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Stem Cells and Society: Sources, Ethics, Applications, and Legality

Brett Oliver Dumas

Worcester Polytechnic Institute

Prashant Krishna Yamajala

Worcester Polytechnic Institute

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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By:

Brett Dumas

Prashant Yamajala

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APPROVED:

Prof. David S. Adams, Ph.D.
WPI Project Advisor

ABSTRACT

The goal of this IQP is to inform the public about stem cell research and its potential to save lives, as well as provide some insight on the underlying ethical and legal issues involved with this controversial technology. By educating the public and dismissing many common misconceptions, this project enables the public to make more informed conclusions. To accomplish this task, the types and sources of the various stem cells were researched, as well as their current and potential uses to improve and save lives. The religious viewpoints of the world's five major religions were provided as a reference for the ethical issues involved, and lastly the legalities of the use of stem cells use were researched. Throughout the project, many misconceptions were clarified with evidence to back up each point. Based on the research performed in this project, it is believed that stem cells offer great promise, and will play a major role in the future of medical treatment and research.

TABLE OF CONTENTS

Signature Page	1
Abstract	2
Table of Contents	3
Project Objective	4
Chapter-1: Stem Cell Types and Sources	5
Chapter-2: Stem Cell Applications	22
Chapter-3: Stem Cell Ethics	32
Chapter-4: Stem Cell Legalities	50
Project Conclusions	62

PROJECT OBJECTIVES

The objective of this project was to educate the general public in all aspects of stem cells used in modern day research. The project is divided into the following four chapters, each with a separate purpose. In chapter one, all types of stem cells and their differentiation capabilities were described, along with how they are isolated and produced. A major distinction was made between embryonic and adult stem cells to set the stage for the rest of the project addressing ethics and legalities. In chapter 2, the present day and potential future uses for the different types of stem cells were provided to give the reader an appreciation for their tremendous capabilities in the medical field. In Chapter 3, the ethical issues regarding stem cells were considered by reviewing the stance of the world's five major religions. The beliefs of the various religions were compared, including their views on abortion, the beginning of life, and stem cells. To contrast with the beliefs of the various religions, the author's opinions on stem cell research were also provided. Lastly, chapter 4 dealt with laws that govern the use of stem cells in today's society and in the recent past. This includes a discussion of how the laws changed with the various US administrations over the past two decades, as well as the laws enacted by different countries. With the information provided throughout this project, it is hoped that the reader will be able to make a more informed decision on stem cells that reflects their true moral feelings.

Chapter-1: Stem Cell Types and Sources

Brett Dumas

For centuries, scientists have been seeking to understand the human body. In today's world of high technology, scientists have made enormous strides in understanding human development, including the discovery of stem cells. Stem cells are relatively long lived cells with the ability to differentiate into different cell types. Because of their ability to form new tissues, many scientists believe that research on stem cells will eventually yield cures to a number of devastating human disorders. However, even with recent successes and promises for the future, stem cells are one of the most misunderstood debated topics of recent scientific research. This debate is focused on the general perception that the production of all stem cells results in destruction of an embryo with the potential to form life. This chapter will define stem cells, introduce their various types, and show that all stem cells are not alike.

Stem Cell Introduction

Stem cells are unique cells that have the ability to divide indefinitely and to differentiate to take on the function of a more specialized cell. Although stem cells are most commonly mentioned in the context of a newly fertilized egg or embryo, they are also found throughout the fully developed human body as adult stem cells. Not all stem cells are equal though, as some have the ability to differentiate into more types of cells than others. In order to characterize stem cells, they are divided into different categories based on the diversity of specialized cells that

they can differentiate into (their potencies), or they are classified based on their origin. By origin, the two major groups are embryonic stem (ES) cells and adult stem cells (ASCs). Embryonic stem cells are isolated from the inner cell mass of blastocyst embryos, and can be programmed to become any type of organ in an adult human. Adult stem cells are located in developed organs and tissues, and are used to maintain and repair the tissue in which they are found.

While stem cells were discovered decades ago in the 1960's, it was not until the last decade or so that much progress was made in understanding and using them (Panno, 2010). Today, countless people have benefitted from stem cell research done over the years. For example, doctors at Children's Hospital in Boston currently use bone marrow stem cells to treat a variety of blood diseases, including leukemia and various anemias (Children's Hospital Boston, 2010).

Stem Cell Potencies

A stem cell's potency provides a measure of how many types of specialized cells it can become (i.e. their plasticity). Based on potency, stem cells are generally broken down into four groups. The first group is referred to as *totipotent* stem cells. Only the newly fertilized egg and cells through the 8-cell stage are considered totipotent. These cells are the most undifferentiated cells possible, and can give rise to any type of cell in the organism and cells of extra-embryonic tissue such as the placenta (Panno, 2010). However, for reasons not yet known, totipotent cells cannot be amplified *in vitro*, so are not used for therapies.

The next most potent stem cell group is the *pluripotent* stem cells. While not as pliable as totipotent stem cells, these cells can still give rise to most organs of the adult, but cannot form extra-embryonic tissues like the placenta. These cells can be found in the inner cell mass of the blastocyst embryo at about 5 to 6 days post-fertilization (**Figure-1**). Embryonic stem cells are examples of pluripotent cells. Because of their ability to form any adult tissue and because they can be grown in culture (unlike totipotent cells), ES cells are the most valuable for use in the medical field. However, obtaining them requires removal of the inner cells mass of an embryo which usually results in the death of the organism. For this reason their use is highly controversial.

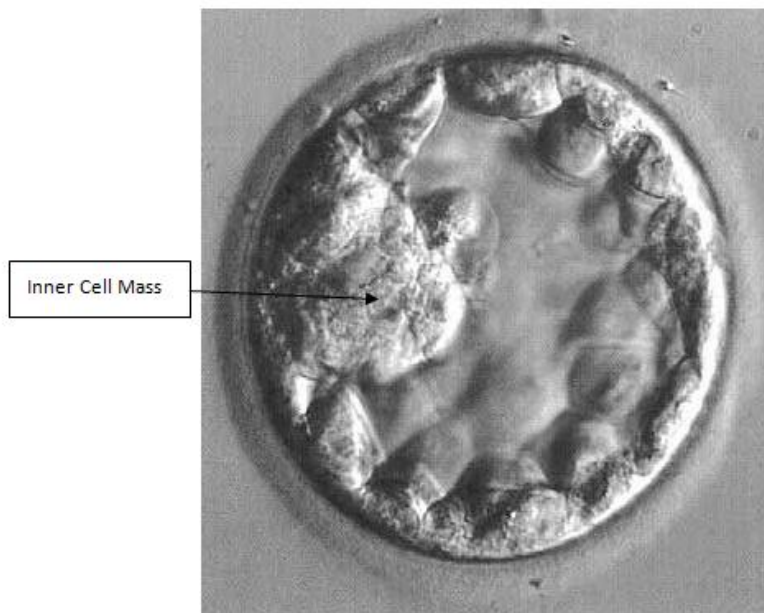


Figure 1: Image of Human Blastocyst. Note the presence of the inner cell mass from which embryonic stem cells are isolated (Muckle and Feinburg, 2008).

The cells with the next highest potency are *multipotent* stem cells which have the ability to become more than one type of tissue, but the cells are usually limited to the types of cells found in the tissue of origin. One example of a multipotent stem cell is hematopoietic stem cells derived from bone marrow, which give rise to most types of blood cells. At the lowest level of

potency are *unipotent* stem cells. These stem cells have the ability to give rise to only one type of cell, the tissue from where they were derived. An example of this would be epithelial stem cells which give rise only to new skin cells to replace old ones (Panno, 2010).

Stem Cell Types

Embryonic Stem Cells

A human embryo is a developing organism from fertilization to the end of the eighth week. As stated above, embryonic stem cells (ES cells) are obtained from the inner cell mass of the blastocyst, usually between days 5 and 14 post-fertilization. ES cells are removed from the embryo using a small needle and a microscope is used to see the embryo which is about the size of the period at the end of this sentence. ES cells can become almost any organ in the adult human body, but not extra-embryonic tissues like the placenta, and therefore cannot give rise to an entire organism so must be considered pluripotent. In culture, these stem cells can divide for years to make ES cell lines, while maintaining their embryonic phenotypes. ES cells that are grown for years to be used for research and other purposes have to be constantly checked to ensure they maintain their pluripotent state. They are commonly distinguished as ES cells by the following set of cell surface markers; SSEA-3, SSEA-4, SCF, and CD30, and by the presence of pluripotency-maintaining transcription factors Oct-4 and nanog. These transcription factors are responsible for keeping specific genes on or off at the right time to help maintain an undifferentiated and self-renewing state (Bethesda, 2010).

