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Drug and cell delivery for cardiac regeneration☆

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ABSTRACT

The spectrum of ischaemic cardiomyopathy, encompassing acute myocardial infarction to congestive heart failure is a significant clinical issue in the modern era. This group of diseases is an enormous source of morbidity and mortality and underlies significant healthcare costs worldwide. Cardiac regenerative therapy, whereby pro-regenerative cells, drugs or growth factors are administered to damaged and ischaemic myocardium has demonstrated significant potential, especially preclinically. While some of these strategies have demonstrated a measure of success in clinical trials, tangible clinical translation has been slow. To date, the majority of clinical studies and a significant number of preclinical studies have utilised relatively simple delivery methods for regenerative therapeutics, such as simple systemic administration or local injection in saline carrier vehicles. Here, we review cardiac regenerative strategies with a particular focus on advanced delivery concepts as a potential means to enhance treatment efficacy and tolerability and ultimately, clinical translation. These include (i) delivery of therapeutic agents in biomaterial carriers, (ii) nanoparticulate encapsulation, (iii) multimodal therapeutic strategies and (iv) localised, minimally invasive delivery *via* percutaneous transcatheter systems.

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Abbreviations: MI, myocardial infarction; CHF, congestive heart failure; CSCs, cardiac stem cells; BMMNCs, bone marrow derived mononuclear cells; MSCs, human mesenchymal stem cells; VEGF, vascular endothelial growth factor; GCSF, granulocyte colony stimulating factor; ADSCs, adipose derived stem cells; HGF, hepatocyte growth factor; β-GP, β-glycerophosphate; HEC, hydroxy-ethyl cellulose; PEG, poly(ethylene glycol); PCL, polycaprolactone; ECM, extracellular matrix; RGD, Arg-Gly-Asp; PG, poly(e-caprolactone)/gelatin; LVEDVI, left ventricular end diastolic volume index; LVR, left ventricular restraint; BCM, bioabsorbable cardiac matrix; PGE2, prostaglandin E2; PGI2, prostaglandin I2; PLGA, polylactic-co-glycolic acid; PP, pyrvinium pamoate; NADH, nicotinamide adenine dinucleotide; DPP-IV, dipeptidylpeptidase IV; miR, microRNA; modRNA, modified RNA; LVEF, left ventricular ejection fraction; PEI, polyethylenimine; APOSEC, apoptotic peripheral blood cells; SDF-1, stromal cell derived factor-1; NRG-1, neuregulin-1; IGF-1, insulin-like growth factor-1; FGF-1, fibroblast growth factor-1; Shh, Sonic hedgehog morphogen; Ang-1, angiopoietin-1; CPC, cardiac progenitor cell; CDC, cardiosphere derived cell; VRD, ventricular restraint device; PTCA, percutaneous transluminal coronary angioplasty.

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1. Introduction

This review encompasses drug and cell delivery for cardiac regeneration. This treatment can be cardioprotective; to protect heart muscle tissue after an acute myocardial infarction (MI), or cardiorestorative; to regenerate tissue in patients with chronic ischaemic heart failure. Acute myocardial infarction occurs upon occlusion of one of the coronary vessels, most commonly due to atherosclerotic plaque, resulting in an ischaemic region of myocardium which, even if reperfused, can produce lasting tissue damage with associated symptoms. Initially, MI produces an inflammatory response and extensive ischaemic death of cardiomyocytes within the affected area, resulting in a partial loss of ventricular function. Over time, especially if the affected area is expansive and transmural, complex alterations occur in the myocardium, a phenomenon known as ventricular remodelling [1]. These adaptations are an attempt to compensate for ventricular malfunction. However, the heart possesses only a limited regenerative capacity. Remodelling encompasses the creation of collagenous, non-contractile scar tissue, thinning of the myocardial wall and progressive enlargement and dilation of the ventricle. This ultimately contributes to a decrease in ventricular contractile function and output. This can progress to congestive heart failure (CHF), where the heart is unable to pump enough blood to meet the metabolic demands of the body [2–4].

MI represents an enormous source of morbidity and mortality on a global scale. Coronary artery diseases such as MI and CHF are the main cause of death in developed countries, and pose a substantial healthcare burden [3]. According to the European Society of Cardiology one in six men and one in seven women in Europe will die from myocardial infarction [5]. The American Heart Association reports that 635,000 Americans have a new myocardial infarction each year and that the number of deaths attributable to heart failure in the US in 2009 was 275,000 [6]. Current therapies for the treatment of MI and CHF include pharmacological intervention, surgical procedures such as ventricular resection, coronary artery bypass or mechanical aids such as left ventricular assist devices. Such approaches serve to restore function or limit disease progression to some degree, but are not always effective long-term [7]. Reperfusion of the culprit artery (with coronary angioplasty and/or stent placement) can have a profound effect on limiting infarct

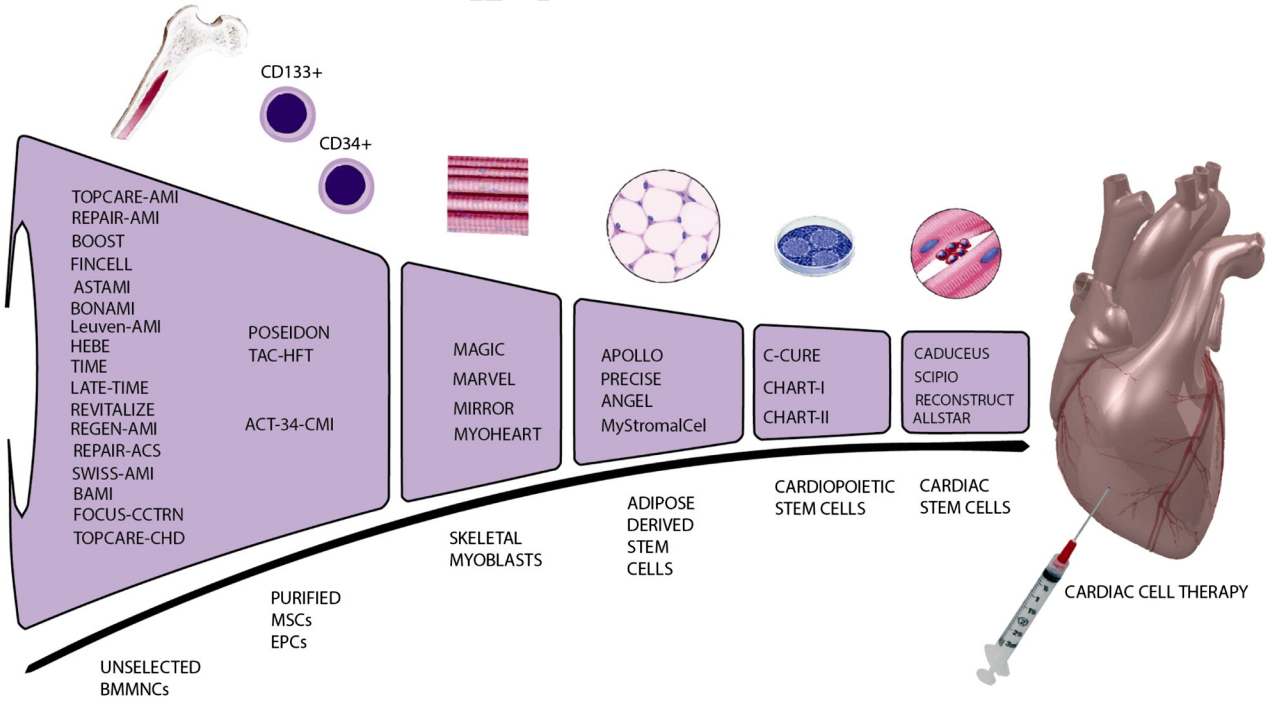

Fig. 1. Clinical trials in cell therapy: This figure shows the range and progression of cardiac cell therapy trials, with cell type underneath (graphically represented above) and depicts the trend of moving from unselected cell populations and different cell types towards cardiopoietic and cardiac stem cells.

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size and increasing patient survival [8]. This technique can also limit ventricular remodelling with the objective of improving ventricular function and clinical outcomes. However, myocardial necrosis begins rapidly following coronary occlusion, usually before reperfusion can be accomplished [9]. Post-infarction remodelling and the progression to heart failure therefore remain a challenge in the treatment of cardiovascular disease. The most effective treatment for end-stage CHF is heart transplantation, which is limited by the availability of heart donors and also requires a highly invasive and complex surgical procedure [2,7].

This review covers cell and drug delivery, and additional cell-free approaches that share a common goal of enabling cardiac regeneration, and attenuation or prevention of negative compensatory remodelling (limiting infarct size, reducing or preventing infarct expansion and reducing ventricular wall stress). These approaches have shown promise in addressing shortcomings in conventional cardioprotective and cardiorestorative treatments for MI and CHF, respectively. However, clinical translation of regenerative therapeutics has been slow to date. Here, we suggest a perspective on how advanced delivery strategies could be synergistically engaged in the facilitation of cardiac regeneration, for enhanced efficacy and treatment tolerability, with greater potential for clinical translation.

2. Cell therapy

2.1. Introduction to cardiac cell therapy

Multiple trials have been initiated addressing the transplantation of stem cell populations for cardiac regeneration. An appropriate regenerative cell population selection is critical for effective therapy. Extensive preclinical and clinical trials have investigated a number of cell types for cardiac regeneration including skeletal myoblasts, mesenchymal stem cells (bone marrow derived and adipose derived), embryonic stem cells, and cardiac stem cells. Although most cell types have produced promising results *in vitro* and in preclinical studies [10–21], and have been shown to be safe in clinical trials, cardiac stem cells, or cardiopoietic stem cells have shown the most promise in terms of efficacy. Thus, the trend is towards delivery of cells derived from the heart, or lineage-specified for optimal therapy for the diseased tissue. The trials are summarised in Fig. 1, and trials for each cell-type are described in the following sections.

2.1.1. Bone marrow derived stem cells — heterogeneous populations (BMMNCs)

Bone marrow aspirate or lineage-unselected bone marrow derived mononuclear cells (BMMNCs) have been used for a significant number of preliminary clinical studies. These studies have consistently demonstrated the safety and feasibility of BMMNC administration, encouraging further investigation, but clinical benefits to date have not been convincing. Orlic et al. demonstrated that intramyocardial injection of BMMNCs improved cardiac contractility and resulted in the formation of new cardiac tissue in a mouse model of MI [10,11]. Kudo et al. reported that BMMNCs could reduce infarct size and fibrosis, and differentiate into cardiomyocytes and endothelial cells [12]. However more recent research showed that these cells likely do not differentiate into cardiomyocytes [22]. Clinical trials such as TOPCARE-AMI [23], REPAIR-AMI [24], BOOST [8,25] and FINCELL [26] have shown increases in left ventricular ejection fraction (LVEF) in cell treated patients compared to controls at time points up to 18 months. Long-term (5-year) benefits were demonstrated in the TOPCARE-AMI trial [27] but not in the BOOST trial [28]. In contrast, the ASTAMI [29], BONAMI [30], Leuven-AMI [31], and HEBE [32] trials showed no significant increase in left ventricular ejection fraction over the control group. A Phase I trial (NCT00114452) [33] with prochymal allogeneic stem cells (Osiris Therapeutics Inc.) showed an increase in LVEF at 6 months after allogeneic BMMNC transplantation, but no improvement in patient physical performance, as measured by the six minute walk test, highlighting the need for a consensus on standardized accepted metrics for cardiac cell therapy efficacy. Trials carried out by the Cardiovascular Cell Therapy Research Network (CCTRN) indicated no clinical benefit of BMMNCs in acute myocardial infarction (AMI), where they looked at timing of post-AMI intracoronary administration in the TIME [34] and LateTIME [35] trials. Numerous multicentre studies are ongoing to investigate autologous bone marrow cell therapy including REVITALIZE (NCT00874354), REGEN-AMI (NCT00765453), REPAIR-ACS (NCT00711542), SWISS-AMI (NCT00355186) and BAMI (NCT01569178). Similarly, no clinical benefit was noted in a trial investigating transendocardial delivery of BMMNCs for heart failure (FOCUS-CCTRN) [36], although TOPCARE-CHD [37] showed a 2.9% increase in LVEF over base-line at 3 months. The overall negative results of these trials have encouraged exploration of other cell types or "next-generation" cell therapy, where cells are subjected to screening assays to predict regenerative potential before cell transplantation [38], or cells are modified or delivered concomitantly with drugs, as will be discussed in subsequent sections. The prevailing concept of BMMNC efficiency is explained by the paracrine hypothesis, where soluble factors (chemokines, growth factors, *etc.*) are secreted by transplanted cells, especially in hypoxic environments, and encourage cardiac repair [39]. This hypothesis has been supported experimentally through demonstration that conditioned media can somewhat replicate the effects of stem cell therapy [40]. Potential mechanisms include increasing angiogenesis, protecting endogenous cells, attuning the inflammatory processes and encouraging cell-cycle re-entry [41].

