via nitroreduction to promote DNA adduct formation and tumorigenesis. NAD(P)H:quinone oxidoreductase 1 (NQO1) has been implicated as the major nitroreductase responsible for 3-NBA activation. We investigate the roles of human aldo-keto reductases (AKR1C1-1C3) in 3-NBA reduction and found that catalytic efficiencies (*k*cat/*K*M) values for AKR1C1, AKR1C3, and NQO1 were equivalent. We also determined that AKR1C1-1C3 and NQO1 contribute equally to the nitroreduction of 3-NBA in lung epithelial cell lines (A549 and HBEC3-KT) and combined they represent approximately 50% of the intracellular nitroreductase activity towards 3-NBA. These enzymes are induced by Nrf2 signaling which raises the question whether Nrf2 activation as a chemopreventive strategy may exacerbate 3-NBA toxification. To evaluate the role of Nrf2 signaling on nitroarene activation, we tested the effects of Nrf2 inducers (e.g. sulforaphane, synthetic triterpenoids) in human bronchial epithelial cells (HBEC3-KT). Since A549 cells have constitutively active Nrf2 signaling due to a KEAP1 mutation, we examined the effect of heterozygous (Nrf2-Het) and homozygous (Nrf2-KO) Nrf2 knockout by CRISPR-Cas9 gene editing. Upregulation of AKR1C1-3 and NQO1 by Nrf2 inducers and downregulation by CRISPR-Cas9 KO was confirmed and quantified by qPCR, immunoblots, and enzyme activity assays. We observed 40% increases in 3-NBA bioactivation due to Nrf2 inducers in HBEC3-KT cells and a reduction of 3-NBA activation in the A549 Nrf2 KO cell lines (53% reduction in Nrf2-Het A549 cells and 82% reduction in Nrf2-KO A549 cells). Enhanced 3-NBA metabolic activation due to Nrf2 activity may lead to an increase in DNA adduct burden which would promote mutagenesis. Nrf2 signaling is considered protective against cancer initiation despite the well-recognized dark side of Nrf2 in cancer promotion and progression. Given these data, it may be appropriate to explore whether Nrf2 activation plays a role in cancer initiation in certain exposure contexts (i.e. diesel exhaust).

*This work was supported by PhRMA Foundation Pharmacology/Toxicology Pre-Doctoral Fellowship to J.R.M. and P30-ES013508 to T.M.P.*

# Air Pollution and Lung Health

## AP2 A Spatial and Longitudinal Analysis of Air Pollution in the Abramson Cancer Center Catchment Area

*Jill Schnall[1], Tom McKeon[2,3], Angela Zhu[1], Anil Vachani[5], Paul Wileyto[1,4], Trevor M.Penning[2,3,4], Wei-Ting Hwang[1,3,4]*

*[1]Departments of Epidemiology Biostatistics and Informatics, [2]Systems Pharmacology & Translational Therapeutics, [3]Center of Excellence in Environmental Toxicology, [4]Abramson Cancer Center, Perelman School of Medicine, [5]Deparment of Medicine, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania | University of Pennsylvania, Philadelphia, PA 19104*

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The Abramson Cancer Center (ACC) has an urban catchment area that consists mainly of Philadelphia and its surrounding counties with higher lung cancer incidence than that of rural Pennsylvania. It is unclear how much environmental factors such as air pollutants contribute to the risk of lung cancer. Using publically available data from the Environmental Protection Agency (EPA), we fit a series of linear mixed effects models for the average daily concentrations of $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $O_3$, and NO2 from 1980 – 2017 to identify yearly and seasonal trends. We then focused on the $PM_{2.5}$ concentration from 2015 – 2017, and mapped the $PM_{2.5}$ concentration in the ACC catchment area using universal kriging. We also conducted a spatio-temporal analysis of $PM_{2.5}$ that considers both the spatial and temporal covariance structures. Finally, we explored weather and other environmental factors that could be associated with $PM_{2.5}$ concentration including Toxic Release Inventory (TRI) data from 2015 – 2017 in 1-mile, 5-mile, and 10-mile buffer regions surrounding each air monitor. We fit a linear mixed effects model with the environmental factors and TRI data as predictors. Based on our analyses, we found that there was a downward trend over time for all pollutants except for $O_3$, and we also saw strong seasonal variations. We found that kriging predictions were highly dependent on which variogram model was used, and a spatio-temporal analysis was more appropriate for our data. The spatio-temporal analysis supported the observations in our longitudinal analysis and kriging predictions with seasonal variations and a general downward trend over time. Finally, we found that an increase in the total number of TRI facilities in a buffer region, the total amount of diesel and IARC emissions, and a decreased distance to a major highway led to an increase in $PM_{2.5}$ for the 1-mile buffer model. In contrast, an increase in average wind speed, humidity, and emission of chemicals with significant evidence of lung carcinogenesis are associated with a decrease in $PM_{2.5}$ concentration. The effects of some predictors changed as we increased the buffer size.

*Supported by ACC Population Science Center of Excellence on Precision Lung Cancer Screening.*

## AP3 The Air we Breathe: Exploring Spaciotemporal Variability to Inform Circadian Studies in Asthma

*Nicholas Lahens[1], Garret A. FitzGerald[1,2,3] & Carsten Skarke[1,2,3]*

*[1]Institute for Translational Medicine and Therapeutics (ITMAT); [2]Department of Medicine; [3]Department of Systems Pharmacology and Translational Therapeutics; University of Pennsylvania Perelman School of Medicine; Philadelphia, PA, 19104*

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**Background:** We determined in our pilot characterization of the human basal chronobiome (Skarke et al. Sci Rep. 2017 PMCID:PMC5719427), that a majority of behavioral, cardiovascular and environmental sensor readouts display time-specific variability, and that 5-6% of the plasma and saliva metabolome and several genera of the saliva microbiome exhibited significant time-of-day-dependent abundances. This suggests that candidate oscillatory variables can be discerned in the wild. **Aims:** Now, we wish to study at scale the basal chronobiome and explore its architecture under evoked and disease conditions. Discerning the variability in the chronobiome attributed to sex, age and season will be instrumental to identify circadian misalignment of clinical relevance outside of tightly controlled conditions. Asthma exhibits time dependence in the severity of its phenotype. To explore how the morning exacerbations relate to personal, hyperlocal exposure to air pollutants, and to subsequently address its mechanistic underpinnings, we adopted in a first step continuous remote monitoring of geocoded environmental, behavioral, and cardiovascular parameters with a focus on air quality. **Methods:** In an IRB-approved pilot study a ChemiSense monitor (Berkeley, CA), Personal Ozone Monitor (POM, 2B Technologies, Boulder, CO), Actigraph (Pensacola, FL), BioPatch EKG monitor (Zephyr Technology, Annapolis, MD) and the smartphone application Beiwe (JP Onnela, Harvard, MA) were deployed to 10 consented healthy volunteers to collect data streams continuously over 48 hours. **Preliminary Results:** On average (±SD), ambient indoor concentrations measured 13.8±51.2 μg/m$^3$ for PM1, 18.5±66.3 μg/m$^3$ for PM2.5, 20±71.6 μg/m$^3$ for PM10, 5.4±3.3 ppm for tVOC, 0.7±0.9 ppm for CO, and 0.04±0.07 ppm for formaldehyde. Ozone concentrations averaged to 5.1±11.3 ppb in the in- and outdoor setting. Time-dependent fluctuations of averaged pollutants were consistent with morning and evening rush hours. However, personal exposure patterns showed substantial dynamic changes. Positional correction of location signals per differential GPS proved necessary to geocode data streams in the urban setting. Analyses of additional remote sensing data is pending. **Perspective:** This pilot study establishes paradigms to capture personal exposure to environmental risk factors at high spatio-temporal resolution.

