

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): Andrew Hall

Project Title: Illuminating lysosomal defects in cystinotic kidney disease

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

Cystinosis causes kidney disease and ultimately kidney failure, which imposes huge medical and psychological burdens on patients and substantially shortens life expectancy. The proximal tubule is the major site of injury in cystinotic kidney disease. Proximal tubular cells have a highly developed endo-lysosomal system that reabsorbs and degrades proteins filtered by the glomerulus. Cystinosis occurs due to genetic defects in the lysosomal protein cystinosin, but exactly how these affect endo-lysosomal function in the proximal tubule is not well understood.

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

We have developed cutting-edge intravital imaging techniques using two-photon microscopy and targeted fluorescent probes to visualize the endo-lysosomal system working in kidney tubules in living mice. With this technique, we can directly assess the consequences of manipulating endo-lysosomal genes that cause kidney diseases.

In this project, we will apply this approach to investigate how endo-lysosomal function is altered in cystinosin deficient mice, which develop a phenotype closely resembling that of human cystinotic kidney disease. We will evaluate several key dynamic processes, including protein uptake and trafficking, vesicular acidification, calcium uptake/release, lysosomal protein degradation and lysosomal exocytosis. This will enable us to better understand what cystinosin normally does and what happens when it is missing.

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.

Identifying the consequences of cystinosin loss on endo-lysosomal function in the proximal tubule is a critical step in elucidating the pathogenesis of cystinotic kidney disease. In the longer term, this new knowledge might lead to the development of new treatment strategies. Moreover, it may have relevance for understanding how cystinosis damages other organs.

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

We expect to shed new light on where and how cystinosin depletion impacts on the endo-lysosomal system in kidney proximal tubules in vivo. This information will help to explain how cystinotic kidney disease arises, and could generate new ideas concerning processes that might be targeted therapeutically in the future.