

August 2012

Stem Cells and Society

Jacob Daniel Aschettino
Worcester Polytechnic Institute

Joseph Victor Szerszunowicz
Worcester Polytechnic Institute

Lee William Keaffer
Worcester Polytechnic Institute

Stephen N. Dalton-Petillo
Worcester Polytechnic Institute

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IQP-43-DSA-4376
IQP-43-DSA-7087
IQP-43-DSA-1425

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:

Jacob Aschettino

Stephen Dalton-Petillo

Lee Keaffer

Joseph Szerszunowicz

August 24, 2012

APPROVED:

Prof. David S. Adams, PhD
WPI Project Advisor

ABSTRACT

The purpose of this project is to help inform the public about the technological advances and applications of stem cell therapies, and to describe some of the key legal and ethical issues that surround them. In the first and second chapters, the existing types of stem cells are explored and examples of their treatment of key diseases are discussed. In the final two chapters, the legality and ethics of stem cell applications are discussed, and then each author provides their own individual conclusions at the end of the report.

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PROJECT OBJECTIVES

The project objective of this IQP was to demonstrate the properties and applications of stem cell technologies, and investigate the controversies surrounding their uses in modern society. In chapter one, stem cells are described and classified based on their sources and potential to differentiate. Chapter two examines the applications of these various types of stem cells and their uses in medicine. The purpose of chapter three is to examine the ethical and moral concerns surrounding the use of stem cells and how they are obtained, in view of each of the five major world religions. Chapter four discusses federal and state U.S. laws, as well as international laws, governing the research and sourcing of usable stem cells. Finally, the authors provide a conclusion that best reflects their opinion on the use of stem cells and the laws that govern them.

Chapter-1: Stem Cell Types

Lee Keaffer

Introduction

Stem cells are long-lived undifferentiated cells with the ability to differentiate into specialized cells. These cells are used by the body to replenish aged cells within tissues. Due to this property, they are the foundation for the field of regenerative medicine, and could be used to replenish diseased cells in a patient. However, obtaining some types of stem cells destroys embryos, which some individuals argue is “murder”, making stem cells is one of the most controversial topics in biology today based on ethical and moral concerns. However, there are many misconceptions about stem cells. For example, many people believe there is only one type of stem cell, and that using all stem cells destroys unborn embryos. Many people also believe that all stem cells have the ability to differentiate into any cell in the body. While these are characteristic of some stem cells, they are not characteristic of all. In this chapter, I will dispel some of the myths about stem cells, as I describe the characteristics of different types of stem cells, how we identify them, where we find them from, and how we isolate them.

Embryonic Stem Cells

Embryonic stem (ES) cells were first derived in 1981 in mice (Martin, 1981; Evans and Kaufman, 1981). It was not until 1998, however, that human embryonic stem cells were derived (Thomson et al., 1998). The reason for the time lapse between the discovery of the mouse and human ES cells was due in large part to the taboo nature of the use of a human embryo for research. ES cells are pluripotent cells derived from the inner cell mass of the blastocyst stage of a fertilized embryo. This stage occurs roughly five days after fertilization. During normal

development, the blastocyst stage occurs just before embryo implantation into the uterus wall. At this point, the cells of the embryo have already gone through one stage of differentiation. The inner cell mass cells have differentiated to be able to form any cell of the fully-grown adult, while the outer layer of cells has differentiated to become the extra-embryonic structures, such as the placenta. To prepare ES cells for experiments, scientists perform in vitro fertilization (IVF) (**Figure-1**). As the fertilized egg divides to the 8-cell stage, the cells are totipotent, meaning they can form an entire embryo. At around day-5 the blastocyst forms (diagram center, with the inner cell mass shown in blue). The isolated ES cells are plated onto a feeder layer of cells in a dish that provides a scaffold and growth factors that aid ES cell survival (diagram, lower). When the technique was first developed in 1998, the feeder cells were mouse fibroblasts, but eventually due to worries about mixing human ES cells with animal fibroblast cells when the ES cells were to be used for therapy, the feeder layer was switched to human cells, or was completely eliminated by adding the growth factors exogenously (Klimanskaya et al., 2005).

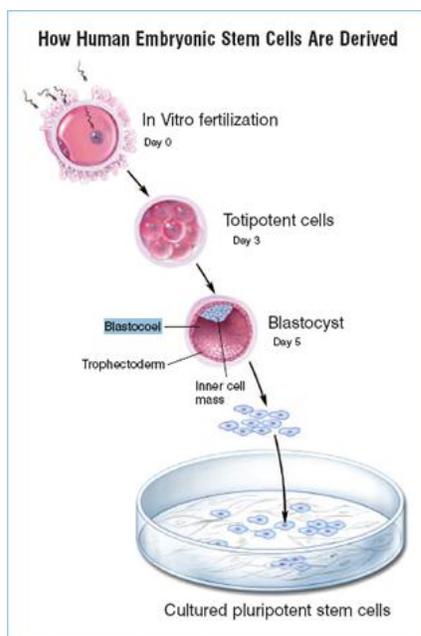


Figure-1: Isolation and Culture of Human Embryonic Stem Cells. Shown is a summary of how ES cells are derived from IVF embryos and grown on a layer of feeder cells. (Thomson, 1998)

With respect to IVF embryos as the source of ES cells for research, currently in the US such embryos must be obtained from IVF clinics where the embryos are originally created for reproductive purposes. IVF embryos cannot be created in the US solely for research purposes. While most of the IVF embryos are used to treat infertility, around 2.8% of them are not needed by the donors, so with donor consent these unused blastocysts can be used for research to make ES cell lines.

When ES cells replicate, either they can create more ES cells, which makes them long-lived, or under the right conditions they can differentiate into other cells. Scientists have spent considerable time analyzing which proteins are required to keep ES cells pluripotent versus which proteins are needed for differentiation into a particular type of cell. Although scientists first used feeder layer cells when growing ES cells, researchers at Yale have found what they believe to be the minimal culture requirements for proliferation of human ES cells (Emanuel, 2006). They found that, when cultured with growth factor Wnt3, basic fibroblast growth factor, insulin, transferrin, B-cell activating factor April/BAFF, cholesterol, and albumin, the human ES cells could proliferate and stay pluripotent. They called this mixture of proteins and lipids “human embryonic stem cell cocktail” (HESCO (Emanuel, 2006). Although this cocktail allows the ES cells to replicate, scientists still do not completely understand what keeps ES cells pluripotent, nor do we understand how to differentiate them *in vitro* into all other types of cells. There are, however, some proteins and genes which serve as markers for ES cells, and which could be the key to their pluripotency. For example, the presence of Oct-4 transcription factor, and its continued expression, is one of the key markers used to identify ES cells. The expression of this protein is also necessary for the cell to retain its pluripotency. Also, the protein Nanog has been found to be a marker of ES cells in mice, and also is necessary for the ES cell to remain

undifferentiated. Nanog is present in human ES cells, but not to the same extent as in mice. There are also genes present in ES cells that are more expressed than in their differentiated counterparts. Studies have found that up to 918 genes whose expression is higher in ES cells.

There is also another new and exciting way to create human ES cells using a patient's own DNA. If this technique of ES cell cloning using somatic cell nuclear transfer (SCNT) can be developed, it would allow ES cells to be created that are genetically identical to a patient, increasing their engraftment potential in the same patient. The SCNT method normally involves removing the nucleus from an egg and replacing it with a diploid nucleus from a skin fibroblast cell. The method was developed in 1996 in sheep (Campbell et al., 1996), and was reported in 2005 for humans (Hwang et al., 2005), but the latter study turned out to be fraudulent. A recent modification of the SCNT technique was developed in which a patient's fibroblast diploid nucleus is injected into a haploid egg to create a triploid embryo from which triploid ES cells can be derived (Noggle et al., 2011). By leaving the egg's haploid nucleus intact and injecting the diploid fibroblast DNA directly into the nucleus, Scott Noggle was able to create a triploid (three complete chromosome sets, two from the human donor and one from the egg donor) from which triploid pluripotent cells could be derived. This process, while controversial, could make it possible to create patient-specific tissue to treat diseases, without the risk of rejection by the recipient of the tissue (Coombs, 2011).

While ES cells are medically some of our most exciting cells, as they are pluripotent, they are also the most controversial since an embryo is usually destroyed to obtain them. The debate (discussed in Chapter-3) centers on when life begins, and the status of excess IVF embryos. And laws have been enacted in some countries, including the US under the Bush administration (discussed in Chapter-4), preventing federal funding of embryo research.

Induced Pluripotent Stem Cells

Induced pluripotent stem (iPS) cells are adult differentiated cells, usually skin fibroblast cells, which have been de-differentiated to a state of pluripotency. They are some of the newest stem cells discovered, and are the subject of some of the most exciting research. A patient's fibroblast cells are de-differentiated by transfecting them with specific genes (discussed below) which induce the pluripotent state. The iPS cells are almost identical to ES cells, in that they express many of the same genes, have many of the same transcription factors (including Nanog and Oct4 which were discussed earlier), and appear to be capable of broad differentiation. The technique was first developed in mice (Takahashi and Yamanaka, 2006) and was later applied to humans (Takahashi et al., 2007). When the technique was first developed, four genes were used to induce the pluripotency: Oct3/4, SOX2, KLF4, and c-MYC (**Figure-2**). The genes were inserted in the fibroblast cells using retroviruses, which was a controversial technique as the vector could cause cancer in some cases.

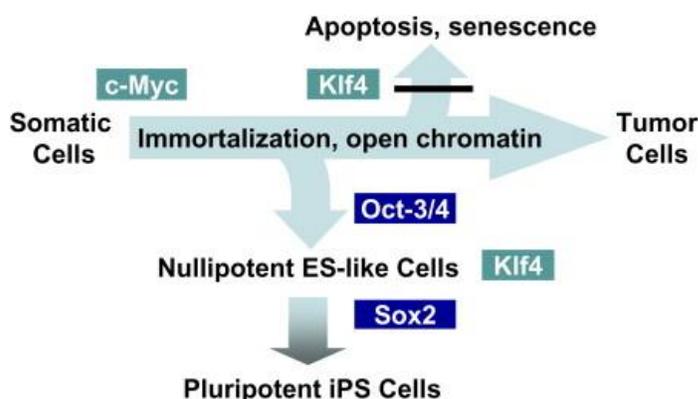


Figure-2: Diagram of the Roles of Oct3/4, Sox2, KLF4, and c-MYC in Creating iPS Cells. Some of the proteins open up the chromatin allowing reprogramming, while others help induce the de-differentiation. (Yamanaka, 2007)

As can be seen in Figure-2, c-Myc induces the opening of chromatin, allowing its reprogramming, and increases the immortality of the cells. However, c-Myc also can induce oncogenesis. c-Myc is an oncogene present in human tumors. KLF4 has been identified as both an oncogene and a tumor suppressor, and plays a crucial role in the switch from cell proliferation to cell differentiation. This protein also can cause the cells to become cancerous. This is countered by Oct3/4, which, along with Sox2, cause the cell to develop into a pluripotent, ES-like stem cell. Like KLF4, Oct3/4 also plays a key role in determining when cells will differentiate. Even with these four genes introduced to the epithelial cells, only about 1% of the cells achieve induced pluripotency (Yamanaka, 2007).

