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Review Article

Dare to dream? Cell-based therapies for heart failure after DREAM-HF: Review and roadmap for future clinical study

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ABSTRACT

Clinical trials of cell-based therapies for heart failure have resulted in significant strides forward in our understanding of the potential the failing heart has for regeneration and repair. Yet, two decades on, the need for novel cell-based therapies for heart failure has never been greater. The DREAM-HF trial, which was presented as a late-breaking trial at the American Heart Association Scientific Sessions 2021 did not meet the primary heart failure outcome, but did show a large, clinically significant reduction in major adverse cardiovascular events (MACE) in patients receiving cells, an effect that was most pronounced in patients with evidence of maladaptive inflammation. These results represent an important step forward in our understanding of how cell-based therapies can exert beneficial effects in patients with heart failure and should serve as a guide for future clinical efforts. In light of the results of DREAM-HF, this review serves to provide an understanding of the current state of cell-based therapies for heart failure, as well as to highlight major knowledge gaps and suggest guiding principles for clinical trials of cell therapy going forward. Using the knowledge gained from DREAM-HF along with the trials that preceded it, the potential for breakthrough cell-based therapies for heart failure in the coming decade is immense.

1. Introduction

Two decades of basic, translational, and clinical research of cell therapy for heart failure (HF) [1–3], have yielded significant advancements in our understanding of the heart's capacity for repair, and serve to emphasize that the need for novel therapies for HF has never been greater. Heart disease remains a leading cause of death worldwide, and HF in particular is an increasing source of morbidity and mortality that consumes enormous health care resources [4]. Improvements have been made over the last decade in the pharmacologic and device management of HF, particularly with the introduction of sucabitril/valsartan (Entresto) and the SGLT-2 inhibitors, but even the most beneficial of these therapies merely serve to help the failing heart adapt and compensate for dysfunction. There remains no therapy available that can replace damaged myocardium and truly restore cardiac function after injury [5]. It is this unmet need that stimulated the initial interest in cell therapy for HF, and drives current efforts to deliver on the promise regenerative therapies hold.

At the American Heart Association Scientific Sessions 2021 the results of the phase III DREAM-HF clinical trial, which investigated mesenchymal precursor cells (MPCs) for patients with symptomatic heart failure with reduced ejection fraction (HFrEF), were presented [6,7]. Although the study did not meet the primary endpoint of reducing hospital admissions or HF severity, there was a signal of reduced major adverse cardiovascular events (myocardial infarction and stroke) that was most pronounced in patients with evidence of maladaptive inflammation, as assessed by high sensitivity C-reactive protein (hsCRP). These provocative results may usher in new directions for the field of cell-based regenerative therapies in the coming decade. Here we seek to a) provide a brief review of the current state of cell therapy for HF, including cells and cell-derived products, b) highlight knowledge gaps, and c) propose guiding principles for clinical investigation of these

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therapies going forward.

2. Major cell types used or poised for use in clinical trials of heart failure

2.1. Hematopoietic cells

Bone marrow derived cells, including bone marrow mononuclear cells (BMMCs), mesenchymal stem cells (MSCs), MPCs, and subsets of these cells are the most studied in patients with now over 40 randomized clinical trials including more than 2000 participants enrolled in studies of ischemic heart disease and HF [8–15] (see Table 1). Across clinical trials these cells have shown to be safe, although efficacy results are mixed. Some studies have shown significant benefit, including the randomized, placebo-controlled ixCELL-DCM study of percutaneous intramyocardial injection CD90+ MSCs and CD45+ macrophages, which met its primary endpoint by reducing adverse cardiac events in patients with ischemic HF by 37% compared to placebo ($p = 0.034$) [13], and the randomized placebo-controlled MSC-HF trial of intramyocardial injection of bone-marrow derived MSCs, which showed significant improvement in ejection fraction ($p < 0.0001$) and end systolic volume ($p < 0.0002$) compared to placebo [14]. But other prominent trials, including the CHART-1 study of conditioned MSCs delivered by intramyocardial injection in patients with ischemic cardiomyopathy, were neutral overall [15].

While early studies were based on the premise that bone marrow-derived cells had the ability to form new cardiac tissue (i.e. cardiac myocytes, vasculature, and connective tissues), it is now understood that these cells exert beneficial paracrine effects primarily via release of factors including: cytokines, growth factors, micro-vesicles, and miRNA, which serve to limit maladaptive inflammation (as seen in DREAM-HF), reduce cell death after injury, promote angiogenesis, and enhance endogenous tissue repair [2,16,17].

It should also be noted that the majority of clinical trials using bone marrow-derived cells have been performed using autologous cells, which has advantages in terms of limiting the chance of adverse immune reaction and sensitization following cell delivery to the heart. However, many patients who suffer from HF have conditions such as diabetes, hypertension, smoking, aging and frailty that may impact the therapeutic potential of their own cells [18]. Indeed, numerous studies have shown that patients who benefit most from bone marrow derived cells are those with higher expression of CD34 and other markers that suggest a more robust cell population [19]. Newer generation cell trials, particularly the CardiAMP Heart Failure Trial, include a cell potency assay which is used to select a subset of patients who, based on prior studies, may be more responsive to BMMC therapy [20,21].

