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

Project Title: To characterize two new *Ctns*-/- mice models.

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

Animal models play a crucial role in understanding the pathophysiology of any disease condition. The widely utilized C57BL/6 *Ctns*-/- mouse model has been instrumental in understanding the mechanisms underlying cystinosis. However, this model has exhibited progressive decrease of kidney phenotype, especially the renal Fanconi syndrome (FS). We have two new mouse models on a pure C57BL/6 background. One harbors a 5bp deletion in exon 5 of *Ctns*. The other model carries a ~50kbp deletion in the entire *Ctns* gene and part of the *Trpv1* and *Carkl* genes, closely mirroring the ~57kbp deletion the most common mutation in cystinosis patients. We aim to characterize these mice models and study how closely they resemble the human disease characteristics.

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

We aim to do detailed characterization of both the mice models to monitor their breeding efficiency, survival, and growth rate. Analysis of their kidney function will be done by collecting 24h-urine and blood samples at 3, 6, 9, and 12 months. Following explant at 12 months of age, the kidneys will be used to measure cystine and for histopathology. Analysis of the non-renal phenotype in these two mice models like eye, bone, muscle, neurocognitive defects will be done by conducting behavior studies, followed by molecular characterization by performing several molecular assays, as well as cystine content determination and histopathological studies.

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.

These models may serve as invaluable tools for researchers, enabling the exploration of novel treatments based on mutations in the *Ctns* gene. We will also be able to determine if the 57 kb deletion led to different phenotype in cystinosis. It holds significant interest to observe how these two models mimic the human phenotype and whether variations arise due to the unique mutations in the *Ctns* gene, and these models will be shared with the community for research.

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

Our objective is a comprehensive characterization of these models, encompassing renal and non-renal aspects, breeding characteristics, and survival, to understand their resemblance to human disease pathophysiology. Our initial finding shows positive indications in both mouse models, reflecting characteristics observed in human patients affected with cystinosis. Our preliminary data show that these mice exhibit as early as 3 months of age characteristics of renal Fanconi syndrome and neurobehavioral anomalies. Cystine storage and cystine crystals, hallmarks of cystinosis, are present in the new models. Additionally, we aim to explore potential differences between the two models, considering the distinct nature of their mutations and their impact on disease onset or progression.