Purpose: Millions worldwide have visual impairments caused by dysfunctional eye components, including cornea, lens, retina, and optic nerve, or the visual cortex in the brain. Insufficient cornea donation and inherent artificial lens problems demand alternative treatment strategies for cornea diseases and cataracts, whereas retinal degenerative diseases, including glaucoma, macular degeneration, and retinitis pigmentosa, still lack effective treatments. Stem cells have been investigated for their potential in various eye-specific pathologies to replace lost retinal ganglion cells and photoreceptors in retinal degenerative diseases and toward engineering transplantable patient-specific cornea or lens.

Design: Many stem cell types, including putative resident eye stem cells, mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells, have been investigated for their potential to generate specific cell types in the eye in culture and after transplantation and to engineer eye tissues in combination with structural scaffolds.

Method: Cultured stem cells and in vitro differentiated eye-specific cells are transplanted into different locations of the eye to test their ability to produce functional cells for supporting eye functions. In addition, stem cells have been directly tested in vitro for their capacity to engineer eye-specific tissues.

Results: Different stem cell types have been shown to have distinct capacities to produce eye-specific cells or even the entire retina.

Conclusions: Stem cells offer great hope for treating various eye pathologies. Despite recent progress, many challenges must still be overcome before the era of stem cell–based therapy in the eye truly arrives.

Key Words: stem cell, regeneration, cornea, lens, retina, ocular diseases, regenerative medicine, retinal degeneration


Each day, millions of people worldwide experience visual impairments caused by ocular diseases such as cataract, glaucoma, age-related macular degeneration (AMD), retinitis pigmentosa, and limbal stem cell deficiency (LSCD). Limbal stem cell deficiency is a severe corneal disorder that is difficult to treat. It is caused by loss of limbal stem cells, which are responsible for replenishing lost or damaged corneal epithelial and cornea cells and for the barrier function of limbus. Limbal stem cell loss results in chronic inflammation, vascularization, pain, and blindness. Standard cornea transplantation is not suitable for LSCD because limbal stem cells are required to restore the corneal epithelium, and this involves harvesting autologous stem cells from the healthy eye. Patients with cornea ulcers and cornea perforations who need a cornea graft are also confronted with the issue of a shortage of cornea donors. Recent advances in the field of tissue engineering have prompted researchers to develop stem cell–based strategies to treat corneal diseases. At this time, cornea tissue engineering has primarily focused on the interaction of stem cells with corneal scaffolds. This section reviews the progress toward using stem cells, including stem cells in the limbus and other epithelial tissues, mesenchymal stem cells (MSCs), embryonic stem cells (ESC), and induced pluripotent stem cells (iPSCs) for cell-based therapies to treat corneal diseases.

STEM CELL–BASED CORNEA THERAPY

Limbal stem cell deficiency is a severe corneal disorder that is difficult to treat. It is caused by loss of limbal stem cells, which are responsible for replenishing lost or damaged corneal epithelial and cornea cells and for the barrier function of limbus. Limbal stem cell loss results in chronic inflammation, vascularization, pain, and blindness. Standard cornea transplantation is not suitable for LSCD because limbal stem cells are required to restore the corneal epithelium, and this involves harvesting autologous, or allogeneic stem cells from the healthy eye. Patients with cornea ulcers and cornea perforations who need a cornea graft are also confronted with the issue of a shortage of cornea donors. Recent advances in the field of tissue engineering have prompted researchers to develop stem cell–based strategies to treat corneal diseases. At this time, cornea tissue engineering has primarily focused on the interaction of stem cells with corneal scaffolds. This section reviews the progress toward using stem cells, including stem cells in the limbus and other epithelial tissues, mesenchymal stem cells (MSCs), embryonic stem cells (ESC), and induced pluripotent stem cells (iPSCs) for cell-based therapies to treat corneal diseases.

