Cystinosis Research Foundation

Lay Abstract Template for Awardees

Please complete this lay-oriented grant abstract form which will be published on the CRF web site, in CRF Star Facts and in the CRF magazine when we announce your grant award. *Please do not exceed 400 words (no more than 1-1/4 page total).* Please submit this form electronically to nstack@cystinosisresearch.org as a Word document.

Principal Investigator (s): Stephanie Cherqui, Ph.D

Project Title: Advancing the understanding of renal Fanconi syndrome in cystinosis

Objective/Rationale: Please write a lay-oriented statement of the scientific rationale for this project. Approximately 75-85 words.

Despite the fact that cystinosin, the protein involved in cystinosis, is expressed in all the organs, the renal Fanconi syndrome is the first manifestation of cystinosis that presents early in life of the patients while other complications appear years later. Numerous studies investigated the cause of the specific sensitivity of the kidney cells to the absence of cystinosin. While the matter is still unresolved, it is apparent that specific function(s) of cystinosin in the kidney beyond cystine transport explain the early Fanconi syndrome in cystinosis.

Project Description: Please write a brief, lay-oriented description of how you will carry out the project. Approximately 125-135 words.

We identified a novel interaction of cystinosin with a transport exchanger protein in the kidney cells that may advance the understanding of cause the renal Fanconi syndrome in cystinosis. The transporter is the Na/H exchanger, NHE3, a major absorptive sodium transporter expressed the apical membrane of the proximal tubules of the kidney and in the gastrointestinal epithelial cells. We confirmed this interaction in both the yeast model and in kidney cells. We also showed co-localization of cystinosin and NHE3 in cells. Furthermore, we showed that NHE3 was mislocalized in a CTNS-deficient kidney cells, and that the trafficking of NHE3 was defective within the kidney cells missing cystinosin. Therefore, cystinosin has a role in the cellular localization and/or function of NHE3 in the kidney proximal tubules, and in its absence, NHE3 is dysregulated participating to the renal Fanconi syndrome in cystinosis. This project aims to determine how cystinosin and NHE3 interacts and the impact of the absence cystinosin on NHE3 and other transporters in kidney proximal tubules. The studies will be conducted *in vitro* in the yeast and human kidney cell models, and *in vivo* in the $Ctns^{-/-}$ mice.

Relevance to the Understanding and/or Treatment of Cystinosis: Please explain how the project will impact cystinosis treatment or increase our understanding of cystinosis. Approximately 75-80 words.

The elucidation of the mechanism of NHE3 transport regulation, expression and function in presence or absence of cystinosin may advance the understanding of the renal Fanconi syndrome and could open new therapeutic avenues in cystinosis treatment.

Anticipated Outcome: Please write a lay-oriented description of what you expect to learn/discover. Approximately 75-80 words.

The proposed project should advance our understanding of the cause of the renal Fanconi syndrome in cystinosis, and the findings may lead to new therapeutic approaches for cystisnosis.