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# STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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# ABSTRACT

The purpose of this project is to evaluate the impact of stem cells, as an innovative technology, on society. This project provides a discussion of the various types of stem cells used in research, applications of these stem cells to the field of medicine, the ethics surrounding the use of stem cells, and the legislation that has been imposed in the US and internationally as a result of stem cell research. With consideration of the information above, despite ethical drawbacks, this project advocates stem cell research, embryonic and adult, for the betterment of society as a whole.

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# PROJECT OBJECTIVES

The purpose of this Interdisciplinary Qualifying Project (IQP) is to examine the subject of stem cells, and to assess the impact of this novel and revolutionary technology on society. The objective of Chapter-1 is to provide a basis for further stem cell discussion. Thus, this chapter contains content on how stem cells are classified, where stem cells are isolated from, and the various types of stem cells and their potencies. Chapter-2's purpose is to document the types of experiments that stem cells have been effectively used for. This chapter distinguishes animal experiments from human clinical trials, as well as future experiments from well-documented success stories, as an aid for realistically focusing the subsequent chapter on ethics. Chapter-3's purpose is to study the ethics surrounding stem cell research, particularly embryonic stem cell research, while Chapter-4 examines the U.S. and international laws governing stem cell use. Finally, this project ends with the author's conclusion on the use of stem cells and which laws best represent the author's point of view.

# CHAPTER-1: STEM CELL TYPES AND SOURCES

Many misinformed individuals still believe that only one type of stem cell exists, and usually they are referring to the type that destroys an embryo to obtain them. In reality, the 21st century has brought with it many different varieties of stem cells, each with their own diverse origin, potentials, and uses. Stem cell types can be divided into four main categories: embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, adult stem cells (ASCs), and parthenogenetic ES cells. The purpose of this chapter is to document the various types of stem cells currently known, and to describe their potencies.

The term "stem cell" dates back to William Sedgwick, who used it to describe the regenerative properties of plants in 1886 (Charmany, 2004). Thus, despite stem cells' sudden rise in popularity, the idea of stem cells as a source of new replacement cells has actually been around for over a century. But before jumping into describing stem cells, an understanding of basic cell biology and structure is needed. To begin with, a cell is the most fundamental biological unit. The basic parts of an animal cell commonly referenced in stem cell research include the cell membrane, nucleus, chromosomes, and DNA (**Figure-1**).

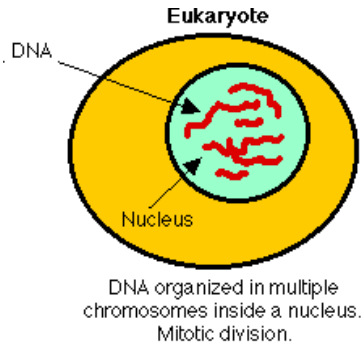


**Figure-1: Fundamental Diagram of a Cell.** The cytoplasm (yellow) is enclosed by a cell membrane (outer black line). The nucleus (green) contains chromosomes (red) that contain DNA. (Terry, 2000)

The cell membrane is the outer barrier of a cell. The nucleus acts as the "brain" of the cell. It contains chromosomes composed of DNA. This DNA codes for specific proteins that provide the genetic identity of the cell. As a result, the nucleus directs the function of the cell. Two different types of cell division, meiosis and mitosis, distinguish respectively germ cells (sperm and egg cells) from somatic cells (any cells in the human body other than germ cells). Somatic cells are used in the genetic reprogramming techniques for iPS stem cells. Germ cells are primarily used for the creation of embryonic stem cells (Scott, 2006).

**Stemness and Stem Cell Potentials**

Before discussing the various types of stem cells, a basic knowledge of "stemness", "the idiosyncrasies that make stem cells stand out from a crowd of millions" is necessary (Scott, 2006). Stemness is determined through two primary characteristics, potency and asymmetric cell division (**Figure-2**). The *totipotent* stage (diagram upper center) occurs in a newly fertilized egg through cells that accumulate during the egg's first few cell divisions. Totipotent stem cells are the most powerful as they can become any cell or tissue in the body, or they can produce extra-embryonic tissue such as the placenta. After a few days of dividing, these totipotent cells have differentiated further to become a blastocyst, a hollow ball of cells. The outer germ layers of the blastocyst have the potential to form the placenta while the inner cell mass (ICM) of the blastocyst has the ability to make an embryo. The ICM cells are embryonic stem cells, and they are *pluripotent* (diagram center). They can become most but not all cell types as they cannot form tissues for fetal development (such as the placenta). Pluripotent cells differentiate further to produce *multipotent* stem cells (diagram lower left). These cells can produce several types of related cells, such as the ability of hematopoietic stem cells to produce all the cellular

components of blood. These cells differentiate further to produce *unipotent* stem cells,that have the ability to form one type of tissue (Scott, 2006). Adult stem cells are either multipotent or unipotent cells. Current research is focused on whether adult stem cells have the ability to differentiate into other types of cells than the tissue from which they are isolated, a process termed *plasticity* ("Origin", 2010). It is currently debated whether adult stem cells exhibit plasticity, however, "…the number of research papers reporting plasticity outnumbers papers that dispute it by 10 to 1" (Scott, 2006).

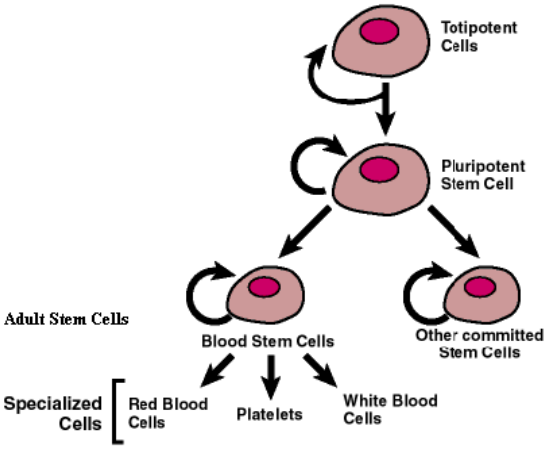


**Figure-2: Diagram of Stem Cell Asymmetric Divisions and Potentials.**
Rotational arrows denote the production of new stem cells, while straight arrows represent differentiation to lower potential cells. ("Origin", 2010)

Cell division is another quality that determines stemness. Stem cells exhibit a distinctive type of cell division. Stem cell division, unlike normal cell division does not follow the "exact copy" rules of mitotic division (Scott, 2006). When stem cells divide, they produce one undifferentiated cell (to replenish the stem cell population) while also producing one differentiated cell. Thus, stem cells have a hybrid cell division that both replenishes the population of stem cells and creates daughter cells with specialized abilities (Scott, 2006). As a result, stem cells both self renew and go through asymmetric cell division.

**Embryonic Stem Cells**

Embryonic stem (ES) cells in animals were first documented in the 1950's by embryologist Leroy Stevens, who at the time worked at Jackson Laboratories in Bar Harbor, Maine. His discovery came as a result of curiosity and chance. One day Stevens came across a mouse with an odd gate. This animal had developed a large tumor on its testes. Stevens dissected the tumor and discovered that it contained a hodgepodge of mouse parts including "skin, teeth, bone, tangles of hair, and marts of muscle" (Scott, 2006). This strange tumor resulted from a benign form of cancer called a teratoma. Stevens transplanted bits of the tumor into the bodies of healthy mice and discovered that they also grew a multitude of cell and tissue types. With some of the fully differentiated cells in the tumor Stevens noticed a uniform group with the ability to replicate themselves. He believed that these cells were the reason for the array of mouse parts in the teratoma. With this hypothesis in mind, Steven's and his lab attempted to isolate and culture strains of these "stem cells".

In the 1960's, other labs learned to culture these "stem cells" that they called embryonal carcinoma cells (Scott, 2006). As time progressed, scientists also found methods to keep these cells alive for longer periods of time by periodically changing the medium (a solution composed of sugar, salts, and a variety of extracellular matrix proteins). In this medium, the cultured cells divided into new populations of cells (Chamany, 2004). This environment kept the cells from differentiating. It was also observed that "…the tumor cells showed amazing flexibility" (Scott, 2006). Indeed they were able to change into a multitude of tissue types when different chemicals and substances were added to the media, "…even cardiac cells appeared, twitching with a spontaneous heartbeat" (Scott, 2006). In 1981, Gail Martin was able to derive a pluripotent cell

line (ES cells) from mouse embryos prepared by *in vitro* fertilization (IVF), and cultured in conditioned medium from teratocarcinoma cells (Martin, 1981).

Using this murine ES cell research as a basis, primate, and later human, embryonic stem cell lines were produced. The first tangible creation of human embryonic stem cell lines did not occur until 1998 when James Thomson from Wisconsin University created an ES cell line from human IVF embryos (Thomson et al., 1998). This advancement remains central to the stem cell controversy lingering in society today. The isolation process begins with the *in vitro* fertilization of sperm and egg from human donors to reproductive clinics. This newly fertilized egg is totipotent, meaning if it is allowed to grow it can develop into a fetus and the extra-embryonic tissue such as the placenta. After 4-5 days of cell division, a hollow ball of cells termed a blastocyst is formed (**Figure-3**).

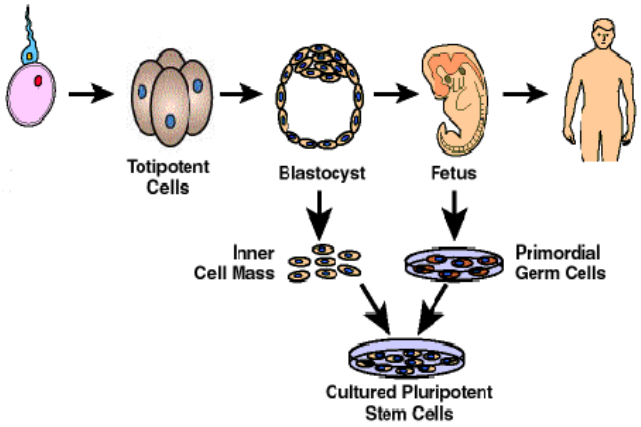


**Figure-3: Diagram Showing the Two Main Methods for Isolating Human ES Cells**. Sperm and egg are united during *in vitro* fertilization (upper left). The zygote is cultured 4-5 days to the blastocyst stage (upper center). The inner cell mass cells can be isolated (diagram center) to produce ES cells (diagram lower). Alternatively, germ cells can be isolated from an aborted fetus (diagram right) to obtain ES cells. (Origin, 2010)

In the blastocyst, the outer layer of cells will eventually form the placenta, while the inner cluster of cells (inner cell mass) will eventually form the fetus (Scott, 2006). The cells of the inner cell mass are pluripotent. This means that they can dedifferentiate into over 220 tissue cell types in the body, but not all types necessary for fetal development (Furcht and Hoffman,

2008). Some of these formed cell types include liver cells, epithelial cells, nerve cells, muscle cells, and white blood cells (Espejo, 2002). It is the ability of ES cells to divide, while also being able to differentiate into many different tissues, that creates their medical potential to regenerate cells in damaged organs. Since ES cells are not totipotent, if inserted into a woman's uterus, they would not create a fetus. However, the removal of the inner cell mass from the blastocyst to obtain the ES cells usually destroys the embryo, and the embryo if implanted could have created a fetus. Thus the ethical dilemma is does the potential ability of ES cells to save human lives outweigh the "death" or potential life of the embryo (Scott, 2006)?

