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# STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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# ABSTRACT

Stem cell research is one of the most promising, yet controversal, medical topics in today's world. The purpose of this IQP is to investigate the potential applications of many different types of stem cells in various diseases, and to explore beyond the technology itself to discuss their legalities and ethics. Based on our research, our group concludes that, despite heated debates from both religious and political standpoints, stem cell therapies show strong benefits to society. We agree that embryonic stem cell research should be expanded, and agree with Obama's recent legislation to allow federal funding to support this new technology.

# TABLE OF CONTENTS

# PROJECT OBJECTIVES

The objective of this IQP project is to examine the topic of stem cells, and to discuss the effect of this controversial new technology on society. The purpose of chapter-1 is to classify stem cells, describe where they are isolated from, highlight their differences, and discuss their different potencies. Chapter-2 documents which types of stem cells have already been used in medical applications, distinguishing animal experiments from human clinical trials, and delineating which experiments remain as future applications. Chapter-3's purpose is to show the ethical views of five major world religions surrounding this topic, while Chapter-4 discusses the U.S. and international laws governing stem cell use. Finally, in the conclusion, the authors of this IQP announce their opinions regarding the use of stem cells based on their research.

# CHAPTER-1: STEM CELLS: TYPES AND SOURCES

*Aaron Sciore*

Twenty years ago, if you told a biologist that we were a few decades away from being able to regrow entire organs, you would have gotten laughed out of the building. Where this idea once solely occupied the realm of science fiction, it is now considered not just a reality, but an inevitability. The reason for this sudden change lies in a special kind of cell known as a 'stem cell', some types of which can reproduce endlessly, and are also capable of transforming into any type of cell in the human body. Named "breakthrough of the year" in 1999 by the journal *Science* (Vogel, 1999), these cells are the focal point of a revolution in biology and medicine known as *regenerative medicine*. Whereas before it was only possible to treat the symptoms of certain diseases, such as giving diabetics insulin, stem cells have given us the ability to actually regrow disabled or dysfunctional organs. Diabetic mice treated with stem cells have regrown a working pancreas (Hess et al., 2003), and rats with spinal cord injuries have achieved new mobility from stem cell therapy (Keirstead et al, 2005).

**Stem Cell Plasticity**

The primary defining feature of a stem cell is *plasticity*, or its ability to become a variety of different cell types. As an organism is created and its cells divide, its cells become more specialized, until they fully differentiate into adult cells which constitute our organs. Stem cells are not all alike, and each type has a different degree of plasticity. The more differentiated a stem cell is, the more it is restricted to which types of adult cells it can make. For instance, hematopoietic stem cells, the stem cells responsible for maintaining the blood system, are

naturally restricted to forming mainly blood and marrow cells, although this is not always the case. The degree of plasticity is most often divided into four categories: *totipotent*, which can form all types of cells, including all of the cells in the adult and the placenta. Currently the only cells known to be totipotent are the very early stages of development, a newly fertilized zygote through blastomere formation to about the 8-cell stage (Chamany, 2004). As the blastomeres continue to develop to about day-4 to 6 post-fertilization, they form a hollow ball of cells termed a blastula, consisting of an outer shell known as the trophoblast, which becomes the placenta, and the Inner Cell Mass (ICM), which consists of the famous and controversial embryonic stem (ES) cells. These ES cells are termed *pluripotent*, which are cells that can differentiate into any cell in the organism, but not the placenta.

Further differentiation yields *multipotent* cells, such as the previously mentioned hematopoietic stem cells, which can form several cell types, but are restricted as to what cell types they can create. 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 Self-Renewal**

A second remarkable characteristic of stem cells is their ability to regenerate. ES cells have the potential to replicate endlesslly, while most ACSs can not. Without any environmental factors that cause differentiation, ES cells will self-renew infinitely. For example, a single ES cell, surrounded by feeder cells (usually mouse fibroblasts are used), can grow into millions of the same type of stem cell. Doing this is called creating a *lineage*. The conditions for creating and maintaining lineages vary between different types of stem cells, and not all stem cells are equally able to generate lineages (Zipori, 2005).

## Naturally Occurring Stem Cells

There are many different types of stem cells which occur naturally in all mammals, but they can be grouped into two major categories: *Embryonic* and *Adult*.

### *Embryonic Stem Cells*

The most well-known type of stem cell is the Embryonic Stem (ES) cell. These cells, found within the hollow mass of a 4-6 day old embryo, are pluripotent, and have the ability to reproduce endlessly. ES cells have the most therapeutic potential of any of the naturally-occurring stem cells, and have been shown to cure many diseases in animal test cases, which will be fully reviewed in Chapter 2. Different lines of embryonic stem cells vary significantly in both their rate of growth on a feeder medium, and their likelihood to differentiate into certain tissue types. In a study of 17 human ES cell lineages, two lineages showed an order of magnitude more potential to enter the cardiovascular lineage than seven of the other lineages tested (Chien, 2008).

When an embryo is forming, its cells will divide from 1 to 2 to 4 to 8, forming a cluster of identical totipotent cells called blastomeres (**Figure-1,** diagram upper center). Upon further division, the embryo will differentiate into a blastocyst (diagram center) containing an outer shell known as the trophoblast, which becomes the placenta, and a cluster of pluripotent cells on the inside known as the Inner Cell Mass (ICM). The blastocyst can be as large as 100 cells before the embryo continues to differentiate. The cells that constitute the ICM are the ES cells, nearly completely undifferentiated and with significant self-renewal ability. At around the five day point, the blastocyst is fully formed and can be harvested for ES cells (diagram lower).

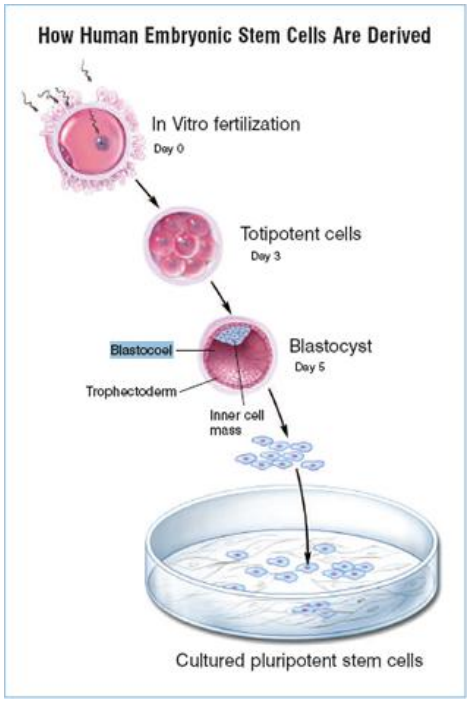


**Figure-1: Diagram of ES Cell Isolation**. ES cells, shown in blue, are isolated from day-5 blastocysts (diagram center) and grown on feeder cells (diagram lower) that provide growth factors. (Regenerative Medicine, 2006)

Unfortunately, the process of gathering ES cells from the ICM inevitably involves the destruction of the embryo. This is of significant ethical concern for many reasons, which will be fully reviewed in Chapter 3. Because this process was illegal under the Bush administration (recently overturned by President Obama), there have been significant efforts to obtain ES cells from non-viable or abnormal embryos (Zhang 2006) with decent success.

*Adult Stem Cells*

Adult stem cells (ASCs) are rare, partially-differentiated cells that exist within many organs in the body. They exist to help repair damaged tissue and grow new tissue within their organ of assignment. The term 'adult' does not refer to the age of the organism, only that it is observed in organisms later than the embryonic stage. The practice of using adult stem cells for

medicinal purposes dates to before the term ‘stem cell’ was coined. Doctors have been using bone marrow transplants since 1939, when it was first successfully applied to treat aplastic anemia (McCann, 1988). Once it was discovered that the active component in bone marrow is adult stem cells, the field took off. Since then, scientists have isolated adult stem cells in many organs in the human body, and have used them therapeutically to great effect.

The main categories of adult stem cells (hematopoietic, mesenchymal, neural) are multipotent, though there are many more types of more differentiated unipotent stem cells that will not be reviewed here. In most areas of the human body adult stem cells are exceedingly uncommon; this has made isolation and characterization of less-prevalent types of ASCs very difficult.

Unlike ES cells, ASCs do not have infinite growth capacity, and do not readily form lineages. It was assumed for a long time that this was a natural product of differentiation, that is, as a stem cell further differentiates it loses more and more capacity to regenerate, until it becomes a terminally differentiated cell which reproduces very slowly. It is now known that this is not at all the way stem cells behave. Renewal potential for different types of stem cells is highly variable and not at all dependent on the renewal potential of the less-differentiated cell (Zipori, 2005). Multipotent neural crest stem cells, for example, regenerated much slower than the bipotent progenitor cells found towards the bottom of the differentiation hierarchy (Trentin et al., 2004). Similarly, T and B lymphocyte cells, a terminally differentiated product of the hematopoietic cell system, reproduce far faster than hematopoietic stem cells (Zipori, 2005). This behavior makes sense, as lymphocytes and other immune suppressors need to be created much more rapidly than most other types of blood cells.

*Hematopoietic Stem Cells*

Hematopoietic stem cells (HSCs) are the precursors to all the different types of blood cells in our bodies. This is no small task – the average human body goes through around 100 billion hematopoietic cells every day (*Regenerative Medicine*, Chap. 2, 2006). HSCs differentiate along a very rigid hierarchy that quickly separates the rapidly-proliferating lymphocyte blood cells from the more slowly renewing myeloid tree (see **Figure-2**).

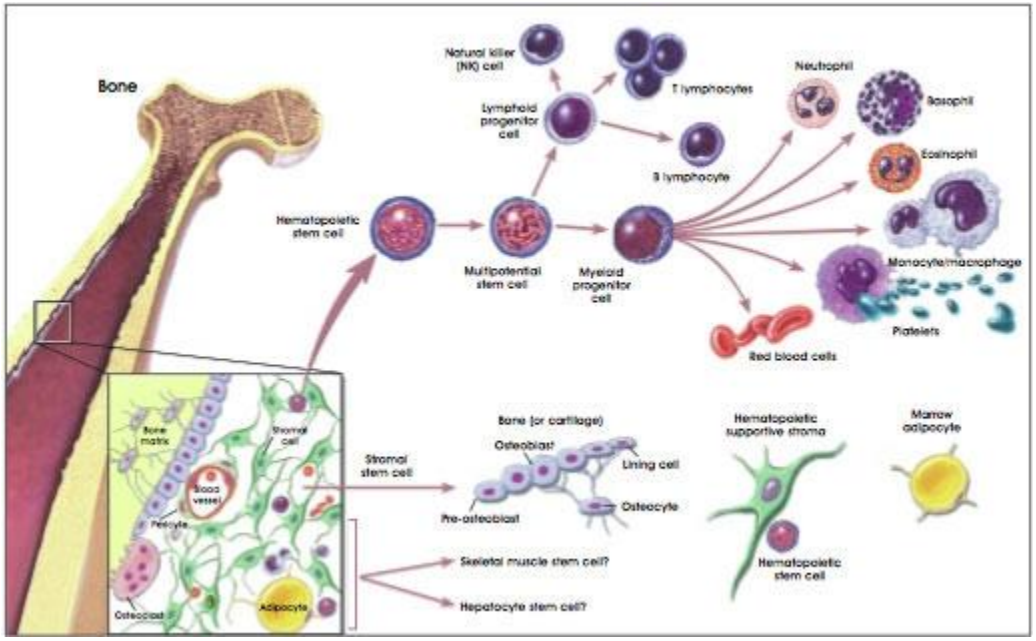


**Figure-2: Diagram of Hematopoiesis and the Role of Hematopoietic Stem Cells**. The diagram shows the isolation of a hematopoietic stem cell (HSC) (center left) from bone marrow (diagram left). The HSC can differentiate into myeloid or lymphoid progenitor cells (diagram upper), which differentiate into more specialized blood cells (diagram upper right). (Regenerative Medicine, 2006)

There are three main sources for HSCs:

1) **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, and the most commonly used source. HSCs are relatively frequent in bone marrow, occupying around 1 in 10,000 cells. This is concentrated enough that extracted bone marrow can be used therapeutically

without needing to further isolate the HSCs. However, collecting bone marrow requires a long needle, and is generally unpleasant, and is slowly becoming phased out with time (*Regenerative Medicine* Chap. 2).

2) **Peripheral blood** is the 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 – only about 1 in every hundred thousand are stem cells. Scientists have been able to increase this concentration by a process known as 'cytokine mobilization', treatment of the donor with cytokine injections which cause the bone marrow to release large quantities of HSCs into the bloodstream, which are then collected. So-called Mobilized Peripheral Blood exhibits over twice as fast a recovery in chemotherapy patients compared to a regular bone marrow transplant (Demirer et al., 1996).

3) **Umbilical cord blood**, as well as placenta, are usually discarded during childbirth, despite it being saturated with HSCs. Many hospitals will allow the mother to freeze the umbilical cord blood and store it at a blood bank, which can subsequently be transplanted 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 they display fewer transplant rejections (*Regenerative Medicine,* Chap. 2, 2006).

*Mesenchymal Stem Cells*

Mesenchymal Stem Cells (MSCs) are the other type of stem cell found in the bone marrow, and it is primarily responsible for the creation of connective tissues, i.e. bone, tendons, muscle, and cartilage. In the bone marrow it forms stroma, the architecture that hematopoietic stem cells grow in. Though they exist in a similar concentration in the bone marrow, MSCs are much easier to isolate, as they readily stick to certain types of plastic, and will propagate readily in a culture medium (Jones, 2007).

Unlike HSCs, MSCs do not have an ordered hierarchy of differentiation, and may differentiate into many different cell types without intermediate steps, even those outside of the traditional mesenchymal system. In tests run on mice infected with gastric ulcers, MSCs were observed to migrate from the bone marrow to the ulcer and differentiate into gastric cells (Zipori,

2005). MSCs have also been observed to contribute to cardiomyocytes (heart muscle), pancreatic and liver cells, and even neural cells (Sell, 2005)

*Neural Stem Cells*

Before the discovery of Neural Stem Cells (NSCs) in the 1990s, the brain was assumed to be a fully mature organ – no new cells were being made, and once the brain starts degenerating, the only medicine was to buy more time. Neural stem cells found in mice and eventually humans challenged that assumption, and gave hope that patients with degenerative diseases such as Parkinson's could be cured. NSCs are tripotent, they can form the neurons which make up the brain and nervous system, as well as glia and oligodendrocytes, the supporting cell structures surrounding the neurons and providing them nutrients (*Regenerative Medicine,* Chap. 3, 2005).

Only since 2001 have NSCs been isolated and cultured, most likely because NSCs 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, and much research is dedicated to uncovering why this is, and how to stimulate their activity. The primary locations for NSCs are two places: the subventricular zone, found on the edge of the brain's fluid-filled cavity, and the hippocampus, though they also have been found in the spinal cord (Shihabuddin et al., 2000) and the olfactory bulb (Pagano et al., 2000). It is even possible to extract NSCs from recently-deceased bodies (Palmer et al., 2001). Recent research suggests that there are a wide range of unipotent neural stem cells, each capable of producing a different type of neuron (Merkle, 2007). While this discovery makes life momentarily harder for researchers, it ultimately will give us much better

control over the brain's activity, for example NSCs that only form dopaminergenic neurons (the primary target of Parkinson's disease) could be isolated, and implanted into a patient's brain.

