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INVITED REVIEW

The promise of stem cell-based therapeutics in ophthalmology

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Abstract
The promising role of cellular therapies in the preservation and restoration of visual function has prompted intensive efforts to characterize embryonic, adult, and induced pluripotent stem cells for regenerative purposes. Three main approaches to the use of stem cells have been described: sustained drug delivery, immunomodulation, and differentiation into various ocular structures. Studies of the differentiation capacity of all three types of stem cells into epithelial, neural, glial and vascular phenotypes have reached proof-of-concept in culture, but the correction of vision is still in the early developmental stages, and the requirements for effective *in vivo* implementation are still unclear. We present an overview of some of the preclinical findings on stem-cell rescue and regeneration of the cornea and retina in acute injury and degenerative disorders.

Key Words: *embryonic stem cells; adult stem cells; induced pluripotent stem cells; cornea; retina; neuroprotection; immunomodulation; tissue recovery; regeneration; acute ocular injury; degenerative retinal disorders*

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Stem Cell Transplantation as a Therapeutic Strategy
Stem cells are highly conserved biological units of development and regeneration with variable capacity to adopt different developmental traits and self-renew in the undifferentiated state. These features have prompted extensive research in recent years into the feasibility of stem cell transplantation as a therapeutic tool to maintain, enhance, and restore tissue viability and organ function. The search for the safest, most accessible and most efficient stem-cell source for regenerative purposes have focused on three main categories: embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem cells (iPSCs). Researchers first successfully isolated cells with pluripotent differentiation capability from mouse embryos in 1981 and, thereafter, from humans (Evans and Kaufman, 1981; Martin, 1981; Thomson et al., 1995). However, later studies showed that this stem cell population harbors a significant risk of tumor formation. In addition, ethical questions were raised regarding the use of human undeveloped embryos as a stem cell source (Simonson et al., 2015). Therefore, attention was directed to multipotent adult stem cells which may be successfully isolated from various tissues and have been found effective in the maintenance of normal tissue function and repair of physiological and pathological wear and tear. The main advantages of adult stem cells are their optimal use in autologous transplants and their low tumorigenic potential compared to other stem cell types. However, some adult stem cells have a limited differentiation capacity and, consequently, a limited regenerative potential (Sousa et al., 2014; Zomer et al., 2015). To counter this problem, in 2006, researchers created iPSCs from mature differentiated cells using four transcription factors: *octamer-binding transcription factor 4 (Oct4), sex determining region Y-box 2 (Sox2), cMyc,* and *kruppel-like factor 4 (KLF4)* (Takahashi and Yamanaka, 2006; Okita et al., 2007; Takahashi et al., 2007). Further investigations showed that iPSCs are pluripotent and have the potential to form any cell in the body, similar to ESCs (Carr et al., 2009). However, in some syngenic recipients, autologous transplantation of iPSCs induces a T-cell-dependent immune response. Additionally, the conversion of cells to iPSCs poses a substantial risk of tumorigenesis (Zomer et al., 2015).

Clinical Challenges in Ophthalmology
Stem cell transplantation may hold the solution to several important clinical challenges in ophthalmology. Cell damage in different structures in the eye requires prompt intervention to prevent secondary damage and irreversible loss of vision.

The cornea
Abrasions, chemical injuries, infections, and autoimmune diseases affecting the cornea (Klintworth, 1977; Bourne,

2003) may result in blurred or cloudy vision, pain, tearing, and sensitivity to light. At present, corneal transplantation is the only definitive, clinically relevant approach to treat severe corneal disease (Wakefield et al., 2015). However, the procedure is hampered by donor shortage, particularly in developing countries, considerable risk of immune rejection (Niederkorn, 2007; De Miguel et al., 2010), and occasional transmission of infections such as hepatitis B and rabies by the donor tissue (Dubord et al., 2013).

