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STEM CELLS

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ABSTRACT

The purpose of this IQP was to investigate the technology of stem cells with emphasis placed upon the ethics and legalities that regulate stem cell research. This was achieved by analyzing the applications of stem cells, considering the ethical issues behind the use of stem cells, and examining the world legal stances on stem cell research. The findings from the investigation indicated that some types of adult stem cell have already been used to save lives for over 35 years, while most embryonic stem (ES) cell applications remain as future applications, predominately based on animal research. Based on our research we concluded that the five major religions in the world approve of adult stem cell research, but ES cell research is opposed by the conservative religions such as Christianity and Buddhism. Furthermore, the legal restrictions placed upon ES cell research by conservative countries such as the United States and Germany greatly hinder the advancement of stem cell therapies.

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PROJECT OBJECTIVES

The objective of this IQP project was to examine the topic of stem cells, and to discuss the effect of this controversial new technology on society. The purpose of chapter-1 was to identify the various types of stem cells and explain why all stem cells are not alike. The purpose of chapter-2 was to explain the kinds of experiments that stem cells have successfully been used for, omitting inconsequential reports while concentrating on the reputable studies. The purpose of chapter-3 was to examine the ethics surrounding stem cell research, while the purpose of chapter-4 was to examine the laws governing stem cell use in the United States and other nations around the world. Finally a conclusion was made by the authors regarding the use of stem cells, and which laws and ethics best represent the authors' point of view.

CHAPTER-1: STEM CELL TYPES AND SOURCES

One of the greatest medical breakthroughs of the 20th century is the stem cell. People have not yet seen the full potential of what these amazing cells can do due to a lack of federal government funding, but this may soon change. Humans suffer from many common diseases such as cancer, heart disease, Alzheimer's, Parkinson's etc. which may result in a permanent loss of vital organs and tissue with a very small chance of replacement. The limitations of organ and tissue donation and the diseases described above are some of the key motivating factors behind researching stems cells. But what exactly are stem cells? And where do we obtain them from? What are the various types? These topics will be discussed in this chapter.

Stem cells can be best described as the master builders of the body. They are the basic unit of cells from which all other cells originate. These cells can further differentiate and specialize into specific cell types and tissues depending on the stimuli and environment they are exposed to. Because of their ability to form new tissues, they are the basis of the new medical field of regenerative medicine.

Stem Cell Types

Not all stem cells are alike. So when a person says they are against stem cell research, it is important to distinguish which type of stem cell research you are against. Stem cells can be grouped into these major categories: totipotent cells, pleuripotent stem cells, multipotent stem cells, and unipotent stem cells, depending on their ability to differentiate into different cell types.

Embryonic stem (ES) cells are present in the inner cell mass of a blastocyst. A blastocyst is an embryo in a very early stage of development. Just 5 days after the zygote is conceived, the embryo exists in a 150-cell organism named the blastocyst. The basic structure of the blastocyst consists of two types of cells: the inner cell mass and the outer layer of trophoblasts. Extracting the ES cells from the inner cell mass causes the embryo to cease to exist. Therefore, one can argue that taking cells from the inner cell mass is destroying the potential human's right to live. This is a great and complex debate discussed in Chapter 3. Also there is an alternate method of extraction called parthenogenesis discussed later in this chapter. The alternative to embryonic stem cells research is research on adult stem cells.

Adult stem cells are undifferentiated cells found in several parts of the body. The main purpose of such cells is to repair damaged tissue. One can, in theory, produce the desired cell type if adult stem cells are exposed to the right growth factors and environmental cues. For example, a stem cell extracted from muscle will differentiate into muscle cells and then eventually form muscle tissue if the right stimuli and culture medium are provided. However, the best researched source for adult stem cells is the bone marrow because of their multipotent characteristics. The adult stem cells in the bone marrow include hematopoietic stem cells (HSCs), endothelial stem cells (ESCs), and mesenchymal stem cells (MSCs) (Frequently Asked Questions, 2006). Adult stem cells are isolated from adult tissues or the umbilical cord. There are many types of adult stem cells that might help researchers to find cures for many deadly diseases. Other types of adult stem cells include neural stem cells (NSCs), mesenchymal stem cells (MSCs), epithelial stem cells, cardiac stem cells, and others. The problem is that there are only a

few adult stem cells in each organ, and the processes proposed to identify and extract these cells are tedious.

Other unique places stem cells are found are the amniotic fluid, baby teeth, and the umbilical cord of a newborn. Although the stem cells obtained from the umbilical cord are essentially easier to extract than from the bone marrow or the brain of an adult, these stem cells can only be grown *in vitro* for a finite duration of time. The research on the stem cells found in the baby teeth and the amniotic fluid is still in the early stage but there are hints that these stem cells can differentiate into many different specialized cells just like the stem cells present in bone marrow.

Adult Stem cells are a good alternative to embryonic stem (ES) cells. Many in the scientific community laude the "plasticity" of adult stem cell because these adult stem cells can specialize into many types of tissues, but do not destroy an embryo to obtain them. The basis of this plasticity originates from the "fusion" found in adult stem cells (Vogel, 2002). However, the latest papers published question the validity of the statements proposed about adult stem cells in the past. For example researchers Derek van Der Kooy, Cindi Morshead from the University of Toronto were unable to get neuronal stem cells to differentiate into blood cells. What they found instead was that the cell reprogrammed themselves in culture over many generations of proliferation. Does this suggest that ES cells are more necessary than we thought (Vogel, 2002)?
Another paper that supports the statement that adult stem cells' plasticity has been exaggerated is one published in science by Amy Wagers that provides evidence about adult hematopoietic stem cells not being as plastic as once thought. Hematopoietic stem cells were marked with a dye and inserted into a rat's body and what was found that

‘transdifferentiation’ of the circulating HSCs (or their progeny) was an extremely rare event, if it occurs at all” (Wagers 2002).

There are numerous myths circulating where one might get the wrong notion about stem cells. One of them says, “all stem cells are alike”. This is false. Embryonic stem cells are radically different from adult stem cells. Embryonic stem cells are extracted from the blastocyst’s inner cell mass and can differentiate into any type of cell in the human body (except the placenta) if exposed to the correct growth factors and culture medium (Frequently Asked Questions, 2006). This is one of the biggest advantages of ES cells over adult stem cells, as adult stem cells are limited in their potential to specialize. The exceptions to this statement are a type of bone marrow adult stem cells known as mesenchymal stem cells (MSCs). As these MSCs cells have multipotent characteristics, they may resemble ES cells. So even when considering adult stem cells, all of the adult stem cells are not alike as there are various types.

Multipotent stem cells are stem cells that can differentiate into multiple types of cells, but they don’t have the same flexibility as pleuripotent stem cells. Examples of multipotent stem cells are: mesenchymal stem cells (MSCs) (that form cartilage, bone, muscle, tendon, ligament and fat), epithelial stem cells (ESCs) (that form skin, corneal epithelium, hair and mammary glands), hematopoietic stem cells (HSCs) (that form different types of blood cells) and neuronal stem cells (NSCs) (that form neurons and glial cells).

Another myth states "all work with stem cells destroys embryos”. This statement is untrue. Research and extraction of adult stem cells does not involve any destruction of an embryo. With their consent, many people can directly donate adult stem cells, but

extraction of embryonic stem cells *may* involve the destruction of embryos which some people might consider murdering a human being. Nevertheless, one should be reminded that currently, researchers strictly take embryos that have been discarded from *in vitro* fertilization clinics with the owner's consent, that are going to be discarded anyway. Hence, it is clear that all work with stem cells does not destroy embryos because of the existence of adult stem cells (Frequently Asked Questions, 2006). Research on adult stem cells is currently the only possible way to conduct stem cell research on a large scale because of the availability of the cells.

Hematopoietic Stem Cells

These are adult stem cells that can be isolated from either the bone marrow, umbilical cord blood, fetal liver, or the peripheral blood if the person has been treated with hormones to stimulate their release from the marrow into the blood (Frequently Asked Questions, 2006). These cells are heavily researched because they can specialize into different types of cells (usually they form the various cellular components of blood) and thus are multipotent stem cells (Hematopoietic Stem Cells, 2005). Certain cells that can arise from HSCs are macrophages and histiocytes. Not only can these stem cells specialize into many different types of cells but they are also found to be mobile as they can move into the blood stream from the marrow. HSCs can also undergo apoptosis, programmed cell death. This property is a very helpful in managing tissue growth by controlling for how long a cell lasts inside a tissue and preventing any cluster of cells from growing too fast to make cancer. Hence, this property of apoptosis is very helpful

to have in stem cells because, if used correctly, will not cause the recipient of the treatment the extra complication of cancer.

However when research was first attempted on HSC in the 1960s, it was found that these stem cells behaved and looked like white blood cells. This made isolating and extracting these kinds of cells extremely difficult. The main factor that helps separate these two types of cells is the cell surfaces. Research on HSCs initiated in mice showed only 1 HSC was found for every 10,000-15,000 bone marrow cells (Hematopoietic Stem Cells, 2005). HSCs are isolated on the basis of surface protein markers specific to them, such as CD34 the hallmark HSC marker. The process was originally developed in 1988 by Irving Weissman. Antibodies are usually used to bind to CD34 and are then used to collect these cells from the blood or marrow cells.

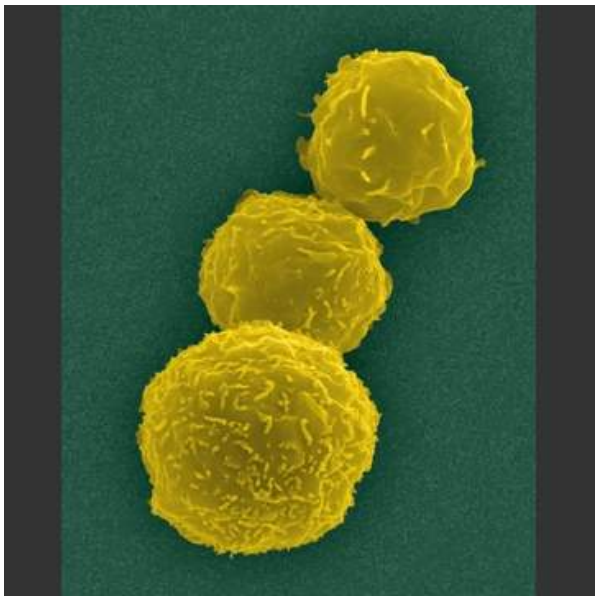

Figure-1: Picture of HScs. Shown are hematopoietic stem cells that have been extracted from the bone marrow. These cells have the ability to form most cells found in the blood with the exception of granulocytes and therefore these HSCs are multipotent (Human Stem Cells, 2004).

Neural Stem Cells

These cells (Figure-2) exist as undifferentiated multipotent cells inside the central nervous system, which includes the brain and the spinal cord. NSCs are believed to be the source of neurons and gilial cells during embryonic development and growth (Frequently Asked Questions, 2007). If NSCs exist, why do so many diseases cause brain damage that is permanent? Why can't the NSCs form additional neurons to repair damage done in the brain?

