Advanced 2D and 3D Cardiomyocyte-based Models for Use in Drug Discovery

Kit Man Tsang, PhD;1 Sofiya Kandellis, PhD;2 Avner Ehrlich, PhD;2 Carolina Lucchesi, PhD*1
1ATCC, Manassas, VA, USA
2Tissue Dynamics, Rehovot, Israel
*clucchesi@atcc.org

Introduction
Cardiovascular disease (CVD) is the leading cause of mortality worldwide, imposing considerable health and economic burden. The lack of relevant in vitro models hinders the development of cardiovascular drugs or the prediction of cardiotoxicity from new drug candidates. Although human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (CMs) provide a promising source of CMs, with the current technology, these in vitro differentiated hiPSC-CMs often fail to recapitulate the phenotype and physiologically relevant functionality. The maturation severely impacts the use of iPSC-CMs in vitro modeling for pathological, pharmacological, or therapeutic purposes since the electrophysiology, mechanical function, and metabolism are suboptimal. Various studies have demonstrated the use of electrical or mechanical stimulation, as well as artificial tissue scaffolds, to promote the maturation of hiPSC-CMs in vitro. However, these techniques often require months and have low throughput.

To address these issues, we have focused our work on harnessing the power of the ATCC Maturation Reagent (AMR™) to effectively propel the maturation of hiPSC-CMs in 2D monolayer culture. This method paves the way for the mass production of high-quality and mature hiPSC-CMs that exhibit a mature phenotype with regard to morphology, structure, gene expression, metabolism, calcium handling, and contractile performance.

In addition, we are integrating this enhanced cardiomyocyte function methodology with the 3D technology Robot-Directed Organoid Deposition (RODEO) to further advance the creation of more in vivo-like cardiac models. The combined power of these technologies holds the promise to revolutionize the creation of in vitro cardiac tissue that truly mimics the structural and biochemical properties of the cardiac environment. The resulting vasculature interwoven cardiomyocytes are highly similar to adult cardiac muscle transcriptionally and respond to drugs that mimic physiological conditions. This disruptive high-throughput technology underlines the utility of microphysiological systems for use in the drug discovery process and improving clinical success rates.

Methods

RODEO technology generated consistently sized organoids, facilitating the high-throughput unbiased screening of organoids in vivo format for drug screening.

Results

AMR™ effectively enhances the maturation of iPSC-derived cardiomyocytes in 2D monolayer culture.

RODEO, a 3D high-throughput technology, advances the creation of in-vivo-like in vitro cardiac models.

These vasculature interwoven cardiomyocytes underscore the utility of microphysiological systems for use in drug discovery.

Summary

AMR™ effectively enhances the maturation of iPSC-derived cardiomyocytes in 2D monolayer culture.

RODEO, a 3D high-throughput technology, advances the creation of in vivo–like in vitro cardiac models.

These vasculature interwoven cardiomyocytes underscore the utility of microphysiological systems for use in drug discovery.

Reference

Acknowledgement
Israel-U.S. Binational Industrial Research and Development Foundation (BIRD)