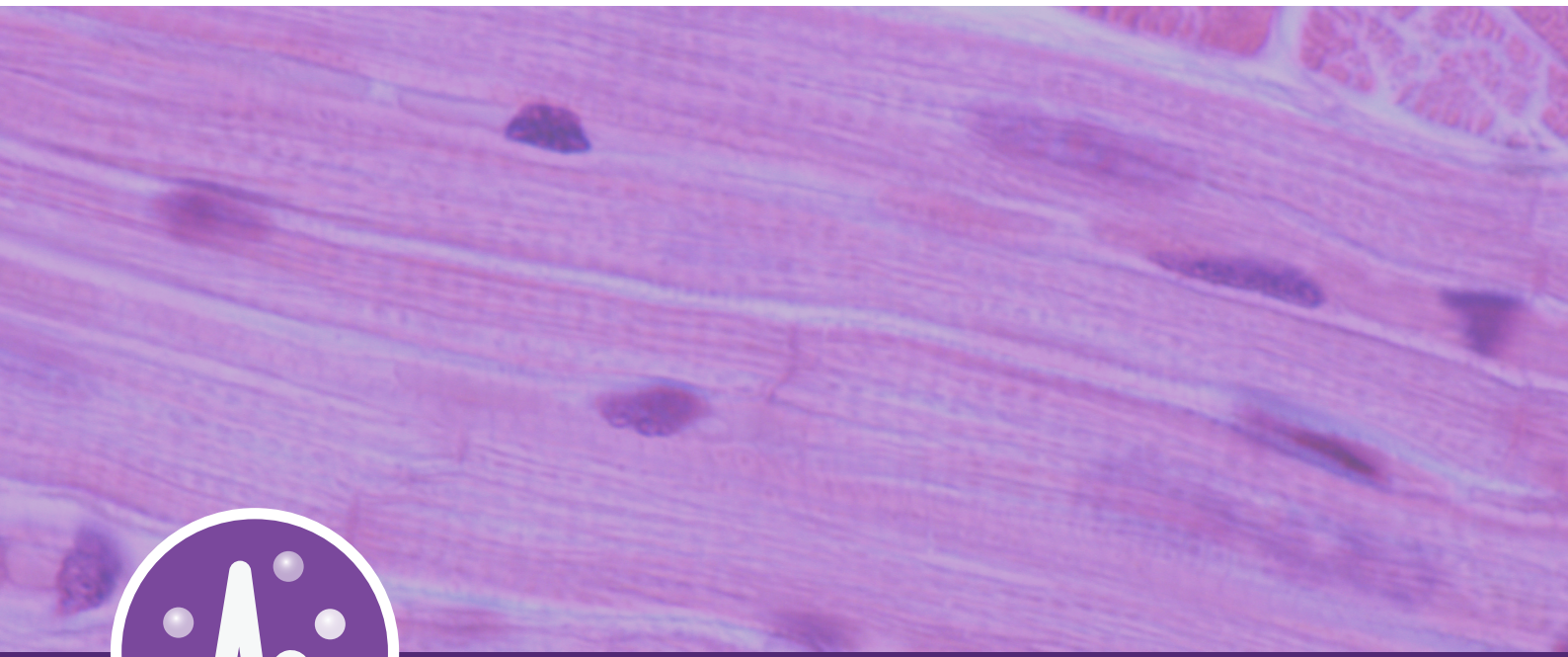
metrion biosciences

Cardiac Safety Screening Services

Reliably evaluate the proarrhythmic and cardiotoxic liabilities of your compounds



Reliably evaluate the proarrhythmic and cardiotoxic liabilities of your compounds

Our specialist team have been developing cardiac safety assays for over twenty years. The cardiac safety screening assays we offer include:

Non-GLP hERG screening to eliminate cardiac risk liability

Due to its link to life threatening drug-induced arrhythmias, such as *Torsades de Pointes*, the hERG potassium channel represents a significant off-target liability. This risk liability is exacerbated by reports that up to 30% of compounds inhibit the hERG channel. Therefore, assessing novel compounds against hERG early in the drug discovery process is essential for eliminating drug-induced proarrhythmic liability.