2.2. Cardiac-derived cells

The two main types of cardiac-derived cells used in clinical trials of HF are C-kit+ cells [22] and cardiosphere-derived cells (CDCs) [23,24]. Both cell types are isolated from cardiac tissue obtained via endomyocardial biopsy or surgical specimens. Clinical studies investigating c-kit+ cells have largely been abandoned after some of the basic research studies supporting their use were withdrawn [25]. Unfortunately, this controversy impacted the CONCERT-HF trial, which was the first clinical trial to compare the effects of two different cell types (allogenic MPCs and c-kit+ cells) in patients [26]. After doubts arose about the veracity of the original basic science studies regarding c-kit+ cells, study enrollment was limited to 125 patients, making the trial underpowered. The final results of CONCERT nevertheless demonstrated that both CPCs and MPCs were associated with improvement in clinical outcomes (MACE and quality of life), albeit without improvement in LV function.

CDCs have now been used in multiple clinical trials of ischemic cardiomyopathy following acute myocardial infarction (MI). In the phase I/II CADUCEUS Trial autologous CDCs delivered by intracoronary infusion resulted in significant reduction in scar size as compared to control patients who received standard of care medical therapy [24]. Isolation and expansion of autologous CDCs was not scalable, however, and in the subsequent phase III ALL-STAR trial allogenic CDCs obtained from cadaver hearts were used. Allogeneic CDCs did not show the same beneficial effect in terms of scar-size reduction, although there was a significant reduction in post MI adverse ventricular remodeling [27]. There is now compelling evidence, however, of benefit of CDCs in patients with cardiomyopathy secondary to Duchenne's muscular dystrophy (DMD). The phase I/II HOPE trial randomized patients with DMD to intracoronary infusion of allogenic CDCs versus standard of care. Those patients receiving CDCs showed a significant reduction in cardiac fibrosis by MRI and a significant improvement in skeletal muscle function [28]. In animals, many of the beneficial effects observed in the HOPE trial can be recapitulated by CDC-derived exosomes, suggesting that the beneficial effects of CDCs, similar to bone marrow-derived cells, are not due primarily to the cells themselves, but instead the factors CDCs release [29].

2.3. Induced-pluripotent and embryonic stem cells

Induced pluripotent stem cells (iPSCs) and embryonic stem cells

Table 1
Cells and cell-derived products for heart failure.

Cell type	Sub-types	Clinical trial data	Notable trials	Observed effects
Hematopoietic (bone marrow-derived) cells	- Bone marrow mononuclear cells - Mesenchymal precursor cells - CD34+ cells	- Extensive; >40 trials, >2000 patients randomized	- REPAIR-AMI [59,61] - BAMI [63] - FOCUS-CCTRN [56] - ixCELL-DCM [13] - DREAM-HF [6,7] - CardiAMP-HF [20,21] (enrolling)	- Reduction in major adverse cardiovascular events (MACE; REPAIR-AMI, ixCELL-DCM, DREAM-HF) - Higher CD34+ concentration associated with improved clinical outcomes (FOCUS-CCTRN)
Cardiac-derived cells	- Cardiosphere-derived cells (CDCs) - C-kit+ cells	- Numerous clinical trials	- CADUCEUS [24] - SCIPIO [22] - ALL-STAR [27] - CONCERT-HF [58] - HOPE-Duchenne	- Myocardial scar size reduction (CADUCEUS, HOPE-Duchenne) - Reduction in adverse remodeling (ESV, EDV) and pro-BNP levels (ALL-STAR) - Improvement in MACE (CONCERT-HF)
Induced pluripotent cells (iPSCs)	- iPSC-derived cardiac myocytes (CM)	- Early stage	- iPS Cell-Derived Cardiomyocyte Sheet for ischemic Cardiomyopathy (enrolling)	- TBD
Embryonic stem cells	- ESC-derived CM	- Early stage	- ESCORT [35] - HECTOR (to start 2022)	- ESC-derived CMs safe at 1 year when surgically implanted in fibrin sheet
Cell-derived products				
Extracellular vesicles	- Exosomes	- None to date	- n/a	- n/a
Micro RNA (miR)	- Numerous	- Early stage	- Anti-miR-92a [44] - Anti-miR-132 [45]	- Well-tolerated with dose dependent reduction of target miR

(ESCs) have the potential to allow for production of large numbers of exogenous cardiomyocytes that theoretically could be used to replace damaged myocardium [30]. Unlike bone marrow and cardiac-derived cells, which exert beneficial effects primarily by the factors they produce, iPSC-CMs have the potential to form new contractile myocardium that could directly contribute to improve cardiac function. Work in pigs and non-human primates have shown that large numbers of iPSC-CMs may be implanted in the heart for up to 3 months with significant improvements in ejection fraction and other measures of cardiac function [31,32]. Similar efforts using cardiac myocytes derived from human embryonic stem cells (hESC) have shown large numbers of immature cardiac myocytes derived from hESCs (up to 1 billion) can be transplanted into the hearts of non-human primates after MI with significant improvement in contractile function over 3 months [33,34]. Importantly, while in the first month after implant of ESC-derived CMs in primates there was a significant burden of ventricular arrhythmia, this resolved over time as the implanted cells matured and became electrically-coupled. In each case, animals were treated with immunosuppressants to prevent rejection, and use of allogenic iPSC-derived or ESC-derived cardiomyocytes immunosuppression will almost certainly be required, a potential limitation to this approach. Also, while use of iPSCs could in theory allow for use of autologous CMs, similar to autologous CDCs, this process would entail significant time and cost in order to generate patient-specific iPSC-derived CMs in sufficient numbers (~1 billion) needed to generate a beneficial effect.

To date, clinical trial data in the use of ESC and iPSCs in the heart is limited, however, a feasibility study of surgical implantation of human ESCs incorporated in a fibrin patch in patients with ischemic cardiomyopathy did show the short term safety of this approach [35]. A phase 1 trial of iPSC-derived cardiomyocytes, also deployed as a sheet and implanted during surgery, is under way in Japan (NCT04696328). The first trial in the United States using cardiomyocytes derived from ESCs, the phase 1 Human Embryonic Stem Cell-Derived Cardiomyocyte Therapy for Chronic Ischemic Left Ventricular Dysfunction (HECTOR) Trial (NCT05068674), will start in early 2022 using intramyocardial delivery with the NOGA catheter. In all of these trials, participants are treated with immunosuppressant therapy to prevent rejection.

