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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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ABSTRACT

The purpose of this project is to bring attention to the impact of stem cells and their applications on society. Despite what many people believe, there are multiple types of stem cells. These stem cells can be utilized for many different applications including regenerative medicine. A topic as controversial as stem cells draws strong ethical concerns, which prompt the creation of legislations to dictate the boundaries of this new technology.

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PROJECT OBJECTIVES

The purpose of this project is to demonstrate the impact that various stem cell technologies have on society. Chapter-1 will focus on the different types of stem cells and their sources, including embryonic and adult stem cells, and describe new stem cell technologies such as iPS cells and parthenotes. Chapter-2 will spotlight stem cell applications for the treatment of debilitating human diseases, such as SCID (severe combined immunodeficiency disease), Parkinson's disease, and diabetes. Stem cell therapies for spinal cord injuries and cardiac damage are also included in Chapter-2. Chapter-3 will discuss the ethical dilemmas associated with stem cell research, particularly for embryonic stem cell research. Different religious perspectives regarding stem cell research will also be provided in Chapter-3. Chapter-4, will focus on stem cell legalities, including the Bush administration's stem cell policy, the Obama administration's stem cell policy, and state and international stem cell laws. Finally, as a conclusion to this project, the authors include their perspective on stem cell research and how it has impacted society.

Chapter 1 – Stem Cells: Types and Sources

Catherine Campbell

Stem cells are the foundation for every cell, organ, and tissue in the human body (ISSCR, 2009). In general, stem cells are undifferentiated cells that have not yet completely specialized into a specific cell type (ISSCR, 2009). These special cells are capable of long-term self renewal, meaning that they can proliferate over extended periods of time, and they eventually give rise to more stem cells (ISSCR, 2009). Stem cells are capable of proliferating indefinitely, and under the proper conditions, will give rise to various cell types found in the body (Kirschstein and Skirboll, 2001). An important characteristic of stem cells is that only one of the daughter cells will go on to differentiate, while the other daughter cell remains undifferentiated to maintain the stem cell reservoir (Kiessling and Anderson, 2003).

Unlike popular conceptions that use the term "stem cells" as if there is only one type, numerous kinds of stem cells exist, all unified by a few unique properties that make them stem cells. All stem cells have the ability to divide and replenish themselves for extended periods of time, they are all unspecialized cells, and they are capable of yielding specialized cell types within the human body (NIH, 2005). Stem cells are able to proliferate numerous times throughout their life cycle. In fact, a small population of stem cells can, over a period of many months within a laboratory setting, eventually yield millions of stem cells (NIH, 2005). If the resulting stem cell line is able to remain undifferentiated, then the cells are considered to have long term self-renewal abilities (NIH, 2005). Stem cells are unspecialized, or undifferentiated, meaning that these cells do not contain tissue-specific structures. These cells are unable to perform specialized functions, and therefore are unspecialized (NIH, 2005). However, these

unspecialized cells can proliferate and produce cells that will eventually become specialized cells, such as cardiac muscle cells and nerve cells (NIH, 2005).

Stem cells can produce specialized cells in a process known as differentiation. During the differentiation process, the cell undergoes a series of steps which allows it to become increasingly specialized. Internal signals that initiate and allow the progression of differentiation are controlled by the cell's genes, which encode proteins and other molecules responsible for cellular structures and functions (NIH, 2005). External signals are also required for the cell to fully initiate the differentiation pathway. Such signals include chemicals released by local cells, cell-cell contact, and various molecules within the microenvironment (NIH, 2005). Signal interactions during the process of differentiation allows epigenetic factors to accumulate in the cells' DNA, which function to restrict protein expression in the cell which can then be inherited by daughter cells through mitosis (NIH, 2005).

Because of the ability of stem cells to grow to large quantities and differentiate into various tissues, they are the basis of the new field of "regenerative medicine". The purpose of this chapter is to document the various types of stem cells and their sources, as a prelude to subsequent chapters on their uses, ethics, and legalities.

Stem Cell Classifications

Stem cells can be divided into three main categories: embryonic stem (ES) cells, adult stem cells (ASCs), and induced pluripotent stem (iPS) cells. ES cells denote any type of stem cell derived from an embryo. Adult stem cells (ASCs), by definition, are stem cells isolated from *adult* tissues, but this category has also evolved to include any type of stem cell that is not produced from an embryo and not induced, thus this category also includes stem cells obtained

from fetal umbilical cord blood. iPS cells are ES-like cells derived from adult fibroblast cells induced to de-differentiate using key developmental transcription factors.

Stem cells can also be divided into types based on their *potencies*. *Totipotent* cells (newly fertilized eggs through the 8 cell stage) can create any type of cell in the body including placenta. *Pluripotent* cells (ES cells) can create any type of cell except placenta. *Multipotent* cells can create several types of cells. *Unipotent* cells (most types of adult stem cells) can create only one type of cell from their tissue of origin.

Adult Stem Cells

Adult stem cells (ASCs) are tissue-specific cells present in various fetal and adult tissues that can only give rise to a limited number of cell types, depending on the type of tissues they reside, meaning they are unipotent or multipotent, but not pluripotent (ISSCR, 2009). This indicates that they can become more than one cell type in the body, however, they are limited to the type of cell they can become. Adult stem cells can proliferate for extended periods of time, give rise to mature and specialized cell types, and generate progenitor cell types before they achieve complete differentiation status (Kirschstein and Skirboll, 2001). Progenitor cells, located throughout adult tissues, are partially differentiated cells that can divide and eventually produce differentiated cell types. Adult stem cells are also capable of long term self-renewal for the lifetime of the organism, and are clonogenic and unilineal (Kirschstein and Skirboll, 2001). The term clonogenic indicates that these cells can generate identical copies of themselves. Unilineal denotes their tendency to differentiate into mature cells of the tissue in which they reside (Adult Stem Cells, 2006). ASCs do not necessarily come from adult human beings, rather

the term ‘adult’ refers to the status of the organ from which stem cells are isolated from, such as fetal and adult organs.

Adult stem cells, or ASCs, are relatively rare in the human body. In fact, it is still unclear exactly which tissues have ASCs, and a fierce debate sometimes occurs with new claims in the literature. The major function of adult stem cells is to replace dead and injured cells with new cells that are able to function properly (Adult Stem Cells, 2006). All of these characteristics allow ASCs to help maintain homeostasis in the body (Kirschstein and Skirboll, 2001).

Plasticity is a term used to describe the ability of adult stem cells to differentiate into a specialized cell type of a *different* tissue (Kirschstein and Skirboll, 2001). This process is also termed trans-differentiation since it denotes a change into a different type of tissue. Several approaches have been used to demonstrate the plasticity of adult stem cells. ASCs can be obtained from a genetically engineered mouse expressing a specific molecular tag in all of its cells which allow these cells to be followed after injection into a host to show how these cells integrate into new tissues in their environment, survive in these new tissues, and function like mature, specialized cells of that type of tissue (Kirschstein and Skirboll, 2001).

Hematopoietic Stem Cells

With 50 years of experience studying hematopoietic stem cells (HSCs) it is expected that no other type of stem cell is better researched and characterized. These stem cells have the greatest self-renewal ability compared to any other cell type in an adult tissue (NIH, 2005). HSCs give rise to blood and immune cells, and are responsible for the constant renewal of blood (NIH, 2005). HSCs can be isolated from blood, bone marrow, and umbilical cord blood, and can renew themselves and differentiate into a variety of specialized blood cells (NIH, 2005). They

are capable of moving out of the bone marrow and into circulation blood and they also undergo apoptosis, or programmed cell death (NIH, 2005) which makes them useful to scientists and the medical field.

The most common and traditional source for HSCs is bone marrow, which has been used for over 40 years. For this method, physicians puncture the donor's hipbone and draw out bone marrow cells using a syringe (NIH, 2005). Unfortunately, only one out of 100,000 cells within the bone marrow sample will be a HSC (NIH, 2005). A second source of HSCs is from peripheral blood, which physicians now prefer to harvest donor stem cells from for clinical HSC transplantations (NIH, 2005). This source is less enriched for HSCs than bone marrow, so to overcome the small number of stem cells in peripheral blood, researchers inject the donor with cytokines to stimulate the release of HSCs out of the bone marrow into the peripheral blood in a larger density (NIH, 2005). Of these collected mobilized cells, about 5 to 20% of them are true HSCs (NIH, 2005). A third source of HSCs is umbilical cord blood. During the 1980's and 1990's, physicians found that blood obtained from human umbilical cords and the placenta is rich in HSCs (NIH, 2005). To date, the HSCs isolated from each of these sources appears to be functionally identical, with maybe the exception of cord HSCs that appear to be more primitive and induce fewer graft rejections (Viacord, 2004). Although HSCs can also be obtained from the fetal hematopoietic system, such cells are not used clinically, but only for research. At about 7 days into the life of a mouse embryo, the earliest level of hematopoietic activity can be detected (NIH, 2005). As embryonic and fetal development progresses, hematopoietic activity increases until it reaches the bone marrow near the time of birth of the fetus (NIH, 2005). All of these sources serve as valuable reservoirs of hematopoietic stem cells.

Adult Neural Stem Cells

Since most regions of the brain lack the capacity for self regeneration, neural cells are particularly vulnerable to irreversible damage and disease (Bjorklund and Lindvall, 2000). Neural stem cells (NSCs) do not have the ability to initiate tissue repair on their own in the adult brain (Levesque, 2005), but these cells can be stimulated to proliferate and to repair damaged brain tissue when exposed to specific conditions that stimulate certain genes (Levesque, 2005). Some regions of the brain are capable of self repair since they contain such neural stem cells (Cassidy and Frisen, 2001). NSCs are located in the brain's ventricle walls, which are cerebrospinal fluid filled cavities, but they are very difficult to isolate since they constitute only 1 in 300 cells located in the ventricles (Cassidy and Frisen, 2001). NSCs have the potential to produce more neural stem cells, or neurons and supporting glia (Cassidy and Frisen, 2001). These recently discovered cells have sparked hope that they can be used to treat neurodegenerative disorders (Cassidy and Frisen, 2001). However, before NSCs can be used to their full potential, it is crucial to achieve a better understanding of their proliferation controls and differentiation pathways (Gage, 2000).

