IQP-43-DSA-6019
IQP-43-DSA-2981

STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By:

_____ _____

Kathleen Foust Nicholas Kelley

October 27, 2010

APPROVED:

_____

Prof. David S. Adams, Ph.D.
Project Advisor

ABSTRACT

The purpose of this project was to investigate the topic of stem cells and to determine the impact of this controversial technology on society. The technology itself was investigated by documenting the various types of stem cells, describing their various medical potencies and listing which diseases have already been treated by stem cells. The effect on society was investigated through a discussion of their complex ethical and legal issues.

TABLE OF CONTENTS

PROJECT OBJECTIVES

The objective of this IQP project was to examine the topic of stem cells, and to discuss the effect of this controversial new technology on society. The purpose of chapter-1 was to describe how stem cells are classified and their sources and potencies. Chapter-2's purpose was to document the types of experiments that stem cells have successfully been used for. Chapter-3's purpose was to examine stem cell ethics, and chapter-4 examined the legal issues of stem cells.

CHAPTER-1: STEM CELL TYPES

Kathleen Foust

Stem Cell Introduction

Originating around the late 1800s, the topic of Stem Cells is a rapidly growing area in science. Stem cells have the extraordinary capability to change or differentiate into different cell types in the body. Since they have the ability to replace dead cells, in adult tissues they serve as an internal repair system, and this repair function is the basis of the new field of regenerative medicine. When a stem cell divides, it can create another stem cell, or it can create a more specialized cell for the body, such as a blood or skin cell. This asymmetric cell division (producing two cell types) is an important characteristic of stem cells since they are able to divide and repair indefinitely. The challenges of research labs are to learn to isolate them, and once isolated learn to grow and differentiate them. The purpose of this chapter is to describe the various types of stem cells as an introduction to later chapters on their applications, ethics, and legalities. Special attention will be paid to describing their various potencies, as this topic directly relates to their ability to cure specific types of diseases.

Contrary to popular belief there are numerous types of stem cells. This fact strongly affects the stem cell debate, as only one type of stem cell destroys an embryo to obtain them. Additionally as you will see in a later chapter, even some religions allow for the use of embryo-destroyed stem cells. The four main types of stem cells are: embryonic stem cells (ESCs), adult stem cells (ASCs), induced pluripotent stem (iPS) cells, and parthenogenetic ES cells. Embryonic stem cells come from the early stages of development, and an embryo is usually destroyed to obtain them, so these cells are the most controversial. Adult stem cells are derived

from an adult organism, and they serve as the tissues repair and replacement cells. Induced pluripotent stem cells, are created from typically adult skin cells that are de-differentiated by transfection with genes. Parthenogenetic ES cells are derived from parthenotes, chemically-treated eggs that divide without fertilization to make a blastocyst from which ES cells are obtained. Stem cell research in the past decade has grown rapidly into one of the most interesting and researched topics in all of science. Stem cell research holds promise for many cures, treatments, and solutions to modern health problems.

Stem Cell Potencies

Different stem cell types have different potencies. *Totipotent* stem cells have the ability to make the entire embryo and extra-embryonic tissue. The only truly totipotent cells are newly fertilized cells though the 8-cell stage. *Pluripotent* stem cells have the capability to transform into any tissue in the body except the placenta. ES cells are of this type. Because ES cells have the ability to repair any tissue in the body, these cells are also the most medically useful. *Multipotent* stem cells have the capacity to make several types of related cells. For example, hematopoietic stem cells (HSCs) can form all of the cellular components of blood, including red blood cells, numerous types of white blood cells, and platelets. Mesenchymal stem cells (MSCs) can form several types of mesodermal derived tissues. Also neural stem cells (NSCs) can form and repair several parts of the nervous system. *Unipotent* stem cells only have the ability to make one type of cell, usually the same tissue the cell is isolated from, and so these cells are the least useful medically. It is important for scientists to understand which stem cells have specific potencies to know which diseases they might treat. Scientists are also working to develop protocols to induce stem cells into more than one potency.

Embryonic Stem Cells

Embryonic Stem Cells (ESCs) are derived from *in vitro* fertilized (IVF) embryos. Mouse ESCs were first isolated independently by two labs (Martin, 1981; Evans and Kaufman, 1981), but human ESCs were not isolated and grown until seventeen years later (Thomson et al., 1998). Egg and sperm from donors are united *in vitro* to make a zygote (**Figure-1,** diagram upper left). The zygote is grown about 3-5 days to make a hollow ball of cells termed a *blastocyst* (diagram center). The blastocyst contains the inner cell mass, the blastocoel (cavity), and the trophoblast (cells lining the cavity). The inner cell mass (blue in the diagram) is the cluster of cells that gives rise to the embryo and then the fetus, the blastocoel is the fluid filled cavity for an early preimplantation stage, and the trophoblast is the outer cell layer of the blastocyst that is responsible for implantation and which develops into the extraembryonic tissues (NIH, 2010). The inner cell mass contains the ESCs. Once the blastocyst is 3 to 5 days old, the inner cell mass is transferred into a laboratory culture dish (lower diagram) that contains a culture medium, nutrients, and a feeder layer. The feeder layer provides a surface to which the ES cells attach, and also provides growth factors.

Figure-1: Derivation of Embryonic Stem Cells. A newly fertilized egg (upper left) is grown about 3-5 days to make the blastocyst (diagram center) from which ES cells are derived from the inner cell mass (blue). The ES cells are grown in a co-culture with mouse fibroblasts or other human cells to provide an attachment surface and growth factors. (Yu and Thomson, 2006)

Once many cell culture dishes are grown, this establishes an embryonic stem *cell line*. Establishing cell lines is important, because these lines can be shipped to other labs or hospitals where they can expand them further for experiments. The best ES cell lines are immortal and can provide the large numbers of cells needed for therapy implantation.

As mentioned previously, ES cells are *pluripotent*, and can generate any cell in the body except for the placenta. These cells can give rise to all three embryoninc germ layers, the ectoderm, mesoderm and endoderm (Yu and Thomson, 2006). Establishing procedures for getting ES cells to differentiate into specific cell types is the subject of current research, and will be discussed in detail in Chapter-2 Stem Cell Applications for specific diseases. But in general, the ES cells are treated in the culture dishes with different growth factors or specific genes are inserted to produce proteins that change the undifferentiated cells into the specific cells that are needed (NIH, 2010). It is imperative that researchers find the specific laboratory protocols for turning ES cells into the differentiated ones so they can be used in therapy.

Although ES cells are the most medically potent because they destroy an embryo to obtain them, they come with ethical concerns. This topic will be discussed in detail in Chapter-3 Stem Cell Ethics, but briefly individuals that argue an IVF embryo has the same rights as a living human are against working with ES cells. The main controversy focuses on when life begins, and should an embryo be used to save other lives.

iPS Cells

Induced pluripotent stem (iPS) cells are one of the hottest topics in all of stem cell research today. Human iPS cells were first derived in 2007 from the facial skin cells of a 36 year old woman and a 69 year old man (Takahashi et al., 2007). In this process, skin fibroblast cells

are transfected with genes encoding transcription factor proteins that help induce a de-differentiation of the skin cells to make ES-like pluripotent cells. In some respects, the scientists created these iPS cells by erasing the cells' "memory", causing them to go back to their embryonic state where they could be reprogrammed into the type of cell needed for therapy (Vogel, 2008). The initial procedure used four transcription factor genes for Oct3/4, Sox2, Klf4, and c-Myc. However, these iPS cells when implanted in mice caused tumors, so subsequent protocols omited the c-Myc component to prevent tumor formation (Nakagawa et al., 2008).

The excitement for these cells is if they are truly pluripotent, they can be used for therapies as a replacement for the more ethically problematic embryo-derived ES cells. No embryo is destroyed to obtain iPS cells; iPS cells are created from adult cells. Moreover, the genotype of the iPS cell line matches that of the donor skin cell, so a specific patient's own skin cells could be used to derive an iPS line for treating that person's disease, without having the iPS cells rejected from the body. So much current research is focused on the exact potency of iPS cells. One key finding is that mouse iPS cells have the ability to make an new entire new mouse, so this demonstrates a very high level of potency of the mouse iPS cells (Boland et al., 2009). But some labs find that human iPS cells divide slower and are less robust than embryo-derived ES cells (Dolgin, 2010). Researchers are continuing to try to create rapidly dividing human iPS cells for human treatments.

Adult Stem Cells

Adult stem cells (ASCs), also called somatic stem cells, maintain homeostasis in the body by replacing damaged or dead cells. Somatic cells are any type of cell in the body other than the gametes. Compared to ES cells, ASCs are less potent, harder to isolate, and harder to grow. In

fact, scientists are still trying to determine exactly which adult tissues contain ASCs. The origin of adult stem cells in some mature tissues is still under investigation (NIH, 2010). Well proven types of ASCs include hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), neuronal stem cells, and epithelial stem cells (NIH, 2010). But no embryo is destroyed to obtain ASCs, so scientists would like to work with these cells so long as they are potent enough to treat a specific disease. The fact that they do not destroy embryos makes ASCs more marketable since they don't have an ethical conflict. Adult stem cells are also important because they limit the risk for rejection from the body. Graft-versus-host disease (GVHD) is a potential risk with all stem cell implants, but if taken from a patient's own body and expanded the incidence of GVHD is minimal (Mayo, 2010).

