IQP-43-DSA-8303
IQP-43-DSA-0522

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:

_____ _____

Jonathan Marokhovsky Mark Meuse

September 9, 2011

APPROVED:

_____

Prof. David S. Adams, PhD
WPI Project Advisor

ABSTRACT

This project's purpose was to compile information critical for understanding the topic of stem cell research to help determine the impact of the technology on society. The authors hope to convey which areas of stem cell research are most crucial to understanding the technology's impact. Early chapters introduced the origins of stem cells and their current and future applications. Later chapters discussed the ethics and legalities surrounding stem cells. Finally, a conclusion was made by the authors based on the information and research presented within the project.

TABLE OF CONTENTS

Signature Page ……..…….. 1

Abstract ……..……. 2

Table of Contents ……..…….. 3

Project Objective ……..……...…… 4

Chapter-1: Stem Cell Types and Sources ……..…… 5

Chapter-2: Stem Cell Applications ..……..…….…….. 19

Chapter-3: Stem Cell Ethics ……..…… 30

Chapter-4: Stem Cell Legalities ……..…….……. 41

Project Conclusions ……..…….…….…… 50

PROJECT OBJECTIVES

The purpose of this IQP is to provide the public with a general overview of the topic of stem cells to aid their understanding of how stem technology has affected society. Chapter 1 will discuss the different types of stem cells, their origins, as well as some basic properties of each cell type. Chapter 2 will analyze the different uses of stem cells, including the treatment of various diseases in regenerative medicine. Chapter 3 will explore stem cell ethics from the perspective of the major world religions, and will introduce ethical reasoning for and against stem cell use. Finally, Chapter 4 will examine the laws that regulate stem cell research in the United States and compare them to various international laws. This project will conclude with a final recommendation of stem cell use by the authors of this report.

Chapter-1: Stem Cell Types and Sources

Mark Meuse

Regenerative medicine has been an area of great interest within the scientific community over the last several years. This particular field of study has seen many recent technological advances and given the history of this field, more are sure to come. It is in the interest of the public to be aware of these advances as there are many ethical and political concerns associated within this area of research. In particular, stem cells are a hotly debated topic within regenerative medicine. Stem cells may hold the key to revolutionize the medical treatments of the twenty-first century, but at a cost that has yet to be determined. Understanding the differences between the types of stem cells and their sources will be crucial to making competent decisions regarding their scientific, ethical, and legal ramifications. It is the goal of this chapter to provide this necessary background information on stem cells.

Defining Stem Cells

Stem cells are unique from other cells in the human body. Perhaps the most notable and significant feature of stem cells is their undifferentiated form. Most cells within the human body have a specific set of functions to perform, and to accomplish this they exhibit specialized structures or characteristics. Stem cells are unique in that they have the potential to become other cell types, allowing them to perform almost any function within the body (Itskovitz-Eldor et al., 2000). The other characteristic they exhibit is the ability to self-renew or proliferate in an undifferentiated state (Itskovitz-Eldor et al., 2000). However, stem cells are not all alike, and each has their own uniqueness.

Embryonic Stem Cells

Embryonic stem cells (ES cells) are a type of stem cell harvested during embryonic development. ES cells are harvested from embryos during the blastocyst stage of development, approximately five days after *in vitro* fertilization (**Figure-1**) (Yu and Thomson, 2006). At this stage of development, cell differentiation and specialization has begun to occur within the outermost layer of the blastocyst known as the trophectoderm, which will eventually form the placenta. The cells inside the trophectoderm constitute the inner cell mass (ICM) that remains undifferentiated and pluripotent (Yu and Thomson, 2006) and are composed of ES cells which can differentiate into any cell type of the adult organism, but not the cells that make up the extra-embryonic tissues (Itskovitz-Eldor et al., 2000). Only the newly fertilized egg and cells through the 8-cell stage are considered totipotent, able to differentiate into any cell type of the adult organism or the extra-embryonic tissue.

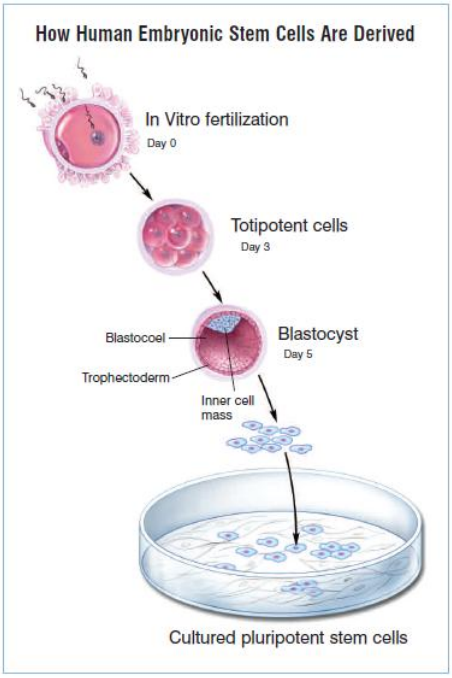

Figure-1: Derivation of Embryonic Stem Cells.
(Yu and Thomson, 2006)

ES cells were first discovered in murine (mouse) embryos in 1981 (Evans and Kaufman, 1981), but it would take almost two decades until human embryos left over from *in vitro* fertilization (IVF) procedures would yield human ES cell lines (Thomson et al., 1998). Within the U.S., researchers are not allowed to use embryos fertilized within a woman's body, so IVF embryos were used to derive the first ES cell lines. In the initial derivation (Thompson et al., 1998), the human ES cells were plated on a layer of irradiated mouse feeder cells to help the ES cells grow and maintain pluripotency. The irradiated feeder layer cells were unable to divide themselves, but could still provide growth factors and a scaffold for growth of the human ES cells. However, the use of a mouse feeder layer was eventually deemed unsatisfactory for culturing human ES cells because animal products could potentially contaminate the human cells making them unsuitable for transplant into humans by containing immunogens "that evoke an immune response and thus lead to rejection upon transplantation", and the animal cells could also carry harmful pathogens (Lu et al., 2006). Recently, human extracellular matrix (ECM) has been used as a feeder layer to derive new ES cell lines not contaminated with animal proteins (Klimanskaya et al., 2005). Once an ES cell population has reached significant size, it can be re-cultured in another dish. ES cells must undergo multiple passages before they can be considered an ES cell line. This process takes several months to complete, and the ES cells must proliferate without differentiating.

Adult Stem Cells

Adult stem cells (ASCs) differ from embryonic stem cells in that they do not require an embryo to be cultured, and as such do not destroy embryos to obtain them. This has made adult stem cells an attractive alternative to ES cells, although ASCs are harder to isolate and grow in

large quantities, and they are less potent. Adult stem cells are only multipotent, and are limited to differentiating into a few types of related cells. However, new research shows that some types of ASCs may be able to become pluripotent (Obokata et al., 2011). More research into this area of adult stem cells is required, but preliminary evidence seems to suggest that the environment in which the cells develop may be the most important factor in determining their potency (Obokata et al., 2011).

Hematopoietic Stem Cells

The best characterized type of stem cell is the hematopoietic stem cell (HSC). HSCs are found primarily in bone marrow, but can also be found in umbilical cord blood and in small quantities in the bloodstream (Domen et al., 2006). HSCs were the first stem cells discovered (Hematopoietic Stem Cells, 2005). The discovery came as a result of researching the effects of radiation treatment and chemotherapy in cancer patients. By studying the effects of bone marrow transplants, it was determined that a cell capable of self renewal and proliferation of multiple blood cell types must be present within the bone marrow. This was determined from the full recovery of the hematopoietic system within patients whose bone marrow had been completely irradiated and was no longer producing new red blood cells. As a result, HSCs are the only type of stem cell to be extensively tested in human clinical trials (Domen et al., 2006). From 1959 to 1995, HSCs were used in more than 40,000 transplants worldwide (Domen et al., 2006). HSCs possess perhaps the greatest proliferative ability among all stem cells which is crucial for maintaining the rapid production of erythrocytes (red blood cells).

Although HSCs divide rapidly *in vivo*, they are extremely difficult to culture *in vitro*. Culture media tend to promote differentiation rather than proliferation, reducing the cell numbers and thus their effectiveness. The use of umbilical cord blood (UCB) as a source of HSCs began

in the 1980s (Domen et al., 2006). HSCs derived from UCB have shown to be the most proliferative and are easier to obtain. They also are less likely to be rejected by the host (Viacord, 2011). However, the overall number of HSCs within a cord is still undesirably low, so these cells would become more promising if *in vitro* cell lines could be derived.

Neuronal Stem Cells

Until recently it was thought that the adult brain had no way to repair any damage it suffered, but with the discovery of neuronal stem cells (NSCs) this way of thinking is beginning to change. NSCs were first discovered in the subependymal cells of the adult mammalian forebrain (Morshead et al., 1993), but were later found to also be present in the subventricular zone and the dentate gyrus of the adult brain (Temple and Alvarez-Buylla, 1999). All these regions are now known to be involved in neuro-regeneration. NSCs are multipotent and can differentiate into all three major cell types of the brain: neurons, oligodendrites, and astrocytes (**Figure-2**) (Rebuilding the Nervous System, 2005).

