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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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ABSTRACT

The purpose of this IQP is to compile information regarding the topic of stem cells, and then draw conclusions about this new technology and its effects on society. Stem cells are undifferentiated cells with the ability to renew and divide indefinitely to generate specialized cells. The seemingly unlimited potential of stem cell research has several medical applications and has founded the new field of regenerative medicine. However, their use draws strong ethical concerns for embryonic type stem cells, which leads to the creation of legislation to dictate the boundaries of this new technology.

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PROJECT OBJECTIVES

The objective of this IQP project was to investigate the controversial topic of stem cells, and to discuss the progression of this new technology and its influence on society. The purpose of chapter-1 is to define the various types of stem cells, where they are found, and how they can be distinguished via potency. Chapter-2 describes how these stem cells are applied in practical experiments that have generated success not only in animal studies but in human clinical trials. The purpose of chapter-3 is to confront the moral concerns surrounding this controversial topic, while chapter-4 dives into U.S. and international laws that govern this growing field. Finally, the author's conclusions are discussed based on the research gathered for this project.

CHAPTER-1: STEM CELL TYPES

Thomas Fontecchio

Stem cells are the foundation for every organ, tissue, and cell in the body. Stem cells are a class of undifferentiated cells that are able to differentiate into a specific cell type. The major function of stem cells is to maintain homeostasis in the body in terms of replacing dead or injured cells with new ones that function properly. A common misconception is grouping stem cells into one large category even though there are a number of different types. When stem cells are brought up in conversation, most people associate the term with the infamous embryonic stem cells, but not all stem cells are the same and some are far less controversial than others. Recent advances in technology and science have provided health care professionals with new opportunities and alternatives to conventional techniques that only treat the symptoms of a disease or injury. These cells have the ability to continuously multiply and develop into various types of cells in the body founding the new field of "regenerative medicine". The purpose of this chapter is to document the various types of stem cells and to lay the foundation for our later chapter discussions on their ethics and legalities.

Stem Cell Potency

The primary defining feature of a stem cell is *potency*, or its ability to become other cell types. Stem cells divide asymetrically, producing one cell that retains the ability to divide indefinitely and another cell that is more specialized than the first. The function of the indefinitely dividing population is to serve as a reservoir of long lived cells, while the more differentiated cells replace damaged or aging tissues. The less potent a stem cell is, the fewer

tissues it can form. There are four varying degrees of potency. *Totipotency* is the ability of a cell to produce all the differentiated cells that form an entire organism, plus the extra-embryonic tissue such as the placenta. Newly fertilized eggs are totipotent. As the cells of the embryo begin dividing, the cells through the embryo 8-cell stage (48 hrs) also remain totipotent, but not thereafter. Embryonic stem cells (ESCs) constitute the inner cell mass of the 5-day old blastocyst, and are termed *pluripotent* because they have the ability to differentiate into any of the three germ layers (endoderm, mesoderm, and ectoderm), and can give rise to any adult tissue. *Multipotent* cells can form multiple related types of cells, but with a limited number of lineages. An example of multipotent stem cells are hematopoietic stem cells that can develop into several types of blood and marrow cells, but which normally lack the ability to develop into brain or nerve cells. Stem cells which are almost fully differentiated are known as *unipotent* cells, which are locked into specific cell fates, depending on the tissue origin.

Stem Cell Background

Recent developments in stem cell research have been considered breakthroughs for science and the field of biology, so with all the press coverage and ethical debates, the layperson might think stem cells are a recent discovery. Stem cell work actually has a long history that dates back to the late 1800s. In 1886, William Sedgwick used the term "stem cell" to describe the regenerative properties of plants (Chamany , 2004). A decade later, E.B. Wilson applied the term to cells in the roundworm that retained genetic material and appeared to regenerate. Contemporary stem cell techniques also arose from embryology work of the late 1800s and early 1900s. In 1912, Jacques Loeb successfully achieved artificial parthenogenesis, the process by which unfertilized eggs undergo chromosome duplication and rapid mitosis to establish a

developing embryo (Chamany , 2004). Loeb subjected sea urchin eggs to various concentrations of salt, stimulating them to undergo cell division as if sperm had fertilized them. The ability to induce an organism that does not naturally reproduce via parthenogenesis was groundbreaking. The work was heralded in newspaper headlines as "The Creation of Life", and made accessible to the public through literature.

More recently in the 1950's and 1960's, *in vitro* fertilization (IVF) techniques were developed for animals, and were later applied to humans in IVF clinics in the late 1960's (Deech, 2008). IVF clinics provided a boost to stem cell knowledge from the research performed with extra discarded embryos that were not reimplanted for reproductive purposes, eventually leading in 1998 to the isolation and growth of human ESCs from 5 day old blastocysts (Thomson et al., 1998). The use of embryos in research has always been a topic of ethical debate, and will be discussed in detail in Chapter-3.

Embryonic Stem Cells

With the discovery of IVF, scientists were able to study the developmental pathways beyond the first stages of embryogenesis and chart the fate of each cell in the developing organism. It was established that all adult cells arise from three primary germ layers: the endoderm, mesoderm, and ectoderm. These cell layers arise early in embryonic development about day-5 when a cavity called the archenteron forms the blastula. The blastula (**Figure-1**) is a hollow ball of cells consisting of the inner cell mass (ICM) which contains ES cells and forms the embryo, and the trophoectoderm which forms the placenta. The ICM over time reorganizes into the three primary germ layers.

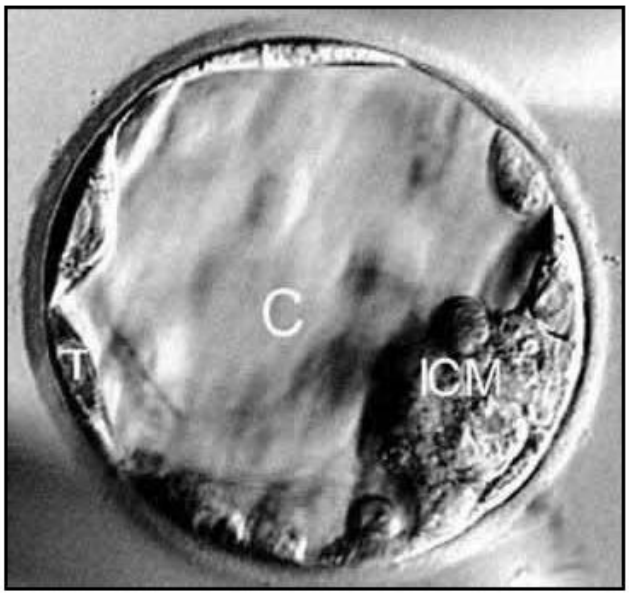

Figure-1: Photograph of a Human Blastocyst at Day-5. The cells of the inner cell mass (ICM) contain ES cells, and eventually become the embryo. The cavity or blastocoel is marked with a C. The outer layer is the trophoectoderm that will form the placenta. (Advanced Fertility Center, 2007)

The endoderm is the first embryonic layer to form, and begins in the human embryo at about two weeks after fertilization. By the fifth week, the endoderm will differentiate into internal structures such as the liver or pancreas. The mesoderm is the next layer to grow. From the mesoderm comes the intermediate organs such as muscle, bone, connective tissue, and the reproductive and urinary systems. The ectoderm is the final germ layer to form, and consists of three separate parts: surface ectoderm, neural ectoderm, and neural crest. The surface ectoderm is responsible for developing skin and other tissue such as eyelid epidermis, tooth enamel, and the mucous membrane of the mouth. The neural ectoderm acts to form the retina, optic nerve fibers, and retinal pigment. This part of the ectoderm contains the neural tube, which is responsible for developing the central nervous system. The cells in the neural crest develop into parts of the skeletal system, autonomic nervous system, and produce hormones (Shiraki et al., 2009).

A fourth set of embryonic cells specifically give rise to the reproductive organs and are called the primordial germ cells (PGCs). During the 1950's and 1960's, work by cancer specialist Leroy Stevens first suggested that some of these PGC cells might be pluripotent and that surrounding cells provide the necessary environmental signal needed to stimulate differentiation (Chamany , 2004). Stevens conducted a series of experiments and found that such cells exist and share similar characteristics with cancer cells. Stevens came across some cells which originate from primordial germ cells and found that they formed teratomas. A teratoma is an encapsulated tumor with tissue or organ components resembling normal derivatives of all three germ layers (Baker, 2009). PGCs normally go on to develop into the cells of the ovaries or the testes in the adult organism, but some cells maintain the capacity to become a variety of cell types, and others can become malignant which develop into tumors. Stevens decided to conduct an experiment with early embryonic cells from the inner cell mass and found that they went on to develop into teratomas upon injection into mice testes. With this discovery came the name embryonal carcinoma cells (ECs), which is another name for a type of germ cell tumor that forms in the ovaries and testes.

