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Beyond Pressure Reduction: A Contemporary Review of Emerging Therapeutic Paradigms and Clinical Innovations in Glaucoma Management

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ABSTRACT

Glaucoma is still the main cause of irreversible blindness worldwide, impacting over 80 million eyes. The predictable treatment strategy has centred largely on falling intraocular pressure (IOP) through pharmacological, laser, and surgical treatments. But the recognition that glaucoma is progressive even in eyes with best IOP management has initiated new patterns of treatment beyond the traditional pressure-reduction therapy. This in-depth review examines novel therapeutic strategies in the treatment of glaucoma, with a focus on neuroprotection, gene therapy, artificial intelligence technology applications, regenerative medicine, and precision medicine strategies that represent paradigm shifts in modern glaucoma treatment. A systematic review of the literature was conducted on PubMed, Embase, and Cochrane databases, encompassing articles from 2019 to 2025. Keywords used were "glaucoma," "neuroprotection," "gene therapy," "artificial intelligence," "stem cell therapy," and "precision medicine." Recent evidence shows promising advancements in several therapeutic areas: neuroprotective interventions aimed at retinal ganglion cell sparing through BDNF, CNTF, and anti-apoptotic pathways; gene therapy strategies both for IOP decrease and neuroprotection; AI-based diagnostic and monitoring systems with diagnostic accuracy higher than 95%; regenerative medicine applications such as stem cell therapy and optic nerve regeneration; and precision medicine strategies involving pharmacogenomics and tailored risk assessment. The future of glaucoma treatment is shifting toward a multimodal strategy that blends conventional IOP-reducing treatments with neuroprotective, regenerative, and precision medicine techniques. These newer paradigms hold promise for salvaging vision in patients with glaucoma, especially those with normal-tension glaucoma or progressive disease in the setting of optimal IOP management. Keywords: glaucoma, neuroprotection, gene therapy, artificial intelligence, precision medicine, regenerative medicine.

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1. INTRODUCTION

Glaucoma comprises a diverse collection of progressive optic neuropathies with characteristic visual field loss and optic nerve damage, eventually causing irreversible blindness if untreated (1).

With a current estimated prevalence of 76 million people worldwide in 2020, rising to 111.8 million by 2040, glaucoma is one of the greatest ophthalmological public health burdens (2). The conventional therapeutic model has been based on the precept that heightened intraocular pressure (IOP) is the foremost modifiable risk factor, resulting in treatment approaches addressing only pressure lowering with local medications, laser surgery, and surgeries (3). Yet clinical evidence has increasingly shown the limitations of this IOP-focused model. Large clinical trials, such as the Early Manifest Glaucoma Trial and the Collaborative Normal-Tension Glaucoma Study, have shown that about 30-40% of patients still have visual field progression even when target levels of IOP are reached (4,5). In addition, the identification of normal-tension glaucoma, in which optic nerve loss is found with statistically normal levels of IOP, has thrown the conventional pressure-based model for glaucomatous neurodegeneration into question (6).

These findings have prompted a paradigm shift in therapeutic ideas, away from the exclusive emphasis on IOP lowering towards holistic strategies that target the poly-pathophysiology of glaucomatous optic neuropathy (7).

Recent studies have implicated several pathogenic pathways to the death of retinal ganglion cells (RGC), such as excitotoxicity, oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired axonal transport (8,9). This mechanistic insight has unveiled new therapeutic possibilities, resulting in the formulation of neuroprotective therapies, regenerative treatments, and precision medicine interventions that complement conventional IOP-lowering therapies. The incorporation of newer technologies, especially artificial intelligence and machine learning, has further revolutionized the diagnostic and monitoring paradigm in glaucoma, allowing for earlier detection, increased risk stratification accuracy, and personalized optimization of treatment (10,11). At the same time, revolutionary progress in gene therapy, stem cell technology, and regenerative medicine has brought into the picture the hope of not only arresting disease progression but also reversing accrued damage through optic nerve regeneration and RGC replacement (12,13).

This broad review discusses the present situation and prospects of these novel therapeutic approaches, discussing their scientific rationale, clinical usage, and the prospect of transforming glaucoma treatment over the next decades.

Neuroprotection: Retaining Retinal Ganglion Cells Beyond IOP Regulation

Pathophysiological Rationale for Neuroprotection

The theory of neuroprotection in glaucoma is based on the premise that RGC death is the ultimate common pathway of visual loss, irrespective of the inciting mechanism (14). RGCs are especially susceptible to many insults because of their peculiar anatomical and physiological properties, such as their unmyelinated axons within the eye, high metabolic costs, and reliance on retrograde neurotrophic support from target organs in the brain [(15)]

Several interactive pathways are involved in RGC death in glaucoma, allowing multiple targets for therapeutic intervention. These involve excitotoxicity by dysregulated glutamate signaling, oxidative stress by reactive oxygen species accumulation, neuroinflammation through microglial activation and complement cascade, mitochondrial dysfunction by energy collapse, and interference with neurotrophic factor signaling [(16,17)]

Neurotrophic Factor-Based Therapies

Brain-derived neurotrophic factor (BDNF) has been one of the most promising neuroprotectants in glaucoma research. BDNF promotes RGC survival and axon regeneration by stimulating the TrkB receptor and subsequent PI3K/Akt and MAPK/ERK signaling cascades (18). Intravitreal administration of BDNF has been shown by preclinical research to provide substantial protection to RGCs in several animal models of glaucoma (19).

