

LIST OF CEHS STANDARD PILOT PROJECTS AWARDS 2016-2017

(Each award is for \$30,000)

PPP AWARD 2016-01

Project Title: Interaction between infectious disease and environmental exposure.

P.I.: Kun Lu, Assistant Professor, and Zhengfa Zhang, Research Assistant Professor, Department of Environmental Sciences and Engineering.

Abstract

In this application, we propose to examine the cross-talk between environmental exposures and infectious diseases, which represents a current void in toxicological and environmental health research. The motivation and significance stem from the fact that humans are constantly exposed to not only a vast number of environmental chemicals, but also many disease-causing infectious agents or other inflammation-inducing factors. However, historically, research on environmental exposures and infectious/inflammatory diseases have seldom been conducted within the same toxicological paradigm. The overall goal of this proposal is to understand the complex infection-exposure interaction and define altering effects of inflammation on the hepatic toxicity of environmental chemicals. Specifically, this study will reveal the functional impact of hepatic inflammation on mediating arsenic-induced capillarization of sinusoidal endothelial cells, arsenic metabolism/microbiome and nitrosylation signaling pathways using innovative systems-level approaches. Success in this proposal will significantly improve our understanding of interaction between infectious diseases and chemical exposures, a current gap in toxicological research. It will also improve our capability of addressing individual response and identifying susceptible populations, critical determinants and/or windows of exposures for human health.

PPP AWARD 2016-02

Project Title: Chemical Mechanism of Ozone-Induced DNA Damage.

P.I.: Zhenfa Zhang, Research Assistant Professor, Environmental Science and Engineering.

Abstract

Ozone is a unique environmental challenge due to its relatively high toxicity and large exposed human population. Ozone is thought to be incapable of penetrating past epithelia cell membrane. However, recently sensors highly specific for ozone were reported to have detected ozone inside cells after ozone exposure. The overarching hypothesis of this proposal is that ozone-induced DNA damage may as well result from the direct reaction of ozone itself with DNA intracellularly. To test the hypothesis, direct ozonolysis of nucleoside in the basis of product identification and characterization is proposed to establish the product profile. Furthermore for comparison, the ozonolysis of DNA will then be analyzed for the products profile of ozone-induced DNA damage. Eventually extracted DNA from cultured cell or biological sample exposed with ozone will be analyzed. Once new adducts are validated, either increased by or unique to ozone exposure, they could be used as quantifiable biomarkers of ozone injury and toxicity.

PPP AWARD 2016-03

Project Title: Impact of common African American SULT polymorphisms on disease risk secondary to environmental exposures.

P.I.: Beverly Koller, Associate Professor Genetics; Rm 5073 Genetics Medicine Bldg, 120 Mason Farm Rd.

Abstract

The sulfonation of xenobiotics and small endogenous substrates, including steroids, hormones and neurotransmitters, occurs in most organisms. The reaction is mediated by cytoplasmic sulfotransferases (SULTs) that transfer the sulfo group of the cofactor 5'phosphoadenosine-3'phosphosulfate to nucleophilic sites of the acceptor chemical. This generally yields a less active molecule with increased hydrophobicity, which is more amenable to excretion. However, in numerous cases sulfonation results in bio-activation of pro-carcinogens to reactive electrophiles. This includes 2-amino-1-methyl-6-phenylimidazol [4,5-b]pyridine (PhIP), the most abundant heterocyclic amine found in fried meat, and 3-Nitrobenzanthrone, an environmental pollutant found in diesel exhaust. SULTs are polymorphic, and in a number of cases their function has been assigned to SULT variants using recombinant enzymes. The focus of this application is evaluation of the functionality of the SULT1A1*3 allele. While uncommon in Caucasians (1.3%), it is found in 22.9 % of African Americans. Here we develop a model system for evaluation of this allele alone and in combination with variants of other metabolic genes. The platform we propose to establish allows for generation of mice expressing the variants as well as for genome wide screening for interacting genes using CRISPR/cas9.

PPP AWARD 2016-05

Project Title: Using CRISPR/Cas9 Technology to Establish the Role of NRF2 as a Driver of Isoprene SOA-Induced Genomic Stress Response.

P.I.: Rebecca Fry and Co-PIs: Jason D. Surratt and William Vizuete, Department Environmental Sciences & Engineering.

Abstract

Our research team has shown that isoprene, the most abundantly emitted non-methane hydrocarbon, has the potential to induce toxic effects in human lung cells. This increased toxicity is a result of atmospheric oxidation of isoprene in the presence of acidic sulfate aerosol that leads to secondary organic aerosol (SOA). We have already shown SOA exposures have equal, or even higher oxidative stress potentials than diesel exhaust PM. Further, our team has also demonstrated that SOA exposures result in expression of oxidative stress and inflammation response-related genes in human lung cells. From this *in vitro* work we showed enrichment for altered expression of gene expression that is transcriptionally controlled by the Nuclear factor (erythroid-derived 2)-like 2 (NRF2). This pathway represents a target pathway influencing population susceptibility to SOA exposure. We propose a truly transdisciplinary study that integrates toxicogenomics, synthetic organic chemistry, and atmospheric analytical chemistry to test the novel hypothesis that NRF2 is a mediator of the genomic response to isoprene-derived SOA on key inflammatory-associated pathways in lung cells. Results from this study have relevance to population-based susceptibility to SOA.

