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)**: Sergio D. Catz, PhD (Mentor), Gennaro Napolitano (Fellow)

**Project Title**: Small molecule regulators of vesicular trafficking to enhance lysosomal exocytosis in Cystinosis

**Objective/Rationale**:

Mammalian cells contain intracellular compartments intended to degrade macromolecules and then recycle some small components back to the main soluble compartments. These components are then utilized to synthesize new macromolecules. In this way, mammalian cells eliminate unwanted macrocomponents while saving energy and resources by maintaining a constant supply of essential elements. Degradation takes place in vacuoles denominated lysosomes (Greek roots: luo means "to destroy" and soma means "body".)

In cystinosis, some essential degradative products cannot be recycled and remain in the lysosomes. This induces lysosomal malfunction, lack of resources, accumulation of degradative products, cell malfunction and cell death. We found that one of the specialized lysosomal functions named Chaperone mediated autophagy (CMA) is defective in cystinosis. Here, we propose to study the mechanisms of CMA and to develop strategies to improve cell function in cystinosis.

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

We found that the expression of an important regulatory protein named LAMP2a is decreased in cystinosis. LAMP2a is the only known receptor for chaperone mediated lysosomal degradation. Defective CMA leads to the accumulation of toxic substrates and is involved in the pathogenesis of human diseases including kidney pathologies, neurological disorders, cancer and aging. We will utilize cystinotic cells from both mouse models and humans with cystinosis to a) understand the mechanisms of defective LAMP2a downregulation and mislocalization in cystinotic cells and to understand the mechanism of defective translocation of substrates for degradation into the lysosomal lumen.

We recently showed that increasing the movement of lysosomes in a cell, facilitates its function by increasing the probability of interaction with regulatory components, in the same way that public transportation enhances the function of a city by facilitating access of citizens to different working areas increasing productivity. We will express trafficking proteins to correct LAMP2a distribution and function. Finally, we will check the hypothesis that the accumulation of degradative products in lysosomes affects LAMP2a function. We will decrease lysosomal overload and study LAMP2a localization and chaperone-mediated degradation in cystinotic cells.

**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.

Defective CMA is directly linked to human disease, including kidney pathologies, an organ in which CMA is markedly active. Our research is highly relevant because it identifies, in cystinosis, previously unrevealed cellular defects associated with human pathologies. Elucidating the mechanisms that lead to abnormal CMA in cystinosis and determining strategies to rescue this phenotype will lead to a better understanding of the physiopathology of this disease and to novel approaches for the treatment of cystinosis.

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

The aim of our study is to discover why cystinotic cells develop CMA defects and how this impairment can contribute to the pathogenesis of cystinosis. Importantly, we will use different approaches aimed at ameliorating these cellular defects and improving cell function. We expect that our approach will lead to a better understanding of the pathogenic events in cystinosis and to the development of new strategies to improve cell function, which is fundamental to define novel treatments for cystinosis.