The use of stem cells to produce artificial cardiac muscle to reduce the number of deaths caused by dilated cardiomyopathy and post-myocardial infarction heart failure

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Shaan Kumar thought of the initial problem and utilised his deep medical understanding and reasoning to arrive to the treatment using stem cells. Evie Schmidt took advantage of her historical dexterity by delving further into the research of stem cells and discovering the potential of IPSCs and CPCs, in addition to investigating ethical issues surrounding the treatment. Scarlett Spink implemented her communication skills from her geographical studies, by eloquently articulating the in-depth research. Divya Hukkeri carried out fundamental research into the affordability of the treatment, as well as the expense of aftercare. Neha Patil used her artistic prowess to produce biological drawings and schematics.

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What is dilated cardiomyopathy?

Dilated cardiomyopathy is when the heart chambers enlarge which stops their ability to contract. It usually starts in the left ventricle and as the disease progresses it can spread to the right ventricle and to the atria. The cardiac muscle dilates and stretches which causes it to thin, stopping the heart from being able to pump blood as effectively which leads to the accumulation of fluid in the lungs and body which leads to heart failure.

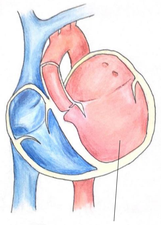
It can be caused by many diseases such as diabetes, infections, high blood pressure, irregular heartbeat/ rhythms, response to heart attack/ blocked arteries, heart valve issues, etc. but the main cause is genetic mutations.

Dilated cardiomyopathy causes around 10% of sudden cardiac deaths - scarring and damage to your heart muscles increase chance of abnormal heart rhythms and therefore heart attacks and is a **common cause of heart failure.**

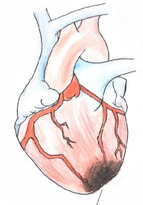
What is a myocardial infarction?

Myocardial Infarction (MI) is commonly known as a heart attack. This event arises when the blood supply to the myocardium (via the coronary arteries) is limited, resulting in the muscle suffering from a lack of oxygen. The most likely cause is atherosclerosis and thrombosis. The cause for lack of regeneration and therefore heart disease is that heart tissue does not divide to reproduce more cells like other body tissues do. A human is born with more than 50% of the heart cells they die with, demonstrating how minimally the heart generates more cells.**The major cause of heart failure is the death of cardiomyocytes**, where a typical large myocardial infarct (MI) kills around one billion myocytes (one-quarter of the heart). This results in a weakened heart as parts of the myocardium is now dead (as illustrated) and blood will not be able to reach peripheral areas - resulting in heart failure.

Both illustrated by Neha Patil



Enlarged LV, thin muscular wall

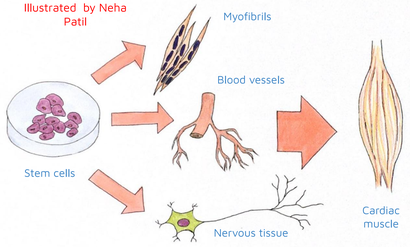


Dead myocardium

The use of stem cells

Stem cells are unspecialised cells which can differentiate into many different types of cell. Under the ideal conditions (which can be mimicked *'in vitro'*) they can divide to form daughter cells and then these can differentiate into many different types of cell - some including cardiomyocytes and other components of cardiac muscle.

Illustrated by Neha Patil



As illustrated above, some stem cells have the capability to be replicated and differentiated indefinitely in a lab to produce the components of cardiac muscle - most notably the muscle cells themselves as well as nervous tissue and blood vessels which would typically be difficult to obtain. Transplantation of this artificial muscle into the heart can **counteract the effects of dilated cardiomyopath**y and also prevent heart failure by **restoring the strength of cardiac muscle which has been weakened due to some ischaemic myocardium.**

Our proposed methods of treatment
We propose the following two methods of treatment as these in particular will massively reduce deaths in the coming years due to their modern approach to regenerative medicine combined with recent discoveries and technology, such as gene therapy.

iPS cells

One of our proposed treatments involves the use of induced pluripotent stem cells, commonly referred to as iPS cells. This plan revolves around the extraction of adult stem cells directly from the patient, from accessible sites such as obtaining blood cells from peripheral blood vessels. These mature stem cells are converted into pluripotent stem cells by the introduction of four specific genes - collectively known as Yamanaka factors. Once pluripotent, these stem cells can then be placed under the same conditions as the other stem cells mentioned, to eventually form cardiomyocytes to form the cardiac muscle. The main advantage of the use of iPS cells rather than any other form of stem cell is the fact that this treatment obtains cells from the patient, significantly reducing risk of immune rejection, such as graft vs host disease - which has a fairly common occurrence rate of 15%. This autologous method of transplantation aims to reduce this statistic and it is proven that autologous transplants have a lower risk of complications than allogeneic transplants. A drawback to this is the sheer cost of manipulating stem cells to become pluripotent £16300 - £28500 However, mass manufacture and new production methods are set to drive down this cost in the future.

