

# STEM CELL THERAPY FOR CORNEAL AND RETINAL REGENERATION: ASSESSING THE EFFICACY AND SAFETY OF STEM CELL-BASED TREATMENTS FOR CORNEAL INJURIES AND RETINAL DISEASES

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## ABSTRACT

*Glaucoma constitutes a comprehensive classification of ocular diseases that are characterized by a progressive and irreversible deterioration of retinal ganglion cells (RGCs) along with the associated axonal projections that extend from these neurons, ultimately leading to significant impairment of visual function. The functions of the cornea, including transparency, refractive properties, and structural integrity, are compromised in various corneal pathologies; however, these functions can be rehabilitated subsequent to corneal transplantation procedures, such as penetrating and lamellar keratoplasties. Nonetheless, the worldwide deficit of available donor corneas for transplantation continues to be a considerable issue, placing patients at enduring risk of immunological reactions and the potential for graft failure. Numerous empirical investigations and scholarly articles have elucidated the remarkable capacity of multipotent mesenchymal stem cells (MSCs) to undergo a complex process of differentiation. Thereby, leading to the generation of a diverse array of specialized cell types that are intrinsic to the structure and functionality of the cornea. In addition to the acellular characteristics of exosomes that address challenges related to cellular fate regulation and the development of tumors, the constituents within these vesicles can be genetically engineered to enhance therapeutic efficacy. At this current juncture in scientific research and clinical practice, there is a conspicuous absence of a robust and effective methodology that can comprehensively tackle and fundamentally rectify the pressing issue of retinal ganglion cell degeneration, which poses significant challenges to both understanding and treating various ocular diseases. Recent breakthroughs show that visual restoration may be possible through stem cell therapy, which replaces damaged RGCs via cell transplants, nourishes injured RGCs, and delivers healthy cellular elements to promote neuroprotection and stimulate the self-renewal of retinal stem cells for intrinsic RGC regeneration. This article explores cutting-edge advancements in retinal stem cell transdifferentiation, corneal, and rejuvenation of RGC aging, while addressing the challenges faced in translating stem cell therapy to clinical practice.*

**Keywords:** stem cells, corneal, immunomodulation, extracellular vesicles, regeneration

## INTRODUCTION

Glaucoma, which is characterized as a heterogeneous array of chronic neurodegenerative disorders that affect the optic nerve, systematically inflicts progressive damage on the retinal ganglion cells along with their axonal extensions, thereby leading to alterations in the visual field and posing significant challenges in terms of treatment and management due to the intricate nature of

the disease and its pathophysiological considerations (A Faiq et al., 2016). It represents the predominant etiology of permanent visual impairment globally (Lakshmanan, Wong, So, & Chan, 2023), presently impacting nearly 80 million individuals. In 2010, glaucoma cast a shadow on 1 in 15 blind individuals and dimmed the vision of 1 in 45 visually impaired folks

(Crossland, 2024). Elevated intraocular pressure (IOP), which is unequivocally acknowledged as the principal indicator associated with the onset and progression of glaucoma, stands as a prominent yet not the only foreboding signal that portends the relentless and often insidious advancement of this multifaceted ocular disease. Yet, various factors may render IOP-lowering treatments ineffective in numerous instances. The IOP measurement values may not accurately represent the true physiological condition, hindering the establishment of target IOP. The fluctuating nature of IOP highlights the urgent need for innovative tools to enable ongoing, long-term monitoring (Konstas et al., 2018). Second, though the surgical intervention is considered the most effective procedure for lowering In many cases of uncontrolled glaucoma with ocular hypertension, most patients struggle to achieve a satisfactory IOP target, particularly in refractory glaucoma (Garg & Gazzard, 2020). Moreover, despite optimal control of intraocular pressure, 15–37% of glaucoma patients continue to suffer from relentless RGC degeneration and advancing optic nerve harm (Breen, 2015). Furthermore, Loss of vision is a global burden. The number of visually impaired people of all ages is estimated to be 285 million worldwide, with 39 million blind. Corneal diseases, a major contributor to visual impairment affecting over 10 million individuals, arise from various clinical conditions—such as traumatic injuries, chemical burns, infections, iatrogenic factors like limbal stem cell deficiency, age-related degeneration, and corneal dystrophies—that can detrimentally alter the cornea's cellular and structural integrity, consequently diminishing patient independence and quality of life (Moshirfar et al., 2023). The development of corneal scars, along with the presence of haze and opacities, in addition to corneal edema, significantly undermines the essential functions of the cornea, ultimately leading to a notable decline in visual acuity and overall vision quality. Nevertheless, it is important to note that the vast majority of cases of corneal blindness are, in fact, preventable, provided that appropriate and timely medical interventions are administered to the affected individuals (Kwok

et al., 2019). A considerable number of patients residing in under-developed and developing nations experience a substantial lack of access to adequate healthcare services, which results in these debilitating conditions frequently remaining untreated and exacerbated over time. This unfortunate reality underscores the critical need for improved healthcare infrastructure and accessibility in order to effectively address and manage these ocular diseases, thereby reducing the incidence of preventable corneal blindness on a global scale. Notwithstanding the considerable progress that has been achieved in the realm of corneal surgical procedures over the last ten years, one must acknowledge and critically examine the persistent challenges that continue to plague this field, including but not limited to the scarcity of donor tissue, the restricted longevity of allografts, the ongoing necessity for the long-term administration of immunosuppressive medications, as well as the indispensable requirement for a high level of surgical proficiency and expertise that is necessary to ensure optimal outcomes for patients undergoing such delicate and intricate interventions (Abdelfattah et al., 2015). Corneal transplantation, which refers to the surgical procedure involving the replacement of a diseased or damaged cornea with healthy donor tissue, stands out as the most prevalent and widely conducted form of transplantation across the globe, with an impressive annual statistic indicating that approximately 180,000 such corneal transplant procedures are carried out each year, highlighting the critical importance and necessity of this medical intervention in restoring vision and improving the quality of life for countless individuals suffering from corneal pathologies (David Rodriguez, Vecino, & therapy, 2011). Despite the fact that there has been a discernible upward trend in the aggregate quantity of eye globes and corneas that have been generously donated by individuals in recent years, as evidenced by the notable increase of 5.2% in the year 2013 when compared to the preceding year of 2012, as reported by the Eye Bank Association of America, it is important to recognize that the persistent demand for transplantable donor tissue continues to far exceed the available supply (Mohan, Martin, &

