IQP-43-DSA-3638
IQP-43-DSA-4860

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:

Batuhan Gizer Anvar Niyetkaliyez

August 26, 2009

APPROVED:

Prof. David S. Adams, Ph.D.
Project Advisor

ABSTRACT

The purpose of this IQP was to investigate stem cell types and applications, and their effects on society via ethics and legalities. From our research we conclude that embryonic stem cells (ESCs) have greater medical potential and future applications than adult stem cells (ASCs) due to their very strong differentiation advantage and ease of growth. All 5 major world religions support ASC use, but working with ESCs is not accepted by some Christian groups. Based on our findings, we believe the current U.S. legislation recently enacted by President Obama should be extended to allow paid egg donors, as in Sweden and South Korea, and agree with its mandate to allow federal funding to support this promising technology.

TABLE OF CONTENTS

PROJECT OBJECTIVES

The goal of this IQP project was to explore the topic of stem cells, and to discuss the impact of this controversial new technology on society by investigating their ethics and legalities. In Chapter-1 the various types of stem cells are introduced, the sources of each type are identified, and their abilities and functions are discussed. Chapter-2's objective is to show examples of animal experiments and human clinical trials to document where the technology currently stands with respect to societal benefits. Chapter-3 shows the point of view on this new biomedical field from an ethical perspective. Chapter-4's purpose is to document various U.S. and International laws that regulate stem cell uses. Finally, a conclusion is made by authors in order to share their thoughts and opinions about stem cells.

CHAPTER 1: STEM CELL TYPES AND SOURCES

Batuhan Gizer

The human body is one of the most complex living entities that occupy this world. Different mechanisms in the human body require an enormous diversity of cells, including white blood cells, red blood cells, skin cells, nerve cells, stem cells, etc. Most of these cells have specific predefined functions throughout their lives, and a limited lifespan. However, stem cells do not follow this pattern; they can divide long-term, and depending on the type of stem cell, can differentiate to form almost any kind of cell in our body. In other words, they are often termed the "master" cells. But stem cells are not all alike, as some have the ability to form multiple cell types, while others can predominately form only one cell type. So this chapter's purpose is to document the different kinds of stem cells, and to discuss their potencies. This topic is important for subsequent chapter discussions on stem cell uses, ethics, and government policies.

Stem Cell Classification

Stem cells can broadly be divided into two main categories: adult stem cells (ASC's) and embryonic stem (ES) cells (ProQuest, 2004). As their names imply, ASCs are usually obtained from adult tissues, while ES cells are usually obtained from an embryo. The ASC category often loosely includes umbilical cord blood as a source of hematopoietic stem cells, even though umbilical cord is not an adult tissue.

Stem cells also can be classified based on their *potencies*. Newly fertilized eggs through the 8–cell stage are considered *totipotent*, and can create any cell in the body plus the placenta. ES cells are considered *pluripotent*, and can differentiate to form any cell type except the

placenta. A common misconception is that ES cells are totipotent, but ES cells cannot form the placenta so they cannot be totipotent. ES cells are obtained from the inner cell mass of a blastocyst embryo. The isolation process kills the embryo, which produces strong ethical controversies in the medical use of this type of stem cell. But ES cells are also the most promising stem cell type in medicine, and they have enormous potential to cure some of the deadliest diseases since they can differentiate into huge variety of tissues. *Multipotent* cells can form several types of related cells. A good example in this category is a hematopoietic stem cell that can form multiple types of blood cells. Another example of multipotent stem cells is neuronal stem cells which can form neurons, astrocytes, and oligodendrites. *Unipotent* cells usually form only one cell type, that of the tissue of origin. An example of unipotent stem cell is a skin stem cell which is only capable of differentiating into other skin cells.

Adult Stem Cell Types

Adult stem cells (ASCs) can be found in different tissues in the adult, or in umbilical cord blood. ASC's are undifferentiated cells, living together with differentiated cells, residing in a tissue or an organ, and can usually differentiate only into the cell type of the specific tissue or organ they reside in (Kirschstein and Skirboll, 2009). Although most studies show ACSs are unipotent, some studies show that certain types of ASCs can differentiate into cells other than the cells they are expected to produce, in a process called transdifferentiation (Kirschstein and Skirboll, 2009). ASC's primary function is the maintenance and repair of the tissue, and to replace the dead or unfunctional cells. ASCs are important since their isolation does not destroy an embryo, so these cells typically have fewer ethical problems than ES cells. However, ASC's are very rare, thus it is very difficult to isolate these cells and grow them in cell culture to

produce large amounts for research or therapy. It is also debatable whether ASCs are capable of providing the same long term therapy that ES cells can, so further research is needed. Below is discussed some of the main types of ACSs.

Hematopoietic Stem Cells (HSCs)

Hematopoietic Stem Cells (HSCs) are responsible for forming all blood and immune cells (National Institutes of Health, Chapter 5). HSCs have been studied for more than 50 years, therefore we know the most about this category of stem cell than any other. Since 1957, HSCs have been used in human bone marrow transplants to treat patients with various types of cancer (Thomas et al., 1957). Currently, about 40,000 HSC transplants are performed annually world-wide (Horowitz, 1999).

The most common source of HSCs is bone marrow, but they can also be obtained from peripheral blood if the person is first injected with hormones to stimulate their release from the bone marrow. They are also obtained from umbilical cord blood, which has proven to be a rich source (Viacord, 2002). Even though HSCs are the most well-known stem cell type, like every other adult stem cell they are very rare and hard to find: "The challenge is formidable as about 1 in every 10,000 to 15,000 bone marrow cells is thought to be a stem cell. In the blood stream the proportion falls to 1 in 100,000 blood cells" (National Institutes of Health, Chapter 5).

Studies show that there are two main types of HSC. One type is called long-term because they are capable of renewing themselves repeatedly long-term, while the second type, short-term progenitor or precursor cells, cannot (**Figure-1**) (National Institutes of Health, Chapter 5). For instance, "a blood progenitor cell may only be able to make a red blood cell". Studies show that short-term progenitor cells can complete a cycle of hematopoiesis in about

three to four months, but scientists still do not know the exact time interval (**Figure-2)** (National Institutes of Health, Chapter 5). From a therapy perspective, it would be best to isolate and perfuse only the true long-term HSCs. "Unfortunately, to date, researchers cannot distinguish the long-term from the short-term cells when they are removed from the bloodstream or bone marrow"(National Institutes of Health, Chapter 5).

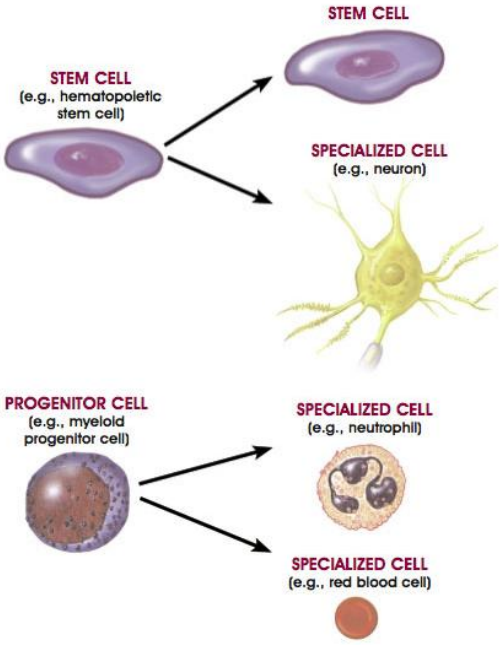

Figure 1: Distinguishing Features of Hematopoietic Progenitor/Precursor Cells and Stem Cells.
(http://stemcells.nih.gov/info/scireport/chapter4.asp)

Scientists continue to research the differences between HSCs taken from different sources. HSCs taken in the earlier stages of development of an organism appear to be more effective in self-replicating and preventing subsequent immune system problems, "making them potentially more useful for therapeutic transplantation" (National Institutes of Health, Chapter 5).

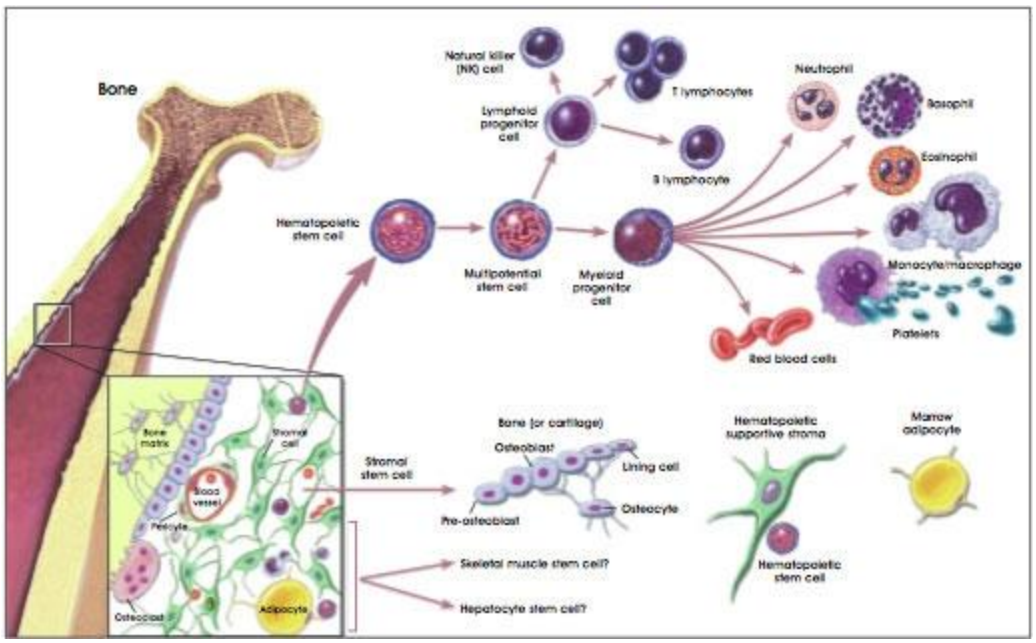

Figure 2: Diagram of Hematopoietic and Stromal Stem Cell Differentiation.
(http://stemcells.nih.gov/info/scireport/chapter5.asp)

