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MINIREVIEWS

Novel developments in retinal regeneration: Advances and future outlooks in stem cell therapy

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Abstract

Retinal degenerative diseases, such as age-related macular degeneration, retinitis pigmentosa, and Stargardt disease, are primary contributors to irreversible vision loss globally. Due to the scarcity of effective curative treatments, stem cell therapy has emerged as a revolutionary advancement in ophthalmology. In the last ten years, significant advancements have been achieved in the derivation of retinal pigment epithelium and photoreceptor precursors from human embryonic stem cells and induced pluripotent stem cells, with initial clinical trials indicating safety and potential efficacy. Innovative delivery platforms, such as biodegradable scaffolds, microcarrier suspensions, and minimally invasive subretinal devices, are tackling prior challenges related to cell survival and integration. Simultaneously, gene-edited and patient-specific induced pluripotent stem cells are positioned to surmount immunological and ethical constraints. Future combin-

atorial strategies that incorporate stem cells with gene therapy, CRISPR-mediated editing, and bioengineered retinal organoids offer potential for personalized and regenerative methodologies. Nonetheless, enduring functional integration, immune tolerance, and oncogenic safety continue to pose significant challenges. To effectively transition from laboratory research to clinical application, collaborative frameworks among academic institutions, biotechnology companies, and regulatory agencies will be crucial for unlocking the complete therapeutic potential of stem cell-based treatments for retinal diseases. Stem cell therapy has transitioned from a distant promise to an advancing reality set to transform retinal care.

Key Words: Stem cells; Induced pluripotent stem cells; Retinal degeneration; Retinal pigment epithelium; Regenerative medicine; Gene editing

Core Tip: Stem cell therapies have a revolutionary potential to restore eyesight in individuals afflicted with retinal degenerative disorders, including age-related macular degeneration, retinitis pigmentosa, and Stargardt disease. Progress in human embryonic stem cell- and induced pluripotent stem cell-derived retinal cells, novel delivery mechanisms, and gene-editing methods is expediting clinical use. Nonetheless, enduring functional integration, immunological tolerance, and carcinogenic hazards persist as unresolved difficulties. Future success will rely on combinatorial strategies and global regulatory alignment to fully realize the potential of regenerative ophthalmology.

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INTRODUCTION

Retinal degenerative diseases, including age-related macular degeneration (AMD), retinitis pigmentosa (RP), and Stargardt disease, are primary contributors to irreversible blindness worldwide[1]. These diseases are characterized by progressive degeneration of photoreceptors and retinal pigment epithelium (RPE) malfunction, ultimately leading to central or peripheral vision loss that severely affects daily activities and quality of life. Despite significant advancements in the molecular genetics and imaging of retinal dystrophies, existing medicines predominantly provide symptomatic alleviation or slight deceleration of disease development, rather than structural or functional restoration. Stem cell therapy has emerged as a highly promising regenerative approach for retinal illnesses, seeking to restore vision by replacing or supporting deteriorating retinal cells[2]. Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) can be induced to develop into RPE and photoreceptor-like cells, providing a theoretically inexhaustible source of autologous or allogeneic transplantable tissue[3]. Pioneering clinical studies have demonstrated the feasibility of RPE transplantation. Schwartz *et al*[4] reported the first hESC-derived RPE transplantation in patients with Stargardt disease and dry AMD, showing evidence of cell survival without tumorigenicity or immune rejection and mild visual function improvement. Mandai *et al*[5] performed the first autologous iPSC-derived RPE sheet transplantation in neovascular AMD, demonstrating safety and graft retention at one year, though without visual acuity gain. Mehat *et al*[6] conducted a phase 1/2 dose-escalation trial of hESC-derived RPE cells in Stargardt disease, showing graft survival and acceptable safety. In the past ten years, preclinical and early clinical trials have demonstrated the safety, feasibility, and preliminary efficacy of these methods. da Cruz *et al*[7] documented enhancements in visual acuity and anatomical integration of a hESC-derived RPE patch in patients with severe exudative AMD, thereby endorsing the feasibility of stem cell-based therapies in advanced retinal disorders.

