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Retinal cell transplantation in retinitis pigmentosa

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Abstract

Retinitis pigmentosa is the most common hereditary retinal disease. Dietary supplements, neuroprotective agents, cytokines, and lately, prosthetic devices, gene therapy, and optogenetics have been employed to slow down the retinal degeneration or improve light perception. Completing retinal circuitry by transplanting photoreceptors has always been an appealing idea in retinitis pigmentosa. Recent developments in stem cell technology, retinal imaging techniques, tissue engineering, and transplantation techniques have brought us closer to accomplish this goal. The eye is an ideal organ for cell transplantation due to a low number of cells required to restore vision, availability of safe surgical and imaging techniques to transplant and track the cells *in vivo,* and partial immune privilege provided by the subretinal space. Human embryonic stem cells, induced pluripotential stem cells, and especially retinal organoids provide an adequate number of cells at a desired developmental stage which may maximize integration of the graft to host retina. However, stem cells must be manufactured under strict good manufacturing practice protocols due to known tumorigenicity as well as possible genetic and epigenetic stabilities that may pose a danger to the recipient. Immune compatibility of stem cells still stands as a problem for their widespread use for retinitis pigmentosa. Transplantation of stem cells from different sources revealed that some of the transplanted cells may not integrate the host retina but slow down the retinal degeneration through paracrine mechanisms. Discovery of a similar paracrine mechanism has recently opened a new therapeutic path for reversing the cone dormancy and restoring the sight in retinitis pigmentosa.

Keywords:

Photoreceptors, retina, retinitis pigmentosa, stem cells, transplantation

Introduction

Retinitis pigmentosa is a diverse group of inherited degenerations caused by more than 3000 mutations in 80 genes which finally lead to progressive degeneration of the rod and cone photoreceptors. It affects 1 in 4000 people worldwide and is accepted as the most common hereditary retinal disease.[1] Causative mutations can disrupt phototransduction, rhodopsin cycling, and cell trafficking pathways and lead to the classical clinical appearance of bone spicule formation, attenuated retinal vasculature, and optic nerve head pallor. In the early stages of the disease, degeneration of rods manifests itself with nyctalopia and peripheral visual field loss, but, later on, loss of cones results in severe visual loss and loss of color discrimination.[2] Depending on the inheritance pattern, retinitis pigmentosa group of retinal degenerations can be classified as autosomal-dominant, autosomal recessive, X-linked, and mitochondrial retinitis pigmentosa. 5%–15% of the cases display X-linked inheritance pattern which has a worse prognosis compared to patients with autosomal recessive (50%–60%) and autosomal-dominant (30%–40%) forms of the disease.[2] Several systemic disorders may also accompany ocular findings in 20%–30% of the cases due to the expression of the mutant protein in other organs. Thirty such clinical syndromes have been described which are termed as the syndromic form of retinitis pigmentosa.[3]

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Several treatments have been employed to alter the course of retinal degeneration. Attempts to slow down the retinal degeneration using dietary supplements, such as Vitamin A,[4] docosahexaenoic acid,[5] or lutein,[6] did not reveal a clear benefit except in a subgroup of patients with high cone amplitude at baseline.[7] Several neuroprotective agents, such as human ciliary neurotrophic factor,[8] valproic acid,[9] topical unoprostone isopropyl,[10] and transcorneal electrical stimulation[11] have also been tried to slow the retinal degeneration but yield no substantial success. Oral or topical carbonic anhydrase inhibitors,[12] steroids,[13] and anti-vascular endothelial growth factor agents[14] have been used to treat cystoid macular edema which develops in 20% of the patients.[15] Epiretinal, subretinal, and suprachoroidal retinal prosthetic devices have been developed providing visual perception to patients with light perception or no light perception vision due to advanced retinitis pigmentosa. Two of these prosthetic devices such as Alpha IMS, developed by Germany-based Retina Implant AG and Argus II developed by U. S.-based Second Sight Medical Products, CA, USA, have received approval from regulatory agencies. Although these devices are associated with serious perioperative complications,[16] the visual improvement they provide improves the quality of life in this subset of patients with advanced retinitis pigmentosa.[17]

