International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	STEM CELL–BASED MYOCARDIAL REGENERATION AFTER INFARCTION: MOLECULAR MECHANISMS, TRANSLATIONAL CHALLENGES, AND EMERGING BIOTECHNOLOGICAL INNOVATIONS
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5045
RECEIVED	03 December 2025
ACCEPTED	18 February 2026
PUBLISHED	02 March 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

STEM CELL–BASED MYOCARDIAL REGENERATION AFTER INFARCTION: MOLECULAR MECHANISMS, TRANSLATIONAL CHALLENGES, AND EMERGING BIOTECHNOLOGICAL INNOVATIONS

Amanda Abramowicz *(Corresponding Author, Email: amanda.abramowicz1@gmail.com)*
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0004-6674-0594

Maja Osuch
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław, Wrocław, Poland
ORCID ID: 0009-0000-9815-2608

Maciej Osuch
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław, Wrocław, Poland
ORCID ID: 0009-0009-2399-2878

Olga Tatarata
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0007-1279-7394

Martyna Jaciubek
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0002-5520-0002

Carmena Luty
118th Military Hospital with Polyclinic SPZOZ in Ełk, Poland
ORCID ID: 0009-0007-6084-0385

Anna Kiełboń
Military Institute of Medicine in Warsaw, Mazovia, Poland
ORCID ID: 0009-0004-9028-6395

Zuzanna Olga Reklewska
The Military Medical Training Center, Łódź, Poland
ORCID ID: 0009-0008-3539-646X

Kornelia Domagała
7th Naval Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0008-4148-9320

Magdalena Rumin
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0009-4281-8971

ABSTRACT

Myocardial infarction (MI) remains a major global health burden, driving substantial healthcare costs and long-term societal impact due to progressive heart failure and reduced quality of life. Conventional therapies improve survival but do not restore lost myocardial tissue. Stem cell–based cardiac regeneration represents a disruptive biomedical innovation situated at the intersection of biotechnology, translational medicine, and health systems transformation. This review examines contemporary regenerative strategies—including mesenchymal stromal cells, induced pluripotent stem cells, and cardiac progenitor cells—with emphasis on their underlying molecular mechanisms and technological advancements. Particular attention is given to exosome engineering, gene-modified stem cells, biomaterial-assisted delivery systems, hydrogel scaffolds, and tissue-engineered cardiac patches. Evidence from preclinical and clinical studies indicates functional improvements mediated predominantly through paracrine signaling, angiogenic stimulation, and immunomodulatory regulation rather than direct cardiomyocyte replacement. However, technological scalability, manufacturing standardization under GMP conditions, safety concerns, regulatory frameworks, and cost-effectiveness remain critical barriers to widespread implementation. The integration of regenerative cardiology with bioengineering, nanotechnology, and precision medicine may enable more sustainable and accessible therapeutic models. By situating stem cell–based cardiac repair within a broader innovation ecosystem, this review highlights both the transformative potential and the systemic challenges associated with next-generation cardiovascular therapies.

KEYWORDS

Stem Cell Therapy, Cardiac Regeneration, Regenerative Biotechnology, Exosome Engineering, Tissue Engineering, Translational Medicine

CITATION

Amanda Abramowicz, Maja Osuch, Maciej Osuch, Olga Tatarata, Martyna Jaciubek, Carmena Luty, Anna Kiełboń, Zuzanna Olga Reklewska, Kornelia Domagała, Magdalena Rumin. (2026) Stem Cell–Based Myocardial Regeneration After Infarction: Molecular Mechanisms, Translational Challenges, and Emerging Biotechnological Innovations. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5045

Introduction

Myocardial infarction (MI) remains one of the leading causes of morbidity and mortality worldwide and continues to impose a substantial socioeconomic burden on healthcare systems. Despite significant advances in early reperfusion strategies, including primary percutaneous coronary intervention and optimized pharmacological therapy, post-infarction heart failure remains a major clinical challenge. Current treatment approaches primarily aim to restore perfusion, limit infarct size, and prevent adverse remodeling; however, they do not reverse irreversible cardiomyocyte loss (Frangogiannis, 2015; McDonagh et al., 2021).

The pathophysiology of myocardial infarction involves a complex cascade of ischemic injury, inflammatory activation, extracellular matrix degradation, and fibrotic scar formation. Acute ischemia triggers necrosis and apoptosis of cardiomyocytes, followed by robust recruitment of neutrophils and monocyte-derived macrophages. While this inflammatory response is essential for debris clearance, prolonged activation promotes matrix metalloproteinase activity, ventricular dilation, and progressive contractile dysfunction (Prabhu & Frangogiannis, 2016). The renin–angiotensin–aldosterone system and sympathetic nervous system further amplify adverse remodeling, ultimately leading to chronic heart failure.

Unlike lower vertebrates and neonatal mammals, the adult human myocardium exhibits minimal regenerative capacity. Mature cardiomyocytes are terminally differentiated and display limited proliferative potential. Following infarction, the damaged myocardium is replaced by fibrotic scar tissue, which lacks contractile properties and contributes to mechanical stress on viable myocardium (Hausenloy & Yellon, 2013). Consequently, the inability to regenerate functional cardiac muscle remains a fundamental limitation of conventional cardiovascular therapy.

Regenerative medicine has therefore emerged as a transformative field aiming to restore myocardial structure and function. Stem cell–based therapy represents one of the most intensively investigated strategies

in translational cardiology. Over the past two decades, multiple cell populations have been explored, including mesenchymal stromal cells (MSCs), induced pluripotent stem cells (iPSCs), embryonic stem cell–derived cardiomyocytes, and cardiac progenitor cells (CPCs) (Segers & Lee, 2008; Madonna et al., 2020).

Early conceptual frameworks proposed that transplanted stem cells would engraft, differentiate into cardiomyocytes, and structurally integrate into damaged myocardium. However, subsequent mechanistic studies revealed that long-term engraftment is limited and that the primary therapeutic mechanism is largely paracrine. Stem cells secrete growth factors, cytokines, chemokines, and extracellular vesicles that modulate intracellular signaling pathways, attenuate apoptosis, stimulate angiogenesis, and regulate immune responses (Ibrahim et al., 2014). Activation of key pathways such as PI3K/Akt, STAT3, and ERK1/2 has been consistently implicated in cardioprotection and survival signaling.

Particular attention has been directed toward extracellular vesicles and exosomes derived from MSCs. These nanoscale vesicles serve as carriers of microRNAs, messenger RNAs, proteins, and lipids, facilitating intercellular communication within ischemic myocardium. Exosome-mediated transfer of regulatory microRNAs has been shown to suppress pro-apoptotic signaling, enhance endothelial proliferation, and modulate macrophage polarization (Gallet et al., 2017). This cell-free approach may reduce immunogenic risk and eliminate concerns associated with uncontrolled cell proliferation.

Despite compelling preclinical data demonstrating significant improvements in left ventricular function and reduction of infarct size, translation into consistent clinical benefit has been modest. Meta-analyses of randomized clinical trials indicate statistically significant but moderate improvements in left ventricular ejection fraction and scar volume reduction (Gyongyosi et al., 2015). Heterogeneity in cell source, preparation protocols, delivery routes, dosing strategies, and timing of administration complicates interpretation and limits reproducibility.

Moreover, translational barriers such as low cell retention, hostile inflammatory microenvironment, oxidative stress, and insufficient electromechanical integration remain critical challenges. Emerging strategies—including genetic modification of stem cells, biomaterial-assisted delivery systems, tissue-engineered cardiac patches, and engineered exosome therapy—aim to overcome these limitations and enhance therapeutic efficacy.

The present review provides a comprehensive and mechanistically oriented analysis of stem cell–mediated myocardial regeneration following infarction. We examine molecular pathways underlying paracrine signaling, immunomodulation, and angiogenesis; evaluate preclinical and clinical evidence; and discuss translational challenges and emerging therapeutic strategies. By integrating recent advances in molecular biology, bioengineering, and clinical cardiology, this review aims to clarify the current state of regenerative cardiac therapy and outline future directions for effective myocardial restoration.

2. Methodology (Expanded Version)

This study was designed as a narrative review with structured elements of systematic literature analysis to ensure methodological rigor and reproducibility. The objective was to provide a comprehensive synthesis of contemporary evidence regarding stem cell–based myocardial regeneration following infarction, integrating mechanistic, preclinical, and clinical perspectives.