3. Cellular-derived therapeutics

3.1. Microvesicles

Exosomes and other micro-vesicles are membrane-bound subcellular particles used for intra-cellular communication. Their contents include growth factors, cytokines, and miRNAs, which can exert biologic effects on cells in which they are received [36]. Exosomes are known to be released by bone marrow-derived cells, particularly MPCs, and by other cells including CDCs, ESCs, and iPSCs [36–38]. CDC-derived exosomes have been shown to recapitulate many of the beneficial effects of CDCs when delivered to the heart after MI in large animal models [39]. In addition, CDC-derived exosomes have shown promise in treating cardiomyopathy secondary to DMD-associated cardiomyopathy in animal and human models [40]. A major attraction of exosomes and other micro-vesicles is that they could be manufactured similar to a drug, and due to limited immunogenicity, could in theory be used as an allogeneic "off-the-shelf" therapy. Still, questions remain in terms of delivery method, how often exosomes would need to be delivered to achieve a sustained clinical effect, and to what extent their contents could be designed ex vivo to achieve an optimal therapeutic potency [36].

3.2. miRNA

One of the major components of exosomes are micro RNA (miRNA), a class of non-coding RNA, which serve as intra-cellular signaling molecules by regulating gene expression at the mRNA level [41–43]. miRNA can serve to either enhance or inhibit expression of a target gene(s) to generate a downstream therapeutic effect. Basic and translational studies have shown promise through targeting the downstream effects of myocardial injury, for instance by promoting angiogenesis and inhibiting maladaptive fibrosis to limit HF progression after MI [42]. Two early-phase clinical trials of miRNA-based therapeutics relevant to cardiovascular disease have been published to date, the first designed to target miR-92a, which regulates angiogenesis and wound healing [44]. The second used an anti-sense olidonucleotide designed to inhibit expression of miR-132, which is upregulated in HF and contributes to adverse remodeling. The authors of the latter study observed that therapy significantly reduced circulating miR-132 levels and resulted in a small decline in NT-proBNP levels and QRS duration compared to placebo [45]. Similar to microvesicles, challenges remain in terms of efficient delivery of miRNA to the heart and other organs, potential need for repeat dosing, and prevention of off-target effects, but the broad appeal of miRNA is that specific oligonucleotide particles, or combinations of particles, could be administered similar to a drug, potentially with a measurable, dose-dependent effect.

4. Major knowledge gaps in cell-based therapy for the heart

While there has been an immense amount of research effort invested in bringing cell-based therapies for HF to clinical trials, a major criticism over the last two decades has been the early introduction of large-scale clinical trials despite a lack of fundamental understanding regarding mechanism of action. Many argue that unmet clinical needs in HF justified the rush, but as a result, 20 years later, there remain important knowledge gaps that must be addressed if cell-based therapies are to mature into proven clinical therapies for HF.

4.1. Lack of understanding of mechanism of action

The early belief that bone marrow- and cardiac-derived cells could generate new myocardial tissue following delivery to the heart has been abandoned. Yet, despite a lack of new tissue formation, delivery of bone marrow-derived cells to the heart has been shown to exert beneficial effects, both after MI and in HF [8,9,12]. The observed beneficial effects are now largely attributed to paracrine effects, i.e. those resulting from the release of soluble factors and exosomes by delivered cells to restore function to damaged, but viable cardiomyocytes. This belief has in turn led to enthusiasm for delivery of these soluble factors alone, without cells. In the case of CDCs there is growing evidence that their beneficial effects in ischemic heart disease and DMD may be re-capitulated using CDC-derived exosomes [39,40]. In theory, there may be an advantage to delivering cells, which have the ability to deliver a spectrum of different factors and vary their release based on the conditions at the site of injury (assuming the cells survive following delivery) [46]. There is more recent evidence that the intramyocardial injection of an immunogenic compound alone replicates the beneficial effects of hematopoietic cells in a mouse model of MI [47]. This uncertainty over whether cell delivery has benefit over paracrine factors or other agents alone, persists because at a basic level, there remains an incomplete understanding of how cell-based therapies exert beneficial effects in patients.

Nowhere was this more evident than in the DREAM-HF Trial designed with the expectation that intra-myocardial allogeneic MPCs (alloMPCs) would improve HF outcomes compared to controls placebo. In results reported as a Late-Breaking Clinical Trial at the 2021 American Heart Association Scientific Sessions [7] there was 60% reduction ($p = 0.002$) in non-fatal ischemic major adverse cardiac events (MACE) due to MI or stroke in patients receiving alloMPCs compared to controls in the total population ($n = 537$). MACE reduction was consistent across both the NYHA class II or III cohorts regardless of an ischemic or non-ischemic HF etiology. Also, in NYHA class II patients ($n = 206$) CV death was reduced by 60% in participants receiving alloMPCs relative to controls ($p = 0.037$), again in both the ischemic and non-ischemic HF

cohorts. This effect was substantially greater than that observed in PARADIGM-HF, in which participants receiving sacubitril/valsartan had a 20% relative reduction in CV death compared to controls [48].

