frontiers in Ophthalmology

OPINION
published: 15 March 2022
doi: 10.3389/fopht.2022.848710

Non-Arteritic Anterior Ischemic Optic Neuropathy: Challenges for the Future

Alison Gibbons[1] *and Amanda D. Henderson*[1,2*]

[1] *Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, United States,* [2] *Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Keywords: non-arteritic anterior ischemic optic neuropathy (NAION), neuroprotection, neuroregeneration, retinal ganglion cell (RGC), neuroinflammation

OPEN ACCESS

Edited by:
Andrew Lee,
Houston Methodist Hospital, United States

Reviewed by:
Rod Foroozan,
Baylor College of Medicine, United States
Nagham Al-Zubidi,
University of Texas MD Anderson Cancer Center, United States

****Correspondence:***
Amanda D. Henderson
ahende24@jhmi.edu

Specialty section:
This article was submitted to Neuro-Ophthalmology Disorders, a section of the journal Frontiers in Ophthalmology

Received: *05 January 2022*
Accepted: *23 February 2022*
Published: *15 March 2022*

Citation:
Gibbons A and Henderson AD (2022) Non-Arteritic Anterior Ischemic Optic Neuropathy: Challenges for the Future. Front. Ophthalmol. 2:848710. doi: 10.3389/fopht.2022.848710

INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute unilateral optic nerve (ON)-related cause of vision loss in people over age 50 (1, 2). However, despite the frequency with which this condition occurs, there is no treatment proven to improve vision in patients affected by NAION. Patient evaluation initially focuses on the exclusion of mimickers, specifically arteritic anterior ischemic optic neuropathy secondary to giant cell arteritis, as well as optic neuritis in atypical cases. After confirmation of the NAION diagnosis, the focus shifts to the identification of modifiable risk factors, including hypertension, diabetes, hyperlipidemia (3), obstructive sleep apnea (4, 5), and phosphodiesterase-5 inhibitor use (6, 7). Optimizing treatment of modifiable risk factors may decrease the risk of developing a sequential NAION in the fellow eye.

The pathophysiology of NAION, while not fully elucidated, is thought to be secondary to decreased perfusion of the anterior ON from short posterior ciliary arteries, leading to the development of optic disc swelling and, eventually, a compartment syndrome (8). The cause of the decreased perfusion (eg, hypotension, microthrombosis, a combination of these, or something else entirely) has not been confirmed. Studies also suggest that the inflammatory response to the initial injury may play a role in the resultant neuronal damage and visual loss (9, 10). Therefore, various potential neuroprotective and neuroregenerative treatments for NAION have been (and continue to be) evaluated.

CLINICAL RESEARCH

Many potential agents and procedures have been clinically assessed in the treatment of NAION, but none have clearly shown benefit and there is no widely accepted treatment regimen.

Medical Treatments

In a small double-masked, placebo-controlled study, no improvement in visual function was demonstrated with phenytoin treatment (11).

Aspirin has not shown benefit for visual outcome in eyes affected by NAION (12). While data have been inconsistent for a role in risk reduction for second eye involvement (13–15), there is no convincing evidence that aspirin prevents future NAION (16). Aspirin may be appropriate for secondary prevention of cardiovascular events (17), but the role of aspirin in primary prevention of cardiovascular events, even in the setting of known vasculopathic risk factors (and/or a prior NAION), is less clear, and recent reports have shown an increase in major hemorrhage without any significant reduction in risk (18). Therefore, the routine use of aspirin in patients with NAION is not recommended.

Both retrospective and prospective studies have evaluated the use of brimonidine, hypothesized to have neuroprotective potential, in patients with NAION. Neither study demonstrated benefit (19, 20).

The use of oral steroids in NAION is controversial. Hayreh and Zimmerman reported on a cohort of 696 eyes with NAION, comparing those treated with oral steroids with those not treated. Notably, the patients themselves selected their treatment group, with no randomization, masking, or placebo control. Among eyes with initial visual acuity of 20/70 or worse, treated within two weeks of onset, visual acuity and kinetic visual fields (assessed subjectively) were more likely to improve in the steroid-treated group than in the group that received no treatment (21). However, other studies (including randomized controlled trials and a meta-analysis) have found no significant benefit from treatment with oral steroids but have shown an increased risk of steroid-related complications (22–25). Therefore, routine use of oral steroids for treatment of NAION is not recommended.