The answer to those questions is that NSCs are found in a deactivated state. Studies published April 15, 2002, in *Nature Neuro*science by Howard Hughes Medical Institute (HHMI) investigator Charles F. Stevens and colleagues Hong-jun Song, an HHMI research associate, and Fred H. Gage at The Salk Institute (Song, 2002), clearly state that these NSCs can become functional neurons. This study was done in rats. Many key processes were involved in proving this theory such as NSC isolation, fluorescent tagging, and co-culturing with normal adult neurons on a medium containing astrocytes that "produce chemical signals that trigger neuronal growth". The results clearly showed neuronal growth (Neural Stem Cells, 2002). These studies conclude that if NSCs can be cultured and differentiated *in vitro*, they can be used as transplantable tissue for the repair of brain injury (Frequently Asked Questions, 2007). In addition to this purpose, further studies show that NSCs can help in determining what environmental, chemical, and physical signals cells require to differentiate. But this research is in a very early stage, and currently only animals are used as test subjects (Frequently Asked Questions, 2007).

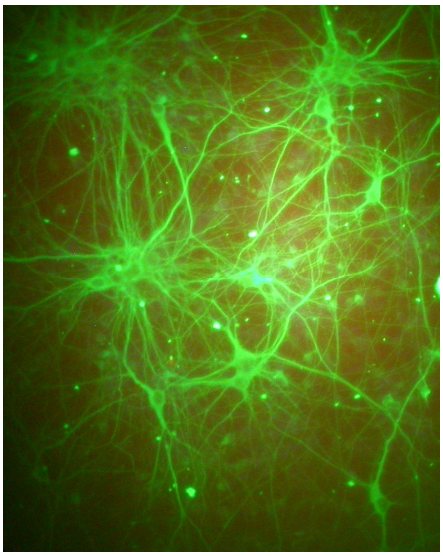

Figure-2: Rat Neuronal Stem cells. Experiments concerning NSCs are currently being performed mostly in animals such as rats. These stem cells have been stained for β-Tubulin. (Rat Neural, 2007)

Mesenchymal Stem Cells

MSCs (Figure-3) are also known as human bone marrow stromal stem cells (The Potential, 2007). These stem cells have the highest variety of specialization among all the adult stem cells, so are almost as sought medically as ES cells. MSCs can differentiate and produce various tissues including cartilage, bone, muscle, tendon, ligament, and even fat. The main role of these cells is tissue sustenance and reconstruction, but they have also been linked to aging (Sethe et al, 2006). MSCs have also been linked to "bone development, bone repair, and skeletal regeneration therapy" because MSCs also produce osteoblasts (bone formation cells) and osteoclasts (bone degradation cells) (Bruder et al, 1994). MSC involvement in fetal development has shown that these cells can be used in multiple therapies if the right factors, nutrients, and other environmental cues are provided. Two examples of human conditions that might be treatable with MSCs are local bone defects (that can be repaired through the process of specific injection of MSCs into the appropriate site) and osteoporosis (which mostly occurs in aging women) (Bruder

et al, 1994). MSCs come close to the variety of differentiation that ES cells provide, however MSCs are still only considered multipotent stem cells.

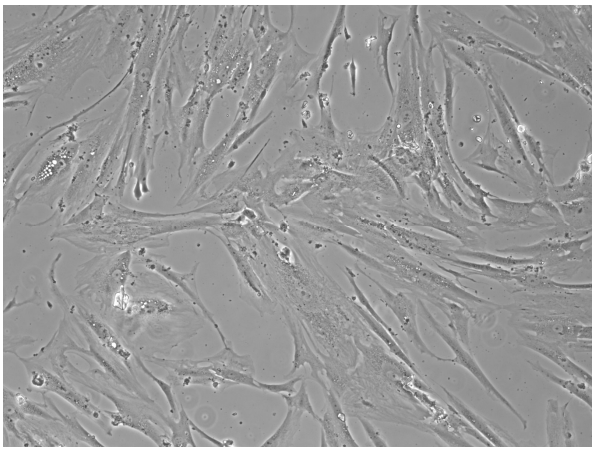

Figure-3: Picture of Mesenchymal Stem Cells. The figure is a snapshot from a Professor Dr. George Plopper's lab (Department of Biology Rensselaer Polytechnic Institute). The photo shows MSCs plated on defined ECM proteins. Working with Dr. George Plopper were Dr. Jan Stegemann, Dr. Adele Boskey, Dr. Kristin Bennett, Dr. Badri Roysam, and Dr. Bulent Yener (Plopper et al, 2007).

Epithelial Stem Cells

ESCs (Figure-4) are found in quickly reproducing epithelial tissue. They are undifferentiated but have the ability to form many types of tissues depending where they are situated and what cues they receive. The types of tissue that can form from ESCs are skin, corneal epithelium, hair and mammary glands. ESCs are located in the epidermal rete ridges, corneal limbus, and hair bulge. Some evidence also indicates ESCs are located in mammary glands. Therefore, ESCs are considered multipotent stem cells because of their ability to differentiate into more than one type of cell. ESCs can also produce other ESCs and TA cells. TA cells are called transit amplifying cells, their main function is to replenish and repair the damaged areas of the epithelium (Cotsarelis et al, 1999).

Skin cells are unipotent. Unipotent stem cells are the most specific type of stem cells as they can only differentiate into one cell type. One prime example of unipotent

stem cells are skin stem cells. These cells are very specific in what they can produce and cannot produce. One of the big advantages of unipotent stem cells is the fact that we know what our end result will be, and it will be easier to find a culture/media to differentiate such cells. Another advantage of unipotent stem cells is the fact that they have a great ability to self-renew. Therefore, they can be used in treating many diseases and in transplants because of this unique ability (Unipotent Stem Cells, 2006).

Specific to skin cells, the skins stem cells can be easily extracted from a patient's own body and used in repairing burns and other injuries on the patient's own body. Here immunorejection does not occur as the cells transplanted are the patient's own cells. One of the limitations of the technology using unipotent skin stem cells is the fact that it is time consuming and therefore the patient is left to suffer longer periods of pain and disfigurement. The main reason that this happens is because the patient's own skin acts as a barrier to the healing process. The technology is improving and therefore this technique is looking to get perfected in the near future (Unipotent Stem Cells, 2006).

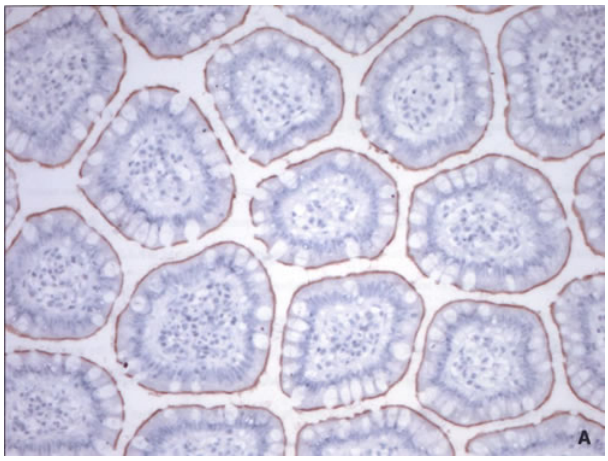

Figure-4: Picture of Epithelial Stem Cells. This shot is of ESCs inside a human colon, from an experiment performed by Jasmin Paris in Liverpool, supervised by Dr Bill Otto of Cancer Research UK. The experiment shows the interactions with myofibroblasts (Paris, 2006).

Cardiac Stem Cells

CSCs (Figure-5) are adult stem cells that localize in the heart and are the original form of heart tissue. These cells can differentiate into heart tissue only, so are unipotent. There have been numerous cases in both humans and rats where CSCs have been reinserted to heal damaged heart tissue whether from cryofreeze test injury or a heart attack. In the case of the rat, "70% of the damaged myocardium was reconstituted within 20 days" (Beltrami et. al, 2002). The findings on CSCs attempting to repair damaged human heart tissue were published in the Proceedings of the National Academy of Sciences (Oh, 2003). Other studies suggest that the CSCs found in the heart are there to grow and are already activated, unlike neural Stem cells that are found in an inactivated state. Many researchers have stated that they can use this property to help discover what helps differentiate CSCs into cardiac tissue, and help solve many heart-related problems (Touchette, 2004).

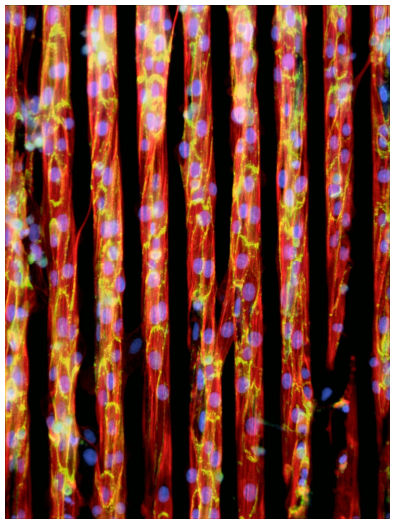

Figure-5: Cardiac Stem Cells. Notice the striations in the picture. The cells have been grown in the laboratory and must be organized so they can form the beating functional heart tissue (Harrill, 2000).

Embryonic Stem Cells

Although adult stem cells are less controversial, the use of ES cells (Figure-6) is the greatest area of interest for scientists and the greatest area of controversy. ES cells are derived from the inner cell mass of a blastocyst, and they have the greatest medical potential due to their ability to differentiate into any cell in the body (except the placenta) if the right physical, chemical, and environmental stimuli are provided, thus they are pleuripotent stem cells. Such cells have the ability to provide nerve cells for a stroke or Parkinson's patient, cardiac cells for heart attack patients, liver cells for a liver cirrhosis patient, and many other types of cells to cure many of the diseases of today. The problem is the process of extraction from the inner cell mass destroys the donor embryo, thus there is a heavy ethical problem as to whether that destruction constitutes murder (Stem Cells, 2007). Many people might consider destroying the embryo murder and therefore the government does not allow federal money to support research on ES stem cells. However, as a contradiction of itself, the government does allow abortions.

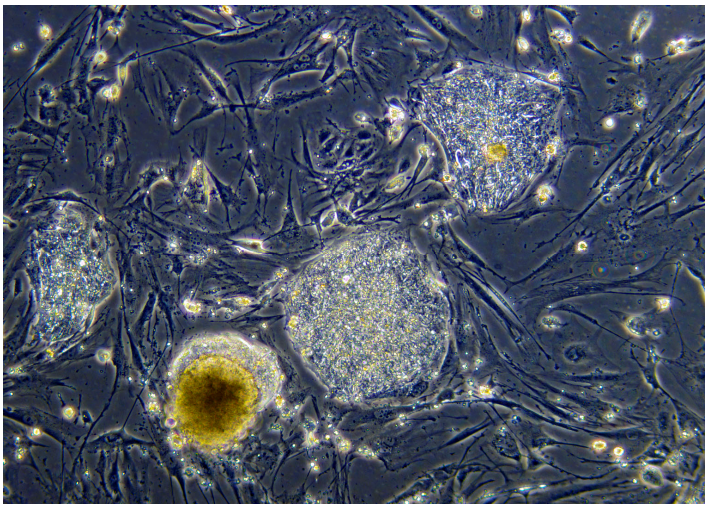

Figure-6: Embryonic Stem Cells. Shown are colonies of ES cells from the lab of biologist James Thompson (University of Wisconsin-Madison) who first isolated human ES cells (Strassman, 2004).