In 1981, two research groups advanced the field of developmental biology one step further when they successfully established animal embryonic cell lines. The ES cells could now propagate indefinitely *in vitro* to provide more cells for analysis. Martin Evans and Matthew Kaufman at Cambridge University were able to culture mouse ES cells from blastocysts using a medium conditioned by the cell lines established by Stevens (Evans and Kauffman, 1981). They also demonstrated that these ES cells spontaneously differentiated into a variety of cell types when injected into an adult mouse.

In the late 1980s, Brigid Hogan, Peter Donovan, and researchers at the Ludwig Institute for Cancer Research in Australia identified a specific factor and cell culturing technique in which mouse ES cells can propagate and maintain an undifferentiated state (Chamany, 2004). This work led to a more thorough understanding of how protein concentration, timing, and cell fates are related. Researchers now understand that each ESC has intrinsic genetic programming or the potential to become any cell of the adult. Extracellular proteins were understood as the extrinsic factors that provide the necessary signals to promote differentiation into one cell type versus another. The animal ES cell work continued into the 1990s, and in 1998 the first human embryonic stem cells (hESCs) were isolated.

Human Embryonic Stem Cells

Human embryonic stem cells (hESCs) are derived from embryos at a developmental stage before the time that implantation would normally occur in the uterus. Fertilization normally occurs in the oviduct, and during the next few days, a series of cleavage divisions occur as the embryo travels down the oviduct and into the uterus (Regenerative Medicine, 2006). The first differentiation event in humans occurs around five days of development when an outer layer of cells committed to becoming part of the placenta separates from the inner cell mass (ICM) (Regenerative Medicine, 2006). The ICM form a cluster of identical totipotent cells known as blastomeres but after implantation, they are quickly depleted as they differentiate to other cell types with limited developmental potential. However, if the ICM is removed from its normal embryonic environment and cultured under appropriate conditions (**Figure-2**), the ICM-derived cells can continue to proliferate and replicate themselves indefinitely and still maintain the development potential to form any cell type of the body.

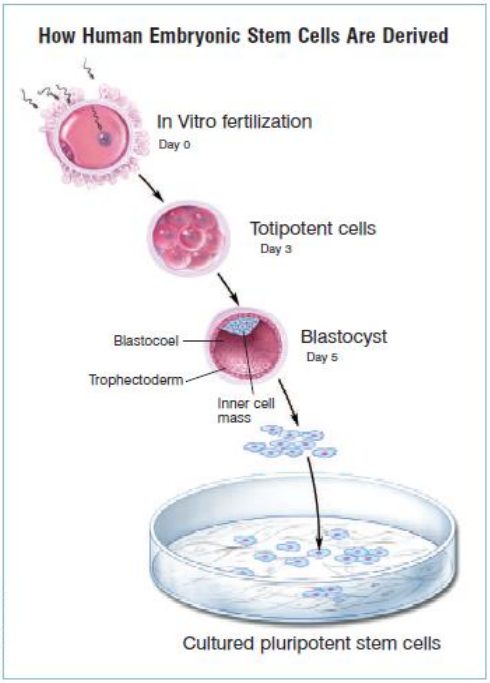

Figure-2: Diagram of Human ES Cell Isolation. ES cells of the blastocyst inner cell mass (blue), are isolated from day-5 blastocysts (diagram center) and grown on feeder cells (diagram lower) that provide a scaffold and growth factors. (Regenerative Medicine, 2006)

In 1998, human ES cell lines were derived from embryos produced by *in vitro* fertilization (IVF), a process in which egg and sperm are placed together to allow fertilization to take place in a culture dish (Thomson et al., 1998). Clinics use IVF to treat certain types of infertility, and sometimes, during the course of these treatments, embryos are produced that are no longer needed by the couples for producing children. Each year, hundreds of thousands of poor-quality embryos are regularly discarded during the course of IVF, and these could provide a source of stem cells for research. Unfortunately, the process of gathering ES cells from the ICM inevitably involves the destruction of the embryo which is of significant ethical concern. The intentional creation and destruction of emerging human life raises serious ethical, religious, legal and political concerns that will be discussed in greater detail in later chapters. However, there are a number of approaches that may allow for the derivation of pluripotent cells that do not involve the generation and destruction of a viable human embryo.

Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem (iPS) cells are a type of pluripotent cell artificially derived from a non-pluripotent cell by inducing a forced expression of specific genes. iPSCs were first generated by Shinya Yamanaka's team at Kyoto University, Japan in 2006 for mouse cells (Yamanaka, 2007) and later in a landmark article for human cells (Takahashi et al., 2007). Yamanaka used genes encoding proteins as particularly important in ES cells, and used retroviruses to transfect those genes into mouse fibroblasts with a selection of those genes. This approach identified four key pluripotency genes essential for iPS cell production; Oct-3/4, SOX2, c-Myc, and Klf4 (Yamanaka, 2007). However, this initial iPS cell line showed errors in DNA methylation compared to original patterns in ES cell lines. In June 2007, the same group published a breakthrough study along with two other independent research groups from Harvard, MIT, and UCLA showing successful reprogramming of mouse fibroblasts into iPS cells.

In November of that same year, two independent research teams created iPSCs from adult *human* cells, laying the groundwork for the potential evolution of stem cell research and it's regenerative application in humans. The two studies released were Science by James Thomson at the University of Wisconsin-Madison (Yu et al., 2007), and the other in Cell by Shinya Yamanaka and colleagues at Kyoto University, Japan (Takahashi et al., 2007). The same principles used earlier in the mouse models were used again for the human work, and human fibroblasts were successfully transformed into pluripotent stem cells using the same four pivotal genes with a retroviral system. The viral transfection system used to insert the genes at random locations in the host's genome created concern for potential therapeutic applications of these iPSC's, because the created cells might be prone to form tumors (Yamanaka, 2007). So in May

of 2009, a team of scientists generated human iPS cells by direct delivery of the proteins, thus eliminating the need for viruses or genetic modification.

Based on current research, iPSCs appear to be similar to natural pluripotent stem cells, with respect to the expression of specific stem cell genes and proteins, chromatin methylation patterns, cell doubling time, embryoid body formation, teratoma formation, and potency and differentiability (Baker, 2009). However, more recent research indicates iPS cells may divide slower and are less robust than true ES cells (Dolgin, 2010). But even if iPS cells eventually prove slightly less potent than ES cells, so long as they can be grown in culture they might serve as an excellent replacement for IVF-derived ES cells. This is an important advance in stem cell research because it may allow researchers to obtain pluripotent stem cells without the added controversy of using embryos. There is also a chance that these cells are less prone to immune rejection than ES cells because they are derived entirely from the same patient.

Parthenogenetic ES Cells

Parthenogenesis is the process by which an egg can develop without the presence of the male counterpart. It is a form of asexual reproduction common in a variety of organisms such as fish, ants, flies, honeybees, amphibians, and lizards and snakes that may routinely reproduce in this manner. Mammals are not naturally capable of this form of reproduction, however mammalian oocytes (eggs) can successfully undergo *artificial* parthenogenesis *in vitro* by mimicking the calcium wave induced by sperm during normal fertilization which causes cell stimulation and division (Berevini, 2008). Parthenogenetic embryos can develop to the blastocyst stage, and so could serve as a source of ES cells. Mouse parthenogenetic ESCs (pESCs) have been shown to have the properties of self-renewal and the capacity to generate cell derivatives of

the three germ layers, confirmed by contributions to chimeric animals and/or teratoma formation when injected into mice. Moreover, the cells do not involve the union of male and female and so genetic material will be derived exclusively from the female oocyte donor. This technique is advantageous because using a woman's own egg to create stem cells almost guarantees a complete genetic match for use in that same woman with a low risk of rejection. However, the genetic match is not perfect, as each egg is created with a slightly modified set of genes due to imprinting, the cell's way of chemically modifying DNA in the genome. Imprinting can silence some essential genes for reproduction and growth because the genes of the opposite sex are not properly expressed. pESCs have been successfully derived from primate parthenote embryos (Cibelli et al., 2002) but not yet from human eggs.

