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): Benjamin Freedman

Project Title: Developing a therapeutic strategy for nephropathic cystinosis with iPS cells

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

The goal of this proposal is to utilize human stem cells and mice to understand nephropathic cystinosis and develop therapeutics. The kidney is a particularly sensitive organ in cystinosis, leading to kidney failure at an early age. We will derive kidney-like structures (organoids) from cystinosis stem cells, to reproduce this disease in lab dishes and understand why kidneys are so vulnerable. We will furthermore test whether stem cells treated with a gene therapy can form healthy kidney tissue in a new mouse strain with cystinosis.

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

We will take powerful stem cells from patients with cystinosis, and use these to reproduce classic symptoms of cystinosis in kidney a petri dish. Through detailed analyses, we will test whether a new form of programmed cell death is causing the disease. We will also test whether treating these cells with gene therapy can alleviate these symptoms. To understand the potential of these cells for kidney regeneration, we will use a new type of cystinotic mouse, which is capable of accepting human tissue grafts. We will implant our cystinosis cells into the kidneys of this mouse, before or after treating these cells with gene therapy. The grafts will be examined for signs of new functional kidney tissue inside the mouse host, and also for any residual symptoms of cystinosis.

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.

This project will (a) provide new insight into the mechanisms and determinants of cystinosis in kidneys, in particular the pathway of programmed cell death that occurs in kidney cells; (b) pave new roads to discover therapeutics, including regenerative therapies and gene therapies, which require further development; and (c) establish a new mouse strain for the sustained study of cystinosis in a variety of cell types and conditions, including new gene therapies and a living animal model capable of accepting human cells.

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

We expect to discover that cystinosis kidney structures in a petri dish will suffer from a new type of programmed cell death, due to increased cystine. We know these cells can die, but we seek to understand how it happens at the molecular level, so that we can develop therapies. Gene therapy to restore proper levels of functional cystinosin protein is expected to have dramatically beneficial effects on kidney cells. Stem cell grafts in our new cystinosis mouse are expected to exhibit more sophisticated signs of cystinosis, such as crystal formation, which we hope will also be remedied by gene therapy.