Neural Stem Cells

Neural Stem Cells (NSCs) are capable of regenerating portions of the human brain. But their potency is still being debated. Unlike most other ASCs, NSCs appear to be able to differentiate into different brain cells, including neurons, astrocytes, and oligodendrites (**Figure-3**) (Brain Cancer Stem….2006). It used to be believed that when a neuron is dead, or damaged, it was impossible to reverse the consequences, but scientists found this is not entirely true and some parts of the brain are capable of repair (National Institutes of Health, Chapter 8). Studies indicate that NSCs "proliferate and migrate toward the site of the damage" (National Institutes of Health, Chapter 8) in order to repair damaged regions, and scientists are trying to harness this ability to treat neurodegenerative diseases and stroke.

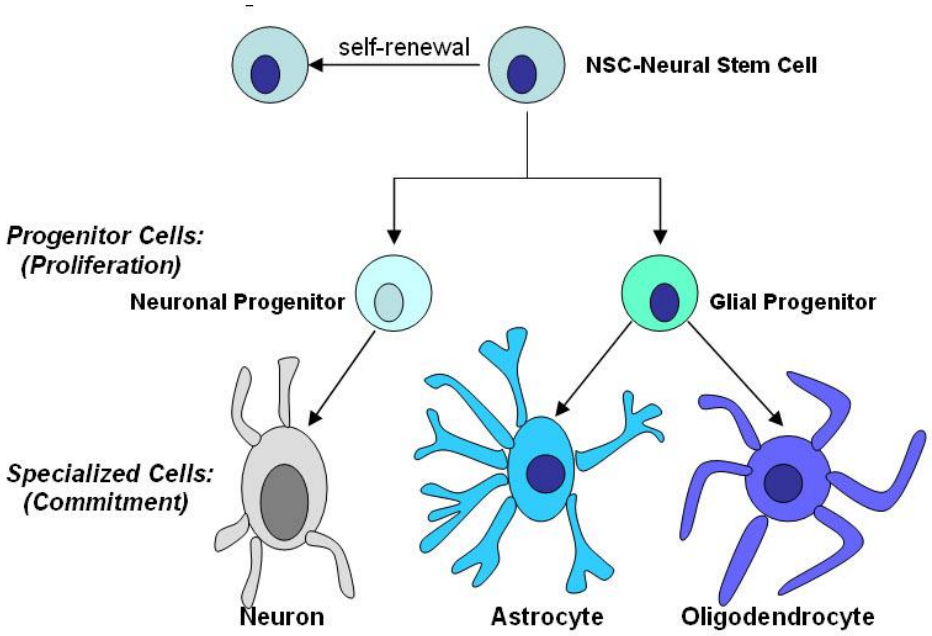

Figure 3: Diagram of Neural Stem Cell Hierarchy.
(University of Medicine and Dentistry of New Jersey, 2009)

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent progenitor cells which are capable of differentiating into numerous kinds of other cells, such as bone, cartilage, and muscle cells (**Figure-4**) (National Institutes of Health, Chapter 4). A common assumption was that MSCs could only be isolated from bone marrow, but recent studies show that MSC's exist "in virtually all organs" (Meirelles et al., 2009). Because of their ability to form multiple types of tissues, while not destroying an embryo to obtain them, MSCs have become one of the most highly researched type of stem cell in the past few years. In spite of their relatively recent discovery, MSCs have already been used in bone marrow transplants, and "besides producing mature, specialized cells that interact with the HSCs, mesenchymal stem cells are also directly involved with regulation of the hematopoietic process" (Meirelles et al., 2009).

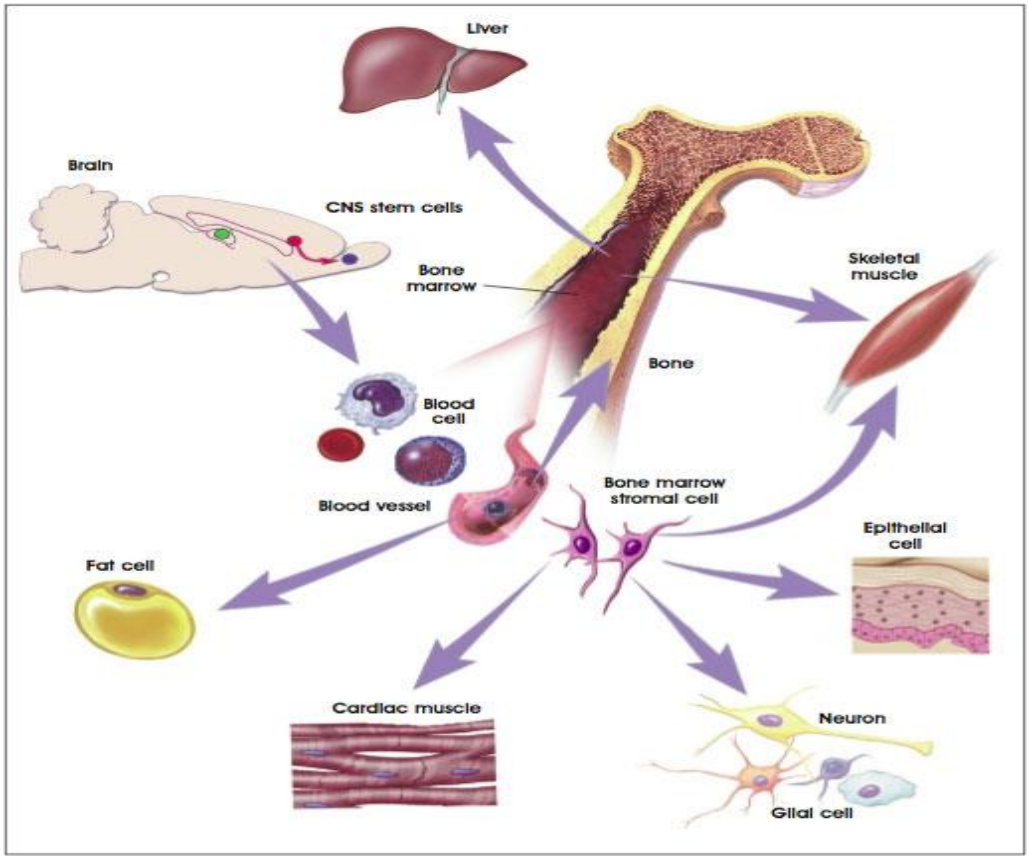

Figure 4: Diagram of Mesenchymal Stem Cell Differentiation.
(http://stemcells.nih.gov/info/scireport/chapter4.asp)

Cardiac Stem Cells

Cardiac stem cells (CSCs) are a relatively recent discovery. Traditionally it was thought that heart tissue cannot regenerate. But recent discoveries have found long-lived cells in heart tissue linings that can form new cardio myoblasts (Beltrami et al., 2003). Therefore it is now believed that heart is capable of regenerating new tissue and can repair after being damaged. These cells appear to reside in the heart atrial wall (**Figure-5**), and scientists are trying to "mobilize these cells to regenerate cardiac tissue. Better yet, researchers could perhaps stimulate cardiac stem cells already living in the heart to grow" (Touchette, 2003).

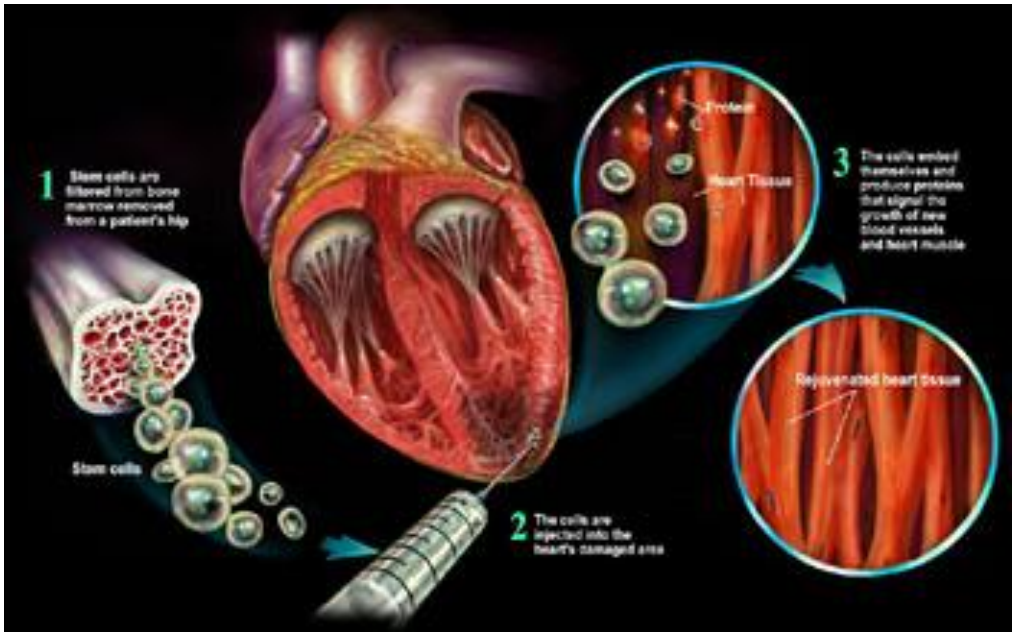

Figure-5: Diagram of the Isolation of Cardiac Stem Cells.
(University of Pittsburg, 2009)

Embryonic Stem Cells

Embryonic stem cells (ESCs) are the most medically valuable of all stem cell types, but unfortunately they are also the most controversial. ESCs are capable of forming new ESCs long-term which can provide large numbers of cells for therapy. They also are capable of differentiating into all of human tissues except the placenta, and because of this unique ability, ESCs are the most important type of stem cell medically. The embryos used to isolate ESCs are obtained from *in vitro* fertilization (IVF) (**Figure-6**, upper left). Excess IVF embryos not required for reproductive purposes are donated for research by the parents with signed consent. The embryos are cultured for about 5 days to the blastocyst stage (diagram upper right). The blastocyst is a hollow ball consisting of an outer trophoblast, and an inner cell mass (ICM). The ICM contains the ESCs. Isolating the ICM usually destroys the embryo.

