HP Groups

Stem Cell Biology, Research & Therapy

Mini Review

Update on clinical trials with stem cells in the retina

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The retina has clearly emerged as a popular therapeutic target in regenerative medicine, owing to a number of factors including relative accessibility and unmet medical need. Research in the area has been active since the late 1990's and more recently a number of projects have progressed to clinical testing. I recently reviewed cell-based clinical activities in the retina in some detail [1]; however, the situation has already progressed to the point that an update is warranted.

To recap briefly, of the potential disease targets, Age-related Macular Degeneration (AMD) and hereditary photoreceptor degenerations such as Retinitis Pigmentosa (RP) and Stargardt's Disease have received the most attention, while in terms of cell types, the candidates can be roughly split into Central Nervous System (CNS) versus non-CNS cell types. Of the former, pluripotent stem cell-derived Retinal Pigment Epithelial (RPE) cells are popular, as are multipotent neural progenitors. The non-CNS cell types tend to be mesenchymal and hematopoietic. As previously, I will consider projects within the framework of the cell type being tested and discuss them in the approximate order in which clinical studies where initiated.

CNS cell types

ACT/Ocata was the first to test an Embryonic Stem (ES) cell-derived RPE product in clinical trials, with dry AMD and Stargardt's Disease as targets and a related trial with the same product was conducted by CHA Biotech in South Korea. Early phase trials are fully enrolled and a 4 year follow up of 18 patients was recently published [2]. In terms of safety, adverse events were attributed to the surgical procedure or use of immunosuppression. There was one case of endophthalmitis (*Staph. epi.*) and one case of vitreous inflammation, and 4 eyes developed worsening cataracts that required surgery, however, there was no evidence of tumorigenicity nor was there evidence of epiretinal membrane formation, despite the observation of what I interpret as refluxed donor cells in the vitreous near the retinotomy in 3 cases. Visual outcome was reported for the 10 patients with 1 year follow up (7 with AMD, 3 with Stargardt's). Of these, the authors report that half the patients showed improvements in acuity in the treated eye. A follow-on Phase 2b trial is currently recruiting.

An early phase trial with the same product is enrolling for treatment of myopic degeneration. Notably, the Massachusetts-based Ocata was recently acquired by Astellas, a major pharmaceutical company in Japan [3]. It will be interesting to see if this impacts the pace or direction of the existing clinical effort.

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Stem Cells Inc. has used brain-derived neural stem progenitors, also for treatment of dry AMD. Their phase 1/2a trial was completed and Phase 2b (RADIANT) initiated. Despite reports of improvement in some outcome measures, particularly contrast sensitivity in the earlier trial, the company announced in December, 2015 that it would suspend the RADIANT trial for economic reasons, while focusing resources on treatment of spinal cord injury [4].

In Japan, the RIKEN-based effort, in partnership with the startup Healios, and using iPS cell-derived RPE in AMD, dosed its first patient in 2014, however, enrollment of the second patient was put on hold due to concerns over mutations identified in the autologous iPS-derived cell product [5]. To clarify, it is my understanding that this reflected an abundance of caution and it was not evident that the product actually posed a clinical hazard (Jeanne Loring, personal communication). To avoid further delays of this type, the project plans to switch to the use of allogeneic iPS cells banked according to tissue types commonly found in the Japanese population (Masayo Takahashi, personal communication).

jCyte, of which I am founder, is currently testing allogeneic retinal progenitor cells in patients with RP. The cells are being delivered by intravitreal injection, under topical anesthesia, without the use of immune suppression. To date, over a dozen patients have received treatment. Safety has not posed an obstacle and enrollment is on track to be completed this year.

Cell Cure Neurosciences, a subsidiary of BioTime, continues to actively enroll patients with dry AMD in their Israel-based Phase 1/2a trials using an allogeneic ES-derived RPE approach. They were granted Fast Track designation by the FDA in September of 2015.

The London Project announced the treatment of the first patient with ES-derived RPE cells in August 2015 [6]. Their project uses RPE cells on a scaffold in a subset of AMD patients with a complicated form of wet AMD not amenable to anti-VEGF therapies.

At the end of 2015, ReNeuron announced that enrollment had opened for its trial with subretinal RPCs in RP and in February, 2016 it was reported that 15 patients had been recruited to their Boston-based trial [7]. Company also announced that it had completed the relocation of its headquarters from England to Wales.

Regenerative Patch Technologies is developing an ES-derived RPE product for dry AMD but has not announced enrollment plans.

Non-CNS cell types

There has been comparatively little reported, since my previous review [1], from trials with non-CNS cell types, including umbilical cells (Centocor) and autologous hematopoietic cells (University of Sao Paulo, University of California, Davis).

MD Stem Cells received media attention for their open label, recipient-funded work using autologous bone marrow-derived cells [8]. Their team reported a case of visual improvement in a patient with idiopathic optic nerve disease [9]. Apparently, this case was selected out of some 200+ patient's treated for a wide range of ocular conditions. Although SCOTS is registered on the clinicaltrials.gov website, it does not appear that this treatment was submitted for formal IND review by the FDA.

Summary

There are now multiple stem cell projects for retinal disease in clinical trials. Enrollment is proceeding, or completed, in a number of Phase 1 and 1/2a studies and while safety remains under close scrutiny, there is room for cautious optimism that the potential for adverse events will not manifest as an impediment to progress. Phase 2b, i.e., clinical proof of concept, remains to be dealt with and will likely pose the next major inflection point for this field.

Date for consultation of referenced websites was March 15, 2016.

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