The potency of ES cells was first shown in the early 1980's when the inner cell mass from a mouse blastocyst was transferred to a mouse cavity and it differentiated into various tissues (Martin, 1981). Human ES cells were first grown by Dr. James Thomson of the University of Wisconsin in 1998 (Thompson et al., 1998). The initial process involved isolating cells from the inner cell mass of a fertilized blastocyst and growing them on a layer of killed mouse feeder cells to provide a scaffold and growth factors. Later culture methods replaced the mouse feeder-layer with human cells to avoid contaminating the ES cells with animal proteins which might hinder transplants. After establishing an ES cell line, the cells can be transferred to different feeder layers and given specific nutrients to differentiate into a specific type of cell (Crosta, 2011). Although ES cells have the greatest ethical concerns due to the way they are obtained, they also have the greatest medical potential because of their plasticity.

Embryos for obtaining ES cells are obtained from *in vitro* fertilization (IVF) clinics with the parent's consent for embryos that are in excess and would be discarded otherwise. A stem cell line is then formed when the ES cells multiply (without differentiating) on a culture plate supported with nutrients and growth factors. Today, over 120 ES cell lines exist (Panno, 2010). Immortal ES cell lines are critical for the production of stem cells for research because it is illegal to obtain embryos outside a reproductive clinic in the U.S. today. However, there may be other options on the horizon. In 2008, researchers from Advanced Cell Technologies in Worcester, Massachusetts reported success in harvesting cells from a blastocyst without killing the embryo. So it is possible that ES cells can be derived without destroying an embryo, although it is unlikely that these manipulated embryos would ever be carried to full term (Chung, 2008). Until recently, ES cells were used exclusively for research purposes; but in 2009, a major

breakthrough occurred when the FDA finally approved the first clinical trial involving the use of ES cells (Wadman, 2009).

Induced Pluripotent Stem Cells (iPS Cells)

A far less controversial type of potentially pluripotent stem cell is called induced pluripotent stem cells (iPS cells). These cells are derived from an already differentiated skin cell treated with pluripotency-inducing transcription factors to induce their de-differentiation to a stem cell state where they have the ability to divide (**Figure-2**).

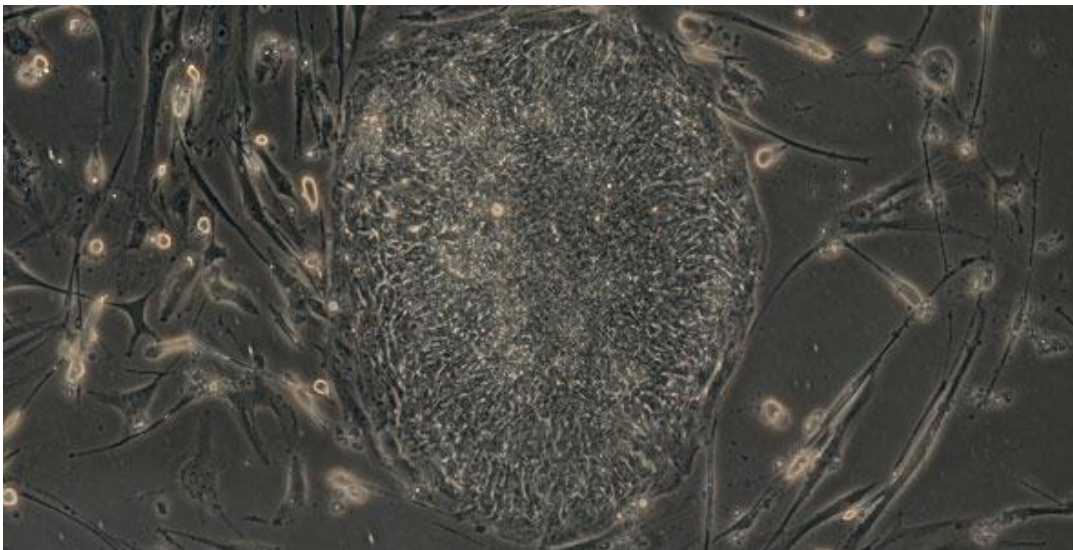


Figure-2: Cross Sectional View of Colony of iPS Cells. (Centeno, 2011)

iPS technology has only recently become available, and is now one of the most researched areas of all of stem cell research. In 2006, Japanese scientists led by Dr. Shinya Yamanaka reported success in transforming a mouse skin cell into a cell resembling an

embryonic stem cell (Takahashi et al., 2006), and this was soon followed by the derivation of human iPS cells (Takahashi et al., 2007). Soon after, many labs reported success in creating iPS cells. In 2009, a team at the Scripps Research Institute successfully used iPS cells to produce a mouse embryo that developed into a healthy adult (Boland et al., 2009). This suggested that iPS cells are an effective means of transforming specialized cells into pluripotent stem cells with the same differentiating capability as embryonic stem cells. However, some scientists argue that iPS cells may contain DNA mutations, are harder to grow, and may not truly be pluripotent like embryo-derived ES cells (Gore et al., 2011). More research is needed to prove the potential of iPS cells. If iPS cells prove to be pluripotent, this would give an alternate option to using embryo-derived ES cells which are highly controversial.

Another outstanding advantage of iPS technology is their genetics. The iPS-derived cell line is genetically identical (or similar) to the person providing the original skin cell for differentiation. So in theory, this would make these cells less likely to be rejected from the patient. This idea has been around for years and is based on genetics. The study of genetics has shown that theoretically it is possible to turn any cell in the human body into any other cell. Every type of cell in our body contains the same identical genes to all other cells in our body. The only thing that makes one type of cell different from another is the way these genes are expressed. Therefore, by manipulating the genes expressed in one type of cell (say a skin fibroblast cell), turning some genes off and others on, we can make it become something different, but it has the same DNA. In order to create these iPS cells Yamanaka's team reprogrammed skin cells by introducing a virus into the cells containing four transcription factors. Transcription factors, as mentioned earlier, are proteins that control gene expression, and in this case the original four genes that were turned on to induce skin cells into pluripotent

stem cells were Oct-4, Sox2, Klf 4, and c-myc (Takahashi et al., 2007). With this combination determined mostly by trial and error, the skin cells reached a state of pluripotency and were able to divide infinitely. The process was later modified to eliminate the c-myc component which tended to cause cancer in the recipient, and to eliminate the use of viral vectors for the delivery. Though there is still much to learn about this process, it offers such great potential because no embryos are used.

Parthenote ES Cells

Parthenogenesis is a word deriving from the Greek language meaning ‘virgin birth’. It is another new field of research in the production of stem cells. Parthenogenesis, or asexual reproduction, is the process of activating an egg without fertilizing it. This process occurs naturally in some insect species, but does not occur naturally in mammals. However, with the use of chemicals, some mammalian eggs can be induced to divide to the blastocyst stage from which ES cells can be isolated. Parthenote ES cells have been successfully produced for some animal species such as monkeys (Cibelli et al., 2002), and there are some unsubstantiated claims for human parthenote embryos. Parthenote ES cells may be less ethically controversial than embryo derived ES cells because mammalian parthenote embryos cannot divide beyond the blastocyst stage, so cannot make an adult. Parthenogenic ES cells can easily be identified because they have two copies of maternal DNA while normal embryos have a maternal and paternal copy (**Figure-3**).

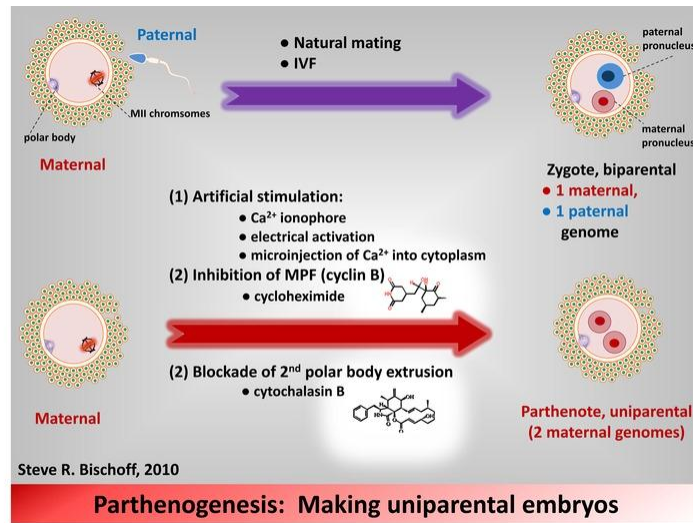


Figure-3: Illustration of Parthenote Embryo Production. (Wikipedia)

Somatic Cell Nuclear Transfer (SCNT)

Somatic cell nuclear transfer (SCNT) is a form of cloning used to create ES cells genetically identical to the patient's cells. While the idea of cloning is a highly controversial topic, it is not always used to create an identical twin of an organism (reproductive cloning), and is sometimes used to create tissues (therapeutic cloning). SCNT is accomplished by removing the nucleus from a regular somatic cell, usually a skin cell, and transferring it into a fertilized egg (Figure-4). At this point, it acts like a fertilized egg with a normal nucleus containing two copies of each chromosome inside the egg cell, and the egg develops like a normal embryo from which ES cells can be removed. Because the skin cells are extracted from the patient, it minimizes the possibility of the host immune system from rejecting the stem cells implanted in the body, although some recent publications indicate rejection can indeed occur.



Figure-4: Image of Fibroblast Cell Nucleus Injected into Egg During SCNT. The lower part of the diagram shows a pipette suction device used to hold the egg (diagram center) in place (Kollipara, 2008).