Importantly, the beneficial effect of alloMPCs was most pronounced in patients with evidence of maladaptive inflammation (hs-CRP $\geq$ 2 mg/dL), in whom MIs and stroke were reduced by 79% ($p < 0.001$). These findings suggest an important mechanism of action is the anti-inflammatory effect of MPCs, but perhaps more importantly, these effects are systemic and not limited to their site of delivery in the heart. The results of DREAM-HF in this way mirror the prior Cardiothoracic Surgical Trials Network studies of intramyocardial MPCs in left ventricular assist device (LVAD) patients [49,50]. Like DREAM-HF, there was no significant difference in the primary outcome, the ability to wean patients from LVAD support in patients receiving MPCs compared to controls, but control patients had a significantly higher rate of gastrointestinal bleeding, a common complication in LVAD patients that is attributed to mucosal inflammation. In this way, while both DREAM-HF and the prior LVAD studies were disappointments in terms of HF outcomes, the results of these studies together provide an important contribution to our understanding of how MPCs can exert beneficial effects in HF and cardiovascular disease in general. Understanding this mechanism of action should lead to more targeted studies in the future, targeting HF patients with evidence of maladaptive inflammation to limit adverse clinical events.

Lastly, while most cell therapy trials to date have focused on patients with HFrEF, elevated inflammatory markers are present in many patients with HF with preserved ejection fraction (HFpEF) [51,52] and patients with arrhythmogenic cardiomyopathy [53]. The results of DREAM-HF suggest those patients with HFpEF and other cardiomyopathies could potentially benefit from MPC therapy as well.

4.2. Patient and cell selection

Along with better understanding of mechanisms of action, it is critical to understand why some patients appear to respond to cell-based therapies better than others. For example, prior clinical trials of BMMCs for ischemic HF have identified the relative presence of CD34+ cells as a biomarker associated with favorable outcomes [21,54,55]. One interpretation of these results is that CD34+ cells are the therapeutically relevant cell fraction, and a higher dose results in a more potent effect. However, there is also evidence from the FOCUS-CCTRN trial that bone marrow characteristics can predict favorable outcomes in chronic HF patients regardless of whether they receive cell therapy [56]. The latter data suggests that the bone marrow CD34+ concentration may be a biomarker reflective of healthier, more robust bone marrow, which in turn may reflect a healthier, less frail patient. It is this reason that novel trials such as CardiAMP-HF, which is using BM cell characteristics as screening criteria for study enrollment [20,21], will be critical to closing existing knowledge gaps regarding patient selection. Ideally, data gleaned from CardiAMP-HF and FOCUS-CCTRN regarding BM characteristics will be paired with data from DREAM-HF regarding inflammatory markers to begin to generate biomarker profiles that could be used to prospectively identify HF patients who stand to benefit most from cell-based therapies.

Lastly, it will be important to determine if the beneficial effects observed in DREAM-HF are specific to MPCs, or whether other cell types, particularly CDCs, can exert a similar effect. Few clinical trials have compared different cell types, but in the TAC-HFT Trial, which compared intramyocardial BMMCs with MSCs [57], and in CONCERT-HF, which compared MSCs with C-kit+ cells [58], there were signals suggesting differences in efficacy end points between cell types. Understanding these differences could help guide cell selection (e.g., MPCs vs CDCs vs selected-BMMCs, etc.) to maximize potential benefit based on the specific condition to be treated.

4.3. Is there any role for cell-based therapies heart failure due to acute MI?

Early studies suggested that intracoronary delivery of BMMCs after MI could improve LV function, reduce adverse remodeling, and limit adverse clinical events [59–62], however, subsequent larger trials showed no significant benefit [63]. One limitation is that with near universal adoption of rapid percutaneous revascularization of STEMI patients, survival has markedly improved after MI, making it difficult to show a survival benefit over standard of care [64]. Yet, subgroups of MI patients who present late, have significant microvascular obstruction, receive incomplete revascularization, or suffer cardiogenic shock, experience rampant maladaptive inflammation and cell death in the infarct zone, which lead to adverse remodeling and HF, and thus are appealing targets for cell-based therapies. While there is theoretical concern that poor survival of intact cells delivered to the recently infarcted heart limits their ability to exert a beneficial effect [59,65,66], recognition of the is anti-inflammatory and anti-apoptotic effects of exosomes and miRNA suggests that clinical studies are needed to establish whether there is a role for cell-derived therapeutics in patients with acute HF after MI. Cell therapies, in particular use of ESC or iPSC-derived cardiac myocytes, could then be reserved for those patients found to have significant left ventricular dysfunction and scar burden in the sub-acute or chronic phase after MI. Similar questions could be asked of cell-derived therapies in acute HF exacerbations, arrhythmias, and other clinically important events, particularly those associated with maladaptive inflammation. Establishing a new therapeutic paradigm using cell-derived therapies, however, will require understanding of the optimal use and timing of different therapies and which patients stand to benefit most, both critical knowledge gaps to be addressed going forward.

4.4. Dosing and retention considerations in cardiac cell therapy

A particularly vexing problem for cell-based cardiac repair is poor intramyocardial retention of investigational cell and cell-derived therapies. Investigators have attempted to overcome low short term retention in animal studies and early human trials through a number of approaches: a) using very high cell doses, which may be impractical in patients [34], b) repeat dosing [67], c) injecting cells using delivery catheters designed to enhance cell retention [68], and d) co-administering cells with retention agents including fibrin, extracellular matrices, and hydrogels that are injected into, or applied to the epicardium, to improve cell retention [69–71]. Determining the best of these agents and optimizing the delivery method will be important to optimize cell-based therapies, but also will be important in the sustained delivery of cell-derived products (micro-vesicles, exosomes, mRNA).