ASCs are difficult to isolate because they are so rare in the body. For example, neuronal stem cells have been estimated to represent about 0.001% of all adult brain cells. The ASCs are surrounded by large numbers of differentiated cells, and they become differentiated only when the surrounding tissue and cells need them. These surrounding cells and the low abundance of ACSs make it more difficult to harvest ASCs than ES cells.

Hematopoietic Stem Cells

The world's most characterized type stem cells are hematopoietic stem cells (HSCs). These cells have been used for over 50 years now in bone marrow transplants to treat specific types of blood disorders (Abbott, 2003; Medscape, 2005). **Figure-2** shows how *multipotent* HSCs differentiate into different types of blood cells, and how stromal stem cells differentiate into cartilage (NIH, 2010). HSCs are traditionally obtained from bone marrow (as shown in the diagram), but more recently they are also obtained from umbilical cord blood, or from peripheral

blood in people treated with hormones to release HSCs into the periphery from marrow. HSC transplants are routinely used to treat specific types of blood cancers, especially leukemia, and other blood disorders (HSCs, 2005). Thus, HSCs are a very clear example of how stem cells are already being used to treat some diseases. With respect to current HSC research, some scientists have been looking into turning HSCs into other types of stem cells to be used in treatments (HSCs, 2005).

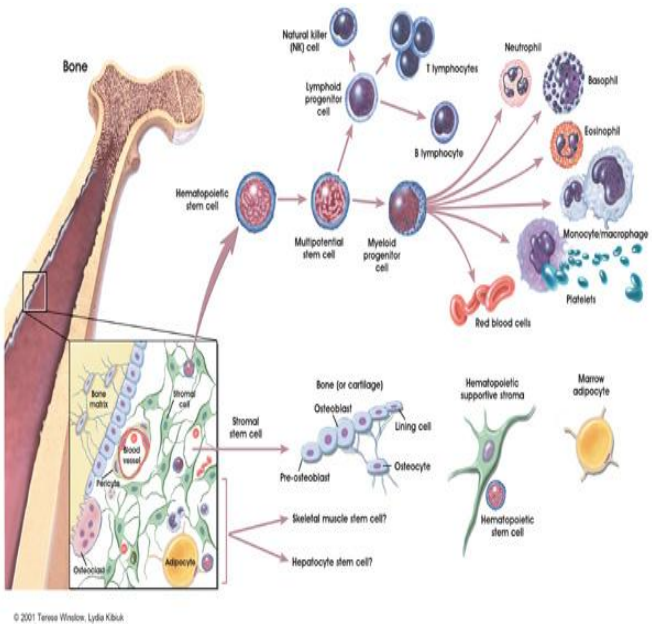

Figure-2: Differentiation of Hematopoietic Stem Cells. HSCs are typically present in bone marrow (diagram left). The HSCs for myeloid and lymphoid precursor cells (diagram center) that differentiate into all the cellular components of blood. (NIH, 2010)

Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) are adult stem cells with the ability to form many different types of tissue including osteocytes, chrondrocytes, adipocytes, astrocytes, oligodendrocytes, and skeletal, smooth, and cardiac muscle (MSCs, 2009). Because MSCs can form so many different types of tissues yet are adult stem cells, these cells have recently been the subject of much research as possible replacements for ES cells, especially for bones and the skeletal system.

Neuronal Stem Cells

The nervous system has its own type of stem cells called neuronal stem cells (NSCs). Before the discovery of NSCs, scientists held the belief that the human brain and spinal cord could not regenerate (Rebuilding, 2005). Adult NSCs are already being used to treat animal models for Parkinson's disease, as we discussed in Chapter-2, but have not yet been tested on humans. But NSCs are very difficult to isolate, so much research focuses on this topic.

Epithelial Stem Cells

Epithelial Stem Cells form 60% of the differentiated cells in the body; they form cells covering the internal and external surfaces of the body (The Adult, 2005). Covering surfaces are constantly being replaced in adult tissue from the action of epithelial stem cells, so the hope is to isolate them to treat skin disorders or burn patients (The Adult, 2005).

Chapter-1 Conclusion

As documented in this chapter, a variety of stem cell types exist, each with different potencies and ethics. ES cells have the best medical potency as they can form any tissue in the body, but they come with strong ethical concerns since embryos are destroyed to isolate ES cells. iPS cells are induced from skin fibroblast cells, and appear so far to represent a possible replacement for pluripotent ES cells, although much more research will be requried to demonstrate whether iPS cells are truly pluripotent and whether they can be used for therapies. Adult stem cells are less potent than ES cells, but might have limited uses for treating some diseases, although they are difficult to isolate and grow. The information discussed in this chapter will serve as a template for helping interpret our subsequent chapters on stem cell ethics and legalities.

Chapter-1 Bibliography

Abbott, Cate (2003) "Bone Marrow Transplantation". London Health Sciences Centre. http://www.lhsc.on.ca/transplant/bnmarrow.htm.

Boland MJ, Hazen JL, Nazor KL, Rodriguez AR, et al (2009) Adult Mice Generated From Induced Pluripotent Stem Cells. *Nature* **461**: 91-94.

Dolgin E (2010) Gene flaw found in induced stem cells. *Nature* **464**: 663.

Evans MJ, Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. *Nature*, 292(5819): 154-156.

Hematopoietic Stem Cells (2005) NIH, Stem Cells, Chapter-5. http://stemcells.nih.gov/info/scireport/PDFs/chapter5.pdf

HemoGenix (2009) Mesenchymal Stem Cell System. http://www.hemogenix.com/the_mesenchymal_stem_cell_system/

Martin, Gail (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci USA*, 78(12): 7634-7638.

Medscape (2005) History and Rationale for hematopoietic stem cell transplants. *Medscape General Medicine*. http://www.medscape.com/viewarticle/499049_2. \

Mesenchymal Stem Cells (2005) NIH, Stem Cells, Chapter-2. http://stemcells.nih.gov/info/scireport/PDFs/chapter2.pdf

Nakagawa M, Koyanagi M, Tanabe K, Takahashi K, Ichisaka T, Aoi T, Okita K, Mochiduki Y, Takizawa N, Yamanaka S (2008) Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. *Nature Biotechnology* **26**(1): 101-106. Epub 2007 Nov 30.

National Institute of Health (2010) Stem Cell Basics. http://stemcells.nih.gov/info/basics/basics2.asp.

Rebuilding the Nervous System with Stem Cells (2005) NIH, Stem Cells, Chapter-8. http://stemcells.nih.gov/info/scireport/chapter8.asp

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007) Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* **131**: 1-12.

The Adult Stem Cell (2005) NIH, Stem Cells, Chapter-4. http://stemcells.nih.gov/info/scireport/chapter4.asp

The Mayo Clinic Staff (2010) *Stem Cell Transplant.* http://www.mayoclinic.com/health/stem-cell-transplant/MY00089/DSECTION=risks

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived From Human Blastocysts. *Science* **282**: 1145-1147.

Yu J, and Thomson JA (2006) Embryonic Stem Cells. *NIH Publication*. Bethesda, MD: Regenerative Medicine. http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf

Chapter-2: Stem Cell Applications

Nicholas Kelley

The application of stem cells to treat chronic diseases, although still in its infancy, shows enormous potential for scientific breakthroughs. This chapter will focus on how stem cells have been applied to treating diseases, as the topic of their benefit to society factors strongly into our subsequent ethics discussions. Currently, adult stem cells (ASCs) are already being used to treat over 73 different medical conditions, and are the subject of over 1400 specific FDA-approved clinical trials (Saunders et al., 2008). These diseases include but are not limited to: autoimmune disorders, diabetes, genetic diseases, heart tissue regeneration, breast reconstruction, leukemia, organ replacement, neuroblastoma, Parkinson's disease, cerebral palsy, sickle cell disease, and spinal cord injuries (Saunders et al., 2008). This chapter will focus on some of these applications, including diabetes, heart tissue regeneration, spinal cord injuries, and Parkinson's disease.

To treat any disease with stem cells, one must first establish a stem cell *line*, regardless of what type of stem cell is used. Establishing a cell line is far easier for embryonic stem (ES) cells than with ASCs, as ES cells are far easier to grow. And in addition, as discussed in Chapter-1, ES cells are far more potent than ASCs. So for these reasons, many researchers perfer to work with ES cells for their medical applications in spite of their ethical controversy.

Treating Diabetes with Stem Cells

Diabetes currently affects 7% of the world's population, and is the sixth leading cause of death. Diabetes is also associated with increased risk for heart disease, stroke, kidney disease, blindness, and amputations. Diabetes accounts for one out of every ten health care dollars

currently spent in the US (Goldwaite, 2006). Although diabetes can currently be managed through insulin injections, it cannot be cured.

