August 2010

STEM CELLS AND SOCIETY

Alexander Jonathan Sterling
Worcester Polytechnic Institute

Gregory Kilcoyne Voyta
Worcester Polytechnic Institute

IQP-43-DSA-2169
IQP-43-DSA-6533

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:

_____ _____

Alexander Sterling Gregory Voyta

August 27, 2010

APPROVED:

_____

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

ABSTRACT

The purpose of this project is to gain an understanding about the controversial topic of stem cells as an example of the impact of technology on society. The first chapter describes the types and classifications of stem cells, and chapter-2 focuses on their benefits to society. Chapter-3 goes beyond the technology to discuss ethical concerns surrounding the use of stem cells, while chapter 4 describes their legal issues. The authors provide their own conclusions based on the project research.

TABLE OF CONTENTS

PROJECT OBJECTIVES

This IQP explored and examined the controversial topic of stem cells and their impact on society. The purpose of chapter-1 is to convince the reader that stem cells are not all alike, so it describes a variety of different types of stem cells, how they are classified, their potencies, and their sources. Chapter-2 discusses a variety of experiments and treatments performed with stem cells, as examples of their benefits to society. In Chapter-3, the ethical concerns of using various types of stem cells were investigated. Chapter-4 examines the laws enacted by the United States and internationally to govern stem cell usage. Lastly, based on their research, the authors provide their own conclusions on the use of stem cells and their laws.

CHAPTER-1: STEM CELL TYPES

Alexander Sterling

Stem cells are a special type of cell that is relatively long lived and is capable of regenerating tissues. Because of these properties, stem cells are the basis of the new field of regenerative medicine. However, not all stem cells are alike. Some types of stem cells destroy an embryo to obtain them, so are ethically controversial. But not all types of stem cells destroy embryos. The purpose of this chapter is to describe the various types of stem cells, as an introduction to later chapters on their uses, ethics, and legalities.

Embryonic Stem Cells

Embryonic stem (ES) cells are probably the most well known type of stem cell. Mouse ES cells were first isolated in 1981 by Gail Martin, who cultured early embryos in media containing growth factors from teratomas (Martin, 1981). Human ES cells were first isolated and grown in the late 1990's by two independent labs who designed *in vitro* co-culture systems for feeding the ES cells (Thompson et al., 1998; Shamblott et al., 1999). ES cells are obtained from *in vitro* fertilized (IVF) embryos (**Figure-1**). Newly fertilized eggs (diagram upper left) are grown about 5 days to the blastocyst stage (diagram upper right), where the cells have formed into a ball containing three structures, the trophoblast, blastocoel, and inner cell mass. The trophoblast is the outer most layer of cells that surrounds the blastocoel which is a void in the mass of cells. The inner cell mass is a group of cells located inside the ball that are segregated to one area, these are the ES cells. When these cells are removed from the blastocyst, this usually destroys the embryo.

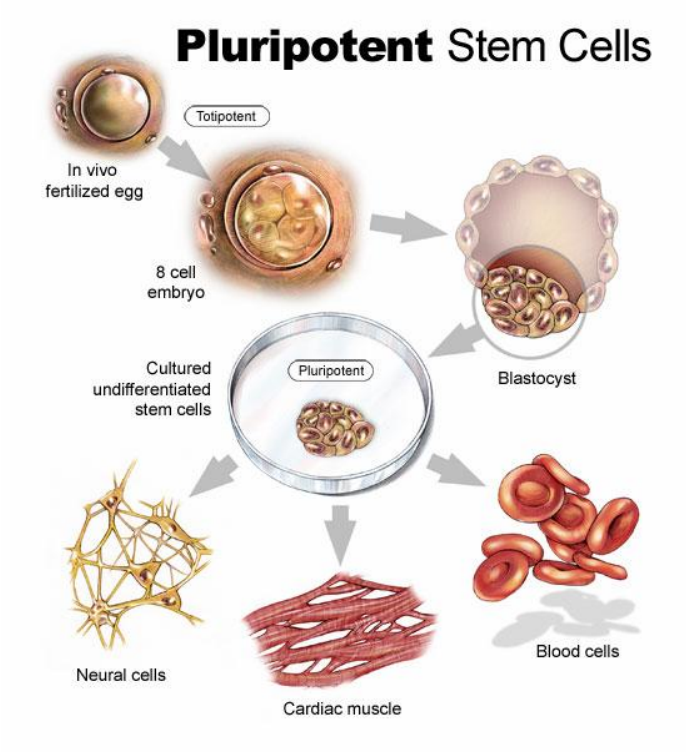


Figure-1: Diagram of the Derivation of Embryonic Stem Cells. The newly fertilized egg (upper left) is grown about 5 days to the blastocyst (upper right), in which ES cells reside. The ES cells can be grown *in vitro* (usually as a co-culture) (diagram center), and can be differentiated into a variety of tissues (diagram lower). (Hyscience.com, 2010)

ES cells are *pluripotent*. Potency refers to the ability of a stem cell to differentiate into other types of cells. There are many different levels of potency in cells. Newly fertilized embryos up to about the 8 cell stage are considered *totipotent*, and can produce all of the different types of cells in the body plus the extra embryonic tissues such as the placenta. ES cells are pluripotent, and have the ability to become any cell in the body. The next level of potency is known as *mulitpotent*. This is when a cell can give rise to numerous, but restricted, lineages. For example a hemocytoblast can differentiate into different types of blood cells, but cannot become a liver cell or a skin cell. *Unipotent* cells can only become one kind of cell, usually the same type of cell representing the tissue the unipotent stem cell resides in.

Tests can be performed to determine how potent a stem cell is. One test is to permit a portion of the stem cells to spontaneously differentiate (NIH.gov, 2006). If the cells become a cell type that is also known to further differentiate, then the original cells have a high level of potency. Researchers can also influence the stem cells to differentiate down a specific pathway. If the differentiated cells show characteristics of the three germ layers, they are considered ES cells. A third test that can be preformed is to inject the stem cells into a mouse that has a suppressed immune system and see if a teratoma or benign tumor forms (NIH.gov, 2006). ES cells are capable of forming teratomas.

ES cells are long lived and can be grown *in vitro*. This growth allows the cells to be expanded, and represents an important property for their medical uses. ES cell batches are usually grown for many months to allow researchers to examine the cells to see if they are growing correctly and normally. ES cells produce key transcription factors which help them maintain their de-differentiated state during growth. Nanog and Oct 4 are two key factors with this purpose, and these factors are also used to induce iPS cells (discussed below). Grown ES cells can also have their chromosomes checked by microscopy for any obvious mutations or irregularities.

The major excitement around ES cells is their potential to cure diseases. Since they have the distinctive ability to transform into any cell type in the body, they might be used to replace or repair almost any damaged areas of the body. A primary example of this is the treatment of diabetes, a condition that occurs when islet cells in the pancreas stop making insulin. Insulin normalizes the glucose and energy metabolism in the body. As discussed in Chapter-2, ES cells have already been shown to be capable of differentiating into insulin producing cells, and have been used to treat mouse models of diabetes.

Induced Pluripotent Stem Cells

One of the most exciting discoveries in the past few years is the ability to form embryonic stem cell-like pluripotent cells from de-differentiated adult cells. These cells are known as induced pluripotent (iPS) cells (**Figure-2**). Human iPS cells were first discovered in 2007 by Yamanaka's group in Japan, who showed that pluripotent cells could be derived from facial skin fibroblast cells (diagram upper center) transfected with a combination of four transcription factors (blue in the diagram) (Oct4, Sox2, c-Myc, Klf-4) that help induce de-differentiation (Takahashi et al., 2007). The iPS cells are able to form ectoderm, mesoderm, and endodermal type cells (diagram lower). Even though iPS cells appear to be able to differentiate into most cell types, at this time it is unclear whether they truly have the same potential as ES cells. In mice, iPS cells have been used to create whole new mice, so these iPS appear to have true ES-like properties (Boland et al., 2009). But other reports have shown that iPS cells grow slower and are less robust than ES cells (Dolgin, 2010).

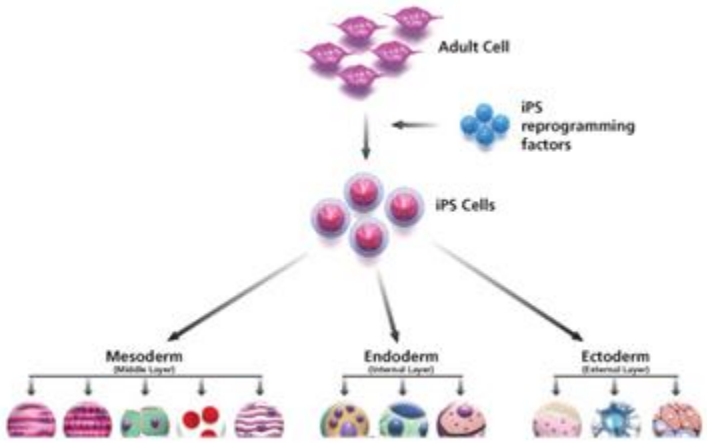


Figure-2: The Formation of iPS Cells from Skin Fibroblasts. Adult facial skin fibroblast cells (upper diagram) are transfected with a combination of genes encoding transcription factors (diagram right, blue) that help induce a de-differentiated state (diagram center). The iPS cells can be grown and differentiated to form the three main embryonic tissues (diagram lower). (SigmaAldrich.com, 2010)

Since the original 2007 discovery of human iPS cells, the procedure for inducing iPS cells has been modified to omit one of the original transcrtiption factors (c-myc), an oncogene that induced tumors when the iPS cells were implanted into mice (Kim et al., 2008). And the original virus method for delivering the transcription factor genes has been replaced by directly delivering the transcription factor proteins themselves into the cells (Yu et al., 2009). One of the biggest potential benefits of using iPS cells for therapy is that because they are derived from the donor, they are genetically identical to the recipient, so there is less chance for the new cells to be rejected by the body. More testing will be required before human trials can begin.