The use of erythropoietin (administered intravitreally or intravenously) to treat NAION also is controversial. One interventional case series reported visual improvement in 55% of eyes treated with intravitreal erythropoietin, with a trend toward initial improvement followed by a gradual decline in vision thereafter (26). There was no control group, but the authors argued that the rate of visual improvement was superior to the rate of 39.5% previously reported in the natural history of NAION (27). One prospective study evaluating treatment with intravenous erythropoietin showed no effect on visual outcomes (23), though another randomized trial with a shorter inclusion window (within five days of vision loss, rather than 14 days) reported that 55% of patients treated with erythropoietin (versus 34% treated with steroid and 31% receiving placebo) gained three or more Snellen lines at the six-month follow up when compared with baseline (28), raising the question of whether erythropoietin could be useful in patients who present soon after vision loss.

A recent randomized, controlled trial evaluating treatment with subcutaneous RPh201 (an extract of gum mastic with possible immunomodulatory and neuroprotective effects) in patients with chronic NAION also was disappointing.

Surgical/Procedural Treatments

The Ischemic Optic Neuropathy Decompression Trial reported that ON sheath fenestration was ineffective and might be harmful in NAION (27). Hyperbaric oxygen treatment has not shown convincing benefit in NAION (29). While intravitreal anti-vascular endothelial growth factor (VEGF) therapy, used widely for the treatment of ischemic conditions of the retina, initially was reported as a promising treatment for NAION (30), no benefit was demonstrated in a non-randomized controlled trial (31). Intravitreal administration of QPI-1007 (a small interference RNA designed to inhibit expression of caspase 2) (32) and G-CSF (33) also have not demonstrated benefit.

BASIC AND TRANSLATIONAL RESEARCH

While the lack of benefit demonstrated in recent clinical trials has been discouraging to patients and the physicians who treat them, progress is being made in the laboratory setting. Two models of NAION, a rodent and primate model (rNAION and pNAION, respectively), have been developed for research into the pathophysiology of the disease, as well as for preclinical treatment trials (34, 35). Both models use laser-induced reactive oxygen species to promote capillary vascular thrombosis without affecting larger vessels (10). The pathophysiology in rNAION and pNAION mirrors the clinical disorder in terms of optic disc edema, ON axon loss, isolated retinal ganglion cell (RGC) loss, and ON dysfunction (10). Further, similar to human NAION, rNAION expresses significant variability in its severity and expression across different subjects, despite consistency of the induction technique (36).

Neuroprotection

The development of the rNAION and pNAION models has facilitated the assessment of a number of potential neuroprotective interventions. Many of these interventions function by suppressing the inflammatory response following RGC injury. Prostaglandin J2 (PGJ_2), an anti-inflammatory prostaglandin synthesized following central nervous system ischemia, led to a reduction in clinical, electrophysiological, and histological damage when administered as a single intravitreal dose five hours after the induction of pNAION (37) and immediately after the induction of rNAION (38). Potentially synergistic combination therapies with PGJ_2 are being explored, though up to this point, none have demonstrated efficacy beyond that of PGJ_2 alone (39). Daily topical ocular delivery of trabodenoson, a selective adenosine A_1 agonist, was shown to reduce ON edema and preserve RGCs in rNAION, when compared with vehicle (40). Further, intravitreal injection of ciliary neurotrophic factor (CNTF) was shown to promote RGC survival when administered one day after rNAION induction (41). Recent work has also found E212, a Rho kinase (ROCK) inhibitor, to have a neuroprotective effect when injected intravitreally immediately following rNAION. E212 was shown to suppress neuroinflammation and oxidative stress, as demonstrated by increased superoxide dismutase activity and decreased reactive oxygen species formation, leading to RGC preservation when compared with vehicle-treated eyes (42). In addition to topical or intravitreal treatment, alternative drug delivery methods have also been

explored. Polyamidoamine dendrimer nanoparticles have been shown to selectively target ischemic ON lesions in both pNAION and rNAION, suggesting that nanoparticle-linked therapeutics may provide a targeted route for drug delivery directly to the affected tissue in the future (43).

