DRIVING INNOVATION IN RENAL THERAPEUTICS BY HARNESSING NOVEL MOLECULAR PATHWAYS OF RENAL INJURY IN NEPHROPATHIC CYSTINOSIS

ABSTRACT. Nephropathic cystinosis (NC) is a rare, genetic disorder caused by mutations in the cystinosin (CTNS) gene, resulting in accumulation of cysteine in lysosomes in all tissues and organ systems. Despite intake of cysteine depletion therapy (cystagon) soon after birth, the kidney alone is uniquely affected by water and electrolyte handling deficits as part of the renal Fanconi syndrome and progressive kidney damage and renal failure by the first decade of life, extendable to the second decade with cystagon. Current treatments in NC focus on managing symptoms rather than addressing the underlying cause of kidney injury, leaving a substantial gap for innovative therapeutics. We have identified that apart from cystine accumulation, other key molecular perturbations in the ATP6V0A1 gene impacts renal tubular integrity and function, could offers rational drug design opportunities to mitigate kidney injury in NC. We present a collaborative multi-PI project from three global key opinion leaders (Sarwal, Callan, Keyes), hailing from three world-class academic institutions (UCSF, UU and DCU), utilizing the Tripartitie (or triple) RO1 mechanism where each PI is funded by their own country- the USA, Republic of Ireland and Northern Ireland. The PI's leverage their strong preliminary data in NC and their combined expertise in translational nephrology, molecular medicine, cellular imaging, robust validation in pre-clinical models of cystinosis, and drug development expertise, to create innovative treatments targeting ATP6V0A1 for mitigating the kidney damage in nephropathic cystinosis. We will explore the interaction between CTNS and ATP6V0A1, which has not previously been characterized, conducting multi-modal imaging, pH and mechanistic studies of disease-relevant mutations and protein domains in their endogenous context (Aim 1). We will improve the bioavailability of ATX (nano-ATX), as it is a compound that restores ATP6V0A1 function, and create a new drug that combines delivery of cystagon and nano-ATX (nanoCysATX), to most effectively treat and limit kidney injury in NC (Aim 2). The new nano-ATX and nano-CysATX formulations will be further evaluated in pre-clinical organ-on-a-chip and a CTNS-/- rodent model (Aim 3). As we have shown that ATX reverses dysfunctional mitochondria-renal tubular-lysosme crosstalk and oxidative stress, the impact of this drug development initiative may have far reaching implications for other (non-NC) causes of chronic kidney disease (CKD). Thus, the clinical impact of developing a reno-protective drug for NC has far reaching impact. As NC is an orphan disease—affecting fewer than 200,000 people in the U.S.— NC qualifies for regulatory incentives such as market exclusivity and fast-track approval pathways that would be critically needed to get ATX to help patients with NC and other causes of CKD.

Public Health Relevance Statement

Cystinosis is a rare autosomal recessive lysosomal storage disease, where the kidney is the first and most severe organ affected functionally. Though lysosomal cysteine depleting therapies exist, renal failure is invariant. A reno-protective drug for cystinosis patients is a critical unmet need and developing this is the focus of this proposal.