Targeting Mitochondria with Bevemipretide: Retinal Exposure and Protective Effects in Models of AMD

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INTRODUCTION:

- In age-related macular degeneration (AMD), mitochondrial dysfunction occurs early in disease and contributes to disease progression. Advances in mitochondrial research have illuminated the development potential for mitochondria-targeted therapeutics for the treatment of AMD (1).
- Bevemipretide (SBT-272) targets the inner mitochondrial membrane where it reversibly binds to cardiolipin, improving mitochondrial function and reducing production of reactive oxygen species (ROS) (2).
- The aim of this study is to evaluate the ocular and systemic distribution of topical bevemipretide and its potential protective effects in models of AMD.

MATERIALS AND METHODS:

Tissue and Plasma Concentrations of Bevemipretide in Rabbits and Minipigs After 28 Days of Dosing:

- New Zealand white rabbits and Yucatan minipigs were administered bevemipretide eyedrops (concentrations up to 5% BID OU) for 28 days.
- Blood samples were collected and both eyes were harvested following euthanasia 24 hours after the final dose.
- Plasma and eye tissue concentrations were analyzed by LC-MS/MS (LLOQ: 0.1-1 ng/mL; 0.2-5 ng/g).

***Effect of Topical Bevemipretide (2% BID) on Total Retinal Thickness in Rats Following Bright Light-Induced Retinal Degeneration* (Figure 1):**

- Rats were treated twice daily with topical bevemipretide (2%) starting 2 days before light exposure and continuing for an additional 2 weeks.
- On day 3, rats were exposed to 10,000 lux bright light for 1 hour to induce retinal damage.
- On day 17, total retinal thickness was measured by OCT imaging.

Figure 1. Study Design Schematic

Effect of Bevemipretide on Viability of AMD Patient-Derived RPE Cells Cultured on a Nitrite-Modified ECM:

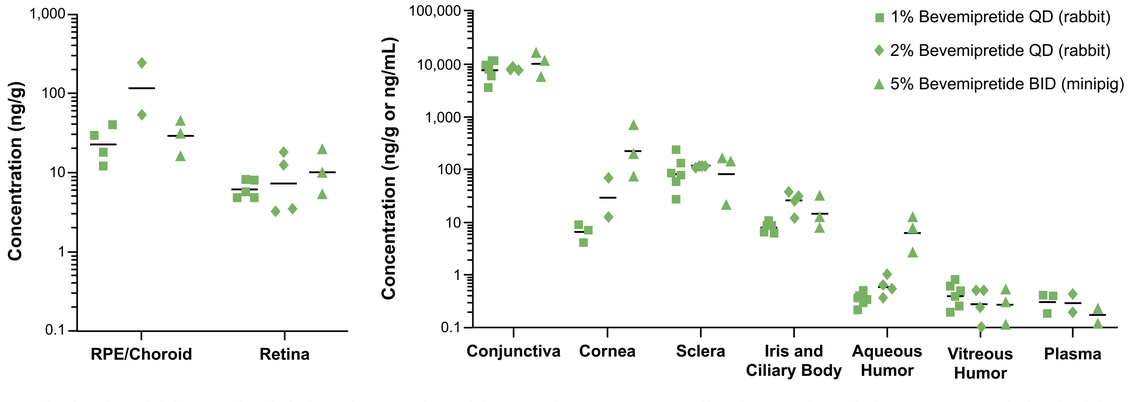
- iPSC-derived RPE cells were generated from patients with AMD (2 atrophic, 1 exudative). RPE cells were cultured on a nitrite-modified extracellular matrix (ECM), a typical modification of an aged Bruch's membrane, for 48 hours with or without bevemipretide treatment (100 nM). Cell viability was measured by RealTime-Glo MT Cell Viability Assay.

Effect of Bevemipretide on Total Cellular and Mitochondrial ROS Production by HQ-Stressed ARPE-19 Cells:

- ARPE-19 cells were pre-treated with bevemipretide (1 or 5 µM) for 24 hours.
- Hydroquinone (HQ; 200 µM) was added for the last 30 min of culture to induce oxidative stress.
- Total cellular and mitochondrial ROS production were measured by flow cytometry.

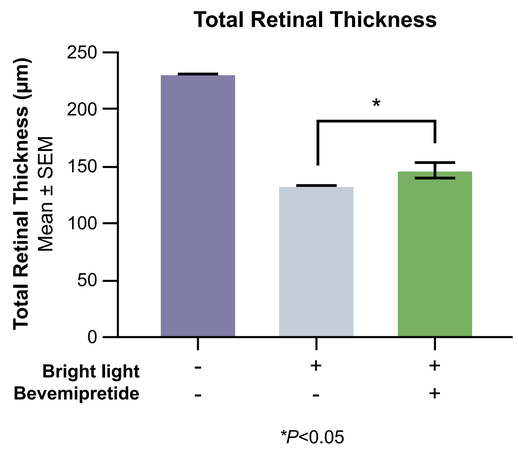
RESULTS:

Figure 2. Optimized Delivery of Topical Bevemipretide to Retinal Tissues with Low Systemic Exposure



- In both rabbits and minipigs, bevemipretide eyedrops were well-tolerated and demonstrated desirable ocular posterior segment and systemic exposure profiles with optimized delivery to the retina and low plasma concentrations (**Figure 2**).

