

## Translational research of adult stem cell therapy

Gen Suzuki

Gen Suzuki, Division of Cardiovascular Medicine, University at Buffalo, Clinical and Translational Research Center, Buffalo, NY 14203, United States

**Author contributions:** Suzuki G wrote the paper and performed data collection.

**Supported by** New York State NYSTEM foundation, No. N08G-433.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Gen Suzuki, MD, PhD, Associate Professor of Medicine, Division of Cardiovascular Medicine, University at Buffalo, Clinical and Translational Research Center, 875 Ellicott Street, Buffalo, NY 14203, United States. [gsuzuki@buffalo.edu](mailto:gsuzuki@buffalo.edu)  
Telephone: +1-716-8292710  
Fax: +1-716-8292665

Received: May 28, 2015  
Peer-review started: June 1, 2015  
First decision: August 4, 2015  
Revised: August 20, 2015  
Accepted: September 25, 2015  
Article in press: September 28, 2015  
Published online: November 26, 2015

### Abstract

Congestive heart failure (CHF) secondary to chronic coronary artery disease is a major cause of morbidity and mortality world-wide. Its prevalence is increasing despite advances in medical and device therapies. Cell based therapies generating new cardiomyocytes

and vessels have emerged as a promising treatment to reverse functional deterioration and prevent the progression to CHF. Functional efficacy of progenitor cells isolated from the bone marrow and the heart have been evaluated in preclinical large animal models. Furthermore, several clinical trials using autologous and allogeneic stem cells and progenitor cells have demonstrated their safety in humans yet their clinical relevance is inconclusive. This review will discuss the clinical therapeutic applications of three specific adult stem cells that have shown particularly promising regenerative effects in preclinical studies, bone marrow derived mesenchymal stem cell, heart derived cardiosphere-derived cell and cardiac stem cell. We will also discuss future therapeutic approaches.

**Key words:** Congestive heart failure; Adult stem cells; Mesenchymal stem cell; Cardiosphere-derived cell; Cardiac stem cell

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Cell-based therapy emerged as a new approach to restore damaged heart function. Although cell therapy in experimental animal models is promising, beneficial effects in clinical trials are variable. This review summarizes recent preclinical and clinical applications on three specific adult stem cells (bone marrow derived mesenchymal stem cell, heart derived cardiosphere-derived cells and cardiac stem cell) and discuss about future approaches.

Suzuki G. Translational research of adult stem cell therapy. *World J Cardiol* 2015; 7(11): 707-718 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i11/707.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i11.707>

### INTRODUCTION

The prevalence of congestive heart failure secondary to chronic coronary artery disease is increasing in spite of

**Table 1 Clinical Trials of mesenchymal stem cells, cardiosphere-derived cells and cardiac stem cells in heart disease**

Trial name	Study design	No. of patients	Delivery method	Cell dose	End point evaluation	Follow-up period	Outcome
<b>MSCs</b>							
Chen <i>et al</i> <sup>[10]</sup>	Randomized, controlled study	MSC <i>n</i> = 34 Control <i>n</i> = 35	Intracoronary	48-60 × 10 <sup>9</sup> cells	Echocardiography	3 and 6 mo	LVEF↑
POSEIDON <sup>[28]</sup>	Randomized, Pilot study	MSC <i>n</i> = 30 Auto <i>vs</i> Allo	Intramyocardial (transendocardial)	20, 100, 200 × 10 <sup>6</sup> cells	Cardiac CT	12 mo	LVEF↔ LVEDV↓
PROMETHEUS <sup>[29]</sup>	Randomized, Pilot study	MSC <i>n</i> = 6 No control	Intramyocardial (transepical)	20, 200 × 10 <sup>6</sup> cells	MRI	18 mo	LVEF↑ Scar size↓
C-CURE <sup>[30]</sup>	Randomized, controlled study	MSC <i>n</i> = 21 Control <i>n</i> = 15	Intramyocardial (transendocardial)	7 × 10 <sup>6</sup> cells	Echocardiography	6 and 24 mo	LVEF↑ LVESV↓
<b>CDCs</b>							
CADUCEUS <sup>[36,37]</sup>	Randomized, controlled study	CDC <i>n</i> = 17 Control <i>n</i> = 8	Intracoronary	12.5-25 × 10 <sup>6</sup> cells	MRI	6 and 12 mo	LVEF↔ Scar size↓
ALCADIA	Pilot study	CDC <i>n</i> = 6 No control	Intracoronary	25-30 × 10 <sup>6</sup> cells	MRI	12 mo	LVEF↑ Scar size↓
TICAP <sup>[38]</sup>	Randomized, controlled study	CDC <i>n</i> = 7 Control <i>n</i> = 7	Intracoronary	2-3 × 10 <sup>6</sup> cells	MRI	18 mo	LVEF↑
<b>CSCs</b>							
SCIPIO <sup>[50]</sup>	Randomized, controlled study	CSC <i>n</i> = 20 Control <i>n</i> = 13	Intracoronary	1 × 10 <sup>6</sup> cells	Echocardiography MRI	12 mo	LVEF↑ Scar size↓

Auto: Autologous; Allo: Allogeneic; MSCs: Mesenchymal stem cells; CSCs: Cardiac stem cells; CDCs: Cardiosphere-derived cells; CT: Computed tomography; MRI: Magnetic resonance imaging.

recent advances in medical and device therapies that delay the progression of disease<sup>[1]</sup>. Currently available medical interventions attenuate neurohormonal activation (e.g., renin-angiotensin-aldosterone system, sympathetic nervous system, and arginine vasopressin), reducing myocyte apoptotic cell death, reducing interstitial connective tissue proliferation and attenuating the progression of myocyte cellular hypertrophy. However, none of the current therapies are effective in reversing myocyte loss and cellular abnormalities associated with myocyte contractile performance which are impaired in the failing heart. Recent investigations have demonstrated that there is an endogenous cardiac repair system that arises from resident cardiac stem cells regulating cardiac engraftment by maintaining a low level of myocyte proliferation, regeneration and cell death<sup>[2]</sup>. Nevertheless, the regenerative capacity of this endogenous stem cell pool is limited.

Expansion of adult stem cells *ex vivo* can stimulate the heart to induce endogenous or exogenous cell based repair. Cell-based therapy has emerged as a promising therapy to regenerate the failing heart through its potential to repair dead myocardium and improve left ventricle (LV) function<sup>[3-5]</sup>. Although clinical trials have demonstrated the safety and feasibility of using bone marrow-derived stem cells [Bone marrow mononuclear cells (MNCs) or mesenchymal stem cells (MSCs)] or heart-derived stem cells [cardiac stem cells (CSCs) or cardiosphere-derived cells (CDCs)] in humans with MI who do not have severe heart failure, the long term clinical efficacy of this approach is variable with a small improvement in LV function<sup>[6-8]</sup>. Although the biological action of adult stem cells *in vivo* is still controversial, for now, the beneficial effects of adult stem cells are

considered to be associated with the secretion of paracrine factors rather than direct differentiation of *de novo* cardiac cells<sup>[9]</sup>. Accordingly, stem cells secrete multiple growth factors and cytokines which reduce scar volume and myocyte apoptosis, increase myocyte proliferation and activate endogenous CSCs to produce new myocytes. Therefore, current research using adult stem cells has focused on optimizing cell based therapy that effectively improves LV function and decreases disease progression. This would have a major impact on the survival and quality of life in patients with ischemic heart disease as well as reduce healthcare expenditures related to recurrent hospitalizations from advanced disease. In this review we will discuss three types of adult stem cells, MSCs, CDCs and CSCs, which are involved in the early phase of clinical trials (Table 1) and address current problems and future directions (Table 2).

## MSCS IN ISCHEMIC CARDIOMYOPATHY

MSCs arise from a small proportion of bone marrow mononuclear cells (0.001%-0.01% of nucleated cells in the bone marrow). Although it has been reported that MSCs can be differentiated into cardiomyocytes and vascular-like structures<sup>[10-14]</sup>, actual *in vivo* differentiation is infrequent. Moreover, current approaches using direct myocardial injection or intracoronary infusion of cells in the infarcted region result in a low myocardial retention of stem cells<sup>[15]</sup>. Thus, most of the beneficial effects derived from MSCs are considered to be related to a paracrine mechanism. MSCs produce a wide variety of cytokines, chemokines and growth factors, and many are involved in restoring cardiac function or regenerating myocardial tissue. Factors such as basic fibroblast

**Table 2 Alternative strategies of stem cell therapy**

Enhancement of cell survival, mobilization and paracrine secretion
Pharmacology (Statins, <i>etc.</i> )
Genetic modification (Akt and Ang1, VEGF and SDF-1, HO-1, bFGF/IGF-1/BMP2)
Preconditioning (Hypoxia, TLR3 stimulation)
Combination of different cell types or delivery approaches
MSCs and CSCs
Stop-flow (infarct area) and global intracoronary infusion (viable area)
Others
Cell infusion immediate after revascularization (allogeneic MSCs, CDCs, <i>etc.</i> )
Repeated cell infusion
Stimulation of exosome release
Direct exosome (or microRNAs) injection
Cell therapy in hypertrophied myocardium or dysfunction due to congenital heart disease

MSCs: Mesenchymal stem cells; CSCs: Cardiac stem cells; CDCs: Cardiosphere-derived cells; VEGF: Vascular endothelial growth factor; SDF: Stromal cell-derived factor; bFGF: Basic fibroblast growth factor; IGF: Insulin-like growth factor; BMP2: Bone morphogenetic protein 2; HO-1: Heme-oxygenase 1; Ang1: Angiopoietin 1.

growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor (TGF)- $\beta$ , and stromal cell-derived factor (SDF)-1 inhibit LV remodeling<sup>[16]</sup> and apoptosis, stimulate proliferation of endogenous myocytes and angiogenesis, activate endogenous CSCs<sup>[4]</sup> and mobilize bone marrow progenitor cells to the heart<sup>[17]</sup>. Importantly, MSC are immunoprivileged because they do not express MHC class II molecules therefore they escape immune-rejection, release immunomodulatory factors and inhibit T-cell proliferation. Allogeneic cells can be expanded *ex vivo* and stored to use in patients<sup>[18,19]</sup>. This would allow for "off-the-shelf" treatment of patients with severe LV dysfunction, without the need to wait for cell processing and expansion<sup>[19]</sup>.

