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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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ABSTRACT

The intention of this IQP is to provide awareness of the subject of stem cells, to help educate the public on the ethical and legal issues of this technology, and to increase exposure to the technological advancements of this field. To achieve this goal, stem cell types and sources were researched, along with present and future applications of stem cells in regenerative medicine. Religious and political controversies were also analyzed, and some shared misconceptions. We then draw conclusions concerning our shared ethical, legal, and moral beliefs surrounding stem cell research.

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PROJECT OBJECTIVE

This IQP was performed to explore a rising controversial subject in the medical field, stem cells. The following chapters will discuss many aspects regarding this topic to investigate the effects of technology on society. It starts by explaining stem cells themselves, describing their classification, type, and the sources we obtain these stem cells from. The following chapter transitions into the applications of these stem cells, to highlight breakthrough treatments that have been, or will be, obtained from stem cell research. In Chapter 3, the ethical perspectives of this subject are brought into play, introducing why stem cells are such a controversial topic today. Next, we discuss the political aspects of stem cells and the influence of legal restrictions on embryo and stem cell research. Finally, the authors describe their own views on the matter in the project conclusion.

Chapter-1: Stem Cell Types and Sources

Bielinsky Brea

In this modern age, scientists have made critical advances in the field of biology. The existence and functions of stem cells is one of those feats. A key distinction between stem cells and regular cells is that stem cells are long-lived and undifferentiated; depending on specific conditions they can develop into specialized organs or tissue. This function allows the human body to replace and repair old cells, maintaining homeostasis. Because of the discovery of stem cells, understanding human development was made possible. Stem cells are the basis of the field of regenerative medicine and hold potential for treating a variety of diseases. But some types of stem cells are very controversial; embryonic stem (ES) cells destroy an embryo to obtain them. So, ethical concerns have hindered federal funding for ES cell research. More people are now reconsidering the benefits of regenerative medicine, as more information is released on the subject. Myths that embryonic stem cells are the only kind of stem cell being studied are also being dispelled. Stem cells, whether isolated from adults or embryos, have been used to treat various diseases. Not unlike the discovery of DNA, they completely changed the way scientists regarded the human body, and one day their stigmas will hopefully cease to exist. The purpose of this chapter is to list the various types of stem cells, explain that not all kinds of stem cells are the same, and establish an introduction to ethical and legal issues for later chapters.

Stem Cell Potentials

A very important characteristic of stem cells is *potency*. Potency is the trait that distinguishes the ability of a type of stem cell to develop into other types of cells. The more potent a cell, the greater number of tissues it can create. The five categories of potency are:

Totipotent, Pluripotent, Multipotent, Oligopotent, and Unipotent. *Totipotency* is the ability to differentiate into every possible cell type and tissue (all cells of the adult and its surrounding tissues in the placenta). Only newly fertilized eggs through the 8-cell stage are considered totipotent. Totipotent cells cannot self-replicate. The human zygote has the capacity to become countless cells, including extra-embryonic tissues such as the placenta, but this trait is lost once the embryo's cell division reaches the 8-cell stage about three days after fertilization (**Figure-1**) (Panno, 2010). Following the 8-cell stage, subsequent cells are not totipotent. As the embryo divides to about 5-days, it forms a hollow ball of about 100-150 cells termed the blastocyst (diagram left). At this point, the first stages of differentiation have begun; the blastocyst contains an outer layer of cells (the trophoblast) and an inner cell mass (ICM). Cells of the ICM are characterized as *pluripotent*. Pluripotency is the ability to differentiate into almost all cell types of the adult organism. Embryonic stem cells are considered pluripotent.

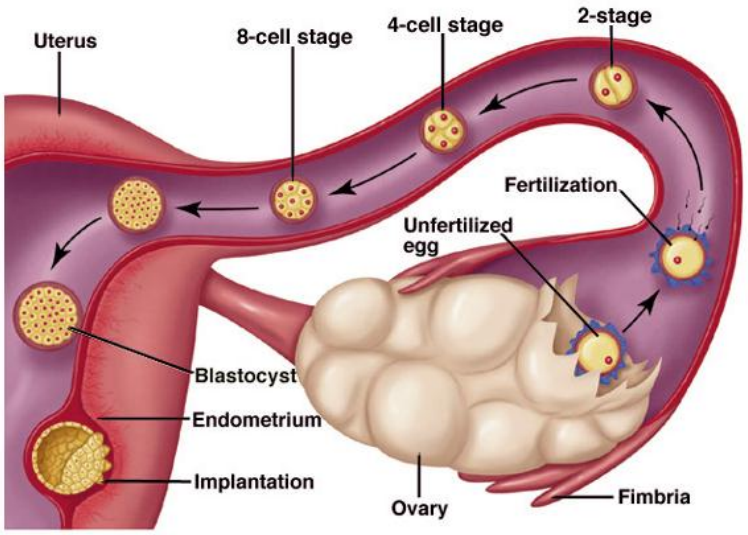

Figure-1: Diagram of the Stages of Early Embryo Development. (**McGraw-Hill 1997**)

A *multipotent* stem cell, derived from the pluripotent cell by further differentiations, can develop into some types of related cells, but not all. Examples of multipotent stem cells include hematopoietic stem cells (HSCs), which are taken from the umbilical cord or bone marrow, and mesenchymal stem cells (MSCs), also taken from bone marrow (Frequently Asked Questions, 2006). HSCs can become all the cellular components of blood (platelets, red blood cells, and white blood cells), while MSCs differentiate into bone cells, cartilage cells, and fat cells. *Oligopotent* stem cells can differentiate into a few types of cells. A lymphoid stem cell is an example, only giving rise to blood cells of the lymphatic system, such as T-cells, but not platelets. Lastly, a *unipotent* stem cell can only develop into one type of stem cell. Unipotency is the ability to produce only cells of their own type. Epithelial stem cells produce skin cells in order to replace older ones (Panno, 2010).

Embryonic Stem (ES) Cells

The blastocyst, comprising of an inner cell mass (embryoblast) and outer trophoblast, contains the stem cells necessary for embryogenesis. On the fifth day post-fertilization the blastocyst is formed. The blastocyst is a hollow structure containing a cluster of cells. The inner cell mass contains the cells that mature into an embryo. Embryonic stem (ES) cells are enclosed in the embryoblast, and are characterized as pluripotent. ES cells can differentiate into any of the three germ layers: ectoderm, endoderm, and mesoderm. The ectoderm, the external layer, differentiates into the nervous system and epidermal tissues. The endoderm, the internal layer, becomes the lungs, the gastrointestinal tract, and interior stomach lining. The mesoderm, the middle layer, develops into bone, blood, muscle, and the urogenital system (Kirschstein and Skirboll, 2001). Unlike totipotent cells, ES cells can be grown indefinitely in an ES cell lines

(**Figure-2**) (Frequently Asked Questions, 2006). This capability is particularly valued for use in human regenerative medicine which requires large numbers of cells.

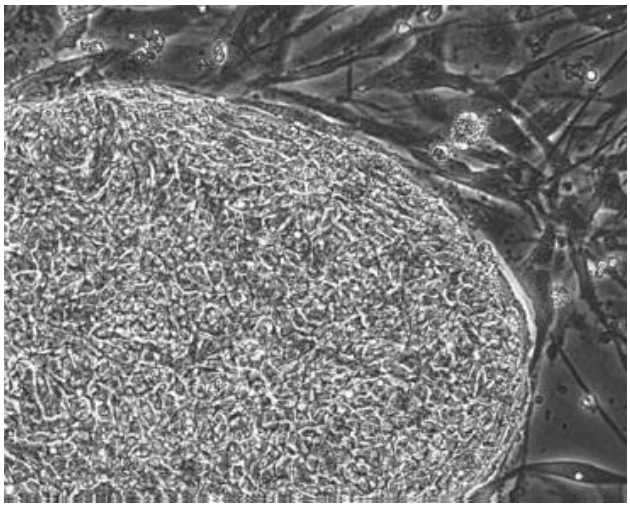

Figure-2: Photograph of an ES Cell Line. (California Institute, 2009)

Human ES cells were first isolated in 1998 from IVF embryos (Thomson et al., 1998). During *in vitro* fertilization (IVF), egg and sperm are combined in a laboratory dish, and grown for about 5 days to generate embryos. In reproductive clinics, the embryos can be implanted into the uterus to create a living being. As it is impossible to determine how many embryos will be required, surplus IVF embryos are usually created. Since the advent of IVF and the birth of the world's first test tube baby Louise Brown (BBC News, 1978), the debate has focused on what to do with the extra IVF embryos. Scientists want to use them to create ES cell lines. This can only occur with explicit written consent from the parents. The blastocyst typically consists of around 100-150 cells, and is about the size of a grain of sand (Regenerative Medicine, 2006). The inner cell mass (embryoblast) is removed via a needle, and placed into a laboratory dish containing nutrient-rich culture medium. Due to stem cell divisions, the ES cell culture must be relocated to fresh subcultures due to lack of growing space. This enables a stem cell line to be

made, and because of their self-renewal, large numbers of embryonic stem cells can be formed. For future use, the cells can also be frozen (Regenerative Medicine, 2006). Acquiring ES cells usually results in the death of the embryo (Bethesda, 2010), thus their usage is extremely controversial and will be further discussed in Chapter 3.

