The Current Status of Stem Cells in Ophthalmology

BY IRV ARONS

From an inauspicious start several years ago, the use of stem cells (SCs) in the treatment of several ocular and retinal diseases has picked up steam over the past year. As shown in Table 1, there are now more than 12 companies and institutions involved in research and clinical trials using a variety of SC types in the treatment of a handful of degenerative problems found in the eye, including several trials involving humans.

WHAT ARE STEM CELLS?

Every organ and tissue in our bodies is made up of specialized cells that originally come from a pool of SCs in the very early embryo (ESCs). Throughout our lives we rely to a much more limited degree on rare deposits of SCs in certain areas of the body (adult SCs) to regenerate organs and tissues that are injured or lost, such as our skin, our hair, our blood, and the lining of our gut.

SCs are like a blank microchip that can be programmed to perform particular tasks. Under proper conditions, SCs develop or differentiate into specialized cells that carry out a specific function, such as in the skin, muscle, liver, or in the eye. Additionally, SCs can grow extensively without differentiating, giving rise to more stem cells. These 2 characteristics of pluripotency and self-renewal distinguish SCs from other cells in the body and give SCs their tremendous therapeutic promise for a wide range of degenerative diseases.

The 4 most commonly used and described classes of SCs are embryonic stem cells (embryonic ESCs, also known as human embryonic stem cells, hESCs), induced pluripotent stem cells (ipSCs), adult SCs, and human parthenogenetic stem cells (hpSCs).

Beside the ESCs and adult SCs already used by the body, 2 other classes of SCs are increasingly used in medical research, the ipSCs and hpSCs.

> Most research efforts appear to be focused on the back of the eye, specifically retinal tissue and diseases.

ESCs are derived from fertilized human eggs (oocytes) in the early stages of development. They are truly pluripotent, in principle enabling them to become any body tissue and thus providing their tremendous clinical potential. However, ESCs are associated with significant ethical, political, and religious controversy because a fertilized egg, under the right circumstances, has the potential to develop into a human being. Another major (albeit much less publicized) issue with ESCs is that, because they are essentially a transplant from 1 person (the fertilized egg) to another (the recipient patient), an allogeneic treatment, therapeutic cells and tissues derived from ESCs can be expected to provoke an immune response from the recipient and be rejected.

In contrast, ipSCs are adult and fully differentiated cells (eg, skin cells) that are chemically, physically, genetically, or otherwise driven back to earlier developmental stages. Although creation of such cells does not involve the use or destruction of a fertilized egg, it does require dramatic changes in gene expression that may have unknown biological impact and likely will be subject to substantial scrutiny by regulatory authorities before any approval for therapeutic use. Also, due to immune rejection, ipSCs have to be derived from the individual patient (autologous therapy) which significantly limits clinical use and adds time and cost that will be increasingly difficult to implement in cost-contained health care systems worldwide. Finally, ipSCs cannot

TABLE 1. STEM CELL COMPANIES ACTIVE IN OPHTHALMOLOGY

Company	Collaborator(s)	Cell Type	Application
Advanced CellTechnology Inc. (ACT)	Oregon Health & Science University (OHSU) • Moorfields Eye Hosp. • UCLA/Jules Stein • Wills Eye Hospital • Aberdeen Royal Infirmary • Bascom Palmer Eye Institute • Massachusetts Eye & Ear Infirmary	hESCs	RPE cells for retinal diseases, including dry AMD NCT01344993 and Stargardt NCT01345006 NCT01469832
AstraZeneca	University College London (UCL)	hESCs	Diabetic retinopathy
Janssen R&D/J&J with iScience Interventional	• Retina Institute of California • Wills Eye Hospital	Adult SCs (CNTO 2746 from umbilicalcord fluid)	RPE cells for geographic atrophy (GA; atrophic dry AMD) NCT01226628
Cell Cure Neurosciences	Teva	hESCs	RPE cells for dry AMD
CellSeed France SARL	FGK Clinical Reserach GmbH • Universitatsklinkum, Erlangen, Germany	oral mucosaepithelial cells	CAOMECS* for corneal tissue repair inthose with limbal cell-deficiencies NCT01489501
Fundacion Clinic per la Recerca Biomedica (Spain)	• Hospital Clinic Barcelona • Instituto Barraquer • Instituto de Microcirugia Ocular	sclero-corneal progenitor cells from the limbus	Replacement of damaged corneal cells NCT01470573
General Hospital of the Chinese People's Armed Police Force(China)		unknown	Optic nerve atrophy ChiCTR-TNRC-11001491
International Stem Cell Corp. (ISCO)	CytoCor - • Absorption Systems - US • Sankara Nethralaya - India • Automation Partnership -UK CytoRet - UC Irvine	hpSCs hpSCs	Corneal tissue for transplantation into degenerated corneas RPE cells and layered retinal structures for AMD
Mesoblast		Adult SCs (VEGF)	Wet AMD
NeoStem Inc.	Schepens Eye Research Institute	Adult SCs (VSELs from bone marrow)	In animal models for treating glaucoma and AMD
Neurotech		encapsulated human RPE cells (CNTF) NT-501 NT-503 (encapsulatedVEGF)	GA/Dry AMDNCT00447954 RP/Usher Types 1 and 2/choroideremia NCT00447993 Wet AMD
Osaka University Graduate School of Medicine (Japan)		oral mucosaepithelial cells	Corneal tissue repair for corneal epithelial cell deficiencies JPRN-UMIN000005400

