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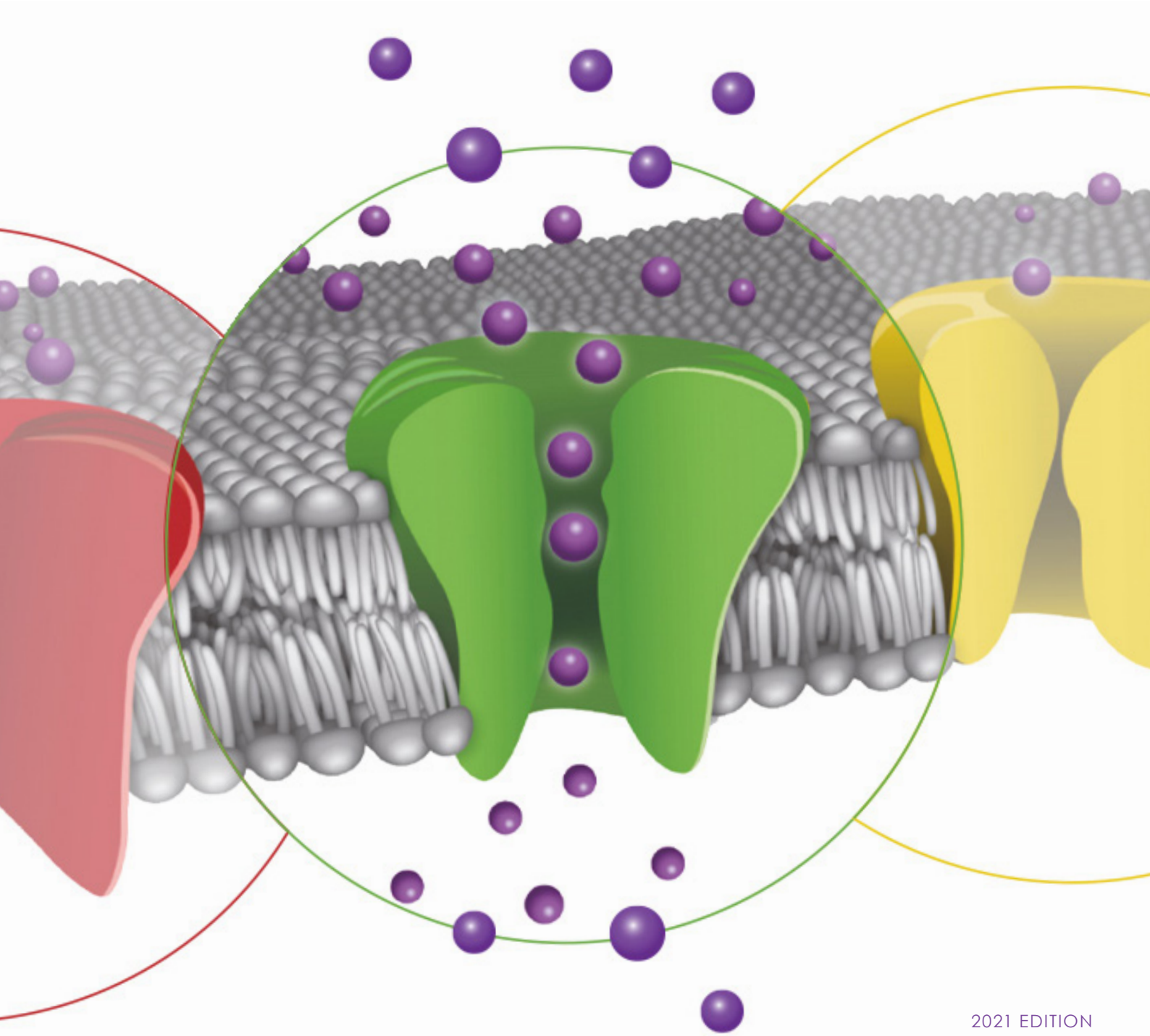
METRION BIOSCIENCES

Cardiac Safety Screening Brochure



2021 EDITION

Welcome.

Welcome to Metrion Biosciences, leaders in ion channel drug discovery.

Metrion Biosciences is a preclinical ion channel contract research organisation formed in September 2015.