Induced Pluripotent Stem (iPS) Cells

Due to the controversial nature of ES cells, scientists have sought methods for preparing pluripotent stem cells without destroying an embryo. Induced pluripotent stem (iPS) cells are adult skin fibroblast cells genetically altered to contain 2-4 transcription factors that de-differentiate the cells to a pluripotent-like state. The transcription factors are combinations of beneficial genes introduced through retroviruses, plasmids, or directly via the protein (Frequently Asked Questions, 2006). iPS technology is a recent innovation; it was first produced in mice by molecular biologist Dr. Shinya Yamanaka, at Kyoto University, Japan in 2006 (Takahashi et al., 2006; Yamanaka, 2007). His first test subjects were mice. He collected skin fibroblast cells to later reprogram them using four key pluripotent genes: c-Myc, Klf4, Oct-3/4, and SOX2. The genes were delivered using a retrovirus. The following year, Yamanaka produced iPS cells from human cells (Takahashi et al., 2007; Yamanaka, 2007). Altering specialized cells into apparent pluripotent cells might fully negates the need for using ES cells, so this finding remains one of the most exciting results in stem cell research of the past decade. In 2009, scientists showed that iPS cells can generate adult mice, so they appear to be potent cells (Boland et al., 2009). Another benefit of iPS cells is they are genetically identical to the donor of the fibroblast cells that was re-programmed, so this process could be used to make patient-specific cells for therapy.

Although the initial protocols used *c-myc* oncogene that tended to cause cancer in mice injected with iPS cells, the *c-myc* component has since been eliminated (Boland et al., 2009).

But not all scientists are convinced iPS cells are as potent as ES cells. Some scientists argue iPS cells grow more slowly, and have DNA mutations which could affect their ability to be used for therapy (Gore et al., 2011; Lister et al., 2011).

Parthenogenetic Embryonic Stem Cells

Parthenogenesis is the biological phenomenon where an egg develops into an embryo without sperm to fertilize it. It is also known as asexual reproduction, and it occurs naturally for some amphibians, insects, plants, and other organisms. Mammalian parthenogenesis does not exist, and must be accomplished artificially *in vitro* through the use of chemicals mimicking the sperm's arrival. Primate embryonic stem cells were obtained via parthenogenesis in 2001 (Mitalipov et al., 2001; Cibelli et al., 2002), and in 2007 for humans (Kim et al., 2007). A parthenogenetic ES cell from a monkey was even found to be able to create a nerve cell able to release dopamine which in theory could be used to combat Parkinson's disease (further discussed in chapter 2). To isolate parthenote ES cells, mammalian eggs (oocytes) are stimulated with calcium, or strontium chloride, or electrical current to mimic fertilization (**Figure-3**, lower diagram). The egg begins dividing but does not extrude one set of chromosomes, so it remains diploid. The parthenote embryo is grown until the blastocyst is formed, then ES cells are removed as usual (Berevini, 2008). No further division occurs beyond the blastocyst stage because the original egg was not fertilized, so the embryos cannot develop further into a living human. Parthenogenetic ES cells also maintain their self-renewal trait like ES cells, but the

genetic material is only from the female donor. So this process might be used to make ES cells compatible with a female patient.

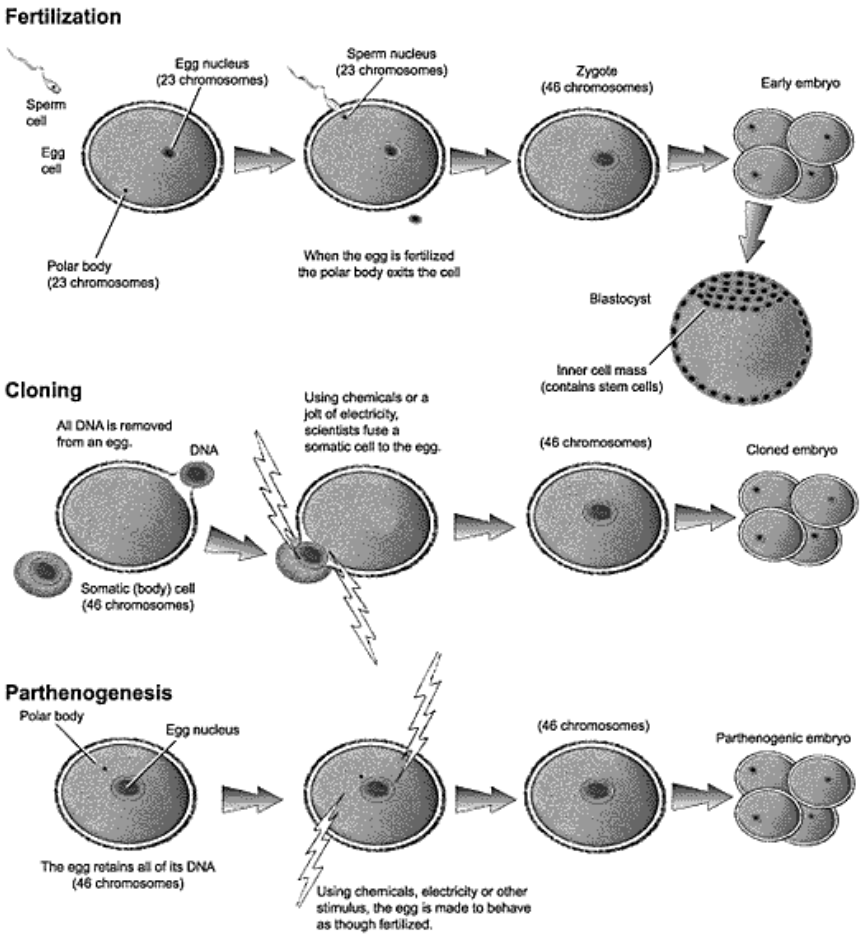

Figure-3: Comparison of Normal Fertilization and Parthenogenesis. (Weiss, 2001)

Some argue that parthenogenetic ES cells are more moral than ES cells because of the fact that the embryos cannot develop into babies, so a parthenote embryo might have less status. These cells may have ethical problems from a religion perspective. Parthenogenesis comes from the Greek words *parthenos* and *genesis*, meaning virgin birth (development of the egg without sperm). People, especially those of the Christian religions, have found this to be extremely upsetting because Christ was born of virgin birth as well.

Adult Stem Cells

Adult stem cells (ASCs) are infrequent (rare) undifferentiated cells found among differentiated cells in tissues or organs that have already been established (Bethesda, 2010). They are not exclusive to adults, they can also be found in children, but the term distinguishes them from embryonic stem cells. Adult stem cells are also called somatic stem cells. ASCs can divide infinitely and rejuvenate damaged tissues. They have the ability to completely regenerate an entire organ just from a few cells. Most tissue and organ cells have a finite lifecycle. The Hayflick limit describes the maximal number of cell divisions typical for a given cell. As a cell divides, the ends of its chromosomes (the telomeres) shorten. The speed at which this occurs varies depending on the cell type, and once the Hayflick limit has been reached, the chromosomes become degraded and apoptosis (cell death) ensures. Adult stem cells tend to have an enzyme (telomerase) which helps them maintain their telomeres during cell divisions, making the cells long lived.

ASCs are found in the amniotic fluid, umbilical cord, and body tissues (**Figure-4**). They are either omnipotent or unipotent. They generally have a lower level potency than embryonic stem cells and are harder to isolate and reproduce. ASCs such as HSCs and MSCs contain higher levels of potency due to the fact that they can differentiate into other kind of tissue cells different than that it originated from (Kirschstein and Skirboll, 2001). Many different processes can be used to isolate ASCs, and they can be frozen until needed.

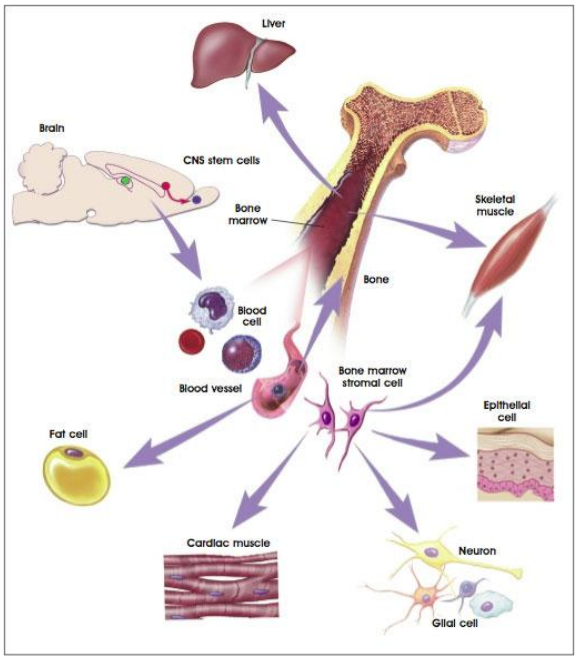

Figure-4: Diagram of the Location of Adult Stem Cells. (NIH, 2001)

Adult stem cells are one of the least debated stem cell topics, especially compared to ES cells, since no human embryo is terminated. This alternative makes them popular for study, and hematopoietic stem cells are the best characterized of all stem cell types. ASCs have been used successfully in human therapies for many years. ASCs are rare within tissues, so it is very challenging to extract them. For ease of tracking, the stem cells have two ways of being marked. The cells can either be labeled *in vivo* while studying their potential (they are label retaining long lived cells), or they can be labeled in cell culture and transplanted into another organism to study whether it creates new tissue (NIH Stem Cell Information, 2006). Another benefit of ASCs is they can be taken directly from the subject to avoid undesirable immune system responses.

Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are multipotent, and can generate every kind of blood cell (**Figure-5**). They have been researched for more than 60 years, so are the best characterized type of stem cell, and one of the least controversial. HSCs have saved more lives than any other kind of stem cell in bone marrow transplants, and have been used to treat both genetic and blood diseases, cancers, and immune system deficiencies like leukemia (Viacord, 2011). HSCs are traditionally collected from the bone marrow, but more recent applications collect it from the peripheral blood or umbilical cord blood. HSCs tend to contain the cell surface marker CD34, and this marker was the first one used to purify them. HSCs are very tough to identify and separate; they behave like white blood cells. HSCs exist in two categories, short term stem cells and long term stem cells. Short term stem cells, also known as precursor cells, have a finite capacity of self-renewal, while long term stem cells can regenerate forever (Panno, 2010).

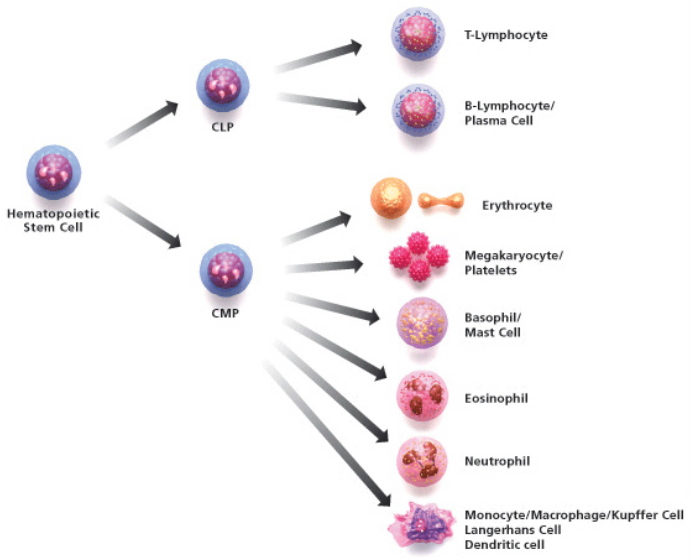

Figure-5: Diagram of Hematopoiesis. (Sigma, 2011)

Bone marrow contains the most HSCs, but the cells are rare; only 1 in 10,000 cells in the marrow are hematopoietic. Bone marrow cells are traditionally extracted from the hip, but the process of extraction is painful, requiring a large needle to remove the marrow. Because of this, scientists have developed other methods for HSC extraction. Peripheral blood is relatively easy to prepare hematopoietic stem cells from compared to bone marrow extraction. HSCs are rare in the peripheral blood in the veins and arteries, but scientists have developed a process to cause HSCs to move from the bone marrow to disperse throughout peripheral blood, thus increasing the final concentration (NIH, 2006). Umbilical cord blood is also an excellent source of HSCs. Cord blood can be collected immediately and painlessly after child birth, and is frozen for possible future use (Viacell, 2006). HSCs in cord blood are more primitive than in marrow, so these HSCs are more effective at self-renewal and have a lower risk of rejection.

Neural Stem Cells (NSCs)

First discovered in the brain in 1967 (Asian Stem, 2012), and later in the spinal cord, neural stem cells (NSCs) are heavily researched so that scientists can hopefully use them to repair brain and spinal cord damage. NSCs can be cultured *in vitro* and they share analogous multi-potent properties to HSCs, such as developing into multiple types of cells once injected into the bloodstream (Mulchandani, 2010). NSCs can differentiate into three different kinds of cells: neurons (nerve cells) and two major categories of "non-neuronal" cells: astrocytes and oligodendrocytes (Frequently Asked Questions, 2006) **(Figure-6)**. Astrocytes are common cells that support the brain structure. Oligo-dendrocytes support the neurons only. Following tissue damage in the brain, neurogenesis occurs in the hippocampus and can spread to the neocortex, so NSCs are located in the hippocampus (NIH, 2006). NSCs are also found in the sub-ventricular zone of the brain. NSCs have also been extracted from human brains after death. It is theorized

that NSCs might be used to treat neurodegenerative diseases such as Parkinson's and Alzheimer's. The problem is that NSCs are rarely active, so studying how to activate them is important.

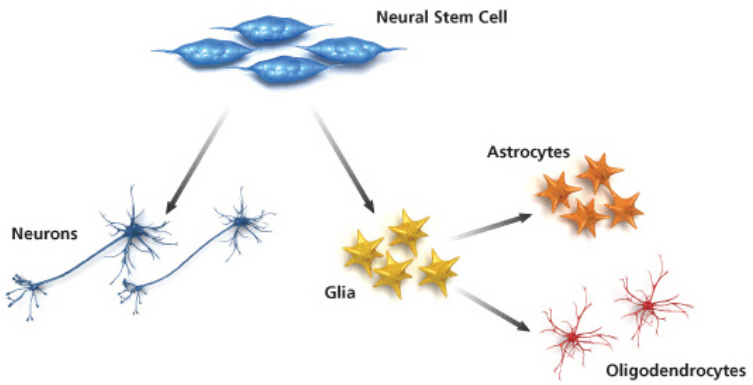

Figure-6: Diagram of the Differentiation of Neural Stem Cells. (Sigma, 2011)

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are another type of multipotent stem cell also located in bone marrow. MSCs can differentiate into bone, cartilage, fat cells, ligaments, muscle, nerve cells, skin and tendons (Friedenstein et al., 1976). They are separated from the marrow with less difficulty than hematopoietic stem cells due to their affinity for plastic tissue culture dishes (Nardi and Meirelles, 2006). MSCs can be distinguished from HSCs due to cell surface markers. They express on their surface CD73, CD90, and CD105, and they lack CD11b, CD14, CD19, CD34, CD45, CD79a, and HLA-DR markers (Nathalbrawn, 2008). In addition to bone marrow, mesenchymal stem cells can also be acquired from blood, lung, placenta, teeth, and umbilical cord. MSCs can be harvested with ease, and they contain the potential to specialize into numerous types of cells.

Epithelial and Cardiac Stem Cells

Epithelial tissue appears to have adult stem cells that facilitate tissue replacement. These epithelial stem cells (ESCs) are located in skin, the digestive tract, and the eye. The majority of ESCs are unipotent, but some are multipotent. ESCs differentiate into absorptive cells (absorbing vital nutrients and vitamins along with lipids, entero-endocrine cells (which produce hormones), goblet cells (which form mucin), and paneth cells (which maintain the gastro-intestinal barrier). For a mammal, epithelial cells comprise up to 60% of all differentiated cells (Blanpain et al., 2007). These ESCs are also thought to be the cause of intestinal and colon cancers.

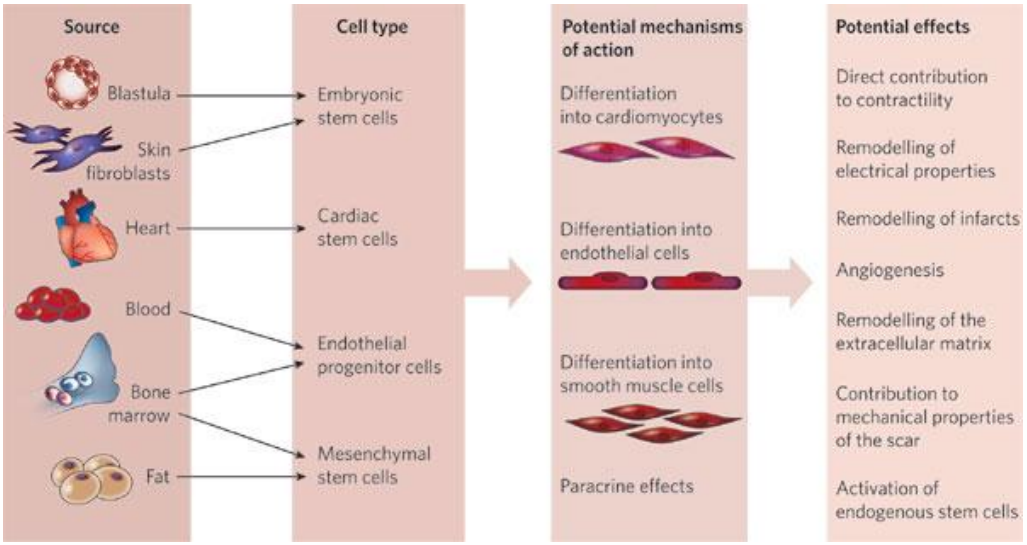

Figure-7: Diagram of Adult Stem Cell Types. (Segers, 2008)

Cardiac stem cells (CSCs) are multipotent, and primarily differentiate into heart tissue. It was previously assumed that heart cells could not regenerate after birth (Touchette, 2003). CSCs were initially shown to contain the surface marker c-Kit+ (Beltrami et al., 2003), and were later shown to also contain Isl1+ (Laugwitz et al., 2005). CSCs have already been shown to improve

heart function in patients following heart attacks by redeveloping heart muscle (Bolli et al., 2011). CSCs have been found to differentiate into epithelial and muscle tissue **(Figure-3**, upper diagram). Cardiomyocytes (heart muscle) of rats have been repaired using CSCs of other mammals, and in one case, human CSCs injected into rats facilitated the formation of a chimeric heart, comprising both human and rat features (Bearzi et al., 2007).

Chapter-1 Conclusion

Stem cells have been researched for over 50 years, and contrary to common belief, not all stem cells are alike. Only deriving embryonic stem (ES) cells destroys a viable embryo. Many different types of adult stem cells exist. Hematopoietic stem cells are among the best characterized of all stem cell types, and have already been used for decades to save human lives in bone marrow transplants. Advocates of stem cell research are optimistic that stem cells and their regenerative potential will be applied to new diseases as we learn more about how to grow and differentiate various types of stem cells. This chapter's goal was to document each type of stem cell, and clarify their differences. The next chapter will discuss the many of the life improving applications that stem cells have provided.

