AMERICAN ACADEMY OF OPHTHALMOLOGY®

Editorial

Neuroprotection, Neuroenhancement, and Neuroregeneration of the Retina and Optic Nerve

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Neurodegenerative conditions that affect the retina and optic nerve cause irreversible vision loss in hundreds of millions of people worldwide. Therapeutic interventions to slow or halt disease progression exist for a subset of these conditions; however, clinical barriers limit the ability to preserve vision in patients with congenital and acquired optic neuropathies or retinal dystrophies and degeneration. The obstacles include late diagnosis, gaps in health care access, suboptimal treatment adherence, incomplete therapeutic responses to existing therapies, and lack of effective treatments for some pathologies. These issues, coupled with a lack of spontaneous repair mechanisms in the mature human central nervous system, have prompted extensive research aimed at identifying innovative approaches to maintain or restore functioning retinal neurons in the face of pathologic insults. Significant advances in the areas of developmental and cellular neuroscience, gene therapy, stem cell biology, pharmacology, and nanomedicine have converged to generate numerous promising therapies now in the clinical pipeline.

Three primary approaches to preserve or restore visual function in patients with retinal and optic nerve diseases are of particular interest. *Neuroprotection* targets cell-intrinsic and non-cell autonomous signaling pathways or extrinsic microenvironmental stressors to circumvent neuronal apoptosis and preserve functioning neural tissue. *Neuroenhancement* seeks to rescue dysfunctional neurons from a quiescent, impaired, or inactive state to augment visual function. Critically, these 2 strategies require that existing retinal neurons remain viable and are, therefore, most applicable to early and moderate stages of diseases. *Neuroregeneration* aims to promote the repair of neuronal compartments (e.g., retinal ganglion cell [RGC] dendrite sprouting within the inner plexiform layer, RGC axonal regeneration within the optic nerve, or photoreceptor outer segment restoration), completely replace dead neurons through de novo cellular repopulation (e.g., neuronal transplantation or transdifferentiation), or technologically bypass endogenous signaling pathways (e.g., optoelectronic stimulation of the retina or visual cortex or optogenetic RGC or bipolar cell transduction) and may be applicable even in end-stage diseases. These complementary and overlapping approaches have garnered enthusiasm for their potential ways to preserve or restore vision in patients with historically incurable blinding diseases.

RGC and photoreceptor death is induced by multiple pathways and noxious stimuli. Despite the availability of treatments to mitigate some of the most prevalent disease-driving processes, including intraocular pressure reduction in patients with glaucoma or anti-VEGF therapy in patients with neovascular age-related macular degeneration, many patients experience continued neuronal death and vision loss even during seemingly adequate treatment. Further, there is a lack of interventions proven to alter the clinical trajectory of less prevalent conditions.

Rigorous investigation of molecular and cellular pathways that are altered in preclinical disease models and postmortem tissues from patients with retinal disease or optic neuropathy has identified new targets for intervention. For instance, RGC caspase-mediated apoptosis in traumatic optic neuropathy and ocular hypertension is driven by cell-intrinsic signaling through pathways that involve dual leucine zipper kinase, mitogen-activated protein kinase kinase 4 and 7, c-Jun N-terminal kinase 1 to 3, c-Jun, and B-cell lymphoma 2 family proteins.[1–4] Transgenic, viral, and, critically, pharmacologic modulation of these pathway components has been shown to dramatically increase RGC survival in numerous disease models.[5–7] Protection from neurotoxic reactive gliosis, oxidative stress, and neurotrophic factor deprivation has also demonstrated neuroprotection in preclinical models of retinal and optic nerve neurodegeneration.[8–10] Recently, single-cell transcriptomic analyses of degenerating RGCs identified not only subtypes that are especially susceptible or resistant to injury but also key molecular regulators of susceptibility and repair that may represent new targets for neuroprotection.[11–14]

Indeed, this review of preclinical literature from the past 20 years highlights a dizzying array of molecules, pathways, and therapeutic approaches that protect RGCs and photoreceptors in animal models. Why have none of these emerged as viable treatments for patients? The factors that have limited clinical translation include the use of animal models that incompletely recapitulate key features of human diseases (including species lacking a macula or collagenous lamina cribrosa), species differences in molecular and cellular signals that drive neurodegeneration, differential pharmacodynamics and pharmacokinetics between animal models and humans, redundancy within signaling pathways, and challenges in identifying druggable targets. Therefore, therapeutic approaches that demonstrate efficacy across a

https://doi.org/10.1016/j.xops.2022.100216
ISSN 2666-9145/22

range of disease models and species are, therefore, likely to be the most promising candidates for clinical translation.