Preliminary trials utilizing hESC-derived RPE suspensions shown positive safety profiles, with no indications of tumorigenicity, hyperproliferation or immunological rejection throughout four years of follow-up[8]. Further studies resulted in the development of polarized RPE monolayers on biodegradable scaffolds or synthetic membranes, enhancing cell alignment, viability, and integration into host tissue[9,10]. Concurrent investigations into iPSCs have facilitated the creation of patient-specific cell lines, thereby addressing ethical dilemmas and mitigating the risk of immunological incompatibility. Recent advancements in non-viral reprogramming and the omission of oncogenic transcription factors, such as c-Myc, have significantly increased the therapeutic attractiveness of iPSC-derived retinal cells[11,12].

Nevertheless, significant challenges persist. Although morphological engraftment has been reported, achieving consistent and enduring functional restoration, including synapse formation, phototransduction, and long-range connection, continues to be a challenging objective[13]. Moreover, apprehensions over genetic stability, the long-term tumorigenic potential, and the intricacies of surgical delivery have moderated extensive clinical use. Innovative approaches integrating stem cell therapy with CRISPR gene editing, neuroprotective agents, and retinal organoids are now being investigated to enhance efficacy and tailor treatment regimens[14]. This analysis highlights recent progress in

cell sourcing, delivery systems, and integrative technologies for retinal regeneration. We evaluate the current state of clinical readiness, outline key translational obstacles, and explore future directions for stem cell-based therapies that could transform the treatment paradigm for blinding retinal conditions.

LITERATURE REVIEW

A narrative synthesis of the latest literature on stem cell-based therapy for retinal degenerative illnesses was conducted. Focus was directed towards investigating the application of hESCs, iPSCs, and RPE progenitors which are characterized as partially differentiated precursors that maintain proliferative potential while demonstrating initial RPE lineage commitment, in contrast to fully differentiated post-mitotic RPE monolayers in addressing conditions like AMD, RP, and Stargardt disease. The aim was to deliver a conceptual framework that amalgamates clinical preparedness with experimental advancement. Relevant publications, with a focus on those indexed in PubMed and applicable to human use and those released between January 2018 and May 2025 were evaluated. The selection prioritized peer-reviewed articles that reported on clinical trials, translational studies including subretinal or scaffold-based administration, and reviews concerning safety, immunogenicity, or combinatorial techniques such as gene editing and organoid integration. Articles were included if they presented data on stem cell derivation methodologies, delivery methods, safety outcomes, and therapeutic effectiveness. Studies devoid of translational aim, those restricted to animal research without addressing human relevance, or publications lacking indexed identifiers were not included.

All included articles were thoroughly analyzed to extract information regarding the type and source of stem cells, differentiation procedures, clinical endpoints, immunomodulatory protocols, surgical platforms, and documented adverse events. Special emphasis was placed on articles concerning long-term follow-up, visual function restoration, and host-graft integration. We recognize the possibility of bias stemming from the emphasis on freshly released literature. Numerous early-phase studies predominantly emphasize short-term safety and feasibility outcomes, but the inadequate representation of long-term follow-up data - particularly for iPSC-derived photoreceptors - restricts conclusive determinations. This review does not seek to deliver a comprehensive systematic analysis. Instead, it provides an academic viewpoint informed by the integration of robust data and clinical practicality.

ADVANCES IN CELL SOURCES

The therapeutic efficacy of stem cell therapy for retinal regeneration essentially depends on the capacity to produce RPE and photoreceptor precursors, which are lineage-committed cells that already express rod or cone photoreceptor markers but have not yet formed fully mature outer segments, through sequential differentiation protocols from renewable and clinically suitable sources. hESCs were the first to undergo clinical testing because to their pluripotency and well-defined differentiation capabilities. Significant research, by Schwartz *et al*[15], established that hESC-derived RPE cells could be safely transplanted into patients with dry AMD and Stargardt disease, leading to anatomical integration and initial indications of visual function recovery over a four-year follow-up period. This trial established a basis for future treatment investigations, particularly by confirming the absence of tumorigenicity, immunological rejection and serious systemic or ocular safety issues.

