

# Heart diseases and stem cell transplantation



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## Abstract

According a report published by the World health organization about the most prevalent causes of mortality for the time periods of 2000 and 2011, it can be seen that Ischemic heart disease is the leading cause of mortality. There are many conditions that can lead to heart failure. Such conditions are raised blood pressure, myocardial infarction as well as atherosclerotic heart disease. Ischemia leads to necrosis of the myocardial cells due to lack of oxygen resulting in permanent loss of heart muscle. Stem cell therapy allows us to restore the motor function of the heart by delivering stem cells to the site of function loss. The aim of this review is to highlight key points about the different stem cell types that are being researched. Most importantly we will look at how and why recent advances are better suited for treatment of different conditions of the heart. This shall be argued by looking at the ways in which the stem cells used are obtained and transplanted as well as keeping in mind the natural behavior and purpose of the different classes of stem cells.

## Different Stem cell Types Being Researched

The two classes of stem cells that have been researched the most are multipotent and pluripotent stem cells. Pluripotent cells have a greater potency than multipotent stem cells meaning that only specific classes of multipotent stem cells can be used to restore cardiomyocytes.

## Multipotent Stem cells

- c-Kit+Cardiac Stem Cells

These cardiac stem cells exhibit c-Kit<sup>+</sup> which is a surface receptor that has tyrosine kinase activity. There have been successful studies using these types of cells for myocyte regeneration. According to Sheng and co-workers (2012) use of these stem cells has led to regeneration of cardiomyocytes in the ventricles. SCIPIO, is a phase 1 study conducted by Bolli et al. This study looked at patients who suffered from an MI and then had cardiac stem cells introduced into their left ventricle. They published their results in 2011 showing that left ventricular function improved from the initial ejection fraction that was below 40%. Makkar et al. in 2012 published findings for the CADUCEUS study. This study again introduced CSCs into patients LV just after an MI. Results showed no harm being done to the patient as well as an increase in the ejection fraction of the LV.

Fuentes and Kearns-Jonker in 2013 released results were application of ephrin A1 can improve CSC treatment in rats. Ephrin A1 is a human protein important for moderating cell maturation that is introduced before transplantation of CSCs occurs. Most notably repopulation of the damaged area (infarct) was twice as much and as well as having improved systolic function as well as reduced number of complications such as arrhythmias.

- Bone marrow derived stem cells (BMSC)

BMSCs are obtained from that patients bone marrow and then used to treat the same patient. BMSCs have been being used for a long time due to ease of acquirement as well as the fact that they don't elicit an immune response when used. According to Sheng and co-workers (2012) BMSC therapy hasn't lead to notable changes in patient quality of life with only temporary mild increase in ventricular systolic function. BMSCs release beneficial paracrine

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effects (Lee et al., 2005). Paracrines have a number of roles including cessation of apoptosis in sites of ischemic heart damage and stimulation of host vascular (angiogenesis) and cardiac tissue (cardiomyogenesis) growth. Inter-conversion of cells from 1 type to another as well as joining of 2 or more cells to become one cell results in formation of endothelial and ventricular muscle tissue from the precursor stem cell (Lee et al., 2005).

- Pluripotent stem cells

Such cells are capable of forming all 3 primary layers.

Embryo Stem cells (ESCs)

ESCs are obtained from the mass of cells inside the blastocyst and are capable of self renewal. Compared to adult stem cells, embryonic stem cells have more inherent ability to replace damaged tissue in the heart. This is due to them being pluripotent they replace not only the muscle lost but also perform angiogenesis. Advancements in regulation of developmental pathways for ESCs have enabled improved results. BMP inhibitor improves the conversion of ESCs to cardiomyocytes but in so doing reduces conversion to other tissues of mesoderm origin (Hao et al., 2008). Hao and his co-workers (2008) also state that dorsomorphin can become a great tool for stem cell therapy in the future.

Wnt/ $\beta$ -catenin signaling control with the use of XAV939 improves ESC differentiation into cardiomyocytes.

Induced pluripotent stem cells (iPS)

Gene Transplantation

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## Direct gene delivery

For different forms of gene delivery the catheter has to both compatible to the site targeted as well as not having any property causing injury or eliciting an immune response. Naimark et al. compared the use of Nitinol stainless steel and Stiletto catheters for epicardial administration as well as endocardial showing that Stiletto catheters were twice as effective.

### **Intrapericardial injection**

Advantage of this method of delivery is that there is no exposure of the heart and other organs. The use of intrapericardial injection in dogs has shown they endure the pain with not too much distress highlighting that the patient will undergo less distress compared to open surgery (March et al., 1999).

This percutaneous method introduces the genes into the pericardial sac which then migrates into the myocardium. (Kawase et al., 2007) There are varying approaches to how to perform the injection. Fromes and coworkers used a transdiaphragmatic method. What was observed was that injection of the stem cells on their own lead to no gene expression difference in the myocardium. Stem cell expression results at the end of week one improved significantly with addition of proteinase in the injection fluid.

