Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 23 May 2011, doi:10.4414/smw.2011.13209
Cite this as: Swiss Med Wkly. 2011;141:w13209

Cardiac repair with allogeneic mesenchymal stem cells after myocardial infarction

Giuseppe Vassalli,[1,2] *Tiziano Moccetti*[1]

[1]Fondazione Cardiocentro Ticino, Lugano, Switzerland
[2]Department of Cardiology, CHUV, Lausanne, Switzerland

Summary

Over the past decade, use of autologous bone marrow-derived mononuclear cells (BMCs) has proven to be safe in phase-I/II studies in patients with myocardial infarction (MI). Taken as a whole, results support a modest yet significant improvement in cardiac function in cell-treated patients. Skeletal myoblasts, adipose-derived stem cells, and bone marrow-derived mesenchymal stem cells (MSCs) have also been tested in clinical studies. MSCs expand rapidly *in vitro* and have a potential for multilineage differentiation. However, their regenerative capacity decreases with aging, limiting efficacy in old patients. Allogeneic MSCs offer several advantages over autologous BMCs; however, immune rejection of allogeneic cells remains a key issue. As human MSCs do not express the human leukocyte antigen (HLA) class II under normal conditions, and because they modulate T-cell-mediated responses, it has been proposed that allogeneic MSCs may escape immunosurveillance. However, recent data suggest that allogeneic MSCs may switch immune states *in vivo* to express HLA class II, present alloantigen and induce immune rejection. Allogeneic MSCs, unlike syngeneic ones, were eliminated from rat hearts by 5 weeks, with a loss of functional benefit. Allogeneic MSCs have also been tested in initial clinical studies in cardiology patients. Intravenous allogeneic MSC infusion has proven to be safe in a phase-I trial in patients with acute MI. Endoventricular allogeneic MSC injection has been associated with reduced adverse cardiac events in a phase-II trial in patients with chronic heart failure. The long-term safety and efficacy of allogeneic MSCs for cardiac repair remain to be established. Ongoing phase-II trials are addressing these issues.

Key words: *myocardial infarction; mesenchymal stem cells; allogeneic; immunogenicity; cardiac regeneration*

Introduction

Growing evidence suggests that the adult mammalian heart harbours stem and progenitor cells that possess a regenerative capacity [1]. Moreover, circulating bone marrow-derived progenitor cells can home to injured myocardium to participate in cardiac repair [2]. Nevertheless, myocardial infarction (MI) results in a massive loss of cardiomyocytes and scar formation. Hence, endogenous regenerative mechanisms appear to be insufficient to replace the huge number of cardiomyocytes that are lost after MI. Chronic heart failure (CHF) eventually ensues in many patients. Recent advances in pharmacological agents, coronary revascularisation and implantable devices have succeeded in alleviating clinical symptoms, prolonging survival and slowing down the progression of CHF; however, they have failed to fully prevent CHF. As a loss of cardiomyocytes is primarily responsible for the development of CHF, the generation of new functional cardiomyocytes remains the ultimate goal for preserving cardiac function.

Ten years ago, a seminal report claimed that adult mouse bone marrow-derived stem cells trans-differentiated into cardiomyocytes to regenerate infarcted myocardium *in vivo* [3]. This report sparked overwhelming enthusiasm in the scientific community, leading to the extremely rapid initiation of clinical studies of bone marrow cell (BMC)-based therapies for cardiac repair [4, 5]. Meanwhile, cardiomyogenic trans-differentiation of mouse BMCs was not confirmed by subsequent studies from other laboratories [6, 7], questioning the very rationale for the initiation of these clinical studies. The first phase-I study of BMC-based therapy for ischemic heart disease [5] was published only 2 years after the initial experimental report on cardiomyogenic trans-differentiation of BMCs [3]. Several other phase-I/II clinical studies were published in the next few years. Most of these studies adopted a "blanket" strategy using autologous unfractionated mononuclear BMCs, rather than selected cell components within the heterogeneous BMC population. A few days after acute MI and percutaneous recanalisation of the infarct-related coronary artery, bone marrow was taken from the patient, and mononuclear BMCs were prepared in the laboratory and immediately infused into the infarct-related vessel using a percutaneous over-the-wire delivery-catheter. Autologous BMC-based cell therapies for cardiac repair have proven to be safe in randomised controlled trials [8–12]. In agreement with these studies, our own data from the phase-I Stem cell Transplantation in Ischemic Myocardium (STIM) trial (n = 23 patients) and preliminary data from the subsequent phase-II SWiss multicentre Intracoronary Stem cells Study

