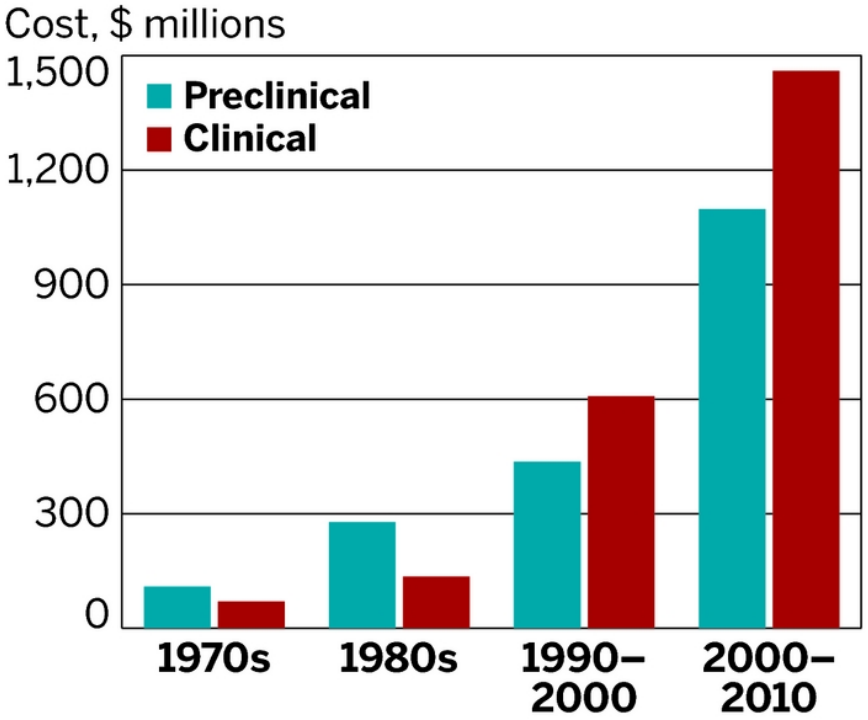
Transforming translational medicine for effective drug discovery

Robert Plenge, MD, PhD

MERCK
Be well

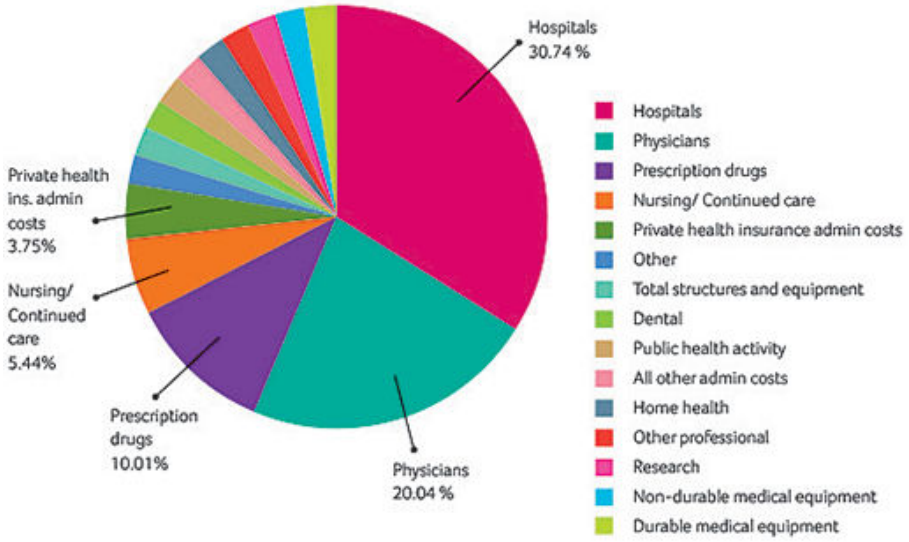
Two key challenges in drug development: high failure rate and insufficient innovation

