IMPACT OF HUMAN GENETICS ON DRUG R&D

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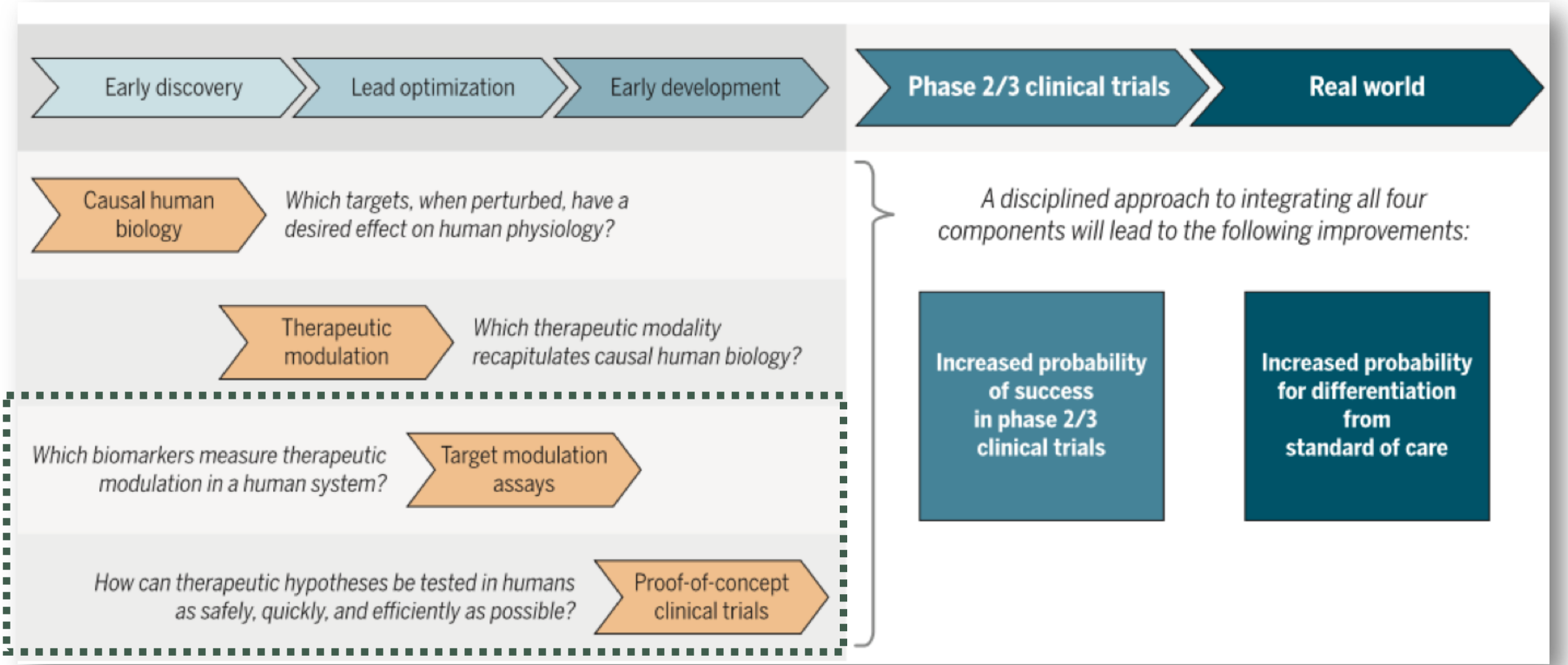
Agenda

- **Introduction**
  - Why human genetics?
- **Day 1**:
  - The model
  - Picking targets and pathways
  - Matching modality and mechanism
- **Day 2**:
  - Predictive biomarkers
  - Clinical development
  - Emerging resources

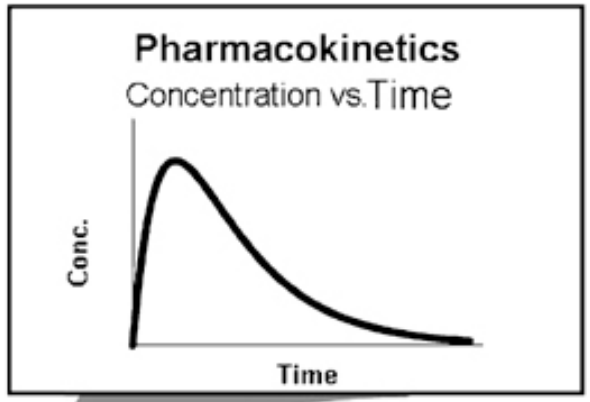


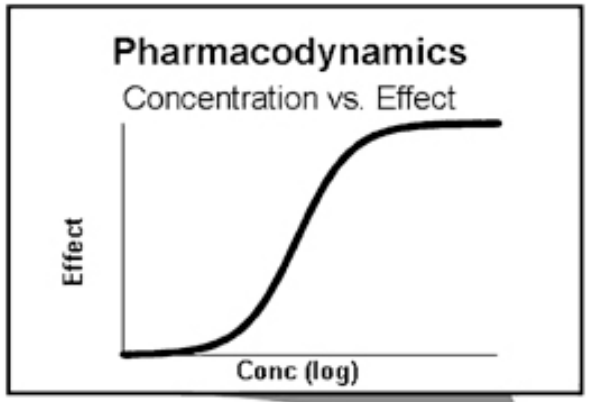
Plenge *Science Translational Medicine* (2016)

What is a biomarker?

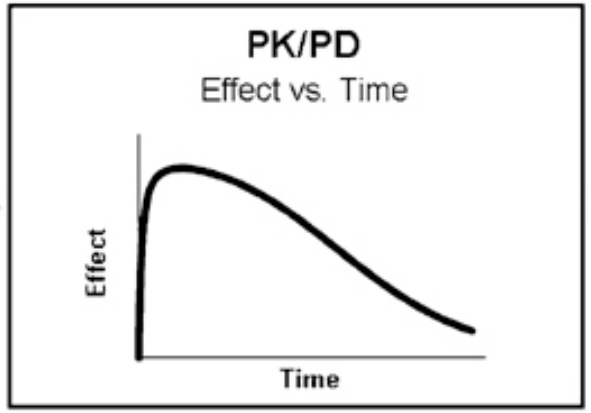
- **Pharmacokinetic (PK)** – what the body does to the drug
- **Pharmacodynamic (PD)** – what the drug does to the body

Concentration vs. Time





Effect vs. Concentration

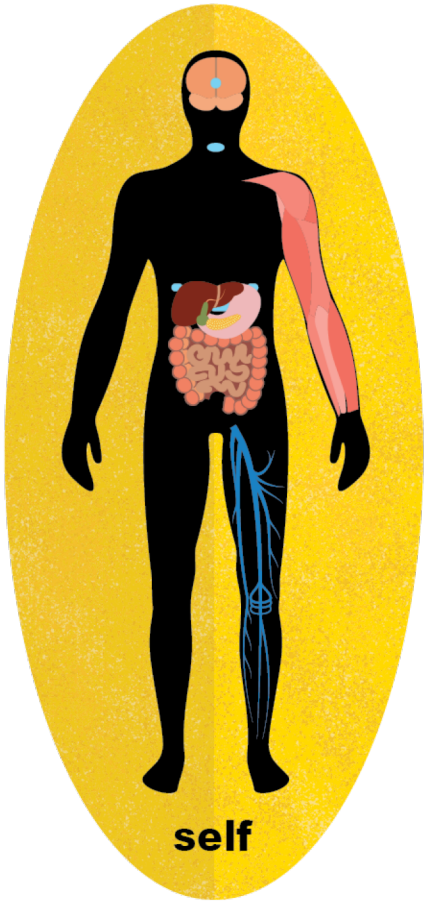


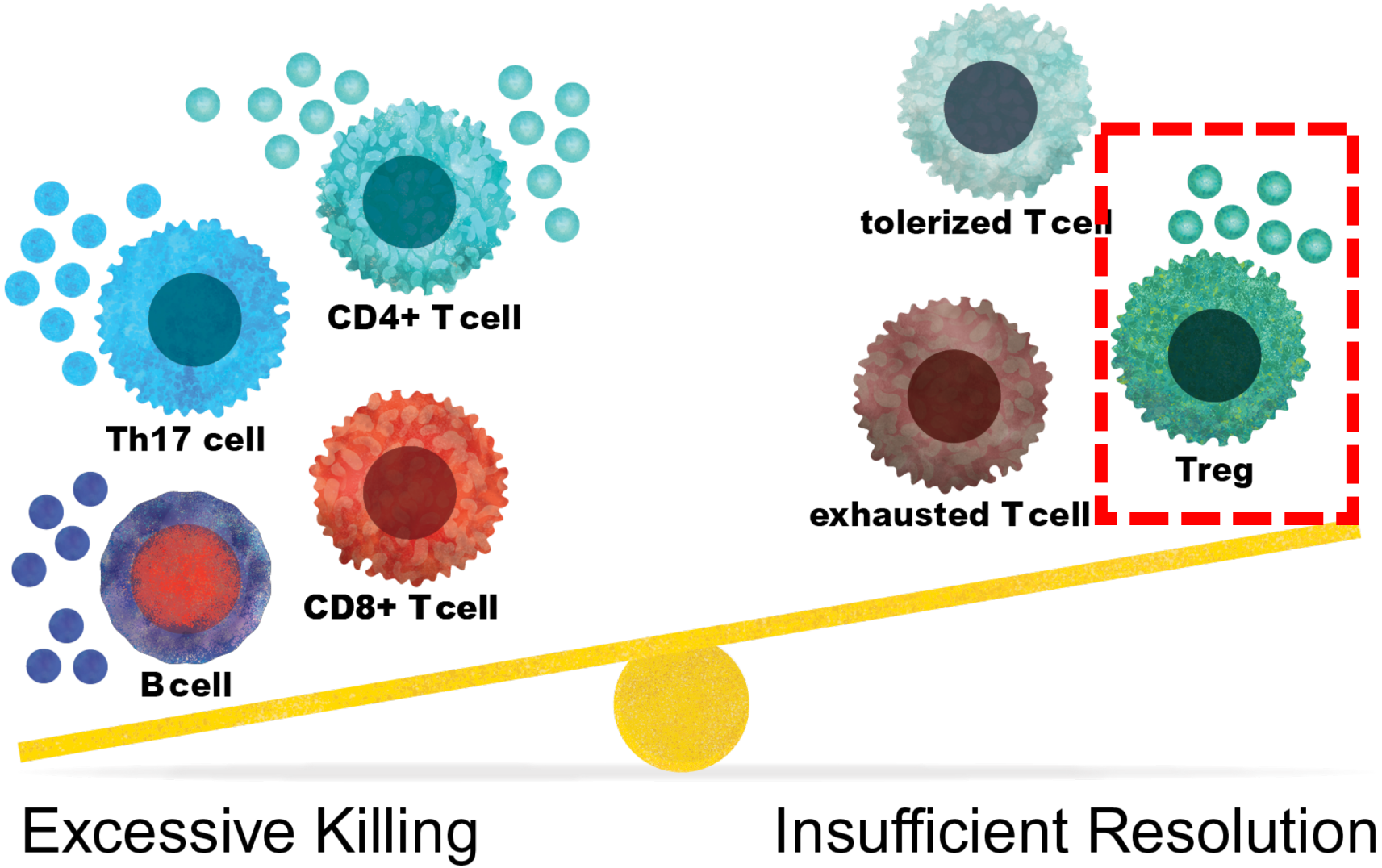
Exposure

Response

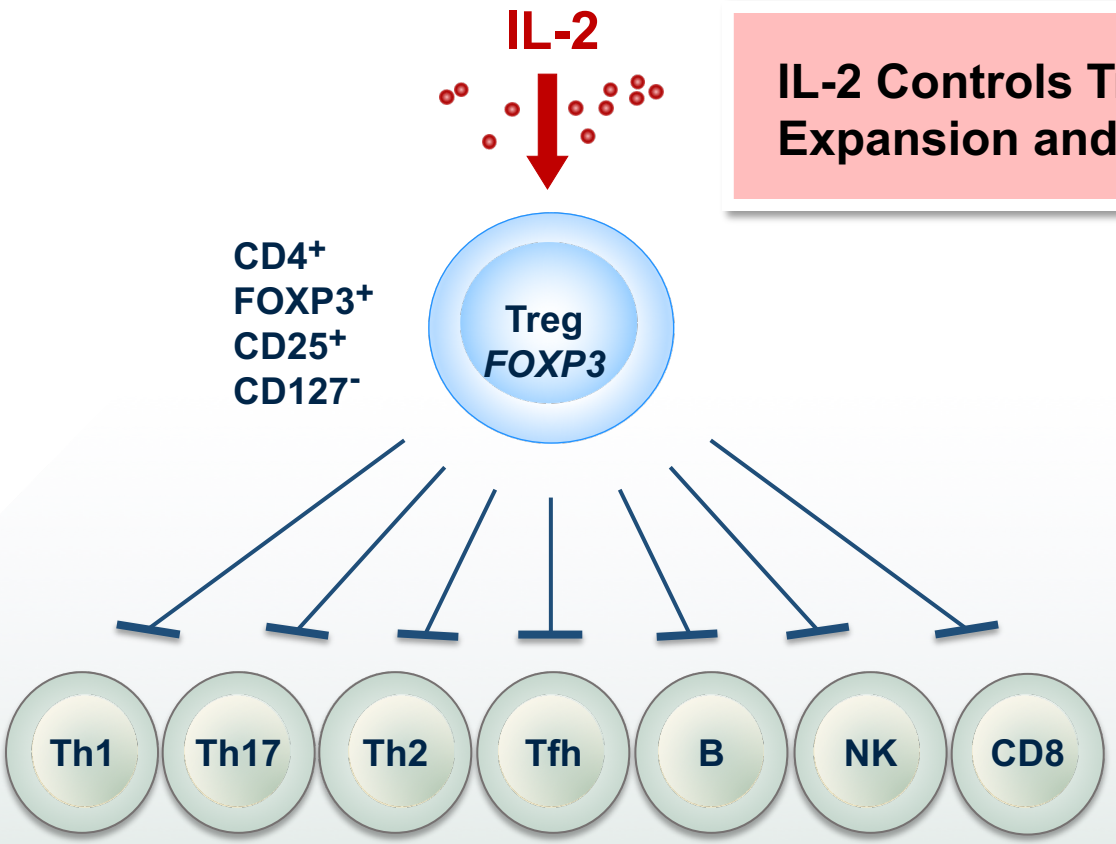
Human genetics can help select PD biomarkers and model exposure-response relationship

