

Unifying principles and AI to transform drug research and development (R&D)

Robert Plenge, MD-PhD

EVP, Chief Research Officer

Problem statements and solutions

Biopharma R&D is...



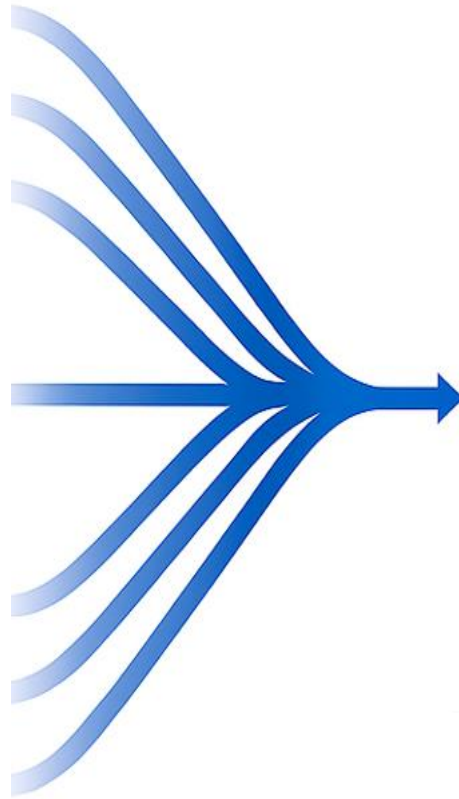
Failure-prone



Expensive



Inefficient



We can solve this by...

- Adhering to rigorous **R&D principles** grounded in causal human biology
- Integrating **AI and automation** to improve efficiency, shorten decision cycles, and enhance the quality of IND output

Problem statements and solutions

Biopharma R&D is...



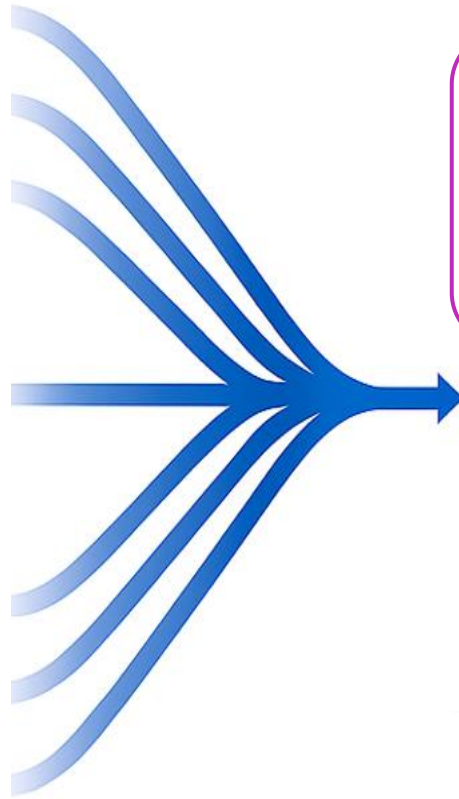
Failure-prone



Expensive



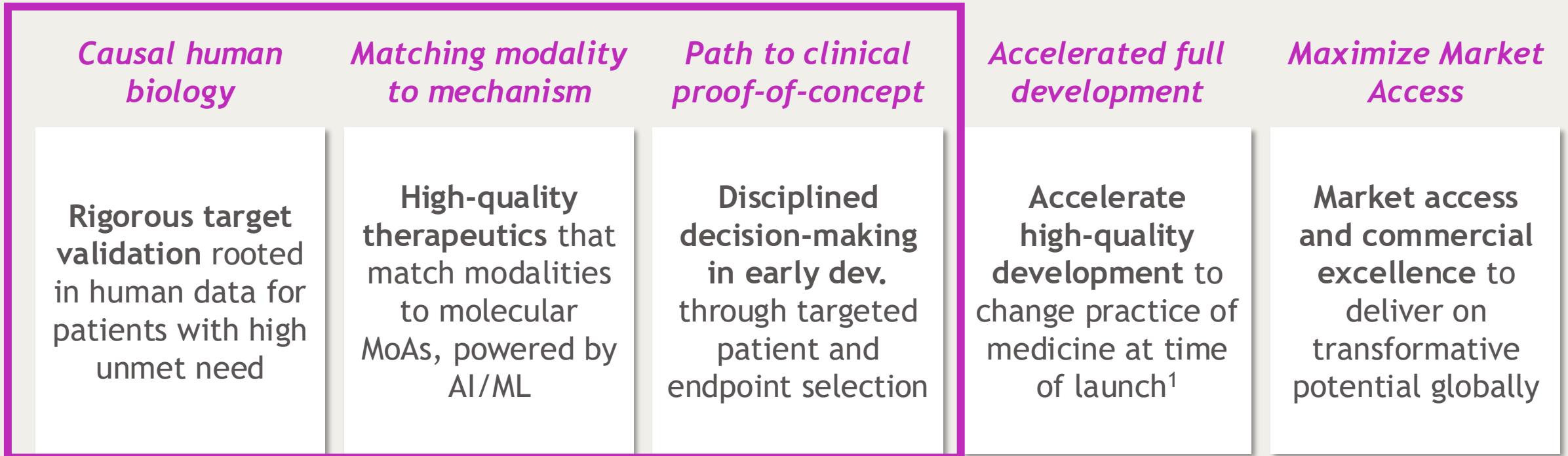
Inefficient



We can solve this by...

- Adhering to rigorous **R&D principles** grounded in causal human biology
- Integrating **AI and automation** to improve efficiency, shorten decision cycles, and enhance the quality of IND output

Our end-to-end R&D principles to achieve top-tier R&D productivity



We apply these principles to (1) advance high-quality programs with transformational potential and increased PoS in clinical development; (2) minimize misalignment across the R&D continuum; and (3) enable decision-making by creating a common language to evaluate and prioritize programs.

