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REVIEW ARTICLE

Regenerative therapies for ischemic heart disease: From cellular strategies to organ-scale solutions

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Abstract

Ischemic heart disease remains the leading cause of death worldwide, yet current therapies cannot restore lost myocardium. Heart transplantation is the only curative treatment, but it is limited by donor shortages and the risk of immune rejection. These challenges have prompted exploration of regenerative strategies designed to support repair or replacement of injured cardiac tissue. This review outlines advances across different levels of intervention. At the cellular level, stem and progenitor populations such as mesenchymal, cardiac, and induced pluripotent stem cells have been explored for their regenerative potential. Tissue engineering approaches, including scaffolds, patches, and injectable hydrogels, aim to enhance cell survival and integration. At a broader scale, organ-level strategies such as decellularization–recellularization and bioprinting represent emerging frontiers. By bringing together these complementary directions, the review highlights how progress in cardiac regeneration spans from cells to whole organs, while also emphasizing the key hurdles that continue to shape their translation.

Keywords: Ischemic heart disease; Heart failure; Myocardial regeneration; Stem cells; Tissue engineering; Bioprinting; Clinical translation

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1. Introduction

Ischemic heart disease (IHD), a set of syndromes characterized by myocardial ischemia, is the leading cause of mortality worldwide, accounting for over 8.99 million deaths in 2021.[1] This debilitating condition arises from a supply–demand imbalance in which the heart does not receive sufficient oxygen-rich blood,[2] leading over time to irreversible myocardial injury and the replacement of viable myocardium with inelastic, non-contractile fibrotic tissue—a process that markedly impairs cardiac function and may culminate in heart failure and death.[1,3]

Current standard-of-care treatments for IHD, including pharmacological therapies and interventional procedures such as angioplasty and coronary artery bypass grafting,[2] primarily focus on symptom management and slowing disease progression. While these treatments can improve blood flow and alleviate symptoms, they do not address the fundamental issue of lost heart muscle.[4] Indeed, the human heart once considered a

terminally differentiated organ, possesses a limited innate capacity for self-renewal.[5] The only definitive, curative treatment available is orthotopic heart transplantation, but this is severely limited by a global shortage of donor organs and the persistent risk of immune rejection.[6] This critical therapeutic gap necessitates the exploration of innovative strategies capable of regenerating damaged cardiac tissue to restore its function.

To effectively regenerate the heart, the initial step is to understand and leverage its cellular components. Although cardiomyocytes (CMs) are essential, they constitute only about 30% of the total cell population.[7] The remaining cells, which include cardiac fibroblasts, endothelial cells, and perivascular cells, are crucial for regulating cardiac function, contributing to processes ranging from electrical impulse conduction to blood vessel formation.[3,7] Cardiac fibroblasts are particularly central to the heart's response to injury. Following an ischemic insult, these cells become activated, differentiate into myofibroblasts, and deposit extracellular matrix that ultimately produces fibrotic scar tissue.[3] While this process is essential for structural stabilization, it reduces contractile function and predisposes the heart to adverse remodeling and failure.[3,5] Cardiac tissue engineering therefore aims to redirect these cellular behaviors, with the goal of promoting repair and regeneration of functional myocardium rather than fibrotic scar formation.[8]

In this review, we explore regenerative strategies for IHD along a continuum, from cellular therapies to whole-organ engineering (Figure 1). We begin with cell-based approaches, then examine advances in tissue engineering, and finally consider ambitious organ-scale solutions such as decellularization and recellularization processes, and whole-heart bioprinting, while also addressing the key challenges that shape their path toward clinical translation.

The most direct of these strategies begins at the cellular level, where different stem and progenitor populations have been explored as building blocks for myocardial repair.