Cardiac progenitor cells (CPC's)

A more recent discovery has been the one of cardiac progenitor cells and their ability to enhance the limited regeneration of cardiomyocytes in the heart. They are a mature form of stem cells, however less mature than adult stem cells - meaning they can only differentiate into cells from their target organ. This maturity is not an issue as they reside in the heart - the target organ of our treatment. However it has been shown that in vitro and when treated with growth factors such as TGF- β, these can fully differentiate into beating cardiomyocytes. These in turn can be structured into cardiac muscle of a desired area. This method provides a major advantage due to the certainty that cardiomyocytes are able to be formed, as well as the relative ease of obtaining the CPCs and the autologous nature of the treatment reduces the risk of autoimmune disease and rejection.

Our Treatment Plan

Our proposed treatment revolves around the production of a graft of desirably-sized myocardium via modern stem cell technology. An open-heart surgery will have this graft surgically attached to the heart of the patient as a seamless addition to their cardiovascular system. This artificial heart muscle will work with the rest of the heart to contract when appropriate to regulate the flow of blood around the patient's body. This will provide major benefits to patients with Dilated Cardiomyopathy. The addition of the graft to a ventricle will add extra myocardial contractility in ventricular systole, allowing proper contraction so all parts of the body receive adequate blood. Additionally, the treatments will reduce the number of deaths due to Post- Myocardial Infarction Heart Failure. During the open-heart surgery, the scar tissue that has formed due to ischaemia can be removed - not dissimilar to ventricular restoration surgery - and artificial cardiac muscle can be added. The replacement of former diseased myocardium will restore the normal strength of each heartbeat so sufficient blood can be transported to major organs - reducing the risk of congestive heart failure.

How it is better than current ones

The most widely used treatments for DCM and Heart Failure overlap, in the form of Ventricular Assist Devices (VAD's) and a heart transplant. These treatments, however, do not address the underlying issue of insufficient myocardium but rather serve its symptoms. They both contain negatives that are eliminated in our treatments - with VAD's being a consistent hindrance in the patient's lifestyle, not to mention an elevated risk of infection via skin ports through which wires pass. The alternative treatment in the form of a heart transplant - although effective when successful - entails further complications. A significant one includes rejection of the donated heart (massively decreased risk due to our autologous treatment). The subsequent need for immunosuppressant medication has side effects such as weight gain, kidney problems, and hypertension, as well as the obvious vulnerability of the patient to infections. The eradication of these many likely complications makes our proposed stem cell therapy the unquestionable way forward in the future.

CLINICAL TRIAL PLAN

Before use on the general public, our proposed treatment must undergo a rigorous clinical trial to test for its toxicity and efficacy. We feel there is no specific age range clinical trials should target, owing to the fact DCM and Heart Failure can be affect a human of any age.

1 Firstly - To check for initial safety and absence of toxicity, tests must occur *'in vitro'* and *'in vivo'* in test tubes and mice respectively.

2 Following the toxicity check, a small number of healthy volunteers will have a miniscule amount of artificial myocardium transplanted into their heart. This will primarily check for its safety in humans as well as side effects.

3 A larger number of volunteers (100-300) with heart muscle in need of strengthening will be used in this stage of the trial, focusing on efficacy. Varying sizes of grafts will be transplanted, and their effectiveness will be monitored throughout. Additionally, this phase aims to obtain preliminary data on whether the graft works in people who have a certain disease or condition.

4 This stage gathers further information about the safety and effectiveness of the treatment, studying different populations and ethnicities and so on - and also the combination of this treatment with other treatments in the heart area. If the trial results upto now are positive, there is strong basis for this treatment to be unveiled for public use.

5 This monitors the performance of our treatment over longer periods of time with more patients, after it has started to be used regularly by the NHS. This is equally crucial as there may be side effects or further complications that only arise in the long term. Any hint of this allows appropriate action to be taken immediately.

Public Acceptance -

The public are likely to have initial scepticism regarding the safety of this treatment, due to the well-known major risks of open-heart surgery. However, detailed information on the success of clinical trials should be easily accessible to the public to allow them to make an informed decision on the risks and benefits of the operation. A patient willing to undergo this transplant should also be extensively briefed on the benefits and risks of the surgery, maintaining respect for the patient's autonomy. This, along with the 3 other pillars of beneficence, non-maleficence and justice, should be observed at every stage of treatment. Ethical issues regarding stem cells have been avoided due to the use of iPS cells or cardiac progenitor cells, but problems may arise with people being possibly uncomfortable in having a lab-made graft transplanted inside them.

