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Perspectives on PRISM

The PRISM (Psychiatric Ratings using Intermediate Stratified Markers) project is a major two-phase EU-funded research initiative that, by identifying quantitative biological features common across the diseases, aims to open the possibility of developing targeted treatments irrespective of traditional diagnosis.

The project has the potential to change the way we think about mental illness, but what does it mean to researchers at different career phases? Here ECNP Press Officer **Tom Parkhill (TP)** interviews Mirthe Ronde and Bastien Hengerer, both of whom are working on back-translating PRISM findings to animals.

Mirthe Ronde (MR) is a PhD researcher at the University of Groningen, investigating the neural basis of social dysfunction in mouse models for brain disorders. This is ultimately aimed at contributing to the development of novel therapeutic interventions for major neuropsychiatric disorders.

Bastian Hengerer (BH) has more than 34 years' experience in the pharmaceutical industry. He joined Boehringer Ingelheim in Biberach, Germany, in 2003, heading the preclinical Parkinson's disease research group and now being responsible for scientific partnering in the field of CNS diseases.

TP: Mirthe, can you tell me a little about yourself. How did you get involved in PRISM?

MR: A few years ago I finished my master's in neuroscience, which had included lectures from Martien Kas (amongst others, of course). When I graduated, Martien came to me with an offer for a PhD position, which combined all sorts of interests. This was part of the PRISM project, so I had a very direct route into the consortium. I had already heard about PRISM before, because of Martien's lectures and the information on the website, and I immediately thought it was a perfect fit for me.

BH: In my case it was pretty clear from the beginning that I had to be involved in the project. Boehringer was one of the EFPIA (European Federation of Pharmaceutical Industries and Associations) partners which had been driving the first phase of PRISM. I discussed this with Bernd Sommer, who was my department head at that time, on how could we contribute to PRISM in the pre-clinical part. I had some ideas on how we could back-translate the clinical findings. It was immediately quite clear that I had to be involved. I'm a molecular neurobiologist, I'm not a behaviour person. So, I was a non-behaviourist setting up a new behaviour social arena which did not exist previously; so perhaps it opened up some possibilities which others had not considered. That's how it all started for me.

TP: So you both come from a scientific background, rather than a clinical background?

MR: Certainly I come from a scientific background. I studied biology as a bachelor's degree, going in the direction of biomedical sciences. Then I noticed that I liked neuroscience a lot, so I picked a master's in that field, where I also chose the molecular path. But within that master's

there were multiple possibilities to include other, related fields, so I included a computational element and a behavioural element. My current PhD combines these three types of neuroscience. My background is indeed not so much of a clinical background.

TP: There's often a conflict between what scientists want to do and what clinicians want to do. You are both heavily involved in animal work, back-translational work. Why is this particularly important to the PRISM project?

BH: So why are pharma companies involved in this kind of exercise? We want to understand the biology, to understand what is happening in the patients. The aim is to develop new treatment options, so we have to understand the biology and how we can test our hypotheses; we have to back-translate what has been seen in the clinical part of the project. So here the motivation for Boehringer Ingelheim, or any of the EFPIA partners, is clearly to look for new therapeutic options for the treatment of the symptoms which we are observing here.

TP: So it's very much that you do want to understand the biology, otherwise it's serendipity.

BH: Yes, we are talking about precision psychiatry, really understanding the biology – what is ongoing, what is going wrong with a patient who is showing certain symptoms. Really, the idea is that if we understand the brain circuitry in these patients, then we can back-translate it to animals and study in detail what is happening in this circuit.

TP: So where are we in this process?

MR: I'm working with two colleagues in the University of Groningen on the development of novel methods to be able to back-translate the findings from human studies of the PRISM consortium. These studies have provided us with some interesting findings. They are still promising, but correlative, and of course we want to be able to prove causation to confirm what we think about the neurobiological basis of neuropsychiatric disorders. So far, my colleagues and I have almost finished building a method that helps us back-translate the findings from these clinical studies in animals.

In this method we combine all kinds of measures and as soon as it is up and running, we can use it in further studies aimed at proving causation of the links found in the human studies I talked about. In our group we are focusing on two main findings, which both identified potential neurobiological causes of disease-related social dysfunction. In Germany, my colleagues focus on similar things, with social functioning centred as well, am I correct?

BH: The focus is social functioning, for sure. Our hypothesis is clearly based on the circuit findings from the clinical part, looking at the default mode network (DMN). How can we disturb the default mode network. With modern technologies, our approach is mainly chemo genetics and demyelination of the forceps minor. And then observing, with different tools, what is happening in the animals; how are they behaving, what is happening to connectivity of different areas of the default mode network and trying to see how this fits with the clinical findings.

MR: We are using the same kind of novel techniques which Bastian has just described. I'm focusing on a method that combines EEG technique and behaviour. My colleague Michael van Dijk is using chemo genetics to manipulate other targets found in clinical research.