At about the same time that Thomson was creating his first human ES cell lines using IVF blastocysts, John Gearhart discovered that ES cells can also be obtained using fetal tissue from germ cells (Shamblott et al., 1999). Despite using different methods, both Gearhart and Thomson managed to create strong long-lived ES cell lines. These lines, and others derived subsequently, are integral to the medical community for ongoing experimentation in biological cures (Chamany, 2004).

ES cells provide the comparative basis through which all other stem cell types are compared. One test for ES cell pluripotency, teratoma formation, involves transplanting potential stem cell lines into an adult animal. If a teratoma forms containing all three germ layers differentiated from the original cells, then the ES cells are pluripotent. Another indicator of all long lived stem cells is the presence of the enzyme telomerase. In humans, only stem cells and germ cells appear to have telomerase. This is an intriguing fact since this protein is also expressed by long lived cancer cells and helps them grow out of control (Scott, 2006). A deeper understanding of the function of telomerase in stem cells will hopefully provide scientists with the knowledge to aid them in their efforts to cure cancers.

**Parthenogenetic Stem Cells**

In 1912, Jacques Loeb first documented artificial parthenogenesis. By placing sea urchin eggs in various concentrations of salt, he stimulated the cells to divide without fertilization, forming an embryo as if they were fertilized. This experiment suggested that a sea urchin egg cell has enough plasticity to create all the cells in a developing embryo (Chamany, 2004). Although some amphibians, especially bees and ants, naturally reproduce using parthenogenesis, in animal cells parthenogenesis does not occur in nature. The first published account of producing human parthenote embryos occurred in 2001 (Cibelli et al., 2001), however the eggs only divided a few times, and did not produce blastocysts from which ES cells could be obtained. In 2003, the human parthenote embryos survived long enough to produce blastocysts from which ES cells were obtained (Westphal, 2003). Then in 2007, unpublished claims surfaced of the establishment of the world's first human ES cell lines from parthenogenesis (Brevini and Gandolfi, 2007). Due to the fact that fertilized embryos are not destroyed to obtain these ES cells, some scientists argue this process is less ethically controversial, and may produce an alternative source of ES cells (Westphal, 2003).

**Induced Pluripotent Stem Cells**

Across the ocean, in 2006 Shinya Yamanaka's team at Kyoto University in Japan generated a technique to create the world's first induced pluripotent stem (iPS) human cell line (reviewed by Vogel, 2006; first published by Takahashi et al., 2007). Although iPS cells represent the newest member of the stem cell community, they appear to have powerful ES-like differentiation potential while no embryo is destroyed to obtain them. These cells are created through the deliberate introduction of nucleic acids encoding stem cell-associated proteins into adult differentiated somatic cells, commonly skin fibroblast cells ("Induced," 2010). The extreme scientific excitement of this success results from the fact that if the iPS cell line is induced from a patient's own skin fibroblasts, the iPS cells would be genetically identical to the patient, so likely would not be rejected by the patient's immune system. And moreover, the technique does not destroy an embryo.

The initial 2006 experiment used viruses to introduce four genes (OCT3/4, SOX2, KLF4, and c-MYC). After culturing these genetically altered cells for several weeks, colonies of cells with properties resembling those found in human ES cells were observed. Indeed these populations of cells contained telomerase, and doubled at approximately the same rate as ES cells. The behavior of these human iPS cells indicates that by introducing particular genes into a skin fibroblast cell, the differentiated cell can be reprogrammed, resulting in the activation of pluripotency genes and the silencing of normal operating fibroblast genes. Yamanaka and his team continued their research to discover that the iPS cells could be "differentiated to make beating heart muscle, and proteins characteristic of neurons", and could also form cells from the three major germ layers (ectoderm, mesoderm, and endoderm) (Baker, 2007).

At the University of Wisconsin, James Thomson and Junying Yu made similar experiments in their attempts to genetically alter neonatal fibroblast cells so that they mimicked the function of ES cells. Their team also used four genes, but two of their genes differed from those used in Yamanaka's experiments. Instead of KLF4 and c-MYC, Thomson's group used NANOG and LIN28. Thomson and Yu found that "from 600,000 neonatal cells, 57 iPS cell colonies were generated with properties similar to ES cells" (Baker, 2007). From those 57 colonies, four lines of iPS cells were cultured. These cells expressed surface proteins like those found in ES cells, and like Yamanka's team's the cells were capable of forming a teratoma containing all three embryonic germ layers.

Eventually, the induction technique was modified to require only two genes, and did not require the genes to be delivered by viruses. One group also succeeded by transfecting the transcription factor proteins encoded by the genes instead of using the genes themselves.

Although iPS cells appear to solve the ethical dilema of embryo destruction, unfortunately they appear to have some problems. iPS cell experiments done in mice indicate that mice treated with iPS cells may be prone to tumors. But luckily, Yamanaka published a subsequent paper in *Nature Biotechnology* showing that both human and mouse adult fibroblasts could be reprogrammed using a gene combination without cMYC (which tends to cause tumors). The genetic reprogramming took a week longer to occur, but produced no detectable tumors. As iPS cells have been shown to form some tissues but not all, some scientists worry that iPS cells are not truly pluripotent. However, future research should help answer that question. Thus, although more studies are necessary, iPS cells hold great potential for advancements in the medical field by providing an easily-attainable, potent stem cell line for experimentation (Baker, 2007).

**Adult Stem Cells**

Adult stem cells (ASCs) are isolated from adult tissues. Their main function in the body is to replace dead or injured cells with new ones that function appropriately (Adult, 2006). ASCs exist throughout our bodies "from head to toe" (Scott, 2006), but are most commonly found in parts of the body such as bone marrow, umbilical cord blood, intestine, skin, and amniotic fluid (Furcht and Hoffman, 2008). Though natural in origin, ASCs have more limited applications in comparison to other stem cell types as they are unipotent and multipotent, as opposed to pluripotent (Espejo, 2002). However**,** special varieties of ASCs have displayed plasticity and can form many types of tissue, including some outside of the narrow region of the body in which they exist. For example, hematopoietic stem cells (HSC's) taken from the blood and marrow are an excellent example of stem cells that exhibit plasticity as they can form nine kinds of blood cells, including red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, and macrophages (Bethesda, 2009), and HSCs have been shown to be capable of differentiating into neuronal cells when treated with appropriate growth factors (Scott, 2006).

Unfortunately, ASCs are far more difficult to isolate than ES cells. The cells are rare in the body and they are surrounded by a vast majority of differentiated cells. Moreover, ASCs have a close relationship with intermediate transitory cells that they produce, making it difficult to tell them apart. This makes their identification far more difficult than identifying ES cells from a blastocyst. However, the progenitor cells divide a limited number of times while adult stem cells can divide indefinitely, so if the cell does not self replicate, it is not a stem cell (Scott, 2006).

How scientists distinguish between different types of adult stem cells is a bit trickier. Theoretically, each cell type has a distinct genetic signature, even if we have not yet deduced what it is. One identifying marker is the expression of specific proteins on the outer layer of the cell (known as antigens). Each cell variety expresses diverse antigen types and combinations. For example, blood cells have surface markers called CD45 (Scott, 2006). It is through the expression of such surface antigens that researchers are able to differentiate between adult stem cells such as mesenchymal stem cells and say neural stem cells. Mesenchymal stem cells can create bone, muscle, cartilage, fat, and other connective tissue (Bethesda, 2009), while neural stem cells found in the brain can form nerve cells, neurons, and two types of non-neuronal cells, astrocytes and oligodendrocytes (Bethesda, 2009). Both of these adult stem cell types hold many possibilities for medicine in the future.

With respect to using ASCs for medical applications instead of ES cells, they have less medical potential (they can only differentiate into limited cell types), they are harder to isolate (as discussed above), and most types are harder to grow in large quantities. Current research is focused on trying to solve these problems to avoid having to use ES cells for medical applications if possible.

## Chapter-1 Conclusion

Overall, it is evident from our discussion so far that stem cells do not come from a single source. In the case of embryonic stem cells, they come from the inner cell mass of a blastocyst. iPS cells come from adult fibroblast cells that have been genetically engineered to function as pluripotent cells. Parthenogenic ES cells are created through the chemical treatment of unfertilized eggs that trick an egg cell into thinking it has been fertilized. Adult stem cells reside

in various locations throughout our body, but are hard to isolate and grow. Stem cell research has been around since the 1800's, so stem cells are not new to the scientific community. However, the possible application of stem cells to 21st century regenerative medicine makes them both intriguing and crucial to understand in the modern world.

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# CHAPTER-2: STEM CELL APPLICATIONS

As discussed in Chapter-1, scientists have discovered multiple types of stem cells, but what makes them worth the moral, mental, and physical effort? This chapter is designed to discuss their worth, various ways in which stem cells can be applied. Stem cell therapy involves replacing cell loss and inducing the body's repair mechanisms to treat some types of disorders (Levesque, 2005). In this chapter, possible stem cell therapies for treating patients with Parkinson's Disease, severe burns, cancer, kidney transplants, and spinal cord injuries will be discussed. In some cases, most of what we know results from experiments on animal models, while in other cases stem cells are being used on human patients.

## Stem Cells and Parkinson's Disease

Parkinson's disease (PD) is a disease of the central nervous system that affects an area of cells in the middle of the brain called the substantia nigra. These brain cells slowly begin to lose the ability to produce dopamine, a neurotransmitter involved in neuromuscular control. The symptoms of PD vary from individual to individual, however common symptoms include difficulty keeping balance, shaking of the hands, arms and legs, and feelings of anxiety or depression ("Our Outstanding…," 2010). More than four million elderly people around the world are affected by Parkinson's disease. One million of those affected reside in North America ("Our Outstanding…," 2010). The causes of PD are unclear, and there is no current preventative cure for Parkinson's disease. Current therapies involve using drugs to mimic dopamine or its precursors, but these treatments have only short lasting effects and often lose their efficacy over time. However, the use of stem cells in certain procedures to regrow

dopaminergic nerve cells seems to bring hope to the community of individuals affected by Parkinson's disease.

At the Parkinson's Clinical Center in Beijing led by the head neurologists Dr. Like Wu and Dr. Xiaojuan Wang, 157 PD patients between the ages of 41 and 86 have been treated with fetal neural stem cells or hematopoietic stem cells from bone marrow or umbilical cord blood, and 91% showed significant improvements ("Our Outstanding…," 2010). Dr. Wu and Dr. Wang use a gene-targeted stem cell transplantation procedure via a subarachnoid lumbar puncture. For the lumbar puncture, a needle is inserted into the spinal canal in the lower back and a small amount of cerebral spinal fluid is taken. This fluid is then mixed with neural stem cells collected from fetuses, or hematopoietic stem cells collected from bone marrow or umbilical cord blood, then injected into the lumbar in four separate injections. The stem cells take six to seven hours to circulate per injection. The circulating stem cells flow through the cerebral spinal fluid in the lumbar and into the brain, where they sometimes grow into neurons to repair the damaged neural system and improve the degenerated neuromuscular state of the patients. For this procedure, medication is also given in order "…to adjust the immune function, provide neural nourishment and clear the internal microenvironment to protect the neurons and help the future growth of injected stem cells" ("Our Unique…," 2010). Thus, at this center, stem cells appear to offer hope where traditional medication cannot. However, this Chinese center's promising results have not yet been published in reputable refereed scientific journals, so it is difficult to judge the quality and reproducibility of the work.