*Cardiac Stem Cells*

Much like the brain, the predominant belief in the scientific community until recently was that the heart was a mature, terminally-differentiated organ incapable of regeneration. The heart naturally produces very little new tissue after birth, and most of the observable new tissue formed in the adult heart after an injury such as a heart attack is scar tissue (Passier, 2008). Evidence now suggests that the body naturally regenerates heart tissue – months after successful heart transplants of mismatched sex donors, the new heart muscle was a mosaic of both XX and XY chromosomes (Quaini et al., 2002). In 2003, a team of scientists identified multipotent cardiac stem cells with clonogenic and regenerative properties. The cardiac stem cells are capable of forming the three major tissues in the heart: myocytes, smooth muscle, and endothelial vascular cells (Beltrami et al., 2003). There is significant debate about where exactly cardiac stem cells reside, though there is evidence they exist in very small numbers in the heart atrium and ventrical walls (Boyle, 2006), and in reservoirs in bone marrow (Orlic, 2001). Cardiac stem cells show remarkable ability to self-renew. When they are purified and injected into a damaged heart, the heart can regenerate over half of the damaged tissue within a few weeks. Like neural stem cells, cardiac stem cells do not appear to work very quickly, though explosive growth has been observed after heart attacks (Beltrami, 2003). There is still a lot to be learned about the biological mechanism that turns these cells on and off.

**Plasticity of Adult Stem Cells**

The traditional model of multipotent adult stem cells (for the major ASC categories discussed above) assumes that each adult stem cell can only differentiate into mature cell types in their respective lineages, e.g. blood stem cells become blood cells and nothing else. However, this assumption has been challenged in recent years by more evidence suggesting that adult stem cells, when induced by certain conditions, can differentiate into cell types far outside their respective lineages. Bone marrow-derived stem cells, consisting primarily of mesenchymal and hematopoietic stem cells, have been shown to differentiate either *in vivo* or *in vitro* into numerous cell types, such as liver, skin, digestive tract, muscle, kidney, heart, and pancreas cells (Prentice, 2003). Bone marrow has been used successfully in differentiating into less common cell types, with bone marrow transplants regenerating retinal cells (Otani, 2002), as well as the protective myelin coating surrounding the spinal cord (Sasaki, 2001). These results indicate plasticity far beyond what was previously thought possible with bone marrow transplants, but increased plasticity is also seen with other types of stem cells. Mesenchymal stem cells have been able to contribute to epithelial lung tissue (Ortiz, 2003). Neuronal stem cells can form blood and muscle cells *in vitro* (Clarke, 2000). Stem cells isolated from skeletal muscle have been used to strengthen both the heart (Atkins, 1999) and the bladder (Lee, 2003). Liver stem cells and pancreatic stem cells can easily and rapidly differentiate into either organ's cell types depending on the environment (Wang, 2001; Yang 2002). And finally, hair stem cells have been able to completely repopulate the mouse hematopoietic system (Lako, 2002). To say that the theories of adult stem cell plasticity are being reviewed is something of an understatement, as the

ability to form difficult tissue like brain from easy to obtain HSCs would be a major therapeutic achievement.

## Other Sources of Pluripotent Stem Cells

Embryonic stem cells are pluripotent and powerful, but they have many innate and legal disadvantages. Using ESCs for therapy can be highly dependent on the genes of the embryo they are harvested from. If that embryo had a faulty heart gene, it would be undetectable since the embryo never had a heart. There are also problems of availability; since there are only several hundred lineages of ESCs that can be purchased, successfully matching donor stem cells to patients can be completely based on good guessing.

### *Tests of Pluripotency*

Pluripotency is not a binary state: it can exist in many different forms and capacities. Simply finding the markers for stemness is the bare minimum requirement for considering a cell pluripotent, it says nothing about the actual ability of that cell to differentiate into other cell types. There are several assays which are currently useful for determining the pluripotent developmental potential of a cell (Jaenisch, 2008):

> -***in vitro*** **differentiation**: The cells are exposed to different sets of conditions known to induce differentiation in pluripotent cells into various types of cells. The pluripotency is measured based on the ability of the differentiated cell to produce cell-specific markers. This test is the least stringent, and it does not provide any information about its ability to differentiate *in vivo*.
>
> -**teratomas**: An immune-compromised mouse is injected with the test cells, and 6-8 weeks later are examined for the presence of a teratoma. A teratoma is a specific type of tumor consisting of a mass of various differentiated cell types. This tests for the cells'

ability to differentiate *in vivo* but cannot test for any abnormalities in development (Baker, 2009).

-**chimeras**: A chimera is a blastocyst with its inner cell mass injected with test pluripotent cells. The pluripotency is evaluated on how well the test cells contribute to the development of the organism.

-**germ line**: The embryonic germ stem cell is a type of stem cell that cannot be produced except by other germ stem cells and pluripotent stem cells. The germ line assay tests the ability of the cells to make a germ cell, which is then fertilized to try and create a healthy and fertile offspring. This is the most stringent test for defects in the genetic code of the stem cell, as it tests for that single cell's ability to create an entire organism.

**Single Cell Biopsy**

Much of the opposition to embryonic stem cell research comes from the process of destroying viable embryos, and for a long time, this was the only way known to isolate embryonic stem cells. In 2005, a team of scientists were able to sidestep this requirement by extracting a single cell from the 8-cell stage blastomeres (Klimanskaya, 2006). The residual 7-cell stage blastomeres continued to grow and behave as normal, and showed only a minimal loss in viability. The biopsied cells were able to be cultured, and made into ES cell lineages with a 2/3 success rate. This technique, originally tested for use on mice and primate embryos, was soon applied to human embryos with significant success (Klimanskaya, Nov. 2006).

**Somatic Cell Nuclear Transfer (SCNT)**

One of the major disadvantages to using stem cells taken from an embryo usually obtained from an IVF clinic is that they will always have a different genetic background than the person they intend to inject the cells into. This histoincompatibility problem can sometimes

(usually infrequently) be worked around by establishing a donor-patient histocompatible matching system, but when the goal of treatment is to regrow large chunks of vital organs, there is always the risk of a dangerous or fatal immune response. Even cell lineages taken from within the patient's family are not foolproof.

The only sure way to guarantee a genetic match is by using the patient's own DNA. Somatic Cell Nuclear Transfer (SCNT), also known as therapeutic cloning, is the process of taking a cell from the patient's body (usually a skin fibroblast cell) and transferring its nucleus into a nucleus-free egg. The skin nucleus is reprogrammed by the egg, rendering it in a totipotent state. The egg is then grown into a blastocyst, from which ES cells are harvested. These ES cells should be both pluripotent and patient-specific, dramatically increasing the odds of a successful transplant procedure. While SCNT has proven to work in mice, the current process itself is costly, difficult, and inefficient (Jaenisch, 2008). Many of the clones formed die or have significant mutations due to the nucleus failing to be properly reprogrammed. It is still a contested question as to which types of cells make the best candidates for reprogramming, but the evidence tends to point towards lower levels of differentiation being better (Jaenisch, 2008). As of now, no one has been able to reprogram a human egg, though in 2007 a primate was successfully cloned, and a lineage of its embryonic stem cells was derived (Byrne, 2007). And the infamous 2005 Korean experiment in Hwang's lab was subsequently proven as fraud.

**Parthenogenesis**

In the mammalian model of reproduction, the sperm cells interact with the egg to produce a zygote, which then develops into a fetus. Many lower organisms, such as fish, amphibians, and some insects, reproduce through a different pathway, in which the egg is 'tricked' to induce

development before the addition of the sperm. This process is known as parthenogenesis. In the right conditions, mammalian eggs can also be induced to start reproducing. This is an unnatural and unsustainable process, so the parthenotes will stop reproducing at certain points. Mice parthenotes can only develop for 10 days without human assistance before going into arrest, while cow parthenotes can last as long as 48 days. Human parthenotes are trickier to work with, and it is only recently that scientists have figured out how to make them proceed past the 8-cell blastomere stage of development (Brevini, 2008). Once the parthenote separates into the trophoblast and the ICM, the ICM is harvested, and the ES cells are made into a lineage. These cells show all the normal genetic markers for pluripotency.

The advantages of this technique should be immediately obvious: by using a woman's own egg to create stem cells, there is a guaranteed genetic match to that woman patient and no risk of rejection. The disadvantages are much less obvious, however. Each egg is created with a slightly modified set of genes due to what is known as *imprinting*, which is the cell's way of chemically modifying DNA in the genome. Imprinting can silence some essential genes for reproduction and growth, requiring the opposite sex's set of unimprinted genes to be properly expressed. This is the suspected cause of mammalian parthenotes being unable to come to term, and it may also be the reason why parthenote ES cells have been shown to be only marginally effective when transplanted into tissues. Additionally, because there is only one set of genetic material, any genetic predispositions to cancer or disease are significantly multiplied within the cell line.

**Induced Pluripotent Cells**

In June 2006, a team at Kyoto University led by Shinya Yamanaka rocked the world of stem cell research when it announced it had created pluripotent stem cells out of adult mouse skin cells (Yamanaka et al., 2006). These cells, dubbed induced pluripotent stem (iPS) cells were shown to differentiate and behave exactly like embryonic stem cells, including the ability to infinitely self-renew. Yamanaka accomplished this feat by virally inserting just four genes into the mouse cell: *c-Myc*, *Klf4*, *Oct4*, and *Sox2*. This was a major breakthrough for many reasons. iPS cells are both pluripotent and are patient-specific – the 'holy grail' of stem cell research. But unlike SCNT, which also possesses these qualities, the process of inducing pluripotency does not have to be done methodically under a microscope (Holden and Vogel, 2008). By using a virus to reprogram somatic cells, iPS cells can be generated in batches, with the best cells selected to make lineages.

The ease of making and refining iPS cells has made inducing pluripotency the fastest growing field in stem cell research. 17 years separated the discovery of mouse embryonic stem cells and human embryonic stem cells; that feat was accomplished with iPS cells in just over six months (Baker, 2009) as Yamanaka's lab succeeded in preparing human iPS cells from a 36 year old woman and a 69 year old man (Takahashi et al., 2007). Since then, thousands of labs have formed or been refocused to work on iPS cells.

What induces the iPS cells to become pluripotent? Scientists have known about *Oct4* as an ubiquitous pluripotency marker since the late 1990's, and it was shown by Yamanaka to be a critical gene in activating pluripotency, but only within the past two years has the mechanism surrounding pluripotency been uncovered. The modern theory of pluripotency revolves around three genes: *Oct4*, *Sox2*, and *Nanog* (Jaenisch, 2008). In all non-stem cells, these three genes are

buried deep within the chromatin, the coils of DNA that are either tightly coiled to silence gene expression, or more loosely wrapped to promote gene expression. These coils are constantly winding and unwinding, either from an outside force or spontaneously. Each of the three pluripotency proteins bind to each other's promoters, the DNA sequence that immediately precedes the genes. In the presence of virally-expressed *Oct4* or *Sox2* proteins, after enough unwinding of the chromatin, the proteins will bind to the endogenous pluripotency genes, preventing them from rewinding and allowing transcription to occur. This creates more pluripotency proteins, which further entrenches the cell into its pluripotent state. As shown in **Figure-3**, these three genes also activate many other genes involved in maintaining pluripotency, while silencing many of the genes that induce differentiation. As differentiation occurs, expression of *Oct4* is quickly silenced, and the genes responsible for differentiation are subsequently activated.

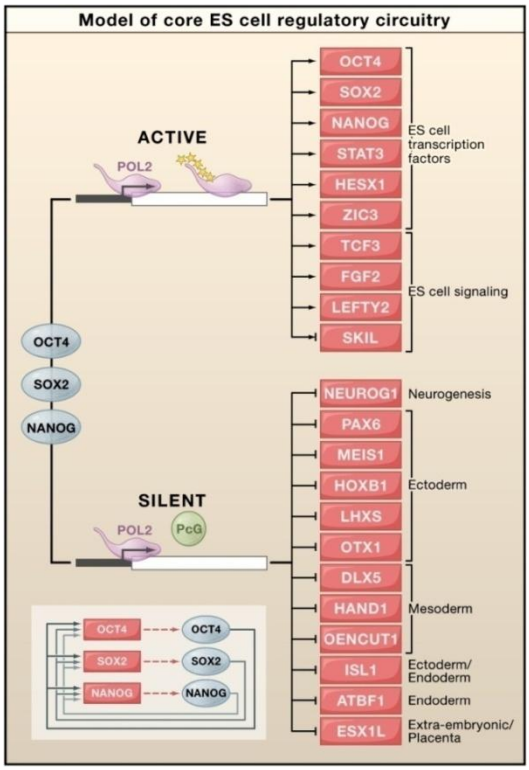


**Figure-3: Diagram of the Role of Oct-4, Sox-2, and Nanog at Inducing Pluripotency.** All the cell specific differentiation factors are silenced (bottom right), while factors responsible for maintaining the ES pluripotency state are activated (top right). Each of the three major pluripotency genes Oct4, Sox2, and Nanog help to activate and maintain each other (Jaenisch, 2008).

But like all new technology, there are some kinks in the process that still need to be worked out. One of the genes used, *c-Myc*, is an oncogene, and its addition to any cell will inevitably increase the risk of cancer. But without the gene, the cell is much more difficult to reprogram and has less therapeutic value when injected into infected mice (Baker, 2009). The very act of inserting genes into a genome, especially via viruses, is dangerous and can lead to many unintended consequences. There is no way to ensure that either the viruses or the genes they transfect will not interfere with expression of critical genes, causing cancer or death (Holden and Vogel, 2008). Numerous workarounds have been tested, such as viruses that are

automatically silenced by normal cell activity (Jaenisch, 2008), or by using adenoviruses which do not integrate themselves into the cell's genome (Stadtfeld, 2008), or by simply splicing out the reprogramming genes after pluripotency was induced (Yu, 2009). The most promising solutions, however, come from using drug-like molecules and proteins to activate the latent stemness genes (Shi, 2008).

Unfortunately, due to the difficulty of performing human research with embryonic stem cells, there are no easy ways to compare the various forms of iPS cells with unmodified traditional ES cells. Without such testing, there is no way to know if an improvement in technique yields a therapeutically improved cell, or if it is just looks like an improvement, but actually bypasses some critical regulatory mechanism (Holden and Vogel, 2008).

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# Chapter-2: Stem Cell Applications

*Hang Nguyen*

The use of stem cell medicine is dated as far back as 1956 when Dr. Donnall Thomas, a bone marrow transplant specialist, administered donor human adult stem cells to a leukemia patient who went into complete remission. In 1981, the first embryonic stem (ES) cell line was developed from mice. After more than a decade, in 1998, James Thompson (University of Wisconsin – Madison) established the first human ES cell lines (Brown University, 2002). Since those discoveries, scientists have gained numerous achievements in the field of stem cell research, including the determination that the active components in bone marrow are hematopoietic stem cells, isolation of human adult stem cells from tissues other than marrow, and recent data showing that ES-like cells can be produced directly from ordinary human skin fibroblast cells. New clinical methods have been developed based on these basic discoveries.

Despite the controversies over issues of embryo destruction for medical purposes, a vast number of cases have proven that ES cells are the key in our quest for finding cures for many fatal diseases. Adult and ES cell applications hold great potential for healing injuries of body parts like skin, heart, bladder, and kidney. The purpose of this chapter is to document and discuss successful stem cell therapies currently being used to treat diseases, using adult or ES cells, and to delineate those applications that have not yet been achieved that remain as future experiments.

## Treatment of Diabetes Using Stem Cells

Diabetes currently affects 250 million individuals worldwide. The greatest increase in diabetes prevalence occurs in Asia and South America. In the U.S., diabetes is the sixth leading

cause of death, impacting the quality of life for 20.8 million American children and adults. An estimated 54 million Americans have been diagnosed with "pre-diabetes" (Goldthwaite, 2006). People with diabetes must tolerate numerous means of treatment, including strict diet, daily check of glucose levels, and insulin shots. At present, diabetes can only be managed but there is no cure.