Parthenogenic Stem Cells

Parthenogenesis is a special process by which an egg is fertilized without the use of a sperm. In nature, this process is used especially in insects to produce worker ants and bees. But the process does not normally occur in mammals, so chemicals such as strontium chloride or elecrical stimuli are used to induce the process. The process blocks the normal expulsion of a set of chromosomes from the egg to produce an embryo with a normal number of chromosomes, but no father (**Figure-3**). In April of 2004, the first fatherless mouse was created in the Tokyo University of Agriculture (Kono et al., 2004). It is doubtful that artificial human parthenogenesis will ever be used to reproduce entire human beings, but parthenogenesis could be used to create embryos that can live long enough to make blastocysts from which ES cells can be derived.

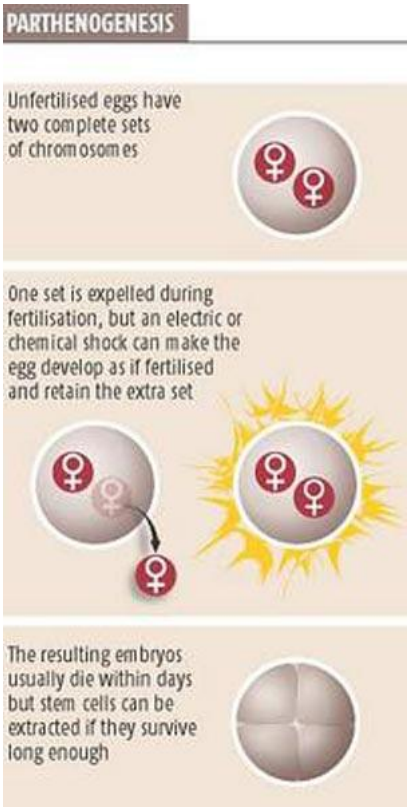


Figure-3: The Formation of Mammalian Partnenotes. Chemicals or electrical stimuli are used to prevent the expulsion of one set of chromosomes from an unfertilized egg (diagram center) producing an embryo with a normal number of chrosomes (lower diagram) but no father. (Parthenogenesis, 2007)

Monkey parthenote embryos were first created in 2001 (Cibelli et al., 2001), and were used in 2007 to derive monkey ES cells (Kim et al., 2007). However, in monkeys and mice the induction of parthenogenesis frequently results in irregular development. The reason for this is that mammals have imprinted genetic regions in their chromosomes. In the case of mammalian parthenogenesis, the embryo would have twice the amount of maternally imprinted genes and no paternally imprinted genes. So mammalian parthenote embryos do not survive long enough to produce adult animals. But they can survive long enough to produce a 5 day old blastocyst from which ES cells can be isolated. If these parthenote ES cells prove to be pluripotent, they could

replace the use of fertilized embryos to derive ES cells. On June 26, 2007, the International Stem Cell Corporation (ISCC), a stem cell research company based in California, stated that they created *human* stem cells via parthenogenesis (Liebertonline.com, 2007). This breakthrough may lead to a treatment for degenerative diseases, but because the ES cells would be identical to the woman providing the egg, only that patient could be treated. The process cannot be duplicated with sperm.

Adult Stem Cells

Adult stem cells (ASCs) are a broad category of stem cells that includes almost any type of stem cell not isolated from an embryo. This category includes any type of stem cell isolated from an adult organism or from umbilical cord blood. Similar to ES cells, they can replicate and differentiate into tissues. But unlike ES cells, they are hard to isolate, hard to grow, and have less differentiation potential. They are ethically more desirable because embryos are not destroyed to obtain them. Some types of ASCs are multipotent, such as mesenchymal stem cells (MSCs) or hematopoietic stem cells (HScs), but most ASCs are unipotent (**Figure-4**). Generally adult tissues create an intermediary cell type prior to producing the completely differentiated state. These intermediary cell stages are known as precursor or *progenitor* cells. The precursor cells in adult tissues are less differentiated than ES cells, but can divide and yield differentiated cells. These types of cells are generally considered as "committed" to being differentiated down a specific cellular development pathway.

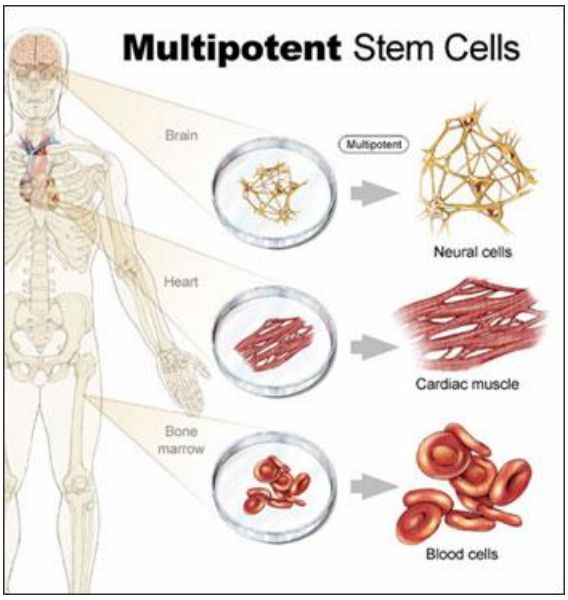


Figure-4: Example of Three Types of Adult Stem Cells. Adult stem cells represent a broad category of stem cells isolated from adult tissues or from umbilican cord blood. Examples include brain, heart, and bone marrow stem cells (upper, middle, and lower diagram, respectively). (Tripod.com, 2010)

Hematopoietic Stem Cells

The hematopoietic system creates blood in the body. There are many cellular components in this system, including red blood cells, platelets, granulocytes, and macrophages. Each of these parts has a specific role in the maintenance and function of the immune system and blood. The erythrocytes transport oxygen over the body, platelets stop bleeding, granulocytes and macrophages help fight off foreign organisms in the body. Hematopoietic stem cells (HSCs) are the source of all these cells. On average each of us produce around one hundred billion (100,000,000,000) new cells from the hematopoietic system daily. HSCs have been used in bone marrow transplants for over 50 years now to treat specific blood disorders, especially leukemia, and represent the best characterized type of stem cell (BMT Success Stories, 2006).

Neuronal Stem Cells

Neuronal stem cells (NSCs) are a rare type of progenitor cell found in brain tissue (for a review see Gage, 2000). These cells are very difficult to isolate as the vast majority of brain cells are not progenitors, but the hope is to be able to use them to treat brain disorders like Parkinson's or Alzheimer's diseases. These cells appear to be especially found in the subependymal cells surrounding the brain ventricles (Morshead et al., 1993). Currently scientists at the Stem Cell Research Group at Washington University are working on identifying factors that regulate neuronal differentiation; the research group is experimenting with the introduction of growth factors that can alter the cell type.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are progenitors for a variety of other cells, including but not limited to osteocytes, chrondrocytes, adipocytes, neurons, oligodendrocytes, astrocytes, and different types of skeletal and cardiac muscle (HemoGenix, 2009). Scientists originally discovered this multi-potency by growing MSCs in a "hematopoietic inductive micro-environment" to make the cells produce hematopoietic supporting cells or stromal cells. But when the cells were allowed to grow there were non-hematopoietic derived fibroblasts, endothelial cells, reticulum cells, fat cells, and macrophages. MSCs have very few distinguishing characteristics, but a few markers used together help define the MSC. This group of markers eliminates other types of cells and what remain is the MSC.

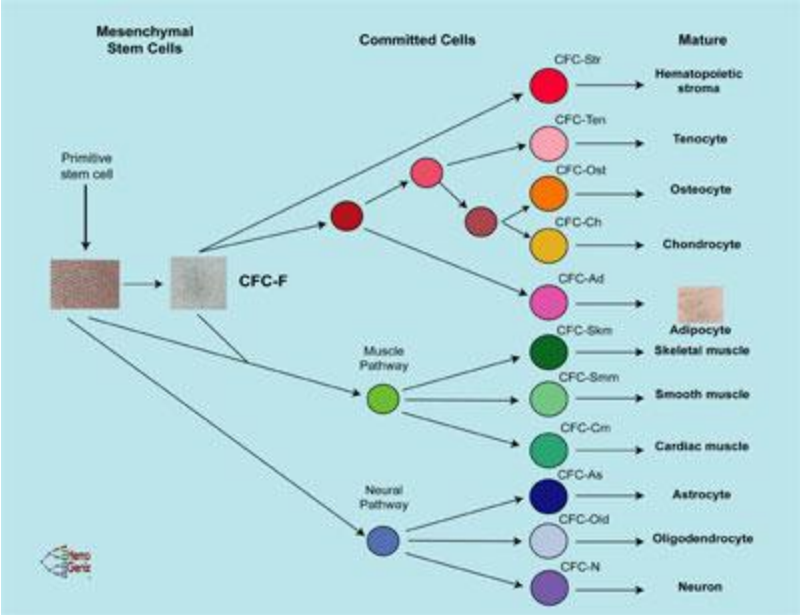


Figure-5: Mesenchymal Stem Cell Differentiation. MSCs (diagram left) are capable of forming a variety of mature cells types (diagram right) depending on the medium used for growth. (HemoGenix, 2009)

Skin Stem Cells

In order to maintain adult epidermal homeostasis, the body employs two types of adult progenitor cells (Cotsarelis et al., 1999; Clayton et al., 2007). The first kind are self-replenishing stem cells that maintain the stem cell base. The stem cells undergo many rounds of division before finally differentiating. The second kind of progenitor cell is the progeny of the stem cells. These progeny cells differentiate into epithelial cells. Epithelial stem cells are currently used to replenish skin cells for burn patients.

