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Stem Cells and Society

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STEM CELLS AND SOCIETY

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ABSTRACT

This research project investigated the topic of stem cells, from various types of stem cells through their effect on humanity. In the first two chapters, the different types of stem cells, and their uses and applications are described. The latter two chapters discuss the ethics and legalities that govern stem cell research among global societies. Through the research presented regarding types, applications, ethical considerations, and legal constraints, the authors of this IQP conclude that, armed with the right knowledge, stem cell research performed in an ethical manner is a technology that should continue to be funded and researched, as great potential of this science has already been proven, and it can potentially improve the quality of life or save the lives of millions.

TABLE OF CONTENTS

PROJECT OBJECTIVES

The objective of the research for this IQP project was to examine the topic of stem cell science and to discuss the effects of this new controversial technology on society as it continues to develop. After a careful gathering and studying of this information, a conclusion will then be made by the authors regarding the use of stem cells, and which ethical and legal considerations best represent the authors' point of view.

The purpose of Chapter-1 is to describe what classifications of stem cells exist and subsequently document the various types, where we isolate each type from, and their potencies. Chapter-2 will document a sample set of a few different examples of successful experimentation that stem cells have been used for, distinguishing animal experiments from human clinical trials, and providing examples of human testing and trials whenever possible while not undercutting the importance of animal research and experimentation. The goal of Chapter-3 is to examine the ethics surrounding this controversial research topic, while Chapter-4 examines both the U.S. and international laws governing stem cell research and the bases on which these laws were developed.

Chapter-1: Stem Cell Types

Sarah Nuccitelli

For as long as there has been life, there have been various types of diseases. While treatments have been discovered for many of these life altering disorders, many of them, like Parkinson's disease and diabetes, cannot yet be cured with medicine. Stem cells are the so-called master cells of the body because they are undifferentiated cells used to create other types of cells. This means that they can repair damaged tissue to provide treatments for many different incurable diseases. Due to this regenerative ability, they are being researched as possible treatments for specific diseases (About Stem Cells, 2010). The hope is to use stem cells to treat some diseases by regenerating cells that have been damaged by aging or disease so function can be regained. As a result, much research has been done regarding the use of stem cells as medical treatments. But as the scientific community struggles to forge on with potential life saving research, there is much debate about whether some types of stem cells are ethically sound. The fight between the scientific and the religious communities makes the stem cell issue seem black and white, but realistically many intricacies must be considered before any individual, or the general public, can take sides. In the debate, one key point of misinformation is that all stem cells are alike. In fact, stem cells come in many different types and potencies; all are unique and have different medical benefits. It is important to understand the differences in stem cell types and potencies to be able to understand their ethics, so this is the purpose of this chapter.

Stem Cell Potencies

Although all stem cell types have the ability to regenerate damaged cells, they cannot do so equally as shown in **Figure-1**. The differences between stem cell types lies in the fact that

some are harvested from embryos, some from adult tissues, some are specific and some hold endless potential. From a broad perspective, all stem cells can be categorized into 4 different groups based on their potency. *Totipotent* stem cells are found in early embryos (newly fertilized eggs through the 8-cell stage) (diagram upper left) and have the ability to form any type of tissue, including the placenta (History of Stem Cell Research, 2010). *Pluripotent* stem cells are found in the inner cell mass of the blastocyst, and can form more than two hundred types of cells, not including the placenta. Embryonic stem cells are pluripotent. *Multipotent* stem cells have the ability to form groups of related types of cells. For example, hematopoietic stem cells can form all the cellular components of blood, but do not usually form neurons. *Unipotent* stem cells can only give rise to one specific type of cell lineage, usually reflecting the type of tissue the stem cell resides in (History of Stem Cell Research, 2010).

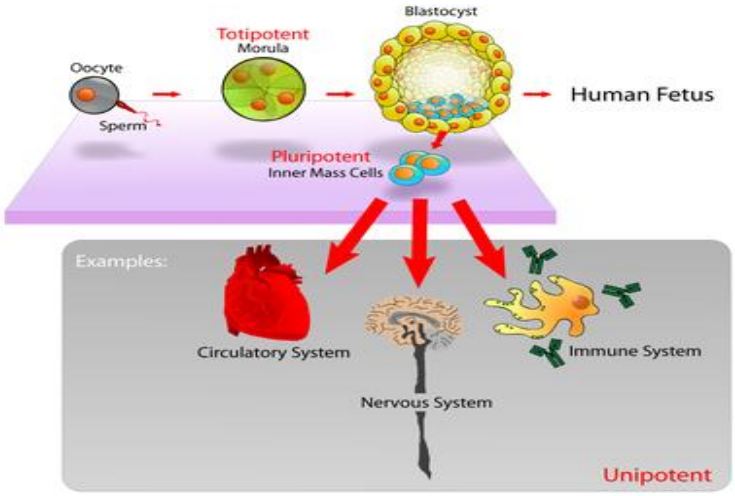

Figure-1: Diagram of Stem Cell Potencies. Newly fertilized eggs through the 8-cell stage are totipotent. Cells of the inner cell mass of a blastocyst (diagram upper right) are pluripotent. Unipotent cells are found in specific tissues, and usually can create only that type of tissue. (Wikipedia.com)

Stem cell potency has a lot to do with *where* the stem cells come from; cells from early

embryos, like embryonic stem cells, are more potent than those that are harvested from adults. Cells found in blastocysts have the ability to turn into almost any type of cell because they are not yet differentiated. However, adult cells, like skin stem cells, can usually only make more skin cells (Adult Stem Cells, 2006). Totipotent cells at the 1-8 cell stage decrease potency at the 5-day blastocyst stage, and then have even less potential for stem cells residing in adult tissues. Overall, younger cells have a greater medical potential, and unfortunately these cells also have the greatest ethical problems.

Embryonic Stem Cells

Embryonic stem (ES) cells are pluripotent cells derived from the inner cell mass of the five to seven-day old blastocyst (How Embryonic, 2010). These cells are obtained from excess embryos from *in vitro* fertilization (IVF) clinics. Although the IVF embryos were originally created for reproductive purposes, once a family has enough children, the parents can consent that their excess embryos be used for research purposes instead of being discarded. At 5-7 days, the embryo is a blastocyst containing about 100 cells. The ES cells are harvested from the inner cell mass (How Embryonic, 2010). This process usually kills the embryo, but makes way for an enormous amount of medical potential. Embryonic stem cells are favorable in the research community because they are relatively easy to isolate, can grow indefinitely, and have the potential to develop into any type of adult cell.

ES cells were first isolated in 1981 from mouse embryos (Evans and Kaufman, 1981; Martin, 1981), and were isolated from human embryos in 1998 (Thomson et al., 1998). **Figure-2** shows the process by which scientists obtain ES cells. Embryos are created by IVF, then grown to the blastocyst stage (diagram left). A micropipette is used to extract ES cells from the inner

cell mass, and the cells are co-cultured with mouse or human cells (diagram center) so that large quantities can be grown (diagram right). Since ES cells are undifferentiated, they have the ability to turn into any type of other cell except the placenta. To induce different types of differentiation, various growth factors are added to the medium to allow the formation of cells like red blood cells, epithelial cells, or muscle cells (How Embryonic, 2010).