NSCs have been used as potential therapies for neurodegenerative diseases such as Parkinson's disease (discussed in Chapter-2). For example, Parkinsonian rats treated with TGFα, a stem cell growth factor, showed that neuronal stem cells had travelled to the damaged sites within the brain and had undergone proliferation, repairing the damaged area and alleviating some of the symptoms (Panchision, 2006). Further research will be required to replicate this process in humans, but it is complicated as human NSCs do not respond to growth factors in the same way as rat NSCs. As more information about NSCs becomes available, their potential applications become more promising.

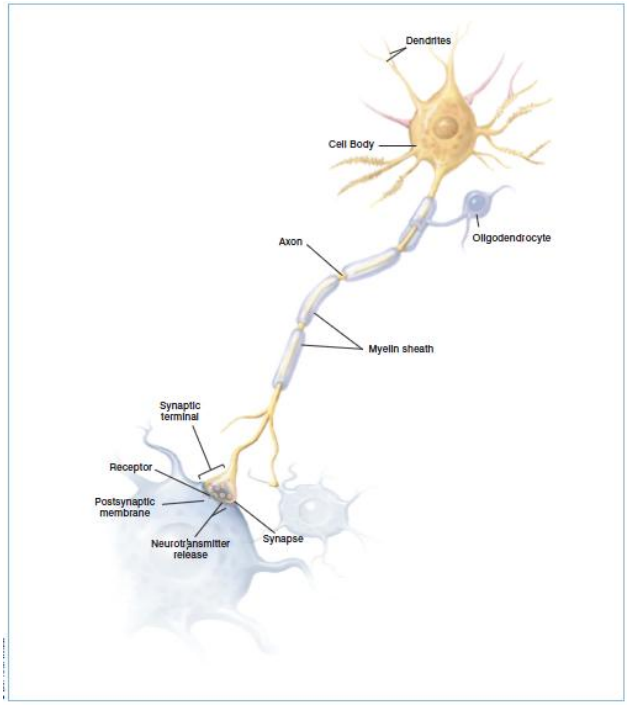

Figure-2: Diagram of Mammalian Neurons and Oligodendrites.
(Panchision, 2006)

Cardiac Stem Cells

Like the brain, the heart was also once thought to be terminally differentiated. But this was disproven when multipotential cells capable of forming myocytes, smooth muscle, and endothelial cells were discovered in the rat heart in 2003 (Beltrami et al., 2003). Researchers noticed that when female rat hearts were transplanted into male hosts, specific surving cells tested Y positive, meaning that they were male. This suggested that CSCs existed and had colonized the transplanted female heart, differentiating into cardiac cells (Beltrami et al, 2003). After testing for many types of cell surface markers, it was determined that the c-kit+ cells in question did not match any other previously known cell type. Once it was shown that these cells could proliferate given the right conditions, and replace damaged tissues within Fisher rats by up

to 50%, they were confirmed to be CSCs. Since c-kit+ is also a marker for hematopoietic stem cells (HSCs), some scientists believe these "CSCs" were actually HSCs that migrated to the heart and differentiated there. Later studies showed strongly that Isl1+ cells may represent true CSCs (Laugwitz et al., 2005).

Epithelial Stem Cells

Skin is the largest organ in the human body and serves as a vital barrier to the outside world. Thus, it comes as no surprise that the skin receives constant damage and is constantly renewing itself, replacing old dead cells or healing wounds. This regeneration would not be possible without the presence of skin stem cells. Adult epithelial stem cells (ESCs) are crucial for maintaining epidermal homeostasis. Bulge stem cells located in a small bulge halfway down the hair shaft (**Figure-3**) migrate downward to the base of the hair follicle and are responsible for maintaining hair growth. The stem cells responsible for replacing dead epithelial cells are interfollicular epidermal stem cells located near the skin surface. The stem cells which make the oil producing cells in the epidermis are located near the sebaceous gland and are called sebaceous-gland stem cells. Skin wounding stimulates the migration of interfollicular stem cells and bulge stem cells to migrate and repair the wound (Blanpain, 2010).

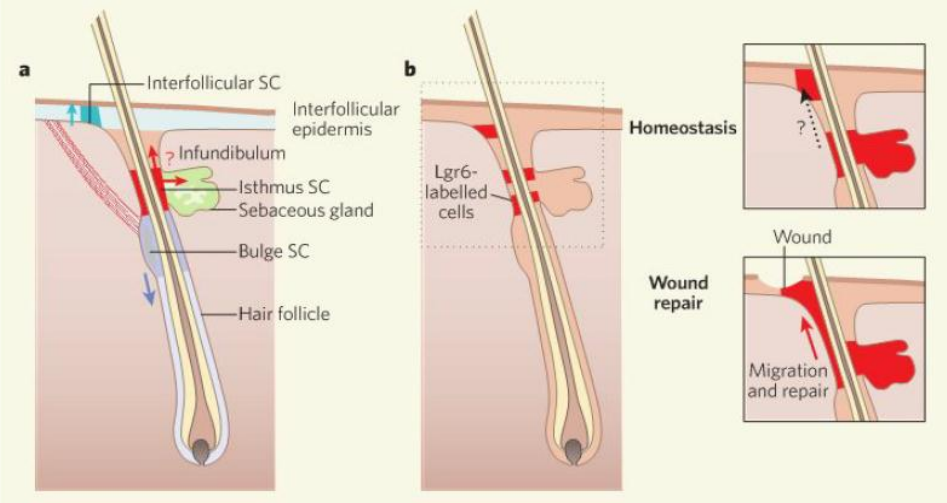

Figure-3: Diagram of Skin Wound Healing by Epithelial Stem Cells. (Blanpain, 2010)

Mesenchymal Stem Cells

The last type of adult stem cell to be covered in this chapter is mesenchymal stem cells (MSCs). MSCs are adult bone marrow stem cells and should not be confused with hematopoietic stem cells which are also located within the bone marrow. MSCs can also be found in UCB and in deciduous teeth (Barry and Murphy, 2004). Like most adult stem cell types, MSCs are multi-potent, but are not pluripotent like ES cells. They are capable of forming osteoblasts, adipocytes, chondroblasts, and myocytes, as well as non-mesodermal cell types like neuronal and glial cells (Song et al., 2009). This multi-potency has led to mesenchymal stem cells being used for regenerative applications in the brain, heart, and spinal cord. Unlike other adult stem cells, a lot of ambiguity and controversy remain when determining exactly which cells qualify as MSCs due to the high variability of the surface antigens among the various cell types. Some researchers suggest that MSCs must express CD105, CD73, and CD90 at levels equal to or

greater than 95% (Dominici et al., 2006). Hopefully, continuing characterization of MSCs will lead to better definitions and more applications.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPS cells) are another classification of stem cells. Unlike the previous types of stem cells, iPS cells do not occur naturally in the body. iPS cells were invented by Shinya Yamanaka from the University of Japan in 2006 in mice (Takahashi and Yamanaka, 2006), and in humans in 2007 (Takahashi et al., 2007). iPS cells are adult skin fibroblast (somatic) cells that are isolated and genetically reprogrammed usually using viral vectors. By inserting genes like Oct3/4, Sox2, c-Myc, and Klf4 into a somatic cell it can be reprogrammed into acting like an embryonic stem cell (Stadfeld et al., 2008; Cyranoski, 2008). iPS cells appear to be pluripotent, forming cells from all three embryonic germ layers. However, their true potency level remains controversial as some scientists report that iPS cells are not as potent as ES cells and are more difficult to grow (Hayden, 2011).

iPS cells have received much attention because if they prove to be pluripotent they may serve as a replacement for ES cells without requiring the destruction of an embryo, and because they would be genetically identical to the patient they may be less likely to be rejected. The early use of viral vectors to achieve pluripotency may increase the chance of rejection, and iPS cells may show mutations which could lead to cancer (Gore et al., 2011; Cyranoski, 2008).

Recent research has focused on transforming the cells without the use of viral vectors (Yu et al., 2009). Matthias Stadfeld was able to induce iPS cells without the use of viral vectors. The method was approximately three magnitudes less efficient, but there was a significant reduction in the number of persisting genetic mutations (Stadfeld et al., 2008). Other researchers have used as few as two or three factors to induce iPS cells in an effort to eliminate the c-myc

component which was responsible for cancer induction in some earlier experiments. The other problem with iPS cells is they proliferate slower than ES cells, and are less robust. In order for iPS cells to become a viable option for therapeutic purposes major improvements will have to occur to make them safe and cost effective.

Somatic Cell Nuclear Transfer

Somatic cell nuclear transfer (SCNT), also known as therapeutic cloning, was supposed to provide true ES cells genetically identical to a patient, and also solve the problems presented by iPS cells. SCNT is a process wherein somatic nuclei are transferred (usually from skin fibroblast cells) into enucleated fertilized zygotes, then when the resultant embryo is cultured in vitro to the blastocyst stage ES cells are harvested from the ICM just like normal ES cells. Using this process creates an ES cell line genetically identical to the person who donated the nucleus, so in theory could create ES cells histo-compatible with a patient, saving patients from having to constantly take immune-suppressants. In addition to being genetically identical to a patient, this process does not use viral vectors or oncogenes, so it was hypothesized to produce fewer mutations and be less likely to cause cancer.

