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Stem Cells

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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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By

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ABSTRACT

The purpose of this project was to examine the topic of stem cells and discuss the impact of this 21st-century technology on society. The paper starts by classifying the various types of stem cells and introducing their up-to-date applications for several example diseases. The report then discusses different views on the ethics of stem cells, and ends with examining the policies and regulations controlling stem cell research. From the author’s point of view, using strong oversight and regulations to prevent misuse, stem cell research including human embryonic stem cell research, and therapeutic cloning, should be permitted and funded to advance human civilization.
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PROJECT OBJECTIVES

The purpose of this IQP was to investigate current knowledge of stem cells and their applications, and to examine the effect of this highly debated new technology on mankind. Chapter-1 documents each type of stem cell, and lists how they are identified and classified. The potency of each category of stem cell is also discussed. Chapter-2 discusses stem cell applications based on five examples of important diseases, noting whether we are still in pre-clinical animal studies or have moved into human clinical trials. Chapter-3 focuses on the ethics of human embryos and stem cells, starting with a discussion about “when the life begins” and then analyzing the five major world religion stances on this controversial topic. Chapter-4 examines the U.S. government’s policies on stem cell research (federal and state), as well as international policies. Finally, a conclusion is made by the author regarding the use of stem cells, and which laws best agree with the author’s point of view.
Chapter-1: Stem Cell Types

Introduction

Stem cells are different from all other types of cells in human body. They have two very interesting attributes: 1) they are unspecialized cells that have the potential to give rise to other specialized cells in a process called differentiation, and 2) they can potentially divide and renew themselves indefinitely as stem cells (although they are not tumor cells). Unlike differentiated blood cells, nerve cells, or skin cells, which do not normally replicate themselves further, stem cells proliferate many times in their life (What Are….2005). If the cells are capable of producing unspecialized daughter cells, the parent cells are identified as having “long-term self-renewal” potential (What Are…..2005).

Scientists are greatly fascinated by stem cells due to their unique abilities. Their ability to form other tissues in the body serve as the basis of the new field of medicine termed “Regenerative Medicine”, in which stem cells are used to replace diseased tissues. But not all stem cells are alike, so the purpose of this chapter is to discuss how stem cells are categorized and their various types.

Stem Cell Categorization

There are many types of stem cells. Stem cells can be categorized by potential or by source. By potential or plasticity, they can be categorized as follows:

- **Totipotent Cells** – cells that have the ability to give rise to all the cell types of the body including those that make up the extra-embryonic tissues such as the placenta (Glossary, 2005). More specifically, totipotent cells refer to newly fertilized eggs through the 8-cell stage. When a sperm cell and an egg cell unite, they create a fertilized egg called *zygote*, and from this cell, the cells remain totipotent until approximately four days of embryonic cell division, when the cells begin to develop into pluripotent stem cells.
• **Pluripotent Stem Cells** – the cells that have the ability to give rise to all cells of the adult, except the placenta. After four days of cell division, the embryo forms into a blastocyst containing two layers – an outer layer (which later develops into the placenta), and an inner mass where embryonic stem cells reside. Though pluripotent cells can form almost any tissue, they don’t have a chance to form the placenta; therefore, they are pluripotent but not totipotent.

• **Multipotent Stem Cells** – the cells that can give rise to a few related cell types, but not as many as pluripotent stem cells. Examples of multipotent cells are hematopoietic stem cells (HSCs), neuronal stem cells (NSCs), and mesenchymal stem cells (MSCs).

• **Unipotent Stem Cells** – the cells that can make only one type of cell. These cells are usually found only in the tissue from which it originates. Skin stem cells are considered unipotent.

Though the list of “proven” stem cells continues to grow each year, below are the most researched and known stem cells.

**Embryonic Stem Cells**

Four to five days after the fusion of the sperm and egg, the embryo forms a blastocyst containing an outer layer and an inner cell mass (ICM) which has separated from the outer layer (Figure-1, upper diagram) (and Figure-2). At this point the embryonic cells are no longer totipotent and have begun one step of differentiation. The ICM cells (embryonic stem cells), if implanted, quickly differentiate into other cell types of the three primary germ layers: ectoderm, endoderm, mesoderm (lower diagram). On the other hand, if they are removed from the embryonic environment and cultured in vitro, they can retain their ability to form other types of cells while proliferating for a prolonged period (Thomson, 2006). These properties make ES cells especially attractive for regenerative medicine, as they are the easiest type of stem cell to grow in vitro.
Figure-1: Diagram of the Main Characteristics of Embryonic Stem (ES) Cells. ES cells represent the inner cell mass of the blastocyst (upper diagram), and have the potential for continuous self-renewal (middle diagram) or for differentiation into tissues of the three main germ layers: ectoderm, mesoderm, endoderm (lower diagram). (Thomson, 2006)
Figure-2: High Quality Photo of Human Blastocyst Embryo Five Days After Fertilization. The clump of cells in the 10 to 12 o'clock area is the inner cell mass (ICM) which are the ES cells that become the fetus. The trophoderm cells (TE) that will form the placenta surround the fluid cavity. The fluid-filled blastocoel cavity is in the center. (Sherbahn, 2012)

ES cells were first isolated from mouse embryos in 1981 (Evans and Kaufman, 1981; Martin, 1981) and from nonhuman primates in 1995 (Thomson, 1995). These findings led to the isolation of ES cells in humans in 1998 (Thomson, 1998; Shamblott et al., 1999). The procedure of Thomson has become the most popular method for isolating ES cells (Figure-3). Fresh or frozen cleavage-stage human embryos are produced by \textit{in vitro} fertilization (IVF), a process in which oocytes and sperm are placed together to allow fertilization to take place in a culture dish (Thomson, 2006). These embryos come from individuals following informed consent and institutional review board approval (Thomson et al., 1998); it currently is not legal in the U.S. to derive embryos solely for research purposes (discussed in Chapter-4). In the original 1998 experiment, 36 embryos were cultured to the blastocyst stage in medium (Gardner et al., 1998), and five ES cell lines were derived. All of them “maintained the potential to form derivatives of all three germ layers” both \textit{in vitro} and by generating \textit{teratoma} (a benign tumor) in mice;
therefore, the ES cells were truly stem cells (Thomson, 1998).

Figure-3: The Derivation of Human Embryonic Stem Cells. The diagram shows how IVF embryos (upper diagram) are grown to the blastocyst stage (middle diagram), from which the inner cell mass (blue) is plated and grown on a feeder layer of cells (lower diagram). (Thomson, 2006)

Scientists are continuing to investigate cellular markers of ES cells that distinguish these cells from other cell types. The research has indicated that Oct4 (Niwa et al., 2000) and Nanog (Chambers et al., 2003) are two key transcription factors that help identify ES cells; these transcription factors activate genes that help the ES cells maintain their pluripotent state. Surface markers, which are proteins that are unique to certain cell types and can be visualized using antibodies or other detective methods, are also sometimes helpful for identifying specific cell types. The human ES cell lines originally obtained by Thomson in 1998 expressed surface markers for stage-specific embryonic antigen (SSEA)-3, SSEA-4, TRA-1-60, TRA-1-81, and alkaline phosphatase (Thomson, 1998).

**Induced Pluripotent Stem Cells**
Although ES cells are very attractive in their clinical use, their use of human embryos has caused great ethical controversies. It is also difficult to generate patient-specific or disease-specific ES cells from embryos (Takahashi et al., 2007). So scientists continue to seek alternative pluripotent cells. One way to avoid ethical issues but retain the clinical potential of pluripotent cells is to induce pluripotent status in somatic cells (non-germ cells) via a de-differentiation process. Induced pluripotent stem cells (iPSCs) are somatic cells that are genetically reprogrammed to an embryonic stem cell-like state. The iPS cells derived so far appear to be similar to ES cells in many ways, including morphology, proliferation, and gene expression (Takahashi et al., 2007), and meet the defining criterion for pluripotent stem cells. The discovery of iPSCs proves that the “differentiated” state, previously thought to be irreversible, can be rolled back.

iPS cells were first reported in mice in 2006 (Takahashi et al., 2006) and one year later were derived from human fibroblasts (Takahashi et al., 2007). Takahashi and his partner generated iPSCs from adult human dermal fibroblasts by retrovirus-mediated introduction of four transcription factors: Oct3/4, Sox2, c-Myc, and Klf4. These four transcription factors reprogrammed the fibroblast cell gene expression patterns to induce pluripotency (Figure-4).
Figure-4: Induction of iPS Cells Using Four Transcription Factors. Pluripotent stem cells are immortal and have open and active chromatin structure. It is likely that c-Myc helps induce these two important properties. However, c-Myc also induces apoptosis (programmed cell death) and senescence, which are probably suppressed by KLF4. Oct-3/4 probably changes the cell fate from tumor cells to ES-like cells. To establish pluripotency, Sox2 is also required (Yamanaka, 2007).

The human iPS cells expressed many undifferentiated ES cell marker genes, such as OCT3/4, SOX2, NANOG, growth and differentiation factor 3 (GDF3), reduced expression-1 (REX1), fibroblast growth factor 4 (FGF4), and embryonic cell-specific gene-1 (ESG1) (Adewumi et al., 2007). The iPS cells also had the ability to differentiate into all three germ layers in vitro and showed lineage-directed differentiation (Takahashi et al., 2007). The iPS cells were also capable of generating major segments of tissues in mice (Boland et al., 2009), providing evidence that they are as potent as ES cells. However, some scientists are not convinced that iPS cells are as potent as ES cells. iPS cell DNA has been shown to have mutations, and the cells are less robust and slower to grow than embryo-derived ES cells (Dolgin, 2010). So, more research is required to determine whether iPS cells will be able to replace the controversial ES cells in patient therapies.

Parthenogenetic Stem Cells

Another technique used to obtain ES cells with fewer ethical concerns is through
Parthenogenesis refers to the biological phenomenon where egg development is initiated by chemical stimulus instead of fertilization. During normal fertilization, one of the two complete sets of chromosomes is expelled from the sperm and egg gametes, making them haploid; however, in parthenogenesis (asexual reproduction), both chromosome sets are retained by the egg, and it develops as if fertilized (Figure -5).