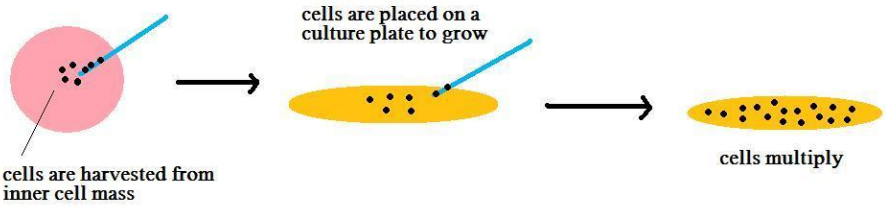

Figure-2: Diagram of Embryonic Stem Cell Isolation. Embryos are created by IVF, and grown to the blastocyst stage (diagram left). A micropipette is used to extract ES cells from the inner cell mass, and they are grown in co-culture with human or mouse cells which provide a scaffold and growth factors (diagram center). (How Embryonic, 2010)

Parthenote ES Cells

Another type of ES cell is a Parthenogenetic ES cell. Parthenogenesis in nature is a type of asexual reproduction common in bees and ants, but it does not normally occur in mammals. In the lab, eggs are chemically treated with strontium chloride to induce cell division without fertilization. The eggs divide to form blastocysts from which ES cells can be obtained (Linzhao, 2008). An interesting fact about mammalian parthenote embryos is that they do not divide beyond the blastocyst stage, so they cannot form fetuses. Some scientists believe parthenote embryos might serve as an alternative source of ES cells since their inability to form fetuses reduces some ethical concerns.

Figure-3 shows the formation of a parthenote. During normal reproduction (left side),

each egg initially begins with 2 complete sets of chromosomes (Howard, 2007), but during oogenesis (egg formation) half the number of chromosomes is lost. After fertilization with a sperm that contains a haploid number of chromosomes, the normal diploid number of chromosomes is reestablished in the embryo. During parthenogenesis (diagram right side), an egg is treated with strontium chloride to prevent expulsion of any chromosomes and to induce cell division. The embryo divides to the blastocyst stage from which ES cells are obtained. When a blastocyst is grown using parthenogenesis, it cannot grow into a full organism, but it can provide a source of ES cells that will be an exact genetic match to the oocyte (egg) donor, and will also be histocompatible with a small percentage of the rest of the population (Linzhao, 2008). Parthenote ES cells have been obtained from monkeys (Cibelli et al., 2002) and mice (Genetically Matched, 2006), but have not yet been obtained in humans.

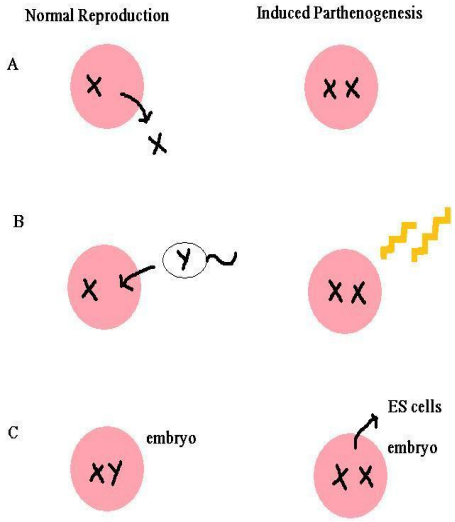

Figure-3: Diagram of Parthenogenesis. During normal reproduction (left side), half the complement of X chromosomes is eliminated from the egg prior to fusion with the sperm where it picks up the other half of the chromosome complement to form a normal diploid embryo. During parthenogenesis (diagram right), the egg is chemically treated to prevent loss of half the chromosomes and to induce cell division. No fusion with sperm occurs, and the embryo grows to the blastocyst stage from which ES cells are obtained. (Howard, 2007)

iPS Cells

Another potential source of ES cells are induced pluripotent (iPS) cells . Due to the controversial nature of using IVF embyos, scientists are always searching for alternative sources of ES cells. In 2007, a glimmer of hope shone through the turmoil when two research groups,

one led by James Thompson at the University of Wisconsin (Yu et al., 2007), and the other by Yamanaka in Japan (Takahashi et al., 2007), discovered a process by which adult cells can be returned to their pluripotent state by means of genetic alteration through viral integration of transcription factors (NB, 2008). Initially the process involved using a virus to integrate four transcription factor genes, including an oncogene, into adult skin fibroblast cells to genetically alter them to regress (Novel Strategy, 2010). Because these cells sometimes formed tumors when injected into mice, subsequent experiments omitted the oncogene, and were still able to obtain iPS cells (Nakagawa et al., 2008). These cells do not form tumors upon injection into mice (Novel Strategy, 2010). Although some reports show that iPS cells appear to be pluripotent, other reports indicate the cells are harder to grow than ES cells (Vogel, 2010).

If these iPS cells prove to be pluripotent and can one day be transplanted safely into human patients, the two biggest issues surrounding stem cell research will be solved. With the use of iPS cells doctors and scientists will eventually be able to take a skin biopsy from any patient and make iPS cells to specifically treat their illness—and since the original cells came from the patient, there will be no risk of immune rejection once the transplant is complete (NB, 2008).

Adult Stem Cells

Adult stem cells (ASCs) are the most uncontroversial type of stem cell. ASCs are found inside different adult tissues, and are specific to those sites. These cells play a critical role in tissue maintenance and repair (Stem Cell Basics, 2010). Research on adult stem cells began in the 1950s with the discovery of multipotent hematopoietic and mesenchymal stem cells in bone marrow, which can generate a number of tissues from lymphocytes and basophils, to fat and

cartilage (Stem Cell Basics, 2010). Now scientists have been able to find ASCs in a plethora of adult tissues that can be used for a number of treatments including the repair of damaged heart muscle, and transplanting insulin-producing cells for individuals with type I diabetes (Stem Cell Basics, 2010).

ASCs are far more difficult to isolate than ES cells, and are difficult to grow. ASCs can sometimes be identified in the body with the use of molecular markers on their cell surface, but because their division is limited, so researchers have been trying to find a more efficient way to grow them (Stem Cell Basics, 2010). An interesting method has been found at Stanford University regarding the growth of adult muscle stem cells. When the cells are in the body they sit on the soft tissue and rub against other cells and tissues—researchers have been able to create a softer culture medium that influences the cells to act as if they were in their home environment (Scientists Develop New Way, 2010). The problem in the past has been that ASCs grown on standard culture plates are likely to stop dividing, so it is hard to obtain enough cells to be medicinally useful. With the use of this new, more elastic growth medium, more cells have been preserved after division and the new cells are less likely to differentiate before transplantation (Scientists Develop New Way, 2010). Researchers at Stanford University transplanted ASCs grown on the new medium into 24 mice with muscle degeneration—12 with the "old cells" and 12 with the "new cells", and the results showed that ¼ of the mice with the new cultured cells responded to the treatment, while none that received the old cultured cells did. Though this new culture method has only been tested for muscle cells, these same researchers believe that it will work for all types of stem cells (Scientists Develop New Way, 2010).

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Chapter-2: Stem Cell Applications

Harry Hovagimian

Now that we have discussed in the previous chapter the various types of stem cells, we now turn our attention to what stem cells have been used for. The purpose of this chapter is to discuss stem cell applications and their benefits to society, to facilitate our subsequent discussion of stem cell ethics where the benefits versus detriments are balanced.

Stem cells have many applications, each in various stages of development, from the discovery stage, to mammalian testing, and even human trials. The legalities (which we will speak about later in Chapter 4) are stricter for human testing, but in most cases animal testing must be done *prior* to testing in humans, so in some cases only animal data is available at this time. Having some applications still in the animal testing stage does not minimize the weight of the data, as this is a required step before proceeding to human testing, but obviously obtaining human data is the desired goal. Animal testing is not a perfect predictor of success in humans, but it has been mostly accurate in the past in a variety of tests, ranging from testing how fish oil supplements affect breast cancer in rats (Su, Hsieh, & Chen, 2010), to xenotransplantation of genetically engineered pigs' organs (Ekser, Rigotti, Gridelli, & Cooper, 2009). Some stem cell treatments are currently being tested in humans, but early clinical experiments usually use patients with poor prognosis who did not respond to conventional therapies, so this can bias against success (Steen & Medsger, 2000). This chapter will focus on applications of stem cell treatments for five different diseases. Each section will introduce a disease, explain how it is being treated presently and in the recent past, and explain how the stem cell treatment is changing or will soon change the patient prognosis.