While we discussed the plasticity of adult stem cells, scientists do have concrete proof of the plasticity of ES cells. Experiments that provide concrete proof for such plasticity are mostly done on mice because of the current lack of government funding for ESCs research and the ethical concerns that would arise from experimentation on human beings. Scientists have, in fact, transplanted ES cells into a rat that has Parkinson's disease and the transplant specialized into neurons. These neurons were specialized to the extent that they secreted the exact neurotransmitter dopamine that the rat needed to help it move its limbs, thus this is a potential cure for Parkinson's. This study has high implications for the potential of ES cells for human beings and possible cures for neuronal diseases (Bjorklund et. al, 2002).

It is clear, however, that currently ES cells derived from the blastomere require the destruction of the embryo. But some studies are being done to try to extract ES cells without hampering the developmental cycle of the embryo. Techniques such as single-cell biopsy and micro-manipulation might get around the ethical dilemma of destroying the embryo to obtain stem cell lines (Klimanskayza, 2006). One alternate method is termed parthenogenesis. Parthenogenesis is the chemical treatment of a non-fertilized egg. This chemical treatment induces the unfertilized egg to begin dividing. The divisions continue to the blastocyst stage, at which ES cells can be obtained, but the divisions continue no further. Because such embryos cannot develop into adults, some ethicists believe they have lower moral status than fertilized embryos. So parthenotes may provide an alternative source of ES cells in the future.

Many people confuse totipotent cells (zygote) with pleuripotent ES stem cells. This happens mainly because these cells exist near the start of birth, but there is a

difference. The zygote has the ability to differentiate into a full organism and the placenta (Definition, 2007). However, in order for the zygote to form such an organism, it divides into many embryonic stem cells that can further differentiate into other multipotent and unipotent stem cells.

Embryonic germ cells (EGCs) are pleuripotent stem cells that can be extracted from the primitively formed gonads of aborted fetuses (specifically the gonadal ridge). These cells can develop into egg and sperm as well as any other cell type in the body. One difference between EG and ES cells is the way they are grown *in vitro*. ES cell lines are immortal, while EG cells can only sustain 70-80 divisions. The only advantage of EG cells is the fact that no tumors are generated once they are injected into a body, unlike what sometimes happens with ES cells. Currently research on EG cells is still mostly in the mouse and thus in a very early stage (Embryonic Germ Cells, 2007).

The third type of pleuripotent stem cell is the Embryonic Carcinoma (EC) Cell. These cells are part of a tumor that grows on the gonad of the fetus, termed teratocarcinomas, and such cells are aneuploid (have more chromosomes than the standard 2n found in diploid cells (Stem Cells, 2007).

Chapter-1 Conclusions

Stem cell research has come a long way since its conception. It is still arduous and time consuming for scientists to find each different type of stem cell and figure out a way to grow them in vitro for a long period of time, but the methodology is constantly improving. There are multiple types of stem cells, each with a different type of potential for creating new tissue. Contrary to popular belief, stem cell use is not new to science,

and some (HSCs) have already been used for decades to save lives from cancer. Even with the current reduced federal funding of ES research, there have been some major breakthroughs in curing some of the serious diseases as well as healing injuries; however most of this work is still in animal systems. Stem cells come in all variety and now that we have identified and classified stem cells as well as dispelled some major myths about stem cells, it is the time to look in the next chapter at the applications of various stem cells in detail.

CHAPTER 2: STEM CELL APPLICATIONS

One key question with respect to stem cells is what has actually been done with them? Because much of what we currently know about stem cells comes from animal experiments, the public often is not aware of the extensive experimental background leading up to human experiments. In the case of ES cells, human clinical trials are only now ongoing, so most of what we know about ES cells comes from animal experiments. The purpose of this chapter is to shed light on what has actually been achieved with stem cells to date, sorting out hype from reality.

HEMATOPOIETIC STEM CELL APPLICATIONS

Leukemia and Lymphoma

Hematopoietic stem cells (HSCs) are the "active component" of bone marrow, umbilical cord blood, or the peripheral blood (when stimulated by hormones to stimulate their release from the marrow). HSCs were first clinically used in the treatment of leukemia and lymphoma, which are both cancers of the blood. Leukemia and lymphoma result from the uncontrolled production of white blood cells, and include acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic myelogenous leukemia (CML), Hodgkin's disease, multiple myeloma, and non-Hodgkin's lymphoma. In these treatments, the cancerous hematopoietic cells of the patient are first destroyed through radiation and chemotherapy. Then they are replaced with a transplant of HSCs taken from the bone marrow or peripheral circulation of a matched donor. The matched donor needs

to have similar human leukocyte antigens on the surface of their cells as the patient to prevent transplant rejection (Thomas and Clift, 1999).

The earlier treatment for chronic myeloid leukemia (CML) using only chemotherapy was largely ineffective, so bone marrow transplants were tested, first in identical twins in which the donor and host tissues were perfectly matched. Later, bone marrow transplants were also used in HLA-matched siblings. There was significant risk of patient death after bone marrow transplant due to infection or from graft versus host disease, but a good majority of patients survived the immediate effects of the transplant procedure, and lived for years or even decades, rather than months, proving the technique could work. Because of marrow transplantation, CML was transformed from a fatal disease to one that is often curable (Thomas, 1999).

Through recent studies, CML researchers have taken their knowledge of hematopoietic regulation one step farther. On May 10, 2001, the Food and Drug Administration approved Gleevec, an oral drug designed for the treatment of CML. Gleevec specifically targets a mutant protein produced in CML cancer cells (Figure-7). This particular protein damages the cell signals controlling the division of progenitor cells. Gleevec silences this protein, this turning off cancerous overproduction of white blood cells. As a result, doctors do not have to resort to bone marrow transplantation. But at this point of time, it is unknown whether Gleevec will provide continued remission or will prolong the life of CML patients (Thomas, 1999).

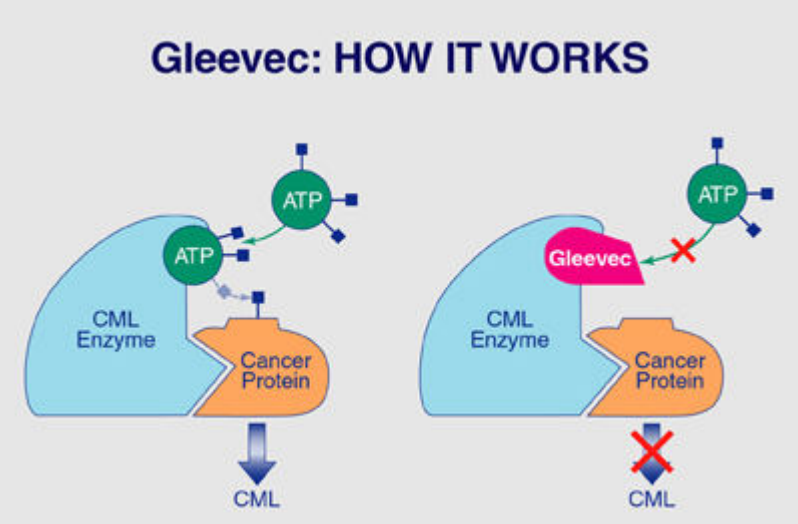

Figure-7. Diagram Showing How Gleevec Works. Gleevec works by blocking the uninhibited production of tyrosine kinase, which leads to excessive levels of WBCs in the blood and bone marrow. This disrupts the overproduction of WBCs (Henahan, 2001).

Cancer Chemotherapy

Hematopoietic stem cells are also being used to treat patients who underwent chemotherapy. Chemotherapy is used for destroying rapidly dividing cancer cells, however, chemotherapy also destroys rapidly dividing hematopoietic cells ("Hematopoietic Stem Cells", 2005). Doctors use hematopoietic stem cell transplants to replace the cells destroyed by chemotherapy. They perform this by mobilizing HSCs from the bone marrow using hormones, then collecting them from peripheral blood. The cells that are harvested are stored while the patient undergoes chemotherapy to destroy the cancer cells. Once the drugs are out of the patient's system, the patient will receive a transfusion of his or her stored HSCs. Since the patients are getting their own cells back, there is no chance of immune mismatch or graft-versus-host disease. A serious issue with

the use of autologous HSC transplants in cancer treatment has been that cancer cells are sometimes accidentally collected and reintroduced back into the patient along with the stem cells (Negrin et al, 2000).

Graft-Versus-Tumor Treatment of Cancer

One of the most exciting new uses of HSC transplantation has to do with using the stem cells to destroy untreatable cancerous tumors. Researchers in NIH's intramural research program have recently described this approach as a potential method to treat metastatic kidney cancer. Approximately half of the 38 patients treated so far have had their tumors reduced. The research protocol is now being modified for the treatment of other solid tumors that resist standard therapy, such as cancer of the lung, prostate, ovary, colon, esophagus, liver, and pancreas ("Hematopoietic Stem Cells", 2005).

This experimental therapy relies on an allogeneic stem cell transplant from an HLA-matched sibling whose HSCs are collected peripherally. The patient's own immune system is then suppressed, but not completely destroyed. The donor's cells are then transfused into the patient. For the next three months, doctors will closely monitor the patient's immune cells using DNA fingerprinting. DNA fingerprinting allows doctors to follow the engraftment of the donor's cells and regrowth of the patient's own blood cells. They must also suppress the patient's immune system as needed to prevent his or her T cells from attacking the donor cells, and also to reduce graft-versus-host disease (Joshi, 2000).

NEURAL STEM CELL APPLICATIONS

The discovery of the regenerative capability of adult neural stem cells gives assurance that it may eventually be possible to repair damage from neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Lou Gehrig's disease, as well as from brain and spinal cord injuries resulting from stroke or trauma ("Rebuilding the Nervous System with Stem Cells", 2005).

Researchers are studying two fundamental strategies to make the most of this discovery. The first strategy is to grow differentiated cells in a laboratory dish that are suitable for implantation into a patient by starting with undifferentiated neural cells. The cells can be treated either in culture to transform them toward the desired differentiated neuronal cell type before implantation, or they can be implanted directly. The undifferentiated cells implanted directly rely on signals inside the body to direct their maturation into the right kind of brain cell. The second strategy relies on finding growth factors, hormones, and other signaling molecules that help cells survive and grow. The idea here is to use some kind of signaling molecule to fire up a patient's own stem cells, and promote repair mechanisms to allow the body to deal with the cell damage caused by the disease or injury ("Rebuilding the Nervous System with Stem Cells", 2005).

