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STEM CELLS AND SOCIETY

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STEM CELLS AND SOCIETY

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ABSTRACT

The purpose of this project was to examine the effects of technology on society, using stem cell research as an example. Stem cell research is far more complex than most believe, so in this project the first two chapters discuss the many different types and variations of stem cells that exist as well as their applications. The latter two chapters deal with the ethical issues that surround this ground breaking research, and the laws various countries have enacted to help control the technology. By the end of this IQP, both authors concluded that stem cell research has tremendous potential, but must be performed in an ethical manner to minimize controversial issues. The progression of this science has the capability to improve the lives of millions which simply cannot be ignored.

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PROJECT OBJECTIVES

The objectives of this IQP project were to examine the topic of stem cells, and to discuss the effect of this controversial technology on society. The purpose of chapter-1 is to describe the many different types of stem cells and their potencies, as well as document how they are isolated and classified. Chapter-2's purpose is to document the advantages and disadvantages of the varying types of stem cells, and discuss the potential applications stem cells could be used for. Chapter-3's purpose is to examine the ethics that surround this controversial topic by describing the ethical position of five of the major world religions, while Chapter-4 examines the laws that the US and international countries have enacted to govern the use of stem cells. Finally, a conclusion is made by the authors regarding the use of stem cells, and which laws best represent the author's point of view.

Chapter-1: Stem Cell Types

Bryan Choate

Over the past couple of decades, stem cell research has become a worldwide phenomenon, infiltrating many aspects of modern day society. Medical research, political agendas, and religious disputes have all been influenced by stem cell technology. But what makes this cell type so different from the plethora of other cell types present in a human body? What makes them so different from say a skin cell or a muscle cell found in the bicep of a person? And to make things more complex, stem cells are not all alike. To help understand the potential of stem cells and their controversies, this chapter provides a brief background on their types and potencies.

General Stem Cell Characteristics

Two main characteristics define a stem cell: the ability to self-renew and the ability to differentiate into other tissues. The capacity to self-renew refers to the ability of the stem cell to divide multiple times giving rise to more stem cells that all exhibit the same traits. Some stem cell lines are so long lived, they last the lifetime of the individual. Differentiation is the ability of a cell to change into specialized cells that constitute the fundamental make up of our tissues and organs (International Society, 2009). Because stem cells have the ability to form new tissues, they have been focused on in the medical world. "This unique quality of stem cells make them ideal for treating injury and disease by repairing or replacing damaged or diseased body cells with healthy new cells" (MedIndia.com, 2006).

Many diseases or injuries can benefit from the implementation of stem cells. One such example of this is a person who has experienced a myocardial infarction (heart attack), where the

blood supply has diminished in a heart vessel, causing tissue necrosis downstream. But, by transplanting stem cells into the damaged area allowing them to differentiate and grow into new healthy tissue, there is the possibility that new myocardial muscle cells may develop regenerating and restoring function to the once damaged organ (MedIndia.com, 2006). Examples like this, among others, are why stem cells have been heavily focused on in the world of medical research. But there is much more to stem cells than there appears, including multiple different types and potencies.

Stem Cell Potencies

In the world of stem cells, there exist multiple types, each with their own unique characteristics that serve as advantages or disadvantages in a given situation. Each of these stem cell types come from a different place in the body, or are formed at different points in development. The four main types include embryonic stem cells, induced pluripotent cells, parthenogenetic embryonic stem cells, and adult stem cells. Each of these various types will be explained in further detail below. However, each cell type also has a different *potency*. Potency refers to which cell types a given stem cell can differentiate into; the higher the potency, the greater number of tissues the cell can form.

The highest level of potency is *totipotency*. Totipotent cells have the ability to form all cells of an adult organism plus extra-embryonic tissues such as the placenta. Only the newly fertilized zygotes through cells of the 8-cell stage are considered to be totipotent; i.e. cells through about 3 days post-fertilization (Types of Stem Cells, 2004). The second tier of potency is *pluripotent* stem cells. These cells can form all cells in the adult, but cannot form placenta. Embryonic stem cells, found in a day-5 blastocyst, are pluripotent. The next level below

pluripotency is *multipotency*. These cells have the potential to make several different cell types of related cells. Examples of multipotent cells include mesenchymal stem cells which have the ability to differentiate into several different tissue types, and hematopoietic stem cells that can form all the cellular components of blood. The lowest level of potency is *unipotency*. As the prefix uni- suggests, this cell type only has the ability to differentiate into one type of cell, typically the tissue from which the stem cells was derived. An example of this can be epithelial stem cells which appear to only be capable of making epithelial cells.

Embryonic Stem Cells:

Embryonic stem (ES) cells are pluripotent cells derived from the 5-day old human embryo. They are pluripotent and have the ability to differentiate into over two hundred different cell types that found in the body. Egg and sperm cells are fertilized *in vitro*, and the zygote is grown about 5-days to the blastocyst stage. The blastula consists of an inner cell mass (from which ES cells are obtained), and an outer trophoectoderm layer. The ES cells are isolated from the inner cell mass, which usually destroys the embryo. Once the cells are extracted from the inner cell mass, they can be grown into ES cell lines (International Society, 2009).

Most of the embryos used for deriving ES cell lines were originally created for reproductive purposes at *in vitro* fertilization (IVF) clinics. Once the family has enough children, the excess embryos are usually discarded, so clinics sometimes ask for donor consent to use the excess embryos for research. ES cell lines were first isolated in 1981 from mice (Martin, 1981) and from humans in 1998 (Thomson et al., 1998). The ES cells are isolated from the inner cell mass of the blastocyst, and plated onto a feeder layer of irradiated mouse fibroblast cells that provides a sticky scaffold to which the human ES cells may attach and releases nutrients into the

culture medium that help stimulate growth (NIH, 2005). If the ES cells continue to grow and divide, they crowd the original dish, and then they are split into other dishes. If these newly transferred cells survive, the re-plating of the cells can be repeated as many times as needed to provide large numbers of cells for therapy. The process in which the cycles of sub-culturing takes place is referred to as passaging.

iPS Stem Cells

"Generating pluripotent stem cells directly from adult cells isolated from patients is one of the ultimate goals in regenerative medicine" (Yamanka, 2007), and over the past five years the most exciting cell type addressing this is the revolution of induced pluripotent stem (iPS) cells. In this process, an adult skin cell is directly reprogrammed by transcription factors to de-differentiate the cell into a pluripotent cell. The strategy of cellular reprogramming was first introduced and pioneered by Shinya Yamanaka of Kyoto University in Japan who first accomplished this in mice (Takahashi et al., 2006), then later in humans (Takahishi et al., 2007). Yamanaka's group first used retroviruses to insert four genes encoding transcription factors Oct3, Sox2, c-Myc, and Klf4 into the chromosomes of mouse skin cells to induce their reprogramming (Aldhous, 2009). Initially, 24 different potential factors were tested for their ability to induce pluripotency, which eventually lead to the identification of the four transcriptions factors mentioned above. Later experiments used three factors, then two, and introduced the transcription factor proteins themselves instead of the genes to avoid genetic reprogramming. But because viruses were used to deliver the genes, and in some cases tumors formed at the injection site, in later experiments viruses were eliminated along with the c-Myc oncogene component to minimize tumor formation (Aldhous, 2009).

Yamanaka is also focusing making iPS cells by fusion between somatic cells and ES cells to produce a hybrid cell that is pluripotent by nature, although this process uses controversial ES cells. His group is also working on packing the necessary genes into a "piggyBac" transposable element that ejects itself from the chromosomes upon reprogramming of the cell (Aldhous, 2009). These techniques offer exciting and fascinating new ways to reprogram generic somatic cells into pluripotent cells that might be used in lieu of ES cells to treat diseases.

