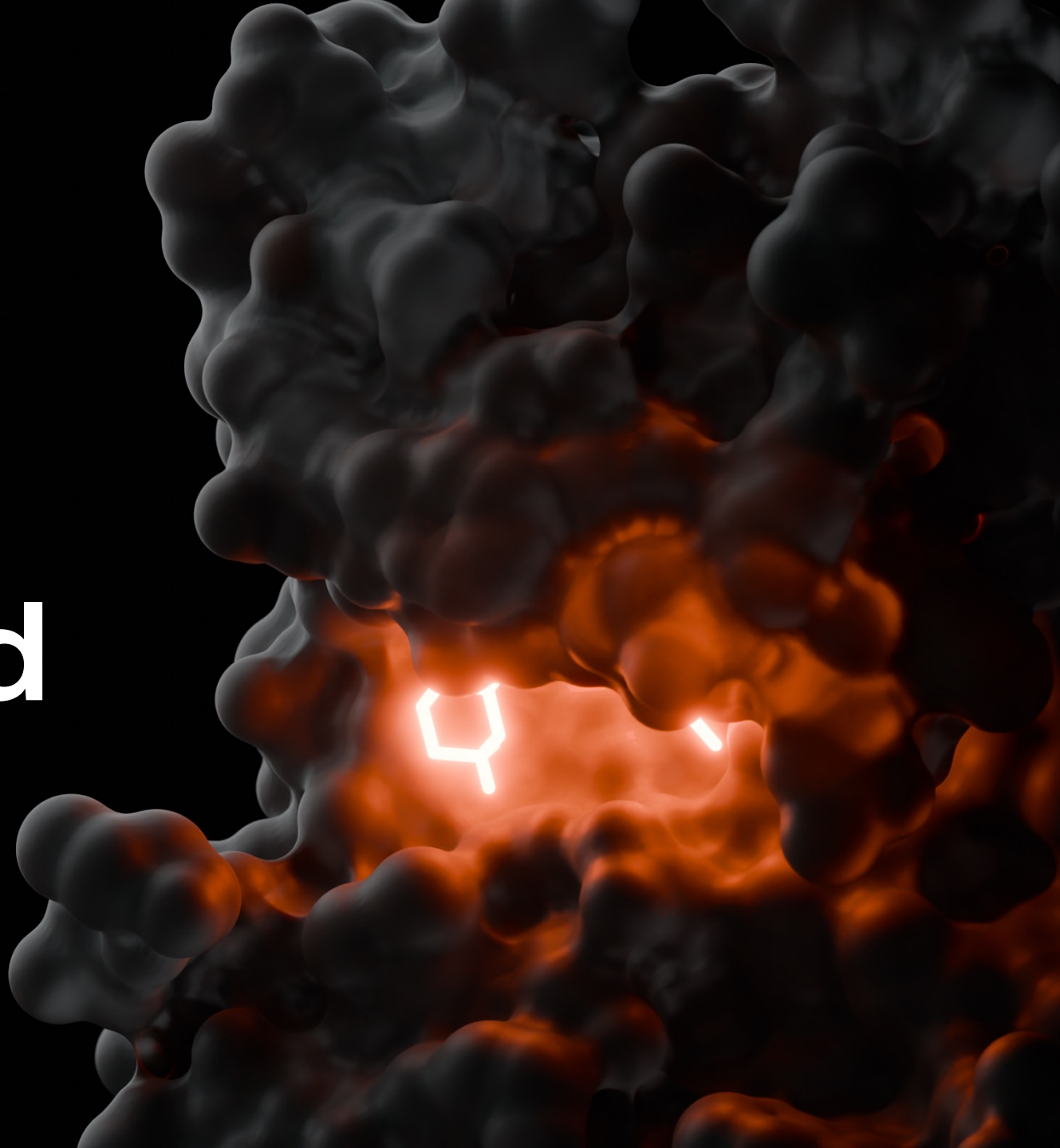
Exscientia

Precision Designed. Personalised Medicine.

March 2024



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Patient-first AI: Integrated technologies to discover, design and develop precision medicines

Encoding & Automating

Accelerated learning to enable more efficient design of higher quality molecules

Precision Medicine

End-to-end patient focused approach to help increase probability of success

Internal Pipeline

Oncology pipeline focused on differentiation and best-in-class opportunities

Multiple Discovery Programmes

Partnerships

Collaborations with partners provide both financial and strategic value

Delivering better pipeline candidates, faster

8

Precision designed development candidates

6

Projects in-licensed by partners

1st

Prospective clinical trial showing improvement in cancer treatment outcomes through AI*

70%

Reduction in discovery time from target ID to candidate

80%

Improved capital efficiency in drug discovery

~$4b

In pre-commercial milestone potential

*Kornauth et al. Cancer Discovery 2021

4 ways we can improve probability of success

	Industry Problem	vs	Exscientia Solution
1 Drug Design	Advancing development candidates with known design flaws		Using AI-based multiparameter optimisation to precision design better quality drugs
2 Target Biology	Pursuing targets with weak target-disease association		Create model systems that more closely match actual disease biology
3 Patient Selection	Heterogeneity of disease not captured in preclinical models used to predict patient response		Use of complex heterogeneous primary samples to identify patients most likely to respond to therapy
4 Clinical Trial Design	Efficacy often obscured due to protocol issues		Use of MIDD and adaptive trial design to identify signals at the earliest timepoint

MIDD = Model-informed Drug Development

2023: Positioned us well for long-term growth

Internal Pipeline

- ELUCIDATE Phase 1/2 trial for CDK7 inhibitor (GTAEXS617) initiated in 1Q 2023
- EXS74539 (LSD1 inhibitor) & EXS73565 (MALT1 inhibitor) announced as new wholly owned development candidates
- New preclinical data for LSD1 and MALT1 inhibitors presented at ESMO in October 2023

Partnered Programmes

- AI drug discovery collaboration with Merck KGaA, Darmstadt, Germany signed in September 2023
- New programme internally discovered by Exscientia added to Sanofi collaboration in 4Q 2023
- First milestone achieved in Sanofi collaboration in 3Q 2023
- Phase 1 study for EXS4318, a PKC-theta inhibitor designed by Exscientia and in-licensed by Bristol Myers Squibb, was initiated in March 2023

Precision Medicine

- EXCYTE-1 initiated in July 2023: Expanding the scope of precision medicine platform into solid tumours (ovarian cancer)
- Presented data supporting pipeline programmes' potential combination and patient selection strategies at multiple medical meetings in 2023

Technology Updates

- Presented data on automated kinase method to be applied at scale in future projects in 2H 2023
- Novel automated discovery laboratory opened in Milton Park in mid-2023

Advancing multiple programmes in 2024

2024

PIPELINE

- Multiple internal and partnered clinical programmes ongoing with potential for data
- **CDK7:** Continue enrolling patients in ELUCIDATE Phase 1/2
- **LSD1:** Clinical study start expected in 2024
- **MALT1:** Update on programme next steps in 1H 2024
- Additional pipeline updates across internal and partnered programmes

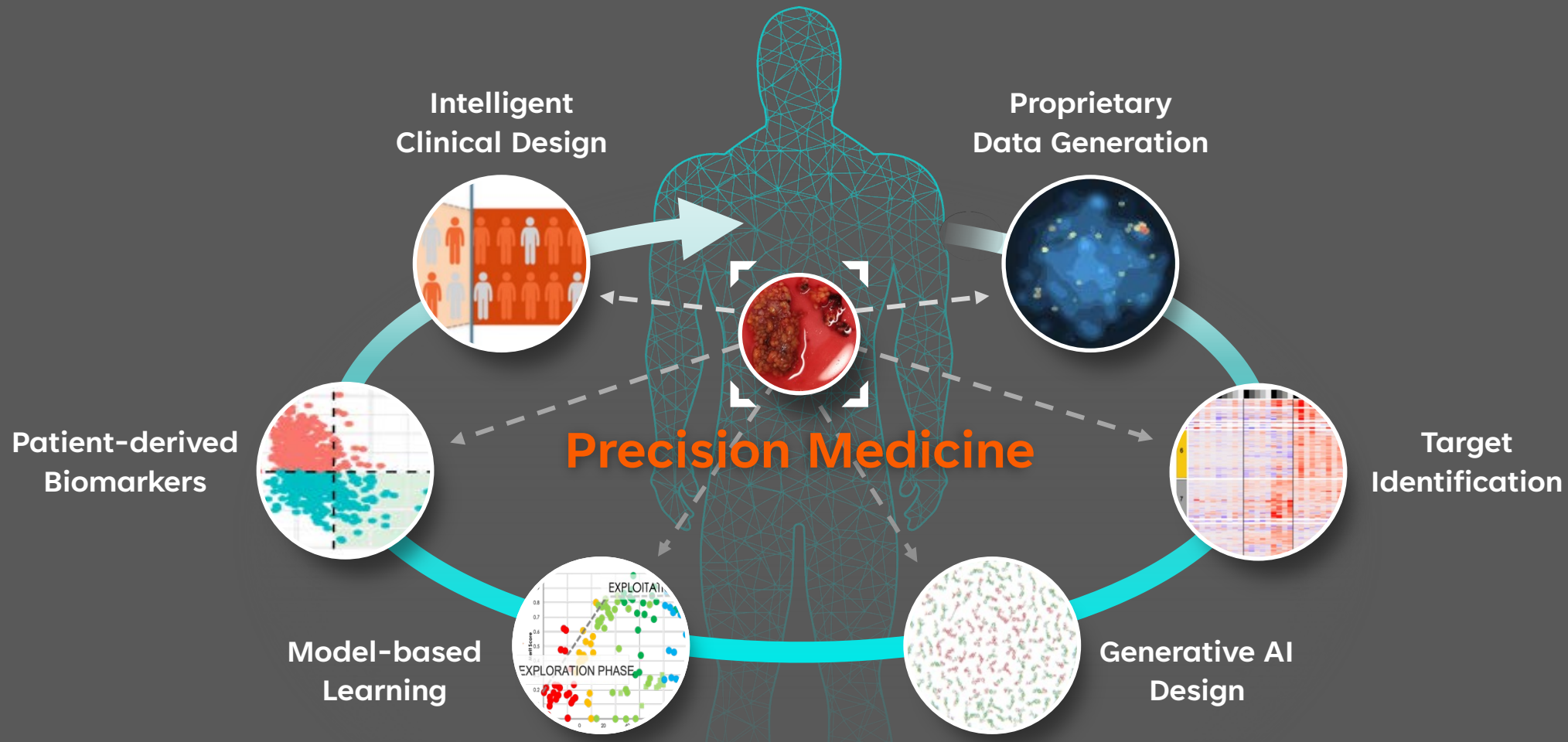
PLATFORM

- **Precision medicine:** Continued clinical evaluation of predictive drug response capabilities; advancement of platform in solid tumours
- **Automation:** Ramp up of productivity in automation facility

PARTNERS

- Advancement of partnered programmes and potential milestone payments
- New business development collaborations expected in 2024

Exscientia's solution: Integrating knowledge of the patient and drug



Why are our clinical candidates different?

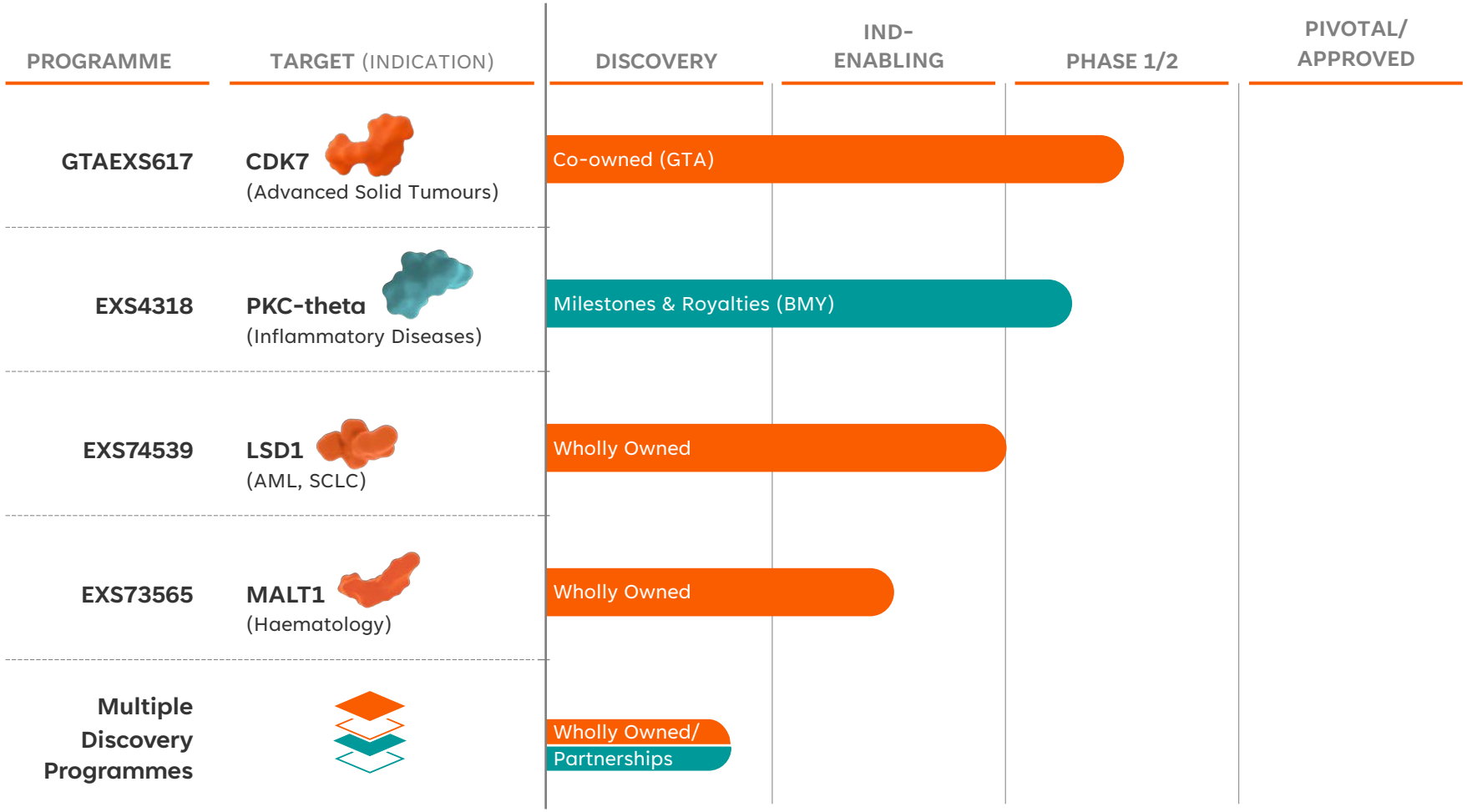
Differentiated through design and personalised medicine

Target	Phase	Target Market	Key Differentiation
CDK7	Phase 1/2	Multiple relapsed/refractory solid tumour indications	Precision designed PK/PD specific for mechanism; Identification of high-grade responders
PKC-theta	Phase 1	Multiple immunology indications	Better selectivity, improvements in whole blood potency and low predicted human dose
LSD1	IND-enabling	AML, SCLC and potential additional indications	Optimised therapeutic index by combining reversibility with short-half life, as well as brain penetration to meet high patient need
MALT1	IND-enabling	Multiple haematology indications	Solved potential dose-limiting toxicity issue present in competitor compounds

Does not include Exscientia-designed programmes that entered clinical trials through DSP collaboration;
AML = acute myeloid leukaemia; SCLC = small-cell lung cancer

Pursuing high quality, differentiated medicines

Precision designed pipeline to fulfill patient unmet needs



Multi-target collaborations with Sanofi, BMY and Merck KGaA

Broad internal focus on precision oncology

Additional clinical programmes through DSP collaboration

PKC-theta is in a Phase 1 healthy volunteer (HV) study;
AML = acute myeloid leukaemia; SCLC = small-cell lung cancer

Exscientia's pharma partnership highlights

	Drug design collaboration of challenging targets		Drug design and translational collaboration
	Bristol Myers Squibb™	Merck KGaA Darmstadt, Germany	sanofi
Partnership collaboration(s)	2	1	2
Cash inflows to date	$100m	$20m*	$109m**
Milestones per target***	$257m	$218m	$343m
Tiered royalties	Low to high-single digits	Mid-single to low-double digits	High-single digits to mid-teens (up to 21% with co-investment)

*Inclusive of $3m withholding tax which will be received in 2H 2024; **Inclusive of milestones achieved in 2023 but received in 1Q 2024
***Related to the most recent collaborations, respectively

Our strategy maintains balance sheet strength

FY 2023 financial performance

($m)	FY23	FY22	Comments
Cash inflows from collaborations	27.4*	117.8	Will continue to remain lumpy around deal announcements and achievement of milestones
Net operating cash inflows/(outflows)	(149.9)	(77.1)	Expect 2024 to be lower operating burn than 2023
Capital expenditures	34.0	28.6	Facilities build largely completed; Expect 2024 capex to be significantly less
Cash balance	462.6	644.6	Cash runway well into 2026**

*Does not include Merck $3m withholding tax which will be received in 2H 2024
**Includes fixed term bank deposits and anticipated milestones
Based on constant currency as of December 29, 2023;
Shares outstanding: 126 million as of December 31, 2023

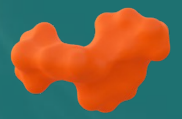
Supporting slides

Target Selection

Precision Design

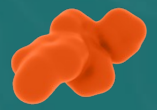
Automation

Precision Medicine



‘617 (CDK7 Inhibitor)

‘4318 (PKC-theta inhibitor)

