Combining electrophysiology and contractility recordings for more complete assessment of hiPSC-CMs

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Introduction

Human induced pluripotent stem cells (hiPSCs) are becoming increasingly important for cardiac safety testing due to their recapitulation of native behaviour, relative abundance and ease of use. We combine automated patch clamp (APC), impedance and extracellular field potential (EFP) measurements to study hiPSC-derived cardiomyocytes (hiPSC-CMs) from different sources. In line with the comprehensive in vitro proarrhythmia assay (CIPA) initiative, cardiac ion channels expressed in heterologous expression systems have been recorded on APC devices at room temperature and at physiological temperature and the effect of different pro-arrhythmic compounds on ion channels was investigated. In addition hiPSC-CMs were used on APC platforms recording from 8 or 384 wells simultaneously. Voltage-gated Na+(NaV), Ca2+(CaV) and K+(Kv) currents were recorded in voltage-clamp and action potentials recorded in current clamp mode. Using the dynamic clamp technique coupled with an APC device, electrically modelled IKr was injected into the cell under current clamp conditions and this resulted in a more hyperpolarized and stable resting membrane potential.

Within the myocyte phase II study of the CIPA initiative, a device combining impedance-based contractility and extracellular field potential (EFP) recordings was used to investigate the effects of different compounds deemed low, intermediate and high risk by the FDA. Different hiPSC-CMs were used in a large cross-site evaluation and the results are summarised here.

Effect of vandetanib on hERG and NaV 1.5:

Comparison with hiPSC-CMs

Vandetanib blocks hERG and NaV 1.5 expressed in HEK cells in electrophysiology (Patchliner) experiments (left) and causes arrhythmia in hiPSC-CMs in impedance and EFP recordings (CardioExcyte 96, right). The red arrows indicate arrhythmic events.

Effect of sotalol on hERG:

Comparison with hiPSC-CMs

Sotalol blocks hERG expressed in HEK cells with an IC50 of 80.2 µM measured at 35°C on the SyncroPatch 384PE (left). Using impedance and EFP measurements of hiPSC-CMs on the CardioExcyte 96 (right), arrhythmic events (red arrows) are detected at low concentrations (10 µM).

Conclusion

- Cardiac ion channels expressed in cell lines have been measured on the Patchliner and SyncroPatch 384PE as part of the CIPA Ion Channel Work Stream.
- hiPSC-CMs have been used on the Patchliner and SyncroPatch 384PE, voltage-gated ion channels have been recorded and pharmacology performed. Action potentials were recorded in current clamp mode and dynamic clamp combined with the Patchliner.
- hiPSC-derived cardiomyocytes were used on the CardioExcyte 96 as a complementary tool for safety screening. The effect compounds on ion channels is often complex and the overall effect in cardiomyocytes on beating parameters is an important and complementary assay to patch clamp in heterologous expression systems.

References

Goverian, B., et al., 2018. Front. Physiol. 9, 1094