The immune system is imbalanced in I&I diseases





Regulatory T cells (Tregs) are key modulators of immune homeostasis



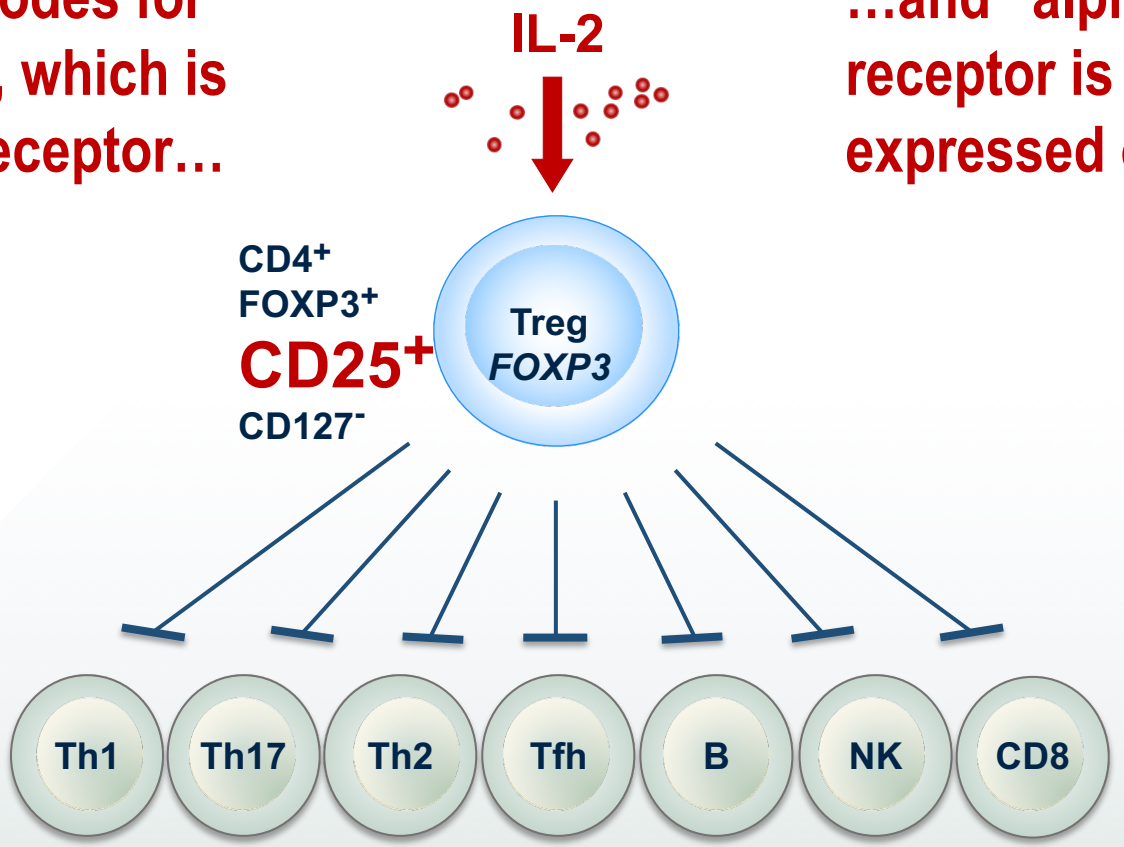
IL-2 Controls Treg Expansion and Function

Tregs Employ Multiple Regulatory Mechanisms:

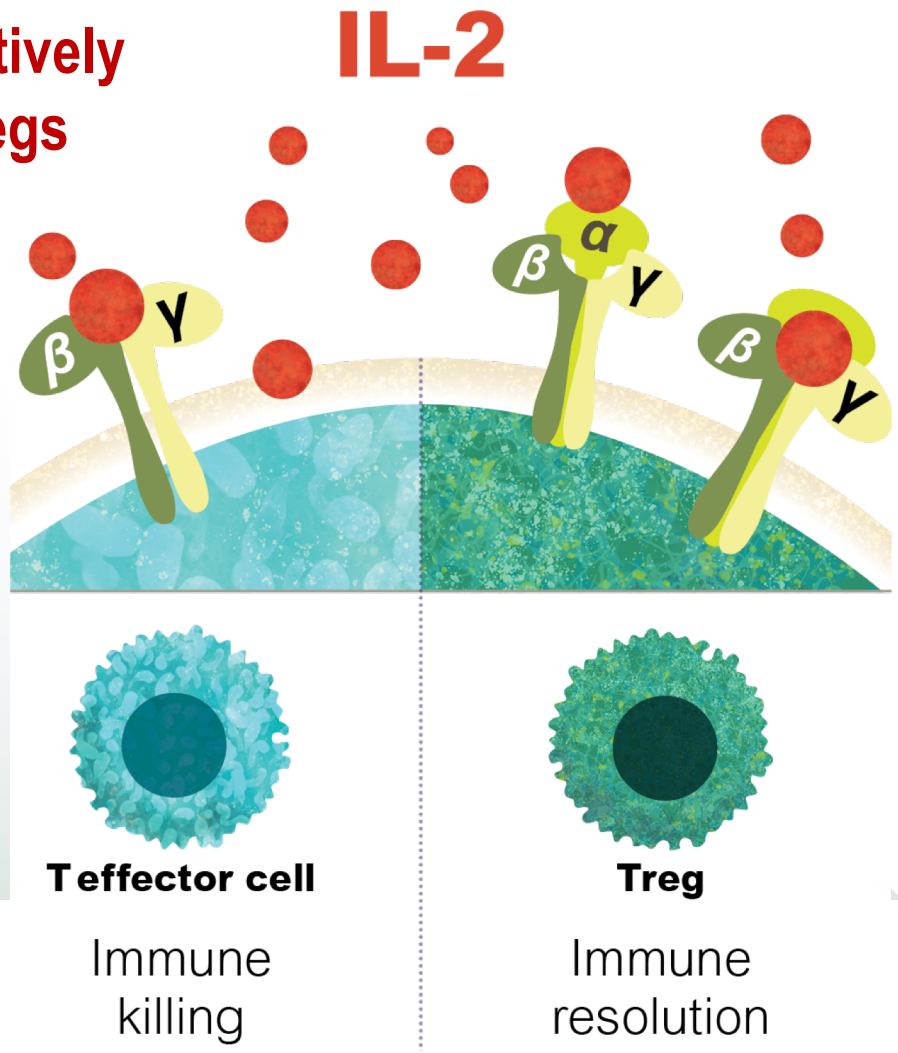
- IL-2 consumption
- CTLA-4
- IL-10
- TIGIT
- CD39/CD73
- GARP

Regulatory T cells are key regulators of immune homeostasis

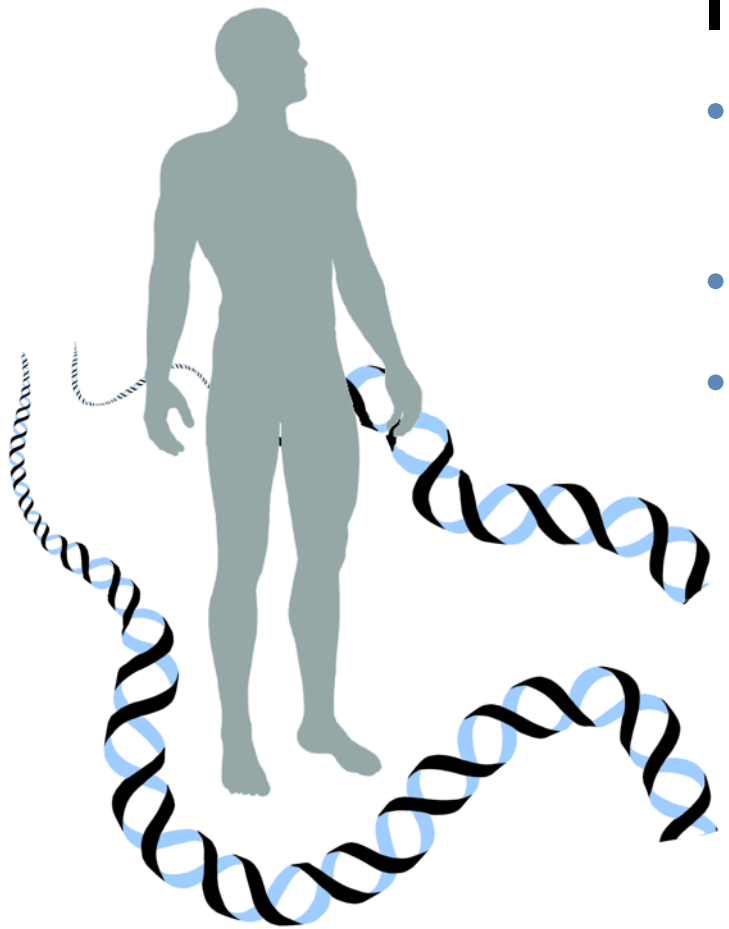
IL2RA **gene codes for CD25 protein, which is the "alpha" receptor…**



…and "alpha" receptor is selectively expressed on Tregs



Human knockouts of *IL2RA* have severe autoimmunity



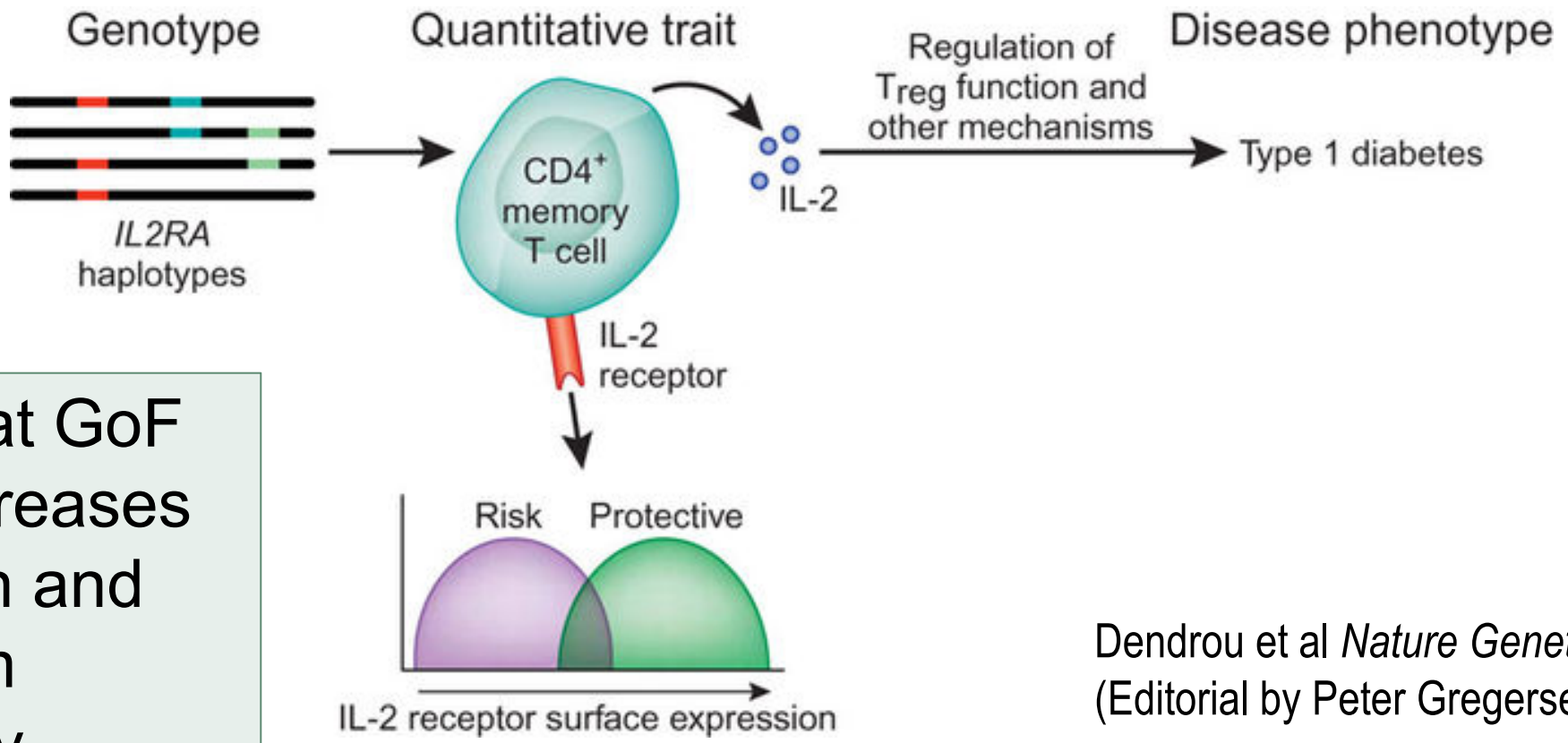
IPEX Syndrome

- Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome
- Rare, fatal immune disorder
- *Skin, intestinal, endocrine autoimmune disease*

- Reduced Treg cell levels and/or function
- Cured by hematopoietic stem cell transplantation
- Loss-of-function mutations in ***FOXP3*** gene
- Also caused by nonfunctional alleles of ***IL2RA***

Common *IL2RA* variants predispose to multiple autoimmune diseases

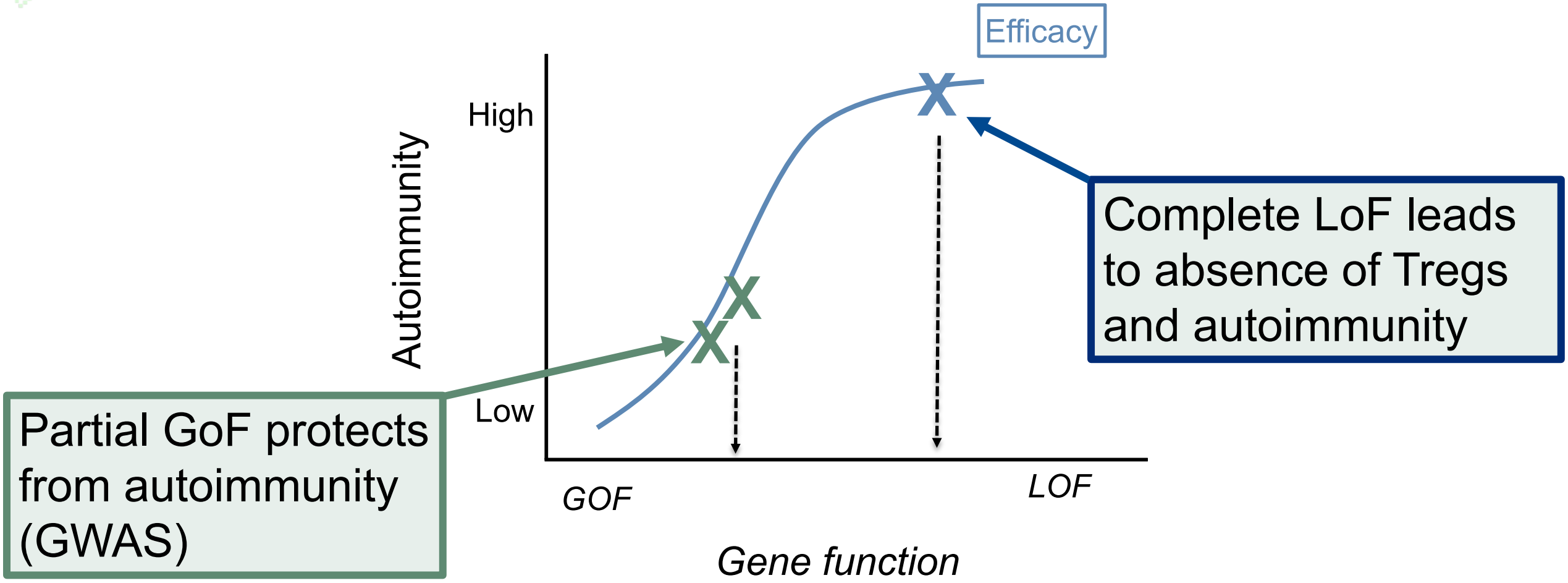
- Story is complicated, but…protective allele is associated with higher expression on CD4+ memory T cells



