What is your background as a scientist, and what led you into the field of psychiatric drug discovery and development?

I have an undergraduate degree in psychology, training in behaviour genetics and a doctorate in pharmacology, providing an ideal platform for a career as a psychopharmacologist. I have also had the great blessing of excellent behavioural pharmacology training at the National Institutes of Health (NIH) and wonderful collaborative colleagues at the Maryland Psychiatric Research Center in the University of Maryland, Baltimore, who have introduced me to clinical psychiatric research in cognitive processing, mood disorders and schizophrenia. Two key collaborators for Pattern Array are Professor Ilan Golani and Dr Neri Kafkafi. In fact, Dr Kafkafi was a true driving force behind the current project.

Can you outline what is meant by Pattern Array – the technique that you have developed to mine data in vivo?

Pattern Array is conceptually similar to a microarray used in large-scale gene expression analysis. However, instead of a quantifying a large number of mRNA expression levels (20,000-50,000) and mining them for characteristics of interest, we quantify a large number of discrete behavioural patterns (approximately 70,000) and mine them for characteristics of interest. Much like microarrays, it is an unbiased technique designed to discover targets – in this instance behaviour patterns – that are highly predictive of a treatment effect. We can then use the response of these ‘targets’ to novel compounds to predict their potential therapeutic value. The advantage of Pattern Array for psychiatric drug discovery is that the prediction is based upon the system’s psychopharmacological effect of the drug in vivo, rather than an in vitro genomics response.

Which different groups of drugs have you tested so far with this technique, and what have been your results?

Thus far we have tested over 54 drugs across six clinically relevant drug classes – antipsychotic, antidepressant, opioid, psychotomimetic, psychomotor stimulant and α-adrenergic – and have uncovered two principle findings. Firstly, we have identified a single behaviour pattern that is useful for psychoactive threshold dose-determination across all drug classes. Secondly, in a series of experiments designed to classify ‘unknown’ drugs, we successfully classified nine out of 11 compounds. Interestingly, even ‘misclassifications’ matched known alternative therapeutic indications, illustrating drug ‘repurposing’ potential. In a single behavioural assay we are capable of threshold dose determination and therapeutic classification.

The emotional and cognitive faculties of humans are undoubtedly far more advanced than those of mice; how can using mouse models give an accurate idea of the effects of psychiatric drugs?

Preclinical models can attempt to simulate the psychiatric effect of a drug or be predictive of its outcome – the distinction between simulation and prediction is important. Simulation models are designed to understand aetiology and mechanism, while predictive models are designed to identify compounds with clinical efficacy based on proven therapeutics. Our model predicts psychoactive properties of a drug that are predictive of therapeutic utility. We attempt to improve the fidelity of this process by using complex, highly characterised and ethologically relevant behaviour patterns as a readout for psychoactive effect.

How would you like to see this project developing in the future?

First and foremost, I’d really like to see Pattern Array used on a larger scale in order to discover drugs that truly alleviate suffering – that is the ultimate goal. The advantage of this strategy is that the model can be systematically updated to improve its predictive power and add therapeutic classes and subclasses with each additional diversification of the database. Another area of interest is to mine patterns that are highly reflective of acute and chronic stress exposure. Since stress is an aetiological factor across diagnostic categories – including post-traumatic stress disorder, depression and schizophrenia – identifying patterns highly associated with the consequences of acute or chronic stress may provide an opportunity to screen compounds for therapeutic intervention. In this scenario, the test drug would return the disrupted constellation of patterns to normal.

The main advantage of Pattern Array is that it has been designed to mine data in vivo, tapping into the complexity of the brain’s neuropharmacological response to drugs

A psychiatric systems approach

Using a systems pharmacological approach and innovative data mining techniques, researchers from the Maryland Psychiatric Research Center at the University of Maryland, Baltimore, are laying the groundwork for progression in psychiatric drug discovery

DESPITE SIGNIFICANT FINANCIAL investment, psychiatric drug discovery is a daunting process that has largely failed to provide new medications in recent years. In contrast to other types of illness, there is a lack of clear neuropathology and biomarkers in psychiatry, which hampers drug development and prevents the advancement of fully efficacious treatments. Unfortunately, overreliance on a handful of pharmacological mechanisms – along with a target-centric drug discovery approach – is causing psychiatric drug discovery to lag behind other areas of drug development. These issues stem from the highly complex nature of emotional and cognitive disorders, which cannot simply be attributed to a single casual molecular abnormality.