The subsequent enhancement of differentiation methods enabled the generation of RPE monolayers exhibiting polarized morphology and tight connection formation, so emulating the native subretinal architecture. This progress led to a phase I clinical trial conducted by da Cruz *et al*[7], in which a fully differentiated hESC-RPE patch, derived from the SHEF-1.3 line and seeded onto a synthetic polyester membrane coated with vitronectin, was successfully transplanted into the subretinal space of two patients with advanced exudative AMD. After 12 months, both patients showed sustained patch survival and clinically meaningful gains in best-corrected visual acuity (29 and 21 ETDRS letters). The study used local immunosuppression and a specifical designed microsurgical delivery device to ensure precise implantation and minimize trauma.

The emergence of iPSCs has changed regenerative ophthalmology by facilitating the autologous generation of retinal cells. iPSCs can be produced from patient-derived somatic cells, including skin fibroblasts or peripheral blood mononuclear cells, and subsequently developed into RPE or photoreceptor precursors under xeno-free and good manufacturing practice (GMP)-compliant conditions[16]. These characteristics make iPSCs particularly advantageous for tailored therapy, particularly in hereditary retinal dystrophies where patient-specific gene repair is preferable.

Despite their potential, iPSC-based medicines have not attained the same degree of clinical maturity as hESC-based alternatives. Concerns about genetic and epigenetic instability, regulatory complexity, and inconsistent differentiation efficiency have hindered the speed of translation[17]. Nonetheless, preliminary trials and preclinical investigations indicate that iPSCs provide a scalable and ethically permissible option for autologous transplantation. Current initiatives focus on creating universal donor iPSC lines that can be immunologically compatible with extensive patient demographics, thereby integrating the advantages of both autologous and allogeneic methods[18,19].

Additional cellular sources being examined include Müller glial cells, mesenchymal stem cells (MSCs), and retinal progenitor cells, which are earlier multipotent precursors that can differentiate into various retinal lineages under suitable conditions. While MSCs have neuroprotective and immunomodulatory properties in animal models of retinal degeneration, they do not develop into functional photoreceptors or RPE cells, hence restricting their application to supplementary therapy[20]. Müller cells obtained from cadaveric retinas may possess restricted capacity for photoreceptor-like development, although encounter considerable scalability and ethical obstacles[21]. Thus, the present emphasis in the

research is on optimizing hESC and iPSC platforms to achieve a balance among safety, efficacy, and manufacturability.

Recent preclinical advances underscore the potential of photoreceptor precursor transplantation for treating end-stage retinal degeneration. For example, pluripotent stem cell-derived cone precursors transplanted into Pde6brd1 mice integrated into the host retina, differentiated into functional cones, and elicited measurable light responses[22]. In another report, hESC- and iPSC-derived photoreceptor progenitors transplanted into mice with advanced degeneration demonstrated partial restoration of visual behavior and synaptic integration[23]. Over the past decade, there has been a shift from proof-of-concept tests to clinically supervised therapies utilizing stem cell-derived retinal cells. Improvements in differentiation procedures, quality control, and reprogramming accuracy have markedly enhanced the therapeutic applicability of hESCs and iPSCs. Ongoing head-to-head comparisons and longitudinal follow-up investigations will be crucial to ascertain the most suitable cell source for particular retinal diseases.

