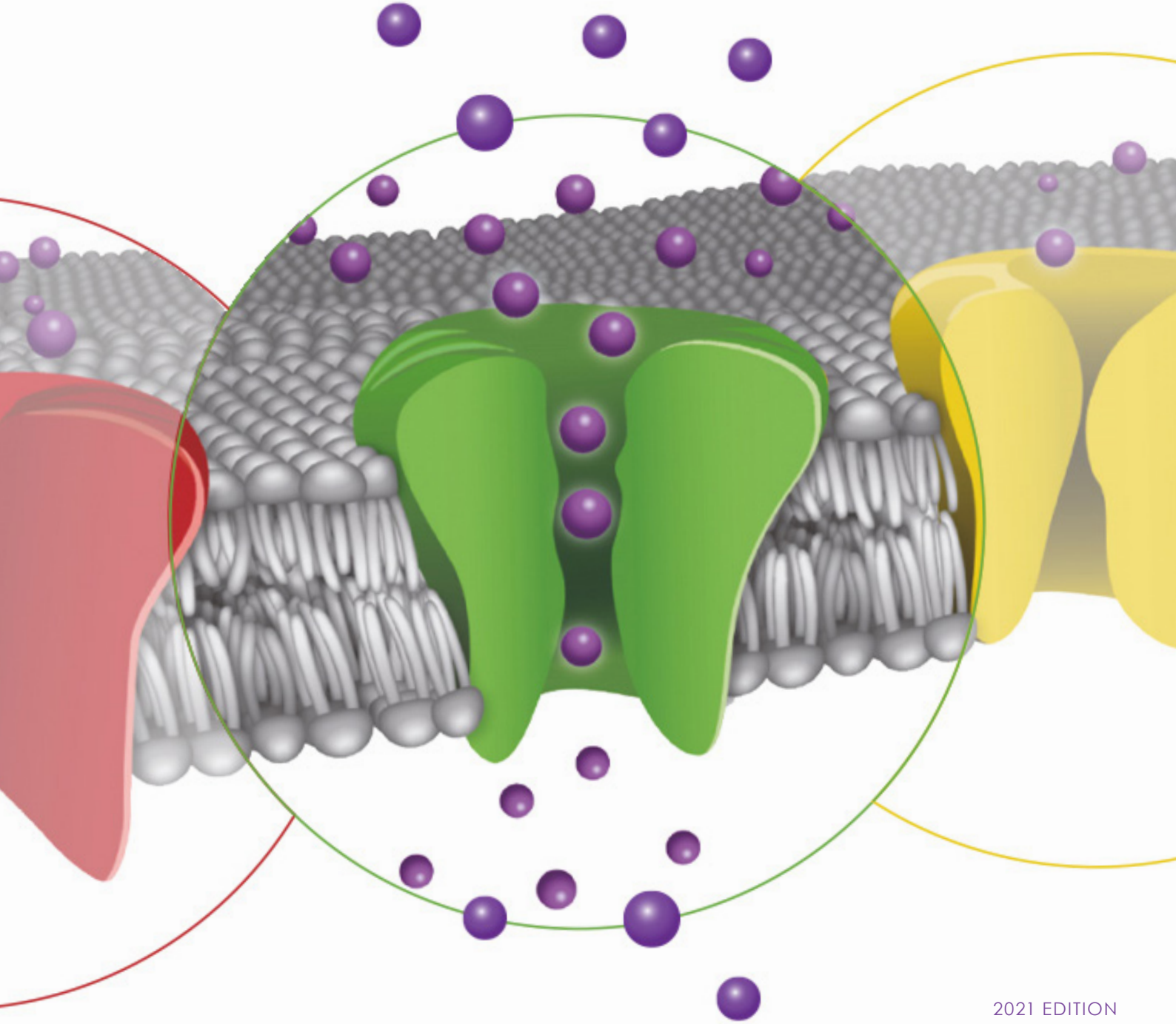
METRION BIOSCIENCES

Translational Assays 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.

metrion biosciences

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.

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.