SCNT was first applied in 1952 to produce the first cloned animal which was a tadpole (Evidence for God, 2004). It took until 1996 for the first mammal, Dolly, the sheep to be cloned by Ian Wilmut (Campbell et al., 1996). Despite several claims, there has been no conclusive evidence of a human embryo ever being cloned. Since this procedure results in the death of an embryo that could grow into a human being, it remains highly controversial, and with the less controversial promise that iPS cells have to offer, it is highly unlikely that SCNT will be used for therapeutic purposes, unless it proves to be fully histo-compatible with the patient (Cibelli, 2007).

Adult Stem Cells

An adult stem cell (ASC) is an undifferentiated cell found among differentiated cells in an adult tissue or organ that can renew itself and can differentiate to become some or all of the types of cells in that tissue or organ (Bethesda, 2010a). The majority of cells comprising a tissue usually have a specific function for that tissue, and have a defined life span (termed the Hayflick limit), so they eventually die off and are replaced by the stem cells. Adult stem cells are multipotent or unipotent, so their uses are more limited than other types. ASCs are harder to isolate than ES cells, and harder to grow and differentiate. However, there are ASCs for every type of tissue. There are various procedures for isolating and extracting adult stem cells depending on the tissue and type of stem cell involved. The advantages to ASCs are they are less ethically controversial than ES cells and they can minimize Graft versus Host Disease (GVHD) that can occur with ES cells. When introducing cells that are from one human to another, the host's immune system often responds by mounting an immune attack against the foreign cells. In using ASCs, the transplanted cells can be taken directly from the patient to minimize this problem. A few of the most researched ASCs are described below.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are the best characterized of all the stem cells types, and have been studied for more than 50 years. These multipotent adult stem cells give rise to most types of blood cells, and even have shown potential to differentiate into a few other types of tissues. HSCs are usually obtained from bone marrow. Bone marrow is a tissue found in the medullary cavity which is located in the center of many bones in the body. Due to the pain

associated with bone marrow donation, more recently scientists have resorted to isolating HSCs from umbilical cord blood, or from the peripheral blood of patients treated with hormones to stimulate HSC release from the marrow. HSCs are among the most proliferative cells in the body and today are being used to treat patients with cancer and other blood and immune disorders. This treatment involves irradiating a patient to destroy their cancer cells (and bone marrow), then replacing the marrow from a histo-compatible donor. The first evidence that HSCs exist came from studies of people exposed to lethal doses of radiation in 1945. In 1969 the first successful bone marrow transplant was performed (Besthesda, 2010).

Only about 1 in 10,000 cells in the bone marrow are HSCs, so these cells are hard to identify and purify. HSCs are sometimes defined as containing the cell surface marker CD34, and can be tested for differentiation by the presence of markers specific for adult blood cells, such as CD4 or CD8 (Panno, 2010).

Nerve Stem Cells

Although scientists initially believed the nervous system lacks the ability to repair damage on its own, scientists now know that new neurons are continuously produced small scale by adult neural stem cells. In 1989, Sally Temple first described these multipotent stem cells in the subventricular zone of the mouse brain (Temple, 1989). In 1992, Brent A. Reynolds and Samuel Weiss were the first to isolate neural stem cells from the adult mouse brain tissue (Reynolds and Weiss, 1992). Neural stem cells possess the capability to differentiate into any neural cell type by asymmetric cell division (Mulchandani, 2010), including astrocytes (structural support cells), oligodendrites which provide support and insulation for neurons, and

neurons themselves which are the cells that send the electric impulses. If scientists learn how to create specific types of new neurons, they could potentially use them to replace damaged cells, enabling them to conquer such debilitating diseases as Alzheimer's and Parkinson's. In recent years, scientists have determined that adult neural stem cells are located primarily in two regions of the brain: the lining of the brain's fluid-filled cavity known as the subventricular zone, and a horseshoe shaped area known as the hippocampus (O'Brien, 2007).

Cardiac Stem Cells

For almost twenty years, researchers have debated whether hearts have the ability to repair themselves after damage by generating new tissue. Research in the early 2000's first showed that the heart indeed has a reservoir of stem cells (Touchette, 2003). These cardiac stem cells can divide, are multipotent, and can differentiate mostly into cardiomyocytes (heart muscle) and even smooth muscle and endothelial cells (Bearzi et al., 2007). Researchers at New York Medical College in Valhalla isolated cardiac stem cells from rats and found that when injected into the damaged heart of other rats they rebuilt the injured tissue (Beltrami, 2003). The same reservoir of cardiac stem cells has been found in humans. The researchers are planning to submit a protocol to the U.S. Food and Drug Administration for a Phase I Clinical Trial to test the safety of injecting cardiac stem cells in humans (Touchette, 2004). In a recent study, when locally injected in the damaged myocardium of immune-deficient mice and immune-suppressed rats, human cardiac stem cells generated a chimeric heart (i.e., a heart made from two organisms), which contains human myocardium composed of myocytes, coronary resistance arterioles, and

capillaries. The human myocardium was structurally and functionally integrated with the rodent myocardium and contributed to the performance of the damaged heart (Bearzi et al., 2007).

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) were first identified in the 1960's in Russia by Fridenstein as a source of bone, cartilage, and fat cells derived in adult bone marrow (Friedenstein et al., 1976). Since then, MSCs have been found in all other tissues in the human body including umbilical cord blood (Tomomi et al., 2009). MSCs are special because they have the unique ability to differentiate into cartilage, muscle, tendon, and ligament tissue giving them tremendous medical potential (Wobus, 2008), although they are not pluripotent like ES cells. Today they are used to treat nearly 80 types of diseases (ViaCord, 2011).

MSCs are identified from hematopoietic stem cells by the expression of many cell surface markers including CD105 (SH2) and CD73 (SH3/4), and are negative for the hematopoietic markers CD34, CD45, and CD14. Their relative ease of isolation and multipotent properties make these cells potentially ideal candidates for tissue engineering because of their potential to give rise to connective tissue. It has been shown that MSCs when transplanted systemically are able to migrate to sites of injury in animals, suggesting that MSCs possess migratory capacity (Nathalbrawn, 2008).

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Chapter-2: Stem Cell Applications

Prashant Yamajala

Worldwide there is a growing need for stem cells for the treatment of life threatening diseases. Some types of stem cells have been used for over 50 years to treat various blood disorders, and the use of other types in treating nervous system diseases, diabetes, and heart attacks is slowly growing. In 2007, the leading causes of death in the United States were diabetes, heart disease, Parkinson's, and cancer (CDC, 2011). The clinical applications of stem cells is an important topic when discussing stem cell ethics since it relates directly to their benefit to society, so the purpose of this chapter is to bring the reader up to date on the use of stem cells for treating five main categories of diseases as examples.

Spinal Cord Injuries and Stem Cells

The use of stem cells for treating spinal cord injuries has shown some success in rodent models, but is only recently underway in human clinical trials. The stem cells are used for treating spinal cord injuries when neurons and their myelin coating become harmed. Spinal cord injuries do not usually heal on their own, causing complications from the inability to control a range of bodily functions, and can be fatal. Thousands of new cases of spinal cord injuries occur each year in United States (National Spinal Cord Injury Statistical Center, 2011). Stem cells can be used to treat spinal cord injuries by helping to renew the cells that make myelin sheaths through injection at the injury site.

In tests with adult rats that had sustained spinal cord injuries, the data showed a successful proliferation of myelin creating cells and increased locomotor abilities after injecting

embryonic stem (ES) cells between seven to nine months of the sustained injury (Keirstead et al., 2005). The trials suggested that the best time for treating spinal cord injuries was limited to a short period after the injury was sustained.

Another trial that involved mice also supports the use of ES cells in treating spinal cord injuries. The ES cells were used to induce motor neuron generation which in turn helped proliferate axons and allow motor function. The trial showed that ES cells could be applied to the central nervous system and can potentially help spinal and neurological injuries (Wichterle et al., 2002).

Embryonic germ cells have also been tested in rats for treating spinal cord injuries. The trial involved initially inducing motor neuron degeneration in rats by injecting neuro-adaptive sindbis virus. After 28 days the rats had shown serious neuron degeneration eventually reaching the spinal cord and causing paralysis. Then, the rats were treated with embryonic germ cells that were able to adhere to meninges in the spinal cord. At 12 weeks post-surgery, the rats were subjected to a blind rating system and the raters noticed that the rats had better motor function. At 24 weeks, there was an even more significant recovery (Kerr et al., 2003). The embryonic germ cells in the spinal cord were also measured for their ability to produce different growth factors, specifically neurotrophins. The results showed that the neurotrophin levels secreted from the stem cells were not as high as the injected ones, but they were delivered more effectively (Kerr et al., 2003).

In addition to these rodent experiments, adult neural stem cells are being used to treat human spinal cord patients, but these trials only recently have begun (New York Times, 2009).

