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*

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%

Attrition problem

Innovation problem
The Attrition Problem

...now it is efficacy/safety

It was drug metabolism & pharmacokinetics (DMPK)…
The Innovation Problem

“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?
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
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?

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Human genetics helps to identify potential drug targets to kick-start drug discovery

The key steps are:
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?
There are anecdotal examples of human genetics leading to new drug targets (\textit{PCSK9}), and…

Many genes influence cholesterol levels and risk of heart disease

\begin{itemize}
  \item Atherosclerotic Plaque
  \item Blood Flow
\end{itemize}

We can now find these disease genes…

\begin{itemize}
  \item Disease
  \item Healthy
\end{itemize}

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

\begin{itemize}
  \item LDLR
  \item PCSK9
  \item LDL-C
\end{itemize}

\begin{itemize}
  \item Lysosome
  \item mAb
\end{itemize}

\begin{itemize}
  \item LDLR Recycling
\end{itemize}
...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
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

Gene function

Human Phenotype

High

Low
New target for drug screen!

Pick a human phenotype for drug efficacy

Efficacy

Toxicity

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.

Human Phenotype

High

Low

Gene function

GOF

LOF

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>LOF</th>
<th>GOF</th>
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</thead>
<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>
</tr>
</tbody>
</table>

... 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?

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

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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

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
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.
Is there a dose-dependent relationship in human subjects?

Healthy Volunteers

Drug

Low dose
High dose

CSF

Biomarker

Alzheimer’s Patients

Drug

Low dose
High dose

CSF

Biomarker
MK-8931 lowers $A\beta$ 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 Aβ peptide levels

(2) Phase III clinical trials are now underway – *the ultimate test of a therapeutic hypothesis*
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?

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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

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>TST (min)</th>
<th>SEI (%)</th>
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<tbody>
<tr>
<td>PBO</td>
<td>440</td>
<td>90</td>
</tr>
<tr>
<td>10mg</td>
<td>450</td>
<td>92</td>
</tr>
<tr>
<td>50mg</td>
<td>460</td>
<td>94</td>
</tr>
<tr>
<td>100mg</td>
<td>460</td>
<td>96</td>
</tr>
</tbody>
</table>

**Comparison**

- **Total Sleep Time (TST)**: MK-4305 shows a dose-dependent increase compared to PBO.
- **Sleep Efficiency Index (SEI)**: MK-4305 also shows an increase, with 100mg achieving the highest SEI.

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*Images and diagrams are not included in the natural text representation.*
How to apply Mendelian randomization in this framework
Proof-of-concept Clinical Trials

**Prediction:** increase probability of success for breakthrough therapies

**Phase II-III Clinical Trials**

**Lead Optimization**

**Target ID and Validation**

**Causal Human Biology**

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

**Target Modulation Assays**

Which biomarkers measure therapeutic modulation in a human system?

**Proof-of-concept Clinical Trials**

How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?
Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery.
Ph III clinical study in >18,000 CHD patients

- 32.7% vs 34.7% w/ primary event
- HR=0.936, p=0.016
- 6.4% relative risk reduction

Sequencing NPC1L1 in >7,000 patients and >14,000 controls

- 15 NPC1L1 inactivating mutations
- Carriers w/ lower plasma LDL
- 53% relative risk reduction
Rule-out targets: genetic evidence does not support adiponectin as a T2D target

Yaghoottkar et al, Diabetes (2013)
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…