Psychiatry Consortium

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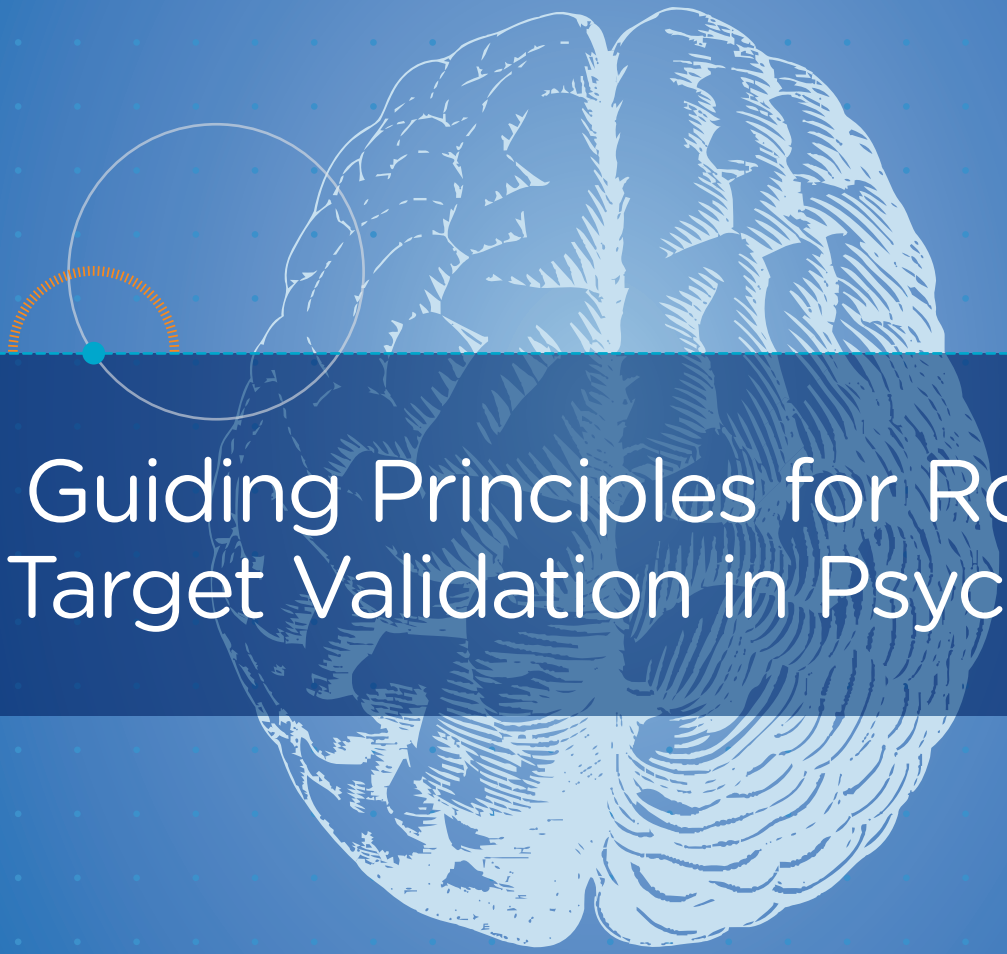

Guiding Principles for Robust Target Validation in Psychiatry

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Introduction

Target identification (TI) and target validation (TV) are two critical parts in the early stages of the drug discovery process. In brief, TI begins with identifying the function of a possible therapeutic target (mainly proteins but also DNA, lipids and RNA) and its potential role in the disease, disorder or condition; the characteristics of a 'good' target will be further explored below. TV is the demonstration that a molecular target is directly involved in a physiological/ pathophysiological process that leads to the emergence of symptoms. Thus, modulation of the target can be expected to produce a change in a biological pathway and a possible therapeutic effect. While there are different approaches to TI and TV, confidence is significantly increased through converging lines of evidence. Following the initial steps of TI and TV, later-stage drug discovery efforts include hit identification, lead selection and lead optimisation – for the purpose of this document, we focus on the early stages of selecting and validating molecular targets for potential therapeutic use.

Scope & Assumptions

The scope of the guidance described here is by no means exhaustive; the approaches and considerations for TI and TV are intended to assist academic researchers in developing a robust TV proposal to ready a project for industry collaboration and funding. Collaborative partnerships, when cultivated early, can take a project in a whole new direction for the benefit of those working on the science, the patient and the investor.

The following principles may apply to multiple indications within psychiatry. However, each disease or condition should be approached independently with relevant customisation of the guidance points.

How To Use This Guide

This document is not a definitive checklist but a guidance document intended to encourage researchers to critically appraise existing knowledge of the proposed target in line with key considerations deemed important by the drug discovery community.

The guidance will help build a TV project that aims to address gaps in our knowledge and strengthen the body of evidence to support the target's role in a particular disease or condition and/or its potential as a therapeutic target. We also acknowledge that addressing all of the considerations is unlikely to be within the expertise of a single researcher, and some of the challenges mentioned are not typically addressed in academic labs.

