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Human ventricular stem cell cardiomyocytes: *in vitro* assays and screening platforms for pro-arrhythmia risk prediction

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Existing cardiac safety testing regimes have successfully prevented new drugs coming to market with pro-arrhythmic risk, but they are expensive (e.g. TQT clinical studies ICH E14) and the reliance on preclinical hERG screening (ICH S7B) is undermined by the exclusion of new chemical scaffolds from further drug development while older drugs that inhibit hERG are not associated with arrhythmia. This prompted the FDA to implement the Comprehensive *in vitro* Pro Arrhythmia initiative (CiPA) which involves 3 parts: 1) High quality *in vitro* cardiac ion channel assays, 2) Comprehensive *in silico* action potential (AP) models and 3) Predictive phenotypic assays using human stem cell-derived iPS cardiomyocytes.

We present recent work on ventricular stem cell iPS cardiomyocytes funded by the Eurostars-2 and EU Horizon 2020 research and innovation programme. iPS cardiomyocytes were generated using maturation protocols employed at Leiden University Medical Center and their molecular and biophysical properties compared with leading commercial ventricular stem cell iPS lines. Spontaneous and evoked cardiac APs and ionic currents were monitored using current- and voltage-clamp manual patch electrophysiology, respectively. AP waveform and AP duration pharmacology was assessed using selective ion channel antagonists and voltage protocols to reveal the ratio of Nav, Cav and Kv currents, while phenotypic measurements of impedance and field potentials were made using the CardioExcyte96 platform (Nanion). A variety of compounds selectively targeting ventricular and atrial ion channels were also utilised to explore the relative mix of functional cardiac phenotypes and establish the functional maturity of the various cell lines tested.