#1929

SCO-116 protects retinal pigment epithelium from oxidative insult *in vitro* and preserves visual function and retinal structure in sodium iodate-induced geographic atrophy in rats *in vivo*

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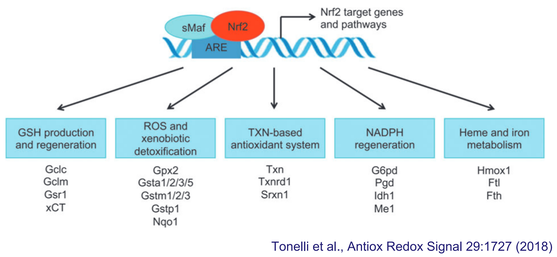
Purpose

Dry AMD is a major threat to the vision of millions worldwide. Recent drug approvals offer the possibility to slow lesion progression in advanced AMD, but offer no relief from the inexorable decline in visual acuity. Further, for the many patients with earlier disease, the only available therapies are antioxidant vitamins. Therefore, new therapeutic approaches in AMD remain desperately needed.

The pathophysiology of intermediate dry AMD is characterized by oxidative stress and decreased mitochondrial function in the retinal pigment epithelium (RPE). This biology interests well with that of the nuclear factor erythroid 2-related factor 2 (NRF2) pathway. NRF2 is the master regulator of the antioxidant defense pathway of the cell, and NRF2 activation promotes a broad phenotype of improved mitochondrial function, decreased inflammation, and decreased oxidative stress.



Tonelli et al., Antiox Redox Signal 29:1727 (2018)

Kuria Therapeutics is developing SCO-116 as a novel NRF2 activator for ophthalmic diseases. SCO-116 potently activates NRF2 in retina of rats, rabbits, and monkeys. The purpose of the present studies was to evaluate the ability of SCO-116 to protect RPE from oxidative insult *in vitro* and to protect rat retina *in vivo* from the prototypical oxidative insult, sodium iodate.

Methods

In vitro studies

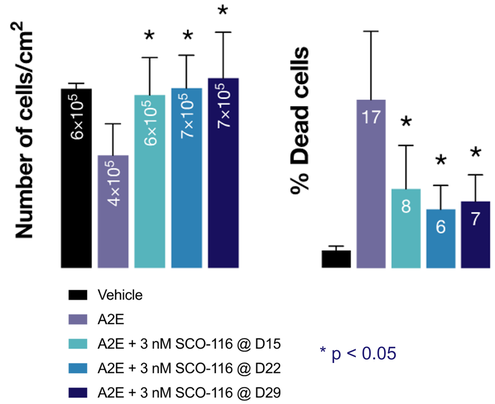
In vitro studies were conducted at Phenocell SAS (Grasse, France), using a commercially available model system. Human RPE cells derived from wild-type pluripotent stem cells were plated and matured for 2 weeks. On Day 15, media for all cells was switched to one containing A2E (N-retinyl-N-retinylidene ethanolamine) to induce oxidative stress and a dry AMD phenotype. Then, on Day 30, cells were subjected to a daily challenge with blue light for 3 days along with the A2E insult to exacerbate the oxidative injury. SCO-116[a] (3 nM) or DMSO were administered starting on either Day 15, 22 or 29, with cell viability and apoptosis assessed on day 33. Viability was assessed using a calcein-AM assay, and apoptotic cells were evaluated using Hoechst counterstain.

In vivo studies

Animal studies were conducted at EyeCRO (Oklahoma City, OK), using a commercially available model system. Geographic atrophy (GA) was induced in 10-week old female Brown Norway rats on Day 4 via bilateral subretinal injection of sodium iodate at 10 µg/eye. On Day 1 and 4 (immediately following GA induction), the animals were administered via bilateral intravitreal (IVT) injection either vehicle (1M $NaHCO_3$) or SCO-116 at 3 or 30 µg/eye. On Day 17, optokinetic tracking was used to evaluate visual function by measuring spatial frequency and contrast thresholds, and on Day 21, OCT was used to assess retinal integrity and thickness.

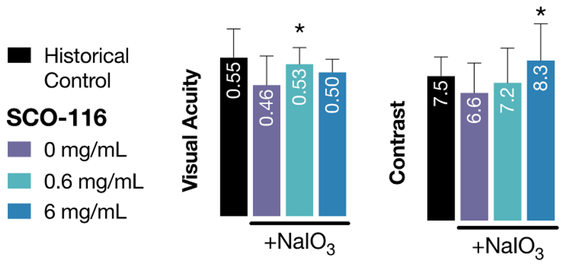
Results

SCO-116 Protects RPE In Vitro from Dry AMD



In human RPE, SCO-116 prevented the loss of cell viability induced by the A2E-blue light insult, whether administered at Day 15, Day 22, or Day 29, and also significantly decreased the number of apoptotic cells induced by A2E-blue light insult.

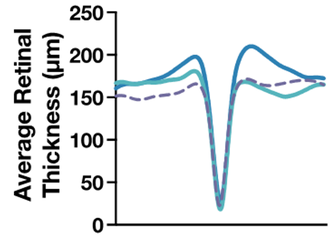
SCO-116 Provides Functional Protection from Dry AMD in Rats In Vivo



In rats, SCO-116 prevented GA-induced decreases in visual acuity and contrast sensitivity, although not in a strict dose-response manner.

Results, continued

SCO-116 Provides Structural Protection from Dry AMD in Rats In Vivo



When retinas were evaluated via OCT, sodium iodate demonstrably decreased retinal thickness (owing to destruction of the RPE layer), which was ameliorated by SCO-116 treatment.

Conclusions

In both RPE *in vitro* and in the rat subretinal sodium iodate model, an aggressive animal model for GA, SCO-116 demonstrated protection from injury using both functional and structural endpoints. These data support continued investigation of SCO-116 as a potential future development candidate for patients with dry AMD.

Acknowledgements

The authors gratefully acknowledge the contributions of the expert scientific staff at Phenocell SAS for their work on the *in vitro* dry AMD model in iPSC-derived human RPE.

Disclosures: O: K W Ward, D Flory, B Gentry, R Henry, and M Stevens 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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