

Human Adult Umbilical Stem Cells: Potential Treatment for Atrophic AMD

A phase 1 clinical trial is assessing safety.

BY ALLEN C. HO, MD

Each year the Young Physicians Section of the American Society of Retina Specialists (ASRS) presents the Crystal Apple Award to an ASRS member who has gone to great lengths to advance the education and professional development of young vitreo-retinal specialists. This year, the award was presented to Allen C. Ho, MD. Allen has trained more than 45 fellows and 150 residents during his tenure at the University of Pennsylvania and Thomas Jefferson University Retina Service and Wills Eye Hospital in Philadelphia. He has been a mentor and friend to his trainees and colleagues, and is well deserving of this important distinction. The following article provides a summary of his lecture "Surgical Delivery of Human Adult Stem Cells for Atrophic AMD: Rationale and Preliminary Experience."

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Geographic atrophy (GA) is a slowly progressive pathology in nonexudative ("dry") age-related macular degeneration (AMD) for which there is currently no safe and effective treatment (Figure 1). Investigational strategies for treatment of atrophic AMD include oral nutraceutical formulations, vitamin A visual cycle modulators, and injectable molecular interventions with molecular targets such as complement system modulators to retard the progression of GA. The goals of these investigational interventions include preventing photoreceptor and retinal pigment epithelial (RPE) cell loss, reducing the load of toxic metabolites in these cells, and suppressing or modulating inflammation.

Another approach under investigation in relation to preventing photoreceptor and RPE cell loss in GA is cell-based therapy—the harvesting and transfer of stem cells to support or replace diseased cells. Traditional pharmaceutical agents work on a molecular level; cell-based therapies work on a cellular level to restore or preserve cellular function.

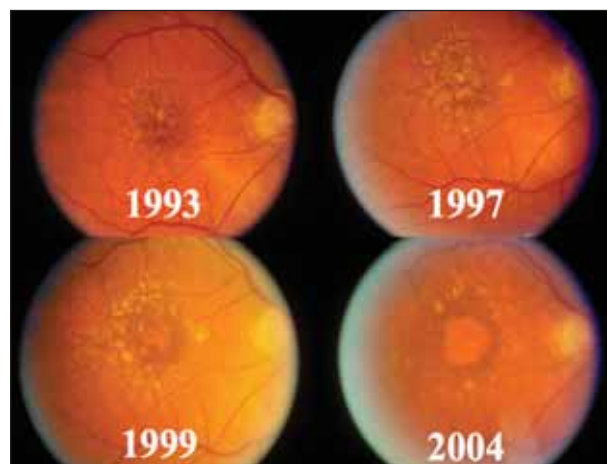


Figure 1. Geographic atrophy (GA) is a slowly progressive pathology in dry age-related macular degeneration; case example: in 1993, confluent drusen are seen; 4 years later, hyperpigmentation with confluent drusen; by 1999, GA is evident; in 2004, GA is progressive.

The main sources for the cells used in cell-based therapies include embryonic stem cells, which have been controversial, and adult stem cells. Sources for adult stem cells include bone, blood, umbilical cord, and, in the eye, the corneal limbus.

TWO APPROACHES

Two approaches are used in stem-cell therapies: regenerative and trophic (Figure 2). In the regenerative approach, embryonic or adult stem cells are isolated, expanded (grown to larger number of cells), and differentiated into the stem-cell therapy product. That is, they are progressed to become another cell type: for example, corneal stem cells. These functional cells are intended to replace lost or injured native cells to restore organ function.

In the trophic approach, the stem cells *are themselves* the product. The adult cells are isolated, characterized, and expanded, but they remain differentiated, not progressed to become another cell type. In this approach, the role of the cells is to support or repair injured native tissue and preserve function by altering the microenvironment of the injured tissue, for example through cytokines or cell-to-cell interactions.

In the regenerative approach, the stem cells are the precursor to the product. An example of regenerative stem-cell-based therapy is corneal limbal stem cell transplantation, in which autologous allogeneic adult corneal limbal stem cells from the palisades of Vogt are transplanted to help the corneal epithelium regenerate.¹ The corneal limbal stem cells are transplanted onto the surface of the eye, repopulating the damaged cornea.

One example of trophic cell-based therapy is the NT-501 (Neurotech), an intraocular device that delivers ciliary neurotrophic factor (CNTF), a protein that has been investigated for the treatment of motor neuron disease, to the posterior segment. The implant contains human RPE cells that have been genetically modified to secrete CNTF. In a phase 2 clinical trial, NT-501 slowed the loss of vision in patients with GA due to dry AMD. Implanted in an OR-based procedure, the technology was superior to sham injection in stabilizing best corrected visual acuity (BCVA) at 12 months. No serious adverse events were reported, and the implant was well tolerated.² Further study of this technology is ongoing.

Another example with a putative trophic mode of action is human adult umbilical stem cell rescue of photoreceptor cells.³ In the Royal College of Surgeons rat,

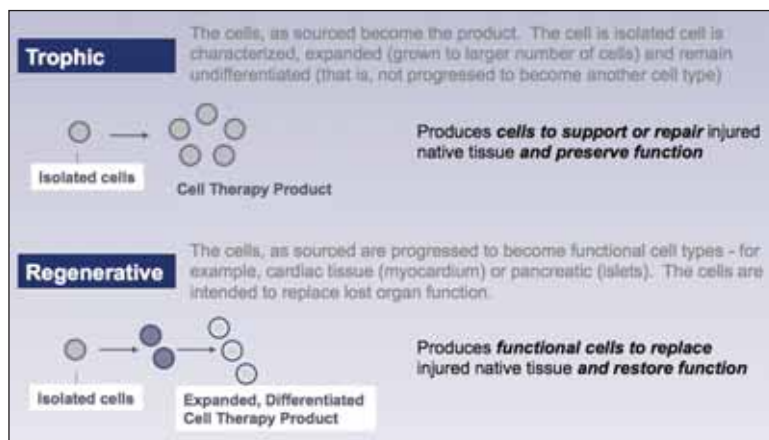


Figure 2. Regenerative (A) and trophic (B) stem-cell therapy. In the regenerative approach, embryonic or adult stem cells are isolated, expanded (grown to larger number of cells), and differentiated into the stem-cell therapy product. In the trophic approach, the stem cells are themselves the product.

