Recent Developments in Cardiovascular Research: The goal of "Recent Developments" is to provide a concise but comprehensive overview of new advances in cardiovascular research, which we hope will keep our readers abreast of recent scientific discoveries and facilitate discussion, interpretation, and integration of the findings. This will enable readers who are not experts in a particular field to grasp the significance and effect of work performed in other fields. It is our hope and expectation that these "Recent Development" articles will help readers to gain a broader awareness and a deeper understanding of the status of research across the vast landscape of cardiovascular research—*The Editors*.

Recent Developments in Cardiovascular Stem Cells

Rosalinda Madonna, Peter Ferdinandy, Raffaele De Caterina, James T. Willerson, Ali J. Marian

Heart failure, a common consequence of ischemic heart disease, is a major cause of morbidity and mortality in the world.[1–3] Pharmacological treatment with β-blockers and inhibitors of the renin–angiotensin–aldosterone system has improved the clinical outcomes in patients with heart failure.[4–7] Likewise, mechanical unloading with left ventricular assist devices and resynchronization therapy have led to partial reversal of cardiac structural and molecular remodeling and symptomatic improvement.[8–10] Despite these remarkable advances, however, mortality and morbidity of patients with heart failure, with or without reduced ejection fraction remains high.[1,2] Moreover, heart transplantation, while an effective option, is available only for a selected number of patients and is not without considerable negative consequences.[11] Furthermore, gene therapy still remains in early investigational stages and not yet ready for clinical applications.[12] The high residual mortality and morbidity of patients with heart failure might be inherent to the shortcomings of the current therapeutic approaches, as none directly targets the underlying causal problem in heart failure, that is, loss of or intrinsically dysfunctional myocytes. Consequently, novel therapeutic approaches are necessary to further improve the clinical outcomes in patients with heart failure.

The heart is considered, by and large, a terminally differentiated organ with a limited intrinsic regenerative capacity that alone is insufficient to compensate for the pathological loss of cardiac myocytes during the postnatal period.[13–15] The discovery of cardiac progenitor cells (CPCs) in the heart more than a decade ago along with the recent data showing that the existing myocytes undergo a gradual turnover have raised the potentials for regenerative cardiac repair.[16,17] Likewise, the discovery of mesenchymal stem cells (MSCs), which was thought to have the potential to differentiate to cardiac myocytes, but yet to proven, or enhance differentiation of the endogenous cardiac stem cells has offered a cell transplantation approach for regenerative cardiac repair.[18–20] Furthermore, advances in generation and characterization of cardiac myocytes from induced pluripotent stem cells using the Yamanaka factors or a combination thereof, have expanded the therapeutic options for cardiac repair.[21–24] In addition, direct reprogramming of the resident fibroblasts to myocytes, whether using a defined set of transcription factors or microRNAs, has further advanced the field of regenerative cardiac repair.[25–28] Finally, combination of different cell types has been used to gain additive and synergistic effects.[29] Recent advances have offered considerable insight into molecular biology, self-renewal, and differentiation cardiac stem cells, as well as phenotypic characteristics that are would be expected to offer clinical applications.[30–37]

The potential use of stem cells in repairing injured myocardium and improving heart failure has raised considered excitement in patients, physicians, and researchers alike.[38] The field, however, is in infancy and faces considerable challenges in attaining its goal of repairing the damaged myocardium and restoring cardiac function in ischemic heart disease (Table 1). Even the identity of the resident CPCs remains unsettled.[39–43] Resident cells expressing the c-kit antigen but not markers of the hematopoietic or mast cells are considered bona fide CPCs sufficient and necessary to repair the damaged myocardium.[40,44] And yet, genetic fate mapping experiments have shown minimal contribution of the c-kit$^+$ cells to cardiac myogenesis.[45] Human embryonic stem cells have been shown to differentiate to beating cardiomyocytes, SA nodal-like cells and mesodermal

Original received November 4, 2014; revision received November 4, 2014; accepted November 5, 2014.

From the Center of Excellence on Aging, Institute of Cardiology, Department of Neuroscience and Imaging, "G. d'Annunzio" University, Chieti, Italy (R.M., R.D.C.); Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary (P.F.); Pharmahungary Group, Szeged, Hungary (P.F.); Texas Heart Institute, Houston (R.M., J.T.W.); Division of Cardiology, Department of Internal Medicine (R.M., J.T.W., A.J.M.), and Institute of Molecular Medicine, The University of Texas Health Science Center, Houston (A.J.M.).

Correspondence to Ali J. Marian, MD, Institute of Molecular Medicine, The University of Texas Health Science Center, Center for Cardiovascular Genetics, 6770 Bertner St, DAC900, Houston, TX 77030. E-mail Ali.J.Marian@uth.tmc.edu

(*Circ Res*. 2014;115:e71-e78.)

Circulation Research **is available at http://circres.ahajournals.org** **DOI: 10.1161/CIRCRESAHA.114.305567**

Nonstandard Abbreviations and Acronyms	
CPC	cardiac progenitor cell
MSC	mesenchymal stem cell

cells.[46–49] However, their clinical use is overshadowed by the occurrence of serious cardiac arrhythmias in the transplanted animals, likely because of poor electromechanical coupling of the injected cells with the host cells.[50] Moreover, the use of induced pluripotent stem cell–derived cardiac myocytes for cardiac repair is hampered by their immature phenotype and the presence of epigenetic and genetic changes.[24,51,52] Resident and bone marrow cells and cortical bone–derived cells are considered as potential sources for differentiation to cardiac myocytes but lacking compelling evidence for cardiac myogenesis and perhaps exerting their salutary biological effects through paracrine mechanisms.[19,29,53–58] Equally exciting and challenging are the discovery and characterization of other CPCs that could give raise to various cardiac cells types, including smooth muscle cells, endothelial cells, and fibroblasts.[59–63] An important problem to overcome is the multiple comorbidities and their comedications of ischemic heart disease patients with heart failure that may affect cytoprotective signaling triggered by the different stem cell, as well as survival and differentiation properties of such stem cells in the injured tissue.[64–66] Clearly, the rapid face of discoveries is dazzling and a complete coverage of the recent developments in cardiovascular stem cells would be beyond the scope of this article. We regret that many valuable works were not covered in part or at all included in the present overview on Recent Developments.

