#4177

SCO-116, a novel small-molecule NRF2 activator, potently induces NQO1 in multiple rabbit ocular tissues

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Purpose

Multiple ophthalmic diseases are characterized by decreased mitochondrial function and increased oxidative stress as core pathological features. Nuclear factor erythroid 2-related factor 2 (NRF2) regulates a network of hundreds of antioxidative, anti-inflammatory, and bioenergetic proteins, and NRF2 activation results in increased antioxidative capacity and improved mitochondrial function. We evaluated the ability of a novel NRF2 activator, SCO-116, which is under development for macular degeneration and Fuchs' dystrophy, to induce target protein expression in ocular tissues of rabbits *in vivo*.

This study was performed to evaluate and quantify the expression of NQO1 protein, as an indicator of NRF2 target activation, in the corneal endothelium and other ocular tissues of albino rabbits dosed with sterile, preservative-free, topical ophthalmic solution of test article, SCO-116.

Methods

In vivo studies

The *in vivo* portion of this non-GLP study was performed by iuvo BioScience, LLC. Male New Zealand white rabbits (n=2/group) were administered topical vehicle or SCO-116[a] bilaterally once daily (50 µl/eye) from Days 1-5. A single untreated control animal was monitored concurrently with the treated test and control animals but was not dosed at any time. On Day 6, animals were euthanized by overdose of sodium pentobarbital and ocular tissues were collected from all animals. Both globes for each animal were excised, processed, fixed, and embedded in paraffin blocks.

Methods, continued

Histology and Staining

Paraffin blocks, each containing a formalin-fixed rabbit globe, were sectioned at 4 µm and stained with hematoxylin and eosin (H&E). From the H&E slide, the best sample from each globe was selected for immunohistochemistry. Routine immunohistochemistry targeted to NQO1 antigen was performed. Staining was conducted on the Biocare Oncore Pro X using chromogenic methods. Slides were heated for 2 hours at 70C in pH9 buffer for antigen retrieval. Primary antibody incubation (1:50, A180 clone; Cell Signaling, #3187) was performed at room temperature for 30 minutes. An HRP-conjugated anti-mouse secondary antibody for antibody binding detection with visualization via DAB application and hematoxylin counterstain was used for analysis.

Image Analysis

Images were evaluated using Fiji image analysis software to obtain optical density data. For each sample eye, unique images of the different tissues were taken (for corneal endothelium, epithelium, and stroma, and lens epithelium, n=10; for ciliary body and trabecular meshwork, n=2; for retinal pigment epithelium, n=5-10), such that the sections captured do not overlap.

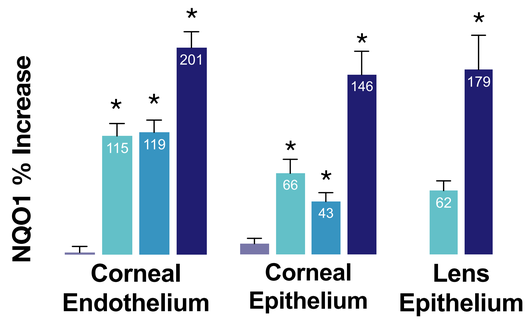
Statistical Analysis

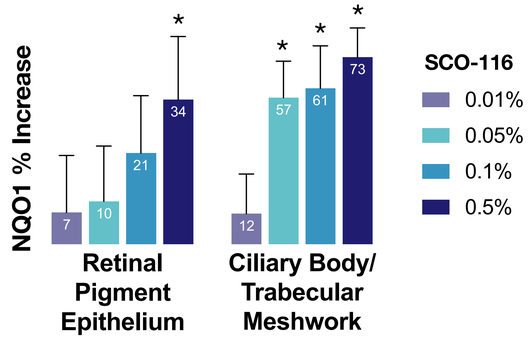
Optical density values were compared using an ordinary one-way ANOVA followed by Dunnett's multiple comparisons test between groups. GraphPad Prism software. $P < 0.05$ was considered statistically significant.

Results

SCO-116 induces NQO1 expression in the corneal endothelium and multiple other ocular tissues

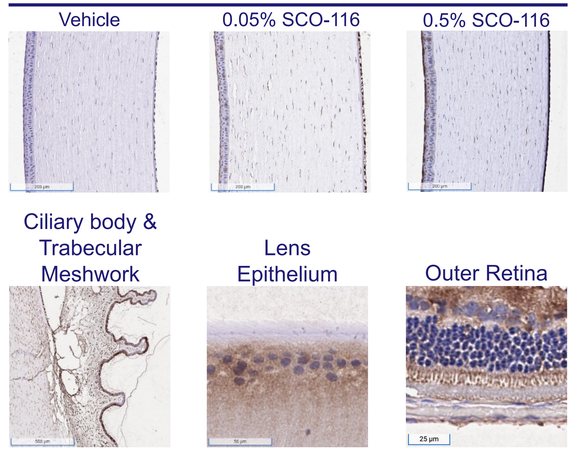
Optical density data from each tissue were averaged for each treatment from both eyes. These data were then normalized to the vehicle treatment staining and are presented graphically.





Results, continued

Sample images from stained target tissues



Conclusions

Overall, topical ocular treatment of SCO-116 was associated with broad induction of NQO1 protein across multiple structures of the eye. As anticipated, robust induction was observed at the ocular surface, in the corneal epithelium. The ciliary body and trabecular meshwork also exhibited robust NQO1 induction, as did the lens epithelium.

Intriguingly, topical ocular treatment with SCO-116 resulted in a significant increase in NQO1 protein expression in retinal pigment epithelial cells. These observations offer the potential that topical treatment could deliver effective concentrations to the retina and warrant further evaluation.

Disclosures: O: M Stevens, B Gentry, D Flory, R Henry, and K Ward are co-owners and co-founders of Kuria Therapeutics.
[a] SCO-116: a macrocyclic benzotriazole disclosed in US Patent 11,518,763

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