2.1.2. Purified stem cell populations: MSCs and EPCs

More recently, bone marrow aspirate has been purified by phenotypic features into two multipotent cell populations; human mesenchymal stem cells (hMSCs) and endothelial progenitor cells (EPCs). Purified sub-populations were demonstrated to show higher engraftment, and can induce endogenous cardiomyogenesis [42]. BMMNCs have been delivered *via* intracoronary injections for the treatment of acute MI, but these purified subpopulations can be used for the treatment of chronic ischaemia and refractory angina. Clinical trials have been initiated for both subpopulations. The POSEIDON trial compared autologous and allogeneic hMSC transplantation in patients with ischaemic cardiomyopathy at different doses, and showed that allogeneic cells did not elicit donor-specific immune reactions, and that both groups favourably affect patient functional capacity and ventricular remodelling, although they did not increase ejection fraction [43]. The TAC-HFT trial compared BMMNCs and hMSCs for heart failure, and reported that both were safe, with a trend towards reverse remodelling and regional contractility. Adipose tissue is also being used as a source for hMSCs. When adipose stem cells and bone marrow stem cells were compared in a porcine MI model, they both showed similar improvements in cardiac function and increased capillaries in the infarct [44]. In a study by Zhang et al. [21], adipose derived stem cells (ADSCs) transplanted into the myocardial scar tissue formed cardiac-like structures, induced angiogenesis and improved cardiac function. The APOLLO trial (NCT00442806) investigated transplanting fresh adipose derived MSCs to ST-elevated MI patients, and showed positive trends towards cardiac function, perfusion and neovasculogenesis (generally attributed to EPCs) [45]. The PRECISE trial (NCT00426868) looked at delivering adipose derived MSCs to patients with retractable angina, and noted no improvement in ejection fraction, but an increase in patient symptoms and exercise tolerance [46]. ANGEL is a Phase I trial that has completed enrolment for BioHearts Adipocell® therapy. Two Phase II studies have been initiated for adipose derived stem cells using intramyocardial injection; ATHENA (NCT01556022) for chronic myocardial ischaemia and MyStromal Cell (NCT01449032) [47] for chronic ischaemic heart disease and refractory angina where cells are pre-stimulated with vascular endothelial growth factor (VEGF). With regard to EPCs, early clinical studies have pointed to symptomatic benefits in patients with angina and cardiomyopathy [48–52]. In the ACT-34-CMI trial [49] investigators

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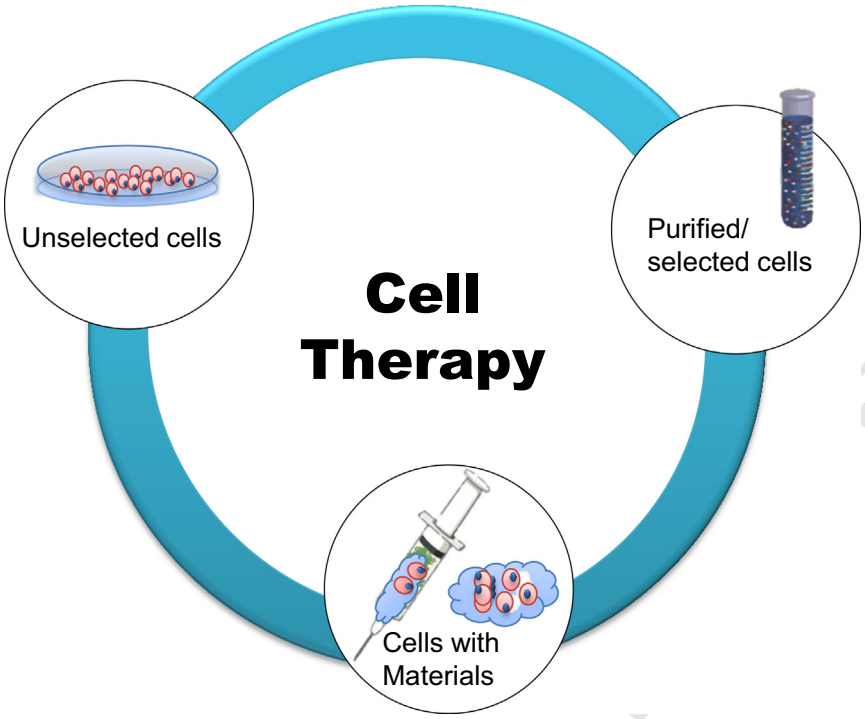

Fig. 2. Cell therapy: This figure shows different cell therapy approaches with different levels of sophistication and translational potential; unselected cells, purified cells and cells with materials.

assessed EPCs (or CD34+ cells) that were mobilised from bone marrow using granulocyte colony stimulating factor (G-CSF) for improving myocardial perfusion. The frequency of angina was significantly reduced compared to the control with the low-dose but not high-dose arms.

2.1.3. Skeletal myoblasts

Beginning almost 20 years ago, animal studies demonstrated that skeletal satellite cells or skeletal myoblasts showed promise in their ability to differentiate into myotubes or new myocardium and improve cardiac function post-infarction [53–60]. Skeletal myoblasts were transplanted from the skeletal muscle of a patient, purified, expanded and implanted into the heart [61]. The MAGIC trial revealed attenuation in LV remodelling, but no improvements in cardiac function, and was ultimately terminated due to increased risk of ventricular arrhythmias [62]. The failure to improve myocardial function may be attributed to the inability of skeletal myoblasts to differentiate into cardiac myocytes [63] or integrate electrically with the syncytium of the myocardium [63,64]. Muscle derived stem cells [65] or cardiogenic muscle derived cell populations [66] may hold promise. MyoCELL® is a skeletal muscle myoblast cell therapy developed by BIOHEART [67] and is in Phase II/III trials in the US (MARVEL NCT00526253) in conjunction with the MyoCATH and MyoSTAR delivery catheters. Phase I trials and Phase II trials in Europe showed mixed results regarding increase in left ventricular ejection and clinical benefit [68–71].

2.1.4. Cardiac stem cells

Cardiac stem cells or CSCs are stem cells specific and resident to the heart. They are clonogenic, multipotent, self-renewing and can differentiate into three lineages; cardiomyocytes, endothelial cells and vascular smooth muscle cells. They express three cell-surface markers; MDR-1 (multi-drug resistant protein), C-kit (the receptor for stem cell factor), and/or Sca-1 (Stem cell antigen 1). Three methods for isolation of human cardiac stem cells have been described: (i) homogenizing large pieces of cardiac tissue and selecting CSCs using antibodies (usually limited to patients that undergo cardiac interventions such as bypass or transplant) [72], (ii) culturing a single biopsy and selecting CSCs with antibodies as a subpopulation [73] and (iii) CSCs form cardiospheres and can be selected by exploiting this property without the use of antibodies [74]. CSCs reside in stem cell niches similar to those of highly regenerating tissues in the post-natal senescent heart, and can undergo symmetric or asymmetric division, giving rise to more CSCs or committed cells. When the heart tissue is injured, diseased or aged, resident stem cell niches can also be affected, so the capacity of the heart to self-heal is affected [75,76]. C-kit+ progenitor cells are a candidate for cell therapy and can be found in multiple species, and are reported to be both essential and adequate for myocardial repair, without ruling out participation of other cell types [77]. C-kit+ cells have all the aforementioned properties of cardiac stem cells, and were the first cardiac-specific stem cell to be approved for a Phase I clinical trial SCIPIO (NCT00474461) [78]. In the SCIPIO trial c-kit+ cells were isolated from a biopsy from the right atrial appendage taken during bypass surgery and 1 million cells were delivered (mean of 115 days after MI) *via* intracoronary injection to the infarction. Investigators reported significant increases in LVEF and decreases in a scar size of >30% [78,79]. However, this is an area of significant controversy in the literature, and caution must be exercised with regard to the reported cardiogenic potential of these cells. Recent work has reported that c-kit+ cells can only generate cardiomyocytes at a functionally insignificant level (<0.03%), and that injection into diseased heart is unlikely to be responsible for new cardiomyocytes [80]. Other work points towards the concept that c-kit+ precursors can generate cardiomyocytes in the neonatal heart, but not the adult heart [81] or that in the neonatal heart they are responsible for myocardial regeneration and vasculogenesis, but in the adult heart they are only involved in vasculogenesis [82], potentially explaining the reported clinical effects. Another Phase I trial, CADUCEUS [83] examined the benefit of CSCs for heart regeneration after myocardial infarction. C-kit+ cells were harvested by an endomyocardial biopsy, and explants were cultured to form cardiospheres [74,84]. Selected cardiospheres were infused into the culprit arteries at 6 weeks to 3 months after MI ($1.25–2.5 \times 10^7$ cells). Scar size and left ventricular volumes benefitted from CSC therapy, but LVEF was not significantly increased. Follow-up studies have

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been initiated, and include RECONSTRUCT (NCT01496209) and ALLSTAR (NCT01458405) for autologous and allogeneic CSCs, respectively.

2.1.5. Cardiopoietic stem cells

Directing the lineage of stem-cell populations towards specific organs is promising, as cells can be obtained from more abundant sources than the target organ itself. Additionally, risks associated with biopsy of organs and issues with poor cell yields can be eliminated. Directing lineage towards specific organs was originally described for pluripotent embryonic stem cells [85–87], but can also be applied to adult stem cell populations, including human MSCs. When exposed to certain growth factors to upregulate cardiogenic potential, the cells are directed down the cardiopoietic lineage [38,88]. The C-CURE trial investigates delivery of cardiopoietic mesenchymal stem cells to ischaemic cardiomyopathy patients. The trial demonstrated efficacy and safety of the approach — with an increase in LVEF of 7% and positive effects on haemodynamics and exercise tolerance [89]. Phase III trials CHART-I and CHART-II are starting in Europe and the US. These studies further underline the trend towards pre-conditioning cells with growth factors and even a hybrid approach where cells are delivered with growth factors or drugs, as discussed in the following section.

2.2. Additional considerations for cell therapy

Clinical translation needs to be the key consideration for cell therapy. The optimal timing for cell administration and the effect of the extracellular matrix must be fully understood. Studies are ongoing to elucidate the mechanical changes in the infarct and mechanism by which the extracellular environment of the infarcted area regulates the therapeutic potential of stem cells. In a recent study researchers isolated and characterized a diseased matrix to understand the effect of changes in infarct stiffness over time on stem cell therapy [90]. Another factor for consideration is the optimal endpoints for clinical trials. Many have used ejection fraction as a metric of functional benefits, but whether this translates into clinical benefits is not fully implicit and often doesn't correlate with other functional parameters such as end systolic volume. A metric of physical performance, such as the 6 minute walk test has been included in recent trials, which makes sense, as the ultimate goal of such regenerative therapy is to restore the patient's exercise tolerance and overall lifestyle to the pre-disease condition. Furthermore, the timing of this type of functional testing is important, and in order to evaluate the contribution of regeneration, a 6 minute walk test at 12 months should be employed to draw meaningful conclusions (Fig. 2).

Table 1
Fold-increase in cell retention over intramyocardial saline delivery reported with various injectable hydrogels.

Study	Hydrogel	Time(s) of analysis	Fold-increase in retention compared to saline control
Zhang et al. [105]	PEGylated Fibrin + HGF	4 weeks	1.3 for unaltered gel 15 pro-survival HGF included
Yu et al. [106]	Alginate Microspheres	24 h	1.3 (*NS)
Christman et al. [107]	Fibrin	5 weeks	~2
Habib et al. [108]	PEG diacrylate	48 h	~2.5
Wang et al. [100]	PEG based	4 weeks	2.5
Martens et al. [109]	Fibrin	90 min	1.77
Liu et al. [98]	Chitosan/β-GP/*HEC	24 h	1.5
		4 weeks	8
Lu et al. [110]	Chitosan/β-GP/*HEC	24 h	1.75
		4 weeks	2
Wang et al. [99]	Chitosan/β-GP/*HEC	1 day	~1.5
		1 week	~1.9
		2 weeks	~2
		4 weeks	Presence of cells in chitosan group, none in control

*HEC = Hydroxy-ethyl cellulose.

