IQP-43-DSA-3327
IQP-43-DSA-6629

# STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

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October 28, 2008

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# ABSTRACT

The purpose of this IQP was to explore the technology of stem cells, focusing on ethics and legalities. Our findings indicate that although most human embryonic stem (ES) cell applications remain as future applications, some types of adult stem cells (ASCs) have already been used to save lives. None of the five major world religions is against working with ASCs, especially when used to save human lives, however ES cell research still has not received much approval from many conservative Christian groups. Restrictive U.S. legislations on ES cell research by conservative governments such as the current US administration has hindered ES cell progress.

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# PROJECT OBJECTIVES

The goals of this IQP were to explore the topic of stem cells and their applications, and to discuss the effect of this controversial technology on society. Key debate points were discussed from the last few decades, to the present and future. The specific aim of chapter-1 was to describe and contrast the various types of stem cells, to clarify the key point that not all stem cells are alike. The objective of chapter-2 was to investigate examples where stem cells have successfully been implemented and studied, paying particular attention to distinguish hype from reality. The purpose of chapter-3 was to explore the ethics surrounding stem cell research, especially the view of the five major world religions. The purpose of chapter-4 was to examine the laws governing stem cell use in the United States and other countries. Finally, the authors of this project provide their own conclusions about this controversial topic.

# Chapter-1: Stem Cell Types and Sources

Stem cells are "immortal" cells in the body that can not only replicate themselves, they can also change (differentiate) into other cell types. Due to this differentiation potential, these cells are thought to have medical applications in regenerative medicine, a promising new field of 21st century medicine. But controversies arise regarding where these stem cells are obtained, opening up ethical and legal concerns. Not all stems cells are equal, and not all stem cells require the destruction of an embryo to obtain them. The purpose of this chapter is to shed light on what stem cells are, and where we get them.

**Stem Cell History**

Scientists have been interested in cell biology since the invention of the microscope in the 1800's, a time when the discovery that cells generate other cells was made. However, in the early 1900's, cells were discovered that not only reproduce themselves, they also change into other cell types, in this case a type of cell from bone marrow could generate other blood cells (Stem Cell Research, 2007). Research focused on whether such cells could be used in medicine to regenerate blood. In 1968, the first bone marrow transplant, containing hematopoietic stem cells (HSCs), was performed to treat two siblings with severe combined immunodeficiency disease, and since the 1970's bone marrow transplants have been used for treatment of thousands of patients with immunodeficiencies and leukemias (Deem, 2004).

Ten years later, the first *in vitro* stem cell line was developed from mice. In 1988 embryonic stem (ES) cell lines were derived from a hamster and about 7 years after that discovery, ES cell lines were created from a primate. In 1997 two different events happened:

Dolly a lamb was the first mammal cloned from stem cells, and the origin of leukemia was determined to be due to the replication of abnormal hematopoietic stem cells, indicating proof that cancer can result from abnormal stem cells. But in 1998, the entire stem cell field achieved much greater public awareness when James Thomson (University of Wisconsin – Madison) isolated cells from the inner cell mass of an early human blastocyst embryo, and developed the first human ES cell lines. In the same year, John Geahart (Johns Hopkins University) derived human embryonic germ cells (EGCs) from fetal gonadal tissue (primordial germ cells). In 1999 and 2000, it was discovered that different cell types can be produced by manipulating adult mouse tissues; nerve cells or liver cells could be produced from adult bone marrow stem cells (Stem Cell Research, 2007). Soon after, the journal *Science* claimed that advances in stem cell research was the "breakthrough of the year".

The stem cell field has continued to expand and attract the attention of scientists, as well as but also policy-makers, business interests and ethicists. All these discoveries were exciting for the area of stem cell research, giving scientists the hope of obtaining greater control over stem cell proliferation and differentiation for medical purposes. Various laws and procedures regarding stem cell harvesting, development and use have been created because of national debates among the public, religious groups, scientists, and government officials. The main goal of such policies is to safeguard people from the unethical use of stem cells, while still supporting new discoveries. But before attempting to understand these ethical and legal problems, it is necessary to understand the basic science of stem cells, including sources and types of stem cells.

## Types and Sources

Stem cells have two important characteristics that distinguish them from other cell types. The first is the ability to renew themselves for long periods through cell division, and the second is their ability to differentiate into endodermal, mesodermal, or ectodermal lineages under certain physiological or experimental conditions. Therefore, during every cell division *in vitro*, one stem cell produces one daughter stem cell (that remains undifferentiated) and one differentiated cell whose properties are more specialized than the parent cell (Stem Cell Basics, 2008). Some scientists have questioned this basic definition of stem cell, preferring to think of "stemness" as a transition state between regeneration and differentiation that changes depending on need and location.

Stem cells can broadly be divided into two types, embryonic stem (ES) cells and adult stem cells (ASCs), each with particular functions and characteristics that will be explained later in this chapter. Stem cells can be obtained from many different sources, but not all of them are equal in their potentials. Some stem cells are said to be pluripotent, meaning that they have the ability to develop into many different cell types of the body, some are multipotent and able to develop into a few other cell types, while others are mostly unipotent and somewhat restricted in which cell types they can become.

## Embryonic Stem Cells

Embryonic stem cells (ES) are pluripotent cells derived from embryos generated by *in vitro* fertilization (IVF). If IVF is successful, the sperm head enters the egg, leaving the tail behind. Later, the fertilized cell divides by binary fusion. About 5 days after fertilization, a multicellular ball of cells called a blastocyst is formed (Figure-1). Typically, a blastocyst is a

hollow ball made of two cell types, an outer layer called the trophoblast, which eventually forms the placenta, and an inner cluster of cells known as the inner cell mass which becomes the embryo. The inner cell mass consists of ES cells, which can be picked up with a pipette and transferred to a Petri dish. The resulting colonies can be further propagated by transferring cells to new Petri dishes. Under particular culture conditions these cells start self-renewing, or dividing, and the cell mass starts growing (Human Embryonic Stem Cells, 2007) .

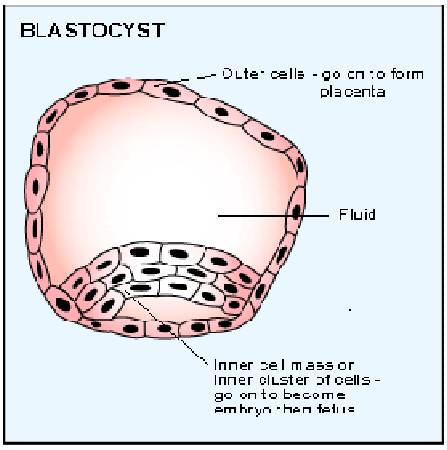


**Figure-1: Diagram of a Human Blastocyst.** The embryo at this stage is composed of the trophoblast or outer layer of cells, and the inner cell mass from which ES cells are obtained. http://www.mydr.com.au/content/images/categories/Pregnancy/blastocyst.gif

The addition of specific growth factors or signaling molecules to ES cells can coax them to differentiate into a certain cell type, such as pancreatic cells, muscle cells, or nerve cells. The main goal of cell replacement therapy is to use this kind of cell for transplantation to replace old or diseased tissue and to renew function.

Since ES cells have such a large variety of types of cells they can become, they are said to be pluripotent. Moreover, they have an ability to divide, or self-renew indefinitely while retaining their pluripotent, undifferentiated state. For example, small numbers of ES cells can be placed in a Petri dish to divide, and the cells from one Petri dish can be used to seed many other plates. In this case, an indefinite number of pluripotent cells can be produced (Human Embryonic Stem Cells, 2007).

**SCNT**

When transplanting ES cells obtained from an IVF embryo, the genetic component of the ES cells in the dish will be different from the genetic background of the patient, because the patient did not provide the IVF embryo. Hence, the tissues and organs grown from these cells will have a different genetic background from the patient, which can cause immunorejection of the transplanted tissues. One solution that might help in eliminating this rejection is the somatic cell nuclear transfer (SCNT) technique (Figure-2). During SCNT, the nucleus of the egg with its genetic material is removed. Later, a biopsy from the patient is taken (with mice this is usually a skin fibroblast cell), and the nucleus from one of these cells is transferred into the enucleated egg. Following activation, the egg divides to the blastocyst stage from which genetically identical ES cells can be obtained whose genetic content is identical to the patient. In this manner, patient-specific stem cells could be derived and used to produce cells and tissues for transplantation that will not be rejected (Soon-Chye, 2001). This SCNT procedure has not yet been achieved in humans, but has worked in mice.

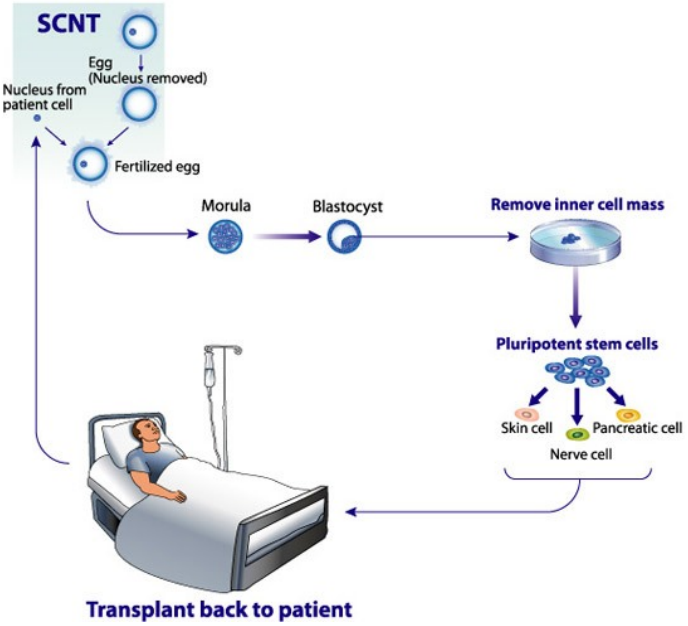


**Figure-2: Diagram for Obtaining Patient-Specific ES Cells**. In this process, the egg nucleus is removed (upper center) and is replaced by the nucleus from a patient (upper left). The egg is stimulated to divide, from which a blastocyst is obtained (center). ES cells can then be isolated from the blastocyst for treating the patient. This procedure has not yet been successful with humans, but has been done in mice.
http://www.kumc.edu/stemcell/images/scnt.jpg

**Adult Hematopoietic Stem Cells**

Hematopoietic stem cells (HSCs) are stem cells present in bone marrow or umbilical cord blood that can give rise to all blood cell types, including lymphoid and myeloid lineages. Hematopoietic tissue consists of cells with short and long-term regeneration capacities, including committed unipotent, oligopotent, and multipotent progenitors. Unipotent are cells that can produce only one cell type, but still are able to self-renew, which distinguishes them from non-stem cells. Oligopotent stem cells can differentiate into a few types, and multipotent stem cells can produce a larger variety of a closely related family of cells. HSCs can be found in adults' bone marrow, which includes ribs, hip, sternum and other bones. They are often removed and collected from the hip using a needle and syringe, or from peripheral blood from individuals pre-treated with cytokines to stimulate the release of HSCs into the bloodstream. HSCs are also relatively abundant in umbilical cord blood, which has recently become a popular source for their extraction (Viacord, 2008).

HSCs are widely used in bone marrow transplants (Hematopoietic Stem Cells, 2001) giving hope to people with various diseases such as myelodysplasia, acute leukemia, and congenital immune deficiencies (BMT: Success Stories: Interview with Michael Green). The current challenge is to reduce the rejection risk of this kind of transplant, and increase the number of patients who can safely access this treatment.

**Adult Neuronal Stem Cells**

It used to be thought that people are born only with a particular number of neuronal cells that would not replenish. However, now it is known that in some regions of our brain, neuronal cells are continuously replenished. These neurons are derived from neuronal stem cells (NSCs).

NSCs are adult stem cells that are capable of differentiating into different neuronal family cell types, like neurons and glia. This property gives hope for scientists to use NSCs for treating neurodegenerative diseases such as Parkinson's or Alzheimer's diseases (Björklund and Lindvall, 2001).

However, it is incredibly difficult to isolate NSCs. They are located in the walls of brain ventricles – cavaties filled with cerebrospinal fluid, but only one out of 300 cells of this region are NSCs. Over the last few years, it was shown that changing the cellular environment might be able to cause a transdifferentiation of NSCs into non-neural tissue; under certain experimental conditions NSCs can generate a large number of non-neuronal cells, such as muscle cells (Cassidy and Frisén, 2001).

