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Review Article

# Research Progress and Human Clinical Trials of Mesenchymal Stem Cells in Ophthalmology: A Mini Review

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## Abstract

Ocular diseases are devastating as most of them would cause irreversible visual impairment and blindness. Conceptually, cell replacement therapy with new ocular cells generated by ocular stem cells can substitute the degenerated or damaged cells in the diseased tissue. This concept has first been applied in the limbal transplantation by limbal progenitor cells. Unfortunately, patients with limbal stem cell deficiency and the endogenous progenitor cells present in human corneal endothelium as well as retina have limited regenerative power. In recent decades, other stem cell sources for ocular cell regeneration have been explored and are now feasible with the use of pluripotent stem cells, such as the embryonic stem cells (ESCs) and the induced pluripotent stem cells (iPSCs). Nevertheless, autologous transplantation would not be applicable using ESCs, whereas the variability of reprogramming methods as well as genetic instability of iPSCs has hindered their direct applications. Alternatively, human adult stem cells, such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are found throughout the body and can be efficiently isolated from patients while maintaining the characteristics of self-renewal and multipotency. Superiorly, adult stem cells harness the potential to protect the ocular cells, where MSCs are able to modulate the microenvironments of the diseased eye for neuroprotection. This article compiled the current progress of MSCs in ocular research. Moreover, the updated clinical trials of adult stem cells in ocular diseases are summarized. In addition, potential challenges and future prospects of stem cell research in ophthalmology would also be discussed.

## Human Adult Stem Cells

Stem cells are undifferentiated cells defined by their abilities to self-renew and differentiate into functional mature cells. They can be characterized according to their differentiation ability (potency) as well as their spatio-temporal emergence at different developmental stages. Firstly, stem cells can be classified into totipotent, pluripotent, multipotent, oligopotent or unipotent cells. Pluripotency refers to the capacity of individual cells to differentiate into all cell type of the 3 germ layers (ectoderm, endoderm and mesoderm). Pluripotent stem cells are the origin of all somatic and germ-line cells in a mature organism [1], while multipotent stem cells can only differentiate into a limited lineage of cells.

Secondly, stem cells can be originated from embryos or adult tissues. Embryonic stem cells (ESCs) are pluripotent stem cells derived from the inner cell mass of a blastocyst prior to gastrulation. In contrast, adult stem cells found in fully developed tissues are considered to be multipotent and tissue-specific. The functions of adult stem cells are believed to maintain adult tissue specificity by homeostatic cell replacement and tissue regeneration [2]. They are presumably quiescent within adult tissues, but divide intermittently to generate a stem cell clone with transiently-amplifying cell. The transiently-amplifying cells will undergo a limited number of cell divisions before terminal differentiation into mature functional tissue cells. The existence of adult stem cells has been reported in multiple organs; This includes: brain, heart, skin, intestine, testis, muscle and blood. In recent years, adult stem cells, such as the Hematopoietic Stem Cells (HSCs), Mesenchymal Stem Cells (MSCs), Neural Crest-Derived Stem Cells (NCSCs) and Spermatogonial Stem Cells (SSCs) have been reported with great potentials in regenerative medicine and tissue engineering (Table 1).

HSCs are the most characterized adult stem cell population. They function to generate all cell lineages found in mature blood (erythroid, myeloid and lymphoid) to sustain blood production during the entire life of an animal [3]. Adult bone marrow, umbilical cord blood and mobilized peripheral blood are sources of hematopoietic stem cells for transplantation in many blood-related diseases. Hematopoietic stem cells can be characterized by the positive selection of CD34, CD45, and CD133 markers with the negative selection of CD31, CD105 and CD146 markers [4].

The NCSCs are a group of cells originated from the dorsal margins of the neural folds during the development of vertebrates. NCSCs undergo epithelial-mesenchymal transition, and they are widely distributed within the embryo after a phase of extensive migration. At post-migratory stages, development potentials of NCSCs are restricted. However, NSCSs can still be found in adult tissues, such as the peripheral nervous system, dorsal root ganglia and gut [5]. Cranial NCSCs can be easily

**Table 1:** Conveniently accessible adult stem cells and their characterization

| Adult stem cells | Feasible sources | Characterization |
|---|---|---|
| Hematopoietic stem cells | Bone marrow, umbilical cord blood, mobilized peripheral blood | (+): CD34, CD45, CD133<br>(-): CD31, CD105, CD146 |
| Mesenchymal stem cells | Bone marrow, adipose tissue, umbilical cord, menstrual blood | (+): CD29, CD44, CD73, CD90, CD105, CD146, STRO-1<br>(-): CD31, CD34, CD45, CD49f, CD133 |
| Neural crest-derived stem cells | Periodontal ligament, dental pulp, skin, hair follicles | (+): p75, nestin, Slug, SOX10 |
| Spermatogonial stem cells | Testis | (+): CD9, CD49f and GPR125 |

isolated from the periodontal ligament, dental pulp, skin as well as hair follicles. These cells express NCSC markers, such as p75, nestin, Slug and SOX10 [6]. Interestingly, NCSCs display with multipotency as they can express some of the pluripotent markers, including Nanog and SSEA-4 (Figure 1).

