Human genetics and drug discovery

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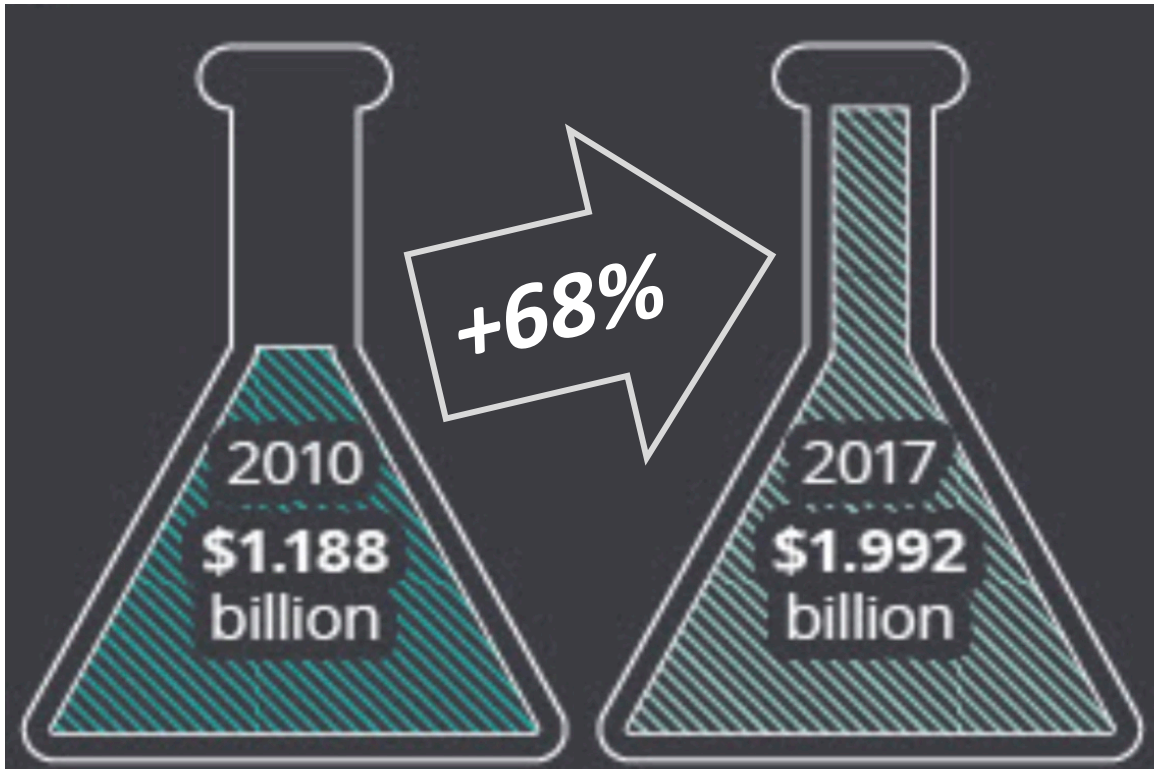
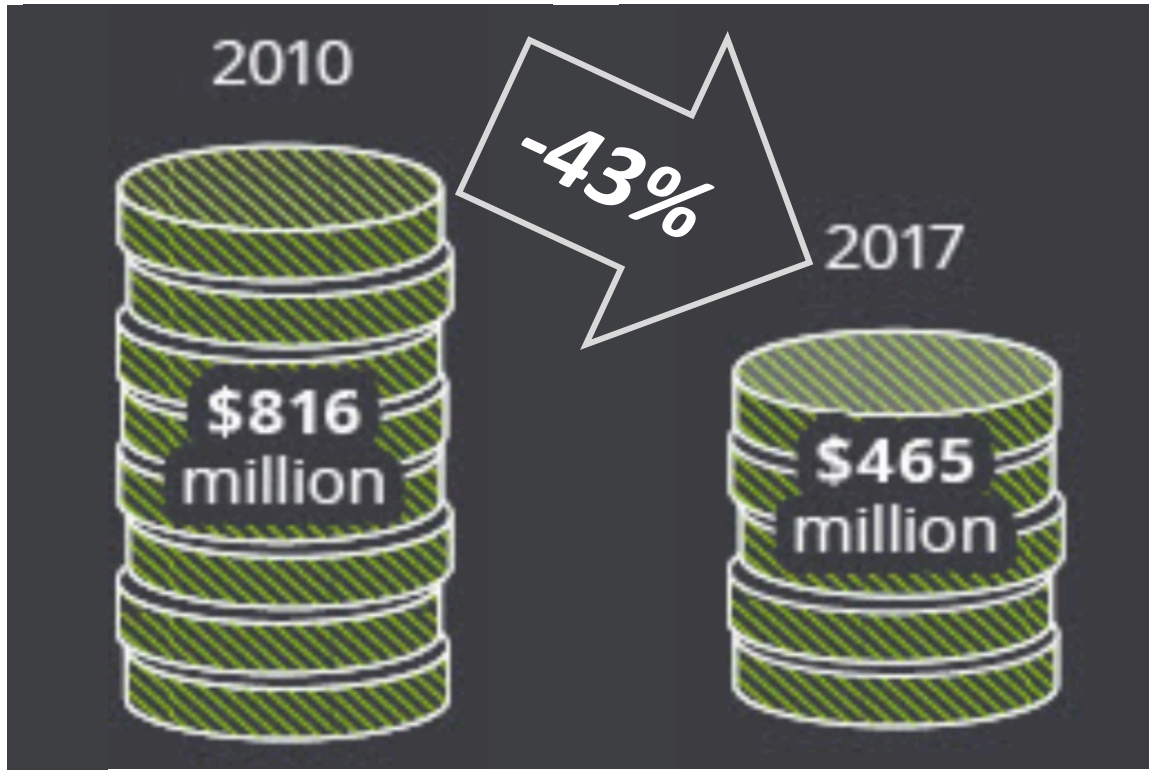
Bristol-Myers Squibb

BWH Division of Genetics
Dec. 17, 2019

The Problem

Two fundamental challenges to drug R&D





Attrition problem

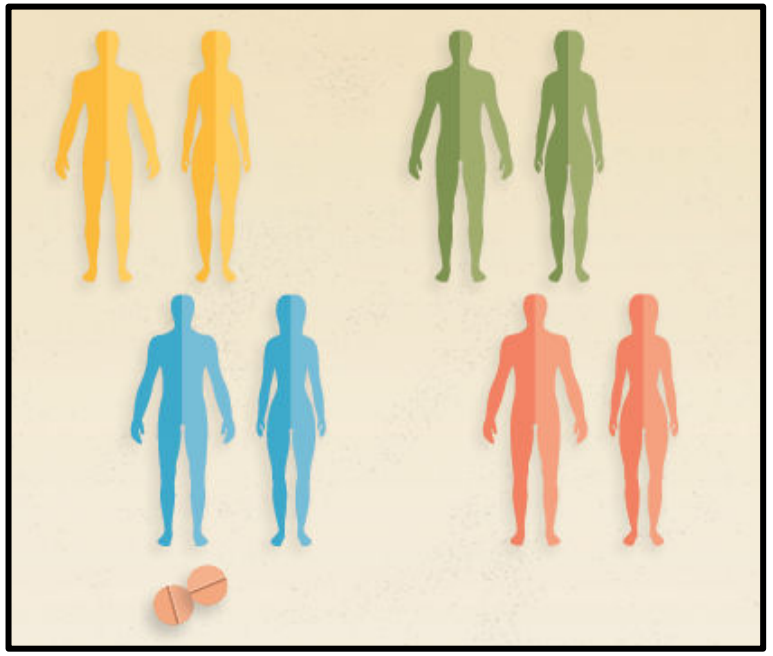
Innovation problem

Deloitte Centre for Health Solutions

A Solution

We relied on preclinical models to pick targets and estimate efficacy in heterogeneous human populations

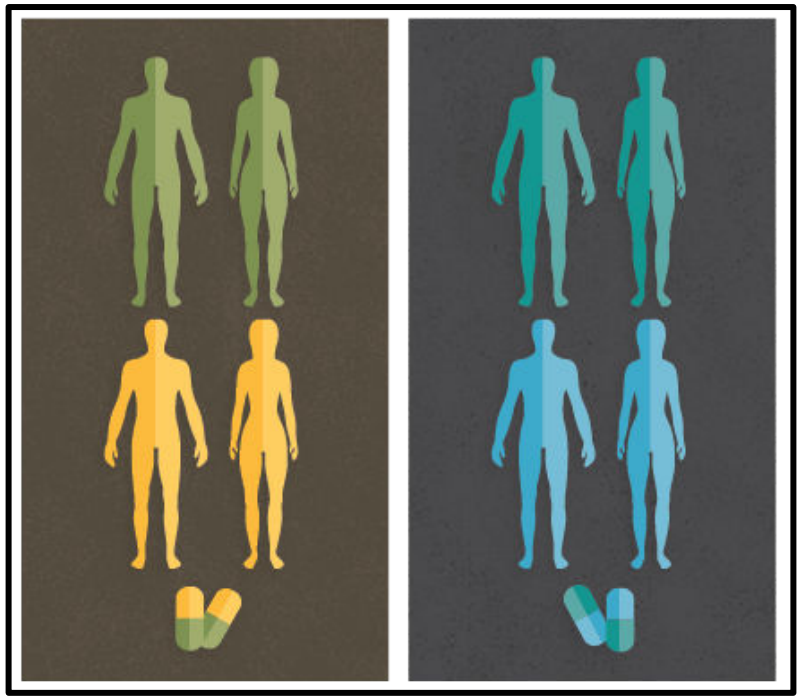
It was…



Discovery → Pre-clinical → Phase 1

Humans are the "model organism" of choice for new targets and precision medicine

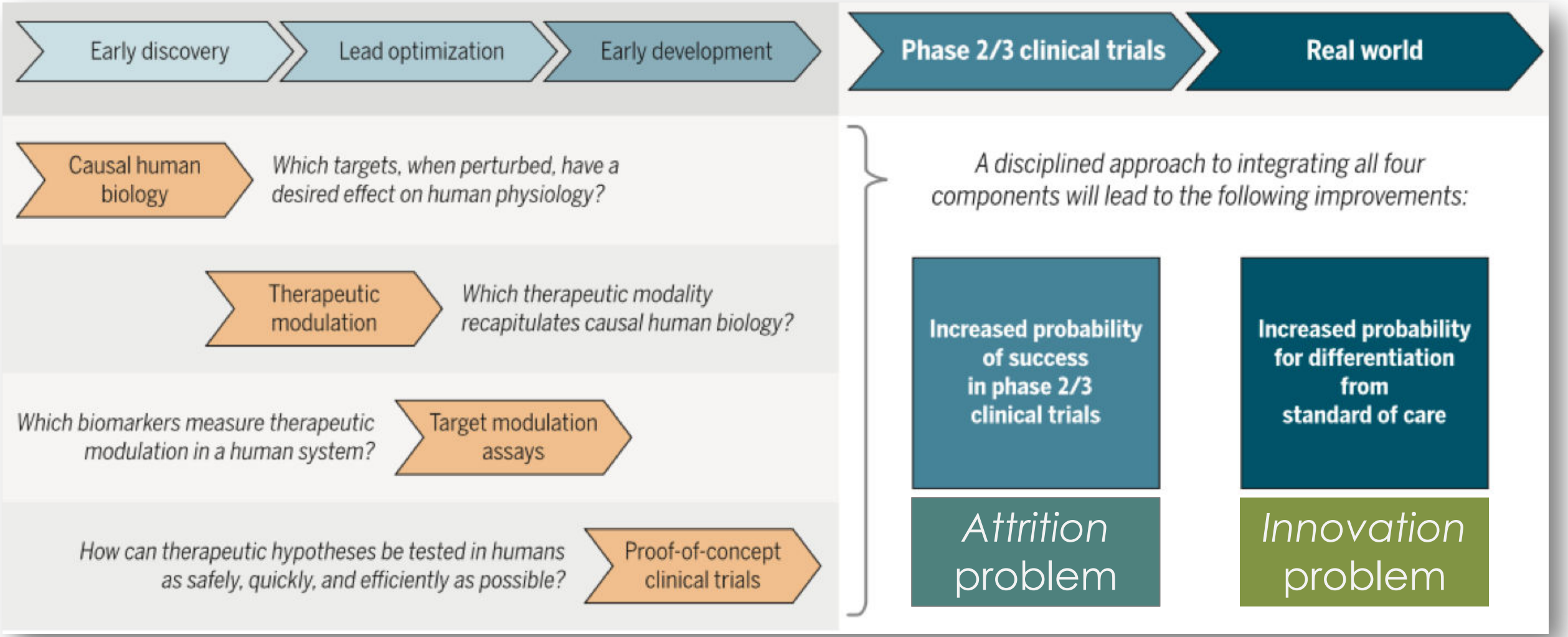
But today…



Discovery → Pre-clinical → Phase 1

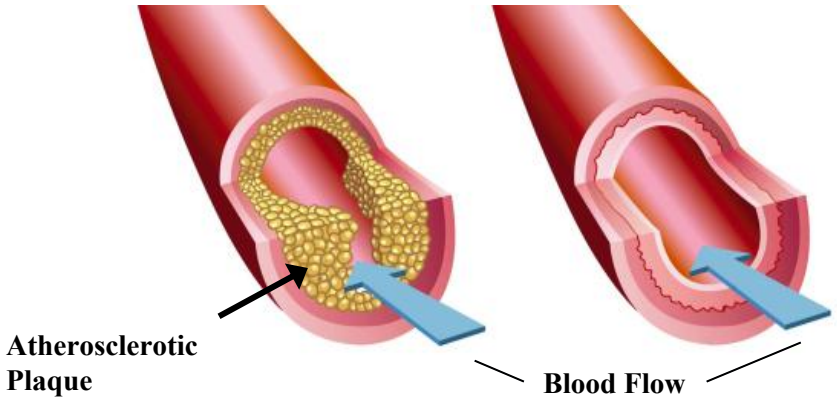
Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

Why Genetics

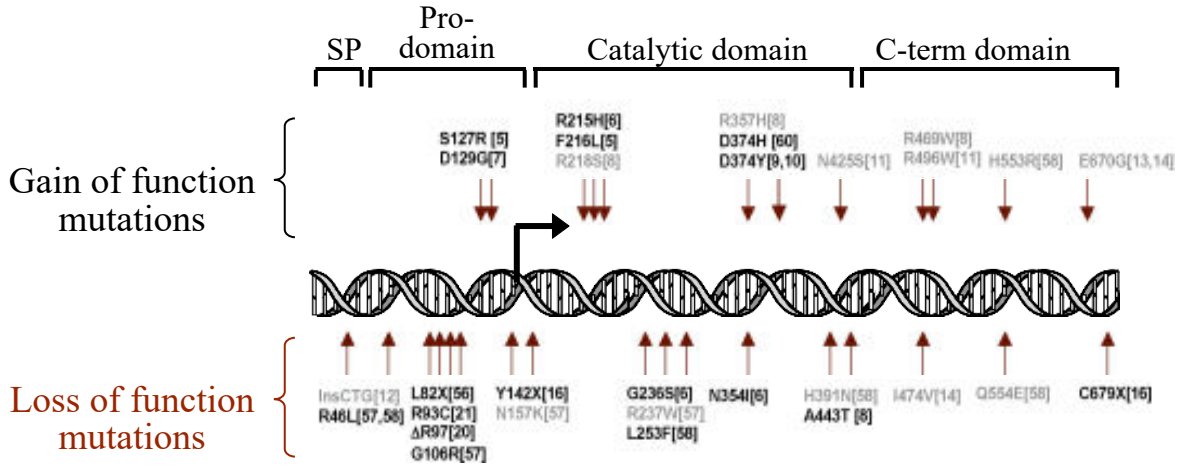


Plenge *Science Translational Medicine* (2016)

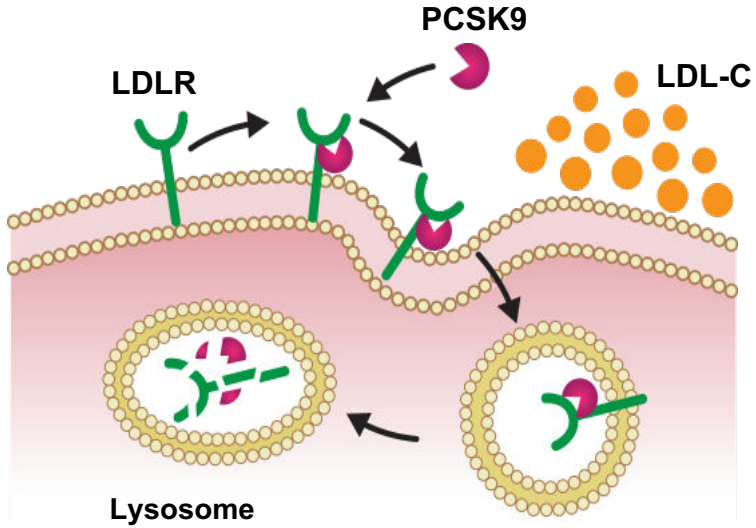
Many genes influence cholesterol levels and risk of heart disease



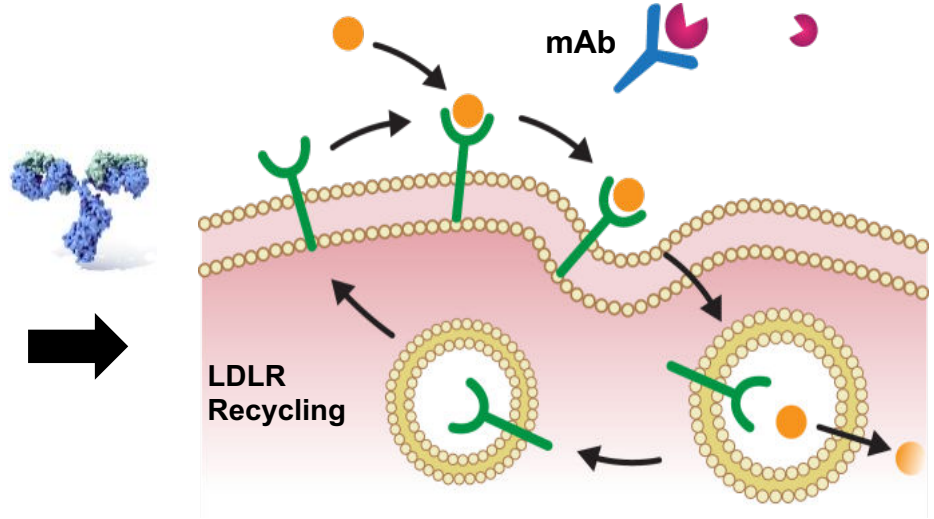
PCSK9 mutations associated with high and low LDL cholesterol levels (and heart disease)



PCSK9 binds to LDL receptor outside of cells to reduce LDLR on cells

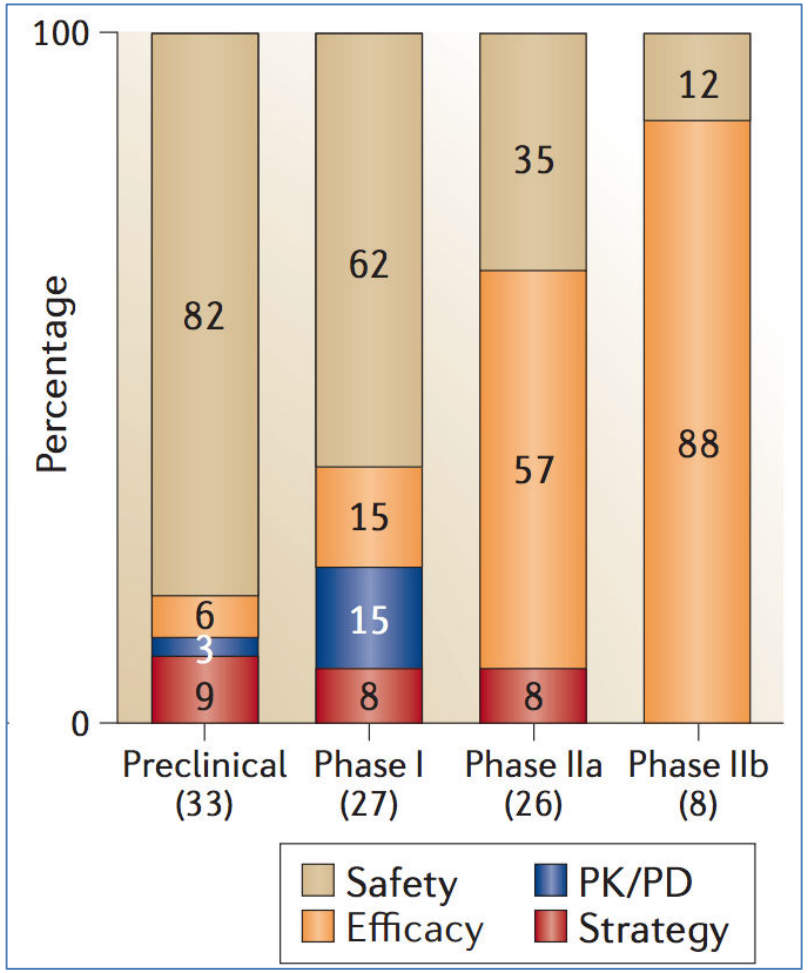


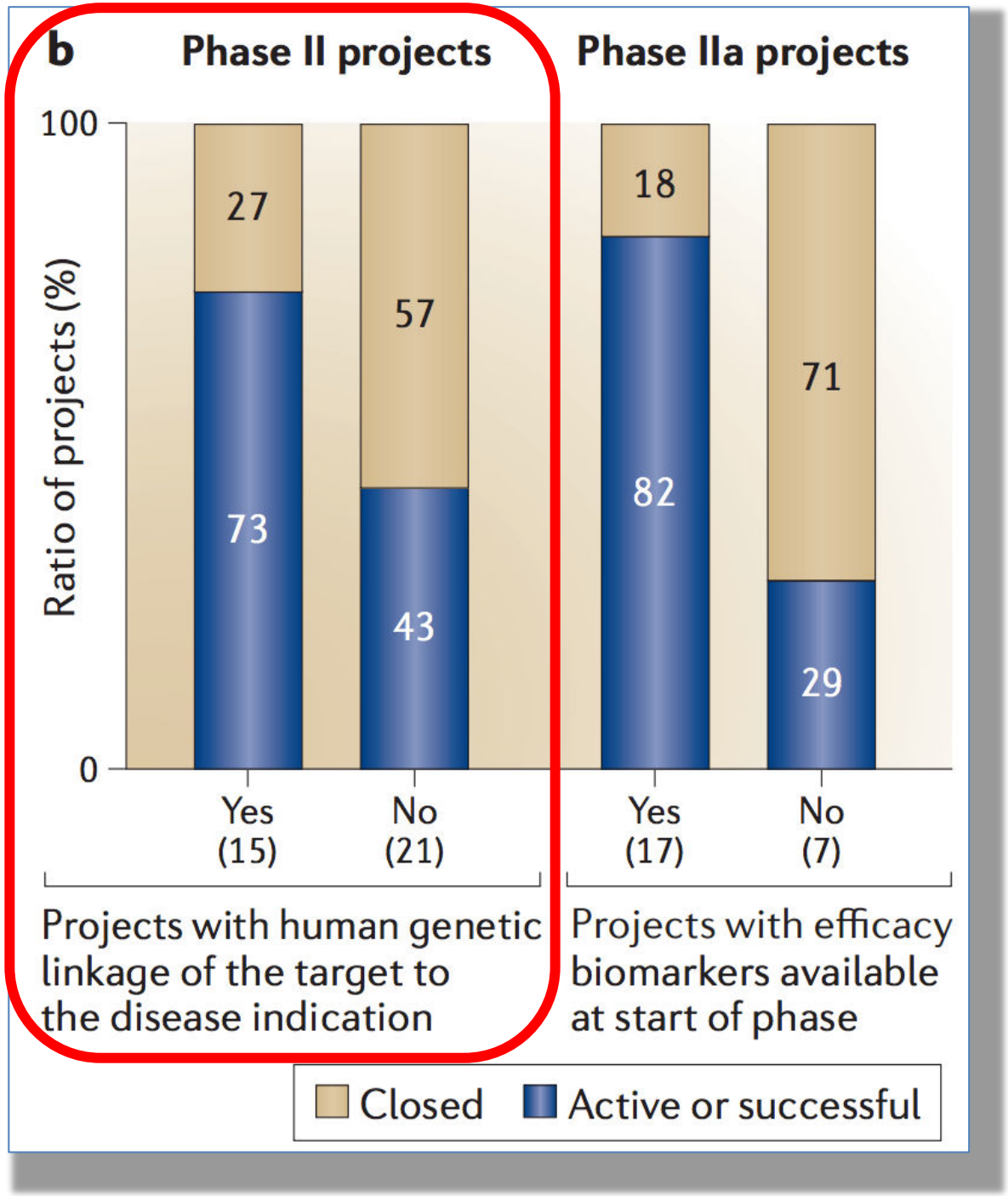
drugs that mimic the mutation & lower LDL and protect from heart disease