METRION BIOSCIENCES – LEADERS IN ION CHANNEL DRUG DISCOVERY

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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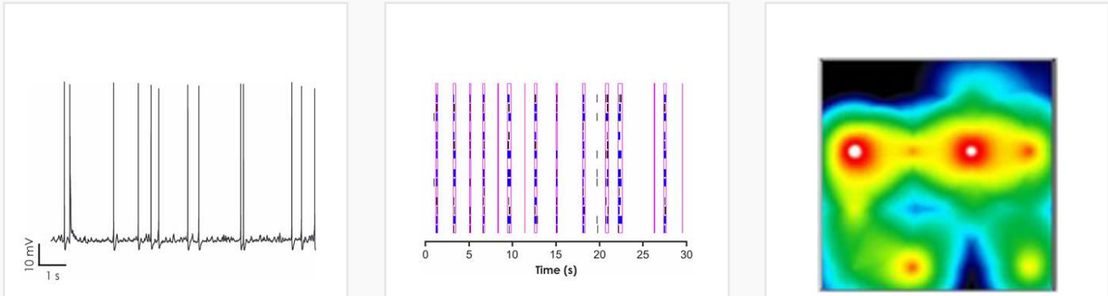
Translational Neuronal Assays.

Metrion has a range of phenotypic assay platforms to enable its customers to validate the efficacy and mechanisms of their compounds in rodent and human neurons to help translate them towards preclinical testing and eventually into clinical trials. These assays use technologies such as manual patch clamp and multi-electode array (MEA) recordings to offer a direct read-out of physiological function in native tissue or human stem cell-derived neurons.

Central Neurons

Central neuron phenotypic assay platforms at Metrion include manual patch-clamp and MEA techniques, which can be used to validate compound target efficacy, establish target engagement in native tissue, and explore species selectivity. Access to CNS neurons from different brain regions and developmental stages also allows for a comparison of compound effects on cells with different functional profiles, as well as the potential to test compounds on native and iPSC-derived neurons from different, genetically validated, disease states.



Physiological activity is monitored from native CNS neurons such as rodent cortical neurons by measuring their firing behaviour with manual patch clamp (**left**) and MEA electrophysiology platforms (**centre/right**), where single cell excitability as well as metascale network bursting can be visualised with heat maps (**right**) and other sophisticated analysis and visualisation tools.

Current Clamp Recording

This technique allows recordings from individual neurons to measure changes in membrane potential or firing behaviour in response to compound application or current input.

Recordings can be used to compare firing characteristics from different cell types, verify findings from other sources (such as MEA) and to ascertain the MOA of compounds.

At Metrion, we are highly experienced at recording from native rodent neurons and are currently developing further translational assays such as recordings from stem cell derived neurons and human dorsal root ganglion neurons.

Multi-electrode array (MEA)

MEA enables simultaneous recording of the physiological activity in multiple peripheral neuronal cells.

Extracellular field potentials are recorded in a non-invasive manner to characterise neuronal firing before and after compound addition.

These techniques can be used to examine cells in sensory pathways, such as rodent dorsal root ganglia neurons, and their response to ligand application.

The electrophysiological behaviour of populations of disease modified neurons or cells from different sources can also be compared with relative ease.

Human iPSC-derived neurons

Metrion has experience utilising human iPSC-derived neurons in translational assays.

We work closely with leading commercial iPSC providers to evaluate and validate their neuronal reagents in our own laboratory, and also collaborate with academics and clients to profile bespoke iPSC neuron assay formats and reagents such as patient-derived neurological disease models.

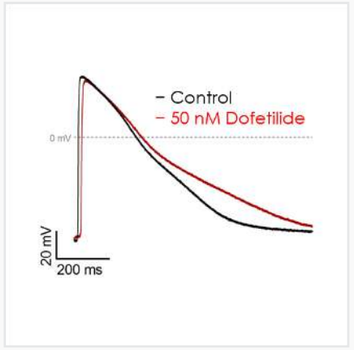
Translational Cardiac Assays.

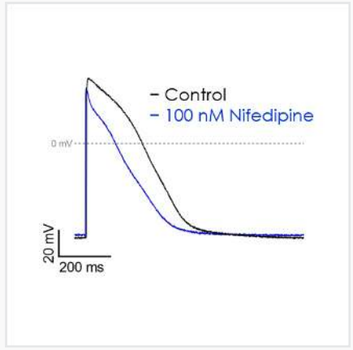
High quality cardiac toxicity data generation and interpretation is vital to the efficient progression of a drug discovery campaign. Metrion offers a range of translational cardiac assays and platforms that have been validated using commercially available iPSC-derived cardiomyocyte cell lines.