Sinha, 2021). The cornea, which serves as a critical component of the eye's anatomy, presents itself as an exceptionally suitable organ for the application of regenerative cell therapy, primarily attributable to its unique characteristics of immune privilege—which significantly diminishes the likelihood of rejection by the host's immune system—and its avascular nature, meaning it lacks direct blood supply, thereby creating an optimal environment for cellular regeneration and repair without the complications typically associated with vascularized tissues (Arora & Verma, 2024). The cells that have undergone transplantation exhibit a significantly reduced likelihood of being rejected by the host organism when compared to other types of tissues or organs, which is a critical factor in the field of regenerative medicine. In particular, mesenchymal stem cells (MSCs), which possess remarkable regenerative properties and the ability to differentiate into various cell types, have garnered increasing interest and attention from ophthalmologists and visual scientists alike, as they represent a promising alternative approach in the therapeutic management of corneal diseases that can severely impact vision and quality of life. This growing body of research highlights the potential of MSCs in not only addressing the underlying pathophysiology of corneal disorders but also in advancing our understanding of cellular dynamics and their applications in ocular therapies, thereby paving the way for innovative treatment strategies in ophthalmology. The paracrine influence exerted by mesenchymal stem cells (MSCs), which is facilitated through the release of exosomes, has been postulated as a significant mechanism underlying their therapeutic efficacy in various medical contexts. Furthermore, the acellular characteristics inherent to exosomes have garnered notable attention within the scientific community, particularly concerning the implications for safety and the minimization of potential adverse effects associated with cellular therapies.

A revolutionary therapy targeting RGCs and optic nerve restoration is essential, with stem cells' boundless growth and versatile differentiation making them a beacon of hope

for cell replacement solutions. The application of stem cell therapy as a potential treatment modality for conditions such as corneal blindness, macular degeneration, and retinitis pigmentosa represents an area of research that is currently experiencing a remarkable surge in interest and scholarly investigation, as evidenced by the multitude of clinical trials being conducted across various countries around the world that are specifically aimed at the replacement of corneal and retinal pigment epithelial cells (Liu, Liu, Li, & Yao, 2022). Currently, the quest for a revolutionary substitute for photoreceptor cells and RGCs remains unfulfilled. The advancement in swapping out photoreceptor cells is anticipated to happen swiftly, given their ability to detect light directly and their close proximity to inner retinal neurons. In order to reinstate retinal ganglion cells (RGCs), it is imperative that stem cells integrate harmoniously into the inner layer of the host retina and extend their axons towards the brain, thereby establishing accurate synaptic connections with specific targets such as the dorsal lateral geniculate nucleus, suprachiasmatic nucleus, and superior colliculus to facilitate the uninterrupted flow of signal transmission. Recognized in scholarly discourse as the pivotal and often termed “last mile” in the extensive and complex journey that stem cells undertake in the domain of visual neuro-regeneration, this multifaceted and intricate process is characterized by the presentation of substantial and formidable challenges that researchers and practitioners must navigate in order to achieve successful outcomes. This review explores cutting-edge advancements in stem cell-driven regeneration and replacement of retinal ganglion cells (RGCs), highlighting potential cell sources, key strategies for regeneration and protection, and the hurdles to clinical application.

## 2. Methodology

A thorough and extensive examination of the existing and relevant literature was meticulously carried out by utilizing the PubMed database, which is renowned for its vast collection of biomedical literature, and was further augmented by a systematically organized search specifically targeting clinical trials that are cataloged on the

ClinicalTrials.gov platform, known for its comprehensive registry of clinical studies. The comprehensive inquiry meticulously examined and scrutinized a diverse range of pivotal and significant phrases, which included but were not limited to terms such as “stem cell,” “stem cell treatment,” “retinal degeneration disorders,” “age-related macular degeneration,” “retinitis pigmentosa,” “Stargardt’s disease,” “embryonic stem cells,” “induced pluripotent stem cells,” and “mesenchymal stem cells,” with the objective of capturing and encompassing a wide array of studies and research activities that are pertinent to this intricate and evolving domain of scientific inquiry. Overview of human cornea has been

mentioned in Figure 1. Furthermore, a comprehensive consideration was given to a wide array of publications that were available in diverse languages, on the condition that these works contained a detailed summary as well as an abstract written in English, thereby ensuring that a complete and nuanced understanding of advancements occurring on an international scale could be achieved. The references and citations extracted from each individual scholarly article were meticulously examined and analyzed in a thorough manner to uncover additional significant and pertinent research that could contribute to the overall understanding of the subject matter at hand.

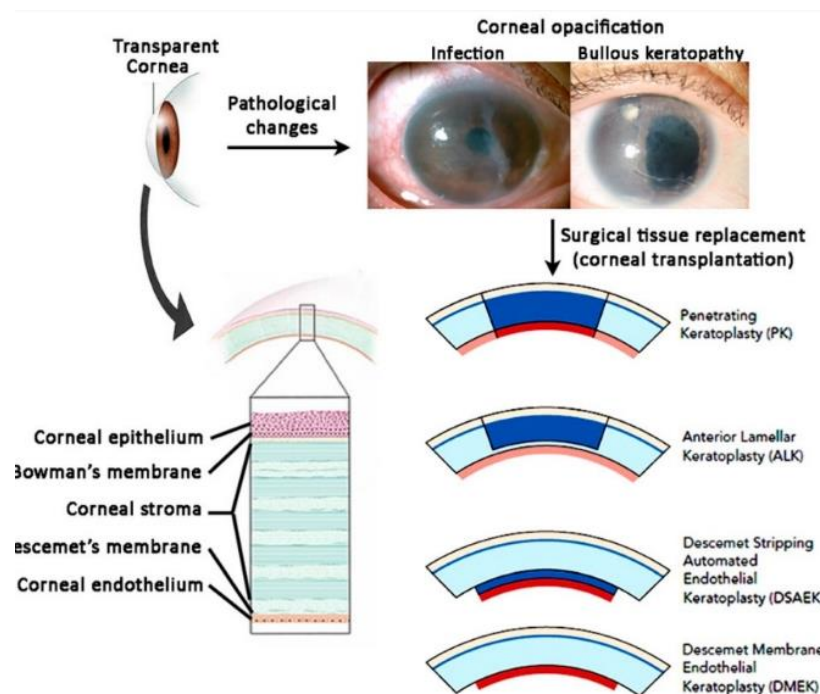


Figure 1. Overview of human cornea (e.g., infection, ulcer, injuries) lead to corneal opacification (Mansoor et al., 2019)

