Cystinosis Research Foundation

*Lay Abstract Template for Awardees*

Spring 2013 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.

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**Principal Investigator (s)**: Daryl Okamura, MD

**Project Title**:

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| Elucidating the role of aberrant macrophage activation in nephropathic cystinosis  |

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

Despite the vast improvements cysteamine bitartrate has brought to the treatment of patients with cystinosis, kidney disease remains a significant clinical problem and is associated with early mortality.Several long-term follow up studies demonstrate that even patients who initiate cysteamine therapy early in life, the majority will develop end-stage kidney disease before the age of 15 years. Studies in our laband othershave demonstrated that macrophages play a major role in the generation of oxidative stress and in the relentless progression of kidney fibrosis.

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

The goal of the proposed studies is to further extend our investigations from the previous funding period by defining the cystinosin-deficient (CTNS-/-) macrophage phenotype and determining the mechanisms involved in its activation during nephropathic cystinosis. Our overall hypothesis is that *CTNS*-/- macrophages are genetically programmed to execute a more aggressive injurious, fibrotic response to kidney injury that serves an essential role in the pathogenesis of cystinosis-associated chronic kidney disease. Two specific aims are proposed to continue our investigation of this new mechanistic paradigm: (1) To determine the *Ctns-/-* macrophage phenotype in response to cytokine activation and the mechanisms that lead to its altered behavior; and (2) To investigate the functional impact of the *Ctns-/-* macrophage phenotype on regeneration and fibrosis after kidney injury.

**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 results of these studies should provide the foundation for translational research studies based on the use of novel molecular and cellular adjunctive therapies directed at macrophages to prevent the development of nephropathic cystinosis.

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

Based on our preliminary data, it is anticipated that the results of the proposed studies will clearly establish that the cystinosin-deficient macrophage plays a critical role as a perpetuator of pro-fibrotic pathways initiated by injured kidney tubular epithelial cells and together promote the progression of nephropathic cystinosis.