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Transforming heart disease research with cardiac organoid technologies

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ABSTRACT

Background

Cardiovascular diseases (CVDs) remain the leading global cause of morbidity and mortality, necessitating innovative research approaches to bridge the translational gap between preclinical and clinical settings. Traditional models, such as two-dimensional (2D) cell cultures and animal models, are limited in replicating human cardiac physiology. Cardiac organoids, derived from human pluripotent stem cells, have emerged as transformative tools in cardiovascular research, offering 3D models that recapitulate key structural and functional features of the human heart.

Objectives

This study aims to explore the potential of cardiac organoids in disease modelling, drug discovery, and regenerative medicine while addressing current limitations and proposing future directions for their translational application.

Methods

A comprehensive review of recent advancements in cardiac organoid research was conducted, focusing on methodologies for organoid generation, their applications in preclinical research, and innovations to overcome technical and biological limitations. Emphasis was placed on integrating multi-omics technologies, artificial intelligence (AI),
and bioengineering approaches.

Results

Cardiac organoids have successfully modelled various cardiac conditions, including myocardial infarction, genetic cardiomyopathies, and congenital heart defects. Multi-omics technologies, such as genomics, transcriptomics, and proteomics, have elucidated molecular mechanisms, while AI-driven computational modelling has enhanced data analysis and predictive simulations. Despite their promise, challenges persist in achieving vascularization, cellular maturity, and scalability, limiting their clinical translation.

Conclusions

Cardiac organoids offer a physiologically relevant platform for advancing cardiovascular research. Their potential to revolutionize drug testing, personalized medicine, and regenerative therapies underscores their transformative impact. Addressing current limitations through interdisciplinary innovations, such as vascularized organoid systems and organoid-on-chip platforms, will enhance their translational utility. With continued advancements, cardiac organoids hold promise for improving therapeutic outcomes and understanding human heart diseases.

KEYWORDS

Cardiovascular diseases; Cardiac organoids; Stem cells; Multi-omics technology; Myocardial infarction

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with approximately 18 million deaths annually, according to the World Health Organization (WHO) [1]. These conditions, including myocardial infarction, cardiomyopathies, and congenital heart defects, impose a substantial burden on healthcare systems globally. Despite advancements in diagnostics and therapeutics, the complex pathophysiology of CVDs poses significant challenges in developing effective treatments [2]. Bridging the gap between preclinical models and clinical outcomes remains a critical hurdle, necessitating innovative approaches to better understand and combat these diseases.

Traditionally, cardiovascular research has relied on two-dimensional (2D) cell cultures and animal models. While these systems have advanced our understanding of cardiac biology, they have inherent limitations. 2D cell cultures fail to replicate the complex three-dimensional (3D) architecture and physiological interactions of the human heart. Animal models, though valuable for in vivo insights, often exhibit species-specific differences, limiting their translational applicability to human conditions. These challenges highlight the need for physiologically relevant models to bridge the translational gap. Organoid technology has emerged as a transformative platform in biomedical research, offering a

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promising solution. Organoids are 3D, self-organizing structures derived from stem cells, recapitulating key structural and functional features of their corresponding organs [3,4]. Human cardiac organoids (hCOs), in particular, hold immense potential in cardiology by mimicking the architecture and functionality of native cardiac tissue [5].

Recent advancements in organoid technology have expanded its applications in cardiovascular research. hCOs have been utilized to model a range of conditions, including congenital heart diseases, myocardial infarction, and genetic cardiomyopathies. For example, studies have demonstrated the utility of hCOs in replicating ischemic injury to study the pathophysiology of myocardial infarction [6]. Additionally, cardiac organoids serve as effective platforms for evaluating cardiotoxicity in drug development, enhancing the safety and efficacy profiles of new pharmacological agents. Beyond disease modeling, hCOs are being explored in regenerative medicine to investigate myocardial repair processes and test stem cell-based therapies. These advancements emphasize the growing role of organoids in addressing key questions in cardiovascular science [7].