*Supported by a CEET Pilot Grant (P30-ES013508) to CS.*

## EEC1 Spatial Analysis of Lung Cancer Incidence and Toxic Chemical Releases in the Abramson Cancer Center Catchment Area

*E. Paul Wileyto[1,2,4], Vicky Tam[1], Thomas McKeon[2], Karen Glanz[1,2], Trevor Penning[2,3,4], Wei-Ting Hwang[1,2,4]*

*[1]Department of Biostatistics, Epidemiology, and Informatics, [2]Abramson Cancer Center, [3]Center of Excellence in Environmental Toxicology, [4]Penn Superfund Research Program, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104*

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Many researchers have explored the association between environmental toxicants and incidence of cancer but few studies have assessed the spatial relationships between hazardous environmental exposures and cancer using a community based analysis. In this analysis, we aim to describe the spatial distributions of cancer cases and some specific environmental pollutants that are carcinogens, and to evaluate exposure-outcome associations from a community sample collected in the Abramson Cancer Center (ACC) catchment area. Lung cancer incidence rates for the ACC catchment were calculated by census tract using data from the Pennsylvania Cancer Registry (PCR – 2005 to 2015), combined with census data. Data were restricted to the 5-county Southeastern Pennsylvania region that accounts for 54% of the cancer cases seen in the ACC during the time-period of interest. Environmental exposures such as toxic chemical releases and waste management activities were captured through Toxic Release Inventory (TRI), a publicly available EPA database using the web tool *MyEnvironment*, and by proximity to known sources of pollution such as major highways. We will first generate density maps of cancer incidence and toxic exposures and then estimate the adjusted rate-ratio using spatial autoregressive models or generalized additive models while controlling for participant's demographic and social characteristics, and locations of the toxic sources.

*Supported by P42-ES023720 Penn Superfund Research Program and ACC supplement fund (P30-CA016520-40) and ACC Population Science Center of Excellence on Precision Lung Cancer Screening*

## EEC2 Mapping and Clustering of Lung Cancer Incidence in the Abramson Cancer Center Catchment Area

*Angela Zhu[1], Tom McKeon[2,3], Anil Vachani[5], Jill Schnall[1], Paul Wileyto[1,4], Trevor M.Penning[2,3,4], Wei-Ting Hwang[1,3,4]*

*[1]Departments of Epidemiology Biostatistics and Informatics, [2]Systems Pharmacology & Translational Therapeutics, [3]Center of Excellence in Environmental Toxicology, [4]Abramson Cancer Center, Perelman School of Medicine, [5]Deparment of Medicine, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania | University of Pennsylvania, Philadelphia, PA 19104*

*Email: yazhu@pennmedicine.upenn.edu*

Lung cancer is the leading cause of cancer death, contributing the most to new cancer cases diagnosed. The resulting mortality and morbidity motivates a need to understand the risk factors associated with the disease. The Abramson Cancer Center (ACC) of the University of Pennsylvania has a catchment area that covers 12 counties in the greater Delaware Valley and has been observed to have a greater incidence of lung cancer than rural Pennsylvania; however, the impact of environmental exposures on lung cancer risk is not well understood. The objective of this project is to create spatial maps of cancer incidences and to identify clusters of high incidence areas using data from the Pennsylvania Cancer

Registry. The cancer registry data under study consists of 202,569 lung cancer cases diagnosed from 1995 to 2014, inclusive. The average zip-code level age-adjusted incidence rates have changed from 77.023 per 100,000 per year in 1995-1999 to 62.628 per 100,000 per year in 2010-2014. Moran's I, Geary's C, and Kulldorff statistics were used to assess spatial clustering of incidence. Furthermore, we explored the association between demographic and environmental factors, such as median income, Hispanic proportion, number of TRI facilities nearby, and distance to I-95, and lung cancer incidence rates through spatial regression analysis. Based on our analyses, we conclude that spatial autocorrelation exists overall in the region of interest. Local indicators of spatial autocorrelation (LISA) suggest that clusters of higher lung cancer incidence exists in Philadelphia county, especially along Interstate 95 and the Delaware River, which defines part of the boundary between Pennsylvania and New Jersey. Higher lung cancer incidence rates were associated with increased air and chemical pollutants as well as proximity to industrial facilities and infrastructure but were not associated with demographic factors. Because unusually high risks for lung cancer are observed in certain areas that are likely to be exposed to potential lung carcinogens, lung cancer screening that focuses on spatially vulnerable populations is recommended.

*Funding: Supported by ACC Population Science Center of Excellence on Precision Lung Cancer Screening*

## EEC3 **Elucidating the Roles of Estrogens in the Development and Prognosis of Malignant Pleural Mesothelioma.**

*Guannan Zhang[1], Ling Duan[1] and Trevor M. Penning[1,2]*

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Asbestos is a carcinogen that causes mesothelioma rare cancer that arises from the mesothelial lining of the pleura. Malignant pleural mesothelioma is an aggressive tumor that is resistant to conventional treatment including chemotherapy, surgery or radiation. Epidemiological observations show that for non-occupational exposure the incidence of mesothelioma is higher in women than men. However, women diagnosed with malignant pleural mesothelioma respond better to the treatment and have a better prognosis than men. This prompted us to assess the role of estrogen and estrogen receptors in determining the risk and prognosis of this cancer. Our hypothesis is that mesothelioma cells express estrogen receptors and they can generate their own ligands for these receptors. As a positive control, MCF-7 cells were shown to express ERα at the transcript and protein level, proliferate in response to 17β-estradiol and proliferation was blocked with fulvestrant an ERα antagonist. qPCR showed that three different malignant mesothelioma cell lines (MSTO-211H, REN, and IST) expressed ERα at very low levels when compared with MCF-7 cells and this was supported by immunoblot analysis. However, treatment of MSTO-211H cells with 17β-estradiol induced growth proliferation that was not blocked by fulvestrant. These data suggest that 17β-estradiol exerts survival and proliferative effects in malignant mesothelioma cells through a pathway that is independent of ERα. Using an antagonist for GPR30 preliminary studies indicate that the growth proliferation observed with 17β-estradiol is blocked in MSTO-211H cells. We now aim to measure the expression of ERα, ERβ and GPR30 in malignant mesothelioma cells with IP-based LC-MS/MS proteomics and their clinical and biological significance.

*Supported by P30-ES013508 to TMP*

## EEC4 **Distinguishing Secreted HMGB1 Proteoforms as Biomarkers of Environmental Exposures**

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The chromatin-associated protein high mobility group box 1 (HMGB1) has been identified as a potential circulating biomarker of mesothelioma and asbestos exposure. Although HMGB1 is present in the nucleus and binds to certain types of damaged DNA damage, it may also be transported from the nucleus and released to the extracellular space in cells undergoing necrosis and in some cells that can actively secrete it, including some malignant mesothelioma cells. Since there are a variety of cell types and conditions that result in HMGB1 release, HMGB1 levels lack the necessary specificity for diagnostic purposes. However, a consensus has emerged that post-translational modifications (PTMs) mediate the secretion of HMGB1, and differences in HMGB1 proteoforms may therefore have biomarker utility. Using Western blot, we have found that mass-shifting modifications to HMGB1 vary among cell types and chemical exposures. We have found that HMGB1 is released from human hepatocellular carcinoma (HepG2) and adenocarcinomic human alveolar basal epithelial (A549) cell lines following exposure to certain DNA-damaging agents, such as cisplatin. In addition, both chrysotile and crocidolite asbestos induce HMGB1 secretion from HepG2 cells in a dose-depended manner, and certain mesothelioma cell lines release HMGB1 without asbestos treatment. We have analyzed HMGB1 released in these disparate contexts to explicitly interrogate specific covalent modifications to lysine and cysteine residues that may regulate HMGB1 transport and release. For these analyses, we have followed in-gel protease digestions with analysis of the resulting two-dimensional-nano-ultra high-performance liquid chromatography-parallel reaction monitoring/mass spectrometry (2D-nano-UHPLC-PRM/MS). Chemical derivatization of lysine residues with [$^2H_6$]-acetic anhydride and of cysteine residues with [$^2H_4$]-iodoacetamide and iodoacetamide in sequence have enabled us to determine the endogenous acetylation sites and endogenous oxidation state of the cysteine residues. The different HMGB1 proteoforms released by cisplatin and asbestos treatment and by mesothelioma cell lines are being established by 2D-nano-UHPLC-PRM/MS.