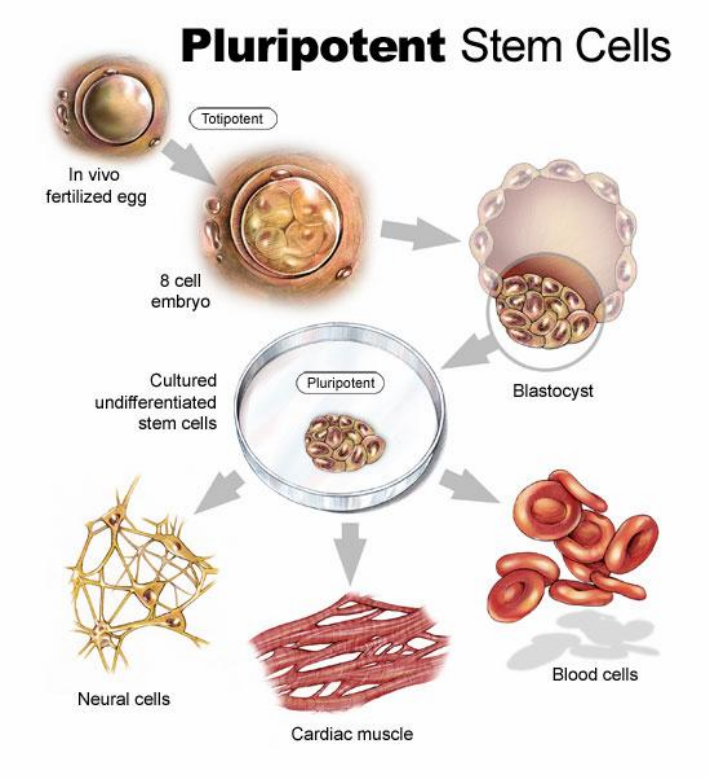

Figure-6: Diagram of the Isolation of Embryonic Stem Cells.
(http://www.csa.com/discoveryguides/stemcell/overview.php)

Scientists are still trying to define the properties of ESCs, but according to the NIH they have the following properties (National Institutes of Health, Chapter 2):

- Are derived from the inner cell mass/epiblast of the blastocyst.
- Are capable of undergoing an unlimited number of symmetrical divisions without differentiating (long-term self-renewal).
- Exhibit and maintain a stable, full (diploid), normal complement of chromosomes (karyotype).
- Are pleuripotent cells that can give rise to differentiated cell types derived from all three primary germ layers of the embryo (endoderm, mesoderm, and ectoderm).
- Are clonogenic: that is a single ES cell can give rise to a colony of genetically identical cells, or clones, which have the same properties as the original cell.
- Express the transcription factor Oct-4, which then activates or inhibits a host of target genes, and maintains ES cells in a proliferative, non-differentiating state.
- Can be induced to continue proliferating or to differentiate.
- Lacks the G1 checkpoint in the cell cycle. ES cells spend most of their time in the S phase of the cell cycle, during which they synthesize DNA. Unlike differentiated [adult] cells, ES cells do not require any external stimulus to initiate DNA replication.

- Do not show X inactivation. In every [adult] cell of a female mammal, one of the two X chromosomes becomes permanently inactivated by X inactivation which does not occur in undifferentiated ES cells.

Induced Pluripotent Stem Cells

Unlike other types of stem cells, induced pleuripotent (iPS) cells do not occur naturally in the body, instead they are reprogrammed adult skin fibroblast cells. Fibroblast cells are isolated from the skin of an adult, and are induced to de-differentiate to a pluripotent state by transfecting DNA encoding 2-4 transcription factor genes. The transcription factors induce the cells to resort back to a stem like state from which they originated. These cells appear to be as potent as ESCs, but they do not destroy an embryo, so they have become one of the hottest topics in all of stem cell research.

iPS cells were first isolated in Yamanaka's lab in mice in 2006 (Vogel, 2006) using a technique that delivered 4 transcription factor genes to skin fibroblast cells (Oct4, Sox2, c-Myc, and Klf-4) (**Figure-7**). These same four transcription factors were used in 2007 to convert human fibroblast cells to an ES-like state (Takahashi et al., 2007). In 2008, it was found that using only two transcription factors could do the conversion, and it was especially important to leave out c-Myc as it caused the cells to divide uncontrollably (Kim et al., 2008). In 2009, it was dicovered how to do the conversion using no transcription factors, instead using polyarginine proteins (Reprogramming..2009).

Through reprograming and inserting reprogrammed genes, or using polyarginine proteins, scientists are trying to achieve the goal of preparing pluripotent stem cells for use in medicine, without all the ethical controversy (Kolata, 2007). In fact, since iPS cells are induced

from an adult cell, the resulting ES-like cells are genetically identical to the patient, and should not be immuno rejected following the transplant.

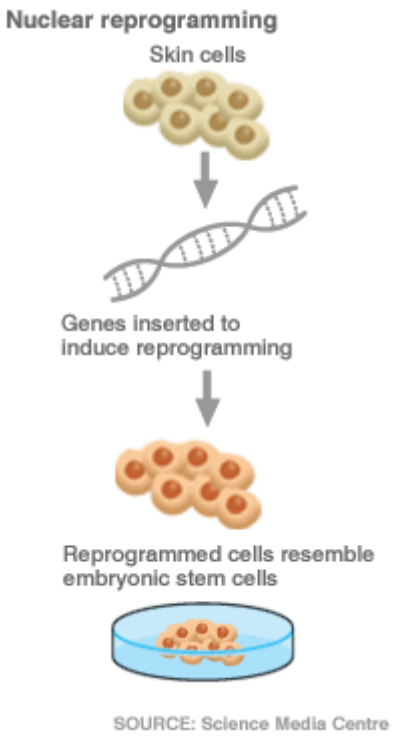

Figure-7 - Induced Pluripotent Stem Cells.
(http://news.bbc.co.uk/2/hi/health/7101834.stm)

Chapter Conclusion

Unlike common conceptions, all stem cells are not alike. There are many different types of stem cells, with very different capabilities. ES cells are the most potent and carry the best hope medically, but because they destroy an embryo they are the most controversial. Thus scientists have been searching for substitute cells that do not destroy an embryo, such as adult stem cells, or even iPS cells. Although ACSs can form tissues, their isolation is very difficult, and they are very hard to grow. iPS cells likely offer the best long-term solution since they appear to be pluripotent, and can be induced from a skin fibroblast cell, so it is possible to prepare an ES cell line genetically identical to a patient which would avoid immuno-rejection.

Chapter-1 Bibliography

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.

Brain Cancer Stem Cells and Beyond Scientific Review (2006) Michael J. Poynton III , Graduate School of Biomedical Sciences.
http://www.umdnj.edu/gsbsnweb/stemcell/scofthemonth/scofthemonth2/braincancerstemcellsci.htm

Horowitz MM (1999) Uses and Growth of Hematopoietic Cell Transplantation. In: Forman SJ, ed. *Hematopoietic Cell Transplantation*. Second ed. Malden, MA: Blackwell Science Inc. pg. 12-18.

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.

Kirschstein R and Skirboll LR (2009) "Stem Cells: Scientific Progress and Future Research Directions". National Institutes of Health, Department of Health and Human Services.
http://stemcells.nih.gov/info/basics/

Kolata, Gina (2007) "Scientists Bypass Need for Embryo to Get Stem Cells". New York Times.
http://www.nytimes.com/2007/11/21/science/21stem.html?em&ex=1195880400&en=18114796981c0299&ei=5087%0A

Meirelles LD, Caplan AI, and Nardi NB (2009) The Stem Cell Niche. In Search of the *In Vivo* Identity of Mesenchymal Stem Cells.
http://stemcells.alphamedpress.org/cgi/reprint/26/9/2287.pdf

National Institutes of Health, Chapter 2. The Embryonic Stem Cell. 24 March 2009.
http://stemcells.nih.gov/info/scireport/chapter2.asp

National Institutes of Health, Chapter 4. The Adult Stem Cell, 06 April 2009.
http://stemcells.nih.gov/info/scireport/chapter4.asp

National Institutes of Health, Chapter 5. Hematopoietic Stem Cells. 06 April 2009.
http://stemcells.nih.gov/info/scireport/chapter5.asp

National Institutes of Health, Chapter 8. Rebuilding the Nervous System with Stem Cells. 06 April 2009. http://stemcells.nih.gov/info/scireport/chapter8.asp

ProQuest (2004) "What Are Stem Cells?"
http://www.csa.com/discoveryguides/stemcell/overview.php

Reprogramming Offers Hope of Safer Stem Cells (2009) *NewScientist.*

http://www.newscientist.com/article/dn17008-reprogramming-offers-hope-of-safer-stem-cells.html

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.