Parthenogenetic Embryonic Stem Cells

Parthenogenesis, "virgin birth", is a biological process in nature which allows lower organisms such as reptiles and insects to initiate embryonic development without a male counterpart. This form of asexual reproduction has surprisingly become a promising source of ES cells. Although parthenogenesis does not normally occur in mammals, mammalian eggs can be chemically treated to induce cell division without fertilization. Once the treated embryo begins cell division, it can be grown to the blastocyst stage from which ES cells are obtained (Linzhao, 2008). Even though ES cells can be isolated, the embryo is not capable of surviving more than a few days, so some scientists believe parthenote embryos are advantageous to fertilized embryos. There is no chance that human parthenote embryos would develop into a human being, which might reduce their ethical concerns (Westphal, 2003).

Though the potential for this parthenogenetic technique is great, there are still many unknowns that might limit progress for parthenote-derived ES therapies. An example of such a limitation would be the determination of the normality of the stem cells retrieved from a parthenogeneic embryo; since the parthenote cells are derived from one parent there is the possibility that these cells will be dangerously inbred which could lead to complications if used

in human patients (Weiss, 2001). Other concerns focus on whether they are more prone to metastasize like tumor cells? At this time there simply is not enough information to address these concerns, but in time and with further research perhaps these cells can be proved to be safe and effective.

Adult Stem Cells

Within the many adult tissues of the body there exists a particular type of cell specific to each tissue type with the ability to replace cells in that tissue that have died or that can heal tissue after an injury. These cells are referred to as adult stem cells (ASCs), which inhabit many areas of the body ranging from skin, to muscle, to bone marrow. ASCs are either multi-potent or uni-potent, so they can only differentiate into a limited number of mature cell types, usually the one tissue in which these stem cells reside. ASCs are often very difficult to isolate due to their rarity (International Society…2009). However, a few cell types such as hematopoietic or cardiac stem cells have allowed researchers to investigate this type of stem cell further.

Hematopoietic Stem Cells

The most widely studied ASC is the hematopoietic stem cell (HSC). These cells are found in bone marrow, but are also located in umbilical cord blood or peripheral blood. Traditionally, HSCs are isolated from the bone marrow and contain the ability to renew or to form all types of blood cells (white blood cells, red blood cells and platelets). HSCs behave as normal white blood cells in culture, which makes isolating and growing them particularly difficult. Instead of using morphology, scientists today try to identify HSCs by cell surface markers. It is estimated that one in every 10,000 to 15,000 bone marrow cells are HSCs, and that

number jumps to one in 100,000 in the blood stream. Even though HSCs are difficult to identify, scientists have determined that there exist two unique types: one with the ability to regenerate all types of blood cells, and the other with the potential to regenerate the bone marrow tissue itself over a span of a few months (Hematopoietic Stem Cells, 2005).

Cardiac Stem Cells

Another very exciting discovery in the world of adult stem cells is cardiac stem cells (CSCs). It was thought for decades that the heart could not repair itself by regenerating damaged tissue, and that the number of cardiac cells a person was born with was the number that person would have for the rest of their lives. But recent studies have proven that the heart actually maintains a pool of cardiac stem cells that have the ability to differentiate into new cells if damage to the organ occurs.

CSCs were first isolated as c-kit^{+} cells (Beltrami et al., 2003), and later as Isl1^{+} cells (Laugwitz et al., 2005). Researchers have been able to isolate cardiac stem cells from the rat, and once cultured they were able inject those stem cells into rats with heart damage thereby regenerating 70% of the damaged myocardium within a 20 day period (Touchette, 2003). Similar cells have also been discovered in humans by researchers who were examining patients that had undergone cardiac surgery. It appears that the stem cells had actually been trying to repair the damaged heart tissue, although usually insufficiently. Now that these cells have been identified in humans, the next step is to learn how to mobilize them and stimulate their ability to grow and differentiate into new healthy cardiac tissue (Touchette, 2003).

Neural Stem Cells

Like cardiac tissue, neurological tissue was once thought not to be able to regenerate after trauma or death. However, in the mid 1990's that idea would soon become irrelevant with the discovery of neural stem cells (NSCs). During this time neuroscientists learned that particular parts of the adult human brain under certain conditions had the ability to generate and give rise to new neurons. The most interesting part of this revelation was that these new neurons were formed from a neural stem cell that appeared to reside in a fetal state resembling cells in a fetus that form the brain and spinal cord (NIH, 2005). Researchers also found that these undifferentiated cells were able to generate almost every type of cell in the human brain, including neurons, the main messenger carrier in the central nervous system (NIH, 2005).

Mesenchymal Stem Cells

Within the adult stem cell universe there exists yet another type with immense potential, mesenchymal stem cells (MSC). Unlike most ASCs, MSCs are relatively easy to isolate, culture, and manipulate in *in vitro* environments (Nardi and Meirelles, 2006). These cells have great potential when it comes to therapeutic applications due to their plasticity; however, most of their properties are not fully understood. MSCs are located in bone marrow and many other tissues. They are usually identified by a combination of their physical, phenotypic, and functional properties (Nardi and Meirelles, 2006). Most of our knowledge derived from MSCs comes from *in vitro* studies where millions of MSCs have been cultured. Due to the great potential that MSCs have when it comes to replacing damaged tissues like bone, cartilage, tendon, and ligament, MSC research will continue until their properties and location are fully understood (Nardi and Meirelles, 2006).

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Chapter-2: Stem Cell Applications

Rebecca Paz

Recent advances in stem cell (SC) research have increased our understanding of cellular differentiation and human development. Their potential for self-renewal and differentiation into specific cell types has resulted in a great deal of enthusiasm for their current and potential applications in medicine to repair tissue or restore function. The previous chapter introduced the reader to the various types and sources of stem cells, and provided a few examples of their uses. The purpose of this chapter is to expand on their uses providing detailed information on how stem cells are being used to treat a selected group of four main categories of diseases. This information on stem cell medical benefits will serve as introductory material for subsequent discussions on ethics and legalities.

Table-1 provides a brief summary of the information presented in Chapter-1 on stem cell types relative to their advantages and disadvantages. This information helps scientists select the most suitable cell type(s) for a wide range of applications.

Table-1: Advantages and Disadvantages of Different Stem Cell Types.

STEM CELL TYPE	ADVANTAGES	DISADVANTAGES
Embryonic (ESCs)	-Pluripotent -Relatively easy to isolate -Highly productive in culture -High capacity to integrate into host tissue	-Immune rejection unless derived from patient as iPS cells. -Might differentiate into wrong cell type or induce tumors -Risk of contamination from required feeder layers -Ethical concerns from embryo sources -Tight government regulation
Adult (ASCs)	-Multipotent or unipotent	-Scarce and difficult to isolate

	-Less likely to induce immune reaction if autologous -May be stimulated by drugs -Fewer ethical concerns -Less government regulation	-Grow slowly -Differentiate poorly in culture -Difficult to handle and produce in adequate amounts for transplantation
-Mesenchymal stem cells (MSCs)	-Easy *in vitro* isolation and expansion -Capacity to migrate to sites of tissue damage, inflammation and neoplasia -Reduced immune rejection	
-Adipose-derived stem cells (ASCs)	-Secrete cytokines and growth factors -Reduced immune rejection	
-Induced pluripotent stem cells (iPSCs)	-Likely pluripotent -No immune rejection: patient specific therapy -Easy harvesting and production with high yield	-Risk of cancer formation

(Sources: Liras, 2010; Leeb et al., 2011; Daniele et al., 2011)

According to Liras (2010) by the year 2010, stem cell therapy procedures used the following types of cells: human embryonal stem cells (hESCs) 13%, fetal SCs 2%, umbilical cord SCs 10%, and adult SCs in 75% of the reported treatments. The main strategies used in the clinical applications of SCs include the stimulation of endogenous SCs with growth factors, cytokines or secondary messengers, the direct administration of unaltered SCs, and the transplantation of SCs after *in vitro* culturing (Liras, 2010; Terskikh et al., 2006; Leeb et al., 2011). Following are the most common clinical applications of SCs to date, including applications for hematologic disorders, cardiovascular and ischemic disorders, spinal cord injury and central nervous system disorders, and diabetes.

