Stem/progenitor Cell Based Therapies for Repair of Myocardial Infarction: Current Developments in Methods of Cell Delivery

Jialiang Liang and Yigang Wang*

Departments of Pathology and Laboratory Medicine, College of Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio, USA

Abstract

Regenerative medicine offers hope for patients with myocardial infarction (MI). A good deal of clinical evidence shows that the transplantation of stem/progenitor cells from numerous sources can produce significant protective effects in the injured heart, such as enhanced perfusion and contractility. The therapeutic effects of transplanted cells depend on appropriate delivery into the damaged area of the heart. Thus, the method of cell delivery is an important aspect of stem/progenitor cell based therapy, because it affects the fate of transplanted cells and consequently determines the clinical outcome. It is still difficult to determine the optimal cell delivery strategy for MI treatment from the current preclinical and clinical studies, although cell injections have been widely used in the delivery of various types of progenitor cells in clinical trials. Additionally, cell patch engineering has emerged as one of the most promising new approaches. This review summarizes the methods, feasibility, safety, efficacy, and advancements of these two approaches from recent publications. The combined use of various delivery approaches with stem/progenitor cell transplantation emerges as an important administration method in tissue engineering to promote cardiac regeneration.

Keywords: Stem/progenitor cells; Transplantation; Myocardial infarction; Injection; Cell patch

Introduction

Myocardial Infarction (MI) can irreversibly destroy distal blood vessels and myocardium, eventually triggering cardiac remodeling, heart failure, or sudden death [1,2]. Traditional therapeutic approaches focus on the limitation of the initial injury and secondary maladaptive complications. Alternatively, regenerative therapy seeks to induce angiomyogenesis for replacing lost or damaged tissues [3,4]. For the past decade, multiple clinical trials of cardiac regenerative therapy have been performed, but the effects of progenitor cells are still intensely debated. Detailed discussions on the therapeutic effects of various stem/progenitor cells, including Bone Marrow Mononuclear Cells (BMMNC), Mesenchymal Stem Cells (MSC), Hematopoietic Stem Cells (HSC), induced Pluripotent Stem Cells (iPSC), embryonic stem cells (ESC), Cardiac Stem Cells (CSC), and other endogenous stem/progenitor cells have been introduced [5-7]. Undoubtedly, the mechanism of action and implementation of various cell resources differ from each other, which are important preclinical aspects to be studied. However, a common requirement is the delivery of cells to the region of interest, in order to develop a safe and effective cell therapy for clinical applications.

The methodology of transplantation is a critical aspect of tissue regeneration. This will affect the retention, survival, and functionality of donor cells and consequently determine the outcome of cell transplantation [8]. Retention is defined as the fraction of transplanted cells remaining in the myocardium for a short period of time (hours). Increased cell retention has been shown to enhance stem cell engraftment and improve therapy outcomes [9,10]. Retention may be a function of the local milieu, which influences cell survival, adhesion, and migration [11]. Transplanted cells cannot have any therapeutic effect if death occurs to a great extent or the cells are not maintained in the ischemic/border zone. Recently, low cell retention and engraftment have been demonstrated to be key factors limiting successful cell transplantation, regardless of the type of cell or the delivery method [12]. Thus, we focus on the ability of different cell delivery approaches to enhance cell retention. Most importantly, the optimal cell delivery strategy should be safe and without risk of secondary damage to the

host heart. Additionally, it should allow for the transplantation and engraftment of a sufficient number of functional stem/progenitor cells. Moreover, the cost, manipulation, availability, and application of the delivery strategy should be taken into consideration.

Multiple delivery approaches have been developed in recent preclinical and clinical studies. Injection has been widely used in the delivery of various types of progenitor cells in clinical trials. Additionally, the cell patch has been recognized as one of the most promising new approaches. This review summarizes these two approaches and highlights their major advancements.

Conventional Delivery Routes in Stem/Progenitor Cell Based Therapy

There are numerous cell delivery approaches, which are derived from existing clinical and surgical techniques. Briefly, they can be divided into intramyocardial injection (including transepicardial, transendocardial, and perivascular injection) and intravascular infusion (including systemic intravenous infusion, intracoronary infusion, and retrograde coronary sinus delivery).

Intramyocardial injection

In preclinical animal studies, intramyocardial injection is the approach by which stem/progenitor cell suspensions are directly injected into the infarcted myocardium with a needle in open thoracic surgery. In clinical studies, the approach is conducted with the assistance of imaging from NOGA mapping (cells are injected directly

***Corresponding author:** Yigang Wang, M.D., Ph.D., Associate Professor, Department of Pathology and Laboratory Medicine, College of Medicine, University of Cincinnati Medical Center, 231 Albert Sabin Way, Cincinnati, Ohio, USA, Tel: 513-558-5798; E-mail: okontakelechi@yahoo.com

Received February 16, 2013; Accepted May 30, 2013; Published June 07, 2013

Citation: Liang J, Wang Y (2013) Stem/progenitor Cell Based Therapies for Repair of Myocardial Infarction: Current Developments in Methods of Cell Delivery. *Surgery Curr Res* 3: 131. doi:[10.4172/2161-1076.1000131](https://doi.org/10.4172/2161-1076.1000131)

Copyright: © 2013 Liang J, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

into the heart via the femoral artery in a manner similar to angiography and angioplasty using an additional special machine), angiography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or echocardiography. It is a preferred route for patients with chronic myocardial ischemia when transvascular cell delivery is precluded due to limited vascularity [8]. Additionally, the technique is suitable in the delivery of large cells, such as MSC or myoblasts, which may cause micro-embolization [11-14]. Electromechanically-guided intramyocardial injection of MSC has been proven as a superior method to intracoronary infusion in different animal studies [15,16]. Indeed, the intramyocardial injection technique showed high cell retention with an increased vascularity and improvement of cardiac function [15]. Additionally, this delivery route has been shown to be safe for patients with end-stage ischemic heart failure [13,17].

