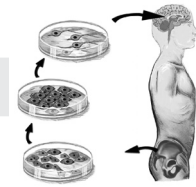


# Stem Cell Research



## Myocardial Regeneration by Adult Stem Cells

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**Key Words:** stem cell, myocardial regeneration, heart failure, cardiomyocytes

### Abstract

Ventricular remodeling and heart failure are the inevitable consequences of myocardial infarction. Current options to cure myocardial infarction and subsequent heart failure suffer from specific limitations. Thus, alternative, additional long-term therapeutic strategies are needed to cure this costly and deadly disease. Cardiac regeneration is a promising new therapeutic option. Through cellular and molecular therapies, the concept of *in situ* "growing" heart muscle, vascular tissue and manipulating the extracellular matrix environment promises to revolutionize the approach of treating heart disease. Recent studies have suggested that stem cells resident within the bone marrow or peripheral blood can be recruited to the injured heart. The regeneration of damaged heart tissue may include the mobilization of progenitor or stem cells to the damaged area or stimulation of a regenerative program within the organ. There is now evidence accumulating that the heart contains resident stem cells that can be induced to develop into cardiac muscle and vascular tissue. The present review aims to describe the potential, the current status and the future challenges of myocardial regeneration by adult stem cells.

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directly by transplanting cells capable of new blood vessel formation or indirectly by the local release of pro-angiogenic factors. Several cell types have been investigated in an attempt to assess their capability to achieve the goal of myocardial regeneration [Figure 1]. These can be divided into two major categories based on their origin. Cells derived from embryonic tissue (e.g., embryonic cardiomyocytes or embryonic stem cells) and cells derived from adult tissues. Table 2 summarizes the advantages and disadvantages of each cell source. The present review summarizes the data from basic and clinical works with adult stem cells or progenitor cells with special emphasis on *in situ* cardiac precursors.

### Bone marrow-derived stem cells

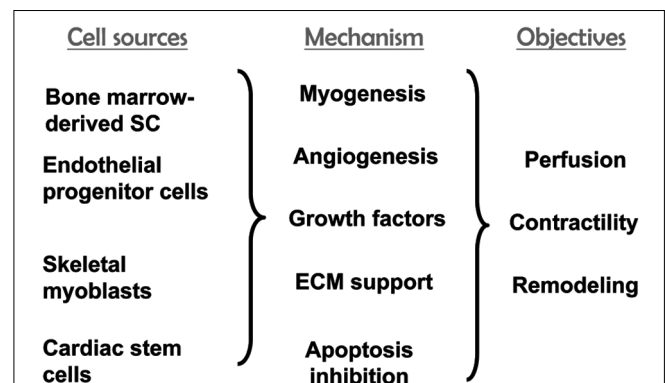
In the adult patient, the bone marrow is a relatively rich source of stem/progenitor cells. Apart from hematopoietic stem cells, the bone marrow stroma contains additional cell populations in different differentiation stages serving as the microenvironment and

Cardiovascular disease is one of the major public health problems in the western world. Costs of hospitalization amount to more than 10 billion U.S. dollars annually, quality of life is poor, and thousands of lives are lost every year. Following myocardial infarction, irreversible loss of cardiomyocytes leading to decreased myocardial contractility is the major cause for the progression to heart failure. The injured myocardium is replaced by a fibrous scar, leading to ventricular function loss. Furthermore, the damage is often progressive: in response to cardiac injury, triggered molecular, cellular and physiologic responses lead to left ventricular dilatation, cardiac aneurysms, myocardial free wall rupture, life-threatening arrhythmia, sudden cardiac death or the transition to end-stage heart failure.