Myths About Stem Cells

As is typical for any complex technology, misinformation is abundant. One myth is that all stem cells destroy embryos to obtain them. This is false because of ASCs and iPS cells. Another myth is ASCs are as potent as ES cells. This is not true based on current research, but

perhaps ASCs can at least be used to treat specific types of diseases, even if they are not as medically potent as ES cells. Another myth is that stem cells have never been used to save any human lives yet. This is false, as bone marrow transplants (containing hematopoietic stem cells) have been used for over 50 years now to save thousands of lives from leukemia.

Another myth is that U.S. scientists are prohibited from doing ES cell research based on current laws. This topic will be discussed in Chapter-4, but the answer is under the Bush administration no new ES cell lines could be derived with *federal* funding, but this policy changed in 2009 with the Obama administration.

Chapter-1 Conclusion

Multiple types of stem cells exist, from embryonic stem cells derived from fertilized eggs, to iPS cells induced from skin fibroblasts, to parthenote ES cells derived from unfertilized eggs, to adult stem cells isolated from an adult body. Stem cell research at this point indicates that ES cells are the most potent in treating animal models of disease, they are the easiest to isolate and the easiest to grow. Future research may prove that iPS cells provide a less controversial source of ES cells, even if they are not quite at potent as ES cells derived from fertilized eggs.

Chapter-1 Bibliography

Boland MJ, Hazen JL, Nazor KL, Rodriguez AR, et al (2009) Adult Mice Generated From Induced Pluripotent Stem Cells. *Nature* **461**: 91-94.

BMT Success Stories (2006) University of Michigan Comprehensive Cancer Center, Interview with Michael Greene. http://www.cancer.med.umich.edu/cancertreat/treatment/bmt/bmtgreene06.shtml

Cibelli JB, Grant KA, Chapman KB, Cunniff K, Worst T, Green H, et al (2002) Parthenogenetic Stem Cells in Non-human Primates. *Science* **295**: 819.

Clayton E, Doupe DP, Klein AM, Winton DJ, Simons BD, Jones PH (2007) A Single Type of Progenitor Cell Maintains Normal Epidermis. *Nature* **446**: 185-189.

Cotsarelis G, Kaur P, Dhouailly D, Hengge U, Bickenbach J (1999) Epithelial stem cells in the skin: definition, markers, localization and functions. *Experimental Dermatology* **8:** 80–88.

Dolgin E (2010) Gene flaw found in induced stem cells. *Nature* **464**: 663.

HemoGenix (2009) Mesenchymal Stem Cell System.
http://www.hemogenix.com/the_mesenchymal_stem_cell_system/

Huettner, Jim (2006) Neurons From Stem Cells. Washington University St. Louis.
http://www.cellbio.wustl.edu/faculty/huettner/nfsc1.htm

Hyscience.com (2010) Pluripotent Stem Cells.
http://www.hyscience.com/archives/PluripotentStemCells.jpeg

Kim K, Lerou P, Yabuuchi A, Lengerke C, Ng K, West J, Kirby A, Daly M, Daley G (2007) Histocompatible Embryonic Stem Cells by Parthenogenesis. *Science* **315**: 482-486.

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.

Kono T, Obata Y, Wu Q, Niwa K, Ono Y, Yamamoto Y, Park E, Seo J & Ogawa H (2004) Birth of Parthenogenetic Mice That Can Develop to Adulthood. *Nature* **428**: 860-864.

Liebertonline.com (2007)
http://www.liebertonline.com/doi/abs/10.1089/clo.2007.0033?journalCode=clo

Martin, Gail (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci USA*, 78(12): 7634.

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.gov (2006) Chapter-2: Bone Marrow (Hematopoietic) Stem Cells.
http://stemcells.nih.gov/info/2006report/2006chapter2.htm

Parthenogenesis (2007) http://64.202.120.86/upload/image/articles/2007/shedding-light-on-blindness/parthenogenesis.jpg

Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR, Gearhart JD (1999) Derivation of Pleuripotent Stem Cells From Cultured Human Primordial Germ Cells. *Proc Natl Acad Sci USA* **95**: 13726-13731.

SigmaAldrich.com (2010) Stem Cell Biology. http://www.sigmaaldrich.com/etc/medialib/life-science/stem-cell-biology/ipsc-pathway.Par.0001.Image.566.gif

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.

Tripod.com (2010) http://rt475cmustudent.tripod.com/image/MultipotentStemCells.jpg

Yu J, Hu K, Smuga-Otto K, Tian S, Stewart R, Slukvin I, Thompson JA (2009) Human Induced Pluripotent Stem Cells Free of Vector and Transgene Sequences. *Science* **324**: 797-800.

CHAPTER-2: STEM CELL APPLICATIONS

Gregory Voyta

The tissue regenerative potential of stem cells provides new therapies for treating a variety of conditions caused by damage to the body. Some of the major areas currently being researched include diabetes, spinal cord injuries, Parkinson's disease, cancer, stroke, autoimmune disorders, and others. The main problems now include the difficulty of isolating adult stem cells (ASCs), getting ASCs or embryonic stem cells (ESCs) to differentiate down a specific pathway, and preventing their migration to other parts of the body. This chapter focuses on the wide variety of applications for stem cells in the medical field and how far the different treatments have advanced. This detailed discussion of their *benefits* is required to more fully discuss the topic of stem cell ethics in Chapter-3.

Diabetes and Stem Cells

Stem cells are currently being used to attempt to treat diabetes. Diabetes is one of the most widespread diseases, affecting millions of people worldwide. It is steadily becoming more common, especially within the obese population. There are two types of diabetes; type I occurs when the body attacks beta cells that produce insulin, while type II occurs when the body becomes partially resistant to insulin to a point where the body's beta cells cannot produce enough insulin for the body (NIH, 2006, Chapter-7). Through the use of stem cells, scientists are attempting to create healthy β-cells that can be reintegrated into the body, and that secrete insulin in a glucose-regulatable manner. In researching possible ways to treat diabetes, scientists have used embryonic stem (ES) cells and adult stem cells (ASCs) from the bone marrow to attempt to

create new endocrine cells that will secrete insulin. Research has been done on mice showing that it is possible to create functional pancreatic endocrine beta-cells (the cells that produce insulin) using ES cells. A number of studies have produced results that suggest the ES cells are being properly accepted by the body and create more endocrine cells to produce insulin (Soria et al; 2000; Beilhack et al., 2003).

Research into using bone marrow to make endocrine cells has had its drawbacks, there have been mixed reviews in the studies done, some methods suffering from the injected cells inability to fuse with the body (Ianus et al., 2003), while others showed limited success (Hess et al., 2003. Another approach to fighting diabetes uses stem cells to attempt to prevent the initial autoimmune destruction of the beta cells (Beilhack et al., 2005). They used NOD (non-obese diabetic) mice, injecting them with hematopoietic stem cells, and found that the stem cells could block the development of autoimmune diabetes.

So overall, ES cells and ASCs do have the ability to differentiate into insulin producing cells, but for now have limited capacity to fuse properly in the body, so the overall efficiency of the treatments need to be improved before clinical testing on human patients can begin.

Heart Disease and Stem Cells

Cardiovascular diseases are responsible for the deaths of millions of Americans annually, but leading the fight against these diseases are stem cells. The causes of death from cardiovascular disease are mainly heart failure due to heart damage from a variety of causes including a pulmonary infarction (a heart attack), hypertension, and congestive heart failure (NIH, 2006, Chapter-6). All of these symptoms occur from the heart overexerting itself and eventually exceeding the rate at which it can pump blood to the body. Stem cells are now being

used to replace cells damaged in heart suffering from a variety of debilitating conditions. The ultimate goal of the procedure is for the stem cells to fuse with cells in the damaged heart and help the body restore some of its cardiovascular functions. The process should give people with heart problems more energy to live a more fulfilling life.

The process has been attempted using adult stem cells in animals, and has found that when hematopoietic cells are injected into areas around a recently damaged heart, the cells are able to differentiate into cardiac muscle and vascular endothelium (Jackson et al., 2001), increasing the function of damaged heart. Other research has shown success in rodent models for ischemia, using a variety of stem cells, from myoblasts (Leobon et al., 2003) to mesenchymal stem cells (Amado et al., 2005). These successes in animal studies bring hope for potential aid for people suffering from any of a variety of cardiovascular diseases.