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## EEC5 **Asbestos Dimensional Distribution Control for its Use in Biological Assays**

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The control of variables that are in play in experiments involving minerals and cells, tissue, or living organisms is of critical importance. The presented method aims at reducing the dimensional variability of asbestos, elongated mineral particles, and other asbestiform minerals to be used in biological assays. In this method, the asbestiform mineral is first filtered through two meshes of different sizes (e.g. 5 and 20 μm) to obtain a narrower dimensional distribution, which follows a power law. After the

dimensional selection procedure, a sterilization and/or deoxygenation procedure is applied before adding the mineral into biological cultures. This approach avoids the use of highly reactive chemicals as well as the modification of mineralogical characteristics and surface properties, which can play a major role in the interaction with cells. Therefore, the method could be combined with any other selective method(s) (e.g. sieving, magnetic separation, density separation, and/or separation based on settling velocity) to further refine the dimensional range of the minerals. Furthermore, this method is advantageous since it a) uses just distilled water and 2-propanol; b) avoids highly reactive chemicals; c) uses an easy sterilization procedure before the experiments; and d) is applicable to various hazardous asbestiform and elongated mineral particles.

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## EEC6 The Synthetic Lignan Secoisolariciresinol Diglucoside (LGM2605) Prevents Asbestos-Induced Inflammation and Genotoxic Cell Damage in Human Mesothelial Cells

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**Background:** Although macrophages play a critical role in malignant transformation of mesothelial cells following asbestos exposure, inflammatory and oxidative processes continue to occur in the mesothelial cells lining the pleura that may contribute to the carcinogenic process. Malignant transformation of mesothelial cells following asbestos exposure occurs over several decades, however, amelioration of the molecular signatures of DNA damage, inflammation, and cell injury may impede the carcinogenic process. We have shown in an *in vitro* model of asbestos-induced macrophage activation that LGM2605 given preventively reduced inflammatory cascades and oxidative/nitrosative cell damage. We therefore, hypothesized that LGM2605 could also be effective in reducing asbestos-induced activation and damage of pleural mesothelial cells. **Methods:** LGM2605 treatment (50 μM) of human pleural mesothelial cells was initiated 4 hours prior to exposure to asbestos (crocidolite, 20 μg/cm$^2$). Supernatant and cells were evaluated at 0, 2, 4, and 8 hours post asbestos exposure for reactive oxygen species generation (ROS), DNA damage (8-oxo-2'-deoxyguanosine; 8-oxo-dG), inflammasome-associated pro-inflammatory cytokines (IL-1ß, IL-18, IL-6, TNFα, and HMGB1), and markers of oxidative stress (malondialdehyde (MDA) and 8-iso Prostaglandin F2α (8-isoP)). **Results:** Asbestos induced a time-dependent ROS increase that was significantly ($p<0.0001$) reduced by LGM2605. Importantly, LGM2605 pretreatment reduced levels of asbestos-induced 8-oxo-dG formation by 73.6 ± 1.0 %. Asbestos-induced Inflammasome activation and cytokine secretion were significantly ($p<0.0001$) reduced by LGM2605 to either levels comparable to baseline, non-asbestos exposed (HMGB1, IL-1ß and IL-18) or remained undetectable (IL-6 and TNFα). Importantly, levels of MDA and 8-isoP and markers of DNA injury were similarly reduced by the drug. **Conclusions:** LGM2605 reduced inflammatory mediators release and DNA damage implicated in asbestos-induced malignant transformation of normal mesothelial cells.

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## EEC7 Microbe-mineral Interactions Between *Thermovibrio Ammonificans*, a Deep-sea Vent Microbe, and Asbestos Minerals.

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Asbestos, a group of naturally occurring silicate minerals, is well known for causing mesothelioma and other terminal human diseases via asbestos fiber inhalation. As such, technologies that can reduce asbestos toxicity before exposure, such as bioremediation techniques utilizing plants or fungi, are desirable. Here, we explore bacteria from mid-ocean ridges that are capable of colonizing silicate-rich substrates as potential agents for asbestos bioremediation. Specifically using *Thermovibrio ammonificans*, a bacterium from deep-sea hydrothermal vents able to incorporate Si into biofilms, we are investigating in vitro microbe-mineral interactions in the presence of chrysotile and tremolite-actinolite. Our goal is to evaluate the capability for and mechanism of Si removal from two types of asbestos minerals as a way to reduce their hazards. Initial results show that the presence of *T. ammonificans*, whose growth was unaffected by the presence of asbestos, increased the extent of amorphous coatings on both types of asbestos fibers after 48 h at 75°C. With chrysotile, aqueous [$Mg^2$+] and [Si] increased in the external medium in both the absence and the presence of bacterial cells in a 1.45 [$Mg^2$+] to 1 [Si] ratio. This agrees with transmission electron microscopy (TEM) and energy-dispersive X-ray spectroscopy (EDXS) investigations showing loss of Mg in chrysotile fibers. Yet, scanning electron microscopy (SEM) coupled to EDXS revealed a decrease in Mg/Si ratios within biofilms, perhaps due to Si accumulation. On the other hand, assays with tremolite-actinolite displayed minimal increases in aqueous [$Mg^2$+] and [Si] after 48 h and SEM-EDXS showed no fluctuations in Mg/Si ratios within biofilms, suggesting minimal interactions between *T. ammonificans* and tremolite-actinolite. Altogether, these results highlight the need for tailored bioremediation technologies that account for crystallochemical variations among different asbestos minerals.

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## EEC8 Identification of Krt15+ Basal Progenitor Cells in Human Esophageal Organoids Provides Additional Perspective on Esophageal Development

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The human esophageal lumen is lined by a stratified squamous epithelium comprised of proliferative basal cells that differentiate while migrating towards the luminal surface. Recent work from our group has demonstrated that the keratin 15 (Krt15) promoter marks a long-lived basal cell subpopulation in the mouse esophageal epithelium that is able to self-renew, proliferate, and generate differentiated cells, consistent with a progenitor/stem cell population (Giroux et al. JCI 2017). However, the mechanisms

underlying human esophageal developmental processes are not yet well elucidated, including species-specific differences. Therefore, we used human pluripotent stem cell-derived esophageal organoids (HEOs), which comprise complex, multicellular three-dimensional structures that express tissue-specific differentiation markers (e.g. Ivl, Krt13, Krt14), to identify a subpopulation of Krt15+ basal cells and study their role in human esophageal development. Immunofluorescence staining revealed the presence of Krt15+ cells in HEOs with decreased expression upon organoid differentiation, analogous to expression during development of the native tissue. Furthermore, fluorescence-activated cell sorting of HEOs using the EphA2 receptor and TMEM8A as cell-surface markers allowed isolation of Krt15+ cells and to characterize their higher organoid generation potential as compared to Krt15- cells. To our knowledge, these are the first insights into the presence of a Krt15+ progenitor cell population in the human esophageal epithelium that provides additional perspective on esophageal development, and establishes HEOs as a platform to study the role of Eph/ephrin and TMEM8A-mediated esophageal development. Future work includes studying the role of EphA2 signaling pathway in HEO proliferation and differentiation, as well as establishing the use of an engineered hydrogel as a delivery vehicle for HEO transplantation for tissue regeneration using a murine injury model.