Testicular SSCs are the germ-line cells for spermatogenesis, an ongoing process throughout the lifespan of the male animals. They are unipotent in nature and continuously generate differentiating daughter cells for subsequent production of spermatozoa [7]. Human spermatogonial stem cells can be purified by antibodies against cell surface markers CD9, CD49f and GPR125 [8].

The rest of this article will focus on mesenchymal stem cells (MSCs) and its application of ocular research and human clinical trials in ophthalmology.

## Current Progress of Mesenchymal Stem Cells in Ocular Research

MSCs, also called marrow stromal cells, belong to an adult stem cell population of stromal progenitor cells of mesodermal origin [9]. MSCs were originally identified in bone marrow, representing 0.001-0.01% of the bone marrow population. They appear fibroblastic-like in culture (Figure 2). According to the International Society of Cellular Therapy [10], the minimal criteria to define MSCs are: (1) grown in adherence to plastic surface of dishes when maintained in standard culture conditions; (2) positive expression of cytospecific cell surface markers (CD105, CD90 and CD73) and negative expression of other cell surface markers (CD45, CD34, CD14 and CD11b); (3) capacity to differentiate into mesenchymal lineages, under appropriate *in vitro* conditions. In addition to the expression of the three cell surface markers, MSCs also express CD29, CD44, CD146 and STRO-1 [4]. They can be found throughout the body in many different systems, such as adipose tissue, liver, umbilical cord, central nervous system (CNS) and dental tissues [11].

MSCs can differentiate into osteocytes, chondrocytes, myoblasts and adipocytes [12,13]. An increasing number of studies, however, reported that MSCs are capable to give rise to cells of a distinct lineage. Trans-differentiation of MSCs into neurons has already been demonstrated [14]. In ocular research, bone marrow-derived MSCs can differentiate into retinal neuronal-like cells in culture [15]. Adipose tissue-derived MSCs can be induced to a retinal pigment epithelial cells (RPE) phenotype [16]. In addition, MSCs from trabecular meshwork as well as conjunctiva have been used to generate photoreceptor-like cells *in vitro* [17,18]. Furthermore, our group has adopted an established retinal differentiation protocol for Embryonic Stem Cells (ESCs) [19] and developed a platform to direct our MSCs into retinal lineage [20]. These differentiated cells not only express photoreceptor markers, but also show glutamate-induced calcium response. Even though intravitreal injection of human umbilical cord blood-derived mesenchymal stem cells in neonatal rats does not demonstrate neural cell differentiation or integration into the retina [21], subretinal injection of MSCs has been reported to form photoreceptor cells, exhibit RPE morphology and preserve the retinal layer integrity in a sodium iodate-induced retinal degeneration rat model [22,23]. These fundamental studies could be the important stepping stones for cell replacement therapy on retinal diseases [24].

Apart from the differentiation capacity for cell replacement therapy, MSCs are also neuroprotective because of their paracrine effects, which have not been demonstrated in ESCs and induced