The retina

In the eye, the degeneration of neural cells may occur in the inner retinal ganglion cell (RGC) layer due to optic nerve damage and in the outer photoreceptor layer mainly in hereditary genetic diseases. The death of RGC cells is an end product of both anterior ischemic optic neuropathy (AION), which obliterates the blood supply to the optic nerve head, and glaucoma, which causes chronic elevation of intraocular pressure. Primary loss of the photoreceptors is the underlying cause of *retinitis pigmentosa* and of the damage to the retinal pigment epithelium (RPE) (Landau and Kurz-Levin, 2011; Alonso-Alonso and Srivastava, 2015) in age-related macular degeneration (AMD). Retinal dysfunction due to cell death may also be secondary to such systemic disorders as diabetic retinopathy and arterial hypertension. Current approaches to the prevention, arrest, and reversal of cell loss in the retina are largely inefficient in restoring visual function (Levin, 2007; Winter et al., 2007; Landau and Kurz-Levin, 2011; Seung and Sumbul, 2014).

Stem Cell Treatment of Ophthalmic Disorders

Studies evaluating the use of stem cells for ophthalmic disorders have reported three potential approaches: sustained drug delivery, immunomodulation, and tissue regeneration.

Stem cells as vehicles for drug delivery

The need for continuous drug delivery to the eye is a major concern in ophthalmological practice (Roth et al., 2008). The solution may lie in stem cells owing to their unique ability to sustain viability throughout the lifetime of the organism. The cells may be grafted at the desired location without the need for repeated interventions.

Neurotrophic factors (NTF) are a family of proteins that participate in the regulation of the development, function, and survival of neurons and other cells in the nervous system (Mey and Thanos, 1993; Unoki and LaVail, 1994; Huang and Reichardt, 2001; Sofroniew et al., 2001; Buch et al., 2007). They have been shown to prevent RGC loss in neurodegenerative diseases of the eye. Recent studies have highlighted the potential of NTF-secreting stem cells in the treatment of several ocular disorders. The most prominent NTF in this setting is brain-derived neurotrophic factor (BDNF), a tyrosine receptor kinase B (TrkB) ligand expressed primarily in RGCs (Jelsma et al., 1993; Perez and Caminos, 1995). BDNF has been found to promote neuronal survival both in culture and in rodent models of retinal damage (Johnson et al., 1986; Mey and Thanos, 1993; Mansour-Robaey et al., 1994; Peinado-Ramon et al., 1996). Implantation of BDNF-transduced mesenchymal stroma cells (MSCs) into the rat retina was associated with a significant increase in BDNF levels for periods of up to 14 days (Park et al., 2012). Others found that intravitreal transplantation of BDNF-secreting MSCs in a rat model of chronic ocular hypertension improved RGC survival and preserved optic nerve structure (Harper et al., 2011).

Neuroprotective effects on RGCs and photoreceptors have also been reported for ciliary neurotrophic factor (CNTF) (Tao et al., 2002; Thanos et al., 2004; Buch et al., 2007). CNTF is a member of the interleukin (IL)-6 cytokine family and serves as a ligand for the heterotrimeric receptor complex that consists of CNTF receptor alpha (gp103) and leukemia inhibitory factor receptor beta (Wen et al., 2012). Intravitreal injection of CNTF-secreting neural stem cells in murine *Pde-6b*^{rd1} and *Pde6b*^{rd10} models of *retinitis pigmentosa* resulted in significant photoreceptor protection (Jung et al., 2013). Stem cells might also serve for the delivery of glial cell-line-derived neurotrophic factor (GDNF), a ligand for the RET/GDNF alpha receptor complex, previously shown to slow retinal degeneration (Andrieu-Soler et al., 2005; Buch et al., 2006). For this purpose, researches induced ESCs and neural progenitor cells to express and secrete GDNF (Gregory-Evans et al., 2009; You et al., 2011). Subsequent intravitreal injection of the GDNF-expressing ESCs in a *rhodopsin TgN S334ter-4* rat model of *retinitis pigmentosa* had a neuroprotective effect for up to 90 days (Gregory-Evans et al., 2009). To test the effect of a combination of different neuroprotective factors on RGC, bone marrow-derived MSC were induced to secrete high levels of BDNF, GDNF, and vascular endothelial growth factor (VEGF) and then injected into rat eyes following optic nerve transection. A significant increase in mean RGC survival was noted after 8 days (Levkovitch-Verbin et al., 2010).

Overall, current preclinical data support the use of stem cells for the delivery of drugs for various ophthalmic disorders. However, it remains unclear whether the modest therapeutic efficacy is due to limited activities of the neurotrophic factors, suboptimal delivery, a lack of combination of co-factors, reduced secretion over time, or the presence of an inhibitory agent.

