Next-Generation Cardiac Chips: Combining Nanomedicine, Stem Cells, And Perfusion Models

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Abstract:

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for millions of deaths annually[1].Despite major advances in pharmacotherapy and clinical interventions, translating laboratory discoveries into effective cardiac therapeutics is hindered by the limitations of traditional preclinical models that fail to accurately mimic human cardiac physiology[2].The emergence of organ-on-chip (OOC) technologies—especially cardiac chips—has revolutionized preclinical research by integrating microengineering, nanotechnology, and stem cell biology to simulate functional human cardiac tissue in vitro[3].Next-generation cardiac chips combine nanomedicinetools, stem cell-derived cardiomyocytes, and perfused microfluidic networks to replicate the heart's mechanical, electrical, and biochemical microenvironment [4] .These hybrid systems enable precise model of disease mechanisms, high-throughput drug screening, cardiotoxicity assessment, and regenerative research [5].By incorporating nanoscale biosensors, diffusible, vascular channels, and dynamic flow systems, cardiac chips provide a human-relevant, predictive platform for translational cardiology[6]. This review explores the convergence of nanomedicine, stem cell engineering, and perfusion-based organ-chip platforms to create physiologically relevant cardiac models. It also discusses technological innovations, validation parameters, and the translational potential of these systems in personalized medicine and drug discovery.

Keywords: Cardiac-on-chip, nanomedicine, stem cells, perfusion models, microfluidics, tissue engineering, regenerative cardiology, organ-on-chip.

Introduction:

Cardiovascular diseases represent a growing global health challenge, responsible for over 17 million deaths per year and expected to surpass 23 million by 2030[7] .Traditional in vitro models and animal studies have played a critical role in cardiac research, yet they suffer from poor translatability due to interspecies differences, static culture conditions, and lack of human-like mechanical and electrical signalling. These limitations have led to a

high attrition rate in cardiovascular drug development, with approximately 90% of candidate drugs failing during clinical trials due to unpredicted human responses. To overcome these barriers, the concept of organ-on-chip (OOC) technology has emerged as a groundbreaking platform that integrates microfluidics, biomaterials, and living cells within a controlled microenvironment. Among various OOC models, cardiac-on-chip systems have attracted particular attention because of their ability to replicate heartbeat rhythm, contractility, and electrophysiological behaviour under near-physiological conditions.These devices use microelectromechanical systems (MEMS) and microfluidic channels to simulate the dynamic perfusion, oxygen gradients, and nutrient exchange that occur in native myocardium. Recent innovations have elevated these systems beyond simple heart-tissue mimics. The integration of nanomedicine, stem cell-derived cardiomyocytes, and perfusion-based bioengineered scaffolds represents a transformative step toward next-generation cardiac chips. Nanomedicine enhances these models by incorporating nano sensorsdisease, nanoparticles, and nanostructured materials that enable precise drug delivery, real-time bio sensing, and molecular tracking within the chip environment [9]. Stem cell technologies, particularly human induced pluripotent stem cells (hiPSCs)—provide an ethically sustainable and patient-specific source of cardiomyocytes that mimic genetic and phenotypic variability.Thus, next-generation cardiac chips stand at the crossroads of bioengineering, nanotechnology, and cellular therapy, offering a bridge between traditional bench models and in vivo physiology. The integration of these multidisciplinary components holds immense potential for improving drug discovery, disease modelling, and precision cardiology [10].

Fig.1: Different types of Organ-on-a-Chip.

Overview of Cardiac Chips:

The development of organ-on-chip (OOC) technology originated in the early 2000s from advances in microfabrication and lab-on-a-chip systems designed to miniaturize biological assays [11].The concept of a “heart-on-a-chip” first appeared when researchers demonstrated that cardiomyocytes cultured on micro engineered substrates could exhibit synchronized contractions similar to native heart tissue .Over time, the field evolved with the integration of soft lithography, microelectromechanical systems (MEMS), and biocompatible polymers, allowing scientists to design microscale environments that support cell alignment, electrical conduction and mechanical strain [12].

Today, the evolution of cardiac chips encompasses multicellular integration, real-time monitoring, and biomimetic perfusion, creating physiologically accurate models of human myocardium that replicate both healthy and diseased states [13].

