Recent Developments in Cardiovascular Research: The goal of "Recent Developments" is to provide a concise but comprehensive overview of new advances in cardiovascular research, which we hope will keep our readers abreast of recent scientific discoveries and facilitate discussion, interpretation, and integration of the findings. This will enable readers who are not experts in a particular field to grasp the significance and effect of work performed in other fields. It is our hope and expectation that these "Recent Development" articles will help readers to gain a broader awareness and a deeper understanding of the status of research across the vast landscape of cardiovascular research—*The Editors*.

Recent Developments in Stem and Progenitor Cell Therapy for Cardiac Repair

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Making our way through the beginning of the 21st century, we have seen the field of cardiovascular medicine make significant advances in both biomedical research and patient care. Despite these advancements, we continue to face statistics, which force us, time and again, to report heart failure (HF) as a leading cause of death in the United States and in much of the rest of the developed world.[1] Indeed, refined pharmacological and surgical approaches have proven effective in management of acute and chronic cardiovascular diseases, but more frequently than not, only palliative measures are available, which serve to merely alleviate the burden of symptoms and delay disease progression to end-stage HF. HF itself is most accurately defined by the heart's inability to sufficiently deliver blood to the surrounding organs and tissues of the body. Although there are a host of pathologies that can contribute to this condition, myocardial infarction (MI) resulting from atherosclerotic coronary artery disease is the leading event culminating in HF. After infarction, the heart experiences significant myocyte death and tissue necrosis. Damaged cardiac parenchyma is eventually replaced with fibrous scar, which lacks the contractile and conductive properties of normal myocardial tissue. The process of wound healing fulfills the immediate objective of preserving ventricular structural integrity and resisting further myocardial attrition. Impending cardiac remodeling, which is a compensatory reaction, follows suit[2]; long term, it comprises a maladaptive response contributing to progression of ventricular fibrosis, rigidity, and dilatation—culminating in HF. Thus, based on pathogenesis, 2 principal avenues warrant novel therapeutic interdiction: detrimental cardiac remodeling and loss of mechanical performance.

With many previous therapeutic modalities failing to adequately address these key areas, the field experienced a rapid shift toward regenerative medicine at the turn of the century. The idea was that by delivering a progenitor cell type of sufficient developmental plasticity into injured myocardium, one could replace/regenerate those basic contractile units of the heart (ie, cardiomyocytes) that were lost after the initial insult. Since its introduction, cardiac cell therapy has proceeded at a significant pace—largely fueled by rousing early reports of bona fide cardiac tissue regeneration and significant functional recovery in preclinical animal models of HF.[3] These and subsequent investigations have kick-started a lasting proverbial arms race in the stem cell field, which has kept clinical and basic science laboratories hastily searching for the next best endogenous progenitor cell or cell-based product with superior cardiac reparative capabilities. Despite mixed and often lackluster results regarding the efficacy of various progenitor cell types in early-phase clinical trials, as well as reports of limited engraftment and differentiation of transplanted cells, the cell therapy field continues to advance with the hopes of identifying the most suitable and efficacious cell type or cell-based product for cardiac repair. With this Recent Developments, we seek to focus the readers' attention on some of the fields' most current findings regarding progenitor cell therapy for cardiac repair, with specific emphasis on existing and novel instituted cell types, cell-derived products, and meta-analyses investigating efficacy.

Existing and Novel Instituted Cell Types for Cardiac Regenerative Therapy

The most significant hurdle facing the cell therapy field is the identification of the most suitable progenitor cell type for cardiac repair. Within the last decade, the field has been inundated with various progenitor cell types, from both cardiac and extracardiac sources, reported to exhibit salutary effects on cardiac function in preclinical HF models or early-phase clinical trials. Some of these have included unfractionated bone marrow