Diabetes results from the body's inability to either produce or respond to a hormone called insulin. Insulin plays a vital part in transporting glucose from the bloodstream to inside our cells where glucose is used as energy (**Figure-1**). When pancreatic β-cells, the manufacturer of insulin, fail to produce enough insulin (Type I), the blood glucose concentration dramatically increases and body systems are obliged to carry a metabolic burden. There are two major types of diabetes: type I and II. Type I, previously known as juvenile-onset diabetes, results when a person's immune system mistakenly attacks and destroys β-cells. People with type I diabetes have a complete dependence on exogenous sources of insulin (Assady et al., 2005). Type II, also referred as adult-onset diabetes, results from a progressive decline in β-cell activity combined with insulin resistance, a condition in which different tissues in the body such as liver, muscles, and fat no longer respond to insulin action (Goldthwaite, 2006). Type I diabetes accounts for 5-10% of total cases, while type II diabetes is found to be more common but preventable if a person has healthy life-style.

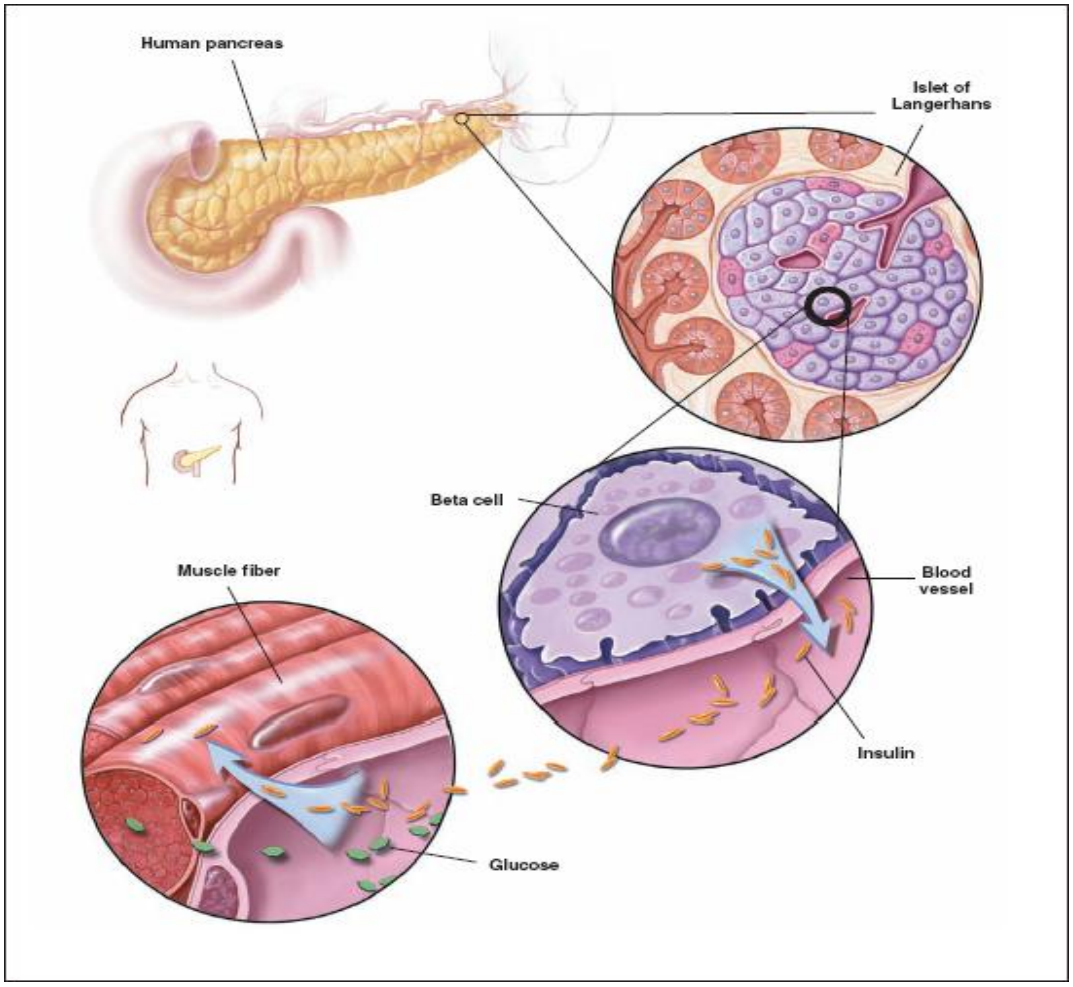


**Figure-1: The Role of Insulin in Glucose Update.** The pancreas (upper left) is located in the abdomen, adjacent to the duodenum (the first portion of the small intestine). A cross-section of the pancreas (upper right) shows the islet of Langerhans which is the functional unit of the endocrine pancreas. Encircled in black is the beta cell that synthesizes and secretes insulin (lower right) Beta cells are located adjacent to blood vessels and can easily respond to changes in blood glucose concentration by adjusting insulin production. Insulin facilitates the uptake of glucose (lower left), the main fuel source, into cells of tissues such as muscle. (Goldthwaite, 2006)

In 1990, the first human transplant of cadaver-supplied pancreatic islet tissue in patients with type 1 diabetes was successfully performed by the physicians at the Washington University Medical Center (Goldthwaite, 2006). With further improvements, the so-called "Edmonton protocol" involving the transplant of islets from cadaveric pancreatic tissue from multiple donors

and infusing them into the recipient's portal vein became popular. However, a long-term follow-up study of Edmonton transplant patients indicated that less than 10% of recipients remained insulin-sufficient five years post-transplant (Goldthwaite, 2006), due mainly to the damage of transplant tissues during islets isolation and the side effects of drugs necessary to keep the body from rejecting transplanted tissues. Although pancreatic islet transplantation technologies and procedures continue to be improved, the lack of available matched donors is a main issue, so scientists turned to stem cells for regenerative medicine.

*Diabetes and Adult Stem Cells*

Recent studies in rodents have indicated that the adult pancreas contains endocrine progenitor cells that can differentiate into β-cells (Seaberg et al., 2004). The progenitor cells from the adult mouse pancreas differentiated into a group of cells containing exocrine cells, neurons, glial cells, and β-like cells which demonstrated glucose-dependent insulin release, suggesting the possible therapeutic application of adult stem cells to diabetes (Seaberg et al., 2004). Several subsequent studies have also confirmed the existence of pancreatic stem cells *in vitro* and *in vivo*. According to research at the Howard Hughes Medical Institute in collaboration with Harvard University and Boston Children's Hospital, fully differentiated adult exocrine cells can be directly reprogrammed into cells that closely resemble β-cells in adult animals by a combination of just three transcription factors (Zhou et al., 2008).

Mouse bone marrow, essential for immunity and circulation, has also been described in scientific reports as being capable of inducing the differentiation of endogenous pancreatic tissue into insulin-producing cells, and as a feasible approach for treating type II diabetes (Hess et al., 2003). Transplant of mouse bone marrow cells into mouse models for diabetes can reverse

hypoinsulinemia and hyperglycemia. The mechanism by which the bone marrow−derived stem cells induce endogenous pancreatic tissue repair is not yet known, however the rapidity of the regeneration process cells suggests that endogenous pancreatic stem cells may mediate the restorative process through endothelial interactions (Hess et al., 2003).

Human adult stem cells have also been shown to be capable of differentiation into insulin secreting glucose-regulatable cells, demonstrating the potential for treating diabetic patients in the future. At a 2008 International Conference on BioMedical Engineering and Informatics, researchers at King's College (London, UK) showed that human marrow stromal cells (hMSCs) are an excellent source for unlimited surrogate insulin-producing glucose-regulated cells. They developed a robust system involving the non-viral delivery of DNA encoding three key transcription factors Ngn3, Pdx1, and Mafa, to direct the differentiation of hMSCs into insulin-producing cells. The cells also expressed stem cell markers and a panel of key genes required for the development and maintenance of functional phenotypes of pancreatic β-cells. How the cells developed into the functional phenotype is still not clear and is worthy of further exploration, but the study offers the potential for generating new islet cells from a patients' own bone marrow (Zhao et al., 2008).

*Diabetes and Embryonic Stem Cells*

In 2001, scientists at the National Institutes of Health performed an experiment using mouse embryonic stem cells to generate cells expressing insulin and other pancreatic endocrine hormones (Lumelsky et al., 2001). The differentiated cells were also found to respond to glucose by a mechanism similar to that used *in vivo*. When injected into diabetic mice, these cells underwent rapid vascularization and maintained an islet-like organization (Lumelsky et al.,

2001). With respect to human ES cells, Novocell Inc., a stem cell engineering company located in San Diego (CA) has developed an *in vivo* mimicking process that coverts human embryonic stem cells (hES cells) to insulin secreting endocrine cells (D'Amour, 2006). They developed a five-step protocol for efficiently differentiating hES cells to insulin-expressing cells through a series of endodermal cell intermediates resembling stages of pancreatic development. The technique demonstrates that hES cells are a renewable source of cell replacement in type 1 diabetes (D'Amour, 2006). This differentiation process was also observed by a different group of researchers in 2005 who differentiated hES cells to produce numerous types of cells, including a subset that have many characteristics of β-cell function, including proinsulin and/or insulin production, insulin release, and the expression of other β-cell markers (Assady et al., 2005).

Thus the stem cell treatments to date indicate that ES cells have successfully been differentiated into insulin-producing cells in mice and humans. The ES derived cells have been shown to reverse diabetes in mouse models, but have not yet been used to treat diabetes in patients. Adult mouse and human pancreatic progenitor cells and bone marrow have also been shown to differentiate into insulin-producing cells. Murine bone marrow cells have been used to treat diabetes in mouse models, but neither ES cells nor adult stem cells have been used yet to treat human diabetic patients.

## Treatment of Damaged Heart Muscle Using Stem Cells

Sixteen-year-old Dimitri Bonnville, who suffered a massive heart attack, was the first to receive a stem-cell therapy to revive his damaged heart tissue and substantially recovered a week later (Philipkoski, 2003). But not everyone is as lucky as this boy; according to a National Health and Nutrition Examination Survey, cardiovascular disease (CVD) (including

hypertension, coronary heart disease, stroke, and congestive heart failure) killed approximately 1.4 million people in America in 2002. CVD has been ranked as the number one cause of death in the U.S. every year since 1900 (Goldthwaite, 2006). Myocardial infarction, so-called heart attack, is characterized by a loss of heart muscle cells and an impairment of cardiac performance. It has been assumed that if enough cardiac muscle cells could be generated to compensate lost or damaged cells (**Figure-2**), contractile function of the heart would be restored. Recently, intensive research on stem-cell-based therapies have provided persuasive results to justify the claim of stem cells' usefulness in the war against myocardial infarction, and the National Institutes of Health spent $2.5 billion on stem cell research from 2004-2007 for this purpose (Passier et al., 2008).

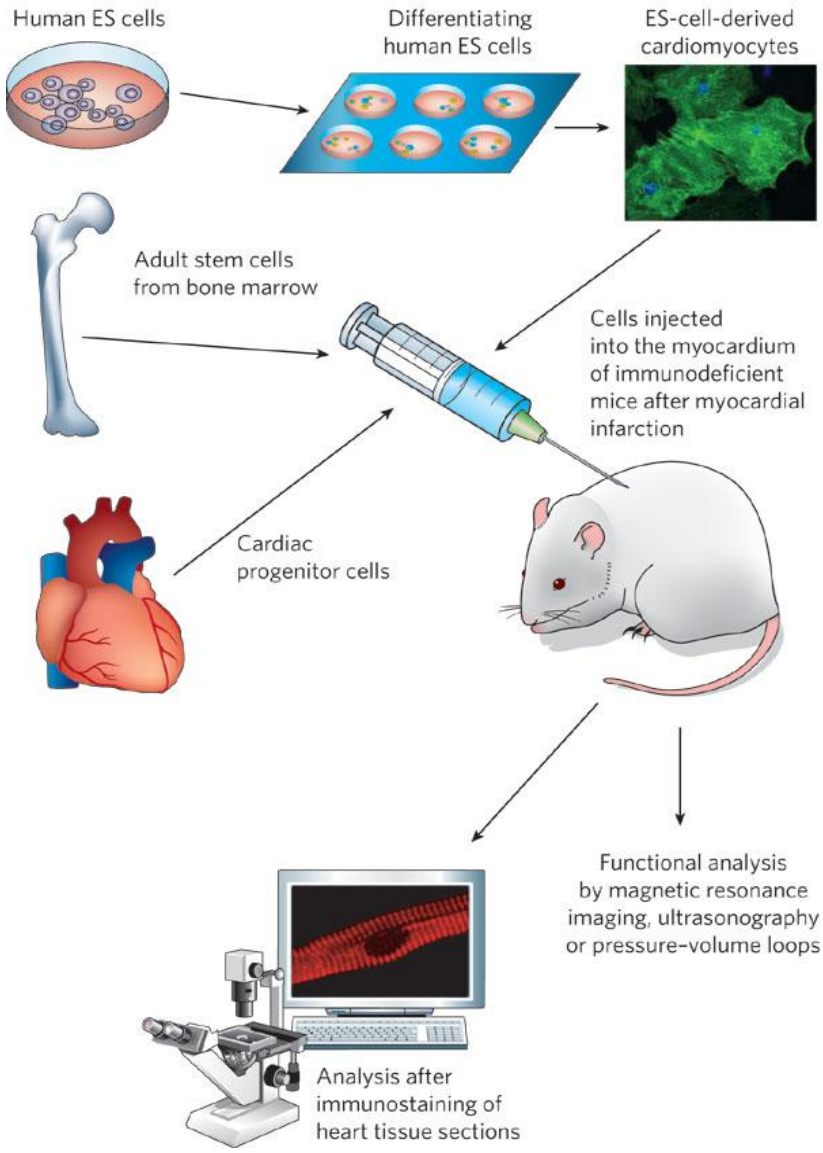


**Figure-2: The Use of ES and Adult Stem Cells to Heal a Wounded Heart.** Adult stem cells, cardiac progenitor cells or human ES-cell-derived cardiomyocytes (upper left) are isolated and injected into the heart (diagram center) of an immunodeficient mouse that has had a myocardial infarction. At different time points after transplantation, cardiac function is analysed (diagram lower) by using magnetic resonance imaging, ultrasonography, or ventricular pressure–volume loops. To determine cell survival, cell phenotype, and cell integration, hearts are isolated after transplantation, and transverse heart sections are used for immunostaining with specific fluorochrome-conjugated antibodies (cardiomyocytes are identified by antibodies specific for α-actinin), followed by confocal microscopy. (Passier et al., 2008)

*ES Cells and Heart Repair*

Because ES cells can proliferate indefinitely *in vitro*, they can supply a cell reservoir for extensive tissue regeneration. Although multiple candidate cell types have been shown to display varying degrees of cardiogenicity, ES cells derived from the inner cell mass of the blastocyst possess the most recognized capacity to yield cardiomyocytes. ES cells are usually first demonstrated to fulfill key criteria for ES cells: derivation from the pre-implantation embryo, prolonged undifferentiated proliferation under special conditions, and the ability to form all three germ layers. When cultured with mitotically inactivated mouse embryonic fibroblast feeder layer, hES cells could be maintained in the undifferentiated state for prolonged periods.

With respect to ES cell differentiation into cardiomyocytes, initial information was obtained from mouse ES cells. Recapitulating the development of murine cardiomyocytes from very early cardiac precursor cells to terminally differentiated cells provided researchers with important insights of cardiomyogenesis, including the origin, commitment, patterns of gene expression, ion channel development, and function. However scientists now realize there are key differences between murine and human ES cells, but morphologically, the *in vitro* differentiation of human and mouse ES cells into cardiomyocytes appears to follow parallel pathways (**Figure-3**) (Kehat et al., 2001).