Diabetes and Stem Cells

Diabetes is another disease that affects a large percentage of the population. In 2008, 10.9% of the adult population of the United States was estimated to have diabetes (CDC, 2011). Diabetes is considered an epidemic that will increase as the population ages. There are two types of diabetes. Type-I diabetes is known as insulin-dependent diabetes, and occurs when the immune system destroys the insulin producing cells in the pancreas. Type-I usually appears in children, and is also known as juvenile-onset diabetes. Type-II diabetes is known as non-insulin dependent diabetes, and is much more common. It affects the body's ability to respond to insulin, and occurs because of many factors that can be genetic, or lifestyle factors such as diet and exercise. Insulin is a hormone made by beta cells in the pancreas that helps store and use glucose in cells after meals. Once the beta cells in the pancreas are no longer functioning or if the body can no longer respond to the hormone, blood sugar increases, intracellular sugars decrease, and diabetes occurs. Treatment of diabetes usually involves taking insulin via an injection.

A different treatment for diabetes could be provided by stem cells, more specifically, ES cells and their ability to differentiate into insulin secreting cells. ES cells can be used to replenish the beta cells that have stopped producing insulin in the pancreas. Studies so far have shown that ES cells can create cells that secrete insulin and can help with the treatment of Type 1 diabetes (Assady et al., 2001).

However, there is a shortage of available human ES cell lines for performing these treatments. Scientists are not yet able to derive new ES cells lines from a patient's own skin cell nuclei, so this remains a future application. And with respect to using rodent ES cells, those could potentially contain viruses or would be immune-rejected (Assady et al., 2001).

With respect to human ES cells, scientists have shown that these cells have the ability to differentiate into insulin-producing cells (Assady et al., 2001; Lumelsky et al., 2001; D'Amour et al., 2005). In the D'Amour study, the results showed that an endodermic layer secreting insulin was able to form (D'Amour et al., 2005). Human ES cells have also been used to treat mouse models for diabetes (Kroon et al., 2008).

In addition to ES cells, adult pancreatic stem cells are also another viable option for treating diabetes. Trials have indicated that different types of adult pancreatic cells from mice can form insulin producing cells used to treat a mouse model of diabetes (Soria et al., 2005). The precursors were used to derive different types of cells including the islet cells needed for insulin distribution. More recently, mouse diabetes models have been treated with iPS cells reprogrammed from mouse skin fibroblasts (Alipio et al., 2010), so this approach may eventually be applied to human patients. These approaches are promising as they do not destroy embryos, so they have fewer ethical issues.

Leukemia and Stem Cells

Leukemia is a disease treated for over 50 years by bone marrow transplants containing hematopoietic stem cells (HSCs). Leukemia involves the increased proliferation of white blood cells that do not function normally. WBCs are produced in bone marrow which also makes red blood cells, so the cancerous-forming marrow is destroyed by radiation or chemotherapy, then the marrow is replaced from a noncancerous donor.

SCID mice lack an immune system so are sometimes used to test HSC transplant protocols. Results of one trial showed that the HSCs are able to perform hematopoiesis for

around twenty weeks (Kyoizumi et al., 1992), and subsequent studies show an even longer survival.

The use of human HSCs in clinical trials and for generally treating patients with blood cancers has a long rich history. Some cases date as far back as 1959 showing that HSCs can cause a temporary remission of leukemia (Thomas et al., 1959). In those early cases, the remission was temporary and required multiple HSC doses. Later trials done in the 1970s by the same scientist yielded longer term results (Thomas et al., 1977). The study was done on 100 patients with acute leukemia, and the trial compared chemotherapy, total body irradiation (TBI), and allogenic bone marrow transplant with HSCs. The trial showed that patients with acute myeloid leukemia had a higher survival and remission rate with the usage of bone marrow transplants than the patients who had just the chemotherapy or radiation therapy (Thomas et al., 1977). These trials also pointed out the importance of histocompatibility. The human leukocyte antigen (HLA) present on the surface of blood cells allows the immune system to identify self versus foreign, and helps determine whether the immune system should destroy foreign cells (like HSC transplants) in the body. In the 1977 trial, about 40% of the patients had a sibling with a matching HLA, so there was a lower risk of rejection.

Heart Disease and Stem Cells

According to the American Heart Association (2011), cardiovascular disease killed more than 150,000 Americans in 2007. That number is predicted to rise as the population ages and the rate of obesity increases. Cardiovascular disease affects thousands of individuals every year and can be treated in a multitude of ways. The disease is often fatal because the cardiac system and the heart are vital to leading a healthy life. Cardiovascular disease usually involves the arteries

developing blockages (atherosclerosis). Once the arteries become blocked to a certain extent, a heart attack can happen where the heart beat can be unsteady and sometimes stop. The results of atherosclerosis can also cause cardiovascular problems in other parts of the body including stroke.

The heart was once thought to be incapable of regeneration, however with the discovery of adult cardiac stem cells or the use of HSCs to treat heart attacks, scientists now believe heart tissue can partially regenerate. Cardiomyocytes are the cells that control the pumping of the heart muscle. Once a heart attack has occurred, the cardiomyocytes damaged must be replaced, so stem cells may be able to help.

Trials were performed in mouse models using bone marrow stem cells to see if myocardium could be restored to a heart following myocardial infarction. The results of the study showed that after injecting the site with the bone marrow stem cells, there was an increase in the amount of new myocardium after nine days (Orlic et al., 2001). A later study showed that adult progenitor stem cells (adult cardiac stem cells) can form cardiomyocytes, endothelial cells, and smooth muscle cells, all of which are vital to a functioning heart (Bu et al., 2009). Another trial using HSCs from mouse umbilical cord blood showed that the survival rate for mice with the injected HSCs was higher after a heart attack than those without the cells. The trial was also able to show that cord HSCs could incorporate into the myocardium and help repair the heart (Hirata et al., 2005).

Human clinical trials have also yielded promising results in post myocardial patients. A trial involving 28 patients treated with either blood transfusions or bone marrow derived stem cells showed that the progenitor stem cells had a greater impact on the growth of vascular tissue in the heart after myocardial infarction (Britten et al., 2003). The trial concluded that further

studies on the long term impacts of cardiac stem cells on a larger population would have to be performed.

ES cells have also shown evidence of being progenitors to different cardiac tissues. One trial found that ES cells can expand and renew into cardiac lineages (Bu et al., 2009), so these cells may also be used in the future to treat heart disease, although they have more ethical concerns.

Parkinson's Disease and Stem Cells

Parkinson's disease (PD) affects a large portion of the US population. According to the CDC, in 2009, PD was the 14th leading cause of death with around 20,552 deaths (CDC, 2011). PD is a debilitating disorder that occurs in the central nervous system when dopamine-producing cells in the brain stop functioning and no longer produce dopamine. The loss of dopamine causes tremors and greatly affects motor function. The disease especially affects older individuals and causes a decrease in the quality of life. Stem cells could potentially be used for replacing the damaged dopaminergic cells.

Rat Parkinson's models have been used to test ES cells. The experiment showed that transplanted ES cells can develop into functional dopamine producing neurons in vivo (Bjorklund et al., 2002). A similar result was obtained two years later by transplanting neural cells derived from human ES cells into rat models (Ben-Hur et al., 2004).

Adult neural stem cells have been used to treat PD patients. One patient whose motor skills had deteriorated for three years was treated via a neural stem cell transplant (Freede et al., 2001). The treatment showed promise because dopamine-producing cells were made, and the cells were derived from the patient so no immune-suppressors were required. Another clinical

trial used 40 patients and adult neural stem cells. The results showed that in younger patients below 60 years of age there was more improvement than in the older patients (Ertelt, 2009). The trials must be extended to observe the long term effects of the transplanted neurons.

Chapter-2 Conclusion

Stem cells have already been used to save lives, and their applications are increasing. Hematopoietic stem cells have been shown to be effective in treating a variety of blood disorders, and have even been used to regrow cardiac muscle in heart attack patients. Human embryonic stem cells have been shown to be capable of differentiating into a variety of potentially therapeutic tissues, and have been used to treat animal models of diabetes, but their use in patients awaits more data. The applications of stem cell research are widespread, and appear to be increasing constantly.

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Chapter-3: Stem Cell Ethics

Brett Dumas

Introduction

After learning about the types and sources of stem cells, and their potential to save lives, it is important to discuss the ethical controversies associated with them. The ethical controversies, often referred to as bioethics, are focused on the fact that stem cells that are taken from an embryo usually result in the destruction of the embryo. So the question is whether the benefits of stem cells to society outweigh the harm they may do. The benefits to society include their ability to save and improve the quality of life for countless people, while the harm to society is the moral dilemma that embryonic stem cells pose regarding the destruction of embryos. Unfortunately, a common misconception in today's society is that the production of all stem cells results in the destruction of embryos. The ethical concerns of stem cells and whether or not the benefits of using them outweigh the harm of using them is the focus of this chapter.