For these points, where researchers consider the ask to be out of their area of expertise, we reiterate that we do not expect a single researcher to have all of the answers but highlight them as they are important considerations for industry collaborations and should be given some thought – if only to highlight the need to fill the gap. **A successful research collaboration should make use of both industry and academic strengths and capabilities.**

Selecting a Target for Validation Efforts

Our relatively poor understanding of the brain and brain dysfunction associated with disorders, diseases and conditions of the brain is one of the main reasons for the paucity of new targets in psychiatric medicines research that are currently available. A target will remain putative in the context of the specific disease, disorder or condition until robust supporting evidence has been generated. Once this is achieved the target can be prosecuted by generating 'hits' which can then results in 'lead' compounds.

Identifying novel targets results from a deep understanding and its causative molecular mechanisms, alongside the application of relevant TI and TV technologies. Characteristics of a suitable target largely depend on the particular indication being considered; however, general key factors for selecting a 'good' target for subsequent validation include:

Testable Therapeutic Hypothesis

- Is there a novel hypothesis or new target concept to understand how mechanisms, pathways and neural circuits are involved in developing symptoms?
- Is there a robust hypothesis of how target modulation could lead to clinical efficacy, i.e., will modulation of target x, with compound y, and with the direction of effect z, in a specific brain tissue be beneficial for a particular patient population?
- Is there clinical precedent (ideally Proof of Concept (PoC) in humans) for the target or mechanism? It is recognised that evidence from published clinical PoC studies is unlikely to exist for proposals aimed at novel mechanisms. However, in some cases, supporting evidence can be gathered from modulation of the mechanism, or even the target, and the serendipitous observations in patients caused by drugs selective for that target and used for different diseases or conditions.

Link to Disease or Condition

- Is there a clear understanding of the link between the target and neural circuit/pathway/mechanism, and do we know how this relates to the disease or condition?
- Is there more than one data source linking the target to disease or condition? Evidence could include;
  - Genetic-based evidence e.g. loss or gain of function mutations identified in the target population, or evidence from genome-wide studies
  - Evidence from animal models of altered disease-relevant biological pathways
  - Supporting evidence from human iPSC/*in vitro* models
- Psychiatric diseases/conditions are polygenic. Are there convergent pathways/downstream pathways that lead to the same effect that should be considered as alternative targets?
- Is the target expressed differently in patients exhibiting the disease or condition and **not** ubiquitously distributed throughout the body?
- Is modulation of the target expected to have a meaningful therapeutic effect? For neurodevelopmental disorders, it is important to consider the temporal nature of changing biology – is the target implicated at all stages of development?
- Are pharmacodynamic, biochemical, physiological or behavioural biomarkers of target engagement available?
- Psychiatric diseases/conditions are highly heterogeneous and can often be fractioned into distinct subpopulations. Is there a subpopulation of patients within whom modulating this target may benefit?

2 Building the Evidence Base – Considerations for a Robust TV Project

The following guidance provides a framework to establish the evidence required to progress a target from putative to validated and to generate a level of confidence that modulating the target will result in a therapeutic effect.

When submitting a funding application, researchers would not be expected to provide evidence for all the points below; instead, researchers are advised to review what is currently known about the target of interest and use the considerations below to help plan the validation effort with the aim of addressing any gaps in our knowledge.

Role in a Pathway, Circuit, or Mechanism Relevant to Disease or Condition

- While strong evidence from one source is good, the convergence of different types of evidence, such as genetic, molecular, and preclinical models, particularly with a translational focus, would add considerable support to the potential role of a target proposal.

Target Tractability

- Is there evidence that the target can be modulated? For example, are there known ligands or tool compounds? Are there other targets with similar features that have been successful in other drug discovery programmes?

- If a tool compound (e.g. agonists, antagonists, inverse agonists, modifiers) is available, is there evidence of target engagement and target/pathway/circuit modulation? Target engagement experiments can also help elucidate if a lack of efficacy is due to the compound not engaging with the intended target or failure of the hypothesis.

- Is the target druggable? i.e., Is there structural information available for the target? Is there evidence from this target or related proteins that it is amenable to therapeutic modulation, e.g., have a site or sites capable of binding drug-like molecules?

- Is achieving selectivity for this target likely to be challenging? I.e., are there multiple sub-types of the target family similar in structure? Are other target family members associated with safety risks?

Reagent and Assay Availability

- Are assays for screening and molecules or reagents (which can be used as tools for investigating the hypothesis) readily available, or will these need to be generated?

Disease Model Availability

Given the challenge of translating the findings of animal models in psychiatry and the general desire to move away from such models, building the link between the target, its pathways, and thecondition in patients via other techniques that use a translational biomarker such as neurochemistry, electrophysiology, and neuroimaging is valuable. This guiding principles document should be used in conjunction with the RDoC framework, a new taxonomy for mental health conditions.