![Figure-5: Parthenogenesis](image)

Parthenogenesis is common among flies, ants, lizards, snakes, fish, birds, and reptiles. Although *Eutherians* (placental mammals) cannot naturally reproduce this way, their eggs can be artificially activated by chemicals or electricity to initiate cell division without extruding one chromosome set, so they remain diploid. If the parthenote embryo divides for 3-5 days to the blastocyst stage, ES cells can be derived from the inner cell mass. These stem cells are derived
without the need to destroy a fertilized embryo, and are referred to as “parthenogenetic stem cells” (PSCs).

Monkey parthenote embryos were first derived in 2001 (Mitalipov et al., 2001), and parthenogenetic stem cells were successfully obtained from them in 2002 (Cibelli et al., 2002). In 2003, Vrana et al. created four monkey parthenote embryos, from which one ES cell line (Cyno-1) was derived (Vrana et al., 2003). The PSCs demonstrated many features of ES cells; when cultured under selective conditions, they divided for over 2 years, and they were capable of differentiating into all three germ layers (Vrana et al., 2003). Although some scientists have reported deriving human parthenote ES cells (Brevini and Gandolfi, 2007), such findings remain unproven.

**Adult Stem Cells**

Adult stem cells (ASCs) are stem cells found in an adult tissue or umbilical cord blood that can give rise to some or all the major specialized cell types of a specific tissue or an organ. Their primary roles are to maintain and repair the tissue in which they are found (What Are …2005). Unlike ES cells which can differentiate into basically any cell type of the adult organism, adult stem cells produce a more limited number of cell types based on their tissue of origin. ASCs are also more difficult to grow in culture, and are rare in tissues, so it is hard to obtain large numbers of them for therapies. However, scientists believe that ASCs have less chance to be rejected after transplantation compared to ES cells, and have fewer ethical issues, which represents a huge advantage in clinical applications.

Currently to identify adult stem cells, scientists typically use one of two methods: 1) label the cells with molecular markers and observe the cell types they generate; or 2) remove the cells
from a living animal, label them in cell culture, and transplant them back to another animal to see whether these cells repopulate their tissue of origin (What Are Adult Stem Cells, 2005). To confirm a cell is indeed an adult stem cell, scientists demonstrate that they can give rise to genetically identical daughter cells, one of which is differentiated and one which is another stem cell, or show that the cells can repopulate or reform the tissue after transplanted into an animal. Below is an introduction to five of the best known adult stem cells.

**Hematopoietic Stem Cells**

Blood and the system that forms it make up the so-called hematopoietic system. Blood is home to many cell types, including red blood cells, white blood cells (B-cells, T-cells, neutrophils, macrophages), and platelets. Many of these cells are short-lived, so they need constant replacement (NIH, 2006). The stem cells that form the cellular components of blood are termed hematopoietic stem cells (HSCs) and are the most researched of all the stem cells. After the bombing in Hiroshima and Nagasaki in 1945, people were reported with compromised hematopoietic systems after a long period of low doses of radiation. They could not generate enough white blood cells to fight infections or could not clot blood because of lack of platelets. Mice were reported with the same symptoms after exposure to radiation (Jacobson et al., 1949). However, if the radiation was given with the shielding of bone fragments or the spleen, the mice would survive. Later, scientists showed the irradiated mice would survive if given bone marrow (Lorenz et al., 1951). They later demonstrated that these bone marrow cells directly regenerate the blood-forming system (Ford et al., 1956; Nowell et al., 1956). Recovery of the mice and rats from a lethal challenge of radiation by replenishing the blood cells indicated the bone marrow cells contained HSCs (Hematopoietic Stem Cells, 2005). Currently, the transplantation of
healthy bone marrow HSCs remains the most effective means to treat hematopoietic failure
(Weissman, 2000; Manz et al., 2004).

Many markers have been discovered to distinguish HSCs from mature blood cells. These
include red blood cell and macrophage lineages, known as “Lin”, Sca-1, CD27, CD34, CD38,
AA4.1, and MHC class I (Spangrude et al., 1988; Uchida and Weissman, 1992). For human cells,
established HSC markers include Lin, CD133, CD34, CD38, CD43, CD45RO, CD45RA, CD59,
CD90, CD109, and HLA DR (Miraglia et al., 1997; Yin et al., 1997). Metabolic labels can also
tag HSCs, such as rhodamine-123, Hoechst-33342, Pyronin-Y, and BAAA. The use of
combinations of various markers mentioned above helps scientists purify near-homogenous
populations of HSCs.

Neuronal Stem Cells

Neuronal stem cells (NSCs) are a subtype of progenitor cells found in the nervous system
that are capable of renewing themselves and generating both neurons and glia (Temple, 2001).
Progenitor cells represent a type of cell between a classic stem cell and the final differentiated
cell. Adult neuronal stem cells have been found in two principal adult neurogenic regions, the
hippocampus and the subventricular zone (SVZ), and also in some non-neurogenic regions like
the spinal cord (Figure-6) (McKay, 1997; Rao, 1999; Gage, 2000). These breakthroughs raised
the possibility that the central neural system (CNS) might have regenerative powers (Temple,
2001).
Figure 6: The Location of Neural Stem Cells. The right panel depicts the principal regions of the adult nervous system from which neuronal stem cells have been derived. The left panel denotes the corresponding regions in the embryonic nervous system. (Temple, 2001)

Markers for neuronal stem cells are largely still under development (Capela and Temple, 2000; Uchida et al., 2000; Kawaguchi et al., 2001; Rietze et al., 2001). Instead of using markers to identify NSCs, scientists often rely on cellular behavior (Temple, 2001).

Cardiac Stem Cells

Heart is also home to stem cells which are responsible for repairing heart damage, such as during a heart attack. These stem cells are called cardiac stem cells (CSCs). CSCs are self-renewing and multipotent, giving rise to myocytes, smooth muscle, and endothelial cells (Beltrami et al., 2003). Figure 7 shows a cluster of cardiac stem cells (blue) among heart muscle cells (red) in human heart tissue (Touchette, 2004).
Researchers have successfully isolated cardiac stem cells from mice (Beltrami et al., 2003). CSCs were isolated from interstices between muscle cells in mouse hearts. When these cells were transplanted into mice with heart injury, they reconstituted 70% of the damaged myocardium in 20 days (Beltrami et al., 2003). A similar finding was also reported in humans (Laugwitz et al., 2005). A variety of markers have also been discovered for CSCs, including cardiac differentiation markers cTnl and ANP, endothelial markers KDR (human)/flk-1(mouse), CD31, and stem cell markers CD34, c-kit, and sca-1 (Messina et al., 2004).

**Mesenchymal Stem Cells**

Mesenchymal stem cells (MSCs) are multipotent cells residing in the stromal fraction of the bone marrow. In 1976, Friedenstein first reported methods on the isolation and differentiation of mouse MSCs (Friedenstein, 1976; Friedenstein et al., 1987). Later, isolated MSCs were found capable of differentiating into many different types of mesenchymal cells, including osteoblasts, chondrocytes, and adipocytes (Pittenger et al., 1999). The ability of clonally expanded cells to
form these three distinct cell types remains the only reliable functional criterion to identify
genuine MSCs (Jackson et al., 2007). CD13, CD29, CD31, CD44, CD54, CD63, CD73, CD105,
CD106, CD140b, CD166, and Strol, are some of the markers used to identify human MSCs
(Gronthos et al., 1994; Bruder et al., 1998; Pittenger et al., 1999; Covas et al., 2003; Vogel et al.,
2003; Mitchell et al., 2006).

_Epithelial Stem Cells_

The ultimate source for a corneocyte or hair cell is an epithelial stem cell (ESC). ESCs are
self-renewing, multipotent, and clonogenic cells living in an adult skin that help tissues like
epidermis and hair follicle to continuously generate new cells to replace dead squamous cells and
hairs. The existence of epidermal stem cells can be proved by three observations: 1) clones
formed from radioisotope-resistant (slow cycling, long lived) epidermal cells repopulate the skin
after severe radiation depletion (Withers, 1967; Potten and Hendry, 1973); 2) allogeneic grafts
from epidermal basal keratinocytes expanded at least 10-fold in culture have lasted for years on
burn patients (Rheinwald et al., 1975; Compton et al., 1989), and 3) heterogeneity in the basal
cell cycle was discovered, in which a small subpopulation of cells was shown to retain a tritiated-
thymidine label for up to 240 days (Bickenbach, 1981), suggesting a very long cell cycle
(Cotsarelis et al., 1999). All these observations show the anticipated properties of ESCs.

Scientists are not quite sure about markers for identifying ESCs. $\beta_1$ integrin (Jones and Watt,
1993) and cytokeratins 15 (Michel et al., 1996) and 19 (Lyle et al., 1998) may represent
epithelial stem cell markers. Since cell surface markers have not been well established to
distinguish ESCs from other cells, isolation of pure ESCs is not yet possible. However,
enrichment of ESCs can be achieved using specific antibodies to some of the above mentioned
proteins.

Chapter-1 Bibliography


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Chapter-2: Stem Cell Applications

The benefit that stem cells provide to society usually focuses on their medical applications and the knowledge they provide about biological development. These societal benefits strongly weigh into the ethical debate on whether to allow ES cell usage. The purpose of this chapter is to describe how stem cells have been used to treat five example diseases, paying special attention to inform the reader about whether the application remains in animal studies or is already in human clinical trials.

Hematopoietic Stem Cell Applications

Among all the stem cells, hematopoietic stem cells (HSCs) are perhaps the best characterized. Bone marrow transplants have been used by scientists to treat “blood cancers” such as leukemia and lymphoma for decades. They have also been used to treat inherited blood disorders.

HSC Treatment of Leukemia and Lymphoma

Leukemia and lymphoma are types of blood cancers that result from the uncontrolled proliferation of white blood cells. The solution to these diseases, which was the first application of HSCs, is to destroy the patient’s cancerous hematopoietic cells by radiation or chemotherapy, and introduce healthy HSCs either by a bone marrow transplant (initial source) (Thomas et al., 1957), or by a transplant with HSCs collected from the peripheral circulation of a matched donor (current source) (Korbling and Freireich, 2010). A matched donor is typically a sister or brother of the patient who has inherited similar human leukocyte antigens (HLAs) on the surface of their cells (Hematopoietic Stem Cells, 2005). How well the HLAs of the donor and the recipient
match is critical to the success of the transplant as it determines the chance of graft rejection (the recipient’s immune system views the new stem cells as foreign and attacks them) and *graft-versus-host* diseases (new stem cells turn against the immune system).

