August 2012

# Stem Cell IQP

Abdulla Zakaria Al Abri
*Worcester Polytechnic Institute*

Ali Saad Algarni
*Worcester Polytechnic Institute*

IQP-43-DSA-5832
IQP-43-DSA-3825

# 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:


Abdulla Al-Abri

Ali Algarni


August 24, 2012

APPROVED:

Prof. David S. Adams, PhD
WPI Project Advisor

# ABSTRACT

This project focuses on expanding the reader's knowledge on the subject of stem cells, and investigating how this technology affects society. We will initially describe the different types of stem cells and how they are being used to benefit society. The later chapters will investigate stem cell ethics and the laws regulating research funding in this area, domestically and internationally. At the end, the authors provide their own conclusions on this complex but interesting technology.

# TABLE OF CONTENTS

# PROJECT OBJECTIVES

The purpose of this IQP is to investigate the technology of stem cells, and view the impact of this technology on society. In Chapter-1 we discuss the different types of stem cells, where we obtain them from, their potential for differentiation, and the classifications under which they fall. Chapter-2 describes the different types of medical applications stem cells have been used for, focusing on both animal experiments and human clinical trials. Chapter-2 also gives insight into which applications can be accomplished in the near future. In Chapter-3 we take a different approach by looking into the ethics of stem cells from the point of view of the five major world's religions. Chapter-4 looks at various domestic and international laws regulating stem cell funding. Finally, the authors make their own conclusions based on their point of view of the subject, and discuss which stem cell laws the authors agree with best.

# Chapter-1: Stem Cell Types

*Ali Algarni*

Stem cells are long-lived cells that have the ability to differentiate into other kinds of tissues. These cells have caused much excitement in the medical community due to their potential to replace wounded or diseased tissues in the body, and are the basis of the field of regenerative medicine. But their use is also accompanied by much controversy, as the use of some types of stem cells destroys a living embryo. However, not all stem cells are alike, and in fact most do not destroy an embryo. The purpose of this chapter is to describe the main types of stem cells, and describe their potencies and origins. The topic of stem cells is well suited for a WPI IQP project designed to investigate the impact of technology on society.

## Stem Cell Potencies

Stem cells differ on the basis of their ability to differentiate into other tissues. The more tissues a stem cell can form, the higher its potency. *Totipotent* cells have the potential to form an entire organism plus extra-embryonic tissue (such as the placenta) (Brown University, 2002). Newly fertilized eggs through about the 8-cell stage are classified as totipotent. As these cells continue to divide, they rapidly lose their totipotency, so these cells are not used for therapy.

*Pluripotent* stem cells have the ability to form any cell in the organism, but not extra-embryonic tissue. These cells are taken from an embryo at about the 100-cell stage (blastocyst). The blastocyst consists of an outer layer of cells termed the trophoblast, and an inner cell mass (ICM) containing embryonic stem (ES) cells (Explore Stem Cells, 2012a; NIH Basics, 2012).

*Multipotent* stem cells have the ability to differentiate into several types of related cells, but these cells cannot create all cells in the body (Explore Stem Cells, 2012b). One example in

this category is a hematopoietic stem cell (HSCs) which can form all the various cellular components of blood, such as red blood cells, T-cells, B-cells, and platelets. However, HSCs do not normally form cells unrelated to blood (NIH Chapter-5, 2012). Another example is a mesenchymal stem cell (MSC) that forms various kinds of mesodermal tissues, such as bone, fat, and muscle (Medwell Journals, 2011). Neural stem cells (NSCs) can form glia and neural cells, but they are not capable of creating blood cells (NIH Chapter-8, 2012).

*Unipotent* stem cells are derived from multipotent stem cells, and exist in adult tissues to help replenish specific tissues with ageing (Biology…2012). These cells have a limited ability to differentiate, and usually replace only the tissue in which they are found. One example in this category is a skin stem cell which is continuously dividing to replace dead or damaged skin cells (Alonso and Fuchs, 2003).

## Stem Cell Types

Stem cells can also be classified on the basis of their origin. Embryonic stem cells are obtained from embryos, parthenote stem cells are obtained from unfertilized eggs, and the remainder are obtained from adult tissues or umbilical cord blood.

### *Embryonic Stem Cells*

Embryonic stem (ES) cells are derived from an embryo at about the 100-cell stage. This type of stem cell is the most controversial because the embryo dies after the ES cells have been extracted. In the U.S., these embryos are created by *in vitro* fertilization (IVF) for reproductive purposes. Extra embryos are created for couples for these reproductive purposes. However, this process is not efficient and there is no guarantee of success. It is not currently legal to fertilize

the embryos solely for research purposes. But once the family has enough children, with consent their extra embryos can be used for research purposes. Human ES cells were first isolated and grown in 1998 (Thomson et al., 1998). In this process, at an IVF clinic, donated sperm and egg are mixed together in a test tube, and left to culture for about four to five days until it reaches the blastocyst stage (about 100 cells). The blastocyst consists of an outer layer of cells, termed the trophoblast, and an inner cell mass composed of ES cells (Figure-1). The inner cell mass is extracted from the embryo, and plated onto a feeder layer of cells that provide the right environment for the ES cells to divide.

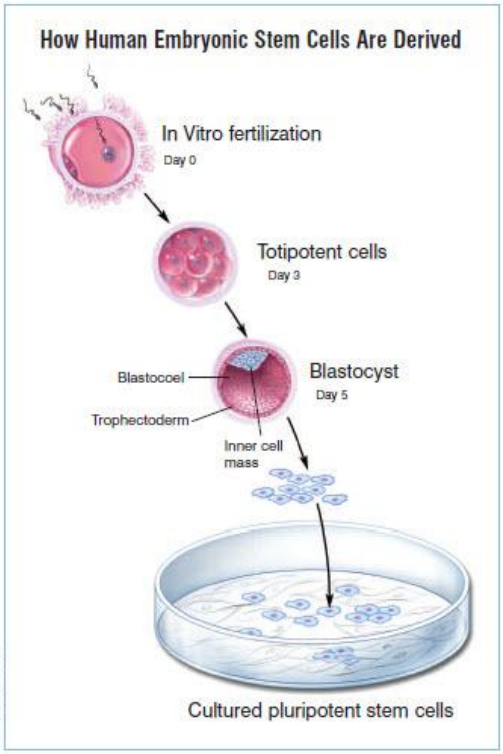


**Figure-1: The Isolation of Human ES Cells.** This figure shows how embryonic stem cells are isolated and grown. IVF embryos (diagram upper left) are grown to the blastocyst stage (middle diagram) from which the inner cell mass (blue) is isolated and plated onto a feeder layer of cells (lower diagram) for growth. (Thomson and Wu, 2006)

ES cells are medically the most important type of stem cell due to their ability to form any cell in the adult organism (Explore Stem Cells, 2012a). In animal experiments, the growth and differentiation of ES cells has allowed us to produce most tissues in the body. Because the

embryo is usually killed while extracting ES cells, much research has focused on trying to avoid the embryo if possible, and on adult stem cell alternatives to ES cells for treating specific diseases. One recent group claims to be able to create ES cell lines from single blastula cells without destroying the embryo (Klimanskayza et al., 2006). And in 2005, the same group at Advanced Cell Technology created ES cell lines without using any feeder layer, which lowers the risk of possible viral contaminants (Klimanskayza et al., 2005).

### *Hematopoietic Stem Cells*

Hematopoietic stem cells (HSCs) are responsible for creating all the cellular components of blood, including red blood cells, white blood cells (T-cells, B-cells, neutrophils, macrophages), and platelets (NIH Chapter-5, 2012). Scientists first speculated on the existence of HSCs in 1956 when it was shown that bone marrow has the ability to reconstitute the blood in mice following radiation treatment (Ford et al., 1956). Since then, HSCs have been used for over 50 years in bone marrow transplants for treating various cancers of the blood (like leukemia or lymphomas) following chemotherapy or radiation treatments (Thomas et al., 1957). HSCs are usually obtained from bone marrow, where they reside to help replace blood cells in the body. The blood cells usually die after about 90 days. However, their extraction from the donor's bone marrow can be painful, so scientists have researched procedures for obtaining HSCs elsewhere.

One alternative procedure for obtaining HSCs isolates them from the peripheral blood of a donor after injection with hormones to induce the migration of HSCs from the marrow into the periphery. Although the HSCs represent only a small percentage of cells in the peripheral blood, they can be concentrated by selecting them on the basis of cell surface markers, such as CD-34+ (Spangrude et al., 1988). Another alternative source of HSCs is umbilical cord blood, which is

very rich in these cells. Umbilical cord blood is donated at time of birth, and frozen in case the child develops problems later in life. HSCs obtained from cord blood are more primitive than those isolated from bone marrow, so they are less likely to be rejected by the patient (Viacord, 2011).

Researchers have also discovered that HSCs may be able to form cells *other* than blood, such as blood vessels, bones, and muscle tissues. This property is termed *plasticity*. These observations have only been made in animals, but if plasticity is found in human HSCs it might mean HSCs could be used to create a wider variety of tissues than originally thought. This could provide for the replacement of organs such as the liver or heart without using ES cells. However, not all scientists believe in this plasticity, so more research is needed to show that it actually exists.

### *Neural Stem Cells*

Previously, many scientists thought that once brain cells got damaged they could never be replaced. Most of our current treatments for brain or spinal cord injuries attempt to stabilize the damage to make sure it doesn't get worse. But recently scientists have discovered that some areas of the brain contain adult brain cells with the ability to give rise to new neurons and their support cells. Brain "blast" cells capable of division were first isolated from rat brains in 1989 (Temple, 1989), and in 1993 neural stem cells were first isolated from the ependymal zone of mouse brains (Morshead et al., 1993). It was observed that some areas of the brain can produce new neurons which rise from neural stem cells. NSCs are very similar to the cells of the developing fetus that first give rise to the brain and the spinal cord. The research eventually showed that NSCs can give rise to all cell types in the adult brain, which raises the hope of

someday being able to repair damage from neuro-degenerative diseases like Parkinson's disease or Alzheimer's disease, as well as from brain and spinal cord injuries (NIH Chapter-8, 2012).

### *Mesenchymal Stem Cells*

MSCs are multi-potent stem cells isolated from bone marrow periosteum and muscle connective tissue. They have the ability to differentiate into many kinds of mesodermal lineages, including bone, fat, muscle, and cartilage (Pittenger et al., 1999; Medwell Journals, 2011). MSCs are usually isolated from bone marrow due to the relative ease of extraction. MSCs were the second type of stem cell discovered (after HSCs), and resulted from research in Russia by Friedenstein on muscle-generating cells (Friedenstein, 1976). Due to their multi-potency, relative ease of isolation, and lack of embryo destruction, MSCs have become one of the most popular cells to research. One of their many potential applications is bone formation where they are used to help fill in bone fractures or to restore bone to its original state.

### *Cardiac Stem Cells*

Just as scientists originally thought that brain cells were incapable of regeneration, they also thought that heart cells could not regenerate. But recent studies have found that c-kit positive cells located in rat heart muscle can help replace cardiomyocytes, so these cardiac stem cells (CSCs) might be suitable for heart therapy (Beltrami et al., 2003). At the Heart Institute of Japan, scientists isolated c-kit (+) cells, placing them in culture (Miyamoto et al., 2010). The cells showed cardiosphere generation and the potential to differentiate into three main lineages: cardiomyocytes, smooth muscle, and endothelial cells *in vitro* (Miyamoto et al., 2010). Over

long term culture, the cells were also able to differentiate into cells other than cardiac lineages, such as adipocytes and skeletal myocytes.