TABLE 1. STEM CELL COMPANIES ACTIVE IN OPHTHALMOLOGY (CONTINUED)

Company	Collaborator(s)	Cell Type	Application
Pfizer Regenerative Medicine/Pfizer Ophthalmics	• UCL (London Project to Cure Blindness) • EyeCyte Inc. with Scripps Research Institute	hESCs Adult SCs (from bonemarrow)	RPE for wet and dry AMD and other retinal diseases Treating retinal diseases including diabetic retinopathy, ROP, RVO, AMD, and RP
ReNeuron	Schepens Eye Research Institute	Adult SCs (ReN003)	RP (preclinical) and AMD
Stem Cells Incorporated	OHSU with Casey Eye Institute	Adult SCs (HuCNS-SCs - purified humanneural stem cells)	Retinal degenerative diseases, including photoreceptor protection to preserve visual function in AMD and RP
Stemedica	Fyodorov Eye Microsurgery Center, Moscow	Adult SCs	Stem cell injection following spot laser damage of retina, for RP, AMD, DR Glaucoma
Tohoku University Graduate School of Medicine (Japan)		oral mucosaepithelial cells	Corneal tissue repair in those with corneal epithelial cell deficiencies JPRN-UMIN000006745

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NCT - National Clinical Trial (ClinicalTrials.gov)
*Cultured Autologous Oral Mucosal Epithelial Cell-sheet (CAOMECS)

be used for hereditary disease therapy because they bear the genetic defects of the donor-patient.

Adult SCs are rare cells found in various organs or tissues in a person that have a limited ability to differentiate into cells with specific functions. They are older and less powerful than other types of SCs. While these SCs do not require use or destruction of a fertilized egg or extensive manipulation of gene expression, they are rare and hard to identify and they generally proliferate poorly, thus making it hard to produce therapeutic amounts.

hpSCs are derived from activated human oocytes. Parthenogenesis is a form of asexual reproduction in some amphibians and plants but does not occur naturally in mammals, including humans. Scientists have discovered a process for chemical activation of human eggs, similar to what the sperm does in normal fertilization but without any involvement of sperm. Some companies claim that this process results in hpSCs that are as pluripotent and proliferative as ESCs, yet avoid the ethical, political, and religious controversy surrounding use or destruction of human embryos with potential for viable human life. Furthermore, since there is no forced change of gene expression patterns, hpSCs are not likely to face the same safety and regulatory hurdle as ipSCs. Most important and unique relative to all other SC classes, hpSCs can be produced in a simplified immunogenetic (homozygous) form that enables each line to be an immune match for many millions of people.

APPLICATIONS FOR STEM CELLS IN OPHTHALMOLOGY

Cornea. Scarred and degenerative corneas represent 1 prime area of research for the use of SCs. Because of a lack of donated human eye bank corneas for transplantation, particularly in populous nations such as India and China and the emerging regions, the use of SCs to regenerate damaged corneal tissues could become highly valuable in those countries, where blindness due to damaged corneas is prevalent.

Glaucoma. There are only a few research programs using SCs for the middle areas of the eye, specifically in treating glaucoma. NeoStem has said it is working with Schepens Research Institute using the company's very small embryonic-like SCs (VSELs) in the treatment of glaucoma and age-related macular degeneration (AMD), and Stemedica claims to be working with the Fyodorov Eye Institute in Moscow on a glaucoma program.