Stem Cell Treatment of Diabetes

Diabetes is a chronic disease that affects a patient's blood sugar levels. It is currently the sixth leading cause of death in the United States (Goldthwaite, 2008). The two most common types, type 1 and type 2, are symptomatically similar in that the patient's blood glucose levels are high, but this is where any similarities end. Type-1 diabetes is an autoimmune deficiency in which the body attacks the pancreas, where insulin is made. This results in the patient not having enough insulin to properly control blood sugar levels. Type-2 diabetes transpires when the insulin the body creates is not efficient enough for removing the sugar from the blood. In this case, the pancreas produces insulin, but the tissues have decreased their response to it. The treatment for type-2 typically involves controlling weight and diet, and increasing physical activity. The current treatment for type-1 is usually limited to monitoring the patient's blood sugar levels closely and controlling it with insulin injections. While the economic cost of diabetes is in the hundreds of billions annually in the US, we still can only treat the symptoms of the disease (Goldthwaite, 2008).

Stem cells have the capacity to create the insulin-producing β cells, which are necessary to treat type-1 diabetes. The pancreas is the organ that monitors and controls the levels of insulin, and therefore glucose, in the blood stream. The study of pancreatic regeneration is strongly under investigation, but by generating new islet cells, we could possibly treat this disease (Goldthwaite, 2008).

Another organ being investigated as a source for islet producing stem cells is the spleen. The spleen has regained research attention after the discovery of the multipotent stem cells within this organ that are strongly capable of self-renewal and injury repair, including producing insulin manufacturing cells. These cells, when successfully harvested, have been shown to

secrete insulin, while being less likely to form cancerous tumors unlike embryoinc stem (ES) cells (Faustman & Davis, 2010).

With respect to ES cell treatments of diabetes, although ethical and legal disputes control the use of these cells, experiments have shown that human ES cells are capable of being differentiated in vitro into insulin producing cells (Assady et al., 2001), and that ES cells can be used to treat animal models for type-1 diabetes (Soria et al., 2000). This latter study corrected hyperglycemia in nonobese diabetic (NOD) mice within one week (Soria, Roche, Berná, León-Quinto, Reig, & Martín, 2000). The Assady study showed that human ES cells had greater potential to create cells with insulin-producing capacity than mouse ES cells (Assady, Maor, Amit, Itskovitz-Eldor, Skorecki, & Tzukerman, 2001). Human ES cells have not yet been used to treat type-1 patients, so this remains a future possibility.

One interesting study showed that the transplantation of MHC-matched hematopoietic stem cells (HSCs) in diabetic NOD mice led to successful blocking of disease formation, so perhaps these adult stem cells can be used in patients in the near future (Beilhack et al., 2003; 2005).

Stem Cells and Systemic Sclerosis

Systemic sclerosis (also known as scleroderma, diffuse scleroderma or SSc) is an autoimmune disease which can manifest in different forms. ‘Sclero’ is the Anglo version of the Greek word *sklero* meaning hard (MedicineNet, 2004), and *derma* is the Greek word for skin (MedicineNet, 2004). While literally translated scleroderma means hardening of the skin, other organs are often affected, including the lungs, heart, kidneys, and gastrointestinal tract. This systemic involvement is frequently associated with an ultimately fatal prognosis, while localized

sclerosis primarily affects the patient's skin and has not been shown to impact the patient's mortality (Hunzelmann & Krieg, 2010) (International Scleroderma Network (ISN), 1998-2010). Like other autoimmune diseases, SSc develops when a person's immune system malfunctions in response to an unknown trigger and the immune system attacks itself. SSc patients are categorized by the extent of skin involvement, though, as previously stated, other organs are typically affected.

Current treatments for SSc often target the organ fibrosis. Current treatments include general immunosuppression, corticosteroid treatments, anti-fibrotic therapies, and a wide array of anti-inflammatory drugs, though there is no clear proof that any other these methods treat the underlying disease (Hunzelmann & Krieg, 2010) (Mouthon, Bérezné, Guillevin, & Valerye, 2010).

One current use of stem cells for this disease is to treat finger joint deformity (known as clawing) in patients with diffuse scleroderma. A study was done to assess the effects of autologous hematopoietic stem cell transplantation (ASCT) on scleroderma finger clawing, and promising results were shown on both structural and functional levels for the patients' hands. Prior to ASCT, the patients' Rodnan skin scores for the hands ranged from 6-12 out of 12 (the lower the better). Following ASCT, the scores ranged from 0-6. The modified Rodnan skin score (MRSS) is an assessment of the thickness of the patients' skin in various types of SSc (Englert, et al., 2008).

Hematopoietic stem cell treatments have also been shown to reverse capillary bed damage and loss in scleroderma patients who had undergone immunosuppressive therapy followed by autologous HSC transplantation. The capillaries in the dermis of these patients not only benefitted from capillary regeneration, resulting in reduced pain and increased mobility, but

it affected capillary beds in other organs, reducing the risk for heart failure, hypertension, and pulmonary fibrosis for example, which ultimately increased the patient's expected life span (Fleming, et al., 2008).

Another treatment still in development focuses on the disease's autoimmune defects. Most current treatments use chemotherapy to destroy the patient's immune system, followed by various anti-inflammatory drug treatments. Some new treatments use radiation and chemotherapy to destroy affected bone marrow, followed by ASCT to create a new immune system in the patient's bone marrow (Hunzelmann & Krieg, 2010). This high-dose chemotherapy and radiation followed by ASCT is not limited to treating SSc, it is also being researched for lupus, rheumatoid arthritis, and other autoimmune diseases (Green, 2006) (Fisher, 2006).

Stem Cell Treatment of Stroke

A stroke, sometimes called a cerebrovascular accident (CVA), is caused when the blood supply to the brain is rapidly decreased, resulting in rapid loss of function. There are two types of stroke, ischemic and hemorrhagic, in which blood flow is decreased due to a blockage or the leakage of blood, respectively. Stroke is the third leading cause of death in developed countries, with ischemic stroke accounting for more than 80% of all strokes (National Stroke Association, 2009) (Sims & Muyderman, 2010). There are a number of risk factors for strokes, ranging from age, behavior, health, and previous stroke. Current treatment varies, but typically includes thrombolysis, breaking down the clot, or physically removing the clot via a thrombectomy. Time is the limiting factor with a stroke, as brain cells will continue to die without sufficient blood flow and ultimately lead to death if untreated. During a stroke, brain cells die, and the abilities

controlled by that area of the brain are lost. This can include physical abilities such as speech and muscle movement, or loss of memory, depending on the location damaged, the extent of damage, and the duration before the thrombus is removed.

With respect to animal studies, mesenchymal stem cell (MSC) therapy has shown improvements in behavioral and neurological recovery from ischemic stroke in rats. Tests have shown improved recovery in rats treated with MSCs isolated from the rat's own bone marrow, although the optimal timing and dosage still need to be investigated further (Pavlichenko, et al., 2008). To find these critical answers, two federally funded studies investigated how many cells should a dose consist of, and when is the optimal time to administer such doses (Medical College of Georgia, 2008). Drs. Hess, Yu, Borlongan, and other investigators are neuroscientists at the Medical College of Georgia and have worked on many types of cells in the transplantation therapy in ischemic stroke rat model.

MSCs are not the only type of stem cells to be successfully transplanted into ischemic rats. Human fetal NSCs have been shown to survive, migrate, and differentiate in the brains of ischemic rats, and further testing will reveal if these new neural cells affect the recovery of motor function. These NSCs are known to survive in non-obese diabetic (NOD) mice, a study discussed earlier in treating diabetes. The survival of the ischemic rats significantly increased 3.8% over a four week post-transplant time period. As a comparison, a 3.8% increase of a human's average life span of 70.2 years (CIA, 2010) would be roughly two years and eight months (Kelly, et al., 2004).

