Novel brain-mapping technology could revolutionise pre-clinical drug screening

Dr Pavel Osten, MD, PhD, is co-founder of Certerra Inc., a company whose Pharmacomap™ technology uses a novel method called iDISCO to generate whole-brain maps of drug activation. With this approach, Certerra provides its customers, small and large pharmaceutical companies, with a comprehensive screening tool to help identify which new potential drugs are the best candidates for clinical trials, greatly improving on existing preclinical methods and accelerating the process of drug development.

Q&A

What motivated you to target CNS drug assessment?

There have been very few new psychiatric medications brought to the market in recent decades; most of the medications that we have, have come from serendipitous discoveries made a long time ago, in the fifties and sixties of the last century. In my view, this lack of progress is largely due to a lack of preclinical methods that could be used to quantitatively and rapidly assay drug-evoked activation at the level of the whole animal brain. Having worked on questions of basic neuroscience research in my earlier carrier, I was motivated to try to improve existing technologies and set up the first quantitative and high-throughput method for preclinical drug screening.

What came first, your whole-brain screening methods or the desire to hone the process of pre-clinical drug testing?

The desire came first. I was thinking about how to image the whole brain of a mouse or a rat for screening drug-evoked responses. At that time, two-photon microscopy, that we used to establish our first pipeline based on STP tomography, was the most advanced high-resolution imaging method. Since then, a method called light-sheet fluorescence microscopy (LSFM), has become a faster and cheaper alternative and we have moved quickly to adapt this method, together with the whole-brain immunostaining protocol iDISCO, into our drug-screening pipeline.

How similar are neurological disorders in mice and humans?

They are certainly not similar. We also don't think that there really can be a good animal model of psychiatric medications and the use of such 'models' (either behavioural or pharmacological) in the past has not led to any new drug developments. What we believe is that the rodent brain has a sufficient computational capacity (it's a big enough computer) to 'distinguish' responses evoked by different drugs, both between classes (for example, antidepressants from antipsychotics) and, within classes, between different generations of antipsychotics (for example, SSRI's from MAOI's from TCA's). We have, in fact, shown that this is true by screening all 61 medications commonly used in psychiatry today, and generating a specific Pharmacomap™ for each drug. Having done this, we can now use this library to test new compounds and identify:

1) Whether they have any activity in the brain at all (for example, many drugs do not cross the blood brain barrier and thus fail *in vivo* even though they had the desired activity in *in vitro* assays).
2) Whether this activity resembles the activity of the known drugs.
3) Whether the activity may have possible side-effects.

The side-effect question we can address based on structure–function homologies between the rodent and the human brain, since most side-effects involve brain regions that regulate autonomic and endocrine functions and those are well shared between rodents and humans.

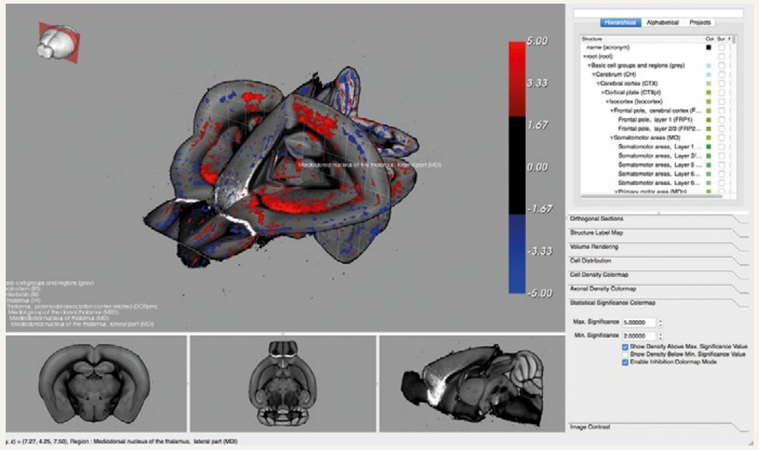
You say you've had a positive response from the pharmaceutical industry – has anyone been able to suggest improvements?

With our first pipeline based on STP tomography, our throughput was much slower and therefore the cost per test was quite high (about $25,000 per one compound). We were also limited to only one gene – c-fos – that we could use as a marker of neuronal activity. Thus the main suggestions/requests from our customers have been for a lower price, larger volume and a broader assay. We are now able to offer all those improvements.

