Human genetics and drug discovery – *the role of Mendelian randomization*

Robert Plenge, MD, PhD

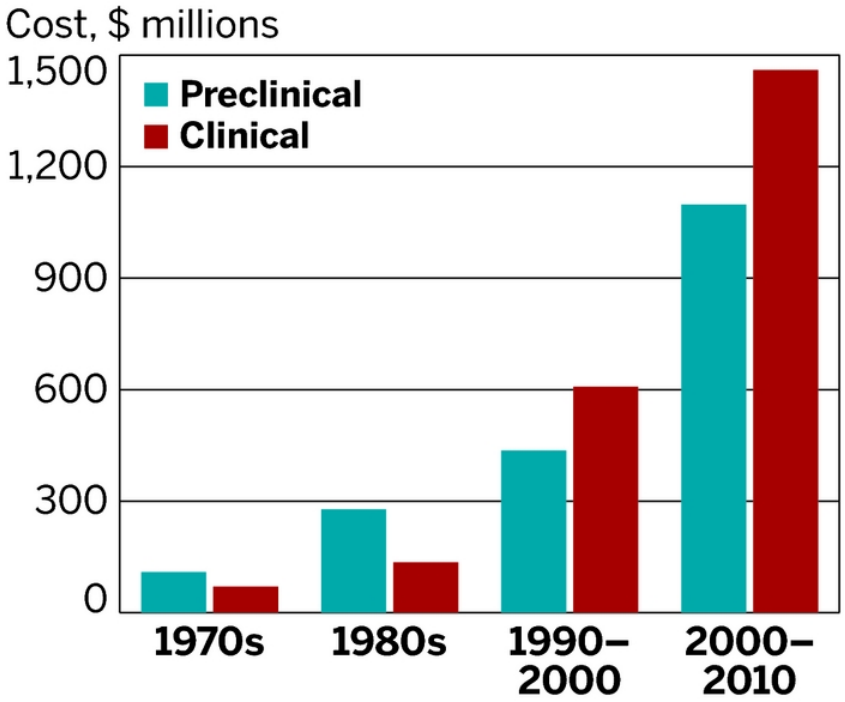
June 23, 2015

MERCK
Be well

The Problem

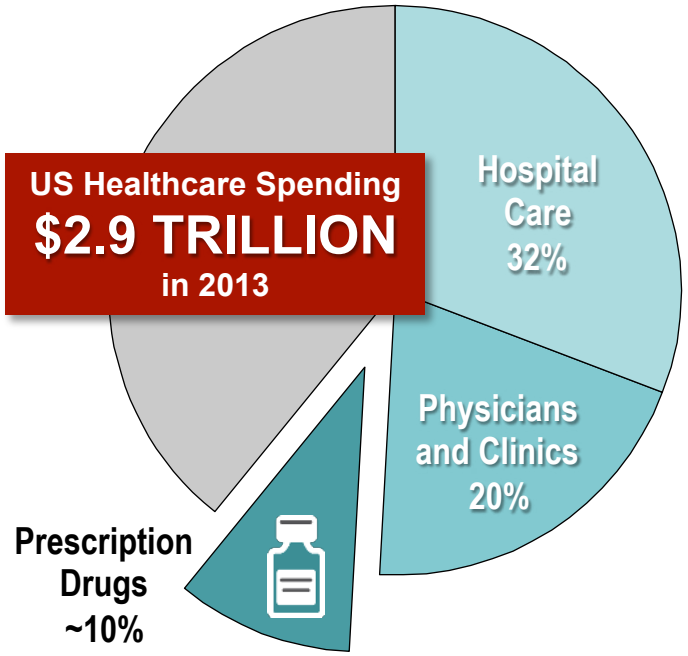
Two key challenges in drug development: *high failure rate and insufficient innovation*

Phase II/III failures drive high cost of drug development



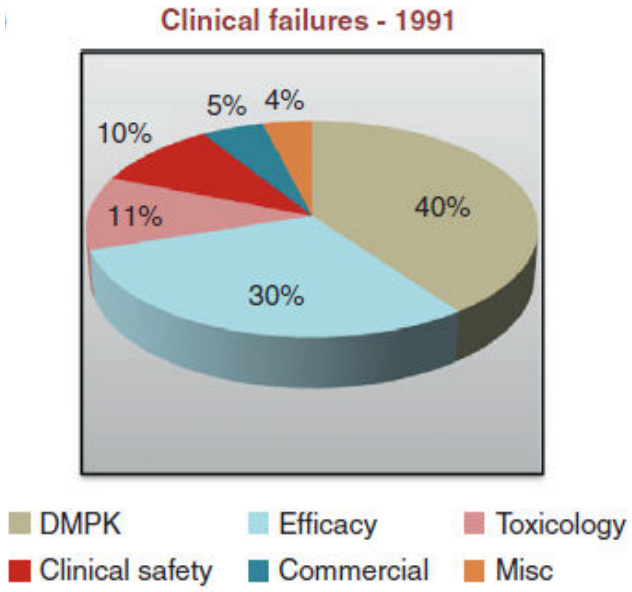
Attrition problem

Rising healthcare costs driving demand for innovative, breakthrough therapies

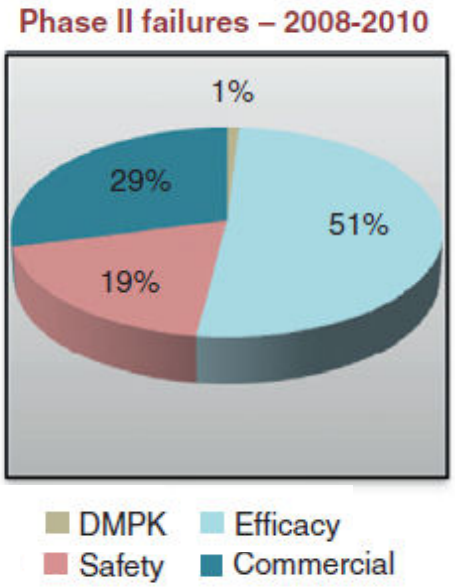


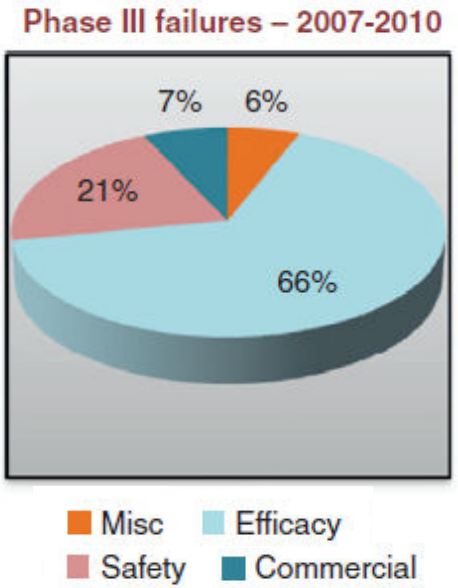
Innovation problem

The Attrition Problem



…now it is efficacy/safety





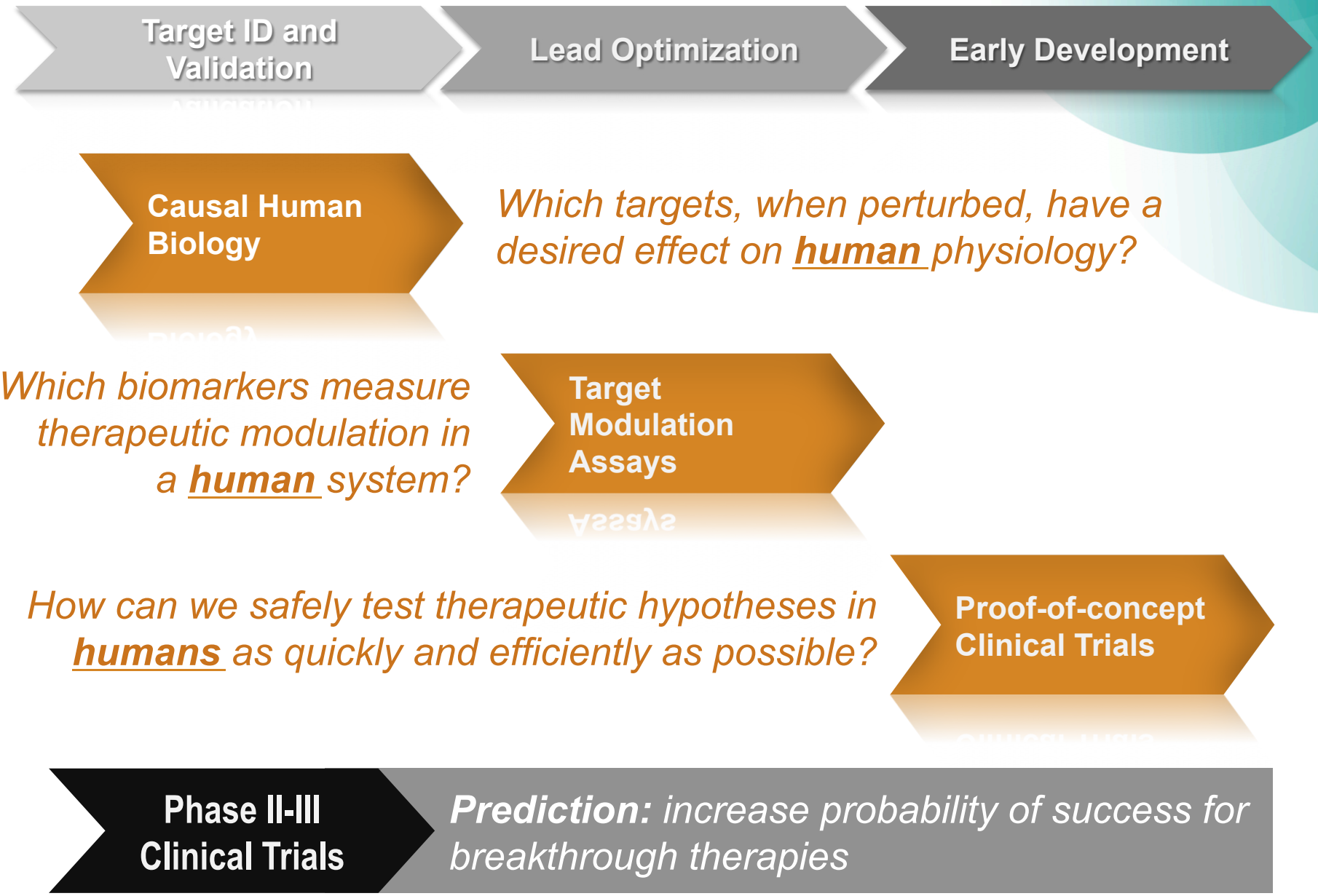
It was drug metabolism & pharmacokinetics (DMPK)…

Pr Proprietary

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?