Some data is also available for human stroke patients. Dr. Rich James, a chiropractor and resident of New York City, suffered a massive stroke in February 2006. Through the internet, he contacted Stem Cell Therapy International, Inc, a company located in Florida devoted to the

development of stem cell transplantation therapy for regenerative medicine. James, who suffered crippling effects to his left side, underwent stem cell therapy with an affiliate clinic overseas in Kiev, Ukraine (Vega, 2006). Within six weeks, he was back home in Manhattan, able to ride the NYC subway on his own, a feat that was previously difficult with his quad cane and brace or his wheelchair. Although this report shows promising data, it does not represent a well-controlled clinical trial, so a proper study remains in the future (Vega, 2006).

Stem Cell Treatment of Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative brain disorder, and it accounts for approximately two-thirds of all cases of dementia. Named for the German physician who first described the disease at the turn of the 19th century, Alzheimer's is the most common form of dementia in people over the age of 65. It is currently incurable, largely because its causes are not fully understood. Presently, treatments for AD offer patients temporary symptomatic relief, but do not delay the disease's progression. While most AD cases occur in patients over the age of 65, early-onset AD can occur in patients as early as 40 years old. The average mortality for AD is five years, but this can range from three to twenty years. AD patients require a dedicated caregiver, and two-thirds of those patients living in the United States are taken care of by a family member or friend in their own home. This disease is not only taxing emotionally on the patient's family, but the annual cost to family members is typically in the thousands of dollars up to $100,000 (Bloom, de Pouvourville, & Straus, 2003)

Current AD research shows that amyloid-β (Aβ), a short neurotoxic polypeptide chain, is likely associated with neurodegenerative diseases such as Alzheimer's. The deposition and build up of these small protein fragments into senile plaques was observed as far back as Auguste

Deter, the first AD patient studied by Alois Alzheimer in 1906. Reducing the production and buildup of these peptides may be part of treating this disease. Although Aβ is thought to initiate the disease, tau protein participates in the downstream effects. Tau is a protein normally associated with microtubules inside a cell that help maintain cell shape. In AD patients, tau becomes hyper-phosphorylated, which ruins microtubule formation and cell shape, forming neurofibillary tangles (Alzheimer's Association, 2010).

With respect to potential stem cell treatments, researchers at the Kyungpook National University in Daegu, South Korea, tested the potential therapeutic effects of bone marrow-derived MSCs in mice. The 2009 study was able to successfully confirm that BM-MSC transplantation accelerated the removal of amyloid-β plaques from the brains of acute AD mice (Lee et al., 2009). This study also showed that the BM-MSCs can induce normally-quiescent microglia to clear out amyloid-β build-up (Lee, Jin, & Bae, 2009). The three professors who performed the 2009 study in Korea reported in early 2010 that the decreased amyloid-β deposition was directly related to microglial activation (Lee et al., 2010). They also showed that the microglia ameliorate memory deficiencies in the AD mice. This finding was supported by a version of the Morris water maze test known as the hidden platform. Subjects which received PBS injections deteriorated as expected in their ability to learn and memorize the maze, while those treated with BM-MSCs displayed navigational patterns that resembled control subjects. Furthermore, they reported that the MB-MSC transplantation was able to reduce tau hyperphosphorylation (Lee, Jin, Endo, Schuchman, Carter, & Bae, 2010).

Another type of stem cell being investigated as a possible AD treatment is adult neural stem cells (NSCs). Recent advances in isolation techniques for NSCs have made NSCs exciting candidates for a variety of therapeutic strategies, including the treatment of AD. NSCs are

multipotent cells that generate various cells in the central nervous system (CNS). Research using NSCs will determine their ability to reduce tau hyperphosphorylation and amyloid-β deposition. Surprisingly, at this time there appears to be no discussion about using NSCs to generate activated microglia.

Stem Cell Treatment of Lung Carcinoma

Carcinoma of the lung, or lung cancer, is typically classified within two main types. The most common type is non-small cell lung carcinoma (NSCLC) which comprises approximately 80% of all cases. Small cell lung carcinoma (or SCLC) constitutes the remaining cases. At the time of diagnosis, SCLC is typically widespread in the patient's body, so treatment is usually limited to radiation and/or chemotherapy. With NSCLC, the cancer may remain centralized, allowing for surgical removal of the tumor (Healthcommunities.com, Inc., 2007).

Presently, SCLC is typically treated with radio-chemotherapy, since there is no centralized tumor for resection. This is where stem cells come into the picture as a possible treatment. A group at the University of Berne in Switzerland treated patients with limited-disease SCLC with intensive chemotherapy, supported by stem cell-enriched whole blood and radiotherapy. Although they have not obtained enough results to determine whether this is a significantly improved treatment method, they were able to determine that the treatment was less toxic than standard treatments with ifosfamide, carboplatin and etoposide. SCLC patients may even have a good survival benefit with this treatment (Calderoni, von Briel, Aebi, Solenthaler, & Betticher, 2002). Further reporting on this study could not be located at the time of writing this project.

Other possible uses of stem cells for treating lung cancer have shown interesting results. In 2006, a group from the JG Brown Cancer Center at the University of Louisville presented their findings regarding ES cells used as a treatment for lung cancer in mice (Eaton et al., 2006). Mice were given two possible treatments, then tumors were implanted. Treatment with ES cells alone proved 80% effective in preventing tumor growth, while using ES cells plus granulocyte-macrophage colony-stimulating factor (GM-CSF) prevented 100% of tumor growth. The work done by Professor Eaton and his colleagues at the Center was funded mostly by small local grants, with larger federal agencies remaining disinterested in funding and supporting such work (Eaton, et al., 2006).

A Japanese study was presented in the journal *Lung Cancer* in mid-2003. It was designed to show the survival of patients who had first undergone radiation and chemotherapy treatments with high-dose ifosfamide, carboplatin and etoposide (HD-ICE), supplemented with peripheral blood stem cell transplantation (PBSCT) for SCLC (Katakami, et al., 2003). This study showed promising results in 5-year survival rates. Based on the excellent data from the first study, a further investigation, a comparative phase III study of radio-chemotherapy and radio-chemotherapy followed by HD-ICE with PBSCT, is currently was underway at the time of this IQP.

Another study tested HD-ICE (defined above) with autologous PBSCT in a phase II trial conducted with patients who had not previously undergone any treatment for their LD-SCLC (Nakanishi et al., 2003). The phase II trial seems to have started concurrently with the previously discussed study, and showed an overall survival rate at around 50 to 55.6% ± 11.7%. The results show that HD-ICE combined with auto-PBSCT is a viable treatment option. This data, combined with the data from the previously mentioned trial, show that a treatment involving

HD-ICE combined with PBSCT is a viable treatment option for patients with small cell lung carcinoma.

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Chapter-3: Stem Cell Ethics

Sarah Nuccitelli

The use of embryonic stem cells as medical treatments sometimes involves the destruction of embryos that hold the potential to grow into a complete human organism, so it is important to consider the ethics behind this science—religious groups and people around the world have many different opinions as to how society should proceed with stem cell research. In this chapter, we will investigate the views of the world's five major religions on stem cells: Judaism, Christianity, Hinduism, Islam, and Buddhism. The purpose of this chapter is to explore different ethical stances of world religions to provide an understanding as to the morality of stem cell research. Surprisingly, all of these religions support the research and use of adult stem cells (ASCs) as long as they are used to save lives (Griffin, 2010).

The Stem Cell Debate

The stem cell debate is mainly centered around embryonic stem (ES) cells and the controversy of when human life begins. Some believe that life begins as early as conception, while others believe life begins much later at birth (Yearwood, 2001). When life begins is an important factor in determining whether the harvesting of ES cells kills human beings. Individuals opposed to ES stem cell research believe that the blastocyst (from which ES cells are derived) should be considered with the same respect as a fully developed human, and they compare the killing of the blastocyst to murder (Doerflinger, 1999). Thus, in our discussion of each religion below, we will focus on their beliefs of when life begins.

