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SAHA: FDA APPROVED HISTONE DEACETYLASE INHIBITOR DEMONSTRATES EXCEPTIONALLY HIGH INHIBITION OF CORNEAL HAZE FOLLOWING PRK SURGERY IN RABBIT MODEL

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Purpose: TGFβ induces the transformation of corneal keratocytes into fibroblasts and myofibroblasts resulting in the formation of corneal haze (scar) following injury. We investigated whether epigenetic modifications can prevent development of corneal haze *in vivo* using a rabbit model.

Methods: *In vivo* studies with New Zealand white rabbits were performed with –9.0 diopter photorefractive keratectomy (PRK) surgery using an excimer laser. Human stromal fibroblasts (HSF) were used for *in vitro* studies. HSF cultures at 70% confluence were exposed to TGFβ (1ng/ml) with or without SAHA (vorinostat) under serum-free conditions for five minutes. SAHA (25.0nM=0.06%) was applied topically on the rabbit cornea immediately after PRK. Cornea tissue was harvested at four weeks post-operatively and studied with Trypan blue exclusion, slit lamp biomicroscopy, TUNEL assay, real-time PCR, immunocytochemistry, immunocytochemistry, and western blotting techniques.

Results: Treatment with the FDA approved histone deacetylase inhibitor SAHA (0.06%) significantly reduced cellular markers of myofibroblast transformation and haze development (αSMA, fibronectin and phalloidin) in the rabbit cornea *in vivo* (up to 73%; $p<0.001$) and in HSF *in vitro* (46-83%; $p<0.001$). Furthermore, this dose appeared to be well tolerated and did not cause redness, swelling, or inflammation in the rabbit eye *in vivo* or alter HSF viability or phenotype *in vitro.* Other tested doses showed low efficacy or high toxicity.

Conclusions: This study suggests that epigenetic modification is a novel approach for treating corneal haze *in vivo*. Additionally, vorinostat (0.06%) is highly efficacious in reducing PRK-induced corneal haze with minimal side effects in rabbit eyes *in vivo*.