Diabetes manifests itself in two major forms type 1, and type 2. In type 1, the body's immune system identifies the insulin-producing beta cells (β-cells) of the pancreas as a hostile presence, and proceeds to attack them, causing a reduction in the amount of insulin produced and a dysregulation of blood glucose. Type 2 diabetes, afflicting many more than type 1, is characterized by insulin-resistance which increases over time. **Figure-1** shows the normal checks and balances of glucose homeostasis that are no longer adhered to in diabetic patients.

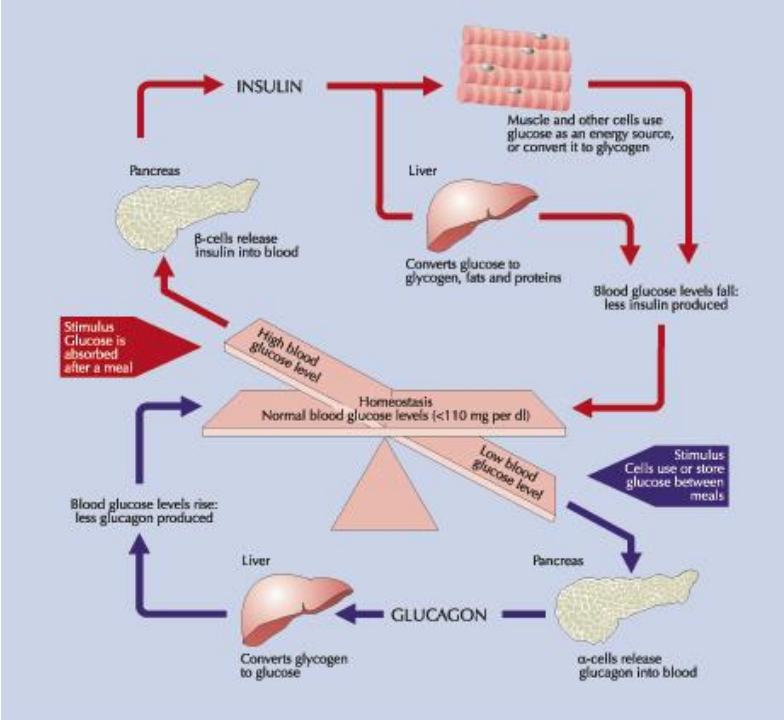

Figure-1: Diagram of Glucose Homeostasis in the Body. Shown are the main ways in which glucose levels are increased and decreased in the blood, as regulated by the hormones insulin and glucagon. (Keiran, 2009)

Transplanting β-cells to "cure" type 1 diabetes was first successfully performed in 1990 at the Washington University Medical Center in St. Louis. By 2000, many islet transplants had

been performed using a so-called Edmonton protocol (named after the University of Alberta in Edmonton), which involves isolating islets from cadavers and placing them into the portal vein of the diabetic patient. Unfortunately, this process damages the transplantable tissue, requiring β-cells from at least 2-3 cadavers, and along-term study on Edmonton transplant patients showed that less than 10% of the recipients remained insulin injection independent after five years. Apparently the immune system continued to destroy the implants and the remaining islets.

These challenges led researchers to believe that type 1 diabetes may be an appropriate candidate disease for stem cell therapy because the damage is initially localized only to a particular cell type (Goldwaithe, 2006). Perhaps ES cells could be grown in culture, then differentiated into insulin-producing cells, and placed into the patient. In fact, it has already been shown that, in both mice and humans, ES cells have the ability to differentiate into insulin producing cells (Assady et al., 2001; D'Amour, 2006). And these cells have been used to treat diabetic mice producing normal glucose regulation. But this ES cell treatment has not yet been performed in humans. In humans, eventually induced pluripotent stem (iPS) cells could be produced from a specific patient, and then differentiated into insulin producing cells that are genetically identical to that patient, but this also has not yet been achieved. Once perfected, this technique would eliminate the need for immune suppressing drugs.

Treating Damaged Heart With Stem Cells

Cardiovascular disease (CVD) is a broad term that includes hypertension, congestive heart failure (CHF), stroke, and coronary heart disease. CVD has been the leading cause of death in the U.S. every year since 1900, except for 1918, when there was a large influenza epidemic (NIH, 2006). In 2002, CVD claimed as many lives as cancer, chronic lower respiratory

diseases, accidents, influenza, and pneumonia combined (World Health Report, 2004). Within a year of being diagnosed with CHF, one in five people die. This accounts for the deaths of approximately 2600 Americans every day, or one death every thirty-six seconds. Cardiovascular disease also cost about 400 billion dollars in health care costs in FY 2005 (NIH, 2006). With the aging U.S. population and increased incidence of obesity and type 2 diabetes, CVD will become an even larger problem in the future.

Regardless of which type of CVD strikes, the result is damage to cardiac muscle cells (cardiomyocytes) placing a larger burden on the cells that remain. This stress to the heart causes the formation of non-contractile scar tissue, ventricle blood thinning, and the stretching of viable cardiac cells. Current methods of treating this problem such as changing the shape of the left ventricle, or implanting a pacemaker or defibrillator, while helpful, do not restore function to the damaged tissue (NIH, 2006). Restoring the damaged heart tissue through repair or regeneration, represents the best chance of restoring the heart to its normal function. While heart transplantation does offer a viable alternative to replacing damaged tissue or inserting assist devices, organ availability and graft vs host disease limit this approach severely.

Currently clinical trials using stem cells to repair heart tissue have been performed in human patients with adult stem cells (Britten et al., 2003; Siminiak et al., 2004). But it is too early to gauge the effectiveness or make comparisions because of a variety of reasons, including differences in the condition being treated, the method of delivery, and the primary outcome measured by individual studies. Despite the issues of comparing the effectiveness of trials to one another, the results have been promising. In 2001, Menashce et al. reported the successful implantation of autologous skeletal myoblasts (cells that repair or enlarge voluntary muscles) into the scar tissue of a patient with severe ischemic heart failure who was also undergoing

coronary bypass. Examination of the heart five months after surgery showed that the treated heart pumped blood more efficiently and seemed to improved the patients' health. The results of this individual study allowed the development of Phase I and Phase II clinical trials. These trials included many different stem cell types, including ES cells, skeletal myoblasts (SMs), adult bone-marrow derived cells, and adult cardiac stem cells. **Figure-2** shows a basic outline of treatment using autologous bone marrow stem cells.

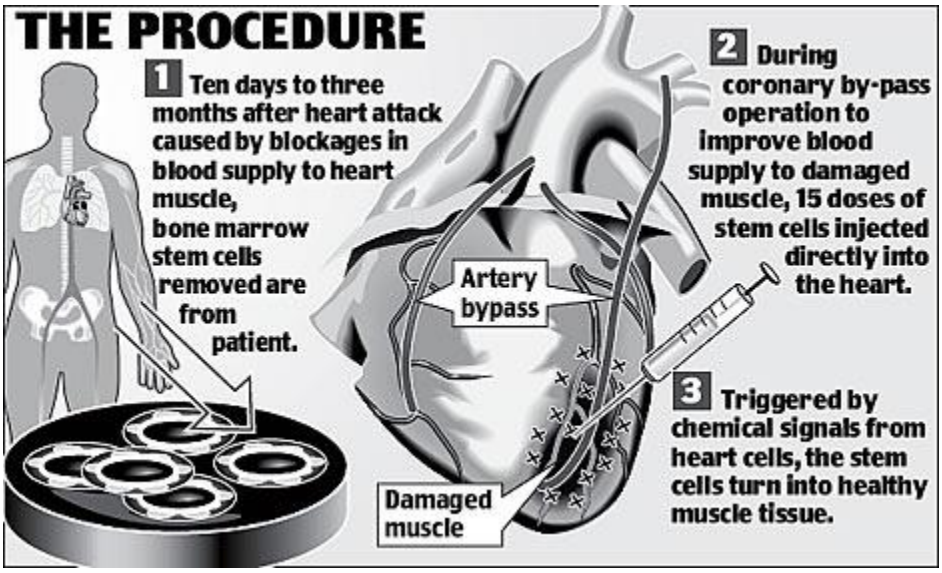

Figure-2: Healing a Wounded Heart by Autologous Bone Marrow Stem Cells. (Derbyshire, 2007)

While skeletal myoblasts are normally committed myogenic producers, their autologous origin and high proliferation potential encouraged their use as the first major stem cell type used as treatment. Studies in both rats and humans have shown that these cells are able to repopulate the scar tissue, improving heart function. But the major issue with these cells are their inability to function in complete harmony with the native heart muscle, creating small heart murmurs. Despite this fault, human Phase II studies of therapies using skeletal myoblasts are underway (NIH, 2006).