1. Indication expansion should adhere to same basic principles and considered in the context of LCM value opportunity with agreed ROI

TYK2 inhibitor (Sotyktu) recapitulates human genetics and has shown clinical benefit in psoriasis and SLE



Causal human biology

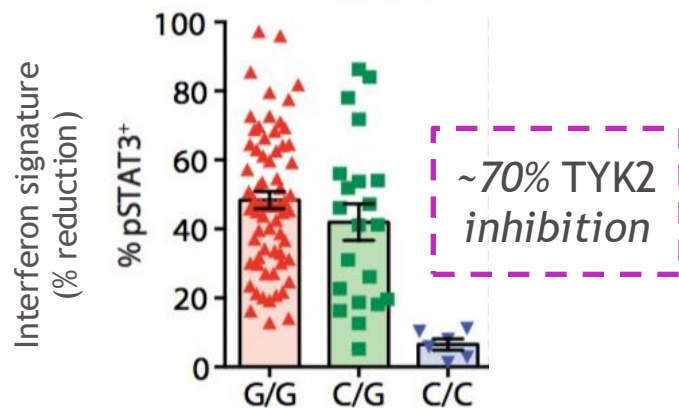


Matching modality to mechanism

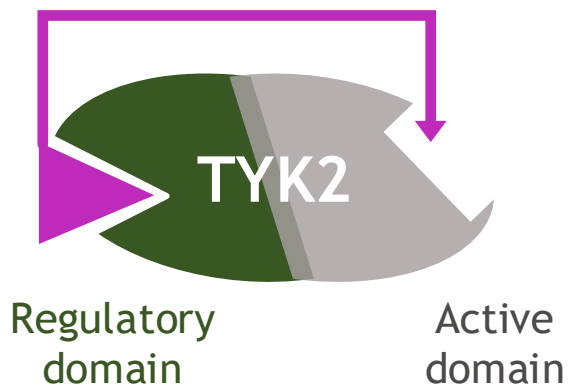


Path to clinical proof-of-concept

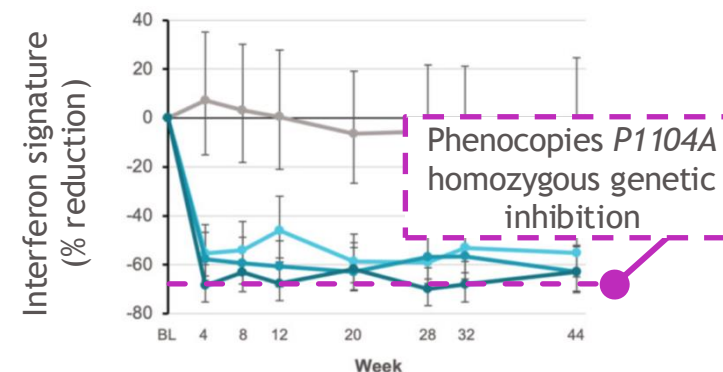
Human genetics (*P1104A*): implicates TYK2 in multiple immunologic diseases



Allosteric inhibitor: A highly selective small-molecule drug



Initially psoriasis: now systemic lupus erythematosus (SLE)



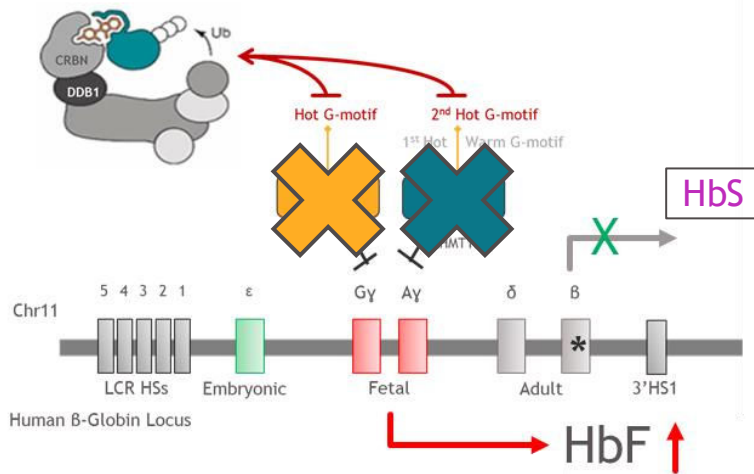
Sotyktu is approved in psoriasis, and BMS has two ongoing Phase 3 registrational studies with Sotyktu in SLE

HbF activating CELMoD™ (BMS-986470), which selectively degrades ZBTB7A and WIZ, recapitulates human genetics and has shown pre-clinical benefit *ex vivo* in SCD patient blood



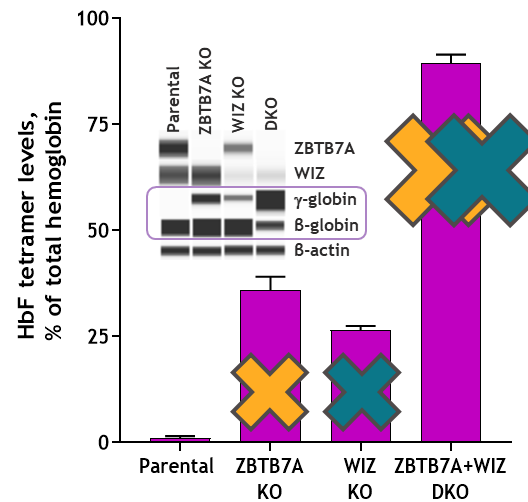
Causal human biology

Degradation of repressors (WIZ and ZBTB7A) induces higher levels of HbF



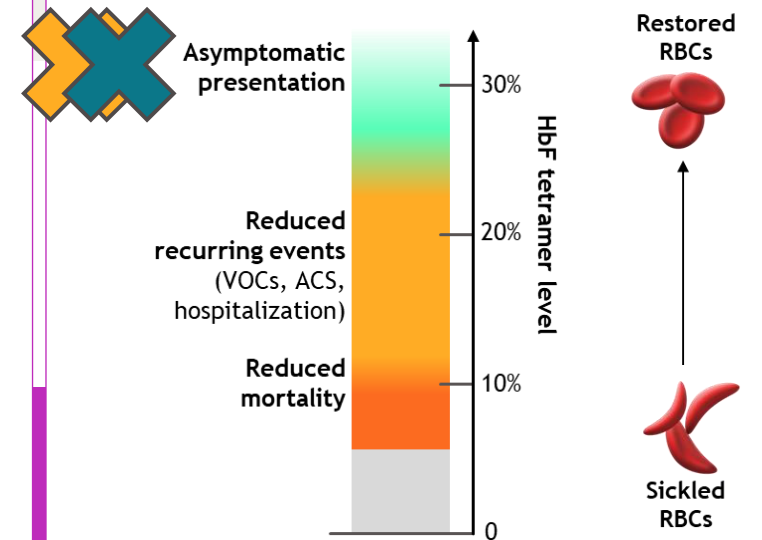
Matching modality to mechanism

Genetic silencing of ZBTB7A and WIZ synergistically induces HbF



Path to clinical proof-of-concept

Elevating HbF levels can improve the comorbidities associated with SCD



BMS-986470 is currently enrolling for a Phase 1/2a PoC study (CA230-1019) and has transformative potential for SCD