Although some studies show that the injected stem cells have the ability to differentiate into the correct cells to repair the heart, the cells seem to have a tendency to migrate to many other parts of the body. When using mononuclear bone marrow cells (Lunde et al., 2006) or intracoronary progenitor cells (Schachinger et al., 2006), researchers found the cells had been distributed all over the body, and the major factor in the success of the treatment was whether the cells stayed in the heart. Other studies suggest that after acute myocardial infarction, there is less of a chance for significant repair at the wound site (Lunde et al., 2006; Schachinger et al., 2006), likely due to scar tissue formation, but this may change if more cells can be delivered to the damaged area or if scar tissue can be minimized. Other general results suggest that the timing of the therapy after ischemia is important, and the *sooner* patients receive cell injections after cardiovascular problems the better chance they have at increasing heart function. The field of heart regeneration through stem cells has potential to bring relief to millions who suffer from

heart problems, but it will require fine tuning of methods of injection to see effective and consistent results.

Neurological Disorders and Stem Cells

Stem cells are also being used to repair damage done to nerve cells in a person's brain to treat degenerative diseases like Parkinson's disease and Huntington's disease. Neurological disorders stem from the lack of ability for the neurons in a person's nervous system to communicate, so stem cell research is looking to successfully integrate new neural stem cells that have been created from stem cell lines (NIH, 2006, Chapter-3). The new cells would have the ability to fill in the neural gaps in the brain creating a functioning nervous system (Sanberg, 2007).

For Parkinson's disease, deriving neurons that produce dopamine from stem cells and integrating them into the brain might allow the person to regain body function. The human brain has the potential to regenerate itself, so it is also possible to stimulate those areas of the brain to respond and repair the damage. Tests show in mice that when the correct growth factor is injected into the brain the stem cells already inside the brain to begin proliferation, directed migration, and neurodifferentiation (Fallon et al., 2000), effectively allowing the mouse brain to do most of the healing with its own material as opposed to putting the material in the body and hoping it will attach to the correct place. Results from mouse models of Parkinson's disease indicate adult neural stem cell and growth factor treatments when properly injected can be effective tools to alleviate problems caused by neurological disorders and aid in the repair and regeneration of the damaged nervous system (Kim et al., 2002).

With respect to human studies, some experiments injecting embryonic neuronal cells into PD patients have been somewhat successful. Some factors like age and the severity of the condition decreased the effectiveness of the treatments, and there were some side effects like dyskinesia (loss of voluntary movement in the body). But the side effects have been minimal in other studies that are able to inject the cells without causing direct brain damage (Dunnett et al., 2001). The results of patient treatments vary from experiment to experiment, and one protocol has not proven to be substantially better. Patients neurological scores improve after receiving treatment, but most trials only showed a substantial marked improvement in younger patients (Dunnett et al., 2001; Freed et al., 2001). But in future experiments, as cell treatments are eventually optimized, cell therapy should give people who suffer from neurological damage a chance to partially alleviate their symptoms.

Stroke and Stem Cells

Stem cells have also been applied to help patients recover from stroke more quickly and more completely. The therapies for stroke target recovery of neurons in the brain, helping them regenerate. The regeneration allows better communication between nerves in the body, and recovering motor functions. The stem cells are converted into endogenous precursor cells which help integrate into the brain and take the place of neurons that die during strokes (Arvidsson et al., 2002). There have been multiple studies done on animals using embryonic stem cells (Lindvall and Zaal, 2004; Steinbury, 2008).

The animal results suggest that treatments might eventually apply to human patients, but there are some problems that need to be worked out first. The problems presented by stem cell treatments for stroke could easily leave the patients in worse condition than they started. One of

the problems with using stem cells is there is a chance that they will form tumors. During lab testing on animals, scientists identified some tumors in the brain after the injection of stem cells and that would be an unacceptable risk to a human patient (Steinbury, 2008). Other studies need to be conducted to minimize tumor formation, and the efficiency of the treatments needs to be improved so that the types of cells the stem cells differentiate into can be better controlled (Lindvall and Zaal, 2004). With enough research, the field of stem cell therapy for stroke should bring much needed relief.

Spinal Cord Injuries and Stem Cells

The field of spinal cord repair gained significant ground when research revealed stem cells as a possible treatment. When people suffer from spinal cord injury their body no longer is able to send and receive signals from the spinal column, which results in diminished locomotion. Depending on the severity and location of the damage, it can produce a variety of injuries that prevent people from having complete use of their muscles and nerves. The idea behind stem cell treatments is to restore the body's neural receptors and transmitters and allow patients to recover some of the locomotion lost (Davies, 2006).

Some success has been reported in patients suffering from mild spinal cord damage (Liu et al., 2000). The study showed that ES could differentiate in transplant patients into oligodendrites that stimulated axonal growth along the spinal cord (Davies, 2006). Other studies in rats have shown that a variety of methods and cell types show potential for restoring a wide range of spinal column injuries (Kerr et al., 2003; Harper et al., 2004). The potential to restore some level of locomotion to the body continues to be one of the most exciting fields in stem cell applications.

Stem Cells and Cancer

Not all the abilities of stem cells are positive; research has been done to try to discover if stem cells are directly related to cancer. Recent theories in oncogenesis state that stem cells growing uncontrollably may initiate tumors. Early theories on cancer were that residual fetal tissues in an adult body metabolize and expand into tumors, but this theory was soon discredited due to the lack of fetal tissues in most adults (Kneller, 2007). Now, the most widely accepted theory is that adult stem cells that already exist in the body are exposed to the right set of conditions that cause them to become cancerous (Kneller, 2007). This would explain why cancer is able to form in almost every part of the body, and how it can reappear after chemotherapy or other treatments. The stem cell origin of cancer idea has launched a large field of research to isolate cancer causing stem cells throughout the body. Most cancer-causing stem cells have been isolated by looking at the types of stem cells found in cancerous tumors (Kneller, 2007). Looking at where the cancer originated and the types of stem cells present in the tumor, scientists have been able to identify stem cells present in a variety of tumors. The ultimate goal of the research is to create a drug that will prevent each type of stem cell from mutating into a cancerous cell.

However, not everyone supports the new cancer theory. The idea of cancerous stem cells has led to debates over the validity of the research, and the idea that not just one type of cell (stem or otherwise) leads to a tumor. For example, in the field of breast cancer research, scientists have identified what appear to be progenitor cells interacting with stem cells in a breast tumor (Polyak, 2007). Thus, both types of cells would have to be targeted to destroy the tumor, and multiple drugs might be needed to prevent the disease.

Scientists are also looking into blocking the signaling pathways of cancer-causing cells, which would prevent initial tumor growth. One study showed that when two kinases that interact with MAP kinase (Mnk1 and Mnk2) are inhibited, the rate at which tumors grow is severely impeded (Ueda, 2002). So more research must be performed to identify which cells contain these critical kinases, and what long term effects will result from their blockage. This new branch of stem cell research suggests that it might be possible to prevent the outbreak of cancer if the right signaling pathways are blocked. Hopefully when the field is more heavily researched we can find a way to stop stem cells from becoming cancerous.

Stem Cells and Organ Growth

One of the most intriguing fields in regenerative medicine is the growing of new organs with stem cells. The science behind these advanced procedures is to place a scaffold made of proteins into the site that needs repair. The scaffold acts as a blueprint for the repair, and attracts stem cells to the region differentiating them into the cells needed for the body to regain function. The field has shown that it is possible to create parts of hearts and livers from scaffolds (Subbaraman, 2010). Other studies have shown that bone growth can be initiated in animals using similar procedures, and once regeneration is complete the animals have nearly identical joint function as animals of the same age (Weintraub, 2010). These studies show the potential to grow new organs for transplant and heal broken bones by using stem cells naturally found in the body. Other researchers are using stem cells to grow bladders that have been used in Phase II testing on patients that suffer from spina bifida (Flanagan, 2007). The new organs are grown using the patient's own tissue to grow a new bladder from a scaffold the new bladder. The new approach prevents many of the side effects like organ rejections that complicate organ

procedures on a regular basis. This field may have the potential to replace almost any damaged organ.

But first many challenges must be overcome to grow a complete organ. The growth of a human bladder was done because of the simplicity of the organ and the overall ease of surgical placement (Flanagan, 2007). But most organs have not been grown in completion or at full scale, so the developing scaffolds that will cause a stem cells to differentiate in the correct types of cells to create a functional organ is the most critical step preventing more advanced organ growth. But the field has made many recent strides, like creating heart muscles that were able to beat under electric stimulation (Subbaraman, 2010). The applications of this science have the potential to dramatically change the organ donor program, and allow people to have new organs grown from their own cells, but the ability to develop new organs is still inhibited by the complexity of the scaffolds created so far.

Chapter-2 Conclusion

In conclusion, stem cells have the potential for almost unlimited applications when it comes to dealing with disease. Depending on the type of stem cell used, their regenerative abilities allow them to differentiate into any type of cell in the body. Our challenge is to control their growth to prevent cancer, and to devise methods to ensure the correct differentiation pathway is taken. Most fields of stem cell research still need years of testing before trials can reach human patients, and it will be years after that before the treatments become available to the general public. And many still believe that the use of ES cells is unethical, so the challenge will be to determine whether any adult stem cell treatment can work for a particular disease in lieu of using ES cells (this topic will be discussed in the next chapter). The sheer variety of diseases

that stem cells are able to combat illustrate that stem cells might be able to help almost any person at some point in their lives, whether they have broken bones or need a new organ. For now, stem cells show a great deal of promise in a wide variety of applications, and show the potential to revolutionize the way many major diseases are treated.