Current research on iPS cells focuses on how potent they are, and identifying the least number of required inducing factors. Some scientists claim iPS cells are extremely similar to ES cells, claiming they have the same growth rate, telomerase is active (as it is in ES cells), and pluripotency genes like Nanog are active in the iPS cells. In mice, iPS cell have been shown to create entire body structures, showing their high potency (Boland et al., 2009). Much research has focused on eliminating the oncogenes KLF4 and c-MYC in the treatment. Recent discoveries have shown that NANOG and LIN28 can be used in place of KLF4 and c-MYC. These cells contain very similar markers to ES cells, and to the other iPS cells, and their differentiation to full body structures of mice was possible (Baker, 2007; Kim et al., 2008). However, other scientists argue that iPS cells grow slower than ES cells and contain mutations in their DNA (Gore et al., 2011), so it is still debatable whether iPS cells can serve as a replacement for ES cells.

Parthenogenetic Stem Cells

Parthenogenesis is the Greek word for “virgin birth”. In the world of biology, parthenogenesis is the mode of asexual reproduction in which a female egg begins cellular division and creates an embryo, with no involvement from sperm. This process is used in nature in some insect species to rapidly create worker bees and ants. Although parthenogenesis does not normally exist in mammals, scientists have developed artificial methods using chemicals to stimulate egg replication through the blastocyst stage from which ES cells can be obtained (Weiss, 2001). Fertilization generally replaces one of the sets of chromosomes. However, with a chemical or electrical stimulus, some eggs can be induced to proceed as if fertilized, while retaining their second chromosome set (**Figure-3**). However, this embryo generally dies within a few days, so these embryos are not as viable as fertilized embryos. Perhaps parthenote stem cells could serve as a replacement for ES cells and would be less of a concern ethically, as full embryos are not used.

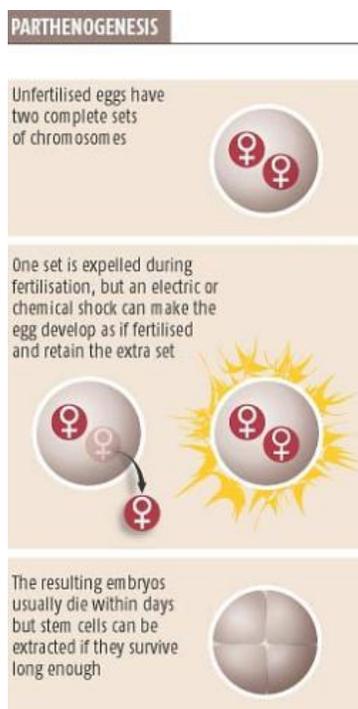


Figure-3: Diagram of Artificial Parthenogenesis. In this process, an egg is induced to begin cell division without extruding its second set of chromosomes, keeping it diploid. The egg can divide to the blastula stage from which ES cells can be derived. (Vrana et al., 2003)

Scientists first achieved success with monkey parthenote ES cell lines in 2001 (Mitalipov et al., 2001). Mouse parthenote ES cells were derived in 2007 (Kim et al., 2007). More recently, David Wininger was able to grow a human parthenote to the blastocyst stage and extract ES cells (Vrana et al., 2006). This is very exciting, because these parthenote ES (pES) cells may be as potent as normal ES cells, although more research will be required to prove this. This is also very exciting from an ethical point of view. Because parthenote eggs are not fertilized, and the created blastocyst cannot develop into a viable embryo, parthenote embryos may have fewer ethical concerns (discussed in Chapter-3) (Pagan, 2003).

Adult Stem Cells

In contrast to embryonic stem cells, adult stem cells (ASCs) are isolated from adult tissues (or umbilical cord) and do not destroy an embryo to obtain them. There are many different types of adult stem cells, which can range from adult hematopoietic stem cells, which are the most researched form of stem cells, to neuronal stem cells, cardiac stem cells, epithelial stem cells, and mesenchymal stem cells. In this chapter section, I will focus on four types of adult stem cells: adult hematopoietic stem cells, neuronal stem cells, cardiac stem cells, and mesenchymal stem cells.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are frequently called bone marrow stem cells, since this is their most common source. Due to the many different types of blood cells in the body, and the fact that many of them have short lives (around 90 days) and need to be replenished rapidly,

there is a strong need for stem cells that can produce whatever type of blood cell is necessary. HSCs fill this role. These cells are not pluripotent, but they can differentiate into several types of related blood cells, so they are considered *multipotent*. HSCs have the ability to differentiate into any kind of blood cell, ranging from several types of white blood cells to platelets to red blood cells (**Figure-4**).

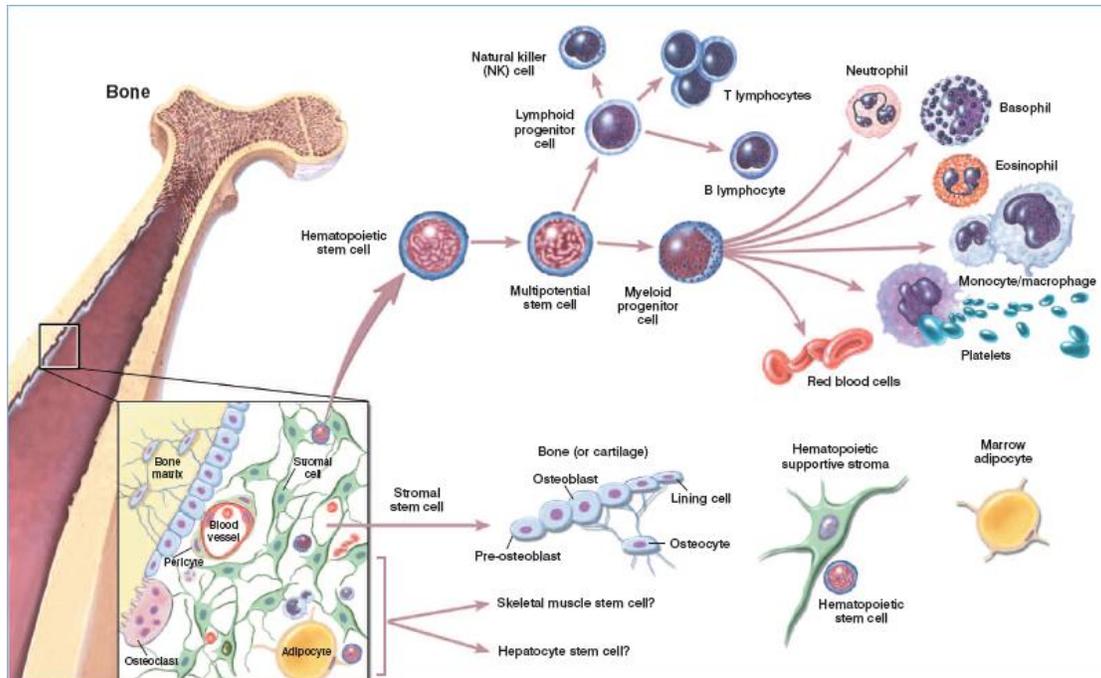


Figure-4: Diagram of the Various Blood Cells Hematopoietic Stem Cells Can Differentiate Into. HSCs in this case are isolated from bone marrow (diagram, left), and can form lymphoid or myeloid progenitor cells from which all other blood cells are derived. (NIH, 2006)

Hematopoietic stem cells were first seen in 1956, when three separate laboratories found that when mice were exposed to lethal amounts of radiation, if they were injected with bone marrow, their damaged blood-forming systems regenerated (NIH, 2006). This finding proved valuable for treating patients affected by radiation poison in Japan, and was also very important for the treatment of cancer, because it gave the possibility of radiation therapy to destroy tumors

followed by bone marrow transplants to replace the blood components. The first human bone marrow transplants for cancer were performed in 1957 (Thomas et al., 1957).

HSCs are traditionally isolated from bone marrow, but more recently are obtained from the peripheral blood of donors injected with hormones to mobilize their HSCs from the marrow into the blood. HSCs can also be found in umbilical cord blood, and these HSCs may be better suited for therapies than bone marrow-derived HSCs, as they are more primitive so are less likely to be rejected by the host (Viacord, 2011).

In addition to performing bone marrow transplants, HSCs can sometimes be purified prior to injection into a host. The most popular method of HSC purification is labeling them with fluorescent antibodies against a cell surface marker specific for HSCs, such as CD-34. The antibodies stick to the surface of HSCs, then the cells are passed through a cell sorter which separates labeled from unlabeled cells. The cells can be sorted with a great deal of accuracy, however the process can be somewhat time consuming, and requires expensive equipment. Scientists continue to debate the best markers for identifying HSCs. CD34 was the first one identified, but others include CD38, Lin, CD90, and CD133 (Domen et al., 2000).

Neural Stem Cells

In adults, neuronal stem cells (NSCs) are also present. Not long ago, it was thought that once neurons died in the adult body, they were gone for good. However, in 1989, this was shown to be untrue with the finding of NSCs in the brain (Temple, 1989). Further proof of the existence of NSCs was obtained in the mid 1990's, in the fetal and adult brain, which have the ability to regenerate neurons under the right conditions. They found that these neuronal stem cells, "resemble cells in a developing fetus that give rise to the brain and spinal cord" (National

Institute of Health, 2009). They found that these cells had the ability to regenerate almost all of the cells present in the human brain.

The presence of adult NSCs with the ability to regenerate the cells of the brain and central nervous system is a very exciting discovery, and increases our hope for treating neurodegenerative diseases. Methods to use NSCs to regenerate neural cells for a patient are already underway, by either growing the NSCs in culture and then treating with growth factors to differentiate the cells into the desired neural cell, or by treating a patient directly with specific growth factors to trigger stem cells inside the patient's body to differentiate into the desired neural cell.

Cardiac Stem Cells

Just as the brain was thought to not be capable of regeneration, so was the heart, until cardiac stem cells (CSCs) were discovered. First found in rats in 2003 (Beltrami et al., 2003), these multipotent cells could have the ability to repair damaged tissue in the heart. In rats with heart disease, CSCs were cultured and injected into the hearts where they helped repair it. CSCs have also been found in humans (Laugwitz et al., 2005). CSCs isolated from rats or humans with heart disease were found to already be in the process of attempting to repair the heart. Now that scientists have located where the cardiac stem cells reside, the next step is to find how to increase their efficiency of repairing cardiac muscle, and this will be discussed in chapter-2. **Figure-5** shows an image of human cardiac heart cells, with the blue cells representing stem cells, and the red cells cardiac muscle cells (Touchette, 2003).