2. Cell-based strategies and molecular building blocks

Early attempts in cardiac regeneration focused on readily available cell types thought to have regenerative potential. Performance of skeletal myoblasts was initially encouraging in preclinical studies, but clinical trials showed an increased risk of ventricular arrhythmias,[9,10] which has limited their use.[9] Bone marrow-derived cells, including mononuclear cells, then became the most widely studied in myocardial infarction. However, early work demonstrated that these cells rarely formed new CMs.[11] Clinical trials that followed, while proving that the cells were safe, yielded only modest

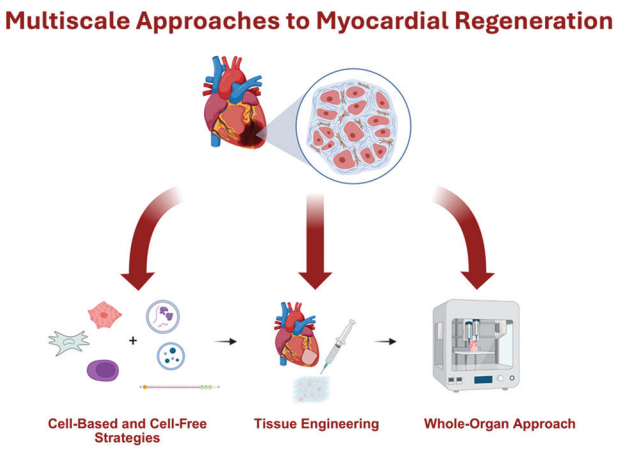

Figure 1. Regenerative strategies for ischemic heart disease. Schematic overview of approaches to cardiac regeneration across scales. Cell-based and cell-free strategies aim to restore function through stem and progenitor cells, exosomes, or molecular therapies. Tissue engineering develops structured constructs such as scaffolds, patches, and injectable hydrogels to enhance survival, retention, and integration. Whole-organ approaches, including decellularization/recellularization and 3D bioprinting, remain experimental solutions aimed at replacing the entire heart. Image created by the authors.

and inconsistent benefits,[12-14] prompting a shift in thinking toward other mechanisms and cell types.[15]

Building on the limitations of these early approaches, in this section, we examine in greater detail mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), and induced pluripotent stem cells (iPSCs), which have emerged as the most representative and extensively investigated strategies in cardiac regeneration.

2.1. MSCs

MSCs have gained recognition for their therapeutic potential in cardiac regeneration due to their multipotent nature and ability to differentiate into various cell types.[16] Isolated from tissues such as bone marrow, adipose tissue, and umbilical cord, MSCs possess key attributes including self-renewal, multipotent differentiation, and low immunogenicity, which render them suitable for allogeneic transplantation.[16,17] These properties support their application in cell-based therapies aimed at repairing myocardial damage following myocardial infarction. The therapeutic efficacy of MSCs primarily arises from their paracrine actions, involving the release of bioactive factors, such as exosomes, growth factors, and cytokines, which promote angiogenesis, reduce inflammation, prevent apoptosis, and modulate the immune response, thereby contributing to myocardial repair and enhanced cardiac function.[18-20]

However, significant challenges remain in the clinical translation of MSC therapies. One primary hurdle is the

poor survival and retention of transplanted MSCs in the hostile ischemic environment of the damaged heart, characterized by low migration rates to the ischemic myocardium and insufficient tissue retention post-transplantation.[19,21] Research indicates that many MSCs undergo apoptosis after transplantation due to these harsh conditions, limiting their therapeutic effectiveness.[22] Consequently, ongoing research is exploring strategies to enhance MSC viability, including preconditioning and genetic modifications, to improve their homing and delivery to target tissues.[23] Thus, MSC therapy remains promising, but its clinical impact depends on overcoming engraftment challenges. These limitations motivated interest in resident CPCs, which offer greater lineage specificity.

