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G/T Independent Research

Annotated Source List

Baraniak, Priya R, and Todd C. McDevitt. “Regenerating Function in Vivo with Myocytes Derived From Embryonic Stem Cells.” *Regenerating the Heart: Stem Cells and the Cardiovascular System.* New York: Springer, 2011. Pg 25-33. *Google Books.* Web. 11 Oct. 2012.

Cellular Cardiomyoplasty is the transplantation of cells into a damaged myocardium in order to restore blood flow and regenerate scarred heart tissue. Many heart specialists and doctors are interested in the ability of donor embryonic stem cells to successfully engraft in the patient’s myocardium, differentiate into mature cardiomyocytes, and electrically and mechanically “couple” with the host cardiomyocytes in the patient’s heart. The three main delivery techniques of transferring embryonic stem cells to the heart is through a intramyocardial injection involving open heart surgery, an intracoronary transplant involving a catheter, or through a endocardial injection involving simply an injection and mapping technology. Since only 1% of embryonic stem cells differentiate into cardiomyocytes, many growth factors and proteins are added in order to increase the cardiomyocytes differentiation from embryonic stem cells. Purification of these embryonic stem cells is also necessary because they are then able to engraft and survive with the myocardium, align with the host cardiomyocytes, have no tumor formations, and differentiate into “mature” cardiomyocytes.

This article in this online book gave some new, detailed information that related to the delivery techniques of embryonic stem cell derived cardiomyocytes into the myocardium (cardiac muscle) of the heart. Most of the information in the article was repeated from other articles, which made the information a little redundant. Due to the nature of Google Books, about two pages of information which related to the background of heart disease and on the transplantation of differentiated cardiomyocytes were not included in this book’s preview.

Bernstein, Harold S. and Deepak Srivatava. “Stem Cell Therapy for Cardiac Disease.” *Pediatric Research.* 71 (2012): 491-499. Web. 17 Nov. 2012. <http://www.nature.com/pr/journal/v71/n4-2/full/pr201161a.html>.

Stem cell therapy is the only realistic way to treat and reverse heart damage done to the heart by a heart attack because the heart does not have the capability to repair itself and heart transplantations can be very expensive. Mesenchymal and embryonic stem cells have been shown to improve left ventricular function and reduce the infarct size in the heart based on various animal models. Embryonic stem cells are able to differentiate into cardiomyocytes with the structural and mechanical properties similar to the indigenous population of cardiomyocytes that already reside in the heart. There are a lot of areas that need to be studied more in depth concerning embryonic stem cells, like their engraftment time in the host myocardium, baseline beatings between the donor and host cardiomyocytes, and strategies for purification. According to animal models, tissue engineering efforts have been shown to provide structural and electrical integration between the donor and host myocardium as well as form stable grafts between them. For the future, researchers hope to further investigate numerous aspects of embryonic stem cells that need to be studied before they become viable for transplantations in human hearts.

Overall, some parts of this article describing the differentiation process and animal model studies for various types of stem cells were very hard to read and understand because of new medical terminology. The descriptions of the different stem cells and various clinical trials with them were well-explained and informative. The picture in this journal article was very informative and eye-catching and also gave information on the process of embryonic stem cell transplantation in animal models.

“Bone Marrow Transplantation and Peripheral Blood Stem Cell Transplantation.” *National Cancer Institute*. National Institutes of Health, 24 Nov. 2012. Web. 9 Nov. 2012. <http://www.cancer.gov/cancertopics/factsheet/Therapy/bone-marrow-transplant>.

This article explains how bone marrow transplants are used with peripheral blood stem cells in order to help treat patients suffering from leukemia, lymphoma, or any other type of blood cancer. Doctors match their patients with a donor based on the similarities between their stem cells and how well their human- leukocyte associated antigens (HLA) match. This source also explains how doctors obtain bone marrow and peripheral blood stem cells from the donor through the use of a hypodermic needle and specific medication respectively. The patient then undergoes chemotherapy which destroys all cells, cancerous and healthy, and is later injected with donor stem cells that migrate to the patient’s bone marrow and starts producing new, healthy blood cells. During this process, patients have an “increased susceptibility to infection and bleeding”, a chance to regain the cancer, and a possibility to acquire graft vs. host disease, which is when donor stem cells start attacking your own healthy blood cells thinking they are foreign invaders.

This article was very helpful since it gave very specific, detailed information on each step of the transplantation process using new medical terminology. Though this article was not related directly to embryonic stem cells, it gave a basal background and the preliminary processes to transplanting bone marrow and stem cells in a cancer patient. This article raises another question worth researching: Can other types of stem cells help treat types of blood cancer or is it limited to only one specific type of stem cell?

Boyle, Andrew J., Joshua M. Hare and Steven P. Schulman. “Stem Cell Therapy for Cardiac Repair: Ready for the Next Step.” *Circulation* 114 (2006): 339-352. Print.

This article focuses on the ample data obtained from previous animal studies that has proved the overall safety and efficacy of stem cells which should be enough to start clinical trials with humans. Animal models with embryonic stem cells have shown differentiation into almost bona fide cardiomyocytes, their organization to form intercalated disks, and their demonstration of forming a functional syncytium with the host heart. Animal models with bone marrow derived stem cells have shown increased capillary formation, more circulation in the heart, and a decreased infarct size. Mesenchymal stem cells have shown the regeneration of the myocardium, a reduced infarct size, and improved heart function in an animal model involving a pig. The two main guidelines in relation to clinical testing involving humans are patient safety and a balance of risk. Scientists and researchers also agree that human clinical trials are important because the positive and negative information that would come from previous trials would help give insight on a treatment that could possibly work in the future, therefore giving heart disease patients hope.

