# SURGICAL STEM CELL THERAPY FOR ADVANCED HEART FAILURE PATIENTS

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## Introduction

Despite current treatment, heart failure is a contributing factor in just under 15 million deaths worldwide every year.[1] Currently available options for heart failure patients consist of medical management, cardiac transplantation, device therapy, and now stem cell-based therapies. Although cardiac stem cell therapy has been performed in other countries, new surgically based trials with innovative advanced stem cell products are now being initiated in the United States.

## Overview of Stem Cell Therapy

Cardiovascular disease causes an estimated 14.3 million deaths worldwide per year.[1] Advances in stem cell research, such as methods for intraoperative enrichment of bone marrow-derived mononuclear cells as reported by Ghodsizad et al,[2] have made the development of stem cell therapies for cardiovascular disease possible. Research into cell-based therapies has yielded promising results pointing to their potential to halt remodeling of the myocardium after ischemic or nonischemic injury. These somatic stem cell based treatments involve the delivery of cells to a damaged or hypoxic region of the heart, typically by direct injection. The cells can then engraft, proliferate and differentiate, restoring functionality to the damaged tissue.

So far, the transplanted cells used most frequently have been autologous skeletal myoblasts, peripheral blood stem cells and bone marrow-derived stem cells. Granulocyte colony-stimulating factor (G-CSF) has also been used to mobilize stem cells from the bone marrow and to allow their migration into the heart. Clinical trials employing each of these sources of stem cells have reported different degrees of success in the effort to slow, stop or even reverse myocardial remodeling. In contrast to early trials performed around the world,

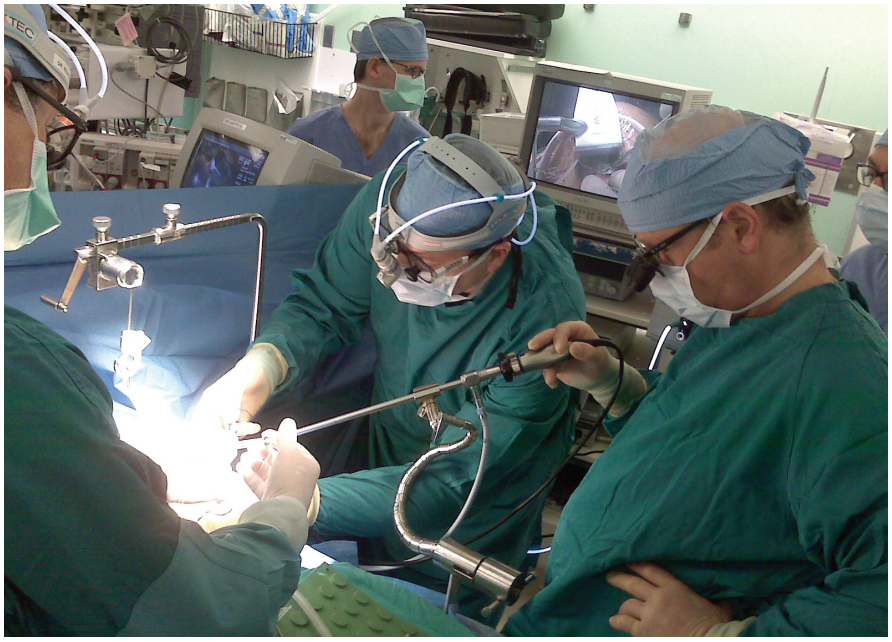


**Figure 1a.** In late 2008, surgeons Michael Reardon, Brian Bruckner and Matthias Loebe of the Methodist DeBakey Heart & Vascular Center were the first in the nation to inject stem cells directly into the beating heart of a patient with ischemic dilated cardiomyopathy.