2.1 Literature Search Strategy

A structured literature search was conducted across major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science. The search encompassed publications from January 2010 to March 2025, with emphasis on high-quality studies published between 2018 and 2025 to ensure inclusion of the most recent translational advances.

Search terms were combined using Boolean operators and included:

- “myocardial infarction” OR “ischemic heart disease”
- “cardiac regeneration”
- “mesenchymal stem cells” OR “mesenchymal stromal cells”
- “induced pluripotent stem cells”
- “cardiac progenitor cells”
- “exosomes” OR “extracellular vesicles”
- “angiogenesis”
- “immunomodulation”
- “PI3K/Akt pathway”

- "STAT3"
- "ERK1/2"
- "hydrogel" OR "biomaterials"
- "clinical trial"
- "meta-analysis"

Medical Subject Headings (MeSH) were applied where appropriate to increase search sensitivity. Reference lists of relevant review articles and meta-analyses were manually screened to identify additional eligible studies.

2.2 Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

1. Original research articles, randomized controlled trials, cohort studies, meta-analyses, or systematic reviews.
2. Investigation of stem cell–based therapy in the context of myocardial infarction or ischemic cardiomyopathy.
3. Evaluation of mechanistic pathways, functional cardiac outcomes (e.g., LVEF), infarct size reduction, angiogenesis markers, apoptosis indices, inflammatory modulation, or ventricular remodeling.
4. Publication in peer-reviewed scientific journals with available DOI.

Exclusion criteria were:

- Non-peer-reviewed reports.
- Case reports with insufficient methodological detail.
- Studies lacking measurable functional or mechanistic endpoints.
- Theoretical publications without experimental or clinical validation.
- Non-English language articles.

2.3 Study Categorization

Eligible studies were categorized into three major domains:

1. **Mechanistic and molecular investigations**, focusing on intracellular signaling pathways, microRNA regulation, immunomodulatory mechanisms, and mitochondrial function.
2. **Preclinical experimental studies**, conducted in small (murine, rat) and large (porcine, ovine) animal models, evaluating cardiac function, infarct size, capillary density, apoptosis, oxidative stress, and biodistribution.
3. **Clinical studies**, including phase I–III trials and meta-analyses assessing safety, feasibility, functional improvement, quality of life, and incidence of major adverse cardiovascular events.

2.4 Data Extraction and Synthesis

For preclinical studies, extracted endpoints included:

- Change in left ventricular ejection fraction (LVEF),
- Infarct size reduction (histological or MRI-based),
- Capillary density and angiogenic markers,
- Apoptotic cell counts,
- Oxidative stress parameters,
- Retention and biodistribution of transplanted cells.

For clinical trials, data extraction focused on:

- Study design (randomized vs. non-randomized),
- Sample size,
- Cell type and source,
- Route of administration,
- Timing relative to infarction,
- Functional outcomes (LVEF, NYHA class),
- Major adverse cardiovascular events (MACE),
- Long-term follow-up outcomes.

Due to heterogeneity in study design and endpoints, quantitative pooling was not performed within this review. Instead, a qualitative synthesis was conducted, emphasizing consistency of mechanistic findings and reproducibility of functional outcomes across experimental platforms.

2.5 Methodological Limitations

The narrative review design, while comprehensive, inherently limits statistical aggregation. Heterogeneity in stem cell preparation, dosing protocols, imaging modalities, and outcome definitions complicates direct comparison across studies. Additionally, publication bias toward positive findings may influence the perceived efficacy of stem cell–based therapies.

Nevertheless, by integrating mechanistic insights with translational and clinical evidence, this structured synthesis aims to provide a balanced and critical overview of current regenerative strategies in myocardial infarction.

3. Types of Stem Cells Used in Myocardial Regeneration (Expanded Version)

3.1 Mesenchymal Stromal Cells (MSCs)

Mesenchymal stromal cells (MSCs) remain the most extensively investigated cell population in myocardial regenerative therapy. Defined by plastic adherence, expression of CD73, CD90, and CD105, and absence of hematopoietic markers such as CD34 and CD45 (Dominici et al., 2006), MSCs possess multipotent differentiation capacity and, more importantly, robust paracrine and immunomodulatory properties.

3.1.1 Tissue Sources and Biological Variability

MSCs can be isolated from bone marrow, adipose tissue, umbilical cord blood, and perinatal tissues. Increasing evidence suggests that tissue origin significantly influences their biological characteristics. Bone marrow–derived MSCs have been widely used in early clinical trials, whereas adipose-derived MSCs offer higher yield and less invasive procurement. Umbilical cord–derived MSCs exhibit enhanced proliferative capacity and reduced immunogenicity, potentially improving allogeneic applications.

However, biological heterogeneity remains a critical translational issue. Differences in donor age, culture conditions, passage number, and cryopreservation affect secretome composition, proliferative capacity, and therapeutic potency. These variables contribute to inconsistent clinical outcomes and underscore the need for standardized manufacturing protocols.

3.1.2 Paracrine Mechanisms and Secretome Profiling

It is now widely accepted that MSCs exert therapeutic effects primarily via paracrine signaling rather than direct differentiation into cardiomyocytes. Conditioned medium from MSC cultures has been shown to reproduce many cardioprotective effects observed with whole-cell therapy, emphasizing the importance of secreted factors.

The MSC secretome includes:

- Vascular endothelial growth factor (VEGF)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factor 1 (IGF-1)
- Fibroblast growth factor 2 (FGF-2)
- Stromal cell–derived factor 1 (SDF-1)

These molecules activate survival and angiogenic signaling pathways, including PI3K/Akt and STAT3, promoting endothelial proliferation and cardiomyocyte survival (Madonna et al., 2020).

Recent advances in proteomic and transcriptomic profiling have identified complex regulatory networks within the MSC secretome. Extracellular vesicles, particularly exosomes, are enriched with cardioprotective microRNAs such as miR-21, miR-126, and miR-210. These microRNAs suppress pro-apoptotic genes, enhance endothelial migration, and modulate hypoxia-responsive pathways (Ibrahim et al., 2014).

3.1.3 Immunomodulation and Macrophage Polarization

Inflammatory regulation constitutes a major component of MSC-mediated cardiac repair. Following myocardial infarction, excessive pro-inflammatory macrophage activity contributes to extracellular matrix degradation and ventricular dilation. MSCs modulate immune responses by suppressing T-cell proliferation and promoting macrophage polarization toward the reparative M2 phenotype (Vagnozzi et al., 2020).

M2 macrophages secrete anti-inflammatory cytokines and pro-angiogenic factors, facilitating scar stabilization and tissue repair. Emerging data also suggest that MSCs influence immunometabolic reprogramming of macrophages, shifting energy metabolism from glycolysis toward oxidative phosphorylation, thereby enhancing reparative functionality.

3.1.4 Mitochondrial Transfer and Metabolic Support

An emerging mechanism involves mitochondrial transfer from MSCs to injured cardiomyocytes via tunneling nanotubes or extracellular vesicles. This process restores mitochondrial membrane potential, improves ATP production, and reduces reactive oxygen species accumulation. Although still under investigation, mitochondrial transfer represents a promising mechanism of metabolic rescue in ischemic myocardium.

3.1.5 Clinical Translation and Limitations

Despite strong preclinical evidence, clinical trials demonstrate only moderate improvements in cardiac function. Limited cell retention, poor engraftment, and hostile inflammatory microenvironment remain key obstacles. Consequently, current research increasingly focuses on enhancing MSC survival and optimizing delivery systems.

3.2 Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) provide a theoretically unlimited source of patient-specific cardiomyocytes. Reprogramming of adult somatic cells through transcription factors such as Oct4, Sox2, Klf4, and c-Myc restores pluripotency (Takahashi & Yamanaka, 2006), enabling differentiation into cardiomyocytes, endothelial cells, and smooth muscle cells.

3.2.1 Cardiomyocyte Differentiation and Structural Integration

iPSC-derived cardiomyocytes (iPSC-CMs) demonstrate spontaneous contractile activity and expression of cardiac-specific markers. In preclinical large-animal models, transplantation of iPSC-CMs improves systolic function and reduces scar formation.

However, integration into host myocardium requires proper electrical coupling through gap junction proteins such as connexin-43. Inadequate synchronization increases arrhythmogenic risk, representing a significant safety concern (Eschenhagen & Weinberger, 2024).