2.2. CPCs and cardiosphere-derived cells (CDCs)

CPCs embody the limited intrinsic regenerative potential of the adult heart, demonstrating capabilities for self-renewal and differentiation into critical cardiac cell types, including CMs, endothelial cells, and smooth muscle cells.[24] Their role in myocardial repair is multifaceted: CPCs can directly differentiate into new cardiac cells and exert significant paracrine effects by secreting cytokines, chemokines, growth factors, and extracellular vesicles.[25] These molecules facilitate crucial processes such as angiogenesis, cardioprotection, and immune modulation, which aid in restoring myocardial function.[24]

CDCs, a derivative of CPCs, are obtained from myocardial explant cultures and represent a derivative progenitor population with multilineage potential and a particularly rich paracrine secretome that enhances angiogenesis, modulates inflammation, and supports cell survival[24,26]. Their cardiac origin has been proposed to provide a reparative advantage compared with extracardiac cell types.

Despite their promise, the therapeutic application of CPCs and CDCs remains limited by their small resident populations in the adult heart, the practical challenges of isolation and expansion, and their poor long-term engraftment. Reported benefits remain modest and variable, underscoring the need for strategies to enhance their survival, persistence, and integration.[24] These obstacles encouraged exploration of scalable, patient-specific sources such as iPSCs.

2.3. iPSCs

iPSCs have emerged as a transformative tool in regenerative medicine. Their unique ability to differentiate into functional CMs offers a promising strategy for restoring myocardial function following myocardial infarction and heart failure.[27] iPSCs are generated through the reprogramming of adult somatic cells using key transcription factors OCT4, SOX2, KLF4, and c-MYC, which reinstate pluripotency and confer self-renewal capacity.[28] These properties make iPSCs attractive for scalable therapeutic applications and personalized medicine.[27,29]

Preclinical studies have shown that iPSC-derived CMs (iPSC-CMs) can promote cardiac tissue regeneration by structurally integrating with host myocardium and functionally coupling with native CMs, thereby enhancing contractility and electrical conduction while supporting neovascularization within ischemic regions.[30] Patient-specific iPSC therapies are particularly valuable, as they offer tailored regenerative approaches while minimizing risks of immune rejection.[31] Despite these advances, translation into clinical practice faces significant hurdles. A major concern is the potential for tumorigenesis due to residual undifferentiated iPSCs,[32] emphasizing the need for stringent purification and monitoring protocols before transplantation. Furthermore, limited engraftment and poor long-term retention of transplanted cells in the infarcted myocardium remain critical challenges.[27,33]

2.4. Other cell types and cell-free approaches

The field of cardiac regeneration extends beyond MSCs, CPCs, and iPSCs to include other cell types and cell-free strategies. Endothelial progenitor cells are a subpopulation of adult peripheral-blood cells capable of differentiating into mature endothelial cells.[34] They contribute to vascular regeneration by forming new capillaries and secreting pro-angiogenic factors, supporting revascularization of ischemic myocardium. Despite their promise, clinical translation is limited by their low abundance in peripheral blood and reduced functionality in many cardiovascular disease states.[34]

Table 1 provides a comparative overview of the principal cell-based strategies for cardiac regeneration, highlighting their cellular sources, mechanisms of action, advantages, and limitations.

Recognizing that much of the benefit of cell-based therapies arises from paracrine signaling, attention has shifted toward cell-free approaches.[35,36] Exosomes are nanoscale extracellular vesicles secreted by stem and progenitor cells. They carry proteins, lipids, and nucleic acids, including microRNAs, which modulate angiogenesis, CMs survival, and immune responses.[36,37] Recent studies have explored non-invasive delivery methods such as inhalation, which may bypass challenges of local injection and improve distribution.[38] Similarly, therapeutic microRNAs can be delivered directly to regulate gene expression and promote myocardial