However, SCNT has not been achieved in humans to date. Initial papers claiming human therapeutic cloning were fraudulently published and were later retracted. Even if the process is eventually achieved, there is still no guarantee that this method will produce histo-compatible cells, or will not produce mutations which are often present in cloned animals (Yu and Thomson, 2006). Cloned animals have demonstrated a number of other issues including high pregnancy loss, prolonged gestation, and higher rates of peri- and post-natal mortality, all of which are factors in the low survival of clones (Dinnyes and Szmolenszky, 2005).

Parthenotes

Another alternative to classic ES cells that has been proposed are parthenotes. Parthenogenesis is a type of asexual reproduction that in nature allows some insect species to create worker bees and ants without the use of male DNA. Daughter parthenotes are nearly identical to the mother. Mammals are not usually able to reproduce in this manner, but mammalian oocytes can be artificially induced to undergo parthenogenesis *in vitro* (Brevini and Gandolfi, 2007). To achieve this, parthenogenetic activation is performed on metaphase-2 oocytes by exposure to an actin polymerization inhibitor or strontium chloride which stimulates calcium flow into the oocyte initiating cell division (Brevini and Gandolfi, 2007). If the parthenote embryo survives to the blastocyst state, ES cells can be isolated to make an ES cell line. However, culturing oocytes to the blastocyst stage is very difficult because of the unstable genome of the parthenogenic oocytes. In a recent study, only 9 out of 104 parthenotes were able to be cultured to the blastocyst stage, an 8.65% success rate (Brevini and Gandolfi, 2007). And the long term viability of these cells remains to be seen. Major mutations are possible, and may occur in as many as 15-20% of parthenotes and increases with age.

This process has been achieved with monkeys (Cibelli et al., 2002), but it is controversial whether it has been achieved with human eggs. Like SCNT, the immune system would be unlikely to reject such genetically similar ES cells from the woman who provided the eggs, and could prevent the need for immuno-suppressants. Without the male genetic component, parthenotes do not have the potential to develop into a human being, so some ethicists believe parthenote ES cells may have fewer ethical concerns than ES cells derived from traditional IVF embryos. As with many of the other types of stem cells, more research is required to make parthenote ES cells a viable alternative to traditional ES cells. Improvements in this type of stem

cell may be slow to develop given the small numbers of human oocytes available for research purposes, but parthenotes are an extremely attractive alternative if such improvements are made.

Chapter-1 Bibliography

Barry F, Murphy M (2004) Mesenchymal Stem Cells: Clinical Applications and Biological Characterization. *International Journal of Biochemistry and Cell Biology*, **36**: 568-584.

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.

Blanpain C (2010) Skin regeneration and repair. *Nature*, **464**: 686-687.

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

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.

Cyranoski D (2008) Five Things to Know Before Jumping on the iPS Bandwagon. *Nature*, **452**: 406-408.

Dinnyes Andras, Szmolenszky Agnes (2005) Animal Cloning by Nuclear Transfer: State-of-the-Art and Future Perspectives. *Acta Biochimica Polonica*, **52:** 585-588.

Domen J, Wagers A, Weissman I (2006) Bone Marrow (Hematopoietic) Stem Cells. *NIH Publication*. Bethesda, MD: Regenerative Medicine. http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf

Dominici M et al. (2006) Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy*, **8**: 315-317.

Evans MJ, Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. *Nature*, **292**(5819): 154-156.

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

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

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

Itskovitz-Eldor J, et al (2000) "Differentiation of Human Embryonic Stem Cells into Embryoid Bodies Comprising the Three Embryonic Germ Layers." *Molecular Medicine,* **6**: 88-95.

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

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

Lu J, Hou R, Booth C, Yang S, Snyder M (2006) Defined Culture Conditions of Human Embryonic Stem Cells. *Proceedings of the National Academy of Sciences*, **103**: 5688-5693.

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.

Obokata Haruko, Kojima Koji, Westerman Karen, Yamato Masayuki, Okano Terou, Tsuneda Satoshi, Vacanti Charles (2011) The Potential of Stem Cells in Adult Tissues Representative of the Three Germ Layers. *Tissue Engineering*, **17**: 607-615.

Panchision D (2006) Repairing the Nervous System With Stem Cells. *NIH Publication*. Bethesda, MD: Regenerative Medicine.
http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf

Rebuilding the Nervous System with Stem Cells (2005) NIH, Stem Cells, Chapter-8.
http://stemcells.nih.gov/info/scireport/chapter8.asp

Song CH, Honmou O, Ohsawa N, Nakamura K, Hamada H, Furuoka H, Hasebe R, Horiuchi M (2009) Effect of Transplantation of Bone Marrow-Derived Mesenchymal Stem Cells on Mice Infected with Prions. *Journal of Virology*, **83**: 5918-5927.

Stadfeld M, et al (2008) Induced Pluripotent Stem Cells Generated Without Viral Integration. *Science*, **322**: 945-949.

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

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

Temple S, Alvarez-Buylla (1999) Stem Cells in the Adult Mammalian Central Nervous System. *Neurobiology*, **9**: 135-141.

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

Viacord (2011) www.viacord.com

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

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

Jonathan Marokhovsky

Researching stem cells is important so that scientists can find more treatments to diseases previously thought to be incurable. Stem cells have been used to successfully treat many advanced cancers such as leukemia and blood diseases such as sickle cell anemia. Because of the success with these diseases, scientists have been searching for other applications, including repairing slow-reproducing cells such as heart muscle cells, or using stem cells to cure Type-1 diabetes. Examples of stem cell benefits will be discussed in this Chapter. These benefits to society are an important part of discussions on stem cell ethics (Chapter-3), where benefits are weighed against the loss of an embryo.

Hematopoietic Stem Cell Applications

The stem cells which have so far had the most applications are Hematopoietic Stem Cells (HSCs) which have been utilized via bone marrow transplants (BMTs) since 1959 to treat cancers occurring in the circulatory system, and have since been applied to other diseases of the blood and autoimmune diseases (Donnall, 2000). Because we have been using HSCs for so long, we have a much greater understanding of how they work. **Figure-1** illustrates the main differentiation pathways for HSCs and how they form the cellular components of blood. Although these cells can be used to regenerate the blood system, they have risks including rejection by the patient if they are not histo-compatible, or the implanted cells (typically referred to as grafts) can attack the host (Graft-Versus-Host Disease; GVHD), which is only slightly less lethal than when the host's immune system rejects the graft (Wright, 2005).

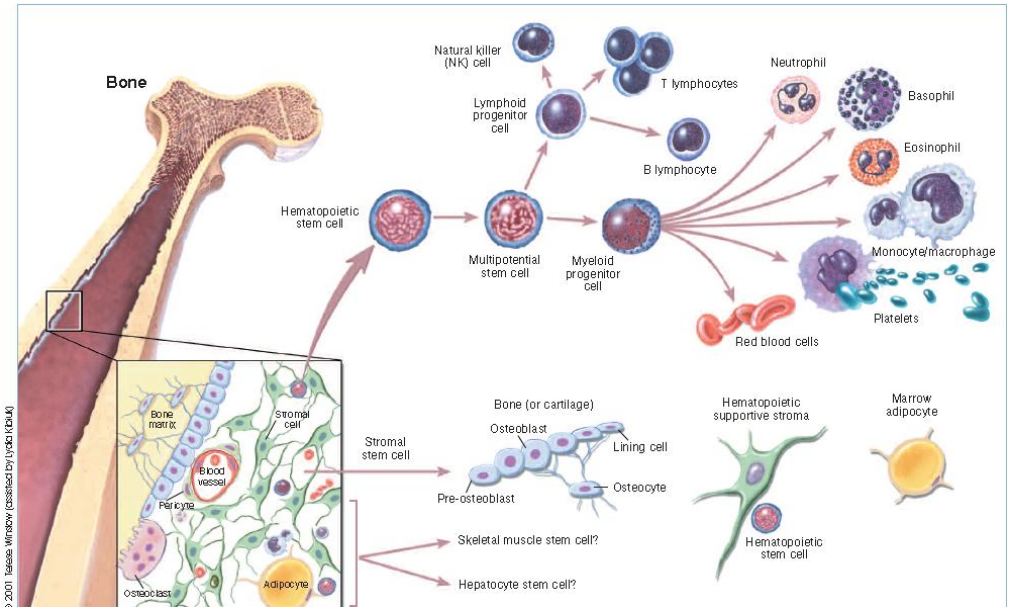

Figure-1: Diagram of Hematopoietic and Stromal Cell Differentiation.
Shown are the main differentiation pathways of hematopoietic stem cells to form all the cellular components of blood. (Regenerative Medicine, 2006)

However, despite the risks associated with bone marrow transplants, many patients still decide to have BMTs because if everything goes well there's a high chance they will make a full recovery from what likely is a fatal disease (Wright, 2005). Every year, about 40,000 bone marrow transplants are performed worldwide (Horowitz, 1999; Santos, 2000). Though most of the applications are for cancers such as leukemia, HSCs can also be used to treat other disorders.

The group of diseases named "leukemia" all have in common that they are related to the hematopoietic system failing to obey normal regulatory signals. If such signals are no longer obeyed, these leukemic cells are either less likely to undergo cell apoptosis (cell death) or they start replicating much more rapidly than normal hematopoietic cells (Reya et al., 2001). And in either case, the blood cells become less functional. **Figure-2** shows how fast mildly to fully leukemic stem cells (purple and red cells, respectively) reproduce in comparison to normal

hematopoietic stem cells (blue cells). After leukemic cells have reproduced, they will either differentiate into large numbers of damaged specialized cells (Panel-A), or will not be able to differentiate at all (Panel-B) (Regenerative Medicine, 2006).