With respect to human PD stem cell reports published in the refereed literature, several labs have reported success with fetal tissue transplants (containing neural stem cells) (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002). And some success has

been reported with adult olfactory mucosal stem cells (Levesque, 2005). Currently, embryonic stem cells have not been used to treat human PD patients, but human ES cells have been shown to be able to differentiate into dopamine-producing cells (Perrier et al., 2004).

**Epithelial Tissues Engineered from hES derived Keratinocytes**

In the United States, approximately 2.4 million burn injuries are reported each year. Of those hospitalized, 20,000 have major burns involving at least 25% of their total body surface ("Burn", 1992). Skin, one of the most important organs in our body due to its ability to protect us from desiccation and harm, is commonly in short supply within medical facilities. Currently, there are already processes for the production of autologous epidermis tissues in the lab, however these tissues, made from the patient's own keratinocytes, take at least 3 weeks to culture. Allografts from cadaver skin can sometimes be used as a temporary cover for full thickness burns, or semisynthetic products using bovine collagen or allergenic fibroblasts can be functional as well, but these contain adult cells which commonly induce an immune rejection called graft versus host disease (GHVD). Thus, there is a need for an autologous epidermal tissue that avoids immune rejection and is easily accessible (Guenou, 2009).

Keratinocytes derived from human embryonic stem cells (K-hESC's) can form an epithelium (skin layer) with multiple levels that resembles the normal outer layers of human skin, both in cell culture (*in vitro*) and through the application of these grafts on the body (*in vivo*). The culture of this tissue-engineered skin is produced using a co-culture of hESCs with feeder cells over 40 days. The feeder cells temporarily support the stem cells in culture until the cells have divided enough to support themselves. BMP4 (a growth factor) is also used in the

culture medium to stimulate the hESCs in the preliminary steps of differentiation to grow in a flat, tissue-like pattern.

This hESC approach could provide an unlimited source of temporary skin replacement for patients with extensive burns waiting for autologous grafts (Guenou et al., 2009). Because the ES cell line is immortal, issues with accessibility would be eliminated. Moreover, due to their early developmental stages, "K-hESCs express little major histocompatibility complex (MHC), so should produce less graft-versus-host disease (Guenou et al., 2009). K-hESCs also produce certain components that form an epidermal-dermal junction in the body, which is important for integrating the foreign tissue in the body. Though more extended clinical trials are necessary to determine whether this tissue will truly function effectively, K-hESC-engineered epithelium appears to be a promising, new medical tool for burn victims.

**Treatment of Cancer with hESC Derived NK Cells**

Cancer kills one of four individuals on Earth (Scott, 2006). Possibly the greatest hot spot for stem cell research is oncology. Researchers have experimented with multiple techniques in their search for a cancer cure, but cancer is a tricky, versatile, and prominent enemy. Luckily, with stem cell therapy there appears to be hope for the future.

Multiple cell-based remedies using hematopoietic stem cell (HSC) transplantation and T cell immunotherapy for malignant tumors are already in clinical practice. In fact, the use of HSCs from bone marrow to treat leukemia has been in use for over 50 years (since 1959) with about 40,000 bone marrow transplants performed annually worldwide (Horowitz, 1999). Thus, HSCs remain the most characterized of all the types of stem cells.

Some tumors disrupt antigen presentation which allows them to avoid being recognized by our T-cell-mediated immune response. The inability of tumor cells to activate an effective antitumor immune response allows the cancer to persist within the body. But luckily, T-cells are not the only immune response in our body. Natural killer (NK) cells are an integral part of our antitumor immunity. These cells recognize and lyse cells in our body not presenting MHC on their surface, so if cancer cells present no MHC due to antigen presentation disruption, they can be lysed by NK cells.

CD56+ and CD45+ NK cells can be derived from human embryonic stem cells (Woll et al., 2009). In recent studies, hESC-derived NK cells have removed established human tumors in immune-deficient mice. The testing that took place involved using tumor inoculated mice. These mice were divided into three groups. One control group received no NK-cell infusion. The second group was given systematic infusions of $2x10^6$ NK cells derived from hESCs, and the third group was given periodic shots of $2x10^6$ NK cells derived from umbilical cord blood. After three weeks, eighteen out of the twenty mice that did not receive any NK cell treatment developed large tumors. All of the mice treated with hESC-NK cells demonstrated clearance of the primary tumor in 2 weeks, and 5 of 13 mice treated with UCB-NK cells were tumor-free. Through bioluminescent imaging at 8 weeks, no evidence of tumor recurrence was observed in the hESC and UCB-NK mice (Woll et al., 2009). Thus, hESC-NK cells and UCB-NK cells are efficient at removing human tumor cells and preventing their growth in mice. In addition, this study proved that hESC-NK cells are more proficient at clearing tumors than UCB-NK cells (Woll et al., 2009).

However, there are some drawbacks to using NK cell procedures, as “NK cells are limited to specific cancer types [especially those not presenting MHC on their surface], and not

all patients demonstrate an optimal response" (Woll et al., 2009). Similarly, since only the H9 human embryonic stem cell line was used in these experiments, studies on whether the other hES cell lines behave in the same manner needs to be completed. In addition, NK clinical trials on human patients need to be started to see if hESC NK cells can clear cancers in the human body.

**Using Mouse ESCs to Predict Future Cancer Risk**

Stem cells have also proven helpful in identifying who may be at risk for getting cancer in the future. In fact, the National Cancer Institute has developed a new test for breast cancer called a functional assay. This test was initially created using mouse ES cells, and it evaluates mutations in a gene known to increase breast cancer risk in women. Proteins produced by BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) function as tumor suppressors. Genetic defects in these tumor suppressors cause an increased risk of breast or ovarian cancer in these individuals. Indeed, "studies have shown that a woman who has a mutation in one of these genes has a 35-85% risk of developing breast cancer by age 70, compared to the average American woman's lifetime risk of 12.3%" (Sharan, 2008). As a result, many women undergo genetic testing to determine if they are at risk, and if so should plan ahead with their physicians.

This new functional assay helps scientists evaluate the effects of less common mutations in the BRCA2 gene through using mouse embryonic stem cells. Functionally normal human BRCA2 gene variations (mutations that would not cause cancer so would be of no concern) will compensate for mouse BRCA2 deficiency in BRCA2-deficient mouse embryonic stem cells. Since mouse BRCA2 is necessary for the survival of mouse embryonic stem cells, if the human variation of the BRCA2 gene being tested does not function properly to supply BRCA2 for the BRCA2-deficient mouse stem cells, the cells will die, and the genetic variation is of clinical

concern. It has been found that "if a sequence variation does not alter the function of BRCA2, the risk of developing cancer is probably the same as that of the rest of the population, but if the genetic change is disruptive, the risk of developing cancer increases significantly" (Sharan, 2008).

Research is also being performed to see if functional assays for BRCA1 are possible, as there are over 1,900 known BRCA1 and BRCA2 variations. Many of these variations are uncommon and thus their functional effects, without testing, are unknown. Without functional assays, scientists are limited to determining the effects of BRCA1 and BRCA2 alterations through segregation analysis, a process that analyzes genetic alterations in families with high risk cancer patterns. This process is effective, but it only provides data for a small portion of the 1,900 known BRCA1 and BRCA2 variations found in our population.

Overall, BRCA2 testing, using mouse embryonic stem cells *in vitro*, seems to be a promising method for the detection of harmful mutations of the BRCA2 gene. So far, 17 variants have been tested by this functional assay at a rate of "three to five gene variants every two to three months" (Sharan, 2008). However, FDA approval for the use of this functional assay in a clinical setting is still necessary before it can be used for diagnostic testing.

**Kidney Transplants: Using Adult Blood Stem Cells to Create a Mixed Chimera**

Although bone marrow and organ transplants are relatively common procedures in the 21st century, the results are far from perfect. For example, kidney transplant patients have to take approximately 30 different immunosuppressive drugs daily to prevent their body's rejection of their genetically foreign kidney. These drugs compromise the immune system and increase the risk for heart disease, diabetes, and cancers. Additionally, studies have found that in

approximately 10 to 15 years, the transplanted kidney would likely be rejected and another kidney transplant would be needed (Fox, 2007).

Luckily, a new technique for kidney transplants has been created using embryonic stem cells. This technique involves giving the patient both a new kidney transplant and a new immune system created from the kidney donor's adult blood stem cells. This new immune system, which works in conjunction with the original immune system of the patient, prevents the kidney transplant patient's body from rejecting the kidney and eliminates the need for immuno-suppressive drugs that prevent graft versus host disease (GVHD). GVHD is a common complication of allogeneic bone marrow and organ transplants where the donor cells attack the patient's organs and tissues ("Graft vs Host Disease", 2010).

The simple theory behind this procedure is that by pre-treating the patient with donor hematopoietic stem cells (HSCs) tolerance to the transplanted kidney cells can be induced. In a more thorough explanation, our immune system identifies foreign cells through the expression of human leukocyte antigens (HLAs). HLAs are present in allogeneic organ and bone marrow transplants. As a result, in order to get a human body to accept a foreign kidney, a mixed chimerism that creates a duel immune system must be formed. This new process involves giving immunosuppressant drugs such as cyclosphosphamide, and partially irradiating the patient's thymus. Then a same-donor bone marrow transplant is completed followed by the donor kidney transplant. In doing so, the T cells of the donor and the host are kept at bay which allows the donor and host stem cells to learn to accept each other. Once the donor and host stem cells establish their peace, a duel immune system is created. When this process is completed, the patient can stop taking immunosuppressant drugs.

In preliminary animal testing at the Massachusetts General Hospital, "the approach created a mixed chimerism and total graft acceptance with immunosuppressives in 100 percent of the mice" (Fox, 2010). In humans, in 1998, Dr. David Sachs from the Massachusetts General Hospital was the first to treat a human patient, a kidney failure/cancer patient. Surprisingly the patient not only accepted their new kidney, but the mixed chimerism caused their cancer to go into remission. Five other kidney failure/cancer patients were then treated with this procedure in addition to three kidney failure-only patients. Eight out of nine accepted their kidneys and are completely without immunosuppressives. Only one patient suffered the rejection of their kidney (Fox, 2010).

Further advances in the world of bone marrow and organ transplantation are being investigated at Harvard by a man named Gorge Daley. Daley is working on creating hematopoietic stem cells (HSCs) from human embryonic stem cells that would produce human chimeras with organs and blood made entirely form embryonic cells. Though he is still in the preliminary stages of his research, his idea shows great promise for the medical community. As he wrote in a 2003 paper on experimental hematology, "…an important role for ES-derived HSC may be the ability to induce hematopoietic chimerism in individuals undergoing transplants with other types of ES-derived tissues. This chimeric effect would enable a large patient population to access cellular therapies from a limited bank of approved ES cell lines" (Fox, 2007).