Human adult bone marrow-derived stem cells were proven in 2001 by Jackson et al. to be able to regenerate endothelial cells in a mouse heart attack model. Also during 2001, Orlic et al. showed that by directly injecting mouse bone marrow-derived cells into damaged heart muscle, they could form new cardiomyocytes, vascular endothelium, and smooth muscle cells. Nine days after these stem cells were injected, it was found that "newly formed myocardium occupied nearly seventy percent of the damaged portion of the ventricle" (NIH, 2006). It was also seen that survival rates in mice that received the injection were much greater than those that did not. However, these results are controversial, as other studies have found no improvement upon treatment, so larger trials are currently under way examining this issue more closely.

Recent evidence suggests that the heart itself is home to a small population of endogenous adult stem cells, helping the heart to facilitate minor repair, as well as replacing small numbers of cells do to cell death. These cells have been isolated and characterized in mice, rats, and human tissues. These cells however can only be harvested in limited numbers, and require separation and expansion *ex vivo* for several weeks. Injecting these cells into the scar tissue have shown cardiomyocyte formation and improvements in systolic function. Despite the limited ability to harvest and grow these cells long term, resident cardiac stem cells are viewed by most scientists as a possible replacement for ES cell treatments. This has led the National Heart, Lung, and Blood Institute to fund several clinical trials that will further explore the use of these cells as a regenerative medicine.

Regardless of which stem cell type eventually becomes the prominent leader in heart regenerative therapy, the method in which cells are successfully delivered to the site will play a large role. Currently there are three common approaches to insert stem cells into the heart. The first is intravenous injection in which stem cells are placed with blood into the patients veins.

The second is direct infusion, which is the direct insertion of stem cells into the coronary arteries, allowing a more controlled approach of where the stem cells attach. The third approach is when stem cells are injected directly into the ventricular wall, further increasing control of where they attach. However, despite improvements in the delivery efficiency, these methods remain very limited due to the high percentage of death of the injected cells. As many as 90% of the cells die shortly after implantation (NIH, 2006). Currently there is another method in development to deliver stem cells to the heart. Here at WPI, Genn Gaudette, PhD, an assistant professor in biomedical engineering, is attempting to restore function to damaged hearts using bone marrow derived stem cells. Professor Gaudette has developed a novel system for " seeding biopolymer micro-threads with hMSCs, then stitching those threads directly into a damaged heart" (NIH Funds, 2009). This technique significantly improves the precision in which stem cells are placed into the damaged area, and it may also improve the survival rate of the transplanted cells.

Treatment of Spinal Cord Injuries Using Stem Cells

Every year 12,000 people in the United States sustain spinal cord injuries. These injuries are usually caused by automobile accidents, falls, sports injuries, and gunshot wounds. The annual cost of these injuries in 2006 approached ten billion dollars, and may well be over this amount currently (Stem Cell Treatment, 2006). In a spinal cord injury, numerous different cell types are damaged. These damaged cells include the neurons that signal from the body to the brain and vice versa. While in many injuries the spinal cord itself is not severed, there is a large amount of damage to the axons and oligodendrocytes. The surviving axons cannot carry signals strong enough to reach the brain due to the loss of the insulating myelin sheath, which is created by oligodendrocytes, resulting in paralysis. Even if the myelin sheath is not damaged, it has

been shown that while it promotes normal neuronal function, it also inhibits the growth of new neurons.

Due to the fragile nature and the importance of the spinal cord, researchers first established studies on the safety these experiments. The first lab to successfully differentiate human embryonic stem cells to become oligodendrocytes was accomplished by Keirstead et al. This important study was done on two sets of rats, one that had mild spinal injury, and one that had severe spinal injury. In both cases the rats were injected with oligodendrocytes seven days after the initial injury. In rats with severe spinal cord injury, the cells were seen to correctly migrate to the appropriate site in the spinal cord, and begin forming new myelin sheaths. However, those that were only mildly injured showed no increase or decrease in myelin production, resulting in no change in their walking ability after transplantation. This study proved " ..in animals that are only slightly injured, the transplantation does not cause visible harm, and the injury is not hiding any damage the cells may have caused to the spinal cord or surrounding tissue" (Study Establishes 2006). With this study, researchers can go into further clinical trials without worry that injections would further injure a patient.

A treatment developed by Hans Keirstead et al. using human ES stem cells improved the mobility in rats with spinal injuries, and provided the first evidence that stem cells were capable of helping to treat the damage caused to spinal cords. This study was done on two groups of rats, one that was injected seven days after injury, and another that was injected with the same treatment ten months after the injury. The time frames allowed researchers to conclude that most spinal cord damage occurs during the first two weeks after injury. In the rats treated seven days after their injury, myelin tissue was found to be forming as oligodendrocytes were beginning to wrap themselves around damaged tissue. Two months later the injected rats showed significant

improvements in their ability to walk compared to those that received no treatment. It was found that rats treated ten months after their injury did not have their motor skills return to them after any length of time.

The first human patient treated with hES cells for spinal cord injuries was injected on October 11, 2010 by Geron Corporation. "The primary objective of the phase I study was to assess the safety and tolerability of human embryonic stem cell-derived oligodendrocyte progenitor cells (GRNOPC1) in patients with 'complete' American Spinal Injury Association (ASIA) Impairment Scale grade-A thoracic spinal cord injuries" (US Treats 2010). Those participating in this study must have received their spinal cord injury within fourteen days of applying. Due to the fact that the study is currently in its beginning stages, no further information on the effectiveness of this treatment is known.

Treating Parkinson's Disease with Stem Cells

Parkinson's Disease (PD) is the second most common form of neurological disease. The disease manifests itself as a progressive degeneration of midbrain dopamine-secreting neurons. Dopamine is the chemical involved in communication between neurons and muscles. It is essential for the proper strength and execution of motor function. As dopamine-secreting neurons continue to die, communication is severed, and symptoms appear such as tremors, rigidity of limbs, hypokinesia, and difficulties with walking and balance. The primary treatment for years has been the supplement of dopamine with levadopa. But this treatment does not stop or even slow the progression of the disease at all, and creates Dyskinesia, another movement disorder. The cause of PD is still unknown, but is believed to be a combination of environmental and genetic factors, shown below in **Figure 3**.

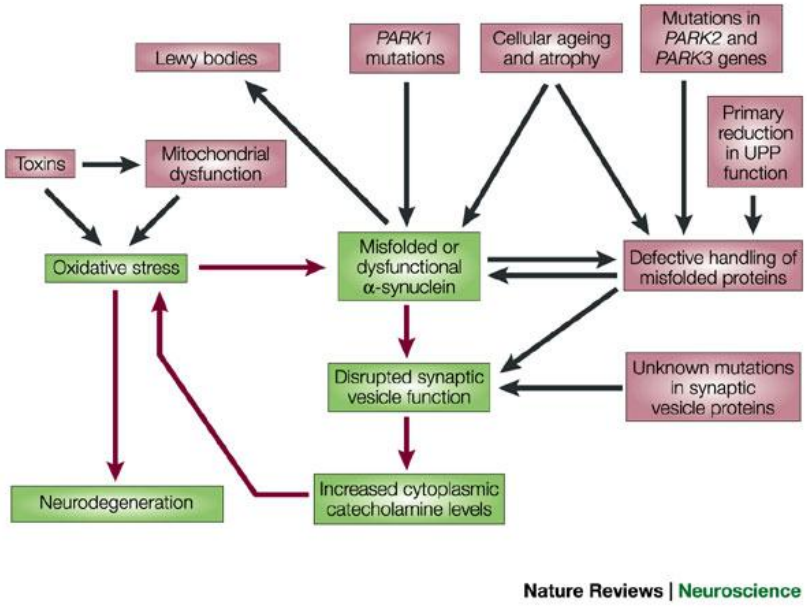

Figure-3: The Various Causes of Parkinson's Disease. The neuro-degeneration of PD can be caused by oxidative stress induced by toxins, misfolded proteins, mutations in PARK genes, etc. (Lotharius et al., 2002)

The first cellular studies attempting to treat PD began in the 1970s, where fetal tissue from a mouse substantia nigra was transplanted into an adult rat eye. These cells were found to develop into mature dopamine neurons. Surgeons first attempted to transplant dopamine-releasing cells into a human brain in the 1980s, and while some patients achieved some relief, it was deemed that the risk to the patient out-weighed the benefits. Due to these trials, the NIH funded two large controlled clinical trials beginning in 1988. These trials involved the transplantation of tissue from aborted fetuses into patients with PD. Both studies showed however only mild benefit, as well as the negative side effect of dyskinesias. Promising findings from this trial emerged as well. It was found that younger patients with only mild PD responded well to the grafts. PET scans of these patients showed that transplanted dopamine neurons had survived and were maturing. Researchers in Sweden meanwhile were following transplant patients for eleven years after surgery and concluded that the side effect of developing

dyskinesias was related to the disruption caused to other cells in the brain during transplant. This gives hope that this side effect can be minimized by future improvements in surgical technique.

Because PD targets only one specific cell type, like Diabetes, it is a very appropriate choice for stem cell therapy. The fragile nature of the brain, and the large incidence of death once brain tumors are found, led to studies to establish the safety of stem cell treatments. These studies found that when transplanting *adult* neural stem cells into rats, the cells do not continue to divide once differentiated, and none formed tumors. They did not form irregular tissue and were found to have normal karyotypes.