Identification of rhodopsin mutation as a cause of autosomal-dominant retinitis pigmentosa 1990[18] paved the path for the development of gene therapy to modify or manipulate the expression of mutated genes with several gene treatment techniques. These efforts recently led to the approval of an AAV vector-based RPE-65 gene delivery treatment (Voretigene neparvovec-rzyl; Luxturna™, Spark Therapeutics, PA, USA) aimed to correct the biallelic mutations of the RPE65 gene causing Leber's congenital amaurosis and some forms of retinitis pigmentosa.[19] A number of studies are in the pipeline for delivering the correct copy of the mutant genes or to perform gene editing using the CRISPR/Cas system to inactivate mutant genes.[20] Unfortunately, heterogeneity of the causative genes stands as a major obstacle for the development of an universal gene treatment that may be used for all forms of retinitis pigmentosa. Treatments that can be applied to all forms of retinitis pigmentosa are also underway, such as rewiring of the retinal circuity using optogenetics[21] or reactivation of the dormant cones by restoring glucose transport.[22]

The Rationale for Retinal Cell Transplantation

The idea of retinal cell transplantation for retinitis pigmentosa stems from the early histopathology reports which revealed relative preservation of the inner retina even in late stages of retinitis pigmentosa.[23] Lack of synaptic input and trophic factors inevitably causes transneuronal degeneration of the inner retinal neurons as photoreceptors die; however even in severe retinitis pigmentosa, 30% of the ganglion cells and approximately 80% of the inner nuclear layer neurons remain intact.[23] This fact gave rise to the idea to complete the retinal circuitry by transplanting photoreceptors into the subretinal space with the hope that grafted photoreceptor cells will integrate into the host retina by establishing synapses with the host's bipolar cells. The eye is considered an ideal organ for cell transplantation due to the low number of cells required to restore visual function.[24] Similar to the anterior chamber,[25] it also provides a partial immune privilege which may limit the rejection of the graft by downregulating delayed-type hypersensitivity response observed after transplantation of tissues to conventional sites.[26,27] Availability of established safe surgical and imaging techniques facilitates the transplantation and *in vivo* tracking of the cells.

Initial Attempts

Initial attempts of full-thickness retinal transplantation date to 1946 when differentiation of grafted embryonic retina was observed in the brain of the rats.[28] This was followed by transplantation and survival of the fetal rat retina in the anterior chamber.[29,30] First, transplantation of neonatal rat retina into the subretinal space was done in 1986 through a transscleral incision. Graft survival seemed to be better by younger donors. These promising results led to initial human full retina transplantation attempts.[31] Two patients with autosomal retinitis pigmentosa received whole sheets of fetal human retina into the subretinal space. Although no immune rejection was observed, only a transient multifocal electroretinography response was obtained in one patient. Subsequent attempts included transplantation of intact fetal human neuroretinal sheets into the subretinal space of 5 patients with retinitis pigmentosa in a Phase I study[32] followed by a Phase II study with 6 patients with retinitis pigmentosa.[33] None of the five patients enrolled in Phase I study show any visual benefit. Three patients who received the fetal retinal grafts in the Phase II trial gained mediocre visual improvements, but two patients experienced worsening of their vision after surgery. A detailed histopathology of fetal full-thickness grafts transplanted into the subretinal space of transgenic pig carrying the mutation Pro347 Leu demonstrated that the grafted cells do not form connections with the host neurons.[34] This makes it difficult to interpret the results which may also be attributed to trophic effects of the graft or simply to the impact of transplantation surgery on the remaining retinal neurons.[35]

Transplantation of photoreceptors into the subretinal space was first done in 1991.[36] A suspension of newborn rat photoreceptors labeled with tritiated thymidine was injected into the subretinal space of RCS rats. Some of the transplanted photoreceptor cell bodies were found in clusters in the outer nuclear layer region for as long as 3 months after transplantation. However, transplanted photoreceptors slowly degenerated over time and failed to develop outer segments. Subsequent studies indicated higher rates of grafted photoreceptor survival and relatively better development of outer segments if aggregates of neonatal photoreceptors were used rather than dissociated neonatal photoreceptors.[37] One major limitation for the use of retinal aggregates was identified as photoreceptor rosette formation in the host's subretinal space.[38,39] In parallel with this *in vitro* work, injection of human fetal retinal cell suspension into the subretinal space of 14 patients did not yield any functional benefit.[40]

