Differentiation and Validation of Human iPSC-Derived Atrial Cardiomyocytes

Kathy Sutton[1], Said El Haou[1], Sarah William[1], Harsha Devalla[2], Sonja Stölzle-Feix[3], Krisztina Juhasz[3], Leo Doerr[3], Matthias Beckler[3], Claudia Haarmann[3], Michael George[3], Robert Passier[2,4], Niels Fertig[3], Marc Rogers[1].

[1]Metrion Biosciences, Granta Park, Cambridge. CB21 6AD, UK
[2]Dept.of Anatomy & Embryology, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands
[3]Nanion Technologies, Ganghoferstr. 70a, 80339 Munich, Germany
[4]Department of Applied Stem Cell Technologies, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, 7500 AE, The Netherlands.

There is a growing trend for utilization of native human cells in drug discovery to overcome common translational disconnects between *in vitro* screening data, preclinical animal models, and clinical trials in man. Translational assays using cardiomyocytes derived from human induced pluripotent stem cells (hiPSC) are increasingly appreciated as an accessible cell source for cardiac disease modeling, drug screening and safety pharmacology.
Previously, we have shown that human embryonic stem cell derived atrial cardiomyocytes (ACMs) can be used for assessing atrial-selective pharmacology. Here, we show improved, robust monolayer-based production of functional hiPSC-ACMs for atrial drug screening.
Functional validation was performed using manual patch clamp techniques to make current clamp measurements of action potential (AP) parameters at room temperature. In control conditions, hiPSC-ACMs fired spontaneously at 0.5 Hz and exhibited a hyperpolarised MDP (-70.6 ± 0.8 mV), fast upstroke velocity (35.4 ± 3.4 V/s), and action potential durations (APD) at 20, 50 and 90 % of repolarisation of 174, 256, and 573 ms, respectively. Cardiac pharmacology was assessed using a core panel of ion channel modulators in addition to atrial-specific reference compounds. Activation of the atrial-selective I_{KACh} current (Acetylcholine-activated potassium current) by Carbachol (1 µM) hyperpolarized the resting potential and slowed spontaneous AP firing. Selective inhibition of I_{Kur} current ($K_V1.5$) by 4-Aminopyridine (50 µM) prolonged the early phase of spontaneous AP repolarization, as expected for atrial cardiomyocytes.
Chip-based automated patch clamp (APC) approaches allow parallel patch clamp recordings from multiple cells without compromising data quality or technical sophistication. To complement the manual patch findings, high-throughput voltage and current clamp recordings were made on APC platforms (Nanion Patchliner and Syncropatch 384 PE) to obtain biophysical parameters and test specific reference compounds, such as cardiac I_{Na} channel blockers. In addition to patch-clamp experiments, hybrid impedance (cell contractility) with multi-electrode array-like extracellular field potential recordings were also completed.
Taken together, these data confirmed that hiPSC-ACMs derived using a monolayer differentiation protocol express an atrial-like phenotype and are amenable for screening on both electrophysiological and phenotypic platforms. Therefore, hiPSC-ACMs are a promising assay reagent for studying the role of ion channels implicated in atrial fibrillation.