5. Guiding principles for cell therapy trials going forward

Regaining momentum for cell-based therapies to address unmet clinical needs in HF and heart disease in general will require dedication to basic scientific principles and focus on clinical outcomes that matter to patients. Important pillars of the way forward include:

5.1. Novel clinical trials designed to close knowledge gaps

A challenge of translating cell therapy for the heart from bench to bedside is that animal models do not fully replicate clinical HF and thus promising pre-clinical results often do not translate to patients. Despite variable efficacy, bone-marrow and cardiac-derived stem cells are consistently safe, providing some latitude for design of novel clinical trials designed to rapidly assess for efficacy. Similar to the approach championed by the NIH-run Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, smaller, more nimble clinical trials could allow for rapid evaluation of a broader

range of potential therapies, with the goal being abandonment of those with no obvious benefit so that others may be tried. In this paradigm, "silo" studies in which a single cell type or therapeutic is tested could be avoided in favor of studies designed to compare the relative effects of different cell types and products to one another (or combinations thereof) [3]. This will be particularly important to answer whether there is any advantage in delivering intact cells as opposed to the exosomes, miRNA, and other factors that cells release. Lastly, too many clinical trials of cell-based therapies for HF have been conducted without rigorous controls. Inclusion of placebo arms, particularly those that address the question whether the delivery method itself can result in significant biologic effects, are essential.

5.2. Differentiating applications for acute and chronic heart failure

Acute HF and chronic HF are manifestations of the same disease process, but represent disparate ends of the spectrum in terms of the underlying pathophysiology. For example, in acute HF after MI, therapies focused on addressing maladaptive inflammation and limiting unnecessary cell death will presumably be important, but chronic ischemic cardiomyopathy will ultimately require applications that can also repair or replace scar tissue with functional myocardium. Expecting that one particular cell-based therapy can address the full spectrum of HF is optimistic at best, and naïve at worst. The need to treat the full course of HF highlights will require breaking down research silos and investment in investigations designed to evaluate multi-faceted biologic therapies to achieve an optimal clinical effect.

5.3. Focus on clinical endpoints

While ejection fraction, change in left ventricular end diastolic volume, and myocardial scar size are important phenotypic outcomes, what matters most to patients are clinical endpoints: survival, protection from MI and stroke, time spent out of the hospital, and quality of life. The mainstays of medical therapy for HF, including ACE inhibitors, beta-blockers, statins, and defibrillators, have all been shown to have benefit in terms of survival, reduction in hospitalizations, and other hard clinical end points. For cell-based therapies to join these proven treatments, they must be held to the same high standards. While most early HF cell therapy trials focused on phenotypic and structural outcomes: LVEF, LV volumes, etc., often to disappointing results, the results of DREAM-HF, ixCELL-DCM, and other trials have shown significant clinical benefits can be achieved without structural improvement(s). Ultimately, clinical outcomes are most important to patients and their providers, and clinical trials of cell-based therapies should be refocused and designed to with these outcomes in mind.

6. Conclusion

In the last two decades significant strides were made in bringing cell-based biologic therapies for HF closer to reality. While such therapies at this point remain aspirational, by harnessing the knowledge gained over the last two decades along with renewed focus on mechanism of action, identification of patients who stand to benefit most, and multi-faceted biologic therapies designed to address the full continuum of HF, the potential for important therapeutic breakthroughs in the coming two decades is enormous.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Authors PVJ, ANR, JHT, and CJP are members of the Executive Steering Committee for the CardiAMP Heart Failure Trial and have received consultancy fees and/or grant support for their activities from BioCardia, Inc., the trial sponsor.

References

[1] H. Hashimoto, E.N. Olson, R. Bassel-Duby, Therapeutic approaches for cardiac regeneration and repair, Nat. Rev. Cardiol. 15 (10) (2018) 585–600, https://doi.org/10.1038/s41569-018-0036-6, 10.

[2] J. Zhang, R. Bolli, D.J. Garry, et al., Basic and translational research in cardiac repair and regeneration: JACC state-of-the-art review, J. Am. Coll. Cardiol. 78 (21) (2021) 2092–2105, https://doi.org/10.1016/j.jacc.2021.09.019.

[3] F. Fernández-Avilés, R. Sanz-Ruiz, A.M. Climent, Global position paper on cardiovascular regenerative medicine, Eur. Heart J. 38 (33) (2017) 2532–2546, https://doi.org/10.1093/eurheartj/ehx248, 09 01.

[4] S.S. Virani, A. Alonso, H.J. Aparicio, et al., Heart disease and stroke Statistics-2021 update: a report from the American Heart Association, Circulation 143 (8) (2021) e254–e743, https://doi.org/10.1161/CIR.0000000000000950.

[5] E. Marbán, A phoenix rises from the ashes of cardiac cell therapy, Nat. Rev. Cardiol. 18 (11) (Nov 2021) 743–744, https://doi.org/10.1038/s41569-021-00625-1.

[6] K.M. Borow, A. Yaroshinsky, B. Greenberg, E.C. Perin, Phase 3 DREAM-HF trial of mesenchymal precursor cells in chronic heart failure, Circ. Res. 125 (3) (2019) 265–281, https://doi.org/10.1161/CIRCRESAHA.119.314951, 07 19.

[7] E.C. Perin, The DREAM-HF trial results, late-breaking clinical trials, American Heart Association Scientific Sessions, November 14, in: American Heart Association Scientific Sessions. November 14, 2021.

[8] S.A. Fisher, C. Doree, A. Mathur, D.P. Taggart, E. Martin-Rendon, Stem cell therapy for chronic ischaemic heart disease and congestive heart failure, Cochrane Database Syst. Rev. 12 (2016), CD007888, https://doi.org/10.1002/14651858.CD007888.pub3, 12 24.