The neurons that die in patients with Parkinson's Disease connect a structure in the brain called the substantia nigra to another structure called the striatum. These neurons release the chemical transmitter dopamine onto their target neurons in the striatum. Dopamine's major role is to regulate the nerves that control body movement. As these neurons die, less dopamine is produced, leading to movement difficulties. A drug

called levodopa, which the brain converts into dopamine, is used to treat most patients suffering from Parkinson's Disease. The drug initially helps most patients, but the side effects of the drug increase over time and it becomes less effective (“Rebuilding the Nervous System with Stem Cells”, 2005).

The idea of growing dopamine producing neuronal cells in the laboratory to treat Parkinson's is the most recent approach to reverse the cell damage caused by this devastating disease. The concept is to implant cells into the brain that can replace the lost dopamine-releasing neurons (Figure-8), and this technique has been achieved in mice by transplanting ES cell derived neurons.

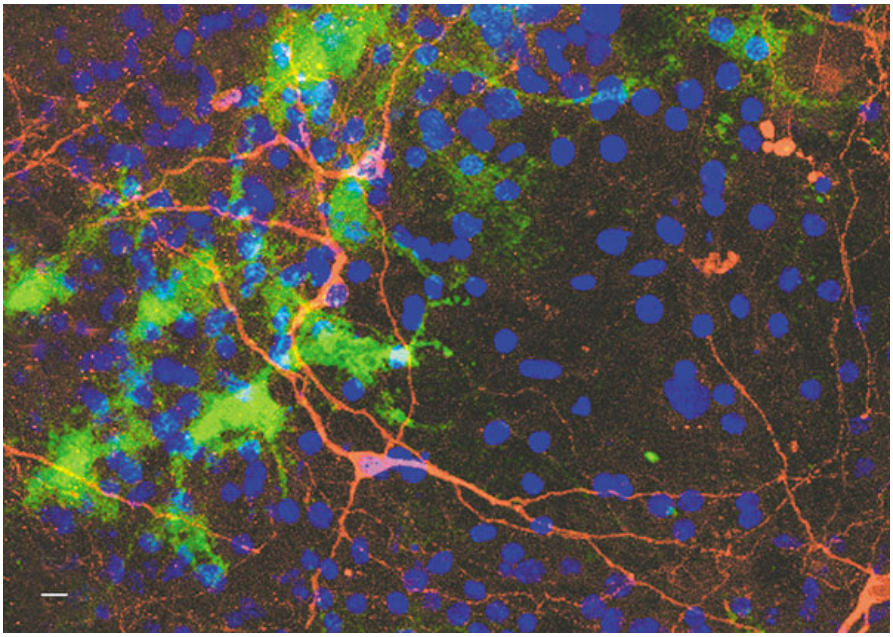

Figure-8. Picture of Dopamine-Producing Neurons Derived From Mouse ES Cells. The ES cells, labeled with green fluorescent protein, were induced to differentiate into midbrain neurons that produce the enzyme tyrosine hydroxylase, labeled with the red dye. These neurons will produce dopamine and form synapses with their normal brain targets (McKay, 2000).

Although this ES cell differentiation concept is conceptually straightforward, practically it is very difficult to achieve. Direct transplantation of fully developed and differentiated dopamine neurons is not an option since they do not survive trans-plantation. Also, a full functional recovery depends on more than just cell survival and dopamine release, the transplanted cells must also make appropriate connections with their normal target neurons in the striatum ("Rebuilding the Nervous System with Stem Cells", 2005).

The first attempts at using cell transplantation in humans were attempted in the 1980s. In this surgical approach, dopamine-producing cells found in the adrenal glands were used for transplantation. Neurosurgeons in Mexico reported that they had achieved dramatic improvement in Parkinson's patients, but surgeons in the United States observed only very modest and inconsistent improvements in their patients. The improvements seen disappeared within a year after surgery (Quinn, 1990).

Another strategy for fighting Parkinson's is based on transplanting developing dopamine neurons from fetal brain tissue and this yielded far better results. In the early 1970s, Lars Olsen and his colleagues showed that fetal tissue transplanted directly from the developing nigro-striatal pathways of embryonic mice into the anterior chamber of an adult rat's eye continues to mature into fully developed dopamine neurons (Dunnett et al, 2001). In the early 1980s, Anders Bjorkland showed that transplantation of fetal tissue into the damaged areas of the brains of rats and monkeys used as models of the disease could reverse their Parkinson's-like symptoms. Researchers were also able to refine their surgical techniques to demonstrate that functional recovery depends on the implanted

neurons growing and making functional connections at the appropriate brain locations (Dunnett et al, 2001).

The encouraging results in animal models led to human trials in the mid-1980s. The tissue removed from a fetus seven to nine weeks after conception was used in the human trials. The early human transplantation studies were encouraging, but showed inconsistent results to patients. In the best cases, patients receiving fetal tissue transplants showed a clear reduction in the severity of their symptoms. Researchers were also able to measure an increase in dopamine neuron function in the striatum of these patients by using a brain-imaging method called positron emission tomography (PET).

MESENCHYMAL STEM CELL APPLICATIONS

Applications for Osteochondral Repair

MSCs are one of the few adult stem cells already in use in the clinic. MSCs are currently used to develop new therapies for a number of skeletal conditions. The osteogenic potential of MSCs has been utilized to treat cases of defective fracture healing, both alone and in combination with scaffolds to repair large bone defects with a high degree of success (Quarto et al, 2001). MSCs have also been used for cartilage repair. Autologous MSCs were embedded in a collagen gel and re-implanted into areas of articular cartilage in osteoarthritis patients. In this study, the formation of hyaline cartilage-like tissue was improved in the experimental group compared to control (Jackson et al, 2007).

Systemic transplantation of MSCs has been in place for a long time in hematopoietic stem cell transplants. Recently, children suffering from osteogenesis imperfecta were treated systemically with allogenic MSCs. Transplanted MSCs were shown to migrate to the bone and produce collagen, thus providing a new and efficient route to improve the devastating consequences of this genetic condition (Horwitz et al, 1999).

MSC Applications for Myocardiac Repair

The potential of MSCs for the treatment of myocardial infarctions are currently being investigated through clinical trials. The current *in vivo* approach consists of injecting undifferentiated MSCs or whole bone marrow directly into the heart. Although significant improvement has been detected, the principal mechanisms have not been clearly understood (Jackson et al, 2007).

Applications Beyond Mesenchymal Lineage

The ability of MSCs to migrate to the site of injury has also been reported following transplantation in the brain. MSCs transplanted into rat striata were seen to migrate across the corpus callosum and populate the striatum and the thalamic nuclei (Hellmann et al, 2006). Untreated MSCs systemically infused into animals with damaged brain tissue have also been seen to migrate to the trauma site and improve recovery, although it is still remains unclear whether this includes differentiation into neural tissue.

CARDIAC STEM CELL APPLICATIONS

Researchers at the University of California, San Diego, have found evidence that native cardiac progenitor stem cells, previously thought to be absent after birth, exist in the hearts of newborn rats, mice, and humans. The cells are thought to be capable of differentiation into fully mature cardiac tissue. The researchers first identified the cells called isl1+ progenitor cells in the tissue of newborn rats and mice (Figure-9). Later these cells were also identified in heart tissue taken from five newborn human infants who were undergoing surgery for congenital heart defects. If these cells are given an appropriate environment, cultured isl1+ cells divide and renew themselves into mature cardiac muscle tissue. The cells exhibited contractivity, pumping ability, correct electrical physiology, and normal structure (Karl-Ludwig et al, 2005).

These cells are found in the regions of the atrium that are normally discarded during routine cardiac surgery. This finding raises the chance of individual infants receiving their own cardiac stem cells to correct a wide range of pediatric heart diseases.

Another potential use of these cells is for cardiac transplantation therapy. The researchers also discovered that a few of the progenitor cells found in a newborn heart could be expanded into millions of cells in laboratory culture dishes. As a result, isl1+ cells could potentially be harvested from an individual's heart tissue, multiplied in a laboratory, and then reimplanted into the patient (Karl-Ludwig et al, 2005).

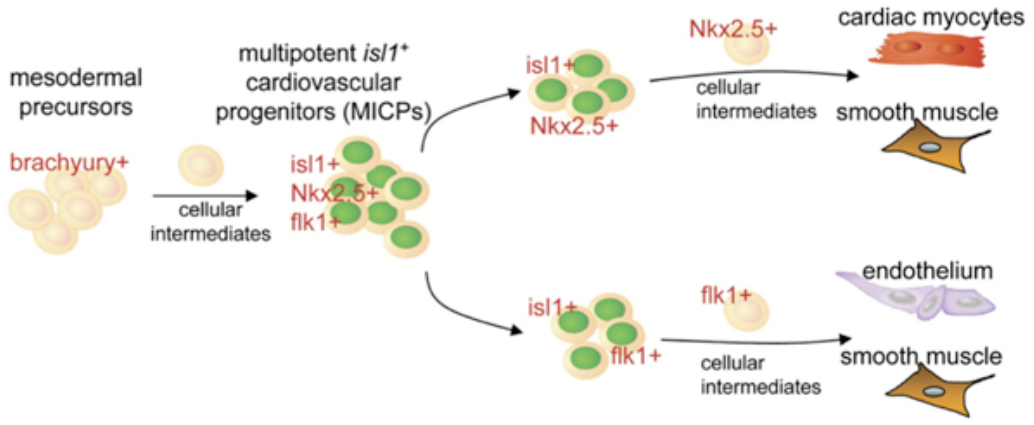

Figure-9. Model of the Cellular Hierarchy of Cardiovascular Progenitors and Their Lineage Specification (Moretti et al, 2006).

EMBRYONIC STEM CELL APPLICATIONS

Diseases that could potentially be treated using human embryonic stem (ES) cells include a wide variety of disorders including Parkinson's disease, diabetes, traumatic spinal cord injury, Duchenne's muscular dystrophy, heart failure, etc. However, in order to treat these diseases with ES cells, the ES cells must first be directed to differentiate into specific cells types before they can be transplanted to treat a particular disease. Unfortunately, ES research is limited because so few laboratories have access to human ES cells (discussed in Chapters 3 and 4). As a result, therapies based on the use of human ES cells are still in the experimental stage ("The Human Embryonic Stem Cell", 2005). Since the discovery of methods to isolate and grow human embryonic stem cells by Thompson at the University of Wisconsin in 1998, several teams of researchers have

been investigating the possibility that human embryonic stem cells could be developed as a therapy for treating diabetes.

Insulin-Secreting Cells Derived From ES Cells

Researchers in Spain used mouse ES cells that were genetically engineered to allow them to select cells that differentiated into insulin-producing cells. Bernat Soria and his colleagues at the Universidad Miguel Hernandez in San Juan, Alicante, Spain, added DNA containing the insulin gene to ES cells from mice. The insulin gene was linked to another gene that made the ES cells containing the DNA resistant to an antibiotic drug. The cells were then grown in the presence of an antibiotic. The cells that activated the insulin promoter were the only ones able to survive. The cells that survived were cloned, and then cultured under various conditions. The researchers found that the cells cultured in the presence of low concentrations of glucose differentiated. As a result, they were able to respond to changes in glucose concentration by increasing insulin secretion nearly sevenfold. The ES cells were then implanted into the spleens of diabetic mice, and researchers found that symptoms of diabetes reversed (Soria et al, 2000).