2.3. Cells with biomaterial carriers

One of the major challenges in the clinical translation of cell therapy is delivering and retaining viable cells in the heart tissue. The development of cell therapy as a feasible therapeutic option is dependent on methods to enable viable cells to reside in infarcted tissue and exert therapeutic effects for extended periods. In cell therapy, isolated cell suspensions in saline are usually administered systemically *via* intravenous infusion or directly injected into the injured heart *via* the myocardium, or perfused into the coronary arteries or veins. The cell therapy clinical trials discussed in previous sections have primarily utilised such simple cell delivery strategies. Saline solutions don't have the capacity to localise and retain cells at the target site, and do little to cater for the unique requirements of living cells with regard to providing biological cues to influence cell viability, behaviour and fate [8,33]. Poor cell retention is likely to be a major contributing factor in the failure of cell-based therapies for MI to achieve consistent and substantial efficacy to date [3,91]. Among the possible mechanisms underlying the phenomenon of poor retention are exposure of cells to ischaemia and inflammation, mechanical washout of cells from the beating heart, flushing by the coronary vessels, leakage of cells from the injection site and anoikic cell death [92–94]. To address these issues there has been a significant amount of preclinical research into material-based cell therapy for cardiac repair. Delivered biomaterials can produce better spatial distribution and potentially less problems with arrhythmogenicity than simple saline injection techniques. A biomaterial scaffold can provide a surrogate ECM for encapsulated cells to enhance cellular viability and enable physical retention at the infarct site. Biomaterials can provide protection from noxious insults like ischaemia and inflammation and reduce cell death due to anoikis. Cell-loaded biomaterials address the issue of mechanical dispersal of cells from the injection site, which is a major source of cell loss within the myocardium and several studies have shown that biomaterial delivery vehicles can enhance myocardial cellular retention [95–97]. In short, biomaterials can help to deliver more cells to the target site, keep cells localised and viable, and enhance sustained production of beneficial paracrine factors at the target site. To date, there exist two major biomaterial approaches to achieving cellular delivery to the myocardium, namely cell-loaded injectable hydrogels which encapsulate cells and polymerize *in situ* in the myocardial wall, or preformed cell-seeded scaffolds which are affixable to the epicardial surface [7], and both of these approaches will be addressed briefly here.

2.3.1. Injectable hydrogels

Hydrogels can typically be injected *via* three routes: intracoronary, epicardially or transendocardially. Such hydrogels have the potential to rapidly exploit advancements in catheter technology for minimally invasive delivery, reduced cost, shorter hospital times and potential for multiple spatial and temporal administrations. To ensure injectability the material and cells must facilitate loading into a catheter, the solution must gel quickly at the site (but avoid premature gelation and catheter blocking) and the gel must remain structurally sound for the course of the therapy (to avoid embolization), and must degrade after cell therapy without producing toxic byproducts. The gel should also have mechanical properties suitable for supporting the ventricular wall — it must be robust, and endure the fatigue cycling of the heart throughout the course of cell therapy. The increase in cell retention achievable can become more dramatic over time. For example, Liu et al. reported a 1.5-fold increase in cell retention of adipose-derived stem cells encapsulated in chitosan/β-glycerophosphate/hydroxy-ethyl cellulose (chitosan//β-GP/HEC), 24 h post-administration *via* intramyocardial injection, compared to cells delivered in saline [98]. However, an 8-fold increase in retention was observed in hydrogel-injected animals at day 28, which was likely related to a greater loss of cells from saline

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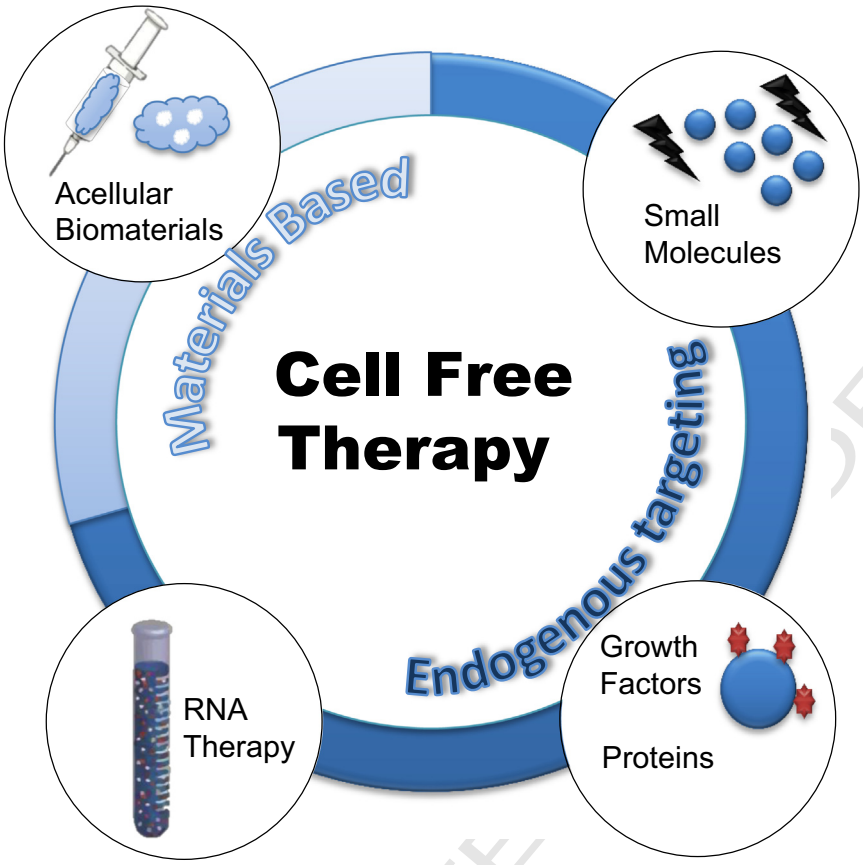

Fig. 3. Cell-free therapy: Two types of cell-free therapy are discussed here; material based cell free-therapy and endogenous targeting, including RNA therapy, growth factors and proteins and small molecule therapy.

injected hearts over this time. A recent study shows that injectable chitosan not only improves retention of cells over time but also enhances cardiac differentiation of brown adipose derived stem cells and enhances functional improvements in the rat model [99]. Wang et al. used an α-cyclodextrin/poly(ethylene glycol)–b-polycaprolactone-(dodecanedioic acid)-polycaprolactone–poly(ethylene glycol) (MPEG–PCL–MPEG) hydrogel for bone marrow stem cell delivery, and showed improved retention in gel-injected animals, correlating with improved left ejection function and attenuation of scar expansion and left ventricular dilation, corroborating the hypothesis that biomaterial delivery can result in tangible enhancements in efficacy [100]. Collagen and laminin are the main components of myocardial extracellular matrix (ECM) and so can support cardiomyocyte attachment and elongation but the shape and dimensions of collagen and laminin biomaterial constructs have not yet been optimised. Future research may include designing 3-D shapes for these hydrogels, for example a collagen type 1 tubular scaffold has also been investigated [101], and shape memory injectable gels have been developed and should be considered for cardiac cell therapy [102,103]. An emerging technique for combining the advantages of hydrogel approaches with controllable, tailored tissue shape and size is bioprinting, enabling precise control over where cells are in the construct and the overall construct architecture to affect a particular cell fate or behaviour (Table 1) [104].

2.3.2. Preformed porous scaffolds

Porous or fibrous preformed scaffolds are the most common way for creating 3D constructs for cell delivery. In many cases, cells are grown on these constructs pre-implantation and patches are surgically attached to the epicardial surface. Leor et al. used a 3D alginate scaffold to construct a bioengineered cardiac graft in a rat model of MI [111,112] and subsequently optimised it for cell seeding and distribution. A collagen patch was also used as a successful delivery vehicle for human mesenchymal stem cells and human embryonic stem cell derived-mesenchymal cells for cardiac repair [113,114]. Cell attachment is an important consideration in such constructs and they can be modified with short peptides such as Arg-Gly-Asp (RGD); a peptide sequence derived from the fibronectin signalling delay [115–119]. The selection, density and patterning of binding sequences depend on the cell type to be seeded on the matrix, and the natural ECM environment. Here, we discuss porous scaffolds as carriers for cells to improve retention, but a large volume of work has explored engineered heart tissue, so the reader is referred to a comprehensive review [120] for more detail on this. As an example, pre-conditioning of engineered heart patches by cyclical mechanical stretch has shown to improve morphology and contractile function of patches [121–128]. In a recent study electrospun poly(e-caprolactone)/gelatin nanofibres were formed into a nanofibrous patch to act as an improved method of cell retention (grafted MSCs resulted in angiogenesis and facilitated cardiac repair) [129] as well as providing mechanical support to the wall and acting as a ventricular restraint, as discussed in the following section. The nanofibrous PG-cell scaffold produced improvements in cardiac function (increase in fractional shortening and ejection fraction, reduction in scar size and increase in thickness in the infarcted area). Combinations of cell-loaded gels and patches have been explored. Soler-Botija et al. describe preliminary work on a fibrin loaded patch and an engineered bioimplant (combination of elastic patch, cells and peptide hydrogel (Puramatrix, Bedford, MA)) [130]. Electrical stimulation combined with 3D cell cultivation has also been explored. Nunes et al. describe the Biowire for pluripotent stem cell-derived cardiomyocytes, consisting of a collagen gel surrounding an electrically stimulated silk suture. These biowires had

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a stimulation rate-dependent increase in myofibril ultrastructural organization and conduction velocity (Fig. 3) [131].

3. Cell-free approaches

Cell-based strategies for cardiac repair involve delivering cells with potential for repair or regeneration to ischaemic or damaged areas of the heart. Despite the initial expectation regarding the cardiogenic potential of transplanted cells, in most studies the number of delivered cells that actually differentiate into cardiomyocytes is not large enough to account for observed clinical benefits, primarily due to low engraftment. The paracrine hypothesis may explain this, whereby released soluble factors from transplanted cells aid in regeneration [39,132]. There are a number of proposed mechanisms for such paracrine effects including increased angiogenesis, control of inflammatory responses, promotion of cardiac cell cycle re-entry and recruitment of endogenous stem cells, suggesting that paracrine targeting of endogenous cells may underlie many of the effects of cell therapy [41]. Similarly, delivery of cells has also been shown to produce mechanical reinforcement to the infarct scar area [133]. The field has undergone a paradigm shift, and investigators are renouncing the notion that therapy must be fixated solely around cells. Instead strategies such as acellular material-based approaches to produce mechanical reinforcement and tissue bulking in the myocardial scar and endogenous cell targeting through bioactive molecule delivery are subjects of extensive research to complement cell-therapy or to stand alone as cell-free therapy. Acellular strategies to cardiac repair have inherent advantages in that the lack of a required cell source could aid clinical translation.

3.1. Acellular material-based scaffolds

Material-based approaches target the important mechanical changes that occur post-myocardial infarction (or in chronic heart failure) resulting in ECM breakdown, geometric changes, LV dilation, stretched cardiomyocytes that can't contract, a growing borderzone and a spherical, thinning left ventricular wall [134–136]. Surgical ventricular restoration [137] (SVR), endoventricular circular patch plasty technique (Dor procedure) [138], partial ventriculectomy (Batista procedure) [139] and passive restraint devices such as the Acorn CorCap™ device [140,141], the Paracor Medical HeartNet restraint device [142], and the Myocor® coapsys device [143] all share the primary goal of reducing ventricular wall stress, and restoring left ventricular geometry. According to LaPlace's law $T = P \cdot R/t$, where T, in this instance, is tension in the myocardial wall and varies proportionally to P (intraventricular pressure) and R (radius of curvature) and is inversely proportionally to t (myocardial wall thickness). By thickening the wall with a reinforcing material, stress can be decreased in the wall, especially around the infarct border zone [144]. Acellular injectable hydrogels and epicardial patches can be used to provide this tissue bulking wall reinforcement. If engineered to have specific biomechanical properties, this acellular material can promote the endogenous capacity of the infarcted myocardium to attenuate remodelling and improve heart function following myocardial infarction [145]. The elastic modulus can be tailored to match that of healthy myocardium or can be manufactured to have a higher elastic modulus to enhance tissue reinforcement [146], and numerical based simulations are valuable in predicting the response [144]. An optimal biomaterial should be able to balance the high forces that occur at the end of contraction in order to prevent or reverse maladaptive modelling [146]. The scaffold should be able to transfer the stress from the infarcted myocardium and border zone, and if the scaffold is biodegradable, cellular infiltration, vascularisation and formation of tissue should be sufficient to transfer the stress from the scaffold to the new myocardium before degradation. Injectable biomaterials used for acellular tissue reinforcement in animal models include fibrin [107,147], alginate [148–151], collagen [152], chitosan [98,110], hyaluronic acid [146,153], matrigel [124,154], polyethylene glycol (PEG)-based materials [155–157], acrylamides [158,159] and composites [160] of these materials. Both small animal studies [148,150] and large animal models [149,160–162] have demonstrated benefit of this tissue bulking effect. For example, a biodegradable, thermoresponsive hydrogel for bulking of the ventricular wall based on copolymerization of N-isopropylacrylamide (NIPAAm), acrylic acid (AAc) and hydroxyethyl methacrylate-poly(trimethylene carbonate) (HEMAPTMC) was designed and characterized, and demonstrated an increase in wall thickness and capillary density, and ingrowth of contractile smooth muscle cells, thus offering a potential attractive biomaterial therapeutic strategy for ischaemic cardiomyopathy [158].