[9] R. Diaz-Navarro, G. Urrútia, J.G. Cleland, Stem cell therapy for dilated cardiomyopathy, Cochrane Database Syst. Rev. 7 (2021), CD013433, https://doi.org/10.1002/14651858.CD013433.pub2, 07 21.

[10] M.M. Lalu, S. Mazzarello, J. Zlepnig, Safety and efficacy of adult stem cell therapy for acute myocardial infarction and ischemic heart failure (SafeCell Heart): a systematic review and meta-analysis, Stem Cells Transl. Med. 7 (12) (2018) 857–866, https://doi.org/10.1002/sctm.18-0120, 12.

[11] S.H. Lee, J.H. Hong, K.H. Cho, J.W. Noh, H.J. Cho, Discrepancy between short-term and long-term effects of bone marrow-derived cell therapy in acute myocardial infarction: a systematic review and meta-analysis, Stem Cell Res Ther 7 (1) (2016) 153, https://doi.org/10.1186/s13287-016-0415-z, 10 20.

[12] S.A. Fisher, C. Doree, A. Mathur, E. Martin-Rendon, Meta-analysis of cell therapy trials for patients with heart failure, Circ. Res. 116 (8) (Apr 2015) 1361–1377, https://doi.org/10.1161/CIRCRESAHA.116.304386.

[13] A.N. Patel, T.D. Henry, A.A. Quyyumi, et al., Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial, Lancet 387 (10036) (2016) 2412–2421, https://doi.org/10.1016/S0140-6736(16)30137-4.

[14] A.B. Mathiasen, A.A. Qayyum, E. Jørgensen, Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial, Eur. J. Heart Fail. 22 (5) (2020) 884–892, https://doi.org/10.1002/ejhf.1700, 05.

[15] J. Bartunek, A. Terzic, B.A. Davison, et al., Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial, Eur. Heart J. 38 (9) (2017) 648–660, https://doi.org/10.1093/eurheartj/ehw543.

[16] M. Gnecchi, Z. Zhang, A. Ni, V.J. Dzau, Paracrine mechanisms in adult stem cell signaling and therapy, Circ. Res. 103 (11) (Nov 2008) 1204–1219, https://doi.org/10.1161/CIRCRESAHA.108.176826.

[17] M.N. Banerjee, R. Bolli, J.M. Hare, Clinical studies of cell therapy in cardiovascular medicine: recent developments and future directions, Circ. Res. 123 (2) (2018) 266–287, https://doi.org/10.1161/CIRCRESAHA.118.311217, 07 06.

[18] P.V. Johnston, H.J. Duckers, A.N. Raval, T.D. Cook, C.J. Pepine, Not all stem cells are created equal, Circ. Res. 123 (8) (2018) 944–946, https://doi.org/10.1161/CIRCRESAHA.118.313425, 09.

[19] P.K. Kresnik, M. Krasna, P. Rozman, B. Vrtovec, E. Malicev, Collection and immunoselection of CD34+ cells: the impact of age, sex, and diabetes in patients with chronic heart failure, Transfusion 56 (7) (2016) 1792–1800, https://doi.org/10.1111/trf.13646, 07.

[20] A.N. Raval, T.D. Cook, H.J. Duckers, The CardiAMP heart failure trial: a randomized controlled pivotal trial of high dose autologous bone marrow mononuclear cells using the CardiAMP cell therapy system in patients with post myocardial infarction heart failure: trial rationale and study design, Am. Heart J. 201 (2018) 141–148.

[21] A.N. Raval, P.V. Johnston, H.J. Duckers, Point of care, bone marrow mononuclear cell therapy in ischemic heart failure patients personalized for cell potency: 12-month feasibility results from CardiAMP heart failure roll-in cohort, Int. J. Cardiol. 326 (2021) 131–138, https://doi.org/10.1016/j.ijcard.2020.10.043, 03 01.

[22] R. Bolli, A.R. Chugh, D. D'Amario, Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial, Lancet 378 (9806) (2011) 1847–1857, https://doi.org/10.1016/S0140-6736(11)61590-0, 11 26.

[23] R.R. Smith, L. Barile, H.C. Cho, et al., Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens, CIRCULATIONAHA.106.655209 [pii], Circulation 115 (7) (2007) 896–908, https://doi.org/10.1161/CIRCULATIONAHA.106.655209.

[24] R.R. Makkar, R.R. Smith, K. Cheng, et al., Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial, Lancet 379 (9819) (Mar 2012) 895–904, https://doi.org/10.1016/S0140-6736(12)60195-0.