Despite their potential, cardiac organoids face significant challenges. One major limitation is achieving full maturation to accurately reflect the adult human heart. Current hCOs often resemble embryonic or fetal stages, restricting their utility for studying adult-onset or age-related diseases. Another significant hurdle is replicating the complex vascular networks essential for long-term viability and functionality. Avascular organoids lack adequate nutrient and oxygen delivery, limiting their physiological relevance [8]. Scalability and reproducibility also pose challenges, as variations in size, shape, and functional properties between batches hinder consistency, particularly in high-throughput applications.

Addressing these limitations is crucial for advancing organoid technology. Enhancing the structural and functional fidelity of cardiac organoids requires innovative approaches. Advances in vascularization techniques, such as integrating bioengineered vascular networks, are essential for improving organoid viability. Strategies to accelerate maturation using biochemical cues or co-culture systems with stromal cells are also promising. Furthermore, integrating multi-omics technologies like genomics, transcriptomics, and proteomics can provide deeper insights into disease mechanisms and cardiac development [9]. Despite these promising directions, robust frameworks to translate findings from organoid models into clinical applications remain underdeveloped.

This article aims to advance a theoretical understanding of cardiac organoid applications in cardiovascular research. Specifically, it will:

1. Explore methodologies for the development and characterization of cardiac organoids.
2. Highlight their applications in disease modeling, drug discovery, and regenerative medicine.
3. Critically analyze the challenges and limitations of organoid technology.
4. Propose future directions to enhance their translational potential.

By addressing these objectives, this article seeks to provide a comprehensive overview of cardiac organoid technology, its transformative potential in cardiovascular research, and the steps required to overcome existing barriers.

Conceptual Foundations

Definition and basics of organoids

Organoids are 3D cell culture systems derived from stem cells that replicate the architecture and functionality of native organs [10]. These structures are generated using either embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) and are capable of self-organization due to intrinsic cellular signalling mechanisms. This self-organization is further guided by external cues such as growth factors and extracellular matrix (ECM) components, creating an environment that promotes differentiation into organ-specific cell types [11]. Organoids have gained recognition as versatile tools in biomedical research for modelling human organ development, understanding disease mechanisms, and testing therapeutic interventions (Table 1) [12].

Table 1. Types of organoids and their source cells.

Organoid Type	Source Cells	Key Characteristics	Applications
Cerebral Organoids	Human pluripotent stem cells (hPSCs)	Mimic early brain development; exhibit diverse neuronal cell types and cortical-like regions.	Study of neurodevelopmental disorders, brain evolution, and neurodegenerative diseases.
Gastric Organoids	hPSCs or LGR5+ adult stem cells	Recapitulate stomach epithelium; contain functional gastric cell types, including mucus-secreting cells.	Modeling gastric diseases, Helicobacter pylori infection studies, and cancer research.
Intestinal Organoids	LGR5+ intestinal stem cells	Form crypt-villus structures; contain enterocytes, goblet cells, Paneth cells, and enteroendocrine cells.	Research on intestinal physiology, cystic fibrosis, and drug absorption studies.
Liver Organoids	hPSCs or adult liver progenitor cells	Exhibit hepatocyte functions; capable of drug metabolism and protein synthesis.	Modeling liver diseases, hepatitis virus infection studies, and toxicology assessments.
Pancreatic Organoids	hPSCs or adult pancreatic ductal cells	Contain insulin-producing β-cells; exhibit glucose-responsive insulin secretion.	Diabetes research, pancreatic cancer studies, and regenerative medicine applications.