To understand the ethical issues regarding stem cells, one must first recall the types of stem cells discussed in chapter one. There are two main types of stem cells, embryonic and adult stem cells, both of which have tremendous potential benefits. Although adult stem cells have shown significant progress and have no ethical concerns, researchers continue to pursue embryonic stem (ES) cells because they are relatively easy to isolate and grow in culture, and are pluripotent, giving them great therapeutic potential. On the other hand, adult stem cells can be difficult to isolate and manipulate, and they are less potent (i.e. can differentiate into a more limited number of cells than ES cells). Ethical issues are focused on the use of ES cells which usually result in the destruction of an embryo. These stem cells are typically extracted from an embryo between five and six days after conception, which in most cases results in the death of

the embryo. The debate focuses on when a human life begins. If we deem the embryo to be a developing human being when the stem cells are obtained, this could potentially be considered murder. Also, if extracting these embryonic stem cells constitutes murder, then is this acceptable to use these stem to save another human being? In essence is it ethical to trade one life for another.

Before discussing the moral issues associated with ES cell research, it is relevant to know how ES cells are currently produced. An embryonic stem cell line is a group of stem cell produced *in vitro* by constantly dividing stem cells from a single parent group. Embryos to isolate these ES cell lines are obtained from reproductive in vitro fertilization (IVF) clinics with the written consent of the donors. The use of IVF involves the production of many excess embryos, many of which are eventually destroyed if not used for reproductive purposes.

In attempting to understand the ethics of doing ES cell research, we first consider how these cells are obtained and when life begins. To simplify this discussion, the moral issue can be broken into three sub-issues. First, should embryos be harvested for the sole purpose of performing ES cell research? To answer this question, one must first ask when human life actually begins. Secondly, should unneeded embryos obtained through the reproductive IVF process be used for ES cell research, or should they be destroyed? To answer this question, one must scrutinize the use of IVF which creates excess embryos, only to exist as replacements if earlier ones fail. Finally, all discussion to this point has been for embryos resulting from the fertilization of a human egg. How about moral issues for ES cells obtained by alternate means such as SCNT and parthenotes? In these cases, the question of when does life begin transforms to the question of does this organism achieve the same status as a normal human being?

It can be extremely difficult to reach agreement on such highly debated ethical questions such as when human life actually begins, or can an organism potentially become a human being, or more generally, is the use of stem cells ethical. For this reason, we will look at the world's five major religions and consider their opinion on the beginning of life and their stance on the use of all stem cells. Ultimately it is a decision that is yours to make personally.

In Vitro Fertilization

Infertility affects around 2 million married couples in the United States every year (Statistics, 2011). In vitro fertilization (IVF) is one of several different options for couples struggling to have a child. In IVF clinics, the sperm and egg cells are combined in a lab dish where fertilization occurs. The embryo is then grown for a few days to increase its vigor, and then it is transferred to the women's uterus where it can implant and continue to develop like a normal embryo. The first successful human IVF was in 1978 (Luciana, 1978) and since then over 250,000 babies have been born with this technology. The process of IVF usually involves the production of several embryos (ranging from 1 to 10) in hope that one will become sufficiently strong and implant in the uterine wall causing pregnancy (Garcia, 2010). It is then up to the donor couple what they will do with the excess embryos. There are several options: put them up for "adoption" by another couple wishing to have a baby, donate them to research providing that their state allows this, keep the embryos frozen until they decide what to do, or they can thaw the embryos and let them die.

Stance of the Five Major Religions

The five major religions of the world include Christianity, Islam, Hinduism, Buddhism, and Judaism. They have a combined membership of 3.5 to 4 billion people worldwide. This constitutes about 80 percent of the world's total population (Griffin, 2010). With such a large percentage of the world's population falling into these religions, they provide a general idea of the world's perspective on stem cell research. Unfortunately, many people do not even know the exact stance of their own religion on stem cells. For example, many Christians believe that their religion is completely against the use of all stem cells. Contrary to popular belief, each of these five major religions supports the use of adult stem cells, as long as they are used to improve lives. The real issue here is the use of ES cells which leads directly to the question of when human life actually begins. While these religions all agree that ending a human life is unethical, their opinions of when life begins in a developing embryo is what sets them apart.

Christianity

Christianity is a combination of numerous denominations that share a belief in the same God and in the bible as a sacred book (American Catholic Association, 2006). Christianity is the major religion in Europe and the Americas, and has the greatest number of members worldwide with about 2.1 billion people (Major Religions of the World, 2005). Moreover, Christians have perhaps the strongest ethical issues with stem cell use, and are the most outspoken religion.

Because Christians believe that human life begins at conception, they feel that it is morally wrong to harm an embryo for any reason. While the bible itself never provides a direct answer on when life begins or even on the stages of development prior to birth, many have made

interpretations that agree with the current stance of the Christian officials. The strongest evidence comes from the statement that life is God's gift. Therefore one should not harm the embryo, which is the beginning stage of God's gift, any more than one would harm a full grown human being. The view of the Christians is also very clear from their stance on abortion, where abortion is never accepted unless the health of the mother is at risk.

The Catholic Church is completely against ES cell research because it involves the destruction of human embryos. Several religious leaders have spoken out against the use of any ES cells. Bishop Joseph A. Fiorenza, president of the U.S. Catholic Conference of Bishops, spoke out against President Bush's decision in 2001 to allow ES cells to continue to be obtained (although without federal funding) and researched. The Bishop stated "We hope and pray that President Bush will return to a principled stand against treating some human lives as nothing more than objects to be manipulated and destroyed for research purposes" (Shannon, 2006). Based on the above reasoning, it's obvious that Christians are also opposed to In Vitro Fertilization as well. In fact, "the Catholic Church condemns as gravely evil acts, both IVF itself, and stem cell research performed on IVF embryos" (Shea, 2003).

Due to the intense ethical controversy regarding the use of ES cells, scientists have searched persistently for alternatives. Three promising alternatives are parthenotes, SCNT, and iPS cells. Parthenotes are eggs chemically treated to divide without fertilization; they develop into an embryo where ES cells can be isolated in the same way that they are isolated from a normal embryo. SCNT involves injecting the nucleus from a somatic cell into an enucleated oocyte, chemically stimulating the egg to divide, and then either deriving an ES cell line from the embryo (therapeutic cloning) or implanting the embryo into the uterus to produce a live birth (reproductive cloning). iPS cells are skin fibroblast cells reprogrammed into a pluripotent like

state using transcription factor proteins; isolating these cells uses no embryos. Although the parthenogenetically-activated human eggs appear to provide an alternative to destroying human embryos, many Christians argue that “unless we have moral certainty that a dividing parthenogenetically activated human oocyte is not an embryo, we have an obligation to avoid research with human parthenotes” (Brugger, 2011). And to no surprise, Christians are opposed to all forms of SCNT (therapeutic and reproductive cloning).

Islam

Islam is the second-largest religion in the world, with over 1.3 billion followers referred to as Muslims. Muslims believe in a single God called Allah, and their faith was founded by a prophet named Muhammad. The majority of the Muslim population comes from the Middle East and Southern Asia, and the sacred book is called the Qur’an (Muslim Beliefs, 2004). The Islamic religion is comprised of two major denominations, the Sunnis and Shias. Muslims believe that one should live their life in such a way as to please Allah so that one day, they will attain Paradise. Islam teaches that even when a person dies, their soul lives on eternally. (Muslim Beliefs, 2004).

Muslims believe that the fetus does not become a person until it receives its soul, often referred to as when the soul is “breathed” into it. According to the Prophet Muhammad, the soul is breathed into the fetus at 120 days post conception. This belief comes directly from a hadith, a saying from the Prophet Muhammad (Alamri, 2011). Although other hadiths indicate that life begins at day 40 or 42, the majority of Islamic scholars believe that the fetus receives the soul after 120 days. Either way, the Islamic stance on ES cells obtained at day-5 remains the same. According to most interpretations of Islamic law, the embryo is not considered a person, and

therefore ES cell research does not violate Islamic law (Weckerly, 2002). In fact, using the same reasoning, stem cells from aborted fetuses would be permitted if the abortion was performed before the 120th day of pregnancy. Furthermore, Islamic law prohibits surrogate parenting and adoption of human embryos due to the importance placed on determining a child's true parentage and inheritance rights (Weckerly, 2002). Therefore, excess embryos can only be used for reproductive purposes by the couple who created them, freeing up many embryos for research purposes. The Washington based Islamic Institute stated that they believe "it is a societal obligation to perform research on these extra embryos instead of discarding them" (Ayesha, 2001). Additionally, Muslims believe that all knowledge comes from God and that it is their duty to seek out that knowledge to serve mankind (Weckerly, 2002).

Despite their beliefs allowing ES cell research, Muslims still take the safety of a developing embryo very seriously, realizing that it has the potential to become a human being. Abortions prior to 120 days are permissible only when the health of mother or baby are at risk, or when the pregnancy resulted from extenuating circumstances such as rape or incest (Alamri, 2011). Because Muslims support the use of ES cells before the 120th day after conception, it stands to reason that they do not have issues with the parthenogenic production of stem cells or with SCNT stem cells obtained from 5-day old nuclear-injected embryos. Regarding cloning, there is not a clear consensus on this. While some Muslims feel it is acceptable in the interest of knowledge and research, others are very fearful that such technology can be misused. Although Muslims are interested in pursuing medical research, they are careful to maintain regulation over such research by their Shari'ah experts (Islamic View on Cloning, n.d.).