Table 1. Some of the Challenges Facing Clinical Use of Myocardial Regeneration

1. Does postnatal heart contain bona fide stem cells that could regenerate cardiac myocytes?
2. What are the characteristics and markers of bona fide cardiomyogenic stem cells?
3. How to provoke controlled proliferation and differentiation of bona fide cardiomyogenic stem cells to mature cardiac myocytes?
4. What are the determinants—transcription factors, noncoding RNA and others—of differentiation of bona fide cardiomyogenic stem cells to mature myocytes?
5. How to reduce or eliminate aging of the bona fide cardiac stem cells and enhance their survival under pathological conditions?
6. How to enhance differentiation of other resident progenitor cells to mature cardiac myocytes?
7. How to enhance recruitment and retention of the circulating progenitor cells to the heart and enhance their differentiation to mature myocytes?
8. Which type of progenitor cells to inject or implant in the myocardium to obtain most efficient differentiation to mature cardiac myocytes?
9. How to enhance engraftment of injected/implanted progenitor cells in the myocardium?
10. How to reduce or eliminate antigenicity of the progenitor cells into the myocardium, and reduce or eliminate rejection?
11. How to enhance survival of the injected/implanted cells in the heart?
12. How to enhance cell–cell communications and electromechanical coupling among the transplanted cells as well as among the transplanted and the host cells?
13. How to generate induced pluripotent stem cell–derived cardiomyocytes with molecular and phenotypic characteristics closer to mature cardiac myocytes?
14. Is the recovery of myocardial function because of myocardiogenesis or secondary to expression and secretion of paracrine factors? And if the latter, what are these paracrine factors and how to garner their effects to enhance cardiomyogenesis?

Clinical Trials In Human Patients

The ClinicalTrials.gov lists >1000 clinical trials including >600 studies in the United States alone that tests effects of various stem cells in human patients (http://www.clinicaltrials.gov/). The list includes 71 including 38 active clinical trials in patients with heart failure using various stem cells, such as adipose-derived, mesenchymal, human embryonic, autologous $CD133^+$ and $CD34^+$ stem cells among the others.[18,67–74] Autologous skeletal myoblasts were probably the first cell type used to regenerate functional myocardium. It was tested initially in a rabbit model of myocardial cryoinjury, which showed incorporation of the injected myoblasts and improved myocardial performance.[75] Subsequent observational studies were followed by randomized clinical trials in human patients with heart failure injected with autologous skeletal myoblasts. The results in small size studies were somewhat promising.[18,76–78] However, despite the encouraging results in small and observational studies, the overall results of larger clinical studies have not been impressive but rather null. Given the risk of cardiac arrhythmias associated with injection of myoblasts and the availability of other cell types, autologous skeletal myoblasts are not considered the prime cell type for heart failure therapy.

To date, the initial results of clinical trials with cardiac stem cells have been mostly promising, although they remain inconclusive in terms of long-term effects and often contradictory. The findings of REPAIR-AMI trial showed that intracoronary delivery of bone marrow cells in patients with acute myocardial infarction improved cardiac function, which were preserved >2 years.[79] In contrast, the BOOST trial, which was similarly constructed, showed only an initial improvement with little sustained effect over the 18-month and 5-year follow-up periods.[80] The differences in the outcome might reflect differences in the study population characteristics and subtleties of the experimental design including preparation and characterization of the bone marrow–derived cells. Likewise, the mechanisms responsible for the beneficial effects of exogenously applied stem cells remain unclear, as data to show fate, function, and differentiation of the injected cells to cardiac myocytes, as well as production and secretion of paracrine factors are lacking. Two recent clinical trials SCIPIO and CADUCEUS, which used 2 different sets of CPCs, reported improved cardiac function.[81,82] In both trials, the underlying mechanism(s) responsible for improved clinical outcomes remains to be determined but is speculated to be secondary to expression and secretion of paracrine factors rather than direct differentiation of the injected progenitor cells to cardiac myocytes. Paracrine factors released from the injected CPCs might direct manyrestorative processes, including myocardial protection, neovascularization, and cardiac remodeling.[83] Consequently, there is considerable interest in identification and characterization of secretome of the CPCs for therapeutic gains. For

example, fibroblast growth factor 9, which is secreted from bone marrow cells, has been shown to promote myocardial vascularization and myocytes hypertrophy, preserves cardiac function, and reduce mortality in an experimental model of myocardial infarction.[84] Fibroblast growth factor signaling is also implicated in suppression of autophagy and prevention of premature differentiation of CPCs.[85] It is anticipated that several paracrine factors contribute to improvement in cardiovascular function in clinical trials of cardiac stem cells. Overall, the results of the clinical trials performed to date have been less than spectacular, despite the plausible rationale, which raises the necessity of novel approaches. Table 2 provides a partial summary of the published clinical trials of patients with heart failure using various types of progenitor cells.

Rejuvenation of Cardiac Stem Cells

Stem cells are not exempt from senescence.[100,101] As a result, resident cardiac stem/progenitor cells in older humans are expected to have a decreased reparative capacity in response to myocardial injury. Consequently, there is considerable interest in rejuvenating the endogenous CPCs.[102] Several molecules are implicated in rejuvenation of CPCs, including Pim-1 kinase, NOTCH1 signaling, and telomerase, just to name a few. Pim-1 kinase has been shown to impart antisenescence and antiapoptotic effects in CPCs, as well as in MSCs.[103–107] Genetic modification of aged human CPCs with Pim-1 kinase results in remarkable rejuvenation of the CPCs associated with enhanced proliferation, increased telomere lengths, and decreased susceptibility to replicative senescence.[104,105] Likewise, activation of NOTCH1 signaling pathway is implicated in rejuvenation of myogenic responses to satellite muscle cells.[108] Activation of telomere–telomerase axis is known to contribute to cell survival and proliferation, and to prevent cellular senescence.[109] Madonna et al[109] recently identified a subpopulation of adipose tissue–derived MSCs that expresses high levels of myocardin (MYOCD), a nuclear transcription cofactor for myogenic genes, and telomerase reverse transcriptase, the catalytic subunit of telomerase. Adipose tissue-mesenchymal stem cells

Table 2. A Partial Summary of Controlled Clinical Trials of Stem Cell Delivery in Ischemic Heart Disease

