Zebrafish as an Age Susceptibility Platform for Evaluation of Mitochondrial Targeted Therapies for Toxic Chemical Exposure

Todd Kilbaugh, MD (PI)

Abstract

Acute chemical poisoning poses a severe global public health problem resulting in more than 700,000 accidental suicide-related deaths annually [1]. Due to thinner skin, a high body-surface-area-to-mass ratio and higher respiratory and metabolic rate, children are the most at-risk population [2-5]. Impaired mitochondrial function and resulting cellular energy crisis is a common mechanism of toxicity for several important classes of chemical threats, including environmental toxins. However, there are currently no interventions available that counter these effects [6-13]. In addition, little is known about the age susceptibility to chemical-induced mitochondrial injury. The overarching goal of this proposal is to develop zebrafish models of chemical intoxication at various developmental ages, addressing a critical knowledge gap regarding susceptibility to chemical-induced mitochondrial injury and to also develop mitochondrial targeted countermeasures against chemical threats. The resulting in vivo screening platform will provide a vital link between our in vitro, rodent and porcine platforms to investigate mitochondrial toxicity and develop pharmacological therapies against toxic chemicals; resulting in a one of a kind drug development program.

This proposal builds upon our current R21, where we demonstrated in vitro that Chlorpyrifos, Diisopropyl fluorophosphate, N-succinimidyl N-methylcarbamate and Sodium Fluoroacetate inhibit mitochondrial function, and that these effects can be counteracted by the novel drug class of cell-permeable succinate prodrugs. Aspects of this work is currently under review in the journal Toxicological Sciences. Our preliminary data for this proposal further show rescue of acute SF poisoning by the cell-permeable prodrugs in zebrafish. Given these promising data, we propose to develop zebrafish models of intoxication with environmental toxins at different developmental ages, leading to reduced mitochondrial and neuromuscular function, increased mortality and developmental delay. Furthermore, we hypothesize that cell-permeable succinate prodrugs can counteract these changes and that susceptibility to mitochondrial toxicity and treatment efficacy will vary in zebrafish of different developmental ages.