The first bone marrow infusion of HSCs for the treatment of acute leukemia was performed as early as in 1957 (Thomas et al., 1957). In the following years until the discovery of the HLA system (Dausset, 1958; Van Rood, 1968), a number of transplants were reported successful while most of the patients died of graft failure afterwards (Bortin, 1970). The subsequent knowledge of the HLA system and the selection of identical siblings as matched donors reduced the chance of host body rejection. In the space of twenty years since then, HSCs transplantation has transformed leukemia from a fatal disease to one that is frequently curable (Thomas and Clift, 1999). Currently, about 40,000 transplants are performed annually world-wide (Horowitz, 1999; Santos, 2000). Bone marrow registries have been initiated to help patients without an identical sibling find a matched donor. The number of bone marrow and peripheral HSC donors has increased worldwide, with more than 18 million registered donors, including 500,000 cord blood donors (Gluckman, 2011). Improvements have also been made in identifying new sources of HSCs besides bone marrow (Aversa et al., 1998; Gluckman, 2009) and autologous HSC transplantation (Dicke et al., 1979) in which a patient’s own HSCs are re-injected after a complete depletion of their cancer cells.

*HSC Treatment of Inherited Blood Disorders*

Bone marrow transplants can also be used to treat hereditary blood disorders, such as various kinds of inherited anemia (failure to produce blood cells), and inborn errors of metabolism (genetic disorders characterized by defects in key enzymes need to produce essential
body components or degrade chemical byproducts (Hematopoietic Stem Cells, 2005). For example, allogeneic HSC transplantation (HSCT) has been proven to be the only solution to Fanconi anemia (FA)–associated bone marrow failure (Grewal et al., 2004). HSCT is one of the methods used to treat Hunter syndrome (Warkentin et al., 1986; Bergstrom et al., 1994; Coppa et al., 1995; Li et al., 1996; McKinnis et al., 1996; Vellodi et al., 1999).

**HSC Rescue in Cancer Chemotherapy**

When patients are treated for cancers by chemotherapy, it not only kills cancer cells but other rapidly dividing cells like HSCs. One way to save HSCs is through autologous stem cell transplantation. HSCs from the patient’s own peripheral blood are collected and stored before intensive chemotherapy or radiotherapy destroys the cancer cells. After the chemotherapy, these HSCs are then injected back into the patient’s blood. Since the transplant uses the patient’s own cells, there is no immune system rejection. However, it is possible that the supposedly pure HSCs contain cancer cells and these cancer cells will be re-infused into the patient along with HSCs. To avoid reintroducing cancer cells, one team reported a purifying method of HSCs by preserving those that are CD34^+^, Thy-1^+^ (Negrin et al., 2000).

**Graft-Versus-Tumor Treatment of Cancer**

Recently, HSC transplantation has also been used to attack otherwise untreatable tumors. A group of researchers in NIH’s intramural research program recently reported successfully reducing metastatic kidney cancer (Childs et al., 2000). Another study showed that umbilical cord blood and peripherally harvested human HSCs have antitumor activity in the test tube against leukemia cells and breast cancer cells (Joshi et al., 2000). Researchers also found that at
least in the test tube and in mice, untreated cord blood can greatly enhance the activity and numbers of natural killer lymphocytes (Lin et al., 2000; Joshi et al., 2000).

Stem Cell Treatment of Parkinson’s Disease

Parkinson’s disease (PD) is a progressive disorder of motor control that begins with minor tremors, and later develops into limb and body rigidity and difficulty initiating movement. PD is caused by the death of neurons in a brain region called the substantia nigra. These neurons are responsible for releasing the chemical neurotransmitter dopamine that regulates the nerves that control body movement. Once these neurons die, less dopamine is released and therefore movement becomes more difficult. However, the reason why these neurons die remains unknown (NIH Stem Cell Information Chapter-3, 2006).

One strategy to treat PD is to transplant dopamine-releasing cells from a patient’s own adrenal glands (Backlund et al., 1985; Madrazo et al., 1987). Another strategy is to transplant fetal tissue-derived cells (from the substantia nigra of aborted fetuses) which later develop into mature dopamine neurons; mouse transplants of this kind were successfully performed in the 1970s (Olson and Malmfors, 1970) followed by human transplants a decade later (Madrazo et al., 1988; Lindvall et al., 1989). For both strategies, it was observed that Parkinson’s symptoms were lessened or reversed, especially in the animal studies.

However, the larger clinical trials on human PD patients engrafted with fetal tissue in the subsequent 15 years turned out less rewarding than expected. In Colorado and New York, PD patients were evaluated after receiving transplanted tissue from aborted fetuses (Freed et al., 2001; Olanow et al., 2003). Compared with another groups of patients not receiving the implants, the treated patients showed disappointing responses. While some patients showed relief of
symptoms, others suffered from dyskinesias, jerky involuntary movements that are often side effects of long-term L-dopa treatment and graft rejection (NIH Stem Cell Information Chapter-3, 2006). Another trial on three PD patients grafting cells into their striatum and the substantia nigra showed modestly better results: no adverse effects but some modest improvement in patient movement (Mendez et al., 2002).

The limited success of these fetal tissue transplant trials may be due to the variations in the tissue used for the transplantation (NIH Stem Cell Information Chapter-3, 2006). Therefore, further Parkinson’s research calls for an ampler supply of cells that can be grown in the laboratory in a standardized way, and then differentiated into dopamine neurons efficiently when transplanted into the brain of a Parkinson’s patient. Stem cells seem to be a proper candidate. In one preliminary study, dopamine neurons derived from stem cell-like mesencephalic precursors from the rodent ventral midbrain were injected into rats with their own dopamine neurons killed (Studer et al., 1998). The dose of dopamine neurons, though very low, was able to lessen Parkinson’s symptoms.

ES cells are believed to be a promising source of dopamine neurons. Mouse ES cells grafted into 6-hydroxy-dopamine (6-OHDA)-treated rat brains (a mouse PD model) developed into dopamine and serotonin neurons, and helped relieve Parkinson-like symptoms (Bjorklund et al., 2002). Following the availability of human ES cells, dopamine neurons were differentiated and derived from human ES cells by the use of a special type of companion cell plus specific growth factors (Perrier et al., 2004). In addition, in an effort to refine the production of patient-specific more transplantable human dopamine neurons, experiments on rats and nonhuman primates were conducted using nuclear transfer, a method in which genetic material from one individual donor is injected into a recipient egg cell with its own nucleus removed. Though this therapeutic
cloning process is controversial in humans, both mouse ES cells and parthenogenetic primate stem cells differentiated this way showed promising results treating Parkinson’s symptoms in 6-OHDA-treated rats (Barberi et al., 2003; Vrana et al., 2003). Since nuclear transfer produces genetically-matched cells, the possibility of graft rejection is eliminated, and therefore transplantation becomes more viable.

Adult neural stem cells (NSCs) also show the ability to correct Parkinson’s disease. Unlike ES cell transplants which are often accompanied with graft rejection or graft-versus-host disease, NSCs transplants can be performed with cells isolated from the brain of the patient. NSCs derived from human ES cells were successful in the treatment of the disease in rats in 2004 (Ben-Hur et al., 2004). In 2009, the first successful patient-derived adult NSC transplant in a human model not only reversed the effects of Parkinson’s disease but also demonstrated long-term stability. “For the five years following the procedure the patient’s motor scales improved by over 80% for at least 36 months” (Ertelt, 2009).

**Stem Cell Treatment of Damaged Heart Muscle**

Cardiovascular disease (CVD), including hypertension, coronary heart disease (CHD), stroke, and congestive heart failure (CHF), results from damaged cardiac tissue. As the number one killer in the United States since 1900 (with the exception of 1918 when a flu epidemic occurred) (America Heart Association, 2005), the disease begins by ischemic heart failure when cardiac tissue is deprived of oxygen. When the loss of oxygen is severe enough to kill a critical number of cardiac muscle cells (cardiomyocytes), a series of damages to the heart are made, including formation of a non-contractile scar, ventricular wall thinning (**Figure-8**), an overload of blood flow and pressure, ventricular remodeling (the overstretching of viable cardiac cells to
sustain cardiac output), heart failure, and eventual death (Rosenstrauch et al., 2005).

![Diagram of Normal versus Infarcted Heart](image)

**Figure-8: Diagram of Normal versus Infarcted Heart.** The left ventricle has a thick muscular wall, shown in cross-section in A. After a myocardial infarction (heart attack), heart muscle cells in the left ventricle are deprived oxygen and die (B), eventually causing the ventricular wall to become thinner (C). (NIH Stem Cell Information Chapter-6, 2006)

Restoring damaged heart muscle tissue has therefore become the strategy to treat CVD. However, for serious damage, endogenous repair mechanisms such as the proliferation of cardiomyocytes under the conditions of severe blood vessel stress, are not sufficient to restore the tissue. And current pharmacologic interventions such as beta-blockers and surgical treatment options cannot restore function to damaged tissue. Heart transplantation has the problem of lack of donor organs and host rejection.

These difficulties led researchers to look into the possibility of using stem cells to repair damaged heart tissue. To date, a variety of cell treatments have been tested, including ES cells, cardiac stem cells that naturally reside within the heart, adult bone marrow-derived cells, and mesenchymal stem cells etc.
Treating Damaged Heart with Embryonic Stem Cells

As mentioned in Chapter-1, ES cells are able to generate any cell in the adult organism, including cardiomyocytes, endothelial cells, and smooth muscle cells that are critical to damaged heart tissue. In mouse models, ES cells have been shown to differentiate into endothelial and smooth muscle cells in vitro (Vittet et al., 1996) and in vivo (Marchetti et al., 2002; Yamashita et al., 2000). Human ES cells have been shown to differentiate in vitro into myocytes structurally and functionally similar to cardiomyocytes (Westfall et al., 1998; Kehat et al., 2001; Kehat et al., 2002). Moreover, rat ES cells were reported to differentiate into normal myocardial cells in rats after transplanted into ischemically-injured myocardium, and remained viable (Min and Yang et al., 2002).