In addition to injectable materials, patches can be placed epicardially in order to provide wall thickening and reinforcement. Elastic patches such as polyester urethane urea have demonstrated an ability to produce an increase in fractional area change, and an attenuation of ventricular dilation in a rat MI model [163]. Engineered scaffolds or patches, such as a recently reported type 1 compressed collagen patch [145] can provide mechanical support to infarcted tissue, reducing dilation and fibrosis, increasing wall thickness and also increasing angiogenesis at the infarct zone and in the patch and border zone. This can lead to increased oxygen delivery and reduction in ischaemic tissue, and generation of new cardiomyocytes [145]. Clinically, an injectable hydrogel called Algisyl-LVR™ (LoneStar Heart, Inc., CA) has been used in a recently initiated Phase II trial AUGMENT-HF (NCT01311791). Circumferential intramyocardial injections of the alginate hydrogel remain in the heart (at the mid-ventricular level) as a permanent implant with the goal of increasing wall thickness, reducing wall stress and restoring ventricular geometry. Pre-clinical studies and a pilot study [164] show that the device has promise for decreasing ventricular volumes, increasing ejection fraction and wall thickness and decreasing myofibre stress at six months [164]. The AUGMENT-HF trial will evaluate the safety and efficacy of Algisyl-LVR™ as a method of left ventricular augmentation in patients with dilated cardiomyopathy, with a primary efficacy endpoint of change in peak VO_2 (maximum oxygen uptake) from baseline to six months. This trial should provide some insight into the clinical benefits of the therapy. Another injectable alginate implant that has moved to clinical study is Bioabsorbable Cardiac Matrix (BCM), also known as IK-5001. After encouraging animal studies [148], recruitment is ongoing for PRESERVATION I (NCT01226563); a trial which investigates an *in situ* forming version of this hydrogel. An aqueous combination of sodium alginate and calcium gluconate is delivered in a bolus intracoronary injection, and into the heart muscle to form a flexible matrix that supports the heart physically and eventually dissipates and is excreted through the kidneys. The primary efficacy outcome measurement is left ventricular end diastolic volume index (LVEDVI).

The current limitations of acellular biomaterials are that optimal design parameters for therapeutic efficacy, including stiffness, degradation rate and bioactivities have yet to be determined. The experimental results in the literature reveal a complex biological and mechanical interaction between material and tissue. Experimental assessment of tissue bulking agents is mainly undertaken using a rat model of MI, which is not as clinically representative as a large animal model in terms of injection volume, injection method and volume of left ventricle. Injection time and data collection time also vary in these studies [165]. Further work is warranted to fully understand the specific mechanisms behind reported functional improvements. Only a small number of studies have directly compared different acellular biomaterials [166,167], and the ideal acellular material properties have yet to be identified. It remains challenging to distinguish benefits resulting from changing the mechanical environment or benefits resulting from cardiac remodelling that is simultaneously occurring [168]. The *in situ* gelation rate of injectables must be rapid to avoid loss of material, but rapid gelation can make catheter delivery difficult. Lack of vascularisation in 3D scaffolds may also represent a limitation if scaffolds are intended for cell ingrowth and not just as a tissue bulking material. Cell survival may only be possible at the peripheries of 3D constructs, without

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vascularisation [169]. Furthermore, in the ischaemic human heart, there may be a decreased production of factors that would promote vessel sprouting. Provided tissue replacement is eventually envisaged, tissue ingrowth and vascularisation must be sufficient for stress transfer to newly generated myocardium before degradation, and the timing of degradation to match tissue ingrowth will be critical to successful translation. If the purpose of the acellular biomaterial is to design an environment for endogenous cells to proliferate and regenerate, endogenous cell numbers may not be high enough to initiate desired cell processes. Acellular scaffolds cannot fully function as viable cardiac tissue replacements, and are not fully biomimetic, potentially limiting the full potential of endogenous cells to recover through infiltration of the implant. Acellular constructs negate the opportunity to pre-condition to enhance functionality and integration with cardiac tissue. For example, cell-loaded scaffolds can undergo mechanical and electrical pre-conditioning that may result in a mature cardiac structure, higher force generation and electrical coupling in the heart [122,127,128,170,171]. Although true of all biomaterials, limitations for synthetic materials include difficulties with scale-up of complicated chemical reactions and lack of innate bioactivity, and with natural biomaterials limitations include difficulties with regulatory approval and batch-to-batch variability [133]. Finally, degradable materials can cause an inflammatory response and phagocytosis [168], the effects of which are not fully characterized, and are currently reported to have beneficial [158] and counter-productive effects [155].

3.2. Endogenous targeting

3.2.1. Small molecules

Small molecule drugs represent a promising therapeutic deliverable for the treatment of ischaemic cardiomyopathy. These compounds are often inexpensive to make and store. Advances in synthetic chemistry mean that large libraries of structurally diverse molecules can be produced and screened for efficacy in modulation of a specific molecular target. Similarly, a library of small molecules can be screened in a biological system to determine novel drug targets and elucidate previously unknown signalling systems implicated in myocardial disease. Structure activity relationship data can enable molecular modification to optimise specificity, stability and efficacy. Such approaches are of distinct utility in clinical development. Small molecule drugs are currently at an early stage of development for the purpose of myocardial regeneration (for review see Jung and Williams [172]). Here, we discuss a concise selection of candidate drug classes, with a particular focus on advanced delivery to improve treatment outcomes.

3.2.1.1. Prostaglandins. Prostaglandins are endogenous small-molecule fatty acid derivatives which mediate a variety of physiological effects. Prostaglandin E2 and Prostaglandin I2 have a regenerative role in the ischaemic myocardium and may have therapeutic potential post-MI.

3.2.1.2. Prostaglandin E2 (PGE2). Hsueh et al. demonstrated that daily intraperitoneal administration of PGE2 enhanced cardiomyocyte replenishment at the infarct border zone in a murine model of MI. Prostaglandin I2 (PGI2) did not produce such effects, in this study. PGE2 increased the presence of Sca-1 + cells and regulated their potential for a cardiomyogenic differentiation, suggesting that PGE2 could activate and mobilise the endogenous CSC population. In addition, PGE2 treatment rescued the ability of old mouse hearts to replenish cardiomyocytes at the infarct border [173]. PGE2 is FDA approved for induction of labour, and so possesses significant translational potential. However, PGE2 is rapidly metabolised *in vivo* and so repeated dosing was necessary in this study, which utilised a simple systemic route of administration. This underpins the need for protective encapsulation and delivery for long-term treatment and/or synthesis of more stable prostaglandin mimics.

3.2.1.3. Prostaglandin I2 (PGI2). PGI2 is a vasodilator and potent anticoagulant and has been FDA approved for the treatment of hypertension. Like PGE2, PGI2 has a short half-life *in vivo* which is decreased in conditions of myocardial infarction [174]. Ishimaru et al. delivered ONO1301, a stable small molecule PGI2 agonist on an epicardial collagen patch to hamster hearts in a model of dilated cardiomyopathy (but the observed therapeutic actions are likely also applicable to acute MI), and found that ONO1301 treatment upregulated myocardial expression of cardioprotective HGF, VEGF, SDF-1 and G-CSF. ONO1301 concentrations were found to be significantly higher in left ventricular tissue than in systemic circulation for as long as two weeks after treatment, highlighting the importance of local delivery and sustained release. ONO1301 treatment preserved cardiac performance, increased myocardial vascularisation, reduced fibrosis and prolonged survival [174]. In a second study, Nakamura et al. encapsulated ONO1301 in polylactic-co-glycolic acid (PLGA) microspheres which produced a sustained release of drug for 10 days. The microspheres were injected intramyocardially in a mouse model of acute MI and increased local HGF and VEGF expression, increased vascularisation of the infarct border zone by day 7, decreased left-ventricular dilatation and improved survival by day 28. ONO1301 was well tolerated when delivered intramyocardially in PLGA microspheres. A Phase I clinical trial, where ONO1301 was administered orally was discontinued due to diarrhoea in participants and systemic administration has been shown to produce hypotension in experimental animals, highlighting the importance of localised and controlled delivery in realising the full potential of a given therapeutic strategy and avoiding off-target effects [175].

3.2.1.4. Pyrvinium Pamoate. Pyrvinium Pamoate (PP) is an FDA approved anthelmintic drug, which inhibits NADH-fumarate reductase activity essential for the anaerobic respiration of parasitic worms. Murakoshi et al. postulated that the administration of PP could produce a differential cytotoxic effect in fibroblasts which proliferate in the myocardial scar after infarct, and are reliant on anaerobic respiration in ischaemic conditions, and hence enable anti-fibrotic therapy. PP was administered orally, daily, beginning at 24 h after permanent left coronary artery ligation (when the cardiomyocytes in the infarct area were likely dead) in a mouse model of MI. There was a significant reduction in the presence of fibroblasts in the infarct and border regions by seven days and fourteen days and LVEF increased in PP treated animals. The authors also report an increase in scar vascularisation, which they attribute to the permissive microenvironment created by inhibition of fibrosis. PP therapy was well tolerated [176].

This is in contrast to a different study where Saraswati et al. administered PP *via* a single intramyocardial injection in a saline carrier at the time of coronary artery ligation in a mouse model of MI, and observed a significant increase in animal mortality upon PP treatment. It is likely that administration of PP at this early stage enhanced cardiomyocyte death in ischaemic conditions, resulting in larger infarcts and mortality, and highlights the importance of time of dosage. Surviving animals did not display a significant enhancement of cardiac regeneration or reduction of fibrosis. A once off injection of PP in saline may not have enabled significant myocardial retention of the drug up to the time of initiation of fibrosis. Therefore, utilisation of a biomaterial carrier, administered at a minimum of 24 h post-infarct, which facilitated sustained release may have ameliorated these results. Similarly, stimulus responsive nanoparticles, tuned to deliver drug in a fibrotic environment or at the time of initiation of fibrosis may have improved treatment outcome [177]. While PP treatment was well tolerated when administered orally, the risk for cytotoxicity to cardiomyocytes in the border zone where perfusion is limited, or CSCs are naturally present in a hypoxic niche, may justify the use of targeted nanoparticulate carriers to ensure increased specificity for fibroblasts and decreased risk for toxicity in future studies [178].

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3.2.1.5. Dipeptidylpeptidase IV (DPP-IV) inhibition. DPP-IV is a membrane bound peptidase which cleaves SDF-1. Pharmacological inhibition of DPP-IV aims to stabilise myocardial SDF-1 after MI, thereby enhancing recruitment of CXCR4+ circulating stem cells to effect regenerative efficacy. Zaruba et al. administered either Diprotin A, a small molecule DPP-IV inhibitor (twice daily systemic administration), G-CSF, to mobilise circulating progenitors or a multimodal administration of both in a mouse MI model. Combining G-CSF mobilisation and DPP-IV inhibition resulted in an increase in CXCR4+ cell homing to the myocardium, attenuation of infarct remodelling, neovascularisation in the infarct border zone, enhanced myocardial function and increased survival. Only the combination of Diprotin A and G-CSF treatment significantly attenuated myocardial remodelling, highlighting the potential of multimodal therapeutic strategies [179]. In addition, Theiss et al. demonstrated that a G-CSF/Diprotin A multimodal therapy significantly increased numbers of resident CSCs [180]. Given that it was necessary to administer Diprotin A twice daily to maintain efficacious concentrations within the myocardium, a sustained release formulation could greatly aid clinical translation. A Phase III clinical trial with another DPP-IV inhibitor, Sitagliptin, which has been approved for the treatment of hyperglycaemia, in conjunction with G-CSF administration in patients with acute MI reported that the approach was well tolerated and appears feasible, but has yet to publish efficacy data [181].

3.2.2. RNA therapeutic strategies

3.2.2.1. Modified messenger RNA. A novel therapeutic strategy which has emerged recently is the delivery of modified messenger RNA (modRNA). Kormann et al. demonstrated that a collection of nucleotide modifications inhibited mRNA interaction with certain toll-like receptors, reduced immunogenicity and consequently enhanced stability when the modRNA was administered to mice. An intramuscular injection of modRNA produced a significant increase in target protein production *in vivo*. modRNA delivery to the lungs ameliorated a fatal genetic deficiency in mice despite only producing a very transient protein expression [182]. Warren et al. used modRNA delivery to create induced pluripotent stem cells, demonstrating that the transient expression of target proteins achievable could exert lasting effects on cell fate and differentiation [183].

