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Stem cells in clinical trials for treatment of retinal degeneration

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Introduction: After decades of basic science research involving the testing of regenerative strategies in animal models of retinal degenerative diseases, a number of clinical trials are now underway, with additional trials set to begin shortly. These efforts will evaluate the safety and preliminary efficacy of cell-based products in the eyes of patients with a number of retinal conditions, notably including age-related macular degeneration, retinitis pigmentosa and Stargardt’s disease.

Areas covered: This review considers the scientific work and early trials with fetal cells and tissues that set the stage for the current clinical investigatory work, as well the trials themselves, specifically those either now completed, underway or close to initiation. The cells of interest include retinal pigment epithelial cells derived from embryonic stem or induced pluripotent stem cells, undifferentiated neural or retinal progenitors or cells from the vascular/bone marrow compartment or umbilical cord tissue.

Expert opinion: Degenerative diseases of the retina represent a popular target for emerging cell-based therapeutics and initial data from early stage clinical trials suggest that short-term safety objectives can be met in at least some cases. The question of efficacy will require additional time and testing to be adequately resolved.

Keywords: age-related macular degeneration, cell-based, intravitreal, photoreceptor, progenitor, retinal pigment epithelial, retinitis pigmentosa, Stargardt, subretinal, transplantation

1. Introduction

Degenerative diseases of the CNS remain an important area of unmet medical need, particularly in developed nations with rapidly aging demographics. Diseases of this type are progressive in nature, can be hereditary or acquired and can effect any part of the CNS including the brain, spinal cord or retina. Some are common while others are rare. Examples include Alzheimer’s disease, Parkinson’s disease and Huntington’s disease in the brain, as well as age-related macular degeneration (AMD), retinitis pigmentosa (RP) and Stargardt’s disease in the retina.

A fundamental challenge presented by these disorders is the loss of neurons within a complex system incapable of spontaneous regeneration. This problem was long seen as intractable, however, a substantial body of experimental work in animals has now made significant technological inroads to the point where multiple clinical trials are either in progress or in the process of getting underway, with more following closely behind. Of these, trials directed towards retinal degenerations are particularly well represented and is the primary focus of this review.

1.1 Transplantation research

Work performed by the pioneering neuroscientist Ramón y Cajal a century or more ago resulted in his gloomy, yet essentially accurate, conclusion that the mammalian CNS is incapable of substantial levels of self-repair. On a more positive note, he also
stated that it would be up to the future generation of scientists to determine whether a workaround could be identified so as to overcome this conundrum. For several decades following his death in 1934, there was little reason to believe the situation was going to change any time soon. There was, however, a series of experiments by various authors, notably including Sperry, who showed that amphibians exhibit substantial levels of neural regeneration into adulthood, to the extent that these animals can regenerate a functional optic pathway with appropriate internal topography. Results of this type definitely demonstrated that neural regeneration was in fact possible in a vertebrate, however, a path from frogs to humans was by no means evident.

Beginning in the 1970s, work by another pioneering neuroscientist, Björklund, showed that prenatal brain tissue could survive transplantation to the rat brain for extended periods and that these grafts extended neural processes into host brain structures and reduced behavioral deficits in a model of Parkinson’s disease [1]. A succession of efforts over the past half century have capitalized on this initial breakthrough.

Tissue transplantation involving the retina was developed by Klassen and Lund as an intracranial model to study regeneration of the primary visual pathway in rodents. During doctoral studies in Lund’s laboratory, I showed that intracranial retinal grafts were capable of functional integration into the host visual system to the extent that they could elicit pupilloconstriction when exposed to light [2]. This work demonstrated the restoration of a synaptic pathway in the mammalian brain, but how to capitalize on that finding in terms of a clinically directed program was not readily apparent at the time.

Taking a more direct approach, other groups explored transplantation of retinal pigment epithelial (RPE) cells to the subretinal space as a potential treatment for AMD. The cells did not integrate into the native RPE monolayer, but survived and were associated with rescue of host photoreceptors in the Royal College of Surgeons (RCS) rat model of retinal degeneration (3,4), although it should also be noted that there was also a significant sham effect (5). Others transplanted neural retinal tissue to the eye [6]. Work in this area did have translational aspirations and clinical trials followed.

