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Review Article

Eyeing the Future: Stem Cell Therapy Landscape in Ophthalmology

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Abstract

The eye's immune-privileged status and unique anatomical accessibility make it an ideal target for regenerative medicine. Over the past two decades, stem cell-based therapies have emerged as transformative approaches for blinding ocular disorders that currently lack curative treatments. Advances in cell biology, bioengineering, and high-resolution ocular imaging have accelerated the translation of stem cell technologies from bench to bedside, particularly for posterior segment diseases such as Age-Related Macular Degeneration (AMD), Inherited Retinal Dystrophies (IRDs), and glaucoma. Retinal progenitor cell transplantation and gene-corrected Induced Pluripotent Stem Cells (iPSCs) have demonstrated encouraging safety and preliminary efficacy in early-phase trials for IRDs. Parallel strategies targeting Retinal Ganglion Cell (RGC) loss in glaucoma-currently managed solely by intraocular pressure reduction-include stem cell-derived RGC replacement and neuroprotective paracrine signaling by Mesenchymal Stem Cells (MSCs). Similarly, Limbal Stem Cell Deficiency (LSCD) and corneal scarring, major causes of blindness in low-resource settings, are increasingly addressed through ex vivo expansion and transplantation of autologous or allogeneic limbal stem cells. Pluripotent and adult stem cell sources, including embryonic stem cells, iPSCs, and MSCs, have been differentiated into Retinal Pigment Epithelium (RPE), photoreceptors, and corneal epithelial cells with increasing fidelity. MSC-derived extracellular vesicles (EVs) represent a particularly promising cell-free therapeutic strategy, delivering neurotrophic and immunomodulatory factors that preserve retinal structure and function in degenerative models. Recent trials confirm favorable safety profiles and early signals of efficacy in conditions such as retinitis pigmentosa and glaucoma. Concurrently, innovations in cell delivery systems, scaffold engineering, and immune modulation continue to refine engraftment outcomes and reduce off-target effects. This review synthesizes current clinical and preclinical evidence across major ocular conditions, highlights emerging bioengineering and regulatory considerations, and delineates future directions for stem cell-based interventions aimed at restoring vision and preventing irreversible blindness.

Introduction

The eye represents a uniquely accessible and immune-privileged organ, offering an ideal context for the development and implementation of regenerative therapies [1]. Over the past two decades, stem cell-based strategies have emerged as transformative tools in addressing a wide range of blinding ocular diseases for which current treatments are either inadequate or nonexistent [2]. The complexity of ocular tissues (i.e., retina, cornea, and optic nerve) requires targeted regenerative approaches that align with the distinct anatomical, cellular, and immunologic features of each compartment [3]. Concurrently, advances in imaging technologies, have enabled precise monitoring of disease progression and therapeutic response, accelerating the translation of stem cell therapies into early-phase clinical trials [4].

These technological and therapeutic innovations are particularly relevant for posterior segment diseases. Age-Related Macular Degeneration (AMD) and Inherited Retinal Dystrophies (IRDs), including Retinitis Pigmentosa (RP), represent leading causes of irreversible vision loss [5]. RP and other IRDs, characterized by photoreceptor degeneration due to mutations in over 250 genes, are currently incurable, though Retinal Progenitor Cell (RPC) transplantation and gene-corrected iPSC strategies are in early-phase trials with promising safety and engraftment results [6,7].

