

# Retinal Stem Cell Research: Promise, Progress, and Pause

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Since their initial description in the scientific literature, human stem cells have garnered considerable attention in the press, to the point where they have become part of modern culture. And largely for good reason, since stem cell technology has created exciting new possibilities for understanding and treating diseases that have perpetually plagued humankind. Driving the impressive advances in the field are a continuously growing number of legitimate academic and corporate efforts aimed at not only harnessing the power of stem cell biology, but also pointing out and overcoming current limitations of the field. As with all new therapies, there is a balance that must be struck between the desire to move purposefully toward human use and the overarching obligation to “first do no harm.” Finding this balance requires an understanding of both the diseases being targeted and the treatment itself (in this case, the nature of the cells being investigated). To be sure, there is no magic to stem cells. They have unique but variable properties that, if thoughtfully tested and applied, may be of considerable help to some patients in the foreseeable future. This article attempts to provide basic knowledge that will assist patients and practitioners to critically assess the merits of stem cell therapies for retinal diseases.

To begin, it is important to understand what the retina is and what types of retinal conditions are being targeted for stem cell treatment. The retina is a light-sensing, transparent, film-like tissue that lines the back of the eye. While it may be nondescript to look at, it is actually a complex “layer cake,” with each layer containing specific types of cells (or biological building blocks) that perform a precise job and connect to other cells to form a neural circuit. Deepest within the retina lies a layer of photoreceptors – rods and cones – that detect light and initiate a cascade of events that ultimately lead to our perception of vision, which actually occurs in the brain. Photoreceptors signal to intermediate neurons in the middle layer of the retina, which in turn connect to retinal ganglion cells (RGCs) in the top layer. RGCs then collectively extend over one million output axons (or “wires”) to the brain. In addition to these components, there is a layer of cells beneath the photoreceptors known as the retinal pigment epithelium (RPE) that is essential for photoreceptor health and function. Without well-functioning RPE, photoreceptors eventually become dysfunctional and die.

Blindness can come about for a multitude of reasons, many of which have nothing to do with the retina (for example, corneal diseases or untreated cataracts). However, some of the most devastating and incurable causes of blindness are rooted in the death of retinal cells – more specifically the photoreceptors, RPE (with resulting photoreceptor death as discussed above), and/or RGCs. Examples of diseases that affect RPE and/or photoreceptors include age-related

macular degeneration (AMD), retinitis pigmentosa (RP), Usher syndrome, Stargardt disease, Best disease, and the list goes on. The primary blinding disease affecting RGCs is glaucoma, which is actually a catch-all term for many different diseases, similar to RP. Other common diseases, such as diabetic retinopathy, affect multiple layers of the retina simultaneously and thus present an even more complex challenge. While the majority of cases of glaucoma and diabetic retinopathy (DR) can be at least partially controlled with available medications or preventative measures, some cases worsen inexorably despite the best possible treatment. Furthermore, for the vast majority of those affected by retinal diseases like RP, the “dry” form of AMD, and many others, there are no treatments available. The same holds true for injuries that irreversibly harm the retina and its component cells.

Regardless of the cause, the end result in these untreatable or unresponsive conditions is death of retinal cells. Unfortunately, the human retina has no innate ability to replace these cells once they are lost. In other words, we are born with all the retinal “parts” we are ever going to have. Fortunately, there is some redundancy built into the retina, such that we can lose a surprisingly large number of cells before our vision is appreciably compromised. This functional buffer is why some people develop advanced disease unbeknownst to them, and why regular eye exams are important to detect problems before they reach our awareness in day-to-day life.

So, where do we turn when too many retinal cells die and vision is significantly compromised? One option is to bypass the missing cells altogether by coercing remaining healthy parts of the retina or visual system to do jobs they aren’t normally tasked with. For example, when most or all of the photoreceptors are lost, one can attempt to get intermediate retinal neurons or RGCs to respond to light (or a surrogate stimulus) directly. This is the basic idea behind retinal prosthetics (implantable “chips”) and optogenetics. Another option is to replace the lost cells either by 1) getting the retina to fix itself (regeneration), or 2) introducing new cells obtained from an outside source (transplantation). While each of these approaches holds unique potential, the present article is directed at the last strategy.

