## Understanding Stem Cell Therapy

Dan Roberts with Professors Claudio Stern and Pete Coffey

A stem cell is an unspecialized (progenitor) cell that can do one of two things. It can reproduce unlimited copies of itself, or it can differentiate into any of the nearly 220 cell types that make up the human body, such as a heart cell, a brain cell, or a spinal cord cell.

Sources of stem cells found so far in the human body are:

- Cornea
- Bone marrow
- Peripheral blood
- Spinal cord blood
- Skin
- Hair

Our bodies also contain dormant skin cells that lie in wait for whenever we need them.

There are four types of stem cells:

- Embryonic (pluripotent) stem cells are taken from embryos, which is ethically objectionable to many people. They have the ability to turn into any cell type, and they are young, powerful, and versatile. But, coming from a foreign source, they can provoke an immune response and be rejected by our bodies. The potential is great, but the embryonic cell's transformative power makes it difficult to control.

- Adult stem cells found in various organs or tissues in the patient's own body, can be removed, cultured, and then re-introduced, which solves the problems of rejection and ethics. Adult stem cells, however, are older and less powerful than the other types.

- Parthenogenic stem cells come from unfertilized oocytes by way of a process called "Skint," or Somatic Cell Nuclear Transplant (SCNT). Oocytes are cells that become ovum if allowed to develop. They are, therefore, young, but if undeveloped, they are not embryonic. So again, the problems of ethics and rejection are solved.

- The fourth type of stem cells are called induced pluripotent. Like most other cells in the human body, stem cells contain a nucleus which contains an individual's entire set of genes. We now know that gene expression patterns in any cell are not necessarily fixed, as we once thought. With insertion of only one to four genes, adult stem cells from the patient's own body can actually be transformed to their embryonic (pluripotent) state and then developed into any of the cell types in our bodies. Thus, the name "induced" pluripotent stem cells. These cells not only solve the rejection problem, but they are also young and powerful.

And Professor Stern reminded us of an important use for stem cells other than direct transplantation. They can also be used, instead of patients, to study

almost any disease, as well as for drug research and development. And this may lead to development of new drugs that can stimulate our bodies to repair themselves at the cellular level.

Let's take a look at the fast and interesting history of stem cell therapy development over the past decade.

It all started with the discovery that stem cells have certain characteristics of photoreceptor cells. This was reported in the year 2000 by Dr. Derek van der Kooy (University of Toronto) and Dr. Iqbal Ahmad (University of Nebraska).

In 2001, President George W Bush limited government funding for research using embryonic stem cell lines.

In the same year, researchers showed that transplanted cells from a mouse retina were able to reproduce, and that some of them contained the photoreceptor-specific protein, rhodopsin, which initiates the visual cycle (phototransduction).

In 2002, the Scripps Research Institute (TSRI) in La Jolla, California reported success in forming new retinal blood vessels in mice with ocular disease. The process uses pluripotent adult stem cells derived from bone marrow and injected into the vitreous of the eyeball.

Not only could adult bone marrow stem cells be used to form new vessels, but they could also be used to deliver powerful antiangiogenic drugs to prevent neovascularization. This was promising news to people with wet AMD.

In 2004, Advanced Cell Technology (Alameda, California) announced that they had engineered human embryonic stem cells which could be used to repair a damaged retina. Dr. Robert Lanza (Scientific Director) said the results illustrate the need to use cloning technology to eliminate the risk of rejection by the patient's immune system.

A month later, the Department of Medical Biophysics (University of Toronto, Ontario, Canada) announced that their researchers had cultured and transplanted stem cells from human retinas into the healthy retinas of young mice. After four weeks, most of the cells had migrated to the new retinas and successfully differentiated themselves into photoreceptor cells.

Later that year, California became the first state to circumvent the federal government’s restriction on funding for stem cell research by passing Proposition 71 with a majority vote of 69%. This allowed nearly three billion dollars to be put aside for stem cell research in that state over the next 10 years.

Almost simultaneously, scientists from Harvard's Schepens Eye Research Institute successfully, and for the first time, improved the vision of mice with transplanted progenitor stem cells from day-old mice. The procedure had preserved existing cells and restored health to those that were degenerating--a major step toward the therapeutic use of stem cells for people with all forms of retinal degeneration.