Recent research has also provided more evidence that human ES cells can develop into cells that can produce insulin. Melton and Benvinisty of the Hebrew University in Jerusalem, and Josef Itskovitz-Eldor of the Technion in Haifa, Israel, reported that human ES cells could be manipulated in culture to express the PDX-1 gene (Figure-10). PDX-1 is a gene that controls insulin transcription (Schuldiner et al, 2000). The researchers cultured human ES cells and allowed them to spontaneously form embryoid bodies. Embryoid bodies are clumps of ES cells composed of many types of cells from all three

germ layers. The embryoid bodies were then treated with various growth factors. Based on the results, the researchers found that both untreated embryoid bodies and embryoid bodies treated with nerve growth factor expressed PDX-1. ES cells did not express PDX-1 before they formed into aggregated embryoid bodies. The expression of the PDX-1 gene is linked with the formation of beta islet cells. As a result, the beta islet cells may be one of the cell types that form in the embryoid bodies. Researchers predict that nerve growth factor may be one of the key signals that induces the differentiation of beta islet cells (Schuldiner et al, 2000).

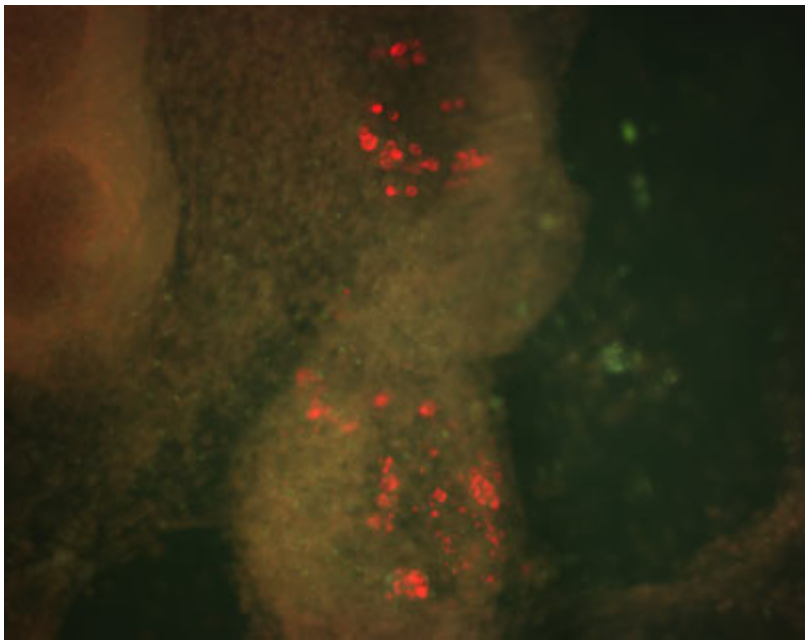

Figure-10. Immunofluorescence Picture of Human ES cells Differentiating into PDX1-Expressing Cells (red) That Produce Insulin ("Embryonic Stem Cells Pictures", 2004).

ES Cells Can Improve Movement in Paralyzed Mice

Researchers at Johns Hopkins University recently reported initial findings showing that cells derived from ES cells can restore movement in an animal model of amyotrophic lateral sclerosis (ALS) (Kerr et al, 2001). ALS, more commonly known as Lou Gehrig's disease is a degenerative disorder that progressively destroys special nerves found in the spinal cord. These nerves known as motor neurons have the function of controlling movement. A rat model was used by researchers in this ALS study to explore the motor neuron-restoring properties of ES cells. The rats were first exposed to Sindbis virus, which infects the central nervous system and destroys the motor neurons in the spinal cord. This process results in rats with paralyzed muscles in their hindquarters and weakened back limbs (Kerr et al, 2001). The researchers wanted to see whether ES cells could restore nerves and improve mobility in rats. Since they had difficulty sustaining stem cell lines derived from rat embryos, the researchers conducted their experiments with embryonic germ cells that were isolated from human fetal tissue. These cells can produce identical copies of themselves in culture, and form into clumps called embryoid bodies (Shamblott et al, 1998). The prepared cells from the embryoid bodies were injected into the fluid surrounding the spinal cord of the paralyzed rats based on the assumption that the nonspecialized embryoid body cells might become specialized as replacement neurons if placed into the area of the damaged spinal cord.

Three months after the injections, many of the treated rats were able to move their hind limbs and walk, while the untreated rats remained paralyzed. Through an autopsy of

the rats, researchers were also able to confirm that cells derived from human embryonic germ cells had migrated throughout the spinal fluid, they continued to develop, and displayed both the shape and molecular markers characteristic of mature motor neurons (Shamblott et al, 1998). But it is important to realize that these ALS results are preliminary, and researchers are not yet sure how well this strategy will translate into a human ALS therapy.

Chapter-2 Conclusions

Various applications of adult stem cells have already been used to save human lives for the past 35 years, thus not all stem cell applications are recent news. However, most of the current research involving embryonic stem (ES) cells remains as future human applications, and is currently based primarily on animal research. The ethical stances of the major religions vary pertaining to ES cell research, but remain consistently in favor of working with adult stem cells, and this is the subject of our next chapter.

CHAPTER-3: STEM CELL ETHICS

Now that we have documented the technology of stem cells, we now consider the ethical considerations that come with using stem cells in research and therapeutics. The main ethical conflict comes from the use of ES cells because the embryo used to obtain them is the precursor to a human being. This debate is complex, and to get a stance on such a topic, many people turn to their religion for an answer. Do these religions offer any perspectives on stem cells? Would the people following a particular religion go against its stance if they had more ethical perspectives as a reference? What exactly are the positions held by the major world religions on stem cells and what is their reasoning behind these conclusions? These are some of the questions I will try to answer in this chapter. Let us first look at a less controversial topic, adult stem cells.

ADULT STEM CELL ETHICS

Christianity

Christianity is by far the most widespread and strongly followed religion in the world, so not surprisingly, Christianity has many different denominations. However, many of the core beliefs are the same in all sects of Christianity. Around 2.1 billion people follow Christianity (this consists of 33% of the world's population) (Major, 2005). Christians tend to have a strong position of support for the preservation of life. Therefore, stem cells have always been a polarizing issue for Christians and they stand as the forefront of resistance against ES cell research. However, because adult stem cells are not

potential human beings, and no embryo is harmed when extracting them, Christians have no resentment against adult stem cells extraction, research, or therapies. Most scientists believe that ES cells have more potential than adult stem cells (ASCs), but this is not well established (Hook, 2004). While few human ES applications have been documented in the medical literature, scientists know more about adult stem cells and their therapeutic potential right now than ES cells (discussed in Chapter-2). Adult stem cells have already been used to treat "spinal cord injuries, heart failure, Parkinson's disease, diabetes and many other conditions" (Thomas, 2007).

"The Roman Catholic Church has declared its opposition to any biomedical research using fetal stem cells, saying alternative "adult" sources are available" (Holmes, 2004). The Pope also showed his support for adult stem cell research: "Pope Benedict XVI endorsed stem-cell research and therapy utilizing stem cells harvested from adults and umbilical-cord blood" (Glatz, 2006).

Islam

Islam is the second most widely followed religion in the world, garnering around 1.5 billion (21%) followers. There are 2 main sects in Islam, Shiite and Sunni, while other minor sects add together to make a third majority (Major, 2005). Compared to Christianity, Islam's stance on stem cell research is relatively liberal. Adult stem cell research is wholeheartedly encouraged, so much so that they believe that research in this field could eclipse the therapies that rely on ES cell research. The Shari'ah, also known as sacred law, advocates further the research into improving methods of extraction of adult stem cells (Siddiqi, 2007).

Hinduism

Hinduism is one of the ancient religions still alive in the modern world. Hinduism is deeply followed in India, but also in some African nations, and scattered followers across the world. Approximately 900 million Hindus make up the human population, representing 14% of the world's population (Major, 2005). Hinduism has evolved continuously since its conception and is still evolving. Hinduism might be the easiest and yet the most complex religion to follow. However, many people have criticized modern Hindus with being too close to atheism. And yet others have criticized Hindus of fanaticism (burning a widow after her husband dies, although this mostly happens in rural areas). Hindu followers learn from the holy book Gita, and the many Vedas. Hinduism does protect the embryo at various stages of its production, but there has never been a negative statement conveyed against adult stem cell research. In fact, many companies in India have chosen to use adult stem cells because of the lack of political and religious tensions (Indrajit, 2005).

Buddhism

Buddhism started out as a derivative of Hinduism, and spread quickly to many places in the world, most notably China and India. Today, Buddhism has around 376 million followers, representing around 6% of the world's total population (Major, 2005). Buddhists believe in the doctrine of no harm. They try to preserve all life equally. On adult stem cells Buddhism have an apparent non-issue with their use: "While Buddhism has no central authority competent to pronounce on ethical dilemmas, like other religions [except Catholicism], it would appear that there is no ethical problem in principle with

the therapeutic use of adult stem cells" (Keown, 2004). Hence, it is clear that Buddhism directly support the use of adult stem cells.

Judaism

Judaism is one of the oldest religions currently in practice. Around 14 million people still follow Judaism (mostly located in Jerusalem) and their beliefs have been consistent in their long history (Major, 2005). Judaism has a strong stance on using adult stem cells to help human kind. Barbara Weinstein, legislative director of Union for Reform Judaism (URJ) firmly states the URJ is in "support of 'research using both adult and embryonic stem cells, in addition to the existing lines currently approved for funding by the United States and Canadian governments....'" (Wahrman, 2006). Hence, from the above statements, it is clear that even though Judaism is older than Christianity and Islam, its stance on ESCs research is still quite liberal by comparison.

EMBRYONIC STEM CELL ETHICS

Considering the clear religious positions on adult stem cells discussed above, the ethical debate continues to this day whether using ES cells is immoral. In the U.S., the key debate is about using federal funding for extracting ES cells. The only way people have a say in this matter is through voting, however, how can a layperson ever understand the delicate balance between scientific progress and the ethical concern for human life? How can we educate the public? How can we let people who really know nothing about stem cells, and who believe all stem cells are alike, vote on whether federal funding should be allowed to support stem cell research?