Design Principles and Functional Architecture: A typical cardiac-on-chip model consists of a micro fluidic chamber lined with human cardiomyocytes, endothelial cells, and supporting fibroblasts, embedded within a flexible biopolymer matrix such as poly dimethylsiloxane (PDMS) or gelatinmethacrylate (GelMA). These devices incorporate microchannels that deliver continuous perfusion, providing oxygen and nutrients while removing metabolic waste, mimicking the vascular system's function.The structural design of cardiac chips is critical to ensuring physiologically relevant performance [14].

Three major design categories have emerged:

1. Single-layer chips, which provide basic static culture models for cell growth and alignment.
2. Multilayer chips, integrating perusable microchannels and flexible membranes to allow dynamic fluid exchange.
3. Hybrid chips, combining 3D bioprinter cardiac tissues with perfusion and electrical control systems for advanced modelling.

Biological Components and Materials: The functional performance of cardiac chips relies heavily on the biological cell sources and biomaterials used. Primary human cardiomyocytes have limited availability and lifespan; thus, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have become the gold standard due to their self-renewal, differentiation capacity, and patient specificity[15]. These cells can be reprogrammed from somatic cells and differentiated into cardiac subtypes—ventricular, atrial, or pacemaker cells—to model various cardiac functions and pathologies [16].

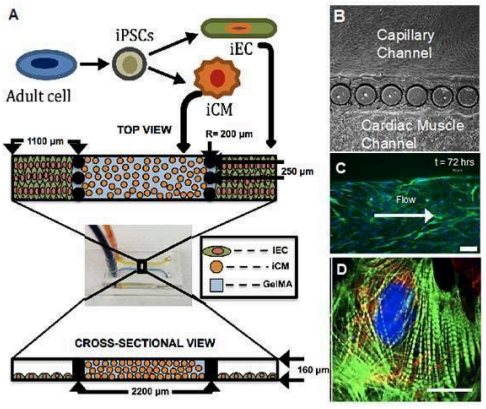

Fig.2: Illusion of Heart on a chip.

Working Principles: Cardiac-on-chip systems replicate the core physiological processes of the human heart, including electromechanical coupling, hemodynamic flow and metabolic exchange. Perfusion microchannels continuously circulate culture media to simulate blood flow, while integrated pumps or gravity-driven systems.Generate pulsatile shear stress similar to vascular forces. Electrical stimulation is applied to synchronize contractions, while strain sensors measure the resulting contractile force.

The role of Nanomedicine in Next-Generation Cardiac Chips

The Nanomedicine for Cardiac Tissue Engineering: The use of nanostructured materials significantly enhances the mechanical, electrical, and biological characteristics of cardiac chips. Carbon-based nanomaterials such as graphene, graphene oxide (GO), and carbon nanotubes (CNTs) have been widely used due to their excellent conductivity, biocompatibility, and mechanical strength. When embedded within polymeric scaffolds, these nanomaterials promote electrical coupling between cardiomyocytes, synchronize contractions, and support the transmission of action potentials. Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have also been used for improving signal transduction, enabling optical sensing and surface plasmon resonance-based measurements of cardiac electrophysiology. These nanofiber networks replicate the nanoscale fibrillar structure of the myocardium, promoting proper cardiomyocyte alignment contraction.

Fig.3: Different models of Organ-on-a-Chip on a single chip.

Integrating nanomedicine-derived biosensors into cardiac chips has revolutionized the monitoring of cellular behaviour, electrical activity, and biochemical responses[17]. Nano sensors based on graphene field-effect transistors (GFETs), nanowires, or quantum dots can detect minute changes in ionic currents, pH, and oxygen levels, providing high-resolution real-time data.

Nanoparticle-Assisted Drug Delivery and Therapeutic Testing: Nanoparticle-assisted drug delivery systems (DDS) provide an advanced strategy to evaluate pharmacodynamics and toxicity directly within cardiac chips[18]. By adjusting flow dynamics and concentration gradients, researchers can model dose-response relationships and tissue penetration profiles with unprecedented precision[19].

