Challenges in the Translation of Cardiovascular Cell Therapy

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Ischemic cardiovascular diseases cause a significant burden of morbidity and mortality throughout the world. Over the past decade, we have learned a tremendous amount about the biology of various stem and progenitor cells. Multiple preclinical experiments have demonstrated significant bioactivity in a wide variety of stem and progenitor cells. Early clinical trials have also shown some promising results. This review will focus on the current challenges in the translation of cell therapy to a viable clinical therapy. Additionally, we will highlight the role of cardiovascular imaging and molecular imaging in the future of stem cell therapy.

Key Words: stem cell; progenitor cell; ischemic; cardiovascular disease; clinical trials

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Ischemic cardiovascular diseases are the number one cause of mortality in the United States and a major cause of morbidity and health-care use (*1*). There are many medical, percutaneous, and surgical therapies that are commonly used to treat patients with cardiovascular diseases; however, a substantial portion of patients continues to develop progressive deterioration marked by ongoing end organ dysfunction, worsening symptom burden, greater functional limitation, and increasing need for hospitalization. Despite multiple effective therapies for cardiovascular diseases, the rates of congestive heart failure are increasing (*2*), partly related to better treatments and increased survival for acute myocardial infarction, as well as an aging population. In addition, peripheral vascular disease continues to pose a significant problem, with limited medical therapies for relief of claudication, frequent need for multiple percutaneous and surgical treatments, and ongoing risk of amputation (*3,4*). Therefore, new therapies for ischemic cardiovascular diseases are desperately needed.

Stem cell biology has captivated the scientific community, particularly over the past decade. A wide variety of stem and progenitor cells, including adult bone marrow progenitor cells, endothelial progenitor or circulating progenitor cells, mesenchymal stem cells (MSCs), resident cardiac stem cells, and embryonic stem cells, have been shown to have bioactivity in preclinical studies and therefore hold promise for the treatment of end-stage cardiovascular diseases. Several of these types of stem cells have been tested in early-stage clinical trials. Although there remains much controversy about which cell type holds the most promise for clinical therapeutics and by what mechanism stem cells mediate a positive effect, there is some consensus that signals of bioactivity do exist, and further research should be able to answer these questions.

This review will focus on challenges to the translation of stem cell therapy into a viable clinical therapy for cardiovascular diseases. We have focused on cardiovascular diseases because several clinical trials have already been performed in this area and the challenges for translation in this area are likely applicable to other clinical situations in which stem cell therapies may provide benefit.

Currently, embryonic stem cell therapies are still in basic research phases and clinical translation will require addressing multiple significant hurdles, including potential risks of teratoma formation (*5*) and host immune response to allogeneic embryonic stem cells as well as ethical considerations about the source of embryonic stem cells. Induced pluripotent stem cells (reprogrammed differentiated somatic cells) are a focus of intense investigation and hold promise as a means to circumvent ethical and immunologic problems associated with embryonic stem cells. However, clinical translation of induced pluripotent stem cells will require addressing the risk of tumor and teratoma formation and the use of lentiviral or retroviral vectors for gene transfer in order to induce pluripotency (*6*). Because lentiviral and retroviral gene transfer is associated with insertional mutagenesis and malignant transformation (*7*), nonintegrating viral or nonviral methods to achieve induced pluripotency will likely be necessary before translation to human diseases can be considered (*8–10*). Adult, autologous stem cells, including bone marrow–derived progenitor cells, circulating progenitor cells, MSCs, resident cardiac progenitor cells, and skeletal myoblasts, have already been tested in early-phase clinical trials in humans or are currently being examined in clinical trials. Therefore, we will focus on adult, autologous

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progenitor cells that have been tested in clinical trials in our discussion of ongoing and future challenges to the translation of stem cell therapy.

SELECTED CLINICAL TRIALS OF STEM CELL THERAPY FOR CARDIOVASCULAR DISEASES

Several clinical trials have been conducted with various types of stem cells, different cell preparation and delivery methods, and varying clinical conditions. Interpretation of these studies requires careful attention to these variables and to clinical endpoints, control treatments, and other aspects of clinical trial design.

