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Activation of the Melanocortin System Increases Aqueous Outflow, Reduces Intraocular Pressure (IOP), and Protects Neurons in Glaucoma Models

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Purpose

- Glaucoma is a leading cause of irreversible blindness, characterized by degeneration of retinal ganglia cells (RGCs)[1,2]
  - New approaches, particularly those that protect RGCs, could provide substantial benefit towards addressing unmet clinical needs[2]
- The melanocortin system (MS) has been shown to be efficacious in a range of ocular diseases,[3] reestablishing tissue homeostasis and resolving inflammation[4]
  - In contrast to current therapies that work by modulating the inflammatory response, MCR agonists simultaneously reduce tissue stress signaling and the stress response, initiating the cellular resolution phase[5]
  - Stimulating the MS can protect the retina from inflammation and ischemia/reperfusion (I/R)[6,7]
- PL9588 is a melanocortin receptor ligand that is being investigated as a potential treatment option for glaucoma
  - Recent studies of PL9588 in normotensive rabbits have shown that it can reduce intraocular pressure (IOP)[8]
- This study aimed to investigate PL9588 therapy through a series of experiments to determine whether augmenting the MS provides neuroprotection while simultaneously lowering IOP

Methods

In vitro fluid outflow study

- A disease state was induced with transforming growth factor beta 2 (TGFβ2, 5 ng/mL) treatment for 6 days using a proprietary human donor trabecular meshwork (TM)/Schlemm canal scaffold (n=3)
  - This is a reproducible model for pressure build-up in the human eye[9]
- Scaffolds were treated with PL9588 (0.2 nM, 20 nM, 1 μM) or positive control rho kinase (ROCK) inhibitor (Y27632; 10 μM) and outflow was measured

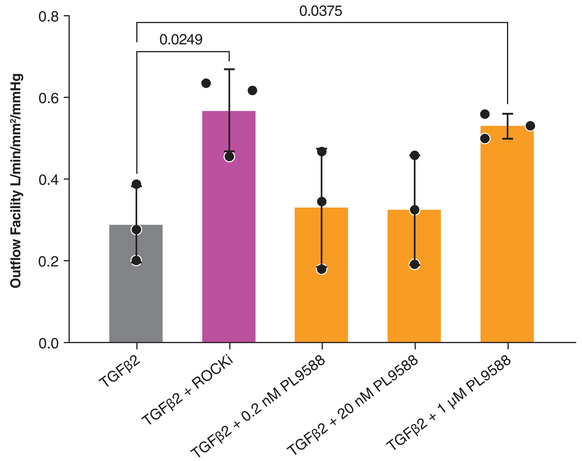
Neurodegeneration studies

- A rat ocular hypertension (OHT) model was used to measure retinal cell stress/death
  - Animals were dosed twice daily with topical PL9588 (0.1 mg/mL) or positive control (nerve growth factor [NGF]; n=6/group)
  - Detection of Apoptosing Retinal Cells (DARC) imaging of retinal cells undergoing stress or apoptosis was carried out after 3 weeks
  - IOP was measured 1 day after episcleral injection and every 7 days up to 21 days
- An I/R mouse model measured the efficacy of PL9588 for retinal neuroprotection compared with untreated mice or active α-MSH control
  - Ischemia was induced for 60 minutes by hydrostatic increase in IOP (90 mmHg)
  - Following I/R, vehicle, α-MSH (1 μg/mL), or PL9588 (1 μg/mL) (n=12/group) was applied through anterior chamber injection on Day 1 and Day 5; eyes were collected on Day 7
  - Retinal sections were stained with H&E for histology scoring, cell nuclei of the RGC layer were stained with Brn3a, and viable RGCs were measured by Tuj-1 staining

Results

- Measurements of human TM/scaffolds treated with TGFβ2 to induce a disease state showed significantly increased fluid movement with PL9588 (1 μM) on par with the positive control ROCK inhibitor (both $P<0.05$) (**Figure 1**).

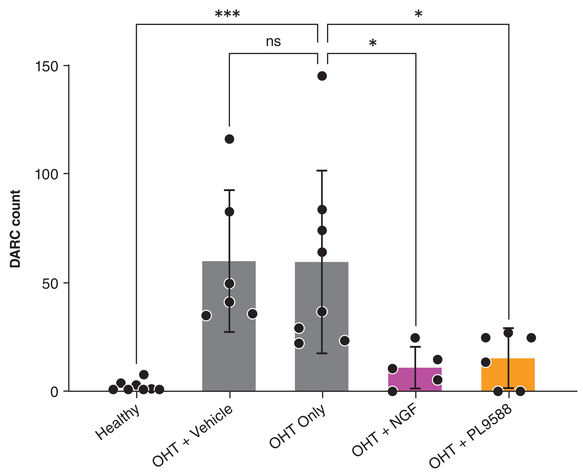
Figure 1. PL9588 increases fluid outflow in human TM/scaffolds



ROCKi, rho kinase inhibitor; TGFβ2, transforming growth factor beta 2.
Each dot represents 1 human donor.

