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Autologous Cellular and Acellular Strategies for Cardiac Repair: Mechanisms, Clinical Evidence, and Emerging Precision Technologies

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Abstract

Heart failure (HF) remains fundamentally driven by irreversible cardiomyocyte loss and maladaptive ventricular remodeling. These processes are the target of current guideline-directed therapies which mitigate but do not reverse progression. Over the past two decades, autologous cell–based interventions have been tested across acute myocardial infarction (MI) and chronic HF to address this unmet biological substrate. However, the mechanistic basis and clinical expectations of these therapies have been reshaped by advances in developmental biology, genetic lineage tracing, and translational bioengineering. Genetic fate-mapping has refuted the concept of a physiologically meaningful endogenous cardiomyogenic stem-cell compartment in the adult heart, establishing that adult c-Kit$^+$ and Sca-1$^+$ populations do not replenish cardiomyocyte mass. This paradigm shift has redirected the therapeutic rationale toward paracrine-driven modulation of the post-injury milieu.

Contemporary clinical evidence and recent meta-analyses demonstrate that autologous platforms, i.e., mesenchymal stromal/stem cells (MSCs), bone marrow mononuclear cells, endothelial-enriched progenitors (eg, $CD133^+$), and cardiac-derived cells, exhibit a consistently favorable safety profile. In addition, these autologous platforms can produce modest but reproducible benefits in selected patients, with greater consistency for hospitalization, adverse remodeling indices, and composite clinical events than for large, sustained improvements in left ventricular ejection fraction. The observed effects are mechanistically congruent with multi-compartment paracrine signaling that reprograms inflammation, stabilizes microvascular integrity, suppresses maladaptive fibroblast activation, and enhances cardiomyocyte stress tolerance. Extracellular vesicles (EV) have also emerged as a principal transferable effector of these benefits, motivating cell-free therapeutic development. Emerging technologies, including (but not limited to) exosome-only therapeutics, scaffold-free cell-sheet patches, injectable/pericardial biomaterial delivery systems, gene-enhanced autologous products, and artificial intelligence–guided potency/responder stratification, are enabling a transition from empiric transplantation to precision biologics**.** Although autologous cell therapy does not re-muscularize the adult heart through direct cardiomyogenesis, integration of optimized delivery, standardized potency assays, and biomarker-guided selection may yield durable, clinically meaningful benefit in defined HF phenotypes.

Keywords

Heart failure; Autologous stem cells; Mesenchymal stromal cells; Extracellular vesicles; Cardiac regeneration; Precision medicine.

Highlights

- Adult human myocardium lacks a functional cardiomyogenic stem-cell compartment.
- Autologous cell therapies act predominantly through paracrine mechanisms rather than engraftment.
- Clinical benefits are modest but reproducible and include reduced hospitalization and adverse remodeling.
- Exosome-based therapeutics and scaffold-free cell-sheet strategies represent next-generation platforms.
- Precision patient selection and timing of intervention are critical determinants of efficacy.

Introduction

Heart failure (HF), a multi-faceted clinical syndrome remains a leading cause of morbidity and mortality worldwide, affecting more than 64 million individuals globally. HF accounts for substantial healthcare utilization despite advances in pharmacologic, interventional, and device-based therapies. Central to HF pathogenesis is the irreversible loss of cardiomyocytes following ischemic injury and the subsequent maladaptive remodeling of ventricular architecture. Existing therapies primarily slow disease progression but do not restore lost myocardial tissue. As such, there is sustained interest in regenerative approaches.

Autologous cell-based therapies emerged in the early 2000s following seminal preclinical studies demonstrating improved ventricular function after transplantation of bone marrow–derived progenitor cells into infarcted myocardium. Early clinical translation was facilitated by patient-derived cells, which

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circumvent alloimmune rejection, eliminate the need for immunosuppression, and simplify regulatory pathways. However, over the past decade, advances in developmental biology, genetic lineage tracing, and clinical trial outcomes have profoundly reshaped the conceptual foundation of cardiac regeneration.

Contemporary evidence has overturned the notion of a self-renewing endogenous cardiac stem-cell compartment capable of cardiomyocyte replacement. Instead, autologous cell therapies are now understood to function predominantly through paracrine-driven biological modulation, influencing inflammation, angiogenesis, fibrosis, and cardiomyocyte survival (ref). This paradigm shift has catalyzed the development of next-generation strategies that seek to maximize biological efficacy while preserving safety.