A large number of preclinical investigations have been performed using MSCs, and demonstrate a significant beneficial effect on cardiac structure and function<sup>[13,20-23]</sup>. In a large animal model, Quevedo *et al*<sup>[18]</sup> demonstrated that administration of allogeneic MSCs to a swine model of chronically infarcted myocardium resulted in improvements in regional contractility and myocardial blood flow, as well as engraftment, differentiation and enhanced survival. Williams *et al*<sup>[24]</sup> assessed serial cardiac MRI in animals with post-MI LV remodeling and showed progressive scar size reductions, improvements in ejection fraction (EF) and reverse LV chamber remodeling in animals receiving allogeneic MSCs as compared to controls<sup>[24]</sup>. Mesenchymal precursor cells (MPCs) are subpopulation of MSCs expressing the STRO-3 cell surface marker. MPCs are highly proliferative and secrete abundant paracrine factors. Houtgraaf *et al*<sup>[25]</sup> demonstrated that slow infusion of allogeneic MPCs (12.5 to 37.5 million cells) to an bovine model with acute MI improved

regional and global function and reduced scar volume and LV remodeling. Interestingly, MPC infusion in the infarct-related coronary artery caused myocyte cell size reduction in the infarcted and remote regions. Based on these data a clinical trial is currently ongoing (NCT01781390, phase II) that investigates the safety of MPCs in patients with *de novo* anterior MI.

We have demonstrated that slow infusion of allogeneic MSCs into the three major coronary arteries in swine with hibernating myocardium increased regional cardiac function in both the ischemic left anterior descending (LAD) artery and remote regions (wall thickening: LAD: 24% to 43%, Remote: 60% to 85%,  $P < 0.05$ )<sup>[17]</sup>. Intracoronary MSCs (icMSCs) significantly increased cKit+/CD133 positive cells (or bone marrow-derived progenitor cells) in the bone marrow and circulation corresponding to the increase in myocardial localization of cardiac progenitor cells (cKit+/GATA4 or Nkx2.5+). icMSCs also induced myocytes to enter the cell cycle and increased the production of small cardiac myocytes indicating the presence of cardiac regeneration. Although some laboratories have identified rare myocytes arising from MSCs in swine<sup>[18]</sup>, our own studies using multiple reporter genes could not identify cardiac myocytes differentiating from labeled MSCs<sup>[26]</sup>. Thus, cardiac regeneration after icMSCs is related to a bone marrow-derived progenitor cell mediated endogenous cardiac repair mechanism.

Chen *et al*<sup>[10]</sup> administered 48-60 billion bone marrow derived MSCs by intracoronary injection into 34 patients and reported a 13% increase in EF compared to placebo groups at 3-6 mo follow-up. The Percutaneous Stem Cell Injection Delivery Effects on neo-myogenesis (POSEIDON) trial, by Hare's group, tested the ability of autologous and allogeneic MSCs (20, 100 and 200 million cells) in patients with ischemic cardiomyopathy to promote cardiac recovery following transendocardial stem cell injection<sup>[27,28]</sup>. Using multidetector computed tomography and biplane left ventriculography, this study reported a 32% reduction in scar size in allogeneic MSCs group vs a 35% reduction in autologous MSCs groups without improvement of LV EF. Subgroup analysis demonstrated that 20 million MSCs improvement in LV EF and LVEDV. Furthermore, autologous MSCs showed improvement in the 6 min walk test and allogeneic MSCs reduced LVEDV. Additionally, allogeneic MSCs did not stimulate a donor specific alloimmune reaction. Thus, this study clearly demonstrates the importance of cell injection site and the safety of using allogeneic MSCs in patients. The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial investigated injection of autologous MSCs (20-200 million cells) into akinetic or hypokinetic areas in hearts that were unsuitable for surgical revascularization during coronary artery bypass graft surgery (CABG)<sup>[29]</sup>. Cardiac MRI analysis demonstrated that MSC injection increased EF by 9.4% as well as increased scar reduction by 48%

and contractile improvement in dysfunctional areas where surgical reperfusion was not performed<sup>[29]</sup>. Although this study lacked a placebo control group and had a limited patient number (6 patients), it demonstrates the potential benefits of injection of MSCs directly into non-revascularized myocardium. The Cardiopoietic stem Cell therapy in heart failure (C-CURE) trial tested the ability of a "cardiogenic cocktail" to enhance the therapeutic benefits of autologous MSCs<sup>[30]</sup>. Bartunek *et al*<sup>[30]</sup> pretreated MSCs with growth factors to enhance their cardioprotective functions. Twenty-one patients with class 2 or 3 heart failure received over 700 million cardiogenic cocktail treated MSCs by electromechanically guided endomyocardial injections. No adverse events or systemic toxicity was observed. Moreover, in LV EF, end-systolic volume and the 6-min walking test were significantly improved. Subsequently, the Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure (CHART-1) trial is currently ongoing. This study is investigating the efficacy and safety of Bone Marrow-derived Mesenchymal Cardiopoietic Cells for the Treatment of Chronic Advanced Ischemic Heart Failure. The safety and efficacy of MSCs and modified MSCs in patients have been confirmed. In the future, randomized controlled trials involving a large population of patients are anticipated.

## CDCS IN ISCHEMIC CARDIOMYOPATHY

Smith *et al*<sup>[31]</sup> expanded in culture tissue from percutaneous myocardial biopsies to form cardiospheres as the basis for cardiac stem cell expansion. They selected floating cardiospheres (out-growing cells) for culture and expanded them in a monolayer to isolate what is termed CDCs. Cardiospheres and CDCs express antigens specific for stem cells (cKit, CD90, CD105 and the absence of CD34 and CD45) as well as proteins vital for cardiac contractility (Nkx2.5, GATA4) and electrical function (Cx43)<sup>[32]</sup>. This defines cardiospheres and CDCs as a population of cardiac progenitor cells. Cardiospheres are heterogeneous groups of cells that contain not only adult CSCs, which are capable of long-term self-renewal and cardiomyocyte differentiation, but also vascular cells and differentiated progenitor cells<sup>[33]</sup>. Preclinical investigations were exclusively reported from Marban's group, they demonstrated that administration of CDCs in an experimental acute MI model reduced LV remodeling, improved contractility and reduced the infarct size without improvement in cardiac function<sup>[5]</sup>. Specifically they show that injection of 10 million of autologous CDCs to a swine model of infarcted myocardium resulted in a significant reduction in infarction size (approximately 5%) compared to a 2.4% reduction in placebo with no change in global function<sup>[5]</sup>. Malliaras *et al*<sup>[34]</sup> showed that injection of 12.5 million of allogeneic CDCs significant reduced scar size (3.6%) and preserved EF in a swine model of MI compared to no reduction in scar size (0.4%) and deterioration of EF (approximately

9.9%) in placebo. Lee *et al*<sup>[33]</sup> compared the effects of CDCs and their precursor cells, cardiospheres, in a swine MI model. They found that the effects on infarct reduction and preservation of EF were similar in both CDCs and cardiospheres whereas there was improved hemodynamics and regional function and preservation of LV chamber remodeling (all quantified by serial cardiac MRI) in animals receiving cardiospheres.

We previously demonstrated that slow infusion of CDCs into the three major coronary arteries (total dose 30 million CDCs) in swine with hibernating myocardium improved regional function in ischemic LAD (wall thickening: 23% to 51%,  $P < 0.05$ ) as well as in the normal right coronary artery (RCA) regions (68% to 107%,  $P < 0.05$ ) and global function (EF: 54% to 71%,  $P < 0.05$ )<sup>[35]</sup>. Quantitative histochemical analysis demonstrated that CDCs increased myocyte nuclear density and significantly reduced myocyte cellular hypertrophy in hibernating LAD and normal RCA regions indicating viable myocardium is a main therapeutic target.