Although ES cells seem to have promise in human regenerative therapy, ethical issues remain an obstacle to the avenues of investigation. Moreover, ES cells must go through rigorous testing and purification process before the cells can be used as sources to regenerate tissue (NIH Stem Cell Information Chapter-6, 2006). In addition, the pluripotency of ES cells can be a double-edged sword to clinical applications. If injected regenerative cells accidentally contain undifferentiated ES cells, the transplant could result in the formation of a tumor (Rosenstrauch et al., 2005). With all these challenges, there is still much research to be done before ES cells can be beneficial to cardiac patients.

Treating Damaged Heart with Resident Cardiac Stem Cells

Heart contains a small population of endogenous stem cells that most likely facilitate minor repair and cell replacement (Boyle et al., 2006). Cardiac stem cells have been isolated and
harvested from mouse and human tissues (Beltrami et al., 2003; Messina et al., 2004) and proved to promote cardiomyocyte formation and improvements in systolic function if injected to the spot of infarction (Britten et al., 2003; Messina et al., 2004). Based on this, clinical trials will be funded to explore the use of cardiac stem cells for myocardial regeneration.

Treating Damaged Heart with Human Adult Bone-Marrow Derived Cells

In 2001, Jackson et al. (Jackson et al., 2001) and Orlic et al. (Orlic et al., 2001) demonstrated, respectively, that new cardiomyocytes could be generated by introducing bone marrow-derived stem cells in mouse models. Following the success in mice, researchers actively investigated the possibility of using human adult bone marrow as a source of stem cells for cardiac repair. In particular, bone marrow mononuclear cells (BMMUCs), comprised of blood cells, HSCs, and progenitor cells, have been explored the most (Boyle et al., 2006). Several studies, including the “Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration” (BOOST) and the “Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction” (TOPCARE-AMI) trials, have shown that intracoronary infusion of BMMNCs following a heart attack significantly improves the left ventricular (LV) ejection fraction, or the volume of blood pumped out of the left ventricle with each heartbeat (Assmus et al., 2002; Schachinger et al., 2004; Wollert et al., 2004). However, other studies have indicated either no improvement in LV ejection fraction upon treatment (Janssens et al., 2005) or an increased LV ejection fraction in the control group (Cleland et al., 2006; NIH Stem Cell Information Chapter-6, 2006). While the outcomes from these trials were certainly promising, the discrepancies in the results demand further exploration.

Interestingly, two groups conducted the similar study only to draw the opposite conclusions.
The two groups both wanted to show improvement in left ventricular function after intracoronary injection of autologous cells derived from bone marrow (BMC) in the acute phase of myocardial infarction. In one group, patients with acute ST-elevation myocardial infarction were either injected autologous mononuclear BMC or nothing as in the control group (Lunde et al., 2006). Left ventricular function was assessed 2-3 weeks after the infarction and repeated 6 months after the infarction. However, with the methods used, they found no effects of intracoronary injection on global left ventricular function. In another group, 204 patients with acute myocardial infarction were randomly assigned an intracoronary infusion of progenitor cells derived from BMC or placebo medium into the infarct artery 3-7 days after successful reperfusion therapy (Schächinger et al., 2006). At 4 months, the absolute improvement in the global left ventricular ejection fraction was significantly greater in the BMC group than the placebo group; and at 1 year intracoronary infusion of BMC was associated with a reduction in the pre-specified combined clinical end point of death, recurrence of myocardial infarction, and any revascularization procedure (Schächinger et al., 2006).

_Treating Damaged Heart with Mesenchymal Stem Cells_

Mesenchymal stem cells (MSCs) have also brought good news to cardiac tissue regeneration. Cultured with vascular endothelial cells and DNA-demethylating agent (5-azacytidine), MSCs have been shown to differentiate into endothelial cells (MacKenzie and Flake, 2002) and cardiomyogenic (CMG) cells (Davani et al., 2003), respectively. Transplanted into the heart following myocardial infarct (MI), MSCs can also differentiate into cardiomyocytes and endothelial cells _in vivo_ in pig, mouse, or rat models.

Several studies of MSCs in animal models have shown significant improvement in
myocardial function and capillary formation (Makino et al., 1999; Min et al., 2002; Shake et al., 2002; Toma et al., 2002). It was also shown that MSC have the advantage of low immunogenicity and reduced rejection (Amado et al., 2005). One human clinical trial has also been performed with MSCs (Chen et al., 2004). The results showed an improved global and regional LV function. Other trials are still underway to examine the possible solution to acute MI and myocardial ischemia using MSCs.

**Stem Cell Treatment of Diabetes**

Diabetes is caused by an insufficient production of insulin, a hormone that regulates glucose levels in the blood (Type-I), or by various tissue’s decreased sensitivity to the secreted insulin (Type-II) (Figure-9). For Type-I, the insulin insufficiency results from the patient’s immune system mistakenly attacking and destroying insulin-producing pancreatic beta cells (β-cells). When β-cells fail to produce enough insulin to counteract blood glucose increases, tissue glucose decreases, and the risk of premature cardiovascular disease, stroke, and kidney failure is dramatically increased.
Figure-9: Insulin Production in the Human Pancreas. The pancreas is located in the abdomen, adjacent to the duodenum (the first portion of the small intestine) (diagram upper left). A cross-section of the pancreas (upper right) shows the islet of Langerhans which is the functional unit of the endocrine pancreas. Encircled is the beta cell that synthesizes and secretes insulin. Beta cells are located adjacent to blood vessels (lower right) and can easily respond to changes in blood glucose concentration by adjusting insulin production. Insulin facilitates the uptake of glucose, the main fuel source, into cells of tissues such as muscle (lower left). (NIH Stem Cell Information Chapter-7, 2006)

The key to curing Type-I diabetes inevitably lies in expanding the population of functional \( \beta \)-cells. Successful cell transplants have been reported, including a transplant of pancreatic islet tissue in 1990 (Scharp et al., 1990) followed by others using an “Edmonton protocol” of islet transplantation supplemented with immunosuppressive drugs (Shapiro et al., 2000; Ryan et al., 2001; Ryan et al., 2002). However, few patients achieved long-term success, as the islet function dropped sharply after the transplantation. In addition, the general lack of islet donor tissues and the damaging nature of the islet isolation process add more difficulty to transplantation. These challenges made scientists turn to stem cells to regenerate pancreatic tissue, although it turned out to not be easy.
Scientists began by looking for stem cells (either embryonic or adult) that could be sources of insulin-secreting cells. Mouse (Yasunaga et al., 2005) and human ES cells (D’Amour et al., 2005) were reported to successfully differentiate into endodermal cells, the precursors of pancreatic cells. Insulin-producing have also been derived from mouse (Lumelsky et al., 2001; Soria et al., 2000) and human ES cells (Seguev et al., 2004). However, since β-cells are at the relatively late stage of ES cell development, obtaining them requires the knowledge of a considerable number of gene controllers; thus β-cells have not been derived directly from ES cells yet. Burdened with ethical issues that always surround ES cells, ES cells research still has a long way to go.

Treating diabetes with adult stem cells is also controversial. Analysis by Dor and his colleagues showed that in mice new β-cells are generated from pre-existing β-cells, which casts doubt whether true adult stem cells exist in pancreas (Dor et al., 2004). Soon after however, several studies reported the existence of pancreatic stem/precursor cells and their differentiation into β-like cells with glucose-dependent insulin release (Seaberg et al., 2004; Baeyens et al., 2005; Minami et al., 2005; Lee et al., 2006). Other labs have reported the production of various pancreatic tissues from adult stem cells, including pancreatic islets (Guz et al., 2001, Zulewski et al., 2001), pancreatic ducts (Oshima et al., 2007; Xu et al., 2008), exocrine acinar cells (Baeyens et al., 2005; Minami et al., 2005), using unspecified pancreatic locals in rodent models (Seaberg et al., 2004; Raimya et al., 2000), human adult pancreatic cell lines (Tsang et al., 2007), and islet tissue (Abraham et al., 2002). Many of these adult stem cells are relatively rare and difficult to identify, which presents a challenge for clinical applications. To date, the possibility still remains that β-cells are regenerated by differentiation of endogenous stem cells, by the proliferation of existing β-cells, or by a combination of the two (NIH Stem Cell Information Chapter-7, 2006).
Recently, iPS cells were also tested in a mouse diabetes model and reversed the hyperglycemia (Alipio et al., 2010).

**Treatment for Spinal Cord Injuries**

Stem cells have also been explored for treating spinal cord injuries. There are two main types of spinal cord injuries: 1) the injury is severe enough that the cord is totally severed destroying the messages between the brain and the rest of the body; 2) the injury does not completely sever the cord but the messenger neurons (neuronal axons) no longer function properly as a result of oligodendrocyte loss. Oligodendrocytes normally produce myelin, which is necessary to shield axons.

In order to replenish these lost oligodendrocytes, scientists have experimented with cultured ES cells. They first obtained cultures containing oligodendrocytes from the human ES cells. After an injection of these cells into their spinal cords, chemically-demyelinated rats recovered a limited ability of their hind limbs (Liu et al., 2000). Although whether the recovery was indeed due to the cell therapy was not certain, scientists made progress in regenerating myelin-producing cells. In addition, a highly enriched population of myelinating oligodendrocyte precursors was generated from cultured human ES cells transplanted into mouse model lacking myelin (Brustle et al., 1999; Nistor et al., 2005). The same cells were later shown to improve the movement of rats with spinal cord injury (Keirstead et al., 2005).

Myelin not only promotes normal neuronal function; it also inhibits the growth of new axons following spinal injury (NIH Stem Cell Information Chapter-3, 2006). Therefore, growing new axons to reconnect with their targets is even more challenging, as myelin can be beneficial or detrimental depending on its location. In a recent study, ES cells were treated with a
combination of factors to promote motor neuron differentiation in vitro before transplantation into spinal-cord-injured rats (Harper et al., 2004). Although the new neurons did not send out signals until scientists turned off the inhibitory effects of myelin by drugs, the results did show the potential to produce neurons that reconnect to their targets. Still, much needs to be done before human clinical trials can be performed using stem cell therapies to repair the trauma-damaged nervous system.