**Adult Cardiac Stem Cells**

For several decades scientists debated whether a human heart can repair itself by producing new tissue after serious injuries, such as heart attack. But nowadays, researchers are sure that the human heart contains stem cells that enable the heart to generate new cells when it is damaged. Cells that give rise to cardiomyocytes (heart muscle cells) located on the surface of the heart (epicardium) may be able to regenerate heart (Andrews, 2008). Scientists have isolated these cardiac stem cells from rats and showed that after these cells are injected into a rat's damaged heart, the tissue was completely renewed (Touchette, 2003). A similar procedure was performed in a human body. After being accidentally shot, one person suffered a massive heart attack. Cardiac stem cells were isolated from his own heart and placed in the artery that carried blood to the front of his heart producing a successful regeneration of heart muscle (Philikovski, 2003).

**Adult Epithelial Stem Cells**

It has been known for some time that hair follicles within the cutaneous epithelium harbor a population of slowly dividing "label-retaining" cells of exceptional proliferative capacity. These proliferative cells reside within a 'bulge' of the outer root sheath (Figure-3), and are capable of participating in morphogenesis of hair follicle and the adjacent interfollicular epidermis. According to an article published in *Nature Biotechnology* in 2004, some of the studies have indicated that cells from the bulge are bipotent, and can migrate downward in the hair follicle and also outward to resurface the epidermis in response to wounding.

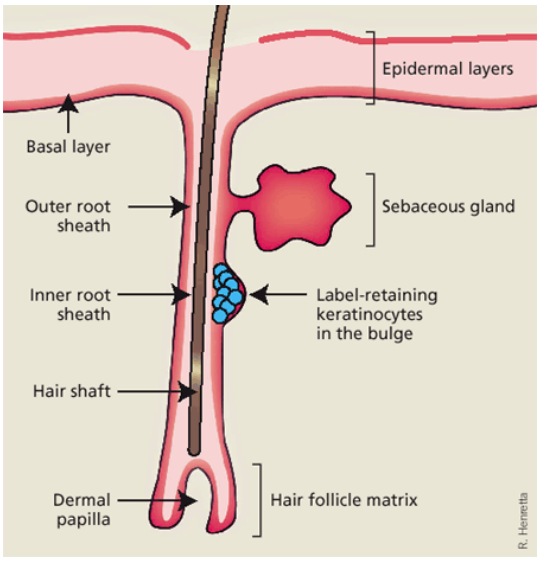


**Figure-3: Diagram of the Location of Epidermal Stem Cells.** The epidermal stem cells are located in a bulge midway down the shaft (shown in blue), and are thought to regenerate epidermis following wounds, or to regenerate additional follicles.
http://www.nature.com/nbt/journal/v22/n4/pdf/nbt0404-393.pdf

Another type of epithelial stem cell is able to regenerate mouse mammary glands. In an article published in *Nature* in 2006, experiments performed both *in vitro* and *in vivo* show that mammary cell differentiation originates in uncommitted stem cells with self- renewal potential (Khavari, 2004).

> "Here we report the use of multi-parameter cell sorting and limiting dilution transplant analysis to demonstrate the purification of a rare subset of adult mouse mammary cells that are able individually to regenerate an

> entire mammary gland within 6 weeks *in vivo* while simultaneously executing up to ten symmetrical self-renewal divisions. These mammary stem cells are phenotypically distinct from and give rise to mammary epithelial progenitor cells that produce adherent colonies *in vitro*. The mammary stem cells are also a rapidly cycling population in the normal adult, and have molecular features indicative of a basal position in the mammary epithelium." (Khavari, 2004)

**Mesenchymal Stem Cells**

Mesenchymal stem cells (MSCs) (Figure-4) are another well characterized type of adult stem cell. These cells are found in bone marrow (in addition to HSCs) and can differentiate *in vitro* and *in vivo* into a variety of tissues, including osteoblasts, chondrocytes, myocytes, adipocytes, and pancreatic β-islet cells. Culturing marrow stromal cells in the presence of ascorbic acid, or other osteogenic stimuli, can promote their differentiation into osteoblasts. Whereas, culturing them in the presence of transforming growth factor-beta (TGFβ) can induce chondrogenic markers. Unlike other types of adult stem cells, MSCs can easily be obtained in quantities sufficient for clinical applications. The techniques for their isolation and amplification in culture are well known and they can be maintained and propagated in culture for long periods of time.

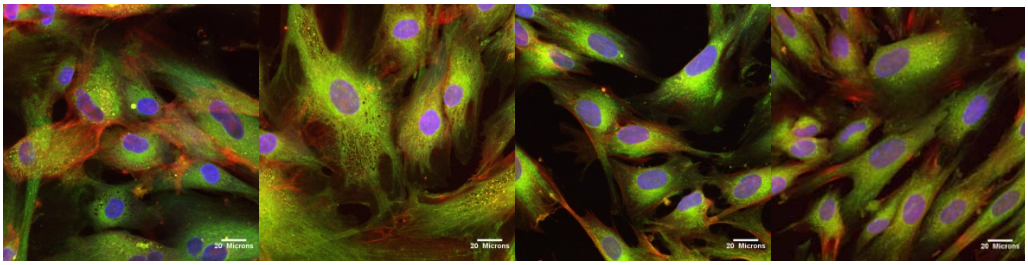

**Figure-4: Immunohistochemical Staining of Mesenchymal Stem Cells.**
http://www.hyclone.com/advancestem/somatic_cellular_engineering.htm

**Adult Intestinal Stem Cells**

Adult intestinal stem cells are one of the best studied of all the adult stem cells. Since the intestinal lining wears out every two to five days, intestinal stem cells are required to produce new cells. Intestinal stem cells give rise to various cell types inside the small intestine, including cells to absorb foods, cells that produce mucus, cells that excrete substances used in cell-cell communication, and cells involved in protection against different diseases, including bacteria and viruses. These cells are thought to self-renew throughout adult life due to the presence of both multipotent stem cells and unipotent progenitor cells.

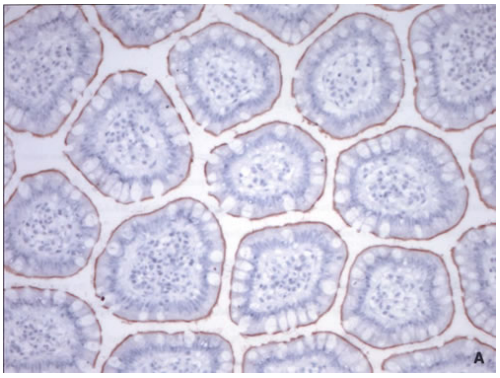

**Figure-5: Photograph of Epithelial Stem Cells in the Colon.** http://www.rvc.ac.uk/Education/Undergraduate/BScVetPathology/ResearchProjects200304.cfm

Recently it was discovered that there are several types of adult intestinal stem cells present in the intestine at the same time. The June 8th online issue of *Nature Genetics* reported that Mario Capecchi, the University of Utah's Nobel Laureate, and geneticist Eugenio Sangiorgi, noticed that a gene named Bmi1, used to mark adult stem cells, showed the presence of adult stem cells only in the upper third of the intestines of mice. That means that at least one or two types of adult stem cells must be present in the intestine to maintain the other two thirds of the intestine. This discovery also raises the possibility of using these cells to replace damaged intestine (More Than One Kind ….. 2008).

**iPS cells**

Induced pluripotent stem cells (iPSs) are adult cells induced to a de-differentiated state by transfection of specific genes. The first iPS cells were discovered by Shinya Yamanaka and his team at Kyoto University, Japan in 2006. The experiments involved transfection of mouse adult fibroblast cells with four genes using retroviruses. The transfected genes included Oct3/4, Sox2, c-Myc, and Klf4. The new cells took on an ES-like state, which could provide an alternative source for ES cells rather than destroying embryos. However, it is not clear whether such cells will have the same full potentials as ES cells. The iPS cells differed from ES cells in their DNA methylation pattern and when injected into developing embryos, the iPS lines were not able to produce chimeras (Cyranoski, 2008).

Nevertheless, in June 2007, the same group published a breakthrough article along with other independent research teams from Harvard, MIT, and UCLA showing that transfection of mice fibroblasts can be successful and the production of chimeras is possible. Compared to the first studies, the scientists used a different marker (Nanog, instead of Fbx 15). DNA methylation differences were eliminated, and viable chimeras were produced, showing that Nanog is a major determinant of pluripotency. The only issue occurring during these studies was the fact that one of four genes turned out to be carcinogenic, causing cancer in about 20% of mice. In later reports Yamanaka managed to create chimeras without using c-Myc, even though it took a much longer time and the process, in general, was not efficient.

In November 2007, two different articles published in *Science* and *Cell* claimed that *human* iPS cells were created. Two different research groups – James Thomson and colleagues at the University of Wisconsin, Madison and Shinya Yamanaka with his group at Kyoto University, Japan, successfully transformed human fibroblasts to pluripotent stem cells using the

same technique that was earlier applied in experiments with mice. In Yamanaka's studies the same four genes tested earlier with a retroviral system were used; whereas Thomson used Oct4, Sox2, Nanong, Lin28 and a different lentiviral system in his studies (Yu, 2008).

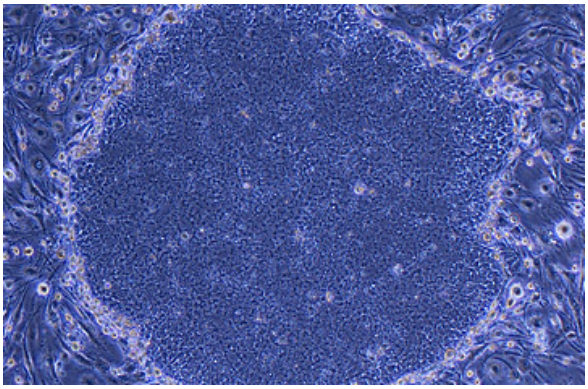

**Figure-6: Photograph of Human Induced Pluripotent Stem Cells.** Shown are human fibroblast skin cells induced by transfection to become ES-like. Such cells may eventually serve as an alternative source for ES-like cells without destroying an embryo.
http://www.foxnews.com/story/0,2933,312294,00.html

The biggest problem according to "Stem Cell Alchemy Refined", published by Brandon Keim on September 25,2008 with iPS cells is the fact that the viruses used to reprogram cells tended to fuse with the cell DNA, which leaded to various mutations and cancer.

Nowadays, scientists are working on developing new methods of transferring the de-differentiation inducing genes and discovering new alternative sources of stem cells. A new source of pluripotent stem cells was discovered in Januray 2007, when a group of scientists from Wake Forest School of Medicine extracted amniotic cells and grew them in the laboratory. The resulting cells turned out to be pluripotent stem cells very similar to ES cells, but not exactly the same. For example, ES cells injected into the muscle can form teratomas, while amniotic derived ES like cells do not. According to Dr Paolo De Coppi who worked on this research, he believes that " the range of applications for these amniotic ES-like cells may be more narrow than for ES cells". Moreover, there are lots of limitations, that can prevent usage of this type of cells, such as difficulties with collecting the amniotic fluid, and even ethical and moral issues (New Stem Cell…2007).

An article saying that another new source of ES-like cells was recently published in the October 8, 2008 online edition of *Nature*. A group from the Center for Regenerative Biology and Medicine in Tuebingen, Germany, harvested stable ES-like stem cells from spermatogonial (sperm producing) cells taken from the routine tissue biopsies of the testes of 22 adult male humans. The ES-like cells could be differentiated into all three germ layers by using the same techniques used to differentiate ES cells. According to the lead author Thomas Skutella, "the advantage of these cells in comparison to embryonic stem cells is that there are no ethical problems and they are natural". The Professor also claims that cells in women's eggs might be equivalent to the male testicular stem cells, but George Daley a stem cell scientist at Children's Hospital in Boston and the Harvard Stem Cell Institute said this is unlikely, leaving women without this easy ES cell method (Paddock, 2008).

**Existing ES Stem Cell Lines**

Federal money currently can not be used for deriving new ES lines, as will be discussed in more detail in Chapter-4, but ES lines derived *prior* to this deadline are available for federally funded research, as are ES lines generated with private or state funding. For example, two scientists from Harvard Universirty used private funding to establish seventeen freely available stem cell lines. One hundred fifty new stem cell lines were recently generated by Reproductive Genetics Institute and scientists from UCSF have established ES cell lines using human feeder cells instead of the usual mouse feeder cells. Today, both UK and the US are moving forward in establishing private stem cell banks to help researchers all over the world (Charmany, 2004).