Lens. I know of no programs targeting the lens.

Retina/Macula/Vitreous. Most research efforts appear to

TABLE 2. STEM CELL THERAPY IN OPHTHALMOLOGY: ONGOING CLINICAL TRIAL DETAILS

Disease State	Clinical Trial	Sponsor	Clinical Sites	Status	Number Patients to be Treated	Number Treated to Date
Stargardt Disease	NCT01345006 NCT01469832	Advanced Cell Technology	• UCLA/Jules Stein - R • Wills Eye Institute - R • Moorfields - R • Aberdeen Royal Infirmary - R	Phase 1/2 Phase 1/2	12 12	3 1+
Dry AMD/GA	NCT01344993 NCT01226628 Pending	Advanced Cell Technology Janssen (Johnson & Johnson) StemCells Inc.	• UCLA/Jules Stein - R • Wills Eye Institute - R • Bascolm Palmer Eye Institute - R • Massachusetts Eye & Ear Infirmary - R • Moorfields • Retina Institute of California - R • Wills Eye Institute - R Pending	Phase 1/2 ND-Prep Phase 1/2a Phase 1/2	12 56	3
Corneal Surface Repair/ Limbal Cell Renewal	NCT01489501	CellSeed France SARL/FGK Clinical Research GmbH	Universitatsklinkum, Erlangen, Germany - NYR	Phase 3	82	
Ocular Surface Repair	NCT01470573	Fundacion Clinic per la Recerca Biomedica (Spain)	• Hospital Clinic Barcelona - R • Instituto Univ. Barraquer - R • Instituto de Microcirugia Ocular - NYR	Phase 1/2	15	10
Corneal Epithelial Stem Cell Deficiency	JPRNUMIN000006745 JPRNUMIN000005400	Tohoku University Graduate School of Medicine (Japan) Osaka University Graduate School of Medicine (Japan)	Tohoku University Graduate School of Medicine (Japan) - NYR Osaka University Graduate School of Medicine (Japan) - R	Phase1 Phase 1	10 10	 4
Optic Nerve Atrophy	ChiCTR-TNRC-11 001491	General Hospital of the Chinese People's Armed Police Force (China)	General Hospital of the Chinese People's Armed Police Force (China) - NYR	Phase 1/2	20	

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NYR - Not yet recruiting
R - Recruiting

be focused on the back of the eye, specifically retinal tissue and diseases. Areas of interest I have identified include regeneration of retinal epithelial cells for the treatment of both dry and wet forms of AMD; replacement of damaged photoreceptors; the growth of artificial retinas, again for treating AMD; and direct treatments for diseases such as retinitis pigmentosa, retinopathy of prematurity, diabetic retinopathy, Stargardt disease (Stargardt macular dystrophy), and retinal vein occlusion.

CLINICAL TRIAL STATUS

Table 2 shows the various clinical trials under way in the United States, Europe, Japan, and China to treat a variety of primarily retinal conditions. It should be noted that Advanced Cell Technology's clinical trials for both Stargardt disease and for treating dry AMD, at several eye institutes in the United States and Europe, have shown positive results in human patients.[1] At least 21 patients have received SC treatments to date: 4 for Stargardt disease, 3 for dry AMD, 10 for ocular surface repair, and 4 for corneal epithelial SC deficiency.

SUGGESTED LINKS:

http://bit.ly/M8dLCY

bit.ly/ynoTOa

SUMMARY

As stated by Stephen Rose, PhD, Chief Research Officer at The Foundation Fighting Blindness, in his *Eye on the Cure* blog recently, "Of course, it would be nice if all the parts of our bodies, including our retinas, came with extended warranties so you could just swap them out when they go bad. But now that I think about it, that's what stem cells might do for us someday."[2] ■

Irv Arons is a retired consultant to the ophthalmic industry who now writes a blog, Irv Arons' Journal*, focused on new technologies, including stem cells and gene therapy, for treating retinal diseases. His blog can be found at http://tinyurl.com/ijablog. He may be contacted at iarons@erols.com.*

1. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720.
2. Rose S. There's more than one way to correct a genetic defect. *Eye on the Cure*. April 11, 2012. Available at: http://www.blindness.org/blog/index.php/theres-more-than-one-way-to-correct-a-genetic-defect/. Accessed June 6, 2012.