

Session 5: Predicting Alterations to the Immune System

Gene-Environment Interactions: Effects of Arsenic on the Innate Immune Response

Carol Kim, PhD

Department of Molecular and Biomedical Sciences, University of Maine

Cystic fibrosis (CF) is a multiorgan, autosomal recessive genetic disorder that affects approximately 30,000 children and adults in the United States. Triggered by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) chloride channel gene, eighty percent of CF patients eventually develop chronic infections with *Pseudomonas aeruginosa*, leading to chronic inflammation of lung tissue and eventual death. We are interested in the gene–environment interactions associated with CF. Using our zebrafish model for human CF, we have recently shown that *cfr* and arsenic each mediate aspects of innate immunity. Our current studies are aimed at determining whether low doses of arsenic affect the innate immune response to *P. aeruginosa* infection through Cfr function. We have performed RNA-seq and small RNA-seq to interrogate the transcriptomes of zebrafish depleted of Cfr, exposed to arsenic at environmentally relevant doses, and infected by *P. aeruginosa*. From these data, we have identified protein-coding and non-protein-coding (miRNA and lncRNA) genes affected by *cfr* function, arsenic exposure, and/or *P. aeruginosa* infection. The overall objective of this research has been to expand our knowledge on an important and prevalent environmental toxicant and the mechanisms through which it modulates innate immunity in CF, in hopes of unraveling novel gene–environment linkages.

Strategies for *In Vivo* Immunotoxicology Assays With Zebrafish Larvae

Jeffrey A. Yoder, PhD

Department of Molecular Biomedical Sciences, North Carolina State University

For more than 25 years, the zebrafish has been employed to model the effect of chemical exposure on immunity. In this time frame multiple *in vivo* immune assays have been developed for zebrafish larvae that possess an intact innate immune response but do not yet possess a functional adaptive immune response. These *in vivo* assays include (1) assessing the ability of larvae to recover from experimental infections, (2) quantifying the release reactive oxygen species after immune stimulation, (3) visualizing leukocyte chemotaxis and (4) quantifying NFkB activation. Our lab is developing methodologies for incorporating these *in vivo* immune assays into low- to medium-throughput immunotoxicity screens. Each assay has its strengths and weaknesses when applied to higher throughput screens. Our goal is to screen large numbers of chemicals for immunosuppressive properties using zebrafish larvae providing alternative immunotoxicity screens while still employing a vertebrate “whole organism” innate immunity model.