**ES Cells from Excess IVF Embryos**

According to the "Stem Cell Primer", published in 2004 by Chamany K,"(I)n 2003 the RAND Institute for Civil Justice and Health determined that there were 396,526 frozen embryos stored for *in vitro* fertilization (IVF) clinics in the U.S." Of these, about 11,000 embryos are destined for scientific research, 2.2 % are planned for discard, 2.3 % are to be donated to other recipients, 4.5 % of the donors have lost contact with the clinics and the rest of the embryos are destined for future implantation. Because some embryos were inadequately preserved, only 275 of 11,000 destined for research are viable. However, even though they are available for research, they cannot be used for *therapeutic* purposes for a number of reasons. There is a high possibility of getting genetic problems, since most of the people who get involved with IVF carry fertility-related genetic abnormalities, and genomic imprinting patterns could be irregular. Using extranumerary IVF embryos causes a lot of debate between scientists and ethicists because those embryos would not be used for reproductive purposes, as will be discussed in Chapter-3 (Charmany, 2004).

**ES Cells from Embryos Created Specifically for Research via IVF**

Most of the stem cell institutes and IVF clinics nowadays are asking women to donate their unused oocytes for stem cell research. This involves making women undergo the IVF procedure so that ES cells can be derived by removing the inner cell mass. But as mentioned above this method of obtaining ES cells causes a lot of ethical issues (Charmany, 2004).

**ES Cells from Artificial Parthenogenesis**

Parthenogenesis is a form of asexual reproduction, in which an egg develops into a new individual without being fertilized. This process is common for some animals, mainly ants, aphids and bees. In mammals, the process is not natural but can be induced by chemicals. In order to mimic the sperm's arrival, scientists use starvation, electrical current, or chemicals to stimulate the unfertilized egg to begin dividing. Soon after this, the unfertilized egg becomes diploid by duplicating its genetic content but does not become haploid thereafter. Studies in monkeys and mice have shown that pluripotent ES cells can be derived from blastocysts formed through artificial parthenogenesis (Cibelli et al., 2002). Since these embryos are not capable of completing their development, the ethical concerns about potential life can be minimized, although egg donation must still occur (Charmany, 2004). In humans, the first six-cell embryos created by artificial embryogenesis were generated by Jose Cibelli and his group at Advanced Cell Technology. These embryos did not grow to the blastocyst stage from which ES cell lines could be established, so this technique in humans requires further development.

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# CHAPTER 2: STEM CELL RESEARCH AND APPLICATIONS

The purpose of this chapter is to discuss examples of stem cells and their applications in many biomedical and scientific fields, especially for the possibility of finding treatments for some very complicated diseases. Much knowledge about stem cells and their potential arise from animal experiments that allow us to proceed into human clinical trials with appropriate regulations. With the recent success in isolating human adult stem cells from tissues other than bone marrow (a stem cell source which has already been in use for decades), it is now possible to consider human clinical trials for diabetes, Parkinson's disease, or spinal cord injury, that can not be treated by bone marrow transplantation. Additionally, current advanced blood stem cell treatments applied beyond the traditional uses for chemotherapy and radiation have been expanded to include other non-blood uses. The purpose of this chapter is also to help sort hype from documented medical studies.

## HEMATOPOIETIC STEM CELL APPLICATIONS

### *HSCs and Cancer Chemotherapy*

Hematopoietic stem cells (HSCs) are the most characterized of all the stem cell types. HSCs have been in use for over 30 years to treat specific types of blood diseases, so this type of stem cell will be the first discussed in this chapter. HSCs have long been used to treat patients who have undergone chemotherapy and radiation treatments for cancer that destroy rapidly dividing cancer cells in the patient's body, but which also destroy the patient's own rapidly dividing HSCs and weaken the patient's immune system making him or her extremely susceptible to many opportunistic infectious diseases ("Hematopoietic Stem Cells", 2005). HSCs

transplants help replace the blood cells destroyed by chemotherapy. HSCs are collected either from the patient himself, or from a histocompatible donor, and are traditionally obtained from the bone marrow, or from the peripheral blood following stimulation of their release from the bone marrow using hormones (such as G-CSF). The HSCs are stored until the patient is clear from drugs in chemotherapy, and then the patient will receive a transfusion of his or her stored HSCs. When the patient receives his own HSCs back, there is no chance of immune mismatch or graft-versus-host disease (GVHD). However, cancer cells are sometimes accidentally collected with their HSCs, which can be reintroduced back in the patient along with the HSCs, so current research focuses on purifying HSCs from other cells prior to infusion, and on using umbilical cord blood which has broader compatibility. In the case of an allogeneic transplant, where HSCs are obtained from a matched donor (generally a family member, sibling, preferably an identical twin) patients can be placed at high risk to acquire GVHD and possible rejection of HSCs if not treated with additional medications ("Hematopoietic Stem Cells", 2005).

***HSC Treatment of Leukemia and Lymphoma***

Leukemia and lymphoma are specific cases of blood cancers where HSC treatments were first clinically applied. These cancers result from the uncontrolled production of white blood cells, and include acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), chronic myeloblastic leukemia (CML), Hodgkin's disease, multiple myeloma, and non-Hodgkin's lymphoma (Thomas and Clift, 1999; "Hematopoietic Stem Cells", 2005).

Some clinical studies have been performed over the past decade to compare the effect of various types of HSCs for treating these particular types of blood-cancers. The study of Utsunomiya et al (2001) reviews the outcome of a clinical trial of allogeneic stem cell

transplantation (allo-SCT) on 10 Japanese patients who had adult T cell leukemia/lymphoma (ATL). Allo-SCT is only an option for patients with a human leukocyte antigen (HLA)-genetically-identical sibling. Some of the symptoms of ATL are lymph node swelling, enlarged liver and spleen, skin lesions, and irregular peripheral blood lymphocytes (i.e. convoluted or lobulated nuclei). Human T-lymphotropic virus type I (HTLV-I) is one of the documented causes of ATL. During the clinical period of ATL, patients usually suffer severe infectious diseases since their immune system is highly compromised. Conventional chemotherapy treatment is poorly effective for ATL due to a high rate of drug resistance for the cancer cells. Other alternative treatments have not yet been established (Utsunomiya et al, 2001).

In this study, the 10 patients included seven males and three females. Nine of them received allo-SCT from their HLA-identical siblings, while one patient received HLA from an unrelated donor. Eight patients had acute ATL, one a lymphoma, and one chronic ATL. Compared to the general medial survival rate for patients with acute or lymphoma-type ATL during conventional chemotherapy or allogeneic bone marrow transplantation (allo-BMT), the medial survival rate for patients in this trial was significantly greater, 17.5 months (range 3.7 to 34.4 months) versus 3 to 9 months with conventional treatments. In addition, the relapse rate was relatively lower. Only two patients relapsed during clinical ATL, and four patients died because of complications (GVHD, pneumonitis, gastrointestinal bleeding, or renal insufficiency). Two of the four died because their donors actually were positive HTLV-I carriers, which strongly affected the overall outcome of the treatment efficiency. The outcome of this clinical study suggests that allo-SCT can become a more effective treatment if post-transplant complications can be limited (Utsunomiya et al, 2001).

In another study, Korbling and colleagues (1995) performed a human clinical study on nine patients with refractory leukemia or lymphoma using peripheral blood HSCs for allogeneic transplantation (allo-PBSCT). This study focused specifically on the issues of unstable engraftment durability, and the risk of GVHD compared to allo-BMT. All the donors were patients' HLA-genetically-identical siblings. The drug filgrastim was subcutaneously administered to each donor to stimulate the mobilization of HSCs into peripheral blood. The authors found that the neutrophil recovery rate after allo-PBSCT was not significantly different from that the control group of allo-BMT, however there was a higher engraftment durability, higher rate of survival, and lower risk for acute GVHD. Only one patient died of parainfluenza pneumonia while the other nine remained in complete remission. The acute GVHD occurred mostly on the skin and was manageable with medication and close follow-up. This favorable outcome indicates that the use of peripheral HSCs in allo-PBSCT provides great potential for controlling post-transplant complications (Korbling et al, 1995).

By studying the efficiency of each type of treatment, scientists are learning to improve the outcome of the treatment and to minimize possible risks. The above studies have shown a possibility of reducing the risk of GVHD by using HSCs from peripheral blood that offers more potential than from HSCs from traditional bone marrow. GVHD has been a major concern for patients who receive HSCs, even from matched donors. Further knowledge of different sources of HSCs will help to overcome this challenge to improve the survival rate for these patients.

***HSCs and Umbilical Cord Therapy***

A more recent application for HSCs involves their isolation from umbilical cord blood. Figure-1 illustrates how HSCs from the umbilical cord can be stored and later used for a patient's

autologous stem cell transplantation (auto-SCT) for leukemia treatment. Using the patient's own purified filtered stem cells can help reduce the risk of transplant rejection, limit complications, and shorten the patient's treatment period. Due to the success of cord HSC treatments, by 2006 more than 20 public banks to collect, store, and distribute donated umbilical cord blood or hematopoietic progenitor cells (HPCs) existed in the United State. Recognizing the success of this technique, a national umbilical cord stem cell bank has been recommended by the U.S Congress to establish a coordinated system with well-structured regulations and oversight. In states with fewer restrictions on stem cell research, such as California and Massachusetts, there has already been an increase in the number of private stem cell banks for collection, storage, and distribution services. New England Cord Blood Bank and ViaCord are examples of large cord companies located in Boston. Countries such as Canada, Australia, New Zealand, and the U.K. also have both national and private banks (Open Directory Project, 2008).

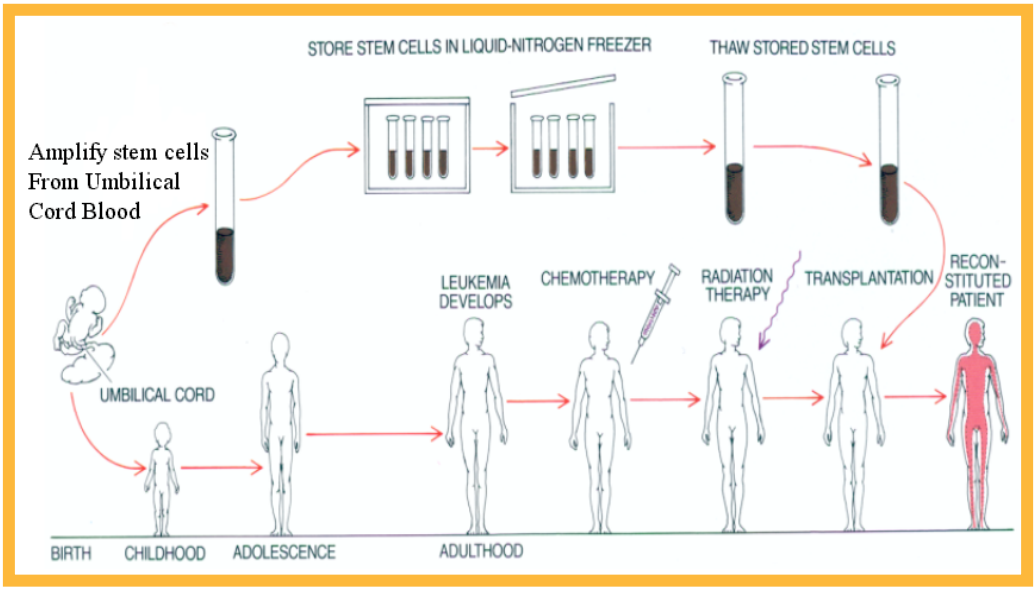


**Figure-1: Umbilical Cord Blood HSCs.** This diagram describes the isolation of umbilical cord blood from a donated cord (upper left), its amplification (upper center), and subsequent perfusion into a patient following chemotherapy or radiation therapy (upper right). Cord HSCs represent an excellent alternative source for these cells compared to bone marrow or peripheral blood. (Verfaillie, 2002)

## NEURAL STEM CELL APPLICATIONS

The recent discovery of the regenerative capability of adult neural stem cells (NSCs) gives hope to possibly repairing damage from neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, stroke, or brain and spinal cord injuries.

