From Ion Channel Modulation to Network Excitability: A Scalable Integrated Seizure Liability Screening Platform

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Introduction

Drug-induced seizures remain a significant safety concern during drug development (1). Early identification of compounds with proconvulsant potential is critical (1), yet seizure liability assessment remains challenging due to the complex relationship between molecular targets and neuronal network activity and the ethically debated, labor intensive, and expensive techniques currently used to detect seizure (2).

To address this challenge, IQVIA Laboratories has developed a high-throughput, scalable in vitro seizure assessment platform that combines a targeted ion channel panel with a neuronal multi-electrode array (MEA) assay. The ion channel panel provides mechanistic insight into compound effects on key regulators of neuronal excitability, while the MEA assay captures functional changes in neuronal network activity.

Together, these complementary assays provide mechanistic and functional insights into seizure liability, enabling efficient screening, early hazard identification, and informed decision-making throughout drug discovery and development

Methods

- Four ion channel families were included in the panel:
  - Voltage-gated Sodium Channels – $Na_V1.1$, $Na_V1.2$, $Na_V1.3$ and $Na_V1.6$
  - Voltage-gated Potassium Channels – $K_V1.1$, $K_V4.2$/ChIP2.2, $K_V7.2/7.3$, $K_V7.4$ and $K_V7.3/7.5$
  - Ligand-gated Ion Channels – GABAA α1β2γ2, α2β2γ2 and α5β2γ2, NMDA NR2A, Nicotinic receptor α4β2
  - Calcium-activated Potassium Channels – $K_{Ca}1.1$ (BK)
- Electrophysiology was carried out on the Sophion Qube 384 well automated patch-clamp platform recording from 384 wells simultaneously. All experiments used multi-hole Qchips. Up to 8 compounds as 10 point concentration-response-curve (CRC) (4 wells per concentration) can be tested in one plate.
- Multi-electrode array (MEA) was carried out on Axion Maestro Pro system using Axion Cytoview 48 well plates. Extracellular field potentials recorded from 16 electrodes per well in neuronal co-cultures typically consisting of Glutamatergic and GABAergic iPSC-derived neurons and primary astrocytes. Cultures formed synchronous network following supplier protocols. Data processed using Axion neural metric tool and bespoke Genedata Screener tools for downstream analysis.

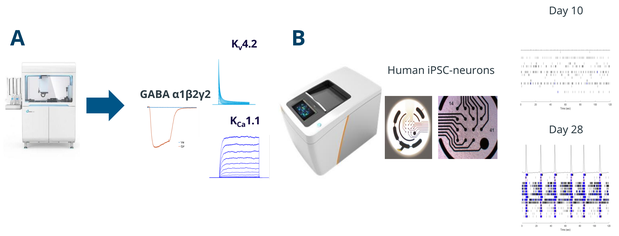


Fig1. **(A)** Sophion Qube384 allows recording of ion channels involved in cellular excitability, providing mechanistic insights. **(B)** Axion Maestro Pro MEA allows maturation and monitoring network activity of neuronal co-cultures over time.

Results

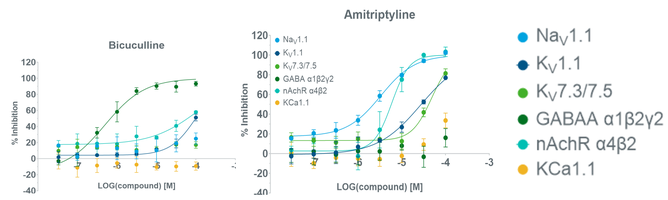


Fig2. Summary of concentration-response curves for bicuculline and amitriptyline, against some of the cell lines included in the panel.

Conclusions

- Combining high-throughput ion channel profiling with human iPSC-derived neuronal MEA assays provides a robust and translational approach for early assessment of seizure liability.
- Screening a broad panel of ion channels involved in neuronal action potentials identifies mechanistic insights into potential seizure liability through four key families of ion channels.
- Assessing neuronal phenotypes by MEA captures phenotypic alterations in neuronal networks, with the ability to test novel compounds for their ability to reverse phenotypic changes.
- This combined approach assessing target-specific and network-related effects of compounds improve confidence in prediction of seizure liability using translatable in vitro models to support drug discovery and development programs.