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

Touchette, Nancy (2003) Stem Cells Found in the Heart.
http://www.genomenewsnetwork.org/articles/10_03/cardiac.shtml

University of Medicine and Dentistry of New Jersey (2009)
http://www.umdnj.edu/gsbsnweb/stemcell/scofthemonth/scofthemonth2/braincancerstemcellsci.htm

University of Pittsburg Newsletter (2009)
http://www.mirm.pitt.edu/Newsletter/Mirm/0409_businessweek.jpg

Viacord (2002) www.viacord.com

Vogel G (2006) Four Genes Confer Embryonic Potential. July 7. *Science* **313**: 27.

CHAPTER-2: STEM CELL APPLICATIONS

Anvar Niyetkaliyev

Chapter 1 discussed the various types of stem cells and their sources. In this chapter, the discussion of stem cell technology continues by investigating what stem cells have been used for. Various types of stem cells have been used to treat complicated diseases such as blood cancers, damaged heart muscle, diabetes, spinal cord injuries, Parkinson's disease, and others, either in animal models or in humans. Describing stem cell medical applications serves as an introduction to the Chapter-3 discussion of stem cell ethics, and allows the delineation of which applications remain in animal experimentation, versus those that have proceeded to human clinical trials.

Hematopoietic Stem Cell Applications

Hematopoietic stem cells (HSC) are the most researched type of stem cells. Scientists have more than 50 years of experience using HSCs to treat different types of blood diseases, especially treating cancer patients recovering from chemotherapy and radiation to re-establish their blood cell system. Chemotherapy destroys rapidly dividing cancer cells in the body, but it also destroys a patient's rapidly dividing blood cells and HSCs, which constitute the immune system. Doctors may give patients HSC transplants to restore the immune system. HSCs are traditionally isolated from a patient's bone marrow, then they are stored while the patient undergoes intensive cancer therapy. Once the chemotherapy drug has been eliminated from the patient's body, he or she gets a transplant of his or her own stored HSCs, or from a histocompatible donor if one can be found (Hematopoietic Stem Cells, 2005). One problem with

HSC transplants is the cells are sometimes contaminated with cancer cells which then get perfused back into the patient.

Table I shows a list of various diseases treated with HSCs using either autologous transplantation with the patient's own stem cells (left side of table), or allogeneic transplantation with an HLA matched donor (right side of table). Approximately 30, 000 autologous and 15, 000 allogeneic transplant procedures are performed yearly world wide (Powell, 2008).

Autologous Transplantation		Allogeneic Transplantation	
Malignant Disorders	**Nonmalignant Disorders**	**Malignant Disorders**	**Nonmalignant Disorders**
• Neuroblastoma • Non-Hodgkin lymphoma • Hodgkin disease • Acute myeloid leukemia (AML) • Medulloblastoma • Germ-cell tumors • Multiple myeloma*	Autoimmune disorders Amyloidosis	• AML • Non-Hodgkin lymphoma • Hodgkin disease • Acute lymphoblastic leukemia (ALL) • Chronic myeloid leukemia (CML) • Myelodysplastic syndromes • Multiple myeloma* • Chronic lymphocytic leukemia*	• Aplastic anemia • Fanconi anemia • Severe combined immunodeficiency • Thalassemia major • Diamond-Blackfan anemia • Sickle cell anemia • Wiskott-Aldrich Syndrome • Osteopetrosis • Inborn errors of metabolism • Autoimmune disorders

Table I. A List of Diseases Treated With Autologous and Allogenic Type Bone Marrow Transplants (Powell, 2008).

Table II shows the survival rate of children with different illnesses following treatment with HSCs. For allogeneic transplantation, the data is stronger for a sibling donor compared to an unrelated donor.

Disease	Stage	Survival Rate (%)		
		Autologous Transplantation	Allogeneic Transplantation	
			Sibling Donor	Unrelated Donor
Acute lymphoblastic leukemia (ALL)	Complete response (CR)1	N/A	65	45
	CR2	N/A	55	35
Acute myeloid leukemia (AML)	CR1	60	65	30
	CR2	40	45	50
	No remission	20	N/A	25
Chronic myeloid leukemia (CML)	Chronic phase <1 y	N/A	70	55
	Chronic phase >1 y	N/A	60	50
Hodgkin disease	CR1	80	N/A	N/A
	CR2	70	N/A	N/A
	No remission	45	N/A	N/A
Diffuse large-cell lymphoma	CR1	65	25	30
		50	25	N/A
		45	20	N/A
Neuroblastoma		40	N/A	N/A

Table II. Survival Data for Various Diseases Following HSC Transplants (Powell, 2008).

The literature documents many personal cases of individuals treated with HSCs. Recently, in Leeds UK, Sophie Edward, an 8 year old, was found to have a rare form of leukemia, acute lymphoblastic. Chemotherapy was performed to kill cancer cells, then doctors transplanted bone marrow tissue. After 3 months Sophie fells much better (Amitava, 2009).

In 2008, a Colombian citizen became famous for her windpipe treatment. Her windpipe leading to the left lung was damaged dramatically in an accident, and 30 year old Claudia Castillo could barely breathe. In Barcelona, doctors found a donor from which a cartiledge scaffold could be taken. Researchers at the University of Bristol took HSCs from Castillo's bone

marrow and used them to coat the windpipe scaffold. The new organ was transplanted in June 2008 safely in Barcelona. The surgery went successfully, and 6 months later the world saw that she was fine and her breaths were normal. **Figure-1** shows a computer simulation of the windpipe before (left) and after (right) surgery. This case demonstrates the huge potential HSCs have for future research (Coghlan, 2008).

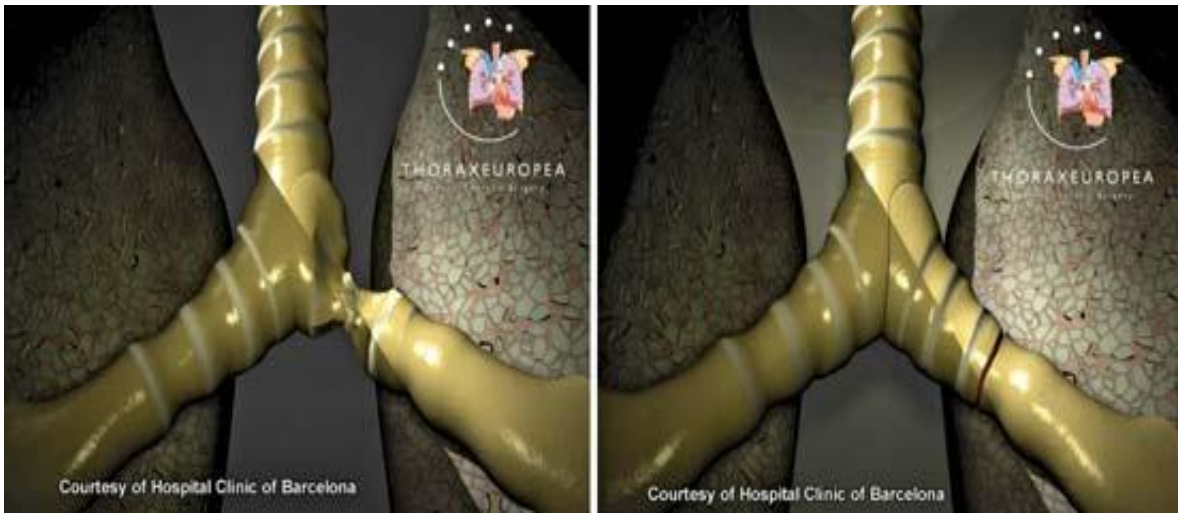

Figure 1. Computer Simulation of the Windpipe Surgery Before (left) and After (right) HSC Transplantation (Coghlan, 2008).

Stem Cell Treatment of Diabetes

Of the millions of people who suffer from diabetes, nearly 5-10% have type-1. This type of diabetes usually occurs as a result of autoimmune destruction of pancreatic islet β-cells, which normally produce insulin. The disruption of insulin production requires exogenous insulin intervention. Although some success has been achieved with islet transplants, the severe shortage of pancreas donations has caused researchers to seek alternative sources for β-cell substitution therapy.

Pluripotent embryonic stem (ES) cells have been shown to have the potential to differentiate into insulin producing cells. Animal ES cells have been shown to differentiate into insulin producing cells either *in vitro* or *in vivo*. Transplant experiments with human ES cells have not yet been performed, but human ES cells have been shown to have the potential to produce insulin. The *in vitro*-differentiated hES cells included the generation of insulin-making β-cells (Assady et al., 2005). Immunohistochemical spotting for insulin was discovered in an astonishingly high percentage of the differentiated cells. Thus, hES cells might be used in the future to treat diabetes (Assady et al., 2005).