Suggests that GoF on Tregs increases Treg function and protects from autoimmunity

Dendrou et al *Nature Genetics* (2009)
(Editorial by Peter Gregersen)

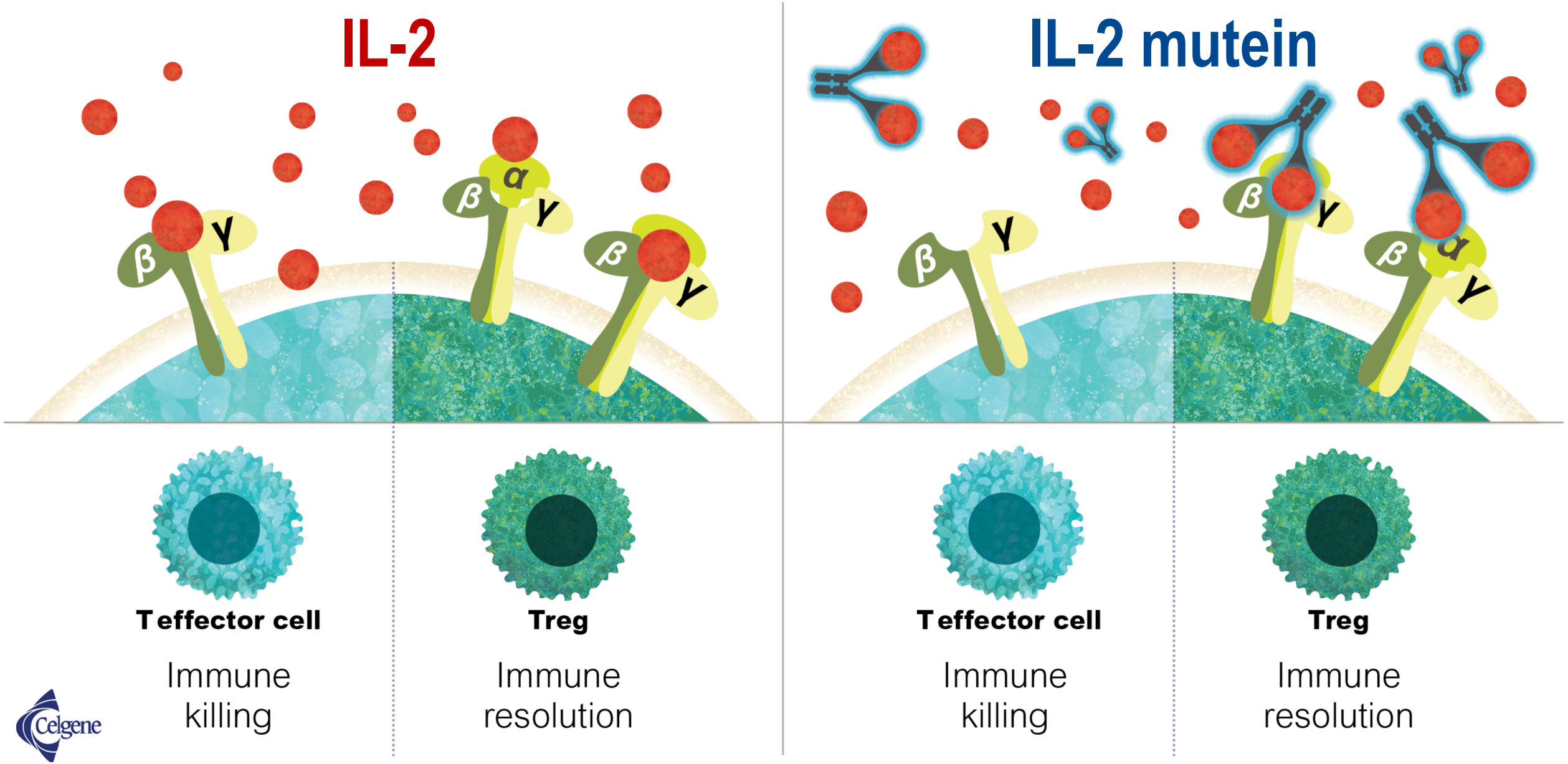
Function-phenotype dose-response curve for *IL2RA*



Therapeutic hypothesis

Agonizing **CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders**

IL2 “muteins” selectively bind to CD25 (*alpha* subunit of IL2R)

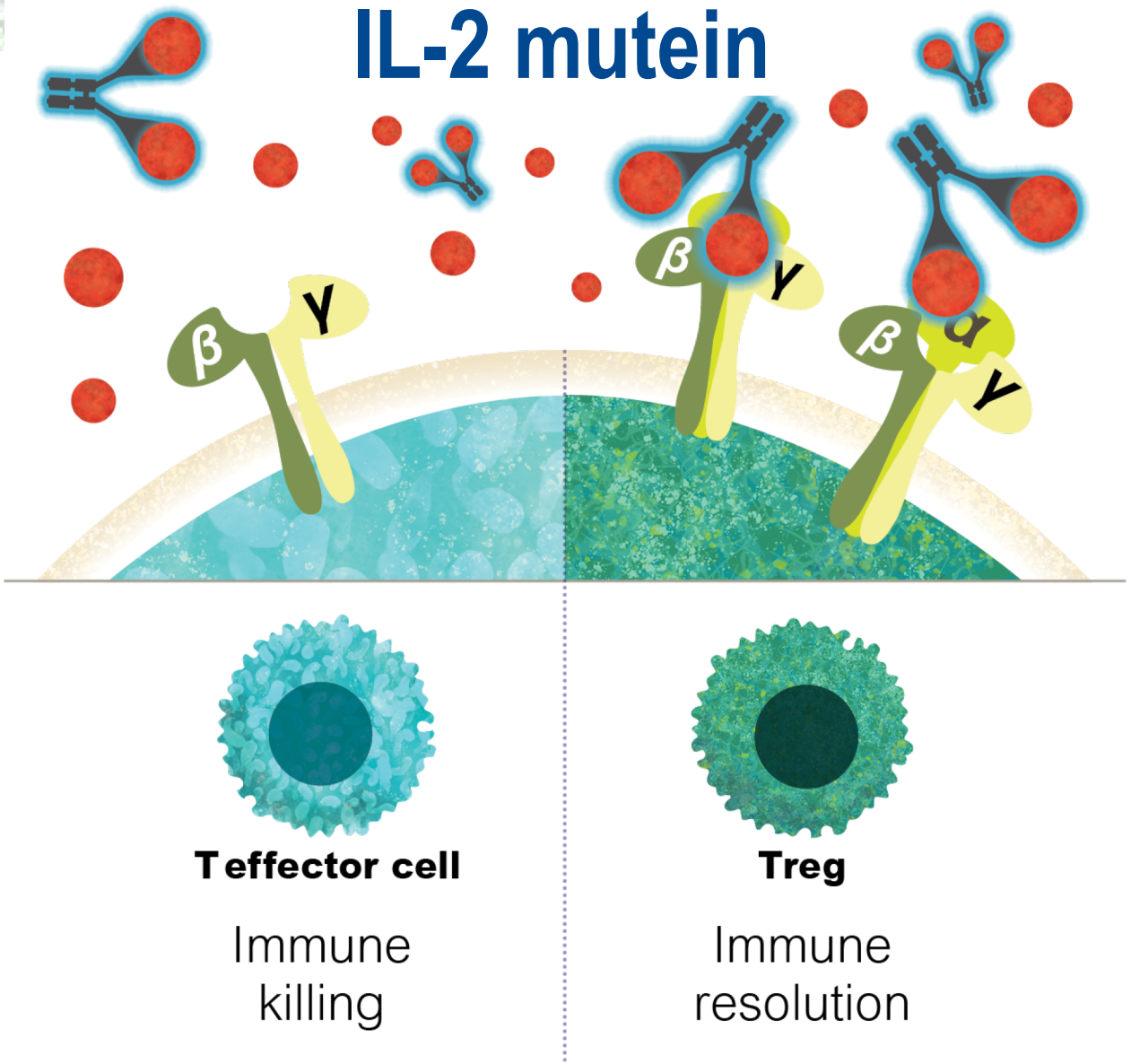


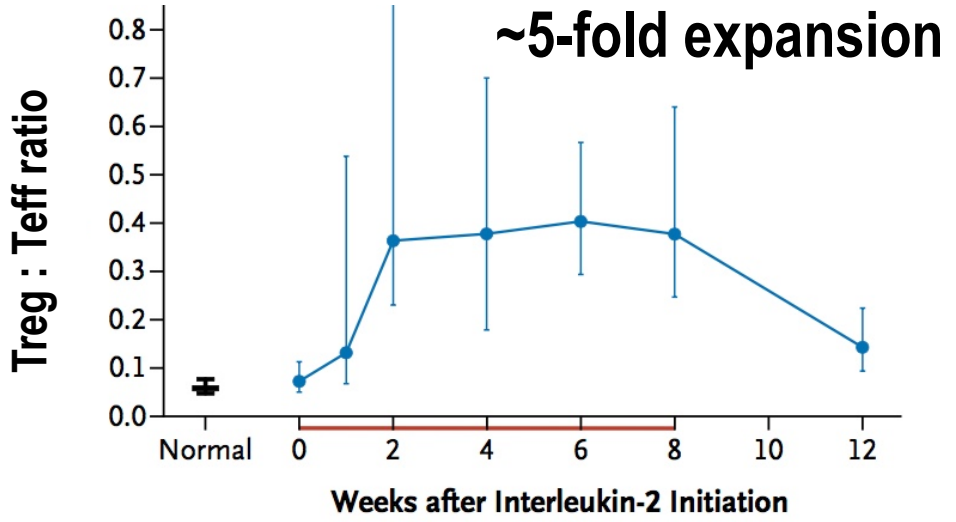
Therapeutic hypothesis

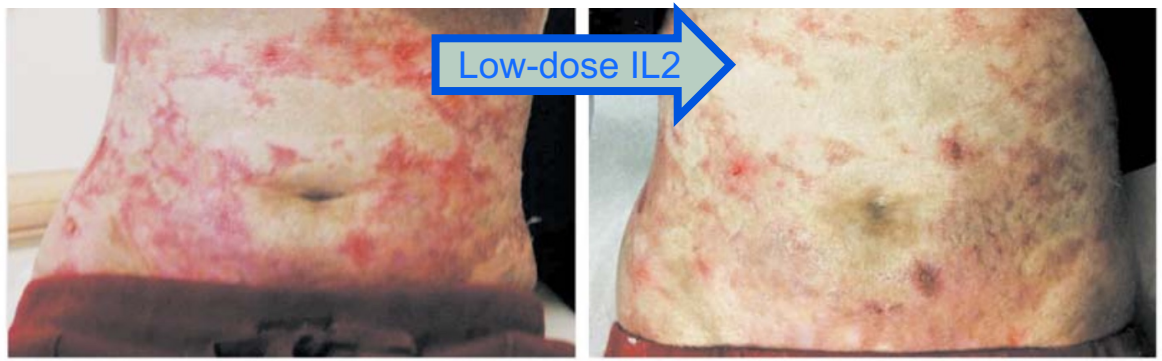
Agonizing **CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders**

What PD biomarkers should be used to measure exposure-response in Phase 1?

Treg : T effector ratio is a good PD biomarker







Koreth et al *NEJM* (2011)

Therapeutic hypothesis

Agonizing **CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders**

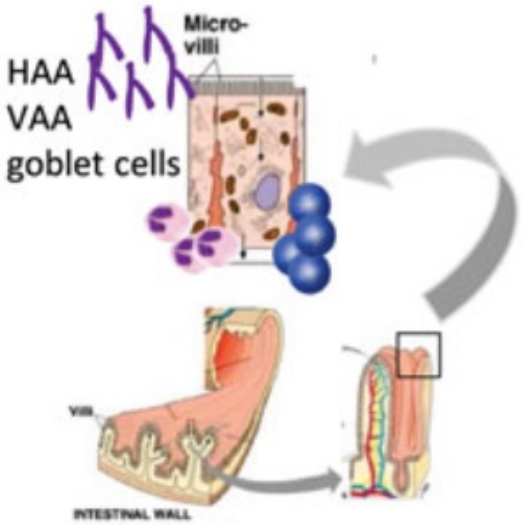
What PD biomarkers should be used to measure exposure-response in Phase 1?

What indications should be pursued for PoC?

Rare LoF IPEX mutations guide indication selection

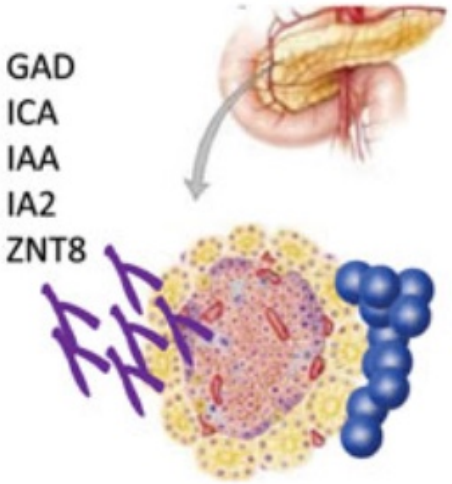
C

Gut



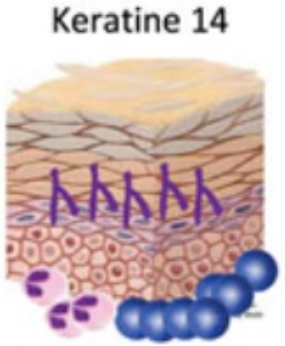
Patey-Mariaud de Serre, *et al.*[70] *Mod. Pathol.*
Moes, *et al.*[75] *Gastroenterology*

Pancreas



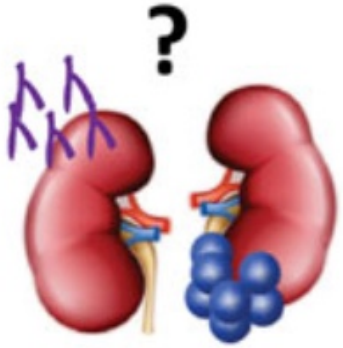
Rubio-Cabezas, *et al.*[118] *Diab. Care*
Scaillon, *et al.*[114] *J. Pediatr. Gastroenterol. Nutr.*

Skin



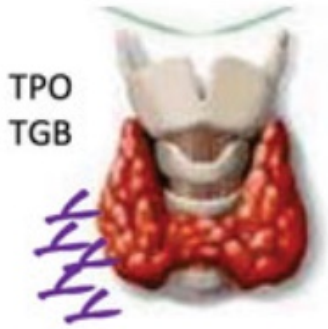
Huter, *et al.*[141] *J. Invest. Dermatol.*
Nieves, *et al.*[56] *Arch. Dermatol.*
Halabi-Tawil, *et al.*[124] *Br. J. Dermatol.*