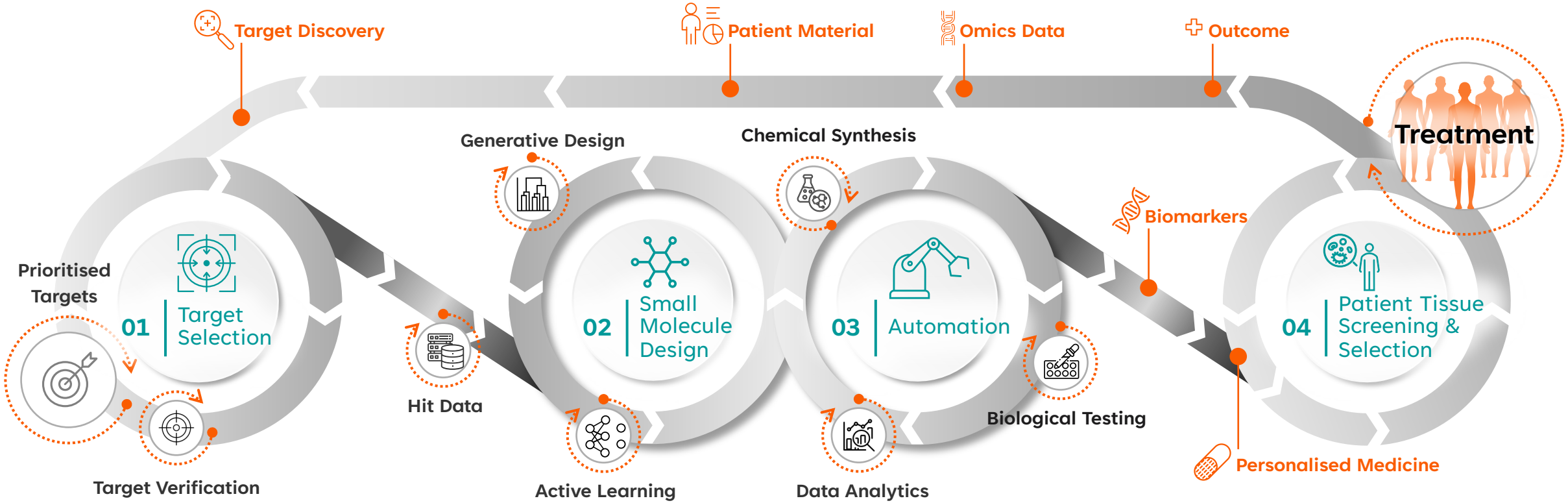


‘539 (LSD1 inhibitor)

‘565 (MALT1 inhibitor)

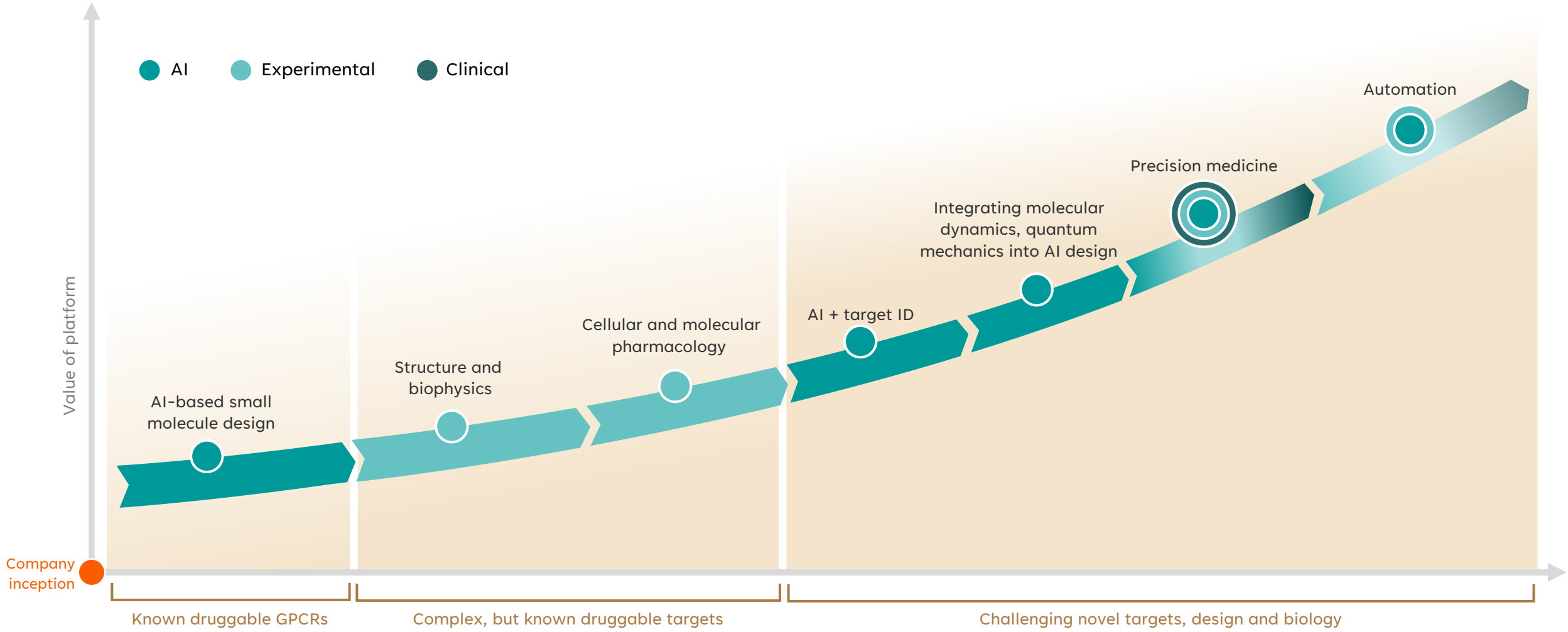
Operating at the interface of human ingenuity and technology

Encoding and automating to drive patient-focused design



Expanding technologies enhance value creation

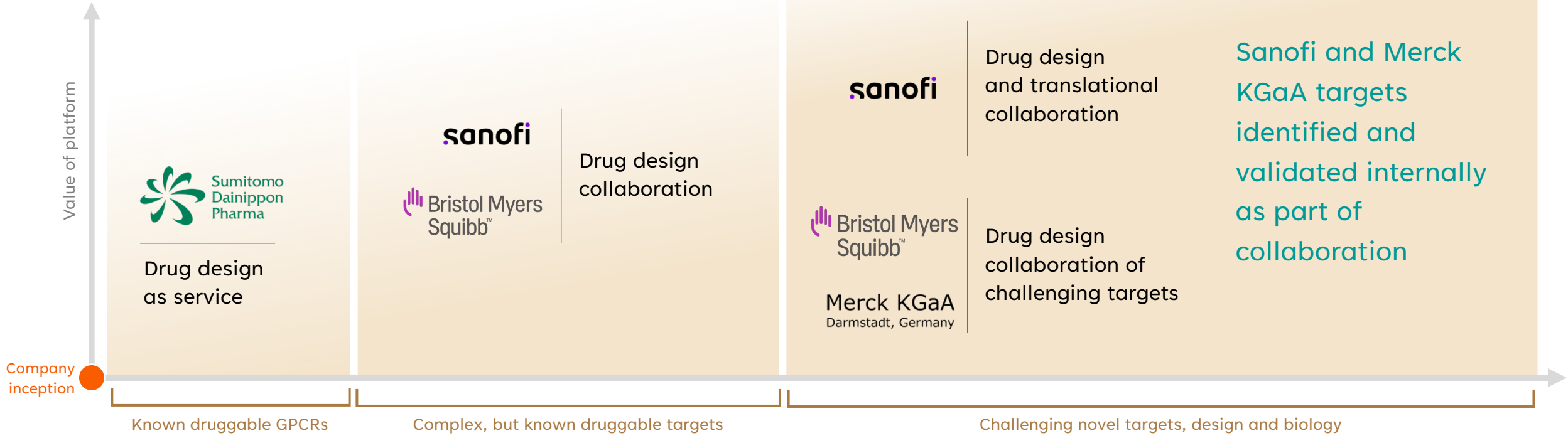
Advancements of AI-driven drug design



Timeline for illustrative purposes

Expanded technologies have translated to partnerships

Collaborations complement our internal pipeline



Partnerships criteria:

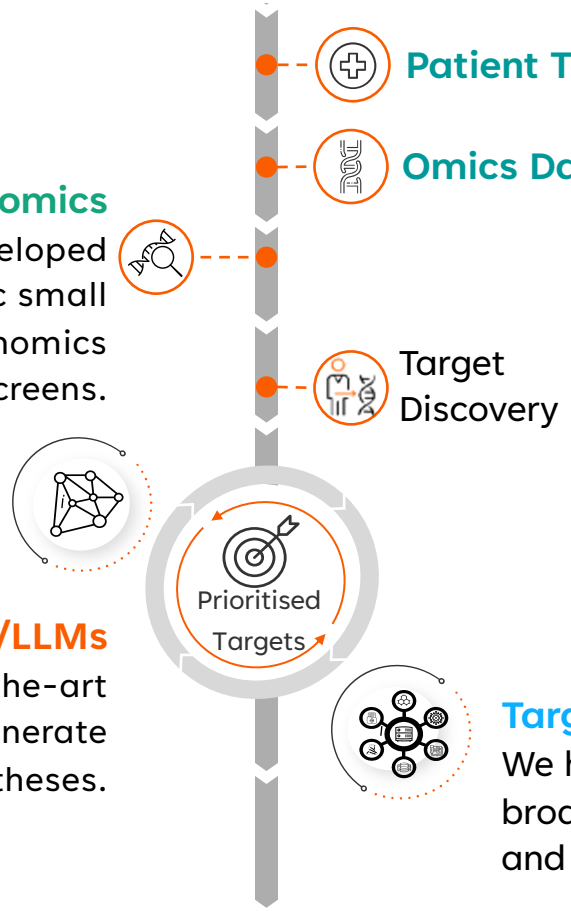
- Clear long-term value creation
- Expand our platform and capabilities
- Leverage the expertise of our partners
- Cover at least direct costs during the discovery phase for drug discovery collaborations
- All drug discovery programmes, whether internal or partnered, need to have meaningful differentiation and market opportunity

Timeline for illustrative purposes

Target Selection

Exscientia target generation engine

Multidisciplinary patient-centric and data-driven target discovery & validation



Data-informed Functional Genomics

Disease-relevant assays developed into high-throughput phenotypic small molecule screens & functional genomics genome-wide or custom phenotypic screens.

Knowledge Graphs/LLMs

Exploitation of knowledge graphs, state-of-the-art NER/NLP text analytics and LLMs to generate genome-scale ranked target hypotheses.

Patient-centric Discovery

Identify novel targets, expected response and combination potential using primary patient cohorts long before entering the clinic.

Target Verification

We have multiple experimental biology teams with a broad range of expertise to perform target validation and pathway analysis of our emerging targets.

Custom trained LLM to refine biological relevance of targets

Large language model specifically built to rank targets

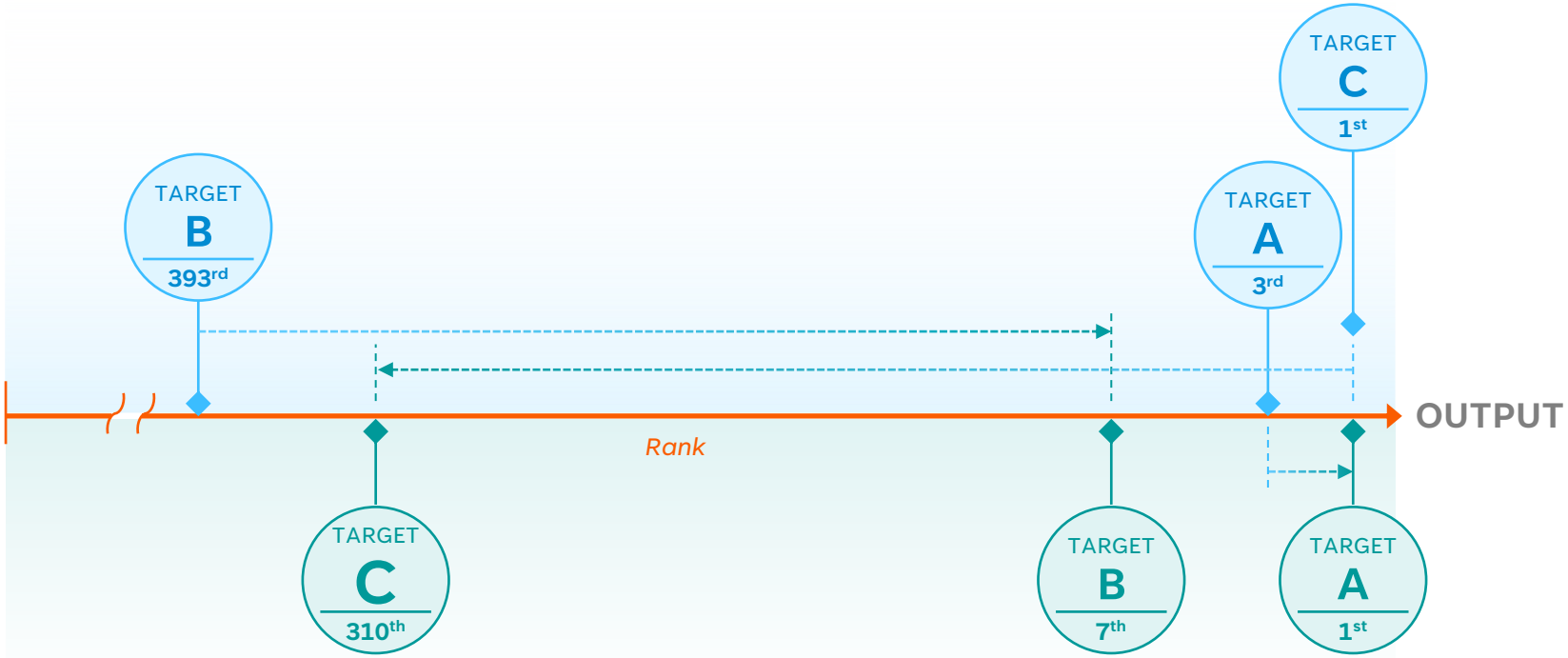
INPUT: Prompt 1 (Default)

the human gene symbol representing a therapeutic drug target for ***influenza*** is...

Total = ~20,000 Human Genes

INPUT: Prompt 2 (Precision)

the human gene symbol representing a therapeutic drug target for ***influenza targeting cell binding and fusion*** is ...



The target-LLM ranking dramatically changed with additional context

LLM = Large language models

LLM enhanced research

Using existing tools to improve accuracy

Identify entities in the question

The model tabulates relevant source documents based on the question/entities and summarises relevant information

Model generates verification statements/questions and repeats steps ① ② for each of the verification questions