### 3. Results and Discussion

#### 3.1 Source Cells for RGC Replacement

As the retinal ganglion cells (RGCs) in mature mammals and humans are unable to regenerate on their own and their natural repair mechanisms are suppressed by specific signals, the primary source for RGC replacement arises from the induced differentiation of retinal progenitor cells or stem cells. In light of the scarce availability of retinal progenitor cells, numerous investigations have concentrated on harnessing

technology to induce the transformation of stem cells into RGCs, resulting in a remarkable series of advancements over the last ten years. Recently, we elaborated comprehensively on the diverse systems of differentiation induction that are presently employed in the quest for RGC replacement research (Ohlemacher et al., 2019). Typically, studies focused on the in vitro generation of RGCs predominantly utilize

human or murine embryonic stem cells (ESCs) as well as induced pluripotent stem cells. The induction replicates the intricate journey of retinal maturation by introducing essential compounds or implementing gene modifications in a timely manner, thereby orchestrating a symphony of transcription factors that enhance the generation of RGCs, allowing them to fulfill their purpose more effectively. The key transcription factors of interest encompass Pax6, Math5, and Notch, among others. The duration for induction and differentiation fluctuates depending on the nature of the source cells and the techniques used for induction, spanning anywhere from 10 to 60 days. The variation in induction efficiency is remarkably vast, spanning an impressive range from as low as 0.3% to as high as 50%, a disparity that potentially reflects the diverse proportions of retinal ganglion cells, or RGCs, present during the various stages of normal retinal development, which is a complex and intricate process that unfolds as the eye matures. (Teotia et al., 2017) Incorporated elements for differentiation in RGC evolution phases and achieved 53.67% induction efficiency in 15 days, establishing a promising induction framework. Over the course of the past decade, the advent of three-dimensional retinal organoids has remarkably contributed to the advancement and proliferation of a diverse spectrum of retinal neuronal types, which notably includes retinal ganglion cells, commonly referred to as RGCs (O'Hara-Wright & Gonzalez-Cordero, 2020). The three-dimensional induction framework mirrors the in vivo developmental landscape and the intricate architecture of retinal cells, resulting in a relatively advanced state of the harvested target cells; thus, it has emerged as the primary mechanism for procuring RGCs via in vitro differentiation induction (Wright, Phillips, Pinilla, Hei, & Gamm, 2014). Nevertheless, a multitude of intricate challenges still lies ahead that must be surmounted to secure an ample supply of viable RGCs for in vivo implantation. To begin with, refining and enhancing are crucial for the optimal performance of cells and in preventing the emergence of tumors following transplantation. At this point in time, the

predominant techniques utilized for the purification of retinal ganglion cells (RGCs) encompass a variety of advanced methodologies, which notably include the innovative process of immunopanning, the sophisticated technique known as fluorescence-activated cell sorting (FACS), and the highly efficient magnetically activated cell sorting (MACS), each contributing uniquely to the refinement and isolation of these crucial neural components in the field of biomedical research (U. S. Kim, Mahroo, Mollon, & Yu-Wai-Man, 2021) (Arthur et al., 2022). Therefore, in the event that there exist various forms or classifications of ganglion cells emerging throughout the intricate and complex process of stem cell differentiation, it becomes increasingly evident that the integrity and purity of the retinal ganglion cells, often referred to as RGCs, cannot be assured or guaranteed with certainty. For this purpose, delving into the intricate surface markers of RGCs holds paramount significance, particularly the newly identified surface antigens CD184 and CD171. These markers are believed to possess promising applications for isolating RGCs and their precursors effectively (Cerna Chavez, 2023). Furthermore, it's essential to identify the most appropriate developmental phase of RGC for in vivo transplantation. This is crucial in the exploration of photoreceptor cell replacement (Bleckert, Schwartz, Turner, Rieke, & Wong, 2014), research revealed that introducing photoreceptor precursor cells into the eye of a newborn, specifically during the 4-8 day window, enhances the likelihood of these cells merging seamlessly with the existing retinal tissue and markedly boosts visual capabilities. Yet, one must not hastily conclude that a prior phase of donor cell maturation invariably ensures an enhanced therapeutic outcome. Certain research indicates that retinal cells in their nascent developmental phase might forfeit their capacity to transform into specific target cells following transplantation (I.-J. Kim, Zhang, Meister, & Sanes, 2010). Thus, in the current landscape of scientific understanding and medical exploration, it can be surmised with considerable confidence that the specific phase of development in which the transplanted cells exist plays a profoundly

significant role in determining the overall efficacy and success of the therapeutic interventions being applied (Chintalapudi et al., 2017). The emergence of single-cell transcriptomics and RNA sequencing technologies addresses previous challenges by providing molecular profiles of retinal ganglion cell subgroups across developmental stages, sourced from human tissues or 3D retinal organoids from hiPSCs. This process significantly enhances the capability to deliver identification markers that are relatively precise in nature for retinal ganglion cells (RGCs), which consequently empowers researchers and clinicians alike to effectively discern and classify the various subtypes of RGCs that exhibit a remarkable degree of resistance to damage, thereby advancing our understanding of neuroprotection in the visual system.

### 3.2 Stem Cell Transplantation and Replacement

The therapeutic approach that employs stem cells is fundamentally oriented towards rectifying the significant deficiency of neurons that have been irretrievably lost, achieved primarily through the intricate and meticulously orchestrated procedure known as cellular transplantation, thereby compensating for the inherent limitation that human retinal ganglion cells (RGCs) lack the ability for self-repair. Nevertheless, subsequent to the implantation of poorly differentiated stem cells into the retinal tissue, the instances of their successful differentiation into specific retinal neuronal types are infrequent. For instance, in the aftermath of the direct transplantation procedure that involves the introduction of induced pluripotent stem cells (iPSCs) into the vitreous cavity or the subretinal space of an experimental glaucoma animal model, it has been observed that these cells predominantly engage in an autonomous differentiation process, wherein they primarily evolve into oligodendrocytes, a critical type of glial cell in the central nervous system (D. C. Wu, Boyd, & Wood, 2007). Consequently, at present, the predominant approach in investigations concerning cellular replacement involves the preliminary induction of transplanted cells into a designated cellular lineage *ex vivo*,

