Most glaucoma specialists spend their days focused on controlling IOP. The fundamental problem in glaucoma, however, is that retinal ganglion cells (RGCs) and the optic nerve degenerate and fail to regenerate after optic nerve injury. Although, undoubtedly, one of the unmet needs in glaucoma is improved pharmacologic and surgical approaches to IOP lowering, we also need better treatments beyond IOP control. As we look to the future of glaucoma care, the development of one or more therapeutic interventions that addresses RGCs and optic nerve axons will be key.

Such interventions can be grouped into three types of efforts: neuroprotection, regeneration, and neuroenhancement. Neuroprotection refers to the ability to keep the RGCs alive and functioning in order to prevent degeneration. Regeneration is the ability to heal injured RGC axons so that they can reenter the brain and navigate back to the appropriate targets, or potentially to replace RGCs that have died using stem cell therapy. Neuroenhancement refers to the ability to intervene and enhance the function of RGCs that are sick but not yet dead.

GLAUCOMA PATHOPHYSIOLOGY

Insults and pathophysiologicals occur early in the glaucomatous disease process. At some point, the RGC axon is physically damaged and then later the cell body dies. This window between damage and death is crucial for intervention. But several questions remain, including where is the pathophysiology? and where should we intervene? Some factors, such as vascular insufficiency and obstruction of axoplasmic flow, have long been studied. However, until we show that intervening in one of these factors prevents degenerative disease in humans, we have not yet nailed the pathophysiology of glaucoma. These remain (strong) hypotheses.

Great progress has been made in identifying candidate therapies that warrant further investigation and testing. Looking at factors that target RGCs themselves, much attention has been given to neurotrophic signaling for survival and axon growth, particularly to ciliary neurotrophic factor (CNTF) and brain derived neurotrophic factor (BDNF) and their receptors. To optimize signaling through such pathways, though, it turns out that when RGCs and other neurons in the central nervous system are stressed, they need to be electrically active and depolarized to maximally promote RGC survival and growth. Thus, it may be that combining multiple survival signals is important as well.

OLD PARADIGM, NEW PARADIGM

The old school of thought maintained that, because glaucoma is typically a slow disease, neuroprotection takes a long time to measure. But our field has arrived at a number of realizations that inform a new way of thinking about trial design and moving candidate therapies out of the lab and into clinical trials. With short-term studies for neuroenhancement, we want to think about improving the function of sick-but-not-dead RGCs. We also want to select rapidly progressing patients, cluster visual field testing to guard against variability, and incorporate new and exploratory biomarkers—ie, ways to measure the health of the retina and see whether the drug being tested has an effect.

INVESTIGATIONS UNDERWAY

CNTF. For me, the concepts of neuroprotection and regeneration started moving from the laboratory to the clinic when I began working...
with a CNTF implant for glaucoma (NT-501 ECT [Renexus], Neurotech). This implant is loaded with genetically engineered retinal pigment epithelium cells that express therapeutic doses of CNTF. It is implanted into the vitreous through a single incision and sutured in place in an outpatient procedure.

In the first trial I participated in—a single-center, investigator-initiated, open-label phase 1 trial—we treated 11 patients with glaucoma and 11 patients with nonarteritic anterior ischemic optic neuropathy. No serious adverse events occurred. Importantly, we observed structure-function correlations with hypertrophy of the retinal nerve fiber layer and changes in visual field testing that were consistent across many patients. However, these were not randomized, controlled trials; thus, limited conclusions could be drawn.

Neurotech is currently conducting multiple investigations of NT-501 ECT, including clinical trials in patients with glaucoma and patients with macular telangiectasia. Patients have been enrolled in three separate phase 2 studies in the United States, with some patients reaching more than 50 months post-implantation.

NGF. Another trial was designed to investigate a different peptide trophic factor called recombinant human nerve growth factor (rhNGF). A lower dose of rhNGF is approved in the United States as Oxervate (Dompé) for the treatment of neurotrophic keratitis. My coinvestigators and I at the Spencer Center for Vision Research at the Byers Eye Institute at Stanford tested a higher dose in a double-masked, placebo-controlled trial of 60 patients with glaucoma, who were randomly assigned to 8 weeks of therapy or placebo. The drug was very well tolerated. Safety and efficacy data for that trial will be presented soon.

C1q. In October, Annexon Biosciences announced the results of a phase 1b dose-ranging clinical trial to evaluate its anti-C1q antibody, ANX007, in patients with glaucoma. C1q is involved in stripping the synapses off of RGCs and killing them in glaucoma, and it is strongly associated in other neurodegenerative diseases as well. Inhibition of C1q may provide neuroprotective benefit by preventing the aberrant loss of functioning synapses in the inner retina in a variety of optic neuropathies. In the phase 1b trial (n = 15), ANX007 was well tolerated and resulted in full target engagement and inhibition of C1q in the eye for at least 4 weeks after a single intravitreal treatment. These data are being analyzed for presentation and dissemination in early 2020.

VR. My research team is also conducting an open-label pilot study to evaluate the potential of virtual reality (VR) and visual stimulation. Specifically, we are using VR goggles to deliver RGC-specific stimuli in an attempt to address the observation noted above that activity enhances trophic factor responsiveness. Others are studying electrical stimulation with the same principle in mind.

**CONCLUSION**

As evidenced by this ongoing work, neuroprotection and neuroenhancement therapeutic candidates can be studied in patients with glaucoma. Future directions involve merging therapeutic testing with biomarker exploratory endpoints to cross-validate. If the promising results observed so far continue on this track, these interventions could, over the next few years, join IOP control as effective means to address glaucomatous damage.

**JEFFREY L. GOLDBERG, MD, PHD**

- Professor and Chair, Department of Ophthalmology, Byers Eye Institute at Stanford University, Palo Alto, California
- eye-chair@stanford.edu
- Financial disclosure: Clinical investigator (Annexon Biosciences, Dompé, Neurotech)