The Metrion team has substantial experience of providing high quality drug discovery services for ion channel targets to clients on a fee-for-service or collaboration basis.

Metrion is a leading provider of safety pharmacology services including cardiac safety profiling and neurotoxicology testing, as well as offering cardiac and neuronal translational assays using native cells and iPSC models. Our state of the art laboratory facility is located at Granta Park, the largest research park in Cambridge (UK), and the Metrion team takes pride in providing a knowledgeable, collaborative and flexible service to our clients.

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Our Services

Ion channel screening.
Metrion has developed validated screening assays against an extensive panel of ion channel cell lines using a variety of high quality ion channel screening platforms.

Cardiac ion channel screening.
Metrion offers screening services against a premium panel of validated Comprehensive In Vitro Proarrhythmia Assay (CiPA) compliant human cardiac ion channel screening assays.

Neuroscience ion channel screening.
Metrion offers a range of neuroscience related ion channel screening assays and platforms, including native tissue and species selectivity testing.

Translational Assays.
Metrion are developing phenotypic assays to aid the translation of in vitro cardiac safety and neuroscience data to the pre-clinical stage.

Integrated drug discovery.
Our highly experienced interdisciplinary team provides clients with a fully integrated drug discovery service by bringing together experts in ion channel biology, medicinal chemistry, specialist chemistry, translational biology, ADMET & DMPK.

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What we do

Metrion staff offer proven ion channel electrophysiology expertise and reliable assays for our clients. Our services include:

- High quality, cost-effective compound screening assays
- Detailed characterisation of lead compounds in human cells and native tissue
- Confirmation of efficacy in stem cell and other phenotypic models
- Rapid reporting and data interpretation by our experienced ion channel team
- A dedicated, flexible service tailored to your requirements

Who we work with

From our Granta Park base in Cambridge, UK, we work with scientists and researchers from biotech and pharmaceutical companies, research institutions, disease charities and start-up companies worldwide to enable them to study this fascinating class of membrane proteins with confidence and insight.

We currently work with clients located in over 20 countries across five continents, many of whom are looking to validate, develop or de-risk ion channel modulators as they progress towards a nomination for clinical development.

Why choose Metrion?

- **Highly experienced and diligent team with over 100 years combined knowledge of automated patch clamp (APC) and experience within academia, the pharmaceutical industry, contract research organisations and biotech companies.**
- **High quality data, with knowledgeable interpretation, within the defined timeframe.**
- **Fee for service and collaboration project options available.**
- **Client testimonials available.**
- **Flexible support for assay development, primary target screening, hit confirmation, lead optimisation and SAR, mechanistic and phenotypic studies.**

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Cardiac Safety Screening.

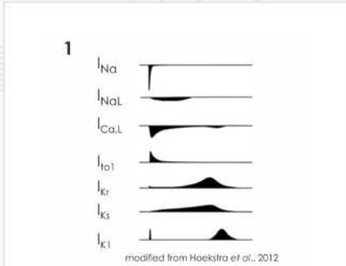
Metrion offers a range of high quality Cardiac Safety Screening assays, including hERG profiling and components of the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) initiative. This include assays that evaluate the proarrhythmic liabilities of compounds using:

- **A extensively validated panel of cardiac ion channels, including the six CiPA ion channels, using gigaohm seal quality automated electrophysiology devices.**
- **Action potentials recorded from human iPSC-derived cardiomyocytes using multi-electrode array and manual patch clamp platforms.**
- **The viability of human iPSC-derived cardiomyocytes using an impedance platform.**

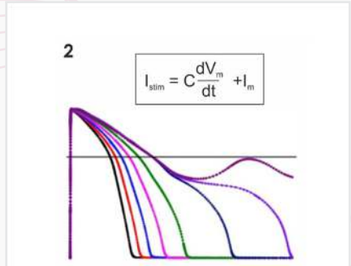
What is CiPA?

The International Council on Harmonization (ICH) S7B and E14 regulatory guidelines were introduced in 2005 to evaluate the proarrhythmic liability of new drugs. It was discovered that inhibition of a cardiac potassium channel (encoded by hERG) is associated with prolongation of the QT interval and a potentially deadly arrhythmia, Torsades de Pointes.

