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# Application of Subretinal Stem Cell Transplantation in the Treatment of Wet Age-Related Macular Degeneration: Current Approaches and Future Perspectives

**Mei Xin[1,2#*], Shiyu Liu[1,2#], Zhengfang Wu[1], Baiyu Hu[1], Yu He[2], Liuzhi Zeng[2], and Junguo Duan[1*]**

[1]Eye School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province 610095, China; [2]Department of Ophthalmology, Chengdu First People's Hospital, Chengdu, Sichuan Province 610041, China.

* **Correspondence to**: Mei Xin, Department of Ophthalmology, Chengdu First People's Hospital, Chengdu, Sichuan Province 610041, China; Email: xinmei_cyn@163.com.
Junguo Duan, Eye School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province 611137, China; Email: duanjg@cdutcm.edu.cn.
#These authors contribute equally.

## ABSTRACT

Wet age-related macular degeneration (wAMD) is a leading cause of vision loss among the elderly, characterized by choroidal neovascularization (CNV) and retinal damage. Current treatments, such as anti-vascular epithelial growth factor (VEGF) therapies, offer symptomatic relief but do not restore lost retinal tissues or address the underlying degenerative processes. Subretinal stem cell transplantation has emerged as a promising therapeutic strategy aimed at regenerating damaged retinal cells, particularly the retinal pigment epithelium (RPE), to promote retinal repair. This review provides an overview of the pathophysiology of wAMD, highlighting the critical roles of RPE dysfunction and pathological vascular changes. It explores various stem cell types, including embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells, which show potential for retinal regeneration. The scientific rationale behind subretinal transplantation is discussed, along with advancements in cell differentiation protocols, surgical techniques, and biomaterial-assisted delivery systems. Recent preclinical and clinical studies are examined, demonstrating the feasibility and safety of stem cell transplantation, although challenges remain regarding cell survival, integration, and immune rejection. Emerging technologies, such as gene editing and combination therapies, are also reviewed for their potential to enhance therapeutic outcomes. This comprehensive analysis highlights the future potential of subretinal stem cell transplantation as a disease-modifying approach for wAMD.

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## 1. Introduction

Wet age-related macular degeneration (wAMD) is a leading cause of irreversible visual impairment and blindness in the aging global population [1-4]. As the neovascular form of age-related macular degeneration, wAMD is characterized by the development of choroidal neovascularization (CNV), which disrupts the retinal pigment epithelium (RPE) and leads to subsequent photoreceptor degeneration [5-8]. These pathological changes progressively result in the loss of central vision, severely affecting patients' quality of life and creating a substantial socioeconomic burden [2, 9, 10]. Given the aging global population, the prevalence of wAMD is expected to rise further, underscoring the urgent need for effective, long-term therapeutic strategies.

Currently, the standard treatment for wAMD primarily involves intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents [11-13]. These treatments have significantly improved visual outcomes by inhibiting pathological neovascularization and vascular leakage. Other approaches, such as photodynamic therapy (PDT), have also been utilized in certain cases [14-16]. Despite their clinical benefits, these treatments remain symptomatic and do not restore damaged retinal tissue. The inability to reverse RPE and photoreceptor loss, coupled with frequent injections, variable pa-

tient responses, and treatment resistance, highlights the limitations of current therapies [5, 17, 18]. Furthermore, prolonged suppression of VEGF may adversely affect retinal homeostasis, emphasizing the need for complementary or alternative therapies that address the underlying degenerative processes.

In recent years, stem cell-based therapies have emerged as a promising strategy for retinal regeneration and functional restoration in degenerative retinal diseases [19-31]. Various stem cell types, such as embryonic stem cells (ESCs) [5, 26, 32], induced pluripotent stem cells (iPSCs) [27, 29, 33-36], and mesenchymal stem cells (MSCs) [18, 27, 31, 36-38], have shown potentials to differentiate into RPE-like cells, provide trophic support, and modulate the retinal microenvironment. Among the different delivery routes, subretinal transplantation has garnered particular attention due to its ability to place therapeutic cells directly at the site of RPE and photoreceptor damage [18, 31, 39-42]. Advances in stem cell differentiation protocols, surgical techniques [22], and biomaterial-assisted delivery systems have accelerated the translation of these therapies from preclinical studies to early phase clinical trials [43, 44]. Collectively, these developments position subretinal stem cell transplantation as a potential disease-modifying approach for wAMD, offering the possibility of retinal repair beyond mere symptomatic control.

