Published in final edited form as:
Drug Discov Today Ther Strateg. 2008 ; 5(1): 73–78. doi:10.1016/j.ddstr.2008.05.001.

Stem cell therapies in cardiovascular disease A "realistic" appraisal

Chohreh Partovian and **Michael Simons**
Angiogenesis Research Center, Section of Cardiology, Departments of Medicine, Pharmacology and Toxicology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA

Abstract

The possibility of reconstituting the damaged heart has introduced a new paradigm in cardiovascular biology and created the potential for a new therapeutic approach in the cardiovascular field, where there is a compelling need for innovative treatments. While the results of animal and early clinical studies are encouraging, the more direct use of cell-based therapies in patients is still long-reached. Gaps in our basic understanding of mechanisms, lack of important randomized, double blind, and controlled clinical trials, as well as technology development for cell production are among challenges to be overcome before full translation of cell based therapies in clinical arena. This review focuses on summarizing the latest knowledge in stem cell therapy for cardiovascular diseases.

Keywords

Ischemic cardiomyopathy; stem cells; regeneration; angiogenesis; clinical trials

"Science must begin with myths, and with the criticism of myths. The scientific tradition is distinguished from the pre-scientific tradition in having two layers. Like the latter, it passes on its theories; but it also passes on a critical attitude towards them. The theories are passed on, not as dogmas, but rather with the challenge to discuss them and improve upon them." Karl Popper

Introduction

World Health Organization projects almost 20 million deaths from cardiovascular diseases (CVD), mainly from heart disease and stroke, in the next 10 years. Myocardial infarction complicated by heart failure remains a lethal condition for 25% of patients over three years after the event, despite recent therapeutic advances in restoring the flow in the infarct-related artery using thrombolytics or urgent mechanical revascularization. Since none of these procedures or of the currently available medications have any ability to stimulate replacement of the lost myocardium, development of new treatments that will regenerate the cardiac muscle and its vascular components represents an exciting prospect in the treatment of CVD.

Address correspondence to: Michael Simons, MD, Section of Cardiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH 037566, Phone: 603 650 3540, e-mail: michael.simons@dartmouth.edu.

Does Myocardial Regeneration Exist?

The traditional concept of myocardial biology assumes that the adult human myocardium is a terminally differentiated tissue without regenerative capacity. This dogma has been recently challenged by the identification in the adult heart of replicating myocytes [1]. The phenotype of these cycling myocytes—telomerase-positive, significantly smaller than the average myocytes, present in very small number, negative for all the markers for the hematopoietic lineages (Lin^-) and positive for three membrane epitopes – c-Kit, Sca-1-like and MDR1, commonly expressed by stem cells— led to hypothesize that they were progenitor cells derived from cardiac stem cells (CSC) [1].

The key characteristics of stem cells are self renewal, clonogenicity and pluripotency. They show an asymmetric division in which one of the daughter cells remains undifferentiated and has similar properties to its precursor, while the other daughter cell is committed to a mature lineage differentiation. Studies indeed suggested that cardiac stem cells are also multipotent and can differentiate into endothelial cells, smooth muscle cells, and functional cardiomyocytes [2]. The cases of sex-mismatched cardiac and bone-marrow transplants in the adult, where Y chromosome myocytes and vascular cells were detected in the heart from a female donor [3, 4] suggested for the first time in human beings that the heart can receive new cells from an extracardiac source and that cardiac regeneration may indeed take place. However, this process seems to occur at very low levels. The mean percentage of cardiomyocytes arising from the host was estimated to be 0.04% with a median of 0.016% and mainly associated with regions of acute rejection [5]. While these observations have raised a hope for the potential of stem cells to generate replacement for the damaged myocardium and to reverse the disease process, they remain highly controversial.

A strong but indirect evidence for the presence of cardiac stem cells in adult mammals was recently provided by Hsieh et al [6]. Using an inducible cardiomyocyte-specific transgenic mouse fate-mapping approach to determine the frequency with which cardiomyocytes are refreshed from stem or precursor cells, the investigators observed an increased presence of new progenitor-cell-derived myocytes. Interestingly, this was observed after an acute myocardial infarction but not during the normal aging process.