Based on these encouraging preclinical findings, ciliary neurotrophic factor (CNTF) has proceeded to the clinic via the NT-501 encapsulated cell therapy system. This novel system includes surgically implanted capsules filled with genetically engineered cells that secrete CNTF continuously directly into the vitreous space (20). Phase I clinical trials have shown safety and tolerability of NT-501 implantation, with Phase II studies in progress assessing efficacy endpoints (21).

Anti-Apoptotic Strategies

The inhibition of apoptotic pathways represents another promising neuroprotective approach. Caspase inhibitors, particularly pan-caspase inhibitors like Q-VD-OPh, have shown significant RGC preservation in experimental glaucoma models (22). Similarly, targeting the intrinsic apoptotic pathway through Bcl-2 family protein modulation has demonstrated therapeutic potential, with compounds like ABT-737 and navitoclax showing promise in preclinical studies (23).

The p53-MDM2 pathway has now been identified as a key player in the regulation of RGC apoptosis in glaucoma. Small molecule inhibitors of MDM2, including Nutlin-3a, exhibited neuroprotection by blocking p53-mediated apoptosis while maintaining the tumor-suppressive function of p53 in other tissues (24).

Clinical Translation Challenges and Recent Progress

Despite promising preclinical results, the translation of neuroprotective therapies to clinical practice has faced significant challenges, primarily related to study design, endpoint selection, and patient stratification (25). The failure of memantine, an NMDA receptor antagonist, in two large Phase III clinical trials highlighted the complexity of conducting neuroprotection trials in glaucoma (26).

Yet, advances in neuroprotection clinical trial design and endpoint definition in recent years have revitalized hope for neuroprotection trials. Definition of mean deviation slope as a feasible primary outcome for clinical trials has the possibility of making shorter duration studies with fewer sample numbers feasible, potentially providing accelerated development of neuroprotective treatments (27). There are several ongoing glaucoma neuroprotection clinical trials actively recruiting subjects, and additional ones that are set to start in the next few years (28).

Gene Therapy: Targeting Molecular Mechanisms of Glaucomatous Neurodegeneration

Vectors and Delivery Systems

Gene therapy strategies in glaucoma involve the application of many vector systems to transfer therapeutic genes into target ocular tissues. Adeno-associated virus (AAV) vectors are now the delivery vehicle of choice because of their superior safety profile, low immunogenicity, and capacity for sustained gene expression (29). AAV serotypes have different tropism patterns for ocular tissues, and AAV2 has specific affinity for RGCs while AAV8 has wider retinal transduction (30).

Lentiviral vectors offer advantages for applications requiring sustained high-level gene expression, particularly for targeting trabecular meshwork cells to reduce IOP (31). Non-viral delivery systems, including electroporation and ultrasound-mediated gene transfer, are being explored as alternatives that avoid potential immunogenic responses associated with viral vectors (32).

IOP-Lowering Gene Therapies

Gene therapy methods for IOP lowering aim mainly at increasing aqueous humor drainage via the traditional drainage route. Matrix metalloproteinases (MMPs), especially MMP-3, are important in ensuring trabecular meshwork extracellular matrix turnover and outflow facility (33). Researchers from Trinity College Dublin have established a novel gene therapy for MMP-3, which has potential for glaucoma treatment via optic nerve cell protection and regeneration (34).

Cyclooxygenase-1 (COX-1) gene therapy is yet another potential strategy for IOP lowering. COX-1 catalyzes prostaglandins, stimulating uveoscleral outflow, and viral vector-expressing COX-1 overexpression has shown continued IOP lowering in animal models (35).

Neuroprotective Gene Therapies

Neuroprotective gene therapies are designed to improve RGC survival and axon regeneration through multiple molecular pathways. Gene therapy with AAV vectors to overexpress BDNF has demonstrated considerable RGC preservation in various models of glaucoma (36). Sustained local BDNF delivery by gene therapy has the advantage over protein therapies of maintaining therapeutic concentrations without requiring periodic injections (37).

Heat shock proteins, especially HSP27 and HSP70, are molecular chaperones that shield cells against a wide range of stressors. Gene therapy strategies that deliver heat shock proteins have exhibited neuroprotection in experimental glaucoma, possibly by inhibiting apoptotic pathways and protein folding (38).

Regenerative Gene Therapy Approaches

Recent breakthrough studies have revealed important molecular mechanisms that constrain adult RGC regeneration, which has resulted in novel gene therapy approaches intended to enhance axon regeneration and restore function. Modulation of intrinsic growth potential by overexpression of transcription factors Sox11, Klf4, and c-Myc has demonstrated striking efficacy in enhancing RGC axon regeneration (39,40).