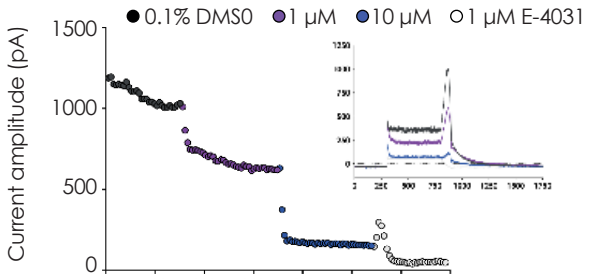


Figure 1. Peak hERG tail current (recorded at 37 °C) plotted against time for a representative cell treated with 1 and 10 µM ondansetron followed by 1 µM E-4031. Inset: representative current traces in 0.1% DMSO, ondansetron and E-4031.

Comprehensive *in vitro* proarrhythmia assay

Metrion has been an active participant in the CiPA ion channel working group and a member of the Health and Environmental Sciences Institute (HESI) cardiac committee.

Table 1. Assays for a wide range of different human cardiac ion channels.

Ion Channel Panel	Target	Platform		
		Manual Patch	QPatch 48	Qube
CiPA	hERG	✓	✓	✓
	$hNa_V1.5$	✓	✓	✓
	$hCa_V1.2$	✓	✓	✓
	$hK_{ir}2.1$	✓	✓	-
	$hK_V4.3\_KChIP$	✓	✓	-
CiPA+	Dynamic hERG	✓	✓	-
	Late $Na_V1.5$	✓	✓	-
Other	hHCN4	✓	✓	-
	$hK_V1.5$	✓	✓	✓

hiPSC-derived cardiomyocyte model for early cardiac derisking

Our clinically translatable cardiomyocyte model utilises the VOLTA and provides early decision-making data on the potential cardiac risks of novel early-stage discovery compounds, thereby, significantly reducing the reliance on costly animal studies.

This high-throughput model:

- Provides comprehensive safety pharmacology and toxicology data from acute and chronic (24 h or greater) exposure of compounds
- Is a cost effective 96-well plate-based assay, that accurately assesses changes in action potential morphology
- Aligns with current ICH S7B guidelines and adheres to the principles of the FDA Modernization Act 2.0

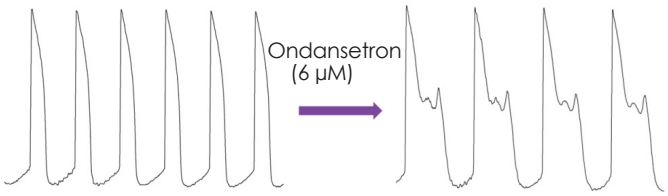


Figure 2. Assessing the effect of compounds on the ventricular action potential waveform in a high-throughput hiPSC-derived cardiomyocyte model.

Evaluate the effect of compounds on action potentials recorded from hiPSC-derived cardiomyocytes using manual patch screening

Successfully detect differences between compounds with low, medium and high proarrhythmic risk profiles, by evaluating the effect of compounds on action potentials recorded from hiPSC-derived cardiomyocytes using conventional manual patch-clamp methodology.

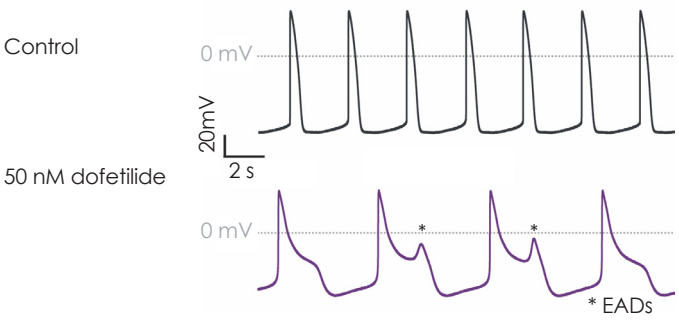


Figure 3. Action potentials recorded from iPSC-derived cardiomyocytes showing the effect of 50 nM dofetilide on the action potential profile.

Chronic cardiotoxicity assay: hiPSC-derived cardiomyocytes to measure the cardiotoxic potential of test compounds

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 chronic cardiotoxicity assay using hiPSC-derived cardiomyocytes, which has been validated with several cardiotoxicants.