Table 1. Principal cell-based strategies for cardiac regeneration

Strategy	Source	Mechanism of action	Advantages	Limitations	References
Skeletal myoblasts	Skeletal muscle biopsy	Differentiate into muscle-like cells; provide contractile support	Autologous, preclinical safety	High risk of ventricular arrhythmias; poor electrical coupling	9,10
Bone marrow-derived cells	Bone marrow aspirate (heterogeneous population)	Mainly paracrine signaling; very limited CM formation	Readily available; simple isolation;	Rarely generate new CMs; modest and inconsistent clinical benefit	11-15
MSCs	Bone marrow, adipose tissue, umbilical cord	Paracrine signaling; immunomodulation	Multipotent; low immunogenicity; suitable for allogeneic use	Poor survival/retention; apoptosis in ischemic myocardium; low homing efficiency	16-23
CPCs	Resident in adult myocardium	Differentiate into CMs, endothelial cells, smooth muscle cells; paracrine secretome	Lineage specificity; cardiac origin	Low abundance; difficult to isolate/expand; poor long-term engraftment	24,25
CDCs	Myocardial explant cultures	Rich paracrine secretome; angiogenesis, immunomodulation	Multilineage potential; strong paracrine activity	Limited survival; modest and variable benefits	24,26
iPSCs	Reprogrammed somatic cells (OCT4, SOX2, KLF4, c-MYC)	Differentiate into functional CMs; structural and electrical integration	Patient-specific; scalable; immunocompatible	Risk of tumorigenesis; poor retention/engraftment	27-33
Endothelial progenitor cells	Peripheral blood	Differentiate into mature endothelial cells; secrete pro-angiogenic factors	Promote vascular regeneration	Low abundance; reduced functionality in cardiovascular disease	34

Abbreviations: CDCs: Cardiosphere-derived cells; CM: Cardiomyocyte; CPCs: Cardiac progenitor cells; iPSCs: Induced pluripotent stem cells; MSCs: Mesenchymal stem cells.

regeneration. Preclinical studies show that localized delivery of pro-regenerative microRNAs improves CM survival, reduces fibrosis, and enhances cardiac function after myocardial infarction.[37] This reflects a broader move away from cell-based implantation toward more targeted, molecular approaches that aim to overcome some of the practical limitations of earlier strategies.

These insights naturally lead to tissue engineering, which seeks to pair biological therapies with structural support to improve survival, retention, and functional integration.

3. Tissue engineering

Persistent limitations in cell survival and engraftment have, in turn, catalyzed the move toward tissue engineering strategies.[8] Unlike direct cell injection, tissue engineering integrates living cells into structured environments that provide supportive physical and biochemical conditions to promote cell survival, retention, and functional integration.[39] By mimicking aspects of native cardiac tissue, these engineered constructs enhance regenerative outcomes, enabling more effective myocardial repair and restoration of cardiac function.[8,40]

3.1. Scaffold design and biomaterial strategies

Biomaterials form the foundational framework of engineered cardiac tissues, offering structural templates that reproduce essential features of the myocardial environment.[39] Natural materials such as collagen, fibrin, and alginate are attractive due to their biocompatibility and biodegradability, though their limited mechanical strength and variability can restrict performance.[41] In contrast, synthetic polymers such as polylactic acid and polyglycolic acid provide tunable mechanical stability and degradation rates, but careful design is required to avoid inflammatory or toxic byproducts.[41-43] Increasingly, hybrid systems that combine natural and synthetic components are being explored to merge biological activity with structural robustness, aiming to overcome the limitations of each individual class.[44]

Alongside material selection, progress in fabrication methods such as electrospinning and three-dimensional (3D) bioprinting has enabled the creation of sophisticated scaffold architectures that guide cell adhesion, alignment, and maturation.[39,45] These scaffolds are commonly seeded with therapeutic cell types—including MSCs, CPCs, and iPSC-CMs—to generate constructs intended for

implantation.[39] Preclinical studies of engineered heart tissues containing human pluripotent stem cell-derived CMs have reported improved cell retention, vascularization, and functional recovery, highlighting the therapeutic potential of scaffold-based strategies.[8,39] However, one of the major barriers remains vascularization, since constructs thicker than ~200 μm are prone to nutrient and oxygen deprivation, which compromises survival and functionality.[45]

3.2. Cardiac patches

Building on scaffold-based approaches, cardiac patches have emerged as one of the most widely studied strategies for myocardial repair. These constructs are designed to reinforce the weakened ventricular wall while also delivering regenerative cells and bioactive factors.[46] Compared with direct cell injection, patches achieve higher cell retention and survival, and they provide mechanical stabilization that helps limit adverse remodeling after injury.[46]