Neuroregeneration

Published studies using NAION-specific animal models have primarily focused on neuroprotective interventions, with the goal of preventing RGC loss after injury. However, ON regeneration, with the goal of restoring vision following RGC death, is an alternative approach to the treatment of NAION and other optic neuropathies. In 2013, the National Eye Institute (NEI) Audacious Goals Initiative (AGI) in Regenerative Medicine established the goal "to restore vision through regeneration of neurons and neural connections in the eye and visual system", thus directing significant resources toward this aim (44). Replacement of RGCs holds strong potential for restoring vision loss due to optic neuropathy and has been studied primarily in reference to glaucoma. RGC transplantation to restore vision requires multiple complex steps, each with its own unique challenges, including establishing a source for the RGCs, delivering the RGCs, promoting their survival and correct localization within the retinal structure, forming dendritic connections within the retina and growing axons toward the ON and, ultimately, further posterior to synapse in the lateral geniculate nucleus in a retinotopic arrangement, and ensuring myelination of the axons (45). While a complete review of the research in this area is beyond the scope of this paper, we will briefly discuss some exciting research breakthroughs.

Human-derived RGCs have been produced from numerous lineages, thus allowing for further study of transplantation *in vivo* (45). Some studies have shown functional improvements following RGC transplantation, including light-evoked electrophysiological responses from donor RGCs (46) and documented improvements in visually guided behaviors in recipient animals (47). However, there are still many challenges, particularly with regard to low rates of RGC engraftment and survival following transplant (45). One substantial limitation to engraftment of RGCs from an intravitreal approach is the structural barrier of the internal limiting membrane (ILM) (48). However, recent work has shown that the use of proteolytic enzymes to disrupt of the ILM prior to transplant is associated with a profound increase in neurite ingrowth in the retina (49).

Additionally, recent work has demonstrated that both molecular signaling and the external application of electric fields can be used to direct the growth of RGC axons. One study showed that a combination of neural activation and elevation of the pro-cell growth pathway mammalian target of rapamycin (mTOR) led to RGC axons regenerating long distances and forming connections with their correct targets (50). Another group demonstrated that ectopic expression of the *Oct3*, *Sox2*, and *Klf4* genes (three of the Yamanaka factors that can trigger mature cells to revert to an immature state) in mouse RGCs restored youthful DNA methylation patterns, promoted axon regeneration after injury, and reversed vision loss in a mouse model of glaucoma (51). Additionally, the application of electric fields was shown to direct axon growth from RGCs toward the cathode (52). A combination of these approaches may be required to promote and direct long distance axonal growth (initially toward the ON in the retinal nerve fiber layer, then through the ON, optic chiasm, and optic tract, to ultimately synapse in the lateral geniculate nucleus, all while maintaining retinotopic organization) following transplantation of RGCs.

DISCUSSION

While recent clinical trials have not identified an effective NAION treatment, they have collected vast amounts of data from patients affected by NAION. Further analyses of these data likely will advance our understanding of the factors surrounding NAION and perhaps provide insight into the similarities (and differences) between NAION in humans and experimental NAION in the animal models with which we work, thus clarifying the ways in which we interpret our laboratory results.

Regarding potentially neuroprotective treatments in the setting recent NAION, one key remaining challenge is to identify treatments that are effective within a clinically relevant treatment window, as most patients affected by NAION present days to weeks after the onset of vision loss, rather than within hours. Therefore, a treatment for which clinical trial recruitment would be feasible, and that could be anticipated to provide benefit in clinical trials and beyond, would need to be effective within this longer time window, rather than only when administered before or immediately following the onset of NAION. It is possible, and perhaps probable, that this may require combination therapies to address different inflammatory mediators at different time points after the acute ON injury. Studies in this area are ongoing.

Regarding RGC transplantation and ON regeneration, while exciting progress is being made on the various aspects of this approach, much work remains to develop a process to make this treatment a reality for our patients. Significant progress has been made in this area since the establishment of the NEI's Audacious Goal. Collaboration between teams of vision scientists working on the different steps of this process will continue to be of utmost importance moving forward.

