A study of Ischemic Cardiomyopathy and how future developments in Stem Cell technology can be used in its treatment

By

Joshua Evans

Jake Flynn

PASS WITH DISTINCTION

Research Paper

based on Pathology Lectures

at Medlink 2008 and Vet-Medlink 2008

Abstract

Heart failure and in particular, *Ischemic Cardiomyopathy* (ICM) causes a great number of deaths each year. This has been the most prolific killer in the United States since 1900 (with the exception of 1918 as a result of an influenza epidemic). Even as recently as in 2002, 2600 Americans died each day, which is an average rate of almost one death every 34 seconds [1]. Ischemia is the general term for tissue damage caused by an insufficient supply of blood and oxygen to an organ and in many cases the damage to the tissue is almost impossible to repair. When this occurs in the heart, severe cases can cause the cardiac muscle cells (cardiomyocytes) to be crippled and this is the main cause for the drastic reduction in life expectancy (40% mortality within 1 year) [2]. Current treatments tend to improve the quality of the patient's life rather than extending it [3]. The discovery and advancements in the medical use of Stem Cells could provide a "cure" by reversing the damage (previously thought irreversible) and prolong the life of the sufferer to a greater extent than conventional methods.

The aim of this study is to investigate the different types of Stem Cell and their application in treating ICM, compared with conventional methods. We will also attempt to formulate an effective means of administering the treatment of our choice.

Introduction to Ischemic Cardiomyopathy

A thorough understanding of the causes, effects and traditional treatments will be a necessity for considering the development of a treatment to ICM. The condition is most likely to present itself in people who have type-two diabetes or hypertension, and who are overweight and do not take regular exercise [1]. Given the trend towards increasing prevalence of these factors, as a result of the fast food culture and the fact that the British work longer hours than other European countries, this is by no means a condition on the way out. Despite its lengthy tenure in the forefront of medical research, we are still under-equipped with effective procedures to treat this kind of heart failure.

Ischemic heart failure is the result of an insufficient amount of blood and oxygen being supplied to the cardiac tissue. In a serious case of ischemia in the heart there is a radical loss of cardiomyocytes (muscle cells in the heart). This can trigger a rapid deterioration of the heart. There is a plethora of associated complications including an excessive pressure and flow of blood as well as ventricular remodelling (viable cardiac cells are stretched and damaged to sustain cardiac activity causing long term implications). This is a life-saving response in the short term, but it is accompanied by ventricular wall thinning. A non-contractile scar is another common feature of the condition. [4]

Conventional Treatment

A variety of traditional treatments are applied to deal with ICM, and these can be split into two categories: medicinal and surgical. There are many options available from a medicinal perspective including Beta Blockers, nitrate-based drug therapy, drugs to treat hypercholesterolemia, diuretics and ACE (angiotensin-converting enzyme) inhibitors. The benefits and drawbacks of these will be detailed later on [6]. The variety of surgeries available include angioplasty (where a small balloon is inflated inside a blocked blood vessel), surgery to reverse the remodelling of the left ventricle and implantation of devices such as pacemakers and defibrillators [1]. Heart transplants are also an option, along with coronary artery bypass surgery.

After a heart attack, unlike with external injuries, the damaged tissue in the heart is not repaired, or at least not as fully nor as quickly as with other injuries. There are mechanisms in the body known as endogenous repair mechanisms, which attempt to heal the body through proliferation of cardiomyocytes. This lack of self repair becomes an obvious target for treatment of heart conditions. The nitrate-based **drug therapies** such as Isosorbide Dinitrate help to dilate Coronary Arteries, which in turn helps reduce blood pressure and increase the supply of oxygen to the heart [3]. This is also an effective method of pain relief as a prophylactic to reduce the oxygen demand from the cardiovascular muscle tissue. Another drug that decreases the demands placed on the heart in cases of hypertension is the Beta-Blocker group of drugs, such as Propranolol. This forces a decrease in the heart rate which can often result in hypotension [3]. If this becomes a chronic condition the patient is at risk of not receiving enough blood, resulting in loss of consciousness, and damage to the brain.

Surgery is not without its share of problems. For example, coronary artery bypass grafting surgery only significantly impacts upon the quality of life, not on life expectancy, with some exceptions [3]. There are also many drawbacks since bypass surgery involves extensive damage to the torso to gain access to the heart. This places great demands on the stability of the patient and makes this a very traumatic experience, psychologically, physically and aesthetically.