Limbal Epithelial Stem Cells

Limbal epithelial stem cell (LESC) therapy was first described by Pellegrini et al. in 1997. Pellegrini took the limbus of a healthy eye of a patient with unilateral LSCD and cultured the limbus to generate an epithelial cell sheet, which he successfully transplanted onto the patient’s damaged eye. Alternatively to autografting, LESC can also be algofrilled from a living relative; however, the inefficiency of in vitro growth of primary
limbal epithelial cells has been a recurrent setback. A novel strategy involving coculture of limbus with ESCs has been shown to promote corneal epithelial cell proliferation and enhance the functional properties of corneal epithelial cells. Although cell expansion is promoted by the coculture system, both cultured autologous and allogeneic LESC therapies have drawbacks in that there is a potential risk of LESC deficiency at the donor site (autografts) or the requirement for long-term systemic immunosuppression (allografts). To date, isolation and cultivation of stem cells from corneal or limbal epithelial cells have not been achieved, although there are a number of candidate markers that warrant further investigation. Apart from the limbus, there are other tissue sources that could provide ophthalmologists with transplantable stem cells. Stem cells from oral mucosa or cutaneous epithelium, immature dental pulp, bone marrow, embryo, and iPSCs have been used as an alternative source of cells to repair corneal epithelia.

Stem Cells in Other Epithelial Tissues

In addition to stem cells that reside on the ocular surface, stem cells also exist in other continuously regenerating epithelia, including those in the mouth and skin where they are essential for self-renewal and tissue homeostasis. Stem cells are located in the basal layer of oral mucosal epithelium and can be identified with LESC markers, such as p75, CK-15, and Np63. Oral mucosal epithelial cells have been demonstrated to possess the potential to differentiate into cells with a corneal phenotype. A clinical study of 40 eyes in 36 patients with total LSCD suggested that the transplantation of cultivated oral mucosal epithelial sheets offers a viable and safe alternative for the reconstruction of a stable ocular surface. Another retrospective interventional case series also found that an oral mucosal graft with human amniotic membrane (HAM) transplantation is a viable alternative for treating total LSCD in eyes where transplantation of allogeneic limbal stem cells has failed or is not feasible.

Stem cells of the epidermis are thought to reside in the hair follicle bulge. Epidermal stem cells isolated from the skin of an adult goat with LSCD have been successfully used to repair the goat’s damaged cornea with autografted stem cells. Blazewiwska et al. were the first to describe the transdifferentiation of hair follicle stem cells (HFSCs) into corneal epithelial cells with several limbal stem cell markers, including CK-15, p63, and p75, by mimicking a limbal microenvironment composed of corneal stromal fibroblasts and laminin-5. Reconstruction of the ocular surface by HFSC transplant was reported in 80% of transplanted animals, which demonstrates the strong therapeutic potential of HFSCs for treatment of corneal diseases.

Mesenchymal Stem Cells

Mesenchymal stem cells are relatively simple to isolate and capable of transdifferentiating into cells of epithelial lineage. Several studies have demonstrated that MSCs can repair the alkali-burnt corneal epithelium of rabbit and rat, and recently, studies in rabbits have shown that human immature dental pulp stem cells possess the ability to transdifferentiate into corneal epithelial cells, expressing typical LESC markers, such as ABCG2 and p63. Bone marrow MSCs (BMSCs) are also a candidate source of cells for cornea repair and reconstruction. In a transwell coculture system with rat corneal stromal cells, BMSCs from the femurs of rats began to express CK12 and also demonstrate remarkable success in the treatment of rat corneal alkali burn and the reconstruction of the corneal surface.

Embryonic Stem Cells

Embryonic stem cells also have the ability to differentiate into corneal epithelium cells both in vitro and in vivo. Homma et al. transplanted ESC-derived corneal epithelium onto the cornea of a rabbit, with no teratoma formation. Pax6-transfected mouse ESCs could also be induced to form a monolayer of epithelium-like cells with the expression of E-cadherin, CD44, and cytokeratin 12, which could histologically reconstitute the corneal epithelium of the damaged mouse cornea. In addition to mouse ESCs, human ESCs (hESCs) have also been demonstrated to have the potential to differentiate to corneal epithelial cells. In vitro, hESCs transplanted onto the human corneal basement membrane, in which the epithelial layer has been removed and limbus is absent, have differentiated into corneal epithelium-like cells.

Induced Pluripotent Stem Cells

Many studies have shown that various cell lineages, such as neurons, cardiac myocytes, and retinal cells, can be differentiated from iPSCs, and thus, they are a promising candidate in cell-based therapy for treatment of corneal diseases. Human adult dermal fibroblast–derived iPSCs and human adult corneal limbal epithelial cell (HLEC)–derived iPSCs are able to differentiate into corneal epithelial cells, although the differentiation efficiency is different. Hayashi et al. first demonstrated a strategy for corneal epithelial cell differentiation from human iPSCs and further suggested that the epigenetic status influences the propensity of iPSCs to differentiate into corneal epithelial cells.