In drug discovery projects, the purpose of an animal model is to predict efficacy in the clinic. Models should be considered for their construct validity, whether they arise through the right mechanism and their predictive validity, will the results in the model translate to humans; models can have low construct validity but high predictive validity. The interpretation and translatability of models is a significant barrier to the discovery and development of novel therapeutics. While models of disease can be poor, RDoC-relevant constructs exist and can be tractably challenged. Some considerations when using models are;

- Do the models available for testing efficacy resemble the human disease and reveal cognitive or behavioural impairments or deficits as closely as possible, and do they ensure the disease state is a consequence of the mechanism being tested?
- If available, is the approach developed and validated in cell-based assays reflective of the target biology and animal models?
- Can IPSC models be used as a surrogate tool to identify a causal relationship to the biology in humans?

Risks

The following ‘red flags’ are noted for researchers to be aware that some factors may make targets less attractive for industry investment. However, there are no common criteria or standards within industry for what constitutes an acceptable degree of validation, and each company will have different perceptions for risk. None of the below factors are insurmountable and are not intended to act as blockers to progress, or to say any target meeting the below criteria is a ‘no-go’. Rather, we list them below so researchers can be mindful that additional steps may be required to overcome them.

Target Novelty

Consider how much is already known about the target; extensively studied targets and relatively unknown targets lacking significant supporting data and evidence may be less attractive for investment.

Previous Target Investigations

Are clinical failures associated with the target or pathway that would make the proposal unattractive for investment? If so, consider how this approach differs from what has been done before.

Link to Other Disorders or Conditions

If the target is involved in other conditions, e.g., cancer, is there a risk that modulating the target could trigger different disease phenotypes? How could the risk be mitigated?

Is Brain Distribution Known?

Is the target ubiquitously expressed, and would modulating the target affect other target organ biology with potential safety considerations?

Intellectual Property

Does the target have a favourable IP situation? Are there existing treatments on the market which modulate this target? Is there freedom to operate? How does this approach differentiate from existing treatments, and is there a space for a new product on the market?

Intractable Targets

Is the target deemed 'intractable'? How could you overcome this? (For example, there are examples of small molecule drugs that do not fully comply with Lipinski's Rule of 5 or through the use of other drug modalities such as peptides or interfering RNAs.).

A Note on Repurposing

Due to the high risk of novel drug discovery, drug repurposing (also called drug repositioning) is an alternative strategy for identifying new indications for approved drugs or drug candidates. Repurposing leverages existing data and learnings and aims to seek a new indication in a different population than that described by the product label. Such learnings could help strengthen new hypotheses, and repurposed drugs are often excellent TV tools.

Following a 25-year hiatus, there has been a steady revival of human psychedelic medicines research, with compounds such as lysergic acid diethylamide (LSD), dimethyltryptamine (DMT) and psilocybin in separate clinical trials for treating depressive symptoms.

Note - Studies solely exploring repurposing existing drugs for new indications are out of scope for Psychiatry Consortium funding but may be used as a tool for validating new molecular targets.

Funding for projects investigating novel therapeutics for the treatment of psychiatric conditions is available through the Psychiatry Consortium. For more details and to apply for funding, visit the website.

psychiatryconsortium.org/apply-for-funding

Definitions

Druggability

The ability of a novel drug-like compound to bind to engage with its target. A successful drug target must have a site capable of binding drug-like molecules, i.e. a druggable site, must have a causal link to a disease process, and be able to reach its target tissue e.g. BBB permeability.

Lipinsky's Rule of 5

The guideline was developed to set 'drugability' guidelines for new molecular entities. In the drug discovery setting, the Rule of 5 predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500 Daltons and the calculated partition coefficient (measured or calculated logP) is greater than 5.

Pharmacokinetics (PK)

PK represents 'what the body does to the compound. It focuses on determining concentration profiles usually in blood and the fate of the drug molecules in the body following administration.

Pharmacodynamics (PD)

PD can be defined as 'what the compound does to the body', as measured by a particular biochemical or physiological or behavioural effect. The study of the variation with time, the effects of an administered substance on the body.

PK-PD

A PK-PD relationship describes the relationship between the dose of the test compound and its biochemical, physiological or behavioural effect.

Research Domain Criteria (RDoC)

A research framework for the investigation of mental disorders to foster new research approaches that will lead to better diagnosis, prevention, intervention and cures. The RDoC framework currently includes six major functional domains. Different aspects of each domain are represented by three to six psychological/biological dimensions, also known as constructs, which are studies along the full range of functioning from normal to abnormal.

Target tractability

The likelihood of identifying a ligand that effectively interacts with a protein.

Workshop Attendees

The following people contributed to the development of this document, following a workshop to discuss the key factors that create a successful proposal for a TV collaborative project. The workshop participants are representatives of the Psychiatry Consortium and the British Neuroscience Association.

All views are the authors own and do not necessarily reflect the views of their organisations.

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