Because none of the markers used to identify the CSC are specific and each one is expressed in other cell types, it has not been possible to unambiguously determine CSC origin. The progenitor cell maybe a circulating cell, a bone marrow-derived hematopoietic or mesenchymal stem cell or even an organ-specific progenitor cell (resident cardiac stem cell) that may transdifferentiate into endothelial cell and cardiac myocyte. Studies involving injection of bone marrow-derived hematopoietic stem cells constitutively expressing green fluorescent protein (GFP) in a mouse myocardial infarction model reported a very high rate (67 to 82%) of contribution of these cells to myocardial repair as well as a significant functional recovery [7]. Similar experiments using either $c\text{-}Kit^+$ cells isolated from the bone marrow [8] or a human bone marrow-derived multipotent stem cell [9] also reported a robust cellular engraftment as well as differentiation into cardiomyocytes and coronary vessels. However, these high percentages of incorporation have not been reproduced in other studies. For example, an injection of bone-marrow-derived hematopoietic stem cells constitutively expressing lacZ in lethally irradiated mice with acute coronary artery occlusion, was reported to generate only ~0.02% of lacZ expressing cardiomyocytes and 3.3% lacZ positive endothelial cells [10].

Furthermore, a new wave of studies questioned not only the high degree of incorporation, but also the fate of these transplanted stem cells [11-14]. In these studies, the injected HSCs were isolated from mice carrying transgene that controlled the expression of LacZ or GFP through the cardiac α myosin heavy chain promoter (αMHC). Therefore, only HSCs that would express

αMHC as a result of their trans-differentiation into cardiomyocytes would also express LacZ or GFP. These studies concluded that trans-differentiation of bone marrow-derived cells to cardiomyocytes occurs very uncommonly if at all, and that most of positive results are either the consequence of HSC-cardiomyocyte cell fusion or an inaccurate identification of a two side by side cells as a single positive myocyte.

What are the Effects on the Heart and the Mechanisms of Action?

Despite apparent paucity of trans-differentiation or stem cell-myocyte differentiation event, nearly all studies using cell transplants (somatic, embryonic or bone marrow-derived stem cells) in animal models of myocardial infarction showed some favorable effect on tissue perfusion and contraction of the injured myocardium. The mechanisms by which cellular therapy improves cardiac function remain elusive. The number of cardiac cells produced by cardiac regeneration seems unlikely to explain the observed cardioprotective effects. Evidence is emerging that these cells may provide paracrine signals by secreting angiogenic growth factors and cytokines to enhance angiogenesis, survival and growth. Recently Grunewald et al [15] described a model in which induction of VEGF expression in the heart by a genetic approach was followed within 4 days by an abundant infiltration of bone marrow-derived monocytic cells, termed “recruited bone marrow-derived circulating cells or RBCCs”. The investigators further demonstrated that a chemokine, stromal derived factor-1 (SDF-1) whose expression is markedly increased in ischemic tissue in a VEGF-dependent manner, plays an important role in trapping and correctly positioning these RBCCs around the forming vessels. Indeed, RBCCs did not line the vessel wall but rather underwent extravasation around the growing blood vessels. RBCCs have been shown to be angio-competent by releasing a number of angiogenic factors such as matrix metalloproteinase 9 (MMP9) in a SDF-1 dependent manner.

Human CSCs have growth factor receptors and respond to a number of growth factors by mobilization, expansion and differentiation [16]. Ex-vivo amplification and / or genetic manipulation have also been successfully employed to further enhance their therapeutic function. Cells modified to express VEGF have been shown to induce a greater improvement in blood flow and angiogenesis, in animals models of ischemia, than progenitor cells alone [17,18]. Rat bone marrow-derived mesenchymal stem cells overexpressing the survival gene *Akt1* were superior to control mesenchymal stem cells transduced with green fluorescent protein for cell therapy of acute myocardial infarction [19]. Another illustration of the “paracrine theory” came from the ground-breaking study of Fraidenraich and colleagues who reported the rescue of lethal cardiac defects in Inhibitor of DNA binding (Id) knockout mutant mouse embryos by injection of embryonic stem (ES) cells into preimplantation stage embryos [20]. ES cells are highly proliferative and totipotent, capable of giving rise to all tissues of the adult body. In vitro, both mouse and human ES cells have been demonstrated to generate the range of cell types found in the myocardium including cardiomyocytes, endothelial cells, vascular smooth muscle cells and fibroblasts. Remarkably, when the authors examined the rescued hearts, few ES cells (5-45%) were found to have been incorporated. They actually demonstrated that the rescue was not due to transplanted ES cells giving rise to functional new tissues within the defective embryonic heart, but instead, due to various secreted factors such as Insulin –like growth factor 1 and Wnt5a, emanating from the transplanted cells.