The cardiosphere-derived autologous stem cells to reverse ventricular dysfunction (CADUCEUS) involved 25 patients who were given 12.5-25 million autologous CDCs<sup>[36]</sup> after successful percutaneous coronary intervention. The CDCs were expanded for approximately 36 d in culture from right ventricular endomyocardial biopsies taken 2-4 wk after acute MI. After expansion CDCs were injected into the previously stented coronary artery between 6-12 wk after heart attack. Despite the lack of improvement in left ventricular EF or patient reported outcomes, the scar reduction was 28% and 46% at 6 and 12 mo respectively and regional wall thickening was significantly improved in treated patients by 7.7%<sup>[37]</sup>. Serious adverse events were also reported to be three times higher in the treated group, however due to the relatively small number of patients enrolled, this trial cannot ascertain to the safety of CDCs. The autologous human cardiac-derived stem cell to treat ischemic cardiomyopathy (ALCADIA) trial investigated CDCs expanded from cardiac (endomyocardial) tissue isolated during CABG. This trial combined the use of stem cells, bioengineered scaffolds and biologics to create a hybrid therapy. CDCs were cultured for 1 mo before intracoronary injection followed by placement of a gelatin sheet containing bFGF over the injection site. Six months after therapy, cardiac MRI indicated a 12.1% increase in EF, a 3.3% reduction in infarct size and a significant improvement in wall motion as well as maximum aerobic exercise capacity. Since this study enrolled only 6 subjects, study is anticipated to enroll larger patients.

The transcatheter infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology trial involved in 14 patients who had hypoplastic left heart syndrome. Tissue was isolated from the right atrium of patients receiving stage 2 (Glenn) or stage 3 (Fontan) surgeries<sup>[38]</sup>. Cardiospheres were expanded from this right atrium tissue for 2-3 wk in culture. CDCs (2-3



million autologous cells,  $n = 7$ ) were injected into the 3 major coronary arteries 1 mo after surgery<sup>[38]</sup>. At 18 mo post injection, cardiac echo and MRI indicated an increase in right ventricular EF from 46.9% to 54.0% ( $P = 0.0004$ ) compared to no change in EF (46.7% to 48.7%,  $P$ -ns) in control. This was a small study (only 7 patients received CDCs) but indicates that viable and dysfunctional myocardium can be treated with autologous CDCs. Although CDCs are beneficial in patients with heart disease, CDCs have many characteristics that overlap with MSCs<sup>[39]</sup>. Therefore, it is necessary to identify the similarities and differences in biological responses of both MSCs and CDCs prior to further proceeding with clinical applications.

### CSCS IN ISCHEMIC CARDIOMYOPATHY

Several investigators have demonstrated the presence of small clusters of Sca-1+, cKit+ or a side population cells (multipotent stem cells identified by the ability to efflux Hoechst dye) in the cardiac atria and apex<sup>[40-42]</sup>. These cells were named CSCs and are most abundant during postnatal cardiac development after birth. Progeny of CSCs acquire a cardiomyocyte phenotype therefore resident CSCs are optimal candidates for cardiac regeneration studies. CSCs are self-renewing, can replace senescent and apoptotic CSCs *via* mobilization of BM-derived stem cells, and participate in maintaining the CSC pool in the heart<sup>[43-45]</sup>. In adulthood, the cells are quiescent and reside within the heart. Following ischemic injury, activation by paracrine signals induces CSCs to divide. Nevertheless, their proliferative potential is limited and the extent of the myocardial injury (e.g., necrosis and fibrosis following MI) is frequently too large to be compensated by new cardiomyocytes formed from dividing resident CSCs<sup>[40]</sup>. In the normal organism the heart retains a pool of CSCs that regulate cardiac homeostasis by maintaining a low level of myocyte proliferation, regeneration and cell death<sup>[2]</sup>. It is well known that CSCs are a rare population in the myocardium making their isolation and cultivation difficult and time-consuming. Since these cells are located in the heart and are primed for cardiac repair, protocols to enhance their endogenous activity or expand these cells *in vitro* before re-implanting them in the heart are currently being tested. A limited number of animal studies indicate that the administration of CSCs can slow left ventricular remodeling and cardiac improve function after ischemic injury<sup>[40,46,47]</sup>. Welt *et al.*<sup>[48]</sup> demonstrated that intramyocardial injection of autologous CSCs in a canine infarct model with permanent LAD occlusion resulted in the preservation of global function (31% to 33%) and reduced LV remodeling compared to functional deterioration (35% to 26%,  $P < 0.05$ ) and LV remodeling in vehicle animals<sup>[48]</sup>. Bolli *et al.*<sup>[49]</sup> demonstrated that administration of autologous CSCs to a swine model of chronically infarcted myocardium

resulted in improvements in regional and global contractility (45.4% to 51.7%,  $P < 0.05$ ) as well as engraftment and differentiation of injected CSCs<sup>[49]</sup>.

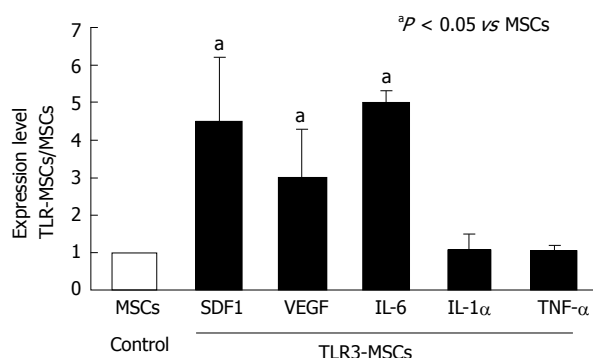
The stem cell infusion in patients with ischemic cardiomyopathy (SCIPIO) trial isolated autologous CSCs during CABG<sup>[50]</sup>. SCIPIO involved 23 patients who had experienced MI in the past and exhibited an EF of under 40%. One million of cKit positive and lineage negative CSCs were isolated with magnetic beads from cultures of right atrial appendage tissue and administered *via* intracoronary infusion 1 mo after CABG. Twelve months after the treatment, infarct size was decreased by 30.2%, regional wall thickening was increased by 18% and left ventricular EF was increased by 8.2%. The benefits of treatment continued to increase and left ventricular EF was increased by 12% after 2 years<sup>[51]</sup>. Although studies have shown the beneficial effects of CSCs on the infarcted myocardium, their biological actions in the heart are still controversial<sup>[52]</sup>. Further studies are necessary to clarify the significance of CSCs in clinical applications.

### FUTURE DIRECTIONS

Based on current achievements in experimental large animal studies and clinical trials of cell-based therapies, it is evident that cell therapies still require significant progress to be registered in the daily practice of modern medical therapies. The following strategies are solutions to overcome current limitation of cell-based therapies.

### PRECONDITIONED MSCS

Since the safety and efficacy of MSCs has been demonstrated by clinical work, there has been an increasing interest on enhancing the benefits of MSC therapy. For example, combining MSC and pharmacotherapy<sup>[53]</sup>, genetically modifying MSCs<sup>[54-56]</sup> and pre-conditioning MSCs<sup>[57]</sup> are approaches that are being explored to augment MSC-mediated cardiac repair. MSCs transfected to overexpress Akt or cell survival protein promoted myocardial protective function<sup>[16,55]</sup>. Furthermore, MSCs engineered to express combinations of gene products such as Akt and angiopoietin-1 (Ang1) have also shown functional benefits in experimental animal models<sup>[58]</sup>. MSCs overexpressing VEGF and SDF-1 improved cardiac function by activating Akt pathway<sup>[54]</sup>. MSCs transfected to express heme-oxygenase 1 (HO-1), an enzyme that improves MSC tolerance to hypoxia, infused into a cardiac ischemia-reperfusion model improve EF and lower end systolic volume compared to controls<sup>[59]</sup>. MSCs pretreated with growth factors, bFGF, IGF-1 and bone morphogenetic protein 2 (BMP2), improved myocardial repair in a rat model of MI<sup>[60]</sup>. Those preconditioned MSCs improved engraftment and survival of transplanted cells. Although data are promising, the safety of these cells must be carefully evaluated before use in humans.



**Figure 1 Toll-like receptor 3-mesenchymal stem cells enhance to secrete paracrine factors.** RNA mimetic polyinosinic-polycytidylic acid [poly(I:C)] stimulated TLR3 system on MSCs. TLR3-MSCs secreted a variety of paracrine factors. RT-PCR detected significant upregulation of SDF1, VEGF and IL6 while inflammation related cytokines (IL-1 $\alpha$ , TNF $\alpha$ ) were downregulated. Injection of TLR3-MSCs in cardiomyopathy model improved cardiac function more than standard MSCs in association with increasing myocyte proliferation, reducing fibrosis and myocyte apoptosis. TLR3: Toll-like receptor 3; MSCs: Mesenchymal stem cells; SDF1: Stromal cell-derived factor-1; VEGF: Vascular endothelial growth factor; IL: Interleukin; TNF: Tumor necrosis factor.

