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# Stem Cells

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# **STEM CELLS AND SOCIETY**

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By:

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## **ABSTRACT**

The purpose of this project is to describe the impact of stem cells on society by describing their types, how they are isolated, and their medical benefits, while also investigating the ethical and legal issues surrounding their use. Chapter-1 and Chapter-2 describe different types of stem cells and their sources, and explain various applications of stem cells and how they can contribute to treating different diseases. Chapter-3 and Chapter-4 discuss ethical issues surrounding stem research, and the laws that govern their use. Based on the project research, the authors provide conclusions about the future directions of stem cell research.

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## **PROJECT OBJECTIVES**

The objective of this IQP is to discuss and research the topic of stem cells, and examine the effects of this technology upon society. The purpose of chapter-1 is to describe the various types and sources stem cells, their functions and properties, how stem cells are isolated from their sources, and explain the levels of potency. Chapter-2's purpose is to document the use of stem cells to treat different diseases, in both animal experiments and human clinical trials. Chapter-3's purpose is to address the different ethical issues facing the use of stem cells, and explain various reasons why people support or do not support stem cell research. Chapter-4's purpose is to describe various domestic and international laws governing the use of stem cells, and discuss future legislation that will strongly stem cell research. Finally, an overall conclusion will be generated by both IQP authors discussing the future implementation of stem cells, and which stem cell laws each author agrees with the most.

# **Chapter-1: Stem Cell Introduction: Types and Sources**

*Shaaz Shuttari*

When one talks about stem cells, one delves into a subject full of amazing promise to the human race that's also filled with controversy. Stem cells are described as the body's master cells that have a long life span and can differentiate into other cell types to perform various functions (American Federation, 2003). Under ideal conditions in the body or a laboratory, stem cells divide to form more daughter stem cells (Mayo Clinic, 2006). The newly formed daughter cells can turn into specialized cells with a specific function, such as bone, blood, or brain cells (Mayo Clinic, 2006). Daughter cells can also self-renew to form new stem cells (Mayo Clinic, 2006). Stem cells are highly unique from any other type of cell because no other cell in the human body can self-renew and differentiate. Because of these regenerative properties, stem cells have become the central focus of the new field of regenerative medicine. Researchers are interested in the study of stem cells, with the hope of solving some of humanities worst health problems, increasing our knowledge of a disease, testing new drugs for safety and effectiveness, and generating healthy cells that can replace diseased ones.

Some types of stem cells are obtained by destroying embryos, which some believe is murder and others believe is a miracle. The topic of attaining stem cells from embryos is highly controversial. But not all types of stem cells destroy embryos during their production, and these cells are not as controversial. The purpose of this chapter is to document the various types of stem cells, and to focus on their relative strengths and weaknesses for medical purposes, as a basis for subsequent chapters on stem cell ethics and legalities.

## **Stem Cell Types**

Stem cells can predominately be divided into three main types: embryonic stem (ES) cells that are isolated from an embryo, adult stem cells that are isolated from various adult cells, and induced stem cells that are induced to form from adult fibroblast cells. ES cells are sometimes referred to as “unlimited stem cells” since they are immortal, while adult stem cells are termed “limited stem cells” (ISSCR, 2006). ES cells are usually isolated from the inner cell mass of a five-day-old blastocyst embryo obtained from an *in vitro* fertilization (IVF). Adult stem cells can be obtained from the umbilical cord blood and various tissues within the adult human body, such as in bone marrow, brain, and skin (Yu and Thomson, 2006).

Stem cells can also be categorized by their *potentials*. Totipotent cells are newly fertilized eggs that can form any type of cell, through the eight-cell stage. Pluripotent cells can form any cell of the adult organism, but not extra-embryonic tissue such as the placenta. Multipotent cells can form into several types of related cells. Unipotent cells can mostly form into one other type of cell. Stem cells can be grown in a lab with highly specialized incubators, without changing their composition until enough are grown for therapy (Scott, 2007).

## **Embryonic Stem Cells**

ES cells are among the most pluripotent type of stem cell, meaning they have the ability to develop into numerous cell types of the body (ISSCR, 2006). These cells are obtained from an embryo that has undergone *in vitro* fertilization (IVF) outside a living organism in a controlled environment (Bellomo, 2006). When fertilization occurs, a sperm head containing a nucleus enters the egg and its tail is cut off and left behind (Bellomo, 2006). The embryo begins

dividing, and after five days a hollow ball of cells forms as a blastocyst (Bellomo, 2006). The blastocyst is made up of two cell types, an inner layer of a cluster of cells known as the inner cell mass which develops into an embryo, and an outer layer referred as the trophoblast which forms the placenta (Bellomo, 2006). Embryonic stem cells are found in the inner cell mass of the blastocyst (Bellomo, 2006). ES cells have the greatest medical potential of all the stem cell types due to their pluripotency. Because an embryo is usually destroyed to obtain ES cells, they are also the most ethically controversial.

Generally researchers collect ES cells using a pipette and transfer them to a Petri dish for culturing (Bellomo, 2006). Numerous colonies form in the Petri dishes and are transferred into new Petri dishes. Depending on the culture conditions, the ES cells either self-renew or differentiate. Added signaling molecules can lead towards differentiation into a specific type of cell, such as nerve, bone, cardiac, and pancreatic cells (Bellomo, 2006). From these newly created cells, cell replacement therapy can be used to replace tissues and restore their functions (Bellomo, 2006).

During ES cell transplantation experiments in mice, to reduce the risk of immunorejection of the transplant, a technique termed somatic cell nuclear transfer (SCNT) has been devised to produce ES cells with the same genetic traits as the donor. This technique when applied to human patients should eventually revolutionize medicine. This technique works through removal of the nucleus from a donor egg (Bellomo, 2006). A biopsy is then taken from the patient in need, for example skin cells, and a nucleus from one of the donor cells is transferred into the enucleated donor egg (Bellomo, 2006). The egg is then cultured *in vitro* to the blastocyst stage from which ES cells genetically identical to the donor are obtained (Bellomo, 2006). Though SCNT has been used on mice and cattle to produce stem cells, the cloning of

human embryos using somatic donor cells has been problematic and has not yet been reported by any researcher (Cibelli et al, 2001). Scientists feel that SCNT in humans would be unsafe and is ethically questionable (Cibelli et al, 2001). Beyond therapeutic cloning, there has been a mutual agreement among most scientists and physicians that any type of *reproductive* cloning in humans should be banned (Michigan Citizens...2006).

Although stem cell applications are the subject of Chapter-2, one medical application that ES cells may help in is spinal cord trauma. The process of repairing a damaged spinal cord is very difficult because the destroyed neurons must be replaced by neurons that make proper connections, and the newly placed neurons must be insulated with myelin (Transplantation of Neural Stem Cells...2003). Thus stem cell researchers trying to repair damaged spinal cords must create stem cells that become neurons to restore the neural circuit and oligodendrocytes to produce myelin insulation. Dr. Ronald McKay, a stem cell researcher at the National Institute of Health, has shown that mouse ES cells can repair neural damage when injected into rats (Transplantation of Neural Stem Cells...2003). A team of researchers at the Washington University School of Medicine has been able to successfully differentiate mouse ES cells into oligodendrocytes to remylenate axons in vitro (Transplantation of Neural Stem Cells into the Spinal Cord, 2003).

### **Adult Stem Cells**

The second main class of stem cells are adult stem cells (ASCs). ASCs are much harder to extract from the human body because they are relatively rare compared to the surrounding differentiated cells, but they have the potential to be more widely used in medicine due to less ethical issues of how they are extracted versus ES cells. Adult stem cells have been identified in

many organs and tissues, including brain, bone marrow, peripheral blood, umbilical cord blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis (Scott, 2007). ASCs are thought to reside in a specific area of each tissue, called a "stem cell niche" that serves to aid their survival (Scott, 2007). ASCs, also referred as limited stem cells, are rare cells that can be found only in certain organs and tissues, but not in all (ISSCR, 2006). These limited cells can only be used in repairing the types of tissues and organs that they came from, e.g. skin adult stem cells can only be used to repair the skin and no other organ or tissue, and not every organ or tissue has been found to have them, making them difficult to obtain.

Once stem cells are injected into the body, some have the ability to home in on their tissue of origin, while others do not. Undifferentiated ES cells lack homing potential, while differentiated ES cells, or adult stem cells, have this homing potential (Bellomo, 2006). ES cells typically form teratomas in various parts of the body, and start to associate with one another, while adult stem cells are differentiated enough to find the specific tissue or organ that they derive from. For example, injected hematopoietic stem cells will return to the bone marrow.

One of the most abundant sources for ASCs is the placenta of a developing fetus. It has up to ten times as many stem cells as the blood of an umbilical cord, and the latter has 10 times more than bone marrow (The Stem Cell Debate, 2001). Overall, the odds of identifying and finding an ASC is small since only one cell in 100,000 is an ASC (The Stem Cell Debate, 2001).

The process of differentiation helps convert ASCs or progenitor cells into more specialized cells that can be used to replace cells in the specific organ or tissue that they came from (Scott, 2007). ASCs can either be differentiated *in vivo* after the cells are injected, or can be differentiated *in vitro* by growth in the presence of various growth factors (Scott, 2007). For example, when producing neurons or epithelial cells, scientists will select specific growth factors

such as nerve growth factor (NGF) and epidermal growth factor (EGF), which both contribute to generate the production of these cells *in vivo* (Scott, 2007). This procedure requires a lot of experimentation. Compounds known to bring about specific types of gene expression will be tested for inducing differentiation, and existing differentiation will also be tested (Scott, 2007). In a way, scientists are coming up with an index of culture additives that can lead to production of specific cell types. Directed differentiation may also help scientists understand the molecular nature of plasticity and specific factors that distinguish adult and embryonic stem cells.