EMERGING DELIVERY PLATFORMS

Although progress in stem cell derivation has facilitated the production of RPE and photoreceptor precursors appropriate for transplantation, the clinical efficacy of these therapies is fundamentally reliant on efficient and secure delivery systems. The subretinal space, delineated by the RPE and the photoreceptor layer, provides a natural environment for cell transplantation. Nonetheless, traversing this intricate anatomical area poses various technical and biological obstacles, such as restricted surgical access, the potential for retinal detachment, and suboptimal cell viability in suspension[24]. Preliminary experiments using direct subretinal injections of cell suspensions indicated that transplanted hESC-derived RPE cells may last *in vivo* and assimilate inside the host retina. However, these approaches frequently experienced inconsistent dispersion and diminished engraftment efficacy. To address these limitations, researchers have progressively utilized scaffold-based delivery techniques that provide structural support and spatial structure for transplanted cells[25]. For instance, da Cruz *et al*[7] developed a composite implant comprising a monolayer of RPE generated from hESCs cultivated on a vitronectin-coated polyester membrane. The patch, delivered by a specialized microsurgical instrument, exhibited strong anatomical integration and functional enhancement in individuals with advanced AMD.

Biodegradable scaffolds composed of materials like polycaprolactone, parylene, or gelatin-based hydrogels have broadened the spectrum of delivery alternatives. These biomaterials provide transient structural support while progressively dissolving *in situ*, facilitating the integration of transplanted cells into host tissue without prolonged foreign body exposure[26]. Material properties, including degradation rate, porosity, and mechanical stiffness, substantially affect scaffold efficacy. Polymers with slower degradation rates, such as polycaprolactone, provide extended structural support, facilitating the development and orientation of RPE monolayers. Conversely, rapidly degrading materials like gelatin-based hydrogels may improve host integration but pose a danger of premature scaffold integrity loss. Optimal designs equilibrate mechanical stability and biocompatibility, reducing inflammation and facilitating tight junction formation for effective RPE repair. Besides subretinal methods, suprachoroidal and intravitreal pathways have been explored, especially for stem cell varieties that do not necessitate direct interaction with photoreceptors to achieve therapeutic outcomes. These encompass MSCs, which function predominantly by secreting neurotrophic and anti-inflammatory substances. Despite being less invasive, these administration methods typically yield diminished anatomical integration and are more appropriate for complementary or supportive therapy[27,28].

Delivery methods are advancing with the introduction of less invasive subretinal cannulas, microfluidic devices, and real-time intraoperative imaging to ensure precise placement and evaluate graft integrity[29]. Notwithstanding these advancements, consistent distribution and prolonged viability of transplanted cells continue to be challenging objectives, particularly with bigger, more delicate cell sheets or intricate organoid formations. The necessity for immunosuppression in allogeneic contexts significantly complicates long-term survival. Most clinical regimens to date have utilized short-term local immunosuppression, generally employing oral prednisolone and perioperative corticosteroids[30]. Scaffold-assisted delivery platforms and advanced microsurgical instruments have augmented the accuracy and efficacy of stem cell-based retinal therapies. Subsequent versions will probably integrate real-time sensors, drug-eluting matrices, or gene-encoded tracking devices to enhance monitoring and modulation of post-transplantation behavior.

GENE EDITING AND RETINAL ORGANOIDS

As stem cell-derived retinal therapies progress from feasibility to clinical implementation, combinatorial strategies have surfaced as effective supplements to address the constraints of isolated cell replacement. The amalgamation of gene editing, bioengineered organoids, and multi-modal regenerative approaches signifies the forthcoming advancement in individualized retinal treatment. Gene editing tools, particularly CRISPR-Cas9, have facilitated the accurate rectification of disease-inducing mutations in patient-derived iPSCs. This potential is particularly relevant in inherited retinal degenerations like RP and Stargardt disease, where single-gene abnormalities can now be rectified at the cellular level prior to transplantation[31,32]. CRISPR-Cas9–based genome editing is emerging as a promising transformative modality for inherited retinal diseases. Preclinical studies have demonstrated successful gene correction in models of RP and Leber congenital amaurosis, and the first *in vivo* clinical trial (EDIT-101, BRILLIANCE) in CEP290-associated LCA10 has shown safety and early signals of visual function improvement following subretinal CRISPR/Cas9 delivery[33]. However, clinical translation faces challenges, including off-target editing risks, delivery efficiency, and evolving regulatory and ethical barriers surrounding somatic genome editing in the eye. Delivery of CRISPR-Cas9 as ribonucleoprotein complexes reduces integration risk and off-target activity, but achieving high-efficiency, clinical-grade non-viral editing in iPSC lines