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





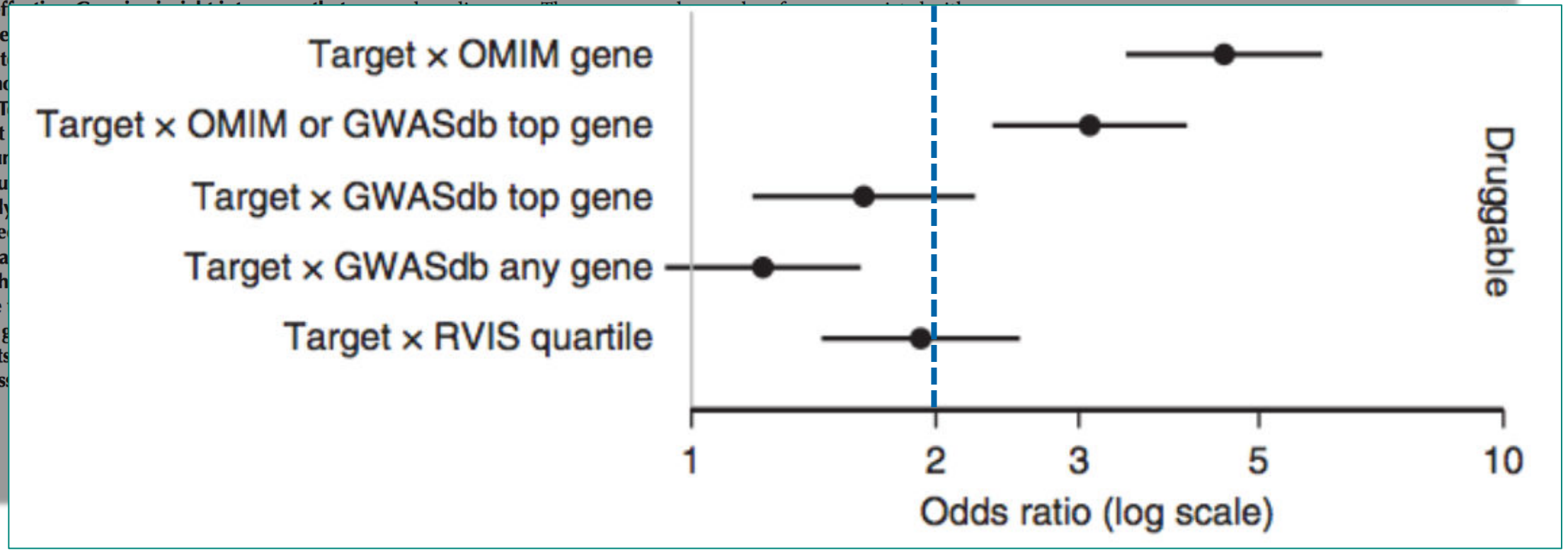
The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

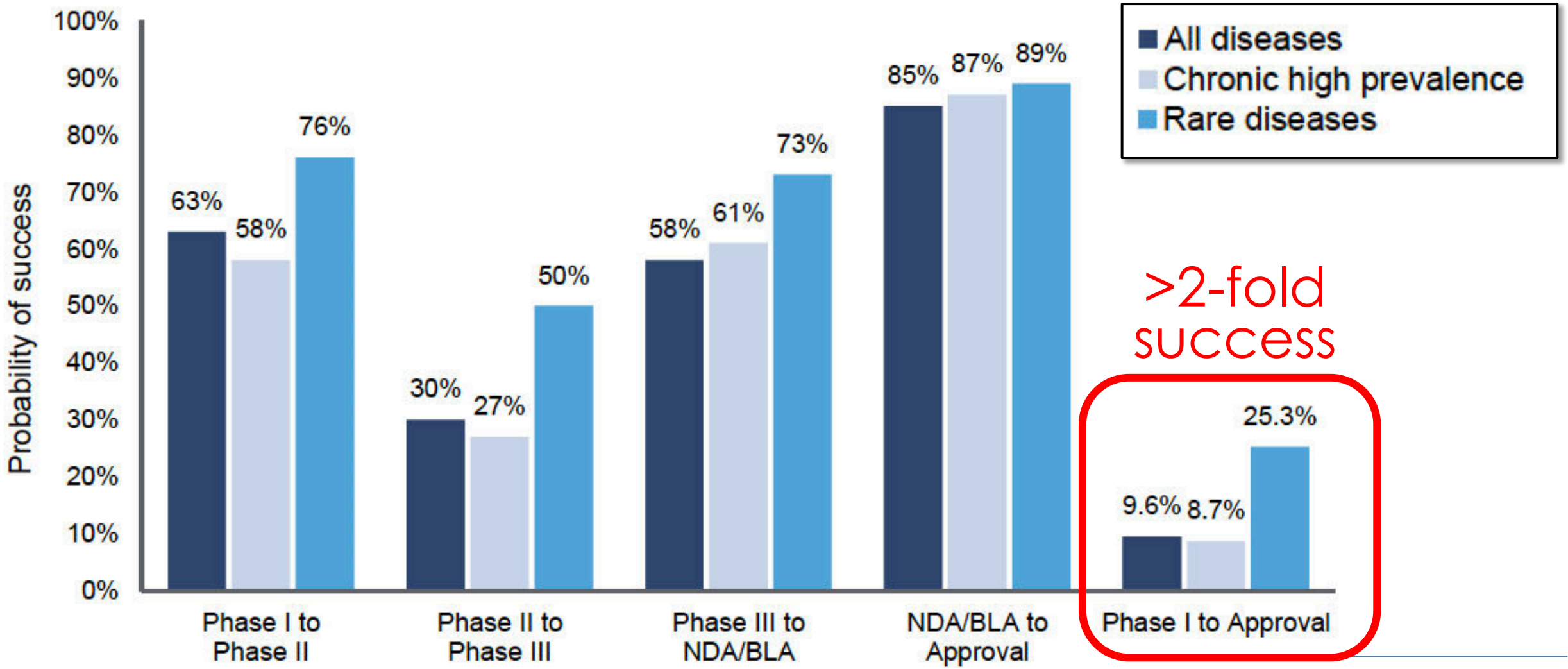
~2-fold increase in success for genetic targets

Over a quarter of drugs that enter clinical development fail because they are ineff
influence human dise
indications are select
how much weight sh
these key decisions. T
how well the current
mechanisms. We four
the proportion of dru
increases significantly
from 2.0% at the pre
for approved drugs, a
areas. We estimate th
targets could double
Therefore, using the g
select the best targets
impact on the succes