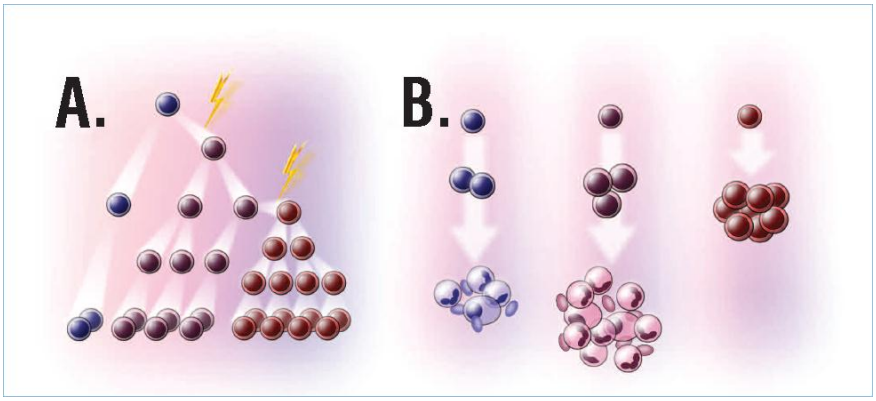

Figure-2: Diagram of the Leukemic Progression at the Hematopoietic Stem Cell Level. Panel-A shows the rapid division of leukemic blood cells into non-functional cells (red). Panel-B denotes leukemic hematopoietic stem cells that have lost their ability to differentiate. (Regenerative Medicine, 2006)

Because scientists have discovered that HSCs can be found in peripheral blood and in umbilical cord blood, we no longer only use the term "bone marrow transplantation" and sometimes refer to the process as hematopoietic cell transplantation (HCT). Stem cells found in peripheral blood are called Peripheral Blood Stem Cells (PBSCs) (Goodman and Hodgson, 1962; Cavins et al., 1964; Storb et al., 1977), while stem cells found in umbilical cord blood are called Cord Blood Stem Cells (CBSCs) (Gluckman et al., 1989). Two major advantages of using these newly discovered stem cells are that the donor does not need an operating room to donate their cells, and they are less likely to induce GVHD (Donnall, 2000).

One current area of HSC research is how Leukemic Stem Cells (LSCs) that tend to divide uncontrollably, are formed, act, and reproduce, etc. As scientists discover more about LSCs,

they hope to find more ways to attack them or, better yet, find ways of detecting those at risk and prevent the formation of LSCs in the first place (Al-Hajj et al., 2004; Guzman and Jordan, 2004; Jones et al., 2004). And scientists continue to refine all aspects parts of the transplantation process, seeking better ways to identify MHC matches between donor and recipient to lessen GVHD, and making the process less painful. The preparative regimens prior to transplantations are being modified to be less toxic to the patients. In particular, scientists are looking to CBSCs to reduce GVHD, as those cells are younger and immunologically immature lowering the chances of GVHD (Donnall, 2000).

Stem Cell Therapy of Damaged Heart Muscles

Heart disease occurs when the heart becomes damaged or weakened, and this disease takes the most lives per year than any other condition. Despite this, there are relatively few treatments. The reason this disease is so lethal is because the heart, like the brain and spinal cord, does not repair itself as fast as other parts of the body (Baker, 2009). However, hope for treating this disorder recently improved with the identification of adult cardiac stem cells, which are responsible for repairing heart tissue. But these cells are rare in heart muscle, and can only be distinguished by a nuclear protein called Isl1. This complicates isolating the cells for therapeutic purposes because usually cells are isolated on the basis of unique surface markers and Isl1 is not found on the cell surface (Bu et al., 2009). Because of this, some scientists believe it may never be possible to have clinical trials for cardiac stem cells and damaged hearts, while others believe it is only a matter of time before we discover a surface protein exclusive to these cells (Baker, 2009).

Research is starting to be performed on both animal models and human patients. Though some groups have obtained promising results, other groups remain skeptical because their studies

indicate no beneficial effects of stem cell treatments. As is depicted in **Figure-3**, several trials are attempting to test a variety of therapeutic cells, from bone marrow cells to mesenchymal stem cells (Baker, 2009).

SELECTED HEART CELL-THERAPY TRIALS

Trials of bone-marrow cells dominate the field of heart stem-cell therapy. All except the Osiris trial use patients' own cells.

Sponsor	Cell type	Phase	Expected enrolment
Bioheart, Munich, Germany	Skeletal myoblasts	II/III	390
Osiris Therapeutics, Columbia, Maryland	Mesenchymal stem cells	II	220
Cedars-Sinai Medical Center, Los Angeles, California	Cells from heart biopsies	I	30
Ministry of Health, Brazil	Bone-marrow cells	III	300
Johann Wolfgang Goethe University Hospitals, Frankfurt, Germany	Bone-marrow cells	III	200
Barts and The London NHS Trust, UK	Bone-marrow cells	II/III	165
Seoul National University Hospital, Korea	Circulating blood cells	II/III	116
Source: clinicaltrials.gov			

Figure-3: Chart of Current Heart Cell-Therapy Trials.
(Baker, 2009)

Two studies in particular are at odds with each other, and came out the same year. Both studies used intracoronary injection of bone marrow cells on the left ventricle in human patients. Half of the patients were randomly picked for the therapy procedure and the other half acted as controls. One study found "no effects of intracoronary injection of autologous mononuclear BMC on global left ventricular function" (Lunde et al., 2006), while the other group found that "intracoronary administration of BMC is associated with a significant increase in the recovery of left ventricular contractile function in patients with optimally treated acute myocardial infarction" (Schächinger et al., 2006). The former group did state that "differences in cell preparation and cell numbers may be important" (Lunde et al., 2006).

One group of scientists has shown that mesenchymal stem cells (MSCs) have the ability to fix some parts of the heart muscle. MSCs are a type of stem cell present in bone marrow in addition to HSCs. The scientists used pigs as their subjects, and treated some of the pigs with a placebo and others with allogeneic MSCs. They concluded that injecting allogeneic MSCs "into regions of damaged myocardium three days after myocardial infarction stimulated cardiac regeneration, and profoundly decreased myocardial infarct size" (Amado et al., 2005).

Stem Cells and Parkinson's Disease

Parkinson's disease (PD) occurs when the brain damages cells in the *substantia nigra* which produce dopamine. Since dopamine is a neurotransmitter that helps with motor control, when Parkinson's progresses it makes it difficult to initiate and control movements. Even though the change may not yet be noticeable in the person's motor control, extensive and permanent damage could already have been done to the dopamine producing cells, and it is extremely difficult if not impossible to diagnose Parkinson's early enough where this is not the case (Transplanted Brain Cells…, 2006).

Currently there is no cure for Parkinson's disease, but to treat it, patients are sometimes given L-Dopa (a synthetic dopamine) which tends to minimize symptoms for three to five years, eventually warranting a higher dose. As the disease progresses, the drug starts being less effective, and increasing to a larger dose can sometimes lead to dyskinesia, an uncontrolled movement caused by the drug (Transplanted Brain Cells…, 2006).

Research on PD stem cell therapies has started to progress to human trials, though the majority of the studies are still in animal models, especially rodents. Levesque and colleagues (2005) successfully performed an autologous adult neural stem cell transplant in a human patient. They removed some neural stem cells from the patient, cultivated those same cells, and re-

implanted them into the PD patient (Levesque, 2005). Because it was an autologous transplant, there was no need for immunosuppressants. After the procedure, the patient's motor skills "improved by over 80% for at least 36 months" according to Levesque, when only half of the patient's brain was treated with the stem cells (Ertelt, 2009). Although the procedure needs refinement, this is a very promising result.

Borlongan and colleagues used a neurotoxin to artificially recreate Parkinson's disease in rats, then transplanted human brain stem cells and found that one month later the cells had survived and started to produce synapses (connections in the brain). Two months later the rats were still improving. The only problem with this procedure is it mimics PD in its earliest stages, before the disease noticeably affects movement, and before a patient would present to a doctor (Transplanted Brain Cells…, 2006). These findings would be more meaningful if there was a way to detect PD in humans before it damages the *substantia nigra* significantly.

Ben-Hur and colleagues (2004) transplanted human embryonic stem cells (hESCs) into Parkinsonian rats and found that they showed "… significant improvement in stepping and placing… behavioral tests". But because this study was the first of its type, there should be more extensive long-term studies to determine the safety of hESC transplantation to rule out the potential hazards seen in other hESC treatments, including tumor formation and the stem cells developing into non-neural cells (Ben-Hur et al., 2004).

Stem Cells and Type-1 Diabetes

Type 1 diabetes (T1D) occurs when an individual's pancreas has less than 10 percent of the β-cells functioning. These cells normally produce insulin that helps regulate glucose uptake by cells, so without it there is glucose deregulation (Thorel et al., 2010). β-cell destruction results from autoimmune attack (Assady et al., 2001). Past treatments for T1D generally

provided the missing insulin, but did not treat the underlying cause (Thorel et al., 2010). Currently the only curative therapy for T1D is pancreatic and islet cell replacement, but these donor cells are always in short supply (Assady et al., 2001), thus scientists are seeking alternative cell treatments.