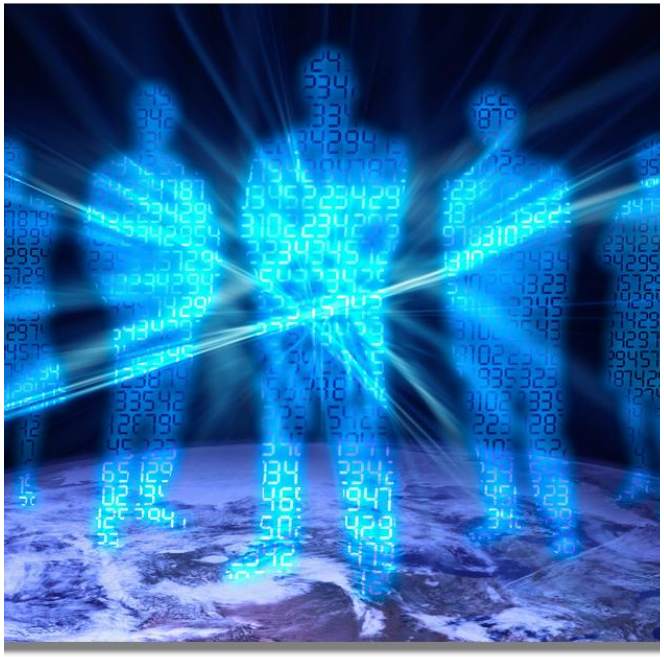

Target ID and Validation
Lead Optimization
Early Development
Causal Human Biology
Which targets, when perturbed, have a desired effect on human physiology?
Which biomarkers measure therapeutic modulation in a human system?
Target Modulation Assays
How can we safely test therapeutic hypotheses in humans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

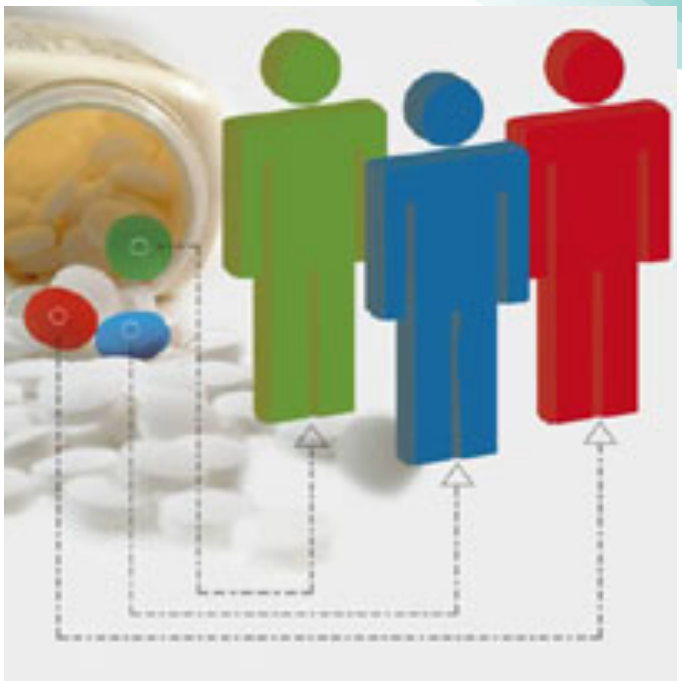
Technology is changing the ideal model organism for drug discovery and development

It was…

Target ID and Validation → Lead Optimization → Early Development

Today, *humans are the model organism of choice* for new targets and precision medicine





Target ID and Validation → Lead Optimization → Early Development

Three examples (focused on human genetics)

Target ID and Validation | Lead Optimization | Early Development

Causal Human Biology

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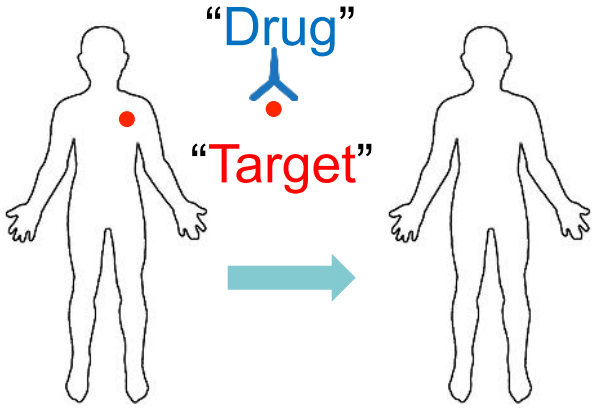
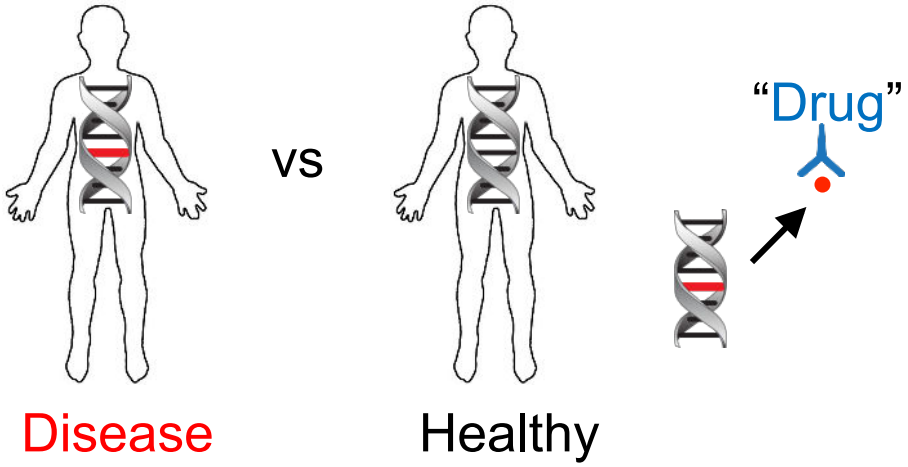
Human genetics helps to identify potential drug targets to kick-start drug discovery



But, tens of thousands of potential targets…

…and which one causes disease?

…and how do you perturb the target?

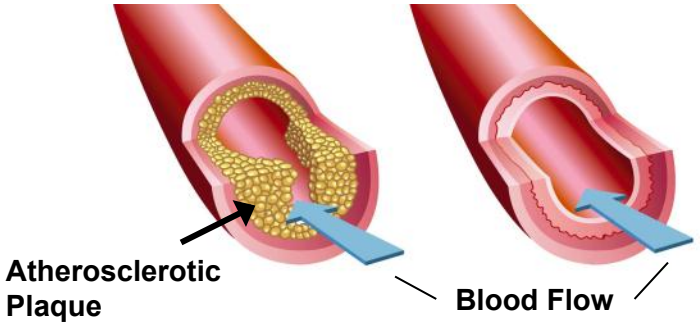


The key steps are:

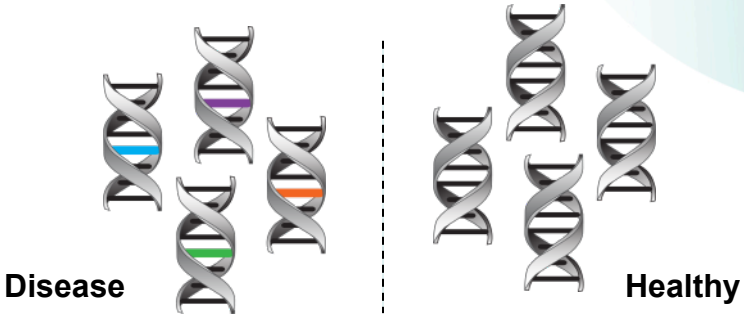
1. Map genetic differences in those with disease vs healthy;
2. Understand how these genetic differences lead to disease;
3. Develop drugs against these targets that reverse disease processes in the population.

There are anecdotal examples of human genetics leading to new drug targets (*PCSK9*), and…

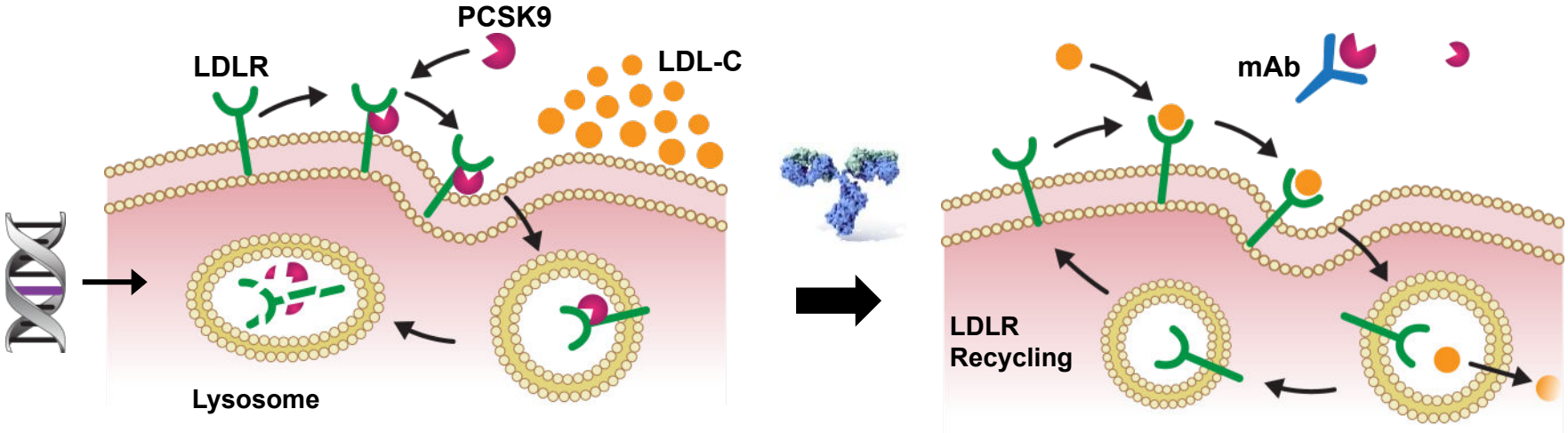
Many genes influence cholesterol levels and risk of heart disease



We can now find these disease genes…



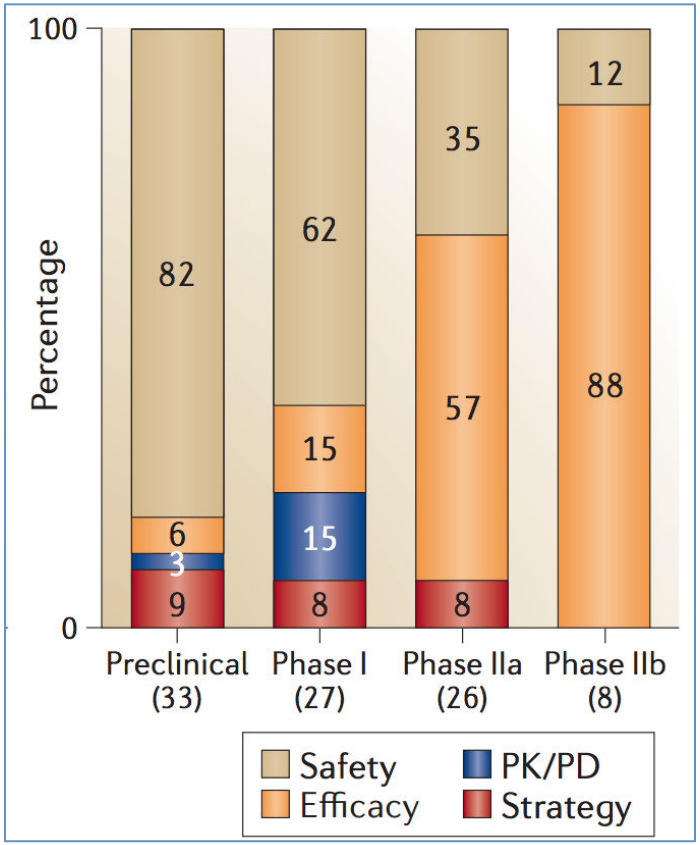
…and design studies to find drugs that fix the underlying molecular defects – for example, blocking PCSK9 lowers LDL (or "bad") cholesterol in the blood.