CD19 cell therapy approaches to induce immune reset in multiple autoimmune disease indications



Causal human biology

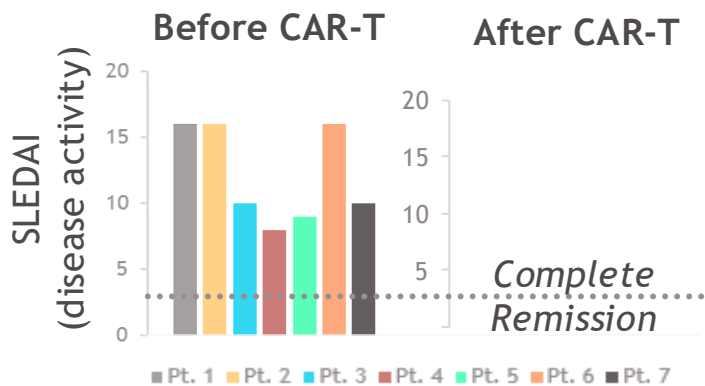


Matching modality to mechanism



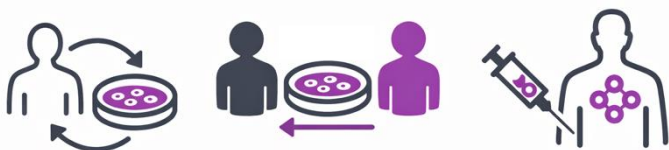
Path to clinical proof-of-concept

Academic study of CD19 CAR T: B cell memory reset and functional cure in SLE



Adapted from Taubmann, J., et al EULAR (2023): 93-94

Autologous, allogeneic & in vivo programs to induce immune reset

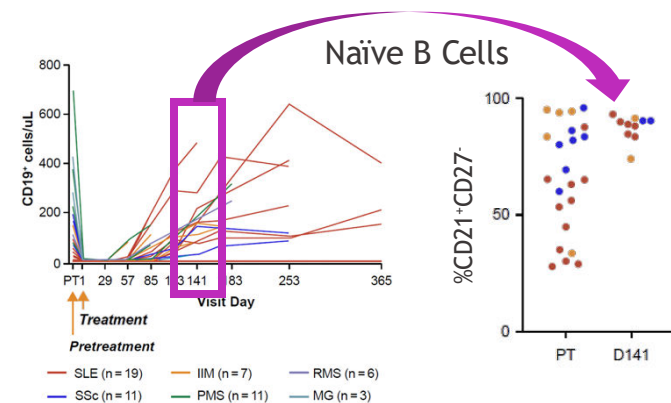


Zola-cel: Autologous CD19 CAR T on NEX T platform

BMS-986515: Healthy donor allogeneic CD19 CAR T

BMS-986553, OTX-201: In vivo LNP-circ RNA CD19 CAR T

Zola-cel: robust B cell depletion with recovery of naïve B cells across AID indications



Zola-cel pivotal trials underway in SLE and SSc, HD Allo Ph1 enrolling, and CD19 in vivo CAR T IND planned for 2026

Problem statements and solutions

Biopharma R&D is...