Cell Type	Study Design	Route of Administration	Sample Size	Number of Cells	Follow Up	Outcome
Skeletal myoblasts	Nonrandomized	Transendocardial	Treated: 6; Controls: 6	$210\pm150\times10^6$	12 mo	Improved LVEF and walking distance[86]
Skeletal myoblasts	Nonrandomized	Intramyocardial	Treated: 12; Controls: 14	5×10^6	12 mo	Improved myocardial viability, reperfusion, and function[87]
Skeletal myoblasts	Nonrandomized	Transendocardial	Treated: 14; Controls: 28	$3\pm50\times10^6$	4 y	No benefits, increased risk of arrhythmias[88]
Skeletal myoblasts	Randomized	Intramyocardial	Treated: 97; Controls: 30	$400–800\times10^6$	6 mo	Improved cardiac function[77]
Skeletal myoblasts	Double-blind randomized	Transendocardial	Treated: 12; Controls: 11	$30–600\times10^6$	12 mo	Improved myocardial viability and function[89]
BM-MNC	Double-blind Nonrandomized	Transendocardial	Treated: 14; Controls: 7	$25.6\pm6.3\times10^6$	4 mo	Improved myocardial function and perfusion[67]
BM-MNC	Open-label randomized	Intracoronary	Treated: 52; Controls: 23	$205\pm110\times10^6$	3 mo	Improved myocardial function[90]
BM-MNC	Randomized	Intramyocardial	Treated: 10; Controls: 10	$60\pm31\times10^6$	4 mo	Improved regional but not global cardiac function[91]
BM-MNC	Randomized	Intracoronary	Treated: 14; Controls: 14	$20–32\times10^6$	3 mo	Improved myocardial viability and function[92]
BM-MNC	Randomized single-blind	Intracoronary	Treated: 24; Controls: 23	12×10^6	6 mo	Improved diastolic function[93]
BM-MNC	Randomized single-blind	Intramyocardial	Treated: 42; Controls: 23	$84–56\times10^6$	6 mo	No effects on infract size or cardiac function[94]
BM-MNC	Randomized double-blind	Transendocardial	Treated: 20; Controls: 10	30×10^6	6 mo	Symptomatic improvement[95]
BM-PC	Randomized double-blind	Intramyocardial	Treated: 10; Controls: 10	22×10^6	6 mo	Improved cardiac function[96]
BM-PC	Nonrandomized double-blind	Intramyocardial	Treated: 20; Controls: 20	5.8×10^6	6 mo	Improved cardiac function[97]
BM-PC	Randomized double-blind	Intracoronary	Treated: 28; Controls: 27	123×10^6	12 mo	Improved cardiac function, exercise tolerance, and reduced mortality[98]
$CD34^+$	Randomized double-blind	Intracoronary	Treated: 55; Controls: 55	$113\pm26\times10^6$	5 y	Improved cardiac function, exercise tolerance, and survival[74]
CSCs	Randomized open-label	Intracoronary	Treated: 16; Controls: 7	1×10^6	12 mo	Improved cardiac function and reduced infract size[81]
CSCs	Randomized open-label	Intracoronary	Treated: 17; Controls: 8	$12.5–25\times10^6$	12 mo	Increased viable myocardium and reduced infract size[99]

BM-MNC indicates bone marrow–derived mononuclear cells; BM-PC, bone marrow progenitor cells; CSCs, cardiac stem cells; and LVEF, left ventricular ejection fraction.

(AT-MSCs) that coexpress telomerase reverse transcriptase and MYOCD show increased levels of endogenous octamer-binding transcription factor 4, myocyte-specific enhancer factor 2c, and homeobox protein NKX2-5, and exhibit high cardiovascular regenerative potential.[109,110] These cells also show decreased frequencies of both spontaneous cell death and Fas-induced apoptosis.[109] The delivery of the telomerase reverse transcriptase and MYOCD genes into AT-MSCs was shown to restore MSCs from aged mice by increasing cell survival, proliferation, and smooth muscle myogenic differentiation in vitro.[109] The therapeutic efficacy of these rejuvenated cells was further demonstrated in an in vivo hindlimb ischemia model.[109]

Novel Delivery Systems for Stem Cell Therapy

Although encouraging results have been reported in cardiac cell therapy, only a few of the transplanted cells survive in the myocardium and integrate into the host myocardium.[111,112] Transplanted cells quickly disappear from the site of injection because they are removed by the blood flow and degraded by specific enzymes located in the extracellular microenvironment.[111] However, despite a quick disappearance from the myocardium, CPCs impart considerable improvement on cardiac function, implying a paracrine mechanism.[111] Several approaches have been suggested to overcome these hurdles. Conventional strategies such as overexpression of prosurvival genes, such as *Akt*, β adrenergic stimulation, cotransplanting with others, such as the endothelial cells, modification of the extracellular matrix and immune system are used to enhance survival and retention of CPCs in the heart.[113–119] Recently, there has been increasing focus on development of novel biomaterials that are coated with stem cells are functionalized with growth, mitotic and chemotactic factors, cytokines, and other biologically active materials. These new biomaterials are biocompatible and biodegradable polymers made of poly (D, L-lactide-co-glycolide acid) or poly(lactic-co-glycolic acid) that allow prolonged and controlled delivery of growth factors in situ and better cell retention in the transplanted area.[120–122] The combination of the stem cells, biomaterials and growth factors may enhance the efficacy of cell therapy by mobilizing endogenous stem/progenitor cells in vivo, promoting cell proliferation and differentiation, and augmenting cell engraftment and survival in the injured myocardium[120–122] (Figure). Likewise, transplantation of AT-MSCs coated on fibrin polymers and CPCs with immobilized insulin growth factor type 1 on peptide nanofibers has been shown to be beneficial.[123,124] The use of cardiac-specific decellularized matrices[125–127] might also serve as platforms for injectable biomaterials to deliver stem cells in a more sustainable and effective manner.[125,126] The so-called environmentally responsive systems are designed to match the release of the functional molecular with a patient's physiological need at the appropriate time or the correct site.[127,128] They are constituted of sensitive hydrogels that can control the release of drugs by changing the gel structure according to environmental stimulation, such as temperature, pH, or ion concentration.[127,128] Poly *N*-isopropylacrylamide hydrogel is a typical example of temperature-sensitive hydrogels, which shows sol-to-gel transformation at a critical solution temperature of ≈35°C.[129] This polymer releases the drug when it transforms from gel-to sol-and is of particular interest

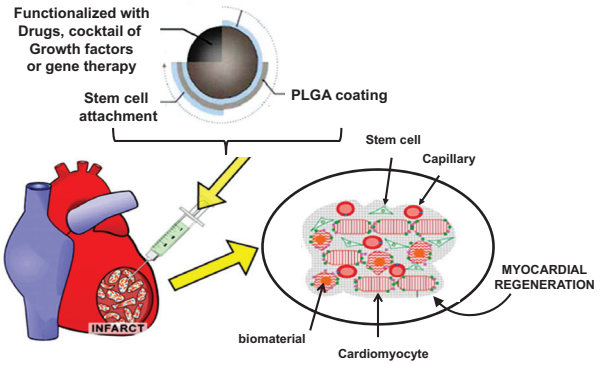

Figure. Potential use of PLGA (poly[lactic-co-glycolic acid]) biomaterials in enhancing effects of stem cell transplantation. PLGA microparticles can be functionalized with drugs and growth factors or gene therapy, externally coated with stem cells and injected/transplanted into the myocardium for optimizing therapeutic benefits.

in those clinical situations, such as tissue ischemia, characterized by low temperature in the tissue.[130] The interest in pH-sensitive polymers is in their capability of releasing a drug when the environmental pH decrease and hence, promoting proliferation and differentiation of CPCs on such conditions.

