IMPACT OF HUMAN GENETICS ON DRUG R&D

Robert Plenge
Harvard Medical School, Executive Education
June 4, 2018
Agenda

- **Introduction**
  - Why human genetics?

- **Day 1:**
  - The model
  - Picking targets and pathways
  - Matching modality and mechanism

- **Day 2:**
  - Predictive biomarkers
  - Clinical development
  - Emerging resources
Introduction

- Approach most applicable outside of oncology and ID
- References
  - Plenge *Science Translational Medicine* (2016)
A disciplined approach to integrating all four components will lead to the following improvements:

- Increased probability of success in phase 2/3 clinical trials
- Increased probability for differentiation from standard of care

- Which targets, when perturbed, have a desired effect on human physiology?
- Which therapeutic modality recapitulates causal human biology?
- Which biomarkers measure therapeutic modulation in a human system?
- How can therapeutic hypotheses be tested in humans as safely, quickly, and efficiently as possible?
But first...what is the evidence that human genetics helps with R&D productivity?
PCSK9 binds to LDL receptor outside of cells to reduce LDLR on cells

Many genes influence cholesterol levels and risk of heart disease

PCSK9 mutations associated with high and low LDL cholesterol levels (and heart disease risk)

Atherosclerotic Plaque

Blood Flow

Lysosome

LDL

mAb

drugs that mimic the mutation & lower LDL and protect from heart disease
Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

![Bar chart showing the percentage of projects in different phases and their outcomes.]

![Bar chart showing the ratio of projects with human genetic linkage and efficacy biomarkers available at the start of each phase.]

Projects with human genetic linkage of the target to the disease indication

Projects with efficacy biomarkers available at start of phase

- **Phase II projects**
  - Yes (15): 73%
  - No (21): 43%

- **Phase Ila projects**
  - Yes (17): 82%
  - No (7): 29%
The support of human genetic evidence for approved drug indications

Matthew R Nelson1, Hannah Tipney2, Jeffery L Painter1, Judong Shen1, Paola Nicoletti3, Yufeng Shen3,4, Aris Floratos3,4, Pak Chung Sham5,6, Mulin Jun Li6,7, Junwen Wang6,7, Lon R Cardon8, John C Whittaker2 & Philippe Sanseau2

Over a quarter of drugs that enter clinical development fail because they are ineffective. Growing insight into genes that influence human disease may affect how drug targets and indications are selected. However, there is little guidance about how much weight should be given to genetic evidence in making these key decisions. To answer this question, we investigated how well the current archive of genetic evidence predicts drug mechanisms. We found that, among well-studied indications, the proportion of drug mechanisms with direct genetic support increases significantly across the drug development pipeline, from 2.0% at the preclinical stage to 8.2% among mechanisms for approved drugs, and varies dramatically among disease areas. We estimate that selecting genetically supported targets could double the success rate in clinical development. Therefore, using the growing wealth of human genetic data to select the best targets and indications should have a measurable impact on the successful development of new drugs.
9 approved new molecular entities so far in 2018 (May 15)
Of these, 4 are for non-oncology / non-ID indications
All 4 have *some degree* of genetic support for the targets
- tezacaftor / ivacaftor for CF → strong prospective evidence (*CFTR*)
- burosumab for hypophosphatemia → strong prospective evidence (*FGF23*)
- fostamatinib for ITP → weak retrospective evidence (*SYK*)
- tildrakizumab for psoriasis → strong retrospective evidence (*IL23A*)
9 approved new molecular entities so far in 2018 (May 15)

Of these, 4 are for non-oncology / non-ID indications

All 4 have *some degree* of genetic support for the targets
- tezacaftror / ivacaftar for CF $\rightarrow$ strong prospective evidence (*CFTR*)
- burosumab for hypophosphatemia $\rightarrow$ strong prospective evidence (*FGF23*)
- fostamatinib for ITP $\rightarrow$ weak retrospective evidence (*SYK*)
- tildrakizumab for psoriasis $\rightarrow$ strong retrospective evidence (*IL23A*)
IL23 signaling

*IL23A* (IL23p19)

*IL23R*

*IL12B* (IL12p40)

*IL12Rβ1*

*TYK2*

*Jak2*

*Tyk2*

O'Shea and Plenge Immunity (2012)
15 approved new molecular entities so far in 2018 (June 2)
Of these, 10 are for non-oncology / non-ID indications
Most have some degree of genetic support for the targets
- tezacaftor / ivacaftor for CF → strong prospective evidence (CFTR)
- burosumab for hypophosphatemia → strong prospective evidence (FGF23)
- tildrakizumab for psoriasis → strong retrospective evidence (IL23A)
- avatrombopag for thrombocytopenia → strong prospective evidence (MPL)
- pegvaliase for PKU deficiency → strong prospective evidence (PAH)
- baricitinib for rheumatoid arthritis → strong prospective evidence (JAK1)
- fostamatinib for ITP → weak retrospective evidence (SYK)
- lofexidine for opioid withdrawal → no genetic evidence (ADRB2)
- erenumab for migraine → no genetic evidence (CGRPR)
- zirconium cyclosilicate for hyperkalemia → no genetic evidence (N/A)
Next…breaking down the individual components, from target identification to clinical proof-of-concept (PoC)
A disciplined approach to integrating all four components will lead to the following improvements:

