

Cardiac Safety Screening

Comprehensive *in Vitro* Proarrhythmia Assay (CiPA) Initiative

The current cardiac safety regulatory guidelines have successfully prevented any new drugs coming to market with an unknown proarrhythmic risk. However, the current paradigm, which includes a thorough QT interval clinical study, is extremely expensive and time-consuming. Accordingly, the FDA and other industry stakeholders are working to create a new regulatory framework called the **Comprehensive *In Vitro* Proarrhythmia Assay (CiPA)** initiative, which is composed of three components:

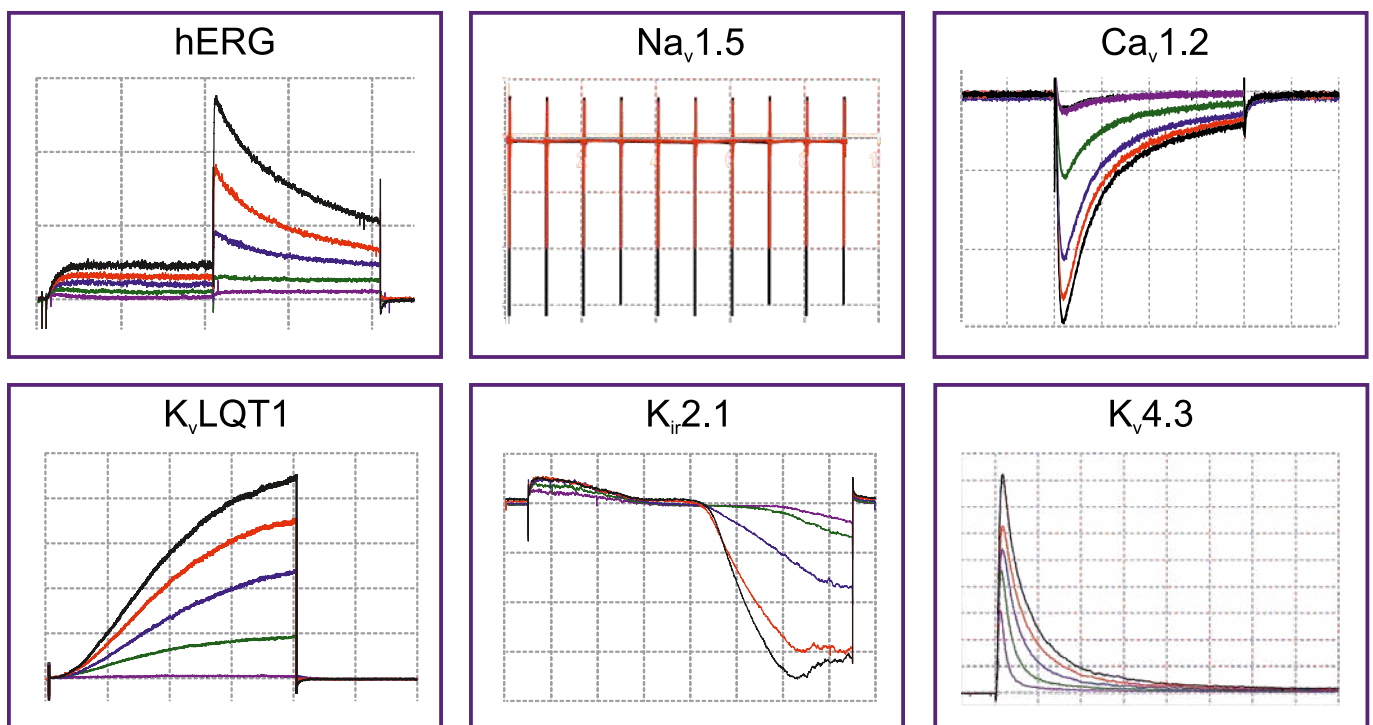
- Screening against a comprehensive panel of cardiac ion channels
- Incorporation of screening data from the CiPA ion channel panel into an *in silico* model of a human ventricular action potential
- Confirmation of the *in silico* predictions using translational assays employing human induced pluripotent stem cell (iPSC) derived cardiomyocytes

Metrion offers a fully integrated cardiac safety screening service that is composed of all the different components of CiPA.

CiPA Ion Channel Panel

Metrion has validated a premium panel of CiPA-compliant human cardiac ion channel assays on the QPatch. High fidelity gigaseal automated patch clamp platforms generate high quality *in vitro* data that can be incorporated into *in silico* models of the human ventricular action potential.

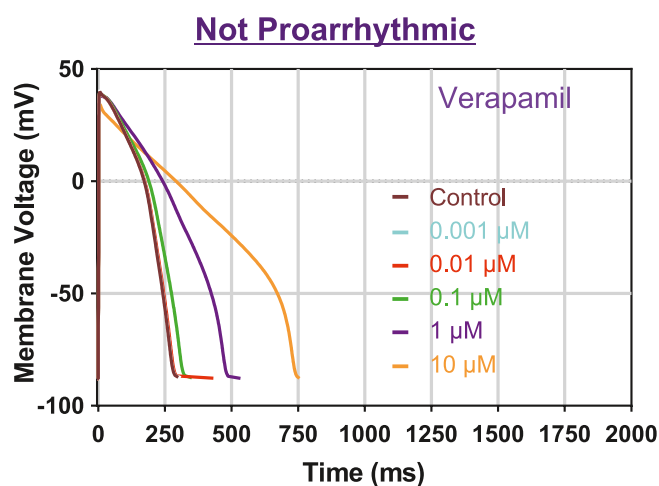
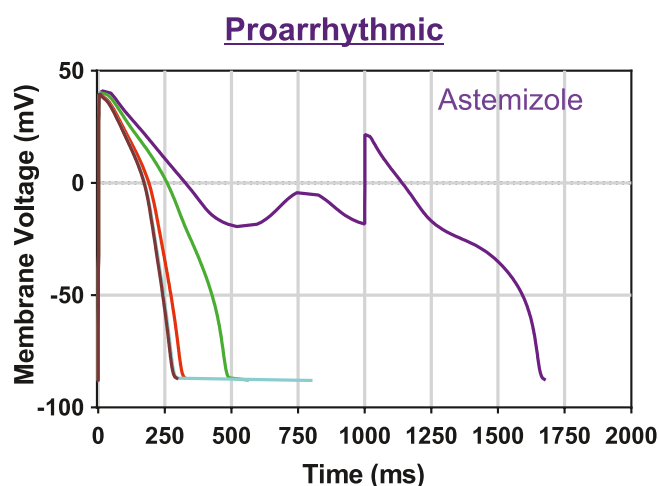
Gigaseal quality recordings of CiPA cardiac ion channels on QPatch-48



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In Silico Modelling

The second component of CiPA involves incorporating data collected from *in vitro* screening against the CiPA ion channel panel into an *in silico* model of a human ventricular action potential. The *in silico* model predicts whether a compound increases the action potential duration, which is a surrogate marker of QT interval prolongation. In addition, the model can predict early after depolarisations (EADs), which are indicative of proarrhythmic liability.



Translational Assays

Metrion has characterised several commercially available iPSC-derived cardiomyocyte cell lines and validated screening assays using the manual patch clamp technique to investigate compound effects on action potentials and membrane currents. Additionally, Metrion has established plate-based assays on the CardioExcyte96 to record cell beating and electrical activity using impedance and MEA measurements respectively.