However, some scientists believe the c-kit+ cells are not true CSCs and are merely HSCs that have migrated to the heart from the blood. In 2005, another group of scientists isolated Isl1+ cells from mouse, rat, and human hearts, and they believe these cells represent true CSCs (Laugwitz et al., 2005).

### *Adult Eye Stem Cells*

Our own eyes have recently been shown to contain nerve stem cells (Salero et al., 2012). New research has revealed that a single layer of cells at the back of the eye, termed the retinal pigment epithelium (RPE), contains cells that help replace photoreceptors. Hopefully, the use of these cells can help patients with some types of vision loss. However, these new cells have not been fully tested for their differentiation capacity.

### *Adult Lung Stem Cells*

A new discovery has revealed that stem cells reside in the lungs, and are able to differentiate to a variety of cell types (The Huffington Post, 2012). The cells were taken from a human lung and injected into a mouse to allow engraftment and differentiation. The cells successfully formed lung airways, air sacs, and blood vessels. Although we need more research into this type of stem cells, many scientists believe that the finding may help treat certain types of lung diseases.

### *Skin Epithelial Stem Cells*

Mammalian skin was first shown to have cells capable of replenishing skin in 1981 (Bickenback, 1981). This type of cell supplies the skin with its replacement cells and can be used to generate new skin for burn patients. But skin stem cells are still not easily distinguishable from cells surrounding them. Recently scientists have made attempts to characterize these cells more fully in mice and humans (Bach et al., 2000). Some of the cells exhibited prodigious proliferative potential, and were adapted for treating burn patients in one of the first applications for stem cells (apart from bone marrow transplants).

### *Renal Stem Cells*

Kidney stem cells may also exist, especially in the epithelial ureteric bud cells. If these cells help replace kidney epithelium, perhaps they could be used to help generate tubules in kidney patients. However, there is not much research about this type of cell.

### *Adult Intestinal Stem Cells*

Intestinal stem cells are found at the base of intestinal crypts (Bach et al., 2000), and are always undergoing the process of altruistic apoptosis because they are exposed to toxic stimuli. Intestinal epithelial cells turn-over at a very high rate due to the grinding forces associated with food movement and digestion. Arguments exist between scientists about whether the mature intestinal cells derived from the crypt derive from either single or multiple stems. Research has also focused on determining the potential role of these cells in colorectal tumors, and whether tumors originate from single mutated intestinal stem cells (NIH Chapter-3, 2012).

### *Parthenogenic Stem Cells*

Parthenogensis is a mode of asexual reproduction in which embryonic development can begin without any sort of sperm or male participation. This is a common way of reproduction in some insects and lower organisms, such as ants, lizards, snakes, and crayfish. Mammalian parthenogenesis does not exist in nature, but can be artificially induced. Monkey parthenote embryos were first created in 2001 (Mitalipov et al., 2001). The parthenogenesis was initiated using chemicals such as strontium chloride or electrical current, and the unfertilized egg began dividing without extruding one set of chromosomes as it normally does during egg development. Thus, the egg remained diploid. The parthenote embryo divided through the blastocyst stage from which ES cells could be isolated, but the embryo did not survive much longer. Further experiments on monkey parthenote embryos were performed in 2002 by scientists at Advanced Cell Technology (ACT) (Cibelli et al., 2002). They tricked 77 monkey eggs by chemicals to believe that they had been fertilized. Twenty-eight embryos started dividing, and four reached the blastocyst stage during which ES cells were extracted and cultured into an ES cell line.

In 2001, Advanced Cell Technology also made a claim of making the world's first human parthenote embryos (Cibelli et al., 2001). But all their parthenote embryos never reached the blastocyst stage, so as a result no ES cell lines were derived. In 2007, Brevini and Gandolfi also claimed to have made human parthenote ES cell lines (Brevini and Gandolfi, 2007), but this finding has not yet been verified. If human parthenote ES cell lines can be derived, some scientists claim these cells would have fewer ethical concerns than fertilized embryos. This topic will be discussed in more detail in Chapter-3.

### *Induced Pluripotent Stem Cells*

For the past few years, the stem cell world has been excited by a new type of stem cell called the induced pluripotent stem (iPS) cell (Baker, 2007). This new type of stem cell may be virtually as potent as an ES cell, but would not destroy an embryo to derive them. And equally importantly, they would be genetically identical to the patient used to derive them, so would be less likely to be rejected. If iPS cells were shown to be as potent as ES cells, they could be used to create any type of cell in the body. These cells were first derived from mouse skin fibroblast cells in 2006 (Takahashi and Yamanaka, 2006), and one year later were derived from human skin fibroblast cells (Takahashi et al., 2007). In these initial experiments in Japan, skin fibroblast cells were reprogrammed from a differentiated state to an undifferentiated state by introducing genes encoding four transcription factors: OCT3/4, SOX2, KLF4, and c-Myc. The cells could be expanded into more iPS cells, or they could be differentiated.

The level of iPS cell potency is controversial. Some scientists claim iPS cells are as potent as ES cells derived from fertilized embryos. Their doubling time is about the same, and the types of tissues formed are about the same as well. The activity of the enzyme telomerase, which helps maintain the ends of chromosomes during long periods of cell division, was also about the same between the two cell types. And their overall gene expression patterns appeared to be about the same. However, other scientists have shown that iPS cells have mutations in their DNA (Gore et al., 2011), so they may not be as potent as ES cells (Hayden, 2011).

## Chapter-1 References

Alonso L, Fuchs E (2003) Stem cells of the skin epithelium. *Proceedings of the National Academy of Sciences* USA, 100: 11830-11835.
http://www.pnas.org/content/100/suppl.1/11830.abstract

Bach SP, Renehan AG, Potten CS (2000) Stem cells: the intestinal stem cell as a paradigm. *Carcinogenesis*, 21: 469. http://carcin.oxfordjournals.org/content/21/3/469.full

Baker, Monya (2007) Adult Cells Reprogrammed to Pluripotency without Tumors. *Nature Reports Stem Cells.* Nature Publishing Group: Science Journals, Jobs, and Information. 06 Dec. 2007. http://www.nature.com/stemcells/2007/0712/071206/full/stemcells.2007.124.html

BBC News (2002) Issue, January 31. Unfertilized eggs give stem cells. http://news.bbc.co.uk/2/hi/science/nature/1794661.stm

Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, et al (2003) Adult Cardiac Stem Cells Are Multipotent and Support Myocardial Regeneration. *Cell*, 114: 763-776.

Bickenback JR (1981) Identification and behavior of label-retaining cells in oral mucosa and skin. *Journal of Dental Research*, 60: 1611-1620.

Biology.About (2012) Unipotent Stem Cells. http://biology.about.com/od/biotechnologycloning/ss/stem-cells_2.htm

Brevini X, Gandolfi F (2007) Parthenotes as a Source of Embryonic Stem Cells. Cell Proliferation. http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1365-2184.2008.00485.x

Brown University (2002) Totipotent Stem Cells. http://biomed.brown.edu/Courses/BI108/BI108_2002_Groups/pancstems/stemcell/stemcellsclassversatility.htm

Cibelli JB, Kiessling AA, Cunniff K, Richards C, Lanza RP, West MD (2001) Somatic Cell Nuclear Transfer in Humans: Pronuclear and Early Embryonic Development. *Journal of Regenerative Medicine*, 2: 25-31.

Explore Stem Cells (2012a) Pluripotent Stem Cells. http://www.explorestemcells.co.uk/pluripotentstemcells.html

Explore Stem Cells (2012b) Multipotent Stem Cells. http://www.explorestemcells.co.uk/multipotentstemcells.html

Ford CE, Hamerton JL, Barnes DH, Loutit JF (1956) Cytological identification of radiation-chimaeras. *Nature*, 177: 452-454.

Friedenstein AJ (1976) Precursor Cells of Mechanocytes. *International Review of Cytology*, 47: 327–359.

Gore A, Li Z, Fung H, Young J, Agarwal S, et al. (2011) Somatic Coding Mutations in Human Induced Pluripotent Stem Cells. *Nature*, 471: 63-67.

Hayden, Erika Check (2011) The Growing Pains of Pluripotency. *Nature*, 473: 272-274.

Klimanskaya I, Chung Y, Meisner L, Johnson J, West MD, Lanza R (2005) Human Embryonic Stem Cells Derived Without Feeder Cells. *Lancet*, 365: 1636-1641.

Klimanskayza I, Chung Y, Becker S, Lu S, Lanza R (2006) Human Embryonic Stem Cell Lines Derived from Single Blastomeres. *Nature*, 444: 481-485.

Laugwitz KL, Moretti A, Lam J, Gruber P, Chen Y, et al. (2005) Postnatal Isl1+ Cardioblasts Enter Fully Differentiated Cardiomyocyte Lineages. *Nature*, 433: 647-653.

Medwell Journals (2011) Mesenchymal Stem Cells.
http://www.medwelljournals.com/fulltext/?doi=javaa.2011.2317.2330

Mitalipov SM, Nusser KD, and Wolf DP (2001) Parthenogenetic Activation of Rhesus Monkey Oocytes and Reconstructed Embryos. *BiolReprod*, 65: 253-259.
http://www.biolreprod.org/content/65/1/253.full.pdf+html

Miyamoto S, Kawaguchi N, Ellison GM, Matsuoka R, Shin'oka T, Kurosawa H (2010) Characterization of long-term cultured c-kit+ cardiac stem cells derived from adult rat hearts. *Stem Cells and Development*, 19: 105-116.
http://www.ncbi.nlm.nih.gov/pubmed/19580375

Morshead CM, Reynolds BA, Craig CG, McBurney MW, Staines WA, Morassutti D, Weiss S, and van der Kooy D (1993) Neural stem cells in the adult mammalian forebrain: A relatively quiescent subpopulation of subependymal cells. *Neuron*, 13: 1071-1082.

NIH Basics (2012) Embryonic Stem Cells.
http://stemcells.nih.gov/info/basics/basics3.asp

NIH Chapter-5 (2012) Hematopoietic Stem Cells.
http://stemcells.nih.gov/info/scireport/chapter5.asp

NIH Chapter-8 (2012) Neural Stem Cells.
http://stemcells.nih.gov/info/scireport/chapter8.asp

Pittenger MF, Mackay AM, Beck SC, et al. (1999) Multilineage potential of adult human mesenchymal stem cells. *Science*, 284: 143-147.

Salero E, Blenkinsop TA, Corneo B, Harris A, Rabin D, Stern JH, Temple S (2012) Adult human retinal pigment epithelium can be activated into a multi-potent stem cell that produces mesenchymal derivatives. *Cell Stem Cell*, 10: 88. DOI:
http://www.sciencedaily.com/releases/2012/01/120105131637.htm

Spangrude GJ, Heimfeld S, Weissman IL (1988) Purification and characterization of mouse hematopoietic stem cells. *Science*, 241: 58-62.