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## EEC9 **Environmental and Genetic Drivers of Telomere Length Variation in Ethnically Diverse Africans**

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Telomeres are repetitive non-coding sequences at the ends of chromosomes that maintain DNA integrity. Telomeres progressively shorten at each cell division until a critical length is reached and cell division stops. Thus, telomere length is closely associated with aging and lifespan. In addition, longer telomeres are associated with increased risk of many cancers, while shorter telomeres are associated with elevated cardiovascular disease risk. Finally, telomeres shorten as a result of many intrinsic and extrinsic factors, including chronic stress and infection status. However, relatively little is known about the genetic architecture underlying telomere length, or the environmental factors that influence telomere loss. Here, we investigate the relationship between telomere length, genetics, and environmental factors in a set of ethnically diverse African people (n=1820) originating from populations in Botswana, Tanzania, Ethiopia, and Cameroon. We find significant variation in telomere length among populations after adjusting for age and sex, with the San hunter-gatherers from Botswana having the longest telomeres, and pastoralists from Cameroon having the shortest telomeres. After accounting for genome-wide ancestry and relatedness among individuals, we find that a large proportion of inter-individual variation in telomere length (>40%) is explained by genetic factors. Finally, telomere length varies significantly with environmental factors across Africa, as we find that altitude, UV-B radiation, and temperature explain small but significant additional amounts of variation in telomere length after adjustment for age, sex, and genetic ancestry. Ongoing work examines the relationship between telomere length and

other phenotypes, including cardiovascular traits, as well as whether patterns of selection at genetic loci underlying telomere length vary with environmental factors across Africa. This research will help elucidate the evolutionary basis of telomere length variation in humans, which will provide insight into the basis of telomere-related disease risk.

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## EEC10 Conversion of 11-Ketoandrogens to 11-Ketotestosterone by AKR1C3; Implications for Castration Resistant Prostate Cancer

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Prostate cancer (PC) is the most frequently diagnosed cancer in men and is the second leading cause of male death due to cancer. The development of PC is androgen-dependent, and it can be treated by androgen depletion therapy via physical or chemical castration. However, recurrence of PC can occur which leads to castration-resistant prostate cancer (CRPC). CRPC is still androgen-dependent and is regulated through signaling of the androgen receptor (AR). Consequently, there must be other sources of androgens. High physiological concentrations of the precursor androgen 11β-hydroxyandrostenedione (11OHA4) have been observed in the adrenal vein of patients. 11OHA4 may follow an alternative metabolic pathway to produce 11-ketoandrostenedione (11KA4) catalyzed by HSD11B2, and then converted to 11-ketotestosterone (11KT) and 11-ketodihydrotestosterone (11KDHT). 11KT and 11KDHT are just as potent at activating the AR as dihydrotestosterone (DHT), a potent androgen which drives PC. Aldo-keto reductase family 1 member C3 (AKR1C3) is upregulated in PC and accelerates conversion of androstenedione to testosterone and the conversion of androstane-3,17-dione to DHT via its 17-ketosteroid reductase activity. Thus, AKR1C3 may also drive the formation of 11-KT and 11KDHT in CRPC. The kinetic parameters for these reactions catalyzed by recombinant AKR1C3 were estimated by using discontinuous RP-HPLC enzyme assays. Previous studies were performed in HEK293 cells transiently transfected with AKR1C3, which did not permit the accurate determination of kinetic constants or their comparison with the conversion of androstenedione to testosterone. Our work led to the characterization of the formation of the 11-ketosteroids by human recombinant AKR1C3. Determining kinetic parameters of the substrates 11KA4, 11OHA4, and 11-keto-5α-androstanedione (11K-5α-dione) by AKR1C3 will help understand if this alternative pathway using 11-ketosteroids is a possible mechanism to drive androgen formation in CRPC.

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## EEC11 Estrogenic Activity of Polycyclic Aromatic Hydrocarbon Metabolites in Human Endometrium

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Polycyclic aromatic hydrocarbons (PAHs) are byproducts of incomplete combustion of organic materials, including fossil fuels, food, and tobacco. Cigarette smoking is associated with reproductive abnormalities in women, and some PAHs are uterine toxicants in rodents. Moreover, PAHs or their metabolites can activate estrogen receptors (ER), resulting in endocrine disruption. Once in the body, PAH are metabolized by the family of CYP-450 enzymes to more water-soluble hydroxy-PAHs (OH-PAHs). Additionally, aldo-keto reductases (AKRs) convert PAH trans-dihydrodiols into PAH ortho (o)-quinones. Given the similarity between planar PAH and estrogens, we hypothesize that PAH and PAH metabolites activate ERs in estrogen target tissues e.g. endometrium. We used inducible alkaline phosphatase activity in Ishikawa cells, a human endometrial adenocarcinoma cell-line, and estrogen response element (ERE) luciferase activity as the read-out for ER activation. We tested the estrogenicity of various PAH and their metabolites, including benzo[a]pyrene (BaP), 3 PAH o-quinones (benzo [a] pyrene-7,8-dione (BPQ), benz[a]anthracene-3,4-dione and 5-methyl-chrysene-1,2-dione), and 3-OH-BaP in endometrial cells. We demonstrated that these compounds induce ER activity with $EC_{50}$ values in the low micromolar range, and that this activation is inhibited by Fulvestrant, an ER antagonist. We have also shown that nanomolar concetrations of BPQ induce the translocation of ERα into the nucleus to modulate cell cycle gene expression. Using high performance liquid chromatography and APCI mass spectrometry in the selected reaction monitoring mode, we find that BaP can be metabolized to the estrogenic BPQ and 3-OH-BaP in Ishikawa cells in sufficient amounts to activate ER. Low nanomolar concentrations of BPQ increase Ishikawa cell proliferation to the same level observed with picomolar concentrations of 17-α-ethinyl estradiol, and both effects are blocked with Fulvestrant. Our work indicates that planar PAH metabolites may play a role in the disruption of ER signaling in the endometrium. Additionally, differences in reporter gene response and cell proliferation were noted, raising the question of whether or not the estrogenic effects are mediated through ER.

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## WS1 Gender and Dose-specific Impacts on Liver Metabolome of C57BL/6J Mice after Direct or Gestational Exposure to Bisphenol A

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Endocrine disrupting chemicals (EDCs) disrupt hormone action and are linked to development of metabolic disease. Bisphenol A (BPA) is a high production volume chemical used in manufacture of polycarbonate plastics and epoxy resins. BPA is persistent in the environment, and biomonitoring studies reveal pervasive human exposure. Rodent models demonstrate BPA-induced impacts on body weight, pancreatic function, glucose homeostasis and insulin signaling. However, specific molecular mechanisms of BPA-induced diabetes and obesity related outcomes remain to be elucidated. In parallel, the circadian clock is a critical regulator of metabolic homeostasis. The potential for EDCs to disrupt circadian clock and circadian-driven cellular metabolism is not well characterized. Mass spectrometry-based metabolomics provides a platform to assess EDC-driven impacts on cell and organ-specific metabolite profiles. The purpose of the current study was to assess metabolomic changes in C57BL/6J adult mouse liver after direct or gestational BPA exposure. Mass-spectrometry based metabolomics was conducted to profile 340 aqueous phase liver metabolites harvested from adult mice after direct or gestational exposure to lower dose BPA (10 μg/kg/day), upper dose BPA (10 mg/kg/day) or to control (7% corn oil). Multivariate modeling using orthogonal partial least squares discriminant analysis (OPLS-DA) revealed significant metabolomic impacts following BPA exposure. In females directly exposed to BPA, metabolomic changes were observed as a result of exposure to upper but not lower dose BPA, with alterations seen in pyrimidine and cyanoamino acid metabolic pathways following upper dose BPA exposure. Metabolomic alterations were observed in adult male offspring as a result of gestational exposure to both lower and upper dose BPA. Pathways impacted by BPA exposure in male offspring include purine and pyrimidine metabolic pathways and aminoacyl-tRNA biosynthesis. The current analysis has revealed metabolic fingerprints of BPA exposure stratified by generation, dose and gender. Exposure-induced impacts on amino acid as well as nucleotide metabolic pathways warrant further investigation as these pathways are important for nutrient cycling and energy homeostasis and have a strong aspect of circadian regulation.