Adult stem cells have had some success treating diabetic patients. In 2007, in the UK 15 patients with Type-1 diabetes volunteered to participate in a human clinical trial to use HSCs to treat the disease. After the injection of HSCs, the patients were able to get rid of their needles and pills to control sugar and diabetes. The successful results were fascinating to scientists all over the world, as it appeared that the HSCs had the *plasticity* to differentiate outside the blood cell lineage to produce β-like cells. One patient was completely cured. Two patients required insulin injections for an additional year, but eventually put aside pills and injections (Times Online, 2007).

Stem Cell Treatment of Damaged Heart Muscle

Heart muscle cells (cardiac myocytes) are the contractile cells of the heart, and can become damaged after a heart attack or an accident. Heart attacks leave scars in place of contractile tissue. Currently in the United States, about 5 million citizens live with damaged hearts, and each year about 400,000 new cases appear (NIH, 2009). Heart transplants have been successful in some cases, but they are expensive and donated hearts are in short supply.

Transplants using cardiac myocytes have been attempted, but the transplanted cells rarely become contractile. Thus, scientists are searching for stem cell treatments to repair wounded hearts.

In 2009, doctors with the help of scientists healed a patient's heart using his own cardiac stem cells. Kenneth Miles, a construction worker had a heart attack at age 39 on the left side of his heart. Doctors located the exact position of scars on the heart and excised them. Adult cardiac stem cells were removed from the patient's heart, cultured at Cedars Sinai Hospital, and perfused back into the patient where they became contractile (Ani, 2009).

A very interesting case happened in 2003 with 16 year old Dmitri Bonnville. He accidently shot himself in his heart when doing some home repairs. While undergoing surgery, Dmitri had several heart attacks, and some of his cardiac myocytes were damaged. Surgeons stated that heart transplantation was needed immediately to save him, but a donor was not available so doctors offered a medical treatment never done before using the patient's own bone marrow HSCs cells. They said that adult stem cells would be taken from his bone marrow (or from hormone stimulated blood) and injected into his heart to repair it. Dmitri's parents agreed, and the results were exciting, the harvested stem cells reached the damaged part of the heart and appear to have replaced the dead cells. This kind of experiment used adult HSCs without destroying an embryo, and strengthened the evidence for HSC plasticity (Philipkoski, 2003).

This approach of using a patient's own HSCs to treat heart attacks subsequently underwent a larger trial at the University of Bristol, where 60 heart attack patients received HSCs from their own bone marrow. The trial was of low risk since the grafts were autologous. In 2-3 months, most patients' hearts fully recovered and worked properly. This clinical trial was lead by Doctor Raimondo Ascione using a grant of £210,000 (Science Daily, 2007). Thus adult HSCs

have shown some clinical success in treating heart attacks. With respect to ES cells, although human ES cells have not yet been tested for heart attack treatments, they have been shown to be capable of differentiating *in vitro* into cardiac lineages (Kehat et al., 2001).

Stem Cell Treatment of Spinal Cord Injuries

With respect to treating spinal cord injuries, most of this data so far is based on animal experimentation. In 2008, approximately 300,000 people in the US had spinal cord injuries (SCI) (FSCIP, 2009). In a recent 2009 article, the US Food and Drug Administration permitted scientists to perform a clinical trial with ES cells treat 10 SCI patients (Shoute, 2009). After years of studying similar tests on rats and mice, doctors decided it was time to test the therapy on human beings. Each patient had injuries located close to the neck. The experiment is still in phase I, and no data has been reported. If everything goes well with respect to phase I safety, scientists will proceed to phase II to determine effacacy (Shoute, 2009).

Adult stem cells have also been tested for spinal cord injuries, but the results have not been published in the refereed literature yet. In Ecuador, 52 patients with SCI were injected with their own autologous bone marrow HCSs, and the outcomes were successful. Doctor Silva stated the following:

> *"*To date, we have administered BMCs into 52 patients with SCI, and have had no tumor formations, no cases of infection or increased pain, and few instances of minor adverse events. We also found that the patient quality of life improved*" (Don Margolis 2009).*

Stem Cell Treatment of Parkinson's Disease

One of the major diseases of the brain is Parkinson's disease (PD). In this disease, neurons in the *substantia nigra* area of the brain become damaged, and are unable to produce an

important neurotransmitter dopamine. Without dopamine production, patients show multiple types of muscle tremors, and difficulty initiating movements. A well known professor from UCLA, Michel L. Levesque, testified before the US Senate on a Parkinson's case that he treated using olfactory mucosal stem cells (Levesque, 2005). In 2005, at the Congress of PD and Movement Disorders in Rome, Dr. Levesque introduced the results of his 3 year experiment using autologous and derived adult stem cells:

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

Rat models of PD have been treated with adult NSCs (Studer et al., 1998). Adult neural stem cells (NSCs) are extracted from the brain and are expanded *in vitro*, then are injected back into the brain to form dopamine producing neurons. The injected cells did not form brain tumors, and produced dopamine. Rat and mouse PD models have also been treated with ES cells (Bjorklund et al., 2002; Kim et al., 2002; Ryan, 2004). For example, one experiment took place in UK in 2004 where human ESCs were injected into 10 PD mice. The outcome showed that no tumors appeared, and the neural systems improved in 12 weeks (Ryan, 2004). Human ES cells have not yet been used to treat PD patients, but have been shown *in vitro* to be capable of differentiating into dopamine producing neurons (Perrier et al., 2004).

Chapter-2 Conclusions

As can be seen in the discussions above, some types of stem cells have already been used to save human lives, while in other cases human applications remain in the future. Scientists all

over the world are trying to adapt stem cell treatments for various diseases. This chapter focused on several example applications, and attempted to distinguish animal experimentation from human trials. Successful experimental outcomes in human patients can sometimes sway the debate on stem cell ethics and legalities, which will be discussed in the next two chapters. More research is needed to adapt stem cell treatments to a greater number of diseases, and to adapt the findings from animal models to humans. Each year, new applications have saved lives under conditions where no other medical treatments help.

Chapter-2 Bibliography

Amitava (2009) Stem Cell Research Blog.
http://stemcell.taragana.net/archive/stem-cell-treatment-appears-to-be-effective-against-rare-form-of-leukaemia/

Ani (2009) Stem Cell Research Blog.
http://stemcell.taragana.net/archive/worlds-first-stem-cells-from-own-organ-used-to-treat-damaged-heart/#more-3609

Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki K, and Tzukerman M (2005) "Insulin Production by Human Embryonic Stem Cells".
http://diabetes.diabetesjournals.org/cgi/content/full/50/8/1691

Bjorklund LM, Sanchez-Pernaute R, Chung S, Andersson T, Chen IYC, McNaught KSP, Brownell AL, Jenkins BG, Wahlestedt C, Kim KS, Isacson O (2002) Embryonic Stem Cells Develop Into Functional Dopaminergic Neurons After Transplantation in a Parkinson Rat Model. *Proceedings of the National Academy of Sciences USA* **99**(4): 2344-2349.

Coghlan, Andy (2008) "Woman receives windpipe built from her stem cells". *New Scientist*.
http://www.britannica.com/EBchecked/topic-art/565211/121456/Neural-and-hematopoietic-stem-cells-have-tremendous-potential-in-the

FSCIP (2009) Spinal Cord Injury Statistics.
http://www.fscip.org/facts.htm

"Hematopoietic Stem Cells" (2005) NIH, Stem Cells, Chapter-5.
http://stemcells.nih.gov/info/scireport/PDFs/chapter5.pdf

Kehat, I, Kenyagin-Karsenti, D, Druckmann, M, Segev, H, Amit, M, Gepstein, A, Livne, E, Binah, O, Itskovitz-Eldor, J, and Gepstein, L (2001) Human Embryonic Stem Cells Can Differentiate Into Myocytes Portraying Cardiomyocytic Structural and Functional Properties. *Journal of Clinical Investigation* **108**: 407-414.

Kim JH, M J, Auerbach, Rodriguez-Gomez JA, Velasco I, Gavin D, et al (2002) Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature* **418**: 50-56.

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

Morgolis, Don (2009) Voice of Arizona.
http://www.voiceofarizona.com/Stem_Cell_Research_Helps_52_Spin-5031-4-42293.htm

NIH, U.S. Department of Health and Human Service. August 15, 2009.
http://stemcells.nih.gov/info/scireport/chapter9.asp

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.

Philipkoski, Kristen (2003) "Stem Cells Heal a Broken Heart".
http://www.wired.com/news/medtech/0,1286,57944,00.html

Powell, Jonathan (2008) Hematopoietic Stem Cell Transplantation.
http://emedicine.medscape.com/article/991032-overview

Ryan C (2004) "Stem Cell Therapy for Parkinson's". BBC News.
http://news.bbc.co.uk/1/hi/health/3853791.stm

ScienceDaily. June 25, 2007, http://www.sciencedaily.com/releases/2007/06/070621194256.htm

Shoute, Nancy (2009) U.S. News.
http://health.usnews.com/articles/health/2009/01/23/3-ways-that-stem-cells-may-speed-new-cures.html

"Stem cell" (2009) *Encyclopedia Britannica*.
http://www.britannica.com/EBchecked/topic/565211/stem-cell

Studer L, Tabar V, and Mckay RDG (1998) Transplantation of Expanded Mensencephalic Precursors Leads to Recovery in Parkinsonian Rats. *Nature Neuroscience* **1**: 290-295.

