IMPACT OF HUMAN GENETICS ON DRUG R&D

Robert Plenge

Harvard Medical School, Executive Education

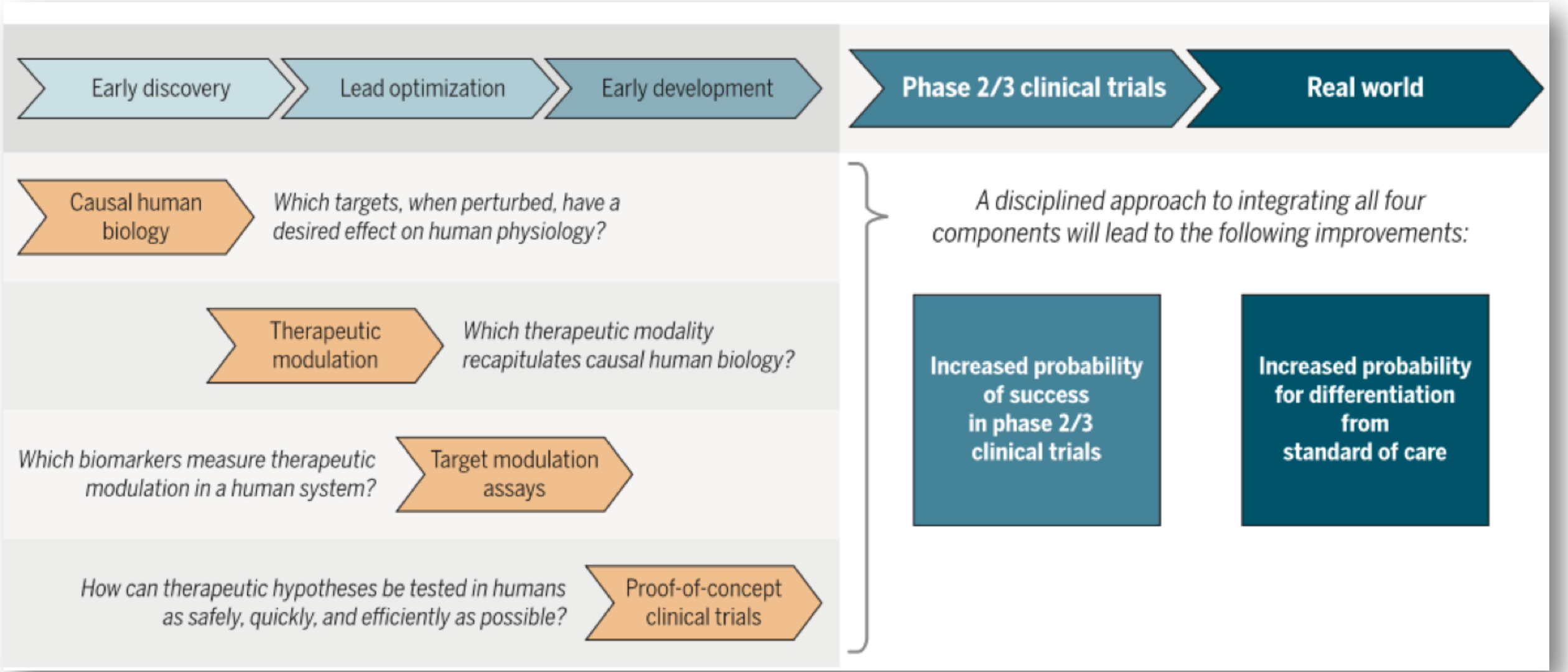
June 4, 2018

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

Introduction

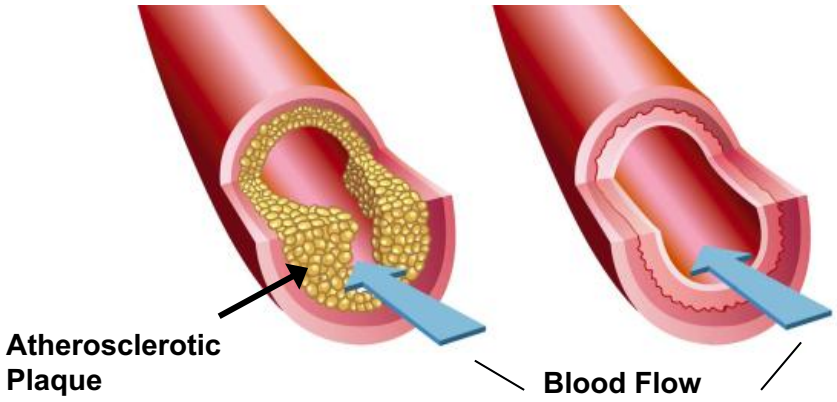
- Approach most applicable outside of oncology and ID
- References
  - Plenge *et al* Nature Reviews Drug Discovery (2013)
  - Cook *et al* Nature Reviews Drug Discovery (2014)
  - Nelson *et al* Nature Genetics (2015)
  - Plenge Science Translational Medicine (2016)
  - Dendrou *et al* Science Translational Medicine (2016)
  - Kennedy *et al* Science Translational Medicine (2016)
  - Egan *et al* New England Journal of Medicine (2018)



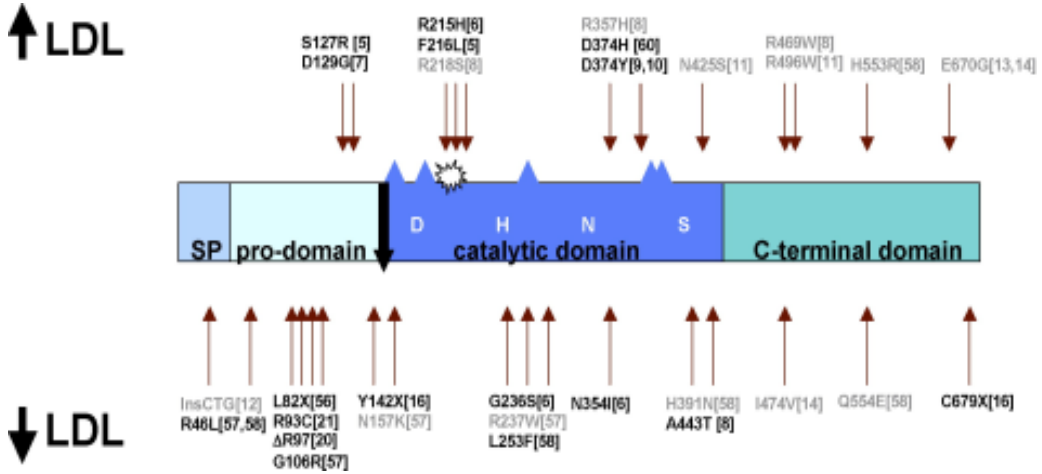
Plenge *Science Translational Medicine* (2016)

But first…what is the evidence that human genetics helps with R&D productivity?

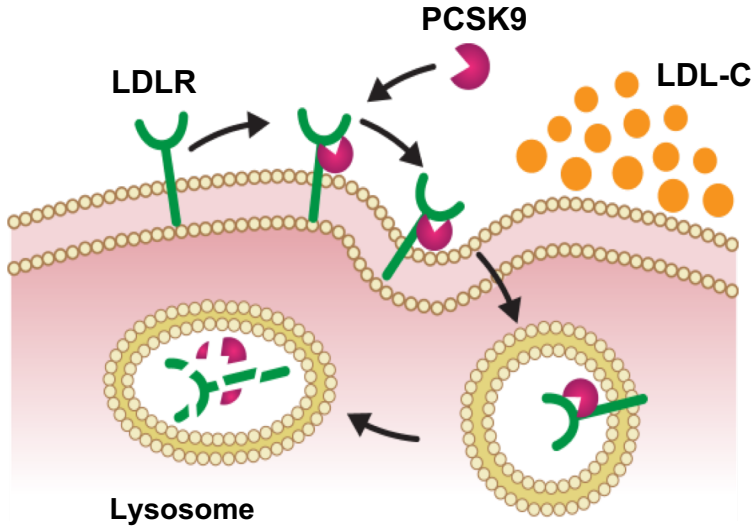
Many genes influence cholesterol levels and risk of heart disease



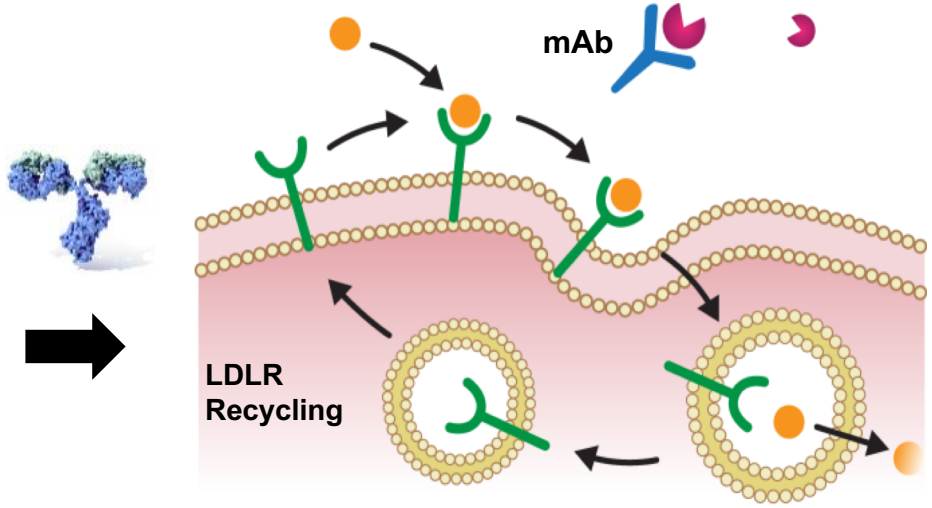
PCSK9 mutations associated with high and low LDL cholesterol levels (and heart disease risk)