Hematologic Disorders: The Use of Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are multipotent adult stem cells that can renew themselves and differentiate into all types of blood cells (white blood cells, red blood cells, and platelets). HSCs are responsible for the highly complex process of hematopoiesis (blood formation), which allows the body to respond to events such as infections and bleeding. HSCs were originally obtained from the bone marrow, but they are also present in the peripheral blood after stimulation with growth factors, and are present in relatively large quantities in umbilical cord blood (Hematopoietic Stem Cells, 2005). Recently, HSCs have also been derived by the differentiation of human ES cells and from induced pluripotent stem cells (iPSCs) (Kaufman, 2009). Due to their accessibility, HSCs have been extensively studied in the research and clinical settings, and represent the best characterized of all stem cell types.

After World War II, there was an intense interest in the effect of radiation on the body. Initial experiments in animals after exposure to intense radiation showed that the decreased blood cell counts associated with radiation could be remedied by the infusion of bone marrow from healthy animals. Later studies led to the discovery of HSCs as the regenerating component of the bone marrow infusions, and to the realization of their potential medical uses. Animal models of bone marrow transplantation were successful and were eventually followed by the first human bone marrow transplants (Thomas et al., 1957). Most of the initial transplants in humans were not successful, due in part to a host of complications including graft rejection, graft-versus-host disease (GVHD), disease relapse, and infections. Better understanding of the biology of stem cells, improvements in the technology, availability of new drugs, and increased donor pools eventually led to better clinical results (Little and Storb, 2002). Although hematopoietic stem cell transplants continue to be complicated and risky procedures, they are currently used to treat

a variety of hematologic malignancies like leukemia and lymphoma, to rescue the bone marrow after intense cancer chemotherapy, and to treat bone marrow failure and genetic disorders. A retrospective study conducted by the Worldwide Network for Blood and Bone Marrow showed that of 50,417 hematopoietic stem cell transplants performed worldwide in 2006, 54.5% were for lympho-proliferative disorders, 33.8% for leukemias, 5.8% for solid tumors, and 5.1% for non-malignant conditions (Gratwohl et al., 2010).

HSCs and Leukemia and Lymphoma

Leukemia and lymphoma result from the uncontrolled proliferation of blood cells. The treatment for these disorders usually involves the destruction of the malignant cells and the HSCs that form them by chemotherapy and/or radiation therapy. In some hematologic malignancies a hematopoietic stem cell transplant from a donor (allogeneic transplant) may be the treatment of choice. In these cases, the patient receives intense chemo and/or radiation therapy to kill the malignant cells and bone marrow prior to the transplant, then receives an intravenous infusion of the donor's bone marrow or peripheral blood cells containing HSCs. Peripheral blood transplants (from patients treated with growth hormones to stimulate release of HSCs into the blood) have the advantage of a less invasive extraction than bone marrow and yield a higher concentration of HSCs (Koca and Champlin, 2008). In some instances, HSCs can be harvested from the patient and replanted after therapy (autologous transplant) avoiding immune rejection of transplanted extraneous cells, so long as the patient's own HSCs are not cancerous.

These therapeutic approaches are not without risk. HSC transplants are often associated with serious complications, including infections, veno-occlusive disease (VOD) of the liver, GVHD, graft failure, and relapse. The patient's immune system can be severely compromised by

pre-transplant conditioning therapy and the immunosuppressive drugs used post-transplantation. Prophylactic antibacterial, antifungal, and antiviral medications are often used in an attempt to prevent infectious complications frequently encountered, and these can carry a high mortality. VOD of the liver is a poorly understood condition characterized by jaundice, abdominal pain, hepatomegaly, fluid retention and weight gain that may be seen in 20-50% of transplanted patients treated with chemotherapy and radiation. GVHD is a condition in which lymphocytes from the donor recognize foreign antigens in the host cells and mount an immunologic reaction against them, causing tissue destruction in different organs including dermatitis, hepatitis and enteritis. Prophylactic therapy with drugs that suppress the immune response reduces the incidence of GVHD. Graft failure results from failure of the transplanted SCs to thrive, which may occur in association with disease relapse (Tabbara et al., 2002).

HSC Rescue of Cancer Chemotherapy

The treatment of certain non-hematologic malignancies, such as breast carcinoma, depends on how advanced the disease is, and usually involves the removal of the tumor by surgery. In advanced cases, high doses of chemotherapy and/or radiation therapy are used. In addition to killing the tumor, the treatment causes the destruction of rapidly growing normal bone marrow cells, resulting in low blood counts and increased risk of infection and bleeding. In the 1980s, autologous stem cell transplants were used in patients with advanced cancer in an attempt to rescue the patient's bone marrow cells after intense chemo or radiation therapy. A recent study by the German Institute for Quality and Efficiency in Health Care (Autologous Stem Cell Transplant, 2009) reviewed 19 clinical trials involving autologous stem cell transplants in the treatment of advanced breast cancer, and concluded that compared to conventional

chemotherapy, autologous SCT can significantly extend clinical event-free survival, but may also give rise to severe complications (Peters et al., 2000). Similar results have been found for autologous HSC transplants (HSCT) for neuroblastoma and other non-hematologic malignancies (Kremer, 2011). Most importantly, the transplant's graft-versus-tumor effect, in which an immunologic reaction of donor lymphocytes is mounted against molecules present in cells from the patient's cancer cells, increases the anti-tumor effect (Takahashi et al., 2008) and can contribute to the overall elimination of malignant cell growth.

HSCs and Hematologic Non-Malignant Disorders and Inborn Errors of Metabolism

The first successful allogeneic HSCT on a patient with severe combined immunodeficiency (SCID) was performed in 1968 (Sullivan et al., 2000). SCID is a genetic disease that destroys a patient's immune system leading to severe infections and early death. Since 1968, HSCT has been used to treat a variety of non-malignant blood disorders, including aplastic anemia, Wiskott-Aldrich syndrome, thalassemia, sickle cell disease, and storage diseases such as Hurler syndrome. The best results are obtained in young patients and those that have HLA-matched identical siblings. HSCT is potentially curative in these disorders, but can be associated with complications like GVHD and opportunistic infections. It is reserved for severe cases without alternative therapy (Sullivan et al., 2000; Neven et al., 2009). In gene therapy, the patient's HSC are isolated, genetically engineered to express a normal copy of the defective gene, and transplanted back to the patient. This technique has curative potential and has been successfully used to treat SCID (Malech et al., 1997; Cavazana-Calvo et al., 2000; Bordignon, 2006). Several ongoing clinical trials may shed some light in this promising technology (http://clinicaltrials.gov/).

