Chapter 10
Delivery Modes for Cardiac Stem Cell Therapy

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10.1 Introduction

Stem cell delivery to the heart is considered a potential breakthrough therapy for injury induced heart failure with particular reference to myocardial infarction. After a heart suffers a myocardial infarction, potentially at least a billion functioning cardiomyocytes can be lost due to the resultant ischaemia and this damage cannot be repaired in any meaningful manner by unaided endogenous repair mechanisms. Certainly this is the case in the human heart with the apparent very limited regenerative capacity of the human cardiomyocyte, with a renewal rate most reliably determined to be around 1–2 % per annum in the adult heart (Bergmann et al. 2009; Senyo et al. 2013). So after a myocardial infarction, the lost cardiomyocytes are inevitably replaced by a relatively avascular scar. This scar formation forms part of the complex and compensatory remodelling process, which also incorporates hypertrophy of the surviving cardiomyocytes, and allows for the heart to recover some function and strengthen the infarcted region. However though compensatory in the

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first instance, this process predisposes patients to a vicious and cyclical progression towards heart failure (Opie et al. 2006). Present optimal therapeutic interventions do not directly address the root cause of the heart failure, namely the death of cardiomyocytes and thus it is little surprise that stem cell based approaches with their potential promise of regeneration have received such wide spread attention over the last two decades. The vast majority of phase I/II clinical trials thus far have utilised the adult stem cell populations, in particular those derived from the bone marrow. This use of stem cell populations with ill-defined potential for differentiation toward cardiomyocyte lineage resulted in part from their ease of isolation, better safety profile, lack of ethical burden and initial small animal studies demonstrating striking cardiac tissue regeneration (Orlic et al. 2001). However, the hope of meaningful levels of regeneration due to transdifferentiation were quickly quashed by follow up animal studies (Murry et al. 2004) and also the, even when viewed optimistically, disappointing outcomes from the clinical trials. The most recent meta-analyses demonstrate this quite clearly with two meticulous analyses coming to differing conclusions, one finding modest improvements in a range of clinical end points (Fisher et al. 2015) and the other determining there to be no therapeutic benefit (Gyongyosi et al. 2015). It is also now widely accepted that when benefits are observed in these trials and related animal studies, they most likely predominately result from a paracrine effect (Gnecchi et al. 2008). There are many nuances in the relevant arguments with respect to efficacy of injected stem cells that are covered in detail elsewhere in this book but two threads that are common to reviews and analyses of adult stem cell delivery for myocardial infarction induced heart failure are the apparent safety of the approach and the very poor retention of delivered cells. The former finding is a necessity for any further work to proceed and the latter a conundrum for all cell-based approaches. It is beyond the scope of this chapter to consider the efficacy of stem cell delivery to the heart in restoring lost function and indeed this aspect is both hotly contested (see above) and covered by a plethora of meta-analyses. Most likely, several ongoing multi-center phase III trials will supply some of the definitive answers that the stem cell therapeutic community requires (de Jong et al. 2014). However, if the actual delivery of stem cells presently is inadequate and cannot achieve a therapeutic dosage, it is possible that these keenly awaited results may be less definitive in nature than hoped for. The future use of cells with greater potential for regeneration than bone marrow derived cells or the potency of any achieved paracrine effect will both be severely hampered by inefficient delivery. Thus in the first instance, we shall focus on studies, clinical and pre-clinical, where stem cells have been specifically tracked after being suitably labelled. These will be categorised according to their delivery routes.

10.2 Stem Cell Delivery Routes

In clinical trials, cells have been predominantly delivered to the heart either through infusion-based routes via major cardiac vessels or direct injection into the cardiac muscle (Fig. 10.1).

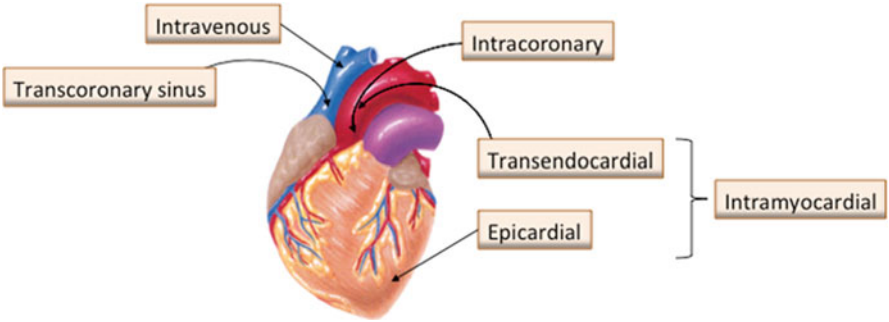

Fig. 10.1 Different delivery routes for cardiac cell delivery

10.2.1 Infusion Delivery

The leading route of delivery in clinical trials (Campbell and Suzuki 2012; Sanganalmath and Bolli 2013) has been through the infusion of a bolus of stem cells into the coronary vasculature with coronary arteries being the main vessels of choice. Systemic intravenous infusion has also been explored.

Intracoronary Infusion

In antegrade methods, the proximal aorta is reached usually by the femoral artery and the target coronary artery is then catheterised. In the clinic, cells are then normally infused under pressure to potentially facilitate ingress into the cardiac tissue. This is achieved by inflating a balloon and infusing the cells distally, thus limiting backflow of cells and also coronary flow forward past the balloon. It is envisaged that this scenario will assist cell delivery by increasing residence time in the infarcted region. Subsequently, several rounds (3–4) of pressurised cellular infusions are then applied. Certainly, this route of delivery is favoured as the access method is one most interventional cardiologists are familiar with, it can be achieved without complex mapping required for catheter based intramyocardial (IM) injections and has the potential to be used in high risk patients due to its minimally invasive nature. Further to this, it may have the potential to aid engraftment, as cells will necessarily tend to reach reasonably perfused cardiac tissue that might be less hostile to cell survival. Of course as a corollary to this, more compromised regions of the infarct may be poorly supplied. Concerns exist regarding the safety of the technique for the delivery of larger stem cells such as mesenchymal stem cells (MSC) with reports of pulmonary embolisms resulting from their migration away from the heart (Freyman et al. 2006; Furlani et al. 2009; Vulliet et al. 2004).

Retrograde delivery where access for the percutaneous catheter is gained through the femoral vein via the right atrium, cannulating the coronary sinus and catheterising the target coronary vein has received less attention than the coronary artery route. This method where cells are also infused under pressure avoids issues of occluded arteries precluding access but due the tortuous nature of the venous system is more technically challenging.