Stem Cell Therapy Without the Cells

The improved cardiac function observed in preclinical studies using traditional stem cell transplantation is in discord with the data showing poor long-term stem cell engraftment.[111] Systemically administered c-kit$^+$ cells, bone marrow cells, adipose tissue–derived cells and blood-derived endothelial progenitor cells exhibit low homing efficiency, and limited capacity for transdifferentiation into cardiomyocytes post transplantation.[111] Thus, the prevailing assumption is that the injected stem cells do not contribute directly to replenishing cardiomyocyte populations in the heart. This notion has shifted the focus on paracrine effects derived from the stem cell secretome, such as growth factors, microRNA, antioxidants, proteasomes, and exosomes, as the underpinning mechanisms responsible for improved cardiac function after stem cell transplantation.[131,132] Consequently, there is a considerable interest in identification and characterization of the paracrine factors, which might offer the opportunity to achieve the effects of stem cell transplantation without truly injecting them, and hence, the so called stem cell therapy without the cells. Current secretome-based approaches have shown some promise in preclinical models. For example, exosomes have been implicated in mediating some of the proangiogenic paracrine effects of CD34$^+$ stem cells[133] and cardioprotection by remote conditioning.[134]

The Road Ahead: Toward Clinical Application

There are currently several clinical studies that are investigating clinical uses of various stem cells in myocardial repair and regeneration.[79–82,99,135] The ongoing multicenter trials, such as ADVANCE (NCT 2010-022153-42), BAMI-01 (NCT 2012-001495-11), or 2011-01-01REPEAT (NCT 2011-000595-33), are expected to provide more compelling evidence for the clinical use of stem cells and offer insight into the mechanisms of their effects (reviewed in the study by Sanganalmath and Bolli[18]). Currently, the paracrine mechanisms are considered

the key events responsible for neoangiogenesis and cardioprotection imparted by the transplanted stem cells in the ischemic myocardium. New insights in the nature of the secretome and their mechanisms of effects might further enhance the clinical use of cardiac regeneration. Likewise, alternative approaches to enhance differentiation of the endogenous CPCs and direct reprogramming of the resident noncardiac cells to cardiac cells would be expected to offer further opportunities to treatment of human patients with ischemic heart disease and consequent heart failure.

Disclosures

None.

Sources of Funding

We acknowledge the funding support from NIH/NHLBI (R01 HL088498 and R34 HL105563), Leducq Foundation, Roderick MacDonald Foundation (13RDM005), TexGen Fund from Greater Houston Community Foundation and George and Mary Josephine Hamman Foundation.

References

1. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.
2. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8:30–41.
3. Roger VL. Epidemiology of heart failure. *Circ Res*. 2013;113:646–659.
4. Pitt B, Pfeffer MA, Assmann SF, et al; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
5. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med*. 2014;370:1694–1701.
6. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
7. Sallach JA, Goldstein S. Use of beta-blockers in congestive heart failure. *Ann Med*. 2003;35:259–266.
8. Birks EJ. Molecular changes after left ventricular assist device support for heart failure. *Circ Res*. 2013;113:777–791.
9. Kirk JA, Kass DA. Electromechanical dyssynchrony and resynchronization of the failing heart. *Circ Res*. 2013;113:765–776.
10. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, Banner NR, Khaghani A, Yacoub MH. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med*. 2006;355:1873–1884.
11. Davis MK, Hunt SA. State of the art: cardiac transplantation. *Trends Cardiovasc Med*. 2014;24:341–349.
12. Kranias EG, Hajjar RJ. Modulation of cardiac contractility by the phospholamban/SERCA2a regulatome. *Circ Res*. 2012;110:1646–1660.
13. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisén J. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324:98–102.
14. Kajstura J, Gurusamy N, Ogórek B, et al. Myocyte turnover in the aging human heart. *Circ Res*. 2010;107:1374–1386.
15. Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, Sadek HA. Transient regenerative potential of the neonatal mouse heart. *Science*. 2011;331:1078–1080.
16. Hierlihy AM, Seale P, Lobe CG, Rudnicki MA, Megeney LA. The post-natal heart contains a myocardial stem cell population. *FEBS Lett*. 2002;530:239–243.
17. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E, Urbanek K, Leri A, Kajstura J, Nadal-Ginard B, Anversa P. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell*. 2003;114:763–776.