Microenvironment Requirement for Stem Cell-Based Corneal Therapy

Stem cells have the capacity to differentiate or transdifferentiate into corneal epithelium if appropriate conditions are met. The concept that a stem cell niche provides a unique and appropriate microenvironment to support stem cell self-renewal and maintain multipotency was first proposed in the late 1970s. Niches are 3-dimensional, stem cell–harboring, highly organized, interactive structural units that commonly occur at tissue intersections or transition zones. The physical and chemical signals that are critical for regulating stem cell function are frequently provided by or facilitated by molecular interactions between stem cells and their niches. Therefore, scaffolds for cornea bioengineering should mimic the stem cell niche as closely as possible.

Acellular corneal matrix and HAM are the most common natural materials used as scaffolds in developing tissue-engineered cornea replacement. When compared with entirely synthetic biomaterials, naturally occurring biomaterials are favored because they often offer more appropriate anatomical structure, flexibility, and suitable physical and mechanical properties. After decellularization of the acellular porcine cornea matrix, its basic corneal molecular structure and main extracellular matrix (ECM) components are maintained. Although the use of acellular xenografts as biological scaffolds for tissue engineering seems a promising approach, the long-term effects of chemicals currently being used for cell extraction on the remaining ECM has to be further examined.

Human amniotic membrane, first used to repair the ocular surface in the 1940s, is currently used as a substrate for therapeutic ex vivo expansion and transplantation of LESC to repair patients’ damaged corneas. Corneal epithelial cells have been shown to colonize on denuded HAM more quickly than on intact amniotic membrane with a higher propensity to differentiate into a corneal phenotype in patients with unilateral LSCD. In addition, Rama et al. demonstrated that after transplantation of limbal epithelial cells derived from autologous biopsies and...
cultured and autografted on a fibrin substrate, 14 of 18 LSCD patients displayed regression of conjunctivalization and a stable transparent cornea.

**STEM CELL–BASED LENS THERAPY**

Systematic study of human cataract is hampered by the lack of appropriate animal models and limitations of human primary lens cultures. To date, full regeneration of human crystalline lens has not been demonstrated. There is ample evidence indicating that the lens epithelium is capable of proliferation and transdifferentiation in both animal and human, although clinical evidence has shown that the proliferation of lens epithelial cells in humans contributes to secondary cataract formation on the posterior surface of intraocular lenses after removal of the crystalline lens by cataract surgery. The natural lens lacks both enervation and vasculature, making it particularly ideal for tissue replacement therapy. With the increasing popularity of stem cell research, much attention has been directed toward lens epithelial stem cells, ESCs, and iPSCs, all of which have a reported capability to differentiate or transdifferentiate into lens or lens-like cells and will be reviewed below.

**Lens Epithelial Stem Cells**

A lifetime of cell division in the lens implies the existence of a lens stem cell population, termed lens epithelial stem cells, but the identity and location of this stem cell population has yet to be defined. Studies using BrdU and 3H-TdR tracer analysis led Zhou et al to suggest that lens epithelial stem cells may reside in the central part of the anterior capsule. However, others have inferred that lens epithelial stem cells reside outside the lens capsule and in the nearby pigmented and vascularized ciliary body. After removal of the lens capsule contents, the normal physical nature of the regenerated lens in New Zealand albino rabbits was observed. Studies on the comparison of protein composition between normal and regenerated rabbit lens have shown that they are grossly similar; in particular, the entire major classes of crystallins (α, β, and γ-crystallin) are synthesized, but the global changes in gene expression have not been studied. Regenerated lens is typically irregular in shape because of a lack of lens growth at the site of the anterior capsulotomy and its adhesion to the posterior capsule. Sealing the capsulotomy and refilling the bag to maintain its shape seem to promote more normal lens regeneration.

Further studies should investigate the functional capacity of lens regenerated from the remaining lens capsule of humans.

**Embryonic Stem Cells**

Monkey ESCs and hESCs have been shown to be able to generate lentoids that express α-crystallin and Pax6. Treatment with increasing concentration of basic fibroblast growth factor (bFGF) and colony density promotes the formation of lentoids. Combined stimuli of factors derived from PA6 stromal feeder cells and basic fibroblast growth factor (bFGF) may also be necessary for the efficient induction of eye-like structures. Fully defining the factors vital for lens development in nature will aid studies of mechanisms of cataractogenesis. Furthermore, an in vitro system to direct ESC differentiation toward progenitor and mature lens cells with high efficiency still remains to be developed.

