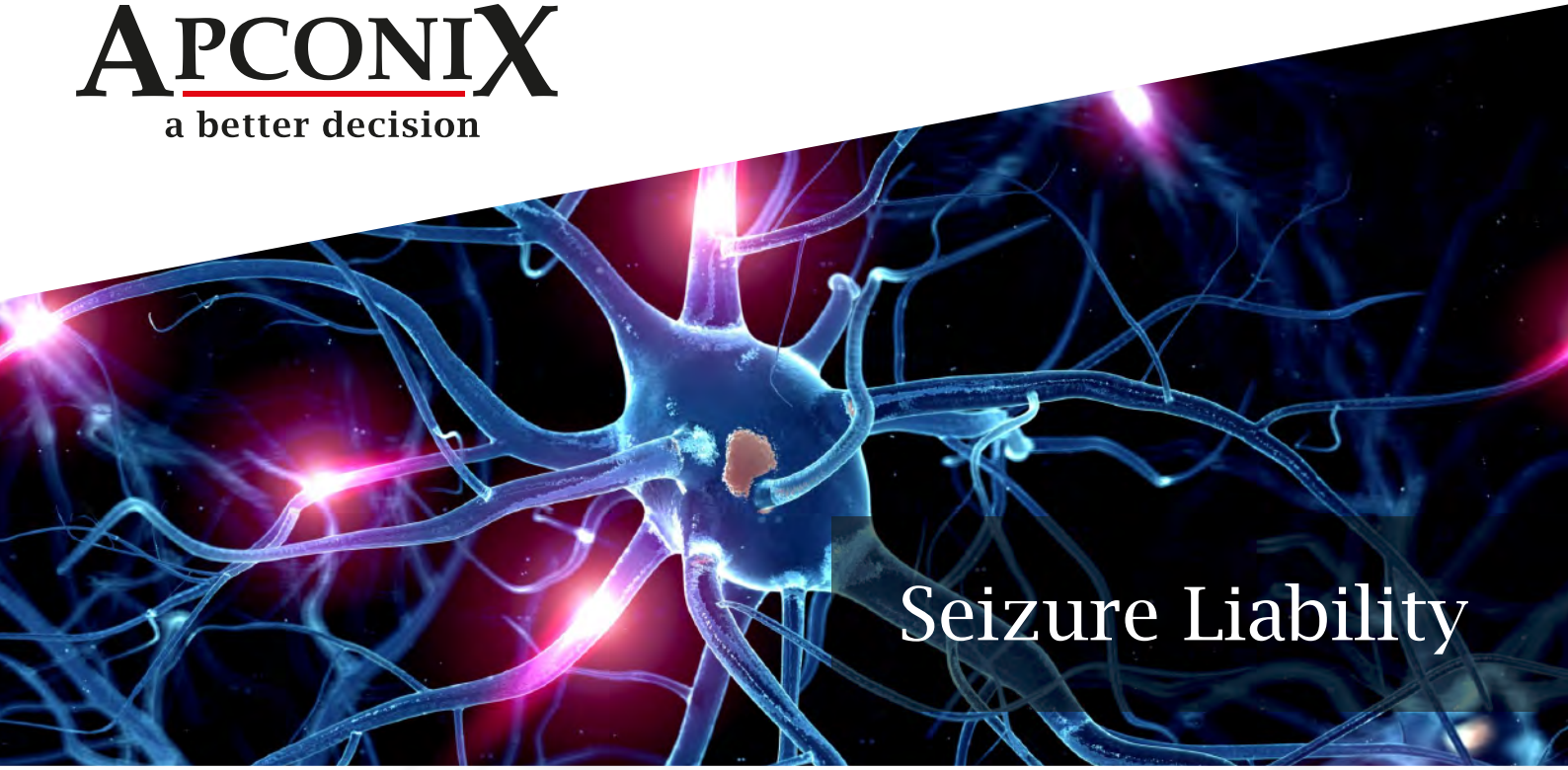
APCONIX
a better decision



Seizure Liability

Innovative Ion Channel and MEA Seizure Liability Assays

An integrated in vitro screening approach for seizure liability to support hazard identification and decision making in early drug discovery

- A panel of 15 human ion channels related to seizure screened by automated electrophysiology
- A microelectrode array (MEA) assay that measures the electrical activity of human derived neuronal stem cells

iSLA
in vitro Seizure Liability Assay

THE KING'S AWARDS FOR ENTERPRISE 2024 INTERNATIONAL TRADE

THE QUEEN'S AWARDS FOR ENTERPRISE: INTERNATIONAL TRADE 2022

We were delighted to be cited in a recent FDA/CDER paper (Avila et al 2023) where the authors provide a perspective on the opportunities and challenges of using NAMs in drug development.