Adult Stem Cells

An adult stem cell (ASC) is a rare undifferentiated cell found among differentiated cells in tissues or organs that have already been developed. ASCs can differentiate to yield some or all of the major specialized cell types of that tissue or organ. The primary roles of ASCs are to maintain and repair the tissue in which they are found. The term "adult" does not refer to the age of the organism, only that it is observed in organisms later than the embryonic stage. Unlike ES cells, which are defined by their origin in the inner cell mass of the blastocyst, the origin of adult stem cells in some mature tissue is still under investigation. ASCs have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They are thought to reside in a specific area of each tissue called a "stem cell niche" where they remain inactive for long

periods of time until they are activated by a need to maintain tissue whether caused by disease or injury.

Research on ASCs has generated a great deal of excitement, as these cells may represent alternatives to ES cells, although they are lesss potent, and are harder to isolate and grow. The history of research on ASCs dates back to the 1950's when researchers discovered that bone marrow contains at least two types of stem cells (NIH Stem Cell Information, 2006). One population, called hematopoietic stem cells (HSCs), forms all the types of blood cells in the body. The second population, called mesenchymal stem cells (MSCs) was discovered a few years later, and make up a small proportion of the stromal cell population in the bone marrow. MSCs can generate bone, cartilage, and fat cells that support the formation of blood and fibrous connective tissue.

Hematopoietic Stem Cells (HSCs)

HSCs are multipotent stem cells that give rise to all the blood cell types. This is no small task considering the average human body goes through around 100 billion hematopoietic cells every day. The most prominent application of stem cell research has been bone marrow transplants using HSCs. In the early 1900's, physicians administered bone marrow by mouth to patients with anemia and leukemia. Although such oral therapies were unsuccessful, other experiments eventually demonstrated that mice with defective marrow could be restored to health using infusions into the blood stream of marrow taken from other mice. This caused physicians to speculate whether it was feasible to transplant bone marrow from one human to another. In 1958, Jean Dausset identified the first of many human histocompatibility antigens. These proteins, found on the surface of most cells in the body, are called human leukocyte

antigens, or HLA antigens. These HLA antigens give the body's immune system the ability to determine what belongs in the body and what does not. Whenever the body does not recognize the series of antigens on the cell surface, it creates antibodies and other substances to destroy the cell. A bone marrow transplant between identical twins guarantees complete HLA compatibility between donor and recipient. These were the first kinds of transplants performed in humans (Abbott, 2003).

Compared to adult stem cells from other tissues, HSCs are fairly easy to obtain and can be found in the three main sources; bone marrow, peripheral blood, and umbilical cord blood. Bone marrow is the place where HSCs were first discovered, and it is the location where both the majority of the human body's HSCs are found, as well as the most commonly used source. There is a relatively high concentration of HSCs in most bone marrow that can be used therapeutically without the need of further isolation. However, extraction of bone marrow requires a large needle and can be a very painful procedure. The second source is peripheral blood that runs throughout your arteries and veins, which is much easier to collect than bone marrow. However, the concentration of HSCs in peripheral blood is much smaller, so scientists have been able to increase this concentration by a process known as "cytokine mobilization" (NIH, 2006). The donor is treated with cytokine hormones to mobilize HSCs from the marrow into the peripheral blood. The last source of HSCs is umbilical cord blood, as well as the placenta, and both are usually discarded during childbirth even though HSCs are prevalent. Some hospitals allow the mother to freeze the umbilical cord blood and store it at a blood bank in the event of family blood problems. Cord blood is generally considered to be better at self-renewal than HSCs taken from an adult, and this type also displays fewer transplant rejections (Viacell, 2006).

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are another well-characterized population of adult stem cells that are also found in the bone marrow. MSCs are cells that can be cultured and differentiate into a large range of tissue including fat cells, cartilage, bone, tendon and ligaments, muscle, skin, and even nerve cells. In the bone marrow it forms stroma, which is the architecture that hematopoietic stem cells are grown in. Though they exist in a similar concentration in the bone marrow, MSCs are much easier to isolate than HSCs because they readily stick to certain types of plastic and can propagate easily in a culture medium.

The presence of non-hematopoietic stem cells in bone marrow was first suggested by the observations of the German pathologist Cohnheim. His work raised the possibility that bone marrow may be the source of fibroblasts that deposit collagen fibers as part of the normal process of wound repair. Friedenstein and his colleagues began the work of studying bone marrow contents that could differentiate into other mesenchymal cells, as well as fibroblasts (Nardi, 2006). They placed whole bone marrow in plastic culture dishes and removed the nonadherent cells after 4 hours, thus discarding most of the hematopoietic cells. They reported that the adherent cells were heterogeneous in appearance and formed two to four types of cells. These cells remained inactive for 2-4 days and then began to multiply rapidly. They also found that these cells could differentiate into colonies that resembled small deposits of bone or cartilage. Friedensteins's observations were exteneded by other groups throughout the 1980's, and it was established that the isolated cells were multipotent. In test runs on mice infected with gastric ulcers, MSCs were observed to migrate from bone marrow to the ulcer and differentiate into gastric cells. MSCs have also been observed to contribute to cardiac cells, pancreatic and liver cells, and even neural cells. Unlike most other human adult stem cells, MSCs can be easily

obtained in quantities appropriate for clinical applications, making them good candidates for use in tissue repair. Techniques for their isolation and propagation for long periods of time without losing their capacity to form numerous cell types have been established.

Neural Stem Cells (NSCs)

In the past, most treatments for damage to the brain or spinal cord aim to relieve symptoms and limit further damage. Recent research into the regeneration mechanism of the central nervous system, including the discovery of stem cells in the adult brain, has raised hopes that researchers can find ways to actually repair the damage. In the mid-1990s, neuroscientists learned that some parts of the adult human brain do, in fact, generate new neurons under certain circumstances. They found that these neurons arise from "neural stem cells" in the adult brain. Stem cells in the adult brain occur in two locations; the subventricular zone which is an area under fluid-filled spaces called ventricles, and the dentate gyrus of the hippocampus (NIH, 2006). These two areas of the brain along with areas in the spinal cord contain dividing cells that ultimately become nerve cells. Researchers showed in the mid 1990s that when the brain is injured, stem cells in these two areas proliferate and migrate toward the site of the damaged tissue. These undifferentiated cells resemble cells in a developing fetus that give rise to the brain and spinal cord.

NSCs are tripotent, they can form the neurons which make up the brain and nervous system, as well as glia and oligodendrocytes. Glial precursors give rise to astrocytes and oligodendrocytes. Astrocytes make up to 80 percent of the cells in the adult brain, and lend both mechanical and metabolic support for neurons. Oligodendrocytes create myelin, the fatty material that ensheathes nerve cell axons and functions to speed nerve transmission (NIH, 2006).

NSCs have been isolated and cultured since 2001, and are only found in a few areas in the brain. The reason why NSCs have been so difficult to find relative to the other forms of adult stem cells is their inactivity. NSCs do not produce very many new neurons in normal activity so extensive research is dedicated to figure out why this is and how to stimulate their activity.

Cardiac Stem Cells (CSCs)

For twenty years or so, scientists have debated whether the human heart can repair itself by regenerating new tissue after injury such as a heart attack. New research strongly suggests that the heart maintains a reservoir of adult stem cells that enable the heart to make new cells when it is damaged. Human cardiac stem cells (hCSCs) are self-renewing, clonogenic, and multipotent. hCSCs differentiate predominantly into cardiomyocytes and, to a lesser extent, into smooth muscle cells and endothelial cells (NIH, 2006). Researchers have identified pockets of stem cells in the interstices, or spaces, between muscle cells in the hearts of rats. When the stem cells were cultured and injected into rats with damaged heart tissue, 70 percent of the damaged myocardium was reconstituted within 20 days. Researchers also found similar cells in humans by examining tissue from patients with heart disease who underwent cardiac surgery. It appeared that the accumulated stem cells had been attempting to repair the damaged heart. The space where these cells reside has been identified, and the next step is to determine how to mobilize the cells to regenerate and proliferate. Researchers are spending considerable effort to stimulating cardiac stem cells already living in the heart to grow without surgical implantation. For years the general belief has been that the number of cells in the heart was established at birth. Now it is understood that the heart could not contract for so many years using the same cells, and that a

pool of stem cells is needed to repair any damaged tissue. There is still a lot to be learned about the biological mechanism that turns these cells on and off.