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## WS2 IUGR Causes Pancreatic Inflammation in the Neonatal Rat

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The intrauterine milieu influences fetal development and perturbations can have lifelong effects on the offspring. Intrauterine growth restriction (IUGR) is a common complication of pregnancy and increases the risk of type 2 diabetes (T2D) in the offspring. Using a rat model of IUGR, bilateral uterine artery ligation, we identified immune pathways that are causal to beta cell failure. Previously we have shown that Th2 cytokines are transiently elevated at day 19 in islet lysates of IUGR fetuses. Postnatal administration of interleukin 4 (IL4) neutralizing antibody to IUGR pups on days 1-6 of life reduced postnatal day 14 (PD14) cytokine expression and ameliorated the IUGR phenotype in adult IUGR rats. The aim of this study was to identify immune cells in the pancreas, spleen, and lymph nodes during the postnatal period. At PD7, the number of T cells and macrophages increases in the non-islet portion of the pancreas of male IUGR pups. Finally, at PD14 immune cell populations normalize in the non-islet or islet portion of the pancreas. However, RNAseq and immunohistochemistry demonstrate a change in immune cell activation as evidenced by an increase in TNF, IL1B, CXCL9 and CCL3 gene expression and COX2 protein expression in the islets of IUGR pups at PD14. Overall, this work demonstrates a complex and transiently altered immune cell response to IUGR in the postnatal period. Further investigation of altered immune cell populations and pathways will further our understanding of IUGR caused T2D.

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## WS3 Elucidating the Epigenetic Mechanisms Involved in the Transmission of Adult Metabolic Phenotypes Following in uteri DEHP Exposure

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Environmental perturbations during fetal development lead to molecular changes that increases the risk to develop diseases in adulthood. Endocrine disrupting chemicals (EDCs) are ubiquitous in the environment due to their usage in many consumer products. One highly produced EDC is di-(2-ethylhexyl)-phthalate (DEHP). Prenatal exposure to DEHP can alter fetal metabolism in utero and disrupt critical setpoints that promote metabolic changes such as insulin resistance, glucose intolerance and obesity. However, the molecular mechanisms that are involved in the establishment and transmission of these phenotypes are unknown. Recent evidence suggests that EDC-induced changes in metabolic gene profiles may stem from an altered epigenetic landscape. DNA methylation, an epigenetic mark vulnerable to environmental exposures as it changes dynamically throughout fetal development. Thus, we hypothesize that one mechanism driving adult metabolic phenotypes may be through stable changes in DNA methylation. To test this, we exposed F0 dams to two human relevant doses of DEHP through their diet from preconception until either embryonic day (E) 10.5 or weaning age (PND21). At PND21

offspring are either on a control diet or challenged with a western diet until adulthood (PND140-184) to assess their metabolic health. Global DNA methylation levels were determined at E10.5 in embryos and placentas using a luminometric methylation assay. Results show that E10.5 male embryos exposed to our lowest dose (50 μg/kg bw/day) have significantly increase on global DNA methylation. F1 adult males exposed to our highest dose (10 mg/kg bw/day) and subsequently challenged with the western diet have significant increase in body fat and a trend towards glucose intolerance. DEHP exposure in utero alters global DNA methylation in the embryo and disrupts glucose homeostasis in adult offspring in a dose- and sex-specific manner. Future work will involve validation through additional cohorts and more tissue specific molecular and histological analysis focused on the liver, pancreas, adipose tissue, and bone. The ultimate goal of this work is to understand the mechanisms involved in the emergence of early-life phenotypes and how they can predict predisposition to adult metabolic disorders and to improve our knowledge on the risks EDCs represent to public health.

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## WS4 In Utero Exposure to Gestational Diabetes Alters the Transcriptome and Methylome of Human Fetal Stem Cells Revealing an Enrichment of Interferon Pathways

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Gestational diabetes (GDM) has profound effects on the intrauterine metabolic milieu, induces marked abnormalities in fetal glucose and insulin secretion and is linked to obesity and diabetes in the offspring, but the mechanisms remain largely unknown. In order to gain a better understanding of the mechanisms responsible for fetal programming of obesity and diabetes after in utero exposure to GDM exposure, we sought to measure changes in gene expression and genome wide DNA methylation in human amniocytes, a fetal stem cell, exposed to GDM in utero. For this study we used a nested case control design from which cases and controls were selected from an established biospecimen repository of amniocytes and amniotic fluid samples. Cases affected by GDM were identified by post-delivery questionnaire and confirmed by measuring amniotic fluid c-peptide (fetal derived). Matching criteria for the nested case control design included maternal age, gestational age at amniocentesis and gestational age at birth. All samples were from uncomplicated, healthy singleton term pregnancies without maternal complications other than GDM or known fetal abnormalities. RNA was isolated from amniocytes and used for creation of RNA-Sequencing libraries. EdgeR was used to identify differentially expressed genes from RNA sequencing data via fold change, p-values, and q-values calculated after Bonferoni correction (n=8; 4 per sex). Selected RNA-Seq results were confirmed via QPCR. Ingenuity Pathway Analysis (IPA) identified enriched biological pathways. Differentially methylated regions (DMRs) were determined from Enhanced Reduced Representation Bisulfite Sequencing (ERRBS) (n=16; 8 per sex) by identifying sequential CpGs with significant changes in DNA methylation >5%, and with $p<0.05$ over the entire DMR. We identified 20 differentially expressed genes ($q<0.10$) analyzing data from

male and female amniocytes together, but only 4 genes in male only and 2 in female only analyses. Using a significance threshold of $p<0.01$, we identified 65 differentially expressed genes when grouping male and female samples together, 46 genes in the male only analysis and 68 in the female only analysis. QPCR confirmed increases in IFI44, ULBP1 and SAMD9L. Differentially expressed genes were strongly enriched for interferon inducible proteins, a novel fetal programming pathway after in utero GDM exposure. IPA showed enrichment in molecular mechanisms regulating growth, oxidative stress metabolism and GCPR signaling pathways. Offspring sex-specific analysis greatly enhanced DMR identification. Nine DMRs were identified in all, 41 in male and 20 in female samples. These experiments suggested that early exposure to GDM in utero leads changes in gene expression and DNA methylation in amniocytes showing strong enrichment in interferon related pathways. These results provide insight into the mechanisms by which GDM exposure leads to metabolic health effects in the offspring by highlighting a novel role for interferon related pathways.

