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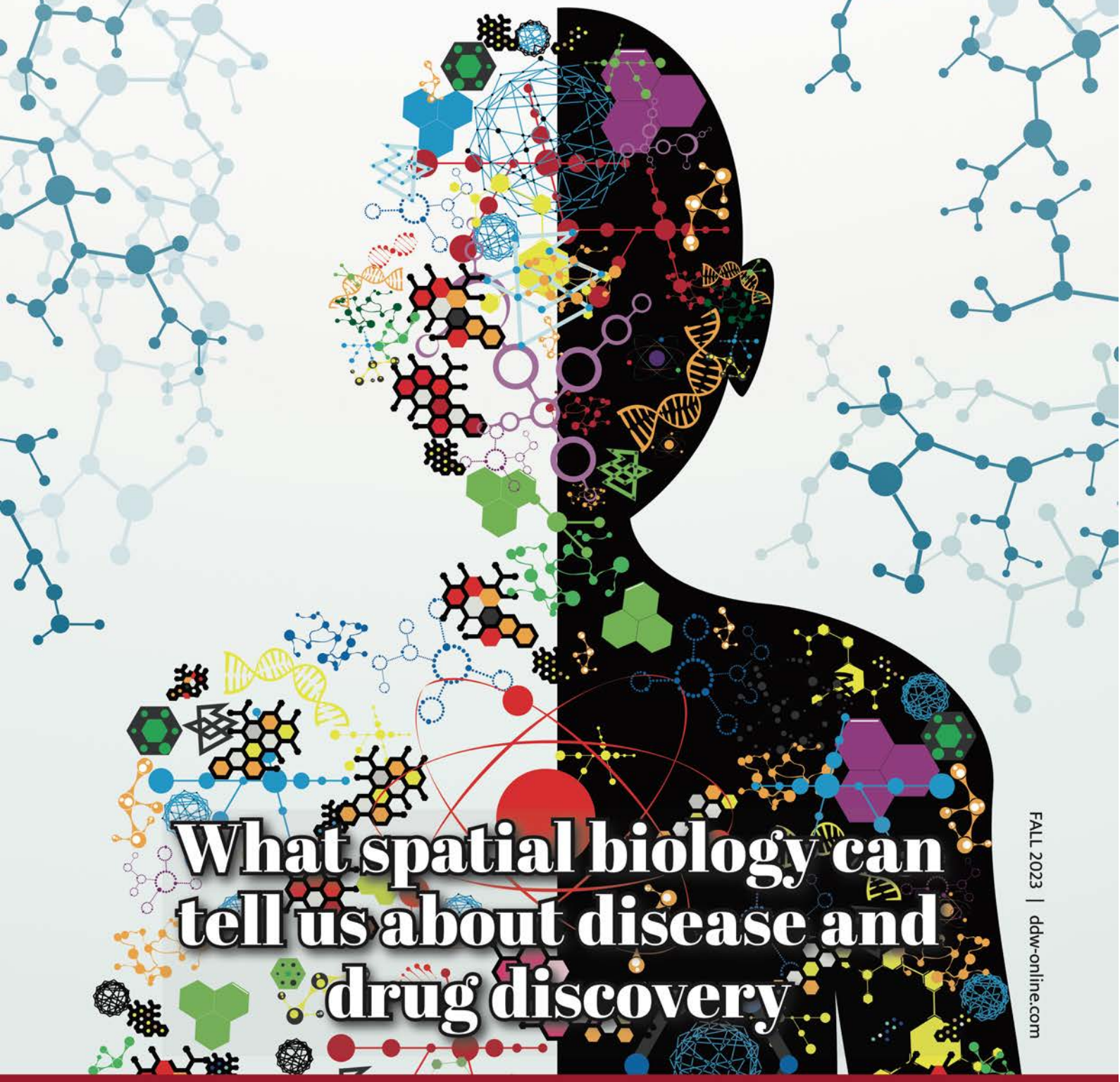

