REVIEW

Intravitreal stem cell paracrine properties as a potential neuroprotective therapy for retinal photoreceptor neurodegenerative diseases

Kevin Puertas-Neyra[1, #], Ricardo Usategui-Martín[1, #], Rosa M. Coco[1, 2, 3], Ivan Fernandez-Bueno[1, 2, 3, *]
1 Instituto Universitario de Oftalmobiología Aplicada, Universidad de Valladolid, Valladolid, Spain
2 Centro en Red de Medicina Regenerativa y Terapia Celular de Castilla y León, Valladolid, Spain
3 Red Temática de Investigación Cooperativa en Salud, Oftared, Instituto de Salud Carlos III, Valladolid, Spain

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Abstract
Retinal degenerations are the leading causes of irreversible visual loss worldwide. Many pathologies included under this umbrella involve progressive degeneration and ultimate loss of the photoreceptor cells, with age-related macular degeneration and inherited and ischemic retinal diseases the most relevant. These diseases greatly impact patients' daily lives, with accompanying marked social and economic consequences. However, the currently available treatments only delay the onset or slow progression of visual impairment, and there are no cures for these photoreceptor diseases. Therefore, new therapeutic strategies are being investigated, such as gene therapy, optogenetics, cell replacement, or cell-based neuroprotection. Specifically, stem cells can secrete neurotrophic, immunomodulatory, and anti-angiogenic factors that potentially protect and preserve retinal cells from neurodegeneration. Further, neuroprotection can be used in different types of retinal degenerative diseases and at different disease stages, unlike other potential therapies. This review summarizes stem cell-based paracrine neuroprotective strategies for photoreceptor degeneration, which are under study in clinical trials, and the latest preclinical studies. Effective retinal neuroprotection could be the next frontier in photoreceptor diseases, and the development of novel neuroprotective strategies will address the unmet therapeutic needs.

Key Words: *clinical trials; growth factors; intraocular injection; intravitreal injection; neuroprotection; paracrine properties; photoreceptors; preclinical models; retinal diseases; stem cells*

Correspondence to:
Ivan Fernandez-Bueno, PhD,
ifernandezb@ioba.med.uva.es.

#Both authors contributed equally to this work.

orcid:
0000-0003-3380-4040
(Ivan Fernandez-Bueno)

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Introduction
The functional and structural complexity of the retina makes this tissue susceptible to multiple types of pathogenic damage (Cuenca et al., 2014). Retinal degeneration results in retinal deterioration caused by different injuries that lead to progressive degeneration and ultimately cell death. This condition is the leading cause of incurable visual loss and blindness worldwide, especially if the diseases affect the macula (Gagliardi et al., 2019). The major retinal disease related to photoreceptor and retinal pigment epithelium (RPE) cell death, and thus, visual impairment, is age-related macular degeneration (AMD). Furthermore, genetic retinal diseases related to photoreceptor degeneration and death, such as retinitis pigmentosa (RP), Leber's congenital amaurosis, Usher's syndrome, and Stargardt disease, are other main causes of irreversible visual loss worldwide. Thirty-four million people in the European Union are estimated to have photoreceptor-related degeneration due to conditions such as AMD or inherited retinal degenerations (Li et al., 2019). In addition, ischemic retinal disorders, such as ischemic diabetic maculopathy and ischemic central retinal vein occlusion, cover a range of ocular diseases that affect the blood vessels and that may lead eventually to photoreceptor degeneration within the retina (Kadłubowska et al., 2016). Nevertheless, many different etiologies that cause retinal degeneration often share common mechanistic pathways affecting the cellular response and remodelling, which lead to the same final result, i.e., photoreceptor loss and consequent visual loss (**Figure 1**) (Gagliardi et al., 2019).

Despite the impact on daily life and the social and economic effects, there is no cure for retinal diseases in which photoreceptor atrophy and death are the main causes of impaired vision. Current therapies are focused primarily on the etiology or specific late consequences, such as neovascularization. The currently available clinical treatments, such as neurotrophic factors or anti-angiogenic agents delivered intraocularly, only delay the onset or slow progression of visual impairment (Gagliardi et al., 2019). Therefore, given the magnitude and severity of this problem, it is not surprising that new therapeutic strategies are being investigated, such as gene therapy, optogenetics, or cellular replacement (Cuenca et al., 2014; Trapani and Auricchio, 2018; Jin et al., 2019; Simunovic et al., 2019).

However, sustained neuroprotection is currently the only potential strategy that seems applicable to different types of retinal degenerative diseases mainly at their initial stages (Cuenca et al., 2014; Kolomeyer and Zarbin, 2014). Considering this, neuroprotection via cell-based therapies

offers a new all-encompassing approach. Specifically, the paracrine properties of stem cells injected into the eye allow continuous secretion of neurotrophic, immunomodulatory, and anti-angiogenic factors that could potentially impact deteriorating retinal cells for a considerable period of time (Labrador Velandia et al., 2018; Lejkowska et al., 2019), with the advantage of superior potential than neurotrophic factors with a shorter half-lives and injected in a timely manner (LaVail et al., 1992; Kurokawa et al., 1999; Vidal-Sanz et al., 2001; Takahata et al., 2003; Li et al., 2009; Levkovitch-Verbin et al., 2010, 2019; Kolomeyer and Zarbin, 2014).