Limitations of photoreceptor transplantation as cell suspensions or aggregates led to the techniques of transplanting intact photoreceptor sheets. Initial isolation of photoreceptor sheets with a vibratome proved to be highly traumatic to the retina and results in abnormal morphology.[41,42] Vibratome was replaced with excimer laser for atraumatic harvest of photoreceptor sheets[41] [Figure 1]. Pure adult human photoreceptor sheets harvested with excimer laser were shown to preserve >86.5% viability for 72 h *in vitro*. These cells interacted with the host retinal pigment epithelium after transplantation into rhesus monkeys as evidenced by phagocytosis of shed photoreceptor outer segments by the retinal pigment epithelium [Figure 2]. Adult human photoreceptor sheets harvested with excimer laser were then used in the first human photoreceptor sheet transplantation study.[43,44] Eight patients with advanced retinitis pigmentosa received 3.0 mm × 1.0 mm trapezoidal adult human photoreceptor sheets and followed for 12 months. No functional improvement was observed. Although patients were not put on any immunosuppressive regimen, no homograft reaction was observed.[44]

Requirements for Successful Transplantation

In animal models of retinitis pigmentosa, only a few transplanted cells establish synapses with the host bipolar cells. These cells produce outer segments and bear a resemblance to rods morphologically.[45] The main reason for the lack of functional success in photoreceptor transplantation in retinitis pigmentosa is the failure of the grafted cells to integrate the host retina and establish functional synaptic circuitry. Histopathology of the eyes with retinitis pigmentosa provides clues why grafted photoreceptors do not integrate to host retina. In eyes with advanced retinitis pigmentosa, extensive remodeling of the retina occurs with dramatic rod neurite sprouting, especially at or near the areas of photoreceptor death.[46] Rather than establishing synapses with bipolar cells, rods extend these neurites along activated Muller cells as far as to the inner limiting membrane. Neurite sprouting is also observed in amacrine and horizontal cells.[47] Rod sprouting and Muller cell activation is the result of the altered retinal homeostasis due to degenerating retina in retinitis pigmentosa. This microenvironmental shift can also affect the behavior of the grafted cells resulting in a similar neurite sprouting and bypassing the targeted bipolar cells. Rod spouting does not occur in rodent models of retinitis pigmentosa which may be the reason for the discrepancy between the relatively successful

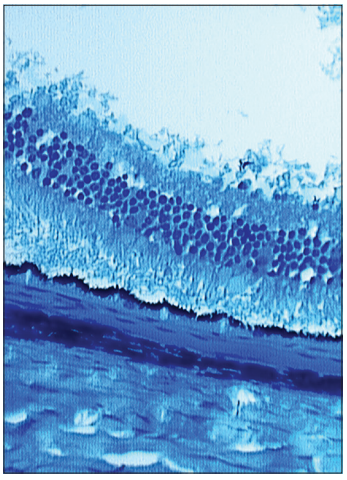

Figure 1: Adult human photoreceptor sheet harvested with excimer laser. Inner retinal neurons were removed using excimer laser. A depth guidance method allows the operator to ablate tissues down to outer plexiform layer precisely. These grafts were subsequently used for the first human photoreceptor sheet transplantation

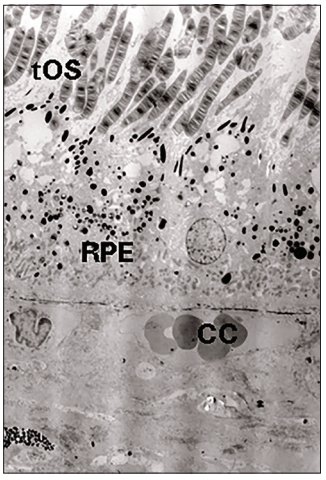

Figure 2: Transmission electron microphotograph after transplantation of adult photoreceptor sheet into rhesus monkey subretinal space. Host retinal pigment epithelial cells engulf outer segments of the (tOS) of the transplanted adult human photoreceptor cells. Patent choriocapillaris is seen below the retinal pigment epithelium

results of retinal cell transplantation in rodents compared to human trials.[46] However, experiments with animal models of outer retinal degeneration have given us some important clues about the prerequisites of synapse formation with the host retina:

1. Use of immature nonretinal neurons or other neural progenitor cells may not yield high numbers of differentiation of these cells into photoreceptors and integration to the host retina. Results indicate that most of these cells do not differentiate into mature retinal neurons[48,49]
2. Survival and integration of the transplanted photoreceptor cells is dependent on the developmental stage of the transplanted photoreceptor cells. Eloquent experiments conducted by transplanting Green Fluorescent Protein (GFP)-expressing photoreceptors under the control of the rod-specific postmitotic transcription factor *Nrl*, into *Gnat1*$^{-/-}$ murine model of stationary night blindness, indicate that highest integration could be obtained with transplantation of immature postmitotic photoreceptor precursor cells destined to differentiate into rod photoreceptors. Integration of the cells to host retina is poorer if progenitor cells or mature photoreceptors are used.[50] Decreased synapse formation and poorer viability of the mature photoreceptors[51] have caused a shift toward using cells at earlier development stages
3. The stage of the outer retinal degeneration is a key factor in determining the integration of the transplanted cells to host retina. Experiments conducted with six murine models of inherited photoreceptor degeneration indicated that integration to host retina is mainly determined on the stage of glial scarring and the integrity of the outer limiting membrane during disease progression.[52] A good example can be given by looking at the results from three different models of retinal degeneration. Integration gradually decreases in Gnat1−/−; Rho$^{-/-}$ model of where the outer limiting membrane remains intact and gliosis becomes more prominent as the disease progress. In contrast, an increase in host integration with progression of the outer retinal degeneration was observed in Prph 2$^{+/}$Δ307 model where gliosis decreases in time and outer limiting membrane integrity is not preserved. Integration rate does not change with disease progression in PDE6β$^{rd1/rd1}$ mutation where the outer limiting membrane is disrupted, but gliosis progresses with disease progression
4. Outer retinal degeneration creates an environment that prevents the ability of the cells to migrate and form synapses with the recipient's cells. Like central nervous system injury or degenerations, outer retinal cell death in retinitis pigmentosa evokes a gliotic scar formation. During this process, chondroitin sulfate proteoglycans production is dramatically upregulated by glial cells which form a glial scar. Chondroitin sulfate proteoglycans are known to limit cell migration, axonal plasticity, and regeneration.[53] Inhibition of the retinal gliosis,[54] targeted disruption of the outer limiting membrane,[55] or enzymatic digestion of the chondroitin sulfate proteoglycans[56] are shown to increase the integration of the transplanted photoreceptor cells into the host retina
5. Fluorescent markers used to identify the grafted cells may be misleading due to cytoplasmic material transfer between the grafted cells and host retina. Thus, previous reports relying on reporter expression to conclude about integration of the grafted cells to the host retina and even functional benefits after photoreceptor transplantation must be reinterpreted cautiously since both findings might simply be the result of reporter material or functional proteins transfer from donor cells to remaining host photoreceptors.[57]

Animal experiments indicated that highest synapse formation can be obtained using postmitotic rod precursor cells.[50] In human development, a comparable stage occurs during the early phases of the second trimester. Limited availability of fetal tissue and several ethical as well as legislature considerations have aroused interest in the potential to generate new photoreceptor precursors from various stem cell sources. A good source for generating photoreceptors has been the pluripotent embryonic stem cells. These cells are derived from the inner cell mass of the blastocysts and can be directed to retinal fate under conditioned media.[58,59] Human embryonic stem cells have been transplanted into the subretinal space of rodent[60] and primate[61] models of retinal degeneration. Grafted cells can differentiate into a range of retinal cell types, including rod and cone photoreceptors. Embryonic stem cell-derived photoreceptor transplantation studies confirmed the previous observations that photoreceptor precursors at earlier developmental stages integrate with the host better.[62] Transplantation of the retinal cultures earlier than 20 days of culture produced large tumors and prolonged retinal culture resulted in mature photoreceptors but no integration to the host retina.[63] The use of embryonic stem cells to generate photoreceptors also suffers from ethical and legal restrictions. Furthermore, immune-mediated rejection of embryonic stem cell-derived grafts is a concern since these cells are allogeneic to the recipient patients.[64] These difficulties were thwarted with the discovery that forced expression of four transcription factors (*Oct4, Sox 2, c-Myc*, and *Klf4*) the nuclei of differentiated somatic cells can be reprogrammed toward a pluripotent state.[65] Pluripotential stem cells generated with this method bear multipotentiality and self-renewal characteristics such as

embryonic stem cells. They are not subject to immune rejection and can be expanded *in vitro* and differentiate to all retinal cells,[66] including photoreceptors.[67] Moreover, these cells can form three-dimensional retinal organoids that can allow production of vast number of photoreceptors for transplantation and genetic engineering.[68,69] This vast source of photoreceptors can allow selection and transplantation of cones that are essential for visual acuity, color, and foveal vision. Pluripotential stem cell-derived photoreceptor cells have been purified from the rest of the cells using fluorescence-activated cell sorting and transplanted into the subretinal space of rodents. Integration of these cells to host retina has been reported[69] along with several studies revealing improved visual function after transplantation in various rodent models of retinitis pigmentosa;[63,70] however, these observations should be reinterpreted considering the possibility of cytoplasmic material transfer between the grafted photoreceptors and to recipient's retinal cells. The ability of human photoreceptor progenitors derived from both human embryonic and induced pluripotent stem cells in integrating the retina and improving the visual function was also tested in *PDEβ*$^{rd[1]/rd[1]}$ mouse which exhibits end-stage retinal degeneration.[71] This model allows a better understanding of the fate of the grafted cells in patients with retinitis pigmentosa due to the resemblance of the stage of outer retinal degeneration. Human photoreceptor progenitors transplanted into *PDEβ*$^{rd[1]/rd[1]}$ mouse differentiated into mature photoreceptors and established connections with host retinal neurons. Behavioral tests showed improved visual function after transplantation.