Zangi et al. showed that modRNA encoding VEGF could transfect adult rat cardiomyocytes with a high efficiency (68%), using Lipofectamine, a commercially available transfection agent. The translational potential of Lipofectamine is unclear, however, since some authors have reported very low transfection efficiencies in large animal models or significant cytotoxicity *in vitro* [184,185]. One injection of modRNA/Lipofectamine transfected a significant portion of the mouse myocardium (25% of the left ventricle). Transgene expression peaked at 18 h and returned to baseline at 2–3 days, in contrast with DNA/Lipofectamine which peaked at 72 h and maintained high levels of expression for 10 days. VEGF modRNA/Lipofectamine was administered to infarcted mouse hearts, in comparison with VEGF plasmid DNA. Both VEGF DNA and VEGF modRNA increased vascular density in the infarct region but vessels produced by VEGF DNA were leaky, contributing to oedema which likely resulted in an observed increase in short-term mortality in VEGF DNA treated animals when compared to untreated controls. In contrast, modRNA VEGF treated animals showed decreased long-term mortality and improved cardiac function when compared to untreated controls, highlighting the importance of expression kinetics on functional outcome. VEGF modRNA treatment also upregulated *Wt 1*, an epicardial cardiac progenitor marker, in the infarct region, and *in vitro* data suggested that VEGF modRNA induced this cell type to undergo an endothelial differentiation, which may have contributed to treatment outcome [186].

The use of modRNA as a deliverable therapeutic confers several advantages over more conventional DNA therapy. Cytosolic expression avoids the risk of insertional mutagenesis associated with DNA therapy. A transient, pulse-like expression more closely mimics endogenous paracrine signalling, in which sustained, high levels of expression over long periods, as produced with certain methods of DNA delivery, do not occur. Rather, a transient, strong signal, which is spatiotemporally controlled to act in the time and place it is required, is likely to be more efficacious and avoid undesired effects. While Zangi et al. has clearly demonstrated elements of this concept, further investigation into more clinically translatable nanoparticulate delivery vectors (as opposed to Lipofectamine) or localised therapy involving a biomaterial carrier will aid in unlocking the full potential of this technique. Such approaches may enable greater myocardial targeting and retention and spatiotemporal presentation of modRNA to maximise efficacy. modRNA therapy is currently in its infancy, and further investigation with other target genes to produce myocardial regeneration or offset the effects of ischaemic damage *in vivo* is warranted.

3.2.2.2. MicroRNA targeting. MicroRNAs (miRs) are endogenous, non-coding strands of RNA of around only 22 nucleotides in length. miRs are effectors of epigenetic regulation of protein expression, whereby a single miR demonstrates binding affinity for complementary oligonucleotide sequences in an array of mRNA targets, resulting in an inhibition of mRNA translation and/or mRNA degradation. Given that one miR typically has many mRNA targets, miR-mediated changes in protein synthesis are involved in a variety of complex intracellular signalling and modification of miR activity can have significant and multifaceted effects on cell phenotype.

miRs represent an attractive therapeutic target since they are extensively involved in cardiac development and postnatal disease processes including ventricular remodelling and fibrosis following infarction and processes with therapeutic applicability in acute infarction such as angiogenesis or myocardial regeneration (for review see Fiedler and Thum [187]). Strategies to modify miR activity can take two forms — up-regulation of miR expression *via* transfection or viral transduction of target cells with a functional copy of a miR (a miR mimic), effectively inhibiting target protein expression, or inhibition of endogenous miR activity *via* complementary binding to synthetic anti-sense miRs or antagomirs, leading to an upregulation of target protein expression. Here, we highlight a concise selection of promising miR targeting strategies with different modes of action and discuss methods to enhance the delivery of miR to the infarcted heart.

Eulalio et al. undertook a high-throughput screening analysis of 875 miR mimics to identify 2 candidates (miR-590-3p and miR-199a-3p) which enabled the re-entry to cell cycle and proliferation of post-natal rat cardiomyocytes. These miRs were then delivered *via* intramyocardial injection of an adeno-associated viral vector to the infarcted mouse myocardium *in vivo* and significantly enhanced LVEF, increased wall thickness and reduced infarct size, primarily by stimulating cardiomyocyte proliferation [188]. Bonauer et al. demonstrated that miR-92a was expressed in endothelial cells and overexpression of this miR suppressed a variety of angiogenic processes *in vitro*. Conversely, a miR-92a antagomir enhanced angiogenesis *in vitro* and increased vascularisation of infarcted myocardium, reduced infarct size and enhanced cardiac function in a mouse model of acute MI, when administered intravenously. A panel of miR-92a target genes involved in vessel growth and development were identified [189]. Boon et al. determined that miR-34a demonstrated an increased expression in aged rat hearts which was related to age related decline in cardiac function. A miR-34a antagomir inhibited H_2O_2-mediated apoptosis in rat neonatal cardiomyocytes *in vitro*, and enhanced cardiac function, reduced cardiomyocyte apoptosis and enhanced vascularisation in a mouse model of acute myocardial infarction, when administered intramyocardially [190]. Hu et al. demonstrated that HL-1 cardiomyocytes transduced with miR-210 increased expression of pro-angiogenic growth factors and reduced caspase activity under hypoxic stress. When delivered intramyocardially *via* a minicircle non-viral vector in a mouse acute myocardial infarction model miR-210 reduced the presence of apoptotic cells

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and increased capillary density in the infarct area while enhancing left ventricular function. A panel of pro-angiogenic and anti-apoptotic miR-210 target genes were identified [191].

While these studies have demonstrated the preclinical potential of miRs for myocardial regeneration, significant hurdles to clinical translation remain. miRs not only represent a potentially powerful target to exert desired changes in cellular behaviour but also come with the risk of unpredictable off-target effects. Multiple target genes are controlled by a given miR, resulting in complex pharmacodynamics in both target and non-target tissues. miR delivery poses a challenge as unmodified miRs are rapidly degraded by systemic nucleases, may provoke an immune response and demonstrate low or unpredictable uptake by target cells. Significant modification of miRs to enhance stability has been achieved but sometimes at the cost of decreased specificity [192]. Therefore, targeted delivery of miR therapeutics to the myocardium utilising local delivery coupled with nanoparticulate and/or biomaterial encapsulation is of the utmost importance.

The majority of studies investigating miR therapy for MI have used methods of miR delivery such as intramyocardial injection of viral vectors or simple systemic delivery of unencapsulated antagomirs. Such approaches not only provide a proof of concept for miR regenerative efficacy in the myocardium, but also pose translational hurdles such as safety concerns and lack of specificity for myocardial tissues. A range of nanoparticulate delivery vectors have been investigated for the targeted delivery of miRs, in a variety of different disease models outside of the cardiovascular field, with varying degrees of success and translational potential, including viral vectors, Poly(lactide-co-glycolide) (PLGA) particles, dendrimers, lipid based systems, Polyethylenimine (PEI)-based delivery systems and microvesicles such as exosomes (reviewed by Zhang et al., Muthiath et al. and Chistiakov et al. [193–195]). Gill et al. showed that ultrasound responsive microbubbles could transfect HL-1 cardiomyocytes with miR-133 upon application of ultrasound, which reversed cardiomyocyte hypertrophy. Such an approach could facilitate systemic delivery, but mediate miR uptake and expression only in tissues which are exposed to an externally applied ultrasound field [196]. Delivery of miRs in biomaterial carriers has also shown promise. Monaghan et al. determined that a collagen scaffold produced a sustained, bioactive release of miR-29B, which reduced maladaptive remodelling in a rat wound model [197]. In addition, local miR delivery in an injectable hydrogel has been shown to be an effective therapeutic strategy [198]. However, these approaches remain underexploited in the field of miR therapy for myocardial regeneration and their future exploration may provide more translatable, safer and efficacious therapeutic strategies.

3.2.3. Direct reprogramming

A novel approach to effecting myocardial regeneration involves direct reprogramming of cardiac fibroblasts to functional cardiomyocytes or cardiac progenitor cells. Due to the limited regenerative potential of cardiomyocytes, the majority of the myocardial scar after MI is composed of fibroblasts with no ability to contribute to the contractile activity of the myocardium. This technique involves therapeutic deliverables which aim to convert cardiac fibroblasts to cell types which can ultimately contribute to cardiac output. This has been investigated using several different approaches, including over-expression of cardiac transcription factors and delivery of microRNAs or small molecule drugs. Here, we discuss a concise selection of studies with a view to investigating clinical potential and suggesting scope for improvement using advanced delivery.

Recent research has identified sets of genes which, when overexpressed, can facilitate a direct reprogramming of cardiac fibroblasts to cardiomyocytes, while bypassing a pluripotent stem cell state (and the potential concomitant risk of tumour formation) [199]. Such transdifferentiation has been demonstrated *in vitro* [200] and has also shown clinical potential *in vivo*. Qian et al. reported that intramyocardial injection of three transcription factors, Mef2c, Tbx5, and myocardin (GMT) encoded within retroviral vectors, resulted in minimal cardiomyocyte viral infection but significant transduction of fibroblasts in the myocardial border region of the infarcted mouse heart. 35% of cardiomyocytes in the infarct border zone were newly generated upon treatment and GMT delivery resulted in a decrease in infarct size and produced modest improvements in cardiac function [201]. Song et al. delivered GMT plus an additional factor, Hand2 (GHMT), *via* a retroviral vector through an intramyocardial injection in a mouse MI model and determined that GHMT-treated animals had an LVEF of 49% compared to an untreated LVEF of 28%, which corresponded to twice the improvement of the controls and which persisted for up to 12 weeks [202].

Jayawardena et al. transfected murine cardiac fibroblasts with a combination of miRs 1, 133, 208 and 499 and reported transdifferentiation to a cardiomyocyte-like cell *in vitro*. The addition of a small molecule, JAK inhibitor 1, increased the efficiency of reprogramming 8–10 fold demonstrating the potential for small-molecule enhancement of this process. The miR cocktail was delivered intramyocardially *via* a lentiviral vector in a mouse model of MI, and the results suggested that cardiac fibroblasts underwent a cardiomyocyte differentiation *in situ* but the authors did not investigate or report any potential effects treatment had on cardiac function [203]. In a recent study, Wang et al. utilised a small-molecule cocktail to reduce the number of genetic manipulations required to produce transdifferentiation of mouse fibroblasts to beating cardiomyocytes to just one — overexpression of Oct4. Cells passed through a cardiac progenitor stage during this transdifferentiation. Further development of this approach could lead to a fully pharmacological reprogramming, which could potentially circumvent some of the safety concerns of genetic manipulation. However, Wang et al. did not investigate this approach *in vivo* [199].

Clinical translation of fibroblast reprogramming techniques could be of significant therapeutic value. Direct reprogramming is a recent concept and consequently the majority of studies to date have served to provide a proof of concept, without significant focus on translational delivery approaches. As this field evolves, more clinically relevant delivery approaches and therapeutic deliverables will be explored. The use of viral vectors and stably expressed transgenes will likely pose translational hurdles due to safety concerns. In addition, the heart contains a large pool of fibroblasts, necessary for normal function [204]. It may be detrimental to target all cardiac fibroblasts non-selectively, and nanoparticulate targeting for fibroblasts present in or near the myocardial scar could aid in avoiding potential off-target effects of non-selective transdifferentiation. Such nano-particles could be responsive to stimuli in the scar environment itself, such as inflammation or reactive oxygen species, if a sufficient differential in molecular targets is not present between fibroblasts present in the scar and those elsewhere in the heart. Similarly, local delivery in biomaterial carriers could help to produce spatial control and retention of a therapeutic payload at the border zone.

3.2.4. Growth factors and proteins

Among the different therapeutic agents aimed to regenerate the damaged heart tissue after an ischaemic disease, peptides and proteins represent a well-consolidated acellular resource. The increased accessibility to these biopharmaceutical drugs and the advances in chemical modifications to enhance protein half-life *in vivo* and minimize immunogenicity [205] offer a broad range of new therapeutic modalities. Modified peptides and proteins can enable cardiac repair through activation of endogenous cardiac progenitor cells present at the injury site, the induction of cardiomyocyte proliferation and the recruitment of progenitor cells to damaged myocardium or of functional cells able to trigger neovascularisation.

With the aim to replace stem cell therapy in the treatment of acute myocardium ischaemic injury, Pavo et al. recently suggested the use of the secretome of apoptotic peripheral blood cells (APOSEC). The paracrine effects of this mixture of cytokines and growth factors were assessed after intramyocardial injection in a porcine model of acute

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MI. The administration of APOSEC produced downregulation of inflammatory and apoptotic genes 1 month after injection, whereas some angiogenic factors and regulators of vascular tone and homeostasis were upregulated. As a consequence, a reduced infarct size and improved hemodynamic function were found in APOSEC-treated animals [206].