This article explained the many successes of some animal models and/or clinical trials performed with various stem cell types like embryonic stem cells and bone marrow derived stem cells. This article gave many examples of how the successes of various stem cells types in animal models have given credible proof that human clinical trials can now be done with them. The pictures and charts in this article also give information on the various clinical trials being done with specific stem cell types and the process of clinical trials in humans.

Cannon, P. Christopher, Elizabeth Vierck. *New Heart Disease Handbook: Everything*

*You Need To Know To Effectively Reverse and Manage Heart Disease.* USA: Fair

Winds, 2009. Print.

This book mostly investigates how stem cells can be “coaxed” into specific, articulate cells which can then be used to repair damaged organs, in this case, using heart muscle tissue to treat a damaged heart. Embryonic stem cells are pluripotent cells that have the potential to divide into identical daughter cells which would also have the capability to be pluripotent. Unlike embryonic stem cells, adult stem cells can only divide into cells that their “parent” cells were, therefore limiting the diseases that can be treated with them. This article also mentions how these stem cells can be used to treat various heart diseases or conditions like: replacing dead heart tissue, increasing the heart rate, and increasing blood flow after a heart attack or stroke. There are also some negative thoughts/opinions against using stem cells because it is not known whether stem cells will have a significant impact on “prolonging life” and reducing heart disease symptoms, as well as whether these stem cells are safe to use in the long run.

This book was very helpful because it showed which heart conditions and diseases stem cells would most likely help treat and how successful the treatment would be. The background information on the potentials of each type of stem cell was also explained as well as the positive and negative aspects of the use of each. Though the book as a whole was not fully dedicated to the use of stem cells and their treatment of heart disease, most of the articles in the book gave very detailed information on the potential uses of stem cells that could eventually improve some heart conditions if not all of them.

“Cardiomyocytes Could Fix Broken Hearts.” *Genetic Engineering and Biotechnology News.* Genetic Engineering and Biotechnology News, 6 Aug. 2012. Web. 19 Nov. 2012. <http://www.genengnews.com/gen-news-highlights/cardiomyocytes-could-fix-broken- hearts/81247142/>.

This article explains an experiment done by Dr. Michael LaFlamme from the University of Washington’s Institute for Stem Cells and Regenerative Medicine in which he and his colleagues transplanted human embryonic stem cell derived cardiomyocytes (ESC-CM) into guinea pigs. The control group (no stem cells) resulted in 785% more tachycardias than the group with the ESC-CM’s. The researchers also noticed that the group of guinea pigs that were injected with ESC-CM was able to integrate and contract synchronously with the host myocardium. The researchers then used two tests to further test the results of the group with ESC’s: a programmed electrical simulation (PES) which would induce tachycardias in order to see their electrical stability with the host myocardium and treatment of the ESC’s with a fluorescent chemical that would glow every time the ESC-CM and host CM’s contracted together. These two tests showed that the ESC group did have electrical stability and also contracted in synchrony with the host myocardium. Since there was no presence of arrhythmias throughout the whole experiment, researchers think the injected stem cells demonstrated an arrhythmia -suppressive effect.

This article gave very specific information on the process that took place with the cells before the transplantation and the results that occurred after. This information was taken from an article called “Human ES-Cell Derived Cardiomyocytes Electrically Couple and Suppress Arrhythmias in Injured Hearts” because the original article cost money. Overall, this article was very informative and articulate.

Caspi, Oren, et al. “Transplantation of Human Embryonic Stem Cell-Derived Cardiomyocytes Improves Myocardial Performance in Infarcted Rat Hearts.” *Journal of the American College of Cardiology* 50 (2007): 1884-1893. Web. 25 Nov 2012. <http://content.onlinejacc.org/article.aspx?articleid=1138622>.

This article provides information on an experiment conducted in order to assess specific things: whether the heart provides the appropriate environment to differentiate embryonic stem cells, whether embryonic stem cell derived cardiomyocytes (ESC-CM) can integrate and survive in the host myocardium, and whether the cell graft can improve heart performance. Three groups of rats were tested: the control group of rats that was injected with saline, a group that was injected with a heterogeneous population of cells derived from embryoid bodies, and a group that was injected with pure ESC-CM. The results of this experiment showed that cardiac tissue is not the suitable environment to guide the differentiation of human ESC’s and that teratomas formed when undifferentiated ESC’s were injected in the heart. This experiment also showed that when differentiated ESC’s were injected into the heart, the engrafted cardiomyocytes survived, replicated, and integrated with the host myocardium. The transplantation of human ESC-CM also has a positive effect on the remodeling process of the heart. Some techniques that need to be worked on is a more efficient differentiating process for the ESC’s, purity techniques, and the differentiation process of ESC into mature cardiomyocytes, much like the ones that reside in the myocardium.

This article was very descriptive and informative about the preliminary process of the experiment, as well as its results. The pictures in this article were also very nice and gave a visual representative of the effect of ESC-CM’s on the heart. Overall, this article was very articulate and helpful.

Choi, Sunh Hyun, Seok Yun Jung, Sang-Mo Kwon, and Sang Hong Baek. “Perspectives on Stem Cell Therapy for Cardiac Regeneration.” *Official Journal of the Japanese Circulation Society* 76 (2012): 1307-1312. Print.