Epithelial Stem Cells (ESCs)

Most, if not all, epithelial tissues contain stem cells. They are responsible for normal tissue renewal and replacement after damage. With certain exceptions, epithelial stem cells are considered to be developmentally committed such that they can form the differentiated cells of their own particular tissue type, but not those of any other tissue. Our present knowledge of their properties is limited and is mainly derived from studies of cell kinetics and from clonal analysis. About 60% of the differentiated tissue types in a mammalian body are epithelia. Most epithelial tissues self-renew throughout adult life due to the presence of multipotent stem cells and/or unipotent progenitor cells (Blanpain, 2007). Epithelial stem cells are specified during development, and are controlled by epithelial-mesenchymal interactions. Despite morphological and functional differences among epithelia, common signaling pathways appear to control epithelial stem cell maintenance, activation, lineage determination, and differentiation. However, a deeper understanding of these regulatory pathways must be gained, as their deregulation can lead to human disorders including cancer.

Chapter-1 Conclusion

Twenty years ago, if you told a biologist that we were a few decades away from being able to regrow entire organs, you probably would have been laughed at. This idea of regeneration solely occupied the realm of science fiction but today it is considered an inevitable reality. Stem cells are the building blocks for every living cell in our body and as technology advances so too

will the practicality of this field. The controversy surrounding embryonic stem cells has bogged down research for many years, focusing on the legal and moral issue of destroying a life. This debate has also been detrimental to the field in more ways than one. The argument over embryonic stem cells has created a negative stigma that associates all stem cells to the current issue at hand. As societies' knowledge of stem cells progresses, alternatives to the current moral dilemma will arise as well as innovative techniques for isolating, growing, and applying these cells.

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CHAPTER-2: STEM CELL APPLICATIONS

Brandon Cooney

Numerous diseases worldwide currently have no cure. But fortunately, treatments for some of them my lie with stem cells and the new field of regenerative medicine. Since stem cells have the ability to renew themselves and form various types of cells, the hope is to use them to replace aged or damaged tissues. But for the most part, this new field of medicine is relatively unexplored, leaving some stem cell applications as hopes for the future. And for embryonic stem cells, some people deem their use as unethical. The purpose of this chapter is to help document the *benefit* to society of some stem cell applications, as the benefits weigh will heavily in our ethical discussions of Chapter-3. Some applications have already been used successfully for 50 years now (bone marrow transplants), while other applications remain "pie in the sky". This chapter will show how stem cells can be applied to help people diagnosed with certain illnesses, to inform the reader of the great potential of this area of medicine, before discussing the ethics and legalities behind stem cells in later chapters.

Fanconi's Anemia

Fanconi's anemia is a genetic disorder that occurs in 1 of every 350,000 births, and occurs more frequently in Afrikaans in South Africa and Ashkenaze Jews (Moustacci, 2003). There are seven different mutations of Fanconi's in genes encoding proteins that are responsible for DNA repair. As a result of this, over 20% of Fanconi's anemia patients develop a form of cancer, and 90% develop bone marrow failure by 40 years old. The life expectancy of someone diagnosed with Fanconi's anemia is 30 years. At this time, there is no cure for Fanconi's, but

there are ways to make it more bearable and give the patient a better chance at surviving. The first option is to do androgen therapy and hematopoietic growth factor therapy. But not all patients respond to this protein supplement treatment and it is temporary. The best treatment is a hematopoietic stem cell transplation.

As described in the previous chapter, hematopoietic stem cells (HSCs) are multipotent stem cells that give rise to all of the various types of blood cells. Because HSCs have been used for 50 years in bone marrow transplants to treat blood disorders (Thomas et al., 1957), they represent the most characterized of all the stem cells. According to a study done in Paris in 2000, allogeneic stem cell transplantation is the only treatment that can cure a Fanconi's anemia patient. But to increase the odds that the transplant will not be rejected, HLA typing must be done, and the odds of finding a compatible donor are low.

One future application would be to use histocompatible embryonic stem (ES) cells to treat the anemia. In this procedure, the parents would create embryos by *in vitro* fertilization (IVF), grow them 5 days to the blastocyst stage, then isolate ES cell lines. These ES cell lines should have a high likelihood of being histocompatible as they would represent "siblings" of the anemia patient (Grewal et al., 2004).

But one downside to using stem cells is the formation of cancer in some patients. There is a significantly higher chance (4.4 times more likely) for a Fanconi patient to get squamous cell cancers (SCC) in the head, neck, and esophagus after the transplantation (Rosenberg et al., 2005). And the people who receive the transplantation are diagnosed with SCC at a much earlier age than those without the transplant (median age of 18 and 33, respectively). The chance of SCC survival is very slim. So Fanconi's anemia serves as an example of a stem cell application in which hundreds of lives have already been saved, even if a small percent get cancer from the

treatment. Scientists are currently working on understanding why some stem cells form cancer, and how to prevent it from happening.

Another promising stem cell approach to Fanconi's anemia is to treat the patient's own iPS cells. In this approach, a patient's skin cell is treated with transcription factors to de-differentiate it to an ES-like state. The ES cells are genetically identical to the patient, so are less likely to be rejected. This approach has worked *in vitro* to derive the cells, but has yet to be applied to anemia patients (Delgado, 2009). The current research being done on this new strategy for helping patients with Fanconi's anemia is only at the preclinical level, but is showing signs of hope. The hope is that these iPS cells will not cause tumors, like ES cells can (Delgado, 2009.)

Parkinson's Disease

Parkinson's disease (PD) is the most prevalent disorder of the central nervous system. PD causes impaired motor skills, and difficulty initiating other seemingly routine functions. The primary symptoms of PD are bradykinesia, tremors, rigidity, and poor balance (HelpGuide.org, 2010). Bradykinesia is slowness in voluntary movements, such as sitting and standing. Tremors most often occur in the hands, fingers, and feet when the limbs are at rest. Almost all of PD symptoms are caused by the loss of dopamine producing cells in the brain. Dopamine is a neurotransmitter used by the brain to perform muscle movements. In the United States alone, 50,000 new people are diagnosed annually with PD.

Since 1998, stem cells have been used in rat models of PD as a possible treatment. Rat models have shown improved symptoms when treated with adult neuronal stem cells (NSCs) (Studer et al., 1998), with embryonic stem (ES) cells (Bjorklund et al., 2002; Kim et al., 2002; Ryan, 2004), or with NSCs derived *in vitro* from ES cells (Ben-Hur et al., 2004).

Monkey stem cell trials were done in Georgia in 2006. In this study, researchers compared the difference in the animals that received a placebo versus those that received an adult neural stem cell transplant, or received protective neurotrophic factors secreted by stem cells (Science Daily, 2006). Although most of these trials were done in animals with very early stages of Parkinson's, the results were good. The animals that received the stem cell transplants regained control over their motor skills, and after a month when the researchers re-examined the monkey's brain, the transplanted cells had survived and formed synapses in the part of the brain that creates the dopamine. The monkeys that received no treatment did not recover, and the ones that received the NTF treatment, partially recovered (Science Daily, 2006).

With respect to treating human PD patients, some early successes were obtained by transplanting *fetal* brain tissue (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002), but fetal tissue is even more controversial than ES cells as it is obtained from aborted tissue. One study reported the successful treatment of a human PD patient by transplanting adult olfactory mucosal stem cells (Levesque, 2005). With respect to human ES cells, these cells have been shown to be capable of differentiating into dopamine-producing cells *in vitro* (Perrier et al., 2004).

In 2009, a team of UCLA researchers published their findings, saying "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," said lead author Dr. Michel Levesque (Ertelt, 2009). The research team was only able to have one PD patient for this initial trial, but their patient's motor skills significantly improved. Prior to this trial, the lab reported their ES cells were rejected. The biggest points

made by the researchers is that their approach using adult NSCs does not use the more controversial ES cells, nor did it produce any cancers.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that can cause damage to various tissues, organs, and joints. It is a disease that affects 1% of the world's population. RA is far more prevalent in women than in men, and normally begins about age 40-50. The disorder can be a very painful condition that can lead to a significant loss in the patient's ability to function. Currently, various treatments suppress the symptoms and make the disorder more bearable, but there are no cures.