Transepical injection

Stem/progenitor cell delivery by transepical injection has been performed during open heart surgery, such as coronary artery bypass grafting [18,19]. Cell suspensions can be directly injected into the visualized scarred areas and/or the border zone. Nonetheless, the invasiveness, especially sternotomy or left thoracotomy, and high financial cost of this approach limit its clinical application. Also, it is complicated to evaluate and ascertain the efficiency of cell transplantation, if other heart surgery is performed simultaneously.

Transendocardial injection

With three-dimensional Left Ventricular (LV) endocardial maps, the tissue damage is less extensive in transendocardial injection than in transepical injection. Briefly, an injection needle catheter from peripheral vessels can be navigated across the aortic valve and positioned against the endocardial surface, and then cell suspensions can be injected into the LV wall [20]. The contact NOGA cardiac mapping system has been used in clinical trials to inject stem/progenitor cells [17,21]. In addition, a novel non-contact catheter system (Endocardial Solutions (ESI)TM system) for transendocardial injection is under investigation [22]. Specifically, the body electrode patches of NOGA system provide electromechanical (electrical voltage) mapping of the endocardial surface, which can delineate viable, ischemic myocardium, and direct electrophysiological catheters inside cardiac chamber [23,24]. Several other catheter systems, such as Helix and Myostar, have also been integrated with electromechanical mapping and are being tested in clinical trials [25-27]. This approach has been reported to deliver autologous stem/progenitor cells to improve LV dysfunction of heart failure patients [28,29].

Perivascular injection

Unlike transendocardial administration approach, perivascular injection can be achieved by cannulating a percutaneous catheter into the left anterior descending artery. Then, the donor cells can be injected into the target territory of damaged myocardium using a specific needle [30]. Thus, the catheter system can deliver donor cells parallel to the ventricular wall and deep into the ischemic myocardium, which results in greater cell retention and is less invasive than the epicardial approach [14,31].

Currently, the optimal method for intramyocardial injections is still controversial. Thus, compared evaluations between intramyocardial, transepical, transendocardial and transcoronary injections are required to improve the retention and viability for various donor cells. Intramyocardial injection of stem/progenitor cells is able to improve cardiac function in chronic heart failure, but a risk of ventricular arrhythmia potentially occurs [32]. Moreover, its application in

serious MI patients remains to be considered, because perforation of the friable necrotic cardiac tissues remains a matter of concern. Some studies showed that its disadvantages may be prevented by using the intracoronary route [32,33].

Intravascular infusion

In contrast to intramyocardial injection which directly targets ischemic area, the intravascular approach delivers donor cell suspension into the coronary circulation with less myocardial injury [15,32]. Systemic intravenous infusion is the simplest cell delivery route, but its application is extremely limited due to poor migration and retention of the transplanted cells in the heart [34,35].

Intracoronary infusion

Compared to systemic intravenous delivery, intracoronary infusion (typically through the femoral artery) is an ideal approach for intravascular delivery, in order to reduce the homing of cells to other organs [34]. Similar to percutaneous coronary intervention, a standard balloon catheter is introduced into the cardiac arterial system under fluoroscopic screening. When the catheter is advanced to the distal end of the infarcted coronary artery, an over guide-wire balloon is inflated to cease coronary flow to prevent backflow of the donor cells. Subsequently, the cell suspension can be released through the inner lumen of the balloon, and then the balloon is deflated to restore the coronary flow [36-38]. Since most interventional cardiologists are familiar with the noninvasive percutaneous technique, this approach has been regularly utilized in cell therapy trials. The intracoronary delivery of autologous stem/progenitor cells is a safe procedure, which reduces infarct sizes, and improves cardiac function for patients with MI [30,39,40]. One multicenter trial showed that the functional improvement after intracoronary administration of autologous progenitor cells persists for at least 2 years [41]. The intracoronary deliver strategy is especially suitable for the treatment of infarcted myocardium when the arterial stenosis is reopened by intervention donor cells cannot be delivered to an area where blood supply is occluded. For the past decade, multiple clinical studies have been performed using this approach, particularly in delivering bone marrow mononuclear cells, as summarized in references [8,22].

Retrograde coronary sinus delivery

This delivery method provides a cell infusion to the ischemic heart via retrograde flow through the coronary sinus or coronary veins [27]. Typically, the femoral vein is cannulated with a sheath, and then a specialized catheter is placed in the coronary sinus to access the target coronary vein. Donor cells are transplanted during balloon occlusion of the distal coronary sinus [42]. Coronary veins without obstructive disease can provide a means for cell delivery, thereby achieving lower risk of coronary embolism, which is beneficial for ischemic areas with severe coronary artery stenosis [8,43]. This route has been proven safe and feasible in patients with healed MI, although the positioning of coronary sinus catheterization requires additional training even for experienced interventional cardiologists [14,44]. Coronary sinus injury is a rare but potentially lethal complication of the retrograde cell delivery technique. A small sinus in a frail patient may be stretched to the point of rupture during inflation of the balloon. Furthermore, it is not suitable for heart failure patients with resynchronization devices and may cause risk of occlusion if delivering large cells.

Notably, some comparison studies have highlighted that the retention of the intracoronary-delivered cells remains a central issue [15,16,33,45]. The question was raised whether ceasing coronary flow would enhance cell retention within the infarcted area, but

similar persistence was observed after intracoronary infusion with or without balloon occlusion, suggesting that the balloon procedures are not necessary [46]. Discouragingly, a significant quantity of the transplanted cells failed to home and stay in the heart after balloon deflation [47]. CT detection showed that less than 10% of transplanted cells were retained within the myocardium, while the majority migrated to or were taken up by non-cardiac organs (such as spleen and liver) after intracoronary administration [48]. These studies concluded that intramyocardial injection may be superior to intracoronary delivery in terms of longer term persistence of implanted cells.

In addition, emerging evidence showed that intracoronary delivery of stem/progenitor cells was associated with coronary artery re-stenosis and blood flow obstruction [49,50]. Furthermore the intracoronary approach may require a large quantity of stem/progenitor cells, which is not feasible for the autologous cell transplantation in older patients with chronic heart failure. Moreover, some studies showed minor or even no effects after intracoronary infusion of autologous stem/progenitor cells on LV function of MI patients [37,51,52]. Taken together, intracoronary infusion remains controversial with regard to its actual impact on the restoration of cardiac function, which should be elucidated by larger sample size studies in the near future. These challenges can be overcome through the development of new approaches and technology to increase cell retention.