In order to cure heart failure several revolutionary treatment approaches were proposed. Recent years have seen tremendous excitement and controversy in the fields of stem cell biology and cardiac regeneration. Myocardial regeneration is the replacement of damaged myocardium by new myocardium and has the potential to directly augment cardiac contractility in several cardiac patient subgroups [Table 1]. Another approach is to increase perfusion into the ischemic area by the formation of new blood vessels, a process known as therapeutic angiogenesis – either

**Table 1.** Subgroups of cardiovascular patients who may benefit from cell therapy

Subgroup	Clinical trials [ref]
Patients with myocardial infarction	[12,13,15,18]
Patients with cardiomyopathy	[38]
Patients with advanced heart failure	[15,19,20]
Patients with refractory angina	[39]
Patients with peripheral vascular disease	[40]



**Figure 1.** Cell-based therapy for myocardial repair

**Table 2.** Characteristics of embryonic versus adult stem cells

Adult stem cells	Embryonic stem cells
<b>Advantages</b>	
Autologous	Multipotent
Expandable	Expandable
Clinical experience	
<b>Disadvantages</b>	
Rare	Teratogenic
Affected by age and diseases	Allogeneic
Difficult controlled differentiation	Difficult controlled differentiation
	Ethical limitations

supporting the proliferation and differentiation of hematopoietic stem cells. These cells are isolated from the bone marrow stroma according to various characteristics (e.g., the ability to adhere to culture plate) and surface markers. However, controversy still exists regarding the precise phenotype of the true bone-marrow derived mesenchymal stem cell [1-3].

### Mesenchymal stem cells

Mesenchymal stem cells are isolated from several sources such as the bone marrow or adipose tissue, based on their capability to adhere to the culture plate while other progenitor or fully differentiated hematopoietic cells lack this property [4]. The mesenchymal stem cells are pluripotent and can differentiate *in vitro* into osteoblasts, chondrocytes, adipocytes, fibroblasts, myoblasts and cardiomyoblasts [1,4-6]. *In vitro* studies have shown that incubation with 5-azacytidine (a reagent that causes hypomethylation of specific genes and possibly activates the myogenic regulatory master gene – *MyoD*) [7] or co-culture with cardiomyocytes reprogram these cells to adopt a cardiac phenotype [8]. Furthermore, Tomita and his colleagues [9] demonstrated that the transplantation of 5-azacytidine-treated mesenchymal stem cells into scar tissue in a rat model of myocardial infarction decreased the scar area, limited left ventricular dilatation, and increased regional angiogenesis. Mesenchymal stem cells are considered immune privileged cells [10]. Thus, allogeneic cell transplantation from young healthy donors to sick elderly patients is possible.

### Side population cells

A distinct type of cells located within the bone marrow, named side population cells, are capable of actively pumping out of the cell an intracellular fluorescent dye, the *Hoechst* dye. This property, responsible for their typical location in the low *Hoechst* zone after fluorescence-assisted cell sorting, was proven to be associated with typical characteristics of stem cells. Following transplantation of this highly enriched marrow-derived hematopoietic cluster of differentiation CD34+/side population cells, the engrafted cells differentiated into cardiomyocytes and endothelial cells primarily in the peri-infarct region, suggesting that these cells indeed have the potential to differentiate into myogenic lineage [11].

### Clinical trials with bone marrow-derived cells

Bone marrow-derived stem cells are currently gaining favor because of their seeming plasticity, which could allow them to

alter their phenotype in response to cues from the target organ, and the possibility of using the patient's own cells. A few recent clinical studies advocate the simple extemporaneous re-injection of unfractionated bone marrow cells in patients with acute myocardial infarction. Crude bone marrow cells are readily available, autologous, and easily expanded *in vitro*.

Several feasibility and safety clinical studies were done with bone marrow-derived progenitor cells. The TOPCAREAMI trial (Transplantation of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction) [12] compared the efficacy of different heterogeneous populations of autologous bone marrow-derived cells (CD34+/CD45+/CD133+) versus peripherally isolated heterogeneous population of circulating progenitors (KDR+/CD105+/vWF+/PECAM-1/CD31+/CD146+) in a setting of acute myocardial infarction with relatively preserved left ventricular function. No control group was included in this study. No significant complications were associated with the cell treatment. During 1 year of follow-up, cell transfer was associated with improved global left ventricular ejection fraction (8.7%) and attenuated left ventricular remodeling as assessed by magnetic resonance imaging.