Kidney



Sheikine, *et al.*[46] *Pediatr. Nephrol.*
Hashimura, *et al.*[111] *Pediatr. Nephrol.*
Bae, *et al.*[132] *Eur. J. Pediatr.*

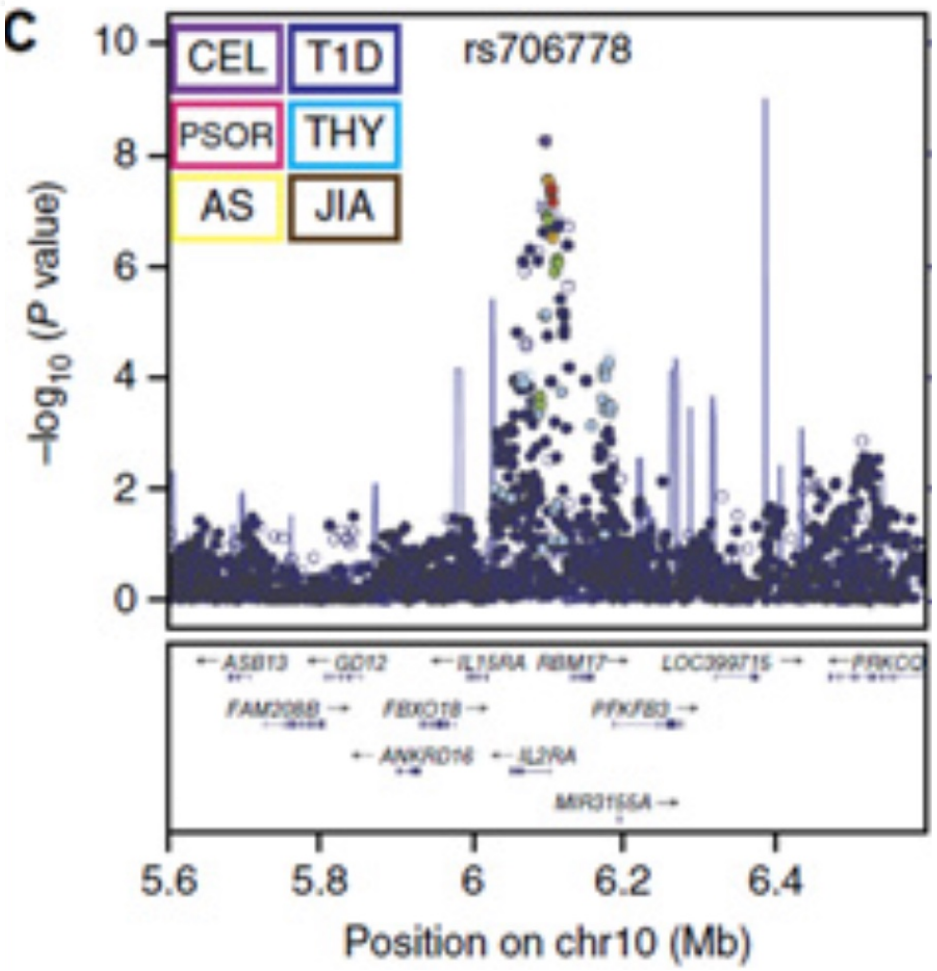
Thyroid



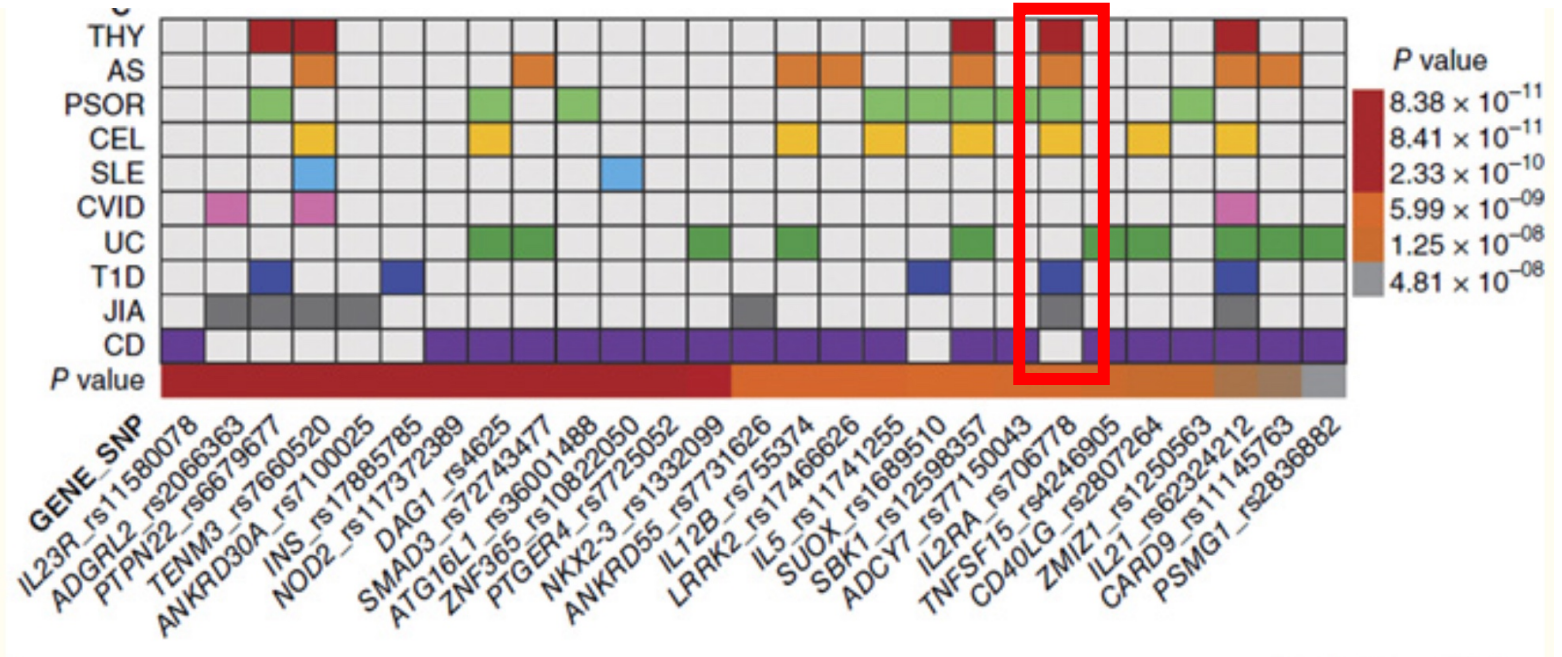
Rubio-Cabezas, *et al.*[118] *Diab. Care.*

Bacchetta et al *Annals NY Ac Sci* (2016)

Common GoF GWAS variants guide indication selection



_IL2RA_ variant



Psoriasis, inflammatory arthritis, type 1 diabetes, other

Li et al *Nat Genet* (2015)

Phenome-wide association studies (PheWAS)

EHRs, Claims, Questionnaires, etc.

Disease-agnostic cohort

Clinical data

SNP

Genetic data

GWAS, exome sequencing, etc.

Test association of selected SNP with clinical endpoints

PheWAS code 1 — risk — surrogate for efficacy

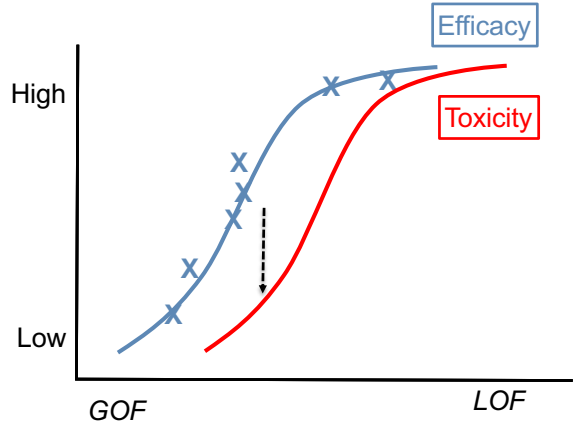
PheWAS code 2

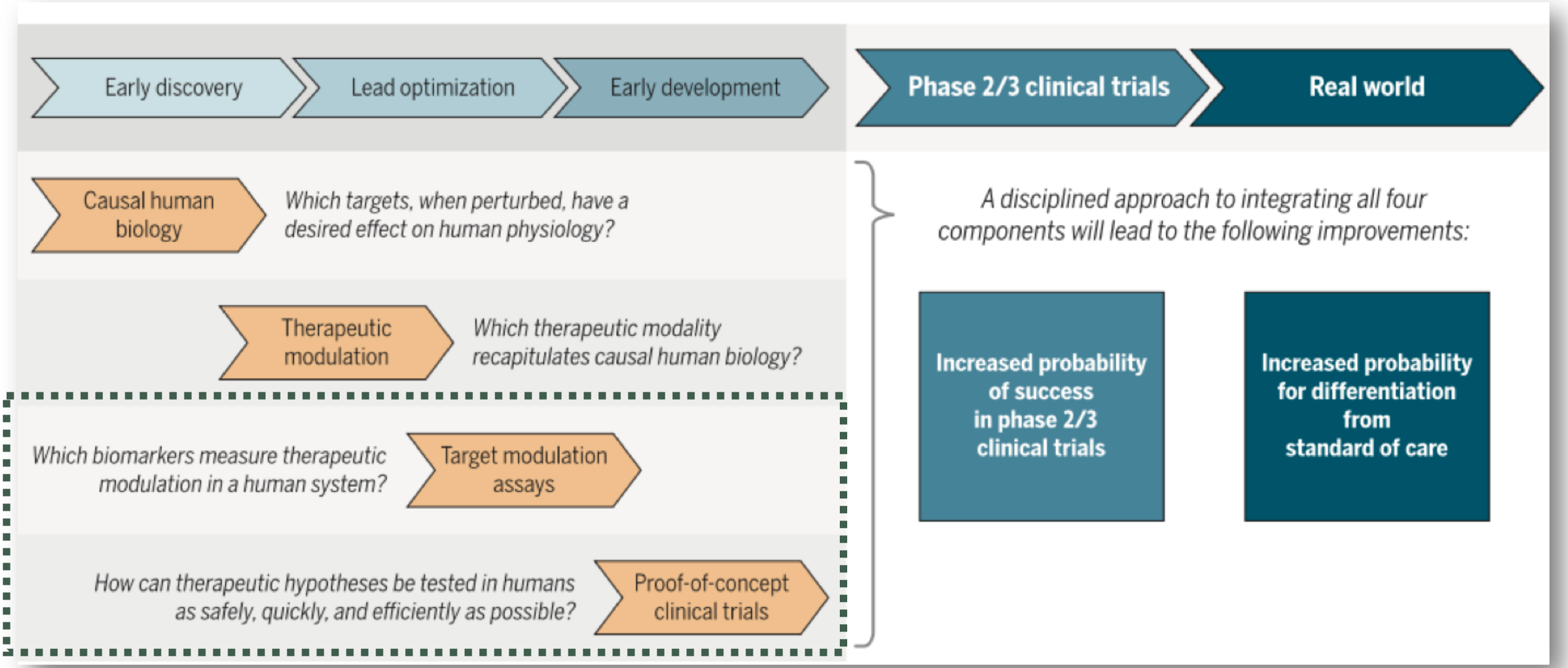
PheWAS code 3

PheWAS code 4

PheWAS code 5 — risk — surrogate for toxicity

PheWAS code 500

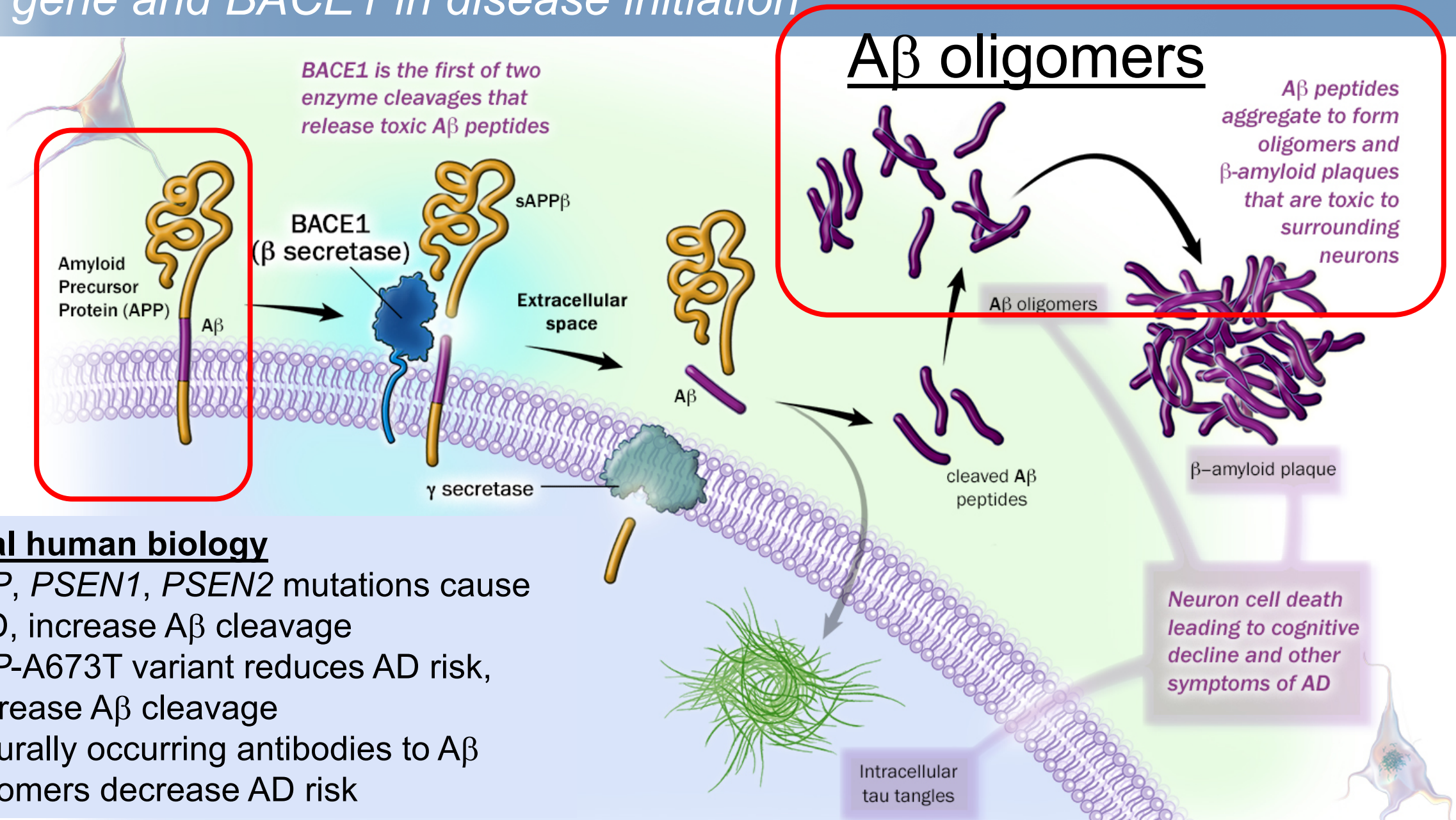




But it doesn't always work!

