Environmental and Occupational Health Sciences
2 Funded PhD Traineeships, for up to 5 years, beginning autumn 2020
PI and Faculty Adviser: Julia Cui

Study I. Diabetes is a pandemic, causing grave social and economic burdens. This complex disease is caused by an interaction among genetic, metabolic, behavioral, and environmental factors. Epidemiology studies and animal experiments demonstrate that developmental exposure to the persistent environmental toxicants polybrominated diphenyl ethers (PBDEs) is associated with increased diabetes prevalence and persistent diabetic phenotype in adulthood. However, mechanisms governing early life PDBE exposure and the diabetogenic phenotype remain unknown. Current literature supports the mechanistic link between gut microbiome and metabolic syndrome in humans and animal models. We showed that oral exposure to PBDEs in adult mice results in dysbiosis with profound changes in bacteria known to be associated with inflammation and obesity, as well as reduced tryptophan microbial metabolites including indoles, which are novel activators of the host pregane X receptor (PXR) which is known to contribute to obesity and diabetes. Building on our findings that there is a gene-environment interaction between PXR and PBDEs through gut microbiome and indole metabolites, we seek to establish a causal relationship between developmental PBDE exposure, a change in the gut microbiome, and diabetes later in life using humanized PXR transgenic (hPXR-TG) mice in conventional (CV) and germ-free (GF) background. We hypothesize that developmental PBDE exposure causes acute and persistent dysbiosis, which contributes to diabetes through suppression of microbial tryptophan metabolism and selective PXR modulation (sPXRm) in early life and beyond. To test our hypothesis, in Aim 1 we will determine if developmental PBDE exposure perturbs the gut microbiome and microbial metabolism of tryptophan, leading to sPXRm in early life and beyond. In Aim 2 we will determine whether microbial metabolites, mainly including indoles and indole-derivatives, can reduce inflammation and rescue the diabetic phenotype following developmental PBDE exposure. In Aim 3 we will determine that reprogramming the gut microbiome using fecal transplant mechanistically contributes to developmental PBDE exposure mediated disruption of PXR signaling and delayed onset of diabetes. The expected outcome of the proposed research is a new research paradigm demonstrating that dysbiosis of the gut microbiome mechanistically contributes to early life PBDE exposure-induced diabetes and metabolic syndrome later in life, and more importantly, enables a toxico-metagenomics approach targeting metabolic disorders resulted from exposure to PBDEs and potentially other persistent organic pollutants.

Study II. Exposure of the developing brain to environmental toxicants such as polychlorinated biphenyls and heavy metals and disruption of the gut microbiome have independently been implicated in the etiology of neurodevelopmental disorders (NDDs). Both phenomena likely interact by two mechanisms to cause adverse neurodevelopmental outcomes: environmental neurotoxicant-mediated changes in the gut microbiome *(1)* alter the profile of neuroactive microbial metabolites distributed to the developing brain and *(2)* affect neurotoxicant disposition in the developing brain by modifying host and microbial neurotixcant metabolism. A mechanistic understanding of these interactions is required to address the *critical need* for interventional strategies that effectively reduce the impact of neurotoxicant-induced NDDs on individuals, families, and society. The *long-term goal* is to determine the role of the gut microbiome–liver–brain axis in modulating susceptibility to neurotoxicant effects on the developing brain. Conventional and germ free mouse models will be used, along with state-of-the-art technologies including second generations sequencing, metabolomics, and proteomics. The outcome of the research will have a *significant impact on public health* by informing future studies of cellular mechanisms of the developmental origin of chemical neurotoxicity and, ultimately, provide critical insights regarding the plausibility of microbiome-based approaches to diagnose and treat NDDs induced by exposure to neurotoxicants.