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What Stem Cells May Mean to Ophthalmology

News from London on a potential breakthrough underscores the impact that stem cell research may have in our field of medicine.

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Stem cells, those progenitor, prodigious and primordial little cells have been credited with everything from curing cancer to restoring sight to the blind. Why then is such a small group of cell types the center of such a tempest that even God himself is brought into the mix? Have we found the Holy Grail of medical cures at last?

Somewhere between the hype of the ongoing political and scientific debate and the real science that is taking place, there lies a glimmer of hope. The exhaustive research and millions of dollars already spent in chasing the stem cell microcosm is beginning to live up to its expectations. As the unraveling of the human genome that enhanced our understanding of disease, our knowledge of how stem cells go about their business could forever change how we practice medicine.

Science is on the cusp of something big from which a new field of regenerative medicine is emerging. Should ophthalmologists care? If recent work is any indication, we eye specialists may have a special stake in the outcome of the stem-cell wars (*See sidebar, below*). The impact of this specialized science on how we treat our patients could be profound.

Promise and Controversy

Stem cells, of which there are three main types—embryonic (derived from blastocysts), umbilical cord blood stem cells, and adult stem cells—are common to all organisms. These pluripotential cells possess the unique ability to renew themselves and to differentiate into an almost limitless range of cell types.

Stem cell research, first pursued in the 1960s by Canadian scientists Ernest A. McCulloch and James E. Till, is as vast and complicated a field as the human genome itself. Stem cells can be nudged to grow and differentiate by a promoter gene sequence of DNA that can tell the cell precisely what to do, when to do it, and how to act when it grows up. The real interest rests with embryonic

cells, for they are truly pluripotential. These cells possess all the genetic information that is required to become anything from a skin cell to a retinal photoreceptor.

Once they divide through the process of mitotic division however, they are already well on their way to differentiating into fully functional adult cells. The secret is to isolate the post-mitotic precursor that can be coaxed into going one direction or the other, much like your teenager deciding to become a Rhodes Scholar or a gang member. The progenitor cells are the immature, yet undifferentiated cells that become something special, and therefore less able to differentiate themselves than the original stem cell from which they came. It is the stem cell, the stem of the plant that has yet to flower, that has created all the fervor.

The controversy about stem cell research is centered on the source for these little wonders: either fetal tissue or established stem cell lines. Researchers confined to using only established cell lines are limited in the directions that their cells can take. Providing a fresh source of fetal cells for science opens limitless possibilities.

Where do ophthalmologists fit in? Let's take a look at where stem cell lines could be utilized in the eye.

Skin. Stem cells could be grown in vitro to yield new human skin. Imagine the possibilities, from grafts for burn victims to reconstructive surgery replacements for cancer.

Two types of stem cells protect and regenerate the anterior surface of the eye.

Conjunctiva. Stem cells reside at the conjunctival fornice and provide a rich source for repair of damaged conjunctiva. Limbal stem-cell deficiency results in epithelial defects, scarring, vascularization and loss of ocular function. Replacement of the stem cell population could reverse conjunctival surface diseases.

Cornea. Epithelial stem cells reside in the basal region of the limbus. They are responsible for repairing any defect of the corneal surface following injury. Stimulated to divide, they transform into transient amplifying cells (TACs). Further division leads to non-dividing post-mitotic cells (PMCs) that differentiate and migrate onto the central cornea.

One line of research is focused on growing limbal epithelial cells *in vitro* that can then be transplanted onto the ocular surface. The patient's own stem-cell population can further be cryopreserved and used in repeat grafts. Bioengineered tissue replacements could become the future of ocular surface repair.

Beyond the Surface

Lenticular. One of the most exciting areas of research is the cultivation of lens epithelial cells from primordial precursors. Imagine replacing an opaque crystalline lens with a patient's own cellular, completely biocompatible (and accommodative) living intraocular lens.

Retina. Research into isolating and growing retinal stem cells is just

beginning. The key to success in this complex tissue is the proper integration and subsequent differentiation of a cellular population into a preferred cell type. Although much needs to be done, for the need is great, recent work is encouraging.

Retinal cell replacement therapy for the blinding diseases of retinitis pigmentosa, age-related macular degeneration and diabetic retinopathy is within reach.

UK Scientists Sight Stem Cell 'Cure' for AMD

Research in London will explore what they call a "groundbreaking surgical therapy capable of stabilizing and restoring vision" in the vast majority of patients who currently suffer blindness from age-related macular degeneration. The therapy will be developed by the London Project to Cure AMD, a collaborative project bringing together some of the leading specialists in the field and centered at the University College London Institute of Ophthalmology, Moorfields Eye Hospital and the University of Sheffield. The Project is open access and will be made completely available to scientists, clinicians and all those with an interest worldwide.

The London Project's approach will involve production of a cell replacement therapy from human embryonic stem cells, which are effective in replacing dysfunctional RPE and photoreceptors found in AMD, leading to a surgical therapy capable of stabilizing and restoring vision in the vast majority of patients. Surgical procedures already developed and tested in a number of patients using the patients' own cells have illustrated that a cell replacement therapy can work.

Professor Pete Coffey, UCL Institute of Ophthalmology and director of the London Project, said: "The London Project aims to deliver treatment for a disease which has no alternative therapy. Using stem cells—which are far more adaptable—can only improve success of what has already been achieved and in addition establish this as a global therapy. This is achievable as a result of bringing together a number of groups who previously were trying to solve the same problem in isolation. The project aims to engage scientists, clinicians and the public to ensure success through actively attracting and promoting the inclusion of other laboratories, hospitals and institutions by an open access policy and by informing the public of progress."

Optic nerve. Recent development in advanced molecular methods has yielded previously unattainable progress in identifying the existence of multipotential cells that are the precursors to both neurons and glia. Work presently under way has revealed that fetal cells removed from the developing brain and placed in tissue culture in vitro could give rise to differentiated neurons. Armed with that knowledge, clinical trials demonstrating neuron replacement therapies for such neurodegenerative diseases as Parkinson's and Huntington's disease have already been attempted. Can reversal of glaucomatous damage to the optic nerve be far behind?

Despite the ongoing moral, religious and political debate, stem-cell research is well under way. We have already made great strides in understanding how a single cell gives rise to a highly differentiated organ. Regenerative medical therapies won't be here for a while, but they are on their way. Understandably, it will take time, tissue and lots of money. For those suffering from the blinding eye diseases, the breakthroughs will come none too soon. If we are to build upon the modest successes achieved so far, we, as physicians, must encourage the move of scientific discussions out of the halls of Congress and into the halls of research laboratories where they rightfully belong.

Dr. Kershner is president of Eye Laser Consulting with offices in Boston and Palm Beach Gardens, Fla. He has no financial or proprietary interest in any of the technologies described in this article. Adapted and reprinted with permission from Better, Worse or About the Same: Seeing for Life-Clear Vision to Age 88