2. Early clinical studies

Based on work in animals, as described above, a number of initial clinical trials were performed, as follows.

2.1 Fetal tissue or cells

Algvere et al. focused on the RPE transplantation approach using fetal human RPE cells to the subretinal space of patients with various forms of AMD [7]. The patients were not immuno-suppressed. After 2 years of follow-up, 12 of 16 grafts were lost and this was attributed to immune rejection [8]. Interestingly, a subset of grafts survived, however, no improvements in vision were reported.

Kaplan et al. transplanted adult photoreceptor cells to the subretinal space in two patients with advanced RP without immunosuppression. There was no apparent rejection or improvements in vision [9].

Das et al. transplanted dissociated fetal retina in 14 patients with advanced RP, without immunosuppression [10]. They did not report graft rejection with follow-up ranging between 12 and 40 months. Positive visual trends were noted in 5 of 14 patients, generally of a marginal nature, but in one case from light perception to 20/200.

In a similar study, eight patients with advanced RP received allografts of dissociated fetal retina and one patient with AMD received an undissociated retinal sheet, again without systemic immunosuppression [11]. Of these, three of nine patients showed transient improvement in light sensitivity on dark-adapted threshold testing between 1 and 3 months.

Radtke et al. transplanted fetal retinal sheets to two patients with RP without signs of rejection and some transient enhancement in visual sensitivity was reported [12]. Later, they co-transplanted fetal retina together with the adjacent RPE layer in five patients with advanced RP, again without immunosuppression [13]. There was neither indication of rejection, nor improvement in vision, although a later report described sequential improvement in one patient over a 1-year time span, from 20/800 to 20/160 and a follow-on paper reported improved vision in 7 of 10 patients [14].

Taken together, these clinical studies demonstrated the technical feasibility of subretinal transplantation in humans with retinal degenerations and provided evidence that allografts of fetal retinal tissue do not typically elicit immune rejection in this location, whereas RPE grafts might be at higher risk, although perhaps not fetal RPE. Despite data suggestive of sporadic improvements in vision, the study samples were small and the authors were noted to be generally cautious in their assessments of functional outcome.
2.2 Encapsulated RPE for drug delivery
A markedly different approach to RPE transplantation was pioneered by Neoreotech (Cumberland, RI, USA), in which proprietary encapsulated cell technology was used to contain transformed human RPE cells genetically modified to overexpress a neurotrophic factor, in this case a variant of CNTF [15,16]. In this way, it was largely incidental that the donor cells were of RPE origin, the fundamental goal being secretion of the protein. The small, capsule-like device, which protected the host and cells from each other, was implanted in the vitreous cavity and anchored at the pars plana.

Phase I and II trials were conducted in patients with RP and AMD and the device appeared to be well tolerated [17]. Positive treatment effects proved difficult to document, although adaptive optics scanning laser ophthalmoscopy provided some indications of structural cone preservation in a subset of patients.

This approach served to highlight the use of intravitreal cells to provide sustained delivery of a neuroprotective factor to the retina. However, it does not appear that the company remains interested in pursuing their RP project at present. Current efforts emphasize the use of this technology to deliver anti-angiogenic agents to the retina [18].

3. Stem cells research

In parallel with the clinical studies using fetal tissues and cells, a separate but related line of work emerged suggesting an alternate approach that promised to leverage the positive aspects of the fetal work, while introducing a number of significant advantages. Here I am referring to basic science studies with stem cells, specifically as directed towards use in retinal degenerative diseases. As with the clinical studies above, this body of work can be rather conveniently divided into two major approaches, namely, the use of fetal neural progenitor cells (NPCs) versus the generation of RPE cells from pluripotent stem cells.

3.1 Transplantation of neural progenitors to the retina
The initial studies were performed in rats by Takahashi, using NPCs developed by Gage and collaborators [19]. This work showed that NPCs could survive in the vitreous as allografts and also integrate as neurons into the retina during the neonatal period in rats. The work was extended by Young et al., who showed that this could be replicated in adult rats using the RCS disease model, indicating that the presence of an ongoing disease process served as an important stimulus for the homing and integration of the progenitor cells [20].