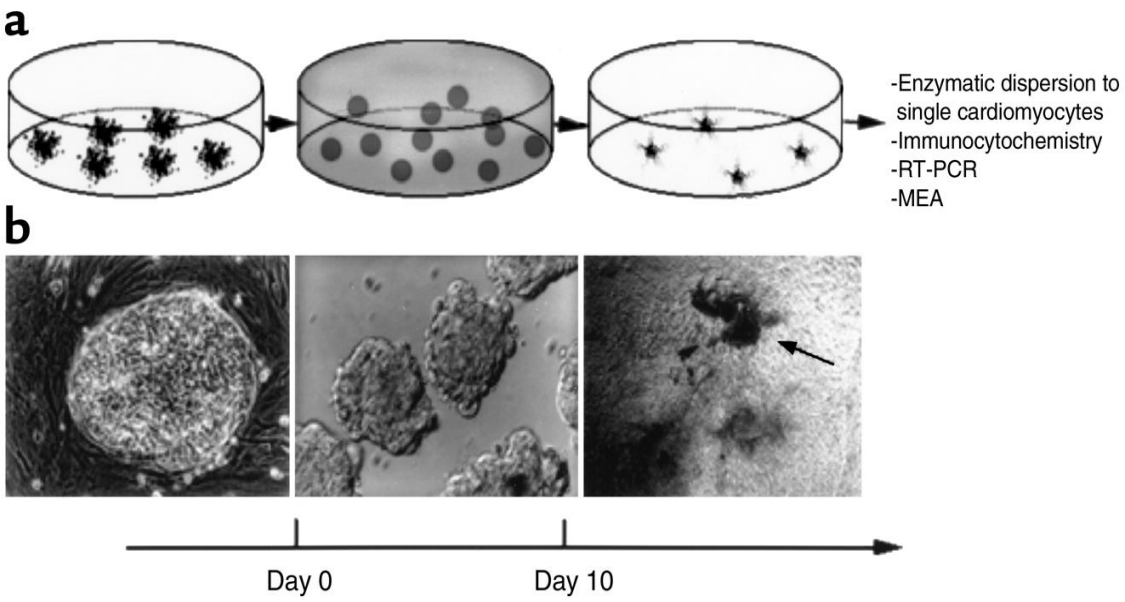


**Figure-3: The Stages of Human ES Cell Differentiation Into Cardiomyocytes.** (**a**) Schematic of the three stages in human ES cell differentiation. Initially, the ES colonies are grown on top of the MEF feeder layer (left). To induce differentiation, cells are transferred to a suspension, where they aggregate to form embryoid bodies (EBs) (middle). After 10 days in suspension, EBs are plated on gelatin-coated culture dishes, where they are observed for the appearance of spontaneous contractions (right) typical of cardiomyocytes. (**b**) Photomicrographs depicting the three mentioned stages: ES colony (left), EBs in suspension (middle), and a contracting area in the outgrowth of an EB (right, arrow). (Kehat et al., 2001)

In 2004, scientists at the Mayo Clinic College of Medicine (Rochester, Minnesota) performed an experiment to support the potential for ES cell-based reparative treatment of myocardial infarction (Terzic, 2004). A transition of mouse ES cells to cardiomyocytes occurred under the direction of rat host paracrine signaling that assists the cardiac-specific differentiation. The produced cells expressed characteristics of cardiac phenotypes and illustrated cardiac functional markers. Furthermore, when transplanted into injured rat hearts, the propagated cardiomyocytes repopulated significant regions of the rat dysfunctional myocardium, and resulted in better tissue contraction with reduced mortality (Terzic, 2004). A 12-week follow-up period proved that the presence of mouse ES cell-derived cardiomyocytes within the infarct area was directly associated with a preserved left ventricular structure and lessened scar tissue. They

also found no evidence of rejection of transplanted cells, despite the xenotransplantation of murine ES cells into rat heart (Terzic, 2004). Thus according to this rodent study, ES cell myocardial regeneration has an impact on ventricular remodeling and can provide stable impact after heart failure.

*Adult Stem Cells and Heart Repair*

Although ES cells may provide a unique method to reduce the morbidity of prevalent heart disease, it is not a favorable long-term solution due to the restricted ES cell access for pre-clinical study. However, a shot of adult bone marrow straight into the heart may be the answer to heart attack survivors, as revealed by scientists in Germany and Norway after conducting a drastic trial (Couzin, 2006). Two hundred and four volunteers who had had a heart attack within the previous week and another 75 whose heart attack hit more than 6 years before participated in the study. Half of the patients were offered an infusion of their own bone marrow into the affected coronary artery, while the others received a placebo injection. The study then looked at left ventricular ejection fraction, a measure of the heart's pumping capacity. A year later, only 2 of the treated people had died and none had had another heart attack, compared with 6 deaths and 5 heart attacks in the placebo group (Couzin, 2006).

In mice, locally-transplanted Lin-negative c-*kit*-positive bone marrow stem cells have been shown to form new myocytes, endothelial cells, and smooth muscle cells, generating coronary arteries, arterioles and capillaries. The differentiating myocytes synthesized nuclear and cytoplasmic proteins characteristic of cardiac tissue. 12 out of 30 (40%) female mice demonstrated myocardial regeneration when their peri-infarcted left ventricles were injected with male $Lin^{-}c\text{-}kit^{+}$ bone marrow cells, although an immunological reaction to the histocompatibility

antigen on the Y chromosome of the donor bone marrow cells could account for the relatively small percentage of repair (Orlic et al., 2001).

In 2006, Dr. Schächinger and his coworkers designed a double-blinded, placebo-controlled, randomized multicenter trial to determine whether this adult bone marrow cell reperfusion strategy enhances global left ventricular operation in patients. Their finding was that intracoronary infusion of enriched bone marrow cells (BMC) is associated with an increase in left ventricular function of patients with acute myocardial infarction (Schächinger et al., 2006). This suggested that intravascular administration of progenitor cells derived from BMC contributes to regeneration of infarcted myocardium.

Thus, the stem cell treatments to date indicate that ES cells have successfully been used to induce heart damage repair in mice, and in humans have been shown to differentiate *in vitro* into cardiac-like cells, but ES cells have not been used in humans yet to treat heart attacks. Adult bone marrow cell injections have been shown to induce heart repair in both mice and humans.

## Treatment of Nervous System Diseases Using Stem Cells

The nervous system, the most complex organ of human beings, is composed of neurons and other specialized cells called glial cells that aid in the function of neurons. Sensory neurons and connecting neurons, belonging to the peripheral nervous system, and all the neurons in the spinal cord and brain (which make up the central nervous system) generate electrochemical signals and neurotransmitters to induce impulses within the system. When one's nervous system is marred, a self-repairing mechanism inside the brain is activated, but unfortunately, new neurons only originate at a few sites in the brain and turn into a few types of nerve cells. While most current treatments aim to limit the damage of nervous system diseases, advances in stem

cell research indicate this damage can be reversed by replacing lost cells with new ones to restore brain function.

*Parkinson's Disease*

Parkinson's disease (PD) is a progressive disorder that results from a loss of midbrain dopamine-secreting neurons (**Figure-4**). These motor neurons regulate body movement, so when these cells die off, the nervous system loses control of body parts leading to movement difficulties, a notable trait of Parkinson's disease. The causes of death of these neurons remain unknown, though there is evidence showing that a combination of environmental factors and genetic predisposition are precursors to the disease. For many years, doctors have treated Parkinson's patients with L-dopa that the brain converts into dopamine, but the drug eventually loses its effectiveness and yields side-effects (Goldthwaite, 2006).

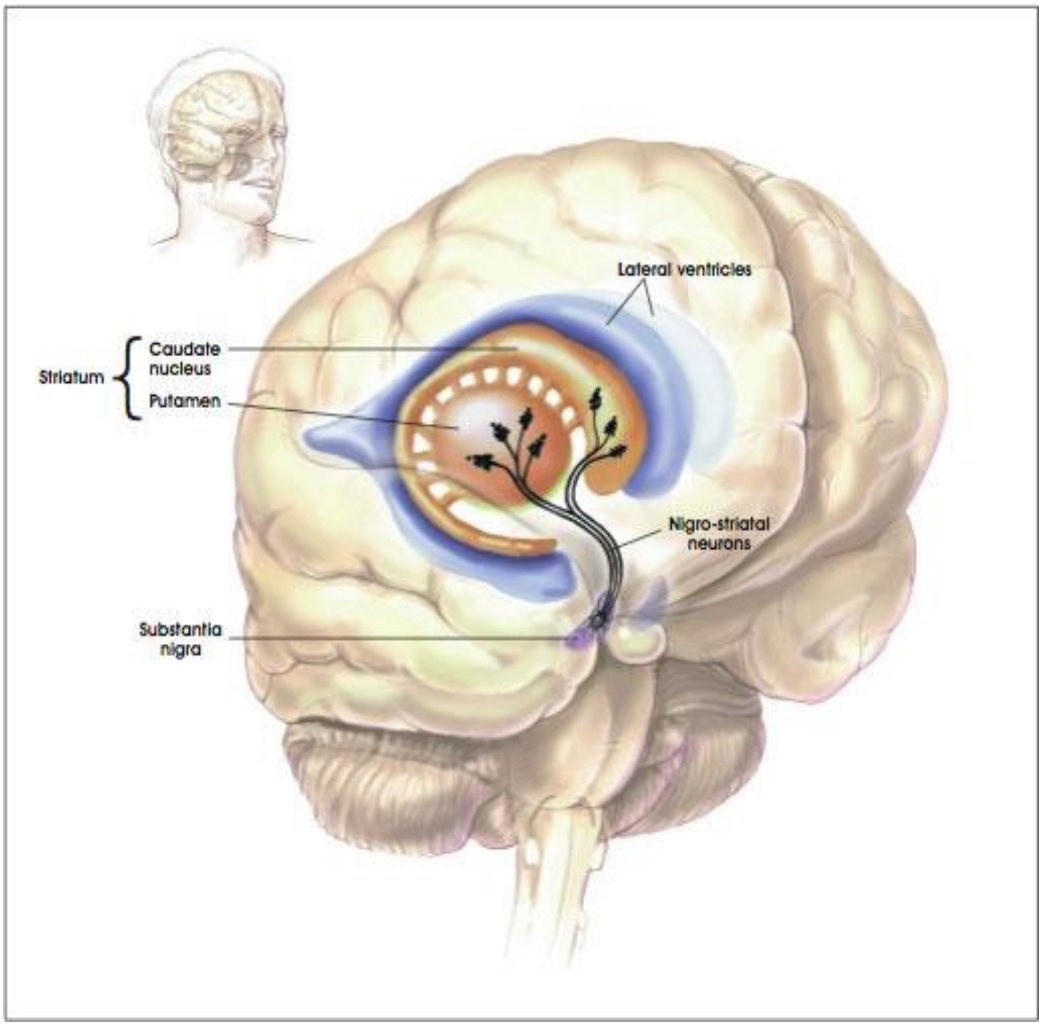


**Figure-4: Diagram of the Neuronal Pathways that Degenerate in Parkinson's Disease.** Electrical signals that control body movements travel along neurons that project from the substantia nigra (lower center) to the caudate nucleus and putamen (collectively called the striatum) (diagram center). These "nigro-striatal" neurons release dopamine at their stargets in the striatum. In Parkinson's patients, dopamine neurons in the nigro-striatal pathway degenerate for unknown reasons. ("Rebuilding the Nervous System with Stem Cells," 2005)

The National Institute of Health has funded two large clinical trials in the past 15 years in which researchers transplanted tissue from aborted fetuses into the striatum of patients with Parkinson's disease. These studies, performed in Colorado and New York, were double-blinded and well-controlled. The patients' progress was followed for up to eight years and promising findings emerged. Younger and milder Parkinson's patients responded relatively well to the

grafts, and positron emission tomography (PET) scans of patients showed that some of the transplanted dopamine neurons survived and matured. Autopsies on three patients who died of unrelated causes also indicated the presence of dopamine neurons. However, 15% of the patients in the Colorado study, and more than half of the patients in the New York study, did not gain improvement and began to suffer from dyskinesias and jerky involuntary movements (Goldthwaite, 2006). Although this embryonic tissue transplant technique showed promise, the aborted fetus source of the tissue remains extremely controversial, thus alternative stem cell treatments are being researched.

*ES Cell Treatment of Parkinson's Disease*

Much progress has been made the last several years to differentiate ES cells into dopamine producing neural cells. A project was performed in 2002 by a group of scientists at the National Institute of Health to encourage the use of ES cells in cell-replacement therapy for Parkinson's disease (Kim et al., 2002). They reported that a highly enriched population of midbrain precursors and dopamine neurons can be derived from mouse ES cells. A functional analysis of the ES-cell-derived neurons was conducted by anatomical, neurochemical, electrophysiological, and behavioral tests, which showed the cells had strong dopaminergic functions. The study demonstrated a method of further increasing the efficiency of midbrain-specific generation of dopamine neurons from ES cells, and injection of the cells led to recovery in a rodent model of Parkinson's disease (Kim et al., 2002).

In 2004, a team from Israel's Hadassah University announced that for the first time, hES cells had been used to treat a rat model for Parkinson's disease (Ben-Hur et al., 2004). They generated a culture of neural progenitors from hES cells and grafted those into the brains of

Parkinson rats. They then noticed that the rats were able to modulate their movements while being dragged across a surface, which was a great improvement compared to their pre-treatment continuous turning and inability to make side steps. Post-mortem examination found that the stem cells had developed into dopamine-producing cells and they did not continue to change or proliferate to generate cancerous tumors. "These observations are encouraging, and set the stage for future developments that may allow the use of embryonic stem cells for the treatment of Parkinson's disease," said Dr. Benjamin Reubinoff (Ben-Hur et al., 2004). These hES-derived cells, however, have not yet been used to treat Parkinson's patients.

*Adult Neural Stem Cell Treatment of Parkinson's Disease*

Scientists are also studying the possibility that the human brain may be able to repair itself with therapeutic support. Even in adults, new nerve cells are born in a brain region called the dentate gyrus of the hippocampus, and their presence suggests that neural stem cells (NSCs) in the adult brain may have the potential to re-wire dysfunctional neuronal circuitry. A study investigated how the adult rat brain responds to transforming growth factor alpha (TGFα), a protein important for early brain development, but which is expressed only in limited quantities in adults. Injection of TGFα into a healthy rat brain causes NSCs to divide for several days before ceasing division. In Parkinsonian rats, the NSCs actually proliferated and migrated to the damaged areas, and the TGFα-treated rats showed few of the behavioral problems associated with untreated Parkinsonian rats. It is not clear, however, if stem cells are responsible for this repair or if the TGFα activates a different repair mechanism (Panchision, 2006).

*Stem Cell Treatment of Spinal Cord Injuries*

Spinal cord trauma destroys numerous cell types, including the neurons that carry messages between the brain and the rest of the body. In many spinal injuries, the cord is not actually severed, but the signal-carrying neuronal axons do not work correctly. There is no cure for spinal cord lesions at present, and the most common current treatment – high doses of methylprednisolone to lower inflammation – is of questionable value. Transplantation of stem cells into an injured cord could lead to benefits mainly due to trophic factor secretion or remyelination of spared axons (Lindvall and Kokaia, 2006).

Reasoning that pre-differentiation of embryonic neural precursors to astrocytes, which are thought to support axon growth in the injured immature central nervous system, would be helpful for spinal cord injuries repair, a novel strategy was developed by scientists to restore locomotion after acute transection injury of adult rat spinal cord. After establishing pure populations of astrocytes directly from glial-restricted progenitor cells, transplantation was administered. A growth of 60% of ascending dorsal column axons into the centers of lesions was observed, 66% of these extending beyond the injury site. Grid-walk analysis of transplanted rats with rubrospinal tract injuries revealed significant improvements in locomotor function. The procedure also induced a striking level of tissue reorganization, suppressed initial scarring, and rescued axotomized central nervous neurons (Davies, 2006).