Since ischemic heart failure has the leading mortality rate in the U.S., stem cell therapy has gotten a lot of recognition in hopes of treating the heart, rather than drug treatments and heart transplants. The heart is posmitotic, meaning that heart cells are not capable of dividing and reproducing anymore, therefore giving embryonic stem cells recognition to be “agents” for heart cell regeneration. Embryonic stem cells are pluripotent and can also functionally and electrically integrate and interact with the host’s heart tissue. On the contrary, embryonic stem cells have many disadvantages too; there can be teratoma development, possibilities of rejection, lack of human trials conducted, and the surrounding ethical controversy. Many other types of stem cells in this journal article also have some advantages and many disadvantages. According to researchers and scientists, the “perfect” stem cells have to show normal function after they are transplanted, have the potential to treat a damaged myocardium, have a standardized cell dosage, have a safe administering method, and overall be safe.

This was very informative because of the ample advantages and disadvantages of various types of stem cell like bone marrow derived stem cells. It also gave slightly more information on the specific characteristics that are needed for the “perfect” stem cell that will help treat cardiovascular diseases than other articles. This article also stresses the multiple limitations and challenges that researchers and scientists will have to overcome in order to start human trials to help heart disease.

Elchin, Erica. “Prochymal Significantly Reduces Hypertrophy, Arrhythmia and Progression to Heart Failure in Patients Suffering a Heart Attack.” *Market Watch.* Market Watch Inc, 2 July 2012. Web. 20 Sept. 2012. <http://www.marketwatch.com/story/prochymal- significantly-reduces- hypertrophy-arrhythmia-and-progression-to-heart-failure-in- patients-suffering-a-heart-attack-2012-07- 02>.

This article is about a clinical trial funded by Osiris Therapeutics, Inc to give heart attack patients a drug called Prochymal, which is made of stem cells taken from the bone marrow of other healthy patients. Prochymal is the first and only approved drug with stem cells that is recognized by a “regulatory authority” and is available in the United States, Canada, and eight other countries. Out of the 220 patients, 110 patients were given the Prochymal drug, while the other 110 patients were on the placebo. After six months, patients who were given Prochymal overall had a reduction in heart failure, while patients who were given placebo progressed to heart failure and were eventually re-hospitalized due to cardiac problems. This clinical trial was initially put into effect in order to determine the overall safety and the efficacy of Prochymal which was contradictory due to five people having died; this was overlooked as a cause of the already present heart failure in the patients.

This article was very helpful because this clinical trial gave information that proved that stem cells did have a significant impact on treating and possibly curing the heart after a heart attack. Though the trial is still going on, the article emphasizes the possible long term uses of stem cells and its future affiliation with heart conditions and diseases. This article could also lead to more articles on the positive and/or negative effects on Prochymal being used to test cardiac patients because of its unique potential.

“Embryonic Stem Cells.” *Genetics.* (2003). *Gale Science In Context.* Web. 12 Sept. 2012.

Embryonic stem cells can become any type of cell (pluripotency) and can reproduce infinitely into identical cells. Mice were used to research the effects of embryonic stem cells in their bodies and how it would pass to their offspring, which was eventually what had happened. This was done using “gene-targeting” and “knockouts” which meant a specific gene would be modified or removed from the embryonic stem cell respectively. Embryonic stem cells are mostly being used in diseases and conditions where a person’s cells are “defective or degenerated”, like Parkinson’s, heart disease, and diabetes. The ethical controversy of using embryonic stem cells is being “solved” by the creation of new types of stem cells like induced pluripotent stem cells which are made from human skin cells.

This article was very difficult to understand at times because of the new medical terminology and the extensive detail between the relations of embryonic stem cell research to mice. Though the article gave some information on the background of embryonic stem cells, it mostly focused on the passing down of embryonic stem cell genes in the offspring of mice transplanted with embryonic stem cells already. Overall, this was not a helpful article because it was not directly related to use of embryonic stem cells in humans and their relation to the various treatments of heart diseases and/or conditions.

Gepstein, Lior. “Embryonic Stem Cells for Myocardial Repair.” *Stem Cells and Myocardial Regeneration.* Totowa: Humana, 2007.101-111. *Google Books.* Web. 11 Nov. 2012.

There is a great demand in the medical community for a therapy that can help treat or reverse the damage done to the heart by a heart attack because of the heart’s inability to repair itself and the lack of heart donors for patients suffering from heart failure. Previous studies using fetal cardiomyocytes have shown the transplanted cells to survive, align, and form cell-to-cell contact with host cardiomyocytes, as well as a reduced infarct size and improved ventricular function. The ideal donor cell type for myocardial regeneration must have the structural and mechanical properties of mature cardiomyocytes, integrate structurally and functionally with the host myocardium, retain its proliferative potential, and be available in large quantities for clinical use. Embryonic stem cells have most of these attributes which gives it recognition as potentially being able to treat the heart. Since only 10-20% of cells that differentiate from embryoid bodies are cardiomyocytes, scientists and researchers want to be able to increase the cardiomyocytes that form by using different growth factors. The purification of these cardiomyocytes from embryonic stem cells are also essential because the mixture of cells that form from embryoid bodies are heterogeneous and therefore have a risk to form teratomas in the heart.

This article was helpful because it gave information on the multiple advantages of embryonic stem cells and the potential it has to treat the damaged myocardium following a heart attack. Some information in this article was hard to understand because of the medical terminology and some vague information in the article. Unfortunately, there was only little information on the clinical trials that used embryonic stem cells.