The first question that often comes to mind when contemplating retinal cell transplantation is ‘Where will the donor cells come from?’ Prior to the advent of human pluripotent stem cell technology, the only potential source was cadaver human eyes, but this option was neither practical nor particularly effective. Stem cells are – by their broadest definition – capable of replicating themselves (dividing) and maturing (differentiating) into one or more cell types. As such, stem cells are more primitive versions of the cells they can produce. However, not all stem cells are alike. There are some types of stem cells that can only make one cell type, whereas others may make multiple cell types that together form a tissue or organ (tissue-specific stem cells). Unfortunately, true tissue-specific stem cells do not exist in the human retina. Thus, we are unable to auto-replace cells in the retina like we can in other parts of our body like blood or superficial skin.

Unlike the aforementioned types of stem cells, pluripotent stem cells (PSCs) can theoretically make any cell in the entire body. That capability makes PSCs very powerful, but also potentially hard to control. How does one direct them to make a single cell type (or a handful of cell types) that are needed by a particular patient? Remarkably, there has been tremendous progress made in recent years on this front, such that many highly differentiated and specialized cell types,

including photoreceptors, RPE, and RGCs, can be produced from human PSCs. While we need to continue to improve the manufacture of these cells, perhaps the biggest hurdle remaining is how to get them to connect to existing cells in a patient in order to restore function. This “installation challenge” is formidable for all cell types, but conceptually more so for some cell types (RGCs) than others (RPE).

Within the broader definition of human PSCs, there currently exist two types: embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). A method for generating human ESCs from blastocysts was first described by Dr. James Thomson at UW-Madison in the late 1990’s, whereas human iPSCs (genetically reprogrammed adult human skin cells) were first reported 10 years later by both Dr. Thomson and Dr. Shinya Yamanaka in Japan. Now, iPSCs can be created from many adult cell types, including certain blood cells.

As mentioned earlier, of all the different types of human stem cells, only PSCs (that is, ESCs and iPSCs) can serve as possible sources of retinal “spare parts.” And therein lies the confusion when it comes to the growing number of private clinics that are attempting to financially capitalize on the stem cell fervor. At risk are the people who feel they have nowhere else to turn and who lack an in-depth knowledge of the stem cell field. To be clear, this is not the fault of the patient or family – the length of this article shows how difficult it can be to convey the true nature (both the promise and pitfalls) of a new therapeutic. In many cases, the “stem cells” that are being transplanted in these for-profit private clinics are from fat, bone marrow, blood, or some other source that has no proven ability to replace missing retinal cells. Indeed, even if they were to somehow improve a person’s vision, no one would really know how or why.

Is there any harm that could come from these private stem cell clinics touting miracle cures? Sure. No matter how far advanced your eye disease is, there is the potential to lose what vision you have left – or your entire eye – due to infection, tumor, or other catastrophic event. Furthermore, even if the treatment causes no physical harm, it can result in significant financial damage, with individual costs often reaching into the tens of thousands of U.S. dollars.

So how does a cautious but hopeful individual dealing with a devastating blinding disorder make sense of what is being offered? First, ask questions – and direct them not just at the people trying to sell you the stem cell procedure, since they have an inherent conflict of interest. Their livelihood is tied to you saying *yes* and writing the check. Also, know that being listed on the website “clinicaltrials.gov” does not assure that there is sound science - or even common sense - behind the procedure. A simple rule of thumb is to be highly skeptical of any experimental therapy that requires you to pay a fee or that claims to be a cure-all (i.e., lists myriad diseases that can be treated by a particular product or procedure).

To end, I want to reiterate that there is a great deal of excellent, well-designed, and well-intentioned research being performed in the stem cell field – at UW-Madison and around the world. There is real hope that this technology will – in the foreseeable future – help people who otherwise have no therapeutic options. However, the difference between *hope* and *hype* is a single letter and a compelling website with cherry-picked patient testimonials. As scientists and physicians, we need to move ahead with cautious optimism and an unshakable focus on safety and patient education, both of which require an open and honest dialogue.