Cell function is controlled by growth factors through the activation of specific signalling pathways [207]. The modulation mediated by these proteins may involve different biological routes and organs in the body. Therefore, the selection of cardiac-specific growth factors and safe dosing regimens should help prevent undesirable off-target effects. In the case of angiogenesis, *vascular endothelial growth factor* (VEGF) has been demonstrated to be a major regulator of vascularisation under hypoxic conditions. As a potent growth factor for endothelial cells, VEGF administered after MI can induce angiogenesis and improve cardiac function. Despite its proven efficacy in preclinical models, VEGF has failed to achieve successful translation to clinical practice, in part due to dose limitation derived from the risk of nitric oxide-mediated hypotension [208]. Additionally, some concerns have been raised about the progression of metastatic tumour lesions as side effects of the prolonged administration of angiogenic growth factors.

The chemotactic *stromal cell derived factor-I* (SDF-I) has been described as a potent stem cell homing agent that is also involved in the regeneration of the vasculature. By binding to the CXCR4 receptor, SDF-I does not act as a growth factor on endothelial cells but increases the recruitment of endothelial progenitor cells [205]. This fact suggests a safer mechanism in the induction of angiogenesis since a therapy based on SDF-I may limit the uncontrolled formation of abnormal vessels. However, a major drawback of using SDF-I lies in its rapid cleavage by enzymes in the heart, such as DPP-IV and matrix metalloproteinases, leading to low efficacy. To surpass this disadvantage and improve its pharmacokinetics and activity, approaches based on altered SDF-I chemokine designs that resist proteases or nanofibre-mediated delivery of SDF-I have been suggested [209]. In a complementary strategy, the conjugation of SDF-I to the soluble platelet collagen receptor glycoprotein VI, which preferentially binds to collagen at exposed extracellular matrix in the damaged vasculature, enabled the targeted delivery of higher concentrations of SDF-I to the infarct site. This approach produced an enhanced recruitment of functional cells and a significant reduction of the infarct size in mice after MI [210]. Alternatively, gene transfer has been shown as a safe option in a Phase I clinical trial with a DNA plasmid encoding human SDF-I, JVS-100. The endomyocardial injection of the naked plasmid in patients with HF was well tolerated at all dose levels tested and led to improvements in clinical endpoints after 4 months [211].

Early clinical studies have also been performed with recombinant human *neuregulin-I* (NRG-I), a member of the epidermal growth factor family that promotes increased cell cycle activity and proliferation of cardiomyocytes through ErbB4 receptor binding. Patients with stable chronic HF showed an improved cardiac function with favourable acute and sustained hemodynamic effects after daily injections of NRG-I for eleven days [212]. Similarly to NRG-I, *periostin* can induce cell cycle reentry in adult cardiomyocytes. Kuhn et al. demonstrated that differentiated mononucleated cardiomyocytes have proliferative potential, and that periostin injected into the myocardium of rats after infarction has a regenerative effect, improving cardiac function after 12 weeks and reducing fibrosis and hypertrophy [213].

Hepatocyte growth factor (HGF) is a mesenchyme-derived pleiotropic factor with a stimulating effect on hepatocyte multiplication. Its implication in the regulation of cell growth, motility and morphogenesis of various cell types extends to the modulation of cardiovascular growth in pathological conditions. The antiapoptotic effect of HGF on cardiomyocytes has been demonstrated in rats after transient myocardial ischaemia and reperfusion [214]. Moreover, HGF may influence angiogenesis and progenitor cell recruitment. Urbanek et al. showed that a gradient of HGF facilitated translocation of CSCs from the atrioventricular groove to the infarcted myocardium in mice [215]. A Phase II multicentre clinical trial evaluating a small-molecule mimetic of HGF, BB3, is currently ongoing with the aim to assess the safety of this drug in conjunction with standard care and its efficacy in improving heart function in patients following MI [216].

Growth and differentiation of recruited stem cells may be supported by *insulin-like growth factor I* (IGF-I). This hormone binds a tyrosine kinase receptor and enhances cell survival. IGF-I has been shown to reduce myocardial necrosis and apoptosis, and its overexpression in transgenic mice leads to an increase in myocyte turnover thus compensating for the extent of cell death in the ageing heart [217]. Moreover, in patients who had a diagnosis of ischaemic heart disease, low circulating IGF-I levels are associated with an increased risk in the development of cardiovascular disease [218]. The key role of IGF-I in cardiomyocyte homeostasis suggests a strong therapeutic potential. However, higher dose regimens have been associated with side effects such as hypotension and tachycardia. As proposed by O'Sullivan et al., a single local administration of low-dose IGF-I at 2 h into reperfusion may provide a prosurvival activity while avoiding significant side effects. In a porcine model of acute MI, the authors showed a reduced cardiomyocyte death at 24 h after IGF-I injection, which translated into structural and functional benefits in the regional and global myocardium 2 months after treatment [219].

In order to increase the bioavailability and control the release of growth factors in the cardiac tissue, drug delivery systems have been suggested as a means to protect and accumulate the protein cargo. Davis et al. reported the use of biotin–streptavidin to bind IGF-I to self-assembling peptides without interfering with bioactivity. These peptides provided a sustained IGF-I delivery for more than 1 month in rat myocardium. However, the co-injection of neonatal cardiomyocytes was necessary to achieve a therapeutic effect in rats after experimental MI [220]. To avoid the use of cell therapy, Chang et al. developed a delivery system based on PLGA nanoparticles functionalized with pPEI, which was able to electrostatically complex IGF-I. After comparing growth factor-loaded particles of different sizes (60 nm, 200 nm and 1 μm), the authors found that the 60 nm-sized nanocarriers displayed the highest IGF-I activity in cultured cardiomyocytes. Following injection of these particles in the infarcted myocardium of mice, it was shown that the polymeric carriers prolonged IGF-I retention time and reduced cardiomyocyte apoptosis by more than 25%. Remarkably, a single administration of IGF-I-loaded nanoparticles improved cardiac systolic function, reduced infarct size and prevented ventricular remodelling at 3 weeks post-infarction [221].

The feasibility of controlled delivery using polymeric carriers was also shown for other proteins involved in repair of the damaged heart. Formiga et al. encapsulated *FGF-I* and NRG-I separately in PLGA microparticles to assess the effect of cytokine sustained release on cardiac regeneration. The microparticle formulations showed very similar release kinetics with nearly 70% cumulative release within 1 month. The injection of the loaded particles into the ischaemic myocardium of rats produced reductions of the infarct size and fibrosis as well as an increase of the left ventricle thickness 3 months after treatment, with no significant differences among particles loaded with FGF-I, NRG-I or both [222]. In a different study with isolated rat cardiomyocytes *in vitro*, Johnson and Wang evaluated the protection from degradation and the Q20 sustained release of the morphogen *Sonic hedgehog* (Shh) from a coacervate delivery system [223]. Shh is known to control the epithelial/mesenchymal interactions during the embryonic development, and has demonstrated potential to restore blood flow in a mouse model of hindlimb ischaemia after multiple injections for 1 month [224]. The formulation of Shh-heparin complexes in poly(ethylene argininylaspartate diglyceride) prolonged the release of Shh for over 3 weeks and provoked an upregulated secretion of VEGF, IGF-I, SDF-I and Shh by cardiac fibroblasts for at least 2 days. Q21

As an alternative to particle formulations, the encapsulation of proteins in carrier gels also provides a controlled release and enhances

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retention in the target area. In a rabbit model of MI, Fujita et al. showed efficient angiogenesis and collateral flow induced by *FGF-2* loaded in photocrosslinkable chitosan hydrogels. The chitosan aqueous solution containing FGF-2 was applied on the surface of the ischaemic myocardium and subsequently crosslinked by UV-irradiation for 30 s. Notably, the chitosan hydrogel allowed an extended delivery of FGF-2 for a period longer than 1 month [225]. An ideal growth factor carrier should have the ability to flow through a catheter, enabling minimally invasive application, and thereafter form a solid gel to avoid the injected drugs to be pumped out of the heart. In an attempt to develop such system, Wu et al. synthesized a biodegradable aliphatic polyester hydrogel, poly(δ-valerolactone)–poly(ethylene glycol) (PEG)–poly(δ-valerolactone), which gels when heated at physiological temperature. The injection of the hydrogel in the infarcted myocardium of rats attenuated adverse cardiac remodelling and improved ventricular function for up to 35 days. These effects were strengthened by covalently attached VEGF, which additionally provided increased regional angiogenesis in comparison with free VEGF co-injected with the hydrogel [226]. With the same aim to design an injectable biomaterial, Bastings et al. proposed pH-sensitive ureido-pyrimidinone PEG hydrogels, which are fluid above pH 8.5 and instantaneously gel at neutral pH. By transcatheter injection of the synthetic hydrogel incorporating both HGF and IGF-I in a porcine model of MI, the authors demonstrated a safe administration and a reduction in scar collagen after 1 month [227].

Tissue regeneration is often characterized by complex cascades of growth factors with critical roles in cell proliferation and differentiation. The combination of several growth factors is required to mimic the native environment and promote the formation of functional tissue [208]. Since myocardial repair involves the contribution of different signalling pathways, the combined activation by co-administered growth factors represents a promising approach for an enhanced performance of CSCs and may also enable effective and safe angiogenic interventions.

Ellison et al. demonstrated the superiority of co-administered HGF and IGF-I to induce myogenic differentiation of endogenous porcine CSCs in the presence of adult rat ventricular myocytes *in vitro*. The injection of a small dose of IGF-I and HGF through the coronary artery supplying the infarcted region in pigs produced a dose-dependent protective effect on myocardial survival and reduced hypertrophy in the peri-infarct zone. Furthermore, a reduced infarct size and enhanced left ventricular function were measurable 2 months after the treatment [228]. In a different approach, Song et al. recently reported the combination of SDF-I with the angiogenic tetrapeptide *Ac-SDKP* to activate regenerative mechanisms in a model of chronic HF in rats. The authors immobilized Ac-SDKP in acrylated hyaluronic acid hydrogels, in which SDF-I was added before crosslinking. Interestingly, hydrogels with single SDF-I or Ac-SDKP failed to show a significant regenerative activity whereas the dual therapy led to increased angiogenesis, improved left ventricular function, decreased infarct size and higher wall thickness at 4 weeks after hydrogel injection [229]. In spite of these promising preliminary results, more extensive knowledge on the role of different stem cell homing factors and the potential synergies with differentiation and proliferation mechanisms is needed. As exemplified by some negative reports on the use of SDF-I therapies for MI *in vivo* [230], a tight control of the complex molecular signalling is likely required to avoid unexpected effects.

Temporal control on the release of proteins is another key factor to realise their maximal potential for cardiac regeneration. In the case of *granulocyte colony stimulating factor* (G-CSF), which induces proliferation of haematopoietic stem cells with the capacity to regenerate the infarcted myocardium, an effect was found only in patients who received G-CSF early after MI [231]. As hypothesized by Ruvinov et al., a sequential delivery of IGF-I and HGF may favour the regenerative process: a fast release of IGF-I could enhance survival of the remaining functional myocardium, while a more sustained release of HGF could induce angiogenesis and more favourable remodelling at later stages. By bioconjugating IGF-I and HGF individually with alginate-sulphate, and combining both complexes with low viscosity sodium alginate solution, dual-release injectable hydrogels were obtained. The intramyocardial injection of the alginate gels in a rat model of acute MI produced an increased cytoprotection and angiogenesis in the infarct after 1 month when compared to the administration of IGF-I and HGF in saline. Furthermore, the sequential treatment induced a higher level of cell proliferation at the infarct border after 1 week, as well as a higher expression of GATA-4 after 4 weeks, indicative of angiogenesis, survival and stem cell recruitment [232]. In another example, albumin–alginate microcapsules were employed to separately incorporate FGF-2 and HGF with different release kinetics. As the authors of this study suggest, the sequential release of FGF-2, which generates a potent angiogenic activity, followed by the arteriogenic signalling induced by HGF, resulted in a mature vessel network that prevented cardiac hypertrophy and fibrosis and led to improved cardiac perfusion after 3 months in a rat model of chronic HF [233].

Furthermore, a time-controlled combination of immune response inhibition and neovascularisation was recently achieved by Projahn et al. By crosslinking thiol-functionalized copolymers of ethylene oxide and propylene oxide with different agents, *i.e.* hydrogen peroxide or PEG-diacrylate, the authors obtained degradable gels with disulphide or thioether bonds, respectively. In the presence of reduced glutathione, the disulphide-based gels degraded in 1 day (fast degradable hydrogel, FDH) while complete degradation of thioethers occurred after 1 month (slow degradable hydrogel, SDH). On the one hand, an inhibitor of neutrophil infiltration, *MetCCL5*, was released from FDH to block the immune response during the first hours. On the other hand, SDF-I was released from SDH for a sustained recruitment of haematopoietic stem cells. The co-administration of both loaded hydrogels in the infarcted myocardium of mice preserved cardiac function, promoted angiogenesis and facilitated wound healing processes [234].