NSCs are formed from a unique portion of the embryo, which only produces precursor cells that will become the central nervous system (Levesque, 2005). Researchers have been studying adult NSCs to determine better methods for isolating and characterizing them. Once these cells are isolated, they can be propagated for several months in a laboratory without undergoing differentiation (Levesque, 2005). Adult NSCs have the ability to self replicate and to eventually form all the cell types present in the adult central nervous system (Levesque, 2005).

There are numerous sources of NSCs in the adult mammalian brain. One source are ependymal cells (Johansson et al., 1999). Ependymal cells give rise to a cell type which proliferates to produce neurons which migrate throughout the brain (Johansson et al., 1999). It has been shown that these cells increase the production of migratory cells which differentiate into differentiated neuronal cells in response to tissue injury in the central nervous system (Johansson et al., 1999). Another source for NSCs is the subventricular zone (SVZ) cells (Lois and Alvarez-Buylla, 1993). These cells can proliferate spontaneously in the adult brain, and can differentiate directly into neurons and glia *in vitro* (Lois and Alvarez-Buylla, 1993). Another source of NSCs is the periventricular region of the adult mammalian brain (Rietze et al., 2001). The periventricular region of the brain contains functional stem cells that have the ability to generate neural and non-neural differentiated cell types of the central nervous system (Rietze et al., 2001). Another source of NSCs is the adult striatum (Reynolds and Weiss, 1992). Although neurogenesis in the central nervous system is believed to end after the birth of the fetus, cells obtained from the striatum of an adult brain have been shown to proliferate *in vitro* (Reynolds and Weiss, 1992). This finding provided substantial evidence that neural stem cells exist in the striatum of the adult brain, and have the capacity to proliferate and differentiate into neurons and astrocytes (Reynolds and Weiss, 1992). In mice, neural stem cells can also be obtained from the lateral ventricles of the adult mouse central nervous system, and have been shown to participate in cell repopulation in the forebrain *in vivo*, and can expand *in vitro* when exposed to epidermal growth factors (Weiss et al., 1996). The spinal cord and the ventricular neuroaxis of the adult central nervous system has also been shown to be a vital source of multipotent neural stem cell (Weiss et al., 1996).

Adult Cardiac Stem Cells

The heart, like the brain, is almost completely composed of terminally differentiated cells (Beltrami et al., 2003). However, the heart should not be considered as a terminally differentiated organ since it contains cardiac stem cells that can mildly support tissue regeneration (Beltrami et al., 2003). Adult cardiac stem cells are self-renewing, clonogenic, and multipotent, and have been shown to give rise to various cell types including myocytes, smooth muscle cells, and endothelial cells (Beltrami et al., 2003). When these cardiac stem cells are injected into an ischemic heart, cardiac stem cells will differentiate and proliferate into myocardial tissue (Beltrami et al., 2003). Also, recent research has shown that the heart contains stem cell reservoirs which allow the cardiac muscle tissue to produce new cells after damage, disease, and injury (Touchette, 2004). In rats when cardiac stem cells are injected into damaged rat hearts, new cardiac cells are generated to reconstitute the damaged cardiac tissue (Touchette, 2004). The existence of these adult cardiac stem cells holds many opportunities for the medical advancement of myocardial repair and treatment.

Adult Epithelial Stem Cells

Homeostasis of the adult epidermis, the outer layer of skin tissue, is maintained by two different populations of progenitor cells (Clayton et al., 2007). These two populations include self renewing stem cells and their progeny, both which have the ability to differentiate into specialized epidermal cell types (Clayton et al., 2007). Cutaneous epithelial stem cells are considered to be the main source for this type of epidermal tissue regeneration (Cotsarelis et al., 1999). Through research, it has been determined that these cells undergo both symmetric and asymmetric cell division at rates which maintain homeostasis of the epidermis (Clayton et al.,

2007). Such scientific findings suggest that adult epithelial stem cells play an important role in the maintenance of epidermal tissue, and might be used in the future for treating various skin diseases or burn patients.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent adult stem cells which can be derived primarily from adult bone marrow (Hellmann et al., 2006). They are capable of differentiating into numerous cell types, such as osteogenic, adipogenic, and chondrogenic cells (Jackson et al., 2007), and it has even been suggested that these cells can differentiate into cell types beyond the mesenchymal lineage (Jackson et al., 2007). For example, MSCs can differentiate into neural cells *in vivo* and *in vitro* (Jackson et al., 2007). It is this multipotency property of MSCs, coupled with their adult source with few ethical concerns, which makes them especially attractive to researchers seeking future applications in regenerative medicine.

The differentiation pathway of mesenchymal stem cells has been shown to be controlled by their contact and exposure to certain extracellular matrix (ECM) proteins (Plopper et al., 2007). By exposing these stem cells to specific ECM proteins, specific integrin-associated signaling pathways can be activated, resulting in a specific differentiation fate of mesenchymal stem cells into bone, cartilage, or adipose tissue cells (Plopper et al., 2007).

Mesenchymal stem cells are responsible for adult bone fracture repair and remodeling, and for bone formation in the embryo (Bruder et al., 1994). Such cells proliferate for extended periods of time while a subpopulation of these cells will go on to differentiate into mesenchymal cell lineages. Mesenchymal cell lineages include bone, cartilage, ligament, tendon, and muscle cells (Bruder et al., 1994). The manner in which mesenchymal stem cells differentiate into each

cell lineage is dependent on the presence of certain nutrients, bioactive factors, and various environmental influences (Bruder et al., 1994). It is believed that new methods of cell therapy can be derived from understanding the cellular and molecular mechanisms involved in osteogenic differentiation of mesenchymal stem cells (Bruder et al., 1994).

Adult Intestinal Stem Cells

One of the most rapidly self-renewing tissue in the human body is the adult intestinal epithelium (Barker et al., 2007). In a mouse model, it has been shown that the epithelial layer of the small intestine, which is responsible for a majority of nutrient absorption in the body, self renews once every three to five days (Barker et al., 2007). In order to support such a rapid turn-over rate, the intestinal epithelium contains numerous cell types, all which have differentiated from intestinal stem cells.

Until recently, intestinal stem cells have been difficult to identify due to a lack of markers and efficient stem cell assays (Barker et al., 2007). But with the use of mouse chimeras and post-injury tissue regeneration research, intestinal stem cells can now be defined and characterized (Barker et al., 2007). These self-renewing stem cells continuously proliferate into cells that will eventually differentiate into all intestinal cell lineages (Barker et al., 2007).

Adult Eye Stem Cells

The epithelial layer of the cornea is constantly renewing itself once every seven to fourteen days in most mammals (Majo et al., 2008). In pigs, the whole ocular surface, including the cornea, is rich in eye stem cells (Majo et al., 2008). These eye stem cells are oligopotent and possess the ability to produce colonies of cells that comprise the cornea and conjunctiva (Majo et

al., 2008). A majority of these stem cells are contained within the limbal region of the eye, and these cells are responsible for long term self-renewal of the cornea (Majo et al., 2008).

Embryonic Stem Cells (ES cells)

ES cells are pluripotent cells derived from the inner cell mass of a mammalian blastocyst cultured in an *in vitro* fertilization (IVF) procedure for about 5 days. The *in vivo* equivalent would be the embryo prior to its implantation in the uterine wall (Edwards, 2001). The blastocyst is the resulting structure of a newly fertilized egg which has divided multiple times for about 5 days, and consists of a hollow sphere of about 150 cells made up of two cell types: the surrounding trophoblast and the inner cell mass (ISSCR, 2009). The trophoblast is a group of cells which will eventually become the placenta, while the inner cell mass (constituting the ES cells) gives rise to the fetus.

ES cells are capable of long term self renewal, meaning that they can undergo indefinite symmetrical cell divisions without differentiating into a specialized cell type (Kirschstein and Skirboll, 2001). ES cells exist only at the earliest stages of embryonic development, and are pluripotent, meaning they give rise to all cell types in the body except the placenta (ISSCR, 2009). They maintain a normal karyotype, meaning that they exhibit and maintain a stable, normal diploid complement of chromosomes which is important with respect to their potential clinical use (Emanuel, 2006). ES cells are able to integrate into all fetal tissues in development and to colonize germ lines and produce gametes (Kirschstein and Skirboll, 2001). They are also clonogenic, which means that a single ES cell can give rise to an entire colony of genetically identical cells, or clones, that all exhibit the same properties and characteristics as the original ES cell. ES cells express a hallmark transcription factor Oct-4, which is responsible for either

activating dedifferentiation genes or inhibiting differentiation target genes, and for maintaining ES cells in their proliferative, unspecialized state (NIH, 2005). They can be induced to proliferate and grow in culture, and to differentiate under the proper conditions. A unique quality of ES cells is they lack the G1 checkpoint in their cell cycle (Kirschstein and Skirboll, 2001). ES cells spend a majority of their time in the S phase of the cell cycle, when DNA is replicated and synthesized in preparation for nuclear and cytoplasmic division during mitosis . Also, ES cells express high levels of active telomerase, which is a ribonucleoprotein enzyme that adds telomere repeats to the ends of chromosomes to maintain their length (Odorico et al., 2001). High telomerase activity is highly correlated with immortality in other human cell lines (Odorico et al., 2001), and likely helps ES cells maintain their long life spans. ES cells also do not require external stimuli to initiate DNA replication, unlike most other types of cells found in the body (Kirschstein and Skirboll, 2001). ES cells do not exhibit X inactivation since they are undifferentiated. X inactivation is a process that occurs in every somatic female cell, in which one of the two X chromosomes is permanently inactivated in the female organism (Kirschstein and Skirboll, 2001). All of these characteristics are particularly unique to ES cells.