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Chapter-2: Stem Cell Applications

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After having discussed the various types of stem cells, it is time to explore how we are using them. Their uses weigh strongly into the topic discussed later of whether we *should* be using these cells, as it directly relates to their *benefits* to society. Stem cells are being studied in regenerative medicine for treating many diseases. Such cells are already being used to cure some types of leukemia and lymphomas, and are being investigated as potential cures for other diseases such as heart disease, diabetes, cancer, Parkinson's disease, and Alzheimer's disease. (Chapman, 1999). Some types of stem cells (like hematopoietic stem cells) were discovered a long time ago, and are already being used to treat diseases in patients, while other types (like pancreatic stem cells) have only recently been discovered. This chapter will investigate stem cell applications for five chosen example diseases. Acute myeloid leukemia is already being treated with hematopoietic stem cells with high effectiveness. For diabetes, scientists have already shown that human ES cells can be differentiated to produce insulin. Cardiac stem cells and mesenchymal stem cells are already being tested in human heart attack patients. Neural stem cells are being used in animal models to treat Parkinson's and strokes. Less progress has been made in human patients with embryonic stem cells because of ethical issues and a lack of federal funding in the recent past. Each disease comes with a different set of roadblocks that must be overcome.

Hematopoietic Stem Cell Treatment of Leukemia

The transplantation of hematopoietic stem cells (HSCs) has been researched for over 50 years, and has come an established protocol for "reestablishing hematopoietic function in

patients with damaged or defective bone marrow or immune systems" (Samavedi, 2011). This use of stem cells is the best characterized; the world's first human bone marrow transplants to treat leukemia were performed fifty five years ago in 1957 (Thomas et al., 1957). Today, it is commonplace to see patients with hematological malignancies undergo an HSC transplant. Acute myeloid leukemia (AML) is a blood cancer that can advance very quickly if left untreated. AML is the most common type of blood cancer in adults (Acute Myeloid…2012). In general,

> "In a healthy person, bone marrow makes the blood stem cells that mature into infection-fighting white blood cells, oxygen-carrying red blood cells and blood-clotting platelets. When a person has AML, cells called myeloid stem cells usually develop instead into a type of immature white blood cell called myeloblasts, which never go on to become healthy, infection-fighting white blood cells." (Acute Myeloid….2012)

AML can also result from the proliferation of mutated stem cells that differentiate into leukemic red blood cells and platelets. The lack of healthy white blood cells in an AML patient makes them more vulnerable to infection.

The transplantation of stem cells to treat leukemia is done by withdrawing HSCs either from the patient themselves (autologous transplantation) or from a donor that either fully matches or partially matches the patient genetically (allogeneic transplantation). Bone marrow is the traditional source of HSCs, but more recently peripheral blood is used as a source after mobilizing the movement of HSCs from the marrow to the periphery using hormones (Korbling and Freireich, 2011). A third source of HSCs is umbilical cord blood, donated by the parents at time of birth (Gluckman, 2009). The stem cells are taken from the umbilical cord blood when a baby is born, and stored frozen until needed. Because these stem cells are not as mature as the cells taken from bone marrow, there is less of a need for genetic matching, and less graft versus host disease (Bone Marrow Transplant, 2012). In most myeloid leukemia cases, chemotherapy or radiation are used, either in high or low dose treatments, to help destroy the patient's diseased

hematopoietic system. A low dose is primarily used with older patients or patients already having other health problems. Higher doses (myeloablative treatments) are used to kill almost all of the myeloid cancer cells in the patient's bone marrow. After the initial remission of the leukemia, the transplant is done. According to John Koreth of the Dana Farber Cancer Institute:

> "First complete remission does not mean you are cured. It doesn't mean that you have eradicated every last cancer cell; in fact, we know you haven't. If we stop therapy [at this point], then almost invariably the disease will relapse, and you die from a relapse of the leukemia." (Reinberg, 2012)

Following the initial remission, the patient receives either more radiation or a stem cell transplant. In the same article Koreth sites how recent research has showed that allogeneic transplants with matched donors have been proving more successful. In one study done in 1971-72 at the Department of Medicine, Pediatrics, and Pathology, University of Washington, one hundred patients with acute leukemia who had been treated by chemotherapy and total body irradiation also underwent allogeneic marrow transplantation from histo-compatible donors. Of the one hundred patients, 54 had acute myelogenous leukemia (AML) and 46 had acute lymphoblastic leukemia (ALL). All of the 100 patients received a marrow graft from an HLA-identical sibling after also receiving total body irradiation (TBI) (Thomas et al., 1977). There is about a one in four chance of having siblings match (Wright, 2005). Throughout the experiment patients were given the DNA alkylating agent cyclophosphamide that acts to suppress the immune system. Eventually all of the 100 patients underwent a marrow infusion (Thomas et al., 1977.) In spite of the HLA match, some patients experienced graft rejection, in the form of graft versus host disease (GVHD). Pneumonia affected 54 of the patients, and was said to be correlated to the GVHD, and caused death in 34. Some patients showed a leukemic relapse, but after two years post-transplantation the relapse rate was very low. According to the study,

> "Patients in fair clinical condition at the time of transplantation showed significantly longer survival times than patients in poor condition (p=0.001). This observation, coupled with the observation that some patients may be cured of their disease, indicates that marrow transplantation should now be undertaken earlier in the management of patients with acute leukemia who have an HLA-matched sibling marrow donor." (Thomas et al., 1977)

This study provided a comprehensive look at the data from a clinical trial of HSCs for treating leukemia, and provided the basis for a continued usage of the transplant process to treat other hematologic malignant cancers.

Stem Cell Treatment of Diabetes

As of 2010, approximately 285 million people are living with diabetes worldwide, and this is expected to rise to 438 million by 2030 (World Diabetes Foundation, 2012). In type-I diabetes, a patient's own immune system attacks pancreatic β-cells that produce insulin. Insulin is a hormone that increases the uptake of glucose from the blood into tissues. Without insulin production, serum glucose increases (hyperglycemia) and tissue glucose decreases. If left untreated, it leads to complications and death. The current treatment for type-I diabetes is insulin injections, but this is not a cure, and it is difficult to maintain normal glycemic levels using injections. In addition, scientists have experimented with pancreatic tissue grafts to replace diseases pancreatic tissue. In one 1990 study (Scharp et al., 1990):

> "In 1990, physicians at the Washington University Medical Center in St. Louis reported the first successful transplant of donor supplied pancreatic islet tissue (which includes β-cells) in humans with type 1 diabetes. By the end of the decade, many other transplants had been reported using various protocols, including the widely known "Edmonton protocol". This protocol involves isolating islets from human cadaveric pancreatic tissue of multiple donors and infusing them into the recipient's portal vein." (Goldthwaite, 2010)

But since the number of available pancreas donors is low, β-cells need to be found elsewhere for transplantation.

Scientists have investigated the possibility of using stem cells to replace the damaged β-cells in diabetes. All the experiments performed to date have been done in diabetic animal models, not in human patients. Mouse diabetes models have been successfully treated with embryonic stem (ES) cells (Soria et al., 2000), hematopoietic stem cells (to replace the diseased T-cells that mediate the autoimmunity) (Beilhack et al., 2003; 2005), and adult mouse tissues reprogrammed to produce insulin (Zhou et al., 2008; Alipio et al., 2010). Human ES cells have been reprogrammed into insulin-producing cells (Assady et al., 2001; Lumelsky et al., 2001; D'Amour, 2006), and human ES cells have been used to treat mouse models (Kroon et al., 2008), but human ES cells have not yet been used in human patients

In the case of the first 2001 study that differentiated human ES cells into insulin-producing cells, the cells were tested in both "adherent and suspension culture conditions" (Assady et al., 2001). Adherent cultures are grown as monolayers on an artificial substrate like a plastic petri dish or falcon flask, while suspension cultures are free-floating in the culture medium (Life Technologies, 2012). In both types of cultures, the hES cells demonstrated a "spontaneous *in vitro* differentiation that included the generation of cells with characteristics of insulin-producing β-cells" (Assady et al., 2001). The differentiated human cells also showed other hallmarks of β-cell function, leading the scientists to the conclusion that this could provide a base for future testing, not only the "enrichment of human β-cells or their precursors," and as "…a possible future source for cell replacement therapy in diabetes" (Assady et al., 2001).

In a study published in *Nature Biotechnology* in 2008, scientists experimented with a cell therapy for diabetes using human ES cells implanted into mice (Kroon et al., 2008). The mice

were implanted with about 3,000 islets derived from human ES cells. After engraftment, these cells demonstrated many of the properties of, "functional beta-cells, including expression of critical beta-cell transcription factors, appropriate processing of pro-insulin, and the presence of mature endocrine secretory granules" (Kroon et al., 2008). The scientists also showed that the implantation of these hES cell-derived pancreatic endodermal cells protected the mice against hyperglycemia, providing evidence that human ES cell therapy is able to produce cells that provide insulin and respond to glucose *in vivo* (Kroon et al., 2008).

HSCs have also been used to treat diabetes in animal models. Allogeneic HSC transplants have been tested in a mouse non-obese diabetic (NOD) model that mimics type-I diabetes in which the pancreatic β-cells that secrete insulin are destroyed in an autoimmune attack by the animal's own T-cells. HSCs were transplanted into NOD mice to test whether the development of hyperglycemia could be prevented by depleting the diabetic host T-cells prior to damage, and allowing the non-diabetic implanted HSCs to differentiate into T-cells that do not recognize the pancreas as foreign, leaving the tissue intact (Beilhack et al., 2003). The data showed that the implant blocked autoimmunity, even with the presence of some remaining T-cells from the host (Beilhack et al., 2003). The authors concluded that:

> "We conclude that allogeneic HSC transplants block allo- and autoimmunity, despite residual host T-cell presence. These data demonstrate for the first time that purified HSC grafts block the development of autoimmune diabetes and illuminate how HSC grafts alter thymic and peripheral T-cell responses against auto- and alloantigens." (Beilhack et al., 2003)

Although the study was done with mice, it provides a proof of principal that a similar approach could be used in human patients.