Geron. *Geron.* Geron, 2012. Web. 8 Nov. 2012. <http://www.geron.com/>.

Geron is a biopharmaceutical company that manufactures stem cell products and is currently looking for partners that are interested in working with human embryonic stem cells for specific programs like GRNCM1 (ESC – derived cardiomyocytes). Embryonic stem cells have two distinguishing characteristics: an “indefinite replicative capacity” in order to produce a limitless supply of cells for developing products and pluripotency. Geron produces different cell types from embryonic stem cells by: thawing and expanding previously cooled human embryonic stem cells in an undifferentiated state, treating them with specific growth factors to differentiate them into functional cell lineages, and later distributing these stem cell products for clinical trial use. Since no drugs have the potential to restore the damaged part of the heart when a person has a heart attack, Geron has developed a process in which 80% pure embryonic stem cell derived cardiomyocytes might be able to reverse the damage to the heart. Preclinical data with GRNCM1 has resulted in normal contractile function (whether the heart contracts well), no susceptibility to immune responses, improved ejection fraction (amount of blood pumped out of heart), no arrhythmias, and survival and engraftment of transplanted cells into the heart of animals during animal studies.

This website was not able to give a lot of information on embryonic stem cell derived cardiomyocytes because Geron has not started any clinical trials with them in relation to heart disease. This website was recommended to me by Dr. Debra Hursh when she explained that this organization had started conducting clinical trials with embryonic stem cells. The information about the company was also well explained, as well as their history.

Gold, Rachel Benson. “Embryonic Stem Cell Research – Old Controversy; New Debate.” *The Guttmacher Report on Public Policy* 7 (2004): n.pag. Web. 21 Oct. 2012. <http://www.guttmacher.org/pubs/tgr/07/4/gr070404.html#table1>.

This journal article explores the history of the use of embryonic stem cells and the various political controversies surrounding their medical use and research. Many events during the early years of the controversy affected people’s view on stem cell research such as: the Reagan administration prohibiting federal funds for embryonic stem cell research in 1980, the Clinton administration then lifting the ban in 1993, and finally Congress developing and adopting guidelines for any research relating to stem cells and embryos. From 1995 to 2000, Congress banned the use of federal money to create embryos solely for research or their destruction, but later agreed to use federal funds for research as long as the derivation of stem cells were conducted with private funds. As support for embryonic stem cells grew among researchers and anti- abortion Republicans, President Bush, in 2001, ONLY allowed the use of federal money on stem cell lines that were already there or produced. Over the years, support for embryonic stem cell research grew to about 73%, while the anti- embryonic stem cell research group declined from 32% to 15%.

The Guttmacher Institute is an organization that wants to inform people about issues that relate to sexual and reproductive health through the use of journals and other resources. This article gave a lot of information on the political perspective on the embryonic stem cell controversy rather than the ethical view of the controversy. It would have been nice if there was some more information on the current perspective of embryonic stem cell research in 2012.

Gosline, Anna. “Embryonic Stem Cells Repair Broken Hearts.” *News Scientist.* Reed Business Information Limited, 16 Sept. 2005. Web. 12 Sept. 2012. <http://www.newscientist.com/article/dn8006-embryonic-stem-cells-repair-broken- hearts.html>.

Adult stem cells were hoped to be used to discover a treatment for heart disease because there was no ethical or political controversy involving the research and use of them. Now, researchers and scientists are favoring the use of embryonic stem cells because the use of adult stem cells is futile and dubious when it comes to having the quality to “morph into real cardiac tissue” and repair the damage done by various heart conditions like a heart attack, heart block, and heart failure. Since heart disease is the leading killer of people in the United States, researcher Claudine Menard is attempting to see whether embryonic stem cells have a chance to treat heart disease. Menard induced heart attacks in 18 sheep and injected doses of embryonic stem cells in nine sheep. Towards the end of the trial, the nine sheep with the embryonic stem cells had improved heart function, while the other nine sheep’s heart function declined significantly.

This article was very helpful due to the real life experiment/trial performed by Claudine Menard and how she proved that her hypothesis of using embryonic stem cells to help improve or regenerate damaged heart tissue was correct. This article also shows that embryonic stem cells could have very positive effects on society, even though there is a strong ethical and political controversy behind the use of them. The extensive detail throughout the article and the articulate criteria of the experiment helped to explain how well the embryonic stem cells increased heart function that was previously defunct.

Hodgson, Denice M, et al. “Stable Benefit of Embryonic Stem Cell Therapy in Myocardial Infarction.” *American Journal of Physiology- Heart and Circulatory Physiology* 287 (2004): H471-H479. Web. 18 Nov. 2012. <http://ajpheart.physiology.org/content/287/2/H471.full.pdf>.

This article explains an experiment done with embryonic stem cells (CGR8) that were injected into the myocardium of male rats after they were induced with heart attacks. These rats were then randomly divided into a sham group which would not receive any stem cells and a group that would receive embryonic stem cells. The overall results of the group that received embryonic stem cells was a decrease in myocardial necrosis, demonstration of a normal ventricular structure, decreased infarct size, increased contractile (pumping) function, and no formations of abnormalities. The sham group exhibited a decreased contractile function, decreased ejection fraction, formations of abnormalities, and an altered ventricular structure with thinned walls. The positive results of the group with embryonic stem cells demonstrated that these stem cells could “contribute to myocardial repair, demonstrate cardiogenic differentiation”, incorporate with the host myocardium, and provide the opportunity to reduce “the morbidity and mortality of heart disease.” There were no signs of graft rejection, cardiac death, or tumor formation throughout the whole experiment.