in Acute Myocardial Infarction (SWISS-AMI) trial [13] (n = 166 patients enrolled as of March 31, 2011) indicate that intracoronary autologous BMC infusion in patients with acute MI is safe (Corti R, Sürder D, Moccetti T et al.; unpublished data). Efficacy data from randomised controlled trials have been mixed [8–12]. Taken as a whole, these data support a small yet significant increase in left ventricular ejection fraction (EF) in cell-treated patients [14]. Functional improvement seemed to be higher in patients with moderate-severe ventricular dysfunction than in those with mild dysfunction [10, 12]. However, in many instances, functional improvement was transient [15].

Autologous mononuclear BMC-based therapies have several limitations. The cell component within the heterogeneous BMC population that accounts for functional benefit has not been precisely defined. Bone marrow stem cells represent only 1 in 10,000 BMCs [16], and therefore can hardly explain the beneficial effect of BMC transplantation. Also, the proliferative and regenerative capacity of progenitor cells decreases with aging [17, 18], consistent with a reduced efficacy of progenitor cells from old patients. Another practical limitation is that the collection of bone marrow from the patient requires an invasive procedure.

Skeletal myoblasts, adipose-derived stem cells and mesenchymal stem cells (MSCs) have also been tested in a limited number of clinical studies in patients with MI. Skeletal myoblasts form contractile striated myocytes that do not couple electromechanically with cardiomyocytes. Percutaneous intramyocardial injection of autologous skeletal myoblasts using a cell delivery-catheter has proven safe but ineffective in the recent SEISMIC trial in patients with CHF [19]. Intracoronary infusion of autologous adipose-derived stem cells was proven to be safe in the recent double-blind, placebo-controlled APOLLO trial in patients with acute MI [20]. The cell-treated group showed a 5.7% increase in ejection fraction (EF) and improved myocardial perfusion, although these effects did not reach statistical significance in this early trial. The efficacy of adipose-derived stem cells will be evaluated in the phase-II/III ADVANCE trial.

The present short review aims to discuss MSC-based therapies after MI, with a focus on allogeneic MSC products.

Experimental studies of autologous MSCs for cardiac repair

Bone marrow MSCs are multipotent stromal (non haematopoietic) cells capable of differentiating into multiple lineages of the mesenchyme to become fat, bone, tendon and muscle. Cultured MSCs grow rapidly *in vitro*. Systemically delivered MSCs can home to sites of ischemia and tissue injury, including the ischemic heart. This remarkable property allows the non-invasive administration of MSCs intravenously, thus avoiding the need for intracoronary or intramyocardial cell delivery. MSCs treated with the demethylating agent 5-azacytidine or cardiomyogenic growth factors can adopt cardiac phenotypes *in vitro* [21–25]. In many instances, however, cardiac differentiation has been limited to the expression of cardiac-specific genes, without generation of functional cardiomyocytes [26]. Immunohistochemical evidence of cardiomyogenic differentiation of human MSCs implanted into infarcted mouse hearts has been reported [27]. Several experimental studies have shown improvements in cardiac function after MI in animals receiving MSCs [28–33] despite infrequent differentiation [29, 30]. In contrast, no functional benefit was observed in a minority of studies [34]. Over-expression of pro-survival molecules (e.g. Akt) by autologous MSCs significantly enhanced functional recovery after MI [30, 35]. These observations support central roles of paracrine mechanisms that stimulate angiogenesis and endogenous cardiac stem cells [36], rather than cell differentiation, in the therapeutic effects of MSCs.

Clinical studies of autologous MSCs for cardiac repair

Intracoronary infusion of autologous bone marrow-derived MSCs significantly increased EF at 3 months in a randomised study in patients with acute MI [37]. In addition, autologous MSC transplantation has proven safe in several non-randomised studies in patients with acute MI or CHF [38, 39]. Newly initiated phase-I/II studies include the Transendocardial Autologous Cells (hMSC or hBMC) in Ischemic Heart Failure Trial (TAC-HFT; www.clinicaltrials.org/NCT00768066), the Prospective Randomised study Of MSC THErapy in patients Undergoing cardiac Surgery (PROMETHEUS) trial (www.clinicaltrials.org/NCT00587990) which is expected to be completed in mid-2011, and the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) pilot study (www.clinicaltrials.org/NCT01087996) [40], among others.