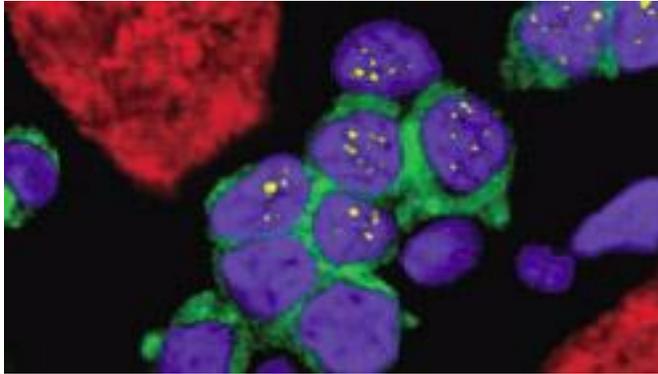


Figure-5: Fluorescence Microphotograph of Human Cardiac Stem Cells. Blue cells are stained with an antibody against cardiac stem cells, while red cells are stained with an antibody against cardiac muscle cells. (Touchette, 2003)

Mesenchymal Stem Cells

Finally, in adults there are also mesenchymal stem cells (MSCs). These multipotent stem cells are present in bone marrow and in many other tissues of adults, and have the ability to differentiate into various connective tissues, such as muscle, fat, and cartilage (Barry and Murphy, 2004). MSCs are usually isolated from bone marrow, and while they do not represent a large portion of the marrow cells, once isolated they can be cultured using normal culturing techniques. In order to isolate them, cell fractionation is used based on cell density. Like many other types of stem cells, MSCs can be identified using cell surface markers and antibodies that detect them. For example, studies performed by Otto and Rao, and Deans and Mosley, found that markers CD 44, CD 29, and CD 90 are specific cell markers used to identify human MSC's. It has also been found that human and rat MSC's are lacking CD34, but can be identified using antigens Stro-1, SH2, SH3 and SH4, and that these cells are also positive for MHC-1 and Sca-1. These antibodies are not enough, however, to be used alone to test a culture of MSC's for purity (Nardi, 2006).

MSCs have become widely used in the past few years, due to their multipotency, their relative ease of isolation and growth, and their isolation from adult not embryonic tissues. They are thought to have widespread applications for replacing connective tissues in a variety of diseases. They are also exciting because, like many others of the adult stem cells, they can be removed from the patient themselves, which will negate the possibility of the recipients body rejecting the graft. Some of the uses of MSCs will be discussed in greater detail in chapter-2.

Chapter-1 Conclusion

Stem cells are a very important and controversial topic, and are widely misunderstood by the general public. Understanding the various types of stem cells, where they come from, and what they do, is critical for changing the public opinion of stem cell research. I hope that this chapter has clarified the different types of stem cells, and has showed that not all stem cells come from embryos, and that not all stem cells are medically identical. The moral and legal implications of the stem cells discussed in this chapter, as well as the possible uses of these stem cells, will be discussed in the following chapters.

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Chapter-2: Stem Cell Applications

Jacob Aschettino

The ability of stem cells to grow and differentiate into other tissues provides the basis of the new field of regenerative medicine in which stem cells are used to replace aged or diseased tissues. Some types of stem cells have been in use for treating diseases for over 50 years, while other types of stem cells have only recently been discovered. Their use in tissue regeneration could provide important cures for untreatable diseases and provide a better understanding of human biology (Chapman, 1999). However, controversy often follows many of science's great innovations, and this holds true for stem cells, as their use will have a strong social impact. For this reason, it is important for the public to have a well informed understanding of the applications for which stem cells can be used (Chapman, 1999), as their benefits to society will have to be understood prior to discussing their ethics in later chapters. The purpose of this chapter is to describe how stem cells have been used to treat different categories of diseases, bringing the reader up to speed on the treatments for some specific disorders.

Stem cell research has already developed treatments for many diseases over the years, some large and some small. However, to focus the scope of this chapter, the treatment of five specific diseases with stem cells will be discussed: leukemia, damaged heart muscle, diabetes, Parkinson's disease, and strokes. Each subheading will begin with a discussion of what the disease is, summarize the contribution of animal models for the treatments, discuss any human clinical or pre-clinical data if it exists, and discuss possible future directions for the research.

Stem Cell Treatment of Leukemia

Cancer is one of the most widespread and rapidly progressing diseases in the world. Although cancer can affect almost any part of the body, cancers result from the cell's inability to control its own growth, division, or differentiation. In the case of leukemia, the cancer cells occur in the blood or the bone marrow, resulting in high levels of immature white blood cells that crowd the area surrounding the bone marrow (Thomas et al., 1977). As a result, the bone marrow is not able to produce enough healthy mature white blood cells for the immune system.

Leukemia has many forms found in both children and adults, and can be acute or chronic. The type found in children tends to be more rapidly progressing and aggressive, due to the fact that in adolescence, a child's immune system is more active because they encounter more germs and are less aware of the health risk associated with their behaviors. This active immune system means that the bone marrow usually produces large quantities of white blood cells, which can be a problem if the cells become cancerous and their production becomes exponentially greater, and the produced cells are immature. Leukemia can also be classified by the type of cells (myeloid or lymphoid) that develop the cancer (Healthwise Inc., 2011). Myelogenous leukemia occurs when the cancer takes hold of the type of marrow that produces red blood cells, some white blood cells, and platelets. Lymphocytic leukemia occurs when the cancer affects the type of marrow that produces lymphocytes, the infection fighting cells in the body.

One of the most important types of stem cells that have been used for decades to treat leukemia is the hematopoietic stem cell (HSC). HSCs are the stem cells in bone marrow that are responsible for producing all types of new blood cells. In the late 1950's, scientists began experimenting with animals for possible treatments for leukemia. The scientists would start by administering a lethal dose of radiation to a model animal such as a rat or a primate to destroy

their endogenous bone marrow, then would inject a suspension of healthy bone marrow taken from a compatible donor. If the healthy marrow engrafted, it survived and replenished the destroyed hematopoietic cells allowing them to resume their normal function. These early animal trials are the precursor to the bone marrow transplants we now perform in hospitals worldwide.

Bone marrow transplants were first performed in human patients around 1957 (Thomas et al., 1957), and they are now used to treat a wide variety of blood disorders with success rates in excess of 98% for some types of cancer, but is not successful for all types (Gratwohl et al., 2010). The procedure has been modified over the years to improve success. Initially, it was thought that total body irradiation (TBI) was required; some treatments now avoid this if the tumor is localized, while others require TBI supplemented by other antileukemic drugs. Scientists have also experimented throughout the 1970's with different methods of injecting the healthy bone marrow, altering the site of injection, the number of cells, and the purity of the injected cell sample. Some recent techniques select for HSCs from the marrow cells using a selection marker. Although this marker is not well defined, most scientists believe CD34+ cells represent HSCs, so they select for them prior to injection. New drugs have also been developed that can help the patient's immune system cope with the after effects of the procedure, lowering the risk of graft rejection, while producing relatively few side effects.

In addition, scientists are developing ways to increase the number of compatible donors, always in short supply. Autologous bone marrow transplants use a patient's own bone marrow cells for perfusion, hoping the cancerous cells have been removed. Allogenic bone marrow transplants use a histo-compatible donor to provide the bone marrow, usually a parent or sibling because of their genetic similarity (Lucile Packard, 2012). Umbilical cord blood transfers use HSCs taken from cord blood donated at hospitals following birth (Viacord, 2011). In this

procedure, HSCs from cord blood are differentiated, typed, and then implanted into a patient with unhealthy marrow. Cord blood HSCs hold a promising future for transplants, as their HSCs appear to be less differentiated than HSCs from bone marrow, so there is less chance of rejection by the patient (Viacord, 2011).

All of these advancements for treating leukemia have been made within the last fifty years or so, and have become a well-established use of stem cells in our society. New and more advanced technologies are being introduced every day and will rapidly increase the progression of this field of research. With the right funding and encompassing understanding, we can limit our biological vulnerability to leukemia and other cancers.

Stem Cell Treatment of Damaged Heart Muscle

The heart serves as one of the most important muscles in the human body, ensuring a healthy flow of oxygen and nutrient rich blood throughout the body. The heart, like any other muscle, can become damaged and lose function. The damage can happen in a variety of ways, but by far the most common occurs with a heart attack, which occurs in over 1 million Americans annually (American Heart Association, 2012). The coronary arteries directly surrounding the heart provide the channels for blood to reach the heart and can sometimes become blocked by small deposits of fat or protein that form plaque. This plaque may buildup in a coronary artery, or buildup elsewhere then breakoff and travel to a coronary artery to block it. At the plaque site, an inflammatory response forms including platelets that block blood flow, so the heart will literally begin to suffocate from lack of oxygen (WebMD, 2012). This can cause part, or all, of the heart muscle to die if untreated. Other ways in which the heart muscle cells

can become damaged include drug addiction, congenital heart defects (defects you are born with), hypertension, and other debilitating diseases that tax the heart (Healthwise Inc., 2011).

Scientists are attempting to use stem cells to regrow damaged heart muscle cells, and with the exception of hematopoietic stem cells, this area of stem cell applications is the furthest in human clinical trials. Human heart attack patients are already being tested in cell therapy experiments by injecting skeletal myoblasts (Menasché et al., 2001; Siminiak et al., 2004), bone marrow stem cells (Britten et al., 2003; Lunde et al., 2006; Schächinger et al., 2006), mesenchymal stem cells (Chen et al., 2004), and adult cardiac stem cells (GEN, 2011). Each of these different kinds of stem cells attempts to replenish the population of healthy cardiac cells in an area of damaged heart muscle. Of the 27 human clinical trials performed to date using adult stem cells to treat heart attack patients, 12 were performed with bone marrow cells, 5 with peripheral blood mobilized HSCs, 2 with mesenchymal stem cells, and 8 with skeletal myoblasts (Stem Cell Therapy.....2012). The end point of all the clinical trials was to verify safety and feasibility, not efficacy, so future experiments will be required to determine whether any of these treatments actually improve cardiac function.

Bone marrow-derived stem cells were among the first to be tested in humans for therapy, and have shown some success in repairing damaged heart (Britten et al., 2003). In a clinical study, 28 heart attack patients of various severities were given a transplantation of circulating blood (CPC) or bone marrow derived (BMC) progenitor cells, or stem cells that already have disposition to differentiate into heart tissue. The experiment showed that, four months after transplantation, the patients showed significant improvement in the remodeling and revitalization of their hearts, and a decrease in infarct size. As a supplemental experiment, the researchers

showed that the CPC and BMC progenitor cells *ex vivo* could migrate towards a gradient of growth factors, showing their capacity for effective remodeling (Britten et al., 2003).

Adult cardiac stem cells (CSCs) were first identified in mice in 2003 as c-Kit⁺ cells (Beltrami et al., 2003), and were also later identified as Isl1⁺ cells in mice, rats, and humans (Laugwitz et al., 2005). In mice, the Isl1⁺ cardiac stem cells were shown to be capable of differentiating into more than just cardiac muscle, and also formed smooth muscle and endothelial cells for forming new arteries and veins (Moretti et al., 2006). The experiments with Isl1⁺ cells were extended to humans in 2009, showing that human Isl1⁺ cells can differentiate into multiple cardiac lineages (Bu et al., 2009). The fact that regenerative adult cardiac stem cells exist in heart tissue suggests that the heart is not a terminally differentiated organ incapable of tissue replacement; it contains stem cells that allow its depleted cell types to replenish themselves on a small scale as needed. Scientists hope these cells can help repair hearts in human clinical trials (Baker, 2009).