In 2008, studies in PD patients conducted by the Instituto Brazzini Radiologos Asociados in Lima, Peru, using autologous adult stem cells derived from bone marrow injected into the patients' blood stream, showed "considerable improvement in Parkinson's symptoms after stem cell implants" (Saunders et al., 2008). Doctors in this study claimed improvement in all forty-seven patients within one week of treatment. And about 75% of the patients saw a greater than 50% improvement of symptoms one month after treatment.

In 2004, another PD study was done by Michel F. Levesque and colleagues using autologous differentiated adult neural stem cells (Levesque et al., 2005). The patient was followed for the next five years to collect data and did not show any adverse side effects to the treatment, and at three years post treatment was found according to the Unified Parkinson's Disease Rating Scale (UPDRS) to have improved symptoms by 81% while on medication, and 83% while off medication. Five years post treatment has shown that the patient's motor scores had returned to control base-line. The study concluded that "the combined GABAergic and dopaminergic cells produced a long-lasting motor improvement. This approach has the potential

to make neural stem cell therapy acceptable and available to a large number of patients" (Levesque, 2009). These results give hope that a cure for PD lies in the foreseeable future.

While there have been many advancements in stem cell therapies in the recent past, there still remains great potential for future treatments of other chronic or terminal diseases. Stem cell treatments may one day lead to regenerating lost limbs or injured organs, and could have a major impact on patient's quality of life.

Chapter-2 Bibliography

Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki K, and Tzukerman M (2001) "Insulin Production by Human Embryonic Stem Cells". *Diabetes* **50**: 1691-1697. http://diabetes.diabetesjournals.org/cgi/content/full/50/8/1691

Britten MB et al (2003) Infarct Remodeling After Intracoronary Progenitor Cell Treatment in Patients With Acute Myocardial Infarction. *Circulation* **108**: 2212-2218.

"Culture of Human Embryonic Stem cells" (hESC) (2006) National Institute of Health. http://stemcells.nih.gov/research/nihresearch/scunit/culture.asp

D'Amour, Kevin A (2006) Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells. *Nature Biotechnology* **24**, 1392-1401.

Derbyshire, David (2007) " Stem cell surgery could repair damage left from heart attack". *Daily Mail.*

Garfinkel, Susan (2005) "Stem Cells and Parkinson's Disease." *International Society for Stem Cell Research.*

Goldwaithe CA (2006) NIH Stem Cell Information, Chapter-7. Are Stem Cells the Next Frontier for Diabetes Treatment? http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Chapter_7_Final.pdf

Kieran (2009) "Type II Diabetes: How To Step It Up To Get It Down." *Savvy Health and Fitness.* http://savvyhealthfitness.com/get-healthy/diabetes/type-2-diabetes-how-to-step-it-up-to-get-it-down

Levesque, Michael F. (2005) "Senate Committee Testimony: Spinal Cord Injured Recipient of Adult Stem Cell Therapy". http://www.leaderu.com/science/stemcelltestimony_levesque.html

Levesque, Michael F. (2009) " Therapeutic Microinjection of Autologous Adult Human Neural Stem Cells and Differentiated Neurons for Parkinson's Disease: Five-Year Post Operative Outcome." *The Open Stem Cell Journal* 2009, 1, 20-29.

Lotharius, Julie et al (2002) " Pathogenesis of Parkinson's Disease: Dopamine, Vesicles and α-Synuclein". *Nature Reviews Neuroscience* 3: 932-942.

"NIH Funds Work At WPI On Regenerating Heart Tissue And Preventing Urinary Tract Infections". *Medical News Today.*

NIH Stem Cell Information (2006) Chapter-6. Mending a Broken Heart: Stem Cells and Cardiac Repair. http://stemcells.nih.gov/info/2006report/2006Chapter6.htm

Panchision, David M (2006) "Repairing the Nervous System with Stem Cells." *Regenerative Medicine.* Department of Health and Human Services.

Saunders WJ et al (2008) Adult Stem Cell Success Stories. *Family Research Council.* http://www.frc.org/insight/adult-stem-cell-sucess-stories-2008-jan-june

Sciencedaily.com (2005) Embryonic Stem Cells Treated With Growth Factor Reverse Hemophilia In Mice: UNC Researchers.

"Shepherd Center Patient Treated in Geron Clinical Trial". http://www.shepherd.org/news/releases/2010/10/shepherd-center-patient-treated-in-geron-clinical

Siminiak T, Kalawski R, Fiszer D, et al (2004) Autologous skeletal myoblast transplantation for the treatment of post-infarction myocardial injury: Phase I clinical study with 12 months of follow-up. *Am Heart J.* **148**: 531-537.

"Stem Cell Research" (2010) *American Diabetes Association.*

"Stem Cell Treatment Succeeds In Spinal Cord-Injured Rats" (2006) *Science Daily.* http://www.sciencedaily.com/releases/2006/03/060328224824.htm

Study Establishes Safety Of Spinal Cord Stem Cell Transplantation (2006) *Science Daily.* http://www.sciencedaily.com/releases/2006/07/060720103810.htm

University of California-Irvine (2005) "Stem Cell Treatment Improves Mobility After Spinal Cord Injury". http://today.uci.edu/news/release_detail.asp?key=1320

"US Treats First Patient with Human Embryonic Stem Cells" (2010) *The Times of India.*

CHAPTER-3: STEM CELL ETHICS

Kathleen Foust

In the previous two chapters we discussed the *technology* of stem cells, describing their various types and how they can be used to benefit society. But so far we have not discussed whether we *should* be working with these cells. In this chapter we focus on the ethics of stem cells, including various religious perspectives and the author's point of view.

The Main Stem Cell Ethical Questions

The debate on stem cells invariably focuses on one type of stem cell, embryonic stem (ES) cells, and when life begins. As discussed in Chapter-1, ES cells are isolated from 5-day old blastocysts created by *in vitro* fertilization (IVF). When ES cells are isolated from the blastula's inner cell mass, it destroys the embryo, so the ethics of ES cells focuses on whether the destruction of IVF blastulas constitutes "murder".

In addition to discussing whether embryos should be destroyed to obtain ES cells, ethicists also focus on the topic of the *source* of the embryos. If ES cells are to be used, should the embryos only be obtained from IVF clinics, where they were originally created for *reproductive* purposes but are now slated for discard? Or is it allowable to create embryos solely for *research* purposes? Each US President and Congress has grappled with these important questions when designing laws for stem cell use (discussed in Chapter-4).

Science vs. religion has been one of the hottest debated topics for the past several hundred years. When it comes to when life begins, each religion has its own perspective, so it's hard to discuss which is the "correct", and each individual has his own beliefs. Does life begin at

conception, as Catholics believe? Or does it begin when the baby actually is born, or somewhere in between? Ethics is a balancing act between the *benefits* to society versus the *detriment* to the embryo. Is it murder to kill an embryo, or does the benefit of saving *existing* lives over come this negative?

With respect to adult stem cells (ASCs), contrary to the situation with ES cells, none of the five major religions are against using them for research and treatments. Isolating and growing ASCs does not require any embryos, so even the conservative Catholic Church is in favor of ASC research so long as lives are being saved, as stated by Pope Benedict XVI (Catholic Online, 2008).

Islam and Stem Cells

There is no *explicit* Islamic ruling on the topic of stem cells (Pew Forum, 2008). But in general, Muslims believe that life begins about day-40 of development, which is well past the day-5 blastocyst, and they make a distinction between the *early* stages of development (up through day-40 where the embryo has less value) and the *later* stages of development where it has more value (Siddiqi, 2002). And since IVF embryos are not in a womb, they will not develop into a human being, so they put less emphasis on IVF embryos. Thus, many in the Islamic community support ES cell research. When the followers of this religion were asked, a majority were in favor of using embryos for stem cell research. Islam's followers are in support of ES cell research because they believe that the extra embryos from IVF should not be just discarded but rather used for research (Ahmed, 2001). When polled, 62% agreed with the overall support for research on human embryos, and 43% said it was acceptable to produce

embryos for research proposes only (Ahmed, 2001). These percentages show that a majority of Muslims are in favor of using ES cell research.

Christianity and Stem Cells

Although Christianity is in favor of using ASCs, this large religion has many subsets that disagree on the use of ES cells and embryos. One subset of the Christian religion, Catholicism has strong opinions against ES cells, as they believe that life begins at conception, which rules out working with embryos. When former President Bush was at one time considering allowing limited funding for ES cell research, the US Bishop Fiorenza, President of the US Catholic Conference of Bishops, was quick to oppose (American Catholic…2006). Fiorenza even stated "… it allows our nation's research enterprise to cultivate a disrespect for human life" (American Catholic….2006). Bush eventually issued his 2001 mandate declaring that no federal money will be spent deriving new embryos or ES cell lines (discussed in Chapter-4). On the other hand, Pope Benedict XVI endorsed his support for ASC research (Catholic Online, 2008). It is imperative for the religion to support some type of stem cells so that they can be used to benefit humanity.

