The use of Stem Cells to Cure Cardiovascular Diseases and the Ethical Benefits of IPS Cells

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Abstract

The aim of this paper is to research the use of stem cells in the treatment of cardiovascular diseases (CVD), the main cause of death in the UK. Advances on current treatment are of upmost importance as on average 24,000 myocardial infarctions occur every year in the UK\(^1\) and can cause long term damage to the heart. The Discussion will look into the future developments of stem cells and the use of induced pluripotent stem cells (IPS cells) - adult somatic cells that have been genetically altered to contain the same characteristics as embryonic stem cells, which are referred to as pluripotent- and the various ethical issues surrounding the topic.

Introduction

Stem cells are unspecialised, totipotent cells; they have the ability to differentiate into 200 different cells with a specific function, such as muscle and nerve cells. Cells differentiate by expressing certain genes, whilst the rest of the genes in the cell’s DNA are ‘switched off’. Another characteristic of stem cells is that they undergo proliferation (continuous self-renewal). Whilst somatic cells replicate a limited number of times by mitosis, stem cells can replicate for longer due to an enzyme called telomerase, which prevents the telomeres at the ends of chromosomes shortening with each cell division.

Stem cells, in particular embryonic stem cells, were discovered in the mid 1800’s and this was with the discovery that some cells could differentiate into others.\(^2\) In the early 1900’s, European researchers discovered that all blood cells came from a similar origin cell, and in 1963, Canadian researcher Ernest A McCulloch and James E Till documented the first self-renewing activities of mouse bone marrow cells. Research into adult stem cells has been carried out since then and bone marrow transplants have been used on patients receiving high dosage of radiation and chemotherapy since the 1950’s. Adult stem cells are predominantly found in the bone marrow, the lining of the intestine and blood. There are less adult stem cells available in the body than other types of stem cells, as by this stage, the stem cells are multipotent. Consequently, they are used to replenish cells such as intestinal epithelial, blood and skin cells.

The real breakthrough for embryonic stem cells was during 1998; James Thomson, a scientist from the University of Wisconsin in Madison, removed embryonic stem cells and grew them in a laboratory for the first time. This was the world’s first ever embryonic stem cell line.\(^3\) Instead of fame and glory the idea of embryonic use was quickly put down by a mass of religious and political outrage.\(^4\)
Embryonic stem cells originate from blastocysts (eggs fertilised in vitro which are 4/5 days old). These are the most sought after as they are totipotent; they have the potential to become any type of cell and this can be used for regenerative medicine and tissue replacement. There has been ongoing research about reducing rejection of the cells derived from embryonic stem cells; they can do this through therapeutic cloning. There are also possible risks to using embryonic stem cells; the major concern is that using embryonic stem cells may cause the formation of a tumour known as a teratoma.5

Unlike embryonic stem cells, adult stem cells are commonly used in medical practice to treat blood or bone cancers through bone marrow transplants. As the patient’s own stem cells can be used, there are two benefits, which include less ethical objection, as the patient can give permission, and less chance of rejection when used on the same patient because the stem cells and the patient’s body cells will have the same antigens. Furthermore, there is no need for immunosuppressant drugs which would leave the patient immunocompromised and developing opportunistic infections such as secondary or tertiary bacterial infections.

Current research has found that umbilical cords are stem cell rich, and are able to cure diseases that can also be cured through bone marrow stem cells. The advantages of umbilical cord stem cells are that they are less prone to rejection—if used on any patient—than both bone marrow and peripheral blood stem cells, this is due to the stem cells in umbilical cord not being developed enough to be recognised by the immune system and attacked by them. These stem cells also overcome a problem known as graft versus host disease, where transplanted cells attack the
patient’s body. This is because umbilical cord blood lacks fully developed immune cells.⁶

Most researchers believe that in the near future, adult stem cells and embryonic stem cells will be able to cure cancer, Type I Diabetes mellitus, Parkinson’s disease, myocardial infarction and many other diseases.⁷ Currently, cancer patients with conditions like leukaemia use stem cells as part of their treatment process, however, there are side effects to using stem cells; patients that undergo chemotherapy lose their hair. This is due to the fact that cytotoxic agents cannot distinguish between leukaemia cells and the haematopoietic stem cells within the bone marrow.⁷

