

# 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](mailto:nstack@cystinosisresearch.org) as a Word document.

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**Principal Investigator (s):** Ming Li and Jakob Kitzman

**Project Title:** Investigating the degradation mechanism of cystinosis mutant

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

While some view it as an "overkill" for grocery stores to discard expired food that is still consumable, a parallel scenario occurs within our cell, where a stringent protein quality control (QC) system occasionally exhibits a tendency to "overkill" newly synthesized proteins. In certain cystinosis patients with genetic mutations, their cystinosin undergoes premature destruction despite its functional status. Investigating this QC system holds the potential to prevent untimely cystinosin degradation in patients, paving the way for innovative treatment strategies.

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

**Aim 1:** Our initial goal is to further characterize fast-degrading CTNS mutants. Employing a low-level expression system, we will screen documented mutants from the ClinVar database and unstable mutants identified by Dr. Liang Feng's laboratory.

**Aim 2:** The second objective is to identify the specific E3 ubiquitin ligases responsible for ubiquitinating the fast-degrading Cystinosis mutants. Once these ligases are identified, our overarching goal is to develop small-molecule inhibitors targeting them. These inhibitors may hold the potential to serve as the basis for a novel treatment strategy by stabilizing cystinosis mutants.

**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.

Our research aims to unveil a novel mechanism contributing to the pathogenesis of Cystinosis. We posit that the premature degradation of specific cystinosin mutants may result from an "overkill" triggered by the protein quality control system. Identifying methods to inhibit this quality control system could emerge as an innovative strategy for treating Cystinosis.

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

Our study aims to illustrate the involvement of protein quality control in the pathogenesis of Cystinosis. Additionally, we will pinpoint the machinery responsible for the premature degradation of cystinosis mutants and unravel their underlying mechanisms.