### *Treatment of Parkinson's Disease Using NSCs*

Parkinson's disease (PD) is a neurodegenerative disease that results in a loss of dopaminergic (DA) neurons in the *substantia nigra* area of the brain. The neurotransmitter dopamine plays an important role in regulating the nerves that control body movement. Therefore, movement difficulties are the main signs of PD. Once administered into the body, Levodopa will be converted into dopamine. So far, it is the most effective drug to help treat symptoms of PD. However, the drug initially helps most patients, but the side effects of the drug increase over time and the drug becomes less effective (Levodopa Information, 2008). A more promising approach to treat PD is to use cell therapy to replace DA neurons to reverse the cell damage caused by this devastating disease. The concept is to implant cells into the brain that can replace the lost dopamine-releasing neurons. Cells tested in animal models for PD include embryonic stem (ES) cells, adult neural stem cells (NSCs), and fetal tissue transplants from the ventral mesencephalon (VM). In humans, only a very limited number of VM tissue transplants have been tested so far (Morizane et al., 2008). In recent years, other cells have also been tested in animal models, including NSCs derived from fibroblasts, and HSCs derived from umbilical cord and bone marrow (Figure 2).

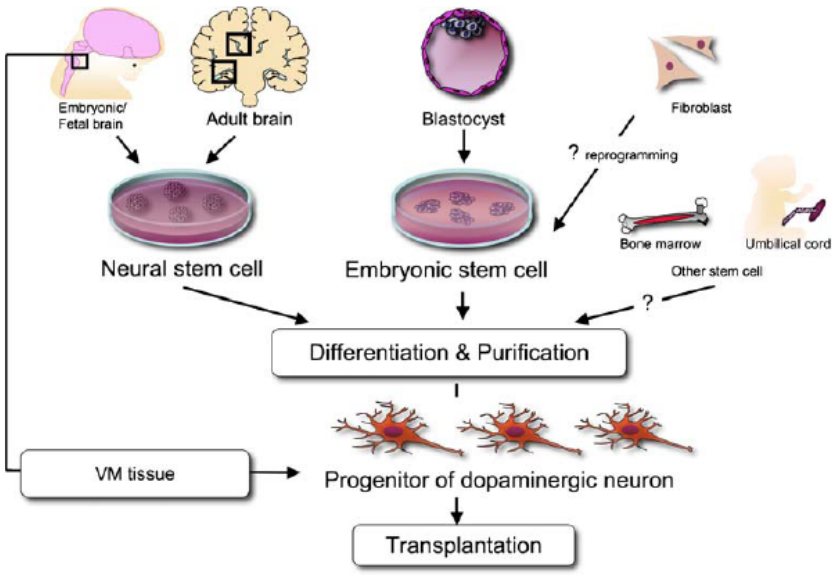


**Figure-2: Strategies for the Cell Therapy of Parkinson's Disease**. This figure shows various possible transplant donor sources for PD including, from left to right, ventral mesencephalon tissue grafts, neural stem cells derived from fetal brain or adult brain, embryonic stem cells derived from blastocysts or induced fibroblast cells, and hematopoietic stem cells. The primary goal is to obtain high enough numbers of DA-neuron progenitors that are functional in the host brain and have no risk of tumor formation (Morizane et al., 2008).

With respect to *animal models* for PD, fetal tissue graft treatments have been investigated for decades now. In the early 1970s, it was found that fetal tissue transplanted directly from the developing nigro-striatal pathways of embryonic mice into the anterior chamber of an adult rat's eye continues to mature into fully developed dopamine neurons. In the early 1980s, researchers extended these observations to investigate transplantation of fetal tissue into the damaged areas of the brains of rat and monkey PD models. Researchers were able to demonstrate that a functional recovery depended on the implanted neurons growing and making functional connections at the appropriate brain locations (Dunnett et al., 2001).

*Human trials* using tissue transplants have not yet shown significant improvements in PD symptoms. The validity of early 1990's trials has been questioned, including lack of a control group, a small sample size, and differences in chosen criteria (Björklund et al, 2003). However, in 2001, a double-blind, fully controlled, large sample size, three year, NIH-funded clinical trial

using VM tissue from aborted fetuses was performed which showed improvement in patients below 60 years of age (Freed et al., 2001). The trial included severe PD patients who underwent sham surgery with no drill penetration through the dura mater but penetrated the frontal bone. All patients received standard PD drug levodopa prior to the study and had shown some responses to it. No immunosuppressant was needed in the trial. The authors could not conclude that their cell therapy technique was more effective than the control in the older group of severe PD patients over 60 years old, did show some improvement in the group below 60 years old (Freed et al, 2001). Patients were asked to record their Unified Parkinson's Disease Rating Scale (UPDRS) Scores as one of the measurement methods for their improvement; the higher the score, the worse the Parkinsonism symptoms (range from 0-176). UPDRS scores improved 34% in the younger group compared to 16% in the total (young plus old) transplant group. Men showed better improvement than women. There was no difference in adverse events recorded from the tested group versus control (Freed et al, 2001). The survival of DA neurons and their growth was measured by the uptake of 18F-Fluorodopa (a dopamine analog) via positron-emission tomographic (PET) scans. Figure-3 shows an increase in the uptake of 18F-Fluorodopa (red) in the bilateral regions of the putamen in the brain twelve months after the surgery (Figure-3, upper right). Before the surgery, uptake occurred only in the caudate region of the PD patient. The sham surgery group (Figure-3, lower) showed no change of uptake.

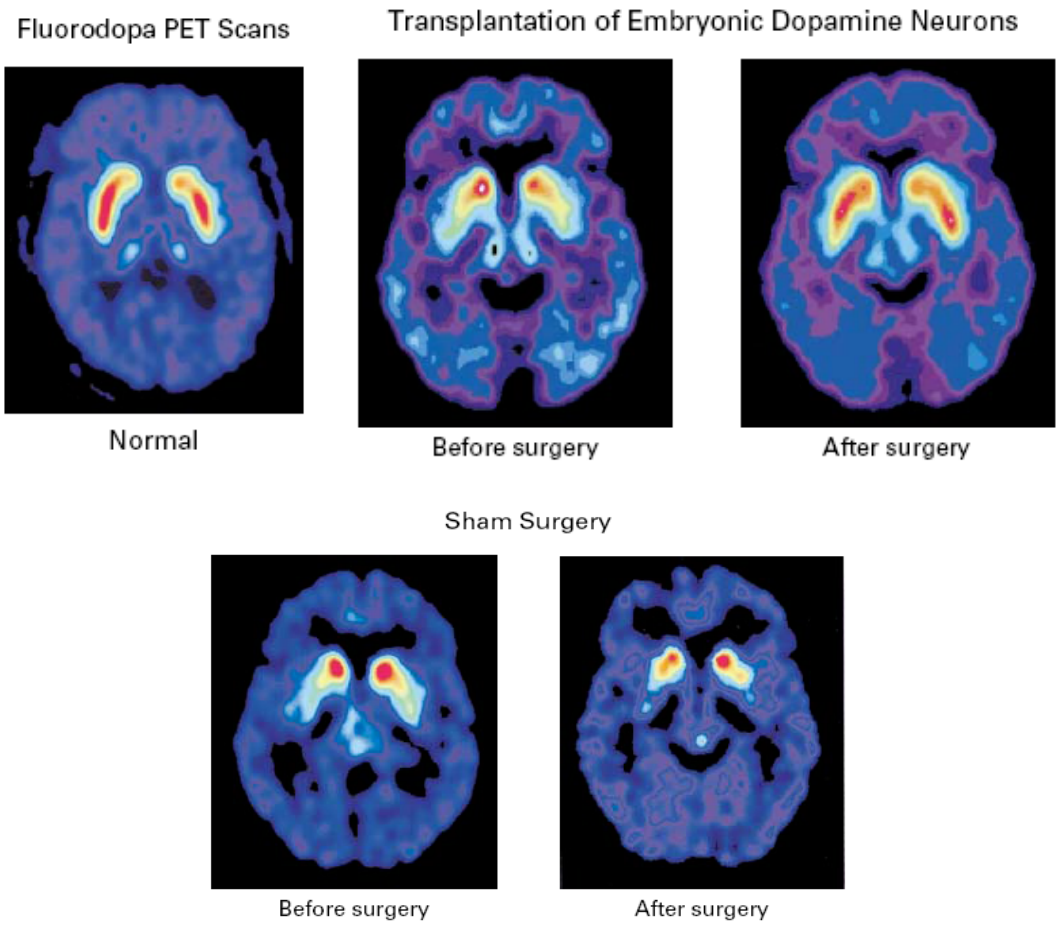


**Figure-3: The Survival of Transplanted Fetal Tissue Grafts in Human Parkinson's Patients.** Fluorodopa PET Scans indicating change in 18F-Fluorodopa Uptake in the Brains of Patients with Parkinson's Disease after transplantation (Freed et al, 2001).

The survival and growth of neurons were observed for another three years after the transplantation, and the authors concluded that the transplantation was successful for the younger group and the treated PD patient's had restored DA neurons. The authors indicated that less severe PD patients might benefit more from the cell transplantation since all of the patients in their study were severe. They also suggested transplanting more cells into the putamen with less injection sites to minimize trauma. Imaging studies might also help monitor which individual patient responds positively to the therapy (Björklund et al, 2003).

Takagi (2005) showed that recent treatments with L-dihydroxyphenylalanine (L-DOPA) *combined with* fetal DA neuron transplantation have not been very effective due a high-risk of post-transplant complications (including involuntary movements or dyskinesia), a limited number of donor cells, and a lack of stability of the donated fetal brain tissues. Other alternative cell sources should be investigated further to reduce these complications for a better treatment outcome.

With respect to ES cells, most of the PD success stories are for animal models of the disease (Bjorklund et al, 2002; Kim et al, 2000; Studer et al, 1998; and Wernig et al, 2008). While the use of ES cell lines has been limited, HSCs from stored cord blood or from a patient's own bone marrow might offer a promising treatment for PD as well as other neuronal diseases (Verfaillie, 2002; and Nikolic et al, 2008).

*Treatment of Alzheimer's Disease Using NSCs*

Another related neuronal disease that is increasingly common and is known to act by killing brain cells is Alzheimer's disease (AD). AD is the most common progressive dementia and is pathologically characterized by deposition of amyloid-β peptide (Aβ) in the brain parenchyma (Nikolic et al, 2008). Scientists still do not fully understand the causes of this destructive deposition pathway, and this limited understanding is a major barrier to the discovery of truly effective and potent therapies that might cure or mitigate this troublesome neurodegenerative disorder (Goldstein, 2005). Recently, there has been a great interest in using human embryonic stem cells in the fight against AD due to their regenerative capacity, however to date little animal and no human clinical trials have been performed for stem cells and AD.

A study done this year by Nikolic et al (2008) shows that human umbilical cord blood cells (HUCBCs) possess a unique immunomodulatory potential. HUCBCs have been shown to "produce a number of neurotrophic factors and cytokines that modulate inflammatory responses, including nerve growth factor, colony stimulating factor-1, thrombopoietin, and IL-11". It has been shown that the modulation of immune responses by diverse strategies including Aβ immunization, nonsteroidal anti-inflammatory drugs, and manipulation of microglial activation states can reduce Alzheimer's disease (AD)-like pathology and cognitive deficits in AD transgenic mouse models. These cells are hypothesized to possibly alter AD-like pathology after infusion into a transgenic mouse model of AD. The authors reported a reduction in Aβ levels or amyloid plaques after the injection of HUCBCs, indicating that these cells can help reduce AD-like pathology through suppression of deleterious inflammatory responses involving the CD40 pathway (which involved in the Aβ-induced proinflammatory microglial activation) (Nikolic et al, 2008). The results also show an improvement in the life spans of the AD mice. As more research is completed, further knowledge of this new stem cell approach can be refined.

## OTHER THERAPEUTIC APPLICATIONS

### *Mesenchymal Stem Cells*

In addition to containing HSCs, bone marrow also contains mesenchymal stem cells (MSCs). MSCs were first identified in the pioneering studies of Friedenstein and Petrakova in 1966 to isolate bone-forming progenitor cells from rat marrow. MSCs were found to be located within the stromal compartment of bone marrow, and have the capacity to differentiate into cells

of connective tissue lineages, including bone, fat, cartilage and muscle (Figure-4). The therapeutic use of marrow-derived MSCs has been reported recently in cardiovascular repair, spinal cord injury, and bone and cartilage repair in animal models (Barry and Murphy, 2004). Local delivered MSCs can generate *de novo* myocardium, indicating that MSC therapy might be useful in treating human coronary artery disease (Barry and Murphy, 2004).

