Presentation Day 1

The Search for Additional Treatments in Nephropathic Cystinosis

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Since more than 3 decades, patients with nephropathic cystinosis have been treated in western countries with cysteamine. Cysteamine has dramatically changed the prognosis of the disease, but cannot prevent all complications. Some symptoms of the disease, such as the renal Fanconi syndrome, are non-responsive to cysteamine. The reasons for that are still poorly understood. However, several studies, many of which have been sponsored by the Cystinosis Research Foundation, have now demonstrated at the cellular level that cystinosis is not only characterized by the accumulation of cystine in lysosomes, but that other important cell functions are impaired. These may be a consequence of the lysosomal disease, but some are likely to represent primary events that are related to other roles of the cystinosin protein in cells. These observations represent the groundwork for exploring the possibility that patients may benefit from other therapies in addition to cysteamine.

To this end, we have adopted different strategies. The first strategy has been to perform a blind screening of repositories of drugs that are approved for human use to find molecules that reduce cystine accumulation and increased cell survival. This led us initially to identify a potential candidate molecule, which however proved to be toxic in cells and animal models of cystinosis. In parallel screenings, we have taken a hypothesis driven approach. Knowing that certain cell functions are activated in order to protect cells with engulfed lysosomes, we have tested molecules that can stimulate these processes. This has led us to test in cells and in animal models molecules that belong to the family of flavonoids and observed that mice treated with these drugs accumulate significantly less cystine crystals, compared to untreated animals. In addition, we and others observed that mitochondria, which are the energy producing organelles of cells, are abnormal in cystinosis. Since ketogenic diet can improve mitochondrial function, we have fed with a ketogenic diet mice and rats and have observed major improvements of their kidney disease. Finally, we also observed that mice fed with certain diets develop different severity of kidney disease. Studies are ongoing to identify which components in diets are toxic or protective.

Taken together, these studies show that in addition to cysteamine, other interventions can improve the clinical expression of cystinosis, at least in animal models. Hopefully, these results will help in the future treating patients.