3.2.2 Immature Phenotype and Metabolic Limitations

A major limitation of iPSC-CMs is their immature phenotype. These cells resemble fetal cardiomyocytes with predominant glycolytic metabolism and underdeveloped sarcomeric organization. Strategies to enhance maturation include:

- Mechanical stimulation
- Electrical pacing
- Three-dimensional culture systems
- Bioreactor-based conditioning

Improved metabolic maturation toward oxidative phosphorylation is essential for durable electromechanical integration.

3.2.3 Tumorigenicity and Safety Considerations

Residual undifferentiated pluripotent cells pose a risk of teratoma formation. Rigorous purification protocols and quality control assays are therefore mandatory prior to clinical application. Gene editing approaches and suicide gene systems are being explored to enhance safety profiles.

3.3 Cardiac Progenitor Cells (CPCs)

Cardiac progenitor cells represent an endogenous population capable of differentiating into cardiomyocytes and vascular lineages. Subpopulations such as c-kit+ cells have been investigated extensively; however, reproducibility and methodological controversies have tempered initial enthusiasm.

While some early clinical trials suggested potential functional improvement, subsequent studies have produced inconsistent results. Limited proliferative capacity, age-related decline, and difficulty in large-scale expansion restrict their translational potential.

Nevertheless, CPCs may retain value in combination strategies, particularly when used alongside MSCs to exploit complementary mechanisms of immunomodulation and differentiation.

4. Molecular Mechanisms of Stem Cell–Mediated Cardiac Repair

Stem cell–mediated myocardial repair is governed by a complex interplay of intracellular signaling cascades, intercellular communication networks, metabolic reprogramming, and extracellular matrix modulation. Contemporary evidence indicates that functional improvement observed after stem cell therapy is not the result of direct structural replacement alone, but rather a coordinated orchestration of survival signaling, angiogenesis, immunomodulation, and anti-fibrotic remodeling.

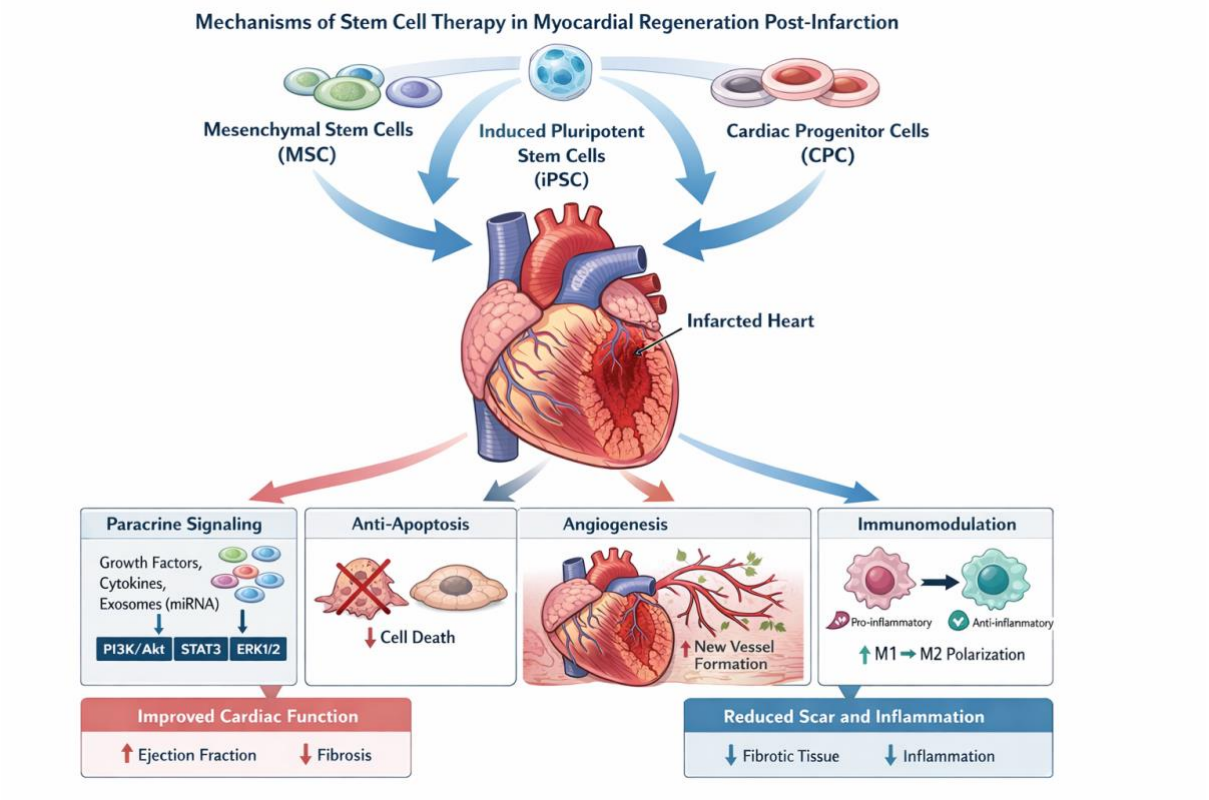

Fig. 1. *Molecular and Paracrine Mechanisms of Stem Cell–Mediated Cardiac Regeneration After Myocardial Infarction*

Abbreviations: MSC = mesenchymal stromal cells; VEGF = vascular endothelial growth factor; HGF = hepatocyte growth factor; IGF-1 = insulin-like growth factor 1; PI3K = phosphoinositide 3-kinase; ERK = extracellular signal-regulated kinase.

Table 1. Comparative Characteristics of Stem Cell Types Used in Myocardial Regeneration

Cell Type	Source	Primary Mechanism	Advantages	Limitations	Clinical Development Stage
Mesenchymal Stromal Cells (MSC)	Bone marrow, adipose tissue, umbilical cord	Paracrine signaling, exosome secretion, immunomodulation	Low immunogenicity, strong safety record	Low retention rate; limited differentiation into cardiomyocytes	Phase I–III clinical trials
Induced Pluripotent Stem Cells (iPSC)	Reprogrammed adult somatic cells	Differentiation into cardiomyocytes; tissue integration	Potential for structural myocardial replacement	Arrhythmogenic risk; tumorigenicity concerns	Preclinical / early translational stage
Cardiac Progenitor Cells (CPC)	Resident cardiac tissue	Paracrine signaling + partial differentiation	Physiological myocardial compatibility	Limited proliferation capacity	Early-phase clinical studies

Abbreviations: MSC = mesenchymal stromal cells; iPSC = induced pluripotent stem cells; CPC = cardiac progenitor cells; iPSC-CM = induced pluripotent stem cell–derived cardiomyocytes; LVEF = left ventricular ejection fraction.

4.1 Activation of Pro-survival Signaling Pathways

4.1.1 PI3K/Akt Pathway

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway represents one of the most consistently implicated cardioprotective signaling cascades activated following stem cell therapy. Activation occurs primarily through paracrine growth factors such as VEGF, IGF-1, and HGF released by MSCs.

Upon ligand binding to receptor tyrosine kinases, PI3K generates phosphatidylinositol (3,4,5)-trisphosphate, recruiting Akt to the plasma membrane where it becomes phosphorylated and activated. Activated Akt promotes cardiomyocyte survival by:

- Upregulating anti-apoptotic proteins (Bcl-2, Bcl-xL),
- Inhibiting pro-apoptotic mediators (Bad, Bax),
- Suppressing caspase-9 activation,
- Enhancing nitric oxide synthase (eNOS) activity.

Experimental models demonstrate that inhibition of Akt signaling abolishes the cardioprotective effects of MSC transplantation (Uemura et al., 2006), underscoring its central mechanistic role.

4.1.2 STAT3 Signaling

Signal transducer and activator of transcription 3 (STAT3) functions as a critical mediator of cardiomyocyte survival and mitochondrial integrity. Paracrine cytokines activate Janus kinases (JAKs), which phosphorylate STAT3, enabling nuclear translocation and transcriptional activation of survival genes.

Beyond nuclear transcription, mitochondrial STAT3 modulates electron transport chain efficiency and reduces reactive oxygen species (ROS) production. Preservation of mitochondrial membrane potential following stem cell therapy has been linked to STAT3-dependent mechanisms.

4.1.3 ERK1/2 and MAPK Pathways

Extracellular signal-regulated kinases (ERK1/2) belong to the mitogen-activated protein kinase (MAPK) family and regulate cellular proliferation, survival, and hypertrophic responses. MSC-derived growth factors stimulate ERK phosphorylation, promoting endothelial cell proliferation and cardiomyocyte resistance to ischemic stress.