Stem Cell Treatments of Cardiovascular and Ischemic Disorders

Myocardial infarction is caused by the obstruction of the cardiac blood flow, resulting in necrosis and loss of heart muscle cells. Regeneration of the lost tissue by stem cell therapy has been the subject of multiple studies reviewed by: Laflamme et al., 2005; Christoforou and Gearhart, 2007; Reinecke et al., 2008. The papers focus on the ability of the different types of SCs to differentiate into functional cardiac cells.

Adult Stem Cell Treatments of Cardiovascular and Ischemic Disorders

Hematopoietic Stem Cells: The use of HSCs in heart regeneration has been studied for a number of years, which is surprising given their primary role of replenishing blood cells, not heart cells. The results have been controversial. Initial studies in mice (Bitter et al., 1999) suggested that HSC from a bone marrow transplant differentiated into cardiac cells; however, later studies (Alvarez-Dolado et al., 2003) indicated that the HSC do not differentiate into heart cells, but rather fuse with them. Clinical trials involving the injection of bone marrow HSCs into the heart of post-infarcted patients have shown mixed results (Lunde et al., 2006; Schächinger et al., 2006; Assmus, 2006). Additional clinical studies are needed to clarify these discrepancies.

Skeletal Muscle Stem Cells: Satellite cells (myoblasts), found in adult skeletal muscle, retain the ability to differentiate and regenerate skeletal muscle. Clinical studies in humans (Siminiak et al., 2004) that administered satellite cells to diseased hearts demonstrated some improvement in cardiac function, but other studies have shown that myoblasts found in skeletal

muscle do not differentiate into heart cells and instead retain their skeletal muscle characteristics (Reinecke et al., 2002).

Endogenous Cardiac Stem Cells: Cells thought to represent true cardiac progenitors have been identified in the heart; these cells can self renew and can differentiate into cardiac cells. *In vitro* and animal studies have suggested they function in cardiac regeneration (Bearzi et al., 2007). Several clinical trials testing the effect of cardiac stem cells in regenerating cardiac muscle are currently being conducted, but the results are still pending (http://clinicaltrials.gov. NCT00474461, NCT00893360).

Mesenchymal Stem Cells: These cells form the bone marrow framework, are able to differentiate into several cell types, and express growth factors and cytokines. They have been proposed as potential treatments for cardiac disorders (Jain et al., 2005), and some clinical studies in humans have shown promising results (Chen et al., 2004). Additional studies are needed to understand their mechanism of action.

Embryonal Stem Cell Treatments of Cardiovascular and Ischemic Disorders

Cardiac progenitor cells have been differentiated from mouse and human embryonal stem cells (ESCs), and have been used *in vitro* to study cardiac disease and cardiac response to drugs. Animal studies have shown that cardiac progenitor cells derived from ESCs have the capacity to differentiate into adult cardiac cells and engraft, but they are associated with *in vivo* complications such as immune rejection and the formation of tumors (Laflamme et al., 2005). A few studies involving human ESCs have been published (Laflamme and Murry, 2005) and have

shown their ability to engraft, but these human studies are complicated by the scarcity of ESCs, immune rejection by the host, the risk of tumor development, and ethical concerns.

iPS Cell Treatments of Cardiovascular and Ischemic Disorders

The discovery of induced pluripotent stem cells (iPSCs) that result from the genetic re-programming of adult somatic cells (Takahashi, 2006; Takahashi et al., 2007) has revolutionized the field of stem cell research. iPS cells may offer the pluripotent advantages of human ESCs, but without the associated ethical concerns because embryos are not destroyed. In addition, iPSCs provide the ability to use a patient's own autologous cells, reducing the chance of rejection. iPS cells have been shown to be capable of differentiation into cardiac lineages (Reinecke et al., 2008). Future animal and clinical studies are needed to explore the use of iPSCs in cardiac regeneration.

Treatment of Neurological Disorders with Stem Cells

Central nervous system (CNS) disorders, often caused by the seemingly irreversible loss of its cellular components, are some of the most devastating diseases in humans. Stem cell therapy may offer the opportunity for tissue regeneration. The CNS has traditionally been seen as a terminally differentiated system, with no regenerating capability. Several studies, however, have demonstrated the persistence of neural stem cells (NSCs) in certain regions of the adult human brain (Eriksson et al., 1998; Pinkus et al., 1998). Studying the normal embryological development of the nervous system has enhanced our understanding of NSCs and the possible applications of stem cell therapy for these disorders.

NSCs are undifferentiated cells found in the embryonic neural tube that have the capabilities of self renewal and differentiation into the three major cell types of the CNS, neurons, astrocytes, and oligodendrocytes. NSCs are identified by the expression of specific marker molecules and have also been found in the periventricular area of adult human brains (Okano, 2010). In culture, NSCs are identified by their ability to form neurospheres. Animal and human NSCs have been cultured and expanded *in vitro* in several studies (Lindvall and Kokaia, 2006; Okano, 2010).

Some of the neurological disorders that may benefit from NSC therapy include acute lesions like spinal cord injury, and degenerative disorders like Parkinson's disease, Huntington's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis (ALS). Spinal cord injury is associated with a loss of neurons and glial cells, inflammation and demyelination (degeneration of the myelin "sheath" of a neuron), resulting in the loss of movement and sensation below the level of the lesion. Spinal cord injury treatment with stem cells has been an area of extensive research (Tewarie et al., 2009; Koch et al., 2009). A study involving the transplant of oligodendrite progenitor cell in rats showed improvement of functions, and suggests that such improvement may be in part the result of remyelination (Keirstead et al., 2005). Additional pre-clinical studies are necessary to optimize this therapy. Some clinical trials are ongoing, primarily involving somatic stem cell transplantation, including hematopoietic stem cells and adipose-derived stem cells (http://clinicaltrials.gov/ct2/home).

Neurodegenerative disorders, like Parkinson's, Huntington's, Alzheimer's, and ALS are characterized by a selective, gradual loss of neurons and or glial cells in particular areas of the CNS, consequently with a variety of clinical manifestations. Transplantation of stem cells into animal models has shown some functional improvement achieved by replacing lost neuron and

glial cells, inducing remyelination, and controlling the inflammatory response (Lindvall and Bjorklund, 2004; Lindvall and Kokaia, 2006; Lindvall and Kokaia, 2010). According to Lindvall, transplanted fetal dopaminergic cells were able to engraft, secrete dopamine, and improve symptoms, although the clinical outcomes of the patients were variable (Lindvall and Bjorklund, 2004). Additional research studies are needed before these therapies become clinically available.

Treatment of Diabetes with Stem Cells

Type-I diabetes is caused by the reduction or the absence of the hormone insulin, while Type-II is caused by a lack of response to insulin. Insulin is produced by the β-cells of the pancreas and stimulates the uptake of glucose from the blood into cells. Without insulin the resulting high levels of glucose in the blood can cause multiple medical complications. Diabetes can be temporarily controlled by the administration of exogenous insulin, but the only potential cure is offered by pancreatic transplantation or by cell therapy. Recent advances in stem cell understanding and technology have suggested the use of pluripotent stem cells as a source of β-cells (Mayhew and Wells, 2010). Much of the research has concentrated on the process of differentiating the insulin-producing cells from stem cell progenitors (Kroon et al., 2008). The natural development of pancreatic human β-cells has been reproduced *in vitro* by stimulating embryonal stem cells with transcription factors, cytokines and other small molecules to differentiate them into functional mature β-cells (Phillips et al., 2007; Kroon et al., 2008; Evans-Molina et al., 2009; Mayhew and Wells, 2010).