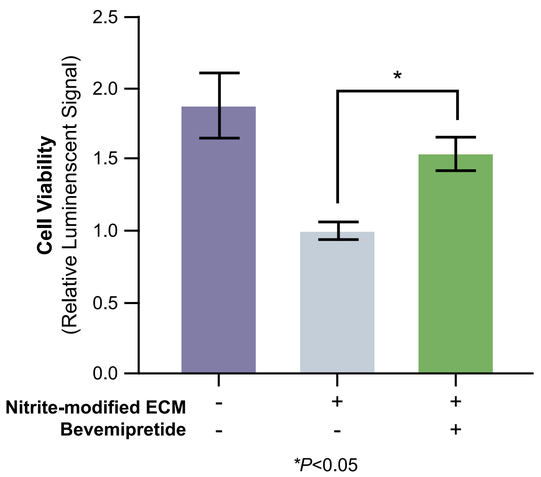
Figure 3. Topical Bevemipretide Partially Preserves Total Retinal Thickness in Rats Following Bright Light-Induced Retinal Degeneration



*P<0.05

- Exposure to bright light significantly reduced total retinal thickness in rats, an effect that was partially mitigated by treatment with topical bevemipretide (**Figure 3**).

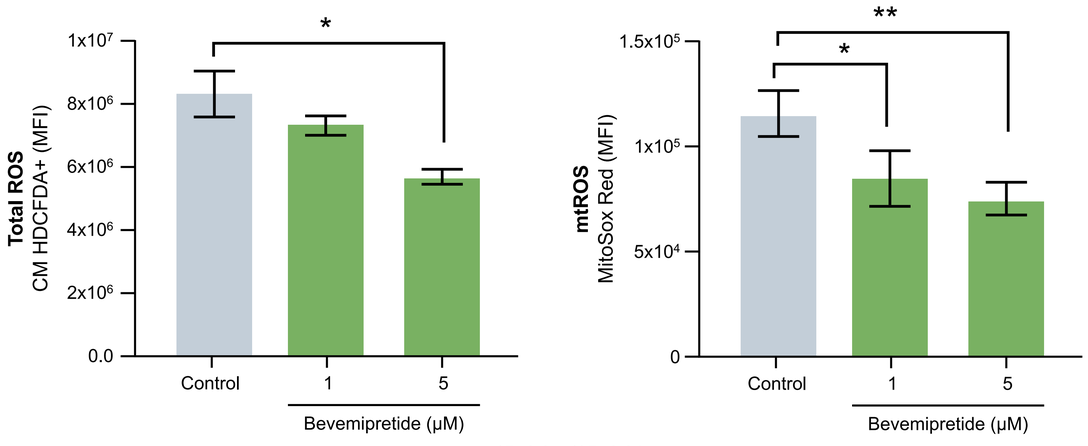
Figure 4. Bevemipretide Improved Viability of AMD Patient-Derived RPE Cells in an Aged Bruch's Membrane Model



*P<0.05

- Treatment with bevemipretide significantly improved viability of patient-derived RPE cells cultured on a nitrite-modified extracellular matrix, a typical modification of an aged Bruch's membrane that reduces RPE cell survival (**Figure 4**).

Figure 5. Bevemipretide Reduced ROS Production by RPE Cells in a Cellular Model of Cigarette Smoke-Induced Oxidative Stress



*P<0.05, **P<0.01

- Bevemipretide significantly reduced total cellular and mitochondrial ROS production by ARPE-19 cells treated with hydroquinone, a model used to mimic cigarette smoke-induced oxidative stress in AMD (**Figure 5**).

CONCLUSIONS:

- Topical bevemipretide is a next-generation mitochondrial therapy developed to enhance drug penetration of the blood-brain/blood-retinal barriers.
- In rabbits and minipigs, topical bevemipretide demonstrated desirable ocular posterior segment and systemic PK profiles with optimized delivery to the retina.
- Topical bevemipretide partially preserved retinal thickness in rats following bright light-induced retinal damage.
- Bevemipretide improved cell viability and alleviated oxidative stress in cellular models of AMD.
- The optimized PK profile and protective effects observed in models of AMD support further development of topical bevemipretide as a disease-modifying therapy.

References:

1. Terluk, et al. *J Neurosci.* 2015;35(18):7304-11.
2. Gautam, et al. *Neurobiol Dis.* 2023;178:106022.

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