Christianity

The Christian stance on ES cell research is one of great opposition. According to Christian teachings, human life begins at conception, and hence it is considered murder to sacrifice a 5-day embryo for research. Therefore only a total ban on ES cell research will suffice. There are many examples of people in the Christian hierarchy speaking against ES cell research. U.S. Catholic bishops protested even limited funding for stem cell research in 2001: "We hope and pray that President Bush will return to a principled stand against treating some human lives as nothing more than objects to be manipulated and destroyed for research purposes…" (U.S, 2006). Pope Benedict XVI himself spoke against the destruction of potential human life: "The resistance the church shows toward embryonic stem-cell research is because the destruction of human embryos to harvest stem cells is 'not only devoid of the light of God, but is also devoid of humanity', and 'does not truly serve humanity,' the Pope said" (Glatz, 2006). The Pope clearly states that in his moral judgment, destroying embryos will do more harm to humanity than good. However, there are divisions in Christianity itself as to how severe the punishment should be for scientists that perform ES cell research. A powerful cardinal named Cardinal Trujillo said "'Destroying an embryo is equivalent to abortion,'... 'Excommunication is valid for the women, the doctors, and researchers who destroy embryos'" (Rosenthal, 2006). But many Christians do not believe a punishment this severe is in order, as stated: "Even some Catholics who are opposed to the use of embryos in research felt that excommunication was too strong a sanction." It is still unclear what the current Pope thinks about how severe the punishment should be.

Islam

The Islamic perspective on ES cell research comes as interpreted from the Shari'ah (holy law of Islam). The Shari'ah states that because the embryo used in ESC research is created in a laboratory, the embryo exists and sustains itself in a different environment than the mother's womb. Also, human life does not begin until day 40 into a pregnancy according to the Shari'ah. Therefore, this embryo cannot be attributed the status of a human being because if this embryo is not placed in a mother's womb, it does not have the potential to become a human being. However, the Shari'ah does go on to state that ES cell research should be limited and used only in careful consideration with full consent from the appropriate donor(s) (Siddiqi, 2007).

Hinduism

Hinduism is a very complex religion and it is very hard to judge what stance the religion has on ES cell research. However, it is stated in Hindu tradition that conception is the beginning of life and is a rebirth of the soul from its previous life. While other Hindu traditions stress that three to five months after conception is the time when personhood begins, a lesser majority propose seven months to gain full personhood. Nevertheless, the majority of the Hindu tradition attributes personhood at conception (General, 2006). One Hindu authors notes that ES cells have great therapeutic potential but warns us about the source. Most Hindus do believe that life begins at conception, and that a fetus should be considered a person according to the Holy book, but Hindus do permit abortion when it is performed to save the life of the mother, implying that they

consider the life of the mother more important than the fetus (the life of the current human more important than the life of the potential human). Nevertheless, it must be stressed that not all Hindus believe this (Dharma, 2005). The main stance of the Indian government and modern Hinduism can be stated and summarized as the following: "The Hindu religion does not consider experimenting with human embryos developed by way of *in vitro* fertilization of human eggs (that creates test-tube babies) immoral, and 'India in fact has an MTP [Medical Termination of Pregnancy] Act that allows [abortion] within 20 weeks of conception" **(**Indrajit, 2005). Hence, we can conclude that although various Hindu traditions state that the embryo gains personhood at various stages of development, Hindu tradition also states that it is not immoral to perform stem cell research during those various times **if** the embryo has been taken from an in vitro fertilization clinic. Supporting the Hindu doctrine, Indian law indirectly permits stem cell research by legalizing abortion up to 20 weeks on a fetus. This all leads to the cutting edge research being performed in various parts of India by various biotechnological groups **(**Indrajit, 2005).

Buddhism

Buddhism is very conservative as far as their stance on ES cell research is concerned. "Buddhism believes in rebirth and teaches that individual human life begins at conception." This new being, as the embryo is described, has the same moral value as an adult human being. However, there is some divide as to whether it is permissible to use stem cells from an aborted fetus/discarded embryo, as this could be synonymous to organ donation. On the other hand, the conservative counter part of Buddhism argues that the initial act of aborting a fetus, or discarding an embryo, is immoral therefore the

second step of extracting the stem cells from this fetus/embryo should be considered immoral as well. Contradicting the above is the fact that the latest breakthroughs and the most ground breaking research is performed in a country where Buddhism is a majority, South Korea. “This suggests there is unresolved dissonance between Buddhist teachings and practice on the moral status of embryonic life” (Keown, 2004).

Judaism

Judaism is a relatively liberal religion when it comes to the topic of ES cell research. Jewish goals are to further the health of humanity and make progress in the fields of medicine to improve the human condition. All three major religious sects of Judaism – the Orthodox Union, Hadassah, and the Religious Action Center of Reform Judaism, all support ES cell research. They showed this support by supporting “the Stem Cell Research Enhancement Act, which would allow federal funding for stem cell research using surplus embryos from reproductive clinics”(Wahrman, 2005). The Jewish faith believes in the fact that personhood is ascribed to an embryo from day 40 and onwards. "Rabbinic opinion is virtually unanimous," Feldman wrote, "that human status cannot be ascribed to pre- implantation embryos.... A fetus, as precious as it is, is only potential in its status ... but the earlier embryo has only the pre-potential status of individual zygotes, of sperm and ovum. They, too, are to be protected and treasured — but where they failed to impregnate they ought certainly to be used for healing" (Wahrman, 2005).

PARTHENOTE ETHICS

Although ESCs might have the most potential in their longevity, efficiency and potential usefulness in therapeutics, many people for various reasons still disagree on their use. As an alternative, scientists have discovered Parthenotes. These are embryos that are produced solely from the female egg by the process of self-fertilization *in vitro*. This self fertilized egg is unable to proceed beyond the stage of embryo in the chain of embryonic development therefore is void of becoming a potential human being. However, the problem with parthenotes is the fact that the current research shows that the efficiency of parthenotes will not be very good in treating illnesses and other therapies (Cheshire, 2003). It is unclear whether parthenotes can in fact become viable human beings. Many religions might consider the embryonic germ cell a potential human being. Other religions might consider using parthenotes completely moral. Let us take a look at the major religion's stances on the use of parthenotes in research.

Christianity

The Christian stance on using parthenotes instead of embryonic stem cells is still conservative (Cheshire, 2003). Although many biomedical scientists might consider the parthenotes as an organism somewhere between a potential human and a mere cell, there is not enough scientific evidence to prove we are murdering a potential human being when experimenting with parthenotes. Christians say there should be enough moral clarity to proceed with such research or to not proceed at all (Cheshire, 2003).

Islam

When one investigates Islam's stance on embryonic stem cell research, one can assume what the majority of Muslims' would think about parthenotes. We are forced to make this assumption because no known statements were found in the research for this project, Islam is relatively liberal when the focus is on the matter of embryonic stem cells and allowing experimentation up to day 40. However, it should be noted that Islam does not consider an in vitro environment natural and therefore Islam does not consider embryos grown in such an environment a potential human being. Judging from this, one can deduce that parthenotes will be allowed wholeheartedly by Islam because they are grown in vitro and the fact that the cell is self fertilized.

Hinduism

Hinduism, like Islam, is very liberal with respect to ESCs research, Indian law permits abortion up to 20 weeks from birth, and various other sources confirm the fact that ES cell research has no moral discrepancy among most Hindus. So we can infer that Hindus would allow the use of parthenotes in research.

Buddhism

Buddhism, on the other hand, is very conservative on the moral ground of ES cell research. Buddhists believe that life begins at conception and that all life is sacred and must be protected. One can argue about whether a parthenotes is a potential human being, but one cannot argue that parthenotes are alive. Therefore, judging from the previous implications, one can assume that Buddhists will not allow parthenotes to be

used in research, since they are alive. The above assumption is only valid if one infers all Buddhists are conservative, as there is a divide among Buddhists. It is safe to assume that Buddhist that consider organ donation similar to taking cells from an embryo would support the use of parthenotes.

Judaism

Judaism is relatively liberal in its position concerning ES cell research as stated in many sources. According to Judaism, life begins at day 40 of embryonic development. Considering the fact that many rabbis consider pre-implementation embryos non-persons, one can assume that Judaism would lean more towards the stance of allowing parthenotes to be used in research.

The use of Parthenotes is a relatively new phenomena compared to adult and embryonic stem cell research, so there has not been enough information gathered about parthenotes. This likely accounts for the lack of stated information on parthenotes from most religions (except Christianity). One can see, however, that most religions except for Buddhism and Christianity should support the use of parthenotes and this support could lead to revolutionary cures and therapies that previously were thought impossible.

Chapter-3 Conclusions

The ethical stances of the world's major religions differ pertaining to ES cell research, but are consistently in favor of supporting adult stem cell research. Two major religions support ES research, while three are against it. Many different laws have been established to control stem cell research, and this is the subject of our next chapter.

CHAPTER 4: STEM CELL LEGALITIES

In today's emerging field of biomedical research, stem cell rersearch is considered by many as one of the most exciting advances of the 21st century. However, research on ES cells in the United States is getting hindered by legislative uncertainties. Stem cell research on human embryos has become an issue of great concern for many Americans. Research on ES cells has become entangled in politics and public misunderstandings, so researchers are concerned about serious delays in understanding and curing life-threatening diseases. Particularly in the United States, research involving human ES cells has slowed because of philosophical doubts, religious views, political opposition, and lack of understanding about the science. The ES cell research field now seems treacherous for scientists, largely due to legislative uncertainties and restrictions on research implemented by the White House. A major step against ES stem cell research was taken by the Bush administration after President George W. Bush took office (Agnew, 2003).

U.S. FEDERAL LAW

Bush 2001 Legislation

President George W. Bush announced on August 9, 2001, that federal funds will be awarded for research using human embryonic stem cells only if certain criteria are met. First, the derivation process, which begins with the destruction of the embryo, must have been initiated prior to 9:00 P.M. EDT on August 9, 2001. Second, the stem cells must have been derived from an embryo created for reproductive purposes and was no

longer needed. Third, informed consent must have been obtained for the donation of the embryo, and that donation must not have involved any financial rewards (“Information”, 2006).

President Bush announced in 2001 that scientists who receive federal research funds can work only with a handful of stem cell lines, specifically those that were in existence before August 9, 2001. The White House initially said that more than 60 usable embryonic stem cell lines were available for research purposes (Agnew, 2003). These existing lines are used in approximately one dozen laboratories around the world in the United States, Australia, India, Israel, and Sweden. President Bush said, “As a result of private research, more than 60 genetically diverse stem cell lines already exist. I have concluded that we should allow federal funds to be used for research on these existing stem cell lines where the life and death decision [of the embryo] has already been made. This allows us to explore the promise of ES cell research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life" (Fact Sheet, 2001). But in reality the number of ES lines is closer to nine since most of the stem cell lines out of the total of 60 are the same stem cell line passed on from laboratory to laboratory. As a result, the assumption that researchers had 60 genetically diverse stem cells lines is no longer true since a lot of them originated from the same place.

