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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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ABSTRACT

The purpose of this project is to create an understanding of the controversial topic of stem cells and their impact on the scientific community and society. This is accomplished by discussing the different types of stem cells and their actual or theorized uses, as well as elaborating on the ethical and legal implications that surround the scientific work. Stem cells have seemingly unlimited potential for treating some of the worst human diseases, but strong ethical opinions and legal limits will continue to affect this technology in the near future.

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PROJECT OBJECTIVES

The objective of this Interactive Qualifying Project is to explore the controversial topic of stem cells and discuss the effect of this new technology on society. Chapter-1 (Stem Cell Types) examines the many different types of stem cells, their potencies, when they were first isolated and by whom, and where in an embryo or the adult body they are isolated from. Chapter-2 (Stem Cell Applications) investigates the experimental successes of stem cells to date in several example diseases, in animal experiments or human clinical trials, and discusses potential future experiments. Chapter-3 (Stem Cell Ethics) discusses the ethical issues surrounding stem cells, including focusing the ethical debate on embryos, describing their formation in IVF clinics, and listing the stances of the world's five major religions on embryo and ES cell usage. Chapter-4 (Stem Cell Legalities) examines current legislation in the United States and internationally that dictates stem cell research. Finally, the authors make a conclusion about the use of stem cells and the ethical dilemma surrounding research based upon current isolation methods.

Chapter-1: Stem Cell Types

Tyler Wood

Stem cell research is one of the most ethically controversial topics in all of biology today. Stem cells are long-lived undifferentiated cells that can develop into many specialized cell types. Most of the ethical concerns that arise from stem cell research originate from the destruction of human embryos to obtain embryonic stem cells, but this is only one type of stem cell, and not all stem cells are created equal. They can be obtained or created through different processes, many of which do not destroy human embryos. In order to introduce the topic of stem cells, this chapter will discuss the various types of stem cells, describing their origins and level of potency.

Stem Cell Potencies

Stem cell types can be classified by their *potency*, or their ability to differentiate into other types of cells (**Figure-1**). *Totipotent* or omnipotent cells, have the highest potency. These cells can differentiate into any type of cell in the human body, or any extra-embryonic tissue such as the placenta. Newly fertilized zygotes through about the 8-cell stage (approximately 2 days after fertilization) are classified as totipotent (Murnaghan, 2010).

Pluripotent stem cells can differentiate into any of the three primary germ layers and eventually make any cell of the adult organism, except for extra-embryonic tissue. Embryonic stem (ES) cells isolated from the inner cell mass of a 5-day old blastocyst are pluripotent (Zwaka and Thomson, 2003).

Multipotent stem cells can only differentiate into a related group of cell types, but cannot form all tissues of the adult organism. Multipotent cells can be found in the bone marrow as hematopoietic stem cells, and in mesodermal tissues as mesenchymal stem cells. Hematopoietic stem cells can form all the related cellular components of blood (red blood cells, white blood cells, platelets), but do not normally form other types of non-blood tissues.

Unipotent stem cells can only differentiate into one type of mature cell. Examples of likely unipotent cells are skin progenitor cells that usually form other skin cells, and pancreatic progenitor cells that can form only pancreatic β-cells.

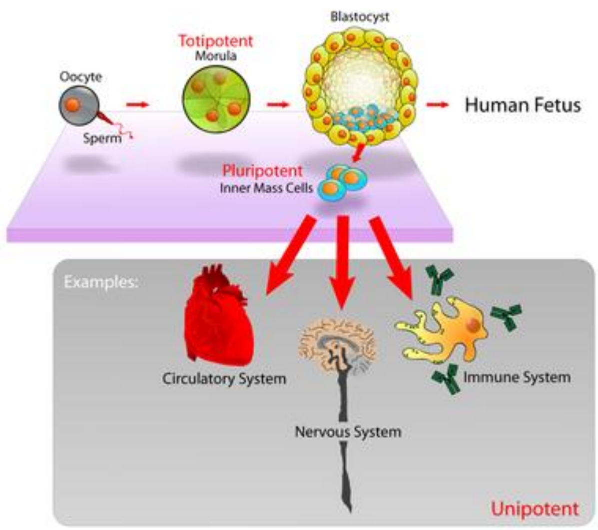

Figure-1: The Progression of Stem Cell Potency in a Human Embryo. The oocyte (female egg) is fertilized by the male sperm *in vitro*, forming a zygote which is totipotent. The zygote divides two days to the 8-cell morula stage (green in the diagram), where the cells are also totipotent. Continued division and differentiation to day-5 forms the blastocyst. The inner cell mass of the blastocyst is comprised of pluripotent embryonic stem cells (blue in the diagram). These ES cells differentiate into primary germ layers, and further into their mature somatic stage (Stem Cells, 2008).

Embryonic Stem Cells

Embryonic stem (ES) cells are pluripotent cells obtained from a human embryo during the blastocyst stage (ISSCR, 2009). After fertilization of sperm and egg *in vitro*, a single diploid cell called a zygote is formed. The zygote divides until it is comprised of 8 cells, and then begins a process called compaction, where the cells bind together in a tight sphere and continue to divide into the morula stage. The next stage, cavitation, pushes fluid into the center of the morula and the number of cells increases to between 40 and 150. After four to six days from fertilization, the embryo is now referred to as a blastocyst, and is made up of an outer layer of cells (the trophoblast) and an inner cell mass (ICM). ES cells are located in the ICM. In 1981, mouse ES cells were the first ES cells to be isolated and grown *in vitro* (Martin et al., 1981; NIH, 2009). In 1998, James Thompson of the University of Wisconsin derived the first human ES cells from frozen IVF embryos (Thomson et al., 1998; Boyle, 2005). The original isolation process involved plating the ES cells extracted from the inner cell mass of a blastula onto a feeder layer of mouse fibroblast cells. This provided a scaffold and nutrients for growth to derive an immortal ES cell line. But due to concerns about animal viruses, the mouse feeder layer was eventually replaced with a non-cellular layer of extracellular matrix as the scaffold (Klimanskaya et al., 2005). The isolation of ES cells destroys the embryo, and thus begins the ethical controversy of working with these cells (discussed in Chapter-3).

During normal reproductive IVF procedures, if the embryo is implanted into the uterus, the trophoblast will implant into the endometrium (inner lining of the uterus) to form the placenta. Cells of the ICM will differentiate into one of "three principal laminae, known as the *primary germ layers*"; the ectoderm, mesoderm, and endoderm (Neas, 2003). The outermost germ layer is termed ectoderm, and is comprised of cells that will further differentiate to construct primarily the skin and nervous system of the fetus (**Figure-2**).

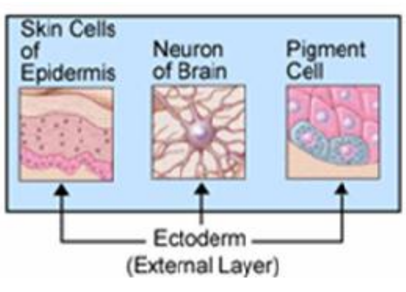

Figure-2: Primary Tissues Formed by Differentiation of the Ectoderm Germ Layer. (Germ Layer 2012)

The middle germ layer, termed the mesoderm, is comprised of cells that will further differentiate to construct primarily the connective tissue, circulatory, muscular, and reproductive systems (with the exception of gametes) of the fetus (**Figure-3**).

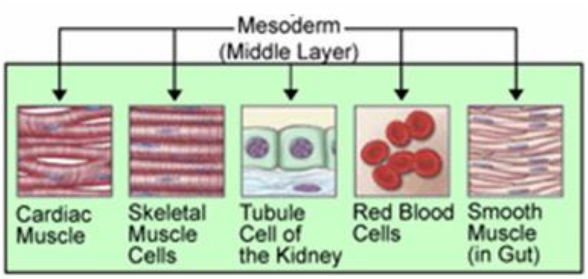

Figure-3: Primary Tissues Formed by Differentiation of the Mesoderm Germ Layer. (Germ Layer, 2012)

The inner-most germ layer is the endoderm, which is comprised of cells that will further differentiate to construct primarily the digestive, respiratory, endocrine, and sensory systems of the fetus **(Figure-4)**.