Using technologies such as manual patch clamp electrophysiology, multi-electrode array (MEA; Maestro platform) or dual MEA/impedance readouts (CardioExcyte96), Metrion can offer a direct readout of physiological function in the iPSC-derived cardiomyocyte cell line of your choosing.

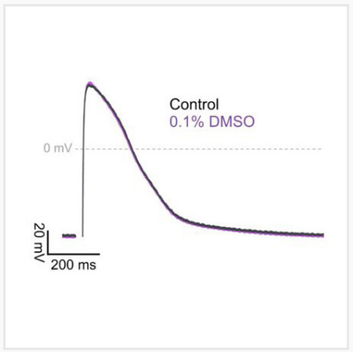
Manual Patch Assays

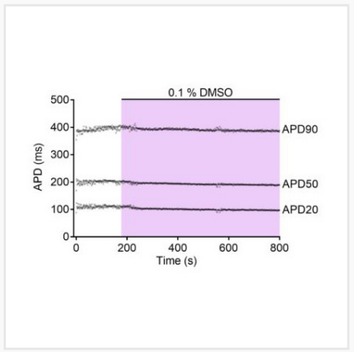
Metrion has considerable expertise working with iPSC-derived cardiomyocytes on the manual patch clamp platform and has characterised various commercially available cell lines. Metrion offers services to screen compounds against action potentials and membrane currents recorded from iPSC-derived cardiomyocytes.

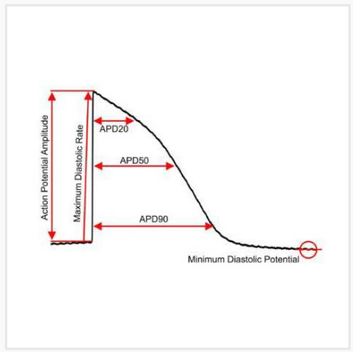




Furthermore, we provide a cell line characterisation service for companies and vendors looking to commercialise their cell lines. Stable action potentials can be recorded from both spontaneously beating or stimulated cardiomyocytes. Compound effects (**above**) are quantified against key action potential parameters, such as action potential duration (APD) which can be a surrogate marker for prolongation of the *in vivo QT interval*.







Stimulated Action Potentials

Stable action potential recordings can be taken for up to one hour using stimulation via a recording bath field potential or current injection through the recording pipette. This enables application of multiple concentrations of a compound during a single experiment (**above**). Frequency-dependent effects on action potential parameters can also be investigated.

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Spontaneous action potential recordings

iPSC-derived cardiomyocytes possess intrinsic pacemaker activity, resulting in spontaneous action potential firing. This allows the Determination of the effect of a test compound on action potential (AP) firing frequency and to identify compounds with the potential to slow (bradycardia) or increase (tachycardia) heart rate *in vivo*. Metrion has tested a toolbox of compounds with cardiac activity and confirmed their anticipated effect on spontaneous action potential parameters, which were consistent with those determined from stimulated cells. For example, the hERG blocker dofetilide significantly prolonged the AP duration of iPSC-derived cardiomyocytes and induced EADs (**below**).

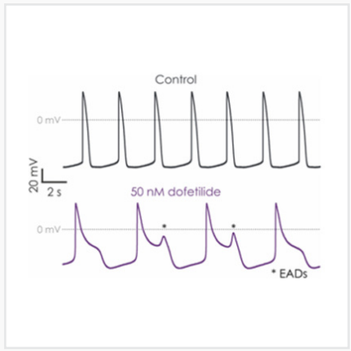

Plate based Assays (MEA and Impedance Platforms)

Metrion has developed plate-based iPSC-derived cardiomyocyte assays using MEA and impedance platforms to add further depth to our range of CiPA-compliant assays. Phenotypic readouts can be correlated with modelling predictions and electrophysiology readouts as part of an integrated CiPA approach.

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About us

Launched in 2015

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