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Renal Organoids	hPSCs	Develop nephron-like structures; exhibit proximal and distal tubule segments.	Study of kidney development, nephrotoxicity testing, and modeling of genetic kidney diseases.
Lung Organoids	hPSCs or adult lung stem cells	Contain airway and alveolar epithelial cells; exhibit branching morphogenesis.	Research on respiratory infections, cystic fibrosis, and pulmonary disease modeling.
Retinal Organoids	hPSCs	Develop layered retinal structures; contain photoreceptors and retinal ganglion cells.	Study of retinal development, degenerative eye diseases, and potential for cell replacement therapies.
Thymic Organoids	Thymic stromal cells	Recapitulate thymic architecture; support T-cell development from hematopoietic progenitors.	Research on T-cell maturation, immunodeficiencies, and thymus-related disorders.
Testicular Organoids	Testicular somatic and germ cells	Mimic testicular tissue organization; support spermatogenesis in vitro.	Study of male infertility, testicular development, and effects of toxins on reproductive health.

The development of cardiac organoids represents a significant advancement in this field. These organoids are created by differentiating pluripotent stem cells into cardiac-specific lineages, including cardiomyocytes, fibroblasts, and endothelial cells (Table 2) [13]. The differentiation process typically involves modulation of the Wnt signalling pathway during mesodermal induction, followed by further maturation with stage-specific growth factors. The resulting cells are cultured in 3D environments, often supported by hydrogels or ECM scaffolds, which allow them to assemble into structures capable of spontaneous contraction and electrophysiological activity. Cardiac organoids exhibit hallmark features of heart tissue, including synchronized beating, response to pharmacological agents, and expression of key markers like NKX2-5 and cardiac troponin T (cTnT) [14]. These properties make them invaluable for investigating heart development, disease modelling, and drug screening in a controlled setting.

Table 2. Different types of cardiac organoids and their source cells.

Organoid Model	Source Cells	Key Characteristics	Applications
Self-Organizing Cardioids	Human pluripotent stem cells (hPSCs)	- Mimic early heart development - Exhibit chamber-like structures - Display spontaneous beating and electrophysiological activity	- Modeling congenital heart diseases - Studying cardiogenesis - Drug screening
Multi-Chambered Cardiac Organoids	hPSCs	- Develop distinct atrial and ventricular regions - Show coordinated contraction - Possess functional cardiac cell types	- Investigating structural heart diseases - Assessing drug responses - Understanding cardiac physiology
Vascularized Cardiac Organoids	hPSCs co-cultured with endothelial cells	- Formation of perfusable vascular networks - Enhanced tissue viability and maturation - Improved nutrient and oxygen delivery	- Studying ischemic heart diseases - Testing pro-angiogenic therapies - Modeling vascular contributions to cardiac function
Engineered Heart Tissues (EHTs)	hPSC-derived cardiomyocytes seeded on scaffolds	- Aligned myocardial fibers - Responsive to electrical and mechanical stimulation - Capable of force generation	- Drug toxicity testing - Modeling myocardial infarction - Tissue regeneration studies
Cardiac Spheroids	Aggregates of hPSC-derived cardiomyocytes, fibroblasts, and endothelial cells	- Spherical microtissues - Exhibit synchronized beating - Simplified model with key cardiac cell interactions	- High-throughput drug screening - Studying cell-cell interactions - Modeling early cardiac development

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Current state of cardiac organoid research

Research on cardiac organoids has advanced significantly, providing insights into both normal heart development and the pathophysiology of cardiac diseases. For instance, studies have demonstrated that cardiac organoids can replicate early cardiac development stages, offering a platform to study congenital heart defects. Specific applications include modelling dilated cardiomyopathy, arrhythmogenic cardiomyopathies, and ischemic heart disease [15]. Additionally, cardiac organoids have proven effective in high-throughput drug screening to evaluate cardiotoxicity and therapeutic efficacy, with some studies highlighting their use in identifying potential off-target effects of cancer therapies, such as doxorubicin-induced cardiotoxicity.