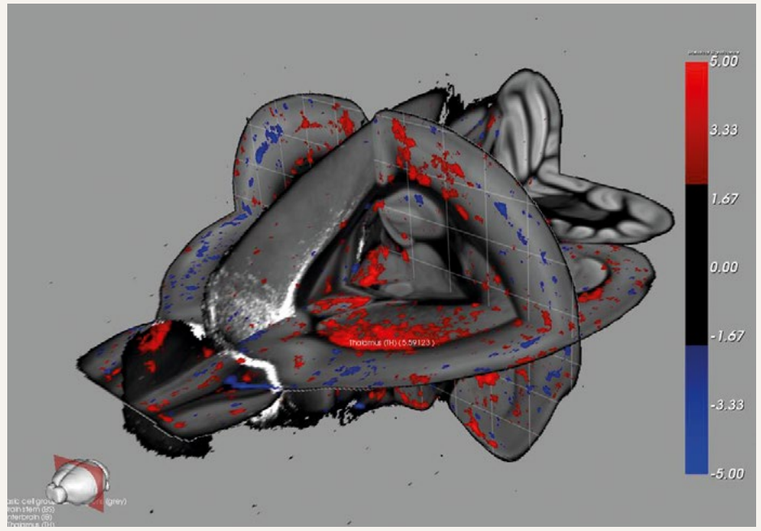
Certerra Inc. has ambitions to expand its horizons beyond CNS drugs – how widely do you think this method could be applied?

We are focused currently on CNS and we want to broaden our service to be able to test drugs, not only for psychiatric disorders, but also for neurodegenerative disorders, including Alzheimer's and Parkinson's. In the non-CNS market, we envision that our assay could help with assessing whether medications targeting peripheral organs may have unwanted CNS-based side-effects. We may think about developing specific assays for other disorders in the future, including cancer, but that is not our immediate focus.

Certerra Inc. was founded in 2011 by Dr Pavel Osten, MD, PhD, Associate Professor of Neuroscience at Cold Spring Harbor Laboratory (CSHL) and Sebastian Seung, PhD, Professor of Neuroscience at Princeton. It is a biotechnology company that has developed a novel type of assessment for central nervous system (CNS) drugs. This approach uses high-resolution brain imaging and sophisticated statistical analysis to map the extent of brain activation induced by potential new drugs in animals. The resulting whole-brain cellular map of pharmacological activation is termed a 'Pharmacomap™'. This method is the first among its competitors to successfully measure the effects of a drug at single neurone resolution across the whole brain, representing a major advance in the preclinical CNS drug discovery market.



Three-dimensional overview of the brain activation pattern – the Pharmacomap™ – evoked by the antipsychotic drug Risperidone, showing robust activation (red color) in several brain areas, including the caudoputamen and cortex.



Working with Otsuka Pharmaceuticals, Certerra Inc. provided a highly valuable preclinical assessment of a new treatment that is now available for schizophrenia and depression

WHY IS THE TECHNOLOGY SO NOVEL AND NECESSARY?

At present, almost 90% of CNS drug trials fail at the clinical testing stage, a key cause for the diminishing returns in the pharmaceutical industry. There is, therefore, a great need to be able to assess the merit of potential pharmaceuticals at the pre-clinical stage. Certerra Inc.'s method greatly assists with this goal.

It is particularly important to test the efficacy of new molecular entities (potential drugs) *in vivo*, i.e. in live animals. This is because CNS drugs work on the most complex part of the body, the brain. Testing them *in vitro* in a petri dish simply cannot replicate the complexity of the living brain.

Clinical trials cost vast sums of money, can be extremely risky and take a lot of time. Certerra Inc.'s technology presents a way of spotting drugs that are more likely to fail, thus avoiding the associated costs in clinical trials. Pharmaceutical companies benefit because they can then invest more time and resources into the research and development of drugs with a higher likelihood of success. This is very important because it will help accelerate the process of making treatments available for neuropsychiatric illnesses, greatly benefitting patients.

CURRENT INDUSTRY UNDERSTANDING

There has been considerable work to improve pre-clinical drug screening, but most methods that aim to improve the predictability of drug trials focus on *in vitro* screening. These assays are used to optimise the drug design process to target specific molecules or properties. However, these methods fail to illuminate how the drug works in complex organ systems.

Other assays quantify changes in rodent behaviour after treatment with a drug. However, animal behaviour is a simplistic and incomplete model of human behaviour, making it difficult to extrapolate animal (rodent) behaviour up to the level of complexity required to determine the potential drug effects in humans.