Chapter-2 Bibliography


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Chapter-3: Stem Cell Ethics

Although regenerative therapy has brought huge benefits to society, the controversy around whether stem cells are more beneficial than detrimental has never stopped. Many argue that the destruction of the embryo when embryonic stem cells are derived can be classified as harm to a potential human being, or more severely can be classified as “murder”, and should not be performed to benefit others. Yet other people consider the embryo merely a collection of cells that are no more alive or human than a tumor, a virus, or something that grows on cheese (Derbyshire, 2001). The purpose of this chapter is to go beyond our previous chapter discussions of stem cell types and how they are used, and instead discuss the topic of whether we should work with stem cells.

Framing the Stem Cell Debate

When an individual says he is against stem cells, likely he is referring to embryonic stem (ES) cells, not to adult stem cells. The ethics of the stem cell debate focuses on the status of a human blastocyst embryo. Although some people incorrectly assume that aborted fetuses are somehow involved in stem cell research, as discussed in Chapter-1, ES cells are derived from the inner cell mass of a 5-day old blastocyst prepared by in vitro fertilization (IVF). The blastocyst consists of about 100 cells and is the size of the period at the end of this sentence. When deciding the status of the embryo, the debate focuses on when life or personhood begins. If a person believes personhood begins at conception, then destroying a 5-day old embryo is wrong. While if a person believes personhood begins later in development, taking a 5-day old embryo to derive ES cells to save lives might be acceptable.

Dr. Michael West, the president of Advanced Cell Technology (ACT), a former Worcester
Biotechnology company now based in California, tried to draw a line between ‘human cellular life’ and ‘human life’ when he was interviewed by Larry King. ‘We’re talking about making human cellular life, not a human life,’ said West. ‘A human life, we know scientifically, begins upwards, even into two weeks of human development, where this little ball of cells decides, “I’m going to become one person or I am going to be two persons.” It hasn’t yet decided.’ (CNN, 2001). Although at first it appeared that West would sidestep the debate, he then went directly to the center of the debate by stating – ‘What stage indeed does an embryo become human life?’

The answer to this central question is fundamental to people’s view on stem cell research. If people believe that life starts at fertilization, they won’t favor stem cell research, at least not for those applications that sacrifice embryos; while if they believe that life starts after the development of the primitive streak, generally around the fourteenth day post-fertilization (Human Cloning….2002), they would most likely permit experimenting with blastocyst-stage human embryos; if they believe that life starts after the birth of the baby, they are probably also proponents of ES cell research.

Many individuals think the stem cell debate is new. Although human ES cells were derived fairly recently in 1998 (Thomson et al., 1998), the embryo debate actually began at the end of the 1970’s with the advent of human IVF technology and the birth of Louise Brown the world’s first test tube baby (BBC News, 1978). Because the IVF process is inefficient, extra embryos are prepared for each couple donating egg and sperm. After the family has enough children, the remaining embryos are in excess, so the debate has focused for over 34 years now on what to do with the excess IVF embryos: destroy them, don’t create them in the first place, or use them for medical research.

The layperson also frequently confuses three different important processes: 1) ES
derivation from embryos, 2) therapeutic cloning, and 3) reproductive cloning. The derivation of ES cells from an IVF embryo does not involve any cloning. Cloning is somatic cell nuclear transfer (SCNT). Therapeutic cloning involves isolating the nucleus from a skin fibroblast cell (for example of a patient), and injecting it into an enucleated egg, which is then grown 5-days to the blastocyst stage and ES cells isolated. The ES cells prepared using this method are genetically identical to the skin cell donor (patient) so presumably would not be rejected by the patient. Therapeutic cloning has been achieved in animals, and one claim from Seoul National University was made for humans, but it turned out to be fraudulent (Hwang et al., 2004).

Reproductive cloning also involves SCNT, but instead of deriving ES cells from the blastocyst, the embryo is implanted into the uterus of a foster mother for the purpose of live birth. Reproductive cloning was first accomplished in mammals with Dolly the sheep (Campbell et al., 1996), but has not yet been accomplished with humans, and most countries ban the process.

**Religious Stances on Stem Cell Ethics**

Religions have always shaped our society in many ways, and this includes taking various stances on stem cells. For example, soon after the South Korean researchers mentioned above claimed to have successfully cloned the first human embryos and used them to derive patient-specific ES cell lines (Hwang et al., 2004), organized religion jumped strongly into the debate. The Christian church sent priests, bishops, pastors, and preachers to the pulpit, issuing strong words of caution or outright condemnation for any research that creates, uses, or destroys human embryos (Frazzetto, 2004), even for embryos that were not cloned by SCNT. So far, the attack has been quite effective; many Western countries including the USA have outright banned all forms of human cloning, reproductive and therapeutic, and have also issued restrictions for
federal funding of human ES cell research (discussed in Chapter-4). However, religious leaders rarely speak with one voice, especially for the world’s large religions. While some have deep rooted beliefs against ES cell research (such as Catholicism), other religions such as Islam or Judaism appear to embrace the new technology, if performed to help humanity. The following discussion focuses on the stem cell stances of world’s five major religions: Christianity, Judaism, Islam, Hinduism, and Buddhism.

*Christianity and Stem Cells*

The Catholic Church has been the leading voice against any form of human cloning and the derivation of human ES cells from IVF embryos (Frazzetto, 2004). The Catholic church’s major argument is rooted in belief that life begins at conception, and is ‘a gift from God’. Based on Holy Scriptures, no matter what claims of healing ES cell research promises, one can never get around the fact that the life of an embryo to Catholics begins at conception and must be willfully taken by ‘perfect will of God’ (Fleischmann, 2000). The Catholic belief that life begins at conception actually began relatively recently. In 1869, probably under pressure of then then crude embryological research advances, Pope Pius IX declared that an embryo bore full human status from the time of fertilization (Lachmann, 2001). Moreover, in a 1987 document called ‘Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation (*Donum Vitae*)’, Roman Catholics were told that cloning is categorically “considered contrary to the moral law, since [it is in] opposition to the dignity both of human procreation and of the conjugal union” (Lachmann, 2001). Therefore, cloning or deriving ES cells from an embryo is inevitably considered condemning the dignity of a human and is thus unacceptable.

Although this is a relatively new stance in Catholicism, ever since the adoption of the
belief that ‘life begins at fertilization’, the Catholic Church has stuck to that position, and the
destruction of an embryo is considered ‘murder’. So, they don’t make a distinction between
embryos conceived naturally and those created from IVF or cloning. In the arguments to justify
their positions against ES cell research, Christian theology reveals natural life and IVF
reproduction are equal; ‘life in the womb – or, tragically in the Petri dish – is always viewed as
human life’ (Fleischmann, 2001)

In contrast, the Christian traditional medieval church, in line with the Aristotelian
doctrine, considered that an embryo acquired a soul only after it took recognizable human shape.
It partially explained why abortion was only a minor crime at that age rather than a felony such
as murder (Fleischmann, 2001). Although most Christian leaders nowadays accept IVF as an
acceptable means of reproduction, they strongly oppose reproductive cloning. As Donald Bruce
from the Science, Religion and Technology Project of the Church of Scotland pointed out,
‘cloning would give someone power to predetermine the whole genetics of another person. I
suggest this is a power that no one should be given. […] It should not be for any human to
predetermine another person’s complete genetics’ (Bruce, 2002).

On the other hand, all Christian leaders accept the use of adult stem cell research, or more
accurately, any stem cell research that does not involve the death of an embryo. Many have
embraced the new technology and are actively promoting it. At an international congress
sponsored by the Pontifical Academy for Life and the International Federation of Catholic
Medical Association, Pope Benedict XVI endorsed adult stem cell research, urging Catholic
scientific institutions to increase their efforts to establish closer working relationships with others
in the field to promote breakthroughs that can relieve needless human suffering (Catholic Online,
2008). As Pope Benedict claimed, the Church has always been, and will always be, supporting of
research “aimed at the cure of illnesses and at the good of humanity” (Catholic Online, 2008).

**Judaism and Stem Cells**

Quite different from the Christian stance on stem cells, the Jewish religion generally favors working with stem cells. This favorable stance can be explained by two fundamental beliefs in Jewish Laws that are distinct from Christianity. First of all, Judaism places high value on scientific knowledge and technologies that preserve human life. “Our theological predisposition is not only to welcome, but to aggressively pursue new technologies that improve our lives and our world” said Rabbi Edward Reichman, Assistant Professor in the Department of Epidemiology and Population Health, and its Division of Philosophy and History of Medicine at Yeshiva University’s Albert Einstein College of Medicine (Frazzetto, 2004). “The preservation of human life, *pikuach nefesh*, is paramount in Jewish law”. Unlike Christians who believe ‘life is a gift from God’, and no one should have the right to manipulate it at a will other than God, Jewish people have no problem of “playing God”. Rather, they deem “playing God” a religious imperative. By teaching and healing, the only two professions ascribed to God Himself, Jewish followers fulfill the obligation to “play God” (Jakobovits, 2006). Therefore, they believe that microscopic manipulation of a faulty genetic blueprint in an embryo for example should be no different than surgical manipulation of a defective tissue or organ.

The second Jewish fundamental belief that relates to embryo research is the belief that human life begins at birth (not conception) (Rich, 1997). This directly addresses the central stem cell debate question. Even if some Jewish scholars argue that life begins at around the 40th day of gestation (Grossman, 2003), this is still well after the blastocyst stage from which ES cells are derived.
Indeed, most Jewish scholars are distrustful of outright government bans on therapeutic stem cell research. “If cloning technology research advances our ability to heal humans with greater success, it ought to be pursued, since it does not require or encourage the destruction of life in the process” said a joint statement between the Union of Orthodox Jewish Congregations of America and the Rabbinical Council of America (Frazzetto, 2004). In this same sense, few Jewish followers object to deriving stem cells from adult or umbilical cord tissue.