Patients with cancer have to be put under large amounts of radiation to remove the cancerous cells and this can damage or destroy the patient’s bone marrow. This is where stem cells come into place, as the destruction of the bone marrow can have severe consequences. For example, the body can lose the ability to make red blood cells and hence affect gas exchange, but more importantly, reduce the number of white blood cells and thus inhibit the specific humoral and non-specific cell-mediated defence systems. A stem cell transplant replaces the destroyed stem cells allowing the bone marrow to produce healthy cells. Cancer therapies that use stem cell transplants are either autologous, allogeneic or syngeneic stem cell transplants.⁸ Autologous transplants are obtained from the same individual the stem cells have been removed from, stored and then later given back to the same person.⁹ Allogeneic transplants involve tissues from a genetically similar person, usually a sibling or close relative. As the genes are not completely identical and the tissue may be immunologically incompatible, these transplants are prone to some rejection.¹⁰ Syngeneic transplants are genetically identical, so immunologically compatible and less likely to be rejected. Syngeneic stem cell transplants involve receiving blood stem cells from the patient’s healthy identical twin.¹¹

IPS cells were first artificially created in 2006 by two different research teams lead by James Thomson and Shinya Yamanaka.

These cells were developed by the introduction of genes that change and transform somatic cells such as skin, liver, stomach etc., into cells with similar characteristics of embryonic stem cells. This gives the IPS cells the ability to become any type of cell that is necessary. Using IPS cells overcomes the ethical issues and objections that occur with embryonic stem cells, thus allowing their application to become more desirable. Other advantages of IPS cells are that they allow the formation of cell lines that can be genetically identical to the patient meaning that there is a less likely
chance for rejection. Also, IPS cells can be easily harvested in any laboratory and do not require the use of human eggs and embryos which have ethical issues surrounding their application.\textsuperscript{12}

**Discussion**

Cardiovascular disease (CVD) includes a range of diseases concerning the heart and surrounding blood vessels. Atherosclerosis, stroke and coronary heart disease are a few examples. CVD is the UK’s biggest killer (Figure 5), consequently there is ongoing research into innovative treatment.

Atherosclerosis is the build up of fatty deposits, such as cholesterol, within the wall of a blood vessel. As the deposits enlarge they form an irregular patch known as an atheromatous plaque, that bulges into the lumen and disrupts blood flow. If atherosclerosis occurs near the arteries close to the heart (coronary arteries), the condition is known as coronary heart disease (CHD). A reduced supply of blood to the heart is known as ischaemic heart disease (IHD), and this has the potential to stop blood flow to the heart muscle, resulting in a myocardial infarction.

Another type of cardiovascular disease is an aneurysm, this is caused by atheromas which can lead to the formation of a thrombus or an embolism (mobile blood clot) resulting in the weakening of the lining of the artery. These weakened points swell into the shape of a balloon and blood passing through that artery can fill this balloon-like structure which is called aneurysm. An haemorrhage can occur if the aneurysm bursts. This can result in loss of blood in that region and this can have severe

![Figure 6](image1.png)

An illustration to show the blockage of an artery

![Figure 5](image2.png)

Statistics to show the causes of death in men and women under the age of 75 in the U.K
consequences to the body. Cerebrovascular accident (CVA) or stroke is the term used for the aneurysm found in the brain.\textsuperscript{13}

Atherosclerosis, CHD, IHD, hypertension (high blood pressure) and aneurysms can cause congestive heart failure (CHF), which is the reduced supply of blood to the rest of the body.