Both neuroprotective and neuroregenerative approaches hold promise to provide treatments for our patients with currently untreatable NAION, as well as other optic neuropathies. Until treatments become available, clinicians must continue to focus on risk factor identification and management in patients with NAION.

AUTHOR CONTRIBUTIONS

AH contributed to conception and design of the work. AG and AH contributed to the data acquisition. AG and AH each drafted initial sections of the paper. All authors contributed to manuscript revision and approved the submitted version.

REFERENCES

1. Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of Nonarteritic Anteripr Ischemic Optic Neuropathy. *Am J Ophthalmol* (1997) 123(1):103–7. doi: 10.1016/s0002-9394(14)70999-7
2. Johnson LN, Arnold AC. Incidence of Nonarteritic and Arteritic Anterior Ischemic Optic Neuropathy: Population-Based Study in the State of Missouri and Los Angeles County, California. *J Neuroophthalmol* (1994) 14(1):38–44. doi: 10.1097/00041327-199403000-00011
3. Liu B, Yu Y, Liu W, Deng T, Xiang D. Risk Factors for Non-Arteritic Anterior Ischemic Optic Neuropathy: A Large Scale Meta-Analysis. *Front Med (Lausanne)* (2021) 8:618353. doi: 10.3389/fmed.2021.618353
4. Sun MH, Lee CY, Liao YJ, Sun CC. Nonarteritic Anterior Ischaemic Optic Neuropathy and its Association With Obstructive Sleep Apnoea: A Health Insurance Database Study. *Acta Ophthalmol* (2019) 97(1):e64–70. doi: 10.1111/aos.13832
5. Chang MY, Keltner JL. Risk Factors for Fellow Eye Involvement in Nonarteritic Anterior Ischemic Optic Neuropathy. *J Neuroophthalmol* (2019) 39(2):147–52. doi: 10.1097/WNO.0000000000000715
6. Pomeranz HD. The Relationship Between Phosphodiesterase-5 Inhibitors and Nonarteritic Anterior Ischemic Optic Neuropathy. *J Neuroophthalmol* (2016) 36(2):193–6. doi: 10.1097/WNO.0000000000000299
7. Campbell UB, Walker AM, Gaffney M, Petronis KR, Creanga D, Quinn S, et al. Acute Nonarteritic Anterior Ischemic Optic Neuropathy and Exposure to Phosphodiesterase Type 5 Inhibitors. *J Sex Med* (2015) 12(1):139–51. doi: 10.1111/jsm.12726
8. Hayreh SS. Ischemic Optic Neuropathy. *Prog Retin Eye Res* (2009) 28(1):34–62. doi: 10.1016/j.preteyeres.2008.11.002
9. Knox DL, Kerrison JB, Green WR. Histopathologic Studies of Ischemic Optic Neuropathy. *Trans Am Ophthalmol Soc* (2000) 98:203–20.
10. Bernstein SL, Johnson MA, Miller NR. Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) and its Experimental Models. *Prog Retin Eye Res* (2011) 30(3):167–87. doi: 10.1016/j.preteyeres.2011.02.003
11. Ellenberger CJ, Burde RM, Keltner JL. Acute Optic Neuropathy. Treatment With Diphenylhydantoin. *Arch Ophthalmol* (1974) 91(6):435–8. doi: 10.1001/archopht.1974.03900060449003
12. Botelho PJ, Johnson LN, Arnold AC. The Effect of Aspirin on the Visual Outcome of Nonarteritic Anterior Ischemic Optic Neuropathy. *Am J Ophthalmol* (1996) 121(4):450–1. doi: 10.1016/s0002-9394(14)70448-9