**Induced Pluripotent Stem Cells**

Patient-specific iPSCs are also ideally suited for studying cataract pathogenesis and repairing damaged lens. Qi et al showed that iLECs from a cataract patient could be reprogrammed into iPSCs, which subsequently differentiated into lens progenitor cells under defined chemical conditions. In addition to patient-matched treatment strategies, wherein gene therapy can be applied to patient-derived iPSCs to generate lens epithelium and treat the disease, these patient-derived pluripotent cells provide a valuable model for studying the molecular mechanisms that underlie lens development and cataract pathophysiology.

**Microenvironment Requirement for Stem Cell–Based Lens Therapy**

Many of the key components of the niche required for lens regeneration have been identified. The capsule factors, including an uninjured posterior capsule, a sound anterior capsule, and an absence of adherence between the capsules, provide a structural framework in lens regeneration. However, the mechanisms involved are still not clear. In addition to the condition of the capsule, the amount of remaining lens cortical tissue may be important, although this is currently under debate.

During differentiation of the lens in nature, the lens vesicle is induced from head ectoderm by signals from the retinal primordium and some ectodermal cells. Researchers have therefore suggested that the ectodermal cells may provide a niche for lens regeneration. This hypothesis has been confirmed by implanting cytolyzed embryonic skin ectoderm or cytolyzed fetal tissue from the lid commissure to the capsule. Additional specific factors critical for lens regeneration have recently been identified, revealing that Pax6 and Sox2 are 2 of the most important transcription factors involved in lens induction and differentiation. Pax6 is expressed throughout all stages of lens development, except in terminally differentiated lens fiber cells and is associated with control of cell proliferation and subsequent lens fiber differentiation. Pax6 is pivotal for initiation of the lens fiber differentiation program in the mammalian eye. Sox2 is associated with maintenance of a progenitor phenotype and stem cell characteristics. Pax6 and Sox2 have been shown to form a functional complex that is required for the activation of crystallin genes at the placodal stage. Pax6 has been shown to bind enhancer sequences of Sox2 and to activate Sox2 expression in lens cells and neuronal progenitors, suggesting a positive effect of Pax6 on Sox2 expression. Cellular signaling pathways, such as Wnt and bone morphogenetic protein, are required for development of primary lens fiber cells and lens epithelial differentiation. Further studies of critical transcription factors and signaling pathways essential for lens development and regeneration will advance the progress toward efficient differentiation of lens epithelial cells from stem cells.

**STEM CELL–BASED RETINA THERAPY**

The benefits of current treatments for retina degeneration, which include topical drug medication, intravitreal antivascular endothelial growth factor antibody injection, gene therapy, photodynamic therapy, and laser photoocoagulation, are limited. These treatments primarily aim to restore the function of damaged photoreceptors or the adjacent retinal pigment epithelium (RPE). Stem cell–based repair, which aims to generate new functional cells, thereby replenishing the damaged or lost cells and restoring vision, is being pursued as a potential alternative approach in the treatment of retinal degenerative diseases. To date, various cell types have been used in studies toward development of stem cell–based therapies for retinal degenerative disease and include retinal stem/progenitor cells (RSCs), ESCs, iPSCs, BMSC, peripheral blood stem cells (PBSCs), and RPE cells. In this section, we review the progress of regenerating RPE and retinal neurons through the use of stem cells.

**Retinal Stem/Progenitor Cells**

Retinal progenitor cells can be derived from fetal or neonatal retinas and comprise an immature cell population that is responsible...
for generation of all retinal cells during retina development. Recently, it has been shown that postmitotic photoreceptor precursors isolated from postnatal day 1 to 5 mouse retinas, when transplanted to the subretinal space, could integrate into the outer photoreceptor cell layer, differentiate into rod photoreceptors, establish visual circuitry all the way to the visual cortex, and restore vision of mouse model of visual impairment.\textsuperscript{78,79} Retinal stem/progenitor cells have been thought to reside in the ciliary body, iris epithelium, and neural retina.\textsuperscript{80} Retinal stem/progenitor cells can be isolated from the aforementioned 3 tissues and have the capacity to generate retinal neurons and RPE.\textsuperscript{71,81} An aggregated coculture system has also been successfully used to differentiate a human retinal progenitor cell line to 3-dimensional retinal-like structures,\textsuperscript{82} which supports the hypothesis that RSC/progenitor transplantation is a potential treatment for retinal degenerative diseases.