Generate final consistent answer

LLM = Large language models

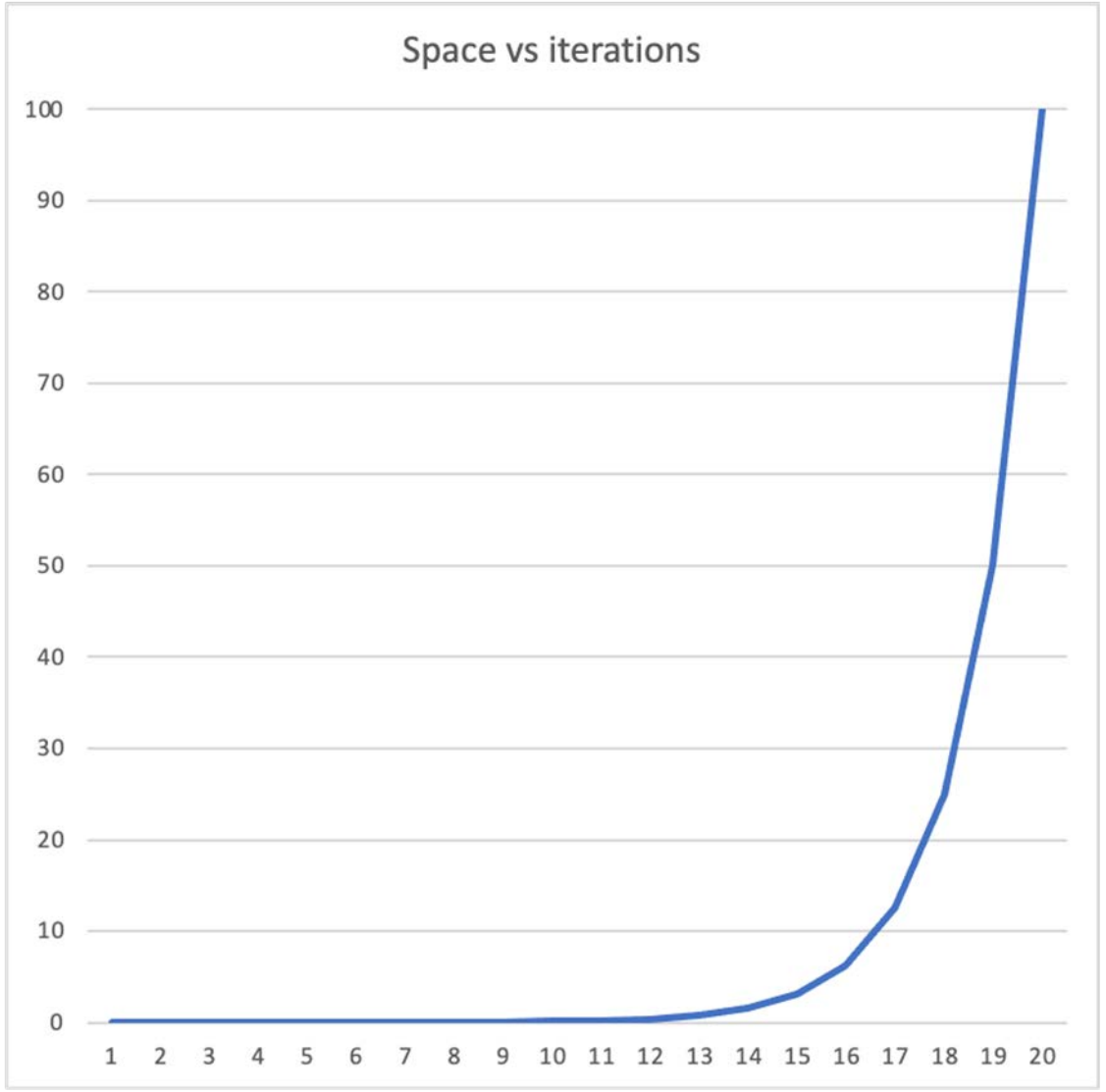
Precision Design

Why learning beats screening

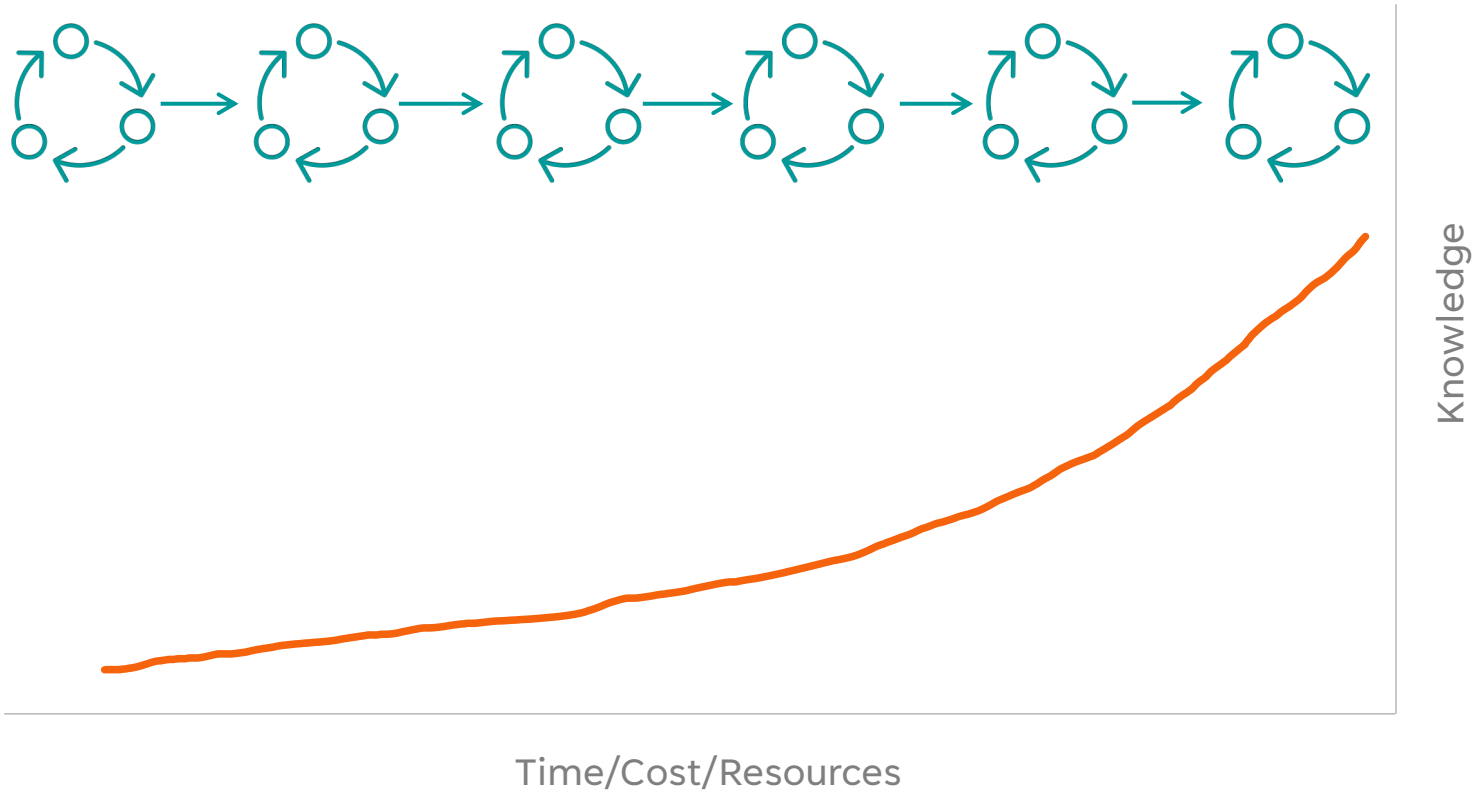
Drug discovery is a learning problem

1. **Think of a word....**
2. **Would you rather have: 20 “yes” or “no” questions or 20,000 guesses?**

- ~600,000 English words
- 20,000 guesses will fail 97% of the time
- In terms of Information Theory:
  - 10 (perfect) questions gives you 10 bits of information (2^{10} = 1024)
  - 15 questions gives 32,768
  - 20 questions gives 1,048,576
  - After 15 questions POS is only 3.1%
- The last 5 questions allow you to hone-in on the right answer



Drug discovery is a learning problem



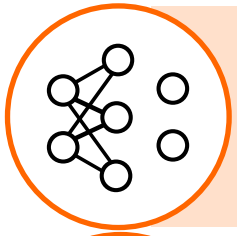
Two critical questions:

1. How fast am I learning?
2. How do I make the most of the information available to me?

Active learning AI leads to creative breakthroughs

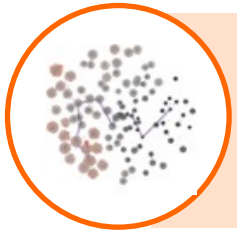
Counterintuitive selection goes against preconceptions and breaks dogma

AI system to maximise information gain



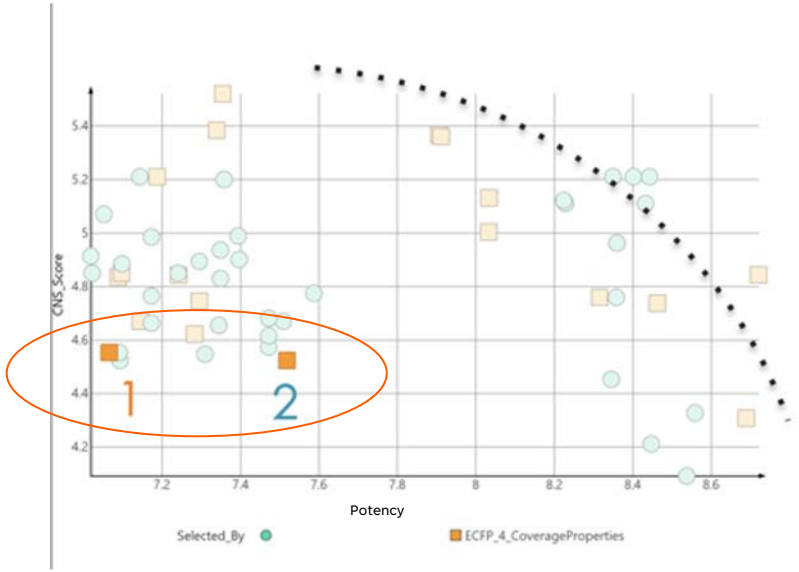
Chooses which compounds to synthesise from output of generative design and predictive models

Mathematically evaluates how much can be learned from each compound



Efficiently explores the available structural and property space

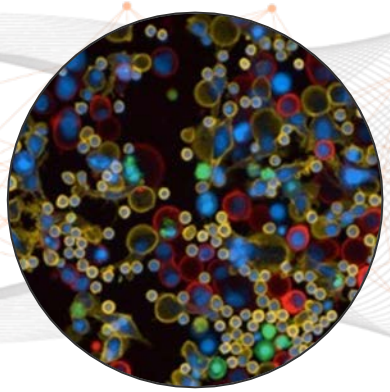
Example of our AI choosing unexpected candidates that led to a design breakthrough and development candidate



20 compounds (square) are selected by active learning

Extensive proprietary data generation capabilities

Over 45,000 sq ft of laboratories producing assays, seed data and structures



Primary tissue disease models

Translation into disease state tissue

Single cell resolution

Deep learning AI

Biobanked samples

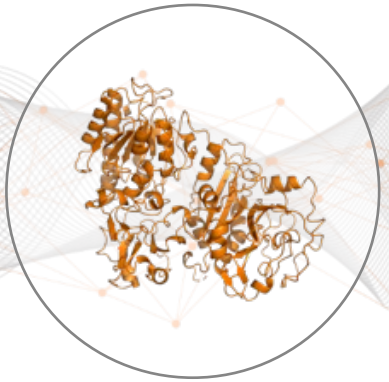
World-class biosensors

Proprietary seed data

GPCRs in native state

Label free and automated

Identified novel chemotypes for orphan targets



High throughput crystallography

Proprietary seed data

Automated Hotspot binding site analysis

Automated assay development

Transducerome mapping

Polypharmacological profiling

MoA studies

DMT studies

MoA = Mechanism of Action; DMT = Design, Make, Test

Precision objectives for precision design

Dozens of endpoints can be optimised in parallel

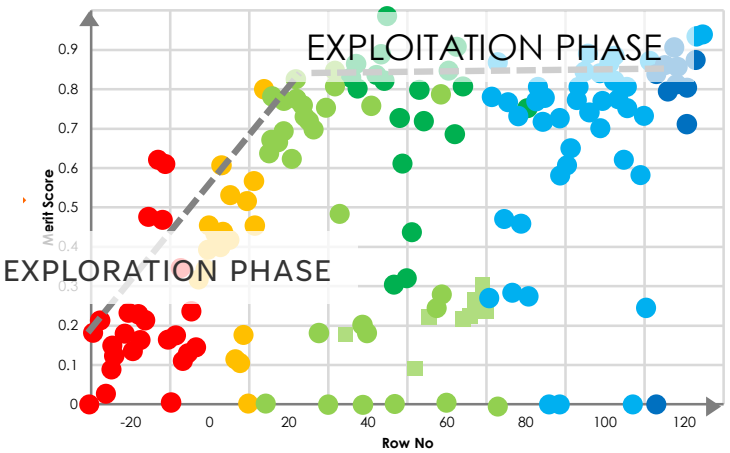
Target Product Profile

Candidate Criteria	Design Goal
CDK7 IC_{50} (nM)	<10
CDK family selectivity	>100 fold
HCC70 (breast cancer) IC_{50} (nM)	<100
OVCAR-3 (ovarian cancer) IC_{50} (nM)	<100
hERG IC_{50} (µM)	>5
Human microsome Clint µL/min/mg	<15
Human hep Clint µL/min/10^6 cells	<15
Caco-2 A2B (efflux) 10^{-6} cm/s	>3 (<5)

MPO: Multiparameter Optimisation

```
import mpo
from reward_bundle import scorer
from reward_bundle.reward_function import RewardFunction

sascore = scorer.SAScoreScorer()
colab = scorer.ColaboronModelScorer(targets=["P24941", "P58613", "P50750"])
cute = scorer.CuteScorer("chembl27-oral-approved")

rbfunc = RewardFunction(name="CDK7", components=[sascore, cute, colab])

# example MPO configuration
rbmpo = mpo.MPO(
    [
        mpo.Gaussian(
            input=sascore.column_names[0], output=f"{sascore.column_names[0]}::scaled",
            mu=1.4512761893947217, sigma=0.4751618871037742, scaled=True,
        ),
        mpo.Linear(
            a=-1, b=1,
            input=colab.column_names[0],
            output=f"{colab.column_names[0]}::inverted",
        ),
        mpo.Linear(
            a=-1, b=1,
            input=colab.column_names[2],
            output=f"{colab.column_names[2]}::inverted",
        ),
        mpo.Distance(
            p=2,
            weights={
                colab.column_names[1]: 1,
                f"{colab.column_names[0]}::inverted": 1,
                f"{colab.column_names[2]}::inverted": 1,
                "cute::chembl27-oral-approved::score": 1,
                f"{sascore.column_names[0]}::scaled": 1,
            },
            target={
                colab.column_names[1]: 1,
                f"{colab.column_names[0]}::inverted": 1,
                f"{colab.column_names[2]}::inverted": 1,
                "cute::chembl27-oral-approved::score": 1,
                f"{sascore.column_names[0]}::scaled": 1,
            },
            output="distance",
        ),
        mpo.Minus(input="distance", output="distance"),
        mpo.Gaussian(
            input="distance",
            output=rbfunc.reward_column_name,
            mu=0, sigma=0.5,
            scaled=True,
        )
    ]
)

rbfunc.set_mpo(rbmpo)
```