**Spinal Cord Injuries**

Another promising use for stem cells is in the repair of spinal cord injuries. The use of stem cells to treat animal models of spinal cord injuries first occurred in 1999 with the use of embryonic stem cells (McDonald et al., 1999), and has since been tested with human ES cells

(Kerr et al., 2003). Many different types of cells including neurons are destroyed during spinal cord injuries. In a numerous accident cases, the cord is not broken and some of the neuronal axons that carry signals from the body to the brain remain intact. But these axons have lost their ability to transport messages due to the loss of oligodendrocytes of which the axon's insulating myelin sheath is composed. Lack of this myelin sheath causes paralysis. Scientists have used hESCs to make mixed cultures that contain oligodendrocytes. When chemically-demyelated rats were given shots of this stem cell mixture, they regained a fractional improvement in the use of their hind limbs in comparison to ungrafted mice (Panchision, 2006). In another experiment at the Krembil Neuroscience Center at the Toronto Western Research Institute and the University of Toronto, Michael Fehlings and his team used cells from the brains of adult mice and transplanted them into rats with damaged spines. When transplanted a maximum of two weeks after the injury, supplemented with various growth factors and immune-suppressing drugs, "more than one-third of the transplanted cells traveled along the spinal cord, were incorporated into damaged tissue, developed into the type of cell destroyed at the injured site, and produced myelin" ("Stem Cell…," 2006).

More recently, bone marrow mesenchymal stem cells (BMSCs) have been shown to increase the healing of injured spinal cords in animal models (Gu, 2009). In an experiment injecting $3x10^5$ BMSCs into one group of injured mice, and a placebo injection into the control group of mice, at 8 weeks there was an increase in the reduction of the cavity caused by the spinal cord injury in the BMSC injected mice in comparison to the control. A transmission electron microscopic examination displayed that there was also a greater number of axons in BMSC rats than in the control. Moreover, a coculture system displayed that "The length and the number of neuritis from spinal neurons significantly increased when they co-cultured with

BMSCs" (Gu, 2009). As a result it appears that BMSCs promotes the regrowth of injured spinal cords and decreases the wound's volume.

**Chapter-2 Conclusion**

Stem cells with their functional powerhouse of tissue regeneration and medical possibilities provide a means through which many incurable diseases like cancer or severe wounds such as spinal cord injuries may be reduced or cured. Thus far, in most cases, stem cell studies using animal models have successfully been completed. These animal tests are imperative as such tests must be done in advance of human testing, and is many cases animal data remains our only source of information.

However, it is not true that no human data exists on stem cell applications. In the U.S., studies on the safety and efficiency of stem cell therapies on human patients occur more frequently than many believe. In areas such as China, clinics for stem cell therapies for Parkinson's Disease have begun to treat previously incurable patients, but their data have not yet been evaluated in the refereed scientific literature. Although hematopoietic stem cells have been used for over 50 years to treat leukemia, for other stem cell applications it is hard to determine whether the therapies will live up to their predicted potential. But through progress in stem cell cancer treatment techniques, the alleviation of Parkinson's disease symptoms, the creation of organs such as skin for the treatment of burns, the creation of mixed chimerism for kidney transplants, and the advanced repair rate in spinal cord injuries, the possible medical applications of stem cells appear to be both exciting and promising.

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# CHAPTER-3: STEM CELL ETHICS

"Suppose a fire broke out in a fertility clinic, and you only had enough time to save either a five-year-old girl or a tray of twenty frozen embryos. Would it be wrong to save the girl?" (Sandel, 2007) This type of ethical question encompasses the main debate surrounding stem cell research, namely to what extent should an embryo be treated as a human being. In this chapter, the discussion of stem cell ethics goes beyond the technology to converse about whether stem cell research is more of a benefit or detriment to society, and whether this research should continue.

The benefits of stem cell research vary depending upon the type of stem cell under discussion. Some cells such as iPS cells are extremely new, and have not yet been used to save any lives. Other cells such as adult stem cells (ASCs) and embryonic stem (ES) cells are well established, and have already been used in successful clinical applications. However, both adult stem cells and iPS cells are not obtained through the "killing" of an embryo whereas embryonic stem cells are. As a result, the usage of ES cells is a popular debate in America and around the world, focusing on whether the ability of ES cells to medically save lives outweighs destroying an embryo to obtain them. Ultimately this debate revolves around the question of when life begins; an individual's conclusion on this topic affects their stance on whether destroying an embryo is murder.

Even within the scientific community, the answer to the question of when life begins varies. For example a geneticist may believe that the beginning of life starts when chromosomes from the sperm and the egg unite within the nucleus. One the other hand, a developmental biologist might say that life starts at gastrulation, a point just after the embryo has been

implanted into the uterus of the mother (a key step for embryo survival). Whereas a neurologist may believe that life begins with the appearance of brain waves in the fetus at approximately the second trimester of pregnancy. Brain waves represent an intriguing biological marker of life, as a lack of brain waves marks the legal definition of death in many jurisdictions ("Stem Cell Research…", 2005). Yet questions still remain. Does human life begin at birth? Does it start at conception? To be quite honest, there is no wrong answer. At this point it depends upon an individual's religious belief, views on scientific doctrine, and personal opinion.

**Stem Cell Ethics and Religion**

People's beliefs on stem cells are not identical. A given individual's belief may vary depending on his/her country of origin or his/her religion. Different countries have enacted various policies on stem cells (**Figure-1**). For example, England, Sweden, Finland, India, China, and Australia have enacted broadly encompassing policies that allow embryo donations for research purposes, the derivation of ES cells from fertilized embryos, and human therapeutic cloning. Alternatively, countries such as Chile, Mexico, Greenland, Africa, Saudi Arabia, Tibet, and Malaysia have enacted no stem cell policies. Since a particular nation's stem cell policy is strongly affected by that nation's predominant religion, most of our discussion will focus on the various religious stances on stem cells.

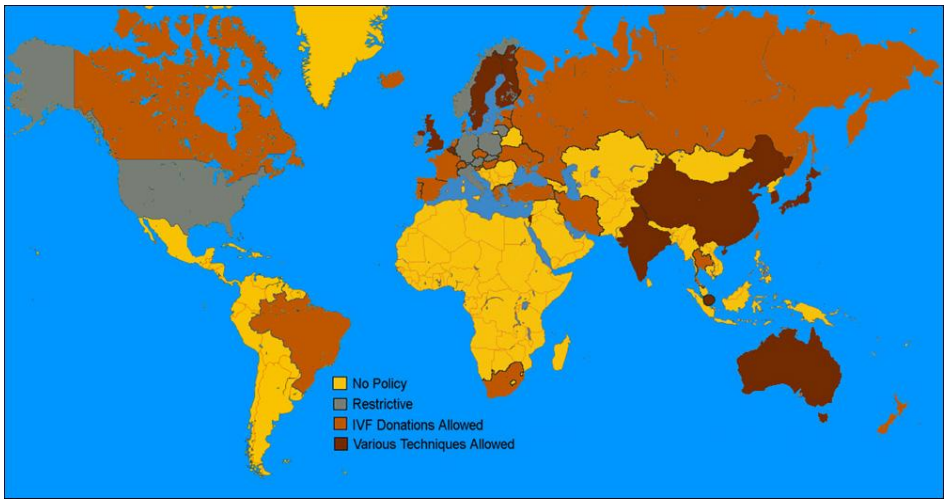


**Figure-1: World Map of Various Stem Cell Policies.** Yellow: Country with no stem cell policy; orange: IVF donations allowed; grey: country with restrictive stem cell policies; burgundy: various stem cell techniques are allowed. ("A Global…," 2009)

With respect to various religious beliefs, the question of when life begins is especially important for their standpoint on ES cell research. The Roman Catholic Church provides some of the greatest opposition to using any human embryos for research, because Catholic belief holds that "life is sacred from the moment of fertilization, and the embryo is the inception of personhood no matter where it exists" ("Stem Cell Research," 2005). In addition, the Orthodox Christian and Methodist churches believe that embryo research is a violation of human life (Scott, 2006). On the other hand, a majority of Protestants hold that stem cell research should be allowed as long as the embryos do not pass the fourteen or fifteen day window after fertilization when the fetus begins to take shape and the totipotency of the cells is lost. Many individuals are surprised to learn of this very strong dissent of views on stem cells within a major religion such as Christianity. And even more shocking is that despite Catholic belief in life at conception, "in a Harris Poll conducted in August 2004, 73 percent of Catholics voted in favor of embryonic stem cell research; and only 11 percent were against it" (Scott, 2006). Thus, some

Catholic individuals still believe that the benefits of ES cells toward aiding humanity outweigh the risks to the embryo, even if the formal Catholic stance is against such cells.

As for the Islamic community, Muslims believe that life begins on the 40th day of development after fertilization. There is no explicit ruling for Islamic views on stem cell research, however adherents to this religion believe that since an embryo is not in the womb, it will not survive and develop into a human being. Thus, many in the Islamic community support embryonic stem cell research, especially if this research has the potential to cure diseases (Siddiqi, 2002). More intriguingly, Islam makes a distinction between the *early* stages of pregnancy (composed of the first 40 days post-fertilization) and the embryo's *later* stages. For example, if a pregnant woman in an early stage of zygote development is attacked and the baby is aborted, the attacker's punishment will be less severe than if he committed the same act during full pregnancy. This distinction between early and late embryo development allows the majority of Sunni and Shiites to support ES cell research.

Those of the Jewish faith also believe that human status is obtained after 40 days of gestation, and that the fetus only achieves personhood at birth. As a result, all of the major Jewish denominations support the use of embryos for research for therapeutic purposes.

The Hindu belief is based on the idea that "… conception is the beginning of a soul's rebirth from a previous life" ("Stem Cell Research," 2005), thus individuals with this belief are generally against ES cell research. But despite this fact, Hinduism has no official position on stem cell research, and many Hindus tend to support the therapeutic benefits of ES cell research for the betterment of humanity. Buddhists also believe that the beginning of life starts at conception. Many Buddhists believe that ES cell research is in accordance with the Buddhist tenet of seeking knowledge and ending human suffering. Others view it as a disobedience to the

Buddhist belief of not harming others. Thus some Buddhists support ES cell research while others do not (Vestal, 2008).

Thus, with respect to religion and stem cells, a surprising five out of five of the primary religions across the world are not completely against ES cells. The religions most strongly in favor of ES cell research are those religions that argue life begins at day 40, for this time is well after the 5 day period necessary to obtain a blastocyst to derive the ES cells. It is also important to note that all major religions support the use of adult stem cells to save lives, as no embryo is destroyed to obtain these cells. However, it is true that some individuals within a few religious denominations are against the use of ES cells. Thus, individuals who feed off of the media's hype and claim that they are against all stem cell research as a result of their religion are sometimes misinformed about their own religion. Indeed, with the exception of the formal Catholic stance, none of the major religions reject ES cell research outright, and thus believe in furthering a greater good for humanity through stem cell research.

**The Moral Status of an Embryo: Does Destroying a Blastocyst to Obtain ES Cells Constitute Murder?**

Opponents of stem cell research believe that removing the inner cell mass from an embryo is like murdering a child to save others' lives. Individuals such as Senator Sam Brownback of Kansas believe that "it is never acceptable to deliberately kill one innocent human being to help another" (Sandel, 2007). His logic follows Kantian ethics that "persons should never be used as a means for someone else's ends" (Scott, 2006). If embryos are indeed persons, destroying an embryo for scientific research would be equivalent to killing a child. But are embryo's truly human beings?