Islam and Stem Cells

Lacking the absence of one central institution, such as the Vatican, Islamic scholars cannot reach one agreed opinion on stem cell research or reproductive cloning when consulting the Shari’ah, the law of Muslims. In terms of the moral status of an embryo, various schools of Islam have independent thoughts. Many believe that an embryo acquires its soul 120 days after fertilization (Muhammad, 2011), a stance that would allow ES cell research. In addition, a potential life is different from an actual life. Therefore, an embryo representing potential life should draw less protection than a newborn baby. Under most interpretations, an embryo is not considered to be a person, and using it to create stem cell lines does not violate Islamic Law (Frazzetto, 2004).

On the other hand, Islamic scholars remain concerned with reproductive cloning, largely due to their awe and respect for familial relationships. ‘Islam regards interpersonal relationships as fundamental to human religious life,’ said Abdulaziz Sachedina, Professor of Islamic Studies at the University of Virginia, and a leading scholar of Islamic views on cloning (Frazzetto, 2004). To Muslims, the parent-child lineage encourages parental love which is of highest importance in life. In this sense, Muslims are most worried about the moral impact that genetic replication and
embryonic manipulation would bring to society. They would endorse reproductive cloning only if it does not break familial relationships. Interestingly, because of Muslims’ generally prohibitive attribute of surrogate parenting, adoption, or cloning human embryos (as it breaks the traditional parent-child lineage), more cloned embryos would possibly be freed for research as Islamic Law allows their growth only by the couple who created the embryo.

Another key concept in Islam is the strong value of knowledge. Similar to Judaism, Islamism emphasizes the obligation to use knowledge gifted by God to serve society. Research on stem cells is therefore regarded as an act of faith in the ultimate will of God (Frazzetto, 2004).

**Buddhism**

If not for the unique perspective Buddhism carries, the first human embryo cloning would have perhaps taken place in the United States rather than the (fraudulent) attempt in South Korea. Unlike most other religions that believe life is a gift from God, and reproductive cloning and embryonic manipulation are against natural sexual reproduction and therefore against God’s will, Buddhism does not have such opposition. In Buddhism, there is no supreme or divine creator; therefore there is no fear that the Will “might be distorted by human tinkering with nature” (Frazzetto, 2004). Moreover, Buddhists believe that the creation of life is not a fixed or unequivocal process. “Buddhism teaches that life may come into being in a variety of ways, of which sexual reproduction is but one, so sexual reproduction has no divinely sanctioned priority over other modes of procreation,” said Damien Keown, a Reader in Buddhism in the Department of History at Goldsmiths College, University of London, UK, and an authoritative voice on Buddhist responses to cloning and other biomedical issues (Frazzetto, 2004). Since life can begin in many forms, cloning might be considered one of them. In addition, as human individuality is
taken by Buddhists as an illusion or mirage, cloning would not threaten or devalue the personality or character of an individual. Also, Buddhists place high value on the central virtues of knowledge (prajña), compassion (karuña), and its long tradition of practicing medicine in the monasteries. So in these respects, Buddhism has no major objection to the therapeutic use of stem cells (Keown, 2004).

But while some Buddhist beliefs clearly favor stem cells, other beliefs do not, especially ES cell research. This pertains to the principle of ahimsa, or non-harming (Keown, 2004). In this view, research involving the intentional destruction of human life, whether in the form of an adult or embryo, is problematic. In addition, Buddhists also believe in rebirth and that human life begins at conception. The new being, bearing the karmic identity of a recently deceased individual, is entitled to the same moral respect as an adult human being (Keown, 2004). In this sense, there is no distinction between destroying a naturally conceived embryo and an embryo grown for IVF treatment. In a word, Buddhism condemns the practice of using human embryos (either surplus, unwanted, frozen embryos created for IVF treatment, or cloned embryos) for research purposes, regardless of the good intentions.

**Hinduism and Stem Cells**

Hinduism largely embraces stem cell research and related technologies, based on the core doctrines at the heart of Hinduism. The Hindu Vedas dictate that ‘all life is sacred’, including animal and plant life. This belief is at the root of the Hindu doctrine of non-violence or ahimsa, which requires Hindus to love all living things and to show their love to God. However, there seems to be a paradox in this stance; if all creatures are beloved, why must people kill and consume plants (and animals) to survive? The ancient Rishis, or divine sages, resolved this
paradox by introducing the concept of evolutionary consciousness. Human beings are believed to be the top of the evolutionary hierarchy, enjoying the most consciousness, above plants, followed by animals. Within the development of a human, there are also different levels of consciousness. It is the birth (Bahnot, 2008). After birth, human life carries more value than an embryo at a primordial stage, where there is no sensation (Bahnot, 2008). Combining the belief that lives with lower consciousness can be sacrificed at the need of lives with higher consciousness to achieve better evolution toward God, Hindus believe modern science such as stem cell research should be supported as it works on the same basis.

With respect to the Hindu stance on cloning, “the general opinion appears to be in favor of ‘therapeutic cloning’ which enables the cloning of human organs,” said Dr. Muthuswamy from The Hindu (The Hindu, 2006). But the reproductive cloning of entire human beings was considered “playing against nature”.

**iPS Ethics**

Because ES cell research has encountered ethical controversies, researchers have researched alternative procedures for preparing pluripotent cells. Induced pluripotent stem (iPS) cells are adult skin cells reprogrammed to a pluripotent state by genetic manipulation. Although, as discussed in Chapter-1, the exact potential of such cells is still being debated, iPS cells have been derived from human skin cells, and are currently being researched as alternatives to embryo-derived ES cells. iPS cells require no destruction of a human embryo, only adult cells and genetic reprogramming. Surprisingly, no other stem cell type is more hotly debated than iPS cells are today.
Gregory Kaebnick first suggested in *Bioethics Forum* that iPS cells and embryos created from somatic cell nuclear transfer are much more alike than people thought (Baylis, 2008). He argued that since both techniques involve the reprogramming of somatic nuclei – either the introduction of gene transcription factors directly to somatic cells (for iPS cells), or the involvement of egg cytoplasm (for cloning, and to generate embryos), they are morally the same. He suggested that a “clonote” “looks much like a zygote,” and just as a “clonote” appears to be a new kind of embryo, an iPS cell may also be a new kind of embryo. Therefore, those who object to cloning should also not embrace iPS cells either, because iPS cells in reverse may actually create an embryo, and in that case iPS cells would not get around the moral difficulties associated with the destruction of human embryos since it just created one that would not be used for reproduction (Cohen and Brandhorst, 2008). While this seems to be a logical statement, it is mostly wrong. iPS cells are simply skin fibroblast cells that are directly reprogrammed to a pluripotent state, and no study has shown iPS cells to be totipotent, only pluripotent at best.

In response to Kaebnick’s argument, Cohen and Brandhorst maintained that iPS cells are more akin to the ES cells themselves than to the embryo ES cells are derived from (Cohen and Brandhorst, 2008). They pointed out iPS cells and ES cells share a very important attribute that a cloned embryo usually does not have: they cannot grow into a human being even if transferred into the bodies of women. Why? First of all, they lack the extracellular layer required prior to the implantation. Secondly, they are too small to have the internal organization needed to function as zygotes. Thirdly, they are not totipotent. Cohen and Brandhorst further confronted Kaebnick’s view that iPS cells and embryos are alike because iPS cells form the embryoid bodies of teratomas. By arguing these embryoid bodies would continue to be a tumor even if implanted in a woman’s uterus, and a tumor is clearly not an embryo, Cohen and Brandhorst drew the
conclusion that iPS, as well as ES cells are distinct from embryos (Cohen and Brandhorst, 2008). Thus, there is still good reason to be enthusiastic about iPS cells.

In addition to the two opposite points of view, Baylis, a third voice, differentiated iPS research from cloning-based research by emphasizing the different impact brought on women by iPS and cloning (Baylis, 2008). Unlike iPS cell research, cloning-based stem cell research utilizes human oocytes. These oocytes come from women who put themselves at considerable physical risk by undergoing hormonal stimulation and surgical egg retrieval. They may develop ovarian hyper-stimulation syndrome, which includes nausea, vomiting, respiratory difficulty, and can lead to death. Besides physical harm, they may also experience mental frustration if they are infertility patients. Furthermore, since human eggs are of great value to cloning research, women become potential victims of coercion and exploitation of their reproductive tissues, and their labor might harm them. In contrast, iPS cell research has none of these problems. Thus, Baylis pitched that iPS cells should be preferred to cloned human embryos for stem cell research (Baylis, 2008)

Clearly, our moral views have not yet been developed for words like ‘clonotes’, ES cells, and iPS cells, to allow for a sharp conclusion here, as their seemingly unlimited capacity still remains largely a myth to us. Likely, the moral status of iPS cells, and their comparable ES cell peers, will continue to be debated.

Chapter-3 Bibliography


Chapter-4: Stem Cell Legalities

Stem cell research has become so entangled in ethical controversy and religious beliefs that laws have been enacted to control its funding and use. The laws regulating stem cell use are an interesting blend of politics, ethics, and science. In the U.S. the laws enacted often reflect the political administration in power at that time. This chapter reviews the latest three U.S. presidential administrations, and some individual U.S. states, and examines the policies they have on stem cell research. It also briefly explores stem cell laws in some countries outside the US.

U.S. Federal Stance on Stem Cell Research

Most basic biomedical science in this country, especially early-stage exploratory research, is funded by federal dollars. Led by the National Institutes of Health (NIH), federal government support, as much as $20 billion annually, is granted to various fields of research (Dunn, 2005). Federal funds are so important to research that this topic has been the focus of the stem cell debate. Currently, even under the Obama administration, no equipment purchased by federal funds is allowed for creating new human ES cells or cloned human embryos, however each is allowed using private funding (Federal Stem Cell Policy, 2012).

