Stem Cell Treatment for Age-Related Macular Degeneration: the Challenges

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Submitted: March 24, 2018
Accepted: June 11, 2018
Citation: Singh MS, MacLaren RE. Stem cell treatment for age-related macular degeneration: the challenges. Invest Ophthalmol Vis Sci. 2018;59:AMD78–AMD82. https://doi.org/10.1167/iovs.18-24426

Keywords: regeneration, age-related macular degeneration, retinal degeneration, stem cells

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dge-related macular degeneration (AMD) became a lead disease in the arena of regenerative medicine in 2012, when the short-term results were published of two patients who underwent subretinal transplantation of human embryonic stem cell (ESC)-derived retinal pigment epithelium (RPE) cells. It was the first description of a pluripotent stem cell derivative transplanted into any human being; follow-up data showed the safety of the intervention. In a separate effort, autologous induced pluripotent stem cell (iPSC)-derived RPE cells were safely transplanted into an AMD patient without systemic immunosuppression. The safety of this procedure was documented at 1 year, demonstrating the potential of using self-derived cells from an aged patient as source material for AMD treatment. More recently, two patients with severe exudative AMD were reported to have experienced improved vision through 12 months after each received a subretinal transplant of an ESC-derived RPE monolayer on a coated synthetic basement membrane. Encouraging safety and potential efficacy data from these clinical trials have fueled optimism amongst physicians, patients, and commercial partners. Perhaps it is timely to discuss the extent to which the promise of stem cell treatment for AMD will be fulfilled—how close are we, actually? Is this truly the panacea to restore vision, in patients who could otherwise face a grim visual prognosis from conditions such as fovea-involving RPE rips, following treatment with anti-VEGF agents. In the former circumstance, RPE rips may occur when serous fluid progressively accumulates beneath the RPE basement membrane and stretches it up to and beyond its elastic limit. It tears, separates from overlying photoreceptor cells, and rolls up under the influence of intrinsic elastic forces. Currently, there are no treatments available to reverse this change in RPE configuration and so the degeneration of these now “exposed” photoreceptor cells is, for all practical purposes, almost inevitable. The therapeutic goal in this circumstance is to expeditiously restore a monolayer of healthy RPE cells into the rip site in order to prevent or ameliorate photoreceptor degeneration. Whist clinical trials assessing stem cell treatments in standard exudative AMD can no longer be justified ethically without concomitant administration of anti-VEGF agents, the RPE rip scenario perhaps provides the ideal scenario for RPE replacement using stem cells as a mechanism of preventing photoreceptor loss.

A clinical trial sponsored by Pfizer and conducted in collaboration with University College, London (clinicaltrials.gov identifier: NCT01691261), included patients with a diagnosis of exudative AMD plus rapid recent vision decline. Patients with RPE rips involving the fovea qualified for inclusion—however, early results are available for only two patients who had large subretinal and sub-RPE hemorrhages secondary to AMD that involved the fovea. The intervention was the subretinal transplantation of PF-05206388, which is a monolayer of human ESC-derived RPE cells immobilized on a polyester membrane (animal data suggest that RPE cell delivered as a preformed monolayer survive better than cell suspensions) under long-term local immunosuppression with an intraocular steroid implant. Interestingly, the authors did not intentionally remove the offending choroidal neovascular membrane, so recurrence is a possibility. The lack of a control—other than data from the Submacular Surgery Trials, in which no patient achieved the levels of vision improvement that were reported in this stem cell study—makes it somewhat challenging to conclusively attribute the visual gains to the transplanted stem cells. Nevertheless, this is a promising strategy to rapidly restore the RPE layer in an attempt to preserve or improve vision, in patients who could otherwise face a grim visual prognosis from conditions such as fovea-involving RPE rips,
large submacular hemorrhages, or exudative AMD that is unresponsive to anti-VEGF treatment. Scientifically, the trial supports the hypothesis that ES cell derived RPE can support photoreceptor function over time when orientated as a monolayer; although—as with all RPE transplantation trials—only postmortem histological data will confirm the precise identity of the pigmented cells that are presumed to be mature RPE cells of donor origin.