This operation can greatly weaken a patient, which is not at all ideal, because it means that this is not necessarily an option available to the most seriously affected. Also since this is not a permanent solution, the costs that accompany this procedure are great; encompassing the cost of operating, the cost of a hospitalised patient for weeks afterwards, the cost of further treatment and also the fact that the patient is rendered unable to work for a considerable period of time. It is estimated that cardio-vascular disease cost the US $393.5bn in 2005 [1]. Transplantation is the closest thing to a cure that is widely used to combat the complications of heart failure; however, this depends on the availability of donor hearts as well as issues with rejection which make this answer less than ideal. Ventricular assist devices are also an option which has seen a fair amount of success. But like every other solution, it has its drawbacks: it carries a risk of infection and can contribute to blood clotting.

The body has many natural mechanisms falling under the endogenous repair umbrella. These include the propagation of the muscle cells that make up the ventricle wall, occurring under conditions of severe blood vessel stress or vessel formation. The most interesting of the mechanisms is the ability to generate fresh tissue by relocating bone-marrow based stem cells [1]. Stem Cells have the ability to develop into any cell type in the body, assuming they are pluripotent. Different types of stem cells have disparate levels of differentiation. There are examples of bone-marrow-derived stem cells differentiating into both mesoderm [9] and ectoderm [10] germ layers, meaning that bone marrow is potentially capable of giving rise to muscle, blood, connective tissue or similar as well as neural tissue, skin, hair, eyes and other sensory tissue.

Discussion of Future treatments using Stem Cells

Stem Cell research has already proved its effectiveness in the treatment of many other conditions in recent times. One such example is that of the team led by Dr. Mike Modo at the Institute of Psychology, University College London and also at the University of Nottingham. This example involved attempting to treat stroke damage in rats using neural stem cells attached to a tiny scaffold of a biodegradable polymer called PLGA to fill the cavities in the neural tissue. Previous attempts had seen only limited success because the stem cells were absorbed by the surrounding brain tissue and the damaged region remained unfilled. However, with the insertion of structure, rapid improvement has been observed [5]. The next step that needs to be taken is to investigate the use of a factor called VEGF and to compare the successes of scaffold directly with the success of simple injection [6].

Another example of success in the stem cell field is the transplant of a 7cm segment of trachea. This procedure included tissue engineering to free the trachea from the possibility of rejection as in a conventional transplant, to treat a collapsed airway. This procedure was a much safer and a more successful alternative than the conventional lung removal (which involves a relatively high mortality and complication rate). To engineer the donated trachea, it was necessary over a 6 week period to decellularise the trachea, so no donor cells were remaining and then seed stem cells derived from the patient's bone marrow. The operation was performed by Professor Paolo Macchiarini of the University of Barcelona and was an overwhelming success, with complete functionality regained within 1 month [7].

Arguably even more interesting than these success stories is the US Food and Drug Administration (FDA) clearance granted on 23rd January 2009 to the Geron Corporation for its Investigational new drug for clinical trials in humans. What makes this case so special is that it is a first for the world – a chance to trial embryonic stem cells in humans. The patients have "complete" American Spinal Injury Association (ASIA) grade A sub acute thoracic spinal cord injuries. These involve the breach of the myelin, a layer of white fatty substance, which sheaths nerves to protect them and insulate the electrical messages, which are carried. The treatment comprises of an injection of "human embryonic stem cell -derived "Oligodedrocyte" progenitor cells directly into the lesion site of the patient's spinal cord" [8]. This treatment, if successful, will be a step forward in the progression of stem cell research. It should be possible to apply this type of procedure to other neurological diseases such as Parkinson's, though this is centred in the brain itself, so it may be more difficult to treat.

Cardiovascular opportunities for the use of stem cells are less pronounced because the heart has previously been described as terminally differentiated [9]. However, Anversa and others have observed that the myocardium has capacity for regeneration, albeit a limited one. Between 250 and 500cc of bone marrow was extracted from the hip (iliac crest) and treated to obtain a population of cells with greater than 70% positive response for CD34 – an indicator of potency as a stem cell (a marker of endothelial lineage). This was subsequently diluted in 30cc of a subject's plasma and a suitable sample generated. This was then injected into the viable tissue (not into the myocardial scarring) with promising results. This yielded a 12 to 16% improvement in "ventricular ejection fraction" in the group that also received an 'off pump coronary artery bypass grafting' after 1 month [9].

