Delivering the next generation drug discovery pipeline: New Approaches to Target Identification and Target Validation

Introduction
Psychiatric drug discovery has the potential to be re-invigorated by recent advances in genomics. Increases in whole genome sequencing and larger genome-wide association studies (GWAS) have yielded an unprecedented trove of new knowledge about the genetic underpinnings of psychiatric diseases and, with it, a host of novel targets and biological pathways now implicated in disease. However, the major challenge of turning interesting potential drug discovery targets into successful drug discovery projects remains.

On 1st May 2020, the Psychiatry Consortium and Psychiatric Genomics Consortium co-hosted a workshop to bring together key opinion leaders and experts from the worlds of pharma, biotech, academia and the charity sector to discuss the challenges that arise in the early stages of the psychiatric drug discovery pipeline and how we can collaborate to take advantage of opportunities in these areas in future.

Overall Key Findings
Across all groups, despite varied expertise, research background and current role, the same key issues were raised;

1. Psychiatric drug discovery must be a truly collaborative process if it is to be successful.

2. We need a more sophisticated understanding of the emerging genomic studies and what this means for drug discovery. Only then, with a clear genetic link to a therapeutic hypothesis in a patient population, can we have increased confidence of success.

3. Translatable preclinical models, both cellular and animal, are required that better replicate the heterogeneity of the human condition.

Recommendations

More focused outputs from genomic studies are needed to enable translation
Circuits, pathways and nodes, rather than single gene targets, are now being pursued, but selecting the right target remains a challenge. A high throughput mechanism to triage targets based on their biology could reduce the number of false positive predictions and progress only those targets that are most promising. More certainty around the functional effect of modulating proposed targets would support this and provide further confidence in the target. Ideally, we want a group of single nucleotide polymorphisms (SNPs) in the same biological pathway that all point to the same cellular or mechanistic phenotype. This will offer additional evidence for a pathway’s role in disease and potentially could provide more druggable targets elsewhere in the wider pathway that may also avoid unwanted side effects or toxicity.

We must also find a way to interpret genetic associations in a meaningful biological context. By focusing on clinical phenotypes, we will identify targets that influence specific and relevant clinical symptoms, and hence provide a strong therapeutic hypothesis.

For information on how to work with us on these important issues and for details of future events, sign up to the Psychiatry Consortium mailing list.
Activity throughout the target validation process must be patient-led
Target validation should be viewed with the perspective of the desired clinical end points, rather than from the biology-driven evidence that one can create pre-clinically. Back-translation, considering the heterogeneity of the clinical presentation, and a focus on patient phenotypes rather than complete disorders, will provide a better opportunity to translate the findings to the clinic at a later stage.

Preclinical drug discovery should be supported by both in vivo and vitro systems
Though sometimes controversial, there is still great value in animal models in psychiatry, both as model systems to replicate specific endophenotypes of disease, and as tools for drug discovery. Further clarity on how we can use animal models in a way that gives confidence and provides in vivo proof-of-concept required to initiate further drug discovery endeavours is required (and will be investigated at a future event—see 'Next steps'). However, there is an additional need for an effective in vitro model prior to moving into animals. This could be a cellular model, and should include a large variety of cell lines, including IPSC-derived relevant cells from people with very high and very low genetic risk scores. This 'disease in a dish' could form the basis of the cascade of confidence required to move from a cellular phenotype to a circuit-based hypothesis in an animal model, which can ultimately be extrapolated to human clinical data.

Action should be taken in the clinic to improve our chance of successful translation to patients
Psychiatric diagnosis is symptom rather than biology-led, with diseases grouped by clinical presentation rather than underlying biology. The inherent heterogeneity and co-morbidity of psychiatric disorders therefore further complicates translation. In order to facilitate translation, we must start in the clinic, with better phenotyping and physiological assessment of the patient, to enable us to identify and progress targets which show relevant clinical presentations.

Large, re-contactable patient cohorts (including patients with the most severe presentations, who are not often included in population cohorts, and those that are are not responsive to treatments) can provide the genetic environmental and population variability required to create biologically distinct sub-categories and support effective patient stratification in clinical trials (and ultimately translation).

Pharma and funders want the same thing – line of sight to the clinic
Research funders, pharma and other industry alike want to see early on the package of information needed to initiate a drug discovery programme. Pharmacodynamic markers and a clear therapeutic hypothesis within the disease context are key attributes of a successful project. Early consideration to the 'Target Product Profile' and what exactly would be treated within the disease, along with a plan for how disease aetiology will be changed, are key.

**From the Patient to the Bench and Back**

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**Suggested pathway to take an identified target through the drug discovery process.**

In the proposed pathway, targets identified via genomic studies such as GWAS would inform the identification of relevant biological pathways; modulation of these pathways would be explored in *in vitro* systems; *in vivo* model systems would be required to assess relevance for specific symptoms; a clear understanding of the biological basis of such symptoms would lead to patient subgroups (within or across indications) ultimately leading to testable a hypothesis via exploratory Ph1b clinical studies and beyond.

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Conclusion – collaboration is the key to success

To enable collaboration, we need a better handover between disciplines and a systematic and structured pathway to take an identified target through the drug discovery process. Continued close collaboration between expert geneticists with a nuanced understanding of genetic outputs, academic neuroscientists with a deep understanding of disease biology (and access to advanced technologies) and those in pharma or biotech with drug discovery expertise, is essential. Action is required from all parties, in order to ensure knowledge and data from academia and industry are shared more effectively, and that both party’s motivations are transparent.

Coming together as a community has helped us identify gaps in the drug discovery process which we must fill. An often-cited need is to identify tool compounds to support target validation. For academics without access to medicinal chemistry expertise and chemical and fragment libraries, this step is challenging, and as such, there is a large gap in both time and resource between finding a genetic hit and finding a tool compound to validate it. ‘Linking players’ positioned at key points in the chain could effectively join such gaps. Consortia such as the Psychiatry Consortium can support academics to translate and validate targets to industry standards and bridge the gap between academia and industry; academic experts, ‘Gene whisperers’, can play a key role by identifying the critical nodes in biological pathways where pharmacological intervention can influence specific phenotypic presentations that we often see in the clinic; and clinicians, translational scientists, and those with a lived experience of mental health, all have an important role to play in linking pre-clinical drug discovery to unmet clinical needs.

Next Steps

The Psychiatry Consortium is keen to join forces with others in the psychiatry research community to action and champion these recommendations. The wider discussions captured as part of this workshop are currently in preparation for submission to a peer-reviewed journal to enable further dissemination and appreciation of the challenges and opportunities facing the discipline.

In collaboration with the British Pharmacological Society (BPS) and the Laboratory Animal Science Association (LASA), the Psychiatry Consortium will be hosting a workshop in February 2021 to further investigate the issues raised during this meeting around the use of preclinical models in psychiatric research. The workshop will provide a 360 overview of the status of preclinical models of psychiatric disorders - their validity and scope for successful translation. A key aim of the workshop will be to outline a set of minimum requirements for preclinical models in a variety of co-morbid psychiatric symptoms (and highlight how to use them correctly) to increase the chance of successful translation to the clinic.

Following on the discussions around enhancing and focusing the outputs of genomic studies, the Psychiatry Consortium and the Psychiatry Genomics Consortium also propose a further workshop to identify how best to use genomics in psychiatry in a more sophisticated manner in order to support successful translation of novel targets to industry. We hope that by recognising the challenges and opportunities for growth in this space, we will encourage scientists from all research backgrounds to work collaboratively and explore new approaches to drug discovery in psychiatry.

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