of selecting the best drug targets and indications[6], the key decisions in

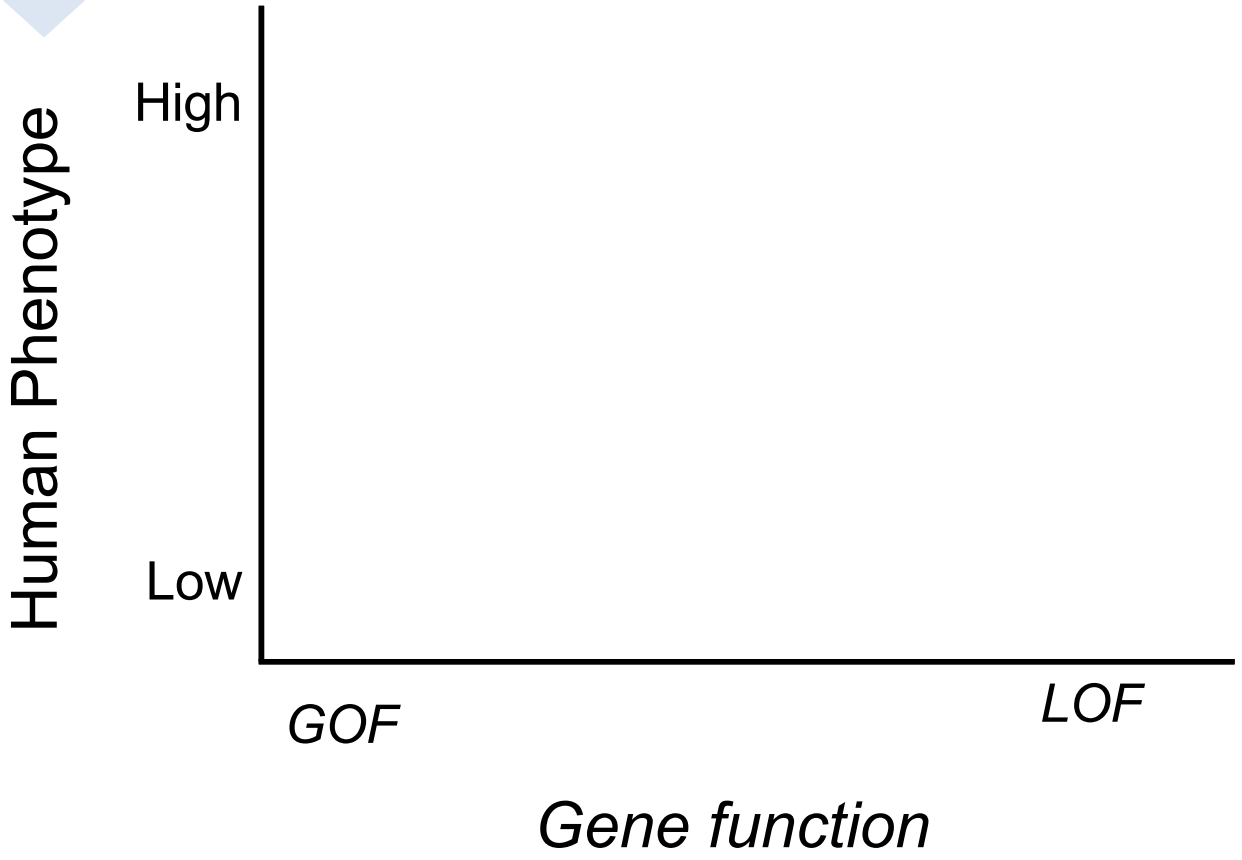


Rare genetic diseases have >2-fold higher success rate



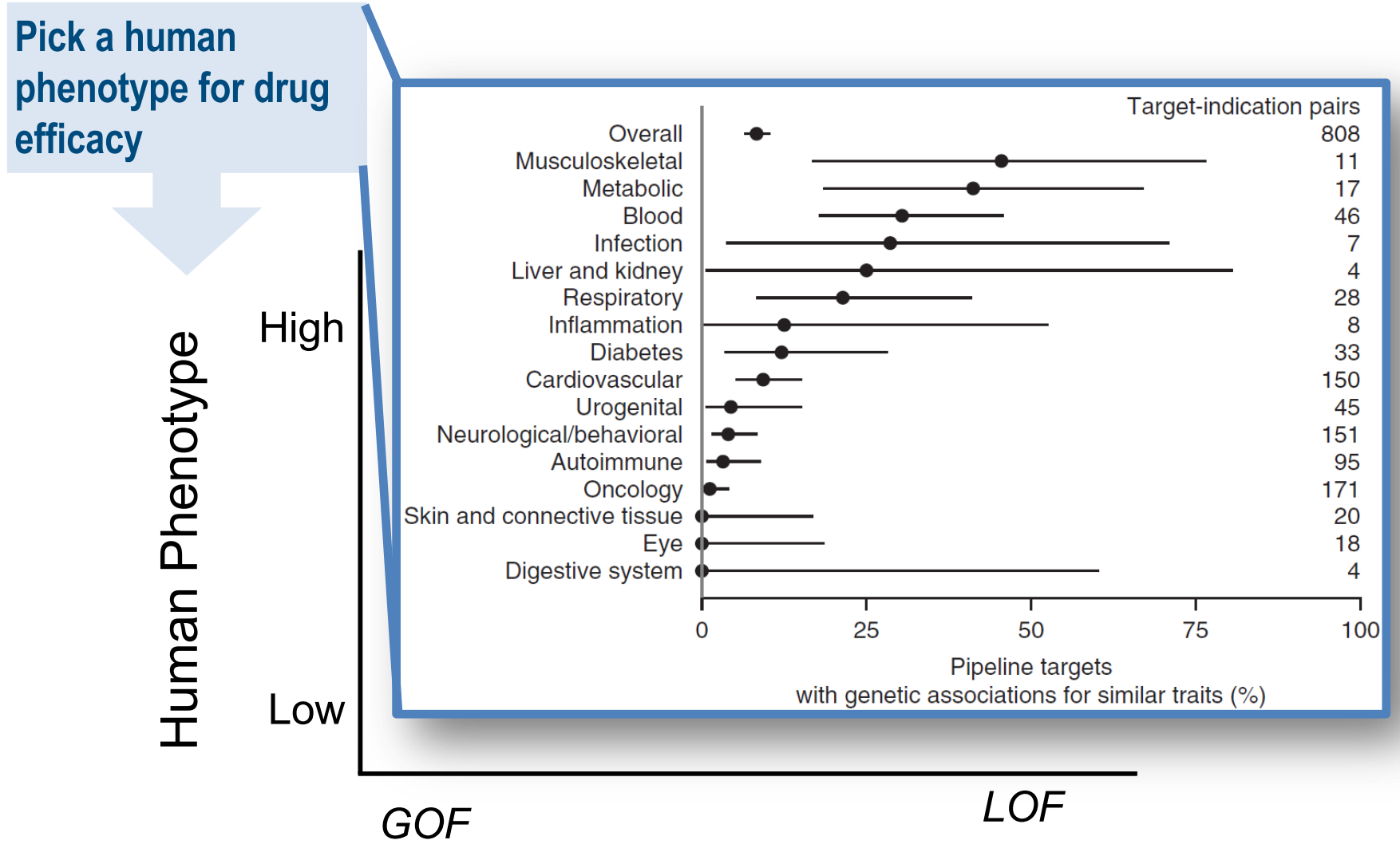
A model

Pick a human phenotype for drug efficacy

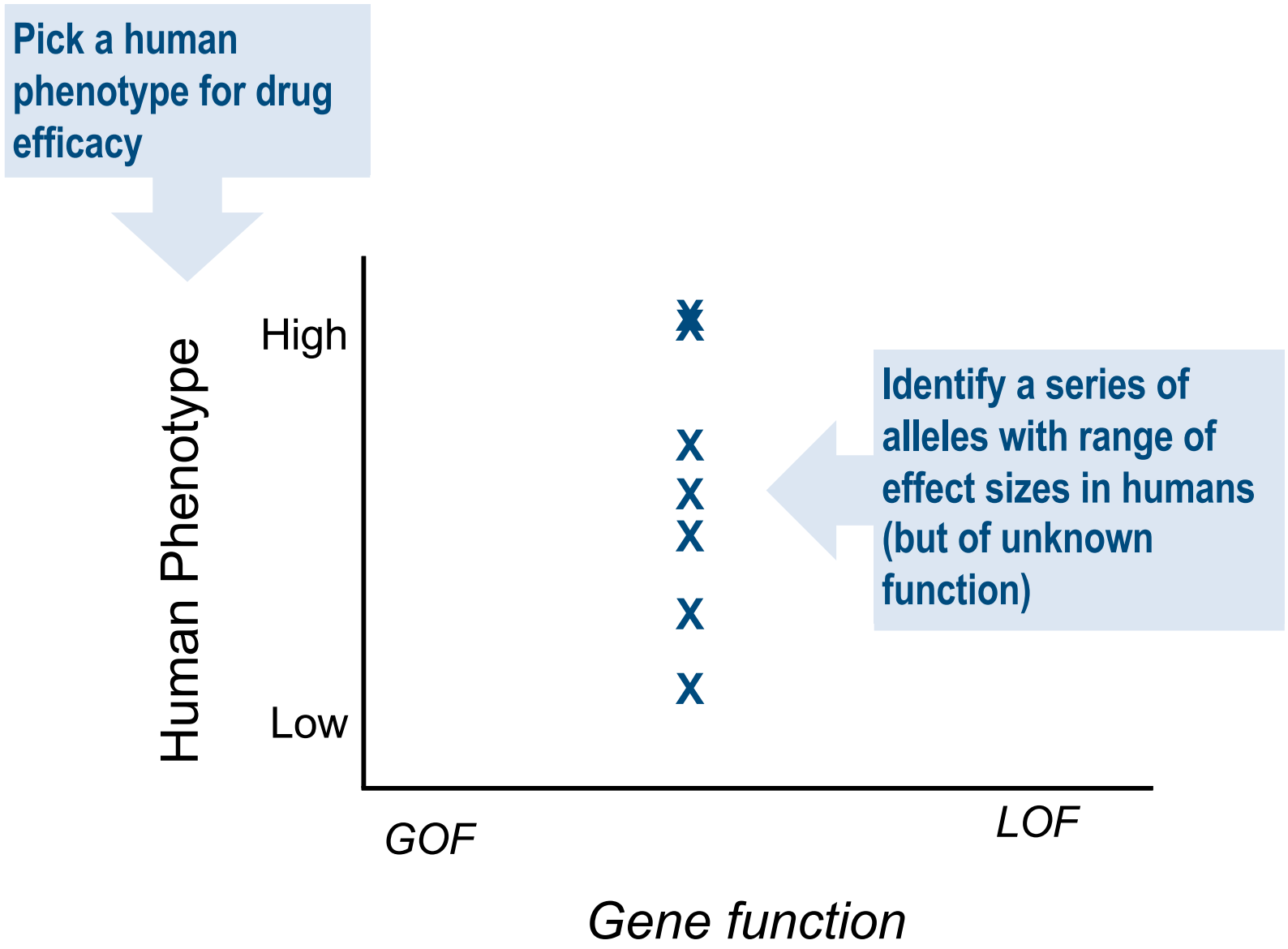


Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

Pick a human phenotype for drug efficacy

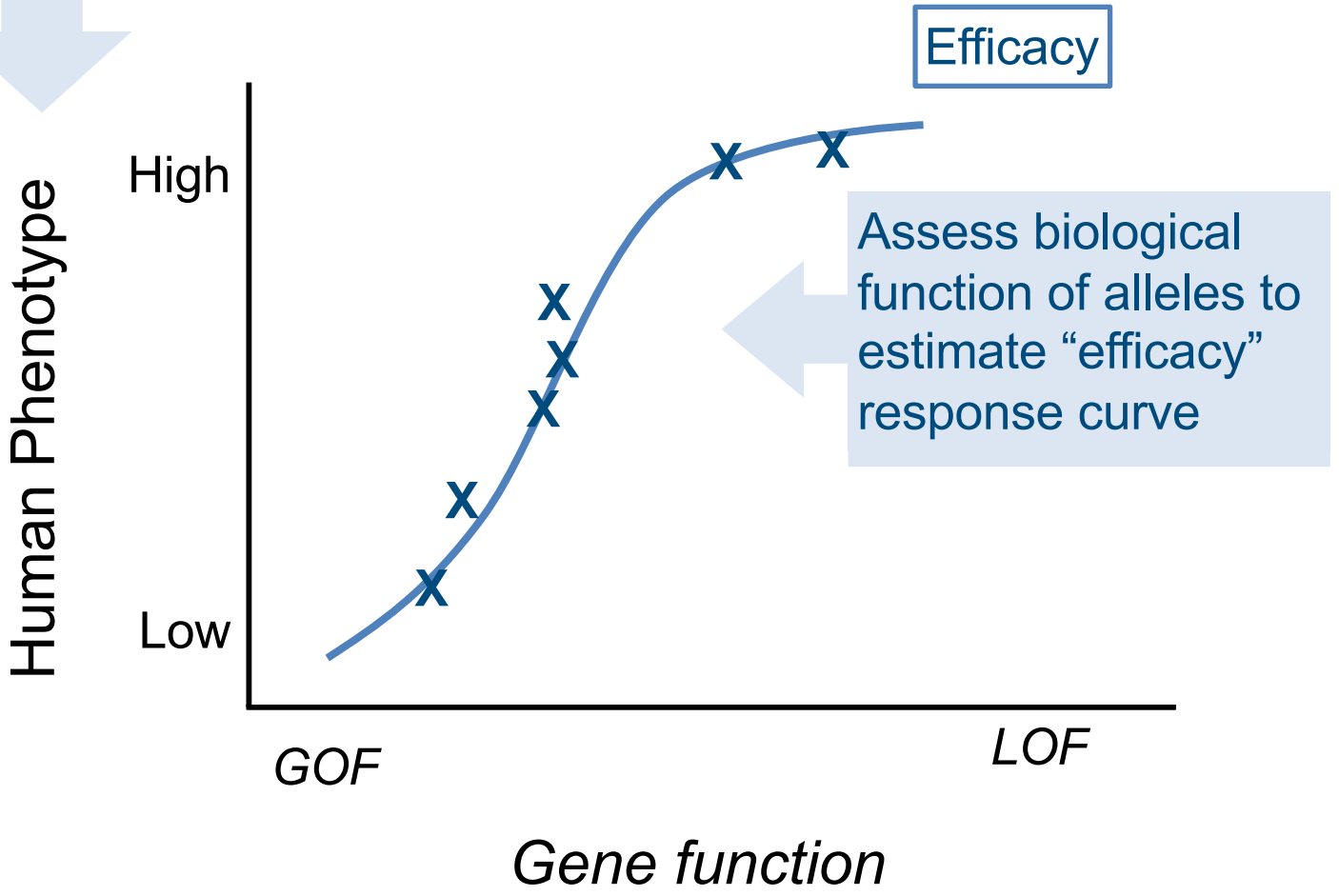


Nelson et al *Nature Genetics* 2015



Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

Pick a human phenotype for drug efficacy

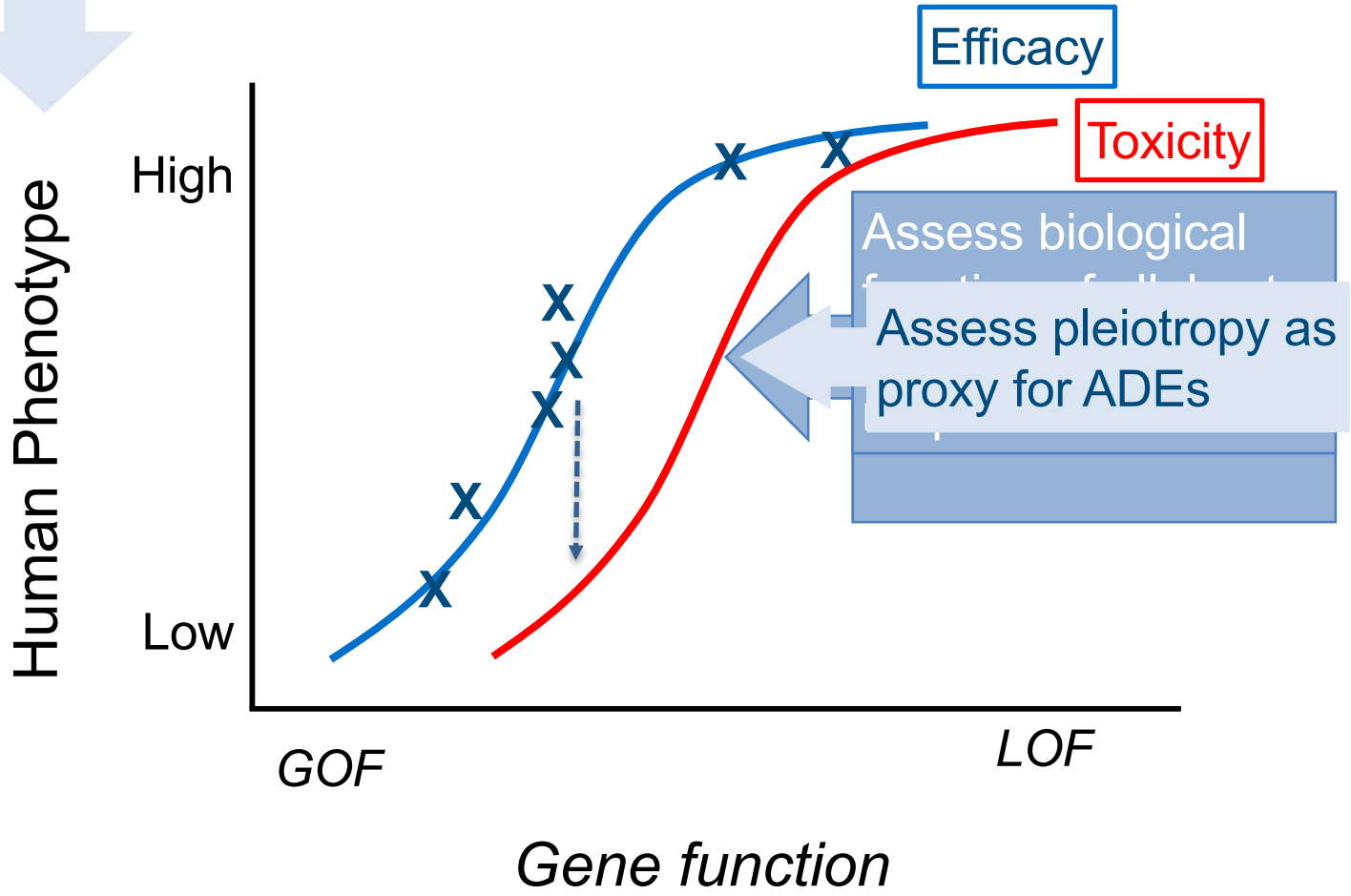


Assess biological function of alleles to estimate "efficacy" response curve

High-throughput functional interrogation is a bottleneck

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

Pick a human phenotype for drug efficacy

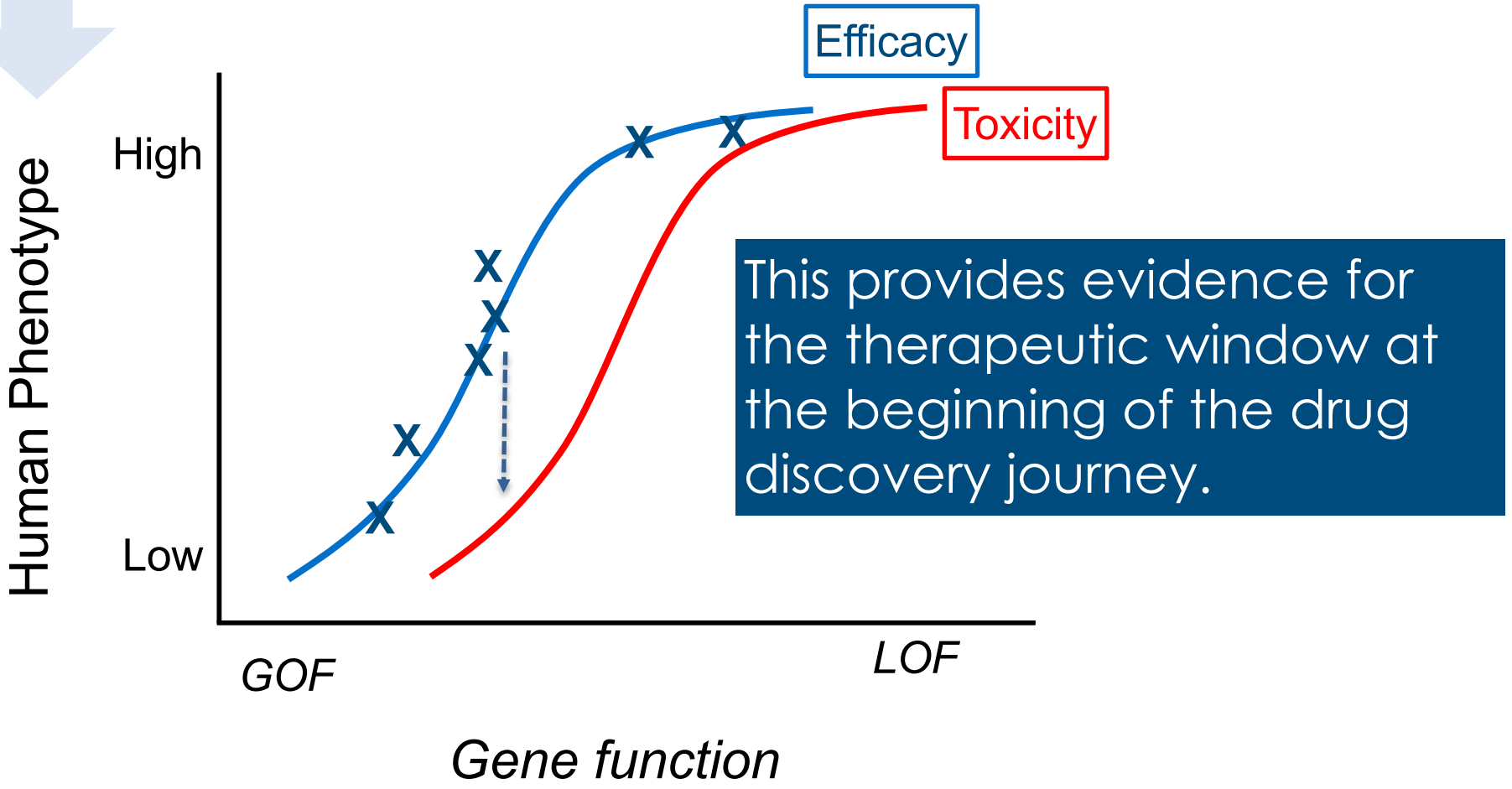


Need to release genetics into the wild

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

New target for drug screen!

Pick a human phenotype for drug efficacy



This provides evidence for the therapeutic window at the beginning of the drug discovery journey.

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

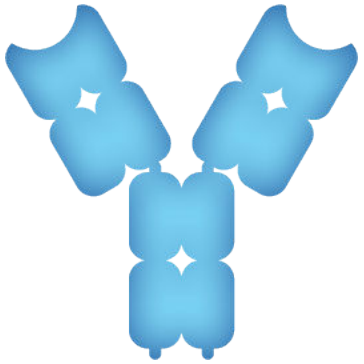
An example in immunology

Example of allelic series model: *TYK2*

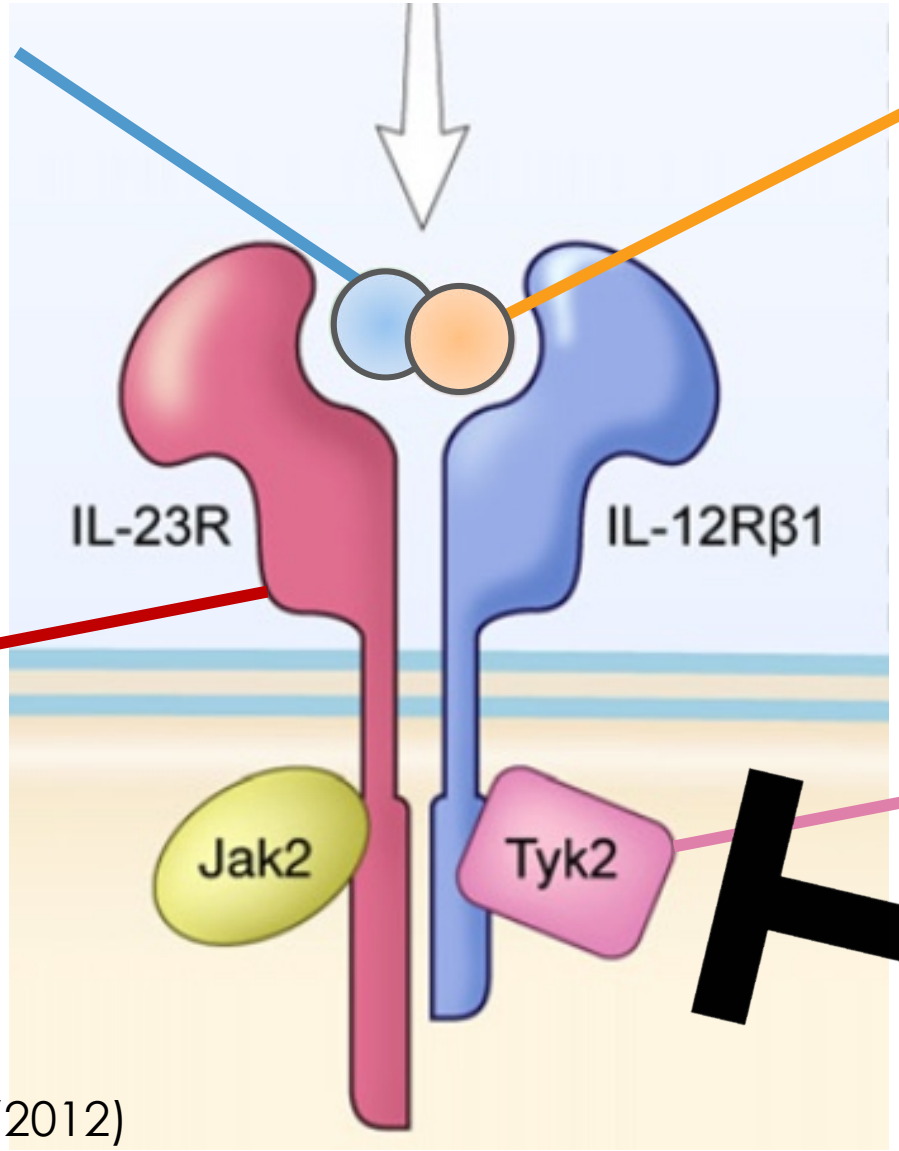
- TYK2 is an intracellular signaling molecule (next slide)
- Rare, complete human knockout is associated with immunodeficiency and risk of infection
- Common protein coding alleles reduce TYK2 function and protect from risk of autoimmune disease (*e.g.*, psoriasis, RA, SLE, IBD)
- Same common alleles do not increase risk of infection

IL23 signaling and psoriasis

IL23A (IL-23p19)



IL12B (IL-12p40)



IL23R

TYK2

?

O'Shea and Plenge *Immunity* (2012)

nature genetics

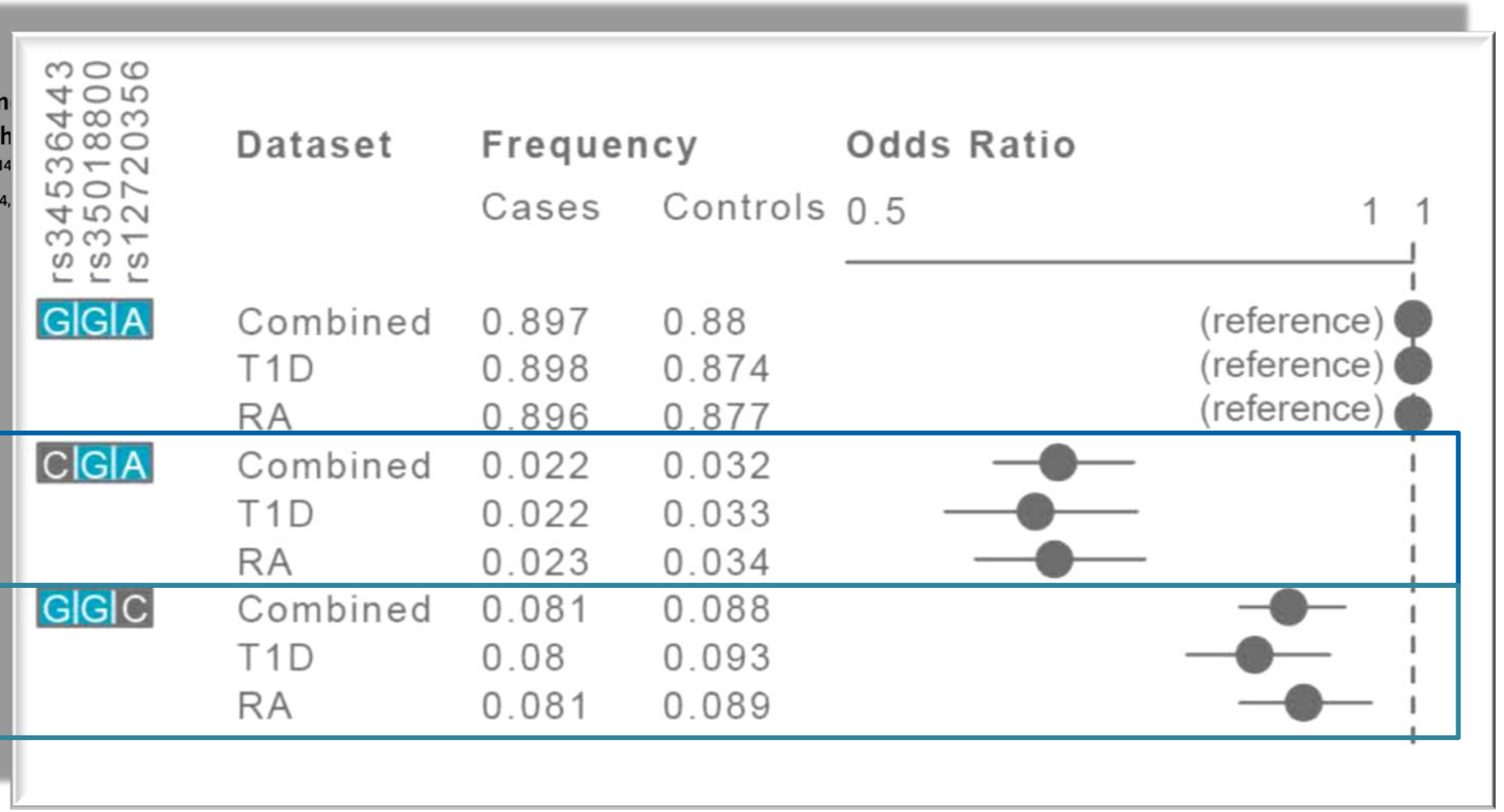
LETTERS

https://doi.org/10.1038/s41588-018-0216-7

TYK2 gene

Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes

Harm-Jan Westra[1,2,3,4,5,20], Marta Martínez-Bon
Yang Luo[1,2,3,4], Nikola Teslovich[1,2,3,4], Jane Worth
Lars Klareskog[13], Solbritt Rantapaa-Dahlqvist[14]
John A. Todd[17], Steve Eyre[9,10], Peter A. Nigrovic[4,
Soumya Raychaudhuri[1,2,3,4,9,19]*



P1104A

I684S

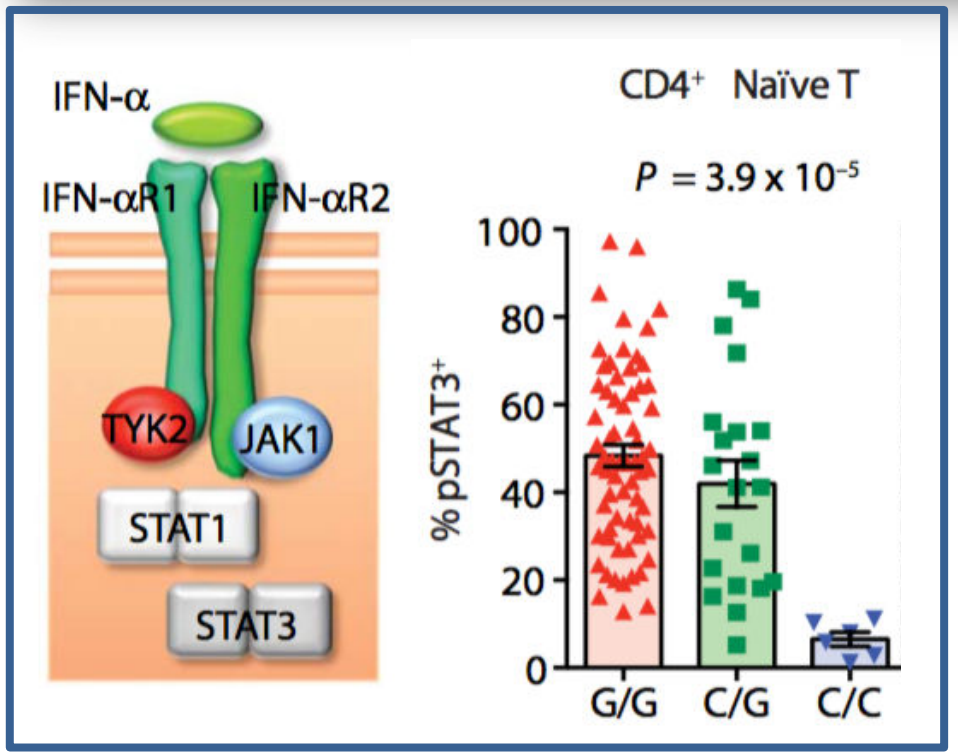
(low freq: A928V)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

AUTOIMMUNITY

Resolving *TYK2* locus genotype-to-phenotype differences in autoimmunity

Calliope A. Dendrou,[1] Adrian Cortes,[1,2] Lydia Shipman,[1] Hayley G. Evans,[1] Kathrine E. Attfield,[3] Luke Jostins,[2] Thomas Barber,[1] Gurman Kaur,[3] Subita Balaram Kuttikkatte,[3] Oliver A. Leach,[1] Christiane Desel,[1] Soren L. Faergeman,[1,4] Jane Cheeseman,[5] Matt J. Neville,[5,6] Stephen Sawcer,[7] Alastair Compston,[7] Adam R. Johnson,[8] Christine Everett,[8] John I. Bell,[9] Fredrik Karpe,[5,6] Mark Ultsch,[8] Charles Eigenbrot,[8] Gil McVean,[2] Lars Fugger[1,3,4]*



P1104A allele that protects from autoimmunity is associated with ~80% loss-of-function (LoF) in C/C homozygous state

Same LoF allele has no obvious increased risk of infection

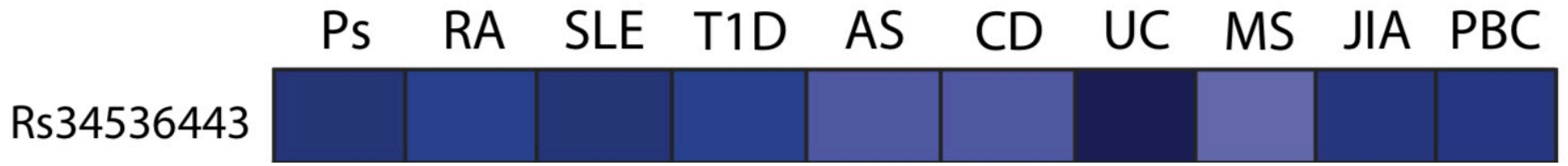
		Rs34536443 genotype			
		G/G	*G/C*	*C/C*	Total
normal	In U.K. Biobank	105,794 (90.63%)	10,689 (9.16%)	249 (0.21%)	116,732 (100%)
Infections	Mycobacterial	20 (86.96%)	3 (13.04%)	0 (0.00%)	23
	Specific bacterial (For example, *S. aureus*)	54 (90.00%)	5 (8.33%)	1 (1.67%)	60
	Specific viral (e.g. HSV, VZV, viral encephalitis)	93 (96.88%)	3 (3.12%)	0 (0.00%)	96
	Mucocutaneous candidiasis	46 (88.46%)	6 (11.54%)	0 (0.00%)	52
	Total	213 (92.21%)	17 (7.36%)	1 (0.43%)	231

