Characterizing the Genomic Landscape of Adult Onset Wilms' Tumors to Generate Faithful Preclinical Models for Therapeutic Testing

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Abstract: Wilms' tumor (WT), while constituting 95% of all pediatric kidney cancers, is extremely rare in adults. The adult manifestation of the disease is histologically similar to the childhood disease, but presents itself in the clinic as phenotypically distinct. Current treatment options for adult WT mirror those used for the childhood disease but are associated with significantly worse morbidity and mortality. Our preliminary studies have revealed that adult WT are characterized by unique mutations not typical of childhood WT. Hence there is an *urgent need* to define the biology of adult WT and generate faithful preclinical models to define improved therapeutics. To expand our understanding of adult WT as compared with the pediatric disease we propose to compare their genetic profiles in Aim 1 using advanced whole-genome and whole transcriptome techniques as well as DNA-methylation array analyses which we expect will allow us to identify molecular vulnerabilities that can be functionally tested. To compare treatment responses between pediatric WT models which we have previously generated and adult models, in Aim 2 we will leverage the combined expertise of our adult Urology colleagues and external collaborators to develop novel patient-derived adult WT models to test both FDA approved as well as other promising exploratory therapies for the adult disease. At the successful conclusion of our studies, we anticipate we will not only garner significant insights into the biology of adult WT but we will develop innovative therapeutics for the disease which will have a substantial impact on the outcome of adult WT.