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## WS5 Maternal Obesity and Perfluorooctanoic Acid Synergize to Alter Lipid Metabolism in Human Fetal Hepatocytes Predisposing the Offspring to NAFLD

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Per- and polyfluoralkyl substances (PFAS), including the frequently used compound perfluorooctanoic acid (PFOA) are persistent non-biodegradable pollutants that are wide spread environmental contaminents (including drinking water) in the US including the Philadelphia area.. PFOA is a surfactant used in fire-fighting foams, non-stick cookware, waterproof clothing, carpets and food packaging due to its water repelling properties. Human have persistent and chronic exposure to PFOA due to its half life of 3-5 years which has been linkded to altered immune responses, abnormal cholesterol and lipid levels hepatomegaly, abnormal liver enzymes and fatty liver disease, obesity and insulin resistance. There is limited information regarding early life exposure to PFOA and later development of obesity, metabolic disease and hepatic toxicity. However, maternal obesity has profound effects on the intrauterine metabolic milieu, induces abnormalities in glucose homeostasis and insulin secretion in the fetus and is linked to obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) in the offspring, although the molecular mechanisms are not well defined. Multiple studies support the concept that there is a critical developmental window of programming in which in utero exposures can make an individual more susceptible to adult diseases such as NAFLD. We hypothesize that gestational exposure to PFOA in the setting of maternal obesity leads to increased lipotoxicity in the fetal liver resulting in steatohepatitis and an exacerbated immune response and ultimately to NAFLD later in life. We created an in vitro system to study the potential combined effects of PFOA and maternal obesity (with palmitic acid as a surrogate) on the development of NAFLD using HepaRg cells, a human derived fetal-like hepatocyte cell line.. Here we report that exposure to PFOA combined with palmitic acid leads to to

increased expression of critical genes regulating de novo lipogenesis (SCD1, SREBP f1, FASN) . In addition, combined exposure to PFOA and palmitic acid results in suppression of fatty acid oxidation as measured by $^{3}H$ labeled palmitate. Furthermore, PFOA and plamitic acid reduce the mitochondrial content and superoxide generation and increase activation of NFκβ and production of IL1β. We are expanding these experiments to a mouse model of gestational exposure to PFOA and maternal obesity to better characterize the molecular mechanisms involved in fetal programing of NAFLD.

*Funding: NCAT UPenn ITMAT, NIEHS P30 ES013508*

# Environmental Neuroscience

## EN1 **Metabolomic Response to Rotenone and Paraquat Exposure**

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Environmental exposures to the mitochondrial toxins, rotenone and paraquat, have been suggested to increase the risk of developing Parkinson's Disease, a neurodegenerative movement disorder. Monitoring changes in the mitochondrial metabolic pathways is critical to understanding the mechanisms and effects of these compounds. We have developed an accurate, robust, and sensitive method to monitor and quantify metabolites through ultra-high- performance liquid chromatography-high resolution mass spectrometry. Hepatocellular carcinoma (HepG2) cells were treated with increasing concentrations of rotenone and paraquat. Higher concentrations of rotenone led to decreasing levels of glycolysis and TCA cycle metabolites, which correlate with rotenone's mechanism of inhibiting complex I of the mitochondrial electron transport chain. Increased concentrations of paraquat led to increasing levels of pentose phosphate pathway metabolites. As a result of observing changes in a large number of metabolites due to the two pesticides, the developed high resolution mass spectrometry method was confirmed to be robust and accurate.

*Supported by P30-ES013508*

## EN2 **Investigating the Molecular Mechanisms of Hr38-proteasome Regulation in *Drosophila Melanogaster* in Response to Environmental Compounds**

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Hormone receptor-like in 38 (Hr38) is a nuclear receptor found in *Drosophila melanogaster (D. melanogaster)*. Hr38 has been shown to play a role in ecdysteroid signaling in flies, a process that plays a critical role during fly development, especially during molting. Nuclear receptor related-1 protein (Nurr1) is the human ortholog to Hr38. Nurr1 is known to regulate dopaminergic development in mice and as such has been implicated in Parkinson's Disease (PD). Alpha-synuclein is the main protein component of Lewy bodies, which are protein aggregates found in the nerve cells of PD patients. The presence of protein aggregates suggests abnormal protein homeostasis. Work from our lab has found that Hr38 regulates proteasome function in *D. melanogaster*. This finding suggests that protein aggregation observed in PD patients may be linked to abnormal proteasome-mediated protein degradation. This observation is striking because exposure to pesticides has been associated with a 70% increased risk of developing PD. Moreover, it has been shown that Nurr1 expression was altered in response to exposure to endocrine-disrupting chemicals (EDCs) *in vitro*. Thus, we hypothesize that some environmental compounds may alter proteasome function through a Nurr1-/Hr38- mediated pathway and this may provide a mechanism for increased risk of PD upon pesticide exposure.

*Supported by T32-ES019851 to LRR*

## EN3 Phthalates & Neurodevelopment: A comparison of Prenatal Phthalate Exposure Measurement in Infant Meconium to Maternal Urine

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Phthalates are a class of endocrine disrupting chemicals with ubiquitous human exposure. Prenatal exposure to phthalates is thought to be detrimental to fetal neurodevelopment, but quantification of fetal exposure is challenging. Though metabolites of phthalates have been detected in several human biosamples, prenatal phthalate exposure is commonly measured in maternal urine samples. Meconium is a promising matrix to measure cumulative exposure to exogenous and endogenous chemicals, but data on phthalates measured in meconium is sparse. The objective of this study was to measure prenatal phthalate exposure in meconium and compare the exposure assessment to the commonly used matrix of maternal urine. We measured 14 phthalate metabolites from eight diesters in maternal urine samples collected at the 2$^{nd}$ and 3$^{rd}$ trimesters, and 13 metabolites from ten diesters in meconium samples collected in the Early Autism Risk Longitudinal Investigation (EARLI) study, a pregnancy cohort of 236 mothers with a child diagnosed with Autism Spectrum Disorder (ASD). Metabolites in urine were measured using high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS), and those in meconium were measured using liquid chromatography-high resolution mass spectrometry (LC-MS/HRMS). We used Spearman's correlation to evaluate the association between different metabolites within each matrix and correlations between the same metabolites measured in urine and meconium. All except three metabolites were detected in over 90% of the urine samples. Most urine measured metabolite levels were similar in magnitude to nationally representative biomonitoring studies from the same time period and demonstrated known metabolite-to-metabolite correlation patterns. In meconium, only six of 13 metabolites were detected in 90% or more samples. Meconium measured metabolites in our sample were similar to the small study that developed the analytic methods to quantify phthalates in human meconium and were higher in magnitude than reported in the only other large epidemiological study in North America, but considerably lower than reports from Asia. Metabolite-to-metabolite correlations were substantially lower in meconium than in urine, but the patterns were similar. Correlations between the same metabolites measured in urine and meconium were low in magnitude and varied by metabolite and by trimester of urine collection. Prenatal phthalate exposure can be detected in infant meconium with observable correlations between related metabolites. However, meconium measures may not correlate well with a single assessment in in maternal urine from a discrete point in pregnancy.

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## EN4 Beauty Sleep: Skin Collagens Regulate Sleep in Response to Cell Stress in *C. elegans*

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When animals are sick or injured from an exposure that results in cell stress, they respond by sleeping; such behavior is called sickness or stress induced sleep (SIS). The pathway regulating SIS may be conserved from nematodes to vertebrates. Cellular stress in *C. elegans* leads to activation of the epidermal growth factor (EGF) receptor on the ALA neuron, which releases neuropeptides. ALA neuropeptides induce SIS behavior, which consists of movment and feeding quiescence, elevated arousal threshold, and rapid reversibility. While much is known about ALA activation and its down stream mechanisms, the SIS pathway upstream of EGF remains poorly understood. This part of the pathway is the focus of our work.