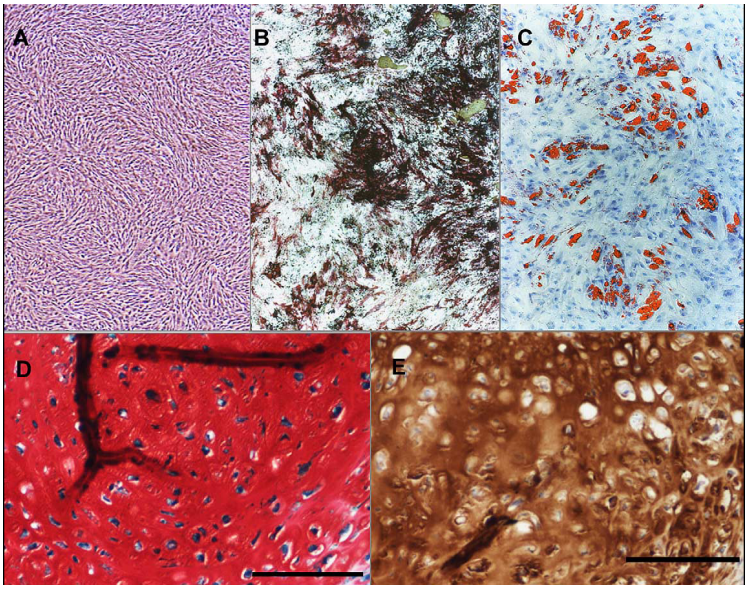


**Figure-4: The Differentiation of MSCs Into Various Tissues**. Undifferentiated MSCs grown in monolayer culture (A) and after differentiation along the osteogenic (B), adipogenic (C) and chondrogenic pathways (D) and (E). Cell differentiation is these cultures was observed following staining with von Kossa (B), Nile red O (C), Safranin O (D) and by immunostaining with an antibody specific for type II collagen (E) (Barry and Murphy, 2004).

In 1999, a study done by Gussoni and his colleagues showed that murine MSCs can be induced to express dystrophin in association with the muscle fiber sarcolemma when injected into the quadriceps muscle of *mdx* mice. This is considered as a potential direction for therapy to treat the devastating condition of muscular dystrophy. In another study, after β-galactosidase-expressing human MSCs were injected into the left ventricle of CB17 SCID/*beige* adult mice, the labeled cells were found to disperse throughout the myocardium and expressed desmin,

cardiac-specific troponin T, α-actinin and phospholamban, all indicative of differentiation of the engrafted cells to a mature myocardial phenotype (Toma et al., 2002). MSCs have also been shown by Ortiz et al. (2003) to engraft at high levels in lung tissue following exposure to bleomycin, and to offer protection against bleomycin-induced lung injury, including inflammation and collagen deposition.

Currently, most clinical data has supported the therapeutic efficiency of transplanted MSC therapy but additional information is necessary to understand the mechanisms of engraftment, homing, and *in vivo* differentiation of these cells. Further studies should explore other methods for better tissue-specific delivery of cells to improve the long-term effect of the therapy (Barry and Murphy, 2004).

*Adult Cardiac Stem Cells (CSCs)*

Adult cardiac stem cells (CSCs) (Figure-5) have been shown in animal models to differentiate into multiple cell types in the heart, including cardiac muscle cells, indicating that the adult heart still has the ability to differentiate into functional cells and tissues (Segers and Lee, 2008). This alternative cell-based therapy does not have any of the ethical concerns of ES cells, and may help treat cardiac related diseases (Segers and Lee, 2008).

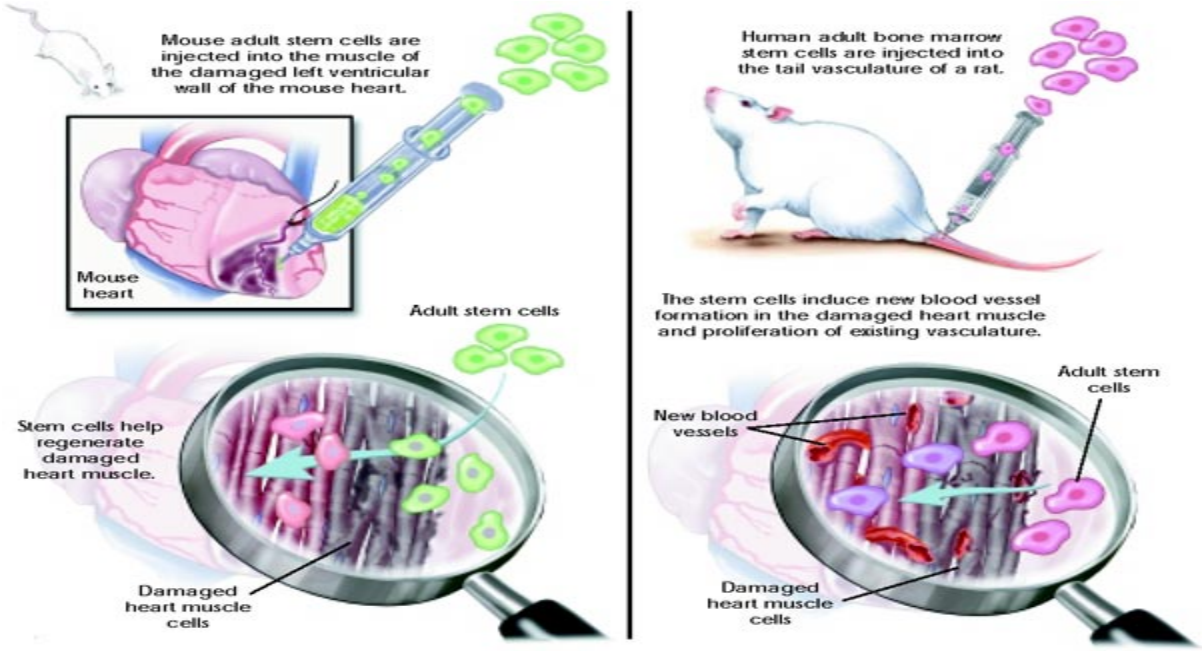


**Figure-5: Heart Muscle Repair Using Cardiac Stem Cells or HSCs.** This figure shows the repair of heart muscle in a rat model for heart disease using either adult cardiac stem cells (upper left) or adult bone marrow HSCs (upper right) ("Can Stem Cells Repair a Damaged Heart", 2005).

In 2005, Laugwitz and colleagues at the University of California discovered a rare cardiac progenitor cell called isl1+ cells in the atrium of the human newborn's heart. These cells can fully differentiate into mature heart muscle while in fetal growth stage. This extraordinary finding brings hope for potential therapeutic treatments of various newborn cardiac diseases, and to replace damaged heart muscle cells in people suffering heart attacks.

Much progress in treating heart damage using HSCs in many rodent studies has led researchers to conduct human trials. Small trials have been implemented in which patients were injected with their own HSCs to avoid transplant rejection. However, the findings from those studies were mixed (Schächinger et al., 2006). Other human studies still have not found much improvement compared to rodent studies, with no statistically significant difference among the treated group and the non-treated group (Lunde et al, 2006).

In conclusion, the experience learned from these cardiac studies suggests that more studies need to be performed while controlling factors that can affect the outcomes, such as the stage of the disease, and the number of transplanted cells delivered at targeted sites. It was observed that most patients from the above human trials were at the advanced stage with very low chance of recovery. It seems that while both adult and ES cells still hold a great interest for treatment of these dangerous illnesses, prevention through lifestyle risk reduction should always first be taken into account to avoid suffering from heart disease.

*Treatment of Diabetes Using Stem Cells*

Diabetes mellitus is a disease in which pancreatic beta cells become destroyed preventing the production of insulin. Diabetes is currently the seventh leading cause of death in the United States, with nearly 200,000 deaths reported each year. The American Diabetes Association estimates that nearly 16 million people, or 5.9 percent of the United States population, currently have diabetes ("Stem Cells and Diabetes", 2005). Animal research has indicated stem cells may also be used to treat this disease. Additionally, the limited amount of cadaver-donated islet tissue available for transplant has focused on using renewable stem cells for treatment. A substantial body of research in animal models for diabetes indicates that either ES cells or iES cells induced from fibroblast cells might be successful (Roche et al, 2003; Lumelsky et al, 2001; and Itkin-Ansari et al, 2003).

Despite the current controversial issues surrounding ES cells, their self-renewal and differentiation ability can be applied to create insulin-secreting structures similar to pancreatic islets (Soria et al., 2001a). Soria et al (2001b) studied the ability of transplanted mouse ES cells to restore beta-like insulin-secreting cells and normal blood glucose levels in diabetic mice

(Figures 6 and 7). These immortal ES cells offer a wide range of advantages compared to conventional pancreatic transplantation, as they can be produced in large quantities, at relatively low cost, and with relatively low risk for infection or complications. The insulin producing cells can also easily be purified *in vitro* by selecting cell lineage specific surface markers (in this case, for insulin-containing cells) along with drug resistant genes (Soria et al, 2001a,b).

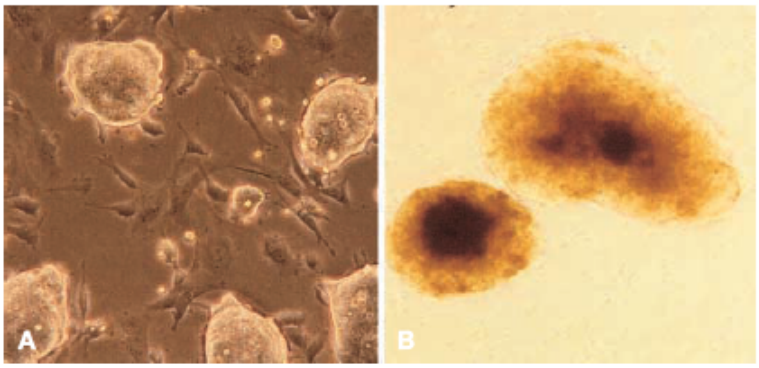


**Figure-6: Differentiation of Mouse ES Cells Into Insulin Producing Cells.** Panel A: Undifferentiated ES cells (light color) growing on a feeder layer of mitotically inactivated mouse fibroblasts (dark color). Panel B: Production of insulin-secreting cells (brown) after undergoing 3 wks of selection and maturation (Soria et al, 2001b).

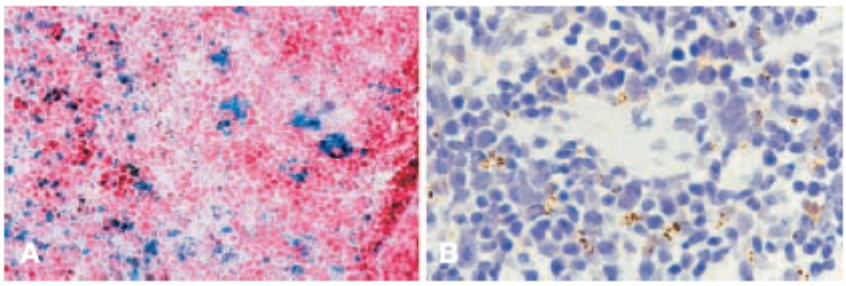


**Figure-7: Analysis of Insulin Producing Cells 4 Months Post-Transplant.** Panel A: X-Gal staining showing the presence of cells transfected with drug resistence genes. Panel B: Visualization of insulin producing cells 4 months post-transplant using insulin antibody (Soria et al, 2001b).

## Chapter-2 Conclusion

Scientific studies over the last 30 years have shown that stem cell therapy has the potential to cure some devastating diseases, however more research needed before cell-based

therapy can broadly be applied in clinical practice. This chapter has discussed the potential of stem cells through numerous studies over the last few decades. Stem cell treatments are still in their premature stage that involves complex mechanisms we do not yet fully understand. The process may require many more years to practice in clinics. With respect to future research, we can be certain that with less restrictive legal regulations, more federal support, open-minded public awareness, and worldwide collaboration, many current obstacles both technical and social can be overcome.

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# Chapter-3: Stem Cell Ethics

Perhaps more than any other new technology in recent memory, the topic of stem cells is as controversial as topics get, focusing on the very meaning of life itself and when it begins. Although the vast majority of people are in favor of working with adult stem cells (ASCs) because no embryo is destroyed, work with embryonic stem (ES) cells is highly controversial based on the way those cells are obtained. The purpose of this chapter is to discuss the ethics of stem cell research, as one way of documenting the effects of this controversial technology on society.

**Ethical Overview**

Although stem cells have been researched in animals since the mid 1960's, the public's awareness of stem cells greatly increased in 1998 with the discovery of a method for isolating and growing *human* ES cells (Thompson et al., 1998), thus the topic has received much recent debate. The ethics of the destruction of an embyro has been discussed extensively since the early 1970's when human IVF embryos began widespread use.

There are few serious ethical concerns with extracting adult stem cells from bone marrow, skin, or umbilical cords, so long as donor permission is obtained. Although the most potentially useful stem cells are still considered to be ES cells derived from early human embryos because they are pleuripotent, during the process of extraction of ES cells from the inner cell mass of a blastocyst the embryo is usually killed.

