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HEART FAILURE

Cells as biologics for cardiac repair in ischaemic heart failure

Jozef Bartunek,1,2 Marc Vanderheyden,1 Jonathan Hill,3 Andre Terzic4

The epidemic of heart failure due to coronary artery disease is a leading cause of morbidity and mortality worldwide. The hallmark of this pathology is maladaptive ventricular remodelling that precipitates contractile dysfunction, and ultimately leads to the overt syndrome of congestive heart failure. The central feature in this malignant cascade is the massive loss of cardiomyocytes, followed by replacement with fibrotic scar; this ultimately leads to organ failure which is further accelerated by haemodynamic overload, inflammatory—oxidative stress, and/or impaired vascularisation. Despite continuous advances in disease management, the available medical, interventional or surgical treatments fall short of addressing the root cause of disease and are typically limited to palliative strategies mitigating disease symptomatology.

The rationale for stem cell based regenerative medicine applied to the treatment of heart diseases is based on the realisation that natural self renewing processes innate to the myocardium, while sufficient to sustain normal homeostasis, fall short of salvaging heart muscle following massive injury—as in the setting of myocardial infarction.1 Accordingly, boosting the cardiac reparative capacity through supplementation of stem cell pools has been increasingly considered as a novel therapeutic approach. Indeed, it is now recognised that extracardiac (eg, bone marrow) in addition to intracardiac progenitor cells are mobilised and home to the site of the myocardial injury to participate in the compensatory healing response.1 Furthermore, there is growing evidence that such cells participate in the maturation and induction of collateral vascular growth and neovascularogenesis, and may acquire phenotypic properties of neighbouring cardiac myocytes.1 These findings, propelled by recent progress in developmental biology, offer an unprecedented opportunity to achieve repair of damaged myocardium using stem cells as new therapeutic tools. Here, we focus on the current clinical experience as well needs for successful translation of the emergent field of cell based therapy from proof-of-concept to practice.

ACUTE MYOCARDIAL INJURY VERSUS CHRONIC HEART FAILURE: TARGETS AND DIFFERENCES

Although not necessarily sufficient to salvage the injured myocardium, the discovery of natural healing processes has led to the postulate that stem cell based therapy may, in principle, halt or even reverse the events responsible for progression of organ failure. It should be noted that while early after myocardial injury, the primary therapeutic goal is the salvage of the jeopardised myocardium to prevent further myocardial expansion and negative remodelling, at later stages of developed ischaemic left ventricular dysfunction, the aim is to reverse maladaptive remodelling and ensure improved contractility.5 In particular, excessive inflammatory response, oxidative stress and apoptosis are the primary targets in the initial stages, whereas fibrosis, loss of fibre organisation, and impaired excitation—contraction coupling are key features of florid ischaemic cardiomyopathy. In addition, multidimensional interactions between cardiomyocytes, extracellular matrix and blood vessels determine the outcome of global remodelling and ventricular dynamics. Thus, differences in the molecular and cellular substrate during the course of disease pathogenesis are likely to require distinct regenerative strategies to prevent progression or treat overt heart failure (figure 1).

CURRENT CLINICAL STATUS AND LESSONS FOR FUTURE TRIAL DESIGN

To date, approximately 3000 individuals worldwide have received stem cells in clinical trials addressing safety and efficacy in the treatment of heart disease. Meta-analyses of case—controlled trials in patients with recent myocardial infarction suggest significant, albeit limited, benefit on the surrogate end point—recovery of left ventricular ejection fraction beyond ‘state-of-the-art’ reperfusion therapy (table 1).2 Among these trials based on the use of blood or bone marrow derived stem cell populations, the double blinded, placebo controlled REPAIR-AMI (Repair of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction) trial has set the benchmark for cell therapy trials in this clinical setting.3 The trial reported a modest, but significant, improvement in left ventricular function 4 and 12 months after cell therapy. The trial was based on angio graphic evaluation of ejection fraction, with positive outcome corroborated by cardiac magnetic resonance imaging (MRI). Interestingly, the largest benefit was observed in patients with low ejection fraction. An independent randomised placebo controlled trial by Janssens et al reported significant reduction in infarct size which, however, did not
translate into superior functional recovery 4 months after coronary cell transfer. In this trial, cells were transferred within 24 h after reperfusion, while in the REPAIR-AMI, the overall benefit was driven by improvement observed only when cells were transferred ≥5 days after infarction. Of note, the randomised, but not placebo controlled, BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial showed only transient improvement in left ventricular function at 6 months compared to controls that disappeared at 18 months due to late recovery in controls. In addition, the randomised controlled ASTAMI (Autologous Stem Cell Transplantation in Acute Myocardial Infarction) trial failed to demonstrate significant improvement in ejection fraction as assessed from either cardiac MRI, single photon emission computed tomography (SPECT) or echocardiography. These apparently controversial effects may relate to different study designs, heterogenous patient populations, cell number and processing, time of cell injection, or methods used to assess outcome. Collectively, these studies demonstrate the feasibility and safety of a stem cell approach in the setting of acute ischaemic heart disease.

