

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

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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 considerable 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

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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 rise 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

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?

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 pace 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.

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 many restorative 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 anti-apoptotic 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 al¹⁰⁹ 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	$210 \pm 150 \times 10^6$	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	$3 \pm 50 \times 10^6$	4 y	No benefits, increased risk of arrhythmias ⁸⁸
Skeletal myoblasts	Randomized	Intramyocardial	Treated: 97; Controls: 30	$400\text{--}800 \times 10^6$	6 mo	Improved cardiac function ⁷⁷
Skeletal myoblasts	Double-blind randomized	Transendocardial	Treated: 12; Controls: 11	$30\text{--}600 \times 10^6$	12 mo	Improved myocardial viability and function ⁸⁹
BM-MNC	Double-blind Nonrandomized	Transendocardial	Treated: 14; Controls: 7	$25.6 \pm 6.3 \times 10^6$	4 mo	Improved myocardial function and perfusion ⁸⁷
BM-MNC	Open-label randomized	Intracoronary	Treated: 52; Controls: 23	$205 \pm 110 \times 10^6$	3 mo	Improved myocardial function ⁹⁰
BM-MNC	Randomized	Intramyocardial	Treated: 10; Controls: 10	$60 \pm 31 \times 10^6$	4 mo	Improved regional but not global cardiac function ⁹¹
BM-MNC	Randomized	Intracoronary	Treated: 14; Controls: 14	$20\text{--}32 \times 10^6$	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	$84\text{--}56 \times 10^6$	6 mo	No effects on infarct 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	$113 \pm 26 \times 10^6$	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 infarct size ⁸¹
CSCs	Randomized open-label	Intracoronary	Treated: 17; Controls: 8	$12.5\text{--}25 \times 10^6$	12 mo	Increased viable myocardium and reduced infarct 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 pro-survival 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 $\approx 35^\circ\text{C}$.¹²⁹ This polymer releases the drug when it transforms from gel-to sol-and is of particular interest

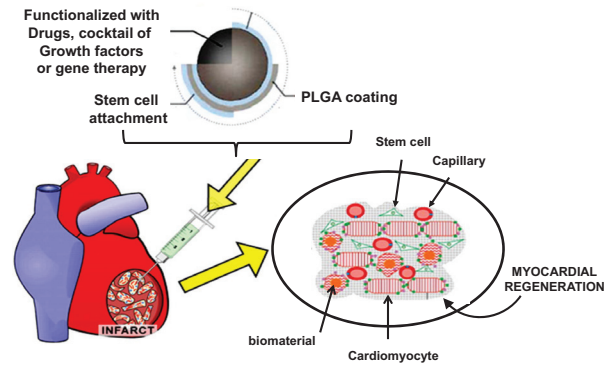


Figure. Potential use of PLGA (poly[lactic-co-glycolic acid]) biomaterials in enhancing effects of stem cell transplantation. PLGA microparticles can be functionalized with drugs and growth factors or gene therapy, externally coated with stem cells and injected/transplanted into the myocardium for optimizing 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 $c\text{-kit}^+$ 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 cells¹³³ 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 Bolli¹⁸). 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.

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