18. Sanganalmath SK, Bolli R. Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. *Circ Res*. 2013;113:810–834.
19. Singh MK, Epstein JA. Epicardium-derived cardiac mesenchymal stem cells: expanding the outer limit of heart repair. *Circ Res*. 2012;110:904–906.
20. Hatzistergos KE, Quevedo H, Oskouei BN, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ Res*. 2010;107:913–922.
21. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007;131:861–872.
22. Yamanaka S, Blau HM. Nuclear reprogramming to a pluripotent state by three approaches. *Nature*. 2010;465:704–712.
23. Narsinh K, Narsinh KH, Wu JC. Derivation of human induced pluripotent stem cells for cardiovascular disease modeling. *Circ Res*. 2011;108:1146–1156.
24. Ma T, Xie M, Laurent T, Ding S. Progress in the reprogramming of somatic cells. *Circ Res*. 2013;112:562–574.
25. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, Srivastava D. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell*. 2010;142:375–386.
26. Song K, Nam YJ, Luo X, Qi X, Tan W, Huang GN, Acharya A, Smith CL, Tallquist MD, Neilson EG, Hill JA, Bassel-Duby R, Olson EN. Heart repair by reprogramming non-myocytes with cardiac transcription factors. *Nature*. 2012;485:599–604.
27. Jayawardena TM, Egemnazarov B, Finch EA, Zhang L, Payne JA, Pandya K, Zhang Z, Rosenberg P, Mirotsou M, Dzau VJ. MicroRNA-mediated in vitro and in vivo direct reprogramming of cardiac fibroblasts to cardiomyocytes. *Circ Res*. 2012;110:1465–1473.
28. Heinrich EM, Dimmeler S. MicroRNAs and stem cells: control of pluripotency, reprogramming, and lineage commitment. *Circ Res*. 2012;110:1014–1022.
29. Williams AR, Hatzistergos KE, Addicott B, McCall F, Carvalho D, Suncion V, Morales AR, Da Silva J, Sussman MA, Heldman AW, Hare JM. Enhanced effect of combining human cardiac stem cells and bone marrow mesenchymal stem cells to reduce infarct size and to restore cardiac function after myocardial infarction. *Circulation*. 2013;127:213–223.
30. Anversa P, Leri A, Kajstura J. Biased DNA segregation during stem cell division. *Circ Res*. 2012;110:1403–1407.
31. Burt RK, Chen YH, Verda L, Lucena C, Navale S, Johnson J, Han X, Lomasney J, Baker JM, Ngai KL, Kino A, Carr J, Kajstura J, Anversa P. Mitotically inactivated embryonic stem cells can be used as an in vivo feeder layer to nurse damaged myocardium after acute myocardial infarction: a preclinical study. *Circ Res*. 2012;111:1286–1296.
32. Courties G, Nahrendorf M. Enlightened stem cells in the heart: more efficient and safer reporter gene imaging. *Circ Res*. 2012;111:1486–1487.
33. Dey D, Han L, Bauer M, Sanada F, Oikonomopoulos A, Hosoda T, Unno K, De Almeida P, Leri A, Wu JC. Dissecting the molecular relationship among various cardiogenic progenitor cells. *Circ Res*. 2013;112:1253–1262.
34. Harvey RP, Tajbakhsh S. Biased DNA segregation and cardiac stem cell therapies. *Circ Res*. 2012;111:827–830.
35. Ishida M, El-Mounayri O, Kattman S, Zandstra P, Sakamoto H, Ogawa M, Keller G, Husain M. Regulated expression and role of c-Myb in the cardiovascular-directed differentiation of mouse embryonic stem cells. *Circ Res*. 2012;110:253–264.
36. Kajstura J, Bai Y, Cappetta D, Kim J, Arranto C, Sanada F, D'Amario D, Matsuda A, Bardelli S, Ferreira-Martins J, Hosoda T, Leri A, Rota M, Loscalzo J, Anversa P. Tracking chromatid segregation to identify human cardiac stem cells that regenerate extensively the infarcted myocardium. *Circ Res*. 2012;111:894–906.
37. Lee P, Klos M, Bollensdorff C, Hou L, Ewart P, Kamp TJ, Zhang J, Bizy A, Guerrero-Serna G, Kohl P, Jalife J, Herron TJ. Simultaneous voltage and calcium mapping of genetically purified human induced pluripotent stem cell-derived cardiac myocyte monolayers. *Circ Res*. 2012;110:1556–1563.
38. Deutsch MA, Sturzu A, Wu SM. At a crossroad: cell therapy for cardiac repair. *Circ Res*. 2013;112:884–890.
39. Bailey B, Fransioli J, Gude NA, Alvarez R Jr, Zhang X, Zhan X, Gustafsson ÅB, Sussman MA. Sca-1 knockout impairs myocardial and cardiac progenitor cell function. *Circ Res*. 2012;111:750–760.
40. Ferreira-Martins J, Ogórek B, Cappetta D, et al. Cardiomyogenesis in the developing heart is regulated by c-kit-positive cardiac stem cells. *Circ Res*. 2012;110:701–715.
41. Magenta A, Avitabile D, Pompilio G, Capogrossi MC. c-kit-Positive cardiac progenitor cells: the heart of stemness. *Circ Res*. 2013;112:1202–1204.
42. Molkentin JD, Houser SR. Are resident c-Kit+ cardiac stem cells really all that are needed to mend a broken heart? *Circ Res*. 2013;113:1037–1039.
43. Yaniz-Galende E, Chen J, Chemaly E, Liang L, Hulot JS, McCollum L, Arias T, Fuster V, Zsebo KM, Hajjar RJ. Stem cell factor gene transfer promotes cardiac repair after myocardial infarction via in situ recruitment and expansion of c-kit+ cells. *Circ Res*. 2012;111:1434–1445.