One such solution is the application of xenografts, where a patient receives stem cells originating from an animal genetically modified to be histo-compatible. If this procedure can be worked out, it could provide cells desperately needed for therapy. But there are drawbacks, as xenografts put the patient in danger of zoonotic infections for porcine viruses (although these could be pre-screened) and phenotypic instability (Assady et al., 2001).

With respect to stem cell treatments, some scientists have taken bone marrow from healthy donors and injected it into a diabetic patient. This has shown some positive results so this technique may eventually work (Thorel et al., 2010). Scientists have also shown that human embryonic stem cells are capable of differentiation into insulin producing cells, and show other β-cell markers (Assady et al., 2001). One group of scientists found that HSC and BMTs from MHC-matched mice successfully prevented T1D. This proved to the scientists that non-MHC genes expressed on hematopoietic cells can confer disease protection. This also proved that complete elimination of T1D hematopoietic cells was not required in the recipient because the nonmyeloabative transplantations were 100% protective. Thus, the mouse experiments proved that diabetes protection does not require complete donor chimerism, and the presence of non-functional β–cells does not hinder the therapy; so mixed chimerism was effective for this kind of procedure (Beilhack et al., 2005). Another group of scientists demonstrated that adult mouse bone marrow harbors cells that are capable of differentiation towards a pancreatic endocrine β-cell phenotype *in vivo* (Ianus et al., 2003).

Thorel and colleagues (2010) studied the inherent regenerative capacity of the adult pancreas for producing new β-cells after a near-total cellular loss. Their procedure mimicked T1D except for the autoimmunity, and allowed the scientists to explore whether new insulin-producing cells can emerge from other types of cells than pre-existing β-cells. They found that pancreatic α-cells are capable of insulin production, without hindering their normal production of glucagon. The scientists found that all mice who survived six months after the procedure made a complete recovery (Thorel et al., 2010).

Chapter-2 Bibliography

Al-Hajj M, Becker MW, Wicha M, Weissman I, Clarke MF (2004) Therapeutic implications of cancer stem cells. *Curr Opin Genet Dev.,* 14: 43-47.

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.

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

Baker, Monya (2009) How to Fix a Broken Heart. *Nature,* **460**: 18-19.

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

Ben-Hur T, Idelson M, Khaner H, Pera M, Reinhartz E, Itzik A, Reubinoff BE (2004) Transplantation of Human Embryonic Stem Cell–Derived Neural Progenitors Improves Behavioral Deficit in Parkinsonian Rats. *Stem Cells,* **22**: 1246-1255.

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

Cavins JA, Scheer SC, Thomas ED, et al (1964) The recovery of lethally irradiated dogs given infusions of autologous leukocytes preserved at -80 C. *Blood*, **23**:38-43.

Donnall, Thomas E (2000) "Bone Marrow Transplantation: A Historical Review" *Medicina*, **33**: 209-218.

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

Gluckman, E. Broxmeyer HE, Auerbach AD, et al (1989) Hematopoietic reconstitution in a patient with Fanconi.s anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med*, **321**: 1174-1178.

Goodman JW, Hodgson GS (1962) Evidence for stem cells in the peripheral blood of mice. *Blood*, **19**: 702-714.

Guzman ML, Jordan CT (2004) Considerations for targeting malignant stem cells in leukemia. *Cancer Control*, 11: 97-104.

Horowitz MM (1999) Uses and growth of hematopoietic cell transplantation. In: Forman SJ, ed. *Hematopoietic cell transplantation.* Second ed. Malden, MA: Blackwell Science Inc; 1999: 12-18.

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.

Jones RJ, Matsui WH, Smith BD (2004) Cancer stem cells: are we missing the target? *J Natl Cancer Inst.*, **96**: 583-585.

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

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.

Regenerative Medicine. Department of Health and Human Services. August 2006. http://stemcells.nih.gov/info/scireport/2006report.

Reya T, Morrison SJ, Clarke MF, Weissman IL (2001) Stem cells, cancer, and cancer stem cells. *Nature*, Vol **414**: 105-111.

Santos GW (2000) Historical background to hematopoietic stem cell transplantation. In: Atkinson K, ed. *Clinical bone marrow and blood stem cell transplantation.* Cambridge, UK: Cambridge University Press; 2000: 1-12.

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.

Storb R, Graham TC, Epstein RB, et al (1977) Demonstration of hematopoietic stem cells in the peripheral blood of baboons by cross circulation. *Blood,* **50**: 537-542.

Thorel F, Nepote V, Avril I, Kohno K, Desgraz R, Chera S, and Herrera P (2010) Conversion of adult pancreatic α-cells to β-cells after extreme β-cell loss. *Nature,* **464**: 1149-1154.

Transplanted Brain Cells Hold Promise for Parkinson's Disease. *Science Daily* (2006). Issue December 7, 2006. http://www.sciencedaily.com/releases/2006/12/061204123212.htm

Wright, Matthew (2005) "Bone marrow transplant patients celebrate survival". Stanford News Service. http://news-service.stanford.edu/news/2005/august24/med-reunion-082405.html

Chapter-3: Stem Cell Ethics

Mark Meuse

Stem cell research has been perhaps the most controversial area of scientific research in the last two decades. Understanding both the proponent and opponent issues on this topic is necessary for enacting fair laws that improve medical capability while respecting human dignity. The majority of ethical concern is directed toward embryonic stem (ES) cell lines because embryos are destroyed to generate the lines. However, other types of stem cells do not destroy embryos. The purpose of this chapter is to investigate the ethical nature of each of the various categories of stem cells and the processes used to obtain them, including ES cells, iPS cells, parthenotes, adult stem cells, and somatic cell nuclear transfer (SCNT), as an example of investigating the impact of new technology on society.

Many opponents of stem cell research are strongly influenced by their religious beliefs. To determine how various religions influence stem cell ethics, the world's five largest religions and their respective positions will be examined. These religions include Christianity, Judaism, Islam, Buddhism, and Hinduism. It is important to remember that these religions have varying views of the ethical nature of stem cells depending on which category of stem cell is being discussed, so each stem cell category will be discussed from the perspective of all five of these religions to present an overview of the subject.

Focusing the Stem Cell Debate

In general, the stem cell debate focuses on the issue of when life begins. So an introduction to the human prenatal life cycle is invaluable in understanding various religious perspectives. The potential for human life begins when sperm and ovum (egg) combine to form a diploid zygote that is genetically unique (Eberl, 2000). The zygote then undergoes cell division until about day-5 when a blastula forms. The blastula is comprised of about 100 cells, and contains an inner cell mass (from which ES cells are derived) and an outer cell layer. Blastocysts can be formed by *in vitro* fertilization (IVF) using sperm and egg provided by donors in reproductive IVF clinics, and can be used to derive new ES cell lines. *In vivo*, during normal pregnancy, the blastula implants in the uterine wall at about day 8-10, and the inner cell mass begins to differentiate. Brain and heart activity begin around week-6 of pregnancy, and development continues until a 9 month period has elapsed. Understanding early human development is crucial to stem cell ethics because much of the debate surrounding stem cells focuses on when within this development process human life begins.

Catholicism, Hinduism, and Buddhism believe that life begins at conception (Teaching About Religion, 2006). Jewish tradition holds that personhood begins at day-40, and Islamic tradition does not provide an exact moment when life begins, but believes it is between the 40th and 120th day (Teaching About Religion, 2006).

Embryonic Stem Cell Ethics

Embryonic stem (ES) cells are the most controversial of the different categories of stem cells. ES cells have the highest medical potency of all stem cell types, but destroy an embryo during their isolation. Within the complex array of Christian denominations, the Roman Catholic stance on ES cells is the most out spoken and clearly defined. Pope John Paul II

outlined the Catholic Church's stance on ES cells during a speech in 2005, stating that "the human embryo is a subject identical to the human being" and that "any form of scientific research which treats the embryo merely as a laboratory specimen is unworthy of man" (Pope John Paul II, 2005). This statement clearly shows that the Catholic Church treats the human embryo as having the same rights as any living person, so most Catholics are strongly against ES stem cell research as a violation of this belief. The Catholic stance that life begins at conception is well documented, so a 5-day old blastocyst is a living human being from this perspective. The human embryo from the moment of conception "has the full complement of human genes, and is actively expressing those genes to live and develop in a way that is unique to human beings, setting the essential foundation for further development…Just as each of us was once an adolescent, a child, a newborn infant, and a child in the womb, each of us was once an embryo" (UCSSB, 2008). Since 5-day old embryos have the potential to become a human being (if implanted in the uterine wall), the Catholic Church treats 5-day embryos as human beings.

Inherent within Jewish culture is the need to seek knowledge that would benefit humankind, especially within the area of medicine (Dorff, 2001). It is this imperative that both compels and allows ES cell research under the Jewish tradition, provided such research is undertaken with responsibility and care. ES cell lines derived from extra IVF embryos are allowable under Jewish law because "genetic materials outside the uterus have no chance of developing into a human being, so they have less legal status in Jewish law than zygotes and embryos in the first stages of gestation" (Dorff, 2001). Jewish law also permits the harvesting of sperm and eggs specifically for medical research. Since embryos are seen as pre-human from the Jewish perspective, the destruction of an embryo for stem cell research is not considered murder,

and is an acceptable means to improve the medical capabilities of humanity because the societal benefits far outweigh the costs.