Chapter-2 Bibliography

Amado LC, Saliaris AP, Schuleri KH, et al (2005) Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. *Proc Natl Acad Sci USA.* **102**: 11474-11479.

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

Beilhack GF, Landa RR, Masek MA, Shizuru JA (2005) Prevention of type 1 diabetes with major histocompatibility complexcompatible and nonmarrow ablative hematopoietic stem cell transplants. *Diabetes* **54**: 1770-1779.

Beilhack GF, Scheffold YC, Weissman IL, et al (2003) Purified allogeneic hematopoietic stem cell transplantation blocks diabetes pathogenesis in NOD mice. *Diabetes* **52**: 59-68.

Bu L, Jiang X, Martin-Puig S, et al (2009) Human Isl1 Heart Progenitors Generate Diverse Multipotent Cardiovascular Cell Lineages. *Nature* **460**: 113-117.

Davies, Jeannette E (2006) Astrocytes derived from glial-restricted precursors promote spinal cord repair. *Journal of Biology* **7**: 1-21.

Dunnett, S.B., Bjorklund, A., and Linvall, O (2001) "Cell Therapy in Parkinson's Disease-Stop or Go?" *Nat. Rev. Neurosci.* **2**: 365-369.

Fallon J, Reid S, Kinyamu R, et al (2000) *In vivo* induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain. *Proc Natl Acad Sci USA.* **97**: 14686-14691.

Flanagan, Nina (2007) Regenerative Medicine Enters Realm of Reality. *Genetic Engineering News*, Vol **27**, Number 7, pp. 1. April 1, 2007.

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. *N. Engl. J. Med*. **344**: 710-719.

Harper JM, Krishnan C, Darman JS, et al (2004) Axonal growth of embryonic stem cell-derived motoneurons *in vitro* and in motoneuron-injured adult rats. *Proc Natl Acad Sci USA.* **101:** 7123-7128

Hess D, Li L, Martin M, Sakano S, Hill D, Strutt B, Thyssen S, Gray DA, Bhatia M (2003) Bone Marrow-Derived Stem Cells Initiate Pancreatic Regeneration. *Nature Biotechnology* **7**: 763-770

Ianus A, Holz GG, Theise ND, Hussain MA (2003) *In vivo* derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. *J Clin Invest.* **111**: 843-850.

Jackson KA, Majka SM, Wang H, et al (2001) Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. *J Clin Invest*. **107**: 1395-1402.

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.

Kerr DA, Llado J, Shamblott MJ, et al (2003) Human embryonic germ cell derivatives facilitate motor recovery of rats with diffuse motor neuron injury. *J Neurosci*. **23**: 5131-5140.

Kneller, Alyssa (2007) Shedding light on cancer stem cells. *Paradigm Magazine* http://www.whitehead.mit.edu/news/paradigm/fall_2007/cancer_stem.html

Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, Charpak S (2003) Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. *Proc Natl Acad Sci USA.* **100**: 7808-7811

Lindvall Olle, Kokaia Zaal (2004) Recovery and Rehabilitation in Stroke. *American Heart Association* http://stroke.ahajournals.org/cgi/content/full/35/11_suppl_1/2691

Liu S, Qu Y, Stewart TJ, et al (2000) Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. *Proc Natl Acad Sci USA.* **97**: 6126-6131

Lumelsky N, Blondel 0, 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

NIH Stem Cell Information (2006) Chapter-3. Repairing the Nervous System with Stem Cells. http://stemcells.nih.gov/info/2006report/2006Chapter3.htm

NIH Stem Cell Information (2006) Chapter-6. Mending a Broken Heart: Stem Cells and Cardiac Repair. http://stemcells.nih.gov/info/2006report/2006Chapter6.htm

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

NIH Stem Cell Information (2006) Chapter-8. Alternative Methods for Preparing Pluripotent Stem Cells. http://stemcells.nih.gov/info/2006report/2006Chapter8.htm

NIH Stem Cell Information (2006) Chapter-9. Are Stem Cells Involved in Cancer? http://stemcells.nih.gov/info/2006report/2006Chapter9.htm

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.

Polyak, Kornelia (2007) Study questions "cancer stem cell" hypothesis in breast cancer. *Dana Farber Cancer Institute* http://www.dana-farber.org/abo/news/press/2007/study-questions-cancer-stem-cell-hypothesis-in-breast-cancer.html

Sanberg, PR (2007) Neural Stem Cells for Parkinson's Disease: To Protect and Repair. *Proceedings of the National Academy of Sciences* **104**: 11869–11870.

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

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.

Steinbury, Gary (2008) Human Stem Cells Aid Stroke Recovery in Rats. *Science Daily* http://www.sciencedaily.com/releases/2008/02/080219203542.htm

Subbaraman, Nidhi (2010) Growing Organs and Helping Wounds Heal. *Technology Review* http://www.technologyreview.com/biomedicine/25918/

Ueda, Takeshi (2002) Combined deficiency for MAP kinase-interacting kinase 1 and 2 (Mnk1 and Mnk2) delays tumor development. *Nation Academy of Science* http://www.pnas.org/content/107/32/13984.full.pdf+html

Weintraub, Karen (2010) Helping Joints Regrow Themselves. *Technology Review* http://www.technologyreview.com/biomedicine/25893/

Chapter-3: Stem Cell Ethics

Gregory Voyta

The previous chapter focused on the *benefits* to society of stem cells (their medical uses), but in this chapter we go beyond stem cell technology to ask whether we *should* work with these cells. Stem cell ethics usually focuses on embryonic stem cells and the embryos destroyed to obtain them, but these cells represent only some of the types of stem cells in use today. This chapter will discuss different sides of the ethics debate, which is critical for understanding the legal issues in Chapter 4.

As discussed in detail in Chapter-1, stem cells are *not* all alike, and each type has its own ethics. As a brief reminder, there are four main types of stem cells: adult stem cells (ASCs), embryonic stem (ES) cells, embryonic germ (EG) cells, and induced pluripotent stem (iPS) cells. ASCs are isolated from an adult body (or sometimes from cord blood) and have the potential for limited differentiation. ASCs are hard to isolate and grow, but no embryos are destroyed to obtain them. ES cells are isolated from 5-day old embryos created by *in vitro* fertilization (IVF). The embryo is usually destroyed during the isolation procedure. ES cells are pluripotent, so have the best medical uses, and are relatively easy to isolate and grow in large numbers. ES cells can also be obtained in animals by cloning via somatic cell nuclear transfer (SCNT), also known as therapeutic cloning (Devolder, 2005). EG cells are isolated from aborted fetuses, and also have pluripotent potential, but not quite to the degree of ES cells (Devolder et al., 2005). iPS cells are adult cells (usually skin fibroblast cells) induced to de-differentiate into pluripotent cells using transcription factors. iPS cells do not destroy embryos to obtain them, but it is not yet proven whether they are truly as potent as ES cells.

Early Human Embryo Development

A discussion of early human development will help provide a framework for embryo ethics. Following fertilization at day-0, the zygote begins dividing. The cells remain totipotent through about the 8-cell stage (48 hrs). At day-5, the embryo has become a blastocyst and between 5-8 days implants into the uterine wall. The embryo in its second month of development may mark the beginning of sentient human life, because as the embryo approaches its eighth week many of the features that make a human start emerging. Brain cells exponentially increase, forming almost 100,000 cells per minute (ScienceClarified.com, 2010). The development of the brain cells coincides with the emergence of the pineal gland in the brain, which generally becomes active on the 49th day of gestation (Johnston, 2009). This time period of the second month coincides well with Jewish, Muslim, and old Christian beliefs about when a fetus becomes distinctly human, which is around 40 days (Johnston, 2009). Besides the emergence of the pineal gland and advanced brain growth, the seventh and eighth week also eliminates the tail that was originally present in the fetus, finishes creating most major organs, and moves them to the proper locations in the body, creates fingers and toes that are no longer webbed, closes the eyes of the fetus by creating eyelids (which will not be reopened until around the twenty-sixth week), begins the initial growth of distinct sex organs, and starts fetal muscular movement (Hagan et al. 1997; ScienceClarified, 2010). After the eighth week the fetus begins to grow rapidly in size, having just finished the initial growth of most major organs.

Religious Views of Stem Cells

The ES cell debate focuses on the status of the 5-day old human embryo destroyed to obtain these cells. Is it murder to destroy the embryo? When does life begin: at conception, at

implantation, at birth? Looking into different religious perspectives will help explain people's opinions on stem cell research, especially since most people identify with a religion. The world's major religions have different views on when life begins. Although most large religions are so complex they have multiple points of view, most religions have general trends and leaders to help interpret how the creators of each religion might view complex topics today. These leadership views by no means represent all people of a certain religion, but should represent a majority.

To begin the discussion, all five of the major religions support research with adult stem cells. These cells do not destroy an embryo during their isolation, so even conservative Catholics support using ASCs so long as the cells are used to try to save lives according to Pope Benedict XVI (Catholic Online, 2008). No lives are threatened by the ASC extraction. But the main problem with using adult stem cells is they are not as effective as their embryonic counterparts. ASCs do not have the ability to differentiate into as many tissues as ES cells, and it is difficult to grow enough of them to actually use in therapies. Although hematopoietic stem cells (HSCs) have been used for decades to save lives in bone marrow transplants, other strong applications are still being researched. The use of mesenchymal stem cells (MSCs) looks especially promising, and perhaps these cells can eventually replace ES cells for some disease treatments.

