#0192

SCO-116 exhibits potent, selective activation of NRF2 suitable for use in treatment of ocular diseases

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1. Kuria Therapeutics 2. SCOHIA PHARMA

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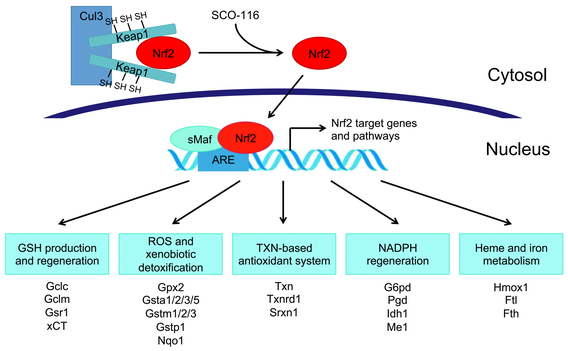
Purpose

Retinal and corneal disorders that stem from mitochondrial dysfunction, including macular degeneration and Fuchs' dystrophy, exhibit oxidative stress and increased inflammatory activity as key contributors to their pathogenesis. Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that regulates proteins required for normal mitochondrial function, removal of cellular oxidants, and control of the inflammatory response, and represents a therapeutic target to restore normal cellular function.

We have performed *in vitro* studies designed to determine the activity, potency, selectivity, and cytotoxicity of a novel NRF2 activator, SCO-116, for ocular use.



Model for activation of NRF2 by SCO-116

Adapted from Xie *et al., Toxicol Appl Pharmacol* **460**:116375 (2023) and Tonelli, *Antioxid Redox Signal* **10:**1727 (2018).

Methods

Time-resolved fluorescence resonance energy transfer (TR-FRET) was used to determine the activity of SCO-116[a] to release NRF2 from its negative regulator, KEAP1, following a 1-h incubation. Experiments were conducted with 0.5 nM GST-tagged KEAP1 protein in the presence of 125 ng/mL Anti GST-Tb cryptate and 12 nM FAM-conjugated NRF2 peptide. Results were expressed as a ratio of emission at 520nm: emission at 486nm. IC_{50} values were calculated in a four-parameter logistic fit equation using Prism 7.

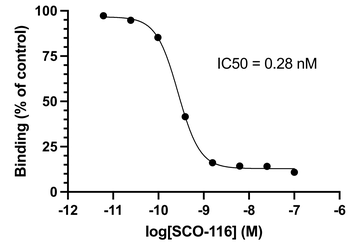
The ability of SCO-116 to activate the antioxidant response element was measured in HEK293T cells transfected with antioxidant response element-Nano-luc reporter following a 6-h incubation with SCO-116 or vehicle. Data were expressed as EC_{30}, the concentration required to increase luminescence signal by 30%.

Cytotoxicity was examined in HMEC-1, AC16, and HK2 cells incubated for 24-48 h with either SCO-116 or vehicle, with ATP content measured using CellTiter Glo.

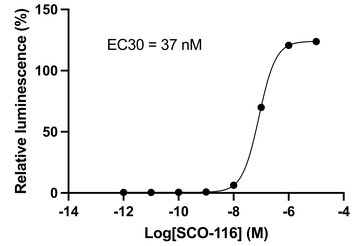
A Eurofins SafetyScreen87 panel was performed to assess SCO-116 interaction with a series of 87 G-protein-coupled receptors, ion channels, enzymes, transporters, and nuclear receptors. See eurofins.com for methodological details.

Results

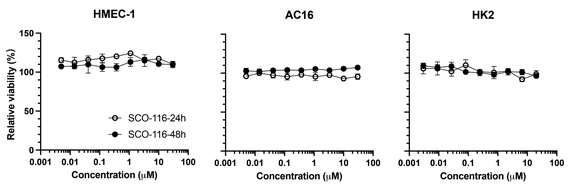
SCO-116 is a potent inhibitor of the KEAP1-NRF2 interaction in a cell-free system.



SCO-116 potently activates the NRF2-mediated antioxidant response in cells *in vitro*.

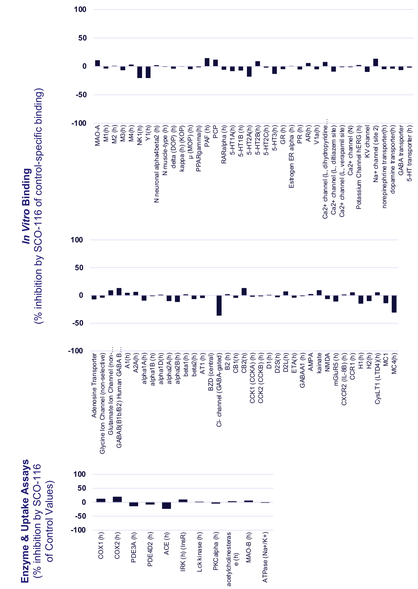


SCO-116 lacks cytotoxicity in all cell types and at all concentrations tested.



Results, continued

An extensive safety screen revealed no significant inhibition of any of the 87 targets assayed. Inhibition or stimulation >50% would represent a significant effect of SCO-116.



Conclusions

SCO-116 is a novel NRF2 activator; the present data demonstrate potent interaction with its molecular target (KEAP1) and subsequent activation of NRF2 at concentrations not associated with cytotoxicity or off-target effects. SCO-116 is currently under investigation for treatment of both corneal (Fuchs' dystrophy) and retinal (macular degeneration) disease, and these data support this continued evaluation.

Disclosures: O, E: R Henry, D Flory, B Gentry, and K Ward are co-owners and co-founders of Kuria Therapeutics; Y Katayama, R Koyama, S Matsumoto, Y Moritoh, and M Watanabe are/were employees of SCOHIA Pharma.

[a] SCO-116: a macrocyclic benzotriazole disclosed in US Patent 11,518,763.

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