

Viability of Transplanted de Novo Retinal Ganglion Cells in Human Donor Eyes Maintained Under Elevated Intraocular Pressure

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Purpose: Glaucoma is a group of optic neuropathies characterized by visual field loss, classically due to increased intraocular pressure (IOP) and retinal ganglion cell (RGC) degeneration. Current treatment options reduce IOP, but existing RGC degeneration is irreversible. RGCs can be differentiated from reprogrammed human corneal fibroblasts and transplanted into the retina to potentially restore vision in patients with late-stage disease when most RGCs are irreversibly damaged. We investigate the survival of these human induced pluripotent stem cell (iPSC) derived RGCs after culturing them in human donor posterior eye cups under conditions of elevated and normal IOP using the ocular translaminal autonomous system (TAS) pressurization chamber.

Methods: Human iPSCs were generated by reprogramming human donor corneal fibroblasts using Sendai virus vectors with Yamanaka

factors. These iPSCs were then differentiated into retinal organoids from which RGCs were obtained. The RGCs were then transduced with AAV2-GFP and transplanted into donor posterior eye cups obtained from control individuals. They were pressurized for approximately 5 days, with the left eye maintained at normal IOP and right eye at elevated IOP. Viability was measured by expression levels of pro-survival pathways via qRT-PCR, fluorescent microscopy, and electroretinography for retinal function (ERG).

Results: We successfully transplanted human RGCs into human donor eyes and visualized them after GFP transduction. We maintained a pressure differential between the two eyes for approximately 5 days using the TAS model. Differential expressions of survival, inflammatory and apoptotic genes were identified between normal and high IOP. We identified retinal function changes under normal and high IOP after iPSC derived RGC transplantation.

Conclusions: Human iPSC derived RGCs provide a potential strategy to regenerate vision in patients with diseases that damage RGCs like glaucoma, Parkinson's, Alzheimer's, multiple sclerosis, and traumatic optic neuropathy. Future work involves directing the transplanted RGC axons toward visual centers of the brain.

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Biggest takeaway: Thanks to my colleagues in Dr. Sharma's lab I learned a tremendous amount about glaucoma, induced pluripotent stem cells (iPSCs), and scientific communication. This was my first experience doing cell culture, so learning how to take care of stem cells and differentiate them into retinal ganglion cells for transplantation into donor eyes was very interesting and challenging. The most special part of my summer was working with human cadaveric donor eyes and pressurizing them to simulate glaucoma to measure the survival of our transplanted iPSCs. I am now preparing my project for publication.

