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Eye Stem Cells and the Future of Regenerative Ophthalmology

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Abstract

Stem cell-based regenerative medicine has emerged as one of the most promising strategies for treating ocular diseases characterized by irreversible tissue damage. The eye provides a particularly attractive target for regenerative medicine because several ocular tissues contain endogenous progenitor populations, while pluripotent stem-cell technologies can generate clinically relevant corneal and retinal cell types. Among current applications, limbal stem-cell transplantation has achieved the strongest clinical translation, particularly for limbal stem cell deficiency (LSCD). In parallel, human embryonic stem cells and induced pluripotent stem cells (iPSCs) are being investigated as sources of retinal pigment epithelium (RPE), photoreceptors, retinal progenitors, and retinal organoids for degenerative retinal diseases. Recent clinical studies have demonstrated encouraging safety profiles for selected RPE-based therapies, while advances in retinal organoids, genome editing, biomaterials, and tissue engineering are opening new possibilities for functional retinal reconstruction. Nevertheless, substantial challenges remain, including cell heterogeneity, incomplete maturation, limited survival and integration, immune rejection, tumorigenic potential, manufacturing variability, and the absence of standardized potency assays. The field is therefore moving from conventional cell transplantation toward integrated regenerative strategies combining precisely characterized cells, engineered microenvironments, genetic correction, biomaterials, and advanced monitoring. This editorial discusses the current state and future direction of ocular stem-cell therapy and emphasizes the need to translate biological promise into reproducible, evidence-based clinical benefit.

Keywords: eye stem cells; limbal stem cells; regenerative ophthalmology; limbal stem cell deficiency; retinal regeneration; retinal pigment epithelium; induced pluripotent stem cells; retinal organoids; cell therapy; tissue engineering

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1. Introduction

Vision depends on the integrity of highly specialized tissues, including the corneal epithelium, corneal stroma, retinal pigment epithelium, photoreceptors, retinal neurons, and optic nerve. Although some ocular tissues exhibit substantial regenerative activity, many forms of severe ocular injury and retinal degeneration exceed the intrinsic repair capacity of the eye. Consequently, conditions such as severe LSCD, geographic atrophy associated with age-related macular degeneration (AMD), inherited retinal diseases, and advanced retinal dystrophies can produce permanent structural damage and irreversible visual impairment. These limitations have made ophthalmology an important field for the development of regenerative medicine and cell-based therapies [1-3]. The contemporary concept of ocular stem-cell therapy extends considerably beyond the simple replacement of lost cells. Adult stem or progenitor populations have been identified in multiple ocular compartments, including the cornea, limbus, trabecular meshwork, lens, iris, ciliary body, retina, choroid, conjunctiva, lacrimal gland, and orbital tissues [1]. At the same time, pluripotent stem-cell technologies have enabled the generation of differentiated ocular cells in quantities and developmental states that were previously difficult to obtain. These advances have created new opportunities not only for transplantation but also for disease modeling, drug discovery, toxicity testing, and precision medicine [4-6]. An important conceptual distinction, however, must be maintained between biological potential and clinical efficacy. The identification of a stem-like population does not necessarily establish that it can be expanded, standardized, delivered, and safely integrated into diseased human tissue. Modern regenerative medicine therefore requires simultaneous consideration of cell identity, potency, manufacturing, delivery, host–graft interactions, immune responses, and clinically meaningful functional outcomes [4,7]. This distinction is particularly relevant as ocular stem-cell research moves rapidly from experimental laboratories toward clinical applications.