One of the best-characterized types of ASC is the hematopoietic stem cell (HSC). These cells are usually obtained from bone marrow, but are more frequently found in umbilical cord blood. In a common procedure to treat leukemia, HSCs are obtained from a bone marrow tap of a donor then perfused into a patient who previously had radiation or chemotherapy to destroy their own bone marrow. If the graft grows, the donor cells colonize the patient's bone marrow to begin producing various cellular components of blood. A future adaptation of this procedure may allow HSCs to be differentiated *in vitro* to change the cells into another type of tissue prior to infusion (Mayo Clinic, 2006). This potential is termed plasticity or trans-differentiation, to denote the process of changing into a cell type different than its origins. This application could remove the ethical problems with obtaining embryos. If cells were obtained from the same patient it would solve problems related to immunorejection (Mayo Clinic, 2006). The cost of this procedure would not likely exceed a standard bone marrow transplant, but might take longer to perform since the cells need to be transdifferentiated (Mayo Clinic, 2006).

Dr. Catherine Verfaillie and her associates at the University of Minnesota have studied the transdifferentiation process. This team showed that stem cells isolated from adult bone marrow might have the plasticity equivalent to ES cells (University of Minnesota, 2002). They isolated

mouse bone marrow cells and differentiated them *in vitro* into cell types representing the three essential germ layers, which are the endoderm, mesoderm, and neuroectoderm (University of Minnesota, 2002). When injected into a mouse, the cells were able to contribute to most types of somatic cells. The application of this stem cell procedure could prove effective for implementing stem cell therapy in patients, especially for repairing simpler types of tissues such as liver or bone marrow (University of Minnesota, 2002).

### **Different Types of Adult Stem Cells**

There are many types of adult stem cells that come from numerous locations of the body. Adult hematopoietic stem cells (HSCs) come from bone marrow, and form into different types of blood cells, and they can provide protection for fighting various infections. Adult neuronal stem cells (NSCs) form from the brain, and give rise to three major cell types as neurons, astrocytes, or oligodendrocytes. Adult cardiac stem cells (CSCs) come from the heart and can provide cardiac repair in damaged tissue such as from a heart attack. Adult epithelial stem cells come from the lining of the digestive track, and can give rise to different cell types, such as goblet and enteroendocrine cells that can replace cancerous ones. Mesenchymal stem cells (MSCs) are found in bone marrow, and can form into a variety of cells, such as nerve and muscle cells. Adult intestinal stem cells come from the villi and crypts of the intestine, and have the ability to divide rapidly on a daily basis. Adult eye stem cells are mainly found in the retina, and can work towards curing blindness. Parthenotes can be used as a source of embryonic stem cells, which result from parthenogenesis or “virgin birth,” which can turn human eggs into “embryo-like balls” using embryos that can never develop into human beings (Brevini and Gandolfi, 2007).

## **Adult Hematopoietic Stem Cells**

In the history of stem cell research, adult hematopoietic stem cells (HSCs) have been used successfully in therapies for decades. These stem cells turn into different types of blood cells, and are very easy to obtain for research. They can be used to treat multiple types of leukemias, sickle-cell diseases, multiple myelomas, or cancer of plasma cells. In 2006, there were fifty thousand successful transplants of HSCs worldwide (Medscape, 2008).

There are two classes of transplant HSCs: autologous and allogeneic. Autologous transplants use HSCs that were removed from the same patient before cancer treatment (Medscape, 2008). Allogeneic transplants involve HSCs removed from another person (Medscape, 2008). Blood from the umbilical cord of a placenta is one of the richest sources of HSCs (Medscape, 2008).

HSCs are critically important in the production of all types of blood cells, such as red blood cells, lymphocytes, neutrophils, and macrophages. These stem cells have the ability to self-renew and are multipotent (Medscape, 2008). HSCs have been used in bone marrow transplants for decades to treat leukemia and other diseases of the spinal cord or blood (Medscape, 2008).

## **Adult Neuronal Stem Cells**

The existence of neuronal stem cells (NSCs) was found during neurogenesis, which leads to the creation of new neurons. These stem cells can grow into new brain cells in two areas of the brain, the olfactory bulb where odor is processed, and the dentate gyrus in the central part of the hippocampus for memory and learning (Rebuilding the Nervous System with Stem Cells,

2005). When these stem cells divide, they must choose either to remain a NSC, turn into a nerve cell, or convert into astrocytes that hold neurons in place or oligodendrocytes that are hair-like extensions that send signals from one neuron to the next (Rebuilding the Nervous System with Stem Cells, 2005). In a petri dish these stem cells can differentiate into any type of brain cell, however when these stem cells are placed in their natural environment they typically become neurons (Rebuilding the Nervous System with Stem Cells, 2005). NSCs have been known to have beneficial effects with patients with Parkinson's or Alzheimer's disease, through their potential to grow back dead tissue and restore function in neural regions.

### **Adult Cardiac Stem Cells**

Adult cardiac stem cells (CSCs) are found in the heart, and are beginning to be used to treat heart disease. Bone marrow resident CSCs are usually induced by a variety of growth factors to differentiate into specialized cells called Angiogenic Cell Precursors (ACPs) (Touchette, 2004). Plaque build up in an artery can lead to a reduction in the volume of blood being pumped in and out of the artery to the heart. ACPs are then attracted to this ischemic area by growth factors, and then travel through the vessel wall into damaged tissue (Touchette, 2004). This action helps form new blood vessels and repair any damaged tissue. For this treatment, more ACPs are sometimes grown and placed back into the body through a regular cauterization (Touchette, 2004). From this cauterization, ACPs will be able to differentiate into endothelial cells that lead to the formation of new blood vessels and help ease symptoms for patients with severe heart problems (Touchette, 2004). There are a lot of positive cases of regeneration of new cells in damaged tissue using cardiac stem cells (Touchette, 2004).

## **Mesenchymal Stem Cells**

Used highly in regenerative medicine, mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into cells of mesodermal origin (Jackson et al., 2007). These multipotent stem cells form in bone marrow. In lab conditions, MSCs are grown into a variety of cells such as tendon, ligament, bone, and cartilage (Jackson et al., 2007). Fortunately, substantial knowledge exists on how to grow these stem cells in culture. These stem cells have been approved for use in clinical trials, and have beneficial effects for tissue repair (Jackson et al., 2007). These stem cells are easy to culture for differentiation into different cell types, which can lead scientists to make strides in understanding their molecular pathways. These stem cells also can take up and maintain introduced genes in a process that could be used to deliver helpful molecules to targeted locations (Jackson et al., 2007).

An important application of MSCs is their use in human trials where they are derived from a small bone marrow sample in a patient, and then grown in culture and given back to the same patient (Jackson et al., 2007). This autologous application could be used to solve problems associated with immune rejection of foreign cells and tissues (Jackson et al., 2007). These stem cells have proven beneficial in patients with arthritis.

## **Adult Epithelial Cells**

Adult epithelial stem cells (ESCs) come from the lining in the digestive track. In adult self-renewing tissue such as the skin, ESCs are thought to maintain regular tissue homeostasis and can act as a reserve for tissue replacement (Harvard Medical School, 2007). These stem cells have a relatively long life span, and are normally tagged as label-retaining cells (LRC) (Harvard Medical School, 2007). Label retention has been used to identify somatic stem cells

and locate their location within the stem cell niche (Harvard Medical School, 2007). Although label-retaining cells rarely grow at rapid rates, they have a high proliferation potential when tissue expands, such as during wound healing (Harvard Medical School, 2007). Researchers have found that cutaneous tumors can arise from these stem cells, thus targeting these stem cells can be important for the study of carcinogenesis.

The p63 gene has been known to be “the master regulator of epithelial stem cells” (P63 and The Epithelial Stem Cell: More Than Status Quo?, 2004). Researchers have found that mice mutated in p63 run out of regenerative epithelial stem cells (P63 and The Epithelial Stem Cell: More Than Status Quo?, 2004). This study, led by Frank McKeon of Harvard Medical School, shows that p63’s role is not involved with tissue differentiation, but instead helps “stemness” or renewal to occur in regenerative cells in tissues (P63 and The Epithelial Stem Cell: More Than Status Quo?, 2004). McKeon and his team used ESCs as a method to show that p63’s key role was to make potential stem cells divide (P63 and The Epithelial Stem Cell: More Than Status Quo?, 2004). As McKeon commented about his p63 research, “dissecting genetic programs controlled by certain regulators will tell us much about how stem cells normally function, and how control goes away in cancer” (Harvard Medical School, 2007). This research shows that epithelial stem cell research can greatly help in the treatment of cancer in the skin, prostate, and breast.

### **Adult Intestinal Stem Cells**

Adult intestinal stem cells come from the villus and crypt areas of the intestine. Scientists found that the transcription factor Achaetes-like2 (Ascl2) turns on a stem cell-creating program in intestinal cells (Barker et al., 2007). When the Ascl2 gene turns on, any dividing cell

in the intestine turns into a stem cell that is able to produce any other cell type in that tissue (Barker et al., 2007). Crypts are the main location of stem cells, and Paneth cells protect these stem cells (Barker et al., 2007). Every five days the intestinal lining is completely replaced by the remaining stem cells and their Paneth cell defenders (Barker et al., 2007).

As Han Clevers of Hubrecht Institute in The Netherlands explained about intestinal stem cells, “these stem cells can produce 200-300 grams of new cells daily” (The Making of An Intestinal Stem Cell, 2009). Clevers and his team found that tiny cells within the Paneth region of the intestine have stem cell like features (The Making of An Intestinal Stem Cell, 2009). These cells are derived from the expression of gene Lgr5 (Barker et al., 2007). When Clevers and his team induced Ascl2 transcription factor in the intestinal lining of a mouse, it caused crypts to overgrow and develop within villi (The Making of An Intestinal Stem Cell, 2009). Clevers’s research showed that adult mouse intestines lacking Ascl2 will cause the Lgr5 stem cells to stop developing (The Making of An Intestinal Stem Cell, 2009). Thus Ascl2 is the key factor to the overall status of an intestinal stem cell. These stem cells can help in the treatment of colon cancer and various types of GI infection.