With respect to embryonic stem (ES) cells, in early work with animal ES cells, scientists have found that pluripotent mouse ES cells injected into mice can differentiate into all the major types of cells in the heart (Klug et al., 1996). Later, human embryonic stem (ES) cells were shown to be capable of differentiating into various cardiac lineages *in vitro* (Kehat et al., 2001), but these human ES cells have not been approved for treating patients due to ethical issues, and due to technical issues of sometimes forming tumors at the injection site.

With respect to human induced pluripotent stem (iPS) cells, human iPS cells have been shown to be capable of differentiating into cardiac lineages *in vitro* (Burridge et al., 2011), but have not yet been tested in patients. This experiment was performed at the Johns Hopkins Institute for Cell Engineering, and tested over 45 different experimental variables to define a

universal *in vitro* cardiac differentiation process for either ES cells or iPS cells. The final method used a staged exposure to physiological (5%) oxygen, and optimized concentrations of morphogens BMP4 and FGF2, polyvinyl alcohol, serum, and insulin. By using a highly controlled environment and chemically-specific medium, the scientists were able to create cells that were structurally the same as cardiomyocytes and were responsive to cardiac drugs (Burrige et al., 2011). This procedure could lead to a safe and viable way to produce an unlimited number of cardiac stem cells for future therapies. Human clinical trials will lead to a deeper understanding of any complications that follow injection.

Further research into the use of embryonic and/or adult stem cells to treat cardiomyopathy will hopefully provide a fuller understanding of how the heart can be repaired and its health maintained. Injecting patients with adult stem cells is already improving cardiac function. Hopefully in the near future, cell therapy will provide doctors with a new arsenal of treatments for heart attack patients.

Stem Cell Treatment of Diabetes

Diabetes is a metabolic disease that affects the ability of the body to use glucose. Type-I diabetes, also called juvenile onset diabetes, is caused by the body's attack on pancreatic beta cells that produce insulin. The inability to make the hormone insulin results in less glucose uptake into tissues from the blood, resulting in hyperglycemia. Type-II diabetes, also called non-insulin dependent diabetes, is the most common type and is caused by the body developing a resistance to insulin, also resulting in hyperglycemia (American Diabetes Association, 2012). This type of diabetes correlates with obesity, and is becoming increasingly common in children. A third type of diabetes is called gestational diabetes, and occurs in some women who are

pregnant and have higher levels of blood glucose than normal. This is thought to be caused by the many hormonal changes that occur in a pregnant woman's body trying to regulate the exchange of nutrients from mother to child; as a result the body becomes resistant to insulin. Gestational diabetes is not very common, only effecting approximately 4% of births. If left untreated, it can lead to birth defects and a higher rate of miscarriage (WebMD², 2012). Diabetes symptoms include excessive thirst, urination, or eating, and death in some instances (WebMD², 2012). The current treatment for type-I diabetes is insulin injections to replace the insulin not produced from the damaged beta-cells. But even with insulin injections, it is difficult to precisely control serum glucose levels, so hyperglycemia and hypoglycemia often result. And the use of adult pancreatic islet transplant tissue into humans is hindered by the lack of donated tissue. So scientists are currently trying to use stem cells to re-grow damaged pancreatic tissue to treat type-I diabetes.

With respect to treating diabetic animal models with stem cells, the mice have shown restored normal glycemia when treated with mouse embryonic stem (ES) cells (Soria et al., 2000), with hematopoietic stem cells (to produce T-cells that do not attack the pancreas) (Beilhack et al., 2003), with induced pluripotent stem (iPS) cells derived from mouse skin cells (Alipio et al., 2010), or with human ES cells that differentiated *in vivo* into insulin-producing cells (Kroon et al., 2008). The iPS cell approach is most exciting if it can be expanded to humans because it does not destroy any embryos.

With respect to human diabetic patients, patients have not yet been injected with stem cells; however, several studies have proven that human ES cells can differentiate into insulin-producing cells *in vitro* (Assady et al., 2001; Lumelsky et al., 2001; Seguev et al., 2004; D'Amour, 2006).

For the experiment in which mouse diabetic models were treated with adult hematopoietic stem cells (HSCs) (Beilhack et al., 2003), a group of researchers at Stanford university conducted an experiment with non-obese diabetic (NOD) mice, one of our best models for type-I diabetes. In this model, the T-cells of the immune system attack the beta-cell tissue, as occurs in type-I patients. If autoreactive T-cells (directed against the pancreas) are transferred from NOD mice into normal mice, the normal mice get diabetes, showing that the T-cells destroy the pancreatic tissue. If the autoreactive T-cells in the NOD mice are destroyed by radiation or chemotherapy and replaced with normal T-cells derived from bone marrow HSCs, the mice do not develop diabetes, offering hope for diabetic patients (Beilhack et al., 2003).

Another experiment using diabetic mice showed that a mouse ES cell clone (IB/3x-99) was able to engraft into NOD mice and differentiate into insulin producing cells *in vivo*. A group of these cells (1×10^6) were implanted into the spleen of diabetic animals. After one week their hyperglycemia had ceased, and after 4 weeks their weight normalized (Soria et al., 2000)

With respect to human ES cells, in 2001, scientists in Israel performed an experiment to determine whether human pluripotent embryonic stem cells cultured *in vitro* would respond to signals and differentiate into insulin secreting cells (Assady et al., 2001). By seeding a gel medium with non-essential amino acids and other nutrients required for cell growth, the scientists followed the previously published methods for inducing differentiation in mouse ES cells, and were successful. The cells produced insulin in response to an increase in glucose (Assady et al., 2001). However, the percentage of insulin producing cells was not determined, and if found to be low, scientists must do more experiments to increase the efficiency.

Advancements like these hopefully will allow doctors all over the world to provide viable and effective treatments to diabetes patients. There is no doubt that further research will expand the horizon of available treatment options for these patients.

Stem Cell Treatment of Parkinson's Disease

Parkinson's disease (PD) is neurodegenerative condition that affects the part of the brain that controls movement and coordination. PD is progressive, eventually causing rigid stiff joints, tremors in the extremities, and slow lathargic movements. Approximately one million people currently live with PD in the United States, and over 10 million worldwide, most of whom are over the age of fifty (Parkinson's Disease Foundation, 2012). Though there has been decades of research, the cause of PD is unknown, and there is no cure. In PD, the dopamine producing neurons of the *substantia nigra* die. Dopamine is a neurotransmitter that functions in movement; without it movement is hindered (National Center for Biotechnology Information, 2011). Current treatments for PD include the use of chemical precursors to dopamine, or drugs that increase neuromuscular transmission, but these drugs act transiently, and are not a cure.

Scientists are attempting to develop methods for treating PD with stem cells to regrow dopaminergic neurons. The very first cell therapy treatments for PD involved injecting patients with fetal tissue transplants isolated from aborted fetuses (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002), but this technique proved to be highly controversial, and the public worried about the inducement of abortions solely to support medical research, so this technique is no longer used. With respect to stem cell treatments, PD patients have been treated with adult olfactory mucosal stem cells (Levesque, 2005), and with adult neuronal stem cells (Ertelt, 2009).

In one interesting study with a rat PD model, scientists designed an experiment to determine whether human embryonic stem cells could serve as a replacement for the damaged dopamine-producing neurons in a rat PD model (Ben-Hur et al., 2004). They were able to generate a large number of neuronal progenitors *in vitro* using a mytomyacin-C-treated mouse fibroblast feeder layer in gelatin-coated tissue culture dishes. They then transplanted these human neural progenitor cells into the striatum of the rats and observed differentiation of the cells into dopamine-producing neurons. Although this led to significant behavioral recovery from PD symptoms, it also caused brain teratoma formation (large tissue-encapsulated tumors) in 20% of the treated rats (Ben-Hur et al., 2004), which appears to be a recurring problem with some ES cell treatments.

With respect to the fetal tissue transplant approach, in an experiment in the late 1980's conducted on two consenting adults with PD, doctors grafted cells from a fetal adrenal gland and fetal *substantia nigra* into the caudate nucleus of the brain (Madrazo et al., 1988). Basal nuclei reside in an area of the brain responsible for body movement and coordination (MedicineNet Inc, 2012). Doctors chose the adrenal gland and the *substantia nigra* for tissue grafts because they are areas involved with dopamine production. The procedure showed promise at first, with a reduction in tremors and behavioral improvements, but later the side effects of the procedure were significant and the grafted tissue did not integrate fully. This opened the door for other researchers to experiment instead with stem cells.

With regard to human embryonic stem cells, scientists have shown they can differentiate into dopamine-producing cells *in vitro* (Perrier et al., 2004). In 2004, Dr. Perrier and colleagues tested several different species of ES cells (primates, mice, and humans) to try to determine a process of differentiation for dopamine-producing neuronal progenitors. In their experiment,

neuronal differentiation was induced using a modified stromal based-feeder system, where stromal cells are taken from bone marrow and used to prompt the differentiation of ES cells. The exact chemical nature of these stromal cells is unknown, however in this experiment MS5, FGF8, and SHH stromal growth factors were shown to induce the *in vitro* differentiation of ES cells into midbrain dopamine-producing cells (Perrier et al., 2004). The cells remained healthy in culture, but were never transplanted into any animal models or patients for testing. This experiment showed that it is possible to induce the differentiation of human ES cells into midbrain dopamine neuronal tissue.

PD is a debilitating disease for its victims and their loved ones, and future research can hopefully increase our understanding of its causes. Stem cells offer a potential treatment alternative that could become the capstone of a full recovery.

Stem Cell Treatment of Strokes

A stroke occurs with a blockage in blood flow in the blood vessels leading to or inside the brain. This can cause cells upstream from the blockage to starve for oxygen and lose their function. This lack of oxygen can also occur when a blood vessel bursts open in the brain. Strokes are common among the elderly, and can be physically debilitating; in addition to a loss of speech, expression or other mental capacities, patients can also experience paralysis of one side of the body or total loss of mobility (National Institute for Neurological Disorders and Stroke, 2012).

Scientists are researching the possibility of using stem cells for regrowing damaged brain cells following a stroke. Human stroke patients have already been treated with mesenchymal stem cells (MSCs) (Bang et al., 2005).

Scientists working with a rat stroke model used human ES cells to try to decrease the damaged area of the brain (Steinberg, 2008). In this experiment at Stanford University's School of Medicine, scientists spent months differentiating high numbers of neuronal precursors from human ES cells, which were then injected into the brains of host rats. They observed the neuronal precursors migrating to the lesion site, which began the repair of damaged tissue (Steinburg, 2008). A similar study done earlier by the same group showed that injection of undifferentiated ES cells into the brains of stroke induced rats also migrated to the lesion site and regenerated brain cells (Steinberg, 2004).