Most of the initial studies used ESCs as a source of pluripotent stem cells. More recently, iPSCs have been shown to offer several advantages over ESCs, including the ability to use

patient-specific cells, avoiding the need for immunosuppression, and fewer ethical and regulatory issues. Recent studies have demonstrated the ability to generate *in vitro* insulin secreting cells from iPSCs derived from human and murine fibroblasts (Tateishi et al., 2008) and to control hyperglycemia *in vivo* (Alipio et al., 2010). Although technical obstacles remain, these studies offer hope that iPSCs can eventually provide a patient specific cure for diabetes.

Other Clinical Applications for Stem Cells

A recent search for clinical trials with stem at ClinicalTrials.gov shows a total of 3,273 ongoing studies encompassing a wide variety of applications including those already stated, as well as for eye diseases, cartilage and liver regeneration, wound healing, autoimmune disorders, AIDS, and others (Bainbridge, 2008; Chun et al., 2010; Sellheyer and Krahl, 2010; Kitchen and Zack, 2011). Stem cell therapy is still in its infancy and we are only beginning to understand its potential. New applications will continue to emerge, but much research is needed before specific therapies are validated clinically in humans and gain widespread use.

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Chapter-3: Stem Cell Ethics

Bryan Choate

Although stem cells have been shown to save lives, and their potential to do so increases daily, a raging debate exists over whether stem cell research *should* continue. The purpose of this chapter is to go beyond a discussion of stem cell technology to discuss this ethical debate. As a framework, the stances of the five major world religions on stem cells will be reviewed.

Introduction to Stem Cell Ethics

The stem cell debate arises from disagreements about when life begins and the status of the embryo, and unfortunately is also based on misconceptions that the general public as well as high ranking officials have. Some of the many misconceptions popular among those against stem cell research include: stem cells can only come from embryos, embryonic stem (ES) cell research has the greatest promise, and every cell is somehow an embryo thus a human life (Pacholczyk, 2008). But these are true misconceptions. As discussed in Chapter-1, there are multiple sources of stem cells and not all of them destroy an embryo, such as adult stem cells (ASCs) and induced pluripotent stem (iPS) cells. And these latter cells have been shown in recent years to show promise for treating some types of diseases. In fact, more human lives have been saved at this point in time from adult stem cells (especially hematopoietic stem cells) than from embryonic stem cells (Pacholczk, 2008).

The main focus of the stem cell debate is the status of the human embryo. Religions that believe life begins at conception argue that the 5-day old blastocyst (from which ES cells are obtained) have the same status as a living human being, so destroying it is murder. Religions

that believe life or personhood begins much later, or that saving current lives outweighs the status of potential life, allow the use of an embryo. So the debate focuses on a balancing act between the benefits to society versus the detriment to the embryo. Although not everyone is convinced of the medical benefit of stem cells, most in the scientific community now have a fairly broad consensus on the benefits of stem cells for science and biomedicine, and the evidence increases daily on new applications. Chapter-2 attempted to alleviate some misconceptions about their past medical achievements and promise. On the other hand, there is the controversial issue of "killing" human embryos and when life begins (Devolder, 2005). Is it murder to kill an embryo that has the *potential* to become life? It can become human only if implanted back into the uterus and carried to birth. Is it murder to destroy a hollow ball of cells to grow immortal cell lines that can save lives?

Catholic Stance on Stem Cells

Of all the world's major religions, the Catholic stance against ES cells is perhaps the best known (American Catholic Organization, 2006). The Catholic Church believes that life begins at conception, so destroying a 5-day old embryo (obviously post-conception) is murder. President Bush, listening to his Catholic advisors, struck what he thought was a balance with them. On August 9, 2001, President Bush announced to the nation that he would be supplying government funding only to institutions that conduct ES cell research on ES cell lines derived *prior* to 2001, and would *not* allow federal funding to be spent to derive new cell lines. The embryos used to derive the previous cell lines had already been "murdered", and could not be murdered twice, so he allowed funding their use. Even given Bush's nod to the church's stance by banning federal funding for the destruction of new embryos, because he allowed *private* funding for this, his act

sent the Catholic Church into an uproar (Fastiggi, 2010) causing the U.S. Catholic Bishop Joseph A. Friorenza who is president of the U.S. Catholic Conference of Bishops to issue a statement deeming this action morally unacceptable saying that "The federal government, for the first time in history, will support research that relies on the destruction of some defenseless human beings for possible benefits to others" (American Catholic Organization, 2006). Bishop Friorenza would continue to say "We hope and pray that President Bush will return to a principled stand against treating some human lives as nothing more than objects to be manipulated and destroyed for research purpose. As we face a new century of powerful and sometimes even frightening advances in biotechnology, we must help ensure that our technical advances will serve rather than demean our very humanity" (American Catholic Organization, 2006).

Judging from statements like this, it is clear how the Catholic Church associates itself with embryonic stem cell research. But, this is not to say the Church is against all forms of stem cell research. In fact in 2006 Pope Benedict XVI released a statement endorsing adult stem cell research as a means to respect human life. Speaking at a summer stem cell conference, Pope Benedict urged the Catholic scientific institutions to double their efforts to create a closer relationship with others working in the field to strive for a breakthrough [with adult stem cells] that could relieve the suffering of many human lives (Catholic Online, 2006 2008?). The Church has always been there to help and cure suffering, so it was only fitting that Pope Benedict would endorse advancements in biotechnology to accomplish that goal, so long as no embryos are destroyed. Though the Catholic Church draws ethical lines when it comes to the different forms of stem cell research, the fact that they are willing to back adult stem cells is a tremendous step in the right direction that could help increase funding for those cells, and save millions of lives.

Christian Stance on Stem Cells

Like the Catholic Church, the Christian Church generally maintains a pretty strict stance against embryonic stem cell research, although unlike the Catholic Church with its single spokesperson in the Pope, non-Catholic Christians have multiple spokespersons so this large religion has multiple opinions. The Christian Church generally realizes the potential of this research and the lives that can be saved, but at what cost? To answer that question Christians often look to the Holy Scriptures of the New and Old Testaments to try and decipher what their stance should be. In the Scriptures it is clearly stated that life is God's creation and his gift. This view typically demands that members of the Body of Christ must reject any technology that destroys another human beings life, even if that technology seeks "good" in terms of the chronically ill or injured. "In Christian theology the ends may never justify the means. Rather, life in the womb or tragically, in the petri dish is always viewed as human life" (Fleishmann, 2001). Regardless of whether the embryo is growing inside a woman or being grown for a scientific purpose, the Christian Church generally believes that all embryos are human beings and to "deny this denies the witness of the Scriptures and the Faith of the Church" (Fleishman, 2001).

However, not all Christians are against ES cell research. Some churches hold a more balanced stance that the lives saved outweigh the status of a 5-day embryo. Such churches include some Methodists and Episcopalians (Faithful Progressive, 2005).

Jewish Stance on Stem Cells

Unlike the two Christian religions, when it comes to playing God the Jewish people strive to emulate God by saving lives, as long as it is according to God's rules as expressed by

authentic Jewish legal mandate. The idea of emulating God is a religious tradition of paramount importance, as that concept mandates the Jewish people to heal and provide medical relief wherever possible (Jakobovits, 2006). According to Jewish Scripture, the two professions undertaken by God were to teach or to heal, and if that requires the microscopic manipulation of cells to relieve suffering, the Jewish people have fulfilled their obligation to God (Jakobovits, 2006).