44. Ellison GM, Vicinanza C, Smith AJ, et al. Adult c-kit(pos) cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. *Cell*. 2013;154:827–842.
45. van Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, Middleton RC, Marbán E, Molkentin JD. c-kit+ cells minimally contribute cardiomyocytes to the heart. *Nature*. 2014;509:337–341.
46. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998;282:1145–1147.
47. Mummery CL, Zhang J, Ng ES, Elliott DA, Elefanty AG, Kamp TJ. Differentiation of human embryonic stem cells and induced pluripotent stem cells to cardiomyocytes: a methods overview. *Circ Res*. 2012;111:344–358.
48. Ohtani K, Zhao C, Dobreva G, Manavski Y, Kluge B, Braun T, Rieger MA, Zeiher AM, Dimmeler S. Jmjd3 controls mesodermal and cardiovascular differentiation of embryonic stem cells. *Circ Res*. 2013;113:856–862.
49. Scavone A, Capilupo D, Mazzocchi N, Crespi A, Zoia S, Campostrini G, Bucchi A, Milanesi R, Baruscotti M, Benedetti S, Antonini S, Messina G, DiFrancesco D, Barbuti A. Embryonic stem cell-derived CD166+ precursors develop into fully functional sinoatrial-like cells. *Circ Res*. 2013;113:389–398.
50. Chong JJ, Yang X, Don CW, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. *Nature*. 2014;510:273–277.
51. Okano H, Nakamura M, Yoshida K, Okada Y, Tsuji O, Nori S, Ikeda E, Yamanaka S, Miura K. Steps toward safe cell therapy using induced pluripotent stem cells. *Circ Res*. 2013;112:523–533.
52. Knollmann BC. Induced pluripotent stem cell-derived cardiomyocytes: boutique science or valuable arrhythmia model? *Circ Res*. 2013;112:969–976.
53. Raynaud CM, Halabi N, Elliott DA, Pasquier J, Elefanty AG, Stanley EG, Rafii A. Human embryonic stem cell derived mesenchymal progenitors express cardiac markers but do not form contractile cardiomyocytes. *PLoS One*. 2013;8:e54524.
54. Duran JM, Makarewich CA, Sharp TE, Starosta T, Zhu F, Hoffman NE, Chiba Y, Madesh M, Berretta RM, Kubo H, Houser SR. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. *Circ Res*. 2013;113:539–552.
55. Gu M, Nguyen PK, Lee AS, et al. Microfluidic single-cell analysis shows that porcine induced pluripotent stem cell-derived endothelial cells improve myocardial function by paracrine activation. *Circ Res*. 2012;111:882–893.
56. Ong SG, Wu JC. Cortical bone-derived stem cells: a novel class of cells for myocardial protection. *Circ Res*. 2013;113:480–483.
57. Penn MS, Ellis S, Gandhi S, Greenbaum A, Hodes Z, Mendelsohn FO, Strasser D, Ting AE, Sherman W. Adventitial delivery of an allogeneic bone marrow-derived adherent stem cell in acute myocardial infarction: phase I clinical study. *Circ Res*. 2012;110:304–311.
58. Wang WE, Yang D, Li L, et al. Prolyl hydroxylase domain protein 2 silencing enhances the survival and paracrine function of transplanted adipose-derived stem cells in infarcted myocardium. *Circ Res*. 2013;113:288–300.
59. Fadini GP, Losordo D, Dimmeler S. Critical reevaluation of endothelial progenitor cell phenotypes for therapeutic and diagnostic use. *Circ Res*. 2012;110:624–637.
60. Galasso G, De Rosa R, Ciccarelli M, Sorriento D, Del Giudice C, Strisciuglio T, De Biase C, Luciano R, Piccolo R, Pierri A, Di Gioia G, Prevete N, Trimarco B, Piscione F, Iaccarino G. Beta2-adrenergic receptor stimulation improves endothelial progenitor cell-mediated ischemic neoangiogenesis. *Circ Res*. 2013;112:1026–1034.
61. Spinetti G, Cordella D, Fortunato O, Sangalli E, Losa S, Gotti A, Carnelli F, Rosa F, Riboldi S, Sessa F, Avolio E, Beltrami AP, Emanueli C, Madeddu P. Global remodeling of the vascular stem cell niche in bone marrow of diabetic patients: implication of the microRNA-155/FOXO3a signaling pathway. *Circ Res*. 2013;112:510–522.
62. Thal MA, Krishnamurthy P, Mackie AR, Hoxha E, Lambers E, Verma S, Ramirez V, Qin G, Losordo DW, Kishore R. Enhanced angiogenic and cardiomyocyte differentiation capacity of epigenetically reprogrammed mouse and human endothelial progenitor cells augments their efficacy for ischemic myocardial repair. *Circ Res*. 2012;111:180–190.
63. Yin L, Ohanyan V, Pung YF, Delucia A, Bailey E, Enrick M, Stevanov K, Kolz CL, Guarini G, Chilian WM. Induction of vascular progenitor cells from endothelial cells stimulates coronary collateral growth. *Circ Res*. 2012;110:241–252.
64. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev*. 2014;66:1142–1174.
65. Sluijter JP, Condorelli G, Davidson SM, Engel FB, Ferdinandy P, Hausenloy DJ, Lecour S, Madonna R, Ovize M, Ruiz-Meana M, Schulz R, Van Laake LW; Nucleus of the European Society of Cardiology Working Group Cellular Biology of the Heart. Novel therapeutic strategies for cardioprotection. *Pharmacol Ther*. 2014;144:60–70.
66. Madonna R, Görbe A, Ferdinandy P, De Caterina R. Glucose metabolism, hyperosmotic stress, and reprogramming of somatic cells. *Mol Biotechnol*. 2013;55:169–178.
67. Perin EC, Dohmann HF, Borojevic R, et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation*. 2003;107:2294–2302.
68. Willerson JT, Perin EC, Ellis SG, et al; Cardiovascular Cell Therapy Research Network (CCTRN). Intramyocardial injection of autologous bone marrow mononuclear cells for patients with chronic ischemic heart disease and left ventricular dysfunction (First Mononuclear Cells injected in the US [FOCUS]): rationale and design. *Am Heart J*. 2010;160:215–223.
69. Traverse JH, Henry TD, Pepine CJ, Willerson JT, Ellis SG. One-year follow-up of intracoronary stem cell delivery on left ventricular function following ST-elevation myocardial infarction. *JAMA*. 2014;311:301–302.
70. Traverse JH, Henry TD, Pepine CJ, et al; Cardiovascular Cell Therapy Research Network (CCTRN). Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA*. 2012;308:2380–2389.
71. van Laake LW, Passier R, den Ouden K, Schreurs C, Monshouwer-Kloots J, Ward-van Oostwaard D, van Echteld CJ, Doevendans PA, Mummery CL. Improvement of mouse cardiac function by hESC-derived cardiomyocytes correlates with vascularity but not graft size. *Stem Cell Res*. 2009;3:106–112.
72. Perin EC, Sanz-Ruiz R, Sánchez PL, et al. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. *Am Heart J*. 2014;168:88–95.e2.
73. Gold JD, Wu JC. Returns of the living dead: therapeutic action of irradiated and mitotically inactivated embryonic stem cells. *Circ Res*. 2012;111:1250–1252.
74. Vrtovec B, Poglajen G, Lezaic L, Sever M, Domanovic D, Cernelc P, Socan A, Schrepfer S, Torre-Amione G, Haddad F, Wu JC. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. *Circ Res*. 2013;112:165–173.
75. Taylor DA, Atkins BZ, Hungspreugs P, Jones TR, Reedy MC, Hutcheson KA, Glower DD, Kraus WE. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med*. 1998;4:929–933.
76. Menasché P, Hagège AA, Scorsin M, Pouzet B, Desnos M, Duboc D, Schwartz K, Vilquin JT, Marolleau JP. Myoblast transplantation for heart failure. *Lancet*. 2001;357:279–280.
77. Menasché P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, Vilquin JT, Marolleau JP, Seymour B, Larghero J, Lake S, Chatellier G, Solomon S, Desnos M, Hagège AA. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. *Circulation*. 2008;117:1189–1200.
78. Brickwedel J, Gulbins H, Reichenspurner H. Long-term follow-up after autologous skeletal myoblast transplantation in ischaemic heart disease. *Interact Cardiovasc Thorac Surg*. 2014;18:61–66.
79. Assmus B, Rolf A, Erbs S, et al; REPAIR-AMI Investigators. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail*. 2010;3:89–96.
80. Schaefer A, Zwadlo C, Fuchs M, Meyer GP, Lippolt P, Wollert KC, Drexler H. Long-term effects of intracoronary bone marrow cell transfer on diastolic function in patients after acute myocardial infarction: 5-year results from the randomized-controlled BOOST trial–an echocardiographic study. *Eur J Echocardiogr*. 2010;11:165–171.
81. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet*. 2011;378:1847–1857.
82. Chugh AR, Beache GM, Loughran JH, Mewton N, Elmore JB, Kajstura J, Pappas P, Tatooles A, Stoddard MF, Lima JA, Slaughter MS, Anversa P, Bolli R. Administration of cardiac stem cells in patients with ischemic cardiomyopathy: the SCIPIO trial: surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. *Circulation*. 2012;126:S54–S64.
83. Mirotsou M, Jayawardena TM, Schmeckpeper J, Gnecchi M, Dzau VJ. Paracrine mechanisms of stem cell reparative and regenerative actions in the heart. *J Mol Cell Cardiol*. 2011;50:280–289.
84. Korf-Klingebiel M, Kempf T, Schlüter KD, Willenbockel C, Brod T, Heineke J, Schmidt VJ, Jantzen F, Brandes RP, Sugden PH, Drexler H, Molkentin JD, Wollert KC. Conditional transgenic expression of fibroblast growth factor 9 in the adult mouse heart reduces heart failure mortality after myocardial infarction. *Circulation*. 2011;123:504–514.