Clinton Administration and Stem Cells

Although Bush was repeatedly claimed as “the first president ever to allow funding” for human embryonic stem cell research (Republican National Convention, 2004; White House Press Briefing, 2005; Fox News Sunday, 2005), it was indeed the Clinton Administration that
was a much greater advocate of human ES cell research. In 1993, by enacting the National Institutes of Health Revitalization Act, Congress and President Clinton gave the NIH direct authority to fund human embryo research for the first time (National Institutes of Health Revitalization Act of 1993). NIH then established the Human Embryo Research Panel, made of scientists, ethicists, public policy experts, and patients’ advocates, to discuss the moral and ethical issues involved, and to discuss which types of experiments should be eligible for federal funding (Dunn, 2005). In September 1994, this NIH Panel released a report that recommended federal funding for some areas of human embryo research, including the destruction of spare embryos from fertility clinics to obtain stem cells (NIH, 1994). The recommendation was accepted by Clinton, with some exceptions. Clinton did “not believe that federal funds should be used to support the creation of human embryos for research purposes” (Clinton Presidential Materials….1994), and thus directed NIH not to allocate any fund for that research. However, the President’s directive did not apply to research involving “spare IVF embryos”, or research involving human parthenotes, which are eggs activated artificially rather than by fertilization (Stith-Coleman, 1998). Therefore, under Clinton’s administration, NIH proceeded to develop guidelines to support research using spare embryos.

But during the Gingrich era, Congress questioned the ethical concerns of human embryonic stem cell research, and the NIH guidelines were soon halted on January 26, 1996, when the Congress enacted the Dickey-Wicker amendment that prohibited NIH from using funds for human embryo research altogether (Stith-Coleman, 1998). The ban was passed as a rider attached to the appropriations bill for the Department of Health and Human Services (HHS). Since then, Congress has actively renewed the ban every year and relegated all human embryo research to funding from the private sector (Dunn, 2005).
The first human embryonic stem cell lines were created under such circumstances, being funded by private funds. In 1998, using private funds, James Thomson of the University of Wisconsin successfully created the first human ES cells (Thomson et al., 1998). NIH recognized the historic achievement, and Harold Vermus, director of the NIH, testified at a Senate hearing “This research has the potential to revolutionize the practice medicine” (NIH Director’s Statement…1998). However, the research could not flourish with the Dickey-Wicker Amendment in the way.

In 1999, Harriet Rabb, the top lawyer at the Department of Health and Human Services, released a legal opinion that reset the course for Clinton Administration policy. Since the Dickey-Wicker Amendment emphasized a ban on research involving creation or destruction of human embryos, it did not apply to human ES cells because they “are not a human embryo within the statutory definition”, according Rabb (Letter from HHS Gen, 1999). Despite the debate triggered by such a statement (Republican Senator Sam Brownback called it a bit of “legal sophistry”), the NIH, with the input from the National Bioethics Advisory Commission and others, went on to develop guidelines outlining the types of human ES cell research that would be eligible for federal funding (Dunn, 2005). These guidelines, known as the National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells (Guidelines), forbade the use of federal funds to destroy human embryos to derive stem cells, but permitted funding research with stem cells that had already been derived via private funds (National Institutes of Health Guidelines…2000). President Clinton strongly endorsed the new guidelines, stating that federally funded research on human stem cells offer “potentially staggering benefits” (Clinton touts…..2000). With the guidelines in place, the NIH began to accept grant proposals from scientists, but in the end the funding was not granted as President Bush entered the office in
2001. But it was President Clinton who first opened the door for human ES cell research.

*Bush Administration and Stem Cells*

When President Bush took office in January of 2001, he began to re-examine the policies set by his predecessor. First, Tommy Thompson, HHS Secretary of the Bush Administration, ordered a review of Rabb’s legal decision as well as the *NIH Guidelines*. During the review process, applications pursuant to the *Guidelines* would still be processed. In April 2001, however, Bush unilaterally imposed a complete moratorium on implementation of the *Guidelines*, and canceled the April 25, 2001 meeting that was to evaluate the first set of applications under the *Guidelines* (Memorandum in Support….2001). This decision saddened, angered, and frustrated supporters of human ES cell research.

On August 9, 2001, Bush went further. He announced that federal funding would now be restricted to “existing stem cell lines where the life and death decision has already been made” (Bush, 2001). He claimed the decision “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.” On the other side, for stem cells that do not involve embryos, the President made it clear that the federal government would continue supporting these other sources, including from umbilical cord blood, placentas, and adult and animal tissues, “which do not involve the same moral dilemma.” Three months later, his administration ordered an official withdrawal of the *Guidelines* that Clinton had authorized.

Under the 2001 Bush policy, federal funds only applied to research on existing stem cell lines that were derived 1) with the informed consent of the donors; 2) from excess embryos
created solely for reproductive purposes; and 3) without any financial inducements to the donors (The White House, 2001). NIH was asked to examine the derivation of all existing stem cell lines and create a registry of those lines that satisfied the Bush Administration criteria. The NIH Human Embryonic Stem Cell Registry was established, and stem cells eligible for federal funding and available to be shipped to scientists were listed there (NIH Human Embryonic Stem Cell Registry). As of August 11, 2004, the NIH registry listed a total of 22 stem cell lines available from seven sources (Johnson and Williams, 2005). However, as scientists noted, dozens of other stem cell lines had been created with private funds, which were easier to access, easier to maintain in the lab, and easier to differentiate into cell types of interest, compared to the limited presidentially-approved lines.

Efforts were made to loosen Bush’s restriction. On April 28, 2004, 206 Members of the U.S. House of Representatives sent a letter to President Bush, seeking to ease the federal policy on funding ES cell research (Legislative Report: 2004). On June 4, 2004, 58 U.S. Senators sent a similar letter, among who were 14 Republicans, including abortion opponents Trent Lott and Orrin Hatch. Also in June, 48 Nobel laureates, including Clinton’s NIH director Harold Varmus, endorsed John Kerry’s presidential candidacy, citing, among other things, the “unwarranted restrictions on stem cell research” imposed by President Bush. In April of 2005, in Congressional testimony, Bush’s NIH director Elias Zerhoni acknowledged that there is “mounting evidence” that a policy change would benefit science. Other top NIH officials agreed (Dunn, 2005). Despite these increased efforts, President Bush was resolute about stem cell research, and vowed on May 20, 2005 to veto legislation intended to ease the restrictions he imposed on stem cell research in 2001, dashing 201 sponsors’ hope to reach the 218 votes necessary to pass in the House before sending it to the Senate (Baker, 2005). “I’m a strong
supporter of adult stem cell research, of course.” Bush said in a meeting with the visiting prime minister of Denmark.” But I made it very clear to the Congress that the use of federal money, taxpayers’ money, to promote science which destroys life in order to save life is – I’m against that. And therefore, if the bill does that, I will veto it” (Baker, 2005). Bush showed his resolution again in July 2006 when he vetoed Congress’s bid to lift funding restrictions on human ES cell research (Babington, 2006).

In general, the Bush Administration supported and favored adult stem cell research and any other type of stem cell research that does not involve embryos. However, under his administration, human ES cell research suffered. Many scientists believe that the lack of federal funding during the Bush years hindered U.S. advancements in the stem cell field, as the number of available ES cell lines was actually far fewer than originally claimed (Holden and Vogel, 2002).

Obama Administration and Stem Cells

As Bush’s successor, President Obama turned out to be another advocate for ES cell research after Clinton Administration. In March 2009, President Obama issued an executive order (EO 13505) overturning the 2001 Bush restriction on federal funding for human ES cell research (President Barack Obama, 2009; Childs and Stark, 2009). The 2009 order cast new light for human ES cell research and stem cell research as a whole. The order also instructed the NIH to establish new guidelines for human stem cell research within 120 days of the executive order.

In July 2009, under the order’s instruction, the NIH issued “National Institute of Health Guidelines for Human Stem Cell Research” (Guidelines) that outlined the new policy (Federal Register, 2009). The Guidelines specified many other sources of human ES cells (hESCs) that
became eligible for federal funding, including hESC lines derived from embryos created expressly for research purposes or created using in vitro fertilization (IVF), and cell lines created by parthenogenesis or somatic cell nuclear transfer (SCNT) (Federal Register, 2009). However, the guidelines did not allow federal funding to create embryos solely for research purposes; those embryos have to be created with private funding, and then federal funding can be used to work with the ES cell lines derived from those embryos. The changes were largely great news to the stem cell society, although it still limited some very promising avenues of research, including the creation of stem cell lines using federal funds (Federal Stem Cell Policy). It also inadvertently limited the genetic diversity of federally funded hESC lines (Federal Stem Cell Policy).

Surprisingly on August 23, 2010, federal judge Royce C. Lamberth issued an order that not only overturned President Obama’s EO 13505, but also halted research approved even during the Bush Administration. He said in his ruling that the federal support for hESC research violated a federal law (the Dickey-Wicker Amendment) barring the use of taxpayer money for experiments that destroy human embryos (Stein and Hsu, 2010). As a consequence, the NIH was prohibited to operate under the new Guidelines. Many proponents for hESC research including Harriet S. Rabb from the HHS, and Sean Tipton from the American Society for Reproductive Medicine, argued that ES cell lines are themselves not embryos, thus “the NIH’s support of ES cell research did not violate Dickey-Wicker” that banned federal dollars from funding the destruction of embryos, and the Lamberth ruling was not accurate (Stein and Hsu, 2010). After much struggles, in 2011 the lawsuit against the Obama Administration’s funding of ES cell research was finally revoked. Judge Royce Lamberth, chief of the federal court in Washington, overturned his own lawsuit (Mears, 2011). On July 27, Lamberth finally stated that he was bound by the D.C. Circuit’s reasoning and conclusions that ES cell research is not “research in which a
human embryo or embryos are destroyed”, and therefore working with ES cell lines did not violate the federal law (Federal Stem Cell Policy). After that ruling, the Obama Administration’s rules successfully expanded the number of ES cell lines created under private funding eligible for federal funding from 22 during the Bush administration, to 128 and more. As of now, the eligible lines have increased to a total of 178, according to the latest statistics from NIH Human Embryonic Stem Cell Registry (NIH Human Embryonic Stem Cell Registry).

Despite the great success that President Obama has brought to stem cell research, certain areas are still unquestionably banned under the Dickey-Wicker Amendment, including the creation or destruction of human embryos for research using federal funding. As for reproductive cloning, the President was also quite determined to forbid it, saying: “We will ensure that our government never opens the door to the use of cloning for human reproduction. It is dangerous, profoundly wrong, and has no place in our society, or any society” (CBS/The Associated Press, 2009).