In addition to when life begins, several other arguments also contribute to the opposition of ES cell research. Somatic cell nuclear transfer (SCNT), or therapeutic cloning, is a process

that involves removing the nucleus from an unfertilized egg, and replacing it with the nucleus from an adult cell. The reconstituted egg is then stimulated to divide for 5 days to the blastocyst stage from which ES cells can be derived (Somatic Cell Nuclear Transfer, 2003). The advantage of SCNT is that ES cell lines could be created from a specific patient to be used for treating that same patient without fear of graft rejection. But so far SCNT has successfully been performed in mice, not in humans. Though SCNT offers a way to obtain many ES cell lines, the manipulation of embryos solely for science (not reproduction) is considered by some to be unethical because these embryos are being created merely to be destroyed (Committee on Ethical Guidelines et al., 2005). Other ethical concerns also surround using a technique that mixes human and nonhuman cells. Scientists sometimes grow ES cells on animal cell feeder layers, which can increase the risk of viral transmission to the human cells. In addition, sometimes human ES cells are transplanted into nonhuman animals to create chimeras (hybrids), so that the human cells can be studied for applications (Karpowicz et al., 2004). Chimeras, whose name is derived from the Greek word for an interspecies mythical beast, raises concerns for some religious groups because some historical influences suggest that creating these hybrids is evil (Karpowicz et al., 2004).

ES cells hold more medical potential than adult stem cells (ASCs) because they are easier to grow in large quantities, are easier to isolate, and can differentiate into a larger variety of tissues. Because ES cells hold so much medical potential, a new kind of ES cell is being studied that does not destroy an embryo. Induced pluripotent stem (iPS) cells are regular skin fibroblast cells that have been reprogrammed back to their pluripotent state by transfection with DNAs encoding stem-inducing transcription factors. This process allows the fibroblast cells to develop into ES-like cells (Brind'Amour, 2009). As discussed in Chapter-1, iPS cells are very promising

because some scientists believe they have the same abilities as ES cells, however other scientists believe iPS cells divide slower and are less robust (Dolgin, 2010).

Christianity and Stem Cells

Christianity is the world's largest religion, divided into nearly 400 million Protestants, and over 1 billion Catholics (Griffin, 2010). As is typical for the very large religions, multiple stances exist within one religion. Some followers of Christianity, especially Catholics, oppose the use of ES cells as they believe life begins at conception, thus an embryo is a form of human life, and its destruction constitutes murder, a sin in the eyes of god (Doerflinger, 1999). Before there was advanced biological knowledge about human embryonic life, followers of Christianity believed that the embryo only attained human status when it took a general human shape; but in 1869 Pope Pius IX declared the fetus to have full human status (Fazzetto, 2004). In a direct quote from Pope John Paul II, he stated that "In reality from the moment in which the ovum is fertilized, a new life begins which is not that of the father or of the mother but of a new human being which develops of its own accord. It would never be made human if it were not human already. This has always been clear, and modern genetic science offers clear confirmation" (Robinson, 2006). The Pope is an idyllic figure to most Catholics, and his beliefs and opinions represent the general views of the Catholic church. At a 1996 U.S Bishop's conference, concern was expressed that any approval from the Catholic Church on ES cell research would encourage further degradation of humanity for the purposes of scientific advancement (O'Brien, 1996). This means that if religious role models supported the use of ES cells, it would increase the exploitation of blastocysts, whether they are from IVF clinics or grown *in vitro*. The pro-life document presented by the 1996 Bishops committee disputes stem cell research on the grounds

that medical potential and hope for the greater good does not justify direct killing (O'Brien, 1996). They believe that embryos deserve the same respect as all other human beings based on the fact that the fertilized egg contains all of the genetic material needed to become a human being—which can lead to the conclusion that there is no real difference between an embryo and a full grown person (Robinson, 2006). With such a strong stance against ES research, it is not surprising that Catholicism also does not support the use of discarded embryos for research. In respect to IVF clinics, it was stated that "ultimately each of us will die, but that gives no one the right to kills us" (O'Brien, 1996). Although Catholics are strongly against embryo research, the Pope has been quoted as being in favor of working with adult stem cells (Pope Benedict XVI, 2008).

While Catholics have tight restrictions against embryo research, other Christians such as Methodists and Episcopalians, approve of it (Faithful Profressive, 2005). Such research is supported as "ethically responsible advances" (O'Brien, 1996). This support for some types of research show that large religions are often divided, and some Christians understand the importance and potential that stem cells hold.

Judaism

Judaism is the oldest major religion, with approximately 18 million followers—one third of which live in the United States (Griffin, 2010). The Jewish community is divided, and there exists no official singular stance on the subject of stem cell research (Yearwood, 2001). However, Jewish faith requires its members to seek scientific knowledge, and most see fit to pursue ways to improve human life (Fazzetto, 2004). For this reason, a large portion of Jewish members feel that "Pikuach nefesh" or the "Preservation of life" can be best served using stem

cells for the betterment of existing and ailing humans; however others believe that the destroying embryos by dissecting their stem cells goes against the idea of improving humanity (Yearwood, 2001). With over 100,000 frozen embryos in IVF clinics, most members of Judaism are at least in favor of researchers trying to use them to save lives (Yearwood, 2001). Jewish tradition permits the destruction of an embryo for the benefit of other living human beings because Jewish law declares that life begins at birth not at conception (Rich, 1997). In addition, the destruction an embryo is especially allowed if it is only grown *outside* the body because that embryo has no chance to develop, so it is ethically of lower status than an implanted embryo (Yearwood, 2001). This Jewish acceptance of an *in vitro* state also allows for therapeutic cloning, as that embryo would also grown only outside the body (Fazzetto, 2004).

Islam

Islam is the world's second largest religion to Christianity, whose followers (Muslims) believe in the Prophet Muhammed, who was sent from God (Allah) to guide them—mortal life is believed to be a preparation for the after-life (Griffin, 2010). There exists no solid Islamic stance on ES cell research, but it is common Muslim belief that it takes the embryo 120 days (4 months) after fertilization to obtain a soul (Deem, 2009). And in most cases, the embryo is not considered the equivalent of a full grown human because Islamic law clearly depicts a difference between *potential* life and *actual* life (Fazzetto, 2004). This fact, coupled with the the part of Islamic law stating that any preserved embryo can not be used by anyone other than the parents, means that the use of unwanted embryos in IVF clinics is supported (Fazzetto, 2004). Consequently, research using embryos is supported by most Muslims.

However, Muslims do have some issues against cloning. In the Muslim tradition, family relationships and parental love are of extreme importance, making the idea of cloning these cells by SCNT disturbing (Fazzetto, 2004). The fertilizing of an egg by a sperm is seen as creating or validating a relationship between the male and female donors, so the fertilization process, for purposes other than helping infertile couples, violates this extremely important set of morals (Fazzetto, 2004). Overall, Islam is divided on the issue—conservative opinions coming from Egypt state that the embryo represents an early human life that should not be destroyed, while other North American Islamic liberal views believe that since the cells are not part of the body they do not hold any potential to become a human life (Deem, 2009).

Hinduism

Followers of Hinduism believe in reincarnation after death, or a life-cycle consisting of birth, death, and rebirth in another form, known as the wheel of life (Griffin, 2010). In this religion, it is believed that all souls merge with the supreme spirit, and to compensate for wrong doing many Hindu societies are divided into upper, middle, and lower classes based on spiritual purity (Griffin, 2010). Hinduism teaches that all life, including plants and animals, should be considered sacred— so in this sense research using embryonic stem cells is unethical (Bahnot, 2008). But an alternative Hindu view states that humans can only survive by consuming and exploiting other forms of life (Bahnot, 2008). Through reincarnation Hindus believe that every soul is evolving, from species to species, to reach the human stage and obtain the highest level of consciousness in order to reach God (Bahnot, 2008). Therefore, *existing* human life is seen by some Hindus as more important than human life in the embryonic stage of development. Hinduism teaches that it is ethically responsible to help preserve each human life, so *adult* stem

cell research is accepted by a vast majority of the Hindu population (Deem, 2009). But for ES cells, although prolonging human life is extremely important, the idea of reincarnation means that most Hindus see *conception* as the beginning of human life, so because of this it is not generally acceptable to destroy embryos under the constraints of Hinduism (Deem, 2009).