Phase II/III failures drive high cost of drug development

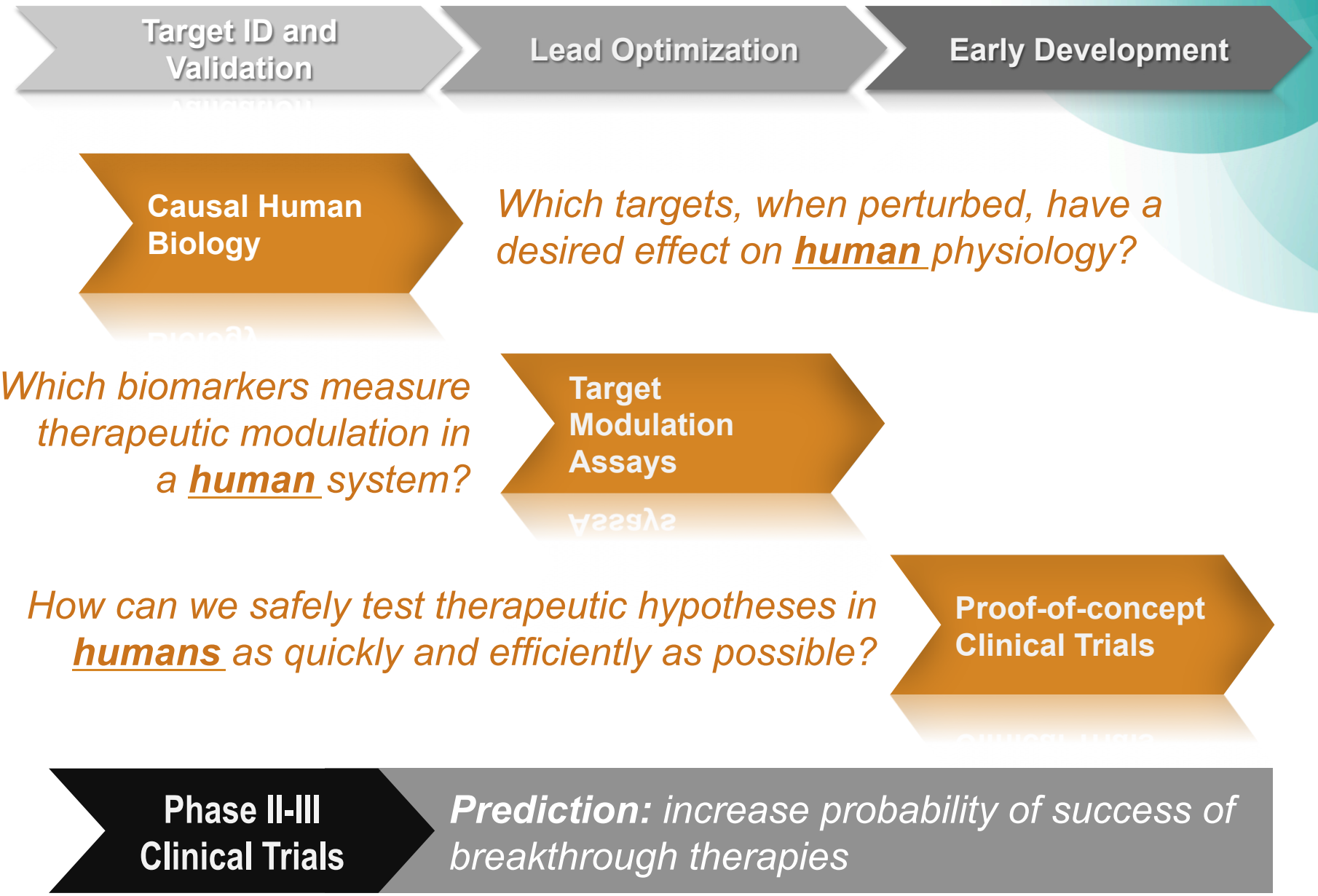


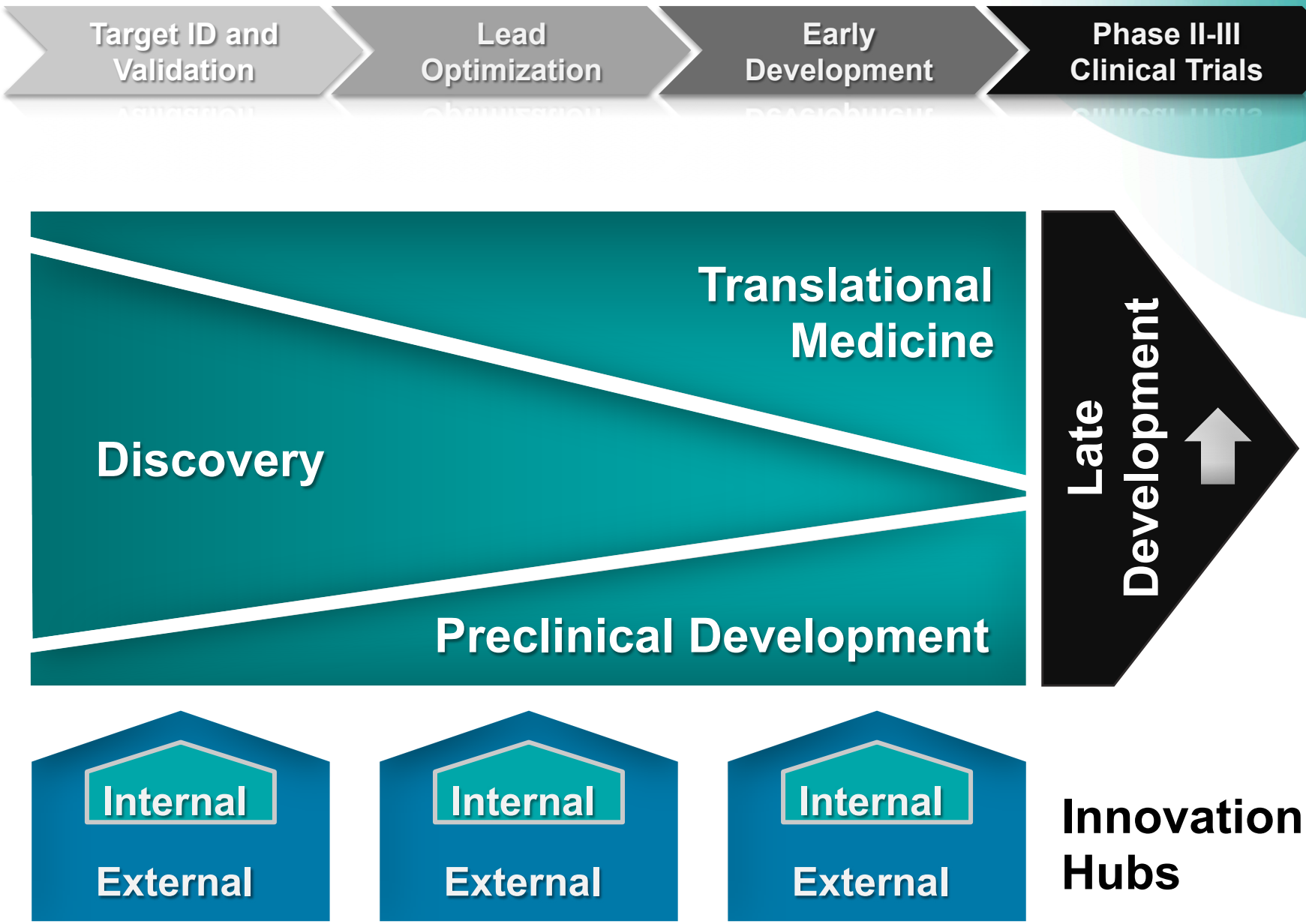
http://csdd.tufts.edu/

Economic forces demand innovative, breakthrough therapies



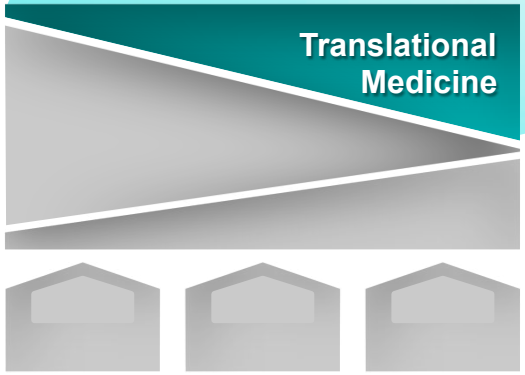
http://www.aetna.com/health-reform-connection/aetnas-vision/facts-about-costs.html


Target ID and Validation
Lead Optimization
Early Development
Causal Human Biology
Which targets, when perturbed, have a desired effect on human physiology?
Which biomarkers measure therapeutic modulation in a human system?
Target Modulation Assays
How can we safely test therapeutic hypotheses in humans as quickly and efficiently as possible?
Proof-of-concept Clinical Trials
Phase II-III Clinical Trials
Prediction: increase probability of success of breakthrough therapies


Target ID and Validation
Lead Optimization
Early Development
Phase II-III Clinical Trials
Translational Medicine
Discovery
Preclinical Development
Late Development
Internal
External
Internal
External
Internal
External
Innovation Hubs

Translational Medicine

- Genetics & Pharmacogenomics
- Translational Biomarkers
- Translational Pharmacology



Target ID and Validation | Lead Optimization | Early Development

Causal Human Biology

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

*Which biomarkers measure therapeutic modulation in a **human** system?*

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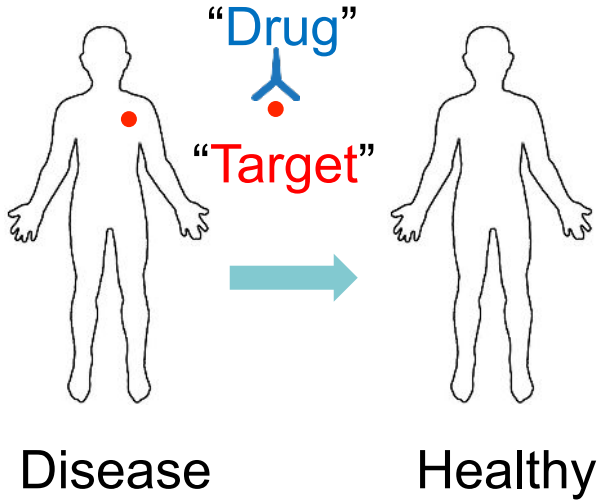
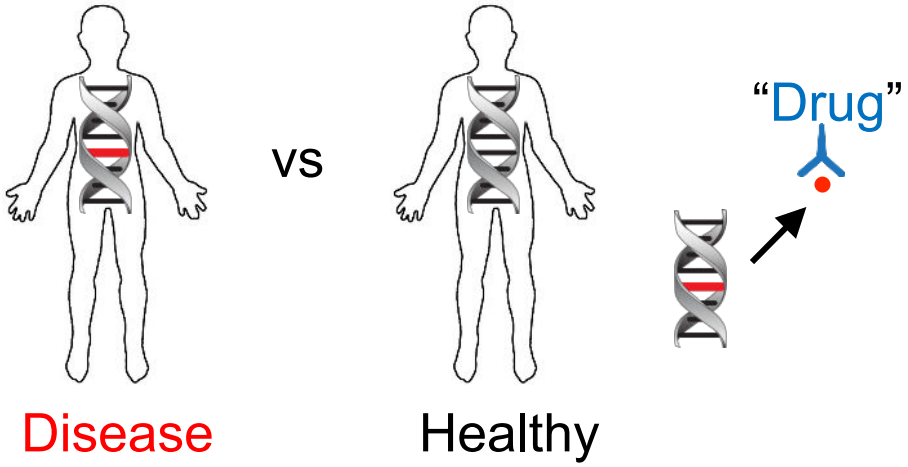
Human genetics helps to identify potential drug targets to kick-start drug discovery