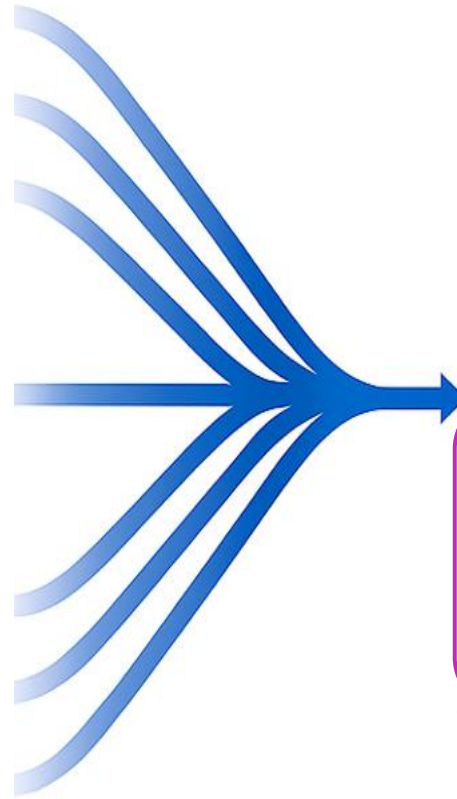
Failure-prone



Expensive



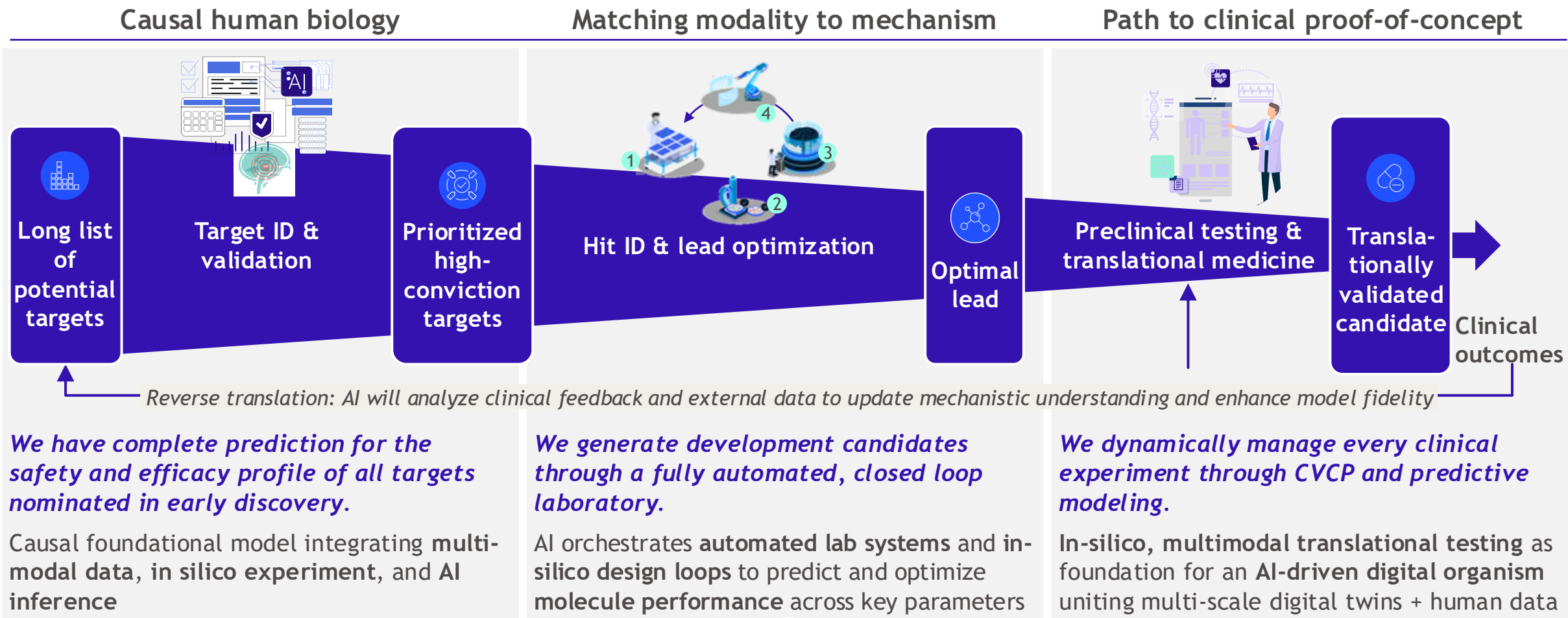
Inefficient



We can solve this by...

- Adhering to rigorous **R&D principles** grounded in causal human biology
- Integrating **AI and automation** to improve efficiency, shorten decision cycles, and enhance the quality of IND output

Our aspiration (**dream**): AI-enabled research organization of the future

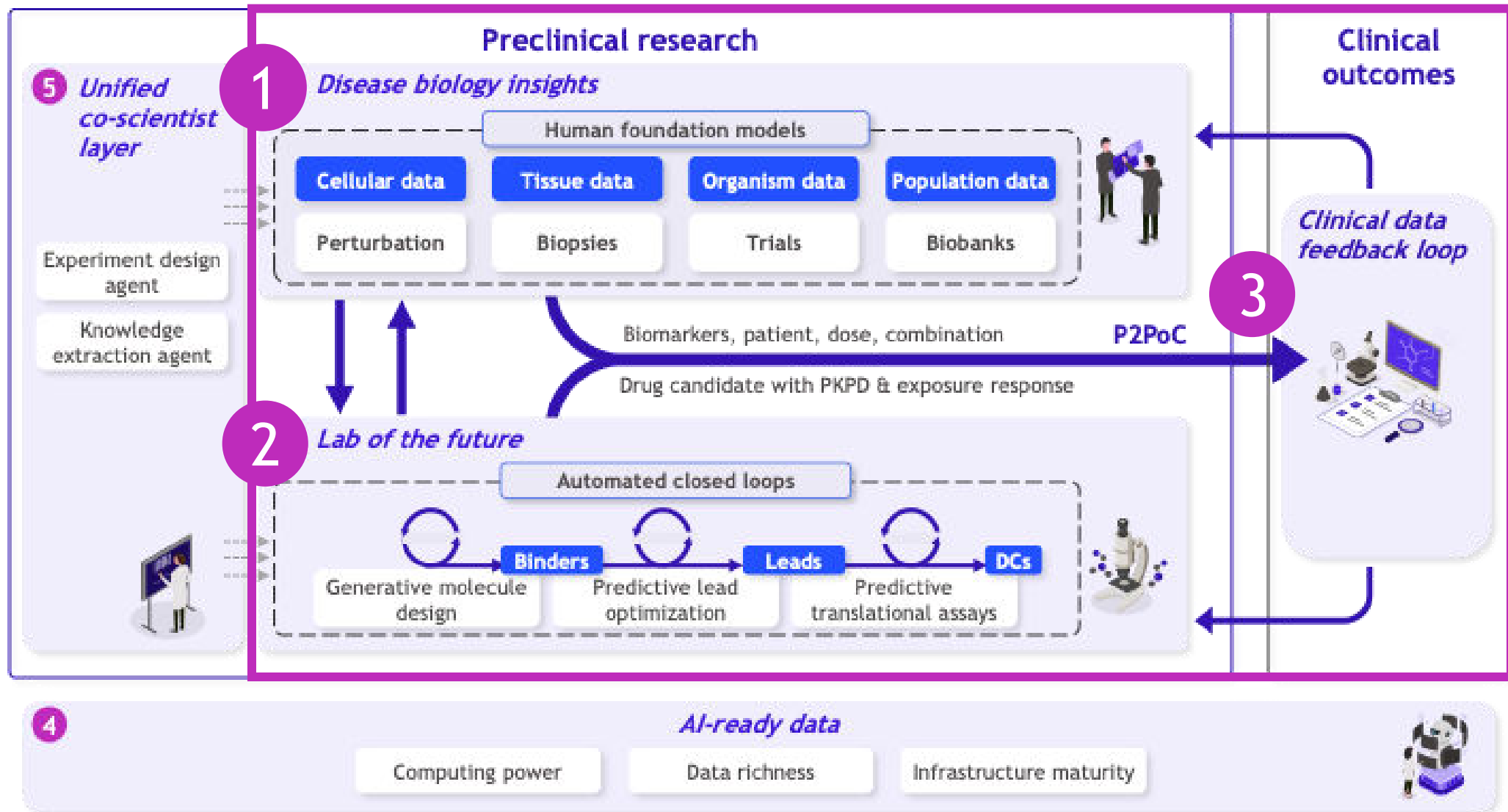


Expand portfolio with improved prioritization

Faster cycle speed with fewer iterations

Increased PoS in development

Our practical implementation (**build**): five interdependent capabilities to build an AI-driven R&D engine



1. Low: early momentum with limited/fragmented pilots; Medium: early proof points emerging; High: on a clear path to future state with coordinated build underway and sizable impact to date