While efforts to restore photoreceptors in IRDs are advancing, parallel regenerative strategies are being explored for inner retinal degeneration. Glaucoma, involves irreversible loss of Retinal Ganglion Cells (RGCs), with current therapies focused solely on intraocular pressure control, Stem cell-derived RGC replacement and neuroprotective paracrine signaling by MSCs represent novel avenues under active preclinical investigation. In addition, Limbal Stem Cell Deficiency (LSCD) and corneal scarring contribute significantly to global blindness, particularly in regions with limited access to corneal transplantation8. Glaucoma, a leading cause of irreversible blindness worldwide, further underscores the need for neuroregenerative approaches to restore or protect Retinal Ganglion Cells (RGCs) beyond conventional intraocular pressure-lowering therapies [8]. Recent scientific progress has enabled the derivation of Retinal Pigment Epithelium (RPE), photoreceptors, and corneal epithelial cells from pluripotent and adult stem cell sources, including embryonic stem cells (ESCs), Induced Pluripotent Stem Cells (iPSCs), and Mesenchymal Stem Cells (MSCs) [9]. These advances are being translated into clinical trials that not only demonstrate feasibility and safety but also begin to demonstrate functional benefit [10,11]. At the same time, cell delivery techniques, scaffold design, and immune modulation are rapidly evolving to improve engraftment and reduce the risk of rejection or off-target effects [12]. This review aims to comprehensively evaluate the current landscape of stem cell-based therapies across major ocular conditions, including AMD, LSCD, IRDs, and glaucoma. We synthesize recent findings from both clinical and preclinical studies, emphasizing advances in cell sourcing, differentiation protocols, delivery strategies, and outcome assessment. Additionally, we discuss emerging technologies and regulatory considerations that will shape the next generation of regenerative therapies in ophthalmology. By integrating recent scientific and translational developments, this review provides a forward-looking perspective on the promise and challenges of stem cell applications in restoring vision and preventing blindness.

Opportunities for Stem Cell Therapeutics in Ophthalmic Conditions

AMD remains the leading cause of irreversible central vision loss in individuals over 60. Current treatments are limited, largely related to anti-VEGF agents for the neovascular form and no effective therapies for geographic atrophy. Given the relatively immune privileged context of the eyes and the significant unmet need researchers recently developed protocols for differentiating EPCs and iPSCs into RPE [13,14].

The advent of highly advanced diagnostic technologies, the ability to document disease progression and monitor response to treatments has significantly enhanced targeted therapeutic strategies in recent years. The enhanced diagnostic resolution has been particularly impactful for conditions where early detection of epithelial instability and precise delineation of conjunctival invasion inform both prognosis and treatment selection (e.g., LSCD). Autologous limbal grafting is used in unilateral cases, yet bilateral disease lacks effective long-term options [15,16].

Current Landscape of Stem Cell Modalities and Therapeutic Strategies

Mesenchymal stem cells (MSCs) represent a versatile therapeutic platform for retinal degenerative diseases, including glaucoma and RP, largely through paracrine-mediated neuroprotection rather than direct cell replacement [17]. MSCs secrete a complex "secretome" composed of neurotrophic factors (e.g., Brain-Derived Neurotrophic Factor [BDNF], Ciliary Neurotrophic Factor [CNTF], Glial Cell Line-Derived Neurotrophic Factor [GDNF], Nerve Growth Factor [NGF]), angiogenic and growth factors (e.g., Platelet-Derived Growth Factor [PDGF], Vascular Endothelial Growth Factor [VEGF]), cytokines, and Extracellular Vesicles (EVs), including exosomes. These bioactive molecules modulate the retinal microenvironment by attenuating oxidative stress, suppressing inflammatory cytokines, and inhibiting apoptotic pathways, thereby preserving neuronal integrity [18,19]. In glaucoma, where Retinal Ganglion Cell (RGC) degeneration remains irreversible despite intraocular pressure control, MSCs delivered intravitreally or periocularly have demonstrated the ability to promote RGC survival and preserve optic nerve axons in preclinical models, primarily via secretion of BDNF, CNTF, and NGF [20,21]. Similarly, in RP models, MSC-derived EVs have been shown to reduce photoreceptor cell death, dampen local inflammation, and maintain retinal architecture without requiring long-term cellular engraftment [22]. These preclinical

findings are being translated into early-phase clinical trials evaluating both autologous and allogeneic MSCs. Recent studies report favorable safety profiles and preliminary evidence of visual function stabilization in patients with advanced-stage RP [23]. In parallel, bioengineering approaches aim to enhance the therapeutic potency of MSCs by increasing trophic factor secretion or enabling targeted delivery to specific retinal layers. While key challenges remain, including defining optimal dosing strategies, administration routes, and long-term durability MSC-based interventions offer a promising, cell-based or cell-free approach to modulate neuroinflammation, support neuronal survival, and potentially slow disease progression in otherwise intractable retinal conditions.