The predictivity of the MEA assay to seizures clinically is 87.5%

Case study 1 - Translation of MEA data from hiPSC neurones to humans (panel 1)

- Concentration response data for amoxapine, a known seizurogenic drug
- At low concentrations, equivalent to the therapeutic concentration, amoxapine has no/minimal effect on MEA parameters
- With increasing concentrations, perturbations in MEA parameters increase from baseline
- At high concentrations, equivalent to clinically toxic concentrations, amoxapine has dramatic effects on MEA parameters
- Amoxapine showed activity against 8 ion channel targets relevant to seizure giving possible mechanistic insight into its seizurogenicity

Panel 1

MEA parameters		Amoxapine				
		0.1µM	0.3µM	1µM	3µM	10µM
Spike	Mean firing rate (Hz)	NC	NC	↑	↑↑	↓↓↓
	Interspike Interval (ISI) Coefficient of variation - Avg	NC	NC	NC	↓	↓↓↓
Bursts	Burst frequency - Avg (Hz)	NC	NC	↑↑	↑↑*	↓↓↓
	Burst duration - Avg (sec)	NC	NC	↓	↓↓	↓↓↓
	Number of spikes per burst - Avg	NC	NC	↓	↓↓	↓↓↓
	Mean ISI within burst - Avg (sec)	NC	NC	NC	↓↓	UNC
Network Bursts	Network burst frequency	NC	NC	↑↑	↑↑*	N/A
	Network burst duration - Avg (sec)	NC	NC	↓	↓↓	N/A
	Number of spikes per network burst - Avg	NC	NC	↓	↓↓*	N/A
	Mean ISI within network burst - Avg (sec)	NC	NC	NC	↑↑	N/A
	Network IBI Coefficient of variation - Avg	NC	NC	NC	↓↓	UNC
Synchrony	Area under normalized cross-correlation	NC	NC	NC	NC	↓↓↓

Case study 2 - Ability of MEA to detect seizurogenic metabolites without the need for in vivo studies

- Client compound known to cause seizures in dogs only
- Human and rodent metabolites have no effect on MEA parameters (panel 2)
- Canine metabolite causes significant effects on MEA parameters at the highest concentration (panel 3)
- When tested against a panel of ion channel targets, the canine metabolite was active at the NMDA receptor. This gives a possible mechanism of action for the observed seizures

Panel 2

MEA parameters		1µM	3µM	10µM	30µM	100µM
Spike	Weighted mean firing rate (Hz)	NC	NC	↑	NC	NC
	Interspike Interval (ISI) Coefficient of variation - Avg	↑	NC	NC	NC	↑
Bursts	Burst frequency - Avg (Hz)	NC	NC	NC	NC	NC
	Burst duration - Avg (sec)	NC	NC	↑	↑	↑
	Number of spikes per burst - Avg	NC	NC	↑↑	↑	↑
	Mean ISI within burst - Avg (sec)	NC	NC	↓	↓	NC
Network Bursts	Network burst frequency	NC	NC	NC	NC	↓
	Network burst duration - Avg (sec)	NC	NC	NC	NC	NC
	Number of spikes per network burst - Avg	NC	NC	NC	↑	NC
	Mean ISI within network burst - Avg (sec)	NC	NC	NC	NC	NC
	Network IBI Coefficient of variation - Avg	↓	↑	↑	↓	UNC
Synchrony	Area under normalized cross-correlation	NC	NC	NC	NC	NC

Panel 3

MEA parameters		1µM	3µM	10µM	30µM	100µM
Spike	Weighted mean firing rate (Hz)	NC	NC	NC	↑	NC
	Interspike Interval (ISI) Coefficient of variation - Avg	NC	NC	NC	NC	↓
Bursts	Burst frequency - Avg (Hz)	NC	NC	↑	↑	↑↑
	Burst duration - Avg (sec)	NC	NC	NC	NC	↓
	Number of spikes per burst - Avg	NC	NC	NC	NC	↓↓
	Mean ISI within burst - Avg (sec)	NC	NC	NC	NC	NC
Network Bursts	Network burst frequency	NC	NC	↑	↑	↑↑
	Network burst duration - Avg (sec)	NC	NC	NC	↓	↓
	Number of spikes per network burst - Avg	NC	NC	NC	↓	↓↓
	Mean ISI within network burst - Avg (sec)	NC	NC	NC	NC	↑↑↑
	Network IBI Coefficient of variation - Avg	UNC	UNC	UNC	UNC	UNC
Synchrony	Area under normalized cross-correlation	NC	↑	NC	↓	↓↓

NC	No change (±10%)
One arrow	11 – 29% change
Two arrows	30 – 49% change
Three arrows	>50% change

ToxSpotlight Article

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