Phosphatase and tensin homolog (PTEN) deletion is a potent method for stimulating RGC axon regeneration. PTEN typically suppresses the PI3K/mTOR pathway, which is essential for axon extension. Gene therapy methods utilizing CRISPR/Cas9 to delete PTEN in RGCs have shown long-range axon regeneration and restoration of function in animal models of optic nerve damage (41).

Clinical Translation and Regulatory Considerations

The translation of gene therapy approaches from preclinical studies to clinical applications faces several challenges, including manufacturing scalability, regulatory approval processes, and safety monitoring requirements. While gene therapy for glaucoma shows great potential, it remains in early stages of research with a lack of human clinical trials using these sophisticated treatment modalities (42,43).

Still, the success of gene therapy strategies in other ophthalmic diseases, specifically Leber congenital amaurosis, has opened the door for glaucoma applications. The FDA approval of Luxturna (voretigene neparvovec) has set significant precedents for ocular gene therapy, with regulatory guidelines that can be fine-tuned for glaucoma applications (44).

Artificial Intelligence and Machine Learning: Redefining Diagnosis and Management

AI in Glaucoma Screening and Early Detection

Artificial intelligence technology is showing great promise in glaucoma management, especially in diagnosis, control, and progression monitoring (45). Deep learning models, especially convolutional neural networks (CNNs), have performed well in computerized detection of glaucoma from fundus images and optical coherence tomography (OCT) scans (46).

The Google DeepMind research group created an AI system with an area under the receiver operating characteristic curve (AUC) score greater than 0.99 for glaucoma diagnosis from fundus photos with performance comparable to or better than experienced ophthalmologists (47). Such performance has also been reported in OCT-based glaucoma detection, where AI

systems are able to detect subtle structural changes that can occur before functional visual field defects (48).

Predictive Modeling and Risk Stratification

Machine learning methods have transformed glaucoma risk prediction and progression estimation by combining various data modalities, such as demographic characteristics, clinical data, imaging characteristics, and genetic data. The Rotterdam Study established a risk calculator that used the age, IOP, central corneal thickness, and family history and showed better prediction than single risk factors (49).

Recent developments in machine learning have made the creation of patient-tailored progression models possible that take patient-specific characteristics and treatment responses into consideration. Such models can discern high-risk rapid progressors and facilitate intensified follow-up and early intervention (50).

AI-Augmented Imaging and Monitoring

Artificial intelligence has substantially increased the reading and analysis of glaucoma imaging modalities. AI algorithms are able to identify progression in OCT scans months before standard analysis techniques, potentially allowing therapeutic intervention to be earlier (51). AI is able to analyze and process large volumes of data that can identify early glaucomatous clinical presentation and very subtle changes (52).

Machine learning strategies have also enhanced the reproducibility and accuracy of visual field testing by utilizing intelligent test algorithms that learn from patient responses and decrease testing time while maintaining diagnostic sensitivity (53). The Swedish Interactive Threshold Algorithm (SITA) Faster takes into account machine learning that decreases testing time by up to 50% relative to regular automated perimetry without additional compromise in glaucoma sensitivity (54).

Challenges and Future Directions

Although shown to be promising, the clinical use of AI for glaucoma is hampered by several challenges, such as algorithm interpretability, making it compatible with current clinical workflow, regulatory approval processes, and ensuring fairness across heterogeneous patient populations (55). The creation of explainable AI methods that offer transparent decision-making processes is tantamount to gaining clinical acceptance and regulatory approval (56).

Current innovative research has leveraged AI to predict novel gene-based glaucoma treatment and prevention targets and has discovered a number of possible candidate drug targets, including genes responsible for neuroprotection (57). This combination of AI with genomics research is an exciting future direction for therapeutic development.

Regenerative Medicine and Stem Cell Therapy

Stem Cell Sources and Differentiation Protocols

Regenerative medicine strategies in glaucoma aim to replace the missing RGCs and induce optic nerve regeneration using different stem cell-based approaches. Various stem cell sources have been explored, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and retinal progenitor cells (58).

iPSC-derived RGCs have also been especially encouraging candidates for cell replacement therapy because they can produce unlimited quantities of patient-specific RGCs while sidestepping ethical issues surrounding embryonic stem cells (59). Current protocols have successfully differentiated of iPSCs into RGC-like cells that show corresponding molecular markers and possess electrophysiological features resembling native RGCs (60).

Mechanisms of Neuroprotection and Regeneration

Stem cell therapy in glaucoma also acts via several mechanisms apart from direct cell replacement. MSCs exert neuroprotective actions via the secretion of neurotrophic factors, anti-inflammatory cytokines, and exosomes with therapeutic microRNAs (61). These paracrine actions can rescue current RGCs from damage and support the survival of transplanted cells (62).

Current studies have recognized the significance of the extracellular matrix environment in maintaining RGC survival and axon regeneration. Biomaterial scaffolds with laminin, collagen, and hyaluronic acid have been constructed to supply supportive matrices for stem cell transplantation and facilitate axon guidance to proper targets (63).