Some neuroprotective strategies have reached the stage of human clinical trials. For example, memantine is a noncompetitive N-methyl-D-aspartate receptor antagonist that has been approved for the treatment of Alzheimer and Parkinson disease; it was hypothesized to reduce excitotoxic injury to RGCs in patients with glaucoma. It was studied in 2 large, phase III, randomized controlled clinical trials involving almost 2300 patients with open-angle glaucoma and unfortunately failed to meet clinical perimetric or structural end points.[15] Although disappointing, the results of these trials generated important insights related to study design for neuroprotection treatment trials of slowly progressing diseases. For instance, temporal clustering of structural and functional testing modalities and the use of trend-based, rather than event-based, outcomes may have greater sensitivity for detecting neuroprotective treatment effects, requiring smaller sample sizes and shorter observation periods.[16–18] Further, continuously advancing diagnostic technologies, including swept-source OCT, OCT angiography, and direct visualization of apoptotic neurons,[19] afford increasingly precise measures of relatively small degrees of neurodegenerative worsening. Therefore, substantial optimism surrounds the numerous neuroprotection treatment trials currently in progress.

Although the definitive demonstration of neuroprotection requires long-term studies that establish the persistence of neural structure, neuroenhancement may produce observable benefits over much shorter periods of time. Many of the strategies to confer neuroenhancement may also be neuroprotective on longer time horizons. Thus, these approaches are closely related, and it would be of interest to assess whether they have additive or synergistic effects when used in combination.

Studies of nicotinamide adenine dinucleotide (NAD) serve as an example of how rigorous preclinical investigation might lead to disease-modifying treatments for patients. Experiments in animal models of optic neuropathy have established that impaired energy metabolism and mitochondrial dysfunction undermine normal neurophysiologic function and precede overt RGC death.[20] Nicotinamide adenine dinucleotide hydrogen, generated from NAD^+ by the citric acid cycle, is a key substrate for adenosine triphosphate synthesis by the mitochondrial electron transport chain, and retinal NAD levels are reduced in rodent models of optic neuropathy.[20] Circumstantially, the plasma NAD levels are reduced in patients with glaucoma compared with those in healthy controls, and epidemiologic evidence has suggested that diets high in niacin are associated with reduced prevalence of glaucoma.[21,22] High-dose dietary supplementation of nicotinamide reduces RGC soma loss, dendrite pruning, axonal degeneration, and electrophysiological defects across multiple models of RGC damage in both mice and rats.[20,23–25] These findings have prompted small clinical trials of nicotinamide supplementation in patients with open-angle glaucoma, demonstrating modest but detectable improvements in the RGC-specific electroretinographic photopic negative response and automated perimetry in as little as 6 to 10 weeks.[26,27] Although still preliminary, these findings suggest potential avenues for improving visual function in patients with glaucoma using currently available nutritional supplements and support the rationale for ongoing studies of longer-term neuroprotection by nicotinamide supplementation.

Structural alterations to neurons require regenerative approaches to restore function. Before overt cell death, pathological changes in subcellular neuronal compartments typify many neurodegenerative processes. For example, afferent synapse loss and degeneration of dendritic arbors occur early in experimental models of glaucoma.[28–30] Interventions that reverse such early changes may restore circuit function. Insulin signaling and the complement cascade, for example, have been successfully modulated to preserve dendritic arbor structure and synapses in animal models of optic neuropathy.[31–33] Metabolic regulation plays a major role in the maintenance and, possibly, regeneration of photoreceptor outer segments.[34] Tremendous advances in optic nerve regeneration have identified numerous cell-intrinsic and microenvironmental regulators of both cell death and axonal regeneration from injured RGCs.[35–40] Combinatorial targeting of these pathways has, in some instances, resulted in long-distance axonal regrowth to subcortical visual centers in the brain.[41,42]

Once retinal neurons are lost, cellular repopulation or functional repurposing (e.g., optogenetics) are necessary to restore vision. Repopulation might be achieved through at least 2 potential approaches. Cell transplantation involves the introduction of new cells, typically differentiated from pluripotent stem cell sources, into the eye. Ophthalmology has led the field of regenerative medicine with pioneering clinical trials involving transplantation of the retinal pigmented epithelium into the subretinal space for the treatment of macular dystrophies and age-related macular degeneration.[43,44] After preclinical experimentation began $>$ 15 years ago,[45,46] photoreceptor transplantation is now being evaluated in humans. Although RGC transplantation lags behind, because of the complex cytoarchitecture and spatially intimidating neural connectivity that must be attained,[47] it is conceivable that even RGC replacement may one day be achieved.[48–50]

Transdifferentiation involves induced reversion of endogenous retinal cells into a progenitor state, which may then proliferate and differentiate into retinal neurons. Varying degrees of spontaneous retinal regeneration in amphibians, teleost fish, and young avians have prompted investigations into why this capacity is lost in mammals. The responses of Müller glia to injury and how transcriptional regulation in these cells might be altered to drive neuronal repopulation in neurodegenerative retinal disease have become a focus of attention. Cross-species comparisons have identified several key regulators of Müller cell transdifferentiation, including Ascl1 and the nuclear factor 1 family of transcription factors.[51,52] Provocatively, the ectopic expression of these genes in mammalian Müller

glia allows them to adopt a progenitor fate after injury and even produce inner retinal neurons, some reminiscent of RGCs.[53–55] The production of photoreceptors through this mechanism is promising but is yet to be achieved.