In The Netherlands, researchers have conducted a study in which they found a new therapy option for RA, high dose chemotherapy followed by HSC transplantation (Teng et al., 2005). Similarly, a study was conducted in Australia in 1998, in which stem cells derived from bone marrow were given to 3 patients (Snowden et al., 1998). This method of treatment was so successful, it was dubbed as a potential RA cure. As the result of these studies, 76 patients with RA were signed up for a study. Of these patients, 73 received HSC transplantations, and of all of the patients after 12 months had an ACR score (American College of Rheumatology criteria) of less than 50% (Snowden, 2004). There were also cases tested with sibling HSC transplants, in which the treatment helped lower the symptoms of RA in a 52 year old woman (Nowak, 2004). She originally had arthritis in 28 of her joints, and the treatment helped her rid morning stiffness and aches and pains that all RA patients have (Nowak, 2004).

Mesenchymal stem cells (MSCs) from the umbilical cord have recently been used to help treat various diseases, including RA (SCT, 2010). And there is current speculation that

providing cord HSCs could help reduce the risk in cardiovascular disease along with reducing damages done to the joints from RA.

Cardiovascular Disease

Cardiovascular disease affects the heart and blood vessels, and is the number one cause of death in the United States. The four most common types of cardiovascular diseases are high blood pressure, stroke, coronary heart disease, and heart failure. Cardiovascular diseases claimed 1 in every 2.9 deaths in 2006 (American Heart Association, 2006). The main cause of cardiovascular disease is the build of plaque in the heart and circulatory system, as the result of unhealthy eating, lack of exercise, or smoking.

With respect to stem cell treatments, the heart does not normally have the ability to fix itself from large scale damage, so using stem cells could provide an answer to this problem. In the heart, there are three different types of cells: myocytes, vascular endothelial cells, and smooth muscle cells (Semsarian, 2002). Injecting myocytes does not appear to work well as they usually fail to integrate into the existing tissue (Goldthwaite, 2006), but injecting heart stem cells has shown some success in animal models.

On June 26, 2009, the first FDA-approved human phase-I clinical trial in the United States was completed using heart stem cells (Medical News Today, 2009). In the procedure, they took the patient's own heart tissue, used it to isolate and grow the heart stem cells, and injected those stem cells back into the patient's heart. In the phase-I trial, there are 24 patients who have had heart attacks, and who will undergo the stem cell procedure.

Chapter-2 Conclusion

This chapter shows some of the medical success stories with stem cells as an example of their benefits to society. Although some stem cell treatments are more advanced than others, the new science has the potential to revolutionize medicine. But beyond their benefits lie medical and legal concerns, which will be the subject of the next chapters. With the regenerative properties of stem cells, there seems to be no ceiling for the good that might come from further research in regenerative medicine.

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Chapter-3: Stem Cell Ethics

Thomas Izzo

Chapter Introduction

The first two chapters described the different types of stem cells and the applications for which they are used. We now turn our attention to the topic of whether these cells *should* be used. Human ethics is a crucial side of the stem cell discussion. Ethics is a philosophy of morality within a person, guiding them on how to conduct life and act. Stem cells touch on ethics in several different ways, including topics such as: when does human life begin, should human cloning be allowed, or should one potential life be sacrificed to save another? In theory, stem cells are an amazing tool for scientists to use to heal and save lives. Their value lies in the ability to create nearly every cell type in the body. But, has this research gone too far, and has it crossed the boundary of moral limits? Ethics is incorporated in the stem cell debate in this chapter as an example of the impact of technology on society.

Many people form personal opinions on stem cells while being unaware that stem cells are not all alike. Each type has its own ethical dilemmas. As discussed in Chapter-1, embryonic stem (ES) cells are the most debated form of stem cell, as an embryo is destroyed to obtain them. ES cells are extracted from the inner cell mass of five day old blastocysts formed by *in vitro* fertilization (IVF). If one believes that life begins at conception, then destroying a five day old embryo might be considered murder. So is the life of the embryo more valuable than the life of say a three year old girl? But, if one believes that life begins later in development, say at time of embryo implantation or at the time of birth, one would have fewer issues with destroying an embryo to save other lives. Or perhaps one can view the embryo as *potential* life, because the

embryo must be implanted into the uterus to form a fetus, so does *potential* life have a different moral status than a living person? Is murder worth healing others?

Adult stem cells (ASCs) are obtained from adult tissues. These cells come from teeth, umbilical cords, blood, bone marrow, skin, brain, etc. Obtaining them does not destroy an embryo. ASCs are programmed to repair a specific damaged tissue in the body, and are being used to treat more than seventy types of pathology conditions today, including several types of cancers and blood disorders. Using ASCs does not destroy the embryo, and the practice is accepted by all major religions. "Adult stem cells - do not have the potential to become any cell of the body. They are still called stem cells because they have the potential to become other cells, but their trajectory is limited to a small number of cell types" (Hinman, 2004) This is the drawback with using adult stem cells because they have a limited number of applications; they do not grow as well as ES cells and they are not as medically potent.

Somatic cell nuclear transfer (SCNT), also known as *therapeutic* cloning, is the process by which the nucleus of an egg cell is removed and is replaced with the nucleus of a skin cell. The egg then receives an electric shock and begins to divide. The dividing cells form a blastocyst after three to five days, from which ES cells can be extracted. SCNT has been successful with mice, but not yet in humans (Memorial Sloan-Kettering, 2008). Using this process to collect ES cells is medically desirable because the cells are duplicates of the patient's own cells (the genotype matches the donated skin cell nucleus), making them less likely to be rejected by the body. But SCNT is also surrounded by large ethical debates because this same process would be used in theory to create a *reproductive* clone. Many people confuse therapeutic cloning with reproductive cloning. Most people, including our current President Obama, believe reproductive cloning is highly unethical, especially the idea of creating humans to provide tissues to treat the

person from which the clone was made. Others argue that therapeutic cloning, once it has been achieved in humans, will be a great technique in the field of stem cells and regenerative medicine. The Ethics Advisory Board believes that "therapeutic cloning research has lifesaving potential and could dramatically address urgent medical needs" (Green, 2008).

Formulating Public Opinions on Stem Cells

One of the major causes for ethical dilemmas comes not from what people know about stem cell research, but rather what they are told about it. In a 2008 poll conducted on the knowledge people had about stem cells, only seventeen percent of the poled population had an in-depth understanding of the topic (Levin, 2008). This demonstrates that the vast majority of people are formulating their opinions on stem cells without understanding key concepts. The source of much of the population's knowledge on stem cell research comes from religious information or the media. Religion has always gone hand in hand with ethical arguments within science because many people base their ethics around their religion. However, as time passes the public is becoming more informed on the top stem cells, "Three years ago, Americans were only dimly aware of and fairly evenly divided over stem cell research. Since then, support for this research has grown among most demographic and political groups" (Fact Sheet, 2006).

Because of the public's general lack of knowledge on stem cells, they can more easily be influenced on which side of a poll to choose. Someone casting the poll who favors stem cells could pose a question in the form of "Do you support stem cell research? Research that could cure many diseases such as: Parkinson's, Alzheimer's, spinal cord injuries, and possibly even save lives in the future." That question might lead a person who does not know much about the subject matter to support the research. While on the other hand, a poll performed within the

Catholic Church could pose the question "Do you support stem cell research? Research that destroys embryos and potential life." When the question is asked like that, a negative connotation is given to stem cell research which could persuade someone to vote against the research. Or by not stipulating whether the question specifically pertains only to embryonic stem cells, a poll could miss those individuals who actually support research on adult stem cells. This poll swaying does not allow for a very accurate conclusion on voter stance.

The topic of stem cells is such a controversial topic that it is constantly debated in political agendas. The stance taken by a Politian can drastically affect the political race by influencing not only voters but also contributors. Laws and regulations politicians put on stem cells affect federal research funds, which are where a majority of scientists get their funding, and this topic will be discussed in detail in Chapter-4.

Religious Views on Stem Cells

When discussing the ethics of stem cells, it is important to understand the views of the world's major religions. Religion has a deep impact on people's views throughout the world, giving guidance on what is ethical and what is wrong within that faith. Embryonic stem cell research, being the most controversial, focuses on the topic of when life begins. Each religion has its own belief as to when life begins, so from that stance we can derive a discussion of whether it is permissible to destroy the embryo to retrieve ES cells. On the opposite spectrum, the use of adult stem cells is accepted by all major religions, and encouraged to be continually studied to try to save lives. All major religions also agree that *reproductive* SCNT must not be performed, while grouping *therapeutic* SCNT with their particular stance on ES cells.