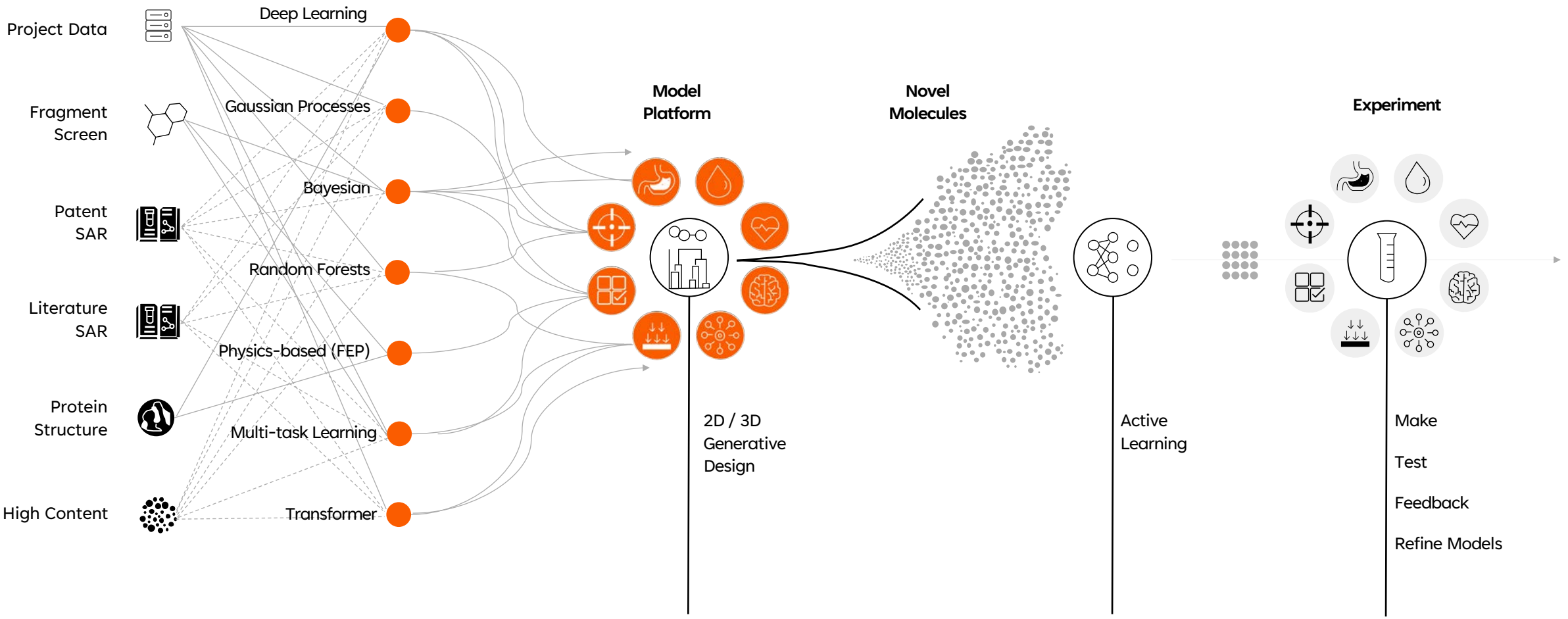
Merit: Project Telemetry

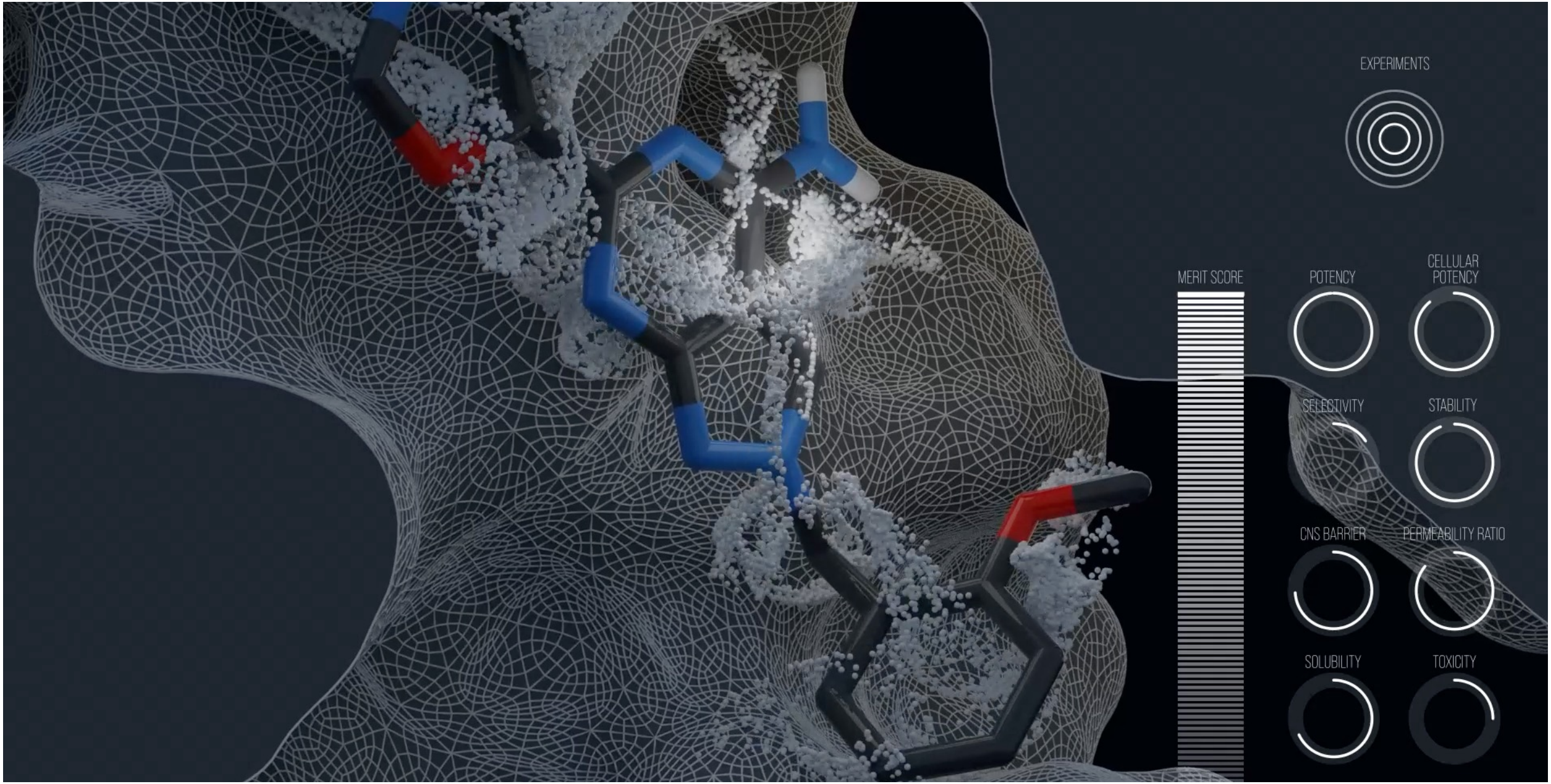


For illustrative purposes

Data and model agnostic

Our AI design platform can optimise complex drugs from diverse starting data





Watch video at: https://bit.ly/EXAIvideo

Automated and scalable MD toolbox

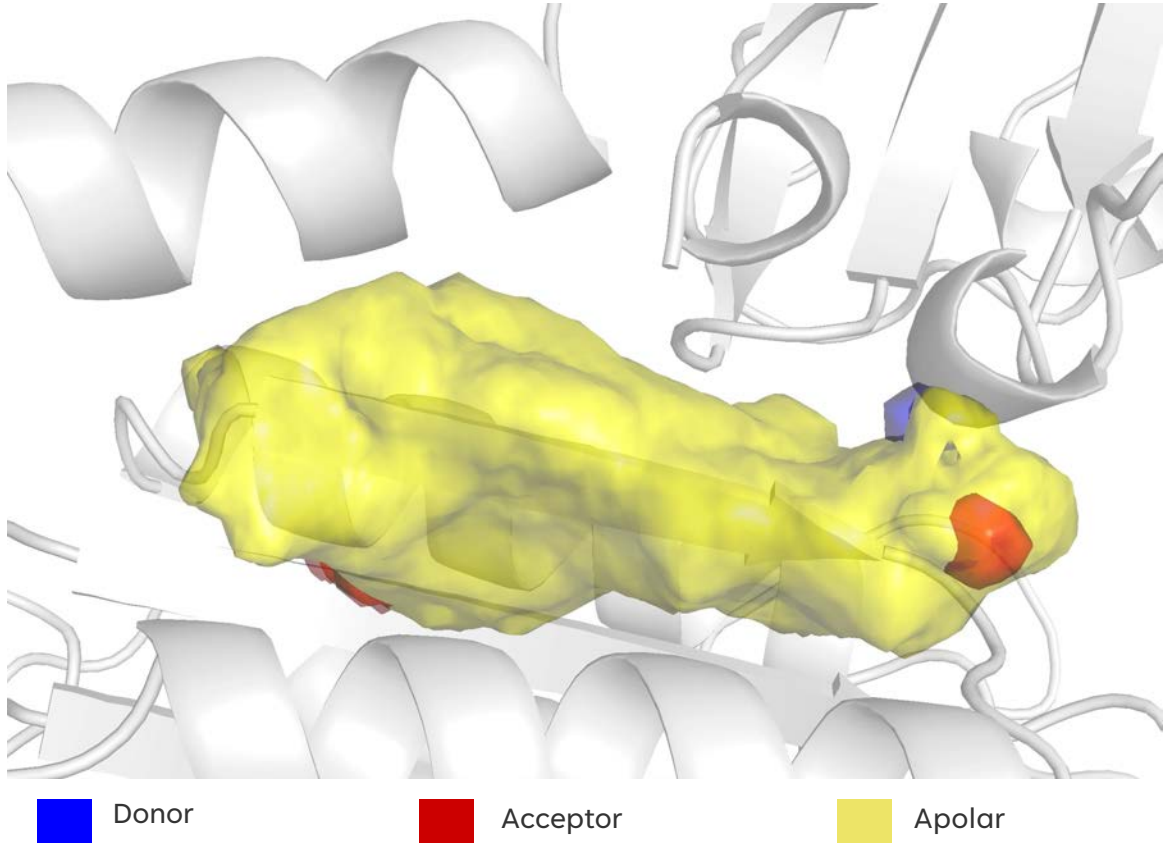
Automated MD toolkit actively applied on discovery projects

MD methods actively used to provide improved precision pose and potency prediction

Pose prediction: Metadynamics simulations can accurately determine real binding pose from possibilities from our algorithms

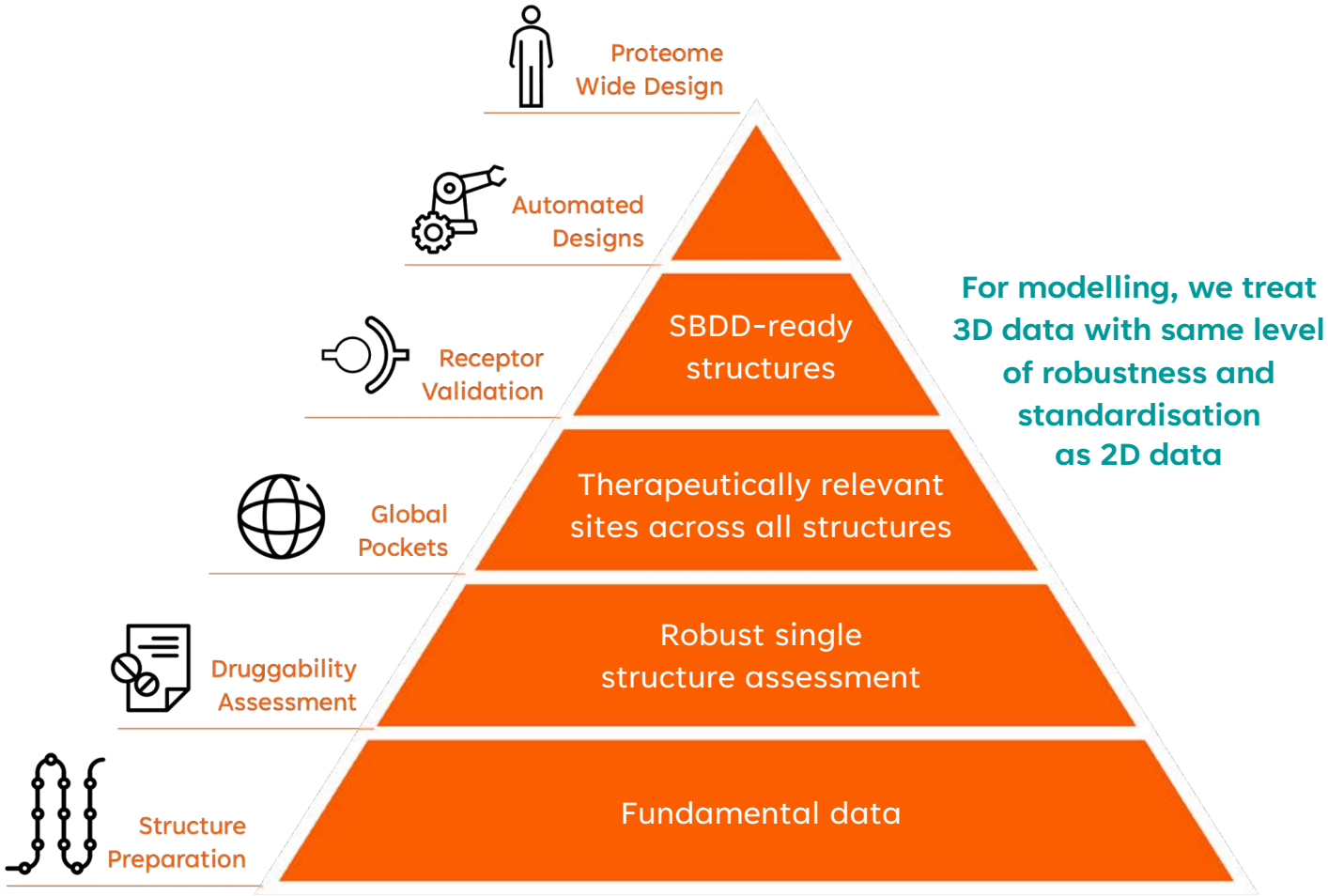
Potency prediction: Relative and absolute binding energy prediction – physics-based methods

Automation and accuracy: Developing novel methods to enhance sampling (e.g., Monte Carlo water sampling and 3D edge mapping) along with absolute free energy method



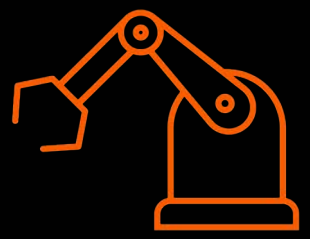
Automated design of kinase inhibitors

Leveraging AlphaFold2 for generative design



For modelling, we treat 3D data with same level of robustness and standardisation as 2D data

- Learnings from prior successful projects were encoded to develop fully automated AlphaFold2 structure-to-hit workflows
- Automated design can find novel and diverse hits – majority of scaffolds from our work were novel
- Aiming to apply this at scale for future projects

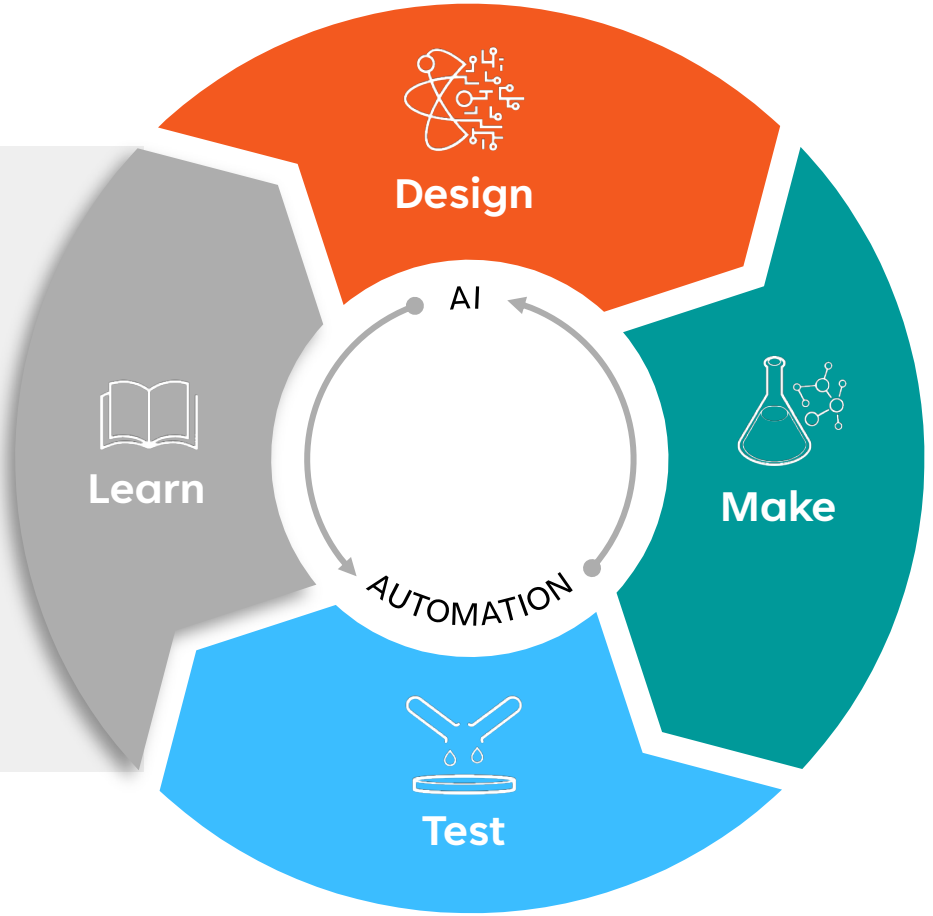


Automation

Integrating learning into the loop

Accelerating discovery efficiency through AI & automation

- Automation enables AI to be deployed in a continuous learning system
- Tight integration of AI-driven generative design with high performance make and test
- Speed and quality of cycles will determine success



Our new automation facility

Automation of laboratory processes

4,500 sq ft automation studio

Encode & automate laboratory workflows

Building modular & scalable platforms

Closing the Loop

Synthesis Sympathetic
Generative Design

Physics-based
Platform

ML Models

Route
Prediction

Workflow platform, automated design

High Content
Data

ADME

In Vitro

Proprietary AI-driven laboratory automation systems

Biological Testing

Compound Management

Chemical Synthesis

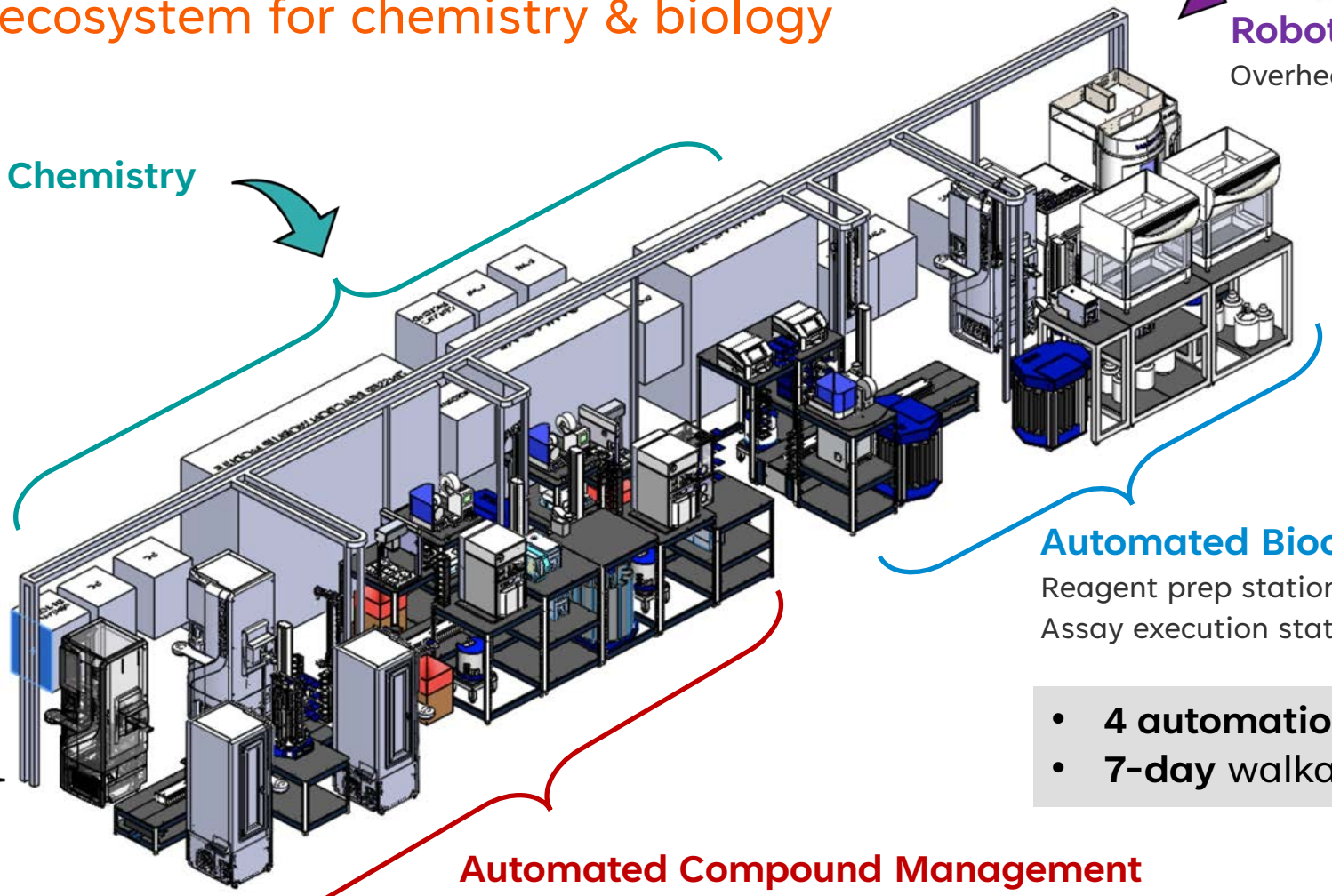
Our automation studio

Automated ecosystem for chemistry & biology

Robotic Transport Conveyor

Overhead track to connect islands

Automated Chemistry



Automated Biochemical Screening

Reagent prep station

Assay execution station

- **4 automation islands**
- **7-day** walkaway time

Mobile Co-bots

Additional robotic connectivity for sample transport & restocking consumables

Automated Compound Management

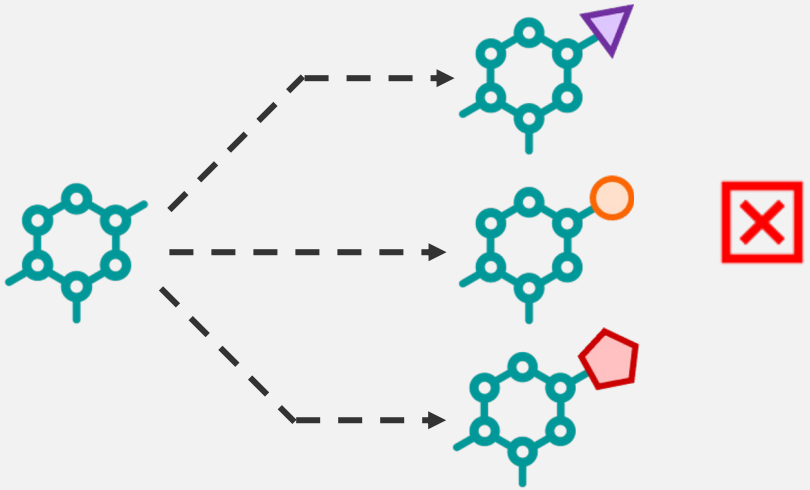
Automated compound stores

Automated assay plate production

Automating synthesis with AI-driven design in mind

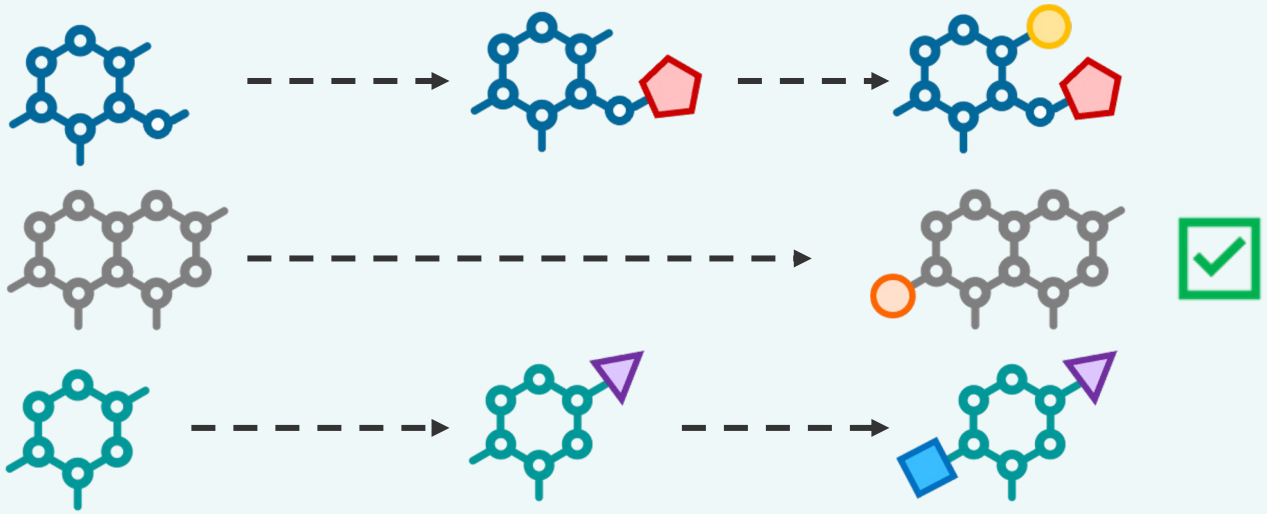
- Conventionally applied to **parallel synthesis** (making many similar molecules)
- AI design requires automation of **bespoke synthesis** (fewer, but more diverse, molecules)