Is it Transferable into the Clinical Arena?

Almost simultaneously with these biological discoveries and in spite of controversy regarding the mechanism by which these cells might improve the cardiac function, a number of clinical trials were initiated. These trials used a variety of designs, cell types and cell delivery methods. They also differed in their choice of patients and the end-point measurements to assess cardiac

function. Most of them were small and mainly focused on evaluating safety and feasibility, while measuring functional changes in an exploratory way.

Type of Cells

Skeletal myoblasts were one of the first cell types studied for cardiovascular repair [21]. These cells can be isolated from the patient's own skeletal muscle, expanded *in vitro* and transplanted back into the patient's heart thus providing the advantage of an autologous source of cells. Myoblasts are already committed to the myocyte cell lineage and are highly resistant to ischemia. Evidences suggest that skeletal myoblasts do not form electromechanical junctions with existing cardiomyocytes [22]. In addition, cases of sustained ventricular tachycardia were reported within the first weeks following myoblast transplantation in patients with chronic myocardial ischemia [23]. While several clinical trials showed a beneficial effect on the left ventricular function [23-26] the interpretation of the results is complicated by the fact that myoblasts were used as an adjunct to coronary bypass procedures. The first randomized placebo-controlled trial (MAGIC) was stopped early because it was considered unlikely to show benefit [27]. Overall, it seems unlikely that myoblast therapy will prove effective in CHD.

Bone-marrow-derived stem cells can be used either as an unfractionated solution or after purification using specific cell surface markers. The subpopulations that have been used in clinical trials include hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and endothelial progenitor cells (EPC). HSC (Lineage^{-}, c-kit^{+}, Sca-1^{+}, CD34^{lo} and CD38^{hi}) represent the prototypical adult stem cell population [28]. Mesenchymal stem cells (MSC) represent the bone marrow non-hematopoietic cells that have the potential to differentiate into cells of mesenchymal origin such as chondrocytes, osteoblasts, astrocytes, neurons, skeletal muscle and cardiomyocytes [29]. Their concentration is 10-fold lower than HSC but they are easily isolated and highly expandable in culture. In addition, they display local immunosuppressive properties that allow them to survive transplantation in an allogenic setting [30]. EPC express CD133 and CD34 and Flk-1 (VEGFR-2). They can be isolated form the bone marrow or from the peripheral circulation and also expanded in vitro. There are presumed to be capable of stimulating the formation of new blood vessels.

Summary of Clinical Trials

Clinical studies using bone-marrow-derived cells infused by intracoronary injection after a recent myocardial infarction suggest the possibility of a functional benefit (table 1). In the BOOST trial, patients received an intracoronary transfer of autologous bone marrow cells, following a percutaneous coronary intervention (PCI)[31]. Six months later, patients receiving the cell infusion demonstrated better LV systolic function in a myocardial segment adjacent to the infarcted area when compared with patients who only received the PCI intervention. However these effects were no longer significant at 18 months [32].

In the TOPCARE-AMI trial, patients with reperfused acute myocardial infarction were randomly allocated to receive intracoronary infusion of either bone marrow-derived or circulating blood-derived progenitor cells into the infarct artery 4 days after myocardial infarction (MI) [33]. At 4-month follow-up, transplantation of either progenitor cells population was associated with a significant increase in global left ventricular ejection fraction, improved regional wall motion and reduced end-systolic left ventricular volumes, in comparison with a nonrandomized matched reference group. In addition, analysis of serial contrast-enhanced magnetic resonance imaging demonstrated a beneficial effect in post-infarction remodeling process [34]. Interestingly, a randomized crossover study from the same team in the setting of chronic stable ischemia (cells injected at least 3 months after myocardial infarction) showed only a small benefit in the left ventricular ejection fraction [35].

