Drug Repurposing for the Treatment of Experimental Alport Syndrome
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Awarded 2015

Alport Syndrome (AS) is an inherited form of chronic kidney disease (CKD) associated with blood and protein in the urine. It can progress to end stage renal disease (ESRD). CKD is also associated with increased cardiovascular (CV) morbidity and mortality. Blockade of the renin angiotensin system (RAS) is the guideline recommended approach to the treatment of patients with AS and CKD but it only slows and does not prevent progression towards ESRD. In the current proposal, we will utilize a mouse model of AS that is associated with proteinuria and progressive loss of kidney function. We will study a new treatment that targets patterns of gene expression in the kidney associated with progression of kidney injury. The drug is called vorinostat and it already approved for use in humans (although not for AS). Specifically, we will determine if treatment with vorinostat limits the progression of chronic kidney disease and prolongs the lifespan of mice with experimental AS. The mechanism of action of vorinostat differs from drugs used to block the RAS so we will also determine if combined treatment with vorinostat and RAS blockade confers additional benefit in mice with experimental AS. This project specially aims to determine: 1) if inhibition of lysine deacetylation with vorinostat will attenuate kidney injury and increases the lifespan of Col4a3-/- mice, and 2) if the addition of vorinostat to angiotensin converting enzyme inhibitor treatment, the current treatment standard, will further attenuate kidney injury and increase the lifespan of Col4a3-/- mice. This project is significant because in silico drug repurposing in a murine model of AS has identified a novel drug therapy that reversed the gene expression changes observed with progression of kidney injury. In vivo studies should provide more insight into the effects of inhibition of lysine deacetylation on progression in experimental AS and determine if the treatment is also effective in mice already treated with an ACEI. These findings should support the development of a new treatment approach in humans with AS that can be readily applied to clinical testing.