ES cells can be differentiated into specialized cells via several mechanisms. One of the most common approaches for directing differentiation in ES cells is to alter the growth conditions by adding specific growth factors to the culture medium. The addition of growth factors triggers specific gene expression patterns to induce a specific differentiation pathway (Conrad et al., 2008). Another method for inducing and directing differentiation is to change the chemical composition of the surface of the plate. If the plate surface is changed to an adherent substrate, then the ES cells will be prevented from interacting and differentiating in culture. However, if the plate surface is altered to become a nonadherent substrate, then the ES cells will

be allowed to aggregate and will then differentiate (Kirschstein and Skirboll, 2001). Another method for directing differentiation is to insert foreign genes into the ES cells via transfection, which will insert the new genes into the host genome, thus triggering a specific differentiation pathway (Kirschstein and Skirboll, 2001). All of these mechanisms are commonly used to produce differentiated cells from ES cells in culture.

The most widely studied ES cell line originated from mouse ES cells (ISSCR, 2006). Mouse ES cells have taught researchers a great deal concerning how pluripotent cells grow and differentiate, and the processes involved in embryonic development (ISSCR, 2009). Mouse ES cells have served as a significant research subject for analyzing gene function and human disease (ISSCR, 2009). Human ES cells were first isolated in 1998, and have been proven to be more difficult to work with than mouse ES cells (ISSCR, 2009). Although relatively little is known about human ES cells, scientific researchers are making substantial progress in learning about human development, modeling human disease, and developing methods that could potentially produce cell therapies to restore damaged tissues (ISSCR, 2006).

The derivation of human ES cells currently demands the destruction of the human embryo *ex utero*, or outside the uterus. However, a recent study in mice has indicated that it could be possible to produce ES cells from only a single cell biopsy, which would not disrupt the developmental potential of the remaining embryo (Klimanskaya et al., 2006). This ability to produce new stem cell lines without requiring the destruction of the human embryo would undoubtedly address the many ethical concerns associated with ES cell derivation. To further test this idea, experiments were conducted to determine whether human ES cells could be obtained from a single blastomere (Klimanskaya et al., 2006). Unused embryos from *in vitro* fertilizations (IVFs) were used to obtain individual blastomeres separated from the embryo. ES

cell cultures were then allowed to overgrow and form embryoid bodies, which readily differentiated into the cells comprising all three germ layer (Klimanskaya et al., 2006). Based on the results, single-blastomere-derived human ES cells could be directed to differentiate into specific cells of interest, *in vitro*, in this case endothelial cells (Klimanskaya et al., 2006). Based on this conclusion, human ES cells can be obtained without destruction of the human embryo.

Induced Pluripotent Stem Cells

Induced pluripotent stem (iPS) cells are stem cells created from reprogrammed adult cells (Cyranoski, 2007). iPS cells are derived from specialized adult cells (usually skin fibroblasts) reprogrammed to an unspecialized state that is similar to that of an ES cell (ISSCR, 2009). It is believed that iPS cells may be the equivalent of ES cells in their gene expression (Aoi et al., 2008). iPS cells are produced by inserting copies of transcription factor genes crucial to ES cell pluripotency, into specialized cells using viral vectors (ISSCR, 2009). iPS cells also require a specific and correct culture media in order to prevent them from differentiating into specialized cell types (Cyranoski, 2007). In the future, it is hoped that iPS cells can be used for patient specific cell therapies while not requiring the destruction of an embryo.

iPS cells can be generated from mouse and human fibroblast cells via retroviral transduction of four transcription factors (Aoi et al., 2008). However, iPS cells can also be produced without the use of viral vectors.

The first derivation of iPS cells was in mice in 2006 (Takahashi et al., 2006). Shinya Yamanaka's lab reported that they had successfully reprogrammed mouse skin cells into an embryonic-like state by infecting them with a virus containing four transcription factors (Check and Baker, 2009). These cells were then termed "iPS" cells, for induced pluripotent stem cells.

Later, Andreas Nagy inserted genes, which encoded Yamanaka's four transcription factors, into a DNA segment that also contained a jumping gene referred to as *piggyBAC* (Check and Baker, 2009). This DNA segment, or cassette, could then be inserted into the genome of mouse or human skin cells, which would reprogram them back to an embryonic-like state (Check and Baker, 2009). A transposase would then be used to remove the cassette from the mouse or human cells (Check and Baker, 2009), which allowed researchers the ability to produce iPS cells without the use of viruses as vectors. Subsequent experiments showed that removing the c-Myc gene from the coctail treatment eliminated the formation of cancer cells from the iPS colonies (Kim et al., 2008; Nakagawa et al., 2008), and eventually allowed only 2 transfection factor genes to be used. Later experiments even showed iPS cells could be induced from mouse fibroblast cells with no transcription factor genes, when the cells were incubated with four polyarginine proteins (New Scientist, 2009). In the future, so long as iPS cells show the same pluripotency as ES cells, they may completely replace their use in the clinic.

Parthenotes

Due to the numerous ethical concerns associated with the isolation and use of human embryonic stem cells, alternative sources of pluripotent stem cells have been explored. Through extensive research, it has been discovered that parthenotes may serve as an alternative and ethical source of pluripotent stem cells (Brevini and Gandolfi, 2007). Parthenotes are entities created via artificial parthenogenesis, in which human oocytes are artificially activated by chemical treatments to produce pluripotent stem cells (Brevini and Gandolfi, 2007). In the process of parthenogenesis, embryonic development can be initiated just from maternal oocytes in the absence of a male's sperm (Cibelli et al., 2002). Although parthenogenesis is a process

commonly used frequently in less complex organisms, such as insects and sea urchins, mammals are unable to initiate a successful pregnancy via parthenogenesis (Cibelli et al., 2002). In primates, parthenogenesis in monkey oocyte development *in vitro* can successfully generate blastocysts from which ES cell lines were derived (Cibelli et al., 2002). These pluripotent stem cells can be maintained undifferentiated *in vitro* for extended periods of time (Cibelli et al., 2002). Although parthenogenetic mammalian blastocysts will not survive long enough to be implanted into the uterine wall, they do last long enough to be used as a pluripotent stem cell source (Marchant, 2006). Due to these results, parthenotes may serve as a replacement for human embryonic stem cells for patient-specific cell based therapies since they avoid the need to create human embryos for use.

Recently, pluripotent stem cells from *human* parthenotes have been isolated by researchers at the University of Milan (Marchant, 2006). Donated eggs were used to derive these stem cell lines (Marchant, 2006). Based on extensive research, the human parthenogenetic ES cells appear to be the equivalent of normal ES cells, while bypassing the need to create human embryos (Westphal, 2003). Although such stem cells are slightly more difficult to manage and store *in vitro* than normal human ES cells, researchers are hopeful that they will eventually replace the need for fertilized embryos (Marchant, 2006).

Somatic Cell Nuclear Transfer (SCNT)

A major issue associated with allogenic tissue transplantation is graft rejection by the host, in which the patient's immune cells attack the transplanted tissue (Byrne et al., 2007). This complication could be potentially bypassed completely with the help of SCNT created stem cells, which would contain the genetic information of the recipient patient (Byrne et al., 2007).

Somatic cell nuclear transfer (SCNT) is a process in which embryonic stem cells can be made genetically identical to a patient (Byrne et al., 2007). In this process, a nucleus from an adult skin fibroblast cell of the eventual recipient is injected into an enucleated egg. The egg is cultured 5 days in vitro to the blastocyst stage from which ES cells are then obtained genetically identical to the donor of the nucleus. The technique has been successful in mice, but has not yet been done in humans. SCNT techniques have the ability to potentially treat and cure numerous debilitating diseases while avoiding graft rejection in patients (Byrne et al., 2007). ES cell lines created via SCNT have been shown to express markers specific to stem cells, exhibit typical ES cell morphology, and are able to transcriptionally maintain an undifferentiated state and control differentiation into various cell types *in vivo* and *in vitro*, similar to normal embryonic stem cells (Byrne et al., 2007). Based on this information, it is evident that SCNT techniques can alleviate the risk of tissue rejection associated with many transplants, thus allowing the development of more personalized treatments for patients.

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CHAPTER-2: STEM CELL APPLICATIONS

Kristin Newell

Stem cells have a tremendous potential for use in regenerative medicine, and have been used to repair various damaged tissues (such as the spinal cord) and organs (like the heart), repair congenital defects, and reverse or improve many debilitating diseases such as Parkinson's disease, SCID, and even diabetes. These applications of the use of stem cells in regenerative medicine and their benefits to society will be the focus of this chapter, as a prelude to subsequent chapters on their ethics and legalities.

Treatment of Severe Combined Immunodeficiency Disease (SCID)

Severe combined immunodeficiency disease (SCID) is a disorder in which both the B cells and T cells of the immune system are defective. This disease is also commonly called "bubble boy" disease because of the famous case of David Vetter who suffered from SCID. SCID is most commonly caused by a defect in the γc T-cell receptor, and less commonly (as in David's case) by a defect in adenosine deaminase (ADA). Individuals with SCID lack essentially all immune function and usually die within their first year of life due to severe recurrent infections, which a properly functioning immune system would be able to take care of (MedicineNet, 2003). It is estimated that 40-100 cases of SCID are diagnosed each year in the United States, but there is no way to tell how many undiagnosed infants die each year of SCID (National Human Genome Research Institute, 2009).

Hematopoietic stem cells (HSCs) present in bone marrow or umbilical cord blood are among the best characterized of all stem cell types, and have been used the longest to treat

diseases. HSCs have been used for over 50 years in attempts to treat various forms of cancer (Thomas et al., 1957), with the 40th anniversary of the first clinical success occurring in 2009 (Bortin et al., 1994). With respect to SCID treatments, as is typical for most new treatments, experiments were initiated in animals, and then later extended to humans. In 1992, researchers implanted human bone marrow pre-treated with mast cell growth factors into SCID mice, which resulted in a re-population of mouse bone marrow with human erythroid and myeloid progenitors, that gave rise to all cells of the blood and immune system (Lapidot et al, 1992). The recipient SCID mice that received implants without growth factor pre-treatment did not generate erythroid and myeloid progenitors, and produced few human cells in the mouse bone marrow, and only granulocyte-macrophage progenitors (Lapidot et al, 1992). Thus, growth factor treatments are important when priming the HSC transplants. A subsequent study found that SCID mice treated with a cytokine mixture for four months then implanted with human bone marrow (or a human bone fragment) established human blood cell lineages, detectable up to a year after implantation (Heike et al, 1995).