Re-Imagining TYK2 Discovery in the AI Era

How We Discovered Sotyktu

Empirical Discovery

Phenotypic Pathway Screen

Broader disease-relevant mechanism screening



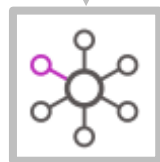
Sequential Deconvolution

Serendipitous allosteric MOA finding



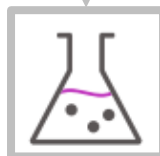
Allosteric Site Screen

Allosteric site chemistry expansion



Lead Optimization

Drug-like property optimization



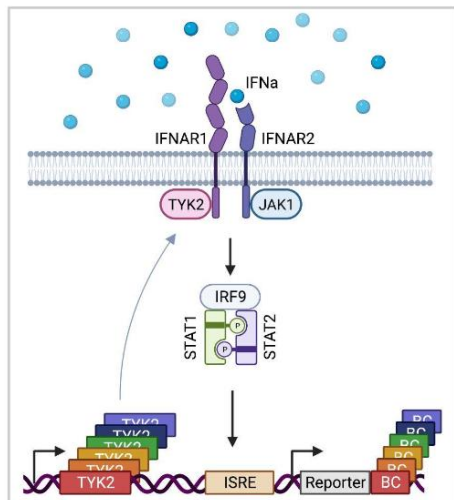
~5-7 years

Screen to Candidate

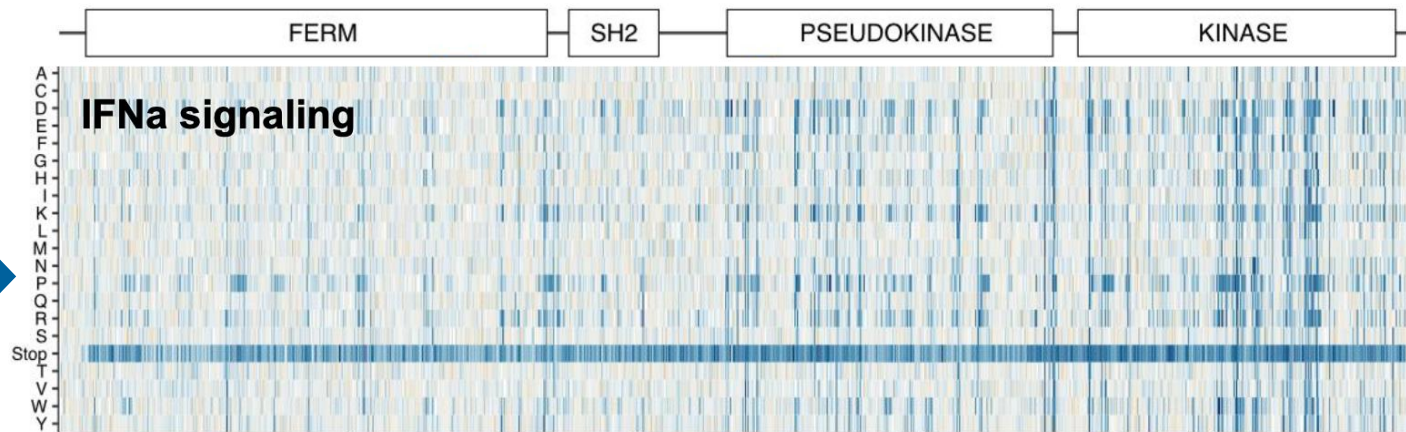
*Do we have the data to
build the right AI models?*

1

We partnered with Octant to test >20,000 TYK2 variants in two deep mutational scans (DMS)

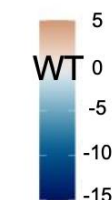


~11%



z-statistic

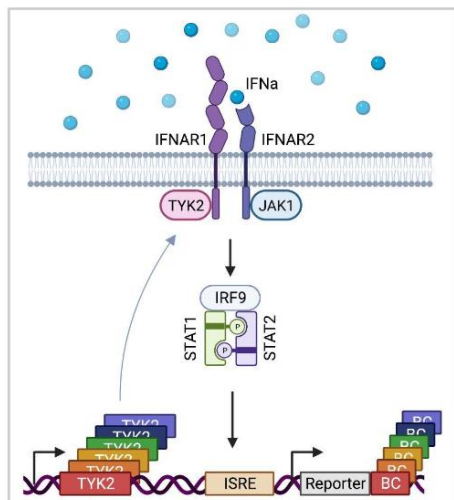
GoF



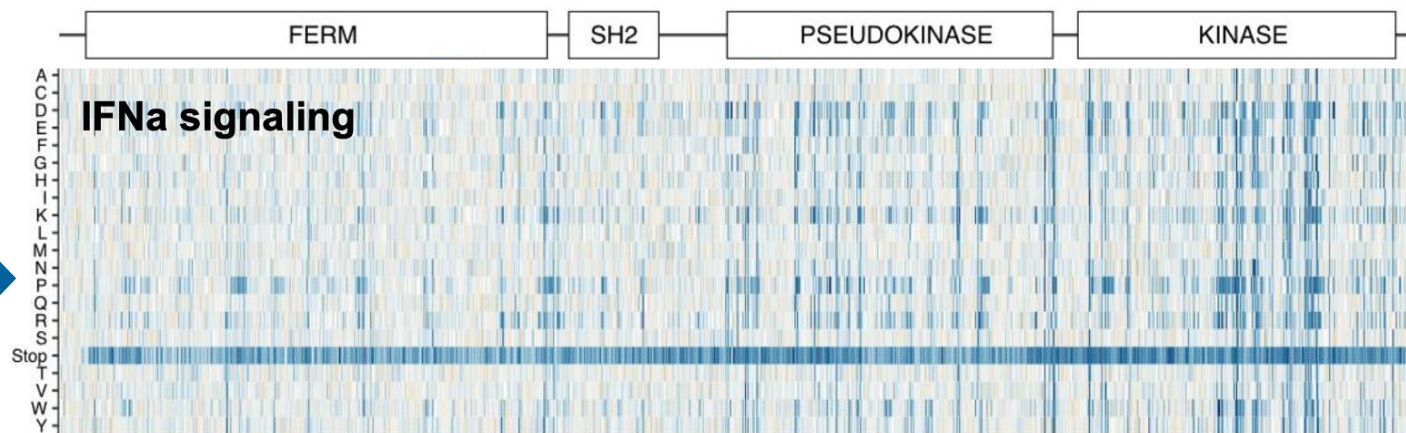
LoF

1

We partnered with Octant to test >20,000 TYK2 variants in two deep mutational scans (DMS)