### **Adult Eye Stem Cells**

Adult eye stem cells isolated from the eye were initially believed to be retinal cells, but researchers at St. Jude Children’s Hospital found these cells were actually adult stem cells (Reuters, 2001). Retinal stem cells could help provide treatments for those suffering from retinal degeneration (Reuters, 2001). The goal is to re-engineer stem cells into light-sensitive photoreceptor cells to treat retinal degeneration.

A team led by Dr. Michael Dyer, researcher at St. Jude Children’s Hospital, proposed that

a layer of ciliary epithelial cells lining the inside of the eye contains retinal stem cells that, when grown in culture, produce tiny spheres of a thousand cells (Reuters, 2001). These tiny spheres could self-renew, and can be cultured to produce more spheres (Reuters, 2001). These new spheres have gene traits similar to adult eye cells, which were found by culturing these sphere-forming cells in the same growth area used for stem cells (Reuters, 2001). Dyer's continuing research involves taking samples of adult cells from patients with retinal degeneration and uses genetic factors to revert these cells into stem cells (Reuters, 2001). These cells are considered iPS cells (see below) and can be configured to grow into light-sensing photoreceptor cells for transplantation in a patient's eyes to restore vision (Reuters, 2001). These stem cells may prove beneficial for people with blindness or any type of visual impairment.

### **Parthenotes**

Parthenotes do not face the same ethical, religious, and legal issues that embryonic stem cells face. A parthenote embryo does not develop beyond the early fetus stage, and can never grow into a human being (Brevini and Gandolfi, 2007). As an alternate source for pluripotent cell lines, artificial parthenogenesis can be used to create parthenotes that make desired pluripotent cell lines. In "virgin birth" or parthenogenesis, an unfertilized egg retains both sets of chromosomes and begins to develop (Brevini and Gandolfi, 2007). This egg usually dies within a few days, however stem cells can be extracted if they can live to the blastocyst stage, usually 5 days (Brevini and Gandolfi, 2007).

Parthenote ES cells have been derived from mice and monkeys, but not yet man. The most successful results have been found in monkey eggs, where cell lines have been growing for over two years (Brevini and Gandolfi, 2007). Analysis of the monkey parthenote ES cells shows that

they are impossible to differentiate from embryonic stem cells derived from fertilized eggs (Brevini and Gandolfi, 2007). Further research is needed to confirm that tissues derived from parthenogenetic stem cells are fully functional. Jerry Hall of the Institute for Reproductive Medicine and Genetics in Los Angeles is hopeful in saying, “patients are so interested in this procedure, and we are confident enough in its feasibility that we have been willing to store eggs for use as soon as safety and effectiveness is shown” (Carpenter, 2008).

The use of parthenogenetic stem cells can not be used for obtaining autologous stem cells for men, or from women after menopause, however using therapeutic cloning (discussed below) could achieve results for any patient (Brevini and Gandolfi, 2007). In the future, banks for parthenogenetic stem cells could provide cells for patients in need. The hope is to use differentiated cells derived *in vitro* by parthenogenesis to eliminate the need to produce or disassemble a normal fertilized embryo. This would avoid most ethical issues in the use of parthenotes (except for those associated with normal egg donations) and may provide a positive impact for the development of stem cell research.

### **Induced Pluripotent Stem Cells**

One of the most exciting findings in stem cell research of the past decade is the development of a technique for producing ES-like cells from adult skin fibroblast cells. This technique does not destroy an embryo, so in theory could provide ES-like cells for therapy without strong ethical concerns. And moreover, the ES-like cells would be genetically identical to the patient. These cells are termed induced pluripotent stem cells (iPS), also termed induced embryonic stem cells (iES). In this technique, skin fibroblast cells are isolated and transfected with plasmid DNAs encoding various key transcription factors that activate the fibroblast cells to

de-differentiate to a stem like state (Bellomo, 2006). iPS cells are similar to ES cells due to their pluripotent capacity to become almost any type of cell (Bellomo, 2006). Of the four ways to obtain a pluripotent stem cell, ES, SCNT, parthenote, and induced, all except the induced technique require an embryo (Bellomo, 2006). This induced method has caused a lot of excitement around the scientific community.

iPS cells were first produced from mouse fibroblast cells in 2006 using plasmids to encode six pluripotency-inducing transcription factors, Sox-2, Oct-4, c-Myc, Nanog, Lin28, and Klf4 (Takahashi et al., 2007). Following transfection, after a few short weeks, some of the cells turned into pluripotent cells with characteristics of ES cell lines (Takahashi et al., 2007). The iPS cells showed several important traits of pluripotent stem cells, including the formation of all three germ layers, and their ability to aid in growth of various tissues when injected in mouse embryos (Takahashi et al., 2007). The iPS cells express various stem cell markers and are not programmed to display development of gene problems or tumors (Takahashi et al., 2007). In terms of cellular morphology, mouse iPS cells were more clustered and less flattened than normal human ES cells. Subsequent iPS studies showed that plasmids encoding three transcription factors, then only two transcription factors, could produce mouse iPS cells (Scott, 2007).

Human iPS cells were first derived, in 2007, by Dr. Shinya Yamanaka of Kyoto University in Japan (Takahashi et al., 2007). Yamanaka and his team used retroviruses encoding the five transcription factors of Oct-3, Oct-4, Sox-2, c-Myc, and Klf4, to perform the dedifferentiation of skin fibroblast cells (Takahashi et al., 2007). The human iPS cells had tight, flat, and sharp-edged cell colonies similar to human ES cells. It was determined that the c-Myc caused some of the cells to become tumorous, so in a subsequent experiment c-Myc was omitted

from the transcription factor mixture (Takahashi et al., 2007). In February 2008, James Thomson and Junying Ju of the University of Wisconsin-Madison used a lentiviral system encoding transcription factors of Oct-4, Sox-2, Nanog, and a different gene of Lin28, with no c-Myc, to create iPS cells (University of Wisconsin, 2007). This research team genetically reprogrammed human dermal fibroblasts from a baby's foreskin to create iPS cells that do not derive from embryos (University of Wisconsin, 2007).

As Ian Wilmut, the famous English embryologist at the University of Edinburgh who produced Dolly the world's first cloned mammal, said about iPS cells, "These new cells are expected to live a very long time, while retaining the ability to form into different tissues in the human body" (Bedford Research Foundation, 2008).

More recently, in April 2009, stem cell researcher Sheng Ding and his team at the Scripps Research Institute in La Jolla, CA, found that iPS cells could be created without any genetic alteration by inducing the cells with poly-arginine anchors (Reprogramming Offers Hope of Safer Stem Cells, 2009). Using mouse fetuses the researchers isolated connective tissue fibroblasts, and then incubated them in a bath of four polyarginine proteins for twelve hours, removed the proteins for thirty-six hours, and continued this cycle of events four times (Reprogramming Offers Hope of Safer Stem Cells, 2009). After two weeks, iPS cell colonies were created and all colonies did not develop cancer (Reprogramming Offers Hope of Safer Stem Cells, 2009).

## **Chapter-1 Summary**

Embryonic, adult, and induced pluripotent cells are the three main groups of stem cells in research. Embryonic stem cells are derived from the inner cell mass of an early stage embryo

known as a blastocyst. The embryos are usually obtained from *in vitro* fertilization (IVF) clinics from couples who decide to donate their embryos for research. Adult stem cells are undifferentiated cells that come from different organs and tissues in the adult body, and have a role to repair and maintain the tissue or organ that they are found in. Examples of these cells include hematopoietic and mesenchymal stem cells that are beneficial for treating numerous diseases. Induced pluripotent stem cells (iPS) or induced embryonic stem cells (iES) are stem cells that have the ability to become any type of cell in the adult body, but which are usually derived from non-pluripotent cells through expression of certain de-differentiation genes without using an embryo. Among all the types of stem cells, iPS cells seem to hold the most promise for advancements in stem cell research, and will hopefully show the same pluripotency as ES cells derived from a fertilized embryo. Future research seems to be focusing more on the use adult and iPS cells, as opposed to using embryonic stem cells.

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# CHAPTER-2: STEM CELL APPLICATIONS

*Baurzhan Negmetzhanov*

## **Introduction**

Since the discovery of stem cells, these master cells of the body have been of great interest in the medical community because of their ability to differentiate into other cell types and regenerate tissues in the body. Scientific research on stem cells has the potential to revolutionize the practice of medicine, and improve the quality and length of life. The hope is that stem cell therapy can be used to treat devastating diseases such as cancer, spinal cord injuries, and Parkinson's disease. The purpose of this chapter is to describe some of the applications of stem cell research, delineating applications still in the animal stage of research versus those applications already in human clinical trials.

Stem cells are regenerative cells that have the ability to specialize and develop into different tissues of the body. Unspecialized cells can be transformed to become heart tissue, skin cells, and other tissues. As discussed in chapter-1, embryonic stem (ES) cells are obtained from an embryo, while adult stem cells (ASCs) are obtained from adult tissues. ES cells are ethically controversial since they destroy an embryo when obtaining them, while ASCs do not destroy an embryo and are less controversial. ASCs are present in organs such as bone marrow, pancreas, brain, and umbilical cord blood. With ASCs, physicians have already treated autoimmune diseases such as lupus, multiple sclerosis, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, and spinal cord injuries (Earll, 2005; Hughes, 2005). However, adult stem cells are less potent than ES cells, and are incapable of developing into every type of adult tissue (Weiss, 2005).

