Biomere

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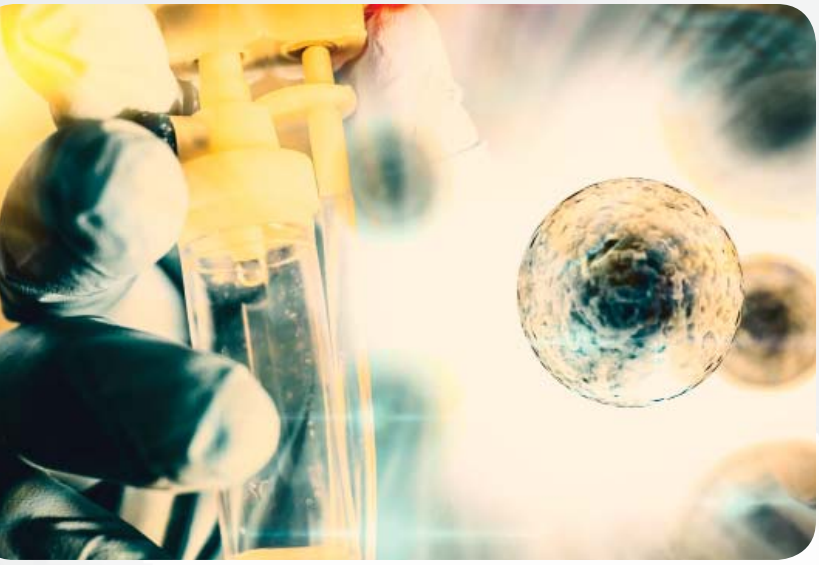
CELL THERAPIES FOR EYE DISEASES

INTRODUCTION

Vision loss can be due to either light not reaching the retina or the inability to convert the light signal into an electrochemical signal that is sent to the brain. Cataracts are an example of light not reaching the retina and it is a condition that can be corrected surgically. However, there are several eye diseases where the light signal is not converted to an electrochemical signal due to the loss of photoreceptor cells. The lack of photoreceptor cells leads to disorders such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). Stem cells are being actively investigated as a source of new and healthy cells to replace damaged or deteriorated cells in the eye. Developing stem cell-based therapies for the eye offers unique advantages in that the eye is a compartmentalized organ that is easily accessible for therapy administration and follow up monitoring. Additionally, the eye is relatively a small organ, so does not require the administration of a large number of cells.

While retinal pigment epithelial (RPE) cell therapies are a major focus, other cell types are also being investigated such as stem cell derived corneal endothelial cells. In fact, the one approved stem cell therapy for eye diseases targets corneal blindness[1]. Corneal blindness is reported to be the fourth leading cause of blindness and one of the causes is Fuchs dystrophy, a genetic disorder[2]. Currently, complicated transplants methods are used to address corneal deterioration but cell therapy is being investigated as an alternative therapeutic approach.



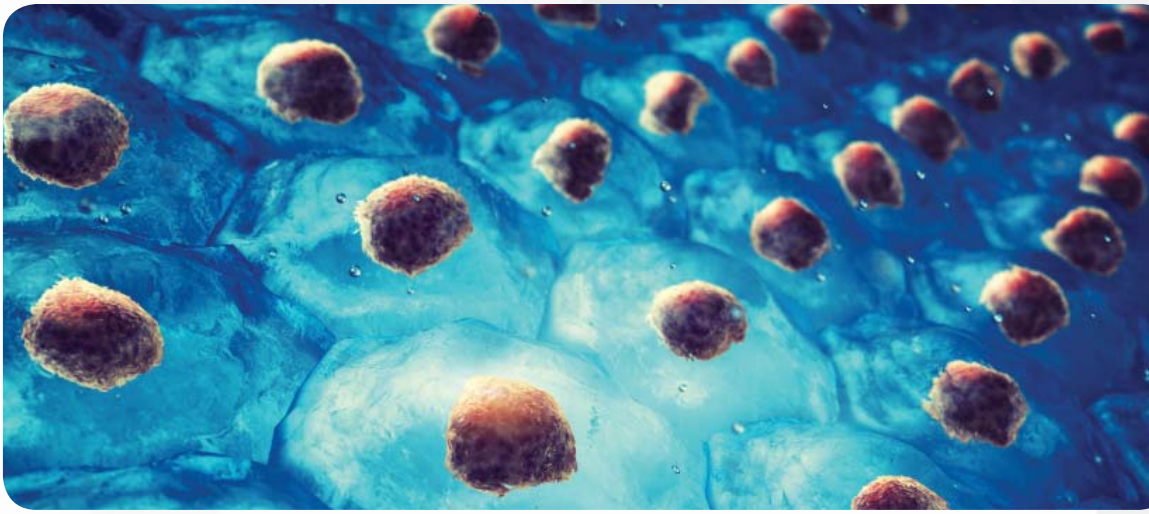
Stem cell-derived differentiated corneal endothelial cells, corneal endothelial progenitor cells and allogeneic corneal endothelial cells from donor cadavers are being investigated as cell sources. Delivery methods of the cells to the cornea include scaffold matrices that are coated with cells for accurate delivery. Another approach is to load cells with magnetic particles that are then oriented in the eye using an external magnetic field[2].