Improvements and Advances of Injection/Infusion Modes

Recently, some injection/infusion strategies have been developed to improve the retention and survival of transplanted cells. For instance, during the advanced phase of global ischemia-reperfusion, cell retention was increased via P-selectin-dependent cell-endothelium interaction [53]. Moreover, a multi-welled methylcellulose hydrogel system was reported to cultivate human amniotic-fluid stem cells to produce spherically symmetric cell bodies for intramyocardial injection, which can attenuate cell loss and enhance cell retention by providing an adequate physical size and an enriched extracellular matrix (ECM) environment, thereby improving heart function [54]. Similarly, a thermo-responsive methylcellulose hydrogel system was used to fabricate cell fragments that can preserve the endogenous ECM, contributing to the improvement of ventricular function via differentiation of stem cells into cardiovascular lineage cells [55]. Additionally, a biodegradable porous scaffold has been described, which has desirable characteristics for cell therapy; this could be used to study attachment, growth, differentiation, and survival of stem cells in the future [56]. An injectable biopolymer (fibrin) scaffold was reported to improve the survival and retention of transplanted cells, thereby enhancing angiogenesis and cardiac function in animal experiments [57-59]. Furthermore, injectable scaffolds with shape-memory properties provided enhanced survival, higher local retention, and extended engraftment of transplanted cells at the injection site [10]. However, these injectable scaffold systems are specific for the direct transepical approach, and a good deal of work remains to evaluate their safety and efficacy before their clinical application.

As discussed above, some studies suggest that an inherent disadvantage of the intracoronary approach is low cell retention after transplantation [15,45]. In a study designed to compare transendocardial injection and intracoronary infusion through delivery of the same dose of labeled MSC, transendocardial delivery showed a higher local retention of cells at the mid-papillary level in the target area, while intracoronary infusion showed widespread distribution of cells in the infarcted area [60]. The authors didn't find a significant

difference in the delivery efficiency to the heart between these two modes, although transendocardial injection led to less retention of cells in the pulmonary tract [60]. They found that the transendocardial delivery was hampered by the occurrence of ventricular arrhythmias as a result of injection, and/or the presence of the posterolateral papillary muscle, leading to less stable catheter and needle position. The injected cells left the target area via the myocardial venous or lymphatic system [60]. Other studies compared the safety and feasibility of early and late delivery of stem/progenitor cells with combined intracoronary and intramyocardial administration, which improved outcomes for patients with acute MI, highlighting the optimal timing and mode of delivery of stem cells [61,62].

With rapid advancements in imaging devices and catheterization techniques, injection modes are becoming viable, feasible, and safe for clinical trials. For example, a recent report described the safe transendocardial transplantation of cells under real-time 3D echocardiography guidance, which improved cardiac function in a chronic MI model [63]. In addition, the novel microneedle catheter has been shown to have no significant effect on the viability or paracrine ability of transplanted stem/progenitor cells, which improved cardiac function as indicated by enhancing the ejection fraction of MI patients [30,64], although its long-term safety profile should be investigated.

Engineered Tissue Transplantation

In addition to injection modes, there are several novel approaches for delivering stem/progenitor cells to the ischemic heart by biomedical engineering. Engineered tissue transplantation is a novel solution to poor cell retention, engraftment, and survival, which are problematic issues in conventional injection/infusion modes [65,66]. These methods aim to repair the injured heart by providing cells growing on patches or scaffolds.

The general biomaterial approaches for MI treatment include LV restraints, injectable scaffolds, and cardiac patches (sheets) [67]. Although they are not used for cell delivery, LV restraints are biomaterial supports that can prevent negative LV remodeling and LV dilation, as introduced in other reviews [67,68]. Injectable scaffolds are well established for intramyocardial injection, and can improve cellular retention and viability; clinical trials using this technique are now underway (NCT00557531, ClinicalTrials.gov). The cell patch technique will be discussed below.

Cell Patch Engineering

Cell patch technology is one of the most promising new approaches for MI treatment. The application of cell patches can enhance cell engraftment and provide the microenvironment to support cellular survival, differentiation, and proliferation [69]. The transplantation of various stem/progenitor cells by a variety of cell patches/scaffolds has been shown to improve LV function of infarcted heart [70]. The delivery efficiency of cell patches is dependent on the properties of the scaffold biomaterial. Both natural materials and synthetic materials have been reported in cell patch/scaffold applications. Natural materials include ECM components, such as gelatin, matrigel, and collagen [68,71,72]. Additionally, perfusion-decellularized scaffolds providing the complex milieu of the native ECM have been used to create cardiac patches for myocardial regeneration [73,74]. Myoblast cell patches prepared from a fibrin-coated culture plate or a myoblast seeded collagen sponge can result in significantly greater angiogenesis and graft functionality in rats after MI, compared to intramyocardial injections [75]. Our research group has established a cell patch method by seeding progenitor cells on parietal peritoneum, which can enhance tissue nutrition, reduce

myocardial remodeling, and improve heart function of MI animal models [76,77]. Although natural scaffolds can protect cellular viability and function, their inconsistent material properties, rapid degradation kinetics, and weak mechanical properties hinder their application in clinical trials [70]. By contrast, synthetic polymers have the advantage of allowing precise control of hydrophilic/hydrophobic characteristics, degradation rate and mechanical properties.

Currently, there is a broad range of synthetic copolymers being explored in tissue engineering [78]. Initially, biodegradable synthetic materials emerged as one of the most promising new approaches for MI treatment. An elastic biodegradable polyester urethane urea cardiac patch was applied onto the infarcted heart, which reduced ventricular remodeling and improved performance [79]. The implantation of biocompatible, biodegradable stem/progenitor cell-seeded scaffolds, such as poly-glycolide-co-caprolactone and poly-lactide-co-epsilon-caprolactone, aided cell migration into infarcted areas, and effectively improved LV systolic dysfunction [80,81]. However, these kinds of traditional synthetic polymers have a number of drawbacks. They can't reproduce a physiological matrix environment and are stiffer than heart tissue. Furthermore, their biodegradation processes are considered to be potentially harmful as they induce inflammatory responses [70,82]. Interestingly, these issues can be overcome by the implementation of thermo-responsive polymers that avoid the use of any additional materials such as carrier substrates or scaffolds.

