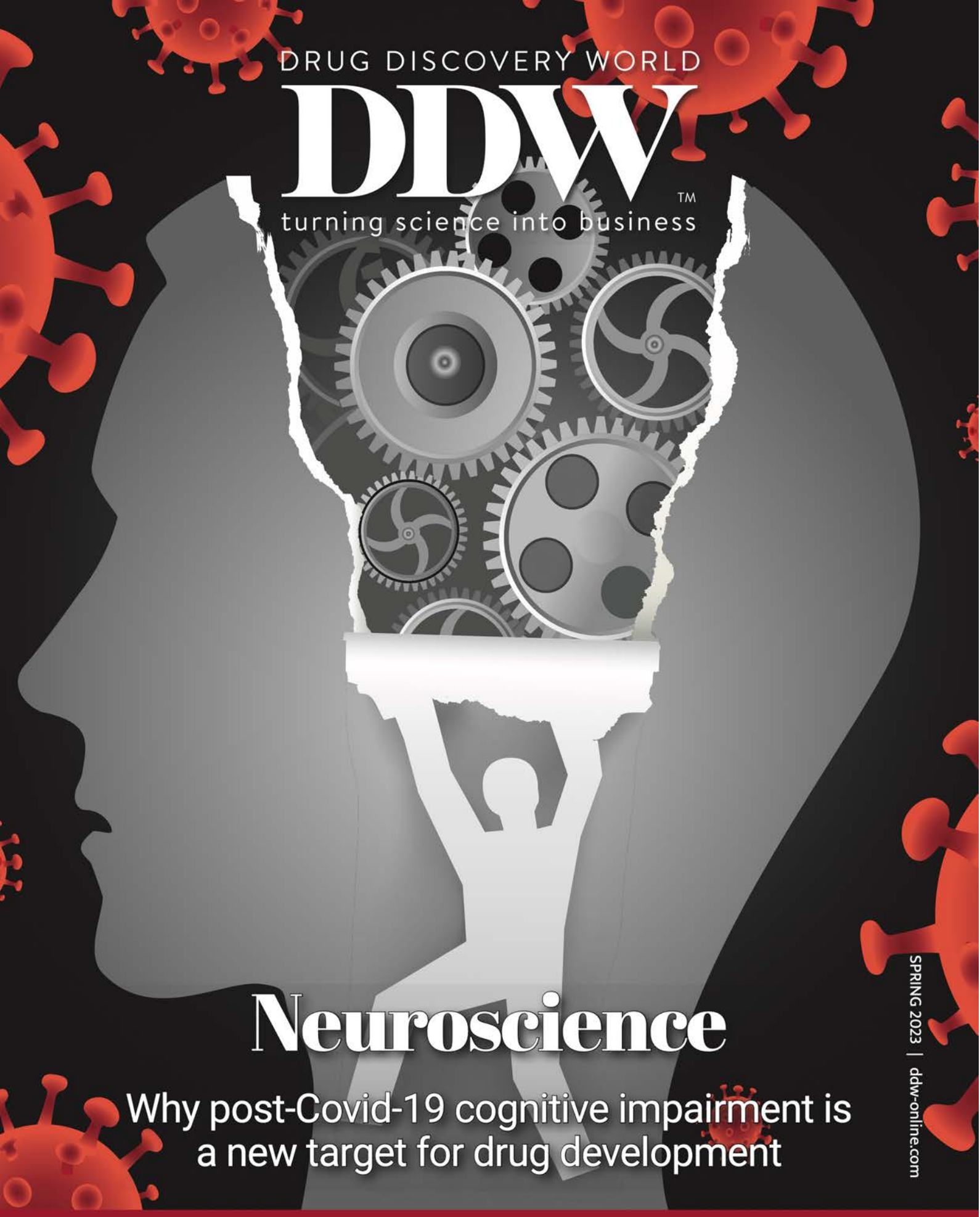
DRUG DISCOVERY WORLD
DDW™
turning science into business



# Neuroscience

## Why post-Covid-19 cognitive impairment is a new target for drug development

SPRING 2023 | ddw-online.com

# The benefits of early ion channel screening

A recent DDW Sitting Down With podcast covered The Benefits of Early Ion Channel Screening. **Lu Rahman** selects some of the highlights of this chat with **Dr Michael Morton**, Director and Co-founder, ApconiX and **Dr Kimberly Rockley**, ApconiX.

## The background

Dr Michael Morton, Director and Co-founder, ApconiX, and Dr Kimberly Rockley of ApconiX discuss The Benefits of Early Ion Channel Screening. The podcast covers the hERG ion channel and its importance in cardiac safety screening in drug discovery.

Morton and Rockley outline the options available, the advantages of these approaches and how the results of hERG should and could be used to inform the drug discovery pathway.

The ApconiX lab is involved in drug safety testing of client compounds for potential effects on ion channels. Ion channels are proteins that regulate electrical activity in the body and have particular importance in the heart and the brain.