The loss of photoreceptor cells in retinal diseases is largely due to issues with the RPE. The RPE is a monolayer of cells that keeps photoreceptor cells functional and healthy by transporting nutrients and removing byproducts such as photoreceptor membranes, and also plays a key role in maintaining the visual cycle. Importantly, the RPE helps preserve the immune-privileged state of the eye by being a part of the blood-retina barrier (BRB) and by secreting immunosuppressive factors. The RPE is critical to maintaining vision so it is a prime target for the development of novel cell therapies[3].

AVAILABLE THERAPIES

Holoclar® is the only approved stem cell therapy for eye diseases and was approved in 2015 for use in Europe. Currently, there are no FDA approved stem cell therapies for eye diseases. Holoclar was developed at the University of Moderna in Italy in collaboration with Chiesi Farmaceutici S.p.A and is used in adults with moderate to severe limbal stem cell deficiency (LSCD) that is caused by physical injury or chemical burns[4]. The therapy utilizes a patient's limbal stem cells that are cultured to form a corneal sheet that is then grafted into the eye.

There are concerns among the ocular disease community about misleading and even dangerous promotion of unapproved cell therapies for eye diseases[5]. While there are multiple active clinical trials that are investigating cell therapies in various eye diseases, there are commercial clinics that offer unproven cell therapies direct to patients. The cell sources used in the clinics are primarily autologous adipose-derived iPS (induced pluripotent stem) cells but autologous bone marrow derived stem cells or cord blood stem cells are also used[6].