~11%



z-statistic

GoF

5

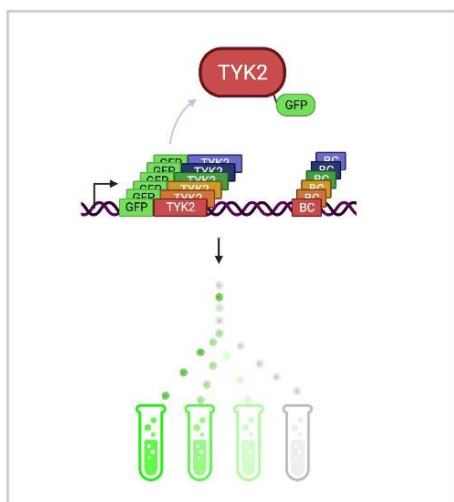
WT 0

-5

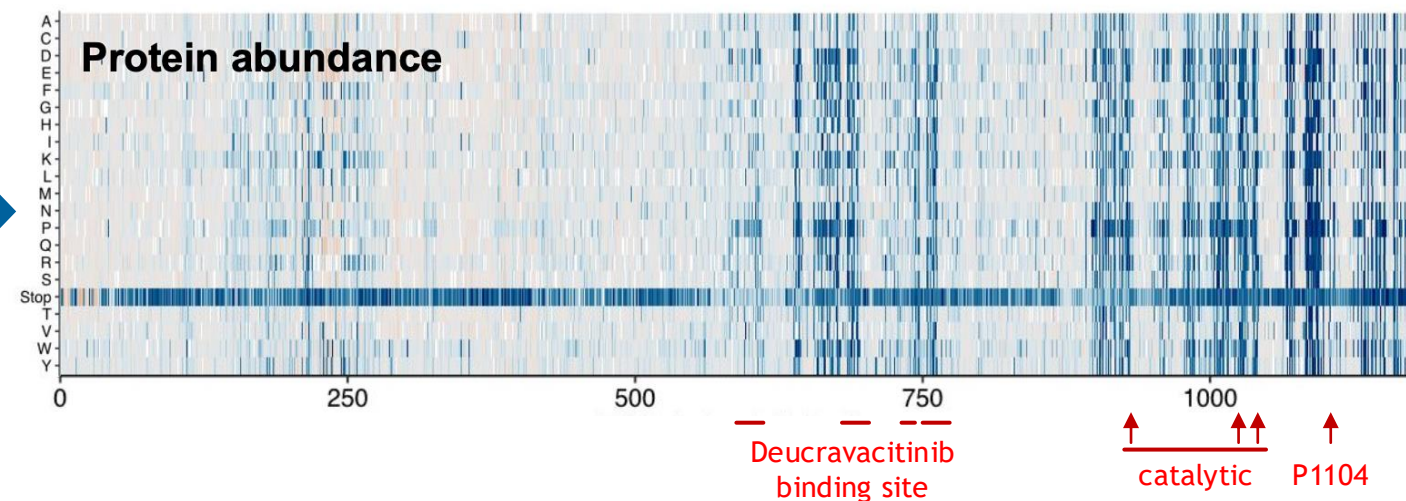
-10

-15

LoF



~20%

Deucravacitinib
binding site

catalytic P1104

Future state: gather additional functional information on all genetic variants to identify druggable sites that are also functional. [eLife](#). 2026; 15: RP110149

Re-Imagining TYK2 Discovery in the AI Era

How We Discovered Sotyktu

Empirical Discovery

Phenotypic Pathway Screen

Broader disease-relevant mechanism screening



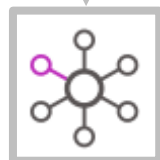
Sequential Deconvolution

Serendipitous allosteric MOA finding



Allosteric Site Screen

Allosteric site chemistry expansion



Lead Optimization

Drug-like property optimization



~5-7 years

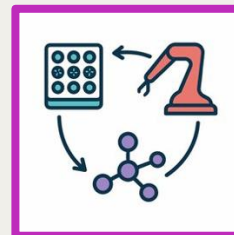
Screen to Candidate

How We'd Discover Sotyktu Today

Prediction-Driven, Mechanism-Informed Discovery

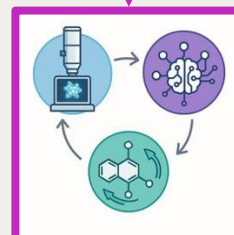
Mechanism-Guided Lead Discovery

Lead discovery enriched by structure-function insights from human genetics and functional genomics (TYK2 Octant collaboration)



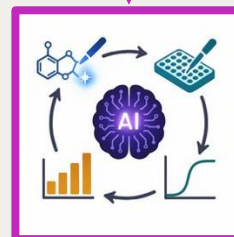
Prediction & Structure Informed Design

Cryo-EM and structure prediction (physics and ML)-enabled rational molecular design and chemistry exploration