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

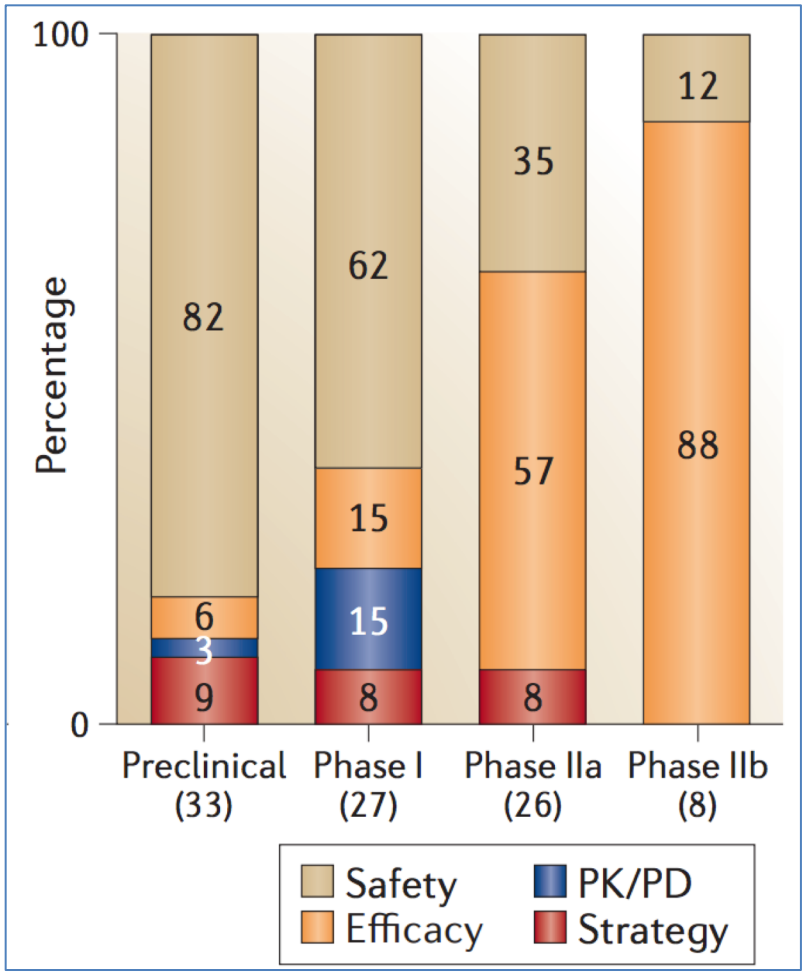


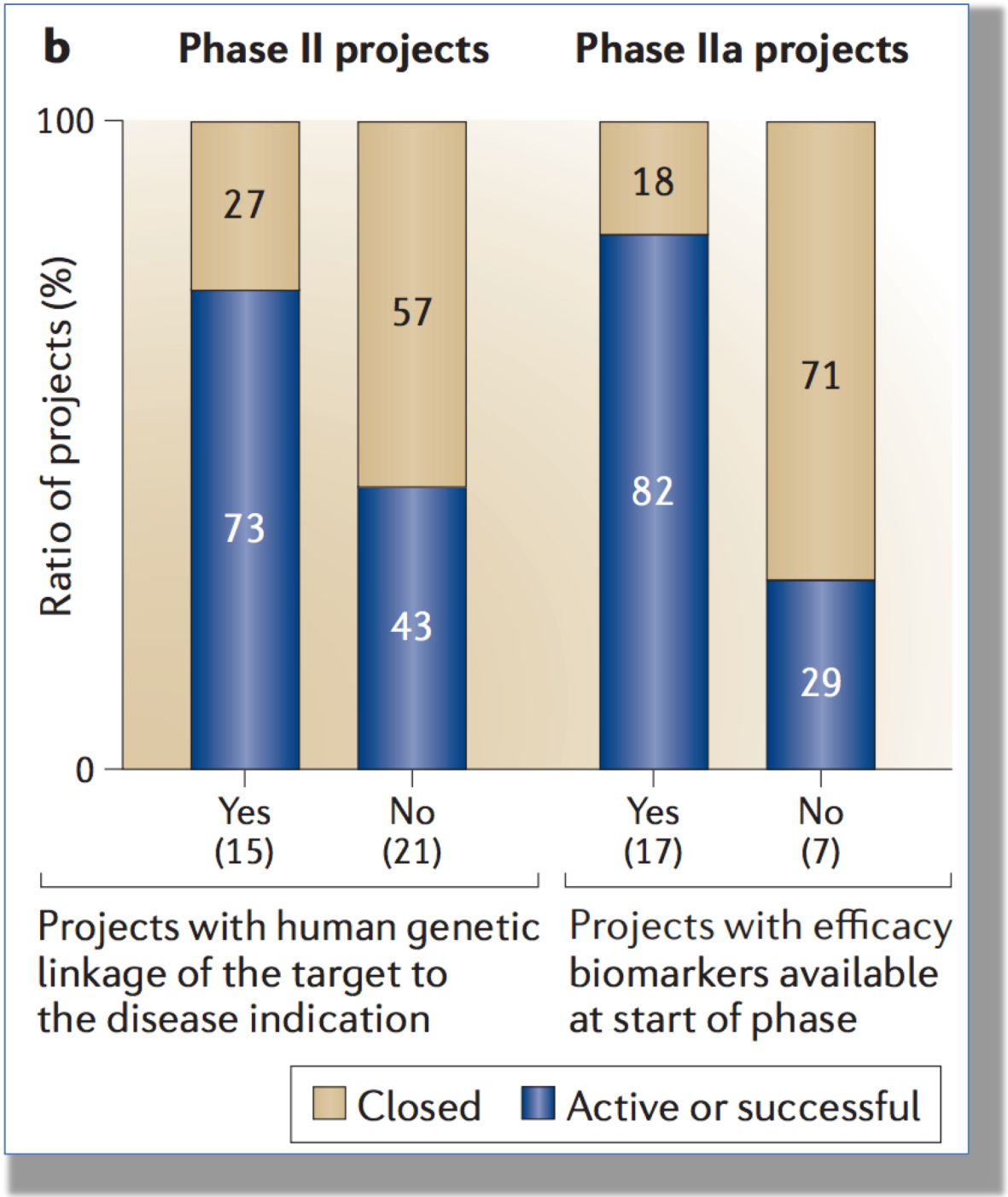
drugs that mimic the mutation & lower LDL and protect from heart disease



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

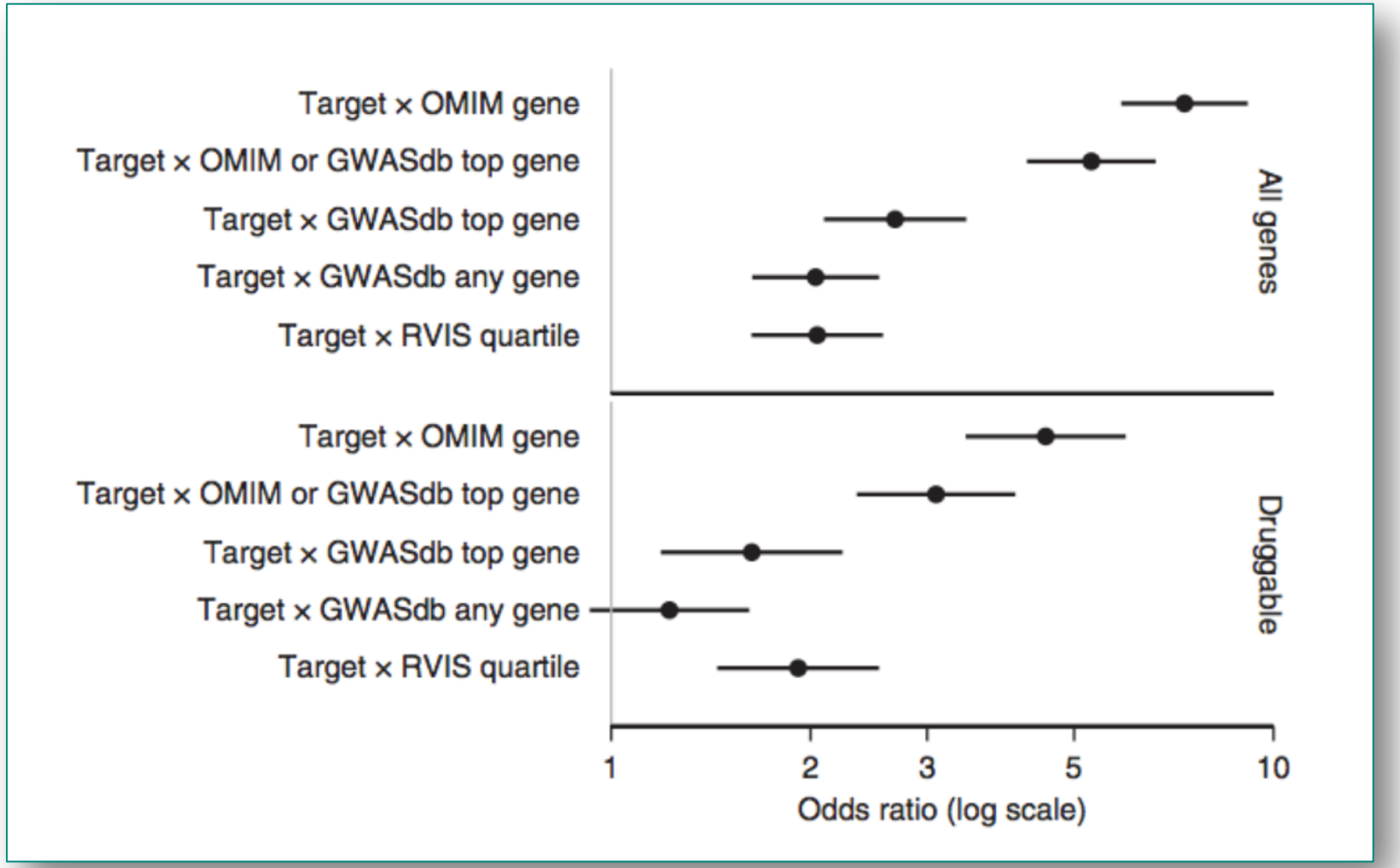




The support of human genetic evidence for approved drug indications

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]

Over a quarter of drugs that enter clinical development fail because they are ineffective. Growing insight into genes that influence human disease may affect how drug targets and indications are selected. However, there is little guidance about how much weight should be given to genetic evidence in making these key decisions. To answer this question, we investigated how well the current archive of genetic evidence predicts drug mechanisms. We found that, among well-studied indications, the proportion of drug mechanisms with direct genetic support increases significantly across the drug development pipeline, from 2.0% at the preclinical stage to 8.2% among mechanisms for approved drugs, and varies dramatically among disease areas. We estimate that selecting genetically supported targets could double the success rate in clinical development. Therefore, using the growing wealth of human genetic data to select the best targets and indications should have a measurable impact on the successful development of new drugs.