The eye is an ideal target for advanced therapies such as cell therapy because of the ease of accessibility and the wealth of surgical expertise dealing with the retina facilitated by the transparent cornea. In addition, the eye is a small, highly compartmentalized organ and fewer cells would be sufficient for potential therapy; which facilitates specific targeting of the neuroretina; and the blood-brain barrier separates the eye from the rest of the body, which ensures ocular immune privilege and avoids systemic dissemination of physiologic conditions (Gagliardi et al., 2019). In addition, many retinal diseases are clinically well characterized. Finally, the availability of high-resolution and non-invasive imaging techniques allow monitoring of retinal changes after treatment (Gagliardi et al., 2019).

For these reasons, much research has been undertaken recently to advance the preclinical knowledge about stem cell management and properties, and, from the clinical standpoint, to confirm their intraocular safety and efficacy to prevent and/or reduce retinal degeneration. All of these steps are necessary for future neuroprotection strategies by using intraocular stem cells in patients with degenerative retinal diseases. We review the recent literature about stem cell-based neuroprotective strategies based on their paracrine properties for photoreceptor cell degeneration, the research about which is currently in clinical trials, and discuss the future direction of this field as described in the latest preclinical research publications.

Search Strategy and Selection Criteria

The review cited the preclinical studies and clinical trials that have been performed recently on the role of intravitreal stem cell paracrine properties in photoreceptor neuroprotection (**Figure 2**) and searched PubMed, Web of Science, Scopus, Embase, and ClinicalTrials.gov electronic databases from 2013 to September 2019. Potentially relevant articles were sought by using the following search terms in combination as Medical Subject Headings terms and text words: animal models, cell culture, cell therapy, clinical trials, growth factors, *in vitro* models, *in vivo* models, intravitreal injection, intraocular injection, neurodegeneration, neuroprotection, organ culture, organotypic culture, paracrine properties, photoreceptor, preclinical studies, retina, retinal diseases, secretome, and stem cell. No language restrictions were applied. English abstracts were used for non-English articles when available. We also scanned the reference lists of the retrieved publications to identify additional relevant articles (cross-reference strategy), and using the MEDLINE option "Related Articles" and consulting review articles on the topic supplemented the search.

Healthy and Diseased Photoreceptors

Photoreceptors, rods and cones, are highly specialized neurons with a clearly differentiated morphology, that are comprised of an elongated outer segment, connecting cilium, inner segment, cell body, and axon with a synaptic terminal (Cuenca et al., 2014; Bachmann-Gagescu and Neuhauss, 2019) (**Figure 3A** and **C**).

The changes in photoreceptors and their synaptic connectivity that lead to dysfunction and cell loss are evident in several human neurodegenerative diseases and animal models of neurodegeneration, which result in visual impairment and eventually blindness (Jones et al., 2012; Cuenca et al., 2014; Gasparini et al., 2019). Photoreceptor degeneration is also accompanied by remodelling of other neuroretinal cells, such as horizontal, bipolar, amacrine, ganglion, and Müller cells (Cuenca et al., 2014; Gasparini et al., 2019). The neural retinal degenerative process usually is divided into different phases (1 to 4) by the scientific community (Marc and Jones, 2003; Marc et al., 2003, 2007; Jones and Marc, 2005; Carr et al., 2009; Vugler, 2010; Jones et al., 2012; Cuenca et al., 2014; Gasparini et al., 2019); therefore, changes at the cellular level can be associated with the stage of retinal degeneration:

Phase 1 is characterized by photoreceptor stress that induces a cascade of events that culminates in molecular changes and eventual cell death. However, the function and morphology of photoreceptor cells and other retinal neurons appear normal as does the retinal layering.

Phase 2 is characterized by continuous photoreceptors stress that leads to truncation of the outer segments, aberrant extension of neurites, dendrite retraction, and progressive photoreceptor death (**Figure 3B** and **D**). In parallel, bipolar cell modifications and activation of Müller glia cells are observed. However, before photoreceptor death, several molecular modifications are apparent, such as delocalization of rhodopsin in the rods and transduction in cones, or synaptophysin redistribution and loss (**Figure 3D**).

Phase 3 is characterized by large-scale photoreceptor cell death followed by retraction of bipolar and horizontal cell dendrites and the beginning of the inner nuclear layer neuronal death. The loss of neuronal cells leads to Müller cell hypertrophy, formation of a glial seal over the neuroretina, and microglial activation.

Phase 4 is characterized by progressive global neuroretinal disorder and neuronal cell migration between the layers and finally death, with rewiring of the retinal circuitries. Furthermore, hypertrophy of Müller cells and epiretinal membrane formation, and retinal invasion by blood vessels and migrating RPE cells can be observed.

