Human genetics and drug discovery – the role of Mendelian randomization

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The Problem
Two key challenges in drug development: *high failure rate and insufficient innovation*

**Attrition problem**

**Innovation problem**

Phase II/III failures drive high cost of drug development

Rising healthcare costs driving demand for innovative, breakthrough therapies

US Healthcare Spending $2.9 TRILLION in 2013

- Hospital Care 32%
- Physicians and Clinics 20%
- Prescription Drugs ~10%

Cost, $ millions

- Preclinical
- Clinical

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<tr>
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<tbody>
<tr>
<td>Preclinical</td>
<td>100</td>
<td>200</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Clinical</td>
<td>200</td>
<td>400</td>
<td>800</td>
<td>1300</td>
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The Attrition Problem

...now it is efficacy/safety

It was drug metabolism & pharmacokinetics (DMPK)…
“to be Earth’s most customer-centric company, where customers can find and discover anything they might want to buy online, and endeavors to offer its customers the lowest possible prices”
What are guiding principles?
Proof-of-concept Clinical Trials

**Prediction:** increase probability of success for breakthrough therapies
Technology is changing the ideal model organism for drug discovery and development

It was...
Today, *humans are the model organism of choice* for new targets and precision medicine.
Three examples (focused on human genetics)
How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?

Which targets, when perturbed, have a desired effect on human physiology?

Which biomarkers measure therapeutic modulation in a human system?

Prediction: increase probability of success for breakthrough therapies
Human genetics helps to identify potential drug targets to kick-start drug discovery

1. Map genetic differences in those with disease vs healthy;
2. Understand how these genetic differences lead to disease;
3. Develop drugs against these targets that reverse disease processes in the population.

But, tens of thousands of potential targets…
…and which one causes disease?
…and how do you perturb the target?

The key steps are:
There are anecdotal examples of human genetics leading to new drug targets (*PCSK9*), and...

Many genes influence cholesterol levels and risk of heart disease

![Diagram showing atherosclerotic plaque and blood flow](image)

We can now find these disease genes...

![Diagram showing DNA sequences](image)

...and design studies to find drugs that fix the underlying molecular defects – for example, blocking PCSK9 lowers LDL (or “bad”) cholesterol in the blood.

![Diagram showing LDLR, PCSK9, and LDL-C](image)
...portfolios of drug targets with human genetic support have a higher probability of success

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 ratio of projects across different phases and conditions.

Projects with human genetic linkage of the target to the disease indication:
- Yes (15): 73 closed, 43 active or successful
- No (21): 57 closed, 82 active or successful

Projects with efficacy biomarkers available at start of phase:
- Yes (17): 18 closed, 82 active or successful
- No (7): 71 closed, 29 active or successful]
What is a genetic strategy?
We determine dose-response in clinical trials, after many years and millions of dollars. We aspire to determine dose-response at the time of target ID and validation.
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
Pick a human phenotype for drug efficacy

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

Assess pleiotropy as proxy for ADEs

This provides evidence for the therapeutic window at the time of target ID & validation.

New target for drug screen!
The list of genes with an “allelic series” is growing

<table>
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<tr>
<th>Gene</th>
<th>LOF</th>
<th>GOF</th>
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<tbody>
<tr>
<td>PCSK9</td>
<td>low CAD risk, low LDL-C</td>
<td>high LDL-C, high CAD risk</td>
</tr>
<tr>
<td>APP/BACE1</td>
<td>high AD, dementia risk</td>
<td>low AD, dementia risk</td>
</tr>
<tr>
<td>LRRK2</td>
<td>high PD risk</td>
<td>low PD risk</td>
</tr>
<tr>
<td>SCN9A</td>
<td>pain insensitivity</td>
<td>neuropathy, hyperexcitability</td>
</tr>
<tr>
<td>PNPLA3</td>
<td>low LDL-C, TG</td>
<td>high NAFLD, NASH, PBC, HCC risk</td>
</tr>
<tr>
<td>CARD9</td>
<td>low IBD risk, high risk for fungal infections</td>
<td>high IBD, AS, PSC risk</td>
</tr>
<tr>
<td>TYK2</td>
<td>low RA, psoriasis, SLE, MS risk, high risk for PID</td>
<td>high T-ALL risk</td>
</tr>
<tr>
<td>IFIH1</td>
<td>low T1D risk, high risk for PID</td>
<td>high SLE risk, AG, SM syndromes</td>
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... and there are further genes with protective LoF variants, for example:
SLC30A8 (T2D), IL6R (RA), NPC1L1 (CAD), APOC3 (CAD), CCR5 (HIV)
And we are at the beginning of what will be an explosion of genetic discoveries across populations

Cost of genome sequencing continues to drop rapidly…

…which results in many more human genomes being sequenced…

…and a more accurate molecular understanding of human disease.
Initiatives now link human genetics with clinical phenotypes in a setting for recall.
How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?

