CEHS STANDARD PILOT PROJECT PROGRAM

AWARDS 2017-2018

(Each award is for $30,000)

SPPP 2017-01

Project Title: Exploring a causal among toxic metals and hypertension using genomics

P.I.: Nora Franceschini, MD, MPH, Research Associate Professor, Department of Epidemiology

Abstract:

This project directly address the Center for Environmental Health and Susceptibility (CEHS) request for translating interdisciplinary research on environmental health threats to improve public health in the focus area of cardiopulmonary disease. Cadmium is associated with cardiovascular disease and mortality, endothelial dysfunction, oxidative stress, and hypertension. However, the causal relationship between cadmium exposure and hypertension has not been established. This pilot study will address this hypothesis using Mendelian Randomization, a statistical approach that relies on the assumption that genetic variants are distributed independently and randomly with respect to behavioral and environmental factors, and can be used to estimate the effect of exposure-outcome even confounders are present, for example, smoking. We will use the existing comprehensive data from 531 Women's Health Initiative participants on blood pressure, smoking, urinary cadmium and genome-wide genotypes. To increase the genome coverage, we will impute existing whole genome sequencing data to candidate genes, and test the association of variants with urinary cadmium (Aim 1). We will compare the estimates from the association of a cadmium-derived genetic risk score and blood pressure with the estimates of cadmium and blood pressure using Mendelian Randomization approaches (Aim 2). Findings from this project will provide preliminary data to study environmental toxic metals toxicity and a role of genes and their regulation (methylation, transcripts, omics) in hypertension.

SPPP 2017-02

Project Title: Development of a structural-functional optical imaging platform for environmental exposure studies in an organotypic model of the mammary gland.

P.I.: Amy L. Oldenburg, Associate Professor, Department of Physics and Astronomy (Primary). Also *affiliated with:* Biomedical Research Imaging Center, Department of Biomedical Engineering and Lineberger Comprehensive Cancer Center.

Abstract:

Environmental cancer research is hampered by long study times and resources needed to measure tumor latency in animal models. Organotypic models recapitulate many features of the human mammary gland, while providing a scalable and controlled platform for environmental exposure studies. One of the biggest challenges to the rapid adoption of organotypic models is a dearth of imaging methods that can rapidly capture the entire volume of an organoid. We propose to employ optical coherence tomography (OCT) to provide high speed imaging of mammary epithelial cell (MEC) organoids in 3D culture for environmental studies.

Obesity-associated changes in the mammary gland microenvironment are suspected to be conducive to tumor growth, contributing to increased female cancer deaths. *We hypothesize that obesity-driven changes in the mammary gland microenvironment are linked with increased susceptibility to environmental toxicants, and that OCT can quantify relevant biomarkers for toxicant-induced breast cancer risk in this model system.* We propose to establish a 3D *in vitro* MEC-adipocyte co-culture model, and subsequently employ OCT structural-functional imaging to measure the exposure-response of MEC organoids to the environmental toxicant tetrabromobisphenol A.

SPPP 2017-03

Project Title: Airway Extracellular Vesicle MicroRNA Profiling in Ozone-Induced Asthma

P.I.s: Gregory J. Smith, Ph.D. and Samir Kelada, Ph.D., M.P.H., Department of Genetics

Abstract:

Exposure to traffic related air pollution, including ozone, is well known to cause asthma exacerbations. Recent epidemiological studies also indicate that ozone exposure is associated with *incident* asthma, suggesting that ozone promotes the development of asthma. We have observed that ozone exposure primes allergen sensitization in a mouse model of asthma, establishing support for the plausibility of ozone-induced asthma. We propose to test the mechanistic hypothesis that ozone-induced allergen sensitization is coordinated in part by airway extracellular vesicle (EV)-derived microRNAs, a newly appreciated form of intercellular communication. To accomplish this, we propose unbiased, global sequencing of airway EVderived microRNAs and mRNA of likely target cells, alveolar macrophages (AMs), from ozone and filtered air exposed mice. After the identification of differentially expressed EV-miRNAs and mRNAs in AMs, we will predict specific EV miRNA - AM mRNA targeting relationships using an established bioinformatic pipeline developed here at UNC. Using these approaches, we will establish the first EV-miRNA profiles associated with ozone exposure and identify novel mechanisms by which ozone alters the immunobiology of the airways to enhance the likelihood of developing asthma.

SPPP 2017-04

Project Title: Use of isotopic ratios to characterize newborn blood lead measures and environmental lead contamination from operating industrial sites in Forsyth County, North Carolina

P.I.: David Richardson, PhD, Associate Professor, Epidemiology Department; CEHS member

Abstract:

Epidemiologists in the North Carolina Division of Public Health recently uncovered clusters of children with elevated blood lead levels that are linked to parental occupational lead exposure. These investigations implicated industrial facilities in Forsyth County, NC at which there are substantial occupational lead exposures and very limited environmental controls. The degree of environmental lead contamination outside the facilities, and the extent to which vulnerable subpopulations, including pregnant women and children, are exposed are unknown. We propose an extensive environmental exposure assessment to strengthen understanding of the problem and its scope. Lead concentrations and isotope ratios will be measured in soil, lichen, and dust samples. Furthermore, we will assess the feasibility of measuring lead in archived newborn screening blood samples to complement available childhood lead screening data. We

propose innovative measurement of lead isotopic ratios in this medium to characterize lead resulting from maternal exposure. The proposed pilot project will support our future research to characterize environmental lead contamination from industrial facilities in North Carolina. This is a unique opportunity for an interdisciplinary team to address an urgent public health concern.