2.Limbal Stem Cells: The Most Mature Ocular Stem-Cell Therapy

Among ocular stem-cell populations, limbal epithelial stem cells have reached the most advanced stage of clinical translation. These cells maintain the corneal epithelium throughout life and reside within a specialized limbal niche that regulates self-renewal, proliferation, differentiation, and interaction with the surrounding extracellular matrix [8,9]. Damage to this population can lead to LSCD, characterized by persistent epithelial defects, conjunctivalization of the cornea, vascularization, inflammation, recurrent epithelial breakdown, and progressive visual impairment [10]. The clinical development of limbal stem-cell transplantation represents an important proof of concept for regenerative medicine. Current approaches include simple limbal epithelial transplantation (SLET), cultivated limbal epithelial transplantation (CLET), conjunctival-limbal autografting, living-related allografting, and keratolimbal allografting [8,11]. A large meta-analysis published in 2020 demonstrated clinically meaningful anatomical and functional outcomes across different limbal stem-cell transplantation strategies, although success rates varied according to disease severity, transplantation technique, donor source, and follow-up duration [12]. SLET has become particularly attractive because it requires a relatively small amount of donor tissue and can avoid the extensive laboratory infrastructure associated with ex vivo cell expansion. Contemporary clinical evidence suggests that SLET can restore and maintain a stable ocular surface in severe LSCD caused by ocular burns, with outcomes comparable to or better than CLET in selected settings [13]. These findings are particularly relevant to the broader dissemination of regenerative ophthalmology because simpler procedures may be more accessible in resource-limited healthcare systems. Nevertheless, successful transplantation depends on more than delivering cells to the ocular surface. The condition of the limbal niche, ocular inflammation, corneal vascularization, conjunctival pathology, tear-film abnormalities, and previous surgical interventions can all influence treatment outcomes [9,10]. Recent literature increasingly emphasizes that restoration of the stem-cell niche should be considered an integral component of therapy rather than a secondary issue [14,15]. The

treatment of bilateral LSCD illustrates this complexity particularly well. When autologous tissue is unavailable, allogeneic transplantation may be required, but immune rejection becomes a major concern. A 2024 report by the American Academy of Ophthalmology reviewing keratolimbal and living-related conjunctival-limbal allografts highlighted the importance of donor selection, immunosuppression, and long-term surveillance in determining clinical outcomes [16]. Thus, although limbal stem-cell therapy is currently the most clinically mature ocular stem-cell application, it remains a biologically and surgically demanding intervention.

3.Ocular Stem Cells Beyond the Limbus

The broader ocular stem-cell landscape is considerably more diverse. Adult stem or progenitor populations have been investigated in the cornea, conjunctiva, trabecular meshwork, lens, ciliary body, retina, choroid, sclera, and lacrimal gland [1]. Their potential applications range from ocular surface reconstruction to glaucoma research and retinal repair. However, the strength of evidence differs substantially among these populations, and only a limited number have progressed toward meaningful clinical translation [1,17]. Mesenchymal stromal cells (MSCs) represent a separate and extensively investigated category. Their potential therapeutic effects may not depend primarily on direct differentiation into ocular cell types. Instead, MSCs can release trophic and immunomodulatory factors, extracellular vesicles, cytokines, and other mediators that influence inflammation, epithelial repair, oxidative stress, fibrosis, and cell survival [18]. These properties have generated interest in MSC-based approaches for corneal injury and ocular surface disease. Importantly, clinical evidence for MSC therapy in ocular surface disease remains less mature than the evidence for limbal stem-cell transplantation. A 2025 critical review of clinical studies concluded that MSC-based approaches are promising but remain limited by substantial heterogeneity in cell source, manufacturing, administration route, dosing, and outcome assessment [18]. This highlights a general problem in cell therapy: the term “stem cell treatment” encompasses biologically diverse products that cannot automatically be considered equivalent.

4.Pluripotent Stem Cells and Retinal Regeneration

The retina presents a substantially more complex regenerative challenge than the ocular surface. The mature human retina has limited endogenous regenerative capacity, and loss of photoreceptors, RPE cells, or retinal neurons can therefore result in progressive and permanent visual dysfunction [19,20]. Consequently, retinal regenerative medicine has focused heavily on embryonic stem cells (ESCs), iPSCs, retinal progenitor cells, RPE cells, and photoreceptor-lineage cells. The RPE is one of the most attractive targets for cell replacement because it performs multiple essential functions, including photoreceptor support, phagocytosis of photoreceptor outer segments, visual-cycle activity, metabolic exchange, and maintenance of the outer blood-retinal barrier. RPE dysfunction is central to the pathophysiology of several retinal degenerative disorders, including AMD and Stargardt disease [19,21]. Human iPSCs provide an especially valuable platform because they can be differentiated into RPE and retinal cell populations while also allowing patient-specific disease modeling. Recent reviews have highlighted the potential of iPSC-derived RPE for personalized regenerative strategies in AMD and other degenerative retinal disorders [21]. At the same time, substantial work is required to ensure that differentiated cells demonstrate appropriate morphology, molecular identity, polarity, barrier function, and long-term