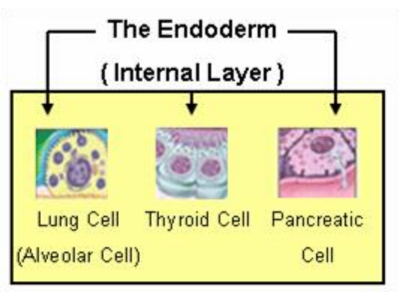

Figure-4: Primary Tissues Formed by Differentiation of the Endoderm Germ Layer. (Germ Layer, 2012)

Most of the ES cell research performed to date has been done on mouse embryos because they are much easier to work with and come without most of the ethical concerns of destroying human embryos. Due to their pluripotent nature, ES cells have the most potential for medical applications in regenerative medicine.

Adult Stem Cells

As their name implies, adult stem cells (ASCs) are isolated from adult tissues. These cells exist within various tissue of the developed human body, and are also called somatic stem cells. Adult stem cells have been found in the "brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis" of humans (NIH, 2009). ASCs exist primarily to maintain homeostasis in the body by repairing their dedicated tissues. Adult stem cells are usually considered *multi-potent* because they can only differentiate into a specific related group of cell types. The major advantage of ASC research is that no embryos are destroyed during their extraction, but they still present many difficulties. ASCs are rare cells, and they can be difficult to locate in human tissues. Even after being identified, ASCs are usually difficult to grow. And ASCs are not as medically potent as ES cells.

However, some recent developments in somatic stem cell research have shown promise in a phenomenon known as "transdifferentiation", or coercing an adult stem cell to differentiate into a cell type other than the tissue it was derived from (Graf, 2011). This would, in theory, allow for adult stem cells to exceed their multi-potent classification for use in other tissues. An example of this would be using hematopoietic stem cells (which are relatively easy to isolate from bone marrow) to transdifferentiate into cardiac muscle for the purpose of treating heart attack patients (Britten et al., 2003).

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) can be found in human bone marrow, umbilical cord blood, or they can be isolated from the peripheral blood of donors treated with hormones to stimulate HSC release from the marrow. HSCs usually differentiate into any of the mature blood cell types (**Figure-5**), including red blood cells, white blood cells, and platelets. The ability of bone marrow cells to reconstitute blood tissue was first observed in 1956 (Ford et al., 1956), and these cells remain the best characterized of all the stem cell types.

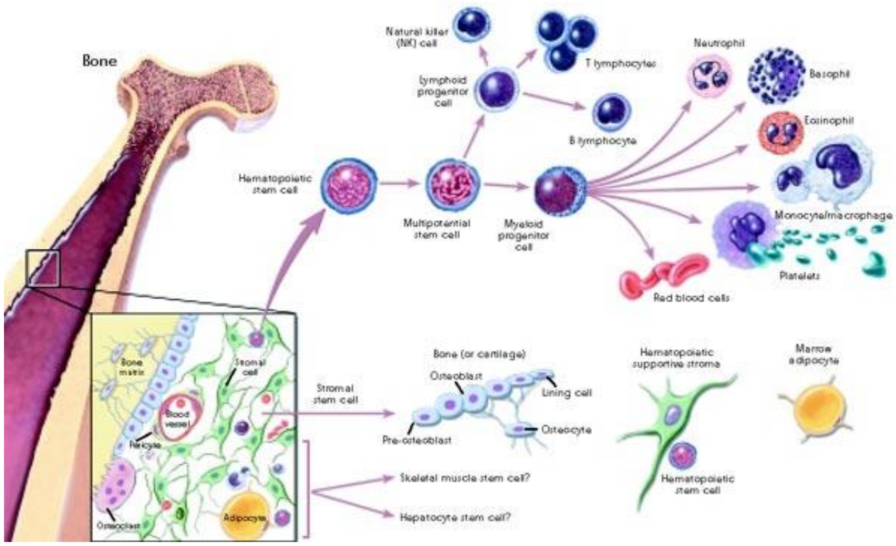

Figure-5: Differentiation Hematopoietic Stem Cells Into Various Blood Cell Lineages. HSCs in the bone marrow differentiate into the many different types of mature somatic cells in the blood. (Kirschstein and Skirboll, 2001)

The average person requires one hundred billion new blood cells every day, and all of these are derived from HSCs. For therapy purposes, HSCs traditionally are extracted from bone marrow, but the extraction process from bone marrow can be costly and painful (Hematopoietic Stem Cells, 2005), so presently these cells are usually obtained from umbilical cord blood or from the peripheral blood. Cord blood HSCs are easy to collect, and appear to be more primitive than marrow HSCs, so they are less likely to be rejected by the host. Cord blood HSCs have been used to treat over eighty diseases (Cord Blood Registry, 2004; Viacord, 2007).

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are also found in bone marrow, and can differentiate into many types of connective tissues, including bone, cartilage, and fat. MSCs were first characterized in the mid-1970s in Russia (Friedenstein, 1976), and are the second best characterized type of stem cell. They are relatively easy to isolate and grow (for an adult stem cell), and their multipotency provides hope for treating a wide variety of patients, including osteoporosis and cancer victims enduring chemotherapy. MSCs also "support the *in vitro* growth of human embryonic stem cells" (Kass, 2004; Jackson et al., 2007).

Neural Stem Cells

Neural stem cells (NSCs) are found primarily in the brain and the spinal cord, and can be grown *in vitro*. NSCs were first isolated in 1989 from rat forebrain, and could be grown *in vitro* and differentiate to form neurons and glia (Temple, 1989). Although they are not yet well characterized relative to other stem cell types, NSCs are being tested in animals to research their efficacy for regenerative therapy of central nervous system problems such as spinal cord injury, Parkinson's disease, Huntington's disease, and multiple sclerosis.

Epithelial Stem Cells

Epithelial stem cells (ESCs) are found in the regenerating linings of epithelial tissue in the body, such as the skin, gastrointestinal tract, and eyes. They tend to be unipotent, or only able to differentiate into one type of mature adult cell, depending on the tissue from which they were extracted. Skin stem cells are produced at the base of hair follicles and the basal layer of the epidermis, where they can differentiate into cells for the epidermis and hair follicles

(Cotsarelis et al., 1999). ESCs are relatively easy to extract and replicate, making them useful for skin grafts with a minimal risk for patient rejection.

Other Types of Adult Stem Cells

Cardiac stem cells (CSCs) are multipotent stem cells found in the heart. CSCs were first isolated in 2003 as c-kit+ cells (Beltrami et al., 2003) and in 2005 as Isl1+ cells (Laugwitz et al., 2005). Research in 2011 by Dr. Roberto Bolli and colleagues with the University of Louisville found positive results in 16 heart attack patients treated with c-kit+ cardiac stem cells collected from the same patient (autologous transplant) during coronary bypass surgery. Four months after the procedure, 14 of the 16 patients showed improved cardiac function (Bolli et al., 2011; Brown, 2011).

Dental pulp stem cells (DPSCs) are multipotent stem cells found in the soft living tissue inside the human tooth. They are most abundant in baby teeth that children begin losing around the age of six. Dr. Songtao Shi of NIH discovered DPSCs in January of 2003, and they were shown to replicate easily, and “induce the formation of specialized dentin, bone, and neuronal cells” (NIH, 2003).

Testicular stem cells are multipotent stem cells found in the human testes. They were first isolated in January 2009 by Renee Reijo-Pera of Stanford’s School of Medicine and Dr. Paul Turek of San Francisco’s Turek Infertility Clinic (Stem Cells Isolated from Human Testis, 2009). Since testicular stem cells are newly discovered, further research must be done to determine the potency of the cells. It is hoped that they could be used treat infertility and other reproductive diseases in men.

Oogonial stem cells are unipotent stem cells found in the human ovaries. They were first isolated by Jonathan Tilly of Massachusetts General Hospital in 2012. For almost 60 years, it was believed that women are born with all the eggs they will ever have, but the discovery of ovarian stem cells has challenged this idea with the potential for them to someday be used for differentiation into egg cells. It is hoped that they can be used to help cancer patients, sterile women, and those with premature menopause (Powell, 2012).

Potential Alternatives to Embryonic Stem Cells

Due to the ethical issues associated with human ES cells, scientists are attempting to cultivate ES cells without destroying an embryo. These alternatives to date include induced pluripotent stem (iPS) cells, somatic cell nuclear transfer, and parthenogenesis.