This ideology especially encourages the advancement and implementation of stem cells from adult tissues, but when it comes to embryonic tissues that is where problems begin to arise. The view of an embryo in the Jewish religion is on par with the Christian religions but slightly different. The Jewish people consider a fetus to be a full-fledged human in most situations, stating that one may not intentionally harm a fetus, and sanctions would be placed upon anyone that tries to deliberately cause a woman to have a miscarriage (Eisenberg, 2006). However, an embryo is not a fetus, and IVF embryos do not reside within a woman, so the Jewish interpretation of this varies. In some circumstances, if an embryo comes in conflict with an already born individual then that person take precedence over the embryo. For example the only way an abortion may take place in the Jewish Faith is if the embryo inside the woman constitutes a danger to the survival of the woman, but even then the embryo would not be used for harvesting stem cells. Even embryos before day 40 which are considered to be just water would not be aborted with the intent to just harvest stem cells (Jakobovits, 2006). However, an IVF embryo that does not reside within a uterus, and is used prior to day 40 where it has the rights of water, appears to be acceptable to most in this faith, especially if those cells are used to save lives. This is reflected in Israel's flexible laws that allow ES cell research, along with other

countries such as Australia, Belgium, China, India, Japan, Singapore, South Korea, Sweden, and the United Kingdom (discussed in Chapter-4).

Islam

Islam, like Judaism, shares strong traditions of legal and religious laws, including supporting most forms of stem cell research. With respect to when Islam considers the embryo alive, and is it acceptable to destroy those embryos for the advancement of scientific research, chapter 23, verse 12-14 of the Qur'an (the major authority in Islam) depicts an image of the creation of man starting from a clot and developing into tissue, then bones, and finally another creature. This passage has been interpreted to indicate that the fetus is considered a human life only after about the fourth month of pregnancy (Weckerly, 2002). Since the fetus is not considered to be alive until about 120 days after fertilization, most interpretations of Islamic law suggest that an embryo is not considered to be a person, so to use an embryo for scientific research does not violate any law in the Islamic society (Weckerly, 2002). Moreover, since the embryo is not in its natural environment and is not going to be placed in the womb, it will not survive and become a human, so most agree that the Islamic religion finds nothing wrong with conducting this kind of research, especially if it has the potential to cure disease and stop the needless suffering of individuals (Sachedina, 2000).

Buddhism and Hinduism

Like so many other religions, the Buddhist religion considers medical research as valuable, as long as it is intended to help others. So Buddhists tend to approve of adult stem cell research, but when it comes to fetal stem cell research it it quite the opposite. According to

Buddhism, the embryo is considered life, and to destroy it would go against everything they believe in as Buddhists place a great importance on the principle of non-harming life; therefore embryonic stem cell research would not be permitted (Holmes, 2004). Although, when it comes to aborted fetuses, some believe that since life is already deceased it is permissible to harvest stem cells from the aborted fetus (Keown, 2004). But the other side says the action of abortion itself is tainted by immorality, so the cells should not be harvested due to that fact alone (Keown, 2004).

The Hindu religion believes that all life is scared including animal and plant life. The heart of the Hindu doctrine is to live a life of non-violence and respect every living creature that inhabits this land by showing love to all things. Though to survive humans must kill those animals and plants for food, the religion focuses mainly on preserving the highest level of consciousness possible (Bahnot, 2008). Hindus believe the soul passes through as many as 8.4 million species before it reaches the highest level of consciousness reborn as a human. Thus, human life is much more valuable than an embryonic cell that has not reached full consciousness, so it becomes permissible to sacrifice a few cells for the greater good of saving already reincarnated humans (Bahnot, 2008).

iPS Cell Ethics

The hottest topic in stem cell research today is that on induced pluripotent stem (iPS) cells. Unlike ES cells that destroy an embryo, iPS cells are derived from a generic skin cell from a donor and reprogrammed to have similar pluripotent capabilities. Although their potency is still being debated and investigated, some scientists believe iPS cells can be stimulated to differentiate into many different cell types (Brind'Amour, 2009). Because they destroy no

embryos, and appear to be pluripotent, the promise of these iPS cells is immense. Initially, retroviruses were used to transform the fibroblast cells, but the resulting cells sometimes developed tumors, so now the transformation is performed directly by adding the reprogramming proteins themselves not by viruses delivering the genes (Brind'Amour, 2009).

If iPS cells are shown in experiments to be truly pluripotent, they could seemingly replace embryonic research all together. The fact that numerous laboratories have been able to reproduce iPS cells independently is a testament to how robust the technique is (Deem, 2009). The alternative technique of using somatic cell nuclear transfer (SCNT) has never been accomplished in humans, and would use an embryo anyway, so at this point iPS cells remain our best alternative to embryo-derived ES cells (Deem, 2009). Although it is unlikely, if iPS cells were eventually demonstrated to be *totipotent*, the level of potency that can create a new human life, then essentially these induced cells would essentially become cloned human embryos, which is illegal in most countries, and their advantage would be negated (Brind'Amour, 2008). Some scientists have shown that mouse iPS cells have the ability to form a new mouse (Boland et al., 2009) which demonstrates a high level of potency, but most scientists believe iPS cells are at least multi-potent. Some scientists have shown that iPS cells carry DNA mutations relative to embryo-derived ES cells, which make them harder to grow and might cause cancer (as was shown earlier with the viruses) (Dolgin, 2010). So the potency of iPS cells is still being investigated.

Author Chapter-3 Conclusion

In this last section I will weigh in on the ethical concerns addressed in this chapter, and share my views. With respect to embryos, I am not against their use for research. Unlike so

many of the religions that faced this question, I do not believe that an embryo, which is essentially a ball of cells the size of the period at the end of this sentence (at the 5-day stage), is a living human being, therefore I do not see any problem using embryos for research purposes, especially if they are going to be used for the greater good. With respect to embryo sources, I am in favor of using the old discarded IVF embryos that were originally created for reproduction purposes, since they are going to be discarded anyway, so why not use them for research purposes. Scientists could gain much knowledge from ES cells derived from IVF embryos, but if we destroy them before that happens, we might miss curing some diseases. With respect to creating IVF embryos solely for research purposes, I personally have no problem this, so long as the male and female donors provide informed consent.

With respect to adult stem cells, and whether they should be used in lieu of ES cells, this question really comes down to which type is more effective for a particular disease. Clearly adult stem cells have few ethical concerns compared to ES, but ES cells might prove more effective at say treating spinal cord injuries than adult neuronal stem cells. I would say to continue the development of adult stem cell therapies, but use ES cells until equal therapies can be developed. As to iPS cells, I am strongly in favor of using these cells, so long as they are as effective as ES cells and don't cause cancer. These cells have great potential with far fewer ethical concerns than ES cells. Perhaps if adult stem cells and iPS cells were used more frequently, religious groups and opponents of stem cell research would help strengthen our funding to help pave the way to treat many diseases that affect millions of lives.

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Chapter-4: Stem Cell Legalities

Rebecca Paz

The first successful identification and culture of human embryonic stem cells (hESCs) in 1998 (Thomson et al., 1998) opened the door to a promising future in regenerative medicine in which hESCs could potentially cure many diseases, but the discovery also sparked a political and ethical debate that continues to this day concerning the moral and legal status of the human embryo, which is destroyed in the process of obtaining hESCs. While one side sees it as a human being with all the rights and legal status of a person, the other side sees the embryo as a collection of cells that at day-5 lack the capacity to think or feel pain, with no interests or rights (Roberston, 2010). The purpose of this chapter is to discuss the evolution of laws regulating embryo research. Adult stem cells and induced pluripotent stem cells (iPSCs) are not directly derived from embryos and are therefore less controversial so will not be included in this chapter.