85. Zhang J, Liu J, Huang Y, Chang JY, Liu L, McKeehan WL, Martin JF, Wang F. Frs2alpha-mediated FGF signals suppress premature differentiation of cardiac stem cells through regulating autophagy activity. *Circ Res*. 2012;110:e29–39.
86. Ince H, Petzsch M, Rehders TC, Chatterjee T, Nienaber CA. Transcatheter transplantation of autologous skeletal myoblasts in postinfarction patients with severe left ventricular dysfunction. *J Endovasc Ther*. 2004;11:695–704.
87. Gavira JJ, Herreros J, Perez A, Garcia-Velloso MJ, Barba J, Martin-Herrero F, Cañizo C, Martin-Arnau A, Martí-Climent JM, Hernández M, López-Holgado N, González-Santos JM, Martín-Luengo C, Alegria E, Prósper F. Autologous skeletal myoblast transplantation in patients with nonacute myocardial infarction: 1-year follow-up. *J Thorac Cardiovasc Surg*. 2006;131:799–804.
88. Veltman CE, Soliman OI, Geleijnse ML, Vletter WB, Smits PC, ten Cate FJ, Jordaens LJ, Balk AH, Serruys PW, Boersma E, van Domburg RT, van der Giessen WJ. Four-year follow-up of treatment with intramyocardial skeletal myoblasts injection in patients with ischaemic cardiomyopathy. *Eur Heart J*. 2008;29:1386–1396.
89. Dib N, Michler RE, Pagani FD, et al. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. *Circulation*. 2005;112:1748–1755.
90. Assmus B, Honold J, Schächinger V, Britten MB, Fischer-Rasokat U, Lehmann R, Teupe C, Pistorius K, Martin H, Abolmaali ND, Tonn T, Dimmeler S, Zeiher AM. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med*. 2006;355:1222–1232.
91. Hendrikx M, Hensen K, Clijsters C, Jongen H, Koninckx R, Bijnens E, Ingels M, Jacobs A, Geukens R, Dendale P, Vijgen J, Dilling D, Steels P, Mees U, Rummens JL. Recovery of regional but not global contractile function by the direct intramyocardial autologous bone marrow transplantation: results from a randomized controlled clinical trial. *Circulation*. 2006;114:I101–I107.
92. Gao LR, Wang ZG, Zhu ZM, Fei YX, He S, Tian HT, Zhang NK, Chen Y, Xu HT, Yang Y. Effect of intracoronary transplantation of autologous bone marrow-derived mononuclear cells on outcomes of patients with refractory chronic heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol*. 2006;98:597–602.
93. Yao K, Huang R, Qian J, Cui J, Ge L, Li Y, Zhang F, Shi H, Huang D, Zhang S, Sun A, Zou Y, Ge J. Administration of intracoronary bone marrow mononuclear cells on chronic myocardial infarction improves diastolic function. *Heart*. 2008;94:1147–1153.
94. Ang KL, Chin D, Leyva F, Foley P, Kubal C, Chalil S, Srinivasan L, Bernhardt L, Stevens S, Shenje LT, Galiñanes M. Randomized, controlled trial of intramuscular or intracoronary injection of autologous bone marrow cells into scarred myocardium during CABG versus CABG alone. *Nat Clin Pract Cardiovasc Med*. 2008;5:663–670.
95. Perin EC, Silva GV, Henry TD, et al. A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF). *Am Heart J*. 2011;161:1078–1087.e3.
96. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel HC Jr, Kormos R, Benetti F. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2005;130:1631–1638.
97. Stamm C, Kleine HD, Choi YH, Dunkelmann S, Lauffs JA, Lorenzen B, David A, Liebold A, Nienaber C, Zurakowski D, Freund M, Steinhoff G. Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies. *J Thorac Cardiovasc Surg*. 2007;133:717–725.
98. Vrtovec B, Poglajen G, Sever M, Lezaic L, Domanovic D, Cernelc P, Haddad F, Torre-Amione G. Effects of intracoronary stem cell transplantation in patients with dilated cardiomyopathy. *J Card Fail*. 2011;17:272–281.
99. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, Czer LS, Marbán L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marbán E. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet*. 2012;379:895–904.
100. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153:1194–1217.
101. Rohani L, Johnson AA, Arnold A, Stolzing A. The aging signature: a hallmark of induced pluripotent stem cells? *Aging Cell*. 2014;13:2–7.
102. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell*. 2012;148:46–57.
103. Borillo GA, Mason M, Quijada P, et al. Pim-1 kinase protects mitochondrial integrity in cardiomyocytes. *Circ Res*. 2010;106:1265–1274.
104. Mohsin S, Khan M, Toko H, et al. Human cardiac progenitor cells engineered with Pim-I kinase enhance myocardial repair. *J Am Coll Cardiol*. 2012;60:1278–1287.
105. Mohsin S, Khan M, Nguyen J, Alkatib M, Siddiqi S, Hariharan N, Wallach K, Monsanto M, Gude N, Dembitsky W, Sussman MA. Rejuvenation of human cardiac progenitor cells with Pim-1 kinase. *Circ Res*. 2013;113:1169–1179.
106. Del Re DP, Sadoshima J. Enhancing the potential of cardiac progenitor cells: pushing forward with Pim-1. *Circ Res*. 2012;110:1154–1156.
107. Sundararaman B, Avitabile D, Konstandin MH, Cottage CT, Gude N, Sussman MA. Asymmetric chromatid segregation in cardiac progenitor cells is enhanced by Pim-1 kinase. *Circ Res*. 2012;110:1169–1173.
108. Conboy IM, Rando TA. Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. *Cell Cycle*. 2012;11:2260–2267.
109. Madonna R, Wu D, Wassler M, De Caterina R, Willerson JT, Geng YJ. Myocardin-A enhances expression of promyogenic genes without depressing telomerase activity in adipose tissue-derived mesenchymal stem cells. *Int J Cardiol*. 2013;167:2912–2921.
110. Madonna R, Taylor DA, Geng YJ, De Caterina R, Shelat H, Perin EC, Willerson JT. Transplantation of mesenchymal cells rejuvenated by the overexpression of telomerase and myocardin promotes revascularization and tissue repair in a murine model of hindlimb ischemia. *Circ Res*. 2013;113:902–914.
111. Hong KU, Guo Y, Li QH, Cao P, Al-Maqtari T, Vajravelu BN, Du J, Book MJ, Zhu X, Nong Y, Bhatnagar A, Bolli R. c-kit+ Cardiac stem cells alleviate post-myocardial infarction left ventricular dysfunction despite poor engraftment and negligible retention in the recipient heart. *PLoS One*. 2014;9:e96725.
112. Wu KH, Mo XM, Han ZC, Zhou B. Stem cell engraftment and survival in the ischemic heart. *Ann Thorac Surg*. 2011;92:1917–1925.
113. Gnecchi M, He H, Liang OD, Melo LG, Morello F, Mu H, Noiseux N, Zhang L, Pratt RE, Ingwall JS, Dzau VJ. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. *Nat Med*. 2005;11:367–368.
114. Lee WY, Wei HJ, Wang JJ, Lin KJ, Lin WW, Chen DY, Huang CC, Lee TY, Ma HY, Hwang SM, Chang Y, Sung HW. Vascularization and restoration of heart function in rat myocardial infarction using transplantation of human cbMSC/HUVEC core-shell bodies. *Biomaterials*. 2012;33:2127–2136.
115. Khan M, Mohsin S, Avitabile D, Siddiqi S, Nguyen J, Wallach K, Quijada P, McGregor M, Gude N, Alvarez R, Tilley DG, Koch WJ, Sussman MA. Beta-adrenergic regulation of cardiac progenitor cell death versus survival and proliferation. *Circ Res*. 2013;112:476–486.
116. Konstandin MH, Toko H, Gastelum GM, Quijada P, De La Torre A, Quintana M, Collins B, Din S, Avitabile D, Völkers M, Gude N, Fässler R, Sussman MA. Fibronectin is essential for reparative cardiac progenitor cell response after myocardial infarction. *Circ Res*. 2013;113:115–125.
117. Lauden L, Boukouaci W, Borlado LR, López IP, Sepúlveda P, Tamouza R, Charron D, Al-Daccak R. Allogenicity of human cardiac stem/progenitor cells orchestrated by programmed death ligand 1. *Circ Res*. 2013;112:451–464.
118. Xiao Q, Zhang F, Lin L, et al. Functional role of matrix metalloproteinase-8 in stem/progenitor cell migration and their recruitment into atherosclerotic lesions. *Circ Res*. 2013;112:35–47.
119. Zhang J, Klos M, Wilson GF, et al. Extracellular matrix promotes highly efficient cardiac differentiation of human pluripotent stem cells: the matrix sandwich method. *Circ Res*. 2012;111:1125–1136.
120. Karam JP, Bonafe F, Sindji L, Muscari C, Montero-Menei CN. Adipose-derived stem cell adhesion on laminin-coated microcarriers improves commitment toward the cardiomyogenic lineage. *J Biomed Mater Res A*. 2014.
121. Karam JP, Muscari C, Montero-Menei CN. Combining adult stem cells and polymeric devices for tissue engineering in infarcted myocardium. *Biomaterials*. 2012;33:5683–5695.
122. Sarkar D, Ankrum JA, Teo GS, Carman CV, Karp JM. Cellular and extracellular programming of cell fate through engineered intracrine-, paracrine-, and endocrine-like mechanisms. *Biomaterials*. 2011;32:3053–3061.
123. Danoviz ME, Nakamuta JS, Marques FL, dos Santos L, Alvarenga EC, dos Santos AA, Antonio EL, Schettert IT, Tucci PJ, Krieger JE. Rat adipose tissue-derived stem cells transplantation attenuates cardiac dysfunction post infarction and biopolymers enhance cell retention. *PLoS One*. 2010;5:e12077.