The heart does not appear to be particularly responsive to stem cell treatment, in comparison to other parts of the body. However, compared to conventional treatments of ICM, even in the infancy of the field, stem cell research has yielded promising results. Although a marked improvement can be observed, it is not close to the success of the other example procedures above. However if we look at the outcome of a research project on the curing of spinal injuries using autologous bone marrow derived stem cells (as carried out by a team led by researchers from DaVinci Biosciences, including Dr. Francisco Silva), we can see that this showed a marked improvement, but the marked improvement is short of the improvement expected from the embryonic stem cell clinical trials of the Geron Corporation. Of the eight patients who were given the autologous bone marrow-derived stem cells (ABMCs) transplantation over two years through various routes, several functional improvements were reported, most importantly bladder control [10]. This illustrates a limited success, like that of the ABMCs transplantation to treat ICM, which pending Geron Corporation's findings being as expected, being far greater in the pluripotent cells derived from a blastocyst, within an embryo, pre-implantation.

The Varieties of Stem Cell

Based on the assumption that Stem Cells are the most viable option for a new treatment plan for ICM, the remaining question is: from which source should these stem cells be taken? There are several options, each with their own benefits and drawbacks. The types of stem cell that will be discussed in the following section are as follows: Embryonic stem cells, Cardiac cells resident in the heart, Umbilical cord blood cells, Skeletal Myoblasts and Human adult Bone-marrow cells.

Embryonic Stem Cells

Embryonic stem cells are the most adaptable of the stem cells, and can differentiate into any other type of cell, a property known as pluripotency. Testing on Ischemically injured cardiomyocytes in rats proved very successful, involving the stem cells differentiating into normal cardiomyocytes. This is a promising indication of the success to be had in human trials. To be able to use embryonic cells in humans, a human stem cell line must be established whereby samples of the stem cells undergo rigorous testing, involving immunocompromised mice. By injecting stem cells into the mice it can be observed whether or not the stem cells are pluripotent. If the test is positive then a benign tumour comprised of all three germ layers, called a teratoma is formed, implying that the substrate gives rise to all types of cell. Also, a method exists which can separate cardiomyoctes from the other cells during differentiation, which makes this type of cell a much more feasible solution [1]. Embryonic stem cells must be studied to make sure that they do not have any undesirable side effects. They are still relatively untested as the discipline remains in its infancy. Before this becomes a recognised technique, the treatment should be monitored very carefully over the course of clinical trials, to assess the stability of the differentiated cells after transplant and any subsequent effects, for example a benign tumour [1]. Currently, the embryonic stem cells available have not been made to match the patient, unlike the trachea transplant by Professor Paolo Macchiarini, [7] which means that an immunosuppressant would be needed to limit the body's reaction to reject the injected cells.

Cardiac Stem Cells

It has been discovered relatively recently that limited quantity of stem cells is housed in the heart, which most likely serve to carry out minor repair [1 & 9]. However, these are not sufficient for dealing with the level of infarction present in the wake of ICM. These cells can be extracted from the heart and proliferated in a lab environment, to be reinserted in greater quantities, to aid the reconstruction of the scar tissue more effectively. This process takes many weeks to gain sufficient quantities, so it may be wise to utilise a stem cell bank, in the cases of people perceived to be at risk of heart failure.

Umbilical Stem Cells

Stem cells derived from the umbilical cord are of a relatively high concentration, compared to bone marrow or adult blood samples. In the study of a mouse, when injected into the tail, a marked improvement in the condition of the construction of new blood vessels in the infarcted portions of heart was seen. When injected, although the cells mainly homed in on injured areas of the heart, there was also evidence of cells migrating to other parts of the body such as the spleen. An improvement in ventricular function was recorded [1].

Skeletal Myoblast Stem Cells

A skeletal Myoblast cell is a type of stem cell which can differentiate into muscle cells that is a possible source for treatment using stem cells. There are many reasons why this type of cell is well suited to this application. Skeletal Myoblasts are autologous in origin, which means that not only will there not be an issue of the immune system attempting to destroy a foreign body that might otherwise be used. The cells have a high resistance to ischemia, which is perfect for a patient recovering from infarction, and therefore vulnerable to such a condition and also, it has great potential in terms of quantity of production of new cells.

