EARLY INTERVENTION WITHIN NEUROPSYCHIATRY

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Moritz von Heimendahl trained in physics and did PhD and PostDoc work on neuronal coding in rats, using in vivo electrophysiology. In 2014, he joined the CNS discovery research department of Boehringer Ingelheim as a laboratory head, and has since worked on early drug discovery projects on the treatment of psychiatric symptoms. He has also led, since its inception two years ago, a working group that aims to identify novel targets for treatment of cognitive symptoms by investigating circuit dysfunctions underlying cognitive symptoms and back-translating these into preclinical research.

What is your company's translational approach in neuropsychiatry?

We follow several approaches. One can classify them into two major ideas. One is to say we haven't been particularly successful in pharma, in terms of treating the false syndromes. This may be because they are so heterogeneous that it's hard to identify the underlying neurobiology and for all approaches to focus on symptoms. This is an approach which has been promoted by the publication of our DOC research of the main criteria from the National Institute of Mental Health. The idea is not to treat depression, but rather to focus on anhedonia, for instance, as one of the constitute symptoms of depression, and try and understand the neurobiology underlying that. Only then would we move onto the treatment; particularly the brain circuitry that is dysregulated in anhedonia and trying to fix that pharmacologically. Most patients will not just have this one symptom, but several and then you can have a precision medicine approach where you treat the symptoms with polypharmacy. That is one approach. The hope is that that would allow you to have a precision medicine approach in the clinic. In terms of translation, it is probably much more realistic to generate an animal model off a motivational deficit, meaning anhedonia, but we'll never have a depressed mouse. It's essentially an approach that will make translation better, and eventually lead to more successful treatments. This is the approach which we call circuit symptoms - focus on the symptoms and try to identify the circuits that underlie them. We recently also became interested in early intervention, particularly schizophrenia - viewing it as a neurodevelopmental disorder and trying to identify teenagers who are on the road to schizophrenia, which is not to say we don't also treat chronically-ill adults, but we also try to catch the symptoms early.

Are there any technological innovations that have furthered your ability for early intervention?

There are neurodevelopmental models, but I don't think they're particularly new or really technology-driven. It's more obvious for the circuit symptom story, where we have the progress in neuroimaging in humans, which has helped to begin to understand which circuits are impaired in patients. Then we have techniques and rodents, which allow you to either monitor or influence circuits. What is also very helpful in this is the recent development of translational tasks. In particular, tasks that don't just look translational but have a good construct validity. Even if an animal doesn't do something that looks the same as what humans do, a lot of work has gone into really making sure that the process going on in the animal is comparable, like a specific cognitive process.

What are the models that you use for target identification and validation?

In the circuit symptom approach, there are circuit models. It's a loop; we start with a patient and we try to understand which circuit is wrong in the patient. For example, we know that in schizophrenic patients we've got a deficit in the excitation inhibition balance. It's a micro circuit between a pyramidal neuron and an inhibitory neuron. The balance between the two is off, and there's an impairment in the subtype of interneurons, which are the Parvalbumin-expressing interneurons. This has been described in patients and postmortem studies. We take this and translate it back into rodents. Using optogenetics, we impair the Parvalbumin interneurons in mice. We hope to observe deficits, both in terms of behaviour and physiology that resemble what's observed in the patient. If we see the deficit, then that tells us this circuit is relevant. In terms of target identification, one could just start looking for targets right in that circuit, so in this case, targets in Parvalbumin interneurons. Once you've established such a model with a circuit impairment, that's manifested in both the behavioral and physiological consequence, then, of course, you can try and reverse these deficits, and that would give us high confidence that this will be translated into benefits in humans.

What are the main challenges in the translational approach that you take, and what translational challenges have you overcome?

The main challenge is that it's the brain and it is incredibly complex. It's a no brainer to say, but I think one hurdle is that you find a circuit in humans, and then you're going to find the same circuit in rodents. It's not always obvious or even possible, because the brain is different. So many structures are evolutionarily conserved, but others are not. In particular, the most interesting ones like in the prefrontal cortex, it gets difficult to pinpoint, e.g. the medial orbital frontal cortex, what is that exactly in a mouse? In terms of the behavioral tests, you can't ask the mice how they feel. You always have to get your answer in a very indirect way. There's always the risk of measuring something but not what you think you're measuring.

What are the top three takeaways that you hope the delegates will take from your presentation?

This general approach of saying, we want to treat specific symptoms rather than the syndromes. That is one important message. As I previously said, I don't think this is an idea our company invented. This is an idea that is out there. We believe in this approach and we'd like to promote it. I think an important message is also for the animal models. Animal models have been criticized a lot and an important message is if you can't have an animal model of a disease, you can still have an animal model of a more restricted deficit and that then still makes sense. We have to keep justifying why we use animal experiments and that is a very clear and concrete way to justify this.