As MSCs are rare among BMCs, they need to be expanded *ex vivo* for autologous applications. This procedure may take between 10 days [37] to 4-5 weeks [40] or longer depending on the cell number needed, and the age and comorbidities of the donor, as progenitor cells from old patients have reduced proliferation potential [17, 18, 41]. Cell expansion requires a Good Manufacturing Practice (GMP) cell therapy unit (Figure 1). Allogeneic MSCs from young donors have several advantages over autologous MSCs, in-

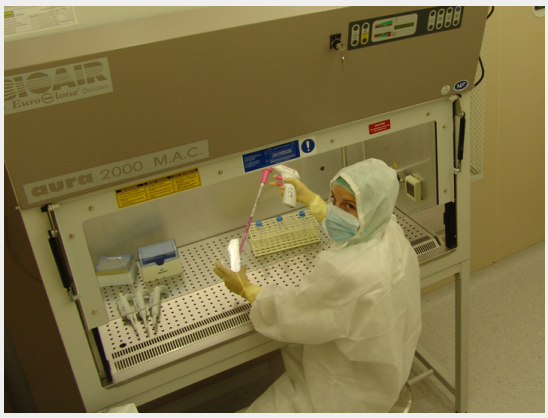

Figure 1

Good Manufacturing Practice (GMP) cell therapy unit at the Cardiocentro Ticino, Lugano. GMP facilities are required for *ex vivo* expansion of cells used in clinical studies.

cluding a high regenerative potential and availability for clinical use at any time point. In addition, no bone marrow collection from the patient is required. Moreover, MSCs from a single donor can be used for many patients, thus tremendously reducing the manufacturing costs of the cell product. On the other hand, the potential immunogenicity of allogeneic MSCs remains an unresolved issue that may affect clinical efficacy.

MSCs can switch immune states

Bone marrow-derived MSCs secrete immunoregulatory cytokines (e.g., IL10) and inhibit lymphocyte proliferation, dendritic cell maturation and alloimmune rejection [42–48]. Due to their immunomodulatory properties, MSCs have been tested in initial clinical studies of graft-versus-host diseases [49], osteogenesis imperfecta [50], glycogen storage diseases [51], Crohn's disease [52] and organ transplantation [53].

MSCs have been shown to express major histocompatibility complex (MHC) molecules, including MHC class II (MHC-II). Expression of MHC molecules is regulated by pro-inflammatory cytokines. Adult human MSCs express intermediate levels of MHC-I but do not express human leukocyte antigen (HLA) class II or co-stimulatory molecules on the cell surface under normal *in vitro* conditions. However, HLA-II has been detected in lysates of unstimulated MSCs, presumably reflecting intracellular deposits of the antigen. Treatment with interferon-γ was found to induce expression of HLA class II on the cell surface [43]. Another study showed that MSCs express MHC-II as antigen presenting cells in the presence of low levels of interferon-γ, whereas MHC-II expression was decreased by high levels of interferon-γ [54]. Inducing MSCs to acquire cardiac phenotypes by 5-azacytidine or cytokine treatment increased expression of immunostimulatory MHC-Ia and MHC-II, while decreasing that of immunomodulatory MHC-IIb, resulting in enhanced cytotoxicity of MSCs in co-culture with allogeneic leukocytes [55]. These observations suggest that MSCs can switch immune states from immunomodulatory to immunostimulatory (figure 2). Several studies have shown delayed host responses to allogeneic MSCs *in vivo* around 2 weeks after transplantation, suggesting that tolerance of MSCs across the allogeneic barrier may not be absolute [55–58].

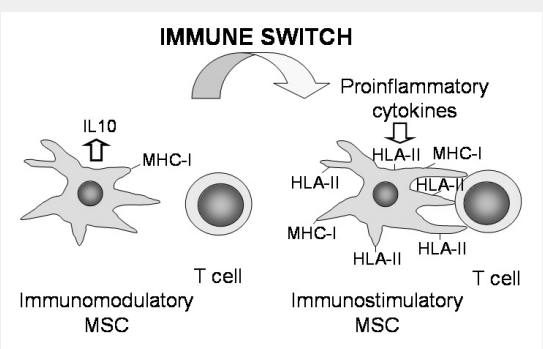

Figure 2

Cartoon depicting MSC immune switch. Under normal *in vitro* conditions (left), human MSCs express low MHC-I and no HLA class II, while secreting IL10. They mediate immunomodulatory effects on T cells. In the presence of pro-inflammatory cytokines (right), HLA class II is expressed on cell surfaces. MSCs acquire antigen presenting cell properties and stimulate T cells.

