Development and Characterization of a Rodent Model of CKDu

Agricultural workers are subjected to a unique combination of occupational stressors that may impact health. Across the globe, there has been a growing realization of an increase in chronic kidney disease (CKD) and renal failure, primarily among agricultural workers in hot and humid climates, of unknown etiology (CKDu). Increased CKD in the US have been identified in agricultural communities in the South of the United States. In contrast to other forms of kidney disease, CKDu disproportionately affects young men (< 40 years of age) with little evidence of diabetes or hypertension, and current evidence indicates interstitial, as well as glomerular damage in the kidney. While epidemiological studies note an association with heat exposure and agricultural chemical use, and exposure to several common agricultural chemicals in animal models can result in kidney toxicity, the cause(s) of CKDu remain controversial. Importantly, no biomarkers have been identified, so far, which can predict the development of CKDu, detect pre-symptomatic CKDu, or assess disease severity. Previously, in NIOSH funded work, we assessed the impact of acute exposures to agricultural chemicals and/or heat on the development of kidney toxicity in a rat model. In this work, we will extend these efforts to assess the relationship between chronic and repeated heat stress and agricultural chemical exposure in the development of kidney disease in both human and animal studies. **Our central hypothesis is that urinary, exosome based, biomarkers of CKDu (UEBs) could identify those individuals at most risk, enable pre- symptomatic intervention and prevent development of renal failure.**

Relevant Aim from NIOSH grant
Aim: Characterize urinary exosome biomarkers (UEBs) of heat and agricultural chemical stressors. *Hypothesis: Nephrotoxic agents affecting different parts of the kidney will produce distinct urinary exosomes with characteristic biomarkers.* CKDu manifests with a unique renal tubulo-interstitial disease, and we will use our established rat model and well characterized renal toxicants to identify region-specific UEBs of glomerular injury, tubular necrosis, and interstitial nephritis confirmed by histopathology. We will subsequently evaluate these UEB in rats in response to acute and intermittent chronic exposure to agricultural chemicals and/or environmental stressors (heat, dehydration) for their capability to identify region specific renal damage associated with these stressors. We will compare region/stressor specific UEBs defined in this rat study to the human equivalent UEBs indicative of kidney disease in farmworkers to identify candidate stressors/region specific toxicity contributing to the renal effects in CKDu. We expect to identify UEBs indicative of acute and chronic toxicity associated with CKDu relevant stressors in years 1-3 which overlap with UEBs identified in farmworkers with acute and chronic renal disease.

FVSP student role: The student would work with Post-doctoral fellow and research scientist as part of the team working on the rat model of CKDu. The specific project would be dependent on the interests and skills of the student. The rat model requires survival surgery for temperature probe placement, gavage treatments, metabolic cage collection of urine samples, and collection of tissue samples for analysis. Urine samples will be processed for exosomes and biomarker discovery. The kidneys will be analyzed using histopathology in collaboration with Dr. John Roberts and AI based histopathology software.