The challenge related to this approach was that NPCs did not spontaneously differentiate into rod photoreceptors in the host retina. This may be related to fate restriction owing to the sourcing of NPCs from the brain. In fact, we overcame this challenge by deriving similar cells from the immature retina, hence retinal progenitor cells (RPCs), in mice [21] and humans [22]. These RPCs showed immune privilege as allografts and not only differentiated into rod photoreceptor-like cells, but also rescued host rods in the degenerating retina. Therefore, RPCs appeared to have clinical potential for both the rescue and replacement of photoreceptor cells. In addition to sourcing product from fetal tissue, similar strategies have utilized cells derived from pluripotent cultures [23,24].

3.2 Transplantation of stem cell-derived RPE
A very different strategy is the use of RPE cells generated from pluripotent stem cells. RPE cells are not neuronal in nature but are derived from the primitive neuroepithelium of the embryonic eye cup. This RPE-oriented approach is an extension of the basic and clinical research discussed earlier, but differs in terms of the derivation of the cells which can be generated from human embryonic stem cells (hESC) [25,26] or induced pluripotent (iPS) cells [27,28]. The cells are transplanted as a suspension [29] or an intact monolayer [30,31] with the intent of rescuing host photoreceptors or local replacement of the host RPE layer. In the latter case, transplanting the graft on a membrane or synthetic substrate is often employed. In addition to sourcing product from pluripotent sources, similar strategies have utilized cells isolated from adult RPE [32].

3.3 Cells of non-neural lineages
While much of the work in retinal repair has focused on cells of neuroectodermal origin, there are other, non-neural lineages that have also been explored. These have generally related to immature cells of the hematopoietic and vascular compartments, as represented by cell types of bone marrow and placental origin, specifically umbilical tissue-derived stem cells (UTSCs), mesenchymal stem cells and hematopoietic (CD34+) stem cells, for example, as explored by Janssen/Centocor (Horsham, PA, USA) [33], Friedlander (La Jolla, CA, USA) [34] and Park (Sacramento, CA, USA) [35], respectively.


At this time, a number of trials with stem cell-based products of neural lineage have been initiated in AMD, Stargardt’s disease and RP (Table 1).

4.1 Allogeneic embryonic stem cell-derived RPE
The first US FDA-approved test of an hESC product in the eye was initiated in 2011 by Advanced Cell Technology, now known as Ocata (Marlborough, MA, USA) Therapeutics. In closely related Phase I/II trials, hESC-derived RPE cells were injected to the subretinal space of patients with either Stargardt’s disease [36] or the atrophic form of AMD [37]. The studies included a dose-escalation protocol. At this time, both trials are ongoing but no longer recruiting patients. Reports to date have been consistent with a lack of...
major adverse events. Although assessment of safety is the primary objective of the study, a degree of improvement in visual improvement was reported in two patients [38]. A similar trial with the identical cell product was launched in South Korea by CHABiotech (Seoul, South Korea). In addition, Ocata has revealed plans to initiate a trial with the RPE product in patients with myopic macular degeneration [39].

4.2 Autologous iPS cell-derived RPE
The RIKEN (Kobe, Japan)-based effort in Japan lead by Takahashi utilizes iPS cells to generate RPE cells for use in exudative AMD [41]. The initial patient was enrolled in September 2014, following regulatory approval by the Ministry of Health, Labour and Welfare and represents the first use of the radically innovative iPS technology developed by Yamanaka in a clinical setting. The cells were transplanted to the subretinal space as a 1.3 x 3.0 mm sheet, without surgical complications [42].

4.3 Allogeneic neural stem cells
The company StemCells, Inc. (Newark, CA, USA) is testing their human fetal-derived neural stem cells in patients with the atrophic (dry) form of AMD [43]. The cells are delivered as a cell suspension to the subretinal space. The study was initiated in June 2012 at the Retina Foundation of the Southwest [44]. The company recently provided an update that reported favorable safety results to date, as well as possible indications of delayed disease progression and improved contrast sensitivity, while avoiding premature conclusions at this stage [45]. As this review was being written, the company announced treatment of the first patient in their new Phase II trial [46,47].