Hinduism

Hinduism is the third largest religion of the world with more than 1 billion followers (occupying about 14% of the world population) and is also the oldest known religion. Although Hinduism originated in India, there is no single founder. Hindus believe in one God named Brahman, but view other Gods and Goddesses as manifestations of Him. According to Hindu beliefs, the human body may die but the soul is immortal and is continually re-born when the body dies. The soul simply changes bodies as a new human is born (Hinduism, 2011). Two fundamental tenets or beliefs of Hinduism are first, the importance of practicing compassion toward others, and secondly, the mandate to avoid harming other living things (Knowles, 2008).

Hindus, like Catholics, believe that life begins at conception (Mishra, 2005). In fact, one may find more support that the embryo is a person in ancient Hindu texts than in the bible (Mishra, 2005). This ties into the Hindu belief that the soul lives on even after death, only to be transferred to another body. After death destroys the body, the soul soon finds a new home (Mishra, 2005). So the important question to the Hindus is when does the embryo or fetus receive its soul? According to the *Caraka Samhita*, a Hindu medical text, the soul is already joined with matter in the act of conception (Moad, 2004). So based on Hindu beliefs, there is no doubt that life begins at conception, however, regarding the ethics of ES cell research, the Hindu stance is still not so clear. In fact, there appear to be contradictions in Hindu beliefs (Hinduism and Abortion, 2009). Based on the two Hindu tenets mentioned above, ES cell research is certainly supported based on practicing compassion for others, however, it would not be supported based on the mandate to avoid harming other living things. Many Hindus will argue that because embryonic stem cells are at such an early stage of life and cannot feel pain, under the Hindu Karma principles of sacrificing for the greater good, ES cell research is not a difficult

choice to make (Bhanot, 2008). However, others remain steadfast in their argument that a human life is still being destroyed, so the debate continues.

The use of parthenote stem cells in the view of Hinduism is basically the same as their view on normal ES cells. Those in favor of using ES cells must also support parthenotes. The question is whether or not a parthenote embryo is valued as a true embryo and if so then those against ES cells would also oppose parthenotes. According to the Hindu faith cloning of any type including SCNT is wrong. This goes back to the tenet that prevents us from doing harm to others. With the huge failure rate from experiments on animals, and the defects that have occurred in the successful attempts, the Hindu faith opposes the use of cloning (The Ethics of Human Cloning, 2005).

Buddhism

Buddhism is the world's fourth largest religion with around 350 million followers (6% of the world population). The majority of Buddhists are located in countries throughout Asia, but they can be found throughout the world (Buddhist Studies, 2008). In Buddhism there is no divine creator, this religion encompasses a variety of traditions and beliefs attributed to Siddhartha Gautama, commonly known as Buddha (Frazzetto, 2004). Buddhists live under three basic fundamental beliefs or "tenets." The first is prajna, which is compassion. Second is karua, which is developing treatments to do away with human suffering. Third is ahimsa, which is non-harming or destroying others (Keown, 2004).

As medical research seeks to help others, Buddhists have no ethical issues with the use of adult stem cells. Buddhism teaches that all human life begins at conception. Buddhists believe in reincarnation and that an individual's soul is eternal (Knowles, 2008). Therefore, Buddhists

believe every soul is reborn. What they mean by this is that when a person dies, a new human being is born and has the soul of one who has just died. Buddhists believe this new individual must be given the same rights as an adult. As a result, there is controversy among some Buddhists. Some feel embryonic stem cell research is justified because of *karua*, because it can help end human suffering. On the other hand, others argue it is a violation of *ahimsa*, which is not harming others. Yet, since Buddhists all believe life begins at conception and this new life has the soul of one who is deceased, there is opposition to ES cell research. This is because this new individual has the soul of a person who was once living and they feel no life should be interfered with or destroyed. Buddhism has problems with ES cell usage because it involves *in vitro* fertilization which involves destroying spare embryos, and is along the same principles as abortion. Some Buddhists feel it is wrong to take stem cells from fetuses that have been aborted (Buddhism and Abortion, 2009). These same Buddhists feel it would also be immoral to use surplus or frozen embryos even if they would eventually be destroyed. While others feel that in an aborted fetus, no life has yet begun because there was no conception, so no life is being destroyed because this fetus was never living and never had a soul. Therefore, it is alright to use these stem cells to help relieve others from suffering. Buddhists are also against abortion for social reasons, but there have been 1.5 million abortions reported in the Buddhist region of South Korea (Keown, 2004). This shows that there are some discrepancies between Buddhists practices and the moral status of embryonic life.

The use of parthenotes is again similar to the Hinduism viewpoint. The big question is still whether or not to consider a parthenote embryo a true embryo since it cannot become a human. If it is considered a true embryo then Buddhism generally opposes their use. The use of SCNT and therapeutic cloning has some support in the Buddhism faith because it ties in well

with their belief in reincarnation. The concept of individuality is not as important to the Buddhists as in other religions and the Buddhists are more accepting of suffering and death. In SCNT used for ES cell production, the view remains the same as general ES cells because a potential life is being destroyed (The Ethics of Human Cloning, 2005).

Judaism

Judaism is the oldest monotheistic religion. Though it has the smallest population worldwide of the five major religions with around 14 million members, its opinions remain highly influential in the modern world. Judaism follows the laws of two major books, the Torah and the Talmud (Judiasm, 2011). According to the Talmud, for the first forty days post conception the developing embryo is considered to take on the status of 'water', and therefore has less value than a human for these 40 days (Dorff, 2002). Also, according to the Jewish faith, our bodies belong to God and have been given to us to live under a set of conditions. Most importantly, we must strive to save and preserve human life. This includes finding cures and treatments to diseases. On the same note, harming human life in order to find these cures disobeys this rule and is not acceptable in the eyes of God (Dorff, 2002).

When it comes to the stem cell debate the answer lies in the Jewish opinion on the beginning of life. Because they believe that life begins after 40 days, they consider even abortion acceptable within 40 days, when performed for adequate reasons (Eisenberg, 2001). Although embryos are not given much value at this stage, the embryo does have the potential to become life, so destroying them is only justified in cases such as ES cell research or for treatment of disease. Furthermore, extra embryos from IVF clinics which would otherwise be discarded are completely suitable to be used for research because of their potential to benefit human life. In

regards to parthenote stem cells, these ES cells do not have potential to become human beings and therefore would be given less value than a true embryo so their use is supported by the Jewish faith. On the other hand the use of SCNT for obtaining embryonic stem cells is not as clear. Since cloning has not yet been successful when done in humans, there is not much current debate over the issue. However, there have been several highly distinguished rabbis who have taken opposing sides on the issue, so the answer remains unclear (Eisenberg, 2010).

iPS Cell Ethics

As described in chapter one, induced pluripotent stem (iPS) cells are adult cells that have been transformed by treatment with transcription factor genes (inserted by viruses) or proteins to take on the role of a pluripotent stem cells from their specialized state. iPS cells are not embryonic in nature and therefore we cannot include them in our ES cell discussion for the major religions. Generally fibroblasts (skin cells) are the type of cell used to produce these iPS cells. These stem cells do not have the potential to form a human being on their own, i.e., they are only pluripotent and not totipotent. Therefore we remove any possibility for the loss of a life through destruction of an embryo. This fact makes iPS cells fit more into the adult stem cell category, and makes them very attractive to all religions, which totally eliminates any discussion regarding destruction of an embryo while providing a means to help preserve human life. Such widespread support makes iPS a great option to pursue.

Summary of the Five Major Religions

Table-I summarizes the various bioethical viewpoints of the five major religions. As mentioned in the introduction, stem cell ethics is based on how the particular stem cells are obtained. The table shows summary information for eight major ethical questions, which can be

broken down into three broad categories. The first major set of questions considers whether it is acceptable to use ES cells extracted from embryos produced solely for the purpose of creating stem cells. A religion's viewpoint on this topic can be supported by the two subtopic questions (in the chart) of when human life begins and should abortion be allowed.

The second group of questions considers whether it is acceptable to use excess embryos from IVF clinics, rather than discarding them. A religion's viewpoint on this issue is generally closely aligned with their viewpoint on the use of IVF for reproduction. For example, Christians are opposed to doing research on these IVF embryos and they are also totally opposed to the use of IVF.

Finally, the third group of questions considers whether it is acceptable to use alternate means of creating ES cells (i.e., not the result of fertilizing an egg with a sperm). Three alternate methods to consider are 1) parthenotes (non-fertilized eggs chemically treated to induce mitosis), 2) SCNT (a chemically stimulated oocyte whose nucleus has been replaced with a somatic nucleus; either an ES cell line can be derived from the blastocyst embryo (therapeutic cloning), or the embryo can be implanted (reproductive cloning), and 3) iPS cells (somatic cells reprogrammed into a pluripotent state, no embryos are involved). iPS cell ethics is typically straightforward, as those cells are considered a type of adult stem cell, so all religions favor that option.