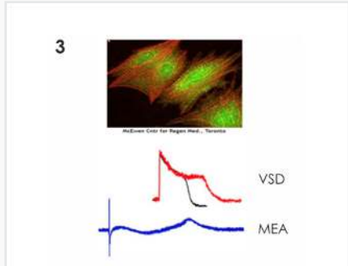
The guidelines utilise hERG inhibition and QT interval prolongation as surrogate markers of proarrhythmic liability, which are highly sensitive and effective at preventing proarrhythmic drugs from reaching the market. However, these markers have low specificity, with only a modest correlation between hERG inhibition, QT prolongation and proarrhythmic liability.



Compounds evaluated against panel of 6 cardiac ion channels



Use *in silico* modelling to evaluate proarrhythmic risk



Confirm predictions in human iPSC-derived cardiomyocytes

Therefore, to address these limitations, the **Comprehensive *In Vitro* Proarrhythmia Assay (CiPA)** initiative was launched by the FDA in July 2013 and aims to improve the accuracy and reduce the cost of predicting cardiac liability using three 'pillars' (**above**):

1. Compounds will be profiled against a panel of human ventricular ion channels
2. This *in vitro* data will be incorporated into an *in silico* model of a human action potential to provide a proarrhythmic risk classification
3. Compounds will be tested using human induced pluripotent stem cell-derived cardiomyocytes to confirm the risk classification derived from the *in silico* model

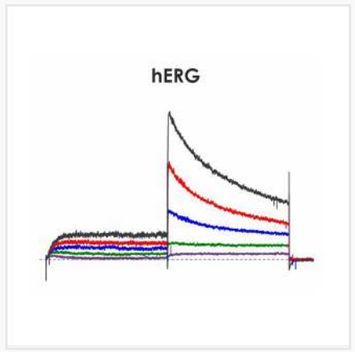
Step 1: Comprehensive ion channel panel

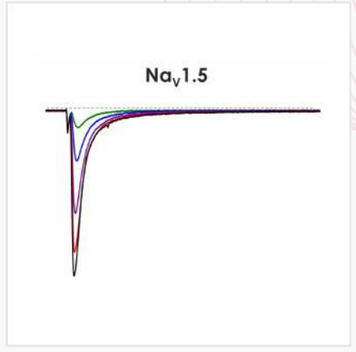
Metrion is an active participant in the CiPA ion channel HTS sub-team and on the Health and Environmental Sciences Institute (HESI) cardiac committee. We work closely with HESI to help reduce data variability between screening sites and provide validation data.

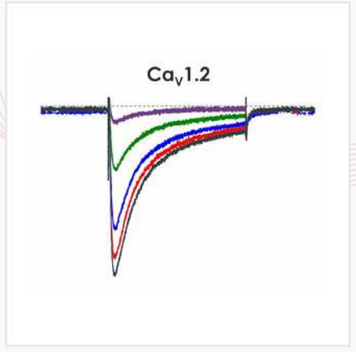
Metrion has validated assays for the full CiPA panel (below, right) (hERG, peak and late $Na_v1.5$, $Ca_v1.2$, KCNQ1/KCNE1, $K_{ir}2.1$ and $K_V4.3$). Metrion also offers screening services against HCN4 and $K_v1.5$, plus supplementary assays including dynamic hERG and a LQT3 late $Na_v1.5$.

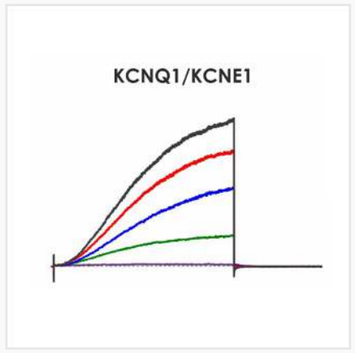
Metrion provides potency assessment against each of these channels using single-point or four-point concentration-response assays on the QPatch48.

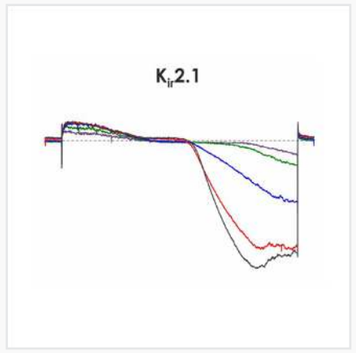
Compounds can also be screened using manual patch clamp methodology.