Together with fibroblast growth factors, *bone morphogenetic proteins* (BMPs) and *wingless-type* (Wnt) proteins are involved in the initial specification of cardiac cells. Yoon et al. showed that the combination of BMP-2 with FGF-4 induced myogenic differentiation of MSCs *in vitro*, and that the implantation of MSCs treated with the growth factors enhanced engraftment and myogenic differentiation in infarcted myocardium in rats [235]. BMP-2 has been demonstrated to improve the contractility of individual spontaneously beating cardiomyocytes. Moreover, intravenous injection of BMP-2 in a mouse model of acute MI induced a reduction in cardiomyocyte apoptosis up to 4-fold in the border zone and up to 2-fold in the remote myocardium when compared to negative controls 5 to 7 days after administration [236]. In the case of Wnt, Duan et al. found that Wnt1 and Wnt7a were significantly upregulated after acute cardiac injury. The expression of Wnt1 peaked within 2 days after injury and was sustained at lower levels for two weeks, driving an early repair response in mice myocardial ischaemia [237]. It has been demonstrated that the Wnt1/β-catenin signalling system mediates a pro-fibrotic repair in cardiac fibroblasts after MI. A close correlation of the responsiveness of cardiac fibroblast to Wnt and the temporal pattern of Wnt1 expression after heart injury suggests the role of this pathway during cardiac disease [238].

In addition to its main role in haematopoiesis, erythropoietin (EPO) presents antiapoptotic and pro-angiogenic properties that have shown efficacy against MI in different animal models. In rats, intraperitoneal administration of EPO once every 3 weeks induced new vessel formation associated with enhanced mobilisation, myocardial homing and vascular incorporation of endothelial progenitor cells. Accordingly, VEGF levels increased 4.5-fold in the groups treated with EPO [239]. Kawachi et al. showed that subcutaneous injection of EPO enhanced angiogenesis in pigs following MI by upregulating HGF and FGF systemically and VEGF and IGF in the border and infarct areas [240]. Despite substantial evidence of EPO effectiveness *in vivo*, clinical studies failed to show expected therapeutic efficacy [241]. As suggested by Roubille et al., meta-analysis of the available data from clinical trials could help in assessing the impact of factors such as the route of administration

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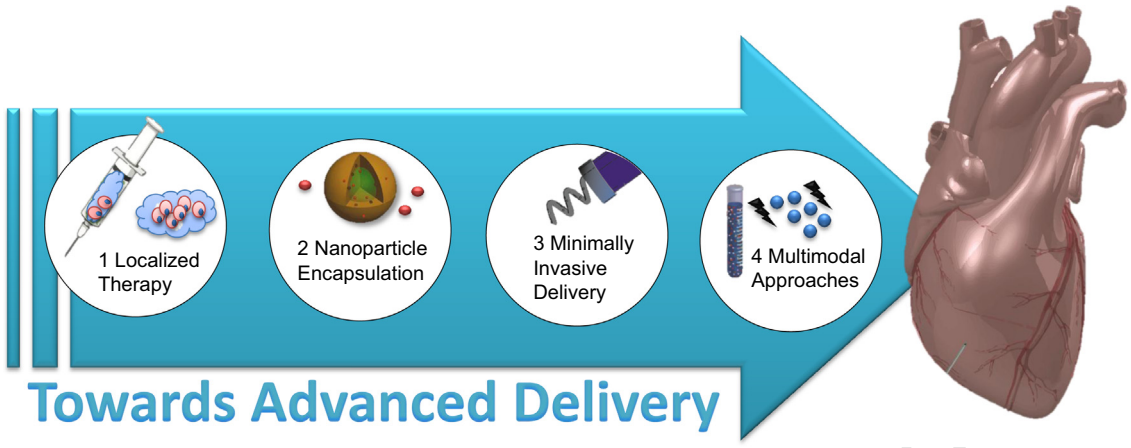

Fig. 4. The case for advanced delivery, as discussed here, is summarised by four main concepts; localised therapy, nanoparticle encapsulation, minimally invasive delivery and multimodal approaches.

or the timing of EPO treatment [242]. To facilitate the clinical translation of the cardioprotective role of EPO found in animals, larger clinical trials with consistent inclusion/exclusion criteria might be needed.

Given increasing knowledge on the different molecular pathways in which growth factors and cytokines are involved and new developments in biopharmaceutical drug combinations to maximise therapeutic potential, enhanced treatment options for cardiac regeneration are expected to occur in the coming years. In addition, the formulation of these therapeutic agents in drug delivery systems will facilitate a safer administration and more effective dosing patterns, leading to improved clinical outcomes.

4. The case for advanced delivery

Regenerative therapy for ischaemic cardiomyopathy is an extremely active area of research and a variety of potential treatment strategies have emerged over recent decades. Cell therapy has arguably progressed furthest towards clinical translation, as evidenced by a significant number of clinical trials, but is still hampered by poor and unpredictable efficacy when implemented in large patient cohorts. Indeed, translation of the positive results achievable in preclinical models has been largely slow and unsatisfactory for all avenues of myocardial regenerative therapy. With this in mind, we elected to review a selection of therapeutic approaches with a particular focus on advanced delivery strategies as a method to enhance efficacy, reduce deleterious effects and aid clinical translation. These concepts are summarised here.

1. Localised therapy in biomaterials — this encompasses the local delivery of therapeutic agents in biomaterial carrier vehicles as opposed to simple systemic delivery. This is of particular importance for cellular payloads where a biomaterial can act to mimic the natural ECM, to enhance survival and provide biological cues for cellular behaviour and fate. In addition, the localised delivery of small molecules or growth factors within a biomaterial matrix permits for sustained release over extended periods to enhance efficacy in target tissues.
2. Nanoparticulate encapsulation — this involves the delivery of therapeutics in a nanoparticulate carrier to reduce interaction with off-target tissues and enhance targeting to the ischaemic myocardium.
3. Multimodal approaches — the concurrent delivery of more than one therapeutic (for example cells with small molecule drugs) can achieve synergistic efficacy. Release of therapeutics from either an implantable biomaterial or nanoparticle system can also be tailored to mimic a biological cascade. For example, sequential release of two or more agents can be utilised to target early and late stage efficacy in a physiological process such as angiogenesis [243].
4. Minimally invasive delivery approaches — percutaneous catheter systems can be utilised to locally deliver therapeutic agents to the heart in a minimally invasive manner, reducing surgical time and cost, and allowing multiple administrations of therapy.

The first two concepts have been addressed in the context of the previous sections and the following section will focus on the latter points, discussing the potential of these delivery approaches in the pursuit of clinical translation and improved treatment outcomes. In particular, we will discuss the potential for multimodal therapeutics primarily involving the combination of cells with an additional co-delivered therapeutic, and the state of the art with regard to minimally invasive catheter delivery to the myocardium.

4.1. Multimodal therapeutic strategies

A multimodal combination of cells with an additional therapeutic agent represents a particularly attractive therapeutic strategy. This approach confers the potential for therapeutic agents to act on co-delivered cells, as well as exert efficacy in target tissues. Co-delivery in a biomaterial carrier can ensure that both cells and a second therapeutic deliverable are kept in close proximity for the duration of therapy to enhance synergistic interaction (Fig. 4). Q22

A number of studies have addressed the potential of co-delivering cells with growth factors to produce therapeutic angiogenesis, which could be of significant utility in the treatment of ischaemic cardiomyopathy. The hindlimb ischaemia model is often used to gauge the potential of a given therapeutic strategy to produce vascular growth. For example, Saif et al. administered PLGA microparticles containing a triple combination of VEGF, HGF and Angiopoietin-1 (Ang-1) alone, human cord blood vasculogenic progenitor cells (ECFCs) alone, or a combination of both, *via* intramuscular injection in a murine hindlimb ischaemia model. Cells or growth factor loaded particles alone produced a modest increase in vascularisation and limb perfusion but a multimodal combination produced a substantial further increase. The biomimetic rationale was to combine two potent pro-angiogenic agents, VEGF and HGF, with a vessel pro-maturation agent, Ang-1. This was proposed to avoid the phenomenon of leaky and poorly functional vessels which can in some cases occur upon treatment with VEGF alone. In an ear tissue leakage assay, the authors showed that administration of VEGF alone produced significantly leaky vessels, which was somewhat ameliorated by co-administration of HGF and significantly reduced by triple administration of VEGF, HGF and Ang-1. The triple combination also produced more vessels than VEGF/HGF co-administration, highlighting the importance of multimodal administration and biomimetic strategies to enhance efficacy [244].

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Table 2
Comparison of commercially available cell injection catheters by access, core needle outer diameter, material and shape.

Device	Manufacturer/research group	Needle shape
Endocardial delivery		
Helix	BioCardia	Helical
MyoCath	Bioheart	Straight, can be deflected
MyoCath II	Bioheart	Weeping
C-Cath®	Cardio3 Biosciences	Curved, large-to-small side holes
Myostar	Bioheart	Straight
Stiletto		Straight
Transvascular		
TransAccess	Medtronic	Curved
Cricket/Bull-Frog	Mercator Medical	Straight, mounted on balloon
Epicardial		
Cell-Fix	Chachques group	Straight, attached to "sucker" fixation system
Intracoronary perfusion		
PTCA devices	Multiple	No needle, cells delivered through guidewire lumen

Multimodal combinations of cells and growth factors have also been investigated in the infarcted myocardium. Dvir et al. investigated the delivery of neonatal rat cardiac cells on an alginate patch containing bound IGF-1, SDF-1 and VEGF to act as a co-delivered pro-survival and pro-angiogenic cocktail. The patch was prevascularised on the omentum before implantation on the infarcted rat heart. Patches containing growth factors demonstrated enhanced vascularisation on the omentum, and prevascularised patches produced greater myocardial regeneration in terms of increase in left ventricular function and reduction in ventricular remodelling, although patches containing no growth factors were not investigated in the infarcted heart [245].

Padin-Iruegas et al. injected self-assembling peptide nanofibres with tethered IGF-1 (NF-IGF-1) alone, rat CPCs (rCPCs) or a combination of both in a rat myocardial infarct model, with the rationale that co-delivered IGF-1 would increase delivered cell survival along with enhancing the regenerative response of resident CPCs. Both CPCs and NF-IGF-1 were injected intramyocardially and NF-IGF-1 facilitated presentation of bioactive IGF-1 for a sustained period. Combination therapy produced greater enhancement in LVEF, increased the presence of newly formed cardiomyocytes (230% compared to NF-IGF-1 alone), and increased infarct vascularisation and reduction in infarct size, with respect to the delivery of cells or IGF-1 nanofibres alone. In addition, combination therapy enhanced the activation of resident CPCs [246].

Takehara et al. administered bFGF in a gelatin hydrogel sheet alone, human cardiosphere derived cells (hCDCs) alone, or a multimodal combination of both to the infarcted porcine myocardium *via* intramyocardial injection (hCDCs) or surgical implantation on the epicardium (hydrogel sheet). Sustained release of bFGF from the gelatin sheet for up to three weeks was achieved. Delivery of bFGF/gelatin alone enhanced myocardial perfusion and LVEF while hCDCs alone enhanced LVEF and reduced infarct volume. Co-delivery of hCDCs and bFGF/gelatin significantly enhanced hCDC engraftment in the myocardium and resulted in synergistic increases in LVEF and reductions in infarct size, compared with delivery of either hCDCs or bGF/gelatin alone. No synergistic effects were observed when bone-marrow-derived hMSCs were co-delivered with bFGF, supporting the hypothesis that cardiac-derived stem cells are likely more suited for cardioregenerative applications [247].

On the basis of these promising results this approach (CSC/bFGF therapy) has progressed to a small Phase I clinical trial, ALCADIA (AutoLogous human CArdiac-Derived stem cell to treat Ischemic cArdiomyopathy) to determine the safety of the approach. Autologous CSCs were administered to patients *via* intramyocardial injection and bFGF/gelatin sheets were implanted epicardially, during bypass surgery. Patients demonstrated increased LVEF and reduced infarct size after the surgical procedure, but in the absence of a control group and as a result of a small patient cohort, definitive conclusions about efficacy were not possible. The trial demonstrated that the approach was safe and feasible and further trials will establish the efficacious potential of this approach [248].

