Bristol Myers Squibb®

Managing an R&D portfolio through the critical value creation period (CVCP)

Robert Plenge, MD-PhD

EVP, Chief Research Officer

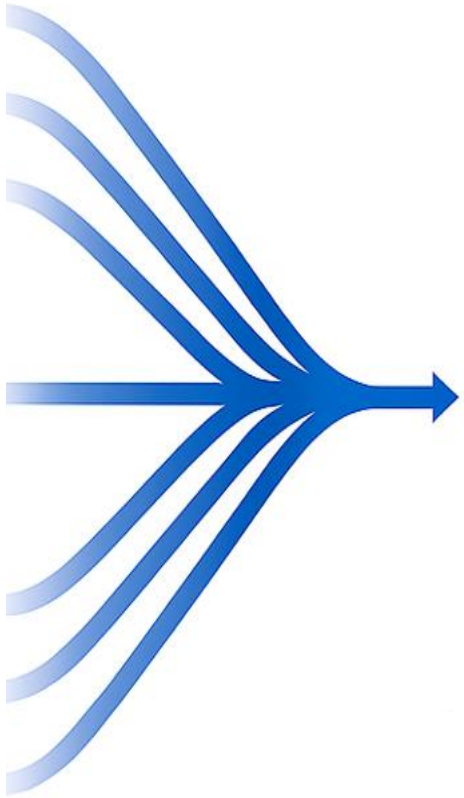
Problem statements and solutions

Biopharma R&D is…

Failure-prone

Expensive

Inefficient



We can solve this by…

- Adhering to rigorous R&D principles and managing through clinical proof-of-concept (PoC)
- Integrating AI and automation to improve efficiency, shorten decision cycles, and enhance the quality of IND output

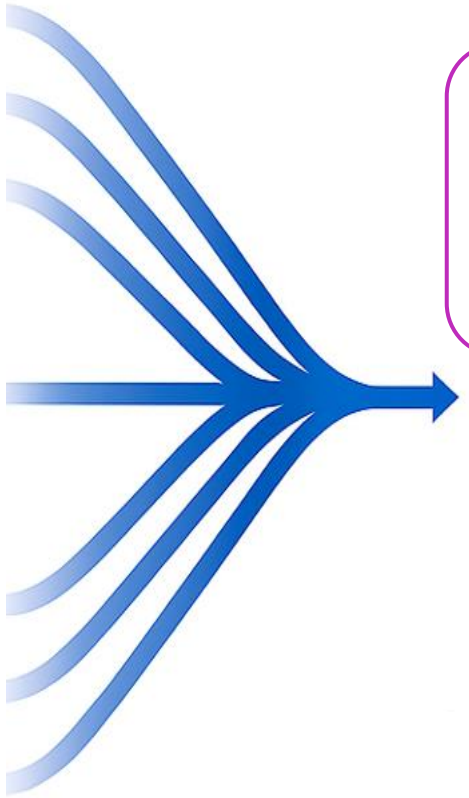
Problem statements and solutions

Biopharma R&D is…

Failure-prone

Expensive

Inefficient



We can solve this by…

- Adhering to rigorous R&D principles and managing through clinical proof-of-concept (PoC)
- 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

Causal human biology	*Matching modality to mechanism*	*Path to clinical proof-of-concept*	*Accelerated full development*	*Maximize Market Access*
Rigorous target validation rooted in human data for patients with high unmet need	**High-quality therapeutics** that match modalities to molecular MoAs, powered by AI/ML	**Disciplined decision-making in early dev.** through targeted patient and endpoint selection	**Accelerate high-quality development** to change practice of medicine at time of launch[1]	**Market access and commercial excellence** to deliver on transformative potential globally

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

Bristol Myers Squibb®

What is the inflection point that creates the most value in biopharma?

The critical value creation period (CVCP)