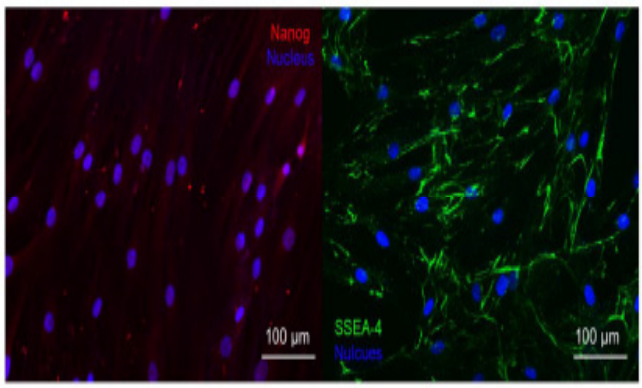


**Figure 1:** Neural crest-derived stem cells express some of the pluripotent markers.

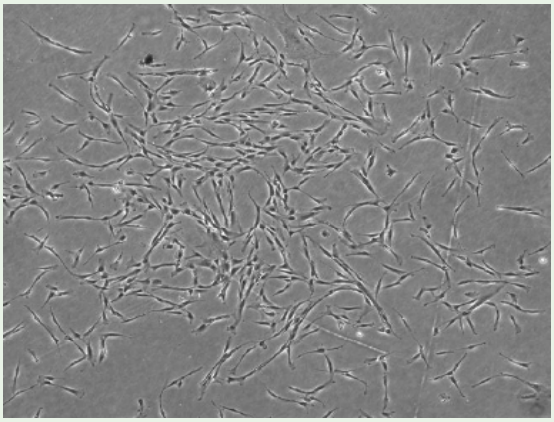

**Figure 2:** Mesenchymal stem cells in culture.

**Table 2:** Registered stem cell-based clinical trials for glaucoma

| Identifier | Sponsor | Country | Status | Study | Phase of trial | Cell type | Delivery | Estimated number of patients | Estimated trial end |
|---|---|---|---|---|---|---|---|---|---|
| NCT01920867 | Retina Associates of South Florida | United States | Recruiting | Stem Cell Ophthalmology Treatment Study (SCOTS) | | Autologous bone marrow-derived MSCs | Retrobulbar, Subtenon, Intravenous, Intravitreal, Intraocular | 300 | 2017 |
| NCT02144103 | Burnasyan Federal Medical Biophysical Center | Russian Federation | Enrolling by invitation | Effectiveness and Safety of Adipose-Derived Regenerative Ils for Treatment of Glaucomatous Neurodegeneration | Phase 1/2 | Autologous adipose-derived regenerative cells (ADRC) | Subtenon | 16 | 2017 |
| NCT02330978 | University of Sao Paulo | Brazil | Recruiting | Intravitreal Mesenchymal Stem Cell Transplantation in Advanced Glaucoma | Phase 1 | Autologous bone marrow-derived MSCs | Intravitreal | 12 | 2016 |

Pluripotent Stem Cells (iPSCs). MSCs modulates the plasticity of damaged host tissues, secretes neurotrophic and survival-promoting growth factors (basic fibroblast growth factor, brain-derived growth factor, ciliary neurotrophic factor, nerve growth factor, neutrophin-3/4, glial cell-derived neurotrophic factor and platelet-derived growth factor), restores synaptic transmitter release, integrates into existing neural and synaptic networks, and re-establishes functional afferent and efferent connections [25]. In culture, adipose tissue-derived MSCs can rescue mitomycin C-treated RPE cell lines (ARPE-19) from death in culture [26]. Moreover, condition medium from human bone marrow-derived MSCs enhances the survival and proliferation of chemically injured human corneal epithelial progenitor cells, and inhibits their apoptosis [27]. Similarly, condition medium from bone marrow-derived MSCs also stimulates proliferation and neuronal differentiation of retinal progenitor cells [28]. In addition, MSCs isolated from sclerocorneal tissue are able to support the growth of human corneal epithelial progenitor cells in a three-dimensional culture system [29]. Furthermore, bone marrow-derived MSCs can reduce retinal ganglion cell (RGC) loss in a retinal explant model [30]. In animal studies, bone marrow-derived MSC transplantation increases RGC survival in a model of transient ischemia followed by reperfusion [31], and reduces RGC loss in ocular hypertension models [32,33]. Coherently, transplantation of human umbilical cord blood MSCs promotes RGC survival after 7 days of optic nerve crush injury [34], whereas intracranial human umbilical cord blood MSC transplantation at the site of optic tract transaction protects RGCs and induces axonal regeneration [35]. Moreover, transplantation of bone marrow-derived MSCs can rescue photoreceptor cells of the dystrophic retina in the rhodopsin knockout mouse model [36]. Intravenous injection of bone marrow-derived MSCs can rescue photoreceptor cells as well as visual function in the Royal College of Surgeons rat model [37]. In addition, intrastromal and subconjunctival injections of MSCs improve the healing of alkali-injured cornea by reducing the expression Serum Glutamic-Pyruvic Transaminase (SGPT) and Vascular Endothelial Growth Factor (VEGF) [38]. Interestingly, intravenous application of MSCs promotes corneal allograft survival in rats by suppressing peripheral immune responses [39]. Systemically administration of MSCs specifically home to the inflamed ocular surface, and promote allograft survival by inhibiting APC maturation as well as alloreactive T cell induction [40]. Furthermore, intravenous application of human adipose-derived MSCs can ameliorate diabetic retinopathy in streptozotocin diabetic rats by reducing blood glucose levels and improving blood-retinal barrier integrity [41] although MSCs can promote angiogenesis *in vitro* by the secretion of VEGF [42,43].