Embryonic Stem Cells (ESCs), derived from the inner cell mass of blastocysts, offer a pluripotent and renewable source of RPE cells, making them an attractive platform for cell replacement therapies in AMD. Given their standardized differentiation potential and scalability, ESC-derived RPE cells have progressed into clinical trials, showing early evidence of structural integration and long-term safety. One of the most notable studies, conducted by [24], demonstrated that a monolayer of hESC-derived RPE cells delivered on a biocompatible scaffold could survive subretinal implantation, support photoreceptor function, and potentially halt or reverse visual decline in patients with geographic atrophy [24]. Subsequent follow-up studies have confirmed persistence of the transplanted cells and visual function stability over several years [25,26]. ESC-derived RPE therapies are currently being developed by several companies, including Lineage Cell Therapeutics and Astellas Institute for Regenerative Medicine, with the latter advancing products like MA09-hRPE through early-phase trials. Importantly, ESCs offer a more uniform and well-characterized cell source than patient-specific iPSCs, though ethical considerations and potential immunogenicity remain challenges [27]. Nonetheless, ESC-based therapies represent one of the most mature and translational applications of pluripotent stem cells in ophthalmology.

Induced Pluripotent Stem Cells (iPSCs) generated by reprogramming somatic cells into a pluripotent state, provide a promising alternative to ESCs for retinal cell replacement therapy, particularly in AMD. iPSCs offer the unique advantage of autologous derivation, enabling personalized regenerative approaches with reduced risk of immune rejection [28]. Early proof-of-concept studies demonstrated that iPSC-derived RPE cells could be differentiated, expanded, and transplanted safely into the subretinal space in both animal models and humans. [29] conducted the first autologous iPSC-RPE transplantation in a human patient with exudative AMD, showing stable engraftment without adverse immune responses or tumorigenicity at one-year follow-up. More recently, allogeneic iPSC-RPE cell sheets have entered clinical trials to improve scalability and manufacturing consistency while maintaining safety and potential efficacy [30]. iPSC-derived therapies are also being explored for inherited retinal degenerations, such as retinitis pigmentosa and Stargardt disease, due to their ability to generate patient-specific photoreceptors and RPE cells for in vitro modeling and transplantation [31]. While iPSC platforms introduce risks of genomic instability and variable differentiation potential, advances in reprogramming techniques, CRISPR-based gene editing, and standardized manufacturing are rapidly mitigating these limitations [32]. Compared to ESCs, iPSCs circumvent some ethical concerns and offer broader applicability in precision medicine. Together, these advances underscore iPSC-derived RPE cells as a versatile and clinically relevant strategy for vision restoration in degenerative retinal disorders.

Limbal Epithelial Stem Cells (LESCs), located at the corneoscleral junction, are critical for maintaining corneal clarity by continuously renewing the corneal epithelium and preventing conjunctival encroachment. LSCD, whether due to chemical burns, autoimmune conditions, or genetic disorders such as aniridia, leads to conjunctivalization of the cornea, neovascularization, chronic inflammation, and progressive vision loss. Ex vivo expansion and transplantation of LESCs has emerged as a regenerative therapy capable of restoring the ocular surface and preventing disease progression. The most mature clinical approach involves autologous LESC transplantation, particularly in unilateral LSCD, where a small limbal biopsy from the unaffected eye is expanded on a carrier (commonly amniotic membrane or fibrin gel). In a landmark Phase II/III study by [33], 76.6% of patients (76 out of 112) with unilateral LSCD achieved a stable, avascular corneal epithelium with long-term success lasting up to 10 years. This led to the EMA approval of Holoclar, the first Advanced Therapy Medicinal Product (ATMP) for ocular surface reconstruction, now commercially available in the EU. For bilateral LSCD, where autologous tissue is unavailable, allogeneic LESC transplantation is required, but success rates are generally lower due to the need for systemic immunosuppression and a higher risk of immune-mediated rejection. Clinical trials such as the SLET (Simple Limbal Epithelial Transplantation) approach, developed by Sangwan and colleagues, have shown encouraging results using small limbal explants from living-related donors without ex vivo expansion, achieving over 70% success at 1-2 years follow-up [34]. However, outcomes vary widely depending on the extent of ocular surface inflammation and comorbidities. A 2022 multicenter trial reported that 60% of patients receiving allogeneic LESCs with systemic immunosuppression achieved clinically stable epithelialization, but long-term visual improvement was more modest, and immunologic rejection remained a limiting factor [35]. Limbal Stem Cells (LSCs) are adult stem cells located at the limbus ensuring the continuous renewal of the corneal epithelium, critical to maintaining an optimal visual function [36]. Recent findings suggest that residual LSCs exist in eyes presenting with clinical signs of total LSCD, which opens new regenerative therapeutic strategies for partial LSCD [36]. These evolving insights into limbal stem cell biology underscore a broader paradigm shift in ocular regenerative medicine, extending beyond the cornea to encompass photoreceptor loss in inherited retinal dystrophies. Recent trials are evaluating iPSC-derived corneal epithelial-like cells and xeno-free

