Impact of Human Genetics on Drug R&D

Robert Plenge
American Society of Human Genetics
October 16, 2018
The Problem
Two fundamental challenges to drug R&D

Attrition problem

Innovation problem

Deloitte Centre for Health Solutions
Attrition: where things go wrong and what that costs

Attrition: where things go wrong and what that costs

1 out of 10 make it to approval

Expense and failures in Phase 2/3 that drive the cost

Most late-stage failures are due to lack of efficacy.

**Phase II failures (2008-2010)**

- Strategic: 29%
- Misc.: 1%
- Safety: 19%
- Efficacy: 51%

**Phase III failures (2007-2010)**

- Strategic: 7%
- Misc.: 6%
- Safety: 21%
- Efficacy: 66%

Arrowsmith Nature Reviews Drug Discovery (2011)
Attrition: where things go wrong and what that costs

A Solution
We relied on preclinical models to pick targets and estimate efficacy in heterogeneous human populations

*It was...*
Humans are the “model organism” of choice for new targets and precision medicine

**But today…**
A model
Pick a human phenotype for drug efficacy

Pick a human phenotype for drug efficacy

Gene function

GOF  LOF

High  Low

Human Phenotype

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)

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

Pick a human phenotype for drug efficacy.

Pick a human phenotype for drug efficacy

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

Assess pleiotropy as proxy for ADEs

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.

It is not common or rare…

It is common and rare variants
An example in immunology
TYK2 is an intracellular signaling molecule (next slide)

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

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

Same common alleles do not increase risk of infection
IL23 signaling and psoriasis

IL23A (IL-23p19)

IL23R

IL-23R

IL12B (IL-12p40)

IL12B

TYK2

O'Shea and Plenge Immunity (2012)
Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes

Harm-Jan Westra\textsuperscript{1,2,3,4,5,20}, Marta Martínez-Bouzet\textsuperscript{6}, Yang Luo\textsuperscript{1,2,3,4}, Nikola Teslovich\textsuperscript{1,2,3,4}, Jane Worth\textsuperscript{5}, Lars Klareskog\textsuperscript{15}, Solbritt Rantapaa-Dahlqvist\textsuperscript{16}, John A. Todd\textsuperscript{7}, Steve Eyre\textsuperscript{9,10}, Peter A. Nigrovich\textsuperscript{11}, Soumya Raychaudhuri\textsuperscript{1,2,3,4,9,19,*}

**TYK2 gene**

\[ P1104A \]

\[ I684S \]

( low freq: A928V )
P1104A allele that protects from autoimmunity is associated with ~80% loss-of-function (LoF) in C/C homozygous state.
Same LoF allele has no obvious increased risk of infection

<table>
<thead>
<tr>
<th>Infections</th>
<th>G/G</th>
<th>G/C</th>
<th>C/C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: 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 (e.g., S. aureus)</td>
<td>54 (90.00%)</td>
<td>5 (8.33%)</td>
<td>1 (1.67%)</td>
<td>60</td>
</tr>
<tr>
<td>Specific viral (e.g., HSV, VZV, viral encephalitis)</td>
<td>93 (96.88%)</td>
<td>3 (3.12%)</td>
<td>0 (0.00%)</td>
<td>96</td>
</tr>
<tr>
<td>Mucocutaneous candidiasis</td>
<td>46 (88.46%)</td>
<td>6 (11.54%)</td>
<td>0 (0.00%)</td>
<td>52</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>

~80% LoF is not associated with increased infection

Dendrou, et al. (2016)
Science Translational Medicine
P1104A protects from multiple autoimmune diseases

Dendrou, et al. (2016)
Science Translational Medicine
But I684S variant shows a more complicated pattern!

<table>
<thead>
<tr>
<th></th>
<th>Ps</th>
<th>RA</th>
<th>SLE</th>
<th>T1D</th>
<th>AS</th>
<th>CD</th>
<th>UC</th>
<th>MS</th>
<th>JIA</th>
<th>PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rs34536443</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rs9797854</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rs12720356</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**OR (of minor allele)**

- Protection
- Risk

- No prior evidence of association
- No association

Dendrou, et al. (2016)
Science Translational Medicine
Complete TYK2 knockout increases risk of infection.

~80% LoF protects from autoimmunity but is not associated with infection.
**Therapeutic hypothesis:** Partial inhibition (~80%) of TYK2 will protect from autoimmunity without risk of infection.
But matching *modality with mechanism* is challenging, especially selectivity over JAKs.
HTS assay was used in a phenotypic screen to find selective inhibitors of TYK2 over other JAKs.
Tokarski et al (2015) JBC

Retains selectivity over JAKs

~80%
50-80% TYK2 inhibition safe and effective in Phase 2 (psoriasis)
Emerging resources
Mendelian randomization
Mendelian randomization: *nature’s clinical trial*

Randomized controlled trial

Randomization into groups

Intervention
- Protein biomarker lower
- Disease risk lower

Control
- Protein biomarker **HIGHER**
- Disease risk **HIGHER**
Mendelian randomization: nature’s clinical trial

Randomized controlled trial

- Randomization into groups
  - Intervention
    - Protein biomarker lower
    - Disease risk lower
  - Control
    - Protein biomarker HIGHER
    - Disease risk HIGHER

Mendelian randomization

- Random allocation of alleles
  - Protein increasing allele(s) absent
    - Protein biomarker lower
    - Disease risk lower
  - Protein increasing allele(s) present
    - Protein biomarker HIGHER
    - Disease risk HIGHER
Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery.