Experimental studies of allogeneic MSCs for cardiac repair

Intravenous [59] or intracoronary infusion, as well as transendocardial [60] or intramyocardial injection [28, 61, 62] of allogeneic MSCs has resulted in cell engraftment, reduced scar formation and improved cardiac function in various animal models of MI. Male MSCs injected into infarct scars and border zones in female allogeneic recipients differentiated towards multiple cell types including cardiomyocytes, vascular muscle cells and endothelial cells, as evidenced by co-localisation of Y-chromosome-positive cells and tissue-specific markers [62]. MSC-derived cardiomyocytes integrated into host myocardium, forming gap junctions. In sheep, intracoronary infusion of allogeneic mesenchymal progenitor cells (MPCs) improved EF and blood vessel formation 2 months after MI (Henry T et al.; www.mesoblast.com). In a rat model, both allogeneic and syngeneic MSCs improved EF 3 months after MI; however, allogeneic cells were eliminated from the heart by 5 weeks and functional benefit was lost within 5 months [55]. Circulating antibodies against differentiated allogeneic MSCs, but not against undifferentiated MSCs, were detected in the recipient by 5 weeks. In contrast, syngeneic MSCs were not eliminated and functional benefit lasted for more than 5 months. In a pig model, allogeneic MSCs were not immunogenic *in vitro* but elicited immune responses after intracardiac injection *in vivo* [58]. These experimental findings indicate that bone marrow-derived MSCs can induce immune responses in allogeneic hosts.

Clinical studies of allogeneic MSCs for cardiac repair

The results of the first phase-I, randomised, double-blind, placebo-controlled, dose-escalation study of intravenous allogeneic adult MSCs in patients with acute MI were published in December 2009 [63]. This study tested an "off-the-shelf" cell product (Prochymal™, Osiris Tx.) made from MSCs of a single healthy donor. A total of 53 patients who had suffered a first MI in the previous 10 days were randomised to receive one of three intravenous doses of Prochymal™ or placebo, without immunosuppression. The study's primary end point, adverse event rates at 6 months, was similar in the cell-treated group and the placebo group, indicating that the procedure was safe. No procedure-related complications were observed. Renal, hepatic and hematologic laboratory indexes were similar in the two groups. No patient developed tumours. Cell-treated patients had less episodes of ventricular tachycardia and a better lung function compared with controls. Although the study did not primarily aim to assess clinical efficacy, there was a trend towards improved clinical symptoms and increased EF at 3 months, but not at 6 months, in the cell-treated group. A phase-II multicentre trial of Prochymal™ has been started.

Endoventricular injection of an allogeneic MPC product (Revascor™, Mesoblast Ltd.) along the infarct border zone in patients with moderate-severe CHF has been evaluated in a phase-II, randomised, single-blind, placebo-controlled, dose-escalation, multicentre study. There were no procedure-related complications. The first cohort in the study (n=20 patients), receiving the low dose of Revascor™ in the trial, showed a 33% increase in EF at 6 months (p=0.029), whereas EF decreased 6% in the control group [64]. Interim data analysis after all patients had reached 6 months follow-up (www.mesoblast.com/news-room/asx-announcements/archives) showed that the number of patients who developed any severe adverse cardiac events over the follow-up period was 44.4% in the cell-treated group (n=45) versus 93.3% in the control group (n = 15; p = 0.001). The number of patients who developed any major adverse cardiac events, defined as the composite of cardiac death, heart attack or coronary revascularisation procedures, was 6.7% in the cell-treated group versus 40% in the control group (p = 0.005).