Takahashi K, Yamanaka S (2006) Induction of Pluripotent Stem Cells From Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, 126: 663-676.

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007) Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell*, 131: 1-12.

The Huffington Post (2012) Human Lung Stem Cell Discovered. July 1 issue. http://www.huffingtonpost.com/2011/05/12/human-lung-stem-cell-discovered_n_861137.html

Thomas ED, Lochte HL, Lu WC, et al. (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New England Journal of Medicine*, 257: 496-496.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. (1998) Embryonic stem cell lines derived from human blastocysts. *Science*, 282: 1145-1147.

Thomson JA, Yu J (2006) Embryonic Stem Cells. Department of Health and Human Services. http://stemcells.nih.gov/staticresources/info/scireport/PDFs/C.%20Chapter%201.pdf

Viacord (2011) www.viacord.com

# Chapter-2: Stem Cell Applications

*Abdulla Al-Abri*

In spite of great advances in medical research over the past century, human illnesses continue to deprive people of health, independence, and well-being (Chapman, 1999). Scientists are continually seeking new remedies for human diseases. Recently, advances in science, medicine, and technology have created a new field of medicine termed *regenerative medicine* that is based on the ability of stem cells to regenerate tissues. As discussed in the previous chapter, stem cells are unspecialized cells capable of renewing themselves through cell division. They may replicate many times creating new stem cells, or they can become induced to differentiate into tissue-specific or organ-specific cells with specialized functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues on a small scale, so the idea of regenerative medicine is to use these properties to repair damaged tissues on a larger scale to treat organs damaged by diseases.

As discussed in Chapter-1, stem cells are of two main types: embryonic stem (ES) cells and adult or somatic stem cells. ES cells can be used to create cell lines for producing large numbers of cells for therapy, and are pluripotent, so they can create any type of tissue in the adult organism (Hughes, 2005). Because ES cells are derived from 5-day old blastocyst embryos (Yu and Thomson, 2006), and their derivation destroys the embryo, ES cells are ethically controversial. Adult stem cells are isolated from adult tissues, and have fewer ethical issues. Medically, ES cells and adult stem cells are not equal. ES cells can relatively easily be grown to large cell numbers *in vitro* and are pluripotent, while adult stem cells are rare in adult tissues, are hard to isolate and purify, are hard to grow, and usually can create relatively few types of tissue.

The ability of stem cells to treat diseases, or their *potential* to do so, represents their benefits to society, which strongly factor into their ethics. The purpose of this chapter is to describe how stem cells have been used, or potentially will be used, to treat six specific example diseases. Special attention will be paid to whether the treatments are well proven or are only in experimental stages, as this relates strongly to their ethics.

## Hematopoietic Stem Cell Applications

The hematopoietic system refers to the blood forming system of the body (Weissman et al., 2001). The cells that produce all the cellular components of blood are termed hematopoietic stem cells (HSCs). These cells are multi-potent, with the ability to form several types of related cells, such as red blood cells, white blood cells (T-cells, B-cells, neutrophils, macrophages), and platelets. But HSCs are not pluripotent, and usually do not form cells unrelated to blood.

Bone marrow is the traditional source of HSCs, and these cells have been researched for over 50 years, representing the best characterized of all the stem cell types. Some of the best success stories for stem cells come from the treatment of blood cancers (leukemia and lymphoma) with HSCs, with cure rates as high as 98% for some types of cancer (Abbott, 2003; Gluckman, 2009; Gratwohl et al., 2010). During blood cancer treatments, the patient's own bone marrow cells are destroyed by chemotherapy or radiation, and then they are replaced by a bone marrow transplant, either from their own bone marrow or a histo-compatible donor. The first successful bone marrow transplants for leukemia were performed in 1957 using identical twin donors (Thomas et al., 1957). Since then, other more convenient sources of HSCs have been used instead of bone marrow, including the now more popular use of a donor's peripheral blood following the injection of hormones that stimulate the movement of HSCs from the marrow to

the blood, and the use of umbilical cord blood (Viacord, 2011). By 1995, more than 40,000 transplants were performed annually worldwide (Panchision, 2006).

Embryonic stem cells also provide a potential future source of HSCs. Both mouse and human ES cells have yielded HSCs *in vitro*, and they do so relatively readily (Weissman et al., 2001). However, recognizing actual HSCs in those cultures has proven problematic, which may reflect the difficulty in identifying HSC markers. CD34 was the first cell surface marker identified for HSCs in Irving Weissman's lab (Spangrude et al., 1988), but since then other newer markers have also been identified, and ES cells have been shown to also create these cells. However, using ES cells for therapy remains only a theoretical possibility for now because of host-recipient compatibility problems, and due to ES cell ethical issues.

### Stem Cell Treatment of Diabetes

In people who suffer from Type-I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. Insulin is a hormone that increases the uptake of blood glucose into tissues, so in its absence, serum glucose increases. Although pancreatic tissue transplants have been performed in diabetic patients, one of the major challenges is an insufficient supply of histo-compatible tissue (Goldthwaite, 2006).

New studies indicate that it may be possible to treat diabetes using stem cells, either adult pancreatic stem cells, or ES cells differentiated into insulin-secreting cells. Animal studies show that mouse ES cells can be differentiated *in vitro* to insulin-producing cells, and these cells restore normal glycemia in a mouse diabetes model (Soria et al., 2000). Mouse diabetic models have also been successfully treated with induced pluripotent stem (iPS) cells derived from mouse skin cells (Alipio et al., 2010). This iPS cell approach has scientists excited, because the

therapeutic cells can be prepared from a skin cell of the same diabetic patient they are to be transplanted back into, and the process does not destroy an embryo, unlike ES cells. Mouse diabetic models have also been successfully treated with human ES cells that differentiated *in vivo* into insulin-producing cells (Kroon et al., 2008).

Treatment of human diabetes *patients* with stem cells has not yet been performed. However, several studies have shown that human ES cells are capable of differentiating into insulin-producing cells (Assady et al., 2001; Lumelsky et al., 2001; Seguev et al., 2004; D'Amour, 2006). Current efforts to treat diabetic patients with human islet transplants to restore insulin secretory function are limited severely by the small numbers of donated pancreas available each year, combined with the toxicity of immunosuppressive drug treatments required to prevent graft rejection (Chapman, 1999).

### Stem Cell Treatment of Damaged Heart Muscle

Cardiovascular diseases can deprive heart tissue of oxygen, thereby killing cardiac muscle cells. This loss can result in the formation of scar tissue, overstretch the remaining cardiac cells, and decrease cardiac output. Because donated hearts are always in short supply, restoring damaged heart muscle tissue through regeneration is a potentially new strategy to treat heart failure (Goldthwaite, 2006).

The treatment of human heart attack patients with stem cells is the second most advanced area of stem cell applications (following the HSC treatment of leukemia). Usually these procedures are performed in patients who are already undergoing open-heart surgery, and involve either injecting the cells into the circulation or directly into the injured heart tissue. The exact mechanism of repair remains somewhat controversial, but the stem cells likely regenerate

heart tissue through several cardiac-specific pathways (Goldthwaite, 2007). Human heart attack patients were first treated with skeletal myoblast cells in 2001 (Menasche et al., 2001; Siminiak et al., 2004), and were later treated with bone marrow stem cells (Britten et al., 2003; Lunde et al., 2006; Schächinger et al., 2006), then mesenchymal stem cells (Chen et al., 2004), and finally adult cardiac stem cells (GEN, 2011). Menasche (2002) summarizes the results of several phase-I clinical trials using skeletal myoblast transplants to treat human heart ailments. One phase-I study using autologous skeletal myoblast transplantation was initiated on June 15, 2000, and has already been completed with 10 patients. The phase-I trial established the general feasibility of the myoblast procedure, and demonstrated the ability to reach a specified number of target cells within a pre-set time frame of 2 to 3 weeks. The operation by itself was shown to be safe without specific procedure-related complications. The only adverse event was ventricular tachycardia, which occurred in 4 patients. It has suggested that the incidence and severity of the arrhythmias could be reduced by an appropriate prophylaxis using the drug amiodarone. Other phase-I studies were also done, and support the feasibility and safety of the myoblast procedure.

Heart attack patients have not yet been treated with embryonic stem cells, but human ES cells have been shown to be able to differentiate into various cardiac lineages (Kehat et al., 2001).

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

Intensive research aimed at curing Parkinson's disease (PD) with stem cells is a good example of the various strategies, successful results, and remaining challenges of stem cell-based brain repair. PD is a progressive neurological disorder of motor control that affects roughly 2% of persons 65 years and older. PD often begins with minor muscle tremors that eventually

progress to limb and bodily rigidity, and difficulty initiating movement. PD is triggered by the death of neurons in a brain region called the "*substantia nigra*". Those neurons connect via long axons to another region called the striatum, composed of subregions called the caudate nucleus and the putamen. The *substantia* neurons release the chemical transmitter dopamine onto their target neurons in the striatum. One of dopamine's major roles is to regulate body movement. As these dopaminergic cells die, less dopamine is produced, leading to the movement difficulties. Currently, the causes of death of the *substantia* neurons are not well understood (Pachision, 2006).

For many years, doctors have treated PD patients with the drug levodopa (L-dopa), a chemical precursor to dopamine, which the brain readily converts into dopamine. Although the drug initially works well, levodopa eventually loses its effectiveness, and side-effects increase. Ultimately, many doctors and patients find themselves fighting a losing battle. For this reason, a huge effort is underway to develop new treatments (Pachision, 2006).

With respect to cell therapy, human PD patients were initially treated with fetal tissue transplants isolated from aborted fetuses (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002). Although this technique had some success, the use of aborted tissue in medical research was too ethically controversial, so this technique is no longer used. Human PD patients have also been treated with adult olfactory mucosal stem cells (Levesque, 2005), and with adult neuronal stem cells (Ertelt, 2009). The latter technique appears to hold some promise, as no tumors formed at the injection site. Using adult NSCs to treat PD may hold promise, based on related work treating stroke patients with similar cells (Arvidsson, et al., 2002). That pioneering study on neuronal replacement using adult neural stem cells after stroke was the first to comprehensively show that new neurons have the capability to replace cells lost at the site of

an insult. The experiments confirmed that the increase in newly born cells at the ipsilateral striatum (ST) was a result of increased cell proliferation and recruitment of neuroblasts. However, the apparent regeneration of new neurons only accounted for 0.2 % of the lost striatal neurons in the stroke (Arvidsson et al., 2002).

Embryonic stem cells have had some success in PD animal models, but have not yet been used to treat human patients, although human ES cells have been shown to be capable of differentiating into dopamine-producing neurons (Perrier et al., 2004). These ES cells were shown to have differentiated into both dopamine and serotonin neurons. This latter type of neuron is generated in an adjacent region of the brain and may complicate the response to transplantation in PD patients. Since ES cells can generate all cell types in the body, unwanted cell types such as muscle or bone could theoretically also be introduced into the brain, although hopefully the injection environment will prevent this from happening. As a result, a great deal of effort is being currently put into finding the right way to turn ES cells only into dopamine neurons (Pachision, 2006).