Parallel Synthesis



- Common starting material
- Similar reaction conditions

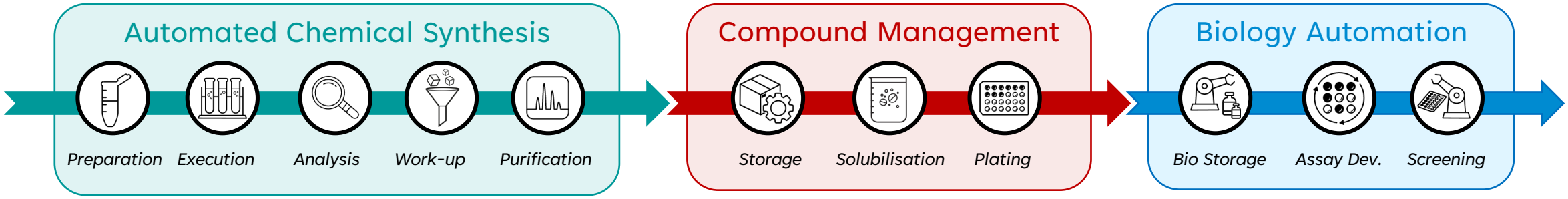
Bespoke Synthesis



- Unique starting materials
- Variety of reaction conditions
- Varying number of reaction steps

Robotic connectivity

Various robotic transport solutions required to maximise connectivity and flexibility



Maglev transport systems
Enable connectivity within a platform

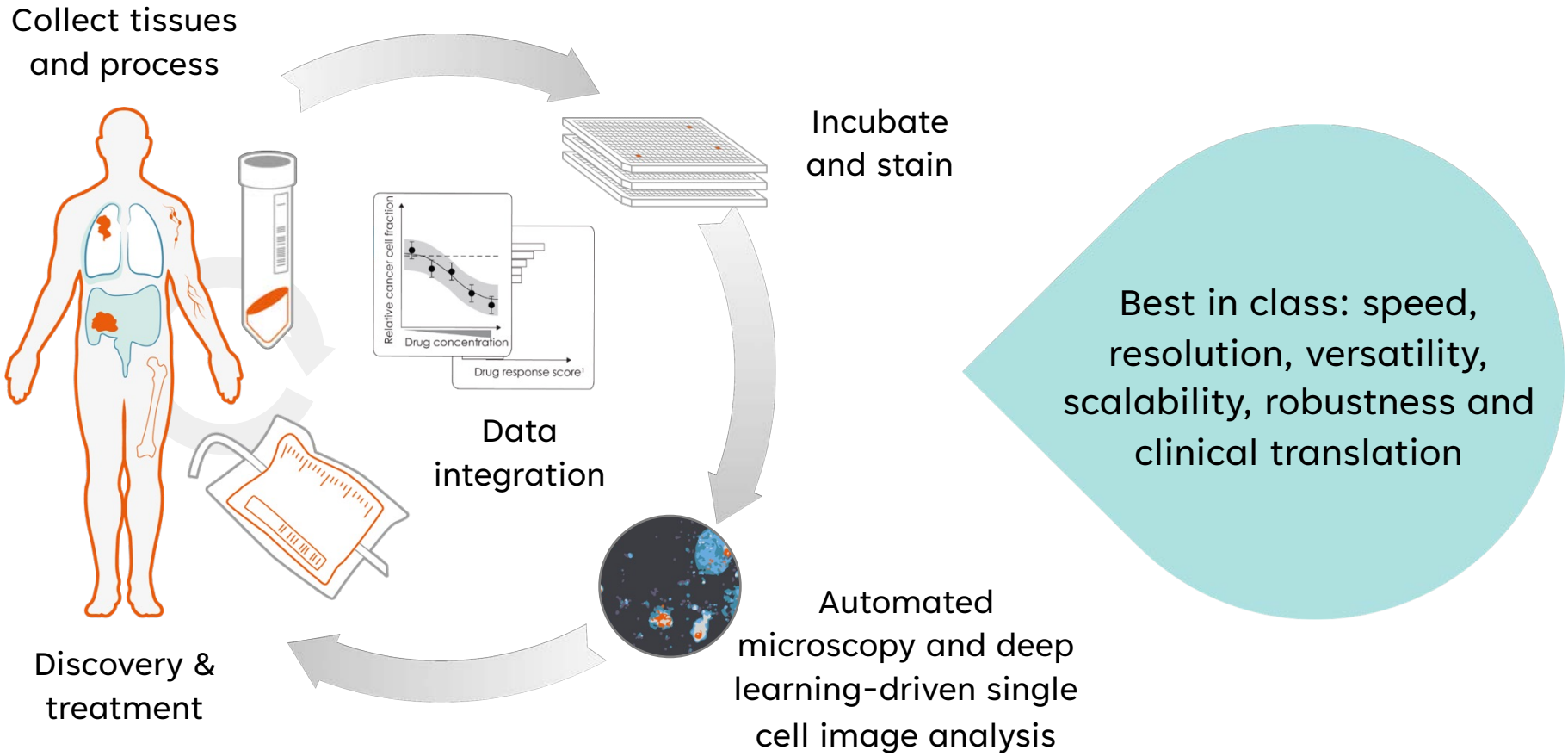
Mobile co-bots
Enable connectivity between platforms

Overhead conveyors
To maximize floorspace

Precision Medicine

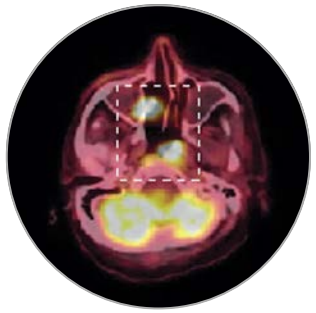
Our differentiated process

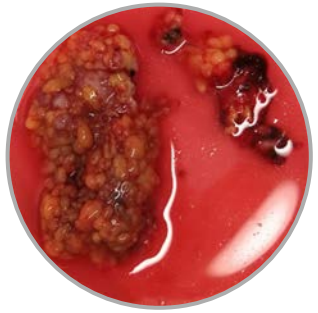
Interrogating drug action in complex primary tissues at the single cell level

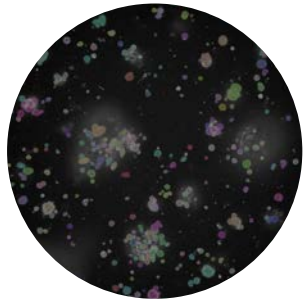


Vladimer et al. *Lancet Hematol*. 2017; Vladimer, Snijder et al. *NCB* 2017; Schmidl, Vladimer et al. *NCB* 2019; Kornauth et al. *Cancer Discovery* 2021

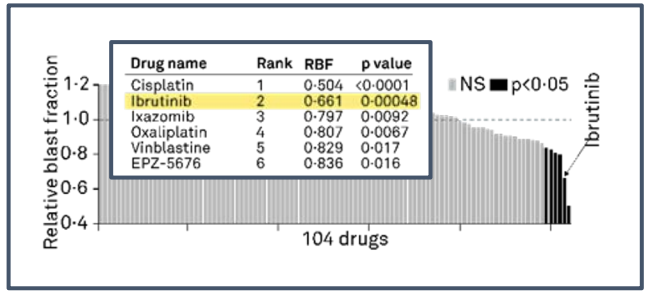
EXALT-1 study: First AI-driven functional precision medicine platform to directly improve cancer treatment & patient outcomes

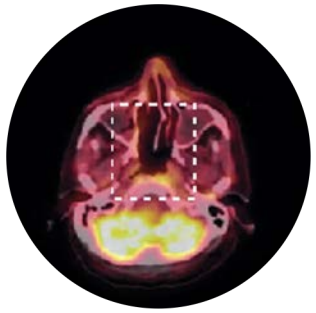






Select the best tolerable treatment in the tumour board





82-year-old DLBCL patient intolerant to chemotherapy

Collection of viable tumour tissue – not organoids

Expose to >100 clinically usable drugs in the lab – automate microscopy and single cell image analysis

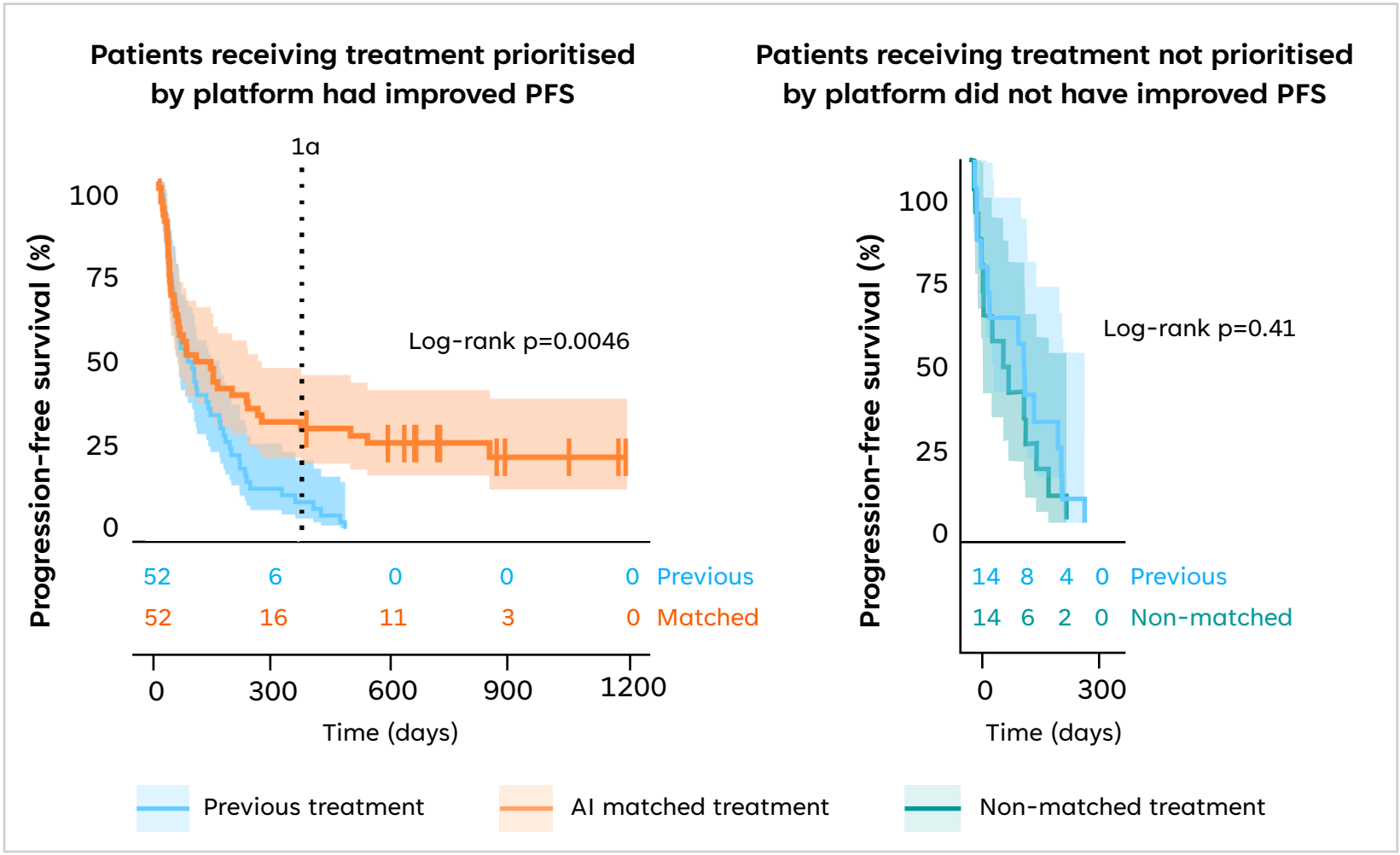
Measure drug response using image-based screening

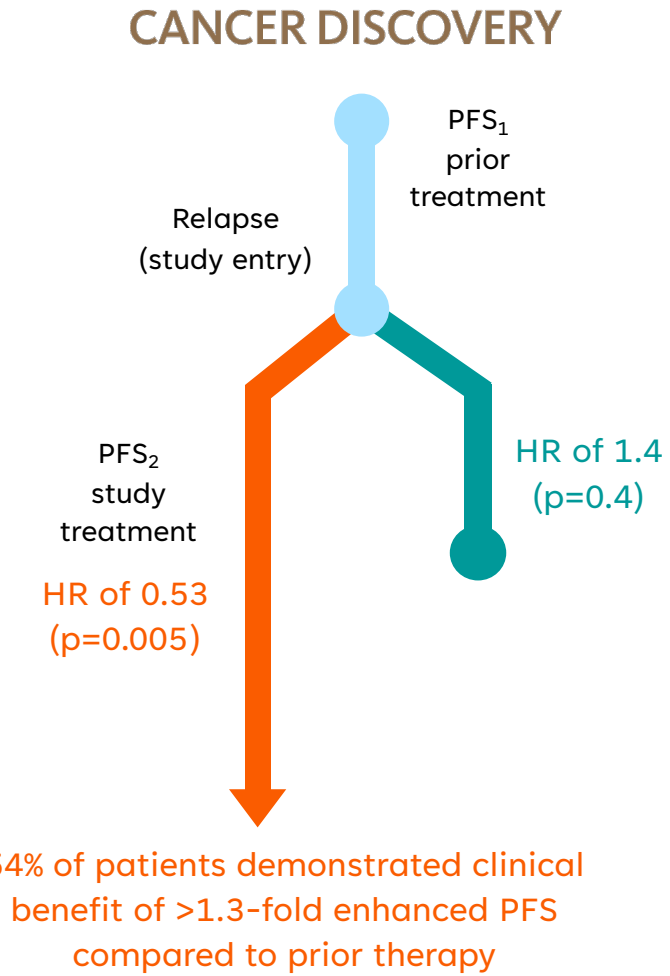
Complete remission 2-years survival at fraction of cost of CAR-T

DLBCL = diffuse large B-cell lymphoma

EXALT-1 study results

Patients receiving drugs prioritised by platform had significantly better outcomes



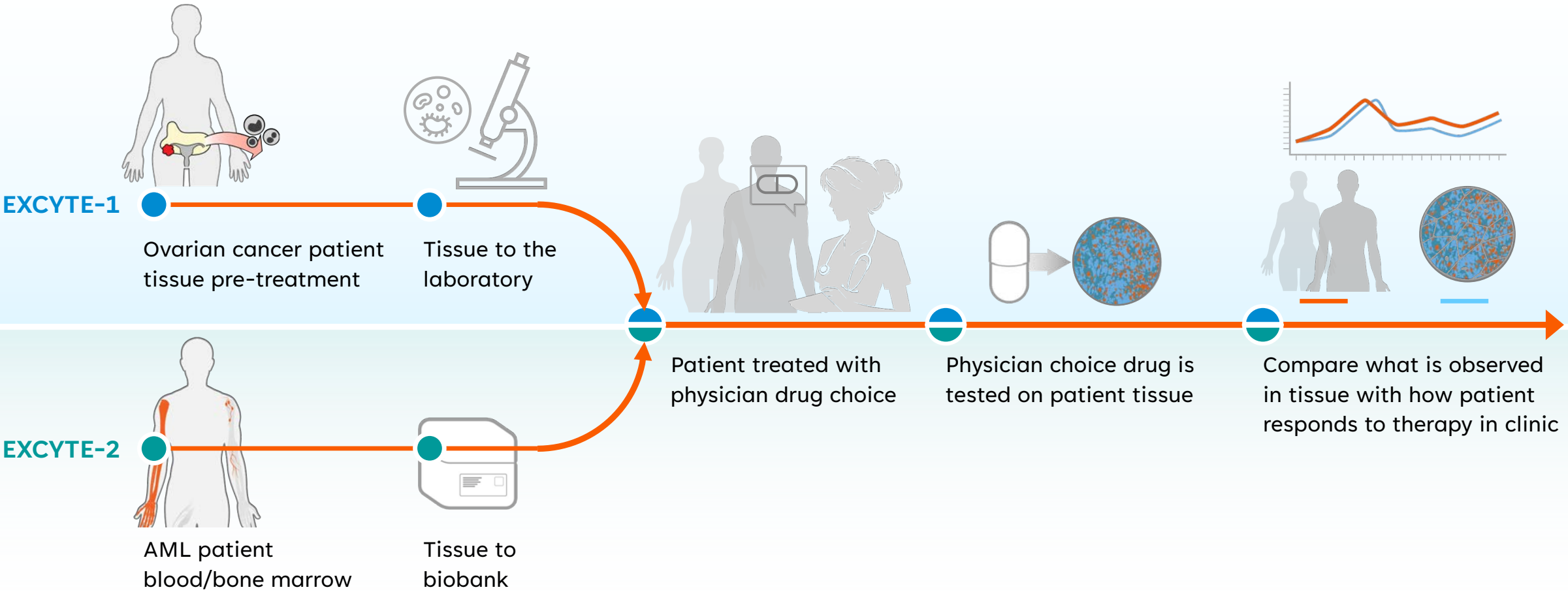


54% of patients demonstrated clinical benefit of >1.3-fold enhanced PFS compared to prior therapy

Kornauth et al. *Cancer Discovery* 2021, 1a: Kaplan–Meier plot comparing scFPM-matched treatment with previous treatment. Dotted line denotes 1-year follow-up