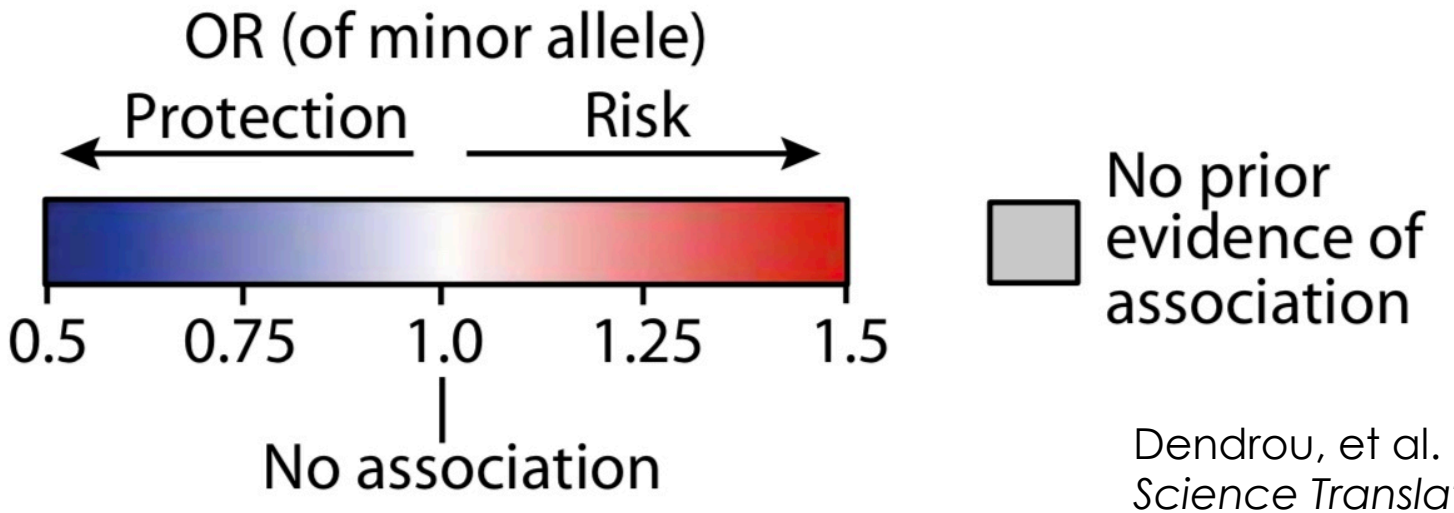
~80% LoF is *not* associated with increased infection

Dendrou, et al. (2016)
Science Translational Medicine

P1104A protects from multiple autoimmune diseases

P1104A



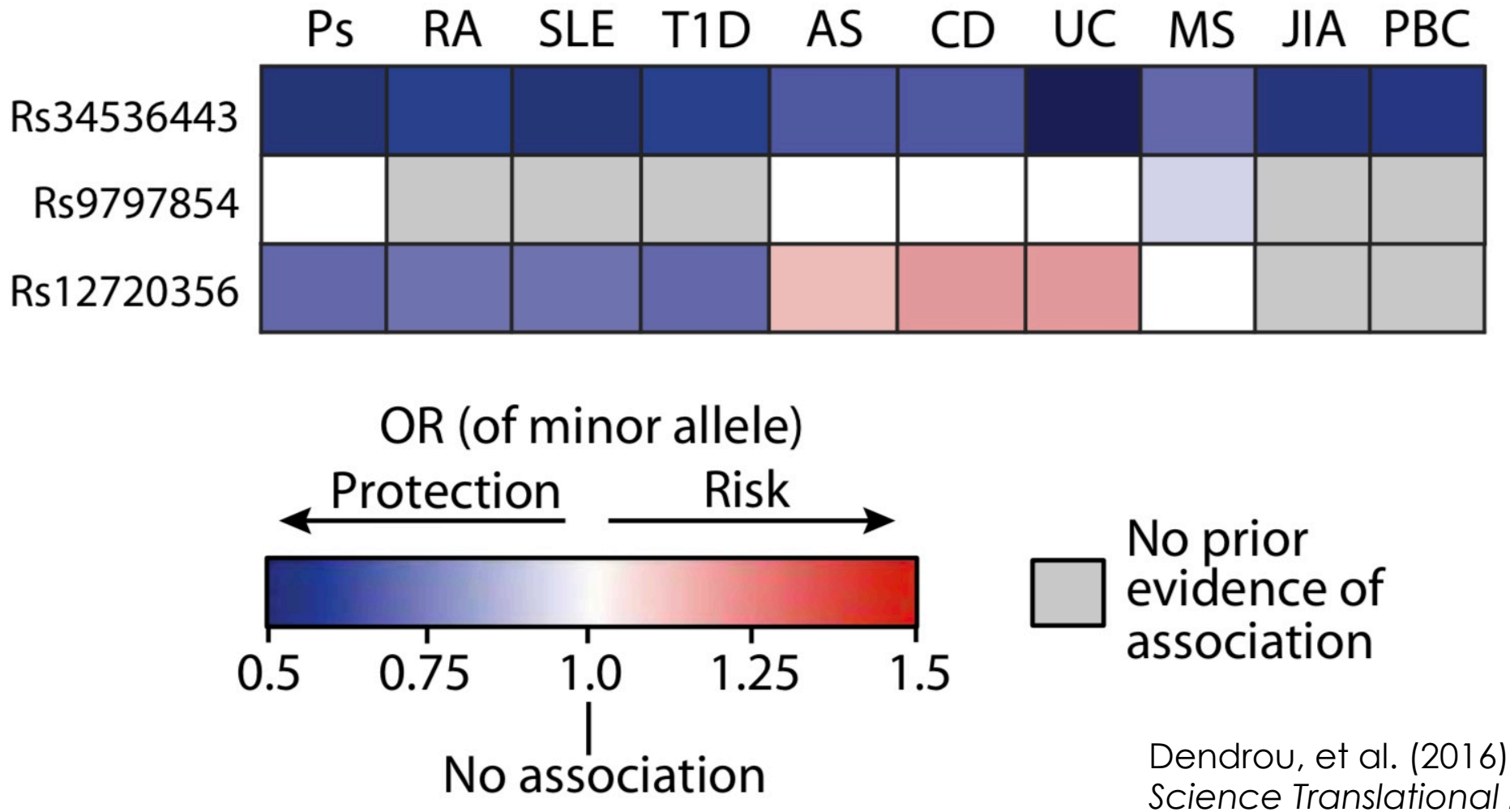


Dendrou, et al. (2016)
Science Translational Medicine

But *I684S* variant shows a more complicated pattern!

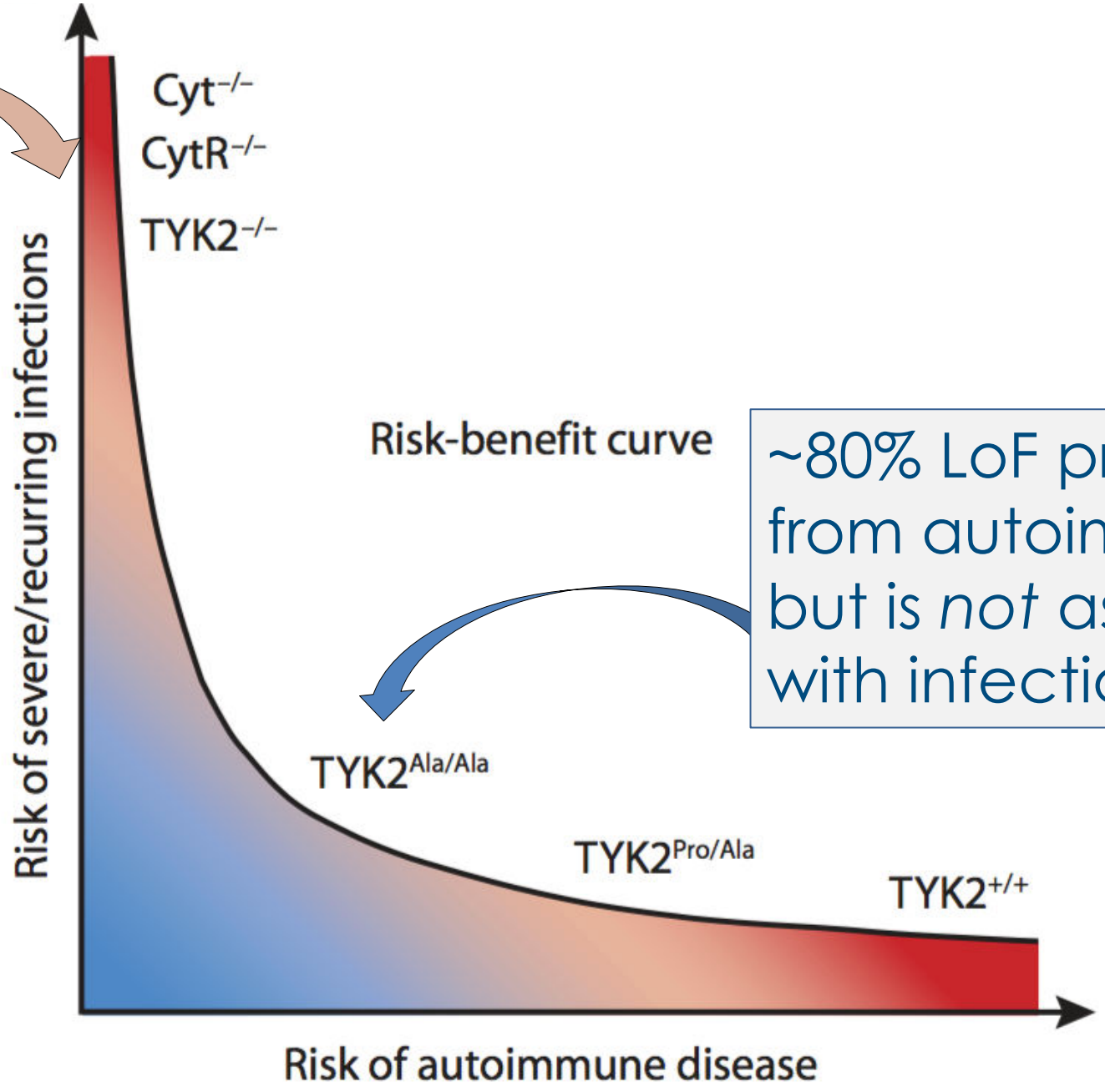
P1104A

I684S

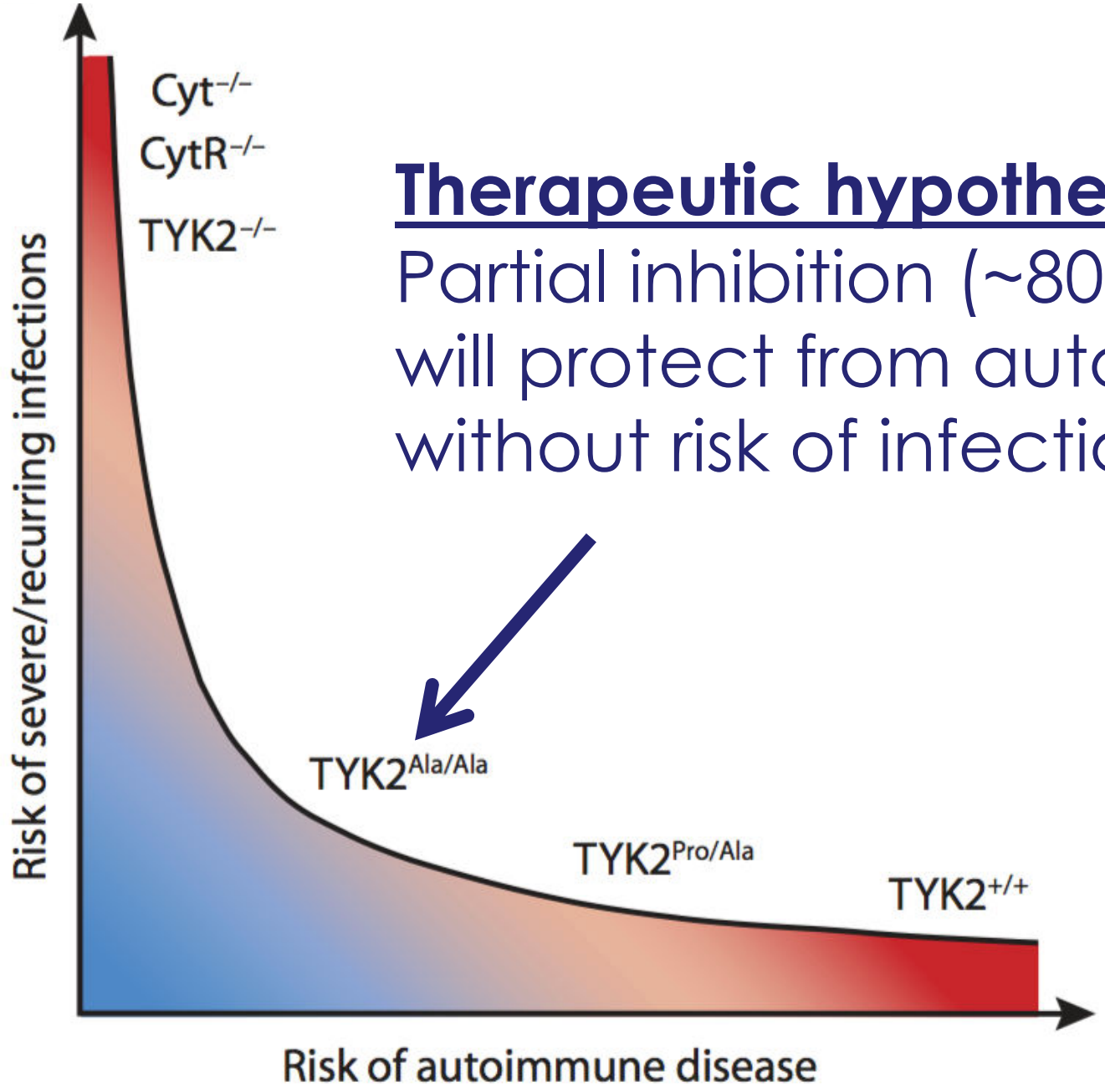


Dendrou, et al. (2016)
Science Translational Medicine

Complete TYK2 knockout increases risk of infection

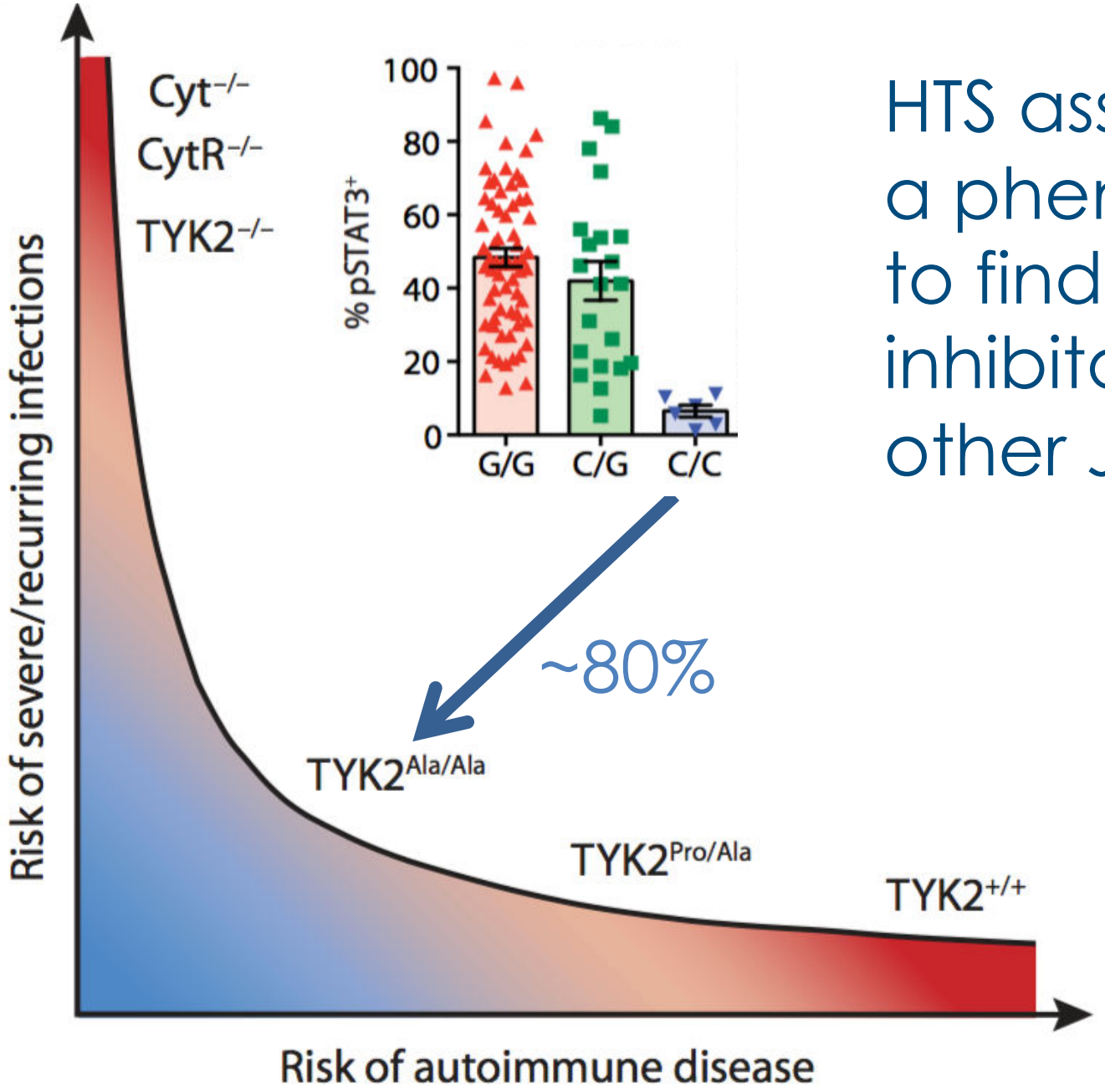


~80% LoF protects from autoimmunity but is *not* associated with infection

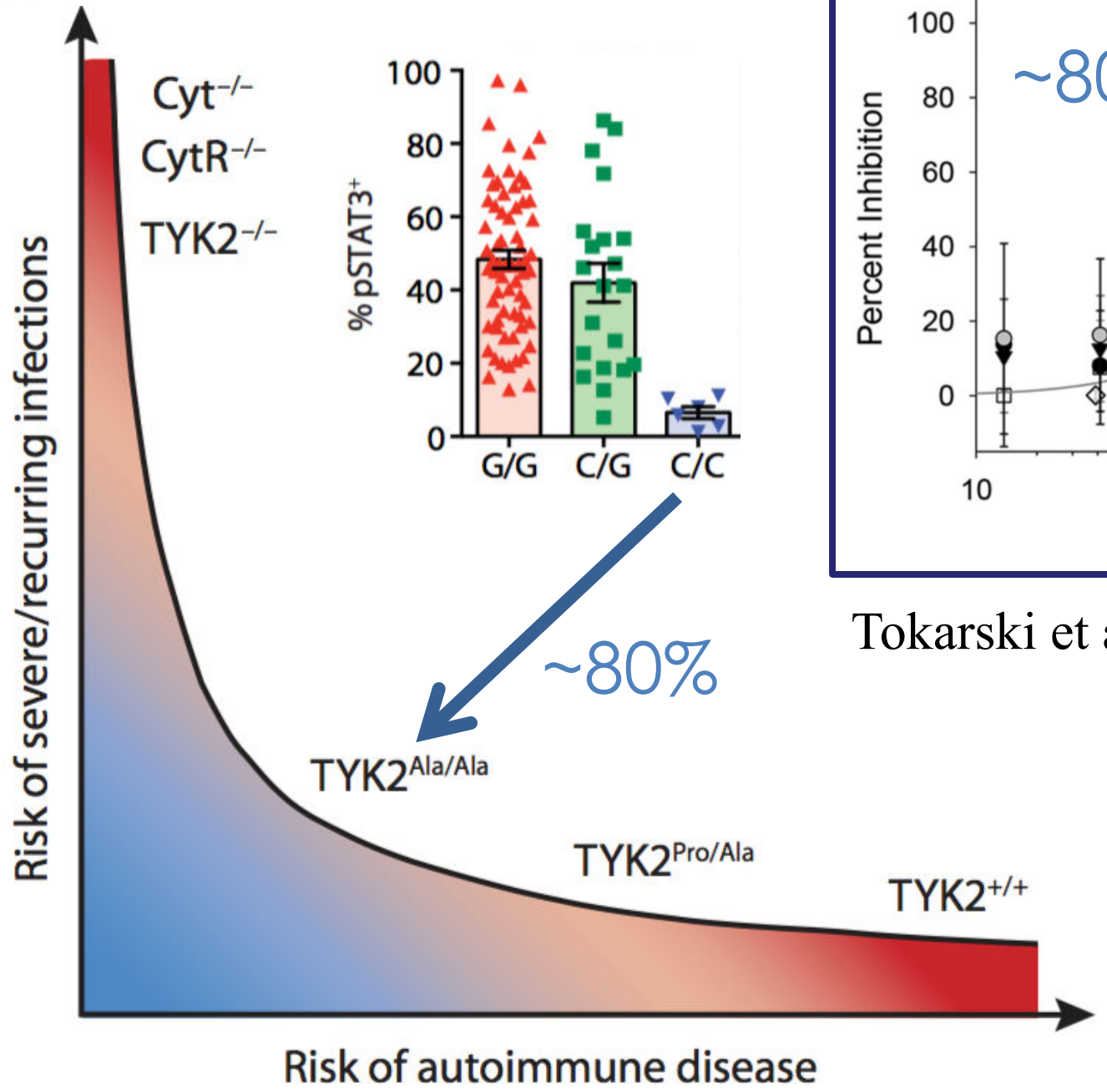


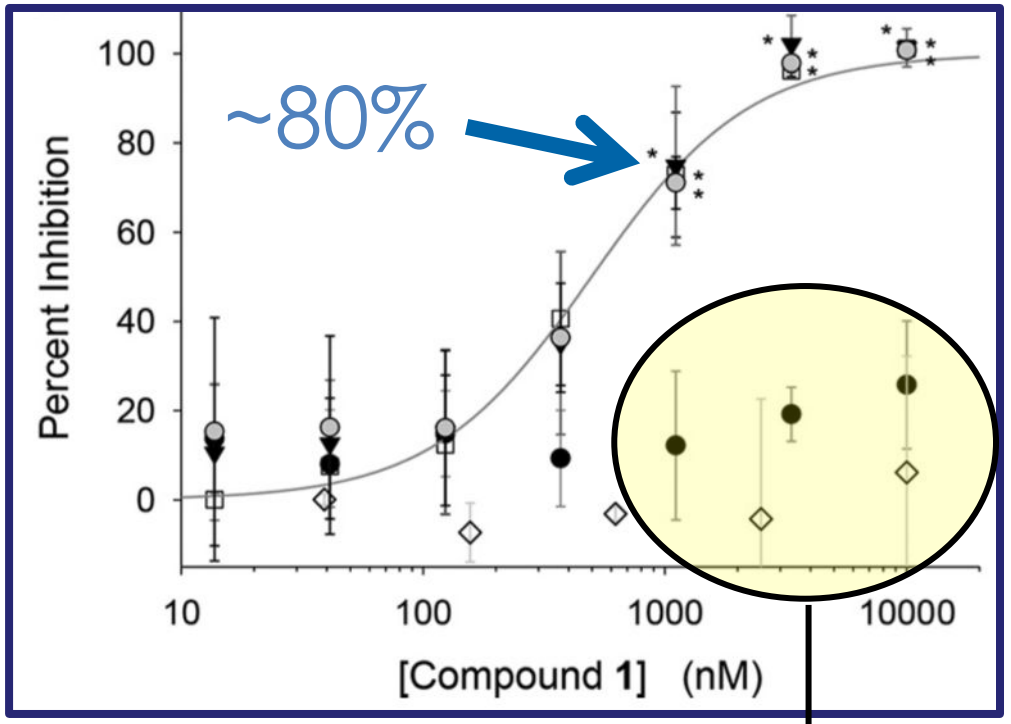
<u>Therapeutic hypothesis</u>:
Partial inhibition (~80%) of TYK2 will protect from autoimmunity without risk of infection