Coronary artery bypass surgery is a current treatment to CVD. It is the process by which an artery from somewhere else in the patient’s body (i.e. the leg) is grafted onto coronary arteries to bypass (provide a different route from) the arteries narrowed by the build up of plaque. In the UK, an average of 28,000 coronary artery bypass surgeries are performed a year.\textsuperscript{14}

Angioplasty is the widening of a blocked or narrowed vessel using an unfilled balloon on a guide wire known as a balloon catheter. This is taken to the narrow or blocked area and is inflated using water pressures from 75-500 times more than normal blood pressure. This crushes the fatty deposits into the side of the vessel therefore unblocking the blood vessel.\textsuperscript{15} Angioplasty is the more preferred method because it is a less dangerous procedure and they both accomplish the same job. There has been ongoing research and it has stated that angioplasty is much more effective in the long term. Although both treatments resume normal blood flow to the heart, they do not undo damage to the cardiac muscle, thus the patient does not recover from CHF.

Cardiomyocytes are specific heart muscle cells, whose role is to contract and allow blood to eject from the ventricles. Destruction of cardiomyocytes occurs during a myocardial infarction and can have long-term effects such as hypertension and CHF. Despite the treatments talked about in this paper and drug therapies (that can limit cardiomyocyte destruction), a high percentage of CHF patients die within the first 5 years of diagnosis. New research into stem cells looks to replace cardiomyocytes – which are thought to be post mitotic, meaning they cannot self replicate- and therefore cure CHF.
Two other vital cells for a healthy heart are vascular endothelial cells that form the inner lining of new blood vessels and smooth muscle cells, which form the wall of blood vessels, as they provide oxygen and nutrients to the cardiomyocytes.

Stem cells have the potential to differentiate into these types of cells, which in turn hold the possibility to repair damaged hearts and cure CHF as they could provide replacement tissue for the damaged heart and blood vessels. This is a huge step forward for medicine as current treatment is inadequate for patients to maintain a long healthy life. This procedure also shortens the queue for transplants due to the lack of donors.

Recently, Donald Orlic, from the National Human Genome Research Institute, used haematopoietic stem cells (HSCs) – found in bone marrow - for regeneration of tissues in the heart. In his study, he stimulated a heart attack in mice by tying off the left main coronary artery. A select group of adult bone marrow cells with a high capability to develop into multiple types were isolated and injected into the ventricle wall. This led to the formation of cardiomyocytes, vascular endothelium and smooth muscle cells, hence replacing the dead myocardium. This research went on to show that a higher proportion of mice with these transplanted stem cells survived after a myocardial infarction than those who did not.

Another Study by Jackson et al. showed that stem cells could be delivered through bone marrow transplantation as well as direct injection into the cardiac tissue. Both these studies showed the ability of adult bone marrow cells to develop into cardiomyocytes, vascular endothelium and smooth muscle cells, cells they would not usually become, under certain culture conditions. Therefore the researchers had to be very specific of the group of haematopoietic stem cells that they isolated.16

Continuing research is taking place into human embryonic cells as they have the ability to differentiate into any type of adult cell. Using embryonic stem cells would be an advantage compared to adult stem cells, as there are more available and are easily obtained from embryos not used in IVF. However there is a lot of controversy to this research as many ethical issues surround embryonic stem cell research, due to the fact that many religious people consider an egg straight after fertilisation to be a living being so consider destroying the embryo as murder.
The main advantage of using IPS cells over embryonic stem cells is that it overcomes the issue of destroying an embryo. IPS cells also allow permission to be given by the adult to use their cells to revert them back to an embryonic stem cell state.

The initial production of IPS cells was carried out on mice cells, the researchers used four genes that they identified as being an important gene in the embryonic stem cells and then they placed those genes into the nucleus of the mice cells. This was carried out to change the potency state of the mice cell to pluripotent. After this was accomplished they carried out research into human skin cells and changed the potency of the skin cell. The researchers used the same gene that they used on the mice cell. The one cell line treated five to ten thousand cells. This was a breakthrough as this would provide new possibilities for the world of medicine and that embryos would not have to be destroyed for their stem cells.17

As presented in the Introduction, IPS cells hold many medical advantages including a much smaller chance of rejection. There is a less chance of rejection to an IPS cell as it is in the pluripotent stage similar to the embryonic stem cell. This is due to the stem cell not being differentiated into any cell in the body so it is quickly able to adapt to the body’s immune system. IPS cells can be used to cure Alzheimer’s disease, neurone damage, muscle damage etc as well as CHF. Although IPS cells avoid the ethical issue surrounding the destruction of embryonic stem cells and the exploitation of women, there are other problems with the use of IPS cells such as reproductive cloning due to it having the same characteristics as an embryo, this means it has a potential to become a human
being. This is not an issue for the current time as an IPS cell has not been able to create the outer layer of the embryonic cell which is needed for it to grow.