Those who support ES cell research enjoy stressing that the embryo from which stem cells are extracted is not human in form, nor is it implanted and growing in a woman's uterus. Instead it is a blastocyst, "… a cluster of 180 to 200 cells, growing in a petri dish, barely visible to the naked eye" (Roleff, 2006). Cells in this stage of development have not differentiated into tissue and organs, thus their usefulness lies in scientific experimentation for cell repair. It is only at the fourteenth day of fertilization that the cells lose their totipotency and begin to develop into an individual. This point is past the five day period necessary to obtain a blastocyst.

Cells within an embryo are alive, but how many cells constitute a person? Is it the same as the number of grains of wheat that comprises a heap, an indeterminate value that varies by perception? An embryo is a being devoid of consciousness made up of a couple hundred cells whereas a human is a conscious being composed of many millions of cells. As Pulitzer-prize winning zoologist E.O. Wilson writes, "The newly fertilized egg, a corpuscle one two-hundredth of an inch in diameter, is not a human being. It is a set of instructions set adrift into the cavity of the womb" (Scott, 2006). Therefore, an embryo and a human being are unlikely equivalents. Indeed many proponents of stem cell research point out the argument that just as an acorn is not an oak tree, human embryos and a developed human being are two different things (Sandel, 2007).

In determining whether or not an embryo is a living being, ethicists have also considered the idea of sentience, "the capacity to feel psychic or physical pleasure or pain"(Scott, 2006). A being must be conscious of its existence to be sentient. In different terms, "consciousness, whether it is explained behaviorally or neurochemically, is the experience of being a being" (Scott, 2006). Through experimentation it has been determined that major divisions of the mind are not formed until around four weeks after fertilization, and the brain's first electrical activity

does not occur until six weeks after fertilization. However, the beginnings of a nervous system appear at around fifteen days after fertilization which is another reason why this time period is normally the cut off for embryo development in countries such as the United Kingdom (Scott, 2006).

As the idea of sentience implies, membership to a species is not the property that determines the moral status of a being. It is the psychological and cognitive traits that we associate with mature human beings that determine moral status which is why humans commonly regard dogs, cats, pigs, and other animals as having the moral statue of a person (Ethics of Stem Cell Research, 2008). There are no guidelines for traits that comprise a human being. However, in Philosopher John Locke's terms, embryos are not people, as he believes it is "trying to find some capacity - perhaps self-awareness, reasoning power, or sense of oneself as having a history - that marks the point at which human beings become persons (or cease to be persons)" (Scott, 2006).

Despite their lack of cognitive awareness, embryos deserve to be thought as more than just things, as they are a potential human life. Indeed, "the life of a single human organism commands respect and protection … no matter in what form or shape, because of the complex creative investment it represents, and because of our wonder at the divine or evolutionary processes that produce new lives from old ones" (Ethics of Stem Cell Research, 2008). Yet, this fact should not prevent research from occurring. For example, "If we were persuaded that embryonic stem-cell research were tantamount to infanticide, we would not only ban it but treat it as a grisly form of murder and subject scientists who performed it to criminal punishment" (Sandel, 2004). Indeed, "… an extracorporeal embryo - whether used in research, discarded, or kept frozen - is simply not a precursor to any ongoing personal narrative. An embryo properly

starts on that trajectory only when the gamete sources intentionally have it placed in a womb" (Espejo, 2002). In fact, the 5-day-old blastocyst from which hESCs are obtained is "a few dozen cells that together are too small to be seen without a microscope. (They have) no conclusions, no self-awareness, no ability to feel love or pain. The smallest insect is far more human in every respect except potential" (Roleff, 2006).

Other opposition to ES cell research comes from philosophers that believe that science should withdraw to simpler, more familiar practices. Other individuals believe that embryonic stem cell research will be used for human enhancement instead of for therapeutic reasons. As ethical council member Michael Sandel states, "the trouble with biotechnology is that it represents the one-sided triumph of willfulness over giftedness, of dominion over reverence, of molding over beholding" (Scott, 2006). Similarly, many worry that stem cell research will evolve into dehumanizing practices "such as embryo farms, cloned babies, the use of fetuses for spare parts, and the co-modification of human life" (Sandel, 2007). However, though these worries could be valid in the eventual future, adopting regulatory safeguards for stem cell research will prevent it from being exploited in such a disturbing manner.

Such limitations would include the following. Human embryos should only be used in research if the research goals cannot be obtained with alternate means, such as the use of adult stem cells. Stem cells should be used only under stringent laws regulating how long the embryos can be allowed to grow, where these embryos can be obtained, and how embryonic stem cell research can be applied. An example of this legislation is the UK's Human Fertilization and Embryology Act of 1990 that allowed scientists to only use human embryos that had not developed past fourteen days (Furcht and Hoffman, 2008). Researchers should avoid buying and

selling embryos as property, and should recognize that the destruction of an embryo should be respected and provoke a sense of regret (Espejo, 2002).

**Embryos and IVF Clinics**

Some believe that "… if it is immoral to sacrifice embryos for the sake of curing or treating devastating diseases, it is also immoral to sacrifice them for the sake of treating infertility" (Sandel, 2004). However, proponents of *in vitro* fertilization (IVF) emphasize that embryo loss in IVF pregnancies is less frequent than in natural pregnancy. Indeed more than half of all fertilized eggs in normal pregnancies fail to implant or are otherwise lost. With such a high natural mortality rate, the loss of an embryo should not be considered the infanticide many view it to be. Indeed strict religious burial rituals and mourning rites are not mandated or performed for the loss of an embryo as they are for the loss of an infant. The diverse way humanity naturally responds to the loss of an embryo compared to an adolescent implies that the embryo's death is not the moral equivalent of a child's. Moreover, if the embryo loss from natural reproduction were equal to the death of a kid "…alleviating natural embryo loss would be a more urgent moral cause than abortion, *in vitro* fertilization, and stem-cell research combined" (Sandel, 2004).

Yet the ethical question still stands, if the production of embryos for IVF clinics is morally acceptable, why is the creation of embryos for stem cell research unacceptable? Around 400,000 unused frozen embryos reside within the U.S. IVF clinics (Sandel, 2007), with approximately 19,000 excess frozen embryos added each year (Espejo, 2002). After all, curing diseases such as Parkinson's and cancer is at least as important as fixing infertility (Sandel, 2007). Indeed, it is surprising how many individuals in the U.S. alone could benefit from

potential stem cell treatments. For example, approximately 58 million Americans suffer from cardiovascular disease, another 30 million from autoimmune diseases, 16 million from diabetes, 10 million from osteoporosis, 8.2 million from cancers, 5.5 million from Alzheimer's, and 5.5 million from Parkinson's (Roleff, 2006). Since ESC research aims at curing these illnesses, "those who create embryos for research no more aim at destruction or exploitation than those who create embryos for fertility treatments aim at discarding spares" (Roleff, 2006). As a result, excess IVF clinic embryos that will eventually be discarded are viewed as a valid alternative for obtaining embryos for ES cell research, and this is reflected in President Obama's July 2009 policy on stem cells currently in effect in the U.S. (discussed in Chapter-4).

**Adult Stem Cell Ethics**

Adult stem cells (ASCs) were first discovered over fifty years ago with the characterization of hematopoietic forming cells present in bone marrow (reviewed in Horowitz, 1999). Some believe that adult stem cells are just as promising, or in some cases more promising, than ES cells due to the fact that they do not destroy an embryo. Indeed, some individuals find ES cell research unnecessary for the advancement of medical practices.

However, despite the fact that ASCs yield promising research and clinical success (as discussed in Chapter-1), these cells are not the biological or medical equivalents of ES cells. ASCs have been isolated from bone marrow, skin, mesenchyme, skin, and brain, but not from all tissues of the body. ASCs can self-renew and replace damaged tissue for only certain specific forms of tissue in which they reside. As Verfaillie noted, "the fact is that stem cells from fertilized eggs have the ability to grow into any type of cell or organ in the body. Adult tissue stem cells appear to have a much more restricted path for development, limiting their usefulness

in therapies of specific diseases" (Roleff, 2006). As a result, many scientists still believe that the potential for fighting diseases lies in ES cell research, until proven otherwise.

**iPS Cell Ethics**

Induced pluripotent stem (iPS) cells are one of the newest, most popular, and most promising variety of stem cells being researched today. iPS cells appear to be pluripotent stem cells, but they are formed without the destroying an embryo. Instead, genes within somatic cells are reprogrammed to create these cells via de-differentiation. In some studies, iPS cell lines function similarly in comparison to ES cell lines, however more recent studies question their true pluriopotency (Dolgin, 2010). Soon after their 2007 discovery (Takahashi et al., 2007), early studies indicated iPS and ES cell populations grow at the same rate; telomerase is present in both, and several genes active in ES cells and silenced in fibroblast cells are active in iPS cells. As stem cell researcher James Thomson states, "the human iPS cells described appear to meet the defining criteria we originally proposed for human ES cells, with the significant exception that iPS cells are not derived from embryos" (Deem, 2009). Thus, these iPS cells appear to have the potential to be a moral substitute for hES cells, but further research will be required to prove this point. Nevertheless, even if iPS cells prove to be slightly less potent than ES cells, they may still represent a means for treating some diseases without destroying embryos.

Unfortunately, this new stem cell technique has a number of drawbacks. In the original 2007 study (Takahashi et al., 2007), one of the genes used for reprogramming (c-MYC) produced an increase in tumors and cancers, although subsequent experiments successfully formed iPS cells in the absence of c-Myc (Nakakawa et al., 2008). Another problem with iPS cells in the earlier studies is that the genes for iPS cell production were introduced using a

retrovirus that incorporates into the host cell DNA. This process is unstable, for depending on where the gene sequence inserts, it can cause random mutagenesis. However, newer techniques for iPS creation have eliminated the problematic c-MYC gene and switched to a lentivirus reprogramming system or, in some cases, have eliminated viral delivery altogether through reprogramming genes cloned into a circular piece of DNA called a plasmid (Stadtfeld et al., 2008; Deem, 2009).

IPS cells have already been used to treat some diseases in mouse models. Indeed, "a team from Rudy Jaenisch's lab at the Whitehead Institute, along with a group led by Tim Townes at UAB, announced in *Science* that it has used induced pluripotent stem cells to treat sickle cell anemia in mice" ("iPS Cell Therapy," 2007). Yet, embryonic stem cells still seem to be the gold standard. As Jaenisch states, "all the progress in this field was only possible because we had embryonic stem cells to work with first. We need to make more ES cells and really define which are going to be the best ones for different applications" ("IPS Cell Therapy," 2007).

Overall, iPS cells have the potential to be a safe and effective stem cell treatment for some diseases, even if they are not quite ES cell-equivalent. Even the President's Council on Bioethics called iPS cells "ethically unproblematic and acceptable for use in humans" (Gorelick, 2009). Moreover, it is apparent through the iPS cells produced in various laboratories across America that this technique is powerful and easily reproducible. Thus, through the correction in many of the initial 2007 drawbacks to inducing iPS cells, iPS techniques hold the potential to soon possibly replace ES cells for therapies.