Induced Pluripotent Stem Cells (iPS)

iPS cells are adult cells (usually skin fibroblast cells that are easy to obtain and grow) that have been "reprogrammed" into a pluripotent-like state by adding transcription factors that aid the reprogramming (**Figure-6**). iPS cells were first produced in 2006 from mouse skin fibroblasts (Takahashi and Yamanaka, 2006) and in 2007 from human skin fibroblast cells (Takahashi et al., 2007). These cells are among the most exciting in stem cell biology today, and provide hope that pluripotent cells can be obtained without the destruction of human embryos (Aldhous, 2009). The initial method of inducing pluripotency on somatic cells used viral vectors encoding four transcription factor genes, but this was found to induce cancer at the injection site in certain cases. Newer methods have been developed that omit the viral vector and the *c-myc* oncogene transcription factor component to try and circumvent these challenges (Kim et al., 2008). Another advantage of iPS cells is they are a genetic match to the donor of the fibroblast cell. This allows for the creation of ES-like cells that are matched individually to a patient and are less likely to be rejected. However, not all scientists are convinced that iPS cells are suitable for therapy, as some have found them to contain DNA mutations and grow more slowly than ES cells (Dolgin, 2010; Gore et al., 2011).

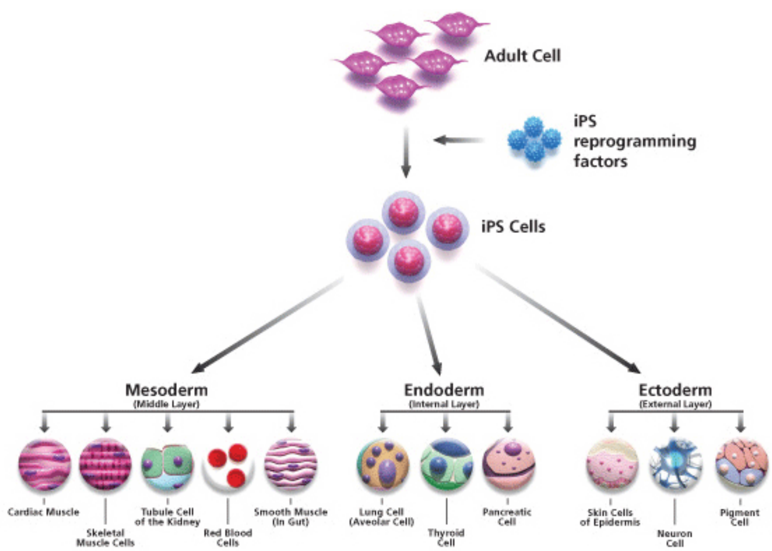

Figure-6: Creation of iPS Cells from Adult Cells. (Sigma-Aldrich, 2011)

Somatic Cell Nuclear Transfer

Somatic cell nuclear transfer (SCNT), or “therapeutic cloning”, is a method of creating a cloned embryo specific for a patient from which ES cells can be derived. Following *in vitro* fertilization (IVF), the nucleus of a host egg cell is removed, and replaced with the nucleus of a skin cell from a patient. The embryo is then grown 5-days to the blastocyst stage, from which ES cells are derived (HESC, 2012). SCNT was first applied to cloning Dolly the sheep (Campbell et al., 1996). It has not yet been used in humans except for non-enucleated triploid cells that are not useful in therapy (Noggle et al., 2011). Somatic cell nuclear transfer has been found to have experimental and ethical limitations; many people dislike the thought of human cloning, even when done only therapeutically not reproductively. SCNT has somewhat been replaced by iPS cells for providing patient-specific cells.

Parthenogenesis

Parthenogenesis, the Greek word for "virgin birth", is a method of asexual reproduction in which a female egg develops into an embryo without being fertilized by a male sperm (Weiss, 2001). Although it occurs naturally in plants and some animal species, mammals are incapable of naturally undergoing parthenogenesis. However, scientists have developed methods for inducing mammalian eggs to begin dividing as if they were fertilized, using chemicals such as strontium chloride or electrical current. ES cells were derived from monkey parthenote embryos in 2001 (Mitalipov et al., 2001), and some claims have been published for ES lines derived from human parthenote embryos (Bervini and Gandolfi, 2007), but this remains controversial. As a new method of stem cell extraction, much is still to be learned about parthenogenesis including their true potency. Studies suggest that human parthenotes do not have the potential to grow into a fetus, but scientists are unsure if there will be genetic problems in the extracted stem cells because of their forced asexual reproduction (Weiss, 2001).

Chapter-1 Conclusion

Stem cells, with their long lives and their ability to differentiate into various somatic cells of the body, are the future of regenerative medicine to replace damaged tissues. When understanding the ethical problems of stem cell research, it is important to note that there are different types of stem cells. Embryonic stem cells have shown the most promise in medical applications for disease and tissue repair because they are relatively easy to grow to large numbers required for therapy, but new methods offer hope for creating other pluripotent cells without destroying human embryos. New fertilization and extraction techniques will allow for breakthroughs in stem cell research in the coming years.

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Chapter-2: Stem Cell Applications

Timothy Beane

Taking advantage of the highly diverse functions of various types of stem cells discussed in the previous chapter, scientists are investigating using stem cells to potentially treat a variety of human ailments. Utilizing the ability of various kinds of stem cells to differentiate into any cell type needed can hopefully provide a means to replace dysfunctional or destroyed cells, to heal cells that would otherwise never heal, and to improve a patient's quality of life. The purpose of this chapter is to discuss how stem cells are being used to treat a few selected example diseases, to lay the foundation of their benefits to society which will factor into a discussion of their ethics in later chapters. Five prevalent diseases were chosen for discussion based on their widespread occurrence and lack of current cures: leukemia, diabetes mellitus, spinal cord injuries, heart damage, and Parkinson's disease.

Stem Cell Treatment of Leukemia

Leukemia is a cancer of the blood or bone marrow where a person produces abnormal white blood cells, generally leukocytes. Leukemia develops during the early stages of blood cell formation (hematopoiesis) often due to DNA mutations in progenitor cells (Leukemia and Lymphoma Society, 2012). These cells divide at an increased rate, producing immature non-functional leukocytes. The large population of abnormal cells in the blood causes circulatory problems such as loss of bone marrow (which leads to anemia from less red blood cell production), and a lack of blood platelets (which leads to increased bleeding and bruising). In addition, immunological problems arise as white blood cells are still immature or dysfunctional and cannot fight infections. Symptoms such as fatigue, fevers, and weight loss are common (NIH, 2005).

Leukemias are divided into several groups depending on the speed of onset and the cells affected (NIH, 2005). Acute leukemia occurs rapidly with the buildup of immature cells that flood bone marrow and prevent the production of healthy cells. Acute leukemia must be treated immediately to prevent spread to other organs (metastasis). Chronic leukemia is similar, except white blood cells are mature and dysfunctional. In this case, the buildup of abnormal cells occurs over a period of months or years. These leukemias can be further broken down into lymphoblastic or lymphocytic (which affect precursor B and T cells) and myelogenous (which affects precursor cells to red blood cells and platelets), and other rarer types of leukemias. Standard treatments of leukemia include chemotherapy and radiation to kill the rapidly-dividing cancerous precursors. Measures are also taken to prevent metastasis in acute and high-risk chronic leukemia cases (NIH, 2005).

Hematopoietic stem cells (HSCs) have been used in therapies for over 50 years now, and are some of the oldest, most trusted, and well-known of all stem cell therapies. HSCs have been used to treat leukemias, HIV, SCID, and sickle cell disease. As early as 1957, HSCs derived from bone marrow were used to treat patients that underwent radiation and chemotherapy treatments for late-stage leukemia (Thomas et al., 1957). These early trials were only slightly successful, as the host would usually reject the implanted cells, but cells that were donated from a histocompatible donor proved successful in restoring functional blood cell activity, providing partial and complete remissions (Thomas, 2000).

Originally, HSCs were obtained from bone marrow of large bones, predominantly the hip bone with a long needle. But this procedure is uncomfortable for the donor, so scientists developed other procedures for obtaining HSCs. Peripheral blood was found to contain HSCs in low quantities, but the cell numbers increased drastically in donors injected with hormones to stimulate the mobilization of HSCs from the marrow into the peripheral blood system. In addition, scientists have also determined that umbilical cord blood (donated at time of birth) is an excellent source of HSCs, and these cells appear to be more primitive than marrow HSCs and cause less graft-versus-host disease in the recipient (Gluckman, 2009). Like marrow transplants, peripheral blood stem cell (PBSC) transplants can be autologous (from the same patient) or allogeneic (matched), but involve only a four to six hour procedure where blood is filtered by apheresis to separate out immature blood cells that are similar to those in bone marrow by using specific cytokines to promote progenitor cell migration. PBSC transplants are far less invasive and are phasing out the old method of extraction of bone marrow in large bones (NIH, 2005).