A persistent obstacle, however, is ensuring sufficient vascularization within thicker patches to prevent necrosis at their core.[47] Approaches to overcome this limitation include the incorporation of vascular cells, the design of pre-vascularized scaffolds, or the addition of angiogenic growth factors.[46-48] Notably, studies in non-human primates demonstrated that engineered cardiac patches derived from reprogrammed cells embedded in a collagen-based matrix survived after implantation, developed a vascular network, and led to thickening of the ventricular wall with improved cardiac function.[49] Despite these encouraging advances, the need for surgical implantation continues to restrict broader application, particularly in patients with advanced disease who may not tolerate invasive procedures.[46]

3.3. Injectable hydrogels as minimally invasive therapies

To address the limitations of surgical patch implantation, injectable hydrogels have been developed as a minimally invasive, catheter-delivered alternative.[50] These systems are injected in liquid form and solidify *in situ*, creating a matrix that reinforces damaged myocardium and serves as a vehicle for regenerative cells or therapeutic molecules.[51] By combining mechanical stabilization with targeted delivery, hydrogels aim to restore myocardial integrity while avoiding open-heart surgery.[52]

Recent innovations have expanded the functionality of these materials. Conductive hydrogels, for example, are being engineered to restore electrical conduction across scar tissue and resynchronize contraction.[51,52] Stimulus-responsive hydrogels represent another important advance: designed to react to pathological signals such as elevated reactive oxygen species (ROS) or matrix metalloproteinases, they can scavenge ROS, stimulate angiogenesis, or inhibit fibrosis.[51] While still largely experimental, these "smart" hydrogels illustrate the field's move toward multifunctional materials capable of addressing both the structural and biological challenges of myocardial regeneration.[50]

Table 2 summarizes the principal tissue engineering strategies for cardiac regeneration, highlighting their design concepts, advantages, and limitations.

While these methods strengthen and repair portions of the heart, they fall short of replacing the organ itself. The next frontier therefore aims at whole-organ solutions.

4. Whole-organ approach

The long-term goal of cardiac regenerative medicine is to develop organ-scale solutions capable of replacing a failing heart.[53] Beyond cell injections and tissue patches, two major regenerative strategies dominate current research: decellularization and recellularization of donor hearts, and whole-heart bioprinting using advanced additive manufacturing.[54,55] Both approaches face the central challenge of achieving a viable, vascularized, and electrically functional construct that can integrate seamlessly with the host.[56,57]

Table 2. Principal tissue engineering strategies in cardiac regeneration

Strategy	Core concept	Advantages	Limitations	References
Scaffolds/ Biomaterials	Natural, synthetic, or hybrid matrices designed to mimic myocardial environment	Support cell adhesion, alignment, maturation; improve functional recovery	Constructs >200 μm limited by poor vascularization; variability in natural materials; potential toxicity in synthetics	39-45
Cardiac patches	Engineered constructs applied to epicardium, seeded with cells or bioactive factors	High cell retention; provide mechanical support; reduce adverse remodeling	Require surgical implantation; vascularization remains a challenge	46-49
Injectable hydrogels	Catheter-delivered materials that gel in situ, carrying cells or therapeutic molecules	Minimally invasive; reinforce myocardium; enable targeted delivery	Still experimental; uncertain long-term durability; limited vascularization	50-52

4.1. Decellularization and recellularization

Decellularization removes all living cells from a donor heart, leaving behind an extracellular matrix (ECM) scaffold that retains the native 3D structure and biochemical cues. This acellular scaffold can then be repopulated with patient-derived cells—such as iPSC-CMs, endothelial cells, and fibroblasts—with the goal of generating a contractile, immunocompatible heart.[55,58]