President Bush insists on using existing embryonic stem cell lines mainly because of his belief in the fundamental value and sacredness of human life. The President made this decision because he is committed to preserve the value and sacredness of human life

and at the same time, he has the desire to encourage vital medical research using existing embryonic stem cell lines. The President's decision will provide federal funding for research using the more than 60 existing stem cell lines already available. President Bush will not give consent to make more stem cell lines or encourage the destruction of additional human embryos. The President claims that the embryos from which the existing stem cells lines were made have already been destroyed, and have lost their ability to develop as human beings. As a result, President Bush believes the use of existing stem cell lines for research will not sacrifice the sanctity and sacredness of human life. George W. Bush claims that federal funding for medical research on existing stem cell lines will promote the sanctity of life "without undermining it." It will permit scientists to investigate the potential of this research to benefit the lives of millions of people who suffer from life threatening diseases (Fact Sheet, 2001). "I made my position very clear on embryonic stem cells," Bush told reporters in the Oval Office during a meeting with the visiting prime minister of Denmark. "I'm a strong supporter of adult stem cell research, of course. But I made it very clear to the Congress that the use of federal money, taxpayers' money, to promote science which destroys life in order to save it, I'm against that" (Baker, 2005). The opponents of embryonic stem cell research praised Bush for his courage to take a firm stand on a matter of principle in spite of the politics surrounding the issue. "We are happy to see the President defending life at all stages and refusing to allow further taxpayer money to fund the unethical science of embryonic stem cells," said Tony Perkins, President of the Family Research Council (Baker, 2005).

Figure-11 shows a summary over 3 years of the public stance for or against stem cell research. In 2005, only about 18% of the U.S. public agreed that stem cell research should be forbidden, while about 65% disagreed with that statement. Similar numbers were found in 2004 and 2001, so this means that the majority of the U.S. public is against Bush's 2001 legislation.

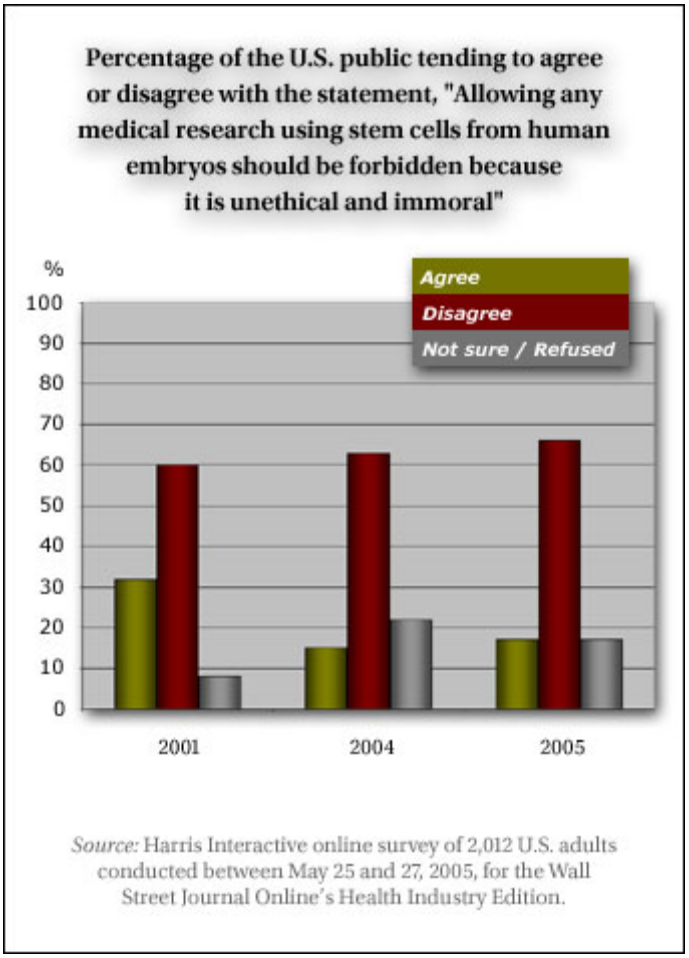

Figure-11. Chart Showing the Public Support for Stem Cell Research. ("Public Support", 2005)

The House Republican leadership agreed to a vote on a key bill in March of 2005. The bill would relax Bush's restrictions on human embryonic stem cell research. In July

of 2006, President Bush issued the first veto of his administration by rejecting Congress's bid to lift funding restrictions on human embryonic stem cell research. Bush said taxpayers should not support research on surplus embryos at fertility clinics, even if they offer possible medical breakthroughs. The President said the vetoed bill "would support the taking of innocent human life in the hope of finding medical benefits for others" (Babington, 2006). As of today, officials say that about 400,000 frozen embryos are stored at U.S. fertility clinics. The vast majority of these frozen embryos will be disposed because the couples that produced these embryos have successfully had children. However, most of the couples do not want another person to use their embryos, and raise their biological child, thus there will be very few adoptions of embryos created by other couples because most couples seeking a child through in vitro fertilization want that child to be their biological child. Sen. Arlen Specter (R-Pa.) said, "even with federal funding available to encourage adoption, the number is 128 [adoptions per year], which makes it conclusive that these 400,000 embryos will either be used for scientific research or thrown away" (Babington, 2006). President Bush and his allies on embryonic stem cell research claim that frozen embryos are equivalent to humans, therefore embryos are no more suitable for medical research "than are death row inmates" (Babington, 2006). Bush said if this bill gets passed, "American taxpayers would for the first time in our history be compelled to fund the deliberate destruction of human embryos." Others who are against President Bush and his allies on ES cell research reject that analysis, saying "it would make killers of every couple that produces an unused embryo, and every employee and official who allows fertility clinics to produce and store such embryos" (Babington, 2006).

STEM CELL RESEARCH IN U.S. STATES

New Jersey

Several states in the United States have authorized funding for stem cell research due to the lack of adequate federal funding. New Jersey became the first state in the United States to provide state money specifically for adult and ES cell research in early 2004. A total of $23 million in general revenues were given to the New Jersey Stem Cell Institute. In December 2005, New Jersey also awarded its first grants to 17 institutions for research on stem cells from embryos and other sources. In December 2006, legislation was passed that allows the disbursement of $270 million in bonds for construction projects such as the stem cell research facilities in New Brunswick and Newark, and for cord blood collection facilities (National Conference of State Legislatures, 2006).

California

Later that same year, in November 2004, California followed the path of New Jersey by passing Proposition 71, the California Stem Cell Research and Cures Initiative, to fund adult and ES cell research. Under Proposition 71, bonds were issued in the amount of $3 billion beginning in 2005, and an average of $295 million per year in bonds will be disbursed over a 10-year period (National Conference of State Legislatures, 2006). The California Institute for Regenerative Medicine or CIRM was established in early 2005 after the passage of Proposition 71. Proposition 71, which provided $3 billion in funding for stem cell research at California universities and other advanced medical

research facilities throughout the state, was approved by California voters on November 2, 2004 (California Institute for Regenerative Medicine ,2006). The new state agency, CIRM, was established to make grants and provide loans for stem cell research, research facilities, and other essential research opportunities.

About half of the families in California have a child or adult who has suffered or will suffer from a serious medical condition that could potentially be treated or cured with stem cell therapies (Text of Proposed Laws, 2006). The state of California is aware when several patients face a medical crisis, the health care system may find it difficult to meet the needs of patients and control rising medical costs, unless the treatments focus switches away from managing the illness and toward prevention and cures. Sadly, the federal government is not providing states with adequate funding necessary for the research and the development of facilities needed to advance stem cell therapies to treat and cure diseases. Many scientists believe that the funding gap that currently exists prevents the rapid advancement of research that could benefit millions of Californians. The California Stem Cell Research and Cures Act is designed to close this funding gap through the establishment of an institute, CIRM, which will issue bonds to support stem cell research. The CIRM will place emphasis on pluripotent stem cell and progenitor cell research for the advancement of life-saving medical therapies and cures. California wants to maximize the use of research funds by giving priority to stem cell research that has the greatest potential for therapies and cures (Text of Proposed Laws, 2006). They want to focus particularly on research opportunities that cannot, or are unlikely to receive, sufficient federal funding, due to limitations placed to hinder research on ES cell research by the Bush administration.

Massachusetts

In March 2005, the Massachusetts legislature approved a bill that clarifies state law on research on human ES cells and therapeutic cloning. The bill ensured that such research is permitted within a regulatory framework. Governor Mitt Romney vetoed the stem cell bill because he is opposed to the therapeutic cloning portion of the bill (Johnson et al, 2006). But, the House overrode the Governor's veto and Massachusetts legislators added two new sections to the state law on stem cell research. The first additional section creates an institute for stem cell research and regenerative medicine at the University of Massachusetts, and $1,000,000 will be spent on the stem cell biology. The second additional section launches a life sciences center to promote life sciences research, including stem cell research, regenerative medicine, biotechnology, and nanotechnology. A Life Sciences Investment Fund of $10,000,000 will also be set up to provide funds for the development and investment in stem cell research and other areas of research (National Conference of State Legislatures, 2006).

On May 8, 2007, new Gov. Deval Patrick announced his plan for a $1.25 billion proposal intended to help the state of Massachusetts maintain its status as one of the top places for stem cell research and other life sciences (Belluck, 2007). The money would provide grants for scientists working in universities and hospitals to establish special research centers to make their work more efficient. It would also establish the first stem cell bank in Massachusetts, a place to store all the stem cell lines created in Massachusetts laboratories. This place would also be used as a stem cell lending library to scientists around the world. "In many ways the health of this industry and the health of

our society are very closely linked," Mr. Patrick said at an international biotechnology convention in Massachusetts. "That's why we will not rest on our laurels" (Belluck, 2007). Gov. Patrick's plan involves $1 billion in state money over 10 years, plus $250 million in matching money from private business for stem cell research. Governor Patrick said, “There is no place in the world with as much talent in life sciences and biotech as here in Massachusetts. Now is the time for us to invest in that talent and bring together the resources of our unparalleled research universities, teaching hospitals, and industry to work towards a common goal – to grow ideas into products to create cures and jobs” (Official Website of the Governor of Massachusetts-Press Release, 2007).

Figure-12 shows a map of the U.S. depicting each state and its stem cell policies. Red means that state has restricted stem cell policies, while blue means stem cell research is encouraged.

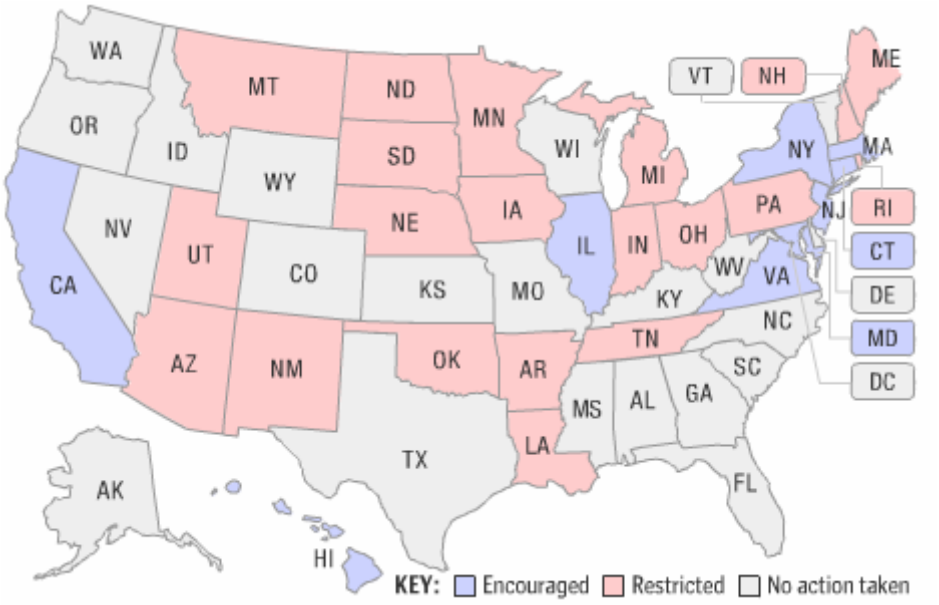

Figure-12. Map of U.S. Stem Cell Legislation by State (“Stem Cell”, 2005).