Trophic Effects of the Transplanted Cells

Cell transplanted into the subretinal space may exert a positive effect on the survival of the remaining retinal neurons regardless of their types and independent of their ability to synapse with the host retina. This paracrine effect was eloquently demonstrated in an outer retinal degeneration model of *Rho*$^{P[23]\ H/+}$ mice.[72] An intriguing hypothesis was put forward using the pig model of autosomal-dominant retinitis pigmentosa to explain this paracrine effect.[22] Cone photoreceptors which last longer than rods along the course of retinitis pigmentosa depend on glucose delivery from the retinal pigment epithelial cells to maintain their high metabolism and regeneration of their outer segments. In the setting of retinitis pigmentosa, glucose is not delivered to the subretinal space by retinal pigment epithelial cells resulting in starvation of the cones and subsequent loss of their outer segment and mitochondria-rich inner segments. Transplantation of rod precursors or even subretinal injection of glucose restores cone metabolism and outer segment synthesis.

Another stem cell type that can exert trophic effects is the umbilical stem cells. Umbilical stem cells can be a mixed population of hematopoietic and mesenchymal stem cells that can be harvested from the cord blood or cord tissue. Cells generated from umbilical stem cells exert a protective effect in animal models of retinal degeneration[73,74] and laser injury.[75] This trophic effect was found to be related to restoration of retinal pigment epithelium phagocytosis in Royal College of Surgeons (RCS) rats by secreting several humoral factors and bridge molecules that enhance the binding of photoreceptor outer segments to retinal pigment epithelium.[74]

Bone marrow stem cells have the potential to differentiate into various lineage cells including neural cells. Although there have been reports indicating that these cells may incorporate into host retina and express some retinal cell markers,[76,77] it is believed that most of their beneficial effect occur through paracrine mechanisms.[78,79] Another stem cell that can be harvested from the bone marrow is the CD34+ hematopoietic stem cell which is shown to exert a neuroprotective effect in eyes with retinal degeneration.[80] After intravitreal injection, these cells gather around retinal vasculature rather than the degenerating retina suggesting a paracrine effect.[78]

Intravitreal injection of bone marrow-derived mesenchymal stem cells has also been used in 14 patients with retinitis pigmentosa.[81] A short-term improvement of visual acuity returned to preoperative levels. Several adverse effects were reported, including posterior synechia, choroidal detachment, intraocular ossification, tractional retinal detachment, vitreous hemorrhage, and intraocular lens subluxation. Bone marrow-derived mesenchymal stem cells exert their effect mainly through the paracrine route. Previous studies revealed that mesenchymal stem cell secretomes possess neuroprotective properties and delay photoreceptor cell loss due to their paracrine effects.[82,83]

Adipose tissue-derived mesenchymal stem cells were also transplanted into the subretinal space of 11 patients with advanced retinitis pigmentosa.[84] Apart from one patient, no major visual benefit was observed. In contrast, one patient developed choroidal neovascularization and five patients required repeat vitrectomy and silicone oil tamponade due to epiretinal membrane formation.

Another cell type that exerts its effect through paracrine mechanisms is the neural stem cell. Once transplanted into the subretinal space of the *rd1* mice, these cells delay retinal degeneration by suppressing microglia activation.[85]

Human Trials

Human trials of retinal cell transplantation for retinitis pigmentosa are listed in Table 1. Currently, 8 of these 19 trials are still active and 6 of them are recruiting patients. Cells planned to be transplanted into patients with retinitis pigmentosa include autologous CD34+ stem cells harvested from bone marrow, human umbilical cord-derived mesenchymal stem cells, human embryonic stem cell-derived retinal pigment epithelial cells, bone marrow-derived stem cells, and human retinal progenitor cells.

