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# Stem cell clinical trials: toward cell-based therapy for retinal degenerations

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"...the next several years will mark a critical inflection point in the so-far frustrating history of treating blindness due to the scourge of retinal degeneration."

Stem cell-based therapeutic strategies are central to the emerging field of regenerative medicine. The past two decades have seen many spectacular results in animal models and at this juncture the clinical translation of much of this work is in progress. It should be evident that the technical and regulatory challenges facing the development of novel cell-based therapeutics are not insignificant, yet a number of early milestones have already been achieved. While it is too soon to predict the eventual outcome of these efforts, early indications could be characterized as cautiously optimistic. Certainly, hopes have been raised that something efficacious will emerge within the next several years. In particular, diseases of the CNS represent an area of vast unmet medical need, particularly in light of aging demographics in much of the world. It is therefore not surprising that strategies aimed at the treatment of CNS conditions have received much of the attention. Of these, retinal degenerative diseases have proven to be disproportionately popular among potential disease targets. Currently, there are clinical trials underway in which a range of different stem cell types are being transplanted to the diseased retina of patients with a variety of retinal disease phenotypes, including the atrophic form of age-related macular degeneration (AMD), as well as a number of other degenerative retinal conditions.

## Advantages to targeting retinal disease

The high level of interest in retinal degenerative diseases as therapeutic targets can be attributed to the convergence of a number of factors, including unmet clinical need, relative near-term feasibility and the inspiration provided by the commercial success of the antibody-based biologics Lucentis® (ranibizumab) and Avastin® (bevacizumab), both developed by Genentech (CA, USA) and now routinely used to treat the neovascular variant of AMD [1]. Relative feasibility includes consideration of a number of factors such as the accessibility of the retina compared with the brain or other internal organs, both in terms of surgical access and ease of clinical evaluation. The retina also exhibits a greater simplicity of anatomical organization compared with many other CNS tissues and, furthermore, is generally tolerant of cell or tissue grafts from unrelated donors. Importantly, intervention in just one eye presents a limited risk to the patient. In addition, many hereditary retinal conditions are designated as orphan diseases and as such confer helpful regulatory advantages.

## Retinal degenerative diseases

In terms of clinical familiarity, the major disease entity among the retinal degenerations is AMD [2]. Being a disease associated with the elderly, the prevalence of this

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condition is increasing rapidly as the population ages, to the extent that the situation has been likened to a looming 'epidemic' [101]. The pathology associated with AMD is first clinically evident at the level of Bruch's membrane, an extracellular structure that lies between the retinal pigment epithelium (RPE) and the blood supply provided by the choriocapillaris. Progression of the pathology leads to loss of both the RPE and choriocapillaris and, eventually, the overlying photoreceptors. This results in permanent visual defects, although these tend to be restricted to central vision, with the periphery spared. As noted above, antibody-based biologics directed towards neutralization of the angiogenic factor VEGF have shown efficacy in treating the neovascular complications of AMD. However, there are as yet no therapeutics that directly address the resulting blindness due to photoreceptor loss.

Considerably less common, but often more severe, are the retinal dystrophies. These comprise a diverse group of inherited pathologies also affecting the outer retina. Of these, retinitis pigmentosa (RP) is the most common. This condition can result from well over 100 specific mutations in over 40 different genes [3]. Most of these genes are specific to photoreceptor cells, although others are related to cilia, or to mitochondrial function. In RP, the rod photoreceptors degenerate first, followed by cones, with constriction of blood vessels as well as the aberrant migration of RPE cells, which gives this condition its name. RP begins in the peripheral retina but as cones are lost, central vision is eventually impaired as well. The condition is progressive and associated with severe visual disability. Another retinal dystrophy is Stargardt's Disease. Compared with RP, this condition is less severe overall, yet tends to impact central vision earlier in the course of the disease.

The diseases mentioned above are currently targeted by various stem cell programs. There are many other such conditions and presumably these will be addressed as clinical efforts progress.