Plenge *Science Translational Medicine* (2016)

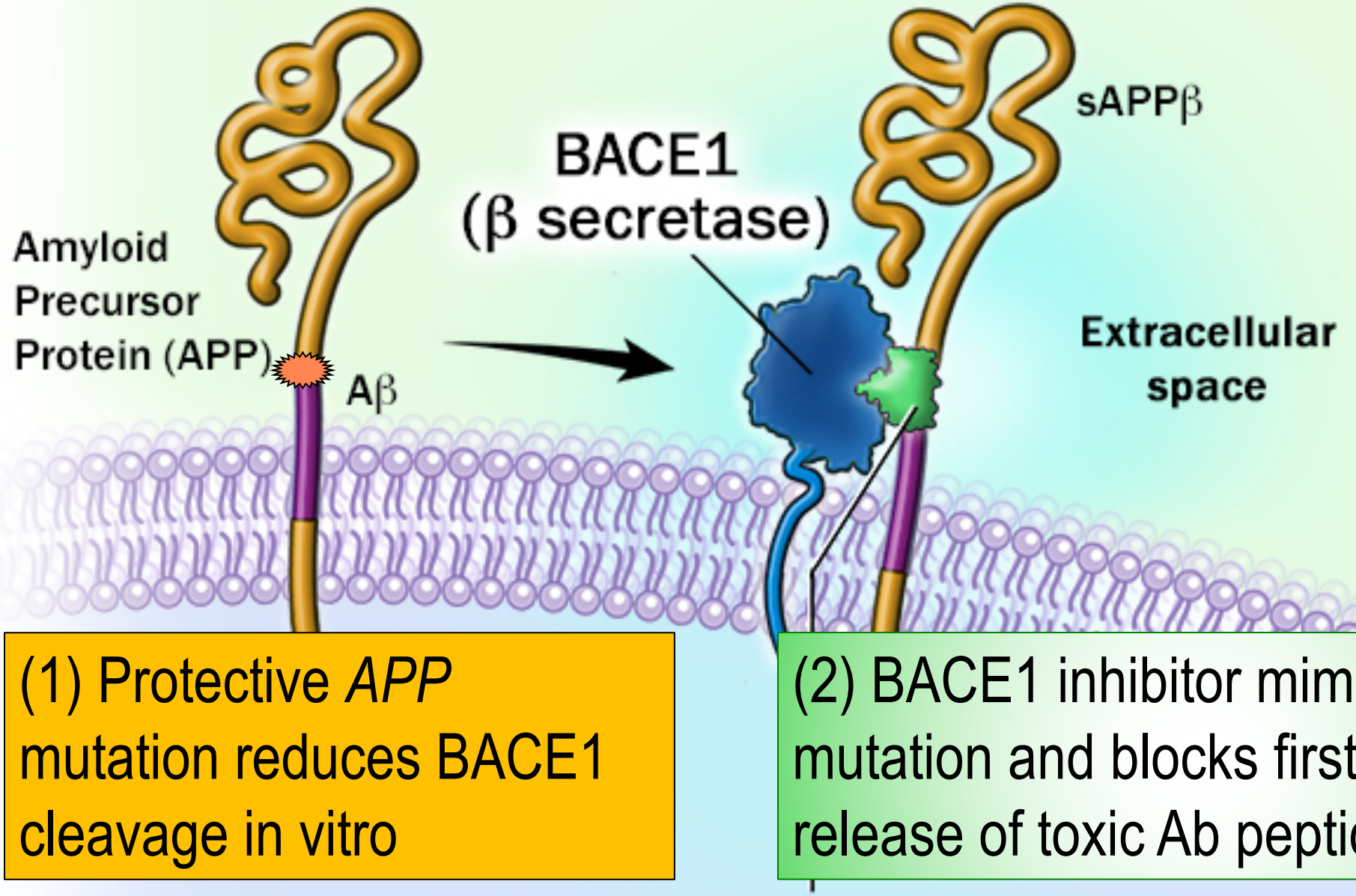
Amyloid hypothesis and Alzheimer's disease: *the role of the* APP *gene and BACE1 in disease initiation*



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*

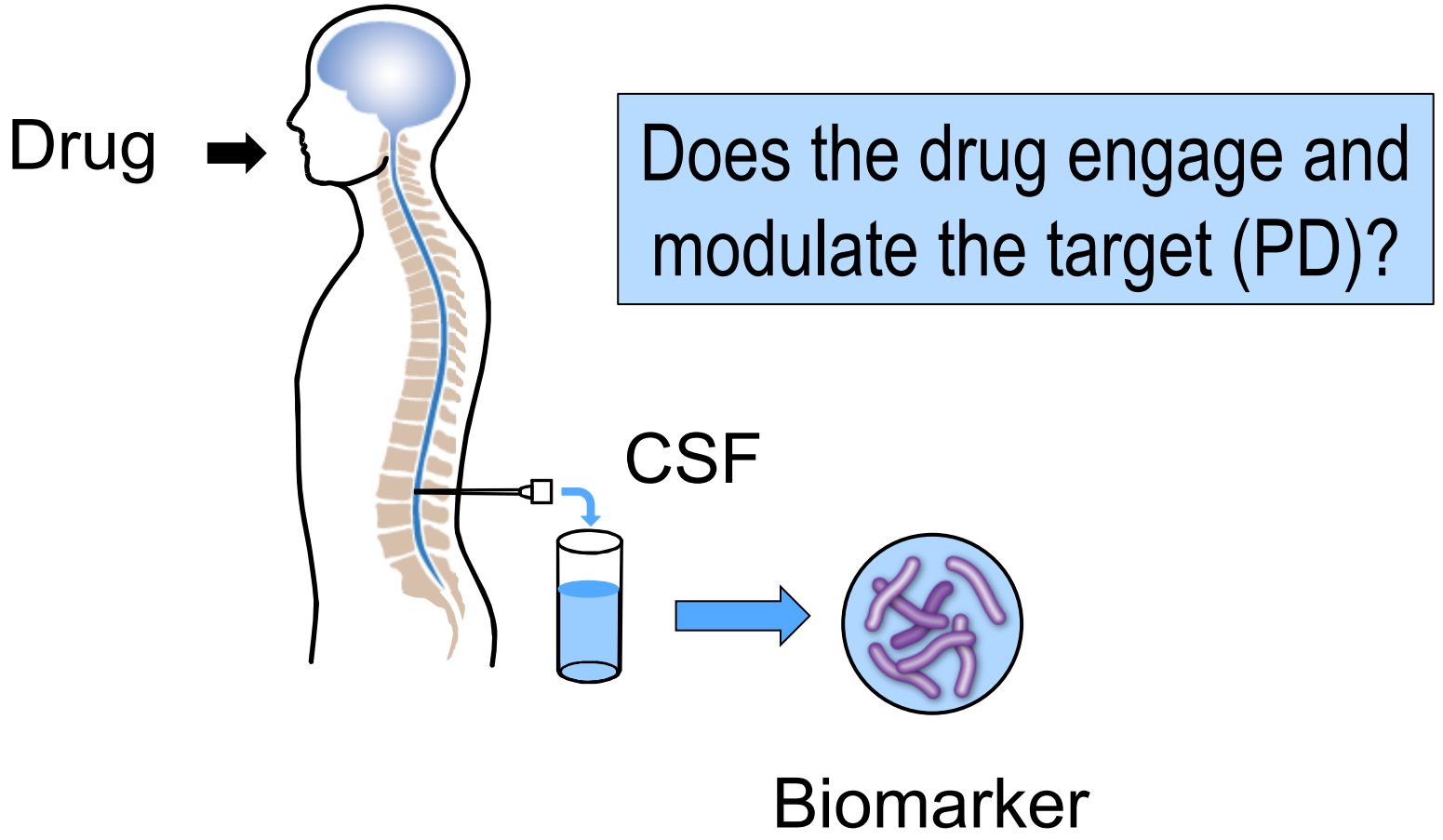


(3) Decrease in Aβ oligomers in brain protect from AD

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

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

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

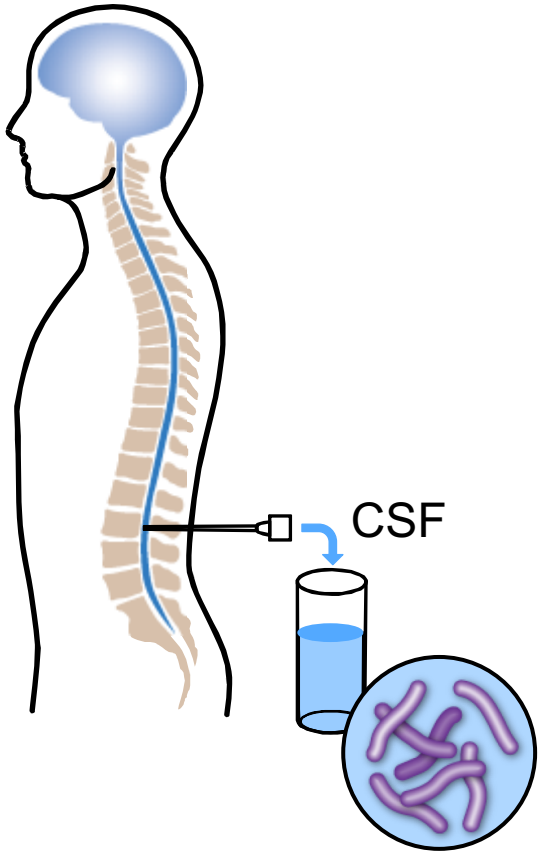


Kennedy et al *Science Translational Medicine* (2016)

Is there a dose-dependent relationship in human subjects?

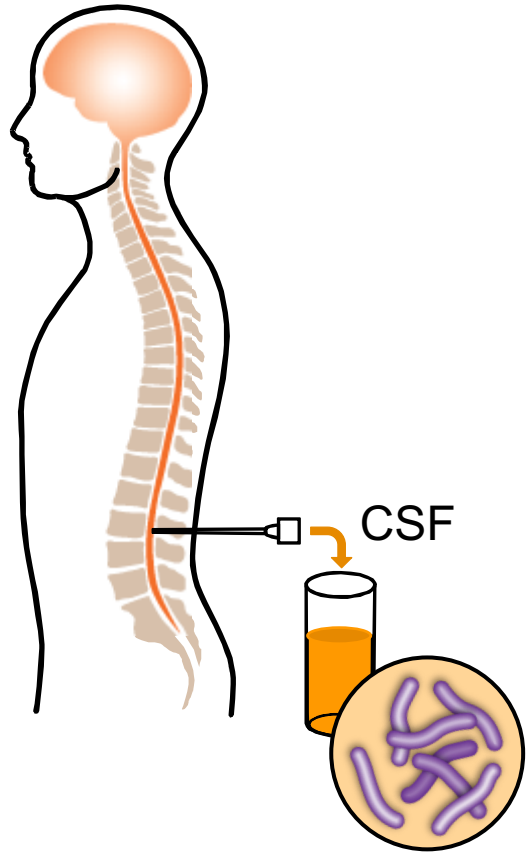
Healthy Volunteers

Drug
Low dose
High dose



Alzheimer's Patients

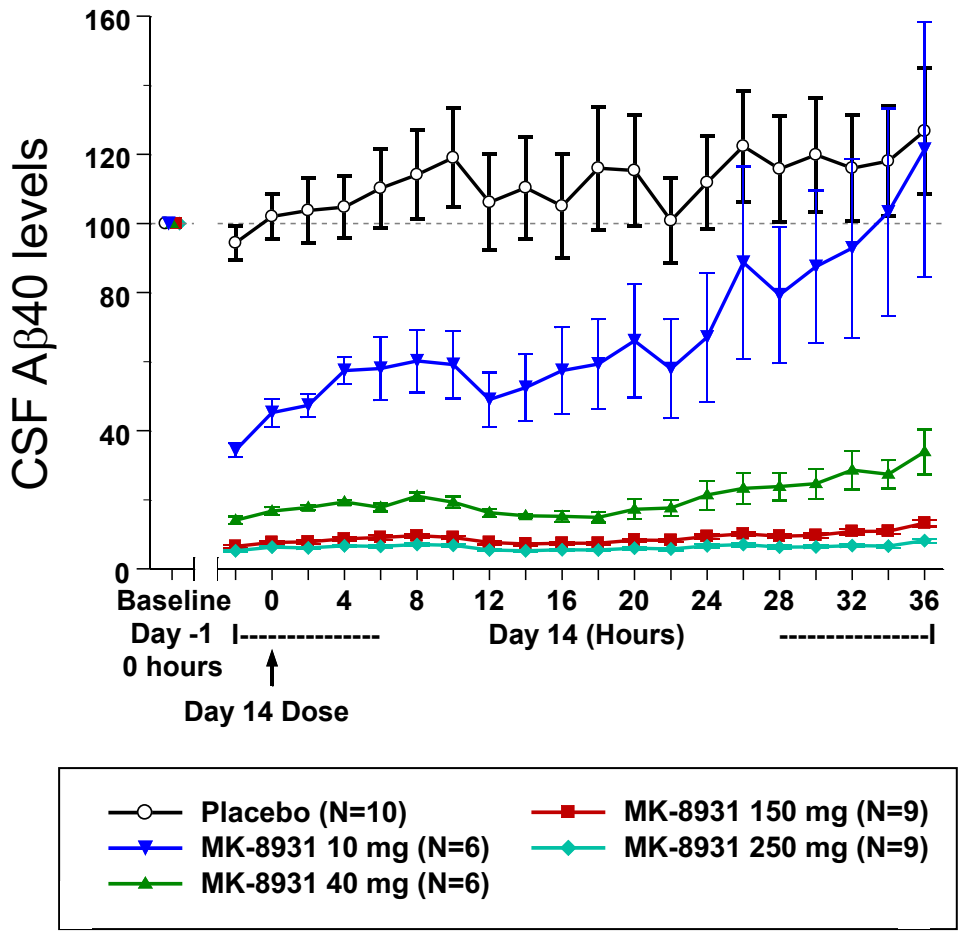
Drug
Low dose
High dose



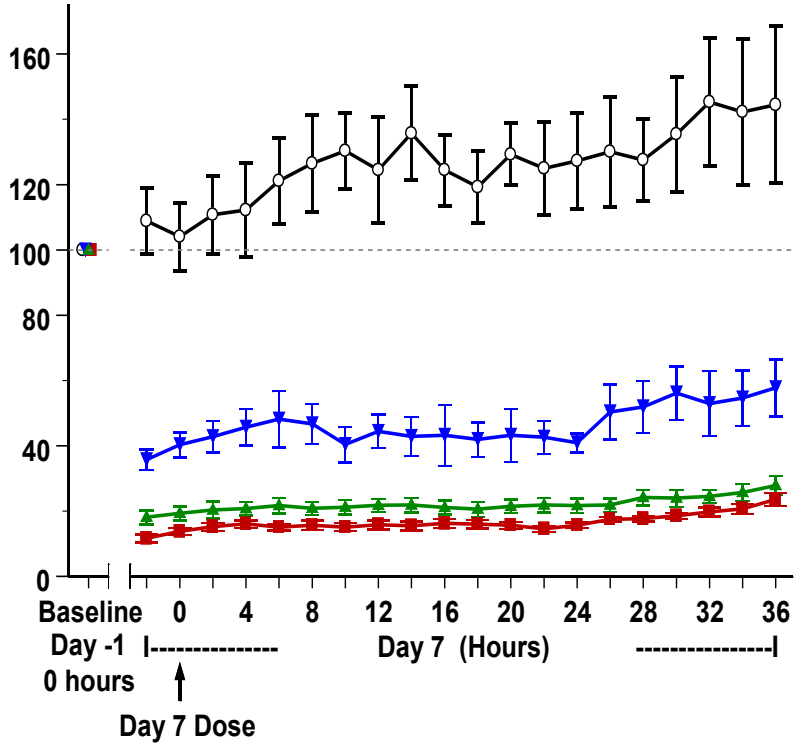
Kennedy et al *STM* (2016)