Within Christianity, however, other subsets *support* ES cell research, including the Methodists and Episcopalians (United Methodist Church, 2004; Faithful Progressive, 2005).

Judaism and Stem Cells

Along with Christianity and Islam, Judaism is in favor of using ASCs (Jakobovits 2002). However, when it comes to ES cell usage they have various circumstances in which they can and cannot be used. In general, those of the Jewish faith believe that *human* status is obtained after

40 days of gestation, and that the fetus only achieves full *personhood* at birth (Dorff, 2001). So prior to 40 days the IVF embryo is not a human, and Jewish law allows research on 5 day old embryos. Jewish law does not allow post implantation tissue, an embryo that has already been implanted in the uterus to be used for research, but if the fetus causes harm to the mother in any way then it is allowed to be removed and possibly used for research (Jakobovits, 2002). Thus, Judaism is in favor of using both ASCs and ES cells, under the appropriate conditions, especially if the stem cells are being used for medical purposes (Pew Forum, 2008).

Buddhism and Stem Cells

The Dalai Lama has put a significant amount of thought about the scientific process, to be able make educated decisions research advances. The Dalai Lama even meets with leading scientists on a yearly basis to explore ethical questions (Dalai Lama, 2003). It is important for religious leaders, philosophers, and scientists to meet to discuss current topics such as stem cells, so that each group can have well educated decisions on the matters at hand. Buddhism is divided on the topic of stem cells, as the Dalai Lama states, "From the classical Buddhist standpoint [of doing no harm], it has become a sentient being and extermination of that would be morally equivalent, almost, to killing a human being (Dali Lama, 2003). On the other hand, Buddhism supports research that has "compassionate motivation", meaning that if the intentions of the scientists are pure then it is permissible to carry out the research (Dali Lama, 2003). Because the scientists researching stem cells are doing so to produce treatments for diseases, it can be implied that they are practicing good intentions. The two tenets that divide the Buddhist community are 1) the prohibition of harming or destroying others, and 2) the pursuit of knowledge and compassion (Pew Forum, 2008). With respect to Buddhism and when life actually begins,

according to the Dalai Lama it is more of a grey area. He believes that there has to be more to life than just a fertilized egg, it has to have some sort of consciousness to become a human life (Dali Lama, 2003).

Hinduism and Stem Cells

Hinduism supports ASCs research, however when it comes to ES cells, Hindu's believe that life begins at conception, meaning it would kill a life to destroy a 5 day old embryo (Manickavel, 2004). However, Hindu's also recognize the difference between people and embryos, as they support abortion if the mother's life is at stake (Manickavel, 2004). These views appear to be contradicting, as it is acceptable to "murder" an embryo to save the life of the mother, so then scientists should be able to use ES cells to save people from terrible diseases. Hindus give higher significance to an already existing human that has existed longer than the embryo.

One interesting aspect of the Hindu debate about stem cells is they are strongly against any process where only the rich will benefit (Dharma Discussions, 2003; Manickavel, 2004). Hinduism traditionally looks out for the poor. In medicine, most early stages of drug development are extremely expensive, so when the drugs are first placed on the market they are expensive which benefits the rich and the pharmaceutical companies produce the drug. Therefore it will take a significant amount of time for the poor to be able to access the drugs, making it a moral controversy for the Hindus regarding the creation and distribution of the treatments. Overall, Hinduism does not support killing an embryo, but they do support saving lives with ASCs.

The Author's Personal Opinions

Personally, I believe that a 5-day embryo does not have the same moral status as a living person; they have the *potential* to become a person but are not yet a full person. At five days post-fertilization, the embryo has not even had the chance to attach itself to the endometrium lining of the uterus. At around 2 months, after the embryo has attached to the uterus and developed to begin looking like a human, I give it higher moral status. With respect to IVF embryos, I believe the excess embryos originally created for reproductive purposes by couples, who have had enough children, and who give their *consent* to use the embryos for research, should be used to create more ES cell lines to benefit someone who is already alive.

I am also in favor of producing embryos *solely* for research purposes. If these stem cells can help save lives then they should be created to do so. People should be able to decide whether to allow their embryos to be used for ES cell research. These people should be fully educated on all sides of the stem cell debate to make an educated personal decision. And when making this choice, they should not have to be swayed one way or another, for scientific or religious points of view.

With respect to using adult stem cells, I am in favor of using them as long as they are used to maximally benefit the patient. If the ASCs perform better in some cases than ES cells, then they should be used. Whether ASCs should be used in treatments because they are "ethically" better to some should not be a factor. Patients should be able to receive the best treatment for their disease, even if this involves ES cells. When treating a specific disease, if ES cells and ASCs are shown to have exactly the same ability to treat that particular disease, I agree that ASCs should be used first, as a nod to others who view ES cells as controversial.

With respect to induced pluripotent (iPS) cells, I am in favor of using them if they are shown to help a particular disease. These cells do not involve destroying an embryo, and they

are less ethically controversial than ES cells. Again as a nod to others who find ES cells ethically controversial, I would use iPS cells before ES cells in treatments if they work. But if ES cells are shown to work much better for a particular disease, I am not against using ES cells to treat that particular disease.

Overall, I am in favor of using all types of stem cells. The benefits to the treated individual, and society, outweigh the ethical controversies, and so scientists should be allowed to use whichever stem cell works best for that particular disease.

Chapter-3 Bibliography

Ahmed, Ayesha (2001) "U.S. Muslims Give Support to Embryonic Stem Cell Research – Survey" http://www.islamonline.net/english/News/2001-08/29/article6.shtml

American Catholic Organization (2006) "U.S. Bishops Protest Embryo Stem-cell Research". http://www.americancatholic.org/News/StemCell/bishops_stemcell.asp

Catholic Online (2008) "Benedict Endorses Adult Stem-Cell Research as Respecting Human Life." *Catholic*. http://www.catholic.org/international/international_story.php?id=21301

Dalai Lama (2003) "When Does a Stem Cell Become a Human Being?" http://www.mandalamagazine.org/archives/mandala-issues-for-2003/march/when-does-a-stem-cell-become-a-human-being/

"Dharma Discussions -- Mela 2003." *Hinduism Today*. Himalayan Academy. http://www.hinduismtoday.com/archives/2004/1-3/28-35_discussion.shtml

Dorff, Elliot (2001) "Embryonic Stem Cell Research: the Jewish Perspective." *United Synagogue of Conservative Judaism*. Dec. 2001. University of Judaism in Los Angeles. http://www.uscj.org/Embryonic_Stem_Cell_5809.html.

Faithful Progressive (2005) "Why Christians Should Support Stem Cell Research." *Christian Alliance for Progress.* http://blog01.kintera.com/christianalliance/archives/2005/05/why_christians.html

Jakobovits, Yoel (2002) "Judaism and Stem Cell Research" http://www.torah.org/features/secondlook/stemcell.html#

Manickavel, Valavandan (2004) "My Opinion on Stem Cell Research." *Hinduismtoday.* 2004.

Himalayan Academy. http://www.hinduismtoday.com/archives/2004/10-12/09_opinion.shtml

Pew Forum (2008) "Religious Groups' Official Positions on Stem Cell Research" http://pewforum.org/docs/?DocID=319

Siddiqi, Muzammil (2002) "An Islamic Perspective on Stem Cell Research." *IslamiCity.com*. 27 Feb. 2002. http://www.islamicity.com/articles/Articles.asp?ref=IC0202-404
United Methodist Church (2004) *Ethics of Embryonic Stem Cell Research.* http://archives.umc.org/interior.asp?ptid=4&mid=6560

Chapter-4: Stem Cell Legalities

Nicholas Kelley

Research using human embryonic stem (hES) cells is one of the most controversial topics not only in the U.S. but around the world. Because many ethical and moral issues must be considered when working with hES cells, laws have been enacted to regulate their use and funding; this chapter will investigate these laws.

Federal Stem Cell Laws in the U.S.

Because the U.S. is a Democratic Republic, it has executive orders issued by the President, and laws enacted by Congress. And there has been much fluxuation in these laws over the years, depending on which President was in office, and which party had control of Congress at the time. This led over the years to an inconsistent funding of hES cell research. This inconsistency and fear that their funding will be removed has left many scientists wary of this field, hindering the development of therapies. This section will be a consolidation of previous laws passed at the federal level.

The first of these federal laws was passed by Congress on July 12th, 1974, which banned all federally funded Fetal Tissue Research, while establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission was to devise guidelines for the protection of human subjects during medical or other scientific experiments. One year later in 1975, the commission established its guidelines, creating an ethics advisory board for fetal and fetal tissue research originating from abortions. (Stem Cell Tracker, 2009)

In 1980, President Reagan decided not to renew the Ethics Advisory Board's charter, which effectively denied their recommendation that federal funds be used for investigation of the safety of *in vitro* fertilization. The disbandment of the board resulted in a lack of federal funding for human embryo research. In 1988, a Federal panel voted to reopen this issue, and voted 18-3 in favor of approving federal funding of embryo research. However, the Department of Health and Human services accepted the testimony of the three dissenters, and extended this moratorium on funding this research. Congress attempted to override this moratorium again in 1990, but President George H.W. Bush vetoed the bill.