Integration of Stem Cells in Next-Generation Cardiac Chips :

Stem cells possess unique capabilities for self-renewal and differentiation, making them indispensable tools for regenerative medicine and disease modelling.The advent of human pluripotent stem cells (hPSCs)—including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)—has revolutionized cardiology by enabling the derivation of patient-specific cardiomyocytes that reflect individual genetic and pathological characteristics[20].

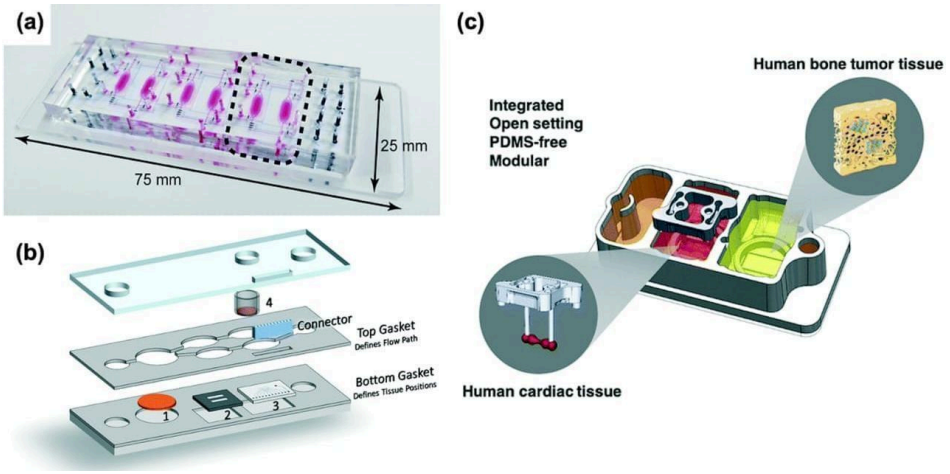

Fig.4: Heart-on-a-chip

Types of Stem cells Used in Cardiac Chips: Different classes of stem cells are employed to tailor the physiological relevance and complexity of cardiac-on-chip (COC) platforms:

1. Embryonic Stem Cells (ESCs):ESC-derived cardiomyocytes exhibit robust electrical coupling and spontaneous contractility, offering a model for early cardiac development. However, ethical considerations and immunogenicity limit their clinical translation[21].

2. Induced Pluripotent Stem Cells (iPSCs):iPSCs are reprogrammed from somatic cells and provide a non-invasive, patient-specific alternative. They retain genetic information from donors, making them ideal for personalized disease modelling and pharmacogenomic screening [22].

3. Mesenchymal Stem Cells (MSCs):MSCs, derived from bone marrow, adipose tissue, or umbilical cord, support paracrine signalling, promote angiogenesis, and reduce inflammation. In cardiac chips, they enhance tissue remodelling and extracellular matrix deposition, mimicking repair processes following myocardial infraction [23].

Disease Modelling Using Stem-Cell-Based Cardiac Chips: Stem-cell-derived cardiac chips have opened new horizons for patient-specific disease modelling, particularly for genetic cardiac disorders such as long QT syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. iPSC-derived cardiomyocytes from affected patients exhibit characteristic electrophysiological defects when cultured on microelectrode-embedded chips[24] .

Perfusion and Microfluidic Models in Cardiac Chips: Perfusion is fundamental to maintaining oxygenation, nutrient delivery, and metabolic waste removal in cardiac tissue. The myocardium is among the most metabolically active organs, requiring a constant and finely regulated blood supply. In vitro systems without perfusion often suffer from hypoxia and necrosis due to limited diffusion of oxygen and nutrients beyond 100–200 µm [25].

There are three main types of perfusion designs used in cardiac chips:

- Continuous-flow systems Maintain steady laminar flow through peristaltic or syringe pumps, ensuring uniform nutrient delivery.
- Pulsatile-flow systems Employ pressure controllers or pneumatic pumps to simulate rhythmic cardiac pulsation.
- Gravity-driven systems Provide passive flow without mechanical pumps, suitable for long-term culture with minimal mechanical disturbance.

Integration of Perfusion with Stem Cells and Nanomedicine: Acts as the connective link that unites nanomedicine and stem-cell technologies within next-generation cardiac chips. When combined with stem-cell-derived cardiac tissues, perfusion channels promote the formation of vascularized microtissues, thereby improving oxygen diffusion and metabolic coupling. Nanoparticle-based biosensors embedded within perfusion channels allow continuous monitoring of ionic balance, reactive oxygen species and metabolic fluxes[26].