Judaism

The Judaic religion is in favor of ES cell research because of two important reasons. First, in their faith it is believed that the human body is merely a loan from God, and it is their duty to find cures for diseases. The second reason is that an embryo is not considered to have life until after forty days, and prior to these forty days it is just a mass of cells (Ayon, 2002). This removes the argument of whether ES cell research is ethical because the cells are harvested at day five, well before the embryo is considered to have life. "Our bodies belong to God; we have them on loan during our life. God, as owner, can and do impose conditions on our use of our bodies. Among those is the requirement that we seek to preserve our life and health" (Dorff, 2001). Rabbi Dorff, a professor of Jewish theology at the American Jewish University, interprets both Judaic law and theology, and explains the obligations of the followers to protect the body. The pursuit of curing disease to protect the body makes ES cell research mandated by the faith. The use of SCNT as a source for therapeutically cloned ES cells is also approved in the Judaic religion because it is furthering the pursuit of healing. The one stipulation in dealing with this method is that the cloned stem cells must be used for therapeutic reasons only, not reproductive cloning. (Samber, 2001)

Hinduism

The Hindu religion does not report to one central source, making the exact stance of all Hindu followers undeterminable. The sources of information on Hindu ethics of stem cell research come from various Hindu scholars speaking on their interpretation of beliefs. "In traditional Hindu belief, conception is the beginning of a soul's rebirth from a previous life. Some Hindu traditions place the beginning of personhood between three and five months of

gestation, while few believe that the soul's rebirth can occur as late as the seventh month" (Knowles, 2010). This wide variety of defining when life actually begins does not give a clear opinion to formulate the Hindu ethical stance on stem cell research. However, another source from which to draw a conclusion is to look at Hindu stance on abortion. "Destruction of an embryo could still be justified if it is considered to be an "extraordinary, unavoidable circumstance" and an act "done for greater good"", says Swami Tyagananda, Hindu chaplain at the MIT Religious Activities Center in Cambridge, Massachusetts (Reichhardt et al., 2004). The Hindu debate then comes down to whether stem cell research is for the greater good, curing diseases and saving lives.

Buddhism

Buddhism also does not have a central authority to state its religious opinion on stem cell research. There is no teaching within Buddhism that directly articulates the morality of the research, making it difficult to document whether Buddhists support stem cell research.

> *The Buddhist religion places great importance on the principle of ahimsa, or non-harming, and therefore has grave reservations about any scientific technique or procedure that involves the destruction of life, whether human or animal... Buddhism teaches that individual human life begins at conception. By virtue of its distinctive belief in rebirth, moreover, it regards the new conceptus as the bearer of the karmic identify of a recently deceased individual, and therefore as entitled to the same moral respect as an adult human being (Davis et al.,2006).*

This interpretation of Buddhist beliefs shows a general disposition for doing no harm, so even though stem cell research potentially saves lives, the cost of harming living things to get there is not acceptable. This also includes the use of SCNT to obtain ES cells, because it also destroys an embryo. The only acceptable method in the Buddhist religion is the use of adult stem cells because there is no destruction of life. (Holmes, 2004)

Christianity

Christianity is made up of many faiths, such as Catholic, Orthodox, and Protestant Churches. The Christian faith generally teaches that the life begins at conception, and the embryo has a soul, so it must be treated as a human being. The Catholic Church is the most clear Christian religion on the topic of ES cell research, with the Pope making direct statements on the topic. "When human beings in the weakest and most defenseless state of their existence are selected, abandoned, killed or used as pure 'biological material,' how one can deny that they are being treated not as 'someone' but as 'something?'" (Pullella, 2008). This quote comes from Pope Benedict in an address to members of the Vatican department on doctrinal matters, demonstrating his strong displeasure with ES cell research. This matter is of high importance to the Catholic Church even though there is no direct link to passages in the Bible that demonstrate when life begins, making it hard to derive the church's stance from the Bible. The stance from the Catholic Church towards ES cell research is that it relies on the destruction of some defenseless human beings for the possible benefit of others (Fastiggi, 2010). The form of stem cells research that is approved by the Catholic Church is adult stem cells. Pope Benedict XVI in 2008 approved of this method of stem cell research giving it an ethical approval in an article form Catholic.org "Adult Stem Cell research is fully supported by the Catholic Church. In fact, the Church is helping to fund it" (Deacon Keith Fournier, 2010).

The Methodist church, a branch of Christianity, is not as strict when it comes to embryonic stem cell research. Many of the core beliefs are about the same about the embryo having life and needing to be treated with respect and dignity; however there is a place for the acceptable use of embryos for research. "Given the reality that most, if not all, of these excess

embryos will be discarded—we believe that it is morally tolerable to use existing embryos for stem cell research purposes" (United Methodist Church, 2004). This instance of using embryonic stem cells is only tolerable because the research is for the benefit of mankind. So within very extensive global religions, such as Christianity, different stances on stem cells can exist.

Islam

The Islamic faith is guided by two sources of law, The Qua'ran and the Shari'ah. But, from these two documents of the history of the religion there is no direct discussion about embryos or life. The interpretation from the Qua'ran is that life begins when ensoulment, the breathing of Allah's spirit into the fetus, takes place. There is a difference in opinion whether this takes place at forty days or one hundred and twenty days from conception, depending on one's interpretation of the Qua'ran (Fadel, 2007), but in either case it is well after five days after conception, so deriving ES cells is not considered destroying a life. The following is a translated interpretation of religious opinion from the Muslim world league's Islamic Jurisprudence Council conference in December 2003.

> *It is permissible to acquire, grow and use stem cells for therapy or scientific research as long as the cells' sources are permissible. Examples of permissible sources are adults who consent as long as it does not inflict harm on them, children whose guardians consent for a legal benefit without inflicting harm on the children, placenta or umbilical cord blood with the permission of the parents, spontaneously aborted embryos or those aborted for a legally acceptable cause and with the permission of the parents, and excess fertilized eggs produced during the course of IVF and donated by the parents with assurance that they are not to be used to produce an illegal pregnancy. It is forbidden to obtain or use stem cells if its source is forbidden. Examples of this include fetuses intentionally aborted without a legal medical reason, intentional fertilization between a donated ovum and sperm (Fadel, 2007).*

This statement gives a very precise stance on stem cell use from a high official within the Islamic faith. Stem cell research is allowed as long as other forbidden laws of faith are not violated at the same time, and the research is going to benefit the good of mankind. The use of SCNTs is

permitted because it strives to achieve benefits for the greater good, as long as it stays away from reproductive cloning.

iPS Cell Ethics

Induced pluripotent stem (iPS) cells were first produced from humans in 2007 (Takahashi et al., 2007) and this brought forth a new direction in stem cell research. As discussed in Chapter-1, iPS cells are an alternative to using ES cells derived from fertilized embryos, and open new paths for research in stem cells. iPS cells are pluripotent cells induced to a de-differentiated state by treating an adult cell (such as a skin fibroblast cell) with a combination of transcription factors to induce the change to the ES-like state. iPS cells are less controversial than embryo-derived ES cells because no embryo is destroyed. Being able to stray away from having to use embryonic stem cells allows scientists to remove themselves from controversy because there is no destruction of the potential life. The discovery of iPS cells hopefully creates another alternative to using ES cells, but it is critical for scientists to prove that iPS cells are as medically potent as ES cells. iPS cells also provide less chance of immune rejection than ES cells because the cells are created from the patient's own body. After the initial announcement of the first human iPS cells, President George Bush's Press secretary released, "By avoiding techniques that destroy life, while vigorously supporting alternative approaches, President Bush is encouraging scientific advancement within ethical boundaries" (Ertelt, 2007). This new technique has even shown light to President Bush, someone who was strongly against using ES cells.

Chapter-3 Conclusion

The topic of stem cell research will always be surrounded by an ethical debate because it is on the forefront of science, and it is still being determined as to what is capable from this research. Embryo research was started in the 1960's with the application of IVF to humans, and since then has gone through many stages and developments. The hope is that the research will lead to cures for major diseases, but for this to happen research must be strongly supported.

Although some religions feel working with ES cells is unethical, this author feels that sacrificing something that is smaller than the tip of a needle to cure diseases is well worth it. With respect to the source for embryos, the use of excess IVF embryos originally created for *reproductive* purposes is the most logical place to begin. Now that those excess embryos are no longer needed, they should be used to save lives in the future. If those embryos become depleted, then the author of this chapter believes IVF embryos should be created solely for research purposes, with donor consent. To this author, it does not matter whether the embryos come from reproductive IVF clinics or are created in a lab solely for research, it is important to have these embryos to continue ES cell research.

