Cystinosis Research Foundation

Lay Abstract Template for Awardees

Please complete this lay-oriented grant abstract form which will be published on the CRF website, 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): Sergio Catz and Danni Chen

Project Title: Novel mechanistic and translational studies of inflammation in cystinosis

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

Lysosomal damage induces alteration in immune cells leading to inflammation. Our preliminary data show that a subtype of specialized white blood cells, neutrophils, are characterized by dysregulated secretion of pro-inflammatory components that have the potential to contribute to tissue damage in cystinosis. Our work focuses on the characterization of this process and the development of approaches to counteract inflammation in cystinosis.

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

We found altered posttranslational modification and lysosomal localization of a regulatory kinase in cystinotic neutrophils. Inhibition of this protein with specific inhibitors decreases the secretion of toxic components in *Ctns*$^{-/-}$ neutrophils. We will study a) The mechanisms of action of this kinase in cystinosis, in association with the regulation of small Rab GTPases; b) The mechanisms mediated by this kinase to induce secretion in cystinosis and c) The cross-regulation of the kinase with other inflammatory processes including the inflammasome. To test these hypotheses, we will use state-of-the-art technical approaches including Elisa, flow cytometry, immunoblotting, CyTOF, and immunofluorescent staining. These assays will be complemented with comparative phospho-proteomics to identify potential kinase substrates that are affected in cystinotic neutrophils.

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.

Proximal tubule cell de-differentiation is associated with increased pro-inflammatory signaling and increased neutrophil infiltration into cystinotic kidneys. We found altered posttranslational modification and mis-localization of regulatory kinases in cystinosis. We will utilize a pharmacological approach to inhibit this regulatory protein in cystinosis mouse models. We propose that specific inhibitors of this process will decrease kidney inflammation and possibly improve renal function in cystinosis patients.

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

I expect to identify new dysregulated mechanisms in cystinosis. We also anticipate that the manipulation of upstream lysosomal damage sensors could help reduce neutrophil-mediated inflammation in cystinosis mouse models.