Target Validation in Drug Discovery

Lon Cardon
GlaxoSmithKline
Translation and Genetics

21st century genetics clearly contributing to
- Understanding disease etiology
- Mechanistic hypotheses and (sometimes) direct insights
- Broad spectrum of trait-gene relevance
- Technology and unforeseen tools

Translation?
- Diagnostics, prognostics, treatment?
- Pharmacogenetics?
- Novel targets?

✓ Oncology, rare diseases and (ad hoc) drug safety
Otherwise, “Valley of Death” is as wide as ever
The genetics of drug efficacy: opportunities and challenges

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**Figure a:**
- **y-axis:** Minor allele frequency
- **x-axis:** Effect size (OR or HR)
- Red line: Non-PGx
- Blue line: Efficacy PGx

**Figure b:**
- **y-axis:** Minor allele frequency
- **x-axis:** Effect size
- **Legend:**
  - Non-PGx
  - Safety PGx
  - Efficacy PGx

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*Note: The nature of the data and the exact nature of the genetics and drug efficacy relationship are not detailed in the image.*
The support of human genetic evidence for approved drug indications

Drugs with human genetic information >2x more likely to be successful

Those that succeed are more likely to be genetically validated

or

Failures at each stage are more likely to be those without genetic validation
Genetics in clinical studies today

Proportion of new targets with genetic support for ongoing or another indication

Major pharmaceutical companies
Target validation and cost reduction

- 10-15% targets have genetic data today
- If increase to 50%, expect 13-15% cost reduction
- If increase to 100%, expect 25% cost reduction

Cost savings per successful drug

Proportion of targets 'genetically validated'

Tufts Center for the Study of Drug Development

November 18, 2014

Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion

BOSTON – Nov. 18, 2014 – Developing a new prescription medicine that gains marketing approval, a process often lasting longer than a decade, is estimated to cost $2.558 million, according to a new study by the Tufts Center for the Study of Drug Development.

The $2.558 million figure per approved compound is based on estimated:

- Average out-of-pocket cost of $1,395 million
- Time costs (expected returns that investors forgo while a drug is in development) of $1,163 million

The $2.6 Billion Pill — Methodologic and Policy Considerations

Jerry Avorn, M.D.

The NEW ENGLAND JOURNAL of MEDICINE
Not all genes are targets

...GWAS catalogue is not enough. DNA sequencing is not enough

- Mechanism of action (GoF, LoF, Dom Neg, ...)?
- Pleiotropy, generalized vs undesirable effects?
- Druggability? Chemical tractability?
- Predicting drug effect size from lifelong exposure (genetics)?
- Position in pathway?
- Tissue specificity, delivery?

Mech of action

Animal models to validate

Unwanted effects of target manip.

Position in pathway

Accuracy of genetic localization

Regulatory effects

Chemical tractability

Changes from gene to protein

Tissue specificity

Unwanted effects of target manip.
It is not going to be easy ...

...and this may not be the exception

GWAS SNPs not in LD w/ SNPs in DHS

GWAS SNPs in DHS

GWAS SNPs in perfect LD with SNPs in DHS

Maurano, Science 201
Early observations

1. **Genetics** yielding actionable findings for translation

2. **Complexity** is increasing, leading to more specialization
   - Biology & genetics becoming ‘big data’ problem.
   - Drug discovery evolving from previous comfort-zone of approaches.
   - Separation of basic sciences and translation remains large, possibly *worsening* (“valley of death”)

3. Targets themselves can be **Pre-Competitive**
Comprehensive, robust data integration
Responsive, dynamic human cellular experiments
A pioneering partnership

www.targetvalidation.org
• **Premise:** no single entity, *public or private*, has all of the skills to fully exploit the information emerging

• Consortium of 3 founders, **computational, experimental, translational**

  ![EMBL-EBI](logo.png), ![Wellcome Trust Sanger Institute](logo.png), ![GlaxoSmithKline](logo.png)

• **Formal agreement to share findings openly**

• Pooling of expertise
  – Joint approach, joint expertise, pre-competitive
  – Enable a new generation of translational scientists
Key premise: no single entity, public or private, has all of the skills to fully exploit the information emerging today.

Consortium of 3 founders, each with different expertises.

State of art experimental and computational approaches previously not fully deployed for translation.

Formal agreement to share findings openly.

Pooling of expertise:
- Joint approach, joint expertise.
- Train a new generation of translational scientists.
Target Validation is one piece of puzzle. Current paradigm: (Im-)Precision Medicine Development

<table>
<thead>
<tr>
<th>Target ID</th>
<th>Lead ID</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Post-registration</th>
</tr>
</thead>
</table>

**Variable target evidence**
- ‘Hunch’
- Mechanistic hypothesis
- ...
- Previously drugged

**Traditional translation to clinic**
- Tenuous animal models
- Intermediate endpoints
- Limited tox understanding
- High attrition rate

**Clinical trials**
- Small number doses
- Ph III clinical endpoints don’t match models or Ph I/II endpoints
- Little sample stratification

*Missing the link from (new) phenotypes to (better) targets*
To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.

**PMI for Oncology**  
**PMI Cohort Program**

Key principles around privacy & trust:  
*Governance, transparency, participant empowerment, data access & sharing*
Focus on the individual

New diagnostics, prognostics, treatments

Trait/disease refinement

Population samples

Integrating biological and clinical information

Rare diseases

Disease cohorts