**Specific Aims**

The maintenance of water balance in animals is one of the most important physiologic processes, and is critical for survival. Indeed, humans are exquisitely sensitive to changes in osmolality, with slight derangement eliciting physiologic compromise. When the loss of water exceeds dietary intake, dehydration - and in extreme cases, death - can occur. In contrast, animals living in desert habitats are subjected to long periods of extreme heat and intense drought. As a result, desert animals have evolved mechanisms through which physiologic homeostasis is maintained despite severe and prolonged dehydration. Despite being a well-known ecological phenomenon with obvious implications for human health, *we know very little of the underlying mechanisms that allow for survival***. The proposed research uses a novel approach integrating physiology, evolutionary genomics, and computational biology** to better understand how animals survive in what appear to be non-survivable conditions. This proposal represents the foundational steps toward developing *Peromyscus eremicus* as a model system for the study of physiologic water conservation. Indeed, this model offers the scientific community a unique opportunity to gain a deep understanding into the physiology and genomics of osmoregulation in extreme environments – a critically important insight that is impossible using traditional model system like *Mus*. While not a part of this proposal, this project lays the groundwork for my *long-term research goal* – to identify the causal links between phenotype and genotype, using emerging technologies like the CRISPR-Cas9 system.

**Specific Aim 1:** Using captive desert-adapted mice, I will link multiple physiological variables, as well as their genomic underpinnings to differences in temperature, relative humidity, and water availability.

My working hypothesis is that while mice may demonstrate physiological signs of dehydration (*e.g.* elevated Na), patterns of renal gene expression, isoform use, and methylation will be distinct from those typical of illness.

**Specific Aim 2:** Given the transition from the obligate intake of fluids as infants, to it’s complete absence later in life, the ontogeny of physiologic water conservation will be elucidated.

I hypothesize that patterns of renal gene expression during fetal development through weaning will resemble patterns of gene expression, isoform use, and methylation typical of adult mice when water is freely available.

The proposed project aims to integrate studies of physiology, genomics, and computational biology to gain a deep understanding of a fundamental physiological problem – how to conserve water when intake is limited. *Although dehydration is both common and dangerous, a large swath of the biology underlying its physiological effects is currently invisible to researchers using traditional mammalian models of disease that lack the eco-evolutionary history present in desert-adapted mice*. This project will fill a critically important gap in our understanding, which is in support of the specific research aims of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).