Systemic Intravenous Infusion

Intravenous injection has received quite significant interest due to the simple and non-invasive manner through which delivery might be achieved. Successful delivery would be reliant on homing to the cardiac site of injury and this has been demonstrated for cells such as bone marrow mononuclear cells (BMMNC) (Abbott et al. 2004). It is considered to most likely be effective in the context of acute myocardial infarction due to homing signals production being most pronounced at this stage (Frangogiannis 2006). However, it has been calculated based on blood flow rate to the left ventricle that infused cells would have to circulate many times to come into contact with the region of injury allowing time for deposition in other organs (Strauer and Steinhoff 2011).

10.2.2 Intramyocardial Injection

As implied, intramyocardial (IM) injection refers to the most direct way of delivering cells to the injured heart, namely by injection either epicardially, endocardially or through the coronaries. Epicardial delivery is mainly achieved through surgical exposure of the heart and the latter two routes through catheterisation.

Epicardial Delivery

Direct injection into the exposed heart has significant appeal due to the ease with which the injured or scarred region can be visualised and cells precisely delivered to infarcted and/or peri-infarct tissue. Multiple injections with large numbers of cells are also feasible and as with other IM routes, the need for reliance on homing of cells is removed. Due the reduced risk of coronary embolism, larger stem cells such as MSC can be delivered by this route. However, the invasive nature of this approach has generally limited its application clinically to studies where cell delivery is achieved in conjunction with open-heart surgeries such as coronary artery bypass grafting. This unavoidably reduces the number of patients who can be treated in this way. There have been limited reports on the use of minithoracotomies (Klein et al. 2007; Pompilio et al. 2008) to access the heart for direct injection but greater emphasis has been placed on development of catheter based IM injection methods.

Endocardial Delivery

Catheterisation is achieved usually through the aortic valve and injections are delivered perpendicularly to the endocardial surface. Placement is typically guided by electromechanical mapping using the NOGA® system (Biosense Webster, Diamond Bar, CA, USA) that allows for visualisation of the infarct and peri-infarct zones (Kharlamov et al. 2013). Thus this approach presents most of the advantages

of direct surgical delivery in a minimally invasive manner and has been shown to be feasible and safe (Perin et al. 2003). However, the electromechanical mapping procedure is technically challenging and the equipment expensive.

Trans-coronary Delivery

The coronary sinus is accessed via the venous system with the catheter being passed though the right atrium. Injection is achieved parallel to the direction of the vein and it has been postulated that this may improve engraftment relative to the perpendicular manner in which cells are injected endocardially. The technique has been shown to be feasible and safe with BMMNC in pigs (George et al. 2008) and with skeletal myoblasts in a small clinical trial (Siminiak et al. 2005).

10.3 Engraftment

We have in the main focussed on studies that utilise in vivo imaging techniques to track cellular engraftment within the heart as these approaches allow for longitudinal analysis of cellular fate. They also avoid the potential inaccuracy of histological techniques were only a small fraction of the target area is visualised (Freyman et al. 2006).

The imaging techniques commonly used in cardiac studies (reviewed in (Azene et al. 2014; Chen and Wu 2013; Ransohoff and Wu 2010)) to quantify cellular engraftment exploit either direct physical labelling of the cell population or the introduction of a reporter gene to the cell. Direct labelling has thus far been the method of choice for clinical trials where cellular retention has been analysed, in part because it avoids the alteration of the genetic makeup of the delivered cells with its associated concern for possible mutagenesis. Cells labelled with a suitable contrast agent can then be imaged using the clinically available modalities of positron emission tomography (PET) and single-photon emission computed tomography (SPECT). PET and SPECT have been most widely used, usually with ^{18}F-FDG as a label for the former and ^{99m}TC-HMPAO the latter. PET scanners have a 1–2 order higher sensitivity than SPECT, detecting label at 10^{-11} to 10^{-12} mol/L. Cells that have been directly labelled are only really suitable for acute retention studies due to the labels having relatively short half-lives and concerns regarding retention of the label at the site after cell death through for example macrophage engulfment. The use of reporter genes is required for long term tracking as once their stable transfection or transduction into the cell's genome is achieved, cell signal should be proportional to the number of live cells. The Herpes Simplex Virus type 1 thymidine kinase (HSV1-TK) and thyroidal sodium iodide symporter (NIS) are suitable for PET and SPECT respectively when used in conjunction with imaging probes such as [18 F]FEAU (Perin et al. 2011) and ^{123}I (Templin et al. 2012). However, bioluminescence imaging (BLI) surpasses these techniques in sensitivity by at least 3 orders of magnitude (10^{-15} mol/L) through the detection of light

generated from a reporter gene such as firefly luciferase. This modality at present only finds utility in small animal models due to attenuation of the light as it travels through tissue.

10.3.1 Infusion Studies

There have been a number of clinical studies where acute cellular retention has been assayed for infusion based delivery but not for IM (Table 10.1). The first PET feasibility study was carried out by Hofmann et al. (2005) to assess the retention of autologous BMMNC 75 min after either anterograde intracoronary (IC) or intravenous (IV) delivery to patients who had suffered a myocardial infarction 5–10 days prior. Only 1.3–2.6 % of the 18-F-FDG cells were retained in the heart with IC delivery and none could be detected after IV infusion. The majority of the cells were observed to have accumulated in the liver and spleen. A similar outcome was observed in a slightly larger study of similar design where 17 and 3 patients (3 to >300 days post-myocardial infarction) were enrolled for IC and IV delivery of peripheral blood stem cells (PBSC), respectively (Kang et al. 2006). Again IV delivery did not result in any detectable levels of cells in the heart and were only found in the lungs 2 h later. 2 % of IC delivered cells remained in the heart with the remainder lodged in the spleen, liver and bone marrow.

A variety of animal trials largely substantiate the observations of very poor levels of homing after IV delivery. In a canine study, 111In oxine-labeled bone marrow MSC (BMMSC) were found by SPECT to mainly reach the lungs after 24 h but there was a low level of redistribution to the heart (1.65 % of lung uptake) by 48 h indicating possible homing (Kraitchman et al. 2005). By 7 days as assessed by radioactive counting only 0.05 % of cells infused persisted in the heart. In a mouse BLI study where luciferase expressing BMMNC were injected through the tail vein into either sham operated or ischaemia/reperfusion (I/R) infarcted mice, a significant increase in homing to the infarcted mice's hearts was observed (Sheikh et al. 2007). However overall levels of engraftment were very low with only 0.1 % of cells residing in cardiac tissue at 14 days post-injection.