By comparing the religious views in the table, it is obvious that the Christians provide the strongest opposition to ES cell research, while the Jewish and Muslims appear to be the most supportive of ES cell research. Buddhists and Hindus fall into a more neutral category, where their religious beliefs are often conflicting, leaving the decision to the people. These religions are somewhat adaptable and often agreement is not reached on such ethically charged topics.

One interesting note is that all religions appear to have a certain degree of apprehension regarding the use of SCNT. This may be due to the fact that many people across religions are concerned about the use of cloning and its potentially negative impact on society. Although with their negative interpretations, it is not clear whether there is an understanding between *therapeutic* cloning and *reproductive* cloning. Therapeutic cloning (if it is eventually successful in humans) would produce an ES cell line genetically identical to a patient; the ES cell line would be derived from an embryo created by injecting the patient's skin fibroblast nucleus into an enucleated fertilized zygote. This has not yet been achieved with human cells, but is one of the holy grails of stem cell research. Reproductive cloning would produce an individual genetically identical to another person by performing the same injection procedure, except the embryo would be implanted into the uterine wall for the purpose of giving birth. This process is outlawed in most countries, and has been successful with some animal species.

Table-I: Summary of the Five Major Religions on Bioethics.

Religion	Christianity	Islam	Hinduism	Buddhism	Judaism
Should embryos be harvested for ESC research?	No	Acceptable, prior to 120 days after fertilization.	Unclear, still debated	Unclear, still debated	Yes, acceptable prior to 40 days
When does human life begin?	At conception	When soul received, 120 days after conception.	At conception	At conception	At birth, the true human life begins
Viewpoint on abortion.	Not accepted under any circumstances unless mother's health is at risk	Acceptable after 120 days only if mother's life is at risk. Allowed prior to 120 days if extenuating circumstances, e.g., rape, incest	Decision based on what will do least harm to fetus, mother and father. Abortion is considered sinful	Highly discouraged, however Buddhists feel that morally, it is the mother's choice	Acceptable for first forty days if justifiable reason, acceptable if mother's life is at risk
Should existing embryos from IVF be used for ESC research rather than discarded?	No	Yes	Unclear, still debated	Unclear, still debated	Yes
Viewpoint of use of IVF for reproduction.	No	Yes, it's not just permissible, it's their duty	Yes, better than having no children	Yes, better than having no children	Yes, infertile couples are expected to be treated so they can have children
Use of parthenotes to create ESCs for research.	No	Yes	Unclear	Unclear	Yes
Use of SCNT to create ESCs for research.	No	Unclear	No	Unclear	Unclear
Use of iPS stem cells	Yes	Yes	Yes	Yes	Yes

Chapter-3 Conclusions

While the use of adult stem cells appears to be universally accepted in all five major religions, ES cells have been the source of much debate. To summarize the ethical debate on the use of stem cells, the author feels that stem cells are an essential part of medical research that

must be pursued. This means that both embryonic and adult stem cells should both be used for research and treatment of various diseases and disorders. The author especially supports the use of adult and iPS stem cells and encourages their use because these stem cells do not require the destruction of an embryo and therefore pose the least ethical concern. However, in the case of research, much can be learned from ES cells, and these pluripotent cells have far more potential than adult stem cells. Therefore research in this area should certainly continue. The author also supports the use of excess embryos generated from IVF clinics that would otherwise be discarded. The author feels that ES cells should only be obtained from these IVF clinics and these embryos should be used only with the consent from the parents. The author feels that creating embryos solely for the purpose of research is unethical and should not be allowed. While the author feels that the status of an embryo is below that of functioning human being, embryos have the potential to become fully developed human and should be used conservatively for research. But by the same token, the author feels that it is equally unethical to discard excess embryos from IVF clinics rather than donate them to research, where they could be used to save lives. Additionally, with regard to the use of stem cells for patient treatment, it is the author's opinion that the most favorable treatment option available to the patient should be used, regardless of whether it entails the use of ES cells or adult stem cells.

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Chapter-4: Stem Cell Legalities

Prashant Yamajala

The ethical issues surrounding the use of embryos and human embryonic stem cells (hESCs) has worked its way through the political and legal systems of a variety of countries as laws are enacted to control their use. In the US, the laws reflect which president was in office at the time and the mood of congress. Throughout the past twenty years, each presidency has had a differing view on the use of hESCs. In this chapter, the shifting views on stem cells by Clinton, Bush, and Obama will be discussed through the laws that have been passed, rejected, and proposed by the government. Various policies around the world will be considered from several countries, to illustrate the differing viewpoints on stem cell research.

Clinton Administration Policies

During the Clinton administration, many advances were made in science in relation to human embryos and stem cells. Prior to his administration, the 1972 *Roe v Wade* Supreme Court decision legalizing some types of abortions caused a backlash from congress against using aborted tissue for research purposes. In the late 1970s *in vitro* fertilization (IVF) was proven to be successful in the first human patient, so the debate expanded to include whether excess unwanted IVF embryos could be used for research.

In 1994, the National Institute of Health through its Human Embryo Research Panel advised Clinton that studies on human embryos should be allowed and should receive government funding. In general, Clinton was in favor of embryo research (Clinton, 1994). He had personal knowledge about diabetes, and knew how it affected a large percentage of the US population. His former chief of staff Erskine Bowles also had children with diabetes which gave

him an insight into the disease's symptoms. Clinton supported stem cell research and the applications of stem cells to diabetes, and knew that any information gathered would be vital for the future (Clinton, 2004). He created an advisory commission called the National Bioethics Advisory Commission, who recommended using only excess IVF embryos.

In response to Clinton's general acceptance of embryo research, in 1995, the republican controlled congress enacted the *Dickey-Wicker Amendment*, banning all federal funding for embryo research (House Panel, 1995; Senator Smith, 1996). However, the bill allowed the use of private funds for embryo research. Each year, congress has re-enacted this amendment.

By 1998, Thomson and his colleagues at the University of Wisconsin discovered a way to isolate and grow human embryonic stem cells from 5-day old blastocysts (Thomson et al., 1998). This discovery increased the pressure to allow federal funding for embryo research, as it would allow hESCs to potentially be used to save lives.

In 1999, Harriet Rabb who was a lawyer at the Department of Health and Human Services under the Clinton administration, wrote a letter to the director of the NIH, Harold Varmus, stating that pluripotent stem cells should not be considered human embryos (Rabb, 1999). Also it stated that all restrictions on human fetal tissues should still be applied. The Clinton administration responded to Rabb's statement by supporting the *private* sector usage of stem cells (Marshall, 1999).

Also in 1999, the National Bioethics Advisory Commission published its findings regarding stem cells, which included 15 recommendations for the Clinton administration. One vital recommendation (number-2) stated that stem cells that were derived from embryos left over from IVF treatments should receive federal funding (NBAC, 1999). Recommendation number-8 called for a database to be set up to help certify different types of stem cells and their donors.

Recommendation-9 stated that stem cell derivation protocols should be reviewed often, and revised by private panels before reaching national panels (NBAC, 1999). Recommendation-12 stated that hESCs derived from embryos specifically created for research would not be funded by the government (NBAC, 1999).

Bush Administration Policies

A month after becoming president, Bush put all federal funding for stem cells on hold (Godoy and Palco, 2006). The reasoning for the hold was to review all the guidelines set by the previous administrations and committees. By revising policies set in the Clinton administration, funding was cut for many stem cells research programs. In general, George Bush had a narrower stance on stem cells than Clinton. Bush's policies reflected his belief that adult stem cells would be a better alternative to hESCs (Bush, 2001).

In August of 2001, Bush approved a bill preventing federal money for deriving any new hESC lines after that date, while allowing funding for hESC lines created prior to that date. The hope was that by cutting funding for embryo research there could be a shift to adult stem cell research, but it indirectly set back all types of stem cell research. Relatively few hESC lines satisfied the criteria for funding, and some scientists worried the US would lose its edge in the stem cell field with this setback.

In response to the federal ban on funding newly derived hESCs, as was done in the Clinton era, private companies and colleges began to acquire their own funding for research. Some colleges that started their own private research projects were Johns Hopkins, University of California San Francisco, and Stanford (Check, 2002). Some states also began funding their own stem cell centers, including New Jersey, California, Massachusetts, and Connecticut.

California's Proposition 71 allowed for up to three billion dollars in funding to be appropriated for stem cell research. The bill also supported many different lines of stem cells including embryonic ones (Proposition 71, 2004). Using private funds and passing state laws allowed for stem cell research to continue even with less federal funding for a smaller set of stem cells.

In 2005, President Bush was at a standoff with congress. In response to the public's general support of stem cell research, Congress was debating whether to vote on whether to make hESC policies less restrictive, but the president threatened to veto the law (Baker, 2005). Defying Bush, the House voted to pass a bill allowing federal funds to be allotted to hESC research on IVF embryos (Allen, 2005), but Bush vetoed it.

An important bill was also passed in the senate during the Bush administration. The Stem Cell Research Enactment Act of 2005 was passed to allow more research on hESCs. The bill allowed for left over embryos from fertility treatments to be used in research and for embryo donation (Congress, 2005), but President Bush vetoed the bill (Bash, 2006).