Ethical Issues

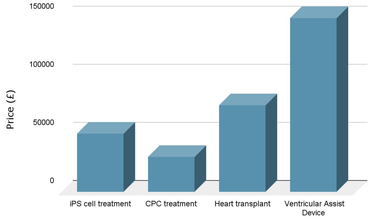
- **Use of animal testing in preclinical trials -** this is rather unethical as it could cause harm to the animals being tested on aswell as potentially inducing stress, lonelieness and fear due to the cramped cages they are kept in. Despite the use of animals being obviously cruel, some think it is morally acceptable to treat animals in such ways so long as it produces great benefits for humans, it can also be a necessary step to test the toxicity and dosage before administering it to humans, as otherwise would put the lives of humans at great risk if the trial drug were to be unsuccessful or harmful.
- **Use of humans in clinical trials** - this can be seen as unethical as the humans involved in the trial could be harmed. This is intensified by the wage given to those taking part in the trials as the people could feel pressured to put themselves at unnecessary danger in order to earn some money.
- Initially we planned on using **embryonic stem cells** for our treatment, however this proved rather ethically problematic due to lots of debate over their morality. Where some people believe that embryonic stem cells should be used without restrictions for research, perhaps because they regard an embryo merely as a clump of cells rather than a potential human being. Others, however, are firmly against the use of stem cells as they believe that the embryo has a moral status equal to that of an adult and therefore has rights that must be respected, this essentially means that the destruction of embryonic stem cells is equivalent to murder. These contrasted views have led to some countries (e.g. Italy) issuing prohibitions on any research involving human embryonic stem cells, yet in other countries eg the UK it remains legal. This controversy could have potentially negatively impacted our treatment as some people may be opposed to receiving it due to ethical objections, so in order to overcome this we decided to use iPS or cardiac progenitor cells so that no embryos are harmed in the production of our stem cells..

Risks of our treatment

Inappropriate cell migration - stem cells may migrate to other areas eg the brain which could cause a risk of abnormal brain functions, however this risk is massively reduced when stem cells are pre-differentiated before transplantation.
Tumour formation + teratoma - risk that the expression of oncogenes may increase when cells are being reprogrammed, high chance of this (almost 20% in some cases) in undifferentiated stem cells. The risk of the appearance of a teratoma (a type of germ cell tumour that may contain several different types of tissue, such as hair, muscle, and bone) can be extremely high - between 33-100% when embryonic stem cells were transplanted directly into immunodeficient mice. However the risk of both tumour and teratoma formation can be reduced massively if you were to differentiate them into desired and mature cell type before injection and screen them for the presence of undifferentiated cells. When such procedures were rigorously followed, teratomas were not observed in over 200 animals transplanted with hESC-derived cardiomyocytes. However, unwanted and uncontrolled differentiation of hESCs was still noticed despite following up this procedure.
Transplantation of infected stem cells - risk of transmission of infectious agents, however this risk can be reduced with routine checks for common pathogens(due to bad handling of stem cells) and screening procedures for infections such as HIV, Hepatitis B, cytomegalovirus, etc.
Postoperative infection - risk with all operations not just stem cell, due to inadequate sterilisation of surgical instruments or inadequate post operative care, to prevent postoperative infection patients are prescribed antibiotics.
Graft vs host disease - this is much more common if stem cells collected from others are transplanted, as the host's immune system can recognise the transplanted cells as foreign so starts attacking them which can lead to rejection, this would mean that the patients would have to be put on immunosuppressant drugs (eg ciclosporin), however these result in people becoming much more predisposed to infections, to prevent this we would aim to use autologous stem cells in our treatment which would massively reduce this risk however it cannot be ruled out so the patients should still be made aware of the symptoms of this disease (itchy rash, diarrhoea, feeling sick, dry mouth/eyes/skin, shortness of breath, jaundice and joint pain) so in the rare event they did contract it they could seek appropriate help.

Affordability

The chart below shows the average UK cost of our proposed treatments as opposed to the cost of the two most popular treatments for heart failure and dilated cardiomyopathy. Note: VAD is replaced every few years, this graph shows the cost of a 20 year implant. Our treatments are clearly cheaper, with advancements in technology also likely to drive down the price of producing iPS cells, further widening the gap between these futuristic treatments and current ones. Additionally, a heart transplant includes a wait of minimum 3 years, before the staggering fee of £75,000 on average.



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