Currently, over 40,000 stem cell transplants are performed annually for a wide range of diseases (Horowitz, 1999; Santos, 2000). Most patients who have undergone such treatments have been successfully cured of the disease with no sign of remission after five years (King, 2001; Ooi et al., 2004; Hughes, 2005). HSC transplants have had a large degree of success with leukemia due to how relatively easy stem cells can be obtained from a compatible host such as a relative (allogeneic transplant) or from the patient themselves from an unaffected part of the body (autologous transplant).

HSC transplants by themselves carry a high risk. Infections are fairly common due to myeloablation, where the host's bone marrow is destroyed through radiation or chemotherapy, so the host cannot produce ample amounts of white blood cells to mount an immune response. Invasive fungal infections (IFI) are a persistent problem, where overall incidents range from 10-25%, and can cause severe complications (Bow, 2005). This can be further complicated post-transplantation when immunosuppressive medications (to prevent graft-versus-host disease) dampen the ability of the patient to fight off infections. Graft-versus-host disease (GVHD) is a risk with allogeneic (histo-matched) transplants, since even histocompatible tissue may be rejected by the host. Acute GVHD generally occurs within the first three months after transplantation with skin, intestine, and liver inflammations. High doses of immunosuppressant drugs are standard treatment, but their application risks fatal infections. Chronic GVHD can also develop, and is a source of complications during post-treatment (Cutler et al., 2006; Fraser et al., 2006). Along with inflammation, chronic GVHD may lead to fibrosis (scar tissue) forming, and cause functional disabilities. Using HSCs from umbilical cord blood can reduce the chance of GVHD in HSC transplant patients (Laughlin, 2001).

For leukemia patients, HSC transplants are appropriate for high-risk or relapsing acute lymphoblastic leukemia (ALL) patients, and as permanent treatments to chronic leukemias. Despite the considerable risks, HSC transplants have proven to be formidable treatment options with benefits that usually far outweigh the risks. Such success opens up doors to using stem cells to treat other types of diseases.

Stem Cell Treatment of Diabetes

Diabetes is the seventh leading cause of death in the U.S., with 20.8 million US adults and children affected. An estimated 54 million people are also thought to be pre-diabetic (Goldthwaite, 2006). Diabetes has two forms, type-1 (diabetes mellitus, or formerly juvenile-onset diabetes) where the immune system recognizes the insulin-secreting beta islet cells within the pancreas as foreign, and type-2 diabetes (adult-onset) which is linked with obesity, older ages, and sedentary lifestyles. In type-2 diabetes, cells become resistant to insulin from various types of cellular stress, and no longer respond to insulin binding its receptor. Glucose is not taken up from the blood at normal rates to maintain normal glucose levels. Both types of diabetes are characterized by abnormally high amounts of glucose in the bloodstream due to the absence or ineffectiveness of insulin. High blood glucose levels lead to such ailments as blindness, kidney failure, heart disease, stroke, neuropathy, and amputations (American Diabetes Association, 2012).

There are no cures for diabetes, but individuals can lead relatively complication-free lives with proper care. Type-1 diabetes requires constant monitoring of blood glucose levels and administering insulin injections when glucose levels are too high. Type-2 diabetes can usually be controlled through regular diet and exercise, but may ultimately require insulin regulation if the disease progresses further. Currently, pancreatic transplants are available for type-1 diabetes patients, but there is a far greater demand than there is a supply of healthy pancreases. And the dangers of having immunosuppressive medications after the transplant in some cases may outweigh the dangers of the diabetes itself (NIH, 2006).

Stem cell treatments are being pursued as viable, permanent treatments for type-1 diabetes. Non-obese diabetic (NOD) laboratory mice (that simulate type-1 diabetes with an immune attack on islet cells) have been tested with a variety of stem cell treatments. HSCs (that normally form blood cells) have alleviated diabetic symptoms in NOD mice by replacing the autoimmune T-cells that mediate the disease. By using HSC transplants, NOD mice avoided hyperglycemia when their bone marrow was ablated and replaced with stem cells that produce non-autoimmune cells. The resulting NOD mice that underwent the HSC transplant with modified major histocompatibility complexes to prevent their autoimmune conversion remained diabetes-free (Beilhack et al, 2003; 2005).

Other experiments with mouse diabetes models show other ways for obtaining beta islet cells. By expressing a series of developmental transcription factors, differentiated adult exocrine cells in the pancreas can re-differentiate into cells very similar to beta islet cells (Zhou et al., 2008). These new cells are nearly the same as β-cells in form and function, containing the necessary genes for insulin production in response to glucose spikes (Zhou et al., 2008). In addition, undifferentiated mouse embryonic stem (ES) cells can be grown *in vitro* to create insulin-secreting cell clones, and then implanted within mice poisoned with streptozotocin (a chemical that induces diabetes). These animals showed decreased hyperglycemia and weight regain within one week of treatment (Soria et al., 2000). The same restoration of β-cells has been done with induced pluripotent stem (iPS) cells, where β-like cells were derived from skin cells and reprogrammed to a pluripotent state, then differentiated down a pancreatic lineage. The iPS cells reduced hyperglycemia in diabetic lab mice (Alipio et al., 2010).

Using stem cells to treat diabetes has not entered human trials yet, despite the above discussed proof of concepts established with rodent models. Tests with human ES cells have concluded that they can differentiate into β-like, insulin-secreting cells (Assady et al., 2001; Lumelsky et al., 2001). Such cells have been implanted into mouse models and appeared to diminish diabetes symptoms in the streptozotocin model, providing proper insulin responses to glucose fluctuations (Kroon et al., 2008). Human trials of ES cell implants for diabetes may start as early as 2013 (Dance, 2011).

Stem Cell Treatment of Spinal Cord Injuries

Injuries that damage or break the spinal cord usually cause long-term disabilities such as paraplegia and quadriplegia, bowel dysfunction, sexual dysfunction, and in some cases inability to maintain heart rate and core body temperature. Spinal cord injuries (SCIs) are common with high-trauma events such as car accidents, sport injuries, and falls. Direct damage to the cord can also occur from stabs or gunshots. Non-traumatic causes can come from cancer, infections, diseases of the vertebrae, conditions restricting blood flow to the cord, and even birth defects where the spinal cord does not fully develop (van den Berg et al., 2010)

In most accident cases, a spinal injury is assumed by medical staff until definite proof is obtained that one is not present. A patient is immobilized to prevent any further damage to the spine. If cord damage has occurred, surgery may be necessary to stabilize the spine or to remove damaging debris such as bone fragments. High doses of steroids may improve the overall outcome of the injury (Bracken, 2012). Patients with mild injuries have a greater chance of recovering from paraplegia or other disability than those with strong damage to the spinal cord, where such injuries may cause lifelong disabilities and dependence on others for survival.

The application of stem cells may help address the source of the problem - the extensive damage to the spinal cord. Nerve cells in the central nervous system (CNS) (brain cells and spine nerves) do not regrow large portions when damaged. However, at key stages of development, CNS nerves are derived from neural stem cells (NSCs). NSCs were first discovered in 1989 (Temple, 1989), and are thought to replace damaged neurons on a small scale throughout life. Perhaps adult NSCs or ES cells differentiated into neurons could be utilized in repairing spinal cord damage. Such research into the use of such cells has only been recent. Rat spinal cords have been treated *in vitro* with ES cells programmed to become spinal nerve cords motor neurons. The result showed an elongation of axons, the formation of neuron-muscle junctions, and muscle contractions when the cells were co-cultured with muscle cells (Harper et al, 2004). Rat models have been treated seven days after injury with human ES cells, and showed increased nerve tissue repair and a return of motor functions (Keirstead et al., 2005). However, rats treated ten months after injury did not have any response to the treatment, perhaps due to the extensive formation of scar tissue. So, this scarring problem must be overcome for patients treated late in the process. Other experiments using adult NSCs derived from the rodents' brains demonstrated repairing effects under conditions with ample amounts of growth factors and immunosuppressive drugs, but the window to performing such repairs appeared to be limited to very early after the spinal injury occurred (Keirstead et al., 2005). Human embryonic germ pluripotent stem cells have also demonstrated the ability to restore neurological function in a rodent model (Kerr et al, 2003).

