POSTER 116

AAV5-MEDIATED TARGETED DECORIN GENE THERAPY: EFFECTIVE AND SAFE FOR CORNEAL FIBROSIS

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Purpose: Corneal fibrosis is 3rd leading cause of global blindness according to WHO report. At present, no agents are proven to clinically reduce corneal fibrosis without causing significant side effects. It was hypothesized that decorin gene delivered into keratocytes prevents corneal fibrosis in the cornea *in vivo* by blocking transforming growth factor β (TGFβ), which converts keratocyte to myofibroblasts and cause fibrosis.

Methods: New Zealand White rabbits were used. Fibrosis in the cornea was produced with photorefractive keratectomy (PRK) using excimer laser. 50µl AAV5 titer ($5X10^{12}$ vg/ml) expressing decorin was topically applied on the PRK-treated and untreated eyes. Slitlamp biomicroscopy was used to evaluate the health of the eye and clinical scoring of corneal haze. Real-time PCR, immunoblotting and immunocytochemistry techniques were used to measure the hallmarks of fibrosis [alpha smooth muscle actin (αSMA), F-actin and fibronectin]. Transmission electron microscopy investigated ultrastructural features. Dot-blot and real-time PCR quantified delivered-decorin gene copies.

Results: The AAV-decorin treated rabbit eyes did not show inflammation, redness or structural changes in the cornea in slitlamp biomicroscopy. A statistically significant (44.9-67.4%±4.3; $p < 0.001$) decrease in the expression of fibrotic markers (αSMA, F-actin and fibronectin) was detected with immunocyctichemistry and immunoblotting in decorin-delivered corneas. Significantly high (8-10 fold, $p<0.001$) decorin mRNA expression was noted in AAV-DCN-treated rabbit corneas.

Conclusions: AAV-mediated decorin gene therapy can effectively reduce fibrosis in the rabbit cornea *in vivo*. Our preclinical studies suggest that decorin gene therapy has potential for treating corneal haze in patients, and set the stage for undertaking clinical trials.