Islam is considered to be a way of life performed in submission to the will of Allah (God) (Fadel, 2007). When reflecting on the ethical nature of ES cells from an Islamic perspective, one must consider three sources: Quranic teaching, the hadith (sayings of the Prophet Muhammad), and the Fuqua (Islamic legal scholars). Since, the Prophet Muhammad commanded Muslims to seek out cures for diseases, and the Quran does not specifically address when life begins, most Fuqua have come to the conclusion that ES cell research is permissible, provided the cells are harvested from acceptable sources (Fadel, 2007). Acceptable sources of ES cells include embryos aborted for legal purposes and excess embryos from IVF clinics (Fadel, 2007). However, it is unlawful to procure ES cells from intentionally aborted fetuses without medical reason or from intentional fertilization between ovum and sperm for the sole purpose of ES cell research (Fadel, 2007). Thus, ES cell research is acceptable under these provisions, and may even be preferable in cases where excess IVF embryos are going to be destroyed.

Hinduism's view of ES cell research is more closely related to the Catholic viewpoint. The Hindu tradition believes in a hierarchy of consciousness. At the bottom of this hierarchy is plant life, above that is animal life, and finally humanity rests at the top (Bahnot, 2008). The other central belief found in Hinduism is that of reincarnation. Reincarnation is the rebirth of a soul after death into another living being. In Hinduism, this cycle of birth and rebirth is the way in which a soul elevates its consciousness by eventually being born into the human form. Along the way, a soul could travel through as many as 8.4 million species (Bahnot, 2008). As a result, Hinduism highly respects human life, because one must pass through the human form to attain Nirvana or enlightenment. Hindu's are called by their sacred text, the Vedas, to treat all life as

sacred, but humanity is placed above all other life (Bahnot, 2008). Thus, Hinduism views ES cell research as preventing a soul from going through a necessary life cycle to reach salvation, so most Hindu's are against this type of research.

Buddhism, like all other major religions, seeks to support the elimination of suffering through medical advancement. However, a constant struggle over the ethical nature of sacrificing human embryos for medical advances continues in Buddhist culture. Buddhism believes that human life begins at conception, and it would be morally wrong to sacrifice human lives to further ES cell research (Keown, 2004). Unlike other religions though, Buddhism does not have one central authority or leading figure, which has led to widespread differences on the Buddhist view of ES cell research (Keown, 2004). Buddhism is an atheistic religion, not relying on a God. As such, there is no religious text to draw upon. Also, the Buddha's teachings are not considered to be dogma (Prompta, 2004). There appears to be a disparity between what Buddhism teaches and what the average Buddhist believes. This issue may be caused by other Buddhist teachings. For example, Buddhism seeks to eliminate both the *self* and the *other* in order to reach a more enlightened state, but this leads to the question of "why should people act ethically if there is no act, no actor, and no consequences of action (Hughes and Keown, 1995). Buddhism, of the major five religions, is easily the most divided on the matter of ES cell research, as there are claims to both sides of the argument.

Ethics of Somatic Cell Nuclear Transfer

Somatic cell nuclear transfer (SCNT), also called therapeutic cloning, is also a hotly debated topic in stem cell research, as it also requires the destruction of embryos. As discussed in Chapter 1, during therapeutic cloning the nucleus is removed from a skin fibroblast cell and implanted into an enucleated fertilized zygote. The zygote is grown to the blastocyst stage, and

ES cells are isolated. The process has the potential to generate an ES cell line genetically identical to the patient providing the fibroblast nucleus, so the ES cell line is less likely to be immuno-rejected. Therapeutic cloning should not be confused with reproductive cloning in which the injected blastocyst would be implanted in the uterine wall to lead to the birth of a genetically identical individual.

With respect to the various religions stances on therapeutic cloning, they mostly reflect their previously described beliefs on embryo research. The Catholic Church is against such practices as it violates human life, removes the human element from conception, and thus essentially places humans in the role of "playing God", and threatens the commodification of women (Statement of the Catholic Leadership, 2001). Jewish law would permit the use of SCNT as long as the women who provided the eggs are not placed at risk (Dorff, 2001); ovarian hyper-stimulation syndrome is a side effect of the drugs used to induce oocyte release, and may be linked to ovarian cancer. From the Islamic perspective therapeutic cloning falls under the listed forbidden sources of stem cells and is not allowed for similar reasons to Catholicism (Fadel, 2007).

Hinduism also expressly forbids SCNT as violation of its religious law; it is immoral to create embryos solely to be destroyed for scientific research (Prompta, 2004). The Indian Council for Medical Research (ICMR) is a biomedical research body established by the Indian government whose purpose is to determine which areas of stem cell research should be allowed. In 2007, the ICMR released its findings; therapeutic cloning was placed within the restricted, (but not prohibited) category of stem cell research (Indian Council of Medical Research, 2007). This restriction but not prohibition is an interesting conclusion since according to the 2001 Indian census, approximately 80% of India affiliates themselves with Hinduism.

Buddhism, with its lack of a centralized authority and no unifying text, provides no consensus about therapeutic cloning. It is not against the Buddhist tradition to make sacrifices for the greater good (Prompta, 2004), but this is not routinely advocated. Among these five religious perspectives, there appears to be a general consensus against therapeutic cloning. The vast majority of the population does not appear to be ready to accept this technology.

Ethics of iPS Cells and Adult Stem Cells

Induced pluripotent cells are adult skin fibroblast cells genetically reprogrammed to produce pluripotent stem cells. Father Tadeusz Pacholczyk, also known as Father Tad, is a Roman Catholic priest with a PhD in neuroscience from Yale University who is a common spokesperson for the Catholic Church on matters concerning bioethics. Father Tad explains that the crucial ethical difference between iPS cells and other sources of pluripotent stem cells is that iPS cells do not require the destruction of human embryos. Therefore, from a Catholic perspective this type of stem cell research is "certainly preferable to embryonic stem cell research" (Smith, 2006; Catholic Church Apologetics, 2009). Although Father Tad remains optimistic that iPS cells will produce beneficial advances in regenerative medicine, his greatest hope lies with advances with adult stem cells (ASCs). The Catholic Church has been an outspoken advocate of ASCs because, like iPS cells, they do not require the destruction of human embryos and do not pose major ethical concerns. Father Tad believes that ASCs have a greater potential to be successful because ASCs have already been used clinically (Catholic Church Apologetics, 2009), however other scientists warn that ASCs are more difficult to isolate and are more difficult to grow than ES cells.

With respect to the other religious perspectives on iPS cells and ASCs, because these do not destroy embryos and do not violate the dignity of the human person at any point in

development, all five major religions not only accept, but encourage these two types of stem cell research.

Parthenote Ethics

Parthenote-derived ES cells are another type of stem cell around which there is much debate. Recall from Chapter-1 that parthenotes are formed from oocytes that have been chemically treated to undergo mitosis without having been fertilized. This process is achieved using an actin polymerization inhibitor or a strontium chloride solution to stimulate calcium flow, starting cell division. The parthenote embryo is grown to day-5 to make a blastula, then ES cells are harvested from the inner cell mass. The main question concerning parthenotes is their level of humanity; mammalian parthenote embryos are incapable of developing normally and cannot make an adult organism, so some scientists argue parthenote blastulas do not have the potential to become an adult human, so have lower moral status than blastulas derived by fertilization.

The Catholic Church has elected to err on the side of caution, arguing first that the process of parthenogenesis is immoral because, like SCNT, it removes the sexual act from creation (UCSSB, 2008). Parthenotes do undergo some development, enough to derive ES cell lines from them, but since this development is "predestined from the beginning to be abortive, can [it] really be considered the development of a new individual" (Latkovic, 2006)? For the Catholic Church this lack of development and potential does not influence their decision to oppose parthenotes.

Judaism has so far been more open to scientific advancement in relation to stem cells, and this appears to apply to parthenotes. As previously stated, Judaism treats "genetic materials outside the uterus [as having]…even less legal status in Jewish law than zygotes and embryos in

the first stages of gestation" (Dorff, 2001). Parthenotes have a more questionable human status than zygotes outside the womb because they contain no recombined genetic material of a zygote. It stands to reason then, that in Jewish culture parthenotes would be seen as an acceptable type of stem cell research, although there is no clear declaration of this fact yet.

Islam appears to occupy the middle ground between the Catholic and Jewish stances on parthenotes. It is true under Islamic law that it is forbidden to use embryos that have been intentionally fertilized specifically for stem cell research. But, these embryos are not fertilized, and unless an action is categorically forbidden (i.e. believing in a God other than Allah), then it is technically allowable (Fadel, 2007). So here the question becomes do oocytes that are intentionally harvested and programmed to undergo parthenogenesis fall under the Islamic law that forbids the use of embryos to be intentionally fertilized for stem cell research? It could be argued that although the oocytes were harvested for the intention of stem cell research because they are not fertilized embryos that they do not fall under the aforementioned law. However, using such a technicality to circumvent a law may be looked down upon. The deciding factor may not be physical differences between parthenotes and fertilized embryos, but rather the motive behind why they were attained. Since in Islam it is unlawful to procure ES cells from intentional fertilization between ovum and sperm for the sole purpose of ES cell research (Fadel, 2007), then likely Islam would not allow parthenotes ES cells.

