Dr. Rosemary Sampogna

Developmental defects of the urinary tract are the most common cause of pediatric kidney failure. In humans, kidney development does not progress after birth therefore the number of nephrons (filtration units) is permanently decreased in the setting of prematurity, low birth weight, intrauterine stress and congenital kidney defects. This reduction in renal reserve has in turn been linked to increased risk of hypertension and chronic kidney disease of diverse etiology in the adult population. Thus much of the burden of pediatric and adult renal disease originates from developmental defects, indicating that elucidation of molecular mechanisms of organogenesis may provide significant opportunities for diagnosis, intervention and therapy.

Mammalian kidneys develop via a process of repeating bi-directional signaling between the ureteric bud (UB) and metanephric mesenchyme (MM) that ultimately generates and organizes ~1 million nephrons per kidney. Although it is well established that reciprocal transmission of UB- and MM-derived signals drive specific aspects of nephron formation, central genetic regulation of this developmental process remains undefined. We have developed a longitudinal method that reconstructs the three-dimensional kidney with respect to time and analyzes detailed morphometric parameters throughout development. When devising this approach, we in parallel discovered that cyclical circadian clock gene expression correlated with timing of branching events and with nephron number. Moreover, mutation of core clock genes resulted in significant kidney structural defects.

We hypothesize that the circadian clock coordinates the repetitive mechanisms of kidney development by regulating precise exchange of molecular signals between the UB and MM. This proposal aims to use real time bioluminescent imaging of rhythmic signals, high-resolution phenotype analysis as well as genetic and biochemical methods to comprehensively characterize the circadian regulation of branching and nephron formation during kidney development. We outline a unique opportunity to discover novel molecules required for kidney development by exploiting circadian biology.