In the setting of chronic ischaemic heart disease or heart failure, initial clinical experience was gathered with injection of skeletal myoblasts. After several small trials with controversial safety outcomes, the MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) trial demonstrated safety of dose escalating skeletal myoblasts injections administered in addition to cardiac bypass surgery in patients with left ventricular dysfunction. Although the incidence of major cardiac adverse event, namely ventricular arrhythmias, was similar in myoblast and placebo treated groups, the trial failed to meet the primary end point of improvement in global or regional left ventricular function. Nevertheless, the highest dose of skeletal myoblasts was associated with reverse remodelling with reduction in left ventricular volumes. Similar trials of skeletal myoblasts using endoventricular delivery are underway. In contrast, there are only a few, mostly non-randomised, studies employing bone marrow cells in patients with ischaemic heart failure.

**Figure 1** Factors to consider in the clinical translation of cardiac regenerative therapy. The outcome of cell therapy depends on the ‘cellular’ factors as well as a number of non-cellular factors including the stage of tissue remodelling, risk profile and delivery techniques. For details see text.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected clinical trials for cardiac regeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients and design</strong></td>
<td><strong>Cell type</strong></td>
</tr>
<tr>
<td>Coronary cell transfer after STEMI</td>
<td></td>
</tr>
<tr>
<td>Boost</td>
<td>60 R-SB</td>
</tr>
<tr>
<td>Janssens</td>
<td>67 R-DB</td>
</tr>
<tr>
<td>Repair-AMI</td>
<td>504 R-DB</td>
</tr>
<tr>
<td>ASTAMI</td>
<td>100 R-SB</td>
</tr>
<tr>
<td>REGENT</td>
<td>200 R-controlled</td>
</tr>
<tr>
<td>Congestive heart failure (coronary and myocardial transfer)</td>
<td></td>
</tr>
<tr>
<td>Van Ramshorst</td>
<td>50 R-DB</td>
</tr>
<tr>
<td>Stamm</td>
<td>55 cohort</td>
</tr>
<tr>
<td>MAGIC</td>
<td>97 R-DB</td>
</tr>
<tr>
<td>SEISMIC</td>
<td>18</td>
</tr>
</tbody>
</table>

BMNC, bone marrow derived mononuclear stem cells; EF, ejection fraction; MI, myocardial infarction; R-DB, randomised double blind; R-SB, randomised single blind; STEMI, ST elevation myocardial infarction.
Endoventricular or coronary delivery has demonstrated feasibility and safety, yet efficacy remains to be proven in appropriately powered trials. Nevertheless, a recent randomised and placebo controlled study of the Leiden group indicates improved myocardial perfusion and function in patients with chronic myocardial ischaemia. Surgical delivery has been championed by the Rostock group, whereby myocardial delivery of enriched CD133 cells suggests benefit in left ventricular perfusion and function in addition to bypass grafting.

So far completed clinical trials underscore the stepwise development of cardiac stem cell therapy. Current indications include early post-infarction recovery, along with treatment of chronic heart failure and refractory ischaemia in patients not amenable to revascularisation. Next generation clinical trials applying cell transfer early post-ST elevation myocardial infarction (STEMI) should focus on patients with significantly compromised left ventricular function where anticipated improvements are clinically most relevant. It is also intriguing to note that patients with low ejection fraction and large myocardial injury show low systemic concentrations of circulating progenitors early after infarction. Though these observations do not explain why such patients are poor mobilisers or if low levels of circulating bone marrow cells reflect higher myocardial uptake in case of greater myocardial injury, it should be addressed as to whether and how naturally occurring bone marrow mobilisation and its interplay with injured myocardium relates to effects of exogenously administered stem cells. Additional clinical needs include patients with prolonged ischaemic times or microvascular dysfunction who are poor responders to standard reperfusion and medical treatments.