As previously stated, both Hinduism and Buddhism believe that life begins at conception (Teaching About Religion, 2006), but with parthenotes there is no conception, so there is a high likelihood that Buddhists would be in favor of parthenote research, especially if made as sacrifices for the greater good. Hinduism might be more reluctant to accept parthenotes than Buddhists because the use of parthenotes could prevent a future reincarnation. Hinduism might

also take a similar stance as Catholicism and prefer to take a more conservative route solely to protect human dignity. While this is also a possibility for Buddhists, the constant variation of opinions within this large religion suggests that not all Buddhists would adhere to these conservative beliefs. Because the Hindu religious text, the Vedas, promotes the sanctity of human life (Bahnot, 2008) it is more likely that Hindus would take a conservative standpoint which would not allow parthenotes.

Chapter-3 Conclusions

Ethically speaking, stem cells will continue to be an area of great debate. All five major religions differ in their opinions on when life begins, and some religions even hold contrasting opinions within themselves. These differences of opinion are influenced not only by religion but by race, socio-economic status, and gender. With so many different factors that apply to stem cell research, it will be difficult to come to a general consensus on the matter, especially when the proponents believe that stem cells likely hold the key to curing numerous diseases. Hopefully, by understanding the positions of these religions, it helps focus the debate, allowing more educated decisions regarding stem cell ethics and the need to respect the personal beliefs of others.

Chapter-3 Bibliography

Bahnot, Anil (2008) The Ethics of Stem Cell Research: A Hindu View. *Bio News*. 17 Oct. 2008. http://www.bionews.org.uk/page_38022.asp

Catholic Church Apologetics (2009) "Ethicist hopes new breakthrough will eliminate 'need' to destroy human embryos". 25 July 2009. http://ccaapologetics.multiply.com/journal/item/7775/7775

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.

Eberl, Jason (2000) "The Beginning of Personhood." *Bioethics,* **14:**134-157

Fadel, Hossam E (2007) Prospects and Ethics of Stem Cell Research: An Islamic Perspective. *JIMA,* 39 (2), 73-83.

Hughes, James J., and Damien Keown (1995) "Buddhism and Medical Ethics: a Bibliographic Introduction." *Journal of Buddhist Ethics,* **2** (1995): 104-124. http://ftp.cac.psu.edu/pub/jbe/acrobat/hughes.pdf

Indian Council of Medical Research (2007) "Guidelines for Stem Cell Research and Therapy" November 2007. http://www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf

Keown, Damien (2004) "'No Harm' Applies to Stem Cell Embryos: One Buddhist's Perspective". *Belief Net*. http://www.beliefnet.com/story/143/story_14399_1.html

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

Pope John Paul II (2005) "Address of his holiness Pope John Paul II to the diplomatic corps accredited to the holy see for the traditional exchange of new year greetings." The Vatican. 10 Jan. 2005. http://www.vatican.va/holy_father/john_paul_ii/speeches/2005/january/documents/hf_jp-ii_spe_20050110_diplomatic-corps_en.html#top

Promta S (2004) *Human Cloning and Embryonic Stem Cell Research - A View From Therav*. Bangkok, Thailand: Chulalongkorn University. http://www.stc.arts.chula.ac.th/Cloning%20and%20Stem%20Cell-Buddhist.pdf

Smith PJ (2006) Catholic Church NOT Opposed to Stem Cell Research. *Catholic Bioethicist.* http://www.lifesite.net/ldn/2006/jul/06072709.html

"Statement of the Catholic Leadership Conference on Human Cloning" (2001) *Priestforlife*. Nov. 2001. Priests for Life. http://www.priestsforlife.org/articles/01-11-01humancloningclc.htm

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

UCSSB (2008) "On Embryonic Stem Cell Research" http://www.usccb.org/prolife/issues/bioethic/bishopsESCRstmt.pdf

Chapter-4: Stem Cell Legalities

Jonathan Marokhovsky

Stem cells, particularly human embryonic stem cells (hESCs), have been controversial in politics since their initial discovery. While researching embryos and hESCs has never been outright banned in the United States, federal funding is the main driving source and has been used as a political tool to limit the research from the beginning. This chapter focuses on the laws regulating embryo and stem cell use in the United States and abroad, and serves as an example of how strongly politics affects science.

U.S. Presidential Administration Policies

The Clinton Administration (1993 – 2000)

The Bill Clinton presidential administration pushed hard for stem cell research. Clinton later stated in his book "My Life, by Bill Clinton" that the driving reason behind this and his diabetes care program was that the children of his chief of staff, Erskine Bowles, had diabetes as did Clinton's second step father, Jeff. Clinton and Bowles both believed that researching stem cells would be "essential to unlocking the mysteries of diabetes and other presently incurable medical conditions" (Clinton, 2004).

Clinton, at first, allowed federal funding for embryo research, but had to change his decision on the matter in 1994 because he received thousands of letters asking him to do so. In 1995, in response to the growing public debate, Congress passed the Dickey-Wicker Amendment which prohibited the federal government from funding the creation of human embryos for the sole purpose of research, or for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero." Despite this amendment banning federal funding, private institutions could

continue the research, and in 1998, James Thomson isolated human embryonic stem cells and showed their potential to specialize into tissues (Thompson et al., 1998). Although the Dickey-Wicker Amendment banned federal funding for research on embryos, hESCs technically were not covered by this, but scientists still had to find their own funding to acquire the embryos to make hESCs. As Clinton's time in office was coming to a close, the National Institutes of Health (NIH) published their "Guidelines for Research Using Human Pluripotent Stem Cells" which stipulates that hESCs must be derived with private funds using excess frozen embryos from fertility clinics created for reproductive purposes and must be acquired with the consent of the donor (Vestal, 2008; Stem Cell History, 2011).

The Bush Administration (2001 – 2008)

The George W. Bush presidential administration greatly accelerated embryonic stem cell research – outside the United States (Cook, 2004). After being sworn into office, Bush requested a review of the guidelines NIH published during the dusk of Clinton's administration. On August 9, 2001, Bush announced his decision to limit the federal funding of stem cell research to only those embryonic stem cell lines in existence as of that date. To make matters worse, most of these lines were unsuitable for research due to contamination or genetic mutation (Godoy and Palco, 2006). Because of this limitation, many scientists in the field started moving to the UK or other countries where they were allowed to make new hESC lines, and those countries' programs started to grow until the United States was replaced by the United Kingdom as the leader in stem cell research (Ford, 2006). The scientists remaining in the United States had to make a choice, to either respect these restrictions and keep working with the limited cell lines, or look for private funding (Cook, 2004).

As other countries' advancements in stem cell research started to pull away, individual states started to take matters into their own hands, starting with New Jersey who passed a state budget on June 24, 2004 which included $9.5 million in funding for the newly chartered Stem Cell Institute of New Jersey. And Congress also joined in, passing their Stem Cell Research Enhancement Act of 2005, allowing the federal funding of new hESC lines derived from fertility clinic embryos (Stem Cell Research Enhancement Act, 2005). This bill had a lot of backing from both parties, including support from President-to-be Barack Obama, and even conservative Sen. John McCain (Vestal, 2008). But despite all the popularity of the bill, on July 19, 2006 Bush vetoed the bill, and the House of Representatives did not have the two-thirds majority to overrule the veto (Babington, 2006).

With the Bush veto as motivation, more states started to fund stem cell research on their own. In an attempt to divert attention, Bush started encouraging research on alternative sources of pluripotent stem cells. On June 20, 2007, Bush requested that the Human Embryonic Stem Cell Registry be renamed the Human Pluripotent Stem Cell Registry. In November of that same year, Shinya Yamanaka and the original isolator of embryonic stem cells himself, James Thomson, both published papers on their separate discoveries of induced pluripotent stem cells (Takahashi et al., 2007). Finally in May 2008, as Bush's time in office was coming to a close, scientists were further restricted in hESC research as it was found that of the 21 remaining hESC lines, only 16 were ethically derived (Stem Cell History, 2011).

The Obama Administration (2009 – Present Day)

One of the first executive orders President Barack Obama issued when he entered office was to reverse one of former President George W. Bush's first executive orders. On March 9, 2009 President Obama lifted the ban on federally funding the creation of new hESCs by using

excess embryos from fertility clinics (Borenstein and Feller, 2009). Obama stated that he wants his administration to make "scientific decisions based on fact, not ideology." His executive order also encompassed requirements about guidelines which would be drafted by the NIH. Obama's director of his Domestic Policy Council, Melody Barnes, said that the administration wants the NIH to "… work with others around the country to make sure we're handling [the guidelines] responsibly" (Childs and Stark, 2009). NIH has rigorously upheld the guidelines they made, when in June of 2010 NIH rejected 47 new hESC lines because the advisory panel found the consent forms which donators signed contained unusually broad language and donors gave up all rights to sue the clinic. When asked about this, NIH Director Francis Collins said "It was frankly rather painful for my expert advisory committee to recommend against approval of 47 additional lines because of a consent problem, but rigorous guidelines are only meaningful if they are rigorously applied" (Stein, 2010). To help ensure the guidelines were ethically strong, Obama's biggest restriction was that cloning is in no way allowed, stating that cloning is "dangerous, profoundly wrong, and has no place in our or any society" (Borenstein and Feller, 2009).