Conclusions

"Off-the-shelf" allogeneic MSC products have proven safe in phase-I/II trials in patients with acute MI or CHF [63, 64]. Preliminary efficacy data are encouraging. Several issues remain unresolved, however. Little is known regarding the *in vivo* survival of allogeneic MSCs. Experimental evidence suggests allogeneic MSCs may switch immune states *in vivo*, inducing alloimmune rejection [55]. The long-term safety and efficacy of allogeneic MSC-based therapies for cardiac repair are currently being tested in phase-II clinical trials. If immunogenicity of human allogeneic MSCs turned out to limit the clinical efficacy, pharmacological immunosuppression for limited periods of time after cell transplantation might be worth considering as a possible option, although the effectiveness of this approach remains to be demonstrated. Moreover, minimizing donor-recipient HLA-II mismatch might attenuate alloimmune rejection of transplanted MSCs. On the other hand, paracrine mechanisms of action [35] suggest that long-term survival of transplanted MSCs might not even be required to achieve sustained clinical effects.

Funding / potential competing interests: Support by the Swiss Cardiology Foundation and the Cecilia-Augusta Foundation, Lugano, is gratefully acknowledged.

Correspondence: *PD Dr Giuseppe Vassalli, Fondazione Cardiocentro Ticino, via Tesserete 48, CH-6900 Lugano, Switzerland, giuseppe.vassalli@cardiocentro.org*

References

1 Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell. 2003;114:763–76.

2 Fazel S, Cimini M, Chen L, Li S, Angoulvant D, Fedak P, et al. Cardioprotective c-kit+ cells are from the bone marrow and regulate the myocardial balance of angiogenic cytokines. J Clin Invest. 2006;116:1865–77.

3 Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001;410:701–5.

4 Strauer BE, Brehm M, Zeus T, Gattermann N, Hernandez A, Sorg RV, et al. [Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction] (German). Dtsch Med Wochenschr. 2001;126:932–8.

5 Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet. 2003;361:45–6.

6 Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. Nature. 2004;428:668–73.

7 Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature. 2004;428:664–8.

8 Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breindenbach C, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet. 2004;364:141–8.

9 Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, et al; REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. 2006;355:1210–21.

10 Assmus B, Honold J, Schächinger V, Britten MB, Fischer-Rasokat U, Lehmann R, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. N Engl J Med. 2006;355:1222–32.

11 Janssens S, Dubois C, Bogaert J, Theunissen K, Deroose C, Desmet W, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet. 2006;367:113–21.

12 Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med. 2006;355:1199–209.

13 Sürder D, Schwitter J, Moccetti T, Astori G, Rufibach K, Plein S, et al. Cell-based therapy for myocardial repair in patients with acute myocardial infarction: rationale and study design of the SWiss multicenter Intracoronary Stem cells Study in Acute Myocardial Infarction (SWISS-AMI). Am Heart J. 2010;160:58–64.

14 Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. Arch Intern Med. 2007;167:989–97.

15 Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, Fichtner S, 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;113:1287–94.

16 Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: Mesenchymal stem cells: Their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007;25:2739–49.

17 Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, Wang T, Gregg D, Ramaswami P, et al. Aging, progenitor cell exhaustion, and atherosclerosis. Circulation. 2003;108:457–63.

18 Heiss C, Keymel S, Niesler U, Ziemann J, Kelm M, Kalka C. Impaired progenitor cell activity in age-related endothelial dysfunction. J Am Coll Cardiol. 2005;45:1441–8.

19 Duckers HJ, Houtgraaf J, Hehrlein C, Schofer J, Waltenberger J, Gershlick A, et al. Final results of a phase IIa, randomised, open-label trial to evaluate the percutaneous intramyocardial transplantation of autologous skeletal myoblasts in congestive heart failure patients: the SEISMIC trial. EuroIntervention. 2011;6:805–12.

20 Duckers HJ, Houtgraaf J, van Geuns RJ, van Dalen BD, Regar E, van der Giessen W, et al. First-in-man experience with intracoronary infusion of adipose-derived regenerative cells in the treatment of patients with ST-elevation myocardial infarction: The Apollo trial. Circulation 2010;122:A12225 (abstr.)

21 Tomita S, Mickle DA, Weisel RD, Jia ZQ, Tumiati LC, Allidina Y, et al. Improved heart function with myogenesis and angiogenesis after auto-

logous porcine bone marrow stromal cell transplantation. J Thorac Cardiovasc Surg. 2002;123:1132–40.