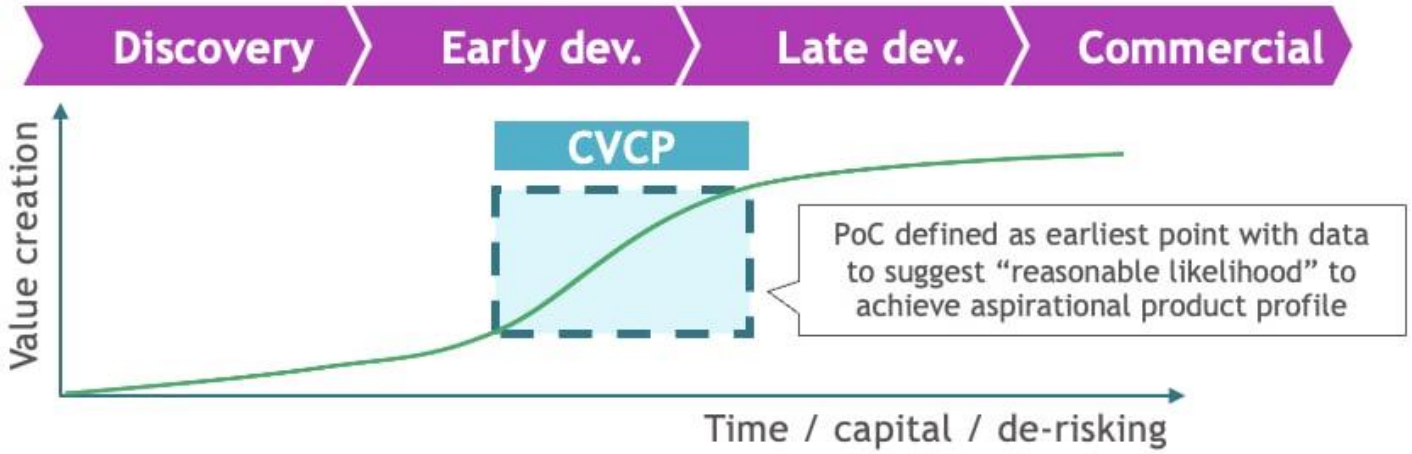
Key assumptions

Not possible to predict a stable vs mega-blockbuster product until PoC is completed

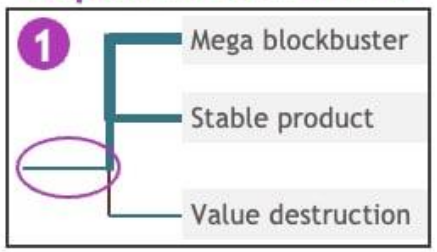
However, we can **estimate commercial potential** by defining an aspirational product profile

Important to define path to high quality PoC to achieve aspirational product profile up-front and understand the time & cost needed

Critical Value Creation Period (CVCP) Model

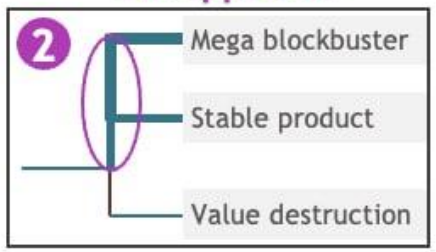


Minimize time and capital to clinical PoC



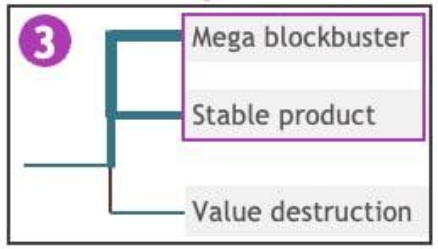
How much time and money is required to deliver PoC and an aspirational product profile?

Increase POS at PoC and approval



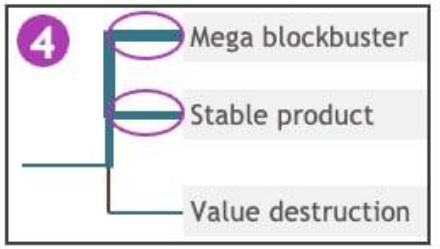
What is the probability to achieve the aspirational product profile, based on R&D principles?

Increase ratio of MBBs to stable products



What trade-offs are needed to increase the ratio of MBBs to stable products; how does this vary by TA?

