Mechanisms Underlying Neurocognitive Changes in Cystinosis , John Foxe, PhD Co-Principal Investigator, Sophie Molholm, PhD Co-Principal Investigator, Steven U. Walkley, DVM, PhD Co-Principal Investigator

Cystinosis has long been known for its significant impact on renal and thyroid function. It is only in recent years, however, due to the emergence of effective life-prolonging treatment regimens for these primary clinical symptoms that researchers and clinicians have been able to turn greater attention to the impacts this disease has on brain function. To date there is only limited work in this area. To address this shortcoming of knowledge, investigators in Pediatrics and Neuroscience at the Albert Einstein College of Medicine (Molholm, Walkley) and the University of Rochester Medical Center (Foxe) are evaluating individuals with cystinosis as well as mice in which the cystinosis gene has been knocked out.

The human studies involve the use of high-density electroencephalographic (EEG) recordings of brain activity being carried out by Drs. Molholm and Foxe in Einstein's Cognitive Neurophysiology Laboratory. Dr. John Foxe, lead investigator on the human project, reports observing a strikingly "normal" pattern of multisensory behavior and brain responses in cystinosis, a finding that stands in stark contrast to those obtained in another lysosomal storage disorder where significant impairment is observed (Niemann-Pick type C disease). The group will continue to collect data for this study, to see if this finding holds up in a larger sample. In addition, following these "positive" results indicating intact sensory processing, they are turning to measurement of cognitive processes that require highly coordinated activity across extensive networks of cortical regions, as these are likely to be more sensitive to any neural damage incurred.

For the mouse studies, spearheaded by Dr. Walkley, director of Einstein's Sidney Weisner Laboratory of Genetic Neurological Disease, mice with genetically-induced cystinosis have been established in a breeding colony and are being evaluated for changes in selected brain regions (hippocampus, neocortex and cerebellum) in an attempt to determine with greater precision just how this genetic disease impacts the function of individual types of brain cells. Analyses here range from exploring connectivity and the structure of individual neurons to changes in the metabolic activities secondary to the disease-induced defect in lysosomes. As phenotypic biomarkers related to cystinosis are identified in these brain regions, the impact of treatment (e.g., with cysteamine) in preventing, delaying and/or reversing these changes will be pursued. The ultimate goal of these tightly collaborative studies from the two labs is to more fully understand the effects that cystinosis has on brain structure and function and how factors leading to such compromise could be alleviated.

Altered protein kinase signalling as a cause of reduced adhesion and increased motility of renal epithelial cells in cystinosis – 6 month report, June 2016, E. Ivanova, L. van den Heuvel, E Levtchenko (Principal Investigator)

Cystinosis is a genetic disease manifesting early in life (≈ 6-12 months) with progressive kidney disease resulting in renal failure early during childhood if not treated. In cystinosis the metabolism of the amino acid cystine is defective leading to its accumulation in the kidney and other organs. This cystine accumulation results in cellular damage and death, but the direct mechanisms beyond this phenomenon are largely unknown. Some harmful cellular events in cystinosis might not be directly related to cystine accumulation and are the subject of our research project.

Based on our previous work we hypothesized that the loss of highly specified renal cells like glomerular podocytes and renal proximal tubular cells in urine is a major mechanism causing renal pathology of cystinosis. Increased rate of cellular abundance in urine can be explained by either the decreased adhesion of renal cells to their matrix or their increased motility or by a combination of both mechanisms. Indeed we demonstrated that both events occur in cultured human renal cells derived from cystinosis patients.

We further tried to explore the mechanisms beyond this cellular loss. It has been reported in other diseases that increased cell motility and defective adhesion can be associated with the altered protein kinase signaling. In cystinotic podocytes we found an increased expression of activated or phosphorylated Akt kinases compared to control cells. This could explain, at least partially, the abnormal phenotype. We are currently testing other protein kinases that might contribute to this mechanism. In addition we tested the gene expression of several integrin in podocytes, as podocytes adhere to the extracellular matrix using integrin receptors. Although only minor differences were found between cystinotic and control cells, cell surface expression of

these proteins still has to be studied. So far most of our experiments were done in podocytes. We recently started to investigate proximal tubular epithelial cells which also showed an increased expression of phosphorylated Akt kinases unifying the concept of the hypothesis over different renal cell types. Our future plan includes also the experimentation with different kinase inhibitors to explore if they can reverse abnormal renal phenotype.