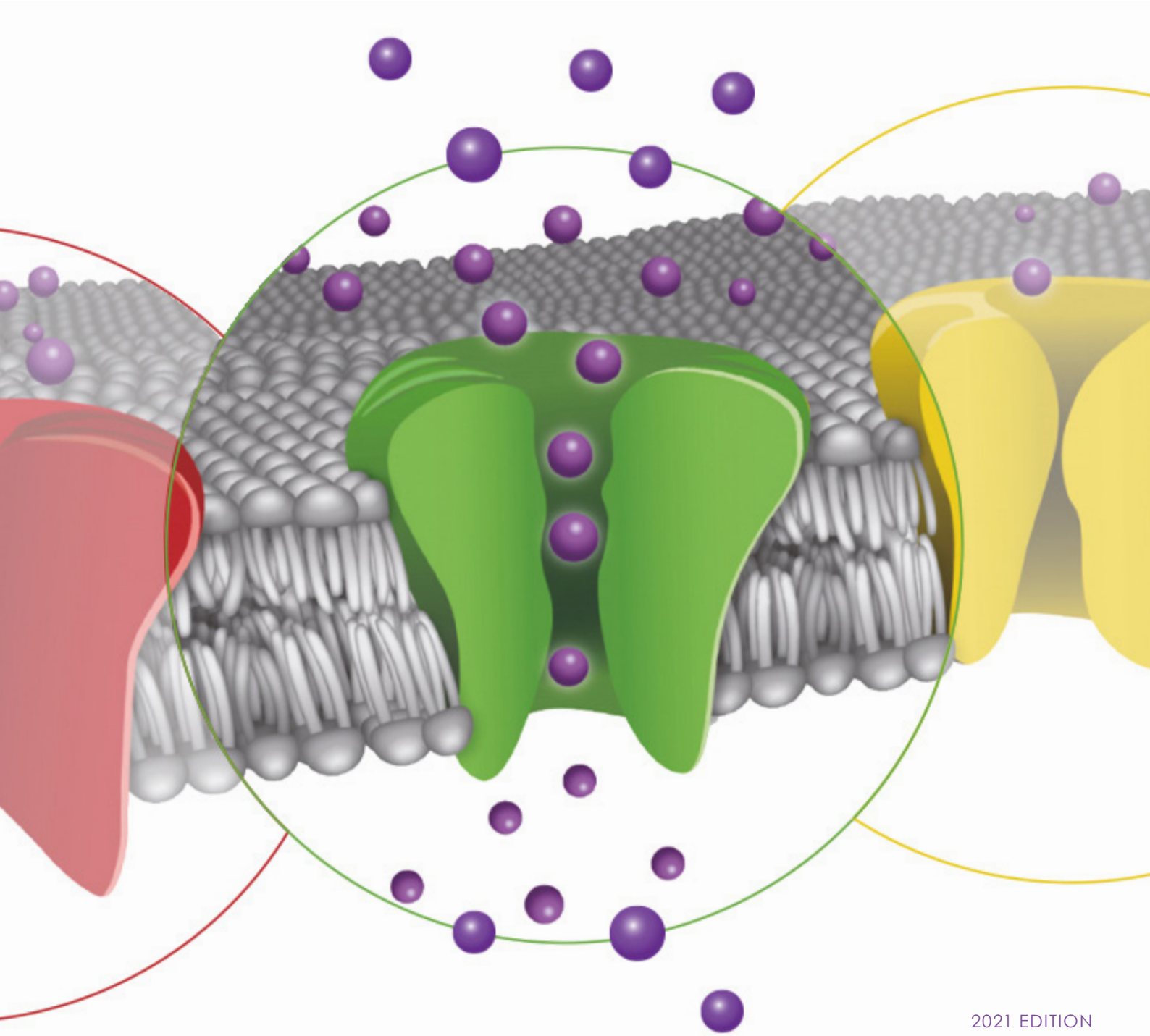
METRION BIOSCIENCES

Ion Channel 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.