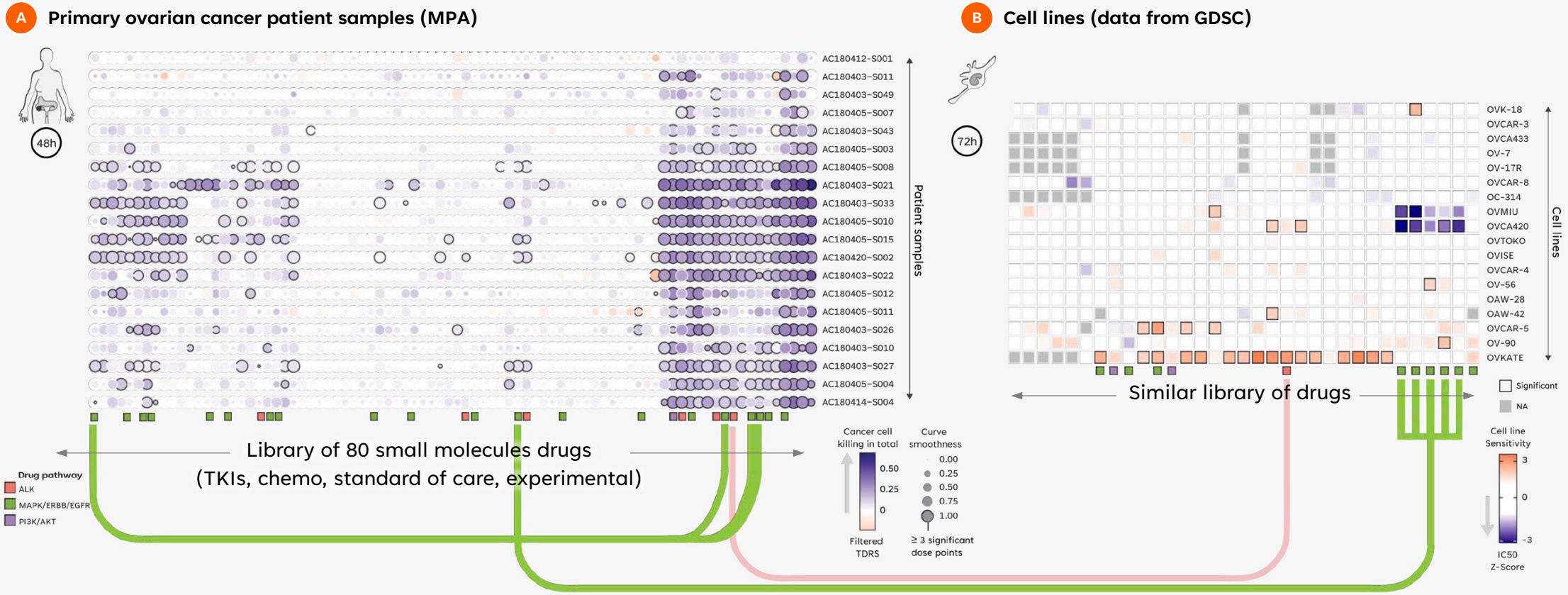
EXCYTE trials: Expansion of precision medicine platform

Observational studies



Cancer is a heterogenous disease

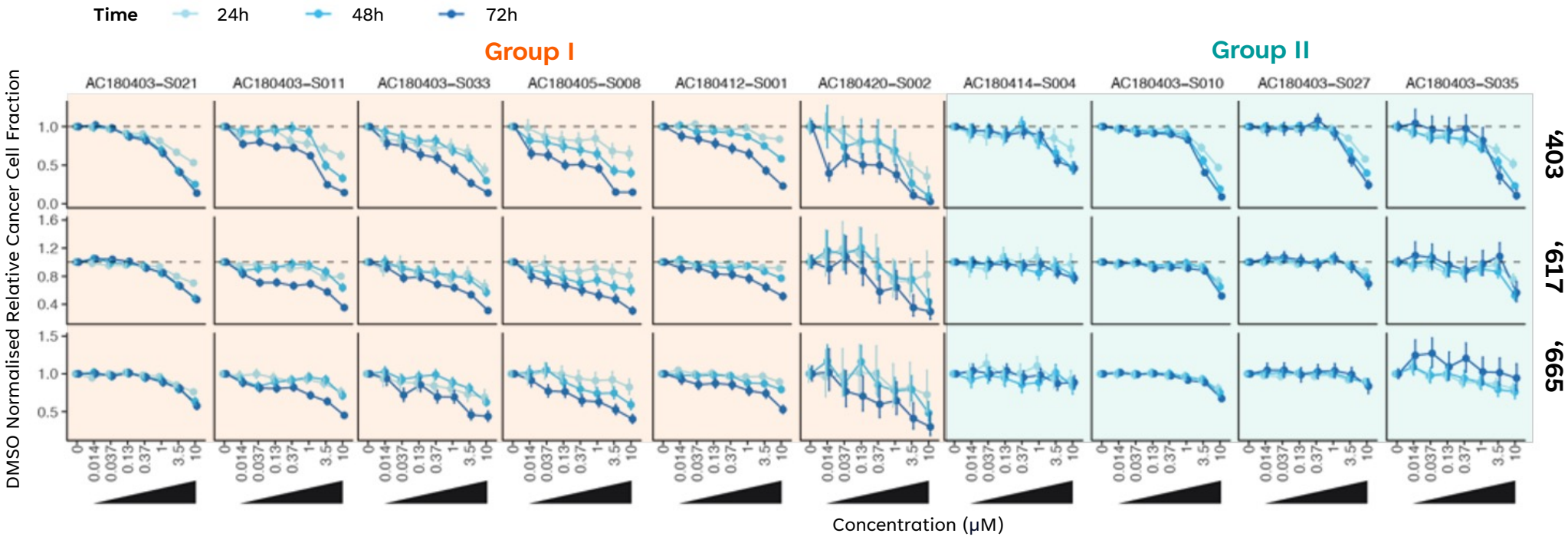
Our platform is designed to better understand differential response

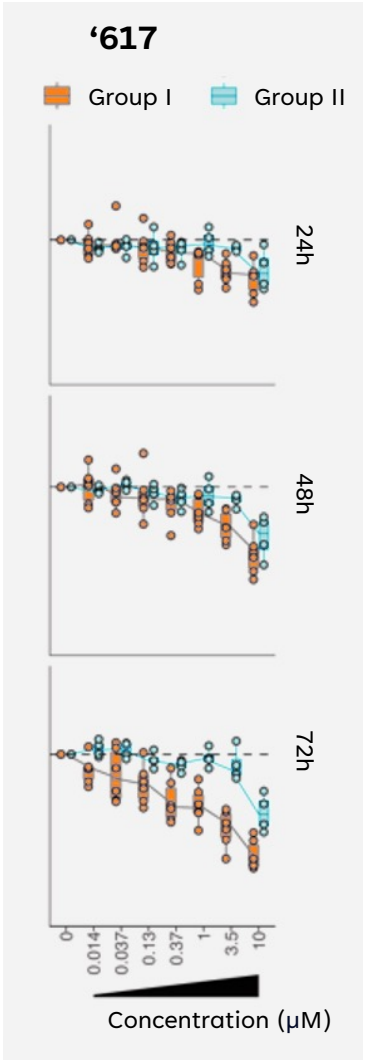


Screening of similar compounds revealed differential cytotoxic activity *ex vivo* compared to cell lines from the same indication

Defining patient selection during drug design

‘617: Ovarian cancer patient samples stratify into two groups





Group II (n=4) require higher concentrations of ‘617 than Group I (n=6) for effect

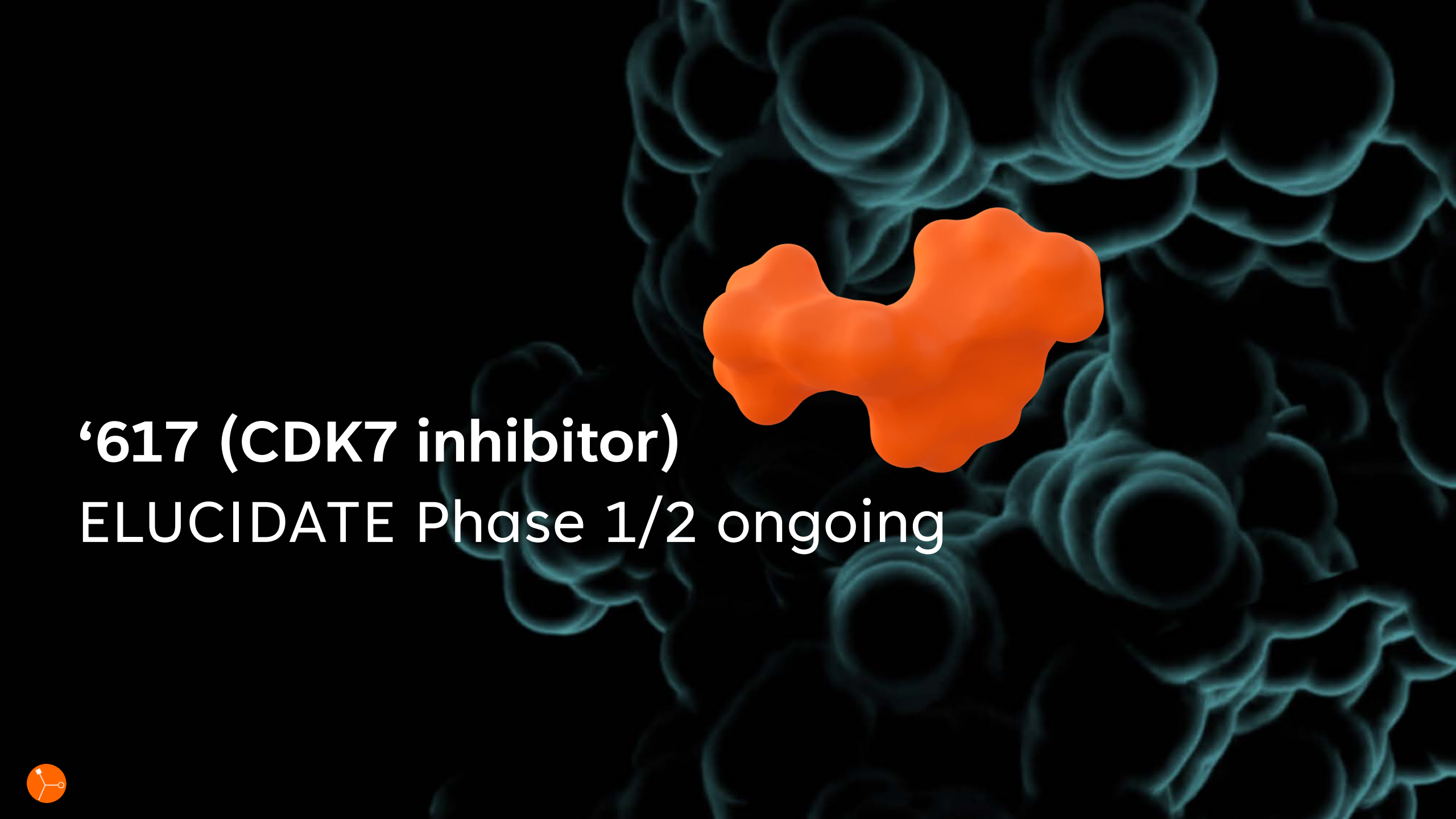
Understanding why will guide patient selection and is the focus of ongoing studies

Besnard et al, AACR (2022)

Advancing to the clinic

Design *patient-centric* drugs with an improved probability of success

- Use precision medicine platform with patient samples to profile high response populations for that specific drug prior to initiating clinical trials
- Validate signatures early in the clinic:
  - Initial clinical trials to occur with concurrent prospective biomarker testing
  - Positive and negative controls provide validation of biomarker/signature
- Use validated biomarker/signature to enrich later clinical trials with patients expected to have the highest response
- Leverage adaptive trial design to build efficiency into clinical programmes
- Platform supports analysis of mono or combination therapies



‘617 (CDK7 inhibitor)

ELUCIDATE Phase 1/2 ongoing

ELUCIDATE: ‘617 Phase 1/2 ongoing in advanced solid tumours

Preclinically identified PD biomarkers to be further assessed in the trial

Two-part trial assessing safety, PK/PD and efficacy of GTAEXS617 in patients with advanced solid tumours*

GTAEXS617 (CDK7 inhibitor)

Part 1: Dose Escalation

Part A: Monotherapy

Part B: Combination with SoC

- n=up to 30 patients to be enrolled in each part across up to 6 dose levels to establish the RP2D and PK/PD
- Data-informed prioritisation of disease specific cohorts for Part 2

RP2D

Part 2: Dose Expansion

n=30-60 patients with monotherapy

n=30-60 patients with combination

n will depend on number of disease specific cohorts

Primary efficacy endpoint: ORR

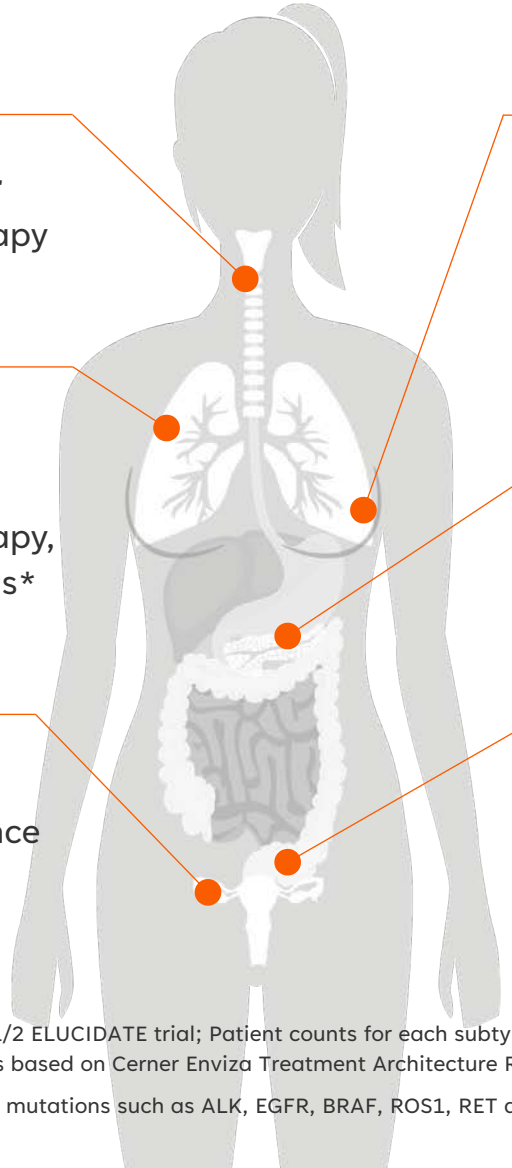
Additional data generation, including clinical endpoints, peripheral and tumour multi-omics, and correlation of data and response to previously collected *ex vivo* results planned

ELUCIDATE (protocol number GTAEXS617-001) is a Phase 1/2 open-label multi-centre study to assess the safety, pharmacokinetics and anti-tumour activity of GTAEXS617 in patients with advanced solid tumours (who have failed on, refused or are ineligible for the standard of care (SoC))

*Solid tumours under consideration include ovarian cancer, pancreatic cancer, HR+ HER2- breast cancer, head & neck cancer, NSCLC and colorectal cancer – SoC will vary for each disease cohort

ELUCIDATE: ‘617 Phase 1/2 ongoing in advanced solid tumours

2022 United States incidence for patient sub-groups included in ELUCIDATE trial



5K

Head & Neck Cancer
2nd or later line of therapy

29K

Non-small Cell Lung Cancer
2nd or later line of therapy, without driver mutations*

6K

Ovarian Cancer
Post relapse on/resistance to platinum therapy

12K

Breast Cancer
HR+ and HER2- disease, post relapse on CDK4/6i

8K

Pancreatic Cancer
2nd or later line of therapy

15K

Colorectal Cancer
2nd or later line of therapy

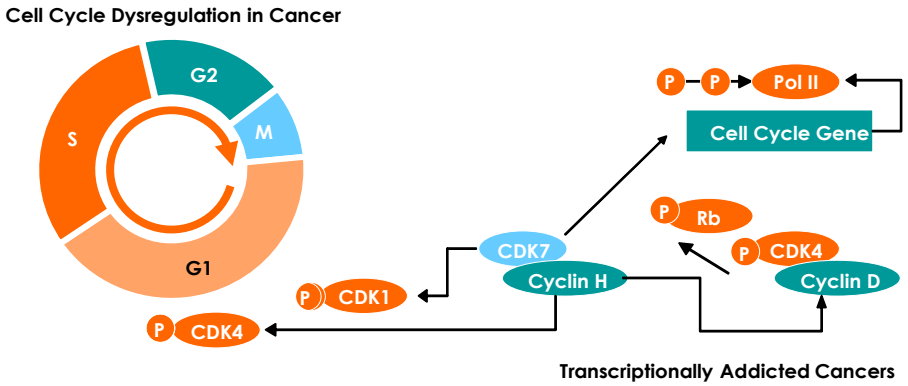
~75K U.S. Patients Lives Annually

Covers all indications included in Ph1/2 ELUCIDATE trial; Patient counts for each subtype based on EvaluatePharma Epidemiology 2022 and primary inclusion criteria for ELUCIDATE Ph 1/2 trial. Treatment rate and progression rates based on Cerner Enviza Treatment Architecture Reports 2022; Numbers have been rounded to the nearest 1000 patients per year;

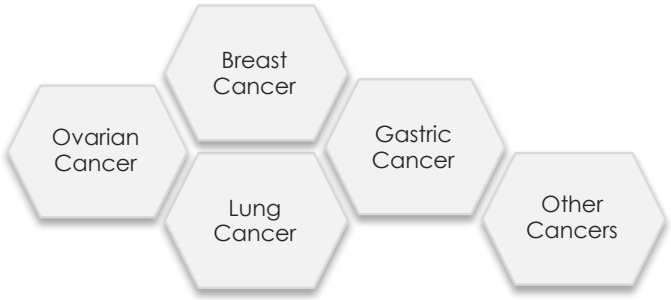
*Excludes currently actionable driver mutations such as ALK, EGFR, BRAF, ROS1, RET and MET

CDK7: Inhibition provides broad oncology opportunity

Dual targeting of cell cycle and transcription mechanisms



CDK7: Potential for multiple cancer indications



Importance of cell cycle inhibition

- CDK4/6 inhibitors have demonstrated the potential for cell cycle inhibitors to impact cancer
  - CDK4/6 inhibitors generated $8.9b in sales in 2022
  - 65-75% of patients show response, but acquire resistance

Transcription and cell cycle dysregulation are both hallmarks of cancer

- Inhibiting both may be more effective in controlling growth
- Aberrant CDK7 overexpression is common in multiple indications and associated with poor prognosis
- Majority of cancers are 'transcriptionally addicted' with c-Myc overexpression

Potential for first line therapy or for CDK4/6 refractory patients

ER+: Oestrogen receptor positive. About 80% of all breast cancers are ER+.
Source: Xu et al. 2020 *Nature*; Sava et al. 2020 *Cancer and Metastasis Reviews*

Precision design to maximise effectiveness

Mechanism requires a tightly controlled target product profile

Non-covalent Potency and Selectivity

- Both potency and selectivity are critically important
- Early entrants targeted higher potency and selectivity by covalent bonding
- This dramatically increased off target toxicity, leading to discontinuation

