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# Advances in Human iPSC Models and Stem Cell Secretome Therapy for Cardiometabolic Diseases

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## Abstract

Cardiometabolic diseases remain a major cause of global morbidity and mortality, with therapeutic progress limited by a persistent gap between preclinical models and clinical outcomes. This review highlights recent advances in human induced pluripotent stem cell (iPSC)-derived cardiac organoids and stem cell secretome–based regenerative strategies as emerging solutions to this challenge. Cardiac organoids recapitulate key features of human heart tissue and enable physiologically relevant modeling of ischemia–reperfusion injury, diabetes-related metabolic stress, and drug-induced cardiotoxicity. In parallel, regenerative cardiology has shifted toward cell-free approaches based on paracrine mechanisms, including secretome delivery via implantable immunoisolated devices. Remaining challenges include organoid standardization, secretome characterization, and evolving regulatory pathways. Continued integration of cardiac organoid platforms with secretome-based delivery technologies is expected to advance translational research and therapeutic development for cardiometabolic diseases.

***Keywords*:** *Induced pluripotent stem cells, Cardiac organoids, Cardiometabolic disease, Stem cell secretome, Translational research*

## Abstrak

**Perkembangan Terkini Model iPSC Manusia dan Terapi Sekretom Sel Punca dalam Penyakit Kardiometabolik.** Penyakit kardiometabolik masih menjadi penyebab utama morbiditas dan mortalitas di tingkat global, sementara kemajuan terapi terus dibatasi oleh kesenjangan yang berkelanjutan antara model praklinik dan hasil klinis. Tinjauan ini menyoroti perkembangan terbaru organoid jantung yang diturunkan dari *human induced pluripotent stem cells* (iPSC) serta strategi regeneratif berbasis sekretom sel punca sebagai solusi yang semakin berkembang untuk mengatasi tantangan tersebut. Organoid jantung mampu menggambarkan karakteristik utama jaringan jantung manusia dan memungkinkan pemodelan cedera iskemia–reperfusi, stres metabolik terkait diabetes, serta kardiotoksisitas akibat obat dengan relevansi fisiologis yang lebih tinggi. Sejalan dengan itu, kardiologi regeneratif telah bergeser menuju pendekatan bebas sel yang bertumpu pada mekanisme parakrin, termasuk penghantaran sekretom melalui perangkat imunoisolasi implan. Tantangan yang masih dihadapi meliputi standardisasi organoid, karakterisasi sekretom, serta perkembangan kerangka regulasi. Integrasi berkelanjutan antara platform organoid jantung dan teknologi penghantaran sekretom diharapkan dapat mempercepat kemajuan riset translasi dan pengembangan terapi penyakit kardiometabolik.

***Kata Kunci:*** *Induced pluripotent stem cells, Organoid jantung, Penyakit kardiometabolik, Sekretom sel punca, Riset translasi*

## Introduction

Cardiometabolic diseases, including ischemic heart disease, heart failure, diabetic cardiomyopathy, and cardio-renal syndromes, are among the leading causes of death worldwide.[1] These conditions are complex, arising from the interplay of multiple overlapping processes, such as metabolic dysfunction, inflammation, vascular damage, extracellular matrix remodeling, electrical abnormalities, and the progressive loss of heart muscle cells.[2,3] Despite significant advances in both basic and clinical research, long-term treatment outcomes for cardiometabolic diseases remain limited. This highlights a persistent gap between laboratory findings and their successful translation into clinical practice. This translational gap is partly due to the inherent limitations of traditional animal models, which differ from humans in important physiological and genetic features, and partly to simplified *in vitro* models that fail to capture the cellular diversity, structural complexity, and mechanical properties of human heart tissue.[4]

Human induced pluripotent stem cell (iPSC) technology has significantly advanced the study human cardiovascular diseases. Human iPSCs provide an unlimited source of cardiac cells from different individuals, enabling the investigation of genetic variations, differential drug responses, and interactions among diverse cardiac cell types. Building on this platform, human cardiac organoids, which are three-dimensional structures composed of multiple cardiac cell types, have been developed to more closely recapitulate native human heart tissue. These organoids represent physiologically relevant, scalable, and ethically favorable models for elucidating disease mechanisms and evaluating novel therapeutic strategies.[5]

Another major advancement in stem cell technology is the shifted in regenerative cardiology from cell-based to cell-free therapeutic strategies. Instead of relying primarily on stem cell transplantation, accummulating evidence indicates that stem cells exert much of their therapeutic benefit through paracrine signalling mechanisms. This process involves the release of bioactive molecules, collectively referred to as the secretome, that modulate tissue repair and regeneration. Recognition of these mechanisms has driven the development of cell-free regenerative therapies. One such approach involves implantable immunoisolated devices capable of delivering the secretome from iPSC-derived mesenchymal stem cells (MSCs) in a controlled and sustained manner, representing a promising strategy for future cardiac therapies.[6]

This review summarizes recent advances in human iPSC-derived cardiac organoids and stem cell-derived secretome therapies. These two research areas are increasingly convergent and hold substantial potential to improve translational research in cardiometabolic diseases. By integrating findings from preclinical models, molecular studies, and early clinical investigations, this review highlights the translational relevance and future potential of these emerging approaches.