In this scenario, therapeutic strategies based on neuroprotection aim to create an adequate environment for preserving the viability of the retinal cells and thus functioning. This can be achieved through delivery to the retinal tissue trophic/growth factors that generally promote cell proliferation,

maturation, survival, and/or regeneration to maintain retinal homeostasis. Therefore, neuroprotective compounds seem crucial for maintaining retinal homeostasis (Cideciyan et al., 2013), but the final success of the treatments, understood as the maintenance or improvement of visual function, also relies on appropriate patient selection (age of patient) and the etiology and stage of the disease (Cuenca et al., 2014). Even though treatment of the retinal pathologies must involve a combination of different therapeutic approaches, retinal neuroprotection via delivery of neurotrophic, antioxidative, antiapoptotic and/or anti-inflammatory factors appears essential in phase 1 and necessary in phase 2 to maintain the viability of the retinal cells (Cuenca et al., 2014). Furthermore, neuroprotection also seems crucial in phases 3 and 4, even when vision has been lost completely (Cuenca et al., 2014).

In this sense, several neurotrophic factors have been studied extensively and proven effective for the protection and survival of degenerating photoreceptors *in vitro* and *in vivo* (Cuenca et al., 2014; Kolomeyer and Zarbin, 2014). These include brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), pigment epithelium-derived factor, and nerve growth factor. Furthermore, their combination has synergistic neuroprotective effects in photoreceptor rescue (Cuenca et al., 2014; Kolomeyer and Zarbin, 2014). Nevertheless, the neuroprotective effects of factors such as CNTF or bFGF are limited to just over 1 week, and for BDNF 2 weeks after intravitreal administration in experimental animals (LaVail et al., 1992; Kurokawa et al., 1999; Vidal-Sanz et al., 2001; Takahata et al., 2003). Moreover, high doses may damage the retina (Kolomeyer and Zarbin, 2014). Indeed, exogenous administration of these factors is limited by their short half-lives and dose safety (Kolomeyer and Zarbin, 2014). Therefore, to obtain prolonged effects, iterative intravitreal injections may be needed (Cuenca et al., 2014). To address this problem, new strategies such as nanoparticle-containing factors, viral-mediated transference, and implants of genetically modified encapsulated cells have been implanted into the vitreous cavity (Birch et al., 2013) with different success levels.

In this case, the potential of the paracrine neuroprotective properties of intravitreally injected stem cells for the production of neuroprotective factors in a sustained manner over time and allowing a synergistic effect is a potential therapeutic option currently under preclinical and clinical investigation for retinal degenerations, i.e., stem cells injected into the vitreous cavity survived 3 months (Lejkowska et al., 2019), and matured and secreted BDNF, CNTF, and bFGF for at least 4 to 5 weeks (Li et al., 2009; Levkovitch-Verbin et al., 2010).

Stem Cells

Stem cells are those that have self-renewing capabilities and differentiate into multiple cell lineages. The most common way to classify stem cells is based on their source: embryos or adult body tissues. Furthermore, stem cells can be categorized according to their potential to differentiate into different cell types, such as totipotent, pluripotent, multipotent, oligopotent, or unipotent. All stem cells may be useful for medical research, but each type has advantages and limitations. Despite the embryonic stem cell (ESC) therapeutic potential, their use is ethically and politically controversial because of the destruction of human embryos (Lo and Parham, 2009). Conversely, adult stem cells are not associated with this problem but others, i.e., in that pieces of tissue are extracted from any part of the body to obtain the stem cells and some types are difficult to maintain *in vitro*. Among the adult stem cells and their usefulness for retinal pathologies are the mesenchymal stem cells (MSCs) derived from bone marrow (bmMSC) or adipose tissue (aMSC) (Nauta and Fibbe, 2007; Xu and Xu, 2011; Berglund et al., 2017; Labrador-Velandia et al., 2019). More recently, the induced pluripotent stem cells (iPSC) are being investigated (Alonso-Alonso and Srivastava, 2015).

Stem cell application in retinal diseases

The possible clinical application of stem cells in retinal pathologies is based on two main therapeutic approaches, cell replacement and/or neuroprotection (through its paracrine action). Cellular replacement has limitations; previous studies have suggested that the adult retina does not provide an environment in which transplanted stem cells can easily migrate, integrate, and differentiate (Mellough et al., 2007; Hill et al., 2009; Johnson et al., 2009; Gagliardi et al., 2019; Gasparini et al., 2019). Although some studies have reported that stem cell-derived photoreceptors and photoreceptor precursors may integrate and/or transfer material to the host cells (MacLaren et al., 2006; MacLaren and Pearson, 2007; Waldron et al., 2018), the differentiation of MSCs into functional retinal cells still requires lengthy exploration. Furthermore, the neurologic recovery enhancement demonstrated by stem cells seem to be derived from an indirect paracrine effect rather than direct cell replacement (Seo and Cho, 2012). Therefore, the paracrine ability of stem cells to secrete trophic factors, neurotrophins, cytokines, and signalling molecules that promote angiogenesis and tissue regeneration, inhibit fibrosis and apoptosis, and modulate the immune system and inflammation could improve the survival of degenerating retinal cells (Levkovitch-Verbin et al., 2010). Among factors secreted by the stem cells, which include neurotrophic factors that belong to the family of neurotrophins (molecules involved in tropism and neuronal plasticity), are exhibited by BDNF, NGF and NT3, and other neurotrophic factors such as CNTF, GDNF, insulin-like growth factor 1 and bFGF, which have been proven effective in protecting retinal cells after acute damage in preclinical models (Labouyrie et al., 1999; Lin et al., 2009; Kolomeyer and Zarbin, 2014; Labrador-Velandia et al., 2019; Lejkowska et al., 2019).