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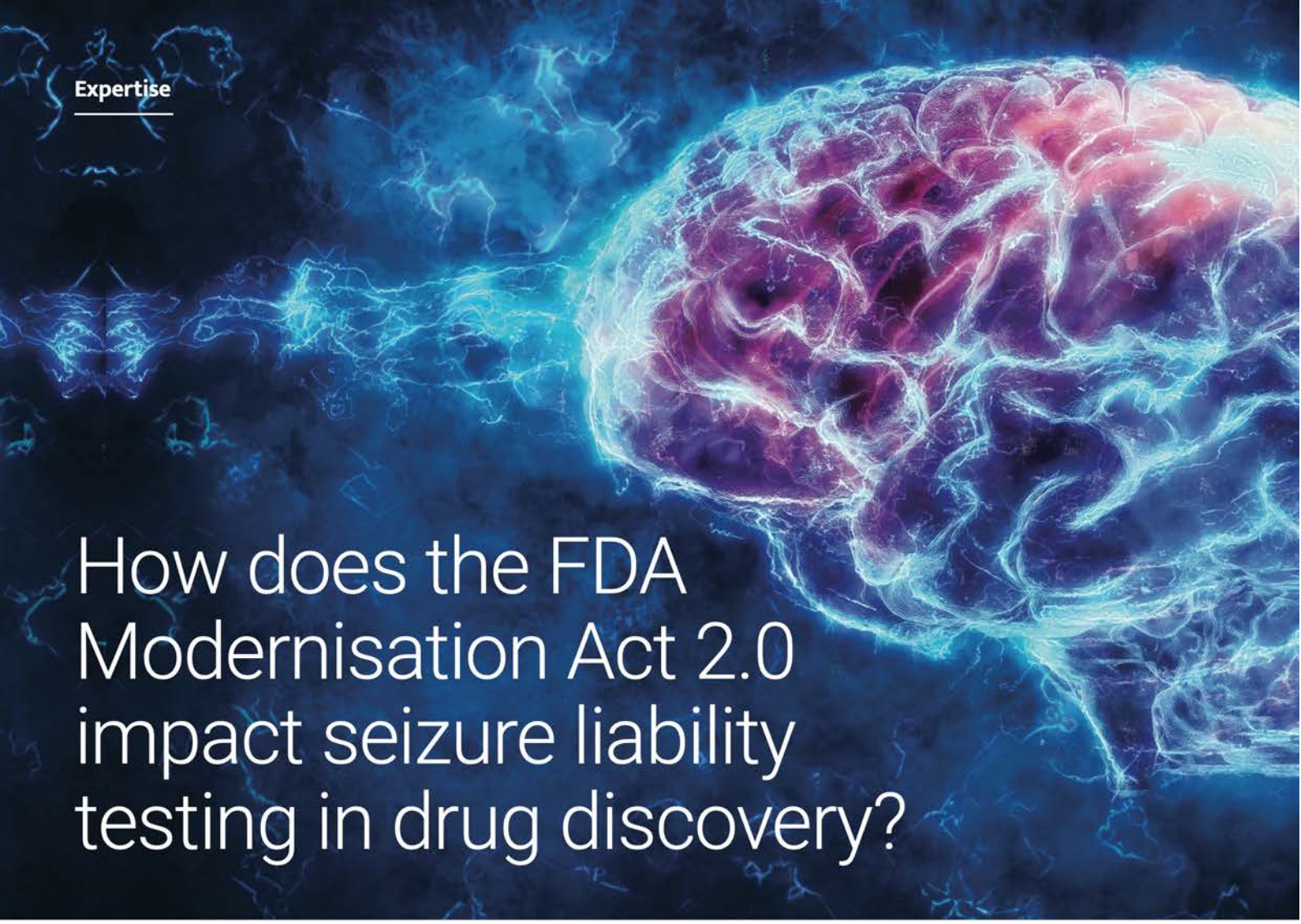

How does the FDA Modernisation Act 2.0 impact seizure liability testing in drug discovery?

A recent DDW Sitting Down With podcast with **Lu Rahman**, heard **Ruth Roberts**, **Michael Morton** and **Kimberly Rockley**, ApconiX, discuss novel alternative methods and the impact of the FDA Modernisation Act 2.0 in relation to seizure liability.

The background

Ruth Roberts and Michael Morton are both co-founders of ApconiX. Kimberly Rockley of ApconiX has a background in cell-based models and joined ApconiX to develop *in vitro* assays for early detection of seizure liability. They discussed novel alternative methods and the impact of the FDA Modernisation Act 2.0 in relation to seizure liability as well as talking about the importance of evaluating seizure liability, how new research supports the refinement and replacement of the use of animals in safety testing, and how these new assays could save time and money in drug discovery plus help clarify results in drug development were also discussed.

Roberts outlined the FDA Modernisation Act 2.0: "It was signed into law in December 2022, and essentially shakes up the Federal Food, Drug, and Cosmetics Act of 1938, which required animal testing for every new drug development protocol." "The original act mandated that all drugs must be tested on animals before human clinical trials. This law was passed in response to the marketing of Elixir Sulfanilamide, a poisonous drug that caused over 100 deaths!"

Roberts said it made perfect sense in the 1930s as animal testing was the only non-human method of testing drug safety before clinical trials, however, science has come a long way since then.

"The federal obligation stipulating that drug testing in animals must be performed has now been eliminated, providing an important gateway for the continued refinement of the use of animal testing in drug discovery and development," she commented.

Alternative methods such as cell-based assays, organ chips, microphysiological systems and computer modelling are used in pharmaceutical research and have been for many years.

"This is a significant step in the right direction and will hopefully encourage project teams to consider using NAMs as an integral part of their drug discovery programmes," said Roberts.

"Originally NAMs were non-animal methods. However as computational methods have become more commonplace, it now stands for new approach methodologies or novel alternative methods."