This review aims to provide a comprehensive up-to-date overview of subretinal stem cell transplantation as a therapeutic strategy for wAMD. We begin by summarizing the current understanding of the cellular and molecular mechanisms underlying retinal degeneration in wAMD, with a focus on RPE dysfunction and pathological vascular remodeling. We discuss why these processes cannot be adequately addressed by existing therapies alone. Next, we review the major stem cell types explored for retinal regeneration, including ESCs, iPSCs, and MSCs, highlighting their therapeutic mechanisms as well as key safety and ethical considerations. Building upon this foundation, we critically examine the scientific rationale, experimental evidence, and clinical progress of subretinal stem cell transplantation for wAMD, alongside the technical challenges and recent advancements in surgical transplantation procedures. Finally, we explore emerging technological innovations, such as biomaterial-assisted cell delivery, gene editing, and combination strategies integrating stem cell therapy with anti-VEGF treatment. Through this integrated analysis, this review aims to clarify the potential of subretinal stem cell transplantation as a disease-modifying therapy for wAMD, while addressing the current limitations and translational barriers in the field.

## 2. Pathophysiology of wAMD

### 2.1 Cellular and Molecular Mechanisms Underlying Retinal Degeneration in wAMD

The pathogenesis of wAMD is driven by a combination of genetic predisposition and environmental factors, which together contribute to inflammation, oxidative stress, and neovascularization [45-48]. At the cellular level, the damage to the RPE and photoreceptors is central to the development of wAMD. One of the hallmark features of the disease is the dysfunction of the RPE, which plays an essential role in maintaining retinal homeostasis by phagocytosing shed photoreceptor outer segments and secreting trophic factors (Figure 1) [49, 50]. As RPE cells degenerate, they lose their ability to perform these crucial functions, leading to the accumulation of waste products and, ultimately, the death of photoreceptors. Concurrently, the choroidal vasculature becomes abnormally activated, resulting in the formation of choroidal neovascularization (CNV), characterized by the outgrowth of abnormal blood vessels from the choroid into the retina [51-54]. These new blood vessels are leaky and prone to rupture, causing retinal edema, hemorrhage, and further retinal damage. At the molecular level, the dysregulation of VEGF plays a pivotal role in CNV formation, driving abnormal vessel growth and vascular leakage [55, 56]. The imbalance between pro-angiogenic factors (e.g., VEGF) and anti-angiogenic factors further exacerbates the pathological vascular changes seen in wAMD.

There are many differences in histological retinal alterations between dry AMD and wAMD, along with associated clinical imaging characteristics (Figure 1). Cross-sectional diagrams of the retina illustrate the key features of each AMD type. The dry AMD is characterized by the accumulation of drusen beneath the RPE, accompanied by progressive thinning of the RPE (Figure 1C). The wAMD is characterized by choroidal neovascularization breaching Bruch's membrane, resulting in subretinal exudate formation (Figure 1D). These histological changes are captured by optical coherence tomography (OCT) and fundus autofluorescence images (Figure 1A and 1B),

