2019 Pilot Projects Summary

Four 2019 Pilot Projects were funded, for a total of $124,993.

**Title: Single-cell Molecular Dissection of the Role of Endocrine Disruptors in Metabolic Dysfunction**

*Principal Investigator:*
Xia Yang, PhD, Associate Professor, Department of Integrative Biology and Physiology, UCLA

*Abstract:*
Despite the fact that numerous human epidemiology and animal model studies have implicated a pathogenic role of developmental exposure to endocrine disrupting chemicals (EDCs) in promoting obesity, type 2 diabetes, and cardiovascular diseases, the underlying molecular mechanisms remain poorly understood. We have recently conducted a systems biology study in mice to comprehensively examine the multi-tissue transcriptome, epigenome, and gut microbiome alterations altered by developmental EDC exposure. As a result, we identified key genes, pathways, and tissue-specific regulatory networks that are perturbed in endocrine and metabolic tissues (hypothalamus, liver, and adipose tissues) and associated with metabolic dysfunctions. However, all previous molecular studies of EDCs, including ours, examined bulk tissues that represent mixtures of heterogeneous cell populations, thereby missing the opportunity to pinpoint the most sensitive and pathogenic cell types and cell-specific molecular pathways. Building on our recent success in implementing high-throughput single cell sequencing technology Drop-seq, here we propose to understand the multi-tissue, multi-cellular molecular perturbations induced by in utero exposure in mice to two common EDCs, namely, the model chemical Bisphenol A (BPA) and its much less well-understood substitute Bisphenol S (BPS) at single cell resolution. We will focus on the liver, adipose, and hypothalamic tissues due to their pivotal roles in obesity and metabolic dysfunction. Using Drop-seq, we will identify the most sensitive cell types and molecular pathways in individual cell types in each metabolic tissue that are affected by developmental exposure to BPA and BPS, and subsequently test the roles of the molecular changes in metabolic dysregulation. Our proposed pilot study will offer the first comprehensive map of the in vivo molecular activities of common EDCs in individual cell types of key metabolic tissues and will reveal key mechanistic commonalities and differences between BPA and BPS to facilitate precision medicine. The findings will help direct future therapeutic strategies to counteract EDC-induced cardiometabolic disorders.

**Title: Hepatotoxic effects of perfluorinated compounds: a new epidemiological approach for studying environmental fatty liver disease**

*Principal Investigator:*
Leda Chatzi, MD, PhD, Associate Professor, Division of Environmental Health, Department of Preventive Medicine, Keck School of Medicine of USC

*Abstract:*
The prevalence of non-alcoholic fatty liver disease (NAFLD) in children has almost tripled over the past 20 years, currently affecting on average 8-12% of the general pediatric population and 34-40% of obese children in the US. Mounting evidence suggests that early
life environmental exposures contribute to the etiology of NAFLD. Animal studies show hepatotoxic effects even at low levels of exposure to perfluorinated compounds (PFASs), persistent compounds widely used in water repellent textiles, nonstick coatings, and food packaging products. PFASs have long half-lives (up to a decade) in humans. Despite abundant evidence from experimental studies demonstrating liver toxicity by PFASs, epidemiologic evidence is limited to a few cross-sectional studies in adults. We therefore propose a novel study design for investigating PFASs hepatotoxic effects, based on clinical and liver histopathological data leveraged from the Follow-up of Adolescent Bariatric Surgery (FABS) study that offers a unique archive of liver tissue and blood samples collected at the time of surgery. We hypothesize that higher plasma and liver PFASs concentrations will be associated with more advance stages of NAFLD and with attenuated improvement in liver injury after bariatric surgery. We will use archived samples collected at the time of surgery to measure PFASs concentrations in plasma and liver. Existing liver gene expression data in the FABS cohort will allow characterization of PFASs associations with underlying mechanistic pathways of NAFLD, including lipid metabolism and inflammation pathways. Findings from these pilot data will support a planned R01 application to investigate further the role of the PFASs chemicals and multi-omics signatures in pediatric liver disease. Our new multidisciplinary collaboration will also be relevant to future directions planned for the upcoming renewal of the Southern California Children’s Environmental Health Center and other major ongoing research projects at USC [e.g., MADRES and ECHO projects].

Title: Air pollution and breast cancer survival in California teachers

Principal Investigator:
Sandrah Eckel, PhD, Assistant Professor, Department of Preventive Medicine, Division of Biostatistics, Keck School of Medicine of USC

Abstract:
This pilot project aims to determine the relationship between ambient air pollution exposures and survival after diagnosis with breast cancer in the California Teachers Study (CTS). Using data from the California Cancer Registry (CCR), our group has previously shown that air pollution exposures after diagnosis are associated with shortened survival in lung and liver cancer patients. This work is based on the exposures occurring at the residential address at the date of diagnosis, the only address available in the CCR data. Despite biological plausibility for a role of air pollutants in breast cancer, we have not observed similar associations in breast cancer patients. We believe this is due to the longer survival of breast cancer patients, which requires access to longitudinal, individual-level data on address history (to produce more accurate exposure assignments) and data on other determinants of survival (potential confounders) which are not available in cancer registries. The CTS is a unique and rich data resource with extensive baseline and follow-up questionnaires, and addresses updated throughout follow-up. Data for those CTS participants residing in California at the time of breast cancer diagnosis are already included in the CCR. This pilot project will result in at least one publication and will lay the groundwork for subsequent NIH grant proposals: (a) an R01 to investigate the combined roles of air pollution and other risk factors on breast cancer survival with improved air pollution exposure modeling and (b) an R21 to investigate the impact of air pollution on lung cancer survival, accounting for smoking.