Multi-Parameter Optimization

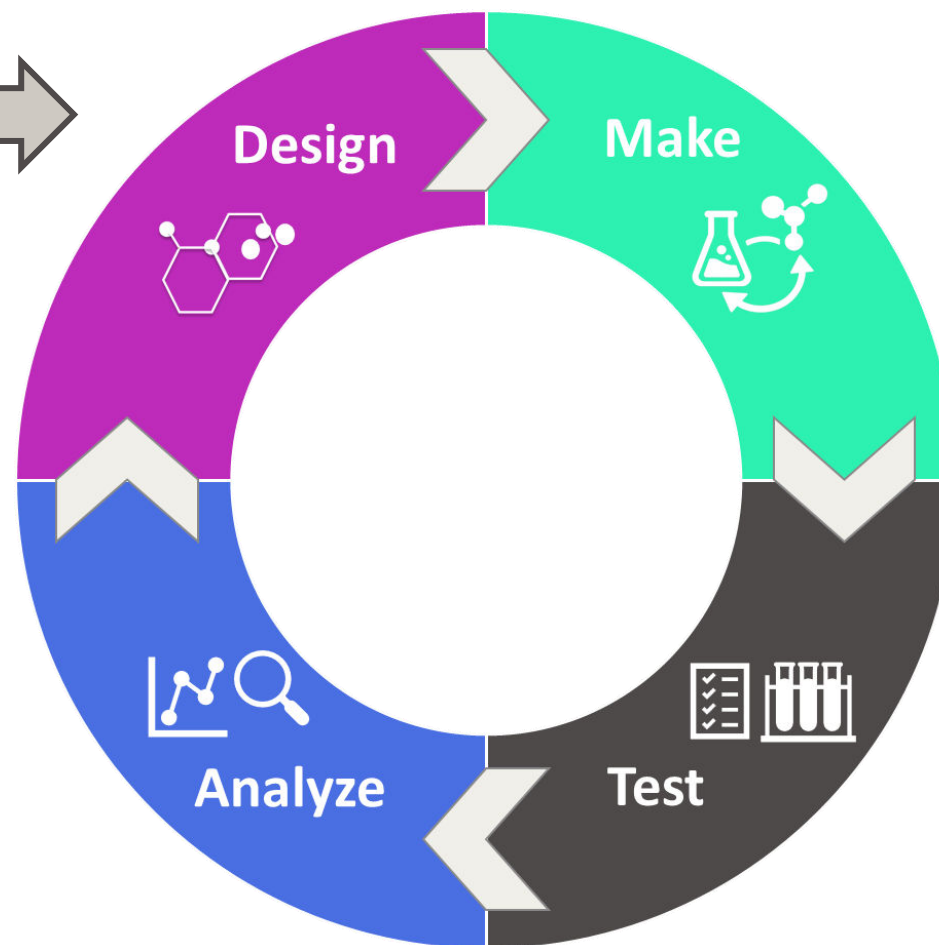
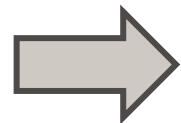
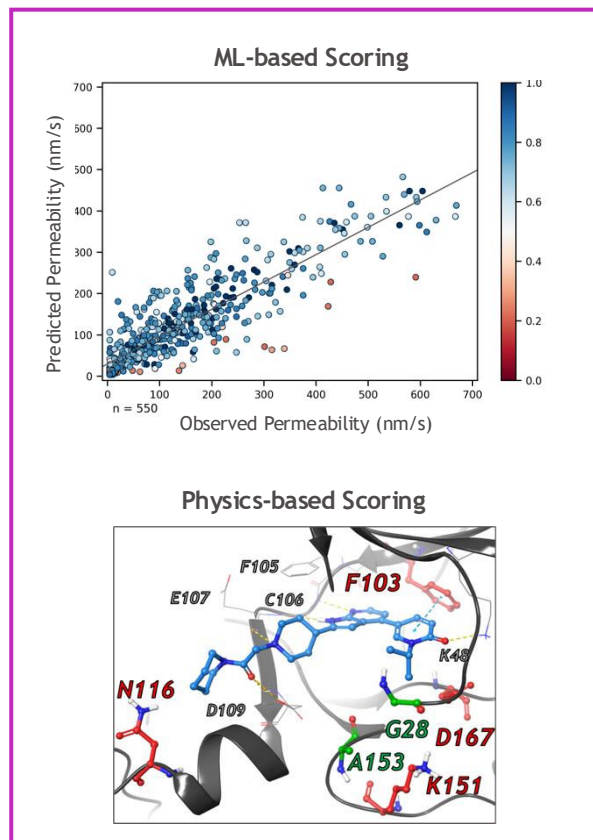
PredictFirst-guided drug property optimization using disease relevant SAR assays, powered by Lab-in-the-Loop



~3.5 years?

Screen to Candidate

Bringing Predict First to small molecules



Key aspects of strategy

Technology

Use every data point and computation to predict and prioritize the best molecules.

Process

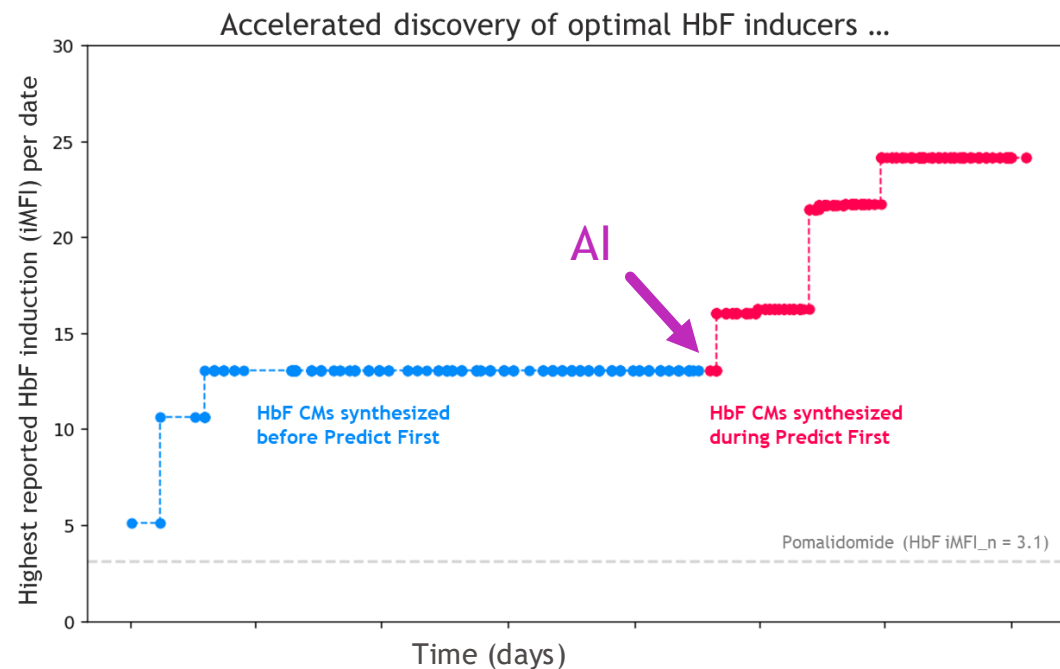
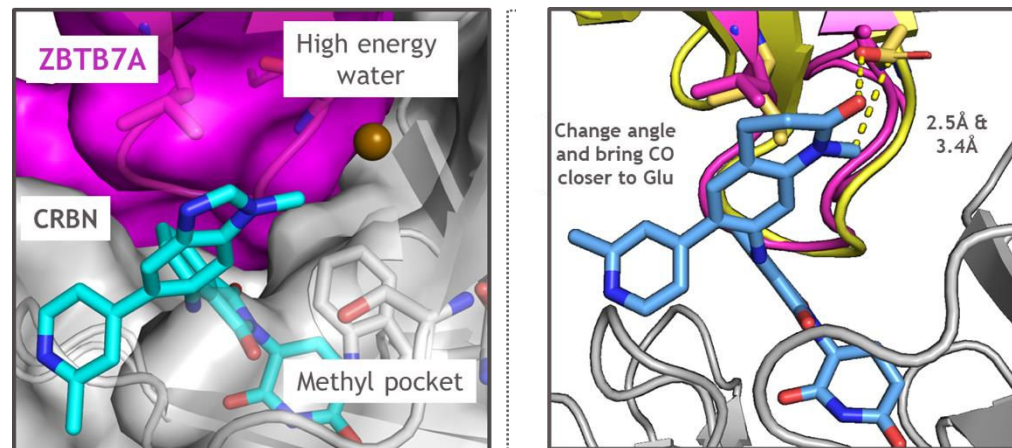
Embed computational scientists into core teams to drive design quality at scale.