In 1993, President Clinton issued an executive order stating that the moratorium be lifted, and the Department of Health and Human Services Secretary, Donna Shalala, lifted the moratorium on federal funding of research according to President Clinton's order. In 1994 however, the President reversed his order due to the large amounts of letters received, so federal funding again was withheld from human embryonic research. In 1995, Congress banned the federal funding of research on embryos through the Dickey-Wicker Amendment. This removed federal funding for "the creation of human embryo or embryos for research purposes; or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in-utero" (Stem Cell Tracker, 2009). This amendment however did not state that federal funds could not be allocated to researchers using embryos donated from *in vitro* fertilization clinics (with donor permission) after the donors no longer required them. This amendment, as with all previous orders and laws, did not prohibit research that is privately funded.

In 1998, James Thomson was the first to isolate hES cells at the University of Wisconsin. This discovery lead to a large ethical debate due to the process in which these cells are isolated,

which also involves the destruction of the IVF embryo. In January of 1999, the department of Health and Human Services General Council, Harriet Rabb, gave a legal opinion to the National Institute of Heath Director Harold Varmus that the Dickey-Wicker Amendment does not apply to funding on research of ES cells. This opinion arose due the inability of these ES cells to meet the definition of an embryo. These new human ES cells however required an embryo to isolate them, therefore this research would still initially have to be derived with private funding. Later that year, Director Varmus appointed an oversight committee to deal with draft guidelines for federally funding ES cell research. Due to the large ethical issues inherent in these cells, this committee included many different professionals, including lawyers, ethicists, scientists, patent sponsors, and patients. The NIH then developed guidelines for funding of hES cell research over the next few months. But the NIH did not actually fund any research proposals then due to presidential candidate George W. Bush's opposition to the research.

In August of 2000, the NIH published guidelines for research using human pluripotent stem cells. The guidelines specifed that human embryonic stem cells must be derived with private funds from frozen embryos from fertility clinics; they must have been created for fertility treatment purposes; be in excess of the donor's clinical need; and obtained with the consent of the donor (Stem Cell Tracker, 2009). One year later, newly inaugurated President Bush prohibited federal funding of any research using ES cell lines derived after August 9, 2001. But this did not affect private sector or state funded research, claiming that this still leaves sixty stem cell lines viable for federal funding. However it was later determined that only twenty-one of these lines were feasible for research, limiting research drastically.

In 2007, President Bush issued an executive order supporting and encouraging research on alternative sources of pluripotent stem cells. Later that year Yamanaka and Thomson both

independently published papers discovering how to create induced pluripotent stem (iPS) cells. This discovery gave hope that the ethical dilemmas of ES cell research may one day be inconsequential. In 2009, President Obama upholding his campaign promises, issued the following executive order:

> ***THE WHITE HOUSE***
> *Office of the Press Secretary*
>
> _____
>
> *For Immediate Release March 9, 2009*
> *EXECUTIVE ORDER*
> - - - - - - -
> ***REMOVING BARRIERS TO RESPONSIBLE SCIENTIFIC RESEARCH INVOLVING HUMAN STEM CELLS***
> *By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:*
> *Section 1. Policy. Research involving human embryonic stem cells and human non-embryonic stem cells has the potential to lead to better understanding and treatment of many disabling diseases and conditions. Advances over the past decade in this promising scientific field have been encouraging, leading to broad agreement in the scientific community that the research should be supported by Federal funds.*
> *For the past 8 years, the authority of the Department of Health and Human Services, including the National Institutes of Health (NIH), to fund and conduct human embryonic stem cell research has been limited by Presidential actions. The purpose of this order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind.*
> *Sec. 2. Research. The Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.*
> *Sec. 3. Guidance. Within 120 days from the date of this order, the Secretary, through the Director of NIH, shall review existing NIH guidance and other widely recognized guidelines on human stem cell research, including provisions establishing appropriate safeguards, and issue new NIH guidance on such research that is consistent with this order. The Secretary, through NIH, shall review and update such guidance periodically, as appropriate.*
> *Sec. 4. General Provisions. (a) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.*
> *(b) Nothing in this order shall be construed to impair or otherwise affect:*
> *(i) authority granted by law to an executive department, agency, or the head thereof; or*
> *(ii) functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.*
> *(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity, by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.*
> *Sec. 5. Revocations. (a) The Presidential statement of August 9, 2001, limiting Federal funding for research involving human embryonic stem cells, shall have no further effect as a statement of governmental policy.*
> *(b) Executive Order 13435 of June 20, 2007, which supplements the August 9, 2001, statement on human embryonic stem cell research, is revoked.*
>
> *(Whitehouse.gov)*

The Obama order had an immediate worldwide effect, with many scientists celebrating the removal of one of the fields major roadblocks. This executive order raised the number of stem cell lines available for federal funding from a meager twenty-one to a much larger pool, with estimates ranging from 400 to 1000 lines. The large allowance in the various estimates is due to the rigorous screening process an ES cell line must pass before being permitted for federal funding.

U.S. State Stem Cell Laws and Funding

Many state laws that affect stem cell research have been enacted to allow state funding of ES cell research, and to address other pressing ethical issues such as abortion and *in vitro* fertilization. There are four sources of ES cells: aborted or miscarried embryos, unused *in vitro* fertilized (IVF) embryos, cloned embryos, and established stem cell lines. While there is no federal law banning human therapeutic cloning in the U.S., the FDA has taken it upon itself to declare that human cloning would be a new investigational drug, and would not approve any projects of this kind. This eliminates the possibility of individual states passing laws funding this type of research (Stem Cell Research, 2008). As seen in **Figure-1** below, individual states have the ability to regulate stem cell research completely, taking various stances from banning the research altogether, to funding ES cells. This creates an interesting and sometimes hostile environment.

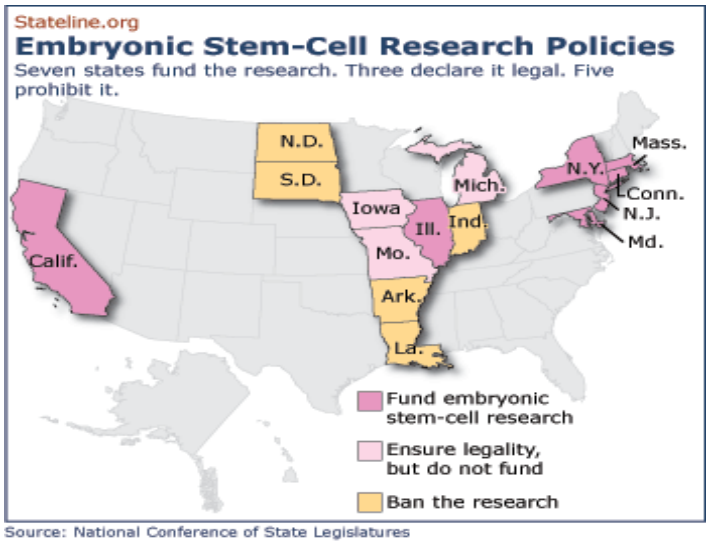

Figure-1: Individual States and Stem Cell Laws. States shown in dark pink support ES cell research with funding. States shown in light pink allow the research, but provide no funding. States shown in yellow ban the research. States shown in gray have no laws on the ES cell research (Vestal, 2009)

The first state to support ES cell research was New Jersey, which in 2004 allocated one million dollars every year for ten years to research. Since then, they have allocated an additional 15 million dollars for grants, and 9.5 million dollars for administration costs. California later that year passed Proposition 71, which allowed for three billion dollars towards funding stem cell research. However, due to legal issues over who would later have the rights to patents resulting from future discoveries, this funding was withheld for a time. Governor Schwarzenegger distributed 150 million dollars to this program two years later due to the still ongoing legal patent battle.

Following their supporting examples, Connecticut passed Senate Bill 934 in 2005, creating a fund to provide ten million dollars a year, every year for the next ten years for the advancement of stem cell research. This bill also proposed guidelines, advisory panels, and a peer review board to oversee the funds, ensuring the regulation of new research.

