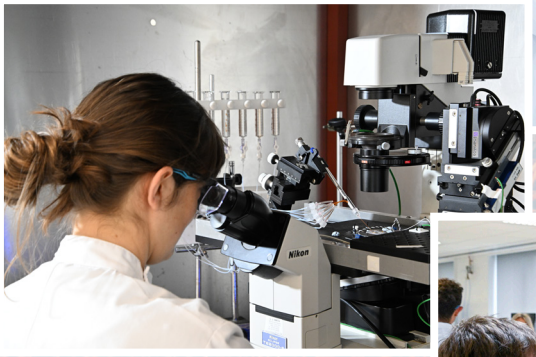
metrion biosciences

Specialist Neuroscience Services

Translational neuronal assays for pharmacological screening



Highly specialised neuronal assays for pharmacological screening and neurotoxicity testing

Our specialist team of neuroscientists have extensive experience in indications such as pain, epilepsy, neurodegeneration and psychiatry.

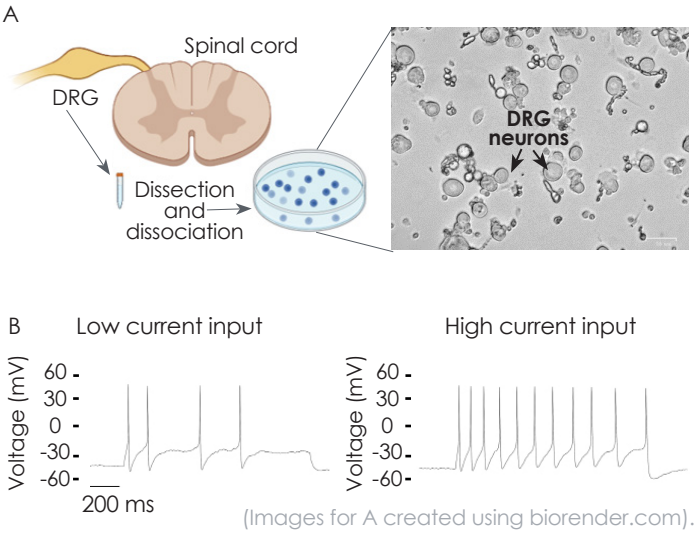
Panel of models with increasing complexity and translational relevance

Our neuroscience assays provide a thorough understanding of compound mechanisms at specific targets within a physiologically relevant environment. Translational assays we provide include central and peripheral neuronal firing, and native ion channel screening assays.

- Ion channel expressing cell lines for central nervous system and pain targets
- Primary neuronal cultures, including dissociated cortical, trigeminal or dorsal root ganglion (DRG) neurons from rodents (Figure 1)
- Effects of test compounds on brain slice physiology
- Human iPSC-derived neurons relevant for new approach methodologies (NAMs)
- Selectivity and safety profiling

These assays will help you:

- Investigate the mechanism of action for pre-clinical compounds
- Confirm compound effects against specific ion channels in native neuronal backgrounds
- Address the neurotoxicity of compounds and assess the effects of compounds on a range of excitability parameters



(Images for A created using biorender.com).

Figure 1. Electrophysiological recordings of primary neuronal cells. (A) Rodent dorsal root ganglion (DRG) neuron preparation for manual patch-clamp studies and a bright-field image of dissociated cells seeded on a coverslip. (B) DRG action potential responses to different current injection protocols.

High-throughput $Na_V1.9$ assays to advance pain drug discovery research

Robust stably expressing $Na_V1.9$ cell lines (human and rat).

- ✓ Stable expression ensures consistent and reproducible results
- ✓ High-throughput, cost-efficient screening campaigns
- ✓ Drug discovery enabled in an underexplored target

www.metrionbiosciences.com/neuroscience/nav1-9-assays

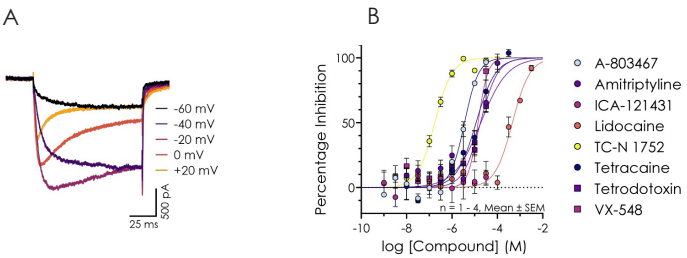


Figure 2. (A) Pharmacological assessment of human and rat $Na_V1.9$ using Qube automated electrophysiology platform. (B) Human $Na_V1.9$ currents evoked using a series of depolarising pulses.

C

Compound	IC_{50} (μM) $hNa_V1.9$	$rNa_V1.9$
A-803467	3.51	8.30
Amitriptyline	18	15.3
ICA-121431	>30	>10
Lidocaine	460	194
PF-05089771	>3	>30
TC-N 1752	0.2	0.22
Tetracaine	11.5	22.4
TTX	18.7	>30
VX-548	14.1	>30

Table 1. (C) Concentration-response curves for a panel of sodium channel inhibitors against human $Na_V1.9$. Summary of comparative pharmacology of sodium channel inhibitors tested against rat and human $Na_V1.9$.