But matching *modality with mechanism* is challenging, especially selectivity over JAKs



HTS assay was used in a phenotypic screen to find selective inhibitors of TYK2 over other JAKs





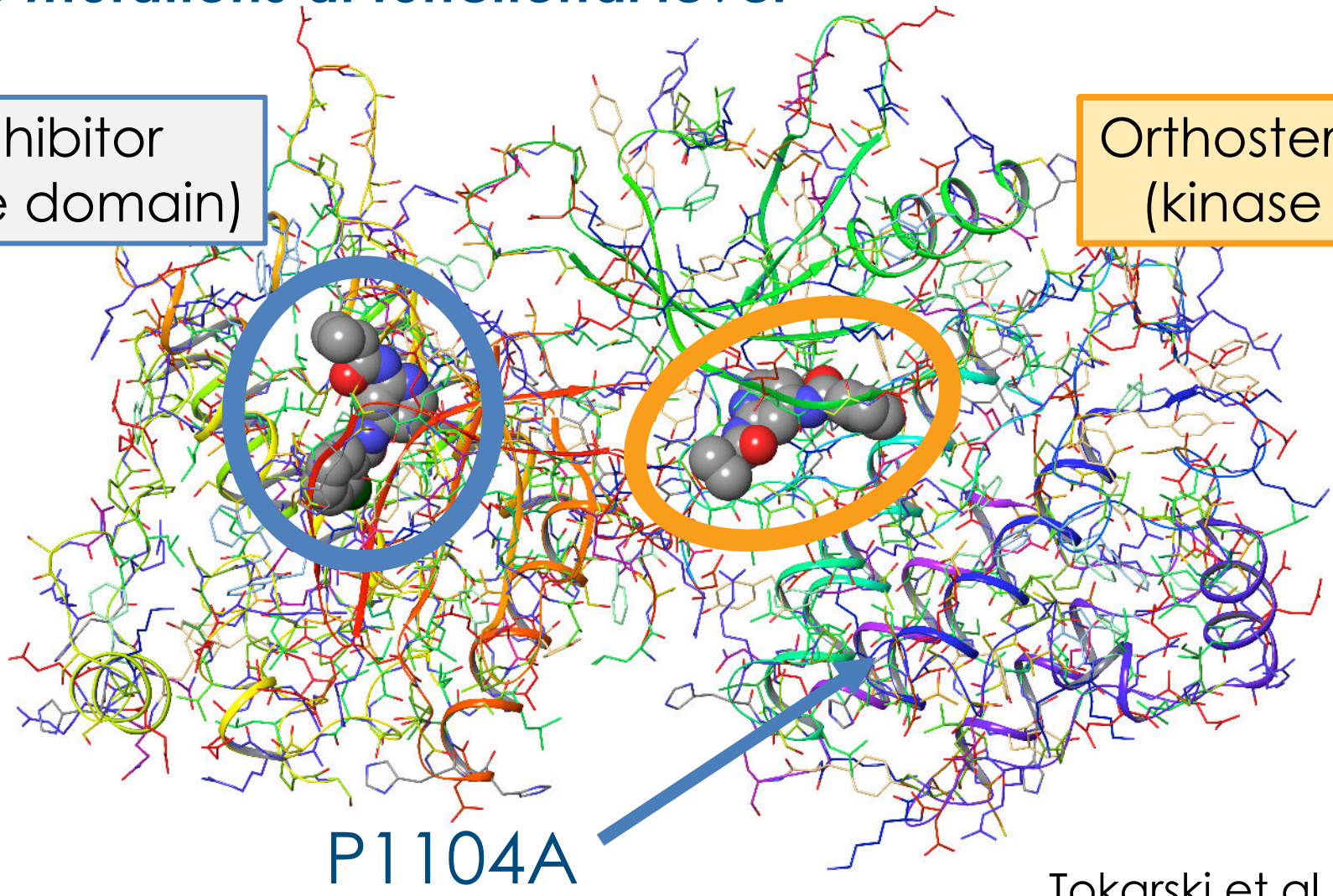
Tokarski et al (2015) *JBC*

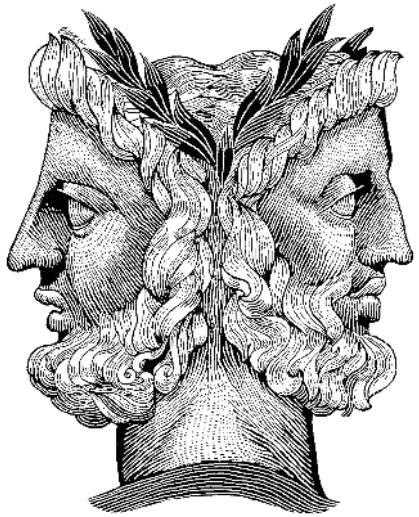
Retains selectivity over JAKs

Matching modality and mechanism: *"pseudokinase stabilizers" recapitulate human genetic mutations at functional level*

Allosteric inhibitor (pseudokinase domain)

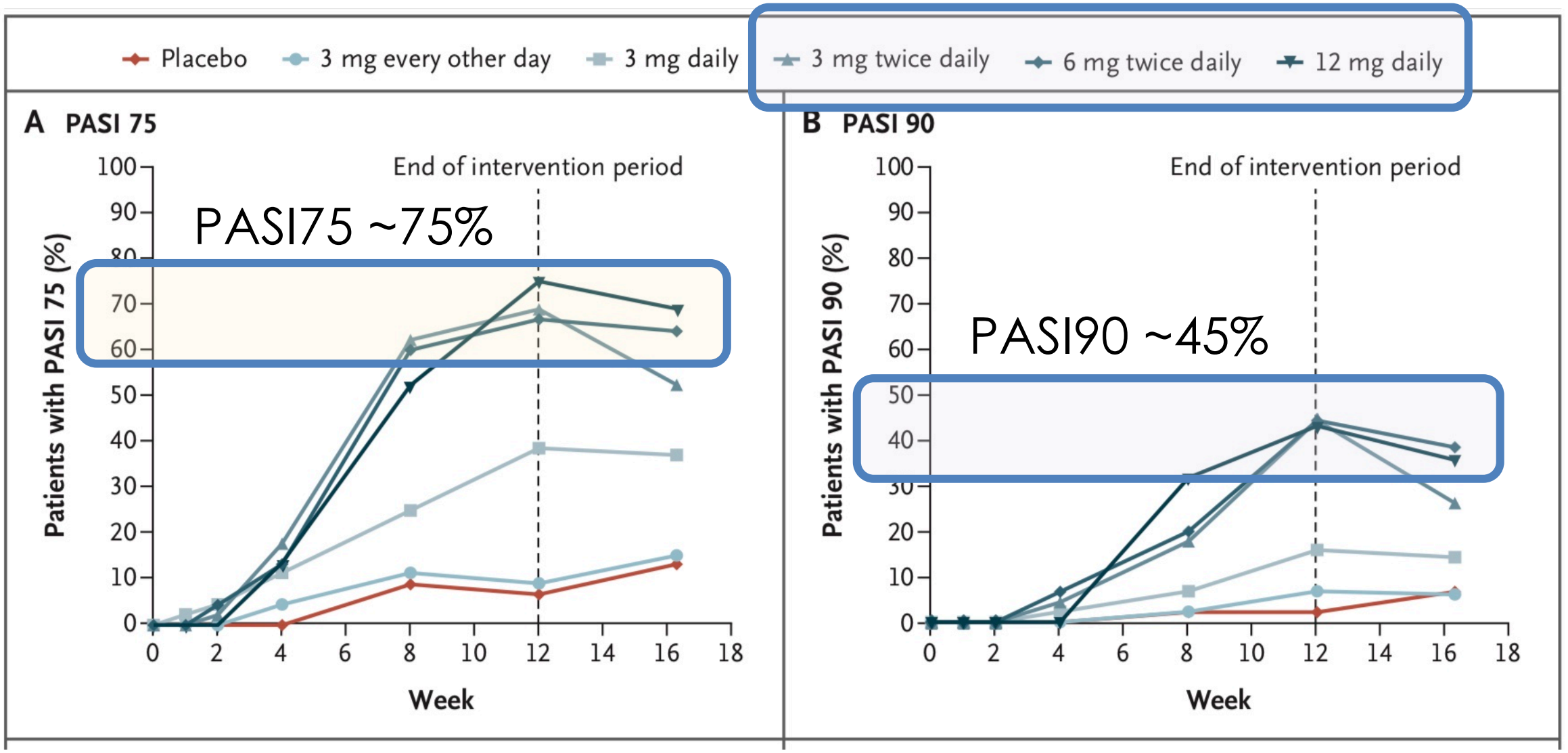
Orthosteric inhibitor (kinase domain)





Tokarski et al *JBC* (2015)
Lupardus et al *PNAS* (2014)

50-80% TYK2 inhibition safe and effective in Phase 2 (psoriasis)

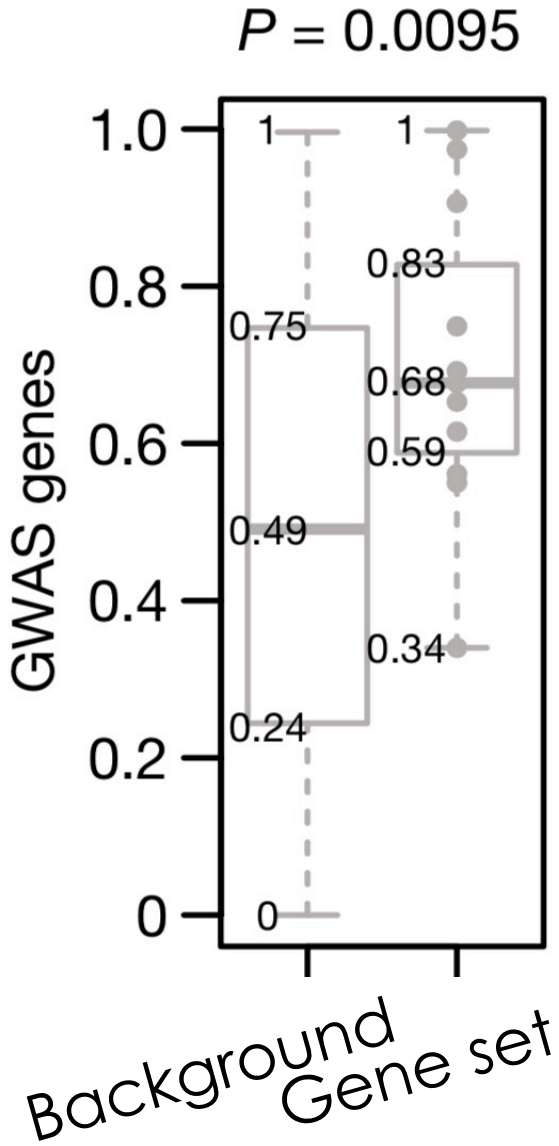


Papp et al (2018) *NEJM*

What fraction of disease-associated genes will fit this model?

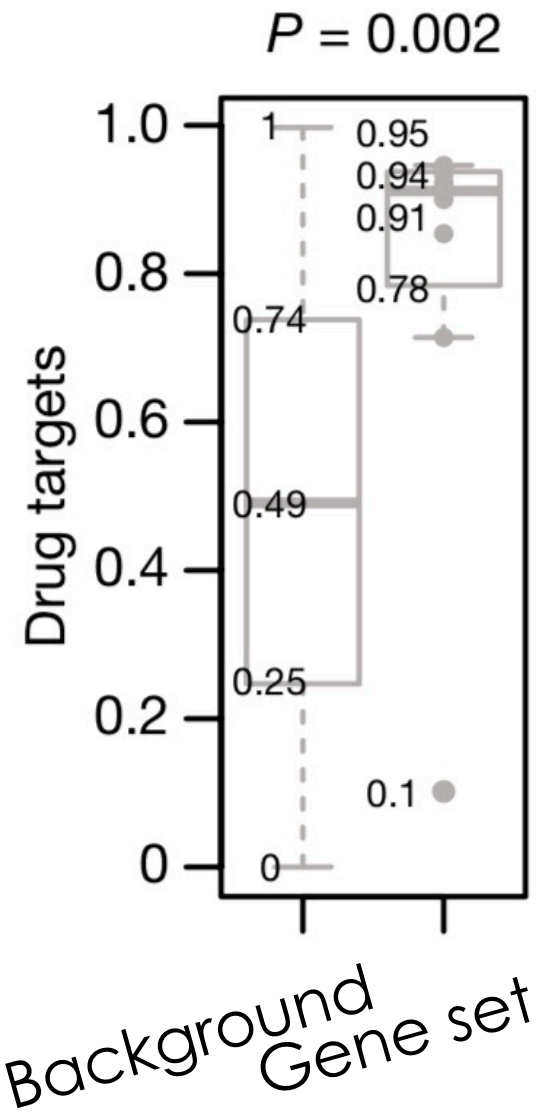
Evidence to support an "allelic series" model

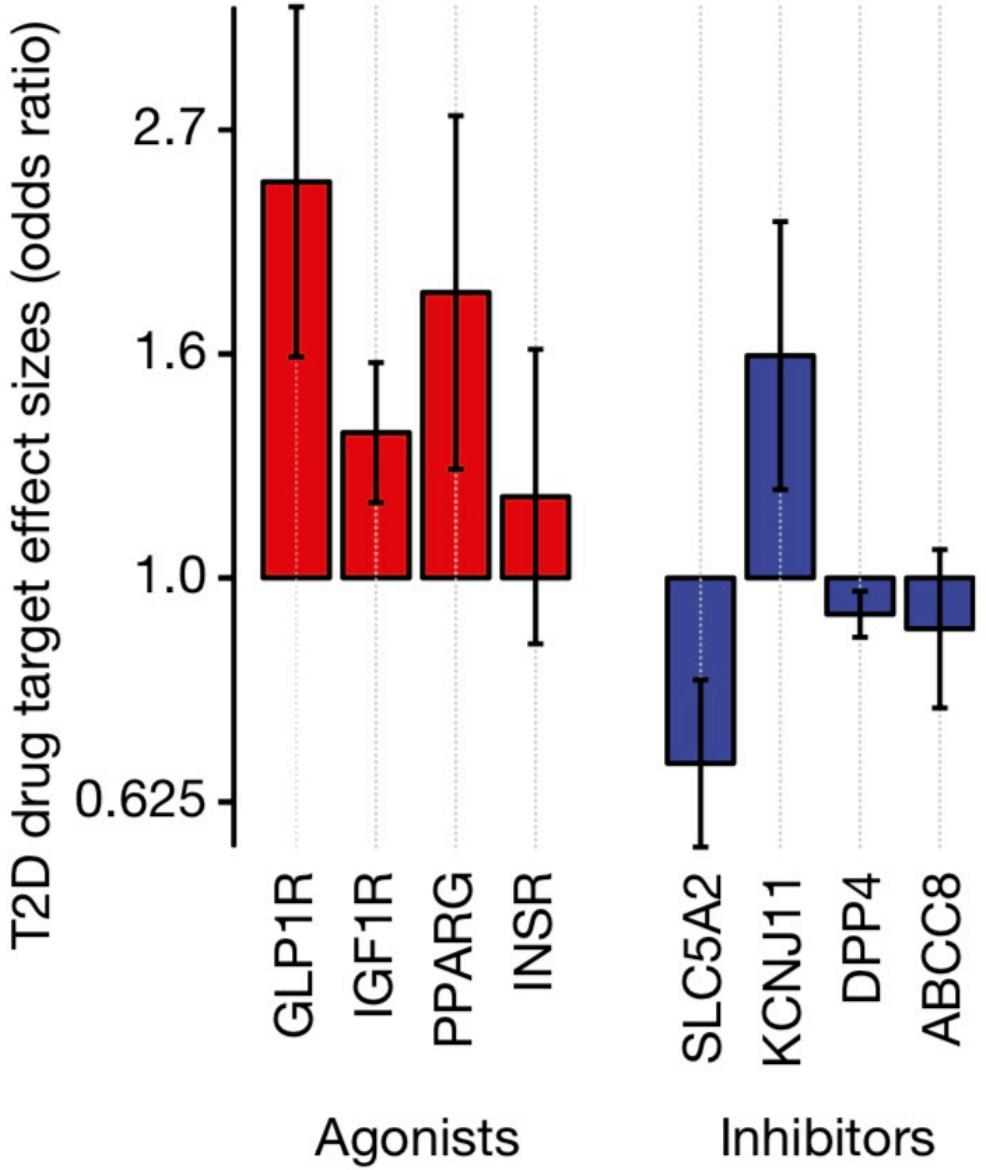
- Most genes implicated in Mendelian diseases harbor multiple risk alleles
  - *CFTR* harbors >2,000 pathogenic mutations that cause cystic fibrosis
- A multiple sclerosis (MS) GWAS found ~20% of loci harbor independent risk alleles[1]
- A GWAS in rheumatoid arthritis (RA) found ~7% of implicated genes also harbor rare mutations that cause primary immune deficiency[2]
- A recent type 2 diabetes (T2D) sequencing study found enrichment for the burden of rare variants in gene sets that did not reach genome-wide significance (see figure)[3]



1. IMSGC Science (2019)
2. Okada *et al* Nature (2014)
3. Flannick *et al* Nature (2019)

For T2D, “allelic series” model predicts approved drugs

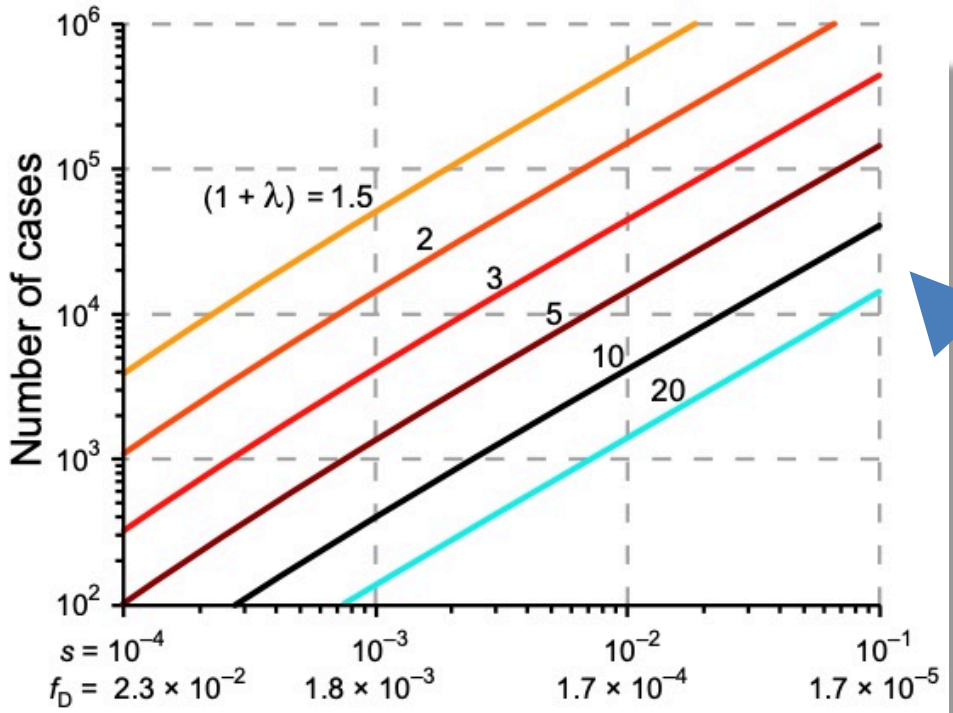




And Shamil assures me that the model is true!

Searching for missing heritability: Designing rare variant association studies

Or Zuk[a,b,1], Stephen F. Schaffner[a], Kaitlin Samocha[a,c,d], Ron Do[a,e], Eliana Hechter[a], Sekar Kathiresan[a,e,f,g], Mark J. Daly[a,c], Benjamin M. Neale[a,c], Shamil R. Sunyaev[a,h], and Eric S. Lander[a,i,j,2]

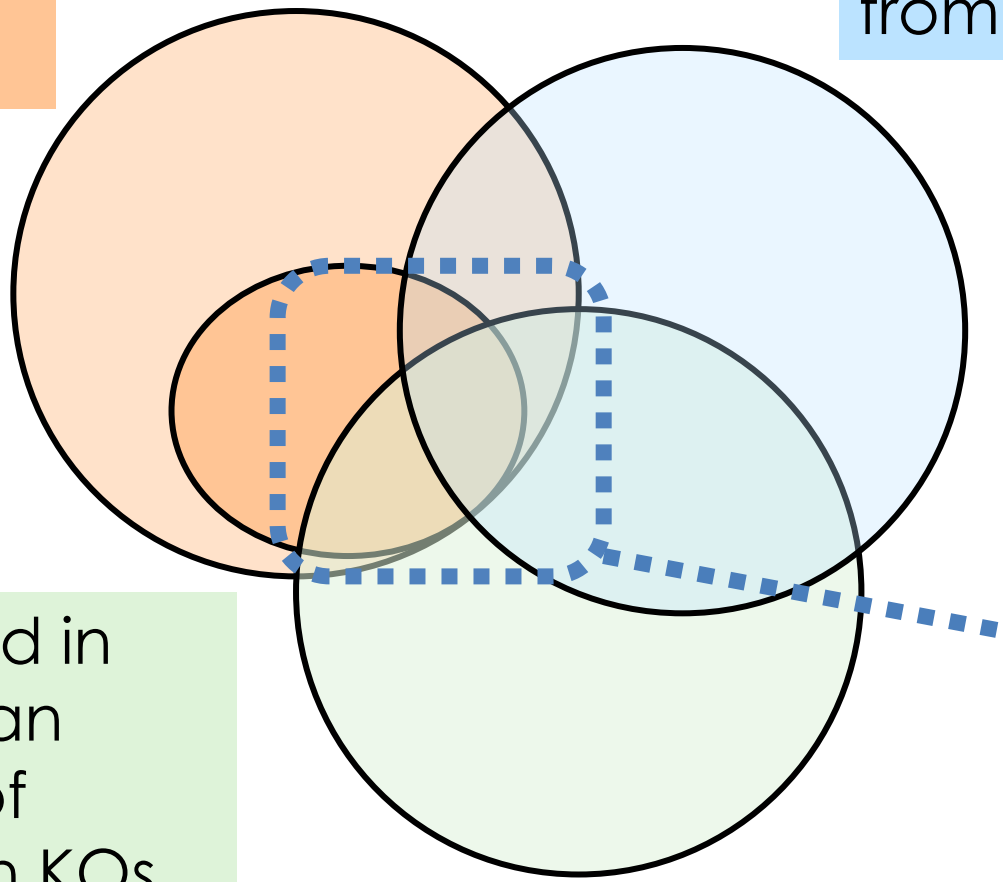


Genetic studies have revealed thousands of loci predisposing to hundreds of human diseases and traits, revealing important biological pathways and defining novel therapeutic hypotheses. However, the genes discovered to date typically explain less than half of the apparent heritability. Because efforts have largely focused on common genetic variants, one hypothesis is that much of the missing heritability is due to rare genetic variants. Studies of common variants are typically referred to as genomewide association studies, whereas studies of rare variants are often simply called sequencing studies. Because they are actually closely related, we use the terms common variant association study (CVAS) and rare variant association study (RVAS). In this paper, we outline the similarities and differences between RVAS and CVAS and describe a conceptual framework for the design of RVAS. We apply the framework to address key questions about the sample sizes needed to detect association, the relative merits of testing disruptive alleles vs. missense alleles, frequency thresholds for filtering alleles, the value of predictors of the functional impact of missense alleles, the potential utility of isolated populations, the value of gene-set analysis, and the utility of de novo mutations. The optimal design depends critically on the selection coefficient against deleterious alleles and thus varies across genes. The analysis shows that common variant and rare variant studies require similarly large sample collections. In particular, a well-powered RVAS should involve discovery sets with at least 25,000 cases, together with a substantial replication set.