Increase speed to high-value markets

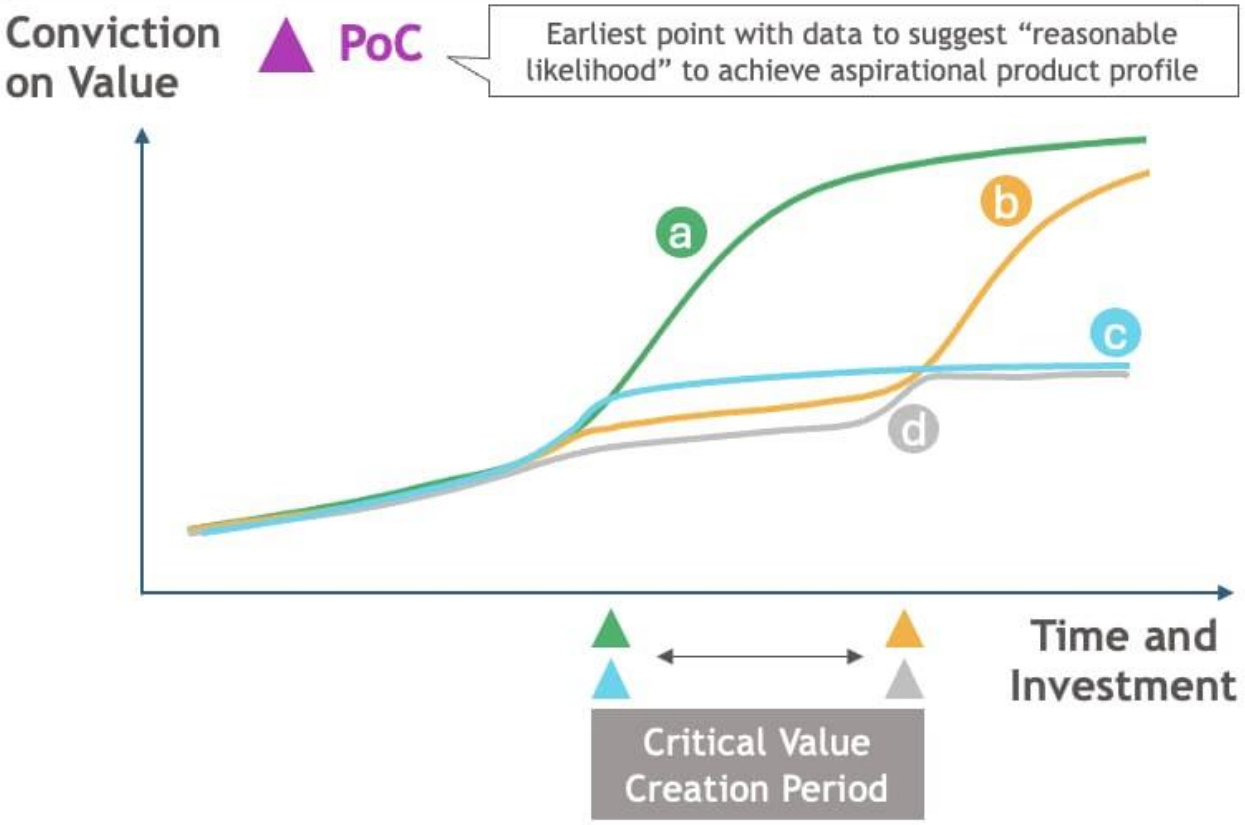


How can we accelerate clinical development once PoC is achieved?

https://plengegen.com/blog/cvcp/

Four examples of programs that navigate the CVCP

Causal human biology | Matching modality to mechanism | **Path to clinical proof-of-concept** | Accelerated full development | Maximize market access

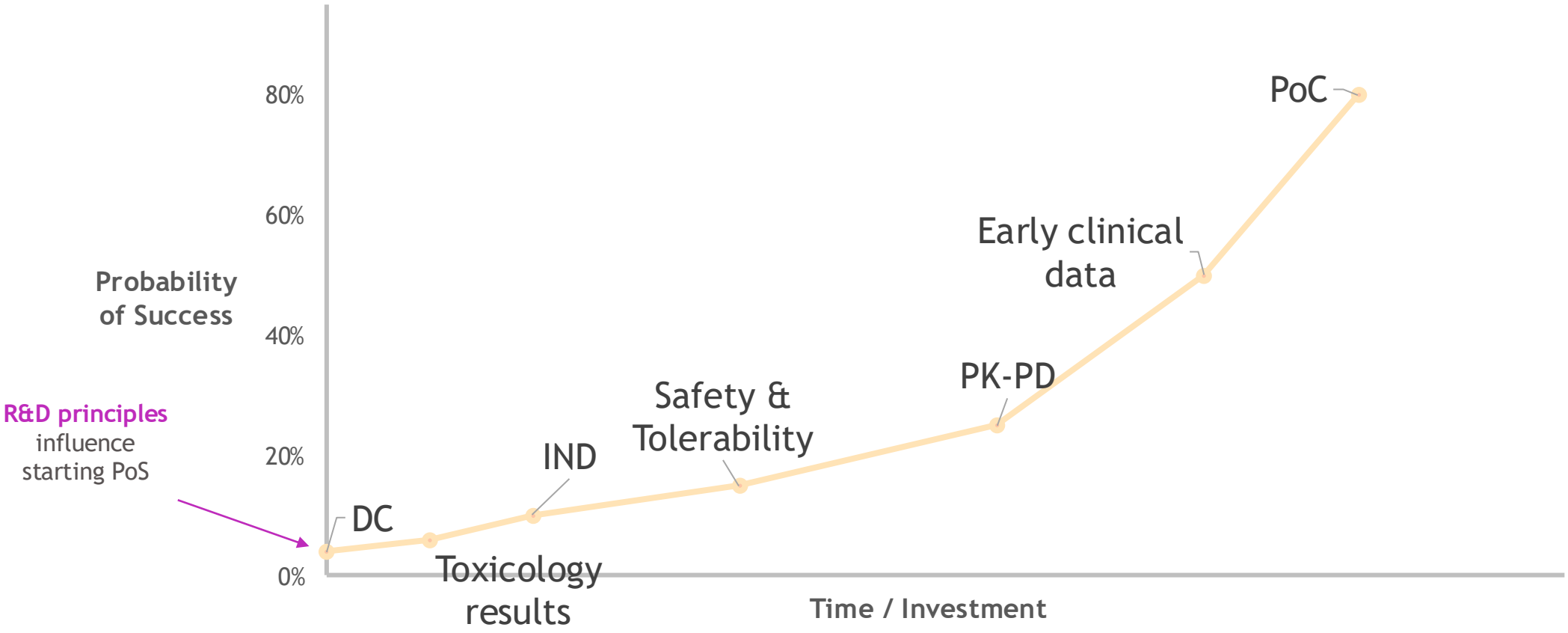


We need to tailor our approach to different assets on time and investment towards PoC

- a **Early evidence of MBB potential:** invest capital to accelerate
- b **Long time or high investment required to determine MBB potential:** optimize path to aspirational product profile
- c **Stable product potential:** reach PoC cost-efficiently
- d **Long time or high investment for stable product:** consider termination

https://plengegen.com/blog/cvcp/

We are developing capabilities to monitor CVCP inflection points – and to manage our Research portfolio