These rodent findings were verified by Hans Keirstead and his colleagues at the Reeve-Irvine Research Center at University of California Irvine who found that rodent derived hES cells promote mobility in rats with spinal cord injuries. A technique was created to entice hES cells to differentiate into early-stage oligodendrocyte cells, these cells then were injected into rats with induced partial injury to the spinal cord – one group was injected 7 days after injury, and

another group 10 months after injury. Although injected cells formed full-grown oligodendrocyte cells and migrated to appropriate neuronal sites within the spinal cord in both groups, only the 7-day post-injury injection group showed significant improvements in walking, likely due to myelin, the biological insulation for nerve fibers critical for the maintenance of electrical conduction in the central nervous system. In the rats with 7-day post-injury treatment, myelin tissue formed as the oligodendrocyte cells wrapped around damaged neurons, but in the other group of rats, myelin could not form because the space surrounding neuron cells had been filled with scar tissue (Keirstead et al., 2005). This study indicates the importance of myelin loss in spinal cord injury and illustrates one approach to treating it.

*Stem Cell Treatments of Stroke*

Stroke, the most common cause of disability in adults, is caused by a blockage of a cerebral artery (**Figure-5**). As a consequence of disrupted blood flow, neurons and glial cells in affected brain regions die from an insufficient amount of oxygen, leading to motor, sensory or cognitive impairment.

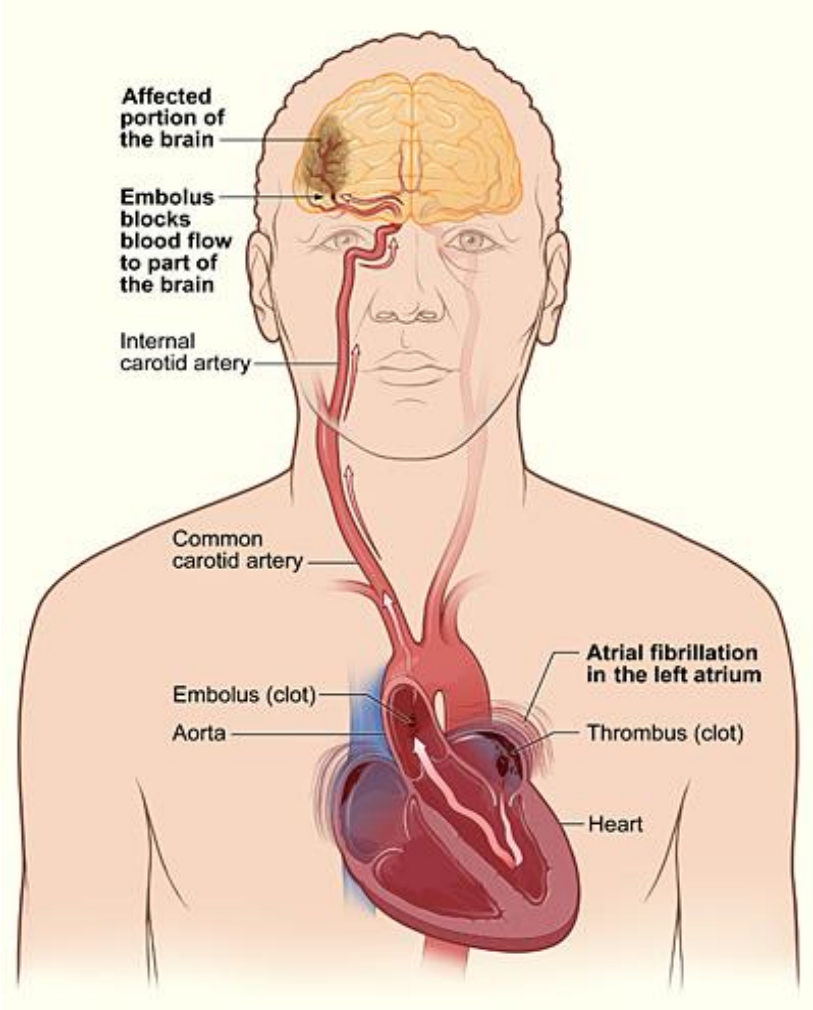


**Figure-5: Diagram of a Stroke Induced by Brain Artery Blockage.** The shaded gray area in the brain denotes brain cells stressed from lack of oxygen. ("Atrial Fibrillation Signs & Symptoms," DCI Home)

Transplanted cells from different sources, such as fetal brain, neuroepithelial cell lines, bone marrow, and umbilical cord blood, have dramatically enhanced the odds of patient recovery. Some results suggest that future stroke treatments may be able to coax the brain's own stem cells to make replacement neurons. A group from University of Tokyo added a growth factor, bFGF, into the brains of rats after a stroke, and determined that large number of new

neurons generated from hippocampus was making connections with other neurons. Another attempt to use transplantation as a means to treat the loss of brain mass in stroke used stem cells encased in a polymer scaffold implanted into stroke-damaged brains of mice, and demonstrated that the seeded stem cells transformed to neurons and the polymer reduced scarring (Goldthwaite, 2006).

Human fetal brain cells have been used to treat rodent models for stroke. Two research groups transplanted human fetal stem cells in independent studies into the brains of stroke-affected rodents. These cells not only survived but also migrated to the damaged areas of the brain (Goldthwaite, 2006). But as was noted in the Parkinson's subsection, the use of fetal cells is highly controversial, thus the scientists are working hard to uncover a more preferable stem cell therapy approach to stroke.

*Treatment of Alzheimer's Disease with Stem Cells*

Alzheimer disease (AD), named after the German physician Alois Alzheimer who first described it in 1906, is a degenerative brain disease. It accounts for 50 to 70 percent of progressive dementia cases, and it is pathologically characterized by the deposition of amyloid-β peptide in the brain parenchyma. Alzheimer causes problem with memory, thinking, and behavior severe enough to disturb work, lifelong hobbies, or social life. Today there is still no cure but scientists are recently considering stem cell treatments. Nikolic and colleagues (2008) have recently used human umbilical cord blood cells (HUCBCs) to alter AD-like pathology in transgenic AD mouse models. Their study showed a marked reduction in amyloid-β levels in the brain and less astrocytosis following multiple low-dose infusions of HUCBCs (Nikolic et al., 2008).

*Krabbe's Disease and Stem Cells*

Krabbe's disease, or globoid cell leukodystrophy, is a rare recessive disorder that influences the nervous system. It results from the shortage of an enzyme called galactosylceramidase. This enzyme deficiency impairs the growth and maintenance of myelin, the protective covering around specific nerve cells that ensure the rapid transmission of nerve impulses. In the infantile form, symptoms appear before six months of age, and are physically characterized by irritability, muscle weakness, feeding difficulties, episodes of fever without any sign of infection, stiff posture, blindness, deafness, mental deterioration, seizures, and death, usually before two years of age. Bone marrow has traditionally been used as the source of donor stem cells for Krabbe's transplantation, but the lack of matched donors and the long time of recruitment of unrelated adult donors can hinder treatment. Allogeneic bone marrow hematopoietic stem-cell transplantation, on the other hand, has been reported to be beneficial in patients with early stages of juvenile Krabbe's disease. In this type treatment, the patient's own bone marrow injected cells repopulate various tissues, delivering enzymes both inside and outside the vascular compartment (Escolar et al., 2005).

Alternatively, umbilical cord blood-derived stem cells can also be used. In a recent clinical trial, 11 asymptomatic newborns (ages ranging from 12 to 44 days) in whom the disease was diagnosed because of a family history, and 14 infants (ages 142 to 352 days) with infantile Krabbe's underwent transplantation of umbilical-cord blood from unrelated donors. Engraftment, survival rate and neurological development were evaluated longitudinally for four months to six years, and the outcomes of the two groups were compared. While the treatment favorably altered the natural progression of the disease among the newborn group, the infant group had a higher

rate of death and minimal neurologic benefits from transplantation. In contrast to untreated patients, the transplanted newborns survived with durable donor chimerism (mixed donor and patient cells) and normal peripheral-blood enzyme activity. They maintained normal vision and hearing and normal cognitive development, gained substantial neurologic benefits, and continued improvement in nerve-conduction studies. Except for areas influenced by gross motor development, hematopoietic stem cell transplantation proved to be a powerful treatment for infantile Krabbe's disease if the newborns were treated before the onset of symptoms (Escolar et al., 2005).

## Chapter-2 Conclusion

As documented in this Chapter, ASCs or ES cells have been used to treat diabetes, heart disease, and nerve disorder in animal models, but such cells have not yet been formally applied to humans (outside of a few senate testimony cases). So the world awaits future clinical trial data. Scientific work over the last few decades in various stem cell applications have brought hope to millions of lives. Rhode Island Democrat Congressman James Langevin, who has been paralyzed since a gun accident at age 16, said "I believe one day I will walk again…Stem cell research gives us hope and a reason to believe. We have a historic opportunity to make a difference for millions of Americans." Although stem-cell therapy is still in a premature stage, it has been discovered as a really promising medical innovation that could someday cure devastating diseases. The road ahead for stem cell research is challenging but exciting. Clinical trials will hopefully provide the key data needed to move stem cell treatments into the mainstream to save countless lives.

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# Chapter-3: Stem Cell Ethics

*Aaron Sciore*

With the promise of curing diseases long ago written off as hopeless, embryonic stem(ES) cells have captured the awe and attention of the world. But as is typical for a controversial technology, it also caught the attention of major religious leaders, who decried that the method for retrieving the ES cells (usually involving the destruction of a human embryo) is an affront to God and human dignity. Primarily Christian groups lobbied Washington to ban all forms of ES research, leading to the 2001 compromise by then-President Bush, banning federal funding for creating new ES lineages while allowing research on previously established cell lines (discussed in detail in Chapter-4). This federal ban has recently been overturned in 2009 by President Obama, leading to the first-ever clinical human trials on ES cells. Although religious groups push for the use of adult stem cells (ASCs) as an alternate to ES cells, since their use does not destroy an embryo, ASCs are difficult to isolate, difficult to grow *in vitro*, and do not have the same potency as ES cells. Thus, scientists continue to push hard for ES cell use. The purpose of this chapter is to discuss the ethics of various types of stem cells, as an example of the impact of technology on society.

**Embryonic Stem Cell Ethics**

The most controversial area of stem cell research is without a doubt the work done on embryonic stem (ES) cells. ES cells are harvested from 4-6 day old IVF blastocysts, destroying the blastocyst in the process. When the process for extracting human ES cells was first published in 1998 (Thomson et al., 1998), there was an immediate and significant backlash in the religious and philosophical community. Many feared the ethical implications of treating potential human lives as scientist's playthings. Others were concerned about the morality of impeding lifesaving research to placate otherwise uninvolved

people. Either way, this topic has sparked a philosophical firestorm about *when*, in an embryo's development, does it become a person worthy of moral consideration.

Some individuals in the scientific community take a non-religious approach to the debate, viewing embryos as groups of cells with no rights whatsoever. However, this view is not shared by most scientists, bioethicists, and citizens who bring various religious beliefs to the debate. After more than a decade since the advent of human ES cell research, each major world religion has had sufficient time to come to their own consensus regarding whether ES research fits within their particular code of ethics. I will explore briefly some of the major world religion stances on ES cells, and describe work done by secular bioethicists on when a human embryo becomes a person worthy of moral consideration.

**Christianity and Stem Cells**

With around 1/3 of the world's population, Christianity is the world's most-followed religion. There are many different sects within Christianity, and not all of them have the same views on stem cell research. The Episcopal and Methodist Churches support the harvesting of embryos left over from the process of *in vitro* fertilization (IVF), if the embryos were going to be discarded anyway (Pew Forum, 2008). However, most of the major Christian sects believe that it is at *conception* that a human life begins, and that even the newly fertilized zygote has a soul, and should not be purposely destroyed (Fleischmann, 2001). Harvesting embryos would be murder, and Christian doctrine specifically forbids murder even if it would be to save another's life (Shannon, 2008).

The Catholic Church has been the harshest critic of ES cell research. In response to President Bush's 2001 ban on creating new ES cell lineages while allowing work with previously established lineages, the President of the U.S. Conference of Catholic Bishops said (referring to the work on the previous lines) "The federal government, for the first time in history, will support research that relies on the destruction of some defenseless human beings for the possible benefit to others...it allows our nation's research enterprise to cultivate a disrespect for human life" (Nairn, 2005). In 2008, the U.S. Conference of Catholic Bishops voted 191-1 in favor of releasing a paper urging Catholics and "all people of good

will" to stand together and denounce embryonic stem cell research as murder (UCSSB, 2008). However all Christian sects, including the conservative Catholic Church (Pope Benedict XVI, 2007), have advocated for research with adult stem cells as an alternative to using embryos.

**Judaism and Stem Cells**

The Jewish view on stem cell research is more complex and uncertain than the Catholic view. The Torah itself does not equate the life of a fetus to that of an adult – accidentally killing a pregnant woman is a capital crime, but causing her to miscarry is only a fineable offense. Abortion is considered murder, and is illegal under Jewish law, but it does not carry the same penalty that other murders have. There is scriptural writing indicating that prior to forty days, the fetus is "mere water" and not considered a person, but this passage's meaning and relevance are hotly debated, and many influential rabbis believe it does not override other relevant passages, such as the prohibition of 'wasting seed' (Eisenberg, 2001). This interpretation still forbids pre-day 40 abortions, but has interesting implications for the topic of stem-cell research, because excess IVF embryos are not truly humans, but are 'seed', so using them for medical purposes (to try to save lives) is not wasting them at all. Thus by this view, it would be more ethical to use embryos for ES cell research than to simply throw them out.

Although there is no complete consensus in the Jewish community regarding ES cells, all of the *major* sects of Judaism, Orthodox, Conservative, and Reform, support ES cell research. Several major Jewish community leaders attended President Obama's signing ceremony for overturning the 2001 Bush ban on deriving new ES cell lines (Fingerhut, 2009).

**Islam and Stem Cells**

Islam is the most permissive of all the Abrahamic religions on the topic of embryonic stem cell research. Islamic tradition dictates that the human fetus exists "first as a drop of matter for forty days, then as a blood clot for forty days, then as a blob for forty days, and then the angel is sent to breathe life into him" (Weckerly, 2002). Only after 120 days does ensoulment occur. Islamic law (Shari'ah) carries

lighter punishments for causing a miscarriage within the first 40 days of pregnancy than it does for a late-term pregnancy, and abortion laws are generally less strict for abortions before the 40-day mark (Siddiqi, 2007). Unlike Judaism and Christianity, Muslims acknowledge that it's a part of nature that most reproductive material inevitably ends up wasted or destroyed. Muslims are also encouraged by Shari'ah to make distinctions between *actual* life [after 120 days] and *potential* life [prior to 120 days], and to always favor actual life (Mohammad, 2009).

Islamic tradition and scripture also puts significant weight on determining a family's *lineage*. Adoption, surrogate mothering, and sperm banks, are all forbidden under Islamic law for this reason. *In vitro* fertilization is allowed, but only when the egg donor is married to the sperm donor and the embryo is implanted into the egg donor. Unless the parents want a second child, the excess embryos created by IVF would be completely unusable by other Muslim couples (Weckerly, 2002). The Islamic Institute, an Islamic advocacy group in Washington, released a statement that "Under the Islamic principle of the 'purposes and higher causes of the Shari'ah (Islamic law)', we believe it is a societal obligation to perform research on these extra [IVF] embryos instead of discarding them." A survey done by the same institute found that 71% of Muslims approve of donating excess IVF embryos for ES research, with 43% saying it was okay to make embryos specifically to harvest for stem cells (Ahmed, 2001).