Importantly, balanced ERK activation appears beneficial, whereas chronic hyperactivation may contribute to maladaptive hypertrophy. Thus, controlled modulation of this pathway is critical for optimal regenerative outcomes.

4.2 Inhibition of Apoptosis and Mitochondrial Stabilization

Apoptosis contributes substantially to cardiomyocyte loss in the peri-infarct zone. Stem cell therapy attenuates apoptotic signaling through both intrinsic and extrinsic pathways.

4.2.1 Regulation of Bcl-2 Family Proteins

The intrinsic apoptotic pathway is governed by mitochondrial outer membrane permeability. MSC-mediated Akt activation enhances expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, while suppressing Bax translocation to mitochondria (Dorn & Molkentin, 2004).

Reduced cytochrome c release prevents downstream activation of caspase-3 and caspase-9, limiting programmed cell death in ischemic cardiomyocytes.

4.2.2 Mitochondrial Bioenergetics and ROS Reduction

Ischemia-reperfusion injury is characterized by excessive ROS production, mitochondrial swelling, and permeability transition pore opening. Stem cell–derived paracrine factors enhance antioxidant defenses by increasing expression of superoxide dismutase (SOD) and catalase.

Emerging evidence suggests that mitochondrial transfer from MSCs to injured cardiomyocytes may directly restore oxidative phosphorylation capacity and ATP production. This mechanism may contribute to improved contractile recovery beyond simple anti-apoptotic signaling.

4.3 Angiogenesis and Neovascularization

Restoration of perfusion in the peri-infarct region is essential for durable myocardial repair. Stem cells promote angiogenesis through secretion of VEGF, FGF-2, angiopoietins, and SDF-1.

4.3.1 Endothelial Activation

VEGF binding to VEGFR2 activates PI3K/Akt and ERK pathways in endothelial cells, stimulating proliferation, migration, and tube formation. Increased capillary density has been consistently observed in preclinical MSC studies.

4.3.2 MicroRNA-Mediated Angiogenic Regulation

Extracellular vesicles derived from MSCs contain angiogenesis-promoting microRNAs:

- miR-126 enhances endothelial repair and vascular integrity.
- miR-210 regulates hypoxia-inducible pathways.
- miR-21 suppresses PTEN, thereby amplifying Akt signaling.

Transfer of these regulatory molecules reprograms recipient endothelial cells and enhances vascular regeneration.

4.4 Immunomodulation and Inflammatory Resolution

Inflammation is a double-edged sword in myocardial infarction. Initial inflammatory infiltration is necessary for necrotic tissue clearance, yet excessive or prolonged inflammation exacerbates remodeling.

4.4.1 Macrophage Polarization

Stem cells promote macrophage polarization toward the reparative M2 phenotype, characterized by secretion of IL-10 and TGF-β. This shift reduces pro-inflammatory cytokines such as TNF-α and IL-1β (Vagnozzi et al., 2020).

Macrophage-mediated extracellular matrix stabilization contributes to scar organization and prevention of ventricular dilation.

4.4.2 T-cell Suppression and Cytokine Modulation

MSCs suppress T-cell proliferation via indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2. This immunosuppressive effect attenuates chronic inflammatory activation and supports reparative processes.

4.5 Extracellular Matrix Remodeling and Fibrosis Control

Adverse remodeling after myocardial infarction is driven by excessive deposition of collagen types I and III. Matrix metalloproteinases (MMPs) regulate extracellular matrix turnover, and imbalance leads to ventricular dilation.

Stem cell therapy has been associated with:

- Reduced MMP activation,
- Modulation of transforming growth factor-β (TGF-β) signaling,
- Decreased myofibroblast activation,
- Reduction of fibrotic scar expansion.

Controlled modulation of fibrogenic pathways may preserve ventricular geometry and improve mechanical efficiency.

4.6 Integration of Molecular Mechanisms

Importantly, these molecular pathways do not function independently. PI3K/Akt activation intersects with STAT3 signaling; microRNA regulation influences mitochondrial stability; and immunomodulation impacts extracellular matrix remodeling.

The therapeutic benefit of stem cell–based cardiac repair arises from coordinated multi-level regulation rather than single-pathway activation. Understanding these integrated networks is essential for optimizing next-generation regenerative strategies.

5. Preclinical Evidence of Stem Cell–Based Cardiac Regeneration (Expanded Version)

Preclinical investigations form the scientific foundation for translational application of stem cell–based myocardial repair. Over the past two decades, numerous studies have evaluated functional, structural, and molecular outcomes in small and large animal models of myocardial infarction. While mechanistic consistency has been observed across experimental systems, translational reproducibility remains a critical issue.

5.1 Small Animal Models (Murine and Rat Models)

Rodent models of myocardial infarction, typically induced by permanent ligation or ischemia-reperfusion of the left anterior descending coronary artery, are widely used to evaluate early-stage regenerative strategies.

5.1.1 Functional Improvement

In murine and rat models, administration of MSCs has been associated with:

- Improvement in left ventricular ejection fraction (LVEF) by approximately 10–15% relative to controls,
- Reduction of infarct size by 20–35%,
- Increased capillary density in peri-infarct regions.

These functional improvements correlate with activation of pro-survival signaling pathways (PI3K/Akt, ERK1/2) and reduced apoptotic indices (Tang et al., 2004).

5.1.2 Histological and Molecular Findings

Histological analyses consistently demonstrate:

- Decreased cardiomyocyte apoptosis (reduction up to 30–40%),
- Reduced collagen deposition,
- Increased expression of angiogenic markers (VEGF, CD31).

Moreover, exosome-based therapy in rodent models has reproduced many benefits observed with whole-cell transplantation, suggesting that paracrine mechanisms dominate therapeutic outcomes.

5.1.3 Limitations of Rodent Models

Despite robust efficacy signals, rodent models have limitations:

- Differences in heart rate and myocardial metabolism,
- Limited resemblance to human coronary anatomy,
- Shorter follow-up periods,
- Overestimation of cell retention.

Therefore, while small animal studies provide mechanistic clarity, they may exaggerate translational efficacy.

5.2 Large Animal Models (Porcine and Ovine Models)

Large animal models more closely replicate human cardiac anatomy, electrophysiology, and remodeling patterns. Porcine models are particularly valuable due to similar coronary circulation and ventricular geometry.

5.2.1 Functional Outcomes

In porcine infarction models, MSC transplantation via intracoronary or intramyocardial delivery has resulted in:

- LVEF improvement of 8–12%,
- Reduction in scar volume by approximately 15–20%,
- Decreased left ventricular end-diastolic volume,
- Improved regional wall motion assessed by MRI.

Cardiac magnetic resonance imaging (CMR) has become the gold standard for objective assessment of infarct size and ventricular remodeling in large animals.

5.2.2 Biodistribution and Retention

A major translational barrier identified in large animal studies is low cell retention. Quantitative tracking using radiolabeled or genetically tagged MSCs reveals that:

- Less than 5–10% of administered cells remain in the myocardium after 24 hours,
- Significant cell washout occurs following intracoronary infusion,
- Intramyocardial injection improves local retention but increases procedural invasiveness.

Strategies such as magnetic targeting (Cheng et al., 2010), hydrogel encapsulation, and scaffold-assisted delivery have been investigated to enhance retention and survival.

5.2.3 Electrophysiological Safety

In large animal models, iPSC-derived cardiomyocytes have demonstrated improved contractility but increased risk of ventricular arrhythmias. Electromechanical mismatch and immature ion channel expression contribute to pro-arrhythmic vulnerability, highlighting safety concerns prior to clinical translation.

5.3 Dose–Response Relationships

Preclinical data suggest a non-linear dose–response relationship. Higher cell doses do not necessarily produce superior functional recovery and may increase microvascular obstruction risk. Optimal dosing appears to balance paracrine efficacy with microcirculatory safety.

Repeated dosing paradigms have also been explored. Some studies indicate that sequential administration may sustain paracrine signaling and enhance long-term remodeling attenuation.

5.4 Comparative Analysis: Whole Cells vs Exosomes

Emerging preclinical evidence indicates that purified extracellular vesicles can reproduce cardioprotective effects comparable to whole-cell therapy. Advantages of exosome therapy include:

- Lower immunogenicity,
- Absence of tumorigenic risk,
- Easier storage and standardization,
- Reduced risk of microvascular obstruction.

