The application of human-induced pluripotent stem cell-derived ventricular cardiomyocytes generated in the chemical-defined and albumin-free condition (CaulisCells) in the MEA cardiac safety assessment

Junjie Pei[1], Shuyun Bai[2], Chuanxiu Yang[1], Yue Ma[2], Haiheng Dong[1]

1, Biology Unit, Research Service Division, WuXi AppTec (Shanghai) Co., Ltd., 288 Fute Zhong Road, Waigaoqiao China (Shanghai) Pilot Free Trade Zone, Shanghai 200131, China

2, National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, 15 Datun Road, Chaoyang District, Beijing 100101, China.

Human-induced pluripotent stem cell-derived ventricular cardiomyocytes (hiPSC-vCMs) have become a useful tool to analyze the proarrhythmic risk of drugs and been involved in the comprehensive *in vitro* proarrhythmia assay (CiPA) paradigm. We reported a method for the generation of hiPSC-vCMs in the chemical-defined and albumin-free environment last year. The hiPSC-vCMs generated with this method, CaulisCells®, have a high purity (over 90%), exhibit ventricular specific genes and proteins, and express key ion channels for cardiac safety evaluation (Pei et al, Stem Cell Research 19:94-103, 2017). In this work we further characterized the cells and evaluated the effects of 13 CiPA reference drugs on the electrophysiologic properties of the cells using the microelectrode array (MEA) platform (Maestro Pro, Axion BioSystems). RT-PCR studies on cells 7, 14 and 28 days after differentiation confirmed gene expression of all cardiac ion channels mentioned in CiPA. Although the action potential (AP) and ionic currents were recorded as early as 10 to 12 days after differentiation, AP duration and current density increased gradually, and reached a stable state at 25 to 30 days after differentiation. The hiPSC-vCMs 30 days after differentiation were used for the MEA study. These cells exhibited stable and reproducible spontaneous beating in the 48-well MEA plate. The beating period was 1720.1 ± 294.1 ms, and the Fridericia-corrected field potential duration (FPDc) was 297.5 ± 44.7 ms (n=74). The high-risk drugs quinidine, dofetilide and sotalol significantly prolonged the FPDc and caused arrhythmia-like events. Another high-risk drug bepridil prolonged the FPDc but did not evoke arrhythmia-like event. All four intermediate risk drugs, ondansetron, cisapride, terfenadine and chlorpromazine, caused moderate FPDc prolongation, and ondansetron and cisapride also evoked arrhythmia-like events. In the five low risk drugs (ranolazine, mexiletine, diltiazem, nifedipine and verapamil) we tested, only ranolazine showed minor increase in FPDc. None of them evoked arrhythmia-like event. The results matched well with data released by CiPA, suggesting the hiPSC-vCMs generated in the chemical-defined and albumin-free environment is also a good tool for the cardiac safety assessment.