Safety Issues

Generation of human embryonic or pluripotential stem cells requires strict control during the manufacturing process to ensure cellular stability, production consistency, eliminate the possibility of tumorigenicity, toxicity, and immunogenicity. For this purpose, "good manufacturing practice protocols have been put forward by Food and Drug Administration. These guidelines describe the required technological and manufacturing standards for creating and maintaining human stem cell lines for regenerative medicine use. Sight-threatening complications seen after the uncontrolled use of stem cell therapy in ophthalmology[86-88] have proved the importance of such regulatory legislature.[89,90]

Unlimited self-renewal and high differentiation potential of both human embryonic stem cells and induced pluripotential stem cells pose a danger to develop teratomas.[91] Embryonic stem cell-derived neural precursor transplants into the subretinal space of rhodopsin-knockout mice yielded teratomas in half of the donor animals 8 weeks after engraftment.[92] This necessitates the employment of screening tests to detect malignant transformation and complex morphogenesis or even organogenesis that may not occur *in vitro*. Another major safety concern is the integration of the viral gene fragments and the use of genetic transcription factors during the production of induced pluripotential stem cells. These may induce endogenous genetic and epigenetic alterations, such as insertional mutagenic lesions leading to tumor formation after transplantation.[93] Several alternative reprogramming techniques have been developed to overcome this possibility, such as nongenetic transcription factors, and nonintegrating delivery systems, such as Sendai virus.[94] Genetic and epigenetic stability should also be strictly controlled during the propagation of human stem cells since reprogramming of somatic cells can alter the integrity of the parental cell genome or conceal chromosomal instabilities.[95] Several reports revealed chromosomal aberrations and mitochondrial genome mutations after the reprogramming process.[96,97] Such alterations occasionally can result in rapid telomere shortening, increased apoptosis, severely limited growth and expansion capability, and early senescence.[98] Deletion of three genes and mutations in another three, including an oncogene, in a cell line halted a human trial of induced pluripotential stem cell-derived retinal pigment epithelium transplantation recently.

Although immune response may not be a problem with the use of induced pluripotent stem cell, a vast number of studies indicate that human embryonic stem cells can still evoke an immune response.[64] Several strategies have been developed to avoid an immune-mediated rejection of the human embryonic stem cell derived cells, including encapsulation of the cells,[99] application of somatic cell nuclear transfer to reprogram patient's somatic cells into pluripotent embryonic stem cells,[100] gene editing to abrogate the HLA surface expression,[101] and bone marrow or hematopoietic stem-cell transplantation to create hematopoietic chimerism.[102] Currently, HLA-matchmaker algorithms are employed to predict the most compatible immunogenic donor HLA types to decrease the host's immune response and increase graft survival.[103] Studies with solid organ transplantation have shown that matching in HLA-A, HLA-B, and HLA-DR groups is still required for long-term graft survival despite the employment of an immunosuppressive regimen.[104] HLA matching also shortens the duration of the immunosuppressive regimen.[105] Unfortunately, this method requires the development of large HLA-matched embryonic stem cell banks.[106] Apart from ethical and legal obstacles, establishing haplobank of human embryonic stem cells will create a challenge itself considering that HLA system is the most polymorphic locus consisting of nearly 10,000 HLA-I and-II alleles.[107] This challenge will be enormous in countries with diverse ethnic backgrounds, such as Brazil,[108] compared to ethnically more homogenous countries such as Japan[109,110] and the United Kingdom.[111]

Bioengineering Semi-Organic Constructs

Thermosensitive gelatin encasing was used in early adult human photoreceptor sheet transplantation which eased the handling and delivery of the graft into the subretinal space.[41] Use of artificial matrices to improve cell growth and synapse formation was first introduced in 2004.[112] The suggested construct was made up of Mylar membranes with an array of perforations of 3–40 μm in diameter. Retinal cells seeded in the microperforations were first cultured and then transplanted into the subretinal space of adult RCS rats. Histopathology revealed retinal tissue growth through these perforations. These early studies were followed by the development of microcylinder scaffolds which allow the vertical growth