In principle, good prognosis for vision can be expected if treatment is instituted before significant photoreceptor cell degeneration takes place. There are however no clear animal or human data on how quickly photoreceptors degenerate in vivo and escape the rescue window following acute RPE removal or exposure to blood components. For the development of an effective stem cell treatment for acute exudative AMD with rapid visual decline, it will be critical to define the time window for treatment with empirical data. Issues such as patient access to rapid clinical evaluation and logistical organization for the timely supply and administration of the stem cell product will come to the fore.

RPE rips are an attractive therapeutic target for stem cell therapy because there is a focal loss of one cell type. In contrast, RPE atrophy in late nonexudative AMD is a more complex therapeutic target wherein multifaceted degenerative changes accumulate chronically and diffusely, being well-demarcated in some areas but not all, leading to progressively enlarging zones of photoreceptor cell degeneration (interestingly, human histological data challenge this view: specimens show areas of preserved RPE and Bruch’s membrane with clear photoreceptor degeneration). GA has been estimated to occur in approximately 50% of patients with late AMD and has been identified as a stem cell treatment target with the principle that replacement of new stem cell derived RPE into the area of GA might promote the protection and/or revitalization of photoreceptor cells—for example, by reforming elongated photoreceptor outer segments or by other mechanisms—that are in proximity to the graft. Photoreceptor cell bodies remaining at the center of a GA lesion are probably more compromised than their counterparts at or just beyond the GA border, which is the annulus of periscleral retina and RPE called the transition zone. RPE transplantation is best targeted to the transition zone, rather than to lesion centers, in order to give those photoreceptors the best chance at recovering. Buying time at the healthiest part of the transition zone in this way could, in principle, facilitate the maintenance of an eccentric preferred retinal locus that could provide reasonable vision for the patient. Adaptive optics, or some other advanced single cell imaging method that can visualize photoreceptor cell bodies and/or nuclei that are out of alignment, will be helpful to select specific transplantation target zones. These sections of the transition zone annulus that have the greatest density of resuable photoreceptor cells. Definitive methods to assay transition zone photoreceptors have not yet been described.

Will stem cell transplantation modify the rate of underlying GA progression? Native RPE cells could continue unabated degeneration under the influence of recipient-specific risk factors, or perhaps local neurotrophic factors from the transplanted cells will modify GA progression. Are there specific lesions that will benefit the most? We do not yet know the lesion characteristics—GA size, location, and progression—by which to select patients for whom the risk-benefit balance of retinal stem cell surgery will be acceptable. To date, there is no consensus definition of the minimum lesion size for GA diagnosis; definitions have ranged from 175 to 453 μm. Nor is there a clear association between GA lesion size and visual acuity; partly because GA can involve or spare the fovea. Submacular transplantation entails risk: with current techniques, this procedure involves a complete vitrectomy and relatively large retinotomy, which are certainly not risk free maneuvers. An additional risk to consider is the retrograde escape of transplanted cells, though the retinotomy, that could divide or transform on the epiretinal surface. So far, pigmented preretal growths have proved innocuous in the context of one clinical trial but may pose a risk of epiretinal membrane formation if more cells escape out of the subretinal space. Aggressive epiretinal membranes and/or proliferative vitreoretinopathy causing severe vision loss are not just a theoretical risk—they have been reported to occur following autologous intraocular cell delivery in several unregulated interventions. Cell delivery via the supraciliary route is one way to reduce the escape of cells into the vitreous cavity.