In porcine models, exosome administration improved cardiac function and reduced scar formation without evidence of arrhythmogenic complications (Gallet et al., 2017).

5.5 Translational Gaps Identified in Preclinical Research

Despite promising outcomes, several limitations hinder translation:

1. Variability in cell characterization and potency assays,
2. Differences in delivery timing (acute vs chronic infarction),
3. Lack of standardized imaging endpoints,
4. Inadequate long-term follow-up,
5. Publication bias toward positive results.

These gaps partly explain the discrepancy between robust preclinical benefits and modest clinical improvements.

Summary of Preclinical Evidence

Collectively, preclinical studies demonstrate consistent improvements in:

- Ventricular function,
- Infarct size reduction,
- Angiogenesis,
- Anti-apoptotic signaling,
- Inflammatory modulation.

However, limited cell retention and heterogeneous protocols remain major translational obstacles.

6. Clinical Evidence of Stem Cell–Based Therapy After Myocardial Infarction (Expanded Version)

While preclinical studies consistently demonstrate significant improvements in cardiac function and structural remodeling, translation into clinical benefit has been more modest and heterogeneous. Clinical trials over the past two decades have primarily evaluated the safety, feasibility, and preliminary efficacy of mesenchymal stromal cells (MSCs), with more limited data available for induced pluripotent stem cells (iPSCs) and cardiac progenitor cells (CPCs).

6.1 Early-Phase Clinical Trials

Initial phase I and II trials were primarily designed to assess safety rather than definitive efficacy. Across multiple studies, MSC therapy demonstrated a favorable safety profile, with no consistent increase in malignant arrhythmias, tumor formation, or severe immune reactions.

6.1.1 POSEIDON Trial

The POSEIDON trial compared autologous and allogeneic bone marrow–derived MSCs in patients with ischemic cardiomyopathy. Results demonstrated:

- Improvement in left ventricular ejection fraction (LVEF) of approximately 5–7%,
- Reduction in scar size assessed by imaging,
- Favorable remodeling indices.

Importantly, no significant difference in safety was observed between autologous and allogeneic groups, supporting the feasibility of allogeneic MSC therapy (Hare et al., 2012).

6.1.2 TAC-HFT Trial

The TAC-HFT study evaluated transendocardial injection of MSCs and bone marrow mononuclear cells in patients with ischemic heart failure. MSC therapy resulted in:

- Improved quality of life scores,
- Increased functional capacity,
- Reduced scar mass.

Functional gains were modest but statistically significant, reinforcing the concept of paracrine-mediated improvement rather than structural myocardial replacement.

6.2 Meta-Analyses and Systematic Reviews

Multiple meta-analyses have attempted to synthesize clinical trial data. A large meta-analysis of cell-based therapies in acute myocardial infarction reported:

- Mean LVEF improvement of approximately 4–6%,
- Reduction in infarct size by 8–12%,
- Trends toward reduced ventricular volumes (Gyongyosi et al., 2015).

However, statistical heterogeneity across trials was substantial, largely due to:

- Variability in cell source (bone marrow vs adipose vs umbilical),
- Differences in cell processing and expansion,
- Timing of administration (acute vs chronic phase),
- Route of delivery (intracoronary vs intramyocardial),
- Imaging modality used to assess outcomes.

These methodological differences limit direct comparison and complicate meta-analytic interpretation.

6.3 Safety Profile

A consistent finding across trials is the favorable safety profile of MSC therapy. Reported adverse events have not demonstrated increased rates of:

- Sustained ventricular arrhythmias,
- Major adverse cardiovascular events (MACE),
- Immune rejection.

Long-term follow-up data suggest that MSC therapy does not increase mortality risk. However, definitive mortality reduction has not been conclusively demonstrated.

In contrast, clinical translation of iPSC-derived cardiomyocytes remains in early experimental stages due to concerns regarding arrhythmogenicity and tumorigenicity. Electrophysiological mismatch between transplanted cells and host myocardium remains a critical barrier.

6.4 The BAMI Trial and Large-Scale Studies

The BAMI (Bone Marrow–Derived Mononuclear Cells for Acute Myocardial Infarction) trial was designed to evaluate mortality reduction following cell therapy. Although enrollment challenges limited statistical power, results did not demonstrate a significant mortality benefit compared to standard care.

This underscores a fundamental issue in regenerative cardiology: while surrogate markers such as LVEF and scar size improve modestly, demonstrating hard clinical endpoints (mortality reduction) remains difficult.

6.5 Long-Term Outcomes and Quality of Life

Some trials have reported sustained functional improvement up to 2–3 years post-treatment, particularly in quality of life metrics and exercise tolerance. Improvements in NYHA functional class have been documented in selected cohorts.

However, durability of benefit varies, and repeated cell administration paradigms have been proposed to maintain paracrine effects over time.

6.6 Clinical Interpretation

Collectively, clinical evidence suggests:

- MSC therapy is safe.
- Functional improvement is statistically significant but moderate.
- Structural regeneration is limited.
- Mortality benefit remains unproven.

The discrepancy between strong preclinical efficacy and modest clinical benefit highlights translational barriers, including low cell retention, hostile post-infarct microenvironment, and variability in cell manufacturing.

Summary of Clinical Evidence

Stem cell therapy following myocardial infarction is clinically feasible and safe, with modest improvements in ventricular function and scar reduction. However, consistent demonstration of robust structural regeneration or survival benefit remains elusive. Optimization of delivery systems, standardization of manufacturing, and enhanced mechanistic targeting are required to improve therapeutic efficacy.

7. Translational Challenges in Stem Cell–Based Myocardial Regeneration (Expanded Version)

Despite compelling mechanistic insights and promising preclinical results, translation of stem cell–based therapies into consistent clinical benefit remains limited. Multiple biological, technical, regulatory, and economic barriers contribute to this translational gap.

7.1 Limited Cell Retention and Survival

One of the most critical obstacles is low myocardial retention of transplanted cells. Quantitative tracking studies have demonstrated that:

- Less than 5% of administered MSCs remain in the myocardium 24 hours after delivery.
- Significant washout occurs following intracoronary administration.
- Injected cells are often trapped in the pulmonary circulation when delivered intravenously.

The post-infarction microenvironment is characterized by:

- Hypoxia,
- Oxidative stress,
- Inflammatory cytokine release,
- Matrix instability.

These conditions promote rapid apoptosis of transplanted cells, limiting long-term engraftment. Consequently, the therapeutic effect may depend on short-lived paracrine bursts rather than durable structural integration.

7.2 Biological Heterogeneity and Manufacturing Variability

MSC populations exhibit significant donor-dependent variability influenced by:

- Age,
- Comorbidities,
- Culture conditions,
- Passage number,
- Cryopreservation protocols.

Differences in secretome composition and immunomodulatory capacity complicate reproducibility across studies.

Good Manufacturing Practice (GMP)–compliant expansion is essential for clinical application. However, large-scale expansion can alter cell phenotype, reduce potency, and induce senescence. Standardized potency assays are not yet universally established, making cross-trial comparison challenging.

7.3 Standardization of Potency Assays

Unlike small-molecule drugs, cell-based therapies lack single measurable active components. Potency may depend on:

- Paracrine factor secretion,
- Immunomodulatory capacity,
- Extracellular vesicle release,
- Viability and metabolic state.

Developing standardized assays that predict in vivo therapeutic efficacy remains a major regulatory requirement. Without validated potency metrics, reproducibility and regulatory approval become more difficult.

7.4 Delivery Route Optimization

The optimal route of administration remains debated:

- Intracoronary delivery is less invasive but associated with cell washout.
- Intramyocardial injection improves local retention but requires invasive catheter-based procedures.
- Epicardial patches or scaffold-based approaches enhance retention but increase procedural complexity.

Emerging biomaterial-based systems aim to create protective niches that enhance cell survival and controlled paracrine release.

7.5 Electrophysiological Integration and Arrhythmogenic Risk

For iPSC-derived cardiomyocytes, incomplete electrophysiological maturation remains a significant safety concern. Immature ion channel expression and conduction heterogeneity may predispose to ventricular arrhythmias.

Ensuring proper gap junction formation and synchronized excitation-contraction coupling is essential prior to large-scale clinical application.