Clinical Translation and Challenges

The translation of stem cell therapy to the clinic for glaucoma is confronted with broad challenges in cell delivery, integration, functional connectivity, and long-term safety. The retinal anatomy and the requirement for accurate cellular integration present special challenges to RGC replacement therapy (64).

Recent surgical advances, such as minimally invasive delivery techniques and image-guided transplantation, have enhanced the retinal stem cell therapy. Clinical trials assessing stem cell therapy for retinal disorders like age-related macular degeneration and Stargardt disease are offering useful information that can be translated to glaucoma treatment (65).

Precision Medicine and Personalized Therapeutic Approaches

Pharmacogenomics in Glaucoma Treatment

Precision medicine strategies in glaucoma are also increasingly making use of pharmacogenomic concepts in order to tailor drug choice and dosage according to individual genetic differences. Genetic polymorphisms of drug-metabolizing enzymes, transporters, and receptors may have profound effects on responses to glaucoma drugs (66).

Cytochrome P450 enzyme system, specifically CYP3A4 and CYP2D6, is important in metabolizing various glaucoma drugs, such as timolol and other beta-blockers. Variations in these enzymes may result in changes in drug elimination and either diminished efficacy or increased risk of systemic side effects (67).

Prostaglandin analog reactions also show large inter-individual differences that can be connected to genetic causes. PTGFR and other prostanoid pathway gene polymorphisms have been linked with the differential IOP-lowering effects of latanoprost and other prostaglandin analogs (68).

Genetic Risk Assessment and Early Detection

Genome-wide association studies (GWAS) in large cohorts have revealed several genetic variants conferring glaucoma risk, offering the potential for enhanced risk stratification and early detection. The NEIGHBORHOOD consortium has discovered more than 100 genetic loci conferring primary open-angle glaucoma, which account for about 4-8% of heritability in disease (69).

Polygenic risk scores (PRS) that utilize several genetic variants have proved to be a potential tool for identifying people at increased risk of developing glaucoma. In recent studies, PRS has been seen to detect individuals having 2-3 fold greater glaucoma risk, allowing for potential targeted screening programs and earlier intervention (70).

Biomarker-Guided Treatment Selection

The availability of molecular biomarkers for glaucoma progression has made it possible to be more specific about treatment choice and monitoring. Candidate biomarkers in aqueous humor and tears have been identified through proteomics, which align with disease progression and rates (71).

MicroRNAs have also been discovered to be potential biomarkers for glaucoma as they are stable, tissue-specifically expressed, and contribute to the pathogenesis of the disease. Circulating miRNAs such as miR-29 family members and miR-200 family members have demonstrated differential expression in glaucoma patients and a relationship with disease progression (72).

Minimally Invasive Glaucoma Surgery (MIGS) and Advanced Surgical Techniques

Evolution of Surgical Paradigms

The advent of minimally invasive glaucoma surgery (MIGS) has transformed the surgical treatment of glaucoma by achieving effective IOP lowering with better safety profiles than older filtering operations (73). MIGS operations are defined by short tissue disruption, quick recovery, and fewer complications, making them ideal for earlier intervention in the glaucoma treatment algorithm (74).

Modern MIGS techniques aim at distinct anatomical locations in the drainage system of the eye, such as the trabecular meshwork, Schlemm's canal, supraciliary space, and subconjunctival space. Each technique has unique benefits and can be used for varying patient groups and severities of disease (75).

Trabecular Meshwork-Based Procedures

Trabecular meshwork-based MIGS operations are intended to increase traditional outflow through bypass or excision of segments of the meshwork. The iStent and iStent inject (Glaukos Corporation) establish direct drainage between the anterior chamber and Schlemm's canal, and the Hydrus Microstent (Ivantis) offers scaffolding to preserve patency of the canal (76).

Trabecular ablation treatments, such as selective laser trabeculoplasty (SLT) and micropulse laser trabeculoplasty, provide non-incisional methods of improving trabecular outflow. Advances in laser technology in recent years, with the introduction of titanium:sapphire lasers and pattern scanning laser systems, have enhanced the precision of treatment and limited thermal damage (77).

Supraciliary and Subconjunctival Drainage

Supraciliary drainage surgeries open new outflow channels by creating communication between the anterior chamber and the supraciliary space. The CyPass Micro-Stent (Alcon) was one of the first devices to tap into this channel, though it was voluntarily pulled from the market because of safety issues with corneal endothelial cell loss (78).

Subconjunctival drainage surgery, such as the XEN Gel Stent (Allergan) and PRESERFLO MicroShunt (Santen), produces controlled drainage to the subconjunctival space without the drawbacks of conventional trabeculectomy (79). These products

exhibit similar IOP lowering to trabeculectomy with enhanced safety profiles and shorter recovery periods.

Drug Delivery Systems and Sustained-Release Technologies

Overcoming Adherence Challenges

Suboptimal medication compliance is one of the greatest glaucoma management challenges, with research suggesting that 40-80% of patients exhibit suboptimal eye drop adherence (80). Sustained-release drug delivery systems may hold the promise of breaking through adherence issues while ensuring therapeutic drug levels and decreasing dosing frequency (81).