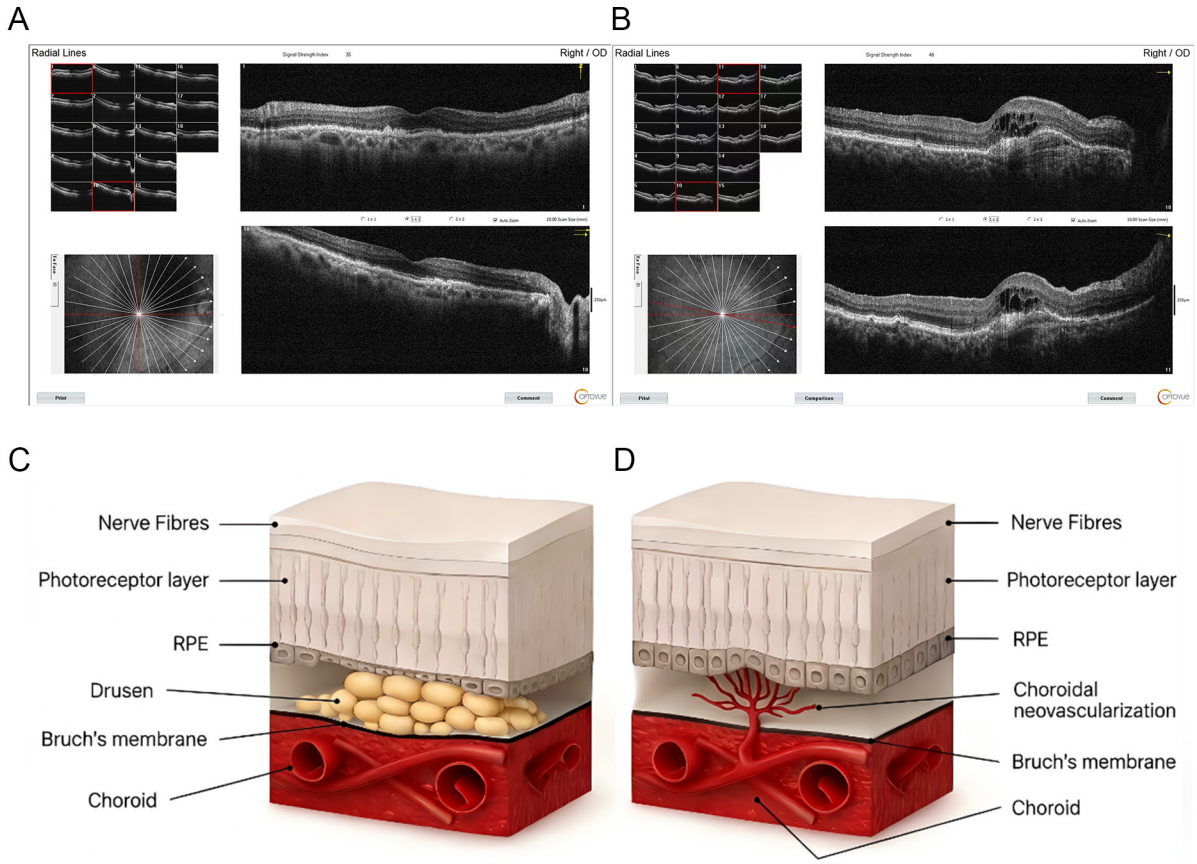


**Figure 1: Retinal changes in dry AMD and wAMD. A**. Optical Coherence Tomography (OCT) of a patient with dry AMD. **B**. OCT of a patient with wAMD. **C**. Illustration of the retinal histological changes in dry AMD. **D**. Illustration of the retinal histological changes in wAMD.

showcasing typical clinical findings, such as RPE disruption, fluid buildup, and changes in reflectivity, all of which are critical for distinguishing between different stages of AMD during diagnosis and ongoing monitoring.

### 2.2 Role of RPE Dysfunction and Vascular Changes

The RPE plays a crucial role in maintaining both the structural and functional integrity of the retina [57]. In wAMD, RPE dysfunction is considered one of the earliest and most significant events in the disease's progression [58]. Under normal conditions, RPE cells are responsible for nutrient transport, waste removal, and protecting the retina from oxidative damage [50]. However, when RPE cells become dysfunctional or undergo apoptosis, they can no longer perform these essential functions, leading to the accumulation of toxic byproducts, such as lipofuscin, and a subsequent decline in retinal function [50]. This damage sets off a cascade of events that promote the breakdown of the blood-retinal barrier, allowing the infiltration of inflammatory cells and growth factors, particularly VEGF, into the retina. VEGF triggers the formation of abnormal blood vessels from the choroid, which is a hallmark of CNV [50]. These fragile, leaky blood vessels lead to retinal edema and hemorrhage, contributing to vision loss. In addition to VEGF, other factors such as pigment epithelium-derived factor (PEDF) and angiopoietins are involved in maintaining vascular homeostasis in the retina [59, 60]. Their imbalance further exacerbates the disease process.