**Chapter-3 Conclusion**

Since a major goal of stem cell research is to create cell-based therapies for human diseases, the lack of support for embryonic stem cell research is distressing. This is especially true considering "… one reason that evidence was lacking that hES cells could treat Parkinson's and other problems was due, in part, to a decades-long U.S. government ban on embryo research. Without embryos as a source of ES cells, knowledge is scarce" (Scott, 2006). Indeed, a stem cell scientist complained to *Newsweek* during the Bush administration's ban on ES research that the government's restrictions on ES cell research to only a few ES cell lines derived prior to 2001 is "like forcing us to work with Microsoft version 1.0 when the rest of the world is already working with 6.2" (Furcht and Hoffman, 2008). With legislature under the Bush administration, there were only 15 stem cell lines available, a number many claimed is not an adequate for current research. And a few of these 15 lines have already been exhausted. Indeed many scientists believe that politics more than ethics stood behind the Bush White House 2001 legislation preventing the funding of new hESC lines. More recently, due to Obama's stem cell policy instituted as of July 2009, the lack of usable ES cell lines has improved (discussed in Chapter-4), but the overall low number still remains a problem.

Even though many would say that killing an embryo is morally problematic, an embryo lacks self-awareness, moral sense, and rationality. If there is a chance that an embryo can improve the lives of numerous human beings where traditional medicine cannot, I do not believe that a small mass of cells should stand in the way of extending their life. Personally, I am for using embryos under any circumstance and agree with James Petersen, Professor of Ethics and Theology, who posed the written argument, "how can we let patients who are unmistakably people die to protect embryos that, even if implanted may or may not turn out to someday

become person? We should not kill people to benefit others, but we should also not let people die to protect tissues such as sperm or ova, even though such gametes have great potential" (Scott, 2006).

Though I am not against the idea of using embryos solely for research purposes, I do believe that if it is possible to get embryos from IVF clinics we should do so there first, before resorting to using embryos from paid donors. After all, embryos as living entities should be used sparingly and with respect. In addition, with such large quantities of excess IVF embryos, ES cell research should be allowed to continue on donated, frozen IVF embryos that would otherwise perish without a contribution to society. Indeed, in 1999 it was estimated that more than 150,000 frozen embryos were stored in IVF clinics with 19,000 added each year (Espejo, 2002).

However, as a nod to those who find that using embryos to create potentially lifesaving stem cell lines is murder, I believe in using ASCs whenever possible. There is no reason for using embryos unnecessarily, and purposefully aggravating other's sense of morality. Yet I do not believe that ASCs should be used all of the time, especially if subsequent ASC treatments prove to be less potent than ES treatments for treating a particular disease. There are medical advantages to using hESC stem cell lines for therapies. Until hES cells can be safely replaced with adult or iPS stem cells in treatments currently using hESC, it makes sense to continue ES cell research. Once we hit this point, hESCs may become obsolete, and there will be no need for the questionable ethics surrounding them.

As for the revolutionary iPS cell research, I am in favor of its continuation, but uncertain as to whether iPS cells will prove to be medically equivalent to ES cells. However, with the rapid advances scientists have made in only a few years with iPS cells, I believe that they eventually

will become a moral substitute for ES cells. If anything, research on iPS cells should be enthusiastically supported as a promising supplement for the far more controversial use of hES cells in medical research.

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# Chapter-4: Stem Cell Legalities

The intent of Chapter 4 is to discuss the impact of technology on society through the laws controlling stem cell use in America and around the globe. Three different presidential administrations, Clinton, Bush, and Obama, have had an influential impact on regulations for embryo and stem cell research in the United States. Overall, the United States has been rather unsupportive and restrictive with its stem cell legislation in comparison to Europe and Asia. When federal funds were lacking, states have occasionally circumvented this by creating their own stem cell legislation. Indeed, despite legal restrictions, most Americans feel that ESC research has the potential to benefit medical practices, and the United States is falling behind in the stem cell race.

## Early U.S. Stem Cell and Embryo Policies

The advent of *in vitro* fertilization (IVF) in the late 1960's began a national debate about the fate of fertilized embryos that were initially created for reproductive purposes but were not implanted. The extra embryos were usually discarded, so the debate focused on whether they could be used for research purposes. Additionally, at this time, abortions became more prevalent, so discussions also focused on whether tissues isolated from aborted fetuses could be used for research purposes. In 1974, the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, initially appointed by President Nixon, recommended a ban on all federally funded research using embryos and fetal tissues. The recommended ban was subsequently enacted by congress. In 1975, President Ford appointed an Ethics Advisory Board to make recommendations on embryo and fetus research, but in 1981

newly elected President Reagan ended the ethics board's charter. This resulted in a defacto moratorium on funding for ESC research, and allowed the original 1974 ban to continue (Stem Cell Tracker, 2009; Wanjek 2009). Congress tried to override this moratorium in 1992, but George H. W. Bush vetoed it (Wanjek, 2009).

**Clinton Administration Stem Cell Policies (1993-2001)**

Once Clinton began his presidency in 1993, he lifted the moratorium on ESC funding put in place by Ronald Regan (Wanjek, 2009). By doing so, President Clinton gave NIH the authority to fund embryonic stem cell research for the first time (Dunn, 2005; Scott, 2006). The first step NIH took was to establish a panel of ethicists, scientists, and public policy experts to evaluate what types of experiments should be qualified for federal funding (Dunn, 2005). In 1994, the NIH Human Embryo Research Panel advised President Clinton to allow federal funding for research on left over IVF embryos, and suggested that funding be allowed for research on embryos created specifically for experimentation as well. Yet, moral and ethical issues/outcrys from prolife supporters caused President Clinton and his administration to agree to fund only stem cell research on excess embryos from IVF treatments. To further evaluate the ethical issues surrounding stem cells and other biotechnology, Clinton established the National Bioethics Advisory Commission (NBAC) in 1995, and gave an executive order that they review the policies and procedures involving "human subjects research, the use of genetic information, and gene patenting" ("BIO," 2005).

*1995 Dickey-Wicker Amendment*

However, Congress at this time thought that any work with human embryos was too radical. Thus in 1995, in response to Clinton's support of ESC research, Congress passed a rider attached to the appropriations bill for the Department of Health and Human Services entitled the *Dickey-Wicker Amendment*, which prohibited any federal funding for embryonic stem cell research regardless of the source of the embryo (Dunn, 2005; "Stem Cell Laws," 2010). Congress has renewed this ban every year since its establishment, until 2009 when newly elected President Obama overturned it for IVF embryos. Thus, taxpayer money until 2009 could not be used for *any* embryo experiment, and post-2009 cannot be used to create an embryo solely for research purposes.

In 1997, Clinton proposed a *reproductive* cloning ban with civil penalties based on NBAC recommendations, but Congress adjourned without taking any action ("BIO," 2005). A year later, the discovery of hESCs from privately funded research led to another flurry of stem cell politics. At this time the Senate considered and rejected legislation that banned all human cloning including therapeutic. Also, BIO (Biotechnology Industry Organization) along with 200 patient and voluntary health groups called for the doubling of the $13.6 billion NIH budget within five years. With the sudden rise in advances within biotechnology, Congress was receptive to their plea, and by 2001 the NIH budget had already risen to $20.3 billion ("BIO," 2005).

*2000 Loophole in Dickey-Wicker Amendment*

Eventually, the NBAC, created by Clinton, provided a list of reasons why the ban on stem cell research should be lifted, such as shortening the time to clinical trials and promoting

competition among biotechnology companies in order to decrease health costs. With respect to the moral status of the embryo, the NBAC wrote, "The embryo merits respect as a form of human life, but not on the same level accorded to humans" (Scott, 2006). However, with the Dickey Amendment in place, the government could not support research used to derive stem cell lines. Luckily, Harriet Rabb, the top lawyer at the Department of Health and Human Services, found a loophole stating that hESCs "are not a human embryo within the statutory definition," and thus the Dickey Amendment does not apply to them. As a result, in 2000, President Clinton endorsed guidelines to allow NIH to accept grant proposals from scientists experimenting with previously derived hESC stem cell lines. In doing so, although no embryos could be destroyed with government finances, NIH funding could be used to research on established hESC lines formed from private dollars. Thus, the Clinton Administration was the first to open the door to federal funding for ESC research. Unfortunately, no grants were ever provided under the guidelines as they were put on hold when President Bush took office in 2001 ("BIO," 2005; Dunn, 2005).

## Bush Administration Stem Cell Policies (2001-2009)

### *August 9th 2001 Policy*

In 2001, President Bush took office and canceled the NIH review of stem cell grant applications for re-evaluation. ("BIO," 2005; Dunn, 2005). On August 9th 2001, Bush made a televised decision to allow federal funding only for a list of pre-existing hESC lines. These lines were allowed, as an embryo had already been destroyed for their creation. But to discourage any further embryo destruction, Bush stated that federal taxpayer money would not be allowed for

research on stem cell lines formed after August 9th of 2001. Many scientists and patient groups took issue with the limitation on stem cell lines. However, *privately* funded hESC research still remained possible (Kruse, 2008).

With respect to the number of human ES cell lines available for federally funded research, at the time of Bush's address to the nation, NIH stated that there were 64 stem cell lines eligible for federal funding. Three months later, the NIH Human Embryonic stem Cell Registry was posted listing all of the cell lines available for federal funding (Kruse, 2008), but there is a discrepancy in the number of cell lines listed in this report: some sources say that the registry approved over 70 lines, while others mention numbers in the 60's. However, after genetic and growth testing were performed on the cell lines, only around 10-20 lines ended up being usable for ESC research (Babington, 2006; Scott, 2006; Kruse, 2008); some lines perished after being removed from the freezer, some lines were duplicates, some stopped growing, and others existed in 10 worldwide organizations outside the US. For the more than thirty lines residing outside the US, James Battey, the NIH official who administered the registry, stated, "We have no indication that any of these institutions will ever seek NIH support to develop their lines, or will make any effort to distribute their lines to the research community" (Scott, 2006).

The major issue with a majority of the hESC lines offered for federal funding was that these lines had been co-cultured with a feeder layer of animal cells (usually mouse fibroblasts) which contaminated the hES cells with animal proteins. Researchers prefer to work only with human cells as there is a concern that mouse viruses could contaminate the lines and harm humans (Babington, 2006; Scott, 2006). Also, human antibodies attack hESC's grown with mouse cells, leading to a severe immune rejection that could be prevented using purely human

stem cell cultures (Scott, 2006). Thus, most of the promised ES cell lines could not be used for biomedical research.

*2001 Weldon Legislation and Brownback Bill*

Later in 2001, the House of Representatives followed the White House ethics panel and created a bill known as the *Weldon legislation* that would ban the cloning of humans and criminalize all SCNT techniques used for therapy or otherwise. Bush backed the bill stating, "I strongly support a comprehensive law against all human cloning. And I endorse the bill wholeheartedly" (Scott, 2006). If this bill had passed, scientists caught using human SCNT would have been subject to a penalty of $1 million and up to ten years in jail. In addition, Senators Sam Brownback and May Laudrieu introduced a proposal in support of the House's bill with the provision (known as the *Brownback bill*) that the same criminal penalties be established for any American who provided or received medical treatments involving SCNT techniques developed in another country. Many individuals were outraged, as Nobel Prize winner Paul Berg states in reaction to the *Weldon legislation* "I couldn't believe the arrogance of a bunch of people in congress saying to 290 million Americans, sorry folks, you're not going to have the therapies to cure your disease because we are offended by this technology" (Scott, 2006). Luckily, this bill was not passed after congressional debates ensued over advise from BIO and other biotechnology companies ("BIO," 2005). Indeed, although a ban on *reproductive* cloning was supported by scientists and biotechnology agencies, banning *therapeutic* cloning would have cost Americans potential medical cures.