But, tens of thousands of potential targets…

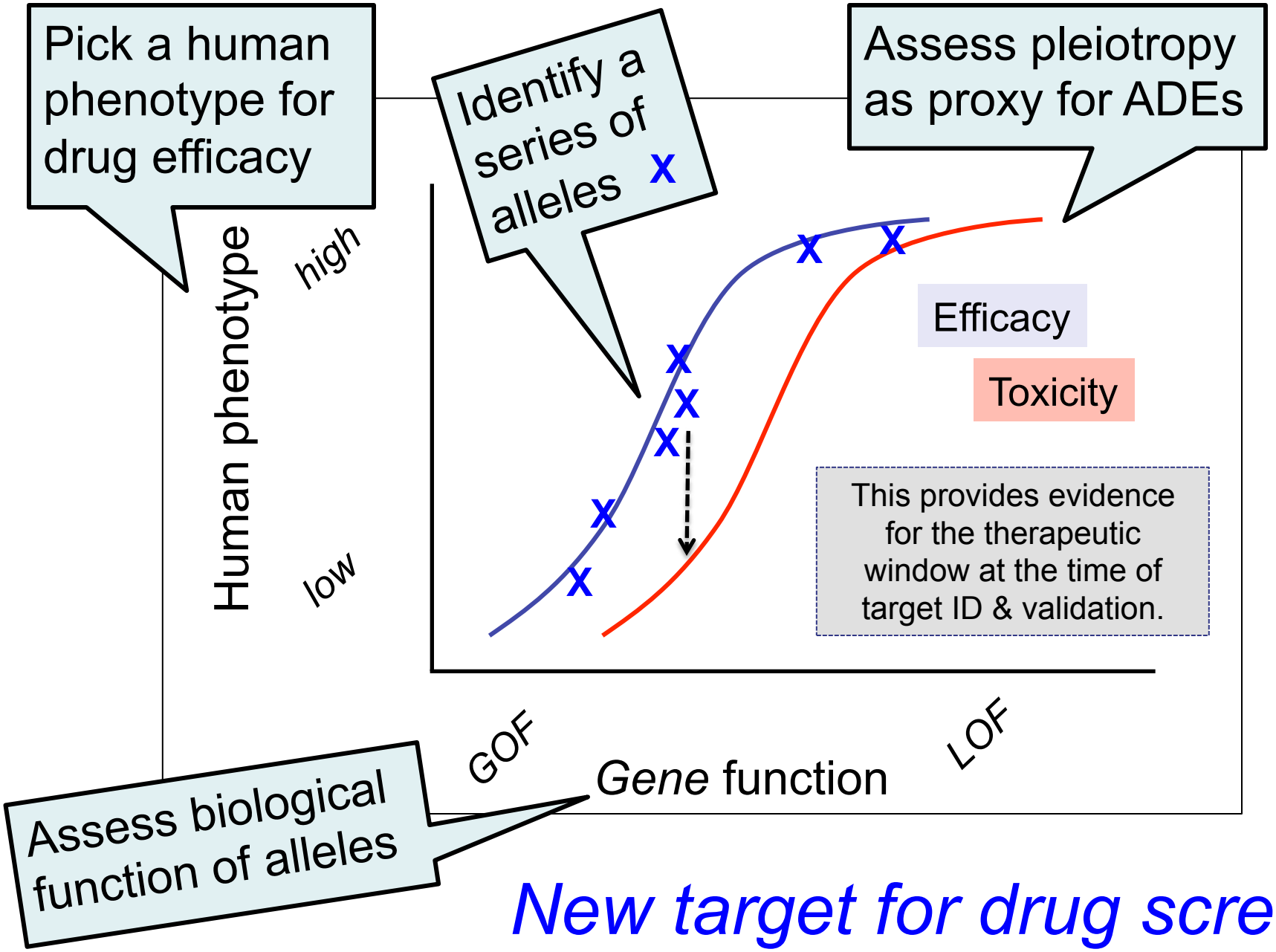
…and which one causes disease?

…and how do you perturb the target?



The key steps are:

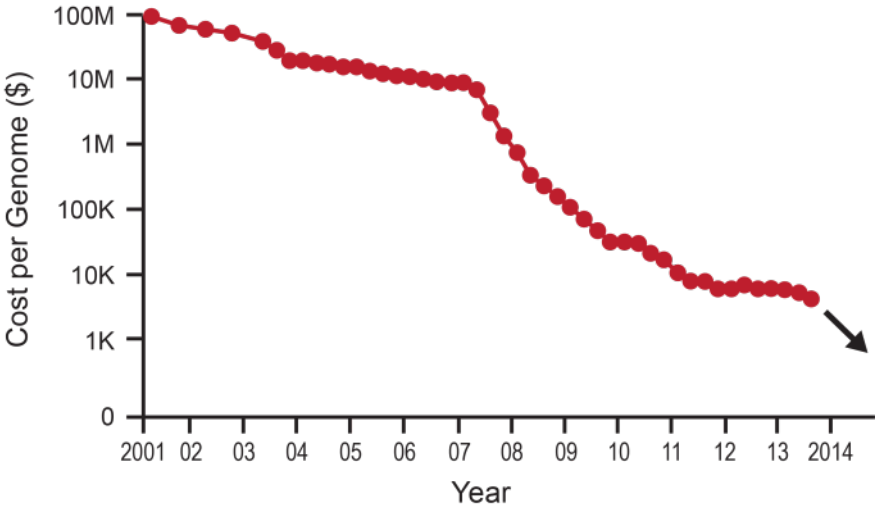
1. Map genetic differences in those with disease vs healthy;
2. Understand how these genetic differences lead to disease;
3. Develop drugs against these targets that reverse disease processes in the population.



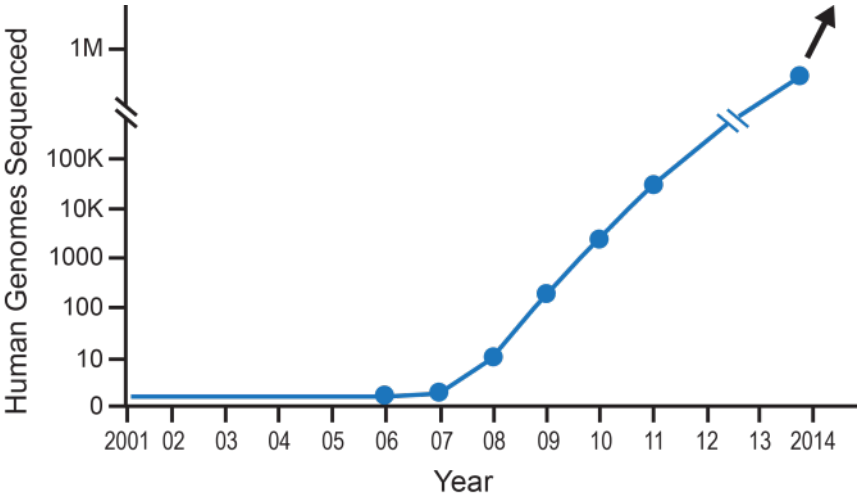
New target for drug screen!

And we are at the beginning of what will be an explosion of genetic discoveries across populations

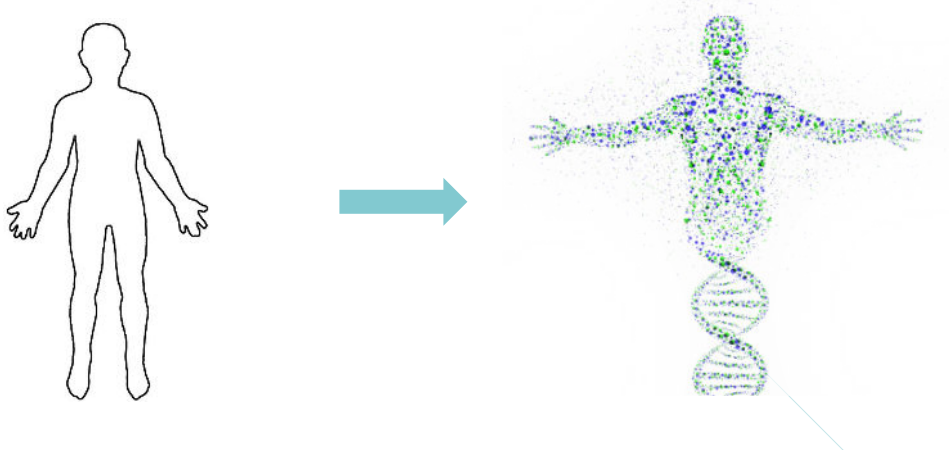
Cost of genome sequencing continues to drop rapidly…