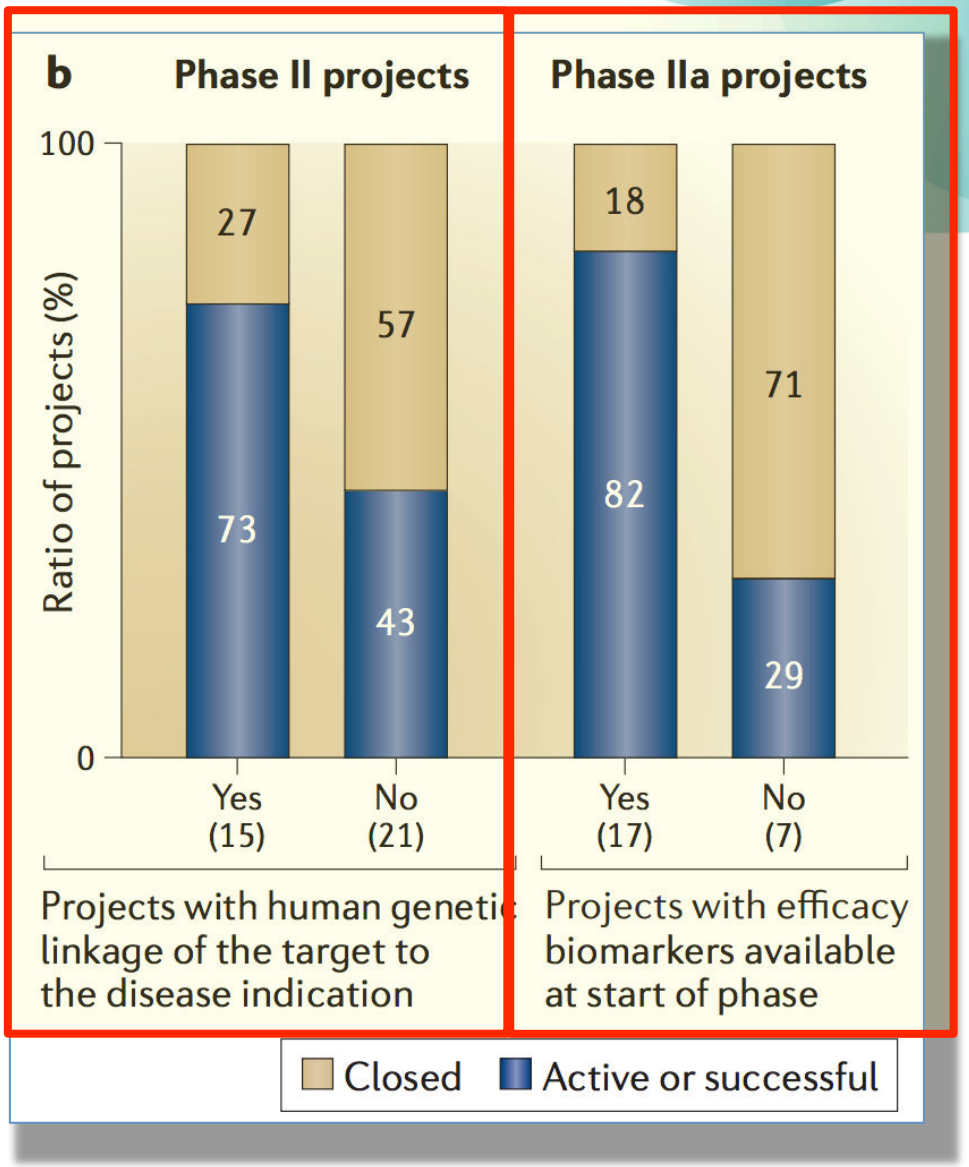


…portfolios of drug targets with human genetic support have a higher probability of success

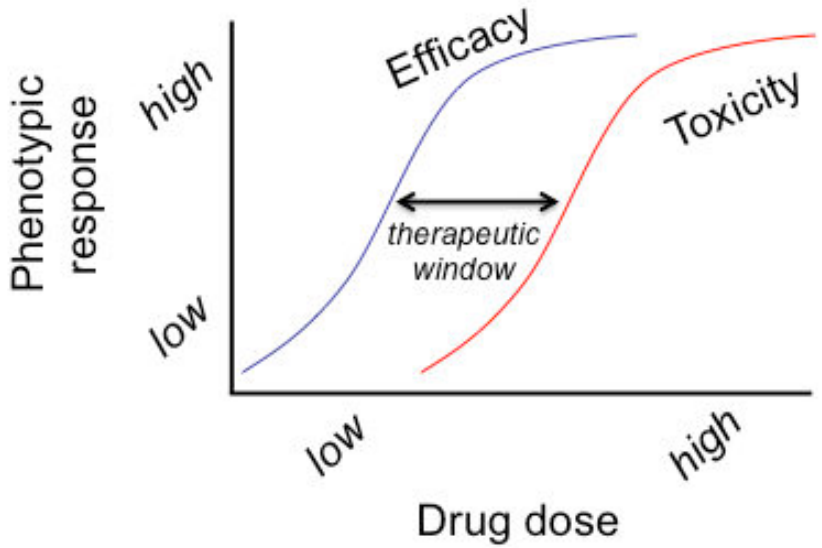
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos





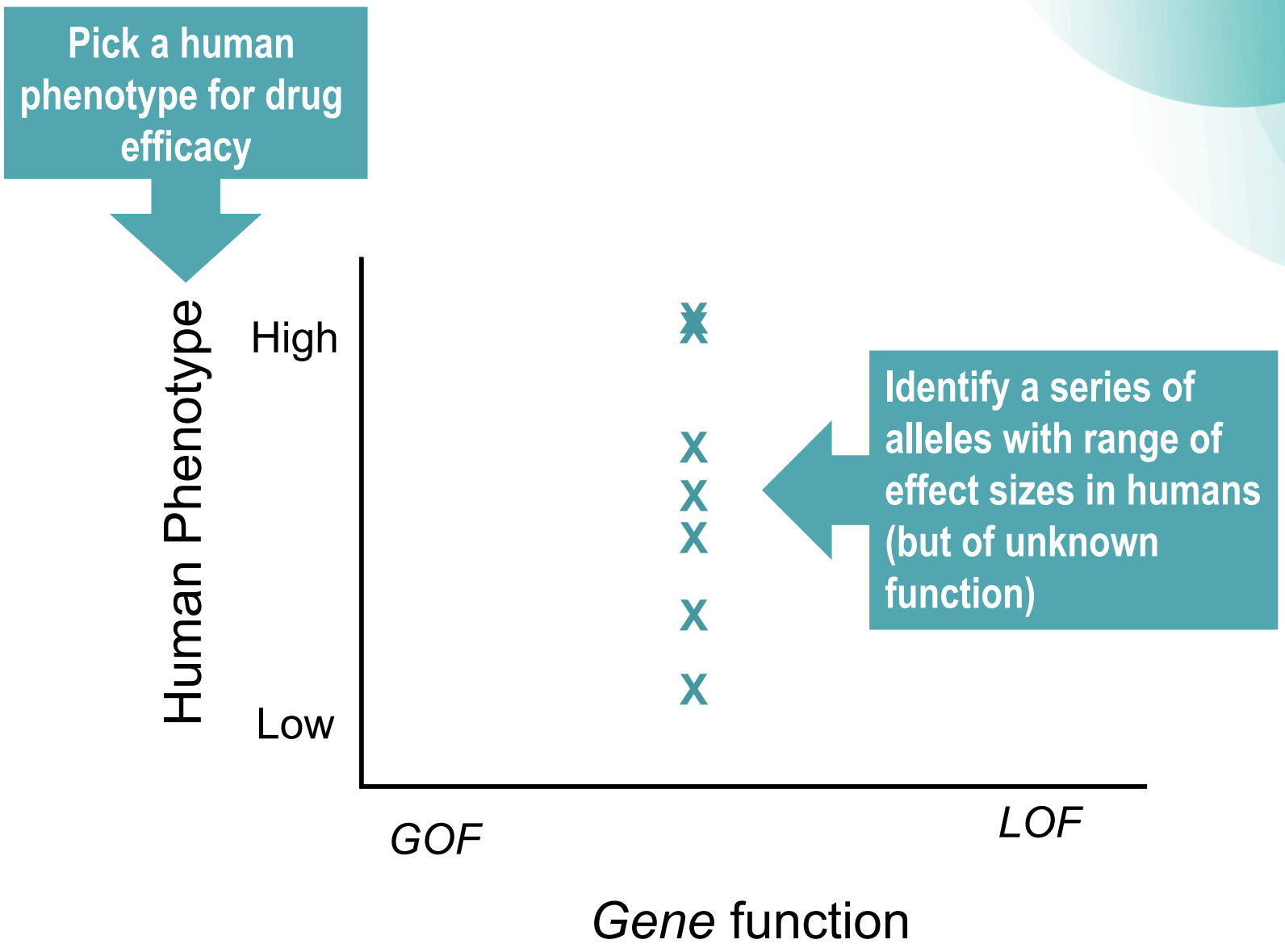
What is a genetic strategy?

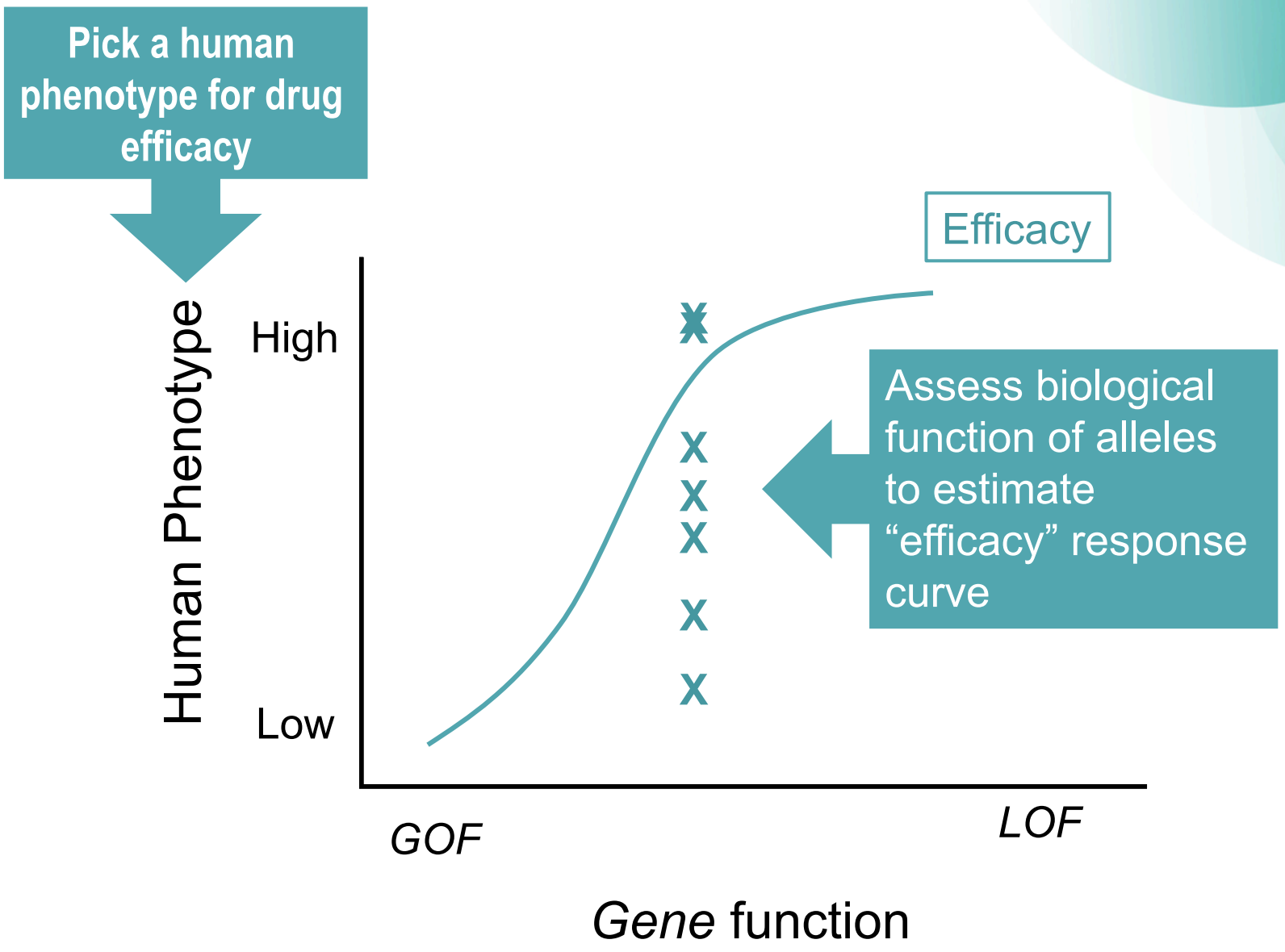


Target ID and Validation → Lead Optimization → Early Development → Phase II-III Clinical Trials