One method with great therapeutic potential is somatic cell nuclear transfer (SCNT). This method fuses the genetic material from the nucleus of a skin fibroblast (somatic) cell of a donor with a recipient egg cell that has had its nucleus removed. If the resulting early embryo can survive for 5 days to the blastocyst stage, ES cells can be derived from the inner cell mass. These ES cells would be genetically identical to the donor of the skin cell, so in theory this technique could be used to make ES cells that are compatible with a human patient. This process is sometimes called “therapeutic cloning”, and is regarded by some to be ethically questionable. SCNT was first performed in sheep in 1996 (Campbell et al., 1996). Human SCNT was claimed in 2007, but was later proven to be a hoax (Hwang et al., 2007). Mouse ES cells have been

derived successfully in this way, and were differentiated into dopamine neurons that corrected Parkinsonian symptoms when transplanted into 6-OHDA-treated rats (Garfinkel, 2005). ES cell lines have also been derived from parthenote embryos created by stimulating unfertilized eggs with chemicals or electric current to stimulate egg division without loss of one set of chromosomes. These alternative approaches may eventually offer the possibility of treating patients with genetically matched cells, thereby eliminating the possibility of graft rejection (Garfinkel, 2005), but have not yet been achieved with human embryos.

Scientists are also studying the possibility that the brain may be able to repair itself with therapeutic support. This approach is in its early stages, but may involve administering drugs that stimulate the formation of new neurons from the brain's own stem cells. The approach is based on research showing that new nerve cells are born in the adult brains of humans in a brain region called the *dentate gyrus* of the hippocampus (Panchision, 2006). While it is not yet clear how these new neurons contribute to normal brain function, their presence suggests that stem cells in the adult brain may have the potential to re-wire dysfunctional neuronal circuitry.

### Stem Cells Treatment of Strokes

Stroke affects about 750,000 patients per year in the U.S. and is the most common cause of disability in adults. A stroke occurs when blood flow to the brain is disrupted. As a consequence, cells in the affected brain regions die from insufficient oxygen. The treatment of stroke with anti-clotting drugs has dramatically improved the odds of patient recovery. However, in many patients the damage cannot be prevented, and the patient may permanently lose body functions.

For stroke patients, researchers are now considering the use of stem cells as a way to repair the damaged brain regions. This problem is challenging because stroke damage may be widespread and may affect many cell types and connections (Panchision, 2006). Human stroke patients have been treated with mesenchymal stem cells (Bang et al., 2005) and with HSCs (Schwarting et al., 2008). In November 2004, Brazilian doctors transplanted a patient's own bone marrow stem cells into a 54 year old woman who had a stroke. She had lost movement on the right side of her body and could not understand other people or communicate with them. 17 days after the transplant she was discharged from hospital, having recovered movement, comprehension and some speech, and further improvements were reported in the following months (Khalip, 2004).

Newer experiments have focused on treating stroke patients with mesenchymal stem cells (MSCs). MSCs, like other stem cells, have the capacity of unlimited self-renewal giving rise to differentiated cells from various cell lineages. Bone marrow (BM)-derived MSCs are the most frequently used MSC type in experimental stroke studies. Application of BM-derived MSCs and, in some studies, transplantation of MSCs from other tissue sources resulted in an improved functional recovery in experimental animals, although stroke volumes were not always improved by the MSC transplantation (Doeppner, et al., 2010).

Taking an alternative approach, another research group attempted a cell transplantation supplemented with a scaffold as a means to treat the loss of brain mass after a severe stroke. By adding stem cells onto a polymer scaffold that they implanted into the stroke-damaged brains of mouse, the researchers demonstrated that the seeded stem cells differentiated into neurons while the polymer scaffold reduced scarring (Park et al., 2002). Two groups transplanted human fetal stem cells in independent studies into the brains of stroke-affected rodents; these transplanted

stem cells not only survived but migrated to the damaged areas of the brain. These studies increase our knowledge of how stem cells are attracted to diseased areas of the brain (Panchision, 2006).

Researchers from Sweden recently observed that strokes in rats cause the brain's own stem cells to divide and give rise to new neurons (Arvidsson et al., 2002). However, these neurons, which survived only two weeks, are too few in number compared to the damaged area. A research group from the University of Tokyo added a growth factor, bFGF, into the brains of rats after stroke, and showed that the hippocampus was able to generate large numbers of new neurons, and the new neurons were actually making connections with other neurons (Nakatomi et al., 2002). These and other results suggest that future stroke treatments may be able to coax the brain's own stem cells to make replacement neurons (Panchision, 2006).

### Stem Cell Treatment of Scleroderma

Scleroderma is an autoimmune disease that affects connective tissue in the body, the tissue that supports skin and internal organs. This disease causes organs to grow hard and thick. Amy Daniels is a successfully treated patient of Dr. Burt on this disease (Stem Cell Research, 2008). Her scleroderma caused her skin to become very tight, she could not bend her head backwards, and she could not make a fist or cross her fingers. Her teeth were getting loose, and she had trouble closing her mouth. Her illness got worse as it attacked her lungs, decreasing their capacity from over 90 percent to 43 percent. She was given chemotherapy and immunosuppressant to eliminate her malfunctioning immune system. In April 2007, her own adult stem cells were re-infused to her body to rebuild her immune system. After 6 months, she returned to work, her skin returned to normal, and her lung capacity increased to 57 percent

(Saunders, 2008). Although this is only one case, it provides hope for others affected by scleroderma.

### General Applications

Human stem cells have also been found to be beneficial in treating other serious medical conditions like cancer and birth defects. Human stem cells isolated from patients can also be used as disease models to test drugs. New medications could be tested for safety on differentiated cells generated from human pluripotent cell lines (Weissman, 2001).

### Chapter-2 Conclusions

The most important potential application of human stem cells is the generation of cells and tissues for cell-based therapies. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells to treat diseases (Weissman, 2001). To realize the promise of cell-based therapies for such pervasive and debilitating diseases, scientists are challenged to be able to manipulate stem cells so that they possess the necessary characteristics for successful differentiation and transplantation.

Human embryonic stem cells have the potential to provide an unlimited amount of tissue for transplantation therapies to treat a wide range of degenerative diseases. These useful cells can be grown into cell lines for producing large numbers of cells for therapies. However, there are a number of challenges associated with ES cell therapies, including histo-compatible matches, the occasional formation of tumors at the injection site, and ethical issues. So, many years of basic research will be required before ES cell therapies can be used to treat patients (Panchision, 2006).

It has been 14 years since the initial derivation of human embryonic cells in 1998 (Thomson et al., 1998). As of 2006, more than 120 human ES cell lines have been established, and 67 of them are included in the National Institutes of Health Registry (Panchision, 2006). Twenty-one cell lines are currently available for distribution. Unfortunately, all of these ES cell lines have been exposed to animal products during their derivation, as they were cultured with mouse fibroblast feeder layer cells (Panchision, 2006). However, scientists have now devised a procedure for deriving ES cells without using any feeder cells (Klimanskayaet al., 2005).

Most of the research studies performed so far have shown that using adult stem cells to treat blood cancers is the most characterized of all the stem cell treatments, and that the treatments the closest to expanding to wide spread use in human patients are treating heart attacks and strokes with adult stem cells. However, experiments with animal models have led the way in most cases, and will continue to provide more opportunities to treat human diseases in the future.

## Chapter-2 Bibliography


Abbott, Cate (2003) Bone Marrow Transplantation. London Health Sciences Centre. http://www.lhsc.on.ca/transplant/bnmarrow.htm.

Alipio Z, Liao W, Roemer EJ, Waner M, Fink LM, Ward DC, Ma Y (2010) Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic β-like cells. *Proceedings of the National Academy of Sciences,* 107: 13426-13431.

Amy Daniels (2008) Testimony on Capitol Hill Briefing in Washington DC on March 13, 2008. http://stemcellresearch.org/testimony/20080313_daniels.html

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nature Medicine,* 8: 963-970.

Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki K, and Tzukerman M (2001) Insulin Production by Human Embryonic Stem Cells. *Diabetes,* 50: 1691-1697. http://diabetes.diabetesjournals.org/cgi/content/full/50/8/1691

Bang OY, Lee JS, Lee PH, and Lee G (2005) Autologous mesenchymal stem cell transplantation in stroke patients. *Annals of Neurology,* 57(6): 874–882.

Britten MB, Abolmaali ND, Assmus B, Lehmann R, Honold J, Schmitt J, Vogl TJ, Martin H, Schächinger V, Dimmeler S, Zeiher AM (2003) Infarct Remodeling After Intracoronary Progenitor Cell Treatment in Patients With Acute Myocardial Infarction. *Circulation,* 108: 2212-2218.

Campbell KH, McWhir J, Ritchie WA, Wilmut I (1996) Sheep Cloned by Nuclear Transfer From a Cultured Cell Line. *Nature,* 380: 64-66.

Chapman A (1999) Stem Cell Research and Applications. Retrieved from: http://www.aaas.org/spp/sfrl/projects/stem/report.pdf

Chen S-I, Fang W-W, Ye F, et al. (2004) Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cells in patients with acute myocardial infarction. *American Journal of Cardiology,* 94: 92-95.

D'Amour KA (2006) Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells. *Nature Biotechnology*, 24: 1392-1401.

Doeppner TR, Hermann DM (2010) Mesenchymal stem cells in the treatment of ischemic stroke: progress and possibilities. Dove Press Journal. November 11, 2010.

Ertelt, Steven (2009) Adult Stem Cell Research Reverses Effects of Parkinson's Disease in Human Trial. LifeNews.com, February 16, 2009. http://www.lifenews.com/bio2751.html

Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, and Fahn S (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *New England Journal of Medicine,* 344: 710-719.

Garfinkel S (2005) Stem Cells and Parkinson's Disease. *International Society for Stem Cell Research*. Retrieved from: http://www.isscr.org/public/parkinsons.htm

GEN (2011) First Clinical Trial of Autologous Cardiac Stem Cells Shows Positive Results. *Genetic Engineering and Biotechnology News*, Issue Nov 14, 2011. http://www.genengnews.com/gen-news-highlights/first-clinical-trial-of-autologous-cardiac-stem-cells-shows-positive-results/81245949/

Gluckman E (2009) History of cord blood transplantation. *Bone Marrow Transplant*, 44: 621-626.

Goldwaithe CA (2006) NIH Stem Cell Information, Chapter-7. Are Stem Cells the Next Frontier for Diabetes Treatment? Retrieved from: http://stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter7.htm

Hughes BR (2005) Real-World Successes of Adult Stem Cell Treatments. Family Research Council. Retrieved from: http://www.frc.org/index.cfm?i=IS04J01&f=WU04K19&t=e

Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, Kim S, Kim SJ, Park SW, Kwon HS, Lee CK, Lee JB, Kim JM, Ahn C, Paek SH, Chang SS, Koo JJ, Yoon HS, Hwang JH, Hwang YY, Park YS, Oh SK, Kim HS, Park JH, Moon SY, Schatten G (2005) Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science,* 308: 1777-1783.

Khalip A (2004) Brazilians to widen stem cell study in strokes. Reuters 19 November 2004. Retrieved from http://www.spuc.org.uk/about/no-less-human/ethicalstemcells.pdf

Klimanskaya I, Chung Y, Meisner L, Johnson J, West MD, Lanza R (2005) Human Embryonic Stem Cells Derived Without Feeder Cells. *Lancet*, 365(9471): 1636-1641.

Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. (2008) Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. *Nature Biotechnology*, 26: 443-452.

LevesqueMF (2005) Senate Committee Testimony: Spinal Cord Injured Recipient of Adult Stem Cell Therapy. http://www.leaderu.com/science/stemcelltestimony_levesque.html

Lindvall O, Rehncrona S, Brundin P, et al. (1989) Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. *Archives of Neurology,* 46: 615-631.

Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, and McKay R (2001) Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets. *Science,* 292: 1389-1394.

Lunde K, Solheim S, Aakhus S, Arnesen H, et al (2006) Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *The New England Journal of Medicine,* 355: 1199-1209.

Madrazo I, Leon V, Torres C, et al. (1988) Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. *New England Journal of Medicine*, 318: 51.

Menasche, Philippe (2002) Cell Transplantation in Myocardium. Department of Cardiovascular Surgery. Paris, France. Retrieved from:
http://ats.ctsnetjournals.org/cgi/content/full/75/6_suppl/S20#BIB34

Menasche P, Hagege AA, Vilquin J-T, et al. (2003) Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol.* 41: 1078-1083.

Mendez I, Dagher A, Hong M, et al. (2002) Simultaneous intrastriatal and intranigral fetal dopaminergic grafts in patients with Parkinson disease: a pilot study. Report of three cases.

*Journal of Neurosurgery*, 96: 589-596.

Nakatomi H, Kuriu T, Okabe S, et al. (2002) Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell*, 110: 429-441.

Olanow CW, Goetz CG, Kordower JH, et al. (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Annals of Neurology*, 54: 403-414.

Panchision DM (2006) Repairing the Nervous System with Stem Cells. *Regenerative Medicine.* Department of Health and Human Services.
http://stemcells.nih.gov/staticresources/info/scireport/PDFs/E.%20Chapter%203.pdf

Park KI, Teng YD, Synder EY (2002) The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. *Nature Biotechnology*, 20: 1111–1117.

Perrier AL, Tabar V, Barberi T, et al. (2004) Derivation of midbrain dopamine neurons from human embryonic stem cells. *Proc Natl Acad Sci USA*, 101: 12543-12548.

Saunders WJ, et al. (2008) Adult Stem Cell Success Stories. *Family Research Council.* Retrieved from: http://www.frc.org/insight/adult-stem-cell-sucess-stories-2008-jan-june

Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, et al. (2006) Intracoronary Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction. *The New England Journal of Medicine*, 355: 1210-1221.

Schwarting S, Litwak S, Hao W, Bähr M, Weise J, Neumann H (2008) Hematopoietic Stem Cells Reduce Postischemic Inflammation and Ameliorate Ischemic Brain Injury. *Stroke*, 39: 2867-2875.

Seguev H, Fishman B, Ziskind A, Shulman M, Itskovitz-Eldor J (2004) Differentiation of human stem cells into insulin-producing cell clusters. *Stem Cells*, 22: 265-274.

Siminiak T, Kalawski R, Fiszer D, Jerzykowska O, Rzeźniczak J, Rozwadowska N, Kurpisz M (2004) Autologous skeletal myoblast transplantation for the treatment of post-infarction myocardial injury: Phase I clinical study with 12 months of follow-up. *American Heart Journal*, 148: 531-537.

Soria B, Roche E, Berna G, Leon-Quinto T, Reig JA, Martin F (2000) Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. *Diabetes*, 49: 157-162.

Spangrude GJ, Heimfeld S, Weissman IL (1988) Purification and characterization of mouse hematopoietic stem cells. *Science*, 241: 58-62.

Thomas ED, Lochte HL, Lu WC, et al. (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New England Journal of Medicine*, 257: 496-496.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived From Human Blastocysts. *Science,* 282: 1145-1147.

Viacord (2011) www.viacord.com
Victims of stroke could be helped by babies. The Times. 20 February 2001. Retrieved from: http://www.spuc.org.uk/about/no-less-human/ethicalstemcells.pdf

Weissman I, Domen J, and Wagers A (2001) Bone Marrow (Hematopoietic) Stem Cells. Retrieved from: http://stemcells.nih.gov/staticresources/info/scireport/PDFs/D.%20Chapter%202.pdf

Yu J, Thomson JA (2006) Embryonic Stem Cells. *NIH Publication*. Bethesda, MD: http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf

# Chapter-3: Stem Cell Ethics

*Ali Algarni*

In the past 14 years, following the 1998 initial isolation of human embryonic stem (ES) cells (Thompson et al., 1998), stem cells have been a very hot topic. The subject has attracted much attention due to the ability of stem cells to save lives, and medical researchers have been amazed at their ability to treat various diseases in animal models and in patients (discussed in Chapter-2). But at the same time, many have not approved of this research, because isolating ES cells destroys a human embryo. These individuals believe the costs of stem cell research outweigh the medical benefits to society. The purpose of this chapter is to discuss the topic of stem cell ethics, paying special attention to the views of the five major world religions.

## The Stem Cell Debate

One type of stem cell in particular has angered many due to the way in which these cells must be obtained. ES cells require the destruction of a blastocyst prepared by *in vitro* fertilization (IVF). Donor egg and sperm are united in a test tube, and the fertilized zygote is grown about 5 days to the 100-cell stage of the blastocyst. ES cells are found in the inner cell mass of the blastocyst, and isolating them destroys the blastocyst. So, the debate focuses on the status of the IVF human embryo. If you argue that life begins at conception, destroying a 5-day old embryo is murder. If you argue that life begins a 40-days, or even later at birth, you have few problems with using a 5-day old embryo to try to save lives. The debate compares the benefits to society (discussed in chapter-2) with the destruction of an embryo. Have stem cells benefited the medical field enough to receive the attention they are getting? And should the destruction of an embryo outside the womb for the sake of saving lives be considered murder?

Surprising to many is the fact that the five major world religions support the use of *adult* stem cells. These cells are isolated from adult tissues (or from umbilical cord blood), and do not destroy an embryo. So when some members of a particular religion argue against the use of stem cells, it is important to note which *type* of stem cell they are against.

### Catholics and Stem Cells

The Roman Catholic view on stem cell research is one that is very well known. Several Popes have been quoted specifically saying they are against embryo research (Pope John Paul, 2001; American Catholic Organization, 2006). Roman Catholics follow not only the Bible, but also the Pope (the Vatican). The Catholic Church is against embryo research because Catholics believe life begins at conception. So destroying a 5-day old blastocyst is murder. Pope John Paul II said ES cell research is related to abortion, euthanasia, and other attacks on innocent life (O'Brien, 2012).

### Non-Catholic Christians and Stem Cells

Non-Catholic Christians have a somewhat similar view on the subject as Catholics. They generally view life's beginning as being at conception, and view the human embryo as a human life. Christians find the creation of human life for the sake of research to be morally unethical, and the destruction of the blastocyst as the killing of an innocent life (Pence, 2009). Although some Christians are still against ES cell research, many, in fact, favor of the idea. A 2010 poll by the Harris Poll Company showed that only 12 percent of U.S. citizens are against stem biomedical research (Gardner, 2010), a very close tie to the statistic of a similar poll the company conducted in 2005. In addition, Humphrey Taylor, Chairman of the Harris Poll, stated

that, "Even among Catholics and born-again Christians, relatively few people believe that stem cell research should be forbidden because it is unethical or immoral" (Gardner, 2010).

## Islam and Stem Cells

Many people view Islam as being a very conservative religion. However, Islam takes a different approach to the subject of stem cell research than Christians. Saudi Arabia and Iran are two countries that practice two different forms of Islam to the fullest, and yet they are two of the leading Middle Eastern countries in stem cell research. This can be a surprise to many, but unlike Christianity, Islam does not look at life beginning at conception, but rather at a later stage in the development of the embryo (Kutty and Siddiqi, 2007). In Islam, life begins after forty days, and anything before that is only flesh. Islam believes that in the early days of the pregnancy, what's inside the woman's body is just flesh, and that the soul enters the body around the 40$^{th}$ day. Therefore it is not against Islamic belief or ethics to use a 5-day old embryo for research. This fact is supported by the authority of Abu Abdul Rahman Abdullah ibn Masood (may Allah be pleased with him) who said:

> "The messenger of Allah (peace be upon him) and he is the truthful, the believed, narrated to us: Each of you is brought together in his mother's abdomen in forty days in the form of a drop of fluid. Then it is a clinging object for a similar [period]. Thereafter it is a lump looking it has been chewed for a similar [period]. The angel is then sent to him and he breathes into him the spirit. Recorded by Al-Bukhari and Muslim. (Az-Zarabozo, 2010).

But unlike Catholics who have one authority, Islam does not have one authority to speak for them or to consult. Most Muslim countries have not yet introduced laws on stem cells. Many Muslims favor ES cell research (Ahmed, 2001), but other Muslims argue that it is unethical to destroy the embryos, even though they believe in that it does not have soul until later

stages. But these latter individuals may fear that the technology could be used to increase the supply of embryos (Stem Cell Debate, 2009).

### Judaism and Stem Cells

Jewish views according to Rabbi Levi Yitschah Halpevin of the Institute for Science and Jewish Law in Jerusalem said, "As long as it has not been implanted in the womb and it's still a frozen fertilized egg, it does not have the status of an embryo at all and there is no prohibition to destroy it…" (Stem Cell Controversy, 2011). The Jewish faith argues that if it's for a good cause like saving lives, there is no ethical problem due to its noble cause. Saving lives is a strong tradition in the Jewish faith, so all major Jewish denominations, from Reform, Conservative, Orthodox and Reconstructionist, are big supporters of ES and adult stem cell research, if pursued for medical purposes (Pew Forum, 2008).

### Buddhists and Stem Cells

Buddhist teachings tend not to discuss the stem cell issue directly, but there are two main tenants of thought that factor into their discussion: 1) the prohibition against harming or destroying others (*ahimsa*), and 2) the pursuit of knowledge (*prajma*) and compassion (*karma*). These two tenants have divided Buddhist scholars and community into two main groups (Keown, 2004). One group argues that it should be ethical to work with embryos due to its fulfilling the tenant about seeking knowledge and ending suffering, while the other group argues that it causes harm to others so it goes against tenant-1. Although Buddhists do not have a central authority, most seem to argue that research involving intentionally destroying an embryo is unethical because it goes against their belief of life beginning at conception (Keown, 2004).

### Hindus and Stem Cells

Hindus also believe that life begins at conception, and like Buddhists do not have a single official position on the subject of stem cell research. Yet Hindus do not support abortions (Manickavel, 2004). Most importantly, Hindus believe in reincarnation, that the cycle of life takes you into many lives until you're one with God. So by destroying an embryo you disrupt a potential reincarnation (Bhanot, 2008). So, overall Hindus do not support destroying an embryo.

Overall, the large religions typically have multiple stances on stem cells. For Islam, even though the authority states clearly that the soul doesn't enter the body until the $40^{th}$ day, some Muslims are still against ES cell research. And although the official Catholic stance is against destroying an embryo, some Catholics are in favor of the research. Buddhists have the internal conflict of rewarding the pursuit of knowledge on one hand, while not harming life on the other hand.