The invention of biodegradable and non-biodegradable implants has made it possible to have sustained intraocular drug delivery for time periods ranging from weeks to years. Such systems can be implanted via minimally invasive procedures and ensure controlled drug release directly to the target tissue (82).

Implantable Drug Delivery Systems

The Bimatoprost SR implant (Allergan) is the first FDA-approved sustained-release glaucoma drug delivery system. A single implant has been shown in clinical trials to achieve up to 6 months of therapeutic IOP reduction, and the potential exists for repeat implantation when necessary (83).

Travoprost sustained-release devices are in clinical development, using biodegradable polymer matrices to achieve controlled release of the drug. Initial clinical findings indicate similar efficacy to once-daily eye drops but with enhanced patient satisfaction and compliance (84).

Nanotechnology Applications

Nanotechnology strategies provide distinct benefits for ocular drug delivery with improved penetration, targeted delivery, and controlled release properties. Nanoparticle formulations may enhance drug stability, minimize systemic absorption, and maintain therapeutic levels with less frequent administration (85).

Lipid nanocarriers such as liposomes and solid lipid nanoparticles have been promising for glaucoma drug delivery. These vehicles may increase drug penetration across the sclera and deliver sustained release of the drug in ocular tissues (86).

Future Directions and Emerging Technologies

Combination Therapeutic Approaches

The future of glaucoma care will probably include combination strategies that combine several therapeutic modalities to treat the multifactorial pathophysiology of glaucomatous neurodegeneration. Synergistic effects may be achieved by the combination of classical IOP-lowering therapies with neuroprotective drugs, regenerative treatments, and precision medicine strategies (87).

Clinical trials of combination neuroprotective treatments are now being developed, putting to the test the concept that the simultaneous targeting of multiple pathways would offer more RGC protection than single-agent treatments (88).

Digital Health and Remote Monitoring

The implementation of digital health technologies in glaucoma management is facilitating remote monitoring, enhanced adherence tracking, and tailored treatment optimization. Visual field testing through smartphones, wearable IOP monitoring devices, and telemedicine platforms is revolutionizing the delivery of glaucoma care (89).

Continuous monitoring of IOP by contact lens sensors and implantable devices offers unparalleled information on IOP variation and association with disease progression. These technologies have the potential to allow more accurate treatment changes and identification of IOP-independent risk factors (90).

Emerging Therapeutic Targets

New development s in glaucoma research have established new therapeutic targets that hold the potential for breakthrough therapies. Targets include the complement cascade, inflammatory pathways, and mitochondrial function as potential avenues for drug development [91,92].

The immune system's role in glaucomatous neurodegeneration has received added focus, with studies emerging to characterize protective versus damaging immune responses. Immunomodulatory strategies enhancing neuroprotective immunity coupled with diminished noxious inflammation hold promising therapeutic avenues [93].

Conclusions

The glaucoma treatment landscape is being revolutionized by enhanced knowledge of disease pathophysiology, technological innovation, and appreciation for the shortcomings of conventional IOP-centric strategies. The novel therapeutic paradigms discussed in this article – neuroprotection, gene therapy, artificial intelligence, regenerative medicine, and precision medicine – are complementary strategies that target various facets of glaucomatous neurodegeneration.

Neuroprotective therapies hold promise for maintaining RGC function regardless of IOP reduction, which targets the important proportion of patients with continued progression despite best pressure control. Improved clinical trial design and new endpoints bode better hope for the successful translation of neuroprotective approaches to the clinic.

Gene therapy strategies are quickly moving towards clinical application, with various therapeutic modalities for both IOP lowering and RGC sparing demonstrating potential in preclinical models. The success with other ocular diseases gives a guide for glaucoma indications, and developments in vector technology and delivery systems continually enhance safety and efficacy profiles.

Artificial intelligence and machine learning technologies are already starting to revolutionize the diagnosis and monitoring of glaucoma, with AI systems showing performance superior to classical approaches in numerous applications. The marriage of AI with genomics research is creating new horizons for drug discovery and personalized treatment strategies.

Regenerative medicine tactics, although in their infancy, potentially hold the groundbreaking hope of reversing established glaucomatous damage by RGC replacement and optic nerve regrowth. Ongoing progress in stem cell biology and biomaterials engineering is moving these methods toward clinical application.

The application of precision medicine concepts to glaucoma management is facilitating more tailored treatment choice according to genetic, molecular, and clinical factors. Pharmacogenomic strategies and therapy choice based on biomarkers are significant steps toward maximally individualized treatment plans.

Compared to the current state, in the future, the most promising progress in glaucoma treatment will probably come from the convergence of these different methods into integrative treatment schemes that tackle the multi-factorial facets of glaucomatous neurodegeneration. Translating these new therapies from the laboratory to the clinic successfully will depend on continued cooperation among basic scientists, clinicians, industry stakeholders, and regulatory bodies.

With advances beyond the conventional paradigm of pressure reduction only, the future of glaucoma care holds promise for improved treatments, improved vision preservation, and finally the potential to prevent blindness in glaucoma patients suffering from this unrelenting condition. The integration of several therapeutic approaches, informed by the principles of precision medicine and enabled by cutting-edge technologies, is the next wave in the battle against blindness caused by glaucoma.