Cardiac decellularized ECM (dECM) preserves key bioactive components, including collagens, laminin, fibronectin, glycosaminoglycans, and growth factors, which provide structural support and regulate cell adhesion, proliferation, and differentiation.[56,59] The architecture of the scaffold is also critical: preserving the vascular tree facilitates perfusion,[58] while anisotropic ECM organization has been shown to improve CMs alignment and functional maturation.[60] Beyond whole-heart scaffolds, dECM has also been processed into hydrogels and patches. In early clinical translation, dECM-based hydrogels demonstrated safety and early signals of functional benefit,[51] while a pericardial tissue-derived patch seeded with umbilical cord-derived MSCs was reported as safe and immunomodulatory, although no significant improvements in cardiac function were observed in its first clinical trial.[61]

Despite these advances, several hurdles remain. Achieving uniform cell repopulation of the thick ventricular walls is technically challenging, and limited vascularization often leads to necrosis in the tissue core.[55,58] The quality of the ECM is also influenced by donor source and age: fetal and neonatal matrices differ in composition and signaling compared to adult and diseased tissues, which tend to be stiffer and less bioactive.[55] Furthermore, decellularization protocols, whether chemical, enzymatic, or physical, can damage ECM ultrastructure or leave cytotoxic residues, reducing recellularization efficiency.[58,59]

To address these limitations, current strategies combine dECM with growth factors, stem cells, or conductive biomaterials, and employ engineering techniques such as electrospinning, microfluidics, and 3D bioprinting to better mimic the myocardium.[56,57,59] Alongside, bioreactor systems that provide perfusion, pacing, and mechanical load can improve the maturation and integration of cells within recellularized cardiac scaffolds.[58,62]

4.2. Whole-heart bioprinting

Building on these advances, whole-heart bioprinting uses 3D printing technologies to assemble living cardiac tissues layer by layer with bioinks composed of cells, biomolecules, and hydrogels.[54,63] Cardiac-specific dECM is frequently incorporated into these formulations to provide biochemical and structural cues that more closely resemble native myocardium.[57,64] The performance of a bioink depends not only on its chemical makeup but also on its flow characteristics during printing and its responsiveness to electrical and mechanical cues, which together influence both fidelity and tissue maturation.[59,64] The introduction of the Freeform Reversible Embedding of Suspended Hydrogels approach marked a major step forward, enabling the use of soft materials such as collagen to fabricate structurally complex cardiac components, including valves and small contractile ventricles.[65]

While advances in bioink formulation and printing methods represent important progress, biological hurdles remain. Chief among them is vascularization: thick engineered constructs lack a perfusable vascular tree, which leads to central necrosis. Pre-vascularized cardiac patches have shown improved survival and host integration,[66] but extending this principle to an entire heart remains unresolved.[62,67] Additional challenges include reproducing the anisotropic myocardial architecture,[62] achieving reliable electrical conduction,[66] providing sufficient mechanical strength,[59] and maintaining the viability of dense cell populations during and after printing.[66]

Table 3 summarizes the principal whole-organ strategies for cardiac regeneration, comparing their conceptual basis, advantages, and persistent limitations.

Advances in "smart" regenerative approaches aim to design engineered tissues that provide not only structural replacement but also instructive mechanical, electrical, and biochemical cues for cell organization and function.[63,66] Among these innovations, optoelectronic strategies have been introduced to modulate CM activity, offering a controllable means of supporting electrical integration within engineered constructs.[68] Another promising direction is the combination of organoid biology with bioprinting; for example, cardioids integrated with vascular networks have been proposed to address persistent barriers in vascularization and maturation.[63] Together with advances in engineered cardiac patches that are already electrically active and contractile, these approaches continue to shape strategies for scaling toward whole-organ constructs.[66]

5. Barriers to translation

The regenerative technologies discussed have potential therapeutic relevance for several cardiovascular conditions characterized by ischemic myocardial injury. These include acute myocardial infarction, chronic coronary syndromes, ischemic and dilated cardiomyopathies, and ischemic heart failure. By promoting neovascularization, replacing necrotic myocardium with contractile tissue, and limiting adverse remodeling, these approaches aim