124. Padin-Iruegas ME, Misao Y, Davis ME, Segers VF, Esposito G, Tokunou T, Urbanek K, Hosoda T, Rota M, Anversa P, Leri A, Lee RT, Kajstura J. Cardiac progenitor cells and biotinylated insulin-like growth factor-1 nanofibers improve endogenous and exogenous myocardial regeneration after infarction. *Circulation*. 2009;120:876–887.
125. Godier-Furnémont AF, Martens TP, Koeckert MS, Wan L, Parks J, Arai K, Zhang G, Hudson B, Homma S, Vunjak-Novakovic G. Composite scaffold provides a cell delivery platform for cardiovascular repair. *Proc Natl Acad Sci U S A*. 2011;108:7974–7979.
126. Singelyn JM, Christman KL. Injectable materials for the treatment of myocardial infarction and heart failure: the promise of decellularized matrices. *J Cardiovasc Transl Res*. 2010;3:478–486.
127. Robertson MJ, Dries-Devlin JL, Kren SM, Burchfield JS, Taylor DA. Optimizing recellularization of whole decellularized heart extracellular matrix. *PLoS One*. 2014;9:e90406.
128. Lin RZ, Chen YC, Moreno-Luna R, Khademhosseini A, Melero-Martin JM. Transdermal regulation of vascular network bioengineering using a photopolymerizable methacrylated gelatin hydrogel. *Biomaterials*. 2013;34:6785–6796.
129. Li X, Zhou J, Liu Z, Chen J, Lü S, Sun H, Li J, Lin Q, Yang B, Duan C, Xing MM, Wang C. A PNIPAAm-based thermosensitive hydrogel containing SWCNTs for stem cell transplantation in myocardial repair. *Biomaterials*. 2014;35:5679–5688.
130. Ren S, Jiang X, Li Z, Wen Y, Chen D, Li X, Zhang X, Zhuo R, Chu H. Physical properties of poly(N-isopropylacrylamide) hydrogel promote its effects on cardiac protection after myocardial infarction. *J Int Med Res*. 2012;40:2167–2182.
131. Liehn EA, Bucur O, Weber C. Role of microparticles as messengers enhancing stem cell activity after genetic engineering. *Circ Res*. 2012;111:265–267.
132. Zhu S, Deng S, Ma Q, Zhang T, Jia C, Zhuo D, Yang F, Wei J, Wang L, Dykxhoorn DM, Hare JM, Goldschmidt-Clermont PJ, Dong C. MicroRNA-10A* and MicroRNA-21 modulate endothelial progenitor cell senescence via suppressing high-mobility group A2. *Circ Res*. 2013;112:152–164.
133. Sahoo S, Klychko E, Thorne T, Misener S, Schultz KM, Millay M, Ito A, Liu T, Kamide C, Agrawal H, Perlman H, Qin G, Kishore R, Losordo DW. Exosomes from human CD34(+) stem cells mediate their proangiogenic paracrine activity. *Circ Res*. 2011;109:724–728.
134. Giricz Z, Varga ZV, Baranyai T, Sipos P, Pálóczi K, Kittel Á, Buzás EI, Ferdinandy P. Cardioprotection by remote ischemic preconditioning of the rat heart is mediated by extracellular vesicles. *J Mol Cell Cardiol*. 2014;68:75–78.
135. Assmus B, Zeiher AM. Early cardiac retention of administered stem cells determines clinical efficacy of cell therapy in patients with dilated cardiomyopathy. *Circ Res*. 2013;112:6–8.

KEY WORDS: heart failure ■ stem cell