## Bridging the Translational Gap with Human iPSC-Derived Cardiac Models

Cardiovascular research has traditionally relied on rodent models; however, these models do not always accurately represent human heart disease. Rodents differ from humans in several important aspects, including ion-channel expression, cardiac electrical activity, metabolism, immune responses, and sensitivity to pharmacological agents. Consequently, many therapeutic approaches that appear effective in rodent studies fail to achieve similar success in human clinical trials.[7] This limitation underscores the need for experimental models that more closely reflect human cardiac physiology.

Human iPSCs offer an alternative approach to address these limitations. iPSCs can be differentiated into a variety of cardiac-related cell types from a single, individual-specific genetic background. These include cardiomyocytes, endothelial cells, smooth muscle cells, fibroblasts, autonomic neurons, and monocyte/macrophage-like cells. As a result, iPSC-based models enable the study of inherited cardiomyopathies, individual variability in drug responses, and disease features associated with sex or ethnicity. In addition, iPSC-derived cardiomyocytes exhibit electrophysiological properties similar to those of human heart cells, making them well-suited for applications such as arrhythmia modeling and drug toxicity assessment.[5]

Recent advances in tissue engineering have further improved iPSC-based cardiac models through the development of three-dimensional cardiac organoids or microtissues.[8] These organoids incorporate multiple supporting cell types, including vascular, neural, stromal, and immune cells, contributing to more physiologically relevant cardiac function.[8, 9] Cardiac organoids display spontaneous contractile activity and organized tissue architecture resembling native heart tissue (Figure 1).[8] When combined with microfluidic systems, they can also model perfusion flow conditions, mechanical stress, and dynamic drug exposure.[8] Together, these approaches provide a powerful platform for studying human cardiac disease mechanisms and evaluating potential therapeutic strategies.

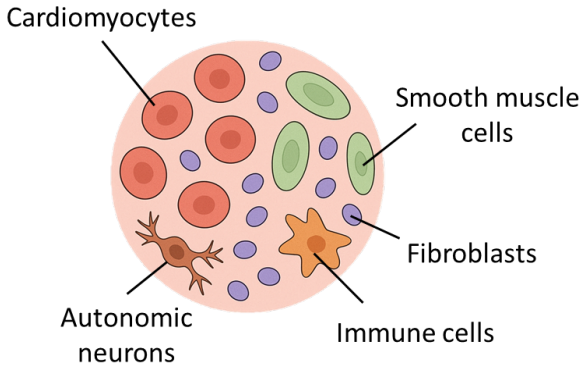


**Figure 1.** Multicellular composition of a cardiac organoid. Schematic showing cardiomyocytes, endothelial cells, smooth muscle cells, fibroblasts, autonomic neurons, and immune-lineage cells within a human iPSC-derived cardiac organoid.

Compared with conventional two-dimensional cell cultures, cardiac organoids exhibit higher levels of metabolic maturity and more consistent calcium handling, both of which are important features of functional heart tissue.[10] These properties enhance their performance in cardiotoxicity assessments relative to simpler *in vitro* models.[11] This capability is particularly valuable in pharmaceutical development, where early identification of potential cardiotoxic effects remains a significant challenging.[11] As a result, human cardiac organoids are increasingly being leveraged as preclinical screening models, offering the potential to reduce or complement the use of certain animal studies.

