Heart-on-a-chip: Innovative microreactor advances disease modeling and drug screening

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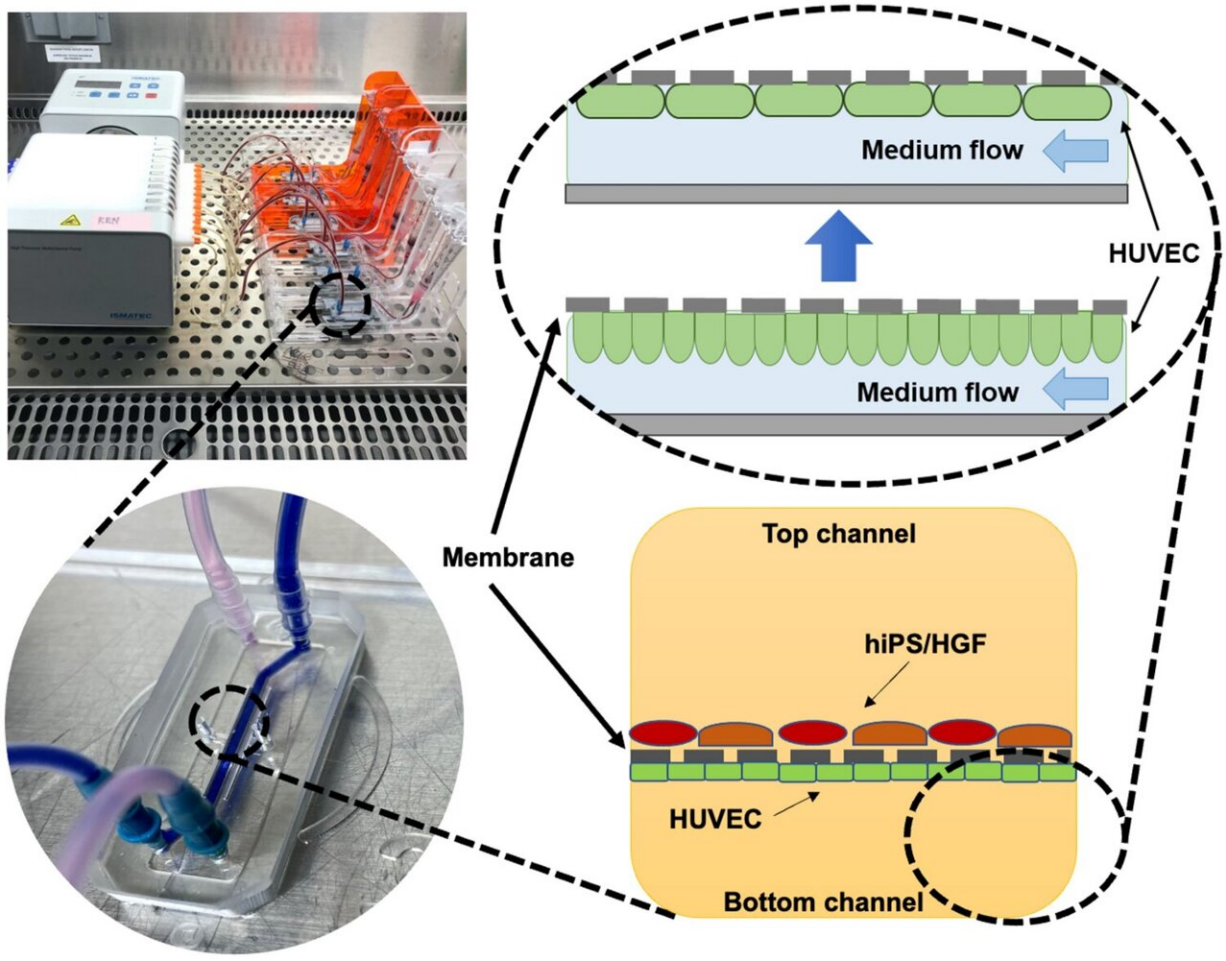

Perfusion system for the heart-on-a-chip. Endothelial cells are seeded in the bottom channel of the microfluidic chip, while induced pluripotent stem cells and fibroblasts are seeded in the top channel. The culture medium is delivered by

a peristaltic pump. Credit: *Scientific Reports* (2024). DOI: 10.1038/s41598-024-68275-0

To address the global burden of cardiovascular diseases, there's an urgent need for early-stage screening technologies and effective therapeutics. However, the medical research community faces significant challenges, including the high failure rate of candidate drugs in clinical trials and the ethical concerns surrounding the use of laboratory animals. Static cell culture models also fall short in replicating the complex tissue-level microenvironment.

Recent advancements in tissue engineering and microfluidics have paved the way for the development of heart-on-a-chip models. These models aim to simulate the roles of cardiomyocytes, fibroblasts, and endothelial cells—each crucial for normal cardiac function.

Cardiomyocytes manage heart contraction and electric signaling, fibroblasts maintain structural integrity, and endothelial cells regulate the vascular system.

Previous studies have reported bi-culture systems incorporating induced pluripotent stem cell (iPSC)-derived cardiomyocytes and fibroblasts, excluding endothelial cell functions.

To address this gap, Associate Professor Ken Takahashi, Professor Keiji Naruse, and Dr. Yun Liu, affiliated with the Graduate School of Medicine, Dentistry and Pharmaceutical Sciences at Okayama University, Japan, published a study in *Scientific Reports* on 8 August 2024.

"In this study, we have developed a 3D heart-on-a-chip model using

iPSCs, fibroblasts, and endothelial cells, designed to mimic the anatomical structure of cardiac tissue," says Dr. Takahashi.

The heart-on-a-chip model was designed to include two channels separated by a central membrane. The human umbilical vein endothelial cells (HUVECs) were seeded in the bottom channel and iPSCs, and human gingival fibroblasts (HGFs) were seeded in the top channel. The microfluidic channels mimicked intracellular blood flow.

The study successfully replicated endothelial cell morphology and functionality. In response to shear stress simulation, endothelial cells aligned themselves parallel to the flow of the medium by orienting F-actin appropriately, thereby mimicking in vivo conditions.

CD31, a cell-cell junction protein, plays a crucial role in regulating vascular permeability. Increased vascular permeability can lead to endothelial dysfunction and contribute to the progression of atherosclerosis. This study demonstrated that medium flow promoted endothelial cell integrity, confirmed by CD31 staining and lower vascular permeability.

Additionally, the presence of cardiac troponin t (cTnT) and IRX4 (cardiomyocyte markers) indicated high contractility.

"The percentage of cells co-expressing cTnT and IRX4 was notably elevated in the tri-culture group (56.3 ± 14.7%, n = 5) in contrast to the bi-culture group (30.2 ± 13.5%, n = 6) (P