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): Paul Goodyer (PI) and Elena Torban (Co-PI)

Project Title:mRNA Thrapy for Cystinosis

Objective/Rationale: Please write a lay-oriented statement of the scientific rationale for this project. Approximately 75-85 words.
Cysteamine delays organ deterioration and has given hope to the cystinosis community. However, cysteamine addresses only one of multiple cellular functions disrupted by CTNS mutations. We propose to capitalize on a "silver lining" to the COVID pandemic. We will collaborate with Moderna to adapt their novel LNP-mRNA technology to restore *CTNS* expression in cystinosis. By optimizing their platform for delivery of CTNS mRNA to kidney and other tissues, our goal will be to restore sufficient mRNA to restore all missing cellular functions of cystinosin.

Project Description: Please write a brief, lay-oriented description of how you will carry out the project. Approximately 125-135 words.
We will submit the sequence for normal *CTNS* mRNA and for *CTNS* attached to a fluorescent "tag" (to track its uptake by cells). After custom modifications to the mRNA, Moderna will package the stabilized mRNA into special "lipid nanoparticles" similar to those they used for their COVID vaccine.

In our lab we will then expose kidney cells (isolated from patient urine) to the tagged *CTNS* mRNA/LNP. This will confirm: a) *CTNS* uptake and expression; b) correction of cystinosis problems (cystine accumulation and "autophagocytosis"). Next, we will infuse *CTNS* mRNA/LNP into normal mice, tracking uptake and expression of the tagged *CTNS* mRNA in kidney and other tissues. Finally, we will infuse untagged *CTNS* mRNA/LNP into our *Ctns* mutant mice and measure the level of *CTNS* mRNA and correction of typical cystinosis abnormalities as above.

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 2-year project will ascertain whether this novel therapeutic strategy can adapt Moderna mRNA technology to the treatment of cystinosis. If we can restore CTNS mRNA to about 10% of normal, this should provide strong impetus for Moderna to consider cystinosis as a priority target for a clinical trial. The long-term vision would be to treat patients with intermittent subcutaneous injections of LNP-*CTNS* and restore enough normal CTNS mRNA to quell the many events that drive organ deterioration.

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

We expect this project will show us how to adapt the Moderna mRNA LNP platform for the treatment of cystinosis