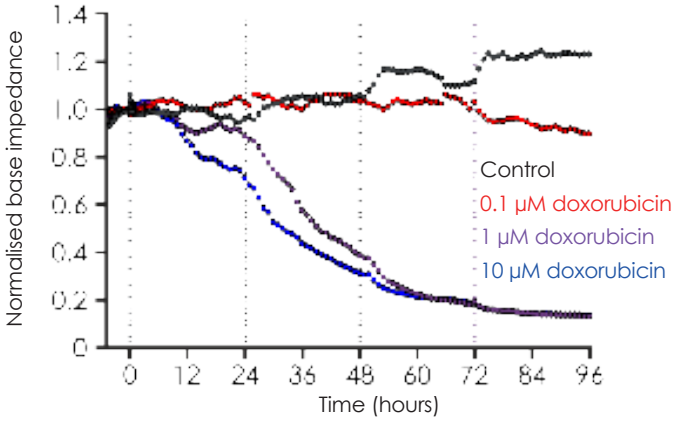


Figure 4. Representative traces showing the effect of doxorubicin on the base impedance signal recorded using hiPSC-derived cardiomyocytes.

High-quality, cost effective and rapid turnaround GLP testing against hERG

We provide specialist GLP hERG testing services using the conventional whole-cell patch-clamp technique.

For most IND filings, GLP compliant hERG testing is included under the ICH S7B guidelines. Metrion is a member of the UK GLP Compliance Monitoring Programme and provides screening services against hERG in accordance with the best practice guidelines provided by the Food and Drug Administration (FDA).

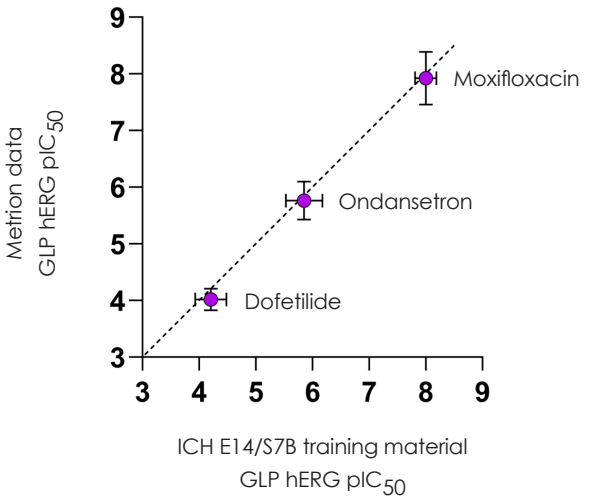


Figure 5. Graph showing the excellent correlation between Metrion's GLP hERG pIC_{50} data and the published ICH E14/S7B training material data.

Supporting an integrated QTc risk assessment using the hERG margin distributions for three positive control agents derived from multiple laboratories and on multiple occasions

Derek J. Leishman, Jessica Brimecombe, William Crumb, Simon Hebeisen, Steve Jenkinson, Peter J. Kilfoil, Hiroshi Matsukawa, Karim Melliti, Yusheng Qu.
Journal of Pharmacological and Toxicological Methods. (2024), **128**, 107524.

GLP hERG data for three reference compounds, generated using ICH best practices, revealed high concordance in intra- and inter-laboratory variability for hERG IC_{50} values. This consistency supports a robust hERG safety margin reference.

The data endorse using a 30-fold safety margin in integrated risk assessments, though a 100-fold margin is advised when no further evaluation is conducted. These findings provide strong evidence for reliable hERG safety margins when aligned with best practices.

Specialist Preclinical Drug Discovery CRO

Metrion Biosciences is a sector-leading CRO specialising in preclinical ion channel drug discovery, cardiac safety and neuroscience research services.

We deliver comprehensive drug discovery outsourcing solutions to pharmaceutical and bioscience customers worldwide; all from our state-of-the art research hub.

Priding ourselves on delivering high quality data, our team use their extensive experience to:

- Complete laboratory studies on time and on budget.
- Carefully interpret the experimental findings.
- Communicate the results.
- Provide strategic recommendations.
- Support your decision making to best inform your screening strategy.

1,000+ projects completed across almost 20 countries and 5 continents

Over 51% staff trained to PhD level and over 75% of team trained to Master's degree level and above

250 years combined experience managing ion channel research programmes

130 different customers worked with in the last 4 years

Testimonials describing how customers value working with Metrion

"We recognize this type of study is very difficult and the cells we provided posed technical challenges. We also appreciate the timeliness of the study execution and the detailed report you provided."

Top 10 pharma
Global

"Attention to detail with executing the study and the quality of reports is the best we have ever seen. By far the most accurate and well interpreted data. Explanations clear for a non-expert to understand."

Biotech
USA

"We appreciate the thoroughness, clearness of explanation and results, and the work done above and beyond to troubleshoot."

Biopharma
USA

"Really good data showing exactly what we would expect for this inhibitor; we know how difficult these recordings are to perform."

Large pharma
UK

info@metrionbiosciences.com

www.metrionbiosciences.com