Christianity and Stem Cells

For Christianity, with its various subtypes, the topic of when personhood begins is complex. Catholics argue life begins at conception (so are strongly against ES cells), while other churches argue a fetus is considered human only after 40 days for males and 80 days for females

(ChristianBibleReference.org, 2000). It was not until 1869 that the Catholic Pope decreed that abortion at any point led to excommunication (ChristianBibleReference.org, 2000). That view still holds today for much of the Catholic church who believe life begins at conception. But other Protestants concede to a 15 day period on newly fertilized eggs, agreeing that research on these young cells is acceptable (Cousins and Geisert, 2005). Some Protestant churches hold the same belief as Catholics, while others feel that stem cell research is appropriate when there are no other ways to conduct the same research (Cousins and Geisert, 2005).

Judaism

Judaism holds that for the first 40 days of gestation a fetus is considered "as if it were simply water", not fully human, and after 40 days the fetus is considered "like the thigh of its mother" (Dorff, 2002). So Judaism allows research on 5-day old IVF embryos. However, this religion does not allow a mother to abort an embryo to use it for research. Judaism holds that the mother does not have a right to abortion unless it is to save her own life, because it is not until birth that the child becomes as fully human and distinct from the mother (Hug, 2006). In relation to stem cell research Jews generally believe that developing cultures of stem cells is okay because they are "simply water" and do not consider it human, in that state the IVF embryos would not have the ability to develop into a full-fledged person (Dorff, 2002). So Judaism permits using aborted fetuses (when done to save the mother's life), and frozen IVF embryos that are planned to be discarded (Dorff et al., 2002). So Judaism permits nearly all types of stem cell research done today, but not reproductive cloning.

Islam and Stem Cells

Islam's Qur'an does not specifically mention stem cells, but guidelines can be taken from their literature gives a general idea of their beliefs. The Qur'an indicates that a person's "life force" is given to them either 40 or 120 days after conception, and after that time period abortions are generally disallowed (Syed, 2001). This belief allows the use of 5-day old embryos. But most Islamic scientists feel that the only type of stem cell research that should be fully allowed is on IVF embryos, not aborted tissue (Siddiqi, 2001). Some Islamic scientists feel that stem cell research needs to be more heavily looked at to see if it goes against the teachings of the Qur'an, but does so far it does not appear to disavow it (Siddiqi, 2001). So this creates varying views on stem cell research within the Muslim community, as with Christianity, but most Muslims believe working on an embryo less than 40 days old is acceptable.

Hinduism and Buddhism

Buddhism and Hinduism typically do not support work on ES cells (Hug, 2005). Their general doctrine sees all life as sacred, and that people are reincarnated after death into a new body (Knowles, 2008). So these ideals would not permit the use of embryos for ES cell research. But Buddhism and Hinduism do believe in seeking out knowledge, which could be gained through this research (Knowles, 2008). With respect to when an embryo becomes alive, this ranges from the moment of conception to seven months into pregnancy, depending on the specific Hindu or Buddhist community (Cousins and Geisert, 2005). But even though these religions tend to respect life, ES research is still conducted in Hindu and Buddhist countries. So in practice, seeking knowledge to benefit the living tends to outweigh the possible consequences to human life. But the research is only allowed if it is for the greater good of mankind; research

for monetary gain is unacceptable (Hug, 2006). So, even though ES cell research tends to go against the Buddhism and Hinduism ideal of preserving life, the overall benefit of mankind is considered more important than that of a small number of 5-day old embryos.

Ethics of Cloning and Genetic Manipulations

Strong debates over cloning and genetic manipulation are pitting the religious and scientific communities against each other. Human *reproductive* cloning is considered an abomination among all of the mainstream religions and governments (Madzarevic, 1998). In fact, human reproductive cloning is currently banned in all countries organized enough to have such policies; no country currently permits it. Some ideas have been proposed to create humans resistant to certain diseases, but such experiments are all banned. Some people argue making disease resistant humans might lead to new diseases that are harder to fight, but that same argument can be applied to current day antibiotic treatments.

With respect to human *therapeutic* cloning, although one Korean study claimed success (Hwang et al., 2005), this study was later withdrawn for data fabrication, so human therapeutic cloning has not yet been achieved. In this process, the nucleus from a patient's skin fibroblast cell would be isolated, and then it would be injected into an enucleated egg. The IVF embryo would be grown 5 days, then ES cells isolated. This process is also known as somatic cell nuclear transfer (SCNT). The advantage of SCNT ES cells is they would be genetically identical to the patient, so would not be rejected. The U.S. currently bans both reproductive and therapeutic SCNT.

Chapter-3 Conclusion

The ethics debate on stem cell research has a wide variety of opinions, ranging from a comlete ban on ES cells cells, to a complete allowance of ES and SCNT research. Many individual's opinions are shaped by their religious background, which helps formulate their opinions on when a fetus becomes a human being. The embryo ethics discussion actually has been going on for decades, since excess embryos were discarded from IVF clinics. Catholics, Hindus, and Buddhists generally do not support ES cell research, while Muslims, Jews, and some Christians support it.

Chapter-3 References

Catholic Online (2008) "Benedict Endorses Adult Stem-Cell Research as Respecting Human Life." http://www.catholic.org/international/international_story.php?id=21301

ChristianBibleReference.org (2000) What does the Bible say about abortion? *The Book of Discipline of The United Methodist Church 2000* http://www.twopaths.com/faq_abortion.htm

Cousins, Jennifer; Geisert, Paul (2005) General Positions on Stem Cell Research and When Personhood Begins. *Science & Theology News.* http://www.teachingaboutreligion.org/WhatsNew/Stem_cell_research.htm

Devolder, Katrien (2005) Human Embryonic Stem Cell Research: Why the Discarded-Created-Distinction Cannot be Based on the Potentiality Argument. *Bioethics* **19**: 167-186.

Dorff, Elliot N (2002) Embryonic Stem Cell Research: A Jewish Perspective. *United Synagogue Review* http://www.uscj.org/Embryonic_Stem_Cell_5809.html

Hagan, Kelly; Kincer, Kelly; Payne, Joni; Scott, Sutti; Sutti, Mickey (1997) Fetal Development. *University of Kentucky* http://www.uky.edu/Classes/PHI/305.002/fd.htm

Hug, Kristina (2006) "Therapeutic perspectives of human embryonic stem cell research versus the status of human embryo: Does one have to be compromised for the other". *Medicina* **42**(2): 107-114.

Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, et al. (2005) Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science,* Jun 17; **308**(5729): 1777-1783.

Johnston, Lauren (2009) Pineal Gland, Melatonin, and Spinal Cord Dysfunction. *Paraplegia News* http://www.healingtherapies.info/PinealGland1.htm

Knowles, Lori (2008) Religon and Stem Cell Research. *Stem Cell Network*. http://www.stemcellnetwork.ca/uploads/File/whitepapers/Religion-and-Stem-Cell-Research.pdf

Madzarevic, Vera (1998) Human Cloning and Molecular Cloning vs. Ethics and Religion. *Istocnik.* http://www.istocnik.com/articles/56/english3.html

ScienceClarified.com (2010) Embryo and Embryonic Development. *Science Clarified.* http://www.scienceclarified.com/El-Ex/Embryo-and-Embryonic-Development.html

Siddiqi, Mazammil (2001) An Islamic Perspective on Stem Cell Research. *Islam 101*. http://www.islam101.com/science/stemCells.htm

Syed, Ibrahim (2000) Abortion in Islam. *Islamic Research Foundation International Inc.* http://www.islamawareness.net/FamilyPlanning/Abortion/abortion3.html

CHAPTER-4: STEM CELL LEGALITIES

Alexander Sterling

As with all great advances in science, there is a storm of controversy with stem cells. As discussed in the previous chapter, there is an ethical/religious debate about the use of ES cells. And as is typical of any controversial technology, there are laws to regulate the use of stem cells. The purpose of this chapter is to describe some of the laws regulating stem cell use, both in the U.S. and internationally.

The biggest debate with stem cell research is the act of collecting ES cells from fertilized embryos is considered by some to be murder. So the stem cell policies enacted usually address the use and source of fertilized embryos for research purposes. Over the years, the United States has had many rulings on this embryo issue, including both national and state rulings. And each new president and Congress has passed new bills and laws regarding the subject.

Early U.S. Embryo Policies

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 placed a ban on all federally funded research using fetal tissue to prevent the mistreatment of human subjects. In 1975, an Ethics Advisory Board was established to oversee research on any fetal tissue originating from abortions, but in 1981 then President Reagan ended the ethics board's charter, allowing the original 1974 ban to continue (Stem Cell Tracker, 2009).