at scale remains a bottleneck due to low transfection efficiencies and complex manufacturing workflows. Rigorous off target validation *via* unbiased whole-genome sequencing or GUIDE-seq is costly and adds substantial time to release testing. Furthermore, the infrastructure required, such as GMP-compliant automation, closed editing systems, and validated quality control pipelines dramatically increases costs, presenting high entry barriers for clinical translation[34]. The production of genetically modified autologous iPSC-RPE cells provides a dual benefit: Precise therapeutic effectiveness and immunological compatibility. Significantly, non-viral delivery systems and base editing technologies are being rigorously developed to reduce off-target effects and insertional mutagenesis, both essential for clinical safety[35].

Concurrently, the application of retinal organoids - three-dimensional, self-organizing tissue constructions originating from stem cells - has broadened the potential of retinal cell therapy. In contrast to monolayer cultures or isolated RPE sheets, retinal organoids encompass stratified photoreceptors, interneurons, and glial cells, thereby mirroring the cytoarchitecture of the normal retina. Organoids have been utilized to produce donor photoreceptor precursors for subretinal transplantation, with preclinical models exhibiting synaptic integration and partial recovery of light responses[36]. In mice with advanced retinal degeneration, organoid-derived sheets survived, formed synapses with host retinal cells, and restored light-responsive behavior in retinal ganglion cells (RGCs)[37]. In non-human primates, subretinal transplantation of hESC-derived organoid sheets in a macular hole model achieved anatomical closure, graft survival over months, rod/cone photoreceptor differentiation, and behavioral fixation improvements, with no signs of tumor formation [38]. Nonetheless, their considerable size, susceptibility to damage, and variable differentiation characteristics present persistent obstacles for surgical application and uniformity.

Nonetheless, the intricacy of these platforms presents considerable regulatory and production hurdles. Every supplementary component - be it gene-editing apparatus, structural materials, or co-delivered agents - augments the evidentiary requirements for safety, repeatability, and scalability. International cooperation, standardized GMP protocols, and real-time pharmacovigilance systems will be essential for the secure implementation of these advanced regeneration technologies. Gene editing and retinal organoids constitute revolutionary enhancements to stem cell therapy. Despite existing technological and regulatory challenges, their incorporation into advanced retinal therapies could significantly improve effectiveness and initiate a new phase of personalized ophthalmic treatment. Table 1 summarizes the principal gene editing and organoid strategies currently under investigation for retinal regenerative therapies, along with their respective clinical applications and limitations[26,27,29-42].

TRANSLATIONAL CHALLENGES

Despite significant advancements in stem cell biology and initial clinical successes, the transition of retinal regeneration therapies from laboratory to clinical application continues to encounter numerous obstacles. These constraints cover technological, immunological, oncological, surgical, and regulatory realms and underline the gap between encouraging laboratory findings and durable clinical outcomes. A primary worry is the long-term safety of grafts produced from pluripotent stem cells. Despite clinical trials utilizing hESC- and iPSC-derived RPE not indicating tumor formation, the potential risk of tumorigenicity - particularly from undifferentiated or partially reprogrammed cells - persists as a theoretical concern that demands stringent batch-level quality control. Moreover, genomic instability, typically emerging during reprogramming or passaging of iPSCs, raises concerns regarding chromosomal abnormalities and insertional mutagenesis[43]. Advanced non-viral reprogramming methods and the elimination of oncogenes such as c-Myc have contributed to reducing these hazards; however, ongoing monitoring of treated individuals remains crucial.