## PRECONDITIONED MSCS WITHOUT GENETIC MODIFICATION

As mentioned above, the currently used approaches to enhance stem cells are mostly through genetic modification. Thus, modified cells are not considered as a clinically relevant approach because genetically engineered stem cells may have increased unwanted long-term side-effects. We demonstrated that stimulation of toll-like receptor 3 (TLR3) produced many trophic factors without induction of inflammatory-related cytokines<sup>[26]</sup>. Poly (I:C) is structurally similar to double-stranded RNA and is known to interact with TLR3, which is expressed on the membrane of B-cells, macrophages, dendritic cells, MSCs and CDCs. Poly (I:C) directly reacts with the TLR3 receptor on the surface of MSCs/CDCs. Thus, after washing and collecting MSCs/CDCs after stimulation, poly (I:C) does not reside within the cells and does not affect the heart environment after injection of cells. Interaction of Poly (I:C) with TLR3 on MSCs causes secretion of the growth factors VEGF and the cytokine IL-6 without up-regulation of the inflammatory cytokines IL-1 and TNF $\alpha$  (Figure 1). Injection of TLR3 activated MSCs (TLR3-MSCs) in a non-ischemic cardiomyopathy model improved cardiac function more than standard MSCs in association with increasing myocyte proliferation, reducing fibrosis and myocyte apoptosis<sup>[61]</sup>. Activation of TLR3 on CDCs (TLR3-CDCs) stimulated the secretion of HGF, IGF1 and IL-6 without up-regulation of inflammatory cytokines. TLR3-MSCs or TLR3-CDCs are safe and feasible to use in the human heart. Further investigation is necessary to confirm the safety and feasibility to use in the heart.

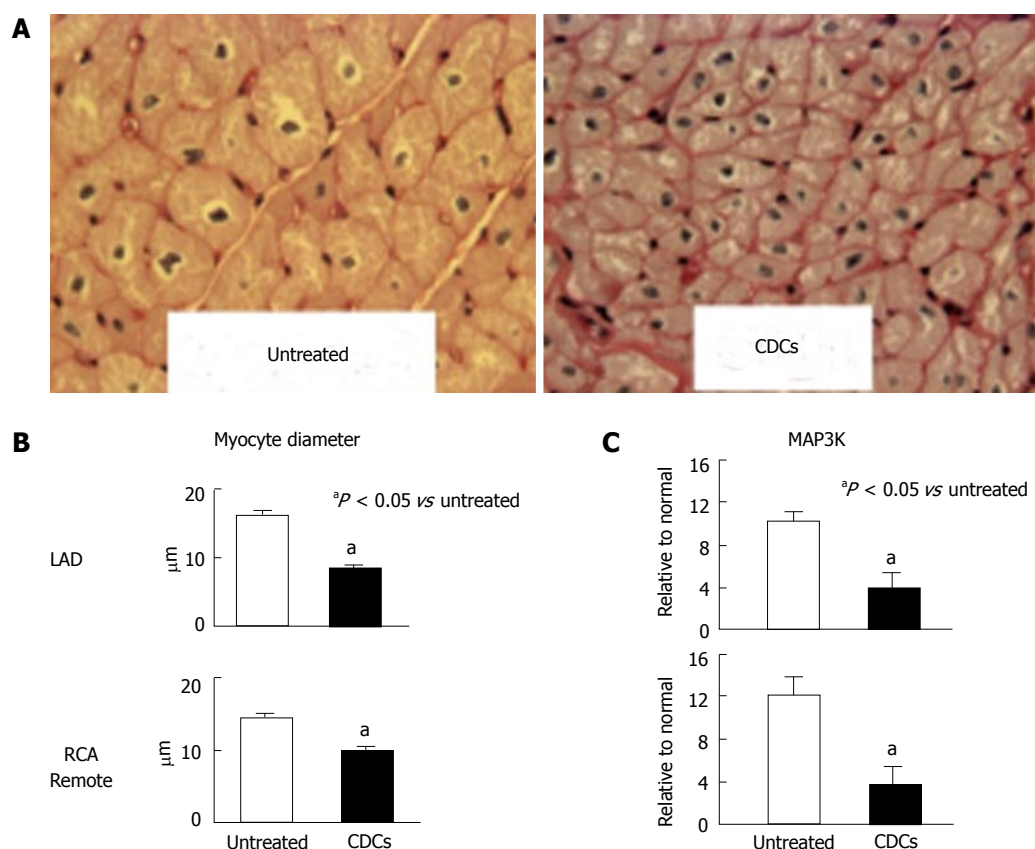
## MSCS AND CSCS

Combining MSC and CSC in post-MI treatment may

further enhance the therapeutic effects of each cell type. Recent work by Williams *et al*<sup>[62]</sup> demonstrated that the combined use of 1 million human CSCs with 200 million human MSCs provided greater recovery, almost to baseline, in a swine model of anterior wall MI<sup>[62]</sup>. While all stem cell treated animals demonstrated improved LV EF compared to placebo controls, notably, animals receiving dual cell therapy had a 2-fold greater reduction in scar size (21.1% for CSC/MSC vs 10.4% for CSC alone or 9.9% for MSC alone) and had improved rates of pressure change during diastole. Overall left ventricular chamber dynamics were improved in both the dual therapy and CSC or MSC alone treated groups. Interestingly, CSC alone treated animals demonstrated better isovolumic relaxation as compared to controls, while MSC alone treated animals exhibited improved diastolic compliance, indicating that the enhanced effect of dual therapy on both systolic and diastolic function may be due to a synergistic effect between CSC and MSC targeted mechanisms.

## REGIONAL INFUSION WITH STOP-FLOW VS GLOBAL INFUSION WITH SLOW INFUSION

Clinically applied techniques for cell delivery include endomyocardial injection using an injection needle or infusion of cells into a coronary artery supplying the infarcted region using a stop coronary flow technique. Although both approaches elicit significant improvements in cardiac function, they increase the risk of endomyocardial hemorrhage and MIs caused by stem cells plugs in the capillaries which could potentially limit the beneficial effects of cell-therapy. We previously demonstrated that slow infusion of MSCs into the three major coronary arteries without stop flow technique (global infusion) did not cause microembolization and stimulated prominent cardiac regeneration in ischemic as well as normally perfused RCA regions in swine with hibernating myocardium<sup>[17]</sup>. Likewise, intracoronary injection of autologous CDCs<sup>[35]</sup> without a stop-flow technique in swine with hibernating myocardium stimulated myocyte proliferation and regeneration in an ischemic LAD region as well as the normally perfused RCA regions. Subsequently, we applied the global infusion approach in an acute MI model, CDC infusion significantly improved cardiac function despite no changes in the size of infarction area. These results indicate that scar reduction and functional improvement are independent phenomenon<sup>[63]</sup>. Accordingly, the approach of stem cell injection in the entire heart is safe and feasible to improve LV dysfunction and our results indicate that normally perfused and viable myocardium could be the target for regenerative therapy. Alternatively, combining stop-flow infusion in the infarcted area with slow flow infusion into the viable myocardium may be a method to enhance therapeutic efficacy.



**Figure 2** The effect of cardiosphere-derived cells on myocyte cell size and MAP kinase in the dysfunctional left anterior descending vs remote regions. A: Images (PAS staining) demonstrate that hypertrophied myocytes in untreated hibernating LAD became smaller after CDCs. Myofibrils were condensed indicating the production of healthy myocytes; B: Myocyte diameter was significantly reduced in hibernating LAD and remote regions; C: Corresponding to the morphological change, protein level of MAP3K was downregulated in LAD and remote regions. Data indicates CDCs induced myocyte regeneration and hypertrophy regression. CDCs: Cardiosphere-derived cells; LAD: Left anterior descending; RCA: Right coronary artery.

## ALLOGENEIC CDCS INFUSION IMMEDIATE AFTER REPERFUSION

Allogeneic CDCs can escape direct recognition of helper T cells due to the lack of expression of MHC class II antigen (SLA class II on pig)<sup>[34,64]</sup> and therefore are immunoprivileged. Based on these observations, a recent clinical trial was initiated using allogeneic human CDC treatment in patients with chronic myocardial infarction (ALLSTAR trial). These allogeneic cells can be expanded *ex vivo* and stored for use at a future time<sup>[18]</sup>. This "off-the-shelf" treatment for patients with AMI immediately after revascularization is unique in that *ex vivo* expanded cells are available immediately for treatment and the patient does not need to wait for cell processing and expansion<sup>[19]</sup>. Recently, administration of CDCs immediately after reperfusion demonstrated the protective effects in swine with acute myocardial infarction<sup>[65]</sup>. Thirty minutes after ischemia-reperfusion, CDCs were injected into the infarct-related coronary artery and reduced the size of the infarct area and myocyte apoptosis in the border region. Although data were collected 48 h post CDCs injection, we recently demonstrated that functional improvement and myocyte regeneration were maintained up to 1-mo follow-up. These data indicate that the cardioprotective

effects at early times were maintained. Previously bone marrow cell and endothelial progenitor cells injection in patients were performed within 7 d after AMI and demonstrated superiority to cell injection within 24 h<sup>[66,67]</sup>. Since stem cell homing factors (mobilization, migration and adhesion) are maximized between day 3 and day 7<sup>[68]</sup>, these therapies are effective for stem cell homing. However, the inflammation caused by MI is already developed and the potential cardioprotective effects (*i.e.*, *via* anti-apoptotic effects or modulation of the inflammatory response) are limited when cells are delivered. Since CDCs secrete multiple cytokines (SDF-1, Akt)<sup>[69]</sup>, growth factors (HGF, IGF-1, VEGF)<sup>[69,70]</sup> and exosomes<sup>[71,72]</sup>, CDCs early after reperfusion might reduce the inflammatory response and protect the heart from functional deterioration due to reperfusion injury.