Opinions on when personhood is actually achieved can be divided into two major groups: pro-lifers and pro-choicers (Robinson, 2002). Most pro-lifers believe that human personhood starts at the conception, and the pre-embryo receives a soul, whereas pro-choicers think that human personhood starts after gestation. Pro-lifers suppose that the extraction of stem cells from the embryo is a form of experimentation on human bodies or a murder.

Ethicists and lawyers that oppose ES cell research believe that an embryo is a human being that has a soul. Extracting stem cells from the embryo is a murder. In "Human Stem Cells. Ethical Concerns: extracting stem cells" stem cell research was compared to manufacturing of lampshades made of human skin during the Nazi holocaust (Robinson, 2002). Even though the lampshades might have been very useful, the person was killed during the production. Moreover, extraction of the initial stem cells from the very first embryo ever used for these purposes was a violation of NIH policy, and the following usage of the cells is not only an immoral act, but also a violation of government regulations (Robinson, 2002). Robert George, a professor of moral and political philosophy at Princeton says, that "embryos possess the epigenetic primordia for internally directed growth and maturation as distinct, self-integrating, human organisms. Because of this, he regards an embryo as being already—and not merely potentially—a living member of the human species" (Robinson, 2002).

Lawyers and medical ethicists that are in favor of using ES cells argue that these cells are not capable of growing into a complete person. "They cannot be considered a form of human life since they can grow only into a certain organ but not a complete human being" (Robinson, 2002). While ES cells have an enormous promise to save millions of lives and to treat diseases, most of the spare embryos in fertility clinics will die anyway following donor consent to end the IVF process, operator error, or equipment malfunction. Linda Bevington, Director of Research

for the Center for Bioethics and Human Dignity stated: “A lot of proponents of ES cell research note that these embryos are extras, and they'll never be implanted, and they're doomed/destined for destruction anyway, so we might as well just take their ES cells and create some therapies and some good (Robinson, 2002). However, it is possible to adopt those embryos, termed 'rescue surrogacy,' and so those embryos aren't necessarily destined for destruction. They can be implanted, and a healthy baby can be born" (Robinson, 2002).

Various religious communities have interpreted key stem cell issues in view of their own beliefs, but some large religions have never come to consensus within their own religion. Key topics include whether the 5-6 day old blastocyst that is destroyed to obtain ES cells has the same moral status as an individual. Which embryos if any should be used for ES research? Are excess embryos created at IVF clinics acceptable for use with parental consent? Should we allow egg donors to get paid? Should we allow the embryos to become genetically engineered if it saves lives? Should we allow the patenting of ES cell lines by private companies? Who should have access to these expensive treatments? These key questions will be discussed in this chapter.

**Oocyte Donors**

In February 2005, Woo Suk Hwang's team (Figure-1) at Seoul National University published their work, where they claimed that they had derived eleven patient–specific ES cell lines (Hwang et al., 2005). This process involves the use of somatic cell nuclear transfer (SCNT) in which the patient’s skin cell nucleus is microinjected into an enucleated egg, and the embryo is grown to the blastocyst stage where ES cells are extracted that are genetically identical to the patient. SCNT previously worked in mice, but not in humans. In their initial experiments,

Figure-1: Photo of Dr. Hwang Woo-suk and his stem cell team at Seoul National University. http://msnbcmedia4.msn.com/j/msnbc/Components/Photos/060109/060109_suk_vmed_7p.widec.jpg

Hwang and his colleagues used cells from a single female donor to try to create ES cell clones. An oocyte nucleus was extracted and injected back into an enucleated egg from the same woman. Since both the nuclei and the egg belonged to one and the same person, the scientists were not able to "rule out the possibility that the ES line was derived from the parthenote". But in his later experiments, Hwang claimed that he had overcome this concern by placing nuclear material from one volunteer into the egg of another volunteer, therefore creating an ES clone matched to the nuclear donor. This was ground breaking, but later it was discovered that much of his data was fabricated (Charmany, 2004). This was just the first of many ethics issues to arise. In the subsequent investigation into his lab, it was determined that a high number (20) of oocytes were used, and the women donors were paid about $ 1,430 each. Moreover, two of his junior lab workers donated their oocytes under pressure (Holden, 2005). However, Dr. Hwang in his interview in *Time* magazine in December 2005, officially claimed that he was never aware of the sources of oocytes. "What we receive is the oocyte, not donor information" (10 Questions for Dr. Hwanf Woo Suk, 2005).

This paper stimulated a widespread ethical debate that continues to this day, about who should provide the eggs, and whether the donors should be paid. The least controversial stance on egg donation, which most U.S. states currently allow, is for the donation of excess *in vitro* fertilization (IVF) embryos. These embryos were originally created for purposes of reproduction

not research, the donors are not paid, and the donors provide their written consent. Since the advent of human IVF technology in the early 1970's, excess embryos are usually destroyed once the couple is done having babies, so why not allow their use to try to save lives instead of being destroyed.

**Stem Cell Recipients**

When human ES cells are derived, to test their plasticity, it is necessary to inject the cells into animal or human tissue to see how the cells adapt and behave in natural environment. The usage of these two types of recipients brings up serious ethical questions. When animals are injected with human ES cells, sometimes a chimera forms that is a combination of human and animal tissues. This process makes most people feel uncomfortable, but some nations still permit this kind of experimentation due to the large amount of useful information obtained. The second type of recipient is people suffering from different diseases. Even though it might seem to be less controversial, human rights organizations still strictly control the use of these patients (Charmany, 2004).

**Universal Access to Stem Cell Therapies**

Many scientists and ethicists have shown concern that potentially expensive stem cell therapies might not be available to under-represented minorities, since it is usually thought that they have less financial capital. But as is typical of any new therapy, it may begin expensive, but eventually costs come down and this issue may diminish over time. In the Stem Cell Primer (Charmany, 2004) they suggest two different ways of overcoming this problem. The first is to use a "maximum coverage approach" to establish universal stem cell banks that would provide

ES cells genetically engineered to be immunologically compatible with any ethnic group. The alternative way is to move forward using an "ethnic representation strategy", which would provide ES cells with HLA types for every ethnic group (Charmany, 2004).

Another approach that will maximize access to stem cell therapies, is to use more widely available adult stem cells, such as umbilical cord blood hematopoietic stem cells (HSCs), since banks storing this type of blood can serve the largest number of individuals. And since this blood is obtained from a newborn baby who has an immature immune system, cord blood HSCs are far less likely to stimulate GVHD (graft versus host disease) than bone marrow HSCs. Moreover, cord HSCs may show high plasticity, and are able to differentiate into other tisues besides blood. In August 2005 a group of scientists published a report showing their capability to expand cord blood cells into those with ES cell properties. This team managed to establish a protocol that offers a large supply of cells that do not require human/animal chimeras, or the destruction of an embryo (Charmany, 2004).

**Genetic Modification and Stem Cell Research**

Genetically modifying stem cells might be used to improve symptoms related to genetic diseases via therapeutic transplants expressing the normal version of the mutated gene, or for developing embryos with inactive genes to help understand the functions and roles of specific proteins (Charmany, 2004). However the genetic manipulation of embryos has been a highly controversial topic since it was first performed by Mengele during World War II. In perhaps the most infamous uses of genetically modification of human cells, at Auschwitz/Birkenau concentration camps, doctor Joseph Mengele performed horrific experiments on people with a goal of creating the best "Aryan" race through genetic modifications (Weber, 1985).

In a more positive use of genetic modification, HSCs have been modified to include therapeutic genes to treat patients using gene therapy. Gene therapy experiments have had great success in animal models and have had some minor success in humans. This technique is viewed by many researchers as life saving medicine (Charmany, 2004). Gene therapy is not yet a perfect procedure, some tests using viruses as vectors caused a mutation in the patient's B cells, and in others it caused anaphylactic shock. One of the most important factors to be taken into account is to ensure no modifications occur to the patient's germ cells, which would permanently distribute the modification to all cells of the patient's offspring. One way to avoid this happening was suggested by Mario Capecchi at the University of Utah, who proposed using artificial chromosomes to allow the scientists to insert genetic information and turn it on or off whenever desired (Charmany, 2004). Reminiscent of Mengele, the idea of creating a "perfect" human being is appealing to some.

Another ethical concern of human genetic modification can be shown in the "Muscle Boy" example. A gene mutation that affected production of a growth regulator caused extreme muscle development and strength. Soon thereafter, to obtain similar muscular effects, a few high school athletic coaches contacted the scientists and asked for help (Charmany, 2004).

**Religious Influences on Stem Cell Research**

The subject of stem cell research is widely discussed by representatives of all major religions. Countless debates have been published and stated in several past decades, however the consensus between the religions on the topic of stem cell research (especially ES cell research) have never been reached. In order to determine whether ES cells should be used, it is necessary to determine the ontological status of the human embryo.

**Judaism**

Representatives of Judaism believe that human bodies belong to God, and we have them on loan throughout our life. Since God is the owner of our bodies, he can impose certain conditions on their use. One of these requirements is that people have to search for ways to preserve human life and health. Hence, we are obligated to find and develop new cures for human diseases. This kind of tradition approves both natural and artificial ways of overcoming illnesses (Dorff, 2002).

According to Jewish biblical and Talmudic laws, the status of human as a person is acquired with time, progressively, not at fertilization (Cousins, 2004). This means that according to the Talmud, during the first forty days of gestation the human fetus is "as if it were simply water", implying that human status is not given to a fetus until it reaches forty first day (Dorff, 2002). Because ES cells are derived from 5-6 day old embryos with the same status as water, Judaism supports the use of ES cells and goes beyond that to encourage it.

Indirectly supporting the destruction of IVF embryos, Rabbi Yosef Sholom Eliyashuv, one of the most influential *poseks* in Israel today, has permitted preimplantation diagnosis and the destruction of the affected zygote in cases with Fragile-X (sex-linked disease), Tay Sachs disease, and neurofibromatosis (Eisenberg, 2001). Pre-implantation diagnosis likely will be accepted in the near future by most Jewish legal experts when used to prevent serious diseases. If the pre-embryo is allowed to be destroyed after this sort of diagnosis, it certainly can be used for ES research and other life-saving work (Eisenberg, 2001). Rabbi David Feinstein also supports using spare IVF embryos (Eisenberg, 2001).

**Buddhism and Hinduism**

Even though some Hindu believers place the beginning of personhood between three and five months, the majority of traditional Hindu believers think that conception is the beginning of soul's rebirth from a previous life (Cousins, 2004). According to Buddhist teaching, it is almost impossible to assume that a particular phenomenon is unnatural. Nowadays it might be difficult for Buddhism to deal with some bioethical problems, since Buddhist ethics "does not utilize the concept of being natural" (Promta, 2004). In general, Buddhism supports the attempts to gain a new knowledge as long as the acquisition is controlled by wisdom, and wisdom is a process of practical long-term learning. Regarding ES cell research, there are many sources in the Buddhist texts saying that killing an embryo is not any different from killing an adult, meaning that the use of ES cells even for curing some diseases is the same as using the life of an adult in order to save another adult's life. However, donating somebody's life for the benefit of another is considered to be goodness, which is proved by several examples described in various Buddhist literatures (Promta, 2004).

**Islam**

In his interview given on April 2007, Muzammil Siddiqi, President of the Fiqh Council of North America states that embryonic stem cell research is supported by Islamic traditions. One of the points that he brought up to prove that ES research is not an amoral act is the fact that embryos being used for ES research do not yet have personhood. According to the beliefs in the *Quran*, life starts after forty days from fertilization, well after blastcyst formation. A clear difference between the early stages of the pregnancy (the first forty days) and its later stages was established by Muslim jurists: it is said that if a woman with an early stage pregnancy is

attacked, and the baby was aborted during the act, the criminal's punishment would be less than that of the criminal who did that act during later stages of pregnancy. And if the child was killed after birth, the criminal would be punished for infanticide (Muzammil, 2008).

The other factor that Muzammil Saddiqi pointed out is the idea that using excess embryos from IVF clinics should be supported and financed by the government, since this has fewer ethical concerns than alternative embryo donations. Muslims believe that there should be a clear distinction between "having something in the test tube or dish versus having something in the body of a human being". If the embryo is not present in its natural environment (the womb), it cannot survive and become a complete human being, hence the excess IVF embryos can be used for ES research (Stem Cell Research in Shari'ah Perspective 2007).