Efforts to improve organoid functionality have focused on enhancing cellular maturity and tissue complexity. For example, the use of biophysical stimulation, such as electrical and mechanical cues, has been shown to promote the maturation of cardiomyocytes within organoids, resulting in electrophysiological and structural properties more akin to adult heart tissue. Furthermore, advancements in co-culture systems have allowed the incorporation of non-cardiomyocyte cells, such as immune and endothelial cells, to better recapitulate the native cardiac microenvironment [16]. These innovations have positioned cardiac organoids as a promising tool for personalized medicine, enabling patient-specific disease modelling and drug testing.

Limitations in translating findings to clinical settings

Despite these advancements, several challenges limit the clinical translation of cardiac organoid research. One significant issue is the immaturity of organoid-derived cardiomyocytes. These cells often exhibit a fetal-like phenotype, characterized by underdeveloped sarcomere structures and inefficient calcium handling. This immaturity can compromise the accuracy of disease models and limit their applicability for studying adult-onset cardiac conditions. Addressing this limitation requires the development of techniques that promote cardiomyocyte maturation, such as prolonged culture durations, metabolic conditioning, and mechanical stimulation [17].

Another limitation is the lack of vascularization within cardiac organoids. The absence of functional blood vessels restricts their size and viability, as nutrient and oxygen diffusion becomes inadequate in larger constructs, leading to necrotic cores. This issue also prevents the modelling of vascularized cardiac diseases, such as coronary artery disease. Strategies to overcome this limitation include incorporating endothelial cells into organoids or integrating bioprinting techniques to create vascular networks [18]. However, these approaches are still in the experimental stages and require further refinement.

Variability in organoid formation and functionality is another critical challenge. Differences in stem cell sources, differentiation protocols, and culture conditions can result in inconsistencies, affecting reproducibility and reliability in research and clinical applications. Standardized protocols, rigorous quality control measures, and batch-to-batch validation are essential to mitigate these issues [19]. Additionally, while cardiac organoids can mimic many aspects of heart tissue, they lack integration with other physiological systems, such as the nervous and immune systems, which play vital roles in heart function and disease progression.

Advancements in Cardiac Organoid Research

Disease modelling frameworks

Cardiac organoids have advanced our understanding of myocardial infarction (MI), genetic cardiomyopathies, and infectious myocarditis by replicating complex cellular interactions and tissue structures in vitro [6]. These models offer a human-relevant platform that overcomes the limitations of traditional two-dimensional cell cultures and animal models.

Myocardial infarction (MI):

Cardiac organoids can mimic ischemic conditions by subjecting them to controlled hypoxic environments. This allows researchers to study cellular responses such as apoptosis, necrosis, and fibrotic remodelling. For instance, studies have shown that hypoxia-induced cardiac organoids exhibit elevated levels of hypoxia-inducible factor 1-alpha (HIF-1α), along with increased expression of fibrotic markers such as collagen type I and type III, mimicking post-MI fibrotic tissue [20]. These models also enable the testing of novel therapeutic agents targeting fibrotic pathways or promoting angiogenesis in ischemic tissues [21].

Genetic cardiomyopathies:

Cardiac organoids derived from patient-specific induced pluripotent stem cells (iPSCs) carrying mutations in sarcomeric or cytoskeletal genes provide insights into disease-specific phenotypes [22]. For example, organoids generated from patients with hypertrophic cardiomyopathy (HCM) have shown pathological thickening of myocardial fibres, altered calcium dynamics, and hypercontractility [23]. These features facilitate a detailed study of the mechanisms driving the disease and offer platforms for testing small molecules that reverse or mitigate these effects.

Infectious myocarditis:

Cardiac organoids have been used to model infectious myocarditis by introducing coxsackievirus and other pathogens into the system [7]. This approach allows researchers to examine viral replication, immune cell recruitment, and tissue-specific damage. However, the absence of integrated immune components in most organoids remains a limitation. Future advancements integrating immune cells into cardiac organoids will enhance their utility in modelling infectious myocarditis and testing antiviral strategies [24].