## Organoid Models of Cardiac Injury, Stress, and Disease Complexity

### *Ischemia-reperfusion injury (IRI)*

Human cardiac organoids enable controlled simulation of myocardial ischemia and reperfusion, a central mechanism in acute myocardial infarction (Figure 2).[12] Experimental protocols incorporating oxygen deprivation, acidic pH, metabolic inhibition, and subsequent reoxygenation reproduce hallmark features of IRI, including cardiomyocyte death, oxidative injury, contractile dysfunction, and beat-rate irregularity.[12] Leukocyte recruitment and endothelial dysfunction observed in these models mirror clinical findings, supporting their utility for testing cardioprotective therapeutics.[9, 12] Because organoids contain fibroblasts and immune-lineage cells, they also recapitulate inflammatory and fibrotic responses, which are often absent in monocellular cardiomyocyte cultures.[9, 12]

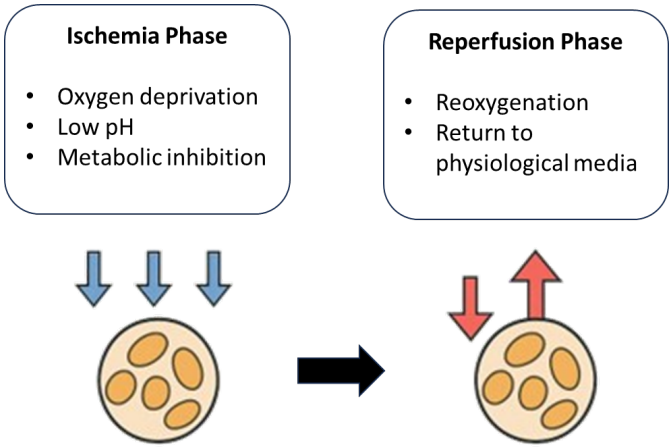


**Figure 3.** Ischemia-reperfusion injury simulation in organoids. Representation of the ischemia phase (oxygen deprivation, low pH, metabolic inhibition) followed by the reperfusion phase (reoxygenation, physiological media).

### *Metabolic stress and diabetic heart disease*

Metabolic syndrome and diabetes mellitus significantly alter cardiac structure and function through mechanisms including lipotoxicity, glucotoxicity, neurohumoral activation, and chronic low-grade inflammation.[13] Organoid models incorporating high glucose, long-chain fatty acids (palmitate, oleic acid, linoleic acid), and endocrine stressors (endothelin-1 and cortisol) reproduce metabolic impairments characteristic of diabetic cardiomyopathy.[14] These models exhibit prolonged contraction–relaxation kinetics, reduced cell viability, metabolic inflexibility, extracellular matrix remodeling, and inflammation. Such findings are particularly important given that individuals with diabetes exhibit distinct patterns of cardiac remodeling and often show poor responsiveness to conventional heart failure therapies.

### *Cardio-oncology and drug toxicity models*

Cardiotoxicity remains a major limitation of several chemotherapeutic agents, notably anthracyclines such as doxorubicin.[15] Human cardiac organoids treated with doxobicin reproduces the dose-dependent cytotoxicity, contractile dysfunction, and arrhythmogenic phenotypes induced by this agent.[16] By providing a multicellular environment, organoids capture interactions among stromal cells, immune cells and cardiomyocytes that modulate drug response, making them more predictive than cardiomyocyte monocultures.[16] These platforms facilitate the identification of cardioprotective adjuncts, screening of next-generation chemotherapeutics, and mechanistic investigation of cardiac vulnerability in cancer survivors.[15, 16]

## Stem Cell Secretome for Regenerative Therapy

### *Shortcomings of traditional stem cell therapy*

Stem cell transplantation has been studied for more than two decades, with mesenchymal stem cells (MSCs) emerging as the most widely studied candidate for cardiac repair.[17] Although numerous early-phase clincial trials have confirmed the procedural safety of MSC adminsitration, the resulting functional benefits have generally been modest.[18-20] Major limitations include poor cell engraftment, rapid cell clearance, immune rejection, variability in cell potency, and hostile microenvironment of the injured myocardium.[18-20] Autologous cell therapies also face challenges related to scalability and patient-specific variability, whereas allogeneic approaches must contend with risk of immunogenicity.[18-20]

### *Paracrine signaling as the primary mechanism of benefit*

A growing body experimental evidence indicatea that the cardioprotective effects of stem cells are mediated predominatly through paracrine signalling rather than direct cellular integration.[21] Stem cells secrete a diverse array of bioactive factors, including cytokines, chemokines, growth factors, and extracellular vesicles, that promote cell survival, stimulate angiogenesis, modulate inflammatory responses, reduce fibrosis, and improve myocardial contractility.[22,23] Notably, extracellular vesicles transport regulatory RNAs and proteins that modulate metabolic pathways, gene expression, and intercellular communication.[22-24] This recognition has shifted therapeutic development away from cell transplantation toward the use of biologically active secretome products.[25]