We found that mutants lacking the cuticular collagens DPY-5, DPY-10, or DPY-13 show impaired feeding and movement quiescence following exposures to ultraviolet (UV) irradiation or heat shock. The loss of skin collagen genes results in short, fat worms, a morphological phenotype referred to as Dumpy or Dpy. To determine where the *dpy* mutants act in the SIS pathway, we crossed each of them into an inducible-EGF background. Each of the three *dpy* mutants showed normal or enhanced SIS following the induction of EGF, suggesting that these genes act upstream of EGF.

We have also found that these *dpy* mutants show impaired movement quiescence following infection with the Orsay virus. Viral infection causes the animals to exhibit bouts of quiescence that have been shown in our lab to act through the SIS signaling pathway. We are currently using qPCR to determine if these animals are resistant to infection or if their infection is comparable to phenotypically wildtype worms exposed to the virus and they are simply not as quiescent.

To determine if mutants with a Dpy phenotype due to mutations other than collagen genes are important for SIS, we tested mutants in *dpy-19*, which encodes a C-mannosyltransferase. *dpy-19* mutants had normal SIS following both UV and heat shock, suggesting that specifically collagen gene disruption and not the Dpy phenotype explains the impairment in SIS in the *dpy-5*, *-10*, and *-13* mutants. We tested mutants in a cuticle collagen that cause a different morphological phenotype to determine whether disruption of cuticle collagens that result in a longer morphology also influence levels of SIS. Animals with mutations in the cuticle collagen *lon-3* ,which causes a morphology that is longer than wildtype, show normal levels of movement quiescence following UV exposure.

We conclude that cuticular collagen disruption impairs stress induced sleep.This information informs our understanding of the relationship between skin collagens and fatigue/sleepiness associated with sickness such as connective tissue disorders in humans.

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## TBC1 Glycosylated High Mobility Group Box (HMGB1) 1 as a Potential Mesothelioma Biomarker

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In order to investigate whether tumor-related biomarkers can contribute towards the evaluation of the carcinogenic risk in populations exposed to asbestos, a non-histone chromosomal protein, high mobility group box 1 (HMGB1), was analyzed in plasma and serum samples. from healthy controls. The concentrations from healthy control subjects were then compared with HMGB1 concentrations found in plasma and serum from mesothelioma patients. Using a stable isotope dilution nano-ultra high performance liquid chromatography/high resolution mass spectrometry (nano-UHPLC/HRMS) assay, unmodified HMGB1 was below the limit of detection (1 ng/mL) in plasma from healthy individuals; whereas, serum levels were a mean of 6.1 ng/mL. This revealed that HMGB1 was secreted during the clotting process and that it was not a circulating biomarker (Weng et al. *Anal Chem.* 2018;90:7552). We have also shown that unmodified HMGB1 is not present in mesothelioma plasma and that acetylation of lysine residues in the two nuclear localization sequences does not occur. However, these studies did not exclude the possibility HMGB1 could have undergone glycosylation on yet to be identified sites prior to its secretion into the plasma. This could have interfered with the immunopurification/ polyacrylamide gel electrophoresis (PAGE) procedure that was used prior to the analysis of HMGB1 by nano-UHPLC/HRMS.

In the current study, our objective was to find and quantify the potential glycosylation locations in HMGB1. Our strategy is to treat asbestos exposed plasma and serum samples with peptide-N-glycos (PNGase F), a glycosidase enzyme that hydrolyzes N-linked oligosaccharides and to quantify the de-glycosylated HMGB1 using nano-UHPLC/HR tandem MS (MS/MS). Recombinant HMGB1 obtained from Speed Biosystems (Gaithersburg, MD) was found to run as two separate band on PAGE as detected by western blotting with an anti-HMGB1 antibody. The slower moving band corresponded to an increase in mass of 1.5 kDa indicating the presence of several glycosylated residues. De-glycosylation with PNGase F increased the mobility of the slower band on PAGE to that observed previously by western blot for unmodified HMGB1. After confirming the migration shift, three possible N-glycosylated sites of which two consensus (asparagine-37 and 134) and one non-consensus (asparagine-135) residues were evaluated. The N-glycosylated asparagine residues were converted to aspartic acids by the action of the PNGase F, which resulted in an increase in molecular mass of 0.984 Da per glycosylation site. The sites of glycosylation were determined as asparagine-35 and 134 by use of both trypsin and Asp-N digestions coupled with analysis of the resulting peptides by nano-UHPLC/HR MS/MS. This approach is now being applied to the analysis of plasma and serum HMGB1 from control healthy subjects and mesothelioma patients.

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## TBC2 **Reduction of Oxidized Methionine Residues for Quantitative Proteomics in Biomarker Research**

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Protein biomarker discovery for environmental toxins exposure and disease state diagnosis have attracted more popularity due to their specificity associated with underline pharmacological mechanisms. liquid chromatography (LC) tandemed with high-resolution mass spectrometry is a powerful platform to analyze and quantify protein biomarkers. However, sulfur-containing amino acid, methionine oxidation, both *in vitro* and *in vivo*, challenges MS-based quantitative proteomics studies due to the resulting loss of sensitivity and increased complexity. We have developed a method that efficiently reduces oxidized methionine residues through the use of recombinant methionine sulfoxide A/B reductases from *Neisseria* sp. (MSRAB). This combination efficiently reduces both methionine sulfoxide enantiomers that are present in proteolytically-derived peptides, which facilitates quantitative proteomics studies. Peptides were re-dissolved in 100 mM ammonium bicarbonate with 15mM DTT together with MSRAB at 37 °C for 1 h. Peptides were recovered by ultrafiltration of 10k Da cut-off filter. Nano-LC-MS data was acquired using a Waters Accquity nano-LC system interfaced with a Thermo Scientific Q-Exactive HF. Peptide quantitation was conducted using Skyline. Incubation of the peptides with the MSRAB methionine reductase enzyme at 37 °C for 1h at converted > 95 % of oxidized methionine residues to their corresponding reduced forms. The results with peptides from leptin and metreleptin with various lengths (8-24) and polarity as well as results from other examples including the important Asp-N peptide from the amino terminus of frataxin isoform E (Acetyl-$M^{76}$NLRKSGTLGHPGSL$^{90}$), and the Arg-C peptide from HMGB1 ($G^{11}$KMSSYAFFVQTCR$^{24}$) demonstrated that this method can be readily applied to a wide range of methionine-containing peptides.

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## TBC3 **Quantification of HMGB1 Release in Drug Induced Liver Injury Models**

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Drug-induced liver injury (DILI) is a common clinical concern as well as a major barrier for the development of new therapeutics. Despite its frequency and severity, there are no specific and predictive diagnostic biomarkers for DILI. Post-translational modifications to secreted proteins have potential to meet the increasing need for specific biomarkers. The highly conserved DNA-binding protein high mobility group box 1 (HMGB1) is widely modified in immune cells, which secrete HMGB1 in response to activation. The intracellular environment of activated immune cells and injured hepatocytes is sufficiently different to warrant investigation of HMGB1 modification differences for potential DILI biomarkers. The behavior of HGMB1 in injured hepatocytes has not been well characterized, however.

Using HPLC-HRMS/MS and live cell immunostaining, we show that HMGB1 dissociates from DNA and is passively released from necrotic hepatocytes following loss of membrane integrity. Multiple cell and hepatotoxin models were used to quantify passive HMGB1 release and show sufficient amounts of HMGB1 are released from necrotic hepatocytes for proteomic investigation. The context and mechanism of HMGB1 release support the potential for unique HMGB1 modification patterns and future proteomic analysis.