Bone Marrow Progenitor Cells

The bone marrow has been extensively studied as a model of stem cell biology because the hematopoietic system must regenerate cells continuously throughout the lifetime of an organism. The idea that the bone marrow contained progenitor cells that could differentiate into cardiac cell types was first introduced in 2001 (*11,12*). Since then, an intense debate has raged on whether bone marrow–derived cells can differentiate into cardiac cell types (*13,14*). It appears that some of the benefit noted in preclinical models is likely a result of paracrine effects, that is, factors secreted by bone marrow–derived progenitor cells that have beneficial effects on the resident cardiac cells (*15–17*). It seems likely that bone marrow–derived progenitor cells may provide clinical benefit for patients with cardiovascular diseases through multiple mechanisms.

Several studies have assessed the therapeutic safety and efficacy of autologous bone marrow for treatment of acute myocardial infarction (*18–20*) and remote myocardial infarction (*21*). These studies used an intracoronary delivery method. In general, intracoronary autologous bone marrow cell therapy for acute myocardial infarction has resulted in a statistically significant improvement in ejection fraction, compared with control treatment (*22*).

Further reports of these randomized controlled trials have provided insights into mechanisms of benefit and subpopulations that may derive greater benefit. An intracoronary Doppler substudy of the REPAIR-AMI trial demonstrated that coronary flow reserve was significantly increased at 4 mo in infarct arteries treated with bone marrow–derived progenitor cells versus placebo (*23*). This study provides evidence of repair of the microvasculature with bone marrow–derived progenitor cell therapy after acute myocardial infarction. A small cardiac MRI substudy of the same trial demonstrated trends toward improved ejection fraction and reduced adverse remodeling with bone marrow–derived progenitor cells, compared with placebo (*24*). The improvement in ejection fraction was greater and statistically significant among patients with baseline ejection fraction less than median (median ejection fraction, 48.9%), suggesting greater benefit in patients with larger myocardial infarctions and worse initial left ventricular function.

Circulating Progenitor Cells

The presence of bone marrow–derived circulating endothelial progenitor cells was first demonstrated by Asahara et al. (*25*). This finding revolutionized the concept of neovascularization by postulating that in addition to vessel wall endothelial cells, bone marrow–derived circulating progenitor cells participate in blood vessel growth, maintenance, and repair.

As an alternative to bone marrow progenitor cells, mobilized peripheral blood progenitor cells may provide a more accessible and feasible source for autologous stem cell therapies. Stem cells can be mobilized from bone marrow niches with cytokines such as granulocyte colony-stimulating factor or with newer agents such as plerixafor (Mobozil [Genzyme]; also known as AMD3100). Circulating progenitor cells can then be collected through leukapheresis. This process is already used for collection of hematopoietic stem cells for transplantation after chemotherapy or radiation-induced bone marrow ablation.

This approach was used for collection of CD34+ circulating progenitor cells to test their efficacy and safety in patients with chronic angina. After granulocyte colony-stimulating factor mobilization, leukapheresis, and CD34+ cell enrichment, CD34+ progenitor cells were delivered into ischemic but viable territories via intramyocardial injections guided by a percutaneous 3-dimensional electromechanical mapping and navigation system (NOGA; Biologic Delivery Systems) (*26*). In this phase I study, early evidence of feasibility was provided and endpoints such as angina frequency and exercise time showed a trend toward benefit with CD34+ cell therapy. A larger phase II study has been completed and was presented at the American College of Cardiology 2009 meeting. These results showed significant increases in exercise time and reduction in angina frequency.

MSCs

MSCs are multipotent stromal cells found in bone marrow, adipose tissue, umbilical cord blood, and other tissues. MSCs have been shown to have antiinflammatory and antiapoptotic properties, as well as proangiogenic effects via paracrine mechanisms (*27*). Their immunomodulatory properties have raised the possibility of using allogeneic MSCs as an "off-the-shelf" treatment, potentially avoiding the cell procurement and ex vivo culture systems that are often used for autologous stem cell treatments. However, the extent of in vivo immune tolerance is controversial (*28,29*), and the effect of allogeneic MSCs in humans will have to be determined with clinical trials. Both allogeneic and autologous MSCs are currently being tested in clinical trials for patients with cardiovascular diseases. A recent report of a phase I, placebo-controlled, randomized, double-blinded trial of intravenous allogeneic MSCs for patients with acute myocardial infarction demonstrated safety and efficacy in some endpoints (*30*).