Design needs to achieve potency and selectivity non-covalently

Short Therapeutic Window

- Ideal therapeutic coverage would be 8-10 hours at IC_{80}
- Longer periods would lead to increasing systemic toxicity

Product needs to be highly potent, but with a short half-life

Bioavailable

- CDK7 inhibition will lead to toxicity if it remains at any site other than the tumour
- Absorption variability will cause either supra-doses or sub-therapeutic dosing

Goal is for very rapid absorption at the lowest possible dose

Our ‘617 candidate resolves critical design issues

Designed in <12 months and just 136 experimental compounds

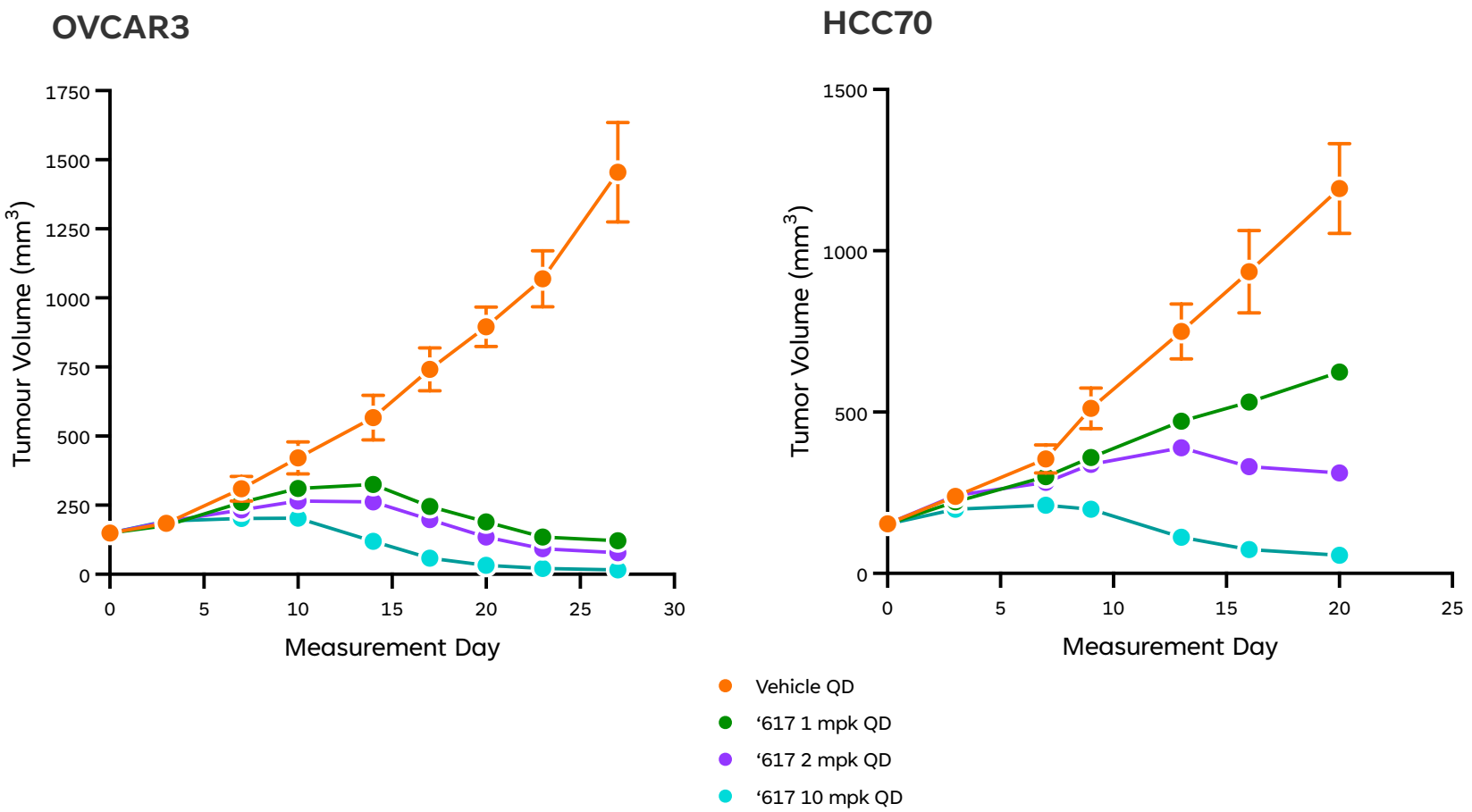
	Assay	Candidate Criteria	Competing Phase 1 Candidate	Competing Phase 1/2 Candidate	Exscientia Candidate ‘617
Target affinity and selectivity	CDK7 IC_{50} (nM)	<10			
	CDK family selectivity	>100 fold			
Cell potency	HCC70 (breast cancer) IC_{50} (nM)	<100			
	OVCAR-3 (ovarian cancer) IC_{50} (nM)	<100			
Safety and metabolism	hERG IC_{50} (µM)	>5			
	Human microsome Clint µL/min/mg	<15			
	Human hep Clint µL/min/10^6 cells	<15			
	Predicted human half-life (hrs)	<15			
Permeability/ transporter liability	Caco-2 A2B (efflux) 10^{-6} cm/s	>3 (<5)			
General properties	Solubility pH 7.4 µg/ml	>50			
	F % (p.o.)	>30%			

- Potent biochemical and cellular activity
- High selectivity
- Optimised half-life
- Excellent bioavailability and efflux

Meets or exceeds criteria | Minor deviation | Major deviation | Not tested

‘617 is highly effective in classical models

Potent anti-tumour activity demonstrated in multiple solid tumour types



Besnard et al, AACR (2022)

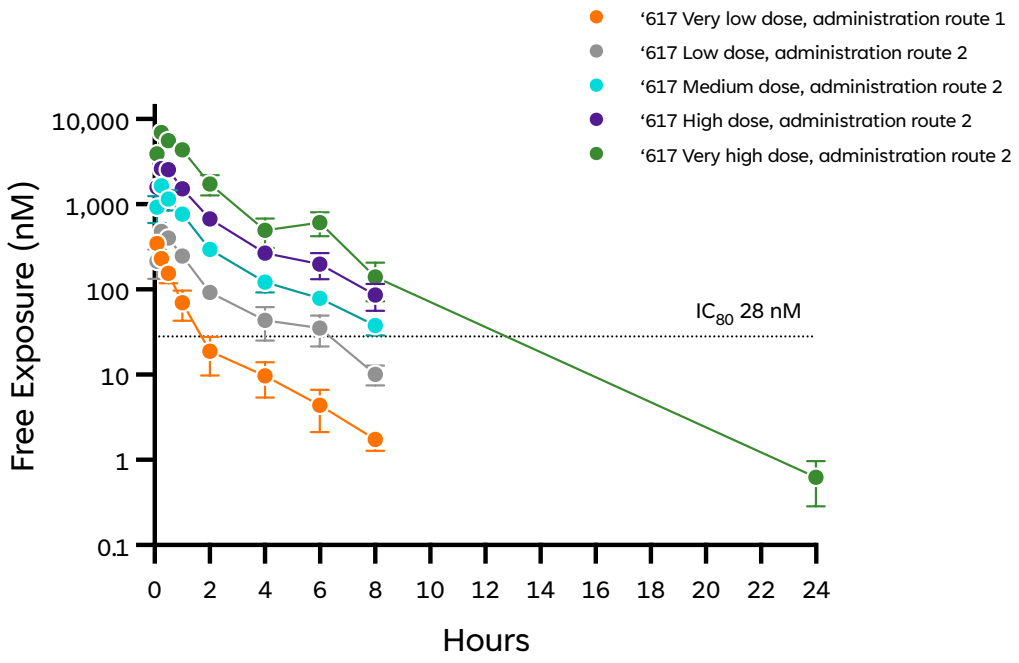
‘617: Differentiated CDK7i

- High on-target potency and selectivity
- Strong *in vivo* anti-tumour profile, as demonstrated in both triple negative breast and ovarian cancer

‘617 half-life optimises benefit-risk

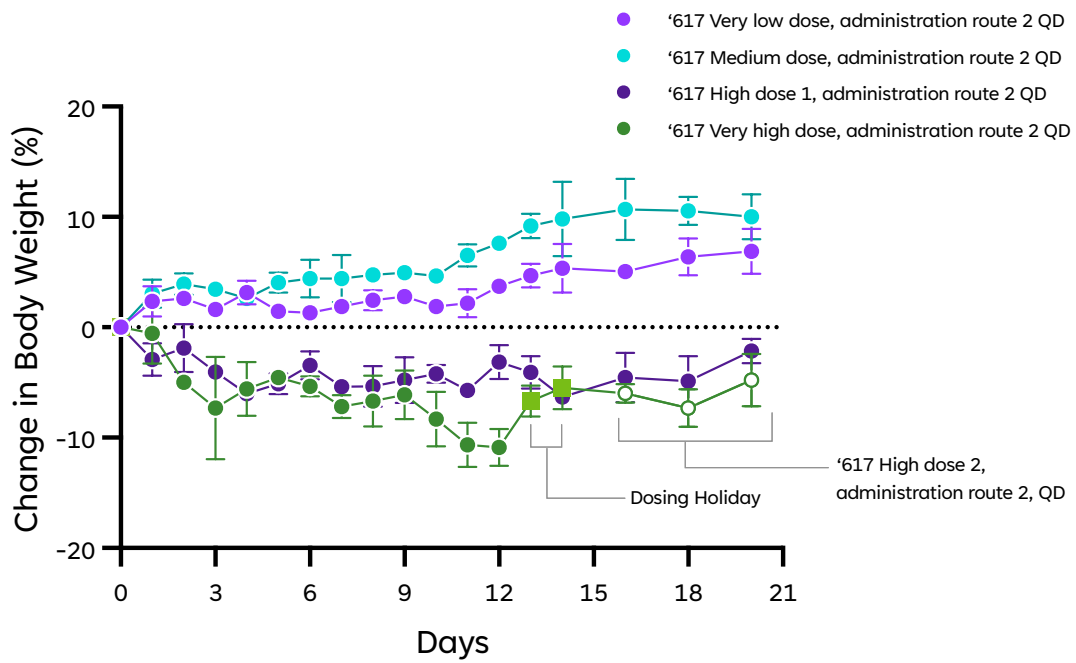
>10 hr of IC_{80} exposure predicted to increase toxicity risk

‘617 Single Dose Pharmacokinetics Data in CD1 Mice



CD1 mouse models predict 8-10 hr of IC_{80} exposure at a medium dose, increasing to >10 hr with a high dose (*Consistent with initial observations in clinic)*

‘617 Preclinical Maximum Tolerated Dose (MTD) Study

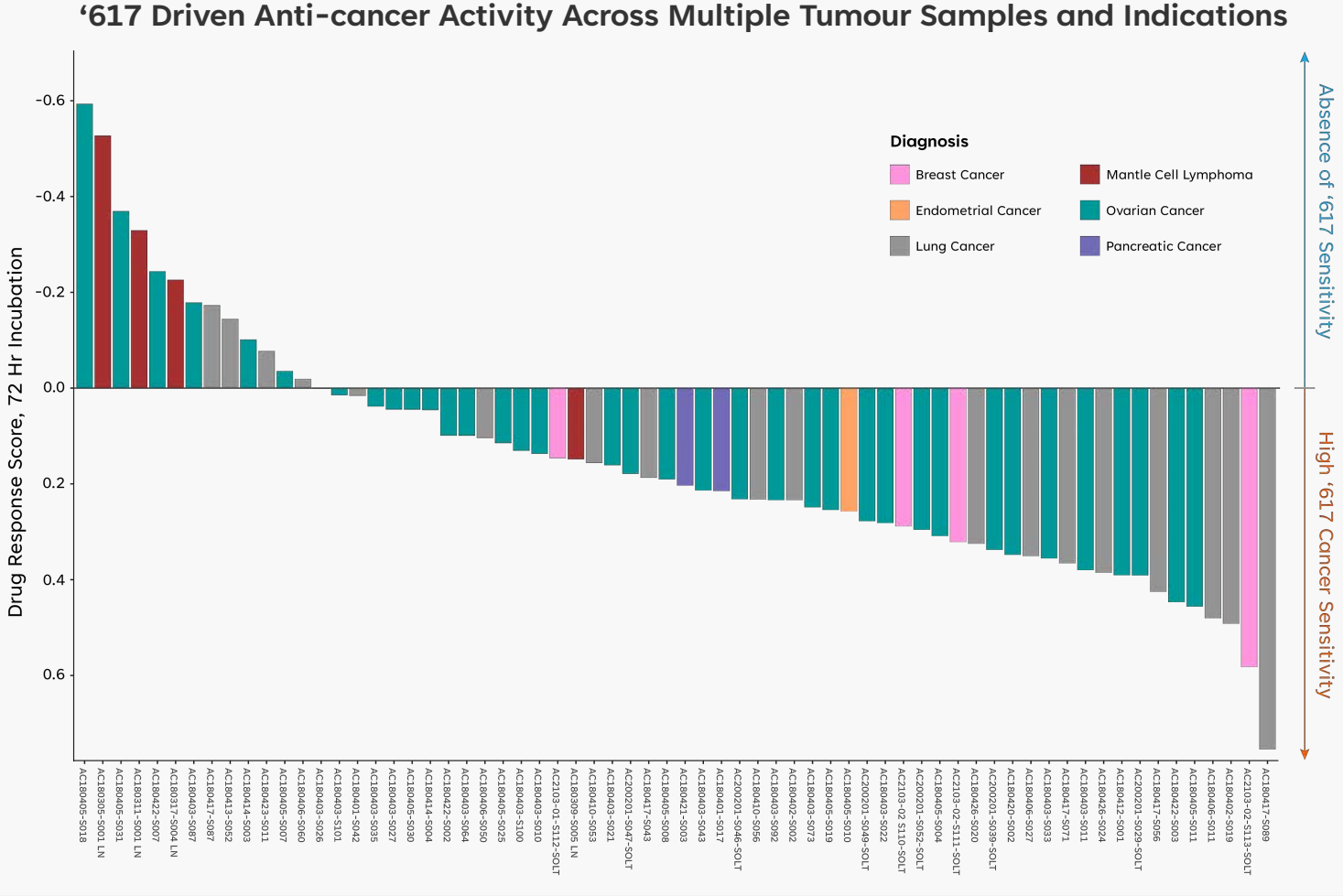


>10 hr IC_{80} exposure with a high dose leads to significant body weight impact, not seen with a medium dose* signalling optimal benefit risk with <10 hr of exposure

*Dose showing maximum tumour growth inhibition in ovarian and TNBC models

Evaluating the potential of ‘617 in primary tissue

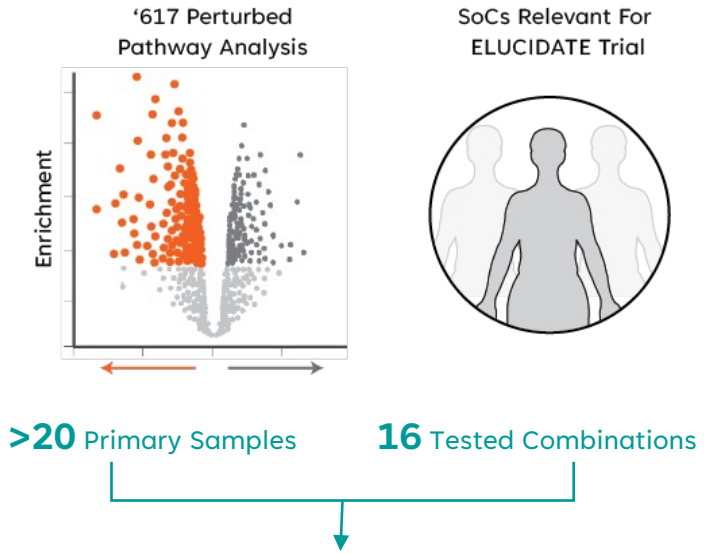
Exploring monotherapy and rational combinations with standard of care



Key Translational Platform Findings

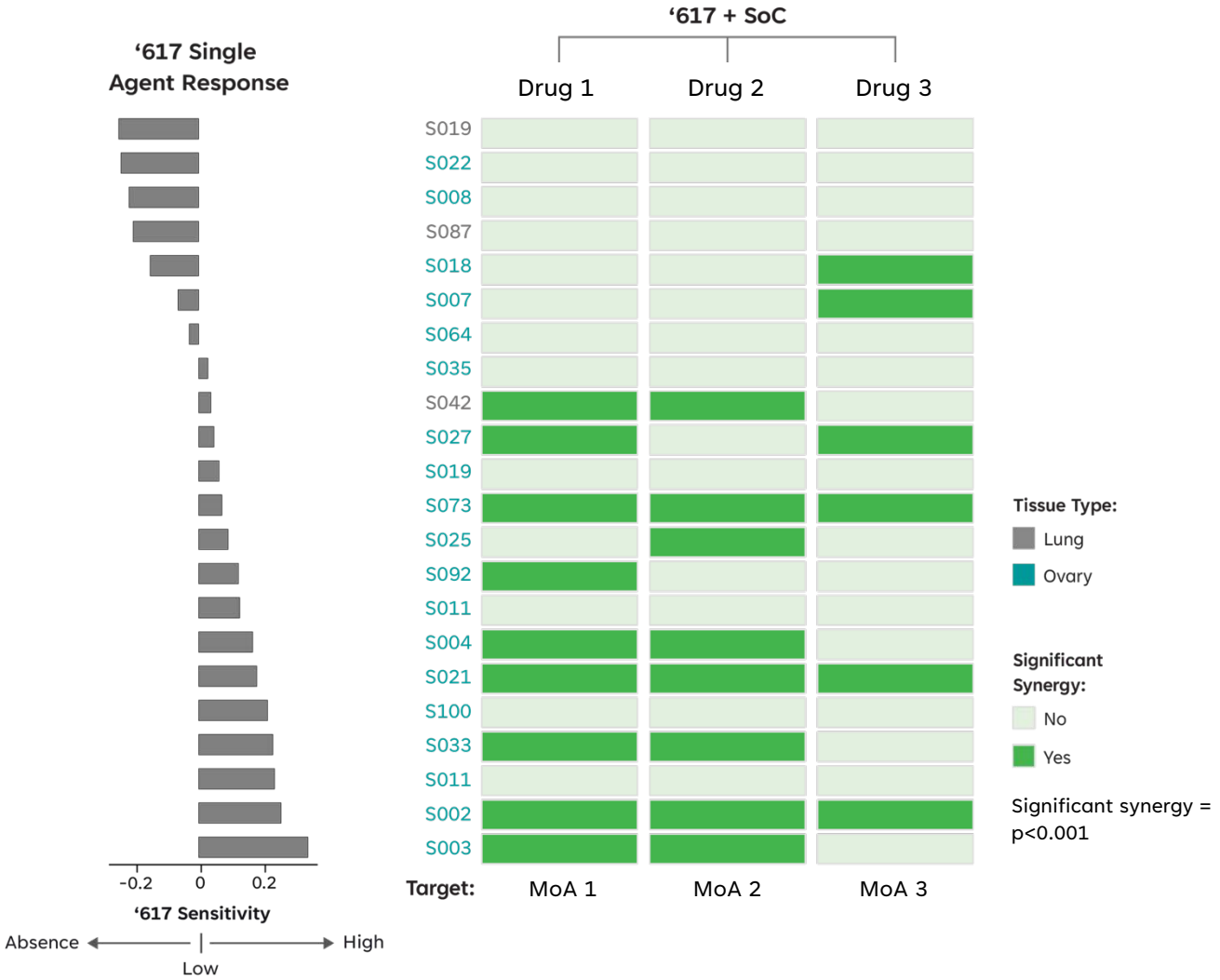
‘617 has demonstrated anti-cancer activity across multiple tumour samples and indications; 4/6 indications to be studied in ELUCIDATE.