The discovery of a temperature-responsive polymer (poly-N-isopropylacrylamide) allows the seeded cells to be harvested as intact sheets by temperature changes, thereby avoiding the use of proteolytic enzymes [82-84]. This technique can be used for tissue regeneration by either direct transplantation of cell sheets or the creation of three-dimensional structures via the layering of individual cell sheets [82,84]. Using the cell sheet technology, seed cells maintained multipotent and self-propagating properties and improved cardiac function in MI rats after transplantation [85]. A chemically defined thermo-responsive hydrogel has been described, which represents a flexible approach for maintaining pluripotency and improving the efficacy and safety of stem/progenitor cell culture systems [86]. iPSC- or ESC-derived cardiomyocyte sheets cultured on thermo-responsive dishes significantly attenuated LV remodeling, provided trophic support, and improved cardiac performance of ischemic hearts [87-89]. Moreover, this technique can preserve cell-cell interactions and ECM, support cell growth, and promote the retention of seed cells after transplantation [84,90,91]. A novel thermo-responsive carrier fabricated from poly-vinyl-methyl-ether on polymeric surfaces meets cell type specific requirements with controllable layer thickness, stiffness, and functionalization [92]. Thus, the preclinical studies of thermo-responsive dishes provide a basis for clinical investigation in cardiac regeneration therapy and the treatment of other diseases [93-95].

Advancements in biomaterial science have provided numerous other approaches to produce cell sheets. For example, dishes coated with fibrin (fibrinogen monomers mixed with thrombin) have been described, that allow for easy dissociation of cell sheets using a cell scraper [96]. Furthermore, a new polyelectrolyte-based platform allow for the controllable detachment of cell sheets by both electrochemically-induced local pH lowering and global decrease of the environmental pH [97]. The addition of nontoxic ions (ferrocyanide) to the cells cultured on polyelectrolyte multilayers resulted in dissolution of biomaterials and rapid detachment of viable cell sheets, which is a promising approach for cell sheet engineering [98]. Nevertheless, the thermo-responsive technique is developing as an ideal approach for manufacture of cell sheets. Notably, the success of fabricating transplantable cardiac-like

tissue using cell-sheet engineering in combination with decellularized tissues has recently been described *in vivo* [99].

Refinement of Cell Patch Approaches

Although tissue engineering for cardiac regeneration is promising, it is still at preliminary, preclinical stage. The transplantation of cell sheets is invasive, but may be enabled as an adjunct therapy to another surgical procedure. Remarkably, a square cell sheet (24×24 mm) was successfully transplanted onto wound sites of porcine lung thoracoscopically, using a novel device inserted through a 12 mm port, which enabled less invasive transplantation of cell sheets [100]. The therapeutic window, number, and delivery mode of stem/progenitor cells should be optimized for the different classifications of MI. A report of the International Society for Cardiovascular Translational Research offers recommendations for successful training on methods of injection delivery of biologics for cardiac regeneration [27], whereas the criteria and training for the application of cell patches has not been officially established, as it still requires more investigation and improvement.

Recently, the issue of poor migration and integration of transplanted stem/progenitor cells into the heart has been raised, although cell retention can be enhanced by the cell sheet approach [65,66]. After MI, epicardial fibrosis and scar formation create a barrier that severely compromises the engraftment of stem cells and limits their blood supply. Our current studies have sought to refine transplantation methods by enhancing the release of paracrine factors, degrading collagen, or building up new vascular networks between the host myocardium and cell sheets (neovascularization) [101,102]. It is crucial for engineered tissues to provide a suitable environment for neovascularization/angiogenesis, to supply nutrients and carry away metabolic products. Other desirable qualities include improvement of cardiac contractility (via direct myogenesis or due to paracrine effects from stem cells) and increased cell survival (via anti-apoptotic signaling), which can combine to reduce myocardial remodeling, limit infarct size, and improve the heart's mechanical performance. It is also very important to modify donor cells prior to administration (preconditioning) with various physical, chemical, or biological manipulations [77,103-105].

A single layer of cells is so fragile that it needs suitable materials to support it. Importantly, the thermo-responsive technique can achieve three-dimensional reconstruction of a tissue *in vitro* by layering individual cell sheets, which increases the sheet's thickness and provides adequate numbers of various seed cells. Thus, the optimal cell deliver methods for MI treatment will be noteworthy in future studies.

Human clinical trials are now beginning to appear. The benefits of cell patch based therapy are considered to include increased LV wall thickness at the infarct region, attenuated LV dilation, and improved heart function [106]. Unfortunately, the current surgical procedure is invasive and requires thoracotomy. This issue reduces enthusiasm and potential significance. However, a novel device for minimally invasive transplantation of cell patches in endoscopic surgery with video-assisted thoracoscopic surgery is now available and offers an alternative minimally invasive approach to applying such tissue patches to regions of MI [100]. The ultimate goal in cell patch application is to generate biocompatible, non-immunogenic heart muscle with morphological and functional properties similar to natural myocardium to repair MI.

Conclusion

In summary, all of the current cell delivery approaches aim to enhance stem/progenitor cell engraftment, survival, and integration

to host tissues after MI. For the past decade, multiple clinical trials of cardiac regenerative therapy have been performed using various cell delivery approaches, but the ideal strategy has still not been established. Although intramyocardial injection is recommended for MI treatment over intracoronary infusion, the latter is less invasive and suited for the treatment of infarcted and reperfused myocardium. Importantly, the cell patch (sheet) technique provides a new hope for the future treatment in MI patients, but requires more evaluation and optimization prior to clinical application. Thus, the most favorable combination of various delivery approaches and biomaterials for cell transplantation in MI therapy will become an important area of research for future study.

