Key Drug Discovery Challenges in Cardiovascular Medicine

Drs. Daniel I. Swerdlow & Michael V. Holmes

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5 Challenges:

1. Identifying new targets
2. Validating new targets
3. Avoiding adverse effects
4. Making better use of existing drugs
5. Integrating novel approaches into drug development

Challenge 1
Identifying new targets
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Conventional therapeutic targets in CVD

How to find new targets?

Genome-wide association studies (GWAS):
A source of novel targets

Compare frequency of c. 1 million SNPs
in cases vs. controls

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Challenge 2
Validating new targets

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Using genetics for causal inference in target validation

Mendelian randomisation: a ‘natural’ RCT

Why use Mendelian randomisation in target development?

- Most drug targets are proteins
- Millions of common genetic variants are mapped across the genome
- Functional variants in protein-coding regions occur frequently
- MR studies are relatively low-cost and quick
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Is the IL-6 – CHD association causal?

Causation
IL-6 \rightarrow CHD

Confounding
IL-6 \leftrightarrow CHD

Reverse causation
IL-6 \leftarrow CHD

Tocilizumab inhibits signaling at IL-6R

A genetic proxy for IL-6R inhibition

IL6R SNP rs7529229
• In linkage disequilibrium with known functional variant: Asp358Ala
Validation of IL6R SNP as a proxy for tocilizumab treatment

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Tocilizumab</th>
<th>IL6R SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>↑ (n=1,446)</td>
<td>↑ (n=29,838)</td>
</tr>
<tr>
<td>CRP</td>
<td>↓ (n=3,010)</td>
<td>↓ (n=76,527)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↓ (n=409)</td>
<td>↓ (n=52,567)</td>
</tr>
<tr>
<td>Soluble IL-6R</td>
<td>↑ (n=1,465)</td>
<td>↑ (n=1,454)</td>
</tr>
<tr>
<td>Albumin</td>
<td>↑ (n=108)</td>
<td>↑ (n=5,787)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>↑ (n=2,072)</td>
<td>↑ (n=17,886)</td>
</tr>
</tbody>
</table>

Swerdlow DI et al., Lancet (March 2012); PubMed ID 22421340

IL6R SNP is associated with lower CHD risk

- 25,458 cases/100,740 controls
- OR 0.95 (95% CI 0.93 to 0.97)
- p = 4.5x10^-5

Sarwar N et al., Lancet (March 2012); PubMed ID 22421339

"The odds ratio per minor allele was 0.97 (95% CI 0.95–0.98, p=4.5x10^-5)"

Swerdlow DI et al., Lancet (March 2012); PubMed ID 22421340
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sPLA₂ inhibition and CHD prevention

Anthera™ VISTA-16 trial

Genetic study
Effect of the PLA2G2A variant on sPLA2-IIA mass

Specificity of the PLA2G2A variant

Expected association between PLA2G2A rs11573156 and major vascular events

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Observed association between PLA2G2A rs11573156 and major vascular events

Holmes et al. JACC 2013 PMID 23916927

Challenge 3
Avoiding adverse drug effects
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Mechanisms of adverse drug effects

Off-target mechanism(s)

Torcetrapib – the ILLUMINATE trial

* A number of trials of torcetrapib trials demonstrated that the drug did indeed increase HDL-C
* The phase 3 ILLUMINATE trial was terminated early because of excess cardiovascular deaths in the torcetrapib-treated arm
* Blood pressure increased in participants treated with torcetrapib, but not those treated with atorvastatin alone
* Implicated a hypertensive effect of the drug as the mechanism behind its dramatic failure

Genetic investigation of torcetrapib and blood pressure

Sofat et al. Circulation 2010
Published ID 201206784
Challenge 3
Making better use of existing drugs

Pharmacogenetics
- The study of genetic determinants of drug response

Scenarios in stratified medicine

<table>
<thead>
<tr>
<th>R_{1+} vs. R_{1-}</th>
<th>Original RCT</th>
<th>Scenario 1</th>
<th>Test for interaction</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1</td>
<td>G2</td>
<td>P=0.5</td>
<td>No interaction</td>
</tr>
<tr>
<td></td>
<td>Test for interaction</td>
<td>Interpretation</td>
<td>Qualitative interaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>G1</td>
<td>P=0.01</td>
<td>Quantitative interaction</td>
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Clopidogrel

- 1st licensed in 1998 in UK as an anti-platelet drug
- #2 selling drug worldwide in 2011 (after atorvastatin)
- Wide range of clinical uses
  - Acute and chronic cardiovascular disease
  - >40 million individuals treated worldwide

Clopidogrel treatment efficacy

- Meta-analysis of 79,613 patients in CVD

Clopidogrel and myocardial infarction

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Clopidogrel and major bleeding

Clopidogrel pharmacokinetics
- Clopidogrel is a pro-drug
- Metabolised into active metabolite by several enzymes
- One of these enzymes is cytochrome P450 2C19

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CYP2C19* alleles

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<th>Normal/increased function</th>
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*CYP2C19* alleles

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*2 to *8 =
Less active drug
Higher CVD risk
Less bleeding

*1 or *17 =
More active drug
Lower CVD risk
More bleeding
**Systematic reviews**

1. **CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events**
   - *A Systematic Review and Meta-analysis*
   - Holmes et al. JAMA 2011
   - PMID 22203539

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3. Genetic effect on intermediate phenotypes: Treatment-only analysis

- 4 studies reported platelet function following a 600mg loading dose of clopidogrel in ≥500 individuals

4. Risk of primary CVD (composite) outcome comparing any copy of CYP2C19 *2 to *8 to CYP2C19 *1 or *17: Treatment-only analysis

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CYP2C19-clopidogrel conclusions

- No effect modification of clopidogrel by CYP2C19
- No evidence to support clinical use

Challenge 5
Integrating novel approaches into drug development
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