22 Pittenger MF, Martin BJ. Mesenchymal stem cells and their potential as cardiac therapeutics. Circ Res. 2004;95:9–20.

23 Pijnappels DA, Schalij MJ, Ramkisoensing AA, van Tuyn J, de Vries AA, van der Laarse A, et al. Forced alignment of mesenchymal stem cells undergoing cardiomyogenic differentiation affects functional integration with cardiomyocyte cultures. Circ Res. 2008;103:167–76.

24 Psaltis PJ, Zannettino AC, Worthley SG, Gronthos S. Concise review: Mesenchymal stromal cells: Potential for cardiovascular repair. Stem Cells. 2008;26:2201–10.

25 Behfar A, Yamada S, Crespo-Diaz R, Nesbitt JJ, Rowe LA, Perez-Terzic C, et al. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. J Am Coll Cardiol. 2010;56:721–34.

26 Rose RA, Jiang H, Wang X, Helke S, Tsoporis JN, Gong N, et al. Bone marrow-derived mesenchymal stromal cells express cardiac specific markers, retain the stromal phenotype, and do not become functional cardiomyocytes in vitro. Stem Cells. 2008;26:2884–92.

27 Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation. 2002;105:93–8.

28 Makkar RR, Price MJ, Lill M, Frantzen M, Takizawa K, Kleisli T, et al. Intramyocardial injection of allogenic bone marrow-derived mesenchymal stem cells without immunosuppression preserves cardiac function in a porcine model of myocardial infarction. J Cardiovasc Pharmacol Ther. 2005;10:225–33.

29 Piao H, Youn TJ, Kwon JS, Kim YH, Bae JW, Bora-Sohn, et al. Effects of bone marrow derived mesenchymal stem cells transplantation in acutely infarcting myocardium. Eur J Heart Fail. 2005;7:730–8.

30 Noiseux N, Gnecchi M, Lopez-Ilasaca M, Zhang L, Solomon SD, Deb A, et al. Mesenchymal stem cells overexpressing Akt dramatically repair infarcted myocardium and improve cardiac function despite infrequent cellular fusion or differentiation. Mol Ther. 2006;14:840–50.

31 Schuleri KH, Amado LC, Boyle AJ, Centola M, Saliaris AP, Gutman MR, et al. Early improvement in cardiac tissue perfusion due to mesenchymal stem cells. Am J Physiol Heart Circ Physiol. 2008;294:H2002–11.

32 Halkos ME, Zhao ZQ, Kerendi F, Wang NP, Jiang R, Schmarkey LS, et al. Intravenous infusion of mesenchymal stem cells enhances regional perfusion and improves ventricular function in a porcine model of myocardial infarction. Basic Res Cardiol. 2008;103:525–36.

33 Krause U, Harter C, Seckinger A, Wolf D, Reinhard A, Bea F, et al. Intravenous delivery of autologous mesenchymal stem cells limits infarct size and improves left ventricular function in the infarcted porcine heart. Stem Cells Dev. 2007;16:31–7.

34 Carr CA, Stuckey DJ, Tatton L, Tyler DJ, Hale SJ, Sweeney D, et al. Bone marrow-derived stromal cells home to and remain in the infarcted rat heart but fail to improve function: an in vivo cine-MRI study. Am J Physiol Heart Circ Physiol. 2008;295:H533–42.

35 Gnecchi M, He H, Liang OD, Melo LG, Morello F, Mu H, et al. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. Nat Med. 2005;11:367–8.

36 Hatzistergos KE, Quevedo H, Oskouei BN, Hu Q, Feigenbaum GS, Margitich IS, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. Circ Res. 2010;107:913–22.

37 Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, 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;94:92–5.

38 Katritsis DG, Sotiropoulou PA, Karvouni E, Karabinos I, Korovesis S, Perez SA, et al. Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium. Catheter Cardiovasc Interv. 2005;65:321–9.

39 Chen S, Liu Z, Tian N, Zhang J, Yei F, Duan B, et al. Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. J Invas Cardiol. 2006;18:552–6.

40 Hare JM. Translational development of mesenchymal stem cell therapy for cardiovascular diseases. Tex Heart Inst J. 2009;36:145–7.

41 Zhuo Y, Li SH, Chen MS, Wu J, Kinkaid HY, Fazel S, et al. Aging impairs the angiogenic response to ischemic injury and the activity of implanted cells: combined consequences for cell therapy in older recipients. J Thorac Cardiovasc Surg. 2010;139:1286–94.