In addition to the neuroprotective effects, MSCs possess strong immunosuppressive properties and inhibit the release of pro-inflammatory cytokines [44]. This allows autologous, as well as, allogeneic transplantation of MSCs without the need of pharmacological immunosuppression. Furthermore, MSCs can be transplanted directly without genetic modification or pre-treatments, and are able to migrate to the tissue injury sites [45]. In addition, there is no teratoma formation after transplantation [46] and no moral objection or ethical controversies involved in their attainment [47]. These advantageous properties, as well as the self-renewal potential of MSCs, facilitate the clinical trials of MSCs on different human diseases, especially ocular diseases.

## Human Clinical Trials using Stem Cells in Ophthalmology

According to the United States National Institutes of Health trial database (www.clinicaltrials.gov), there are 3 registered clinical trials using stem cells for glaucoma (Table 2). All of them selected human adult stem cells for the treatment interventions. The Stem Cell Ophthalmology Treatment Study (SCOTS) in Florida is based on autologous bone marrow-derived MSCs (NCT01920867; http://clinicaltrials.gov/), and this study will be completed in 2017. Similarly, the Phase 1 trial sponsored by the University of Sao Paulo (NCT02330978; http://clinicaltrials.gov/) also adopts the intravitreal injection of autologous bone marrow-derived MSCs. In contrast, the trial in Russian Federation (NCT02144103; http://clinicaltrials.gov/) uses the autologous Adipose-Derived Regenerative Cells (ADRC) by a mean of subtenon injection. Outcomes of these studies have not been reported before the submission of this manuscript.

For Age-related Macular Degeneration (AMD), there are 14 registered stem cell-based clinical trials (Table 3). 5 of them adopted the subretinal transplantation of ESC-derived RPE (MA09-RPE in the United States, Pf-05206388 in the United Kingdom and OpRegen in Isreal) for the treatment intervention (NCT01344993, NCT01674829, NCT01691261, NCT02286089 and NCT02463344; http://clinicaltrials.gov/). Moreover, 3 trials in the United States are based on subretinal delivery of human central nervous system stem cells (HuCNS-SC) in dry AMD patients (NCT01632527, NCT02137915 and NCT02467634; http://clinicaltrials.gov/). Furthermore, there is one Phase 1/2a study using human umbilical tissue-derived cells

Table 3: Registered stem cell-based clinical trials for age-related macular degeneration.

| Identifier | Sponsor | Country | Status | Study | Phase of trial | Cell type | Delivery | Estimated number of patients | Estimated trial end |
|---|---|---|---|---|---|---|---|---|---|
| NCT01226628 | Janssen Research & Development, LLC | United States | Active, not recruiting | A Safety Study of CNTO 2476 in Patients With Age-Related Macular Degeneration | Phase 1/2a | Human umbilical tissue-derived cells (CNTO 2476) | Subretinal | 24 | 2015 |
| NCT01344993 | Ocata Therapeutics | United States | Active, not recruiting | Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration (Dry AMD) | Phase 1/2 | Human embryonic stem cell derived retinal pigmented epithelial (MA09-RPE) cells | Subretinal | 16 | 2015 |
| NCT01518127 | University of Sao Paulo | Brazil | Recruiting | Intravitreal Bone Marrow-Derived Stem Cells in Patients With Macular Degeneration (AMDCELL) | Phase 1/2 | Autologous bone marrow stem cells | Intravitreal | 10 | 2015 |
| NCT01674829 | CHABiotech CO., Ltd | Republic of Korea | Recruiting | A Phase I/IIa, Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial(MA09-hRPE) Cells in Patients With Advanced Dry Age-related Macular Degeneration(AMD) | Phase 1/2a | Human embryonic stem cell derived retinal pigmented epithelial (MA09-RPE) cells | Subretinal | 12 | 2016 |
| NCT01691261 | Pfizer | United Kingdom | Not yet recruiting | A Study Of Implantation Of Human Embryonic Stem Cell Derived Retinal Pigment Epithelium In Subjects With Acute Wet Age Related Macular Degeneration And Recent Rapid Vision Decline | Phase 1 | Human Embryonic Stem Cell Derived Retinal Pigment Epithelium Living Tissue Equivalent (Pf-05206388) | | 10 | 2017 |
| NCT01736059 | University of California, Davis | United States | Recruiting | Clinical Trial of Autologous Intravitreal Bone-marrow CD34+ Stem Cells for Retinopathy | Phase 1 | Adult CD34+ bone marrow stem cells | Intravitreal | 15 | 2015 |
| NCT01920867 | Retina Associates of South Florida | United States | Recruiting | Stem Cell Ophthalmology Treatment Study (SCOTS) | | Autologous bone marrow-derived MSCs | Retrobulbar, Subtenon, Intravenous, Intravitreal, Intraocular | 300 | 2017 |
| NCT02016508 | Al-Azhar University | Egypt | Recruiting | Safety Study of Use of Autologous Bone Marrow Derived Stem Cell in Treatment of Age Related Macular Degeneration | Phase 1/2 | Autologous bone marrow-derived MSCs | Intravitreal | 1 | 2015 |
| NCT02024269 | Bioheart, Inc. | United States | Recruiting | Study to Assess the Safety and Effects of Cells Injected Intravitreal in Dry Macular Degeneration | | Autologous adipose-derived MSCs | Intravitreal | 100 | 2017 |
| NCT01632527 | StemCells, Inc. | United States | Active, not recruiting | Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Age-Related Macular Degeneration (AMD) | Phase 1/2 | Human central nervous system stem cells (HuCNS-SC) | Subretinal | 15 | 2015 |
| NCT02137915 | StemCells, Inc. | United States | Enrolling by invitation | Long-Term Follow-up Safety Study of Human Central Nervous System Stem Cells in Subjects With Geographic Atrophy of Age-Related Macular Degeneration | Phase 1/2 | Human central nervous system stem cells (HuCNS-SC) | Subretinal | 8 | 2019 |
| NCT02286089 | Cell Cure Neurosciences Ltd. | Israel | Recruiting | Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form Age-Related Macular Degeneration | Phase 1/2a | Human embryonic stem cell-derived retinal pigment epithelial cells (OpRegen) | Subretinal | 15 | 2017 |
| NCT02463344 | Ocata Therapeutics | United States | Enrolling by invitation | Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Patients With AMD | | Human embryonic stem cell derived retinal pigmented epithelial (MA09-RPE) cells | Subretinal | 10 | 2016 |
| NCT02467634 | StemCells, Inc. | United States | Recruiting | Study of HUCNS-SC Subretinal Transplantation in Subjects With GA of AMD (RADIANT) | Phase 2 | Human central nervous system stem cells (HuCNS-SC) | Subretinal | 63 | 2017 |