We aspire to determine dose-response at the time of target ID and validation

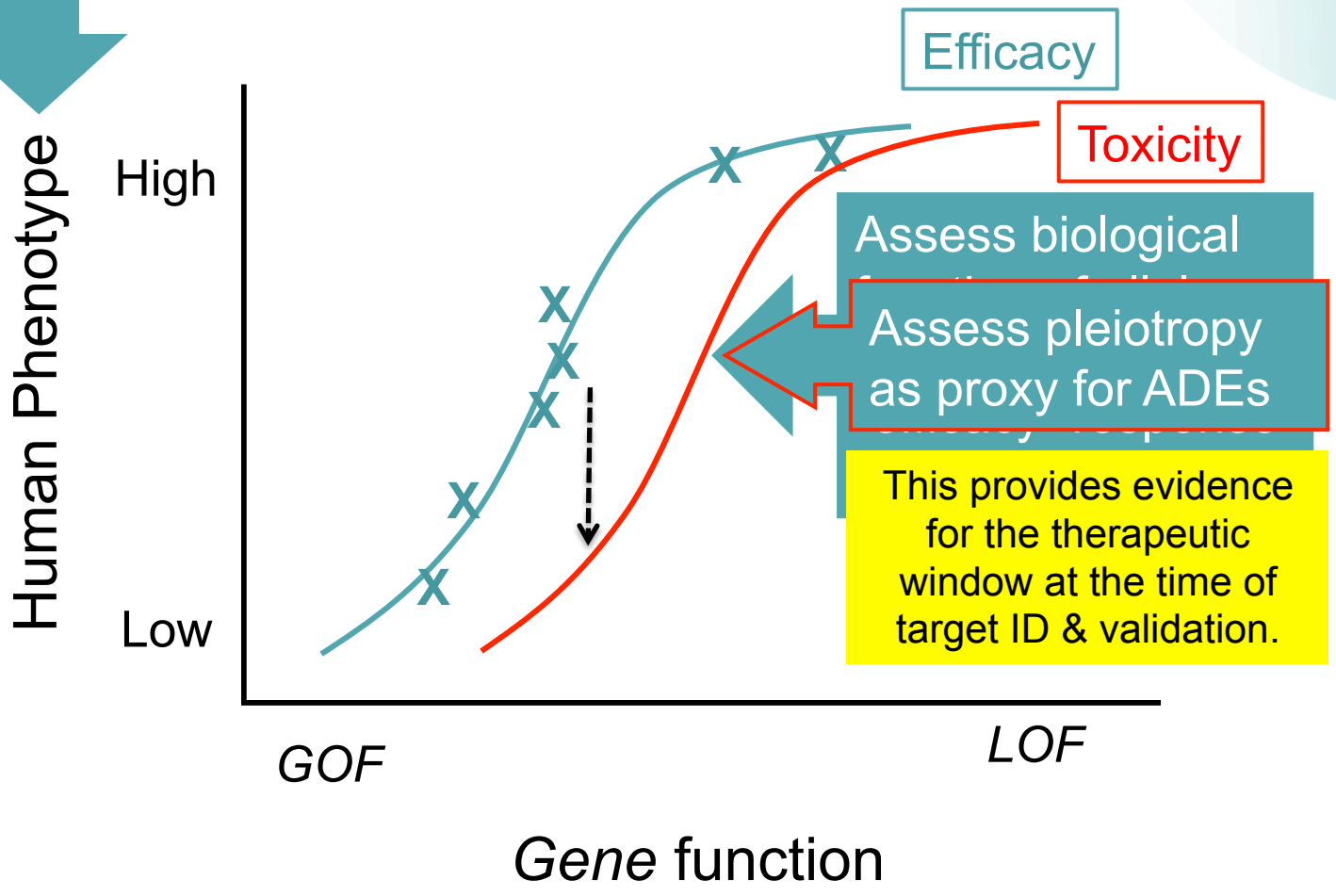
We determine dose-response in clinical trials, after many years and millions of dollars


Pick a human phenotype for drug efficacy
Human Phenotype
High
Low
Identify a series of alleles with range of effect sizes in humans (but of unknown function)
GOF
LOF
Gene function


Pick a human phenotype for drug efficacy
Efficacy
Human Phenotype
High
Low
Assess biological function of alleles to estimate "efficacy" response curve
GOF
LOF
Gene function

New target for drug screen!

Pick a human phenotype for drug efficacy



The list of genes with an “allelic series” is growing

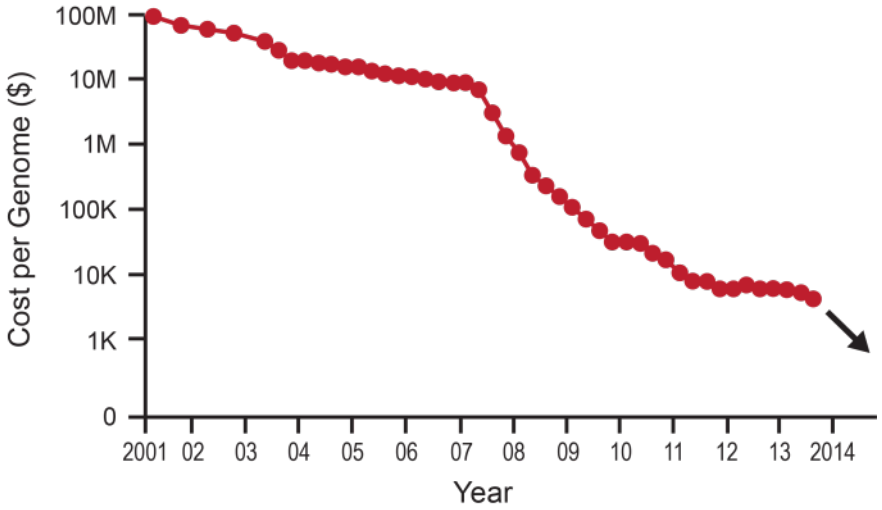
Gene	LOF	GOF
PCSK9	low CAD risk, low LDL-C	high LDL-C, high CAD risk
APP/BACE1	high AD, dementia risk	low AD, dementia risk
LRRK2	high PD risk	low PD risk
SCN9A	pain insensitivity	neuropathy, hyperexcitability
PNPLA3	low LDL-C, TG	high NAFLD, NASH, PBC, HCC risk
CARD9	low IBD risk, high risk for fungal infections	high IBD, AS, PSC risk
TYK2	low RA, psoriasis, SLE, MS risk, high risk for PID	high T-ALL risk
IFIH1	low T1D risk, high risk for PID	high SLE risk, AG, SM syndromes

… and there are further genes with protective LoF variants, for example:

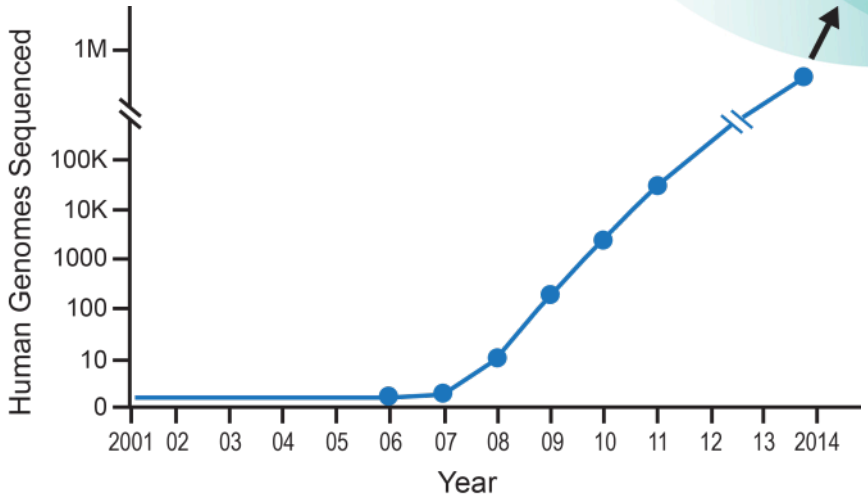
SLC30A8 (T2D), *IL6R* (RA), *NPC1L1* (CAD), *APOC3* (CAD), *CCR5* (HIV)

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

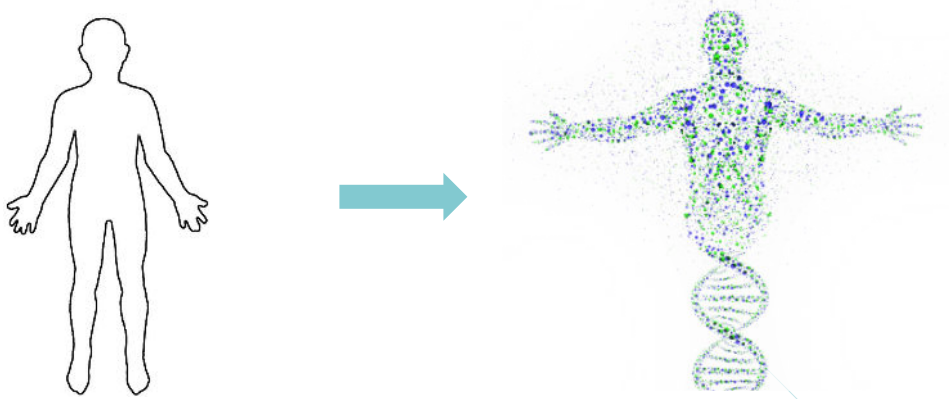
Cost of genome sequencing continues to drop rapidly…



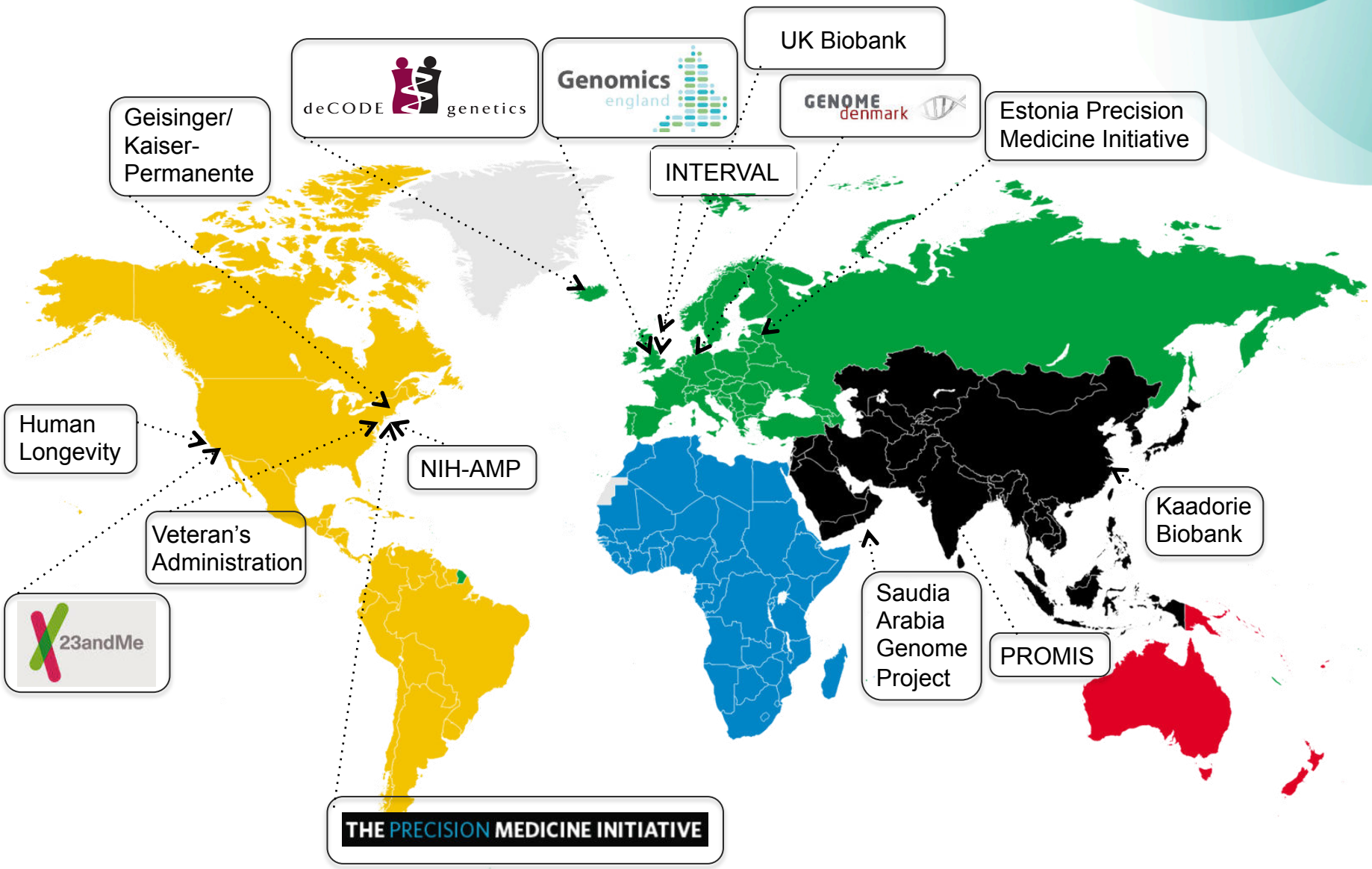
…which results in many more human genomes being sequenced…



…and a more accurate molecular understanding of human disease.