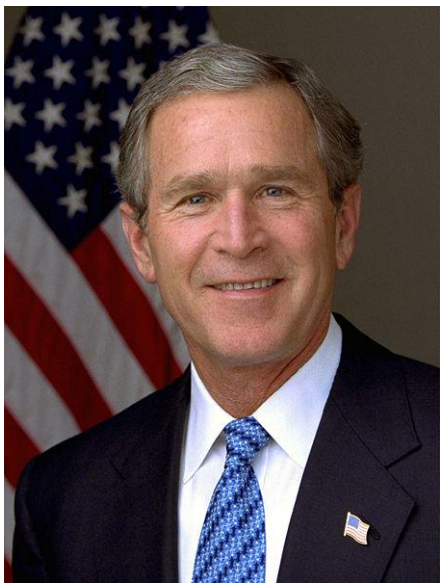
President's Clinton's Stem Cell Policies

(Mokellyreport, 2009)

In President Bill Clinton's 2004 book he says that "Everyone knows life begins biologically at conception. No one knows when biology turns into humanity." (Clinton, 2004) This quote was in reference to his stance on abortion. President Clinton had a pro-abortion position, stating Roe v. Wade was the correct verdict. Abortions used to be one of the primary sources to obtain fetal tissues for research, such as those used to treat Parkinson's disease in animal models, and later in humans. But this practice of using aborted fetal tissues has waned over the years, and has been replaced by a debate over the use of 5 day old *in vitro* fertilized embryos. In President Clinton's book "My Life" he talks about his former chief of staff Erskine Bowles' children, both of which have diabetes. At the time diabetes was responsible for 25% of all Medicaid costs (Clinton, 2004). President Clinton supported ES cell research and the American Diabetes Association's diabetes self-care program.

Because of Clinton's pro stance on embryo research, in 1993, he issued an executive order to overturn the original 1974 ban on embryo research. However, under fire from critics, in 1995, the *Dickey-Wicker Amendment* was passed by congress which prohibited federal funding for embryo research (Stem Cell Tracker, 2009). In 1998, with the isolation and growth of human ES cells generating so much excitement, it was decided by a Department of Health and Human Services (DHHS) advisory committee that the amendment did not apply to ES cells, making their use legal, but not with federal funding. Importantly, the Clinton administration mandated the National Institute of Health (NIH) to publish its *guidelines* on ES cell research. In 2000 it recommended that ES cells not be derived with public funding, the cells must be derived from excess IVF embryos initially created for reproductive purposes, and the embryos must be obtained with donor consent.

President Bush's Stem Cell Policies



(TopNews, 2010)

From the outset of his pre-election campaign, through his entire 10 years as president, President Bush argued that destroying an embryo is murder. In August of 2001, President Bush enacted legislation that banned the federal funding for embryo research and deriving ES cells. Embryos destroyed prior to 2001 could be used for research, since those embryos had already been killed, but federal money could not be used to derive any new ES cell lines. Congressmen floated bills trying to lift the ban, but in July of 2006, President Bush vetoed his first bill which would have lifted the ban on funding for stem cell research (Babington, 2006). The bill would have granted money collect taxes for research and use of ES cells. During the press conference, President Bush was joined on stage by children that were produced through "adopted" embryos that were previously frozen, and which could have been used for research if his ban did not go through. President Bush stated that the taxpayer's money should not go to support research on excess embryos from fertility clinics, even if they hold the possibility of medical breakthroughs and are already scheduled for disposal.

During a meeting with the Prime Minister of Denmark President Bush said "I made my position very clear on embryonic stem cells, I'm a strong supporter of adult stem cell research, of course. But I made it very clear to Congress that the use of federal money, taxpayers' money, to promote science which destroys life in order to save life is – I'm against that. And therefore, if the bill does that, I will veto it." (Baker, 2005)

President Bush said that the vetoed bill "would support the taking of innocent human life in the hope of finding medical benefits for others." He went on to state that "It crosses a moral boundary that our decent society needs to respect", and it also stated that each child was at one time an embryo, and that these children are not additional parts.

There were of course many who opposed the President's decision to veto the bill. Senator Richard J. Durbin said "Those families who wake up every day to face another day with a deadly disease or a disability will not forget this decision by the president to stand in the way of sound science and medical research" (Babington, 2006). President Bush also received criticism on his veto from fellow conservatives. Senate Majority Leader Bill First said "I am pro-life, but I disagree with the president's decision," and he also stated that "Given the potential of this research and the limitations of the existing lines eligible for federally funded research, I think additional lines should be made available" (Babington, 2006). The lines of which he speaks are the ES cell lines that researchers currently use to perform research, however the ban limited the total number of ES lines to relatively few which hindered research.

Celebrities like Nancy Reagan and Christopher Reeve voiced their opinions on the medical potential of embryonic stem cells, and how such cells could be used to treat diseases such as Alzheimer's, Parkinson's, diabetes, spinal cord injuries, and other conditions. They also criticized the use of adult stem cells, saying that embryonic stem cells have the ability to reproduce themselves better and transform into any kind of human tissue (Babington, 2006).

There are an estimated 400,000 frozen embryos stored in U.S. fertility clinics, with most of these expected to be discarded as the donor parents do not want another person to raise their biological offspring. President Bush commended all those who "adopted" these frozen embryos. However, even with federal funding offered to those who adopt a frozen embryo, there are still relatively few parents who actually adopt. In 2006, there were 128 adoptions out of the 400,000 embryos available, with the rest destroyed.

President Bush and his supporters argued that these frozen embryos are synonymous with humans, and that research on them would be no different than doing research on death row

inmates. President Bush said "If this bill introduced by Senator Warren Hatch were to become law, American taxpayers would for the first time in our history be compelled to fund the deliberate destruction of human embryos." This analysis was rejected by others, saying that it would make killers out of every couple that creates an unused embryo. Senator Tom Harkin asked "If that's murder, how come the president allows that to continue?" (Babington, 2006) He goes on to say "Where is the outrage?" Harkin then called the veto "a shameful display of cruelty, hypocrisy, and ignorance."

One alternative to using embryos to collect stem cells is to save the umbilical cord and blood from a birth. The Bush White House showed support for this legislation. White House deputy press secretary Trent Duffy said "We need to look at the specifics of the kind of bill that's being discussed on cord blood, but we think that that has some real promise" (Baker, 2005).

President Obama's Stem Cell Policies

(Uploads, 2009)

Eight and half years after President Bush put a 2001 ban on embryonic stem cell research, the new President Obama rebuked it. On March 9, 2009 President Obama reversed the ban on stem cell research (Hayden, 2009; Wilson, 2009). With this removal of the ban, federal funds will now go towards the study and research of embryonic stem cells. President Obama said "At this moment, the full promise of stem cell research remains unknown, and it should not be overstated, but scientists believe these tiny cells may have the potential to help us understand, and possibly cure, some of our most devastating diseases and conditions" (Childs and Stark, 2009). With the band lifted there is expected to be a great increase in the number of embryonic stem cell lines in existence. The number of lines is expected to range anywhere from 400 to 1,000, instead of the 21 that existed before.

Upon President Obama's order, the National Institute of Health had 120 days to create ethical guidelines for embryonic stem cell research. The National Institute of Health stated they would find ways to streamline the process of research, and evaluate how promptly grant money can be distributed. Most grant requests can take up to nine months to process which can delay the funds to the researchers for up to a year, but the National Institute of Health will try to accelerate the grant process to get the money out faster. Melody Barnes, Director of the President's Domestic Policy Council, said "Encompassed in [the executive order] will also be the requirements around guidelines that will be drafted by the NIH [National Institutes of Health] as they ... work with others around the country to make sure we're handling the issue responsibly" (Childs and Stark, 2009). In July 2009, the NIH Guidelines were published (Federal Register, 2009; Majumder and Cohen, 2009). Although some critics argued with the requirement that embryos be obtained only from IVF clinics created for reproductive purposes, others viewed the guidelines as a reasonable compromise, and far better than the 2001 legislation.

President Obama also signed a memorandum that will “restore scientific integrity in government decision making” says Melody Barnes (Childs and Stark, 2009). The memorandum that was signed covers all types of scientific research, things including but not limited to energy and climate change.

The former first lady Nancy Reagan, wife of the late President Ronald Reagan who had a difficult fight with Alzheimer’s disease, has been a strong supporter for stem cell research, and stated that she is “very grateful” that President Obama lifted the ban (Childs and Stark, 2009). Nancy Reagan said “These new rules will now make it possible for scientists to move forward. Countless people, suffering from many different diseases, stand to benefit from the answers stem cell research can provide. We owe it to ourselves and to our children to do everything in our power to find cures for these diseases – and soon.” Other disease advocacy organizations hail this move as an affirmative towards the treatment of diseases such as Parkinson’s and Type-1 diabetes.

At the conference where President Obama removed the ban were Allen Goldberg and Laurie Strongin, parents of Henry Strongin Goldberg who had a rare genetic Fanconi anemia and died at age 7. His parents had used early stem cell technologies to try to cure their son. In a statement Strongin said "Henry had a rare illness. Not one of the few stem cell lines that President Bush specified in his 2001 stem cell decision provided for research into Fanconi anemia or other devastating illnesses" (Childs and Stark, 2009).

Michael Castle, the co-author of the stem cell legislation that was brought before President Bush and vetoed twice said “This single action symbolizes a new day for scientific research and highlights the importance of a strong federal role in prompting potentially life-saving science” (Childs and Stark, 2009).