Biological basis of autologous cardiac repair

The adult human heart is characterized by an intrinsically limited regenerative capacity that fundamentally constrains recovery after injury. Radiocarbon dating and lineage analyses have established that adult cardiomyocytes renew at a rate of approximately 0.5–1% per year, a level insufficient to compensate for the loss of nearly one billion cardiomyocytes following a typical myocardial infarction (MI). This profound mismatch between injury burden and regenerative potential underlies the progression from acute ischemic injury to chronic heart failure.

In contrast, neonatal mammals retain a brief window of regenerative competence mediated by cardiomyocyte proliferation, rather than stem-cell differentiation. During this period, cardiomyocytes remain mononuclear, diploid, glycolytically primed, and permissive to cell-cycle reentry. However, this regenerative program is rapidly extinguished within the first postnatal week through coordinated processes including cell-cycle arrest, polyploidization, sarcomeric maturation, and a metabolic switch from glycolysis to mitochondrial oxidative phosphorylation (ref). The associated increase in oxidative stress and DNA damage signaling further enforces permanent cardiomyocyte cell-cycle exit, rendering the adult myocardium largely incapable of endogenous remuscularization.

Disproof of an endogenous cardiac stem-cell compartment

For many years, it was hypothesized that adult cardiac-resident progenitor populations expressing markers such as c-Kit or Sca-1 functioned as endogenous cardiac stem cells capable of generating new cardiomyocytes. This concept strongly influenced early regenerative strategies. However, definitive recombinase-based lineage-tracing studies overturned this paradigm. Using genetic fate mapping, multiple independent groups demonstrated that c-Kit$^+$ cells contribute almost exclusively to endothelial and vascular smooth muscle lineages, with cardiomyocyte generation occurring at physiologically negligible frequencies (<0.03%). Similarly, Sca-1$^+$ populations were shown not to meaningfully contribute to adult cardiomyocyte renewal in vivo. These findings culminated in consensus statements concluding that the adult mammalian heart lacks a resident cardiomyogenic stem-cell pool capable of restoring myocardial mass after injury. Importantly, these studies did not negate the biological activity of transplanted or resident cells but instead clarified that any observed functional benefit must arise through non-cardiomyogenic mechanisms. This recognition represented a pivotal conceptual shift in the field.

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Reframing Autologous Cell Therapy: From Replacement to Biological Modulation

This biological reality fundamentally reframed the therapeutic rationale for autologous cell therapy. Rather than serving as structural replacement units, transplanted autologous cells function as biological modulators of the injured myocardium. Their principal mode of action involves secretion of trophic factors, cytokines, chemokines, and extracellular vesicles (EVs) that dynamically reshape the post-injury microenvironment (ref). At the physiological level, these paracrine signals act on multiple interdependent processes that determine ventricular remodeling:

1. Inflammatory resolution, by suppressing maladaptive innate and adaptive immune responses;
2. Angiogenesis and microvascular stabilization, improving perfusion of border-zone myocardium;
3. Anti-apoptotic signaling, preserving stressed but viable cardiomyocytes;
4. Anti-fibrotic remodeling, limiting excessive extracellular matrix deposition and ventricular stiffening.

This systems-level modulation, rather than cellular engraftment or differentiation, underpins all contemporary autologous regenerative strategies.

Autologous cell sources for cardiac repair: mechanistic and physiological considerations

- Bone marrow mononuclear cells (BM-MNCs) were the first autologous population tested extensively in cardiac repair, owing to their rapid accessibility and procedural simplicity. Early clinical trials reported transient improvements in left ventricular ejection fraction (LVEF), particularly when administered in the acute or subacute post-MI setting. [20] However, longer-term follow-up consistently demonstrated attenuation or loss of these functional gains (ref). Mechanistic studies clarified that BM-MNCs do not transdifferentiate into cardiomyocytes and exhibit minimal long-term engraftment. Instead, their biological activity is mediated through short-lived paracrine release of angiogenic and immunomodulatory factors, including VEGF, HGF, and stromal-derived factor-1 (SDF-1) (ref). These signals transiently enhance endothelial repair and reduce early inflammation but lack durability, explaining the modest and time-limited clinical effects.
- Autologous mesenchymal stromal/stem cells (MSCs) represent a more biologically potent autologous platform. MSCs exert broad immunomodulatory effects, including polarization of macrophages toward reparative (M2-like) phenotypes, suppression of T-cell activation, and inhibition of pro-fibrotic fibroblast signaling (ref). In addition, MSCs secrete a rich array of trophic factors and EVs that activate pro-survival pathways (eg, PI3K–AKT, STAT3) in cardiomyocytes and endothelial cells. Clinically, autologous MSC therapy has demonstrated consistent safety and modest improvements in ventricular remodeling parameters, including reductions in left ventricular end-systolic volume and scar burden (ref). However, therapeutic variability is substantial and reflects physiological heterogeneity of the donor, including advanced age, metabolic disease, chronic inflammation, and oxidative stress, all of which impair MSC secretory potency and stress resistance (ref). This donor dependence has emerged as a critical limitation of