followed by their subsequent transplantation for the purpose of retinal ganglion cell (RGC) replacement. The predominant classifications of cells that are subjected to transplantation procedures include, but are not limited to, primary retinal ganglion cells (RGC), neural progenitor cells that are derived from embryonic stem cells (ESC), retinal ganglion cells that are generated from induced pluripotent stem cells (iPSC), RGC precursors that can be sourced from a variety of biological origins, as well as retinal ganglion cells that are produced from spermatogonial stem cells, which represents a remarkable advancement in cellular therapy within the field of regenerative medicine (Xu, Zhang, Jiang, Jin, & Research, 2024). Typically, the most widely utilized methodologies concerning the practice of transplantation predominantly encompass the technique of subretinal space transplantation as well as the approach of vitreous cavity transplantation, both of which have been extensively studied within the field. The cells that are engrafted into the retinal structures demonstrate remarkable survival capabilities that can vary significantly, ranging from just several days to an impressive span of multiple months, during which they effectively assimilate into the host retina, with the ganglion cell layer (GCL) functioning as the primary and most critical site for such integration to occur. Nonetheless, within the intricate framework of these extensive investigations, the systematic evaluation and thorough assessment of visual capabilities are, regrettably, conducted with infrequency and an apparent lack of attention to detail. (Kumar, Saha, Chaturvedi, Singh, & Kumar, 2024) The neural progenitor cells, which were derived from embryonic stem cells, were systematically administered into the vitreous chamber of a rat model that was specifically exhibiting retinal damage that had been induced by the neurotoxic agent NMDA, which is known to cause significant detrimental effects on retinal structures and functions. The behavioral assessment that was meticulously conducted via the strategic implementation of the Light Avoidance Experiment has successfully elucidated a discernible and significant therapeutic influence that not only facilitates the enhancement of visual function but also

suggests intriguing potential avenues for further exploration in the expansive realm of visual rehabilitation as well as corrective therapies that could ultimately lead to improved patient outcomes and quality of life. (Wei et al., 2024) The behavioral assessment that was meticulously conducted via the strategic implementation of the Light Avoidance Experiment has successfully elucidated a discernible and significant therapeutic influence that not only facilitates the enhancement of visual function but also suggests intriguing potential avenues for further exploration in the expansive realm of visual rehabilitation as well as corrective therapies that could ultimately lead to improved patient outcomes and quality of life. Most studies failed to clarify the survival rate of engrafted cells in the recipient retina, the spatial distribution of transplanted cells, or the measurable success rate of the transplantation procedure. Recently, (Li, Ma, Hao, & Disease, 2024) utilized a survival rate over 5% post-transplant as a benchmark and found that miPSC/mESC-derived donor RGCs survive for up to 12 months post-transplantation, achieving over 65% success, significantly higher than the 10% success rate of primary RGCs transplantation. (Zhang, Aguzzi, & Johnson, 2021) transplanted human embryonic stem cell-derived retinal neurons in Squirrel Monkeys exhibited axonal extension along the host's nerve fiber layer toward the optic nerve head, indicating their potential integration into the optic nerve bundle and projection to the central nervous system. The study indicates that retinal ganglion cell replacement therapy is a feasible approach, with engrafted cells effectively integrating into the host's retinal structure, thus showing potential for functional synaptic connections in the visual pathway.

### 3.3 Stem Cell-Mediated Neuroprotection

Intraocular transplantation of mesenchymal stem cells (MSCs) provides neuroprotection for retinal ganglion cells (RGCs). Taking into account the various goals that are inherently linked to this particular modality of medical intervention, one can ascertain that the significant value of stem cell transplantation lies in its remarkable capacity to facilitate the

prolonged release of a diverse array of therapeutic agents, which is achieved through a singular, well-timed administration. This approach consequently mitigates the likelihood of infections and hemorrhaging associated with intraocular injections, in addition to alleviating the demands placed on patient adherence. In recent years, exosomes released by mesenchymal stem cells (MSCs) have increasingly attracted interest in the context of MSC-mediated neuroprotection (Ahani-Nahayati et al., 2022). (Joe & Gregory-Evans, 2010) (Bahlakeh et al., 2021), scholars additionally engineered mesenchymal stem cells (MSCs) to constitutively express elevated levels of brain-derived neurotrophic factor (BDNF) and employed these modified cells in intraocular transplantation trials utilizing glaucoma animal models. The results of the conducted research clearly indicated that the neuroprotective capabilities exhibited by mesenchymal stem cells (MSCs), which were genetically modified to achieve stable overexpression of brain-derived neurotrophic factor (BDNF), on the damaged retinal ganglion cells (RGCs) demonstrated a significantly enhanced level of effectiveness that was markedly pronounced (Przyborski, Hardy, Maltman, & therapy, 2008). To this point in time, an extensive array of methodologies and innovative strategies concerning the application and effective utilization of neurotrophic factors has been proposed, particularly with regard to their potential roles in the therapeutic management and clinical intervention of glaucoma, as well as various other neurodegenerative disorders that significantly impact the nervous system and overall neurological health.

### 3.4 Endogenous Trans differentiation and Nerve Repair

The transdifferentiated retinal ganglion cells (RGCs) demonstrated an appropriate electrophysiological response to light stimuli and formed central projections to the dorsal lateral geniculate nucleus and superior colliculus, thereby successfully reinstating photoreceptive capabilities in the murine model. Nonetheless, in the practical implementation of this innovative methodology within a clinical setting, it

becomes exceedingly crucial to recognize and appreciate the fact that the CRISPR-based strategies elucidated and explored in the context of this research endeavor specifically utilized distinct transgenic murine models, carefully designed and engineered, to ensure that the targeting capabilities of the CRISPR system were exclusively restricted to the specialized retinal cells known as Muller glia. This particular scenario signifies an anticipated and considerable impediment in the therapeutic management of human subjects who may not possess transgenic modifications, particularly in contexts where the underlying biological system is likely to randomly and indiscriminately convert each distinct glial cell type into a myriad of different neuronal phenotypes within the intricate and complex architecture of the retina. Recently, (Xiao et al., 2021) the upregulated expression of *Math5* and *Brn3* effectively converts differentiated Müller cells in mice into retinal ganglion cells (RGCs), which can successfully navigate the optic chiasm to connect with various brain regions involved in both image-forming and non-image-forming visual pathways. This observation indicates that inherently differentiated RGCs display a wide variety of subtype characteristics, while current research on the reversal of senescence in RGCs, alongside transdifferentiation among retinal cell types, provides significant insights (Sheely, 2011). The researchers, through their rigorous investigative efforts, initially elucidated the significant and complex alterations that occur in the realm of retinal epigenetics, which are directly attributable to the multifaceted and gradual process of aging, and, building upon the innovative advancements in the development of induced pluripotent stem (iPS) cells, they posited that the intricate compatibility of various transcription factors might play a pivotal role in modulating the epigenetic landscape associated with cellular senescence, thereby potentially steering it towards a rejuvenated and more youthful state that could have profound implications for regenerative medicine and the understanding of age-related degenerative conditions. This particular discovery not only introduces a plausible and effective neuro-reparative methodology aimed at the restoration and

rehabilitation of retinal ganglion cells (RGC), which are crucial for visual processing, but it also, and arguably with even greater importance, reinforces the hypothesis that the detrimental effects inflicted upon RGCs as a consequence of glaucoma, which is a complex and progressive optic neuropathy, are indeed subject to potential reversal and can be effectively addressed through targeted therapeutic interventions. Nevertheless, it is of utmost importance to acknowledge that the transcription factors utilized in the comprehensive investigation hold a substantial correlation with the complex mechanisms underlying tumorigenesis, which necessitates the prioritization of safety concerns throughout the multifaceted process of clinical translation to ensure that both efficacy and patient well-being are thoroughly safeguarded.