Multi-modal imaging alternatives, such as PET and MRI, can be performed. However, these operate at a low resolution (unable to resolve brain activity at the cellular level), and must be performed on anaesthetised animals. These factors therefore limit the interpretation of the effects of the substance on the brain. Certerra Inc.'s Pharmacomap™ technology, in contrast, achieves analysis of drug-evoked, whole-brain activation in behaving animals, at single cell resolution and high throughput.

Certerra Inc. has moved to a larger facility at the Broad Hollow Bioscience Park (NY) this year and is gearing up to be able to screen thousands of novel compounds per year. This means that Certerra Inc.'s research could greatly improve the predictability of drug effects before clinical testing.

THE SCIENCE BEHIND IT

The central hypothesis that underlies Certerra Inc.'s approach is that 'the effects a drug has on the brain are largely determined by which neurones it activates'. This is rooted in the essential neuroscientific understanding of the way neurones form complex networks and how their activity drives mental activity. Dr Osten and Certerra Inc. believe that this is the key reason that so many CNS drugs fail at the clinical testing stage – the absence of a method to determine brain-wide drug activation of specific neurones at sufficiently high resolution to make it useful.

HOW IT WORKS

The core of Certerra Inc.'s approach is their use of two recently-developed technologies: iDISCO whole-brain immunostaining in combination with light sheet fluorescence microscopy, which can provide automated imaging of whole organs at cellular resolution. Specifically, the iDISCO maps the drug-evoked induction of molecular markers for neural activation called immediate early genes, such as c-fos or Arc. This can be used to create unbiased, whole-brain maps of neural activity when stimulated by particular drugs - Pharmacomaps™.

The whole-brain activity map is then statistically analysed to identify the regions where activity was significantly altered by the drug. Correlations identified between drug effects and structural features in the brain maps can be used to target candidate drugs for further development.

The aim of the (successfully completed) first phase of development at Certerra Inc. was to be able to discern all common psychiatric medications used in the clinics, based on their Pharmacomaps™, essentially generating a fingerprint for each medication.

Having demonstrated that the technology can assesses the extent of drug-evoked activation in the mouse brain, the company now aims to use this data to improve the ability of the technology to predict the efficacy of substances in the human brain.

To do this, Certerra Inc. have created the first animal-to-human (A2H) database of Pharmacomaps™, linking pharmacomaps of 61 psychiatric medications to their clinical effects and side effects. This can be statistically analysed to determine the extent to which the database can be used to predict human outcomes.

Certerra Inc.'s work over the last three years with Otsuka Pharmaceuticals represents a successful application of the Pharmacomap™ approach to preclinical drug screening. In this project, Certerra Inc. was able to provide a highly valuable preclinical assessment of a novel compound, called brexpiprazole that was successfully introduced as a new treatment for schizophrenia and depression in autumn, 2015.

NEXT STEPS

The positive reception from industry veterans suggests that Osten and Seung's technology could go far. The third phase of development will involve Certerra Inc. contracting their services internationally and industry-wide.

In addition to psychiatric disorders, Certerra Inc.'s technology can also be used to study neurodegenerative disorders, such as Alzheimer's and Parkinson's.

Certerra Inc. aims for their technology to become an indispensable part of the drug development pathway, honing the process and speeding up the delivery of new drugs. Given the speed with which the company has grown already, their method may very well become ubiquitous.

Detail

RESEARCH OBJECTIVES

Dr Pavel Osten and the team at Certerra Inc. provide, through their unique Pharmacomap™ technology, an opportunity to assess the likely success of CNS drugs at the preclinical stage.

COLLABORATORS

Sebastian Seung, Princeton

BIO

Dr Pavel Osten obtained an MD from Charles University in Prague and a PhD from State University of New York, Brooklyn. He trained with Dr Ed Ziff at New York University and Dr Peter Seeburg at the Max Planck Institute in Heidelberg. At Cold Spring Harbor Laboratory (CSHL), Dr Osten has led a team of scientists in establishing STP tomography as a state-of-the-art method for standardised, high-throughput and unbiased screening of neuronal activation in the whole mouse brain at cellular resolution. He and a colleague, Sebastian Seung (Princeton), started Certerra Inc. in 2011, in order to commercialise this STP technology for the screening of drugs targeting the central nervous system. Dr Osten has authored and co-authored over 50 papers, reviews, and book chapters, and was the recipient of the McKnight Technological Innovations Award in 2009.

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