13. Beck RW, Hayreh SS, Podhajsky PA, Tan E-S, Moke PS. Aspirin Therapy in Nonarteritic Anterior Ischemic Optic Neuropathy. *Am J Ophthalmol* (1997) 123(2):212–7. doi: 10.1016/s0002-9394(14)71038-4
14. Kupersmith MJ, Frohman L, Sanderson M, Jacobs J, Hirschfeld J, Ku C, et al. Aspirin Reduces the Incidence of Second Eye NAION: A Retrospective Study. *J Neuroophthalmol* (1997) 17(4):250–3. doi: 10.1097/00041327-199712000-00007
15. Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D, et al. The Fellow Eye in NAION: Report From the Ischemic Optic Neuropathy Decompression Trial Follow-Up Study. *Am J Ophthalmol* (2002) 134(3):317–28. doi: 10.1016/S0002-9394(02)01639-2
16. Arnold AC. Aspirin Should Not Be Recommended to Prevent Second Eye Involvement in Patients With Nonarteritic Anterior Ischemic Optic Neuropathy. *J Neuroophthalmol* (2020) 40(2):271–3. doi: 10.1097/WNO.0000000000000931
17. Antithrombotic Trialists' Collaboration. Collaborative Meta-Analysis of Randomised Trials of Antiplatelet Therapy for Prevention of Death, Myocardial Infarction, and Stroke in High Risk Patients. *BMJ* (2002) 324 (7329):71–86. doi: 10.1136/bmj.324.7329.71
18. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med* (2018) 379(16):1509–18. doi: 10.1056/NEJMoa1805819
19. Fazzone HE, Kupersmith MJ, Leibmann J. Does Topical Brimonidine Tartrate Help NAION? *Br J Ophthalmol* (2003) 87(9):1193–4. doi: 10.1136/bjo.87.9.1193
20. Wilhelm B, Ludtke H, Wilhelm H. Efficacy and Tolerability of 0.2% Brimonidine Tartrate for the Treatment of Acute non-Arteritic Anterior Ischemic Optic Neuropathy (NAION): A 3-Month, Double-Masked, Randomised, Placebo-Controlled Trial. *Graefes Arch Clin Exp Ophthalmol* (2006) 244(5):551–8. doi: 10.1007/s00417-005-0102-8
21. Hayreh SS, Zimmerman MB. Non-Arteritic Anterior Ischemic Optic Neuropathy: Role of Systemic Corticosteroid Therapy. *Graefes Arch Clin Exp Ophthalmol* (2008) 246(7):1029–46. doi: 10.1007/s00417-008-0805-8
22. Rebolleda G, Perez-Lopez M, Casas LP, Contreras I, Munoz-Negrete FJ. Visual and Anatomical Outcomes of non-Arteritic Anterior Ischemic Optic Neuropathy With High-Dose Systemic Corticosteroids. *Graefes Arch Clin Exp Ophthalmol* (2013) 251(1):255–60. doi: 10.1007/s00417-012-1995-7
23. Pakravan M, Esfandiari H, Hassanpour K, Razavi S, Pakravan P. The Effect of Combined Systemic Erythropoietin and Steroid on Non-Arteritic Anterior Ischemic Optic Neuropathy: A Prospective Study. *Curr Eye Res* (2017) 42 (7):1079–84. doi: 10.1080/02713683.2016.1270328
24. Chen J, Zhu J, Chen L, Hu C, Du Y. Steroids in the Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy: A PRISMA-Compliant Meta-Analysis. *Med (Baltimore)* (2019) 98(46):e17861. doi: 10.1097/MD.0000000000017861
25. Saxena R, Singh D, Sharma M, James M, Sharma P, Menon V. Steroids Versus No Steroids in Nonarteritic Anterior Ischemic Optic Neuropathy: A Randomized Controlled Trial. *Ophthalmology* (2018) 125(10):1623–7. doi: 10.1016/j.ophtha.2018.03.032