Immunological compatibility poses a second key hurdle. Although autologous iPSCs provide potential immunological privilege, their clinical application is impeded by elevated costs, extended production durations, and logistical intricacies. In contrast, allogeneic therapies originating from hESCs or iPSC banks necessitate either systemic immunosuppression or HLA matching to prevent rejection. In contrast to hESCs, iPSCs present considerable advantages by avoiding ethical dilemmas and minimizing the likelihood of immune rejection *via* autologous sourcing. Moreover, iPSCs allow disease modeling and the rectification of patient-specific mutations by gene editing before transplantation. Nonetheless, issues pertaining to reprogramming accuracy, batch uniformity, and elevated production costs continue to hinder wider deployment. A direct comparison of these platforms is summarized in Table 2.

A significant obstacle pertains to the functional integration of transplanted cells. Although several studies have demonstrated anatomical engraftment of RPE or photoreceptor precursors, evidence for synapse formation, phototransduction, and visual signal transmission to higher-order neurons is still scarce[24]. Functional connectivity poses significant challenges for intricate cell types such as photoreceptors, which must assimilate into the stratified retinal structure and interact accurately with bipolar and horizontal cells. Even with scaffolds and structured delivery, long-term viability and physiological contribution remain uncertain.

Surgical complexity also provides a challenge. Unlike intravitreal injections common in current ophthalmic practice, subretinal delivery requires specialized techniques, including retinotomy, vitrectomy, and precise placement of delicate cell sheets or biodegradable scaffolds[25]. These operations entail a risk of retinal detachment, bleeding, or inadequate graft orientation. The enhancement of microsurgical instruments and intraoperative imaging is mitigating these dangers; nevertheless, implementation necessitates specialized training and infrastructure that may not be universally accessible. Moreover, the intricate retinal microenvironment also obstructs functional integration. Inhibitory signals from the host, including glial scarring, modified extracellular matrix (ECM) composition, and persistent low-grade inflammation, might hinder graft survival and synaptic connection. Müller cell hypertrophy and the overexpression of ECM molecules, such as chondroitin sulfate proteoglycans, establish a non-permissive environment. The absence of suitable paracrine support from adjacent cells, such as brain-derived neurotrophic factor or pigment epithelium-derived factor, diminishes long-

Table 1 Gene editing and retinal organoid strategies in retinal therapy

Strategy	Application	Current limitations	Ref.
CRISPR/Cas9 gene editing	Correction of pathogenic mutations in patient-specific iPSCs	Off-target effects, ethical concerns, and delivery efficiency	[26,27,30,31]
Retinal organoids	Modeling retinal development and disease; source of transplantable cells	Limited maturation, variability, and scalability for clinical use	[29-42]

iPSCs: Induced pluripotent stem cells.

Table 2 Key differences between human embryonic stem cell- and induced pluripotent stem cell-based retinal therapies

	hESC-based therapies	iPSC-based therapies
Ethical considerations	Derived from human embryos; subject to ethical and regulatory scrutiny in many jurisdictions	Generated from adult somatic cells (*e.g.*, fibroblasts, blood cells); avoids embryo use and associated ethical controversy
Immune compatibility	Typically allogeneic; requires systemic immunosuppression or HLA matching to prevent rejection	Autologous options reduce rejection risk; potential for patient-specific therapy; hypoimmunogenic engineered iPSC lines under development
Genomic stability	Established lines with relatively stable karyotype after differentiation	Risk of genomic and epigenetic instability during reprogramming and passaging; batch-to-batch variability
Tumorigenicity risk	Residual undifferentiated cells pose risk but can be mitigated with stringent quality control	Similar risk plus concerns related to incomplete reprogramming and epigenetic memory
Manufacturing cost and timeline	Scalable, standardized production; cost per dose potentially lower when scaled	Personalized autologous production is expensive and timeconsuming; emerging universal donor iPSC banks may mitigate costs

hESC: Human embryonic stem cell; iPSC: Induced pluripotent stem cell.

term survival and differentiation. Surmounting these obstacles may necessitate graft preconditioning, co-delivery of supporting agents, or ECM modification. From a regulatory and ethical standpoint, stem cell therapies are subject to intense scrutiny.