Phase-I human clinical trials to treat spinal cord patients began in January 2009 by Geron Corporation to determine the safety of applying stem cell therapies (New York Times, 2009). However, any determination that the procedures are unsafe could severely hinder future patient experiments (New York Times, 2009). The Geron Corporation started these Phase I trials in 2009, but stopped their testing in 2011 as they ran out of money (Akst, 2011). To gather as much information as possible, the patients already treated will continue to be monitored by the corporation (Akst, 2011).

Stem Cell Treatment of Heart Muscle Damage

Heart disease is the number one cause of death in the U.S., with one in every four deaths is heart-disease related (American Heart Association, 2012). A heart attack occurs when the heart stops receiving oxygen from the blood stream, typically from a blood clot. Small amounts of damage to the heart muscles can heal after some time, but the development of scar tissue can inhibit the strength of the heart. Scar tissue does not contribute to the pumping action like healthy muscles, leading to a decreased ability to pump blood, causing further complications.

Stem cells have the potential to play an important role in the recovery of a damaged heart from a heart attack. Adult cardiac stem cell cells (CSCs), ES cells differentiated into cardiac lineages, or even HSCs could provide healthy, functional heart muscle cells and prevent future complications from scar tissue.

Human clinical trials have already started treating patients with heart damage using various types of human stem cells. Trials were conducted where cardiac stem cells (CSCs) were extracted from patients during coronary artery bypass surgeries, and the cells were allowed to multiply, and then injected into the coronary artery in each patient after a mean of 113 days post-trauma. The results showed a greater blood flow from the ventricles, while cardiac infarct sizes decreased by as much as 24% compared to control groups that did not receive cardiac stem cell injections (Britten et al., 2003). Such improvements continued even after one year post-injections.

Tests have also been done injecting human heart attack patients with bone marrow stem cells. HSCs appear to have plasticity – the ability to differentiate into cells that are not typical of such stem cells. Intracoronary injections of mononuclear bone marrow stem cells into the heart showed a 5% increase in ventricle blood output, and various small improvements such as reduced infarct sizes, improved diastolic function, better regional function, and better clinical outcomes (Lunde et al., 2006). If treated with the bone marrow stem cells plus conventional therapies for post-heart attack patients (such as ACE-inhibitors and beta blockers for hypertension and cardiac arrhythmia), the prognosis is even better.

Human ES cells have been shown to be capable of differentiating into cardiac lineages *in vitro* (Kehat et al., 2001). The plated ES cells formed embryoid bodies, and 8.1% of these bodies demonstrated spontaneous contractions like that of heart muscle cells. The cells also showed activation of cardiac-specific genes, and calcium ion fluxes similar to those of normal heart muscle (Kehat et al., 2001). The ES cells were also shown to differentiate into lineages other than just cardiomyocytes, including endothelial cells.

Human adult cardiac stem cells (CSCs) themselves also have the ability to differentiate into other cardiac cell lineages (Beltrami et al., 2003). In rats, multipotent Isl1+ cardiac progenitor cells were discovered that could give rise to every major cell type found in the murine heart, including cardiomyocytes, smooth muscle cells, and endothelial cells (Beltrami et al., 2003; Bu et al., 2009). These adult stem cells could be derived from individual patients, expanded, and perfused back into the same patient, minimizing the chance of rejection. This could open new therapies for heart muscle repair.

Stem Cell Treatment of Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease that usually in individuals 50 years or older (National Parkinson's Foundation, 2012). PD patients commonly have difficulty walking, have a constant shaking in the extremities, and in advanced stages, dementia and other cognitive problems. In PD, brain cells in the *substantia nigra* die. These dopaminergic neurons normally produce dopamine, a neurotransmitter that functions at neuromuscular junctions. Without dopamine, the patients show muscular problems. The cause of death for the substantia nigra cells remains unknown; multiple studies have been done to try to link Parkinson's with possible outside agents, but none are definitive (National Parkinson's Foundation, 2012). There is no known cure for Parkinson's disease. Management of the disease requires a myriad of therapies including prescriptions to directly provide dopamine precursors, increase dopamine levels in the basal ganglia, diet, exercise, and easing of symptom suffering if dopamine treatments become ineffective.

As early as 1988, scientists proposed transplanting fetal brain tissue (from aborted fetuses) into PD patients (Madrazo et al., 1988). Their results showed improvements for younger patients, but older patients had high mortality rates possibly due to the extensive amounts of invasive surgery needed for the transplants. More recent studies have indicated that such transplants, actually have little effect on the PD progression, perhaps because the transplanted cells undergo a phenotypic change to no longer produce dopamine (Obeso et al., 2010).

Stem cells are a candidate for treatment of PD as a possible way to restore dopamine production. Rat PD models have been treated with adult neural stem cells (NSCs), rat and human ES cells, and NSCs derived from ES cells. Transplanted adult NSCs and ES cell-derived neural stem cells have proven the ability to survive, produce dopamine, and rescue the PD phenotype in rats (Studer et al., 1998; Ben-Hur et al., 2004). Mouse ES cells implanted into the striatum of a PD rat resulted in the differentiation and proliferation of dopamine-secreting cells, and a reversal of declining behavior and motor function (Kim et al., 2002; Björklund et al., 2002).

Human patients for PD have been tested with adult olfactory mucosal stem cells (Levesque, 2005) and with adult neural stem cells (Ertelt, 2009). Olfactory mucosal stem cells have plasticity that allows them to be transplanted from the nasal epithelium of a donor into a patient, and the process appears to reverse the effects of PD (Levesque, 2005). The implantation of adult NSCs into patients also reversed PD symptoms, with no sign of brain tumors developing from the rapidly-dividing implanted stem cells (Ertelt, 2009). Although human ES cells have not yet been used to treat a PD patient, they have been shown to be capable of producing dopaminergic neurons in vitro (Perrier et al., 2004).

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Chapter-3: Stem Cell Ethics

Tyler Wood

Now that we have investigated the different types of stem cells and their potential in regenerative medicine, we arrive at the ongoing debate surrounding the ethics of stem cell research. These discussions of morality are not exclusive to stem cell research; with every new scientific breakthrough, society must determine how to adopt the technology and place boundaries on it. In the case of the stem cell debate, it is not new but began in the late 1970's with the advent of human IVF technologies, and the discussions about whether excess IVF embryos could be used for research. The debate expanded considerably in 1998, with the first derivation and growth of human embryonic stem (ES) cells from IVF embryos (Thompson et al., 1998). Some individuals turn to their religious views to help them form their beliefs about embryo research, focusing on when life begins. Because stem cells are a complex issue, it is often difficult for the general public to reach an informed consensus about what kind of research is morally acceptable.

When taking an ethical stance on stem cells, it is important to keep in mind the many different classifications of stem cells; each with a different potency, isolation and replication technique, and application. It is a common misconception that all stem cell isolations result in the destruction of human embryos, but this is only true in the case of embryonic stem (ES) cells (as discussed in Chapter-1). ES cells are easier to isolate and replicate than most adult stem cells, but raise the most ethical concerns being extracted from a 5-day old blastocyst. Adult stem cells come from a patient's own mature somatic cells, not from a human embryo; however they are more difficult to work with and less medically potent.

The debate on embryos and ES stem cells usually boils down to determining when a human life begins. Does it begin at conception, during gestation, or at birth? This chapter will discuss embryo research, IVF clinics, and the different viewpoints of the world's five major religions (Christianity, Judaism, Islam, Hinduism, and Buddhism) on stem cell research.

In-Vitro Fertilization Clinics

In-Vitro Fertilization (IVF) is a procedure in which conception is performed artificially in a clinical laboratory. IVF is generally used in cases of infertility to allow a couple to have a child when they cannot do so naturally. First, the woman is given medication to promote the development of oocytes (mature human eggs). Using a surgical procedure (with some risks), a couple dozen of these eggs are extracted from the ovaries of the female and mated with sperm in a glass dish. The newly formed embryos are then placed in an incubator for a few days to encourage their growth, and then two to four of the healthiest embryos are implanted in the uterus of the female. In most cases, the remaining embryos will be "cryopreserved", or frozen in liquid nitrogen for potential later use. However, some embryos die in the cryopreservation process while being frozen or thawed, and some embryos that are not frozen will eventually die without being implanted in the uterus (Robinson, 2007). The world's first test tube baby, Louise Brown, was born in 1978 (BBC News, 1978), and since then millions of test tube babies have been born.