### 3.5 Cellular material transfer

In 2009, (West, Pearson, MacLaren, Sowden, & Ali, 2009) it has been conclusively determined through rigorous investigation that there exists a transfer of cellular components between the photoreceptors of the donor that have been transplanted and the retinal cells of the recipient, a process which notably includes the incorporation of fluorescein protein, a fluorescent marker often utilized in biological studies to track cellular activities and interactions. However, despite this insightful revelation regarding the donor-recipient cellular interaction, the presence and operational dynamics of such a mechanism within the specific scope of retinal ganglion cell (RGC) transplantation remain to be firmly validated and substantiated through further empirical research and experimentation. Therefore, it is imperative that future studies focus on elucidating the underlying biological processes and potential implications of cellular component transfer in the context of RGC transplantation, as this could significantly enhance our understanding of retinal repair and regeneration strategies. Moreover, the precise methodologies or mechanisms through which this particular cellular constituent engages in exchange processes—be it through vesicular transport mechanisms, the utilization of exosomes as mediators, or through direct intercellular interactions that facilitate

communication—continues to be an area of uncertainty and is yet to be definitively elucidated within the current scientific literature and discourse. Recent scholarly investigations undertaken by our dedicated research team have unveiled, through the meticulous examination of living cellular structures, that mesenchymal stem cells, which are derived from human induced pluripotent stem cells (commonly referred to as hiPS-derived MSC), possess the remarkable capability to “donate” vital organelles such as mitochondria and lysosomes to a diverse array of ocular tissue cell types, which include but are not limited to corneal endothelium, retinal pigmented epithelium, and photoreceptors, thus highlighting the potential therapeutic applications of these stem cells in regenerative medicine and ocular health. The mitochondria that are transferred exhibit a remarkable capacity to facilitate the reinvigoration of mitochondrial functionality within three separate categories of compromised ocular cells, which in turn plays a crucial role in significantly reducing the occurrence of apoptosis, a process that is pivotal in the regulation of cell survival and death. The successful delivery of operational mitochondria sourced from these human induced pluripotent stem cell-derived mesenchymal stem cells (hiPS-MSCs) to the photoreceptor cells is largely contingent upon the establishment of intricate F-actin-based tunneling nanotubes (TNT), which are specialized cytoplasmic extensions that facilitate intercellular communication and transport between the cells serving as donors and those receiving the cellular components.

### 3.6 Corneal Changes

The process of mobilization, migration, and subsequent colonization of stem cells within the body can be significantly stimulated or induced as a direct consequence of various forms of injury and the presence of inflammatory responses, which serve as critical biological signals that activate the underlying mechanisms of stem cell behavior in the context of tissue repair and regeneration (Kaufman & research, 2000). In the event of corneal injury resulting from various factors such as physical trauma or infectious agents,

there exists a physiological response whereby the endogenous mesenchymal stem cells (MSCs) originating from the bone marrow are activated and subsequently mobilized into the systemic circulation as a consequence of specific chemo-attractant signals. Following their release into the peripheral bloodstream, these circulating MSCs exhibit a remarkable capacity to migrate towards the site of injury located within the cornea, where they can effectively engraft and contribute to the intricate biological processes that facilitate and enhance the mechanisms of wound healing. This sophisticated interplay between the mobilization of MSCs and their subsequent action at the injury site underscores the critical role these cells play in tissue regeneration and repair following corneal damage, thus highlighting their potential therapeutic significance in the context of ocular pathology (Cejka, Cejkova, & longevity, 2015). (D. Wu et al., 2021)the study meticulously documented and provided a comprehensive analysis regarding the phenomenon of the migration as well as the successful engraftment of mesenchymal stem cells derived from bone marrow, which were administered through intravenous injection, into the damaged corneal tissue within a murine model specifically designed to simulate alkali burns. Among the various chemokines, SDF-1 and substance P have been demonstrated to modulate the mobilization and recruitment of mesenchymal stem cells (MSCs) to the corneal region (Wilson & Therapeutics, 2023). Furthermore, the adhesion, transmigration, and passive entrapment of leukocyte-like cells facilitated by selectins and integrin's represent significant mechanisms by which mesenchymal stem cells (MSCs) migrate to various tissues (Williams, Irani, & Klebe, 2013). Nevertheless, it is important to acknowledge that the overall effectiveness and efficiency of mesenchymal stem cell (MSC) homing and subsequent engraftment in target tissues is typically quite limited, primarily due to the significant phenomenon known as first-pass retention that occurs within vital organs such as the lungs, liver, kidneys, and spleen following the systemic administration of these cells into the bloodstream (Lim & Lim, 2020). A considerable amount of research and

investigation has been devoted to enhancing the migratory capabilities of mesenchymal stem cells (MSCs) towards specific ocular tissues, with the ultimate goal of optimizing therapeutic outcomes in ophthalmologic applications. The administration of MSCs via sub-conjunctival injection, along with the innovative approach of co-transplantation utilizing amniotic membrane, has demonstrated a significant enhancement in the local concentrations of MSCs within the context of damaged corneal tissue, thereby potentially facilitating improved healing processes. These findings not only underscore the importance of targeted delivery methods for MSCs but also highlight the promising implications for future clinical practices aimed at addressing various ocular pathologies through regenerative medicine strategies (Alhayek & Lu, 2015). This enhances the efficacy of mesenchymal stem cells (MSC) and diminishes the required dosage for administration. Nevertheless, the processes of MSC migration and homing do not appear to be essential for the therapeutic effects to manifest. In a comparable manner, it has been demonstrated through various studies that the distal ramifications associated with mesenchymal stem cells (MSCs) play a significant role in diminishing the inflammatory response that occurs following a myocardial infarction, while simultaneously enhancing the overall functionality of the cardiac tissue; this beneficial effect is mediated by the secretion of the anti-inflammatory protein TSG-6, which is released from the MSCs that have been inadvertently trapped within the pulmonary vasculature subsequent to their intravenous administration (Saldanha, Lindsley, Lum, Dickersin, & Li, 2019).