While hESCs have been central to early advances in regenerative ophthalmology, their use remains ethically contentious and is subject to strict oversight in many jurisdictions. In contrast, iPSCs offer an ethically favorable alternative and can be generated from patient-specific somatic tissues, reducing the risk of immune rejection. However, iPSC-based therapies - particularly those incorporating genome editing or scaffold-based delivery systems - introduce complex regulatory challenges. These include variability in cell quality, concerns about genomic stability, and the lack of harmonized international guidelines. Regulatory bodies such as the Food and Drug Administration and European Medicines Agency continue to refine frameworks for advanced therapy medicinal products, especially those that integrate multiple components like gene editing tools, living cells, and biomaterial carriers. Regulatory frameworks for gene-edited stem cell treatments vary considerably between the United States and Europe. The Food and Drug Administration categorizes genome-edited stem cell products as biologics, necessitating an Investigational New Drug application, subjecting gene-modified iPSCs to further scrutiny. The European Medicines Agency, while similarly stringent, has adopted the Advanced Therapy Medicinal Products classification, which necessitates centralized clearance *via* the Committee for Advanced Therapies. Ethical discussions vary; whilst the use of hESC is contentious in the European Union owing to embryo destruction, United States legislation authorizes hESC research with National Institutes of Health-approved lines. Induced iPSCs are morally advantageous; yet, they provoke apprehensions about long-term permission[44,45]. Manufacturing obstacles associated with GMP adherence, lot-to-lot uniformity, and scalable production exacerbate the difficulties of widespread implementation.

The economic and infrastructural demands of autologous cell therapy present formidable obstacles. Current personalized iPSC therapies necessitate several months for generation, testing, and differentiation, with expenses potentially surpassing six figures per patient. While centralized iPSC banks with broadly HLA-matched donors may offer a viable solution, their global coordination, donor diversity, and public acceptance are still in preliminary phases[46]. While retinal stem cell therapy is scientifically solid and increasingly clinically supported, its entry into standard care is impeded by a constellation of translational obstacles. Overcoming challenges will require integrated efforts in clinical trial design, surgical training, long-term patient monitoring, ethical governance, and biomanufacturing standardization.

RECENT ADVANCES IN TRANSLATIONAL PHOTORECEPTOR AND RETINAL ORGANOID THERAPY

Recent research has yielded significant insights into photoreceptor transplantation, organoid modeling, and the preclinical validation of stem cell-based retinal therapeutics. Gasparini *et al*[47] have shown that human iPSC-derived photoreceptors can significantly integrate into partly degenerated murine retinas, where they appropriately polarize,

form outer segments, and establish potential synaptic connections with host cells. In contrast to previous suspension transplants, Müller glia aggressively integrated with the graft, forming adherens junctions akin to the outer limiting membrane, thus promoting donor-host communication and facilitating maturation. Electrophysiological recordings revealed that the transplanted cones might facilitate light detection, hence suggesting the potential for functional integration in advanced degeneration models[47].

Liu *et al*[48] have concurrently described the self-organization of telencephalon-eye organoids including concentric domains of telencephalic, optic-stalk, optic-disc, and neuroretinal tissues. These structures facilitated the directional extension of RGC axons, directed by optic-disc cells that expressed fibroblast growth factors essential for RGC specification. The research presented a sophisticated model for human ocular development and emphasized its applicability in simulating RGC diseases, including glaucoma. RGCs derived from these organoids demonstrated electrophysiological excitability, providing translational significance for preclinical drug screening[48].