Should be possible to nominate genes for functional studies

Predicted GWAS causal genes with multiple alleles (~20% of genes)

Genes with evidence of rare-variant burden signal from exome sequencing



discovery engine

Genes implicated in related Mendelian diseases (~10% of genes) or human KOs

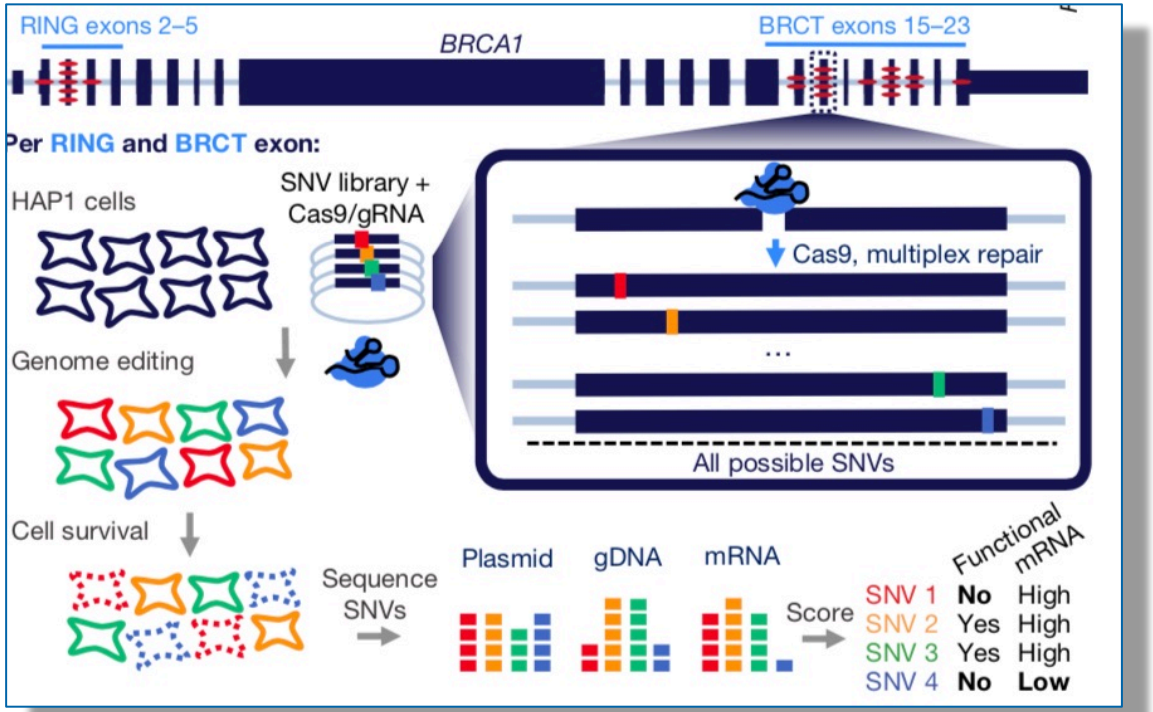
Prioritize these genes for functional studies of all observed protein-coding mutations in assays system relevant to disease

High-throughput functional interrogation is a bottleneck

High-throughput assays to assess function is a bottleneck

Accurate classification of *BRCA1* variants with saturation genome editing

Gregory M. Findlay[1], Riza M. Daza[1], Beth Martin[1], Melissa D. Zhang[1], Anh P. Leith[1], Molly Gasperini[1], Joseph D. Janizek[1], Xingfan Huang[1], Lea M. Starita[1,2]* & Jay Shendure[1,2,3]*

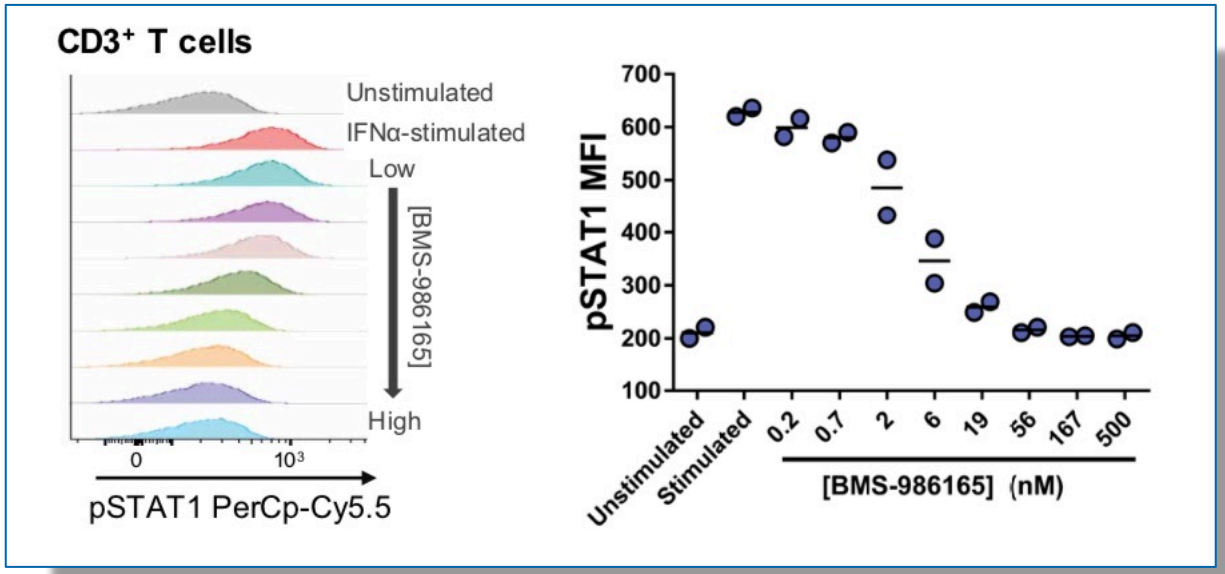


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

AUTOIMMUNITY

Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudokinase domain

James R. Burke[1]*, Lihong Cheng[1], Kathleen M. Gillooly[1], Joann Strnad[1], Adriana Zupa-Fernandez[1], Ian M. Catlett[2], Yifan Zhang[1], Elizabeth M. Heimrich[1], Kim W. McIntyre[1], Mark D. Cunningham[3], Julie A. Carman[3], Xiadi Zhou[1], Dana Banas[3], Charu Chaudhry[4], Sha Li[4], Celia D'Arienzo[5], Anjaneya Chimalakonda[5], XiaoXia Yang[1], Jenny H. Xie[1], Jian Pang[1], Qihong Zhao[1], Shawn M. Rose[2], Jinwen Huang[1], Ryan M. Moslin[6], Stephen T. Wrobleski[6], David S. Weinstein[6], Luisa M. Salter-Cid[1]



Need to release genetics into the wild!

How to extend trait-associations for functional alleles…**PheWAS**

Phenome-wide association studies (PheWAS)

Disease-Agnostic cohort

EHRs, Claims, Questionnaires, etc.

Clinical data

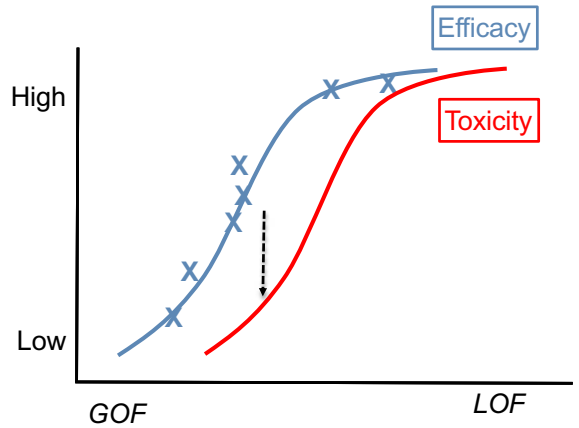
Genetic data

GWAS, exome sequencing, etc.

LoF SNP

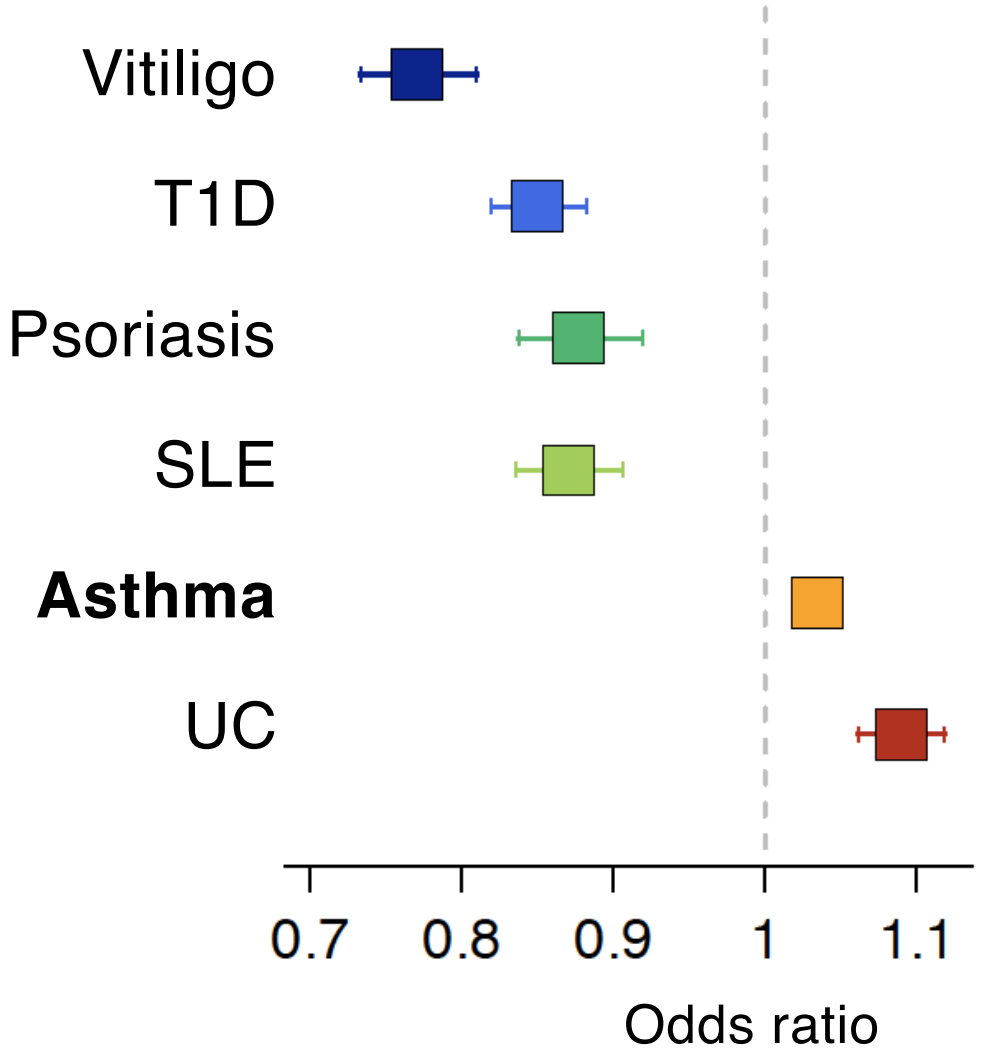
Test association of selected SNP with clinical endpoints

- **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



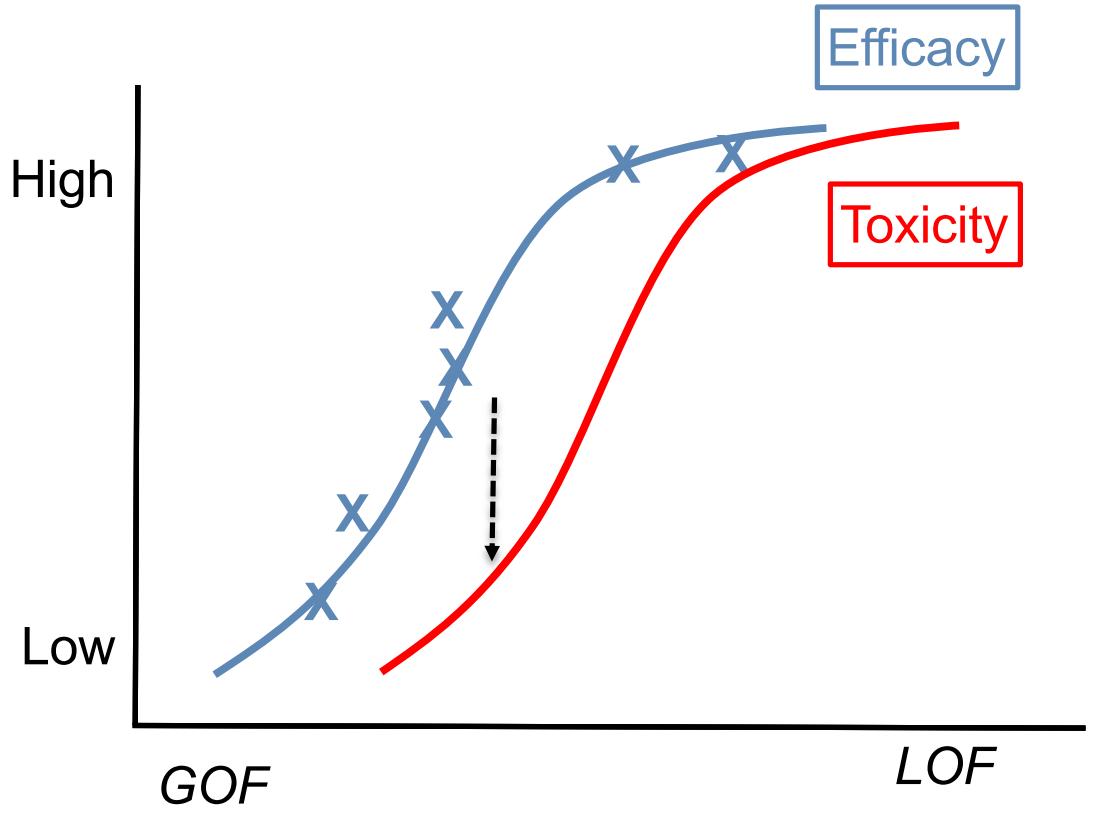
PheWAS example: *IFIH1*, autoimmunity, asthma

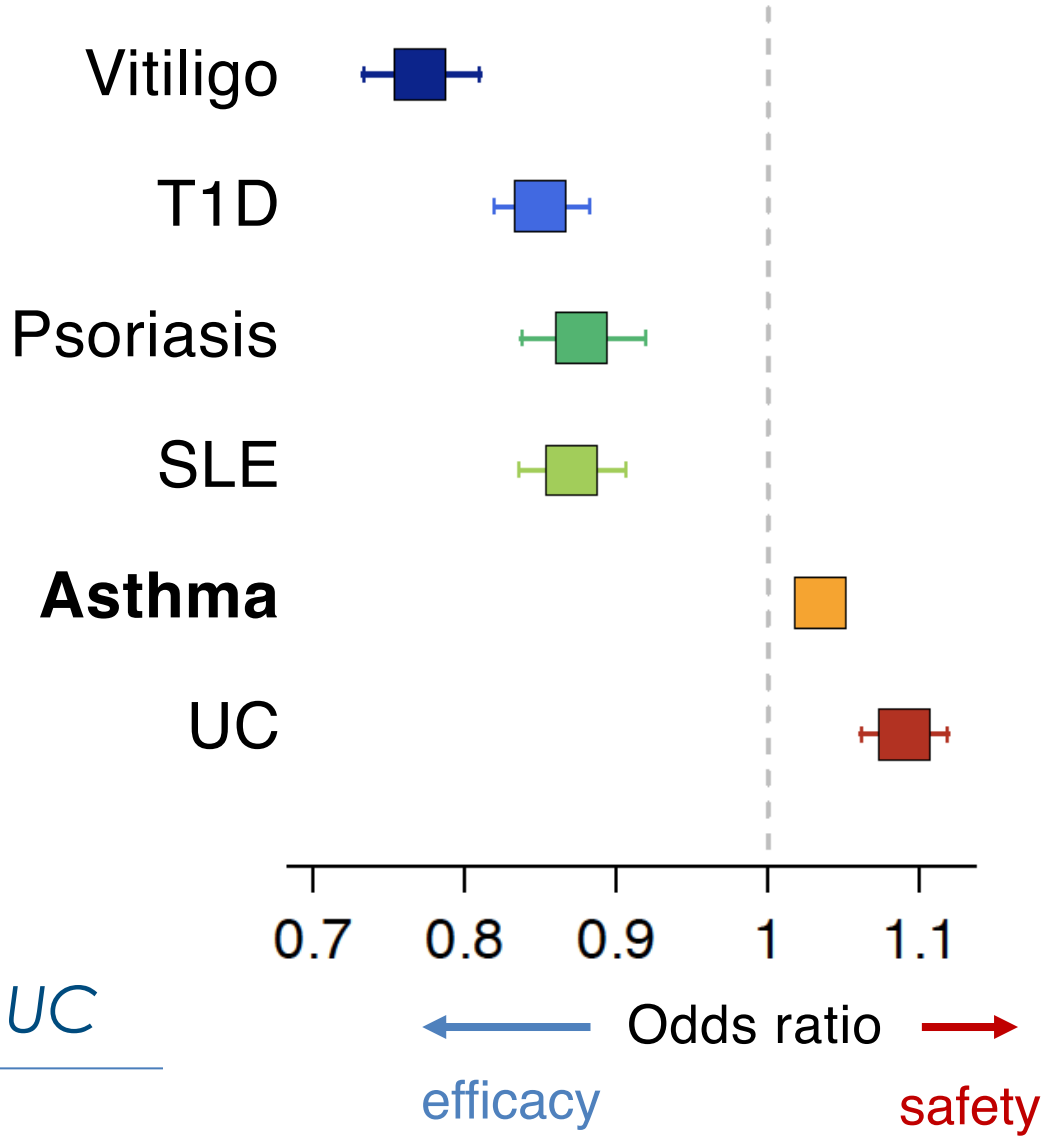
- PheWAS in ~800,000 individuals from four population cohorts
- Tested 25 SNPs for association with 1,683 clinical endpoints
- 10 novel associations discovered
- Example: *IFIH1* LOF allele protects from autoimmunity (known) but increases risk of asthma (novel finding)
- Therapeutic hypothesis: inhibiting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



Diogo *et al* (2018) *Nature Communications*

Predicted impact of therapeutic inhibition of IFIH1

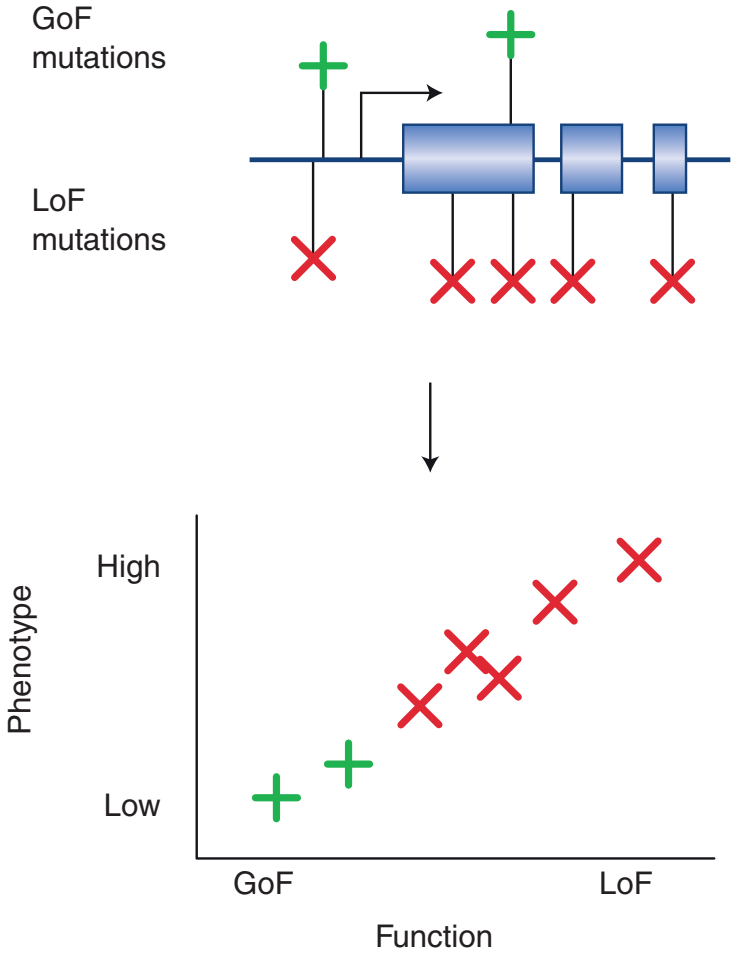




Beneficial effect for some autoimmune diseases, but increase risk of asthma and UC

