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In vitro cardiac tissue models: Current status and future prospects☆

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ABSTRACT

Cardiovascular disease is the leading cause of death worldwide. Achieving the next phase of potential treatment strategies and better prognostic tools will require a concerted effort from interdisciplinary fields. Biomaterials-based cardiac tissue models are revolutionizing the area of preclinical research and translational applications. The goal of *in vitro* cardiac tissue modeling is to create physiological functional models of the human myocardium, which is a difficult task due to the complex structure and function of the human heart. This review describes the advances made in area of *in vitro* cardiac models using biomaterials and bioinspired platforms. The field has progressed extensively in the past decade, and we envision its applications in the areas of drug screening, disease modeling, and precision medicine.

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1. Introduction

Drug discovery and development is a challenging road, and current methods to evaluate drug safety and efficacy are costly and inefficient. The average time between drug discovery and commercialization is 10–15 years, with median costs over $5 billion [1]. During preclinical and clinical development, cardiotoxicity remains a major cause of failure, with high rates of post-approval withdrawal of medicines [2]. Furthermore, effective pre-clinical evaluation of drugs is essential for treating cardiovascular diseases affecting 17.5 million people worldwide and accounting for 31% of all global deaths in 2012 [3]. However, major barriers inhibit current research in human drug screening: experimental *in vivo* interventions have unacceptably high risks for humans enrolled in clinical trials, and non-human animal models fail to fully recapitulate human physiology. For example, the resting heart rate in mice is tenfold higher than in humans, while the mouse QT interval is one-fourth of a typical human [4]. Due to inter-species differences in ion channels, biological pathways, and pharmacokinetic properties, animal models do not faithfully predict human cardiotoxicity. Thus,

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human *in vitro* models of cardiac tissue that are predictive of human drug response would be a significant advancement for understanding, studying, and developing new drugs and strategies for treating cardiac diseases.

An ideal *in vitro* cardiac model should accurately recapitulate the physiological or pathological conditions of the human heart, including three-dimensional (3D) anisotropic tissue structure, orientation of the extracellular matrix (ECM) network, vascularization, and circulation (Fig. 1). Traditional 2D *in vitro* systems, although informative [5,6], cannot accurately mimic the complex 3D conditions due to their inability to recapitulate the dynamics of the biological and mechanical properties of the *in vivo* microenvironment [7]. The 3D models are characterized by establishment of adhesion complexes and tissue polarity, and by changes in cytoskeletal structure and cell volume that are significantly different from those found in cells cultured as monolayers. As a result, the translational results in 2D conditions are fundamentally different from those in 3D [8].

Human cardiovascular conditions *in vitro* can be achieved by developing engineered physiologically relevant 3D models, for instance by embedding cells in biomaterial matrices or microfabricated devices. For the purpose of *in vitro* modeling, biomaterials and microsystems not only serve as scaffolds for tissue formation, but also provide a highly-controllable microenvironment that incorporates key niche elements to enable precise regulation of cell fate and function [9–11]. Specifically, the complex tissue and organ architecture of the heart is maintained by extensive 3D ECM networks, including fibrous proteins (e.g. collagen, elastin), adhesive glycoproteins (e.g. laminin, fibronectin) and proteoglycans [12]. This ECM network, primarily in the form of perimysial collagen fibers, guides the anisotropic alignment of cardiomyocytes (CMs), mechanically confines the cells to connect each other, and contributes to stress-strain relationships for the heart [13]. Perimysial collagen fibers are comprised of bundles of twisted constituent fibrils (~40–50 nm in diameter), forming fibers that range from ~0.5–10 μm in diameter and ~100–200 μm in spacing, allowing several CMs to fit in-between [14]. Furthermore, the perimysial collagen fibers are arranged parallel with the long axis of cardiac muscle and therefore are one of the most significant components of the myocardium that contributes to its non-linear passive stiffness in the direction of the cardiac muscle fibers [15]. The perimysial fibers interact with the CMs via various mechanotransduction pathways, and ultimately affect normal cardiac function. For example, the fibrillar collagen networks register sarcomere Z-line across the CM membrane, and thereby ensure equal stretching of contiguous cells and maintenance of the mechanical continuity between CMs [16]. Given the key role of ECM in heart development and mechanical functions, development of an *in vitro* cardiac model requires biomaterials, methods, and systems to host the cells, control the cell-cell and cell-ECM interactions, and regulate the cell fate and functions.

In this review, we focus on the important role of biomaterials and microsystems used for *in vitro* cardiac models. First, we briefly discuss the cell source used for cardiac tissue models, and emphasize human induced pluripotent stem cells (hiPSCs) as the most promising cell type for generation of human CMs. Then, we highlight key properties of different *in vitro* models, along with their advantages and limitations for

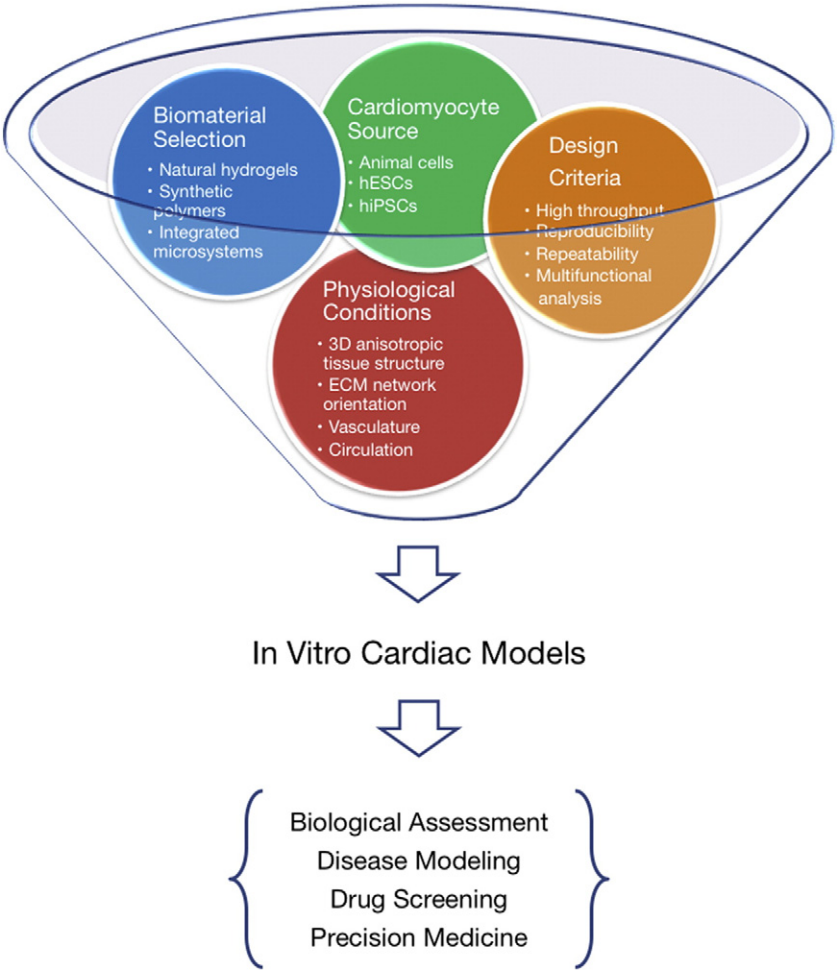

Fig. 1. Overview of *in vitro* cardiac tissue model. New *in vitro* biomaterial-based cardiac tissue models have the potential to be used for fundamental research and translational applications. In particular, the areas of drug discovery, disease modeling, and precision medicine could benefit immensely from these emerging technologies.