stability before clinical use. Clinical studies have provided increasingly important evidence regarding the safety of stem-cell-derived RPE transplantation. A long-term phase 1/2a study of a bioengineered stem-cell-derived RPE implant for geographic atrophy reported favorable long-term safety findings and provided preliminary evidence supporting further investigation of tissue-engineered RPE replacement [22]. More recently, a first-in-human study of an adult RPE stem-cell-derived product in dry AMD reported favorable low-dose safety and tolerability outcomes, with no significant product-related tumor or serious inflammatory events in the initial cohort [23]. These findings are encouraging but should not yet be interpreted as definitive evidence of widespread visual restoration.

The broader clinical literature supports a cautious interpretation. A 2025 review of retinal stem-cell clinical trials concluded that the field is progressing but remains at an early stage, with important unresolved questions regarding the optimal cell type, developmental stage, delivery method, immunological management, and functional endpoints [24]. The distinction between anatomical graft survival and meaningful visual recovery remains particularly important.

5.Retinal Organoids: From Disease Models to Therapeutic Tissues

Retinal organoids represent one of the most significant developments in modern ocular stem-cell biology. Generated from pluripotent stem cells, retinal organoids can self-organize into three-dimensional structures containing multiple retinal cell types and can reproduce important aspects of human retinal development [25,26]. Their applications now extend from developmental biology and disease modeling to drug screening, toxicity assessment, gene-editing validation, and experimental cell replacement. The translational potential of retinal organoids is particularly evident in inherited retinal diseases. A systematic review published in 2025 identified 130 studies using patient-derived iPSC retinal organoids and demonstrated their broad application in disease modeling, therapeutic screening, and generation of candidate cells for transplantation [27]. Patient-specific organoids can reproduce disease-associated phenotypes and provide a human-relevant experimental system for evaluating potential treatments. Recent work has also demonstrated the value of organoids for studying specific genetic disorders. For example, transcriptomic analysis of ABCA4-mutant retinal organoids has provided new information regarding molecular abnormalities relevant to inherited retinal disease [28]. Such approaches illustrate how organoid systems can bridge molecular genetics and therapeutic development. However, retinal organoids are not equivalent to mature human retinas. Important differences remain in vascularization, immune interactions, maturation, retinal architecture, foveal organization, and the interaction between the retina and the RPE–choroid complex [25,29]. A 2026 review emphasized that although organoid technology is rapidly improving, functional integration after transplantation remains incompletely demonstrated and considerable biological variability exists between protocols and cell lines [29]. One particularly exciting development is the combination of organoid technology with genome editing. In 2025, Watanabe and colleagues reported that transplantation of genome-edited retinal organoids could restore selected physiological functions in severely degenerated host retinas in experimental models [30]. Although this remains preclinical evidence, it illustrates the potential of combining genetic engineering with tissue replacement rather than treating these technologies as separate therapeutic strategies.

6.Regenerative Engineering and Biomaterials

The future of ocular stem-cell therapy will likely depend increasingly on regenerative engineering. Instead of viewing the therapeutic product simply as a suspension of cells, regenerative engineering considers cells, extracellular matrix, biomaterials, signaling molecules, and tissue architecture as an integrated therapeutic system [14,31]. For ocular surface regeneration, biomaterials can provide structural support and improve cell retention, differentiation, and survival. Biomolecule-based hydrogels have recently been investigated as delivery systems for limbal stem cells, with the potential to create a more favorable microenvironment and improve the efficiency of transplantation [31]. More broadly, clinical-trial analyses indicate increasing use of biological and synthetic scaffolds in corneal regeneration [32]. The same principle applies to retinal therapy. RPE cells naturally form a polarized monolayer closely associated with Bruch's membrane. Consequently, transplantation of isolated cells may not fully reproduce the architecture and function of native RPE tissue. Bioengineered cell sheets and scaffold-supported RPE constructs attempt to address this limitation by providing spatial organization and mechanical support [22,33].

