

WISE Antibody as a Treatment for Alport Syndrome
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Alport syndrome (AS) 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 eventual treatments necessary to maintain the lives of Alport patients. Alport syndrome is caused by mutations that affects the collagen $\alpha\alpha\alpha4\alpha5(IV)$ 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 the functional deficits in glomerular filtration (hematuria, proteinuria, and reduced GFR) and perhaps also a disturbed balance between matrix degradation and synthesis. Treatment of Alport patients with an angiotensin converting enzyme inhibitor (ACEi) is effective at delaying renal failure and prolonging life. This was predicted by a preclinical study showing that the ACEi ramipril prolongs the life span of the *Col4a3* mutant mouse, a model of autosomal recessive Alport syndrome. Despite the great benefits of ACE, it is not a cure, so additional synergistic therapies are necessary to prolong kidney function further. The goal of this proposal is to test the hypothesis that combined therapy with both an ACEi and a proprietary monoclonal antibody inhibitor of “**W**nt modulator **I**n **S**urface **E**ctoderm” (WISE; also called USAG-1 and SOSTDC1) will have a synergistic effect at slowing Alport disease progression and will extend life span even more than ACEi treatment alone. Preliminary data supporting this hypothesis show that the WISE antibody (called anti-WISE hereafter) significantly reduced proteinuria in Alport mice. Moreover, data in the literature show that Alport mice lacking WISE due to mutation of the WISE gene are also protected; they show reduced glomerular and tubulointerstitial disease, though they are not cured. We hypothesize that anti-WISE treatment will synergize with the effects of ACEi to prolong life span even more than either agent alone. If our hypothesis is validated in mice, this will provide strong support for proceeding with clinical trials, with the hope of eventually using anti-WISE in human Alport patients together with an ACEi to prolong kidney function. It is expected that the Alport Syndrome Foundation and its partners will help facilitate such studies by identifying clinicians willing to be involved in the trial and assisting with patient recruitment.