Acknowledgements

The authors wish to thank Kristin Luther and Christian Paul for technical assistance.

Funding Sources

This work was supported by NIH grants, HL089824, HL081859, and HL110740 (Y. Wang).

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

References

- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, et al. (2012) Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60: 1581-1598.
- Swynghedauw B (1999) Molecular mechanisms of myocardial remodeling. *Physiol Rev* 79: 215-262.
- Pedersen RA, Mascetti V, Mendjan S (2012) Synthetic organs for regenerative medicine. *Cell Stem Cell* 10: 646-647.
- Gurtner GC, Callaghan MJ, Longaker MT (2007) Progress and potential for regenerative medicine. *Annu Rev Med* 58: 299-312.
- Daley GQ (2012) The promise and perils of stem cell therapeutics. *Cell Stem Cell* 10: 740-749.
- Chong JJ (2012) Cell therapy for left ventricular dysfunction: an overview for cardiac clinicians. *Heart Lung Circ* 21: 532-542.
- Akhmedov AT, Marín-García J (2012) Myocardial regeneration of the failing heart. *Heart Fail Rev* .
- Campbell NG, Suzuki K (2012) Cell delivery routes for stem cell therapy to the heart: current and future approaches. *J Cardiovasc Transl Res* 5: 713-726.
- Cheng K, Malliaras K, Li TS, Sun B, Houde C, et al. (2012) Magnetic enhancement of cell retention, engraftment, and functional benefit after intracoronary delivery of cardiac-derived stem cells in a rat model of ischemia/reperfusion. *Cell Transplant* 21: 1121-1135.
- Bencherif SA, Sands RW, Bhatta D, Arany P, Verbeke CS, et al. (2012) Injectable preformed scaffolds with shape-memory properties. *Proc Natl Acad Sci U S A* 109: 19590-19595.
- Wollert KC, Drexler H (2005) Clinical applications of stem cells for the heart. *Circ Res* 96: 151-163.
- Terrovitis JV, Smith RR, Marbán E (2010) Assessment and optimization of cell engraftment after transplantation into the heart. *Circ Res* 106: 479-494.
- Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, et al. (2012) Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. *JAMA* 307: 1717-1726.
- Siminiak T, Fiszler D, Jerzykowska O, Grygielska B, Rozwadowska N, et al. (2005) Percutaneous trans-coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment: the POZNAN trial. *Eur Heart J* 26: 1188-1195.
- Perin EC, Silva GV, Assad JA, Vela D, Buja LM, et al. (2008) Comparison of intracoronary and transendocardial delivery of allogeneic mesenchymal cells in a canine model of acute myocardial infarction. *J Mol Cell Cardiol* 44: 486-495.
- Freyman T, Polin G, Osman H, Crary J, Lu M, et al. (2006) A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. *Eur Heart J* 27: 1114-1122.
- Mathiasen AB, Jørgensen E, Qayyum AA, Haack-Sørensen M, Eklund A, et al. (2012) Rationale and design of the first randomized, double-blind, placebo-controlled trial of intramyocardial injection of autologous bone-marrow derived Mesenchymal Stromal Cells in chronic ischemic Heart Failure (MSC-HF Trial). *Am Heart J* 164: 285-291.
- Siminiak T, Kalawski R, Fiszler D, Jerzykowska O, Rzeznicki J, et al. (2004) Autologous skeletal myoblast transplantation for the treatment of postinfarction myocardial injury: phase I clinical study with 12 months of follow-up. *Am Heart J* 148: 531-537.
- Zhao Q, Sun Y, Xia L, Chen A, Wang Z (2008) Randomized study of mononuclear bone marrow cell transplantation in patients with coronary surgery. *Ann Thorac Surg* 86: 1833-1840.
- Fuchs S, Satler LF, Kornowski R, Okubagzi P, Weisz G, et al. (2003) Catheter-based autologous bone marrow myocardial injection in no-option patients with advanced coronary artery disease: a feasibility study. *J Am Coll Cardiol* 41: 1721-1724.
- Rodrigo SF, van Ramshorst J, Beeres SL, Al YI, Dibbets-Schneider P, et al. (2012) Intramyocardial injection of bone marrow mononuclear cells in chronic myocardial ischemia patients after previous placebo injection improves myocardial perfusion and anginal symptoms: an intra-patient comparison. *Am Heart J* 164: 771-778.
- Wei H, Ooi TH, Tan G, Lim SY, Qian L, et al. (2010) Cell delivery and tracking in post-myocardial infarction cardiac stem cell therapy: an introduction for clinical researchers. *Heart Fail Rev* 15: 1-14.
- Gyöngyösi M, Khorsand A, Zamini S, Sperker W, Strehlow C, et al. (2005) NOGA-guided analysis of regional myocardial perfusion abnormalities treated with intramyocardial injections of plasmid encoding vascular endothelial growth factor A-165 in patients with chronic myocardial ischemia: subanalysis of the EUROINJECT-ONE multicenter double-blind randomized study. *Circulation* 112: 1157-1165.
- Smits PC, van Geuns RJ, Poldermans D, Bountiokos M, Onderwater EE, et al. (2003) Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol* 42: 2063-2069.
- Trachtenberg B, Velazquez DL, Williams AR, McNiece I, Fishman J, et al. (2011) Rationale and design of the Transendocardial Injection of Autologous Human Cells (bone marrow or mesenchymal) in Chronic Ischemic Left Ventricular Dysfunction and Heart Failure Secondary to Myocardial Infarction (TAC-HFT) trial: A randomized, double-blind, placebo-controlled study of safety and efficacy. *Am Heart J* 161: 487-493.
- Minguell JJ, Lorino R, Lasala GP (2011) Myocardial implantation of a combination stem cell product by using a transendocardial MYOSTAR injection catheter: A technical assessment. *Acute Card Care* 13: 40-42.
- Dib N, Menasche P, Bartunek JJ, Zeiher AM, Terzic A, et al. (2010) Recommendations for successful training on methods of delivery of biologics for cardiac regeneration: a report of the International Society for Cardiovascular Translational Research. *JACC Cardiovasc Interv* 3: 265-275.
- Williams AR, Trachtenberg B, Velazquez DL, McNiece I, Altman P, et al. (2011) Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. *Circ Res* 108: 792-796.
- Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, et al. (2004) Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. *Circulation* 110: 1213-1218.
- Penn MS, Ellis S, Gandhi S, Greenbaum A, Hodes Z, et al. (2012) Adventitial delivery of an allogeneic bone marrow-derived adherent stem cell in acute myocardial infarction: phase I clinical study. *Circ Res* 110: 304-311.
- Thompson CA, Nasser BA, Makower J, Houser S, McGarry M, et al. (2003) Percutaneous transvenous cellular cardiomyoplasty. A novel nonsurgical approach for myocardial cell transplantation. *J Am Coll Cardiol* 41: 1964-1971.
- Fukushima S, Varela-Carver A, Coppen SR, Yamahara K, Felkin LE, et al. (2007) Direct intramyocardial but not intracoronary injection of bone marrow cells induces ventricular arrhythmias in a rat chronic ischemic heart failure model. *Circulation* 115: 2254-2261.
- Fukushima S, Coppen SR, Lee J, Yamahara K, Felkin LE, et al. (2008) Choice of cell-delivery route for skeletal myoblast transplantation for treating post-infarction chronic heart failure in rat. *PLoS One* 3: e3071.
- Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, et al. (2003)

- Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation* 108: 863-868.
35. Aicher A, Brenner W, Zuhayra M, Badorff C, Massoudi S, et al. (2003) Assessment of the tissue distribution of transplanted human endothelial progenitor cells by radioactive labeling. *Circulation* 107: 2134-2139.
 36. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, et al. (2006) Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 355: 1210-1221.
 37. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, et al. (2006) Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med* 355: 1199-1209.
 38. Chen SL, Fang WW, Ye F, Liu YH, Qian J, et al. (2004) Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol* 94: 92-95.
 39. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, et al. (2012) Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 379: 895-904.
 40. Chugh AR, Beache GM, Loughran JH, Mewton N, Elmore JB, et al. (2012) Administration of cardiac stem cells in patients with ischemic cardiomyopathy: the SCPIO trial: surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. *Circulation* 126: S54-64.
 41. Assmus B, Rolf A, Erbs S, Elsässer A, Haberbosch W, et al. (2010) Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail* 3: 89-96.
 42. Tuma J, Fernández-Viña R, Carrasco A, Castillo J, Cruz C, et al. (2011) Safety and feasibility of percutaneous retrograde coronary sinus delivery of autologous bone marrow mononuclear cell transplantation in patients with chronic refractory angina. *J Transl Med* 9: 183.
 43. Dib N, Khawaja H, Varner S, McCarthy M, Campbell A (2011) Cell therapy for cardiovascular disease: a comparison of methods of delivery. *J Cardiovasc Transl Res* 4: 177-181.
 44. Assmus B, Honold J, Schächinger V, Britten MB, Fischer-Rasokat U, et al. (2006) Transcatheter transplantation of progenitor cells after myocardial infarction. *N Engl J Med* 355: 1222-1232.
 45. Hou D, Youssef EA, Brinton TJ, Zhang P, Rogers P, et al. (2005) Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials. *Circulation* 112: 1150-1156.
 46. Tossios P, Krausgrill B, Schmidt M, Fischer T, Halbach M, et al. (2008) Role of balloon occlusion for mononuclear bone marrow cell deposition after intracoronary injection in pigs with reperfused myocardial infarction. *Eur Heart J* 29: 1911-1921.
 47. Doyle B, Kemp BJ, Chareonthaitawee P, Reed C, Schmeckpeper J, et al. (2007) Dynamic tracking during intracoronary injection of 18F-FDG-labeled progenitor cell therapy for acute myocardial infarction. *J Nucl Med* 48: 1708-1714.
 48. Kurpisz M, Czepczynski R, Grygielska B, Majewski M, Fiszler D, et al. (2007) Bone marrow stem cell imaging after intracoronary administration. *Int J Cardiol* 121: 194-195.
 49. Kang HJ, Kim HS, Zhang SY, Park KW, Cho HJ, et al. (2004) Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. *Lancet* 363: 751-756.
 50. Moelker AD, Baks T, Wever KM, Spitskovsky D, Wielopolski PA, et al. (2007) Intracoronary delivery of umbilical cord blood derived unrestricted somatic stem cells is not suitable to improve LV function after myocardial infarction in swine. *J Mol Cell Cardiol* 42: 735-745.
 51. Choi JH, Choi J, Lee WS, Rhee I, Lee SC, et al. (2007) Lack of additional benefit of intracoronary transplantation of autologous peripheral blood stem cell in patients with acute myocardial infarction. *Circ J* 71: 486-494.
 52. Traverse JH, McKenna DH, Harvey K, Jorgensen BC, Olson RE, et al. (2010) Results of a phase 1, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction. *Am Heart J* 160: 428-434.
 53. Fukushima S, Campbell NG, Coppen SR, Yamahara K, Yuen AH, et al. (2011) Quantitative assessment of initial retention of bone marrow mononuclear cells injected into the coronary arteries. *J Heart Lung Transplant* 30: 227-233.
 54. Lee WY, Wei HJ, Lin WW, Yeh YC, Hwang SM, et al. (2011) Enhancement of cell retention and functional benefits in myocardial infarction using human amniotic-fluid stem-cell bodies enriched with endogenous ECM. *Biomaterials* 32: 5558-5567.