With respect to adult stem cells (ASCs), medical progress has already been shown with these cells, but the downside to using them as the sole source of stem cells is their capabilities are not as vast as ES cells. They are hard to isolate and grow. So this author feels that ASCs should be used to treat specific diseases when their potency proves high enough, and if not ES cells should be used.

Induced pluripotent stem (iPS) cells are the biggest discovery in the past decade of stem cell research. These cells appear to be pluripotent, and could provide a replacement for ES cells derived from fertilized embryos, but more research must be done to prove their potency. iPS

cells remove the ES cell controversy, and allow researchers to concentrate on moving forward with their work. If iPS cells eventually prove to be as potent as ES cells, the author believes ES cells may become phased out based on their negative ethical associations.

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CHAPTER-4: STEM CELL LEGALITIES

Clinton Biltucci

Introduction

Beyond the ethical and moral issues associated with controversial stem cell research lie the laws that regulate the research. The use of embryonic stem (ES) cells is highly debated due to the demolition of an *in vitro* fertilized (IVF) blastocyst embryo used to isolate the cells. Thus, the laws regulating ES cell research focus on embryos and embryo research. Can embryos be used for research purposes? If so, who pays for it? Must the embryos come from IVF clinics where they were initially created for reproductive purposes? Can embryos be created solely for research purposes? Must donor consent be required to obtain an embryo? Each country must deal with these questions.

Since the advent of IVF in the late 1960's, the topic of embryo research has been highly contested in the United States. Americans have seen both progression and regression in the research and use of stem cells through different presidential terms in the past few decades. And stem cell research is a major issue that has influenced American voters in the past presidential elections. Not only is this a domestic issue, but many countries throughout the world have created stem cell policies. This chapter will document some of the U.S. and international policies on embryos and stem cell research.

U.S. Presidential Stem Cell Policies

Early U.S. Embryo and Stem Cell Policies

In the late 1960's, IVF procedures were first applied to humans. These clinics produce fertilized embryos for reproductive purposes, but not all of the embryos are used. This creates excess embryos, and fierce debates have since ensued whether these excess embryos can be used for research. Moreover, in 1973, the Supreme Court decision on Roe vs. Wade (Vestal, 2008) legalized abortion, and the decision subsequently brought forth a stronger debate concerning the research of tissues isolated from aborted fetuses. Fearing women would be encouraged to have abortions to create tissues for research, Congress decided not to fund embryo research or to allow research on aborted tissues (Wertz, 2002). Thus began the never ending controversy that still surrounds embryo and stem cell research to this day.

In 1974, President Nixon's *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* recommended a ban on all federally funded research using embryos and fetal tissues, and the ban was enacted by congress. Although President Ford in 1975 initially appointed an Ethics Advisory Board to make recommendations on embryo and fetus research, in 1981 President Reagan ended the ethics board's charter, allowing the original 1974 ban to remain in effect (Stem Cell Tracker, 2009).

President Clinton's Stem Cell Policies (1993-2001)

President Clinton was a great supporter of stem cell research. It can be said that much of the former President's support stemmed from a friendship with the former chief of staff Erskine

Bowles. President Clinton made his views apparent on stem cell research with the following statement:

> Diabetes afflicts two children of my friend and former chief of staff Erskine Bowles, as well as millions of other Americans, with a disproportionate impact on our minority population. When I became President, I learned that diabetes and its complication account for a staggering 25% of all Medicaid costs. That's a big reason why, as President, I supported stem cell research (Clinton, 2004).

In January 1993, newly elected President Clinton reversed the original 1974 ban on fetal tissue research by passing the *National Institute of Health Revitalizations Act*. This act allowed the National Institute of Health (NIH) to fund human embryo research (Dunn, 2005). A year later, recommendations came forth from the *NIH Human Embryo Research Panel*, which was created by Clinton to examine both moral and ethical issues surrounding stem cell research. One recommendation included the use of spare embryos from fertility clinics as a source of tissue for research, and as a source for deriving ES cells. Although many scientists viewed these recommendations as valid because no new embryos would be created or used only for research purposes (they would be initially created only for reproductive purposes), the recommendations created an uproar. Within a year, Congress banned the use of federal funds for any experiment in which a human embryo is either created or destroyed by *any* means, including for reproductive purposes (Dunn, 2005).

Later in 1998, the first human embryonic stem cell lines were created (Thomson et al., 1998). This was a major scientific achievement that provided hope for treatment of conditions such as Parkinson's, heart disease, and diabetes. Director of the NIH, Harold Varmus stated "This research has the potential to revolutionize the practice of medicine" (Dunn, 2005). However, with the congressional ban still in place, no *federal* funds could be used to support ES research, so this new human ES research was funded by *private* institutions.

President Bush's Stem Cell Policies (2001-2009)

Stem cell research experienced a deep delay beginning in 2001 due to new laws and legislation that came forth during the Bush administration. In his State of the Union address, President Bush was quoted saying, "...no human life should be started or ended as the object of an experiment" (Agnew, 2003). In 2001, new legislation in both the House and Senate was set in place. First a law was enacted to ban the use of somatic cell nuclear transfer. This was a type of cloning technique used to create a living human organism that had only been used on sheep in the past. And with respect to human embryos, President Bush announced that scientists who received federal research funds could only work with ES cell lines derived prior to August of that year (Agnew, 2003). As President Bush said:

> "I'm a strong supporter of adult stem cell research, or course. But I made it very clear to the Congress that the use of federal money, taxpayers' money, to promote science which destroys life in order to save life is -- I'm against that. And therefore, if the bill does that, I will veto it." (Baker, 2005)

The Bush August 2001 ban on federal funding to derive new ES cell lines severely limited the total number of lines available to researchers. Although initially the number appeared to be near 100, several lines quit growing, some were determined to be genetically identical, and others were unable to differentiate, so the final number was more like 20 (Holden and Vogel, 2002; Rowley et al., 2002; Abbott et al., 2006; Ford, 2006). In 2004, President Bush received a letter sent from 58 Senators, including 14 Republicans, pleading to expand the number of stem cells lines that could be used experimentally for federal funded research (Dunn, 2005). These Senators believed that the restrictions made by the Bush administration were stunting medical advances.

Although in 2006, the Senate voted to loosen restrictions that President Bush had placed on stem cell research, President Bush vetoed the bill (Bash, 2006). "The bill, which the Senate passed....would have loosened the restrictions on federal funding for stem-cell research" (Bash, 2006). President Bush believed the bill would support taking innocent human life in hope of discovering medical benefits for others (Babington, 2006). During his administration, Bush would go on to veto yet another bill proposed by the Senate, claiming that stem cell research was unmoral due to human embryos being destroyed.

President Obama's Stem Cell Policies (2009-Present)

In March 2009, newly elected President Barack Obama signed an executive order in which researchers could apply for grant money to study some of the hundreds of cell lines that were derived from *private* funds under the Bush administration, and would now become available (Childs and Stark, 2009; Hayden, 2009; Wilson, 2009). The funding to support ES research will come from 'Challenge' grants, which will be funded by the economic stimulus package (Kington, 2009). Obama's executive order removed the 2001 restrictions set in place during the Bush administration and expanded NIH support of human stem cell research. Under this order, the Secretary of Health and Human Services may conduct scientifically worthy human stem cell research, including human embryonic stem cell research (Kington, 2009). As President Obama stated:

> "In recent years, when it comes to stem cell research, rather than furthering discovery, our government has forced what I believe is a false choice between sound science and moral values. In this case, I believe the two are not inconsistent" (Wilson, 2009).

President Obama's views on stem cells are evident. "At this moment, the full promise of stem cell research remains unknown, and it should not be overstated" (Childs, 2009). It is

Obamas's hope that the United States will soon become one of the world's leading nations within the field, and enhance the contribution of America's scientists in important new discoveries that will benefit humankind. Obama stated: "We will vigorously support scientists who pursue this research. And we will aim for America to lead the world in discoveries it one day may yield" (Hayden, 2009). However, even with the new order, President Obama was clear this would *not* open the door to human reproductive cloning when he stated:

> "We will develop strict guidelines, which we will rigorously enforce, because we cannot ever tolerate misuse or abuse. And we will ensure that our government never opens the door to the use of cloning for human reproduction. It is dangerous, profoundly wrong, and has no place in our society, or any society" (CBS/AP, 2009).