Stem Cell Treatment of Heart Disease

Heart disease is the leading cause of death in the United States (Heart Disease Facts….2012). Heart attacks stem from coronary artery disease (CAD), which is a thinning of blood vessels due to the buildup of plaque on the vessel walls and the ensuing localized inflammation. A weakened blood supply to the heart can lead to heart failure or significant damage to the heart muscle. Because heart failure causes significant scarring or loss of functionality of heart tissue, scientists for years sought to identify early stage cardiac progenitors that could replace damaged tissue (GEN, 2011).

The science of using stem cells to treat human heart attack patients is relatively advanced compared to most other areas of stem cell research (except for HSCs). Human heart attack patients have been treated with skeletal myoblast cells (Menasche et al., 2001; Siminiak et al., 2004), bone marrow stem cells (Britten et al., 2003; Lunde et al., 2006; Schächinger et al., 2006), mesenchymal stem cells (Chien et al., 2004), and adult cardiac stem cells (GEN, 2011). Although heart attack patients have not yet been treated with human embryonic stem cells, such cells have already been differentiated into various cardiac lineages (Kehat et al., 2001). And human induced pluripotent stem (iPS) cells have also been shown to be able to differentiate *in vitro* into various cardiac lineages (Burridge et al., 2011).

With respect to adult cardiac stem cells, in 2005 scientists first identified Isl1+ cells in mice, rats, and human heart muscle that are capable of differentiating into various cardiac lineages (Laugwitz et al., 2005). One year later in 2006, Isl1+ progenitor cells in the heart were shown to be capable of differentiating into more than just cardiac lineages, including smooth muscle cells and endothelial cells (Moretti et al., 2006). In 2009, scientists further researched Isl1+ cells, verifying that human Isl1+ cells can "…generate diverse multipotent cardiovascular

cell lineages" (Bu et al., 2009). They showed that, "purified Isl1+ primordial progenitors are capable of self-renewal and expansion before differentiation into the three major cell types in the heart" (Bu et al., 2009). Purified Isl1+ cells have not yet been perfused into human heart attack patients, but they provide hope for regenerating heart muscle tissue in heart disease patients in the future.

In 2011, the first clinical trial of transplanted autologous cardiac stem cells (CSCs) in humans was performed at the University of Louisville and Brigham & Women's Hospital (GEN, 2011). Phase-I of the "Stem Cell Infusion in Patients with Ischemic Cardiomyopathy" (SCIPIO) was the evaluation of patients with severe heart failure receiving CSC transplantation. The CSCs were derived from the patient's right atrial muscle at the time of coronary artery bypass surgery, and were amplified and delivered back by intracoronary infusion (GEN, 2011). The scientists evaluated the left ventricular ejection fraction (LVEF) measured in EF units. The results indicated an increase in EF units in the transplant patients compared to controls. According to the study:

> "The benefits of CSC transplantation were even more pronounced at one year in eight evaluated patients, for whom LVEF increased by 12.3 ejection fraction units compared with baseline. In the seven treated patients evaluated using MRI, infarct size was also shown to have decreased by 24% at 4 months, and 30% at one year." (GEN, 2011)

Dr. Roberto Bolli of Louisville, one of the key authors stated that:

> "While we do not yet know why the improvement occurs, we have no doubt now that the ejection fraction increased and scarring decreased. If these results hold up in future studies, I believe this could be the biggest revolution in cardiovascular medicine in my lifetime." (GEN, 2011)

Results like these provide optimism about the future of stem cell therapy, especially for heart disease where more American lives are affected than by any other disease.

Stem Cell Treatment of Parkinson's Disease

An area of the human body where little is known about it relative to other organs is the brain. Parkinson's disease (PD) is caused by the destruction of an area of the brain termed the *substantia nigra*. This area of the brain contains dopaminergic neurons that, as their name implies, secrete dopamine. Dopamine is a neurotransmitter involved in neuromuscular transmission, so patients with a loss of dopamine show symptoms such as muscle tremors and difficulty initiating movements (National Parkinson's Foundation, 2012).

Treating PD with cell therapy has an interesting background, as this disease was treated with some success in human patients as early as 1988 using *fetal* tissue transplants isolated from aborted fetuses (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002). Due to the controversial ethics of using aborted tissues for medical research, this technique is no longer used. Later in 2005, PD patients were treated with adult olfactory mucosal stem cells (Levesque, 2005), and in 2009 with adult neuronal stem cells (Ertelt, 2009). In 2004, Michel Levesque offered his testimony on adult stem cell therapy in humans to the Senate Committee on Science Technology and Space explaining,

> "In accordance with our institutional review board, we transplanted a patient with advanced Parkinson's disease with differentiated neurons derived from an initial needle biopsy. At three years post-operatively, the overall Unified Parkinson's Disease Rating Scale (UPDRS) improved by 81% while "on" medication and 83% while "off" medication. We demonstrated here the long-term clinical remission of Parkinson's disease symptoms in a single patient." (Levesque, 2005)

With respect to treating PD with embryonic stem cells, human ES cells have been shown to be capable of differentiating into dopamine-producing neurons (Perrier et al., 2004). These cells have not yet been used in human PD patients, but have been used to treat rodent PD models (Ben-Hur et al., 2004). In one trial with PD rats, human ES cells were used to derive dopaminergic (DA) neurons that were grafted into the rat's striatum. The results indicated the

"transplanted rats exhibited a significant partial correction of D-amphetamine and apomorphine-induced rotational behavior, and a significant improvement in stepping and placing non-pharmacological behavioral tests" (Ben-Hur et al., 2004).

In 2009, UCLA researchers published the results of their human trial transplanting autologous adult neural stem cells (NSCs) into one PD patient (Ertelt, 2009). In this first ever clinical trial using NSCs, the authors derived the cells from one patient, amplified them *in vitro* and injected them back into the brain as mature neurons. The adult neuronal stem cells proved to out-perform the embryonic stem cells. There was no need for immune-suppressants, as there was no rejection of the injected stem cells by the patient's immune system. Michel Levesque, lead investigator for NeuroGeneration, who has ties with UCLA, stated, "Of particular note are the striking results this study yielded — for the five years following the procedure the patient's motor scales improved by over 80% for at least 36 months. We have documented the first successful adult neural stem cell transplantation to reverse the effects of Parkinson's disease, and demonstrated the long term safety and therapeutic effects of this approach" (Ertelt, 2009). One particular advantage of this approach was that adult neural stem cells, not ES cells, were used successfully, which provides evidence that these cells might be as effective as ES cells for treating some diseases. Dr. David Prentice commented on the study by adding:

> "People need to take notice that it is not [just] embryonic stem cells that provide promise of treatments in the future, but rather it is adult stem cells that are already providing safe and effective therapies for patients now, without the problems of rejection or tumors." (Ertelt, 2009)

Stem Cell Treatment of Strokes

As with Parkinson's disease, a stroke also affects the brain tissue, but in this case brain cell death results from a disruption of the blood supply to the brain. Strokes can be even more debilitating than PD, depending on the severity. Strokes affect about 750,000 patients annually in the U.S. and are the most common cause of adult disabilities (American Heart Association, 2012). Strokes are caused by a temporary loss of blood supply to the brain, either by the rupture of an artery in the brain or by its blockage, which results in areas of brain tissue dying. The symptoms can include loss of bodily functions, speech, and movement (Science Daily, 2008). Like with PD, scientists hope to be able to regrow damaged brain cells using cell therapies.

Human stroke patients have already been treated with autologous mesenchymal stem cells (MSCs) (Bang et al., 2005). In an article published in 2005, Bang and colleagues discuss the effects of MSC transplantation into humans with cerebral infarcts. The study began with 30 randomly selected patients with ischemic stroke. The autologous MSCs were expanded in culture and the patients were intravenously infused with these MSCs, while a control group received no cells. Based on their numbers in the Barthel index and Rankin score, which are used to measure their improvement, the patients that received MSC treatment showed significant functional recovery (Bang et al., 2005).

In 2008, an animal experiment was conducted using human embryonic stem cells to treat a rat stroke model. The rats showed repaired brain damage from the transplanted hESCs, and the function of their forelimbs improved greatly. The authors proclaimed that:

> "This study marks the first time researchers have used human embryonic stem cells to generate neural cells that grow well in the lab, improve a rat's physical abilities, and consistently do not form tumors when transplanted." (Steinberg, 2008)

The authors acknowledge that the rat study needs to be repeated before moving to human clinical trials, but but senior author Gary Steinberg, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor of Neurosurgery and the Neurosciences states, "human embryonic stem cell-based therapies have the potential to help treat this complex disease" (Steinberg, 2008). Steinberg believes this study can be done with human stroke patients within five years.

Although there is less known about the brain and the use of stem cells in that organ, scientists believe that soon such studies will move into human clinical trials. The future of ischemic stroke therapy seems to lie in the usage of MSCs, but more human trials will need to be conducted, hopefully with the same level of success with the results of the trial discussed earlier (Bang et al., 2005).

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Chapter-3: Stem Cell Ethics

Joseph Toto

The use of embryonic stem (ES) cells is one of the most hotly debated topics in all of biology today. Although these cells hold enormous promise for treating various disorders previously thought to be untreatable, ES cell lines are derived from blastocyst embryos, and this process destroys the embryo. So, the ES stem cell debate focuses on the status of the 5-day old human embryo. The purpose of this chapter is to frame this embryo debate, and describe the positions of five of the world's major religions on the topic.