### iPS Cell Ethics

Embryonic stem cells are of strong medical interest because they are pluripotent and can produce any cell in the adult body. But as discussed above, they destroy an embryo to obtain them. So, scientists have sought alternatives for producing pluripotent cells without destroying embryos. In 2007, scientists finally achieved this with human induced pluripotent stem (iPS) cells (Takahashi et al., 2007). As discussed in Chapter-2, iPS cells are skin fibroblast cells reprogrammed to become pluripotent by introducing the genes encoding two to four transcription factors that help reprogram the cells. Because the iPS cells would be genetically compatible to

the patient providing the skin cell, these cells may be less likely to be rejected by the patient. So hopefully these cells will not face the same ethical problems that ES cells face, while having the same ability to save lives.

Although this sounds promising, iPS cells have some flaws, and may not be truly pluripotent. Some scientists have reported that iPS cells grow more slowly than ES cells and may not be as potent (Hayden, 2011). Other scientists have reported that iPS cells have DNA mutations relative to their skin fibroblast cell counterparts (Gore et al., 2011). After reprogramming, some iPS cell lines had a large scale genomic rearrangements and abnormal karyotypes, which can hinder nuclear reprogramming. Twenty two iPS cell lines were examined after reprogramming, and each was found to contain point mutations relative to the parental cells (Chol, 2010; Somatic Coding Mutations…2011). Almost all of these mutations were non-synonymous, nonsense, or splice variants, and were enriched in genes mutated or having causative effects in cancers. About half of the mutations also existed in the parental fibroblast progenitors at low frequencies, so the rest happened during or after the reprogramming. This shows that iPS cells can acquire genetic and epigenetic modifications, so such cells should be screened prior to therapy.

Although the some initial studies indicated the iPS cells could form tumors at the injection site, later studies have omitted the *c-myc* transcription factor during the reprogramming and have not observed tumor formation (Kim et al., 2008).

So, overall more research needs to be done with iPS cells prior to using them for therapy. Stem cell scientist Robert Lanza, chief scientific officer at Advanced Cell Technology in Worcester, Massachusetts stated, "You hear all this dialogue in the media and scientific community about how iPS cells are the same as embryonic stem cells, how they can solve the

whole controversy by removing the need for embryos. But they still can be used to satisfy individuals who think we shouldn't be destroying blastocysts" (Chol, 2012).

## Chapter-3 Conclusions

With respect to the author's stance on stem cells, I have always been a supporter of embryonic stem cells. They have the highest medical potential. Their ability to differentiate into any type of cell in the adult organism, makes them very useful for therapeutic purposes. With an Islamic stance in mind that after 40 days an embryo is living, I don't believe that they should be used after forty days. And like many Muslim officials, I believe their usage should not be abused, and they should only be used to save lives. With respect to the source of the embryo used to derive ES cells, I believe that scientists should use discarded reproductive IVF embryos only after the couples have declared that they have no further need for them. And I believe that embryos created for the purpose of research by IVF or cloning are a valid source for research, providing the egg and sperm donors have informed consent. I see no problem with providing money to the donors, so long as it is done with tight regulation to prevent someone from making a living doing it.

The use of adult stem cells is a great achievement. Although they are not as potent as ES cells, their potential may be higher than originally thought. Scientists showed in 2006 that hematopoietic stem cells can form blood vessels in addition to blood cells (Adult Stem Cells…2006). Although these cells look promising, I still believe that ES cells are much more promising and should receive the most attention. I am also in favor of using iPS cells, although I do not believe they are as potent as ES cells, and should not detract from ES cell research.

## Chapter-3 Works Cited


Adult Stem Cells Show Wider Potential Than Previously Thought. *Science Daily*, Sep 2006. Web. July 2012.

Ahmed, Ayesha (2001) U.S. Muslims Give Support to Embryonic Stem Cell Research – Survey. http://www.islamonline.net/english/News/2001-08/29/article6.shtml

American Catholic Organization (2006) U.S. Bishops Protest Embryo Stem-Cell Research. http://www.americancatholic.org/News/StemCell/bishops_stemcell.asp

Az-Zarabozo, Jamal (2010) Hadith #4: Creation in the Womb. Umm Ibraheem, Oct 2010. Web. August 2012.

Bhanot, Anil (2008) The Ethics of Stem Cell Research: A Hindu View. Bionews. 17 Oct 2008. Web. July 2012.

Chol, Charles (2010) Cell-Off: Induced Pluripotent Stem Cells Fall Short of Potential Found in Embryonic Version. *Scientific American*, Feb 2010. Web. July 2012.

Gardner, Amanda (2010) Most Americans Back Embryonic Stem Cell Research: Poll. U.S. news Health. Oct 2010. Web. July 2012.

Gore A, Li Z, Fung H, Young J, Agarwal S, et al. (2011) Somatic Coding Mutations in Human Induced Pluripotent Stem Cells. *Nature,* 471: 63-67.

Hayden, Erika Check (2011) The Growing Pains of Pluripotency. *Nature,* 473: 272-274.

Keown, Damien (2004) No Harm Applies to Stem Cell Embryos: One Buddhist's View. *Science and Theology News*, April 2004. Web. August 2012.

Kim JB, Zaehres H, Wu G, Gentile L, Ko K, et al (2008) Pluripotent Stem Cells Induced from Adult Neural Stem Cells by Reprogramming with Two Factors. *Nature,* 454: 646-650.

Kutty A, and Siddiqi M (2007) Stem Cell Research in Shari`ah Perspective. http://www.islamonline.net/servlet/Satellite?pagename=IslamOnline-English-Ask_Scholar/FatwaE/FatwaE&cid=1119503545118

Manickavel V (2004) On Stem Cell Research. *Hinduism Today*. Oct 2004. Web. August 2012.

O'Brien, Nancy Frazier (2012) Embryonic Stem Cell Research Immoral, Unnecessary Bishop Says. *Catholic News Service*, Web. July 2012.

Pence, Rep. Mike (2009) The Empty Promise of Embryonic Stem Cell Research. *Christianity Today*, Mar. 2009. Web. August 2012.

Pew Forum (2008) Religious Groups' Official Positions on Stem Cell Research. http://pewforum.org/docs/?DocID=319

Pope John Paul II (2001, Jan 23) A Crisis of Values. *CNN.Com.* http://archives.cnn.com/2001/WORLD/europe/07/23/bush.pope/

Religious Groups' Official Positions on Stem Cell Research. *Pew Forum*, July 2008. Web. August 2012.

Somatic Coding Mutations in Human Induced Pluripotent Stem Cells, NIH Public Access. 2011 March 3. Web. July 2012.

Steinbock, Bonnie. Life Before Birth: The Moral and Legal Statuses of Embryos and Fetuses. Oxford University Press, Inc. 2011. Print.

Stem Cell Controversy. Wikipedia. Jan 2011. Web. August 2012.

Stem Cell Debate in the Muslim World (2009) *BBC Religions*. Sept. 2009, Web. July 2012.

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007) Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell,* 131: 1-12.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived From Human Blastocysts. *Science,* 282: 1145-1147.

# Chapter-4: Stem Cell Legalities

*Abdulla Al-Abri*

Controversial scientific technologies need laws governing their use. As discussed in previous chapters, the topic of stem cells is one of the most hotly debated topics in bio-ethics today. This topic is an interesting and frustrating blend of science, politics, and money. In this chapter, the laws that govern stem cell use will be discussed. Understanding the various actions taken in the U.S. and abroad to regulate stem cell research may help the reader develop his own stand on stem cells. As discussed in previous chapters, the stem cell debate focuses on the status of the human embryo. The wide diversity of views on the use of embryos and stem cell research originates from widely diverse religious and cultural stances, and this creates a strong debate in society. The U.S. federal and state policies on embryo research will be discussed from the Clinton administration to the present Obama administration, along with the policies of several other countries.

## Main Legal Issues with Stem Cells

As discussed in previous chapters, the main stem cell controversy focuses on the status of a 5-day old human embryo used to derive embryonic stem (ES) cells. The embryo is created by uniting sperm and egg *in vitro*, and growing 5 days to the blastocyst stage from which the ES cells are isolated. The ethical debate (and subsequent laws) focuses on whether the destruction of this 5-day old embryo is murder, and if so, it is banned by that administration from receiving *federal* money to support the research. Individual *states* can also fund the research on their own, as occurred during the federal ban by the Bush administration, and we will discuss the leadership roles of California, New Jersey, and Massachusetts in this role.

The embryo debate by U.S. presidents and by congress is not new. It began in the late 1970's with the birth of Louise Brown the world's first test tube baby (BBC News, 1978). These test tube embryos are created at fertility clinics, and are created in *excess* as it is impossible to know in advance how many tries will be needed to achieve a pregnancy. The debate focuses on what to do with the excess embryos once the couple has enough children. Governments have enacted policies since these embryos began being used for research purposes.

## The United States Federal Laws on Embryos

The United States has always been active at governing science and technology. The U.S. has not been mute in the embryo debate, but been very responsive on this issue, changing stances from being highly restrictive to being somewhat permissive with strong oversight.

### *Clinton Administration: Very Pro-Stem Cells*

President Clinton was generally in favor of using federal money to pay for embryo and stem cell research. He claims this interest first developed from seeing his friends' diabetic children and hoping that stem cells might cure them (Clinton, 2004). The American Diabetes Association called the use of stem cells to produce insulin the most important advancement in diabetes research since the development of insulin (American Diabetes Association, 2012). In December 1994, to begin a debate about embryo usage, President Clinton directed the National Institutes of Health (NIH) to temporarily abstain from providing any resources to support the creation of human embryos for research purposes, and established a National Bioethics Advisory Commission to consider the complex topic (Clinton, 1994). After a year, the advisory commission recommended using surplus IVF embryos for research purposes.

However, before much embryo research could be funded, in 1995 congress passed the Dickey-Wicker Amendment that prohibited the Department of Health and Human Services (HHS) from using appropriated federal funds for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death" (Public Law, 1995; Stem Cell Laws, 2005). This law was described under 45 CFR 46.204 and 46.207, and subsection 498(b) of the Public Health Service Act (Genetics and Public Policy Center, 2011).

The restriction of federal money for embryo research caused an increase in private funding. By 1998, the volume of research being conducted using embryos increased, and in this same year James Thomson and co-workers at the University of Wisconsin in a private institute became the first scientists to derive and successfully culture human ES cells from a blastocyst (Thomson et al., 1998). Prior to this achievement, ES cells had been derived from mouse blastocysts in 1981 (Martin, 1981; Guidelines for hES Cell Research, 2005). In August of 2000, the NIH released new guidelines for allowing federal funding of ES cell research (NIH, 2000) and President Clinton supported their recommendations. But before any applications were reviewed or money allocated, President Bush came into office (Kruse, 2009).

In general, although the Clinton administration was in favor of stem cells, for much of his term of office congress acting on public concerns over-rode him. But under his watch, human ES cells were discovered, and embryo research had its first success under private funding.