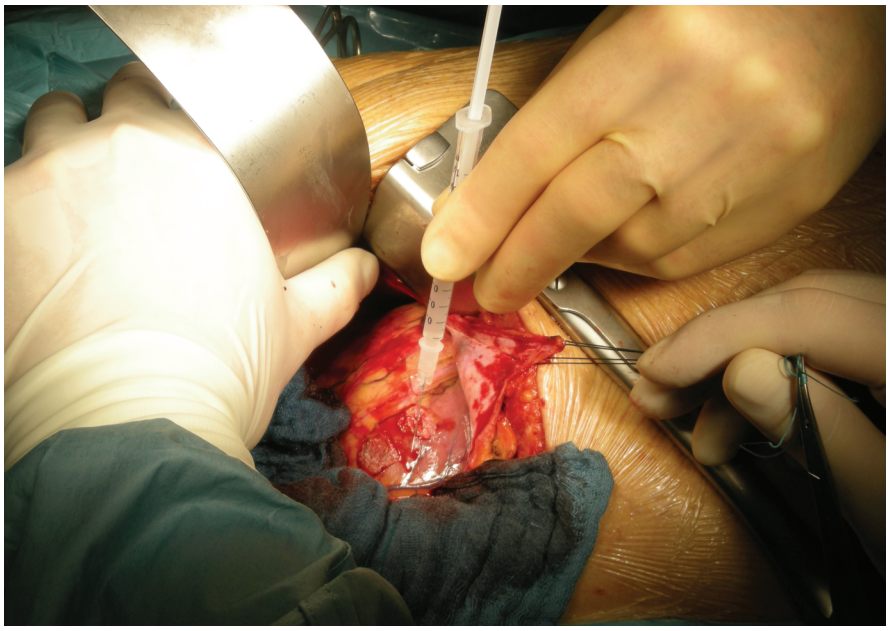


**Figure 1b.** Direct transepicardial injection of bone marrow-derived stem cells through minithoracotomy incision.

current trials are now increasingly focused on bone marrow-derived stem cells. In the majority of trials in the past, bone marrow aspiration was performed on the patient and a mixed cell population was isolated and injected directly back into the patient, usually with a coronary catheter. There were no attempts in these early trials to select specific stem cell types or to obtain high numbers of stem and progenitor cells through expansion in a bioreactor. From the results of animal experiments using bone marrow-derived stem cells, it became clear that certain types of bone marrow constituents had more angiogenic and regenerative potential than others. These findings led investigators to select specific stem cells by cell surface markers for subsequent delivery to the injured myocardium. An even more recent approach uses cells that are cultured ex vivo in an automated bioreactor system to increase the number of stem and progenitor cells.

Not only is the cell composition critically important but the delivery method as well. Early trials used coronary catheterization to deliver the cells after myocardial infarction in the area of ischemia. As larger volumes and more concentrated stem cell mixtures were used, reports of micro-infarctions and embolization following intracoronary injection began to emerge. There is now a growing trend among cardiologists to inject the stem cells via a (investigational) transendocardial injection catheter guided by a navigation system that creates a three-dimensional map of the heart (NOGA). Critics of this approach mention the difficulty of mapping a moving object and ensuring accurate and reproducible delivery of the cells through the endocardium without losing the cells to turbulence and "washout." The latest approach used in several trials that are currently underway, involves the direct, surgical, transepicardial injection of a stem cell mixture. Advantages of this approach include the direct delivery of the cells to the areas of interest under visual control (Figure 1a, 1b). Minimally invasive surgical approaches are being used to minimize the effect of surgery on heart failure patients.

## The Different Types of Stem Cells and the Evolution of Clinical Trials

Various different types of cells are currently under consideration as sources for cell therapy. The two groups are the embryonic stem cells (ESCs) and somatic stem cells, such as bone marrow-derived mononuclear cells (BMCs), mesenchymal stem cells (MSCs), skeletal and cardiac myoblasts, cord blood-derived stem cells, and peripheral stem cells mobilized by G-CSF. Each of these cell types has been studied to assess its effects on ischemic cardiac tissue in animal models.

The first clinical application of cardiac stem cell therapy, reported by Strauer et al, involved the intracoronary infusion of autologous BMCs in a patient who had suffered acute myocardial infarction.[3] The patient in this study had a decrease in transmural infarct area, and an increase in ejection fraction, cardiac index, stroke volume, and end diastolic volume. In the majority of cardiac cell therapy studies, BMCs have been used in patients with ischemic heart disease. In these cases, cell therapy has frequently been used alongside standard treatments such as revascularization and conventional pharmacologic therapy. The BOOST trial, for example, was a trial in which patients received either BMCs and standard post-infarction pharmacologic therapy, or post-infarction pharmacologic therapy without the BMCs.[4] Early results (six months post-implantation) provided evidence that the infusion of BMCs led to a greater improvement of left ventricular function than did standard therapy alone. However, after 18-months follow-up, it was revealed that there was no longer a


**Small-volume bone marrow aspiration collected from patient.**

**Cells produced in centralized GMP manufacturing facility.**

**Patient-specific cell product with increased stem and progenitor cells.**

**Figure 2.** A small volume bone marrow aspiration is performed on the patient. The bone marrow mixture is sent to a centralized GMP facility where selective cell lines are amplified in culture. The end result is a concentrated "super stem cell" mixture that is ready for direct injection into the patient's heart.

