

The Promise of Stem-Cell Therapy for Retinal Diseases

Clinical trials in Stargardt disease and AMD are set to begin.

REVIEWED BY ROBERT LANZA, MD

Human embryonic stem cells (hESCs) hold tremendous promise in the field of regenerative medicine.¹⁻³ In ophthalmology, for disorders such as dry age-related macular degeneration and Stargardt disease, in which dysfunction of the retinal pigment epithelium (RPE) leads to photoreceptor loss, the ability to provide a source of RPE cells derived from hESC could potentially be of great value.

Researchers at Advanced Cell Technology (Santa Monica, CA), in collaboration with investigators at several academic centers, have published a series of papers showing that RPE cells generated by hESCs can be maintained through multiple generations;¹ that these hESC-derived cells can be engrafted into animals without rejection;² and that, when transplanted into an animal model of retinal disease, these cells are capable of extensive photoreceptor rescue.³

As a result of this and other preclinical work, the US Food and Drug Administration has approved investigational new drug (IND) applications clearing the way for two phase 1/2 clinical trials, one in patients with dry AMD⁴ and another in patients with Stargardt disease.⁵ The IND for Stargardt disease was approved in November, and the IND for dry AMD was approved early this year. Both trials are set to begin in the first half of 2011.

A number of pharmacotherapeutic advances have been introduced for the treatment of exudative AMD in the past decade, including photodynamic therapy and intravitreal injection of vascular endothelial growth factor inhibitors. Unfortunately, however, there is still no

approved therapy for the dry or nonexudative form of AMD. Dry AMD is the most common form of AMD and is the leading cause of new blindness in people over age 55 years. Similarly, there are currently no effective treatments for Stargardt disease, the most common form of inherited juvenile AMD. Therapies that safely and efficaciously address these two unmet medical needs would be valuable additions to the ophthalmic arsenal.

PRECLINICAL WORK

In both dry AMD and Stargardt disease, the underlying pathology is degeneration of the RPE, creating an unhealthy environment that damages the photoreceptors. The promise of stem cell therapy is to allow clinicians to put in place new, healthy RPE cells to prevent the progression of the disease.

Klimanskaya and colleagues performed in vivo work evaluating hESC-derived RPE cells in the Royal College of Surgeons (RCS) rat model,³ one of the gold standards for studying the macular degeneration disease process. In these animals, injection of hESC-derived RPE cells resulted in 100% improvement in visual performance over control animals and extensive rescue of photoreceptors. In untreated control animals, the outer nuclear layer of photoreceptors was approximately one cell deep at 100 days after injection. In the treated animals, that layer was five to seven cells deep at that time point.

In a mouse model of Stargardt disease, the RPE cell treatment resulted in near-normal visual function for the 2 to 3 months that the animals were observed.

PROMISE AND CONCERNS WITH STEM-CELL THERAPY

There are a number of reasons why these trials in dry AMD and Stargardt disease are among the first to evaluate the promise of hESCs, according to personnel at Advanced Cell Technology.

One reason is that the eye is relatively immune-privileged,⁶ so the therapy will not be confronted by the full brunt of the body's immune system. Also, neuroectodermal tissue, such as the RPE, is a pathway for pluripotent stem cells, so it is easy to get the hESCs to grow in this environment. They can be grown in large numbers in very pure homogeneous populations.

In addition, these two diseases involve the loss of one well-defined type of cell, so treatment can be accomplished with a small number of cells in a very localized area.

Furthermore, the anatomy of the eye allows researchers to observe the behavior of these cells in situ in real time with high-resolution instruments.

Therapy using hESCs is new territory for regulatory agencies, so there are some concerns. At the FDA's request, researchers at Advanced Cell Technology have performed extensive in vivo studies to show that the hESCs cannot result in teratomas. No adverse effects of hESC injection, including tumor formation, have been seen. [Personal communication, Advanced Cell Technology personnel.]

CONCLUSION

Two phase 1/2 prospective, open-label multicenter clinical studies are planned, to evaluate the safety and tolerability of hESC-derived RPE cells after subretinal transplantation into patients with Stargardt disease and dry AMD. Twelve patients will be recruited for each study at multiple sites, which are yet to be announced. Inclusion and exclusion requirements will be posted soon at clinicaltrials.gov, according to Advanced Cell Technology. ■

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