[25] Expression of concern, 01 15, Circulation 139 (3) (2019), https://doi.org/10.1161/CIR.0000000000000639. e5-e6.
[26] R. Bolli, J.M. Hare, K.L. March, Rationale and design of the CONCERT-HF trial (combination of mesenchymal and c-kit, Circ. Res. 122 (12) (2018) 1703–1715, https://doi.org/10.1161/CIRCRESAHA.118.312978, 06 08.
[27] R.R. Makkar, D.J. Kereiakes, F. Aguirre, Intracoronary ALLogeneic heart STem cells to Achieve myocardial Regeneration (ALLSTAR): a randomized, placebo-controlled, double-blinded trial, Eur. Heart J. 41 (36) (2020) 3451–3458, https://doi.org/10.1093/eurheartj/ehaa541, 12.
[28] M. Taylor, J. Jefferies, B. Byrne, Cardiac and skeletal muscle effects in the randomized HOPE-Duchenne trial, 02 19, Neurology 92 (8) (2019), https://doi.org/10.1212/WNL.0000000000006950. e866-e878.
[29] R.G. Rogers, M. Fournier, L. Sanchez, Disease-modifying bioactivity of intravenous cardiosphere-derived cells and exosomes in mdx mice, JCI Insight 4 (7) (2019), https://doi.org/10.1172/jci.insight.125754, 04 04.
[30] K. Nakamura, C.E. Murry, Function follows form - a review of cardiac cell therapy, Circ. J. 83 (12) (2019) 2399–2412, https://doi.org/10.1253/circj.CJ-19-0567, 11 25.
[31] Y. Shiba, T. Gomibuchi, T. Seto, et al., Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts, Nature 538 (7625) (2016) 388–391, https://doi.org/10.1038/nature19815.
[32] K. Suzuki, S. Miyagawa, L. Liu, Therapeutic efficacy of large aligned cardiac tissue derived from induced pluripotent stem cell in a porcine ischemic cardiomyopathy model, J. Heart Lung Transplant. 40 (8) (2021) 767–777, https://doi.org/10.1016/j.healun.2021.04.010, 08.
[33] J.J. Chong, X. Yang, C.W. Don, et al., Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts, Nature 510 (7504) (2014) 273–277, https://doi.org/10.1038/nature13233.
[34] Y.W. Liu, B. Chen, X. Yang, Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates, Nat. Biotechnol. 36 (7) (2018) 597–605, https://doi.org/10.1038/nbt.4162, 08.
[35] P. Menasché, V. Vanneaux, A. Hagège, Transplantation of human embryonic stem cell-derived cardiovascular progenitors for severe ischemic left ventricular dysfunction, J. Am. Coll. Cardiol. 71 (4) (2018) 429–438, https://doi.org/10.1016/j.jacc.2017.11.047, 01 30.
[36] C. Han, J. Yang, J. Sun, G. Qin, Extracellular vesicles in cardiovascular disease: biological functions and therapeutic implications, Pharmacol. Ther. (2021), 108025, https://doi.org/10.1016/j.pharmthera.2021.108025, 08.
[37] L. Bagno, K.E. Hatzistergos, W. Balkan, J.M. Hare, Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges, Mol. Ther. 26 (7) (2018) 1610–1623, https://doi.org/10.1016/j.ymthe.2018.05.009, 07 05.
[38] L. Barile, T. Moccetti, E. Marbán, G. Vassalli, Roles of exosomes in cardioprotection, Eur. Heart J. 38 (18) (2017) 1372–1379, https://doi.org/10.1093/eurheartj/ehw304.
[39] R. Gallet, J. Dawkins, J. Valle, Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction, Eur. Heart J. 38 (3) (2017) 201–211, https://doi.org/10.1093/eurheartj/ehw240, 10 20.
[40] M.A. Aminzadeh, R.G. Rogers, M. Fournier, Exosome-mediated benefits of cell therapy in mouse and human models of duchenne muscular dystrophy, Stem Cell Rep. 10 (3) (2018) 942–955, https://doi.org/10.1016/j.stemcr.2018.01.023, 03 13.
[41] P.J. Kennel, P.C. Schulze, A review on the evolving roles of MiRNA-based technologies in diagnosing and treating heart failure, Cells 10 (11) (2021), https://doi.org/10.3390/cells10113191, 09.
[42] C.K. Huang, S. Kafert-Kasting, T. Thum, Preclinical and clinical development of noncoding RNA therapeutics for cardiovascular disease, Circ. Res. 126 (5) (2020) 663–678, https://doi.org/10.1161/CIRCRESAHA.119.315856, 02 28.
[43] T. Lucas, A. Bonauer, S. Dimmeler, RNA therapeutics in cardiovascular disease, Circ. Res. 123 (2) (2018) 205–220, https://doi.org/10.1161/CIRCRESAHA.117.311311, 07 06.
[44] W.T. Abplanalp, A. Fischer, D. John, Efficiency and target derepression of anti-miR-92a: results of a first in human study, Nucleic Acid Ther. 30 (6) (2020) 335–345, https://doi.org/10.1089/nat.2020.0871, 12.
[45] J. Täubel, W. Hauke, S. Rump, Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study, Eur. Heart J. 42 (2) (2021) 178–188, https://doi.org/10.1093/eurheartj/ehaa898, 01 30.
[46] P.V. Johnston, C.W. Hwang, V. Bogdan, Intravascular stem cell bioreactor for prevention of adverse remodeling after myocardial infarction, J. Am. Heart Assoc. 8 (15) (2019), e012351, https://doi.org/10.1161/JAHA.119.012351, 08 06.
[47] R.J. Vagnozzi, R.K. Kasam, M.A. Sargent, J.D. Molkentin, Cardiac cell therapy fails to rejuvenate the chronically scarred rodent heart, Circulation 144 (4) (2021) 328–331, https://doi.org/10.1161/CIRCULATIONAHA.120.053080.
[48] J.J. McMurray, M. Packer, A.S. Desai, et al., Angiotensin-neprilysin inhibition versus enalapril in heart failure, N. Engl. J. Med. 371 (11) (2014) 993–1004, https://doi.org/10.1056/NEJMoa1409077.
