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): Dr Jennifer Hollywood and Dr Alan Davidson

Project Title: **Evaluation of a novel drug combination treatment of CF10 and Everolimus for nephropathic cystinosis in a new cystinotic rat model**

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

The only drug treatment available for cystinosis is cysteamine, which removes excess cystine from the cells. However, even if taken regularly and from birth, the kidneys will stop working eventually. Other organs will also eventually fail. This drug needs to be taken regularly and in large doses. It tastes bad and causes bad breath and body odour, as well as damage to the stomach. It is common for small children to vomit daily and for young people to try to stop their treatment to avoid having continuous bad breath which negatively affects their health. To improve the lives of cystinosis patients there needs to be: 1) better versions of cysteamine that have fewer side effects and 2) new therapies to reduce damage to the kidneys (as cysteamine does not stop this). Addressing 1) a new version of cysteamine, CF10, has been developed that reduces cystine build-up in cells but lacks the side effects and can be taken in lower and less frequent doses. Tackling 2) we have shown in cells in the lab that using a drug called everolimus, the damage to the kidneys can be addressed. Using cysteamine and everolimus together all of the problems associated with cystinosis are corrected in these cell models.
In this project we will test, in a rat model of cystinosis that we have developed, if the new drug combination of CF10/everolimus can provide a better treatment.

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

The overall goal of this project is to conduct preclinical drug testing in cystinotic rats to determine whether a combination treatment of CF10 and Everolimus is better at reducing cystine levels in blood and tissues and at preserving kidney function than either drug used alone. To do this we will treat the cystinotic rats with jelly pills containing CF10 (twice daily) and Everolimus (twice weekly) for 6-months. We will collect blood and urine samples each month, measure body weight weekly and perform a number of kidney function experiments. At the end of the study, tissues will be collected to measure cystine levels and to examine the kidneys for damage. Over the course of the study, we will determine if this new drug treatment is more effective at slowing, and potentially stopping the decline in kidney function.

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.

The advent of cysteamine therapy has extended life expectancy into adulthood for people with cystinosis. However, people with cystinosis face a highly challenging treatment regimen and may take dozens of pills a day, on a strict dosing schedule. Our research seeks to greatly improve the treatment of cystinosis and lower the unpleasant side effects of cysteamine by advancing a more potent, less unpleasant, combination therapy based on CF10 and Everolimus. If successful, this proposal will demonstrate that a combination therapy of CF10 and Everolimus is a superior treatment for cystinosis than cysteamine. CF10/Everolimus has the potential to be better tolerated, more potent at reducing cystine levels, more effective at reducing kidney damage, and provide greater longevity and better quality of life than cysteamine alone.

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

Our experimental design will allow us to robustly determine if CF10 is markedly superior to cysteamine in our cystinosis rat model. This will lay the foundation to developing a CF10 therapy in humans that requires less frequent dosing, whilst reducing the highly disruptive side effects of bad taste, odour, stomach problems and nausea. This potential improvement in treatment will also benefit the carers of these patients by enabling a regular night's sleep, rather than 6-hourly doses and sleep disruption. If this is the case, the proposed research will generate the required data needed to progress to clinical trials thereby expediting the clinical development of CF10.

Our experimental design will also allow us to determine if the combination treatment of CF10 and Everolimus will be superior to CF10-alone at preserving kidney function in cystinotic rats. If this is the case, this result has the potential to greatly improve the lives of cystinosis patients and could remove, or substantially delay, the need for a kidney transplant. The evidence generated in this proposal will justify advancing the combination therapy of CF10 and Everolimus to clinical trials in humans, where it is anticipated that it will deliver:

- A new and improved treatment option
- A reduced dosing schedule
- Less side effects, better taste, lower doses
- Prevent or further slow the progressive decline in kidney function
- Improve the quality of lives of patients and carers, and long-term health outcomes