In the multicenter REPAIR-AMI trial [36], 204 patients with acute MI were randomly assigned to receive an intracoronary infusion of bone marrow-derived progenitor cells or placebo into the infarct artery, 3 to 7 days after successful reperfusion therapy. At 4 months, the absolute improvement in the global left ventricular ejection fraction (LVEF) was significantly greater in the BMC group than in the placebo group. Patients with a baseline LVEF at or below 48.9%, derived the most benefit from cell therapy. In another study, patients who received intracoronary autologous bone marrow mesenchymal stem cells versus patients who were injected with saline exhibited improved wall function and a 14% increase in ejection fraction [37].

In contrast two other similar trails failed to demonstrate any significant improvement. The ASTAMI trial included 100 patients with acute MI, who received bone marrow mononuclear cells at 6 days post PCI. At 6 months follow-up there was no improvement in LVEF or infarct size [38]. In another randomized placebo-controlled double blind study including 67 patients, the delivery of autologous bone marrow cells within 24 hours of optimum reperfusion therapy did not augment recovery of global LV function after myocardial infarction [39]. It should be noted that details of BMC handling were different in these trials which may or may not explain the differences in clinical outcomes.

Another therapeutic option that has been investigated uses various cytokines and growth factors to mobilize endogenous progenitor cells. Several factors including granulocyte colony-stimulating factor (G-CSF), granulocyte/macrophage colony-stimulating factor (GM-CSF), stem cell factor (SCF), VEGF and erythropoietin (EPO) have been shown to promote the mobilization of bone marrow-derived stem cells into the peripheral circulation and into the injured myocardium. The FIRST-LINE-AMI trial reported a potential improvement in LVEF and attenuation of LV dilation by using G-CSF in MI patients after reperfusion [40]. However, two subsequent randomized, placebo-controlled clinical trials REVIVAL II [41] and STEMMI [42] failed to reproduce the same benefits. Although there has been some concern about increased restenosis after angioplasty with this method, no adverse events were reported in these three trials [43]. The failure of these mobilization studies to show any clinical benefit is concerning since back-of-the-envelope calculations show that they consistently expose the heart to much higher numbers of progenitor cells than can be achieved with intracoronary injection of partially purified cells.

Conclusion

In summary, the results from these clinical exploratory trials are intriguing or at the best encouraging. Because few side effects were reported, it is now generally considered that cellular therapy can be safely delivered by intracoronary or intramyocardial routes. However, drawing any conclusion regarding the efficacy of cell therapy in CVD would be premature and certainly inaccurate. Proof of efficacy requires the results of randomized, controlled and double blind clinical trials. Some have argued that these studies are too premature since the mechanisms by which any of the methods of stem cell transplantation leads to improvement of cardiac function have not been elucidated [44]. At the same time, others contend that is impossible to be sure about the actual mechanism of benefit of any cardiovascular therapeutic and we are still discovering new mechanisms by which aspirin and beta-blockers work [45]. Clearly more bench work is needed to define cell fate, and to better understand the mechanism of action. The advancing knowledge of stem cell biology will help answering clinically relevant questions such as the choice of the ideal cell type, the best delivery method and the optimal time of grafting after injury which in turn will help designing clinical trials with increased chance of success. A close collaboration between basic biology and clinical research will be required to allow progress towards a worthy goal and to avoid premature failure.

"Good tests kill flawed theories; we remain alive to guess again."