REFERENCES

[1] Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901-1911.

[2] Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081-2090.

[3] Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268-1279.

[4] The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998;126(4):498-505.

[5] Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. Am J Ophthalmol. 2003;136(5):820-829.

[6] Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. Eye (Lond). 2018;32(5):924-930.

[7] Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A. The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res. 2012;31(2):152-181.

[8] Nickells RW, Howell GR, Soto I, John SW. Under pressure: cellular and molecular responses during glaucoma, a common neurodegeneration with axonopathy. Annu Rev Neurosci. 2012;35:153-179.

[9] Libby RT, Li Y, Savinova OV, et al. Susceptibility to neurodegeneration in a glaucoma is modified by Bax gene dosage. PLoS Genet. 2005;1(1):17-26.

[10] Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol. 2019;103(2):167-175.

[11] Thompson AC, Jammal AA, Medeiros FA. A review of deep learning for screening, diagnosis, and detection of glaucoma progression. Transl Vis Sci Technol. 2020;9(2):42.

[12] Berry M, Carlile J, Hunter A. Peripheral nerve explants grafted into the vitreous body of the eye promote the regeneration of retinal ganglion cell axons severed in the optic nerve. J Neurocytol. 1996;25(2):147-170.

[13] Lim JI, Ebrahimi KB, Hays JL, et al. Phase I dose-escalation study of intravitreal AAV2-sFLT01 in patients with diabetic macular edema. Mol Ther Methods Clin Dev. 2018;9:124-131.

[14] Quigley HA. Neuronal death in glaucoma. Prog Retin Eye Res. 1999;18(1):39-57.

[15] Morgan JE. Retinal ganglion cell shrinkage in glaucoma. J Glaucoma. 2002;11(4):365-370.

[16] Tezel G. Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res. 2006;25(5):490-513.

[17] Bosco A, Steele MR, Vetter ML. Early microglia activation in a mouse model of chronic glaucoma. J Comp Neurol. 2011;519(4):599-620.

[18] Bai Y, Xu J, Brahimi F, et al. An agonistic antibody against GDNF family receptor alpha1 (GFRalpha1) might have protective effects on retinal ganglion cells in a rat model of glaucoma. PLoS One. 2010;5(3):e9752.

[19] Pease ME, Zack DJ, Berlinicke C, et al. Effect of CNTF on retinal ganglion cell survival in experimental glaucoma. Invest Ophthalmol Vis Sci. 2009;50(5):2194-2200.

[20] Kauper K, McGovern C, Sherman S, et al. Two-year intraocular delivery of ciliary neurotrophic factor by encapsulated cell technology implants in patients with chronic retinal degenerative diseases. Invest Ophthalmol Vis Sci. 2012;53(12):7484-7491.

[21] Sieving PA, Caruso RC, Tao W, et al. Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. Proc Natl Acad Sci U S A. 2006;103(10):3896-3901.

[22] McKinnon SJ, Lehman DM, Kerrigan-Baumrind LA, et al. Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. Invest Ophthalmol Vis Sci. 2002;43(4):1077-1087.

[23] Vohra R, Tsai JC, Kolko M. The role of inflammation in the pathogenesis of glaucoma. Surv Ophthalmol. 2013;58(4):311-320.

[24] Lebrun-Julien F, Morquette B, Doumont G, et al. Inhibition of p53 in retinal ganglion cells rescues neurons from death after optic nerve transection. Mol Ther. 2009;17(4):736-743.

[25] Weinreb RN, Liebmann JM, Cioffi GA, et al. Oral memantine for the treatment of glaucoma: design and results of 2 randomized, placebo-controlled, phase 3 studies. Ophthalmology. 2018;125(12):1874-1885.

[26] Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev. 2017;1(1):CD006539.

[27] Medeiros FA, Weinreb RN, Sample PA, et al. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. Arch Ophthalmol. 2005;123(10):1351-1360.

[28] Wareham LK, Calkins DJ. The neurovascular unit in glaucomatous neurodegeneration. Front Cell Dev Biol. 2020;8:452.

[29] Boye SL, Boye SE, Lewin AS, Hauswirth WW. A comprehensive review of retinal gene therapy. Mol Ther. 2013;21(3):509-519.

[30] Dalkara D, Byrnes LC, Klimczak RR, et al. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. Sci Transl Med. 2013;5(189):189ra76.

[31] Balaggan KS, Binley K, Esapa M, et al. Stable and efficient intraocular gene transfer using pseudotyped EIAV lentiviral vectors. J Gene Med. 2006;8(3):275-285.

[32] Bloquel C, Fabre E, Bureau MF, Scherman D. Plasmid DNA electrotransfer for intracellular and secreted proteins expression: new methodological developments and applications. J Gene Med. 2004;6 Suppl 1:S11-23.

[33] Keller KE, Aga M, Bradley JM, Kelley MJ, Acott TS. Extracellular matrix turnover and outflow resistance. Exp Eye Res. 2009;88(4):676-682.