The Embryo Debate

As discussed in Chapter-1, embryonic stem (ES) cells are isolated from the inner cell mass of a 5-day old human blastocyst. The blastocyst is created by *in vitro* fertilization (IVF) in reproductive clinics for couples seeking children. The IVF process is inefficient, so excess fertilized embryos are prepared for each couple. Once the couple has enough children, the excess embryos are either destroyed, or are used for research purposes with the couple's (donor's) consent. As will be discussed in Chapter-4, it is not currently legal in the U.S. to prepare an embryo solely for research purposes, it must first be prepared for reproductive purposes.

The ES cell debate focuses on the status of this 5-day embryo. It has the *potential* to become a human if implanted into the uterine wall, but not if it remains unplanted outside the womb. Outside the womb, the embryo dies after the blastula stage. The debate focuses on when live begins. If you believe life begins at conception, the 5-day old embryo is a person, and destroying it becomes murder. If you believe life begins at day-40, well past the blastula stage, a

5-day old embryo is not yet a person, so perhaps it could be used to save other lives by isolating ES cells for therapy. There are many different perceptions as to when an embryo becomes a person. Some religions believe the start of personhood begins at conception, at the time egg and sperm are united. Others believe it begins later after embryo implantation, and others at the time of birth itself.

Although the terms *pro-life* and *pro-choice* usually apply to the abortion debate, which pertains to a fetus much older than an embryo, some of the general ideas also apply to the stem cell debate as they relate to when personhood begins. The idea that life begins at conception is generally followed by *pro-life people*, who are usually Catholics and some conservative Christian denominations. They insist that personhood exists as soon as the child is conceived, so a newly formed zygote to them is a full human being. They believe the soul enters the body once the DNA from both parents unites to create new DNA *unique* to the child. Some religions believe that God injects a soul into the zygote as soon as it is conceived (Robinson, 2006). This theory is exclusive to a few Christian denominations, and they feel that the embryo's right to live should be protected, even of only a single cell (Robinson, 2006). Other pro-lifers believe that personhood begins not quite at conception, but very soon thereafter, as the zygote begins to split into two cells called blastomeres (Robinson, 2006).

Some Christians and Jews believe that personhood begins in an embryo once *blood* is present, which is about 18 days post-fertilization. This concept has origins in the Bible. Followers of this theory believe that blood is the most essential fluid in a human being containing life force, since a person cannot live without enough blood in their system. Early

religions such as Judaism assigned magical powers to both human and animal blood. According to *Leviticus 17,* followers were forbidden to consume any type of animal blood. In the text of *Leviticus*, verse 11 states, "For the life of the flesh is in the blood: and I have given it to you upon the altar to make an atonement for your souls: for it is the blood that maketh an atonement for the soul." Also, Verse 14 says "…it is the life of all flesh; the blood of it is for the life thereof: therefore I said unto the children of Israel, Ye shall eat the blood of no manner of flesh: for the life of all flesh is the blood thereof: whoever eateth it shall be cut off." It is also assumed that once blood makes its first appearance in the embryo, the heart begins to beat. This occurs before any other body parts begin to form such as the head, limbs, or brain (Robinson, 2006).

On the other hand, many *pro-choice* followers and some religions believe that personhood begins later in pregnancy. Such individuals believe that personhood does not begin with the uniting of the spermatozoon and ovum; the newly formed zygote is a *potential* person, but not yet a person. Some pro-choice followers believe that the child becomes a complete human being after it has been delivered and can breathe on its own as a separate individual. There is a Biblical explanation for this theory; *Genesis 2:7* explains how God created Adam's body from the dust of the ground, but he became a full blown human only after God "breathed into it the breath of life". This passage implies that the onset of breathing is important to personhood.

For the abortion debate, these two camps argue about whether abortions should be allowed, and if so, *when* during the pregnancy. If the newly formed zygote is considered a human life, then developing it to the blastocyst stage to isolate ES cells or performing an

abortion at any stage of pregnancy is said to be murder. If the zygote is not a person until, for example the third trimester, then an abortion performed in the first trimester is not considered to be murder (Robinson, 2006).

Different religions have various beliefs about when personhood begins. This Chapter will explore the most popular popular religions, including Catholicism, Christianity, Judaism, Islam, Buddhism, and Hinduism. Although not well known, most of these religions strongly support the use of *adult* stem cells, so long as they are used to try to save lives. However, they differ in their beliefs on ES cells.

Christianity and Stem Cells

The Christian religion is very large, and different denominations within it believe differently about when personhood begins. The best known stance in Christianity is that of the Catholics who argue that life begins at conception (Correa, 2000; Pope John Paul, 2001; American Catholic Organization, 2006; U.S. Bishops, 2006; Filteau, 2007). Catholicism, in general, is against destroying any embryos. This religion also takes a hard stand against abortion, at any stage of pregnancy. The major issue with stem cells in a Catholic's view is the moral status of the human embryo from the time of fertilization. The late Cardinal Joseph Bernardin of the Catholic Archdiocese of Chicago strongly advocated "defending the right to the life of the weakest among us" (Nairn, 2005). He also feels strongly that this religion has a profound respect for human life in all of its forms. The Roman Catholic standpoint on embryonic stem cells can be summed up that although the cells may provide endless benefits to society by

saving lives from diseases, they result in destroying one of the most vulnerable forms of life (Nairn, 2005). It may surprise some Catholics to learn that their leaders have been quoted several times saying the religion approves of working with *adult* stem cells, so long as they are used to save lives (Smith, 2006; Catholic Online, 2008).

Non-Catholic Christian views somewhat parallel those of Catholicism, but also differ in a few ways. Both the New and Old Testaments describe how life should be celebrated, defended, and lived; that life is not only God's creation but also his gift to us, and life represents our hope as human beings (Fleishmann, 2001). The scriptural view of life demands that the followers of the Body of Christ should not comply with any means of technology that requires the death of another human being. And this still holds true even if the death of one being can lead to the healing of another, such as saving the life of the mother if the fetus's life is in jeopardy. Often stressed is the fact that no matter what potential good can result from ES cell research, it still willfully takes the life of another potential human being. Saint Paul explained, "Do not be conformed to this world, but be transformed by the renewing of your mind, that you may prove what is that good and acceptable and perfect will of God" (Fleischmann, 2001). However, Christianity, the world's largest religion, has many different denominations, and some of them are in favor of working with embryos, so long as lives are saved (Faithful Progressive, 2005).

Judaism and Stem Cells

With respect to Judaism, all denominations such as Orthodox, Conservative, Reform, and Reconstructionist, support both adult and embryonic stem cell research, as long as it is for medical purposes (Dorff, 2001; Ayon, 2002). There are several Jewish legal issues regarding

stem cells. Judaism has no issues with emulating God, per say, when one manipulates embryos or tries to save lives, as long as you do so according to God's rules and wishes (Jakobovits, 2006). Effective medical relief is provided to those who are in need. Jews believe the same way about teaching as with healing; the only two professions ascribed by God himself are teaching and healing. But a line is drawn as to what type of healing is allowed, allowing the correction of a child's birth defect, but not allowing genetically manipulating a child into a so-called "perfect" person. Jewish law would allow the correction of a genetic defect that would cause the child to be born with Down's syndrome, but it forbids the allocation of changing a child's potential height from 5'8 to 6' (Jakobovits, 2006).

Traditional Jews believe based on the Bible that complete personhood is reached once the baby is physically half-emerged from the mother's body (Robinson, 2006). Jewish law, or *Halacha*, defines the point at which a fetus becomes a "*nefesh*", or person, stating 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'." In the conflicting case when a baby emerges feet first, not head first, personhood occurs once most of the body has emerged (Robinson, 2006). These Jewish beliefs do not coincide with either the pro-life or pro-choice theories of personhood, but the main ideas can be summed up that the fetus has major value since it is a potential life, but it gains full human status at birth (Robinson, 2006). Thus, Judaism generally allows research on embryos if they are used for healing.

Islam and Stem Cells

Islamic teachings indicate a strong distinction between *actual* and *potential* life, so Islam distinguishes a fertilized embryo in a petri dish from an embryo in a mother's womb (Siddiqi, 2002). Although an embryo is very valuable since it has the *potential* to become human life, they feel there is a major difference as to its location which affects its potential. They allow research on embryos in a dish since they are not in their natural environment, especially if there is the potential to cure diseases. Islam's views disagree with most Catholics who argue working with embryos is "equivalent to infanticide". In the Islamic view, the destruction of embryos in a science lab is not considered abortion due to the embryo not being in the womb, so it cannot survive on its own. The fact that thousands of excess embryos are wasted in fertility clinics around the world each year disgruntles Islamic followers, who argue they could be used to save lives. Followers of Islam also encourage the use of *adult* stem cells before using ES cells whenever possible (Siddiqi, 2002).

Hinduism and Stem Cells

Followers of Hinduism believe that all life is sacred, including animal and plant life (Bahnot, 2008). They believe that showing respect for all life is important, and this, in turn, shows love to God since God both has created and lies within all living things. Although they feel strongly about this, they know that the law of nature demands that for some to survive, others must be sacrificed. Hindu followers believe that all of creation works by taking one life for the survival of another. These two opposing views (respecting all life versus the law of

survival) causes conflict between some Hindu followers, so the ancient Rishis resolved some of the conflict by introducing various stages of consciousness shared among living organisms. Rishis stated that plants were at the lowest level of consciousness, then animals, and then humans. The highest level of consciousness should be protected, even if lower levels need to be killed to protect it (Bahnot, 2008). Also, in Hinduism it is believed that the soul passes through many species until it can evolve into humans and the highest level of consciousness. Thus, Hindus feel that prolonging existing human life to achieve ultimate union with God is of an even greater value than saving an embryo at an early stage in pregnancy (Bahnot, 2008). So, based on the concept that all life is sacred, and that extending consciousness in *existing* life is more important than working with embryos, Hindu's are generally against working with embryos.