### 3.7 Corneal Inflammation

Mesenchymal stem cells (MSCs) are widely recognized in the scientific community for their remarkable and powerful anti-inflammatory capabilities, in conjunction with their ability to regulate angiogenesis effectively, which collectively endows them with significant therapeutic potential for treating various corneal diseases that may adversely impact vision and overall ocular health. The administration of mesenchymal stem cells

derived from bone marrow through topical application and/or sub-conjunctival injection has been demonstrated to significantly mitigate corneal inflammation and the process of angiogenesis following chemical-induced injuries in experimental murine models, thereby highlighting the potential therapeutic efficacy of these cellular interventions in the context of ocular pathologies (Mantopoulos, Cruzat, & Hamrah, 2010). Thus, it can be observed that there exists a significant alteration in the pro-inflammatory environment present within the damaged corneal tissues, which is accompanied by a restoration of the physiological conditions that are essential for the regeneration of corneal epithelial cells, ultimately resulting in the enhancement of the healing processes associated with wounds on the ocular surface (Torrecilla, del Pozo-Rodriguez, Vicente-Pascual, Solinís, & Rodriguez-Gascon, 2018). In the context of both neoplastic growth and regions characterized by insufficient blood supply, these cells secrete a variety of angiogenic factors, which are crucial biochemical substances that facilitate the development of a granulation tissue matrix, thereby promoting the proliferation and movement of endothelial cells essential for the process of angiogenesis (Fortingo, Melnyk, Sutton, Watsky, & Bollag, 2022). Nevertheless, it is worth noting that mesenchymal stem cells (MSCs) possess the remarkable capacity to enhance the expression of thrombospondin-1 (TSP-1), which serves as a pivotal regulator in the inhibition of angiogenesis by effectively interfering with the signaling pathways associated with CD47 and vascular endothelial growth factor receptor-2 (VEGFR-2), while simultaneously exerting a suppressive influence on the VEGF-Akt-endothelial nitric oxide synthase (eNOS) signaling cascade (Alio et al., 1995). Furthermore, it has been observed that the upregulation of the TSP-1 protein significantly facilitates the induction of apoptosis in endothelial cells, while concurrently exerting a downregulatory influence on the expression levels of MMP2, a highly potent inflammatory chemokine that is well-documented for its pro-angiogenic properties and contributions to the complex interplay of cellular signaling in various

physiological and pathological processes (Cursiefen, Maruyama, Jackson, Streilein, & Kruse, 2006). In recent scientific endeavors, it has been elucidated that corneal stromal stem cells (CSSCs), which are derived from the limbal stroma, exhibit significant modulatory activities that have profound implications for the management and treatment of corneal inflammation and scarring, thereby highlighting their potential therapeutic roles in ocular regenerative medicine (Carnt et al., 2007). Upon the application of a meticulously designed experimental framework that utilized an acute corneal wound model in murine subjects, it was observed that these agents effectively inhibited the infiltration of neutrophils, which are crucial components of the innate immune response, while concurrently downregulating the expression levels of various fibrotic markers, including but not limited to tenascin-C,  $\alpha$ -smooth muscle actin, and SPARC, which stands for secreted protein acidic and rich in cysteine, through the intricate signaling mechanisms mediated by the TSG-6 pathway, thereby elucidating the potential therapeutic implications of these findings in the context of corneal wound healing and fibrosis (Amano et al., 1998).

### 3.8 Corneal Transplantation

Numerous scholarly articles and empirical studies have meticulously documented and elucidated the multifaceted roles that mesenchymal stem cells (MSCs) play in enhancing the longevity and viability of grafts, thereby underscoring their critical importance in the field of regenerative medicine and transplantation science (Tan, Dart, Holland, & Kinoshita, 2012). Mesenchymal stem cells (MSCs), which are characterized by their remarkable immunomodulatory capabilities, play a significant role in the inhibition of both the maturation and activation processes of antigen presenting cells (APCs) and dendritic cells, while simultaneously exerting a suppressive effect on the cytotoxic activity of natural killer (NK) cells, thereby contributing to the intricate balance of immune responses within the microenvironment (Singh, Gupta, Vanathi, & Tandon, 2019). They additionally play a significant role in stimulating the secretion of interleukin-10, commonly referred

to as IL10, from immature antigen-presenting cells, which are crucial components of the immune system, and this process subsequently leads to the transformation of these cells into inhibitors of T-cell activity, thereby modulating the overall immune response (Moffatt, Cartwright, Stumpf, & ophthalmology, 2005). The diminishment in the population of mature antigen-presenting cells (APCs) not only influences the dynamics of immune responses but also exerts a significant auxiliary effect on the therapeutic application of mesenchymal stem cells (MSCs), as it plays a crucial role in promoting and augmenting the immune tolerance towards allogeneic grafts, which is essential for the successful integration and acceptance of transplanted tissues or organs within the host organism (Gain et al., 2016). Mesenchymal stem cells (MSCs) exhibit a remarkable capacity to not only impede the proliferation of T-lymphocytes but also effectively suppress the secretion of cytokines by these immune cells, while concurrently influencing and modulating the maturation processes of B lymphocytes, thereby playing a pivotal role in the intricate regulatory mechanisms that govern immune responses within the body (Crawford, Patel, & McGhee, 2013). In conjunction with their pivotal role in the modulation of the generation of regulatory T-cells, commonly referred to as Tregs, these mechanisms also play an essential part in the preservation of graft tolerance, thereby ensuring the longevity and continued viability of allografts within the host organism (Armitage et al., 2019). This particular phenomenon was effectively illustrated through a series of meticulously conducted experiments wherein mesenchymal stem cells (MSCs) were systematically infused into the subjects prior to the actual transplantation procedures, with the primary objective being to significantly extend the duration of graft survival in various murine models that were utilized for this investigation (Bersudsky, Blum-Hareuveni, Rehany, & Rumelt, 2001). Furthermore, it has been observed that mesenchymal stem cells, commonly referred to as MSCs, are endowed with a specialized cell surface glycocalyx that is significantly enriched in a variety of anti-inflammatory biomolecules, including but not limited to the potent

immunomodulatory protein TSG-6, the complex proteoglycan versican, the acute-phase protein pentraxin-3, and a heavily modified form of hyaluronan matrix characterized by its unique heavy chain alterations, all of which collectively serve to effectively modulate and influence the inflammatory responses exhibited by the host organism (Di Zazzo, Kheirkhah, Abud, Goyal, & Dana, 2017).