**Table 4:** Registered stem cell-based clinical trials for retinitis pigmentosa.

| Identifier | Sponsor | Country | Status | Study | Phase of trial | Cell type | Diseases | Estimated number of patients | Estimated trial end |
|---|---|---|---|---|---|---|---|---|---|
| NCT01068561 | University of Sao Paulo | Brazil | Completed | Autologous Bone Marrow-Derived Stem Cells Transplantation For Retinitis Pigmentosa | Phase 1 | Autologous bone marrow stem cells | Retinitis pigmentosa | 5 | 2010 |
| NCT01531348 | Mahidol University | Thailand | Enrolling by invitation | Feasibility and Safety of Adult Human Bone Marrow-derived Mesenchymal Stem Cells by Intravitreal Injection in Patients With Retinitis Pigmentosa | Phase 1 | Bone marrow-derived MSCs | Retinitis pigmentosa | 10 | 2014 |
| NCT01560715 | University of Sao Paulo | Brazil | Completed | Autologous Bone Marrow-Derived Stem Cells Transplantation For Retinitis Pigmentosa (RETICELL) | Phase 2 | Autologous bone marrow stem cells | Retinitis pigmentosa | 50 | 2013 |
| NCT01736059 | University of California, Davis | United States | Recruiting | Clinical Trial of Autologous Intravitreal Bone-marrow CD34+ Stem Cells for Retinopathy | Phase 1 | Adult CD34+ bone marrow stem cells | Non-exudative age-related macular degeneration, Diabetic retinopathy, Retina vein occlusion, Retinitis pigmentosa, Hereditary macular degeneration | 15 | 2015 |
| NCT01914913 | Chaitanya Hospital, Pune | India | Recruiting | Clinical Study to Evaluate Safety and Efficacy of BMMNC in Retinitis Pigmentosa | Phase 1/2 | Autologous bone marrow derived mononuclear stem cell (BMMNCs) | Retinitis pigmentosa | 15 | 2016 |
| NCT01920867 | Retina Associates of South Florida | United States | Recruiting | Stem Cell Ophthalmology Treatment Study (SCOTS) | | Autologous bone marrow-derived MSCs | Retinal disease, Macular degeneration, Hereditary retinal dystrophy, Optic nerve disease, Glaucoma | 300 | 2017 |
| NCT02280135 | Red de Terapia Celular | Spain | Recruiting | Clinical Trial of Intravitreal Injection of Autologous Bone Marrow Stem Cells in Patients With Retinitis Pigmentosa (TC/RP) | Phase 1 | Autologous bone marrow Stem Cell | Retinitis pigmentosa | 10 | 2016 |
| NCT02320812 | jCyte, Inc | United States | Recruiting | Safety of a Single, Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Retinitis Pigmentosa | Phase 1/2 | Human retinal progenitor cells (jCell) | Retinitis pigmentosa | 16 | 2016 |
| NCT02464436 | ReNeuron Limited | United States | Not yet recruiting | Safety and Tolerability of hRPC in Retinitis Pigmentosa (hRPCRP) | Phase 1/2a | Human retinal progenitor cells (hRPC) | Retinitis pigmentosa | 15 | 2017 |

