Decision Process for Committing to a Therapeutic Development Approach: Target Validation Metrics and Biomarkers

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**Major Components/Stages of Drug Discovery and Development Process**

- **Discovery**
  - Target ID/Validation
  - Assay Development
  - Lead Generation

- **Preclinical Development**
  - Lead Optimization
  - First Human Dose Preparation

- **Early Clinical Development**
  - Phase IA (Single and multiple dose)

- **Registration Trials & Submission**
  - Phase III
  - NDA Submit

- **Launch**

**Focus on patient outcomes throughout the process**

Patient outcomes/Customer value
Major causes of failure in Ph 2

- Wrong target?
- Wrong patient population?
- Wrong dose?
Outline

• Conceptual framework:
  • Target validation metrics
  • Biomarkers
Target validation and biomarkers to reduce attrition

Target validation to mitigate selection of
- Wrong target
- Wrong patient population

Biomarkers to enable selection of
- Dose/dosing regimen
- Treatment duration
- Patient population
Major components of target validation

- Clinical experience
- Genetics
- Tissue expression

Increasing importance

- Translational endpoints
- Genetically engineered models
- Pharmacology

Human Data
Target Validation

Preclinical Data
Target Qualification
Major components of target validation

- Clinical experience
- Genetics
- Tissue expression

Examples
- COX-2 / NSAIDs → Prostaglandin pathway
- APP mutations → Amyloid pathway
- TRP channels and neuropathies
Target expression and its relation to disease state/process

- **Clinical experience**
  - Target protein expression is altered in desired disease tissue/iPSCs
- **Genetics**
  - Target mRNA expression is altered in the desired disease tissue/iPSCs
- **Tissue expression**
  - Target protein is expressed or active in the desired organ/sub-region/cells

Human Data

Target Validation

- High
- Med
- Low
Needs

- Biobank: Well annotated and high quality tissues and iPS lines
- Standardized methods for RNA analyses and associated informatics
  - Microarrays, RNAseq, LCM, ISHH……
- Centralized and open access database: “Neuromine” – akin to Oncomine
- Shared resource: specific antibodies for sensitive IHC, WB, ELISAs
- Normative data
- Natural history data
- eQTL: Genotype-expression analyses
Genetic evidence for target association to disease state/process

Human Data

Target Validation

Clinical experience

Genetics

Tissue expression

Monogenic association, large effect size and functionation of gene variant known

Replicated polygenic association with modest effect size and functionated variant

OR

Association with common, low risk variant in a gene that also has rare variant associated with large effect size

Genetic association in small, underpowered (or non-replicated studies) without functionation of the variant
Needs

• Relationship between quantitative traits/endophenotypes and behavioral domains or diagnostic instruments (e.g., RDoC, MMSE, ADAS-Cog)
• Genetics of endophenotypes for psychiatric and pain disorders
  • E.g., genetics of aberrant glutamate vs dopamine neurotransmission
• Genetics of age of onset and disease progression for neurodegenerative disorders (AD, PD, ALS....)
Endophenotypes Provide Quantitative and Translational Markers of Disease Pathophysiology Induced by Genetic Risk Factors

Genetic Risk Factors (common variants)
- CETP, LDLR, APOB, PCSK9
- IRS1, PDX1, FTO
- NRG1, NRX1, ERBB4, GRM3
- APP (Icelandic)

Endophenotype (quantitative traits)
- HDL/LDL cholesterol levels
- Fasting glucose/insulin levels/BMI
- EEG (gamma oscillations), fMRI?
- Aβ production

Clinical Diagnosis/Symptoms
- Coronary Heart Disease
- Type 2 diabetes
- Schizophrenia
- Protection from Alzheimer’s disease

Environmental modifiers
Clinical trial data with selective ligands of target / target pathway

At least one ligand with analogous mode of action on the target/target pathway has “approvable” efficacy in the indication of interest with robust evidence of target engagement.

Clinically relevant efficacy observed with at least one ligand with a different mode of target modulation or with two ligands on biomarkers previous shown to predict efficacy.

Clinically relevant efficacy observed in a small trial but knowledge of engagement of specific target/pathway is lacking.
Needs

• Early markers of efficacy for PoC studies – robust endophenotypic assays?
• Rapid communication of clinical data
• Collaborative studies on clinical trial samples to study disease mechanisms
• Collaborative clinical biomarker studies
Major components of target validation

**Human Data**
- Clinical experience
- Genetics
- Tissue expression

**Preclinical Data**
- Translational endpoints
- Genetically engineered models
- Pharmacology

Increasing importance
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Target pharmacology in preclinical models by selective ligands

Preclinical Data

Target Qualification

* Pharmacological tool may be a small molecule, antibody, peptide/protein, RNAi, etc

Translational endpoints

Genetically engineered models

Pharmacology

Ligands with intended mode of action modulate disease associated pathway in vivo and target engagement-activity relationship established

Ligand with intended mode of action modulates disease associated pathway ex vivo or in native tissue

Tool* modulates disease associated pathway in vitro or in heterologous cell lines at appropriate concentrations

*Pharmacological tool may be a small molecule, antibody, peptide/protein, RNAi, etc
Genetic evidence in model organisms

Preclinical Data

Target Qualification

Human pathogenic mutation of the target in a rodent/primate mimics disease pathway &/or genetic modulation of the target mitigates the same

Genetic modulation in a rodent/non-human primate produces disease-relevant endophenotype