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autologous MSC therapy.

- $CD133^+$ progenitors are enriched for endothelial lineage potential and play a distinct role in microvascular repair rather than myocardial contractile restoration (ref). These cells enhance endothelial cell survival, promote capillary density, and improve perfusion of ischemic myocardium through both direct endothelial support and paracrine signaling. Clinical trials such as PERFECT (NCT02402504) and Ixmyelocel-T demonstrated reductions in adverse cardiac events and heart failure–related hospitalizations without consistent improvements in LVEF. This dissociation between perfusion benefit and systolic function strongly supports a microvascular and perfusion-mediated mechanism of action, consistent with the biology of $CD133^+$ progenitors (ref).
- Although adult cardiac-derived progenitor cells (CPCs) lack cardiomyogenic capacity, they possess a highly active reparative secretome that is particularly well adapted to the myocardial environment (ref). CPCs secrete extracellular vesicles enriched in cardioprotective microRNAs (eg, miR-21, miR-146a, miR-210) that regulate apoptosis, angiogenesis, and fibroblast activation. Preclinical studies have demonstrated that CPC-derived exosomes reduce cardiomyocyte apoptosis, enhance neovascularization, and attenuate fibrosis, recapitulating many benefits of whole-cell therapy while avoiding risks associated with engraftment. These findings have positioned CPC-derived EVs as leading candidates for next-generation, cell-free cardiac therapeutics.
- *Autologous induced pluripotent stem cell–derived cardiomyocytes (iPSC-CMs)* offer theoretical potential for true remuscularization. However, their clinical translation remains constrained by fundamental biological challenges, including genomic instability introduced during reprogramming, electrophysiologic immaturity, and arrhythmogenic risk due to automaticity and conduction heterogeneity (ref). From a physiological standpoint, iPSC-CMs resemble fetal cardiomyocytes, with immature calcium handling, sarcomeric organization, and metabolic profiles, limiting their ability to integrate seamlessly with adult myocardium (ref). While adjunctive strategies such as leukemia inhibitory factor (LIF) enhance survival and stress resistance by suppressing Bax-mediated apoptosis (ref), these approaches do not fully overcome maturation and safety barriers. As a result, autologous iPSC-CM therapy remains experimental and is currently better suited as a platform for engineered tissues or paracrine delivery rather than direct myocardial replacement.

Collectively, these observations demonstrate that the physiological basis of autologous cardiac repair lies not in cardiomyocyte replacement but in coordinated modulation of inflammation, perfusion, survival, and fibrosis. The magnitude and durability of benefit are dictated by the biological potency of the cell source, the host myocardial environment, and the timing of intervention. This mechanistic understanding provides the foundation for emerging precision strategies that seek to optimize signals rather than cells themselves.

Mechanisms Underlying Therapeutic Benefit

A convergent body of evidence indicates that the benefits of autologous cell therapy are mediated primarily through context-dependent paracrine biology rather than durable engraftment,

transdifferentiation, or long-term contractile replacement. Across platforms (BM-MNCs, MSCs, $CD133^+$ progenitors, CPCs, and autologous iPSC-derived progenitors), therapeutic efficacy reflects the capacity to reprogram post-injury physiology during a limited window of myocardial plasticity.

Paracrine factor networks coordinate multi-compartment repair

Autologous products secrete overlapping repertoires of soluble mediators (e.g., vascular Endothelial Growth Factor [VEGF], Hepatocyte Growth Factor [HGF], insulin-like growth factor [IGF]-1, Stromal Cell–Derived Factor [SDF]-1/CXCL12, interleukin [IL]-10, Transforming Growth Factor [TGF]-β modulators) that act in a networked manner on multiple myocardial compartments. Rather than a single dominant ligand, the therapeutic effect appears to arise from systems-level redundancy, simultaneously promoting endothelial survival and sprouting, limiting cardiomyocyte apoptosis, and attenuating pro-fibrotic signaling in activated fibroblasts (ref). This framing is consistent with contemporary reviews emphasizing that "benefit" correlates more closely with secretome composition and host responsiveness than with measurable cell retention.