## **Stem Cell Treatment of Diabetes**

Diabetes is the seventh leading cause of death in the United States today, with nearly 200,000 deaths reported each year. According to the American Diabetes Association, nearly 16 million people or 5.9 percent of the United States population have diabetes (Stem Cells and Diabetes, 2005). Type-I diabetes is a disease that results from the destruction of the pancreatic cells ( $\beta$ -cells) that produce insulin. The glucose level in the blood increases when insulin is insufficient. The common treatment for those who suffer from type-I diabetes is direct injection of insulin. Another treatment for these patients includes human islet cell transplantation to restore insulin secretion; however the transplants are often rejected as with most transplants. Also, this cell transplant technique is rare and only a small percentage of patients get a chance to receive one (Assady et al., 2001).

Embryonic stem cells have the potential to differentiate into insulin producing cells while avoiding immune attack and graft rejection, so these cells hold promise for physicians, researchers, and patients for a cure. Human ES cells have already been shown to be capable of differentiating into insulin-producing cells *in vitro* (Assady et al., 2001; Lumelsky et al., 2001; D'Amour, 2006). Armed with a ready supply of cultured ES cells grown from an ES cell line, these cells could in the future be applied to human patients. Before transplantation, the ES cells could be engineered to avoid immune rejection by placing them in nonimmunogenic media, thus allowing patients to escape the negative effects of immunosuppressant drugs (Stem Cells and Diabetes, 2005).

In addition to using ES cells, the possibility of using adult stem cells to treat type-I diabetes has also been explored on animal models. In one study, researchers genetically induced

mice to become diabetic, and then bone marrow stem cells were injected into the blood stream of the diabetic mice. After two weeks, researchers observed that insulin production had increased and glucose levels had dropped to normal (Hess et al, 2003). Researchers have made a remarkable progress in applying this stem technique in animals; however expanding the approach to humans may be years away.

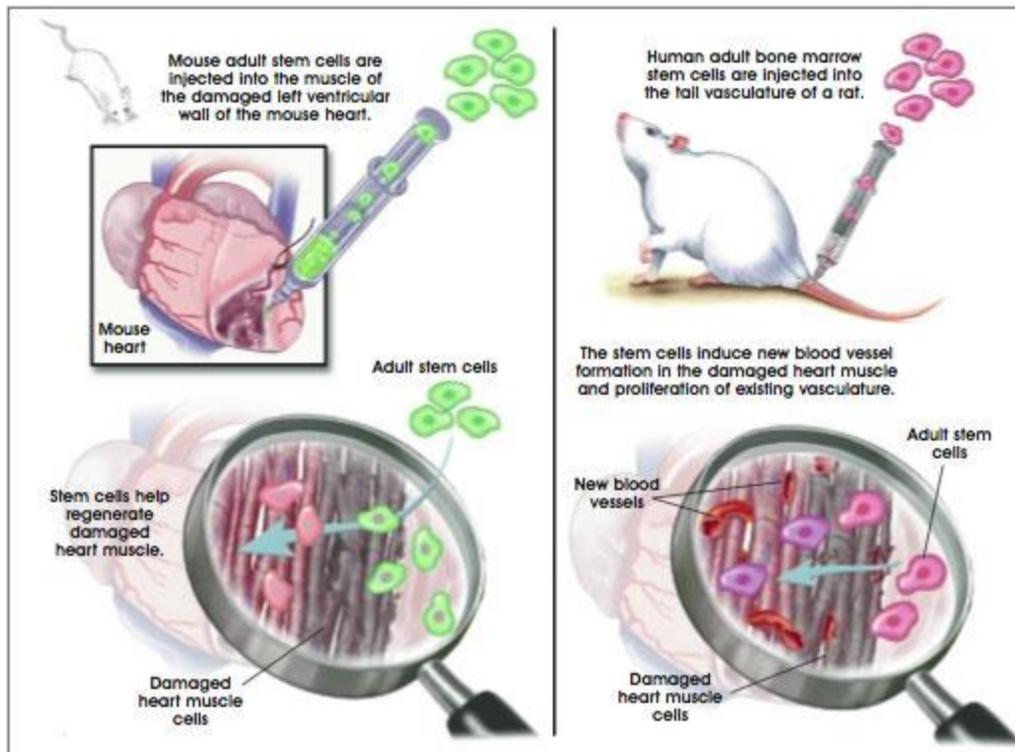
## **Stem Cell Treatment of Damaged Heart Muscle**

Heart disease is the leading cause of death in the world and in the United States. Heart disease and other heart ailments affect millions of people, and the number of cases is increasing with an ageing population. Although there are numerous drugs for treating heart disease, these drugs only alleviate the symptoms, or slow the progression of the disease. But recent research on stem cells has shown that these cells could be used to treat patients who have suffered from a heart attack. This stem cell approach has a great advantage over heart transplantation, since the number of heart attack patients far outweighs the number available organs.

With respect to adult stem cell treatments of heart attacks, human heart attack patients have already been treated with *adult* cardiac stem cells (Britten et al., 2003; Siminiak et al., 2004) or with adult bone marrow stem cells (Lunde et al., 2006; Schächinger et al., 2006). Injection of human bone marrow stem cells into damaged tissues of a patient's heart induced them to form new cardiomyocytes, vascular endothelial cells, and smooth muscle cells, thus partially repairing the damaged region of the heart. Patients treated with bone marrow stem cells experienced a lower number of adverse effects such as cardiac arrhythmias, and showed signs of significant improvements in heart, lung, and global function, compared to those patients who received a placebo (Schächinger et al., 2006). However, other studies showed no statistically

significant difference in patients receiving the stem cell treatment (Lunde et.al, 2006), so more research is needed. With respect to embryonic stem cells, human ES cells have already been shown to be capable of differentiating into various cardiac lineages *in vitro* (Kehat et al., 2001).

The human stem cell experiments were based on prior experiments with mice which showed that mouse ES cells are able to differentiate into contracting cardiomyocytes *in vitro* (Kehat et.al, 2001). Additional experiments have been performed with mice *in vivo*. Injection of hematopoietic stem cells (HSCs) *in vivo* provided an effective stem cell therapy for heart disease (**Figure-1**). It was observed that HSCs were able to differentiate into cardiomyocytes and vascular endothelial cells in the damaged part of the heart (Orlic et. al, 2001). Using this animal model researchers also have discovered that after injection of bone marrow stem cells into the damaged heart, newly formed tissues occupied sixty-eight percent of the damaged region only nine days after treatment (Figure-1). Moreover, the mice treated with stem cells survived in larger numbers than the mice that did not receive any treatment (Can Stem Cells Repair a Damaged Heart, 2006).



**Figure 1: Adult Stem Cell Therapy in Heart Diseased Mice.** *This illustration shows how adult stem cells are injected into the damaged part of a mouse heart, which induces repair of heart tissue and growth of new cells in the region (Can Stem Cells Repair a Damaged Heart, 2005).*

## Hematopoietic Stem Cell Applications

One of the first applications using stem cells *of any kind* was the treatment of leukemia patients with hematopoietic stem cells (HSCs). HSCs have been used since 1959 in bone marrow transplants; world-wide about 40,000 transplants are performed annually (Horowitz, 1999). Leukemia results from an uncontrolled proliferation of immature white blood cells that are the part of immune system. The high level of immature white cells in the blood causes a cancerous blood stream and compromised immune system that can kill the individual. In the leukemia treatment process, the patient undergoes chemotherapy which destroys cancerous HSCs and then his or her HSCs are replaced with a bone marrow transplant from a

histocompatible donor. The bone marrow (containing HSCs) is taken from a donor (usually a close relative) and injected into the patients' blood stream, where the HSCs differentiate into all the cellular components of the blood. The transplant procedure has saved thousands of lives to date, although finding a histocompatible donor remains difficult (Hematopoietic Stem Cells, 2005).

Another way that leukemia has been treated with HSCs involved removing bone marrow from the leukemia patient, irradiating the patient to destroy cancer cells, and then re-injecting the patient's own HSCs back in the bloodstream. Because the patient gets back his own cells, the risk of graft rejection is significantly reduced, however there is a risk that cancer cells may still reside in the returned bone marrow and the patient can regain leukemia (Thomas, 2000). As more immuno-rejection drugs were developed, bone marrow transplants became more common and were applied to other blood diseases that were previously incurable.

The most famous treatment involving HSCs in the United States occurred in 1984. The patient suffered from a genetic disease known as SCID (Severe Combined Immunodeficiency). The disease is very rare, however usually fatal soon after birth. The patient with SCID cannot fight off any infection due to the absence of the primary immune system defense cells. David Vetter (also known as "bubble boy"), a young boy with SCID was living in a germ-free bubble for his entire life. In an attempt at treatment, he was given HSCs in order to overcome SCID. The bone marrow from his sister was injected into "bubble boy" to see if it would specialize into the immune cells needed. Although the experiment was a success, it was discovered that his sister had Epstein-Barr virus in her bone marrow. David could not fight the virus because his immune system was not developed, and he eventually died (McVicker, 1997). The HSC gene therapy treatment has subsequently been applied to other SCID patients with success

(Cavazzana-Calvo et al., 2000). Although HSCs have been successful in treating leukemia, HSCs have a great potential for treating other cancers, while continuing to avoid the ethical traps of working with embryonic stem cells.

## **Stem Cell Applications for Spinal Cord Injuries**

Each year, over 11,000 Americans suffer from spinal cord injury. Spinal cord injuries usually are permanent since myelin cells lose their ability to regenerate. Myelin cells form an insulating layer around nerve fibers to facilitate signal transmission, and are important for transmitting signals from brain. However, according to animal studies, stem cells can repair damaged spinal cord tissue and restore function, which offers hope for treating spinal cord trauma patients. Although much more research is needed, recent rat studies have shown that stem cell therapy holds promise for repairing spinal cord injury (Stem Cell Treatment Succeeds In Spinal Cord-injured Rats, 2005).

