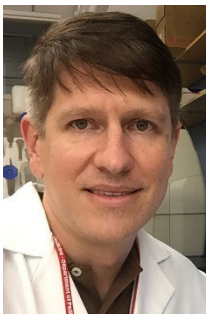
THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

Oleh Akchurin, MD, Ph.D.

Assistant Professor
Departments of Pediatrics

Cornell University



Immunophenotyping of Peripheral Blood Monocytes to Personalize Treatment of Chronic Kidney Disease

Chronic kidney disease (CKD) or chronic renal insufficiency is a gradual loss of kidney function. Birth defects, congenital abnormalities, and hereditary or systemic diseases are the most common cause of CKD in children, which contrast markedly with diabetes and high blood pressure as the most common cause in adults. Children with kidney failure grow at a slower rate than their peers, endure urinary incontinence, anemia, bone fracture and face significant behavioral challenges that may affect learning and social development. The incidence of childhood CKD has been increasing steadily over the last 20 years and while its prevalence in U.S. is unknown, it is conservatively estimated to exceed 200,000 children. Currently, CKD has no cure and inevitably progresses to end-stage kidney disease, which requires dialysis or kidney transplantation. Kidney fibrosis is a hallmark of the disease and the final common pathway to kidney loss. While the mechanism is not well understood, excessive accumulation of extracellular matrix (macromolecules that support tissue growth) replaces functioning kidney cells and infiltration of immune system macrophages produce inflammation. Most of the macrophages that accumulate in kidney fibrosis derive from monocytes in the peripheral blood circulation, which become polarized toward the expression of protein biomarkers (immunophenotype) identifiable with the disease. Depending on the phenotype they adopt, accumulating kidney macrophages can exhibit either pro- or anti-fibrotic activity. Unfortunately, currently available laboratory tests (serum creatinine and other available biomarkers of kidney function) are not sensitive to the timely progression of kidney fibrosis and only signal very advanced kidney damage. Tissue biopsy can provide direct assessment of disease but due to its invasiveness (bleeding and potential loss of the kidney), it is rarely performed in children. To address the unmet need to monitor CKD and guide existing therapies in children, Oleh hypothesizes that circulating blood monocytes are phenotypically indicative of derived kidney macrophages; and that such peripheral monocytes exhibit a distinct pro-fibrotic phenotype in pediatric CKD that is responsible for the progression of kidney fibrosis. His approach will be to use scRNA-seq to characterize and compare the immunophenotype of circulating monocytes collected from the blood of children with CKD to monocytes collected from healthy children. He will then evaluate in a juvenile mouse model how the unique CKD-specific characteristics of circulating monocytes play a role in kidney fibrosis; and confirm that medications known to affect kidney fibrosis have a corresponding effect on monocytes. If Oleh is successful, peripheral blood monocytes can be used as a “liquid biopsy” to assess pro- or anti-fibrotic effects of CKD therapies that together with adoptive transfer of engineered human macrophages, will represent a new and effective, personalized medicine approach for treatment of CKD in children.