5-Ht2b Antagonism As A Strategy To Prevent Renal Function Loss In Alport Syndrome
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Awarded 2016

Alport syndrome shows different severities of symptoms and different rates of progression to kidney failure in different families and even in different patients within the same family. In most cases the appearance of protein in the urine (proteinuria) signals the onset of progressive kidney disease that will eventually lead to kidney failure and the need for dialysis or transplant. Preventing or delaying the onset of proteinuria or reducing the amount of protein in the urine by treatment with ACE inhibitors has been shown in clinical studies to be beneficial for patients, as it can significantly extend the time to the need for dialysis or transplant. However, even patients being treated with ACE inhibitors will eventually experience declining kidney function and kidney failure. The beneficial though not completely curative effects of ACE inhibitor treatment mirror results that were first obtained using a mouse model of Alport syndrome. These and other data suggest that Alport mice are appropriate models for testing potential therapies that might be able to synergize with ACE inhibition and further delay or prevent progression to renal failure. This proposal, which was assembled by an international team of collaborators from two academic medical centers (Washington University and the University of Geneva) and from the pharmaceutical industry (F. Hoffman-La Roche), seeks to prove that preventing activation of the serotonin receptor 2B (also known as 5-HT2B) will reduce kidney fibrosis, slow kidney disease progression, and cooperate with ACE inhibition to prolong kidney function in Alport mice. Although serotonin is best known for its effects on mood via its activities in the brain, data in the literature from multiple labs show that activation of 5-HT2B promotes fibrosis, and, conversely, that inhibition of this receptor delays and/or reduces fibrosis. These effects have been demonstrated in multiple models of fibrosis in several tissues, including kidney. Our approach will be to “repurpose” a drug that was developed by Roche and has already been shown to be safe in humans in Phase 1 trials. The drug, a specific inhibitor of 5-HT2B, will be used to treat Alport mice to test the hypothesis that the drug will slow progression to kidney failure. In parallel experiments, we will study Alport mice with genetic inactivation of 5-HT2B primarily in the kidney. An arm of each of these studies will include ACE inhibitor treatment in addition to 5-HT2B inhibition, because any Alport patient who might

eventually be treated with the drug will likely already be on an ACE inhibitor. The mice will be analyzed by methods used in patients: quantifying blood creatinine and proteinuria during the course of treatment and using microscopy to analyze kidney pathology. With this plan we expect to show that either pharmacological (drug-mediated) or genetic antagonism of the serotonin receptor 2B will slow kidney disease progression in Alport mice, and that combining with ACE inhibition will prolong the time to kidney failure better than either treatment alone. Because the 5-HT2B inhibitor we will use has already been shown to be safe in humans, its movement as a repurposed drug into the clinic for treatment of Alport patients in clinical trials should be feasible and rapid.