The majority of clinical and animal studies examining cell engraftment after IC delivery rendered similar results to the two IC/IV comparative studies described above. Interestingly, in two porcine studies retention of BMMNC was assessed after IC delivery with or without balloon occlusion and found to not significantly differ at either 1 h or 24 h (Doyle et al. 2007; Tossios et al. 2008). This is suggestive that the homing signals expressed by the injured heart are insufficient to enable cellular egress from the circulatory system in the short period of blocked blood flow before the cells are washed away by the released blood.

Initial comparison of the retrograde and more commonly utilised anterograde IC routes in a porcine model showed no significant difference in cellular engraftment at 1 h with 2.6 % and 3.2 % retention of BMMNC for IC and retrograde coronary venous (RCV) delivery (Hou et al. 2005). Two follow up studies indicate that perhaps IC is slightly more effective than RCV with initially higher levels of adipose

Table 10.1 Retention of cell delivery for cardiac repair

Cell type	Model	Route	Duration	Retention	Reference
BMMNC	Human	IC, IV	75 min	1.3–2.6 %—IC, no cell detection—IV	Hofmann et al. (2005)
PBSC	Human	IC, IV	2 h	2 %—IC, no cell detection—IV	Kang et al. (2006)
BMMSC	Canine	IV	7 days	0.05 %	Kraitchman et al. (2005)
BMMNC	Murine	IV	14 days	0.1 %	Sheikh et al. (2007)
BMMNC	Porcine	IC	1 h	8.7 %—balloon occlusion, 17.8 %—single-bolus	Doyle et al. (2007)
BMMNC	Porcine	IC, IM	24 h	3.3 %—IC (balloon), 3 %—IC (without), 15 %—IM	Tossios et al. (2008)
BMMNC	Porcine	IC, IM, RCV	1 h	2.6 %—IC, 11 %—IM, 3.2 %—RCV	Hou et al. (2005)
AdMSC	Porcine	IC, RCV	1 h and 24 h	1 h—57.2 %—IC, 17.9 %—RCV	Hong et al. (2014b)
				24 h—22.6 %—IC, 18.7 %—RCV	
BMMNC	Porcine	IC, IM	1 h	13,579 cells—IM, 7049 cell—IC	George et al. (2008)
BMMSC	Rat	IV, IM	1 week	15 %—IM, no cell retention—IV	Hale et al. (2008)
BMMNC	Rat	IV, LV, IM	24 h	16 %—IM, <1 %—IV, <1 %—LV	Nakamuta et al. (2009)
iPSC-CM	Murine	IM	4 weeks	8 %	Lepperhof et al. (2014)
hCPC	Murine	IM	4 weeks	<5 %	Liu et al. (2012a)
CSC	Murine	IC	24 h	12.7 %	Hong et al. (2014a)
BMMSC	Porcine	IM	10 days	5.8 %	Gyongyosi et al. (2008)
BMMSC	Porcine	EC	35 days	40–50 %	Perin et al. (2011)
iPSC	Porcine	IM	15 weeks	≈2 %	Templin et al. (2012)
EPC	Canine	EC, IM	40 min	57 %—EC, 54 %—IM	Mitchell et al. (2010)

IC Intracoronary, *IV* Intravenous, *IM* Intramyocardial, *RCV* Retrograde coronary venous, *IA* intra-aortic, *LV* Left ventricular cavity, *EC* Endocardial
IPSC-CM induced pluripotent stem cell-derived cardiomyocytes, *hCPC* human cardiac progenitor cells, *CSC* cardiac stem cells, *EPC* Endothelial progenitor cells

derived MSC (AdMSC) engraftment in a porcine model of IC delivery at 24 h though this difference abated at 48 h (Hong et al. 2014b). In a clinical study (Silva et al. 2009), elevated levels of engraftment of ^{99m}TC-BMC were found with IC delivery at 4 and 24 h post administration.

In the majority of the IC, RCV and IV studies, cells were found preferentially located within the pulmonary system. This is of interest as it has been shown that

deposition of human MSC into NOD/SCID mice lungs after IV infusion upregulated the anti-inflammatory protein TSG-6 that was then demonstrated to be responsible for a paracrine based reduction in infarct size (Lee et al. 2009).

10.3.2 Intramyocardial Injection

As noted above, thus far no clinical studies have been reported that assay retention and engraftment after intramyocardial (IM) injection. In one of the earlier studies in a porcine model, it was shown that acute retention at 1 h is significantly higher than the infusion methods (IM 11 %, IC 2.6 % and RCV 3.2 %) (Hou et al. 2005). In almost all other direct comparisons between IM and infusion based deliveries, this has been found to be the case (George et al. 2008; Hale et al. 2008; Li et al. 2009, 2011; Nakamuta et al. 2009; Tossios et al. 2008). It is perhaps not entirely surprising as the need for reliance on homing signals to attract cells out of the circulatory system is avoided. However levels achieved though higher than those by infusion are still low and reporter gene studies tend to indicate further rapid loss of cells from the heart. In BLI studies with a range of cell types, 90 % or more of cells that were initially retained are lost in the medium term (7–28 days post-injection) (Lepperhof et al. 2014; Li et al. 2011; Liu et al. 2012a; Westrich et al. 2010). In addition to these BLI studies, similar decreases in cell numbers in the hear were discerned using a novel real-time PCR analysis of infarcted mouse hearts injected with cardiac derived stem cells (CSC) (Hong et al. 2014a). When autologous porcine BMMSC expressing HSV1-TK and red fluorescent protein (RFP) were injected endocardially via catheterization under NOGA guidance and tracked by PET, signal was detected at 30 h post-injection but the signal was lost at 7 days (Gyongyosi et al. 2008). Though histological analysis for RFP expressing cells indicated around 6 % were still present at 7 days, this is similar to the trends observed in small animals. Very differently in a porcine study utilising HSV1-TK expressing porcine BMMSC where 20-fold greater cell numbers were delivered by NOGA guided catheter injection endocardially, an estimated 40–50 % of cells were seen to survive to 35 days in 3 pigs and in one pig to 5 months though with a decreased signal (Chen and Wu 2013; Perin et al. 2011). Interestingly in a porcine study where NIS expressing human iPSC (immunosuppression with cyclosporine A) were injected under NOGA guidance in similarly large numbers either with or without human MSC, only in the pigs that received iPSC injected with MSCs was a signal still detected by SPECT at 15 weeks (Templin et al. 2012). This raises the questions of whether very large numbers of MSC are required to create a more conducive environment for engraftment and whether this is a species-specific effect.

