2018-2019 CEHS Pilot Project Awards

Title:	**Genomic Influences on Ozone Response in Mice**
PI Name:	**Terrence Furey,** PhD, Associate Professor, University of North Carolina, Department of Genetics, Carolina Center for Genome Sciences, and Lineberger Comprehensive Cancer Center
Project Type:	Team Science
Focus Area:	Cardiopulmonary
Abstract:	Exposure to ambient ozone (O_3) is associated with changes in innate immune function in the airways, leading to heightened susceptibility to viral and bacterial infections. This is mediated in part by the effect of O_3 on key host defense functions of alveolar macrophages (AMs). However, the extent to which variation in genes important to AM function underlies O_3 response is largely unexplored. The goal of this pilot project is to begin illuminating novel pathways of O_3 toxicity in AMs. More specifically, we will examine how O_3 exposure alters gene expression, chromatin accessibility, and key molecular pathways in AMs from genetically diverse Collaborative Cross (CC) mouse strains. The work in this proposal will serve to provide preliminary data for an expanded project to identify genetic and molecular determinants of variation in O_3 response in a larger panel of CC mice and in humans. Our long-term goal is to provide key information on GxE interactions with ozone, assess whether CC strains mimic the diversity of responses to O_3 in human populations, and inform the environmental health risk assessment framework for O_3.

Title:	**Identification of indoor environmental adjuvants in house dust**
PI Name:	**Timothy Moran,** MD, PhD, Assistant Professor of Pediatrics, Pediatric Allergy and Immunology
Project Type:	Single
Focus Area:	Cardiopulmonary
Abstract:	Asthma is the leading cause of chronic lung disease in children. The indoor environment plays a critical role in asthma inception, but the key environmental determinants that drive asthma development are unknown. We have found that house dust extracts (HDE) contain natural adjuvants that promote allergic sensitization to inhaled antigens. Preliminary studies indicate that HDE adjuvant activity is independent of protein allergens or endotoxin, suggesting that other immunogenic molecules within the home are important for allergic airway sensitization. We hypothesize that microbial-derived β-glucan carbohydrates are the primary source of HDE adjuvant activity.

	Using an animal model, we will determine if β-glucans in HDE promote sensitization to inhaled antigens, and if this is dependent upon the carbohydrate receptor Dectin-1. We will also determine if βglucans in HDE activate human respiratory epithelial cells. Finally, we will determine if β-glucan bioactivity in HDE, as measured with a cell-based bioassay, correlates with in vivo adjuvant activity. These studies may identify a key environmental determinant for asthma development, and thus lead to more effective home interventions for asthma risk reduction in children.

Title:	**Susceptibility to arsenic-induced diabetes: The role of As3mt polymorphisms and the microbiome**
PI Name:	**Miroslav Styblo,** PhD, Professor, Gillings School of Public Health, Department of Nutrition, and Adjunct Associate Professor, Department of Environmental Sciences and Engineering
Project Type:	Team Science
Focus Area:	Cardiopulmonary
Abstract:	Exposure to inorganic arsenic (iAs), a common drinking water and food contaminant, has been linked to type 2 diabetes (T2D). The metabolism of iAs has been shown to play a critical role in the susceptibility to T2D in populations exposed to iAs. However, factors that influence iAs metabolism, and thus affect the disease outcomes, are poorly understood. Arsenic methyltransferase (AS3MT) is the key enzyme in the pathway for iAs metabolism. AS3MT polymorphisms have been linked to inter-individual differences in iAs metabolism. The gut microbiome has been also shown to affect the patterns of iAs metabolism in both human and animal studies. However, the role of AS3MT polymorphism or gut microbiome in the susceptibility of iAs-associated T2D has never been examined. This project will use the unique Collaborative Cross (CC) mouse model resource to address this knowledge gap. We will examine the diabetogenic effects of iAs exposure in genetically diverse CC strains that exhibit differences in iAs metabolism and determine how the gut microbiome composition, which depends in part on the host genetics, affect iAs metabolism and the disease phenotype.

Title:	**Defining novel Chk2 functions in suppression of UV-induced skin carcinogenesis**
PI Name:	**Di Wu,** PhD, Assistant Professor, Assistant Professor, Department of Periodontology, School of Dentistry, and Assistant Professor, Department of Biostatistics, UNC Gillings School of Global Public Health
Project Type:	Single
Focus Area:	Environmental cancer
Abstract:	Our long-term goal to elucidate new tumor-suppressive mechanisms that protect against solar radiation-induced skin cancer. We have unexpectedly identified Chk2 (the murine homologue of the human Checkpoint Kinase 2, CHEK2) as a novel suppressor of ultraviolet (UV) radiation-induced skin carcinogenesis *in vivo*. We *hypothesize* that Chk2 has a novel role in maintaining genome stability in UV-irradiated keratinocytes.

	The *rationale* is that elucidating the biological roles of CHEK2 and its interactions with environmental exposures will allow us to better predict, prevent and treat cancer in humans. The *Specific Aims* are: Aim 1 Define mutational patterns of UV-induced skin tumors from *Chk2* $^{+/+}$ and *Chk2* $^{-/-}$ mice. Aim 2 Define the role of Chk2 in regulating cell cycle and transcriptional responses to UV irradiation in primary keratinocytes. For Aim 1 we will use a new pipeline we have established to perform whole exome sequencing and analyze existing tumor samples from WT and Chk2 mutant mice. In Aim 2 we will use primary keratinocytes from WT and Chk2 mutant mice to determine how Chk2 integrates cell cycle progression, DNA repair and gene expression in UV-irradiated cells. These studies will identify fundamental new tumor-suppressive mechanisms that protect against environmentally-induced cancer and new biomarkers of cancer-susceptibility.

Title:	**Does prenatal pesticide exposure exacerbate phenotypes in a mouse model of autism?**
PI Name:	**Mark J. Zylka**, PhD, Professor/Director, W.R. Kenan Distinguished Professor of Cell Biology and Physiology, and American Association for the Advancement of Science Fellow
Project Type:	Single
Focus Area:	Developmental Disease