4.4 Allogeneic RPCs
The first FDA-approved trial with RPCs was initiated by our own team in June 2015, combining the efforts of my laboratory at the University of California, Irvine (UCI) and the startup company jCyte (Newport Beach, CA, USA), together with support from the California Institute of Regenerative Medicine (CIRM). The fetal tissue-derived cells are injected into the vitreous cavity of patients with RP as a cell suspension. Clinical sites for this Phase I/IIa trial include the Gavin Herbert Eye Institute at UCI and Retina-Vitreous Associates Medical Group in Los Angeles [48].

5. Trials with cells of non-neuroectodermal origin
At this time, a number of trials with stem cells of non-neural lineage have been initiated in AMD, Stargardt’s disease, RP as well as at least one patient with retinal vascular occlusion.

5.1 Umbilical tissue-derived cells
A Phase I study sponsored by Centocor was initiated in 2007 in which the proprietary UTSC-based biological agent CNTO 2476 was delivered to the subretinal space of patients
with advanced RP [49]. That study was followed by a Phase I- IIa dose-escalation study sponsored by Janssen in 2010 using the same product in patients with AMD. The latter trial is ongoing but not actively recruiting at this time [50].

5.2 Bone marrow-derived cells
Siqueira initiated a Phase I trial in 2009 at the University of Sao Paulo, using autologous bone marrow-derived stem cells in patients with advanced RP. Cells were given as an intravitreal injection. This study met the proposed safety criteria [51] and a beneficial effect on RP-associated macular edema was reported [52]. Based on these initial findings, a Phase II study was also conducted. Improved quality of life was reported from a sample of 20 patients, although the effect was transitory and no longer evident at 1 year post-treatment [53].

A related approach has been pursued at the University of California, Davis. The project, led by Park, is based on the use of autologous CD34+ bone marrow stem cells, which are injected into the vitreous cavity of patients with a range of retinal diseases, including non-exudative (dry) AMD, Stargardt’s disease and RP, as well as retinal vascular occlusions which are non-degenerative in nature [54]. Preliminary clinical findings from the Phase I patients enrolled between November 2012 and August 2014 have been published and include 6 patients with 6 months follow-up [55]. The autologous cell product appeared to be well tolerated after intravitreal injection. The recorded visual acuity in the treated eyes did not deteriorate and appeared to show evidence of improvement over baseline (0–11 lines, mean = 3, ETDRS), in some cases transiently, in this small open-label study. The study continues to recruit patients at this time.

Additional bone marrow stem cell trials for RP in Spain (Red de Terapia Celular, Murcia), Thailand (Mahidol University) and India (Chaitanya Hospital, Pune), as well as for dry AMD in Saudi Arabia (Al-Azhar University) have been registered online at www.clinicaltrials.gov (for additional details, see Table 1).

6. Imminent trials
In addition to those trials underway, a number of related projects have received regulatory approval for clinical trials, and are anticipated to begin in the very near future. These include the London Project (London, UK) to Cure Blindness [56], which proposes to test hESC-derived RPE cells in AMD associated with underlying RPE tears. Also, the CIRM-supported California Project to Cure Blindness, in association with the startup Regenerative Patch Technologies (University of Southern California, Los Angeles, CA; the University of California, Santa Barbara, Goleta, CA; and the City of Hope Medical Center, Duarte, CA), again using hESC-derived RPE cells, but in dry AMD [57]. Both efforts include sheets of RPE on a synthetic polymer scaffold for support of the grafts. In addition, the company ReNeuron (Guildford, Surrey, UK) has obtained FDA permission to initiate a trial with RPCs in RP using a subretinal approach and plans to initiate clinical testing later this year [58].