### **Endocardial injection**

Microsphere retention varies according to volume used and site of injection. Endomyocardial injection had 28% greater retention than epicardial administration. Further retention can be obtained with the use of 10  $\mu$ L rather than 100  $\mu$ L. Greater spread of the adenovirus which encoded lac-Z was observed going to other organs in lower volumes too (Grossman et al., 2002). Use of fluoroscopy proved that this method is safe and that gene

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expression is present in 81% of the pigs used. Specimens used showed no symptoms and signs of cardiac arrhythmia or disturbance of blood flow. Patients suffering from chronic ischemia can develop complications such as perforation of the ventricle due to its thin nature as well as effusion of fluid in the pericardial sac decreasing cardiac output (Gwon et al., 2001).

### **Intramyocardial injection**

This method has shown great success in many studies due to direct delivery of vector to site of damage. Injection of reporter gene into cardiac tissue and expression of the gene is feasible in canine myocardium. Response showed to be directly proportional to the volume of plasmid DNA used. Interestingly gene expression was uniform throughout the left ventricle independent of the level of injury. Stem cell expression gradually weakens over time showing greatest activity at the end of the first week (von Harsdorf et al., 1993). Use of plasmid DNA for cardiac muscle shows unique property of the tissue in being able to uptake DNA via the use of T tubules. Weakened expression after the first week is due to immune defensive mechanisms targeting transfected cells (Acsadi et al., 1991). Use of plasmid DNA vectors in early studies showed low efficiency in terms of transduction and time interval in which it is active; this led to the use of adenovirus to transfer of  $\beta$ -galactosidase gene and plasmid. However results showed poor expression after day 7 as well as immune reaction generation (Guzman et al., 1993). Use of rAAV proved to be a more successful vector for the LacZ gene showing no immune response generation or inflammation at the site of injection. Expression was strongest after 1 week during weeks 4 to 8 showing very little results in the first 2 weeks. An increase in efficiency in terms of

number of cells that undergo transduction due to perfusion was observed. Half of the cardiomyocytes showed LacZ gene expression (Svensson et al., 1999).

BetaARKct gene produces a peptide that improves betaAR (beta-adrenergic receptor) signaling which is seen to diminish after a myocardial infarct. BetaAR function is interfered upon by G protein-coupled receptor kinase 2. BetaARKct gene product will eliminate G protein-coupled receptor kinase 2 interference. rAAV6 was used as a vector. Introduction of the BetaARKct gene further increased the efficiency of the intramyocardial injection with improved transduction cell number and length of time interval expression is strongest - up to 12 weeks from start of experiment. Long term use of BetaARKct gene lead to raised cardiac contractility as well as a turn around in ventricular remodeling (Rengo et al., 2009). Transfer of vascular endothelial growth factor (VEGF) promoted angiogenesis in damaged myocardium and diminished anginal pain (Koransky et al., 2002).

### **Transvascular gene delivery**

Some diseases such as pulmonary and essential hypertension, long QT syndrome and congestive heart failure require not just a percentage of their cells to undergo transduction but rather the entire myocardium. This can only be done by a method that ensures global delivery to the myocardium (Donahue et al., 1997). This is because it's not just a group of cells that are contributing to the disease but rather every cell. E. g. Intramyocardial injection in these conditions would be useless as it only affects a small area.

**Selective coronary catheterization with antegrade intracoronary delivery**

A single pass method yields poor transduction values showing phenotype expression in only 5% of cardiac muscle at most (Ding et al., 2004). For optimal transduction to take place prolonged exposure time via occlusion of blood supply was necessary. The coronary arteries and coronary venous sinus were the tested targets with the latter producing almost 5 times increase in transduction (Logeart et al., 2001). Donahue and coworkers worked on rabbit myocardium observing key conditions for 96% of myocardial cells to undergo transduction. These parameters included increased virus concentrations, increased exposure, performing experiment at 37°C, increased coronary flow rate and use of crystalloid media with specific compositions.

Almost maximal transduction could be achieved with improved microvascular permeability in a decreased coronary perfusion time period of 2 minutes. Lowered Ca<sup>2+</sup> concentration coupled to bradykinin or serotonin pretreatment and raised virus concentration achieve this (Donahue et al., 1998). Use of catheters to occlude the aorta and venous return in the right atrium in rodents was coupled to cardiopulmonary arrest with the use of esmolol and acetylcholine for 2 and 5 minutes in order to increase viral incubation time proved to increase transduction response in 43% of cardiac muscle after 3 days. Minimally invasive surgical intervention is still required but the fore mentioned method shows a 400 time improvement in phenotype expression contrasted to the sham-operated group. S-Nitroso-N-acetyl-DL-penicillamine and histamine use failed to improve microvacular permeability (Ding et al., 2004).