In the BOOST trial (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) [13], a relatively crude autologous bone marrow cell population containing less than 1% of CD34+ and hematopoietic stem cells were injected intracoronary around 7 days after ST-segment elevation myocardial infarction. The difference in left ventricular ejection fraction improvement between groups was significant after 6 months but not after 18 months.

While these trials in animals and humans raise great hopes for the safe and efficacious treatment with bone marrow-derived cell treatment, better characterization of the most effective cell population is required, and rigorously controlled clinical trials for the assessment of clinical effect are imperative. Furthermore, since such studies have been performed at the acute stage of the ischemic insult, their relevance to chronically infarcted myocardium remains uncertain.

### Endothelial progenitor cells

Endothelial progenitor cells, also termed hemangioblasts, can be transplanted to relieve myocardial ischemia by inducing angiogenesis [14]. These cells can be isolated from peripheral blood, umbilical cord blood or bone marrow, and two non-specific markers identify these cells as a group – as all cells present the CD34 or CD133 antigen. Successful preclinical experiments led the way to several clinical trials. Stamm and co-workers [15] reported the results of a phase I clinical trial during 2003. They showed improved myocardial perfusion without improvement in left ventricular ejection fraction in six patients with recent (more than 10 days old) myocardial infarction who underwent intramyocardial transplantation of bone marrow-derived CD133+ cells in coronary artery bypass graft surgery. The MAGIC cell randomized clinical trial [16] showed similar results, but it raised some disturbing safety issues. In the MAGIC trial CD34+ cells were harvested from peripheral blood after treatment with granulocyte colony-stimulating factor and were injected into a coronary

artery during coronary stenting at least 6 days after myocardial infarction. Patients treated with G-CSF and CD34+ cells showed improved perfusion and left ventricular systolic function at 6 months as compared to G-CSF treatment alone or no treatment. However, significant increases in the rates of in-stent restenosis were documented (2/3 and 5/7 respectively) in both groups of G-CSF alone and G-CSF followed by cell injection. The association of in-stent restenosis or accelerated atherosclerosis with a combined treatment of G-CSF and endothelial progenitors was demonstrated in subsequent studies [17]. However, a possible association with G-CSF treatment alone was revoked in subsequent studies [18].

While evaluating the clinical applicability of endothelial progenitor cells, the process of cell aging must be taken into consideration as most of the patients with ischemic heart disease and heart failure are older. Although the number of endothelial progenitors does not decrease significantly with age, their survival, migration and proliferation capabilities are significantly reduced with older age in patients with and without coronary artery disease. Furthermore, in older ischemic heart disease patients, CD34+ cells are poorly mobilized to peripheral circulation after G-CSF treatment as compared to age- and gender-matched controls.

### Skeletal myoblasts

Skeletal myoblasts are precursors of skeletal muscle cells that participate in regeneration of injured muscle. These cells might have the capability to integrate into ischemic myocardium and augment contractility. Furthermore, as these cells are present in skeletal muscle tissue of all patients, it is theoretically possible to isolate them from a designated patient and perform autologous cell transplantation, thus alleviating the need for immunosuppression. Phase I clinical trials validated the feasibility of growing large numbers of myoblasts from a minimal muscle biopsy, as well as the ability to implant these cells either under direct visualization during cardiac surgery or through catheter-based delivery devices. Pagani et al. [19] performed histologic studies in the hearts of patients with end-stage heart failure who underwent skeletal myoblast transplantation while waiting for heart transplantation. They demonstrated that transplanted cells survived in the myocardium up to 6 months, stained positively for skeletal muscle-specific myosin heavy chain, and small vessel formation was noted in the transplantation area but not in adjacent tissue.