In an interesting acellular hybrid therapy approach Kubota et al. employed an atelocollagen sheet/polyglycolic acid ventricular restraint device (VRD) alone, a small molecule PGI2 agonist ONO1301 on an atelocollagen sheet alone, or a multimodal ONO1301-doped VRD in a canine model of myocardial infarction. At 8-weeks post-infarction hearts treated with the multimodal VRD demonstrated the greatest increase in LVEF, greatest reduction in left ventricular wall stress and ventricular remodelling. All hearts treated with ONO1301 (either alone or in combination with VRD) demonstrated an increase in myocardial vascularisation and upregulation of HGF, VEGF and SDF-1 in the myocardium [249]. In a similar hybrid approach with cells, Shafy et al. showed that the combination of adipose-derived stem cells (injected into the infarct and seeded in a collagen matrix) with a polyester CorCap VRD device resulted in significant improvements in

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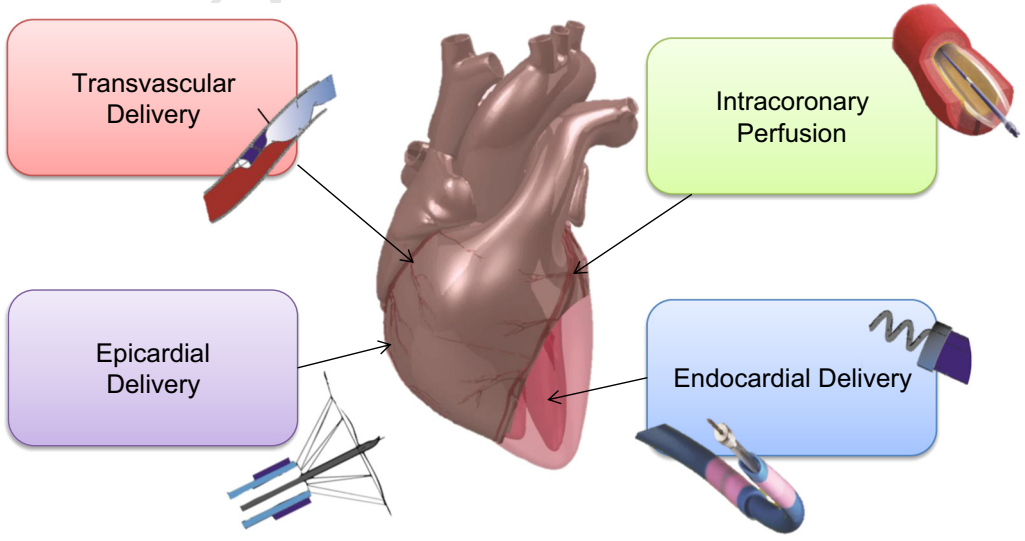

Fig. 5. Current access routes for cell-based therapies to the heart include transvascular delivery, intracoronary perfusion, epicardial delivery and endocardial delivery. An example of a device designed for each delivery route is depicted in this figure.

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ejection fraction, systolic function and diastolic function in a sheep infarct model [250]. This semi-degradable ventricular bioprosthesis approach is an example of biomaterial-mediated cell therapy combined with a constraint device. The CELLWAVE study addressed delivery of BM-MSCs combined with a pretreatment of low energy cardiac shockwave to improve honing of cells and expression of SDF-1 and VEGF. The combination of shock wave with cells resulted in an increase in ejection fraction of 3.2% [251]. Chachques has bioengineered nanobiomaterials with elastomeric membranes to acquire a controlled drug release patch to which they can tailor for local cell attraction and cell differentiation [252].

Multimodal approaches show particular promise for myocardial regeneration. However, the biomedical industry is sometimes reluctant to pursue such therapeutic strategies due to the concern that it could result in a longer regulatory process and consequent delays in bringing a product to market. Multimodal therapeutics can be more difficult to classify and categorise since they involve a variety of therapeutic elements. However, the enhanced potential for improved treatment outcomes and therefore a product with a greater chance of obtaining clinical approval means that multimodal approaches should receive serious consideration for future therapies. This is especially true given the lack of concrete clinical translation in this field to date, despite decades of research, primarily into simplistic treatment approaches involving systemic delivery of single agents or cells. The FDA opened an Office of Combination Products in 2002, specifically to provide guidance to clarify the regulation of combination therapies and to enable timely and effective premarket review of combination products [253]. In addition, preclinical and clinical safety and efficacy data for pre-existing single agent regenerative therapeutics are likely relevant to new combination product applications, reducing the overall regulatory burden.

4.2. Minimally invasive therapy — catheter delivery

It is important that deliverable therapeutic formulations reach the region of the infarcted myocardium where they are most required. The heart resides in the thoracic cavity and in general is accessed *via* highly invasive surgical procedures involving a thoracotomy, contributing to significant costs and patient morbidity. In order to facilitate localised delivery to the myocardium in a minimally invasive way, percutaneous catheter delivery can be employed. Percutaneous catheters are medical devices which generally consist of flexible, hollow tubing and an associated guide wire with a distal 'active' tip which performs an injection. The device can be passed into the vasculature through a small incision, advanced and manipulated *via* a proximal handle, until the tip reaches the therapeutic target.

Catheter delivery of cells alone, typically in a saline carrier, has been more explored than catheter delivery of more advanced materials such as patches or hydrogels, and will be discussed briefly here. The transcatheter cardiac cell delivery field has recently been directed at improving cell retention. In contrast to thoracic surgical injections or patch implantations, transcatheter approaches are less invasive. They allow the effect of cell therapy to be evaluated independently of other surgical procedures, and justify multiple deliveries of cells. The following sections will describe existing delivery systems, their capabilities, and will suggest potential for innovation in areas where suitable devices are not commercially available. For a more detailed insight into current systems the reader is referred to two review papers on this area [254,255]. Several catheter-based access approaches have been used in humans; directly injecting cells into the ventricular wall (epicardial, endocardial and transvascular approaches), and infusing cells into the coronary arteries using existing balloon angioplasty catheters [254,255]. Table 2 and Fig. 5 describe a panel of available devices. The delivery systems differ in their access approach, but share some common features; a low profile core element dedicated to transport cells, which has a bevelled needle to anchor into the myocardium, and outer components to protect the core and deliver it to the infarcted tissue.

The endocardial delivery devices approach the myocardium from inside the ventricle. As for many interventional cardiology catheterizations, they are introduced to the arterial system transfemorally or transradially, guided around the aorta, and through the aortic valve in a retrograde fashion. Catheters are manipulated inside the ventricle by support catheters or steerable designs, and can rely heavily on imaging systems for accurately targeting injection sites at ischaemic areas or the infarct border zone. Transvascular devices approach the myocardium from the epicardial surface. A support catheter is placed through the femoral veins, and tracked around to one of the coronary veins. By using an IVUS (IntraVascular UltraSound) system, the nearby coronary artery and the pericardium can be localised. The coronary vein is then punctured with a small needle, and the injection catheter is passed through this puncture site to the epicardial wall. For epicardial access, the Cell-Fix catheter includes a retractable needle and a polyurethane umbrella shaped suction system which fixes the device to the epicardium when connected to vacuum. This allows stability for penetration and retraction of the injection needle [256]. The goal of intracoronary infusion is to increase the number of cells delivered to the ischaemic myocardium. Vessels are visible by angiography techniques and if cells are injected proximally, they can be distributed to large areas of the myocardium. The method uses established interventional cardiology tools such as Percutaneous Transluminal Coronary Angioplasty (PTCA) devices, where the cells are delivered through the guidewire lumen on removal of the guidewire when the device has been steered through the vasculature to the culprit vessel. Limitations include the fact that large cells in viscous suspensions may not be appropriate due to the risk of obstruction, and cells used must be capable of migrating across the endothelium to perivascular spaces. Furthermore, if patients have chronic total occlusion, this approach is not feasible. PTCA catheters are not designed or approved for cell infusion, and there are no standard tests to compare them for this purpose. Early studies with these devices reported low retention of cells from direct injection, retrograde venous delivery and intracoronary perfusion groups, albeit with slightly higher numbers for the direct injection group [68,257]. More recently, analytical and numerical modelling based on the Darcy Law and transport mass retention has led to optimised needle designs specifically for cell retention [258]. The use of a small-to-large graded side-hole design in a 75° curved Nitinol needle in the C-Cath lessened interstitial pressure during delivery to improve retention and resulted in a significant (>3-fold) increase in cell retention (healthy and infarcted hearts) [258]. While the catheters described here are a huge improvement on simple systemic or invasive local delivery, they are limited in that they are only optimised to deliver a simple saline payload which doesn't facilitate sustained release or cell viability; there is still a need for catheters delivering retentive materials such as injectable hydrogels or epicardial patches.

4.2.1. Catheters for material based approaches

Existing catheter technology may not be appropriate for injecting hydrogels due to considerations such as rapid gelation kinetics, hydrogel viscosity and complications with gelation triggers such as thermal sensitivity or requirements for mixing and incorporation of crosslinking agents immediately prior to injection. Additionally, there is a lack of available devices for catheter-based delivery of preformed scaffolds, patches or cell sheets. For injectable hydrogels, certain catheter design criteria need to be fulfilled to maintain the liquid prepolymer during catheter transit to the injection site, to allow fast gelation *in situ* once the polymer has been injected, and to provide multiple deliveries without issues such as needle blockage. New cyto-compatible catheterized devices such as double-barrel injectors (to mix chemically crosslinked gel precursors with crosslinking agents), cooled catheters (for thermoresponsive gel payloads) and epicardial patch deployment tools are needed. Several preclinical studies have determined the feasibility of delivering injectable hydrogels to the heart using commercially available catheter systems. For example, Leor et al. delivered an alginate

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hydrogel to the coronary vessels in pigs using an injection catheter [149]. Martens et al. determined the optimum viscosity and gelation parameters for a fibrin hydrogel for use with a range of commercially available catheters [109]. Singelyn and Christman determined that an *in-situ* gelling decellularised myocardial matrix was compatible with catheter delivery [91]. Other groups have improved conventional catheters or syringes for their purposes; Kofidis et al. describe a Y-shaped applicator for two syringes where the matrix is contained in one syringe and cell suspension in the other whereby homogeneous mixing occurs on injection [154].

Until now, delivery of patches or scaffolds in preclinical trials has been performed in a surgically invasive manner during open chest procedures. Patches are still largely delivered to the epicardium, due to concerns of embolization upon endocardial deployment. The field of epicardial delivery could learn lessons from other interventional fields, such as that of Total Aortic Valve Replacements (TAVIs) and other procedures using the transapical delivery approach. This access route could be a promising candidate for epicardial material mediated-delivery. In this approach, access to the epicardium is undertaken *via* a mini-thoracotomy and a pericardial incision. Device profile is only limited by the constraints of the pericardial space, therefore design constraints of transapical access catheters are not as limiting as transvascular catheters when delivering a material that requires a higher profile catheter bore. These tangible design targets and the significant amount of research in the evolving field of material based therapy are compelling reasons for innovation in minimally invasive delivery systems for material-based cardiac regenerative therapy. Finally, ventricular restraint devices can be combined with cells, biomaterials or endogenous targeting approaches. Clinical trials have investigated the delivery of cells while patients are receiving left ventricular assist devices (for example the ASSURANCE trial NCT00869024), and the hybrid approach of ventricular unloading with cell delivery has shown promise for improving native cardiac function, allowing removal of mechanical assistance and potentially obviating the need for a heart transplant [259–262]. Future promising work will focus on combining cells with extra-cardiac assist devices for biomaterial-based cell delivery on assist device implantation with multiple follow-ups, consisting of minimally invasive cell administrations (a cell 'top-up' dose) *via* transvascular catheter delivery. Local delivery of biomaterials *via* catheter systems could reduce the time, invasiveness and cost of a given therapeutic procedure while capitalising on the pro-retentive, cytocompatible and sustained release properties of biomaterial therapeutic formulations. Future development of such systems might greatly aid clinical translation of cardiac regenerative strategies.

4.3. Conclusion

Advanced delivery strategies are of the utmost importance in fully realising regenerative therapies for the treatment of ischemic cardiomyopathy. Simple delivery of cells, growth factors or drugs has shown promise, especially pre-clinically. However, clinical translation remains elusive. Physiological and pathological processes in the heart are inherently complex, and consequently more sophisticated therapeutic strategies which fully utilise advanced delivery techniques may be required to enable clinical translation. The preclinical evidence presented in this review suggests that an ideal therapeutic might utilise a combination of the discussed delivery approaches. This strategy might involve minimally invasive catheter delivery of a biomaterial carrier vehicle. The implanted biomaterial bolus should ideally contain a multimodal payload consisting of cardiac-derived stem or progenitor cells combined with biomaterial-encapsulated nanoparticles. Such nanoparticles should facilitate a controlled release of bioactive molecules which exert therapeutic efficacy on co-encapsulated cells and local tissue for sustained periods. Alternatively, bioactive molecules could be free-loaded into the biomaterial matrix, provided a sustained release is possible. The formulation should seek to maximise myocardial retention and uptake. Where possible, the formulation should seek to emulate endogenous biological cues and processes to maximise efficacy, through judicious alteration of design criteria such as duration and sequence of bioactive molecule release, spatial presentation of implanted therapeutics and manipulation of encapsulated cell behaviour and fate. If systemic delivery is required, it should be undertaken using targeted nanoparticles to enhance drug accumulation in myocardial tissue and reduce off target effects.

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