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

Multi-dose, healthy volunteers



Multi-dose, AD patients



>90% lowering

Quantitative PK-PD modeling estimates effective dose

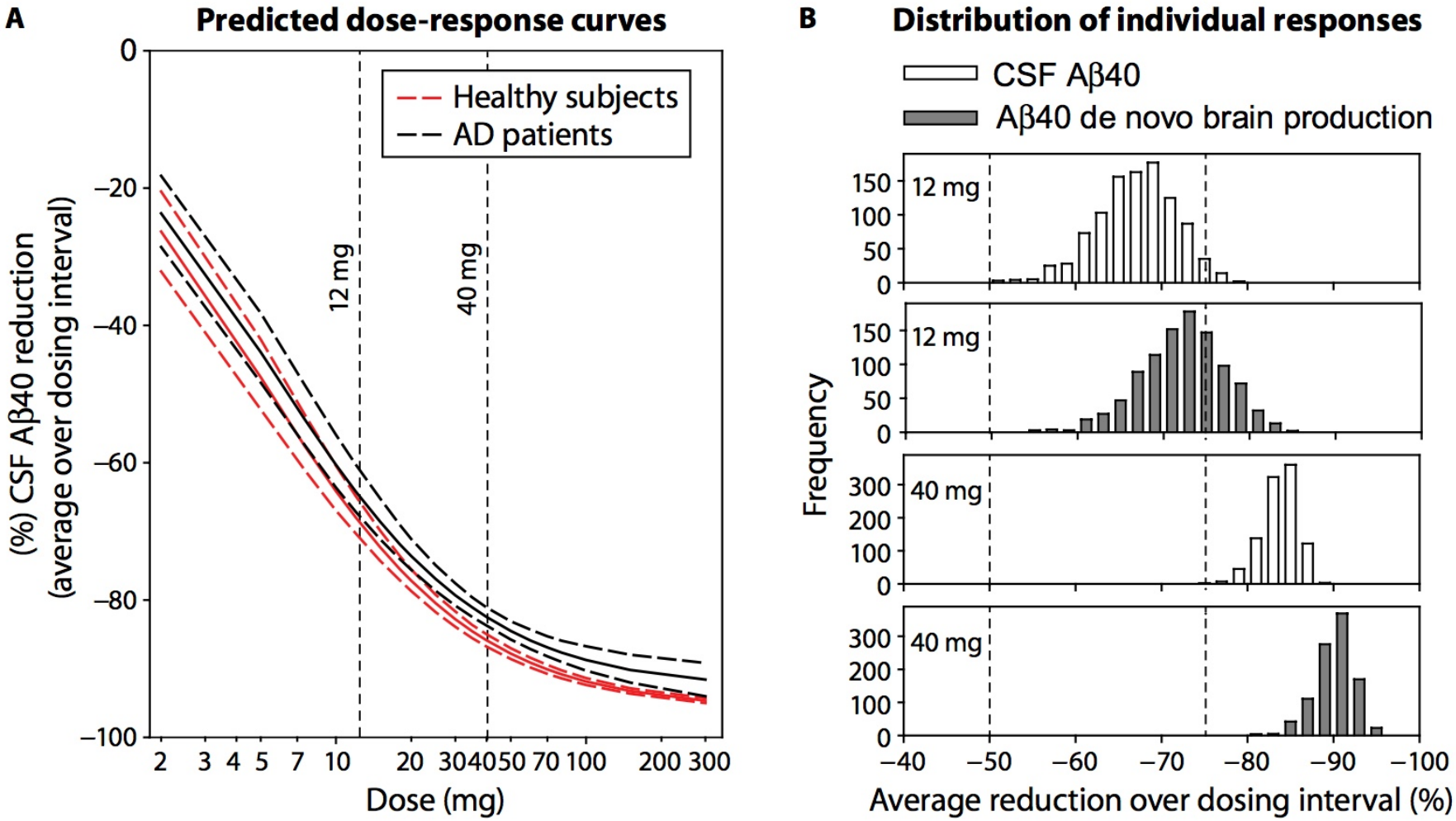
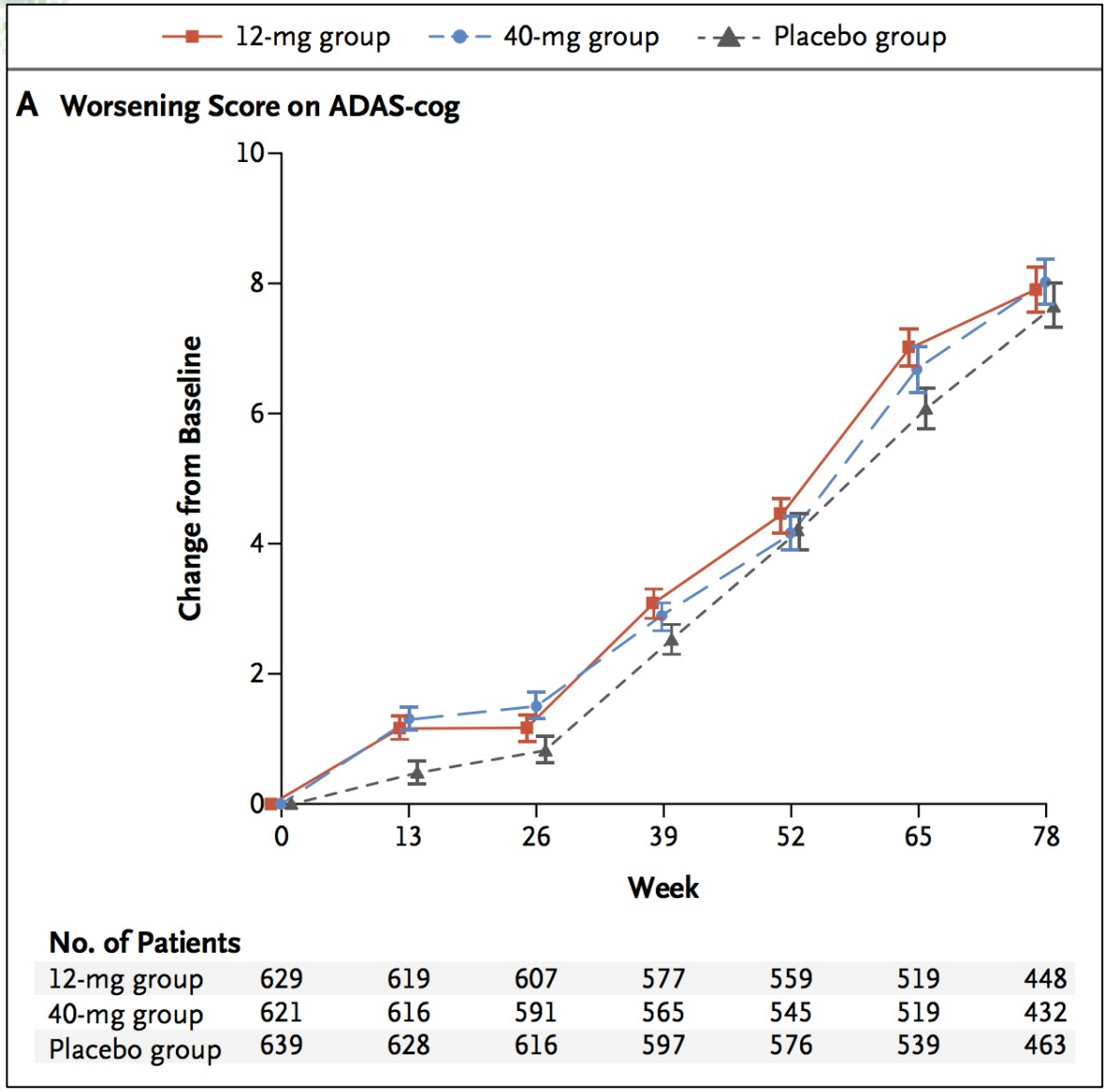


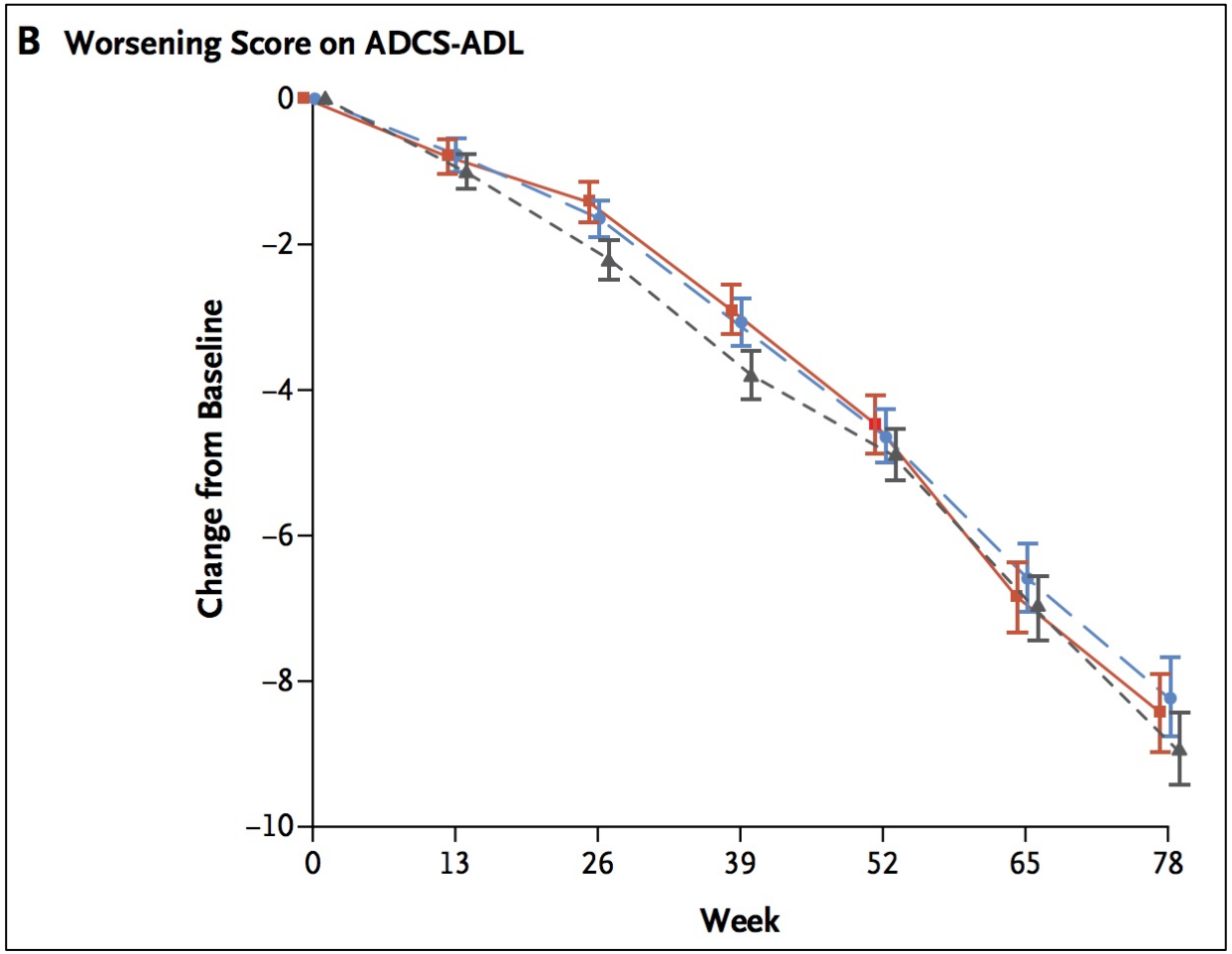
Fig. 7. Simulated steady-state verubecestat dose-response curves and predicted distribution of individual responses. A prospectively planned mechanistic PK/PD model was generated that used data across all time points, CSF PD end points, and studies to develop an integrated characterization of verubecestat effects in humans. (**A**) The solid and dashed lines represent the median and 90% confidence interval, respectively, of 1000 replicates of the response in a typical AD patient (black line) and a healthy nonelderly adult subject (red line). (**B**) Simulated distributions of individual CSF Aβ40 and de novo brain Aβ40 production in AD patients (n = 1000 subjects per dose level).