Genetic support for FDA approved drugs in 2018

- 9 approved new new molecular entities so far in 2018 (May 15)
- Of these, 4 are for non-oncology / non-ID indications
- All 4 have *some degree* of genetic support for the targets
  - tezacaftor / ivacaftor for CF –> strong prospective evidence (*CFTR*)
  - burosumab for hypophosphatemia –> strong prospective evidence (*FGF23*)
  - fostamatinib for ITP –> weak retrospective evidence (*SYK*)
  - tildrakizumab for psoriasis –> strong retrospective evidence (*IL23A*)

FDA website

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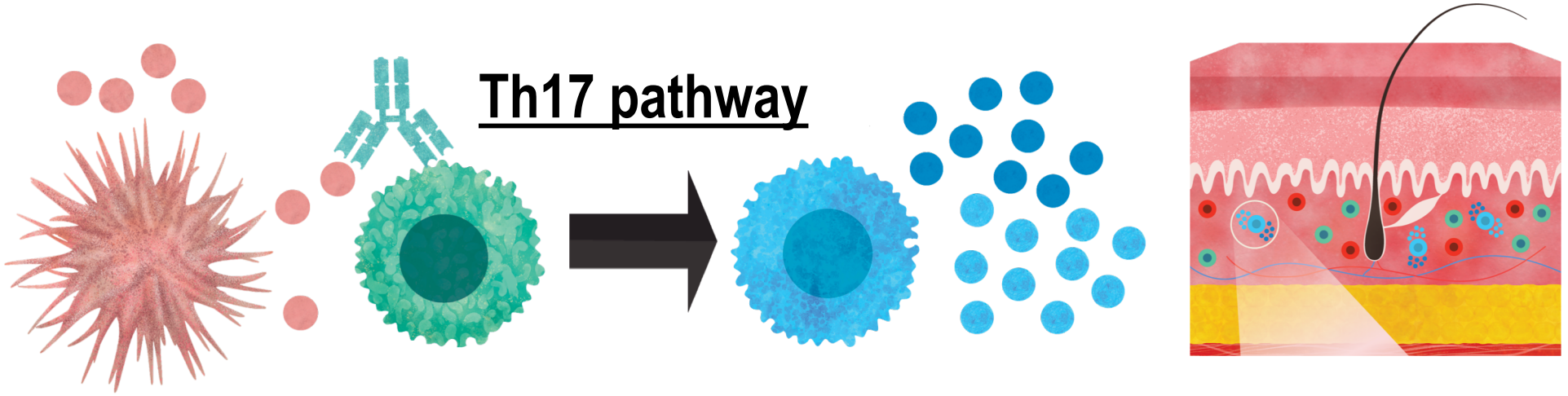
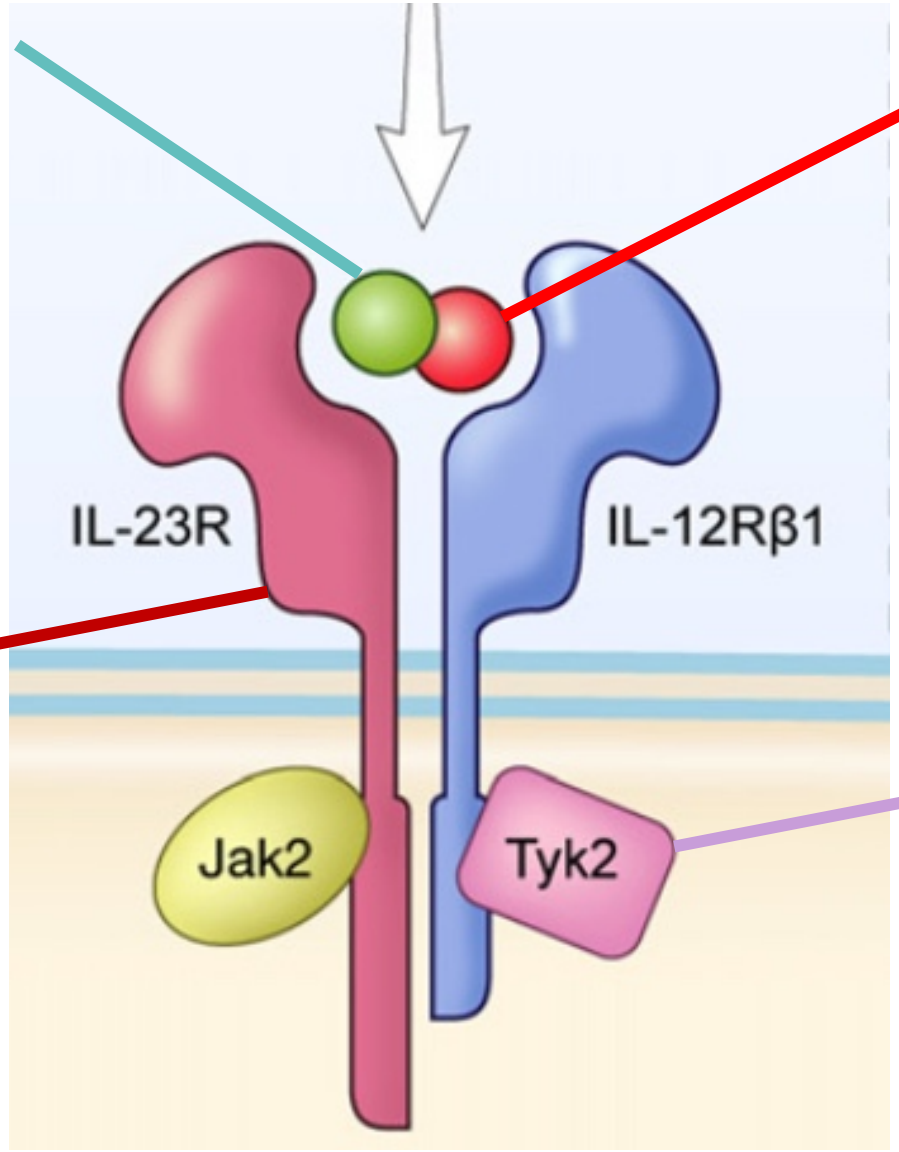


IL23 signaling

IL23A (IL23p19)



IL12B (IL12p40)

IL23R

TYK2

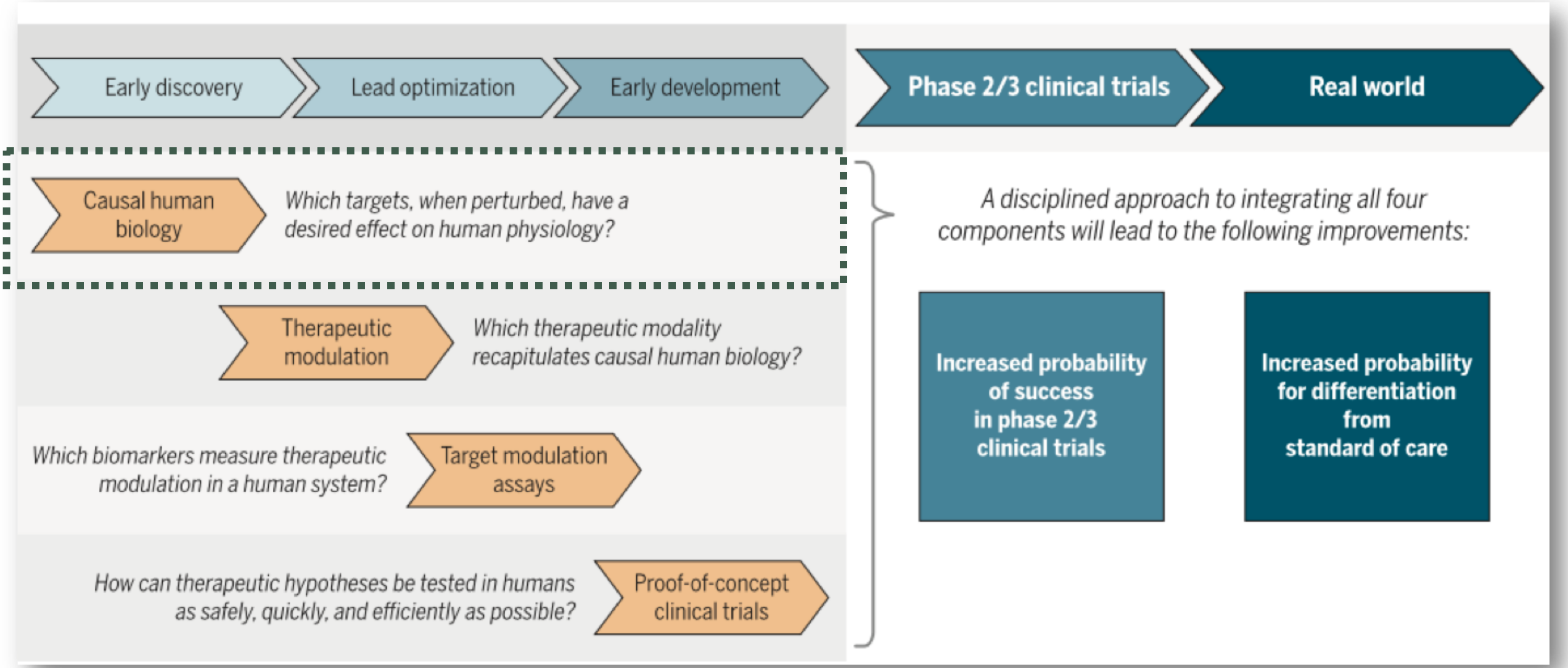
O'Shea and Plenge Immunity (2012)

Genetic support for FDA approved drugs in 2018

- 15 approved new new molecular entities so far in 2018 (June 2)
- Of these, 10 are for non-oncology / non-ID indications
- Most have some degree of genetic support for the targets
  - tezacaftor / ivacaftor for CF –> strong prospective evidence (*CFTR*)
  - burosumab for hypophosphatemia –> strong prospective evidence (*FGF23*)
  - tildrakizumab for psoriasis –> strong retrospective evidence (*IL23A*)
  - avatrombopag for thrombocytopenia –> strong prospective evidence (*MPL*)
  - pegvaliase for PKU deficiency –> strong prospective evidence (*PAH*)
  - baricitinib for rheumatoid arthritis –> strong prospective evidence (*JAK1*)
  - fostamatinib for ITP –> weak retrospective evidence (*SYK*)
  - lofexidine for opioid withdrawal –> no genetic evidence (*ADRB2*)
  - erenumab for migraine –> no genetic evidence (*CGRPR*)
  - zirconium cyclosilicate for hyperkalemia –> no genetic evidence (*N/A*)