Transplantation of Stem Cells for Immunomodulation

Regulation of the immune response is an important factor in the treatment of ophthalmic disorders (Nelson, 1976; Dana and Hamrah, 2002; Wakamatsu et al., 2008; Caspi, 2010). Different subsets of stem cells display variable immunomodulatory activities. The most prominent is the suppression of immune responses and inflammation by bone marrow-derived MSC. Under conditions of ischemia, MSCs induce the expression of immune-modulatory proteins, including Ym1, insulin-like growth factor-1 (IGF-1), Th2 related cytokines, galectin-3 (Gal-3), and class II major histocompatibility complex (MHC) antigen (Ohtaki et al., 2008). Culture studies have yielded some insights into the mechanisms of action of MSCs cells in neural tissues when used for corneal and retinal repair.

Corneal repair

In one study, rat bone marrow-derived MSCs were added to cultures of human corneal epithelial cells stimulated by

interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). This led to a reduction in the inflammatory responses *via* activation and translocation of nuclear factor-κB (NF-κB) and the transforming growth factor-β1 (TGF-β1) signaling pathway (Wen et al., 2014). Other *in vitro* studies showed that MSCs cultivated from the corneal limbus secreted TGF-β1 and suppressed T-cell proliferation (Garfias et al., 2012; Bray et al., 2014). The anti-inflammatory effect of MSCs on the microenvironment was also demonstrated in alkali-burned eyes, in which systemic MSC injection led to a decrease in leukocyte infiltration and in local levels of proinflammatory cytokines such as interleukin-1α (IL-1α), IL-6, and nitric oxide (Javorkova et al., 2014). Moreover MSCs administered to a murine model of dry eye syndrome protected the ocular surface by suppressing $CD4^+$ T-cell infiltration and decreasing levels of inflammatory cytokines such as IL-2 and IFN-γ (Lee et al., 2015).

Retina

The immune-modulatory role of retinal stem cells in the protection of the RGC was shown in an experimental model of glaucoma, wherein a significant reduction in IFN-γ levels in the serum and aqueous humor led to a decrease in RGC apoptosis (Zhou and Xia, 2011). Although bone marrow-derived MSCs can differentiate into cells expressing photoreceptor proteins when injected into the subretinal space, their ability to differentiate into functionally useful retinal cells is under debate. Furthermore, untreated MSCs in an *in vitro* rat retina-explant model seemed to transdifferentiate into microglia1cells (Azizi et al., 1998); therefore, non-autologous MSC transplantation might induce an inflammatory reaction.

Overall, these data suggest that various subsets of stem cells may be used as a clinical option in immune modulation. Several ongoing preliminary clinical trials have so far demonstrated good tolerability and long-term persistence of intravitreally transplanted MSC (Park et al., 2014; Siqueira et al., 2015; Weiss et al., 2015).

Transplantation of Stem cells for Tissue Regeneration

The limited options for tissue rescue in ophthalmic disorders have led to intensive work on the regenerative potential of stem cells. Stem cells that are differentiated to phenotypes of the various ocular layers before transplantation have shown a reduced incorporation capacity compared to undifferentiated stem cells (Gu et al., 2007). Therefore, researchers are testing two competing approaches in corneal and retinal repair: differentiated stem cell grafts to replace selected injured structures, and transplantation of undifferentiated stem cells to correct multiple deficits.