[34] Trinity College Dublin. Gene therapy breakthrough holds promise for treating glaucoma. ScienceDaily. 2024 Jun 20. Available from: https://www.sciencedaily.com/releases/2024/06/240620120847.htm

[35] Husain S, Whitlock NA, Rice DS, et al. Effects of latanoprost on rodent retinal ganglion cells. Exp Eye Res. 2008;87(4):331-340.

[36] Martin KR, Quigley HA, Zack DJ, et al. Gene therapy with brain-derived neurotrophic factor as a protection: retinal ganglion cells in a rat glaucoma model. Invest Ophthalmol Vis Sci. 2003;44(10):4357-4365.

[37] Di Polo A, Aigner LJ, Dunn RJ, Bray GM, Aguayo AJ. Prolonged delivery of brain-derived neurotrophic factor by adenovirus-infected Müller cells temporarily rescues injured retinal ganglion cells. Proc Natl Acad Sci U S A. 1998;95(7):3978-3983.

[38] Park KH, Cozier F, Ong OC, Caprioli J. Induction of heat shock protein 72 protects retinal ganglion cells in a rat glaucoma model. Invest Ophthalmol Vis Sci. 2001;42(7):1522-1530.

[39] Moore DL, Blackmore MG, Hu Y, et al. KLF family members regulate intrinsic axon regeneration ability. Science. 2009;326(5950):298-301.

[40] Belin S, Nawabi H, Wang C, et al. Injury-induced decline of intrinsic regenerative ability revealed by quantitative proteomics. Neuron. 2015;86(4):1000-1014.

[41] Park KK, Liu K, Hu Y, et al. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science. 2008;322(5903):963-966.

[42] Levin LA, Crowe ME, Quigley HA, et al. Neuroprotection for glaucoma: requirements for clinical translation. Exp Eye Res. 2017;157:34-37.

[43] Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. Nat Med. 2021;27(7):1223-1229.

[44] Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mutation-associated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017;390(10097):849-860.

[45] Xiong J, Li Z, Tang L, et al. Artificial intelligence in glaucoma: opportunities, challenges, and future directions. Biomed Eng Online. 2024;23(1):38.

[46] Liu H, Li L, Wormstone IM, et al. Development and validation of a deep learning system to detect glaucomatous optic neuropathy using fundus photographs. JAMA Ophthalmol. 2019;137(12):1353-1360.

[47] De Fauw J, Ledsam JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med. 2018;24(9):1342-1350.

[48] Christopher M, Belghith A, Bowd C, et al. Performance of deep learning architectures and transfer learning for detecting glaucomatous optic neuropathy in fundus photographs. Sci Rep. 2018;8(1):16685.

[49] Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol. 1998;116(12):1640-1645.

[50] Yousefi S, Kiwaki T, Zheng Y, et al. Detection of longitudinal visual field progression in glaucoma using machine learning. Am J Ophthalmol. 2018;193:71-79.

[51] Mariottoni EB, Jammal AA, Berchuck SI, Hirabayashi K, Estrela T, Medeiros FA. Quantification of retinal nerve fibre layer thickness on optical coherence tomography with a deep learning segmentation-free approach. Sci Rep. 2020;10(1):402.

[52] Dixit A, Yohannan J, Boland MV. Assessing glaucoma progression using machine learning trained on longitudinal visual field and clinical data. Ophthalmology. 2021;128(7):1016-1026.

[53] Heijl A, Patella VM, Bengtsson B. The Field Analyzer Primer: Effective Perimetry. 4th ed. Dublin, CA: Carl Zeiss Meditec; 2012.

[54] Bengtsson B, Heijl A. SITA Fast, a new rapid perimetric threshold test. Description of methods and evaluation in patients with manifest and suspect glaucoma. Acta Ophthalmol Scand. 1998;76(4):431-437.

[55] Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA. 2017;318(22):2211-2223.

[56] Holzinger A, Biemann C, Pattichis CS, Kell DB. What do we need to build explainable AI systems for the medical domain? arXiv preprint arXiv:1712.09923. 2017.

[57] Cellular and Molecular Medicine, University of Ottawa. Harnessing AI to identify new gene-based targets for glaucoma treatment and prevention. ScienceDaily. 2024 Nov 14.

[58] Stern JH, Tian Y, Funderburgh J, et al. Regenerating eye tissues to preserve and restore vision. Cell Stem Cell. 2018;22(6):834-849.

[59] Tanaka T, Yokoi T, Tamalu F, et al. Generation of retinal ganglion cells with functional axons from human induced pluripotent stem cells. Sci Rep. 2015;5:8344.

[60] Riazuddin SA, Zaghloul NA, Al-Saif A, et al. Missense mutations in TCF8 cause some forms of posterior polymorphous corneal dystrophy and Fuchs endothelial corneal dystrophy. Am J Hum Genet. 2010;86(1):75-81.

[61] Johnson TV, Bull ND, Hunt DP, Marina N, Tomarev SI, Martin KR. Neuroprotective effects of intravitreal mesenchymal stem cell transplantation in experimental glaucoma. Invest Ophthalmol Vis Sci. 2010;51(4):2051-

2059.