Nevertheless, the use of selected and specific stem cell populations seems to have greater therapeutic potential than bone marrow aspirates and also allows allogenic use (Nauta and Fibbe, 2007; Labrador-Velandia et al., 2019). Thus, much

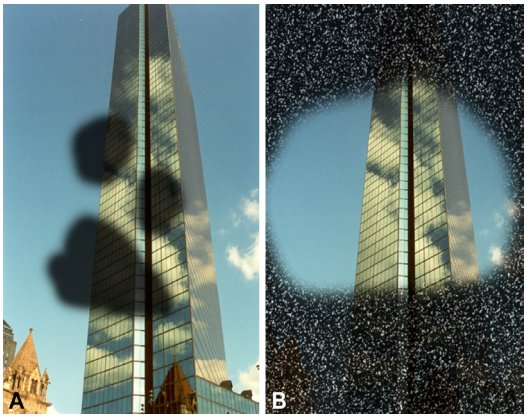

Figure 1 Types of visual impairment.
Central or paracentral scotoma (A), an area of central impairment of the visual field, usually develops in patients with age-related macular degeneration, diabetic retinopathy, or Stargardt disease. While concentric retraction of the visual field (B) occurs in patients with retinitis pigmentosa or glaucoma.

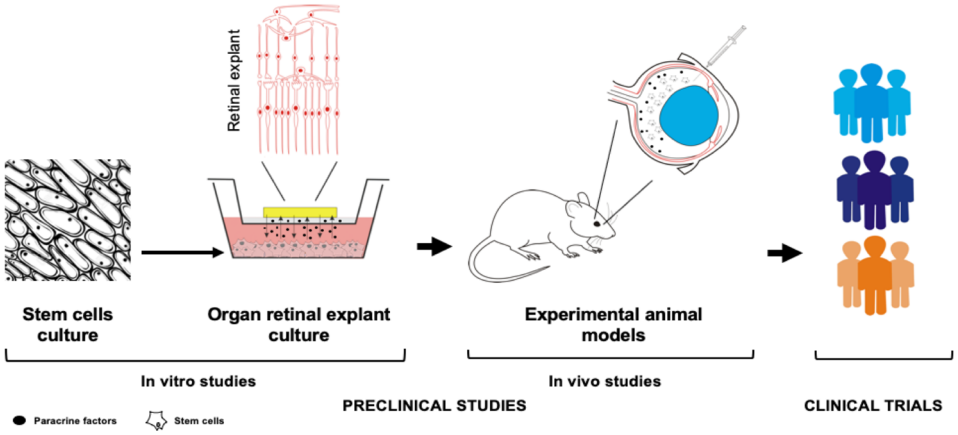

Figure 2 Translational research to evaluate the neuroprotective capacity of the stem cells over photoreceptor cell degeneration.
Organ retinal explant culture is the *in vitro* model most used to study the neuroprotective processes of stem cells. The organ retinal explant-stem cells co-culture is physically separated by a porous membrane that prevents stem cell migration and integration into the retinal tissue; the membrane also allows molecular exchange between the stem cells and retinal tissue. *In vivo* preclinical studies have established that the intravitreal injection is the most appropriate route of stem cell administration to evaluate the effects of paracrine neurotrophic factors. The efficacy of stem cells is attributable to production of factors that promote endogenous neuronal growth and angiogenesis, stimulate the synaptic connection and remyelination of damaged axons, diminish apoptosis, and finally regulate inflammation, as observed in preclinical studies. The last step of translational research, before the clinical application of novel therapies, consists of the design and development of clinical trials to confirm the safety and efficacy of intravitreal stem cells to neuropreserve the photoreceptors from degeneration. Some of the most relevant retinal pathologies that could potentially be addressed with cell-based therapies include age-related macular degeneration, retinitis pigmentosa, Stargardt disease or vascular diseases, such as diabetic retinopathy or vein occlusion.