Cornea

The cornea delineates the anterior border of the eye. It consists of five distinct layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. Tissue stem cells are prevalently located in the limbal palisades of Vogt (Grieve et al., 2015), the transition zone between the cornea and the surrounding tissue, and are considered to be essential for the maintenance of corneal function (Dua and Azuara-Blanco, 2000; Ordonez and Girolamo, 2012; Funderburgh and Funderburgh, 2016). Limbal stem cell deficiency (LSCD) is either a primary condition of aniridia caused by *PAX6* gene mutations (Dua, 1995; Puangsricharern and Tseng, 1995; Li et al., 2015) or a consequence of chemical or thermal injury, Stevens-Johnson syndrome, and repeated corneal surgery. LSCD is characterized by chronic inflammation, pain, conjunctivalization, subepithelial vascularization, and epithelial defects that lead to eventual blindness (Dua and Azuara-Blanco, 2000; Shortt et al., 2007). Currently, transplantation of limbal epithelial stem cells (LESCs) is the only effective means to reverse total LSCD. LESCs may be derived from the conjunctiva of the contralateral healthy eye of the patient (autologous conjunctival limbal autograft) or from the conjunctiva of a living or deceased related donor (allogeneic conjunctival limbal allograft) or unrelated donor (allogeneic keratolimbal allograft) (Basti and Rao, 2000; Javadi and Baradaran-Rafii, 2009; Liang et al., 2009). The cells are collected by biopsy, expanded in culture, and grafted into the diseased recipient eye (Pellegrini et al., 1997). A newer approach, termed simple limbal epithelial transplantation (SLET), involves the cultivation of donor LESCs on amniotic membranes which are then placed on the surface of the recipient eye. Both techniques result in re-epithelialization with comparable success (Sangwan et al., 2012; Mittal et al., 2015; Basu et al., 2016; Vazirani et al., 2016). Their disadvantages include a deficiency of limbal stem cells in the healthy donor eye following extraction, immune responses after implantation of allogeneic grafts, and infections and neoplasms arising as side effects of immunosuppressive therapy administered to prevent rejection (Sahu et al., 2009; Bakhtiari and Djalilian, 2010; Baradaran-Rafii et al., 2013; Han et al., 2015). Therefore, intensive efforts are being invested to develop alternative stem cell sources.

Using a preclinical model, one group found that ESCs cultured over superficial corneoscleral slices or seeded on collagen IV in the presence of limbal fibroblast-conditioned medium differentiated to a corneal epithelium phenotype (Wang et al., 2005; Ahmad et al., 2007; Notara et al., 2012). Similar findings were reported for ESCs derived from murine or monkey embryos engineered to express the transcription factor Pax-6, which is essential in the development of corneal epithelium (Ueno et al., 2007; Kumagai et al., 2010). There is also evidence that human ESC layered over injured human cornea express CK3 and Pax-6 within three days *in vitro* (Hanson et al., 2013). Numerous attempts to differentiate ESCs into corneal phenotypes are ongoing, with variable success, but the limitations of using this source of stem cells still need to be overcome (Chan et al., 2013; Zhu et al., 2013; Brzeszczynska et al., 2014; Zhang et al., 2014; Hertsenberg and Fudnerburgh, 2016).

In a study of the use of adult stem cells to treat ocular disorders, the transplantation of oral mucosal epithelial cells (OMECs) cultured on human amniotic membranes in a rabbit LSCD model created epithelium expressing cytokeratins characteristic of the cornea and connexin-43 (Nakamura et al., 2003; Madhira et al., 2008). OMEC transplants were also successfully applied to treat human LSCD, but the resulting corneal morphology was substantially different from normal (Nakamura et al., 2004; Sugiyama et al., 2014; Haagdorens et al., 2016). Others used stem cells derived from hair follicles to induce differentiation demarcated by Pax-6- and CK12 in

cultures of corneal limbal microenvironments (Blazejewska et al., 2009; Yang et al., 2009; Meyer-Blazejewska et al., 2011). Because MSCs are pivotal to tissue restructuring, they can be induced to differentiate into corneal epithelial cells, as manifested by the expression of CK3 and CK12 *in vivo* and *in vitro* (Ye et al., 2006; Ma et al., 2006; Gu et al., 2009; Liu et al., 2012; Garzon et al., 2014). Differentiation is apparently dictated by the microenvironment, as cells grown on different platforms, such as amniotic membranes, three-dimensional culture systems, and nanofiber scaffolds, have distinct characteristics (Ma et al., 2006; Zajicova et al., 2010; Katikireddy et al., 2014). The extent to which adult tissue stem cells can be manipulated to differentiate is still unknown, and their potential and the consistency of the differentiation methods remains controversial (Harkin et al., 2015).

In preliminary studies of the use of iPSCs to treat corneal defects, researchers showed that iPS-derived differentiated cells from mouse embryonic fibroblasts differentiate into epithelial progenitor cells, express CK1 and CK12, and create polar-stratified epithelial layers on denuded mouse corneas *in vitro* (Okita et al., 2007; Yoshida et al., 2011; Yu et al., 2013). Likewise, iPSCs derived from human dermal fibroblasts and LESCs express CK3, CK12, and Pax-6 (Hayashi et al., 2012) and integrate with denuded corneas when subjected to conditions mimicking the native LESC niche (Sareen et al., 2014).