*President's Council on Biomedical Ethics*

In 2001, Bush also created a new bioethics council to further advise him on stem cells and other ethical issues. This council, known as the President's Council on Biomedical Ethics (PCBE), was headed by University of Chicago professor Leon Kass ("BIO," 2005; Scott, 2006). In July of 2002, the first PCBE recommendations on stem cell research arrived in a report titled Human Cloning and Human Dignity. In this statement, seventeen out of eighteen members voted to ban *reproductive* cloning. On the other hand, in relation to the issue of whether to support *therapeutic* cloning, the council voted ten members to seven, with one abstention, for a four-year moratorium on the issue (Scott, 2006).

Some worry that President Bush stacked his Council to support his policies. This idea may have some grounds. Since the PCBE's decisions in 2002, three members left the PCBE; one was removed, another resigned, and the third's term was not renewed. All of these individuals were supporters of ESC research. In addition, Janet Rowley, a member of the PCBE stated, "I have seen firsthand through the president's council that this administration distorts scientific knowledge on stem cell research, which makes it increasingly difficult to have an honest debate in a field that holds promise for treatment of many serious diseases like Parkinson's and juvenile diabetes" (Scott, 2006). Also, in reaction to the rearranging of the PBCE, the president's spokesperson stated evasively that Bush had "decided to appoint other individuals with different expertise and experience" (Scott, 2006). The Union of Concerned Scientists representative, Henry Waxman, noticed that political interference in science agency appointments also occurred in a number of other areas, including the NIH, NASA, EPA, and the FDA. More intriguingly, the World Health Organization protested that it had to ask for HHS permission each time it needed a US government advisor, rather than just contacting experts

directly as it has in the past (Scott, 2006). Indeed, as bioethicist George Annas wrote in response to the Bush administration, "Bioethics in the United States reflects US culture and tends to be pragmatic, market-oriented and insular" (Furcht and Hoffman, 2008).

By 2003, Congress had begun to notice that younger, talented scientists had started to leave the country to conduct their research in an environment with fewer stem cell research restrictions. England, in particular, was one of the most attractive areas for American scientists looking to work on ESC research (Furcht and Hoffman, 2008). As Keith Yamamoto, vice dean for research at the University of California, San Francisco School of Medicine states, "It's too much work to put together a research proposal only to find out it's going to be made illegal, or that there will be a four-year moratorium proposed" (Furcht and Hoffman, 2008). At this time, the House introduced five stem cell bills, and the Senate two. In 2004, a South Korean researcher reported on cloning their first human embryo, and this displayed how far behind on stem cell research the United States had internationally become (Scott, 2006). That same year, two hundred and six members of the House wrote a letter to Bush urging him to expand the number of stem cell lines allowed for federal funding. In June, fifty-eight Senators sent a similar letter. However, Bush would not budge on stem cell research restrictions (Dunn, 2005; Scott, 2006). Bush's rigidity with stem cell restrictions was intriguing for, as Physician Sherman Elias states, "Current federal limitations on ESC research puts the United States at a competitive disadvantaged in comparison to other countries such as Great Britain. With a nation that takes such pride in being at the forefront of major technological breakthroughs, and with a rising life expectancy, slacking on health care practices seems like a poor action for congress to make" (Furcht and Hoffman, 2008).

*2005 Stem Cell Research Enhancement Act*

Regan's death on June 5, 2004, due to complications of Alzheimer's disease, and his widow's advocacy of ESC research, sparked new public support and interest in reducing stem cell research restrictions (Furcht and Hoffman, 2008). Indeed, unlike the stem cell lines from 2001, the new stem cell lines created with *private* funds were easier to access and maintain in the lab, were not contaminated with mouse cells, and differentiated into cells of interest more easily. Thus, the new ES cells were more likely to contribute to beneficial human therapies (Dunn, 2005). As a poll from the Civil Society Institute in February 2005 reveals, 70% of Americans at that time favored loosening Bush's restrictions on stem cell policy in the US (Dunn, 2005). In addition, in April of 2005, Bush's NIH director Elias Zerhouni admitted that there is "mounting evidence" that a policy change would benefit science (Dunn, 2005). All of these events resulted in the introduction of the *Stem Cell Research Enhancement Act* in 2005. This bill would increase federal funding for ESC research and decrease federal restrictions on stem cell research by allowing federal government funded research on excess embryos from IVF clinics that had donor approval (Scott, 2006; Kruse, 2008). Despite risk of a presidential veto, in May of 2005 the House of Representatives voted 238 to 194 to pass this bill ("Stem Cell Laws," 2010). In July of 2006, the Senate also passed the act. Unfortunately, Bush staunchly adhered to the stem cell policy he employed in 2001, and July 19 of 2006 Bush vetoed the act, frustrating supporters of hESC research (Furcht and Hoffman, 2008; "Stem Cell Laws," 2010). Bush believed that "This bill would support the taking of innocent human life in the hope of finding medical benefits for others. It crosses a moral boundary that our decent society needs to respect. So I vetoed it. If this bill were to become law, American taxpayers would, for the first time in our history, be

compelled to fund the deliberate destruction of human embryos, and I'm not going to allow it" (Baker, 2005; Bash and Walsh, 2006).

The House attempted to override the veto, but the vote was 235 to 193, not the two-thirds majority necessary for the override (Baker, 2005; Bash and Walsh, 2006). Bill Frist R-Tennessee disagreed with Bush's veto stating "I am pro-life, but I disagree with the president's decision to veto the Stem Cell Research Enhancement Act. Given the potential of this research and the limitations of the existing lines eligible for federally funded research, I think additional lines should be made available" (Bash and Walsh, 2006). Several leading Democrats also disapproved of Bush's action. Indeed, Senate Minority Leader Harry Reid (Nev.) said, "President Bush has made the wrong choice, putting politics ahead of safe, responsible science" and Sen. Edward M. Kennedy (Mass.) stated, "The President's threat to veto legislation on bipartisan stem cell research demonstrates how out of touch he is with the priorities of the American people" (Babington, 2006).

*Stem Cell Therapeutic and Research Act of 2006*

Although Bush banned an increase in federal research for embryonic stem cells, he did support furthering research on *adult stem cells*. In fact Bush signed into law a Stem Cell Therapeutic and Research Act of 2006 written by New Jersey congressman, Chris Smith. This Act provided $265 million for adult stem cell therapy, umbilical cord blood and bone marrow treatment, and authorized $79 million for the collection of cord blood stem cells" ("Stem Cell Laws," 2010). Indeed, Bush stated "I am a strong supporter of adult stem cell research, of course. But I made it very clear to the congress that the use of federal money, taxpayers' money,

to promote science which destroys life in order to save life is—I'm against that. And therefore, if the bill does that, I will veto it" (Babington, 2006).

**Obama Administration (2009-Present)**

During the Bush administration's ban on federally funded embryo research, *privately* funded companies led the way in ES cell research at the expense of academic labs. But this changed in 2009 when Obama signed an executive order lifting an eight-year-old 2001 ban on federal funding of embryo research. Through doing so, President Obama ended limits on ESC research funding, and attempted to restore the "scientific integrity" of the American government. Obama said "It is about ensuring that scientific data is never distorted or concealed to serve a political agenda, and that we make scientific decisions based on facts, not ideology" (Childs and Stark, 2009; Windslow and Naik, 2009). Indeed, through his act, the president renewed hope for new ESC research and support for ESC scientists (Childs and Stark, 2009).

The president-signed executive order gave the National Institutes of Health 120 days to compile new guidelines for the manner in which ES cell research was to be carried out (Childs, 2009; Windslow, 2009). The guidelines should address issues such as where embryos used for research should come from, and how consent must be obtained from those who donate them. In addition to supporting ES cells, Obama promised to support the "groundbreaking work" being done on adult stem cells and IPS cells that conservatives advocate (Windslow and Naik, 2009).

However, though loosening restrictions, Obama stated that the government will not undertake ESC research lightly, and emphasized that he will support the necessary ethical restrictions that will promote the responsible use of stem cell research and technology. Initially Obama's policy would not affect federal laws that prevent the use of federal funds to destroy

human embryos (Childs, 2009), so while it would broaden research opportunities on hundreds of privately established cell lines, Obama's executive order would not promote the creation of new ones. But Obama's initial policy may be modified in view of the NIH Guidelines to allow the creation of *new* ES cell lines under strict rules mandating *donor consent* for IVF embryos initially created for *reproductive* purposes (Lo et al., 2010). In addition, Obama's stem cell policy is designed so that it "never opens the door to the use of cloning for human *reproduction*" (Borenstein and Feller, 2009). This particular type of reproductive cloning he considers as "dangerous, profoundly wrong, and has no place in our society or any society" (Borenstein and Feller, 2009).

Obama feels that a majority of Americans support his lifting of the federal funding ban, as this allows the government to support researchers, working with already derived hESC lines, to uncover revolutionary cures for cancer, heart disease, Parkinson's and other illnesses. Obama says "In recent years, when it comes to stem cell research, rather than furthering discovery, our government has forced what I believe is a false choice between sound science and moral values. In this case, I believe the two are not inconsistent" (Borenstein and Feller, 2009; Childs and Stark, 2009; Wilson, 2009). Harvard Stem Cell Institute co-director, Doug Melton, supports Obama's stem cell policy stating "On a personal level, it is an enormous relief and a time for celebration… Science thrives when there is an open and collaborative exchange, not when there are artificial barriers, silos, constructed by the government" (Borenstein and Feller, 2009). Most scientists also support Obama, and hope that the policy change will provide a boost for ES cell research, attract young scientists to the field, and permit America to establish leadership in an area currently headed by Europe and Asia. "We have a long way to go in understanding the basic biology of human embryonic stem cells," said Arnold Kriegstein, who heads stem cell research

at the University of California at San Francisco,"Now that the policy has changed we'll see a resurgence in academic activity" (Windslow and Naik, 2009).

Unfortunately one year after President Obama lifted Bush's restrictions on hESC research, scientists began complaining that the new policy is paradoxically more harmful than helpful to their work. By loosening restrictions on federal funding, Obama opened new ethical issues with NIH's ethical recommendations in their published guidelines (Lo et al., 2010). As a result, the new NIH guidelines state that hESC lines being studied with federal funding must meet strict new ethical criteria. However, it is unclear which of the 21 previously approved pre-2001 ES lines researchers have spent millions of dollars working on fit the new NIH criteria, especially since many of these lines were developed at a time when ethical requirements were not as advanced (Stein, 2010). "Some of these lines were derived more than a decade ago, and some of the researchers who derived them aren't around anymore. Some of those records [proving donor consent and IVF origins] may not be available," states Timothy J. Kamp, director of the stem cell and regenerative medicine center at the University of Wisconsin (Stein, 2010).

So far, the NIH has approved 43 lines, but only one of the 21 Bush lines. One hundred and fifteen lines are still waiting for review, but of these lines only two Bush lines are included. "We're losing access to those lines in this approval process for some period of time—maybe indefinitely. They are the main workhorses for many of our projects" Kamp says (Stein, 2010). However, scientist hope that the NIH will alter their guidelines and allow a 2-year grace period, so that scientists can continue their research until they get formal approval to use their stem cell lines again (Stein, 2010). In any case, even under the new strict NIH ethical guidelines, researchers already have more ES lines available for research than under the Bush administration, and the number continues to rise.

