THE HARTWELL FOUNDATION

2018 Individual Biomedical Research Award

Marie C. Heffern, Ph.D.

Assistant Professor
Department of Chemistry

University of California, Davis

Metal Micronutrient Status as a Biomarker and Treatment Target for Obesity and Metabolic Disease

Obesity is a global health problem affecting 1 in 6 American children and nearly one-third of the pediatric population worldwide. Obese children are at higher risk of developing chronic metabolic diseases compared to children with normal body-mass indexes and many present clinically with evidence of early onset diseases that are typically seen only in adulthood. A major challenge in childhood obesity is in determining molecular mechanisms that trigger progressions from relatively benign obese states to more concerning metabolic diseases. While metals like copper and iron play a key role in protecting the body from oxidative stress and damage, the same chemistries that provide an important function may also induce free radical damage and inflammation if their levels and locations are left unchecked. For example, abnormal distributions and levels of these metals and their associated proteins are observed in obesity and known to be evident in other metabolic diseases. Physiologic and biochemical mechanisms responsible for explaining these observations, however, have received little attention. To address this unmet need, I hypothesize that dysfunctional auto-regulation of metal micronutrients like copper and iron are key drivers in inducing obesity-related health complications and that metal micronutrient phenomena might serve as key biomarkers of obesity and metabolic disease states. As a model of such a metabolic disorder, I will examine non-alcoholic fatty liver disease (NAFLD), a major liver disease associated with pediatric obesity and the most common chronic liver disease in children, to develop a metal-centric biochemical profile that will demonstrate the status of metal micronutrients. By quantifying labile or exchangeable pools of copper and iron, including metal-associated peptide hormones, it will be possible to assess their codependence, as well as their association with markers of oxidative stress and inflammatory tissue damage present in the disorder. Understanding metal/peptide hormone interaction will identify connections between metal regulation and endocrine action, facilitating further use of metal micronutrients for diagnosis and treatment. Cell cultures and a mouse model for juvenile NAFLD will be deployed to disentangle specific molecular mechanisms. Real-time PCR of proteins associated with iron and copper metabolism will be coupled with lipidomic, metabolic, and proteomic profiling. Total metal levels will be quantified by inductively coupled plasma mass spectrometry and labile metal pool levels will be extrapolated from this data. If I am successful in integrating chemical tool development, studies of molecular mechanism, and physiological characterization to determine the impact of copper and iron homeostasis on the progression of NAFLD, it will be possible to identify new clinical biomarkers for monitoring pediatric health in obesity that potentially should provide new strategies for treatment and prevention.