This article provided very valuable information on the potential of embryonic stem cells to treat heart attacks. Since there was no new medical terminology in this article, it made reading and understanding this article very easy. The various pictures and graphs showing the improvement or deterioration of the hearts in each group also proved beneficial and gave more validity to the article.

Kumar, Dinender, Timothy J. Kamp, and Martin M. LeWinter. “Embryonic Stem Cells: Differentiation into Cardiomyocytes and Potential for Heart Repair and Regeneration.” *Coronary Artery Disease* 16 (2005): 111-116. Web. 28 Nov. 2012. <http://www.molpg.wisc.edu/people/faculty/kamp/documents/Pub15735404.pdf>.

Since the heart has a limited capacity to regenerate the lost or damaged cardiomyocytes, cell transplantation or stem cell therapy is considered the optimal choice to help regenerate the heart and its cardiomyocytes by researchers and doctors. In order to form cardiomyocytes from embryonic stem cells, embryonic stem cells are first dispersed and coaxed into forming embryoid bodies which will then differentiate into spontaneously beating cardiomyocytes. These derived cardiomyocytes were positive for proteins and having a phenotype of a typical cardiomyocytes that usually resides in the heart myocardium. Various studies of embryonic stem cell derived cardiomyocytes have resulted in the formation of a stable graft, an improvement in cardiac function, and the demonstration of no tumors. Human embryonic stem cells are known as a tool to repair the heart because of its capability to self renew and form functional cardiomyocytes which would help restore cardiomyocytes and heart function. Concerns include rejection, formations of tumors, lack of data in larger animals, and the need for purification.

This article was very informative only on the definitions of embryonic stem cells and what they have the potential to do in the body. The pictures in this article of embryonic stem cells gave visual representations of what these cells look like. There was also sufficient information on the results of clinical experiments and studies that showed the beneficial advantage of what these embryonic stem cell derived cardiomyocytes can accomplish in the heart.

Malliaras, Konstantinos, and Eduardo Marbán. “Cardiac Cell Therapy: Where We’ve Been. Where We Are, and Where We Should Be Headed.” *British Medical Bulletin* 98 (2011): Pg 161-185. Web. 13 Oct. 2012. <http://bmb.oxfordjournals.org/>.

This article talks about the current issues and beliefs of cardiac stem cell therapy as a whole, as well the many advantages and disadvantages of different types of stem cells like: embryonic stem cells, skeletal myoblasts, bone marrow derived stem cells, and heart derived cells. Since heart disease is the leading cause of death and disabilities in the United States, new approaches like stem cell therapies are encouraged in order to help lower the death rate from cardiovascular disease. Researchers and doctors describe the ideal cell type for transplants as being safe, improving heart function, creating healthy heart tissue, being tolerated by the immune system, and having no ethical concerns. For the future, scientists are looking for ways to improve delivery techniques for stem cells to reach the heart because of the current concerns that are associated with them like clogged capillaries and trapped cells in the lungs. Scientists are also looking for ways to reach out to people with more severe heart attacks because it has been shown that the potential of stem cell therapies is maximized with people that suffer severe heart attacks.

This article from the British Medical Bulletin was provided by Dr. Peter Johnston from John Hopkins Hospital who deals with stem cell therapy research. This article was helpful because it somewhat encouraged the use of embryonic stem cells by belittling and undermining the use of bone marrow derived cells, which is one of the most commonly used stem cells, by displaying all its disadvantages. The lengthy list of the advantages and disadvantages of many stem cells types in this journal article could help a person realize the astounding potential of embryonic stem cells.

Menasché, Philippe. “Embryonic Stem Cells Pace The Heart.” *Nature Biotechnology* 22

(2004): pp 1237-1238. Web. 26 Sept. 2012.

<http://www.nature.com/nbt/journal/v22/n10/pdf/nbt1004-1237.pdf>.

This article talks about the use of embryonic stem cells to treat heart block by the electrical coupling of grafted cardiomyocytes with host cardiomyocytes in order for them to work together to keep the heart pumping. In an experiment with a pig, cardiomyocytes derived from embryonic stem cells were used see if they could replace the function of pacemaker cells, which emits rhythmatic pulses from a pacemaker in the heart that prevents irregular heart beats. In the pig, the transplanted cardiomyocytes eventually replaced the function of the pacemaker cells and helped maintain regular heart rhythm. Bone marrow stem cells and skeletal myoblasts are usually used in clinical trials because of their safety, even though they lack the ability to turn into true cardiomyocytes that could regenerate or replace the parts of an injured heart. According to this article, “the ambitious goal of cardiac regeneration may ultimately be achieved only with embryonic stem cells.”

The diagram illustrating the process of transplanting embryonic stem cell derived cardiomyocytes into the pig was helpful because the pictures gave a visual representation on how the transplanted cardiomyocytes were made and injected. The author also explained how the use of embryonic stem cells would help treat heart block in a very descriptive and explanatory way, so most of the article was easy to understand. Since this article was written by a heart surgeon in Paris, some medical terminology was difficult to understand.

Oettgen, Peter. “Cardiac Stem Cell Therapy: Need for Optimization of Efficacy and Safety Monitoring.” *Circulation* 114 (2006): 353-358. Print.