## REPEATED INJECTION OF STEM CELLS

Since single injection of CDCs improved regional function and reduced scar volume<sup>[36,37]</sup>, repeated injection of stem cells has been considered a more effective approach to regenerate myocardial tissue<sup>[73,74]</sup>. However, the initial infusion of cells activates and enhances the immune response<sup>[34,64]</sup> and the subsequent injected cells are quickly eliminated and ineffective. This quick

reaction is mainly associated with acquired/adaptive rather than innate immunity. Repeated infusion of autologous/allogeneic CDCs may overcome the limited functional recovery from a single injection<sup>[73,74]</sup>. However, the extent of immune activation caused by repeated injections is unclear and optimal immunosuppressive therapy is still undetermined. Development of efficacious CDC platforms administered with optimal immune suppression would circumvent barriers related to multiple injections of stem cells and allow the widespread application of “off-the-shelf” cell therapy to treat the large number of patients in need<sup>[64,75,76]</sup>.

## EXOSOME ACTIVATION AND MICRORNAS

The beneficial effects of adult stem cells are mainly associated with the secretion of paracrine factors rather than direct differentiation of *de novo* cardiac cells<sup>[9]</sup>. They secrete multiple growth factors and cytokines which reduce scar volume and myocyte apoptosis, increase myocyte proliferation and activate endogenous CSCs to produce new myocytes. Recently, it was reported that CDCs secrete exosomes and they play important roles for cardiac regeneration<sup>[71]</sup>. Exosomes transfer microRNAs from cell to cell and they inhibit inflammation and apoptosis and increase angiogenesis and myocyte proliferation. Therefore, a new method of treatment may focus on how to effectively stimulate secretion of exosomes from stem cells or may be directly injecting exosomes in the infarcted myocardium.

## ANTI-HYPERTROPHIC EFFECT

Besides their regeneration potential, adult stem cells have other beneficial effects such as anti-apoptosis, anti-inflammation, extracellular matrix reduction, contractile alternation and anti-hypertrophy. Pathological cardiac hypertrophy in post MI remodeling is a major cause of mortality and morbidity including the risk of sudden cardiac death and heart failure in patients<sup>[77-81]</sup>. It is associated with increased interstitial fibrosis, cell death and cardiac dysfunction. LV assist devices used in heart failure patients as a bridge to heart transplantation not only improved peripheral circulation but also reversed the geometric remodeling of the heart and restored the function of the heart<sup>[82-85]</sup>.

We demonstrated that global infusion of CDCs into hearts with chronically ischemic myocardium's improved myocardial function in the ischemic and remote regions<sup>[86]</sup>. CDCs significantly increased newly formed small myocytes. Interestingly, CDCs also reduced the cell size of pre-existing myocytes and hypertrophic signaling (mitogen activated kinases) in the ischemic and remote regions. Data indicate that CDCs have the potential to reverse cardiac hypertrophy (Figure 2). Future studies are necessary to determine whether hypertrophy regression is primary or secondary to

myocardial regeneration and functional improvement.

## CONCLUSION

Promising data derived from experimental models indicate the potential success of using cell based therapy in clinical applications. To overcome the current limitations in the field, development of new methods to enhance cardiac repair is necessary. In light of their proven safety profiles, MSC, CDC and CSC are prime candidates for cell based therapies. Recently, it was reported that a combination of CSCs and MSCs may be more effective than either one alone, and this approach is under investigation. Similarly, pre-conditioning MSC and CDCs are also promising approaches, and further investigation is anticipated. Optimizing the dose and method of delivery, as well as the timing for delivery are important variables that should be studied. It is anticipated that cell based therapies will become a mainstream treatment for heart diseases due to their potential ability to improve functional outcomes and decrease mortality.

## ACKNOWLEDGMENTS

Author would like to thank Dr. Jessica Reynolds and Mr Takayuki Suzuki from University at Buffalo for proof-reading and data collection.

## REFERENCES

- 1 **Mozaffarian D**, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation* 2015; **131**: e29-322 [PMID: 25520374 DOI: 10.1161/CIR.000000000000152]
- 2 **Kajstura J**, Urbanek K, Perl S, Hosoda T, Zheng H, Ogórek B, Ferreira-Martins J, Goichberg P, Rondon-Clavo C, Sanada F, D'Amario D, Rota M, Del Monte F, Orlic D, Tisdale J, Leri A, Anversa P. Cardiomyogenesis in the adult human heart. *Circ Res* 2010; **107**: 305-315 [PMID: 20522802 DOI: 10.1161/CIRCRESAHA.110.223024]
- 3 **Schuleri KH**, Feigenbaum GS, Centola M, Weiss ES, Zimmet JM, Turney J, Kellner J, Zviman MM, Hatzistergos KE, Detrick B, Conte JV, McNiece I, Steenbergen C, Lardo AC, Hare JM. Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. *Eur Heart J* 2009; **30**: 2722-2732 [PMID: 19586959 DOI: 10.1093/eurheartj/ehp265]
- 4 **Hatzistergos KE**, Quevedo H, Oskoue BN, Hu Q, Feigenbaum GS, Margitich IS, Mazhari R, Boyle AJ, Zambrano JP, Rodriguez JE, Dulce R, Pattany PM, Valdes D, Revilla C, Heldman AW, McNiece I, Hare JM. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ Res* 2010; **107**: 913-922 [PMID: 20671238 DOI: 10.1161/CIRCRESAHA.110.222703]
- 5 **Johnston PV**, Sasano T, Mills K, Evers R, Lee ST, Smith RR, Lardo AC, Lai S, Steenbergen C, Gerstenblith G, Lange R, Marbán E. Engraftment, differentiation, and functional benefits of autologous