Resident Cardiac Stem Cells

Although the human heart has long been thought to be a postmitotic organ, recent investigations have shown that

a rare pool of resident cardiac stem cells has the capacity to form new cardiomyocytes and other cardiac cell types (*31*). Under baseline conditions, the rate of cardiomyocyte turnover is estimated to be 1%−2% per year (*32*). Cardiac stem cells have been isolated from endomyocardial tissue biopsies and then were expanded ex vivo in a culture system (*33–35*). Culture-expanded cardiac stem cells are now being tested in a clinical trial for patients with ischemic cardiomyopathy (Clinical Trials.gov identifiers NCT00474461 and NCT00893360).

Skeletal Myoblasts

Adult mammalian skeletal muscle contains resident stem cells called satellite cells that are normally quiescent but can differentiate to myoblasts after muscle injury or stress and mediate skeletal muscle repair. Skeletal myoblasts can be obtained from muscle biopsy specimens and expanding ex vivo in-culture systems and have been demonstrated to have bioactivity for repair of myocardial injury in preclinical models (*36,37*). Skeletal myoblasts have been tested in several phase 1 clinical trials. In addition, they were tested in the phase II Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) clinical trial that enrolled patients with ischemic cardiomyopathy who had an indication for coronary artery bypass grafting. A muscle biopsy was initially performed, followed by ex vivo culture expansion of myoblasts for 3 wk, and then injection of treatments at the time of cardiac surgery. This study did not find a significant improvement in left ventricular systolic function as determined by echocardiography, although the high-dose myoblast group had a significant decrease in left ventricular volumes, compared with the placebo group. Earlier studies had raised the possibility that skeletal myoblasts may be proarrythmic (*38*). Although the MAGIC study did not find a statistically significant increase in arrhythmic events, many of the patients were prophylactically treated with amiodarone and the number of arrhythmic events was higher in myoblast-treated patients than in control patients.

CHALLENGES FOR TRANSLATION

Although these early clinical trials have established an acceptable safety profile for adult, autologous stem cells and some evidence of efficacy, they have also identified ongoing challenges to translation. At a scientific level, these challenges include decreased cell viability and function in the hostile ischemic tissue environment, poor cell retention in the target tissue, and controversy over the mechanism of action. In addition, various stem cell types and methods of cell delivery have not been definitively compared in head-to-head comparisons. From a clinical trial viewpoint, the challenges include application of stem cell technologies to end-stage or "no-option" patient populations with many years of disease processes and multiple comorbidities that could limit the efficacy of stem cell therapies. Additionally, clinical trial design with appropriate endpoint selection remains challenging in certain cases. Many trials have used surrogate endpoints such as ejection fraction, perfusion measured by SPECT, or exercise treadmill time. Ejection fraction measured by echocardiogram is a rough estimate of overall left ventricular function and may not be sensitive enough to detect a true biologic effect of stem cell therapy. Likewise, SPECT may lack sensitivity to detect local angiogenesis. Endpoints such as exercise treadmill time have significant variability (*39*) and are subject to placebo effect.

Tracking Cell Fate

Multiple imaging techniques have been used to address the question of cell fate and cell retention in the target tissue. In preclinical studies, β-galactosidase, green fluorescent protein, luciferase, and sex-mismatched cells have been used to track the transplanted cells and determine their location and fate after cell therapy. Compared with histologic techniques, the use of bioluminescence imaging to track cell fate has the advantage of requiring cell viability in order to produce the luciferase enzyme, as well as the advantage of being a noninvasive imaging method that can be assessed at multiple time points (Fig. 1).

The ability to label and track stem cells in humans would provide a method to answer some of the ongoing controversies in the field. A safe, noninvasive, and repeatable imaging modality that could identify injected stem cells would be able to answer questions about cell viability and retention in future clinical trials of stem cell therapies, as well as provide the ability to adjust the assessment of bioactivity on the basis of actual delivered doses of cells.