7.6 Regulatory and Ethical Considerations

Cell-based therapies are classified as advanced therapy medicinal products (ATMPs) in many jurisdictions. Regulatory approval requires:

- Rigorous quality control,
- Sterility testing,
- Genetic stability assessment,
- Tumorigenicity testing (particularly for pluripotent cells).

These requirements increase development costs and prolong translational timelines.

7.7 Economic and Scalability Constraints

Production of autologous cell therapies is labor-intensive and costly. Allogeneic "off-the-shelf" MSC products may improve scalability but require strict immunological safety validation.

Cost-effectiveness analyses are limited, and long-term economic viability remains uncertain compared with established pharmacological therapies.

7.8 Discrepancy Between Preclinical and Clinical Outcomes

The contrast between robust functional gains in animal models and moderate improvement in human trials likely reflects:

- Differences in species biology,
- Controlled experimental conditions vs heterogeneous patient populations,
- Comorbidities in human subjects,
- Variability in infarct size and timing.

Bridging this gap requires more predictive translational models and improved trial design.

Summary of Translational Barriers

Stem cell–based myocardial regeneration faces interconnected challenges involving cell survival, manufacturing consistency, delivery optimization, regulatory complexity, and economic feasibility. Addressing these barriers is essential for achieving clinically meaningful regeneration beyond modest functional improvement.

8. Emerging Strategies to Enhance Therapeutic Efficacy (Expanded Version)

Given the biological and translational limitations observed in conventional stem cell therapy, multiple next-generation strategies have been developed to enhance therapeutic potency, durability, and safety. These approaches aim to improve cell survival, optimize paracrine signaling, promote structural integration, and overcome hostile post-infarction microenvironmental conditions.

8.1 Genetic Modification of Stem Cells

Genetic engineering represents one of the most promising strategies to enhance regenerative efficacy.

8.1.1 Overexpression of Pro-survival Genes

MSCs genetically modified to overexpress pro-survival or pro-angiogenic genes demonstrate enhanced therapeutic performance in preclinical models. Examples include:

- Akt overexpression → increased resistance to apoptosis and improved myocardial function.
- VEGF overexpression → enhanced neovascularization and improved perfusion.
- HGF overexpression → anti-fibrotic and cytoprotective effects.

Preclinical studies indicate that Akt-modified MSCs produce greater LVEF improvement compared to unmodified cells, suggesting amplification of intrinsic survival signaling pathways.

8.1.2 Anti-apoptotic and Anti-oxidative Enhancements

Engineering MSCs to enhance antioxidant capacity (e.g., upregulating superoxide dismutase or catalase) may improve resistance to oxidative stress within the infarcted myocardium.

CRISPR-based gene editing approaches are also being explored to eliminate senescence-associated genes and enhance regenerative phenotype stability.

8.2 Biomaterials and Hydrogel-Based Delivery Systems

Low retention rates following conventional injection have driven development of biomaterial-assisted delivery systems.

8.2.1 Injectable Hydrogels

Biocompatible hydrogels can:

- Provide mechanical support to infarcted myocardium,
- Improve local cell retention,
- Enable sustained release of paracrine factors,
- Protect transplanted cells from oxidative stress.

Hydrogel matrices may also modulate inflammatory responses and facilitate angiogenesis through controlled degradation and bioactive factor incorporation.

8.2.2 Scaffold-Based Cardiac Patches

Three-dimensional engineered cardiac patches composed of biomaterials and stem cell–derived cardiomyocytes represent a structural regenerative approach.

These constructs aim to:

- Restore contractile mass,
- Improve mechanical synchrony,
- Promote electromechanical integration.

However, issues of vascularization, immune compatibility, and arrhythmogenic risk remain under investigation.

8.3 Engineered Extracellular Vesicles and Exosome Therapy

Exosome-based therapy has emerged as a promising cell-free alternative.

8.3.1 Advantages Over Whole-Cell Therapy

Exosomes offer several advantages:

- Reduced immunogenicity,
- No risk of uncontrolled proliferation,
- Improved storage stability,
- Easier standardization under GMP conditions.

8.3.2 Engineering of Exosomes

Advanced bioengineering techniques allow:

- Enrichment of specific microRNAs (e.g., miR-21, miR-126),
- Surface modification for targeted delivery,
- Enhanced uptake by ischemic cardiomyocytes.

Targeted exosome therapy may represent a scalable and safer regenerative strategy compared with cellular transplantation.

8.4 Tissue Engineering and 3D Culture Systems

Three-dimensional culture platforms and bioreactors enhance maturation of iPSC-derived cardiomyocytes.

Mechanical loading and electrical stimulation promote:

- Sarcomere organization,
- Improved calcium handling,
- Transition from glycolytic to oxidative metabolism,
- Increased electrophysiological stability.

Large engineered cardiac muscle patches derived from human iPSCs have demonstrated functional integration in large animal models, representing a major advance in structural cardiac regeneration.

8.5 Repeated Dosing Paradigms

Given that paracrine effects are transient, repeated administration strategies are being explored. Sequential dosing may:

- Sustain immunomodulatory signaling,
- Prolong angiogenic stimulation,
- Prevent progressive remodeling.

The "repeated cell therapy paradigm" proposes that regenerative benefits may require ongoing biological modulation rather than single-dose intervention.

8.6 Combination Therapies

Future regenerative approaches may integrate:

- Stem cells + biomaterials,
- Stem cells + gene editing,
- Exosomes + pharmacological cardioprotective agents,
- Regenerative therapy + mechanical unloading devices.

Multimodal strategies may address the multifactorial nature of post-infarction remodeling more effectively than single-intervention approaches.

Summary of Emerging Strategies

Innovative approaches—including genetic enhancement, biomaterial-assisted delivery, engineered extracellular vesicles, and tissue engineering—are actively being developed to overcome limitations of traditional stem cell therapy. While many remain in preclinical or early translational stages, they represent a shift toward precision regenerative cardiology.

9. Conclusions and Future Perspectives

Stem cell–based therapy represents one of the most extensively investigated regenerative strategies in contemporary cardiovascular medicine. Accumulated mechanistic, preclinical, and early clinical evidence demonstrates that stem cells—particularly mesenchymal stromal cells—exert reproducible cardioprotective effects following myocardial infarction. These effects are mediated predominantly through paracrine signaling, activation of pro-survival pathways such as PI3K/Akt and STAT3, immunomodulation, enhancement of angiogenesis, and attenuation of adverse ventricular remodeling.

However, despite strong biological plausibility and consistent functional improvement in animal models, clinical translation has yielded moderate and heterogeneous outcomes. Improvements in left ventricular ejection fraction and scar reduction are statistically significant but modest, and robust mortality reduction has not yet been conclusively demonstrated. The discrepancy between experimental and clinical efficacy underscores persistent translational barriers, including limited cell retention, microenvironmental hostility, biological heterogeneity, and lack of standardized potency assessment.

The field is now transitioning from first-generation cell transplantation approaches toward more refined regenerative paradigms. Emerging strategies—such as genetic enhancement of stem cells, hydrogel-assisted delivery, engineered extracellular vesicles, and tissue-engineered cardiac patches—aim to increase therapeutic precision, durability, and safety. Particularly promising is the development of cell-free exosome-based therapies, which may overcome concerns related to tumorigenicity, arrhythmogenicity, and manufacturing complexity.

Future research should prioritize:

1. Standardization of manufacturing protocols under GMP conditions.
2. Development of validated potency assays predictive of in vivo efficacy.
3. Optimization of delivery systems to enhance myocardial retention.
4. Large, adequately powered randomized clinical trials evaluating hard endpoints.
5. Integration of molecular profiling to personalize regenerative therapy.

Advances in molecular biology, bioengineering, and translational cardiology are progressively reshaping the landscape of myocardial regeneration. While complete structural restoration of infarcted myocardium remains an ambitious objective, incremental improvements in functional recovery and remodeling attenuation suggest that regenerative therapy may become an important adjunct to contemporary heart failure management.

Ultimately, the future of cardiac regeneration will likely depend on integrated, multimodal strategies combining cellular engineering, biomaterials, and precision molecular targeting. Continued interdisciplinary

collaboration will be essential to transform promising experimental findings into durable clinical benefit for patients with ischemic heart disease.