GLOBAL STEM CELL RESEARCH

LIBERAL COUNTRIES

Australia

The international community has taken a variety of actions regarding stem cell research. In 2002, the Australian government awarded a grant of $43.55 million to establish and maintain the Australian Stem Cell Centre. In May 2004, Prime Minister John Howard announced another $55 million grant will be given to support the Australian Stem Cell Centre's activities from 2006 to 2011. Australia currently allows the use of spare in vitro fertilization embryos for stem cell research. In July 2005, the Australian government set up an independent committee to evaluate the laws controlling ES cell research, who will decide whether current laws should be further relaxed to permit more types of ES cell research (Johnson et al, 2006).

China

The Chinese government is believed to have spent approximately $40 million on embryonic stem cell research. China is described as probably being the most liberal environment for ES cell research in the world because the government currently has no laws governing ES cell research, although an approval from the Ministry of Health is required to conduct ES research (Johnson et al, 2006).

United Kingdom

The government of the UK has given $80 million for ongoing stem cell research. On top of that, $15-$20 million from private funds were also provided for stem cell research. In February 2005, the Stem Cell Foundation was formed in UK. The government provided £100 million to fund the center and maintain the UK as one of the world leaders in stem cell research. The United Kingdom allows and regulates the production of new ES lines and therapeutic cloning. It will be funded by the federal government under the terms of the Human Fertilization and Embryology Act of 1990. In 2004, the government declared that it would review the HFEA to make sure that the law remains effective in an acceptable manner to society (Johnson et al, 2006).

Sweden

Sweden's stem cell industry is considered to be far ahead of stem cell science and technology in other countries primarily due to strong public support and adequate government funding. The favorable bioethical atmosphere and the tradition of science and research places Sweden at the forefront of stem cell research with over 30 research groups, and close to 300 people at nine Swedish institutions involved in stem cell research (Sweden's Stem Cell Success, 2002). Unlike many other countries, Sweden has very little debate going on regarding the ethical guidelines regarding stem cell research. Sweden allows stem cells to be taken from embryos that can no longer be used for further IVF treatment, something that is prohibited in many countries. The making of embryos by cloning for medicinal purposes using genetic material from a patient's own cells to get access to stem cells is surprisingly considered ethically justifiable in Sweden.

Government funding and money from outside the country has poured into the bioscience field in Sweden mainly because of its success (Sweden's Stem Cell Success, 2002). In March 2002, a joint US-Swedish research program was announced. This program will provide $7.5 million in additional funding for stem cell research in Sweden. Also in 2002, the Michael J. Fox Foundation for Parkinson's Research awarded Sweden $4.4 million in research grants for the creation of a cell line made to advance the study and treatment of the Parkinson's disease (Sweden's Stem Cell Success, 2002).

CONSERVATIVE COUNTRIES

Germany

While embryonic stem cell research is permitted with varying degrees of control in some countries, it is explicitly prohibited in many others. This category includes countries like Germany, Italy, Ireland, and Switzerland. In Germany, laws enacted on December 13, 1990 ban research on human embryos and only allows the laboratory creation of an embryo for the purposes of in vitro fertilization (Kim, 2002). In February 2002, 340 of 618 German parliamentarians voted to allow the import of embryonic stem cells for scientific research, but only under close government control. Even though at first the German parliament's decision to allow the limited import of embryonic stem cells may seem to be liberalization, the new decision was made to tighten restrictions for researchers. Although the existing German law passed in 1990 banned research on human embryos, it did not take into account the discovery of stem cells, and therefore did not explicitly ban their importation (Kim, 2002).

Italy, Ireland, and Switzerland

In Italy, the law specifically prohibits the creation of supernumerary embryos and the early splitting of the embryo for therapeutic or research purposes. The Italian National Committee on Bioethics has also prohibited reproductive cloning. However, there are no laws regulating the use of supernumerary embryos and therapeutic cloning. In Ireland, the Constitution prohibits research on the embryo by stating the right to life of the "unborn child" is equal to that of the mother. In Switzerland, as of 1999, the Constitution prohibits the use of embryos for research purposes as well as the fertilization of more ova than are capable of being immediately implanted (Israel, 2001).

Figure-13 shows a global map, and each country's stem cell policies. Restrictive policies are shown in grey, policies allowing IVF embryo donations (moderate policies) are shown in orange, and dark brown represents policies allowing a variety of techniques (liberal policies).

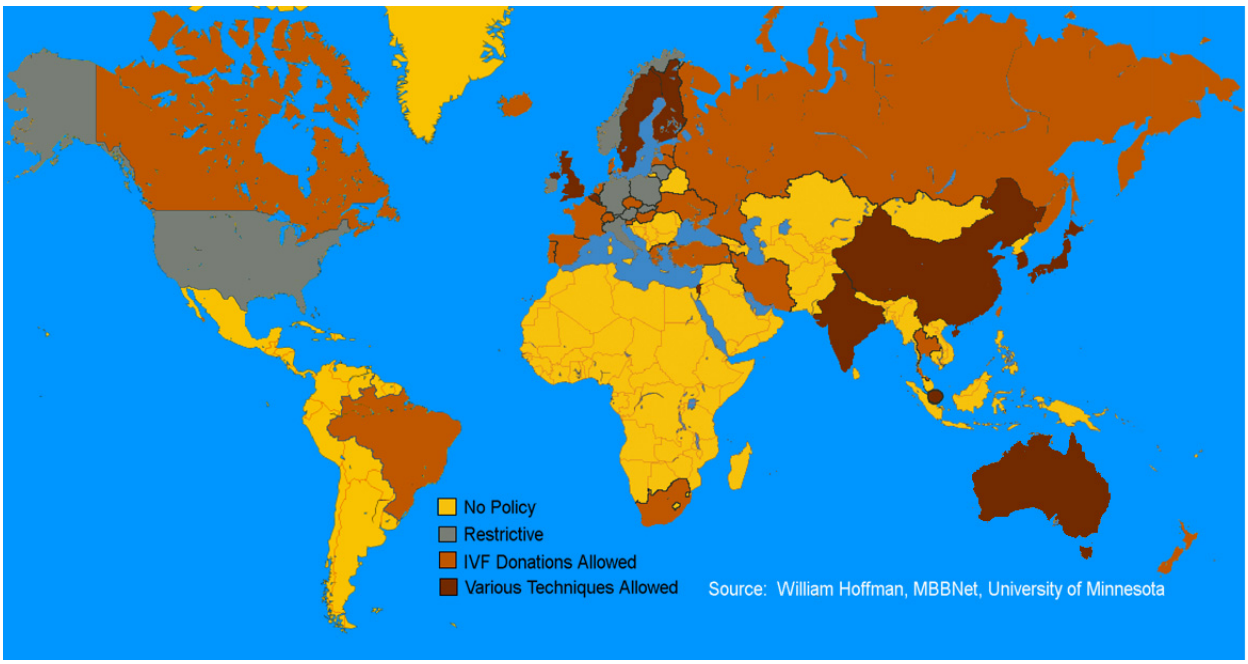

Figure-13. World Stem Cell Policy Map (Hoffman, 2005).

Chapter-4 Conclusions

The research involving stem cells have slowed down in the United States primarily due to the restrictions placed upon the use of ES cells by the Bush 2001 legislation. The lack of federal funding for ES cell research is hindering scientists from finding therapies to cure these deadly diseases affecting millions of people. Law makers in the United States need to look closely at countries that exercise more liberal regulations on ES cell research like Sweden, UK, and Australia. We should give more importance to save the lives of people suffering from deadly diseases rather than giving more significance to preserve embryos that have the potential to develop into a human being. However, it is not reasonable to completely discard the ethical aspects, but as a society our goal should be to find the balance that will satisfy both the liberals and the conservatives. I feel that balance should satisfy the liberals by lifting the federal ban on ES cells research, and satisfy the conservatives by banning the practice of reproductive cloning.

CONCLUSIONS

The ethical stances of major religions differ on ES cell research but agree when supporting adult stem cell research. All 5 major world religions support adult stem cell research. Many conservative religions have dissent among themselves about ES cell research because of the difference in opinions of the different sects and hierarchies. This difference in opinion may surprise most people because conservative religions usually have a firm stance against ESCs research.

There are just as many different laws and regulations governing stem cell use around the world. ES research has slowed down in the United States primarily due to the restriction of federal government funding for ES research by the Bush 2001 legislation. However, privately funded research in the US is still allowed. The Bush 2001 legislation does not place any restrictions on adult stem cells. However, the limitations placed on ES research limits scientists to only nine ES cell lines for research. Current research shows that ES cells have the greatest potential to cure a wide variety of disorders including Parkinson's disease, Alzheimer's disease, diabetes, traumatic spinal cord injury, Duchenne's muscular dystrophy, heart failure, and many more. The lack of federal funding for ES cell research is hindering scientists from finding therapies to cure these deadly diseases affecting millions of people. We believe that the United States needs to adopt more liberal laws regarding the use of ES stem cells to promote research to increase the health of our populations and perhaps for the world. We think the United States should follow in the footsteps of Sweden, United Kingdom, China, and Australia by lifting the current federal ban on ES cells, while continuing to ban reproductive

cloning. We feel that President Bush's rationale of using existing embryonic stem cell lines to preserve the value and sacredness of human life seems ludicrous since the unused embryos in *in vitro* fertilization clinics are simply going to be discarded anyway. We believe that the federal government should help the saving of the lives of people suffering from deadly diseases as their top priority rather than giving more significance to preserving embryos that have the potential to develop into a human being but never get the chance to do so. There are 400,000 embryos in *in vitro* fertilization clinics that are most likely going to be discarded in the future or will be kept frozen.

One would think that since the federal law bans government funding the states would follow suite, however, states like California, New Jersey, and Massachusetts are taking the initiate to promote ES cell research. Nevertheless, we need to understand that state funding alone is not adequate to promote and make considerable progress in ES cell research and therapies. The conservative law makers need to place their differences aside and listen to the American people, the majority of whom support stem cell research. They need to realize the potential of ES cell research, and adopt a more liberal stance to make society better as whole. However, we realize that it is not reasonable to completely ignore the religious and ethical dilemmas that arise from destroying the embryos for the sake of scientific research, so such an endeavor should only be taken after careful analysis of costs and benefit. As a society we need to find the right balance between the conservative and liberal stances to better adopt a plan that will allow researchers to thoroughly explore the potential of stem cells.

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