Challenges and Theoretical Gaps

Technical barriers

Standardization of organoid creation

The generation of cardiac organoids involves intricate protocols that vary widely between laboratories, leading to inconsistencies in size, cellular composition, and functionality. For instance, differences in differentiation media composition, ECM scaffolds, and 3D culture systems can result in variable outcomes. Such variability hinders reproducibility and

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comparability across studies, undermining their utility in both research and clinical applications. Standardized differentiation protocols, automated cell culture systems, and robust quality control metrics are crucial for addressing these challenges [25].

Scalability for high-throughput applications

Scaling up the production of cardiac organoids for drug screening and therapeutic applications remains a significant hurdle. Current methods are labour-intensive, with batch-to-batch variability that compromises efficiency and reliability. Advanced bioreactor systems and organoid-on-a-chip platforms are being developed to enable high-throughput production [26]. For example, microfluidic platforms have demonstrated the ability to culture large numbers of uniform organoids while maintaining functionality [27].

Challenges in vascularization

The lack of functional vasculature in cardiac organoids limits their size and viability. Without proper vascularization, nutrient and oxygen diffusion become insufficient, resulting in necrotic cores. Efforts to address this include co-culturing cardiac organoids with endothelial cells or integrating pre-vascularized scaffolds [28]. Bioprinting approaches have also shown promise, with studies successfully creating perfusable vascular networks within organoids [29]. However, achieving stable and functional vascularization remains an area of active research.

Biological limitations

Replicating adult heart physiology

A major limitation of cardiac organoids is their resemblance to fetal rather than adult heart tissue. Organoid-derived cardiomyocytes exhibit immature sarcomere structures, underdeveloped T-tubules, and inefficient calcium handling, which limits their utility for modelling adult-onset diseases or testing drugs targeting mature heart physiology [30]. Mechanical stimulation, prolonged culture periods, and electrical pacing have been shown to promote maturation, but these approaches are not yet standardized or universally effective.

Immune system integration

The absence of immune components in most cardiac organoids presents challenges for studying inflammatory conditions, such as myocarditis, or immune-mediated drug responses [31]. Emerging techniques, such as co-culturing organoids with immune cells derived from peripheral blood mononuclear cells (PBMCs) or integrating hematopoietic progenitors, offer potential solutions. These approaches aim to recreate the dynamic interactions between immune and cardiac cells, enabling more comprehensive disease models.

Achieving cellular maturity

Immaturity remains a persistent challenge, with organoid-derived cells often lacking the structural and functional complexity of their in vivo counterparts. For example, metabolic immaturity, reflected in the predominant reliance on glycolysis over oxidative phosphorylation, limits their physiological relevance [32]. Optimizing culture environments by incorporating metabolic conditioning and biochemical cues, such as thyroid hormone, can enhance maturity.

Theoretical challenges

Ethical debates

The ethical considerations surrounding cardiac organoid research stem from concerns about the source of stem cells, particularly embryonic stem cells, and the potential for organoids to develop sentience as models become more complex [33]. For instance, ethical debates have emerged regarding the moral status of advanced organoids with neural components. Guidelines from the International Society for Stem Cell Research (ISSCR) emphasize the need for oversight and ethical review of such research to balance scientific progress with societal concerns [34].

Regulatory hurdles

The translation of organoid research into clinical applications faces stringent regulatory requirements. Agencies such as the FDA and EMA mandate rigorous validation to ensure the safety and efficacy of organoid-based systems [35]. This includes demonstrating consistency, functional equivalence to native tissue, and reproducibility. The establishment of standardized assessment protocols, such as those outlined in Good Laboratory Practice (GLP) guidelines, will be essential to overcome these regulatory challenges.

Innovations and Future Perspectives

The integration of interdisciplinary approaches has significantly expanded the scope of organoid research, enhancing our understanding of biological systems and accelerating therapeutic advancements. Multi-omics technologies, artificial intelligence (AI), computational modelling, and novel platforms like organoid-on-chip systems represent transformative tools for the future of organoid studies.