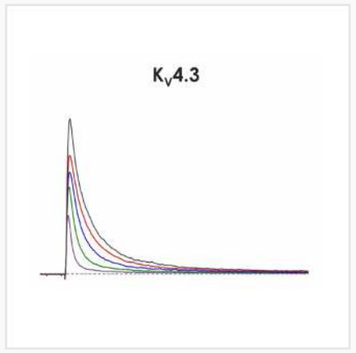












Step 2: *In Silico* Model

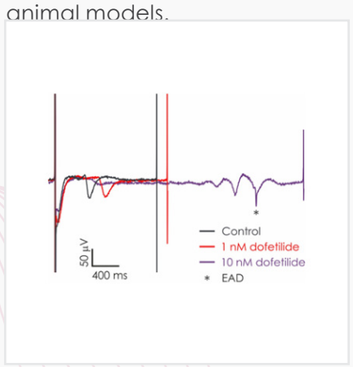
The high quality IC_{50} values derived from these high fidelity platforms are suitable for use in *in silico* action potential models, which is the second 'pillar' of the CiPA initiative.

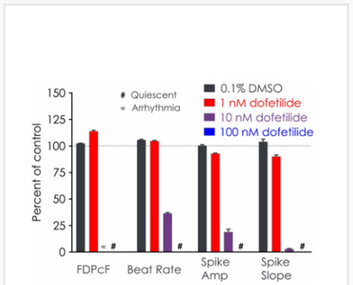
Step 3: Proarrhythmic assessment using human iPSC-derived cardiomyocyte assays

Metrion has developed a range of high quality assays that evaluate the effect of compounds on the electrophysiological properties of **human iPSC-derived cardiomyocytes.**

This includes a **multi-electrode array (MEA) assay** that non-invasively detects action potentials as fluctuations in the extracellular field potential. Metrion has validated its MEA assay using different commercially available iPSC-derived cardiomyocytes and the **CiPA toolbox**, which is composed of 28 compounds that are separated into high, medium and low categories of proarrhythmic risk.

Metrion's standard assay assesses the effect of compounds over a thirty minute application period. Data generated using this assay format yielded sensitivity and specificity values of 83.3% and 88.9% respectively, which exceeds those obtained from commonly used animal models.





Above: The effect of three concentrations of dofetilide on a range of electrophysiological parameters. Data could not be collected for the two highest concentrations, as early after depolarisations (EADs) were observed after five minutes of applications, which later degenerated into fibrillation at the top screening concentration.

Custom MEA assay service

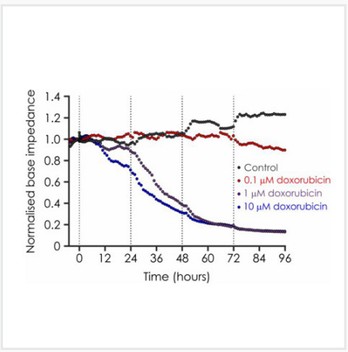
Metrion can provide **custom MEA assays** to evaluate the proarrhythmic liability of compounds. For example, due to the non-invasive nature of the MEA system, the application duration of compounds can be extended to hours or days. This allows for the detection of compounds affecting ion channel function or expression over hours, rather than minutes.