…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

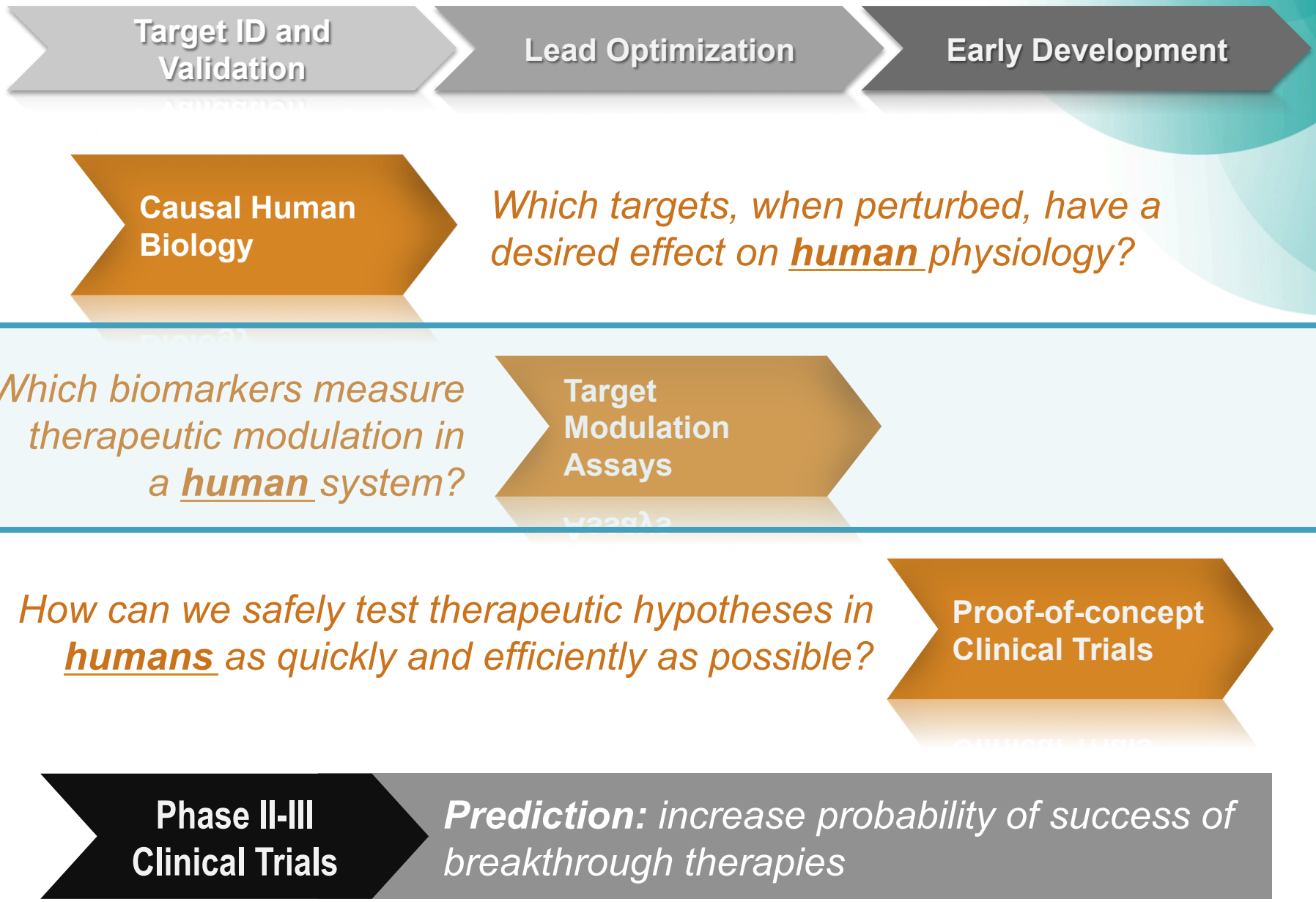
Autoantibodies – autoimmune destruction of orexin neurons and narcolepsy

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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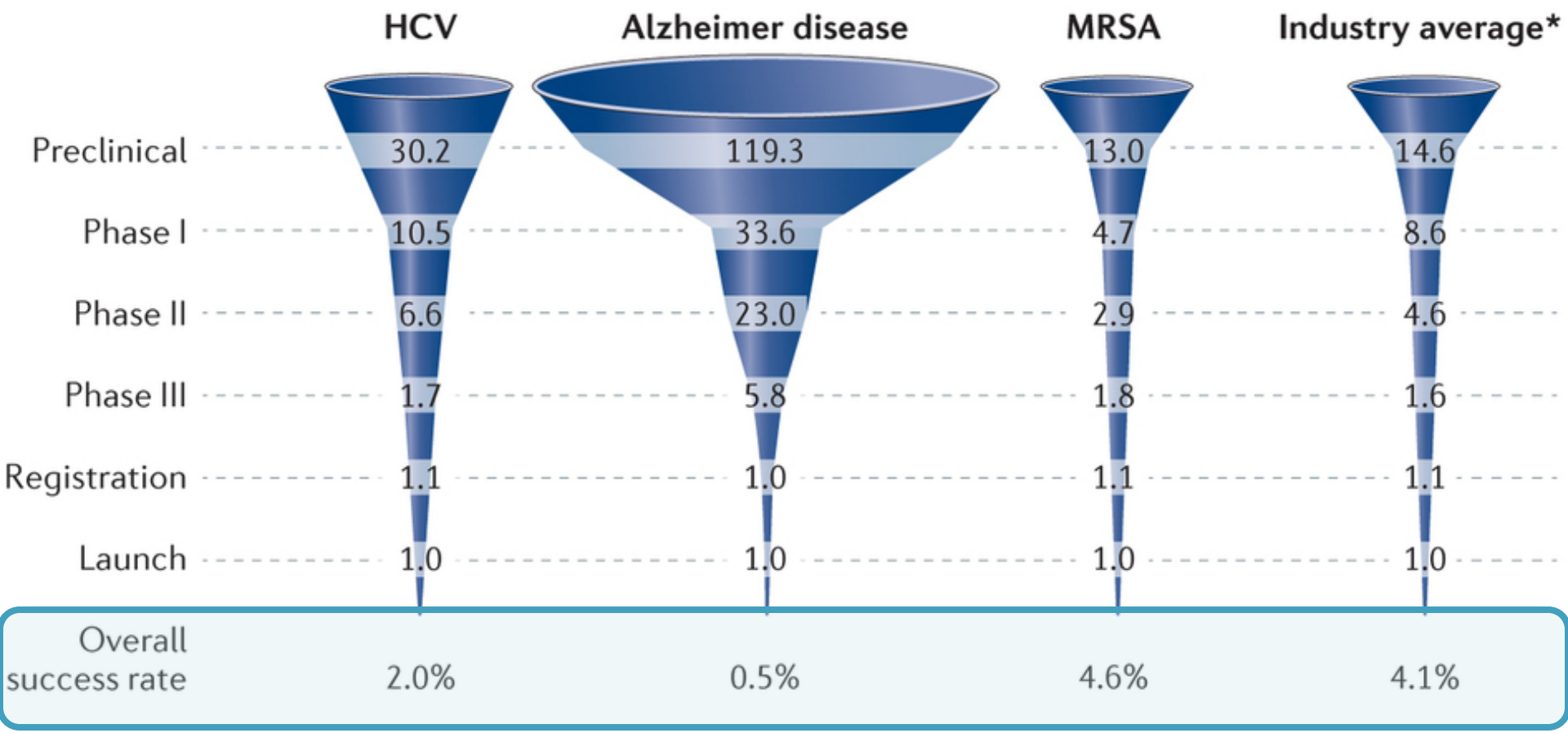
The history of drug development for Alzheimer's disease is not pretty – *very high failure rates*