(CNTO 2476; NCT01226628; http://clinicaltrials.gov/), whereas the AMDCELL study in Brazil intravitreally applied the autologous bone marrow stem cells (NCT01518127; http://clinicaltrials.gov/). There are 3 registered MSC-based clinical trials. Autologous bone marrow-derived MSCs are used in the Stem Cell Ophthalmology Treatment Study (SCOTS) in Florida (NCT01920867; http://clinicaltrials.gov/) as well as a Phase 1/2 trial in Egypt (NCT02016508; http://clinicaltrials.gov/). On the contrary, autologous adipose-derived MSCs were also adopted in intravitreal transplantation in dry AMD patients (NCT02024269; http://clinicaltrials.gov/). The only reported study is a Phase 1 trial using adult CD34+ bone marrow stem cells for ischemic and degenerative retinal disorders, including retinal vascular occlusion, hereditary or nonexudative age-related macular degeneration and retinitis pigmentosa (NCT01736059; http://clinicaltrials.gov/) [48]. In this study, 1 - 7 million of CD34+ cells were applied. No intraocular inflammation or hyperproliferation was reported. Cellular *in vivo* imaging by adaptive optics optical coherence tomography showed new cellular incorporation into the macula of the hereditary macular degeneration eye. However, this therapy may not show rescue effect on AMD patients since mild progression of geographic atrophy was observed in the study eye and the contralateral eye at 6-month follow-up, with decline on multifocal electroretinogram (ERG) and microperimetry.

For retinitis pigmentosa (RP), there are 9 registered clinical trials using stem cells (Table 4). There are 6 studies using bone marrow stem cells, 3 of which are Phase 1 study (NCT01068561, NCT01736059 and NCT02280135; http://clinicaltrials.gov/) and 2 of them have been completed (NCT01068561 and NCT01560715; http://clinicaltrials.gov/). The CD34+ cell study showed no worsening after 6 months with best-corrected visual acuity and full-field ERG [48]. The phase 1 trial in Brazil demonstrated that intravitreal injection of autologous bone marrow-derived mononuclear cells in eyes with advanced RP did not induce any detectable structural or functional toxicity over