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mononuclear cells (BMNCs),[4,5] bone marrow-derived mesenchymal stem cells (BM-MSCs),[6–10] endothelial progenitor cells,[11,12] induced pluripotent stem cells,[13] induced pluripotent stem cell derivatives,[14,15] embryonic stem cells (ESCs),[16,17] ESC derivatives,[18,19] pericytes,[20] cardiac fibroblasts,[21] resident cardiac stem cells (CSCs),[22–24] and placenta-derived amniotic mesenchymal stem cells.[25] Although the safety and efficacy of many of these have been interrogated in early-phase clinical trials, their reported benefits are heterogeneous—raising significant skepticism regarding their utility as an effective future therapeutic modality for patient care. Whether this dilemma relates simply to the cell type used or merely variability in study design parameters (eg, cell dosage, route of administration, cohort characteristics, timing of end point evaluation, and used imaging techniques for assessment of cardiac function) has not been made clear. Within the last couple of years, the former has been addressed with preclinical head-to-head studies, comparing/contrasting the characteristics and cardiac reparative capacity of various previously tested progenitor cell types.[20,26–29] One such study was performed by Mohsin et al,[26] wherein they evaluated and compared the in vitro characteristics of cortical bone stem cells (CBSCs) to other progenitor cell types that had formerly undergone testing in early-stage clinical trials (specifically, mesenchymal stem cells [MSCs] and c-kit sorted CSCs). In their investigation, they showed CBSCs to differ from MSCs and CSCs in both form and function.[26] In vitro, CBSCs displayed distinct morphological characteristics and immunophenotypic profiles that distinguish them from MSCs and CSCs. In addition to these differences, CBSCs exhibited superior proliferative capacity, survival, and cardiogenic lineage commitment when coaxed to differentiate in vitro.[26] Although the results of this study suggests that CBSCs may possess superior cardiac reparative capabilities over that of MSCs and CSCs in vivo, it serves only as a surrogate indicator of the therapeutic benefits they would provide in a real world scenario. Bearing this in mind, other studies have opted to carry out efficacy-based comparisons using in vivo models of HF to more faithfully interrogate the cardiac reparative aptitude of different progenitor cell types.[20,27,28] For instance, the Canty Laboratory recently compared the therapeutic efficacy of intracoronary delivered allogeneic BM-MSCs and cardiosphere-derived cells (CDCs) in a HF swine model with chronic left anterior descending coronary artery stenosis.[27] In their study, MSCs and CDCs exhibited comparable cardiac reparative capacity, inducing equivalent increases in myocardial function, endogenous myocyte proliferation, and recession of myocyte hypertrophy. Thus, in this first study to directly compare the efficacy of allogeneic CDCs and MSCs in a large animal model of chronic myocardial ischemia, Weil et al[27] demonstrated equivalency between intracoronary delivered CDCs and MSCs in terms of their ability to facilitate myocardial repair after ischemic injury. Despite these results, other groups rationalize that different progenitor cell types possess unique characteristics that may provide complementary or synergistic activities in combination therapy.[20,28,30,31] In 2015, Avolio et al[20] compared the reparative potential of human saphenous vein–derived pericytes (SVPs) to CSCs, independently and in combination, in a murine MI model. Alone, SVPS and CSCs improved ventricular performance 14 days after MI; however, this improvement diminished by day 42.[20] Although SVPs and CSCs similarly mitigated detrimental cardiac remodeling, SVPs were more efficient in inducing angiogenesis and CSCs in promoting endogenous stem cell recruitment and myocyte proliferation.[20] Combinatorial treatment with SVPs and CSCs synergistically reduced infarct size and enhanced neovascularization, but failed to outperform the individual therapies at improving indices of ventricular contractility.[20] Contrary to the aforementioned report, Williams et al[30] showed combination therapy with CSCs and MSCs to more powerfully promote functional recovery in a porcine model of myocardial damage vis-à-vis individual cell therapies alone. Despite some discrepancies existing between the above-mentioned combinatorial therapy studies, which could simply relate to the differences in the specific cell types or animal models used, both add weight to the notion that different cell types can complementarily facilitate myocardial repair.

The philosophy of exploiting cell complementarity to enhance cell-mediated myocardial repair has paved the way for the introduction of syncytia (generated through the fusion of 2 distinct cell types to form a multinucleated cell hybrid) into the cardiac cell therapy field. This research direction was spearheaded by the Sussman laboratory, where they have successfully generated a cell hybrid, referred to as a Cardio Chimera (CC), through the ex vivo virus-mediated cell fusion of CSCs with MSCs.[28] In this landmark study, Quijada et al[28] compared the therapeutic efficacy of CCs to their parental constituents alone (CSCs or MSCs) or in combination (CSCs and MSCs) after their intramyocardial delivery in a murine model of acute MI. Six weeks after injury, CC and CSC/MSC combination-treated groups exhibited improved ventricular ejection fractions that were sustained out to 18 weeks. Contrary to the CSC/MSC combination and CSC-treated animals, which exhibited no change in infarct size at 12 weeks, CC-injected mice demonstrated a significant decrease in scar size. What is more, relative to all other groups, CCs exhibited more efficient induction of neovascularization and preservation of myocyte size in accompanying risk regions, suggesting that CCs possess even greater therapeutic potential than that of combinatorial cell approaches in promoting cardiac repair.[28]

