Transforming translational medicine for effective drug discovery

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

Phase II/III failures drive high cost of drug development

Economic forces demand innovative, breakthrough therapies

http://csdd.tufts.edu/

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 of breakthrough therapies
Translational Medicine

• Genetics & Pharmacogenomics
• Translational Biomarkers
• Translational Pharmacology
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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?
Pick a human phenotype for drug efficacy

Identify a series of alleles

Assess pleiotropy as proxy for ADEs

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

Assess biological function of alleles

Gene function

GOF

LOF

Efficacy

Toxicity

New target for drug screen!
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.
Beyond genetics, there are other examples of causal human biology that drive new target discovery

*Autoantibodies* – autoimmune destruction of orexin neurons and narcolepsy

*Infectious disease* – HCV and cirrhosis

*Somatic cell genetics* – neoantigen formation, immune upregulation, and immuno-oncology

*Physiological challenge* – exposure to approved drugs and changes in human physiology

*Longitudinal profiling* – oxyntomodulin and metabolic disease
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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 \textit{APP} gene and BACE1 in disease initiation

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

\textit{Aβ} oligomers

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

\textit{Neuron cell death leading to cognitive decline and other symptoms of AD}

\textit{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
There are new technologies to measure human physiology, including nanotechnologies and NGS.
Bottom line:
Robust biomarkers should allow proof-of-mechanism studies in clinical trials...and new technologies are here now!
Proof-of-concept Clinical Trials

How can we safely test therapeutic hypotheses in \textit{humans} as quickly and efficiently as possible?

Causal Human Biology

Which targets, when perturbed, have a desired effect on \textit{human} physiology?

Target ID and Validation

Target Modulation Assays

Which biomarkers measure therapeutic modulation in a \textit{human} system?

Lead Optimization

Early Development

\textbf{Prediction:} increase POS of innovative therapies in late development
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

![Graphs showing Total Sleep Time and Sleep Efficiency Index](image-url)

* *p<0.05*
There are new technologies to measure clinical outcomes, including real-time patient monitoring.
Bottom line:

Platforms to test clinical proof-of-concept should advance novel targets into the clinic...and new technologies are here now!
We live in an amazing time...