Heart disease is the leading cause of death in the United States with about 250,000 people dying every year due to heart attacks and one million people dying every year due to heart failure. A future advantage of embryonic stem cells is the nuclear transfer technique that will be able to generate an unlimited supply of embryonic stem cells from a heart disease patient. The similar disadvantages of bone marrow derived stem cells, mesenchymal stem cells, and resident cardiac stem cells is that the percent of differentiated cells that can be used is small and the rate of differentiability and survival is very low. The main stem cell delivery route to the heart is the transvascular route that involves a direct injection to the ventricular wall which can be done with an injection, catheter, or open heart surgery. There are three main topics that scientists and researchers need to address before starting clinical trials with humans: safety concerns, the tracking of stem cells, and credible evidence of tissue regeneration.

This article gave lots of information on the few advantages and many disadvantages on other types of stem cells that support the fact that embryonic stem cells could be the best choice to help treat heart attack and heart failure patients. Apart from the advantages and disadvantages of stem cells, this article also addresses how to track stem cells in the body and how to find evidence of tissue regeneration in the heart. The subtitles in this article make the article very organized and easy to navigate which made reading the article and taking notes on the different stem cells easier.

Osiris Therapeutics, Inc. *Osiris Therapeutics, Inc.* OSI, 2012. Web. 6 Oct. 2012.

<http://www.osiris.com/>.

This website is about Osiris Therapeutics, Inc., that develops and markets products that potentially have the ability to regenerate tissue, like a drug called Prochymal. Prochymal is the first FDA approved drug made from mesenchymal stem cells, which is “morphed” from embryonic stem cells, and is being used to treat a variety of diseases through clinical trials like Crohns Disease, Graft vs. Host Disease, and Cardiac Disease. Phase I of the trial consisted of 220 people who had suffered a heart attack within seven days prior to getting the drug, 110 were on Prochymal and 110 were on placebo. During Phase I of Prochymal for Cardiac disease, there was an overall result of reduced chest pain as well as a reduction of heart arrhythmias in the Prochymal controlled group, while the placebo controlled group slowly progressed to heart failure. Safety was the first priority in this trial, and fortunately, there were no adverse reactions reported in the trial.

This entire website gave up-to-date information on the current and previous clinical trials that were being done on patients with cardiac problems/issues. There were many links on the website that gave more information on Prochymal as a drug, Osiris Therapeutics, more articulate information on Phase I of the cardiac clinical trial, and information on the ongoing Phase II of the cardiac clinical trial which is going to determine the overall safety and effectiveness of Prochymal. Since this website also had information on the use of Prochymal with other diseases such as diabetes, and graft vs. host disease, there was somewhat limited and non - specific research involving Prochymal on the use of heart attacks on the primary website (excluding the other links).

Ostrom, Carol M. “Human Stem Cells Fix Heart Damage in Lab Rats.” *The Seattle Times.* The

Seattle Times Company, 27 Aug. 2007. Web. 6 Oct. 2012.

<http://seattletimes.com/html/localnews/2003855008\_stemcells27m.html>.

This newspaper article explains the procedures and results of an experimental trial led by Chuck Murray, director of the Center for Cardiovascular Biology, and Geron, a private biotechnology company, with embryonic stem cells and lab rats. Since heart muscle cells do not regenerate, Murray injected embryonic stem cells into the heart of lab rats that were previously induced with heart attacks. The main concern with this trial was how to derive the correct differentiation of embryonic stem cells to heart muscle cells and to maintain them. This was eventually achieved through the application of chemicals and heat onto embryonic stem cells which caused them to differentiate into the wanted cell as well as keep them alive. The results of this trial included 10% restoration of the damaged hearts and the halted progression of heart failure in the lab rats. Both Murray and Geron hope to experiment more with embryonic stem cells in hope to acquire more knowledge on the potential advantageous ability of using them as opposed using adult stem cells.

The article could have given more articulate information concerning the preliminary process of the trial, the trial itself, as well as some more details concerning the results. It was interesting to know that another organization (Geron) and a group of people (Murray and colleagues) think that embryonic stem cells are a better choice to use to treat heart disease than adult stem cells. Overall, this article was helpful because it gave a different viewpoint on the use of embryonic stem cells by viewing them as a better choice to experiment with because of its characteristics.

Robertson, A. John. “Embryo Stem Cell Research: Ten Years of Controversy.” *Journal*

*of Law, Medicine, and Ethics* 38 (2010): pg 191-203. Web. 24 Sept. 2012.

<http://www.utexas.edu/law/faculty/jrobertson/JLME-10-year-survery-

Robertson-final.pdf>.

This article focused on the ethical, legal, and social controversies on the use of embryonic stem cells (ESC) and their potential to treat various diseases like Parkinson’s, Autism, and Alzheimer’s. People who think embryonic stem cell research is immoral are often religious and have the shared belief that a fertilized egg is “a new human being with all the rights and moral and legal status of fully born persons.” The other side of the controversy is that fertilized eggs are undeveloped and should not be put aside at the cost of “legitimate research.” The legal and funding issues associated with ESC research includes the Supreme Court ruling that fetuses are not people and therefore have no constitutional rights and the Dickey- Wicker amendment which bans the use of federal money to create embryos for “destructive research.” Bush’s administration later banned the use of embryonic stem cells, but allowed funding for its research from only the ESC lines that were already derived; Obama later lifted the ban on ESC research.

This article gave a lot of background information on the controversy towards the use of embryonic stem cells and the different perspectives of whether it should be used or not. The information on the legal issues and the funding of embryonic stem cells also provided some background on the history of embryonic stem cells and their potential use to cure diseases and/or regenerate body parts. The different perspectives toward embryonic stem cell research were also emphasized by the article stating specific problems and views that people, religious or not, have against embryonic stem cell research.