But not every therapy against a genetic target is successful…



No. of Patients

12-mg group	629	619	607	577	559	519	448
40-mg group	621	616	591	565	545	519	432
Placebo group	639	628	616	597	576	539	463



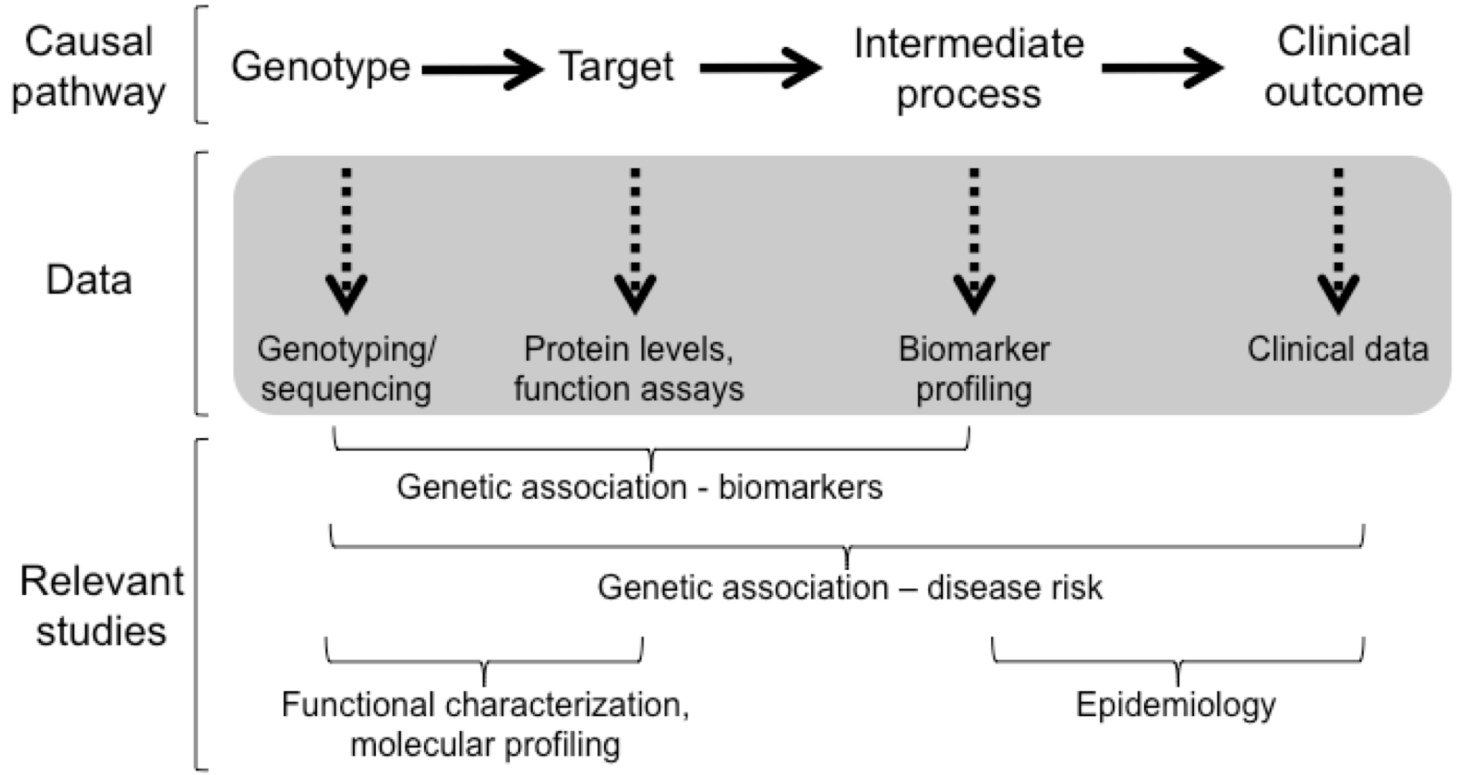
Egan et al *NEJM* (2018)

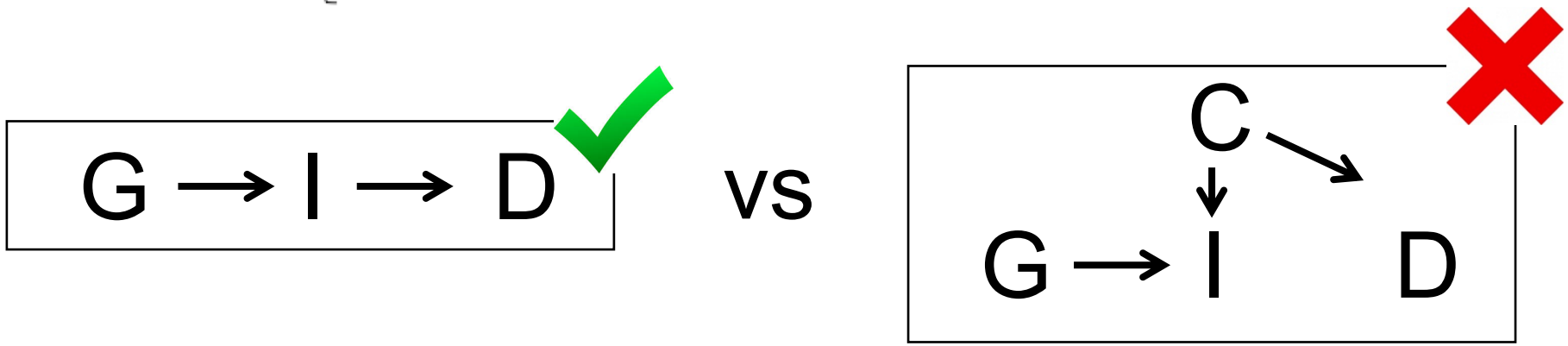
Key points about biomarkers and why genetic targets fail

- Essential to have robust PD biomarkers and PK/PD model to predict safety / efficacy
- Ideally, quantitative PK/PD model should be firmly rooted in human genetics
- Even so, not all therapies based on genetic targets will lead to approved drugs
  - Genetics is lifelong, drugs are not
  - Not all genetic phenotypes are good surrogates for drug discovery
  - Modality and molecular mechanism may not be precisely matched
  - Intervention may not sufficiently test therapeutic hypothesis

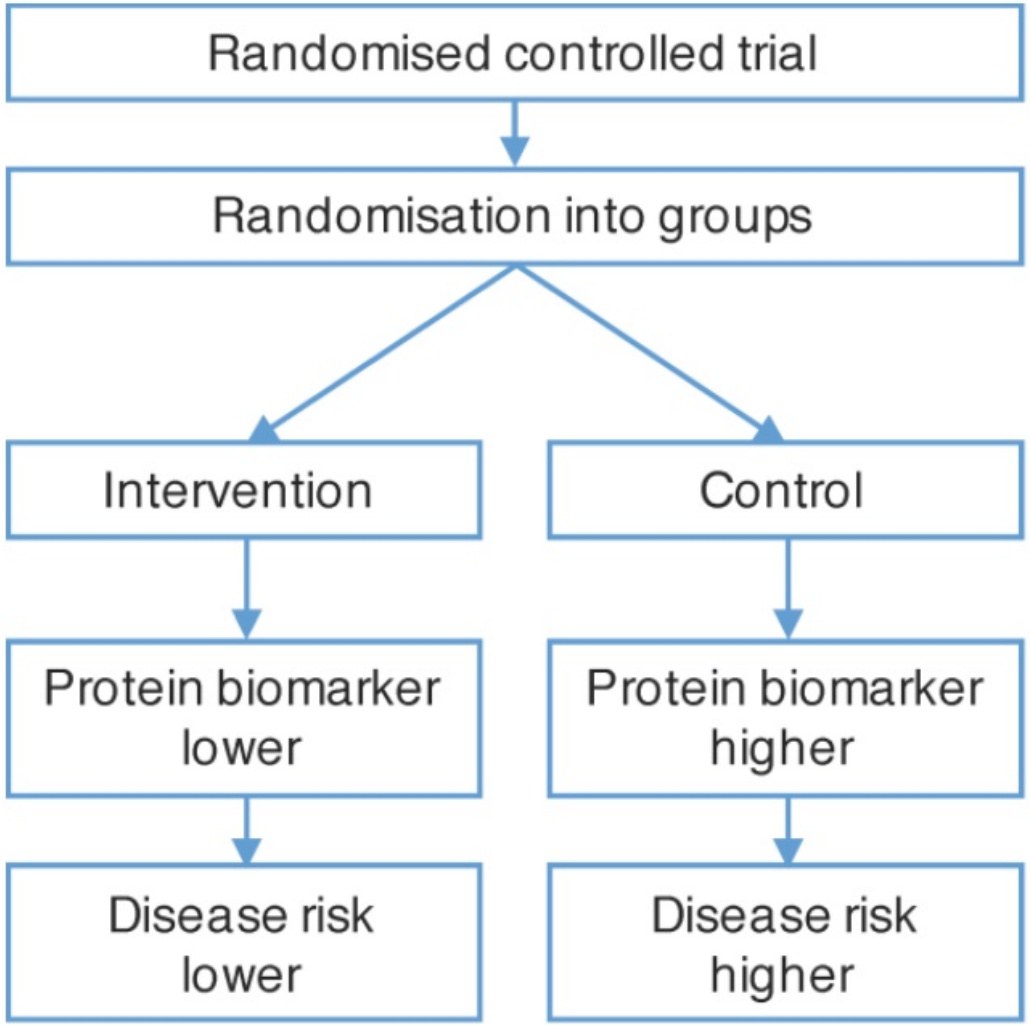
There are emerging resources to help maximize human genetics for drug discovery and development

Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery





Mendelian randomization: *nature's clinical trial*



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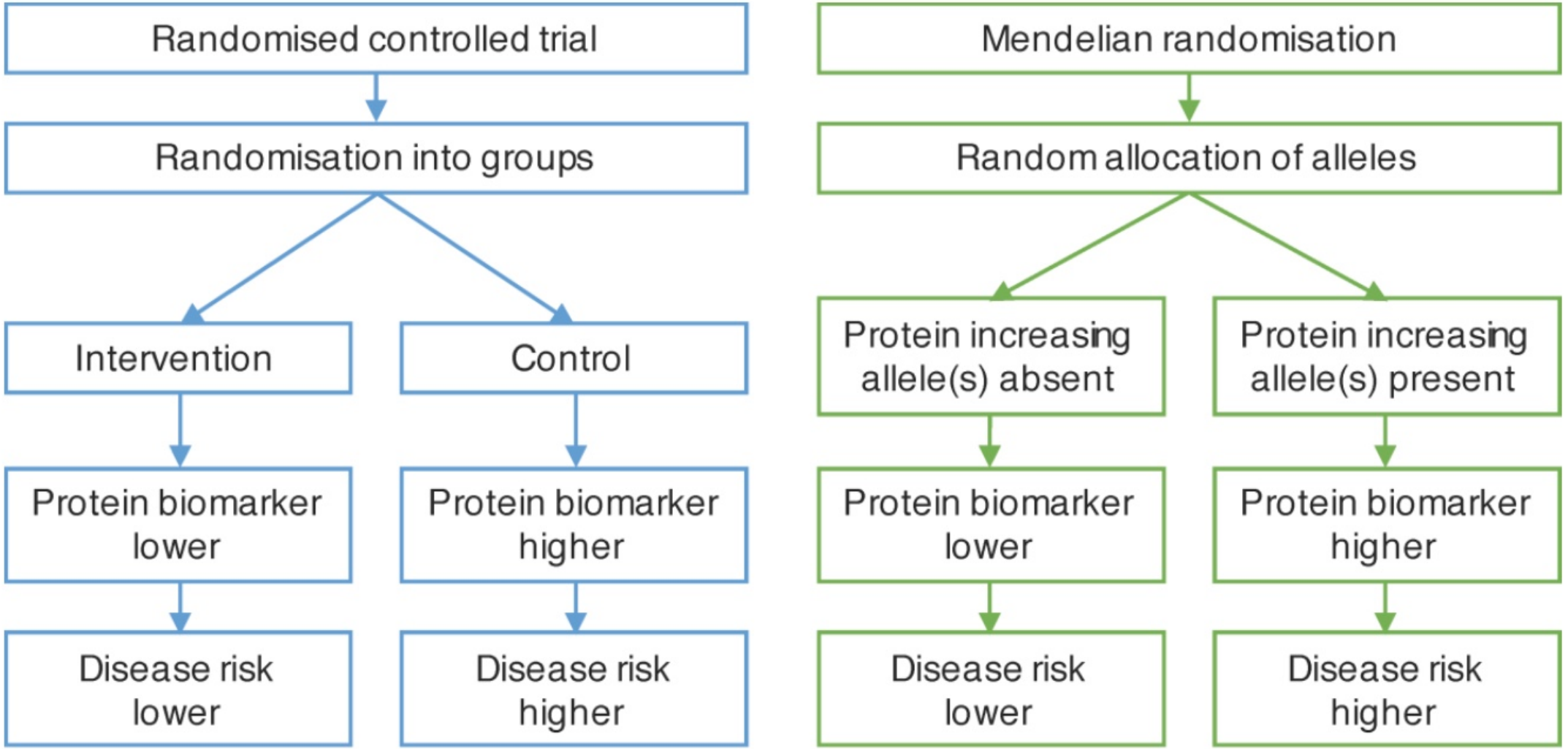
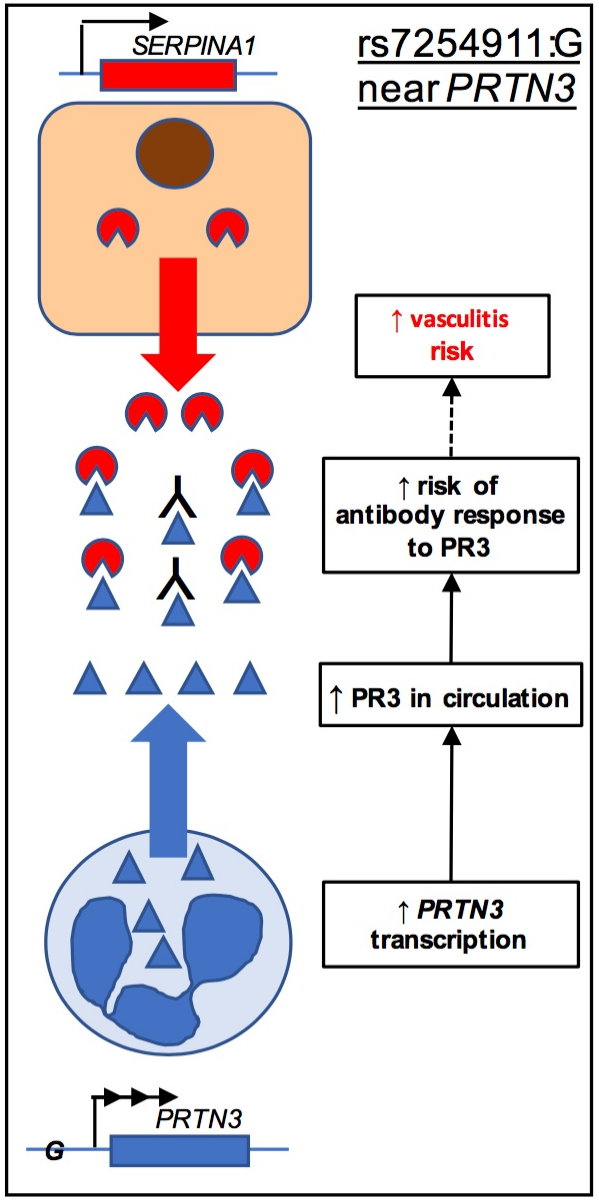


MR example: *PRTN3* and ANCA+ vasculitis

- Tested 3,622 plasma proteins in 3,301 healthy individuals from INTERVAL population cohort
- Identified 1,927 genetic associations with 1,478 proteins
- Example: *PRTN3* GoF allele increases PR3 protein and increases risk of PR3-associated vasculitis
- Therapeutic hypothesis: eliminating PR3 protein or deleting autoantibody secreting B cells may treat vasculitis

Sun, Maranville et al *Nature (*2018)



Phenome-wide association studies (PheWAS)

EHRs, Claims, Questionnaires, etc.

Disease-agnostic cohort

Clinical data

SNP

Genetic data

GWAS, exome sequencing, etc.