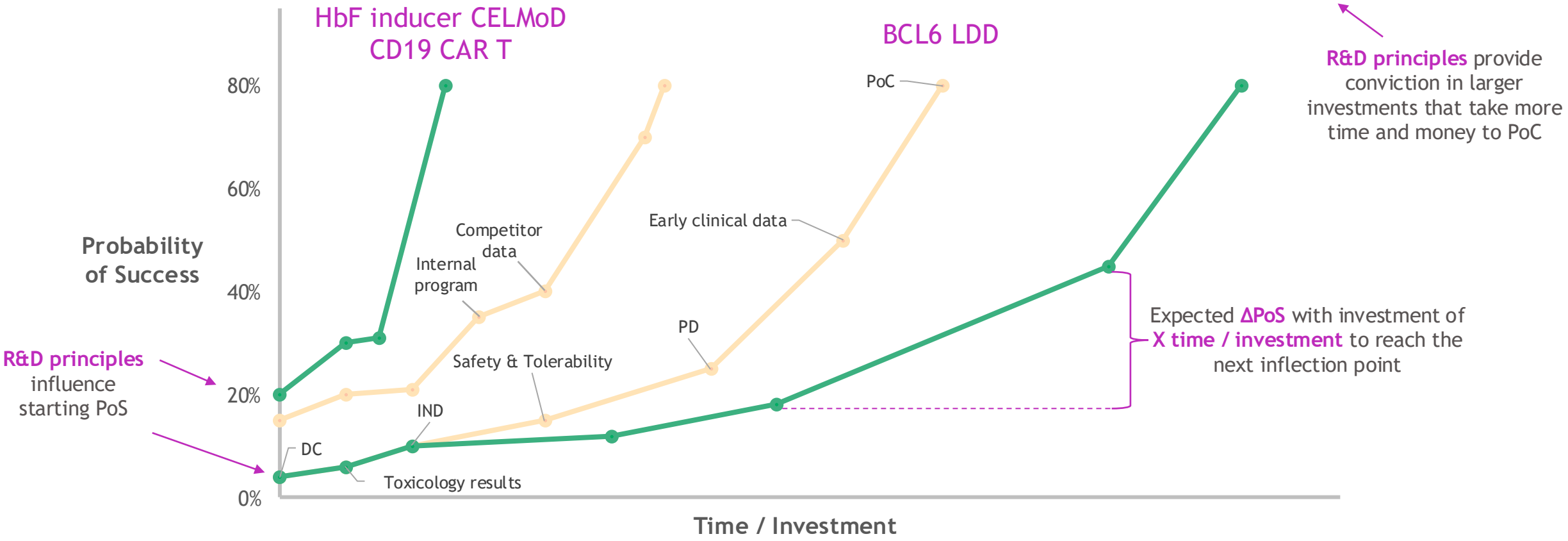
Bristol Myers Squibb®

We are developing capabilities to monitor CVCP inflection points – and to manage our Research portfolio

Fast path to PoC: ideal scenario, regardless of commercial potential

Medium path to PoC: acceptable for medium and large commercial opportunities

Slow path to PoC: acceptable only for large commercial opportunities



R&D principles provide conviction in larger investments that take more time and money to PoC

R&D principles influence starting PoS

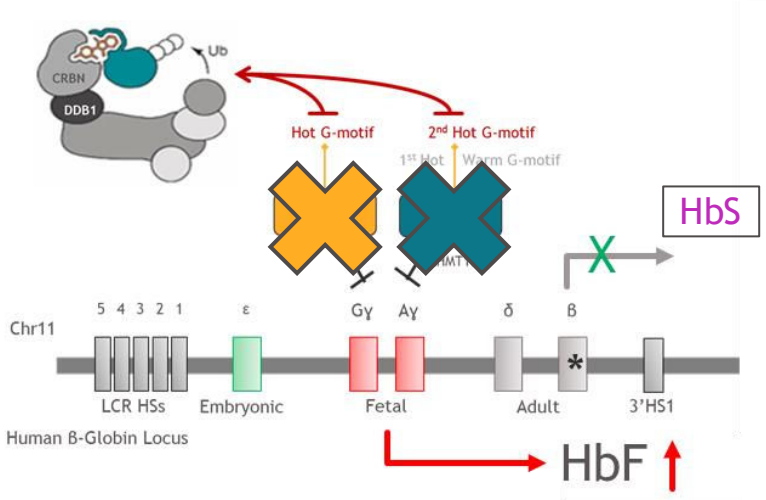
Expected **ΔPoS** with investment of **X time / investment** to reach the next inflection point