## Testing for ion channel safety

There is a best time for compounds to be tested for ion channel safety and Morton explains this: "Looking initially from a hERG perspective, GLP hERG testing is a regulatory requirement for all new potential medicines, before they can be administered to humans. This is of course a terrible time to get bad news when it is too late to modify compound chemistry and you've already invested considerable amounts of money in a raft of preclinical studies...The best time is when you still have the option early in drug discovery to modify the chemistry of the compound and remove any liability or side effect."

He goes on to outline the two prominent approaches to hERG screening. "The first is a binding assay that simply demonstrates whether a compound will bind to the hERG ion channel protein. The other technique is a functional assay measured by electrophysiology. This is a much newer technique, developed initially as a manual patch clamp and won the Nobel Prize in physiology and medicine for Erwin Neher and Bert Sakmann in 1991."

Morton explains that electrophysiology directly measures the effect of the compound at hERG and that binding gives no measure of effect at hERG. "Functional assays must be carried out on any compound going forward in drug discovery and development," he adds.

ApconiX offers a functional assay as it gives information about how the ion channel behaves in the presence of the compound. "The effect a compound has at hERG whether it's activated or blocked is very important and this very different physiological effect needs to be understood," says Morton.

## Recent improvements

Interestingly, Morton outlines the improvements that have been made in recent years to make functional testing more attractive in early drug

> ApconiX offers functional assay as it gives information about how the ion channel functions in the presence of the compound.

discovery. He notes that while manual patch clamp is probably still considered to be the gold standard, the data quality of automated patch clamp is as good as manual patch clamp now and the experiments that can be carried out on an automated patch clamp are also as varied. However, Morton says that the biggest stride forward is throughput: "On a good day manual patch clamp can test 10 cells whereas a high throughput automated patch clamp can do almost 400 an hour."

Where ApconiX clients are concerned, these improvements are significant. "Functional testing provides required data straight away," says Morton. "Automation and other improvements in our lab have enabled turnaround time to be reduced to less than four days in most cases, which would compare very favourably with binding assays. The cost of functional assays is no longer inhibitory for screening compounds early and is very small relative to the cost of taking a compound through later testing and clinical trials. Having all the information presented early does allow for quicker decision making."

## Presenting and interpreting hERG results

"Any biological activity is represented as a potency," says Morton. In hERG, that refers to a blocker which lends itself to a measure of potency known as the IC50, the concentration of the compound that causes 50% inhibition. At ApconiX every data point is returned to the client, and the data is presented numerically as an IC50 as well as graphically. The company also has expert electrophysiologists in the lab who are always available to discuss and interpret results and provide the understanding clients need, particularly when comparing a series of compounds.

Morton explains that any activity at hERG could be potentially linked to a fatal heart attack but what really matters is the safety margin, that is "the gap between the concentration of a drug that might cause an effect at hERG and the concentration of the drug that will treat the condition in humans." He goes on to highlight an example, what can be done to improve uncertainty with a hERG result, and the importance of other cardiac ion channels - the cardiac sodium channel and cardiac calcium channel.

## The CiPA initiative

In the podcast Morton outlines what the CiPA initiative is and when it should be used. "For some of our clients testing to CiPA has been very beneficial and allowed the compound to continue through the drug development pathway," he states.

## ApconiX research

Dr Kimberly Rockley provides insight into the ion channel research ApconiX is now conducting in the field of seizure liability. She explains that on the league table of organs that cause the most drug discovery failures, heart is number one and second is the brain and the central nervous system.

"Looking into the various side effects in the CNS some are very complex such as addiction and suicidal ideation both involving psychology. A more tractable side effect that is ion channel related is seizure," she says.

Rockley outlines how ApconiX has researched detecting seizure liability in client compounds. This is based on two concepts. The first, like CiPA, is a panel of 15 ion channels relevant to seizure. Some of these ion channels are important in brain physiology, mutation of others cause genetic seizure. "This panel could be used in early drug discovery to screen potential side effects in the brain. If seizure has already been detected the panel could be used to rule out some potential causes," she adds.

"The second concept involves taking human stem cell derived cells and using microelectrode array we have demonstrated seizure like activity. We've published several posters at conferences in the past year and have recently launched this service for our clients."

Rockley also outlines future possible areas of research for the ApconiX. This includes sedation as a drug induced side effect. The company is also interested in improving the sustainability of its lab and reducing the amount of animal products – Rockley discusses this in detail.

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

APCONIX

a better decision


# Rapid, High Quality Ion Channel Profiling, Interpreted by Experts

**Whether you need to explore cardiac ion channel activity for safety, or are interested in ion channels as drug targets, ApconiX can help with our dedicated electrophysiology expertise, customer focused flexibility and rapid turnaround times.**

## Our Services Include:

- Ion channel screening for hERG, cardiac and CNS liabilities, and all elements of the CiPA paradigm including the ion channel panel, in silico action potential modelling, and investigation in hiPSC-cardiomyocytes
- Testing on the latest generation automated electrophysiology platforms (QPatch II and Patchliner), with the capacity for large numbers of compounds. Manual patch-clamp also available
- Our nonclinical safety experts are uniquely positioned to interpret your data in the context of your drug discovery programme

**Contact the ApconiX team for more details**

hello@apconix.com | www.apconix.com

Mereside | Alderley Park | Alderley Edge | Cheshire SK10 4TG | UK