Multi-omics integration

The convergence of genomics, transcriptomics, and proteomics with organoid research offers an unparalleled opportunity to elucidate the molecular mechanisms underpinning human biology and disease [36]. These technologies enable researchers to dissect the complexity of organoid development and uncover novel therapeutic targets. Genomics provides insights into genetic variations and mutations that may influence organoid behaviour. For example, sequencing the genomes of patient-derived organoids can identify driver mutations in cancer or susceptibility loci in cardiovascular diseases, thereby enabling personalized medicine. Additionally, CRISPR-Cas9 gene-editing tools have been integrated into genomic studies to validate the functional impact of specific mutations in organoids [37].

Transcriptomics reveals dynamic gene expression patterns at both bulk and single-cell levels. Single-cell RNA sequencing has been instrumental in identifying rare cell populations and delineating cell lineage trajectories during organoid development [38]. This approach has provided critical insights into tissue-specific differentiation, particularly in organoids mimicking neural and cardiac tissues. Proteomics bridges the gap between gene expression and cellular function by analyzing protein composition, interactions, and post-translational modifications. Advanced mass spectrometry techniques have

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been used to identify protein biomarkers and map signalling pathways activated in disease-specific organoids, such as those modelling neurodegenerative disorders [39].

The integration of these multi-omics datasets enables the reconstruction of molecular networks and the identification of key regulatory pathways. For example, cancer organoid models have benefited from multi-omics profiling, which revealed tumour-specific vulnerabilities and therapeutic. Computational tools like Cytoscape and Seurat are widely used to manage and analyze these datasets, facilitating hypothesis-driven research. Challenges such as data storage, integration, and interpretation remain, but ongoing advancements in bioinformatics promise to streamline multi-omics analyses [40].

AI and computational modelling

Artificial intelligence (AI) and computational modelling are revolutionizing organoid research by enabling high-throughput data analysis, predictive simulations, and enhanced experimental design [41]. These technologies provide a framework for understanding complex biological systems and optimizing organoid applications.

Machine learning in organoid research: Machine learning, particularly deep learning, has been employed for tasks such as organoid image analysis and phenotype classification. Convolutional neural networks (CNNs) can automatically segment and quantify organoid structures in microscopy images, significantly accelerating throughput in drug screening studies. For example, CNNs have been used to evaluate growth dynamics and structural organization in cardiac organoids under varying experimental conditions [42].

Beyond imaging, AI algorithms integrate multi-omics data to identify molecular signatures associated with specific organoid phenotypes. For instance, random forest models have been applied to predict drug responses in tumour organoids, providing actionable insights for precision oncology [41].

Computational modelling and predictive simulations: Computational models, such as agent-based and finite element models, simulate the behaviour of individual cells and tissue-level dynamics within organoids [43]. These simulations allow researchers to test hypotheses virtually, reducing the need for exhaustive experimental trials. For example, agent-based models have been used to predict how genetic perturbations affect organoid morphology and function, guiding experimental validation.

The ethical implications of AI and computational modelling, such as data privacy and algorithmic bias, warrant careful consideration. Ensuring transparency in algorithm design and validation is critical to maintaining trust and reproducibility in AI-driven organoid research.

Future research directions

To address current limitations and unlock the full potential of organoids, several promising avenues for future research warrant exploration.

Vascularized organoids: A critical barrier to organoid advancement is the lack of functional vasculature, which restricts organoid size and viability. Recent studies have demonstrated the feasibility of co-culturing organoids with endothelial cells to promote angiogenesis or incorporating perfusable microfluidic channels to mimic vascular networks [44]. These vascularized organoids are particularly valuable for studying diseases such as ischemic heart disease and for long-term drug testing applications.

Organoid-on-chip systems: Integrating organoids with microfluidic devices—organoid-on-chip systems—enables precise control of the cellular microenvironment. These platforms can simulate physiological conditions, such as mechanical forces and fluid flow, to mimic in vivo tissue behaviour. Moreover, organoid-on-chip systems allow for the coupling of multiple organoids, such as heart-liver or gut-brain interactions, to model systemic diseases or multi-organ toxicities [45].