Oxidative stress, a key contributor to wAMD, plays a critical role in regulating these mediators. Babapoor-Farrokhran et al. showed that oxidative stress promoted the nuclear accumulation of hypoxia-inducible factor-1α (HIF-1α) in RPE cells, leading to increased expression of the HIF-1-dependent angiogenic mediators VEGF and angiopoietin-like 4 (ANGPTL4). Using both immortalized and primary RPE cells, the authors demonstrated that treatment with chemical oxidants such as tert-butyl hy-

**Table 1.** Stem Cell Types and Their Roles in Retinal Regeneration Therapy

| Stem Cell Type | Primary Role/Function | Mechanisms of Action |
|---|---|---|
| **ESCs** [85, 117] | Regeneration of retinal cells | Differentiate into retinal cell types (e.g., photoreceptors, retinal pigment epithelium) |
| **iPSCs** [70] | Potential for retinal cell replacement | Differentiate into retinal cells, replace damaged or lost retinal cells |
| **MSCs** [82] | Modulation of inflammation and immune response | Secrete trophic factors to reduce inflammation, promote healing, and protect retinal cells |
| **RPCs** [118, 119] | Direct differentiation into retinal cell types | Differentiate into retinal-specific cells like photoreceptors, ganglion cells, and others |
| **UCSCs** [120] | Tissue repair and reduction of retinal cell damage | Secrete growth factors, enhance tissue repair, reduce inflammation |
| **ADSCs** [81] | Support retinal regeneration and modulate immune responses | Secrete anti-inflammatory factors, promote cell survival and regeneration |

droperoxide (tBH), hydrogen peroxide ($H_2O_2$), and 4-hydroxynonenal (4HNE) resulted in dose- and time-dependent HIF-1α accumulation and nuclear translocation, accompanied by upregulation of VEGF and ANGPTL4 at both the mRNA and protein levels. Furthermore, in a rat model of subretinal lipid peroxide-induced CNV, HIF-1α accumulation was observed in the RPE before the development of CNV, and pharmacological inhibition of HIF-1α significantly reduced CNV formation. These findings suggest that oxidative stress-induced HIF-1α stabilization in RPE cells represents a critical upstream event driving the expression of pro-angiogenic factors and the subsequent development of CNV in wAMD [50].

Over time, progressive damage to the RPE and abnormal vascular changes contribute to the formation of drusen and geographic atrophy, particularly in the advanced stages of wAMD, leading to further impairment of retinal function.

### 2.3 The Need for Novel Therapeutic Approaches to Address These Mechanisms

Despite significant advancements in the treatment of wAMD, particularly with anti-VEGF therapy, current treatment options remain limited [61-63]. Anti-VEGF agents, which block the effects of VEGF, have proven effective in halting disease progression and preventing further vision loss [64]; however, they do not restore damaged retinal tissue. Additionally, frequent injections, variable patient responses, and the development of resistance to these therapies underscore the need for alternative approaches. More importantly, these therapies do not address the underlying mechanisms of retinal degeneration, including RPE dysfunction, chronic inflammation, and oxidative stress. Therefore, there is an urgent need for novel therapeutic strategies that go beyond symptom control and directly target the root causes of the disease. Stem cell-based therapies, gene therapy, and tissue engineering approaches show great promise in this regard. These therapies have the potential to restore RPE function, promote retinal regeneration, and prevent or even reverse retinal damage. By targeting the cellular and molecular mechanisms underlying wAMD, these treatments hold the potential to not only control disease progression but also modify the disease itself, offering hope for long-term, durable solutions for patients with wAMD.

## 3. Stem Cells in Retinal Regeneration

Stem cell-based therapies have emerged as a promising approach for retinal regeneration, offering potential to restore lost vision in degenerative retinal diseases such as wAMD. Stem cells possess unique capabilities, including the ability to differentiate into retinal cell types, secrete trophic factors that promote cell survival, and modulate immune responses to reduce inflammation and promote healing [65-77]. This section reviews the different types of stem cells used in retinal therapy, their mechanisms of action, and the safety and ethical considerations that must be addressed in their application for treating retinal diseases.

### 3.1 Types of Stem Cells Used in Retinal Therapy

Several types of stem cells are being investigated for retinal therapy, each with distinct advantages and challenges. These include ESCs, iPSCs, and MSCs [78, 79] (Table 1).

#### *3.1.1 Embryonic Stem Cells (ESCs)*

Embryonic stem cells are pluripotent cells derived from the inner cell mass of blastocysts. They can differentiate into all three germ layers, including retinal cells. ESCs have shown great promise in retinal regeneration due to their high differentiation potential. In retinal therapy, ESCs are able to differentiate into RPE cells, photoreceptors, and other retinal cell types.