Rupart, Michael, and Loren .J. Field. *Cardiac Repair by Embryonic Stem – Derived Cells.* 20 Jan. 2009. National Institutes of Health. U.S. National Library of Medicine. *National Institutes of Health.* Web. 6 Oct. 2012. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628758/>.

This manuscript mainly focuses on studies as early as the 1990’s with the transplantation of embryonic stem cell-derived cardiomyocytes into the hearts of rats as well as the many successes that have been achieved by them. After the transplantation, various imaging equipment such as photon lasers and a green fluorescent protein (EGFP) is used to determine whether the newly turned cardiomyocytes have formed a functional syncytium with the host myocardium (muscular tissue of the heart). Other stem cell types like skeletal myoblasts and adult stem cells have been proven to cause tachyarrhythmias or unclear and perplexing results respectively. In order to produce “pure” cardiomyocytes from embryonic stem cells, treatment with a chemical called G418 is used on differentiated embryonic stem cells which allows all cardiomyocytes to “survive” by “killing” all non – cardiomyocytes lineages that are produced. With all the studies done in the past years till today, the successes with using embryonic stem cell derived cardiomyocytes include: the formation of stable grafts in the host heart, an occurrence of a functional syncytium, and a functional integration between the host and donor cells.

This manuscript gave very detailed information on the various studies done by scientists and researchers in the past and present that involves that use of embryonic stem cell- derived cardiomyocytes and their effect on the heart of a heart attack patient. The advanced medical terminology in this manuscript was hard to understand as well as some phrases of the manuscript. Overall, this source was very informational and well – written in which a person of little medical knowledge can understand with minimal to moderate effort.

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Studies with embryonic stem cell (ESC) derived cardiomyocytes have shown to form a functional syncytium with the host’s heart, which is when the cardiac muscle cells from the host and donor both work together mechanically, chemically, and electrically so they function as a single heart muscle cell. These studies have also shown that ESC’s can successfully engraft in the host’s heart, go through differentiation into cardiomyocytes, and have many of the characteristics of normal cardiomyocytes. In order to use ESC’s for transplantation in the heart, they must go through differentiation into cardiomyocytes under specific conditions *in vitro* (taking place in a test tube, culture dish, or outside of a living organism). They must also be “purified” by scientists. There are mainly two ways that ESC’s can differentiate into cardiomyocytes: with a FACS analysis that produces three types of cardiomyocytes or treatment with G418 that targets cardiomyocytes and kills the other cell lineages produced. Certain limitations and challenges with these heart and ESC derived cardiomyocytes studies is the failure to check for the coupling of host and donor heart cells and the clarity of whether donor cardiomyocytes can “fix” the heart enough for noticeable impacts on heart function.

This section provided a lot of past studies on animals focusing on the transplantation of ESC derived cardiomyocytes to a patient’s heart and their successes, limitations, and challenges. The new medical terms in the article were difficult and needed to be looked up with a medical dictionary. The studies mentioned in the article also gave some in- depth information on how to determine if the transplantation with the ESC derived cardiomyocytes was successful.

Šarić, Tomo, et al. “Embryonic Stem Cells and Their Therapeutic Potential.” *Handbook of Cardiac Stem Cell Therapy.* London: Imperial College, 2009. 29-50. *Google Books.* Web. 20 Nov. 2012.

Embryonic stem cells are harvested in vitro from the inner mass of cells of a blastocyst in which the mass of cells are pluripotent and undifferentiated. There are two types of embryonic stem cells that are derived from this blastocyst: murine embryonic stem cells and human embryonic stem cells which each have different physical characteristics. To derive cardiomyocytes from these embryonic stem cells, they are first differentiated into embryoid bodies which will then form into spontaneously beating cardiomyocytes. Analyses of these differentiated cardiomyocytes have shown that they have similar structural and functional properties of the cardiomyocytes that reside in the myocardium. Various animal models and studies with embryonic stem cell derived cardiomyocytes overall show an increased contractile function, no inflammatory responses, an improved ejection fraction, and improved left ventricular function. In one study, there were no signs of rejection or tumor formation; though tumors formed afterward. Some obstacles for embryonic stem cell therapy include its ethical concerns, safety issues, need for cell purity before transplantations, and a chance of cell rejection in the heart.

This small chapter of the book gave new information on the history of heart disease and how it happens. The vocabulary and medical terminology for most of this article made it very confusing to read and hard to understand. Fortunately, there were no pages of this book that was missing or unable to be viewed despite the nature of Google Books.

Schalager, Neil, and Josh Laur, ed. “Stem Cells Controversies and Research.” *Science and Its Times* 7 (2001): n. pag. *Gale Student Resources In Context.* Web. 3 Sept. 2012.

Stem Cells are “undifferentiated cells” that have the potential to become any type of cell, reproduce infinitely, repair damage in the body, and provide hope for the treatment of diseases like cancer, Parkinson’s, and Alzheimer’s. All cells come from stem cells that are “created” from an early stage embryo (blastocyst) and are therefore pluripotent (can become any type of cell). Two types of stem cells are adult stem cells (come from the bone marrow) and induced pluripotent stem cells (human skin cells turned to embryonic- like stem cells). When it was announced that stem cells could be obtained through human embryos, it triggered ethical and political debate over the issue of destroying human life for a possibility of curing countless diseases. President Bush banned research on using stem cells from embryos, whereas President Obama later lifted the ban and increased funding for stem cell research.