Matching clinical end points to the presumed mechanism of stem cell action is warranted. The initial assumption that adult stem cell transplantation ensures myocardial tissue regeneration has led to the usual focus on improvement of ejection fraction as the major surrogate end point. However, the choice for a specific end point should be tailored to the clinical setting and hypothesis under study. In addressing the specifics of myocardial salvage and prevention of heart failure after STEMI, end points reflecting infarct size, myocardial blood perfusion or regional function may be favoured. In contrast, in the setting of heart failure and left ventricular dysfunction, indices of left ventricular remodelling or global function or surrogate end points reflective of cardiopulmonary performance should be considered. The left ventricular ejection fraction is the most widely used end point, being a strong independent predictor of survival in patients with left ventricular dysfunction. However, it is load dependent and its improvement failed in the past to translate into overall clinical benefit. Therefore, improvement in ejection fraction should be evaluated in the context of other parameters such as reverse left ventricular remodelling, reduction of left ventricular load, and energy demand in phase I/II studies with surrogate end points. In this regard, mechanisms ascribed to cell therapy do not increase the calcium load or energy expenditure, and thus it can be reasonably expected that improvements in ejection fraction corroborated by reverse remodelling may translate into improved clinical outcome. Nonetheless, in future research, development related to other variables such as the active cell ingredient (ie, the biologics), means of delivery, engraftment as well as mechanistic understanding of repair should be considered to guide the design of hypothesis driven, as well as larger outcome driven, clinical trials.

**ISSUES SURROUNDING CELL TYPE, ORIGIN AND PROCESSING**

Variables range from cell related, patient specific and patient independent related to processing. With regard to cell related aspects, the fundamental strategies of autologous versus allogeneic origin are considered (table 2). Among autologous sources, bone marrow derived mononuclear stem cells are most widely used, given easy harvest and absence of need for ex vivo expansion. An additional potential advantage includes inclusion of potentially all beneficial cell types with functional recovery dependent on the equilibrium between cell subpopulations present in the mononuclear fraction. Progenitors with known function such as mesenchymal cells, mesangioblasts or CD34+ and CD133+ cells comprise only a very low portion of the entire fraction, and thereby multiple progenitors seem to compete for engraftment at least during the transendothelial passage after coronary cell transfer. The recent REGENT (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction) trial compared the effects of selected CD34+/CXCR4+ and unselected mononuclear cells after intracoronary delivery in the post-STEMI setting. Though the trial was negative, likely due to mismatch in the cell number and significant dropouts in the follow-up, new studies exploring potential benefits of the enrichment/selection for haematopoietic or mesenchymal stem cells (MSCs) on functional recovery are underway.

In addition, besides the bone marrow contribution to the progenitor stem cell reserve, other tissues have been identified that appear to harbour stem cells capable of differentiating into cardiovascular cell types. Adipose tissue is an attractive origin offering easy access to adipose derived mesenchymal and stem cells with potent angiogenic properties. The abundant numbers and accessibility of progenitor cells in adipose tissue with minimally invasive and rapid harvest make these cells an attractive source, allowing repetitive cell access. The heart itself also contains a pool of stem cells. However, caveats related to their derivation and expansion may limit a broader clinical application. Nevertheless, despite the identification of several cell types, it remains unclear whether each of these cytotypes...
DELIVERY AND RETENTION OF CELL BIOLOGICS

Delivery of stem cell based biologics demonstrates variable retention rates, typically not exceeding 5–10% of the injected dose regardless of the method or administration. Biodistribution is also variable with potentially large numbers of cells finding their way to remote organs such as the lungs, liver or spleen. In addition, clinical studies indicate a progressive decrease in could be used universally or the choice will need to be tailored with regard to timing after the injury and stage of left ventricular remodelling.