**Nonselective (indirect) intracoronary delivery**

Using a number of injections to transfer genes with the use of surgery has been studied in research extensively (Guzman et al., 1993). Transduction of human beta 2- adrenergic receptor (betaAR) gene in patients diagnosed with chronic heart failure can restore the cardiac beta-adrenergic receptor system. betaAR function is also compromised in acute myocardial function upset. The betaAR signaling pathway is the main target of most drugs on the market today for heart failure treatment (Parsa et al., 2003). Use of catheter to deliver Adeno-beta 2 adrenergic receptor into the left ventricle in rabbits produced at most a ten fold increase in beta 2- adrenergic receptor expression. After 3 weeks improved myocardial function was observed. Left ventricular pressure was improved as a result of increased myocardial contractility and improved ventricle loading conditions. Isoproterenol receptivity was also observed to increase (Maurice et al., 1999). This indirect method of virus introduction will result in virus transport in the systemic circulation possibly resulting in  $\beta$ -AR overexpression in the lungs and liver. Larger doses of the virus result in systemic ischemia and decreased cardiac function (Parsa et al., 2003). According to Hajjar and coworkers gene transfer in vivo results in transduction occurring in more than one location. *In vivo* gene delivery involving adenovirus mediated transmission of betaAR kinase carboxyl terminus (betaARKct) or betaAR has shown that use of betaARKct prohibits smooth muscle hyperplasia in vascular intima after angioplasty. BetaARKct use improves ventricular function via improved betaAR signaling via genetic inhibition of  $G\beta\gamma$ - $\beta$ -adrenergic receptor kinase. Over expression of betaAR improves cardiac function (Eckhart et al., 2000). Gene delivery in

vivo improves ventricular contractility as well as adjustment of ECG intervals (Hajjar et al., 1998).

Global phenotypic changes can be improved via increased transduction with the use of an improved method of to deliver the viruses. Introduction of the catheter into the left ventricular cavity followed by movement superiorly to end in the aortic root is coupled with pulmonary artery and ascending aorta occlusion. As a result a transc coronary perfusion gradient is generated; which improves viral delivery. This method has a number of modifications such as prompting of asystole pharmacologically, hypothermia use to lengthen cross-clamp interval and occlusion of the distal aorta (Beeri et al., 2002), (del Monte et al., 2001) and (Hajjar et al., 2000).

### **Selective coronary sinus or coronary venous catheterization with retrograde delivery**

Intracoronary delivery involves systemic spread of the vector due to the brief interval in which the vector can adhere to the coronary endothelium. This is the great disadvantage of the fore mentioned method as coronary flow and endothelial permeability have a large contribution (Logeart et al., 2001).

Contrasted to intracoronary delivery, retrograde delivery results in improved expression of the delivered gene (Kaye et al., 2007). Adeno-associated viral vectors do not induce an immune response and cause no inflammation. AAV vectors facilitate long-term gene expression (Sakata et al., 2007). Retro-infusion has proven to transfer AAV vectors efficiently as a long term method of gene transfer. This is due to improved endothelial permeability and lengthening of adhesion time for the vector (von Degenfeld et al., 2003).

Systemic spread of vector to liver and lungs was observed however with lack

of gene expression due to use of an enhanced myosin light chain promoter sequence (Raake et al., 2008). Studies have proved that a single administration is enough in order for efficient regional myocyte transfection to occur. The advantages of only a single administration being necessary include minimal washout and controlled dwell times promoting longer exposure. The genes human developmentally regulated endothelial locus-1 and green fluorescent protein were used in this study (Hou et al., 2003).

Pulmonary and hepatic transgene expression can be avoided with the use of adjusted models of myocardial gene delivery. Kaye and coworkers established a high efficiency percutaneous closed-loop system. This closed loop system permits increased transduction in the cardiac muscle due to higher concentration of vector present. This method reduces peripheral systemic spread that results in decreased transgene expression outside the heart in the lungs and liver (Kaye et al., 2007). Bridges states that usage of the percutaneous closed-loop system just mentioned would result in loss of more than 99% of the vector to the systemic circulation and not to the myocardium. On close examination of results obtained 2, 639 vector genomes/ mg DNA were found in the heart contrasted to 69, 595 vector genomes/ mg DNA in the liver. It was suggested that lack of hemiazaygous vein control results in this systemic spread.

#### Ex vivotechnique

Many studies have been carried out on the use of transplantation model for gene transfer. In the study done by Griscelli and coworkers recombinant adenoviruses are injected into coronary vessels of the organ then the heart

is transplanted. This study carried out on piglet hearts have emphasized prolonged exposure time for vector contact to the heart. The advantage of using such a transplantation model is that this takes place with no coronary flow. Expression of transferred gene was noted with little presence of the transferred genome in hepatic and pulmonary tissues (Griscelli et al., 2003). Wang and Knechtle experimented on and compared 2 different methods of vector delivery prior to transplantation; myocardial injection and perfusion. Injection produced a higher degree of transgene expression. Perfusion resulted in greater overall distribution of transgene expression. Use of these methods only provides as a short term method of gene transfer (Wang and Knechtle., 1996).