clear improvement in cardiac function in patients who had received BMCs compared to those who received only standard treatment. These results indicated that BMC transplant possibly accelerated the rate of recovery, but did not provide any additional benefits. Many studies suggest that the mild degree of improvement is due to the fact that BMCs most likely do not differentiate into cardiomyocytes themselves, but rather secrete cytokines and growth factors which improve the survival of cardiomyocytes after ischemia-induced injury, along with the additional benefit of facilitating cardiac stem cell migration to the site of injury. Despite the fact that such trials have shown only mild improvements in left ventricular function and ejection fraction, two important themes have emerged so far from BMC studies: first, BMC treatment seems to be safe, and second, BMC treatment appears to promote vascular repair, as shown in studies such as REPAIR-AMI.[5]

Different subsets of BMCs exist in the bone marrow, which can be characterized by their cell surface markers. For $CD34^+$ and $CD133^+$ cells, antibody conjugates are available which allow for the purification of these cells and their use in clinical applications in patients. In animal models, $CD34^+$, $CD133^+$ and BMC cell application resulted in a significant improvement of the left ventricular ejection fraction (LVEF). Clinical trials involving the implantation of selected BMCs to patients who suffered myocardial infarction have shown that endothelial cell precursor (EPC) therapy can increase LVEF and decrease the size of the infarct.[6] These cell types are found in the bone marrow, cord blood, and peripheral blood.

Another type of stem cells resident in the bone marrow, the mesenchymal stem cells, is capable of differentiating into osteoblasts, chondrocytes, myocytes, tendon or ligament fibroblasts, and adipocytes.[7] Under certain conditions, MSCs have been shown to differentiate into cells expressing cardiomyocyte phenotypes *in vitro*.[7] The same results have been obtained for MSCs *in vivo*, but at much lower rates.[8] MSCs have several advantages when used, including the fact that there is no need for immunosuppression in the patient, as MSCs are poor antigen-presenting cells. MSCs do not trigger immunological T-cell responses. They release anti-inflammatory cytokines and can provide paracrine support to injured myocardium. However, their differentiation into functioning myocytes has not been demonstrated in any human studies to date.

Stem cell therapy has been studied not only in patients with acute myocardial infarction, but also in patients with heart failure. For instance, Seth et al reported the first study of stem cell therapy in dilated nonischemic cardiomyopathy, a study using BMCs whose findings included a significant improvement in ventricular function and an insignificant increase in the ratio of capillaries to myocytes.[9] As far as stem cell therapy in ischemic cardiomyopathy is concerned, several large clinical trials have been conducted. These studies showed cardiac cell therapy with BMCs and circulating progenitor cells resulted in improvement in left ventricular function and reduction in infarct size. In summary, stem cell-based cardiac therapy may be on its way to becoming an established therapy for patients suffering from ischemic cardiomyopathy.

Aastrom Biosciences, Inc. has developed a unique, proprietary process to produce stem cells and early progenitor cells from small volume human bone marrow cell

aspirates. The tissue production process occurs over 12 ± 1 days in an automated, closed system, and has been used safely in over 300 patients (as of December 31, 2008) including completed multi-center clinical trials. The resulting product is generically referred to as Tissue Repair Cells (TRCs). Briefly, a small volume bone marrow aspiration is performed in the clinic and the cell suspension is sent to a centralized GMP lab for further processing which includes selective amplification of multiple cell types (Figure 2). The end result is a highly concentrated and expanded mixture of stem and progenitor cells which is directly injected into the beating heart through a minimally invasive surgical approach.

Cardiac Repair Cells (CRCs) are a TRC-based product that has been optimized for delivery in cardiac patients. CRCs been shown, in *in vitro* assays, to induce endothelial cell migration and vascular tube formation. It is hypothesized that treating ischemic or nonischemic DCM patients with autologous CRCs may significantly reduce or eliminate the progression of the disease.