Karl Popper

Bibliography

1. Anversa P, Nadal-Ginard B. Myocyte renewal and ventricular remodelling. Nature 2002;415(6868): 240–243. [PubMed: 11805849]
2. Beltrami AP, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003;114(6):763–776. [PubMed: 14505575]
3. Bayes-Genis A, et al. Cardiac chimerism in recipients of peripheral-blood and bone marrow stem cells. Eur J Heart Fail 2004;6(4):399–402. [PubMed: 15182763]
4. Quaini F, et al. Chimerism of the transplanted heart. N Engl J Med 2002;346(1):5–15. [PubMed: 11777997]
5. Laflamme MA, et al. Evidence for cardiomyocyte repopulation by extracardiac progenitors in transplanted human hearts. Circ Res 2002;90(6):634–640. [PubMed: 11934829]
6. Hsieh PC, et al. Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury. Nat Med 2007;13(8):970–974. [PubMed: 17660827]
7. Orlic D, et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci U S A 2001;98(18):10344–10349. [PubMed: 11504914]
8. Kajstura J, et al. Bone marrow cells differentiate in cardiac cell lineages after infarction independently of cell fusion. Circ Res 2005;96(1):127–137. [PubMed: 15569828]
9. Yoon YS, et al. Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction. J Clin Invest 2005;115(2):326–338. [PubMed: 15690083]
10. Jackson KA, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. J Clin Invest 2001;107(11):1395–1402. [PubMed: 11390421]
11. Alvarez-Dolado M, et al. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. Nature 2003;425(6961):968–973. [PubMed: 14555960]
12. Balsam LB, et al. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. Nature 2004;428(6983):668–673. [PubMed: 15034594]
13. Murry CE, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature 2004;428(6983):664–668. [PubMed: 15034593]
14. Nygren JM, et al. Bone marrow-derived hematopoietic cells generate cardiomyocytes at a low frequency through cell fusion, but not transdifferentiation. Nat Med 2004;10(5):494–501. [PubMed: 15107841]
15. Grunewald M, et al. VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. Cell 2006;124(1):175–189. [PubMed: 16413490]
16. Urbanek K, et al. Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. Circ Res 2005;97(7):663–673. [PubMed: 16141414]
17. Ikeda Y, et al. Development of angiogenic cell and gene therapy by transplantation of umbilical cord blood with vascular endothelial growth factor gene. Hypertens Res 2004;27(2):119–128. [PubMed: 15005275]
18. Iwaguro H, et al. Endothelial progenitor cell vascular endothelial growth factor gene transfer for vascular regeneration. Circulation 2002;105(6):732–738. [PubMed: 11839630]
19. Gnecchi M, et al. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. Nat Med 2005;11(4):367–368. [PubMed: 15812508]
20. Fraidenraich D, et al. Rescue of cardiac defects in id knockout embryos by injection of embryonic stem cells. Science 2004;306(5694):247–252. [PubMed: 15472070]
21. Menasche P, et al. Myoblast transplantation for heart failure. Lancet 2001;357(9252):279–280. [PubMed: 11214133]
22. Leobon B, et al. Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. Proc Natl Acad Sci U S A 2003;100(13):7808–7811. [PubMed: 12805561]