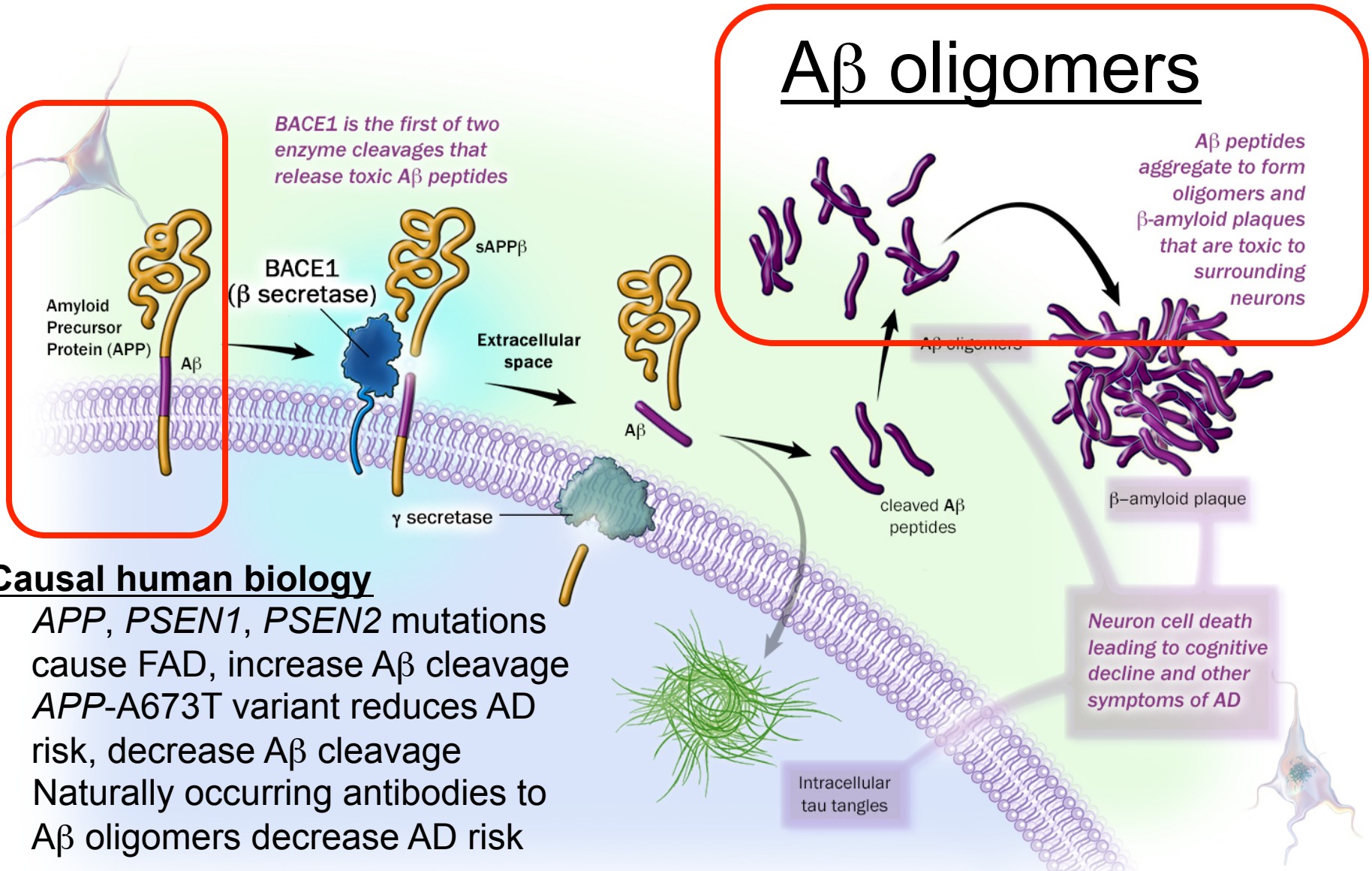


99.5% failure rate!

Nature Reviews | Drug Discovery

Calcoen *et al* (2015) NRDD

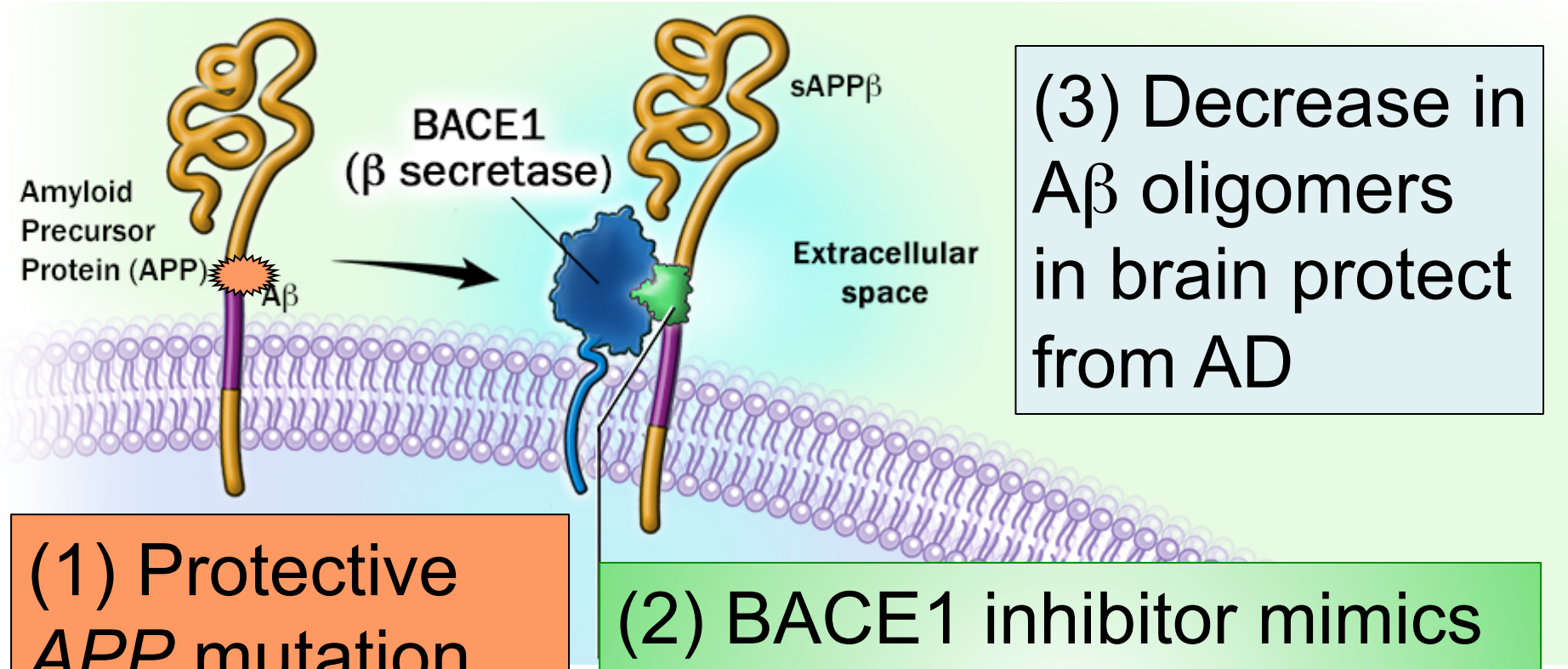
Amyloid hypothesis and Alzheimer's disease: the role of the *APP* gene and BACE1 in disease initiation



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*

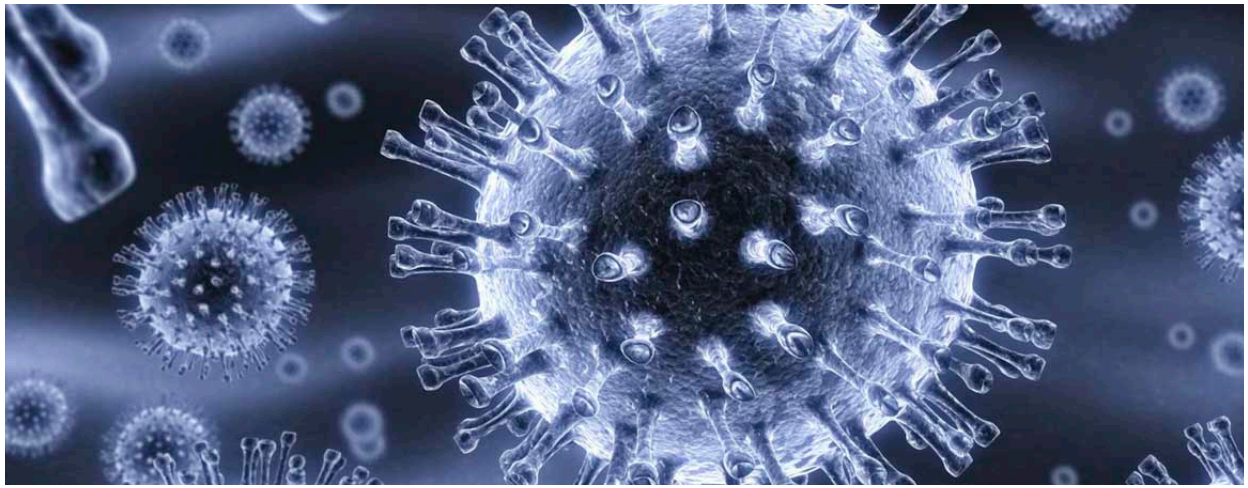


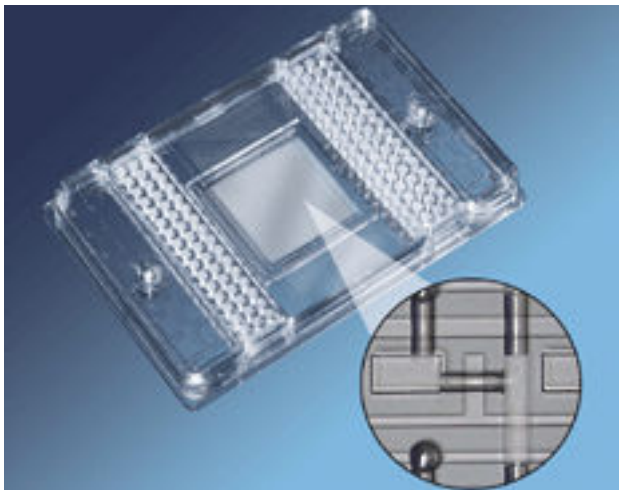
(3) Decrease in Aβ oligomers in brain protect from AD