Test association of selected SNP with clinical endpoints

PheWAS code 1 — risk — surrogate for efficacy

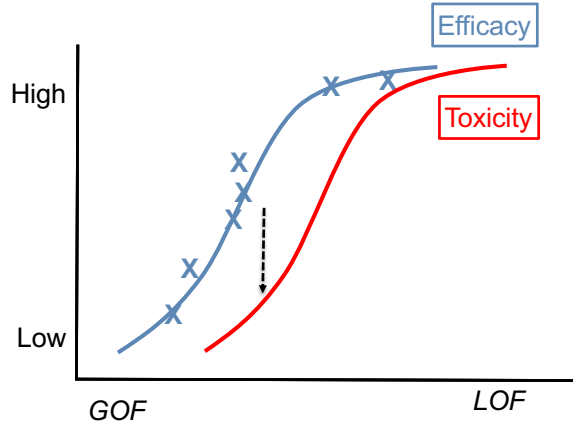
PheWAS code 2

PheWAS code 3

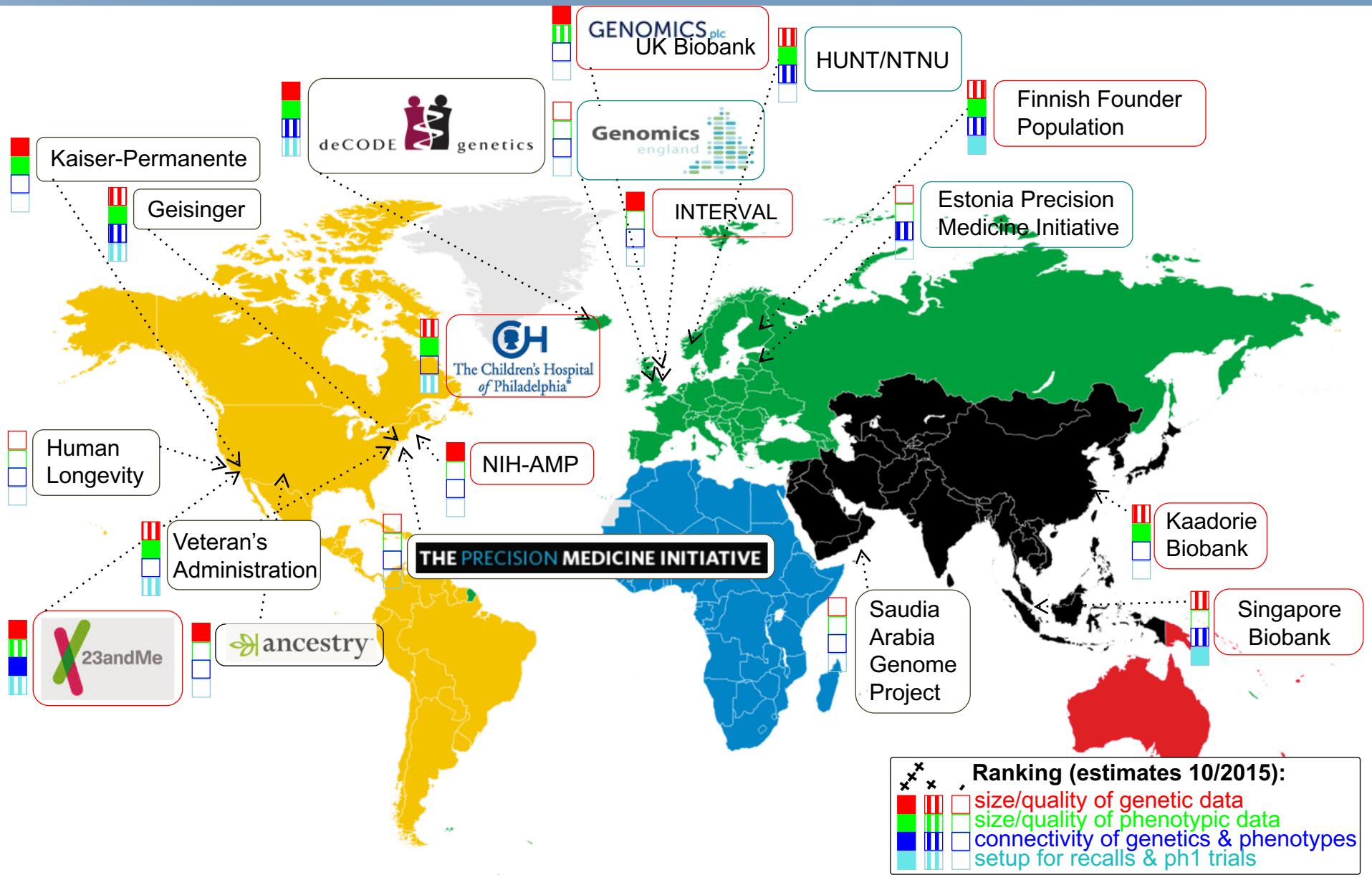
PheWAS code 4

PheWAS code 5 — risk — surrogate for toxicity

PheWAS code 500



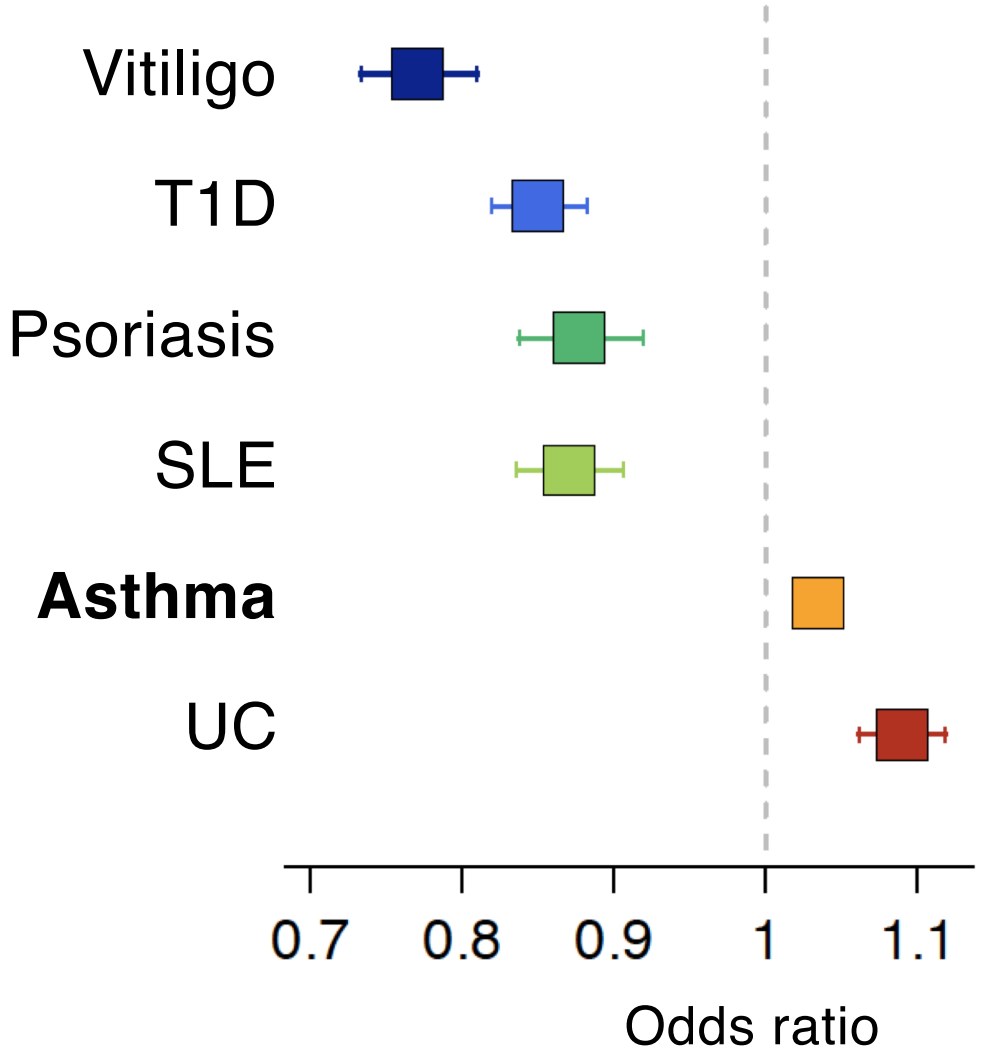
Population cohorts as unique genetic resource



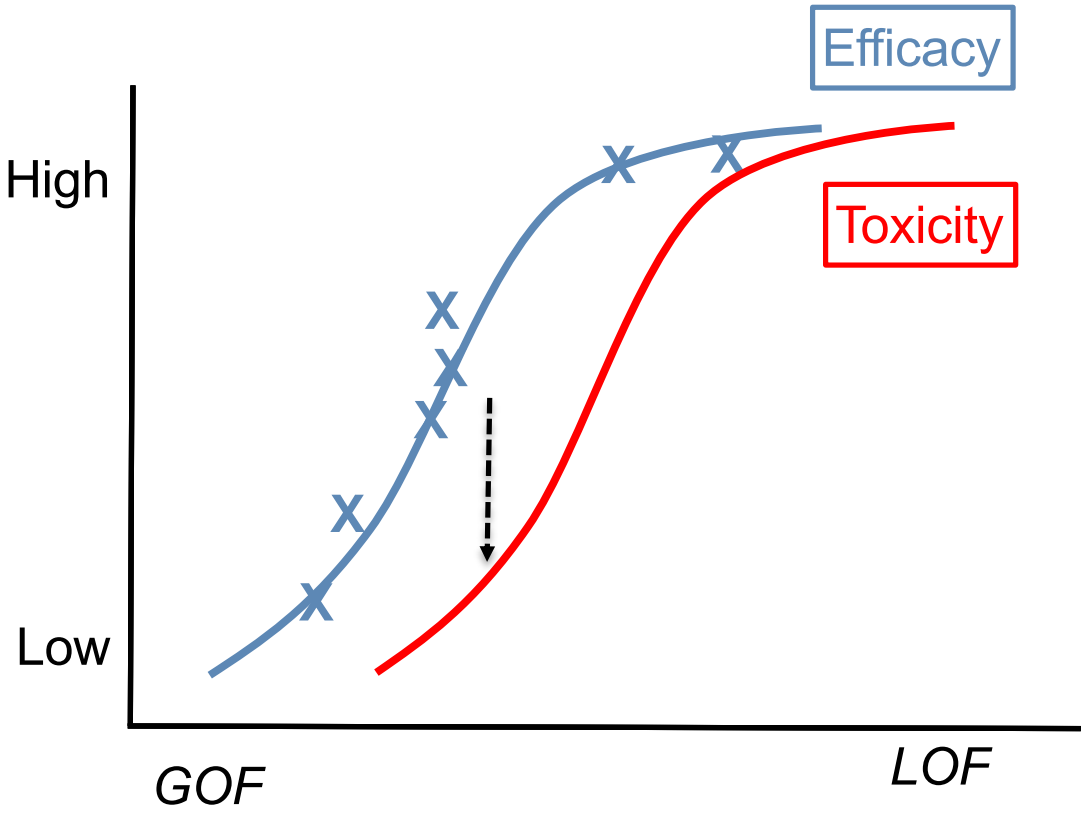
PheWAS example: *IFIH1*, autoimmunity, asthma

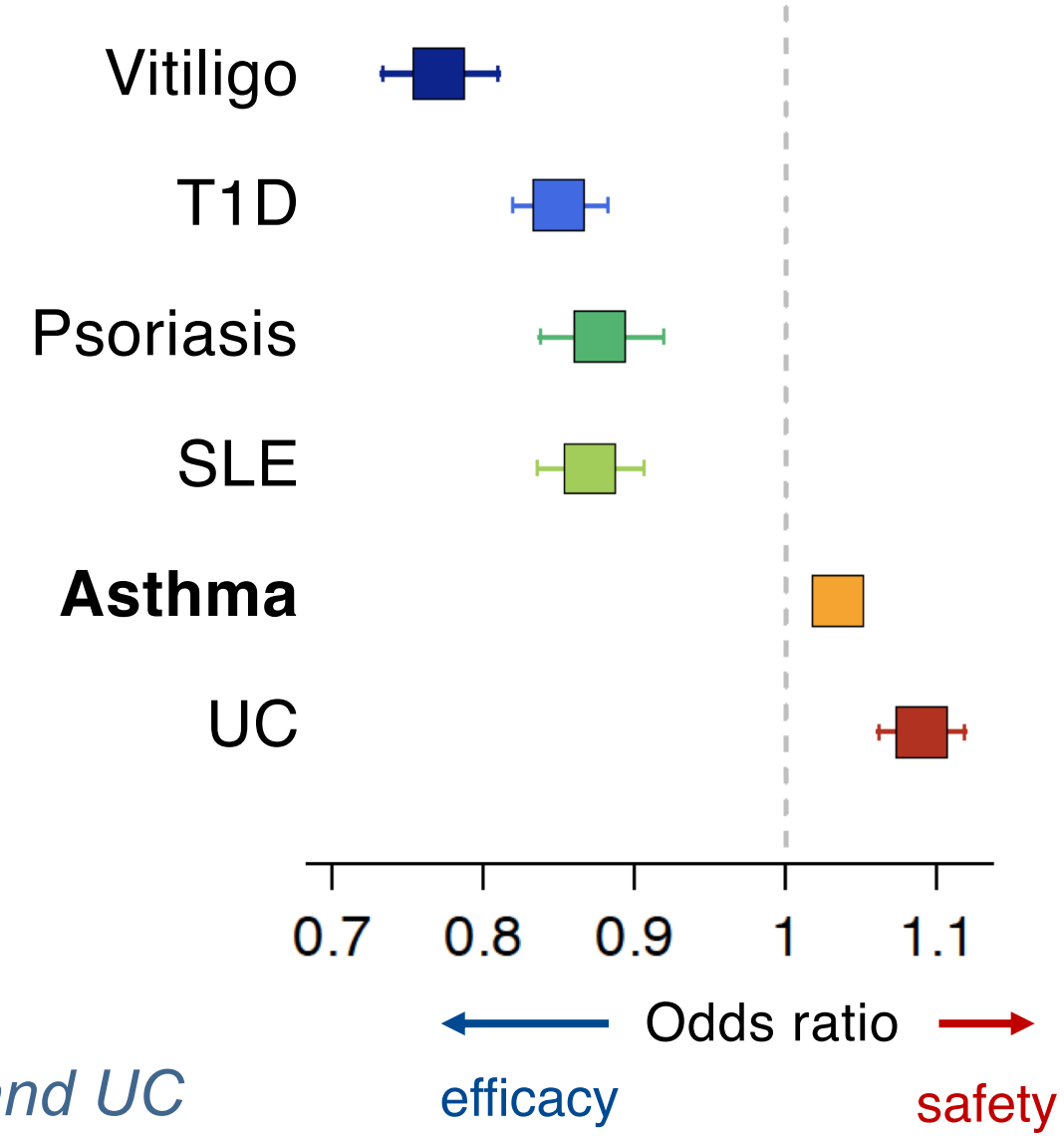
- PheWAS in ~800,000 individuals from four population cohorts
- Tested 25 SNPs for association with 1,683 clinical endpoints
- 10 novel associations discovered
- Example: *IFIH1* LOF allele protects from autoimmunity (known) but increases risk of asthma (novel finding)
- Therapeutic hypothesis: inhibiting IFIH1 may be effective in some autoimmune diseases but may make asthma worse

Diogo et al *under revision*



Predicted impact of therapeutic inhibition of IFIH1





Beneficial effect for some autoimmune diseases, but increase risk of asthma and UC