Cystinosis Research Foundation

Lay Abstract Template for Awardees

Autumn 2011 Grants

Please complete this lay-oriented grant abstract form which will be published on the CRF web site and in the CRF Star Facts with announcement of your award. Please do not exceed 350 words total. Please submit this form to us as a Word file.

Principal Investigator (s): Dr Tara McMorrow and Professor Philip Newsholme

Project Title: Role of nitric oxide in the kidney proximal tubular dysfunction associated with the Fanconi syndrome in cystinosis

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

Oxidative stress (derived from excessive superoxide and hydrogen peroxide production) is a key component of kidney proximal tubule dysfunction in cystinosis. Glutathione, a major intracellular anti-oxidant has recently been shown (in the laboratory of Dr Elena Levtchenko and published in BBA 1812: 643-651) to be increased in concentration following Cysteamine treatment, leading to protection but not full recovery of the cystinotic cells.

We believe, based on pilot studies performed in UCD Dublin, that nitric oxide, (a free radical that causes damage in cells) is generated at elevated levels in cystinotic kidney proximal tubule cells leading to cell dysfunction. Our objectives are thus to define the levels of nitiric oxide generated in cell models of cystinotic cells and to determine the targets of nitric oxide action and the downstream consequences of nitric oxide associated protein modification.

Project Description: Please write a brief, lay-oriented description of how you will carry out the project. Approximately 125-130 words.

We will determine nitric oxide levels and concentrations of nitric oxide modified proteins in various models of cystinotic kidney proximal tubule cells. In addition we intend to measure markers of oxidative stress including reduced and oxidized glutathione levels and cell energy status.

We will determine the level and activity of the key enzyme generators of nitric oxide and superoxide in the normal vs cystinotic cell models. We will additionally measure the levels and activity of key functional markers of proximal tubule cells, the sodium transporters Na+/K+ ATPase and the Type 3 Na/H exchanger.

We will additionally use a state of the art ‘proteomics’ facility available in the Conway Institute, UCD Dublin, to determine the level of ‘nitric oxide’ modified proteins in the various cystinotic cell models

Lastly, we will attempt to reduce levels of protein modification by nitric oxide using pharmacological inhibitors, if the modification is deemed to have a negative effect on cell 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 words.

The project may reveal novel therapeutic targets for the future treatment of kidney malfunction in cystinosis.

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

We anticipate initial discovery of the proteins modified by excessive nitric oxide (and perhaps superoxide) generation in cystinotic cells and as such determine novel pathways that lead to kidney proximal tubule cellular dysfunction in the disease of cystinosis.