Buddhism

Buddhist scientists were one of the earliest to isolate human embryonic stem cells (Fazzetto, 2004). Like Hindus, Buddhists also believe in the wheel of life, and that this cycle continues until the individual is ready to move on to eternal peace (Griffin, 2010). Like all of the previously mentioned religions, Buddhism supports research on *adult* stem cells. However Buddhists reject embryo research on the grounds that each embryo contains the *essence* of an individual and, therefore, deserves the same respect as a living person (Fazzetto, 2004). However, because Buddhists believe there is no higher power or "divine plan", the teachings actually allow using cloned embryos as nothing prevents it (Fazzetto, 2004). While some ethicists believe that embryo research on pre-mature human beings goes against Buddhist teachings, most agree that because *individuality* is not of extreme importance to Buddhists as in other religions, and because it is a Buddhist belief that there are many ways in which life can be created, embryo research involving cloning techniques is somewhat acceptable (Fazzetto, 2004). It is interesting to see the Buddhist distinction placed between embryos *inside* the womb, and those created *outside* the body; this suggests that only life created through standard reproduction contains a soul.

Ethics of iPS Cells

Induced pluripotent stem (iPS) cells are a relatively new discovery, which many scientists hope will provide ES-like cells that are more acceptable to ethicists opposed to embryo research. As discussed in Chapter-1, iPS cells are adult skin fibroblast cells treated with specific transcription factors to induce de-differentiation to an ES-like state. Human iPS cells were first derived in 1997 using a mixture of four transcription factors (Takahashi et al., 2007), but since those early experiments the procedure has been modified to include only two factors (Kim et al., 2008). While research with ES cells or SCNT requries embryos, iPS research can be performed on any human somatic cell (Baylis, 2008), so iPS cells should have far fewer ethical concerns. In addition, eliminating the need for women to donate eggs for SCNT would reduce the chance of harm to the donors.

The main debate with iPS cells is whether they are truly *equivalent* to ES cells. Although some evidence exists that iPS cells in mice can form a variety of tissues, some scientists claim iPS cells are harder to grow (Dolgin, 2010). iPS cells are at best only pluripotent, not totipotent, so they can not develop into a full human organism. iPS cells lack the organization of an ordinary zygote, meaning that if they are implanted they would not develop like an embryo, but would develop into more tissues, or in a worst case scenario would develop like a teratocarcinoma (tumor) (Cohen and Brandhorst, 2008). When the growth processes of iPS cells and ES cells are compared, there is a huge difference in gene expression in about 1300 genes (Deem, 2009). This means that ES cells and iPS cells are definitely not the same. So in summary, more research will be required to determine whether iPS cells can actually be used to treat the same diseases as ES cells.

Chapter-3 Conclusion

Three potential sources of ES cells were discussed in Chapter-1: blastocysts grown by IVF (traditional ES cells), blastocysts grown by parthenogenesis (p-ES cells), and adult stem cells that have been induced back to pluripotency (iPS cells). The author of this chapter supports research on all of these stem cells because it is crucial to learn as much as possible about ES cells to help ailing lives; the source of these cells is not a huge concern to me. It is obvious that the blastocyst is alive, because all cells are alive. And I believe that embryos have the full *potential* to become a human life when implanted into the mother's uterus. But an embryo without its mother can not develop into a human being and could not survive independently. As an analogy, bread dough has the full potential to become bread, but only if it is baked in the oven; otherwise, like discarded embryos, uncooked dough will shrivel up and go to waste. I believe that any embryo, discarded from an IVF clinic or donated for research purposes, should already be considered a lost life, from which the harvesting of stem cells seems perfectly ethical. If the life has already been taken away from the embryo, wrongfully or not, its use in stem cell research could provide a chance for the lost life to have meaning through helping to save other lives. Leaving these beings frozen, forever stuck in their embryonic state, unable to develop, in my opinion, is more disrespectful than putting to use the potential they hold. For those who are not comfortable using embryos, scientists have found a way to produce ES cells by parthenogenesis or by iPS technology, and I am also in favor of those technologies.

With respect to SCNT, a type of cloning, I am also in favor of this. SCNT is the process of injecting the nucleus from a patient's skin fibroblast cell into an enucleated egg, growing it to the blastocyst stage, and isolating ES cells from the inner cell mass whose genetics match that of the skin cell donor. Once this technology has been successful with humans (it only works with

mice so far), theoretically ES cells could be derived that are genetically identical to a patient and would not be rejected. Of course cloning has always been a huge red flag in the religious community, but I agree with expanding this type of research because it will help increase the number of ES cells that scientists have to study, and increase the chance of a successful graft. By creating various types of ES cells and expanding this research, it will help push stem cell research toward potential cures for many diseases. Science already grows human cells, like skin cells, for skin grafts for burn patients. Both SCNT and IVF create embryos solely for research, and some think this is unethical. However, the inability of these embryos to develop and survive on their own is important to me. And with respect to human egg volunteers, during drug testing paid human volunteers are often needed for preliminary testing, so this concept of paid volunteers is not new. So I think that clinics and research facilities should be allowed to offer paid compensation for any embryos donated for research because, in the long run, the ES cells isolated from them will benefit society.

With respect to iPS cells, the technique is relatively easy to perform, but some studies show that iPS cells can be harder to grow than ES cells (Vogel, 2010). Although the upside is the technique produces ES-like cells genetically identical to the patient's de-differentiated skin cell, the downside is only that patient likely can receive the treatment, others would reject it. iPS cell research, although extremely young, has already had some success in animal implantation trials, while ES cells still have not been tested in most applications. Because of this, I support research on iPS cells—they seem to offer real life treatment possibilities for the somewhat near future. However, only time will tell whether iPS cells are as medically potent as embryo-derived ES cells. Although I think that iPS cells hold great potential, I also think the scientific community

should really push for more funding for embryo research because, after all, they do hold the potential to be the most beneficial in the long run.

One of the most interesting research breakthroughs that I read about during this project was the creation of chimeras from the development of human stem cells inside non-human subjects, such as mice (Karpowicz et al., 2004). The ethical concerns surrounding this particular type of chimera experimentation were most valid, in my opinion, because they deal with a side of science that has not been fully explored. On the stance that creating inter-species organisms defies nature, I believe that as long as we do not allow these animals to reproduce and we do not create any new species for habitat population, then science has not defied nature and these chimeric animals can teach us something about the ability of various samples of human ES cells to grow and differentiate. The purpose of these types of experiments is solely to test the effectiveness and safety of stem cell applications so that real life treatments may one day be established for common practices. I do think that this technique can be disrespectful to the species involved, but scientific research has always relied on the use of animal testing before applying certain hypotheses to human treatment—and that is extremely important in this case since the transplantation of ES cells sometimes causes cancer in the host organism (Karpowicz et al., 2004).

With respect to adult stem cells, they can hopefully be isolated from the tissues of patients who need treatment. These cells are found in the body and can mostly form the type of tissue from which they are extracted. These cells do not offer as much potential as ES cells, but they can still benefit the conservative part of society. I support the use of adult stem cells because I think they will always be appropriate in minor cases. I feel that ES cell usage should

not be abused, and the use of adult stem cells should be used whenever possible, or by patient request.

With so many different beliefs on stem cells, it is easy to see how this topic can become extremely controversial between scientific and religious communities. For those who are unsure about scientific facts, or those who do not identify with any particular religion, they can still form opinions based on personal feelings and education. When forming an opinion on this topic, it is important to remember that there are many different types of stem cells, and many ways they can be isolated and grown. Most people can find at least one type of stem cell research that they feel comfortable with, which is important because for any progress to be made, the general public must support the scientists who perform the studies.