In 1998, the Center for Disease Control and Prevention (CDC) ran a survey of IVF clinics in the United States with the goal of developing "quality standards specifically designed to assure the quality performance of embryo laboratory procedures" (Center for Disease Control and Prevention, 1999). Many questions on laboratory procedures were asked of the IVF clinics, but the most surprising results came from the handling procedures for embryos that were neither implanted nor cryopreserved (**Table I**).

Table-I: Results of CDC Assisted Reproductive Technology Survey.

	With donor consent		Without donor consent	
Handling Procedure	**Numbers of labs**	**% of labs**	**Numbers of labs**	**% of labs**
Immediately discarded	115	49.6%	15	6.5%
Cultured to demise (allowed to die) & discarded	107	46.1	28	12.1
Donated - research	55	23.7	0	0
Donated - diagnostic purposes	27	11.6	0	0
Donated - training	52	22.4	9	3.9
Donated - another patient	43	18.5	0	0

Handling procedures of unused embryos based on 232 valid responses from U.S. IVF clinics. Multiple disposal procedures results in the percentages totaling over 100% (CDC, 1999; Robinson, 2007).

The CDC survey does not provide the actual number of embryos discarded, but the RAND Law and Health Initiative estimated in 2003 that almost 400,000 embryos have been cryopreserved since the procedure began in the late 1970's, with approximately 88.2% of the embryos being held for fertilization purposes. Some (4.5%) are kept frozen due to lack of patient interest including patient death, divorce, and other reasons. Of the remaining cryopreserved embryos, 2.2% are discarded, 2.3% are donated to others, and only 2.8% (about 11,000) are used for research purposes. Because the healthiest embryos are implanted, many of the frozen embryos do not survive the thaw process, and even more would not be able to develop to the blastocyst stage from which ES cells could be obtained. The RAND study estimated that only about 275 ES cell lines could be created from the available embryos allocated for research purposes. With all of the debate surrounding the destruction of embryos for stem cell research, the fact that many IVF embryos will die regardless of their use is often overlooked in the debate, and is a broader issue regarding IVF technologies.

When deriving new ES cell lines, surplus IVF embryos grown to the blastocyst stage are used to extract the inner cell mass (which contains ES cells). The extraction usually destroys the embryo. So the ES cell debate focuses on the status of a surplus 5-day old IVF embryo, originally created for reproductive purposes, and no longer needed by the couple. Despite common misconception, the ES cell debate does not involve abortions and whether aborted fetuses can be used for research. No *in vivo* procedures are involved for embryos used for research purposes. When deciding when life begins, many people turn to their religious beliefs for answers.

Christianity and Stem Cell Research

Christianity is a broad term used to describe those who believe in Jesus Christ and follow the teachings of the Bible. With approximately 2.1 billion followers, it is the world's largest religion, encompassing 33% of the earth's population (Major Religions, 2005). Many different Christian churches and denominations have evolved over time from the "one, holy; Catholic Church" (Whitehead, 1995). In Matthew 16, Simon Peter and other disciples state to Jesus that "[Jesus is] the Messiah, the Son of the living God", and Peter moved to Rome to lead the Catholic Church soon afterward as the first Pope. The Eastern Orthodox church split from the Catholic Church in the East-West Schism of 1054 AD. The Protestant church split from the Catholic church in the Protestant Reformation of the 16th Century (Kimbrough, 2005).

Catholicism and Stem Cells

The Catholic Church teaches that "human development begins at fertilization when a male gamete or sperm (spermatozoon) unites with a female gamete or oocyte (ovum) to produce a single cell, a zygote. This highly specialized, totipotent cell marks the beginning of each of us as a unique individual" (Moore & Persaud, 2003). In the *Donum Vitae* of 1987, it is proclaimed that human life must be created within the confines of a loving marriage, and may not be created only to be destroyed for research purposes (Catholic Online, 2006). So clearly, the major stance of the Catholic church is against embryo research and ES cells.

However, Pope Benedict XVI endorsed adult stem-cell research in 2006, stating that "research into somatic stem cells merits approval and encouragement when it brings together scientific knowledge, the most advanced technology in the field of biology, and the ethic that postulates respect for human beings at every stage of their existence" (Catholic Online, 2006). Therefore, it can be concluded that the Catholic Church does not support research on embryonic stem cells, but does support new research for working with adult stem cells or for developing pluripotent adult stem cells in regenerative medicine.

Non-Catholicism Christians and Stem Cells

An enormous number of Christian churches worldwide do not associate with the Catholic Church; many of them have conflicting views on stem cell research. Protestant denominations in general have shown to be more open to stem cell research, with the "General Convention of the Presbyterian Church [voting] to endorse embryonic stem cell research" in 2001 (Holland, 2003). One of the main reasons many Christians support ES cell research is that the IVF embryos frozen in fertility clinics will be discarded anyway, and could instead be used to help others in the future.

The more conservative Protestant churches and the Southern Baptist church tend to side with the Catholic Church on ES cell research, but also support adult stem cell research because it does not involve the destruction of embryos and has life-saving potential in medicine (Holland, 2003).

Judaism and Stem Cell Research

Judaism refers to those who believe that God selected the Jews to be the chosen people of the world, and practice the teachings of the Hebrew Bible (Tanakh). Like Christianity, modern Judaism has different religious movements with their own, including Orthodox and Reform Judaism. A rabbi is a teacher of the Jewish religion who generally leads sermons in a synagogue. While Judaism is one of the oldest known religions, and is well known in the United States, there are approximately fourteen million Jews worldwide, comprising only 0.22% of the world's population (Major Religions, 2005).

There is some confusion surrounding the beliefs of when life begins in the Jewish faith. Jewish law states that "…a baby…becomes a full-fledged human being when the head emerges from the womb. Before then, the fetus is considered a 'partial life'" (Simmons, 2008). According to Rabbi Elliot Dorff (one of the leading Jewish experts on bioethics), the Talmud states that during the first 40 days of gestation the human embryo is "merely water". Abortion is discouraged, but is usually acceptable when a mother's health is endangered by pregnancy, and Jewish doctors are allowed to perform abortions within the first 40 days of conception. Rabbi Dorff is in favor of stem research through IVF embryos "for the sacred purpose of saving human lives" (Gilbert, 2010). Therefore, there is no direct violation of Jewish law regarding embryonic or adult stem cell research.

Islam and Stem Cell Research

Islam constitutes 21% of the world's population, with an estimated 1.5 billion followers (Major Religions, 2005). Its followers "submit freely to The Commandments and Will of The One and Only God (Allah)", and are called Muslims (Islam Beliefs and Practices, 2009). They believe that The Prophet Muhammad received the Word of Allah in a revelation, which is recorded in the book of Islam, The Qur'an. The two largest sects of Islam are Sunni and Shi'ite Muslims, with many smaller groups throughout the world.

In Islam, ensoulment is believed to happen in the fourth month of pregnancy. Islamic law makes clear that even though an embryo can *potentially* become a human, it is not an *actual* life until ensoulment occurs. Therefore, destroying a 5-day old IVF embryo outside the womb does not violate their beliefs, and ES cell research is in progress in Egypt and Iran (Weckerly, 2002).

Hinduism and Stem Cell Research

Hinduism is followed by 1 billion people worldwide, comprising about 14% of the population (Modern Religions, 2005). As the world's oldest religion, it began in India, and is a way of life that is different than Western religions. Hindus believe that the soul is immortal and is reborn in a new body after death (Sivananda, 1999). One of the central ideals of Hinduism is compassion toward others; medical research is encompassed by this. However, another ideal in Hinduism is avoiding the harm of all living things. Many Hindus believe that conception is the beginning of the rebirth process, and they are therefore against embryo and ES cell research, as it blocks the rebirth process. However, adult stem cell research is widely accepted due to its potential for regenerative medicine without destroying an embryo (Knowles, 2009).