- cardiosphere-derived cells in porcine ischemic cardiomyopathy. *Circulation* 2009; **120**: 1075-1083, 7 p following 1083 [PMID: 19738142 DOI: 10.1161/CIRCULATIONAHA.108.816058]
- 6 **Schächinger V**, Assmus B, Britten MB, Honold J, Lehmann R, Teupe C, Abolmaali ND, Vogl TJ, Hofmann WK, Martin H, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. *J Am Coll Cardiol* 2004; **44**: 1690-1699 [PMID: 15489105 DOI: 10.1016/j.jacc.2004.08.014]
  - 7 **Meyer GP**, Wollert KC, Lotz J, Steffens J, Lippolt P, Fichtner S, Hecker H, Schaefer A, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. *Circulation* 2006; **113**: 1287-1294 [PMID: 16520413 DOI: 10.1161/CIRCULATIONAHA.105.575118]
  - 8 **Assmus B**, Fischer-Rasokat U, Honold J, Seeger FH, Fichtlscherer S, Tonn T, Seifried E, Schächinger V, Dimmeler S, Zeiher AM. Transcoronary transplantation of functionally competent BMCs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: results of the TOPCARE-CHD Registry. *Circ Res* 2007; **100**: 1234-1241 [PMID: 17379833 DOI: 10.1161/01.RES.0000264508.47717.6b]
  - 9 **Malliaras K**, Zhang Y, Seinfeld J, Galang G, Tseliou E, Cheng K, Sun B, Aminzadeh M, Marbán E. Cardiomyocyte proliferation and progenitor cell recruitment underlie therapeutic regeneration after myocardial infarction in the adult mouse heart. *EMBO Mol Med* 2013; **5**: 191-209 [PMID: 23255322 DOI: 10.1002/emmm.201201737]
  - 10 **Chen SL**, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S, Sun JP. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94**: 92-95 [PMID: 15219514]
  - 11 **Min JY**, Sullivan MF, Yang Y, Zhang JP, Converso KL, Morgan JP, Xiao YF. Significant improvement of heart function by cotransplantation of human mesenchymal stem cells and fetal cardiomyocytes in postinfarcted pigs. *Ann Thorac Surg* 2002; **74**: 1568-1575 [PMID: 12440610]
  - 12 **Shake JG**, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, Redmond JM, Pittenger MF, Martin BJ. Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. *Ann Thorac Surg* 2002; **73**: 1919-1925; discussion 1926 [PMID: 12078791]
  - 13 **Toma C**, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation* 2002; **105**: 93-98 [PMID: 1172882 DOI: 10.1161/hc0102.101442]
  - 14 **Wollert KC**, Drexler H. Mesenchymal stem cells for myocardial infarction: promises and pitfalls. *Circulation* 2005; **112**: 151-153 [PMID: 16009806 DOI: 10.1161/CIRCULATIONAHA.105.551895]
  - 15 **Hofmann M**, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, Ganser A, Knapp WH, Drexler H. Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation* 2005; **111**: 2198-2202 [PMID: 15851598 DOI: 10.1161/01.CIR.0000163546.27639.AA]
  - 16 **Mangi AA**, Noiseux N, Kong D, He H, Rezvani M, Ingwall JS, Dzau VJ. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nat Med* 2003; **9**: 1195-1201 [PMID: 12910262 DOI: 10.1038/nm912]
  - 17 **Suzuki G**, Iyer V, Lee TC, Cauty JM. Autologous mesenchymal stem cells mobilize cKit+ and CD133+ bone marrow progenitor cells and improve regional function in hibernating myocardium. *Circ Res* 2011; **109**: 1044-1054 [PMID: 21885831 DOI: 10.1161/CIRCRESAHA.111.245969]
  - 18 **Quevedo HC**, Hatzistorgos KE, Oskoue BN, Feigenbaum GS, Rodriguez JE, Valdes D, Pattany PM, Zambrano JP, Hu Q, McNiece I, Heldman AW, Hare JM. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. *Proc Natl Acad Sci USA* 2009; **106**: 14022-14027 [PMID: 19666564 DOI: 10.1073/pnas.0903201106]
  - 19 **Hare JM**, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, Gerstenblith G, DeMaria AN, Denktas AE, Gammon RS, Hermiller JB, Reisman MA, Schaer GL, Sherman W. 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 [PMID: 19958962 DOI: 10.1016/j.jacc.2009.06.055]
  - 20 **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 [PMID: 15812508 DOI: 10.1038/nm0405-367]
  - 21 **Tang YL**, Zhu W, Cheng M, Chen L, Zhang J, Sun T, Kishore R, Phillips MI, Losordo DW, Qin G. Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. *Circ Res* 2009; **104**: 1209-1216 [PMID: 19407239 DOI: 10.1161/CIRCRESAHA.109.197723]
  - 22 **Williams AR**, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. *Circ Res* 2011; **109**: 923-940 [PMID: 21960725 DOI: 10.1161/CIRCRESAHA.111.243147]
  - 23 **Shabbir A**, Zisa D, Suzuki G, Lee T. Heart failure therapy mediated by the trophic activities of bone marrow mesenchymal stem cells: a noninvasive therapeutic regimen. *Am J Physiol Heart Circ Physiol* 2009; **296**: H1888-H1897 [PMID: 19395555 DOI: 10.1152/ajpheart.00186.2009]
  - 24 **Williams AR**, Suncion VY, McCall F, Guerra D, Mather J, Zambrano JP, Heldman AW, Hare JM. Durable scar size reduction due to allogeneic mesenchymal stem cell therapy regulates whole-chamber remodeling. *J Am Heart Assoc* 2013; **2**: e000140 [PMID: 23686370 DOI: 10.1161/JAHA.113.000140]
  - 25 **Houtgraaf JH**, de Jong R, Kazemi K, de Groot D, van der Spoel TI, Arslan F, Hoefer I, Pasterkamp G, Itescu S, Zijlstra F, Geleijnse ML, Serruys PW, Duckers HJ. Intracoronary infusion of allogeneic mesenchymal precursor cells directly after experimental acute myocardial infarction reduces infarct size, abrogates adverse remodeling, and improves cardiac function. *Circ Res* 2013; **113**: 153-166 [PMID: 23658436 DOI: 10.1161/CIRCRESAHA.112.300730]
  - 26 **Leiker M**, Suzuki G, Iyer VS, Cauty JM, Lee T. Assessment of a nuclear affinity labeling method for tracking implanted mesenchymal stem cells. *Cell Transplant* 2008; **17**: 911-922 [PMID: 19069634 DOI: 10.3727/096368908786576444]
  - 27 **Suncion VY**, Ghersin E, Fishman JE, Zambrano JP, Karantalis V, Mandel N, Nelson KH, Gerstenblith G, DiFede Velazquez DL, Breton E, Sitammagari K, Schulman IH, Taldone SN, Williams AR, Sanina C, Johnston PV, Brinker J, Altman P, Mushtaq M, Trachtenberg B, Mendizabal AM, Tracy M, Da Silva J, McNiece IK, Lardo AC, George RT, Hare JM, Heldman AW. Does transendocardial injection of mesenchymal stem cells improve myocardial function locally or globally?: An analysis from the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) randomized trial. *Circ Res* 2014; **114**: 1292-1301 [PMID: 24449819 DOI: 10.1161/CIRCRESAHA.114.302854]
  - 28 **Hare JM**, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, Tracy M, Ghersin E, Johnston PV, Brinker JA, Breton E, Davis-Sproul J, Schulman IH, Byrnes J, Mendizabal AM, Lowery MH, Rouy D, Altman P, Wong Po Foo C, Ruiz P, Amador A, Da Silva J, McNiece IK, Heldman AW, George R, Lardo A. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA* 2012; **308**: 2369-2379 [PMID: 23117550 DOI: 10.1001/jama.2012.25321]
  - 29 **Karantalis V**, DiFede DL, Gerstenblith G, Pham S, Symes J, Zambrano JP, Fishman J, Pattany P, McNiece I, Conte J, Schulman S,

