

DRUG DISCOVERY WORLD

DDWTM

turning science into business



DRUG DISCOVERY
INNOVATORS & INVESTORS
Supported by DDW

From investment to innovation – why we've launched a new event series

FALL 2026 | ddw-online.com

Trends & Analysis

The three generations
of obesity medications

Cell and Gene Therapy Guide

Opportunities and advances in cell
and gene therapy

Market Report

The drug discovery market
in SouthEast Asia

Mitigating ion channel related CNS liability in novel compounds by predicting SAR

The Apconix team are working towards providing a high throughput service to resolve central nervous system (CNS) liabilities earlier in the drug discovery pipeline. Their recently published study is the first reported method to use structure activity relationships (SAR) to help derisk drug design for seizure related ion channels.

CNS liabilities occur frequently in drug discovery and are significant contributors to drug attrition. Although methods for screening CNS liabilities early in the development pipeline do exist—such as using zebrafish larval locomotor assays or hippocampal brain slices—they are relatively limited in both their translational relevance and throughput capacity. This means that the failure of promising drug compounds tends to happen later in the critical path, costing developers considerable time and resources.

To address this challenge, Apconix launched iLA^{Seizure} in 2022—an in vitro liability assay that detects drug induced seizure risk. Winning the King's Award for Enterprise for

Innovation in 2025, the iLA^{Seizure} capability was the result of three years of hard work by the Apconix team. Further research has expanded on this, leading to the development of iLA^{CNS} and iLA^{Sedation}.

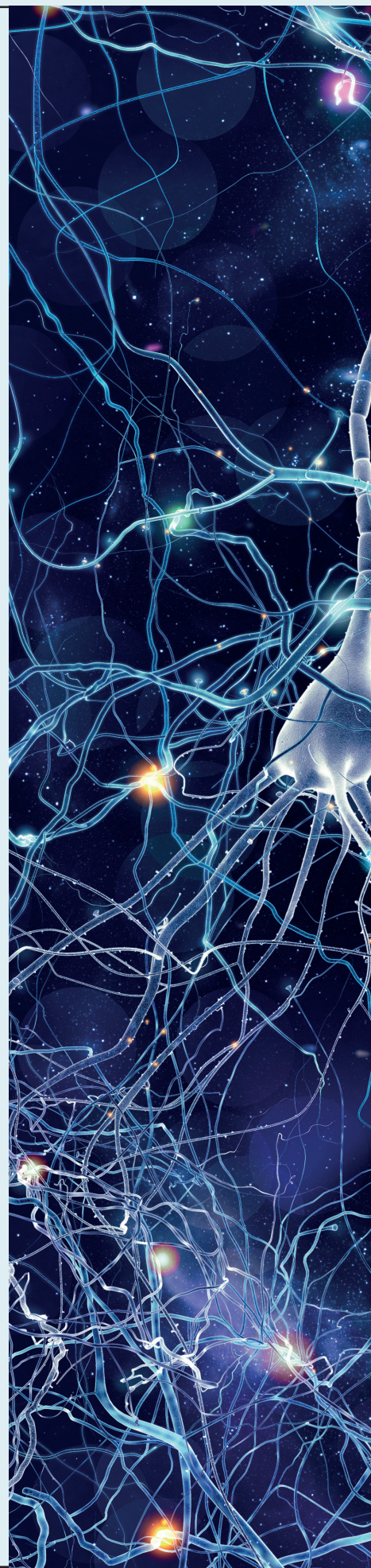
But the team at Apconix want to go even further in tackling CNS related late stage drug attrition.

Scientists at Apconix have recently published a proof of concept study that shows how SAR responsible for drug induced CNS liability could be identified using a high throughput, combined in vitro and in silico method (Zolkiewski et al, 2026). Apconix are now working towards providing this as a wider offering.

Predicting SAR that underlie CNS toxicity in novel compounds

Lead author of the study Dr Louisa Zolkiewski says: "We want to provide a tool that predicts which structural features of a drug compound are associated with CNS toxicity as early as possible, so medicinal chemists can 'design out' CNS liability before nonclinical studies begin."

To demonstrate that they can successfully predict SAR responsible for drug induced CNS liabilities, scientists at Apconix first screened a range of compounds against relevant human ion channels using automated patch clamp electrophysiology. Then, they calculated potency for each compound using IC₅₀ values





that were generated from concentration response curves and used statistical analysis to determine the pharmacophore features associated with changes in ion channel activity. Finally, the team looked to confirm that this altered ion channel activity occurred in real human cells by using microelectrode array (MEA) analysis in human induced pluripotent stem cell (hiPSC) derived neurons.

Key findings

Zolkiewski describes the key results of the study: "We found a change in potency for $K_v2.1$ and $\alpha_4\beta_2$ nicotinic receptor ion

the early, in vitro, prediction of SAR underlying CNS liability and has important and exciting implications for the future of drug discovery.

The iLA suite of in vitro liability assays already offered by Apconix is a key example of its commitment to the 'three Rs'—that is, using New Approach Methodologies (NAMs) to replace, reduce and refine the use of in vivo studies. This latest successful venture by Apconix levels up this commitment, with the potential to offer in vitro and in silico methods to derisk promising drug candidates.

Whilst using this approach to tackle the problem of CNS toxicity in drug development is innovative, researchers can be assured that when it comes to drug safety, the SAR based approach also has a proven track record. In the area of cardiac safety, for example, hERG liabilities have been significantly reduced because of this method, with Ekins', Cavalli's and Pearlstein's pharmacophore models having been used for decades to predict and mitigate drug induced cardiotoxicity.



channels that were treated with compounds that had been specifically chemically modified. When we did the SAR analysis, we found that this change in potency was associated with four statistically significant pharmacophore features common across both ion channels. I think one of the most crucial findings of our study is that this change in potency translates into a change in activity at the cellular level, as shown by MEA analysis in hiPSC derived neurons."

The future of drug discovery

This study robustly demonstrates the feasibility of

Next steps

"This initial study used a small set of compounds which we will expand on," explains Zolkiewski. "If we use many more compounds on a wider range of relevant CNS channels then we'll be able to use advanced machine learning approaches to better understand the SAR associated with CNS toxicity."

REFERENCES:

Zolkiewski LAK, Rockley KL, Roberts RA, Jennings HG, Maizieres M-A, Jones K, McDonagh JL, Newman K, Griffen EJ, Stacey JE, Morton MJ. Building structure activity relationships to avoid toxicity due to unwanted central nervous system ion channel activity. *Toxicological Sciences* [online]. 2026;209(8). [Accessed 28 August 2026]. Available from: <https://doi.org/10.1093/toxsci/kfag094>

Innovative In Vitro Seizure Liability Assays

Proven success in early derisking, candidate prioritisation and problem solving, reducing the need for further animal studies

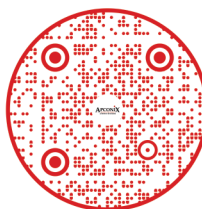
Recently we have supported our clients by:

- Identifying lower risk compounds from a series
- Demonstrating good translation to in vivo studies
- Determining the human relevance of seizures observed in nonclinical studies
- Understanding the potential mechanism of seizure observations in clinical studies

In our latest publication, we share how we can help clients optimise discovery molecules to reduce seizure liability



Apconix was honoured with the King's Award for Enterprise for Innovation for the in vitro seizure liability assay in 2025



**Read our ToxSci
paper here**

Contact us:
hello@apconix.com
www.apconix.com