[49] T.M. Yau, F.D. Pagani, D.M. Mancini, Intramyocardial injection of mesenchymal precursor cells and successful temporary weaning from left ventricular assist device support in patients with advanced heart failure: a randomized clinical trial, JAMA 321 (12) (2019) 1176–1186, https://doi.org/10.1001/jama.2019.2341, 11 26.
[50] D.D. Ascheim, A.C. Gelijns, D. Goldstein, et al., Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices, Circulation 129 (22) (2014) 2287–2296, https://doi.org/10.1161/CIRCULATIONAHA.113.007412.
[51] H.M. DuBrock, O.F. AbouEzzeddine, M.M. Redfield, High-sensitivity C-reactive protein in heart failure with preserved ejection fraction, PLoS One 13 (8) (2018), e0201836, https://doi.org/10.1371/journal.pone.0201836.
[52] J.B. Cohen, S.J. Schrauben, L. Zhao, Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone, JACC Heart Fail. 8 (3) (2020) 172–184, https://doi.org/10.1016/j.jchf.2019.09.009, 03.
[53] B. Asatryan, A. Asimaki, A.P. Landstrom, et al., Inflammation and immune response in arrhythmogenic cardiomyopathy: state-of-the-art review, Circulation 144 (20) (2021) 1646–1655, https://doi.org/10.1161/CIRCULATIONAHA.121.055890.
[54] J.V. Jokerst, N. Cauwenberghs, T. Kuznetsova, Circulating biomarkers to identify responders in cardiac cell therapy, Sci. Rep. 7 (1) (2017) 4419, https://doi.org/10.1038/s41598-017-04801-7, 10 20.
[55] M. Shahrivari, E. Wise, M. Resende, et al., Peripheral blood cytokine levels after acute myocardial infarction: IL-1β- and IL-6-related impairment of bone marrow function, Circ. Res. 120 (12) (2017) 1947–1957, https://doi.org/10.1161/CIRCRESAHA.116.309947.
[56] D.A. Taylor, E.C. Perin, J.T. Willerson, et al., Identification of bone marrow cell subpopulations associated with improved functional outcomes in patients with chronic left ventricular dysfunction: an embedded cohort evaluation of the FOCUS-CCTRN trial, Cell Transplant. 25 (9) (2016) 1675–1687, https://doi.org/10.3727/096368915X689901.
[57] A.W. Heldman, D.L. DiFede, J.E. Fishman, et al., Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial, JAMA 311 (1) (Jan 2014) 62–73, https://doi.org/10.1001/jama.2013.282909.
[58] R. Bolli, R.D. Mitrani, J.M. Hare, A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial, Eur. J. Heart Fail. 23 (4) (2021) 661–674, https://doi.org/10.1002/ejhf.2178, 04.
[59] V. Schächinger, S. Erbs, A. Elsässer, et al., Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction, N. Engl. J. Med. 355 (12) (2006) 1210–1221, https://doi.org/10.1056/NEJMoa060186.
[60] B. Assmus, J. Honold, V. Schächinger, et al., Transcoronary transplantation of progenitor cells after myocardial infarction, N. Engl. J. Med. 355 (12) (2006) 1222–1232, https://doi.org/10.1056/NEJMoa051779.
[61] B. Assmus, A. Rolf, S. Erbs, et al., Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction, Circ Heart Fail. 3 (1) (Jan 2010) 89–96, https://doi.org/10.1161/CIRCHEARTFAILURE.108.843243.
[62] B. Assmus, V. Schächinger, C. Teupe, et al., Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI), Circulation 106 (24) (2002) 3009–3017, https://doi.org/10.1161/01.cir.0000043246.74879.cd.
[63] A. Mathur, F. Fernández-Avilés, J. Bartunek, The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: the BAMI trial, Eur. Heart J. 41 (38) (2020) 3702–3710, https://doi.org/10.1093/eurheartj/ehaa651, 10 07.
[64] T.D. Henry, L. Moyé, J.H. Traverse, Consistently inconsistent-bone marrow mononuclear stem cell therapy following acute myocardial infarction: a decade later, Circ. Res. 119 (3) (2016) 404–406, https://doi.org/10.1161/CIRCRESAHA.116.309231, 04.
[65] J.H. Traverse, T.D. Henry, S.G. Ellis, et al., Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial, JAMA 306 (19) (Nov 2011) 2110–2119, https://doi.org/10.1001/jama.2011.1670.
[66] J.H. Traverse, T.D. Henry, C.J. Pepine, et al., Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial, JAMA 308 (22) (Dec 2012) 2380–2389, https://doi.org/10.1001/jama.2012.28726.
[67] R. Bolli, Repeated cell therapy: a paradigm shift whose time has come, Circ. Res. 120 (7) (2017) 1072–1074, https://doi.org/10.1161/CIRCRESAHA.117.310710, 02 28.
[68] Y. Mitsutake, W.B. Pyun, D. Rouy, et al., Improvement of local cell delivery using helix transendocardial delivery catheter in a porcine heart, Int. Heart J. 58 (3) (2017) 435–440, https://doi.org/10.1536/ihj.16-179.
[69] E.G. Schmuck, J.D. Mulligan, R.L. Ertel, et al., Cardiac fibroblast-derived 3D extracellular matrix seeded with mesenchymal stem cells as a novel device to transfer cells to the ischemic myocardium, Cardiovasc. Eng. Technol. 5 (1) (2014) 119–131, https://doi.org/10.1007/s13239-013-0167-1.
[70] E.G. Schmuck, T.A. Hacker, D.A. Schreier, N.C. Chesler, Z. Wang, Beneficial effects of mesenchymal stem cell delivery via a novel cardiac bioscaffold on right ventricles of pulmonary arterial hypertensive rats, 05 01, Am. J. Physiol. Heart Circ. Physiol. 316 (5) (2019), https://doi.org/10.1152/ajpheart.00091.2018. H1005-H1013.
[71] S. Vasu, J. Zhou, J. Chen, P.V. Johnston, D.H. Kim, Biomaterials-based approaches for cardiac regeneration, Korean Circ. J. 51 (12) (Dec 2021) 943–960, https://doi.org/10.4070/kcj.2021.0291.