Times Online (2007) "Diabetics Cured in Stem Cell Treatment".
http://www.timesonline.co.uk/tol/life_and_style/health/article1637528.ece

CHAPTER 3: STEM CELL ETHICS

Batuhan Gizer

In the previous chapters we discussed various stem cell types, their potencies, and how they have been used in animal models and some human studies to cure or prevent some of the deadliest illnesses. In this chapter, we will discuss the topic of whether we *should* work with stem cells, explaining the ethics surrounding stem cells. As not all stem cells are alike, each type has different ethics to apply. With respect to embryonic stem (ES) cells, because their acquisition usually destroys an embryo, a discussion of their ethics usually focuses on when life begins. This chapter will investigate various religious stances on this topic.

Adult Stem Cell Ethics

Adult stem cells (ASC's) are the stem cell type with the fewest ethical considerations, because no embryo is destroyed to obtain them. In fact, none of the five major world religions is against working with ASCs. Even the conservative Catholic church, which is strongly against working with ES cells, is in favor of ASCs (American Catholic Organization, 2006; Pope Benedict XVI, 2007). The other major world religions, Islam, Judaism, Hinduism, and Buddhism, also do not have any problems with ACS research, especially if human lives can be saved. In fact, most religions go beyond merely allowing ASC research, and actually strongly support it as an alternative to destroying embryos in ES cell research. "Perhaps research using stem cells derived from adults will eventually prove to be most promising. We should encourage further research on the use of adult stem cells, to the point where it will be unnecessary to use embryos for this purpose. Specifically, we should find better ways to isolate existing stem cells

in the human body" (Kutty and Siddiqi, 2007). However, as explained in the previous chapters, ASC's are not as medically promising as ES cells because they are very rare in the body, difficult to isolate, and hard to grow in culture, so most scientists keep pushing to allow federal funding for ES cell research.

Embryonic Stem Cell Ethics

All religions in the world value human life, and believe that human life is very precious. Even before the current discussions for embryonic stem cell research, public debates occurred on topics such as the fate of surplus *in vitro* fertilization (IVF) embryos, and the destruction of an embryo in the womb for abortion. Thus, debates about human embryos have been in the picture since the early 1970's with the advent of IVF clinics (Edwards, 2001). Because obtaining ES cells usually destroys an embryo, the debate focuses on when life begins. If life is considered to start at conception, isolating ES cells from a 5-day old blastocyst is considered to be murder, however if a religion argues life begins at day 40 (or thereafter), early embryos do not have the same moral status as an adult, and can be used to obtain ES cells.

Catholic Point of View on ES Cells

The strong opposition of the Catholic church to embryo destruction is well known. On July 23, 2001, Pope John Paul II, strongly condemned ES cell research, with the following words to then U.S. President George W. Bush: "Experience is already showing how a tragic coarsening of conscience accompanies the assault on innocent human life in the womb, leading to accommodation and acquiescence in the face of other related evils such as euthanasia, infanticide and, most recently, proposals for the creation for research purposes of human embryos, destined

to be destroyed in the process" (Pope John Paul II, 2001). And as subsequently stated by Pope Benedict: human embryonic stem cell research, artificial insemination, and the possibility of human cloning have "shattered the barriers meant to protect human dignity",… Benedict said the Roman Catholic Church wants scientific progress to be based on "ethical-moral principles," including respect for human beings "from *conception* until natural death" (Pope Benedict XVI, 2007). And Pope Benedict went further to state that he church "appreciates and encourages" stem cell research that does not involve the destruction of a human embryo" (Pope Benedict XVI, 2007).

Outside the Catholic church, several other Christian denominations are in favor of ES cell research. For example the American Presbyterian Church believes that ES cell research is ethical if it results in new medical therapies (Teaching About Religion, 2006), and the Episcopal church believes life begins 14 days post-fertilization when the primitive streak begins to form the spinal cord (Kohsl, 2008).

Judaism Point of View on ES Cells

Jewish law attests that life does not begin at conception, but once the fetus has the means to become a *viable* embryo, which is usually considered around day 40. Therefore Jewish law has no opposition to harvesting early day-5 embryos for research (Dorff, 2001).

Islamic Point of View on ES Cells

Islamic belief is based upon "divine and immutable revelation", the main authority of Muslims known as the Qur'an, and none of the Islamic literature indicates any opposition against ES cell research, as long as it is used to better humanity (Weckerly, 2002). Shari'ah is a way of

life for Muslims, interpreted from the Qur'an, indicating the laws and the necessities of Islam to influence their actions and thoughts. The Qur'an indicates that God creates life, and the time is given in the Qur'an as 120 days, life occurs "first as a drop of matter in forty days, then as a blood clot for forty days, then as a blob for forty days, and then the angel is sent to breathe life into him" (Weckerly, 2002). We can clearly see from these words that a 5 day blastocyst from which ES cells are obtained, are not considered as a human being yet since it is younger than 120 days.

In addition, the Shari'ah dictates that there should be a distinction between *potential* and *actual* life. Although it is believed that an embryo has the *potential* to grow into a human being, it is not an actual human, and instead of destroying excess embryos taken from IVF clinics, those embryos should be used to help better the conditions of *actual* life (Siddiqi, 2002). Thus, the main difference between the Islamic and Christian perspectives on stem cells is when life begins, and when the embryo has potential not actual life.

Buddhist Point of View on ES Cells

Buddhists believe that three things are necessary to begin a human life. First, a woman's egg is required to form an embryo. Second, a man's sperm must fertilize the woman's egg. And lastly, "consciousness of being ready for rebirth" is required for the rebirth of a human being, explained as karma-energy or a soul (Mahathera, 1994). So if consciousness occurs at conception, a 5-day embryo is living. And Buddhism also is against *in vitro* fertilization, because it is believed that an artificial process is against the nature of humanity. ES cell research is prohibited because Buddhists believe that any action related to *harm* is immoral, hence it should be forbidden. "Rebirth" of a human being can be the rebirth of an old karma-energy, or

soul, or an embryo can be a new soul, therefore it should be considered and treated as a human (Chamany, 2004).

Parthenote Ethics

Due to the strong opposition by many people against ES cells, scientists are looking for new ways to derive ES cells without destroying an embryo. The parthenote technique is one of these new ways that does not kill a viable embryo yet is able to retrieve ES cell lines. Parthenogenesis, or virgin birth, is used by some insect species such as bees and ants to produce worker animals. In this case the new worker bees or ants grow from non-fertilized eggs stimulated to divide by a female. Human parthenote embryos were first produced in 2001 (Cibelli et al., 2001), by treating donated eggs with chemicals (such as strontium chloride) to stimulate egg division without chromosome loss. No sperm is used in the process. However, human parthenote embryos cannot develop into a human due to the lack of paternal DNA, but are able to form "embryo-like" entities (Latkovic, 2006). If the embryo can be grown to the blastocyst stage, ES cells could be isolated to make an ES cell line, without destroying a viable embryo. However, using this process still requires human egg donations, and it is not clear whether human parthenote ES cells will prove as potent as normal ES cells.

Parthenote ethics focuses on the status of an embryo that cannot form a human. Some people argue that it cannot be defined as a normal embryo since the process does not involve a human sperm, which in my opinion is a valid point. Some religions claim that using parthenotes is still immoral. Some Catholics are against it because the embryo may still have the potential to make life, we just haven't figured out how to do so yet, and it still involves the destruction of a human egg. Buddhists oppose the idea because they believe fertilization should be natural, and

should not involve any chemical substance (Kiessling, 2005).

iPS Cell Ethics

iPS cells are induced pluripotent cells obtained from skin fibroblast cells by treating them with a mixture of transcription factors to induce de-differentiation to an ES cell like state (Takahashi et al., 2007). No embryo is destroyed in the process, and the ES cell line is genetically identical to the patient the skin cells were obtained from, so the ES cells will not be immuno-rejected during transplant back into the same patient. This topic is the hottest topic in all of stem cell biology today, as these cells could potentially replace ES cells derived from embryos if iPS cells are shown to be as potent as ES cells.

Chapter-3 Conclusions

As shown in this chapter, Catholics and Buddhists oppose ES cell research since it is believed that killing a 5-day old embryo constitutes murder, but Muslims and Jews do not since it is believed that life starts at day forty, well after the period of time when blastocysts is retrieved. All major world religions support adult stem cell research. Since ES cell research is highly controversial, scientists are constantly researching new ways to derive ES cell lines without harming or using an embryo, such as iPS cells. I believe that ES cell research should be federally funded and expanded, because I believe that an embryo can help save hundreds of thousands of lives. Excess IVF embryos slated for destruction should be used with donor consent to derive new ES cell lines. Although adult stem cells can be helpful, they are not as medically promising as ES cells. The research should be carefully controlled to prevent unethical use of paid egg donors, and to ensure only excess IVF embryos originally created for

reproduction are used. I do not believe that paid egg donors should be allowed because this might harm innocent people if others forced them to do so in order to be paid. This occurs rather frequent in third world countries that are not economically strong. If paid egg donors are allowed, in my opinion, they should be controlled and protected. In our world, organ donations are insufficient to save the lives of thousands of patients awaiting transplants, so ES cells could in theory alleviate the shortage of transplant tissues.

Chapter-3 Bibliography

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

Chamany K (2004) Stem Cell Primer. Retrieved Aug 15, 2008, from http://www.garlandscience.com/textbooks/cbl/pdflibrary/stemcells_primer.pdf

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.

Dorff, Elliot (2001) "Embryonic Stem Cell Research: the Jewish Perspective." *United Synagogue of Conservative Judaism*. Dec. 2001. University of Judaism in Los Angeles. http://www.uscj.org/Embryonic_Stem_Cell_5809.html.