TP: What are the difficulties you have ran in to in implementing these techniques?

MR: One could argue the translatability of human behaviour into rodent behaviour. Luckily, we focus on social behaviour, which is crucial for all mammalian species – so it is quite a translatable behaviour. Of course, we're not looking at, say, how they use their iPhones, but we can look at how they follow each other, sniff each other and so on. This is social behaviour in the mouse, and it's quite easy to score. There are difficulties, but these can be figured out.
In addition, I am also aware of the differences between a human default mode network and a rodent one. Our default mode network is, as the name suggests, typically active when we are at rest and when we're not focusing on demanding tasks, enabling us to reflect and our minds to wander. These self-referential, mentalising and sometimes empathic processes are highly crucial for healthy social functioning. Rodents show less and different degrees of mentalising and empathy, but they do have a DMN, made up of similar brain areas as we see in humans. And some recent studies have shown that the rodent DMN is also involved in forms of behaviour. So studying the DMN in rodents while back-translating human findings can be difficult, but it is important that we focus on both the differences and the similarities between species.

BH: Yes, these are challenges. I said at the beginning that I'm a molecular biologist, not a behaviour person. So, if we want to backtrack the smartphone analogy to a mouse, we need to observe them without a task, we need to observe each individual animal within the cohort. So if you dye the fur of an animal, can the others really see a difference, see that this animal is somehow different from the others – or can they smell it? We thought of maybe using an RFID tag, which would have been more or less invisible. But there was no technology on the market which would have combined the videotaping and behaviour analysis of more than two mice and combining it with RFID. In PRISM 1 it was really a challenge to set up a methodology for this. We've been working on improving the analysis. It's not all perfect, but now it does work!

TP: If you were on the outside of the project looking in, would you see it as successful? And what needs to be done, not only from a scientific point of view, but also to convince the people in drug companies, in psychiatric bodies, and so on, that what you are doing is going to change the field?

BH: How you measure success in a scientific environment is by publication. We have a few papers out, and we are currently writing three more (including together with the group in Groningen). This is one of the good things about the consortium: we are not competing, we are working together, and we are aware of what the other parts of the consortium are doing.
Overall, the PRISM project is successful. We can confirm and validate a brain circuit identified in the clinical study now within the preclinical study. For us as a pharma partner success would be the identification of a molecular target, but now that we know which neurones are involved, we can look at transcriptomic data – can we identify a specific target in this circuit which we can pharmacologically modulate and thereby modulate the behaviour of the animal?

There are also the dopamine D2 auto receptor studies (performed in Groningen), which have been identified from PRISM 1.

MR: Bastian is right in how we understand success. A good example of working together is the project I'm working on right now with Vasilis Siozos (another PhD student in Martien Kas's lab). We use mice in which the gene for the dopamine autoreceptor 2 (DRD2) is knocked out. This is a gene which is involved in disease-related social behaviour, as was found in previous studies of the PRISM2 consortium. A former colleague of ours, Kevin Ike, showed that these knockout mice had a hypersocial behavioural phenotype; more importantly, they showed different social behaviour when compared to their wild-type controls. Kevin Ike showed this social phenotype on a behavioural level, and we wanted to take it a step further and add a new level, neural activity measures. So we developed a new method to allow us to measure neural activity at the same time as behavioural activity, in other words: we wanted to synchronise both of these useful scientific measures, and hopefully this will teach us something about the neural correlates of this link between a certain gene and social behaviour. Right now we are just starting the analysis; in fact we finished the data collection of this project today. We are happy to work with findings from human studies, from ex-colleagues, and integrate all this novel knowledge in plans for new studies. This is an example of what we can do by working together in this consortium.

TP: I think this is one of the unique elements of PRISM, the ability to work together in such a co-operative way. When does PRISM2 finish?

BH: In May this year. We are currently working on a 'no-cost' extension which will bring us to the end of 2024. We have the existing consortium, which works really well, and we are looking at how we can take it forward; for example, via bilateral collaborations between Boehringer and Groningen, further exploring the co-operations we have developed. But we are also looking at how we might maintain the consortium. It's ongoing.

MR: I'm a big fan of how this consortium works. For me as a young scientist in the consortium, it was good to be involved. You work with people from a whole range of backgrounds – data scientists, clinicians, fundamental scientists. Ideas pop-out from each of these fields, and the breadth of the consortium means that we can address many problems. It's a really nice way to learn how the academic (and business) world can work – to have an idea of what is possible in the future in addition to what I'm doing right now. It's very multi-disciplinary, both from a technical and a social sense,

BH: This social sense is important, being open enough to discuss not only good results, but also the problems and issues. The group co-operates well. I've been involved in several consortia, but this is by far the most productive one, being open, sharing results, and talking them over.

MR: I agree.