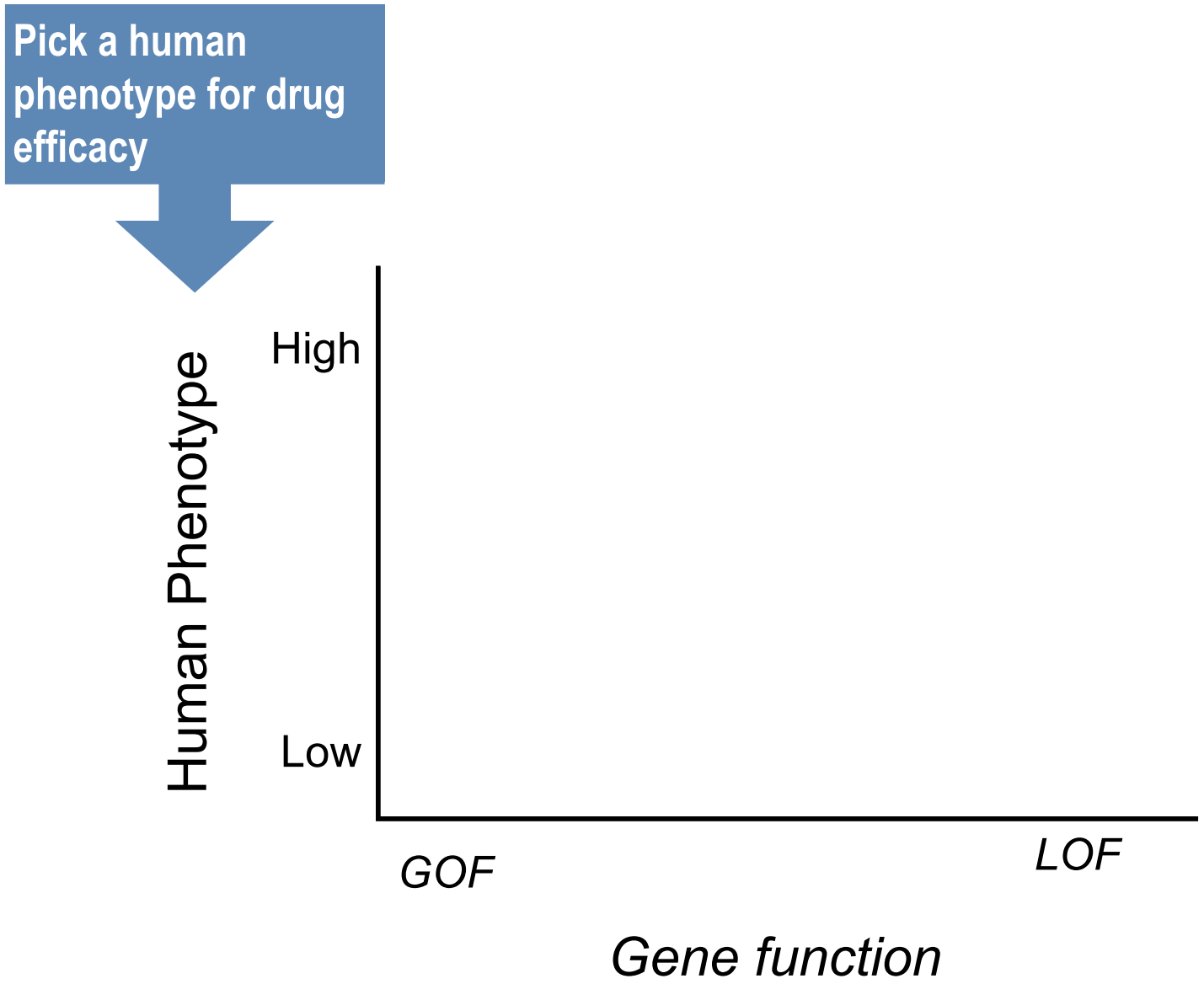
FDA website

Next…breaking down the individual components, from target identification to clinical proof-of-concept (PoC)

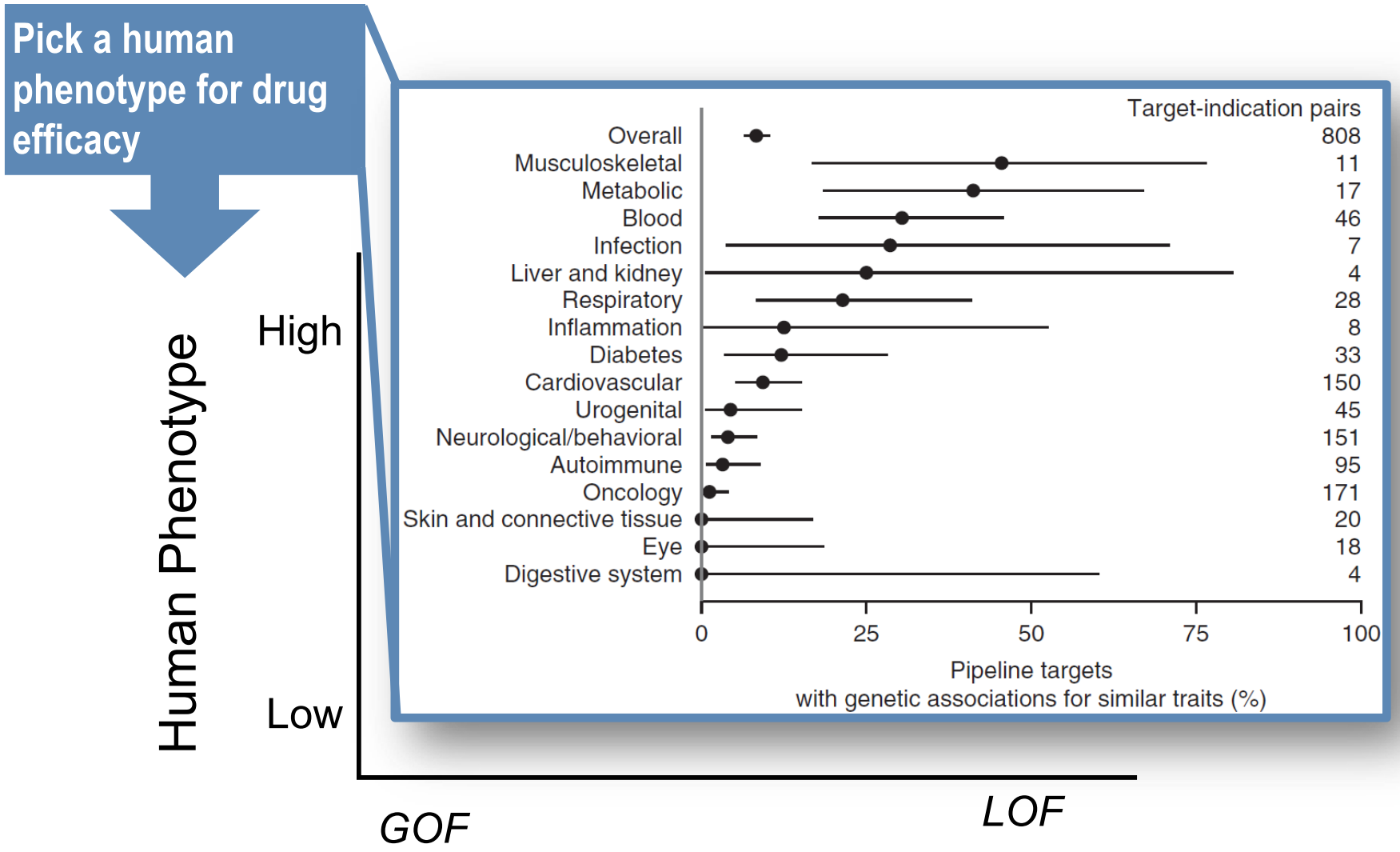


Plenge *Science Translational Medicine* (2016)

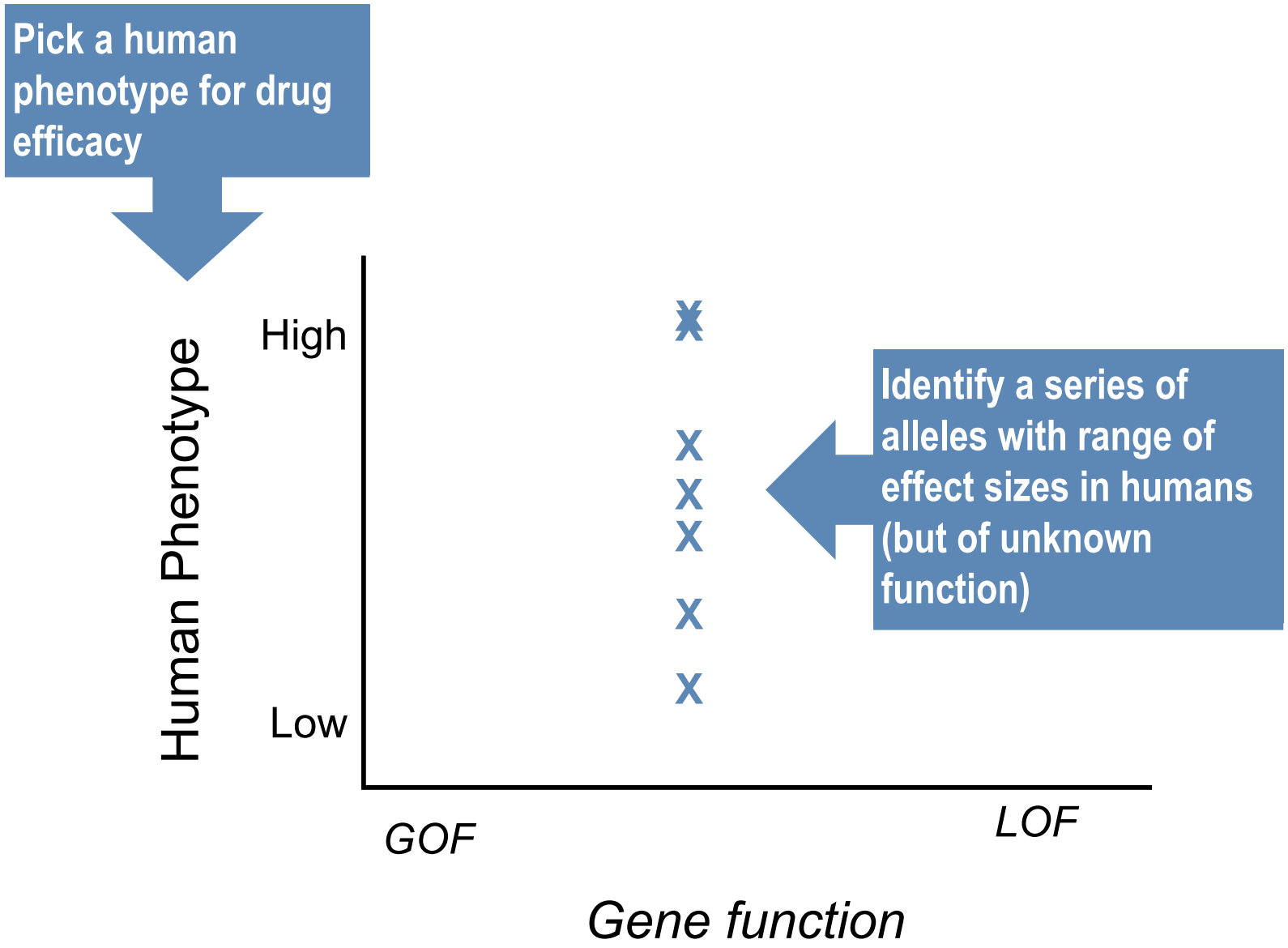
What is the ideal drug target?