From the above it seems reasonable to assume that endocardial delivery via a catheter would be similar in cellular retention to that achieved with direct epicardial injection. A study in a canine model whereby 111In-tropolone labelled endothelial progenitor cells were either directly injected into the epicardium or endocardial injections were performed using the Stiletto Endo-myocardial Injection System

(Boston Scientific) under radio-graphic fluoroscopic guidance (Mitchell et al. 2010), equivalent levels of acute retention at 30–40 min post-injection were observed. It would seem that a retention study on IM delivery retention should be performed in humans to ascertain whether the higher, though still underwhelming, levels of cells retained with this route in animals are also seen in the clinic.

10.4 Aspects Influencing Cell Retention and Engraftment

Simple mechanical ejection from the delivery site could of course play a role in the immediate loss of cells. Intramyocardial injections of 18-F-FDG labelled CSC into infarcted rat hearts that had either been arrested or had their ventricular rate slowed with adenosine when visualized with PET at 1 h showed substantially improved retention for both conditions (control: 17.8 %; arrested: 75.6 %; adenosine: 35.4 %) (Terrovitis et al. 2009). A similar retention to that achieved with adenosine was seen when the injection hole was simply sealed with fibrin glue. The authors argue that the greater retention seen in the arrested heart may reflect that not only was potential mechanical ejection reduced in this condition but also washout by myocardial perfusion. It might be expected that the mechanical influence on retention would be more pronounced in a heart beating at 300–400 bpm than in the clinic but this has not been empirically determined yet.

An important aspect that might be expected to influence retention and long-term survival would be timing of delivery after infarction. The environment within the infarcted tissue changes dramatically during the remodelling process for many parameters that might influence cells inclusive of inflammation, ischaemia, extracellular matrix structure and biomechanics (Holmes et al. 2005). It is therefore perhaps somewhat surprising that in the relatively limited number of studies directly examining the consequence of timing, no marked effect was observed. In a human study where retention of 111IN-oxine labelled PBSC was assessed by SPECT, 6.3 % acute retention was observed in infarcts less than 14 days old relative to the 4.5 % in older infarcts (Schachinger et al. 2008). Small animal studies have seen similar results with little or no difference in retention observed whether cells are injected acutely or at later time points (Bonios et al. 2011; Nakamuta et al. 2009; Swijnenburg et al. 2010).

In a recent meta-analysis of stem cell therapy outcome in the clinic, a positive correlation between mononuclear cell dose infused and increase in ejection fraction was detected (Clifford et al. 2012). The limited studies that have assessed the impact of dosage on retention and survival have also found a similarly positive relationship. 1–2 % of either 10^5 or 10^6 BMMSC or BMMNC were found to survive at 6 weeks after injection into rat hearts (Muller-Ehmsen et al. 2006) and acute retention (Shen et al. 2012) was found to be around 10 % for all dosages (10^4 to 5×10^5) of cardiospheres (a natural mixture of resident cardiac stem cells and supporting cell types (Smith et al. 2007)) with a positive correlation between dosage and functional recovery. An elegant study by Liu et al (Liu et al. 2012a) took advantage of the apparent variability present in epicardial intramyocardial delivery (Hou et al. 2005)

to stratify their treatment cohort (HSV1-TK expressing human cardiac progenitor cell (hCPC) delivered into infarcted SCID mice hearts) into high and low early engraftment groups. A clear and significant improvement in various left ventricular (LV) functional parameters was observed for the high engraftment group, which was ascribed to the paracrine effect.

These latter two studies emphasize that improving retention and survival of stem cells delivered will correspond to improved outcome. We shall devote the remainder of this chapter to exploring the utilization of injectable biomaterial scaffolds to achieve this desired improvement. Biomaterials are attractive as they in their various guises afford the possibility of tackling multiple factors that might influence engraftment such as mechanical entrapment and reduction of anoikis, inflammation and ischaemia.

10.5 Injectable Biomaterial Cellular Vehicles

10.5.1 Biomaterial Injection

Clearly, to act as cellular delivery vehicles injectable biomaterial scaffolds should gel sufficiently quickly after injection to effectively entrap cells, they must be biocompatible and allow for cellular adhesion to reduce anoikis. The ability to stimulate potentially cellular protective mechanisms such as angiogenesis would of course be desirable. These and other related aspects are the subjects of intensive recent research as will be seen below. However, injectable materials can be intrinsically cardioprotective. The cyclical process of pathological left ventricular dilation that ensues after a myocardial infarction is driven by increased stress in the wall (Opie et al. 2006; Sutton and Sharpe 2000). This increased stress can be considered to derive from the interaction between the increasing ventricular volume and the thinning of the infarcted wall as described by the Law of Laplace $T = \frac{p \cdot r}{h}$, where T is the tension in the cardiac wall, p is the blood pressure in the ventricular cavity, r is the radius of the ventricular cavity and h is the thickness of the cardiac wall. As can be seen from this, an increase in wall thickness will reduce the stress experienced by the cellular components of the ventricular wall and thus potentially inhibit the progression towards heart failure. Injection of a material within the wall can achieve such thickening and finite element models (Wall et al. 2006; Wenk et al. 2009) have shown that this resultant bulking can reduce stress by up to 20 % in the critical border zone region and slightly increase the ejection fraction (EF).

The above finite element modelling findings have been widely supported by studies that have looked at injection of a broad range of biomaterials into infarcted hearts, inclusive of both natural materials (e.g fibrin; collagen; matrigel; extracellular matrix derivatives; alginate) and synthetic (e.g. self-assembling peptides; polyethylene glycol; poly(N-isopropylacrlamide) polymers) (reviewed in Nelson et al. 2011, Radisic and Christman 2013). These studies have on the whole observed wall

thickening and varying degrees of functional preservation. There is a paucity of studies that have empirically investigated the mechanism through which these above results were obtained. However, a recent study (Ifkovits et al. 2010) demonstrated as predicted by the mathematical models, a stiffer methacrylated hyaluronic acid hydrogel resulted in less infarct expansion and left ventricular dilation in a porcine infarction model. This type of research is urgently needed to guide the design and optimisation of injectable hydrogels for cardiac therapy. It should be noted that the above finding also raises potential further complexity in development of these hydrogels as cellular vehicles because the stiffness of hydrogels can significantly influence the behaviour of stem cells entrapped within them—both with respect to their ability to migrate within the hydrogel (Ehrbar et al. 2011) and their potential direction of differentiation (Pek et al. 2010).