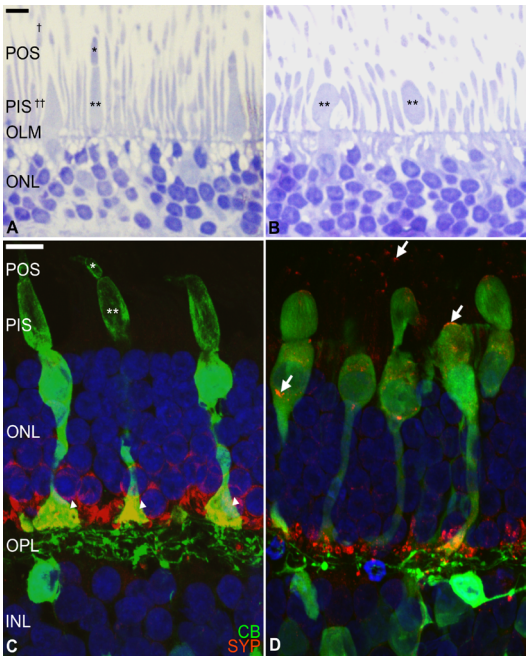

Figure 3 Human photoreceptor degeneration process in an organotypic culture of the neuroretina.
Organ retinal explant cultures are considered useful tools for cellular and molecular research into retinal degeneration and neuroprotection. Briefly, human neuroretina explants were cultured in Transwell® plates, with the photoreceptor layer facing the supporting membrane. Ultrathin and cryostat sections were evaluated after toluidine blue staining (A, B) and after immunostaining for neuronal markers (C, D). Fresh human neuroretina (A) morphologic organization of the photoreceptors show easily recognizable cone and rod outer (asterisk and dagger, respectively) and inner segments (double asterisk and double dagger, respectively), outer limiting membrane, and highly organized outer nuclear layer. After 6 days of culture (B), the photoreceptor degeneration process is evident with loss of the cone outer segments and swollen cone inner segments (double asterisk) and cell bodies. Immunostaining for calbindin (CB, green), a calcium-binding protein of cones and second-order neurons (C), shows the normal morphology of the cone photoreceptors, including the outer (asterisk) and inner (double asterisk) segments and their terminals (arrowheads). After 9 days of culture (D) some inner segments are swollen, and the cones have degenerated inner and outer segments. Synaptophysin (SYP, red), a synaptic-vesicle protein in the photoreceptors and second-order neurons, was located at photoreceptor axon terminals (C) and after culture, it is identified throughout the photoreceptor cell bodies (D, arrows). Scale bars: 10 μm. These images were obtained in collaboration with Dr. Nicolas Cuenca (Universidad de Alicante, Spain). INL: Inner nuclear layer; OLM: outer limiting membrane; ONL: outer nuclear layer; OPL: outer plexiform layer; PIS: photoreceptor inner segment; POS: photoreceptor outer segment.

work remains to be done in the laboratory and clinical practice to harness the stem cell potential for cell-based therapies to treat retinal diseases.

Pre-Clinical Studies

In vitro cell cultures

Based on our search criteria, no studies were published between 2013 and 2019 that specifically evaluated the stem cell neuroprotective potential in photoreceptor cultures.

In vitro organ cultures

The neuroretinal explant with stem cell co-culture is the most used *in vitro* model to evaluate the stem cell neuroprotective ability in the photoreceptors. Organ retinal explant cultures are useful for cellular and molecular research into retinal degeneration and neuroprotection due to the relatively low cost and easy development and they are an excellent resource that bridges the gap between cell cultures and *in vivo* models (Fernandez-Bueno et al., 2012; Di Lauro et al., 2016).

Rodriguez-Crespo et al. (2014), who developed a triple-layered mixed co-culture model of porcine RPE cells and neuroretina with human aMSCs, reported limited neuroprotective effects on the retina. However, the authors hypothesized that various limitations of this triple-layer culture model narrowed the potential positive effects of the stem cells over the retinal parenchyma, such as an insufficient amount of nutrients supplied by the culture medium and/or reduced transmembrane diffusion of necessary nutrients and factors for adequate neuroretina preservation *in vitro* (Rodriguez-Crespo et al., 2014).

In contrast, Mollick et al. (2016) reported that human neural progenitor cell (NPC)-derived factors slowed the spontaneous degenerative processes of adult porcine retinal explants. The results showed that NPCs limit photoreceptor death through better maintenance of the cone outer segments, reduced opsin mislocalization, and maintained synaptic structural integrity (Mollick et al., 2016). Although the authors could not explain the exact mechanism by which NPCs neuropreserve the photoreceptors from degeneration, they hypothesized that NPCs secrete neurotrophic factors in co-culture with the neuroretina that protect the photoreceptors from degeneration and slow the spontaneous degenerative processes of the retinal explants (Mollick et al., 2016).

Labrador-Velandia et al. (2019) performed another study of the neuroprotective paracrine effects of stem cells over the retina and reported that human bmMSCs have paracrine neuroprotective effects over porcine neuroretinal spontaneous degeneration, including the photoreceptors. The authors reported that the observed neuroprotective effect was associated with elevated concentrations of the neurotrophic factors, BDNF and CNTF (Labrador-Velandia et al., 2019).