Current cell products are typically autologous offering the advantage of proper immune match. A limitation of autologous, individualised products is the inter-individual variation in cell functionality. The age, gender, comorbidity and cardiovascular risk factors are main factors affecting functionality and final outcome of the therapy. To overcome this problem and improve the inter-individual variations in the cell functionality, various approaches including cell engineering or use of adjunctive pharmacotherapy with statins or hormones are being explored. As alternatives, allogeneic cell products with uniform biological profiles are tested. Currently, mesenchymal cells devoid of human leucocyte antigen class II antigens (MHC-II) without co-stimulatory molecules CD80, CD86 or CD40 are main candidates for allogeneic use. Other candidates include umbilical cord derived stem cells that are rich in haematopoietic stem cells. Umbilical cord blood can be collected at no risk to the donor, has a wide availability of human leucocyte antigen phenotypes, and does not provoke ethical controversy. The immunogenicity of the stem cell and its modulation represents a new area of research leading to 'off-the-shelf' use, potentially eliminating inter-individual variability in stem cell functionality.

Besides issues surrounding cell choice, cell processing critically affects therapeutic outcome. Recent studies demonstrate that Ficoll based separation can lead to a higher yield of stem cells with superior in vitro and in vivo functional capacity, including induction of neovascularisation in the hind limb ischaemia model as compared to lymphoprep separation. These differences could account for the discrepant outcome between the ASTAMI and REPAIR-AMI study. The major implication for future development is that for any cell type or separation method proposed, extensive in vitro standardisation with rigorous release criteria, including precise description of cell number and in vitro and in vivo functional capacity, should be established before initiation of a clinical study.

Finally, evidence of endogenous cell mobilisation led also initially to pharmacological cytokine induced mobilisation of adult stem cells. However, the results of several small trials with cytokine mobilisation alone or in combination with cell delivery remain controversial with regard to the safety and efficacy of this approach.
myocardial signals after delivery of labelled stem cells, a finding consistent with rapid cell death or washout within hours of administration.\textsuperscript{13} w25 w26

The suboptimal engraftment and retention represents the Achilles heel in clinical translation of cell therapy (table 3). While during the days to weeks after acute ischaemic injury, chemoattractive forces are generally favourable for cells to adhere to vascular or structural myocardial compartments, it is controversial as to whether these signals are present in the setting of remodelled and dysfunctional myocardium.\textsuperscript{w27} A better understanding of the signalling profiles within the diseased myocardium relative to the extent of remodelling and dysfunction is important in predicting the amount of cell adhesion and migration likely to occur after stem cell administration. Armed with this information, efforts aimed at priming the tissue for more efficacious retention can be established, such as being applied in an ongoing clinical study with application of low energy shockwaves.\textsuperscript{w28} Alternative strategies to augment cell retention using pharmacological priming of cells utilising genetic modifications or use of resorbable scaffolds are being tested.\textsuperscript{w29} Besides enhancing the immediate engraftment, these strategies are relevant also with regard to improved cell survival, a major prerequisite of the sustained therapeutic benefit. When considering the extent of negative remodelling including wall thinning and excessive fibrosis replacement, integration of ‘non-cellular’ components with biologics is likely to be critical to balance off a number of factors that adversely affects cell survival and retention. Cell scaffolding or a combination with various self assembling matrices can add not only to the mechanistic support of cells or thinned tissue, but could also be helpful to enhance cell maturation by applying multidimensional spatial relationship or serving as a carrier of nutrients.

There is continuing discussion on the most appropriate technique or device for stem cell delivery.\textsuperscript{13} The choice depends on the assessment of the underlying pathology, the acuteness of the myocardial injury or associated interventional procedure, as well as the actual cell type to be delivered. In the setting of chronically ischaemic myocardium, tissue heterogeneity due to fibrosis and non-viable myocardium profoundly affects cell–tissue–device interaction. The interplay between these components is variable and dependent on their unique properties, and it is for the delivery system to assure effective administration of biologics with minimal trauma to cells or tissue (table S). It is also likely that the cell adhesive and migratory characteristics, their concentration and volume are modifying factors of the immediate retention. Besides the cell–tissue–device interaction, the surveillance of cell delivery using dedicated systems such as electromechanical mapping or intracardiac ultrasound may contribute to optimal cell delivery. Importantly, delivery will also depend on the interventional skills of operators. Intra-myocardial injection catheters function within a different framework from vascular devices and, while a fair body of experience exists, most have seen limited use in clinical trials to date. Even though none are overly demanding in concept or mechanics, learning curves are still being charted for all of them, especially for those in which advanced myocardial disease is being targeted.