Menasche and team [20] were the first to conduct phase I clinical studies in the late 1990s to assess not only histologic properties of transplanted myoblasts but also the effects on left ventricular function. Menasches' group performed successful transplantation of autologous skeletal myoblasts into the scar tissue of 10 patients with severe ischemic left ventricular dysfunction. Transplantation was performed during coronary artery bypass grafting. Compared with the patients' preoperative state, there was increased viability, improved contraction of the grafted scar, and improved clinical status of the patients at

10 months follow-up. Autopsy of one non-cardiac death out of the study participants 17.5 months later showed well-developed skeletal myotubes with a preserved contractile apparatus within the grafted post-infarction scar [20]. More recently, Siminiak et al. [21] reported on the 12 months follow-up study that included 10 post-myocardial infarction patients who received skeletal myoblasts during coronary bypass surgery and had improved segmental contractility in akinetic/dyskinetic areas.

These promising results are limited by several critical issues. Assessment of the fate of myoblasts after transplantation indicates that these cells remain committed to a skeletal muscle progeny [22]. An earlier report suggested that a few transplanted myoblasts convert from fast (skeletal muscle-like) to slow twitch fibers (cardiomyocyte-like), which are more suitable for cardiac-like work [23]. However, mature skeletal muscle cells do not express the adhesion or gap junction proteins required to electromechanically couple with one another or with host myocardium [24,25], and available physiologic data suggest that these grafts do not beat in synchrony with the rest of the heart. Accordingly, a significant number of patients required periprocedural implantation of cardioverter-defibrillator due to development of ventricular arrhythmias following transplantation of skeletal myoblasts, possibly as a result of re-entry circuits established by myoblast engraftment and lack of gap junction formation between transplanted cells and adjacent resident cardiomyocytes [20,21]. Finally, the phase II/III MAGIC trial that randomized patients with heart failure to skeletal myoblast transplantation was recently prematurely ended.

### *In situ* cardiac stem cells

The notion that cardiomyocytes are unable to proliferate beyond fetal life was a traditional concept in cardiovascular research. In 1994, Pierro Anversa and collaborators [26] suggested, based on mitotic indices (e.g., proliferating cell nuclear antigen expression, propidium iodide and nuclear expression of Ki-67), that cardiomyocytes actually divide in certain pathologic conditions such as heart failure or myocardial infarction. However, the significance of this phenomenon was questioned since such mitoses are extremely rare and probably have no clinical significance [27]. Further support to the concept of the cardiac rejuvenation was achieved with the identification of several cell types within the myocardium that are capable of proliferation and differentiation, named cardiac stem or progenitor cells. One example is the rare (< 0.01%) rat myocardial  $lin^- c-kit^+$  cells. These cells have an immature phenotype and contribute to the regeneration of infarcted myocardium. When injected into an ischemic heart,  $lin^- c-kit^+$  cells reconstitute well-differentiated myocardium, formed by blood-carrying new vessels and anatomic, biochemical, and functional properties of young myocytes [28]. Another suggested stem cell population was isolated following depletion of cardiomyocytes and positive cell selection for Sca1. These cells have increased levels of telomerase reverse transcriptase activity and have the capability to home into the myocardium and differentiate with and without fusion into cardiomyocytes following azacytidine treatment [29]. Messina et al. [30] made a

G-CSF = granulocyte colony-stimulating factor

step forward by isolating small, round, phase-bright cells from a primary culture of myocardial derived fibroblast-like cells, named cardiospheres. These cardiosphere-derived cells, which are c-kit<sup>+</sup>, started beating spontaneously soon after their generation and following transplantation into the myocardium, differentiated into cardiomyocytes and participated in the generation of new capillaries.

Although promising, the major limitation of most of the above-mentioned studies is that none had been able to identify the origin of these cells or rule out the possibility that these cells originate from the bone marrow and migrate into the heart.