As a stand-alone cardiac therapy, alginate has been the most intensively investigated. Alginate, an anionic polysaccharide derived from brown seaweed is biocompatible and widely used in the pharmaceutical and medical device industries. A low viscosity version of alginate has been developed that is injectable and polymerises spontaneously within the heart due to increasing calcium ion concentration in the infarct. Landa et al. (2008) investigated the effects of alginate delivery via epicardial injection into rat hearts 7 and 60 days after infarct induction. The alginate was gradually replaced by connective tissue over 6 weeks demonstrating biodegradability. It should be noted that though a non-degradable implant might be considered desirable as stress reduction might also be maintained, we and others have shown this to not be the case even when using very biocompatible polyethylene glycol (PEG) hydrogels (Dobner et al. 2009; Rane et al. 2011). Eight weeks after injection of alginate, infarct scar thickness was increased and left ventricle dilation reduced for injections at both time points though these improvements were diminished in the group receiving injections into the chronic infarct. The latter result emphasising the greater difficulty treating infarcted hearts at that late stage. Of interest, the positive outcomes in the 7 day injection group were at least comparable to a group that received 1×10^6 neonatal cardiomyocytes in saline. In a follow up large animal study, the alginate solution was delivered to infarcted porcine hearts at 4 days post-infarction and again reductions in ventricular dilation and increased scar thickness were observed (Leor et al. 2009). Interestingly, intracoronary delivery was realized through catheter injection within the left anterior descending artery and ingress into the infarcted tissue was achieved through the leaky vessels present in the infarct. Occlusion of the coronary was avoided, as calcium levels were only high enough within the tissue to achieve phase inversion to a hydrogel. This relatively simple minimally invasive approach is certainly appealing for clinical application of alginate as a stand-alone therapy but with respect to use as a route for enhancing cellular engraftment it may be less effective. The probable inefficient migration of cells from the vasculature into the myocardium that blights intracoronary delivery is likely not to be improved by delivery with a hydrogel.

These promising pre-clinical results with alginate resulted in an initial feasibility and safety trial in humans (ClinicalTrials.gov Identifier NCT00557531) whereby 2 mL of the alginate solution (termed IK-5001) was delivered via the infarcted coro-

nary to 27 patients that had undergone a moderate to large myocardial infarction 7 days prior. The patients had been successfully revascularised. The treatment was well tolerated and preservation of LV indices was observed (Frey et al. 2014). This positive outcome has resulted in the enrolment of 300 patients with acute myocardial infarction into an ongoing multicentre, randomized and double-blind phase 2 clinical trial (ClinicalTrials.gov Identifier NCT01226563). In a related human study, an alternative form of alginate was delivered by epicardial intramyocardial injection in 10–15 sites in 11 dilated cardiomyopathy patients that were undergoing coronary artery bypass grafting (CABG) (ClinicalTrials.gov Identifier NCT00847964). In a small subset that could undergo MRI, it was determined by mathematical modelling that myofibre stress was reduced by 35 % (Lee et al. 2013). So though this outcome derives from only three patients and is complicated by the simultaneous CABG procedure, it is the first indication that hydrogel based stress reduction is achievable in humans.

The progression of these types of therapies to the clinic will be facilitated by their ability to be delivered by catheterization. This is a demanding goal as the polymer solutions need to have low enough viscosity to flow through the catheter and remain ungelled till reaching their target site upon which gelation must occur as rapidly as possible. Apart from alginate (see above), there are very few reports describing catheter delivery of a hydrogel to the heart. Recently though a hydrogel solution derived from ventricular extracellular matrix was successful injected endocardially into porcine hearts (Singelyn et al. 2012) using a NOGA® guided Myostar® catheter. In follow up study, the catheter delivered extracellular matrix hydrogel was shown to improve cardiac function in a porcine myocardial infarct model (Seif-Naraghi et al. 2013). More recently a pH-switchable hydrogel (ureido-pyrimidinone-modified PEG hydrogel) was used to deliver growth factors to infarcted porcine hearts (Bastings et al. 2014). Though probably not useful for cellular delivery due to the switch occurring as the solution at pH 8.5 transits to neutral in the heart, the type of rapid and controllable gelling achieved will be desirable for cellular vehicles.

These types of outcomes with biomaterial delivery alone have resulted in significant recent interest in determining the influence of co-delivery of injectable hydrogels with stem cells on both stem cell retention and efficacy.

10.5.2 Biomaterial-Cell Delivery

Biological Materials

Biological materials are inherently attractive as cellular vehicles as they usually have a good level of biocompatibility. They are also readily available but have batch-to-batch variability that can be eliminated in synthetic hydrogels.

Fibrin, a well characterised hydrogel that is derived from the mixing of a solution of fibrinogen with one containing thrombin, factor XIIIa and calcium, was one of the earliest materials used to deliver cells to the heart (Table 10.2). In the initial

Table 10.2 Cell delivery within biomaterials for cardiac repair

BMMSC	Rat	Collagen	1 week	23 % (cells), 16 % (collagen and cells)	No function improvement (collagen and cells)	Dai et al. (2009)
BMMNC	Rat	Hyaluronic acid	4 weeks	2.5-fold increase (cells and biomaterial)	EF: significant improvement with cell and biomaterial combination	Chen et al. (2013)
CDC	Murine	Hyaluronic acid/gelatin	24 h	35 % (cells and biomaterial)	Improved cardiac function (LVEF) $p<0.05$—cells and biomaterial	Cheng et al. (2012)
			21 days	6 % (cells and biomaterial)		
AdMSC	Rat	Chitosan	4 weeks	3.05 % (Cells and biomaterial)	LVEF: 59.29 % (cells and biomaterial), 52.92 %, (biomaterial), 49. 53 % (cells)	Liu et al. (2012b)
BMMSC	Porcine	Alginate	4 weeks	≈12 % (cells and biomaterial)	ND	Panda et al. (2014)
BMMSC	Rabbit	α-cyclodextrin/ MPEG-PCL-MPEG	4 weeks	2.5-fold increase in engraftment (cells and biomaterial)	LVEF: 62.35 % (cells and biomaterial), 47.14 % (cells), 35.14 % (saline)	Wang et al. (2009)
ESC	Rat	Oligo[poly(ethylene glycol) fumarate]	1 day	1 day: 6.54 % (cells), 16.35 % (cells and biomaterial) 4 weeks: 4.56 % (cells), 11.83 % (cells and biomaterial)	FS: cells and biomaterial significantly ($p<0.01$) improved LV function compared to cells and biomaterial alone	Wang et al. (2012)
			4 weeks			
AdMSC	Rat	PNIPAAm	4 weeks	1.5-fold increase in engraftment (cells and biomaterial)	EF and FS: Significant improvement for cells and biomaterial combined compared to controls	Li et al. (2014)
BMMSC	Rat	Self-assembling peptides	4 weeks	Twofold increase in engraftment (cells and biomaterial)	EF: 59.31 % (cells and biomaterial), 48.31 % (cells), 42.06 % (saline)	Cui et al. (2010)
BMMSC	Rat	Self-assembling peptides	4 weeks	Fourfold increase in engraftment (cells and biomaterial)	EF: 53.06 % (cells and biomaterial), 31.23 % (biomaterial), 35.21 % (cells)	Guo et al. (2010)
BMMSC	Porcine	Self-assembling peptides	2 months	Fourfold increase in engraftment at 7 days (cells and biomaterial)	EF of cells delivered at day 1 post MI: 55.1 % (cells and biomaterial), 46.5 % (biomaterial), 46.3 % (cells)	Chang et al. (2015)
BMMSC	Porcine	Self-assembling peptides	4 weeks	Eightfold increase in engraftment at 7 days (cells and biomaterial)	Cells and biomaterial improved both diastolic and systolic function	Lin et al. (2010)