- Wu K, Shah A, Breton E, Davis-Sproul J, Schwarz R, Feigenbaum G, Mushtaq M, Suncion VY, Lardo AC, Borrello I, Mendizabal A, Karas TZ, Byrnes J, Lowery M, Heldman AW, Hare JM. Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. *Circ Res* 2014; **114**: 1302-1310 [PMID: 24565698 DOI: 10.1161/CIRCRESAHA.114.303180]
- 30 **Bartunek J**, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El Nakadi B, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tendera M, Waldman S, Wijns W, Terzic A. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. *J Am Coll Cardiol* 2013; **61**: 2329-2338 [PMID: 23583246 DOI: 10.1016/j.jacc.2013.02.071]
- 31 **Smith RR**, Barile L, Cho HC, Leppo MK, Hare JM, Messina E, Giacomello A, Abraham MR, Marbán E. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. *Circulation* 2007; **115**: 896-908 [PMID: 17283259 DOI: 10.1161/CIRCULATIONAHA.106.655209]
- 32 **Barile L**, Messina E, Giacomello A, Marbán E. Endogenous cardiac stem cells. *Prog Cardiovasc Dis* 2007; **50**: 31-48 [PMID: 17631436]
- 33 **Lee ST**, White AJ, Matsushita S, Malliaras K, Steenbergen C, Zhang Y, Li TS, Terrovitis J, Yee K, Simsir S, Makkar R, Marbán E. Intramyocardial injection of autologous cardiospheres or cardiosphere-derived cells preserves function and minimizes adverse ventricular remodeling in pigs with heart failure post-myocardial infarction. *J Am Coll Cardiol* 2011; **57**: 455-465 [PMID: 21251587 DOI: 10.1016/j.jacc.2010.07.049]
- 34 **Malliaras K**, Smith RR, Kanazawa H, Yee K, Seinfeld J, Tseliou E, Dawkins JF, Kreke M, Cheng K, Luthringer D, Ho CS, Blusztajn A, Valle I, Chowdhury S, Makkar RR, Dharmakumar R, Li D, Marbán L, Marbán E. Validation of contrast-enhanced magnetic resonance imaging to monitor regenerative efficacy after cell therapy in a porcine model of convalescent myocardial infarction. *Circulation* 2013; **128**: 2764-2775 [PMID: 24061088 DOI: 10.1161/CIRCULATIONAHA.113.002863]
- 35 **Suzuki G**, Leiker M, Cimato TR, Canty JM. Intracoronary infusion of cardiosphere-derived cells (icCDCs) improves cardiac function by stimulating myocyte proliferation in non-infarcted hibernating myocardium with no effect in normal myocardium. *Circulation* 2011; **124** (Suppl): A12590. Available from: URL: [http://circ.ahajournals.org/cgi/content/meeting\\_abstract/124/21\\_MeetingAbstracts/A8851](http://circ.ahajournals.org/cgi/content/meeting_abstract/124/21_MeetingAbstracts/A8851)
- 36 **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 [PMID: 22336189 DOI: 10.1016/S0140-6736(12)60195-0]
- 37 **Malliaras K**, Makkar RR, Smith RR, Cheng K, Wu E, Bonow RO, Marbán L, Mendizabal A, Cingolani E, Johnston PV, Gerstenblith G, Schuleri KH, Lardo AC, Marbán E. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (Cardiosphere-Derived Autologous stem Cells to reverse ventricular dysfunction). *J Am Coll Cardiol* 2014; **63**: 110-122 [PMID: 24036024 DOI: 10.1016/j.jacc.2013.08.724]
- 38 **Ishigami S**, Ohtsuki S, Tarui S, Ousaka D, Eitoku T, Kondo M, Okuyama M, Kobayashi J, Baba K, Arai S, Kawabata T, Yoshizumi K, Tateishi A, Kuroko Y, Iwasaki T, Sato S, Kasahara S, Sano S, Oh H. Intracoronary autologous cardiac progenitor cell transfer in patients with hypoplastic left heart syndrome: the TICAP prospective phase 1 controlled trial. *Circ Res* 2015; **116**: 653-664 [PMID: 25403163 DOI: 10.1161/CIRCRESAHA.116.304671]
- 39 **Weil BR**, Suzuki G, Leiker MM, Fallavollita JA, Canty JM Jr. Comparative Efficacy of Intracoronary Allogeneic Mesenchymal Stem Cells and Cardiosphere-Derived Cells in Swine with Hibernating Myocardium. *Circ Res* 2015; **11**: 634-644 [PMID: 26271689 DOI: 10.1161/CIRCRESAHA.115.306850]
- 40 **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 [PMID: 14505575]
- 41 **Pfister O**, Mouquet F, Jain M, Summer R, Helmes M, Fine A, Colucci WS, Liao R. CD31- but Not CD31+ cardiac side population cells exhibit functional cardiomyogenic differentiation. *Circ Res* 2005; **97**: 52-61 [PMID: 15947249 DOI: 10.1161/01.RES.0000173297.53793.faj]
- 42 **Oh H**, Bradfute SB, Gallardo TD, Nakamura T, Gaussin V, Mishina Y, Pocius J, Michael LH, Behringer RR, Garry DJ, Entman ML, Schneider MD. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci USA* 2003; **100**: 12313-12318 [PMID: 14530411 DOI: 10.1073/pnas.2132126100]
- 43 **Mouquet F**, Pfister O, Jain M, Oikonomopoulos A, Ngoy S, Summer R, Fine A, Liao R. Restoration of cardiac progenitor cells after myocardial infarction by self-proliferation and selective homing of bone marrow-derived stem cells. *Circ Res* 2005; **97**: 1090-1092 [PMID: 16269652 DOI: 10.1161/01.RES.0000194330.66545.f5]
- 44 **Liao R**, Pfister O, Jain M, Mouquet F. The bone marrow--cardiac axis of myocardial regeneration. *Prog Cardiovasc Dis* 2007; **50**: 18-30 [PMID: 17631435 DOI: 10.1016/j.pcad.2007.03.001]
- 45 **Kajstura J**, Rota M, Whang B, Casapera S, Hosoda T, Bearzi C, Nurzynska D, Kasahara H, Zias E, Bonafé M, Nadal-Ginard B, Torella D, Nascimbene A, Quaini F, Urbanek K, Leri A, Anversa P. Bone marrow cells differentiate in cardiac cell lineages after infarction independently of cell fusion. *Circ Res* 2005; **96**: 127-137 [PMID: 15569828 DOI: 10.1161/01.RES.0000151843.79801.60]
- 46 **Linke A**, Müller P, Nurzynska D, Casarsa C, Torella D, Nascimbene A, Castaldo C, Casapera S, Böhm M, Quaini F, Urbanek K, Leri A, Hintze TH, Kajstura J, Anversa P. Stem cells in the dog heart are self-renewing, clonogenic, and multipotent and regenerate infarcted myocardium, improving cardiac function. *Proc Natl Acad Sci USA* 2005; **102**: 8966-8971 [PMID: 15951423 DOI: 10.1073/pnas.0502678102]
- 47 **Leri A**, Kajstura J, Anversa P. Cardiac stem cells and mechanisms of myocardial regeneration. *Physiol Rev* 2005; **85**: 1373-1416 [PMID: 16183916 DOI: 10.1152/physrev.00013.2005]
- 48 **Welt FG**, Gallegos R, Connell J, Kajstura J, D'Amario D, Kwong RY, Coelho-Filho O, Shah R, Mitchell R, Leri A, Foley L, Anversa P, Pfeffer MA. Effect of cardiac stem cells on left-ventricular remodeling in a canine model of chronic myocardial infarction. *Circ Heart Fail* 2013; **6**: 99-106 [PMID: 23212553 DOI: 10.1161/CIRCHEARTFAILURE.112.972273]
- 49 **Bolli R**, Tang XL, Sanganalilath SK, Rimoldi O, Mosna F, Abdel-Latif A, Jneid H, Rota M, Leri A, Kajstura J. Intracoronary delivery of autologous cardiac stem cells improves cardiac function in a porcine model of chronic ischemic cardiomyopathy. *Circulation* 2013; **128**: 122-131 [PMID: 23757309 DOI: 10.1161/CIRCULATIONAHA.112.001075]
- 50 **Bolli R**, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beache GM, Wagner SG, Leri A, Hosoda T, Sanada F, Elmore JB, Goichberg P, Cappetta D, Solankhi NK, Fahsah I, Rokosh DG, Slaughter MS, Kajstura J, Anversa P. Cardiac stem cells in patients with ischemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 2011; **378**: 1847-1857 [PMID: 22088800 DOI: 10.1016/S0140-6736(11)61590-0]
- 51 **Chugh AR**, Beache GM, Loughran JH, Mewton N, Elmore JB, Kajstura J, Pappas P, Tatoes 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 [PMID:

