

FINAL PROGRESS REPORT

Project title: Molecular Mechanism of Cystinosis

Xue Guo, Research Fellow; Liang Feng, Mentor

Sep. 1, 2018 – Aug. 31, 2020

Objectives:

In this study, our goal is to decipher the molecular mechanism of membrane transporters found on lysosomes that play critical roles in the pathogenesis of and therapy of cystinosis. We aim to understand how these membrane transport proteins work at the molecular level.

Executive overview of progress:

Membrane proteins play critical roles in many aspects of cystinosis, such as its cause and therapeutic interventions. Membrane proteins are challenging to characterize due to their hydrophobic nature, their relative instability when extracted out of the native membrane environment and their dynamic properties. We have taken multiple approaches to overcome these barriers. We systematically applied and evaluated a variety of strategies and reagents, which led to much improved biochemical behaviors of these membrane proteins. We also developed new reagents that can specifically recognize the target proteins and may help to stabilize the protein in a defined conformation. These provided critical tools to facilitate efforts in figuring out how these proteins work at the molecular level. In addition, we have made significant progress towards understanding the dynamic properties of these proteins, which are essential for their functions. Together, we have developed enabling tools for this challenging project and made substantial progress in multiple fronts, which have laid a solid foundation for deciphering molecular mechanisms of membrane transporters that play important roles in cystinosis.