- Increased probability of success in phase 2/3 clinical trials
- Increased probability for differentiation from standard of care
What is the ideal drug target?
Pick a human phenotype for drug efficacy
Pick a human phenotype for drug efficacy

Gene function

Human Phenotype

High

Low

GOF

LOF

Nelson et al Nature Genetics 2015
Pick a human phenotype for drug efficacy

Identify a series of alleles with range of effect sizes in humans (but of unknown function)
Pick a human phenotype for drug efficacy

Assess biological function of alleles to estimate “efficacy” response curve

Human Phenotype

High

Low

Gene function

GOF

LOF

Efficacy
Gene function

Human Phenotype

High

Low

GOF

LOF

Gene function

Efficacy

Toxicity

Assess biological function of alleles to estimate "efficacy" response curve

Assess pleiotropy as proxy for ADEs

Pick a human phenotype for drug efficacy
New target for drug screen!

Pick a human phenotype for drug efficacy

This provides evidence for the therapeutic window at the beginning of the drug discovery journey.
Causal human biology: Which targets, when perturbed, have a desired effect on human physiology?

Therapeutic modulation: Which therapeutic modality recapitulates causal human biology?

Which biomarkers measure therapeutic modulation in a human system?

Target modulation assays

How can therapeutic hypotheses be tested in humans as safely, quickly, and efficiently as possible?

Proof-of-concept clinical trials

Phase 2/3 clinical trials: Increased probability of success in phase 2/3 clinical trials

Real world: Increased probability for differentiation from standard of care

A disciplined approach to integrating all four components will lead to the following improvements:
TYK2 is an intracellular signaling molecule

Rare, complete human knockout is associated with immunodeficiency and risk of infection

Common alleles reduce TYK2 function and protect from risk of autoimmune disease (e.g., RA, SLE, IBD)

Same common alleles do not increase risk of infection
Allele that protects from autoimmunity (e.g., rheumatoid arthritis) is associated with loss-of-function (LoF)
**Resolution TYK2 locus genotype-to-phenotype differences in autoimmunity**


<table>
<thead>
<tr>
<th>Rs34536443 genotype</th>
<th>G/G</th>
<th>G/C</th>
<th>C/C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>In U.K. Biobank</td>
<td>105,794 (90.63%)</td>
<td>10,689 (9.16%)</td>
<td>249 (0.21%)</td>
<td>116,732 (100%)</td>
</tr>
<tr>
<td>Mycobacterial</td>
<td>20 (86.96%)</td>
<td>3 (13.04%)</td>
<td>0 (0.00%)</td>
<td>23</td>
</tr>
<tr>
<td>Specific bacterial</td>
<td>54 (90.00%)</td>
<td>5 (8.33%)</td>
<td>1 (1.67%)</td>
<td>60</td>
</tr>
<tr>
<td>(e.g., S. aureus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific viral</td>
<td>93 (96.88%)</td>
<td>3 (3.12%)</td>
<td>0 (0.00%)</td>
<td>96</td>
</tr>
<tr>
<td>(e.g., HSV, VZV,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>viral encephalitis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>46 (88.46%)</td>
<td>6 (11.54%)</td>
<td>0 (0.00%)</td>
<td>52</td>
</tr>
<tr>
<td>candidiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>213 (92.21%)</td>
<td>17 (7.36%)</td>
<td>1 (0.43%)</td>
<td>231</td>
</tr>
</tbody>
</table>

Same LoF allele has no obvious increased risk of infection
Complete TYK2 knockout (function)
**Therapeutic hypothesis:** Partial inhibition of TYK2 will protect from RA (and SLE, psoriasis) without risk of infection.
But matching *modality with mechanism* is challenging, especially selectivity over JAKs.
Matching modality and mechanism: allosteric modulation required for TYK2 selectivity over JAKs

Tokarski et al JBC 2015

Dendrou et al STM 2016
Gene therapy
- shRNA
- miRNA
- siRNA

Gene editing
- TALEN
- ZFN
- CRISPR

Biologics:
- Antibodies
- Hormones

Small molecule drugs

Viral vectors

Non-viral delivery

Cell-based therapies

Other mRNA replacement
protein degradation
macrocyclic peptides

...and more to come!
A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease

ASO targets RNA splicing of SMN2 transcript
Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

Alnylam Announces FDA Acceptance of New Drug Application (NDA) and Priority Review Status for Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR (hATTR) Amyloidosis

Feb 01, 2018
– PDUFA date set for August 11, 2018 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 1, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the U.S. Food and Drug Administration (FDA) has accepted for filing its New Drug Application (NDA) for patisiran, an investigational RNAi therapeutic targeting transthyretin (TTR) for the treatment of hereditary ATTR (hATTR) amyloidosis. The FDA also granted the Company’s request for Priority Review and has set an action date of August 11, 2018, under the Prescription Drug User Fee Act (PDUFA). At this time, the FDA is not planning to hold an advisory committee meeting to discuss this application.
CAR-T therapy for B cell cancers

Can this be used for genetic targets outside of oncology?