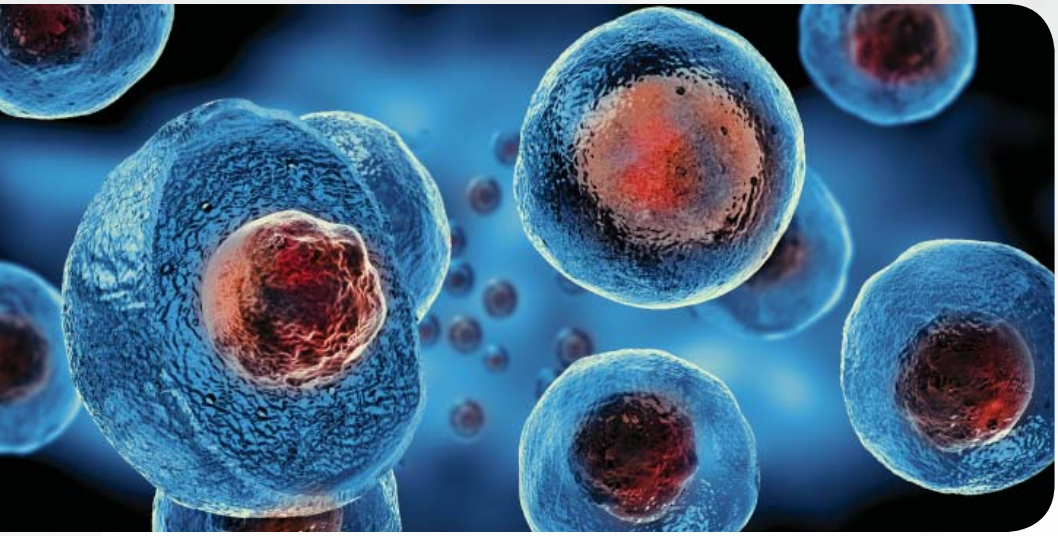
CLINICAL TRIALS

Several clinical trials are ongoing to test various single and combination approaches that include a mix of small molecules, biologics and cell therapies[7]. Currently, there are over 50 clinical trials that are testing multiple cell therapies for various indications including cancers (Retinoblastomas), AMD, RP and Stargardt disease. Most cell therapy clinical trials are in Phase I or Phase I/II, so safety and associated adverse events are the primary endpoints. One of the primary safety concerns with stem cell-based therapies is the oncogenic potential of the injected stem cells. Ensuring that injecting stem cells into the eye does not trigger local or systemic tumor formation is a key outcome measure in clinical trials. Another concern is host rejection of transplanted cells but this is overcome by the use of autologous iPS cells (derived from the patient) instead of allogeneic cells. One of the key requirements that need to be fulfilled before initiating a clinical trial is the established of GMP (good manufacturing practice) protocols and procedures for consistent and reproducible scale-up production of stem cell-derived therapies.

There are two sources of stem cells to develop cell-based therapies – human embryonic stem (hES) cells and iPS cells. A combination of ethical considerations around using hES cells and the rapid development of robust iPS protocols have shifted the focus more to using iPS cells[8]. The first iPS cell-derived clinical trial was started in 2019 and there will likely be more trials using iPS cell-derived therapies in the future[9].

The first reports of clinical trials using embryonic stem cell-derived RPE cells was reported in 2012 when a group at the Stein Eye Institute in Los Angeles transplanted hES cell-derived RPE cells into patients with Stargardt macular dystrophy and dry AMD. The transplanted cells showed a good safety profile with no signs of rejection or abnormal growth and patients and had moderate efficacy in improving vision[10]. A similar report was published in 2015 that demonstrated that hES cell-derived RPE cells had a good safety profile and moderate efficacy in 2 patients with Stargardt disease and 2 patients with dry AMD[11].

Mesenchymal stem cells (MSCs) are increasingly being investigated as valuable sources for cell therapies targeting eye diseases. MSCs from bone marrow and adipose tissues are two examples of cell sources that are being tested in clinical trials[12]. However, one of the main challenges with using MSCs is poor survival of transplanted cells and sensitivity to hypoxic shock. Therefore, it is necessary to integrate biomaterial scaffolds and tissue engineering approaches to maximize the viability of MSCs so that they can differentiate into functional cells[12].



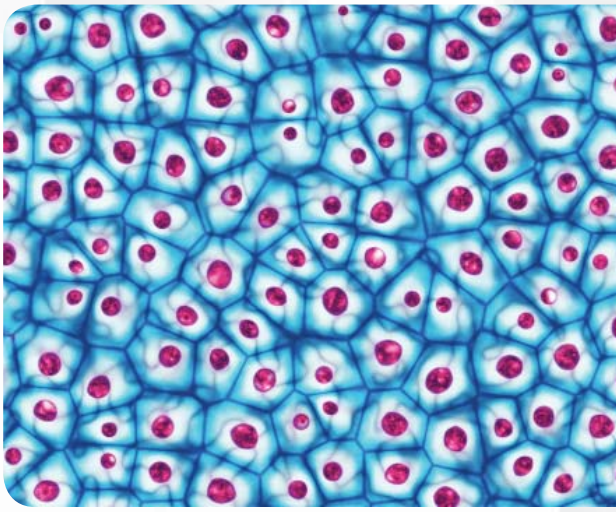
There are a few trials using bone marrow and adipose derived MSCs - autologous bone marrow derived stem cells are being tested in patients with RP disorders and Stargardt disease at locations in Brazil, Spain and the US. The MSCs are administered via intravitreal injection[7]. Adipose tissue-derived mesenchymal stem cells are being tested for dry eyes and tear deficiencies in an early phase I trial[7].

CASE STUDIES: CELL THERAPY APPROACHES

Glaucoma

The only available treatments for glaucoma are drugs or surgery to lower intraocular pressure but in many patients, glaucoma progresses to the point where retinal ganglion cells (RGCs) die, resulting in blindness. Cell therapy approaches to replace RGCs are being actively investigated. Müller glia are a type of human mesenchymal stem cells that can be differentiated into photoreceptor cells via a combination of growth factors and the activation of the Notch pathway[13]. The mechanisms by which Müller cells differentiate into RGCs is actively being studied – for example, Atoh7 has been identified as a key transcription factor that is necessary for the differentiation process. Additionally, neurotrophic factors like BDNF (brain derived neurotrophic factor) and GDNF (glial cell line derived neurotrophic factor) have been shown to be essential to maintain RGC survival post differentiation[14.] Induced pluripotent stem (iPS) cells have been successfully shown to form retinal organoids from which Müller glia can be isolated to form RGCs[13].