Initiatives now link human genetics with clinical phenotypes in a setting for recall



Target ID and Validation | Lead Optimization | Early Development

Causal Human Biology

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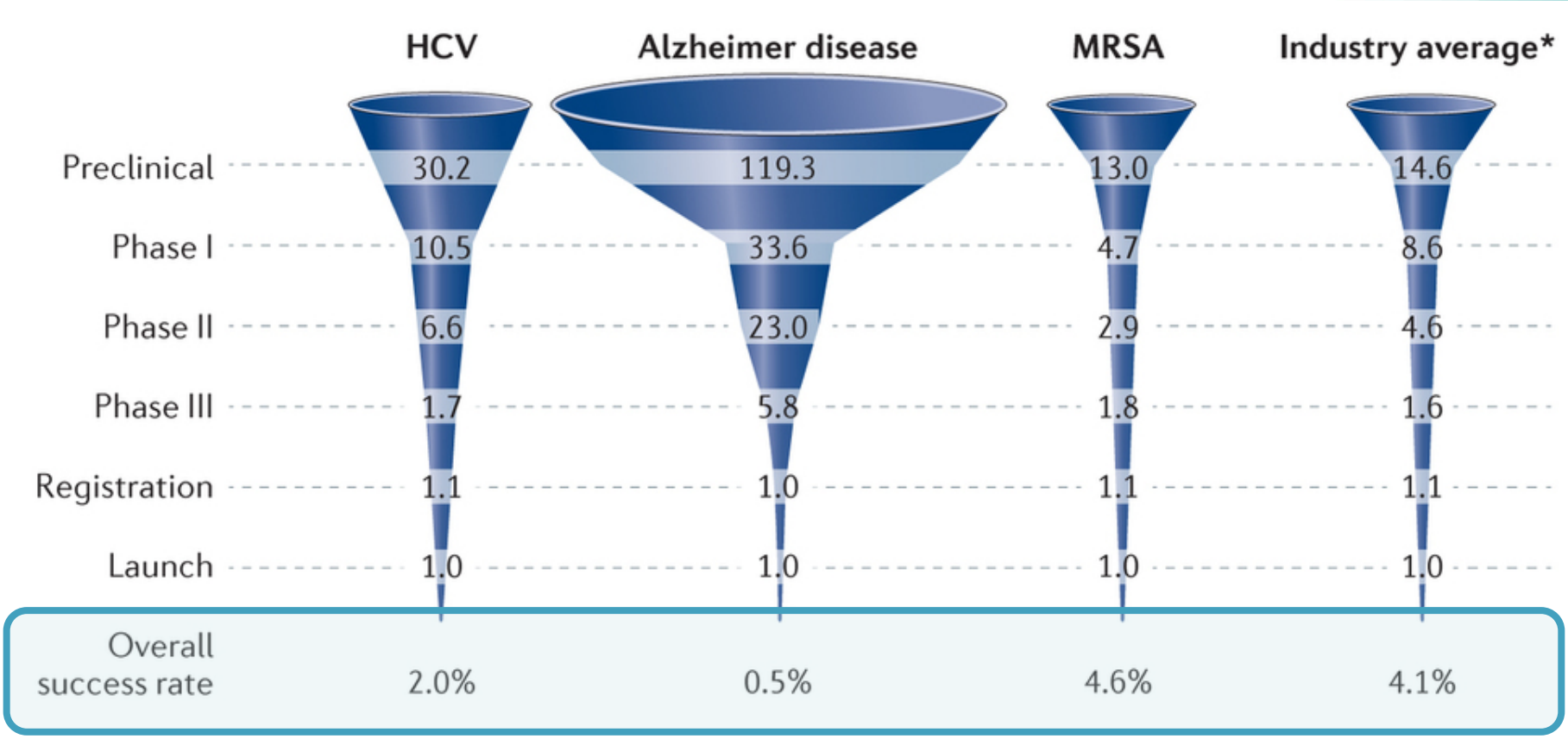
BACE-inhibitor program in Alzheimer's disease

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

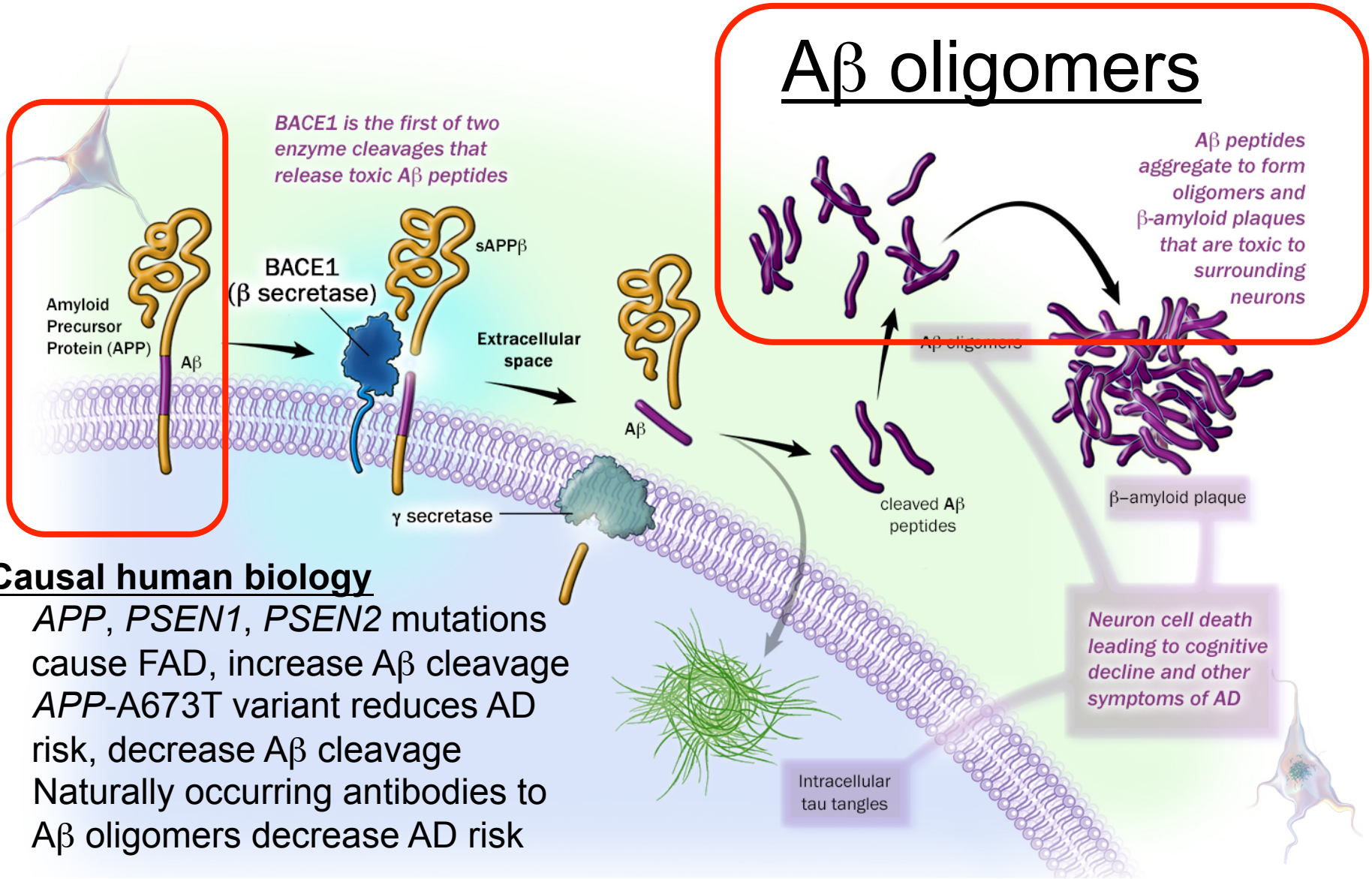


99.5% failure rate!

Nature Reviews | Drug Discovery

Calcoen *et al* (2015) NRDD

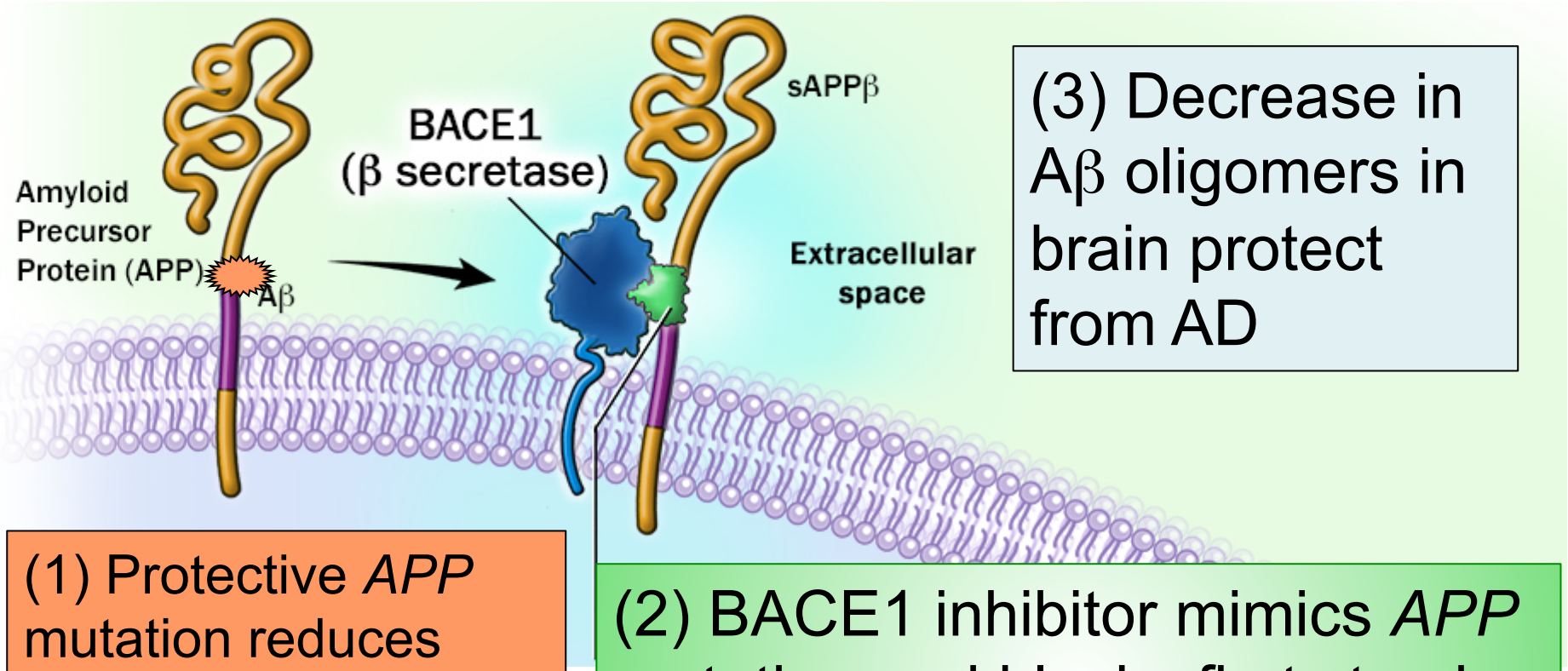
Amyloid hypothesis and Alzheimer's disease: the role of the *APP* gene and BACE1 in disease initiation