Edwards RG (2001) *In Vitro* Fertilization and the History of Stem Cells. *Nature* **413**: 349-351.
Kiessling Ann (2005) Human Parthenotes: An Ethical Source of Stem Cells for Therapies? *Nature* **434**: 145.

Kohsl, Arthur (2008) "Survey of Religious Bodies' View Concerning Human Embryonic Stem Cell Research in the US." *Arthkohsl*. 14 Jan. 2008. http://arthkohsl.blogspot.com/2008/01/survey-of-religious-bodies-view.html

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

Latkovic, Mark S (2006) "The Science and Ethics of Parthenogenesis: Are We Dealing with a Human Being? A Catholic Perspective" http://www.aodonline.org/AODonline-sqlimages/SHMS/Faculty/LatkovicMark/Bioethics/TheEthicsofParth.pdf

Mahathera, N (1994) Fundamentals of Buddhism - Four Lectures. (Free Distribution No. 394/396). Kandy, Sri Lanka: Buddhist Publication Society. http://www.accesstoinsight.org/lib/authors/nyanatiloka/wheel394.pdf

Pope John Paul II (2001, Jan 23) A crisis of values. [Electronic version]. *CNN.Com*, Retrieved Feb 16, 2008 from http://archives.cnn.com/2001/WORLD/europe/07/23/bush.pope/ http://www.medicalnewstoday.com/articles/96123.php

Pope Benedict XVI (2007) "Benedict endorses adult stem-cell research as respecting human life". Catholic Online. http://www.catholic.org/international/international_story.php?id=21301

Siddiqi, Muzammil (2002) "An Islamic Perspective on Stem Cell Research." IslamiCity.com. 27 Feb. 2002. IslamiCity. http://www.islamicity.com/articles/Articles.asp?ref=IC0202-404

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.

Teaching About Religion (2006) "General Positions on Stem Cell Research and When Personhood Begins". 18 Mar. 2006. Instructional Systems. http://www.teachingaboutreligion.org/WhatsNew/Stem_cell_research.htm

Weckerly M (2002) The Islamic View on Stem Cell Research. *Rutgers Journal of Law and Religion.* http://org.law.rutgers.edu/publications/law-religion/new_devs/RJLR_ND_56.pdf

CHAPTER-4: STEM CELL LEGALITIES

Anvar Niyetkaliyev

Nowadays it would be hard to find a more controversial topic than stem cells. As discussed in previous chapters, although adult stem cells (ASCs) have relatively few ethical issues, as obtaining them does not use an embryo, embryonic stem (ES) cells are far easier to isolate, can be grown to large quantities *in vitro*, and are far more potent for repairing a variety of tissues. Scientists have already proven several applications for stem cells in saving lives, but more research needs to be performed to expand the number of diseases that can be treated with this new technology. And this takes money. Typical of controversial scientific discoveries, laws have been enacted to regulate this new science. The purpose of this chapter is to discuss past and current US and international stem laws, as an example of the effects of technology on society.

U.S. Federal Stem Cell Laws

Within the US, stem cells laws have varied over the years, depending on which President is in office. Usually laws change when a new President is elected in January every four years. From one President of the United States to another, the regulations governing stem cell research have changed dramatically.

President Clinton Stem Cell Policies

Former President Clinton was a strong advocate for stem cell research. In 1993, Congress and President Clinton gave direct authority to the National Institute of Health (NIH) to fund human embryo research for the first time. NIH established a multi-background panel to

investigate stem cell ethics, which made a recommendation to use excess IVF embryos (normally discarded with parental consent) to derive new ES cell lines. However, within a year, opponents lobbied congress to pass the now famous *Dickey-Wicker Amendment* which banned federal funding to create or destroy any human embryo (Stem Cell Laws, 2005).

In January 1999, Harriet Rabb of the Department of Health and Human Services (HHS) released a legal opinion that ES cells are not embryos, so the *Dickey-Wicker Amendment* should not apply to those cells. In response to the amendment, in August 2000, the NIH published guidelines recommending federal funding only for research on *previously* derived ES cells (Dunn, 2005). President Clinton quickly endorsed the guidelines to become the first administration to fund ES cell research.

President Bush Stem Cell Policies

In 2001, in his State of the Union Address, newly elected President Bush laid out his views on embryo research, recommending that Congress pass legislation prohibiting all embryo research, and telling NIH to cancel all new federal applications on that topic (Agnew, 2003). On August 9th, 2001, Bush announced he would allow federally funded research only on human ES cell lines derived prior to that date (Stem Cell Laws, 2005). Scientists rushed to determine how many ES cell lines they could work with, and came to realize the initial high numbers were a vast overestimate, as subsequent research showed the majority of the lines died or were non functional. The actual number of useful ES cell lines has varied tremendously depending on the source of information, but one source estimated that out of an original guess of 71 eligible lines, only four were immortal, a number which most scientists agree is far too low to support a

serious research effort (Holden, 2009). Other references have the numbers as 60 total and 9 functional cell lines (Agnew, 2003).

In 2002, Bush created his own Council of Bioethics to provide advice on embryo research, choosing on purpose not to use any well-established scientific organizations, such as the NIH, National Academy of Sciences, or the American Society for Bioethics and Humanities. In April 2004, 206 members of the House of Representatives signed a letter explaining the need to expand the number of ES cell lines, and in June, 58 Senators sent Bush a similar letter, but Bush's position did not change. Bush would later veto any attempt by Congress to overturn his restrictions.

Throughout the Bush administration, debates often focused on the term "cloning", but this term was vastly misunderstood by the public. Most opponents viewed "cloning" as *reproductive* cloning, in which a complete organism genetically identical to another is produced. This process has scientifically only been achieved with animals (such as Dolly the sheep), involves the use of somatic cell nuclear transfer (SCNT), and remains outlawed to this day in all countries who bother to pass embryo legislations. Therapeutic cloning, involves the use of SCNT to create a blastocyst to derive new ES cell lines for treating the same patient that the skin cell nucleus came from. This process has also been achieved with animals, but not yet with human cells. Note that the derivation of ES cells from IVF embryos does not involve any SCNT (Angew, 2003). Under the Bush administration with its tight stem cell policies compared to other developed countries, some scientists argued that unless the ban was soon over turned, US research would suffer.

President Obama Stem Cell Policies

On March 9, 2009, newly elected President Barack Obama, acting on a new set of NIH guidelines (Mahumder and Cohen, 2009; Holden, 2009), over turned the *Dickey-Wicker Amendment* and Bush's 2001 stem cell policy, to create a new stem cell policy that allows federal funding to support embryo research, so long as the embryos are provided by IVF clinics originally created for reproductive purposes, and with donor consent, and no money can be paid for egg donors. Obama stated:

> "*Research involving human embryonic stem cells and human non-embryonic stem cells has the potential to lead to better understanding and treatment of many disabling diseases and conditions. Advances over the past decade in this promising scientific field have been encouraging, leading to broad agreement in the scientific community that the research should be supported by Federal funds. For the past 8 years, the authority of the Department of Health and Human Services, including the National Institutes of Health (NIH), to fund and conduct human embryonic stem cell research has been limited by Presidential actions. The purpose of this order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind."* (National Archives and Records Administration, 2009)

The NIH Guidelines underwent considerable deliberations before their final approval in 2009. The use of IVF embryos allows significantly more ES cell lines to be derived, without resorting to the more controversial method of paid egg donors. The informed consent applies to fertilized embryo donors, not to individual gamete (sperm or egg) donors. Much effort focused on whether to "grandfather in" old ES cell lines, with the final recommendation being no grandfathering, and instead *any* ES cell line must be individually approved by NIH, including any ES cell lines previously approved by the Bush administration. The NIH guidelines do not

allow the use of embryos created for research purposes, such as SCNT or parthenogenesis, which was a disappointment for some scientists including Kevin Eggan of Harvard University, but overall, it seems that researchers are happy with the newly established rules and are ready for new progress in stem cell research George Daley, a stem cell researcher at Harvard University, described the new rules as "a major step in the right direction for stem cell research" (Holden, 2009).

Although most scientists are happy with the new guidelines, some argue that the guidelines from the National Academy of Science (NAS) (**Table I**) should have been the gold standard for the conduct of stem cell research in the country (Mahumder and Cohen, 2009).