Work with humans began in 2006. In April, a research team in India (Dr Rajender Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences) reported that 50 patients severely affected by age-related macular degeneration or retinitis pigmentosa showed significant improvement in vision after one month of injecting stem cells, and that there was further improvement after a gap of three months.

In August, researchers at the University of Washington used a mix of growth factors to coax embryonic cells into becoming retinal cells. This was the first use of human stem cells using the technique for the retina. The team then began injecting the new cells into the eyes of retina-damaged mice, measuring nerve reactions to see whether there was actual vision improvement.

In September, scientists from Moran Eye Center (University of Utah, Salt Lake City) and Advanced Cell Technology reported that cells grown from human embryonic stem cells safely slowed vision loss when injected into the eyes of rats with a disease similar to macular degeneration.

The year 2007 was full of breakthroughs, as researchers continued to look for ways to avoid harming embryos during the production of new stem cell lines.

In January, for example, researchers at the Institute for Regenerative Medicine (Wake Forest University School of Medicine) discovered yet another potential source of embryonic stem cells in the amniotic fluid of the womb. These cells appeared to be almost as malleable as those in the embryo itself, and the advantage would be that harvesting them would be harmless.

On another front, Advanced Cell Technology developed a technique for harmlessly removing a blastomere from an eight-cell human embryo (blastocyst). A blastomere is a cell resulting from the first few divisions of the ovum (egg) after fertilization. In June of 2007, ACT issued a press release announcing successful production of a human embryonic stem cell line (hESC) using that method.

Meanwhile, research was also beginning in the United Kingdom at the University College London, Moorfields Eye Hospital and Sheffield University, in a cooperative effort called the London Project to Cure Blindness. The London Project is a five year research project that began in June of 2007 to develop stem cell therapy for AMD hopefully by the year 2012.

Doctors at Moorfields had some success with human subjects using adult stem cells from the patients' own eyes. Embryonic cells, however, had been shown by the Sheffield scientists to be more malleable and easier to transplant than adult stem cells. Laboratory-grown cells from the blastocyst of a 5-day old embryo require only one injection (a 45-minute procedure), whereas the Moorfields experiments took two hours and two surgical procedures.

This protocol would be very expensive and impractical in general practice, so embryos are being used at Sheffield, and that will take a little longer to get into human trials.

Moorfields scientists are also studying the potential transformation of Müller neuroglial cells from the patient's own eyes. These would be removed from the eye, injected with a triggering chemical (either glutamate or aminoadipate, a derivative of glutamate), grown in vitro (i.e. in a petri dish) and transplanted back into the eye as stem cells.

Late in 2007, two research groups (one at Kyoto University and the Gladstone Institute of Cardiovascular Disease in San Francisco, and the other at the University of Wisconsin) described a method of creating induced pluripotent stem cells by inserting master regulator genes into the chromosomes of human skin cells. These altered cells appeared to behave like embryonic stem cells, which scientists hoped could eventually eliminate the need for using human embryos for research.

Then, in 2008, President Obama lifted President Bush's restrictions on government funding for using embryonic stem cell lines. This opened the door to the world's first test in people of stem cell replacement therapy.

In February of 2009, Geron, a pharmaceutical company, began enrolling paralyzed patients who could be treated within two weeks of their injury. This move set a precedent for more stem cell research in the low vision field.

Then, in August, scientists at the University of Wisconsin-Madison reported that they had reprogrammed skin cells and turned them into different kinds of retinal cells. This added to the growing weight of evidence that stem cells made by reprogramming have similar, if not the same, abilities as embryonic stem cells.

One caveat of the new research, however, was that UW scientists had not yet proved that retinal cells made in a dish can perform all of the functions of those made in the body. But, at least, scientists can now take a skin biopsy from someone with a vision ailment, create retinal cells in a dish, and observe how the disease unfolds and how the cells die over time. Actual stem cell replacement in human retinas is still a little further in the future.

So where do we stand now? Let's hear what Professor Pete Coffey (University College London Institute of Ophthalmology) has to tell us.

[Recording = 5 min]

So our eyes are on the future, and that future is not far away. It has been a fast decade since researchers first noticed the potential of stem cell transplantation as a retinal treatment. And the race continues full speed, as teams of scientists whittle away at the anatomical, monetary and ethical problems in the rush to make stem cell therapy a reality.

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Here is an excellent animated description of culturing stem cells:
www.sumanasinc.com/webcontent/animations/content/stemcells_scnt.html