Physiological implication: even modest changes in inflammatory tone and microvascular competence can translate into measurable improvements in remodeling indices and event rates, without necessarily producing large LVEF shifts. This observation aligns with long-term outcomes literature in HF cell trials. Immunomodulation as a primary determinant of remodeling trajectory.

A defining mechanism, particularly for MSC-based autologous products, is immune reprogramming. MSCs suppress excessive innate activation and bias macrophage polarization away from persistent pro-inflammatory states toward reparative phenotypes, with downstream reductions in cytokine-driven cardiomyocyte stress and fibroblast activation (ref). This effect is mediated by a combination of soluble factors (eg, prostaglandin E2 [PGE2]/cyclooxygenase [COX] 2 axis, IL-10 induction, Indoleamine 2,3-Dioxygenase [IDO] activity) and vesicle-delivered regulatory RNAs (ref). Recent mechanistic syntheses highlight macrophage polarization as a dominant node of the MSC effect network and show that preconditioning and inflammatory context can amplify or blunt this activity.

Physiological implication: by shifting the balance from prolonged sterile inflammation to resolution, autologous therapies can reduce infarct expansion and adverse remodeling even when cell persistence is short-lived. This provides a mechanistic explanation for event reduction with modest LVEF change in some cohorts.

Endothelial stabilization and microvascular repair: perfusion as a mechanistic endpoint

For BM-MNCs and $CD133^+$ progenitors, benefits are best conceptualized as microvascular-centric. These populations enhance endothelial repair, improve capillary density, and stabilize the peri-infarct microcirculation, thereby reducing ongoing ischemia and "hibernating" border-zone dysfunction (ref). In this paradigm, the relevant endpoint is not cardiomyogenesis but microvascular competence. That is, improved perfusion reduces oxidative stress, dampens inflammatory recruitment, and improves the metabolic environment supporting surviving cardiomyocytes. This aligns with contemporary trial syntheses emphasizing heterogeneity of functional endpoints and suggesting that remodeling/perfusion measures may be more sensitive than LVEF alone.

Anti-apoptotic cytoprotection and metabolic stress resistance

Autologous therapies promote cardiomyocyte survival through activation of canonical pro-survival pathways (PI3K–AKT, STAT3, ERK1/2) and attenuation of mitochondrial apoptotic priming in stressed border-zone myocardium. At the cell-product level, improving survival of therapeutic cells can also increase the duration and magnitude of paracrine dosing. In pluripotent-derived cardiomyocytes, leukemia inhibitory factor (LIF) enhances survival by suppressing Bax-associated apoptosis and activating gp130-linked survival signaling, supporting a practical adjunct strategy when iPSC-derived products are used (ref).

Physiological implication: cytoprotection is most impactful early, when apoptotic and necroptotic signaling peaks; late-stage mature scar provides fewer viable cardiomyocytes and thus fewer targets for anti-apoptotic rescue. This is particularly relevant to explain time-dependent efficacy patterns.

Anti-fibrotic remodeling: fibroblast phenotype and matrix mechanics

Adverse remodeling is governed not only by scar size but by fibroblast phenotype, collagen crosslinking, and matrix stiffness, which together drive diastolic dysfunction and impair electromechanical coupling (ref).

Autologous cell–based therapies attenuate fibrotic remodeling through coordinated modulation of the inflammatory–fibroblast axis rather than by directly replacing scar tissue. First, by suppressing prolonged innate and adaptive immune activation, autologous cells reduce the inflammatory cytokine milieu that drives fibroblast activation and myofibroblast persistence in the injured myocardium. Second, these therapies modulate TGF-β/SMAD signaling, the central pathway governing fibroblast differentiation and collagen synthesis, thereby limiting excessive extracellular matrix deposition while preserving essential wound-healing responses. Third, autologous cells deliver extracellular vesicle cargo enriched in regulatory microRNAs and proteins that directly suppress myofibroblast differentiation, reduce collagen I/III production, and temper matrix crosslinking (ref). Through these complementary mechanisms, autologous therapies promote more adaptive scar formation and preserve ventricular compliance, contributing to improved structural remodeling despite the absence of direct cardiomyocyte regeneration.