The animal model experiments for SCID treatments were first successfully applied to humans in 2000 (Cavazzana-Calvo et al., 2000). HSCs corrected for the most common type of SCID (a mutation in the γc T-cell receptor) were used to treat two SCID infants. Both infants showed complete establishment of an immune system, the ability to respond to vaccine treatments, and clinical improvements. It is now estimated that treatment with HSCs could save up to 80% of people diagnosed with SCID (NCBI, 2009).

Treatment of Parkinson's Disease

Parkinson's disease (PD) occurs when nerve cells (neurons) in a part of the brain called the substantia nigra (which produces dopamine) either die off or are impaired in their production of dopamine. Dopamine is an important neurotransmitter that is responsible for smooth muscle coordinated movements. Symptoms occur when 80% or more of these dopamine-producing neurons die or are dysfunctional. The common symptoms of PD are shaking, rigidity, slowness of movement, and difficulty balancing. Other less common symptoms include muffled speech, stiff facial expressions, shuffled walking, small cramped writing, and depression. In the United States, 1.5 million people have PD, with an additional 60,000 new cases diagnosed each year (National Parkinson Foundation, 2009). PD usually occurs at over 65 years of age, but 15% of new cases diagnosed occur in individuals 50 years of age or younger (National Parkinson Foundation, 2009).

There has been some success in treating Parkinson's disease using embryonic stem (ES) cells, as well as neural stem cells (NSCs) already present in the brain, in both PD animal models and in patients. In 2000, injection of transforming growth factor alpha (TGFα) into rats (pre-treated with 6-OHDA to kill dopamine neurons) showed migration of endogenous neural stem cells to the damaged areas of the brain, and neural stem cell division for several days (Fallon et al., 2000). These rats showed fewer PD symptoms than non-TGFα-treated rats who received the 6-OHDA. It is unknown, however, whether the repairs were caused by the TGFα inducing endogenous stem cell division and proliferation, or some other effect of the TGFα on the brain (Regenerative Medicine, 2006, p 40).

In 2004, human embryonic stem cells (hESCs) treated to become neural progenitors were transplanted into the striatum of Parkinsonian rats, which resulted in the *in vivo* generation of a

small quantity of dopaminergic neurons (Ben-Hur et al., 2004). The generation of these dopaminergic neurons resulted a lessening of the PD symptoms, including substantial improvements in stepping, behavioral tests, and a partial increase in apomorphine-induced and D-amphetamine rotational behavior (Ben-Hur et al., 2004). Another 2004 study involving the implantation of hESCs pre-treated to differentiate into neural cells, resulted in a reduction in the Parkinson's like symptoms in mice (Ryan, 2004). A post-mortem investigation revealed the presence of dopamine-releasing cells generated from the transplanted hESC, and the hESC did not continue to proliferate to cause cancerous tumor formation within the 12 weeks the mice were monitored following the treatment (Ryan, 2004).

In animals, scientists have also provided donor animals with genetically matched transplant tissue generated by somatic cell nuclear transfer (SCNT). In this process, the nucleus from a skin fibroblast cell is injected into an enucleated egg. The egg is grown for about 5 days to the blastocyst stage, from which ES cells are isolated genetically identical to the individual from which the skin cell was obtained. This process is of considerable interest lately since it can eventually provide patients with ES treatments eliminating graft rejection. Scientists have had success generating dopamine neurons using this technique in mice and primates (Regenerative Medicine, 2006, p 40).

Stem cells have not yet been used to treat patients with PD, but some studies have used transplants with embryonic tissue. In one 2001 study, human embryonic dopamine neurons (derived from embryonic mesencephalic tissue) were transplanted into the putamen of the brain of individuals with severe Parkinson's disease. Of the patients receiving the transplant, significant improvement occurred in patients younger than 60 compared to those receiving a mock surgery, but no significant improvement was seen in transplant patients over the age of 60.

The improvements were long lasting in a majority of the patients, however for 15% of the patients, after improvement within the first year following the transplant, dyskinesias (difficulty performing voluntary movements), and dystonia (involuntary muscle contraction) returned (Freed et al., 2001). However, as we will learn in Chapter-3, treatments with embryonic tissues (as in the above experiment) are even more controversial than ES treatments since they involve isolating tissues from aborted fetuses. With respect to stem cells and PD, human PD patients have not yet been treated with hESCs, so this application remains in the future.

Treatment of Spinal Cord Injury

Spinal cord injury results most frequently from trauma or disease. The spinal cord is a bundle of nerves that goes through the middle of the spinal column (middle of the vertebra) carrying nerve signals from the brain to the rest of the body and back. The spinal cord does not have to be severed to lose function; in fact, in most spinal cord injuries, the spinal cord is not severed at all (Spinal Cord Injury Resource Center, 2009). Most spinal cord injuries result in the loss of sensation and movement (paralysis) below the injury site. Paralysis affecting the majority of the body, including the arms and legs, is called quadriplegia, and paralysis affecting the lower body is called paraplegia (Mayo Clinic, 2009). In the United States, 40 of every million people have a spinal cord injury. This number does not include those people who die at the scene of the accident. Each year in the U.S. there are 12,000 new cases of spinal cord injuries (Spinal Cord Injury Facts, 2009).

In most spinal cord injuries, although the spinal cord is not completely severed, the remaining intact nerve axons become demyelinated due to the lack of the myelin oligo-dendrocytes as a result of the injury (Regenerative Medicine, 2006, p 40). In one 2000 animal

study, scientists coaxed the hESCs to differentiate into early stage oligodendrocytes (myelin producing cells) before transplantation into chemically demyelinated rats (Liu et al., 2000). In rats that had undergone a partial injury to the spinal cord less than seven days previously, saw myelin growth around the damaged neurons, and showed an increase in walking capability. In rats who received the transplant 10 months after partial injury, no myelin growth was seen, likely due to the preventative effects of the formed scar tissue, regardless of the presence of mature oligodendrocytes at the site of injury. These rats, therefore, saw no increase in walking capabilities. This study was repeated in 2005 where scientists found that hESC-derived cells, after implantation in rats, restored myelin to neurons within seven days of the initial injury and a restoration of motor function (UC Irvine, 2005). In another animal study, mouse ESCs were treated to ensure differentiation into neurons, and then injected into the injured area of a rat's spine that had been severely bruised (Sheppa, 2000). Injection within nine days of injury resulted in restoration of hind leg function, and the presence of new neurons, oligodendrocytes, and astrocytes. Of the roughly 1 million injected mouse ES cells, most had died within 2 weeks, but enough remained to form the oligodendrocytes, astrocytes, and new neurons at the injury site. The blunt trauma the rats suffered from is the same type of trauma to the spinal cord that most people with spinal cord injuries experience (Sheppa, 2000).

In a 2006 study, differentiation of embryonic glial-restricted precursors (GRPs) into GRP-derived astrocytes and injection into a rat damaged spinal cord, promoted axon growth of damaged neurons, in some cases even beyond the injured area. The treatment resulted in a realignment of the injured area, increased locomotion, suppression of scaring, and rescued axons cut from atrophy (Davies, 2006).

Stem cells have not yet been used to treat human spinal cord patients. Some scientists believe that when such treatments are allowed, they will be administered during the recovery stage in which rods and ties are placed around the spinal column for stabilization (UC Irvine, 2005). But before this happens, scientists say more animal research must occur to insure patient safety (Regenerative Medicine, 2006, p 42).

Treatment of Diabetes

Diabetes occurs when insulin is improperly used or is not produced by the body. Insulin is responsible for the conversion of starches and sugars (glucose) into energy. In the United States alone, 23.6 million people have diabetes, and 57 million people in the U.S. have pre-diabetes, a condition in which a person's blood glucose level is higher than normal but not high enough to be considered diabetes. There are various forms of the disease: Type 1, Type 2, and gestational diabetes. In Type 1 diabetes the body does not produce insulin in response to high glucose levels. Type 2 diabetes, the most common form of the disease, is characterized by improper use of insulin by the body (insulin resistance), as well as lower than normal levels of insulin production. Gestational diabetes is a condition in which, during pregnancy, a woman's body does not properly use insulin, and 5% – 10% of women with gestational diabetes are found to have Type 2 diabetes following their pregnancy (American Diabetes Association, 2009).

Stem cells have been shown in animal studies to differentiate into insulin producing cells that can be used to treat diabetes. In mice, scientists have been able to develop pancreatic cells that secrete insulin in response to glucose, as well as other pancreatic endocrine hormones, by differentiating mouse ESC. These cells when injected into diabetic mice, even developed in a three dimensional structure, similar to that seen *in vivo* in pancreatic islets, which retained its

shape and rapidly became vascularized (Lumelsky et al., 2001). Mouse ESCs have been shown to be capable of differentiating into insulin-producing cells and restoring normal glycemia in diabetic mice (Roche et al., 2003).

In addition to ES cells, HSCs have also been used in animal studies to treat diabetes. Administration of mouse bone marrow-derived stem cells into the islets and ductile regions of the pancreas, in STZ poisoned mice (to mimic diabetes) resulted in the proliferation of pancreatic cells, insulin production, and lowered hyperglycemia (Hess et al., 2003). This application of bone marrow-derived stem cells has the potential for use in pancreatic β-cell regeneration.

With respect to human ES experiments, one 2005 study showed that hESCs if treated correctly can, *in vitro*, differentiate into the pancreatic cells responsible for insulin production (β-cells in the islets of Langerhans) (Assady et al., 2005). These β-cells proved to be functional insulin-producing cells, and although such cells have not yet been transplanted into humans, scientists hope they can be used to treat patients with type-1 diabetes (Assady et al., 2005). Scientists have also been able to direct hESCs to develop into endocrine (hormone secreting) cells capable of secreting insulin, glucagon, pancreatic polypeptide, somatostatin, and ghrelin, *in vitro*, that mimic the development of the tissue during fetal development (D'Amour, 2006).