26. Modarres M, Falavarjani KG, Nazari H, Sanjari MS, Aghamohammadi F, Homaii M, et al. Intravitreal Erythropoietin Injection for the Treatment of non-Arteritic Anterior Ischaemic Optic Neuropathy. *Br J Ophthalmol* (2011) 95(7):992–5. doi: 10.1136/bjo.2010.191627
27. The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic Nerve Decompression Surgery for Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) is Not Effective and may be Harmful. *JAMA* (1995) 273(8):625–32. doi: 10.1001/jama.273.8.625
28. Nikkhah H, Golalipour M, Doozandeh A, Pakravan M, Yaseri M, Esfandiari H. The Effect of Systemic Erythropoietin and Oral Prednisolone on Recent-Onset Non-Arteritic Anterior Ischemic Optic Neuropathy: A Randomized Clinical Trial. *Graefes Arch Clin Exp Ophthalmol* (2020) 258(10):2291–7. doi: 10.1007/s00417-020-04781-x
29. Arnold AC, Hepler RS, Lieber M, Alexander JM. Hyperbaric Oxygen Therapy for Nonarteritic Anterior Ischemic Optic Neuropathy. *Am J Ophthalmol* (1996) 122(4):535–41. doi: 10.1016/s0002-9394(14)72114-2
30. Bennett JL, Thomas S, Olson JL, Mandava N. Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy With Intravitreal Bevacizumab. *J Neuroophthalmol* (2007) 27(3):238–40. doi: 10.1097/WNO.0b013e31814b273d
31. Rootman DB, Gill HS, Margolin EA. Intravitreal Bevacizumab for the Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy: A Prospective Trial. *Eye (Lond)* (2013) 27(4):538–44. doi: 10.1038/eye.2012.296
32. Solano ECR, Kornbrust DJ, Beaudry A, Foy JWD, Schneider DJ, Thompson JD. Toxicological and Pharmacokinetic Properties of QPI-1007, a Chemically Modified Synthetic siRNA Targeting Caspase 2 mRNA, Following Intravitreal Injection. *Nucleic Acid Ther* (2014) 24(4):258–66. doi: 10.1089/nat.2014.0489
33. Abri Aghdam K, Aghajani A, Ashraf Khorasani M, Soltan Sanjari M, Chaibakhsh S, Habibi A, et al. Intravitreal Injection Of The Granulocyte-Colony Stimulating Factor For The Treatment Of Non-Arteritic Anterior Ischemic Optic Neuropathy: A Pilot Study. *Semin Ophthalmol* (2021) 36 (8):649–57. doi: 10.1080/08820538.2021.1896749
34. Bernstein SL, Guo Y, Kelman SE, Flower RW, Johnson MA. Functional and Cellular Responses in a Novel Rodent Model of Anterior Ischemic Optic Neuropathy. *Invest Ophthalmol Vis Sci* (2003) 44(10):4153–62. doi: 10.1167/iovs.03-0274
35. Chen CS, Johnson MA, Flower RA, Slater BJ, Miller NR, Bernstein SL. A Primate Model of Nonarteritic Anterior Ischemic Optic Neuropathy. *Invest Ophthalmol Vis Sci* (2008) 49(7):2985–92. doi: 10.1167/iovs.07-1651
36. Guo Y, Mehrabian Z, Johnson MA, Miller NR, Henderson AD, Hamlyn J, et al. Biomarkers of Lesion Severity in a Rodent Model of Nonarteritic Anterior Ischemic Optic Neuropathy (rNAION). *PloS One* (2021) 16(3): e0243186. doi: 10.1371/journal.pone.0243186
37. Miller NR, Johnson MA, Nolan T, Guo Y, Bernstein AM, Bernstein SL. Sustained Neuroprotection From a Single Intravitreal Injection of PGJ(2) in a Nonhuman Primate Model of Nonarteritic Anterior Ischemic Optic Neuropathy. *Invest Ophthalmol Vis Sci* (2014) 55(11):7047–56. doi: 10.1167/iovs.14-14063