7. Conclusion

We now stand at what may, in retrospect, be seen as a historic inflection point in the progress towards effective regenerative clinical treatments for neurodegenerative diseases. At least that would be the optimistic view, which I subscribe to, being actively engaged in one of the clinical trials discussed. Only time will tell if the cell products now being tested can reliably demonstrate clinically significant levels of efficacy in the relevant patient populations. Indeed, safety remains an unresolved issue as well, although there is reason to be cautiously optimistic in that regard. The very worst fears of rampant, uncontrolled proliferation do not appear to have been realized within the existing FDA-approved trials, as far as I can discern at this time. The rigorous standards for preclinical toxicological testing mandated by the Agency may well have provided an effective screen against poorly considered efforts using potentially dangerous cell-based products.

8. Expert opinion
I have long championed the retina as a favorable site for regenerative approaches in the CNS and the disproportionate number of stem cell trials targeting retinal degenerations would seem to validate that concept. The accessibility of the retina relative to the brain and spinal cord, the relative simplicity of the clinical objectives and overall health of the patients, together with the fact that the eye is a paired structure, all provide significant advantages for ophthalmological over neurosurgical approaches in this particular context.

Among the various cell-based treatment strategies for the retina being explored, I would again highlight simplicity as an advantageous feature, particularly at this early stage of clinical experimentation. In this way, the use of neural or RPCs is arguably simpler than pluripotent cells in that their derivation is relatively straightforward and a separate differentiation step is not required as part of the manufacturing process. Similarly, neuroprotection would appear to be a more readily attainable goal than cell replacement and intravitreal injection is clearly preferable over subretinal surgery, at least from a safety standpoint. In this way, targeting RP as opposed to AMD makes sense in that the preservation of host photoreceptors, particularly cones, should be obtainable by way of intravitreal product placement, whereas replacement of the RPE monolayer requires subretinal surgery involving temporary focal detachment of the overlying retina. In addition, our particular RPC-based approach avoids the need for immunosuppressive drugs.

Each of the projects discussed above can be evaluated in terms of these same parameters and when viewed from this particular perspective, our preference for our own strategy should be evident. Nevertheless, at the end of the day what really matters will be visual results. Simplicity and safety
may help ward off adverse outcomes, but cannot be counted upon to confer a positive effect. In that regard, each approach will ultimately stand on its own merits.

Yet I think it is important to point out that even if safety alone is demonstrated within the context of the current trials, that in itself would represent an important milestone for the field of regenerative medicine in general and provide helpful de-risking for stem cell-based retinal therapeutics in particular. It would also serve as a solid jumping off point for a next generation of would-be therapeutics that might, for instance, be specifically tailored to ramp up efficacy to optimal levels. That said, it would be premature to discount the possibility that additional indications of efficacy may emerge from this current batch of projects, particularly considering the painstaking effort that has gone into their development. For now, however, that lies in the future and we must wait to see what comes of it, although we will not have to wait too long.

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Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

★★ This highly influential work showed that by using developmentally immature tissue it was possible to introduce new neurons to existing CNS structures in a mammal.


★★ These studies initiated the field of RPE transplantation.

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Declaration of interest

H Klassen receives ongoing support from the California Institute of Regenerative Medicine (CIRM) and the Polly and Michael Smith Foundation. H Kassen has Intellectual Property related to his co-founding of the startup company, jCyte. The sponsors had no role in manuscript preparation. The author has intellectual property as well as an equity interest in jCyte, Inc., a company that may potentially benefit from the type of results described. He also serves on the company’s Board. The terms of this arrangement have been reviewed and approved by the University of California, Irvine in accordance with its conflict of interest policies. The author consulted for ReNeuron and StemCells, Inc. in the past. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.
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• Stimulated the field of neural progenitor transplantation in the eye.


• These studies informed the field of RPC transplantation.


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23. Lamba DA, Karl MO, Ware CB, Reh TA. Efficient generation of retinal progenitor cells from human embryonic stem cells. Proc Natl Acad Sci USA 2006;103(34):12769-74


• These studies informed the field of RPC transplantation.


43. ClinicalTrials.gov A service of the National Institutes of Health. Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Age-Related...
Macular Degeneration (AMD).


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