culture conditions to standardize and expand the donor pool, while ongoing innovations in biomimetic scaffolds, co-transplantation with mesenchymal stromal cells, and local immunomodulation are being developed to enhance graft survival and function. Tools such as in vivo confocal microscopy and impression cytology now allow earlier diagnosis of LSCD and real-time monitoring of treatment response. Together, these advances position LESC-based therapies at the forefront of regenerative ophthalmology, though optimization of donor selection, immunologic matching, and long-term outcome metrics remain active areas of investigation.

Retinal Progenitor Cells (RPCs): Although considered a group of rare diseases, approximately 5.5 million people are affected by IRDs worldwide collectively as a leading cause of retinal blindness. IRDs are a genetically and clinically heterogeneous group of retinopathies that commonly result in the degeneration and loss of retinal photoreceptors, which results in irreversible visual impairment [37]. There are two main therapeutic approaches in preclinical IRD research: regenerating endogenous photoreceptors and/or other implicated retinal cell populations within the host retina or replacing these retinal cells, and/or their function [38]. Currently, the one FDA-approved IRD treatment, Luxturna (voretigene neparvovec-rzyl), a gene therapy used to treat RPE cells in RPE65-associated retinal dystrophy was the first gene therapy approved for use in humans [39]. Although there have been promising advances in the field of gene therapy research for specific types of IRDs, limitations to the clinical application of these gene-specific approaches exist attributable to the vast number of genes associated with clinical IRDs. Advances in human stem cell technology have led to the development of 2D cultures (flat layers of cells) and 3D organoids (miniature, self-organizing tissues).

In 2D cultures, iPSCs are grown on a flat surface and guided to develop into various retinal cell types. This setup allows researchers to study how these cells mature and how different retinal cell types interact. For example, one study used iPSCs to create 2D cultures that naturally formed different eye cell types, including neural retinal cells, RPE, lens, and ocular surface ectoderm [40]. As these cells differentiated, they organized into distinct regions the researchers called "self-formed ectodermal autonomous multi-zones" (SEAMs) [41]. The way these SEAMs developed closely resembled the stages of actual eye development, offering valuable insights into how human ocular cells differentiate over time. Furthermore, the researchers discovered that cells from the functional ocular surface epithelia zone within these 2D cultures could regenerate, suggesting their potential for use in anterior eye transplant therapies. Retinal organoids are often regarded as "miniature retinas", attributed to their remarkable ability to organize into a 3D laminated, multi-layered structure akin to native neural retina, containing all seven major retinal cell types with some light-responsive functional characteristics, such as bright light response patterns similar to those seen in ON and OFF RGCs of the developing in vivo neural retina [42]. While retinal organoids offer significant benefits for IRD research, they are limited by the absence of critical components like vascular and immune systems, which are vital for retinal development and function. Future research aims to overcome these limitations by integrating vascular structures, as demonstrated in cerebral organoids, and by developing "assembloids" multi-tissue organoid systems [42]. Early successes, such as creating vascularized retinal organoids with improved tissue size and functional retinal-cortical/thalamic assembloids, highlight exciting potential for more comprehensive modeling of the human visual system and its diseases.

Gene and cell therapy hybrids, leveraging iPSCs corrected for specific mutations, capitalizes on the ability to derive patient-specific iPSCs from somatic cells, which inherently carry the disease-causing genetic defect. Through precise gene-editing tools, notably CRISPR-Cas9 technology, these pathogenic mutations can be corrected directly within the iPSCs. This genetic correction addresses the root cause of the disease at the cellular level, offering the potential for an autologous cell source that eliminates concerns of immune rejection following transplantation [43,44]. The genetically corrected iPSCs can be differentiated into specific cell types (e.g., photoreceptors or RPE cells) [45]. Recent advancements demonstrate successful correction of various mutation types (e.g., exonic, deep intronic, dominant gain-of-function) in patient-derived iPSCs, subsequently yielding functional retinal cell types in vitro [46]. The refined control over differentiation protocols, coupled with the safety and specificity afforded by advanced gene-editing tools, is accelerating the translation of these gene-corrected iPSCs into clinical applications, offering a highly personalized and potentially curative approach for a range of genetic disorders [47].