Bristol Myers Squibb®

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

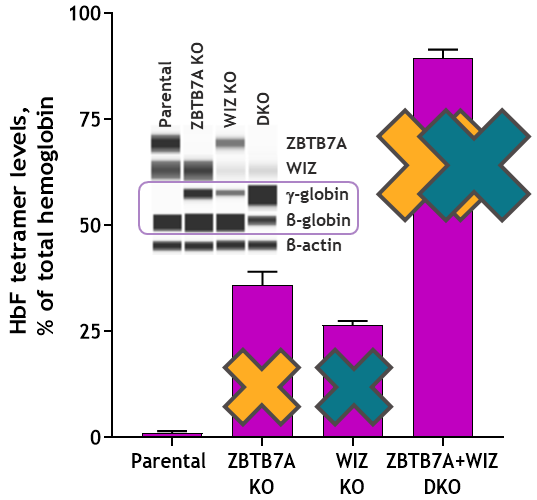
Causal human biology

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



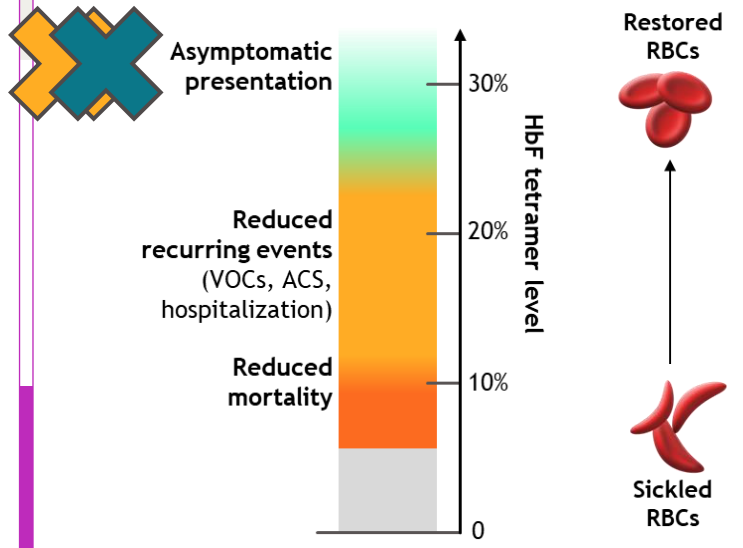
Matching modality to mechanism

Genetic silencing of ZBTB7A and WIZ synergistically induces HbF



Path to clinical proof-of-concept

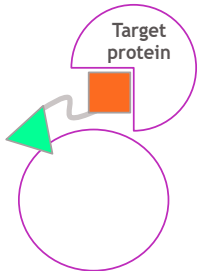
Elevating HbF levels can improve the comorbidities associated with SCD



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

Bristol Myers Squibb®

ACS, acute chest syndrome; DKO, double knockout; HbF, Fetal hemoglobin; KO, knockout; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis; WIZ, widely interspaced zinc finger protein; ZBTB7A, zinc finger and BTB domain containing 7A.



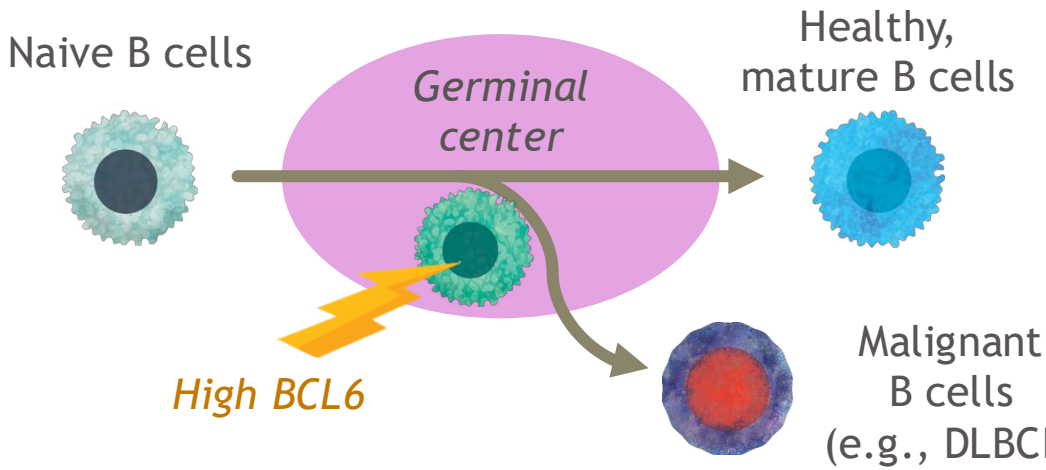
BMS-986458 is a novel ligand directed degrader (LDD) targeting BCL6 in lymphoma

Transformational potential

Oral small molecule medicine to treat B cell lymphomas driven by abnormalities in BCL6 signaling pathway.

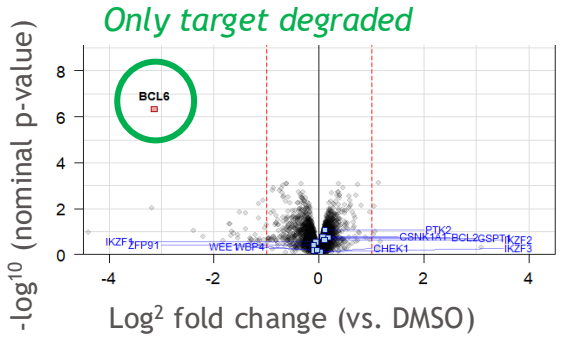
Causal human biology

Gain-of-function somatic *BCL6* mutations lead to B cell lymphomas and **deletion of *BCL6*** prevents B cell maturation.