**Table 5:** Registered stem cell-based clinical trials for corneal diseases.

| Identifier | Sponsor | Country | Status | Study | Phase of trial | Cell type | Diseases | Estimated number of patients | Estimated trial end |
|---|---|---|---|---|---|---|---|---|---|
| NCT00491959 | National Taiwan University Hospital | Taiwan | Terminated | The Application of Oral Mucosal Epithelial Cell Sheets Cultivated on Amino Membrane in Patients Suffering From Corneal Stem Cell Insufficiency or Symblepharon | Phase 1 | Cultured oral mucosa cell sheet | Limbal insufficiency, Symblepharon | 0 | 2010 |
| NCT00845117 | Ethisch Comité UZ Antwerpen | Belgium | Unknown | Cultivated Stem Cell Transplantation for the Treatment of Limbal Stem Cell Deficiency (LECT) | Phase 1/2 | Cultivated limbal stem cells | Limbal stem cell deficiency | 21 | 2014 |
| NCT01377311 | National Taiwan University Hospital | Taiwan | Terminated | The Application of Cultured Cornea Stem Cells in Patients Suffering From Corneal Stem Cell Insufficiency | Phase 1 | Autologous limbal stem cells | Limbal stem cell insufficiency | 0 | 2010 |
| NCT01489501 | CellSeed France S.A.R.L. | Germany | Withdrawn | Multicenter Study of CAOMECS Transplantation to Patients With Total Limbal Stem Cell Deficiency | Phase 3 | Cultured Autologous Oral Mucosal Epithelial Cell-Sheet (CAOMECS) | Limbal stem cell deficiency | 0 | |
| NCT01562002 | Instituto Universitario de Oftalmobiología Aplicada | Spain | Completed | Safety Study of Stem Cell Transplant to Treat Limbus Insufficiency Syndrome | Phase 1/2 | Allogeneic bone marrow-derived mesenchymal stem cells | Limbus insufficiency syndrome | 27 | 2014 |
| NCT01756365 | Centre Hospitalier Universitaire de Québec, CHU de Québec | Canada | Recruiting | Autologous Cultured Corneal Epithelium (CECA) for the Treatment of Limbal Stem Cell Deficiency | Phase 1/2 | Autologous cultured corneal epithelium (CECA) | Limbal stem cell deficiency | 15 | 2017 |
| NCT02148016 | Sun Yat-sen University | China | Recruiting | Corneal Epithelium Repair and Therapy Using Autologous Limbal Stem Cell Transplantation | Phase 1/2 | Autologous limbal stem cell | Corneal disease, Pterygium, Myopia, Hyperopia | 30 | 2014 |
| NCT02202642 | National Taiwan University Hospital | Taiwan | Recruiting | The Improvement of Limbal Epithelial Culture Technique by Using Collagenase to Isolate Limbal Stem Cells | Phase 1 | Collagenase isolated limbal stem cells | Chemical burn of cornea and conjunctival sac, Benign mucous membrane pemphigoid with ocular involvement | 10 | 2015 |
| NCT02318485 | Ethisch Comité UZ Antwerpen | Belgium | Not yet recruiting | Limbal Epithelial Stem Cell Transplantation: a Phase II Multicenter Trial (MLEC) | Phase 2 | Limbal epithelial stem cells | Limbal stem cell deficiency | 60 | 2019 |
| NCT02325843 | Sun Yat-sen University | China | Not yet recruiting | The Treatment of Human Bone Marrow Mesenchymal Stem Cells in Ocular Corneal Burn | Phase 2 | Bone marrow-derived mesenchymal stem cells | Chemical corneal burn | 100 | 2018 |
| NCT02415218 | Siriraj Hospital | Thailand | Recruiting | Transplantation of Autologous Oral Mucosal Epithelial Sheets for Limbal Stem-cell Deficiency | Phase 1/2 | Autologous Cultivated Oral Mucosal Epithelial Sheets | Limbal stem cell deficiency | 12 | 2016 |

a period of 10 months [49]. The follow-up Reticell clinical trial (NCT01560715; http://clinicaltrials.gov/) reported a statistically significant improvement in the quality of life of patients 3 months after treatment [50]. However, there was no statistically significant difference from baseline by the 12th month. Moreover, there is a Phase-1/2 open labeled study in India evaluating the safety and efficacy of autologous bone marrow derived mononuclear stem cell (BMMNCs) in RP (NCT01914913; http://clinicaltrials.gov/). For MSCs, there are only 2 registered clinical trials. The first trial aims to determine the feasibility and safety of human adult bone marrow-derived MSCs by intravitreal injection in patients with RP in Thailand (NCT01531348; http://clinicaltrials.gov/). The second one is the Stem Cell Ophthalmology Treatment Study (SCOTS) in Florida (NCT01920867; http://clinicaltrials.gov/) proposed to use autologous bone marrow-derived MSCs by different means of injection (retrobulbar, subtenon, intravitreal, intraocular, subretinal and intravenous). In addition, there are 2 Phase 1/2 trials testing the safety and tolerability of human retinal progenitor cells in RP patients (NCT02320812 and NCT02464436; http://clinicaltrials.gov/). Results from these studies have not been reported yet.

For corneal diseases, there are 11 stem cell-based clinical trials (Table 5). 9 of them are based on traditional transplantation of limbal stem cells or oral mucosal epithelial cell sheets (NCT00491959, NCT00845117, NCT01377311, NCT01489501, NCT01756365, NCT02148016, NCT02202642, NCT02318485 and NCT02415218; http://clinicaltrials.gov/). Intriguingly, there are 2 registered clinical trials using MSCs. The first Phase 1/2 trial aims to determine the safety of allogeneic bone marrow-derived MSCs to treat patients with limbus insufficiency syndrome in Spain (NCT01562002; http://clinicaltrials.gov/). Outcomes of this study have not been released yet. The second ongoing trial is a Phase 2 trial to investigate the treatment effect of bone marrow-derived MSCs on chemical corneal burn (NCT02325843; http://clinicaltrials.gov/) through subconjunctival injection.