Jones et al. (2019) also reported that retinal tissue co-cultured with human NPCs showed less cell death than retinas cultured alone. In this experiment, retinal samples from the Royal College of Surgeons rats, an *in vivo* model of photoreceptor degeneration, were used. This potential cell therapy is applied to a degeneration model, not "healthy" retinas, as in the previously discussed models. This study also mentioned that NPCs induced nuclear factor (erythroid-derived 2)-like 2 synthesis, which mediates oxidative response signalling and therefore was implicated in the retinal neuroprotection by the NPCs (Jones et al., 2019).

Although an ideal study would use human tissues, the *in vitro* models described here are based on the use of porcine neuroretina because of the anatomic and histologic similarities of the porcine and human retinas (Sanchez et al., 2011) or the use of neuroretina from animal models of retinal diseases, and offer several advantages over dependency on the availability of human sample for research purposes.

In summary, the *in vitro* results showed that stem cells can retard photoreceptor layer degeneration through the paracrine secretion of neurotrophic factors. Those studies provide *in vitro* evidence for the possible application of stem cell paracrine properties in diseases of the retinal photoreceptors.

In vivo experimental animals

Studies in animal models of retinal pathologies have compared intravenous (systemic) injection, subretinal transplantation and intravitreal injection of stem cells (Xu and Xu, 2011). According to these studies, intravitreal injection is the most appropriate route of administration to investigate the effect of paracrine neurotrophic factors, because secreted neurotrophins can cross the inner limiting membrane and diffuse into the retina, while it would also be a natural barrier that prevents stem cells to pass through and, therefore, integrated into the neural retina (Xu and Xu, 2011). Although, according to the search criteria previously defined, no studies between 2013 and 2019 specifically evaluated the paracrine effects of intravitreally administered stem cells on photoreceptor degeneration in laboratory animal models. Conversely, several experiments have evaluated the intravitreal MSCs in different murine models of retinal pathologies, such as retinal degeneration, RP, retinal ischemia, and glaucoma. Those studies attributed the efficacy of MSC therapy to secretion of factors, such as BDNF, NGF, NT3, CNTF, GDNF, insulin-like growth factor 1, or bFGF, that promote endogenous neuronal growth and angiogenesis, stimulate the synaptic connection and remyelination of damaged axons, diminish apoptosis, and finally regulate inflammation (Li et al., 2009; Johnson et al., 2010; Wang et al., 2010; Williams and Hare, 2011; Seo and Cho, 2012; Emre et al., 2015; Lejkowska et al., 2019). Among those studies, Emre et al. (2015) reported that bmMSCs and aMSCs exhibit a neuroprotective effect over retinal degeneration in a rat model of ocular hypertension. The authors attributed the neuroprotective effects to secretion of neurotrophic factors for modulating the inflammatory processes and inhibitory signals that regulate axonal regrowth along with neuronal repair and activation of endogenous repair mechanisms (Emre et al., 2015), as also previously described (Zhang et al., 2007; Johnson et al., 2011). Besides, Lejkowska et al. (2019) showed that BDNF overexpression by genetically modified intravitreally bmMSCs could rescue retinal cells from de-

generative processes and also enhance the neuroprotective properties in the rd6 mouse, a model of retinal degeneration. Those investigators observed that bmMSCs survived for at least 3 months after transplantation and described that the bmMSCs rescued damaged retinal cells, associated with anti-apoptotic signaling (Lejkowska et al., 2019).

Concerning other experimental animals, Labrador Velandia et al. (2018) concluded that human bmMSC cells administered by intravitreal injection are safe and well-tolerated in pigmented immunocompetent rabbits at 2 and 6 weeks after injection, since no signs of infection and/or inflammation or changes in the cells and tissues at the histologic level were observed. Furthermore, the bmMSCs remained inside the vitreous cavity and showed special tropism for the vitreous regions near the posterior capsule of the lens and optic nerve head at 2 weeks after injection. It has not been observed that human bmMSCs pass through the lens capsule or the inner limiting membrane of the rabbit retina to integrate into any ocular tissue other than the vitreous and do not migrate to the main hematopoietic or gonadal organs (Labrador Velandia et al., 2018). Furthermore, bmMSCs survive at least 2 weeks after intravitreal injection (Labrador Velandia et al., 2018), thus allowing the bmMSCs to develop prolonged paracrine action. No other non-murine animal studies that evaluate the neuroprotective properties of intraocular stem cells were found in the databases based on our search, probably because there are only a few animal models of retinal degeneration. Thus, adequate animal models that are easily reproducible and that adequately develop the pathophysiology of photoreceptor diseases are needed to evaluate the safety, bioavailability, and efficacy of the potential cell therapy techniques before being transferred to clinical practice.

In summary, preclinical studies such as those presented here and others performed before 2013, have been the basis for the approach and development of the current clinical trials that apply intraocular stem cell therapy to treat retinal degenerative diseases.