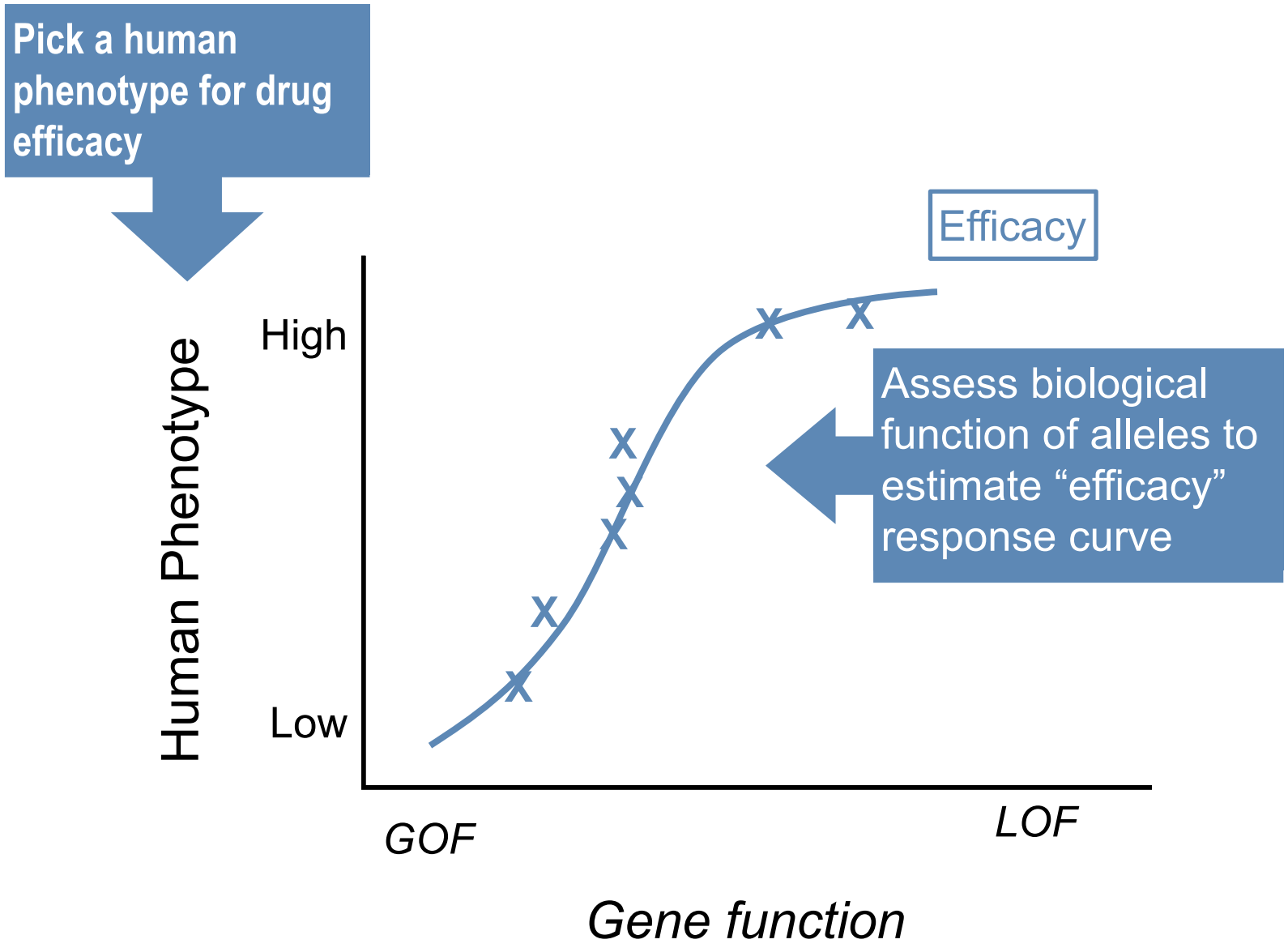


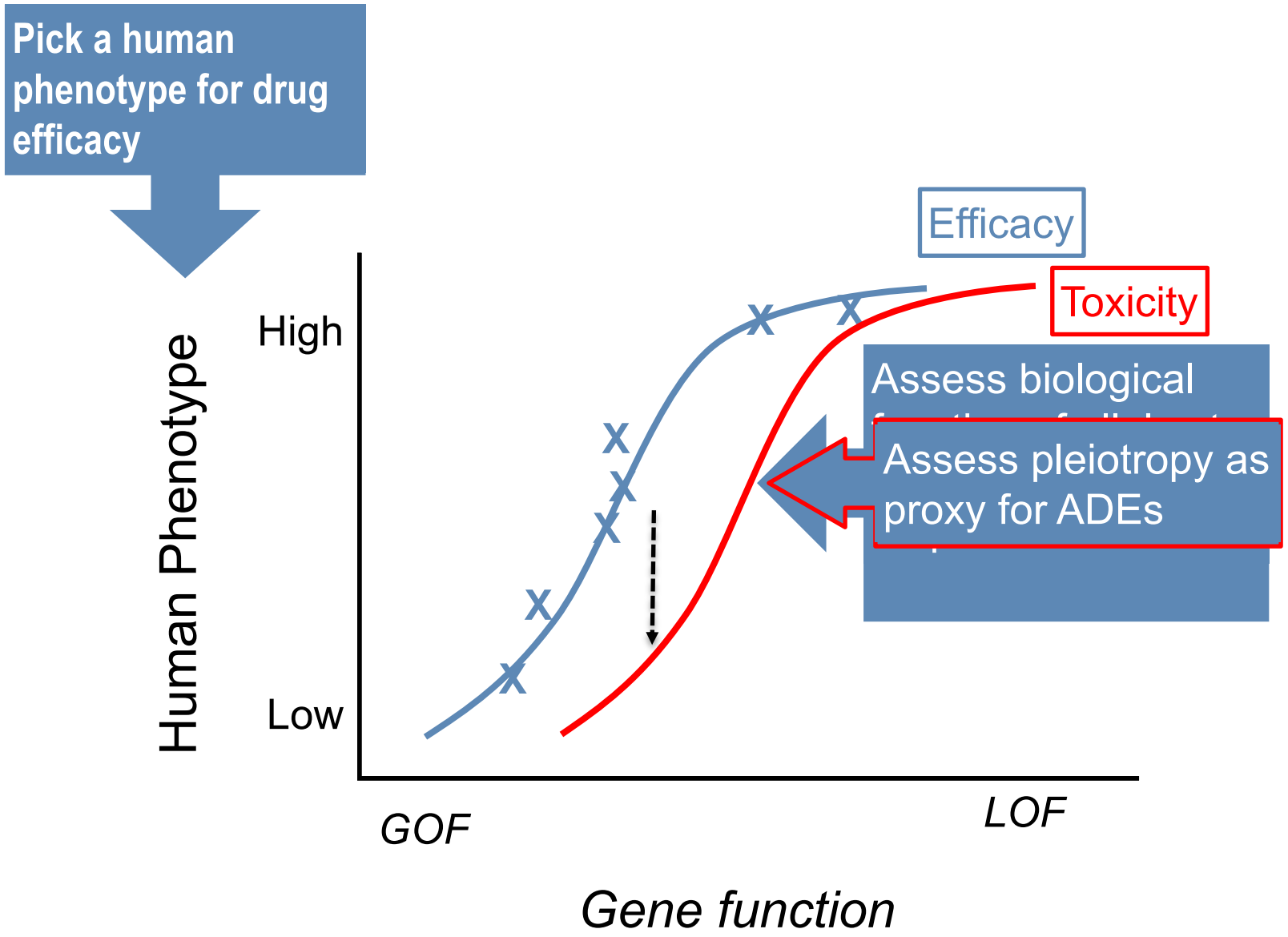
Plenge et al *Nature Reviews Drug Discovery* 2013



Nelson et al *Nature Genetics* 2015

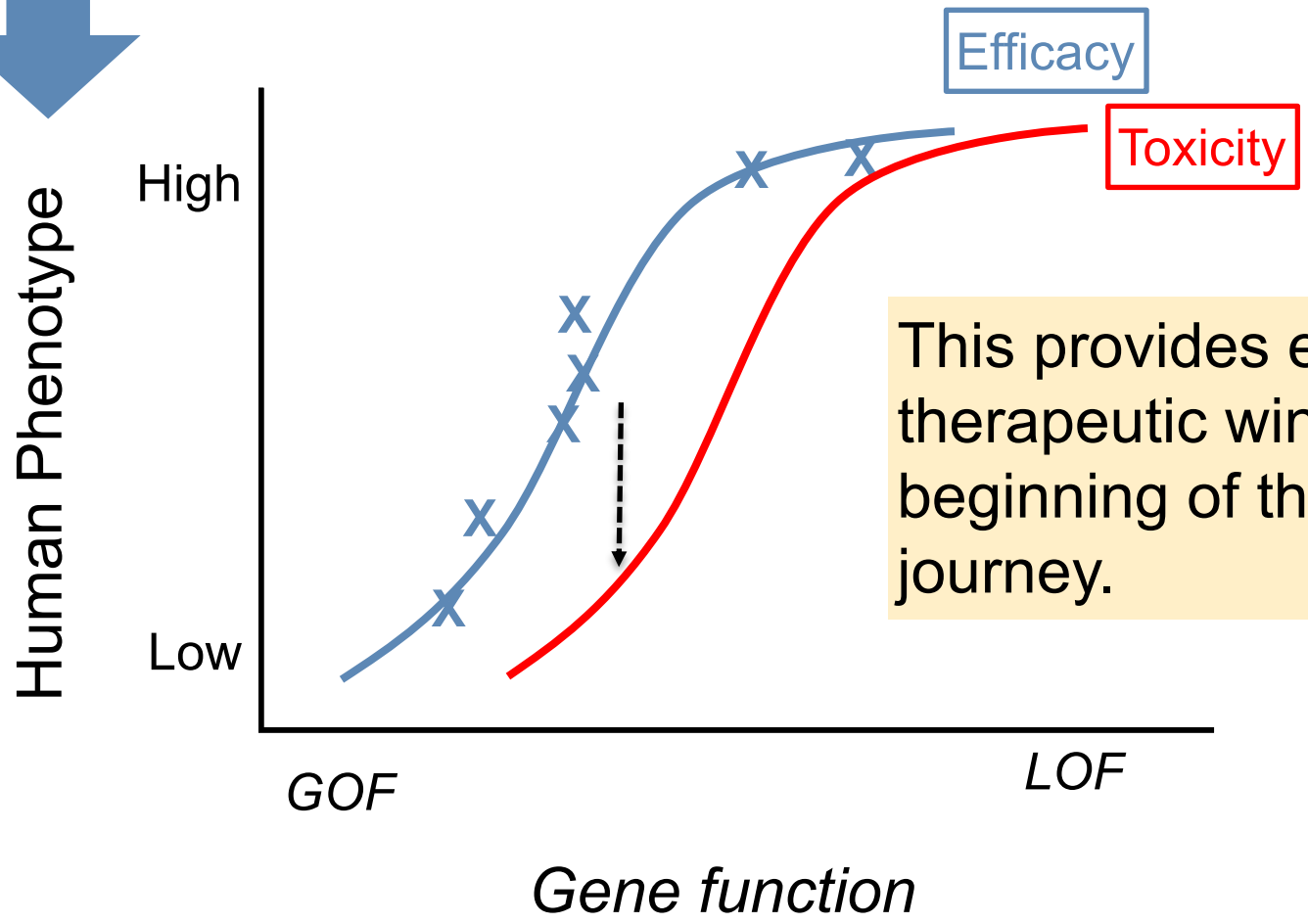

Pick a human phenotype for drug efficacy
Human Phenotype
High
Low
Identify a series of alleles with range of effect sizes in humans (but of unknown function)
GOF
LOF
Gene function