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.**

info@metrionbiosciences.com |

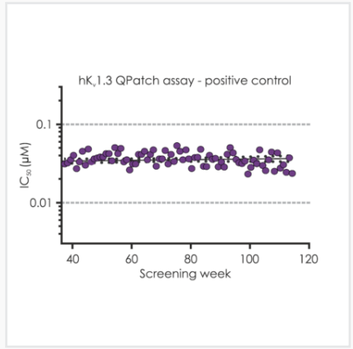
Ion Channel Screening.

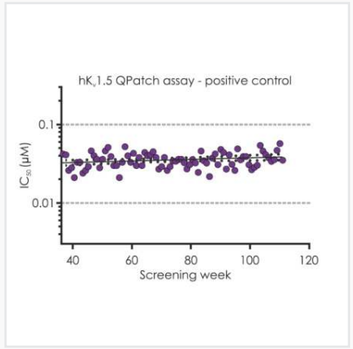
Metrion Biosciences ion channel and drug discovery screening expertise enables us to create and provide efficient assays that deliver reliable, high-quality data to accelerate and validate your drug discovery programmes. Metrion specialises in delivering high-quality ion channel screening services using electrophysiology, label-free and fluorescence-based platforms.

Our assay technologies include QPatch (Sophion) and Patchliner (Nanion) automated electrophysiology, conventional manual patch clamp, plate-based impedance and multi-electrode array techniques, and plate-based imaging using the FlexStation.

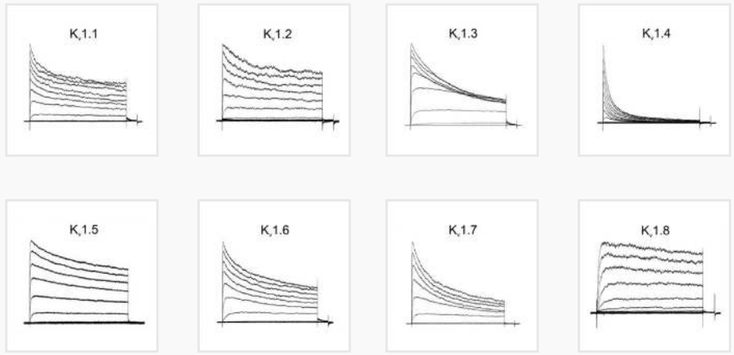
K_V1.3 Ion Channel Screening Case Study

Ion channel assays used for selectivity and SAR screening need to be stable over the entire duration of a drug discovery project, which can last for months or even years. In the example *below,* we show the exceptional reliability of the optimised primary target K_V1.3 (**below, left**) and gene family selectivity K_V1.5 counter-screening assays (**below, right**) used as part of a long-term pharma collaboration, plotting the positive control IC_{50} over the course of two years.



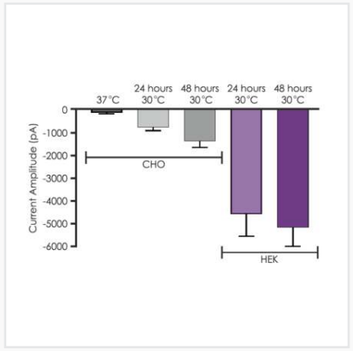


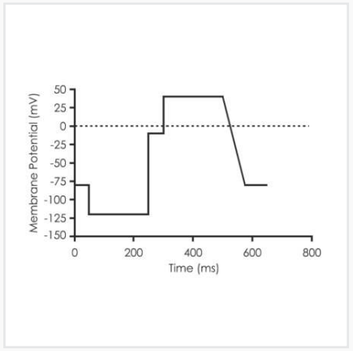
Metrion scientists also developed a complete gene family selectivity panel (**below**) of human K_V1.x ion channel cell lines and assays to complement the primary K_V1.3 screening assay. These assays were critical in supporting this long-term drug discovery project and in successfully identifying selective small molecule modulators able to treat auto-immune disease.



$Na_v1.5$ LQT3 cardiac cell line

During our work with the FDA's CiPA cardiac safety testing consortium it became apparent that a 'late' $Na_v1.5$ assay would be an important part of their selectivity panel to help predict the safety of new drug candidates.





We therefore created stable CHO and HEK cell lines expressing the DKPQ LQT3 mutant protein (**above, left**) and assessed their utility as reagents for automated patch clamp assays that would be compliant with CiPA HTS sub-team requirements (**above, right**).

