Differentiating Embryonic and Induced Pluripotent Stem Cells
By Nathan Haigh

Since the isolation of human embryonic stem cells (hESC) in 1998, stem cell research has gone from being highly controversial to being a source of optimism and promise. What changed? And why does it matter?

The first hESCs came from embryos donated by in vitro fertilization clinic patients. IVF involves the combination of egg and sperm outside the body and subsequent maturation until the embryo would implant into the uterus. These embryos are incapable of developing further without implantation.

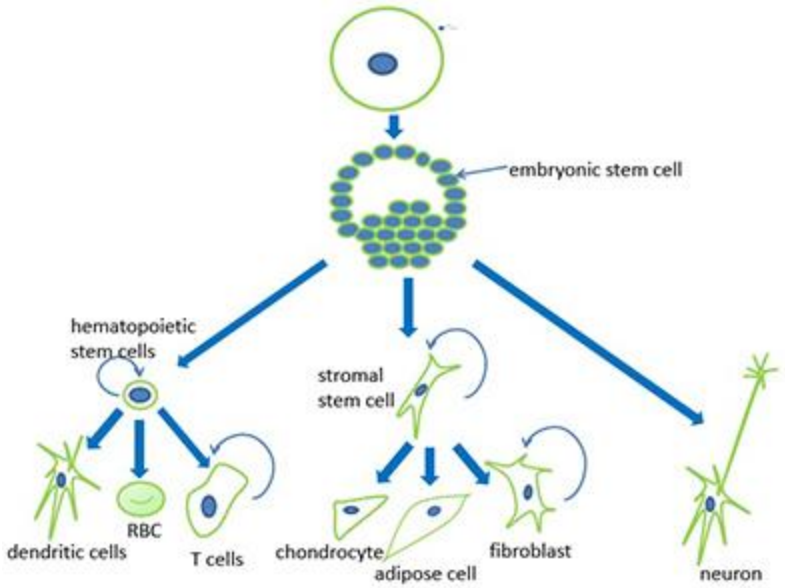
Once hESCs were discovered, beliefs that they came from aborted fetuses and imagined science fiction-style organ farms created dystopian fears. Following the 2001 ban on new Federal funding for stem cell research, a study by Virginia Commonwealth University indicated strong public support for the ban[1].

When Federal funding was cut-off, states like California approved their own funding for stem cell research. This created the California Institute of Regenerative Medicine (CIRM) including the CIRM Bridges program at Sac State, where Dr. Emanual Maverakis studies treatments for chronic wounds.

Chronic wounds to the skin present an abnormally large burden on the healthcare system at an estimated $25 billion per year[2]. This includes the cost of treating infections caused by antibiotic-resistant bacteria like Methicillin-resistant Staphylococcus aureus (MRSA). Recent research suggests that mesenchymal stem cells (MSCs) may be able to reverse MRSA infection[3].

The Maverakis Lab at the University of California, Davis is working on applying MSCs to chronic wounds to improve healing and, therefore, quality of life.

MSCs were first found in bone marrow and were one of the first adult stem cells discovered. But the ability to convert adipose tissue or skin cells into MSCs is far more promising than invasively harvesting adult stem cells.



The idea for inducing adult cells to become stem cells was inspired by pioneering work on animal cloning. Breakthrough experiments showed that scientists could transfer the genome of an

adult cell into an egg that had the nucleus removed, and a clone of the cell donor would be born. This indicated factors in the egg somehow reverted the DNA to an embryonic state normally only found in hESCs. And in 2006, Drs. Kazutoshi Takahashi and Shinya Yamanaka identified these factors, put them into a mouse skin cell and created the first induced plutipotent stem cells (iPSC)[4].

The so-called Yamanaka factors (Oct3/4, Sox2, Klf4, and c-Myc) are master regulatory genes that cause adult cells to become iPSCs. The functional difference between iPSCs and hESCs is that iPSCs cannot become placenta and cannot implant into a uterus; therefore, iPSCs are incapable of producing a viable life. This fact circumvented some of the controversy surrounding the use of donated embryos.

The ability to produce iPSCs means a patient's own cells could be used to produce their own stem cell-based treatment, a process called autologous transplantation. This would likely reduce or eliminate the need for immunosuppresant drugs to prevent rejection of the transplanted tissue because the patient's body would recognize the transplanted tissue as their own.

Stem cell research still has some hurdles to clear before iPSCs are ready for clinical treatments. The creation of iPSCs is based on "unpacking" genes—the parts of DNA that regulate cell function—to allow reversion to a stem cell state. When hESCs differentiate, the genes that are no longer needed are packed by proteins called histones, which can prevent those genes from being accessed. Scientists refer to these packaging patterns as chromatin marks; so far, the chromatin marks of iPSCs are distinct from the original cell and the cell they ultimately differentiate into, as well as hESCs. The concern is that there may be genes available for expression in iPSCs that should be dormant. Having genes aberrantly expressed in stem cells could cause diseases, including cancer.

If iPSC-derived MSCs pose any risk, limiting their ability to travel in the body will be imperative. This is one of the reasons why The Maverakis Lab is working on hydrogel delivery of MSCs. Hydrogels are gelatinous matrices that can provide an environment for MSCs to develop within. The hydrogel has small molecules attached to the matrix that bind the MSCs and cause them to release factors that encourage growth and healing in the surrounding tissue. Not only does the hydrogel provide important stimulus for the MSCs, but it can also localize MSCs to the wound site.

Stem cells offer the promise of personalized medicine: tissue repair without rejection, drug screening to provide accurate dosing and effective medicines with fewer side effects, and custom treatments for diverse cancers. Whether due to advances in stem cell research or for self-preservation in the face of aging, public sentiment has shifted. The last study from Virginia Commonwealth University indicated majority support (62%) even for research on hESCs[5]. Although scientists have discovered many facets of stem cell biology, there is still a veritable treasure trove of opportunities that will undoubtedly improve our ability to treat disease.

[1]Funk, Carey. "VCU LIFE SCIENCES SURVEY." 2002. PDF file. Web. 11 Mar. 2016. http://lifesciences.vcu.edu/media/life-sciences/docs/survey2002.pdf

[2]Sen, Chandan K. et al. "Human Skin Wounds: A Major and Snowballing Threat to Public Health and the Economy." *Wound repair and regeneration : official publication of the Wound*

Healing Society [and] the European Tissue Repair Society 17.6 (2009): 763–771. *PMC*. Web. 11 Mar. 2016.
[3]Guerra, Alberto Daniel et al. "Mesenchymal Stromal/Stem Cell and Minocycline-Loaded Hydrogels Inhibit the Growth of *Staphylococcus Aureus* That Evades Immunomodulation of Blood-Derived Leukocytes." *The AAPS Journal* 17.3 (2015): 620–630. *PMC*. Web. 11 Mar. 2016.
[4]Takahashi, Kazutoshi and Shinya Yamanaka. "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors." *Cell* 126.4 (2005): 663-676. CellPress. Web 11 Mar. 2016.
[5]Funk, Carey. "VCU LIFE SCIENCES SURVEY 2010." 2010. PDF file. Web. 11 Mar. 2016. http://lifesciences.vcu.edu/media/life-sciences/docs/survey2010.pdf