- 22965994 DOI: 10.1161/CIRCULATIONAHA.112.092627]
- 52 **van Berlo JH**, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, Middleton RC, Marbán E, Molkentin JD. c-kit<sup>+</sup> cells minimally contribute cardiomyocytes to the heart. *Nature* 2014; **509**: 337-341 [PMID: 24805242 DOI: 10.1038/nature13309]
  - 53 **Yang YJ**, Qian HY, Huang J, Li JJ, Gao RL, Dou KF, Yang GS, Willerson JT, Geng YJ. Combined therapy with simvastatin and bone marrow-derived mesenchymal stem cells increases benefits in infarcted swine hearts. *Arterioscler Thromb Vasc Biol* 2009; **29**: 2076-2082 [PMID: 19762786 DOI: 10.1161/ATVBAHA.109.189662]
  - 54 **Tang J**, Wang J, Guo L, Kong X, Yang J, Zheng F, Zhang L, Huang Y. Mesenchymal stem cells modified with stromal cell-derived factor 1 alpha improve cardiac remodeling via paracrine activation of hepatocyte growth factor in a rat model of myocardial infarction. *Mol Cells* 2010; **29**: 9-19 [PMID: 20016947]
  - 55 **Gnecchi M**, He H, Melo LG, Noiseux N, Morello F, de Boer RA, Zhang L, Pratt RE, Dzau VJ, Ingwall JS. Early beneficial effects of bone marrow-derived mesenchymal stem cells overexpressing Akt on cardiac metabolism after myocardial infarction. *Stem Cells* 2009; **27**: 971-979 [PMID: 19353525 DOI: 10.1002/stem.12]
  - 56 **Haider HKh**, Jiang S, Idris NM, Ashraf M. IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1alpha/CXCR4 signaling to promote myocardial repair. *Circ Res* 2008; **103**: 1300-1308 [PMID: 18948617 DOI: 10.1161/CIRCRESAHA.108.186742]
  - 57 **Hu X**, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA, Wei L. Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis. *J Thorac Cardiovasc Surg* 2008; **135**: 799-808 [PMID: 18374759 DOI: 10.1016/j.jtcvs.2007.07.071]
  - 58 **Shujia J**, Haider HK, Idris NM, Lu G, Ashraf M. Stable therapeutic effects of mesenchymal stem cell-based multiple gene delivery for cardiac repair. *Cardiovasc Res* 2008; **77**: 525-533 [PMID: 18032392 DOI: 10.1093/cvr/cvm077]
  - 59 **Tang YL**, Zhao Q, Qin X, Shen L, Cheng L, Ge J, Phillips MI. Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction. *Ann Thorac Surg* 2005; **80**: 229-236; discussion 236-237 [PMID: 15975372 DOI: 10.1016/j.athoracsur.2005.02.072]
  - 60 **Hahn JY**, Cho HJ, Kang HJ, Kim TS, Kim MH, Chung JH, Bae JW, Oh BH, Park YB, Kim HS. Pre-treatment of mesenchymal stem cells with a combination of growth factors enhances gap junction formation, cytoprotective effect on cardiomyocytes, and therapeutic efficacy for myocardial infarction. *J Am Coll Cardiol* 2008; **51**: 933-943 [PMID: 18308163 DOI: 10.1016/j.jacc.2007.11.040]
  - 61 **Mastri M**, Shah Z, McLaughlin T, Greene CJ, Baum L, Suzuki G, Lee T. Activation of Toll-like receptor 3 amplifies mesenchymal stem cell trophic factors and enhances therapeutic potency. *Am J Physiol Cell Physiol* 2012; **303**: C1021-C1033 [PMID: 22843797 DOI: 10.1152/ajpcell.00191.2012]
  - 62 **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 [PMID: 23224061 DOI: 10.1161/CIRCULATIONAHA.112.131110]
  - 63 **Suzuki G**, Weil BR, Leiker MM, Goelz A, Fallavollita JA, Canty JM. Global intracoronary infusion of allogeneic cardiosphere-derived cells (CDCs) immediately after reperfusion stimulates myocyte regeneration in remote viable myocardium in swine with acute myocardial infarction. *Circulation* 2014; **130**: A15656. Available from: URL: [http://circ.ahajournals.org/content/130/Suppl\\_2/A15656.short](http://circ.ahajournals.org/content/130/Suppl_2/A15656.short)
  - 64 **Malliaras K**, Li TS, Luthringer D, Terrovitis J, Cheng K, Chakravarty T, Galang G, Zhang Y, Schoenhoff F, Van Eyk J, Marbán L, Marbán E. Safety and efficacy of allogeneic cell therapy in infarcted rats transplanted with mismatched cardiosphere-derived cells. *Circulation* 2012; **125**: 100-112 [PMID: 22086878 DOI: 10.1161/CIRCULATIONAHA.111.042598]
  - 65 **Kanazawa H**, Tseliou E, Malliaras K, Yee K, Dawkins JF, De Couto G, Smith RR, Kreke M, Seinfeld J, Middleton RC, Gallet R, Cheng K, Luthringer D, Valle I, Chowdhury S, Fukuda K, Makkar RR, Marbán L, Marbán E. Cellular postconditioning: allogeneic cardiosphere-derived cells reduce infarct size and attenuate microvascular obstruction when administered after reperfusion in pigs with acute myocardial infarction. *Circ Heart Fail* 2015; **8**: 322-332 [PMID: 25587096 DOI: 10.1161/CIRCHEARTFAILURE.114.001484]
  - 66 **Assmus B**, Schächinger V, Teupe C, Britten M, Lehmann R, Döbert N, Grünwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002; **106**: 3009-3017 [PMID: 12473544 DOI: 10.1161/01.CIR.0000043246.74879.CD]
  - 67 **Wollert KC**, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004; **364**: 141-148 [PMID: 15246726 DOI: 10.1016/S0140-6736(04)16626-9]
  - 68 **Bartunek J**, Wijns W, Heyndrickx GR, Vanderheyden M. Timing of intracoronary bone-marrow-derived stem cell transplantation after ST-elevation myocardial infarction. *Nat Clin Pract Cardiovasc Med* 2006; **3** Suppl 1: S52-S56 [PMID: 16501632]
  - 69 **Chimenti I**, Smith RR, Li TS, Gerstenblith G, Messina E, Giacomello A, Marbán E. Relative roles of direct regeneration versus paracrine effects of human cardiosphere-derived cells transplanted into infarcted mice. *Circ Res* 2010; **106**: 971-980 [PMID: 20110532 DOI: 10.1161/CIRCRESAHA.109.210682]
  - 70 **Li TS**, Cheng K, Malliaras K, Smith RR, Zhang Y, Sun B, Matsushita N, Blusztajn A, Terrovitis J, Kusuoka H, Marbán L, Marbán E. Direct comparison of different stem cell types and subpopulations reveals superior paracrine potency and myocardial repair efficacy with cardiosphere-derived cells. *J Am Coll Cardiol* 2012; **59**: 942-953 [PMID: 22381431 DOI: 10.1016/j.jacc.2011.11.029]
  - 71 **Ibrahim AG**, Cheng K, Marbán E. Exosomes as critical agents of cardiac regeneration triggered by cell therapy. *Stem Cell Reports* 2014; **2**: 606-619 [PMID: 24936449 DOI: 10.1016/j.stemcr.2014.04.006]
  - 72 **Aminzadeh MA**, Tseliou E, Sun B, Cheng K, Malliaras K, Makkar RR, Marbán E. Therapeutic efficacy of cardiosphere-derived cells in a transgenic mouse model of non-ischaemic dilated cardiomyopathy. *Eur Heart J* 2015; **36**: 751-762 [PMID: 24866210 DOI: 10.1093/eurheartj/ehv196]
  - 73 **Gavira JJ**, Nasarre E, Abizanda G, Pérez-Ilzarbe M, de Martino-Rodríguez A, García de Jalón JA, Mazo M, Macías A, García-Bolao I, Pelacho B, Martínez-Caro D, Prósper F. Repeated implantation of skeletal myoblast in a swine model of chronic myocardial infarction. *Eur Heart J* 2010; **31**: 1013-1021 [PMID: 19700775 DOI: 10.1093/eurheartj/ehp342]
  - 74 **Premaratne GU**, Tambara K, Fujita M, Lin X, Kanemitsu N, Tomita S, Sakaguchi G, Nakajima H, Ikeda T, Komeda M. Repeated implantation is a more effective cell delivery method in skeletal myoblast transplantation for rat myocardial infarction. *Circ J* 2006; **70**: 1184-1189 [PMID: 16936434]
  - 75 **Malliaras K**, Marbán E. Cardiac cell therapy: where we've been, where we are, and where we should be headed. *Br Med Bull* 2011; **98**: 161-185 [PMID: 21652595 DOI: 10.1093/bmb/ldr018]
  - 76 **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 [PMID: 23989721 DOI: 10.1161/CIRCRESAHA.113.300219]
  - 77 **El-Sherif N**, Turitto G. Risk stratification and management of sudden cardiac death: a new paradigm. *J Cardiovasc Electrophysiol* 2003; **14**: 1113-1119 [PMID: 14521667 DOI: 10.1046/j.1540-8167.2003.03204.x]
  - 78 **Pacifico A**, Henry PD. Structural pathways and prevention of heart failure and sudden death. *J Cardiovasc Electrophysiol* 2003; **14**: 764-775 [PMID: 12930259 DOI: 10.1046/j.1540-8167.2003.02543.x]
  - 79 **Fallavollita JA**, Riegel BJ, Suzuki G, Valeti U, Canty JM. Mechanism of sudden cardiac death in pigs with viable chronically

- dysfunctional myocardium and ischemic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2005; **289**: H2688-H2696 [PMID: 16085676 DOI: 10.1152/ajpheart.00653.2005]
- 80 **Reinier K**, Dervan C, Singh T, Uy-Evanado A, Lai S, Gunson K, Jui J, Chugh SS. Increased left ventricular mass and decreased left ventricular systolic function have independent pathways to ventricular arrhythmogenesis in coronary artery disease. *Heart Rhythm* 2011; **8**: 1177-1182 [PMID: 21376836 DOI: 10.1016/j.hrthm.2011.02.037]
- 81 **Tamarappoo BK**, John BT, Reinier K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Vulnerable myocardial interstitium in patients with isolated left ventricular hypertrophy and sudden cardiac death: a postmortem histological evaluation. *J Am Heart Assoc* 2012; **1**: e001511 [PMID: 23130141 DOI: 10.1161/JAHA.112.001511]
- 82 **Bruckner BA**, Razeghi P, Stetson S, Thompson L, Lafuente J, Entman M, Loebe M, Noon G, Taegtmeier H, Frazier OH, Youker K. Degree of cardiac fibrosis and hypertrophy at time of implantation predicts myocardial improvement during left ventricular assist device support. *J Heart Lung Transplant* 2004; **23**: 36-42 [PMID: 14734125 DOI: 10.1016/S1053-2498(03)00103-7]
- 83 **Baba HA**, Stypmann J, Grabellus F, Kirchhof P, Sokoll A, Schäfers M, Takeda A, Wilhelm MJ, Scheld HH, Takeda N, Breithardt G, Levkau B. Dynamic regulation of MEK/Erks and Akt/GSK-3beta in human end-stage heart failure after left ventricular mechanical support: myocardial mechanotransduction-sensitivity as a possible molecular mechanism. *Cardiovasc Res* 2003; **59**: 390-399 [PMID: 12909322 DOI: 10.1016/S0008-6363(03)00393-6]
- 84 **Hall JL**, Grindle S, Han X, Fermin D, Park S, Chen Y, Bache RJ, Mariash A, Guan Z, Ormaza S, Thompson J, Graziano J, de Sam Lazaro SE, Pan S, Simari RD, Miller LW. Genomic profiling of the human heart before and after mechanical support with a ventricular assist device reveals alterations in vascular signaling networks. *Physiol Genomics* 2004; **17**: 283-291 [PMID: 14872006]
- 85 **Maybaum S**, Mancini D, Xydas S, Starling RC, Aaronson K, Pagani FD, Miller LW, Margulies K, McRee S, Frazier OH, Torre-Amione G. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. *Circulation* 2007; **115**: 2497-2505 [PMID: 17485581 DOI: 10.1161/CIRCULATIONAHA.106.633180]
- 86 **Suzuki G**, Weil BR, Leiker MM, Ribbeck AE, Young RF, Cimato TR, Canty JM. Global intracoronary infusion of allogeneic cardiosphere-derived cells improves ventricular function and stimulates endogenous myocyte regeneration throughout the heart in swine with hibernating myocardium. *PLoS One* 2014; **9**: e113009 [PMID: 25402428 DOI: 10.1371/journal.pone.0113009]

**P- Reviewer:** Gharaee-Kermani M, Kurpisz MK, Ong HT

**S- Editor:** Ji FF **L- Editor:** A **E- Editor:** Wu HL







Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