**MECHANISTIC UNDERSTANDING**

The mechanisms ascribed to improvements after cell delivery are still incompletely understood but seem multifactorial and related to cytoprotection and paracrine effects, neovascularisation, and possibly cardiomyogenic differentiation\textsuperscript{w13} w14 w15 (figure 2). Similar to the strategy and cell choice, the operational mechanisms are likely to depend on the tissue target and acuteness of myocardial injury. Cytoprotection is accepted as the major mechanism underlying cell therapy benefits after acute myocardial injury. It appears to be mediated primarily by paracrine effects of cells on apoptosis or enhancement of the endogenous cellular repair process.\textsuperscript{w14} w15 It is likely that modulatory effects on the pleiotropic inflammatory pathways participate in the beneficial effects as well. Besides affecting dysregulated inflammatory cascades triggered by injury, stem cells may promote favourable alterations in extracellular matrix which, together with cytoprotection, may be the key mechanisms underlying the reduction of infarct size and thereby improvement in overall function. These mechanisms are not well defined and network based analyses using high throughput genomics and proteomics in relevant in vitro systems or animal models should help to decipher the key molecules and pathways involved in paracrine effects.

The precise mechanism underlying paracrine effects in the setting of chronic heart failure is also not defined. Through inhibition of ongoing apoptosis in failing hearts, cytoprotection of cardiac myocytes against oxidative stress or inhibition of matrix degradation are hypothetically possible but remain unproven.\textsuperscript{13} Other more plausible mechanisms include induction of neovascularisation by stimulating maturation of existing collaterals or by inducing mature endothelial cells into vessel growth.\textsuperscript{w35} Neovascularisation or improved perfusion, as an underlying mechanism at organ level, is supported by several preclinical and clinical findings. However, to what extent cell delivery contributes physically to vascular growth, either by incorporation into pre-existing collaterals or undergoing endothelial differentiation, is controversial and seems variable in various experimental models.\textsuperscript{w35}

Cardiomyogenic differentiation has been extensively studied, but results are conflicting and may depend on the cell type.\textsuperscript{15} w31–35 The potential for cardiomyogenic differentiation is quite well documented in the case of mesenchymal\textsuperscript{10} 11 or cardiac residing stem cells.\textsuperscript{w36} Yet conversion rates in the case of MSCs are low. Initial observations that
haematopoietic stem cells or endothelial progenitors may transdifferentiate into cardiac myocytes due to local microenvironment and cell-to-cell contact was more recently challenged. It has been proposed that cell fusion rather than transdifferentiation may be responsible for the co-expression of cardiac markers in stem cells. Nevertheless, recent studies with genetic-fate tracking bring strong evidence to support endogenous cardiac myocytes replacement after injury and cardiomyogenic differentiation of bone marrow cells. Finally, a new paradigm linking exogenous cell delivery with enhanced endogenous cell tissue repair has been proposed. This new paradigm is based on the assumption that the existing stem cell niche within the heart—that is, cardiac residing stem cells—may be potentiated by exogenously delivered cells. Exogenous cells may provide a new matrix for residing cells and lead to multiple paracrine mediated effects on survival, potential differentiation, and perfusion.

**FUTURE PROSPECTS**

Though recent data seem to corroborate transdifferentiation of adult stem cells, it seems to be a rare event and its efficiency with regard to improved contractility is still questioned. The disappointing observations with regard to stem cell transdifferentiation may be partially related to the inability of the adult myocardium, which is devoid of embryonic signalling, to recapitulate the necessary environment to stimulate myocyte growth or signalling. Furthermore, occasional cautionary reports indicate the potential risk for preferential differentiation of adult stem cells into bone forming osteoblasts. Though only observed in rodent animal models, they highlight the need for a tight control of myocardial effects in clinical translation of the cell therapy and the need for amplification of designated pathways to improve the efficacy either by acting on cell survival, paracrine potential or physical differentiation and integration. In these efforts, the field will be moving from naive adult stem cells into development of second generation biologics, exemplified by guided cell products. The strategies vary from pharmacological pre-treatment and genetic modification to biomimetic approaches. In these rational designs, knowledge from embryonic cardiopoiesis may be critical in defining the optimal strategy for pre-transplantational treatment of adult stem cells. Cardiomyogenic differentiation has been demonstrated by co-culture of MSCs with isolated neonatal cardiac myocytes, supporting the concept that mimicry of the cardiac microenvironment, in a manner similar to natural cardiac embryogenesis, might be a valid strategy to steer at least some types of adult stem cells into designated cardiac signalling and thereby potentiate functional effects after implantation into injured myocardium. Moreover, integrated knowledge of embryonic development and adult stem cell biology has led to the discovery of growth factor cocktails capable of inducing cardiopoietic differentiation in vitro.
In fact, tandem genomic and proteomic analysis of the endodermal secretome has identified cardiogenic factors that match the MSC’s cell surface receptor profile. This approach has been implemented to guide cardiogenic differentiation of MSCs from normal donors. It remains to be established whether such an approach is also useful in guiding MSCs from patients with ischaemic heart disease. The concept requires further testing including optimisation of the proliferative and survival potential of primed cells, and understanding of the relative contribution of differentiation and/or paracrine effects on functional recovery.

