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): Fellow: Aparna Shukla; Mentor: Sergio D. Catz

Project Title: Translational approaches to repair chaperone-mediated autophagy in cystinosis

Objective/Rationale: Please write a lay-oriented statement of the scientific rationale for this project. Approximately 75-85 words.
The objective of our research is to identify small molecules that can improve the localization and multimerization of the lysosomal membrane protein LAMP2A and enhance Chaperone-Mediated Autophagy (CMA) in cystinosis cells. By improving LAMP2A function and CMA, we seek to restore lysosomal malfunction that leads to cystine accumulation in cystinosis. To achieve this, we aim to screen the ReFRAME drug repurposing library and the commercial Maybridge library for potential drug-like small molecules.

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

In cystinosis, cells are negatively impacted by malfunctioning lysosomes, which are responsible for degrading and recycling cellular components. One major issue leading to this lysosomal malfunction is a reduction in Chaperone-Mediated Autophagy (CMA). CMA is a selective autophagy process where KFERQ motif-containing proteins bind to a chaperone and are then delivered to the lysosomal membrane protein LAMP2A, which helps translocate them into the lysosome for degradation. In cystinosis, reduced LAMP2A expression and multimerization prevent proper protein degradation, causing cystine to build up in the cells. Based on our previous work, we aim to identify small molecules that can help LAMP2A localize and multimerize correctly at the lysosomal membrane. To accomplish this, we will apply a translational approach that includes computational modeling and screening, *in-vitro* testing, and *in-vivo* confirmation. Our goal is to identify a small molecule (drug-like candidate) to correct LAMP2A localization and multimerization at the lysosomal membrane in cystinosis cells.

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.
In our previous work, we demonstrated that enhancing CMA using small molecules improves LAMP2A expression, localization, and multimerization in cystinosis cells. Based on these findings, our current research focuses on identifying small molecules that can directly influence LAMP2A multimerization. By targeting LAMP2A, we aim to enhance CMA and restore cellular homeostasis in cystinosis.

Anticipated Outcome: Please write a lay-oriented description of what you expect to learn/discover. Approximately 75-80 words.
We anticipate that our research work will identify potent small molecules that can enhance LAMP2A multimerization and improve CMA in cystinosis cells. These compounds are expected to restore cellular homeostasis, reduce cystine accumulation, and improve cellular and kidney function in cystinotic mice.