**Hinduism and Buddhism and Stem Cells**

Unlike Western theology based around rigid moral codes, Hinduism, Buddhism, and other Eastern-derived religions take a less absolutist approach. These religions do not have any centralized hierarchy, so there is no single officially sanctioned argument on stem cell research. The overarching moral philosophy is known as *karma*, a more individually-based system where people who have done good deeds have good karma, and are reincarnated into a better position, as well as the opposite. Hinduism and Buddhism both believe that a soul is given to a human being at the moment of conception, with the soul being reincarnated from a past life (Hughes and Keown, 1995).

Hinduism deeply respects all human beings' right to life. Abortion is immoral at all stages of development in the Hindu belief system. However, Hinduism teaches that life and death are inseparable parts of the same natural cycle. Destroying life, say, by killing and eating a rabbit, is acceptable, and not bad karma. According to Swami Tyagananda, a Hindu monk and chaplain for MIT and Harvard, consciously taking a life does not cause bad karma if it is done "in extraordinary, unavoidable circumstances, and always for the greater good" (Tyagananda, 2002). In this manner, abortion is allowed if the mother's life is in danger. The Hindu stance on embryonic stem cell research depends heavily on these qualifications. The clause 'extraordinary, unavoidable circumstances' is fairly easy to satisfy, as ES cells have therapeutic properties far beyond the ordinary, and it is unavoidable as to access them involves the death of a living being. The 'greater good' qualification presents a moral question not raised by Western religions – to what end is the scientific research going to be used? If the goal is to advance knowledge and to provide treatment to people with diseases, it would be moral. However, if embryos were used to make a profit, or to cure only the richest patients for exorbitant amounts of money, it would be immoral.

Similar to Hinduism, the First Precept (primary tenet) in Buddhism is to do no harm to any living things. A devout Buddhist might decide against benefitting from embryonic stem cell research, as killing embryos would be bad karma, instead allowing himself to die so that he might be reincarnated with the same karma (Promta, 2004). Unlike most Western schools of theology, Buddhism does not believe there is a line between naturally caused events and human caused events, as humans are inextricably part of nature (Hughes, 1995). To this end, a Buddhist would contend that every embryo created by *in vitro* fertilization also has its own soul, worthy of consideration just as much as an adult human soul would be. Damien Keown, editor of the online *Journal of Buddhist Ethics*, contends that this First Precept overrules the medicinal prospects of ES cells, likening it to a bank robber who donates the stolen cash to charity (Keown, 2001).

But not all Buddhists subscribe to this hard-line view. There is a gradient of Buddhist morality towards the harm of living beings. Butchers are not imprisoned in Buddhist countries, despite their

highly immoral practices of slaughtering animals for money. Likewise, abortions, while they always create bad karma, are viewed to be a decision between the mother and the fetus, and rarely are abortions criminalized in Buddhist society (Hughes, 1995). There are also those that interpret Buddhist tradition to only apply the "prohibition of harm" to sentient beings (Walters, 2004). The Dalai Lama has contended the definition of a soul as inhabiting everything post-conception, stating that "It may be that what you do to a conglomeration of cells that have the possibility of becoming human entails no negative or karmically unwholesome act. However, when you're dealing with a configuration of cells that are definitely on the track to becoming a human being, it's a different situation"(Dalai Lama, 2002).

Much like Hinduism, Buddhists believe that the more important quality to determine the karmic weight of an action is intent. The Dalai Lama, speaking at the 2002 Mind and Life conference, told scientists:

> "From the Buddhist perspective, the general line of demarcation in ethics is based mainly on the long-term consequences-the results of the scientific research. It's very difficult to distinguish the ethical status of an action simply by judging the nature of the action itself. Much depends on the actor's motivation. A 'spiritual' act with negative motivation is essentially wrong. A more aggressive act may seem destructive, but if that specific action is carried out with altruistic motivation, and the proper sort of goal, then it could be positive…If you as scientists have a sincerely compassionate motivation, and a sense of responsibility for the long-term implications, then carry out your work and make your decisions." (Dalai Lama, 2002)

**Areas of Secular Concern for Stem Cells**

As we have seen already, there are a great deal of differing opinions on the topic of embryonic stem cell research. There are the two extremes – those that believe an embryo is a human being and ES research is tantamount to genocide, and those who believe an embryo is merely a collection of cells with no moral weight whatsoever. And in the gap is a wide variety of views aiming to determine exactly what moral consideration we should be giving to these embryos. Weighed against this debate is the enormous medical potential stem cell research has in unlocking cures and treatments for diseases previously considered fatal. What follows is a summary of the work bioethicists have done in investigating these

concerns. First and foremost, we must investigate the indeterminate moral status of a partially-developed human being. Since we are dealing with the ramifications of destroying life, particularly human life, it is important to begin with a grounding in why murder itself is forbidden.

-*Why is Murder Bad?*

There are two primary objections to murder, one being personal – "I wouldn't want to die," and the other being social – "I don't want my friends/family to die." These objections are universal to people with sound minds, so protecting the right to life is codified and made into law.

We can apply these two basic objections to the destruction of embryos to get some moral clarity. The first notable result is that the social objection is completely meaningless in this context. No one is friends with an embryo, as friendship involves shared mutual interests, of which the embryo has none. The embryo has a family, but that family has not watched the embryo grow up, and has no emotional attachment to it. The other objection, the personal objection, does not go away that easily. An embryo may not be able to vocalize it, but avoiding death is a trait universal to all forms of life. This quality must still be respected, but it is still not clear how much weight it should be given.

-*What is a Soul?*

Ignoring the theological implications of such a question, it is useful to invoke the concept of a soul to help shine light on the above question. A soul, in this context, refers to the net sum of the goals and desires of any organism, including the desire to not die. Aquinas categorized souls into three categories: vegetative, sensitive, and intellective. A vegetative soul is found in all organisms, it is responsible for guiding a tree towards sunlight, or for processing nutrients from food. The sensitive soul is found in all animals, it allows the organism to react to stimuli, to feel hunger and respond by going to find food. The intellective soul is human-specific, and it allows people to make rational judgments and engage in abstract conversation (Eberl, 2000).

What kind of soul an organism has is a key factor to the amount of moral weight that organism should be given. For example, a tree being cut down is not a particularly immoral action; the tree has a vegetative soul. However, if there was a family of squirrels living in the tree, it would be more immoral to cut the tree down, thus depriving the squirrels (with a sensitive soul) of their home and comfort. This kind of morality that exists between the various intertwined souls in nature is called *deep ecology* and won't be discussed here in depth.

With this generalized framework, we can be more clearly about the moral consideration that an embryo deserves. An embryo by itself does not have the organs for either sensory or intellective behavior, the only reactions it can possibly make to stimuli is to differentiate. At this point, the embryo has a vegetative soul: it can grow, but can not do much else.

There is some debate over whether the embryo even has a *single* soul. Prior to the formation of the primitive streak at around 14 days, any cell or group of cells in the ICM may break away and form its own, unique organism. This is the *twinning* process by which identical twins are formed. Some believe that since every single ES cell can theoretically become a human, that the embryo cannot be said to have a soul, it is only a collection of pre-ensouled cells that have not yet individualized (Shanon, 2008). Others reject this, believing that even without a distinct soul, the embryo still qualifies for the moral protection that a vegetative soul affords (Eberl, 2000).

*-Potentiality*

If the only consideration was the immediate concerns of the embryo, the debate would already be finished. However, an embryo is not going to remain an undifferentiated mass of cells forever, it is only nine months away from becoming a human being with full human rights. This concept is called *potentiality*, and it is the primary concern most people have with embryonic stem cell research. Not all embryos have the same potential to become a human. Embryos that test positive for debilitating genetic defects are not considered to have the same potential to be a human as negative-testing embryos. Likewise, an embryo successfully implanted into the womb is considered to have a much greater potential

than one left over and stored in a freezer. These distinctions in potential can be categorized into two groups: *active* and *passive* potentials (Eberl, 2000). A passive potential is something that can be done at any moment. For example, I have the potential to cook dinner at any moment. But, if I had taken steps to realize that potential, like a pot of water heating up on the stove, I would be said to have an active potential. An embryo successfully implanted into the uterus has a very active potential – without any impediments, there will be a human person born in nine months. Assuming the parents are intent on keeping it, this activation of potential gives the embryo an additional *social* moral standing – it now has a moral value to the parents, much in the same way that the tree had moral value to the squirrels.

*-Future Persons*

Imagine a perfect world for the opponents of ES research. Embryos are legally treated as persons, and can not be discarded or used for research. Each of the excess embryos that would have been destroyed is eventually implanted and adopted. This is a good thing, it means that suffering of human embryos was avoided. But, a significant percentage of those that would be born will at one point suffer from a disease curable by embryonic stem cells. Those future persons, by virtue of having developed a central nervous system, will feel a lot more pain than embryos with no discernable features. While a person might feel justified in saving lives with this hardline policy, the cost in actual future human suffering is morally unacceptable (Shaw, 2008).

*-Research-Specific Embryos*

While there seems to be a consensus among the bioethical community that spare IVF embryos should be donated to research rather than destroyed, not much has been said about embryos created solely for the purpose of being cannibalized for ES research. To a crusader for embryo rights, this kind of research seems like an unfathomable horror, reminiscent of Nazi medical handbooks and mad scientist ghost stories. The major religions are again divided on this issue: Muslims and Jews generally find this process unobjectionable, Christians of all denominations are horrified by it, and Buddhists and Hindus are

wary of destroying life, but accept it if the research would save lives (Zoloth, 2009). Still, the topic causes moral uncertainty among people regardless of religion: 40% of Muslims that accepted research on spare embryos were morally troubled by research-specific embryos (Ahmed, 2001). Arguments for this distinction often invoke the concept of human dignity, that it degrades the meaning of human life if we make human life into a tool for our own uses, to just be created to be destroyed again. Research on spare embryos is merely a byproduct of the *in vitro* fertilization process, a preferable alternative to the inevitable destruction of spare embryos. But it can also be said that the very procedure of IVF inherently instrumentalizes human life (Devolder, 2005). Many embryos are created in a lab, but only one is chosen for personhood. The rest are frozen or donated or discarded. This reckless disregard for most of the embryos' well-being is currently overlooked to benefit infertile couples. Some say this comparison is not fair, as *in vitro* fertilization uses embryos for their designated purpose, making babies. Others contend the opposite, that if we are to instrumentalize an embryo, using it to save many thousands of human lives is a lot more ethical than using it to create one life. Either way, the moral status of the embryo is already considered negligible compared to the benefit it gives to actual humans, so allowing the creation of embryos purely for research would not considerably devalue human dignity.

## Alternatives to Embryonic Stem Cell Research

Due to the controversial nature of embryonic stem cells, scientists have been trying to derive pluripotent cells from other sources. While these techniques have been successful in treating some diseases in animal models, they ultimately need to be tested against embryonic stem cells to ensure their safety.

### *Parthenogenesis*

Parthenogenesis, a natural process in some organisms where an egg is induced to divide without the presence of a sperm. This is the method many lower organisms use for reproduction, for example to make worker bees and ants. However, in humans and other mammals, parthenogenesis only causes

arrested early development. Since 2002, scientists have been able to grow human parthenotes long enough to harvest ES cells. This raises a very interesting question to the opponents of ES research about the definition of human beings. Several prominent authors in the Catholic Church argued that something that can never be born might not be even considered a human. Others believe that parthenogenesis is equally as immoral as harvesting embryos, even though the human that's created is fatally disfigured (Latkovic, 2006). There is no solid consensus on parthenogenesis, and while it is more accepted than ES research, many in the Church believe it is better to be safe than sorry, especially when dealing with condoning what might be (to them) a massacre.

*Adult Stem Cells & iPS Cells*

Adult stem cells (ASCs) are considered to be the most ethical source of stem cells, as their isolation does not destroy an embryo. Treatments involving adult stem cells have been in use for decades (especially for hematopoietic stem cells), and are as harmful to a human to collect as a blood donation. All five of the major world religions approve adult stem cell research, including garnishing high praise from the Catholic church, declaring that "Catholic foundations and medical centers have been, and will continue to be, among the leading supporters of ethically responsible advances in the medical use of adult stem cells" (UCSSB, 2008). In recent years, the revelation that adult somatic cells (skin fibroblast cells) could be reprogrammed using DNA encoding 2 to 4 transcription factors to be pluripotent (Takahashi et al., 2007) was hailed by opponents of ES research as the end of using embryos forever (Holden and Vogel, 2008).

**Chapter-3 Conclusion**

The debate over stem cells has been very heated, with one side fearing for their eternal souls, while the other side is trying to get lifesaving cures to the public as fast as possible. Each of the five major religions give different explanations based on scripture and tradition, but of them, only Christianity is firmly opposed to any form of embryonic research. A secular bioethical examination of the debate calls

for moral consideration of the embryo, but not enough to jeopardize a potential cure to several major genetic illnesses. Like all new medicines, all types of stem cell-based therapy need to be held to the utmost standards for safety and effectiveness.

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# Chapter 4: Stem Cells Legalities

*Hang Nguyen*

Stem cell research has become one of the most disputed topics of the 21st century. Advocates say stem cell treatment is the future of regenerative medicine, and the cure of deadly diseases, while critics oppose using embryonic stem cells due to the destruction of an embryo. A recent ABC News poll (**Table I**) revealed that 59% of Americans support stem cell research while and only 35% are against it. The survey also pointed out that 6 in 10 say the government should overturn restrictions on federal funding of stem cell research (Langer, 2009).

**Results of ABC News Poll on American's Support of Stem Cells as of Jan. 2009**

| | **Support** | **Oppose** |
|---|---|---|
| All | 59% | 35% |
| Democrats | 68% | 26% |
| Independents | 64% | 30% |
| Republicans | 40% | 55% |
| Liberals | 73% | 22% |
| Moderates | 67% | 28% |
| Conservatives | 38% | 57% |

| | | |
|---|---|---|
| No Religion | 80% | 15% |
| White Catholics | 59% | 37% |
| All Catholics | 54% | 41% |
| All evangelical Protestant | 43% | 52% |
| Evangelical white Protestant | 38% | 58% |
| Trend | | |
| 4/15/07 | 60% | 36% |
| 1/19/07 | 55% | 38% |

**Table-1: Results of ABC News poll on American Support of Stem Cells.** Question asked: Do you support or oppose loosening the current restrictions on federal funding for embryonic stem cell research? (Langer, 2009)

Despite the existence of hundreds of embryonic stem (ES) cell lines worldwide, U.S. scientists have been prevented from using federal money to help research these lines because of reoccurring legislations. This chapter will describe various regulations concerning stem cell research in different countries, focusing on the U.S.

## U.S. Federal Regulations on Stem Cell Research

Most recent U.S. federal regulations relating to ES cell research came out under President Bush's administration, however Bush's immediate predecessor, Bill Clinton, was a far greater supporter of human embryonic stem cell (hESC) research. In 1993, Congress and President Clinton gave the National Institute of Health (NIH) direct authority to fund human embryo research for the first time. In response, the NIH established a panel, including scientists, ethicists, public policy experts, and patients' advocates, to consider the moral issues involved.

This panel made its recommendation that the use of spare embryos from *in vitro* fertilization (IVF) clinics (which are normally discarded with parental consent) for use to derive ES cell lines is appropriate and should receive federal funding. This suggestion created an uproar. Within a year, Congress had banned the use of federal funds for any experiment in which a human embryo is either created or destroyed. Known as the Dickey-Wicker Amendment, this ban was actively renewed each year since then (Dunn, 2005) until President Obama overturned the amendment in 2009.