Pave the way for innovative treatments for lysosome-related disorders

Investigation of ion channels localised to the lysosomal membrane is critical for elucidating the mechanisms underlying lysosomal physiology, maintaining cellular homeostasis, and understanding the pathophysiology of a broad spectrum of lysosome-associated disorders.

To enable the study of ion channels found on the lysosomal membrane we perform the lysosomal patch-clamp technique.

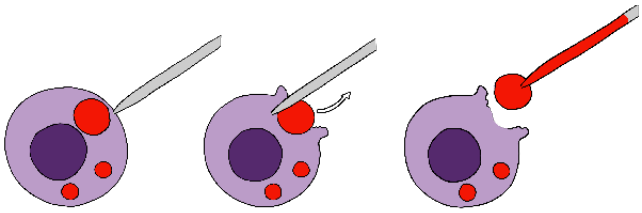


Figure 3. A sharp pipette is used to slice the cell membrane to create a rupture point through which the lysosome can be extracted. A fresh fire polished pipette is then used to patch the lysosome. When a gigaseal has been formed on the lysosome, a zap or voltage pulse is used to break in and achieve the whole-lysosome configuration.

Watch video demonstrating this in action:
www.metrionbiosciences.com/neuroscience/#lyso

CNS discovery: brain slice assay

Preserving the anatomical architecture and synaptic circuitry of specific brain regions enables a more comprehensive assessment of pharmacological effects on excitability and network activity.

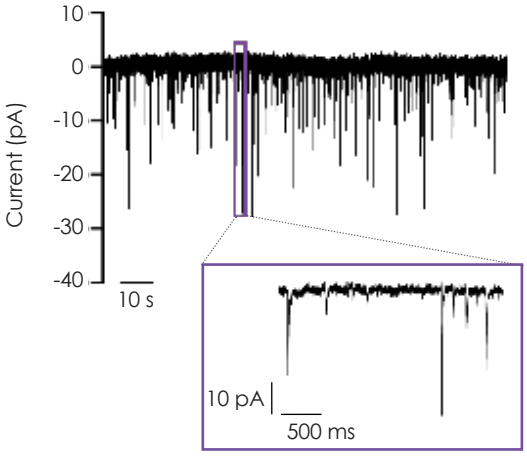


Figure 4. Representative recording of spontaneous post-synaptic currents at -70 mV holding potential. The inset illustrates a zoomed-in area of the recording.

Case Study: Multi-assay high-throughput repurposing screen for rare epilepsy mutation in KCNC1 gene

Eliana is a two-year-old from Canada with a *de novo* V434L mutation in her *KCNC1* gene, which encodes the $K_V3.1$ channel in central nervous system neurons. This mutation can cause various neurological disorders, including myoclonic epilepsy, ataxia, and developmental epileptic encephalopathy (DEE).

www.metrionbiosciences.com/neuroscience/#kcnc1

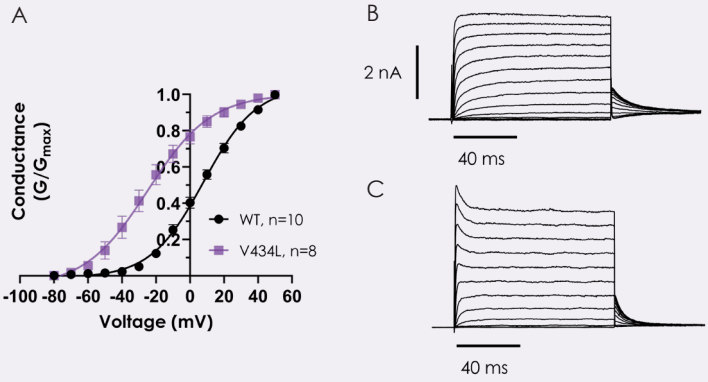


Figure 5. Evaluating the biophysical properties of wildtype and the V434L variant $K_V3.1$ channel. Conductance/voltage relationship (A). Example recordings from $K_V3.1$ (B) and V434L variant (C).

Specialist Preclinical Drug Discovery CRO

Metrion 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.

1,700+ projects completed globally

170+ different customers in the last 5 years

87% of science and senior team hold a Master's degree or higher, with 65% trained to PhD level

250 years combined experience managing ion channel research programmes

Testimonials

"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

"Aligos values the consistency and convenience of working with Metrion. The data is always correct and in a format that imports directly into our systems, making it so quick and easy for our team to review across individual projects.
Metrion are always on top of the regulations as they change - they were incredibly helpful in supporting us navigate the ICH changes."

Dr Dinah Misner, VP,
Aligos Therapeutics, USA

"I've been pleased with the efficiency of the Metrion team, especially with their scientific expertise / practical ion channel knowledge.

It's not every ephys CRO that can make intellectual contributions towards the assay design and troubleshooting, and I've definitely appreciated that."

Dr John Gilchrist, Principal Scientist,
Latigo Biotherapeutics Inc., USA

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