One study performed at Reeve-Irvine Research Center at UC Irvine showed that a human ES stem cell treatment of rats can restore myelin cells and neurons within seven days after the initial injury. The most remarkable result was that the rats regained a limited mobility of their legs that had been previously lost. However, the same treatment did not work on the rats injured for more than ten months, so the treatment needs to be applied soon after the injury (Stem Cell Treatment Improves Mobility after Spinal Cord Injury, 2005).

Another study showed that in cases where rodent brain stem cells restored myelin in the injured rat spine, the rats showed some recovery, and walked with more coordination. Adult neural stem cells (NSCs) taken from the brains of adult mice were labeled with a fluorescent marker, enabling researchers to trace those cells after they were transplanted into rats whose

spines had been crushed. NSCs transplanted into rats only two weeks after the initial injury survived. More than one-third of the transplanted NSCs traveled along the spinal cord, fused with the damaged tissue, developed into the type of cells that were destroyed at the injured site, and produced myelin. As was found in the previous experiment, "the maximal effect of transplanting these cells is *early* after injury," says New York University School of Medicine professor Moses Chao, PhD. "The timing of NSC application therefore is critical to successful therapy in the injured spinal cord" (Society for Neuroscience, 2006). Both of these key studies show the potential of using NSC and ES cell-derived therapies for the treatment of spinal cord damage in rats, and show the treatment is most effective during early stages of the injury (Vasich, 2005).

Thus based on animal research, both ES cells and adult stem cells have a great potential for spinal cord injury cure. The biggest obstacle that researchers will face is applying methods on humans which will require a more in depth knowledge of stem cells and the spinal cord than the animal models can teach us.

## **Stem Cell Treatment of Parkinson's disease**

Parkinson's disease (PD) is a neurological disease that affects a certain part of the brain which contains neurons that secrete a chemical neurotransmitter known as dopamine. The lack of dopamine causes shaking throughout the body and difficulty when walking or maintaining normal posture. This devastating neurodegenerative disease most commonly affects people over the age of 50 (National Institute for Neurological Disorders and Stroke, 2009). Although some drugs are available to improve symptoms (such as Sinemet) the effects are only temporary, thus

researches have been trying to use different types of stem cells in animal models to find an effective treatment for this disorder.

Using a rodent model of Parkinson's disease with symptoms that are similar to human patients, researchers transplanted mouse ES cells into the damaged part of brain of a PD rat (Kim et. al, 2002). The injected ES cells were able to differentiate into neurons that produce dopamine, and the rats regained some lost functions.

Another similar approach was used by Bjorklund and his colleagues who used mouse ES cells to differentiate them *in vitro* into neuronal stem cells, and then transplanted them into a PD rat's brain (Bjorklund et. al, 2002). This study showed that the injected stem cells became dopamine producing cells, and improved the diseased rat's motor function. A possible obstacle that researchers may encounter with this approach is immune system rejection of the ES cells. In the animal model treatments discussed here, the rats were given powerful anti rejection drugs to help prevent loss of the ES cells.

Some success has been observed treating human PD patients. In a recent human clinical trial, fetal brain tissue was transplanted into the brains of Parkinson's disease patients. The results showed major and long-lasting improvements in some of the patients (National Institute for Neurological Disorders and Stroke, 2009). Other studies with fetal tissue explants have also shown some success (Madrado et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002; Vogel, 2005). However, experiments using fetal tissue have even more ethical issues than working with ES cells, since fetuses are more mature than the 5-day old blastocysts used to derive ES cells. Human fetuses are usually obtained from abortion procedures instead of IVF clinics that provide blastocyst embryos. But the experiment provides a proof of principal that

embryonic tissue (containing stem cells) can be used to repair the area of the brain damaged in Parkinson's patients, so a stem cell approach may eventually work in the future.

## **Neural Stem Cells and Alzheimer's disease**

Another neurological disease that has been important in the stem cell debate is Alzheimer's disease (AD). AD is a neurodegenerative disease that usually affects the elderly, and is one of the leading causes of late life dementia. The challenge for the stem cell therapy with Alzheimer's disease is that unlike Parkinson's, AD neurodegeneration affects different regions in the brain, while Parkinson's only affects the substantia nigra. Research showed that treating bone marrow cells with bromodeoxyuridine (a compound that incorporates into replicating DNA) induced the bone marrow cells to develop into brain cells after they were transplanted into adult rat brains (Binette, 2005). A significant advantage of this technique is that there is no danger of immune system rejection because the cells come from the same patient. The positive neural functionality of the transplanted cells observed in this study provides hope for treating Alzheimer's disease in the future (Binette, 2005).

## **Human Clinical Application of Stem Cells**

In those cases where our information on a particular stem cell application comes only from animal studies, scientists debate when to move into human clinical trials. Most physicians agree that many years of animal study are required before moving into human applications, but as discussed above, some diseases are already being tested in humans with stem cells. As discussed above, scientists are still in animal studies using stem cells to treat diabetes and spinal

cord injuries. But scientists have used hematopoietic stem cell transplants since 1959 to treat leukemia and a variety of other disorders, and have already begun to treat heart attack patients with *adult* cardiac stem cells (Britten et al., 2003; Siminiak et al., 2004) or with adult bone marrow stem cells (Lunde et al., 2006; Schächinger et al., 2006). And fetal tissue explants (containing stem cells) have already been used to treat Parkinson's patients (Madrado et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002; Vogel, 2005; Zandonella, 2005).

The use of controversial but powerful ES cells in humans has not yet been performed, but Geron Company suggests that ES cell therapy can be safe and effective for a select group of patients suffering from spinal cord injury. Many researchers caution that Geron's plans can make an already controversial field even worse, as ES cells from mice and humans have proven difficult to control, differentiating into the wrong kind of cell, or migrating away from the injection site. However, on January 23, 2009, the US food and drug administration (FDA) announced the approval of the first clinical trial using human embryonic stem cells to Geron to treat spinal cord injuries. Supporters of stem cell research praised the FDA approval, saying that any trial is important for moving forward (Wadman, 2009). Still, many researchers worry that Geron is moving too fast, warning about the possible side effects and immuno rejection. However, patients who suffer from various disorders ask researchers to continue their studies. The approval of ES cell clinical trials is very significant for the further investigation of stem cell applications.

## Chapter-2 Conclusions

Because stem cells (depending on their type) can differentiate into a variety of tissues, the hope is these cells might be used to treat previously incurable diseases, such as Alzheimer's, multiple sclerosis, diabetes, Parkinson's, heart attacks, spinal cord injuries, etc. More research is needed, but significant progress has already been achieved. Human adult stem cells have already been used to treat leukemia patients since 1959, and have more recently been used to treat patients with heart attacks. Fetal cells have been used to treat patients with Parkinson's disease. Humans have not yet been treated with embryonic stem cells, although the FDA in January 2009 provided approval for Geron to treat spinal cord patients. The stem cell treatments will remain controversial, and the graft may sometimes become immunorejected, but these treatments remain the only hope for some diseases previously thought to be incurable.

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## Chapter 3: Stem Cell Ethics

*Shaaz Shuttari*

The question of the use of the embryos in research has been a hot topic of debate since the late 1960's, when *in vitro* fertilization (IVF) clinics first appeared. With respect to stem cells, as discussed previously ES cells are usually obtained from embryos. This process destroys the embryo, so ES cell usage has ethical considerations. The ethical considerations against using ES cells has led to advancements in less controversial cells such as adult stem cells (ASCs) or induced pluripotent stem (iPS) cells. The purpose of this chapter is to go beyond the technology of stem cell usage to discuss whether we “should” work with such cells.

The stem cell debate invariably focuses on when life begins. According to a poll by ABC News and the Washington Post in 2007, 61% of Americans support embryonic stem cell research while 31% oppose this type of research (ABC News, 2007). For many supporters of this research, such as researchers and family members with cancer, they believe that life begins for an embryo when it is united in reproduction with sperm in a woman's womb (O'Mathuna, 1999). Outside the woman's womb, the embryo is just a lifeless ball of cells, and it should be used to benefit mankind and not be wasted (Dorff, 2001). On the other hand religious fundamentalists, such as Southern Baptists, believe that all embryos have basic human rights of life, liberty, and the pursuit of happiness, regardless of how they were created or what stage of development they are in (“U.S. Bishops Protest”, 2006). No matter what environment the embryo is put under, it is still a potential human being and should not be destroyed for experimentation (Catholic Online, 2008). Different world religions hold different views on when life begins. Religious groups, such as Jews and Muslims, believe that embryos are considered humans only after about day 40

when ensoulment occurs. Prior to this, the embryo is only a “watery substance”, so blastosysts at day-5 can be researched according to these religions. Groups such as Roman Catholics believe that all fertilized embryos, no matter what environment they are placed in or their age, are human beings and should not be experimented with. These opposing religious views constitute the fire of one of the most important debates in all of biomedical research.

### **When Does Life Begin?**

Researchers, philosophers, and politicians have debated when an embryo becomes human for at least 2000 years (Dorff, 2001). Philosophers, such as Aristotle, believed that life comes in three stages, defined as the vegetative, animate, and intellectual stages (Dorff, 2001). In referring to human development, the embryo starts growing in a mother’s womb in a vegetative stage. When muscles begin to form and limbs start to move, this new human being is in an animate stage. Finally the newly created human being will develop its intellect during the intellectual stage (Dorff, 2001). Most people agree that the first two stages occur in the mother’s womb and the last stage appears after birth. Using Aristotle’s thoughts, many believe that the embryo does not become human until after it is born.