Discussions

Cardiac organoids have transformed cardiovascular research, providing unprecedented insights into heart development, disease mechanisms, and therapeutic responses. This discussion synthesises recent theoretical advancements, positions organoid models within the broader cardiovascular research paradigm, and explores their implications for preclinical studies and translational medicine [31].

Synthesis of key theoretical advancements

The development of cardiac organoids has enabled the study of human heart biology in a physiologically relevant and ethically sound manner. Stein JM et al. described these three-dimensional, self-organizing structures that replicate aspects of cardiac tissue architecture and function, allowing researchers to model complex cardiac conditions that were previously difficult to study in vitro [46]. Key advancements include the creation of multi-chambered organoids, which better emulate the structural and functional complexity of the human heart, making them invaluable for understanding congenital heart defects and arrhythmias.

The integration of multi-omics approaches like spanning genomics, transcriptomics, and proteomics has further enhanced the utility of cardiac organoids. Nappi F demonstrated that genomic sequencing of patient-derived organoids reveals genetic mutations associated with specific cardiac pathologies, while transcriptomic analyses uncover distinct gene expression patterns underlying disease phenotypes [47]. Proteomic profiling bridges the gap between gene expression and functional outcomes, identifying biomarkers and signalling pathways critical for cardiac function and pathology.

Artificial intelligence (AI) and computational modelling have also revolutionized organoid research. Machine learning algorithms, such as convolutional neural networks (CNNs), are used to analyze organoid growth, morphology, and drug responses. Computational models provide predictive insights into disease progression and therapeutic efficacy, enabling hypothesis-driven experimental design [48]. These tools have been particularly impactful in modelling inherited cardiac conditions and optimizing treatment strategies.

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Comparison with existing knowledge

Traditional cardiovascular research has heavily relied on two-dimensional cell cultures and animal models, both of which have significant limitations. Duval K et al. noted that two-dimensional cultures lack the structural and functional complexity of three-dimensional tissues, limiting their ability to accurately model in vivo cardiac conditions [4]. Animal models, while valuable, often fail to replicate human-specific gene expression patterns and drug metabolism, leading to high attrition rates during clinical drug development. Approximately 90% of drugs that succeed in animal trials fail in humans, with cardiotoxicity being a major cause.

Cardiac organoids bridge this gap by offering a physiologically relevant platform that mimics the three-dimensional structure and cellular diversity of the human heart. Unlike animal models, human-derived cardiac organoids exhibit species-specific responses, improving the predictive accuracy of preclinical findings. For instance, they have been used to evaluate cardiotoxicity in cancer therapies, identifying adverse effects early in the drug development process [49].

Nugraha B. et al. emphasized that cardiac organoids provide an unparalleled platform for studying human-specific diseases, such as genetic cardiomyopathies and congenital heart defects. They also complement emerging technologies like organ-on-chip systems, which simulate inter-organ interactions and systemic responses, enhancing the versatility of in vitro cardiovascular models [50]. Compared to these systems, organoids excel in modelling cellular heterogeneity and dynamic tissue remodelling, offering complementary insights into disease mechanisms.

Implications for research and practice

The implications of cardiac organoids for preclinical research and translational medicine are profound. Chen X et al. highlighted that these models offer a high-fidelity platform for drug screening, allowing researchers to assess efficacy and toxicity in a human-relevant context. Organoids have already been used to evaluate the cardiotoxic potential of chemotherapeutic agents such as doxorubicin, highlighting their value in improving drug safety and efficacy [51]. In translational research, cardiac organoids facilitate the development of personalized medicine. By generating organoids from patient-specific induced pluripotent stem cells (iPSCs), researchers can study individual disease phenotypes and predict therapeutic responses. This personalized approach has shown promise in treating genetic cardiomyopathies and rare congenital conditions, enabling tailored treatment strategies that minimize adverse effects [52]. The potential of organoids in regenerative medicine is also noteworthy. Advances in tissue engineering have enabled the generation of organoids that could be used for cardiac tissue transplantation. For example, vascularized cardiac organoids have been developed to restore myocardial function in preclinical models of ischemic heart disease. While challenges such as variability and scalability remain, these innovations pave the way for novel therapeutic approaches to treating heart failure and other cardiac conditions.