> "However, it is important that we establish strict rules against the misuse of embryos. Research on embryos has the potential for misuse, for instance in regards to the donors of these cells, and we should anticipate what these misuses might be, and establish safeguards against them. (For example, doctors might have an infertility client inappropriately undergo extra cycles of ovulation just so they can obtain more embryos, or they might pay women to produce embryos, or the embryos might be obtained without the consent of the donors). In making rules, the authorities should also clarify that there is a difference between the use of "spare" embryos from IVF procedures which would be destroyed regardless, compared to the deliberate production of embryos. Each year thousands of embryos are wasted in fertility clinics around the world. Such embryos should not be wasted, they should be used for research" (Muzammil, 2008).

**Catholicism**

The Roman Catholic church is one of the main embryonic stem cell opponents. Catholics believe that a "living human embryo is, from the moment of union of the gametes, a human subject with a well defined identity, which from that point begins its own coordinated, continuous and gradual development, such that at no later stage can it be considered as a simple mass of cells" (deDios, 2000). Moreover, they believe that it is not morally licit to use cloned

human embryos for therapeutic purposes. The church maintains that every single embryo (no matter how it was produced) should be given a chance to develop into a mature human being (Cousins, 2004). With respect to Catholicism, it should also be pointed out that as is the case with very large religions, not all believers agree on their stem cell stance. It is clear the Pope as church leader is against destroying embryos, but several prominent Bishops have taken stances against the Pope on this issue when lives are at stake.

Several days after Yamanaka and his team announced that they had created induced pluripotent stem (iPS) cells, President George Bush claimed that nowadays the research can be conducted "within ethical boundaries". iPS cells are adult skin fibroblast cells induced to de-differentiate into ES-like cells by inserting 2-4 key genes that function in de-differentiation. However, a week later Yamanaka told *Nature* magazine that the discovery of creating pluripotent stem cells from adult stem cells can actually bring even more ethical concerns. For example, producing eggs from the male iPS cells might allow a gay couple to produce offspring. Moreover, scientists working with iPS cells right now can be tempted to create a live, cloned human. Yamanaka's concerns about ethical issues convinced Japan's government to create a regulation forbidding "the implantation of embryos made with iPS cells into human or animal wombs, the production of an individual in any other way from iPS cells, the introduction of iPS cells into an embryo or fetus, and the production of germ cells from iPS cells" (Cyranoski, 2008).

**Protestantism**

Different Christian denominations have completely different views on the embryonic stem cell research. For instance, the American Presbyterian church accepts the idea of using

embryos for therapeutical and research purposes, while the Southern Baptist convention is strongly against it (Cousins, 2004), and Protestants believe that an early embryo should be respected as a complete human being with his own soul. According to Karl Barth, one of the twentieth-century theologians, "No community, whether family, village or state, is really strong if it will not carry its weak, and even its very weakest members" (Holland et al., 2001 pp. 142-143).

**Naturalistic Worldview**

Most people with naturalistic views value the life of an embryo, and do not support any artificial embryo technnology (Cousins, 2004). Naturalists are "for the life of any embryo over any present malady-ridden human". This is one of the reasons they do not support stem cell research (Calamaio, 2007).

The second argument naturalists have against ES cell use is it represents a sophisticated form of cannibalism. Although most people don't view cannibalism as eating an embryo, people with a naturalistic view believe that an embryo's life was ended when its stem cells were consumed by the member of the same species. And from the embryo's standpoint, "whether injected into the receiving body, or chewed up by the recipient - this is a distinction without a difference" (Calamaio, 2007). A species growing and consuming its own preborn cannot be supported by naturalists.

However, other naturalists do support IVF *reproductive* technology, growing embryos (not stem cells) for healthy adulthood. Using the rubberized womb, which they believe can be created using current technologies, people could avoid issues with alcohol damaged babies, tobacco damaged babies, drug damaged babies, or junk food damaged babies. Moreover, this

kind of method might be beneficial for women who don't want to deal with pregnancy and giving birth (Calamaio, 2007).

**Chapter-3 Conclusion**

With respect to stem cell ethics, most of the attention has been paid to ES cell research, mainly because obtaining ES cells requires destruction of an embryo. None of the major world religions is against working with adult stem cells, especially when human lives can be saved. For many people, ES research conflicts with their cultural and religious views, since it involves destruction of potential life. For others (especially Judiasm and Islam who argue that life begins well after the blastocyst stage), the potential of ES research to provide cures and treatments for debilitating diseases is more important. As for the author of this IQP chapter, the possibility of finding a cure for serious illnesses such as diabetes, Alzheimer's disease, Parkinson's disease, heart disorders and many others, overrides most of the ethical and religious concerns, so long as strong oversight is used to ensure egg donors are not paid money and that excess IVF embryos, normally slated for destruction, are used as the primary source of embryos to derive ES cell lines.

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# CHAPTER 4: STEM CELL LEGALITIES

Research on human embryonic stem cells (hESCs) offers much promise for understanding and treating disease that benefits hundreds of thousands of people, however as discussed in Chapter-3, because their derivation destroys an embryo these cells have strong ethical concerns. As is the case for most controversial technologies, laws have been enacted to govern ES cell uses and derivations, so the purpose of this chapter is to discuss some of these laws both in the US and abroad.

With proper regulation and new ways to obtain these potential saving-life cells, hopefully the objections of hESC research can somehow be resolved in favor of the beneficial use of these cells. The U.S. policies on stem cell research seem to change every time a new President is elected. Despite numerous achievements in this promising field, and despite all the efforts to explore new sources of stem cells, the lack of federal support and funding under the current Bush 2001 legislation has left this country behind in novel discovery and practical applications. Countries such as the U.K., India, China, Australia, Canada, Sweden and some other European nations have caught up and even surpassed the U.S for the last decade on the ES topic. The new presidential election is approaching in just a couple of weeks as we are finishing this IQP report, and the future of stem cell research in this country might change dramatically depending on who takes office, especially given that the two candidates hold very different points of view on ES research. This chapter is designed to discuss the current stand of U.S. legislature at both federal and individual state levels, as well as drawing a broad picture of the worldwide view on stem cell research.

**Human Embryonic Stem Cell Research Laws in the U.S.**

***Federal laws***

President Clinton was the first president to endorse stem cell research. Under his legacy, The National Institute of Health (NIH) was authorized to allocate funds to experiments that would create new embryos specifically for research. It had opened many doors to researchers with sufficient grants for creating specific cell lines using embryos in from the IVF process (Dunn, 2005).

However, when President Bush took office in 2001, his restrictive policy reduced a great number of ES cell lines for research. Below is a statement from President Bush on August 9, 2001 allowing federal funding only on ES cell lines established before that date:

> *"As a result of private research, more than 60 genetically diverse stem cell lines already exist" I have concluded that we should allow federal funds to be used for research on these existing stem cell lines " where the life and death decision has already been made", This allows us to explore the promise and potential of stem cell research" without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life."* (Bush, 2001)

Under this policy, the NIH's Human Embryo Research Panel (HERP) was required to withdraw or review grant research that had previously been approved under the Clinton Administration. HERP was also ordered to reexamine the derivation of those existing cell lines, mainly developed from excess embryos created reproductive purposes by in vitro fertilization (IVF). Under this policy, the U.S. government currently provides no federal funding for any therapeutic cloning research for the purpose of creating hESC (Dunn, 2005).

One key assumption of this policy was that the existing number of ES cell lines would be sufficient to evaluate this new technology without having to destroy any new embryos, however the number of ES cells lines has dwindled over the years. In 2001, Bush's advisors estimated there were 64 ES cell lines (Table I).

| Name | Number of cell lines |
|---|---|
| BresaGen, Inc., Athens, Georgia | 4 |
| CyThera, Inc., San Diego, California | 9 |
| Karolinska Institute, Stockholm, Sweden | 5 |
| Monash University, Melbourne, Australia | 6 |
| National Center for Biological Sciences, Bangalore, India | 3 |
| Reliance Life Sciences, Mumbai, India | 7 |
| Technion-Israel Institute of Technology, Haifa, Israel | 4 |
| University of California, San Francisco, California | 2 |
| Göteborg University, Göteborg, Sweden | 19 |
| Wisconsin Alumni Research Foundation, Madison, Wisconsin | 5 |
| | **Total 64** |

**Table 1: Number of ES Cell Lines as of August 9, 2001**. There were 64 cell lines in existence at ten laboratories around the world (AAAS, 2007).

However, of the 9 ES cell lines listed at Göteborg University in Sweden claimed by NIH, it was found by *The New York Times* that "12 were still in early stages, 4 were still being characterized, and only 3 were characterized enough for study " (AAAS, 2007).

In 2002, a year after President Bush announced his stem cell policy, the NIH stem cell registry listed 78 eligible cell lines that met the President's criteria for publicly funded research, but only 16 of those 78 were available for federally funded use. In 2006, according to Guhr et al (2006), there were only 20 out of 71 different hESC lines listed in the NIH Stem Cell Registry available to researchers. With this limited availability of stem cell sources, it is not surprising the U.S. is falling behind in the international competition for this advanced technology.

**Presidential Candidates' Agenda for Stem Cell Research**

The upcoming November 2008 Presidential election will decide whether the doors for advanced biomedical research that existed under the Clinton legacy will be reopened. Senator Obama is a strong supporter for future therapeutic stem cell approach with promise for curing many serious diseases. Senator McCain's point of view is not much different from the current Bush administration. Below is the web release from Senator McCain's campaign to address the moral concerns of stem cell research (underscores provided by IQP author):

> "Stem cell research offers tremendous hope for those suffering from a variety of deadly diseases - hope for both cures and life-extending treatments. However, the compassion to relieve suffering and to cure deadly disease cannot erode moral and ethical principles. For this reason, John McCain opposes the intentional creation of human embryos for research purposes. To that end, Senator McCain voted to ban the practice of "fetal farming," making it a federal crime for researchers to use cells or fetal tissue from an embryo created for research purposes. Furthermore, he voted to ban attempts to use or obtain human cells gestated in animals. Finally, John McCain strongly opposes human cloning and voted to ban the practice, and any related experimentation, under federal law. As President, John McCain will strongly support funding for promising research programs, including amniotic fluid and adult stem cell research and other types of scientific study that do not involve the use of human embryos. Where federal funds are used for stem cell research, Senator McCain believes clear lines should be drawn that reflect a refusal to sacrifice moral values and ethical principles for the sake of scientific progress, and that any such research should be subject to strict federal guidelines." (McCain-Palin Campaign, 2008)

On the other hand, Senator Obama has optimistically expressed his support for this potential biomedical breakthrough as in his statement of support for stem cell research sent to President Bush in 2006. Below is his plan for future stem cell research posted on his campaign website:

> "Advance Stem Cell Research: Human embryonic stem cells have great potential for treating a wide variety of diseases and health conditions and for providing new insights into human development and disease. An Obama Administration will reverse the Bush Administration's ban on federal funding for embryonic stem cell research on cell lines created after August 9, 2001 by executive order and will allow all scientists to participate in this important new field, in accord with the rigorous ethical guidelines proposed by the National Research Council."
>
> (Obama-Biden Campaign, 2008)

**State Laws**

Although there is little support for ES cell research with federal funds, especially blastocyst preimplantation research, some states have become pioneers to use state funding and contributions from private sector for their research progress. These progressive states include New Jersey, California, Massachusetts, Wisconsin, New York, Connecticut, Maryland, and Illinois. On the hand, several states hold very strong voices opposing such research programs. These conservative states have criminalized stem cells research, including North Dakota, South Dakota, Arkansas, Louisiana, Indiana and Michigan (Figure 1).