Modern day researchers such as Dr. John Caplan, a science ethicist, seem to have followed many of Aristotle’s beliefs. Caplan believes that cloned human embryos are not yet human. Even the CEO of Advanced Cell Technology Inc. in Worcester, MA, Dr. Michael West, has agreed with this assessment to allow therapeutic research. However reactions to the completion of the 2003 Human Genome Project have interestingly disagreed with Aristotle’s teachings (Bellomo, 2006). For the first time we now have access to information contained in our genome which can eventually tell what type of person someone is, what shapes someone’s

body, and perhaps even someone's level of intellect (Bellomo, 2006). Human genomes are present in human embryos and these scientists were quoted as saying the embryos are human, although this is different than saying IVF embryos should have the same status as an embryo in a womb (Bellomo, 2006). To counter these arguments, Caplan and West claimed that they were referring to cloned embryos, thinking that they are "less than human" (Bellomo, 2006). Other scientists disbelieve their statements of cloned embryos being different from their true genetic genomes. Dr. Ian Wilmut was the British scientist who led the team that cloned Dolly the sheep and went to great lengths to prove to the world that Dolly was like any other sheep within her breed (Bellomo, 2006). Wilmut and his team showed that Dolly being cloned didn't change the fact that she is a sheep, and if an embryo has any type of sheep genome then it is always a sheep (Bellomo, 2006). Using Wilmut's study, if a human embryo has any type of human genome then that embryo has to be human (Bellomo, 2006). The idea of genomics claims that the identity of a species is shown in its genes and can be used to show that the embryo is human from its date of birth.

As this ethical debate continues, many believe that it is false to redefine ideas related to being a human as listed in the Belmont Report (Bellomo, 2006). It is clear that an embryo containing a human genome is human, but in view of IVF technology, the debate has expanded to determine what status an embryo has *outside* the womb when it can not become fully human.

### **Positions Against ES Cell Research**

Those who don't believe in ES cell research, such as Evangelicalist priests and former President George W. Bush, believe that the ball of cells that make up the early embryo is a human being entitled to certain rights (Catholic Online, 2008). As stated in the Declaration of

Independence, all human beings have the right to life, liberty, and the pursuit of happiness. All human beings are equal because all of us display these three fundamental rights, especially the right to life (Catholic Online, 2008). Without securing the right to life, the two other rights in the Declaration of Independence can't be attained (Catholic Online, 2008). There is a strong belief that any living being should have the right to life, and should not have to be dismantled for any research purposes (Teaching About Religion, 2006). Embryonic research appears to attack these principals as not giving any humanistic rights to human beings (Dorff, 2001). Any person has the right to life. Since this camp argues that embryos are considered humans, these opposers of ES cell research believe that embryos should have full protection under the law (Dorff, 2001).

Before fertilization the egg and sperm are two separate living cells that are genetically part of all human beings, and when these two gametes unite they form a human being (Teaching About Religion, 2006). A human embryo is not a cell, but an organism in the early stage of human development (O'Mathuna, 1999). An embryo needs a well-maintained environment and sufficient nutrition, and has the capability to grow and develop (Catholic Online, 2008). Identity has importance in any type of living being, for example when someone is sick, that person doesn't say, "my body is sick" but "I'm sick." Each embryo is genetically different and should be recognized with the identities the living humans keep (O'Mathuna, 1999).

The terms adult, teenager, and embryo are all manifestations of the same organism that happens to grow with age and go through different life stages. Developmental biology shows that our bodies originate at fertilization, and therefore a human embryo is a person because it is the same human being and organism as it is in an adult (Dorff, 2001). Supporters against ES cell research claim that each person and embryo is valuable, thus other more ethically permissible

methods in regenerative medicine, such as using adult stem cells or induced pluripotent stem cells, should be used to respect the dignity of every human life (Dorff, 2001).

### **Positions for ES Cell Research**

Although numerous people are against ES cell research, there is a much higher number of supporters (Dorff, 2001). For example, recently President Barack Obama signed a bill that lifted the previous restrictions on federal funding for ES cell research. Through painstaking trial and error research, supporters and scientists hope to utilize stem cells to help people with severe illnesses and diseases live longer.

Many of these supporters of ES cell research agree with non-supporters that eggs and sperm are living cells before conception (Bellomo, 2006). Embryos should be considered as human beings of the species *Homo sapiens*, but similarly something as small as a neuron or blood cell is human too (Bellomo, 2006). The main difference is that this ES cell support group believes IVF embryos originally created for reproductive purposes that are discarded, although they are alive, only have the *ability* to produce a life, and have less moral status than an embryo inside the womb. Consider a couple producing IVF embryos to have a family. Because the implantation process into the uterus is inefficient, extra embryos are usually created. The decision as to whether to implant the embryos or to donate them for research is fully the couple's (Bellomo, 2006). The woman then declines for a uterine transfer into her or anyone else, and she and her partner decide to donate the embryo to medicine, clearly stating in their donation no type of uterine transfer (Bellomo, 2006). Outside the womb an embryo can not develop beyond ten days, and if scientists used this embryo for research a full fetus will not develop (Bellomo, 2006). Gestation can't occur for the embryo and it can't experience frustration or pain, as it has

no nervous system. If the donated embryo is not used for research, it is usually destroyed (Bellomo, 2006).

The theory of mutual aid instructs us to come to the help of others in peril, when it can be done effectively (O'Mathuna, 1999). The use of donated embryos could be used to help suffering humans with no cost in real lives but with medical gains (O'Mathuna, 1999). In this manner, mutual aid should be applied to donated IVF embryos, with its reduced role as potential human life (O'Mathuna, 1999).

### **Catholic Stance on ES Cells**

Interestingly, zygotic personhood has not been in agreement with most of the Catholic Church's view for the last two thousand years (Bellomo, 2006). The early Church followed Aristotle's hylomorphic view that not until day forty does an embryo reach a human form with a body and soul (Catholic Online, 2008). As the philosopher Thomas Aquinas said about the status of the embryo, "prior to ensoulment, conception isn't completed" (Catholic Online, 2008). Thus the consequences of abortion were dependent upon the embryo's time of gestation. The views changed in 1869, when Pope Pious IX said that people who believe in abortion shouldn't be regarded as followers of God (Bellomo, 2006). Because Pope Pious IX did not pay attention to the time of gestation, his ideas came to agree with zygotic personhood (Robinson, 2006).

In 1987 a new view by the Catholic Church, *Donum Vitae*, suggested personhood as a philosophical question that was open to different interpretations (Bellomo, 2006). There were no signs of any type of interpretation from scriptures, and ancients did not understand embryos in petri dishes. In 1974, the *Declarato de Aborto Procurato*, suggested that the Roman Catholic Church identifies a person with a new genome (Bellomo, 2006). When fertilization creates a

new genome, it also creates a new person (Bellomo, 2006). The idea that a genome serves as a person, describes a radical view of genetic reductionism that causes mixed views on the concept of fertilization (Bellomo, 2006). Since zygotic personhood occurs before any type of soul, personality, or conscientiousness, then zygotic personhood can interestingly be viewed as a stance against abortion (Robinson, 2006).

A large majority of practicing Catholics has been opposed to ES cell research because it involves the destruction of human life by dismantling human embryos. Pope John Paul II said, “embryonic research is related to abortion, euthanasia, and other attacks on innocent life” (CNN 2001). The basis of their opposition was released in August 25, 2008 by the Pontifical Academy for Life in the “Declaration on the Production and Scientific and Therapeutic Use of Human Embryonic Stem Cells” (Catholic Online, 2008). This declaration listed three major reasons why the Catholic Church opposes ES cell research. The first reason involves the preparation of ES cells and how this process involves the destruction of the embryo, which the Church thinks is an immoral act (“U.S. Bishops Protest”, 2006). The second reason involves the belief that scientists use unnatural techniques to produce embryos to harvest stem cells, which should be considered immoral (“U.S. Bishops Protest”, 2006). The third reason claims that the Church opposes the use of ES cell lines that already exist because these stem cell lines began with the destruction of innocent human life (“U.S. Bishops Protest”, 2006). Overall, the Church does not care if scientific advances are made through ES cell research, as the end does not justify the means. The Church teaches that we can never do anything evil even if benefits come out of it. This harsh stance against ES cell research places strong incentives to work with adult stem cells or iPS cells, which do not destroy embryos. The Pope has been cited several times as being in favor of research with *adult* stem cells (Catholic Online, 2008).

## **Jewish Stance on Stem Cells**

Unlike most Catholic groups, Jews are much firmer supporters of the potential benefits that ES cells have. Jewish tradition believes that our bodies belong to God, and thus God has the right to inflict conditions to our bodies (Eisenburg, 2006). A requirement that Jews seek is to preserve human life, and it is a duty to create cures for diseases and develop methods that can help out with extending human life. Physicians, scientists, and researchers all help towards preserving human life and developing therapies to help others, which all belong to God (Eisenburg, 2006). Jews clearly state that humans aren't God; so all humans must take precautions to ensure our actions don't harm the world or ourselves (Eisenburg, 2006). Jewish law claims that the embryo doesn't become human until forty days after conception, and also explains that the fetus doesn't become a person until its head emerges from the womb (Eisenburg, 2006). Based on this timing, the Jewish stance allows research on embryos that are only five days old, from which ES cells are obtained.

According to the Talmud, during the first forty days of gestation, a fetus is "as if it were simply water," and forty-first day until birth is "like the thigh of its mother" (University of Judaism, 2001). No one can amputate their own thigh because it would injure the body that belongs to God, however if the thigh is infected then it should be amputated to save someone's life. All embryos, *in vitro* or *in vivo*, until forty days old have less legal status in Jewish law than older fetuses, because they are classified by the Talmud "as if simply water" (University of Judaism, 2001). All Jews believe that health care is a community responsibility and it's required to look after those in poor health until they fully recover. With the potential that embryonic research has for curing diseases and ailments, Jews strongly believe that it is a duty placed upon God to proceed with this research (University of Judaism, 2001).