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*

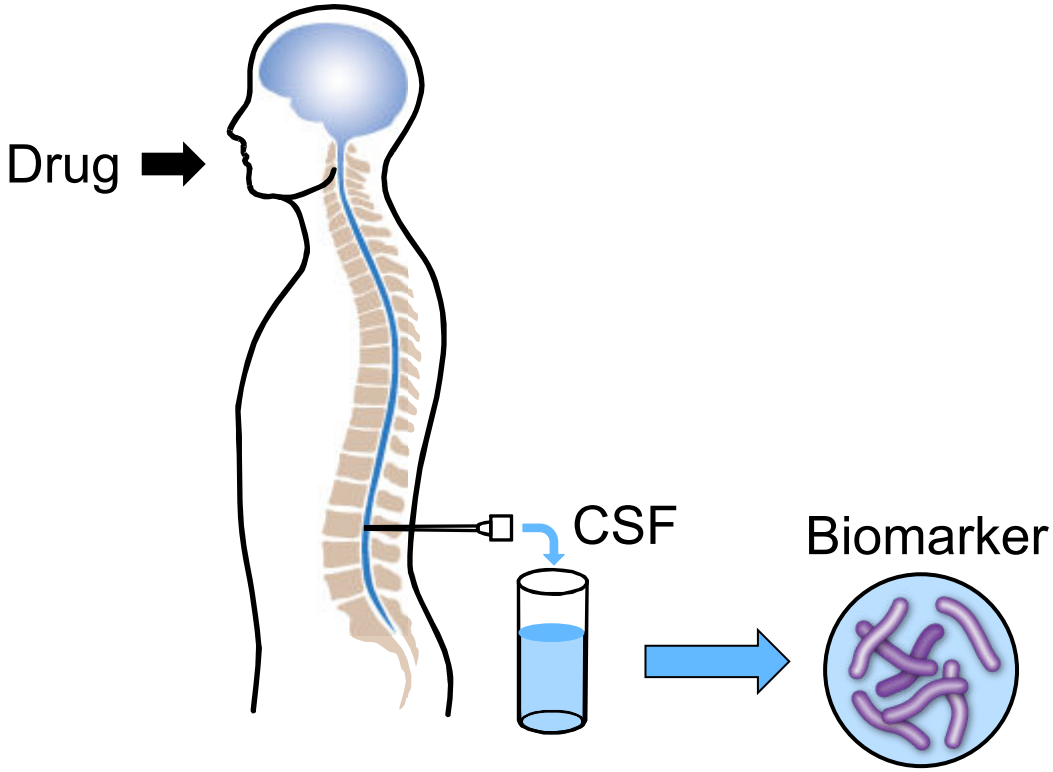


(3) Decrease in Aβ oligomers in brain protect from AD

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

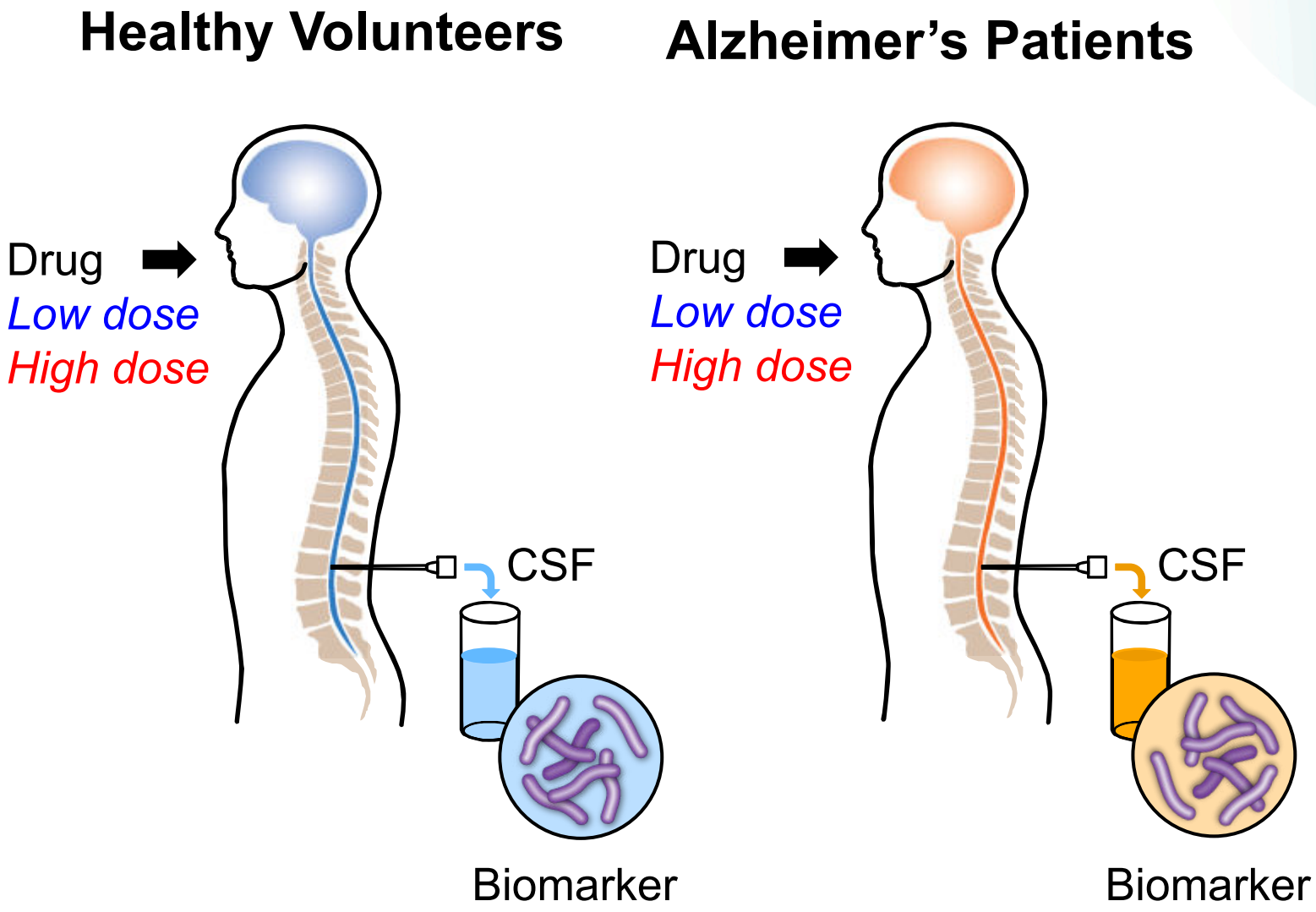
(2) BACE1 inhibitor mimics *APP* mutation and blocks first step in release of toxic Aβ peptides

Aβ peptide levels measured in CSF serve as a biomarker for target modulation



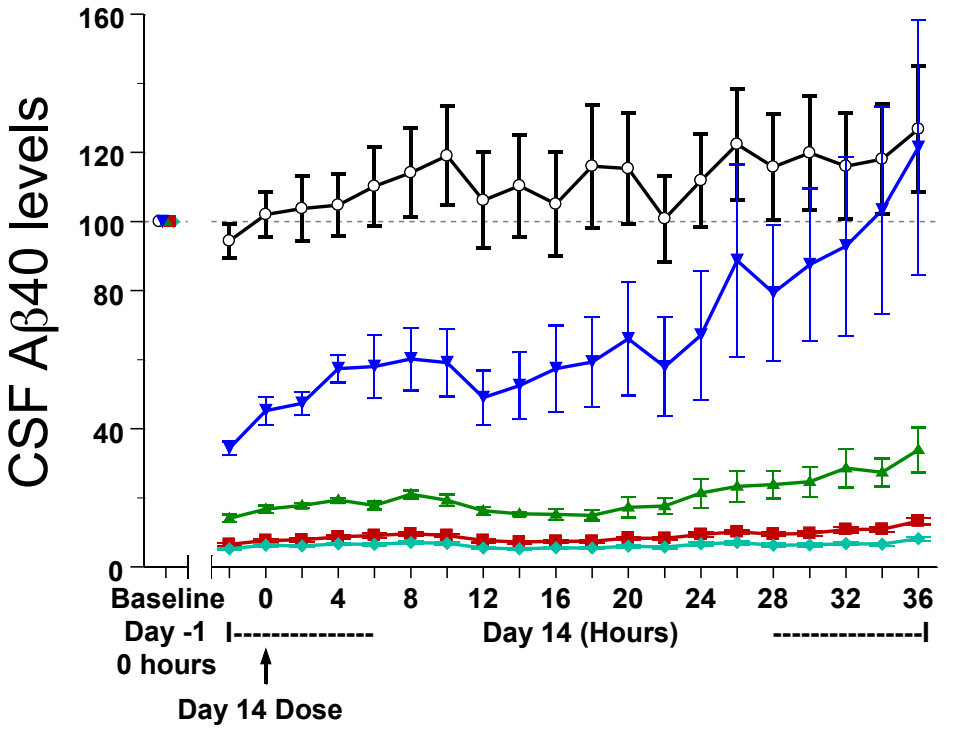
Does the drug engage and modulate the target?

Is there a dose-dependent relationship in human subjects?

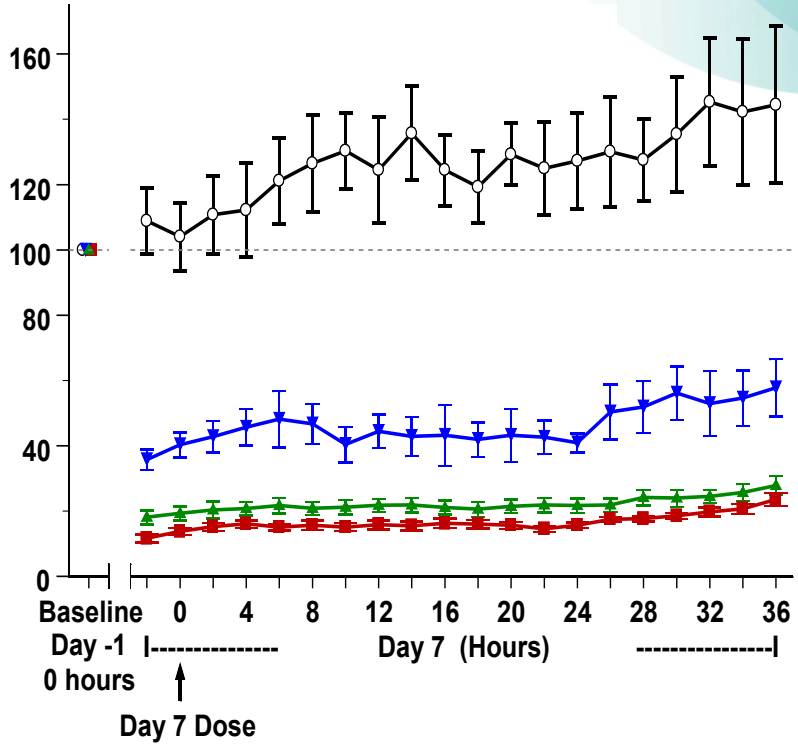


MK-8931 lowers Aβ levels in CSF from healthy volunteers and Alzheimer's disease patients

Multi-dose, healthy volunteers



Multi-dose, AD patients



Placebo (N=10)
MK-8931 10 mg (N=6)
MK-8931 40 mg (N=6)
MK-8931 150 mg (N=9)
MK-8931 250 mg (N=9)

>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*

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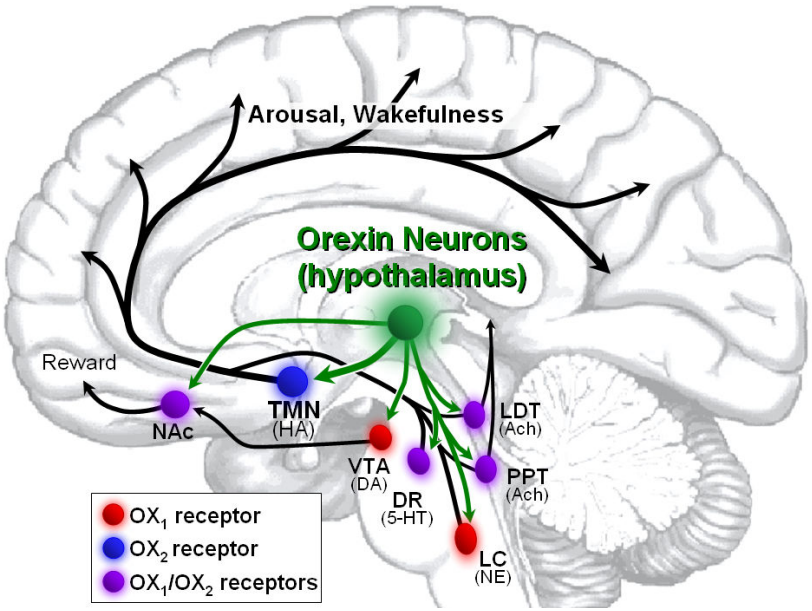
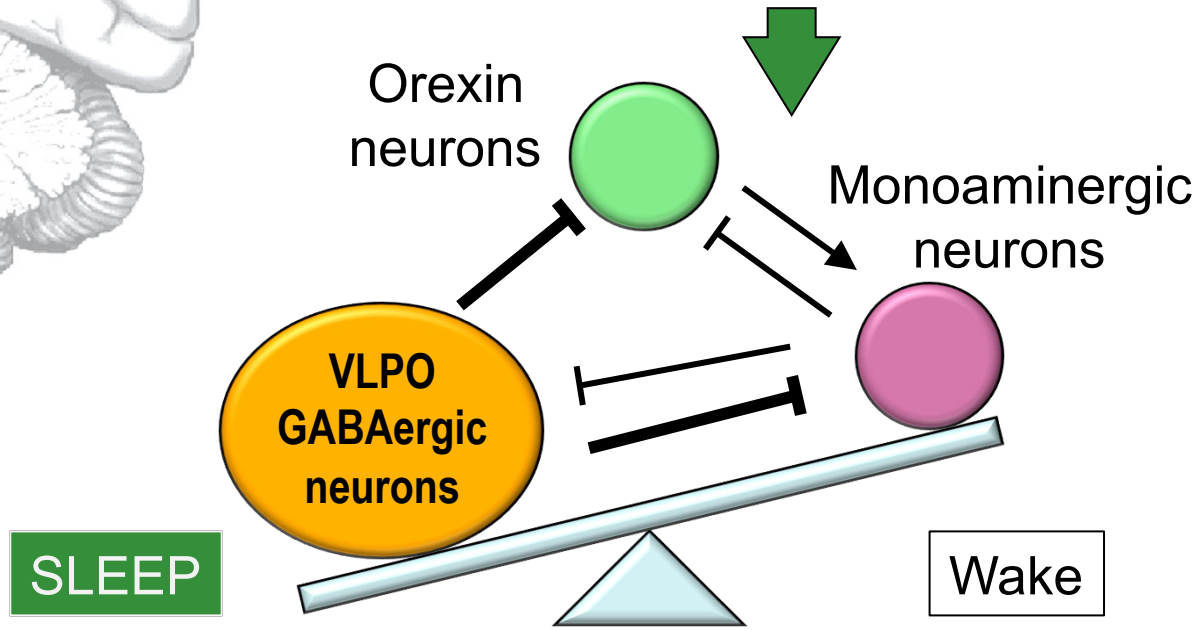
Orexin Receptor Antagonists (ORAs): *a new therapeutic approach to treat insomnia*