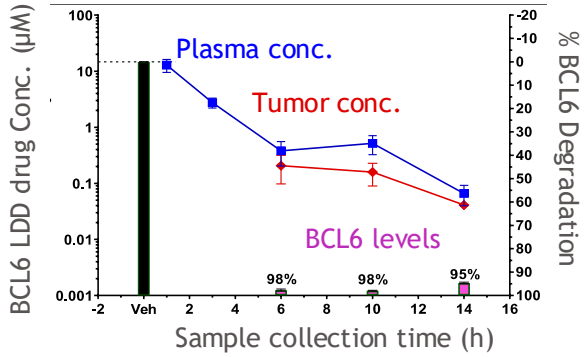
Matching modality to mechanism

We created a BCL6 LDD that has exquisite selectivity relative to the human proteome

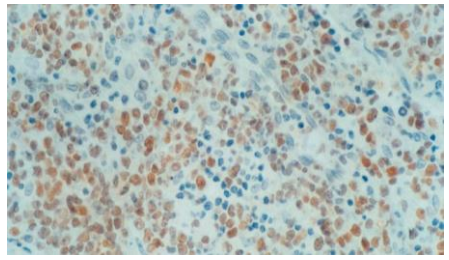


Path to clinical proof-of-concept

Correlate BCL6 degradation with clinical benefit



BCL6 IHC high expression in ~30% DLBCL

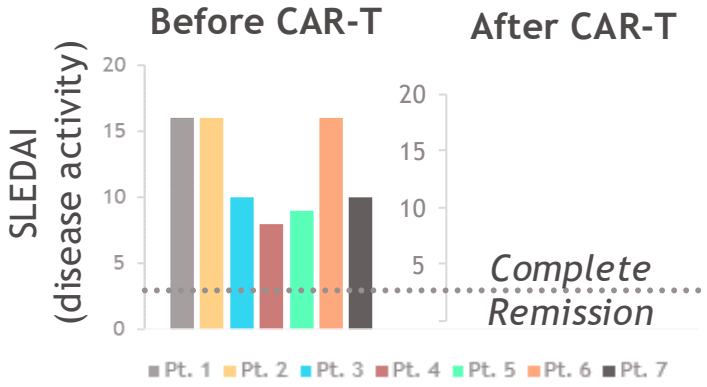


Bristol Myers Squibb®

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

Causal human biology

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

Matching modality to mechanism

Autologous, allogeneic & in vivo programs to induce immune reset



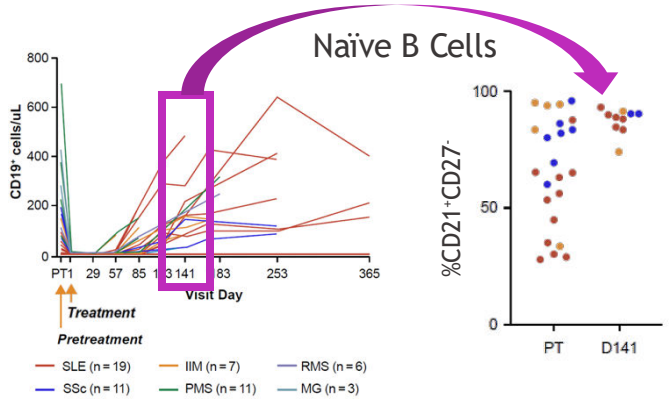
Zola-cel: Autologous CD19 CAR T on NEX T platform