Finally, advances in stem cell biology are likely to propel further the clinical translation of regenerative medicine. Discoveries related to regulation of stemness of adult somatic cells with development of inducible pluripotent cells may overcome limitations of embryonic stem cells and offer new arrays of biologics with therapeutic potential. Though the current efforts primarily focus on ‘cellular’ aspects of regenerative medicine, advances in our understanding of the ‘non-cellular’ factors controlling cardiac development will guide the future leads in translation of tissue engineering which is likely to offer new, sophisticated biologics.

CONCLUSIONS

Despite the promising results of initial observations and randomised trials, cell based treatment can only be fully translated when definite answers are found for aforementioned questions. Progress should follow the well designed path of integrated and coordinated translational science. We should follow the path of randomised, preferably placebo controlled, trials for those cell types/technologies that have passed the test of randomised trials with surrogate endpoints. From the early stages, trials need to use well defined cell products with established release criteria from efficacy and safety aspects. Hypothesis driven studies should address specific issues to define the relationship between homing and functional effects. Clinical translation requires further complementation of fundamental and translational research to address the hurdles related to cell functionality and delivery. It is critical that clinical studies are conducted in close interaction or under leadership of clinicians and scientists with appropriate knowledge spanning the spectrum of stem cell biology as well as integrative myocardial biology and physiology. Finally, continuous safety scrutiny remains our utmost duty and formation of independent data and safety monitoring boards should be an integral part of such clinical and translational research. Concerted multidisciplinary efforts with continuous bench—bedside—bench cycle need to be carefully developed in order to propel the clinical translation of regenerative cardiovascular medicine.

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Provenance and peer review
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Cell therapy for heart failure: key points

- Preclinical studies have demonstrated the ability of cell therapy to augment perfusion and increase myocardial contractility in various animal models.
- Yet, results of randomised trials in the setting of acute myocardial infarction are controversial. Contradictory results could be related to differences in study design, cell number and processing.
- Issues to address before stem cell therapy could become the clinical standard include:
  - Identification of cells mediators relative to onset of tissue injury and extent of remodelling
  - Standardisation of cell processing with release criteria for particular cell product
  - Targeting and retention of cells at the desired sites
  - Mechanistic understanding and surveillance of myocardial tissue effects
- Molecular mechanisms of current stem cell based regenerative therapies include primarily paracrine signalling on vasculogenesis and collateral growth and myocardial protection. Cardiogenic trans-differentiation and cell fusion occur in low frequencies.
- Clues from developmental cardiogenesis could help to devise new strategies to augment the cardiomyogenic differentiation and regenerative effects of naïve non-modified stem cells.
- Development of ‘non-cellular’ components of regenerative medicine, such as delivery devices, imaging and tissue engineering, can synergistically advance cardiovascular regenerative medicine.

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   - Review providing analysis and leads for optimisation of cell retention related to cell, tissue and device related factors.
  ▶ Detailed review of paracrine mechanisms underlying cell mediated effects upon myocardial recovery.
  ▶ Balanced view on cardiogenic differentiation as a potential mechanism underlying the benefits of cell therapy in myocardial regeneration.
  ▶ Review describing the rationale and development of guided cardiopoietic stem cells as a second generation of cell biologics.
  ▶ Pivotal work identifying biological systems and signalling involved in cardiomyogenesis using genomics and proteomics.