23. Menasche P, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. J Am Coll Cardiol 2003;41(7):1078–1083. [PubMed: 12679204]
24. Dib N, et al. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. Circulation 2005;112(12):1748–1755. [PubMed: 16172284]
25. Gavira JJ, et al. Autologous skeletal myoblast transplantation in patients with nonacute myocardial infarction: 1-year follow-up. J Thorac Cardiovasc Surg 2006;131(4):799–804. [PubMed: 16580437]
26. Hagege AA, et al. Skeletal myoblast transplantation in ischemic heart failure: long-term follow-up of the first phase I cohort of patients. Circulation 2006;114(1 Suppl):I108–113. [PubMed: 16820558]
27. Kastrup J, et al. Myocardial regeneration induced by granulocyte-colony-stimulating factor mobilization of stem cells in patients with acute or chronic ischaemic heart disease: a non-invasive alternative for clinical stem cell therapy? Eur Heart J 2006;27(23):2748–2754. [PubMed: 17065171]
28. Spangrude GJ, et al. Purification and characterization of mouse hematopoietic stem cells. Science 1988;241(4861):58–62. [PubMed: 2898810]
29. Pittenger MF, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284 (5411):143–147. [PubMed: 10102814]
30. Le Blanc K, et al. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003;31(10):890–896. [PubMed: 14550804]
31. Wollert KC, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 2004;364(9429):141–148. [PubMed: 15246726]
32. Meyer GP, et al. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. Circulation 2006;113(10):1287–1294. [PubMed: 16520413]
33. Assmus B, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). Circulation 2002;106(24):3009–3017. [PubMed: 12473544]
34. Britten MB, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. Circulation 2003;108(18):2212–2218. [PubMed: 14557356]
35. Assmus B, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. N Engl J Med 2006;355(12):1222–1232. [PubMed: 16990385]
36. Schachinger V, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med 2006;355(12):1210–1221. [PubMed: 16990384]
37. Chen SL, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004;94 (1):92–95. [PubMed: 15219514]
38. Lunde K, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355(12):1199–1209. [PubMed: 16990383]
39. Janssens S, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet 2006;367(9505): 113–121. [PubMed: 16413875]
40. Ince H, et al. Prevention of left ventricular remodeling with granulocyte colony-stimulating factor after acute myocardial infarction: final 1-year results of the Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor (FIRSTLINE-AMI) Trial. Circulation 2005;112(9 Suppl):I73–80. [PubMed: 16159869]
41. Zohlnhofer D, et al. Stem cell mobilization by granulocyte colony-stimulating factor in patients with acute myocardial infarction: a randomized controlled trial. Jama 2006;295(9):1003–1010. [PubMed: 16507801]
42. Ripa RS, et al. Stem cell mobilization induced by subcutaneous granulocyte-colony stimulating factor to improve cardiac regeneration after acute ST-elevation myocardial infarction: result of the double-blind, randomized, placebo-controlled stem cells in myocardial infarction (STEMMI) trial. Circulation 2006;113(16):1983–1992. [PubMed: 16531621]
43. Kang HJ, et al. Differential effect of intracoronary infusion of mobilized peripheral blood stem cells by granulocyte colony-stimulating factor on left ventricular function and remodeling in patients with

acute myocardial infarction versus old myocardial infarction: the MAGIC Cell-3-DES randomized, controlled trial. Circulation 2006;114(1 Suppl):I145–151. [PubMed: 16820564]

44. Chien KR. Stem cells: lost in translation. Nature 2004;428(6983):607–608. [PubMed: 15034595]
45. Martin JF. Stem cells and the heart: ethics, organization and funding. Nat Clin Pract Cardiovasc Med 2006;1:S136–137. [PubMed: 16501621]
46. Strauer BE, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106(15):1913–1918. [PubMed: 12370212]
47. Schachinger V, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol 2004;44 (8):1690–1699. [PubMed: 15489105]

Table 1

Major clinical trials of stem cell therapy in acute myocardial infarction (MI)

Study	Number of patients Treated / control	Time of delivery post-MI (days)	Treatment, route of administration and cell type	Results
Strauer *et al* 2002 [46]	10/10	5 to 9	IC, BM-MNC	Decreased infarct size, improved regional wall motion and perfusion. No change in EF or LVEDV
TOPCARE-AMI [33,34,47]	29 MNC 30 CPC 11 control	3 to 7	IC, CPC or BM-MNC	Significant increase in EF, improved regional wall motion, reduced infarct size, no change in LVEDV
BOOST [31,32]	30/30	6	IC, BM-MNC	Improved EF at 6 months, No difference at 18 months
FIRST-LINE-AMI [40]	25/25	0 to 6	Mobilization by G-CSF	Improved EF and remodeling at 4 months
REPAIR-AMI [36]	102/102	4	IC, BM-MNC	Improved EF and reduced infarct size at 4 months
ASTAMI [38]	100	5 to 8	IC, BM-MNC	No difference at 6 months
Chen *et al* 2004 [37]	34/35	18	IC, MSC	Improved and perfusion at 6 months
JANSSENS *et al* 2006 [39]	33/34	1	IC, BM-MNC	No effect
REVIVAL [41]	56/58	0 to 5	Mobilization by G-CSF	No difference at 6 months
STEMMI [42]	39/39	0 to 6	Mobilization by G-CSF	No difference at 6 months

IC: intra-coronary, BM-MNC: Bone marrow-derived mononuclear cells, CPC: circulating blood-derived progenitor cells EF: ejection fraction, LVEDV: left ventricular end-diastolic volume