Ethical and practical considerations

Despite their promise, the use of cardiac organoids presents ethical and practical challenges. Ethical concerns include the sourcing of stem cells, particularly embryonic stem cells, and the moral implications of creating complex organoid systems that could potentially exhibit sentience [53]. Practical challenges include the cost of production, variability in organoid creation, and the lack of standardized protocols for large-scale applications. Addressing these issues will require collaborative efforts across scientific, ethical, and regulatory domains, as well as advancements in automation and standardization.

Conclusions

The development of cardiac organoids has facilitated significant breakthroughs in modelling heart structure and function. Multi-chambered cardiac organoids now replicate distinct atrial and ventricular regions, exhibiting electrophysiological properties and metabolic activity comparable to native cardiac tissue. These models have been instrumental in studying arrhythmias, congenital heart defects, and cardiomyopathies. Moreover, their integration of diverse cell types like cardiomyocytes, fibroblasts, and endothelial cells has enhanced their physiological relevance, making them invaluable for modelling the complexities of cardiac development and pathology.

The incorporation of multi-omics technologies has further advanced organoid research. Genomic analyses have identified mutations linked to specific cardiac conditions, while transcriptomics and proteomics have revealed key gene expression patterns and protein interactions. These approaches have enhanced our understanding of cardiac biology at the molecular level, informing the identification of disease biomarkers and therapeutic targets. Artificial intelligence (AI) and computational modelling complement these advancements by enabling predictive simulations of disease progression and therapeutic responses, optimizing experimental design and reducing resource-intensive trials.

Despite these advancements, significant theoretical gaps remain. The lack of vascularization limits organoid size and longevity, constraining their ability to model ischemic conditions and chronic diseases. Efforts to co-culture organoids with endothelial cells or incorporate perfusable vascular networks have shown promise but require further refinement for consistent application. Similarly, the absence of neuronal integration restricts the study of neuro-cardiac interactions, which are critical for understanding conditions like arrhythmias and heart-brain signalling. Standardization is another critical challenge. Variability in differentiation protocols, culture systems, and scaffold materials often leads to inconsistencies in organoid structure and function. These discrepancies complicate data interpretation and hinder reproducibility across studies. Developing consensus guidelines for organoid fabrication and characterization is essential to ensure uniformity and comparability, particularly for translational applications.

Ethical concerns must also be addressed. The sourcing of

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embryonic stem cells and the potential creation of highly complex organoid systems raise moral questions. Establishing robust ethical guidelines and regulatory oversight will ensure responsible research practices, fostering public trust and acceptance. Cardiac organoids hold immense transformative potential for cardiovascular research, offering unparalleled insights into human heart biology and disease. Their applications in preclinical drug testing have already demonstrated their value in improving the safety and efficacy of therapeutic agents. Patient-specific organoids are paving the way for personalized medicine, enabling tailored treatments for genetic and acquired cardiac conditions. Moreover, advances in tissue engineering suggest a future where organoids could be used for regenerative therapies, such as repairing damaged myocardium in heart failure. As the field progresses, integrating vascular and neural components into organoid systems will enhance their physiological relevance. Combining these advancements with emerging technologies, such as organoid-on-chip platforms and AI-driven analyses, will further elevate the utility and precision of cardiac organoids. By addressing current challenges, the scientific community can unlock the full potential of these models, revolutionizing cardiovascular research and improving therapeutic outcomes for patients worldwide.

Disclosure Statement

No potential conflict of interest was reported by the author.

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