### *Bush Administration: Anti-Embryonic Stem Cells*

President George Bush was inaugurated in January of 2001. Although more than 50% of Americans (regardless of race or religious affiliation) supported stem cell research and believed it should be funded by the federal government, Bush made his mark on the topic by announcing

in August 2001 that federal funding would not be allowed to derive any new ES cell lines (hES Cell Policy…2001). Only if the derivation process was initiated prior to 9:00 PM EDT on August 9, 2001, and with donor consent, could the ES cell line be used, as those embryos had already been destroyed (Bush, 2001). As a result of this 2001 policy, only 60 hES cell lines were initially available for federal support, and many of these cell lines later turned out to be damaged or aged, making far fewer available lines (Holden and Vogel, 2002). Many in the scientific community worried this lack of ES cell lines would severely hinder the U.S. leadership position in this field (Rowley et al., 2002; Cook, 2004; Ford, 2006). The NIH monitored several stem cell researchers from India, Israel, Singapore, Sweden, and South Korea that became federally funded, as their derivations met President Bush's criteria (hES Cell Policy, 2001). A Human Embryonic Stem Cell Registry was created to list the human ES cell lines that met the eligibility criteria (NIH.gov, 2006).

In 2002, the President's Council on Bioethics released its report titled "Human Cloning and Human Dignity" in which the council unanimously recommended a ban on *reproductive* cloning and a four-year moratorium on *therapeutic* cloning for medical research purposes. The National Academy of Science recommended that human *reproductive* cloning should not be practiced because it is dangerous and most likely would fail, but it recommended that therapeutic cloning to produce patient-specific stem cells should be permitted because of the potential for developing new therapies and advancing biomedical knowledge (Genetics and Public Policy Center, 2011). But in spite of these recommendations, the 2001 ban on federal funding for ES cell research prevailed.

Under the Bush administration, the conduct of research on human ES stem cells remained tightly regulated. Due to an increase in public support for ES cell research (Langer, 2005),

congress twice voted to approve such research, and twice President Bush vetoed the bills. President Bush used his veto power for the first time as he stated that an embryonic stem-cell research bill "crossed a moral boundary" (Bash and Deirde, 2006). He used his veto power to stop a legislation intended to ease the restrictions he originally imposed on stem cell research in. He made it very clear to Congress that he is against the use of federal money, taxpayers' money, to promote science which destroys life in order to save life (Baker, 2005). He stated that the vetoed bill "would support the taking of innocent human life in the hope of finding medical benefits for others." With the presence on stage of children who began their lives from frozen embryos, he emphasized that these boys and girls are not spare parts. Bush said that if the bill were to become a law, American taxpayers would for the first time in the U.S. history be compelled to fund the deliberate destruction of human embryos (Babington, 2006). As expected, many questioned the decisions made by Bush regarding stem cell research, but Bush was firm with his decisions. In 2004, he even replaced two advocates of stem cell research on his bioethics council with three people who are less approving of stem cell research (Stem Cell Laws, 2005).

In general, the Bush administration was anti-ES stem cell research, in spite of rising public support for it. In 2007, a national poll indicated that a slim majority of Americans supported the research, and the Pew Forum on Religion and Public Life and the Pew Research Center for the People & the Press found that only 35% of individuals declare it is more important not to destroy embryos than to use them to save lives (Vestal, 2008). Because of the Bush policy on federal restrictions, scientists looked abroad for collaborators who had access to more ES cell lines (Cook, 2004), and others argued that a lack of support for stem cell research in the US resulted in the country falling behind other nations in this area (Ford, 2006). In

addition, during the Bush administration, several key states took it into their own hands to use state money to fund their own stem cell initiatives, discussed below.

### *Obama Administration: Pro-Stem Cells*

President Obama promised during his presidential campaign that he would overturn restrictions on the federal funding of ES cell research (Langer, 2009). Soon after his inauguration, on March 9, 2009, Obama signed an executive order ending an 8-½ -year ban on federal funding for ES cell research. This was "Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells" (President Barack Obama, 2009). He expressed his vigorous support to scientists who pursue stem cell research, and aimed for America to lead the world in the discoveries it one day may yield. With this order, scientists and researchers can currently use federally funded equipment in their main laboratory and new federal dollars to do ES cell research. Scientists and research advocates worldwide celebrated this over-turn of the 2001 ban (Hayden, 2009). He also lifted the prohibition on U.S. funding for international groups that promote this research, and proposed rescinding job protections for health-care workers who decline to carry out procedures that conflict with their moral beliefs (Wilson, 2009). In appreciation of Obama's decision, the House moved quickly to pass a bill in the hopes of turning Obama's executive order into law (Wilson, 2009).

The National Institutes of Health was given 120 days to develop ethical guidelines for the research (Childs and Stark, 2009), and the guidelines underwent several revisions. But in the end, spare IVF embryos were allowed for ES cell research, if the sperm and egg donors had provided consent. But embryos could not be creates solely for research purposes. And the president's order did not open the door to human reproductive cloning, which was clearly banned. He

reiterated that there would be strict guidelines not to tolerate misuse or abuse of embryos. He further emphasized that human reproductive cloning is dangerous, profoundly wrong, and has no place in society (CBS, 2009).

In 2009, President Obama also signed a memorandum that restores scientific integrity in government decision-making. The memorandum covers all scientific research, and help ensures that public policy is guided by sound scientific advice (Borenstein and Feller, 2009; Childs and Stark, 2009). He relayed that "promoting science is not just about providing resources but is also about protecting free and open inquiry" (CBS, 2009). President Obama indicated that his decision was a "difficult and delicate balance," and an understatement of the intense emotions generated on both sides of the long, contentious debate (CBS/The Associated Press, 2009).

In general, scientists are happy with Obama's stem cell policy (Holden, 2009), but because the executive order still mandated that the embryos come from reproductive clinics, and not be created solely for research, some scientists complained that the new policy remains too restrictive. The NIH Guidelines on human stem cell research established the policies and procedures under which the NIH will be allowed to fund such research. The guidelines were put into effect to ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable laws. The final guidelines were placed into effect on July 7, 2009 (Holden, 2009), and adhered to the well-established norms for informed donor consent. The rigorous NIH guidelines have already been used to ban dozens of ES cell lines from federal dollars. As one scientist said, "rigorous guidelines are only meaningful if they are rigorously applied" (Stein, 2010).

### U.S. State Policies on Embryos and Stem Cell Research

During the Bush administration ban on federal funding to derive new ES cell lines, several states took the initiative to fund the research on their own. Several key states, such as New Jersey, California, and Massachusetts led the way to fund their own stem cell initiatives and institutes.

*New Jersey.* On June 25, 2004, the New Jersey legislators passed a state budget that included $9.5 million for a newly chartered Stem Cell Institute of New Jersey (Palca, 2007). This move made New Jersey the first state to fund research on stem cells including those derived from human embryos. On December 16, 2005, the state's Commission on Science and Technology awarded $5 million to research teams throughout the New Jersey (The Commission on Science and Technology, 2007).

*California.* Five months after New Jersey's June legislative vote, California became the second state to fund ES cell research. On November 2, 2004 California voters approved Governor Schwarzenegger provision of $3 billion to support stem cell research over a decade and to establish the California Institute for Regenerative Medicine (CIRM) (Palca, 2007). In 2011, the governing board of CIRM approved $30 million toward a program that will cultivate partnerships between stem cell scientists and biotech and pharmaceutical companies. CIRM also approved a separate future $38 million to foster scientific innovation in high school students, and to fund basic stem cell discoveries (GEN, 2011).

*Connecticut.* On May 31, 2005 Connecticut allocated $100 million annual funding to fund stem cell therapies for a wide range of diseases, and to be one of the premier stem-cell research centers over the next 10 years. One month later, on June 15, 2005 Governor Jodi Rell signed a public act that permits stem cell research and bans human cloning (Associated Press,

2005). The act appropriates $20 million for conducting embryonic or human adult stem cell research (Palca, 2007).

Illinois. On July 13, 2005, the Illinois state legislature created a stem-cell research institute by executive order. The Public Health Department was given $10 million to fund research (Palca, 2007).

Massachusetts. On June 1, 2005, Massachusetts state legislators overturned Governor Romney's veto of a bill for funding stem cell research (Massachusetts Stem-Cell Bill Becomes Law Despite Veto, 2005). The legislation created an Institute for Stem Cell Research and Regenerative Medicine at the University of Massachusetts Medical School with an appropriation of $1 billion dollars to be spent on the stem cell biology core. It also established the Massachusetts Life Sciences Center (MLSC) to promote life science research in the advanced and applied sciences, and includes regenerative medicine, biotechnology, and nanotechnology (Embryonic and Fetal Research Laws, 2008). With the sufficient funds allocated, the Massachusetts hESC Bank and Registry was designed to serve as an international repository of human embryonic stem cells derived in Massachusetts and beyond (Shelton, 2007).

General States and Stem Cells: As of January 2008, the states of California, Connecticut, Illinois, Indiana, Iowa, Maryland, Massachusetts, and New York permitted ES cell research under certain conditions (State Embryonic & Fetal Research Laws as of January, 2008). But other states have enacted laws banning ES cell research, while other states have no stem cell policies at all. For those states that allow ES cell research, the conduct of such research is still governed by strict guidelines to ensure safety and health purposes, and to avoid misuse and abuse of the use of human embryos.

## Other Countries and Stem Cells

Other countries beside the United States have also welcomed the idea of supporting stem cell research. Research has shown that stem cell research is strongly affected by federal policies in the USA, Japan, Germany, the UK and France (Couffignal-Szymzcak, 2009). These countries were also the top five countries publishing stem cell articles.

On June 6, 2001, Japan banned *reproductive* cloning through its law on Human Cloning Techniques and other Similar Techniques. But in general, Japan is favorable to ES cell research. On July 23, 2004, Japan's Council for Science and Technology Policy approved the final report of its Bioethics Expert Panel on human embryo and stem cell research. The report recommended allowing the creation of human embryos for stem cell research (Couffignal-Szymzcak, 2009).

The 25 member states of Europe took very different regulatory positions on human embryonic stem cell research, reflecting the diversity of ethical, philosophical, and religious beliefs throughout Europe. UK and Belgium have similar legal positions that allow the procurement of human ES cells from surplus IVF embryos, and the creation of human embryos for research. However, Germany and Italy prohibit the procurement of human ES cells from human embryos, while Austria, Bulgaria, Cyprus, Ireland, Lithuania, Luxembourg, Malta, Poland, Romania, and Slovakia have no specific legislation at all in this area (What Does….2007). Germany even called for a number of European countries to reject a proposal that would make European money available for stem cell research (Deutsche, 2006).

On May 1, 2009, China introduced new regulations on the clinical use of stem cells. The regulations promote the development of medical science and technology that improve the quality and safety stem cell care. Under this law, medical technology should follow standardized

scientific and ethical principles for providing safe, effective care (Stem Cell Transplantation Department, 2011).

Other countries have also explored stem cell research, such as Iran, Norway, South Africa, and South Korea. In Iran, stem cell research got both religious and political backing, so Iran is quite liberal regarding stem cell research. In South Korea, biotechnology is an important industry, and stem cell research is one of the government priorities receiving large funding. South Africa allows creating human embryos solely for research. The Research Council of Norway granted 170 million Norwegian kroner to support stem cell research in 2002-2013 (Erik, 2011).