### Human umbilical cord blood cells

Human umbilical cord blood contains relatively large numbers of progenitor cells with differentiation capabilities into various lineages. These cells have several advantages that may position them as promising players in the future field of cell therapy. Cord blood cells can be easily obtained, expanded *in vitro*, cryopreserved for at least 15 years, have reduced immunogenicity and have no complicating ethical concerns. Cord blood progenitor cells are routinely used for stem cell reconstitution in patients affected by major hematologic disorders as an alternative to bone marrow transplantation [31,32]. Our group performed a preliminary study of <sup>199m</sup>Tc-labeled CD133<sup>+</sup> cord blood cells that were injected intracoronary 10 days after ischemia-reperfusion injury in a pig model. Whole-body imaging using a gamma camera showed that most of the cells colonized in the myocardium. Histology studies revealed clusters of human cells that colonized and survived in the infarcted myocardium for at least 1 month, and echocardiographic assessment showed improvement in left ventricular fractional shortening [32]. Cord blood cells may have the potential to improve function of the infarcted heart.

### Current challenges in cell transplantation therapy

There are still many challenges in the field of cell-based cardiac repair. For example, the mode of cell delivery into the scar is unsatisfactory. The phenomenon of "cell washout" from the myocardium was demonstrated by Kloners' group [33], who detected transplanted cardiomyocytes in peripheral tissues after direct injection of the cells into the myocardium. The finding that cell washout was more pronounced in the ischemia-reperfusion model led the authors to suggest that this washout is mediated by coronary circulation. Thus, cell retention is extremely variable, making graft size unpredictable. Development of methods such as improved injection media or scaffolds to increase cell retention to improve cell distribution would help move this work toward the clinic.

An alternative attractive method for cellular transplantation is the injection of cells either intracoronary during coronary interventions or intravenously. We and others have reported very low (around 1%) spontaneous myocardial homing of infused bone marrow-derived stem cells [34]. Furthermore, a study that

assessed the homing capabilities of bone marrow-derived stem cells in humans [35] using three-dimensional positron-emitted tomography found that only 1.3–2.6% of injected cells homed into the myocardium after intracoronary injection, and no cells were found following intravenous injection. The SDF-1/CXCR4 system, which is implicated in migration, proliferation, differentiation and survival of many cell types including human and murine hematopoietic stem and progenitor cells [36], probably plays a significant role in stem cell homing following myocardial infarction. Local manipulations to increase levels of SDF-1 in the myocardium have been shown to increase stem cells homing following myocardial infarction [37]. Thus utilization of the SDF-1/CXCR4 system might be an aid to improve homing efficacy.

Finally, cell-cell fusion is a known phenomenon in the development and physiology of multicellular organisms. While stem cell research indicates that certain mammalian cells, even from adults, maintain a high degree of plasticity for multi-lineage cell differentiation and suggest that the mechanism of benefit and cardiac regeneration is by transdifferentiation, recent reports raise significant doubts regarding this assumption. Various models incorporating sophisticated methods of gene labeling and expression have shown that most of the new acquired phenotype of transplanted bone marrow-derived stem cells in cardiac tissue are fused cells [29]. Thus, future research should use more accurate methods to differentiate between these two processes.

### Summary and Conclusions

Stem cell therapy for the treatment of end-stage cardiovascular disease holds great promise for those patients who currently have no therapeutic option. Promising results in animal studies lead us to believe that this approach may indeed develop into an effective clinical therapy for cardiovascular disease. However, basic issues concerning the precise characterization of the utilized cells and fundamental issues regarding their mechanism of action and differentiation have not yet been elucidated. Numerous clinical studies are yielding varying results regarding efficacy and safety. To avoid a distressing drawback similar to the one that occurred in the field of gene therapy, a more profound understanding of the basic issues of cell biology is mandatory. Thus, efforts should be directed toward those basic open questions. Furthermore, it is essential that myocardial repair strategies be subjected to rigorously controlled clinical trials to determine their effects on clinical outcomes and to increase the chance to achieve the ambitious goal of myocardial regeneration.

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*Power doesn't corrupt. Fear corrupts... perhaps the fear of a loss of power*

John Steinbeck (1902-1868), American novelist whose works, notably *The Grapes of Wrath*, an epic account of migrant farm workers, deal with the social and economic conditions of his native California following the great Depression. *East of Eden* was his most ambitious work. He won the Nobel Prize for Literature in 1962.