Contact lenses offer a minimally invasive, long-lasting, cost-effective means of delivering corneal epithelial cells for the treatment of LSCD. In this manner, suture-related complications can be avoided. Lenses coated with polymers containing a high percentage of acid functional groups were found to promote corneal epithelial cell adhesion and proliferation and transfer and retention of stem cell in a rabbit model of corneal injury. Further studies are needed to determine if the lenses can be used as a substrate for the culture and transfer of limbal cells in the treatment of LSCD (Brown, 2014; Bobba 2016).

Retina

Owing to the intricate structure and interconnections of the retinal layers, repair of injury and prevention of degeneration are particularly difficult. Each retinal disease warrants a different reconstructive therapy according to the distinct ocular layer affected. For example, AMD is characterized by damage to the photoreceptors and RPE; retinitis pigmentosa is associated with photoreceptor loss; and glaucoma may result in the loss of RGCs and their axons (Alonso-Alonso and Srivastava, 2015).

The non-neuronal supportive RPE is composed of melanin-containing cells. It plays an important role in maintaining the photoreceptors and reducing backscattering of incoming light. Photoreceptors are specialized neurons that convert light into electrical signals which are integrated by the RGC and transmitted to relay nuclei. ESCs, adult stem cells, and iPSCs are all able to differentiate into RPE cells, photoreceptors, and RGCs (Osakada et al., 2010; Boucherie et al., 2011; Goldenberg-Cohen et al., 2011, 2014; Ong and da Cruz, 2012).

The implantation of photoreceptors derived from ESCs into the subretinal space has been evaluated in various animal models of retinal disease. One study was conducted in Crx-deficient mice, a model of *Leber's congenital amaurosis*, in which the photoreceptors are present but lack the expression of phototransduction genes (Lamba et al., 2009). Transplanted human ESC-derived photoreceptors were able to function and restored responses to light. Likewise, subretinal grafts of human ESCs-differentiated cells transplanted into a rat model of retinal degeneration and an *Elov14* mouse model of *Stargardt* disease survived for 220 days and sustained visual function and photoreceptor integrity without teratoma formation (Lu et al., 2009). These findings were supported by studies using transplants of human ESC-derived RPE cells in the same models, which showed long-term integration, rescue of photoreceptors from apoptosis, and reduced glial stress, with preservation of the responses to light stimuli (Zhu et al., 2013; Plaza Reyes et al., 2016; Riera et al., 2016).

More recently, the clinical utility of human ESC-derived retinal transplants was evaluated in primate models of retinal degeneration. The models were created by retinal injection of cobalt chloride, a hypoxia-mimicking agent that induces the expression of hypoxia-inducible factor-1α and irradiation at 577 nm to induce coagulation (Shirai et al., 2016). The retinal grafts survived, matured, and integrated to a certain degree with host bipolar cells.

Preclinical studies suggest that adult stem cells might also be used to treat retinal injury without induced differentiation in culture. Photoreceptor cells derived from adult retinal stem cells that were transplanted into a *Pde6b*^{rd1} model of retinitis pigmentosa showed promising incorporation with improved responses to light (Li et al., 2013). Accordingly, human Müller glia, which display some stem cell and progenitor cell characteristics, were induced to differentiate into RGCs by stimulation with fibroblast growth factor-2 and Notch inhibitors and then transplanted into rat retina depleted of native RGCs by N-methyl-D-aspartate (NMDA) (Singhal et al., 2012). A significant recovery of RGC function, measured by electroretinography, was noted. Others found that pretransplantation priming alone may also be sufficient for progenitor cells. Human mobilized PBMCs pulsed with retina *in vitro* for several days migrated from the subretinal space and expressed the human photoreceptor marker rhodopsin (Zhang et al., 2013; Peng et al., 2014). Indeed, some subsets of stem cells may not even require priming. In one study, retinal stem cells isolated from newborn mice and labeled with the red lipophilic fluorescent dye (PKH26) or from green fluorescent protein transgenic mice were implanted intravitreally or subretinally into adult wild-type transgenic mice with slow or rapid retinal degeneration. The cells migrated to the ganglion cell layer and expressed ganglion cell or glial markers (Canola et al., 2007). Cell incorporation was more pronounced in the late disease stages, possibly owing to the greater intensity of injury signals emanating from the degenerating tissue. Only a minority of cells expressed photoreceptor markers, suggesting that *ex vivo* enhancement may be necessary for to the differentiation of retinal stem cells into photoreceptors. In another study, subset of small-sized bone marrow-derived stem cells (BMSC) injected intravitreally and intravenously into an animal model of optic nerve crush differentiated into RGCs in