Beyond an allelic series model

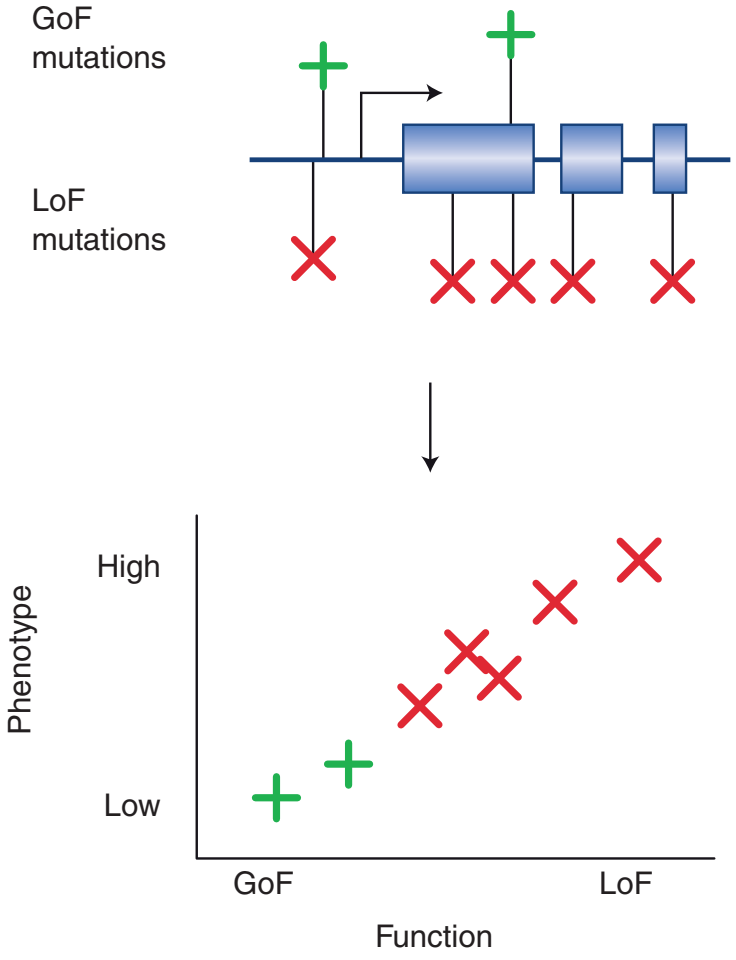
Allelic series model



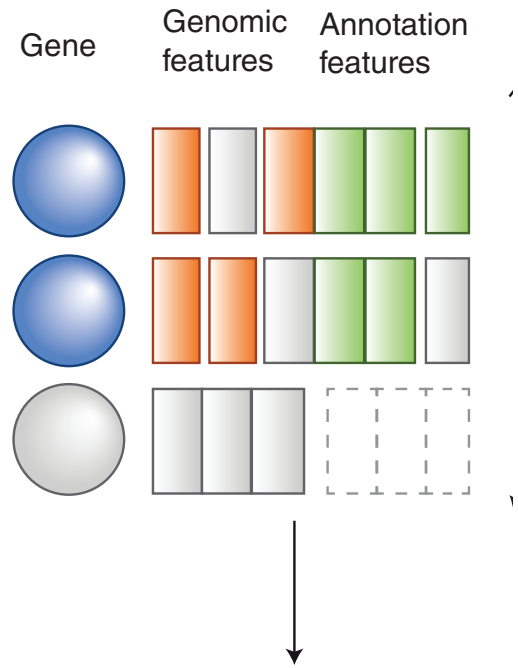
Plenge *Nature Genetics* (2019)

Gene-centric approaches

Allelic series model



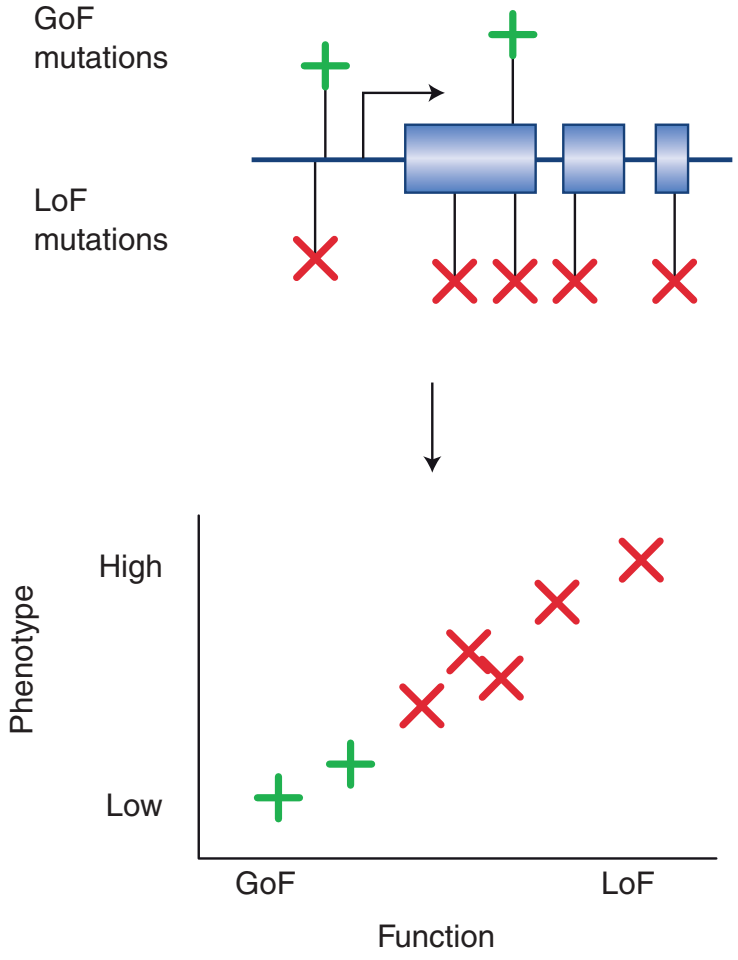
Genomic features model



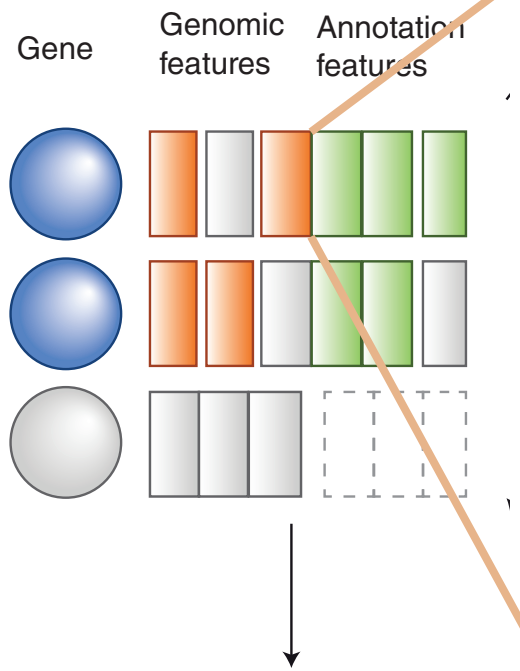
Plenge *Nature Genetics* (2019)

Gene-centric approaches

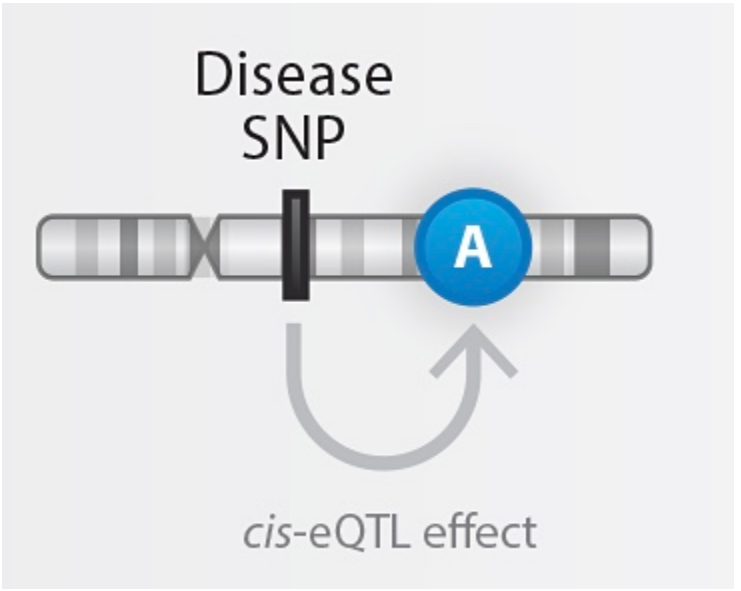
Allelic series model

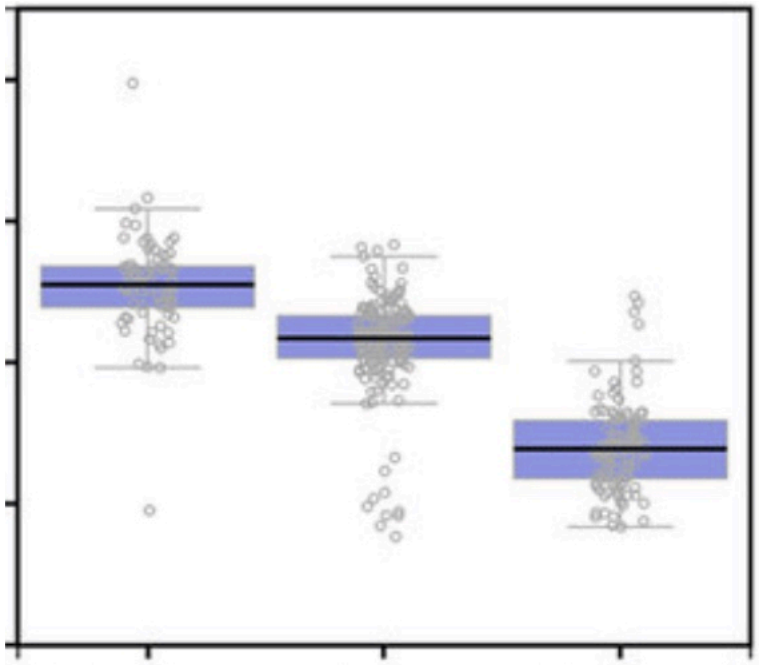


Genomic features model



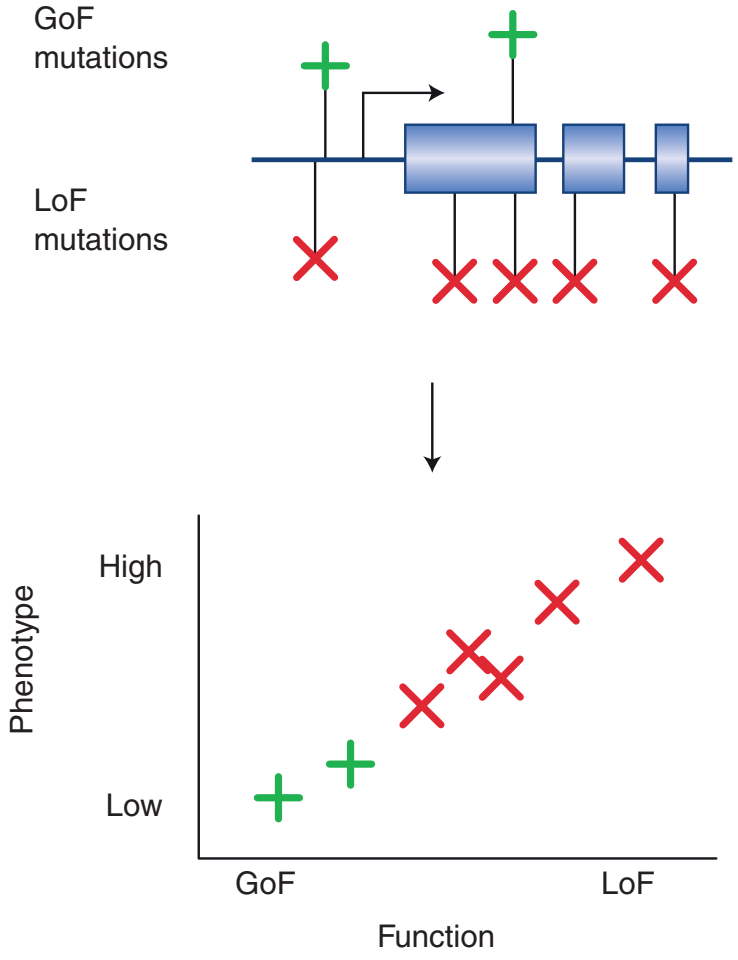
Prioritize targets based on trait-associated variants and genomic features



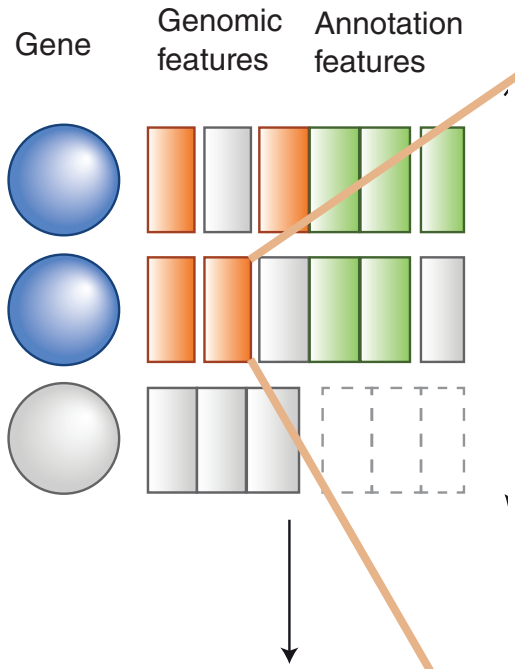


Gene-centric approaches

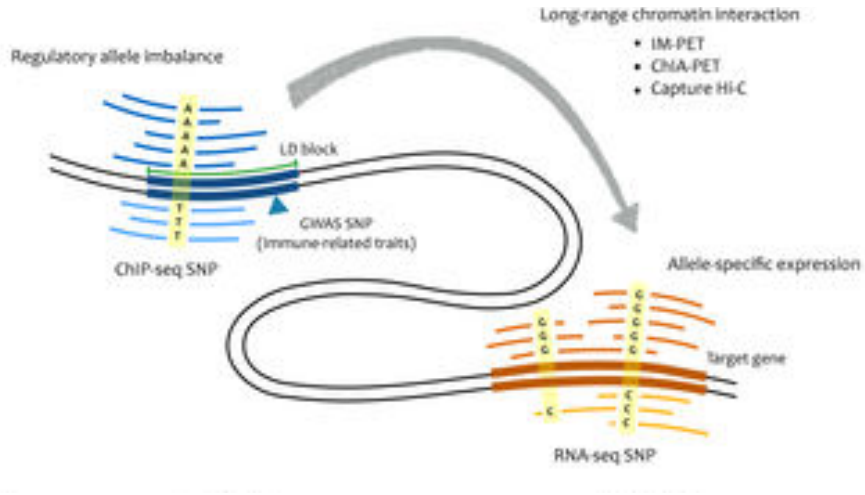
Allelic series model

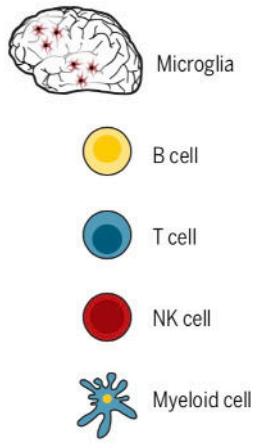


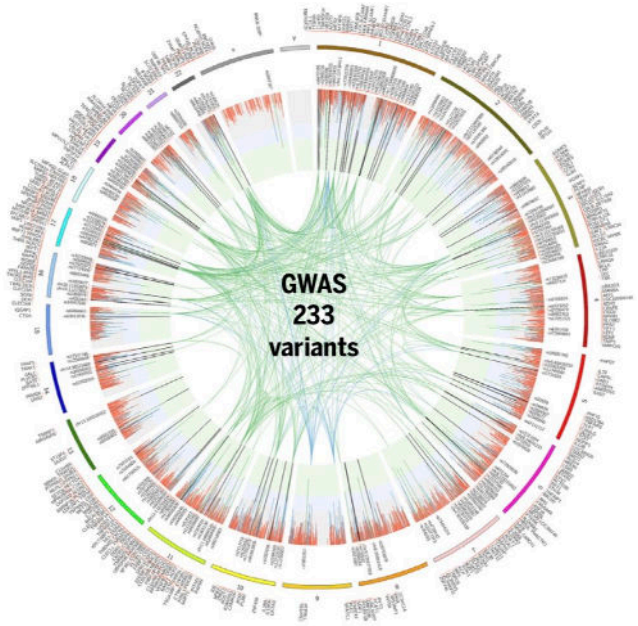
Genomic features model



Prioritize targets based on trait-associated variants and genomic features



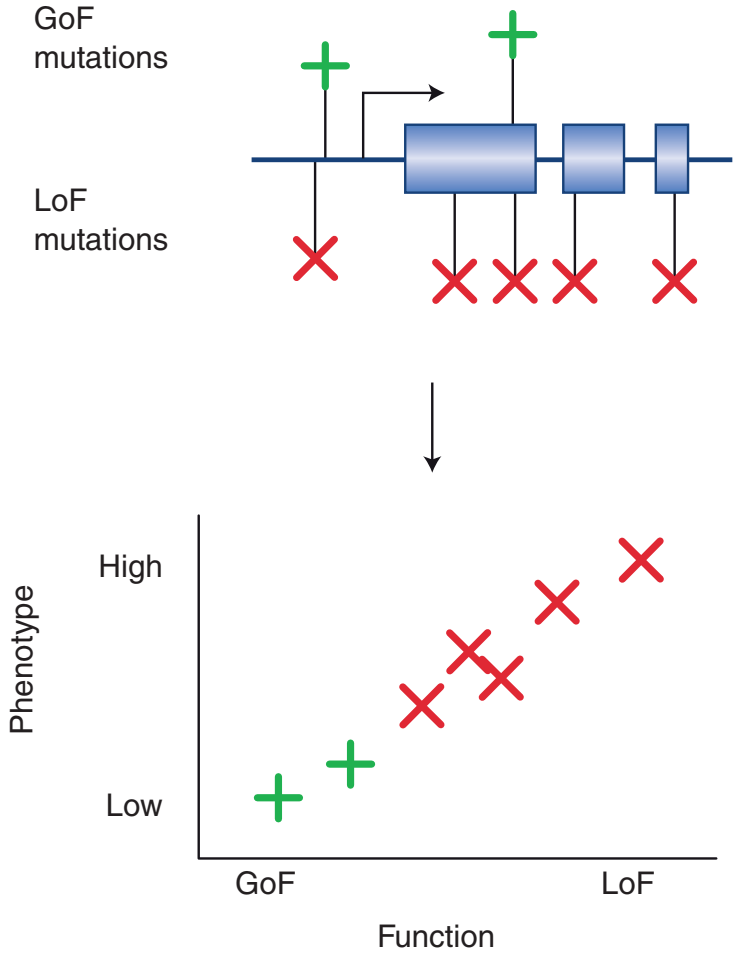




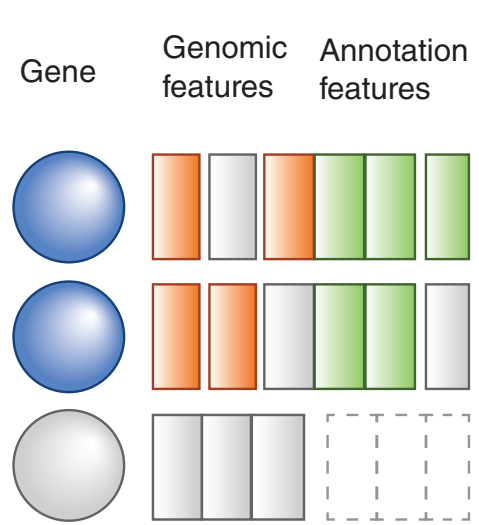
Gene-centric approaches

Pathway-centric approach

Allelic series model

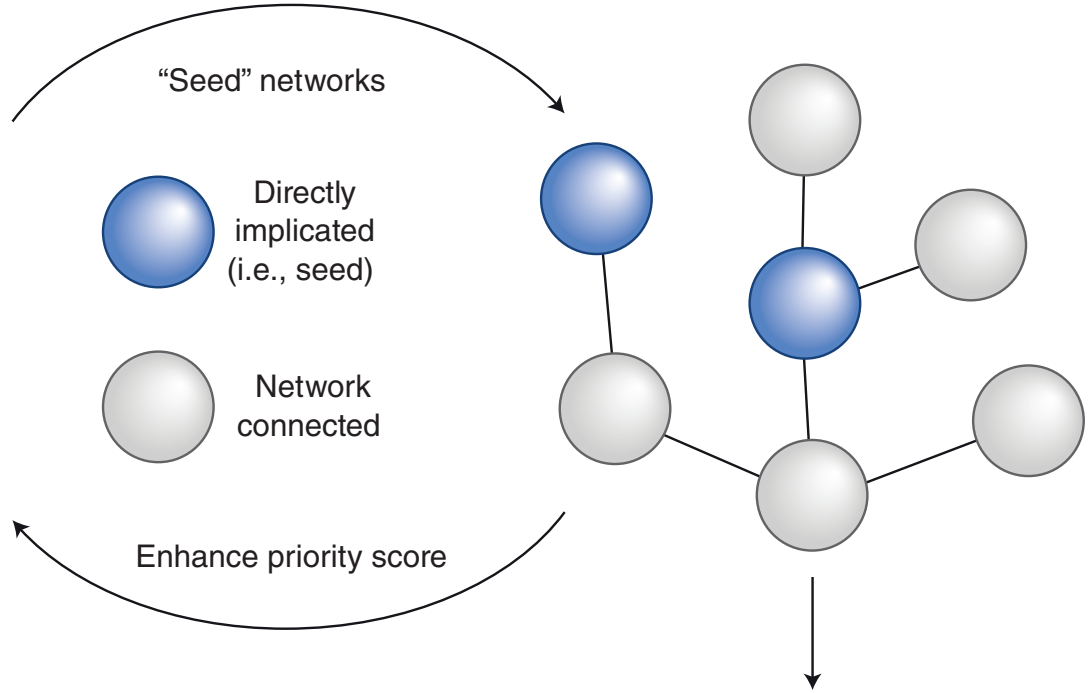


Genomic features model



Prioritize targets based on trait-associated variants and genomic features

Prot-prot interaction model

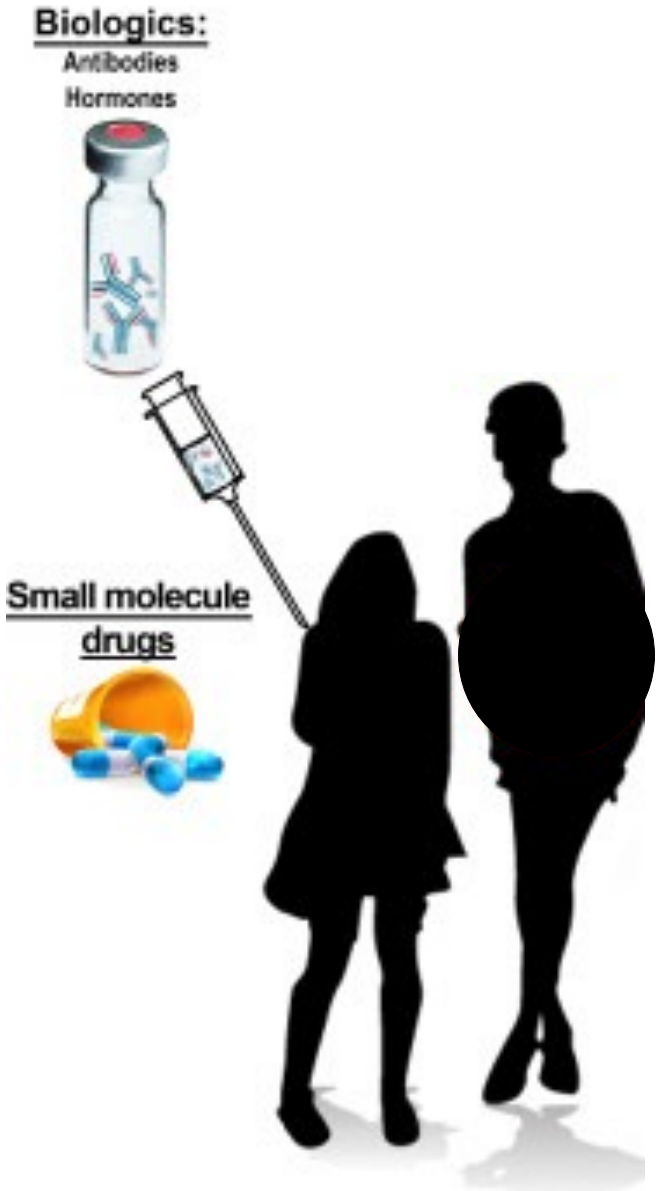


Prioritize targets based on seed genes and protein-protein interaction connectivity