Additionally, shear stress modulation within perfused chips enhances cardiomyocyte maturation, while nanostructured scaffolds within the channels improve cell adhesion and signal conduction. Thistripartite integration establishes a dynamic and physiologically accurate environment that closely mimics in vivo cardiac performance [26] .

Applications of Perfusion-Enabled Cardiac Chips:

Perfusion-based cardiac chips serve multiple applications across translational research and preclinical testing:

- Drug Screening and Toxicity Testing Perfused chips replicate pharmacokinetic conditions, enabling the study of drug absorption, distribution and clearance.
- Ischemia-Reperfusion Modelling Flow interruption and reoxygenation cycles reproduce myocardial infarction dynamics, aiding in therapeutic evaluation.
- Heart Failure Modelling: By altering flow rate and pressure, researchers can mimic ventricular overload, fibrosis, and contractile dysfunction.
- Regenerative Therapy Assessment supports cell engraftment, nutrient supply, and tissue remodelling in regenerative medicine studies.
- Multi-Organ Integration: Cardiac chips can be coupled with liver, kidney or lung chips to study systemic drug responses and organ cross-talk.

Collectively, perfusion models not only enhance the functional lifespan and maturity of cardiac tissue constructs but also elevate the predictive accuracy of in vitro cardiac studies, bridging the translational gap between bench and bedside [27-32].

Challenges, Limitations, and Future Directions:

- Current heart-on-chip systems cannot fully reproduce human cardiac physiology or 3D structure.
- iPSC-derived cardiomyocytes remain immature compared to adult heart cells.
- Integrating multiple cardiac cell types into a single functional model is challenging.

- Accurately mimicking natural mechanical forces such as contraction, pressure, and shear stress is difficult.
- Long-term stability for chronic studies and scalability for high-throughput screening are limited.
- More effective electrical, mechanical, and biochemical conditioning methods are needed to mature iPSC-derived cardiomyocytes.
- Future progress lies in integrating biosensors and AI, enabling patient-specific models, and standardizing fabrication for better reproducibility [33, 34].

Ethical, Regulatory, and Standardization Issues:

Agencies like the FDA, EMA, and OECD have initiated frameworks for organ-on-chip evaluation, but inter-laboratory variations in materials, flow dynamics, and readout metrics make cross-comparison difficult.Ethical issues also persist concerning the use of embryonic stem cells, though the rise of iPSC technology has mitigated many of these concerns; data reproducibility and device standardization remain critical obstacles before these models can be routinely adopted in pharmaceutical pipelines and regulatory toxicology [35,36].

Future Innovations and Translational Outlook:

The next decade will likely witness multi-organ and immune-integrated cardiac platforms, forming complete "human-on-chip" systems that can mimic inter-organ communication and systemic responses. Integration with vascular, hepatic, and renal chips will facilitate realistic pharmacokinetic-pharmacodynamic (PK-PD) modelling. Advancements in 3D bioprinting, smart nanomaterials and biosensor miniaturization will improve functional precision and reduce variability [37,38]. In parallel, wireless and implantable sensors may enable continuous remote monitoring of cardiac activity, bridging preclinical and clinical research. As patient-specific iPSCs and genome editing technologies mature, personalized cardiac chips could become a cornerstone for precision cardiology, offering individualized therapy screening, toxicity profiling, and regenerative interventions[39,40].

Conclusion:

Next-generation cardiac chips represent a paradigm shift in cardiovascular research, combining nanomedicine, stem cell biology, and microfluidic perfusion into a unified, human-relevant platform. These systems transcend the limitations of traditional in vitro and animal models by reproducing the heart's complex electromechanical and biochemical environment under dynamic flow conditions.Despite existing challenges in standardization, scalability, and regulatory acceptance, the convergence of these technologies heralds a new era of human-cantered cardiac modelling, personalized drug testing, and regenerative innovation. The ongoing integration of artificial intelligence, biosensors, and bio fabrication techniques promises to elevate cardiac-on-chip systems from experimental constructs to clinical and industrial cornerstones of next-generation cardiology.

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