iPSC derived cardiomyocyte screening

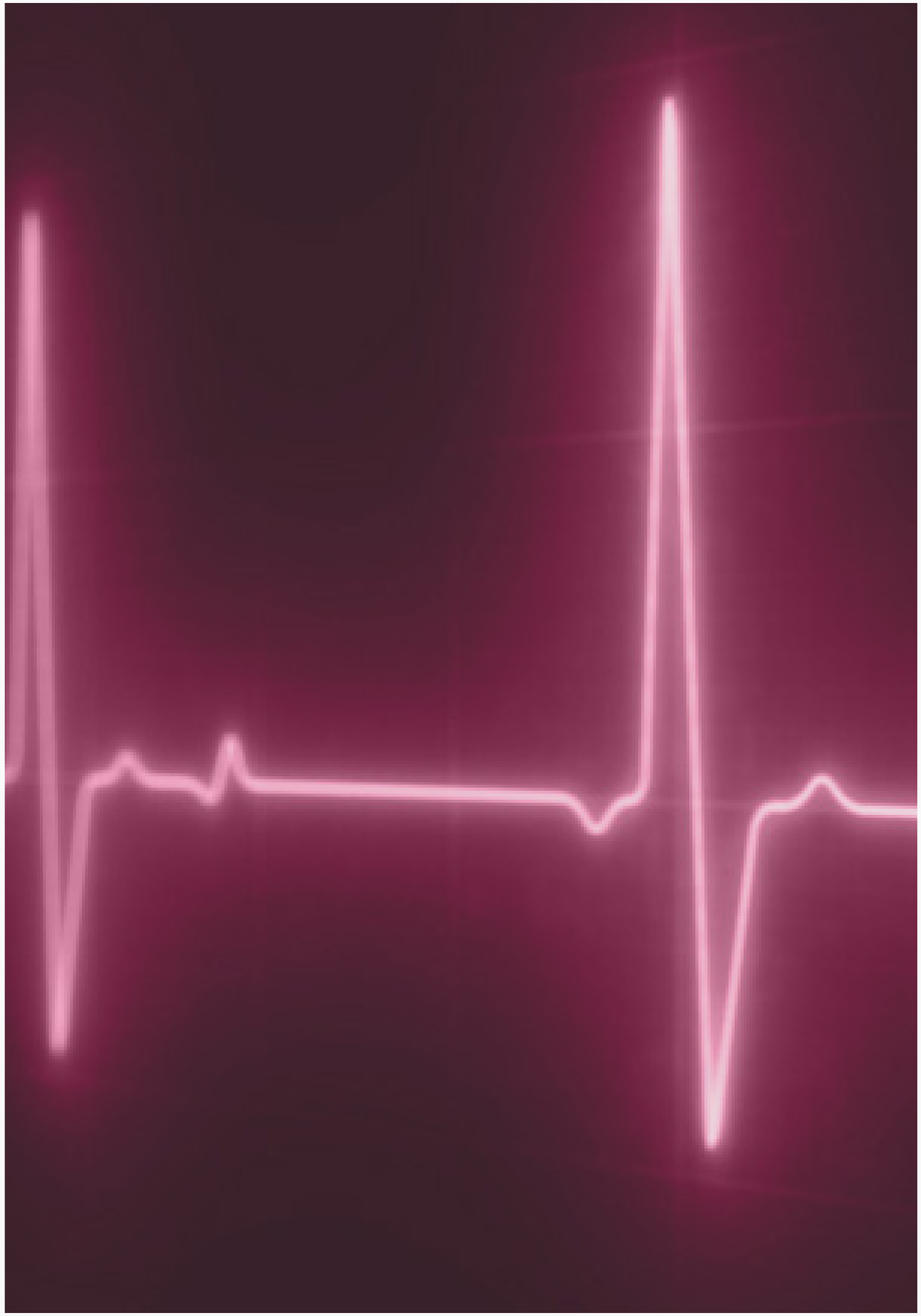
Metrion can evaluate the effect of compounds on action potentials recorded from **iPSC-derived cardiomyocytes** using conventional manual patch clamp methodology. Spontaneous or evoked action potentials can be recorded and used to determine the effect of compounds on a range of action potential parameters. The manual patch clamp assay generates high fidelity recordings that allow the detection of even subtle changes to the action potential waveform. This helps to successfully discern between compounds with low, medium and high proarrhythmic risk profiles.

Chronic cardiotoxicity assessment using human iPSC-derived cardiomyocytes

Base impedance (an indicator of cell viability) can be used to non-invasively identify structural and functional cardiotoxicity over a chronic time course. Metrion has developed a validated **chronic cardiotoxicity assay** using human iPSC-derived cardiomyocytes. The adjacent example features doxorubicin, a member of the anthracycline family used to treat cancer. It is associated with a number of cardiac side effects, including acute atrial and ventricular arrhythmias and congestive heart failure.



Above: Metrion's chronic cardiotoxicity assay recapitulates doxorubicin's cardiotoxic effect by producing a concentration-dependent decrease of base impedance that develops following a 24 hour exposure period.



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About us

Launched in 2015

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