In 2007, another version of the Stem Cell Research Enhancement Act was passed in the House and Senate (Congress, 2007). The bill had the same provisions on embryonic research as the previous one, but once again the president vetoed the bill.

Overall, the Bush presidency marked a shift in the position of the administration on stem cell research away from Clinton's generally favorable stance. The controversy of hESCs and their origin affected research funding and government policies. The conflict between congress and the administration also caused a rift between scientists and the public for or against stem cell research.

Obama Administration Policies

The Obama administration also marked further revisions in policy. In 2009, when President Obama began his term, he overturned Bush's previous ban on using federal funding for hESC research. The president signed an executive order that called for the previous ban on embryonic stem cell research to be lifted (Obama, 2009). However, Obama's executive order had several restrictions. One restriction is the embryos must come from IVF clinics with donor consent, and be originally created for reproductive purposes (paid donors could not be used). The order also outright banned human *reproductive* cloning. The president also passed the Omnibus Appropriations Act of 2009, which was very large and contained many sections. One section supported some aspects of the previous *Dickey-Wicker Amendment* which stated that embryos could not purposefully be created for research, harm, or destruction, so only excess IVF reproductive embryos can be used (Congress, 2009).

International Stem Cell Policies

International stem cell policies are as varied as the countries enacting them. Some countries allow almost all forms of hESC research, including allowing paid donors. Other countries have a more modest stance, allowing only some forms of hESC research. Some countries have outright banned all hESC research, while others have no stem cell policies at all.

Countries that permit ES cell research or therapeutic cloning (dark brown in **Figure-1**) include Australia, Belgium, China, India, Israel, Japan, Singapore, South Korea, Sweden, and the United Kingdom. Countries that do not permit therapeutic cloning but allow research on excess embryos no longer needed for reproduction (light brown in the figure) include Brazil, Canada, France, Iran, South Africa, Spain, The Netherlands, Taiwan, the USA, and others. Countries that

prohibit hESC and permit limited research on only imported stem cell lines (yellow in the diagram) include Austria, Germany, Ireland, Italy, Norway and Poland (Hoffman, 2005).

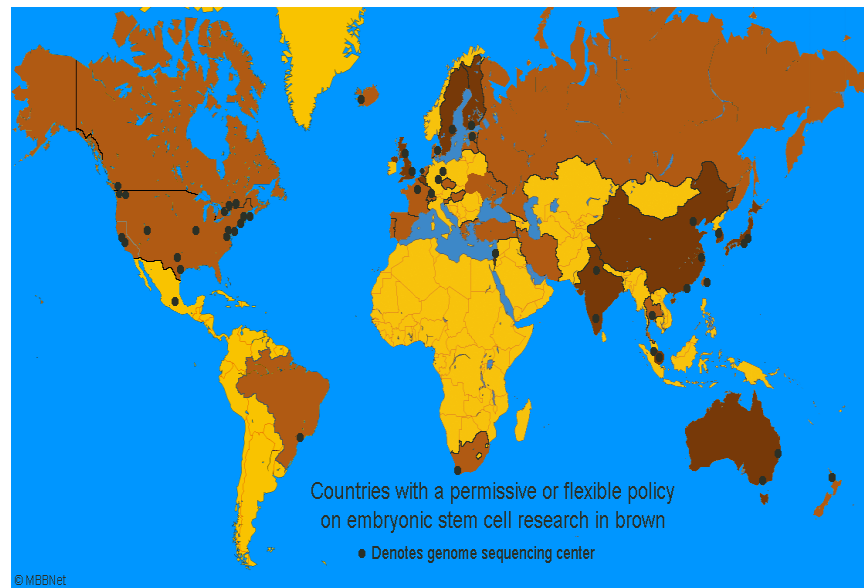


Figure-1: World Stem Cell Policies. The dark brown color denotes permissive policies; medium brown denotes moderate policies; yellow denotes highly restrictive policies. (Hoffman, 2005)

Europe

Countries in Europe have taken different stances towards stem cells. In 1990, Germany passed the Embryo Protection Act, which was an act similar to the one Bush passed, which stated that the usage of embryos other than for reproduction would be criminal (Bundestag, 1990). Cloning of embryos for research was also banned. Later in 2002, Germany passed another law that would affect how hESC research was done. The Stem Cell Act prohibited the use of imported hESC lines, except for extraordinary research circumstances (Taupitz, 2002). The act also only allowed research to be done on hESC lines derived before 2002.

The UK is one of the world leaders in stem cell research. It's "Human Fertilisation and Embryology Act" of 1990 created regulations and a governing body that would supervise all stem cell research. In general, the UK's policies are as tolerant towards hESC research as any country in the world (Parliament, 1990). The act was updated in 2008 to include more regulations, including restrictions on human/animal embryo hybrids (Parliament, 2008).

Most of Europe from the 1990s banned the use of hESCs for research, with the exception of England, Sweden, and Finland. In 1997, the The Convention on Human Rights and Biomedicine agreed that embryos should be protected if research was to be done on them (Council of Europe, 1997). The convention helped to set the standards used by most of the European countries and their relation to stem cell research.

Asia

The countries in Asia involved with stem cell research include Japan, China, South Korea, and India, whose laws are generally permissive for embryo and hESC research. In 2000, Japan initially passed laws prohibiting embryos from being transferred to the uterus for cloning (Japan, 2000), but loosened its regulations on stem cell research a year later, stating that hESCs could be used for research if they were left over from fertility treatments and that embryos could be donated for research purposes (Japan, 2001).

China also had similar laws to Japan regarding stem cell research and cloning. Their guidelines released in 2003 allowed for embryos left over from IVF treatments to be used. However, China also allowed stem cells to be acquired from abortions (Ministry of Science, 2003). The law also called for the creation of ethical committees that would regulate stem cell

research at institutions. China has one of the more liberal stances on stem cell research globally through its policies.

South Korean laws on stem cells were also in line with the global community. The majority of laws regarding stem cells came from a bill passed on cloning, the Bioethics and Safety Act of 2008, which allowed for embryos to be used after a five year period of storage. There were also special provisions for research regarding diseases that could be cured by embryonic research. The President had to specially approve research that could lead to breakthroughs in certain diseases (South Korea, 2008). Somatic Cell Nucleus Transfer (SCNT) was also allowed in the South Korea's bioethics act, but only for the treatment of incurable diseases (South Korea, 2008). The special provisions allowed for research to be conducted with different types of stem cells under special conditions.

South America

Brazil has laws that mirror most moderate countries, but most other South American countries ban the research. The regulations set in place were mainly to prohibit human cloning, but affected stem cell research. Brazil has a more open policy compared to the other countries. Brazil's Bio-Ethics Safety Law on stem cells was set in 2005 and has many similarities to current moderate global policies. The usage of embryonic stem cells left over from IVF clinics in research was permitted (Brazil, 2005).

Stem cell policies in less developed nations are also important to note. In South America and Africa, many nations have not yet enacted stem cell policies. Some developing nations may eventually begin research on allowed hESC lines, and will eventually have an impact on future

stem cell progress. In developing countries, their stem cell policies run the entire spectrum, from not allowing any hESC research to having no policies at all.

Chapter-4 Conclusion

Over the past 20 years, the United States has shown evolving policies on stem cell research, affected by the politics of the administration at the time. Shifts in opinion and administration have affected funding and the advancement of the science. Currently Obama's policies have loosened the earlier Bush restrictions to allow more government funding for some types of hESC research, however some scientists still worry the restrictions will hinder the research progress.

International stem cell policies vary considerably, from countries outright banning the research, to moderate stances, to some of the most liberal stem cell policies in the world. These policies have had an immense impact on the types of stem cell research conducted in those countries, and serves as an example for how politics can strongly affect science. Ongoing stem cell research will affect future policies as various alternatives to hESCs become available clinically.

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PROJECT CONCLUSIONS

In this IQP, the topic of stem cells was thoroughly explored, beginning with a description of what they are and where they come from, to discussions regarding stem cell ethics and legalities. While there is no right or wrong answer when it comes to your opinion on the use of stem cells, it is a moral decision which the authors feel important to make individually and therefore the authors would now like to share their views with the reader. While some argue that using embryos to provide ES cells may end a potential life, it is the authors' opinion that ES cell research provides incredible potential in medicine, therefore it is a field of research that must continued, but under strict regulations. The embryos should be limited to excess embryos obtained from IVF clinics originally produced for reproductive purposes, with donor consent. The authors feel that offering payment or other incentives to donors for obtaining embryos is crossing the line when it comes to ethical issues, and could for example, be used to persuade women to donate eggs against their beliefs for financial benefit. The authors' opinions seem to agree entirely with the current federal laws in place in the US under President Obama. Other countries whose laws generally agree with the authors include Brazil and South Korea, but not Sweden or England. In addition to ES cell research, the authors feel that ASCs and iPS cells should be aggressively pursued and used whenever possible, unless ES cells offer a better treatment option. It is the authors hope that someday ES cells will no longer be needed, and ASCs and iPS cells can be used successfully in all cases.