## Chapter-4 Conclusions

Since the advent of test tube babies in 1978, countries have debated what to do with the surplus IVF embryos. The embryo debate escalated considerably following the 1998 isolation of human ES cells from embryos, and their potential to treat a wide variety of diseases. In the U.S., embryo policies have strongly reflected the particular administration in office, from Clinton to Bush to Obama. What makes the issue complicated, and what calls for specific laws and policies to be formulated and enforced, are the citizen's beliefs of the the value of human life and the status of a 5-day old embryo. People are confronted with the dilemma of whether destroying a 5-day old IVF embryo is murder, versus potentially saving existing lives. Debates have pressured each administration, state, and many countries to pass their own laws on this topic. What can be recognized by the research performed in this chapter is the effort made by a variety of entities to understand the science, and create guidelines to prevent the misuse of the embryo and the stem

cells. All countries appear to ban reproductive cloning, but only some countries have bothered to pass the appropriate legislation on this topic.

Regardless of the debates, laws and guidelines, the world does not hold a singular position on ES cell research. Human ES cells are still perceived to be the best material for tissue regeneration. As this research continues, and new findings become apparent, new laws will need to be enacted. May stem cell researchers never forget that they too come from embryos, and use such embryos cautiously for saving lives.

## Chapter-4 Bibliography


American Diabetes Association (2012) http://www.diabetes.org/
Associated Press (2005) Rell Signs 10 Year, $100 Million Stem Cell Bill. June 16, 2005 http://www.grassrootsconnection.com/june_16_05_Conn_pr.htm

Babington C (2006) Stem Cell Bill Gets Bush's First Veto. *Washington Post.* http://www.washingtonpost.com/wp-dyn/content/article/2006/07/19/AR2006071900524.html

Baker, Peter. May 21, 2005. President Vows Veto on Stem Cell Research. *Washington Post*. http://www.washingtonpost.com/wp-dyn/content/article/2005/05/20/AR2005052000482.html

Bash, Dana, and Deirdre Walsh (2006) Bush vetoes embryonic stem-cell bill. *Politics*. CNN, 25 Sept. 2006. http://www.cnn.com/2006/POLITICS/07/19/stemcells.veto/index.html

BBC News (1978) 1978: First Test Tube Baby Born. http://news.bbc.co.uk/onthisday/hi/dates/stories/july/25/newsid_2499000/2499411.stm

Borenstein S, Feller B (2009) Obama science memo goes beyond stem cells. *The Huffington Post*. 9 Mar 2009. http://www.huffingtonpost.com/2009/03/09/obama-science-memo-goes-b_n_172987.html

Bush, George (2001) Radio Address by the President to the Nation. Whitehouse Archives. http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010811-1.html

CBS/The Associated Press (2009) http://www.cbsnews.com/stories/2009/03/09/politics/100days/domesticissues/main4853385.shtml

Childs, Dan, and Lisa Stark (2009) Obama Reverses Course, Lifts Stem Cell Ban. *ABC News*. 9 Mar. 2009. http://abcnews.go.com/Health/Politics/story?id=7023990&page=1

Clinton WJ (1994) Statement by the President. http://www.pub.whitehouse.gov

Clinton W (2004) My Life, by Bill Clinton: On Abortion. *On the Issues.* http://www.ontheissues.org/archive/my_life_abortion.htm

Cook, Gareth (2004) US stem cell research lagging. *The Boston Globe*. 23 May 2004. http://www.boston.com/news/science/articles/2004/05/23/us_stem_cell_research_lagging

Couffignal-Szymzcak, Sarah (2009) What's Leading the Curve: Research or Policy? http://www.researchtrends.com/issue12-july-2009/country-trends-4/

Deutsche Welle (2006) Germany Calls for EU-Wide Ban on Stem Cell Research. http://www.dw-world.de/dw/article/0,2144,2106539,00.html

Dunn, Kayla (2005) The Politics of Stem Cells. *NOVA Science Now*. April 13, 2005. http://www.pbs.org/wgbh/nova/sciencenow/dispatches/050413.html

Embryonic and Fetal Research Laws (2008) NCSL Home. National Conference of State Legislatures. http://www.ncsl.org/default.aspx?tabid=14413

Erik, Tom (2011) Comparing Stem Cell Research in the US, Iran, South Africa, South Korea and Norway. Stem Cell Research Around the World. https://embrybros.wordpress.com/

Ford, Liz (2006) US Falling Behind in Stem Cell Research. *Guardian.co.uk*. 1 June 2006. http://www.guardian.co.uk/science/2006/jun/01/highereducation.usnews

GEN (2011) California Institute for Regenerative Medicine Agrees to Dole Out $30M to Foster Alliances with Industry. *Genetic Engineering and Biotechnology News*, October 27, 2011. http://www.genengnews.com/gen-news-highlights/california-institute-for-reg-med-agrees-to-dole-out-30m-to-foster-alliances-with-industry/81245881/

Genetics and Public Policy Center (2011) Dickey-Wicker Amendment. http://www.dnapolicy.org/policy.international.php?laws_id=36&action=detail

Guidelines for Human Embryonic Stem Cell Research (2005) The National Academies Press. http://www.nap.edu/openbook.php?isbn=0309096537

Hayden, Erika Check (2009) Obama Overturns Stem Cell Ban. *Nature,* 458: 130-131. http://www.nature.com/news/2009/090309/full/458130a.html

Holden, Constance (2009) Researchers Generally Happy With Final Stem Cell Rules. *Science,* 325: 131. http://www.sciencemag.org/cgi/content/full/325/5937/131

Human Embryonic Stem Cell Policy Under Former President Bush (Aug. 9, 2001) NIH Stem Cell Information Home Page, 2001. http://stemcells.nih.gov/policy/2001policy.htm

Kruse, Laura (2008) Federal Policy: Embryonic Stem Cell Research. *The Boston Channel.* http://www.thebostonchannel.com/stemcells/6939082/detail.html

Langer, Gary (2005) Public Backs Stem Cell Research, Most Say Government Should Fund Use of Embryos. http://www.abcnews.go.com/sections/politics/DailyNews/poll010626.html

Langer, Gary (2009) Stem-Cell Support. *abcNEWS: The Numbers*. http://blogs.abcnews.com/thenumbers/2009/03/stem-cell-suppo.html

Massachusetts Stem-Cell Bill Becomes Law Despite Veto (2005) *Public Health*. Daily News Central, 1 June 2005. http://health.dailynewscentral.com/content/view/000929/44

Martin, Gail (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proceedings of the National Academy of Sciences USA*, 78(12): 7634-7638.

Massachusetts Stem-Cell Bill Becomes Law Despite Veto (2005) Public Health. *Daily News Central*, 1 June 2005. http://health.dailynewscentral.com/content/view/000929/44

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells (2000) *Federal Register*. The Daily Journal of the United States Government. http://www.federalregister.gov/articles/2000/08/25/00-21760/national-institutes-of-health-guidelines-for-research-using-human-pluripotent-stem-cells

NIH.gov (2006) Information on Eligibility Criteria for Federal Funding of Research on Human Embryonic Stem Cells. May 23, 2006. http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp

Palca, Joe (2007) States Take Lead in Funding Stem-Cell Research. *Npr.org*. 30 Mar. 2007. http://www.npr.org/templates/story/story.php?storyid=9244363

President Barack Obama (2009) Removing Barriers to Responsible Scientific Research Involving Human Stem Cells. Executive Order No. 13,505, Federal Register 74 (March 11, 2009): 10667-10668. http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf

Public Law No. 111-8 of 1995. Thomas H.R.1105. The Library of Congress. http://www.gpo.gov/fdsys/pkg/BILLS-111hr1105enr/pdf/BILLS-111hr1105enr.pdf

Rowley JD, Blackburn E, Gazzaniga MS, Foster DW (2002) Harmful Moratorium on Stem Cell Research. *Science,* 297: 1957.

Shelton, Mark (2007) UMass Medical School. Investments mark major landmark in Governor Patrick's commitment to Life Sciences. http://www.umassmed.edu/10_26_07.aspx

State Embryonic & Fetal Research Laws as of January (2008) *StateHealthFacts.org* http://www.statehealthfacts.org/comparetable.jsp?ind=111&cat=2&sub=31&yr=63&typ=5&rgnhl=37&sort=141

Stein, Rob (2010) NIH Rejects Use of Dozens of Stem Cell Colonies by Federally Funded Researchers. *The Washington Post*, June 22, 2010. http://www.washingtonpost.com/wp-dyn/content/article/2010/06/21/AR2010062104395.html

Stem Cell Laws (2005) *Stem Cells: A Look Inside.* http://library.thinkquest.org/04oct/00053/ab_laws.html

Stem Cell Transplantation Department (2011) China Stem Cell Regulations – A Quick Digest. The General Hospital of Chinese People's Armed Police Forces. http://www.sinostemcells.com/articles/china-stem-cell-regulations/

The Commission on Science and Technology (2007) NJCST awards $10 million in stem cell research grants. http://www.state.nj.us/scitech/about/news/approved/20070619a.html

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived From Human Blastocysts. *Science,* 282: 1145-1147.

Vestal C (2008) Stem cell research at the crossroads of religion and politics. *The Pew Forum on Religion and Public life*. http://pewforum.org/docs/?DocID=316

What does the law say about human embryonic stem cell research in Europe? (2007) Retrieved from http://www.eurostemcell.org/faq/56#t56n63

Wilson S (2009) Obama Reverses Bush Policy on Stem Cell Research. *The Washington Post,* 10 March 2009.

# PROJECT CONCLUSIONS

The potential of stem cells to enhance mankind's health and prolong life, regardless of the source of the stem cell, is undeniably commendable. The controversies, ethical and legal, are all valued and should be carefully weighed, so each of us must develop our own conviction about stem cell research but in consonance with what could be better for all. After gaining fundamental knowledge about stem cells, the authors now make their own conclusions on the subject. The authors support the use of all types of stem cells, but do not support the creation of embryos solely for research purposes. As to the source of embryos used to derive the ES cells, the authors support the use of surplus IVF embryos, so long as the donors provided consent that they be used for research. But the authors disagree with each other on whether donors should be allowed to receive monetary compensation; author Ali sees no harm with allocating money to egg or sperm donors, so long as they provide informed consent to use the material for research. On the other hand, author Abdulla argues that providing money to donors could push individuals into performing risky egg donation procedures solely because they are poor, and such an act lessens the value of human life and the essence of reproduction.

Given that all ES cell lines are derived from embryos regardless of how the embryo is created, whenever possible, the authors agree with attempting to use adult stem cells or induced pluripotent stem (iPS) cells instead of ES cells for treating a specific disease. Who knows, perhaps one of the embryos being destroyed has the potential to be a great scientist someday.

With respect to stem cell legislation, the authors most agree with current U.S. laws under the Obama administration. Obama's 2009 overturning of Bush's 2001 policies (that restricted federal funding for ES cell research) now allow new ES cell lines to be derived from embryos

but with some restrictions, including being surplus IVF embryos created for *reproductive* purposes, and the donors must provide their consent that the embryos can be used for research. These policies help show that the government is mindful of the values of human life and the essence of reproduction. Both authors strongly favor allowing *federal* and *state* funding for human stem cell research, and especially appreciate the current NIH ethical guidelines that bans creating embryos solely for research purposes, and bans reproductive cloning. The current Obama policies that exist in the United States are indeed logical and ethical.

Stem cell technology is one of the hottest debates in all of politics and science today, and will continue to be for years to come. The search for safe life-saving applications continues, and so does the challenge for all of us to keep up with this progress without sacrificing the values of human life.