**Individual U.S. State Stances on Stem Cell Research**

While the federal government intensely wrestled with the policies for or against ES cell research, states passed their own laws. California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, New Jersey, and New York are among the states that encourage ES cell research with specific laws, while the law in South Dakota strictly forbids research on embryos regardless of the source (Johnson and Williams, 2005). There are fifteen states which have laws restricting research on aborted fetuses and embryos, and thirteen states which have restrictions on research using fetal or embryonic tissue derived from processes other than abortion (such as IVF or cloning); these restrictions may also preclude some forms of stem cell research (Johnson and
Williams, 2005).

**California**

In September 2002, California enacted the nation’s first law that expressly permits and encourages research involving the derivation of hESCs and cloned embryos (California Health and Safety Code §123440, 24185, 12115-7, 125300-320). The law assured the researchers and sponsors that it does not contradict the 2001 Bush policy which only pertained to federal funding. In 2004, with the support from Governor Arnold Schwarzenegger, California passed Proposition 71, with 59% of the vote, amending the state Constitution to facilitate ES cell research (Johnson and Williams, 2005). Under Proposition 71, a California Institute for Regenerative Medicine (CIRM) was established, and $3 billion of funding was raised through state bonds for ES cell research over the next 10 years. The funds may not be used for reproductive cloning, but may be used for therapeutic cloning (Proposition 71). In early May 2005, San Francisco was selected as the headquarters for CIRM by the 29 member governing board of CIRM.

**New Jersey**

In 2004, New Jersey became the second state to enact a law that specifically permits ES cell research (N.J. Stat, 2004) The law bans reproductive human cloning but allows cloning embryos for research purposes. In May 2004, Governor James McGreevey signed a bill to create the first state-funded ES cell research center (“U.S. States Making Stem Cell Policies”, 2004). One month later, on June 25, the state became the first to fund hESC research apart from the federal government, when the legislature passed a state budget that allocated $11.5 million to the newly chartered Stem Cell Institute of New Jersey (Mantel, 2004). The money has been
attracting private investment, according to the Institute’s founding Director (Mantel, 2004).

In January 2005, at a state speech, Acting Governor Richard Codey called for $380 million for stem cell research (Hawkins, 2005). $150 of it goes for a facility for the Stem Cell Institute of New Jersey near the Rutgers University campus in New Brunswick, and the rest of the money is for research grants. The plan was officially put onto the agenda after the November 2005 election (Margolin, 2005).

Massachusetts

In March 2005, the Massachusetts legislature approved a bill that clarifies state law on research involving hESCs and therapeutic cloning, and ensures that such research is permitted within a regulatory framework (Johnson and Williams, 2005). Despite Governor Mitt Romney’s veto on the bill, on May 31, 2005, the House and the Senate overrode the Governor’s veto, and passed the bill with a vote of 112 to 42, and 35 to 2, respectively.

On May 15, 2007, Governor Deval Patrick proposed a 1- billion plan for advancing stem cell scientific research (Estes, 2007). In the 10-year initiative, academic research and start-up companies would be funded, and most importantly, a stem cell bank at the University of Massachusetts would be established for newly created ES cell lines, a controversial area barred from federal funding at that time (Estes, 2007). Later in the same year, as part of the Governor’s Life Sciences initiative, the Board of the Massachusetts Life Sciences Center (MLSC) approved more than $8.2 million in funding to the University of Massachusetts Medical School (UMMS) to establish the Massachusetts Human Embryonic Stem Cell Bank and an international Massachusetts hESC Registry, and $12 million in funding for matching grants (Shelton, 2007). In 2008, Patrick’s bill was officially approved by the Massachusetts legislature and signed by the
Governor into law on June 16th (News In Brief, 2008).

To date, the Massachusetts Human Embryonic Stem Cell Bank and International Registry have been serving stem cell researchers all over the world. It provides comprehensive information on pluripotent stem cells, high quality stem cell lines, and state-of-the-art training and educational resources (Massachusetts Human Stem Cell Bank and International Registry, 2011).

**International Laws and Embryonic Stem Cell Research**

The international community has also taken a variety of legislative actions regarding stem cell research. In November 2004, the United Nations General Assembly (UNGA) “averted a divisive vote” on two international conventions against human cloning by adopting Italy’s proposal “to take up the issue again as a declaration at a resumed February session” (Andrews, 1998). A convention is a legally binding treaty that comes into force upon ratification by a certain number of member states (United Nations, 1997). Though a declaration initially is not legally binding until ratified, it “carries moral weight because it is adopted by the international community” (United Nations, 1997). The two international conventions were proposed by Costa Rica (backed by the United States), which aimed to allow all human embryonic cloning, and by Belgium, which sought to allow only reproductive cloning. On March 8, 2005, the UNGA further approved a nonbinding resolution urging member states to adopt legislation “to prohibit all forms of human cloning in as much as they are incompatible with human dignity and the protection of human life.” The United States voted for the measure.

The European Union clarified its stance on stem cell research in November 2003 (Committee on Industry…2003). Under the terms of its sixth research framework program (FP6),
the EU may fund ES cell research regardless of the date that the stem cells were procured from embryos. It had considered a cut-off date, such as that specified in the 2001 Bush policy, but finally it abandoned the idea (Softcheck, 2003). FP6 allows funding for research on tissue derived from “spontaneous or therapeutic abortion,” but not for the creation of human embryos for the purpose of stem cell procurement (Softcheck, 2003). It also implies but does not openly state that it will allow funding for research on embryos derived from IVF, and “no longer requires parental consent where embryos have to be destroyed in order to produce embryonic stem cell lines” (Six Framework Programme, 2003). According to Members of the European Parliament, FP6 funding decisions should depend “both upon the contents of the scientific proposal and the legal framework of the Member States involved” (Softcheck, 2003). Below is a list of EU members’ legislative decisions on the subject as of 2004 (Matthiessen-Guyader, 2004):

- **Allowing for the procurement of human embryonic stem cells from excess IVF embryos by law under certain conditions:** Belgium, Denmark, Finland, France, Greece, the Netherlands, Spain (“Spain to Begin ES Cell Research, 2004”), Sweden, Switzerland (Swiss Voters Back Stem Cell Research”, 2004), and the United Kingdom (Hunter, 2004; “HFEA Grants the First Therapeutic Cloning License for Research”, 2004).
- **Allowing some research activities on excess IVF embryos, but having no specific reference to human ES cell research:** Estonia, Hungary, Latvia, and Slovenia.
- **Prohibiting the procurement of hESCs from excess IVF embryos but allowing by law for the import and use of hESC lines under certain conditions:** Germany.
- **Prohibiting the procurement of human ES cells from excess IVF embryos:** Austria, Ireland, Lithuania, Poland, and Slovak Republic.
- **No specific legislation regarding human embryo research or human ES cell research:** Czech Republic, Luxembourg, Malta, Portugal, and the republic of Cyprus.
- **Allowing by law for the creation of human embryos for research purposes:** UK and Belgium.
- **Prohibiting the creation of human embryos for research purposes and for the procurement of stem cells by law or by ratification of the Convention of the Council of Europe on Human rights and Biomedicine signed in Oviedo on April 4, 1997:**
Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Netherlands, Lithuania, Portugal, Slovak Republic, Slovenia, and Spain.

Besides the UN and EU, other countries also sought to regulate stem cell research. In March 2004, Canada enacted legislation that allows stem cell and other research to experiment on donated embryos created but no longer needed for reproductive purposes (Assisted Human Reproduction Act, 2004). Japan permits the creation of embryos for stem cell and other research (Embryo Stem Cell Research OK’d, 2004; Japan Allows for Creation of Embryos for Research, 2004), while Australia permits the use of spare IVF embryos for stem cell research (Research Involving Human Embryos Act, 2002). The Australian government was reported to have allocated $57.9 million to its National Stem Cell Center in 2004 (The National Stem Cell Centre, 2004). In addition, Singapore allows cloning human embryos and keeping them alive for up to 14 days to extract stem cells. It also provides “research-friendly policies and generous government funding that have already helped jump-start the tiny city-state’s nascent stem cell sector. And its resort-like Biopolis, was created to give biotech researchers and their families a place to live and work” (Singapore Hosts Stem Cell Meeting, 2004). South Korea permits reproductive cloning but it also enacted legislation to regulate and license reproductive cloning (Stem Cells Extracted from Human Clone, 2004). In developing countries such as China, stem cell research is still more limited by the funding than by regulations (Murray, 2006).

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The research performed for this IQP has shown that there are a wide variety of views on embryo and ES cell research, reflecting society’s different views on when life begins and the nature of creation. These various views are also reflected in the wide assortment of policies enacted by different nations concerning stem cell research and cloning. Although it is extremely difficult to reach a unified consensus religiously, politically, or scientifically, it is most important that all these views exert a strong influence on the public debate.

The author most agrees with the stem cell policy adopted by the Singapore government, which strongly encourages and funds embryo and ES cell research. It is strongly believed by author herself that stem cell research and therapeutic cloning should be continued and should not be stopped. The debates and objections will certainly continue, but with education my hope is that human civilization will advance. Since embryos and ES cells offer the best possibility for regenerative medicine to treat fatal diseases, if done with good intentions, the research should continue. I encourage the use of embryos, whether discarded from IVF procedures, therapeutically cloned by SCNT, or donated by paid donors solely for research purposes. ES cell lines should also be readily derived from those embryos and used to treat diseases. I do however, agree with most nations that reproductive cloning should be banned, at least for now.

When treating individual patients, cautions should be exerted to protect patient suffering (for example by screening for potential cancer formation at the cell injection site), and certain restrictions should be enforced to avoid the exploitation of women, the abuse and blasphemy of life, and commodification of reproductive tissues and reproductive labor. We also want to show
respect for the moral wisdom that emerges from religious traditions, as this helps to make use of our scientific knowledge in a thoughtful and sensible way. In this view, adult stem cells and iPS cells should be favored whenever possible in place of ES cells to get around with the controversy of working with embryos and ES cells. However, if adult stem cells are not sufficient for treating a particular disease, then ES cells and therapeutic cloning should be pursued.