Table 1: Human Trials of Retinal Cell Transplantation for Retinitis Pigmentosa

NCT number	Title	Status	Intervention	Phase	Sponsor	Study center
NCT04925687	Pilot study of intravitreal autologous CD34+ stem cell therapy for retinitis pigmentosa	Recruiting	Intravitreal autologous CD34+ cells	Phase 1	University of California, Davis Cures within reach	University of California Davis, Sacramento, CA, USA
NCT04763369	Investigation of therapeutic efficacy and safety of UMSCs for the management of RP	Recruiting	Injection of stem cells in suprachoroidal space of eye	Phase 2	Jinnah Burn and Reconstructive Surgery Centre, Lahore The Layton Rahmatullah Benevolent Trust Free Eye Hospital, Township, Lahore CEMB, University of the Punjab, Lahore	Stem Cell laboratory, Jinnah Burn & Reconstructive Surgery Centre, Lahore, Punjab, Pakistan
NCT03963154	Interventional study of implantation of hESC-derived RPE in patients with RP due to monogenic mutation	Recruiting	Human embryonic stem cell–derived retinal pigment epithelium	Phase 1, Phase 2	Centre d'Etude des Cellules Souches	Centre Hospitalier National d' Ophtalmologie (CHNO) des Quinze–Vingts, Paris, France
NCT03944239	Safety and efficacy of subretinal transplantation of clinical human embryonic stem cell-derived retinal pigment epithelium in treatment of retinitis pigmentosa	Recruiting	Retinal pigment epithelium transplantation	Phase 1, Phase 2	Beijing Tongren Hospital Chinese Academy of Sciences	Beijing Tongren Hospital, Capital Medical University, Beijing, Beijing, China
NCT03011541	Stem cell ophthalmology treatment Study II	Recruiting	Retrobulbar, subtenon, intravitreal, intraocular, subretinal and intravenous injection of bone marrow-derived stem cells	N/A	MD stem cells	MD Stem Cells, Westport, CT, USA MD Stem Cells, Coral Springs, FL, USA Medcare Orthopaedics & Spine Hospital, Dubai, UAE Retinal Research Institute, Phoenix, AZ, USA Massachusetts Eye and Ear Infirmary, Boston, MA, USA
NCT02464436	Safety and tolerability of hRPC in retinitis pigmentosa	Recruiting	Subretinal injection of human retinal progenitor cells	Phase 1, Phase 2	ReNeuron limited	Oregon Health and Science University, Portland, OR, USA Institut de la Màcula, Barcelona, Spain Oxford Eye Hospital, Oxford, UK
NCT02709876	Autologous bone marrow-derived CD34+, CD133+, and CD271+ stem cell transplantation for retinitis pigmentosa	Active, not recruiting	Intravitreal injection of autologous bone marrow–derived stem cells	Phase 1, Phase 2	Stem Cells Arabia	Stem Cells Arabia, Amman, Jordan
NCT04604899	Safety of repeat intravitreal injection of human retinal progenitor cells (jCell) in adult subjects with retinitis pigmentosa	Active, not recruiting	Intravitreal injection of human retinal progenitor cells	Phase 2	jCyte, Inc CIRM	Gavin Herbert Eye Inst, University of California Irvine, CA, USA Retina–Vitreous Associates, Los Angeles, CA, USA Ophthalmic Consultants of Boston, Boston, MA, USA

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Table 1: Contd...

NCT number	Title	Status	Intervention	Phase	Sponsor	Study center
NCT01920867	Stem cell ophthalmology treatment study	Enrolling by invitation	Retrobulbar, subtenon, intravitreal, intraocular, subretinal and intravenous injection of bone marrow derived stem cells	N/A	MD stem cells	MD Stem Cells, Westport, CT, USA
NCT01736059	Clinical trial of autologous Intravitreal bone‐marrow CD34+ stem cells for retinopathy	Enrolling by invitation	Intravitreal injection of autologous bone marrow stem cells	Phase 1	University of California Davis, Sacramento, CA, USA	University of California Davis, Sacramento, CA, USA
NCT01560715	Autologous bone marrow-derived stem cells transplantation for retinitis pigmentosa	Completed	Intravitreal injection of autologous bone marrow stem cells	Phase 2	University of Sao Paulo, Brazil	Centro de Pesquisa Rubens Siqueira, Sao Jose do Rio Preto, SP, Brazil
NCT01531348	Intravitreal injection of MSCs in retinitis pigmentosa	Completed	Intravitreal injection of mesenchymal stem cells of autologous bone marrow stem cells	Phase 1	Mahidol University Ministry of Health, Thailand	Siriraj Hospital Mahidol University, Bangkoknoi, Bangkok, Thailand
NCT01068561	Autologous bone marrow-derived stem cells transplantation for retinitis pigmentosa	Completed	Intravitreal injection of autologous bone marrow stem cells	Phase 1	University of Sao Paulo, Brazil	Centro de Pesquisa Rubens Siqueira, Sao Jose do Rio Preto, SP, Brazil
NCT00345917	Safety study in retinal transplantation for retinitis pigmentosa	Completed	Subretinal transplantation of ing human fetal retina and retinal pigment epithelium	Phase 2	Radtke, Norman, M.D Foundation Fighting Blindness	Retina Vitreous Resource Center, Louisville, KY, USA
NCT02320812	Safety of a single, intravitreal injection of human retinal progenitor cells (jcell) in retinitis pigmentosa	Completed	Intravitreal injection of human retinal progenitor cells	Phase 1, Phase 2	jCyte, Inc CIRM	Gavin Herbert Eye Inst, University of California Irvine, CA, USA Retina Vitreous Associates, Los Angeles, CA, USA Ophthalmic Consultants of Boston, Boston, MA, USA
NCT02280135	Clinical Trial of Intravitreal Injection of Autologous Bone Marrow Stem Cells in Patients With Retinitis Pigmentosa	Completed	Intravitreal injection of autologous bone marrow stem cells	Phase 1	Red de Terapia Celular Spanish National Health System Hospital Universitario Virgen de la Arrixaca Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia Public Health Service, Murcia Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca	Clinical Universitary Hospital Virgen de la Arrixaca, El Palmar, Murcia, Spain

