THERAPEUTIC POTENTIAL OF THE ANTI-FIBROTIC DRUG SUBERANILOHYDROXAMIC ACID (SAHA) IN CANINE CORNEAL FIBROSIS

Kristina Gronkiewicz

Dr. Elizabeth A. Giuliano, Thesis Supervisor

ABSTRACT

Purpose: The aims were to (1) investigate the molecular mechanisms mediating the anti-fibrotic effect of SAHA in the canine cornea using an *in vitro* model and (2) to develop a novel *in vivo* model of corneal fibrosis in dogs utilizing alkali burn and assess the ability of SAHA to inhibit corneal fibrosis using this canine model.

Methods: In study 1, CCF were incubated for 24hrs +/- TGF-β1 and SAHA. Western blot was used to quantify isoforms of intracellular signaling proteins. Real-time PCR and zymography quantified MMP mRNA and protein expression, respectively. In study 2, a corneal alkali burn was created in beagle dogs using 1 N NaOH topically. Dogs were randomly and equally assigned into 2 groups: A) vehicle (DMSO); B) anti-fibrotic treatment (SAHA). Degree of corneal opacity and efficacy of SAHA were determined utilizing the Fantes grading scale, OCT, corneal histopathology, IHC and TEM.

Results: In study 1, SAHA treatment reduced phosphorylation of Smad2/3, ERK1/2 and altered MMP protein and gene expression. In study 2, α-SMA staining and minimum and maximum interfibrillar distances were significantly greater in burned corneas.

Conclusion: Corneal anti-fibrotic effects of SAHA involve modulation of canonical and non-canonical components of TGF-β1 intracellular signaling and MMP activity. The alkali burn generates corneal opacity without damaging the limbus, and induces reliable fibrosis. Additional *in vivo* SAHA dosing studies with larger sample size are warranted.