Aside from challenges associated with defining the ideal recipient as explored above, several gaps exist in relation to envisioning the ideal treatment substrate. Isolated RPE transplantation is one piece of the much larger conundrum of how to solve the GA problem through cell replacement therapy. GA is the combination of chronic deficiencies in neuronal cells (photoreceptors), epithelial cells (RPE), vascular cells (the choroid), and noncellular elements (Bruch’s membrane), and so the ideal treatment substrate would replace or regenerate all of these elements. Of the case of synthetic Bruch’s membrane replacements that are in current development for clinical trial application are one step in this direction, but to date no composite grafts containing all these elements have been reported. Available evidence from elegant studies indicates that RPE cells placed directly on aged Bruch’s membrane do not do well, so there is legitimate concern regarding the long-term viability and stability of RPE cells transplanted directly into AMD patients without augmentation or modification of the native Bruch’s membrane. We will probably learn more about the influence of Bruch’s membrane status, and other age-related factors, by comparing the long-term outcomes in young and old transplant recipients; for example, the Stargardt macular dystrophy versus AMD recipients of subretinal MA09-hRPE cell suspension transplantation. Indeed the recent trials with the RPE scaffold may help answer the question as to whether or not a synthetic alternative might support a transplanted RPE cell monolayer.

Putting aside the significant challenges for replacement of the underlying RPE and Bruch’s membrane, a further challenge will be to reconstruct the overlying photoreceptor mosaic, particularly in the foveal region if restoring normal visual acuity is the objective. Rod photoreceptor transplantation is relatively well studied in preclinical models—it is known that transplanted rod photoreceptors can preserve or restore vision in the diseased recipient, especially when transplanted within a defined period of donor cell maturity, although the exact cellular basis of those functional effects are now being re-evaluated in the light of evidence of a newly discovered pattern of interaction between donor and recipient cells—interphotoreceptor cytoplasmic materials transfer—as distinct from the actual integration of transplanted photoreceptor cell soma. Various protocols have been described through which rod photoreceptor cells can be efficiently generated from pluripotent stem cell sources; however, it appears to be more challenging to consistently generate high numbers of cone photoreceptors from stem cells in vitro, although encouraging data are emerging on how to increase the fraction of cone photoreceptor cells generated in culture. In principle, the ideal stem cell derived graft for AMD should be all-cone or...
mostly-cone, to recapitulate the macular rod-cone photoreceptor mosaic in the physiological proportion.

Synaptogenesis remains a great unknown frontier. Transplanting new photoreceptors into the submacular space may place them in the ideal position and polarity on a macroscopic level giving the appearance of outer retinal reconstruction, but the transplanted photoreceptor cells would be functionally isolated without the formation of new synapses between them and the appropriate target neurons.\(^7\) Based on detailed immunohistological evaluation in small and large animal models, it is apparent that transplanted photoreceptor cells express presynaptic proteins.\(^5,11,34\)\(^6,\)\(^8,\)\(^9,\)\(^10\) However, there is a relative lack of data on the efficiency of synaptogenesis and on methods to increase its efficiency or ensure optimal downstream partner-finding.

In this decade, tremendous progress has been made in retinal stem cell transplantation for AMD. Pluripotent stem cell derived RPE cells have been transplanted into numerous patients in several clinical trials—not just a major advance for ophthalmology, but for all of medicine—while significant advances in surgical delivery and Bruch’s membrane augmentation hold great promise for the field. We are probably closer to having a stem cell based treatment to stabilize the disease course in acute exudative AMD, because the photoreceptor layer remains largely intact and only RPE cells with Bruch’s membrane need to be replaced. For GA though, we are a very long way off, because chronic RPE loss will lead additionally to secondary loss of overlying photoreceptors and for AMD this is primarily in the fovea. Reconstructing the fovea to improve visual acuity, whilst at the same time replacing underlying RPE cells and reconstructing Bruch’s membrane and the choriocapillaris presents a gargantuan challenge for stem cell researchers. One might argue that whole eye transplantation provides a more achievable goal.

**Acknowledgments**

Disclosure: M.S. Singh, None; R.E. MacLaren, Oxistem (F)

**References**