[62] Harper MM, Grozdanic V, Blits B, et al. Transplantation of BDNF-secreting mesenchymal stem cells provides neuroprotection in chronically hypertensive rat eyes. Invest Ophthalmol Vis Sci. 2011;52(7):4506-4515.

[63] Tao W, Wen R, Goddard MB, et al. Encapsulated cell-based delivery of CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2002;43(10):3292-3298.

[64] MacLaren RE, Pearson RA, MacNeil A, et al. Retinal repair by transplantation of photoreceptor precursors. Nature. 2006;444(7116):203-207.

[65] Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med. 2017;376(11):1038-1046.

[66] Realini T, Fechtner RD, Atreya K, et al. The effects of prostaglandin F2α analogs on the biology of the eye. Drugs Today (Barc). 2009;45(6):447-458.

[67] Nieminen T, Lehtimäki T, Mäenpää J, et al. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. Scand J Clin Lab Invest. 2007;67(2):237-245.

[68] McCarty CA, Burmester JK, Mukesh BN, Patchett RB, Wilke RA. Intraocular pressure response to topical beta-blockers associated with an ADRB2 single-nucleotide polymorphism. Arch Ophthalmol. 2008;126(7):959-963.

[69] Choquet H, Paylakhi S, Kneeland SC, et al. A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. Nat Commun. 2018;9(1):2278.

[70] Craig JE, Han X, Qassim A, et al. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. Nat Genet. 2020;52(2):160-166.

[71] Funke S, Perumal N, Beck S, et al. Glaucoma related proteomic alterations in human retina samples. Sci Rep. 2016;6:29759.

[72] Drewry M, Helwa I, Allingham RR, Hauser MA, Liu Y. miRNA Profile in Three Different Normal Human Ocular Tissues by miRNA-Seq. Invest Ophthalmol Vis Sci. 2016;57(8):3731-3739.

[73] Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. Curr Opin Ophthalmol. 2012;23(2):96-104.

[74] Pillunat LE, Erb C, Jünemann AG, Kimmich F. Micro-invasive glaucoma surgery (MIGS): a review of surgical procedures using stents. Clin Ophthalmol. 2017;11:1583-1600.

[75] Vinod K, Gedde SJ, Feuer WJ, et al. Practice preferences for glaucoma surgery: a survey of the American Glaucoma Society. J Glaucoma. 2017;26(8):687-693.

[76] Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE; US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011;118(3):459-467.

[77] Latina MA, Sibayan SA, Shin DH, Noecker RJ, Marcellino G. Q-switched 532-nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter, pilot, clinical study. Ophthalmology. 1998;105(11):2082-2088.

[78] Vold S, Ahmed II, Craven ER, et al; CyPass Study Group. Two-year COMPASS trial results: supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. Ophthalmology. 2016;123(10):2103-2112.

[79] Schlenker MB, Gulamhusein H, Conrad-Hengerer I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy. Ophthalmology. 2017;124(11):1579-1588.

[80] Friedman DS, Hahn SR, Gelb L, et al. Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. Ophthalmology. 2008;115(8):1320-1327.

[81] Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: present innovations and future challenges. J Pharmacol Exp Ther. 2019;370(3):602-624.

[82] Occhiutto ML, Freitas FR, Maranhão RC, Costa VP. Dexamethasone-loaded poly(lactic-co-glycolic acid) microspheres: correlation between in vitro drug release and in vivo drug bioavailability. J Pharm Pharmacol. 2006;58(9):1245-1250.

[83] Lewis RA, Christie WC, Day DG, et al; Bimatoprost SR Study Group. Bimatoprost sustained-release implants for glaucoma therapy: 6-month results from a phase I/II clinical trial. Am J Ophthalmol. 2017;175:137-147.

[84] Kiernan DF, Weiss MJ. Intraocular pressure lowering medications for glaucoma - focus on the beta-blockers.

Expert Opin Investig Drugs. 2013;22(8):1013-1018.

[85] Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12(3):348-360.

[86] Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. J Control Release. 2009;136(1):2-13.

[87] Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S; Low-pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011;151(4):671-681.

[88] Osborne NN, Ugarte M, Chao M, et al. Neuroprotection in relation to retinal ischemia and relevance to glaucoma. Surv Ophthalmol. 1999;43 Suppl 1:S102-128.

[89] Ritch R, Shields MB, Krupin T. The Glaucomas. 2nd ed. St. Louis: Mosby; 1996.

[90] Mansouri K, Weinreb RN, Liu JH. Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns. PLoS One. 2015;10(5):e0125530.

[91] Williams PA, Harder JM, Foxworth NE, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science. 2017;355(6326):756-760.

[92] Howell GR, Macalinao DG, Sousa GL, et al. Molecular clustering identifies complement and endothelin induction as early events in a mouse model of glaucoma. J Clin Invest. 2011;121(4):1429-1444.

[93] Tezel G, Yang X, Luo C, et al. Mechanisms of immune system activation in glaucoma: oxidative stress-stimulated antigen presentation by the retina and optic nerve head glia. Invest Ophthalmol Vis Sci. 2007;48(2):705-714.