Buddhism and Stem Cell Research

Buddhism is followed by approximately 376 million people worldwide, comprising about 6% of the population (Modern Religions, 2005). This religion is not based on words or concepts like reincarnation or rebirth, but on a self without birth or death. Thich Nhat Hang, a Vietnamese Zen master, states: “Do not be idolatrous about or bound to any doctrine, theory, or ideology, even Buddhist ones. Buddhist systems of thought are guiding means; they are not absolute truth” (O’Brien, 2006). The Buddhist belief does not specifically address the issue of embryonic stem cell research, but many believe that it agrees with the Buddhist ideals of “seeking knowledge and ending human suffering” (Knowles, 2009). Therefore, there is no firm Buddhist stance on embryo and ES cell research.

Chapter-3, Author Conclusion

Before doing the extensive research on the topic of stem cells for this project, I was against the current methods of their isolation and growth, and was under the impression that all stem cell research destroys human embryos so it was too ethically problematic despite its potential in regenerative medicine. But after coming to understand the concrete differences between ES cells and adult stem cells, my opinion has changed. In the case of ES cells, I believe that IVF patients should be able to decide to donate their own unused embryos to stem cell research instead of the embryos being disposed of or kept in cryopreservation indefinitely. I do not, however, think that donors should be paid money to create embryos for research purposes. ES cells appear to have enormous potential for regenerative medicine, and the answers to some diseases may lie in harnessing these unused IVF embryos.

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Chapter-4: Stem Cell Legalities

Timothy Beane

Controversial technologies need laws regulating them, and stem cells are no exception. The laws regulating stem cell use in this country and abroad are some of the most hotly debated regulations in politics today. Conservative administrations tend to veto any legislation proposing to allow federal funding of embryo research or embryonic stem cells, while other administrations encourage the funding. The purpose of this chapter is to discuss some of these laws in the U.S., describe how some individual states have funded their own stem cell initiatives, and discuss international policies related to embryos and stem cells. This topic is a complex blend of science, ethics, and politics.

Of all of the different types of stem cells, none are more controversial than human embryonic stem (ES) cells. As discussed in earlier chapters, ES cells destroy an embryo when deriving them, so the debate focuses on the status of the embryo at 5-days post-fertilization in vitro when ES cells are isolated. All U.S. administrations support the use of adult stem cells, such as those used in hematopoietic stem cell transplants, as isolating those cells from adult tissues does not destroy an embryo. In the U.S., federal and state governments are responsible for creating the laws that govern the use of embryos and ES cells. Contrary to popular belief, embryo legislation and debates in the U.S. are not new, but began in the late 1970's with the advent of IVF technology and the birth of the world's first test tube baby (BBC News, 1978). In the U.S. the last three presidents and congresses have held widely different views on the debate, and have had strong influences on the way stem cell research is funded. State governments have also played a vital role during times in which the federal government prevented its funds from supporting ES cell research.

Clinton Administration and Stem Cells (1993-2001)

The beginnings of embryonic stem cell research started surfacing in the second term of President Bill Clinton. Abortions were a controversial subject at the time, with the morality of aborting a live human fetus versus the right of a mother to abort a fetus constantly debated socially and politically. And with the development of IVF technology in the late 1970's, debates began in earnest about what to do with the left over frozen IVF embryos not needed by the couple having children.

In 1994, the National Institute of Health (NIH) discussed allocating federal funding for research on embryos left over from *in vitro* fertilization and of embryos specifically created for experimentation. President Clinton at the time agreed with the use of leftover embryos from *in vitro* fertilization for experimentation, but concluded that allocation of federal funding for embryos created specifically with the intent of experimentation would be unethical (Clinton, 1994). However, before Clinton could enact executive legislation, Congress acted to prohibit federal money from supporting any embryo research in the form of the Dickey-Wicker Amendment (104th U.S. Congress, 1995). The federal ban continues to this day, being re-approved and revised every year, although Harriet Rabb helped congress realize that ES cells themselves (already isolated) were not embryos, so the Dickey-Wicker amendment did not directly prohibit ES cell use.

In 1998, the embryo debate reignited with the first isolation of human ES cells from IVF embryos (Thomson et al., 1998) using private funding at the University of Wisconsin. The discovery showed promise of possible future advances in medicine, and prompted the Clinton administration to reconsider some of the financial restrictions placed on embryo research that could stifle ES cell research. Clinton and his administration determined that allocation of some federal funding to the Department of Health and Human Services should be allowed under the Dickey-Wicker Amendment for research, if the ES cell lines were derived with *private* funding first, then *federal* funding could be used to study the ES cells. But before Clinton could act on these ideas, Bush was elected.

Bush Administration and Stem Cells (2001-2009)

The general republican stance on human embryonic stem cells is heavily restrictive. A common party platform for elections includes pro-life stances and "rights for the unborn" that led to the stigma that human embryo experimentation was a denial of pro-life values (Blackford, 2006). President Bush himself stated that he was against the extension of others' lives at the cost of embryos that will never develop, and decided that federal government should not support such research (Bush, 2001).

On August 9, 2001, President George W. Bush signed into law a restriction on human embryonic stem cell research. The restriction called for research to only ES cell lines where the original embryo was destroyed prior to August 8, 2001. In addition, the original embryos must have been created for reproductive purposes, with donor consent to be used in research without any financial inducements (NIH, 2009). This executive law came after the failure of two earlier laws to pass in the Senate in July 2001; one would have placed heavy restrictions on cloning human embryonic cells via "somatic nuclear cell transfer" (transferring an already-existing nucleus into an nucleus-free IVF zygote), and another bill that would have restricted reproductive cloning but allowed somatic cell nuclear transfer. Even if such pro-research bills would have passed both the House of Representatives and the Senate, it is likely that President Bush would have vetoed them (Agnew, 2003).

Despite the initial government claims that over 70 ES cell lines existed qualifying for federal funding, in reality only nine or ten were available to scientists. And most of these could not be used in therapies as they were derived using mouse feeder layer cells, while most scientists preferred "all human" cell cultures for potential therapies (Garfinkle, 2004). Members of both the Senate and House of Representatives sent letters to President Bush asking him to ease his restrictions, but the President decided to stay with his 2001 policies.

In 2005, Congress attempted to pass legislation that would override Bush’s 2001 policy, but President Bush during his second term made it very clear to Congress that his 2001 stance stating that "using life to save life" was immoral and should not have federal support from the taxpayer's money. Any bill that would be presented to him would be vetoed. A bipartisan pro-research bill had enough support to send it to the Senate, but it did not pass with enough support to override any presidential veto (Baker, 2005). A bill was indeed presented to President Bush following his denial to ease up on restrictions, but the bill was vetoed as promised, and Congress failed to override the veto (109th Congress, 2005).

In 2007, President Bush signed Executive Order 13435 that called for the Director of Health and Human Services to provide support and finance for research into stem cells that can be created without the destruction of human embryos (Federal Register, 2007). The decision came during the same year that human induced pluripotent stem (iPS) cells were created in Kyoto (Takahashi et al., 2007), which created pluripotent-like cells without destroying an embryo.

Obama Administration and Stem Cells (2009-Present)

Within three months after being sworn into office, President Barack Obama in an Executive Order reversed the 2001 ban on federal funding for embryo research (Wilson, 2009; Hayden, 2009). President Obama's decision came after a long line of Democratic party pledges to allow for greater funding for stem cell research. Obama recognized the polls showing that many Americans believe federal funding should be allowed for embryo research. However, like former President Bush, President Obama is against *reproductive* cloning (Associated Press, 2009). Obama also required the embryos to be obtained only from surplus reproductive clinic embryos, with donor consent (embryos could not be created only for research purposes).

NIH was asked again to provide guidelines for embryo research. The NIH draft guidelines of 2009 included fewer restrictions on information that must be supplied to embryo donors and lessened oversight by various organizations (Majumder et al., 2009). However, challenges to the NIH recommendations arose from Christian advocate groups that the President's decision to allow federal funding was in direct violation of the Dickey-Wicker Amendment which was still law. A Washington D.C. circuit court ruled 2-1 in favor of the NIH guidelines that the federal funding was not in violation of the Dickey-Wicker Amendment due to ambiguous definitions of "research" and “embryo”. The NIH was barred from funding researchers with federal funds for the *derivation* of human embryos, but they were not barred from funding the research of the ES cells themselves (Kaiser, 2011).

