i. Significance

Dehydration, whether caused by exposure to extreme environmental conditions, water deprivation, or by infection (e.g. diarrheal illnesses) represents a significant threat to human life. When death is avoided, dehydration may lead to chronic health conditions like renal failure. While the mechanisms underlying physiological compromise are well characterized [ref], some animals possess the ability, much unlike humans, to osmoregulate despite extreme heat and a complete lack of extrinsic water intake [ref]. Specifically, highly adapted desert mice may never drink water [ref], produce an extremely viscous urine (or no urine at all) [ref], and excrete urea in the form of uric acid crystals in the feces [ref]. Focusing on osmoregulation, patterns of renal gene expression have been shown to be highly derived in some desert adapted rodents (e.g. *Dipodomys* [ref]), but not in others like (*Notomys*), and therefore the extent to which differences in gene expression underlies phenotype remains unknown. In addition to its' generality, both studies of non-model organisms focus on a limited number of genes, and therefore may not appropriately assay the complexity of the genetics of extreme renal osmoregulation. In contrast with this work, several studies attempting to understand the effects of dehydration in model organisms (e.g. *Mus* and *Rattus*) exist, though while these works benefit from an extensive genomic and physiologic toolbox, that they lack the appropriate phenotype (extreme osmoregulatory abilities) limits insight. In summary, the study of extreme renal osmoregulation is hindered on one hand by a lack of tools, and on the other by a lack of an appropriate phenotype. This limitation may undercut our ability to efficiently develop novel therapies directed at mitigating the untoward effects of dehydration.

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. I develop the genomic and physiologic tools in a novel model for the study of extreme osmoregulation, *Peromyscus eremicus*. It's contribution is to effectively leverage the power of a sophisticated toolset of a model organism against a uniquely adapted rodent, which will allow for a synthetic understanding of extreme osmoregulation, and ultimately novel insights into the cause of - and cure for - dehydration related mortality and morbidity.

ii. Innovation

In spite of modern medicine, millions of people die from dehydration, and millions more are affected by chronic kidney disease. The proposed work recognizes that successful treatment requires an appropriate model, and while traditional models are powerful tools, they lack the biology (extreme osmoregulation) upon which a more successful phenotype may be modeled. The desert-adapted rodent *P. eremicus* retains many of the beneficial characteristics of model organisms, while augmenting existing biomedical infrastructure. In addition to this fundamental innovation, the project it innovative in a number of other ways.

- Leverage an unprecedented level of control over the experimental environment by use of a desert chamber where natural conditions can be replicated while preserving the ability to manipulate water availability.
- Link detailed information on physiology and metabolism to genomic information using powerful and novel analytical tools under active development in the lab.