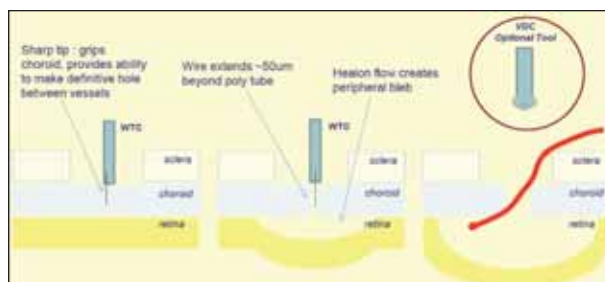


Figure 3. A wire-tipped cannula (WTC) is used to create the choroidotomy and to inject Healon to create a peripheral retinal bleb.

in which most of the photoreceptors degrade before 100 days of age because of a defect in the RPE, both structure and function of the retina were preserved after transplantation of human umbilical-derived cells. Of 4 cell types evaluated, the umbilical-tissue derived cells demonstrated the best photoreceptor rescue.

CLINICAL STUDY

A clinical study of human umbilical tissue-derived cells (hUTC; CNTO 2476, Centocor, Inc.) has been initiated in patients with atrophic AMD.⁴ This phase 1/2 study will assess the safety and clinical response of CNTO 2476 delivered to the subretinal space of the temporal macula through a microcatheter delivery system. Patients enrolled will be at least 50 years old, with a total area of GA in each eye of at least 2.6 mm² involving the fovea. BCVA in the treatment eye will be no better than 20/200 in the phase 1 portion of the trial.

The primary outcome measure of the phase 1 dose-escalation study, being conducted at sites in Philadelphia

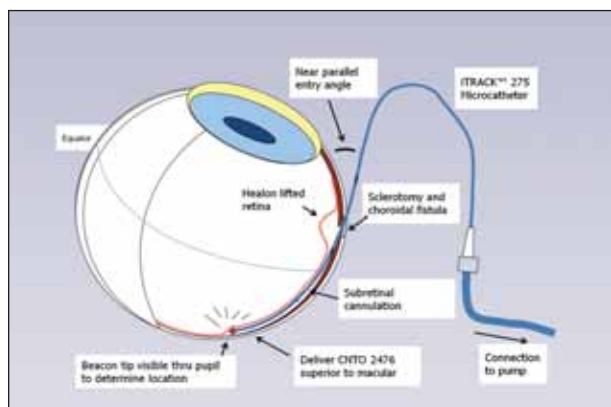


Figure 4. The iTrack is guided from the choroidotomy through the subretinal space to the macula.

and Los Angeles, will be the proportion of eyes with serious ocular adverse events occurring over the first 12 months of the trial. Secondary endpoints include assessment of clinical response, visual acuity, GA lesion size, and findings of optical coherence tomography and fluorescein angiography.

All of the 12 patients have been enrolled in the phase 1 portion of the study. In the phase 2 portion, patients at the current and 4 additional study centers will be randomized to 1 of 2 optimal doses identified during phase 1.

SURGICAL DELIVERY

CNTO 2476 is delivered to the subretinal space with the iTrack 275 microcatheter (iScience, Menlo Park, CA). The microcatheter is combined with a fiberoptic illuminator and a microcalibrated pump, which ensures rate-controlled delivery of the stem cell product.

The microcatheter is inserted through a sclerotomy and choroidal fistula. A wire-tipped cannula is used to inject sodium hyaluronate viscoelastic (Healon, Abbott Medical Optics) to create a peripheral retinal bleb (Figure 3); the retinal elevation allows subretinal cannulation of the probe. Ultrasound is used to visualize the creation of the bleb, and it can be directly visualized with an intraocular endoscope. The illuminated beacon tip of the microcatheter then can be visualized through the pupil to verify its position in the posterior pole, and CNTO 2476 is delivered to the subretinal space near the macular GA (Figure 4). The surgical procedure is challenging and continues to evolve.

CONCLUSION

Clinical trials exploring the safety and potential efficacy of human adult-cell therapy inserted into the subretinal space of patients with atrophic AMD have

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Surgical Delivery

This animation video shows how the iTrack 275 Microcatheter, combined with a fiber optic illuminator and microcalibrated pump provides controlled delivery of stem cell product.



direct link to video:

<http://eyetube.net/?v=dafl>



WATCH IT NOW ON WWW.EYETUBE.NET

Surgical Technique

Dr. Ho's surgical technique for inserting the microcatheter and delivering CNTO 2476 to the subretinal space near the macular GA.



direct link to video:

<http://eyetube.net/?v=pospu>



begun. Specifically, a human adult cell therapy, CNTO 2476, is being evaluated for treatment of GA due to AMD in a phase 1/2 clinical trial. The surgical subretinal stem-cell delivery system will continue to evolve. Preliminary results are forthcoming. ■

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3. Lund RD, Wang S, Lu B, et al. Cells isolated from umbilical cord tissue rescue photoreceptors and visual functions in a rodent model of retinal disease. *Stem Cells*. 2007;25(3):602-611.
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