Obama believes his policy will help the United States reclaim its title as leader in researching stem cells, and regain our scientists, saying that "when government fails to make these investments, opportunities are missed. Promising avenues go unexplored. Some of our best scientists leave for other countries that will sponsor their work. And those countries may surge ahead of ours in the advances that transform our lives" (CBS, 2009).

U.S. State Stem Cell Policies

When Bush made his 2001 executive order to halt federal funding to create new hESC cell lines, some states created their own laws on the matter (Palca, 2007). Most states stayed

neutral on the subject (**Figure-1**), five states used this as an opportunity to completely ban hESC research (North Dakota, South Dakota, Arkansas, Louisiana, and Indiana) (yellow in the figure), three states declared it legal, but did not fund research in the field (Iowa, Missouri, and Michigan) (light pink), and seven states not only declared researching hESCs legal, but funded the research themselves (California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey and New York) (dark pink) (Vestal, 2009).

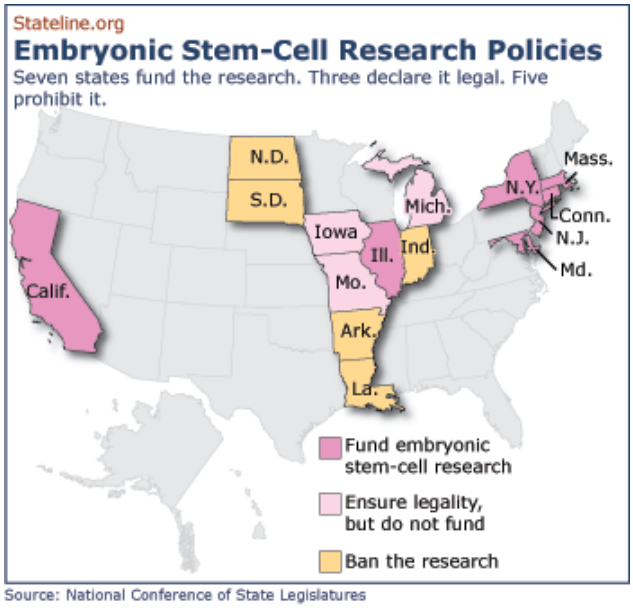

Figure-4: State Stem Cell Policies Circa 2009 (Vestal, 2009)

New Jersey

New Jersey was the first state to pass a state budget for stem cell research including hESC research. On June 25, 2004, their approved bond included $9.5 million for a newly chartered Stem Cell Institute of New Jersey. Included and allowed in this facility was the creation and research of embryonic stem cells (Palca, 2007). New Jersey also set aside $15 million for grants, and earmarked $10 million to be distributed over 10 years (Vestal, 2009). Then in June 2007, the New Jersey Commission on Science and Technology awarded more than $10 million in Stem Cell Research Grants (The Commission….2007).

California

In November of 2004, the same year that New Jersey proposed its state budget for stem cells, California approved Proposition 74, which would distribute $3 billion towards stem cell research over 10 years. This Proposition got stalled in legal proceedings over patent rights, so then Governor Arnold Schwarzenegger gave the program a state loan of $150 million. As of 2009, the program was in danger of running out of money due to California's fiscal crisis (Vestal, 2009). But despite its setbacks, Proposition 74 sets California ahead of the federal government and many other nations (Palca, 2007).

Massachusetts

In June 2008, Governor Deval Patrick approved $1 billion in grants for life sciences, to be distributed over the following ten years (Vestal, 2009). Included in this $1 billion is $8.2 million to be given to UMass Medical School in Worcester for the establishment of the Massachusetts hESC Bank and an international Massachusetts hESC Registry (Shelton, 2007). The proposed stem cell bank would be the world's largest depository for stem cell lines. Another portion of the grant will go towards creating "Life Science Innovation Centers", which are centers aimed at speeding the transfer of technology from labs to the market (Marks, 2007). Gov. Patrick hopes that this investment will bump Massachusetts up to its "rightful place as a global leader in the life sciences" ("Life Science Bill Signing", 2008).

International Stem Cell Policies

Because of the restrictions on hESC research brought about by the Bush administration, research exploded around the world as countries competed to grab the top scientists and provide hESC lines of their own towards research. Countries like the United Kingdom, Australia, South Korea, and China learned from the mistakes of the United States and approached hESC research

with a more permissive approach, only requiring that embryos used to acquire the hESCs should be obtained in an ethical fashion. Other countries such as Germany permitted research on stem cells, but criminalized the extraction of stem cells from embryos (Vestal, 2008). Germany even went so far as to try to ban funding throughout the rest of the European Union for hESC research (Deutshe Welle, 2006).

South Korea

South Korea at one point was leading the pack when it came to stem cell research. On February 12, 2004, scientists in South Korea claimed to have cloned a human embryo and this cloned embryo was to be used for stem cell harvesting. And on May 19, 2005, those same scientists reported they had created a streamlined process that uses less human eggs to produce useable hESCs. But on Jan 10, 2006, all this eventually collapsed when both of these claims were shown to be fraudulent, ruining the credibility of South Korean stem cell scientists (Godoy and Palco, 2006).

China

Because of its fewer religious and moral objections, some Western companies started to look to China for hESC research. The Chinese government had no qualms funding research in the area. The only problem with this was China's well known weakly enforced intellectual property laws compared to Western countries. China also has a weak review and evaluation system when it comes to publishing research results. Although there has not been a major negative event as with South Korea, Chinese incidents of falsified and plagiarized results getting a seal of approval by Chinese academic judges have frequently occurred (Barnes, 2006).

United Kingdom

During the Bush administration, and after South Korea had ruined its reputation as a leader in stem cell research, top American scientists started going to the United Kingdom

because the UK's policies on hESC creation were much less restrictive than the United States. Because of this, leadership in stem cell research shifted to the UK. But even with the spotlight on them, researchers in the UK recognized that the gap created by the large restrictions put on US researchers affected the whole world as research could have been moving much faster (Ford, 2006). To help make up for this gap, the UK opened the UK Stem Cell Bank in 2004 with a $4.7 million grant. The UK requires that all embryonic cell lines created in Britain be stored there upon completion of the bank (Rosenthal, 2004).

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

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

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

CBS/The Associated Press (2009) "Obama Ends Stem Cell Research Ban." http://www.cbsnews.com/stories/2009/03/09/politics/100days/domesticissues/main4853385.shtml

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

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

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

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

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

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

Godoy M, and Palco J (2006) "A Brief Timeline of the Stem Cell Debate." May 10, 2006. http://wistechnology.com/articles/2951/

"Life Science Bill Signing" (2008) Mass.gov http://www.mass.gov/?pageID=gov3terminal&L=3&L0=Home&L1=Media+Center&L2=Speeches&sid=Agov3&b=terminalcontent&f=text_2008-06-16_life&csid=Agov3

Marks, Clifford M (2007) "Patrick Increases Stem Cell Funds." *News*. The Harvard Crimson, 11 May 2007. http://www.thecrimson.com/article.aspx?ref=518859

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

Rosenthal E (2004) "Britain Embraces Embryonic Stem Cell Research". *New York Times*. http://query.nytimes.com/gst/fullpage.html?res=9E02E7DA143EF937A1575BC0A9629C8B63&sec=&spon=&pagewanted=1

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

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

Stem Cell History (2011) "Stem Cell Research Timeline". http://stemcellhistory.com/stem-cell-research-timeline/

"Stem Cell Research Enhancement Act of 2005." The Library of Congress. 109th Congress (2005-2006). http://thomas.loc.gov/cgi-bin/query/z?c109:H.R.810

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.

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

Vestal, Christine (2009) "States Applaud New Stem Cell Funding". *Stateline.org* http://www.stateline.org/live/details/story?contentId=383210

PROJECT CONCLUSIONS

Based on the research performed for this project, the authors provide their own conclusions on the topic. With respect to the use of embryonic stem (ES) cells, the authors have differing opinions. One author believes that destroying a 5-day old blastocyst to derive an ES cell line is not murder, and believes that ES cell research should be expanded in the US. The other author, due to religious principles, cannot support the use of ES cells, but recognizes their potential medical benefit. Both authors agree that given the controversy of ES cells, adult stem cells (ASCs) or induced pluripotent (iPS) cells should be used as alternatives whenever possible. With respect to the source of embryos used to derive ES cells, the authors agree with current US policies under President Obama that require embryos to be obtained from excess IVF embryos originally created for reproductive purposes, should research in the area continue. This comes with the stipulation that the donors must provide their consent for the embryos to be used for research. The authors do not agree that donors should be paid to provide embryos for research, as that might provide financial incentive for a poor individual to donate, even against their moral beliefs. With respect to stem cell laws, the authors agree with all countries that have banned human reproductive cloning (including the US). With regards to therapeutic cloning (SCNT), one author believes that it should not be approved within the US because it destroys human embryos, but the other believe the US should approve therapeutic cloning (SCNT) because of the medical benefit it could provide for an untold number of people. Although the authors differ in their opinions of which stem cell types should be used, both agree that they are the future of modern medicine and research should continue.