ganglion layer of the ischemic retina (Goldenberg-Cohen et al., 2011). Co-administration of neuronal growth factors enhanced the neuroglial differentiation of the BMSC, primarily through their effect on the stem cells rather than a direct neuroprotective effect (Goldenberg-Cohen et al., 2014).

Similar results were reported for iPSCs in preclinical models of retinal dystrophy, retinitis pigmentosa, and AMD. For example, photoreceptor precursors derived from murine iPSCs differentiated to express Crx, recoverin, and rhodopsin. When implanted subretinally into rhodopsin-null mice, they integrated with the retina and restored retinal function, as demonstrated by electroretinography and c-Fos expression in response to light (Tucker et al., 2011). Likewise, subretinal injection of human iPSC-derived RPE cells in the *Rpe65*^{rd12} mouse model of retinitis pigmentosa showed co-localization with the native host RPE cells and long-term survival, without tumor formation. Electroretinography revealed sustained improvement in visual function throughout the lifetime of the mouse (Li et al., 2012). Other studies showed that human iPSC-derived RPE cells maintained visual function and photoreceptor integrity in a dystrophic rat model (Carr et al., 2009) and were associated with negligible tumor formation following injection into nude mice and rats (Kanemura et al., 2014). It is possible that iPSC technology has reached the stage of clinical implementation, with the use of human stem cell-derived RPE cell implantation to treat patients with AMD and Stargardt disease. This method offers hope of protracted graft survival and improved visual acuity and quality of life with minimal adverse effects (Schwartz et al., 2012, 2015; Song et al., 2015).

Future Directions

This review highlights the tremendous potential of stem cell transplantation for the repair and regeneration of ocular structures in a variety of ophthalmic disorders, primarily of the cornea and retina. Advances are being made in novel technologies for the differentiation of embryonic, adult, and induced pluripotent cells to various phenotypes, and data on the manner in which injury signals direct stem cell differentiation are rapidly accumulating. In the cornea, stem cells offer promise as the optimal method of wound repair, and contact lenses offer many advantages as a vehicle for delivery of stem cells to the cornea for the treatment of LSCD.

In the retina, there are many obstacles still to overcome. Injury or damage appears to be essential for eliciting the migration and incorporation of stem cells, and the nature of the injury usually affects the location of the engrafted cells and their phenotype. However, in studies of a mouse model of retinitis pigmentosa with rapid degeneration (rd1), only a few cells differentiated into photoreceptors or incorporated in the outer nuclear layer. Thus, further studies of the incorporation, migration, and differentiation of stem cells in the retina are still needed. While the photoreceptors and the RPE are affected in degenerative retinal disease, in models of optic nerve damage, loss of the RGC was noted but other layers of the sensory retina, as well as the external nonsensory RPE layer, remained intact.

Neuronal differentiation is hard to induce, as the dominant astrocyte differentiation overcomes neuronal differentiation. Neurotrophic factors, either external or internally secreted by the MSCs may enhance their differentiation into neuronal lineages.

Locating the donor cells, especially long after transplantation, is technically difficult. Although the retina is considered an immunologically privileged site, researchers have reported GFP rejection in rabbits after subretinal administration. Furthermore, there is a need to overcome the labeling difficulties in PKH26 techniques and the quenching effect of GFP labeled cells.

One of the major drawbacks of neural models of regeneration is the difficulty in measuring the effect of the neuronal regeneration and repair on retinal functionality. It depends on the correct path-finding and proper preservation of the neuronal network/topographic innervations of the retina. In view of the limited success in applying protective and neurotrophic factors, stem cells will more likely be applied for reconstruction and regenerative purposes, which appear to be feasible and achievable in experimental models. Although preserving and/or renewing visual perception is within the realm of possibility, we still have a long way to go before a newly-generated retinal ganglion cell will transduce axonal signals to the brain.

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