One method to track transplanted stem cells involves cellular uptake of superparamagnetic iron oxide particles and detection by MRI. This method has been used in several preclinical studies of stem cell therapies; however, it was recently noted that inflammatory cells can phagocytose the iron oxide particles after the transplanted cells die, thereby causing an overestimation of the true survival of the transplanted cells (*40,41*). In addition to iron oxide particles, gadolinium chelates can be taken up by cells and used for MRI detection. The major clinical limitation of using cardiac MRI to detect labeled stem cells is that cardiomyopathy patients are a major target for these therapies and often have implantable cardioverter-defibrillators.

Radionuclide imaging with either SPECT or PET can also be applied for cell tracking. Cells can be incubated with radioisotopes, and a high degree of cellular uptake has been demonstrated. However, the short half-life of most radioisotopes would prevent serial imaging at later time points, and there are concerns about possible toxicity to the stem cells from the radioisotope (*42*). In addition, reporter genes for PET and SPECT have been tested in preclinical models (*5,43*). This approach involves transfecting stem cells to express a particular reporter gene that allows for specific expression or uptake of the imaging agent.

Imaging Endpoints in Clinical Trials

Another area in which imaging technologies can help surmount challenges in translation is clinical trial endpoints.

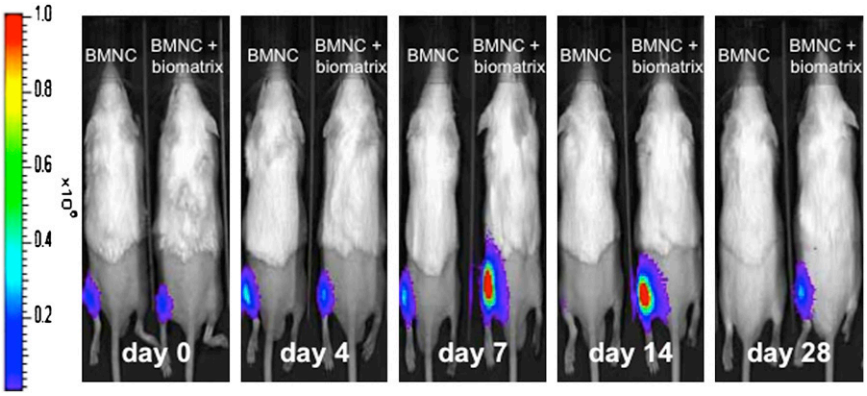

FIGURE 1. Use of bioluminescence imaging to track injected bone marrow mononuclear cells (BMNCs) in vivo. BMNCs were obtained from β-actin-luc mice, which ubiquitously express firefly luciferase gene under control of constitutive β-actin promoter. Either BMNCs alone or BMNCs with specific biomatrix designed to enhance cell fate were transcutaneously injected into limb muscle. Cell fate was serially and noninvasively tracked by measurement of luminescence emission in response to systemic luciferin injection. Serial imaging demonstrates prolonged presence of BMNCs after local application with addition of biomatrix. (Courtesy of Joern Tongers, Feinberg Cardiovascular Research Institute, Northwestern University, and Department of Cardiology, Hannover University Medical School.)

Traditional endpoints in cell therapy clinical trials for myocardial infarction or heart failure have been either ejection fraction determined by echocardiogram or perfusion measured by SPECT. As discussed earlier, these imaging technologies and endpoints have several limitations. Newer imaging techniques such as cardiac MRI and PET may serve as more sensitive and accurate imaging endpoints. In addition to ejection fraction, cardiac MRI would allow for more accurate determination of left ventricular dimensions, as well as infarct size and change in infarct size over time. Both cardiac MRI and PET can be used to measure absolute perfusion (*44,45*). This may provide an advantage over the relative perfusion offered by SPECT and may allow for a more exact determination of changes in perfusion after stem cell therapies (Fig. 2).

Molecular Imaging

Molecular imaging may provide a more tailored method of evaluating stem cell therapies. Recent studies have demonstrated that it is possible to specifically image neovascularization (*46,47*).

If a reproducible measure of neovascularization could be developed, proof-of-concept studies with fewer human subjects could be performed before further development of an investigational agent. This would address some of the inherent differences between preclinical models and clinical situations in which stem cell therapy may be applied by providing early evidence of bioactivity in humans.