This shift from “cell transplantation” toward “tissue reconstruction” may represent one of the most important conceptual developments in regenerative ophthalmology. Successful vision restoration will probably require not only replacing individual cells but also reconstructing the cellular relationships and microenvironment necessary for normal function.

7.Safety and Regulatory Challenges

Safety remains the fundamental requirement for clinical translation. Pluripotent stem-cell-derived products require rigorous assessment for genomic stability, residual undifferentiated cells, inappropriate differentiation, proliferative activity, and tumorigenic potential [4,24]. Manufacturing processes must also be reproducible and capable of producing consistent cellular products under appropriate quality-control standards. The expansion of pluripotent stem-cell therapies across clinical medicine provides important context. A 2025 update identified more than 100 regulatory-approved clinical trials involving human pluripotent stem-cell-derived products worldwide, with ophthalmology representing one of the major therapeutic areas [34]. The growing clinical experience is encouraging, but it also demonstrates the need for standardized manufacturing, potency assays, long-term monitoring, and transparent reporting of adverse events. Immune responses remain another major concern. Even in the relatively immune-regulated ocular environment, transplanted cells may undergo immune-mediated rejection. This is particularly relevant to allogeneic limbal transplantation and retinal cell therapy [16,24]. Donor matching, immunosuppressive protocols, immune-evasive cell engineering, and potentially autologous iPSC-derived products may each contribute to future solutions. The distinction between regulated clinical research and unproven commercial “stem cell treatments” must also remain clear. Patients with severe visual impairment may be particularly vulnerable to unsupported claims of vision restoration. Appropriate regulatory oversight, ethical clinical-trial design, informed consent, and long-term follow-up are therefore essential to protect patients while allowing legitimate innovation to progress [4,34].

8.The Next Generation of Eye Stem-Cell Therapy

The next generation of ocular regenerative medicine is unlikely to be defined by a single universal stem-cell product. Instead, treatment strategies will probably become increasingly disease-specific, patient-

specific, and mechanism-specific. Limbal stem-cell transplantation may remain the preferred approach for selected forms of LSCD, whereas RPE replacement may be more appropriate for particular stages of macular degeneration [15,23,24]. For inherited retinal disease, the convergence of iPSCs, retinal organoids, and gene editing is particularly promising. Patient-derived cells can reproduce disease phenotypes in vitro, while genome editing can potentially correct disease-causing mutations before differentiation into therapeutic retinal cells [27,30]. This creates a conceptual pathway from disease modeling to personalized regenerative therapy. Single-cell and spatial technologies may further improve this process by allowing researchers to characterize therapeutic cells at unprecedented resolution. Identifying the precise molecular state associated with optimal maturation, survival, and integration could help establish more reliable potency assays and reduce variability between cell products [25,28,29]. Extracellular vesicles and cell-free regenerative approaches represent another emerging direction. If some therapeutic effects of stem cells are mediated through secreted factors, future therapies might use selected biological products rather than living cells. Such approaches could potentially reduce some manufacturing and safety challenges, although clinical efficacy and standardization remain to be established [18] Figure1 .