**Neural Stem Cells**

Retina is a part of central nervous system, and it shares its developmental origin with the neural ectoderm.\textsuperscript{83,84} The discovery of adult neural stem cells in the subventricular zone of the lateral ventricle and the dentate gyrus of the hippocampus has revolutionized our understanding of the physiology and pathology of the central nervous system.\textsuperscript{84} When searching for the suitable cellular sources for cell replacement therapy for retinal diseases, numerous researchers have considered neural progenitor/stem cells and tested the survival, integration, and differentiation of neural progenitor/stem cells after being transplanted into the retina.\textsuperscript{83-91} Although the transplanted neural stem cells show limited integration and retinal differentiation, they often provide protective effects on retinal neurons.\textsuperscript{92} Recently, Stem Cell, Inc, announced that human neural stem cells would be used in the phase I/II clinical trial for dry AMD.

**Embryonic Stem Cells**

Human ESCs have been repeatedly shown to be capable of differentiation into RPE and photoreceptors.\textsuperscript{93,94} Human ESCs--derived RPE-like cells express RPE markers\textsuperscript{95} and have the ability to phagocytose rod outer segments and restore visual function in the Royal College of Surgeons rat.\textsuperscript{93,96} Schwartz et al\textsuperscript{97} transplanted hESC-derived RPE to both Stargardt macular dystrophy and dry AMD patients and found that hESC-derived RPE cells form a mature quiescent monolayer and integrate into the RPE layer of patients, resulting in improved corrected visual acuity without hyperproliferation, abnormal growth, or immune rejection during the first 4 months of follow-up. Certainly, further study and long-term follow-up are needed before these treatments can be used in humans in a clinical setting. It was observed that the treatment yielded more positive results with a higher degree of photoreceptor and central visual rescue in patients with early-stage disease. Human ESC--derived neural progenitors have been transplanted to the subretinal space of rat eyes and differentiated into photoreceptors with photoreceptor markers, including neural retina leucine zipper, rhodopsin, and blue cone opsins. The additional use of insulin-like growth factor 1 and the Wnt and BMP inhibitors dickkopf-1 and noggin have been reported to increase photoreceptor differentiation efficiency.\textsuperscript{74}

**Induced Pluripotent Stem Cells**

Patient-derived iPSCs are an ideal stem cell source for cell transplantation because of their low immunogenicity and ease of culture and expansion in vitro. Their low immunogenicity is particularly appropriate for the loss of the immune-privileged state of the diseased eye because of the loss of RPE in retinal degeneration.\textsuperscript{99} Similar techniques used in ESC studies can also be applied to iPSCs to regenerate RPE cells in vitro,\textsuperscript{100,101} which show similar properties to ESC-derived RPE. Studies suggest that there is no significant difference between ESC-derived RPE and iPSC-derived RPE. In addition, photoreceptors have been generated using iPSCs derived from RP patients.\textsuperscript{102} Induced pluripotent stem cells have also been reported to differentiate into neural precursor cells, neuronal cells, and glial cells, both in vitro and in vivo.\textsuperscript{103}

**Bone Marrow Stem Cells**

Bone marrow MSCs have recently been induced with activin A, taurine, and epithelial growth factor to differentiate into cells expressing photoreceptor markers in vitro.\textsuperscript{104} Bone marrow MSCs injected into the subretinal space can differentiate into photoreceptors, integrate into the retina, and decrease retinal cell degeneration in RCS rats.\textsuperscript{105} In addition, intravitreal injection of autologous BMSCs indicated that this strategy is technically feasible, without resulting in inflammation or infection.\textsuperscript{106}

**Peripheral Blood Stem Cells**

Although most blood stem cells reside in the bone marrow, a small number of blood stem cells are present in the bloodstream and termed PBSCs. Peripheral blood stem cells exhibit overwhelming advantages over BMSCs in both basic study and clinical use.\textsuperscript{108} Collection of PBSCs is more easily and safely performed than collection of BMSCs, and they can be collected in large number. In addition, PBSCs are less likely to differentiate into malignant cells than BMSCs. Recent studies have demonstrated that PBSCs have the capacity to not only reconstitute the hematopoietic system but also differentiate into other cell lineages,\textsuperscript{109-111} suggesting that PBSCs hold great potential for applications in tissue engineering beyond the hematopoietic system. However, the characteristic cell markers and function of PBSCs have not been fully clarified and there have been relatively few ophthalmologic studies using PBSCs. Preliminary results show that PBSCs can be induced into neural precursor cells and retinal progenitor cells and the PBSC-derived cells can migrate and integrate into the retina in vivo.\textsuperscript{112} However, precise protocols for isolation and expansion of PBSCs and their differentiation to the retinal lineage are yet to be developed. When considering the multiple advantages of PBSCs over other stem cell sources, PBSCs are undoubtedly an attractive source for cell-based treatment of ocular diseases.