### 3.9 Corneal injuries and various factors

Corneal injuries that result from various factors such as chemical exposures, thermal injuries, physical trauma, and also due to underlying immune system dysfunctions or genetic predispositions, are intricately linked to a series of pathological processes that include inflammation, the formation of new blood vessels (neovascularization), the development of corneal ulcers, and the subsequent formation of scar tissue, all of which can significantly impair visual function and overall ocular health (Venkatakrishnan, Saeed, & Kao, 2022). The failure to administer appropriate therapeutic interventions in a timely manner, whether due to negligence, lack of resources, or misdiagnosis, can ultimately result in severe and irreversible visual impairments, leading to complete blindness. Over the course of the previous ten years, the therapeutic applications of mesenchymal stem cell (MSC) therapy have been extensively explored and subsequently proposed as a potentially effective treatment strategy aimed specifically at addressing a variety of complex pathological conditions characterized by anti-inflammatory processes, the inhibition of angiogenesis, and the modulation of immune system activities, which collectively suggest a promising avenue for advanced medical intervention (Harrell, Volarevic, Djonov, & Volarevic, 2022). The paracrine signaling mechanisms exhibited by mesenchymal stem cells (MSCs) have been extensively documented in various scientific studies, demonstrating their pivotal role in enhancing the intricate processes involved in tissue wound healing, while simultaneously exhibiting the capability to modulate and diminish the inflammatory responses, as well as playing a significant role in the regulation of angiogenesis across a multitude of

experimental tissue models that have been rigorously investigated in the realm of regenerative medicine. The aforementioned cell-free strategy has the potential to exert a profound and significant influence on the processes involved in the repair of corneal wounds, a complex biological phenomenon that necessitates the intricate interplay of various factors that are instrumental in modulating not only the inflammatory response but also the processes of angiogenesis and the overall regeneration of tissue (Tian et al., 2023). Numerous investigations have provided compelling evidence supporting the therapeutic roles of soluble factors found within mesenchymal stem cell-exosomes (MSC-Exo) in relation to corneal wound healing, both in controlled laboratory settings (in vitro) and in living organisms (in vivo). In particular, when rabbit corneal stromal cells were cultured in the presence of exosomes derived from rabbit adipose mesenchymal stem cells, there was a notable enhancement in cellular proliferation rates accompanied by a significant reduction in apoptotic events, as well as an increase in the synthesis and deposition of essential extracellular matrix (ECM) proteins, which prominently includes collagen. Such findings underscore the potential of MSC-Exo as a promising therapeutic avenue for the enhancement of corneal repair mechanisms, thereby contributing to the broader understanding of regenerative medicine and its applications in ocular biology (An et al., 2023). Furthermore, it has been demonstrated through a series of rigorous scientific investigations that the process of wound healing within the corneal epithelium of murine models can be significantly enhanced and accelerated by the application of exosomes derived from human corneal mesenchymal stromal cells, which are known for their regenerative properties and ability to facilitate cellular communication and repair mechanisms (Erkoc-Biradli et al., 2024). The administration of umbilical cord-derived mesenchymal stem cell exosomes that are encapsulated with the enzyme  $\beta$ -glucuronidase has been shown to significantly diminish the levels of accumulated glycosaminoglycans in a murine model of mucopolysaccharidosis, which consequently leads to a notable

reduction in the prevalence of corneal haze (Jia et al., 2022). The findings derived from these comprehensive data sets have significantly underscored and illuminated the remarkable potential and promise associated with the therapeutic application of mesenchymal stem cell-derived exosomes (MSC-Exo) in the treatment and management of various ocular surface diseases, as well as in addressing congenital corneal metabolic disorders that may affect individuals from a young age.

#### 4. Discussion

The primary concern surrounding stem cell replacement therapy pertains to the ethical implications, immune response challenges, and tumorigenicity risks associated with allogeneic transplantation, despite the extensive research on human embryonic stem cells (hESCs) for retinal ganglion cell (RGC) therapy (Lau, Ghevaert, & Medicine, 2021), the transition from laboratory findings to clinical application has been significantly impeded by the aforementioned challenges that have been identified in previous studies. In contrast, the advent of human induced pluripotent stem cells (hiPSCs), which can be generated from an individual's own somatic cells through specialized reprogramming techniques, presents a more feasible avenue for addressing the ethical dilemmas associated with stem cell usage as well as mitigating the complications related to immunological rejection that are often encountered in transplantation scenarios. Nonetheless, when considering the potential application of autogenous induced pluripotent stem cells (iPSCs) within the realm of clinical practice, one must take into account the fact that the financial implications associated with the process of generating these personalized cells for each individual patient are likely to be significantly elevated, which consequently poses a considerable challenge in advocating for and implementing such a personalized medical strategy on a widespread clinical basis (Flahou, Morishima, Takizawa, & Sugimoto, 2021). In contemporary research, scholars have concentrated their efforts on establishing an induced pluripotent stem cell (iPSC) repository aimed at facilitating HLA compatibility, thereby enabling immediate transplantation post-matching, with the

objective of advancing the industrialization of cellular transplantation. In recent times, the esteemed institution of Kyoto University has undertaken the sophisticated application of gene-editing techniques and methodologies to successfully engineer induced pluripotent stem (iPS) cells that exhibit a deficiency in human leukocyte antigen class I (HLAI), with the overarching objective of facilitating the subsequent generation of platelets that are devoid of HLA, thereby contributing to advancements in medical science and therapeutic interventions. Moreover, the researchers conducted a series of rigorous cellular assays along with comprehensive animal model experiments to substantiate their hypothesis, demonstrating conclusively that the platelets which are derived from induced pluripotent stem cells (iPSCs) and exhibit a deficiency in human leukocyte antigen (HLA) expression would remain impervious to the detrimental effects of anti-HLA antibodies as well as the cytotoxic actions of natural killer (NK) cells, thereby highlighting the potential of these modified platelets in therapeutic applications where immune rejection is a significant concern. This study elucidates that platelets derived from induced pluripotent stem cells lacking human leukocyte antigen (HLA) can function as a "universal" and adaptable option for blood transfusions, significantly alleviating the economic strain linked to the extensive manufacturing of diverse HLA-deficient iPSC-derived platelets (Lau et al., 2021), and additionally offers an innovative viewpoint regarding the development of these "universal" RGCs derived from HLA-I-deficient hiPSC origins. If one were to consider that the primary objective of the pathogenic gene in question is indeed aimed at the retinal ganglion cells (RGCs), which play a crucial role in the visual processing pathway, then it would be pertinent to explore the potential of RGCs that have been generated from induced pluripotent stem cells (iPS), which are reprogrammed somatic cells that possess the remarkable ability to differentiate into various cell types, including those necessary for the intricate functioning of the retina (Sugimoto, Eto, & Sciences, 2021) will retain deleterious elements; consequently, It is essential to