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Prediction: increase probability of success for breakthrough therapies
BACE-inhibitor program in Alzheimer’s disease
The history of drug development for Alzheimer’s disease is not pretty – very high failure rates.

99.5% failure rate!

Calcoen et al (2015) NRDD
Amyloid hypothesis and Alzheimer’s disease: the role of the APP gene and BACE1 in disease initiation

**Aβ oligomers**

BACE1 is the first of two enzyme cleavages that release toxic Aβ peptides

**Causal human biology**
- *APP, PSEN1, PSEN2* mutations cause FAD, increase Aβ cleavage
- *APP-A673T* variant reduces AD risk, decrease Aβ cleavage
- Naturally occurring antibodies to Aβ oligomers decrease AD risk

Aβ peptides aggregate to form oligomers and β-amyloid plaques that are toxic to surrounding neurons

Neuron cell death leading to cognitive decline and other symptoms of AD

Intracellular tau tangles
Therapeutic hypothesis: **BACE-inhibition blocks release of toxic Aβ and reduces AD progression**

1. Protective *APP* mutation reduces BACE1 cleavage *in vitro*
2. BACE1 inhibitor mimics *APP* mutation and blocks first step in release of toxic Aβ peptides
3. Decrease in Aβ oligomers in brain protect from AD
Aβ peptide levels measured in CSF serve as a biomarker for target modulation. Does the drug engage and modulate the target?
Is there a dose-dependent relationship in human subjects?

Healthy Volunteers

- Drug
  - Low dose
  - High dose

Alzheimer’s Patients

- Drug
  - Low dose
  - High dose

Biomarker
MK-8931 lowers Aβ levels in CSF from healthy volunteers and Alzheimer’s disease patients

Multi-dose, healthy volunteers

Multi-dose, AD patients

>90% lowering
A note of caution, however:

(1) No Mendelian randomization study with *APP* mutations and CSF A\(\beta\) peptide levels

(2) Phase III clinical trials are now underway – *the ultimate test of a therapeutic hypothesis*
Proof-of-concept Clinical Trials

Prediction: increase probability of success for breakthrough therapies

Phase II-III Clinical Trials

Target ID and Validation

Causal Human Biology

Which targets, when perturbed, have a desired effect on human physiology?

Lead Optimization

Target Modulation Assays

Which biomarkers measure therapeutic modulation in a human system?

Early Development

Prediction: increase probability of success for breakthrough therapies

Proof-of-concept Clinical Trials

How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?
Orexin Receptor Antagonists (ORAs): a new therapeutic approach to treat insomnia

Causal human biology
- Autoimmune orexin deficiency in humans results in narcolepsy
- Genetic deficiency in dogs leads to narcolepsy, and orexin pathway conserved across species

Orexin Neurons (hypothalamus)

Acknowledgements:
John Renger, Matt Kennedy
Therapeutic hypothesis: *Orexin receptor antagonism (ORA) blocks wake promoting signal, enabling sleep*
Clinical proof-of-concept (POC) in healthy volunteers: polysomnography (PSG) sleep study

• **Study Design**: double-blinded, placebo-controlled, 5-period cross-over study in *20 healthy subjects*

• **Measurement**: 8-hr PSG recording

![Graph showing Total Sleep Time (TST) and Sleep Efficiency Index (SEI)]
How to apply Mendelian randomization in this framework
How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?

Which targets, when perturbed, have a desired effect on human physiology?

Which biomarkers measure therapeutic modulation in a human system?

Prediction: increase probability of success for breakthrough therapies
Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery.
Ph III clinical study in >18,000 CHD patients

Sequencing NPC1L1 in >7,000 patients and >14,000 controls
Rule-out targets: genetic evidence does not support adiponectin as a T2D target

Other T2D genetic loci $\xrightarrow{}$ Other biological processes $\xrightarrow{}$ Fasting insulin; Fasting glucose; T2D

ADIPOQ $\xrightarrow{}$ Adiponectin $\xrightarrow{}$ Not-causal

Genetics for quantitative modeling of biomarker and POC studies to guide dose, study design

**Human Genetics of Factor XI (FXI):**
- Complete knockout: spontaneous bleeding rare, likely protection from VTE
- Partial LOF: lower FXI levels associated with increased PTT, protection from VTE
We live in an amazing time...