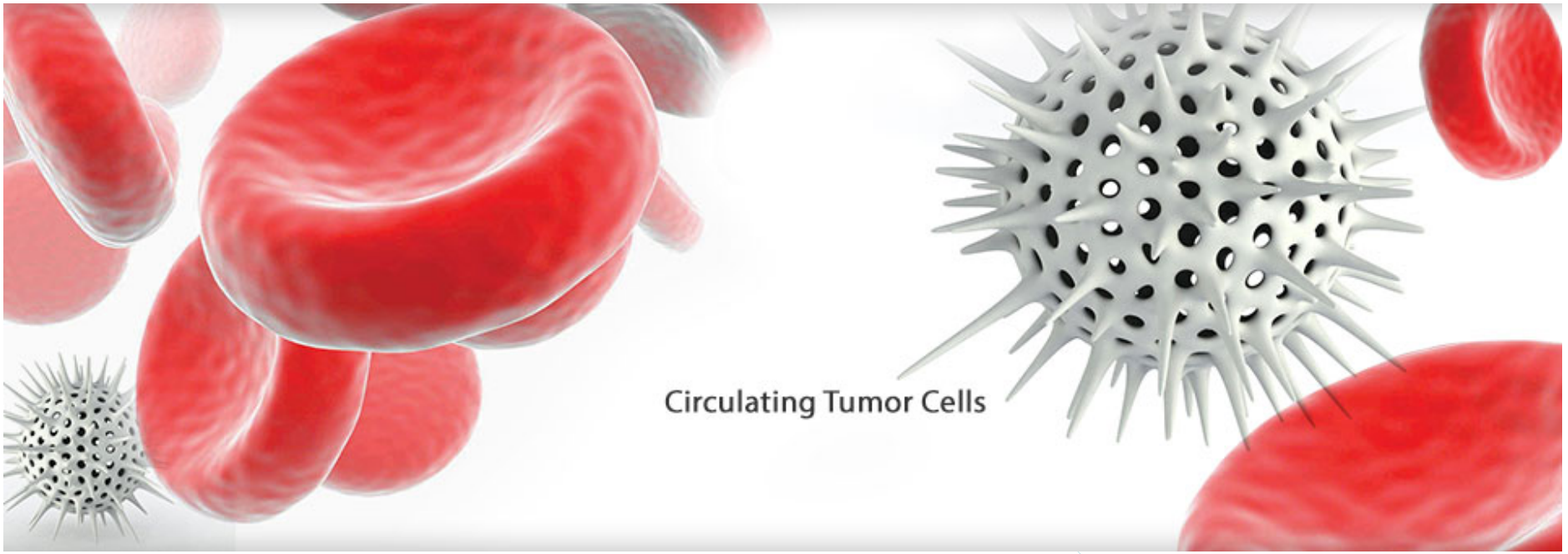
(1) Protective *APP* mutation reduces BACE1 cleavage *in vitro*

(2) BACE1 inhibitor mimics *APP* mutation and blocks first step in release of toxic Aβ peptides

There are new technologies to measure human physiology, including nanotechnologies and NGS

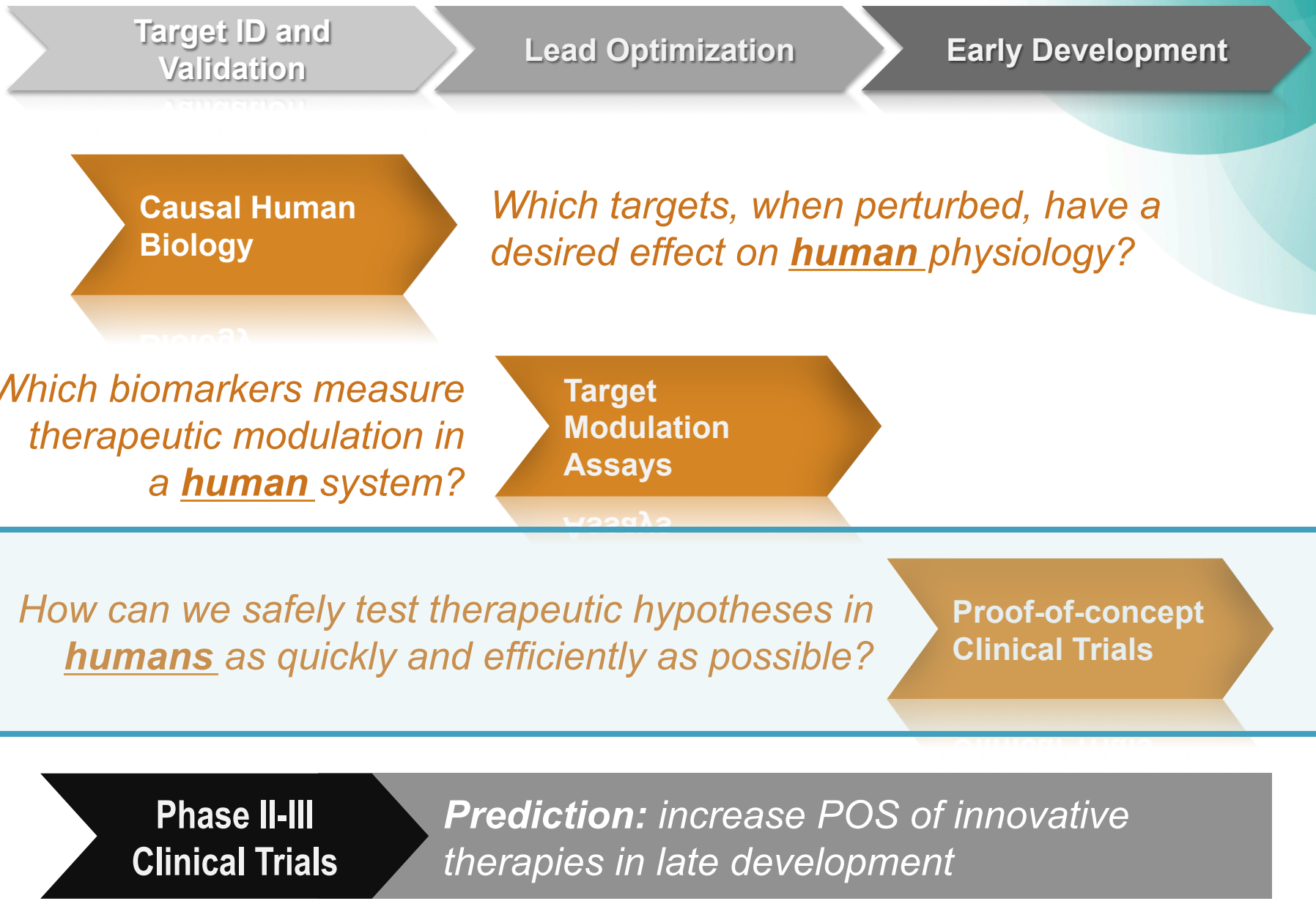






Bottom line:

Robust biomarkers should allow proof-of-mechanism studies in clinical trials…and new technologies are here now!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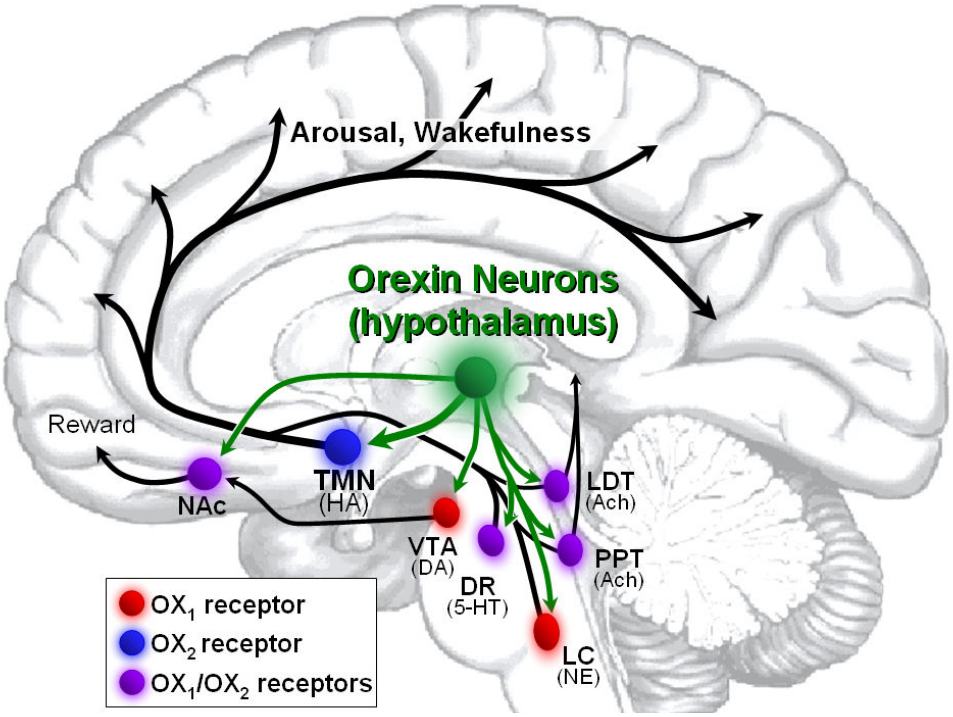
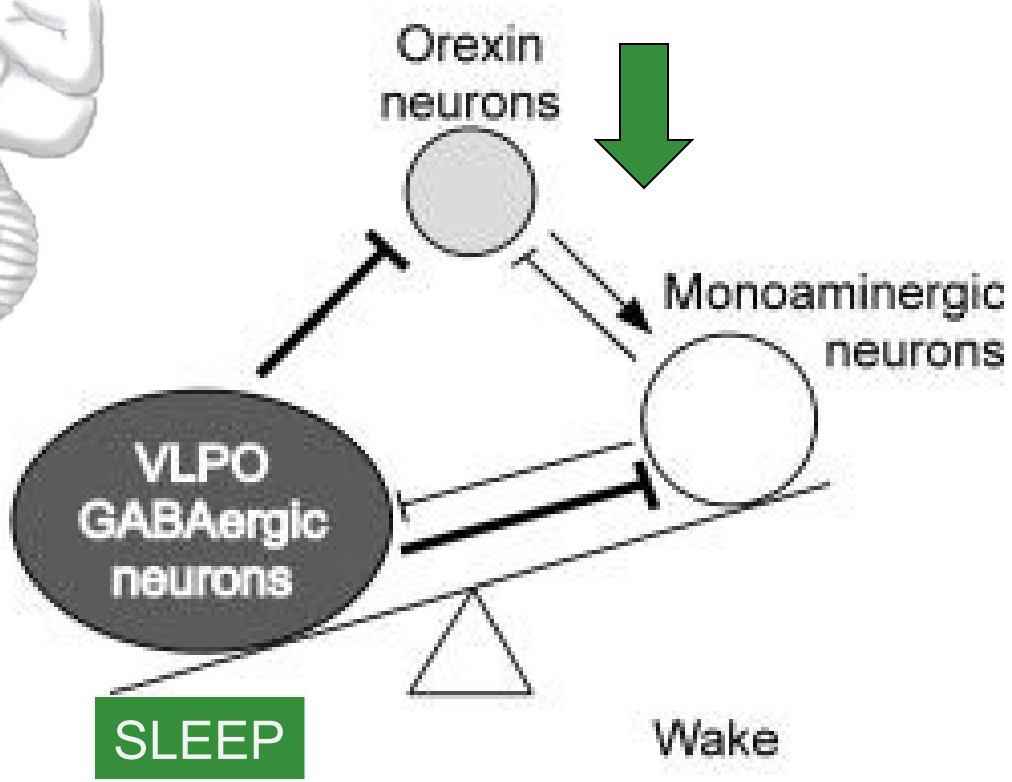
Orexin Receptor Antagonists (ORAs): *a new therapeutic approach to treat insomnia*