Treatment of Cardiac Damage

Congestive heart failure, a condition in which the heart does not pump enough blood out of the heart, occurs from damage such as a heart attack, or a pulmonary embolism. It affects 400,000 new people each year in the United States. It is estimated that there are currently five million people in the United States with congestive heart failure (Optimal Heart Health, 2009).

Various types of cells have been used to treat heart damage. These cells can be delivered to the damaged heart muscle in a few ways: intravenous injection, injection directly into the coronary artery, or injection directly into the ventricular wall (endomyocardial injection) (Regenerative Medicine, 2006, pg 58-59).

Skeletal myoblasts (SMs) were the first "stem" cell type explored for cardiac repair due to their high proliferation rate, commitment to differentiate into muscle tissue, and resistance to ischemia. SMs have been shown to repopulate scar tissue resulting in increased ventricular functioning in rat and human studies (Dowell et al., 2003). However, these SM-derived cardiomyocytes have a contractile function separate from that of the native myocardium, and are unaffected by their electrical impulses (Leobon et al., 2003). Unfortunately early studies using SMs for cardiac muscle repair lead to sustained ventricular tachycardia, a potentially fatal heart arrhythmia, likely caused by the lack of an electrical interaction between the SM-derived cells and the regular myocardium of the heart (Menasche et al., 2003; Siminiak et al., 2004).

In mice, injection of bone marrow-derived stem cells into the ventricular wall following an induced heart attack, resulted in 70 percent of the scar tissue being repopulated with new smooth muscle, cardiomyocytes, and vascular endothelial cells (Orlic et al., 2001). However it has not yet been proven whether this repopulation was actually generated from the bone-marrow derived cells (Regenerative Medicine, 2006, p 60). Mesenchymal stem cells (MSCs), found in bone marrow, differentiate into adipose tissue, muscle, bone, tendons, ligaments and fibroblasts. MSCs remain multipotent *in vitro*, can be frozen, have relatively little immunogenicity, and are easily extracted from autologous bone marrow. Injection of non-host MSCs into damaged heart tissue, in animal studies, has resulted in increased heart muscle function, and capillary formation, and elicited no immune response from the host(MacKenzie, Flake, 2002). MSCs have the

benefit of having a low immunogenicity (ability to cause an immune response) and therefore have an advantage for use in human trials (Amado et al., 2005). Endothelial progenitor cells (EPCs) are bone-marrow derived stem cells that give rise to the endothelium (inner lining of the heart) (Rosenstrauch et al., 2005), and home in on damaged vascular tissue to form new vascular tissue in response to a heart attack or ischemia (loss of blood flow) (Kocher et al., 2001). Within 48 hours after intravenous injection of EPCs (Kocher et al., 2001), the graft helped prevent left ventricular (LV) remodeling and myocyte apoptosis (programmed cell death) (Shuster et al., 2004).

Resident cardiac stem cells have been isolated in rat, mouse, and human specimens (Beltrami et al., 2003; Messina et al., 2004), which have the ability to repair damaged heart tissue and replace dead heart muscle cells (Boyle et al., 2006). However, few cardiac stem cells can be isolated from the heart, so these cells require proliferation *ex vivo* (outside the body) before being injected into the site of myocardial (heart muscle) damage. These cells have the ability to increase systolic function as well as develop into myocardium (Messina et al., 2005).

Injection of umbilical cord blood (UBC) HSCs into a rat having a myocardial infarction resulted in the development of new blood vessels when injected intravenously (Ma et al., 2005), and an increase in ventricular function when injected directly into the damaged tissue (Hirata et al., 2005). Following intravenous injection of UCB HSCs, a DNA assay showed that the UCB stem cells had also migrated to the liver, spleen, and bone marrow of the host (Hirata et al., 2005). Autologous fibroblasts, obtained from adult rat peripheral blood has been shown to cause an increase in elasticity in scar tissue upon direct injection into the site of damage in a post infarction rat heart, although the heart showed no increase in function. Scientists believe that

these cells may be beneficial to elderly patients who have decreased numbers of bone marrow stem cells or autologous skeletal myoblasts (Regenerative Medicine, 2006, p 62).

Scientists discovered that a gene manipulation in differentiating murine (rat or mouse) ESCs results in an essentially pure culture of cardiomyocytes suitable for use in grafts. These engrafted cells lasted longer than seven weeks (the longest time they were tested) (Klug et al., 1996). Undifferentiated rat ESCs used to treat infarcted rat hearts which differentiated into new functional cardiomyocytes occupying the damaged area with little scarring, normal ventricular architecture, and were capable of increased cardiac output. There was also no tumor formation, irregular electrical output, sudden cardiac death, or graft rejection (Terzic, 2004).

With respect to human treatments, scientists have been able to create a differentiation system that can guide human ES cells *in vivo* to develop into cardiac tissue, which holds great potential for use in functional genomics, pharmacological testing, tissue engineering, cell therapy, and the study of early cardiac development. Human ESCs cultured in suspension and treated for differentiation, developed into ESC-derived cardiomyocytes that shared structural and functional properties with early-stage cardiomyocytes (Kehat et al, 2001). A 2006 study showed that patients with acute myocardial infarction showed lower death rates, increased left ventricular contractibility, and increased revascularization following bone marrow stem cell injection (Schächinger et al, 2006). Some success has also been shown in a human stem cell clinical trial. A 16 year-old boy, accidentally shot in the heart with a nail gun, subsequently had a heart attack. Doctors administered a drug to increase the concentration of HSCs in his blood, harvested these stem cells and then injected them into the artery that supplies blood flow to the front of the heart (in his case which contained mostly dead cardiac tissue). A week after the surgery, he was released from the hospital to finish recovering at home. Doctors reported they had never seen a

recovery like his; following his surgery his cardiac function was significantly increased. However, being cautious, Doctors also say that these may be age independent results and the procedure may not obtain the similar results in older patients. And it remains to be proven whether the HSC cell injection resulted in the improvement (Philipkoski, 2003).

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Chapter 3 – Stem Cell Ethics

Catherine Campbell

Stem cell research is one of the most promising areas of medical research. But for research to continue, scientists require stem cell lines, isolated either from adult stem cells (ASCs), or the more controversial embryonic stem (ES) cells. Although there are few ethical issues associated with using adult stem cells, there are numerous dilemmas stemming from ES cell research. Some people are opposed to stem cell research for secular and religious reasons, while others are in favor of stem cell research due to its potential for producing new medical treatments. In a national Gallop Poll conducted in 2005, about 60% of people supported stem cell research and approximately 30% were opposed to it (ABC News, 2007). Meanwhile, 73% of people polled were in favor of using discarded embryos for stem cell research for the development of potential medical cures, while only 19% were opposed to it (ABC News, 2007). It is evident that there is a clear split in opinions regarding stem cell research, a trend identified in almost every population around the world. The purpose of this chapter is to investigate the ethics of stem cell research, both adult and embryonic, to introduce a discussion about whether we "should" work with stem cells, and to also provide a prelude for a subsequent chapter discussion on stem cell legalities.

The Ethics of Adult and Embryonic Stem Cell Research

Among the many areas of scientific study, few have as much potential for producing new medical treatments for debilitating disease as stem cells. Some scientists have even gone as far

as to say that stem cell research may lead to some of the most prominent *miracle cures* of the twenty-first century (Elliot and Porowski, 2005). While adult stem cell use has few ethical issues, ES cell research has produced many heated ethical debates (Elliot and Porowski, 2005). Given the fewer ethical issues associated with ASCs, one might simply argue that ES cell use should be abandoned, however most scientists believe it is far too premature to abandon ES cells because (as discussed in Chapter-2) ASCs are difficult to isolate, difficult grow in culture, and most types have not proven as medically useful as ES cells.

The ES cell debate has its origins in the late 1960's with the advent of human *in vitro* fertilization (IVF) technology. As IVF clinics made their debut, and more couples donated sperm and egg, debates ensued about what to do with the excess embryos after the couple had enough children. Usually the excess IVF embryos were destroyed, which some called murder. The human ES cell debate began in 1998, when scientists in the United States first isolated ES cells from a human embryo (Thomson et al., 1998; Bhikkhu, 2007). As discussed in Chapter-1, ES cells are usually isolated from the inner cell mass of IVF blastocyst embryos provided with donor consent from IVF clinics, so the same debates that began in the 1960's about embryo use still pertain to ES cell research.

With respect to embryo *sources*, relatively few people in the U.S. support the payment of egg donors for research purposes, so those in favor of ES cell research generally believe that it is more ethical to use embryos left over from fertility clinics instead of discarding them (Bhikkhu, 2007). In fact, the United States alone contains possibly hundreds or thousands of such IVF embryos (Bhikkhu, 2007), and Obama's recent stem cell legislations (discussed in Chapter-4) outlaw payment for this purpose.

With respect to *destruction* of the embryo, the debate eventually centers on when life begins. On this topic, ES cell research creates an ethical dilemma for many people in both the secular and religious sense. Some believe life starts at the moment of conception, when an egg is fertilized by a sperm, while others consider life to begin later at the primitive streak, or even at birth (Derbyshire, 2001). Since stem cell research can involve the destruction of human embryos, it is evident that the moral status of the human embryo is heavily debated. Essentially, there are two categories of moral thinking when it comes to opposing ES cell research. There is the belief that the human embryo is a person with rights, including the right to life, and thus the destruction of the embryo is murder (Derbyshire, 2001). Then, there is the belief that the embryo is not yet a person, however, it possesses the *potential* to develop into a human being (Shannon, 2006; Derbyshire, 2001). According to the first type of moral thinking, the human embryo is symbolically valuable, and therefore must be protected from harm (Derbyshire, 2001). Then, there is the supportive side of ES cell research. Some in favor of ES cell research consider the embryo to be a mere collection of cells, and thus the embryo is no more alive or human than a tumor or a virus (Derbyshire, 2001). And some major religions believe that life begins well after day-5 when the ES cells would be isolated (discussed below). According to this second line of thought, the destruction of the human embryo is justified, considering that life begins later, and potential good for society may result from ES cells.