In 1998, James Thomson (University of Wisconsin) successfully generated the first hESC lines using private funds (Thompson et al., 1998). However the field demanded federal money to investigate more fully the potential of human ES cells, so in January of 1999, with the help of Harriet Rabb, the top lawyer at the Department of Health and Human Services (HHS), a turning point was set on the course of Clinton Administration policy. Harriet released a legal opinion which concluded that because human ES cells "are not human embryos within the statutory definition," the Dickey-Wicker Amendment did not apply to them. Guidelines, developed by the NIH with input from the National Bioethics Advisory Commission, were published in August 2000 not recommending the use of federal funds to destroy new human embryos to derive ES cells, but recommending federal funding on research with previously derived ES cells (Dunn, 2005). President Clinton strongly endorsed the guidelines, and his administration was the first to open the door to federal funding for ES cell research.

As President Bush took over the office, his administration made several highly questionable decisions regarding stem cell research. In his State of the Union Address, Bush urged Congress to prohibit all human cloning; the NIH was also told to cancel its plan to review grant applications for hESC research (Agnew, 2003). On August 9$^{th}$, 2001, Bush announced,

after much deliberation, that he would allow federally funded researchers to work with hESC lines as long as the cells were derived before he began his speech at 9:00 pm that day. While this limitation of stem cell sources was portrayed as a clever political maneuver, the scientific community thought that it was "an attempt at pleasing the misinformed masses while at the same time not entirely writing off the possibility of medical advances" (Stem Cell Laws, 2005).

Three months later, George W. Bush ordered an official withdrawal of funding guidelines that Clinton had authorized, making Bush the first President ever to reduce – below what his predecessor had done – the amount of hESC research eligible for federal funding (Dunn, 2005). On the scientific side of the problem, a year after Bush declared the new restriction of hESC research, the NIH crafted a model materials transfer agreement (MTA) to fund a half-dozen research groups that had derived hES cell lines so they could ramp up production, and also procured hES cells for six intramural NIH labs. However, none of these efforts ensured the quality of the hES cell lines, and further research showed the majority of the lines were non functional. As a result, U.S. scientists could only get their hands on 4 functional hES lines out of 71 eligible lines on the NIH list (Holden, 2009).

In 2002, Bush created the Council of Bioethics with an explanation that he needed advice on "bioethical issues that may emerge as a consequence of advances in biomedical science and technology." Since there are already several well-established organizations that could have easily taken on this task, such as the NIH or the American Society for Bioethics and Humanities, the fact that Bush felt it necessary to have his own watchdog on bioethics was an undeniable indication of how strong an opponent he is in hESC matter (Stem Cell Laws, 2005). In June of 2004, 58 U.S. Senators sent a letter to President Bush urging him to expand the number of stem cell lines eligible for federally funded research. Earlier that April, 206 members of the U.S.

House of Representatives had signed a similar letter (Dunn, 2005). Yet, Bush did not change his position.

The first veto of President Bush's five-year-old administration was to reject Congress' bid to lift funding restrictions on hESC research. Bush reasoned that the bill "would have supported the taking of innocent life in the hope of finding medical benefits for others," and that "it crosses a moral boundary that our decent society needs to respect." However, "those families who wake up every morning to face another day with a deadly disease or a disability will not forget his decision to stand in the way of sound science and medical research," said Senator James M. Talent (Babington, 2006). In short, hES cell issues shadowed Bush for much of his presidency. Although newly elected President Obama has now overturned most of President Bush's harsh hES legislation (mentioned later in this chapter), I will first discuss how individual states reacted to over-ride the harsh Bush federal policies.

## U.S. State Stem Cell Legislations

In general, following President Bush's harsh hES policies, private entities and state governments assumed greater responsibility for the funding of biomedical research. Individual U.S. states have passed a patchwork of bills to either outright ban all forms of cloning and hESC research, or to officially endorse hESC research and experiments involving cloned embryos. Several U.S. states launched campaigns against Bush's national policy as soon as the 9 August, 2001 policy went into effect. In January of 2004, New Jersey was the first state to originate a state-supported stem cell research facility, approving $10 million for the project. In November of that year, California became the lead in state funding when Californian voters accredited Proposition 71, a bond measure that provides $3 billion over 10 years to stem cell research,

including work with cloned human embryos and the stem cells they produce (Wadman, 2008). Rather than being despondent over the Bush veto, California Governor Arnold Schwarzenegger, a fellow Republician, took prompt action. He announced that the state is loaning the California Institute of Regenerative Medicine (CIRM) $150 million to get rolling.

Encouraged by California's success, other states followed suit, among them were New York, Connecticut, Maryland, Wisconsin, and Massachusetts. In June 2005, Connecticut Governor Jodi Rell signed into law a bill that earmarks $100 million for hES cell research over 10 years. In 2007, the New York state government enacted a $600-million stem-cell research fund. Recently, the most high-profile fight against Bush decision was in Massachusetts. In March of 2005, under a veto threat by former Republican Governor Mitt Romney, state lawmakers voted in favor of allowing hESC research to continue in Massachusetts, but this was overturned by Romney (Dunn, 2005). In 2007, current Massachusetts governor Deval Patrick proposed $1 billion in state funding for biomedical research – half of which would be used to build a research center housing the nation's largest ES cell bank. That bill was approved by the MA Congress in 2008 (News in Brief, 2008), and was signed by Gov. Patrick in January 2009. Maryland authorized a commission to dole out $38 million, and Wisconsin is considering legislation to spend $750 million on research facilities (Wadman, 2008). "In 20 years, you can't imagine a major university without a stem-cell program," said Andrew Cohn, a spokesman for the WiCell Research Institute, associated with the University of Wisconsin (Scherer, 2004). In Illinois, former Democratic Govenor Rod Blagojevich, wants state legislators to approve $100 million for a stem cell program, and proclaimed a diverted $5 million from his budget for the research on top of $10 million awarded to seven Illinois Institutions (Holden, 2006).

Not surprisingly, opponents of hESC research immediately sprang into action. Six states, including Michigan, Indiana, North Dakota, South Dakota, Arkansas, and Louisiana, criminalized hESC research (Wadman, 2008). In 2005, Ohio Governor Bob Taft used his line-item veto power to strike a ban on state funding of hESC research. The ban was to ensure that no funds under Taft's $500 million Third Frontier initiative heading to voters in November would be used for unproven research. This ban was firmly supported by pro-life organizations. Mark Lally, legislative director of Ohio Right to Life, told LifeNews.com: "Since adult stem cells have produced over 50 clinical treatments while ES cells have produced none, the legislature has wisely decided to invest in the only type of stem cell research that is both ethical and has demonstrated success." Rep. Mike Gilb, the Republican lawmakers who inserted the ban into the budget, said it is necessary because he worries ES cell research will lead to human cloning. After all, initial trials using ES cells proved to be somewhat disastrous, for instance, in one case, Parkinson's patients who were injected with ES cells ended up growing hair in their brains; while adult stem cell research proved to offer promising progress for everything from heart disease to breast cancer (Ertelt, 2005). A summary of various states policies related to cloning and hES cells is shown in **Table-II**.

| State/Jurisdiction Statute Section | Specifically permits research on fetus/embryo | Restricts research on aborted fetus/ embryo | Consent provisions to conduct research on fetus/embryo[3] | Restricts research on fetus or embryo resulting from sources other than abortion | Restrictions of purchase/sale human tissue for research |
|---|---|---|---|---|---|
| Arizona §§36-2302, 2303 | No | Yes, prohibits research on aborted living/non-living embryo or fetus | No | Yes, prohibits the use of public monies for cloning for research | No |
| Arkansas §§20-17-802, 20-16-1001 to 1004 | No | Yes, prohibits research on aborted live fetus | Yes, consent to conduct research on aborted fetus born | Yes, prohibits research on cloned embryos | Yes, prohibits sale of fetus/fetal tissue |

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| California Health & Safety 2004 Proposition 71 §§ 123440, 24185, 12115-7, 125300-320 | Yes, permits research on adult and embryonic stem cells from any source | Yes, prohibits research on aborted live fetus | Yes, consent to donate IVF embryo to research | Prohibits sale of embryos and oocytes; prohibits payment in excess of the amount of reimbursement of expenses to be made to any research subject to encourage her to produce human oocytes for the purposes of medical research | Yes, prohibits sale for the purpose of reproductive cloning or for stem cell research |
| Connecticut §§4-28e; 19a-32d et seq. | Yes, on embryos before gastrulation (a process during embryonic development) | No | Yes, consent to donate IVF embryo to research | No | Yes, prohibits payment for embryos, embryonic stem cells unfertilized eggs or sperm donated following IVF treatment |
| Florida §390.0111 | No | Yes, prohibits on aborted live fetus | No | No | No |
| Illinois 720 ILCS 510/6, 510/12.1 Executive Order 6 (2005);410 ILCS 110/1 et seq. | Yes, permits research on embryonic stem cells, embryonic germ cells and adult stem cells from any source | Yes, prohibits on aborted living/ nonliving fetus | Yes, written consent to perform research on cells or tissues from a dead fetus other than from an abortion | Yes, prohibits research on fetus/fertilized embryo; prohibits funding under E.O. 6 (2005) of research on fetuses from induced abortions and the creation of embryos through the combination of gametes solely for the purpose of research | Yes, prohibits sale of fetus/fetal tissue; prohibits purchase or sale of embryonic or fetal cadaveric tissue for research but permits reimbursement for removal, storage and transportation for research |
| Indiana §35-46-5-1, 16-18-2-5.5 | Yes, permits fetal stem cell research on placenta, cord blood, amniotic fluid or fetal tissue | Yes, prohibits research on aborted living/non-living embryo or fetus | Yes, consent required for fetal stem cell research | Yes, prohibits research on cloned embryos | Yes, prohibits sale of human ovum, zygote, embryo or fetus |
| Iowa §§707C.4 | Yes, ensures that Iowa patients have access to stem cell | No | No | No | Yes, prohibits transfer or receipt of the |

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| | therapies and cures and Iowa researchers may conduct stem cell research | | | | product of human reproductive cloning |
| Kentucky §436.026 | No | No | No | No | Yes, prohibits sale of fetus/fetal tissue |
| Louisiana §14: 87.2 | No | No | No | Yes, prohibits research on fetus/embryo in utero, in vitro fertilized embryo | No |
| Maine 22§1593 | No | No | No | Yes, prohibits research on fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation | Yes, prohibits sale of fetus/fetal tissue |
| Maryland 83A§5-2B-01 et seq. | Yes, permits research on adult and embryonic stem cells | No | Yes, written consent to donate unused IVF material to research | Yes, prohibits donation of unused oocytes for state funded stem cell research; cloning of an organism beyond the embryonic stage is prohibited | Yes, prohibits valuable consideration for the donation or production of IVF material |
| Massachusetts 112§12J, 2005 SB 2039 | Yes, on embryos that have not experienced more than 14 days of development (not including days frozen) | Yes, prohibits research on embryo/live fetus | Yes, written consent to perform research on a dead fetus and informed consent to donate egg, sperm, or unused preimplantation embryos created for IVF | Yes, prohibits research on live embryo or fetus; also prohibits creation of fertilized embryo solely for research | Yes, prohibits sale of neonate, embryo or fetus for illegal purposes; prohibits sale of embryos, gametes or cadaveric tissue for research |
| Michigan §§333.2687-2688, §§333.16274-16275, 333.20197, 333.26401-26403, 750.430a | No | Yes, live embryo/ fetus | Yes, written consent of mother to donate dead embryo, fetus or neonate to research | Yes, prohibits research on a live embryo or fetus, cloned embryo | No |

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| Minnesota §§145.421, 422 | No | No | No | Yes, prohibits research on a live embryo or fetus up to 265 days post fertilization | Yes, permits the sale/purchase of cell culture lines from nonliving human conceptus |
| Missouri §§188.036, 037 | No | Yes, prohibits research on a fetus alive pre-abortion | No | No | Yes, prohibits receipt of valuable consideration for aborted fetal organs or tissue |
| Montana §50-20-108(3) | No | Yes, prohibits research on a live fetus | No | No | No |
| Nebraska §§28-342, 346, 71-7606 | No | Yes, prohibits research on aborted live fetus or the use of state funds for research on fetal tissue obtained from an abortion | No | Yes, limits the use of state funds for embryonic stem cell research; restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars | Yes, prohibits sale, distribution or donation of viable aborted child |
| New Hampshire §§168-B:1, 15 | No | No | No | Yes, prohibits the maintenance of a unfrozen fertilized pre-embryo past 14 days | Yes |
| New Jersey C.26:2Z-1 et seq.; C.2C:11A-1 | Yes | No | Yes | No | No |
| New Mexico §24-9A-1, 3, 5 | No | No | No | Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation | Yes, prohibits abortion for the purpose of selling the fetus to researchers |
| New York Public Health Law Article 2, Title 5A | Yes, permits research on adult and embryonic stem cells from any source | No | No | | |
| North Dakota | No | Yes, prohibits | Yes, requires | Yes, prohibits | Yes, prohibits the |

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| §14-02.2-01, 2; 2003 HB 1424 | | research on a living/non-living embryo or fetus | consent to conduct research on a nonliving fetus or embryo other than from an abortion | research on a fetus born or extracted alive; cloned embryos | sale of a fetus to be used for illegal purposes |
| Ohio §2919.14 | No | Yes, prohibits research on a living/non-living embryo or fetus | No | No | Yes, prohibits sale of fetus or fetal remains from an abortion |
| Oklahoma 63 §1-735 | No | Yes, prohibits research on a fetus/embryo | No | No | Yes, prohibits sale of fetus or fetal remains |
| Pennsylvania 18 §§3203, 3216 | No | Yes, prohibits research on a live embryo or fetus | Consideration may not be given to mothers consenting to research; in cases involving abortion, consent must be provided after decision to abort | No | Yes, consideration may not be given to mothers consenting to research or other transferring tissue except for expenses involved in actual retrieval, storage, etc. |
| Rhode Island §11-54-1 | No | No | Yes | Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation | Yes, prohibits sale of neonate, embryo or fetus for illegal purposes |
| South Dakota §§34-14-16, 17, 20; 34-23A-17 | No | Yes, prohibits research on a living/non-living embryo or fetus | No | Yes, prohibits research on embryo outside of a woman's body; research on cells or tissues derived from an embryo outside a woman's body | Yes, prohibits sale of embryo |
| Tennessee §39-15-208 | No | No | Yes, consent required to conduct research on aborted fetus | No | Yes, prohibits sale of aborted fetus |
| Texas Penal Code §48.02 | No | No | No | No | Prohibits sale of fetus/fetal tissue |
| Utah §§76-7-301, 310 | No | No | No | Yes, prohibits research on a live | Yes, prohibits sale of fetus/fetal |

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|---|---|---|---|---|---|
| | | | | fetus, fertilized embryo post-implantation[1] | tissue; also prohibits sale of live unborn children, which is not defined, but are referred to in abortion statute[1] |
| Virginia §32.1-162.32-2 | No | No | No | May prohibit research on a cloned embryo or fetus[2] | Yes, prohibits shipping or receiving of the product of human cloning for commerce[2] |
| Wyoming §35-6-115 | No | No | No | No | Yes, prohibits sale, distribution or donation of live or viable aborted child, defined to include embryos, for experimentation |

**Table-2: Summary of American States' Stem Cell Policies.**
(Source: Stem Cell Research, 2008)

Private plans to get stem cell research moving were positively embraced at many prominent U.S. universities. In December of 2002, Stanford University in California used non-federal money to establish its Institute for Cancer/Stem Cell Biology and Medicine in an attempt to resolve funding and oversight dilemmas in the controversial hES field. The University of California - San Francisco, Johns Hopkins University in Baltimore, Maryland, and Harvard University in Cambridge, Massachusetts opened similar institutes. Besides developing new therapies for chronic diseases and cancer, it was quite feasible that these institutions would eventually use a method called therapeutic cloning, or somatic-cell nuclear transfer, to create new ES cell lines that are patient-specific (Check, 2002), though this has not yet happened for humans (except for iPS cells recently derived from patient fibroblasts).