Massachusetts has also been in the spotlight produced by stem cell research. After an initial bill was passed by the legislature which was intended to place Massachusetts at the front of ES cell research, then Governor Mitt Romney vetoed the bill. However, the bill then passed back to the house and senate for a new vote. Both the House of Representatives (112-42) and the State Senate (35-2) not only voted in favor of the bill once more, but achieved more than two-thirds votes in each body, over riding the governor's veto. Not to be outdone by the previous legislation, Governor Patrick pushed for new legislation committing one billion dollars to stem cell research. On June 6th 2008, Governor Patrick signed the Life Sciences Initiative into law, stating that:

> *"Tomorrow, when the Life Sciences community gathers from around the world at the BIO Conference in California, Massachusetts will have a new and broader set of tools to help us compete. Massachusetts will have the largest registry of stem cell lines in the world, housed at the University of Massachusetts Medical Center in Worcester. Massachusetts, will have a half-billion dollars in capital funding to offer entrepreneurs, for infrastructure investment and economic growth. Massachusetts will have 250 million dollars to offer researchers for fellowships, matching grants and loans to attract and retain rising stars in this field. Massachusetts will have incentives to offer companies to locate and expand here and five regional tech/innovation centers to extend these opportunities to every region of the Commonwealth."* (Life Science Bill Signing, 2008)

International Stem Cell Legislation

The United States is not the only major player in stem cell research. In the last ten years or so, several European and Asian countries have become leaders in varying aspects of the field. They, along with at least one major country from each continent, have drastically expanded the depth of knowledge pertaining to stem cells, techniques, and applications. **Figure-2** shows a world map of the various countries that allow (dark brown), limit (lighter brown), disallow or have no stance on (yellow) ES cell research (Vestal, 2009). On December 21st, 2006, The

International Society for Stem Cell Research released its first "Guidelines for Conducting Human Embryonic Stem Cell Research."

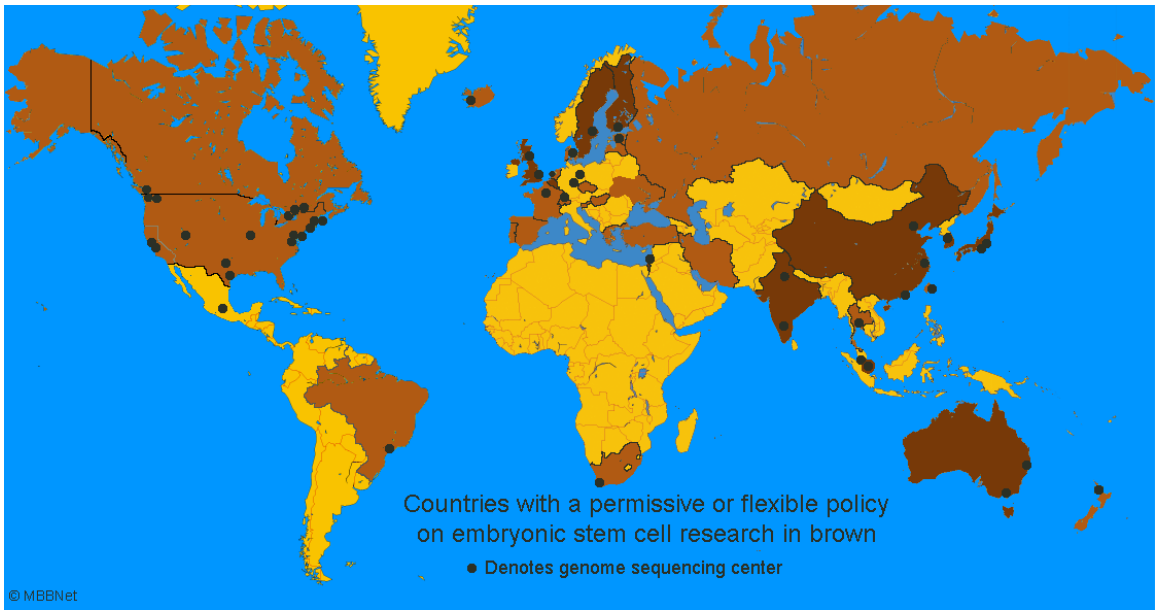

Figure-2: International Stem Cell Laws. Shown is a world map of the various countries that allow (dark brown), limit (lighter brown), disallow or have no stance on (yellow) ES cell research. (Vestal, 2009)

The Middle East, while normally viewed as conservative due to traditional dress and customs, does in fact allow and endorse stem cell research. In 1999, Israel passed legislation which banned *reproductive* cloning, but this country does not ban therapeutic cloning, allowing researchers to continue to have access to ES cells. Israel was in fact the first to extract stem cells from blood, and is currently focused on regenerative medicine. Saudi Arabia first became active in stem cell research in 2002. A legal decree, issued by religious officials, sanctioned the use of embryos for production of stem cells and therapeutic research.

In South America, Brazil passed laws in 2005, permitting ES cell research, with regulations stating that the embryos must have been frozen at least three years before becoming eligible for research. Soon after these laws were passed, a petition endorsed by the Catholic Church of Brazil, challenged the law, stating it was in violation of the "right to life." This petition remained in the courts for three years until being rejected by Brazil's Supreme Court.

In North America, Mexico has a powerful stem cell industry due to its lack of any formal regulations on stem cell research. Doctors are already treating chronically ill patients with stem cells. However due to their lack of any regulations, Mexico has lost some respect in the eyes of the international medical community. In 2006, Canada also began endorsing stem cell research. Canada prohibits the creation of human embryos for research, allowing only extra embryos designated for destruction from *in vitro* fertilization be used. This eliminates much of the ethical debate over the issue, as the embryos will die in either scenario.

Asia has also contributed largely to our knowledge of stem cell research. China, while prohibiting *reproductive* cloning, allows the creation of human embryos for research and *therapeutic* purposes. India is known for its large stem cell banking initiative. It however has banned *reproductive* cloning, and currently limits the use of stem cells to bone marrow transplants. In 2007, Japanese and American researchers discovered the ability to turn adult human stem cells into induced pluripotent cells. South Korea lost a large deal of trust in international credibility due to fraudulent claims by Dr. Hwang Woo-suk who claimed to have achieved human therapeutic cloning. But despite this setback, South Korea still promotes therapeutic cloning of embryos for stem cell research.

Europe has also contributed largely to the attention stem cells are receiving. The United Kingdom's Ian Wilbut and team were the first to successfully clone an animal in 1996, which

resulted in Dolly the world famous sheep. Scientists in the U.K. in 2005 were also the first to successfully clone a blastocyst. Sweden is also a biomedical powerhouse backed by its public and politicians, and it limits its research to *therapeutic* cloning. Germany wary of new medical research due to experiments conducted during World War II, finally authorized the use of imported ES cell lines in 2008.

Due to the large ethical issues brought about by ES cell research, a wide array of laws regarding life have been enacted. The wide range of laws is especially seen in the U.S. with individual states either strongly supporting the research, or banning it altogether.

Chapter-4 Bibliography

Holden, Constance (2009) " Researchers Generally Happy With Final Stem Cell Rules" *Science Magazine* http://www.sciencemag.org/cgi/content/full/325/5937/131

"Life Science Bill Signing" (2008) Mass.gov http://www.mass.gov/?pageID=gov3terminal&L=3&L0=Home&L1=Media+Center&L2=Speeches&sid=Agov3&b=terminalcontent&f=text_2008-06-16_life&csid=Agov3

Palca, Joe (2007) "States Take Lead in Funding Stem-Cell Research." *Npr.org*. 30 Mar. 2007. http://www.npr.org/templates/story/story.php?storyid=9244363

NIH Human Embryonic Stem Cell Registry (2009) http://stemcells.nih.gov/research/registry/

"Massachusetts Stem-Cell Bill Becomes Law Despite Veto" Daily News Central http://health.dailynewscentral.com/content/view/000929/44/

Ralston, Michelle (2008) "Stem Cell Research Around the World". Pew Forum on Religion and Public Life. http://pewforum.org/docs/index.php?DocID=318

Stem Cell Laws (2005) *Stem Cells: A Look Inside.* http://library.thinkquest.org/04oct/00053/ab_laws.html

"Stem Cell Research" (2008) National Conference of State Legislators http://www.ncsl.org/default.aspx?tabid=14413

Stem Cell Tracker (2009) "Stem Cell Research Timeline" http://www.stemcelltracker.com/2009/02/stem-cell-research-timeline.html

Vestal, Christine (2009) " States Applaud new stem-cell funding" Stateline http://www.stateline.org/live/details/story?contentId=383210

PROJECT CONCLUSIONS

This project investigated the topic of stem cells and the impact of this technology on society through ethics and laws. We documented the various types of stem cells, paying special attention to each of their ethical status. Working with any type of adult stem cell (ASC) does not destroy an embryo, so these cells have few ethical concerns. However ASCs are hard to isolate, do not grow well in culture, and do not have the strong medical potency of embryonic stem (ES) cells. ES cells are relatively easy to isolate and grow in culture. Thus, in spite of the ethical controversy of ES cells, such cells may be the best for medical therapies. The authors of this IQP believe that research on ES cells should be allowed, with strong oversight. In particular, due to their ethical controversy, we agree that the source of embryos for ES cell research should be from IVF embryos originally created for reproductive purposes. As a further acceptance of the ES cell controversy, the authors also agree that ASCs should be used for therapies if the ASC research shows that those cells are as effective as ES cells, if not, ES cells should be used. With respect to stem cell laws, the authors believe that countries such as Sweden or China, which allow ES research and paid embryos donations, are laws we most agree with, which should be implemented in the US.