There was an initial outrage about IPS cells as scientists used viruses to change the cells into a pluripotent stage and this raised health risks. This objection was soon overcome and now proteins are used to change the potency of the cell. Another disadvantage in using IPS cells in therapeutic treatment is that an IPS cell is a regular skin cell which has been converted into an embryonic state. For this reason, an IPS cell constantly requires the application of potent regulator genes to allow their cell division and regulation, but these have been linked to cancer. The genes that cause cancer are called oncogenes and if these cells are expressed then there is a possibility that a cancerous cell will arise in the patient that is receiving the IPS cells. An experiment performed by scientists used four somatic cells which were converted into an IPS cell and then used on mice with sickle-cell anaemia and rats with Parkinson’s disease. These experiments were successful and showed that IPS cells have the possibility of curing many diseases in humans. However, two of the cells changed into an oncogenic state, showing the possible risks that surround the use of an IPS cell.

**Conclusion**

To conclude, the use of stem cells can solve the problem of cardiac heart failure, a medical issue that affects a large proportion of the UK’s population. If not affected directly, many people will have lost somebody or live with someone who suffers from a damaged heart. Although adult stem cells (HSCs) could be used to replace damaged cardiac tissue, they have to be carefully selected and there are a limited number available. Future developments of IPS cells will allow adult somatic cells to take an embryonic stem cell like state, which will be useful for treating CHF in this way. Using IPS cells rather than embryonic stem cells decreases the ethical objections. IPS cells also have other advantages to other types of stem cell research such as they are less prone to rejection. Further research is required before CHF can be properly tackled; however the studies recently completed are a big step forward for medicine and a great indicator of what is possible.
References

1. Website showing us the statistics to do with CVD.
   http://www.womens-health-advice.com/heart-disease/statistics-uk.html#stats
2. Website about the history of stem cells.
   http://www.allaboutpopularissues.org/history-of-stem-cell-research-faq.htm
3. Website about the history of stem cell research.
   http://www.ukscf.org/research/history.html
4. Website about the history of stem cells.
5. Website about embryonic stem cells.
   http://en.wikipedia.org/wiki/Embryonic_stem_cell
6. Website about different types of blood cells.
   http://learn.genetics.utah.edu/content/tech/stemcells/sctoday/
7. Website about the possible stem cell treatments.
   http://en.wikipedia.org/wiki/Stem_cell_treatments
8. Website about cancer treatments using stem cells.
9. Website about autologous stem cell transplantation.
   http://en.wikipedia.org/wiki/Autologous_stem_cell_transplantation
10. Website about allogeneic stem cell transplantation.
    http://en.wikipedia.org/wiki/Allogeneic_stem_cell_transplantation
11. Website about syngeneic stem cell transplantation.
12. Website about what IPS cells are.
    http://stemcells.wisc.edu/pdf/What_Are_IPS_Cells.pdf
14. Website about the procedures of coronary artery bypass.
    http://www.nhs.uk/conditions/Coronary-artery-bypass/Pages/Introduction.aspx
15. Website about angioplasty.
    http://en.wikipedia.org/wiki/Angioplasty
16. What cardiomyocytes are and the study of Donald Orlic.
17. Website about the creation of IPS cells.
    http://www.godandscience.org/doctrine/reprogrammed_stem_cells.html
19. Website about the ethical problems surrounding IPS cells.
20. Website about stem cells reducing Parkinson’s disease in rats.
21. Website about the cure for cancer using stem cells.
    http://peggy-williams.suite101.com/are-stem-cells-a-magic-bullet-for-cancer-a90217
Figures

11. http://www.nature.com/scitable/content/ne0000/ne0000/ne0000/ne0000/14465358/f1_rossant_448260a-f1.2.jpg