## Successes with biologics

Clinical success of the antibody-based anti-VEGF therapeutics in AMD has been described above. These same agents can be used for other retinal indications, including macular edema, and alternate protein-based agents targeting the VEGF signaling pathway have also been developed [4]. Of considerable note has been the successful use of the gene-replacement approach in Leber congenital amaurosis caused by mutations in the *RPE65* gene [5].

## Trials for encapsulated cell therapeutics

The scientists at Neurotech (RI, USA) have pioneered a cell-based approach to retinal degenerative diseases using their encapsulated cell technology. Immortalized RPE cells are transduced to overexpress the growth factor CNTF and then encapsulated within a porous capsule that is positioned in the vitreous and suspended from the pars plana such that it does not make direct contact with the retina and can be removed if desired. Clinical trials have shown initial safety and demonstrated that CNTF can be chronically administered using this method [6,7]. Adaptive optics scanning laser ophthalmoscopy provides a new and helpful method of evaluating anatomical results in the living retina, down to the level of individual cones, and could prove helpful in evaluating treatment effects [8]. The Neurotech implant uses transduced cells as a safe method of growth factor delivery; however, other strategies now employ cell transplantation directly to the eye.

## Stem cell trials for the retina

Following preclinical research on human umbilical tissue-derived cells [9], a Phase I study sponsored by Centocor was initiated in 2007 in which a single, unilateral dose of the biological agent CNTO 2476 was delivered to the subretinal space of patients with advanced RP. A new open label safety study with CNTO 2476 in AMD, sponsored by Janssen Research & Development (PA, USA), is currently recruiting participants [102].

In 2009, Siqueira *et al.* of the University of Sao Paulo (Sao Paulo, Brazil) initiated a trial with autologous bone marrow-derived stem cells, also in advanced RP. Cells were given as a single intravitreal injection [10]. This study met the proposed safety criteria and a beneficial effect on RP-associated macular edema was reported [11]. Based on these initial findings, a Phase II study has been initiated.

The first test in the eye of a human embryonic stem cell product was initiated in 2011 by Advanced Cell Technology (CA, USA). In this pair of related trials, hESC-derived RPE cells are injected into the subretinal space of patients with either Stargardt's Disease, a genetic maculopthy, or the atrophic form of AMD. At this time, the trials continue to enroll patients as part of a dose-escalation protocol, consistent with a lack of major adverse events. In addition, improved visual performance has been reported in a small number of patients [12].

Earlier this year, Stem Cells, Inc. (CA, USA) began enrolling patients in a trial using their human fetal-derived neural stem cells in patients with the atrophic form on AMD [13]. In this case, cells are also delivered as a single uniocular subretinal injection.

Another stem cell trial that is now recruiting is led by Park *et al.* at the University of California, Davis (CA, USA). In this Phase I study, autologous $CD34^+$ bone marrow stem cells are injected into the vitreous cavity of

patients with a range of retinal diseases, including atrophic AMD, diabetic retinopathy, retinal vein occlusion or RP [14].

## Looking ahead

While it remains premature to speculate as to what the eventual outcome of the above trials will be, it is clear that a concerted and multilateral effort to bring various different types of stem cells into clinical testing for retinal degenerative diseases is well underway. In fact, another wave of clinical efforts are anticipated in the near future, including the London Project (London, UK), which proposes to test hESC-derived RPE cells in AMD, and the RIKEN (Kobe, Japan) effort, which will utilize the Nobel Prize winning induced pluripotent stem cell technology of Yamanaka *et al.* [15] to generate RPE cells. In addition, the California Institute of Regenerative Medicine (CA, USA) currently has two disease teams aimed at retinal degenerative diseases (atrophic AMD and RP) and both are currently in preclinical development. When all these efforts are considered together, it is therefore conceivable that the next several years will mark a critical inflection point in the so-far frustrating history of treating blindness due to the scourge of retinal degeneration.

## Financial & competing interests disclosure

*H Klassen has intellectual property as well as an equity interest in jCyte, Inc., a company that may potentially benefit from the type of results described. Klassen also serves on the company's board. The terms of this arrangement have been reviewed and approved by the University of California, Irvine (CA, USA) in accordance with its conflict of interest policies. 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 apart from those disclosed.*

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