Some U.S. citizens are opposed to ES cell research not only for religious reasons, but also because of ability of scientists to affect and manipulate human life (Bhikkhu, 2007). They argue that society should strive to free others from debilitating disease using the most ethical means possible (i.e. ASCs not ES cells) (Bhikkhu, 2007). On the other hand, others believe that it would be unethical *not* to try to save lives using ES cells. They argue that potential for medical

breakthroughs lies in both embryonic and adult stem cell research (Bhikkhu, 2007). However, almost anyone can agree that much more research is required before the actual applications for both embryonic and adult stem cell research can be determined, especially given several recent advances on *alternative* sources for embryo-derived ES cells (iPS cells, multipotent mesenchymal stem cells, and parthenotes).

The Ethics of Parthenotes

Due to the controversial nature of ES cell research, and the potency limitations of adult stem cells, scientists have developed human parthenotes as an alternative. Human parthenotes are created from eggs that are persuaded by chemical treatments to develop into an embryo in order to create ES cells (McConchie, 2005). Although human parthenotes are not capable of progressing further into their development to allow for implantation in the uterus, parthenote ES cells are often referred to as *embryonic-like*, due to their ability to produce pluripotent cells (McConchie, 2005). Some believe that parthenotes are a relatively moral source for ES cells compared to human embryos that are capable of implantation.

Although human parthenotes are not capable of developing into a fetus, there are still some ethical concerns to be addressed. The main ethical dilemmas associated with parthenotes are the process still involves the ethics of donating eggs for medical research, and the debate as to the status of an embryo that cannot form an adult (McConchie, 2005). Some people don't consider the parthenote to be a true embryo since it is unable to develop into a fetus, while others believe that they should be given the benefit of the doubt and treated as an embryo regardless of their developmental potential (McConchie, 2005). In order for the moral status of the human parthenote can be determined, such ethical issues will remain.

The Ethics of iPS Cells

As discussed in Chapter-1, one of the hottest topics in all of stem cell research for the past two years has been the topic of induced pluripotent stem (iPS) cells. The process as discovered in 2007 for human cells (Takahashi et al., 2007) involves isolating skin fibroblast cells from a patient, and transfecting them with four transcription factor genes to induce a de-differentiated state to form pluripotent cells. iPS cells are genetically identical to the patient (since they were obtained from the patient's own skin cells), so are less likely to be rejected by the patient during implant therapies. The process has since been refined to using either two transcription factors, or even just polyarginine proteins, but the ethics remain the same, no embryo is used, yet the cells appear (so far) to have the same therapeutic potential as embryo derived ES cells. Thus, much current research focuses on determining whether iPS cells truly are pluripotent, because if so, their use could obliterate the need for embryo-derived ES cells.

With respect to religious stances on iPS cells, due to their recent discovery no church has made a formal comment yet. Although the iPS process creates stem cells genetically identical to a patient, it does not involve any therapeutic cloning from embryos to achieve this. Because no embryos are involved, these cells should have the same moral status as adult stem cells, which even the conservative Catholic church is in favor of (Catholic Online, 2008; Pacholczyk, 2008).

Religious Stances on Stem Cells

The Christian Perspective

Most Christians believe that human life begins at the moment of conception, when an egg is fertilized by a sperm. According to Christian tradition, the embryo is indeed a developing human person, regardless of the fact it is at the earliest stage of development (Jones, 2003).

Therefore, the embryo must be treated with respect regardless of its developmental stage (Bhikkhu, 2007). Their rationale is supported by the Bible, which states that humans are made in the image of God, and therefore, every human being possesses the inherent right to life, dignity, and worth (Bhikkhu, 2007). Therefore, Christianity teaches that the human embryo should be given the same moral status as any other developed human individual (Jones, 2003).

The Roman Catholic Church has been known for its rigid stance on ES stem cell research. They view the destruction of the human embryo, created by any means, as a gravely illicit act which should be avoided at all costs (Correa and Sgreccia, 2000; Barry, 2007). Pope Benedict has often stressed that the Catholic Church strongly opposes research which disrespects the human individual, including the embryo from the moment of conception (Catholic Online, 2008). The Pope also stated that the opposition of the Church to ES cell research "…is against those forms of research that involve the planned suppression of human beings who are already alive, though they may not have been born" (Catholic Online, 2008). According to the Catholic Church, no matter how much mankind may benefit from ES cell research, the unethical means used to achieve those goals can never be justified (Catholic Online, 2008).

A majority of the Catholic Church's ethical concerns to ES cell research are addressed in their article, The Declaration on the Production and the Scientific and Therapeutic Use of Human Embryonic Stem Cells (Correa, 2000). The first dilemma presented was "*Is it morally licit to produce and/or use living human embryos for the preparation of ES cells?"* (Correa, 2000). The answer was negative, based on the belief that the living embryo is a human being from the moment of conception with a defined and unique identity (Correa, 2000). The second ethical problem was "*Is it morally licit to engage in so called therapeutic cloning?"* (Correa, 2000). Therapeutic cloning involves the production of cloned human embryos followed by their

destruction to extract ES cells genetically identical to a patient. According to the Catholic Church, the answer was negative, based on the belief that the destruction of the human embryo to obtain ES cells is immoral (Correa, 2000). The third ethical issue presented was "*Is it morally licit to use ES cells, and the differentiated cells obtained from them, which are supplied by other researchers or are commercially obtainable?*" (Correa, 2000). This was determined to be immoral because participation of any kind in ES cell research is gravely illicit (Correa, 2000).

Although the Catholic Church strongly rejects ES cell research, they do support research involving adult stem cells. According to Father Tadeusz Pacholczyk, a neurologist and priest at the National Catholic Bioethics Center in Philadelphia, PA, the Catholic Church is supportive of adult and parthogenetic stem cell research (Barry, 2007; Catholic Online, 2008). The Catholic Church is also supportive of research involving embryonic germ cells and umbilical cord stem cells, since neither involves the destruction of potential human life (Pacholczyk, 2008). They argue that work being done with adult stem cells does not involve death for any individual involved since the stem cells are isolated from adult tissues, rather than embryonic (Catholic Online, 2008). According to Pope Benedict, adult stem cell research maintains the respect due to every human individual at every stage of life (Catholic Online, 2008). For this reason, the Pope has encouraged scientists to work together and increase research on adult stem cells in order to alleviate human anguish (Catholic Online, 2008).

A number of other Christian groups that are actually in favor of ES research. Groups such as the Unitarian-Universalists, the Episcopal Church, the Evangelical Lutheran Church, the United Methodist Church, and the Church of Jesus Christ of Latter Day Saints, have no official position in the ES cell debate (Derbyshire, 2001). Protestants have a wide range of perspectives regarding stem cell research. Some Protestants, such as the Southern Baptist Convention,

believe that the embryo is the smallest and earliest form of life and thus should never be annihilated (Teaching About Religion, 2006). Other Protestants, such as the American Presbyterian Church, believe that stem cell research would be ethical only if it was the only way to produce new medical therapies (Teaching About Religion, 2006). Another Christian group, the Anglican-Episcopal tradition, believes the early embryo doesn't have the potential to become a human being until the fourteenth day, also known as the primitive streak. The primitive steak is a moment in which the spinal cord begins to develop and the embryo can no longer divide into several embryos (Kohsl, 2008). Thus the Episcopal church would allow research on 5-day old embryos. Overall, most Protestants hold that ES cell research should be limited to up to 15 day old embryos left over from IVF clinics (not from paid donors) (Teaching About Religion, 2006).

The Judaic Perspective

In general, the Jewish population supports stem cell research, particularly ES cell research, for several reasons. During the first forty days of development, the human embryo is regarded as simply water (Dorff, 2000). Since the embryo does not have the same form as a child does, it is not considered to be a human child (Dorff, 2000). According to Judaism, the embryo does not become a human being until 41 days into gestation (Bhikkhu, 2007). Once the embryo is 41 days old, it receives its soul and becomes a human individual. However, the human embryo will not inherit personhood, a characteristic unique to developed human beings, until birth (Teaching About Religion, 2006). Since the embryo is not considered to be a human being or a person until day 41, ES cell research based on the use of the 5-day old human embryo is not controversial (Bhikkhu, 2007). Since the embryo is cultured in a petri dish, outside the human body, it has no potential to develop into a human person (Dorff, 2001). Therefore, its

moral status is much less than that of an embryo developing in the womb during the first stages of embryonic development (Dorff, 2001).

Jewish tradition also supports ES cell research since it has the possibility of producing new medical treatments with the potential to save many human lives (Bhikkhu, 2007). In 1999, Rabbi Dorff sent a report to the White House, explaining that Jewish law endorses stem cell research since it could potentially cure numerous diseases, therefore promoting greater good (Derbyshire, 2001). Jewish law supports the use of embryos left over from fertility clinics in scientific research since such embryos are not implanted in the uterine wall (Castillo, 2006). For this reason, IVF embryos are not capable of developing into a human being, and therefore their use in science is justified. They believe that the benefit of using embryos left over from fertility clinics or miscarriages is infinite, and that it would be immoral to not explore their potential to serve humanity (Bhikkhu, 2007).

According to Jewish tradition, disease can be overcome with the help of both natural and synthetic means (Dorff, 2000). Physicians are considered to be God's helpers, since they are involved in healing mankind (Dorff, 2000). Unlike many other religious populations, the Jewish community has no issue with the concept of "*playing God"* (Jakobovits, 2006). This is permitted as long as we strive to heal and develop new medical treatments when possible (Jakobovits, 2006). Since our bodies are made in the image of God, and thus belong to God, it is believed that humans have an obligation to God to produce and utilize new medical treatments that will allow us to better care for our bodies (Dorff, 2000). Based on this line of thought, human beings have an obligation to God to develop new medical therapies and cures for debilitating disease to better preserve our bodies (Dorff, 2001). According to Jewish law, medical therapies produced by natural or synthetic means are equally good and legitimate (Dorff,

2000). Couples who no longer need the extra embryos created for IVF treatments should be highly encouraged to donate their embryos to scientific research (Dorff, 2001).