In addition, a reproducible, noninvasive measure of neovascularization would allow for finding the appropriate dose in early-phase clinical studies. Currently, doses for cell therapy strategies are based largely on preclinical studies,

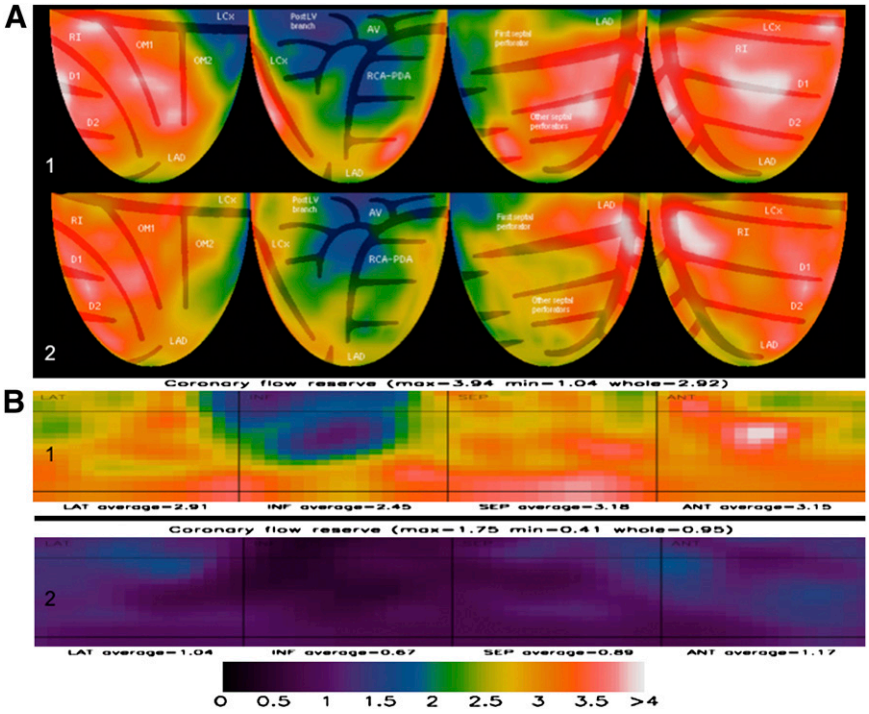

FIGURE 2. Differences between PET of relative and absolute coronary perfusion after adenosine infusion. (A) Stress imaging of relative perfusion for patients 1 and 2 demonstrates similar perfusion defects. Both have decreased perfusion in mid and basal inferior walls. (B) Coronary flow reserve based on absolute flow in mL/min/g demonstrates 2 different patterns. Patient 1 has focal defect in inferior wall, whereas patient 2 has global hypoperfusion consistent with physiology of triple-vessel coronary artery disease. Coronary angiography demonstrated occluded RCA in patient 1 and occluded RCA with severe, diffuse CAD in patient 2. ANT = anterior; AV = atrioventricular node; D = diagonal; INF = inferior; LAD = left anterior descending; LAT = lateral; LCx = left circumflex; OM = obtuse marginal; RCA-PDA = right coronary artery–posterior descending artery; RI = ramus intermedius; SEP = septal. (Reprinted with permission of (*51*).)

with extrapolation from animal models to humans. Traditional metrics used in the early development of pharmaceuticals such as absorption, distribution, metabolism, and elimination are not applicable to cell therapy. The ability to measure neovascularization in humans would allow for more accurate phase I dose-finding studies and progression to phase II studies with a more fundamental understanding of appropriate dosing.

Biomaterials and Cellular Microenvironment

In addition to imaging applications, molecular tools may also be used to improve the efficacy of stem cell therapies. One major area of difficulty is low cell retention in target tissues and low cell survival. Multiple studies have demonstrated low numbers of transplanted cells in target tissues after a few weeks (*48,49*). By providing a method for cell retention and trophic signals that can increase cell survival, biomaterials may be able to address both limitations. Recent work in nanomaterials has led to synthesis of peptide amphiphiles expressing specific epitopes that provide biofunctionality (*50*). These biomaterials were shown to support stem cell function and increase cell retention in preclinical models.