Table 2. Summary of Preclinical and Clinical Outcomes of Stem Cell Therapy After Myocardial Infarction

Study Model	Intervention	LVEF Improvement	Scar Size Reduction	Key Observations
Rodent Models (MI)	MSC Intramyocardial Injection	+10–15%	25–35%	Reduced apoptosis; increased angiogenesis
Large Animal Models (Swine)	MSC / iPSC-derived cardiomyocytes	+8–12%	15–25%	Improved regional perfusion (MRI-confirmed)
Exosome Therapy Models	MSC-derived extracellular vesicles	Comparable to MSC therapy	Significant reduction	Lower immunogenicity; safer profile
Phase I–II Clinical Trials	Autologous/Allogeneic MSCs	+3–8%	Moderate reduction	High safety; modest functional benefit

Note. Summary of selected preclinical and clinical trials evaluating stem cell–based therapy after myocardial infarction.

Abbreviations: MSC = mesenchymal stromal cells; BM-MNC = bone marrow–derived mononuclear cells; iPSC = induced pluripotent stem cells; iPSC-CM = induced pluripotent stem cell–derived cardiomyocytes; CPC = cardiac progenitor cells; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New; York Heart Association functional class; MACE = major adverse cardiovascular events; MRI = magnetic resonance imaging; CMR = cardiac magnetic resonance

POSEIDON = Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis

TAC-HFT = Transendocardial Autologous Cells in Ischemic Heart Failure Trial

BAMI = Bone Marrow–Derived Mononuclear Cells for Acute Myocardial Infarction.

REFERENCES

1. Bolli, R. (2016). Repeated cell therapy paradigm for ischemic heart disease. *Circulation Research, 118*(7), 1094–1096. https://doi.org/10.1161/CIRCRESAHA.116.308203
2. Cambria, E., Pasqualini, F. S., Wolint, P., et al. (2017). Translational cardiac tissue engineering: Advanced models and regenerative strategies. *Circulation Research, 120*(8), 1247–1260. https://doi.org/10.1161/CIRCRESAHA.116.309538
3. Cheng, K., Malliaras, K., Li, T. S., et al. (2010). Magnetic targeting enhances engraftment and functional benefit of mesenchymal stem cells in infarcted myocardium. *Circulation, 122*(11 Suppl), S98–S106. https://doi.org/10.1161/CIRCULATIONAHA.109.928515
4. Chong, J. J. H., Yang, X., Don, C. W., et al. (2014). Human embryonic stem cell–derived cardiomyocytes regenerate non-human primate hearts. *Nature, 510*(7504), 273–277. https://doi.org/10.1038/nature13233
5. Dominici, M., Le Blanc, K., Mueller, I., et al. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. *Cytotherapy, 8*(4), 315–317. https://doi.org/10.1080/14653240600855905
6. Dorn, G. W., & Molkentin, J. D. (2004). Apoptosis in cardiac disease. *Circulation, 109*(12), 1509–1513. https://doi.org/10.1161/01.CIR.0000128492.24761.58
7. Eschenhagen, T., & Weinberger, F. (2024). Challenges of heart repair with pluripotent stem cell–derived cardiomyocytes. *Nature Cardiovascular Research, 3*(6), 515–524. https://doi.org/10.1038/s44161-024-00256-5
8. Frangogiannis, N. G. (2015). Pathophysiology of myocardial infarction. *Circulation Research, 116*(5), 848–865. https://doi.org/10.1161/CIRCRESAHA.116.303535
9. 9.Gallet, R., Dawkins, J., Valle, J., et al. (2017). Exosomes secreted by cardiosphere-derived cells reduce scar size and improve function in porcine myocardial infarction. *Stem Cells, 35*(4), 1154–1167. https://doi.org/10.1002/stem.2568
10. Gyongyosi, M., Wojakowski, W., Lemarchand, P., et al. (2015). Meta-analysis of cell-based cardiac studies in acute myocardial infarction. *Circulation Research, 116*(8), 1346–1360. https://doi.org/10.1161/CIRCRESAHA.116.304346

11. Hare, J. M., Traverse, J. H., Henry, T. D., et al. (2012). A randomized comparison of allogeneic versus autologous mesenchymal stem cells for ischemic cardiomyopathy. *JAMA, 308*(22), 2369–2379. https://doi.org/10.1001/jama.2012.25321
12. Hausenloy, D. J., & Yellon, D. M. (2013). Myocardial ischemia–reperfusion injury: A neglected therapeutic target. *Cardiovascular Research, 99*(1), 1–13. https://doi.org/10.1093/cvr/cvt044
13. Ibrahim, A. G., Cheng, K., & Marbán, E. (2014). Exosomes as critical agents of cardiac repair. *Circulation Research, 114*(11), 1757–1764. https://doi.org/10.1161/CIRCRESAHA.114.303614
14. Jiang, X., Lian, X., Wei, K., et al. (2024). Maturation of pluripotent stem cell–derived cardiomyocytes: Mechanisms and translational implications. *Stem Cell Research & Therapy, 15*(1), 354. https://doi.org/10.1186/s13287-024-03540-7
15. Khan, M., Nickoloff, E., Abramova, T., et al. (2015). Embryonic stem cell–derived exosomes promote cardiac repair. *Circulation Research, 117*(1), 52–64. https://doi.org/10.1161/CIRCRESAHA.117.305990
16. Madonna, R., Van Laake, L. W., Davidson, S. M., et al. (2020). Mesenchymal stem cells and angiogenesis. *Cardiovascular Research, 116*(6), 1142–1154. https://doi.org/10.1093/cvr/cvaa046
17. McDonagh, T. A., Metra, M., Adamo, M., et al. (2021). 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal, 42*(36), 3599–3726. https://doi.org/10.1093/eurheartj/ehab368
18. Prabhu, S. D., & Frangogiannis, N. G. (2016). The biological basis for cardiac repair after myocardial infarction. *Circulation Research, 119*(1), 91–112. https://doi.org/10.1161/CIRCRESAHA.116.303577
19. Segers, V. F., & Lee, R. T. (2008). Stem-cell therapy for cardiac disease. *Nature, 451*(7181), 937–942. https://doi.org/10.1038/nature06800
20. Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells by defined factors. *Cell, 126*(4), 663–676. https://doi.org/10.1016/j.cell.2006.07.024
21. Tang, Y. L., Zhao, Q., Zhang, Y. C., et al. (2004). Autologous mesenchymal stem cell transplantation improves cardiac function in a rat model of myocardial infarction. *Circulation, 110*(11 Suppl 1), II-268–II-275. https://doi.org/10.1161/01.CIR.0000138399.84365.3A
22. Tseliou, E., & Terrovitis, J. (2022). Cardiac progenitor cells revisited: Current evidence and future perspectives. *Trends in Cardiovascular Medicine, 32*(2), 123–131. https://doi.org/10.1016/j.tcm.2021.04.006
23. Uemura, R., Xu, M., Ahmad, N., & Ashraf, M. (2006). Bone marrow stem cells prevent left ventricular remodeling of ischemic heart through paracrine signaling. *Circulation, 114*(1 Suppl), I-8–I-15. https://doi.org/10.1161/CIRCULATIONAHA.105.000661
24. Vagnozzi, R. J., Maillet, M., Sargent, M. A., et al. (2020). An acute immune response underlies the benefit of cardiac stem cell therapy. *Nature, 577*(7790), 405–409. https://doi.org/10.1038/s41586-019-1802-2
25. Zhang, H., Song, J., Chang, Y., & Zheng, B. (2025). Hydrogel materials in myocardial infarction treatment. *RSC Advances, 15*, 31564–31585. https://doi.org/10.1039/D5RA01234A
26. BAMI Investigators. (2020). The effect of intracoronary infusion of bone marrow–derived mononuclear cells on mortality in acute myocardial infarction: The BAMI trial. *European Heart Journal, 41*(4), 370–379. https://doi.org/10.1093/eurheartj/ehz798
27. Fisher, S. A., Brunskill, S. J., Doree, C., et al. (2016). Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database of Systematic Reviews, 12*, CD006536. https://doi.org/10.1002/14651858.CD006536.pub4
28. Forte, E., Skelly, D. A., Chen, M., et al. (2020). Dynamic interstitial cell response during myocardial infarction predicts functional outcome. *Cell, 182*(1), 1–17. https://doi.org/10.1016/j.cell.2020.05.024
29. Gao, L., Gregorich, Z. R., Zhu, W., et al. (2018). Large cardiac muscle patches engineered from human induced pluripotent stem cell–derived cardiomyocytes improve recovery from myocardial infarction in swine. *Nature Biomedical Engineering, 2*(5), 301–311. https://doi.org/10.1038/s41551-018-0227-8
30. 30.Hatzistergos, K. E., Quevedo, H., Oskouei, B. N., et al. (2010). Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circulation Research, 107*(7), 913–922. https://doi.org/10.1161/CIRCRESAHA.110.222703
31. Heldman, A. W., DiFede, D. L., Fishman, J. E., et al. (2014). Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy (TAC-HFT). *JAMA, 311*(1), 62–73. https://doi.org/10.1001/jama.2013.282909
32. Ibanez, B., James, S., Agewall, S., et al. (2018). 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal, 39*(2), 119–177. https://doi.org/10.1093/eurheartj/ehx393
33. Kavousi, S., Hosseinpour, A., Jahromi, F. B., et al. (2024). Mesenchymal stem cell transplantation in heart failure: A meta-analysis of randomized trials. *Journal of Translational Medicine, 22*(1), 786. https://doi.org/10.1186/s12967-024-04567-3