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

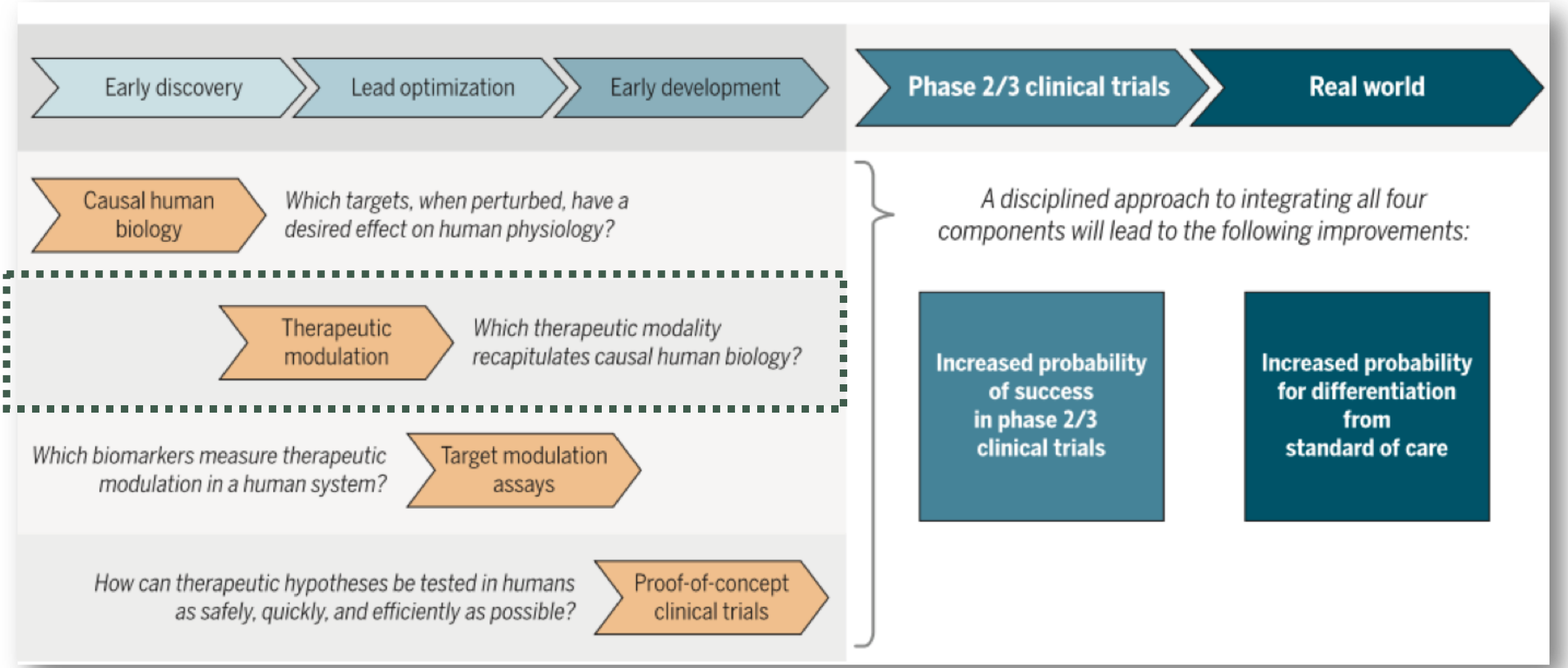

Pick a human phenotype for drug efficacy
Efficacy
Toxicity
Assess biological
Assess pleiotropy as proxy for ADEs
High
Low
Human Phenotype
GOF
LOF
Gene function

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 *Science Translational Medicine* (2016)

Example of allelic series model: TYK2

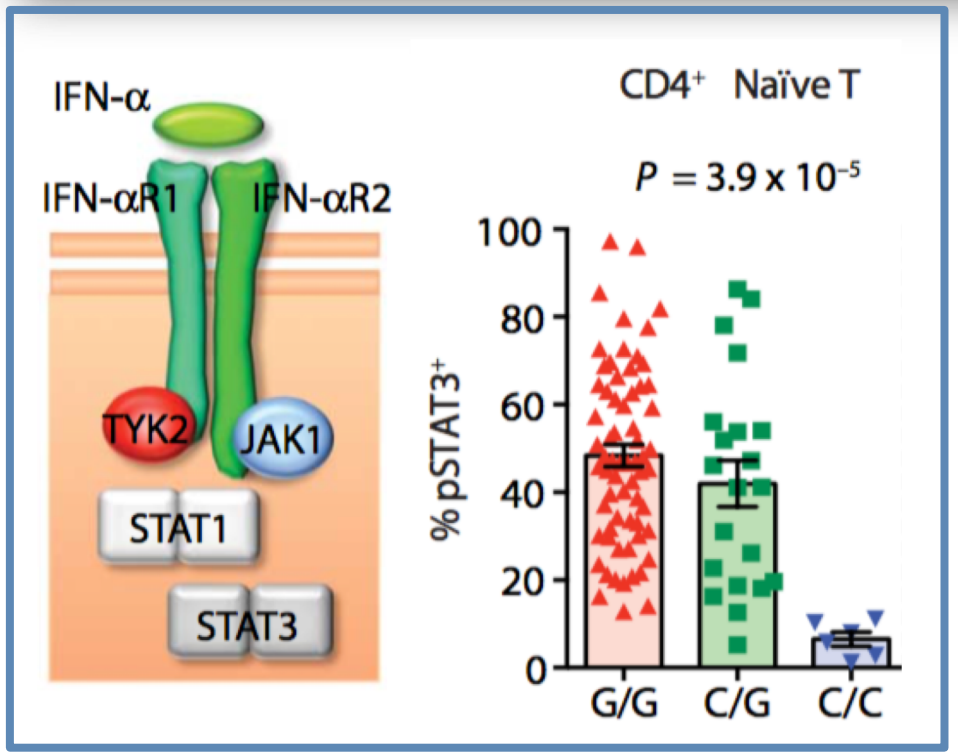
- TYK2 is an intracellular signaling molecule
- Rare, complete human knockout is associated with immunodeficiency and risk of infection
- Common alleles reduce TYK2 function and protect from risk of autoimmune disease (e.g., RA, SLE, IBD)
- Same common alleles do not increase risk of infection

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]*



Allele that protects from autoimmunity (e.g., rheumatoid arthritis) is associated with loss-of-function (LoF)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

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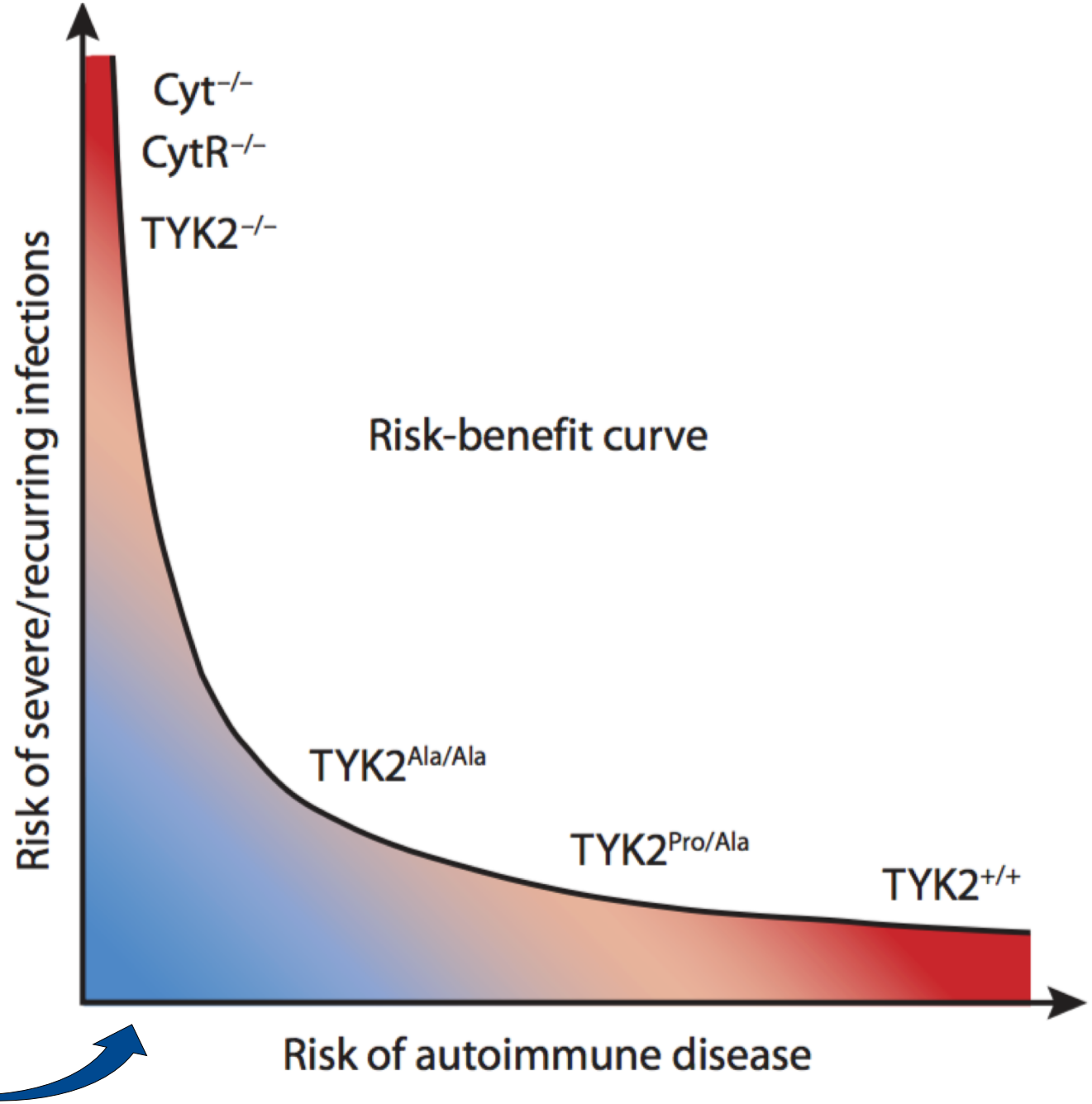
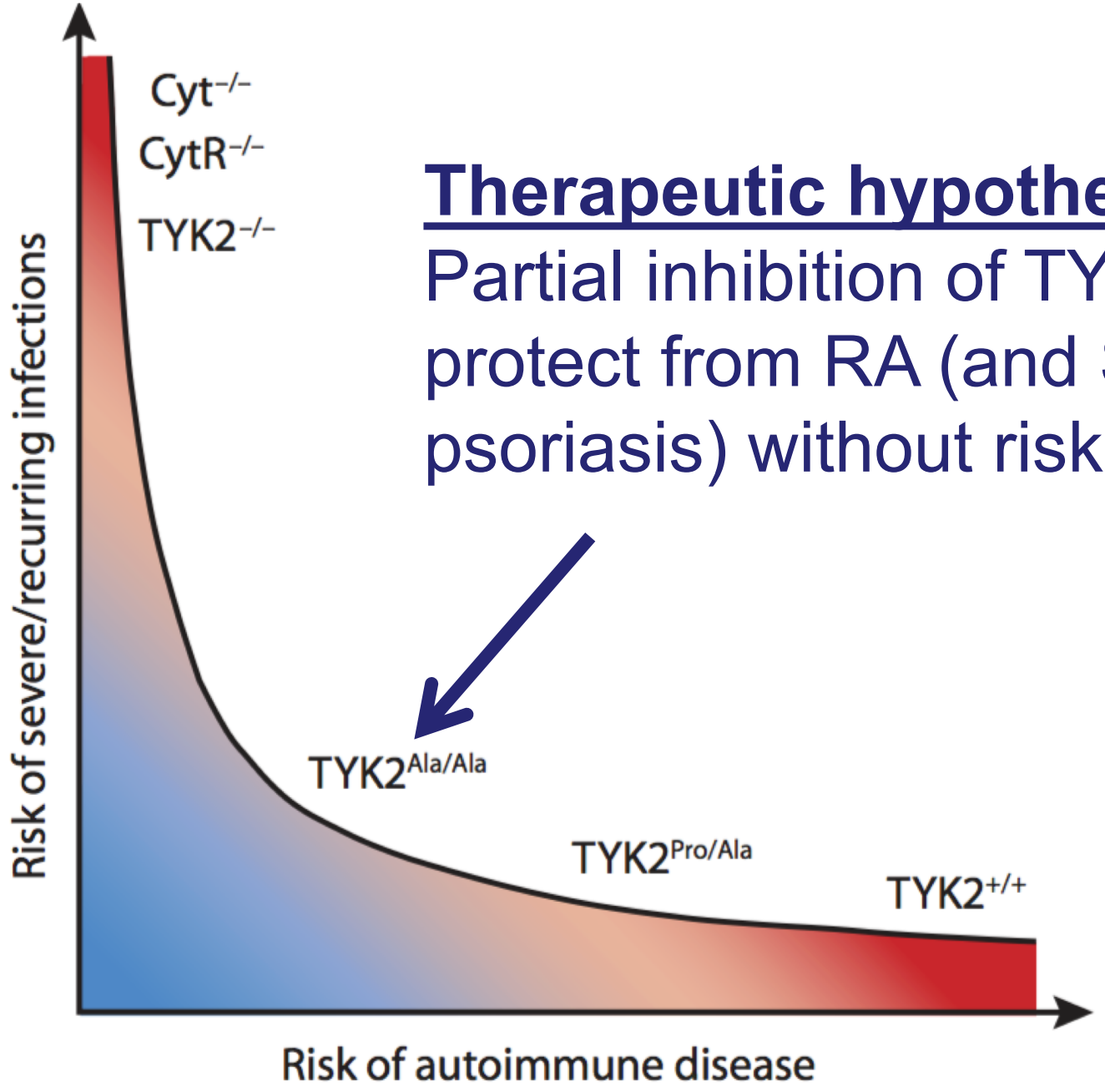
A