LIST OF CEHS INTERDISCIPLINARY PILOT PROJECT AWARDS 2016-2017

(Each award is for \$50,000)

ID-PPP 2016-01

Project Title: Defining MAGEA4-RAD18 as a Novel Mutagenic Driver of Environmental Carcinogenesis.

P.I.: Cyrus Vaziri and Scott Williams, Department of Pathology and Laboratory Medicine, School of Medicine; Di Wu, Department of Periodontology, School of Dentistry.

Abstract

Cancer is an environmentally-induced disease often caused by DNA-damaging mutagenic exposures. There are fundamental gaps in our understanding of how cells tolerate environmental genotoxicity while accumulating mutations that drive carcinogenesis. The DNA damage tolerance and mutability acquired during carcinogenesis also allow established tumors to resist therapy. Thus, gaps in our knowledge of DNA damage tolerance and mutagenesis limit our ability to predict, prevent and treat cancer. Our long-term goal is to solve the related problems of how cells tolerate environmental DNA damage while altering their genomes during carcinogenesis. We recently identified Melanoma Antigen-A4 (MAGE-A4, a protein that is often upregulated during carcinogenesis), as a novel activator of DNA damage-tolerant and error-prone DNA replication. Here we will test the central hypothesis that MAGE-A4 is a new mutagenic driver in environmental carcinogenesis. We will use a novel transgenic mouse to determine how conditional MAGE-A4 expression impacts DNA damage tolerance, mutagenesis and skin carcinogenesis in vivo. The proposed work is significant because it will provide new paradigms for genome maintenance that are relevant to environmental exposures, tumorigenesis and cancer therapy in humans.

ID-PPP 2016-02

Project Title: Non-Invasive Sampling Techniques To Assess Potential Health Disparities In Environmental Triggers Of Asthma.

P.I.: Ilona Jaspers, Michelle Hernandez and Allison Burbank, Department of Pediatrics, School of Medicine.

Abstract

Health disparities are greatly apparent in the disproportionate morbidity associated with asthma among African-Americans. Factors likely contributing to this disparity include the disproportionately high incidence of poorly controlled asthma, higher exposure to environmental triggers, and reduced access to proper medical care. Understanding potential mechanisms mediating asthma health disparities, especially among at-risk groups like African-American adolescents, is further complicated by the reluctance of minority populations to participate in clinical research studies. We propose to use our recently developed and optimized non-invasive, field-deployable technique to sample the nasal mucosa of human subjects. Dr. Hernandez (Co-I) is currently enrolling adolescent patients (age 12-18) with asthma into a clinical trial assessing asthma symptom control and how reduction of environmental triggers could improve the disease.

Using this patient population we propose to use our non-invasive sampling technique to obtain biological samples before and after asthma control adjustment and examine these samples for markers of inflammation. Changes in markers of inflammation will be associated with asthma symptom control measures, thus providing quantitative biological markers associated with changes in environmental asthma triggers in an at-risk population.

ID-PPP 2016-03

Project Title: Etiologic heterogeneity of bladder cancer: Defining the molecular profile of low-grade, non-muscle invasive tumors.

P.I.: Andrew Olshan, Professor and Chair, Department of Epidemiology, Gillings School of Global Public Health; William Kim, Department of Medicine, and Katherine Hoadley, Department of Genetics, School of Medicine.

Abstract

Emerging molecular evidence has indicated that the long-recognized clinical heterogeneity of bladder cancer may be driven by distinct biologic subtypes. Recent molecular research at UNC and elsewhere and by the Cancer Genome Atlas Project has demonstrated, using only high-grade tumors, that pathologic subgroups may be further refined with gene expression data. There are 2-4 distinct subtypes, including basal-like and luminal subtypes that may reflect unique pathways for bladder cancer etiology and progression. There has not been a careful evaluation of the molecular profile of low-grade non-muscle invasive tumors, the most common type of bladder cancer. Confirming the subtype distribution for low-grade tumors is critical before conducting a large-scale epidemiologic investigation of bladder cancer etiologic heterogeneity. We propose to fill this significant gap by conducting a gene expression analyses of 150 low-grade bladder tumors obtained from the UNC Health Registry repository. This proposal will advance our knowledge of the molecular biology of a common form of bladder cancer and contribute essential preliminary data for planning an epidemiologic study of the environmental etiology of bladder cancer.