**Retinal Pigment Epithelial Cells**

The RPE is a monolayer of cells underlying and supporting the neural retina. Although epithelial, RPE shares the same developmental origin with the neural retina. It is specified early in development and remains mostly nonproliferative in adult animals. Embryonic chick RPE can transdifferentiate into a neural retina when exposed to bFGF or acidic fibroblast growth factor (aFGF),\textsuperscript{113-115} which indicates the potential of RPE for transdifferentiation. Ma et al\textsuperscript{116} discovered that chick E6 RPE can be induced to transdifferentiate toward retinal neurons by Sox2, one of the most important factors for maintaining the undifferentiated state of stem cells. Adult human RPE can also be reprogrammed to both neural and mesenchymal progenitors under defined conditions.\textsuperscript{117}

**Microenvironment Requirement for Stem Cell-Based Retinal Therapy**

Currently, there are 2 commonly used routes for transplantation of cells into the retina: subretinal injection and intravitreal injection. These methods rely on the natural microenvironment of the subretinal space and the vitreous, respectively, to foster the health, maintenance, and integration of the transplanted cells.
In addition, the use of scaffolds for subretinal transplantation of intact cell sheets has also been investigated. Seiler et al.\(^\text{18}\) and Sokda et al.\(^\text{11}\) transplanted freshly dissected sheets of fetal-derived retinal progenitor cells, combined with its associated RPE, to the subretinal area and obtained promising results in both animals and human.

Both natural and synthetic sources of scaffolds have been widely investigated. Human RPE has been successfully cultured on natural scaffolds composed of various combinations of ECM proteins or tissues, such as HAM,\(^\text{120}\) collagen,\(^\text{121}\) fibronectin, and vitronectin.\(^\text{122}\) Compared with natural sources of scaffolds, various synthetic scaffolds, including parylene,\(^\text{123}\) poly (glycerol sebacate), and poly (lactic-co-glycolic acid),\(^\text{124}\) have been designed to suit specific transplantation needs, such as altering the rate of degradation or attaching a peptide to improve adhesion or differentiation characteristics. However, biocompatibility risks and survival of retinal cells after transplantation still remain issues for both natural and synthetic scaffolds.

**CONCLUSIONS**

In summary, 4 sources of stem cells can be used to repair ocular damage—target tissue-specific adult stem cells, adult stem cells from other tissues, ESCs, and iPSCs—with or without scaffolds to assist in their delivery and residence in the damaged tissue. With advancements in our understanding of stem cell regulatory mechanisms and the continued development of biomaterials, stem cell–based cellular therapy is widely considered the most promising strategy for treating ocular diseases. Although encouraging, recent advances toward stem cell–based therapies reveal many obstacles that must be resolved before these technologies can be reliably used in the clinical setting. These include development of protocols to obtain cells of the appropriate identity in numbers sufficient for transplantation, generation of suitable biomaterials to be used as support scaffolds, optimization of surgical procedures for delivery of cells or tissues, and improvements toward long-term efficacy of cell or tissue transplantation. Studies in photoreceptor cell replacement therapy have indicated that successful cell replacement therapy requires large amount of cells at the appropriate developmental stage.\(^\text{78}\) Generating sufficient amount of suitable cells to replace lost cornea, lens or retina cells will be the prerequisite for the further investigation of feasibility of cell replacement therapy for eye diseases. Extracellular matrix and signaling molecules are essential components of the niches for both the maintenance and differentiation of stem cells. Although advances have been made, biomaterials currently available are still far from ideal when considering biocompatibility and support for the normal physiology of transplanted cells. Thorough analysis of the composition of the microenvironment of the eye tissues and development of scaffold to be transplanted with the stem cells accordingly will greatly improve the success of the transplantation. Finally, surgical aspects of the cell replacement therapy, such as route, timing, and immune-rejection management, need to be carefully optimized to ensure the success of the procedure. Solving these issues will facilitate the translation of stem cell research to clinical application to fight blindness.

**REFERENCES**


*Living is easy with eyes closed.*

- John Lennon