CONCLUSION

In the last decade, stem cell biology has developed rapidly. The idea of repairing the damaged heart has moved from a fantasy to a reality as many types of stem cells have been tested in preclinical studies and in clinical trials for patients with cardiovascular diseases. The results from these early clinical trials have demonstrated a good safety record and evidence of efficacy. They have also pointed out the challenges that will have to be surmounted for stem cell therapies to be translated into a viable option for patients with cardiovascular diseases. These ongoing challenges can be addressed with innovative preclinical studies and clinical trials involving iterative feedback between these 2 stages of investigation. Imaging technologies and molecular imaging will also help to address some ongoing controversies in the field. Biomaterials may be able to increase cell retention and viability. In summary, the first phase of development of adult, autologous stem cell therapies for cardiovascular diseases has identified successes and ongoing challenges. It is hoped that the next phase of development will surmount these challenges and move this promising new strategy closer to translation into a viable treatment for patients with cardiovascular diseases.

REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics: 2009 update—a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119:480–486.
2. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol.* 2008;52:428–434.
3. Feinglass J, Sohn MW, Rodriguez H, Martin GJ, Pearce WH. Perioperative outcomes and amputation-free survival after lower extremity bypass surgery in California hospitals, 1996-1999, with follow-up through 2004. *J Vasc Surg.* 2009;50:776–783.e.1.
4. Taylor SM, Kalbaugh CA, Blackhurst DW, Kellicut DC, Langan EM III, Youkey JR. A comparison of percutaneous transluminal angioplasty versus amputation for critical limb ischemia in patients unsuitable for open surgery. *J Vasc Surg.* 2007;45:304–310.
5. Cao F, Lin S, Xie X, et al. In vivo visualization of embryonic stem cell survival, proliferation, and migration after cardiac delivery. *Circulation.* 2006;113:1005–1014.
6. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell.* 2006;126:663–676.
7. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science.* 2003;302:415–419.
8. Stadtfeld M, Nagaya M, Utikal J, Weir G, Hochedlinger K. Induced pluripotent stem cells generated without viral integration. *Science.* 2008;322:945–949.
9. Gonzalez F, Barragan Monasterio M, Tiscornia G, et al. Generation of mouse-induced pluripotent stem cells by transient expression of a single nonviral polycistronic vector. *Proc Natl Acad Sci USA.* 2009;106:8918–8922.
10. Lyssiotis CA, Foreman RK, Staerk J, et al. Reprogramming of murine fibroblasts to induced pluripotent stem cells with chemical complementation of Klf4. *Proc Natl Acad Sci USA.* 2009;106:8912–8917.
11. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature.* 2001;410:701–705.
12. Jackson KA, Majka SM, Wang H, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. *J Clin Invest.* 2001;107:1395–1402.
13. Murry CE, Soonpaa MH, Reinecke H, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature.* 2004;428:664–668.
14. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature.* 2004;428:668–673.
15. Gnecchi M, He H, Liang OD, et al. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. *Nat Med.* 2005;11:367–368.
16. Capoccia BJ, Shepherd RM, Link DC. G-CSF and AMD3100 mobilize monocytes into the blood that stimulate angiogenesis in vivo through a paracrine mechanism. *Blood.* 2006;108:2438–2445.
17. Gnecchi M, He H, Noiseux N, et al. Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. *FASEB J.* 2006;20:661–669.
18. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med.* 2006;355:1210–1221.
19. Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med.* 2006;355:1199–1209.
20. Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet.* 2006;367:113–121.
21. Assmus B, Honold J, Schachinger V, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med.* 2006;355:1222–1232.
22. Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med.* 2007;167:989–997.
23. Erbs S, Linke A, Schachinger V, et al. Restoration of microvascular function in the infarct-related artery by intracoronary transplantation of bone marrow progenitor cells in patients with acute myocardial infarction: the Doppler Substudy of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. *Circulation.* 2007;116:366–374.
24. Dill T, Schachinger V, Rolf A, et al. Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging substudy. *Am Heart J.* 2009;157:541–547.
25. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997;275:964–967.
26. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation.* 2007;115:3165–3172.
27. Pittenger MF, Martin BJ. Mesenchymal stem cells and their potential as cardiac therapeutics. *Circ Res.* 2004;95:9–20.
28. Amado LC, Saliaris AP, Schuleri KH, et al. Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. *Proc Natl Acad Sci USA.* 2005;102:11474–11479.