42 Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;100:3499–506.

43 Le Blanc K, Ringden O. Immunobiology of human mesenchymal stem cells and future use in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2005;11:321–34.

44 Liechty KW, MacKenzie TC, Shaaban AF, Radu A, Moseley AM, Deans R, et al. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. Nat Med. 2000;6:1282–6.

45 Yagi H, Soto-Gutierrez A, Parekkadan B, Kitagawa Y, Tompkins RG, Kobayashi N, et al. Mesenchymal stem cells: mechanisms of immunomodulation and homing. Cell Transplant. 2010;19:667–79.

46 Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood. 2005;105:1815–22.

47 Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood. 2002;99:3838–43.

48 Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol. 2002;30:42–8.

49 Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, et al.; Developmental Committee of the European Group for Blood and Marrow Transplantation. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet. 2008;371:1579–86.

50 Horwitz EM, Gordon PL, Koo WK, Marx JC, Neel MD, McNall RY, et al. Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: implications for cell therapy of bone. Proc Natl Acad Sci USA. 2002;99:8932–7.

51 Koc ON, Day J, Nieder M, Gerson SL, Lazarus HM, Krivit W. Allogeneic mesenchymal stem cell infusion for treatment of metachromatic leukodystrophy (MLD) and Hurler syndrome (MPS-IH). Bone Marrow Transplant. 2002;30:215–22.

52 Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut. 2010;59:1662–9.

53 Perico N, Casiraghi F, Introna M, Gotti E, Todeschini M, Cavinato RA, et al. Autologous mesenchymal stromal cells and kidney transplantation: A pilot study of safety and clinical feasibility. Clin J Am Soc Nephrol. 2011;6:412–22.

54 Chan JL, Tang KC, Patel AP, Bonilla LM, Pierobon N, Ponzio NM, et al. Antigen-presenting property of mesenchymal stem cells occurs during a narrow window at low levels of interferon-gamma. Blood. 2006;107:4817–24.

55 Huang XP, Sun Z, Miyagi Y, McDonald Kinkaid H, Zhang L, Weisel RD, et al. Differentiation of allogeneic mesenchymal stem cells induces immunogenicity and limits their long-term benefits for myocardial repair. Circulation. 2010;122:2419–29.

56 Eliopoulos N, Stagg J, Lejeune L, Pommey S, Galipeau J. Allogeneic marrow stromal cells are immune rejected by MHC class I- and class II-mismatched recipient mice. Blood. 2005;106:4057–65.

57 Nauta AJ, Westerhuis G, Kruisselbrink AB, Lurvink EG, Willemze R, Fibbe WE. Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting. Blood. 2006;108:2114–20.

58 Poncelet AJ, Vercruysse J, Saliez A, Gianello P. Although pig allogeneic mesenchymal stem cells are not immunogenic in vitro, intracardiac injection elicits an immune response in vivo. Transplantation. 2007;83:783–90.

59 Wolf D, Reinhard A, Seckinger A, Katus HA, Kuecherer H, Hansen A. Dose-dependent effects of intravenous allogeneic mesenchymal stem cells in the infarcted porcine heart. Stem Cells Dev. 2009;18:321–9.

60 Psaltis PJ, Carbone A, Nelson AJ, Lau DH, Jantzen T, Manavis J, et al. Reparative effects of allogeneic mesenchymal precursor cells delivered transendocardially in experimental nonischemic cardiomyopathy. JACC Cardiovasc Interv. 2010;3:974–83.

61 Amado LC, Saliaris AP, Schuleri KH, St John M, Xie JS, Cattaneo S,et al. Cardiac repair with intra-myocardial injection of allogeneic mesenchymal stem cells following myocardial infarction. Proc Natl Acad Sci USA. 2005;102:11474–9.

62 Quevedo HC, Hatzistergos KE, Oskouei BN, Feigenbaum GS, Rodriguez JE, Valdes D, et al. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. Proc Natl Acad Sci USA. 2009;106:14022–7.

63 Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol. 2009;54:2277–86.

64 Dib N, Henry T, DeMaria A, Itescu S, McCarthy MM, Jaggar SC, et al. The first US study to assess the feasibility and safety of endocardial delivery of allogenic mesenchymal precursor cells in patient with heart failure: Three-month interim analysis. Circulation. 2009;120:S810 (abstr.)