Recent human-cell and mechanistic studies emphasize that post-MI fibroblast states are strongly shaped by hypoxia and TGF-β, reinforcing the plausibility of anti-fibrotic benefits through niche modulation rather than direct tissue replacement (ref).

EVs as the dominant transferable “effector unit”

A major refinement in the field is recognition that many benefits previously attributed to transplanted cells can be recapitulated by EVs/exosomes. EVs enable high-density transfer of microRNAs, proteins, lipids, and metabolites that reprogram recipient endothelial cells, immune cells, cardiomyocytes, and fibroblasts. Balbi and Vassalli describe EVs as a principal functional mediator of cardiac protection and repair, which has driven intense interest in cell-free products with improved manufacturing consistency and reduced safety concerns. Contemporary reviews further outline strategies to increase EV yield and potency (preconditioning, bioreactor scaling), improve homing, and standardize purification, directly addressing the historical variability of autologous live-cell therapy. Thus, EV-based approaches may

preserve the beneficial biology of autologous therapies while reducing dependence on live-cell engraftment, potentially enabling tighter dose control and more reliable biological exposure in the myocardium.

Clinical evidence

Across two decades of randomized testing, autologous cell therapy has demonstrated a highly consistent safety signal with heterogeneous efficacy that is more reproducible for clinical events and remodeling surrogates than for large absolute gains in LVEF (ref). This pattern is mechanistically coherent with paracrine-dominant biology: most adult cell products do not engraft long term, and therefore benefits, when present, are expected to manifest as attenuated adverse remodeling, improved perfusion/ microvascular function, reduced inflammatory burden, and fewer decompensation events, rather than "remuscularization-level" improvements in systolic function (ref). Recent quantitative syntheses support this interpretation. In a 2024 meta-analysis of 17 RCTs (n = 1684) of MSC transplantation for chronic HF, MSC therapy was associated with lower all-cause mortality (RR 0.78; 95% CI, 0.62–0.99) and a trend toward reduced HF rehospitalization overall; importantly, the rehospitalization signal became significant for autologous MSCs (RR 0.67; 95% CI, 0.49–0.90) and the pooled effect suggested LVEF improvement (MD 3.38%; 95% CI, 1.89–4.87).These data indicate that (1) clinical benefits are plausible and measurable, and (2) cell source and trial design materially influence effect sizes. Complementing this, a 2024 dose-response focused meta-analysis restricted to phase II/III RCTs in HFrEF (11 RCTs; n = 1098) concluded that MSC therapy was safe across low and high doses, but suggested greater functional efficacy with lower dose (<100 million cells), including LVEF improvement by 3.01% (95% CI, 0.65–5.38) in the low-dose subgroup, along with improvements in 6-minute walk distance. The implication for trial planning is not merely "more cells is better," but rather that the therapeutic mechanism may be signal-mediated and saturable, and may be perturbed by product quality, inflammatory state, or delivery-induced injury. Finally, a 2025 systematic review comparing autologous vs allogeneic MSCs (13 RCTs; n = 1184) found consistent safety irrespective of source, with autologous MSCs associated with a significant reduction in hospitalization (RR 0.65; 95% CI, 0.42–0.99) and no meaningful between-source difference in LVEF improvement in subgroup analyses; the pooled MACE estimate was near null (RR 1.02; 95% CI, 0.86–1.21). Taken together, the contemporary evidence base supports a risk–benefit profile favorable enough to justify continued development, while emphasizing that reproducible efficacy likely requires biologic enrichment (responder selection), optimized delivery, and clinically appropriate endpoints.

Trial evidence by autologous platform

1. Autologous bone marrow–derived cells (BM-MNCs and selected progenitors) in acute MI: Acute MI trials established feasibility and early signals of improved systolic recovery, but durability varies. The seminal randomized experience with intracoronary autologous bone marrow cell transfer in STEMI reported LVEF improvement at 6 months in some cohorts (eg, BOOST), with attenuation over longer follow-up. This is consistent with anti-remodeling rather than true myocardial replacement (ref). Long-term clinical outcome analyses from REPAIR-AMI indicate that early functional improvements can associate with downstream event signals in selected populations, but effect sizes are modest and depend on baseline LV dysfunction and trial methodology (ref). Acute/subacute delivery likely leverages a biologically permissive window

(active inflammation/angiogenesis) and therefore may perform differently than chronic scar settings. This is congruent with the broader clinical literature emphasizing timing-dependent repair biology.