In a joint Korean-Canadian study, scientists working with animal models also found that the injection of mesenchymal stem cells and bone marrow stromal cells derived from humans can aid in the recovery of the animals from stroke. Doctors injected both types of stem cells into rat stroke models, and in both cases observed cell migration to the infarct site and regeneration of damaged neuronal tissue (Stem Cells Useful...2008).

In a 2005 study done with human subjects, scientists selected 30 patients with lesions in their brains or deficits like those of a stroke patient (Bang et al., 2005). They then administered an injection of mesenchymal stem cells (MSCs) which they observed migrate to the infarct area and facilitate regeneration of the dead tissue. This was a significant improvement when compared with the control group who received no MSC injection (Bang et al., 2005).

A recent and promising procedure took place in 2006 in Kiev, Ukraine when a 50 year-old chiropractor from New York had a stroke and wanted to try stem cell therapy. Dr. Rich James had a stroke, and was left with a whole side of his body completely immobilized. Though it is not known what type of stem cells were used, or the method of injection, months after the procedure was performed Dr. James was able to walk unassisted (Vega, 2006). It is also not

clear from this type of uncontrolled experiment whether the patient would have improved on his own without the stem cell treatment.

Chapter-2 Conclusions

These experiments show examples of the potential that stem cells have in regenerative medicine. Although human clinical trials are somewhat limited (outside using hematopoietic stem cells), and the data is scarce, the promise that the future research hold is priceless, and should lead to much more comprehensive treatment approaches for patients with a variety of diseases. The applications of stem cells are exponentially expanding as we learn more about their properties. The five diseases discussed here are only the tip of the iceberg when it comes to the potential uses of stem cells. But as with any other innovation, there comes the complications of ethics and the boundaries created by regulations, which will be discussed next.

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Chapter-3: Stem Cell Ethics

Stephen Dalton-Petillo

Even with the great promises of regenerative medicine, and the real or potential use of various kinds of stem cells to treat human disorders, all of this science is affected by one of the most controversial bioethical debates of our time, the ethics of researching, using, and harvesting stem cells. Ethics is defined as the moral correctness of a specified conduct, and it is the moral correctness of harvesting a particular type of stem cell, the embryonic stem (ES) cell, that is the center of the debate. The purpose of this chapter is to investigate the ethics of stem cells, especially ES cells.

Introduction to Stem Cell Ethics

As discussed in previous chapters, ES cells are harvested from the inner cell mass of a 5-day old blastocyst embryo prepared by *in vitro* fertilization (IVF). Harvesting the ES cells destroys the embryo, so the debate focuses on the status of the 5-day old embryo. The status of an embryo is affected by political, religious, and personal views, which factor together to provide a complex topic. Although researching and using stem cells in medicine points to a “whole new era of medicine” (Derbyshire, 2001), the center of the debate is whether the benefits of these potential breakthroughs are worth the detriments to the embryo.

The main focus of the debate is on when life begins as an embryo. A person or group’s decision on when life begins in an embryo ultimately determines their beliefs and outlooks on stem cell research. It may surprise some people to learn that the embryo debate is not new, and in fact began decades ago with the advent of IVF technology, and the birth of Louise Brown, the world’s first test tube baby (BBC News, 1978). There are typically three major thoughts about

embryo use. 1) One group believes that personhood begins at conception, and that all human embryos regardless of their age are a person with rights and privileges, and any harvesting or destruction of it is viewed as equal to killing a living person. 2) Another group believes that an embryo is a *potential* person but cannot be considered a person by itself. If the embryo is not implanted into a womb, it cannot develop into a full human. 3) The last view is that the embryo is literally and physically a group of cells “that are no more alive or human than a tumor, [or] a virus” (Derbyshire, 2001).

Generally, individuals who agree with the first two groups are against stem cell use and research, and those who agree with the third group are in favor of stem cell use and research. However, some individuals in the second group allow embryo usage under specific circumstances, so long as the embryo is respected and human lives are saved. It is the potential cure of diseases and the potential for improving the quality human life that some people consider more morally right than protecting a cluster of cells that have yet to become anything substantial in comparison to

The stem cell debate is complicated by the topic of cloning. Harvesting ES cells from an IVF embryo is *not* cloning. *Therapeutic* cloning involves isolating a skin cell nucleus from a patient, and injecting it into an enucleated egg, which is then grown to the blastocyst stage and ES cells isolated. The ES cells are genetically identical to the patient who donated the skin cell nucleus, so should not be rejected by the patient. *Reproductive* cloning is the same process just described, except the blastocyst embryo is implanted into a uterus for the purpose of live birth. Neither therapeutic nor reproductive cloning has been achieved with humans, but both have been achieved with animals. Others believe that reproductively cloning humans will be the next step in line after ES cell isolation, and therapeutic cloning, and fear that allowing unregulated or

unrestricted implementation of parental nuclei in stem cells will pave the way for these practices (Derbyshire, 2001). And regardless of a person's views on cloning, ultimately, one's viewpoint on when life begins in an embryo decides their stance for or against ES stem cell use.

Although the ethics debate of ES cells is important in science and politics, religion plays a very important role in how most people view this topic. The five major religions: Christianity (and Catholicism), Judaism, Islam, Hinduism, and Buddhism, all have different stances on embryo research. Despite this generalization, large religions often have different levels of followers, and some can disagree with a religion's main stance. This chapter will examine each major religion and their stance on embryo research, indicating where they believe life begins, and if there are any major disagreements within the religion important or prevalent enough to mention.

Catholicism and Stem Cells

The first religion we will discuss is Catholicism, a form of Christianity led by the Pope. In 2009, Pope Benedict was quoted saying that, "Research into *somatic* stem cells merits approval and encouragement when it brings together scientific knowledge... and the ethic that postulates respect for human beings at every stage of their existence..." (Catholic Online, 2008). So, it is not true that Catholics disapprove of all stem cells, just ES cells. It is well documented that *most* Catholics believe life begins at conception, so a 5-day old embryo is a living person (American Catholic Organization, 2006). "If there has been – and there still is – resistance, it was and is against those forms of research that involve the planned suppression of human beings who are already alive, though they may not yet have been born..." (Catholic Online, 2008) was a quote from Pope Benedict in the same interview, indicating that manipulating or altering any

form of human life is “devoid of humanity.” The embryo is viewed by the religion, even at its earliest stages as an example of “the weakest [of life] among us” (Nairn, 2005), and susceptible to destruction through ES cell research.

Interestingly, as is typical for a very large religion, not all members hold the exact same view on life’s origins. Although the Pope and the majority of Catholics believe human life begins at fertilization, others believe it begins at birth, or anywhere in between. With this variation, the church’s reluctance to use embryos for research is formed under the theory that “it is objectively a grave sin to dare to risk murder” (Nairn, 2005). It is also believed that the point in which the soul is acquired by the human can never be accurately determined as occurring before or after birth, so this uncertainty also affects the debate. The church generally disagrees with deriving more ES cell lines as this would cause the “destruction of more blastocysts” and “there would be at least an indirect encouragement... diluting the condemnation of the original destruction of human blastocysts” (Nairn, 2005).

In addition, ES cell research not only poses the ethical problems of killing an embryo, but also “increasingly poses the ethical problem of deceiving the public as well” (Benedict Endorses Adult Stem-Cell, 2008). Richard Doerflinger, the interim executive director of U.S. bishops’ Secretariat for Pro-Life Activities strongly believes in this and boldly made a claim in the same article that embryonic stem cells research has promoted a “series of deceptions” and in fact will not cure Alzheimer’s disease. He fears that no change in this “deception” will cause science to lose its credibility (Catholic Online, 2008).

Non-Catholic Christians and Stem Cells

The rest of the non-Catholic Christian faith, Protestant, Methodist, and other denominations have similar opinions to that of the Catholic Church, but there are some differences. For example, Methodists believe that it is “morally tolerable to use existing embryos for stem cell research purposes” (United Methodist, 2004). They believe that the potential therapeutic benefits from this research with already existing excess IVF embryos outweigh the wrong. The use of embryos not introduced into the womb in reproductive efforts is considered “morally tolerable” as long as an embryo is not created for the sole purpose of research (United Methodist, 2004). However, the Christian faith in general rejects the use of human embryos for research.

Judaism and Stem Cells

Judaism, in comparison with Christianity and Catholicism, encourages the research of both adult stem cells and embryos, with some restrictions. The Jewish tradition states that *Pikuach nefesh*, the Preservation of life, is the “most important obligation of all, overriding almost all other laws” (Yearwood, 2006). If the ES cells derived from destroyed embryos possess the ability to benefit society by preserving existing life, then this is in line with Jewish tradition and accepted. According to the Jewish faith and law, it is commonly accepted that “a fetus prior to forty days gestation is not considered to be an actual person” and “destruction of such a [young] fetus is not forbidden by Jewish law” (Eisenberg, 2006). In addition, the faith also permits the abortion of a fetus prior to 40 days following the same guidelines. Since they believe an embryo may be destroyed during the specific time period for abortion, it most certainly can be used to further research in the embryonic stem cell field to save existing lives.

However, embryos *after* the forty day gestational period are considered to have human qualities, and thus there is a prohibition of *retzicha* (murder) mandated by Jewish law (Eisenberg, 2006). There has always been a debate whether using embryos is similar to “playing God” which to some is considered extremely wrong. But two Jewish legal mandates encourage this based on the “two professions” of God Himself: teaching and healing. Thus, researching stem cells to further future therapeutic medical practices is viewed as behaving similar to God, and is condoned when it comes to medical research (Jakobovits, 2006). And as with Christianity where not all members think alike, while these are the opinions of most Jewish leaders, and are in accordance with general Jewish tradition, it was specifically pointed out that all of these conclusions are not unanimous (Jakobovits, 2006).

Islam and Stem Cells

The Islamic stance on stem cell research is very similar to that of Jewish beliefs. The Islamic religion is very proactive when it comes to the support of research that will yield future medical benefits to help maintain a good quality of life. *In vitro* fertilization is widely supported by Islamic people, and logically argues that instead of wasting the thousands of excess IVF targeted for destruction after the couple has enough children, why not use them for research? Adult stem cell research is widely supported and is less controversial than ES cell use, and the Islamic faith encourages this form of an alternative research, although potentially it is less useful (Siddiqi, 2002). The Islamic people similarly believe in the distinction between the point of *potential* life of an embryo and *actual* life; not only distinguishing actual from potential by embryo age in the womb, but also applying the distinction to an embryo in the womb versus a dish (IVF). The potential of an IVF embryo to grow into a human being if implanted into the

uterus is acknowledged, but the fact that it is not yet a human being prior to the forty day mark affirms the difference. So there is nothing wrong in doing this research, “especially if this research has a potential to cure diseases” (Siddiqi, 2002). The Islamic people feel that if this is the case with stem cell research, then it is “not only allowed, but it is *obligatory* to pursue this research” (Siddiqi, 2002). However, they do believe that lines should be drawn with regard to the reckless destruction of embryos solely for research purposes. Basically, ES cell research should be limited to only spare embryos from IVF, rather than creating and destroying an embryo solely for the purpose of research. Also the potential malpractice of doctors having their patients produce more embryos than needed for IVF is a common fear (Siddiqi, 2002), so this must be controlled. Overall, stem cell research is encouraged within Islam using excess IVF embryos (near day 5), but using an embryo *after* day forty is murder.