29. 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;83:783–790.
30. Hare JM, Traverse JH, Henry TD, 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;54:2277–2286.
31. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell.* 2003;114:763–776.
32. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science.* 2009;324:98–102.
33. Bearzi C, Rota M, Hosoda T, et al. Human cardiac stem cells. *Proc Natl Acad Sci USA.* 2007;104:14068–14073.
34. Smith RR, Barile L, Cho HC, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. *Circulation.* 2007;115:896–908.
35. Johnston PV, Sasano T, Mills K, et al. Engraftment, differentiation, and functional benefits of autologous cardiosphere-derived cells in porcine ischemic cardiomyopathy. *Circulation.* 2009;120:1075–1083, 7 p following 1083.
36. Murry CE, Wiseman RW, Schwartz SM, Hauschka SD. Skeletal myoblast transplantation for repair of myocardial necrosis. *J Clin Invest.* 1996;98:2512–2523.
37. Taylor DA, Atkins BZ, Hungspreugs P, et al. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med.* 1998;4:929–933.
38. Menasche P, Hagege AA, Vilquin JT, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol.* 2003;41:1078–1083.
39. Perakyla T, Tikkanen H, von Knorring J, Lepantalo M. Poor reproducibility of exercise test in assessment of claudication. *Clin Physiol.* 1998;18:187–193.
40. Amsalem Y, Mardor Y, Feinberg MS, et al. Iron-oxide labeling and outcome of transplanted mesenchymal stem cells in the infarcted myocardium. *Circulation.* 2007;116:I38–I45.
41. Terrovitis J, Stuber M, Youssef A, et al. Magnetic resonance imaging overestimates ferumoxide-labeled stem cell survival after transplantation in the heart. *Circulation.* 2008;117:1555–1562.
42. Brenner W, Aicher A, Eckey T, et al. ^{111}In-labeled CD34+ hematopoietic progenitor cells in a rat myocardial infarction model. *J Nucl Med.* 2004;45:512–518.
43. Terrovitis J, Kwok KF, Lautamaki R, et al. Ectopic expression of the sodium-iodide symporter enables imaging of transplanted cardiac stem cells in vivo by single-photon emission computed tomography or positron emission tomography. *J Am Coll Cardiol.* 2008;52:1652–1660.
44. Lee DC, Johnson NP. Quantification of absolute myocardial blood flow by magnetic resonance perfusion imaging. *JACC Cardiovasc Imaging.* 2009;2:761–770.
45. Schepis T, Gaemperli O, Treyer V, et al. Absolute quantification of myocardial blood flow with ^{13}N-ammonia and 3-dimensional PET. *J Nucl Med.* 2007;48:1783–1789.
46. Meoli DF, Sadeghi MM, Krassilnikova S, et al. Noninvasive imaging of myocardial angiogenesis following experimental myocardial infarction. *J Clin Invest.* 2004;113:1684–1691.
47. Johnson LL, Schofield L, Donahay T, Bouchard M, Poppas A, Haubner R. Radiolabeled arginine-glycine-aspartic acid peptides to image angiogenesis in swine model of hibernating myocardium. *JACC Cardiovasc Imaging.* 2008;1:500–510.
48. Barbash IM, Chouraqui P, Baron J, et al. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation.* 2003;108:863–868.
49. Hofmann M, Wollert KC, Meyer GP, et al. Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation.* 2005;111:2198–2202.
50. Webber MJ, Tongers J, Renault MA, Roncalli JG, Losordo DW, Stupp SI. Development of bioactive peptide amphiphiles for therapeutic cell delivery. *Acta Biomater.* 2010;6:3–11.
51. Gould KL. Does coronary flow trump coronary anatomy? *JACC Cardiovasc Imaging.* 2009;2:1009–1023.

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