2. Autologous MSCs in chronic HFrEF: Autologous MSCs (bone marrow– or adipose-derived) have the most consistent safety profile and the most mature RCT/meta-analytic evidence for modest improvements in symptoms, functional capacity, and some remodeling indices. In a recent MSC meta-analysis noted above, the autologous subgroup appears to drive HF rehospitalization benefit (RR 0.67; 95% CI, 0.49–0.90). Beyond clinical events, the 2024 dose-response meta-analysis suggests functional and performance improvements (LVEF and 6MWD) with both low- and high-dose regimens, while raising the important possibility that lower doses may be more efficacious in HFrEF. LVEF is load- and rhythm-sensitive, varies by imaging modality, and can be underpowered in small RCTs. Hence, neutral LVEF does not preclude clinically relevant effects on hospitalization or composite events, which may be mediated by microvascular and inflammatory pathways rather than contractile replacement.
3. Autologous $CD133^+/CD34^+$ angiogenic progenitors: Trials using endothelial-enriched progenitors (including $CD133^+$ and related angiogenic populations) report more consistent signals for perfusion-related endpoints and event reduction than for LVEF, supporting a mechanism centered on microvascular repair. Table-based trial syntheses in recent reviews summarize these as modest but clinically plausible subgroup effects, often sensitive to baseline ischemic burden and delivery route (ref).
4. Autologous “expanded” multicellular products (eg, ixmyelocel-T): Expanded autologous products that retain mixed immune/angiogenic lineages have shown some of the most persuasive event-based signals in ischemic cardiomyopathy. The ixmyelocel-T program reported reductions in adjudicated clinical cardiac events relative to placebo, consistent with a mechanism of inflammatory modulation plus vascular support rather than direct cardiomyogenesis (ref).
5. Autologous cardiac-derived cells (CPCs/cardiosphere-derived paradigms): While much of the large-scale experience includes allogeneic approaches, autologous CPC strategies tested in combination frameworks underscore an important clinical concept: the biologically active secretome may outperform expectations based on engraftment biology. Notably, the CONCERT-HF randomized study (autologous MSCs and $c\text{-}kit^+$ CPC arms) showed improvements in quality-of-life measures and signals for reduced HF-related major adverse events in some arms, with neutral findings for several imaging endpoints.
6. “Responder-enriched” autologous strategies (precision cell therapy): A pivotal direction in the modern era is biologic enrichment prior to dosing, either through cell potency profiling or selection thresholds. This concept is increasingly operationalized in contemporary programs that restrict therapy to patients whose harvested marrow/cell product meets prespecified criteria, explicitly aiming to reduce variability driven by age, metabolic disease, and inflammatory phenotype.

Trial / Program	Population	Cell product (source)	Delivery	n (treated/control)	Follow-up	Primary/Key outcomes	Direction of effect
BOOST	STEMI post-PCI	Autologous BMC/BM-MNC	Intracoronary	60 total	6mo; 5 y	Early LVEF improvement at 6mo with attenuation over long-term follow-up[2]	Early functional signal; long-term convergence
REPAIR-AMI	Acute MI	Autologous BMC/BM-derived progenitors	Intracoronary	multicenter RCT	months; 5 y outcomes	Functional recovery signals in subsets; long-term event analyses published[3]	Modest benefit; population dependent
CONCERT-HF	Ischemic HF	Autologous BM-MSC ± c-kit$^+$ CPC	Intracoronary	33/32 (MSC+CPC), 29/32 (MSC), 31/32 (CPC)	12mo	QOL improvement (MSC; MSC+CPC); lowest HF-related MACE signal in CPC arm; neutral LVEF/volumes in several endpoints fphys-14-1344885	Symptom/QOL and event signals; imaging mixed
Ixmyelocel-T	Ischemic DCM/HFrEF	Expanded autologous multicellular product	Transendocardial	phase 2b	12mo+	Reduction in adjudicated clinical cardiac events vs placebo[5]	Event reduction; LVEF inconsistent
SCIENCE	Chronic ischemic HFrEF	MSC (adipose-derived; allogeneic in trial)	Intramyocardial	90/43	6–12mo	No significant differences in LV volumes/LVEF/functional tests vs placebo in published summaries fphys-14-1344885	Neutral
DREAM-HF	High-risk chronic HFrEF	MSC/MPC (bone marrow–derived; allogeneic in trial)	Transendocardial	283/282	mean ~30mo	Reduced MI/stroke risk; greater benefit with inflammation (hsCRP ≥2) per published trial summaries fphys-14-1344885	MACE reduction in biologically enriched strata
CardiAMP-HF (program)	Ischemic HFrEF	Autologous bone marrow cell therapy system	Transendocardial	phase 3	2 y reported	Responder-enriched design; principal results reported 2025 (conference/updates)	Evolving; enrichment strategy central