SkMC Skeletal myoblasts, *CDC* Cardiosphere-derived cells, *ESC* Embryonic stem cells, *ND* Not done

studies, skeletal myoblasts were delivered with fibrin to infarcted rat hearts. The combination and controls were injected 1 week post-infarction and hearts were assessed by echocardiography and histology 4 weeks later (Christman et al. 2004a, b). As assessed by skeletal myosin immunohistochemistry, engraftment was similar for the cell and cell plus fibrin groups at 24 h but by 4 weeks post-injection a twofold increased engraftment of skeletal myoblasts was seen in cells plus fibrin. Similar functional improvements were seen for fibrin, cells and cells plus fibrin and all 3 groups were seen to elicit an angiogenic response. Thus in this instance the simpler route of only delivering the material without the skeletal myoblasts would appear optimal. In another fibrin based study, 99mTc-labelled BMDC were quantified 24 h after injection into infarcted rat hearts through counting the radioactivity in the excised organ in a gamma counter (Nakamuta et al. 2009). In this study, using a more global means of engraftment assessment, a 2.5-fold increase in cell retention was seen for the fibrin plus cells group. Again at 4 weeks post-infarction for both the cell alone and cell plus fibrin groups similar functional improvements were observed though with a trend towards greater scar thickness in the latter. In a BLI based analysis of retention of luciferase expressing AdMSC with or without fibrin injected into infarcted rat hearts, an increasing divergence between cells alone and cells with fibrin was quantified (1 day: 1.3 ×; 7 days: 3 ×, 14 days: 5 ×) till finally at day 28, a signal could readily be detected for fibrin plus cells but none for cells alone (Yang et al. 2013). It should be noted that though there was greater engraftment for fibrin plus cells, there was still a rapid decrease in signal with only about 2 % of the original 5 million AdMSC present in the heart. Finally with respect to fibrin, in a follow up to the study of Nakamuta et al. (2009), the functional recovery after AdMSC delivery to infarcted hearts was assessed in much greater detail (Danoviz et al. 2010). Stroke work measured in the presence of phenylephrine, a global index of cardiac function that depends on both pressure generation and ejection capability was seen to be improved by all cell containing groups but only returned to normality when hearts were injected with a biomaterial plus cells. There was a positive correlation between greater cellular engraftment ((AdMSC/media: 4.8 %; AdMSC/fibrin: 13.8 %; AdMSC/collagen 26.8 %) measured by 99 m-Tc labeling) and stroke work improvement.

In another study in a rat infarction model, collagen was used as a cellular vehicle for BMMSC labeled with europium nanoparticles (Dai et al. 2009). Engraftment was measured at 4 weeks post-infarction and no increase in engraftment was observed for the collagen plus cell group relative to cells delivered in saline unlike that observed in the study of Danoviz et al. (2010) at 24 h. However there was reduced traffic of cells to remote organs in the collagen plus cells group. Somewhat unexpectedly, and again in contrast to the Danoviz et al. (2010) study, the cells and collagen alone groups showed functional improvement relative to the control but the combined group failed to improve function. The reason for this difference is not clear though it is notable that the cells were delivered 24 h and 1 week post-infarction in the Danoviz et al. (2010) and Dai et al. (2009) studies respectively. We have observed markedly different distributions of polymers injected at either 1 week or shortly after infarction (Kadner et al. 2012). Biopolymers injected at 1 week assume a bulky monodisperse

structure whilst those closer to point of infarction have a more delicate fibrillar structure and thus less isolated in distance from the surrounding tissue. Therefore diffusion of oxygen and nutrients to the cells might have been more effectively impeded when injected at 1 week within a long lasting biopolymer implant (Dai et al. 2009). Of course, other differences exist between these studies such as collagen source and cell type utilized that may have played a role in the different outcomes.

Hyaluronic acid is a nonsulfated glycosaminoglycan and component of the extracellular matrix that has been used to deliver BMMNC to infarcted rat hearts immediately post-infarction (Chen et al. 2013). Four weeks after delivery 2.5-fold higher levels of DiI labeled BMMNC were found in hearts where hyaluronic acid and cells were injected together than when BMMNC were delivered alone. Both single treatments reduced apoptosis and scar length and increased the ejection fraction (EF), angiogenesis and arteriogenesis but in all instances a further significant increase was observed for the combination. Very similar findings were reported for human cardiosphere-derived cells injected into the infarcted hearts of SCID mice when a hyaluronic acid/gelatin hybrid hydrogel was used as a delivery vehicle (Cheng et al. 2012). Even greater increases in retention were seen for this combination, with approximately 6–7 fold increases at 24 h and 21 days relative to cells alone. When a hyaluronic acid hydrogel without gelatin was used, no increase was observed at 24 h but the hyaluronic acid alone group was not utilized for the longer-term studies making it difficult to compare these two studies directly. Because overall engraftment in the biopolymer group reduced from 35 % at 24 h to 6 % at 21 days, the authors postulated that the improvements observed for apoptosis, angiogenesis, EF and viable tissue within the infarct were due to the paracrine effect though evidence of differentiation towards cardiomyocytes was observed.