Clinical Trials

A number of completed current clinical trials or those underway have been designed to specifically treat retinal conditions by using intravitreal stem cells through their neuroprotective paracrine properties (**Additional Table 1**).

Among the clinical studies using ESCs, in the clinical trial performed by jCyte, human retinal progenitor cells were injected into the vitreous cavity of 28 patients with RP to potentially rescue and reactivate diseased photoreceptors before cell death (NCT02320812). Furthermore, because many patients reported improved vision, reading ability and better mobility, in a follow-on extension study 22 of the initial 28 patients also were treated in the contralateral eye. Based on those promising results, a phase IIb study (NCT03073733) is ongoing to compare visual function and functional visual changes between one retinal progenitor cell intravitreal injection and a sham-treated control group. Two other interesting trials are recruiting patients. In the first, 10 patients with RP are being recruited to test the safety and efficacy of human ESC-derived RPE (NCT03944239), and in the second, 50 patients with RP are being recruited to evaluate the safety and tolerability of human retinal progenitor cells in a phase I/IIa study (NCT02464436). However, both studies involved subretinal transplantation of stem cells for neuroprotective purposes, not the intravitreal route, and thus, they are outside of the search criteria used in the current review.

Regarding MSCs, the first studies on intravitreal stem cell therapy in humans published by Jonas et al. (2008, 2009) demonstrated the safety and feasibility of an intravitreal injection of autologous bone marrow aspirate as a potential MSC source in three patients with advanced degenerative retinopathies.

Subsequently, Siqueira et al. (2011) reported the safety of an intravitreal injection of autologous mononuclear cells from bone marrow in 5 patients with advanced retinal dystrophies in a phase I clinical trial. This group also reported a time-dependent improvement in the quality of life after intravitreal bmMSC injection in patients with RP (Siqueira et al., 2015b); and improvement in the best-corrected visual acuity after intravitreal injection of bmMSCs containing $CD34^+$ cells in patients with atrophic AMD (Cotrim et al., 2017).

Other active clinical trials are using an intravitreal injection of specifically selected autologous stem cells, i.e., one in patients with several retinal degenerative conditions or retinal vascular diseases that are treated with intravitreal $CD34^+$ from autologous bone marrow aspirate (NCT01736059) (Park et al., 2015), and another in patients with RP will be that injected intravitreally with autologous bone marrow-derived $CD34^+$, $CD133^+$, and $CD271^+$ (NCT02709876).

Among other clinical studies that use autologous bmMSCs intravitreally as a potential neuroprotective therapy, a clinical trial includes 8 patients with RP (NCT02280135) and a prospective phase I/II study on AMD and patients with Stargardt disease (NCT01518127) have been completed, but results are not available yet.

Furthermore, concerning vascular retinopathies, use of intravitreal autologous bmMSCs resulted in decreased macular edema and improved retinal function in 2 patients, one with ischemic diabetic maculopathy and another with ischemic central retinal vein occlusion (NCT01518842) (Siqueira et al., 2015a). A phase I/II clinical trial (NCT03981549) is ongoing to determine whether intravitreal autologous $CD34^+$ is safe, feasible, and potentially beneficial for patients with central retinal vein occlusion. Another active trial is evaluating intravitreal injection of bmMSCs in 30 patients with ischemic retinopathy (NCT01518842).

It is also worth mentioning two studies, the Stem Cell Ophthalmology Treatment Study (SCOTS) and the SCOTS 2 (NCT01920867 and NCT03011541, respectively), that have evaluated the use of autologous bmMSC injections by different routes to treat several retinal and optic nerve diseases (Weiss et al., 2015a, b, 2016a, b, 2017; Weiss and Levy, 2018, 2019a, b). Although the safety of bmMSCs was confirmed, in our opinion these clinical trials include many different diseases and routes of administration that affect the robustness

of the published efficacy results (Weiss and Levy, 2018). Thus, there is variability in treated conditions including degenerative, ischemic, or physical damage of the retina and/or optic nerve. Besides, the eyes were treated by injection of bmMSCs using the following routes of administration: retrobulbar; sub-Tenon and intravenous together, or a combination of retrobulbar, sub-Tenon, intravitreal, and intravenous.

Finally, a study is assessing the safety and effects of aMSCs obtained during liposuction procedures and injected intravitreally in dry macular degeneration (NCT02024269). However, the study was discontinued.

iPSCs have been used to generate $CD34^+$ and $CD45^+$ cells in combination with iPSC-derived mesoderm (vascular wall-derived progenitor cells) or with endothelial colony-forming cells that are intravitreally administered in a clinical trial to evaluate their potentially beneficial effect to prevent development of microvascular complications in diabetic retinopathy (NCT03403699) due to their antioxidative and anti-inflammatory effects.

In summary, clinical trials evaluating intravitreal stem cell potential to treat photoreceptor degenerative diseases have reported adequate tolerance and safety for patients. Nevertheless, future studies are needed to expand the current knowledge about the stem cell neuroprotective potential and to reinforce efficacy.