## **Muslim Stance on Stem Cells**

Islam has similar views to Judaism on ES cell research. Muslims claim that the fetus is considered human life only later in biological development than the time ES cells would be isolated (Siddiqi, 2002). Proof of this statement is found in the Quranic verse “thereafter we produced him as another creature,” referring to when a fully developed fetus is taken out of the mother’s womb (Siddiqi, 2002). Islamic scholars claim that ensoulment of the fetus does not occur until the end of the fourth month of pregnancy or 120 days (Siddiqi, 2002). Islamic tradition describes the ensoulment of the fetus as, “each of you possesses his own formation within his mother’s womb, first as a drop of matter for forty days, then blood clot for forty days, then as a blob for forty days, and then the angel is sent to breathe life into him” (Siddiqi, 2002). Under Shari’ah law there is a difference between potential and actual life, with actual life having more importance and significance than potential life (Kutty, 2007). Thus an embryo at five days is not considered fully human, and its use in ES cell research does not conflict with Islamic law (Kutty, 2007). Current research on ES cells in the early stages of an embryo’s life is perceived as an act of faith towards God as the ultimate creator, and a great humanistic act towards helping others in poor health, a key Islamic principle to help others that are in need.

## **Hindu and Buddhist Stances on Stem Cells**

There are numerous conflicting notions for ES cell research made by Hinduism and Buddhism. These Eastern religions believe in reincarnation and the idea that life starts before conception (Hinduism and Modern Science, 2006). Both religions view human incarnation as the opportunity to attain enlightenment, the best state that a soul can attain. For example as

described in the Upanishads, “the soul is present in any form even in human sperm” (Hinduism and Modern Science, 2006). Hindus view life as sacred in all forms and believe that conception is the beginning of the soul’s rebirth from a previous life (Tyagananda, 2002). Hindu tradition shows that personhood begins between around three to five months of gestation, while incarnation occurs as late as the seventh month (Tyagananda, 2002). A central tenet in Hindu religion stresses to avoid harming living things, and its main tenet preaches to practice compassion towards one another (Tyagananda 2002). Thus, based on this ensoulment stance, these religions would be against ES cell research since the five-day embryo is already ensouled and should not be harmed.

Alternatively the 2,700-year-old epic text of India, The Mahabharata, claims that it is acceptable to sacrifice a son for the family, or the family for the village, which leads to some agreement with ES cell research as an embryo could be sacrificed to save lives (Tyagananda, 2002).

Many Buddhists think that the soul has some effect on where to reincarnate, and the soul may not want to enter an embryo in a Petri dish with no opportunity to ever grow (Mahathera, 1994). The story of the Kaurava brothers offers an early example of human cloning through stem cells extracted from human embryos. The story described how the mother of the Kaurava brothers had obtained a mound of flesh, and two years after pregnancy a sage divided the flesh into a hundred parts, treated with butter and herbs, and kept this mixture in a pot (Tyagananda, 2002). After two years, the Kaurava brothers finally emerged as human beings (Tyagananda, 2002). The two main tenets in Buddhism involve the prohibition against harming or destroying others, and pursuing knowledge and compassion to benefit mankind (Mahathera, 1994). The second tenet agrees with the principles displayed by embryonic research, but the first

tenet would never allow any type of embryonic research. Both Hindus and Buddhists agree that personhood begins at conception and that an individual's self and soul is eternal (Mahathera, 1994). Adult stem cell research is widely accepted amongst Hindus and Buddhists, though there's mixed views on ES cell research displayed by their tenets. Currently a majority of practicing Hindus and Buddhists would agree with ES cell research if it aids the health and well being of society.

### **Chapter-3 Conclusion**

Embryonic stem cells are the only type of stem cell under strong ethical debate. No major world religion or country argues against the use of *adult* stem cells. Supporters of ES cell research point to the many potential benefits to society in aiding people with various diseases, especially utilizing excess IVF embryos that are already slated for destruction. Those opposed to ES cell research argue that the embryo is potential human life, even outside the human body, which has the right to life. Various religions have different views on ES cell research. Many forms of Catholicism are strongly opposed to using embryos for any research claiming life begins at conception, and it is a cardinal sin to destroy any type of life. Judaism and Islam are supporters of ES cell research due to their stances that human life for an embryo does not begin until at least forty days after conception and after the five day period when ES cells would be isolated. Hinduism and Buddhism have mixed views on ES cell research, with opponents explaining that souls are eternal, sperm and egg prior to fertilization have souls, and that life is sacred in any form. Proponents argue Hindus and Buddhists should pursue knowledge and compassion to help those in need. In August 2007, the Pew Research Center for the People and Press asked the question whether ES cell research should continue, and received results that

claim 51% of the public, regardless of religion, are for ES cell research, 35% are against, and 14% were undecided (ABC News, 2007). The ultimate question of whether embryonic stem cell research should continue or not, lies in the hands of politicians, religious leaders, and the general population.

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## CHAPTER-4: STEM CELL LAWS

*Baurzhan Negmetzhanov*

### **Introduction**

Medicine has witnessed an amazing potential transformation in the last few decades from stem cell research. As discussed in Chapter-2, some types of stem cells (especially hematopoietic stem cells) have already been used to save thousands of lives in medical applications. Other types of adult stem cells are already being tested for treating heart attack patients (Adult Stem Cells, 2006). And as of January 2009, the FDA finally approved pharmaceutical company Geron to use embryonic stem (ES) cells to treat spinal cord injuries. But as is typical of any complex technology, laws have been enacted to regulate procedures that can be performed with stem cells. The purpose of this chapter is to discuss some of the past and current US federal, state, and international laws pertaining to stem cell use. This chapter should provide an appreciation of the importance of legislation and the great consequences it has on stem cell research to dictate its progress.

As was stated in earlier chapters, adult stem cell (ASC) research is far less controversial than ES cell research because the former does not destroy embryos. All five major world religions favor working with adult stem cells to try to save lives (Christian Today, 2004). Accordingly few legal hindrances exist for this type of research, other than the usual patient consents, etc. However, for ES cells, several major world religions do not support their use, and laws reflect a tight control over this type of research. Questions arise whether people are willing to let stem cells research progress at the expense of religious and ethical beliefs (Christian Today, 2004). Many people don't see this conflict so they support ES research, but those who

hold ES research is wrong are burdened with a tough choice (Weiss, 2005). Laws and regulations in societies are an expression of these different religious and scientific views. As discussed below, the laws can vary considerably with a change of the variables, including a change in the elected congress, president, and people's views and education. In the US, the past decade witnessed a repression of ES cell research, while the present sees a strong support of this research. The future remains unknown.

## **Stem Cell Legislation of the Past Decade**

### **I) The Federal Level**

Since the development of human *in vitro* fertilization (IVF) techniques in the late 1960's, ethical and legal issues surrounding the use of excess unused human embryos have been debated. In late 1970, the US Ethics Advisory Board decided that research using ES cells is ethically acceptable, so long as the research did not use embryos beyond fourteen days of development, but the research will not be funded by the federal government (Monitoring Stem Cell Research, 2004). In 1993, during President Clinton's presidency, the US Congress enacted the NIH Revitalization Act, which enabled NIH to fund human embryo research using excess IVF embryos. The NIH also created a Human Embryo Research Panel (HERP) to consider stem cell research issues and to propose guidelines for potential research funding. The panel recommended the funding of some areas of embryo research within the limits of ethical issues, even allowing eggs to be donated only for research purposes. President Clinton accepted HERP's recommendations for allowing some types of embryo research, but rejected their suggestion of allowing egg donations solely for research purposes. However, Congress did not

approve of *any* of HERP's recommendations, and banned the use of federal funds for any embryo research (Monitoring Stem Cell Research, 2004).

In the past decade under President Bush and congress, ES cell research was repressed in the US (Dunn, 2005). President Bush, who governed from 2000 to 2008, comes from a conservative Christian background, stating "I'm a strong supporter of adult stem cell research, of course. But I made it very clear to Congress that the use of federal money, taxpayers' money, to promote science which destroys life in order to save life is -- I'm against that" (Baker, 2005). In 2001, the senate was equally divided on the ES cell topic, but the House of Representatives held a republican majority (mostly conservatives). This information is important because there is a great divide between the supporters of ES research (mostly democrats) and those who do not support ES cell research (mostly republicans). Statistics show that 76% of democrats support ES stem cell research, while only 44% of republicans support it (Langer, 2005). These guidelines mostly apply to the US demographic since religions such Islam and Judaism do not oppose ES cell research (discussed in Chapter-3).

The election of George W. Bush as President with a republican majority in the House of Representatives gave conservatives the upper hand. This conservative view was manifested into action in August of 2001. President Bush announced that as of that date, no federal money could be used to derive new ES cell lines, and researchers receiving such funds are restricted to using only ES cell lines derived before August 2001 (White House Press Release, 2001). This effectively reduced the number of ES cell lines to only about 60. This put a huge obstacle in front of ES cell research because the expensive cost of this type of research requires the help of the tax payers. Also, the number of ES cell lines is not enough to progress in the field (Agnew,

2003). And worse, the number of ES cell lines was originally thought to be around 60, but this was subsequently reduced to only 9 viable, non-mutated, unique lines (Abbott et al, 2006).

The rationale behind Bush's decision is a moral and ethical one. He considered ES cell research as committing "murder" since it destroys the embryo that can be considered a human life (Monitoring Stem Cell Research, 2004). Research was allowed on the previously derived cell lines because those embryos were already destroyed. In 2005, Bush vetoed a bill that would have lifted funding restrictions on human ES cell research. Although the House and Senate had passed the bill, it was not by a margin large enough to override the President's veto. The House had voted 235 to 193 to pass the bill. The Democrats voted more heavily than the Republicans in favor of the bill (Babington, 2006).