In early 2019, the FDA granted fast track designation to Neurotech Pharmaceuticals cell therapy, Renexus® for the treatment of AMD and RP, but Renexus® is being tested as a treatment for advanced glaucoma. Renexus® consists of encapsulated cells that secrete ciliary neurotrophic factor (CNTF) that is known to protect photoreceptor cells. It is implanted in the eye to express and deliver CNTF to the photoreceptor cells in a sustained manner. Renexus® has been tested in phase I and II clinical trials and has been shown to have a good safety profile as well as induce promising biomarker changes that are associated with slower disease progression[15].

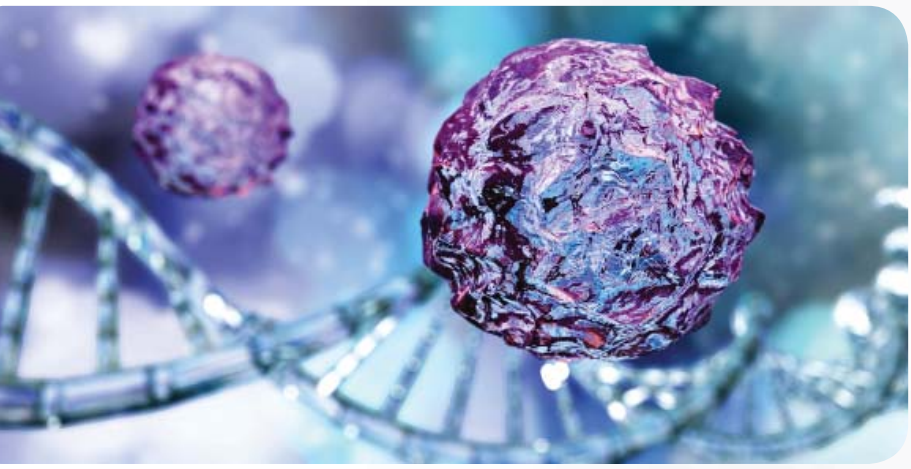


Retinitis Pigmentosa

Retinitis pigmentosa is a group of inherited eye diseases that impact the RPE and/or photoreceptor cells. Typically, patients with RP experience night vision followed by tunnel vision (vision loss in the periphery of the eye). The first gene therapy approved to treat genetic diseases was Luxturna®, an adeno-associated virus (AAV) therapy that is injected subretinally to treat Leber's congenital amaurosis (LCA) or retinitis pigmentosa (RP)[16]. However, this therapy can be used on a small fraction of patients, so there is an unmet need to develop other therapies for RP diseases.

One stem cell approach is to use retinal progenitor cells (RPCs) that differentiate into various types retinal cells including ganglia and photoreceptor cells. jCyte is a company that is able to produce allogeneic RPCs in large scale which is an essential requirement for moving cell therapies into the clinic. The allogeneic RPC cell therapy is easy to administer and requires a single intravitreal injection of cells in a nonsurgical setting and has been shown to have a good safety profile in a phase I/IIa clinical trial. Currently, a phase II clinical trial funded by a multi-million-dollar California Institute for Regenerative Medicine (CIRM) grant is underway to assess the safety and efficacy of the allogeneic cell therapy across various RP diseases[17].

Another approach is to use iPS cell-derived RPE cells. Currently, there is one active interventional trial using iPSC derived RPE cells in the US9. This trial is the first of its kind and is being led by investigators at the National Eye Institute for patients with advanced dry AMD. Currently, there are no treatment options for dry AMD, which accounts for 90% of AMD cases. About 10% of dry AMD progresses to wet AMD which results in blindness in most cases[18]. In this trial, patient's blood cells are converted into iPS cells that are then differentiated into RPE cells. The RPE monolayer is cultured on a biological scaffold that helps integrate the transplanted cells into the retina. The RPE monolayer is then transplanted into one eye of each patient followed by monitoring for one year. If this cell therapy is shown to have a good safety profile and subsequent trials show efficacy, this will be the first therapy for dry AMD.



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