The transition from the Bush administration to the Obama Presidency has seen an increase in the number of available ES cell lines. Estimates of these new lines range from 400 to 1,000 since President Bush cut federal funding for stem cell research in 2001 (Hayden, 2009). The significance of many of these new lines is that they were derived from embryos that had genetic predispositions to specific diseases, so these lines could be more relevant to disease research (Hayden, 2009).

Obama's 2009 executive order also called for the NIH to develop *guidelines* and regulations to govern federally funded human embryonic stem cell research. The NIH titled these guidelines the "*National Institutes of Health Guidelines for Human Stem Cell Research*" (Federal Register, 2009). These *guidelines* were initially published in preliminary form, but were later released in a more finalized form (Holden, 2009). The *guidelines* are based on two main principles. The first being that research with human embryonic stem cells has the potential to improve our understanding of human health and illness, and discover new ways to prevent and/or treat illness. Thus, the guidelines favor working with ES cell lines. The second guiding principle states that individuals donating embryos for research should do so freely, with

voluntary and informed consent (Kington, 2009). The guidelines are divided into several sections that apply specifically to embryos donated in the United States or obtained from foreign countries.

Section I consists of a scope of the guidelines. Section II describes the conditions and review processes for determining human embryonic stem cell eligibility for NIH funds (Kington, 2009). A controversial part of this section is the mandate to obtain embryos only from IVF clinics where the embryos were originally created for reproductive purposes, and with donor consent. Many scientists wanted NIH to recommend creating embryos for research purposes, as currently allowed in some countries, but NIH went with the more conservative stance. Section III is brief, but describes the use of NIH funds to support stem cell research. Sections IV and V describe research that is *not* eligible for NIH funding, such as inserting primate ES cells into blastocysts for implantation to alter the germ line (Kington, 2009). Section V includes two subsections. The first states that NIH funding is prohibited in reference to the derivation of ES cells from human embryos in accordance with the *Omnibus Appropriations Act* (Kington, 2009). The second rejects NIH funding for human ES cells derived from other sources such as somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created solely for research purposes (Kington, 2009). It is the job of the NIH to review and update these guidelines periodically. One recent recommendation is that donor consent be obtained at the time of sperm and egg donation, not afterwards at time of embryo usage (Lo et al., 2010).

Individual State Funding of Stem Cell Research

California

California did not get to where they are today without controversy. In 2002, the International Society for Stem Cell Research (ISSCR) was formed. This is an independent, nonprofit organization that was created to exchange information on stem cell research. That same year, California was declared to be a "restriction-free zone" (allowing them to work with ES stem cells) by then acting Governor Gray Davis (Scott, 2006). The zoning law allowed therapeutic cloning and embryo research, but banned reproductive cloning (Scott, 2006).

In 2004, California voters approved *Proposition 71*, a 10 year, 3 billion dollar funding program for stem cell research (Vestal, 2008). This placed California ahead of the federal government and many other nations in promoting stem cell research. In 2005, scientists in California were able to help partially paralyzed mice walk again (Palca, 2007) by injecting human neural stem cells into the spinal cords of the mice. When the California stem cell funding stalled in 2006, Governor Schwarzenegger provided a state loan of 150 million dollars. "This is why we are not waiting for anyone to do it for us, we are creating the action right here in California," said Schwarzenegger (Palca, 2007). California is also noted for its biotech industry where nearly 11% of the country's biotech scientists work.

New Jersey

New Jersey became the first state in 2004 to actually appropriate state funding for stem cell research. A reported 10 million dollars in funds was to be distributed over 10 years to university, non-profit, and commercial labs in the state (Vestal, 2009). In 2006, governor Jon Corzine signed a bill to establish several stem cell research facilities in New Jersey. A reported

150 million dollars was spent to establish the *Stem Cell Research Institute of New Jersey* (Vestal, 2009). In 2007, the *New Jersey Commission of Science and Technology* (NJCST) awarded more than 10 million dollars in stem cell research grants. Of this 10 million, 5.5 million dollars was given to two core facilities, and the remaining was awarded in individual grants (The Commission, 2007).

Massachusetts

In 2007, Massachusetts Governor Deval Patrick proposed 1 billion dollars in state funding for biomedical research (Estes, 2007). Half of this money would be used to establish a research center that would house the nation's largest embryonic stem cell bank. And Massachusetts legislators added two new sections to the statutes on stem cell research. The first would create an institute for stem cell research and regenerative medicine at the University of Massachusetts; 1,000,000 dollars was to be spent on the stem cell biology core alone (National Conference of State Legislatures, 2008). The second section would grant a reported 10 million dollars in funds to create a life sciences center that would promote research in advanced and applied sciences which includes stem cell research (National Conference of State Legislatures, 2008).

Making this preliminary plan come alive, later that same year the Board of the *Massachusetts Life Sciences Center* (MLSC) voted to approve more than 8.2 million dollars in funding to the University of Massachusetts Medical School (UMMS) (Worcester) (Shelton, 2007). The money was used to establish the *Massachusetts Human Embryonic Stem Cell (hESC) Bank* and an *Iternational Massachusetts hESC Registry* (Shelton, 2007). The Massachusetts hESC Bank serves as an international repository of human ES cells derived from all over the

world, while the hESC Registry promotes efficiency in human ES cell research and the disbursement of the hESC lines.

International Stem Cell Policies

In 2002, German Parliament voted to allow the import of ES cells for scientific research (Kim, 2002). This decision drew much criticism from Germany's Catholic and Protestant Churches who believed that Parliament's decision threatened the "protection of human life from the moment of conception" (Kim, 2002). Today, Germany remains one of the more conservative states in Europe in forbidding the derivation of any new human ES cell lines. New hESC lines can be *imported* for research in Germany, however importation is only permitted under strict conditions (Hoffman, 2005).

Japan is a very liberal nation when it comes to hESC research. Policies regarding the research of human ES cells not only allow research on supernumerary embryos, but also on embryos created specifically for research (Ritter, 2009). Japan also allows scientists to conduct somatic cell nuclear transfer (Ritter, 2009). England, Sweden, China, and Israel are also countries that strongly support ES cell research.

Chapter-4 Conclusion

After researching the legal issues surrounding human ES cell research, I truly believe that the government should fully back this new technology. In the United States, the funding available for ES cell research has been tied directly to the President in office at the time. Our country experienced a period ES cell prosperity during the Clinton administration, but foundered during the Bush administration. Under President Obama, our country now has started taking the

right steps to federally fund ES cell research. I believe that the level of ES cell scientific success in our country has come at the mercy of the President in office at the time. I believe that the strong support of government is crucial for the advancement of science, and this is exactly what scientists need to make medical advances to improve life.

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PROJECT CONCLUSIONS

The authors of this IQP project believe that it is acceptable to work with ES cells considering the number of medical applications that can be used to benefit society. However, there are still many obstacles that inhibit the growth of stem cell research, including political and moral debates, lack of funding, and scientific technical barriers that still need to be crossed before more clinical advances can be accomplished. We believe the potential benefits that can be obtained through the use of stem cells in applied medical therapies, such as Parkinson's Disease, heart attacks, and diabetes, are too great to ignore.

As for an acceptable source of embryos to derive ES cells, the authors believe ES cells may be derived from unused IVF embryos originally created for reproductive purposes, or from paid egg donors. We believe that the 5-day IVF embryo is not yet a full human being when ES cells are removed, rather it is a mass of cells with the *potential* to develop into a human. Although our research documented that some people believe ES cell research to be immoral when life begins at conception, we acknowledge both sides of the argument but believe that ES cell research is about benefiting human life in the most therapeutic and practical ways possible. Induced pluripotent stem cells (iPSCs) and adult stem cells (ASCs) are a great alternative to the moral issue that surrounds ES cells, and these cells should be used whenever possible, but the focus of stem cell research should ultimately be devoted to ES cells as they are the most powerful to benefit patients.

However, a line needs to be drawn as to how far this research will take us in terms of *reproductive* cloning (cloning entire human beings), and so the authors agree with all countries that have currently banned reproductive cloning. With respect to other stem cell policies, our

group members agreed most with England's policies, arguably the most liberal nation. Japan is also another nation with legislation that permits the research on ES cells and also allows SCNT. The main reason our group chose these countries is due to the availability of federal funding. Once group member accredited Japan and England's strong stem cell scientific progress to the strong federal funding in both nations. Everyone agreed that our government should provide more federal funding for ES stem cell research.

The study of stem cells is progressing at an exponential rate, but should always be used for the good of mankind. This means that the patient in need of medical care will receive the most efficient and therapeutic techniques possible, regardless of the source of stem cells needed to obtain these results.