	Rs34536443 genotype			
	G/G	*G/C*	*C/C*	Total
In U.K. Biobank	105,794 (90.63%)	10,689 (9.16%)	249 (0.21%)	116,732 (100%)
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

Same LoF allele has no obvious increased risk of infection

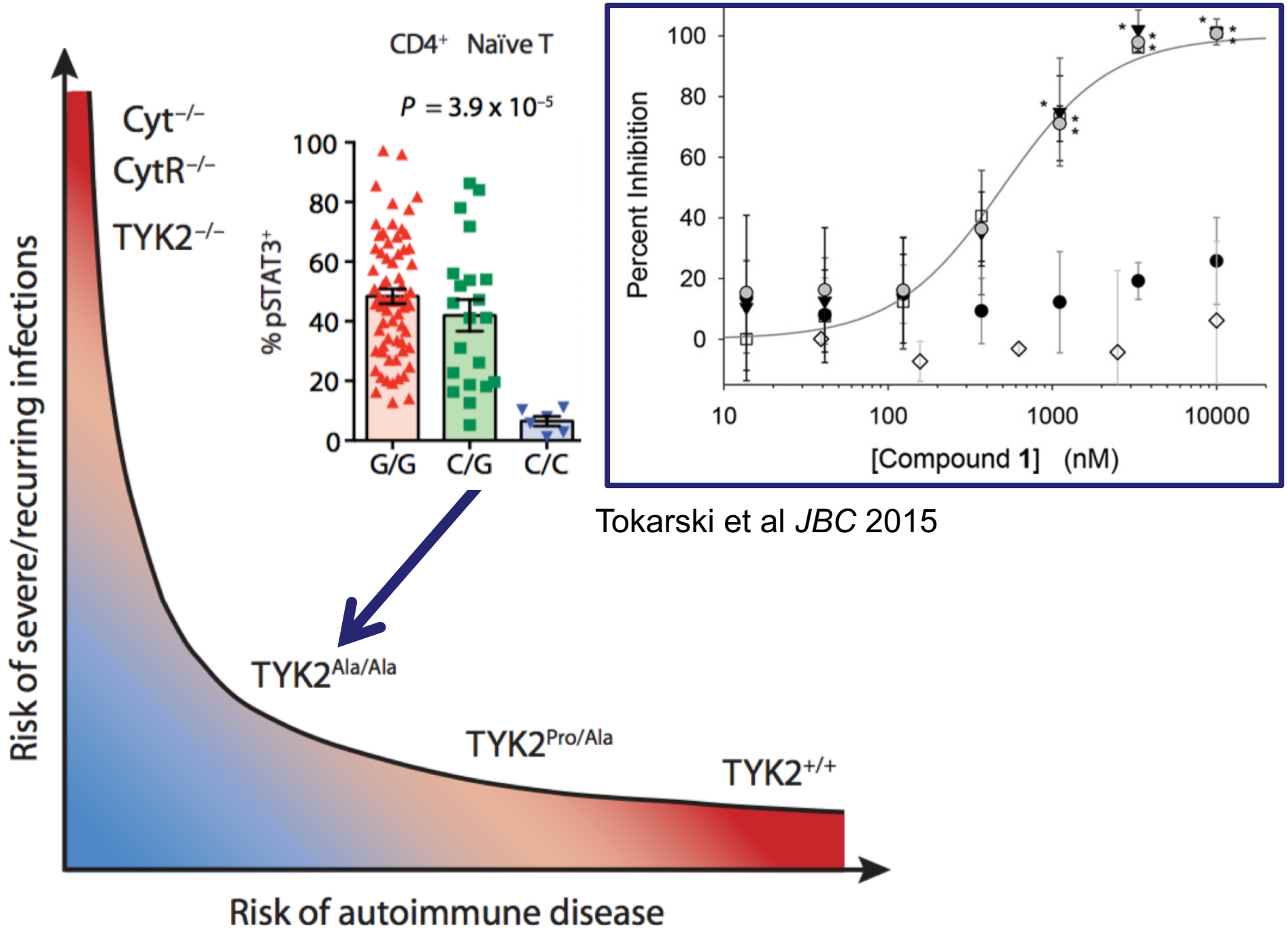
Complete TYK2 knockout (function)





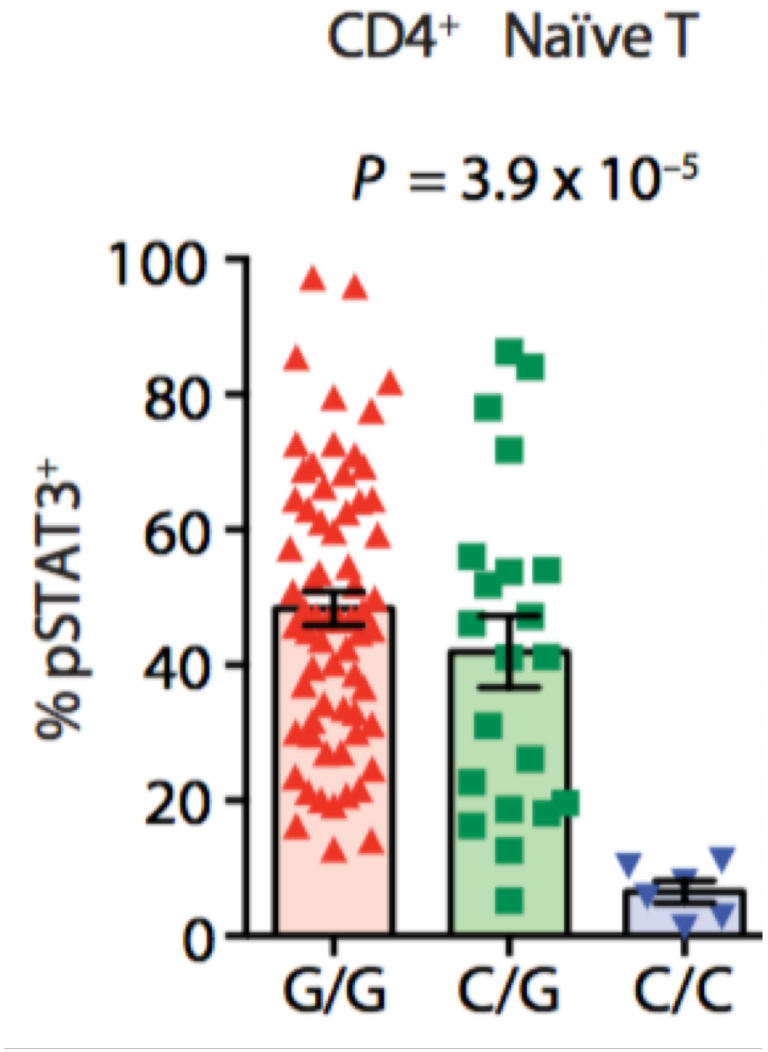
Therapeutic hypothesis:
Partial inhibition of TYK2 will protect from RA (and SLE, psoriasis) without risk of infection