Historical US Federal Funding of Embryo and hESC Research

In the United States, the embryo debate has centered on the use of federal funds for sponsoring embryo and hESC research. Few legal restrictions exist for hESC research performed with private funding, although their use (or any other cell) in human reproductive cloning is banned. Federal funding is often considered the main way to advance science in the early stages of research before the economy is receptive to private funding (Robertson, 2010). The Federal funding of embryo or hESC research in the US historically related to politics. Below is a brief timeline of the main events that have directly or indirectly affected legal policy for the federal funding of hESC research in the United States:

1973- **Roe v Wade:** The US Supreme Court ruled that a fetus is not a person in terms of constitutional rights (Roe v Wade, 1972).

1993 - **William Jefferson Clinton** becomes the 42nd President of the United States and signs into law the NIH Revitalization Act of 1993, superseding the NIH Interim Guidelines banning research on fetal tissue, and creates the NIH Human Embryo Research Panel to oversee the ethics of fetal and embryonic research (NIH Guide, 1993).

1994 - **The NIH Human Embryo Research Panel** advises Clinton that studies on human embryos should be allowed and should receive government funding. President Clinton, in response to increasing political pressure, opposes the use of federal funding for the creation of embryos for research, but allows the use of federal funding for embryos discarded from in vitro fertilization clinics (Clinton Presidential Material, 1994; Robertson, 2010).

1995 - **Dickey-Wicker Amendment:** US Congress, under Republican control, creates the Dickey-Wicker Amendment as a rider to an appropriation bill, banning the use of federal money in hESC research (Robertson, 2010). This amendment has been attached to several other appropriation bills since then. The wording for the 2009 bill is as follows: SEC. 509. (a) None of the funds made available in this Act may be used for (1) The creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* (Public Law No.111-8, 2009).

1998 - **hESC Discovery**: James Thomson and colleagues successfully differentiate and culture hESCs (Thomson et al., 1998).

1999 - **Harriet Rabb Recommendation:** Rabb, General Counsel of the Department of Health and Human Services (HHS), is asked to give advice about the legality of using federal funds in hESC research under the Dickey-Wicker amendment. According to Rabb, "the statutory prohibition on the use of funds appropriated to HHS for human embryo research would not apply to research utilizing human embryonic pluripotent stem cells because such cells are not a human embryo within the statutory definition". (Rabb, 1999).

2000 - **NIH Guidelines:** The National Institutes of Health (NIH) issues guidelines that recommend the federal funding of hESC research (National Institutes of Health Guidelines, 2000).

2001 - **George W. Bush** becomes the 43rd president of the United States. He orders a review of the NIH guidelines and temporarily stops federal funding for hESC research. On August 9, President Bush announces that federal funding will be limited only to currently existing hESC lines, but not for developing any new cell lines (Radio Address, 2001; Robertson, 2010). The NIH implements President Bush's policy (Human Embryonic Stem Cell Policy, 2001).

2005 - **Stem Cell Research Enhancement Act of 2005:** Congress passes a bill that allows federal funding of new stem cell lines, but it is vetoed by President Bush in 2006 (Stem Cell Research Enhancement Act, 2005).

National Academy of Sciences publishes a common set of ethical guidelines for the responsible conduct of research using human stem cells. Amendments are added in 2007, 2008, and 2010 (Guidelines for Human Embryonic Stem Cell Research, 2005).

2007 - **Stem Cell Research Enhancement Act of 2007**: Congress again passes a bill expanding federal funding for human embryonic stem cell research, but again it is vetoed by President Bush (Stem Cell Research Enhancement Act, 2007).

2009 - **Barack Obama** becomes the 44th president of the US. On March 9, he signs executive order 13505, removing some of the limits on the use of federal funds for hESC research (President Barack Obama, 2009).

Updated NIH Guidelines: The NIH updates the guidelines, which become effective on July 7, 2009 (2009 Guidelines on Human Stem Cell Research, 2011).

Sherley v Sebelius: In August 2009, adult stem cell researchers James L. Sherley and Theresa Deisher et al. file a lawsuit against the NIH, alleging that the new stem cell policy violates the Dickey-Wicker Amendment. (Sherley v Sebelius, 2010).

2010 - **Temporary Suspension**: On August 23, "District Judge Royce C. Lamberth, grants the plaintiff's (Sherley) a preliminary injunction barring implementation of the Obama Administration's policy pending the outcome of the court case" (Levine, 2011). In response, the NIH temporarily suspends the federal funding of hESC research and files an appeal. "…on September 9, the U.S. Court of Appeals for the District of Columbia enjoined the preliminary injunction, allowing the NIH to resume funding hESC research" (Levine, 2011)

2011 - **Removal of Suspension:** "On April 29, 2011, in a two-to-one vote, the U.S. Court of Appeals for the D.C. Circuit overruled the lower court decision, vacating the preliminary injunction" (Cohen and Adashi, 2011; USCA-DC Opinions, 2011). The case now returns to the lower court and a final decision by Judge Lamberth. In the meantime, the decision allows federal funding of hESC research to continue.

Current US Federal Policy

On March 9, 2009, President Obama made the following statement: "Today, with the Executive Order I am about to sign, we will bring the change that so many scientists and researchers; doctors and innovators; patients and loved ones have hoped for, and fought for,

these past eight years: we will lift the ban on federal funding for promising embryonic stem cell research. We will vigorously support scientists who pursue this research. And we will aim for America to lead the world in the discoveries it one day may yield" (Remarks of the President, 2009). Following the public address, President Obama signed Executive Order 13505, *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*, changing the federal policy on hESC funding of the previous administration. During the Bush administration, federal funding could only be used on studies using hESC lines derived prior to August 2001. These earlier restrictions had "provided only a few viable cell lines, provided little genetic diversity, and had been cultured with mouse feeder cells, which raised the risk of infection and contamination" (Robertson, 2010). Obama's 2009 executive order states that "the Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law" (President Barack Obama, 2009).

In response to Obama's 2009 stem cell policy, on July 7, 2009, the National Institutes of Health (NIH) modified their Guidelines for Human Stem Cell Research Policy. The following is an excerpt:

> "These guidelines are based on the following principles:
> 1. Responsible research with hESCs has the potential to improve our understanding of human health and illness and discover new ways to prevent and/or treat illness.
>
> 2. Individuals donating embryos for research purposes should do so freely, with voluntary and informed consent." The entire guidelines are available at: http://stemcells.nih.gov/policy/2009guidelines.html

In general, federal funding is currently available for research if the hESCs are derived from embryos created using *in vitro* fertilization for reproduction and are no longer needed for

that purpose, or are donated voluntarily with adequate informed consent that includes a statement declaring that no payments are involved. Research is not eligible for federal funding if it involves introducing human embryonic stem cells into non-human primate blastocysts, if it is prohibited by the Dickey-Wicker Amendment, or if the hESCs are derived from other sources, including somatic nuclear transfer or parthenogenetic embryos.

In addition to the NIH guidelines, the National Academy of Sciences published their *Guidelines for Human Embryonic Stem Cell Research* in an effort to provide ethical and scientific guidance to privately funded hESC research (Guidelines, 2005).

State Stem Cell Policies

In view of the restrictions placed on federal funding for hESC research over the past decade, some states created their own specific funding to support this research. Among the states encouraging and providing funding for hESC research are: California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, New Jersey, and New York. Other states, including Arkansas, Indiana, Louisiana, Michigan, North Dakota, and South Dakota, prohibit the creation or destruction of human embryos for medical research. The following is a brief description of some of the states (listed alphabetically) that provide funding for stem cell research, from the "National Conference of State Legislature" (Embryonic and Fetal Research Laws, 2008):

California: In 2004, California passed Proposition 71 to fund adult and embryonic stem cell research. The California Institute of Regenerative Medicine (CIRM) controls the program.