Other challenges faced during Obama's current administration arose from the lack of funding for embryo donors, and tight restrictions that are still in place for acquiring embryonic stem cells. Legal battles over government funding have left the possibility of using blastomeres (a stage in embryo development where the stem cells can be extracted without destroying the embryo) in a stasis that prevents further research, while other countries such as Spain are capitalizing on such a discovery to create new ES cell lines where the embryo was not destroyed (Ledford, 2011). Tight Obama restrictions also inhibit research of specific types of stem cells such as those donated with genetic screens for diseases like cystic fibrosis and Parkinson's. The NIH had to bar researchers from using such cells because the donors were given consent forms that gave away too many rights, and contained broad, ambiguous language (Stein, 2010).

State Stem Cell Laws

During the ban on federal money for embryo research, individual states took matters into their own hands to fund the research on their own. Most U.S. states enacted their own laws on stem cell research, either allowing it or preventing it. Some states have no stem cell policies at all. A majority have complete bans on ES cell research (NCSL, 2008). However, some states such as Massachusetts, California, and New Jersey are expanding their capacities for stem cell research through large state-sponsored grants, legislature for eased restrictions on research, and facilities to provide stem cells, research, and training for those wishing to use stem cells on an international scale.

Massachusetts is a state considered to be one of the most liberal in the country. In 2005, a bill allowing for ES cell research in Massachusetts was vetoed by Republican Governor Mitt Romney, who cited moral and ethical issues, similar to President Bush's stance that "destroying life [embryos] to save life" was not something that should be federally funded. But in this case, Romney’s veto was quickly overturned in the state legislature by a strong vote, and was made into law (Daily News Central, 2005). The level of funding was later decided under Democratic Governor Deval Patrick, who planned a $1.25 billion funding pool for stem cell research over the next ten years, including plans to build one of the largest stem cell repositories in the world at the University of Massachusetts that would provide stem cells lines and training to research organizations internationally (Marks, 2007; Shelton, 2007). The bill for the funding was passed in 2008 with overwhelming support from state legislation. The stem cell repository at the University of Massachusetts was established in 2007, and has continued stem cell operations since, even establishing partnerships with international stem cell banks such as the United Kingdom stem cell bank (Fessenden, 2011).

New Jersey was one of the first states to allow for state funding for embryonic stem cell research, and is a hub for many biomedical sciences and pharmaceutical companies. More than $10 million were allocated in January 2004 (NJCST, 2007; Wadman, 2008) for stem cell research, including plans to build two state-of-the-art stem cell facilities. The project was spearheaded by Democratic Governor Jon Corzine with the intentions of making New Jersey a forerunner of stem cell research in the country. However in November 2007, additional funding for research was shut down by voters in a ballot due to the concerns of raised taxes (Holden, 2007). The defeat led to decreased funding for researchers and under use of some of the newest facilities constructed only months prior. New Jersey already allocated $270 million in total for stem cell projects, including individual grants for research and facilities, but the overturn in legislature prevented over $400 million more from becoming available in grants (Wadman, 2008). Some pro-stem cell groups in New Jersey plan on fighting a second time to try to approve more funding for stem cell initiatives in the state.

California is another traditionally liberal state, and also the third most populated state in the Union. Proposition 71 in 2004 was an open-ballot question proposed to the people of California determining whether nearly $3 billion in bonds for funding stem cell research over a ten-year period should be allowed (LAO, 2004). The proposal also called for a new commission to oversee stem cell grants and research, named the California Institute for Regenerative Medicine (CIRM). Proposition 71 passed with 60% of voter turnout in favor of the proposal. In 2006, the CIRM awarded its first grants, $12 million for training programs. By December 2007, CIRM had given out almost $400 million in grants, with promises of awarding another $262 million in grants to major stem cell facilities (Hayden, 2008). By 2008, California was the leading state in dollars supporting ES cell research (Wadman, 2008). By 2011, over 500 grants had been awarded to various academic and research institutions (CIRM, 2011) with plans to use $30 million to establish connections with various companies, and fund corporations involved in biomedical sciences, and $38 million to fund educational grants to promote life science education to children (GEN, 2011).

Despite some overwhelming state support for stem cells, many states do not have funding for stem cell research, and some states outright oppose the research, such as North and South Dakota, Louisiana, and Arkansas (Wadman, 2008). The state of Mississippi is preparing a ballot on deciding when in development does a human gain "personhood". If the ballot passes, the state constitution would be amended so that fertilized eggs at the moment of conception would gain equal human rights, effectively outlawing abortion in all circumstances and outlawing all embryo research, as well as putting doctors in difficult positions with IVF procedures for infertile couples (Young, 2011).

Other Nations

The United States is not alone when it comes to stem cell research. Dozens of other countries have taken interest in the field, citing the possible benefits to human health, as well as the economic benefits that could transpire through breakthroughs and possible treatments. Some countries have fewer restrictions on ES cell research than the U.S., and some scientists fear that the restrictions are putting the U.S. behind in the stem cell race (Schmickle, 2008).

A powerful nation researching stem cells is China. China's economy is only second to the U.S. and is steadily increasing. The Chinese generally have a strong work ethic and a drive to become a leading power on the world stage. China does not have the same moral constraints against ES cell research as some Western nations like the U.S. (Barnes, 2006). Western scientists and biotech companies may be drawn to China due to their research liberties, but some companies are reluctant due to China’s vague intellectual property laws that are not as strong as most Western nations, so new discoveries there may not be protected. The only possible repression of any scientific advancement in China might come from its relatively poor national infrastructure (Murray et al., 2006). The communist government may not have the appropriate infrastructure for supporting huge scientific advancements, but the future certainly points to improvements. As of 2009, new regulations for Chinese research institutions using stem cells required the facilities have labs dedicated specifically for stem cells, qualified and experienced researchers with at least three years of experience working with stem cells, and have appropriate equipment and quality controls in place. Failure to do so would result in disapproval of granting any license to work with stem cells (Stem Cell Transplantation Department, 2011).

Europe has been an important source of scientific progress since the 1800's. The European Union does not have a central stance on stem cells; rather each individual country has their own policies. The United Kingdom and Belgium allow for ES cells to be taken from embryos left over from *in vitro* fertilization, and in some rare circumstances for embryos to be created specifically for research. Germany and Italy on the other hand do not allow extraction of

ES cells from human embryos, but do allow importation of ES cell lines for research (EuroStemCell, 2007). Other European nations are generally neutral over the issue, or have no specific laws banning the research. The contrast between the United Kingdom and Germany are apparent through actions in prohibiting or allowing ES cell research. The United Kingdom announced the creation of a £30 million center for stem cell research, in part to promote research and to help stimulate their dampened economy (Neate, 2011). Alternatively, Germany lead a campaign with other nations to convince members of the European Union that funding should not be provided to nations that allow the destruction of embryos for research (Deutche Well, 2006).

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PROJECT CONCLUSIONS

Stem cell research has opened many doors for creating new therapies to combat some of the worst ailments, such as leukemia, Parkinson's disease, diabetes, and cardiac damage. The possibilities to some scientists seem endless, as stem cell research continues to shed light on human development and tissue regeneration. However, the controversy mostly lies with the use of embryonic stem (ES) cells derived from human embryos. Embryo destruction prompts ethical debates over the loss of potential life, and the use of one being to save another.

The authors of this IQP believe that stem cell research provides a number of possible treatments that should be researched, but with limitations to keep boundaries. Adult stem cells do not appear to harm the individual they are extracted from and pose few ethical issues, so the authors believe such cells should be used for therapies if possible. The authors believe that embryonic stem cells should only be derived from leftover embryos from *in vitro* fertilization procedures, with donor consent, rather than disposing of biological material (or leaving it permanently in cryopreservation) that could potentially save lives. Donors should not be awarded incentives, nor should embryos be created solely for the purpose of research, except in a rare case where a specific type of stem cell is desperately needed and is not available otherwise. Education about this complex topic should also be taught to the public, educating them about the potential of stem cells, about ongoing research, and the current laws set out by the state and federal governments.

To help battle ethical concerns, all efforts should be made to prevent embryo destruction upon stem cell extraction. Induced pluripotent stem (iPS) cells should also be further researched to more fully understand their exact potency, and whether protocols can be developed to minimize any DNA damage during the reprogramming process. If, as some legislators fear, iPS cells turn out to be totipotent instead of pluripotent, we agree that iPS would then have the same ethical concerns as embryo-derived ES cells, but this likely will not prove to be the case based on current data. The authors also agree with current U.S. legislation banning *reproductive* cloning, and argue that no genomes should be used to clone a human being. Hopefully through such constraints, research can continue to bring about new cures for some of the worst human diseases.