Although Judaism supports the use of embryos created for fertility purposes in scientific research, creating human embryos for the sole purpose of this research is permitted only under one condition (Bhikkhu, 2007). The best and most moral source for obtaining stem cells is from frozen embryos created for fertility purposes, since these embryos would normally be discarded when not used (Dorff, 2001). However, embryos may also be created for medical and scientific research purposes only if the woman supplying the eggs donates only once or twice (Dorff, 2001). It is important to remember that human embryos, and even the egg and sperm which create them, should be respected for their potential for human life and procreation (Dorff, 2000). Although the destruction of the human embryo before the forty-first day is permitted by Jewish law, it is crucial to bear in mind that Jewish practice requires respect for such embryos, and consequently they should not be destroyed unnecessarily (Dorff, 2000).

The Islamic Perspective

Islam teaches that although the embryo is alive once conceived, it is not a human being (Bhikkhu, 2007). According to this perspective, the embryo does not become a human individual until it is about 4 months old, which is the moment when it receives its soul (Bhikkhu, 2007). Islamists believe that once an embryo is 121 days old (four months), "…an angel comes and blows the spirit into that individual" (Bhikkhu, 2007), and the behaviors and fate of the fetus is established. Once this occurs, the fetus is considered to be a human being (Bhikkhu, 2007).

Islamists have made a vivid distinction between the early embryo and fetus, during the first 40 days it is an embryo, and after a fetus. According to Islam, if a pregnant woman decides

to abort her baby during the early stages of gestation, then the woman's punishment would be less than if she had aborted a fetus later in her pregnancy (Kutty, 2007). This infers that Islamists consider the early embryo to be of lesser value than the late stage fetus. Since ES cells are cultivated from the destroyed early stage embryos, it is assumed that Islam permits ES cell research.

Thus, when it comes to stem cell research, Islam is generally in favor of it. However, the ethical nature of the *use* of the embryo is also important (Bhikkhu, 2007). If the ES cells are used to produce new tissues and organs for medical purposes, then the research is considered to be ethical and encouraged (Bhikkhu, 2007). However, if ES cells are used to selectively generate offspring, then it is unethical and discouraged (Bhikkhu, 2007). Also, the question of the production of human embryos *solely* to create stem cells is still highly debated in Islam (Castillo, 2006). In general, Islamists believe that humans have an obligation to God to use wisdom to improve health (Frazzetto, 2004). Since this is the case, stem cell research is considered to be "an act of faith in the ultimate will of God" (Frazzetto, 2004), as long as the objective is to improve human health.

The Buddhist Perspective

Buddhism teaches that an embryo is alive and human from the moment of conception (Bhikkhu, 2007). However, Buddhists believe that the human embryo does not have a mind or thought until it has been successfully implanted into the uterine wall (Castillo, 2006). Since this is the case, the embryo is not considered to have attained personhood until birth (Hughes and Keown, 1995). Buddhists believe that personhood is characterized by "the awareness of the difference between self and other", and the ability to be conscious of the self and to take

thoughtful action (Hughes and Keown, 1995). Furthermore, embryos that are contained in petri dishes do not possess thought or have a mind since they are not implanted, and therefore Buddhists may agree with ES cell research (Castillo, 2006).

Buddhism places great value on the notion of *ahimsa*, also known as *non-harming* (Keown, 2001). Therefore, there are many stipulations associated with scientific research involving the destruction of the human embryo (Keown, 2001). Actions which result in embryo harm go against the First Precept of Buddhism, which forbids causing injury or death to living individuals (Keown, 2001). Buddhists believe *first* that any scientific research which requires the destruction of the human embryo is immoral (Keown, 2001). Although ES cell research may be very controversial, Buddhists have no issue with adult stem cell research.

The Hindu Perspective

Hinduism teaches that human life begins at conception, when the embryo is immediately given its soul (Castillo, 2006). Since this is the case, Hindus believe that no person has the right to deliberately take life away from anyone, including the human embryo (Bhikkhu, 2007). When it comes to stem cell research involving the destruction of the human embryo, no greater good can possibly be attained since the means are immoral (Bhikkhu, 2007). Some even believe that severe consequences, rather than positive outcomes, will result from the production of medical treatments from human ES cell research (Bhikkhu, 2007). Hindus argue that scientists should strive to determine the underlying source for disease, rather than masking symptoms with new treatments derived from ES cell research (Jyoti, 2007).

Relative to other religions around the world, Hinduism features a strong perspective regarding illness and disease. Ancient medicine is still practiced today in the Hindu culture,

including Ayurvedic medicine. Ayurvedic medicine is an ancient form of medicine that was created by Indian practitioners (Jyoti, 2007). It is based on the concept that disease can be prevented through wisdom, since it encourages healthy lifestyles and certain spiritual practices (Jyoti, 2007). Even though some practitioners may still become ill, it is believed that such illness can be successfully combated with the use of herbal medicine (Jyoti, 2007). Hindus believe that ailments are mostly caused by previous actions, such as overindulging, drug and alcohol abuse, or other lifestyles which put stress on the body (Jyoti, 2007). Such negative actions accumulate during each life and result in bad karma. Bad karma is a personal fault, and Hindus believe that new medical treatments produced from ES cell research would make recovery from bad karma too convenient and easy, so should be avoided.

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Chapter-4: Stem Cell Legalities

Kristin Newell

As is typical of any controversial new technology, laws have been enacted to control it. The purpose of this chapter is to discuss some of the U.S. and international laws that regulate embryo and stem cell usage, as an example of the impact of technology on society.

Bush Administration Stem Cell Policy

On August 9, 2001, former President Bush declared that all research scientists receiving federal funding for embryonic stem (ES) cell research could only work with ES cell lines created before August 9, 2001. The White House claimed that there were over 60 usable ES cell lines already established, when in fact there were only about nine viable lines (Agnew, 2003). A "line" of stem cells is a group of immortal cells derived from one particular embryo. Under the Bush Administration, it was illegal to create or destroy a human embryo in any experiment funded by the federal government. This included using any equipment paid for with federal funds, even if the experiment itself was being privately funded (in the latter case cloning and creating a human embryo is legal) (Dunn, 2005). One year after President Bush placed restrictions on ES cell research, researchers were only able to access about four ES cell lines. The other ES cell lines were unavailable due to practical (non-viable cells) and legal complications. In addition, some cell lines were not real stem cells (Holden and Vogel, 2002). Thus, many scientists became concerned that the Bush ban on federal funding would severely restrict ES cell research in the U.S.

Due to the scientific outcry for more ES cell lines, congress drafted a bill to permit therapeutic cloning. But in a 2003 State of the Union address, President Bush spoke in response to the Senate bill saying "no life should be started or ended as the object of an experiment" (Agnew, 2003). On July 19, 2006, President Bush vetoed Congress' bid to end the governmental funding restrictions on human ES cell research funding in the United States. President Bush vetoed the bill because he believed that it "would support the taking of innocent human life in the hope of finding medical benefits for others." After President Bush's veto, the House of Representatives' bid fell just shy of overriding the President's veto: the bill passed in the House and Senate (235 to 193), but did not quite make the two thirds vote needed to override the President's veto (Babington, 2006). In April 2007, U.S. senators voted for the second time to try to lift the restrictions on ES cell research, but the decision was again vetoed by President Bush (Wadman, 2007).

During the Bush administration and its 2001 federal ban on deriving new ES cells, individual states and private foundations lead the way in stem cell research (Holden, 2006). If states wanted any real progress to be made, they had to provide the legislation and funding to allow it (discussed below).

Obama Administration Stem Cell Policy

On March 9, 2009 President Obama lifted the 2001 restrictions on stem cells set in place by former President Bush (Holden, 2009). This opened up federal grant money to be used to study the hundreds of stem cell lines created since August 9, 2001 when President Bush put in place the restrictions on ES cell research (Hayden, 2009). When President Obama announced the ending of the restrictions on human ES cell research, he spoke of the promise of the research,

and believes it is our obligation as human beings to care for others and to ease those suffering if we have the ability to do so, and believes that this can be achieved through ES cell research. President Obama also hopes that America will be at the forefront of advances in ES cell research, will lead the world in the discoveries that come from it, and the research will lead to better understanding and possibly even treatment of many debilitating and even fatal diseases (Lee, 2009).

Obama's new laws regarding ES cell research make available the unused ES cell lines created by *in vitro* fertilization procedures after the Bush cutoff date, but still prohibits the use of cell lines created by therapeutic cloning with federal money (Holden and Kaiser, 2009). In addition, egg donors are not to be paid, the embryos must come from discarded IVF embryos originally created for reproductive purposes. And the new laws establish an NIH advisory panel to investigate new stem cell scientific findings to help formulate new guidelines.

State Laws

As mentioned above, in spite of the 2001 Bush ban on funding ES cell research, individual states can override the federal policy. On September 23, 2002, Governor Gray Davis, of California signed a law allowing research on embryos, including those created by therapeutic cloning. The law also banned reproductive cloning (Garfinkle, 2004). In 2004, California passed a bill (Proposition 71) allowing $3 billion to be spent over a span of ten years on stem cell research, including experiments working with cloned human embryos and the stem cells they produce (Dunn, 2005). Some of the money from Proposition 71 went toward funding the creation of the California Institute of Regenerative Medicine (CIRM), which runs the state stem

cell research program. Of the 3 billion dollars for adult and ES cell research available through Proposition 71, only $350 million could be distributed each year (Johnson, 2005).

On December 10, 2002, Stanford University (California) announced the establishment of its Institute for Cancer/Stem Cell Biology and Medicine, and joined the many U.S. universities that were trying to bypass the strict federal laws regarding stem cell research by creating privately funded institutions for undergoing stem cell research (Check, 2002).