Clearly, there is a need for a more efficient system for psychiatric drug discovery and development – and one researcher who is making headway in this area is Professor Greg Elmer from Maryland Psychiatric Research Center at the University of Maryland, Baltimore. With a background in psychology, pharmacology and genetics – and an impressive track record of NIH-funded research – Elmer has built up expertise around the concepts of reward and anhedonia in mental illness and addiction. In his research, he combines a behavioural neuroscience approach with novel discovery strategies: “Historically, we approached each diagnostic domain with labour-intensive animal models using a single target-centric approach; yet this approach stifles the discovery of drugs that sit outside classic pharmacological domains,” he points out. “There is a growing realisation that numerous
Examining exploratory behaviour

Elmer and his team chose to study the exploratory behaviour of mice in order to achieve a fuller understanding of the neuropharmacological properties of novel compounds. There are many advantages to studying this type of behaviour:

- Detailed ethological, pharmacological and behaviour genetics studies have demonstrated that exploratory behaviour is highly complex – yet despite this, it can be mathematically described. The subject’s movements are automatically measured as path coordinates, lending themselves to mathematical description.
- The behaviour is complex enough to effectively capture the psychoactive properties of a drug.
- These studies are simple to conduct yet each single one hour unconditioned session offers approximately 70,000-100,000 relevant data points per subject.
- Exploratory behaviour is in large part genetically determined and replicable, meaning that it is likely to reflect ‘hard-wired’ brain mechanisms that will improve the model’s fidelity.

Pattern Array characterises every path coordinate of the animal’s exploratory behaviour along multiple dimensions such as dynamic changes in speed, direction and path curvature and complexity. The insert shows an example of computing the curvature of the path in one data point B of a progression segment. The process is repeated in all data points and in several scales. The frequency of each of the 70,000+ patterns is determined for each drug class. A classification model is ‘trained’ by mining for patterns that best predict each psychopharmacological class. The isolated patterns are then used to predict the potential therapeutic utility of novel compounds or repurpose existing compounds for novel use.

psychiatric constructs – including anxiety and anhedonia – cross diagnostic boundaries and that a ‘systems’ pharmacology approach may be necessary to address the complexity inherent in psychopathology.

**IN VIVO MINING**

It was recognition of the importance of a systems pharmacological approach – coupled with an appreciation of the power of data mining for discovery – that led Elmer and his colleague Dr Neri Kafkafi to develop an innovative behavioural assay to discover new drug targets. Dubbed ‘Pattern Array’, their technique uses a mouse model to reveal drug effects. Importantly, the technique is able to detect psychoactive properties and predict the therapeutic effect of a test drug among multiple classes to a high degree of accuracy. The main advantage of Pattern Array is that it has been designed to mine data in vivo, tapping into the sheer complexity of the brain’s neuropharmacological response to drugs.

Pattern Array works by mining the movement patterns of mice from exploratory behaviour, capturing and isolating those movements that best capture an effect of a genetic or psychopharmacological manipulation: “Each subject receives a drug or vehicle injection prior to being placed in a large arena – a 2.5 metre diameter circle,” explains Elmer. “The path of the subject through the arena is tracked using a camera located above the arena – no behavioural training is necessary.” Following this, the x and y coordinates of the mouse as a function of time are classified into behavioural patterns (>70,000) that consist of a range of complex, ethologically relevant ‘attributes’, such as path curvature or pattern of acceleration. Finally, the frequency of each of the large numbers is quantified – and the relative frequency of these patterns is analysed by the researchers.

**FUTURE GOALS**

Ultimately, the hope is that Pattern Array will be used on a larger scale, leading to the identification of therapeutics that could reduce human suffering – and it is in view of this that Elmer has set himself and his team three goals. The first goal is to reduce the destructive side effects of current psychiatric drugs on mood, motivation and cognition, leading to an improved quality of life. The second is to ensure that the development of new therapeutics is targeted at alleviating the symptom arms that are known to have a destructive impact on mood and cognition. Finally, if schizophrenia is found to be a neurodevelopmental disorder, the third goal is to develop drugs that reshape circuitry: “The first two aims should be obtainable in the near future,” Elmer asserts. “The third is more challenging, requiring long-term investment in systems biology and cognition.”