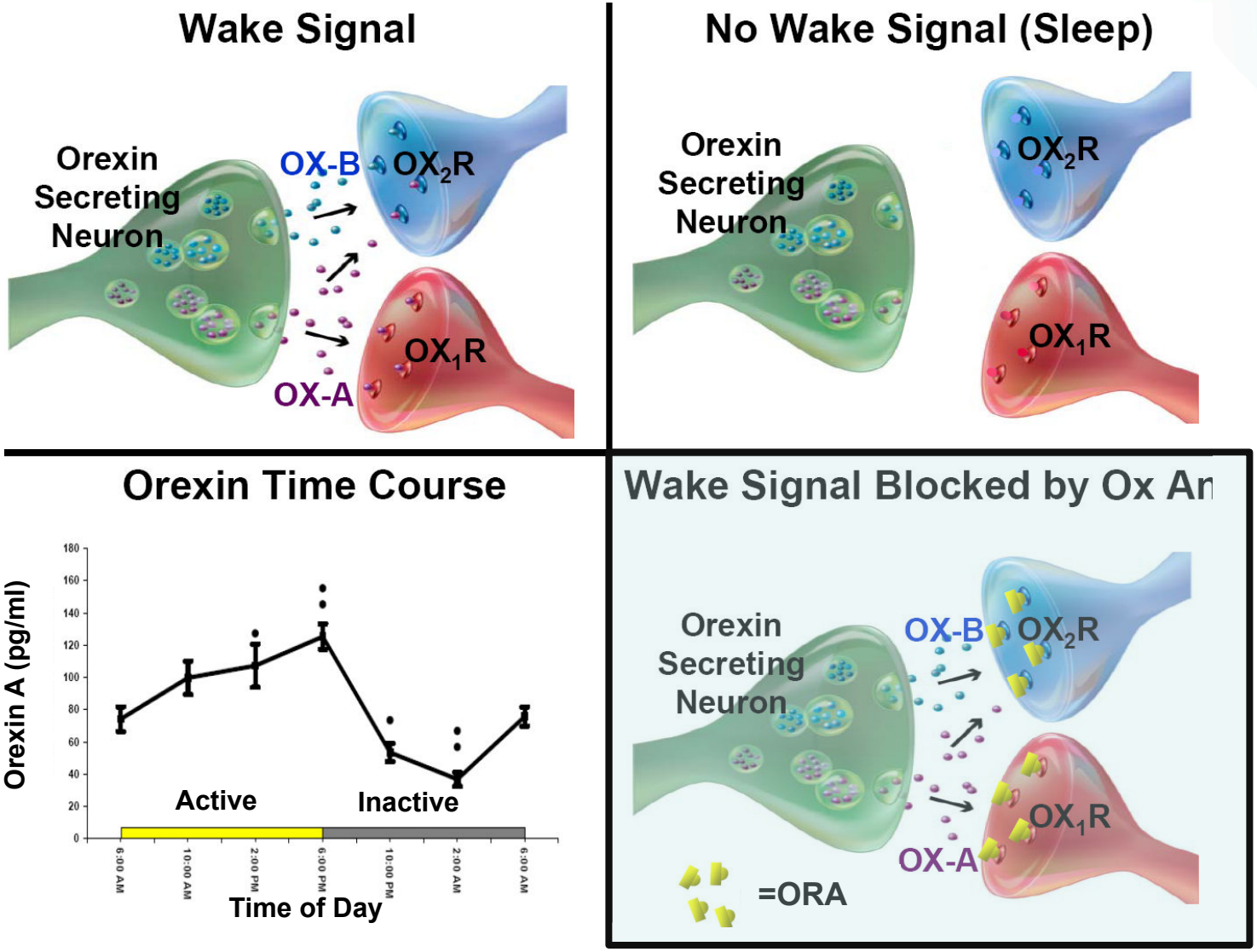
Causal human biology

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



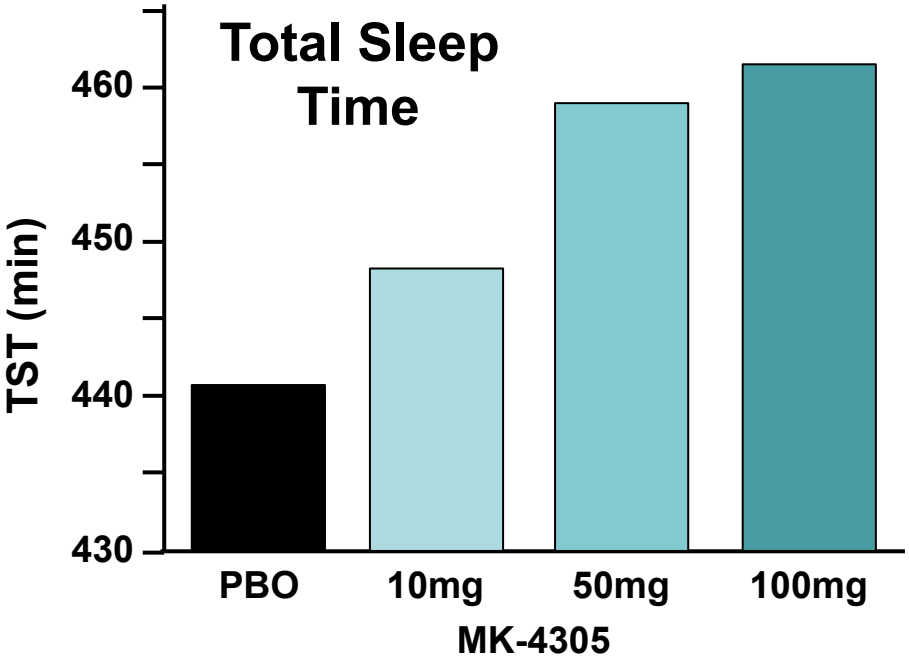
Acknowledgements:
John Renger, Matt Kennedy

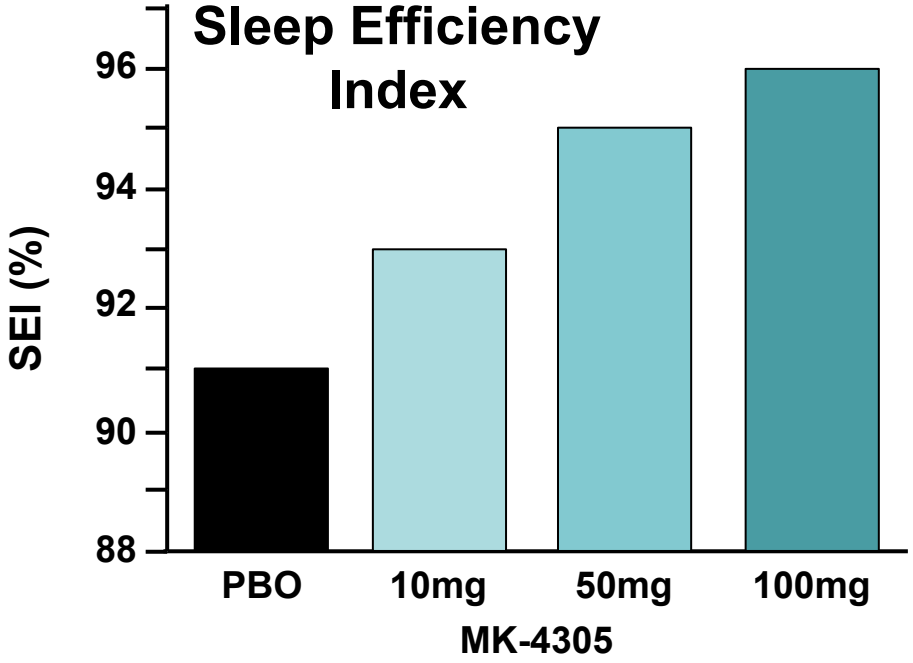
Therapeutic hypothesis: *Orexin receptor antagonism (ORA) blocks wake promoting signal, enabling sleep*



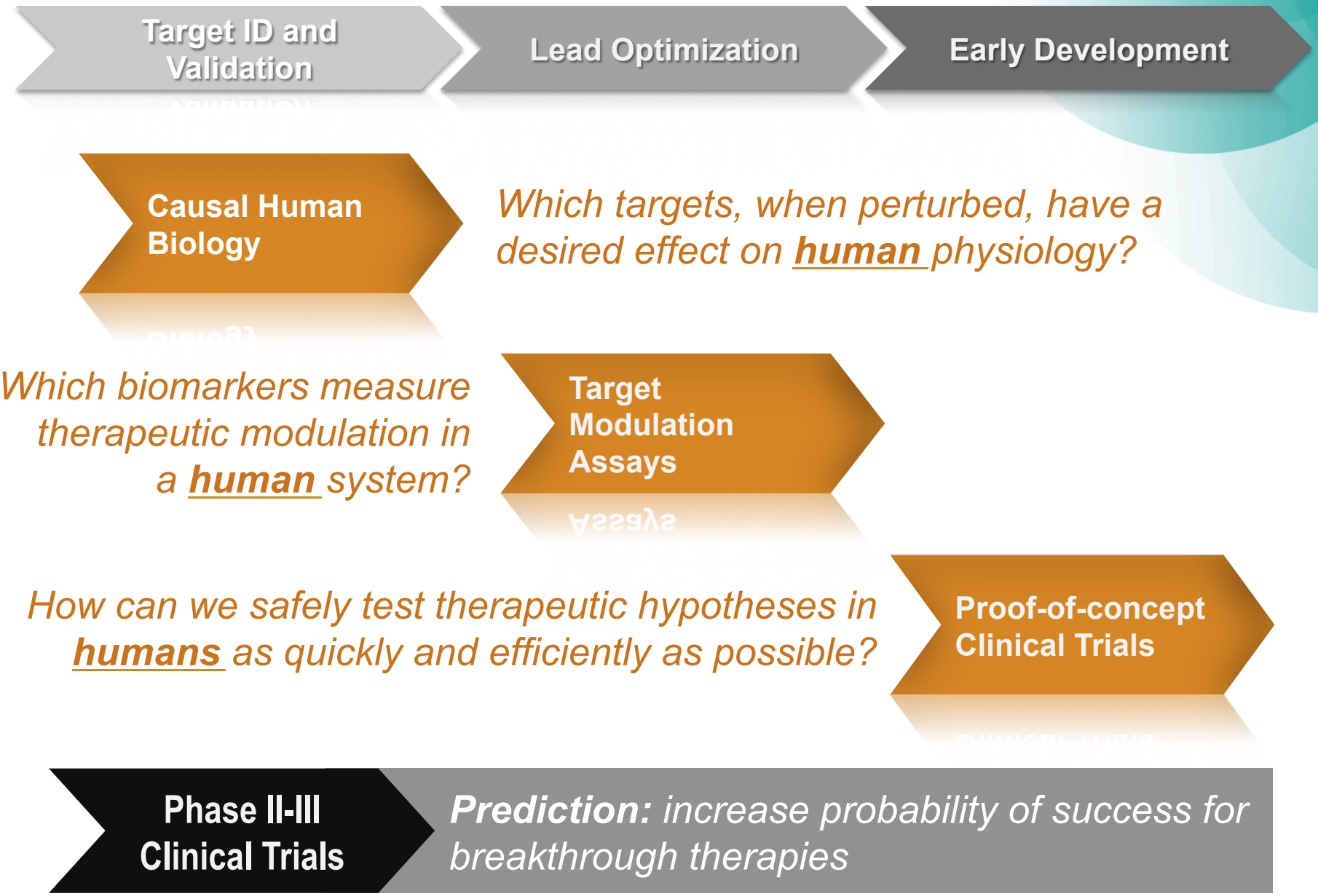
Clinical proof-of-concept (POC) in healthy volunteers: polysomnography (PSG) sleep study