SPPP 2016-05

Project Title: Identifying the Effects of Environmental Toxicant Exposure on miRNA-regulated Adrenomedullin in the Development of Preeclampsia

P.I.: Kathleen M. Caron, Professor and Chair of the Department of Cell Biology and Physiology, SoM

Abstract:

Preeclampsia (PE) is a hypertensive pregnancy syndrome affecting 8% of women causing high blood pressure, breathlessness, and seizure until delivery. PE results from the improper invasion of the fetal trophoblast cells and malformation of the maternal spiral arteries resulting in nutrient deprivation and unstable vasculature. Adrenomedullin (AM) is a vasodilating protein, important for the development of the spiral arteries and PE prevention. Dosage of AM is critical in maintaining the maternal-fetal interface for a successful pregnancy. Indeed, AM is susceptible to estrogenic regulation and our collaborator recently identified placental accumulation of the metal, cadmium, correlates with increased PE risk and decreased AM levels. Through the use of miRNA mapping software, 133 miRNAs were determined to bind at the AM 3' untranslated region (UTR) resulting in AM degradation. Recent data confirms cadmium upregulates specific placental miRNAs, three of which can bind to the AM 3'UTR. **Thus, we hypothesize that exposure to environmental toxicants results in the expression of a unique group of miRNAs targeting AM for degradation, resulting in increased risk for PE.** We will determine the effect of environmental toxin exposure on the expression of AM signaling components. Additionally, we will identify the unique population of AM-targeting miRNA species expressed upon treatment of human trophoblast cells with the phytoestrogen, coumestrol, or cadmium. These results can deepen our understanding of AM regulation to treat and prevent hypertensive pregnancy disorders.

CEHS INTERDISCIPLINARY PILOT PROJECT PROGRAM

AWARDS 2017-2018

(Each award is for $50,000)

ID-PPP 2017-01

Project Title: Alleviating Environmental Toxin Damage via the Gut Microbiota.

P.I.: Matthew R. Redinbo, Kenan Distinguished Professor, Department of Chemistry, College of Arts & Sciences, and Biochemistry, Microbiology, Genomics, School of Medicine; Kun Lu, Assistant Professor, Department of Environmental Sciences and Engineering, and Scott Bultman, Associate Professor, Department of Genetics

Abstract:

Environmental carcinogens are inactivated through glucuronidation but can be reactivated by the gut microbiota back into toxic mutagens. We hypothesize that blocking the action of gut microbial glucuronidase enzymes will reduce environmental toxin-induced intestinal damage by preventing the reactivation of DNA mutagens. We have validated this hypothesis in a mouse model of AOM-induced carcinogenesis using glucuronidase inhibitors that target only the microbiota. Here we propose to complete this study to secure the first joint publication by a new interdisciplinary team composed of Professors Redinbo, Lu and Bultman. A subsequent NIH grant proposal by these CEHS members will focus on other environmental toxins, including heterocyclic aromatic amines and polyaromatic hydrocarbons. In this Pilot Project, we will identify gut metabolites (Aim 1), gut and microbial DNA adducts (Aim 2), and the microbiome-encoded enzymes involved in AOM reactivation and its inhibition in the mouse GI tract. We will use the CEHS Biomarker Mass Spectrometry and DNA Damage Core facilities in this project. The results we obtain will significantly advance our understanding of the microbiome's role in environmental cancer.

ID-PPP 2017-02

Project Title: Environmental Impacts on early Brain Development.

P.I.: Stephanie M. Engel, PhD, Associate Professor of Epidemiology; Weili Lin, PhD, Professor of Radiology, Neurology and Biomedical Engineering, Director of BRIC; Joseph Piven, MD, Professor of Psychiatry, Pediatrics and Psychology, Director of CIDD; Margaret Sheridan, PhD, Assistant Professor of Clinical Psychology and John H. Gilmore, MD Distinguished Professor, Director of the Early Brain Development Program.

Abstract:

We propose to leverage the **UNC Baby Connectome Project** to conduct innovative research linking environmental toxicant exposures to longitudinal neuroimaging data in order to examine *environmental influences on early, post-natal, brain development*. **The UNC Baby Connectome Project, just launched, will follow 285 children prospectively with non-sedated serial magnetic resonance imaging, spanning birth to age 4 years.** In this pilot project we propose to layer biospecimen collection and environmental survey data onto this newly initiated study, so that a future NIEHS R01 proposal can be developed to assess the impact of environmental toxicants on early brain development. We will additionally validate a cottonball based urine collection method for infants, and obtain preliminary reliability data on serial pyrethroid metabolite concentrations in infants. This project creates an unprecedented opportunity to

examine the effects of environmental exposures on early brain development, and will likely have importance to public health.