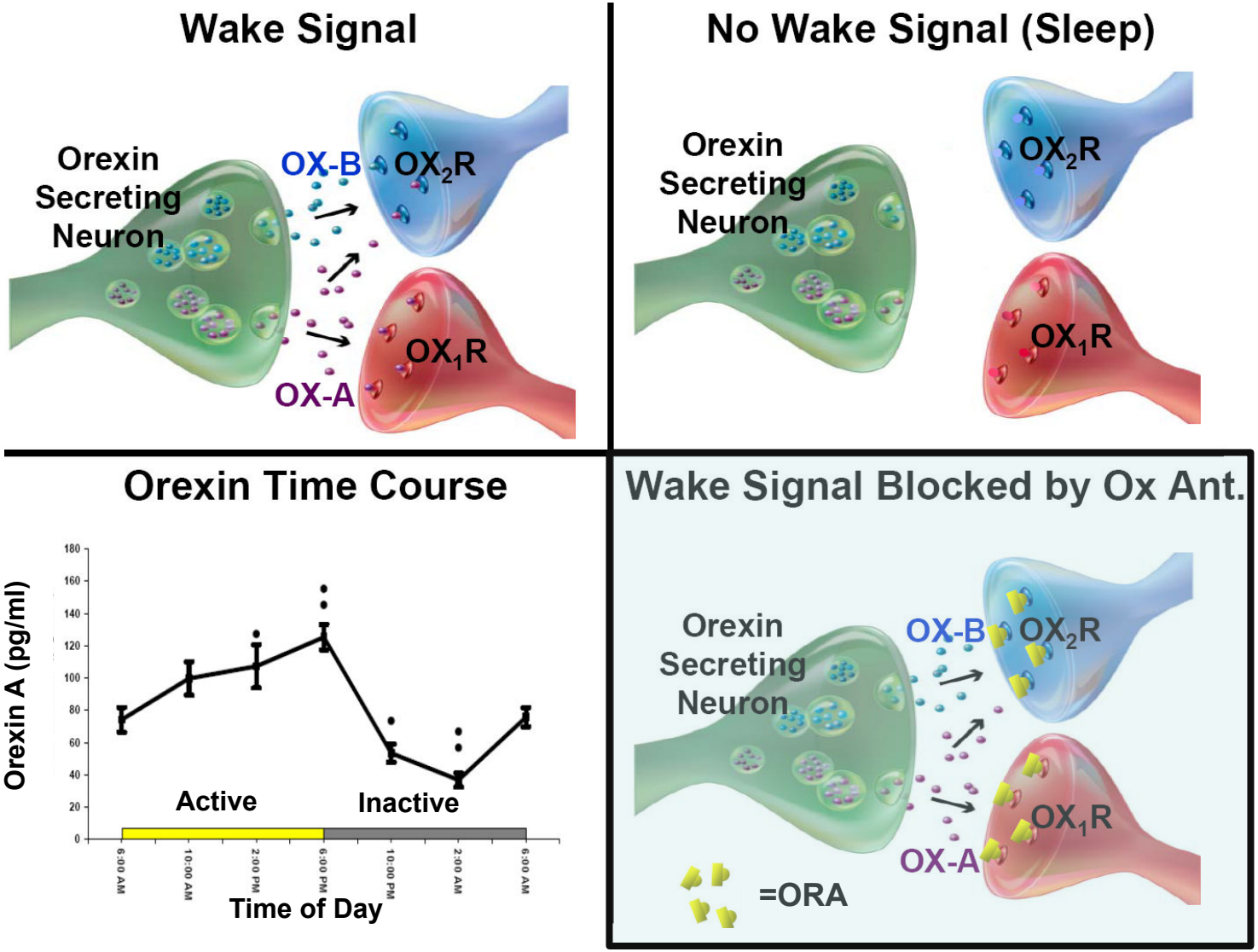
Causal human biology

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



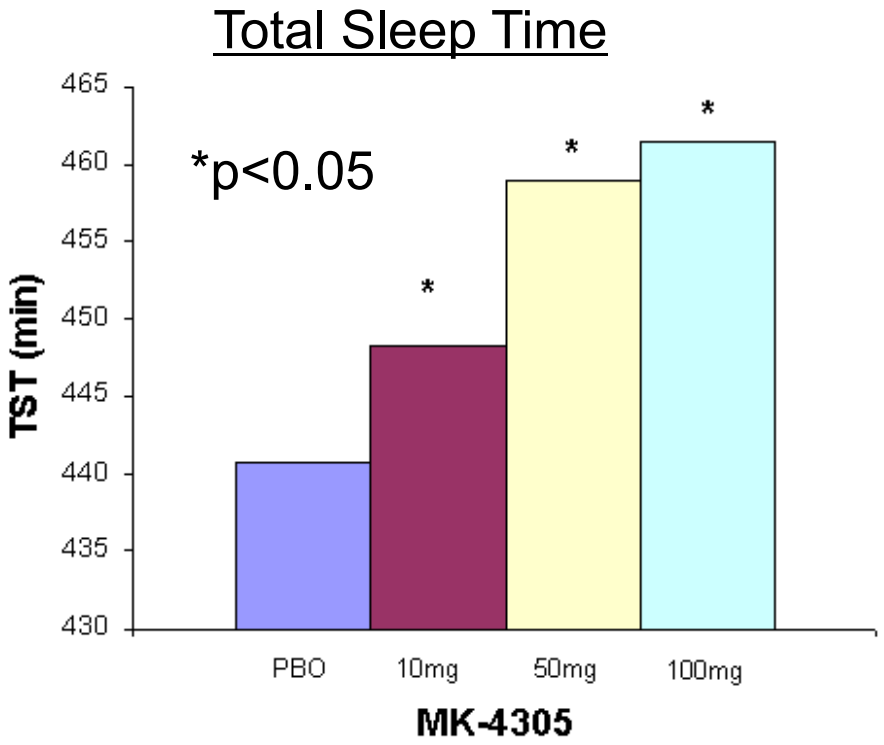
Acknowledgements: *John Renger, Matt Kennedy*

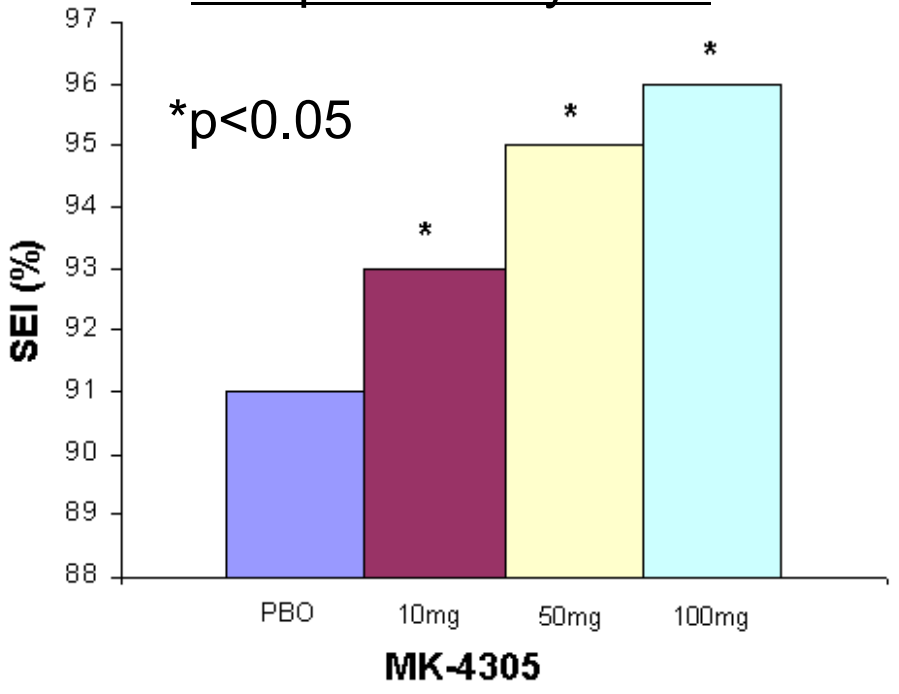
Therapeutic hypothesis: *Orexin receptor antagonism (ORA) blocks wake promoting signal, enabling sleep*



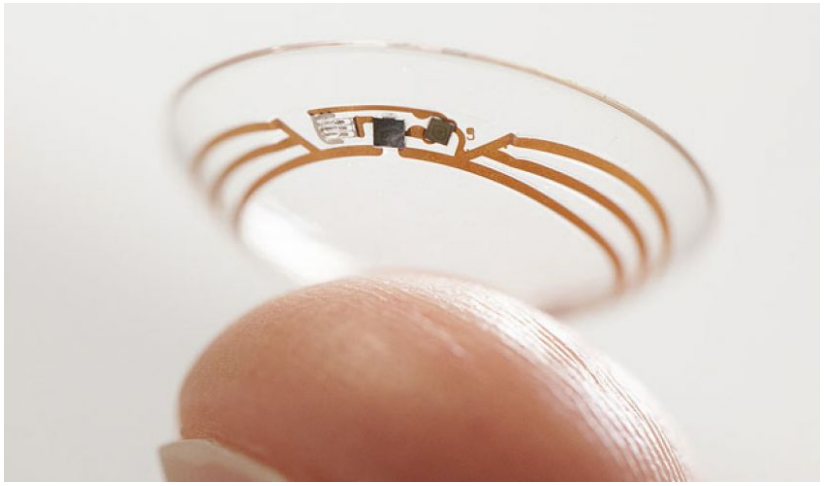
Clinical proof-of-concept (POC) in healthy volunteers: polysomnography (PSG) sleep study

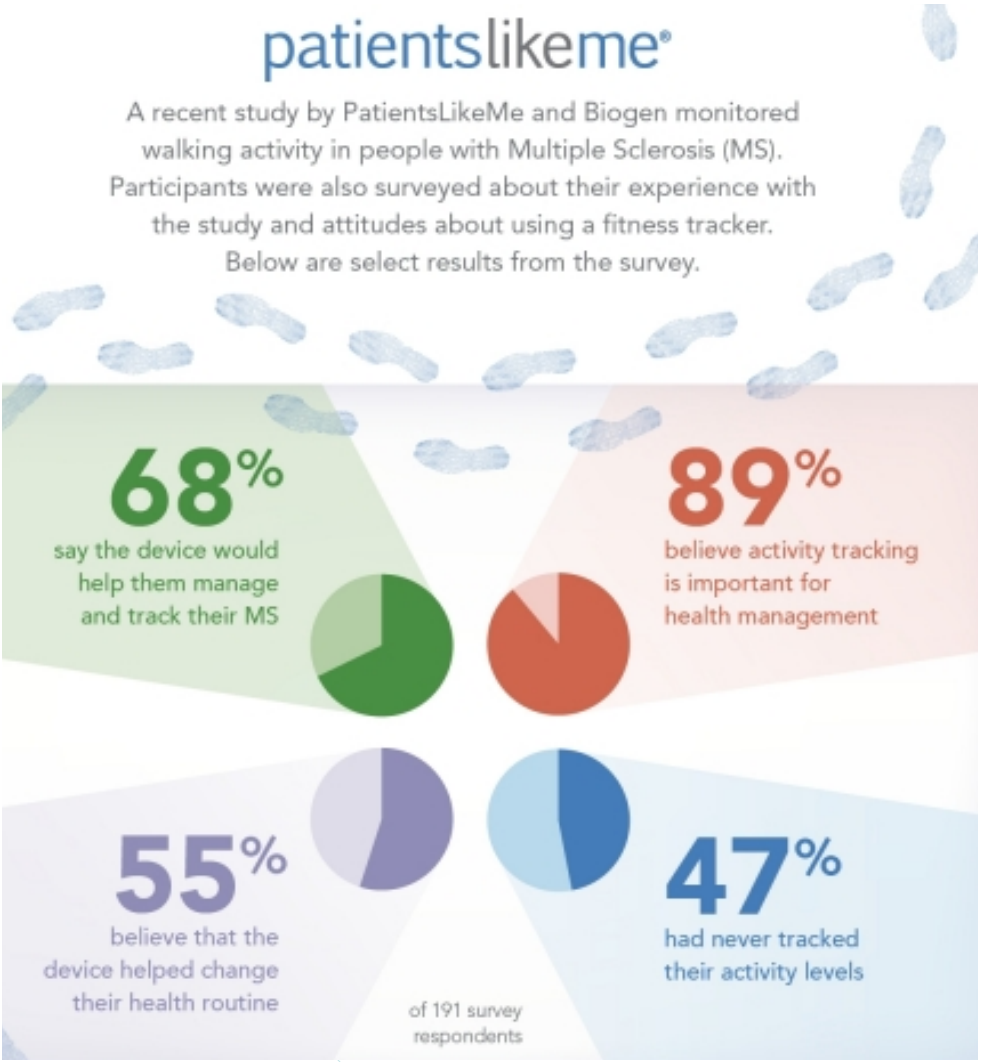
- Study Design: double-blinded, placebo-controlled, 5-period cross-over study in *20 healthy subjects*
- Measurement: 8-hr PSG recording





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…