consider in vitro gene correction before in vivo transplantation; our previous studies successfully generated induced pluripotent stem cells (iPSCs) from retinitis pigmentosa patients and differentiated them into three-dimensional retinal organoids containing the relevant pathogenic genetic variants. Subsequently, we utilized CRISPR/Cas9 gene-editing methodology to amend the mutation and observed that the commencement of retinal degeneration was proficiently prevented, as substantiated by the gene expression profile, protein concentrations, and electrophysiological characteristics of the cells, thereby corroborating the proof-of-concept for cellular rejuvenation prior to tackling the disease itself (Meyer, Ducray, & Widmer, 2008). The patients' pathological condition persisted, and RGCs remained vulnerable to the pathophysiological environment. Thus, post-stem cell intervention, glaucoma patients may require continuous intraocular pressure management and neuroprotective measures for life. Following grafting, the translocation of transplanted cells to the ganglion cell layer is hindered. This is due to the obstruction from the internal limiting membrane and resultant reactive gliosis. Researchers have determined that amino adipic acid (AAA), a pharmacological compound that selectively inhibits glial cell activation, significantly improves cell migration and integration post-transplantation in normal mice and those with suppressed glial responses due to AAA treatment. The research outcomes demonstrated that a significantly higher quantity of the transplanted cellular entities achieved successful incorporation and assimilation within the host retinal environment of mice that had undergone treatment with AAA, when juxtaposed with the respective control group that had not received any such intervention (Brown & Kretschma, 1998). The application of tissue engineering presents an innovative solution by enabling targeted transplantation through a cell sheet format, which enhances identification and integration, while also serving as an effective medium for additional compounds to amplify synergistic effects. (Ladero, Reche-Sainz, & Gallardo, 2024) investigation involved the derivation of retinal

ganglion cells (RGCs) from human induced pluripotent stem cells (hiPSCs) within a three-dimensional neural retina framework, followed by the integration of these RGCs onto a biodegradable poly(lactic-co-glycolic acid) (PLGA) scaffold to create a composite biomaterial of RGCs and the scaffold. Moreover, the engineered human RGC-scaffold biomaterial was introduced into the intraocular environment of rabbits and rhesus monkeys, thereby establishing a production methodology; in the context of glaucoma cell replacement therapy, it is crucial to explore further effective targets and strategies to overcome the integration challenges of transplanted cells within the host retina. An additional significant challenge that has emerged in the field of neurobiology relates to the intricate processes involved in the regeneration and the adept projection of retinal ganglion cell (RGC) axons, which are essential for the proper functioning of visual pathways and the overall integrity of the visual system. In a more exacting manner, the intricate process of functional substitution of retinal ganglion cells (RGCs) fundamentally requires the successful and proficient establishment of synaptic integration within the complex architecture of the retina; furthermore, it is imperative that the axons of the RGCs proficiently navigate the challenging terrain of the optic nerve to reach the specified cortical regions, which is essential for the establishment of effective and reliable signal transmission that underpins visual perception. In spite of the myriad of challenges and complex impediments that significantly hinder the process of axon regeneration within the intricate and highly specialized environment of the central nervous system, a substantial and growing corpus of scientific research has convincingly demonstrated that it is indeed feasible to effectively stimulate and promote the regeneration of retinal ganglion cell (RGC) axons, along with their subsequent and precise projection to designated and specific regions of the brain, through the careful modulation and manipulation of certain key transcription factors and intricate signaling pathways that play crucial roles in cellular communication and regeneration processes (Chen et al., 2024). The regenerated axons of retinal ganglion cells

(RGCs) exhibited a significant capacity for accurate projection to specific brain regions, including the lateral geniculate nucleus and the superior colliculus, facilitating a partial recovery of previously impaired visual function. A separate research team found that synergistically promoting neural activity with the activation of the mTOR pathway markedly improves axon regeneration, facilitating the restoration of essential neural connectivity patterns for optimal visual processing. In consideration of the previously identified challenges, it is clear that stem cell therapy represents a highly promising and potentially revolutionary approach for the regeneration and preservation of retinal ganglion cells (RGCs) in individuals with advanced glaucoma, which is marked by progressive optic nerve deterioration and ensuing visual deficits. The integration of advanced biotechnologies, such as single-cell omics, gene editing, tissue engineering, and nanotechnology, is expected to play a crucial role in utilizing stem cells for the protection, rejuvenation, and restoration of damaged retinal ganglion cells, thereby facilitating vision recovery in glaucoma patients.

## 5. Conclusion

Sight-threatening retinal degenerative diseases, which encompass a wide array of conditions that lead to significant deterioration of the retinal structure and function, represent the predominant and most critical source of visual impairment or, in severe cases, complete blindness on a global scale. Despite the considerable and sustained efforts made by researchers, clinicians, and healthcare professionals in the field of ophthalmology, there remains a notable deficiency in the availability of effective therapeutic strategies that possess the capability to halt the progression of, or even provide a definitive cure for, these debilitating disorders affecting the retina. In light of recent advancements in medical science, a prospective and promising option has been introduced in the form of stem cell therapy, which holds potential as a novel intervention for addressing these challenging retinal conditions and improving patient outcomes. These extensive clinical trials are primarily concentrated on the

comprehensive investigation of the safety profile associated with the therapeutic interventions, the meticulous selection of the most suitable stem cells, alongside their subsequent activation or modification processes prior to their application in clinical settings, the careful optimization of the cellular dosage to be administered, the exploration of various routes of application, as well as the intriguing possibility of substituting the stem cells with their biologically active paracrine products that may yield therapeutic benefits. Despite the existence of numerous unresolved issues and challenges that must be systematically addressed prior to the ultimate regulatory approval of mesenchymal stem cell (MSC) therapy for the treatment of retinal degenerative diseases, the preliminary outcomes derived from both preclinical animal studies and ongoing clinical trials thus far appear to be quite promising and offer a sense of encouragement for the future of this therapeutic approach. Consequently, it can be posited that therapies utilizing stem cells represent a highly promising avenue for treatment, particularly for patients who find themselves devoid of alternative therapeutic modalities that may be available to them. Notwithstanding this potential, prior to the unequivocal and widespread implementation of mesenchymal stem cell (MSC)-based therapies within clinical practice, it is imperative that a multitude of pertinent inquiries be addressed and meticulously validated, including but not limited to the origins from which MSCs are derived, the specific conditions under which MSCs are propagated in vitro, the various methods through which these cellular therapies can be administered, as well as the feasibility and implications surrounding the utilization of products derived from MSCs.

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