In contrast to the above biological materials that are inherent to the mammalian extracellular matrix, others have investigated the utility of polysaccharides derived from sources such as crustacean shells and seaweed. In a series of studies, the ability of chitosan to improve cellular retention and therapeutic efficacy was assessed. A temperature responsive chitosan derivative (Chenite et al. 2000) that gels rapidly and spontaneously when the environmental temperature is increased was found to increase both retention and efficacy of embryonic stem cells (ESC) (Lu et al. 2009), ESC obtained from somatic cell nuclear transfer (Lu et al. 2010) and most recently AdMSC (Liu et al. 2012b) after injection into infarcted rat hearts. Similar results were found for all cell types but the retention of AdMSC was assessed globally by BLI after lentiviral transduction of the luciferase gene in contrast to histological evaluation used in the earlier studies. Relative to the PBS/AdMSC control group, retention of AdMSC in the chitosan group increased from 1.5-fold at day 1 to approximately eightfold at day 28 though even for this group overall cellular retention decreased to around 10 % of cellular retention detected at day 1. This improved retention was associated with functional recoveries in parameters such as EF and +dp/dt, decrease in apoptosis and increased wall thickness and neovascularization. Of note, evidence that chitosan scavenged reactive oxygen species was given as a possible contributing source for the positive outcome. Alginate, another polysaccharide, has been used as a vehicle for epicardial injection of BMMSC into the

border zones of reperfused pig hearts 4 weeks after infarction induction (Panda et al. 2014). The alginate was covalently modified with the cellular adhesion peptide RGD, presumably to overcome the poor cellular adhesion observed for alginate. Interestingly, chitosan has similarly poor cellular adhesion (Luna et al. 2011) but no modifications were utilized in the studies detailed above. Possibly targeting cellular adhesion may further improve the engraftment of stem cells injected in conjunction with chitosan. Alginate RGD was shown to improve the retention of cells 2 weeks post delivery by fourfold but only when 2 % w/v solution was used and not with a 1 % w/v formulation. The effect of improved engraftment on function was not determined.

Thus, marked improvements in retention and therapeutic outcome have been reported when cells are delivered in conjunction with biological hydrogels. However, as indicated above concerns exist with respect to the batch-to-batch variability of these materials and therefore others have investigated synthetic hydrogels that allow for a more clinically acceptable standardisation of the cellular vehicle.

Synthetic Materials

Taking advantage of the rapid gelling of triblock polymer hydrogel (α-cyclodextrin/poly(ethylene glycol)–b-polycaprolactone-(dodecanedioic acid)-polycaprolactone–poly(ethylene glycol)), BMMSC were injected 7 days post infarction in a rabbit model (Wang et al. 2009). Histological evaluation of DAPI labeled cells showed a 2.5-fold increase in engraftment 4 weeks after delivery. This resulted in an elevated EF, decreased infarct size and increased neovascularization relative to the cells alone control. In a preceding study, the hydrogel was found to improve EF and reduce infarct size but did not influence vessel density suggesting that the latter effect resulted from the engrafted cells (Jiang et al. 2009). Another polyethylene glycol composite (oligo[poly(ethylene glycol) fumarate]) that polymerized in the presence of ammonium persulfate and tetramethylethylenediamine was used to deliver GFP labeled mouse ESC 1 week after rat hearts were infarcted (Wang et al. 2012). Co-delivery with the hydrogel resulted in a 2.5-fold increase in cellular retention and the hydrogel/cell combination augmented cardiac function, decreased infarct size and increased capillary density to a greater extent than that observed for single treatment controls. Interestingly, no teratoma formation was observed in this study.

Recently, brown fat AdMSC were injected with thermoresponsive poly (N-isopropylacrylamide) (PNIPAAm) hydrogels into rat hearts immediately after infarction (Li et al. 2014). The hydrogels were loaded with single-wall carbon nanotubes (SWCNT) to elicit improved cellular adhesion, spreading and proliferation within the PNIPAAm environment. Though enhancement of these parameters was observed in vitro, only a relatively modest increase in retention of about 1.5-fold for the combination of hydrogel and cells was seen at 4 weeks. However, significant improvements in cardiac function were observed for the PNIPAAm/AdMSC group, as too was decreased infarct size and increased wall thickness.

Injectable scaffolds can be formed from self-assembling peptides (SAP) and the sequence RARADADARARADADA-CNH2 (RAD16-II) has received particular attention as a cellular delivery vehicle. BMMSC that had been selected for positive expression of c-kit and the cardiac transcription factor NKx2.5 were delivered with RAD16-II 30 min after infarction induction in female rats (Cui et al. 2010). Cellular retention was determined by fluorescence in situ hybridization for the Y-chromosome of the injected male cells. A twofold increase in retention was observed at 4 weeks post-injection for cells plus nanofibers and again this increased retention was associated with further significant improvements to that gained with delivery of cells alone. Decreased infarct size, increased neovascularization and improved EF% resulted from the combined injection group. In a follow-up study (Guo et al. 2010), the SAP was synthesized with incorporation of the potent cell adhesion peptide RGDSP. This modification further increased the twofold retention seen with the unmodified RAD16-II to fourfold and further advances in infarct size, neovascularization and function were achieved.

Importantly the RAD16-II nanofiber scaffolds have been used to deliver cells in the porcine model. In sequential studies the utility of these scaffolds to influence the therapeutic outcome of freshly isolated BMMNC was assessed (Chang et al. 2015; Lin et al. 2010). In the initial investigation, DiI labeled BMMNC with RAD16-II were injected epicardially, immediately after infarction, into the infarct zone of mini-pig hearts (Lin et al. 2010). Scar length ratio% was decreased and scar thickness ratio% increased by all groups but the latter parameter was significantly increased by the combination relative to the other groups. Interestingly, injection of RAD16-II alone was found to predominately improve diastolic function and BMMNC alone mainly enhanced systolic function. Combining the two treatments resulted in an increase in both systolic and diastolic function. This therapeutic outcome was associated with an approximately eightfold increase in labeled cells detected histologically 4 weeks after infarction. Subsequently, the effect of timing of both delivery and isolation of BMMNC was assessed in the mini-pig model (Chang et al. 2015). Autologous BMMNC were isolated 1, 4 and 7 days after infarction and injected on the same day. Only cells isolated on day 1 had similar results to those observed in the immediate delivery study (see above) with cells at 4 days showing lesser therapeutic impact. BMMNC obtained 7 days post-infarction did not result in any improvement for the parameters measured. The proportion of CD14/CD16 positive cells in the BMMNC isolates decreased with time and it was suggested that this decrease in a potentially more cardioprotective sub-population might have contributed to the reduced efficacy. This result further amplifies the general requirement for much greater clarity with respect to these types of finer details in the cell therapy.

Growth Factor Delivery Systems

It is naturally appealing to look to combine the delivery of stem cells with a biomaterial that releases growth factors. The controlled release of growth factors can not only be inherently cardioprotective but also cytoprotective towards the delivered cell

population. Protection for therapeutic cells and surviving cardiac cells can be achieved directly through mechanisms such as apoptosis reduction or indirectly through neovascularisation stimulation for example. Control of growth factor release can result from simple entrapment within the biomaterial or through more sophisticated approaches that exploit ionic or covalent attachment to regions of the scaffold.