Priority index (Pi) pipeline enables genetics-led drug discovery

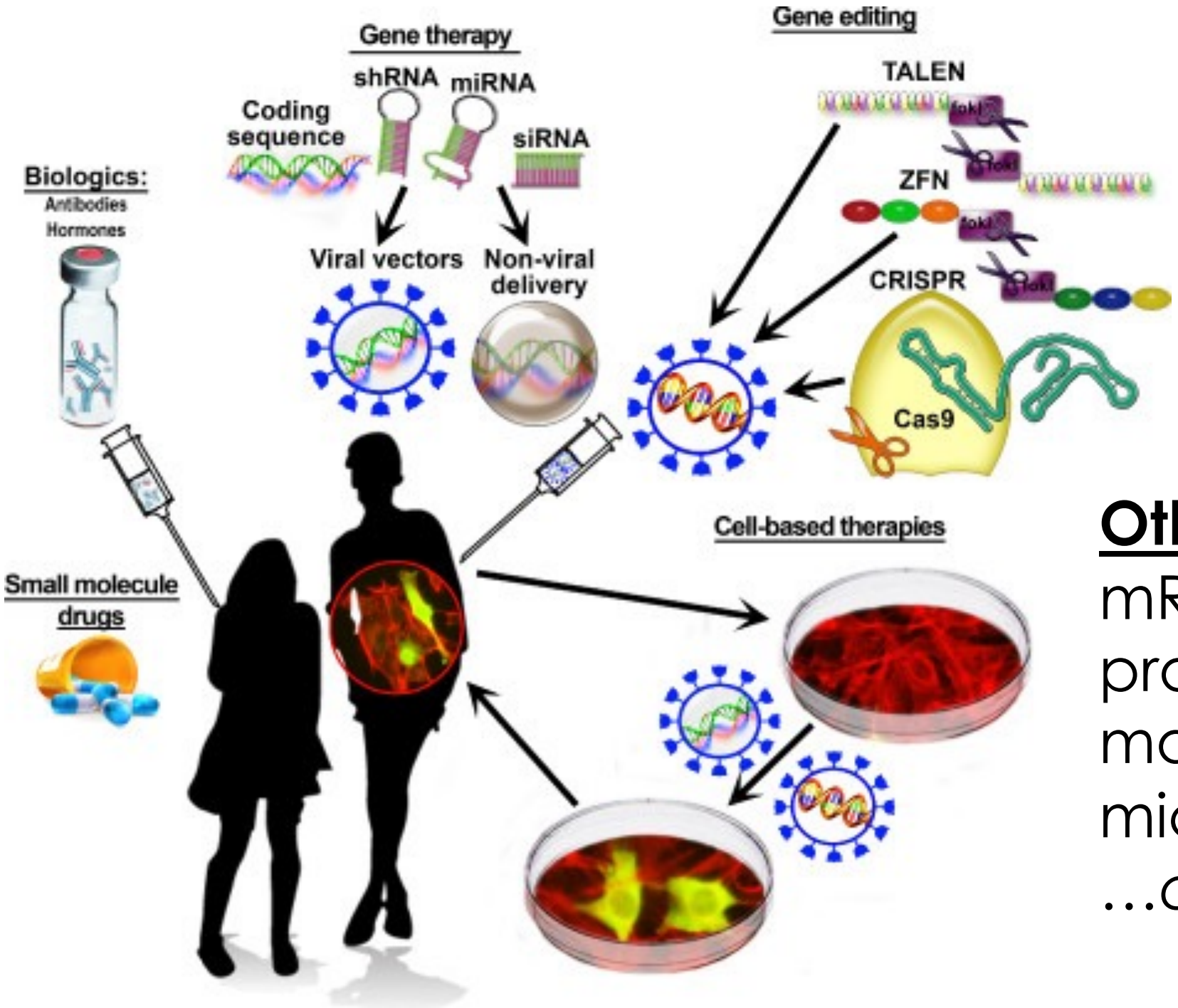
Plenge *Nature Genetics* (2019)

Examples of matching therapeutic modalities with molecular mechanism



While we often first think of "conventional" small molecule and monoclonal antibodies…

…there are many burgeoning therapeutic modalities



Other

mRNA replacement
protein degradation
macrocyclic peptides
microbiome
…and more to come!

ASO targets RNA splicing of *SMN2* transcript

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

Biogen

IONIS PHARMACEUTICALS

RNAi targeting transthyretin (*TTR*)

Alnylam PHARMACEUTICALS

Alnylam Announces FDA Acceptance of New Drug Application (NDA) and Priority Review Status for Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR (hATTR) Amyloidosis

Feb 01,2018

– PDUFA date set for August 11, 2018 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 1, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the U.S. Food and Drug Administration (FDA) has accepted for filing its New Drug Application (NDA) for patisiran, an investigational RNAi therapeutic targeting transthyretin (TTR) for the treatment of hereditary ATTR (hATTR) amyloidosis. The FDA also granted the Company's request for Priority Review and has set an action date of August 11, 2018, under the Prescription Drug User Fee Act (PDUFA). At this time, the FDA is not planning to hold an advisory committee meeting to discuss this application.

Lentiviral *HBB* gene therapy for thalassemia

The NEW ENGLAND JOURNAL of MEDICINE

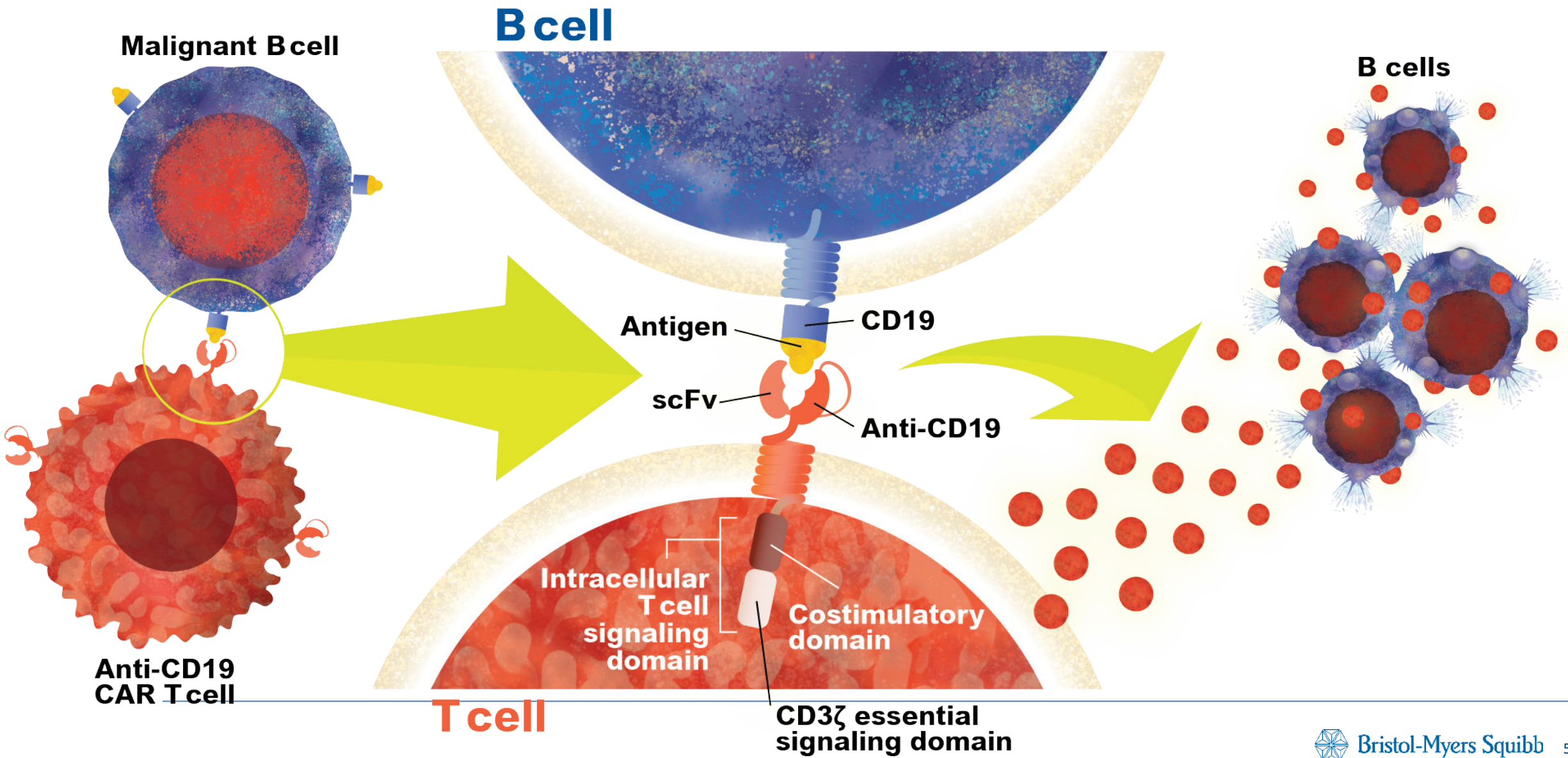
ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller, E. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, L. Caccavelli, J.-S. Diana, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarré, Y. Beuzard, S. Chrétien, T. Lefebvre, D.T. Teachey, U. Anurathapan, P.J. Ho, C. von Kalle, M. Kletzel, E. Vichinsky, S. Soni, G. Veres, O. Negre, R.W. Ross, D. Davidson, A. Petrusich, L. Sandler, M. Asmal, O. Hermine, M. De Montalembert, S. Hacein-Bey-Abina, S. Blanche, P. Leboulch, and M. Cavazzana

bluebirdbio®

CAR-T therapy for B cell cancers



mRNA replacement for vaccines, gene replacement, other

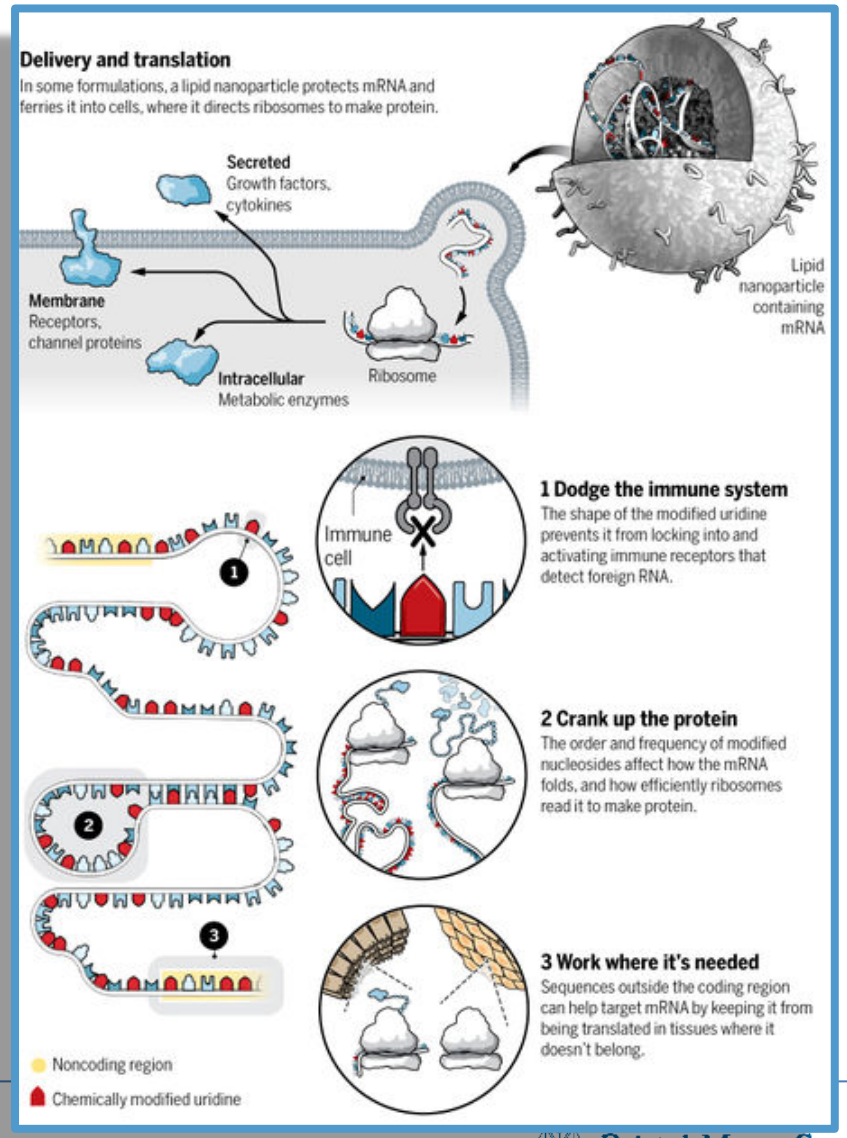
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

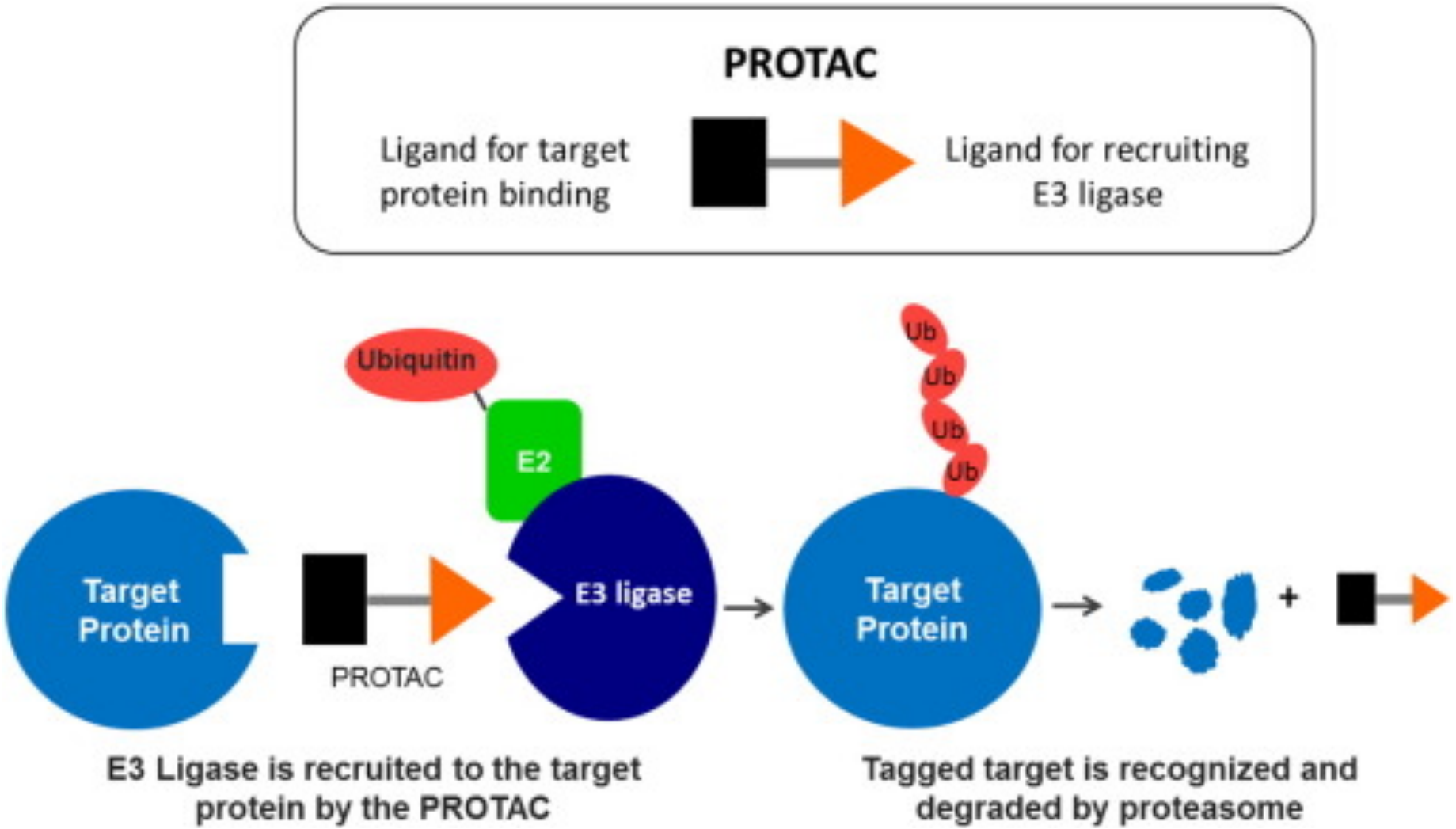
Durable anticancer immunity from intratumoral administration of IL-23, IL-36γ, and OX40L mRNAs

Susannah L. Hewitt*, Ailin Bai*, Dyane Bailey, Kana Ichikawa, John Zielinski, Russell Karp, Ameya Apte, Kristen Arnold, Sima J. Zacharek, Maria S. Iliou, Khushbu Bhatt, Maija Garnaas, Faith Musenge, Ashley Davis, Nikhil Khatwani, Stephen V. Su, Graham MacLean, Samuel J. Farlow, Kristine Burke, Joshua P. Frederick†

Many solid cancers contain dysfunctional immune microenvironments. Immune system modulators that initiate responses to foreign pathogens could be promising candidates for reigniting productive responses toward tumors. Interleukin-1 (IL-1) and IL-12 cytokine family members cooperate at barrier tissues after microbial invasion, in human inflammatory diseases, and in antitumoral immunity. IL-36γ, in classic alarmin fashion, acts in damaged tissues, whereas IL-23 centrally coordinates immune responses to danger signals. In this study, direct intratumoral delivery of messenger RNAs (mRNAs) encoding these cytokines produced robust anticancer responses in a broad range of tumor microenvironments. The addition of mRNA encoding the T cell costimulator OX40L increased complete response rates in treated and untreated distal tumors compared to the cytokine mRNAs alone. Mice exhibiting complete responses were subsequently protected from tumor rechallenge. Treatments with these mRNA mixtures induced downstream cytokine and chemokine expression, and also activated multiple dendritic cell (DC) and T cell types. Consistent with this, efficacy was dependent on Batf3-dependent cross-presenting DCs and cytotoxic $CD8^+$ T cells. IL-23/IL-36γ/OX40L triplet mRNA mixture triggered substantial immune cell recruitment into tumors, enabling effective tumor destruction irrespective of previous tumoral immune infiltrates. Last, combining triplet mRNA with checkpoint blockade led to efficacy in models otherwise resistant to systemic immune checkpoint inhibition. Human cell studies showed similar cytokine responses to the individual components of this mRNA mixture, suggesting translatability of immunomodulatory activity to human patients.

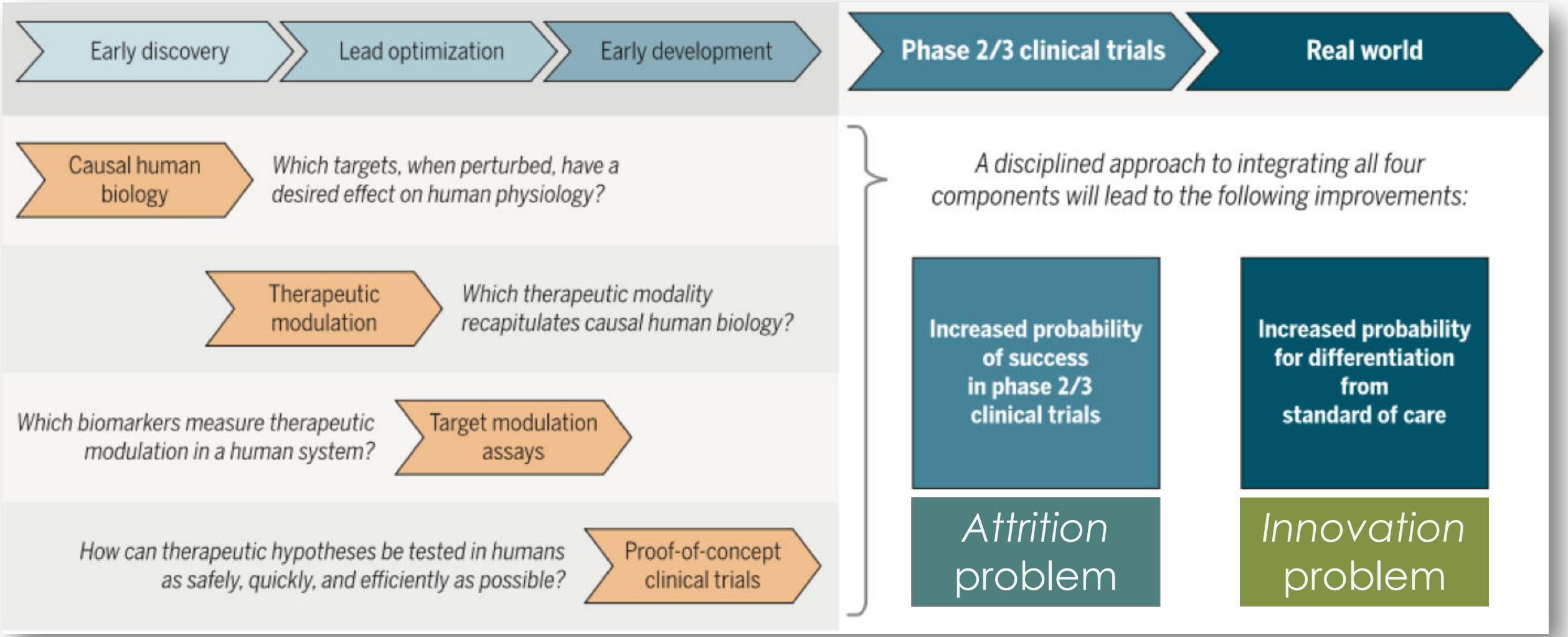


Protein degradation to “knockout” intracellular proteins



Neklesa *et al* (2017) *Pharm & Therapeutics*

Putting it all together…



Plenge *Science Translational Medicine* (2016)

Conclusions

- Two fundamental challenges: attrition problem, innovation problem
- Human genetics offers a potential solution
- "Allelic series" model to build genetic dose-response curves
  - An example in immunology (TYK2)
- Framework to prioritize "allelic series" genes for functional studies
- Saturation mutagenesis to build function-phenotype maps
- Phenome-wide association studies to extend trait-associations
- Beyond allelic series
  - Gene-centric approaches (genomic-features model)
  - Pathway-centric approaches (e.g., protein-protein interaction model)
- Matching modality to mechanism is critical
  - Many new approaches are emerging…*only imagination is limiting!*


Questions?
@rplenge