New Targets, New Modalities, New Challenges – The Inconvenient Path of Human Genetics in Drug Discovery

Enabling Precision Medicine: The Role of Genetics in Clinical Drug Development – A Workshop

March 8, 2017
Overall message

- precision medicine: *patient subsets for whom therapeutic intervention works better*
- few approved drugs will benefit from precision medicine
- greatest impact will be to guide new drug development, which will be tested and approved in patient subsets
- However, this path is *inconvenient*, and will require biological insight into targets, new therapeutic modalities, and a more creative approaches to clinical development
Must improve efficiency of drug R&D.

Cost:
- 2010: $1.188bn
- 2015: $1.576bn

Value:
- 2010: $816m
- 2015: $416m
Disciplined approach to drug discovery and early development

Robert M. Plenge
1. Too many Phase 2/3 studies fail
2. Time between discovery and PoC is too long
Why don’t drugs differentiate?

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

1. Not enough sound therapeutic hypotheses!
How will precision medicine help?

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1. Improve cycle time from therapeutic hypothesis to clinical PoC...efficiently and safely
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Today: 5-7 years
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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?

Early discovery → Lead optimization → Early development → Phase 2/3 clinical trials → Real world

Causal human biology

Therapeutic modulation

Target modulation assays

Proof-of-concept clinical trials

<1 yr
What are potential solutions?

1. Pick targets based on human biology
2. Programmable therapeutics to test PoC
human genetics to pick targets
Pick a human phenotype for drug efficacy

Human Phenotype

High

Low

GOF

LOF

Gene function

Plenge et al *NRDD* 2013
Pick a human phenotype for drug efficacy

Gene function

High

Human Phenotype

Low

GOF

LOF

Nelson et al NG 2015
Pick a human phenotype for drug efficacy

Gene function

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Low

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LOF

Identify a series of alleles with range of effect sizes in humans (but of unknown function)
Gene function

Human Phenotype

High

Low

GOF

LOF

>100 rare variants

6 common variants

RESULTS Among 46,891 individuals with LPL gene sequencing data available, the mean (SD) age was 50 (12.6) years and 51% were female. A total of 188 participants (0.40%; 95% CI, 0.35%-0.46%) carried a damaging mutation in LPL, including 105 of 32,646 control participants (0.32%) and 83 of 14,245 participants with early-onset CAD (0.58%). Compared with 46,703 noncarriers, the 188 heterozygous carriers of an LPL damaging mutation displayed higher plasma triglyceride levels (19.6 mg/dL; 95% CI, 4.6-34.6 mg/dL) and higher odds of CAD (odds ratio = 1.84; 95% CI, 1.35-2.51; \( P < .001 \)). An analysis of 6 common LPL variants resulted in an odds ratio for CAD of 1.51 (95% CI, 1.39-1.64; \( P = 1.1 \times 10^{-22} \)) per 1-SD increase in triglycerides.

Khera et al JAMA 2017
Pick a human phenotype for drug efficacy

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

New target for drug screen!

Pick a human phenotype for drug efficacy

Assess biological function of alleles to estimate "efficacy"

Efficacy

Assess pleiotropy as proxy for ADEs

Toxicity

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

High

Low

Human Phenotype

GOF

LOF

Gene function
programmable therapeutics to test therapeutic hypotheses quickly
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Causal human biology: Which targets, when perturbed, have a desired effect on human physiology?

Therapeutic modulation: Which therapeutic modality recapitulates causal human biology?

Target modulation assays

Proof-of-concept clinical trials

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

Today: 5-7 years
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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?

Proof-of-concept clinical trials

Phase 2/3 clinical trials

Real world

<1 yr
Limitations that we face today

- Biological function of associated variants, genes & pathways incompletely understood
- Conventional modalities (e.g., small molecules, monoclonal antibodies) modulate <20% of targets

- **New modalities are desperately needed**, but today are limited by delivery and pharmacological properties
Other
mRNA replacement
protein degradation
RBC as vehicles
Burning platform for precision medicine

- understand molecular mechanism of disease-associated variants, genes and pathways
- recapitulate mechanism with a credible therapeutic molecule
- shorten cycle time to test therapeutic hypotheses in small PoC trials defined by specific molecular features
Conclusion
Overall message - inconvenient path to precision medicine

- precision medicine: patient subsets for whom therapeutic intervention works better
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