Several key challenges to the implementation of neuroregeneration for vision restoration exist. Some are experimental, including the phenomenon of intercellular material transfer, which potentially confounds the definitive identification of newborn or transplanted neurons.[56,57] Indeed, in early quantifications of photoreceptor engraftment after subretinal transplantation, artifactual inflation was reported because cytoplasmic labels from donor cells were efficiently transferred to endogenous host neurons.[58–61] Rigorous methods to firmly establish bona fide neuronal repopulation are, therefore, critical in the face of the numerous biological challenges to achieve neuroregeneration. Long-term survival of transplanted neurons is a major problem but highlights a key area in which neuroprotective strategies might be leveraged to ensure the success of regenerative strategies. Immune tolerance, spatial patterning, and wiring into established neurocircuitries also represent important areas of further research.

Complete bypass of diseased portions of the visual pathway is an alternative strategy of restoring vision in patients. Optogenetic technology recently restored rudimentary levels of vision in a patient with blindness.[62] Advances in inner retinal and visual cortex stimulation using implantable microelectrode prostheses also hold considerable promise.[63–66]

Ophthalmology Science is pleased to announce its latest virtual special issue "Neuroprotection, Neuroenhancement, and Neuroregeneration," which we hope will propel these fields forward by highlighting advances in preclinical research and early-stage clinical trials geared toward preserving and restoring vision in patients with neurodegenerative diseases of the visual pathway. In this special issue, we are particularly interested in rigorous preclinical research that identifies mechanistically novel targets or approaches for augmenting neuronal survival and function or replacement, and large-animal models are of particular interest. We also seek well-designed, early-stage (phases I and II) clinical trials that evaluate neuroprotection or neuroenhancement in patients with retinal neurodegeneration or optic neuropathy. Open access fees will be waived for this special issue; the deadline for first-round submissions is June 30, 2023.

As clinicians, we are all too familiar with the devastating impact that irreversible blindness has on patients with neurodegenerative diseases of the retina and optic nerve as well as their families. The clinical translation of new therapies capable of better preserving vision or even reversing blindness in such patients would be nothing short of revolutionary for our field. As vision science researchers, we are poised to make key discoveries that will transform the landscape of ophthalmology and potentially even impact the treatment of neurodegenerative diseases outside of the eye. We are thrilled to have the opportunity to engage with the vision science community through this special issue and look forward to the exciting work that is forthcoming.

Footnotes and Disclosures

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors have made the following disclosures:

T.V.J.: Grant – National Eye Institute (K08EY031801, P30EY001765), Research to Prevent Blindness (Career Development Award and unrestricted funding to Wilmer Eye Institute), The Zenkel Family Foundation, the Allan and Shelly Holt Rising Professorship in Ophthalmology; Research support – Perfuse Therapeutics, Alcon, InjectSense, iCare USA; Consultant – AbbVie.

A.D.P.: Grant – National Eye Institute (R01EY030838), Canadian Institutes of Health Research, Department of Defense USA, The Glaucoma Foundation; Chair – Canada Research Chair in Glaucoma, Age-related Neurodegeneration (Tier 1); Research support – Quark Pharmaceuticals, Servier, Unity Biotechnology, Santen Pharmaceuticals; Consultant – Quark Pharmaceuticals, Servier, Unity Biotechnology, Santen Pharmaceuticals.

J.A.S.: Grant – Laboratoire d'Excellence (LabEx) LIFESENSES (ANR-10-LABX-0065),University-Hospital Institute FOReSIGHT (ANR-18-IAHU-0001), The Edward N. & Della L. Thome Memorial Foundation Awards Program in Age-Related Macular Degeneration Research, United States Department of Defense (W81XWH-22-9-0011 & 2019-447-005), NIH National Institutes of HealthCORE Grant (P30EY08098), RPB Research to Prevent Blindness (Unrestricted Grant), European Research Council Synergy Helmholtz Grant (#610110); Consultant – Pixium Vision, GenSight Biologics, SparingVision, Tilak Healthcare, Bluebird, SpliceBio; Stock/stock options – Pixium Vision, GenSight Biologics, Sparing Vision, Prophesee, Chronolife, Tilak Healthcare, VegaVect, Inc., Avista, Tenpoint, SharpEye.

J.S.S.: Grant – National Eye Institute (R01-EY013178, U01-EY033001), BrightFocus Foundation, Research to Prevent Blindness; Consultant/advisor – Aerie Pharmaceuticals, Boehringer Ingelheim, Carl Zeiss Meditec, Ocugenix, Ocular Therapeutix, Opticient Health, Perfuse Therapeutics, Regeneron Pharmaceuticals; Stock/stock options – Aerie Pharmaceuticals, Ocugenix, Ocular Therapeutix, Opticient Health; Intellectual property – New York University, Tufts University, University of Pittsburgh.

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