 55. Yeh YC, Lee WY, Yu CL, Hwang SM, Chung MF, et al. (2010) Cardiac repair with injectable cell sheet fragments of human amniotic fluid stem cells in an immune-suppressed rat model. *Biomaterials* 31: 6444-6453.
 56. Thorrez L, Shansky J, Wang L, Fast L, VandenDriessche T, et al. (2008) Growth, differentiation, transplantation and survival of human skeletal myofibers on biodegradable scaffolds. *Biomaterials* 29: 75-84.
 57. Nakamuta JS, Danoviz ME, Marques FL, dos Santos L, Becker C, et al. (2009) Cell therapy attenuates cardiac dysfunction post myocardial infarction: effect of timing, routes of injection and a fibrin scaffold. *PLoS One* 4: e6005.
 58. Huang NF, Yu J, Sievers R, Li S, Lee RJ (2005) Injectable biopolymers enhance angiogenesis after myocardial infarction. *Tissue Eng* 11: 1860-1866.
 59. Christman KL, Vardanian AJ, Fang Q, Sievers RE, Fok HH, et al. (2004) Injectable fibrin scaffold improves cell transplant survival, reduces infarct expansion, and induces neovasculature formation in ischemic myocardium. *J Am Coll Cardiol* 44: 654-660.
 60. van der Spoel TI, Vrijnsen KR, Koudstaal S, Sluijter JP, Nijssen JF, et al. (2012) Transendocardial cell injection is not superior to intracoronary infusion in a porcine model of ischaemic cardiomyopathy: a study on delivery efficiency. *J Cell Mol Med* 16: 2768-2776.
 61. Gyöngyösi M, Lang I, Dettke M, Beran G, Graf S, et al. (2009) Combined delivery approach of bone marrow mononuclear stem cells early and late after myocardial infarction: the MYSTAR prospective, randomized study. *Nat Clin Pract Cardiovasc Med* 6: 70-81.
 62. Nyolczas N, Gyongyosi M, Beran G, Dettke M, Graf S, et al. (2007) Design and rationale for the Myocardial Stem Cell Administration After Acute Myocardial Infarction (MYSTAR) Study: a multicenter, prospective, randomized, single-blind trial comparing early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of nonselected autologous bone marrow cells to patients after acute myocardial infarction. *Am Heart J* 153: 211-212.
 63. Cheng Y, Yi G, Conditt GB, Sheehy A, Kolodgie FD, et al. (2012) Catheter-Based Endomyocardial Delivery of Mesenchymal Precursor Cells Using 3D Echo Guidance Improves Cardiac Function in a Chronic Myocardial Injury Ovine Model. *Cell Transplant*.
 64. Medicetty S, Wiktor D, Lehman N, Raber A, Popovic ZB, et al. (2012) Percutaneous adventitial delivery of allogeneic bone marrow-derived stem cells via infarct-related artery improves long-term ventricular function in acute myocardial infarction. *Cell Transplant* 21: 1109-1120.
 65. Fukushima S, Sawa Y, Suzuki K (2013) Choice of cell-delivery route for successful cell transplantation therapy for the heart. *Future Cardiol* 9: 215-227.
 66. Sekine H, Shimizu T, Dobashi I, Matsuura K, Hagiwara N, et al. (2011) Cardiac cell sheet transplantation improves damaged heart function via superior cell survival in comparison with dissociated cell injection. *Tissue Eng Part A* 17: 2973-2980.
 67. Christman KL, Lee RJ (2006) Biomaterials for the treatment of myocardial infarction. *J Am Coll Cardiol* 48: 907-913.
 68. Rane AA, Christman KL (2011) Biomaterials for the treatment of myocardial infarction: a 5-year update. *J Am Coll Cardiol* 58: 2615-2629.
 69. Sarig U, Machluf M (2011) Engineering cell platforms for myocardial regeneration. *Expert Opin Biol Ther* 11: 1055-1077.
 70. Sui R, Liao X, Zhou X, Tan Q (2011) The current status of engineering myocardial tissue. *Stem Cell Rev* 7: 172-180.
 71. Akhyari P, Fedak PW, Weisel RD, Lee TY, Verma S, et al. (2002) Mechanical stretch regimen enhances the formation of bioengineered autologous cardiac muscle grafts. *Circulation* 106: 1137-1142.
 72. Kofidis T, Akhyari P, Boublik J, Theodorou P, Martin U, et al. (2002) In vitro engineering of heart muscle: artificial myocardial tissue. *J Thorac Cardiovasc Surg* 124: 63-69.
 73. Ott HC, Matthiesen TS, Goh SK, Black LD, Kren SM, et al. (2008) Perfusion-