Table 3. Principal whole-organ approaches in cardiac regeneration

Strategy	Core concept	Advantages	Limitations	References
Decellularization and recellularization	Removal of cells from donor hearts to preserve ECM, followed by repopulation with patient-derived cells	Retains native 3D architecture and biochemical cues; potential for immunocompatible grafts	Achieving uniform recellularization and vascularization is difficult; ECM quality varies with donor source and decellularization method; risk of cytotoxic residues	51,55-62
Whole-heart bioprinting	Layer-by-layer 3D printing using bioinks composed of cells, hydrogels, and biomolecules	Customizable; scalable; potential for patient-specific organs	Limited vascularization in thick constructs; challenges in electrical conduction, mechanical strength, and long-term cell viability	54,57,59,62-68

Abbreviations: ECM: Extracellular matrix; 3D: Three-dimensional.

to restore ventricular function and prevent progression toward end-stage heart failure.[69] Nevertheless, translating these advances into effective clinical therapies remains difficult, as multiple biological and bioengineering barriers still constrain their broader application (Figure 2).

5.1. Biological challenges

Despite impressive laboratory progress, moving these strategies into the clinic has been slow. Safety concerns remain at the forefront, particularly the risk of tumorigenicity associated with pluripotent stem cell-derived products. Even a small fraction of undifferentiated cells may proliferate abnormally after transplantation, highlighting the importance of stringent purification and long-term monitoring.[70] Immune compatibility is another persistent barrier. Allogeneic and xenogeneic sources can provoke rejection despite immunomodulatory strategies, whereas autologous iPSC-based therapies, although immunologically safer, are limited by time, cost, and scalability.[71] Achieving adequate vascularization also remains difficult. Thick engineered tissues often suffer from insufficient perfusion, leading to central necrosis and poor functional integration.[47] Efforts to pre-vascularize scaffolds or combine cells with angiogenic growth factors and microfluidic bioprinting aim to address this limitation.[63] Collectively, these issues underscore that biological feasibility must be matched by long-term safety, immune tolerance, and stable perfusion before clinical translation becomes realistic.

5.2. Bioengineering and translational challenges

Biological feasibility is only part of the equation. From a bioengineering standpoint, achieving stable electromechanical coupling between the implanted construct and the host myocardium remains a major obstacle. Incomplete electrical integration can result in asynchronous contraction or arrhythmias, limiting functional recovery. To address this, efforts are focusing on conductive biomaterials, bioelectronic interfaces, synchronized pacing systems, and genetic modulation of CMs to improve coupling and rhythm stability.[66]

Equally important are the challenges of reproducibility, scalability, and regulatory compliance. Generating large, standardized batches of cells or engineered tissues that maintain structural integrity and functional performance is technically demanding and expensive.[64] Recent progress in automated bioprinting, modular scaffold design, and controlled differentiation protocols has improved consistency and yield. Nonetheless, successful clinical implementation will require the establishment of validated manufacturing pipelines, rigorous quality-control standards, and cost-effective production processes.[62] Addressing these factors will be critical to translating experimental cardiac constructs into safe and accessible therapies for patients.

6. Future perspectives and conclusion

Future progress in cardiac regeneration will likely arise from the integration of complementary strategies, combining cell-based therapies with tissue-engineered scaffolds, gene editing, and bioactive molecule delivery to enhance graft survival, vascularization, and functional recovery. In parallel, bioengineering continues to evolve rapidly. Approaches such as 3D and 4D bioprinting, smart biomaterials, and conductive scaffolds are being developed to improve tissue organization and electromechanical performance,[62] while genome editing offers the possibility of creating universal, immune-evasive cell lines suitable for large-scale use.[71]

Artificial intelligence and machine learning are also starting to contribute to the field. Early applications include arrhythmia prediction,[72] optimization of cell differentiation and culture conditions, and improved monitoring of manufacturing quality.[73] As data from experimental and clinical studies accumulate, these tools could support personalized approaches to regenerative therapy and streamline translation to the clinic.