The therapeutic potential of ESC-derived RPE cells has been demonstrated in both preclinical and clinical studies. For instance, Liu et al. conducted a phase I clinical trial in which a suspension of hESC-derived RPE cells was transplanted into the subretinal space of three patients with wAMD following removal of the choroidal neovascularization membrane. Over a 12-month follow-up period, no adverse events such as tumor formation or immune rejection were observed. Anatomical evidence from spectral-domain optical coherence tomography (SD-OCT) revealed the formation of a new RPE-like cell layer in the previously damaged area, suggesting graft survival and integration. Functional assessments showed modest improvements in best-corrected visual acuity, with all three patients demonstrating varying degrees of visual gain: two patients improved from hand motion preoperatively to 20/400 at 12 months, while the third patient improved from 20/125 to 20/80. Multifocal electroretinography (mfERG) revealed increased response density in the central macular region in all three patients, while flash visual evoked potentials (FVEP) demonstrated stable or improved P2 amplitudes, indicating preserved or enhanced visual pathway function. These findings provide preliminary evidence supporting the feasibility and safety of hESC-RPE transplantation for retinal repair [78].

However, ESCs pose significant ethical concerns as their derivation involves the use of human embryos, and their pluripotent nature raises concerns about tumor formation, as uncontrolled differentiation could lead to teratomas.

#### *3.1.2 Induced Pluripotent Stem Cells (iPSCs)*

Induced pluripotent stem cells are adult somatic cells reprogrammed into a pluripotent state, similar to ESCs. The advantages of iPSCs over ESCs are that they do not require the use of embryos and can be derived from the patient's own tissues, reducing the risk of immune rejection. iPSCs can differentiate into various retinal cell types, including RPE cells, photoreceptors, and retinal ganglion cells [70]. Recent advances in gene-editing technologies, such as clustered regularly interspaced palindromic repeats (CRISPR)-CRISPR-associated protein 9 (CAS9), have facilitated the generation of patient-specific iPSCs for personalized therapies [80]. While iPSCs offer significant therapeutic potential, challenges remain in controlling their differentiation, minimizing genetic instability, and preventing the formation of tumors or abnormal cell growth.

#### *3.1.3 Mesenchymal Stem Cells (MSCs)*

Mesenchymal stem cells, which are multipotent adult stem cells, can be isolated from a variety of tissues, including bone marrow, adipose tissue, and umbilical cord blood. MSCs have been widely studied for retinal diseases due to their ability to secrete trophic factors that promote cell survival, inhibit inflammation, and facilitate tissue repair [81]. MSCs are typically not as pluripotent as ESCs or iPSCs, but they offer several advantages, such as easy accessibility, low immunogenicity, and a lower risk of tumor formation. MSC-based therapies for retinal diseases focus on providing neuroprotective support and modulating the retinal microenvironment rather than regenerating retinal tissue directly [82]. Clinical studies have shown that MSCs can improve visual outcomes in patients with retinal degenerative diseases by promoting RPE repair and reducing inflammation.

#### *3.1.4 Other Stem Cell Types for Retinal Regeneration*

In addition to the three major stem cell types described above, retinal progenitor cells (RPCs), umbilical cord-derived stem cells (UCSCs), and adipose-derived stem cells (ADSCs) have also shown potential for treating wAMD. RPCs are lineage-restricted progenitor cells isolated from the developing or fetal retina, capable of differentiating into retinal-specific cell types, including photoreceptors, ganglion cells, and bipolar cells. Preclinical studies have demonstrated that human fetal RPCs, following subretinal transplantation into animal models of retinal degeneration, survive, integrate into the host retina, and improve visual function. Compared with pluripotent stem cells, RPCs carry a lower risk of tumor formation due to their relatively restricted differentiation lineage and raise fewer ethical concerns, making them a promising cell source for retinal repair [81,82]. UCSCs, primarily derived from Wharton's jelly of the umbilical cord, represent a readily available, low-im-

munogenicity cell population with high proliferative capacity. These cells exert therapeutic effects mainly through paracrine mechanisms, secreting various growth factors and anti-inflammatory cytokines that reduce retinal cell damage, promote tissue repair, and modulate local immune responses [83]. ADSCs, isolated from adipose tissue, share many characteristics with bone marrow-derived MSCs but offer practical advantages of easier accessibility, minimally invasive harvesting, and higher cell yield. ADSCs have been shown to secrete anti-inflammatory factors, support retinal cell survival, and promote neuroprotection in models of retinal degeneration [84]. Although RPCs, UCSCs, and ADSCs have not been as extensively investigated as ESCs, iPSCs, or MSCs in the context of wAMD, emerging evidence suggests they may serve as adjunctive or alternative cell sources for retinal repair, particularly owing to their favorable safety profiles, lower ethical concerns, and ease of procurement. Future studies are warranted to further evaluate their long-term efficacy and safety in subretinal transplantation for wAMD.