Hinduism and Stem Cells

Hinduism, the most predominant religion of the subcontinent of India, has morals, ethics, and ideas slightly different than that of the aforementioned religions, yet it still poses an intriguing stance on stem cell ethics. One of the core beliefs of the Hindu doctrine of non-violence (*ahimsa*) is that all life is sacred, and that all of God’s creations (which are everything) must be respected (Bahnot, 2008). With that said, another major belief is that the law of nature says that in order for one to survive, another life must be taken, such as humans eating plants or animals. According to the ancient *Rishis* (divine sages), there are a variety of levels of consciousness in existence, with plants at the lowest level, then animals, then humans. The highest level of consciousness beings, humans, must be protected which justifies the killing of lower levels of consciousness beings, plants and animals (Bahnot, 2008). Many practices such

as Yoga were created to rid the body of illnesses and promote a healthy lifestyle with the idea of prolonging one's life. Comparing this "necessity to take lives" belief to the goals of science and stem cell research can justify using an embryo, with the promise that it will further benefit the quality of life of living people (Bahnot, 2008).

Although this is just one opinion on the use of embryos through Hinduism teachings, other groups of Hindus believe that using embryos is unacceptable, as this would constitute harming another living thing due; conception is viewed as "a soul's rebirth from a previous life" (Knowles, 2012). Some believe that the soul's rebirth occurs between three and five months, while others think it happens at the seven month point, resulting in varying beliefs within the religion. Hinduism has no "official" leaders of the entire religion, causing slight confusion to general stances (Knowles, 2012). Regardless, Hindu believers are supportive of using adult stem cells as they cause no harm, yet aim to help heal others.

Buddhism and Stem Cells

Buddhism is very similar to Hinduism in its teachings, thought, and morals. With respect to embryos and ES cells, there is much variance. Buddhism like Hinduism agrees that the therapeutic use of adult stem cells is acceptable because it doesn't cause any harm to life. Also similar to Hinduism is the fact that Buddhism has no official group that makes statements on behalf of the religion (Keown, 2004), which leads to confusion when trying to generalize the stance for stem cells for Buddhism as a whole. There is no singular sacred text like in Christianity to define when life begins or what is right or wrong. Mostly, there are teachings within Buddhism that pose morals and ideals for a particular lifestyle. Buddhists have been said to adopt a similar belief to Hinduism that conception marks the birth of a person, but then again

only some of Buddhists believe this (Knowles, 2012). There are two separate tenets in the Buddhist teachings that apply to embryos: one is against the act of harming others, and another is for the pursuit of knowledge. The first tenet argues against harming embryos, while the second tenet would favor it based on the fact that it holds promise for improving human life in the future (Knowles, 2012). On the other hand, the Buddhist belief in rebirth says that life starts at conception, which means that the newly fertilized embryo is considered a person and “entitled to the same moral respect as an adult human being” (Keown, 2004). Yet going against the idea of rebirth, the use of an embryonic stem cell could be viewed as a *donation* to help benefit the lives of others, which would not be considered an act of evil in Buddhist doctrine (Promta, 2004). It is interesting to note that Buddhists understand that there are two different views on this (and other subjects), an empirical and non-empirical view. The empirical view is the opinions of those in the community, while the non-empirical view belongs to the authorities of the religion or its teachings (Promta, 2004). This dual view confirms the vast differences of stances in Buddhism on the use of embryos and ES cells, based on different codes of conduct.

Induced Pluripotent Stem Cell Ethics

Induced pluripotent stem (iPS) cells, are adult skin fibroblast cells forced into a pluripotent state by introducing 2-4 transcription factors (or the genes encoding them) into the skin cells. As discussed in Chapter-1, these iPS cells appear to be similar to ES cells in that they can be used to make a large variety of tissues. The main difference is that the skin cell undergoing the treatment does not have to be harvested from a human embryo, thus eliminating the main reason for not using ES cells (Deem, 2009; Brind’Amour, 2009). One of the most overlooked concerns of using IVF embryos is the effect of harvesting the eggs on women. This

procedure is a relatively complex medical procedure, and can have complications such as infections that can be life threatening to the donor. In addition, if money is paid to egg donors, it might induce poor women into undergoing an egg donation procedure they otherwise would never undergo (Baylis, 2008). The act of iPS cell induction has been revised from the original method of using viruses encoding 4 transcription factors, to using the proteins themselves, which erased many health issues potentially induced by the viral vectors. In addition, the original 4 transcription factors included *c-Myc* oncogene which induced tumor formation in some cases, and this has now been replaced by a protocol using only 2 factors that does not cause cancer (Kim et al., 2008).

Although there are many advantages to this new iPS cell research, there is still some ethical apprehension. Even though iPS cells do not require human embryos, through the process of being induced to a pluripotent like state some ethicists fear that the iPS cells could eventually become totipotent, and be capable of making a living being if implanted. In this case their ethics would be similar to an IVF embryo (Brind'Amour, 2009), although this has never been shown to be the case. So some ethicists argue destroying iPS cells is equivalent to destroying potential life (Cohen and Brandhorst, 2008).

Chapter-3 Conclusions

The final part of this chapter is an assessment of my opinions with regards to the ethical issues described in this chapter. I am not against the use of embryos for research, as long as the woman donating the eggs for IVF fertilization is willing to undertake a procedure with potential side effects. Although the IVF embryo has potential life, it also has the potential to save existing lives, so prior to the forty day mark I believe it is just a collection of cells. If a man and woman

who donated the egg and sperm for IVF are willing to donate their excess fertilized embryos for research purposes, let it be their decision and no one else's. I am in favor of using excess IVF embryos originally created for reproductive purposes, as this is a great way to use these embryos instead of wasting them from being discarded. It is similar to recycling. If the "product" is being used for one purpose and either fails or was not needed, then its reuse for something else makes sense. Having said that, I am also in favor of using embryos created solely for research purposes using paid donors. If somebody is willing to donate egg and sperm and also receive a compensation for it, then it is entirely up to them, so long as they are aware of the potential health risks of egg donation and understand what the ES cells will be used for. There are much more dangerous things that people in this world agree to do or take part in that yield almost no benefit to mankind (smoking, base jumping, etc.).

I think that to calm the majority of people who think using ES cells is murder, using adult stem cells whenever possible should be encouraged. I also do not think it is right to limit the amount of federal dollars for ES cell research due to political and religious opinions, based on the fact that the cells have so much potential for therapeutic breakthroughs. So ultimately, using adult stem cells whenever possible is a good compromise. I am also in favor of using iPS cells if possible. I think that iPS cells are a clever and crafty discovery to avoid the main issue of using IVF embryos. It is a little ridiculous for those who think that iPS cells are exactly like embryos and have the potential to make a living being, because this has never been shown. iPS cells lack the ability to grow into a form of life even if implanted into a uterus. I think people should be more opposed to the idea of reproductive cloning, than worrying about iPS cells.

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Chapter-4: Stem Cell Legalities

Joseph Szerszunowicz

As is typical for all controversial technologies, laws have been enacted to control the funding for stem cell research. The benefit to society of regenerative medicine through stem cells is unparalleled, but as was discussed in Chapter-3 some types of stem cells are ethically controversial. This is especially true for embryonic stem (ES) cells that destroy an embryo when isolating them. The legalities of stem cells is a fascinating blend of science and politics; whichever administration is in office dictates the types of laws enacted, and the policies vary from state to state. For the past three presidents (Clinton, Bush, Obama), the United States has held widely varying stem cell policies, and the next administration in January may have an entirely different policy. Pro stem cell bills under one president's administration are sometimes completely nullified by the next administration. In some cases, individual states such as California, New Jersey, and Massachusetts have approved their own bonds to fund ES cell research during times lacking federal funding. In addition, the laws on stem cells vary from country to country. The purpose of this chapter is to discuss federal and state laws regulating embryo and ES cell research in the U.S and abroad. The last three U.S. presidential administrations have been the most involved with embryo and stem cell legislation mainly due to the timing of the stem cell technologic boom.

The Clinton Administration and Stem Cells

President Clinton tried to set the stage for a golden age of stem cell research with the National Institutes of Health Revitalization Act of 1993 (NIH Revitalization Act...1993). 'Under this act the NIH was given direct authority by President Clinton and Congress to fund human

embryo research for the first time' (Dunn, 2005). This was a monumental step for researchers who believed that stem cells could lead to the eradication of most of mankind's incurable diseases. With this new direct authority over human embryonic stem cell research, the NIH had to form a panel to oversee this research and to be held accountable to the public and congress. The NIH formed a group of experts called the NIH Human Embryo Research Panel (Robinson, 2005). This panel included scientists, ethicists, and public policy experts whose role was to consider the morals and ethics of embryo experiments and determine what should be federally funded. The panel came to the conclusion that experiments that used excess embryos prepared for *in vitro* fertilization (IVF) to derive new ES cell lines should be federally funded. The NIH Human Embryo Research Panel attempted to kick start a boom in stem cell research by allowing stem cell farming from embryos to be financially backed by the government. Armed with large federal funding, the possibility of new advancements in medicine and rehabilitation looked promising.

However, this "golden age" of embryo research was short lived. In 1996, the Dickey-Wicker Amendment was enacted by congress. The Dickey-Wicker Amendment states that:

SEC. 509. (a) None of the funds made available in this Act may be used for--
(1) the creation of a human embryo or embryos for research purposes; or
(2) 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 under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
(b) For purposes of this section, the term `human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. (Kearl, 2010)

With this 1996 amendment in effect, the earlier recommendation made by the NIH to federally fund embryo research was nullified. The Dickey-Wicker Amendment was written by Republican Representatives Jay Dickey and Roger Wicker. With this ban on federal funding, the only way to

continue to explore ES cell research was with private funding. The Dickey-Wicker Amendment seemed to make Clinton's NIH stop dead in its tracks towards making any further recommendations on how to fund stem cell research.

In 1999, there was a breakthrough for ES cell research. Harriet Rabb, the top lawyer for the Department of Health and Human Services, made a brilliant legal decision observation involving the *privately* funded lab of James Thomson. In 1998, Thomson was the first person to isolate human embryonic stem cells (Thomson et al., 1998). The NIH under Clinton knew this discovery was an immense finding, so Rabb pointed out an obvious loophole in the Dickey-Wicker Amendment, concluding that: although 'federal funds could not be used to make stem cells because this would involve creating or destroying a human embryo, which directly violates the Dickey-Wicker Amendment, on the other hand the stem cells themselves are not under the definition of "human embryo", thus the Dickey-Wicker Amendment does not apply to stem cells. These soon became the standard guidelines under the Clinton Administration in August of 2000' (Dunn, 2005). The federal government was now allowed to fund experiments involving ES cells, but it was up to the *privately* owned research labs to derive the stem cells in the first place. President Clinton heavily endorsed these guidelines, knowing that research from human embryo experiments could solve many problems with currently incurable diseases. This Rabb legal decision solidified the Clinton Administration as the first stepping stone on the road to federal funding for stem cell research.