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Chapter-4: Stem Cell Legalities

Harry Hovagimian

In addition to the stem cell ethical responsibilities faced by scientists and researchers, laws have also been enacted to control this controversial technology. These laws are as complex as the ethics inspiring them, and vary by global region and change over time. In the United States, each presidential era of the past couple of decades has brought about new embryo and stem cell policies, protocols, laws, bills, amendments, and other actions based on their beliefs and their parties beliefs. Each president has either overturned embryo laws created by their predecessors or created new laws.

When a subject so highly controversial as stem cells is discussed, public opinion helps prioritize the regulations, especially for the more controversial topics such as human embryonic stem (hES) cells. These laws govern embryo and stem cell research, and change the way we as a society view the use of such cells.

United States Federal Embryo Policies

While scientific research that led to the discovery of stem cells has been around since the early 1960s, monumental laws regulating the use of stem cells in the United States were not fully developed until the early 1990s. After *in vitro* fertilization (IVF), the *excess* embryos originally created for reproductive purposes are simply discarded by the clinic, so laws must address whether these discarded embryos can be used for scientific research. Shortly after the first successful human *in vitro* fertilization in 1969, and legalized abortions (Roe v. Wade, 1973), the federal government created regulations that prevented the use of federal funds for research on human embryos. The U.S. government's position controlled only federal funding, but in no way

affected or controlled the use of private funds. (Wadman, 1999) In 1974, President Nixon's National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended a ban on all federally funded research using embryos and fetal tissues, and the ban was enacted by congress. These preventative laws were maintained by the Reagan and the first Bush administrations due to their strong anti-abortion sentiments.

Clinton Administration: 1993-2001

The ban on using federal money for embryo research was not reversed until the early 1990s with the Clinton Administration (Wertz, 2002). In January 1993, newly elected President Clinton reversed the original 1974 Nixon ban on embryo research by passing the *National Institute of Health Revitalizations Act*, which allowed the National Institute of Health (NIH) to fund human embryo research (Dunn, 2005). However, this policy caused a backlash in the conservative Congress, and the next year they voted to overturn the Revitalization Act, to restore the original 1974 ban.

Shortly after the overturn, NIH created the Human Embryo Research Panel to make recommendations to President Clinton. The Panel eventually recommended the use of federal funds to support research on embryos specifically created for experimentation, but in an official statement by the president released in late 1994, President Clinton declined to support the recommendation, citing potential ethical concerns (Office of the Press Secretary, 1994).

During the Clinton Administration, a wide variety of scientific advances were made in the United States. From the beginning of his presidency, President Clinton showed overall support for science and technology research regarding stem cells. President Clinton and vice president Gore won respect from researchers during their time in office by not only lifting

Federal funding bans, but by disputing Republican congressional leaders' attempts to slash budgets and insuring growth for science and technology research. (Malakoff, 2000)

Bush Administration: 2001-2009

One of the most well-known actions taken by the Bush administration was on August 9, 2001, when in a nationally televised announcement President George W. Bush announced that he would allow the use of federal funds on ES cell research, but only on those ES cell lines created before that specific date. This decision limited federally funded U.S. researchers to 60 ES cell lines derived from five different countries. Unfortunately, this original estimate of valid ES cell lines proved to be an over-estimate, and subsequent research by *Science* limited the ES lines to about 34 derived from 4 countries (Vogel, Bush Squeezes between the Lines on Stem Cells, 2001). This number of allowed ES cell lines eventually declined to around 21, as some were contaminated. (Wilson, 2009)

Throughout his term as president, George Bush vetoed legislation proposed to ease restrictions imposed on ES cell research (Babington, 2006). President Bush often cited moral positions behind his decisions, stating that "if a bill does that[destroys life], I will veto it" (Baker, 2005). The detrimental effects on U.S. ES cell research from the Bush administration have not been fully quantified. As shown in **Figure-4**, the percentage of research publications referring to human ES cell research decreased during the Bush Administration, compared to other papers published in the United States in that era (Schrope, 2009).

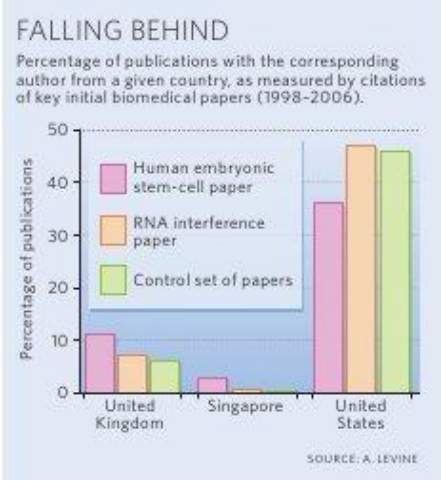

Figure-4: Diagram of the Decrease in ES Cell Research Papers in the U.S. Under the Bush Administration. (Schrope, 2009)

Obama Administration: 2009-Present

During his presidential campaign, Barack Obama promised to prioritize scientific innovation, and to separate scientific research from political or moral influences. Obama said the majority of Americans supported lifting the federal ban on embryo research, allowing researchers to work on cures for things such as cancer, heart disease, Parkinson's, and other illnesses (Wilson, 2009).

Upon entering the Oval Office in 2009, President Barack Obama reversed the eight-year-old ban on federal funding for stem cell research. As only 21 of the 60 stem cell lines authorized for research under the Bush policy proved to be useful to researchers, Obama's decision to overturn this policy was intended to further stem cell research discovery. "In recent years, when it comes to stem cell research, rather than furthering discovery, our government has forced what I believe is a false choice between sound science and moral values," Obama said at the White House (CNN, 2009). During his presidency thus far, President Obama continues to support this policy, but some fear that the topic of stem cell research may possibly just be a pawn in a much bigger political game. Representative Diana DeGette, D-Colo. expressed concerns that stem cell

research could become "a pingpong ball going back and forth between administrations." Representative DeGette voted on Obama's legislation to become federal law, after failing twice in the past to overturn Bush's restrictions (Borenstein & Feller, 2009).

State Laws on Embryo Research

In contrast to common misconceptions, ES cell research has never been directly outlawed federally in the United States, it has only been banned from receiving *federal* money. To overcome this federal ban, some states have reached out a welcoming hand to scientists searching for life-saving discoveries potentially contained within stem cell research. Those states welcoming scientists pursuing these treatments include: New Jersey, California, Massachusetts, Connecticut, and others. (Vestal, 2008)

With respect to Massachusetts, our state has developed legislature funding university research centers, business tax credits, state grants, and other incentives aimed at furthering Massachusetts as a hub of bioscience and biotechnology (Nature, 2008). In this state, Senate bills number 2039 and 2032 were passed in 2005 which laid forth a solid foundation on which the enhancement and development of regenerative medicine within the Commonwealth could be built (Harkins, 2005). The bills allowed for research and clinical applications involving the derivation and use of hES cells. While these bills opened the field for stem cell research in MA, they very carefully laid out some key terms including: specifically stating that any gametes used must be *donated* with consent, human *reproductive* cloning is strictly prohibited, and it allowed the formation of both a Massachusetts stem cell research advisory board of 8 members and a biomedical research advisory council of 15 members (The Commonwealth of Massachusetts, 2005). Senate Bill number 2039 authorized and directed the University of Massachusetts

Medical School in Worcester, MA to establish and maintain a public bank for collecting and storing umbilical cord blood and placental tissue (The Commonwealth of Massachusetts, 2005). These bills also called for a public Institutional Review Board to be formed at UMMS in Worcester. The University of Massachusetts Medical School is also currently constructing a 500,000 square foot facility, known as the Albert Sherman Center, which will hold the Center for Stem Cell Biology and Regenerative Medicine, a facility which will become the world's largest repository for ES cell lines (Marks, 2007).