Assay ready cells for APC

Biological reagents are inherently variable and it is typical for the performance of ion channel assays to fluctuate during extended passaging of stable cell lines. To minimise this variation during extended SAR screening campaigns, Metrion scientists created so-called 'assay ready' cells that are grown under conditions optimised for automated patch clamp assays and then frozen down to fix their state for later use. On the day of an experiment, cells are thawed and used directly on APC platforms to guarantee optimum performance, provide consistent screening results, and increase workflow flexibility to run multiple ion channel assays at short notice.

Cell line and assay optimisation

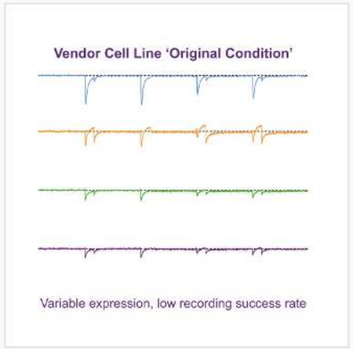
In some cases, cell reagents are not optimal for electrophysiology assays and need improved 'patchability' and expression of the protein of interest in a functional state at the cell surface.

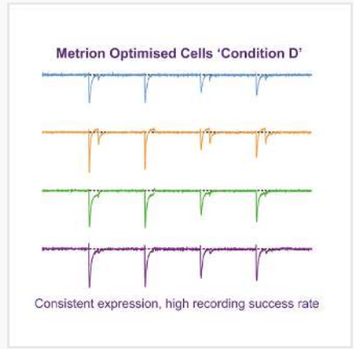
Metrion's scientists have over a decade of experience in developing, optimising and validating automated and manual patch clamp assays for ion channel targets. We can fully customise assays at different stages of the screening cascade, from hit finding and medium throughput structure activity studies, through to specialised biophysical and mechanism-of-action studies.

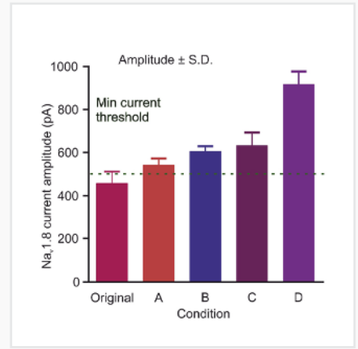
METRION BIOSCIENCES – LEADERS IN ION CHANNEL DRUG DISCOVERY

Na_v 1.x cell line optimisation

A neuronal Na^+ ion channel used as the primary counter-screening target in a major pharma drug discovery collaboration is notoriously difficult to express in heterologous cells, and under standard conditions the original cell line yielded a low success rate assay (**far left, below**). We tested a number of different cell culture, cell biology and experimental conditions (**far right, below**) to develop an optimised assay on the Patchliner (Nanion) automated patch clamp platform.





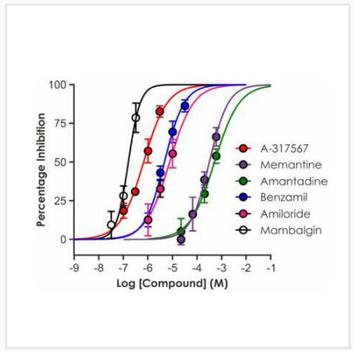


Our efforts significantly improved the low expression seen in the original reagent without affecting 'patchability', yielding a highly efficient gene family selectivity assay (**middle, above**).

Assay Development and Validation

Ion channels are large, complex transmembrane proteins that can be difficult to express with the correct folding and associated auxiliary subunit and scaffolding protein complexes, making it essential to validate cell line reagents and assays before they are used for drug discovery screening. Along with sequence verification, Metrion scientists determine the functional biophysical and pharmacological profile of each cell line reagent on our assay platforms prior to their use in drug discovery screening cascades.

ASIC1a QPatch assay



We recently validated a cell line expressing human ASIC1a, a ligand-gated receptor which is implicated in stroke and ischemia. Assay development efforts concentrated on creating a stable assay on the QPatch automated patch clamp platform and confirming the correct agonist and antagonist pharmacology using a selection of reference and literature compounds (**left**). More details on this assay validation effort is available in our ASIC1a application note which can be found on our website.

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About us

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