NAMs encompass approaches that aim to refine in vivo methods or improve in vitro testing. This includes 3D tissue culture models and the use of computational methods, such

as machine learning. There is increasing interest in NAMs to improve predictivity of human safety risks, including detection of seizure liability.

She also clarified what is meant by seizure: A sudden, uncontrolled burst of electrical activity in the brain. It can cause changes in behaviour, movements, feelings and levels of consciousness.

"A balance between inhibitory neurotransmission and neuronal excitation is critical for normal brain function. At the simplest level, seizures occur when this balance is disrupted, resulting in increased or decreased activity," Roberts added.

Seizures are an important issue in drug discovery and development; they are life-threatening and should be avoided. "The incidence of seizure can negatively impact a drug discovery project," explained Roberts. "For example, the occurrence of seizures within clinical trials can put the candidate drug on clinical hold, and within preclinical development the detection of any irreversible and unmonitorable adverse effect – including seizures – affects safety margins. This often leads to compounds becoming risky investments and no longer being viable. As drug development is a long and costly process, this is a waste of time, money and resources."

Testing seizure liability

Currently animal models are used to test seizure liability. Morton commented: "Unusual movements noted in in-life studies indicative of CNS activity would usually trigger a follow-up electroencephalogram (EEG) study to confirm seizure-like activity. However, this requires more animals and even then, CNS-related signs may be overlooked because they can be sporadic and subtle."

"All of the methods have similar limitations relating to low throughput, cost, use of animals and potentially problematic translatability to humans."

Considering the FDA Modernisation Act, he said, it is timely to add new approaches to the seizure screening cascade. "It is well known that there are differences between rodent and human brains. A shift towards human-based models is a logical step in the right direction."

Morton outlined how NAMs can be incorporated into seizure liability and that advances in stem cell and cell culture biology have opened new research areas in many disciplines. He also explained how ApconiX became involved in NAMs for seizure liability.

"Back in 2017 we were discussing the impact of seizure and had the idea of screening for seizure in the same way as we do for cardiac liability. We organised a workshop at the Society of Toxicology SOT Annual meeting in 2019 and discussed it with experts. It's fair to say some were in favour and others were not but we were sure we were onto something."

"We initiated a conversation with experts to create a long list of ion channels and also a long list of compounds that could be used in testing and we published the output of this in 2021."

ApconiX created a shortlist of around 15 ion channels and pro-seizurogenic compounds. "We also brought the microelectrode array (MEA) technique into the lab to look at the electrical behaviour of human neurones in culture. A few years later, it is all working beautifully, and we are delighted!" said Morton.

How NAMs are being used

Rockley explained how NAMs are already used: "Within cardiac safety testing hiPSC-cardiomyocytes are now routinely used for early identification of cardiac liabilities in drug discovery. This shift occurred following implementation of the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative in 2013 and extensive testing of hiPSC-cardiomyocytes with known proarrhythmic drugs."

"The CiPA initiative aims to engineer an assay to assess the proarrhythmic potential of new drugs with improved specificity compared to current methods. CiPA focusses on the use of emerging new technologies and incorporates ventricular ion channel screening, in silico methods and hiPSC-cardiomyocyte analyses to form an integrated assessment of proarrhythmic risk."

"This broader approach means more potential safety risks are identified, saving time, money, and resources, and ultimately leads to safer medicines going forward to the clinic."

The new seizure assay mirrors the CiPA initiative and Rockley explained how this is so. She also shared the challenges ApconiX encountered along the way.

"With the development of the ion channel panel, we occasionally faced challenges making the recombinant cell lines. It can be a long process, but we expected that to be the case. Ion channels can be difficult to work with, so once the cell lines were created, we had to optimise the assays – for example some ion channels prefer additional reagents in their buffers, or slightly altered voltage protocols."

Now that the optimisation is complete ApconiX has launched these assays commercially and is routinely running these for clients, providing very beneficial data.

Rockley also shared the best time to carry out these assays: "Either early in lead generation/optimisation or later on following GLP toxicology studies. The timing of these assessments will be project specific," she said.

Morton explained that since launching these assays, ApconiX has had a lot of interest and clients are already using these assays to resolve issues and help decision making. He then outlined how these panels are being used.

Rockley added: "The possibilities of this model don't end at seizure detection. We plan to further characterise the model for a liability that is the direct opposite of seizure – sedation. We have demonstrated that we can recreate sedation in hiPSC-neuronal cells with GABA agonists such as muscimol, and Indiplon. Indiplon is a marketed sleeping aid of the benzodiazepine class. As expected, Indiplon reduced neuronal activity, which was reversed with application of flumazenil, a compound that is used clinically to reverse benzodiazepine overdose. Outside of drug safety, we also plan to adapt our model to anti-epileptic drug discovery."

ApconiX will continue to develop novel approaches to streamline drug safety testing, reduce reliance on animal models, and ultimately develop safer medicines.

The full episode can be found at www.ddw-online.com

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