Beyond cell hybrids, the regenerative medicine field has not observed much in terms of newly introduced cell types for cardiac repair within the last few years. But, we have witnessed novel methods for improving efficacy based on unique isolation techniques,[32] as well as reprogramming methodologies to produce more effective cardiac progenitor cells (CPCs).[33–36] In the former, Wysoczynski et al developed an improved method to isolate c-kit^{POS} CSCs based on a plating technique that stratifies cells according to adherence properties (slowly adherent cells versus rapidly adherent cells). In vitro, slowly adherent cells exhibited more efficient preservation of c-kit expression after cell passaging compared with rapidly adherent cells.[32] Further, after postinfarct adoptive transfer in mice, slowly adherent cells significantly enhanced indices of cardiac function (relative to saline controls), whereas rapidly adherent cells afforded no beneficial effects on ventricular performance.[32] Whether the ability of slowly adherent cells to mitigate cardiac dysfunction in this model was the result of their ability to maintain c-kit expression or because of their differential adherence properties was not directly addressed; however, it

has laid the groundwork for more advanced molecular studies, which aim to identify novel activated pathways that may explicate their pro-reparative cytotype.

Although the field has observed some progress with studies of existing and novel instituted cell types for cardiac regenerative therapy in recent years, further progress in developing more effective cell-based therapeutic approaches are likely to derive from new innovations in induced pluripotent stem cell technology,[37–41] and improved understanding of progenitor cell cardiogenic differentiation[42–44] and epigenetic mechanisms of cardiovascular cell lineage specification and disease processes.[45–48]

Paracrine Signaling: Cell-Derived Cytokines and Extracellular Vesicles

The expectation with regenerative cell therapy for cardiac repair was that transplanted cells would survive, proliferate, differentiate, and functionally integrate in host myocardium. Although the philosophy is simple, the biology underlying their therapeutic activities has proven to be anything but that. For instance, the results of numerous cell therapy–based studies report functional recovery in postinfarcted hearts[49]; however, only a small fraction of these cells are retained, differentiate, and persist long term in host myocardium after their delivery[50]—too few, in fact, for differentiation alone to account for their afforded benefits on ventricular performance. Cognizant of these results, the cell therapy field has turned to a more prominent and complementary mechanism to that of direct differentiation—namely paracrine signaling (reviewed in Gnecchi et al[51]), which suggests that transplanted cells may release trophic factors (ie, cytokines, chemokines, microvesicles harboring messenger RNA or microRNA [miRNA]) that could (1) contribute to myocardial protection,[20,28,52,53] (2) promote the recruitment of endogenous CPCs,[20,28,54] (3) stimulate endogenous myocyte proliferation,[20,27] and (4) induce arteriogenesis/neovascularization[20,27,28,55] after ischemic injury.

Some of the earliest works supporting the paracrine signaling hypothesis are those involving progenitor cell–mediated myocardial protection, which includes reports demonstrating the administration of MSC-derived conditioned medium to attenuate myocardial injury and to contribute to improvements in ventricular function in preclinical models of ischemic injury.[52,56–58] The associated mechanisms underlying its salutary effects on cardiac function included preservation of contractile capacity, inhibition of myocyte apoptosis, and promotion of angiogenesis.[52,56–58] Thus, these and other early studies propose that conditioned medium, or rather the resultant extracellular milieu of ex vivo cultured progenitor cells, contain a host of progenitor cell–secreted factors that may function in a paracrine manner to facilitate injury remission. Over the years, succeeding studies have elucidated many of these pro-reparative/cytoprotective factors that mitigate tissue injury—including various cytokines and chemokines.[59] Many of these have been stratified into distinct functional categories based on those biological processes they influence, including immunodulatory factors,[60] angiogenic/arteriogenic factors,[61] antiapoptotic factors, antioxidative factors, and factors associated with cell migration and homing (reviewed in Gnecchi et al[51] and Liang et al[59]).