The Bush Administration and Stem Cells

President Bush had very opposing views than President Clinton on embryo research. As soon as Bush assumed office in 2001, ES cell research in the U.S. began to suffer. President Bush's Secretary of Health and Human Services Tommy Thompson,

“ordered a review of Rabb's legal decision. Then, the Bush Administration told the NIH to cancel its plans to review grant applications—pending completion of the HHS review. If the Bush Administration had done nothing, the NIH would have proceeded to review the applications and to finance those that were successful. Instead, that process was halted, a decision that saddened, angered, and frustrated supporters of human embryonic stem cell research.” (Dunn, 2005)

The Bush administration was seeking to immediately stop any progress the Clinton administration previously made towards federally funded ES cell research. Within the same year, on August 9th, 2001 President Bush would fully undo any strides President Clinton made in ES cell research funding:

“On August 9th, 2001, Former President George W. Bush announced that federal funds may be awarded for research using human embryonic stem cells if the following criteria are met: 1) The derivation process (which begins with the destruction of the embryo) was initiated prior to 9:00 P.M. EDT on August 9, 2001. 2) The stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed. 3) Informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements.” (NIH.gov, 2001)

Days later on August 11, 2001, President Bush made a radio address to the people of the United States about the nation's next step in stem cell research. He was recorded stating the following:

“Embryonic stem cell research offers both great promise and great peril. So I have decided we must proceed with great care. As a result of private research, more than 60 genetically diverse stem cell lines already exist. They were created from embryos that have already been destroyed, and they have the ability to regenerate themselves indefinitely, creating ongoing opportunities for research. I have concluded that we should allow federal funds to be used for research on these existing stem cell lines where the life and death decision has already been made.

Leading scientists tell me research on these 60 lines has great promise that could lead to breakthrough therapies and cures. This allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life.” (Bush, 2001).

Thus, President Bush within 8 months of attaining office halted federal funding for ES cell research, and also reduced the number of qualified ES cell lines available for testing. The only

saving grace for ES cell research was that federal funding would still be allowed for the pre-existing sixty stem cell lines that President Bush agreed on. Unfortunately, the so-called 60 ES cell lines proved to be far less, as further experiments indicated many of the cell lines were genetically identical to each other, were genetically damaged, or were aged, so scientists feared that had far fewer cell lines for work with than originally promised (Holden and Vogel, 2002).

Stem cell issues did not come up again for President Bush until July 19, 2006, when he used his power to veto a bill for the first time to deny the passing of the Stem Cell Research Enhancement Act of 2005 (Stem Cell...2005). This bill would help alleviate the harsh restriction on ES cell lines that President Bush first enacted when he first took office. The bill passed through both the House of Representatives and the U.S. Senate by majority votes, but the final vote in the house was not sufficient to override the president's veto: "the House voted 235 to 193 yesterday to override Bush, falling short of the threshold and negating the need for a Senate override attempt" (Babington, 2006). Even though the bill failed to override Bush's veto, the votes showed that the government outside of President Bush, was trying to take a step in funding ES cell research.

In 2007, Bush would again veto a bill of the same nature on June 20, 2007. The bill was a rehash of the previous research enhancement act, and Congress hoped for a better chance of overriding any veto (Stem Cell...2007). But again President Bush vetoed the bill, stating: "scientific advances now allow researchers to pursue the potentially lifesaving work without destroying human embryos" (Fletcher, 2007). The president put more emphasis on the use of stem cells collected from umbilical cords and amniotic fluid rather than destroying human embryos. This veto put President Bush on the wrong side of Congress, and made sure that any

further stem cell related bills or legislations would be placed on the shoulders of the next administration.

The Obama Administration and Stem Cells

Like President Bush, President Obama made it abundantly clear that stem cells were a hot issue, but this president took a different approach. Instead of following his own feelings on the matter, President Obama said that “his administration would make scientific decisions based on facts not ideology” (Childs and Stark, 2009). So on March 9, 2009 President Obama signed an executive order to end Bush’s 2001 ban of federally funding ES cell research. However, President Obama’s lift of the ban meant he had to determine new guidelines for allowing the funding, so he turned to the NIH and gave them 120 days after the signing of his executive order to create new guidelines (Childs and Stark, 2009). The 2009 NIH revised guidelines involving stem cell research opened the door for the use of ES cells that were originally deemed untouchable by the Bush Administration. The guidelines allowed for research on ES cells:

- I. that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose;
- II. that were donated by individuals who sought reproductive treatment (hereafter referred to as "donor(s)") and who gave voluntary written consent for the human embryos to be used for research purposes; and
- III. for which all of the following can be assured and documentation provided, such as consent forms, written policies, or other documentation, provided:
- IV. All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment.
- V. No payments, cash or in kind, were offered for the donated embryos.
- VI. Policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s).
- VII. There was a clear separation between the prospective donor(s)’s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes. Specifically:
- VIII. Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician

responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize hESCs should not have been the same person unless separation was not practicable.

- IX. At the time of donation, consent for that donation should have been obtained from the individual(s) who had sought reproductive treatment. That is, even if potential donor(s) had given prior indication of their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation for research purposes should have been given at the time of the donation.
- X. Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.
- XI. During the consent process, the donor(s) were informed of the following:
 - XII. that the embryos would be used to derive hESCs for research;
 - XIII. what would happen to the embryos in the derivation of hESCs for research;
 - XIV. that hESCs derived from the embryos might be kept for many years;
 - XV. that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants.;
 - XVI. that the research was not intended to provide direct medical benefit to the donor(s);
 - XVII. that the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development;
 - XVIII. whether information that could identify the donor(s) would be available to researchers.

(Holden, 2009; Childs and Stark, 2009)

The 2009 NIH guidelines loosely followed the same procedures originally made for the Clinton Administration a decade before, but allowed for donated ES cell lines derived from discarded IVF embryos to receive federal funding, however federal funding could not be used to derive the lines in the first place. The same general rules applied as earlier for how the ES cells would be donated; no money could be paid to the donors, and the donor must have written consent to donate the ES cell lines.

Obama's lift of the 2001 ban now allowed fully equipped government-funded labs to be used for research on ES cells, increasing the available lines to 400 to 1,000 (Hayden, 2009). This is a huge improvement from the original 21 lines that could receive funding under President Bush, hopefully allowing new discoveries to be made to save lives. Many embryos that were scheduled for termination can be recycled and put to good use. Because the law prohibits federal funding to derive the ES cells, that portion of the research must be funded by private funds

(Holden, 2009). The author of this chapter believes that the ban lift by President Obama was indeed a choice made using common sense based on science, instead of the ideology of one man.

State Governments' on Stem Cells

During the constant fight over whether federal funding could be allowed to fund ES cell research over three administrations (Clinton, Bush, Obama), various state governments stepped into the debate and created their own laws and regulations to support the research to make crucial breakthroughs in medical technology with ES cells.

Massachusetts and Stem Cells

Massachusetts took a very active role in making ES cell research possible in the United States during the strict policies established in the Bush era. In May 2005, at the 187th Meeting of the General Court of Massachusetts, state legislators declared in section one of the Act Enhancing Regenerative Medicine in the Commonwealth:

(a) human embryonic stem cell research and other research in the life sciences and regenerative medicine present a significant chance of yielding fundamental biological knowledge from which may emanate therapies to relieve, on a large scale, human suffering from disease and injury;

(b) the extraordinary biomedical scientists working within institutions of higher education, research institutes, hospitals, biotechnology companies and pharmaceutical companies can contribute significantly to the welfare of mankind by performing outstanding research in these fields; and

(c) it shall be the policy of the commonwealth to actively foster research and therapies in the life sciences and regenerative medicine by permitting research and clinical applications involving the derivation and use of human embryonic stem cells, including research and clinical applications involving somatic cell nuclear transfer, placental and umbilical cord cells and human adult stem cells and other mechanisms to create embryonic stem cells which are consistent with this chapter. It shall further be the policy of the commonwealth to prohibit human reproductive cloning. (An Act Enhancing Regenerative...2005)

This 2005 Act, approved by a wide margin that overturned Governor Mitt Romney's veto, states that the medical potential of stem cells is too great to keep from being hindered because of

ethical or moral arguments. People can be helped by stem cells now, and the state of Massachusetts saw it as unfair to the people who needed that help. Great strides could be made in the field, and it did not seem logical to hinder the progress. In 2007, to aid in the progression of research, Governor Deval Patrick announced a 1.25 billion dollar funding initiative for stem cell research (Marks, 2007). Much of the funding went to the founding of the Massachusetts Human Embryonic Stem Cell Bank, located in Worcester, MA (Marks, 2007). The bank is located in The University of Massachusetts Medical School (UMMS) and provides an excellent research atmosphere free of most restrictions for both local and international scientists (Shelton, 2007).

California and Stem Cells

California is another state that took a very pro stem cell research stand during the strict Bush administration. On November 2, 2004, California voters approved Proposition 71, also known as the 'California Stem Cell Research and Cures Act' (LAO, 2004). This act allowed for \$3 billion dollars in obligated bonds to be dispersed as loans and grants for stem cell research and research facilities. The act also established the California Institute of Regenerative Medicine (CIRM) that would control how the research money would be dispersed throughout the state, much like the NIH does on the national level. The money would be borrowed from California's General Fund, and would begin to be paid off after ten years (LAO, 2004). This was a clever way to work around the federal stem cell funding issue during the Bush era.

Various Other States on Stem Cells

Other states also followed suit and approved their own ES cell initiatives, while states voted to prohibit embryo research. **Table-I** shows a list of various US states and their stance on embryo and ES cell research.