The Future of Stem Regenerative Medicine in Ophthalmic Conditions

The translational pipeline for stem cell-based interventions in ophthalmology is rapidly expanding, driven by coordinated efforts from academic centers, biotech companies, and regulatory agencies. Notable clinical programs include jCyte's Phase IIb trial of retinal progenitor cells for RP, Lineage Cell Therapeutics' OpRegen for dry AMD, and Holostem's Holoclar, the first EMA-approved limbal stem cell therapy for limbal stem cell deficiency (LSCD) [48,49]. There are also significant innovations emerging through both scientific and technological advances that are reshaping the field's trajectory. Notably, CRISPR-edited iPSCs targeting monogenic retinal disorders, is being leveraged to enable precision-matched, disease-corrected therapies [50]. Numerous smart biomaterials and 3D scaffolds continue to evolve offering enhancements in cell survival, guide integration, and the capacity to mimic the native niche microenvironment [51]. Furthermore, immune cloaking strategies, such as HLA knockout or CD47 upregulation, are in development to facilitate allogeneic transplantation while mitigating rejection risk [52]. In parallel, the identification of non-invasive imaging biomarkers such as adaptive optics and spectral-domain OCT (to name a few) are being validated for real-time monitoring of graft locali-

zation, survival, and functional integration [53]. These technologies aim to address persistent challenges including limited engraftment, poor synaptic restoration, tumorigenicity, and the risk of off-target differentiation, particularly in therapies derived from ESCs and iPSCs [54,55].

As scientific hurdles are progressively addressed through bioengineering and immunomodulatory innovations, commercial interest has grown in parallel. Key examples are reflected in major pharmaceutical investments in stem cell platforms. For instance, Astellas' $379M acquisition of Ocata Therapeutics underscores the strategic value placed on retinal pigment epithelium (RPE)-based therapies in the evolving landscape of regenerative ophthalmology. Similarly, Roche is exploring combination cell/gene therapies, reflecting a growing convergence in regenerative and genetic medicine [56,57]. Venture capital and public funding (e.g., NIH's recent $2.7M award for RP circuitry studies) have continued to support novel therapeutic development and address scalability issues [58].

Global regulatory frameworks are evolving in parallel. Japan and South Korea have implemented accelerated pathways for regenerative therapies, while the FDA's RMAT designation provides expedited support for products addressing unmet medical needs. Stem cell products in the EU are increasingly classified as Advanced Therapy Medicinal Products (ATMPs), allowing for centralized regulatory oversight with bespoke criteria for cell-based interventions [59,60].

Future clinical and manufacturing efforts in ocular stem cell therapies will prioritize the refinement of potency and durability endpoints that reliably reflect neuroretinal cell survival and meaningful improvements in functional vision. Establishing standardized delivery methods will also be essential, particularly in comparing the efficacy, safety, and scalability of subretinal injection techniques, commonly used in retinal therapies, with less invasive approaches such as topical application for limbal epithelial stem cell (LESC)-based corneal treatments. Moreover, researchers and developers must navigate the trade-offs between autologous and allogeneic production models: while autologous therapies offer immunological compatibility and reduced rejection risk, allogeneic products hold greater promise for large-scale manufacturing, quality control, and global accessibility. Harmonizing these variables will be critical to achieving both clinical impact and commercial viability. In particular, startups biotechs are actively pursuing off-the-shelf, scalable, allogeneic solutions for global health deployment [61]. Increasing collaborations with bioengineering firms are facilitating the development of composite cell-scaffold constructs with improved structural and functional integration [62].

Conclusion

The convergence of stem cell biology, gene editing, biomaterials engineering, and imaging diagnostics is positioning ocular regenerative medicine at the forefront of translational science. While considerable challenges remain, the rapid advancement of enabling technologies and evolving regulatory frameworks signals a promising future for stem cell-based therapies targeting blinding diseases.

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Conflict of Interest

None.

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