34. Kim, Y. J., et al. (2021). Clinical-grade mesenchymal stem cell manufacturing under GMP conditions: Standardization and translational considerations. *Stem Cells Translational Medicine, 10*(6), 913–922. https://doi.org/10.1002/sctm.20-0485
35. Luger, D., Lipinski, M. J., Westman, P. C., et al. (2017). Intravenous mesenchymal stem cells improve myocardial function and reduce inflammation after myocardial infarction. *Journal of the American College of Cardiology, 69*(3), 288–299. https://doi.org/10.1016/j.jacc.2016.10.050
36. Madonna, R., et al. (2019). Mesenchymal stem cells and myocardial homing mechanisms. *Frontiers in Cell and Developmental Biology, 7*, 16. https://doi.org/10.3389/fcell.2019.00016
37. Marbán, E. (2018). Breakthroughs in cell therapy for heart disease. *Circulation Research, 123*(2), 139–141. https://doi.org/10.1161/CIRCRESAHA.118.313205
38. Menasché, P. (2018). Cell therapy trials for heart regeneration—Lessons learned and future directions. *European Heart Journal, 39*(21), 188–190. https://doi.org/10.1093/eurheartj/ehx816
39. Sensebé, L., Bourin, P., & Tarte, K. (2013). Clinical grade production of mesenchymal stem cells. *Cytotherapy, 15*(2), 105–116. https://doi.org/10.1016/j.jcyt.2012.10.005
40. Shahannaz, D. C., Sugiura, T., Ferrell, B. E., & Yoshida, T. (2025). Arrhythmogenic risk associated with iPSC-derived cardiomyocyte transplantation. *Medicina, 61*(12),2056.https://doi.org/10.3390/medicina61122056
41. Wan, X., Qian, C., Liu, S., et al. (2025). Stem cell therapy for myocardial infarction and atherosclerosis: Mechanistic insights and clinical implications. *Stem Cell Research & Therapy, 16*, 551. https://doi.org/10.1186/s13287-025-05551-9
42. Yan, W., Xia, Y., Zhao, H., et al. (2024). Stem cell-based therapy in cardiac repair after myocardial infarction. *Journal of Molecular and Cellular Cardiology, 188*, 1–14. https://doi.org/10.1016/j.yjmcc.2023.12.001
43. Zhao, M., Xue, Y., Tian, Q., et al. (2025). Mesenchymal stem cell therapy in acute myocardial infarction: Updated meta-analysis. *Cell Transplantation, 34*, 09636897251359773. https://doi.org/10.1177/09636897251359773
44. Bolli, R., Chugh, A. R., D'Amario, D., et al. (2011). Cardiac stem cells in patients with ischemic cardiomyopathy (SCIPIO): Initial results of a randomized phase 1 trial. *The Lancet, 378*(9806), 1847–1857. https://doi.org/10.1016/S0140-6736(11)61590-0
45. Ellison, G. M., Vicinanza, C., Smith, A. J., et al. (2013). Adult c-kit+ cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. *Cell, 154*(4), 827–842. https://doi.org/10.1016/j.cell.2013.07.039
46. Eschenhagen, T., Bolli, R., Braun, T., et al. (2017). Cardiomyocyte regeneration: A consensus statement. *Circulation, 136*(7), 680–686. https://doi.org/10.1161/CIRCULATIONAHA.117.029343
47. Frangogiannis, N. G. (2017). The extracellular matrix in myocardial infarction. *Circulation Research, 121*(7), 847–861. https://doi.org/10.1161/CIRCRESAHA.117.311148
48. Heldman, A. W., & Hare, J. M. (2018). Cell therapy for heart disease: A review of clinical trials. *Circulation Research, 123*(2), 132–138. https://doi.org/10.1161/CIRCRESAHA.118.312131
49. Heusch, G. (2020). Myocardial ischemia–reperfusion injury and cardioprotection. *Circulation Research, 126*(5), 711–729. https://doi.org/10.1161/CIRCRESAHA.119.315958
50. Karantalis, V., & Hare, J. M. (2015). Use of mesenchymal stem cells for therapy of cardiac disease. *Circulation Research, 116*(8), 1413–1430. https://doi.org/10.1161/CIRCRESAHA.116.305956
51. Laflamme, M. A., & Murry, C. E. (2011). Heart regeneration. *Nature, 473*(7347), 326–335. https://doi.org/10.1038/nature10147
52. Leuschner, F., Rauch, P. J., Ueno, T., et al. (2012). Rapid monocyte kinetics in acute myocardial infarction. *The Journal of Clinical Investigation, 122*(4), 1382–1394. https://doi.org/10.1172/JCI59867
53. Liu, B., Lee, B. W., Nakanishi, K., et al. (2018). Cardiac recovery via exosome-mediated mitochondrial transfer. *Circulation Research, 122*(7), 1000–1015. https://doi.org/10.1161/CIRCRESAHA.117.311599
54. Marbán, E. (2018). The secret life of exosomes: What bees can teach us about next-generation therapeutics. *Circulation Research, 122*(2), 156–158. https://doi.org/10.1161/CIRCRESAHA.117.312000
55. Menasché, P., Vanneaux, V., Fabreguettes, J. R., et al. (2015). Towards a clinical use of human embryonic stem cell–derived cardiac progenitors. *European Heart Journal, 36*(12), 743–750. https://doi.org/10.1093/eurheartj/ehu455
56. Nguyen, P. K., Rhee, J. W., Wu, J. C. (2016). Adult stem cell therapy and heart failure, 2000–2016: A systematic review. *JAMA Cardiology, 1*(7), 831–841. https://doi.org/10.1001/jamacardio.2016.2225
57. Passier, R., van Laake, L. W., & Mummery, C. L. (2008). Stem-cell–based therapy and lessons from the heart. *Nature, 453*(7193), 322–329. https://doi.org/10.1038/nature07040
58. Sanganalmath, S. K., & Bolli, R. (2013). Cell therapy for heart failure: A comprehensive overview. *Circulation Research, 113*(6), 810–834. https://doi.org/10.1161/CIRCRESAHA.113.300219
59. van der Spoel, T. I., Jansen of Lorkeers, S. J., Agostoni, P., et al. (2011). Human relevance of pre-clinical stem cell models. *European Heart Journal, 32*(24), 3055–3063. https://doi.org/10.1093/eurheartj/ehr249
60. Vo, Q. D., Saito, Y., Nakamura, K., et al. (2024). iPSC-derived cardiomyocyte therapy for myocardial infarction: A meta-analysis of preclinical data. *International Journal of Molecular Sciences, 25*(3), 987. https://doi.org/10.3390/ijms25030987

61. Wang, Y., Qi, Z., Yan, Z., et al. (2022). Mesenchymal stem cell immunomodulation in cardiovascular disease. *Frontiers in Cell and Developmental Biology, 9*, 742088. https://doi.org/10.3389/fcell.2021.742088
62. Xu, C., Xie, Y., Wang, B. (2024). Genetically modified mesenchymal stromal cells for myocardial infarction. *Stem Cell Research & Therapy, 15*, 323. https://doi.org/10.1186/s13287-024-03489-7
63. Zhang, Y., Mignone, J., MacLellan, W. R. (2015). Cardiac regeneration and stem cells. *Physiological Reviews, 95*(4), 1189–1204. https://doi.org/10.1152/physrev.00021.2014