### 3.2 Mechanisms of Stem Cell-Based Therapy

The therapeutic potential of stem cell-based therapies in retinal regeneration is attributed to several key mechanisms, including differentiation, trophic factor secretion, and immune modulation.

#### *3.2.1 Differentiation*

Stem cells can differentiate into retinal cell types, including RPE cells, photoreceptors, and retinal ganglion cells [83, 84]. For retinal degeneration such as wAMD, stem cells are often directed to differentiate into RPE-like cells that can replace the damaged RPE layer, which is essential for maintaining photoreceptor health and function [85]. Recent advancements in stem cell differentiation protocols have enabled the generation of RPE cells from various stem cell sources, offering a potential source of autologous material for transplantation [65]. Additionally, stem cells may also differentiate into photoreceptor cells, which could restore lost vision in degenerative diseases like wAMD and retinitis pigmentosa.

#### *3.2.2 Trophic Factor Secretion*

One of the primary roles of stem cells in retinal therapy is the secretion of trophic factors that support retinal cell survival and function [86]. These factors can protect retinal cells from apoptosis, promote cell growth, and enhance retinal tissue repair. For instance, stem cells have been shown to secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), which can enhance neuronal survival and stimulate angiogenesis in the retina. Furthermore, stem cell-derived exosomes have been found to carry a variety of molecules, including microRNAs and proteins, that play a role in cellular communication and regeneration.

In a study by Nan et al., adipose-derived mesenchymal stem cells (ADSCs) transduced with the brain-derived neurotrophic factor (BDNF) gene (BDNF-ADSCs) were evaluated for their expression of neurotrophic factors using Western blot analysis. The results demonstrated that BDNF-ADSCs exhibited significantly higher protein expression levels of BDNF, nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and ciliary neurotrophic factor (CNTF) compared to unmodified ADSCs [90]. This trophic support can be particularly valuable in treating diseases like wAMD, where the retina suffers from both cell death and dysfunctional blood vessels.

#### *3.2.3 Immune Modulation*

Stem cells, particularly MSCs, possess immunomodulatory properties that can reduce inflammation in retinal diseases [87]. The immune response in retinal diseases like wAMD contributes to retinal damage and further degeneration. MSCs can interact with immune cells such as macrophages, T cells, and dendritic cells, leading to suppression of pro-inflammatory cytokines and promotion of anti-inflammatory responses [74]. This immune modulation can prevent further damage to the retina and support tissue repair. Additionally, stem cells can contribute to the regeneration of damaged blood vessels and stabilization of the blood-retinal barrier, both of which are key in diseases with abnormal vascular changes, such as wAMD [76].

### 3.3 Safety and Ethical Considerations in Stem Cell Therapy

Stem cell-based therapies hold great promise for retinal regeneration, but their clinical application is accompanied by significant safety and ethical concerns that must be carefully managed [88-93]. Ensuring the safety of these therapies is crucial to prevent harm to patients. Key safety issues include tumorigenicity, immune rejection, and uncontrolled differentiation. ESCs and iPSCs are particularly associated

**Table 2.** Advances in Subretinal Stem Cell Transplantation for wAMD.

| Study Category | Stem Cell Type | Key Findings | Challenges | Future Directions |
|---|---|---|---|---|
| Preclinical Studies | iPSCs, ESCs, MSCs | Demonstrated retinal repair and reduction in CNV | Cell survival and integration | Optimization of stem cell survival and differentiation |
| Early Phase Clinical Trials | iPSCs, ESCs | Improvement in visual acuity and retinal structure | Short-term results, immune rejection, inflammation | Refining cell delivery techniques and immunosuppressive protocols |
| Combination Therapies | MSCs, ESCs | Combined with anti-VEGF to enhance treatment efficacy | Need for optimized treatment protocols | Integration with other treatments for enhanced outcomes |
| Gene Editing Approaches | iPSCs | Potential to enhance stem cell function through genetic modification | Ethical concerns, technical limitations in gene editing | Expanding gene editing to enhance stem cell efficacy |

with tumorigenic risks, as they may form teratomas or other tumors if not properly controlled [94]. A major challenge is ensuring that these stem cells differentiate into the desired retinal cell types without proliferating uncontrollably, which could lead to malignancies.