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NCT number	Title	Status	Intervention	Phase	Sponsor	Study center
NCT03073733	Safety and efficacy of intravitreal injection of human retinal progenitor cells in adults with retinitis pigmentosa	Completed	Intravitreal injection of human retinal progenitor cells	Phase 2	jCyte, Inc CIRM	Gavin Herbert Eye Inst, University of California Irvine, CA, USA Retina Vitreous Associates, Los Angeles, CA, USA Ophthalmic Consultants of Boston, Boston, MA, USA
NCT01914913	Clinical study to evaluate safety and efficacy of BMMNC in retinitis pigmentosa	Unknown	Autologous bone marrow-derived mononuclear stem cell injections	Phase 1, Phase 2	Chaitanya Hospital, Pune	Chaitanya Hospital, Pune, Maharashtra, India
NCT03772938	Stem cell therapy in degenerative diseases of the retina	Unknown	Progenitor cell transplantation	Phase 1, Phase 2	Pomeranian Medical University, Szczecin	Department of Ophthalmology, Szczecin, Poland

*https://clinicaltrials.gov/; accessed on 25/9/2021. CIRM=California Institute for Regenerative Medicine, CEMB=Centre of Excellence in Molecular Biology, RP=Retinitis pigmentosa, N/A=Not available, hRPC=Human retinal progenitor cells, UMSCs=Umbilical cord-derived mesenchymal stem cells, RPE=Retinal pigment epithelium, hESC=Human embryonic stem cell, MSCs=Mesenchymal stem cells

of the cells and protect them from shear forces that may occur during the transplantation procedure.[113] Since then, several hydrogel polymer scaffolds for culture and transplantation of retinal progenitor cells have been described.[114,115] Poly (L-lactic acid)/poly (lactic-co-glycolide acid) (PLLA/PLGA), poly (methyl methacrylate) (PMMA) and poly(ε-caprolactone) (PCL) has been tried as a polymer scaffold for retinal progenitor transplantations. Ten-fold improved cell survival was observed with PLLA/PLGA, but associated fibrosis and inflammation have limited its use.[116] Nondegradable characteristics and surface modification requirements are PMMA's disadvantages.[117] PCL also carries disadvantages such as inhibition of retinal progenitor cell proliferation and differentiation toward photoreceptors.[118] Surface coating of PCL membranes with vitronectin-mimicking oligopeptides was reported to increase cell adhesion and differentiation.[118] Bioengineering methods were also employed to correctly apposition photoreceptor cells with host retina using ultrathin and biocompatible elastomer films composed of nonbiodegradable polydimethylsiloxane and biodegradable poly (glycerol-sebacate). These "wine glass" scaffold design serves to position the photoreceptors cells in a correctly polarized configuration.[119]

Conclusion

Retinal cell transplantation has covered a long way since its first introduction in 1946. This fact can be exemplified by looking at the fact that 44% (1,673/3,815/) of the scientific publications in this field have been produced within the last 10 years. Recent developments in stem cell technology, ophthalmic imaging systems, tissue engineering methods as well as our understanding of synapse formation and pathophysiology of retinitis pigmentosa provide a unique opportunity to restore the vision of patients with retinitis pigmentosa.

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Conflicts of interest

There are no conflicts of interest.

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