Causal pathway:
- **Genotype** → **Intermediate traits** → **Disease outcome**

Data:
- **Genotyping**, **sequencing**
- **Protein levels**, **functional assays**
- **Clinical data**

Relevant studies:
- Genotype-biomarker association studies
- Genotype-disease association studies
- Epidemiology studies

Confounder: **G** → **I** → **D** vs. **G** → **I** → **D**
Large-scale proteomic databases are limiting

Causal pathway

Data

Relevant studies

Genotype $\rightarrow$ Intermediate traits $\rightarrow$ Disease outcome

Protein levels, functional assays

Clinical data

Genotyping, sequencing

Genotype-biomarker association studies

Genotype-disease association studies

Epidemiology studies

Relevant studies

Genotype $\rightarrow$ Genotype-phenotype association studies

G $\rightarrow$ I $\rightarrow$ D

vs.

G $\rightarrow$ I $\rightarrow$ D

Confounder $\times$
Emerging resource of pQTLs for MR

- Tested 3,622 plasma proteins in 3,301 healthy individuals from INTERVAL population cohort
- Identified 1,927 genetic associations with 1,478 proteins
- **Example**: *IL-6R* RA protective allele increases sIL-6R levels (see figure) but decreases membrane-bound IL6R
- **Therapeutic hypothesis**: preventing IL-6 signaling through IL-6R via blocking antibodies should treat RA symptoms

Mendelian randomization establishes a causal link between IL-6 pathway and risk of rheumatoid arthritis.

**IL-6R** minor variant → Less membrane IL-6R and less signaling → Protection from RA

Thus, therapeutic targeting of IL-6R should be beneficial in treating RA patients.
Tocilizumab mimics mutation by reducing IL-6R signaling.
Phenome-wide association study (PheWAS)
Phenome-wide association studies (PheWAS)

Disease-Agnostic cohort

EHRs, Claims, Questionnaires, etc.

Clinical data

Genetic data

GWAS, exome sequencing, etc.

Test association of selected SNP with clinical endpoints

LoF SNP

PheWAS code 1

PheWAS code 2

PheWAS code 3

PheWAS code 4

PheWAS code 5

PheWAS code 500

risk surrogates for efficacy

risk surrogates for toxicity

Gene function

High

Low

Human Phenotype

Efficacy

Toxicity

GOF

LOF
Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes

rs35667974 – protects from T1D

rs72871627 – protects from T1D

ATA haplotype – protects from T1D
PheWAS example: *IFIH1*, autoimmunity, asthma

- PheWAS in ~800,000 individuals from four population cohorts
- Tested 25 SNPs for association with 1,683 clinical endpoints
- 10 novel associations discovered
- Example: *IFIH1* LOF allele protects from autoimmunity (known) but increases risk of asthma (novel finding)
- Therapeutic hypothesis: inhibiting *IFIH1* may be effective in some autoimmune diseases but may make asthma worse

Predicted impact of therapeutic inhibition of IFIH1

Beneficial effect for some autoimmune diseases, but increase risk of asthma and UC

Vitiligo
T1D
Psoriasis
SLE
Asthma
UC

Odds ratio

0.7 0.8 0.9 1 1.1

efficacy
safety
FinnGen is a unique PheWAS resource

500,000 individuals (~10% of population)

National Registries, EHRs, etc.

Clinical data

Genetic data

SNP

Test association of selected SNP with clinical endpoints

- PheWAS code 1 (risk)
- PheWAS code 2
- PheWAS code 3
- PheWAS code 4
- PheWAS code 5 (risk)
- PheWAS code 500

Surrogate for efficacy

Surrogate for toxicity

Genome sequencing, Axiom array, imputation

FinnGen is a unique PheWAS resource

500,000 individuals (~10% of population)

National Registries, EHRs, etc.

Clinical data

Genetic data

SNP

Test association of selected SNP with clinical endpoints

- PheWAS code 1 (risk)
- PheWAS code 2
- PheWAS code 3
- PheWAS code 4
- PheWAS code 5 (risk)
- PheWAS code 500

Surrogate for efficacy

Surrogate for toxicity

Genome sequencing, Axiom array, imputation
In conclusion
The pharmaceutical industry needs human genetics

Human genetics increases probability of success >2-fold

An “allelic series” model can be used to

– prioritize new targets
– match modality to mechanism
– select pharmacodynamics biomarkers
– determine clinical indications

TYK2 represents a compelling example in human immunology

MR and PheWAS represent emerging resources

( See back-up slides for more details! )
Questions?

@rplenge