KidneyCure Transitional Grant Summary

The goal of this project is to define the molecular pathways that regulate the proper formation and maturation of nephrons in the late embryonic and early post-natal stages of kidney development.

Nephron formation is a reiterative process throughout embryogenesis, forming specialized epithelial segments derived from mesenchymal nephron progenitor cells. However, the process of making new nephrons ceases at ~36 weeks of gestation in humans and by the fourth post-natal day in mice. Pre-mature birth in infants prior to 36 weeks of gestation causes pre-mature nephron cessation, resulting in low nephron endowment and increased risk for hypertension and chronic kidney disease later in life.

Much progress has been made to determine the gene networks that regulate the early patterning and initial differentiation of nephron progenitor cells; however, little is known about the molecular mechanisms that signal the end of nephron formation. We developed a targeted mouse mutant that disrupts the interaction between the transcription factor Sall1 and the chromatin-remodeling complex NuRD. These mutant mice have accelerated differentiation of nephron progenitor cells and pre-mature nephron cessation. Interestingly, these mice have a loss of the specialized loop of Henle segment of the nephron.

Using these mice, we propose to perform snRNA/ATAC-seq and spatial transcriptomics combined with confocal imaging and 3D reconstruction at late embryonic and early post-natal time points to define the molecular pathways that regulate the process of nephron cessation and loop of Henle development. This new knowledge can lead to strategies to prolong nephrogenesis in preterm infants as well as provide new insights for reprogramming the mature kidney to generate new nephrons after injury.