The Bush administrative regulations limiting federal funding for hESC research left much to be desired for researchers. Many scientists wanted to work with stem cell lines beyond those derived before August 2001, thus, state policies designating funding for hESC research in recent years have lured top biotech companies and biologists to their research institutions. While some state legislatures at least considered bans against ES cell research due to ethical issues, other states have been clamoring to pass legislation to offer more funding.

## Obama Administration: A Fresh Start for hESC Research

The moment President-elect Barack Obama took office he swept away the Bush Administration's restriction on federal funding for hES cell research in a move long anticipated by the U.S. scientific community. Researchers at the NIH and the CIRM made it no secret, "I think everybody here is incredibly excited about the new Administration," said Story Landis, director of the National Institute of Neurological Disorders and Stroke and chair of the NIH Stem Cell Task Force (Holden, 2008). "Since Obama was elected, the pharmaceutical industry is clearly much more interested in stem cells," CIRM President Alan Trounson added, "that will be a really big help when we're working through costly and difficult clinical trials to get treatments to patients" (Hayden, 2009).

Within 3 months of his inauguration, as expected, President Obama signed an executive order supporting stem cell research on 9 March 2009 at a White House ceremony attended by scientists, lawmakers, patients, and patient advocates. "We will vigorously support scientists who pursue this research," Obama said. "And we will aim for America to lead the world in the discoveries it one day may yield" (Hayden, 2009). The new order explicitly permits federal

funding for research on ES cell lines derived with parental consent from embryos left over at fertility clinics and otherwise slated for destruction. Estimates of the number of new lines range from 400 to 1,000. Picking up where the Clinton Administration left off in 2000, work is already under way at the NIH in Bethesda, Maryland, to develop guidelines covering the eligibility of various cell lines for federal funding. Some of the scientists are already proposing using the new ES cell lines in applications with $200 million in NIH 'Challenge' grants, which will be funded by the economic stimulus package (Hayden, 2009).

The question now under debate is whether the federally funded ES cell work will still be limited to lines derived from surplus fertility clinic embryos, or whether the government will accept the use of lines from embryos that have been created solely for research. Many scientists would like to work with lines created through research cloning, or somatic cell nuclear transfer (SCNT). The NIH Stem Cell Guidelines, to be finalized this summer 2009, will give the scientists an answer. The draft that came out in April this year, though not perfect, was a big improvement over what scientists had been living with since 2001. The number of hESC lines available to researchers was largely expanded by eliminating the cutoff date for cell lines that qualify for federal funding. But some restrictions remain: the ES cell lines must be derived from surplus embryos donated by couples receiving fertility treatment; not eligible are ES cell lines derived from other sources, including *in vitro* fertilization (IVF) embryos created for research purposes, SCNT, and parthenogenesis. Funding continues to be allowed for research with induced pluripotent stem (iPS) cells – cultivated from adult cells but which have some properties of ES cells – which many think will offer the same promise as cells from SCNT. NIH will not fund work that involves the possible introduction of pluripotent human cells (either iPS cells or ES cells) into the germ lines of any animals, a restriction recommended by the academies' report.

Parthenotes, which are short-lived embryos created from an unfertilized egg, are also forbidden, as they qualify as human embryos under the Dickey-Wicker amendment (Holden and Kaiser, 2009).

Some researchers are really concerned about just how many of the existing hESC lines will be eligible, given NIH's detailed requirements on informed consent. Prominent Stanford University School of Medicine stem cell researcher Irving Weissman says the proposed ban on SCNT goes against the policy implied by Obama's earlier comments. "The NIH has not served its president well. There is no prohibition on SCNT in guidelines established by the International Society for Stem Cell Research (ISSCR) or by the National Academies," said Weissman in a statement. Most researchers, however, share the sentiments of Sean Morrison of the University of Michigan Medical School in Ann Arbor, who says the proposed policy is "a huge advance and a reasonable compromise" (Holden and Kaiser, 2009).

Attitudes towards Obama's policy on stem cell research are starkly divided. While scientists and research advocates worldwide are celebrating the removal of rules restricting research on hESCs in the United States, which is said to have interfered the field's progress for seven and a half years; those who oppose the research criticized Obama for not investigating the situation thoroughly before making his decision.

## International Stem Cell Policies

*European Union*

Only days after U.S. President Bush vetoed a bill that would have significantly broadened federal funding for hESC research, European Union (EU) ministers gave the green light to funding guidelines similar to the U.S. proposal. The seventh Framework Programme for research FP7, which is worth about $63 billion, started in January 2007 and runs until 2013. Although the council does not directly finance the destruction of human embryos, that means researchers cannot use FP7 funding to derive their own cell lines from embryos left over from IVF procedures, but they are able to use the money to buy hESC lines from other sources (Wadman and Abbott, 2006).

*United Kingdom*

In March 2002, a research group from King's College in London received one of the first licenses from the United Kingdom's Human Fertilisation and Embryology Authority (UKHFEA) to isolate stem cells from human embryos and establish cultures of stem cells that could be propagated or frozen. Three separate stem cell populations from 58 embryos came into existence. Although the creation of cell lines was not a surprise, the availability of these cells was significant because this was the first scientific publication describing the isolation of stem cells under government guidelines specific to stem cell research. More important, those lines are to be deposited in the UK's Stem Cell Bank, and will be accessible for more experiments (Garfinkle, 2004).

hESC research field in the UK advanced when the UKHFEA granted a license to the Newcastle Center for Life on August 11, 2004, specifying that colonies of hESCs can be created

for research purposes but not for cloning a human being. After a year, the researchers may continue to work on any stem cell lines they have established though they could not do cloning or stem cell isolation unless a new license is issued (Garfinkle, 2004).

*Germany*

In few countries has the soul-searching over promises and pitfalls of biotechnology been as intense as in Germany, in part because of the Nazis' grisly legacy of experimentation in eugenics. In January 2002, when the German parliament voted on the importation of embryonic stem-cells, 340 out of 618 parliamentarians voted in agreement but only if the process would be kept under close government control. Although this decision to allow the limited import of embryonic stem cells may appear to be liberalization, it actually signified a tightening of restrictions for researchers. Existing German law banned research on human embryos and only allows the laboratory creation of an embryo for the purposes of IVF, yet it does not take into account the discovery of stem cells, thus did not explicitly ban their importation. Now that the parliament decided to prohibit German researchers from creating their own cells and only use stem cells that have already been created, "this means we'll have to do research with cells that will soon be obsolete," said Dr. Kekule , director of the Institute for Medical Microbiology in Halle (Kim, 2002).

In 2006, Germany expressed its firm stand against ES cell research by calling for EU-wide ban on stem cell research. Germany, along with Austria, Poland, Slovakia, Slovenia, and Luxembourg, put pressure on a number of European countries to reject a proposal that would make EU money available for stem-cell projects if the same kind of research is prohibited in some member states. On the other hand, Finland, who held the rotating EU presidency at the

time, recommended funding for research on human stem cells but prohibits money being given to projects dealing with human reproductive cloning, human genetic modification, or the creation of human embryos for scientific research (Deutsche Welle, 2006).

*Sweden*

Sweden, considered to be at the forefront of stem cell science and technology, is ahead of many other countries with their legislations and the recent funding of a national stem cell bank. In September 2002, the Swedish National Research Council granted about $1 million to fund a national stem cell bank for three years. The framework for legislation and ethical guidelines for stem-cell research has been worked out quietly and reasonably fast in Sweden. Sweden allows stem cells to be taken from embryos that can no longer be used for further IVF treatment. The use of SCNT (using genetic material from a patient's own skin fibroblast cells to create embryos to derive ES cell lines for therapeutic purposes) is allowed in Sweden, even though this has not yet been pursued (Sweden's Stem Cell Success, 2002). Government funding has poured into the field, and because of its success, money from outside the country has also come in. In March 2002, a joint US-Swedish research program was announced, securing $7.5 million funding for stem-cell research in the country. In September of the same year, the Swedish Research Council granted $4.5 million for a period of three years in research funds to nine projects and two extensive networks. Later in the fall, an additional $500,000 was awarded for research on ethical and legal issues (Sweden's Stem Cell Success, 2002).

*Australia*

"Australia bans all human cloning whether for reproduction or research. This includes a ban on embryo splitting and other techniques that might create a clone without fertilization. But

Australia does allow the use of embryos remaining after assisted reproduction, as long as those embryos were created before 5 April 2002. This federal law supersedes all previous state-level laws concerning cells and cloning research" (Garfinkle, 2004).

**Figure-1** shows a world map with countries color-coded depending on whether their stem cell policies are permissive (dark brown), flexible (light brown), or restrictive (yellow). An explanation of the various levels follows the figure.

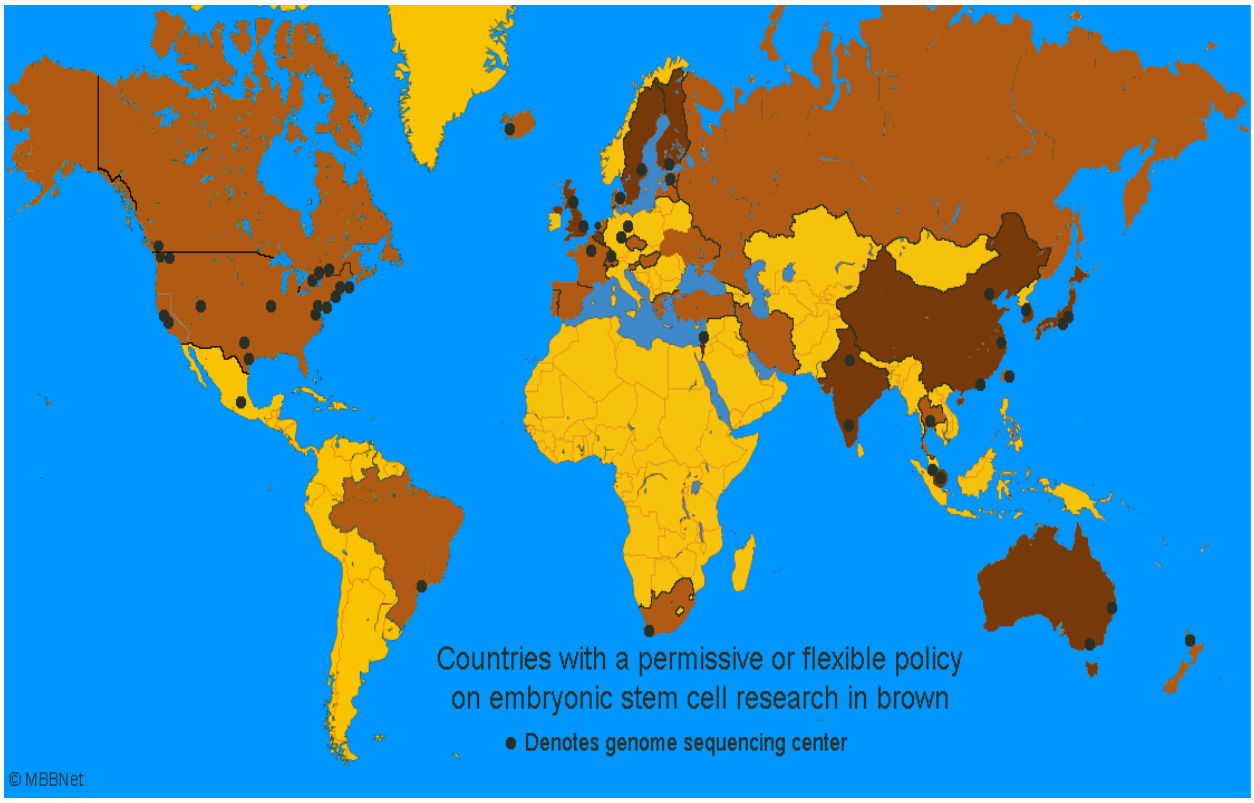


**Figure-1: World Map of Various ES Cell Research Policies.** Countries colored in brown (permissive policies) represent about 3.8 billion people, more than half the world's population. All of them except the U.S. have banned by law human reproductive cloning. (Hoffman, 2005)

Map Explanation

- **"Permissive"** = various embryonic stem cell derivation techniques including SCNT, also called research or therapeutic cloning. SCNT is the transfer of a cell nucleus from a

somatic or body cell into an egg from which the nucleus has been removed. Countries in this category include Australia, Belgium, China, India, Israel, Japan, Singapore, South Korea, Sweden, the United Kingdom and others. These countries represent a global population of more than 2.7 billion people.

- **"Flexible"** = derivations from fertility clinic donations only, excluding SCNT, and often under certain restrictions. Countries in this category include Brazil, Canada, France, Iran, South Africa, Spain, The Netherlands, Taiwan, and others. These countries represent a global population of more than 700 million people.
- **"Restrictive policy or no established policy."** Restrictive policies range from outright prohibition of human embryo research to permitting research on imported embryonic stem cell lines only to permitting research on a limited number of previously established stem cell lines. Countries with a restrictive policy include Austria, Germany, Ireland, Italy, Norway, and Poland.
- Map is designed to reflect **national policy** and whether or not public funds may be used to pursue stem cell research using IVF embryos donated from fertility clinics.
- The **black dots** show the locations of some of the leading genome sequencing research centers. Most U.S. centers are those that have been involved in the Human Genome Project. The genome sequencing centers are meant to indicate the level of scientific infrastructure and not whether stem cell genomic studies are being conducted at a given center. The dots are linked to center web sites.
- **California** in the U.S. supports embryonic stem cell research through Proposition 71, a $3 billion bonding initiative that is projected to provide about $300 million in stem cell research funding annually for 10 years. Approved by California voters Nov. 2, 2004,

Proposition 71 establishes a state constitutional right to pursue stem cell research, including through SCNT or research/therapeutic cloning, and prohibits funding of human reproductive cloning research.

- Map is a Mercator projection that exaggerates the size of areas far from the equator.

## Chapter-4 Conclusions

Laws on stem cell research vary widely across countries and even across states within large countries like the U.S. Ethical controversies surrounding hESCs drive the process of decision-making to complication. In a country with huge political divides from state to state like the U.S., it takes a tremendous amount of effort at both federal and state levels to reach a compromise so that scientists can do their job without hitting a road-block. In Europe, there is a wide variation in governments' regulations on stem-cell research, with countries like the UK encouraging it, while countries like Germany enforce a near total ban on it.

ES cells represent the future of modern biotechnology and medicine, and it would be a mistake for human beings not to take a chance on this controversial technology. People must begin to realize the potential medical benefits of ES cell research, and support ongoing research to create alternative sources for ES cells that would be more widely accepted. Expanding stem-cell research in all countries, while mandating careful and cautious oversights is the best option.

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# PROJECT CONCLUSIONS

After examining the sources, applications, ethics, and legality of stem cells, the authors of this IQP actively encourage the use of all types of stem cells for therapeutic and research purposes. Stem cells are some of the most powerful, and in some cases, only, tools for curing deadly genetic diseases. While many people, specifically some Christian denominations, have ethical concerns with embryonic stem (ES) cells, we feel that all stem cell sources should be tapped, as each has its own unique advantages and drawbacks. There have been great advances in the field of adult stem cells, particularly with the development of induced pluripotent stem (iPS) cells, but there are still many unanswered questions about their efficiency and safety compared to ES cells. A human embryo is still human, and should be afforded some moral consideration, but it is the authors' opinion that this moral value does not outweigh the potential for adult humans to vastly improve their quality of life. Like all new and powerful technologies, stem cells should be strictly regulated to prevent trivial non-medical uses. We believe that stem cell testing for various diseases should be continued, and the potential for therapeutic failure is not sufficient to discourage stem cell research, rather, it is important that stem cells be thoroughly investigated to minimize therapy failures. We applaud President Obama for his decision to allow federal research grants for ES research, and hope that this is a new beginning for many present and future lives and wellbeing.