A matrix metalloproteinase-sensitive PEG hydrogel was used to deliver the pro-angiogenic and pro-survival thymosin β4 in conjunction with hESC-derived vascular cells immediately after infarct induction in nude rats (Kraehenbuehl et al. 2011) (Table 10.3). Cell retention was not assessed but the combined treatment was determined by MRI to more effectively preserve EF and reduce diastolic dilation than the single treatments. Additionally greater neovascularisation was observed with evidence that at least a portion of the new vessels were derived from the delivered vascular cells.

BMMNC were delivered to fresh infarcts in mice using a PEGylated fibrin gel that had covalently incorporated HGF, a growth factor with multiple protective actions (Zhang et al. 2008). Histological analysis showed a 15-fold increase in engraftment at 4 weeks for the combination group relative to the 0.1 % seen in the cell alone group. EF was only significantly increased at 4 weeks and apoptosis reduced both remote to and within the infarct by the combination. PEGylated fibrin hydrogels were also utilised to inject engineered iPS into infarcted SCID mouse hearts (Bearzi et al. 2014). Here growth factors were not specifically released from the biomaterial but rather from the encapsulated cells that had been engineered to express MMP-9 and PLGF. The latter was introduced for its pro-angiogenic effect and the former to take advantage of its potential to break down the scar. Cell retention was not quantified but only when both proteins were secreted together was increases in vascularisation and decreases in fibrosis observed. All single treatments and the combined group equally increased fractional shortening (FS) above that of control but only the latter restored the velocity of blood flow in the left ventricular outflow to almost physiological levels.

The SAP RAD16-II nanofiber system has also been used to supply factors and cells together to infarcted hearts. In an early study, the cytoprotective IGF-1 was biotinylated and bound into biotinylated RAD16-II scaffold via a streptavidin sandwich (Davis et al. 2006). Binding IGF was found to moderately decrease apoptosis and increase engraftment of GFP-labelled neonatal cardiomyocytes 14 days after injection into rat hearts relative to untethered IGF or SAP alone. Only the tethered IGF was seen to improve FS 21 days after injection into infarcted rat hearts. The same system was used for introduction of CPC to infarcted rat hearts (Padin-Iruegas et al. 2009). Again the combination of IGF-1 and CPC was found to better preserve cardiac function and also increase vascularisation and reduce infarct size. The RAD16-II peptide was recently functionalised to incorporate a peptide mimic of the Notch1 ligand Jagged1 (Boopathy et al. 2014). Notch1 signaling is known to have a critical role in cardiac development and survival and differentiation of CPC. The modified SAP was injected with CPC during reperfusion in a rat model of ischemia/reperfusion. Importantly, global retention of CPC labelled with the fluorescent membrane label DiR was analysed in an in vivo

Table 10.3 Cell delivery within biomaterials containing growth factors for cardiac repair

Cell type	Model	Biomaterial	Factor	Duration	Retention	Efficacy	Reference
hESCDVC	Rat	MMP-sensitive PEG	Thymosin β4	6 weeks	ND	EF: Significant improvement for cells, growth factor and biomaterial combined compared to controls	Kraehenbuehl et al. (2011)
BMMNC	Murine	PEGylated fibrin gel	HGF	4 weeks	15-fold increase in engraftment (cells, growth factor and biomaterial)	EF: Significant improvement for cells, growth factor and biomaterial combined compared to controls	Zhang et al. (2008)
iPSC	Murine	PEG-fibrinogen scaffold	PIGF	30 days	ND	FS: 32.3 % (cells, growth factor and biomaterial), 25.1 % (Growth factor and biomaterial), 30.3 % (Cells)	Bearzi et al. (2014)
CMC	Rat	Self-assembling peptides	IGF-1	21 days	Growth factor improved cell retention by 25 %	FS: 45 % (cells, growth factor and biomaterial), 36 % (cells and biomaterial)	Davis et al. (2006)
CPC	Rat	Self-assembling peptides	IGF-1	4 weeks	2.4-fold increase in cell replication (cells, growth factor and biomaterial)	EF: Significant improvement for cells, growth factor and biomaterial combined compared to controls	Padin-Iruegas et al. (2009)
CPC	Rat	Self-assembling peptides	Notch1 ligand Jagged1 peptide	21 days	≈20 % (cells, peptide and biomaterial)	EF: Significant improvement for cells, peptide and biomaterial combined compared to controls	Boopathy et al. (2014)

hESCDVC human embryonic stem cell-derived vascular cells, *iPSC* induced pluripotent stem cells, *CMC* cardiac myocytes, *CPC* cardiac progenitor cells

imaging system. Retention in the peptide mimic group relative to scaffolds either containing a scrambled version of the mimic or only RAD16-II was significantly elevated at above 80 % for the first 7 days but then fell to the 20 % levels observed in the others. Improved cardiac function as determined by haemodynamic parameters such as EF, stroke work and cardiac output was only observed in the peptide mimic/cell group. Similarly infarct size and vascularization were seen be reduced and increased respectively. In vitro studies suggested a paracrine effect as immobilized Jagged-1 mimic was shown to increase PDGF-BB and SCF expression by the CPC.

Survival and engraftment of delivered cells may well need utilization of a range of growth factors and this approach was explored in a study by Laflamme et al. (2007). In initial investigations, factors that influence a number of pathways such as anoikis, inflammation and ischemia were delivered in conjunction with hESC-derived cardiomyocytes to the hearts of athymic rats 4 days after they had undergone ischaemia-reperfusion. None of the treatments increased retention 1 week later as determined by in situ hybridization with a human-specific pan-centromeric genomic probe. This led to the development of a prosurvival cocktail that included Matrigel and a variety of other factors that simultaneously targeted several key points in cell death pathways. The cocktail resulted in a fourfold increase in engraftment relative to Matrigel and cells alone and this enhanced engraftment was associated with increased EF and wall thickness.

It is apparent from above that a variety of biomaterial formulations have enhanced both the engraftment of cells and their therapeutic efficacy. However, there are several aspects that now require optimisation after this initial period of investigation. In the majority of studies thus far where biomaterials have been used as cellular vehicles, engraftment has been assessed by histological based procedures. It would seem necessary to confirm these findings with the more quantitative global assays, ideally utilising in vivo imaging of cells stably expressing relevant reporter genes. Also at this point, very few large animal model studies have been performed but it might be expected that with the positive outcomes reported in small animals that this situation will now start to change. Finally, it may be prudent that direct comparative studies between the various optimal candidates are done before proceeding to the clinic. This may help avoid further disappointments in a field that is already somewhat beleaguered by setbacks.

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