The transplantation of organoids produced from chemically iPSCs (CiPSCs) has enhanced the safety and efficacy potential of stem cell treatment. Zhao *et al*[49] demonstrated that CiPSC-derived retinal organoids encompassed all principal retinal cell types, integrated upon subretinal administration, established synaptic connections, and reinstated visual function in mouse degeneration models. CiPSCs offer a promising alternative cell source for clinical translation by avoiding the genomic instability linked to viral or plasmid-based reprogramming.

From a comprehensive translational perspective, Shrestha[50] has delineated the global progression of iPSC-based medicinal research, highlighting Japan's preeminence in advancing clinical applications. This assessment emphasized the swift growth of iPSC commercialization, clinical-grade biobanking, and pretrial approvals facilitated by advantageous regulatory and political backing. The author emphasized that strategic policy and industry mobilization could expedite the clinical availability of iPSC-derived eye treatments[50].

Watari *et al*[51] have ultimately addressed essential safety and quality-control issues with iPSC-derived retinal sheets. Their preclinical validation included an innovative quantitative polymerase chain reaction-based quality assessment to eliminate off-target differentiation before transplantation. In tumorigenicity assays and retinal degeneration rat models, retinal sheets exhibited sustained engraftment, differentiation into mature photoreceptors, and electrophysiological responsiveness. This study developed a systematic framework for human iPSC-derived sheet treatment, connecting laboratory derivation with regulated clinical-grade transplantation[51].

Collectively, these studies signify a pivotal advancement in stem cell-based retinal therapy by evidencing the consistent integration of human cones, the modeling of intricate ocular structures, the viability of CiPSC-derived organoids, and the establishment of stringent preclinical safety frameworks. The amalgamation of these methodologies could significantly improve the clinical preparedness of regenerative treatments for vision-impairing retinal disorders.

FUTURE OUTLOOK

Stem cell-mediated retinal regeneration now occupies a transitional stage between experimental promise and clinical realization. The field is evolving from isolated proof-of-concept trials toward comprehensive, multidisciplinary therapeutic platforms. Increasingly, cell therapy is being integrated with gene-editing technologies such as CRISPR-Cas9, enabling precise correction of pathogenic mutations in patient-specific cells. The next generation of retinal regenerative therapies is likely to combine stem cells, gene editing, neurotrophic support, and biodegradable scaffolds into unified strategies that promote both anatomical engraftment and functional integration. Concurrently, advances in real-time intraoperative imaging, single-cell transcriptomics, and immunoprofiling may enhance graft monitoring and enabling personalized treatment regimens. The success of these innovations will depend on coordinated efforts across scientific, clinical, industrial, and regulatory sectors. Collaborative biorepositories, standardized GMP-compliant protocols, and adaptive clinical trial frameworks will be essential to accelerate translation while ensuring equitable access. Clear regulatory guidance for genome-edited cells and scaffold-based delivery systems will be a critical factor in achieving safe and effective clinical adoption.

CONCLUSION

Following years of conceptual advancement and preclinical enhancement, stem cell therapy for retinal degeneration has attained a level of clinical legitimacy. Research on hESC- and iPSC-derived RPE cells has continuously shown safety and preliminary efficacy in early-phase trials, while advancements in transport methods, gene correction, and organoid creation are transforming the landscape of regenerative ophthalmology. However, the trajectory towards extensive acceptance remains intricate. Significant challenges - such as functional integration, immunological tolerance, tumorigenic safety, and cost-effectiveness - necessitate meticulously coordinated solutions. Ongoing investment in long-term monitoring, sophisticated imaging techniques, and molecular quality assurance will be crucial for confirming the durability and reproducibility of these medicines. As trial networks proliferate and manufacturing infrastructure advances, the sector is at a pivotal tipping point. The incorporation of stem cell therapy into standard clinical practice will depend on its capacity to both maintain eyesight and achieve significant functional results safely, efficiently, and with a focus on patient needs. Stem cell therapy has transitioned from a speculative concept to a concrete and transformative alternative, set to reshape the standard of care in retinal illness.

FOOTNOTES

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