BMS-986515: Healthy donor allogeneic CD19 CAR T

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

Path to clinical proof-of-concept

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

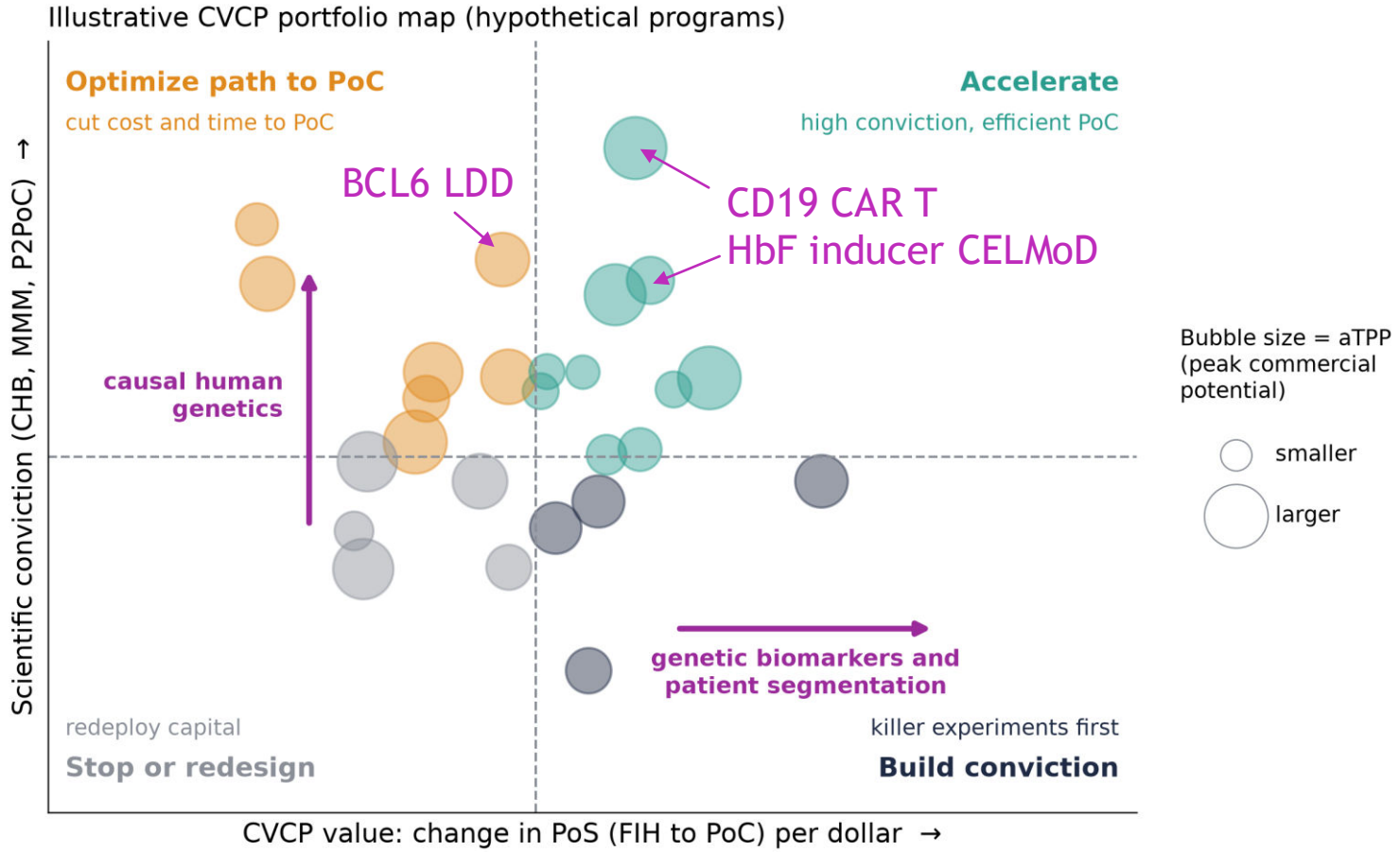
Bristol Myers Squibb®

Arthritis Rheumatol 2025 Oct; 77(Suppl 9): Abstract 0843, Abstract 1529, Abstract LB14

Transplant Cell Ther 2026 Feb; 32(2): S1 — Abstract #1

ILLUSTRATIVE ONLY; HYPOTHETICAL PROGRAMS

Portfolio view: conviction, CVCP value, aTPP on one map



Quadrant	Portfolio action
Accelerate	Fund fully; plan concurrent indications after PoC
Optimize path	Reduce cost and time to PoC with genetic segmentation and biomarkers
Build conviction	Run killer experiments before PoC spend
Stop or redesign	Redeploy capital to the upper right

Genetics moves bubbles: up through causal human biology, right through decisive and cheaper PoCs. Bubble size (aTPP) decides priority within a quadrant.

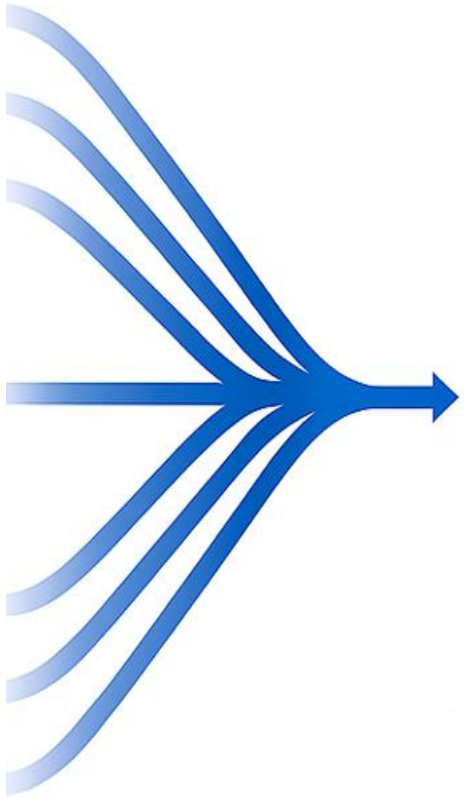
Problem statements and solutions

Biopharma R&D is…

Failure-prone

Expensive

Inefficient



We can solve this by…

- Adhering to rigorous R&D principles and managing through clinical proof-of-concept (PoC)
- 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

Causal human biology



Long list of potential targets

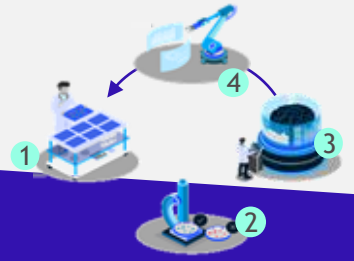
Target ID & validation

Prioritized high-conviction targets

We have complete prediction for the safety and efficacy profile of all targets nominated in early discovery.

