Translational Approaches for Therapeutic Development

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Disclosures

- SAB Member/Advisor /Paid Consultant for: Michael J Fox Foundation, Caraway Therapeutics, Nitrase Therapeutics, Nura Bio, Retromer Therapeutics, Sinopia Biosciences, Angels and private equity investors

- Retiree / share holder of Eli Lilly
Drug discovery/development stages
Estimated phase transition probability and overall success rate for drug approval

For CNS therapies, the success rates are even lower

DiMasi et al., J. Health Econ, 2016
Why do drugs fail in the clinic?

- Poor drug candidate
- Wrong target
- Inadequate efficacy
- Wrong patient population
- Inadequate efficacy
- Wrong Dose
- Toxicity in Select patients
Potential reasons for clinical failure of the drugs

Drug-related factors:
- Did the drug target a key pathobiologic mechanism of PD?
  - Need human disease-informed
    - Target ID/validation
    - Screening models: cell & animal
- Was the dosing regimen optimal?
  - Need biomarkers to establish
    - Intended and unintended organ exposures
    - On and off-target engagement/modulation

Patient-related factors:
- Were the right patients/right end-points selected?
  - Need biomarkers
    - To enrich patients who are most likely to respond (e.g., have aberrant activity of the target/pathway at specific disease stage)
    - To supplement clinical end-points and optimize treatment duration

MDS-PAS, Nov 11, 2022
CNS diseases are syndromic and disease definitions are imprecise. Patients with the same symptoms have “different diseases”. Need translational research to:

- Molecularly define disease states
- Connect drug targets to disease state biology
- Biomarker(s) of disease state biology to enable personalized medicine
- Biomarkers to connect drug to target
Translational Science approaches to refine disease taxonomy and enable personalized medicine

Patient defined by symptoms of syndromic diseases

Molecular phenotyping
- Mol Genetics
- Fnal Genomics
- Histo/clin path
- Proteomics
- Metabonomics
- Lipidomics
- Imaging
- Clinical Assessment (+ digital)

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

Multiscale Analytics/Statistics/Modeling

Personalized Rx
Rx Targets

Screening models:
- Phenotypic/molecular
- Animal models

Patient defined by disease biology
- Target connected to disease state biology
- Drug connected to target
Target Validation vs. Target Qualification

Translational research needs to begin in humans

Human disease state-informed target “validation”

Cellular & animal models for drug discovery/development

Genetics

Pathways

Clinical experience

Human Data

Target Validation

Preclinical Data

Target Qualification

Target/Pathway Mechanistic Role in Disease.

In Vivo Pharmacology, PK-PD

Disease/Target Genetics

Biomarker discovery/val
idation

Target Safety
Major Components Translational Science for Target Validation

Human Data
- Clinical experience
- Genetics & Cell biology
- Tissue expression/activity

Increasing importance

Preclinical Data
- Translational endpoints
- Genetically engineered models
- Pharmacology

Target Validation
Target Qualification

MDS-PAS, Nov 11, 2022
Translational Science Needs to Begin with Human Data

Clinical experience
Genetics & Cell biology
Tissue expression/activity

Disease pathway

Human Data
Target Validation

MDS-PAS, Nov 11, 2022
Is the target expression/activity associated with disease state/process?

- Clinical experience
- Genetics
- Tissue expression/activity

Target protein expression/activity is altered in desired disease tissue/cells/h-iPSCs

Target mRNA expression is altered in the desired disease tissue/cells/h-iPSCs

Target protein is expressed or active in the desired organ/sub-region/cells

Major caveat: Disease-stage, adaptive vs. causal changes
Is there genetic evidence for target association to disease state/process?

Clinical experience

Genetics/Cell biology

Tissue expression

Human Data

Target Validation

**Major caveat: pathogenic mechanism of gene variant?**

- **H** Monogenic association/causality, large effect size and functionation of gene variant known

- **M** Replicated polygenic association with modest effect size and functionated variant

  **OR**

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

- **L** Genetic association in small, underpowered (or non-replicated studies) without “functionation” of the variant
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 without target/pathway engagement evidence.
Target Validation vs. Target Qualification

Translational research needs to begin in humans

Human disease state-informed target “validation”

Cellular & animal models for drug discovery/development

Genetics
Pathways
Clinical experience

Human Data
Target Validation

Preclinical Data
Target Qualification

Target/Pathway Mechanistic Role in Disease.