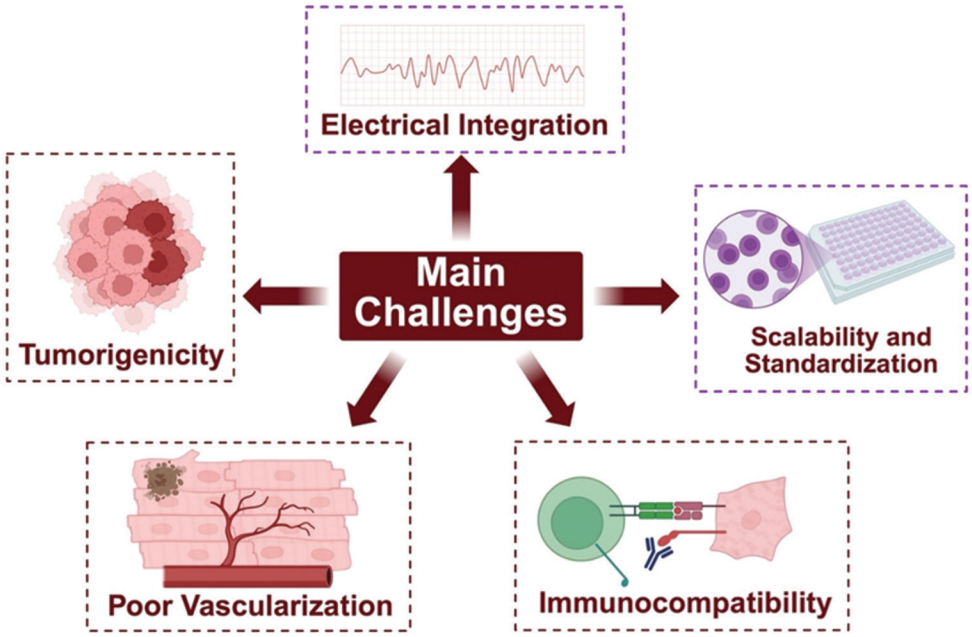

Figure 2. Schematic overview of major barriers to clinical translation of regenerative cardiac strategies. Red dashed boxes denote biological challenges, whereas purple dashed boxes denote bioengineering challenges. Image created by the authors.

Xenotransplantation, while not a regenerative approach *per se*, represents an extension of transplantation medicine aimed at addressing donor shortages. Early pig-to-human transplants have demonstrated survival ranging from several weeks to 2 months,[74] while decedent models have shown short-term graft function without hyperacute rejection.[75] These advances mark important progress but also highlight persistent barriers, including immune rejection, graft overgrowth, physiological incompatibilities, and zoonotic risk.[76] For the moment, xenotransplantation is best regarded as a temporary bridge, while regenerative and bioengineering strategies continue to advance toward development of patient-specific, immunocompatible organs.

Together, these efforts illustrate how progress at every scale, from cells to whole hearts, relies on the convergence of biological, engineering, and clinical innovation. Over the past two decades, cardiac regenerative medicine has evolved from experimental cell injections to sophisticated tissue-engineered constructs and early whole-organ approaches. MSCs, CDCs, and iPSCs each possess distinct regenerative advantages, yet their clinical application remains constrained by limited engraftment, inadequate vascularization, arrhythmogenic potential, and the difficulty of producing consistent, high-quality products. Advances in biomaterials, biofabrication, and genetic reprogramming are gradually addressing these limitations, while improved understanding of cardiac development and repair continues to refine therapeutic design.

The next phase of progress will depend on closer integration between biology, engineering, and clinical research. Combining vascularized, electrically conductive, and immunocompatible constructs with scalable and standardized production platforms may eventually enable functional myocardial restoration. Achieving this goal will require sustained collaboration across disciplines and attention to long-term safety, regulatory standards, and accessibility. As IHD remains the leading cause of death worldwide, the development of therapies capable of achieving true myocardial regeneration represents both a scientific challenge and a clinical necessity.

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