Of the many protein and nucleic acid constituents that comprise a cells' secretome, majority attention has been placed on understanding the mode of action of secreted cytokines in regulating cell-mediated cardiac repair.[62–64] However, within the last 5 to 6 years, the regenerative medicine field has shifted its concentration to a more specific component of the secretome—namely exosomes and their cytosolic contents.[65] One of the first studies highlighting exosomes as a significant component of the paracrine effect in progenitor cell therapy was performed by the Losordo laboratory in 2011.[66] In their study, they demonstrated exosomes secreted from CD34$^+$ stem cells to independently possess angiogenic activities in vitro and in vivo.[66] Although the precise molecular mechanisms dictating this proangiogenic response were not directly investigated, their data did show CD34$^+$ cell–derived exosomes to modify various endothelial cell phenotypic properties that support neovascularization, including augmented cell viability, proliferative capacity, and tube formation.[66] Such investigations have since been extended to show the administration of progenitor cell–derived exosomes to target, in addition to endothelium, other endogenous cardiovascular cell types that support cardiac repair.[67] In one study, Gray et al demonstrated exosomes derived from hypoxic CPCs to promote endothelial cell tube formation and to block cytokine (transforming growth factor-β)-mediated profibrotic gene activation in rat cardiac fibroblasts, in vitro.[67] Consistent with their in vitro findings, they further demonstrated exosome infusion after ischemia–reperfusion injury to significantly improve cardiac function and reduce ventricular fibrosis.[67] Microarray analysis of the exosomes secreted by hypoxic CPCs revealed 11 upregulated miRNAs (compared with exosomes from CPCs maintained under normoxic conditions) predicted to function in physiological processes involving angiogenesis and fibrosis[67]—implying the vesicular transmission of miRNA as the principle mechanism underlying their protective/regenerative effects in vivo. Consistent with this philosophy, other investigations have demonstrated exosome-containing extracellular vesicle (EV) extracts from progenitor cells maintained under normoxic conditions to also provide salutary effects on postinfarcted myocardium via miRNA vesicular transfer.[68,69] In one of these studies, led by the Marban Laboratory, CDC-derived EVs were demonstrated to inhibit apoptosis, induce myocyte proliferation, as well as stimulate angiogenesis in vitro.[68] In agreement with these in vitro surrogate indicators of therapeutic activity, the delivery of CDC EVs significantly improved indices of cardiac function and mitigated detrimental structural remodeling in both acute and chronic murine models of MI.[68] In a synonymous capacity, Barile et al[69] revealed CPC-derived EVs to also impart salubrious effects on postinfarcted rat hearts where their administration mitigated cardiomyocyte apoptosis, induced neovascularization, and improved ventricular ejection fractions.

In the above-mentioned studies, the cardiac reparative/regenerative actions of progenitor cell–derived EVs were linked to the delivery of various miRNA species that exert specific biological effects on host myocardial cell types. And it is from this perspective that additional studies have been performed investigating the cardiac reparative capacity and

associated mechanisms of ESC-derived exosomes.[70] Here, Khan et al[70] demonstrated ESC-derived exosomes to enhance angiogenesis, promote cardiomyocyte survival, and decrease ventricular fibrosis after their delivery in a murine infarct model. Although these findings largely reiterate what other studies have observed with the administration of EVs derived from tissue-specific progenitors,[68,69] Khan et al[70] go on to show ESC-derived exosomes to also boost CPC proliferation, survival, and cardiac lineage commitment. This observation was paralleled with evidence of increased numbers of c-kit^{POS} CPCs in vivo and the formation of new myocytes in injured myocardium after ESC–exosome treatment.[70] The mechanism responsible for their beneficial effects was found to be associated with the transfer of an ESC-specific miRNA (miR-294) to CPCs, which augmented their survival and proliferative capacity.[70]

