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SHORT COMMUNICATION

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Engineered 3D Cardiovascular Tissue Models Within Dynamic Microfluidic Platforms for Personalized Medicine Applications

Sylvia Natividad-Diaz[1,2,5*], Binata Joddar[1,3,5], Wilson Poon[1,4,5], Aibhlin Esparza[1,2], Edgar A. Borrego[1,2], Britanny L Stark[1,2]

[1]Department of Metallurgical, Materials, and Biomedical Engineering, The University of Texas at El Paso (UTEP), Texas, USA;[2]3D Microphysiological Systems Laboratory (3DMPSL), The University of Texas at El Paso (UTEP), Texas, USA;[3]Inspired Materials & Stem-Cell Based Tissue Engineering Laboratory (IMSTEL), The University of Texas at El Paso (UTEP), Texas, USA; [4]Delivery Systems and Nano-Therapeutics Innovaion (DESTINATION) Laboratory, The University of Texas at El Paso (UTEP), Texas, USA;[5]Border Biomedical Research Center (BBRC), The University of Texas at El Paso (UTEP), Texas, USA

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Description

CardioVascular Diseases (CVDs) are the leading cause of death worldwide, accounting for more than 20 million deaths in 2021 [1]. CVDs are difficult to study and treat with pharmacological interventions due to the need for personalized medicine regimens, limited availability of human myocardium samples, and the difficulty associated with culturing primary cardiomyocytes *in-vitro* for preclinical drug testing [1-3]. Current preclinical drug screening models include standard monolayer cell cultures (often referred as "2D" cell culture) and animal models. However, these two methods are significantly limited due to differences in biochemical signalling, gene expression and tissue/organ structure. Novel methods such as 3D cell culture suggest that more advanced and physiologically-relevant experiments can be performed to study organ behaviour *in-vitro*. Moreover, when combined with microfluidics; it is possible to replicate an *in-vivo* environment in organ-on-chip research [4]. Additionally, the use of human induced pluripotent stem cells (hiPSCs) provides a continuous source for a wide variety of somatic cells, including cardiomyocytes [2]. Combining hiPSCs, microfluidic technology and 3D cell culture can create a patient-specific biomimetic platform to study organs, such as the heart, while reducing the drawback of traditional methods. Here, we present some recently published studies that use these novel methods to create cardiac tissue on a chip, and discuss their relevance when used in drug screening and drug testing.

Microfluidics can be used to create organs-on-chip that mimic specific features of the cardiovascular system, leading to platforms that can study the pathogenesis of CVDs [5-7]. Many microfluidic systems are continuously being developed to simulate cardiovascular systems. The initial consideration when developing organs on a chip is the biomaterial to be used. There are two main categories to classify biomaterials: natural and synthetic [4]. Furthermore, bio printing has also been used to create heart-on-chip models. A recent study by Faulker-Jones et al. demonstrated that bio printing does not affect the physiological function of hiPSCs-derived cardiomyocytes. Additionally, the results also showed that the addition of calcium has a negative effect on hiPSCs that were encapsulated in alginate-based hydrogels [8].

Systems used to develop 3D human cardiovascular tissue models need more physiologically relevant microenvironments that provide dynamic fluid circulation and biophysical cues to guide cellular structural organization. For instance, a capillary circuit microfluidic device with microposts was used to develop a mechanically responsive 3D cardiovascular tissue model using Human Umbilical Vein Endothelial Cells (HUVECs) and human cardiomyocytes (AC16s) encapsulated into a fibrin hydrogel [9]. The tissues were cultured in microfluidic devices for 1, 3, and 5 days. These vascular and cardiac tissue models demonstrated statistically significant differences in cell alignment and orientation in devices with micro posts (micro pillars) compared to devices without micro posts and standard trans well inserts [9]. Future development of this system will include the incorporation of hiPSC-derived cardiovascular lineage cells that can represent patient-specific cardiac tissue structure and function for personalized pharmacology testing and applications. This system can also

Contact: Sylvia Natividad-Diaz, E-mail: slnatividad@utep.edu

be used for high-throughput drug discovery, quantification of drug pharmacokinetics, combinatorial drug regimens, and screening of drug carrier formulation design. Cardio toxicity is one of the most common adverse drug effects and there is a large clinical need to test new drug and drug formulations on cardiac models to ensure safety and compliance [10]. In addition to addressing the limited availability of cardiac models, another advantage of this system is its self-driven flow feature and low cost fabrication. This may potentially enable more cost effective, higher adoption of, and greater scale-up to test and screen more drug combinations in *in-vitro* drug pharmacokinetic studies, which increases the chance of a successful clinically translated end-product [11].

Current studies with similar models demonstrate this growing trend toward incorporation of hiPSC-derived cardiovascular tissues in microfluidic platforms for patient-specific preclinical drug screening applications. Recently, an *in-vitro* Ischemia Heart Disease (IHD) model was developed by using hiPSCs-derived Cardio-Myocytes (hiPSC-CMs) to assess the effects of hypoxic stress on cardiomyocytes functionality [12]. Using this model, the drug levosimendan was tested and found to have significant antiarrhythmic properties either during or after hypoxic stress. Additionally, levosimendan either completely removed or significantly reduced changes to structure and sarcomere alteration [12]. Another heart-on-chip platform was developed to study cardiac physiology and drug response *in-vitro* through a microfluidic device. This device is separated into two fluidically independent culture chambers that allows for 8 cardiac tissues, with fluid flowing directly to Endothelial Cells (ECs) without disturbing these cardiac tissues. These cardiac micro tissues were subjected to electrically stimulated pacing using 3D printed pyro lytic carbon electrodes. To test drug administration, isoprenaline was added to the cardiac tissues through a porous membrane, with ranging concentrations of 1 through 30 nM. The study found that isoprenaline increased the beating rate over the course of 14 days. Human induced pluripotent stem cell-derived Endothelial Cells (hiPSC-ECs) were then cultured with these cardiac tissues for 5 days. The micro channel in the device could also be used as a tool to increase shear rate exposure and mimic early stages of ECs in atherosclerosis [13].

Conclusion

3D cardiovascular tissue models combined with tailored microfluidic devices or platforms have the potential to significantly contribute to more effective drug discovery by reflecting human response to pharmaceutical drug therapeutics and help reduce the use of costly animal models. These models will also contribute to expanding the genetic diversity in preclinical drug testing studies so results are more representative of the general population in terms of gender, ethnicity, age, and disease state. Future directions for our system and this field include pacing studies to evaluate the influence of electrical stimulation on the 3D cardiovascular tissue beat rate, synchrony, and gene expression. Our system is also amenable to studying specific diseases: cardiomyopathy, atrial fibrillation, myocardial infarction, and atherosclerosis through the use of genetically modified human induced pluripotent stem cells. Due to the continuous fluid flow and integrated capillary-like networks, this system will also be conducive to study fundamental immune system interactions in normal or diseased myocardium by incorporating human lymphocytes or Bone Marrow Nuclear Cells (BMNCs) in the microcirculation. Preclinical drug screening studies can also be paired with computational approaches for the improvement of patient-specific mathematical models to predict drug-induced changes in human cardiac tissue and facilitate personalized medicine approaches.

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