“Stem Cell Research: Mending Broken Hearts.” *The New York Stem Cell Foundation.* The New

York Stem Cell Foundation, 3 April 2012. Web. 1 Oct. 2012. <http://nyscf.org/about-

us/watch-nyscf-videos/item/1222-video-mending-broken-hearts-highlights>.

This video involves seven doctors discussing the history of heart disease in the United States, the controversy of embryonic stem cells, the beliefs of the scientific community, and the presentation of stem cell therapies to the public by various pharmaceutical companies. According to these doctors, the controversy of using embryonic stem cells has decreased over the years and there is a possibility to continue research with them with fewer objections from the public. These doctors believe that new technology is vital and imperative in order to understand how stem cell derived cardiomyocytes (cardiac cells) function, in order to produce new drugs for clinical trials for the public. Stem cell marketing involves the presentation of new stem cell therapies by pharmaceutical companies to the public which is often deemed unavailable and “bogus” by these doctors. These doctors also believe that multiple studies and clinical trials with stem cells are important for future generations for there to be a possible “cure” for heart conditions and/or diseases.

This video emphasizes the importance of stem cells to help treat heart disease through multiple doctors repeating the potential of curing various diseases through the use of these stem cells. This was an informative video because it discussed the current issues concerning the use of embryonic stem cells to treat various cardiac diseases like heart attacks. This video also gave some information on the embryonic stem cell controversy and the belief that treatment of heart disease is possible only with new technology.

United States. Dept. of Health and Human Services. National Institute of Health.

“Mending a Human Heart: Stem Cells and Cardiac Repair.” *National Institute of*

*Heath.* Dept. of Health and Human Services, Aug 2007. Web. 20 Sept. 2012.

<http://stemcells.nih.gov/info/Regenerative\_Medicine/2006Chapter6.htm>.

According to this article, cardiovascular disease is the number one cause of death in the United States, resulting in one death occurring every 34 seconds and a total of about $393.5 billion being spent on heath care per year. When a person develops ischemic heart failure, cardiac tissue in their heart gets no oxygen resulting in damaged tissue that is no longer useful to the heart. This damaged tissue cannot be regenerated by itself, therefore it needs stem cells. In clinical trials, these stem cells are injected to the primary “site of injury” in the heart which maximizes the chance of restoring function to the specific area of the heart. Clinical trails show that, after the injection of stem cells to the heart, the heart pumps blood more efficiently, heart tissue is improved, and the number of new cardiomyocytes increases. Of the different types of stem cells, embryonic stem cells are thought to have the most potential to improve heart function after a heart condition that destroys the irreplaceable cardiac cells.

This article had a lot of information on the use of embryonic stem cells, as well as other types of stem cells, for the treatment of ischemic heart failure and the regeneration of damaged or dead cardiac tissue, muscle and cells. This source talks about many clinical trials that have taken place over the years and their results pertaining to the heart and the stem cells. Since this article did not provide specific information on embryonic stem cells and their use use for the heart, this article was not very valuable.

“Update: Stem Cell Benefits Getting Closer.” *Harvard Health Letter.* (2012): n. pag. *Gale Student Resources In Context.* Web. 3 Sept. 2012.

Deaths from diseases that involve the loss of irreplaceable cells are usually treatable with stem cells. When a patient develops blood cancer, like leukemia, doctors destroy the blood with chemotherapy and later transplant stem cells that can turn into new, cancer-free blood cells. Embryonic stem cells are able to turn into any cell, while blood and adult stem cells are able to turn into specific types of cells. Harvard Medical School has found that all the cells in our body have the same genes, but different functions because certain genes in each cell can be either “turned on or off. Induced pluripotent (iPS) cells, made from a gene in a embryonic stem cell transplanted into a skin cell, have two main advantages: there is no moral debate because the stem cells don’t come from embryos and all iPS cells are “genetically identical” to your body so there is no chance for rejection.

Weiler- Sagie, Michal, and Lior Gepstein. “Embryonic Stem Cell Derivatives for Cardiac Therapy: Advantages, Limitations, and Long-Term Prospects.” *Regenerating the Heart: Stem Cells and the Cardiovascular System.* New York: Springer, 2011. Pg 53-63. *Google Books.* Web. 12 Oct. 2012.

This article explains the overall advantages, limitations, and new strategies that are linked to the use of embryonic stem cells in relation to the treatment of heart disease. The advantages of embryonic stem cells involve previous data recorded from their use in experiments with animals, their availability, their reproduction rate, their potential to differentiate into bona fide (authentic/genuine) cardiomyocytes, and the disadvantages of the other stem cells (proving embryonic stem cells more efficient). When embryonic stem cells are differentiated into cardiomyocytes, they are considered “genuine” because they have similar characteristics of early stage cardiomyocytes from a human heart. The two main concerns with the use of embryonic stem cells is the decreased number of cardiomyocytes that differentiate from embryoid bodies, and the mass number of differentiated cells dying after being injected into the heart; these concerns are currently being addressed. Safety for using embryonic stem cells during transplantation can include not using undifferentiated cells due to the formation of teratomas.

This article in this book gave current information on the various techniques used to improve the use of embryonic stem cells for transplants in the heart, like genetic manipulation. Since this book article comes from Google Books, two pages were excluded which had information on the differentiation of embryonic stem cells into cardiomyocytes. This article introduced genetic manipulation as a technique to pick cells to inject into the heart which was very interesting and new.