The fact that it is bound to myogenic differentiation means that this type of cell suffers less from the trend of other types of stem cell to partially migrate to other areas, for example the stomach, instead of staying in a high concentration at the insertion point. This is not to say that it will not migrate, but it is less likely to do so because the surrounding organs are predominately made up of endodermic cells. Notwithstanding, there are also some drawbacks which make this type of stem cell less appealing. The cardiomyocytes that are derived from skeletal myocytes (SMs) do not operate completely in harmony with the native cells. This is because there appears to be some imperfection in the electromechanical integration of the SM derived cardiomyocytes [11]. There have also been reports of sustained ventricular tachycardia, which is a life-threatening condition. This may also be linked to the lack of electromechanical coherence [1].

Adult Bone Marrow Stem Cells

There has been much experimentation into the suitability of Adult Bone-Marrow Derived cells, a lot of which has seen degrees of success, for example in the case of Orlic and colleagues. In this study an injection of Adult mouse bone-marrow-derived stem cells to the damaged ventricular wall led to a formation of myocardium that filled nearly 70 percent of the infarcted area. A decrease in mortality compared to the mice that did not receive the treatment was also observed. Other demonstrations have supplied evidence supporting the conclusion that they help to prevent remodelling of the wall of the ventricle [1]. However, studies released more recently have placed whether the cells formed were in fact cardiomyocitic.

It can also be mentioned however that the body naturally calls upon migration of bone marrow cells naturally, though; these cells clearly do not completely heal the heart. There have been many studies involving Adult Bone Marrow-derived stem cells with varied success. The different tests have been on patients with varying conditions so direct comparisons cannot be made, and there have been discrepancies between the tests, for example with the difference in Left Ventricle functionality. Some studies have shown substantial increases, whereas others have not reported any. In the years 2003 - 2006, the transplantation of bone marrow mononuclear cells was the type of cell which has been the subject of more clinical trials than any other method of cardiac repair [1].

Chosen Stem Cell Type

Of the types of cell researched, we think the type that would be best is the Embryonic Stem Cell. The main reason for this is the fact that embryonic stem cells have a greater potential for proliferation than any other type of stem cell, in respect to both quantity and variety of differentiation. Also embryonic stem cells have not been observed to suffer any of the drawbacks associated with other types of stem cells such as uncertainty of the type of cell formed in vivo, a lack of electrochemical coherence or the need for a fairly considerable warning to proliferate the appropriate cells in vitro.

Final Idea for a New Method of Treatment

The idea that we have decided upon comprises elements from several areas of our research. The first part of creating a new procedure to treat ICM was to choose the type of stem cell, as mentioned above.

We have considered the migration of a portion of the stem cells used away from the target area and noticed that there are parallels between this and the case of using stem cells to treat rats with induced strokes. In the study, led by Dr Modo, it was observed that a simple injection of stem cells into the area of damaged tissue merely resulted in the stem cells migrating to the surrounding healthy tissue, leaving the region unoccupied. To overcome this, the team from UCL and Nottingham University attached the cells to a tiny scaffold made of biodegradable polymer known as PGLA, and then filled the void with it [5 & 6]. The results of this study were very promising: within a few days, the cells had formed a primitive section of brain tissue interacting with the host brain. After the scaffold had biodegraded, the repair was more complete. We postulate that a similar approach could be applied to the area of cardiovascular repair. One factor that we thought needed special attention in the adaptation of the technique was that brain tissue is virtually stationary whereas the heart palpitates relatively violently. This could cause a problem; so, rather than using PGLA, we thought that we should use a similar polymer with a degree of elasticity.

The final consideration is the method by which this new treatment should be administered. As was outlined in the analysis of current treatments, we thought that open heart surgery was a risky process which resulted in severe trauma to the patient, so we have tried to avoid an invasive procedure in our scheme. The solution we have come up with is using a catheter similar to one used in connection with an angioplasty; inject the suspension into the damaged cardiovascular wall. The idea was derived from a variety of sources involving first the study of an angioplasty [12], which led us to research of Cardiac and Biopsy Catheterisation [13 & 14]. The incision to insert the catheter can be made at the base of the thigh, on the femoral artery, and the catheter can be fed up the artery and into the heart as shown in figure 1 [14]. This would be a good place to do it because there is an artery that is close to the surface so that minimal damage will be done, and the artery is consistently wide until it reaches the heart.