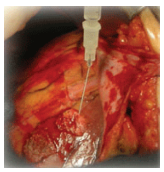
## IMPACT-DCM Trial

DCM represents the final common morphologic outcome of a variety of biological insults and currently effects up to 150,000 patients in the United States. It is characterized by a combination of myocyte apoptosis and necrosis with increased myocardial fibrosis resulting in reduced mechanical function. With myocyte failure and cytoskeletal uncoupling, the chambers of the heart become dilated. It is a complex disease involving the entire heart tissue, including cardiomyocytes derived from the mesenchymal lineage as well as the macro- and micro-vasculature. Arrhythmias occur frequently as a result of impaired electrical coupling due to the rarefication of cardiomyocytes as well as impaired electrical conductance due to excessive extracellular matrix deposition. In the United States, the most common identifiable cause of DCM is extensive coronary artery disease. Such coronary artery disease results in an inadequate blood supply to the heart muscle which leads to permanent injury and death of heart muscle. As a result, the heart's pump function becomes impaired. The dead heart muscle is replaced by fibrotic (scar) tissue. The remaining uninjured cardiomyocytes then stretch and thicken (hypertrophy) to compensate for the lost pumping action. The more the heart muscle is stretched, the more

**Figure 3.** The Impact-DCM trial, sponsored by Aastrom Biosciences, Inc., is a prospective, randomized, multicenter trial involving five U.S. centers.

### Impact-DCM Clinical Trial

U.S. Phase II Dilated Cardiomyopathy (DCM) Trial



**Trial Design**

- Forty patients, randomized, controlled, open-label study
  - Twenty patients with ischemic DCM; twenty patients with nonischemic DCM
  - Randomized 3:1 treatment vs. control
  - Up to five treatment centers
- CRCs delivered as monotherapy
  - Direct injection via lateral thoracotomy or minimally invasive thoracoscopy
- Twelve month patient follow-up

**Target Patients**

- Diagnosed with ischemic or nonischemic DCM
- New York Heart Association class III or IV heart failure
- Left ventricular ejection fraction ≤30% (60-75% is typical for a healthy person)
- 18-86 years old

**Data Collection**

- Safety data
- Incidence of MACE (major adverse cardiac events)
- New York Heart Association classification for heart failure
- Left ventricular ejection fraction
- Left ventricular dimensions/mass/volume
- Myocardial perfusion and viability
- Pulmonary function
- Exercise tolerance (six minute walk)
- Quality of life

Status: First patient treated November 2008. Nine patients enrolled to date.

forcefully it contracts or pumps, but only up to a point. After that point, the stretching and thickening do not adequately compensate and ischemic DCM with heart failure ensues.

The IMPACT-DCM study, sponsored by Aastrom Biosciences, Inc., is a prospective, randomized, multicenter Phase II safety/efficacy study that is being conducted in five centers in the United States. (Figure 3) Two strata will be enrolled: ischemic and nonischemic DCM. A sufficient number of patients will be accrued to deliver 20 evaluable patients per stratum. Within each stratum, patients will be randomized to receive either CRC treatment or control (standard of care) in a 3:1 ratio (15 patients per CRC treatment group and five patients per control group). No attempt to balance treatment and control groups by risk factors, comorbidities, age and/or weight will be made. In the treatment group, patients will undergo small volume bone marrow aspiration as described above. After processing the CRC product, it is directly injected into the beating heart at the time of surgery. The surgical approach to deliver the cells entails either thoracoscopy or lateral minithoracotomy. Minimally invasive thoracoscopy with up to three incisions (each 2 to 3 centimeters) is possible in selected patients and offers several advantages compared to thoracotomy, such as faster recovery, shorter hospitalization, less postoperative pain, and reduced intensity and duration of anesthesia. Candidates are patients without thoracic adhesions nor prior left chest surgery.

Under direct visualization (or via endoscopy) the surgeon identifies and records approximately 25-30 injection sites equally distributed (medially and laterally) across the anterior and posterior areas of the left ventricular wall. Injection sites are a minimum of 1 cm apart and encompass as much of the ventricular free wall as possible. The needle is then advanced into the myocardium at a right angle to the epicardial surface to the preset depth of the penetration depth shield to ensure delivery of CRCs into the mid-myocardium. 0.2 mL of the CRC cell suspension is then slowly delivered via 1cc syringe at each of the injection sites. In an effort to minimize interstitial pressure and the backflow of product from injection site, the needle remains in the myocardium for several seconds after cell administration prior to removal. Injections are repeated in this fashion until the entire ventricular free wall has been treated. On November 20, 2008, our surgical team was the first in the nation to inject these stem cells directly into the beating heart of a DCM patient enrolled in the IMPACT-DCM trial. The patient tolerated the procedure well with a brief hospital stay and has recovered. Follow-up includes the assessment of cardiac function after stem cell therapy by trans-thoracic echocardiograms, cardiac CT scans, cardiac MRI scans, as well as PET and SPECT scans and quality of life surveys. To our knowledge, this represents the most comprehensive array of imaging procedures of any cardiac stem cell trial conducted so far. The comprehensive data set generated from this trial will undoubtedly lead to a better understanding of the biological and clinical effects of CRC stem cell therapy.

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