Another concern is immune rejection, especially when using allogeneic stem cells, such as ESCs or MSCs derived from donors [95]. While autologous iPSCs, derived from the patient's own cells, reduce immune rejection risks, generating personalized therapies remains complex and presents challenges [96]. MSCs are generally considered to have low risk for tumor formation, but their long-term safety, particularly regarding potential tumorigenesis or other adverse effects, requires ongoing monitoring in clinical settings.

Beyond safety, ethical issues are central to the debate on stem cell therapies [90]. The use of ESCs raises significant ethical concerns, as their derivation involves the destruction of human embryos, a practice that sparks moral debates [97]. This makes the use of ESCs in both research and clinical settings controversial. In contrast, iPSCs avoid these ethical issues since they can be derived from adult somatic cells, eliminating the need for embryos [98]. However, the reprogramming process for iPSCs raises new ethical questions, particularly concerning genetic modification and long-term genetic stability [98]. While MSCs, as adult stem cells, are less ethically contentious and have been more widely used in clinical trials, concerns about their ability to fully regenerate retinal tissue and their long-term safety remain [99].

Additionally, stem cell therapies for retinal diseases are subject to stringent regulatory oversight, particularly from agencies like the U.S. Food and Drug Administration and the European Medicines Agency (EMA) [100]. These regulatory bodies set guidelines for preclinical studies, clinical trials, and long-term follow-up. Although these regulations ensure the safety and effectiveness of stem cell therapies, they also slow the translation of promising treatments from the laboratory to clinical practice. The regulatory process ensures that stem cell therapies meet necessary safety standards before being administered to patients, but it can delay innovation and clinical adoption. As stem cell technologies continue to advance, ongoing collaboration among researchers, ethicists, regulators, and clinicians will be essential to address the complex safety, ethical, and regulatory challenges associated with their clinical use.

## 4. Subretinal Stem Cell Transplantation for wAMD

### 4.1 Current Research and Clinical Trials on Subretinal Stem Cell Transplantation for wAMD

Preclinical studies in animal models have shown promising results, with stem cells differentiating into RPE-like cells and integrating into the retinal tissue [101]. These studies have demonstrated that the transplanted stem cells can restore the RPE layer, reduce retinal damage, and improve retinal function. However, challenges such as the risk of tumor formation and the precise control of stem cell differentiation have highlighted the need for further refinement in the stem cell protocols [101] (Table 2).

Several early-phase clinical trials have been initiated to assess the safety of subretinal stem cell transplantation in patients with wAMD [102, 103]. One notable study involved the transplantation of RPE cells derived from hiPSCs into the subretinal space of patients with advanced wAMD. Preliminary results from these trials indicated that the procedure was generally well-tolerated, with no major safety concerns such as tumor formation or immune rejection. However, while some improvements in retinal function were observed, the clinical outcomes in terms of vision restoration have been modest, and long-term follow-up is needed to assess the durability of these benefits (Table 2).

As clinical trials progress, there is increasing interest in combining subretinal stem cell transplantation with other therapies, such as anti-VEGF treatment, to enhance therapeutic outcomes (Table 2) [104]. The integration of these therapies could provide a more comprehensive approach to treating wAMD, addressing both the underlying retinal degeneration and the abnormal blood vessel growth associated with the disease.

### 4.2 Challenges and Advancements in the Transplantation Procedure

Subretinal stem cell transplantation shows promise for treating wAMD, but several challenges remain. One major hurdle is ensuring the consistent and efficient differentiation of stem cells into retinal pigment epithelium (RPE)-like cells that can integrate seamlessly into retinal tissue [105]. Differentiation protocols are still being refined to ensure transplanted cells possess the necessary functional properties to support retinal health.

Another key challenge is the precise delivery of stem cells into the delicate subretinal space. Minimally invasive techniques, such as biodegradable scaffolds or novel biomaterial-assisted systems, could reduce surgical risks and improve cell retention [106].

