Docket #: S21-382

Potential First-In-Class Neuroprotective Agents and Therapeutic Target for Treatment of Glaucoma; Optic Neuropathies

The Hu Lab at Stanford has identified several FDA-approved small molecule medicines with neuroprotective effects on glaucoma. High-throughput screening identified a group of drugs with similar structures and that have potent inhibitory effect on neuronal endoplasmic reticulum (ER) stress. The drugs blocked not only ER stress-induced ATF4 and CHOP expression, but also suppressed all three unfolded protein response pathways and significantly protected retinal ganglion cells, optic nerve, and visual functions in disease models of glaucoma and traumatic optic nerve injury. The drugs provided neuroprotective effects by inhibiting a common receptor. Genetic blocking of this receptor was also shown to provide similar neuroprotection effects. The researchers previously demonstrated the crucial role of neuronal ER stress in glaucomatous neurodegeneration and showed that modulating downstream signaling pathways provides significant neuroprotection in glaucoma animal models.

Related Technologies
Stanford docket S21-363 describes neuroprotective gene therapy developed by the Hu team for treating glaucoma and other optic neuropathies/optic nerve axonopathies.

See Stanford docket S19-014 for more on the Hu team's foundational work on neuronal ER stress and AAV-mediated gene therapy strategy.

Stanford docket S19-013 describes glaucoma animal models based on silicone oil-induced mild/chronic and severe/acute reversible ocular hypertension.

Stage of Development
The team is testing different formulation and delivery strategies to the eyes for

glaucoma treatment.

Applications

- This series of FDA approved medicines can be readily repurposed to treat neurodegenerative diseases, especially glaucoma, with local administration.
- Relevant optic neuropathies include retinal ganglion cell degeneration, optic neuritis, optic traumatic injury and other optic nerve-related diseases.

Advantages

- Currently there are no neuroprotectants available for glaucoma, the leading cause of irreversible blindness.
- A common receptor target – inhibiting this receptor with small molecule antagonists or gene therapy is a promising neuroprotection strategy.
- Potential first-in-class neuroprotectant.

Publications

- Chen, W., Liu, P., Liu, D. et al. Maprotiline restores ER homeostasis and rescues neurodegeneration via Histamine Receptor H1 inhibition in retinal ganglion cells. *Nat Commun* 13, 6796 (2022).

Patents

- Published Application: WO2023102350
- Published Application: 20250295610

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