- decellularized matrix: using nature's platform to engineer a bioartificial heart. *Nat Med* 14: 213-221.
74. Godier-Furnémont AF, Martens TP, Koeckert MS, Wan L, Parks J, et al. (2011) Composite scaffold provides a cell delivery platform for cardiovascular repair. *Proc Natl Acad Sci U S A* 108: 7974-7979.
75. Hamdi H, Furuta A, Bellamy V, Bel A, Puymirat E, et al. (2009) Cell delivery: intramyocardial injections or epicardial deposition? A head-to-head comparison. *Ann Thorac Surg* 87: 1196-1203.
76. Zhang D, Huang W, Dai B, Zhao T, Ashraf A, et al. (2010) Genetically manipulated progenitor cell sheet with diprotin A improves myocardial function and repair of infarcted hearts. *Am J Physiol Heart Circ Physiol* 299: H1339-1347.
77. Huang W, Zhang D, Millard RW, Wang T, Zhao T, et al. (2010) Gene manipulated peritoneal cell patch repairs infarcted myocardium. *J Mol Cell Cardiol* 48: 702-712.
78. Klouda L, Mikos AG (2008) Thermoresponsive hydrogels in biomedical applications. *Eur J Pharm Biopharm* 68: 34-45.
79. Fujimoto KL, Tobita K, Merryman WD, Guan J, Momoi N, et al. (2007) An elastic, biodegradable cardiac patch induces contractile smooth muscle and improves cardiac remodeling and function in subacute myocardial infarction. *J Am Coll Cardiol* 49: 2292-2300.
80. Jin J, Jeong SI, Shin YM, Lim KS, Shin HS, et al. (2009) Transplantation of mesenchymal stem cells within a poly(lactide-co-epsilon-caprolactone) scaffold improves cardiac function in a rat myocardial infarction model. *Eur J Heart Fail* 11: 147-153.
81. Piao H, Kwon JS, Piao S, Sohn JH, Lee YS, et al. (2007) Effects of cardiac patches engineered with bone marrow-derived mononuclear cells and PGCL scaffolds in a rat myocardial infarction model. *Biomaterials* 28: 641-649.
82. Yang J, Yamato M, Kohno C, Nishimoto A, Sekine H, et al. (2005) Cell sheet engineering: recreating tissues without biodegradable scaffolds. *Biomaterials* 26: 6415-6422.
83. Shimizu T, Yamato M, Itoi Y, Akutsu T, Setomaru T, et al. (2002) Fabrication of pulsatile cardiac tissue grafts using a novel 3-dimensional cell sheet manipulation technique and temperature-responsive cell culture surfaces. *Circ Res* 90: e40.
84. Elloumi-Hannachi I, Yamato M, Okano T (2010) Cell sheet engineering: a unique nanotechnology for scaffold-free tissue reconstruction with clinical applications in regenerative medicine. *J Intern Med* 267: 54-70.
85. Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, et al. (2006) Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. *Nat Med* 12: 459-465.
86. Zhang R, Mjoseng HK, Hoeve MA, Bauer NG, Pells S, et al. (2013) A thermoresponsive and chemically defined hydrogel for long-term culture of human embryonic stem cells. *Nat Commun* 4: 1335.
87. Kawamura M, Miyagawa S, Miki K, Saito A, Fukushima S, et al. (2012) Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model. *Circulation* 126: S29-37.
88. Matsuura K, Wada M, Konishi K, Sato M, Iwamoto U, et al. (2012) Fabrication of mouse embryonic stem cell-derived layered cardiac cell sheets using a bioreactor culture system. *PLoS One* 7: e52176.
89. Bel A, Planat-Bernard V, Saito A, Bonnevie L, Bellamy V, et al. (2010) Composite cell sheets: a further step toward safe and effective myocardial regeneration by cardiac progenitors derived from embryonic stem cells. *Circulation* 122: S118-123.
90. Cellesi F (2012) Thermoresponsive hydrogels for cellular delivery. *Ther Deliv* 3: 1395-1407.
91. Narita T, Shintani Y, Ikebe C, Kaneko M, Harada N, et al. (2012) The use of cell-sheet technique eliminates arrhythmogenicity of skeletal myoblast-based therapy to the heart with enhanced therapeutic effects. *Int J Cardiol*.
92. Teichmann J, Valtink M, Gramm S, Nitschke M, Werner C, et al. (2013) Human corneal endothelial cell sheets for transplantation: thermo-responsive cell culture carriers to meet cell-specific requirements. *Acta Biomater* 9: 5031-5039.
93. Miyagawa S, Saito A, Sakaguchi T, Yoshikawa Y, Yamauchi T, et al. (2010) Impaired myocardium regeneration with skeletal cell sheets—a preclinical trial for tissue-engineered regeneration therapy. *Transplantation* 90: 364-372.
94. Washio K, Iwata T, Mizutani M, Ando T, Yamato M, et al. (2010) Assessment of cell sheets derived from human periodontal ligament cells: a pre-clinical study. *Cell Tissue Res* 341: 397-404.
95. Kondo M, Yamato M, Takagi R, Namiki H, Okano T (2013) The regulation of epithelial cell proliferation and growth by IL-1 receptor antagonist. *Biomaterials* 34: 121-129.
96. Itabashi Y, Miyoshi S, Kawaguchi H, Yuasa S, Tanimoto K, et al. (2005) A new method for manufacturing cardiac cell sheets using fibrin-coated dishes and its electrophysiological studies by optical mapping. *Artif Organs* 29: 95-103.
97. Guillaume-Gentil O, Semenov OV, Zisch AH, Zimmermann R, Vörös J, et al. (2011) pH-controlled recovery of placenta-derived mesenchymal stem cell sheets. *Biomaterials* 32: 4376-4384.
98. Zahn R, Thomasson E, Guillaume-Gentil O, Vörös J, Zambelli T (2012) Ion-induced cell sheet detachment from standard cell culture surfaces coated with polyelectrolytes. *Biomaterials* 33: 3421-3427.
99. Turner WS, Wang X, Johnson S, Medberry C, Mendez J, et al. (2012) Cardiac tissue development for delivery of embryonic stem cell-derived endothelial and cardiac cells in natural matrices. *J Biomed Mater Res B Appl Biomater* 100: 2060-2072.
100. Maeda M, Yamato M, Kanzaki M, Iseki H, Okano T (2009) Thoracoscopic cell sheet transplantation with a novel device. *J Tissue Eng Regen Med* 3: 255-259.
101. Dai B, Huang W, Xu M, Millard RW, Gao MH, et al. (2011) Reduced collagen deposition in infarcted myocardium facilitates induced pluripotent stem cell engraftment and angiomyogenesis for improvement of left ventricular function. *J Am Coll Cardiol* 58: 2118-2127.
102. Huang W, Wang T, Zhang D, Zhao T, Dai B, et al. (2012) Mesenchymal stem cells overexpressing CXCR4 attenuate remodeling of postmyocardial infarction by releasing matrix metalloproteinase-9. *Stem Cells Dev* 21: 778-789.
103. Leroux L, Descamps B, Tojais NF, Ségué B, Osés P, et al. (2010) Hypoxia preconditioned mesenchymal stem cells improve vascular and skeletal muscle fiber regeneration after ischemia through a Wnt4-dependent pathway. *Mol Ther* 18: 1545-1552.
104. Noiseux N, Borie M, Desnoyers A, Menaouar A, Stevens LM, et al. (2012) Preconditioning of stem cells by oxytocin to improve their therapeutic potential. *Endocrinology* 153: 5361-5372.
105. Chang W, Song BW, Lim S, Song H, Shim CY, et al. (2009) Mesenchymal stem cells pretreated with delivered Hsp70 protein are protected from hypoxia-mediated cell death and rescue heart functions from myocardial injury. *Stem Cells* 27: 2283-2292.
106. Cui J, Li J, Mathison M, Tondato F, Mulkey SP, et al. (2005) A clinically relevant large-animal model for evaluation of tissue-engineered cardiac surgical patch materials. *Cardiovasc Res* 6: 113-120.