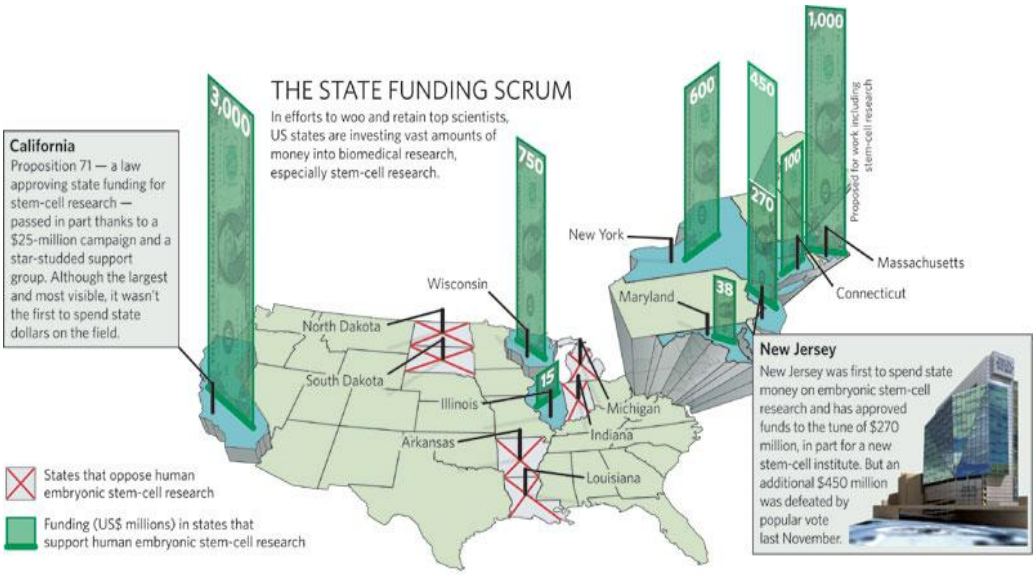


**Figure 1**- Current US States That Individually Support and Oppose ES Cell Research (Wadman, 2008).

*New Jersey*

Three years after Bush enacted his restrictive policies on stem cell research, in January 2004, Governor James McGreevey signed a law that made NJ the first state to use state funding for stem-cell research and somatic-cell nuclear transfer (SCNT) with an initial package of $10

million. Another $270 million was added into the state fund in 2006 with the approval of new Governor Jon Corzine. However, a 2007 bill did not pass for a new funding of $450 million by NJ voters because of complications in the research criteria to use of human embryonic stem cell as well as a deficit for the state budget for that year (Wadman, 2008).

*California*

In November 2004, California became the second state to support ES stem cell research by passing the Proposition 71 research initiative program of $3 billion over the period of 10 years with $300 million in funding annually (CIRM website). Following this historic proposition, the California Institute for Regenerative Medicine ("The Institute" or "CIRM") was established in the following year to monitor and distribute the grant money. Although there were some legal challenges to overcome from the beginning, CIRM has become more organized with its 29 members in the Independent Citizens' Oversight Committee (ICOC). The ICOC members are from areas of patient advocates, research institutes, and the business and general community of the state to provide better grant management with various sub-committees. Grant money of $45 million has been distributed to more than 72 applicants from 2 to 4 years since 2006. Other funding has also been awarded to graduate students, post doctorate fellows, and other major research institutions to support teaching and training projects on stem cell research (Trounson, 2008). CIRM also encourages positive competition and collaboration among institutes within the state, as well as with the other eight states that also support stem cell programs. They have increased efforts to connect major for-profit private sector companies around the country and international collaboration for joint-projects and funding to ensure major impact and success for therapeutic disease treatments (Trounson, 2008).

*Massachusetts*

In May 2007, Governor Deval Patrick proposed $1 billion in state funding for biomedical research over a 10 year period, in which about $500 million of this grant would be used to establish a research centre that would house the nation's largest embryonic stem-cell bank. The plan is to create the Massachusetts Stem Cell Bank for storage of new ES cell lines, which are also made available to all research sectors, both public and private. Major local hospitals with academic institutes have been discussed to participate in this collaboration, including Boston University, Brigham & Women's Hospital, Children's Hospital, Harvard University, Massachusetts General Hospital, the Massachusetts Institute of Technology, Partners HealthCare and the University of Massachusetts. Other projects also include bridging the NIH funding gap, Massachusetts Life Science Fellowship Grants, and funding Innovation Centers (Governor Patrick Public Release, 2008).

In another statement on November 2007, Governor Patrick showed his strong support for the investment in this life science field:

> *"We want Massachusetts to provide the global platform for bringing innovations from the drawing board to the market, from inspiration to commercialization, and from ideas to cures. Our rate of innovation in recent years has been triple that of the national average and I have no intention of letting it slip."* (Governor Patrick, Whitehead Institute, 11/10/07)

The new funding will also offer significant impact on the growth of numerous ongoing projects around the state. In September 2008, the President and CEO of the Massachusetts Life Sciences Center, Susan Windham-Bannister discussed with the WPI community her expectations for the growth and support of research and investment in life sciences in Worcester (WPI News Release, 2008). In recent years, Worcester has experienced a significant increase in the growth of many private life sciences companies, along with the expansion of a research center at the University

of Massachusetts Medical School. Worcester is also the home of WPI Life Sciences and Bioengineering Center at Gateway Park, where appropriate funding will open doors to many great achievements in many fields (WPI News Release, 2008).

It is recognized that federal funding from the NIH plays a major role in providing the fundamental resources for many basic biomedical initiatives. With limited access to NIH to fund novel hESC discoveries, it is necessary to try different approaches to obtain appropriate funding. Besides state and private funding for hESC experiments, each state should also consider investing in less controversial adult stem cell research as an alternative approach. This year, in September, an award of $900,000 was granted to a research group at WPI to explore a novel way of transforming adult skin cells into pluripotent-like cells. The possible application of this research can be used to treat tissue injury, growing new organs, and offers a potential treatment for degenerative diseases like diabetes and Parkinson's (WPI News Release, 2008).

After Massachusetts, Wisconsin and New York are the next two states with a large amount of state funding for stem cell research, with the total amount of $750 million and $600 million, respectively, in 2007 (Figure 1).

## International Stem Cell Laws

Despite numerous achievements in this hopeful field, and despite all the efforts to explore new sources of stem cells, the lack of federal support and funding under the Bush 2001 legislation has left this country behind in hESC research. Countries such as the U.K., India, China, Australia, Canada, Sweden and some other European nations have caught up and even surpassed the U.S in terms of hESC research technology and facilities. Figure-2 shows a global map of which countries are permissive or conservative on ES cell research.

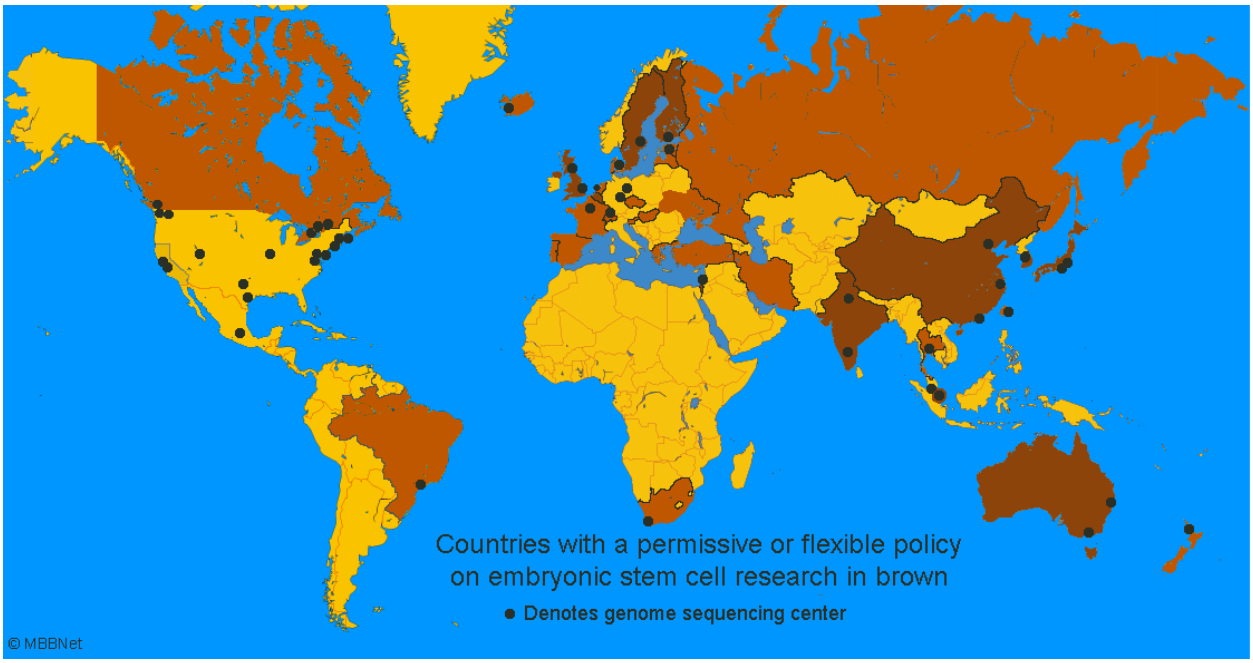


**Figure 2**: **Global Map Indicating Permissive, Flexible, and Conservative Countries on ES Cell Research.** Countries colored in dark brown have a permissive policy on human embryonic stem cell research. Light brown denotes flexible countries, and yellow denotes conservative countries. All countries have banned human reproductive cloning (Hoffman, 2007).

In Figure-2, countries colored dark brown (permissive category) accept the production of human embryos for research purposes through in vitro fertilization and/or nuclear transfer (cloning) (Walters, 2007). These countries include Australia, Belgium, China, India, Israel, Japan, Singapore, South Korea, Sweden, and the United Kingdom.

Countries colored light brown (flexible category) permit the derivation of new human embryonic stem cell lines but only by using the remaining embryos from infertility clinics (Walters, 2007). These countries include Brazil, Canada, France, Iran, South Africa, Spain, The Netherlands, Taiwan, and some others.

The remaining countries colored yellow either exhibit restrictive policies or have not established a stem cell policy. Those countries that do not permit experiments with ES cells include Austria, Ireland, Norway, and Poland. Those with less restrictive policy that do permit

research with existing human embryonic stem cell lines but not the derivation of new stem cell lines through the destruction of human embryos include Germany, Italy, and the United States (Walters, 2007).

Table-2 shows the population of the countries colored brown in Figure 2 that have permissive stem cell policies. These countries represent about 3.5 billion people or more than half of the world's population.

| | |
|---|---|
| Australia | 20.3 M |
| Belgium | 10.4 M |
| Brazil | 188 M |
| Canada | 33.1 M |
| China | 1,314 M |
| Czech Republic | 10.2 M |
| Denmark | 5.4 M |
| Estonia | 1.3 M |
| Finland | 5.2 M |
| France | 62.8 M |
| Greece | 10.7 M |
| Hong Kong | 6.9 M |
| Hungary | 10 M |
| Iceland | .3 M |
| India | 1,045 M |
| Iran | 69 M |
| Israel | 6.4 M |
| Japan | 127 M |
| Latvia | 2.3 M |
| The Netherlands | 16.5 M |
| New Zealand | 4.1 M |
| Portugal | 10.6 M |
| Russia | 146 M |
| Singapore | 4.5 M |
| Slovenia | 2.0 M |
| South Africa | 44 M |
| South Korea | 40.4 M |
| Spain | 40.4 M |
| Sweden | 9 M |
| Switzerland | 7.5 M |
| Taiwan | 23 M |
| Thailand | 65 M |
| Turkey* | 70 M |
| United Kingdom | 60.6 M |

**Table 2: The Total Population of the Permissive Countries Colored in Brown in Figure-2.** The permissive countries represent about 3.5 billion people, more than half the world's population. Population: M = million (Hoffman, 2007).

## Chapter-4 Conclusion

The pursuit and production of knowledge through advanced scientific research has transformed our lives in many ways. Although clinical applications using hESC therapy treatments have currently seen limited use in humans, the extensive experimental research on animals should be expanded to further our understanding of human diseases. The potential health benefits of stem cell technology will require a large and sustained investment in research from both the U.S federal government and individual states. California has successfully demonstrated an excellent model for such programs, with its extensive efforts to collaborate with various research institutes not only within the US but also in other countries. Massachusetts and other states' on-going progress have also proven that proper funding and less restrictive regulation will play a major role for helping provide a promising future for stem cell applications.

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# CONCLUSIONS

Research on human embryonic stem cells (hESCs) offers much promise for treating a variety of diseases that affect society. hESC treatments are still in their premature stages, and involves complex mechanisms we do not yet fully understand, thus human hESC treatments are only now beginning to be tested. However human treatments with adult stem cells (ASCs) are far more common, especially using hematopoietic stem cells, and have already saved thousands of lives. The authors of this IQP conclude that less restrictive legal regulations should be enacted in the U.S., allowing more federal support for hESC research. Open-minded public awareness and worldwide collaboration should help eliminate many current obstacles, both technical and social. Although all five major world religions support using adult stem cells, only two of the five support using hESCs. However, the authors believe that the possibility of finding treatments for many currently incurable human illnesses overrides most of the ethical and religious concerns, so hESC research should be supported. Additionally, alternatives to using hESCs cells, such as parthenotes and iES cells, must be explored based on their fewer ethical concerns. Adult stem cells should be used whenever possible, but some diseases will eventually require the use of hESCs with their greater differentiation potential. We conclude that the current U.S. legal restrictions on using federal funding to support hESC research should be eliminated to create new hESC lines to use for life saving purposes.