New Jersey followed California's lead and created the first state-funded stem cell research facility (Dunn, 2005). On January 2, 2004, Governor James E. McGreevey, of New Jersey, signed a law allowing research as well as the use of human ES cells, human adult stem cells from any source, and germ cells. The law also required infertility doctors to notify their patients about the option of donating human embryos following infertility treatment (Garfinkle, 2004). In 2005, New Jersey was the first state to actually use state funding for human ES cell research (Washington Post, 2005). For 2005-2006 New Jersey allocated $23 million to go to the New Jersey Stem Cell Institute (Johnson, 2005).

In March 2005, Massachusetts lawmakers approved legislation that allowed cloning for stem cell researchers, despite then Governor Mitt Romney's insistence on vetoing the bill (the bill passed by such a majority it could not be vetoed) (Dunn, 2005). Massachusetts legislators, after overriding the governor's veto, added two sections to the statute on stem cell research. The first section allowed for the creation of an institute for stem cell research as well as regenerative medicine along with $1,000,000 to be spent on the biology core. The second section allowed for the creation of a life sciences center promoting life sciences in applied and advanced sciences. These sciences to be studied include fields of life sciences such as regenerative medicine, stem cell research, nanotechnology, and biotechnology. The second section also created the Life

Sciences investment fund of $10,000,000 for allocations, appropriations, loans and grants for the investment or development in stem cell research or many other areas of the life sciences (Johnson, 2005).

Many states created stem cell research centers to counteract the Bush administration's restrictions on ES cell research. In 2003, the Center for Stem Cells and Regenerative Medicine was created in Ohio, to support adult stem cell research, with $19.4 million in state funding. In 2006, Governor Blagojevich of Illinois signed an executive order designating the creation of the Illinois Regenerative Medicine Institute (IRMI), and providing $10 million dollars (in April of 2006) for grants to be awarded to medical research facilities undergoing research on adult and embryonic stem cells, and an additional $5 million dollars in August 2006 to be used in 2007. Indiana legislators appropriated $50,000 for the creation of the adult stem cell research facility at Indiana University. The Maryland legislature created a $15 million fund for the creation of the Maryland Stem Cell Research Fund with the purpose of providing grants to fund adult and embryonic stem cell research (Johnson, 2005). In January of 2006, the New York state assembly approved legislation for the creation of the New York State Institute for Stem Cell Research and Regenerative Medicine as well as for allocating $300 million for regenerative medicine (which includes stem cell research) for the two years to follow (Washington Post, 2005).

Many other states also passed legislation allocating money for stem cell research. Governor Jodi Rell, of Connecticut, in May of 2005, passed a bill providing $100 million over ten years for stem cell research (Washington Post, 2005). Washington created the Life Sciences Discovery Fund to provide money for stem cell research, but the source of the money had not yet been worked out at the establishment of the fund (Johnson, 2005). In 2005, Governor Rod

Blagojevich, of Illinois, earmarked $10 million to be used for stem cell research (Washington Post, 2005).

Not all states followed suit funding stem cell research. Michigan state law bans therapeutic cloning, and therefore research on cloned embryos. However, with written consent mothers are able to donate their fetuses, embryos, and newborn babies to scientific research (Washington Post, 2005). As of 2005 the states in which no action has been taken either way regarding stem cells research are: Vermont, Delaware, Washington D.C., West Virginia, Kentucky, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Wisconsin, Missouri, Texas, Kansas, Colorado, Wyoming, Idaho, Nevada, Oregon, Washington, and Alaska (Washington Post, 2005).

International Stem Cell Laws

On July 20, 2006, Germany announced at the European Union (EU) meeting, " The European Union science program should not be used to give financial incentives to kill embryos," in response to the idea that some of the 51 billion euro would be dedicated to stem cell research for the years 2007-2013. Within the EU, countries such as Germany, Poland, Austria, Lithuania, Slovenia, and Slovakia were opposed to the idea that some of the money to fund scientific research would be dedicated to researching something that is banded in some of the countries of the EU (Deutsche Welle, 2006). German law bans all research on human embryos, and only allows the creation of a human embryo for *in vitro* fertilization purposes. Earlier in 2002, however, Germany had passed a law allowing the import of human ES cells for use in research, but with close governmental control (Kim, 2002).

At the 2006 EU meeting, Finland, who held the rotating EU presidency, suggested that money be designated for ES cell research, but prohibiting the dispersal of funds for projects dealing with human genetic modification, human reproductive cloning, or the creation of human embryos for research (Deutsche Welle, 2006).

Since 1990, the United Kingdom has allowed research to be done using embryos left over from assisted reproduction. In 2001, this law was reinterpreted and expanded beyond just reproductive biology, to include many other types of basic research. United Kingdom law also allows the creation of embryos for the purpose of research. On August 11, 2004, a license was granted to the Newcastle Center for Life by the United Kingdom's Human Fertilisation and Embryology Authority, allowing the creation of colonies of human stem cells for the purpose of cloning, but not to clone a human. This license was good for a year and allowed researchers to continue to work on the ES cell lines they had created after the license had expired, but could not continue the isolation or cloning procedures following the expiration of the license (Garfinkle, 2004).

Sweden allows the use of unused *in vitro* fertilization embryos as a source of stem cells in research (Sweden's Stem Cell Success, 2002), as well as supporting the use of cloning human embryos for therapeutic purposes (Kim, 2002). Therapeutic cloning of embryos for stem cell research, although currently a procedure not yet achieved in humans as of 2009, seemed to be a process which would be "ethically defensible" in Sweden (Sweden's Stem Cell Success, 2002). By 2002, Sweden had established a nationally funded stem cell bank, as well as the equivalent of almost 1 million U.S. dollars being disbursed by the Swedish National Research Council to fund the national stem cell bank for the three years (Sweden's Stem Cell Success, 2002). The Michael J. Fox Foundation for Parkinson's Research, in March 2002, gave $4.4 million in U.S. dollars to

Sweden for the creation of a stem cell line to be used purely for Parkinson's research. Also, in March of 2002, Sweden and the U.S. announced a joint program to provide $7.5 million in U.S. dollars for stem cell research (Sweden's Stem Cell Success, 2002).

On October 19, 2005 the World Stem Cell Foundation was unveiled in Seoul, South Korea, which intends to produce around 100 new ES cell lines each year. These stem cell lines are available to scientists around the world, but particularly in the U.S. where laws about federal funding under the Bush administration limited the research that can be done (Kaplan, 2005).

Australia allows the use of embryos for research as long as they were created for the purpose of assisted reproduction before April 5, 2002. Australia bans all type of human cloning, regardless of whether it is for research or reproduction. This ban includes embryo splitting, and everything that can be considered a form of cloning (Garfinkle, 2004).

There are many countries that do not allow, or have strict regulations regarding embryonic stem cell research. The Swiss Constitution strictly prohibits the use of human embryos for research. It even goes so far as to say how many of a woman's eggs can be fertilized during assisted reproduction procedures (Garfinkle, 2004). French law prohibits research on human embryos (Kim, 2002). Other countries with restrictive policies, ranging from outright banning of ES cell research to allowing research only on imported cell lines, to allowing research to be done on only a few already created stem cell lines, are Austria, Ireland, Germany, Italy, Poland, and Norway (Hoffman, 2005).

Overall, countries with permissive stem cell policies, in which therapeutic cloning is allowed for use in human ES cell research, as well as the use of embryos created by *in vitro* fertilization procedures for embryonic stem cell research are: China, Australia, the United Kingdom, Belgium, India, Singapore, South Korea, Israel, Sweden, Japan and a few others

(Hoffman, 2005). Countries with moderate policies, that allow the use of unused embryos created by *in vitro* fertilization clinics, but not those created by therapeutic cloning include: Canada, France, the United States, Brazil, Iran, Taiwan, The Netherlands, Spain, South Africa, as well as a few others (Hoffman, 2005). And many countries still have no policies one way or another regarding human embryos or human embryonic stem cell research. Turkey is among these countries (Hoffman, 2005).

With respect to induced pluripotent stem (iPS) cell technology, in June of 2008 Japan and the U.S. were competing to develop this technology, but the U.S. seemed to be having more success due to the commercialization of the Japanese developed technology (iPS) (Cyranoski, 2008).

Chapter-4 Conclusion

California and South Korea appear to have the legislation that will lead to the most progress for ES cell research. California and South Korea allow therapeutic cloning to create embryos for use in ES cell research. With the use of therapeutic cloning, ES cells can be created that have the exact same genes as a patient that could be receiving those cells to treat some debilitating or even fatal disease, which would result in no graft rejection and therefore should provide the best possible results. South Korea also has a good thing going for it in its creation and transportation of ES cell lines to other countries; it is this sharing of science and innovation that will lead to the most scientific progress and advances. People all over the world suffer from the many fatal and debilitating diseases, of which treatments are being pursued through stem cell research, especially with ES cells.

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PROJECT CONCLUSIONS

The author of Chapters 1 and 3 believes that it is acceptable to work with ES cells due to their potential applications in medicine. The potential for new medical treatments of currently incurable human diseases definitely outweighs the moral status of an IVF blastocyst. As for the *source* of ES cells, they may be created from unused IVF embryos, originally created for reproductive purposes, or from paid egg donors. However, it is acknowledged that some people believe ES cell research to be immoral. In order to show respect for all varying opinions regarding ES cell research, iPS and adult stem cells should be used whenever possible as a substitute (as long as new medical therapies are being produced). In regards to stem cell legalities, the author agrees most with Sweden's stem cell policies, since they allow the use of unused IVF embryos and support the cloning of human embryos.

The author of Chapters 2 and 4 believes that ES cells should be used in scientific research because they have great potential for use in regenerative medicine. The embryo is not yet a human being when ES cells are removed, rather, it is a mass of cells with the potential for personhood. The author doesn't believe that destroying embryos is murder. iPS and ASCs should be used in stem cell research whenever possible to learn more about various diseases and regenerative medicine. The *source* of embryos used for ES cell research should come from many sources, the best being unused embryos from IVF clinics, which would be discarded anyway, and would not become a human being regardless of whether it is used for research. The country that has the best legislation regarding stem cell research is South Korea. They have the least restrictions on stem cell research, which has the potential for treating many debilitating and fatal diseases that cause suffering in people worldwide.