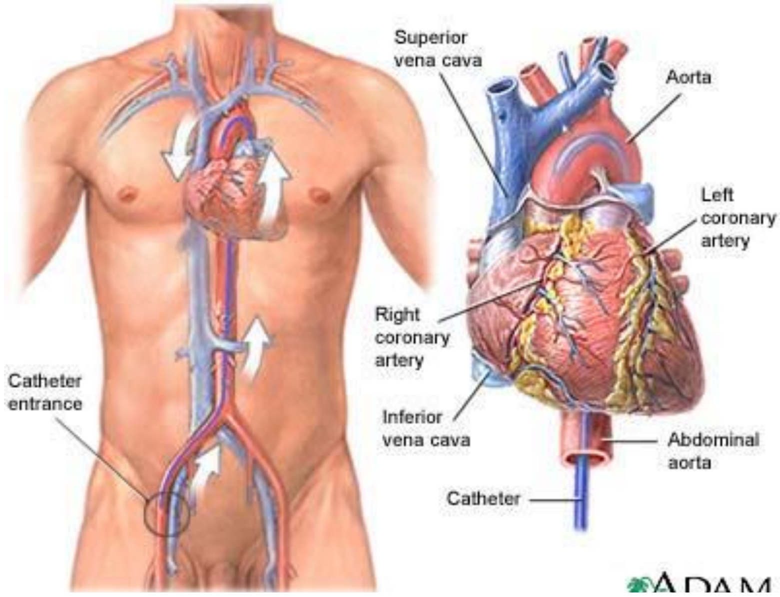

Figure 1

Conclusion

As a result of the research conducted in this paper, it is clear that stem cell research, although in its infancy, is soon to become one of the most powerful tools in medicine. It combines both the medical and surgical fields in the research required to analyse the properties of the different varieties of stem cells and the techniques to implement their findings.

ICM is a particularly difficult condition to treat because it results in a large loss of functioning tissue in and around the ventricle wall. This loss of tissue is permanent, so, using traditional means, it is impossible to cure the patient without transplant and even this has its own problems, as discussed earlier. These implications limit the effectiveness of surgery and medication in common use at the moment. This also limits its development in prolonging the life of the sufferer.

Stem cells are a viable option for an improvement in the treatment of ICM. They have the potential to rebuild the lost tissue by differentiating into the cells that are required. This nullifies the shortfalls of traditional medicine, and in the future it may be possible to comprehensively treat all types of heart failure, with minimal risk and trauma to the patient.

In this study, we have considered a variety of types of stem cell. We have also highlighted the main problems with traditional medicine and we have developed an idea for a new type of treatment. Our idea is to use embryonic stem cells, combined with a scaffold structure to encourage re-growth of tissue in the ventricular wall, to treat Cardiomyopathy. We plan to administer it using a catheter inserted via the femoral artery. We feel that this solution could prove to be an effective treatment of Cardiomyopathy in the future.

References

[1] http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf Regenerative Medicine (2006) (Pages 57 -

[2] http://www.patient.co.uk/40024526

[3] http://chinese-school.netfirms.com/heart-disease-ischemic.html

[4] rosenstrauch D, Poglajen G, Zidar N, Gregoric ID. Stem Cell therapy for ischemic heart failure. Text Heart 1st J. 2005; 32:339-347

[5] http://www.bbsrc.ac.uk/media/releases/2009/090309_stem_cells_stroke_damage.html

[6] http://news.bbc.co.uk/1/hi/health/7927004.stm

[7] http://www.sciencedaily.com/releases/2008/11/081119092939.htm

[8] http://www.stemcellsportal.com/first-human-clinical-trial-ofembryonic-stem-cell-based-therapy.html

[9]http://www.ualberta.ca/~dcl/hype/SC+ischemic+cardiomyopathy-hope+or+hype.pdf

[10] http://www.sciencedaily.com/releases/2009/03/090312130650.htm

[11] Reinecke H, MacDonald GH, Hauschka SD, Murry CE. Electromechanical coupling between skeletal and cardiac muscle. Implications for infarct repair. J Cell Biology. 2000; 149:731-740

[12]http://www.nhs.uk/Conditions/Coronary-angioplasty/Pages/Introduction.aspx?url=Pages/What-is-it.aspx

[13] http://www.nlm.nih.gov/medlineplus/ency/imagepages/1080.htm

[14] http://www.nlm.nih.gov/medlineplus/ency/imagepages/8904.htm