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

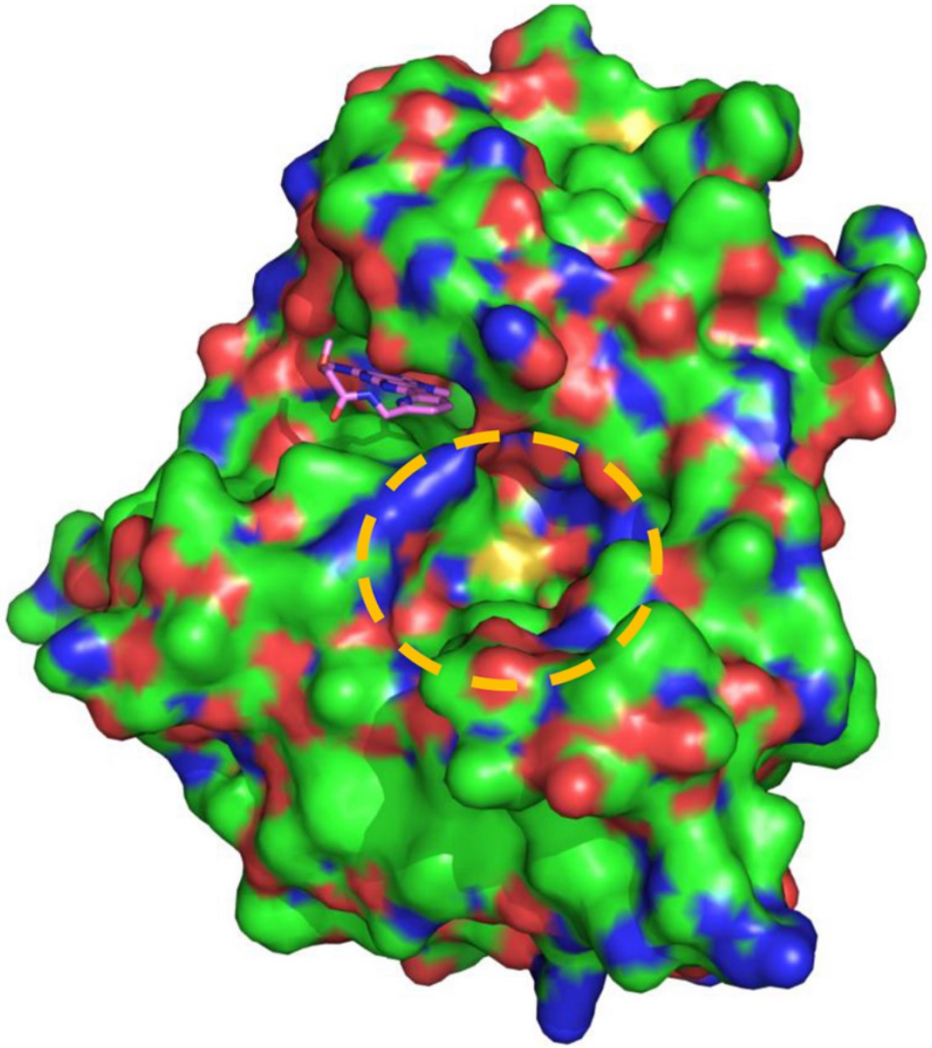


Tokarski et al *JBC* 2015

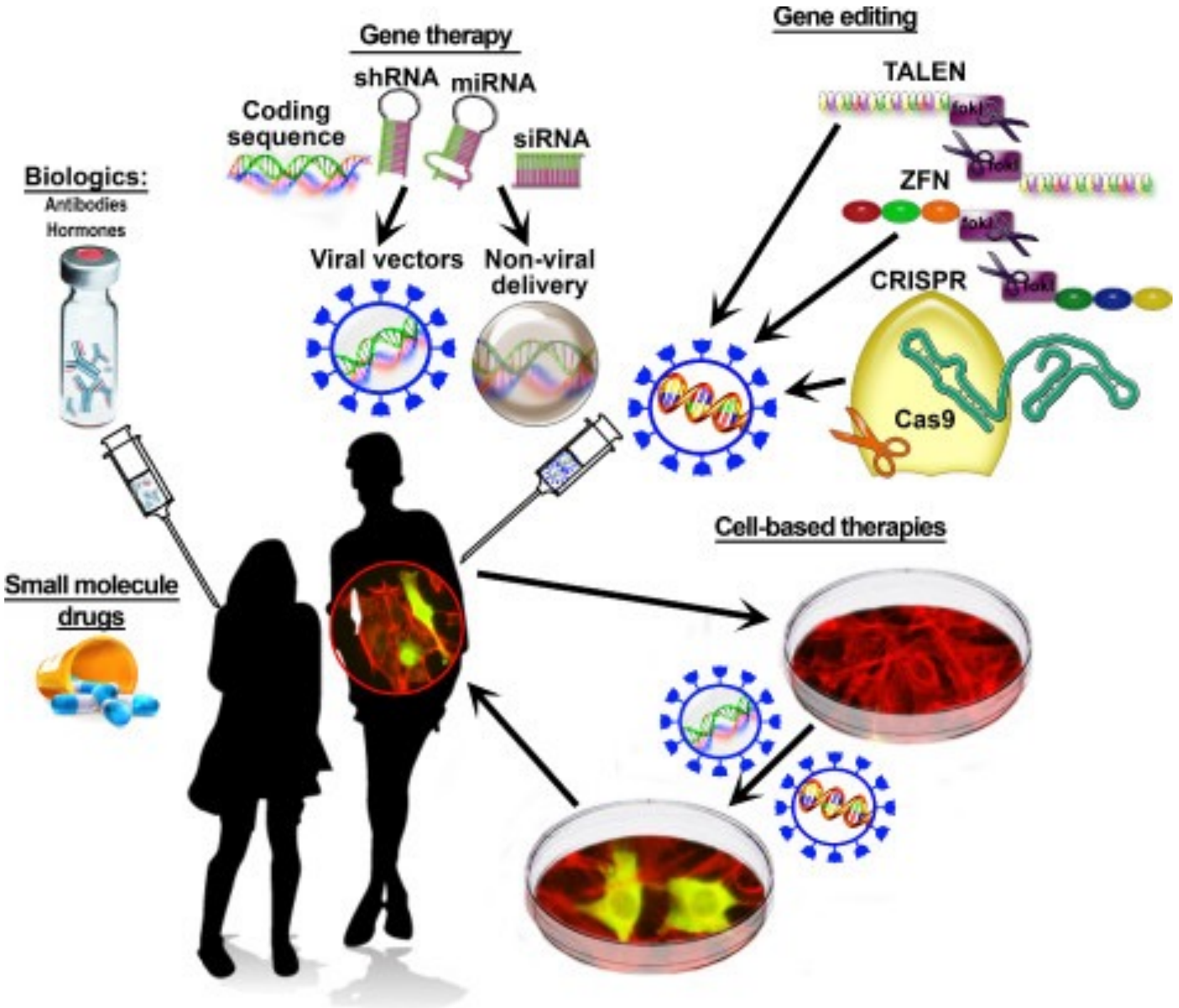
Matching modality and mechanism:
allosteric modulation required for TYK2 selectivity over JAKs



Dendrou et al *STM* 2016



Tokarski et al *JBC* 2015



Other

mRNA replacement

protein degradation

macrocyclic peptides

…*and more to come!*

Antisense oligonucleotide (ASO) targeting *HSD17B13*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease

N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, U.L. Mirshahi, D.J. Carey, C.D. Still, M.D. Feldman, A. Small, S.M. Damrauer, D.J. Rader, B. Zambrowicz, W. Olson, A.J. Murphy, I.B. Borecki, A.R. Shuldiner, J.G. Reid, J.D. Overton, G.D. Yancopoulos, H.H. Hobbs, J.C. Cohen, O. Gottesman, T.M. Teslovich, A. Baras, T. Mirshahi, J. Gromada, and F.E. Dewey

DiscovEHR

REGENERON® GENETICS CENTER

Geisinger mycode

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

Lentiviral *HBB* gene therapy for thalessemia

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®

RNAi targeting transthyretin (*TTR*)

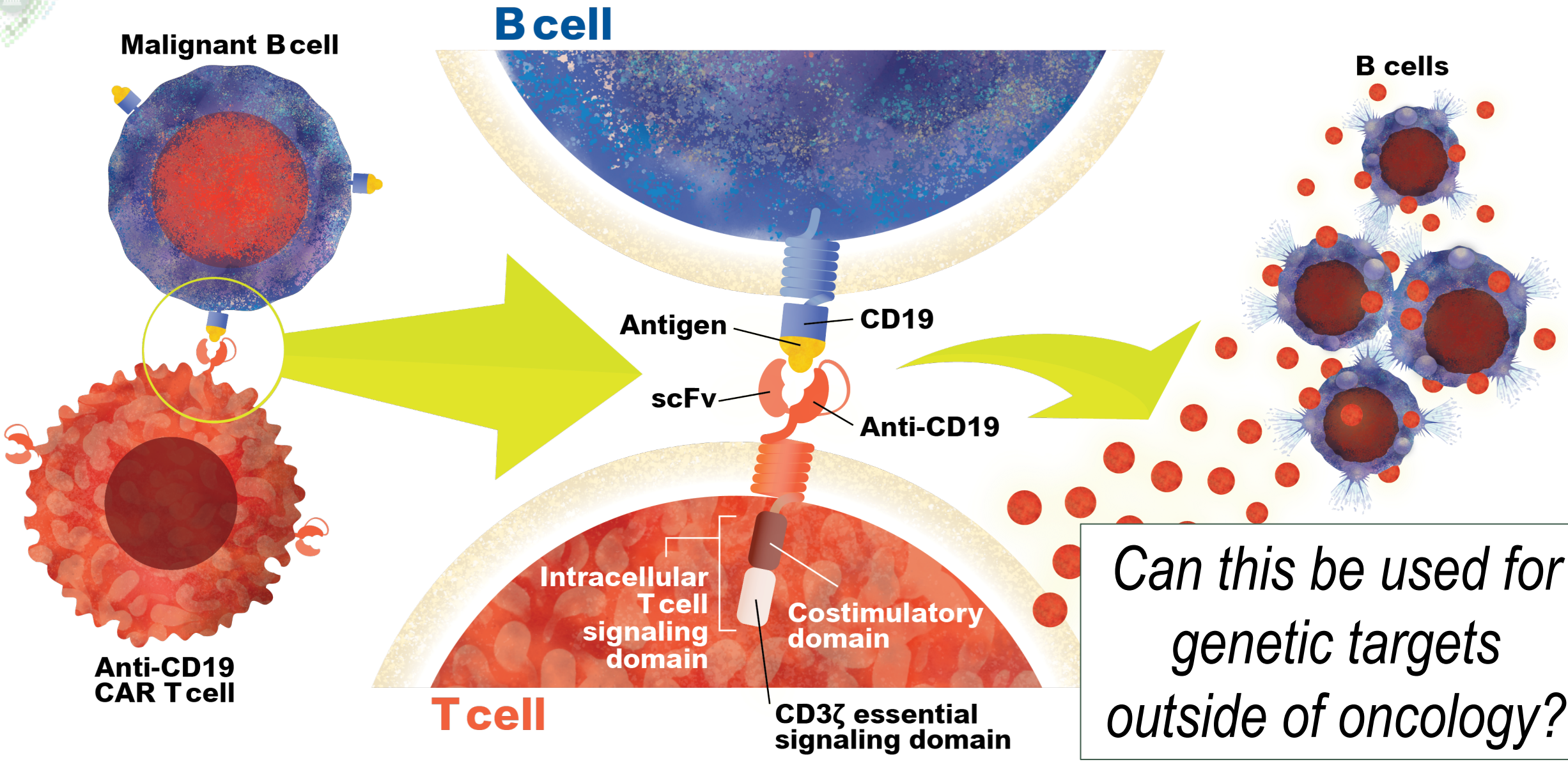
Alnylam Announces FDA Acceptance of New Drug Application (NDA) and Priority Review Status for Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR (hATTR) Amyloidosis

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.

CAR-T therapy for B cell cancers



Can this be used for genetic targets outside of oncology?