In Vivo Pharmacology, PK-PD

Disease/Target Genetics

Biomarker discovery/val idation

Target Safety

MDS-PAS, Nov 11, 2022
Target identification and/or validation: human-informed disease-state models, investigate and establish target connectivity to disease states.
- Establishing target-specific, mechanistic pharmacology (pharmacodynamic response) of drug candidates; set margin of safety, inform clinical dose range via PK-PD.
- Assessment of efficacy - presumably predictive of clinical benefit; set margin of safety.
- Discovery or validation of clinically translatable biomarker(s)
Target pharmacology in preclinical models by selective ligands

Preclinical Data

Target Qualification

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, ASO, viral vector, etc.*
Genetic evidence in model organisms

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

**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.
Translatability of preclinical data to the clinic

Preclinical Data

Target Qualification

- 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
Diverse therapeutic modalities are now becoming possible

Antibodies
Small-molecules
Proximity degraders
Antisense and nucleic acid therapy
Gene therapy
Genome editing

Cell therapy
<table>
<thead>
<tr>
<th>Category of Evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td><strong>Expression/activity</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Weight = 1</strong></td>
<td>Widely expressed/broadly active</td>
<td>Expressed/active in at least the target organ/sub-regions/cells</td>
<td>Expression/activity modulated in many tissues from patients</td>
<td>Expression/activity modulated in effector tissues from patients</td>
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<td><strong>Pharmacol. experimental data on target modulation</strong></td>
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<td>In vivo activity mimics valid disease process/phenotypes/therapeutic response</td>
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<td>Rodent/primate has disease- and RX-relevant phenotype</td>
<td>Human genetic mutations in an animal model mimics and mitigates disease phenotype</td>
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<td><strong>Weight = 4</strong></td>
<td>Robust genetic association in one study</td>
<td>Robust genetic association replicated in many studies</td>
<td>Causative relationship between genotype and disease process/pathology or pathophysiology established</td>
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<td><strong>Weight = 5</strong></td>
<td>Drug affects symptoms in patients but target-engagement not established</td>
<td>Efficacy and safety via target established in PoC study</td>
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## Target Validation Scores: α-synuclein

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Why do drugs fail in the clinic?

- Poor drug candidate
- Inadequate efficacy
- Wrong patient population
- Inadequate efficacy
- Wrong dose
- Toxicity in select patients
- Wrong target
Biomarkers to Improve the Success Rate of CNS Drugs

- **Patient enrichment**
- **Proof of efficacy**
- **Reg. approval**
- **Patient enrichment**
- **Patient enrichment**
- **Proof of efficacy**
- **Dose selection**
- **Dose selection**
- **Patient enrichment**
Investigational mechanisms/drugs that have failed to show efficacy in PD trials: Lessons learned

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
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<tr>
<td>Anti-apoptotic</td>
<td>CEP1347</td>
</tr>
<tr>
<td>Anti-apoptotic</td>
<td>TCH346</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>Selegeline</td>
</tr>
<tr>
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<td>Vitamin E</td>
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<tr>
<td>Anti-oxidant</td>
<td>Pramipexole</td>
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<tr>
<td>Mitochondria Fn</td>
<td>Co-Q10</td>
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<td>Mitoquinone</td>
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<tr>
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<td>Creatine</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Trophic</td>
<td>GDNF/neurturin</td>
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<td>Inosine</td>
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<td>Calcium channel/mito Fn</td>
<td>Isradipine</td>
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<tr>
<td>c-Abl inhibitor</td>
<td>Nilotinib</td>
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A robust pipeline of PD therapeutics has emerged: a testament to insights into disease biology and feasibility of therapeutic development

CLINICAL (N = 130)
- Phase 1: 31%
- Phase 2: 46%
- Phase 3: 11%
- Proof of concept: 8%

RESEARCH/PRE-CLINICAL (N = 135)
- Discovery: 38%
- Pre-clinical: 50%
- Research program: 12%

Adapted from: Kevin McFarthing, P.R.A.G.
Final words…

• Reform disease taxonomy – break-down syndromes into molecularly defined disease states
• Avoid garbage in – garbage out
  • Improve target validation through patient-informed data, multi-scale network analyses and modeling
  • Improve predictive validity of therapeutic screens and animal models through human disease state biology-informed models and end-points
• Use translational biomarkers for preclinical & clinical decisions to enable hypothesis-testing (i.e., test a mechanism not a drug dose)
  • PoC studies supplemented with disease state biomarkers
  • Patient enrichment
  • Dose selection based on target engagement/modulation
• Finally, slowing PD progression is a major unmet medical need. Pharma will take the risk as long as the therapeutic hypothesis is strong and testable
THANK YOU!
SUMMARY

RIGHT TARGETS:
- that are linked to disease biology
- enabled through disease-state models

RIGHT PATIENT, RIGHT DOSE Biomarkers:
- for Proof of Mechanism in early phase trials
- of disease progression
- of patient enrichment (to reduce patient heterogeneity)

RIGHT DRUG:
- linked to a target in individual patient populations
- screening models with improved predictive validity
- objective biomarker-facilitated clinical development