Buddhism and Stem Cells

Buddhism places much emphasis on three central virtues, prajña (knowledge), *karua* (compassion), and *ahisma* (non-harming) (Keown, 2004). Buddhists also believe in rebirth, and the teachings indicate that human life begins at conception. Buddhists feel that there is no ethical issues with the therapeutic and medical uses *adult* stem cells; however, intentionally destroying human life by harvesting ES cells from embryos morally incorrect. They feel that the new being is entitled to the same moral respect as an adult human, since the embryo bears the identity of a recently deceased human being. So, based on the principals of not harming existing life, life begins at conception, and embryos contain a previous life, Buddhists generally do not agree with

embryo research. Although a positive result might occur from the act, it is still immoral (Keown, 2004).

iPS Ethics

Induced pluripotent stem (iPS) cells are stem cells created from an adult differentiated cell (usually skin) which are reprogramed to an undifferentiated state by introducing four specific genes that transform the cell into one with most of the characteristics of an ES cell (Kamp, 2010). This process does not destroy an embryo, so some experts argue iPS cells might replace ES cells in therapies. Gregory Kaebnick feels that the differences between iPS cells and ES cells are not sufficient to warrant the substitution (Baylis, 2008). Kaebnick explains that both techniques have the same potential to generate a human life, so he feels that those who object to the idea of the use of ES cells for research should also object the use of iPS cells. On the same note he feels that individuals in favor of using ES cells should also favor the use of iPS cells since the differences between the two, in a moral view, are not very significant.

However, we should keep in mind whether Kaebnick is referring to the similar pluripotency of these two types of cells, or the ways the cells are derived. There is a huge difference in the ways these cells are derived; preparing ES cells destroys an embryo, while preparing iPS cells only destroys a skin cell. And iPS cells are genetically identical to the skin cell donor, so iPS cells can be created to match a patient with a disease. In any case, pluripotent cells (ES or iPS) cannot form a living being, they can only form tissues within a living being, they are not totipotent cells. In response to Kaebnick's opinion, Bruce Brandhorst argues that the differences between both iPS cells and cloned embryos are morally significant. He feels that

iPS cells are more closely related to ES cells than the cloned embryos are. He says that neither iPS nor ES cells will develop into full human beings if transferred into a woman's body for three reasons, including that they are not totipotent, they lack size and internal organization to function, and they lack an extracellular layer that is required for implantation. And most importantly, preparing iPS cells does not destroy an embryo, while preparing ES cells does. So, Brandhorst feels strongly that there is good reason to be enthusiastic about iPS cells possibly replacing ES cells for therapy.

However, controversies remain about how *potent* iPS cells truly are. Some scientists argue iPS cells are as medically potent as ES cells because they can form many types of tissues (Takahashi et al., 2007), while other scientists have shown that iPS cells have acquired mutated DNA and grow more slowly (Gore et al., 2011). Future research must be conducted to know whether iPS cells can effectively substitute for ES cells (Baylis, 2008).

Chapter-3 Conclusion

The author of this chapter is personally against using embryos for research, except in some circumstances. I am in favor of using discarded IVF embryos or using embryos solely for research, as long as the donors have provided written consent. And I am strongly in favor of using adult stem cells whenever possible, recognizing that some diseases might not be treatable with adult stem cells and require ES cells. I am also in favor of using iPS cells whenever possible as a replacement for embryo-derived ES cells. I am not in favor of using embryos beyond the age of 5-days for research, as those have a higher chance of becoming a human, although this is not generally an issue with *in vitro* fertilization, as embryos cannot be grown

outside the womb for much longer than 5-days before requiring implantation into the uterus for their continued survival, so it is generally not possible to achieve a 40-day old IVF embryo outside the body.

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Chapter-4: Stem Cell Legalities

Andrew Cayer

Over the past couple of decades, America has increased its focus on advancing technology in all aspects of life, especially in the rapidly growing medical fields. As is typical for advancements in technology, with these changes comes rules and regulations for their oversight, which helps protect society, and helps control research and manufacturing costs. However, in the medical field, the regulations can evolve from the moral views of society about the technology, and this is especially true for embryonic stem (ES) cells that destroy embryos during their derivation. The laws enacted to control the federal funding of ES cell research directly reflect the type of administration in place at that time, so this topic is a blend of science, laws, and politics. Individual U.S. states can over-ride the lack of federal funding, by funding their own bonds to fund ES cell research. And different countries stem cell laws reflect that society's religious and moral beliefs. The purpose of this chapter is to describe the U.S. federal and state embryo policies for the past three administrations (Clinton, Bush, Obama), and to summarize some of the laws for other countries.

In a democratic country that focuses on equal rights, we strive for a balance between bettering life while also accepting the fact that (whether for religious or humanitarian reasons) some individuals believe it is wrong to destroy a human embryo when trying to save other lives. As discussed in Chapter-3, among all the topics for debate in the U.S. the medically related topics of abortion and stem cells rise to the top. These debates revolve around the topic of when human life begins, and the status of a 5-day old blastula (from which ES cells are derived) or the status of a much later aborted fetus (from which fetal tissues are derived for medical research). From a legal standpoint, once that life begins (whether at conception, or at implantation into the

uterus, or at day-40, or at birth), it is given natural rights, and has an equal opportunity to live its life, just like stated in the constitution which our country strives to follow very closely.

The embryo debate is actually not new. It began in the late 1970's with the advent of *in vitro* fertilization (IVF) and the birth of the world's first test tube baby Louise Brown (BBC News, 1978). During IVF procedures, extra fertilized embryos are prepared in case the couple needs them, and to replace any that die from miscarriages, etc. Once the couple has enough children, the extra IVF embryos are sometimes destroyed. So the debate focuses on whether to use the excess IVF embryos for medical research, like to derive new ES cell lines. Stem cell research jumped into the limelight in 1998 with the derivation of the first human ES cell lines from IVF embryos (Thompson et al., 1998), starting the never-ending legal process of regulating the federal money spend on embryo research. Since the topic is fairly new, one does not have to go too far back into history to discover the main events in this ongoing debate.

Clinton Administration and Stem Cells

William Jefferson Clinton became the president of the United States in 1993, and was the first president heavily involved with embryo and stem cell research. He was strongly in favor of the research, and soon after taking office enacted the National Institutes of Health Revitalization Act of 1993, which gave the NIH the authority to fund human embryo research for the first time (Dunn, 2005). The NIH formed a Human Embryo Research Panel to help oversee the controversial research and to determine which type of embryo research should be funded. They favored using excess IVF embryos with donor consent, and the stage was set to move forward with embryo research until congress put on the brakes in 1996.

In 1996 congress enacted the Dickey-Wicker Amendment. The Dickey-Wicker Amendment prohibited the use of *federal* funds for creating IVF human embryos that would be destroyed for medical research. At first, the Dickey Wicker amendment ended any positive momentum that Clinton had initiated in 1993. But in 1999, Harriet Rabb, a lawyer representing the Department of Health and Human Services, noted that ES cells could not be defined as an embryo, and were thus exempt from the Dickey-Wicker amendment. So, ES cell lines could be initially derived using *private* funding, and then research on the ES cell lines could be funded with *federal* dollars (Genetics and Public Policy Center , 2011). The Rabb legal decision was quickly adopted by Clinton in August of 2000 (Dunn, 2005), which lasted until 2001 with a new set of policies from the Bush administration.

President Bush and Stem Cells

As Clinton's term in office came to an end, so did the pro-stem cell outlook from his office. As George W. Bush was elected into office in 2001, he expressed a much different view on the subject. On August 9th , 2001 President Bush fully undid any strides President Clinton made in ES cell research funding by declaring that federal funding could be used to support research only on ES cell lines derived prior to August 9th, 2001 (the murder act had already been conducted and could not be undone), and that federal funding could not be spent to derive any *new* ES cell lines (Bush, 2001). Initially it was thought that about 60 ES cell lines were qualified for federal dollars by the Bush administration, but further analysis showed that many of those cell lines were genetically identical, were mutated, or were contaminated, so scientists had far fewer ES cell lines to work with than was originally anticipated (Holden and Vogel, 2002).

On July 19, 2006, Bush vetoed a bill to deny the passing of congress' Stem Cell Research Enhancement Act of 2005 (Stem Cell….2005). The bill to allow more federal funding for stem cell research passed by a large margin in senate (63-37). However Bush used his power to veto it. To display how strongly Bush was against this topic, it was the first time he ever vetoed a bill in his five and a half years as president at that time. When interviewed about the subject later on he replied, "This bill would support the taking of innocent human life in the hope of finding medical benefits for others. It crosses a moral boundary that our decent society needs to respect. So I vetoed it" (Bash and Walsh, 2006).

As news broke out that Bush had vetoed the bill, many associations and health professionals across the country started to show their displeasure. Many religious people were pleased with Bush's decision, but others saw stem cells as a chance to help people in need. Many scientists explained that stem cells could be used to treat such diseases as Parkinson's, Alzheimer's, diabetes, and burns or spinal cord injuries. One well-known chairman of the American Diabetes Association, Lawrence Smith was quoted saying: the veto was "a devastating setback for the 20.8 million American children and adults with diabetes -- and those who love and care for them" (Bash and Walsh, 2006).