Advancements in gene editing, such as CRISPR-Cas9, as well as 3-dimensional (3D) retinal tissue models, offer potential for improving differentiation efficiency and functional integration of stem cells [107].

Long-term safety and efficacy must be evaluated through clinical trials, with follow-up to monitor for adverse effects like tumor formation and retinal degeneration. In conclusion, while subretinal stem cell transplantation has great potential, ongoing research is necessary to refine techniques and overcome current challenges.

## 5. Emerging Techniques and Technological Innovations

One of the most exciting areas of progress is in stem cell delivery systems, where novel biomaterials, scaffolds, and gene editing technologies are playing key roles in improving the precision and effectiveness of transplantation [108]. Biomaterials, such as hydrogels [109], nanoparticles [110], and biodegradable scaffolds [111], are being developed to enhance stem cell retention and survival in the subretinal space, providing a more controlled environment for cell integration and differentiation. These materials also allow for sustained release of growth factors or other therapeutic agents, further supporting retinal repair and regeneration. Additionally, advanced scaffolding systems are being designed to mimic the natural extracellular matrix of the retina, which helps guide the differentiation and integration of stem cells into the retinal tissue, improving their functional outcomes.

Another significant advancement is the integration of stem cell transplantation with existing therapies, particularly anti-VEGF treatments. Combining stem cell therapy with anti-VEGF agents, such as ranibizumab or aflibercept, offers a dual approach that targets both the underlying vascular abnormalities in wAMD (such as choroidal neovascularization) and the regenerative capacity of stem cells to restore damaged retinal tissue [112]. This combination strategy has the potential to enhance therapeutic efficacy by addressing the multifaceted pathology of wAMD, while anti-VEGF treatment controls abnormal blood vessel growth, stem cells can promote retinal regeneration and tissue repair [113]. This integrated approach could provide a more comprehensive solution for patients, improving both vision stabilization and regeneration, especially in cases of advanced retinal degeneration.

In addition to delivery and combination strategies, innovations in stem cell engineering and personalized medicine are further shaping the future of retinal therapy [114]. Personalized medicine approaches, which involve tailoring therapies based on an individual's genetic makeup, are gaining traction [115]. In the context of retinal degeneration, personalized strategies may involve deriving iPSCs from patients to create customized treatments that reduce immune rejection and improve the chances of suc-

cessful retinal regeneration [116]. This personalized approach not only offers the potential for more effective treatments but also ensures that stem cell therapies are optimized to the unique needs of each patient, providing a more targeted and patient-specific therapeutic approach.

In conclusion, the field of stem cell-based retinal therapies is rapidly evolving with the advent of new technologies that improve cell delivery, integration, and differentiation. Combining stem cell transplantation with existing treatments and integrating gene editing and personalized medicine further enhances the potential for treating complex retinal diseases like wAMD. As these innovations continue to develop, they offer the promise of more effective, tailored, and durable therapeutic options for patients with retinal degenerative diseases.

## 6. Conclusion and Future Perspectives

Subretinal stem cell transplantation holds considerable promise as a therapeutic approach for wAMD, offering the potential to address the underlying causes of retinal degeneration rather than just managing symptoms. However, several hurdles remain, particularly in optimizing stem cell differentiation, ensuring long-term survival of transplanted cells, and mitigating immune rejection. To enhance the effectiveness of this treatment, future research should prioritize refining cell differentiation protocols, advancing delivery methods, and exploring combination therapies, particularly with anti-VEGF treatments, to provide a more comprehensive solution.

Moreover, emerging technologies such as gene editing and biomaterial-assisted delivery systems could play a pivotal role in enhancing the precision and effectiveness of stem cell-based therapies. These innovations promise to improve the targeting of stem cells to the retina, reduce potential side effects, and support better integration of the cells within retinal tissue. While early clinical trials have shown encouraging results, it is crucial to conduct larger-scale studies with long-term follow-up to fully assess the safety, durability, and long-term outcomes of these treatments.

In conclusion, while subretinal stem cell transplantation shows great potential in the treatment of wAMD and other retinal degenerative conditions, addressing the current challenges and refining existing protocols will be essential to unlocking its full therapeutic benefits and ensuring its widespread clinical application in the future.

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