***Xist* and Sex-Specific Epigenetic Responses to PCB Exposure in Neurodevelopmental Disorders**

Sex differences in gene regulation are fundamental drivers of health and disease susceptibility, yet their role in mediating individual responses to hazardous environmental exposures remains critically understudied. A primary concern in developmental toxicology is exposure to polychlorinated biphenyls (PCBs), which are persistent organic pollutants and known neurotoxicants. My project aims to understand the role of *Xist* as a potential mediator of these sex-specific effects, investigating how it shapes the brain's response to PCB. Prior research revealed that X-linked genes investigated for their correlations with the sex-specific gene networks as candidates for the sex differences, including *Xist* and *Mecp2*. Interestingly, the female-specific long non-coding RNA (lncRNA) involved in X chromosome inactivation called *Xist*, was identified as a significantly differentially expressed gene (DEG) in response to PCB dosage, showing non-monotonic effects and showed that increased *Xist* levels positively correlated with PCB-associated gene networks, except at the lowest dose. Specifically, in female brain and placenta, *Xist* levels increased at 1 and 6 mg/kg/day doses but decreased in expression at 0.1 compared to 0 mg/kg/day doses relative to controls. For another X-linked gene encoding methyl-CpG binding protein 2 (*Mecp2*), mutations of which in humans lead to the neurodevelopmental disorder Rett syndrome (RTT), show no significant change observed with PCB exposure in either brain or placenta. Since *Xist* is only expressed in female brains, these findings suggest that *Xist* may play a role in regulating X chromosome epigenetic mechanisms in response to PCB exposure, which could explain the sex differences in behavioral responses. This evidence strongly supports the involvement of X-linked epigenetic mechanisms in gene-environment interactions, potentially explaining the heightened susceptibility of males to neurodevelopmental disorders (NDDs) compared to females, who have the *Xist*-mediated "safety net". I hypothesize that *Xist* acts as an epigenetic buffer in response to PCB exposure, but that this is a protective response becomes maladaptive when dysregulated. PCB-induced overexpression of *Xist* may drive an "epigenetic over-correction", destabilizing chromatin structure, impairing gene regulatory networks, and increasing X-linked gene escape. To test my hypothesis, I will investigate whether PCB exposure and *Mecp2* mutation alter the nuclear localization of *Xist* and its association with chromatin on the Xi and map *Xist*-chromatin interactions using RAP-DNAseq and RNA-FISH and immunofluorescence in human and mouse brains. Together, these approaches link *Xist* mis-localization to both epigenetic and transcriptional imbalance, supporting a model in which environmental and genetic perturbations convert *Xist* from a stabilizing regulator of XCI into a driver of genome-wide regulatory disruption underlying sex-biased vulnerability in neurodevelopmental disorders.