Genetic modulation in a non-mammalian model organism produces disease or treatment-relevant phenotype

Translational endpoints

Genetically engineered models

Pharmacology
Translatability of preclinical data to the clinic

Translational endpoints

Genetically engineered models

Pharmacology

PK/PD relationship and Margin of Safety established using a translational biomarker historically associated with clinical efficacy

PK/PD relationship and Margin of Safety established using a translational biomarker of Target Engagement/modulation

Target orthology known and demonstration of target pharmacology identical to human native tissue assays

Preclinical Data

Target Qualification
Identification of key gaps to focus on

<table>
<thead>
<tr>
<th>Human Preclinical</th>
<th>Target Expression</th>
<th>Genetics</th>
<th>Clinical Experience</th>
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Assessment of BACE as a target for Alzheimer’s disease

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Target assessment is a portfolio management tool

Human Level of Validation (function of pharmacology, genetics and disease pathway information)

- High
- Medium
- Low

Target Qualification (state of basic biologic maturity of target)

- Low
- Medium
- High

- Valley of death
- Need high differentiation
- Resource only to fill key gaps

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Important concepts

- Clinical data define clinical relevance
- Make drugs for disease, don’t find diseases for drugs
- A good drug for a bad target won’t change disease
- A bad drug for a good target often works
- Chemical starting point shouldn’t define biology strategy
- Results of a screen don’t affect the relationship between target and disease
- Ease ≠ Disease
## Biomarker Categories and Their Utility

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<th>Intended Utility</th>
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<tr>
<td><strong>Clinical endpoint</strong></td>
<td>Regulatory approval</td>
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<tr>
<td>Defines how a patient feels, functions (often patient reported) or survives and is used for regulatory approvals</td>
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<td><strong>Tailoring Marker</strong></td>
<td>Patient tailoring/companion diagnostic marker</td>
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<tr>
<td>A non objective measure (e.g., genetic, biochemical, imaging) that identifies patient subgroups most likely to have an enhanced benefit and/or decreased risk to a defined drug intervention in clinical trials</td>
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<td><strong>Clinical Response Predictive Marker for PoC studies</strong></td>
<td>• Proof of efficacy (PoC)</td>
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<td>A marker of activity on a physiological system or process that predicts clinical efficacy or safety but is not yet a registrable surrogate biomarker. This could be a biomarker of disease pathology, pathophysiology or disease progression, etc.</td>
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<tr>
<td><strong>Target modulation-based Pharmacodynamic/Safety Marker</strong></td>
<td>• Dose selection,</td>
</tr>
<tr>
<td>Assesses modulation of a physiological system or process induced by compound-target interaction – does not have to relate directly to the disease process but provides demonstration of on-target activity. Proximity of PD marker to the cmpd-target engagement is important for specificity of PD marker</td>
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<td><strong>Target Engagement Marker</strong></td>
<td>• May be a patient tailoring marker</td>
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<td>Demonstrates that compound occupies the intended molecular target e.g., receptor occupancy via PET, or drug tolerant binding assay for mAbs.</td>
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<td><strong>Drug Exposure Marker</strong></td>
<td>Dose selection</td>
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<td>Measures compound in the intended/surrogate target tissue such as CSF, plasma, skin, urine, saliva</td>
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Increasing Value for Improving p(TS)
Redefine the Taxonomy of Psychiatric Indications for Molecularly Targeted & Tailored Therapies

Patient defined by symptoms of syndromic diseases

Molecularly defined disease states
- Molecular etiology
- Molecular pathology
- Molecular pathophysicsology

Data Integration, Mining, Bioinformatics

Molecular phenotyping
- Mol Genetics
- Fnal Genomics
- Proteomics
- Metabonomics
- Lipidomics
- Imaging
- Exp Meicine

Data Integration, Analytics, Mining

Tailoring Approach

Rx Targets

Companion Diagnostics
Phase I/II dose-setting strategy that would enable a test of the intended mechanism in efficacy trials (rather than testing a molecule).

- Is it feasible to assess drug disposition at the site of action and in accessible fluids?
- Is there an option for a direct target engagement biomarker at the site of action?
- Is there an option for a pharmacodynamic biomarker indicative of modulation of the intended target?
- Is the strategy compatible with trials in phase I normal healthy volunteers, or will the strategy require trials in a specific patient population?
Efficacy Biomarker(s) for PoC Trial

• Is there an ability to establish biomarker-based PoC (efficacy or safety)?

• If yes, what is the translatability of the biomarker from preclinical species to the clinic?
Disease Staging/Progression/State-Associated Biomarkers

- Is there a scientific rationale to target a specific disease stage, monitor disease progression or assess effects on disease state via biomarkers?

- If yes- do robust clinical biomarkers/assays already exist for the purpose?

- What is the translatability of these markers from preclinical species to the clinic?
Patient Selection/Stratification/Tailoring Strategy

• Is there a scientific rationale/need to select, stratify or develop a tailored therapy?
  • e.g., patient heterogeneity is known for target mechanism or response to target class

• Would a patient tailoring label be beneficial for this disease indication and/or program?
Important concepts

- Biomarker plans need to be customized
- Inform clinical dose range via PK/PD based on translational biomarkers
- Establish target engagement/modulation in early clinical trials
- Patient heterogeneity is killing us - establishment of objective, biomarkers to select/deselect patients is a must