Connecticut: Senate Bill 934 provides funding for stem cell research.

Illinois: An executive order created the Illinois Regenerative Medicine Institute (IRMI). Funding and a bill allowing stem cell research followed.

Maryland: The Maryland Stem Cell Research Fund provides grants for stem cell research.

Massachusetts: The Massachusetts Life Sciences Initiative was signed by Governor Deval Patrick in 2008. It allotted $1 billion in state funds over a decade, to be used in biotechnology, including stem cell research. The stem cell registry and bank are located at the University of Massachusetts Medical School in Worcester (Dumcius, 2007; Holden, 2009).

Although Massachusetts has several policies restricting the harvest and use of hESCs from the fetus or embryo, these are used in tandem with allotments from the state legislature to establish centers designed specifically for research on stem cell development. One of these centers is the Stem Cell Biology core at the University of Massachusetts, explicitly given support to perform research on stem cells. This core is allowed to carry out experimentation on stem cells, as well as host a public stem cell "bank" in order to store stem cell strains and tissue from which these cells can be harvested. UMass hosts a public institutional review board that is available to institutions of fifty members or less that are interested in pursuing stem cell research. There are certain restrictions placed upon the core: the embryos from which the hESCs are harvested cannot mature past 14 days old nor can they be transplanted to a uterine environment or any environment designed to simulate those conditions; all research conducted on hESCs must be reviewed and approved by a board first (this board being composed of 15 members with a wide variety of experience in the biological and medical field). Cell donation by patients is done through informed consent, and human reproductive cloning, cloning with the intent of creating a human being, is prohibited state-wide (An Act Enhancing Regenerative Medicine, 2005).

New Jersey: In 2004, New Jersey became the first state that approved funding for stem cell research. They started the New Jersey Stem Cell Institute and awarded grants for stem cell research.

New York: The Empire State Stem Cell Trust was created in 2007 to support stem cell research. A recent study by Karmali and collaborators examined and compared some of the state funding programs for hESC research. They observed, "the analysis indicates that state funding for stem cell research has grown into a substantial enterprise that has provided funding on a scale comparable to the NIH" (Karmali et al, 2010). Holden reviewed the current situation of state stem cell efforts to fund stem cell research and found that "programs generally seem to be holding their own in this uncertain environment - at least for now" (Holden, 2009).

The Interstate Alliance on Stem Cell Research (IASCR) is an organization dedicated to advance stem cell research and promotes interstate collaboration. More information is available at: http://www.iascr.org/

International Stem Cell Regulations

The attitudes toward hESC research are strongly influenced by religion and culture, and vary widely around the world. Some countries have government policies determining the type of research allowed, other countries control stem cell research through limits placed on the use of public funding, and still others have no legislation at all. "International and regional policies covering this work are complex and in flux. The resulting situations both between and within jurisdictions can be termed a 'patchwork of patchworks'" (Caulfield et al., 2009). The following is a brief summary of hESC regulation in some parts of the world (Erik, 2011; Ralston, 2008; The Hinxton Group, 2006):

Africa: South Africa allows hESCs to be derived from IVF embryos and allows embryos to be created for solely research (Stem Cell Legislation in South Africa, 2011).

North and South America: Canada permits research on embryos discarded from in vitro fertilization, but prohibits creating them for research. Brazil permits stem cell research using discarded embryos from in vitro fertilization. Mexico does not have a current federal policy governing stem cell research.

Asia: China allows the creation of human embryos for research and therapeutic purposes. Japan allows stem cell research for therapeutic purposes. Singapore permits the use of embryos for therapeutic purposes and is known as "Asia's stem cell center". The Bioethics and Safety Act in South Korea allows leftover embryos to be used for therapeutic research. According to the Indian Council of Medical Research, hESC from IVF embryos can be used for research, but embryos will not be created for that purpose.

Europe: Countries in the European Union vary widely in their regulation of hESC research. Countries that allow hES from super-numerary embryos (embryos not used in reproduction) include: Belgium, Czech Republic, Denmark, Greece, Spain, Finland, France, Netherlands, Portugal, Sweden and the United Kingdom.

Several international organizations are attempting to provide guidance on the ethical use and regulation of stem cells. Among these are: the Hinxton group, the Interstate Alliance (IASCR), the International Society for Stem Cell Research (ISSCR), and the United Nations Educational and Scientific Organization. The information can be found on their websites: http://www.hinxtongroup.org, http://www.iascr.org/, http://www.isscr.org, http://www.iascr.org/ and http://www.idia.net.

Chapter-4 Conclusions

The legal regulation of hESC research is strongly influenced by the religious, social, and political environments of the specific area. Religious and ethical beliefs mold the opinion of the public, which in turn influence politicians and ultimately affect federal and state regulation on the subject. In the United States, where the legislation has centered on controlling the use of federal funding for hESC research, the past decade has seen so many policy changes that it has created "something of a roller coaster" for scientists, according to Aaron D. Levine (Levine, 2011). In his paper, published on February 4, 2011, he states that "A survey of U.S. stem cell scientists shows that uncertainty following the legal challenge to the Obama Administration's hESC research policy has negative scientific and economic impacts, and affects a range of stem cell scientists, not just those working with hESCs". These "impacts" range from delaying plans to begin projects, to impeding ongoing research, to limiting future funding options (Levine, 2011). Thus, stability in policies governing hESC research is essential to advance the science.

Previous limitations placed on US federal funding have resulted in some states creating their own state-supported programs to support stem cell research. Most of those programs

continue to function (Holden, 2009). Regulation of hESC research in the rest of the world is highly variable, with no current world wide accepted guidelines available at the time.

The future of hESC research is currently unknown. It will likely be affected by several factors, including the results of clinical trials involving hESCs, the success or failure of stem cells derived from alternative sources like iPSCs, the funding available, and the regulatory policies affecting it.

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PROJECT CONCLUSIONS

The authors of this project believe that life starts shortly before birth (not at conception) and accept late-term abortions in certain cases, the use of embryonic stem cells (ESCs), and therefore the destruction of embryos, is acceptable as long as informed consent is given. Since the harvesting of ESCs in the US tends to rely on reproductive super-numerary embryos from fertility clinics and similarly discarded embryos (after the donors have used the embryos they wanted), informed consent likely will be provided. We see no major ethical issues with ESC harvesting solely for research purposes, but laws should be put into place to protect potential egg donors, for example to allow only a certain number per person per year; to use discarded embryos first if possible; and people may never be compelled to donate against their wishes.

Given the ethical issues of using ESCs, iPS cells and adult stem cells should be used first whenever possible. These latter stem cells are harvested from the body of the patient, and therefore have certain advantages over ESCs, including a reduced risk of immune rejection. Thus, if these cells are available to treat a particular disease, and have been proven to be effective, then iPSCs/ASCs are the preferable choice.

In terms of stem cell regulations, the authors believe that current policies in countries such as China, Singapore, and Japan, are adequate for the current scope of stem cell use in research and medicine. These countries allow for the use of super-numerary IVF embryos and the creation of embryos for the purpose of research. As for the United States, since the regulation of stem cells varies wildly from state to state, progress should focus not on the regulation of the use of stem cells, but on the availability of federal funding for research on stem cells, as this

large level of funding is required to maintain the US leadership in this technology. Although federal funding of some types of ESC research is currently allowed under Obama, we believe the laws should be expanded to allow all ES cell lines to be researched. Therefore, it is imperative that US laws be changed to allow federal funding for all stem cell research.