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# Community Engagement Core

## CEC1 **Understanding the Contribution of Lead in Soil to Lead Exposure in Philadelphia: Neighborhood by Neighborhood**

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Lead is a heavy metal and potent neurotoxin that is particularly hazardous to the developing brains of children under 5 years of age. Lead exposure can occur from a variety of sources including: deteriorating lead paint, pre-1950 private water service lines, dust from demolition, and soil contaminated by legacy pollutants from lead-based gasoline emissions, paint, and industry. The Centers for Disease Control and Prevention (CDC) categorizes lead poisoning as elevated blood lead levels (EBLLs) meeting or exceeding 5 micrograms per deciliter (μg/dL). In 2016, 3.4% of the 38,350 children screened by the Philadelphia Health Department had EBLLs between 5-9 ug/dL. The highest percentage of children with EBLLs continues to be found in zip codes of high poverty and housing stock built before 1950. Data from the Philadelphia Department of Health revealed that 36 Philadelphia census tracts reported that 10% of tested children had EBLLs.

Research demonstrates that lead in house dust and soil are important contributors to environmental lead exposure. Lead exposure from soil in post-industrial, older cities is expected to be higher due to the multiple lead sources that have contributed to soil. However, there has not been a systematic assessment of soil lead in Philadelphia. Over the last decade, Richard Pepino and his students have been collecting and testing soil for lead through his Academically Based Community Service Course through the Netter Center. Once mapped, the data helped to visualize soil lead at the neighborhood level. Based on the auspicious beginning provided by Mr. Pepino's students, CEC, since 2017, has worked with healthcare professionals, academics, governmental entities, students, and communities to consolidate historic lead soil data and collect samples of soil to test for lead contamination using a Delta X-Ray Fluorescence (XRF) portable analyzer. Our aims in this endeavor are to: 1) Learn the scope of lead soil elevations at the neighborhood level in Philadelphia 2) Identify areas with levels in need of remediation 3) Determine if there are areas/neighborhoods where soil with high lead levels occur 4)Determine if neighborhood soil lead elevations correlate with EBLLs 5) Create an on-line resource for communities to assess potential risks to children use 6) Design engagement opportunities around the mapped data for health education and exposure reduction.

ESRI's ArcGIS permits geocoding of the results. A total of 2,319 samples have been geocoded in Philadelphia, Lancaster, Delaware, and Chester counties. 2,055 of these samples fall within the City of Philadelphia. Samples in Philadelphia range from 0 ppm to 18,064 ppm with a median of 234 ppm, 36.2% >= 400 ppm, 7.2% >= 1,200 ppm and 1.0% >= 4,000 ppm.

As of date, soil samples from 206 out of the 380 Philadelphia census tracts have been tested and geocoded. The CEC continues to collect and test soil with the help of community partners. Efforts are underway to sample soil from schools and playgrounds in census tracts with high rates of elevated blood lead levels as well as known sites of prior smelters.

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## CEC2 CHIRP: The Chester Healthy Infant Research-to-Action Partnership

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The Chester Healthy Infants Research-to-Action Partnership (CHIRP) aims to study environmental exposures and their effects on birth outcomes in a federally designated environmental justice community, Chester City, PA. About 12 miles down the Delaware River from Philadelphia, Chester is 77.6% African American and, although Chester City accounted for 9.1% of all live births in Delaware County, it represented 13.41% of fetal/infant deaths. Chester is flanked on one side by the Delaware River and on the opposite side by a major interstate highway (I-95). On its northeastern end is the Philadelphia International Airport; on its southwestern border are the refinery-rich towns of Marcus Hook and Trainer. Chester City itself is an industrial hub, hosting a major energy-from-waste incinerator, a regional sewage treatment facility with associated sludge incinerator, a paper products plant with its own incinerator, and numerous other industries. The number of air pollution emitters and the volume of their emissions would suggest that Chester is overburdened by environmental pollutants. The fact that Chester has remained out of compliance for air pollution standards ever since the standards were promulgated by the EPA supports this contention. Infants born small-for-gestational age ($<10^{th}$ percentile) are three times more likely to die before their first birthday compared to appropriately grown infants. Poor fetal growth results from an interplay of genetic and environmental factors. Environmental factors, broadly defined, include physical and social exposures that alter the intrauterine fetal environment. Phase 1 of CHIRP is to obtain air pollution monitoring data in residential areas of Chester and compare these data with readings from the single Pennsylvania Department of Environmental Protection (PADEP) air quality monitor in the city; the PADEP monitor is located near the Delaware River, away from most of the major pollution generating facilities and distant from the residential areas. We will place four stationary monitors capable of continuously assessing $O_3$, $NO_2$, $PM_{2.5}$, temperature, relative humidity, and dew point. A single handheld monitor base with interchangeable heads for measuring $O_3$, $NO_2$, $PM_{2.5}$, and $SO_2$ will be used to perform spot measurements near our stationary monitors and that of the PADEP. Working with the Chester Environmental Partnership (CEP), a Chester community member will collaborate on this project to install and maintain the

monitors. Data from this project will be used to demonstrate the feasibility of monitoring air pollution in Chester for research purposes. Phase 2 of CHIRP will be to submit an R01 application in October 2019 to study birth outcomes to determine if there is a correlation between areas of greater environmental exposures with poorer birth outcomes (small-for-gestational age, preterm birth, etc.). Phase 2 will expand the partnership with CEP to include data from community groups providing prenatal and postnatal services to Chester mothers and 911 call data from the Delaware County Emergency Services office. Long-term plans include studying air pollution, noise, and violence as potential detrimental exposures affecting birth outcomes.

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## CEC3 Using Focus Groups to Understand Water Quality Health Literacy among Philadelphia Adults: Developing Materials for a Local Educational Intervention

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In recent decades, concerns about the impact of climate change, population growth, and urbanization on water quality have grown. Maintaining an abundant source of clean drinking water requires that those who have an opportunity to impact water sources have an understanding of the water cycle, water treatment and the impacts of human activity. Currently, not much is known about environmental health literacy of water quality in Philadelphia residents. In order to better understand baseline literacy levels among Philadelphia residents, we designed an interview strategy used in a focus group setting to ask them about key points of knowledge related to the water cycle and their impact on water in their community. The purpose of this information gathering activity was to develop evidence-based recommendations for educational materials. We developed 34 open-ended questions about drinking and non-drinking water topics, including topics about recreation, pollution, conservation, community management, urban water cycle, wastewater treatment, source water, population growth, disaster preparedness, water shortages and environmental changes. 3 focus groups were conducted and 22 adults participated in answering these questions. Each focus group session was transcribed, annotated, and scored as to how responses compare to each question's target response. Environmental health literacy was evaluated based on a National Institute of Environmental Health Science hierarchical model including recognizing, understanding, applying, analyzing, evaluating and creating topic knowledge. Participants tended to agree that healthy water quality is important but were unaware of where they could access accurate information about water quality. Trust in local government and drinking source water varied by region. Seven priority areas with the largest gaps in knowledge were identified: 1) Where to properly dispose of pharmaceuticals and hazardous waste, 2) defining watershed/source water, 3) understanding the water treatment process, 4) wastewater and storm water management, 5) difference between quality and quantity of drinking water, 6) knowing where to go to learn more about water quality, and 7) purpose of drinking water additives fluoride and chlorine. Misconceptions and uncertainty about water pollution, water treatment, and accurate information highlight the need for improved educational materials. Educational materials for an audio tour about water and health have been developed for public use at a Philadelphia environmental center.

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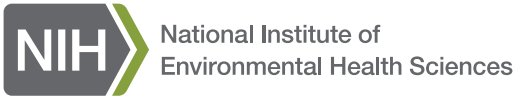
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