Overall, recent evidence implicates miRNA-containing EVs or exosomes derived from various progenitor cell types to possess intrinsic cardiac regenerative/reparative capabilities.[71] Their capacity to transfer regulatory miRNAs to distinct cardiovascular cell types in host myocardium afford them the ability to modulate multiple biological processes that potentiate myocardial repair and regeneration,[72] including promotion of angiogenesis,[73] inhibition of myocyte apoptosis,[74–76] stimulation of myocyte proliferation,[77–79] mitigation of cytokine-induced fibroblast activation,[80] and induction of progenitor cell differentiation.[81,82] For these very reasons, exosome-based cardiac therapy, which may eventually supplant or serve as an effective alternative to cell therapy, has gained significant attention and traction in the cardiovascular field within the last 2 to 3 years. Although considerable progress has been made regarding our understanding of how EVs or exosomes work, the manner in which exosomes mediate their reparative and cardioprotective effects are still poorly understood; impending studies are sure to delve deeper into elucidating their precise mechanisms of action.

Cell Therapy for Cardiac Repair: Current Status and Future Prospects

Numerous phase I–II clinical studies have been conducted in patients with acute MI,[83,84] HF,[85] and ischemic heart disease.[49] Given the dearth of large-scale randomized controlled trials, the field has chiefly relied on meta-analyses of previously performed clinical trials as a means to evaluate the efficacy of cell-based therapies, reconcile incongruent findings across multiple clinical trials, and generate hypotheses for future trial design. In the last couple of years, several important meta-analyses have been published. One should be cognizant of 2 important features of these meta-analyses: (1) most of the included trials in these studies used BMNCs and (2) most authors appropriately separated the trials related to acute MI from trials of HF and stable ischemic heart disease. Fisher et al[83] recently updated one of the most rigorous analyses in the field for the Cochrane collaboration. There they concluded that there is insufficient evidence to report a beneficial effect of cell therapy on clinical outcomes in patients with acute MI.[83] Further, they showed that studies that used cardiac magnetic resonance imaging to evaluate left ventricular ejection fraction, the gold-standard modality for assessing cardiac function, yielded no detectable difference between the treated and control/placebo groups,[83] while those that used echocardiography revealed only small differences in ejection fraction (ranging from 2% to 5% between placebo and treatment).[83] Overall, the aforementioned analysis largely argues against the notion that cell therapy provides significant improvements in cardiac function (based on magnetic resonance imaging), despite the evidence of modest improvements with studies using echocardiography, which could simply be related to inexactness inherent to the method. The meta-analysis by de Jong et al[86] yielded similar conclusions. Interestingly, the majority of other meta-analyses performed in patients with acute MI have reported similar 2% to 4% enhancements in ejection fraction in treated patients; however, the authors of these studies have interpreted the findings more favorably and suggest that there is clinical significance with such improvements.[87,88] On the contrary, 3 meta-analyses, including a recent one by Afzal et al, have concluded that transplantation of BMNCs improves ejection fraction and clinical outcomes in patients after acute MI.[87,89,90] Adding to the debate, the only individual patient data–based meta-analysis in patients with acute MI, ACCRUE (Meta-Analysis of Cell-Based Cardiac Studies; NCT01098591), has reported negative results.[84,91] The major pitfall plaguing ACCRUE is that it included only 60% of all patients with acute MI treated with BMNCs, raising concern for potential bias.[92] So, how could one begin to reconcile such contradictory findings from these meta-analyses, especially given that these studies have pooled mostly the same clinical trials? One issue could simply relate to differences in the methodology used in conducting systematic reviews of the literature. Another issue contributing to these discrepant results is associated with insufficient power of the study. A major caveat with these studies is that because of the small number of outcome events after acute MI in the revascularization era, a majority of the meta-analyses performed thus far are underpowered and are likely contributing to the discrepancy between different studies.[92] Ultimately, the results of meta-analyses are hypothesis generating and do not necessarily constitute conclusive evidence of efficacy of a treatment modality or lack thereof. A well-designed and adequately powered randomized controlled trial must, therefore, be performed to conclusively determine the effect of BMNCs in patients with reduced ejection fraction after acute MI. The hope is that the BAMI trial (The Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells on All Cause Mortality in Acute Myocardial Infarction; NCT01569178), which is planned to enroll 3000 patients, will accomplish such a monumental task. Although not as prominently used as BMNCs, other clinical trials have used cell types such as MSCs in the setting of acute MI. Gao et al[93] reported a phase 2 trial using 116 patients who were randomly assigned to intracoronary MSCs or placebo after acute MI. This study showed a statistically significant improvement in ejection fraction in the treated group compared with placebo.[93]