**Individual State Stem Cell Laws**

Although some previous administrations have placed bans on using federal funding for embryo research, individual states can pass their own legislations funding embryo research. This tactic was especially developed during the Bush administration's 2001 ban. **Figure-1** shows a map of the US with individual states shown in colors. States shown in blue led the way for approving state bonds to fund stem cell institutes and to fund embryo and stem cell research. States shown in pink restricted ES research as of 2005.

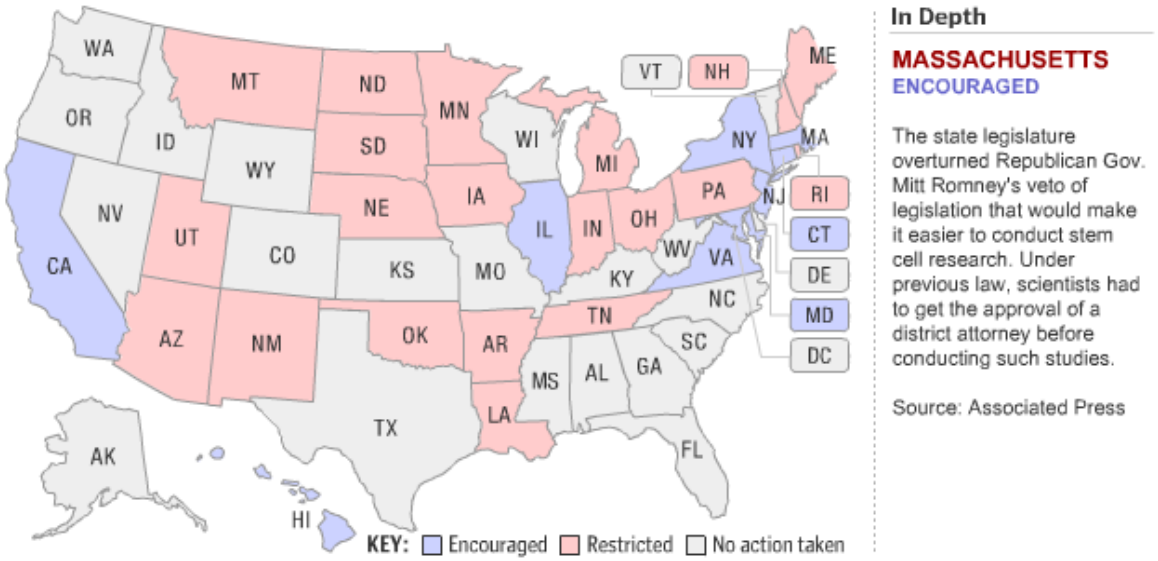


**Figure-1: Map of Stem Cell Legislation in the US by State.** ("Stem Cell Legislation in the US by State," 2005)

In 2002, Governor Gray Davis of California declared that the state was a "restriction-free zone", and signed a law allowing therapeutic cloning and embryo research, but banned reproductive cloning (Scott, 2006). However, not until November of 2004 did California finally accompany the legislation with money through authorizing *Proposition 71*. *Proposition 71*

allowed $3 billion, taxpayer funded, to support stem cell research over a period of ten years. The state was able to issue training grants, but legal issues slowed the distribution of research grants in 2006 (National Conference of State Legislatures, 2008). As a result, that same year, Governor Arnold Schwartzenegger loaned $150 million to support stem cell research. It took until May of 2007 for the California Supreme Court to remove the last preventative to issuing $3 billion in bonds and allow the money to be used for research purposes (Furcht and Hoffman, 2008).

Although California was the first state to support ESC research, New Jersey was the first state to pass a state budget for stem cell research. This occurred with the help of a neuroscience researcher at Rutgers University, Wit Young. Young helped legislature pass a bill in 2004, authorizing stem cell research to be done in New Jersey (Wadman, 2008). In June of 2004, a $9.5 million budget was created for a newly contracted Stem Cell Institute of New Jersey (Godoy and Palco, 2006). In 2005, $5 million in grants were split among seventeen research projects (Furcht, 2008). A year later $270 million was spent on supporting stem cell research, $150 million of which was used to build the Stem Cell Research Institute of New Jersey (Wadman, 2008). New Jersey, like California, also supports therapeutic cloning and bans reproductive cloning.

In Massachusetts, the Harvard Stem Cell Institute, established in 2004, was one of the primary motivators for developments in stem cell legislature. In 2005, the Massachusetts legislature approved a bill that removed ESC researchers from the previously mandatory task of seeking approval from the local district attorney before conducting research. The bill also allowed therapeutic cloning but banned reproductive cloning. This legislation passed despite a veto from Governor Mitt Romney who does not believe in allowing SCNT practices ("Massachusetts Stem-Cell Bill," 2005). At this time, Massachusetts legislators also added two

new sections to the statutes on stem cell research. One established an institute for stem cell research and regenerative medicine at the University of Massachusetts with an appropriation of $1,000,000 to be spent on the stem cell biology core. The second established a life sciences center and created the Life Sciences Investment fund to which $10,000,000 was appropriated (National Conference of State Legislatures, 2008). More recently, during the 2007 BIO meeting in Boston, Massachusetts Governor Deval Patrick pushed for a ten-year $1 billion investment in biotechnology, half of which would be used toward the creation of a Massachusetts Stem Cell Bank at the University of Massachusetts (Furcht and Hoffman, 2008; Wadman, 2008). This proposition passed making way for the construction of the nation's largest stem cell bank.

In Connecticut, in 2005 the state approved legislation to allow and fund embryonic and adult stem cell research. The bill proposed giving $100 million to evolving research over a period of ten years ("Massachusetts Stem-Cell Bill," 2005).

**World Policies**

The UK pioneered *in vitro* fertilization, supplying the world with excess IVF embryos for experimentation of hESC. In 1990, the UK allowed ESC research on excess IVF embryos. Also in 1990, the British Parliament created the Human Fertilization and Embryology Authority (HFEA) to help regulate ESC research. Laws in Britain allow for the creation of embryos for research, but to work with hESCs scientists must obtain a license from the HFEA (Boyd et al., 2009). In 2001, England became one of the first countries to ban human reproductive cloning. In 2002, the UK's National Institute for Biological Standards and Control opened a stem cell bank to house stem cell lines created from adult, embryonic, and fetal tissues. The bank offers over 30 stem cell lines (Furcht and Hoffman, 2008). In 2004 the UK became the third country to allow

scientists to clone human embryonic stem cells for research purposes with SCNT. Recently, in May of 2008, British Parliament decided to permit research on experiments with animal-human hybrid embryos (Ralston, 2008).

In 1999, Israel banned reproductive but not therapeutic cloning (Ralston, 2008). Later, in 2001, Israel allowed the use of stem cells from early embryos and aborted fetal tissue up to nine weeks of age. Then, in 2004, Israel formed a multimillion-dollar consortium uniting five stem cell companies with the country's leading academic labs (Scott, 2006).

Sweden prohibits reproductive cloning and allows therapeutic cloning. This country has a well-established biomedical industry, and in 2002 the Swedish government authorized the creation of Europe's second stem cell bank (Ralston, 2008).

Germany has a restrictive policy for hESC research, due partly to its history of atrocious medical experiments under the Nazi regime. Indeed the creation of ESCs is prohibited. However, in April of 2008, Germany decided to allow the use of imported stem cell lines produced before May 1, 2007 for experimentation (Ralston, 2008).

Australia's 2003 cloning act permitted the development of hESC lines from excess IVF embryos created before April 5, 2002 for research. This act also banned both reproductive and therapeutic cloning (Garfinkle, 2004; Scott, 2006).

The Chinese government has invested hundreds of millions of dollars in stem cell research to make itself a scientific superpower. For example the Tissue Engineering Research Center in Shanghai cost $260 million and seventy percent of this center was government funded (Boyd et al., 2009). Not only does China have governmental financial support, but China also has one of the most liberal stem cell policies in the world, due in part to its Confucian culture that firmly believes human life begins at birth and not at conception (Boyd et al., 2009). Indeed,

China prohibits reproductive cloning but allows the creation of human embryos for medical research. China also permits scientists to conduct clinical trials for stem cell therapy on terminally or chronically ill patients (Ralston, 2008). In addition, China has scientific manpower due to the fact, as Robert Zhao, head of China's National Center for Stem Cell Research states, "No country sends more of its students to America for higher education than China" (Furcht and Hoffman, 2008).

As for stem cell policies in other parts of Asia, in 2007 India's government banned reproductive cloning, but allowed experiments with therapeutic cloning. The Indian Council for Medical Research also set up guidelines for clinical trials with stem cells. So far, only stem cells for bone marrow transplants have been approved. Singapore is one of Asia's stem cell epicenters, with over 40 stem cell research groups residing in the area. In order to boost their biomedical research, Singapore recruits scientists from around the globe, offering them the use of embryos no more than two weeks old for therapeutic research (Ralston, 2008). However, hESCs have to be taken first from existing cell lines, and then with medical merit subject to statutory review, embryos less than 14 days old can be created for research purposes (Scott, 2006).

**Chapter-4 Conclusion**

As the land of opportunity, the United States has a rather conservative stem cell policy compared to the best of the stem cell research hubs across the world. But thanks to President Obama, American scientists can now use *federal* funding to research excess embryos from IVF clinics. However, ESC research in the US has not yet had time to recover from eight years of restrictive policies instituted by President George W. Bush. Indeed, under the Bush administration, America was put in a biomedical research dark age as the hESC stem cell lines

allowable for federal funding were extremely outdated, and in many cases unfit for experimentation. America has become complacent with its technological success leading to excessive congressional squabbling over stem cell ethics. In a nation with a rising elderly population desperate for health care, it seems only natural that the federal government should supply support for improving medical procedures through stem cell research. As a nation we need to turn our arguments into actions to prevent further delays… or we will fall behind on more than stem cell research.

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# PROJECT CONCLUSIONS

As ESCs have not yet been researched to their full potential, I believe that ESC research should continue until it has been proven that iPS cells can effectively replace ESCs in medical treatments. Despite the fact that an embryo must be destroyed to obtain ESCs, I find ESC research falls into the category of doing a small amount of "evil" for a much greater good. As I do not consider a blastocyst to be a full human being, I do not view embryo destruction at this stage as murder, but rather as a way to aid science in saving lives. Yet, though I do believe that the embryos should first be obtained from excess IVF embryos, before any embryos are produced in the lab solely for research purposes, or are obtained through paid egg donors. I also believe that, whenever possible, iPS and ASCs should be used for experimentation as a substitute for ESCs in order to prevent unnecessary embryo destruction, as a nod to individuals who feel ESC research is morally abhorrent. Indeed, I do believe that as a living being embryos deserve some moral respect. As to stem cell laws and federal regulations, I agree with Britain's and Singapore's stem cell policies. They encourage ESC research and allow the production of embryos solely for research, but first they promote obtaining embryos from other sources such as excess IVF embryos. Thus, these countries regulate and limit the creation of embryos for experimentation while supporting ESC research. Personally, I find that even under Obama's administration, the United States is still too restrictive in their stem cell policies, by not allowing embryos to be created solely for research purposes. However, if iPS cells live up to their full potential, current US stem cell policies will not cause America to fall behind in the race to harness the power of the stem cell to benefit society.