Combinatorial Therapeutic Strategy of Stem Cell Retinal Organoids and Neurotropic Factor for Glaucoma

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Purpose**:** Glaucoma is a group of optic neuropathies characterized by retinal ganglion cell (RGC) death and visual field loss. A degenerative mechanism associated with RGC death is disrupted delivery of neurotropic factors due to glaucomatous axonal damage. This transport is critical for protection of long-term neuronal function. Thus, we investigate a potential therapeutic target, human Neuritin 1 (*NRN1*), which has demonstrated neuroprotective effects in rodent axonal injury models. Further, the advent of induced pluripotent stem cell (iPSC) technology allows iPSC-RGCs to be generated *in-vitro* from commercial iPSCs and reprogrammed corneal fibroblasts. We hypothesize delivery of *NRN1* and transplantation of iPSC-RGCs will sustain survival of RGCs and ultimately slow progression of glaucoma-induced neuronal death in our ocular translaminar autonomous system (TAS) perfusion model system. This will allow us to analyze a potential therapeutic approach for both early-stage glaucoma (*NRN1* therapy) to protect dying RGCs, and late-stage (iPSC-RGCs), when most RGCs are lost.

Methods: Human donor eyes were obtained from eye banks according to Declaration of Helsinki. The iPSC-RGCs transfected with AAV2-GFP were seeded into human posterior cups with NRN1 and cultured in TAS model under pressurized conditions for 2 days. Survival of iPSC-RGCs, gliotic and fibrotic pathways were measured through expression by qRT-PCR and immunohistochemistry. Retinal function post-treatment was measured through electroretinogram analysis.

Results: We successfully maintained the human posterior eye cups in translaminar differentials for 2 days. In contrast to controls, we observed increased RGC survival and retinal function after combination therapy of NRN1 and iPSC-RGC. Additionally, we found differential gene expression of apoptosis, inflammation, and gliotic markers.

Conclusion: Our study identified that *NRN1* in conjunction with iPSC-RGC transplantation treatment promotes RGC survival under glaucomatous conditions. This suggests that *NRN1* and iPSC-RGCs could be utilized as a potential combination therapy to save retinal neurons and prevent neurodegeneration in glaucoma patients.