State/Jurisdiction Statute Section	Specifically permits research on fetus/embryo	Restricts research on aborted fetus/embryo	Consent provisions to conduct research on fetus/embryo ³	Restricts research on fetus or embryo resulting from sources other than abortion	Restrictions of purchase/sale human tissue for research
Arizona §§36-2302, 2303	No	Yes, prohibits research on aborted living/non-living embryo or fetus	No	Yes, prohibits the use of public monies for cloning for research	No
Arkansas §§20-17-802, 20-16-1001 to 1004	No	Yes, prohibits research on aborted live fetus	Yes, consent to conduct research on aborted fetus born dead	Yes, prohibits research on cloned embryos	Yes, prohibits sale of fetus/fetal tissue
California Health & Safety 2004 Proposition 71 §§ 123440, 24185, 12115-7, 125300-320	Yes, permits research on adult and embryonic stem cells from any source	Yes, prohibits research on aborted live fetus	Yes, consent to donate IVF embryo to research	Prohibits sale of embryos and oocytes; prohibits payment in excess of the amount of reimbursement of expenses to be made to any research subject to encourage her to produce human oocytes for the purposes of medical research	Yes, prohibits sale for the purpose of reproductive cloning or for stem cell research
Connecticut §§4-28e; 19a-32d et seq.	Yes, on embryos before gastrulation (a process during embryonic development)	No	Yes, consent to donate IVF embryo to research	No	Yes, prohibits payment for embryos, embryonic stem cells unfertilized eggs or sperm donated following IVF treatment

Florida §390.0111	No	Yes, prohibits on aborted live fetus	No	No	No
Illinois 720 ILCS 510/6, 510/12.1 Executive Order 6 (2005);410 ILCS 110/1 et seq.	Yes, permits research on embryonic stem cells, embryonic germ cells and adult stem cells from any source	Yes, prohibits on aborted living/nonliving fetus	Yes, written consent to perform research on cells or tissues from a dead fetus other than from an abortion	Yes, prohibits research on fetus/fertilized embryo; prohibits funding under E.O. 6 (2005) of research on fetuses from induced abortions and the creation of embryos through the combination of gametes solely for the purpose of research	Yes, prohibits sale of fetus/fetal tissue; prohibits purchase or sale of embryonic or fetal cadaveric tissue for research but permits reimbursement for removal, storage and transportation for research
Indiana §35-46-5-1, 16-18-2-5.5	Yes, permits fetal stem cell research on placenta, cord blood, amniotic fluid or fetal tissue	Yes, prohibits research on aborted living/non-living embryo or fetus	Yes, consent required for fetal stem cell research	Yes, prohibits research on cloned embryos	Yes, prohibits sale of human ovum, zygote, embryo or fetus
Iowa §§707C.4	Yes, ensures that Iowa patients have access to stem cell therapies and cures and Iowa researchers may conduct stem cell research	No	No	No	Yes, prohibits transfer or receipt of the product of human reproductive cloning
Kentucky §436.026	No	No	No	No	Yes, prohibits sale of fetus/fetal tissue
Louisiana §14: 87.2	No	No	No	Yes, prohibits research on fetus/embryo in utero, in vitro fertilized embryo	No
Maine 22§1593	No	No	No	Yes, prohibits research on fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-	Yes, prohibits sale of fetus/fetal tissue

				implantation	
Maryland 83A§5-2B-01 et seq.	Yes, permits research on adult and embryonic stem cells	No	Yes, written consent to donate unused IVF material to research	Yes, prohibits donation of unused oocytes for state funded stem cell research; cloning of an organism beyond the embryonic stage is prohibited	Yes, prohibits valuable consideration for the donation or production of IVF material
Massachusetts 112§12J, 2005 SB 2039	Yes, on embryos that have not experienced more than 14 days of development (not including days frozen)	Yes, prohibits research on embryo/live fetus	Yes, written consent to perform research on a dead fetus and informed consent to donate egg, sperm, or unused preimplantation embryos created for IVF	Yes, prohibits research on live embryo or fetus; also prohibits creation of fertilized embryo solely for research	Yes, prohibits sale of neonate, embryo or fetus for illegal purposes; prohibits sale of embryos, gametes or cadaveric tissue for research
Michigan §§333.2687-2688, 333.16274-16275, 333.20197, 333.26401-26403, 750.430a	No	Yes, live embryo/fetus	Yes, written consent of mother to donate dead embryo, fetus or neonate to research	Yes, prohibits research on a live embryo or fetus, cloned embryo	No
Minnesota §§145.421, 422	No	No	No	Yes, prohibits research on a live embryo or fetus up to 265 days post fertilization	Yes, permits the sale/purchase of cell culture lines from nonliving human conceptus
Missouri §§188.036, 037	No	Yes, prohibits research on a fetus alive pre-abortion	No	No	Yes, prohibits receipt of valuable consideration for aborted fetal organs or tissue
Montana §50-20-108(3)	No	Yes, prohibits research on a live fetus	No	No	No

Nebraska §§28-342, 346, 71-7606	No	Yes, prohibits research on aborted live fetus or the use of state funds for research on fetal tissue obtained from an abortion	No	Yes, limits the use of state funds for embryonic stem cell research; restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars	Yes, prohibits sale, distribution or donation of viable aborted child
New Hampshire §§168-B:1, 15	No	No	No	Yes, prohibits the maintenance of a unfrozen fertilized pre-embryo past 14 days	Yes
New Jersey C.26:2Z-1 et seq.; C.2C:11A-1	Yes	No	Yes	No	No
New Mexico §24-9A-1, 3, 5	No	No	No	Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation	Yes, prohibits abortion for the purpose of selling the fetus to researchers
New York Public Health Law Article 2, Title 5A	Yes, permits research on adult and embryonic stem cells from any source	No	No		
North Dakota §14-02.2-01, 2; 2003 HB 1424	No	Yes, prohibits research on a living/non-living embryo or fetus	Yes, requires consent to conduct research on a nonliving fetus or embryo other than from an abortion	Yes, prohibits research on a fetus born or extracted alive; cloned embryos	Yes, prohibits the sale of a fetus to be used for illegal purposes
Ohio §2919.14	No	Yes, prohibits research on a living/non-living embryo or fetus	No	No	Yes, prohibits sale of fetus or fetal remains from an abortion

Oklahoma 63 §1-735	No	Yes, prohibits research on a fetus/embryo	No	No	Yes, prohibits sale of fetus or fetal remains
Pennsylvania 18 §§3203, 3216	No	Yes, prohibits research on a live embryo or fetus	Consideration may not be given to mothers consenting to research; in cases involving abortion, consent must be provided after decision to abort	No	Yes, consideration may not be given to mothers consenting to research or other transferring tissue except for expenses involved in actual retrieval, storage, etc.
Rhode Island §11-54-1	No	No	Yes	Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation	Yes, prohibits sale of neonate, embryo or fetus for illegal purposes
South Dakota §§34-14-16, 17, 20; 34-23A-17	No	Yes, prohibits research on a living/non-living embryo or fetus	No	Yes, prohibits research on embryo outside of a woman's body; research on cells or tissues derived from an embryo outside a woman's body	Yes, prohibits sale of embryo
Tennessee §39-15-208	No	No	Yes, consent required to conduct research on aborted fetus	No	Yes, prohibits sale of aborted fetus
Texas Penal Code §48.02	No	No	No	No	Prohibits sale of fetus/fetal tissue
Utah §§76-7-301, 310	No	No	No	Yes, prohibits research on a live fetus, fertilized embryo post-implantation ¹	Yes, prohibits sale of fetus/fetal tissue; also prohibits sale of live unborn children, which is not defined, but

					are referred to in abortion statute ⁴
Virginia §32.1-162.32-2	No	No	No	May prohibit research on a cloned embryo or fetus ²	Yes, prohibits shipping or receiving of the product of human cloning for commerce ²
Wyoming §35-6-115	No	No	No	No	Yes, prohibits sale, distribution or donation of live or viable aborted child, defined to include embryos, for experimentation

(Source: National Conference of State Legislatures, 2008)

International Views on Stem Cell Research

The US is not the only country enacting policies to control stem cell research. Many countries such as England, Sweden, and China have led the way to supporting embryo research.

China and Stem Cells

China has long approved the use of embryos in research (discussed in Chapter-3), but their poor oversight of researcher qualifications, and loose laws for protecting intellectual property rights has come under some scrutiny. As a result, on May 1st, 2009 China's Stem Cell Transplantation Department enacted new laws regulating new biotechnologies, including stem cell treatments (Stem Cell Transplantation Dept....2011). The 2009 law called for more qualified directors running stem cell research facilities; any director must have 3 years of experience as a senior or technical position in a previous health institute. The clinic in question must also have had a technical audit, and pass standards established by a board of appropriate

authorities (Stem Cell Transplantation Dept....2011). To work on stem cells, any institution must meet the following criterion:

In order to apply for approval, medical institutions should submit a feasibility study report, including:

- The basic profiles of medical technology, including domestic and international applications, indications, contradictions, side effects, technical line, quality control measures, efficacy of standards, assessment, treatment and other medical technology with the risks , efficacy, cost and treatment comparison.
- Main technical personnel's qualification, relevant curriculum vitae, medical equipment, facilities and other auxiliary conditions, risk assessment and contingency plans.
- Clearance from the medical ethics review body.

The approval may not be granted under the following conditions:

- The clinical application of medical technology in the technical review process is deemed to be ineffective.
- Does not comply with the regulations of the appropriate administrative department of health.
- The clinical application of medical technology did not pass the technical audit.
- Beyond the scope of the registered medical subjects.

The license to practice stem cell treatment will be revoked effective immediately in the following conditions

- The respective medical technology has been abolished or prohibited by the Ministry of Health.
- Should there be any variation in the equipment, facilities, key professionals from what is specified in the clinical application.
- Should there be any adverse effects arising from the medical technology employed.
- Medical quality and medical safety hazard.
- Ethical shortcomings of medical technology.
- Inaccurate clinical application of medical technology. (Stem Cell transplantation Dept.....2011)

Thus, in China, although their ethics does not generally prevent working with embryos and ES cells, their government needed to provide stronger oversight of scientist qualifications.

Iran and Stem Cells

There are also countries where religion does not appear to inhibit stem cell research whatsoever.

Iran is an example of a balance between religious morals and science. Iran is a constitutional

Islamic republic, yet stem cell research flourishes (Erik, 2011). There are no laws that prohibit or regulate stem cell research, but instead their research is guided by Islamic ideals and their laws (Fatwa) are interpreted from these ideals by an Islamic scholar (Erik, 2011). “Ayatollah Khamenei, Iran’s religious leader issued a stem cell fatwa in 2002, stating that experimentation with human embryonic stem cells is consistent with Shiite Islam, thus making stem cell research possible in Iran” (Erik, 2011). Thus, Iran is an interesting case of a nation that has no conflict morally about using ES cells because the Islamic religion dictates that life does not begin until the soul enters the body, which is well after the blastocyst stage when ES cells are derived.

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PROJECT CONCLUSIONS

Based on the research performed for this project, the authors believe that the use of stem cells in medicine is practical and has the potential to treat many diseases, both chronic and terminal. Although the source and use of ES cells is controversial, these authors do not believe that embryo destruction is murder for a 5-day old surplus IVF embryo. The authors agree that iPS cells and adult stem cells should be used whenever possible in place of ES cells, if they have been shown to be as efficient at treating that specific disease. The type of stem cell used for treatments or research should be case specific, and based on the needs and demands of the case. Excess IVF embryos originally created for reproductive purposes slated for discard provide the best sourcing of ES cells, and unlike the current Obama administration we believe in allowing federal funding to help support this endeavor. The Obama administration currently allows *private* funding to derive new ES cell lines from IVF embryos, and *federal* funding to support research on the ES cells themselves. In lieu of using surplus IVF embryos, paid egg donors should be an auxiliary source of ES cells, a practice not currently allowed in the U.S. under the Obama administration. Iran's policies for stem cell sourcing and research best reflect our personal views and beliefs, as their loose restrictions on ES research helps to further promote developments in the field.