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





How to apply Mendelian randomization in this framework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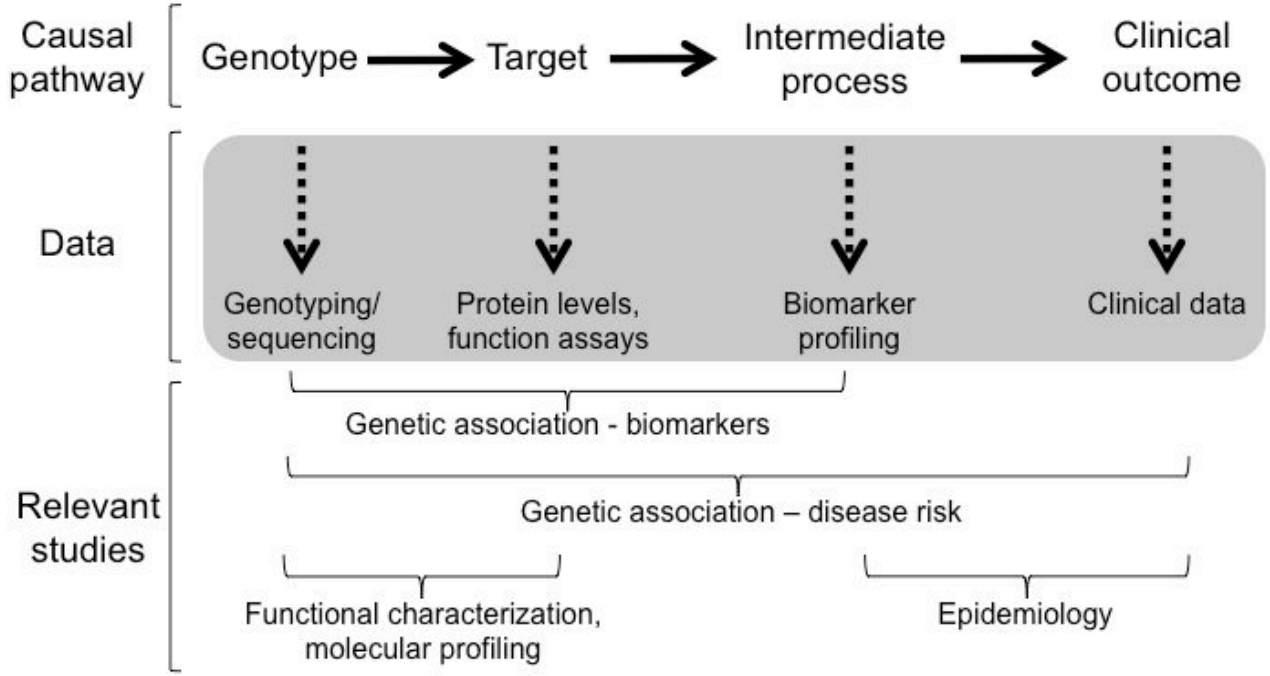
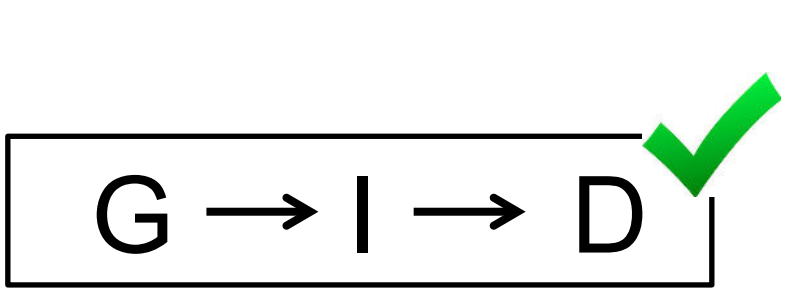
Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery





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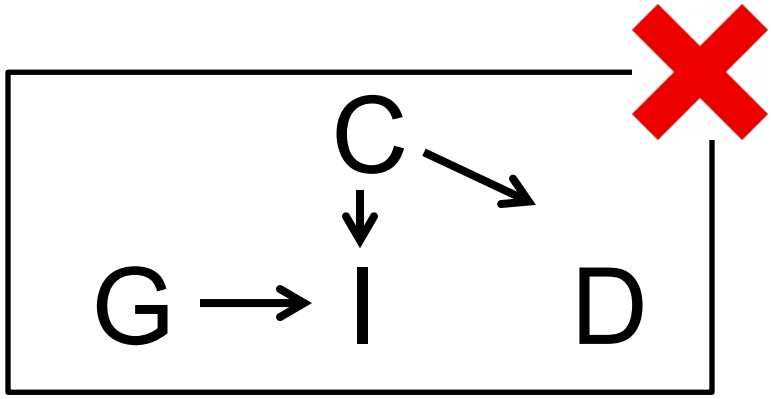


Public

Retrospective example: NPC1L1 protein (target), LDL (biomarker), coronary heart disease (POC)

Ph III clinical study in >18,000 CHD patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

the IMPROVE-IT Investigators*

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

- ***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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

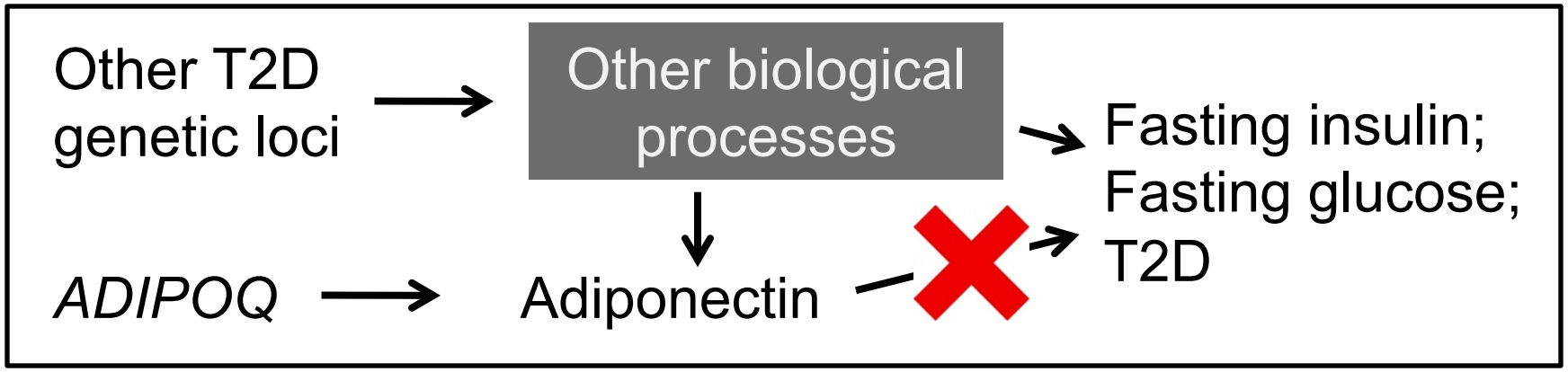
The Myocardial Infarction Genetics Consortium Investigators

CONCLUSIONS

Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease. (Funded by the National Institutes of Health and others.)

- ***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

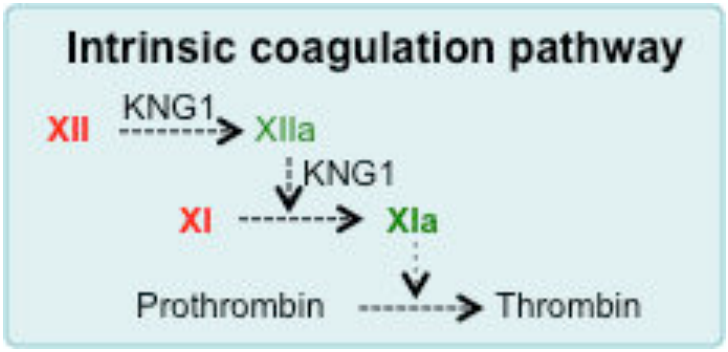


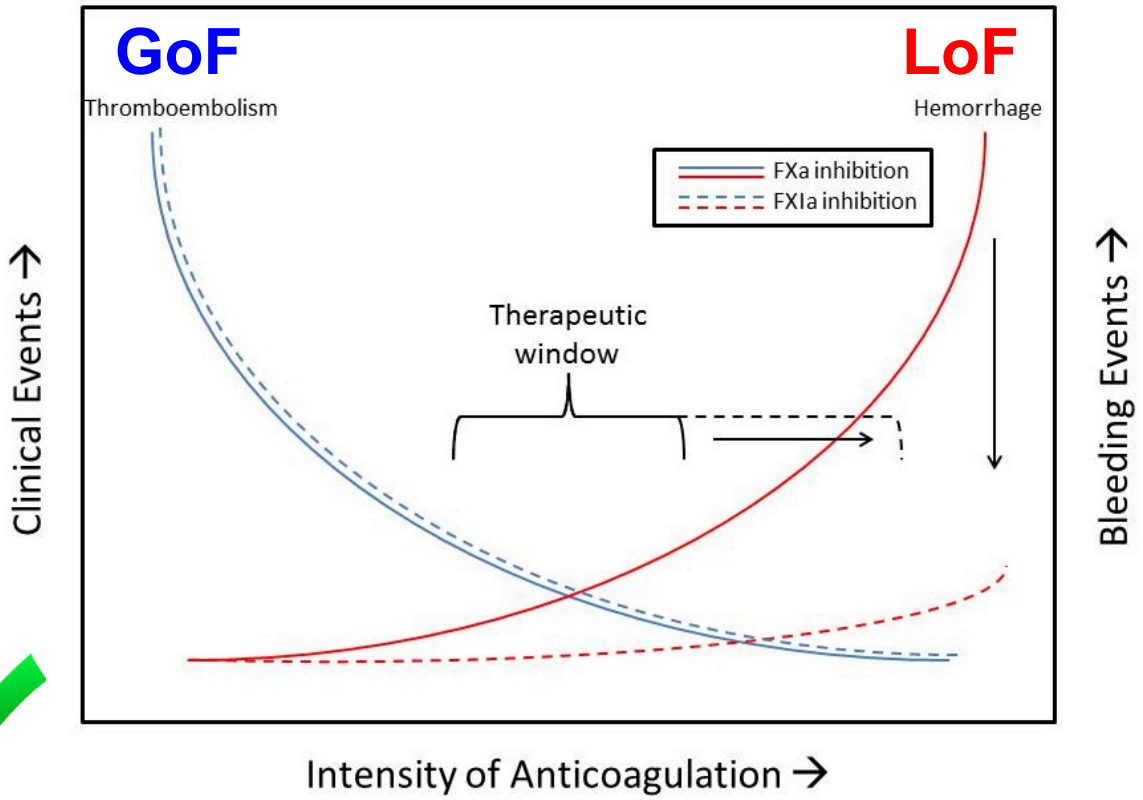
Not-causal

Yaghootkar et al, *Diabetes* (2013)

Public

Genetics for quantitative modeling of biomarker and POC studies to guide dose, study design





G → I → D

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…