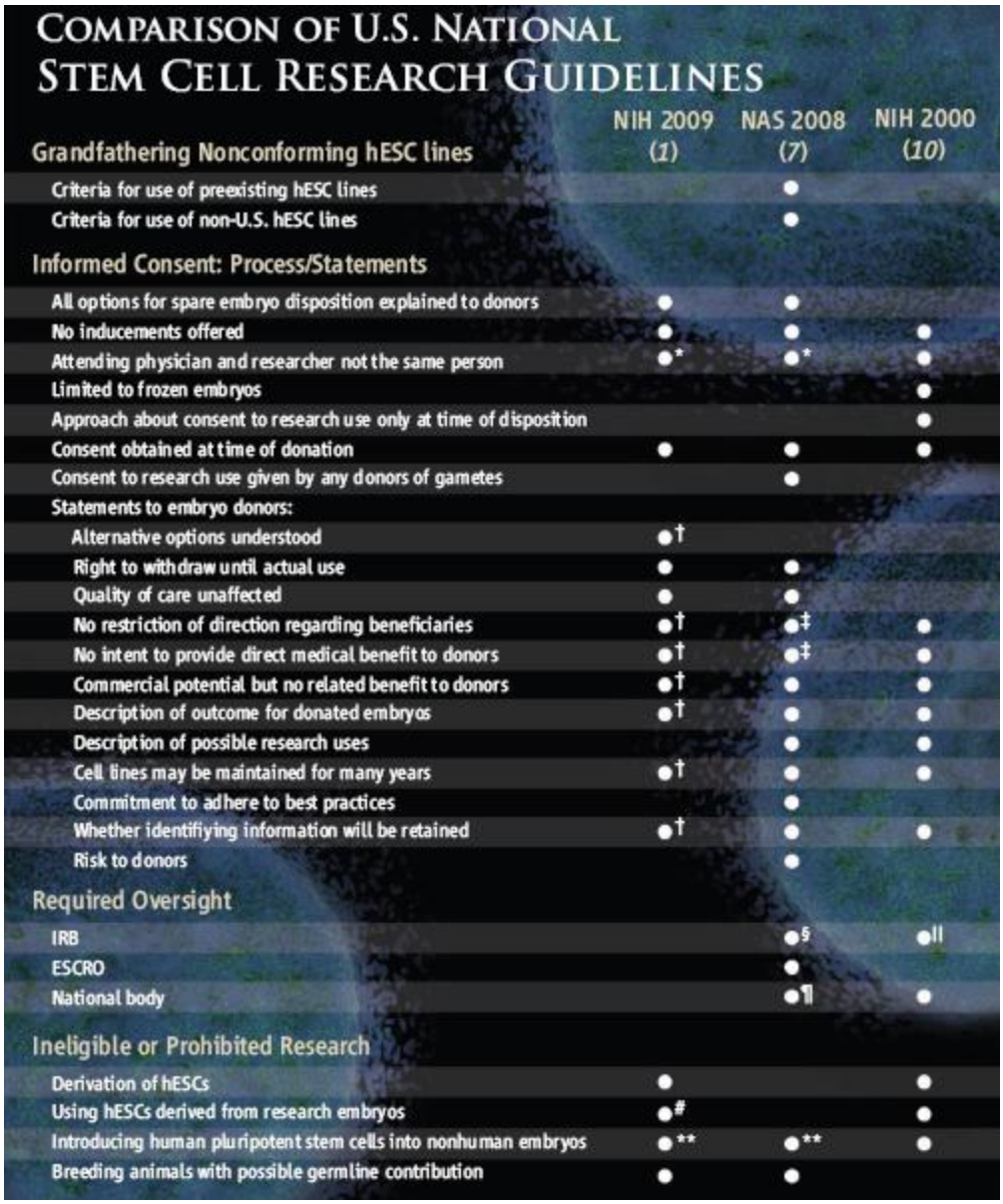

Table I. A Comparison of NIH and National Academy of Sciences Stem Cell Guidelines. *(Mahumder and Cohen, 2009)*

Some scientists feel the new guidelines are too conservative, and efforts should be made to expand the use of egg donors. The International Society for Stem Cell Research (ISSR) urged NIH to begin "open discussions on funding research carried out with human pluripotent stem cell lines derived from sources *other* than excess reproductive IVF embryos" (Holden, 2009).

U.S. State Stem Cell Laws

In the US, individual states can provide their own funding for stem cell research, even when federal funding is not allowed. State policies were especially of strong importance under the Bush administration 2001 ban of federal funding. Some states such as Illinois and South Dakota completely prohibit embryo research for any reason, while other states like New Jersey and California not only permit scientists and institutions to work on ES cells, they also create huge funds to support the research.

After the 2001 ban on federal funding, six states encouraged support by providing much needed funds: California, New York, New Jersey, Massachusetts, Virginia, and Illinois. Other states have various laws, for example Pennsylvania state law prohibits experiments on fetuses and embryos, and in North Dakota it is illegal to use SCNT (Stem Cell Legislation, 2005). Over the years, other states have even changed their views and have started to fund the research.

The first two states that took a big step in supporting stem cell research were New Jersey and California. In November 2004, California voted to approve a fund of $ 3 billion dollars for stem cell research and to create the California Institute of Regenerative Medicine (CIRM). $622 million has already been issued for 2008 and 2009. Due to delays in California with the funding, New Jersey was actually the first state to fund stem cell research, creating the New Jersey Stem Cell Institute. The state supports 17 institutions with $23 million in 2005 and 2006.

With respect to other states, Connecticut has passed a bill in 2005 providing $10 million over several years. The Illinois governor, looking at improvements in biomedicine in other states, decided to fund the Illinois Regenerative Medicine Institute with $10 million for research. In two years a new bill has passed saying that the research is permitted on any of stem cells.

Indiana legislators approved funding to hire stem cell instructors. Maryland has followed its neighbors and approved legislature to open the Maryland Stem Cell Research (NCSL, 2008).

International Stem Cell Laws

Although the study of embryonic stem cells is a very important area in biomedicine, nations across the world have completely different laws and regulations on ES cell research. International policies range from progressive (Sweden, England, China, Australia), moderate (US, Canada), to non-existent (Italy, Germany, France, Saudi Arabia). The author of this chapter believes that Sweden, UK, China and Canada are the most committed to supporting stem cell research. The stem cell policies from some example countries will be discussed below.

Sweden

In 2002, Sweden was a leader in stem cell research because it established a Stem Cell Bank with $1 million and already had 9 institutions performing stem cell research with about 300 research groups. Sweden had advantages over other leading countries such as support of the public, committed scientists, and sufficient funding from the government. Also Sweden has enormous experience with ES cells; Professor Patrick Brundin has used ES cells for over 15 years to treat patients with Parkinson's disease (Sweden's Stem Cells Success, 2002).

The European Union

The European Union has provided a proposal for funding ES cell research for European countries with a budget of $64.3 billion for the years 2007-2013. However, this proposal has

created disagreement between EU nations because each has different regulations. Germany and several other EU countries are against all embryo research, and worry only those countries that support embryo research would receive any of the funding. In 2006, the German research minister Annette Schavan stated that "the European Union science program should not be used to give financial incentives to kill embryos" (Deutsche Welle, 2006).

South Korea

For South Korea, research on stem cells is a key for their future. In 2005, Korean researcher Hwang was the first to claim success preparing human ES cell lines by SCNT (Hwang et al., 2005), one of the holy grails of stem cell research, because that technique would allow ES cells to be prepared that are genetically identical to a patient, however that paper was subsequently retracted for fraud. But the Koreans are still world class in embryo research, and have progressive policies that allow SCNT and paid egg donors. In 2005, Korea approved a stem cell bank that will provide researchers worldwide with ES stem cell lines. During the Bush administration ban on federal funding, the Korean lines were a huge benefit for U.S scientists (Kaplan, 2005).

Chapter-4 Conclusion

Although stem cells have the potential to save countless lives from various diseases, scientists willing to research these cells are not enough, governments should support this research and enact laws to legalize embryo research. This chapter demonstrates that stem cell laws vary greatly internationally, and people's attitudes towards stem cells change regularly. With the support of nations, brilliant scientists, federal funds, and proper laws, the goal of saving human lives using stem cells can be reached.

Chapter-4 Bibliography

Agnew B (2003) "The Politics of Stem Cells." 21 Feb. 2003.
http://www.genomenewsnetwork.org/articles/02_03/stem.shtml

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

Holden, Constance (2009) Researchers Generally Happy With Final Stem Cell Rules, *Science* **325**: p. 131.

Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, et al (2005) Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science,* **308**(5729): 1777-1783.

Kaplan, Karen (2005) "South Korea to Sponsor Worldwide Stem-Cell Bank". *Los Angeles Times*, October 19, 2005. http://www.postgazette.com/pg/05292/590900.stm

Mahumder MA, and Cohen CB (2009) The NIH Draft Guidelines On Human Stem Cell Research, *Science* **324**: p. 1648

National Archives and Records Administration
http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf

NCSL (2008) "Embryonic and Fetal Research Laws". National Conference on State Legislatures. January, 2008.
http://www.ncsl.org/IssuesResearch/Health/EmbryonicandFetalResearchLaws/tabid/14413/Default.aspx

Stem Cell Laws (2005) Thinkquest.org
http://library.thinkquest.org/04oct/00053/ab_laws.html

Stem Cell Legislation in the U.S. by State (2005) *The Washington Post.*
http://www.washingtonpost.com/wp-dyn/content/custom/2005/08/12/CU2005081200827.html

Sweden's Stem Cell Success (2002)
http://www.geocities.com/giantfideli/CellNEWS_Swedens_stem_cell_success.html

PROJECT CONCLUSIONS

Due to the very strong medical potential of using embryonic stem (ES) cells, we think that scientists and doctors should continue to work with these cells to achieve their fullest benefits to society. Based on our research, this new technology is quite promising, and with proper regulations to tightly govern embryo donors, ES cells can save thousands of human lives. We support the idea that the blastula being destroyed to obtain ES cells has less moral status than the thousands of "fully individualized" adult and children lives that would be saved. Adult stem cells (ASCs) should be used whenever possible as an alternative source to ES cells, because they have already been shown to cure some types of injuries and illnesses, but we agree that ASCs may not work for all diseases. All 5 major world religions support the use of ASCs. When deriving new ES cell lines, we agree with the progressive legislations in countries such as Sweden and South Korea, that allow egg donors to be paid. In the U.S., Obama's recent change in the government policies to allow federal funding of ES cell research should positively impact the field of stem cells. We conclude that more research should be performed to help expand the list of treatable diseases using stem cell technology.