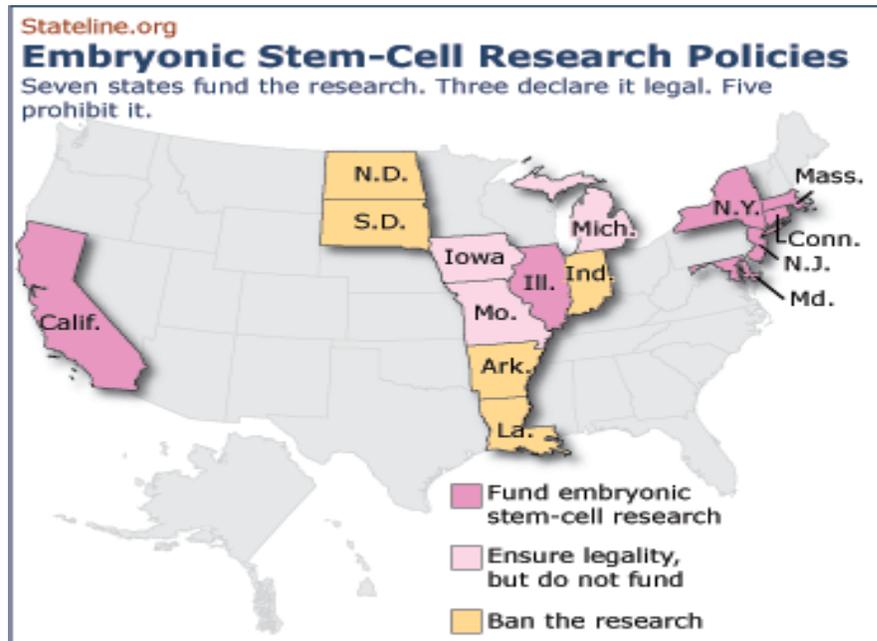
## **II) The State Level**

Seeing the prohibition of federal funding of this important ES cell technology, some states took it upon themselves to fund this research through state bonds (Holden, 2006). In 2004, New Jersey became the first state to support stem cell research funding \$10 million to universities and commercial labs (Wadman, 2008). The move initiated by New Jersey is significant because it emphasizes the discontent that states had towards President Bush's regulations on stem cell research. California was the first state to officially oppose President Bush's restrictive policies on stem cell research. In 2002, the legislators of this state drafted a bill that would fund further research of HSCs using state money. California passed proposition 71, which enabled creation of California Institute for Regenerative Medicine and which provided 3 billion dollars over 10 years to advance stem cell research (Hayden, 2008).

Massachusetts, which is known for being advanced in science and medicine, also responded to President Bush's ES cell research restriction policy. Because many leading medical institutions are located in Massachusetts, it was essential for its legislators to encourage stem cell research. In 2005, Massachusetts Senate President Robert Travaglini created a bill that would formally support the research. The bill encouraged research involving adult stem cells, and also allowed embryos to be created by somatic cell nuclear transfer (therapeutic cloning). The law also explicitly banned human reproductive cloning, and established penalties for those who abuse it (Finer, 2005). Then Governor Mitt Romney vetoed the bill because he believed that the bill did not create safeguards against human cloning or the creation of embryos solely for research purposes (Holden, 2005). However on May 30, 2005, the Massachusetts state legislature approved the bill in the senate 35 to 2, thus overriding Romney's veto (Finer, 2005). In 2007, then new Massachusetts Governor Deval Patrick promised 1 billion dollars to support stem cell research (Estes, 2007). Governor Patrick's plan was very important for the scientific community, especially after Governor Romney's previous opposition towards ES cell research. State legislators were supportive of Patrick's plan, and it was approved in June of 2008 (Vestal, 2009).

Other states such as New York, Connecticut, Illinois, and Maryland also took similar actions (Stem Cell Legislation in the U.S. by State, 2005). As of 2009, seven states have funded, five states have restricted, and three states have legalized ES cell research (**Figure-2**). Although the list of the states supporting ES cell research is growing, these states remain in the minority. Most states have no legislations addressing ES cell research, but fortunately states such as Massachusetts and California support this research, and have many key research facilities and top researchers. Also, the state sponsorship of ES cell research gave birth to a healthy

competition among states which has pushed other states to join the competition. Although state funding is not a substitute for federal money, state funding will make a difference in the progress of the stem cell research.



Source: National Conference of State Legislatures

**Figure 2: Individual State Embryonic Stem Cell Research Policies.** The map shows various U.S. states that approve and fund ES stem cell research. As of 2009, seven states fund this type of research, five have restricted policies, and three states have legalized but not yet funded ES cell research (Vestal, 2009).

### III) The International Level

On the international arena, ES cell research has also attracted both supporters and opponents. The European Union which is comprised of 27 different countries has also been split on whether human ES cell research should be funded. Countries such as Germany and Italy oppose the advance of ES cell research (Kim, 2002). Those countries have exerted an effort to convince the EU to put restrictions on this technology (Deutsche Welle, 2006). However in July of 2006, the legislative body of the EU passed legislation allowing the funding of hES cell

research. 65 billion U.S. dollars will be provided for hES cell research for those countries that made the research legal (Silva, 2006).

Countries such as Australia, Sweden, UK, and South Korea support ES cell research. In the UK, the government created an organization called the Human Fertilization and Embryology Authority to investigate and direct ES cell research on both scientific and ethical grounds (Davies, 2003). South Korea is very active in this field, and is competing with the US in this area. South Koreans have derived almost as many ES lines as the US (Kaplan, 2005). The Australian government enthusiastically supports ES cell research, creating the Australian Stem Cell Center (Stem Cell Research in Australia, 2003). Sweden is at the front line of this research. The ease of its regulations helped create more than 30 research groups, and nine Swedish institutions actively work on ES cell research (Sweden's Stem Cell Success, 2002).

As other countries advanced, fear increased that the US would lag behind in this important technology. The United States has the greatest potential in this field because its institutions are fertile ground for this work, but regulations and laws worked against it in the last decade. In 2009, with a change of president and congress, stem cell research funding did an about face in the US.

## **Current Stem Cell Legislations**

In January 2009, the inauguration of new President Obama, a democrat, opened a new page in stem cell research. Within 3 months, President Obama passed an executive order allowing ES cell research to receive federal funding. Obama said on 9 March, the same day he signed the order, “We will vigorously support scientists who pursue this research, and we will aim for America to lead the world in the discoveries it one day may yield” (Holden, 2009). This

event was celebrated by supporters of ES cell research. This order allows the NIH to provide researchers with grants to work on new ES cell lines.

The new legislation comes with some restrictions. For example, the embryos used to derive new ES cell lines must come from IVF clinics (i.e. are originally created for reproductive purposes) and must be accompanied by donor consent. And no money can be used to pay volunteers to provide eggs solely for research purposes. The legislation also empowers NIH with the authority to oversee the derivation of new ES cell lines to ensure compliance with the new guidelines. But even with these restrictions, the new legislation provides *federal* funding for ES cell research, and according to some, the US is finally back and ready to fully delve into this important field because the world needs it. "This type of science is international, and the whole world has suffered from the previous short-sighted and rather bizarre US policy," remarks Robin Lovell-Badge of the National Institute for Medical Research in London (Holden, 2009).

## **The Future**

The future is unpredictable for ES cell research in the US. Funding and laws will be the determining factor for its success or failure. In the future, if a president who shares a common ground with Bush is elected, we will see a repression of ES cell research. Congress is important because at least a 2/3 support for stem cell research is necessary to be able to override any president's veto if necessary. Also, since congress enacts the legislations, President Obama's support of ES cell research could be disturbed by congress if the current democratic majority were to change in new elections to a republican majority (Holden, 2009).

Some scientists hope to increase public support for ES cell research by teaching the public more about this technology. Many people are not informed about ES cell research, and

the medical potential they have for saving lives. By carefully explaining the process, perhaps more people might change their minds if they discover how many lives could be saved, or once they realize that what is being destroyed is a five day hollow ball of cells the size of a dot, not a fetus with a growing nervous system (Agnew, 2003). A healthy debate with church members with influence might steer them to change their minds about this issue by helping them see the full picture of the research.

## **Chapter-4 Conclusion**

In this chapter, we have discussed stem cell laws and their significance to stem cell research. For this type of expensive technology, legislation can bar ES cell research from receiving tax payers' money which then slows progress. On the other hand, we also emphasized that legislation can strongly stimulate the field, as occurred in some countries like Sweden and England, and in the Obama led US. We highlighted the dynamics of the US legislative system, showing how some states such as New Jersey, California, Massachusetts, etc. were able to override earlier prohibitive federal legislations by offering state bonds to fund this research. We discussed the root of this legal opposition to ES cell research, being the moral stand of some Christians, especially Catholics, on this issue, and how ethics affects laws. Finally, we point out that although ES cell research is faced with fierce opposition by some, alternative stem cell approaches also exist (such as working with adult stem cells or with induced pluripotent cells), but those latter cells may not have the full medical potential of ES cells and may be more difficult to grow, so the push to fund ES cell research continues.

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## **PROJECT CONCLUSIONS**

Both of the authors of this IQP, agree with current US policies that allow new ES cell lines to be derived from embryos, because this type of technology will help cure many of the world's diseases in the future. Unlike current US policy, we agree that the preferred egg source should be women paid to donate their eggs for solely for research purposes, as this type of consent helps ensure that the donor indeed wants to donate the eggs for science. However both authors agree that using alternative stem cell sources, such as iPS and adult stem cells, should be used whenever possible, and this stance agrees with all major religions and with a majority of the public. Some stem cell applications have already proven to save lives in human patients, especially using HSCs to treat leukemia, and using bone marrow stem cells to treat heart attack patients. The countries that both IQP authors agree most strongly with their policies are Israel, Switzerland, and Japan, as their policies go beyond those currently allowed in the US, even under President Obama. Within the United States, we applaud the states of New Jersey, Massachusetts, and California for their individual ES cell policies. The freedom that these countries and states give towards ES cell research should go a long way to opening up this amazing new regenerative medicine technology in the future.