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): Olivier Devuyst and Alessandro Luciani

Project Title: SGLT2 inhibitors reveal new therapeutic opportunities for cystinosis

Objective/Rationale: Nephropathic cystinosis causes inherited dysfunction of the kidney proximal tubule (PT), often complicated by chronic kidney disease (CKD) and life-threatening manifestations. The deficiency of CTNS is consistently associated with defective autophagy-lysosome degradation systems and dysfunction of PT cells, as reflected by low-molecular-weight (LMW) proteinuria. There is an urgent need to identify novel transformative therapies for patients with cystinosis, as the use of cysteamine is limited by side effects and lack of efficacy to alleviate PT dysfunction.

Project Description: Our preclinical studies have indicated that modulation of overactive mTORC1 pathway rescues lysosome storage-related phenotypes and proximal tubulopathy downstream of CTNS loss and cystine storage, offering novel targets for intervention. However, the translatability of mTORC1 inhibitors is hindered by lack of specificity and toxicity, limiting their usefulness. Sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2i), originally designed to treat type 2 diabetes, slow CKD progression in non-diabetic patients. These inhibitors target mechanisms controlling nutrient sensing and mTORC1 signaling pathways in PT cells. We plan to use a combination of preclinical models, cell- and lysosome-based function assays and disease-relevant screening technologies: i) To reveal whether and how SGLT2i counteract the aberrant mTORC1activation in CTNS-deficient tubular cells; ii) To evaluate the preclinical efficacy of SGLT2i on lysosome storage-related phenotypes and proximal tubulopathy in CTNS-deficient/cystinosis-affected kidneys; iii) if successful in preclinical testing, to design a first-in-human clinical trial protocol to determine whether the SGLT2i dapagliflozin improves proximal tubulopathy in young children with cystinosis.

Relevance to the Understanding and/or Treatment of Cystinosis: SGLT2i appear to pharmacologically reproduce many of the beneficial effects of fasting regimens, making them potentially attractive for long-term treatment of chronic mTORC1-related diseases, including cystinosis. In this project, we wish to unlock new therapeutic possibilities for children with cystinosis by extending the therapeutic potential of SGLT2 inhibitors.

Anticipated Outcome: These studies based on screening and validation workflow in innovative model organisms and relevant cellular systems could enable fast therapeutic translation of SGLT2i from preclinical systems to clinical benefit for children with cystinosis.