

Defining Efficacy of Combination Drug Therapy in Alport Mice

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Alport syndrome is a hereditary glomerulonephritis associated with sensorineural deafness. It is usually diagnosed in children and leads to kidney failure in adolescents or in adults. Dialysis and kidney transplantation are the major treatments. Alport syndrome is caused by mutations that effect the collagen 3 4 5(IV) network present in the kidney glomerular basement membrane (GBM), which is an important component of the glomerular filtration barrier. In Alport syndrome, the GBM becomes thinned, thickened and split to form a typical basket weave-type appearance that presumably reflects functional deficits in glomerular filtration (hematuria, reduced GFR) and perhaps also a disturbed balance between matrix degradation and synthesis. A recent exciting paper showed that treatment of Alport patients with angiotensin converting enzyme inhibitors (ACEi) was effective at delaying renal failure and prolonging life. Although the mechanisms for these benefits are currently unknown, the results are very promising, especially given the widespread usage and known safety of ACEi in humans. These results in humans were predicted by a study in mice showing that the ACEi ramipril prolongs life span in a mouse model of autosomal recessive Alport syndrome, the Col4a3 mutant mouse. Additional studies in Alport mice suggest that infiltration of macrophages and other immune cells contributes to kidney disease progression, both in glomeruli and in the tubulointerstitium. The goal of this proposal is to determine whether combined therapy with both an ACEi and a proprietary inhibitor of chemokine receptor 2 and 5 (CCR2 and CCR5) activation will have a synergistic effect at slowing Alport disease progression and will extend life span even more than the ACEi alone.

Our preliminary data show that the CCR2/5 inhibitor attenuates the mobilization of monocytes and macrophages (which express CCR2 and CCR5) into the bloodstream and into the kidney in normal and diabetic mice. We hypothesize that the CCR2/5 inhibitor will have the same effect in Alport mice and will synergize with the effects of ACE inhibition to prolong life span even more. The CCR2/5 inhibitor has been characterized in detail by Pfizer and has already shown to be safe in humans. If our hypothesis is validated in mice, we will apply for funding for trials in human Alport patients under the auspices of the Pfizer/Washington University Biomedical Agreement. This research agreement allows Washington University investigators to access Pfizer's confidential and prioritized collection of molecular mechanisms for patientready biopharmaceuticals. It is expected that the Alport Syndrome Foundation will serve as a partner in such studies by helping to identify clinicians willing to be involved in the trial and assisting with patient recruitment.

October 2013 Update: Dr. Jeff Miner has published the first of three papers regarding his research *Nanoscale protein architecture of the kidney glomerular basement membrane* in the eLife Journal.