### ***Immunoisolated devices for sustained secretome delivery***

A major recent advance in regenerative medicine is the development of implantable, immunoisolated devices that encapsulate iPSC-derived MSCs (Figure 3).[26] These subcutaneous implantable devices support long-term cell viability while protecting the encapsulated cells from host immune surveillance.[26] Importantly, they enable continuous release of therapeutic secretome without the need for repeated cell injections, thereby improving therapeutic consistency and reducing procedural risk.[26-27] Because therapeutic benefit no longer depends on myocardial engraftment, these devices circumvent many of the barriers that limit traditional cell therapy, including ischemia, inflammation and poor cell retention.[27]

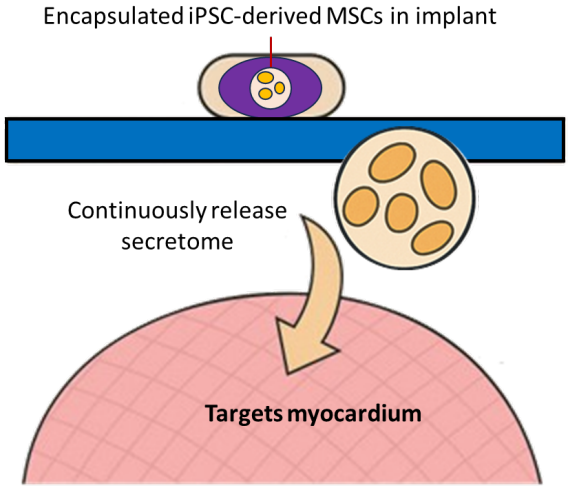


**Figure 3.** Immunoisolated MSC secretome delivery device. Diagram of a subcutaneous implant containing encapsulated iPSC-derived MSCs that continuously release secretome targeting the myocardium.

Preclinical studies in rodent models of myocardial infarction sow that sustained delivery of the stem cell secretome leads to significant improvements in cardiac structire and function, indlcusing increased left ventricular ejection fraction, reduced cardiac hypertrophy, attenuated interstitial fibrosis, and smaller infarct scar size.[27] Histological analyses further demonstrated enhanced neovascularization and attenuation of pathological remodeling in treated animals.[26, 27] Complementary proteomic analyses reveal an enrichment of factors associated with extracellular matrix regulation, tissue homeostasis, immune modulation, and angiogenesis following implantation of cell-encapsulated device, indicating that the encapsulated cells dynamically adjus their secretory profile in response to the physiological environment.[26, 27]

## Translation, Challenges and Future Recommendations

The integration of human iPSC-derived cardiac organoids and secretome-based regenerative therapies represents a major shift in the paradigm of translational cardiovascular science.[6] Organoid platforms offer physiologically relevant, patient-specific models that address many of the limitations inherent to traditional preclinical systems,[7, 12] Their capacity to recapitulate ischemic injury, metabolic dysfunction, inflammatory responses, and cardiotoxicity in a controlled environment makes them invaluable for mechanistic investigation and therapeutic discovery.[12, 14, 16]

Secretome-based therapy, in parallel, reflects a growing recognition that effective cardiac regeneration may depend more on modulating endogenous repair processes than on direct cellular replacement.[25] Immunoisolated cell delivery devices overcome key barriers associated with cell-based therapies, including limited cell survival, immune rejection, and batch-to-batch variability, while providing a scalable and minimally invasive platform for sustained release of therapeutic factors.[26, 27] Together, cardiac organoids and secretome-delivery technologies offer a complementary translational framework in which organoids enhance the fidelity of preclinical modeling, and device-based secretome delivery provides a feasible pathway toward clinical implementation.

Despite their promise, several challenges remain. Organoid maturation varies cosiderably across laboratories, underscoring the need for standardized protocols to ensure reproducibility.[28] Secretome composition is inherently complex and influenced by culture conditions, cellular age, and microenvironmental cues, highlighting the importance of advanced analytical approaches to established potency and quality metrics.[29] In addition, regulatory pathways for cell-free biologics and device-based cell therapies are still evolving and require careful navigation.[30] Nonetheless, continue progress in tissue engineering, stem cell biology, and regenerative medicine suggests that these technologies are well positioned to contribute meaningfully to future cardiovascular therapies.

## Conclusions

Human iPSC-derived cardiac organoids and stem cell secretome-based therapies represent promising strategies for addressing ongoing challenges in cardiometabolic disease research and treatment. Cardiac organoids provide human-relevant, multicellular models that enable detailed investigation of disease mechanisms and therapeutic responses. Secretome-based therapies, particularly when delivered through immunoisolated device systems, offer a minimally invasive regenerative approach capable of modulating multiple disease pathways simultaneously. Collectively, these emerging technologies have the potential to strengthen translational cardiovascular research and ultimately improve clinical outcomes in heart disease.

### Conflict of Interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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