- As shown by DARC counts, PL9588 in the rat OHT model reduced retinal cell stress/death by ≈25% ($P<0.05$) in retinas with increased IOP damage, similar to a positive control (NGF) (**Figure 2**)

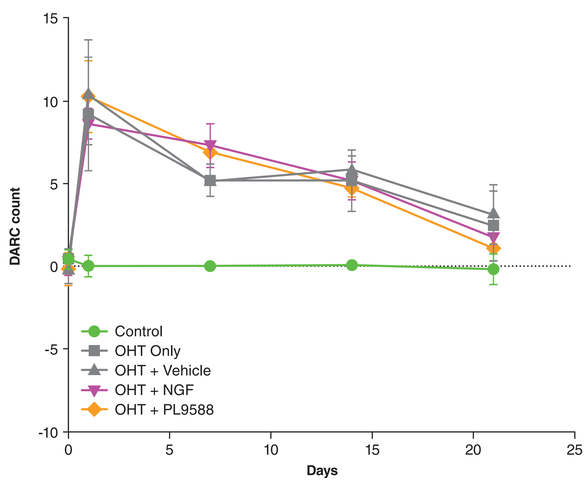
Figure 2. PL9588 protects from retinal cell stress/death induced by increased pressure



DARC, Detection of Apoptosing Retinal Cells; NGF; nerve growth factor; OHT, ocular hypertension.
Each dot represents an individual animal.
*$P\leq0.05$; ***$P\leq0.001$; ns, not significant.

- PL9588 did not reduce IOP levels (**Figure 3**)
  - The OHT model mimics elevated episcleral venous pressure (EVP) in humans; treatment of this condition typically includes reducing aqueous production, increasing outflow through the uveoscleral pathway, or both
  - That PL9588 did not reduce IOP in the OHT model is consistent with activity only in increasing TM outflow

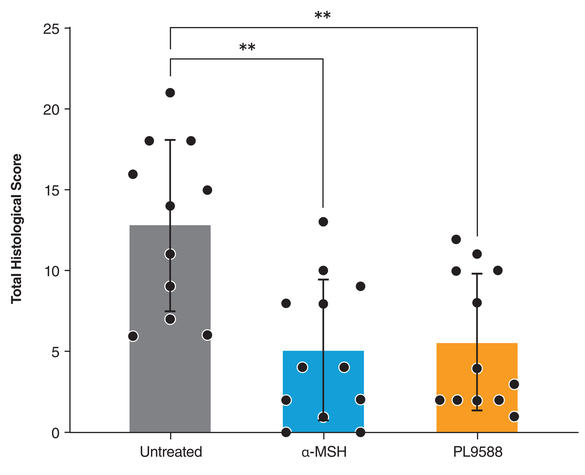
Figure 3. PL9588 does not lower IOP in the OHT rat model



IOP, intraocular pressure; NGF; nerve growth factor; OHT, ocular hypertension.

- Mouse retinas damaged by I/R were scored by histological measurements and showed PL9588 reduced damage similar to α-MSH (**Figure 4**)

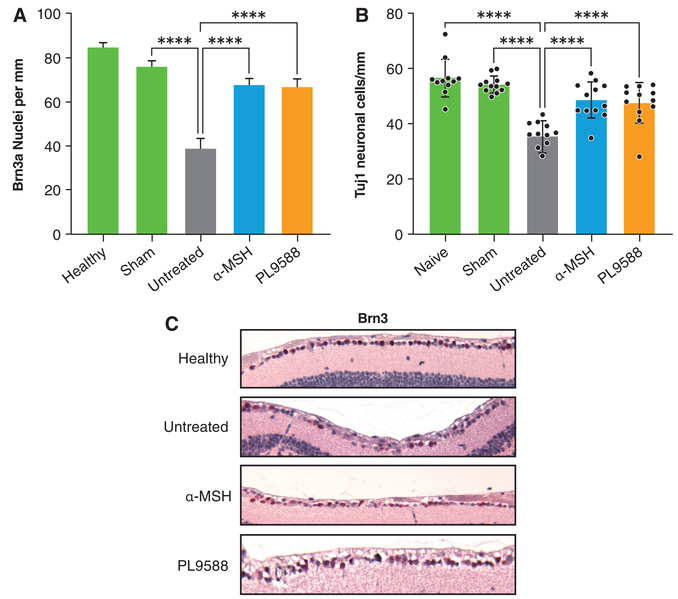
Figure 4. PL9588 Protects the Retina in I/R Mouse Eyes



α-MSH, alpha-melanocyte stimulating hormone.
Each dot represents an individual animal.
**$P\leq0.01$

- Viable RGCs (Tuj-1–positive) were significantly maintained in mouse I/R retinas treated with PL9588 (**Figure 5**)
  - These results are similar to α-MSH treatment, indicating PL9588 protects RGCs from death following I/R ($P<0.0001$)

Figure 5. PL9588 Protects RGC Viability in the I/R Mouse Eye



α-MSH, alpha-melanocyte stimulating hormone.
Each dot represents an individual animal.
****$P\leq0.001$

Conclusions

- The results demonstrate that the effects of PL9588, a novel melanocortin agonist, on IOP are through changes in the aqueous fluid outflow through the TM
- PL9588 provides retinal cell protection independent of IOP lowering
- PL9588 reduces RGC death induced by I/R (a model of acute elevated IOP)
- These results, combined with a defined mechanism of action, support the continued development of PL9588 as a novel approach to treating glaucoma

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Disclosures Alison Obr, John Dodd, Carl Spana, and Paul Kayne are employees of Palatin Technologies. Tat Fong Ng has nothing to declare. Andrew W. Taylor received SRA and consulting fees from Palatin Technologies.

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