With respect to other states, in January 2004, the state of New Jersey was the first to fund ES cell research by designating $10 million to such research. This was followed shortly thereafter when in November 2004, California established a voter approved $3 billion fund. (Vestal, 2008). Shortly after Massachusetts approved its bills in 2005, the neighboring state of Connecticut developed their own strategies involving ES cell research that included a 10 year $100 million plan (Internet Broadcasting Systems Inc., 2005). Other US states have also taken very clear sides on the stem cell research debate. While many states avoid this controversial topic, 14 other states have either banned ES cell research altogether, or ensured legality, with some of those states going so far as to independently fund ES cell research, as seen in **Figure-5**.

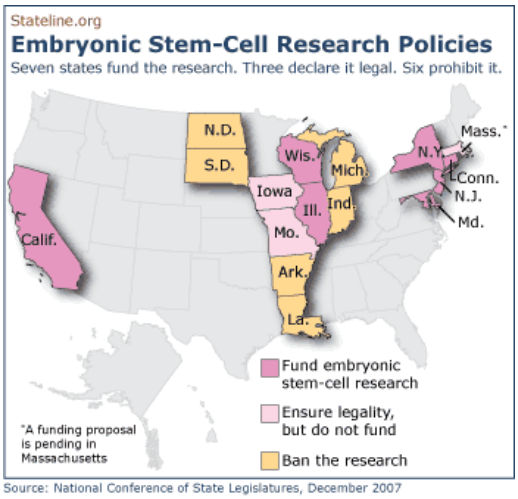

Figure-5: Diagram of U.S. States ES Cell Policies. (Vestal, 2008)

International Stem Cell Policies

The stem cell research technology race is not limited to the United States. Many countries throughout the world are the homes of leading researchers and students in the field of stem cell research and regenerative medicine. Unlike the United States government which technically allows all forms of ES research (except reproductive cloning) and controls it through federal spending, countries throughout the world either have strict policies which restrict or prohibit stem cell research, or they welcome the science and actively fund such innovation (Vestal, 2008).

South Korea announced in 2005 the creation of the World Stem Cell Foundation in Seoul, intended to produce approximately 100 new ES cell lines each year. Initially, the hope in creating this stem cell bank was to sidestep President Bush's restrictive policies in the U.S. to provide U.S. researchers with ES cell lines derived outside the U.S. (Kaplan, 2005).

In Japan, ES stem cell research was allowed from guidelines approved in 2001. While this sounded promising, as it allowed scientists to derive new hES cell lines and research both homegrown and imported lines, it required an approval process that was eventually shown to

stifle the amount of research performed. In 2009, The Japanese Council for Science and Technology Policy pushed new regulations intended to remove some of these burdensome restrictions (Cyranoski, Japan relaxes human stem cell rules, 2009). In 2007, Shinya Yamanaka of Kyoto University created the world's first induced pluripotent stem (iPS) cell (Takahashi, et al., 2007) Unfortunately, due to a lack of legal expertise in this field, Kyoto University stalled over developing a strategy to protect its patents in this very lucrative area. In Japan, patents are usually awarded to researchers who *file* first, as opposed to the laws in the United States where patents are awarded to those who can *prove* they discovered something first. This example of the concern over patenting and intellectual property rights of therapeutic stem cell research shows that this is not just a research race, but more of a race to the commercialization of the technology (Cyranoski, Japan ramps up patent effort to keep iPS lead, 2008).

European countries tend to vary on their ES cell policies, like various US individual states. In Sweden, embryo research is allowed based upon a law passed in 1991, and the Swedish government has funded at least two labs deriving human ES cell lines. While the Swedish Research Council has reported that some loopholes need to be closed, as there are no laws currently preventing human *reproductive* cloning in that country, Sweden is far less politically charged than some other countries (Vogel, Germany Dithers over Stem Cells, While Sweden Gives Green Light, 2001). Most recently, Sweden has allocated SEK 100 million for regenerative and stem cell research (Karolinska Instituet, 2010). Other European countries, such as Germany, have regulations controlling the importation or utilization of hES cells. In 2002, German Parliament enacted a ban on creating and working on hES cell lines; stem cells harvested abroad prior to the cutoff date of January 1, 2002 were allowed to be imported into the country (Kim, 2002). In 2008, an amendment to the German Stem Cell Act of 2002 changed the

cutoff date on importation of ES cell lines to those created before May 1, 2007 (Herrmann, Woopen, & Brüstle, 2008).

Chapter-4 Conclusion

As stem cell research continues to grow, both in the United States and across the world, laws will continue to change and grow with the technology. In order to remain a leader in stem cell research, the U.S. federal laws governing stem cell research need to stay on one path, and not be created based upon a president's own personal moral views. The authors of this IQP share the concerns of U.S. Representative DeGette that stem cell research could become "a pingpong ball going between administrations," as has been seen in recent presidencies. The United States could be considered one of the better countries for conducting stem cell research, as federal laws have never outright banned the research (just prevented it from receiving *federal* funding), but the laws have controlled the major funding, and have left the responsibility in regards to legality to the discretion of the individual state government. While some states have gone the route that some countries have in banning the research, other states have done their best to ensure the legality and funding of such research, and hopefully the research and breakthroughs in these supportive states will eventually positively influence other states.

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Project Conclusions

The stem cell debate is fueled by a lack of accurate information for many people, and by a variety of opinions on embryonic stem (ES) cells and the techniques used to derive them. While there may never be a clear universally accepted ethical answer on whether it is acceptable to work with embryos and ES cells, the technology continues to advance. Thus, it is important to form guidelines that serve the interest of both religious communities and those directly involved with the science. The following section is an overview of the how the authors of this IQP project feel about the main components of the stem cell debate.

While the authors of this report believe that the use of ES cells should continue, these cells should not be abused; their use should be limited to serious cases, like the treatment of Parkinson's and Alzheimer's disease. In the meantime, adult stem cells (ASCs) should be used wherever possible as alternative treatments to those opposing ES cells, as ASCs are more acceptable ethically. Of the three types of ES cells: traditional ES cells, parthenote-derived ES cells (p-ES cells), and induced pluripotent cells (iPS cells), the authors support all types for further research and eventual medical use. In regards to the destruction of embryos, the authors recognize that IVF embryos do have the full *potential* to become a human life when implanted into the mother's uterus. However, an embryo without its mother cannot develop into a human being, so its destruction is not seen as unethical by the authors. For those embryos which have been discarded by IVF clinics, they should undoubtedly be used for research, with donor consent. The unwanted life represented by every excess frozen embryo also has the potential to save human lives through their ES cells. In addition, the authors support the creation of embryos solely for research purposes, as it allows those who fully support ES cell research to really

participate in the advancement of technology. With respect to other techniques for obtaining ES cells, the authors support any research for producing ES cells, including parthenogenesis or induced pluripotency, as well as SCNT (cloning). SCNT should eventually eliminate stem cell implant rejection, as the cells will be genetically identical to the skin cell nucleus donor. Overall, more funding for ES cell research is needed because this is an extremely promising technology that could potentially improve the quality of or save the lives of millions.

With respect to laws regulating stem cell use, it is important to have guidelines that satisfy both those who are against ES cell research and those who support it. The United States, now that Obama has entered the Presidency, has a very good approach to regulating stem cell research in a way that respects most members of the population. Chapter 4 mentions that Obama has made it possible for some labs to get federal funding for the creation and study of ES cell lines, which was impossible under the Bush Administration. However, as a nod to those who oppose the research, only certain ES cell lines can be used in labs receiving federal funding; the ES cell lines must pass stringent NIH guidelines for embryo donations from IVF clinics, must be created only for reproductive purposes, and cannot be created solely for research purposes. The IQP authors support the former stance, but not the latter. While the federal government will fund ES research under certain conditions, it still allows for each state to derive its own laws on whether this research will be funded locally. This shows that the government supports and appreciates this great technology, but also understands the need for strong oversight. The authors support the overall Obama approach, and feel it is very democratic and favorable in the upholding of civility, peace, and the respect of divided public opinions.