## Potential Challenges and Future Prospects

The application of stem cell therapy in ophthalmology has been explored since the successful transplantation of limbal stem cell for ocular surface disorders [51]. The potential of stem cell therapy is greatly demonstrated by studies that generate functional RPE cells from ESCs and these ESC-derived RPE cells are engrafted in patients with Stargardt's macular dystrophy (NCT01345006; http://clinicaltrials.gov/) and AMD (NCT01344993; http://clinicaltrials.gov/) [52,53]. Pluripotent stem cells, such as ESCs and iPSCs, appear to be a desirable source for cell differentiation. However, the isolation of human ESCs from the inner cell mass of human blastocysts makes autologous transplantation impossible since the transplanted donor cells do not originate from the recipient. Additional immunosuppressive therapy is needed concurrent with the ESC transplantation [54]. Moreover, ESC-based therapy has also been hampered by the moral, legal and ethical dilemma concerning the use of human embryos for derivation of the stem cell lines [47]. Furthermore, ESCs have the potential to form teratoma in the transplant recipient. Although tumorigenic potential can be reduced by differentiating the embryonic stem cells into lineage-specific progenitor cells or mature tissue cells prior to transplantation, long-term follow-up is needed to monitor the purity and the presence of residual stem cell activity after transplantation. The discovery of iPSCs can resolve the problem of allogeneic transplantation as iPSCs can be generated from the patients' mature cells [55]. In recent years, optic cup-like structure has successfully generated from human pluripotent stem cells [56]. This synthetic optic cup undergoes spontaneously folding, and the retinal layers are progressively stratified under specific conditions [57]. In addition, functional photoreceptors can be obtained from the three-dimensional retinal tissue generated from human iPSCs, which spatiotemporally recapitulate the mammalian retinal development [58].

For the safety concerns of using iPSCs in therapy, primate and mouse studies have shown that allogenic iPSCs did not provoke any immune response that led to rejection of transplanted cells in the animals nor the transplanted cells were tumorigenic [59,60]. The potential of cell replacement therapy using iPSCs was first demonstrated in Japan in September 2014. A clinical trial was conducted to transplant the iPSC-derived RPE sheet into the sub-retinal space of a 70-year old female AMD patient (http://www.nature.com/news/japanese-woman-is-first-recipient-of-next-generation-stem-cells-1.15915). Unfortunately, this clinical trial has been put on hold recently as a potentially harmful mutation was recently found in an oncogene of the iPSCs generated from the second AMD patient in this study. It remains unclear whether the mutation was also observed in the skin fibroblasts where the iPSC was generated from. Yet, rigorous caution should be taken to assess the reprogramming process. Also, as recommended by the United States Food and Drug Administration [61], the *in vitro* manipulation of autologous stem cells should be minimized in order for a better control of good manufacturing practices and reduce variability as much as possible. Thus, the use of iPSCs in clinical practice would still be challenging.

Alternatively, adult stem cells found all over the body can be readily obtained from different accessible tissues: bone marrow, blood, adipose tissue, teeth and testes. They attractively become an autologous source for transplantation that require minimal manipulation and do not have the risk of forming teratoma. Moreover, adult stem cells are more applicable clinically for therapeutic treatments as they can maintain their differentiation capacity for cell replacement therapy and also modulate the microenvironment of diseased sites as well as the host immune system. The paracrine activities of adult stem cells have not been reported in ESCs or iPSCs.

Particularly, MSCs have been discovered for more than 20 years [62] and have been well-studied. Currently, over 500 MSC clinical trials for different diseases have been registered in the United States National Institutes of Health trial database (www.clinicaltrials.gov). Only 2% of the registered clinical trials are designed for ophthalmology. Owing to the potential of the auspicious application of MSCs, adult stem cell therapy will become a popular trend for the field of regenerative medicine in ophthalmology in the coming years. However, undeniably there are unsolved questions that must be answered. (1) Which types of adult stem cells are optimal for regenerative medicine? Transplantation of CD34+ bone marrow stem cells [48] as well as autologous bone marrow-derived mononuclear cells [50] seems not providing a great improvement in visual outcome. (2) What is the optimal cell number for transplantation? (3) Which transplantation strategy should be chosen for each individual ocular disorder? Systemic administration of MSCs could raise a potential problem of homing the MSCs. Intravenously injected MSCs can travel to multiple sites of injury for tissue repair [63], and most of the transplanted MSCs would be entrapped in the lung, which would reduce the number of MSCs available for therapy in the eye. (4) Would there be any side effects caused by stem cell transplantation? MSCs can migrate to the injured site and accelerate the development of neovascularization [64], which is not desirable for neovascular AMD patients. Fortunately, serious adverse events have never been observed although transient rash, self-limiting bacterial infections or fever might occur in some patients after MSC transplantation. Further investigation is needed to understand the mechanisms elicited by stem cells in replacing and regenerating damaged tissues after transplantation.

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