People

Recruit, train, and cultivate a predictive culture across the organization.

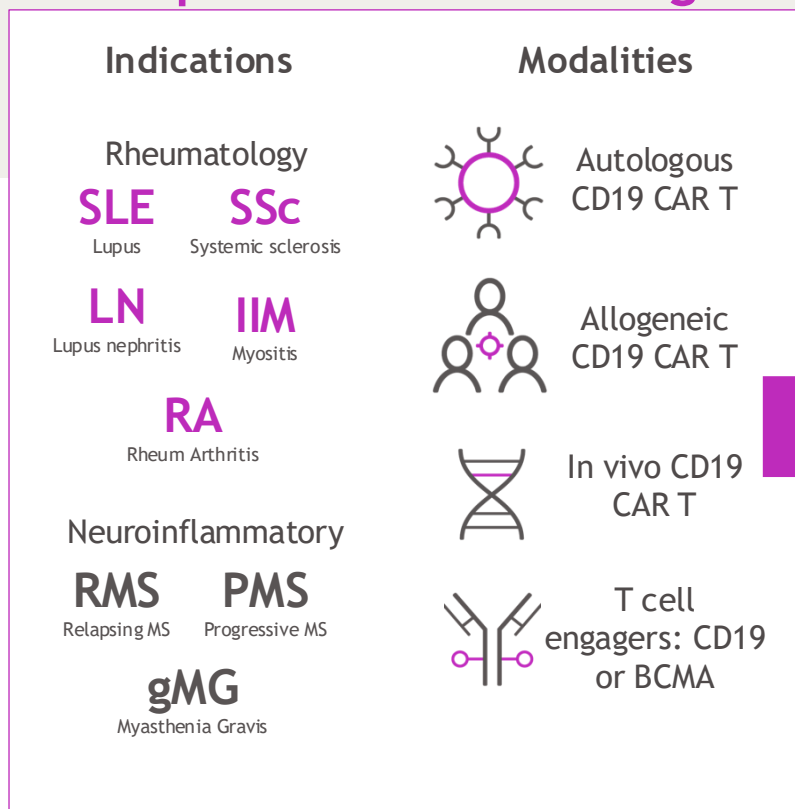
Dual WIZ and ZBTB7A degrader for sickle cell disease was an early adopter of Predict First

- Machine Learning, physics-based design and Medicinal Chemistry drove optimization from hit to BMS-986470
- BMS-986470 has entered clinical trial evaluation in healthy volunteers and patients with SCD, with demonstration of both WIZ and ZBTB7A degradation in Phase 1 studies (NCT06481306)

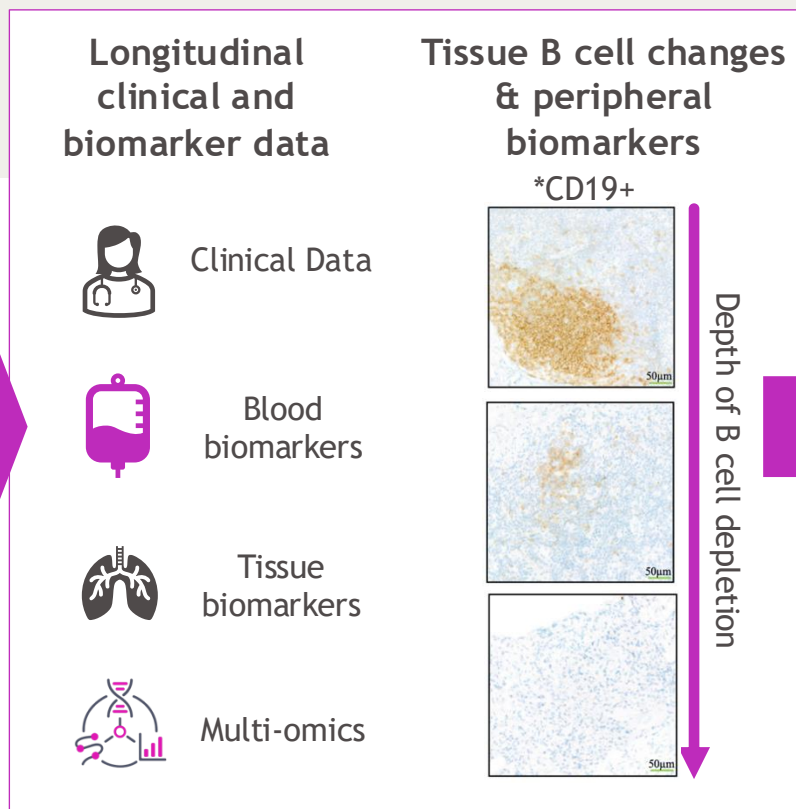


Translational strategies to define immune reset and biomarkers of response across autoimmune disease

Leverage data across autoimmune indications using multiple modalities & targets



Link clinical and translational data with markers of durable immune reset



Accelerate development decision-making and match modality to patient & disease

- ❑ Define peripheral signature of complete immune reset and early surrogate biomarkers of durable response
- ❑ Determine barriers to immune reset: optimize target antigen selection, dose/schedule, and identify patient segments
- ❑ Long term, build atlas of disease subtypes matched to optimal immune reset therapy

Conclusions



Problem statement: drug R&D remains failure prone, expensive, and inefficient



End-to-end R&D principles: high conviction targets paired with the right modality, unlock novel biology and clinical differentiation.



AI and automation: scale these principles to improve speed, quality, and probability of success across the pipeline - ***dream and build!***