The main sponsor of the bill in the Senate, majority leader Bill Frist, explained his view on the bill by adding, "I am pro-life, but I disagree with the president's decision to veto the Stem Cell Research Enhancement Act. Given the potential of this research and the limitations of the existing lines eligible for federally funded research, I think additional lines should be made available" (Bash and Walsh, 2006). This quote turned out to be very crucial to the legal aspects of embryo research, causing a discussion about various alternate ways to research stem cells without using embryos. This discussion led to two separate bill proposals. The first bill was

known as the “fetal farming” bill, whose sole purpose was to ban the commercial production of human fetal tissue. This bill got passed unanimously by both the House and Senate. The second of these bills was to promote alternative sources to obtain stem cells from. This bill passed in Senate however did not pass in the House. Bush was in favor of both bills and was aggravated that the alternative source bill did not pass (Bash and Walsh , 2006).

On June 20, 2007, Bush again vetoed the second attempt at congress to enact a Stem Cell Research Enhancement Act of 2007. This act was a follow-up to the earlier 2005-2006 version, and Congress hoped for a better chance at gaining enough votes to override any veto, but again failed to get enough votes, and Bush vetoed the act (Stem Cell….2007).

President Obama and Stem Cells

In 2009, as the Bush era came to an end, President Obama entered office and brought with him a very different view on stem cells. Obama’s main argument was that Bush was too restrictive in his decisions on the topic. Obama believed that these decisions should be based on scientific fact as opposed to the ideology that Bush favored. If he didn’t allow research on the topic, how could one ever know the truth of the possible healing powers of stem cells? Obama immediately signed Executive Order 13505 to remove the restrictive laws passed by Bush (the ban on using federal funding to derive new embryonic stem cell lines), giving scientists the ability to again create ES cell lines (President Barack Obama, 2009).

As Obama anticipated, his actions caused much commotion. "The action by the president today will, in effect, allow scientists to create their own guidelines without proper moral restraints," argued the Family Research Council (Borenstein and Feller, 2009). Many people argued that scientists had too much power now, and should not have the right to override what

many people felt was morally wrong. However, Obama stood strong and claimed that science was something that politicians should base their decisions on, not vice versa (Borenstein and Feller, 2009).

As the Bush ban was lifted, and Obama's new changes were taking place, it called for new guidelines and a strictly set up course of action to allow for federally funded research. The NIH was heavily involved in establishing a set of rules on conducting the research, with their main focus on where the researchers will obtain their embryonic cells from. On July 7th, 2009, the NIH published their final guidelines (Holden, 2009). The guidelines gave the right to the NIH to decide which ES cell lines meet modern ethical requirements. The ES cell lines had to be derived from excess embryos created for reproductive purposes at IVF clinics, and donated with written consent. In addition, the NIH was required to help manufacture and distribute eligible ES cell lines for researchers to obtain. Overall, most scientists were happy with this result, and new the stem cell movement was heading in the right direction (Holden, 2009).

Individual U.S. States and Stem Cells

During the Bush administration when federal dollars could not be spent to derive new ES cell lines, some individual states took matters into their own hands to provide state dollars to support the research. For example, in 2002 California became the first state to *encourage* (New Jersey was actually the first state to *fund* research as explained later) stem cell. California encouraged the use of ES cells for research, but put a ban on reproductive cloning that would create a cloned baby. In 2004, California passed a bond measure titled Proposition 71 (Lao, 2004). This bond granted $3 billion U.S. dollars over a ten year span to help facilitate ES cell research and to help found the California Institute for Regenerative Medicine (CIRM). This

bond measure was a major step in the biomedical field at the time, providing scientists with hope for research that could help them obtain factual evidence on whether such cells can indeed treat human diseases. California helped lead the way to show that individual states could enact creative ways to "privately" fund their own stem cell institutes without receiving federal funding. This set path for other states to follow suit and pass their own initiatives (Lao, 2004).

In 2004, New Jersey became the first state to actually invest in embryonic stem cell research (Ohio was already providing funds for adult stem cell research). Between 2004 and 2006, New Jersey invested $23 million into the New Jersey Stem Cell Institute, and grants awarded to 17 institutions to fund research (National Conference of State Legislatures, 2008). Just one year later, in 2007, New Jersey approved another $10 million in research funds (The Commission on Science and Technology, 2007).

Perhaps one of the most well-known state-wide movements towards embryonic stem cell research is Massachusetts. This is largely due to the fact that Massachusetts is home to many scholarly colleges, including Harvard University. These colleges were heavily in favor of pursuing stem cell research, and made many attempts to persuade officials to allow the research to be conducted within the state of Massachusetts on various campuses. In 2005, Governor Mitt Romney was the governor of Massachusetts, and was heavily involved with this issue. He supported the matter, however he believed that scientists should only be allowed to use the embryonic stem cells left over at fertility clinics as opposed to scientists creating their own solely for research. In June of the same year, Romney faced a new proposal, which allowed for slightly less restrictive guidelines. The proposal now required the approval of the Health Department to perform the research, instead of the District Attorney. Romney disagreed with this change and vetoed the bill. However, Romney's veto was overruled by a strong vote in the house, which

allowed Massachusetts to become one of the most heavily invested states in stem cell research (Daily News Central, 2005). After overriding Governor Romney's veto, Massachusetts began investing time and money into stem cell research, and created the world's largest stem cell depository in Worcester, Massachusetts at the University of Massachusetts Medical Center (Massachusetts…2011).

By 2008, many other states had followed this precedent and set their own state-wide laws favoring embryo research, including Connecticut, Illinois, Iowa, New York, and Maryland (National Conference of State Legislatures, 2008). Some states, like South Dakota enacted laws *prohibiting* embryonic research. And some states have not specifically enacted laws pertaining to stem cell research yet. Louisiana prohibits research on IVF embryos, while states such as Michigan and Illinois prohibit research on live embryos. Laws prohibiting the cloning of embryos have been enacted in Arkansas, Michigan, South Dakota, North Dakota, Indiana, and possibly Virginia (with some confusion about how a "human being" is defined). Many of the "heavily" pro-stem cell research states ban *reproductive* cloning, but allow *therapeutic* cloning to be conducted for research. Reproductive cloning refers to the act of cloning to produce embryos for live birth. Missouri and Maryland restrict the funding of reproductive cloning, but allow the funding of therapeutic cloning. Arizona restricts the use of publicly collected money for therapeutic and reproductive cloning (National Conference of State Legislatures, 2008).

International Stem Cell Laws

However, the struggle to provide solid funding for embryo research is not just a battle in the United States, but one that swept the world involving a plethora of countries faced with the same debates and obstacles. According to a 2009 study, the topic of stem cells has been most

popular in the following countries United States, Japan, Germany, UK, and France (in order from most to least popular), based on the number of articles on the topic published in those countries (Couffignal-Szymzcak, 2009).

In 2001, Japan passed a law restricting reproductive cloning, and advising the country to focus on guidelines concerning the use of embryonic cells in research (Couffignal-Szymzcak, 2009). It was left to Japan's Council for Science and Technology Policy to approve and publish the official guidelines on the legalities of stem cell research. On July 23, 2004 the council approved an offer from the Bioethics Expert Panel, which allowed the creation human embryos for use of research (Couffignal-Szymzcak, 2009). This was a huge step for the International debate and a strong reason why they became heavily involved in the stem cell race.

Once Germany noticed embryo research spreading worldwide, many German people spoke out to change that country's laws. In 1991, Germany passed a law stating that embryonic stem cell research is prohibited. However, the law was unclear as to whether it pertained to research done on *imported* ES cells. As many researches made a push to legalize research performed on imported lines, their efforts were eventually shot down. In 2002, a new law was passed prohibiting the importation of such cell lines, and prohibited all embryo research unless under very critical conditions (Kim, 2002). Many believe that the passage of this law is the reason Germany's peak output of stem cell research was reached in 2001, and has declined thereafter.

The UK entered the stem cell debate early on. In 1990, England passed its Human Fertilization and Embryology Act which allowed embryo research so long as a license is issued (Rosenthal, 2004). In 2005, the UK passed a 10-year plan to fund embryo research, and this is

reason why the UK is heavily involved in stem cells today, and why so much information has been obtained from their testing (Couffignal-Szymzcak, 2009)

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PROJECT CONCLUSIONS

The most argued current topic in biology today is whether the use of human embryos and embryonic stem (ES) cells is ethical. Although other types of stem cells also exist, including iPS cells, HSCs, NSCs, ESCs, CSCs, and MSCs, these adult stem cells do not destroy an embryo to obtain them, so they are less controversial. The authors of this IQP agree that the experimental use of ES cells is ethical, and should be encouraged in the future. Although we support the use of ES cells, we also believe that if other options exist for treating a specific disease, such as iPS cells or other adult stem cells, then they should be used first. Having an adult stem cell option for those individuals who strongly oppose the use of ES cells is important because educating the public about safer options will encourage further research.

The authors agree with current U.S. legislation requiring the ES cells to be derived only from surplus IVF embryos originally planned for reproductive purposes but set aside for disposal. If the embryos are to be discarded anyways, we believe that with donor consent they should instead be used to potentially save lives. The countries with stem cell policies that match best with our own thoughts are primarily Islamic. The Islamic distinction between potential live and actual life allows the use of 5-day old IVF embryos not implanted into a uterus. Countries that follow Islamic law applied to stem cells include Saudi Arabia, UAE, Algeria, and Somalia. Countries that are primarily Catholic have beliefs that strongly differ and do not support ES cell research. We agree that there needs to be a larger support for ES cell research, and see a bright future in stem cell research.