References

- Larson EA, Accardi MV, Zhong Y, et al. (2021). Drug-Induced Seizures: Considerations for Underlying Molecular Mechanisms. International Journal of Toxicology, 40(5), 403-412.
- Tukker AM, Westerink RHS. (2021). Novel test strategies for in vitro seizure liability assessment. Expert Opinion on Drug Metabolism & Toxicology, 17(8), 923-936.

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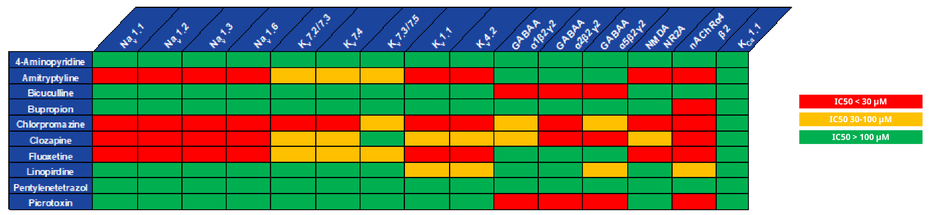


Fig3. Table summarizing the potencies of seizurogenic compounds used to validate all the ion channels included in the panel.

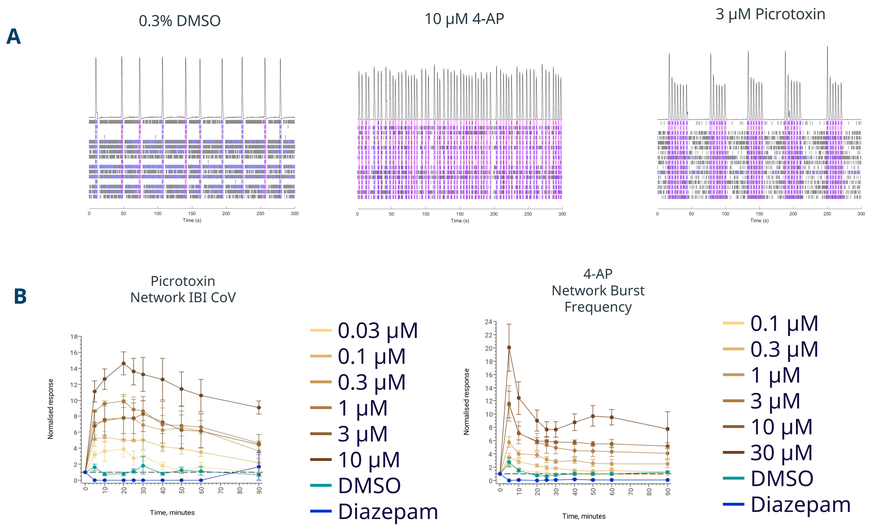


Fig4. Known seizurogenic compounds applied to synchronous neuronal networks to give phenotypic responses (A) which can be quantified and differentiated through specific metrics (B).

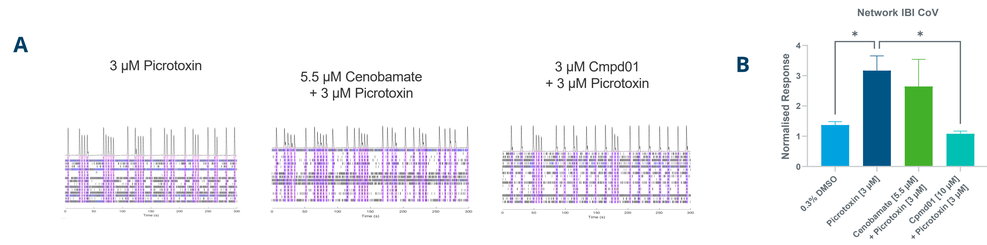


Fig5. Known and novel anti-seizurogenic compounds reverse phenotypic (A) and quantitative (B) differences from known seizurogenic compounds.