## *What Stem Cells are Growing for Ophthalmology*

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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 and seemingly insignificant group of cell types the center of 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 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 it's expectations. Similar to 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 as eye specialists may have a special stake in the outcome of the stem cell wars. The impact of this specialized science on how we treat our patients could be profound.

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 1960's 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 from 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.

*Lenticular*-hold onto your phaco handles Docs, it promises to be a bumpy ride. 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 IOL!

*Retinal*-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.

*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 underway 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 underway. 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.

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