Conclusion

After considerable initial concerns about the use of human stem cells intravitreally as therapeutic agents due to their potential to form benign tumors or trigger an immune response, which would have deleterious effects on the retina, most clinical trials reviewed in this report share the conclusion that the intraocular stem cell approach is generally well tolerated and safe for patients. However, the data from a few completed studies do not yet have sufficient power to demonstrate a significant difference regarding efficacy in humans (Terrell and Comander, 2019). Therefore, it is necessary to continue developing preclinical studies and clinical trials that facilitate broadening of the current knowledge base about the neuroprotective potential of intravitreal stem cells in retinal pathologies that mainly affect the photoreceptors.

In conclusion, adequate retinal neuroprotection is one of the next challenges to overcome in retinal diseases, in which advanced therapies, mainly through the paracrine properties of stem cells, will play a fundamental role in the development of novel neuroprotective strategies. Although it is necessary to continue advancing the basic understanding of retinal diseases and their clinical implications in patients' visual health, we consider that continuous advances in the clinical and preclinical fields will facilitate application of stem cell-based neuroprotection as a therapeutic strategy to reduce the visual loss that affects millions of people worldwide.

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Additional Table 1: *Summary of the current clinical trials completed or in progress designed to evaluate intravitreal stem cells on retinal photoreceptor neurodegenerative conditions*

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Table 1 Summary of the current clinical trials completed or in progress designed to evaluate intravitreal stem cells on retinal photoreceptor neurodegenerative conditions

Reference	Disease	Cell type	Administration route	Status	Sponsor
NCT02320812	Retinitis pigmentosa	ESC	Intravitreal injection	Phase I/II	jCyte, Inc.
NCT03073733	Retinitis pigmentosa	ESC	Intravitreal injection	Phase II	jCyte, Inc.
NCT03944239	Retinitis pigmentosa	ESC	Subretinal injection	Phase I	Qi Zhou
NCT02464436	Retinitis pigmentosa	ESC	Subretinal injection	Phase I/II	ReNeuron Limited
Jonas et al. 2008	Diabetic retinopathy	BMMSC	Intravitreal injection		
Jonas et al. 2009	Diabetic retinopathy	BMMSC			
	AMD		Intravitreal injection		
	Glaucoma				
Siqueira et al. 2011	Retinitis pigmentosa	BMMSC	Intravitreal injection	Phase I	University of Sao Paulo
	Cone-rod dystrophy				
Siqueira et al. 2015b (NCT01560715)	Retinitis pigmentosa	BMMSC	Intravitreal injection	Phase II	University of Sao Paulo
Cotrim et al. 2017 (NCT01518127)	Atrophic AMD	BMMSC	Intravitreal injection	Phase I/II	University of Sao Paulo
	Stargardt disease				
NCT01518842	Ischemic retinopathy	bmMSC	Intravitreal injection		University of Sao Paulo
Park et al. 2015 (NCT01736059)	Atrophic AMD	BMMSC	Intravitreal injection	Phase I	University of California
	Diabetic retinopathy				
	Retinal vein occlusion				
	Retinitis pigmentosa				
	Hereditary macular disease				
NCT02709876	Retinitis pigmentosa	BMMSC	Intravitreal injection	Phase I/II	Stem Cells Arabia
NCT02280135	Retinitis pigmentosa	BMMSC	Intravitreal injection	Phase I	Spanish National Health System
NCT03981549	Central retinal vein occlusion	BMMSC	Intravitreal injection	Phase I/II	The Emmes Company, LLC
Weiss et al. 2015[a, b], 2016[a, b] (NCT01920867)	Retinal disease	BMMSC	Retrobulbar injection		MD Stem Cells
	Macular degeneration		Sub-Tenon injection		
	Hereditary retinal dystrophy		Intravenous injection		
	Optic nerve disease		Intravitreal injection		
	Glaucoma		Intraocular		
Weiss et al. 2015a, b, 2016a, b, 2017, 2018, 2019a, b (NCT03011541)	AMD	BMMSC			MD Stem Cells
	Retinitis pigmentosa				
	Stargardt				
	Optic neuropathy				
	Non-arteritic ischemic optic neuropathy				
	Optic atrophy				
	Optic nerve disease		Retrobulbar injection		
	Glaucoma		Subtenon injection		
	Leber hereditary optic neuropathy		Intravenous injection		
	Blindness		Intravitreal injection		
	Night vision loss		Intraocular		
	Partial vision loss				
	Retinopathy				
	Maculopathy				
	Macular degeneration				
	Retina atrophy				
NCT02024269	Dry macular degeneration	aMSC	Intravitreal injection		Bioheart, Inc.
NCT03403699	Diabetic retinopathy	iPSC	Intravitreal injection		The University of Alabama at Birmingham

AMD: Age-related macular degeneration; aMSC: adipose MSC; BMMSC: bone marrow MSC; ESC: embryonic stem cells; iPSC: induced pluripotent stem cells; MSC: mesenchymal stem cells.