Table 1: Representative clinical trials of cell therapy in HF/ischemic cardiomyopathy and key findings.

Emerging Technologies, Future Directions, and Conclusions

Next-generation autologous cardiac repair strategies are increasingly focused on enhancing biological potency, reproducibility, and translational scalability by shifting from empiric cell transplantation toward precisely engineered, signal-centric biologics. Exosome-only therapeutics have emerged as a leading platform, enabling stable, scalable, and cell-free delivery of reparative molecular cargo that recapitulates the paracrine benefits of live-cell therapy while mitigating risks related to engraftment, differentiation, and manufacturing variability. In parallel, scaffold-free cell-sheet engineering allows generation of electrically coupled, contractile myocardial patches that preserve endogenous extracellular matrix and intercellular junctions without the need for exogenous biomaterials, while injectable and pericardial hydrogels enhance spatial localization, retention, and durability of cells or extracellular vesicles within the injured myocardium. These biological advances are complemented by computational frameworks that integrate multi-omics profiling with machine learning to enable AI-guided patient selection, potency

prediction, and dose optimization, addressing one of the central limitations of autologous therapy, interpatient heterogeneity. In addition, gene-enhanced autologous cells engineered to overexpress pro-survival, pro-angiogenic, or homing factors further amplify therapeutic signaling at lower effective doses. Collectively, these innovations point toward a future in which precision timing of intervention, standardized potency assays, and rational combination biologics (cells with RNA or gene-based payloads) are essential for consistent efficacy. Appropriately designed clinical trials incorporating MRI-based remodeling endpoints, long-term follow-up, and biomarker-guided enrollment will be required to fully realize this potential. Taken together, autologous cardiac regenerative therapy has transitioned from a cell-centric replacement paradigm to a signal-centric precision biologic approach; although direct cardiomyocyte regeneration remains elusive, paracrine-driven modulation of inflammation, perfusion, and fibrosis offers a mechanistically grounded and clinically relevant pathway toward durable improvement in heart failure outcomes.

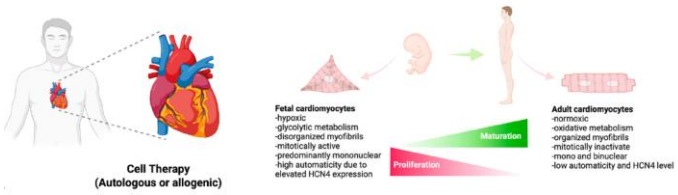

Figure 1: Evolution of Cardiac Regenerative Concepts- create similar to that in PP. Comparison of exosome therapy, cell sheets, hydrogels, and AI-guided optimization.

Create Figure Emerging Technologies in Autologous Cardiac Regeneration.

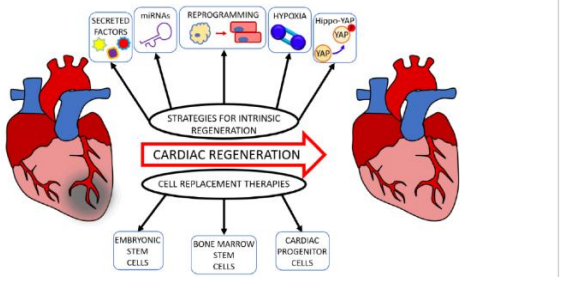

Figure 2: Create similar. Mechanisms of Autologous Cell–Mediated Cardiac Repair.

What Is New?

- Autologous therapies act primarily through paracrine signaling rather than cardiomyocyte replacement.
- Exosome-based and scaffold-free platforms reduce biological and regulatory risk.

What Are the Clinical Implications?

- Precision timing and patient selection are essential for benefit.
- Autologous biologics may complement—not replace—existing heart failure therapies.

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