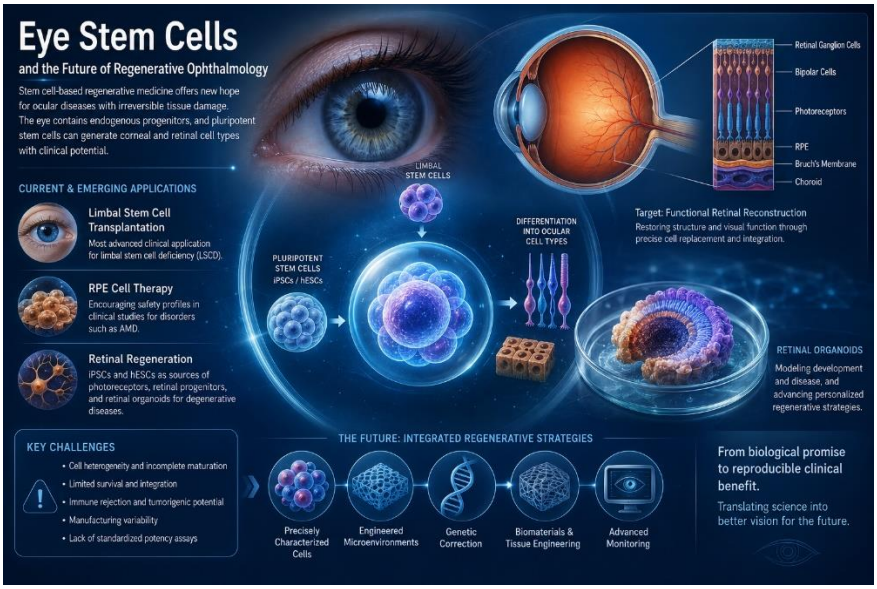

Figure1; Schematic overview of ocular stem-cell applications in regenerative ophthalmology, highlighting limbal stem cells, RPE and retinal regeneration, and retinal organoids. Emerging strategies integrating stem cells, genetic correction, biomaterials, tissue engineering, and advanced monitoring may enable functional and clinically reproducible vision restoration.

9.Editorial Perspective

The development of ocular stem-cell therapy has reached an important transition point. The field has moved beyond the question of whether stem cells can influence ocular tissues and is now confronting the more difficult questions of which cells should be used, in which patients, at what stage of disease, through which delivery system, and with what supporting microenvironment [24,29]. The cornea provides the strongest evidence that regenerative medicine can produce clinically meaningful tissue restoration. Limbal transplantation has demonstrated that appropriately selected cells can restore epithelial homeostasis and improve ocular surface function [12,13]. Retinal regeneration is more complex, but

recent clinical studies of RPE products and advances in retinal organoids suggest that the biological foundations for future therapies are becoming increasingly robust [22,23,27]. In my view, the most promising future lies in combining technologies rather than treating them as independent approaches. A next-generation therapeutic platform could combine genetically corrected patient-specific cells, biomaterial scaffolds, controlled-release systems, immune modulation, and advanced imaging-based monitoring. Such an integrated strategy may be particularly important for advanced retinal diseases, in which genetic defects, inflammation, neuronal loss, and tissue remodeling coexist. The eye is uniquely positioned to serve as a leading model for regenerative medicine. Ocular tissues can often be directly visualized, treated locally, and monitored repeatedly using high-resolution imaging. The lessons learned from ocular stem-cell therapy may therefore extend well beyond ophthalmology and inform regenerative strategies for other organs.

10.Conclusion

Ocular stem-cell research has evolved from the identification of endogenous progenitor populations toward increasingly sophisticated cell, gene, organoid, and tissue-engineering therapies. Limbal stem-cell transplantation currently represents the most clinically established application, whereas RPE replacement, photoreceptor regeneration, iPSC-derived cells, retinal organoids, and engineered retinal tissues represent rapidly developing areas of investigation [1,22,24,29]. The current evidence supports cautious optimism. Several clinical studies demonstrate encouraging safety and feasibility, but durable restoration of complex visual function remains a major challenge. Future progress will depend on rigorous cell characterization, reproducible manufacturing, improved graft survival and integration, appropriate patient selection, and long-term clinical surveillance [23,24,34]. The convergence of stem-cell biology, gene editing, retinal organoids, biomaterials, and precision medicine may ultimately transform selected forms of blindness from conditions that are primarily managed into diseases that can be biologically repaired. The central objective of regenerative ophthalmology should therefore not simply be to transplant cells, but to reconstruct the biological environment required for functional vision.

Declarations

No ethics committee approval was required as this manuscript does not involve human subject research.

Consent for publication

No consent was obtained as this manuscript does not involve human subject research.

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Declaration of competing interest

The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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