However, some oppose the decision by President Obama to allow embryo research. Millions of people are in opposition to this choice said House Minority Leader John Boehner (Childs and Stark, 2009). John Boehner's released a statement saying "Advancements in science and research have moved faster than the debates among politicians in Washington D.C., and breakthroughs announced in recent years confirm that the full potential of stem cell research can be realized without the destruction of living human embryos. The question is whether taxpayer dollars should be used to subsidize the destruction of precious human life. Millions of Americans strongly oppose that, and rightfully so" (Childs and Stark, 2009). Also, David Prentice, the senior fellow for life sciences for the Washington D.C.-based Christian advocacy group Family Research Council, stated similar dissatisfaction, "There are adult stem cells that are helping to improve patients' health and saving lives, and these new iPS cells that are providing basic research tools to study disease. It's really a waste of resources to be moving in that direction now. It's a waste of funding, and it's a waste of lives, both in terms of the embryos and the patients waiting for these advances. ... I think it's clear that this is perhaps just fulfilling a campaign promise that was ill conceived" (Childs and Stark, 2009).

The public opinion of stem cell research has become more popular over the years. In a recent poll, 59 percent of the American population is in support on relaxing the restrictions on stem cell research, and 35 percent are still opposed to this (Childs and Stark, 2009).

The removal of the federal money embryo research ban by President Obama has most scientists and researcher excited about what possibilities are in store for scientific break troughs in the future. Martin Pera a professor and founding director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC said "This [Obama] decision is a major step forward for stem cell research in the United States. The move will enable NIH-

funded researchers to work on valuable new embryonic stem cell lines ... to determine which cell lines are best suited to treat particular diseases" (Childs and Stark, 2009).

Individual State Policies

While there are national rulings on the topic of embryo research, as discussed above, each state can enact its own regulations to fund stem cell research. States can approve their own bonds to fund stem cell institutes to do embryo research. These bonds were especially important during the Bush administration's ban on receiving federal money for embryo research.

California was one of the first states to do this with the enactment of a 2 billion dollar bond to fund the International Stem Cell Center (ISCC) in San Francisco. This was followed in 2007 by Massachusetts that approved a one billion dollar bond to fund embryo research in Massachusetts, and especially to fund the world's largest stem cell depository at the University of Massachusetts medical School in Worcester (Estes, 2007; News in Brief, 2008). Although this legislation initially hit a few snags, it was finally enacted in 2009.

The governor of Ohio, Bob Taft, vetoed a ban that would have restricted state funding for embryonic stem cell research. That ban would have guaranteed that no money from "Taft's $500 million Third Frontier initiative" would go towards research into stem cells. The ban Taft said was too restraining than what President Bush had already put into place. Many pro-life organizations greatly supported the ban. The legislature director of Ohio Right to Life, Mark Lally commented "We strongly support the … amendment prohibiting the use of state grant funds for research that involves the destruction of human embryos to obtain their stem cells"

(Ertelt, 2005). Other supporters of the ban have concerns that embryonic stem cell research will eventually lead to human cloning.

International Stem Cell Policies

The first country to actually conduct human stem cell experiments was China (Barnes, 2006). As controversy and debate over human embryonic stem cells rages in the "western" world, China has had little to no political turmoil over this. Dr. Hong Peng, the vice president of Innovase Consulting says "Chinese scientists have made significant progress in the development of stem cell research." But although China may be advancing in several stem cell research areas, there are legality concerns that still face China. Dr. Albert Wai-Kit Chan said "While the Chinese are making some progress in protecting intellectual property (IP), the enforcement of IP protection laws is still weak compared to that of Western countries" (Barnes, 2006). This means that determining who actually owns the ideas is under some scrutiny. There have been occasional incidents of plagiarism and data falsification. China will lose its competitive edge if these issues are not rectified. Other countries with fairly liberal policies on embryo use include England, Sweden, Finland, India, Japan, and Australia (**Figure-1, countries in dark brown color**).

On the other end of the spectrum from countries with liberal stem cell policies, Germany called for a ban on stem cells research. German Research Minister Annette Schavan said "The European Union science program should not be used to give financial incentives to kill embryos" (Deutsche Welle, 2006). Besides Germany, Austria, Poland, Slovakia, Lithuania Luxembourg, and Malta are also against embryo and ES cell research.

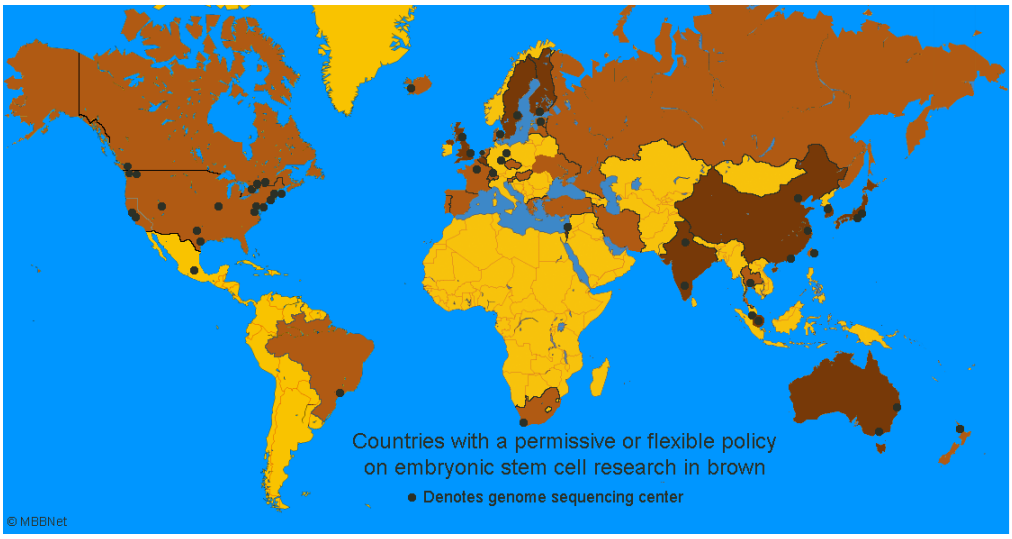


Figure-1: Different Countries Policies on Stem Cells and Embryos. Superimposed on the world map in colors are countries with permissive stem cell policies (dark brown), moderate stem cell policies (light brown), or no stem cell policies (yellow). [http://mbbnet.umn.edu/scmap.html]

Chapter-4 Bibliography

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

Barnes C (2006) China the land of opportunity for stem cell research. *DrugResearcher.com*. http://www.drugresearcher.com/Research-management/China-the-land-of-opportunity-for-stem-cell-research

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

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

Ertelt, Stephen (2005) “Ohio Governor Overturns Embryonic Stem Cell Research Funding Ban”. *LifeNews.com* http://www.freerepublic.com/focus/f-news/1434346/posts

Estes, Andrea (2007) “Mass. Governor Deval Patrick Announces $1 Billion Plan to Advance Stem Cell Work”. The Boston Globe, May 15, 2007. Volume 127, 16.

Federal Register (2009) Draft NIH Guidelines for Human Stem Cell Research. *Federal Register* **74**: 18578. http://stemcells.nih.gov/policy/2009draft

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

Majumder MA, and Cohen CB (2009) The NIH Draft Guidelines on Human Stem Cell Research. *Science* **324**: 1648-1649.

Mokellyreport (2009) http://mokellyreport.files.wordpress.com/2009/07/bill-clinton.jpg

News In Brief (2008) Massachusetts Finally Passes Life Sciences Bill. *Nature* **453**: 969.

Stem Cell Tracker (2009) “Stem Cell Research Timeline” http://www.stemcelltracker.com/2009/02/stem-cell-research-timeline.html

TopNews (2010) http://www.topnews.in/files/george-w-bush-picture.jpg

Uploads (2009) http://www.heatherrobinson.net/wp-content/uploads/2009/04/who-is-barack-obama.jpg

Wilson S (2009) "Obama Reverses Bush Policy on Stem Cell Research." *The Washington Post* 10 March 2009. http://www.washingtonpost.com/wp-dyn/content/article/2009/03/09/AR2009030901194.html?sid=ST2009030901296

PROJECT CONCLUSIONS

Based on the research performed for this project, the authors provide their own conclusions on a few key points for stem cells. With respect to the controversial topic of embryonic stem (ES) cells, the authors believe it is appropriate to work with these cells and to derive new ES cell lines. The authors believe the benefits of ES therapies to exisiting individuals with specific kinds of diseases outweighs the detriment to an IVF embryo only 5-days old. And many of the IVF embryos are slated for discard anyway, so might as well be used to try to save lives. As a nod to others holding that ES cell research is wrong, we believe that induced pluripotent stem (iPS) cells and adult stem cells (ASCs) should be used to treat a specific disease if those cells have been shown to work as well as ES cells for that disease, otherwise ES cells should be used. Unfortunately, the effectiveness of ES cells is usually higher than iPS and ASCs for most areas of stem cell research. Developing ASC treatments, even if not quite as effective as ES treatments, will also be important to treat patients who are against using ES cells.

With respect to the best *source* for the embryos to derive ES cells, the authors believe excess IVF embryos originally created for reproductive purposes should be used first, then if those become exhausted we believe embryos should be created for research purposes. Having women donate eggs is an acceptable option to us, but *without pay* which we believe would provide an incentive to push underpriviledged women who need the money.

With respect to laws regulating stem cell use, the authors of this report support the current United States policies under President Obama, who in 2009 overturned the 2001 Bush ban on using federal money to developed ES cell lines for research. These laws should help

develop treatments for a large variety of diseases, while still being sensitive to the source of embryos. Although some types of adult stem cell treatments using hematopoietic stem cells have been around for decades, and have already saved thousands of lives in bone marrow transplants, hopefully future stem cell therapies will eventually be developed to treat a great variety of diseases.