FUNCTIONAL MAGNETIC RESONANCE IMAGING WITHIN R&D

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Prof. Pradeep Nathan is Vice President and Head, CNS Clinical Development and Experimental Medicine at Sosei Heptares, a Japanese listed biotech with its core R&D activities based in Cambridge, United Kingdom. He is also Professor of Neuroscience at Monash University and an affiliated lecturer at the University of Cambridge. Pradeep trained as a pharmacologist and cognitive neuroscientist. His research focuses on the understanding of the neural substrates of cognition and psychiatric and neurological endophenotypes using behavioural and imaging methods and applying these approaches to drug discovery through development of molecular and functional biomarkers which might aid in the development of more refined and targeted treatment approaches for cognitive and emotional dysfunction in psychiatric and neurological disorders. Pradeep has over 10 years of industry experience in the translational and clinical development of CNS compounds while working at GSK, UCB Pharma and Heptares Therapeutics. He has also published over 200 peer reviewed papers which have been cited over 10,000 times. His research has been recognised by a number of awards including the Australian tall poppy science award, the British Association of Psychopharmacology, clinical research award and the prestigious fellowship of the American College of Neuropsychopharmacology.

What are the main advantages of using functional imaging and drug development?

The main advantage is knowing which area in the brain the drug is having an effect and to determine if the drug is acting on brain circuits of interest to the drug (commonly called functional target engagement). The second advantage is that functional imaging could help compare pharmacodynamic effects of the drug in development with comparator drugs or standard of care to show that the drug has stronger effects. Finally, functional imaging may help determine if brain responses to the drug after a single dose or a few days of dosing could predict long term efficacy. This is however very challenging to show but if this can be demonstrated reliably, shorter and less expensive studies could be done in Phase 2 to make go/no-go decisions.

Are there different technologies, other than functional imaging? Is functional imaging different from functional magnetic resonance imaging?

Functional magnetic resonance imaging is sometimes called functional imaging. It is called "functional" because it measures brain activity (via changes in blood flow) usually when a person is doing a task (i.e. memory test or looking at pictures). As the person is doing the task, areas in the brain that are required to do the task become activated and there is increased blood flow to these areas which are detected with functional magnetic resonance imaging.

Are there any key challenges that you face?

One key challenge is knowing if the changes in brain activation you see are real (i.e. signal) and not noise. Knowing what is a real signal vs random noise can come down to how good your methods are and how big the study is. Larger studies that are statistically powered and methodologically sound would increase signal relative to noise. The second challenge is making sure that the task used in functional imaging studies (for example the memory test) shows good reproducibility in brain activation from week to week. A good task with high test-rest reliability is ideal for imaging studies.

Are there any key technological innovations that have helped with this?

Higher resolution scanners have been developed. MRI scanners have improved over the years from 1.5T to 7T and this has improved the resolution (i.e. you are able to image smaller areas more accurately). This will allow us to find small changes in brain activity in brain areas including areas that have relatively small (i.e. subregions of the amygdala for example). Technological advances have also been made in data acquisition and data analysis which has helped improve the quality of the data.

What are the next steps for your company in this work?

Sosei Heptares is a rapidly growing biopharmaceutical company. Our strategy is to develop new medicines by ourselves as well as in partnership with larger pharmaceutical companies. Our strength and expertise is our structure based drug discovery platform which uses an innovative way to stabilize drug receptor/targets (i.e. G-protein coupled receptors), image their structure and then make drugs that perfectly bind to the receptor in the way we want. This approach has attracted interest from a number of top pharmaceutical companies and we are collaborating with many of them to develop new drugs acting on novel receptors.

What are the top three takeaways from your presentation?

Functional imaging can be used quite effectively early in clinical development and be used in decision making. It can help determine if the drug modulates target systems in the brain. It could potentially be useful for comparing one drug to another to determine if the drug in development is superior to the current standard of care treatment. Finally, it may be used to potentially predict treatment response (i.e. work out which patient responds better to drug). However more work is needed to validate functional imaging as a biomarker in drug development, particularly around improving the reliability of the measurements and improving data analysis methods.

What do you hope to gain from attending this kind of conference?

The scientific program had some very good presentations on topics that were relevant to my area of interest. This made attending the conference worthwhile even though I was an invited speaker for the meeting. I met a number of people doing similar work and this has opened opportunities for collaborations. I thought the networking session useful in this regard.

Were there any specific areas that you are interested in, and would like to see again next year?

I think one or more sessions on digital technologies would have been nice to see given the increasing use of such technologies in clinical trials. It would be nice to see clinical trial data presented on this. I would also like to see more on patient stratification biomarkers in clinical trials for various indications including blood, CSF or brain imaging biomarkers.