With regard to BMNCs used in patients with HF, meta-analyses were able to detect a positive signal in this setting because of the decrease of adverse outcome events, such as mortality and hospital readmission, in HF patients.[85,89,92] Although the salutary effect on left ventricular ejection fraction

remains small—in the 2% to 4% range—similar to that of acute MI, the cumulative evidence is strongly in favor of a beneficial effect of BMNCs therapy on clinical outcomes.[85,89,92] For instance, Fisher et al[85] reported an improvement in left ventricular ejection fraction by 4% to 4.5%, a reduction in risk of mortality and HF hospitalization, as well as an improvement in performance status and quality of life in favor of BMNC therapy. A large randomized controlled trial is eagerly awaited to build on the previous successes of BMNCs therapy; the REPEAT trial (Compare the Effects of Single Versus Repeated Intracoronary Application of Autologous Bone Marrow-Derived Mononuclear Cells on Mortality in Patients With Chronic Post-Infarction Heart Failure; NCT01693042), which is a large phase-3 study, will examine the effect of repeated intracoronary application of BMNCs in 676 patients with ischemic HF. In addition to BMNCs, MSCs are also being used in HF clinical trials. A recently published phase 2 randomized controlled trial of Ixmyelocel-T, a cell product enriched in BM-MSCs and macrophages, injected transendocardially in patients with ischemic HF showed a 37% reduction in adverse clinical outcomes in comparison to placebo, despite minor improvements in left ventricular ejection fraction, lending support to the idea that ejection fraction is a suboptimal surrogate marker for reduction in adverse cardiovascular outcomes.[94,95] Another study using BM-MSCs, CHART-1 (Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure; NCT01768702), a phase 3 randomized controlled trial of cardiopoietic BM-MSCs, delivered transendocardially in 271 patients with ischemic HF did not show any benefit over placebo.[96] In contrast to the results of CHART-1, mesenchymal precursor cells, which are BMNCs sorted for the stromal cell surface antigen STRO-3, demonstrated a significant reduction in adverse events in a phase II clinical trial.[97] Overall, the jury is still out with respect to the efficacy of MSCs in the setting of HF because the number of patients treated with these cells is currently too small to draw any firm conclusions.[98] Fortunately, a large multicenter trial (NCT02032004) is underway investigating the therapeutic efficacy of allogeneic BM-MSCs, delivered transendocardially, for the treatment of HF.

In view of the small numeric enhancement in ejection fraction with cell therapy, some investigators have hypothesized that repeated injection of cells may culminate with a significant improvement in ejection fraction and clinical outcomes. Tokita et al[99] recently reported that repeated administration of c-kit$^+$ CPCs improves both regional and global indices of left ventricular function in a murine model of ischemic HF. The human data, however, is limited to small prospective cohorts and observational studies. A retrospective analysis of outcomes in 297 patients with ischemic HF, from a single-center registry, indicated that repeated intracoronary administration of BMNCs is associated with a significant better 2-year survival compared with a single application.[100] This hypothesis is being tested in the ongoing REPEAT trial (NCT01693042) as detailed earlier. Additionally, multidose administration of BM-MSCs is being investigated in acute MI (RELIEF trial; NCT01652209). Finally, there is robust experimental evidence that combination of different cell types may be additive or even synergistic (see above).[27,30,101] Based on such observations, the phase 2 CONCERT-HF trial (Combination of Mesenchymal and C-kit$^+$ Cardiac Stem Cells as Regenerative Therapy for Heart Failure; NCT02501811) will compare the safety and efficacy of BM-MSCs, c-kit$^+$ CPCs, and their combination in patients with ischemic cardiomyopathy. The results of these ongoing trials are eagerly awaited and undoubtedly will shape the future of cell therapy in MI and HF.

Summary

Improving our understanding of the fundamental mechanisms underlying progenitor cell–mediated cardiac repair lie at the forefront of the regenerative medicine field because one must wholly comprehend their manner of action to harness their full therapeutic potential. Although cell therapy is unlikely to become a mainstay treatment for HF in the short term, the steady introduction of novel cell types and cell-based products will undoubtedly continue to push the cardiac regenerative medicine field forward on a trajectory to success.

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