38. Touitou V, Johnson MA, Guo Y, Miller NR, Bernstein SL. Eye Movements, Strabismus, Amblyopia, and Neuro-Ophthalmology: Sustained Neuroprotection From a Single Intravitreal Injection of PGJ2 in a Rodent Model of Anterior Ischemic Optic Neuropathy. *Invest Ophthalmol Vis Sci* (2013) 54:7402–9. doi: 10.1167/iovs.13-12055
39. Mehrabian Z, Guo Y, Miller NR, Henderson AD, Roth S, Bernstein SL. Approaches to Potentiated Neuroprotective Treatment in the Rodent Model of Ischemic Optic Neuropathy. *Cells* (2021) 10(6). doi: 10.3390/cells10061440
40. Guo Y, Mehrabian Z, Johnson MA, Albers DS, Rich CC, Baumgartner RA, et al. Topical Trabodenoson Is Neuroprotective in a Rodent Model of Anterior Ischemic Optic Neuropathy (rNAION). *Transl Vis Sci Technol* (2019) 8(6):47. doi: 10.1167/tvst.8.6.47
41. Mathews MK, Guo Y, Langenberg P, Bernstein SL. Ciliary Neurotrophic Factor (CNTF)-Mediated Ganglion Cell Survival in a Rodent Model of non-Arteritic Anterior Ischaemic Optic Neuropathy (NAION). *Br J Ophthalmol* (2015) 99(1):133–7. doi: 10.1136/bjophthalmol-2014-305969
42. Wen YT, Huang CW, Liu CP, Chen CH, Tu CM, Hwang CS, et al. Inhibition of Retinal Ganglion Cell Loss By a Novel ROCK Inhibitor (E212) in Ischemic Optic Nerve Injury *via* Antioxidative and Anti-Inflammatory Actions. *Invest Ophthalmol Vis Sci* (2021) 62(6):21. doi: 10.1167/iovs.62.6.21
43. Guo Y, Johnson MA, Mehrabian Z, Mishra MK, Kannan R, Miller NR, et al. Dendrimers Target the Ischemic Lesion in Rodent and Primate Models of Nonarteritic Anterior Ischemic Optic Neuropathy. *PloS One* (2016) 11(4): e0154437. doi: 10.1371/journal.pone.0154437
44. Salowe RJ, O'Brien JM. Nei's Audacious Goals Initiative. *Ophthalmology* (2014) 121(3):615–6. doi: 10.1016/j.ophtha.2013.11.011
45. Zhang KY, Aguzzi EA, Johnson TV. Retinal Ganglion Cell Transplantation: Approaches for Overcoming Challenges to Functional Integration. *Cells* (2021) 10(6). doi: 10.3390/cells10061426
46. Venugopalan P, Wang Y, Nguyen T, Huang A, Muller KJ, Goldberg JL. Transplanted Neurons Integrate Into Adult Retinas and Respond to Light. *Nat Commun* (2016) 7:10472. doi: 10.1038/ncomms10472
47. Divya MS, Rasheed VA, Schmidt T, Lalitha S, Hattar S, James J. Intraocular Injection of ES Cell-Derived Neural Progenitors Improve Visual Function in Retinal Ganglion Cell-Depleted Mouse Models. *Front Cell Neurosci* (2017) 11:295. doi: 10.3389/fncel.2017.00295
48. Zhang KY, Johnson TV. The Internal Limiting Membrane: Roles in Retinal Development and Implications for Emerging Ocular Therapies. *Exp Eye Res* (2021) 206:108545. doi: 10.1016/j.exer.2021.108545
49. Zhang KY, Tuffy C, Mertz JL, Quillen S, Wechsler L, Quigley HA, et al. Role of the Internal Limiting Membrane in Structural Engraftment and Topographic Spacing of Transplanted Human Stem Cell-Derived Retinal Ganglion Cells. *Stem Cell Rep* (2021) 16(1):149–67. doi: 10.1016/j.stemcr.2020.12.001
50. Lim JH, Stafford BK, Nguyen PL, Lien BV, Wang C, Zukor K, et al. Neural Activity Promotes Long-Distance, Target-Specific Regeneration of Adult Retinal Axons. *Nat Neurosci* (2016) 19(8):1073–84. doi: 10.1038/nn.4340
51. Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, et al. Reprogramming to Recover Youthful Epigenetic Information and Restore Vision. *Nature* (2020) 588(7836):124–9. doi: 10.1038/s41586-020-2975-4
52. Gokoffski KK, Jia X, Shvarts D, Xia G, Zhao M. Physiologic Electrical Fields Direct Retinal Ganglion Cell Axon Growth *In Vitro*. *Invest Ophthalmol Vis Sci* (2019) 60(10):3659–68. doi: 10.1167/iovs.18-25118

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.