Target Validation – BioCurate’s Perspective

The aim of this document is to help inventors understand what constitutes “target validation” from an industry perspective. The ultimate validation of a target only occurs in the clinic, where an effective drug engages a target and modulates disease. When thinking about validation of a target in the pre-clinical context, the goal is to establish multiple lines of evidence that independently reinforce the notion that the target might be valuable when interdicted in the clinic.

Pre-clinical Target Validation

Pre-clinical target validation studies should demonstrate (i) that the target of interest has potential for a biologically meaningful effect on modulating disease onset or progression, and (ii) that the target can be modulated therapeutically. Furthermore, studies should demonstrate why responses observed by therapeutically modulating a target are being observed, and how they can be even further improved.

The ideal target validation data set consists of:

a) Genetic evidence that the target modulates biology of interest in the indication of interest.
   e.g. knock out/knock in data using constitutive or inducible gene-editing techniques in in vitro systems and/or animal models, or clinical data sets where genetic deficiencies are causally linked to clinical pathologies. The latter is the highest level of pre-clinical data validating a target and provides clinical “proof of concept” that the target will likely have efficacy in humans.

b) Use of tool compounds which are reflective of the final clinical therapeutic modality that phenocopy the genetic modulation. Such compounds include but are not limited to:
   - small molecule inhibitors
   - antibodies
   - peptides
   - inhibitory RNAs
   It is essential to demonstrate specificity and selectivity of the tool compound for the target of interest (e.g. by SPR, or screening against related families of targets). If in vivo data is available, the tool compounds must be dosed using an appropriate and clinically relevant route of administration and based on pharmacokinetic (PK), pharmacodynamic (PD), and target engagement studies in appropriate tissues. PK/PD/target engagement relationships demonstrate the compounds are entering the tissue of interest, are engaging the target, having the desired biological/biochemical effect, and that there is enough drug available to sustain the response for the desired duration in the desired indication.

c) Histological data illustrating a relationship with a (patho)physiological process and phenotypic presentation. Where possible, orthogonal spacial/visual data should also be presented such as a comparison between formalin fixed paraffin-embedded (FFPE) and fresh frozen staining, immunofluorescence microscopy, RNAscope, or nanostring-based digital spacial profiling. This data is of importance for the development of diagnostic biomarker tests to evaluate the most appropriate patients to include in clinical trials.
d) Expression/concentration levels of the target in human disease tissue versus normal tissue. This data allows the assessment of the potential toxicity and/or unwanted exaggerated pharmacology associated with modulating the target.

It is of utmost importance that experiments to generate the above data are performed rigorously. This includes:

- Ensuring compounds and data analysis is completed in a blinded fashion
- The experiments are completed multiple times, ideally by different investigators across different laboratories where possible.
- Inclusion of positive and negative controls (e.g. inactive tool compound or similar composition that does not hit a mammalian target such as an isotype control). This ensures that the systems used to model biology are robust and the significance of the biological effect of the compound of interest, or genetic modulation is interpretable.
- Inclusion of a benchmark (“gold standard”) compound(s) such as standard of care therapy. This allows demonstration of a commercial or clinical advantage over what is currently in development or in clinical use.
- Appropriate statistical analysis and data presentation to understand the significance of the data.
- Animal models require:
  - randomisation of animals
  - pre-specified power calculation
  - dose-response data
  - demonstration of a PK/PD relationship to inform dosing. It is not sufficient to simply dose based on published works. There also needs to be data to show that at the appropriate dose, there is evidence of an attainable “therapeutic window” (safety versus efficacy).

Clinical Target Validation

A target is validated clinically if there is an existing approved drug against the target. The hurdle is very high for a proposed therapeutic against a clinically validated target and clear differentiation must be shown.

NB. It is not anticipated that, on submission of BioCurate’s Expression of Interest form, a proposed project will meet all the criteria outlined above. BioCurate will work with the applicant to build this data set over time.

However, if the data is available, or partially available, it is strongly recommended that it be included in the initial application as its inclusion will substantially strengthen the proposal.

For further information on this, or any other topic related to the drug discovery and translation process, please email the BioCurate team on info@biocurate.com