Causal foundational model integrating **multi-modal data**, **in silico experiment**, and **AI inference**

Matching modality to mechanism



Hit ID & lead optimization

Optimal lead

We generate development candidates through a fully automated, closed loop laboratory.

AI orchestrates **automated lab systems** and **in-silico design loops** to predict and optimize **molecule performance** across key parameters

Path to clinical proof-of-concept



Preclinical testing & translational medicine

Transla-tionally validated candidate

Clinical outcomes

We dynamically manage every clinical experiment through CVCP and predictive modeling.

In silico, multimodal translational testing as foundation for an **AI-driven digital organism** uniting multi-scale digital twins + human data

Reverse translation: AI will analyze clinical feedback and external data to update mechanistic understanding and enhance model fidelity

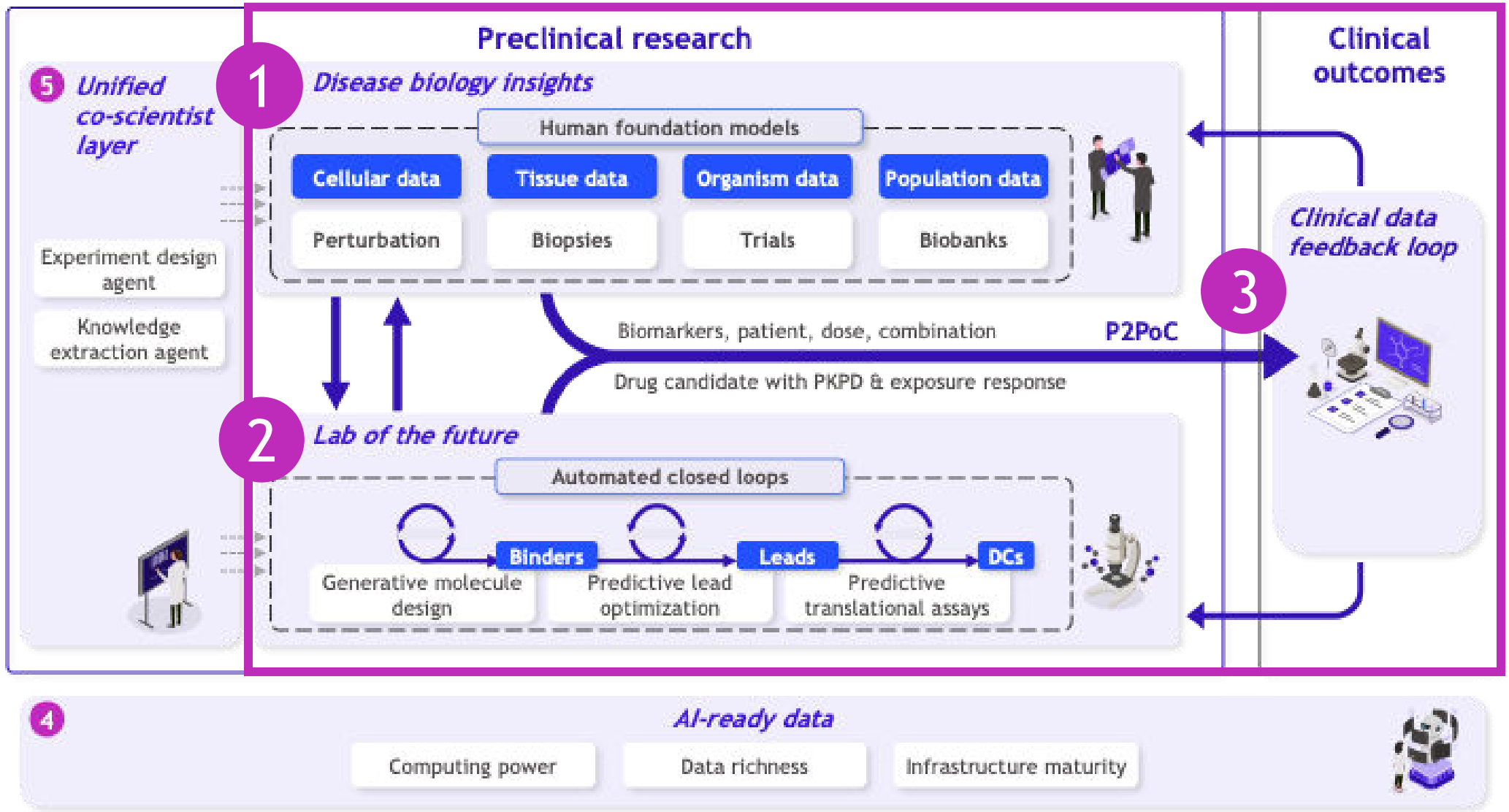
Expand portfolio with improved prioritization

Faster cycle speed with fewer iterations

Increased PoS in development

Bristol Myers Squibb®

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

Conclusions



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



R&D principles and **CVCP:** 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!***