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Closing in on biomarkers – interview with PRISM's Martien Kas.

The PRISM project (Psychiatric Ratings using Intermediate Stratified Markers), is a joint Industry-Academia project to relate biological characteristics to clinical diagnosis in mental health. The first part of the project, PRISM1, was initiated in 2016. PRISM2 was recently funded by the EU's Innovative Medicines Initiative to build on the findings from the original PRISM project.

PRISM aims to build on the RDoC (Research Domain Criteria) concept, put forward by Tom Insel and Bruce Cuthbert at the NIMH in the USA, to correlate clinical diagnosis with measurable biomarkers, and so to move on from the traditional diagnosis of mental health problems based only on an analysis of symptoms. Of course, reliable biomarkers are seen as something of a 'Holy Grail' for mental health medicine, and while several labs are working on this, the international PRISM collaboration is probably the most ambitious.

Here, Professor Martien Kas is interviewed by Tom Parkhill. Professor Kas is the PRISM academic project coordinator and Professor of Behavioural Neuroscience at the University of Groningen. He is also the President-elect of the ECNP.

TP: Tell me about the history of PRISM – what does it aim to do and how did it come about?

MK: Firstly, PRISM is funded through the EU's Innovative Medicines Initiative (IMI). It was funded to address a call for studies on quantitative biology for neuropsychiatry, to provide us with quantitative parameters for symptoms which are seen across neurological and psychiatric disorders. The PRISM consortium wrote a project proposal to assess 4 different domains across these disorders, ranging from social functioning, sensory processing, working memory, and attention. We chose these because they were 4 domains the consortium felt were highly affected across disorders.

The main focus has been on the social domain, because we know, from input from the EUFAMI patient family organisation, among others, that social withdrawal and isolation is one of the major burdens which patients experience. As part of the project, EUFAMI surveyed patients and families. Social isolation has an effect on the lives of patients, but also on the lives of their close relatives who may be taking care of them. And really, there isn't much in the way of treatment for this particular symptom.

PRISM is a joint Industry-academia initiative; how did this come about, and what's the history?

The general concept of an IMI project is that they are funded partly through the EU's Horizon 2020 initiative, with an equivalent cash contribution coming from industry. The European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the biopharmaceutical industry operating in Europe, coordinates the industry input. PRISM1, which ran from 2016, received €16.5m funding in total, and had 22 participants, including 7 from the pharmaceutical industry. PRISM2 will receive €7.9m funding, and will have 14 participants. The ECNP is a participant in both stages.

We kicked off in 2016 with a clinical study where we did a lot of deep phenotyping in schizophrenia and Alzheimer's disease patients, who were characterised for high and low social withdrawal. These patients, and a control group, were assessed for all kinds of quantitative biological parameters in the 4 domains I have mentioned. These assessments ranged from neuroimaging assessments (both structural and functional), EEG and scan data, but also social measurements using for example questionnaires and smartphones. Many other measurements were included. Based on this dataset we obtained more than 4000 biological endpoints, and used advanced statistical analysis we tried to see if we could group these patients on the basis of biology, rather than on the original clinical diagnosis.

And how did that go?

We found a relationship, at different levels, between the default mode network and social functioning, irrespective of the traditional diagnosis. This seems to mean that the variations in the default mode network relate to certain variations in social functioning, irrespective of diagnosis. This is what we want to confirm and investigate in PRISM2. In PRISM 1 we found evidence for this in resting state connectivity measures, as well as structural and EEG measures – also at the level of questionnaires and the digital measures of social functioning. In a genetic part of the study we were able to identify 19 loci for sociability, and that many of these genes are expressed in circuits related to the default mode network.

So PRISM has started to build a neurobiological framework, where there could be a potential relationship between the level of social dysfunction in these different disorders and the functional and structural integrity of a specific brain network.

In parallel, PRISM 1 has developed a preclinical test-battery to assess phenotypes corresponding to those assessed in the human clinical study, This platform will be used in PRISM2 to back translate the human findings and to provide causality between the identified neural network and social functioning in rodents.

On top of that, PRISM started a dialog with the EMA Innovation Task Force, on the digital measures of social functioning.

What's the plan for PRISM2?

The PRISM 2 project will run for 3 years. Looking forwards, there are 3 pillars that PRISM 2 will be built on. In PRISM 2 we will:

Replicate the findings of the relationship between social functioning and the default mode network – both at the functional and structural level. To do this, we will repeat the PRISM1

clinical study in a new group of schizophrenia and Alzheimer's patients. This will show reproducibility and robustness of the findings. We would like to extend this work to a 3rd patient group – to include major depression - to understand the broadness of the finding.

The second pillar will be testing causality, so we will use the animal studies to start testing the functional relationship between these networks which can be identified in animals, and start to target them directly using chemo-genetic strategies, among others, to locally activate brain circuits, and so to see if we can change the social functioning in these rodents.

The third part has to do with interaction with stakeholders, and how we communicate and translate our findings. For example, we will be expanding our interaction with the EMA with respect to the digital biomarker for social functioning, and we hope to receive a scientific advice opinion from the EMA by the end of the project.

So what would the Scientific Advice Opinion mean?
It will recognise that we have indeed obtained a digital social marker that can be assessed in this patient group, and that this has validity as regards social functioning.

This is the first practical implication of the RDoC idea
Yes, Insel and Cuthbert announced this idea of precision medicine according to the RDoC principles in a 2015 Science paper. The funding call was announced in this paper, and ours is one of the first examples to try to implement this transdiagnostically. In fact, we are attempting to push beyond the RDoC concept by looking for 'biotypes' within and across the cohorts in addition to correlating to established symptom-based diagnoses and traits. But I think we can now say that we have provided proof of concept.

That's interesting – you feel you have proof of concept
At least for the relationship between social functioning and the default mode network. But of course we are scientists, so we'd like to see it being replicated, and ideally to see it being extended to a new patient group, and this is what PRISM2 tries to establish.

Is PRISM the only project trying to implement the RDoC principles?
There is other work ongoing, mainly in the US, which is of course where RDoC idea was born. As far as I know, they mainly focus on this principle within disorders, so for example identifying biotypes in schizophrenia using quantitative biology. I don't think there are initiatives to assess this across a whole range of disorders. The psychiatric genetics consortium published a paper in *Cell* 2 years ago where they looked at genetic correlations between disorders; they were able to report that there is more intense genetic correlation between some disorders than others. And that means that there is some evidence of biological overlap between disorders.

So what stage are you at with PRISM2? When did it begin, and how would you describe where we are?
We had the kick-off meeting in June of this year. In the last few months we have been working very hard to complete our clinical protocol, and we are just about to submit the protocol to the various medical ethical committees for their review. After that, we plan to start patient recruitment in January 2022. The preclinical groups are currently implementing technologies where they would like to target these very specific neuronal networks which

have been identified in the clinical study – so they are investigating several ways to see which is the most effective. Once that is done they will start testing that hypothesis regarding the causality of this brain network on social functioning in rodents.

To sum up, we are facing a very high, unmet medical need in mental health. We need to rethink how we classify these patients, and do the best we can to optimise their quality of life. The PRISM approach has quite a strong biological component, but we should not forget other components – these are complex disorders, biology is important, certainly from my perspective, but as a field we should not forget other components.

The PRISM2 website contains more information, see https://prism2-project.eu/en/prism-study/

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