Rational Design for Combination Testing



Expanding potential ‘617 efficacy with rational combinations

Synergies for ‘617 in combination preclinically in ovarian and lung cancer models



Drug 1 + ‘617
Related MoA

Synergy in 9/22 patients

Drug 2 + ‘617
Complementary MoA

Synergy in 8/22 patients

Drug 3 + ‘617
Multi-indication SoC

Synergy in 6/22 patients

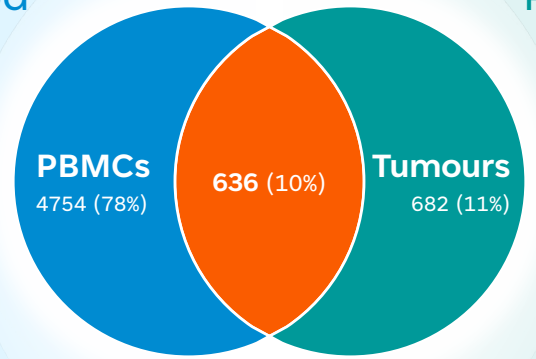
Importantly, some of this synergy is observed for samples with both low ‘617 and Drug 3 sensitivity

We are now integrating functional and omics data to validate the combination biology in sensitive primary patient material.

Proposed PD biomarker of ‘617 exposure

Preclinically identified PD biomarkers to be validated alongside ELUCIDATE

Cancer Patients’ Peripheral Blood

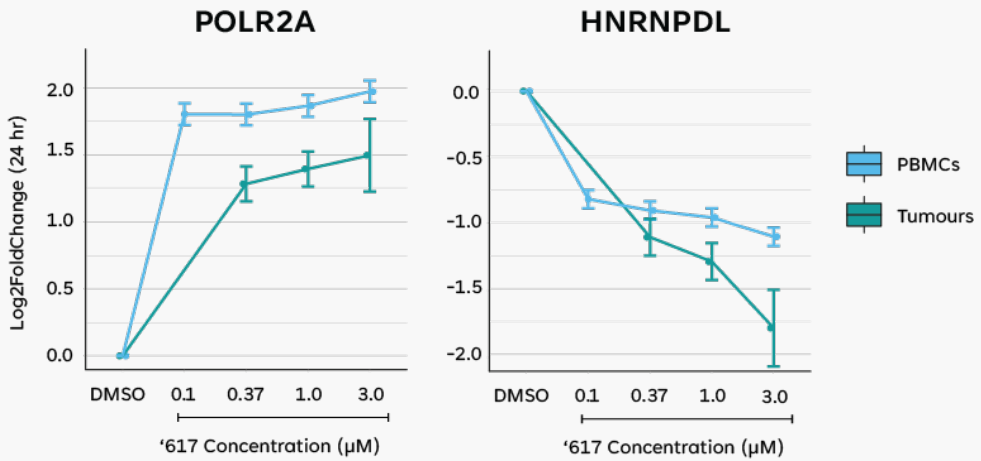


Number of genes modulated upon 24 hr ‘617 exposure

- \+ Provide non-invasive biomarkers
- \+ ‘617 effects on healthy cells
- − Partially informative of tumour effects

Cancer Patients’ Primary Tumours

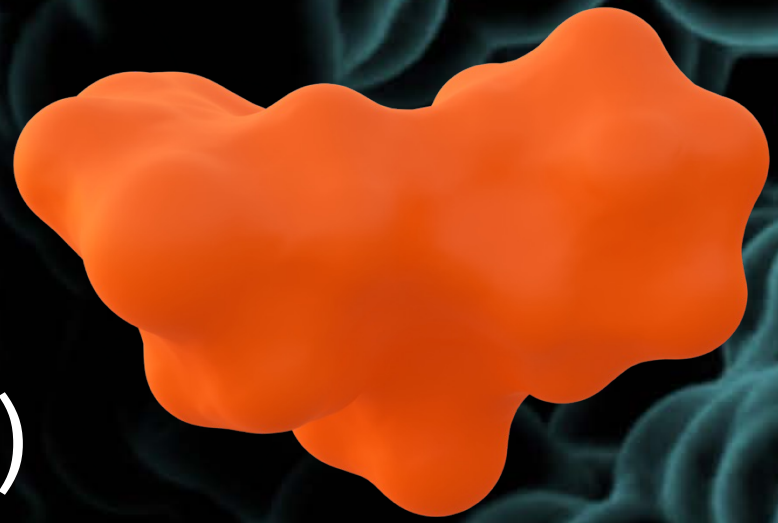
- \+ ‘617 effect on cancer cells
- \+ Comparison vs healthy cells



Two examples of preclinically identified PD biomarkers to be evaluated via transcriptomic profiling of peripheral blood and FFPE tumour samples from ELUCIDATE

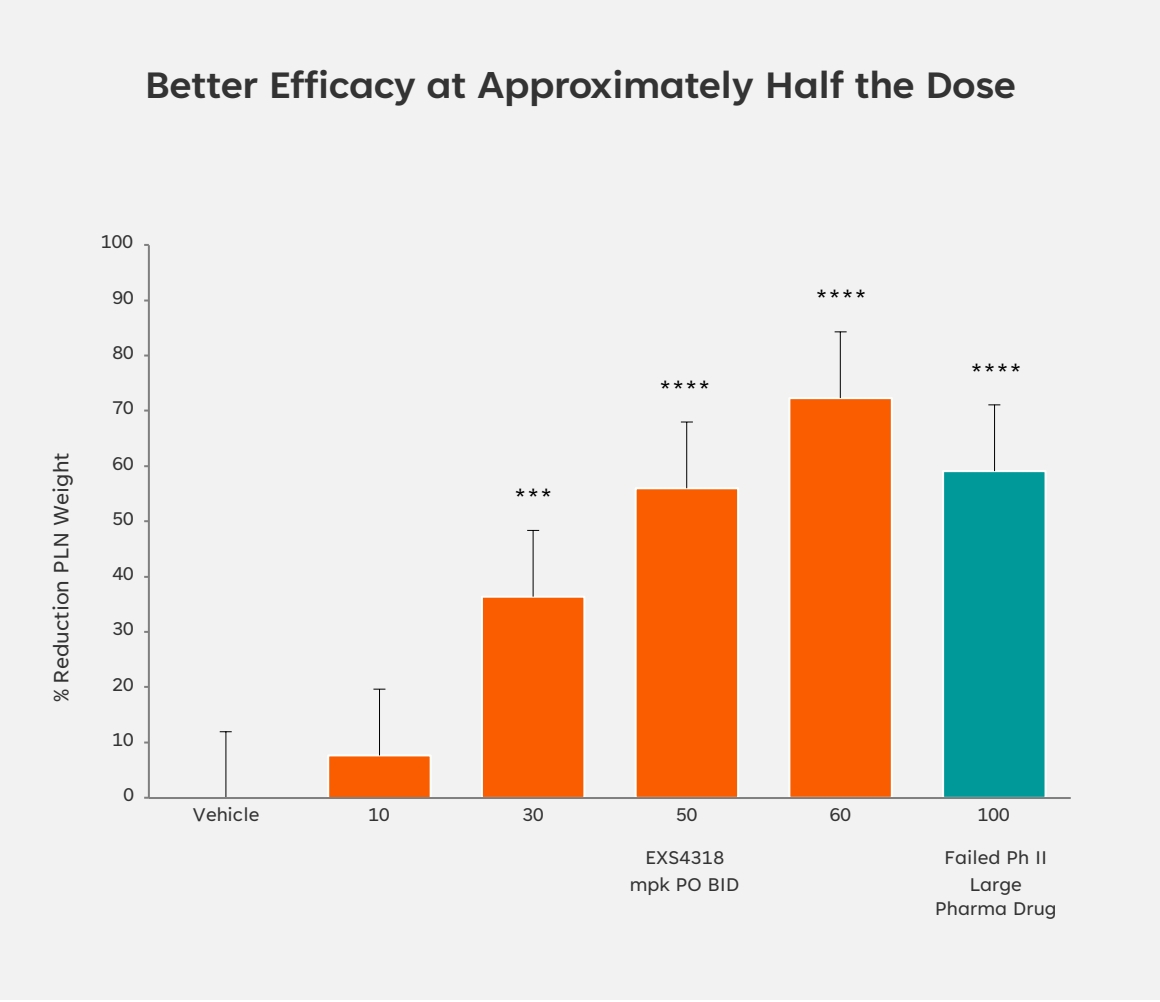
PBMC = peripheral blood mononuclear cells; FFPE = formalin-fixed paraffin-embedded

‘4318 (PKC-theta)
(in-licensed by BMY)
Phase 1 study ongoing



PKC-theta: In-licensed by BMY in August 2021

Expert led AI-design to deliver against a high-value target



Potential First-in-class Immunology Asset

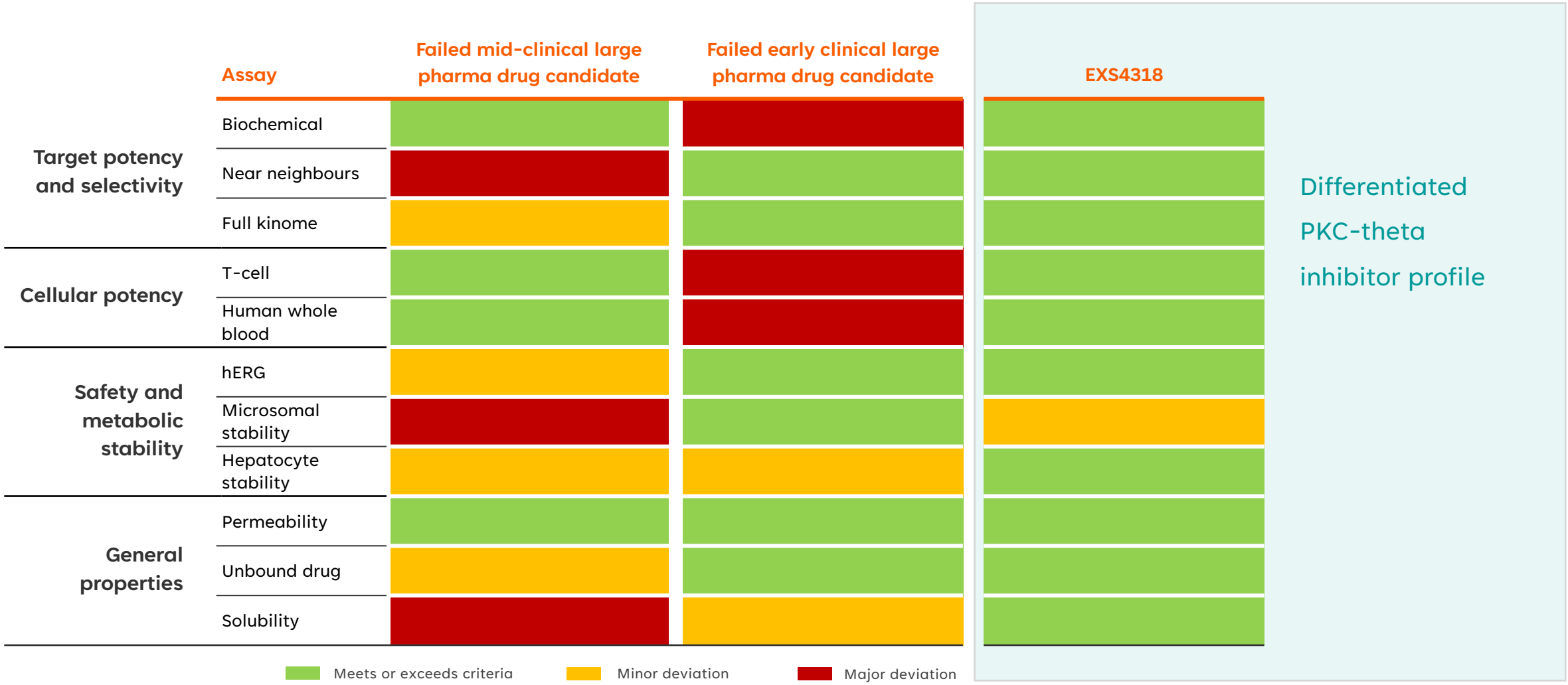
- High-value immunology target that had **eluded many large biopharmas** due to selectivity challenges
- **Balanced profile** provided improvements in human whole blood potency and predicted human dose <200 mg/day
- **Excellent selectivity** versus near neighbours and broad kinome

Key Elements of TPP

- 24 hrs coverage of IC_{80} required to drive efficacy
- Predicted human dose <200 mg/day
- High demands on target potency, selectivity, pharmacokinetics
- Robust translation into cellular and human whole blood assays

Large pharma failures on an attractive target

Potential first-in-class immunology target



Our approach

Fragments. 2D and 3D generative design. Hotspots and multi-task models

Experiment

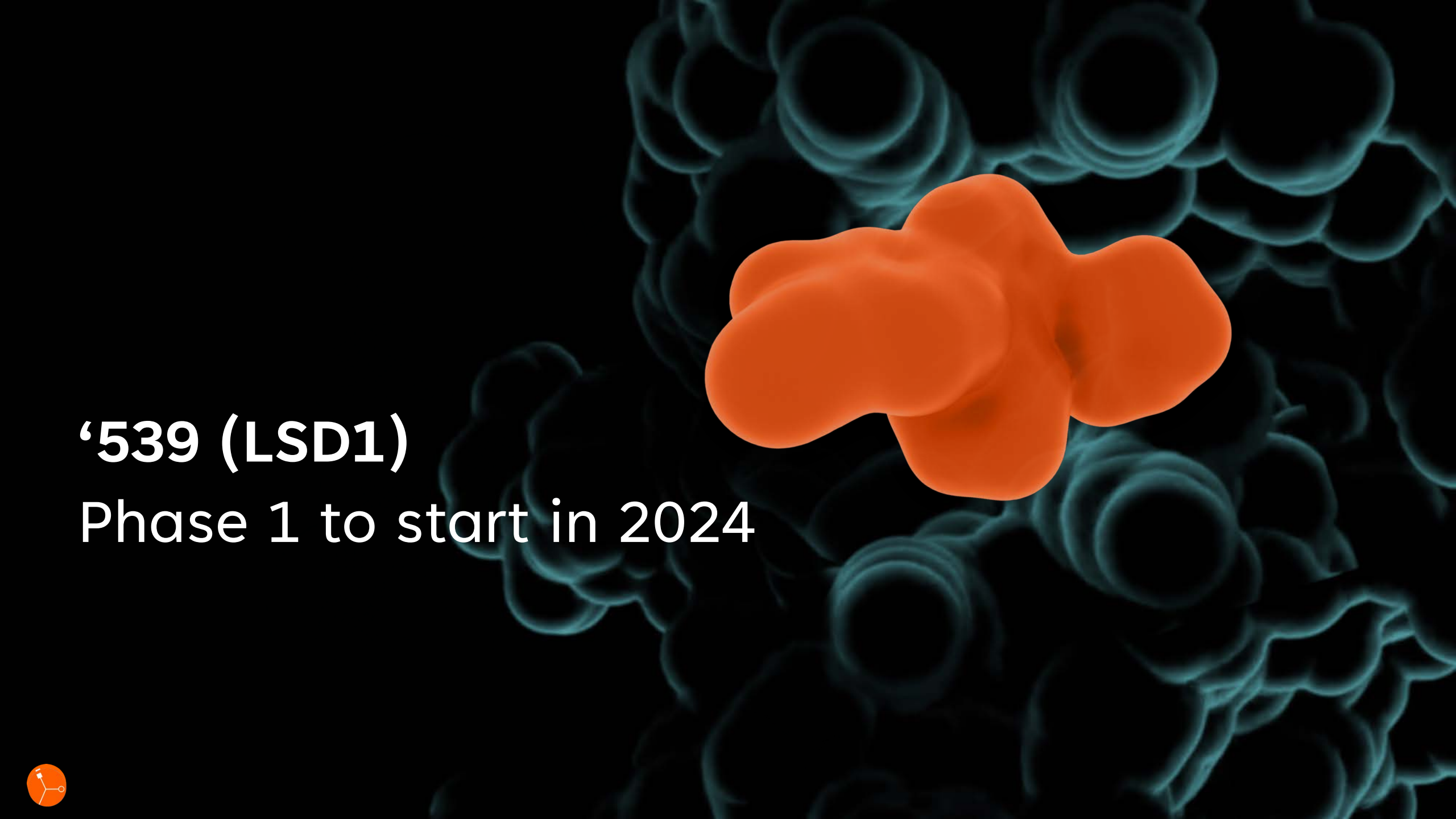
- Diverse ligand data sources. Proprietary fragment and kinase focussed **SPR screens** provided additional **seed data**
- Established and routinely executed key human whole blood assay

Expert-led AI Solutions

- **Generative design** rapidly explored selectivity-focussed scaffolds; **MERIT** analysis quantified the most promising
- **Hotspot** and **multi-task models** drove local and global kinase selectivity, respectively

Best-in-class Compound

- Nominated candidate designed in **<11 months** and was **150th novel compound** prepared
- Demonstrates close relationship at Exscientia of AI and experiment
- Elegant solution to a challenging problem. Nominated candidate <400 MW



‘539 (LSD1)

Phase 1 to start in 2024

‘539: LSD1 inhibitor moving into patient trials

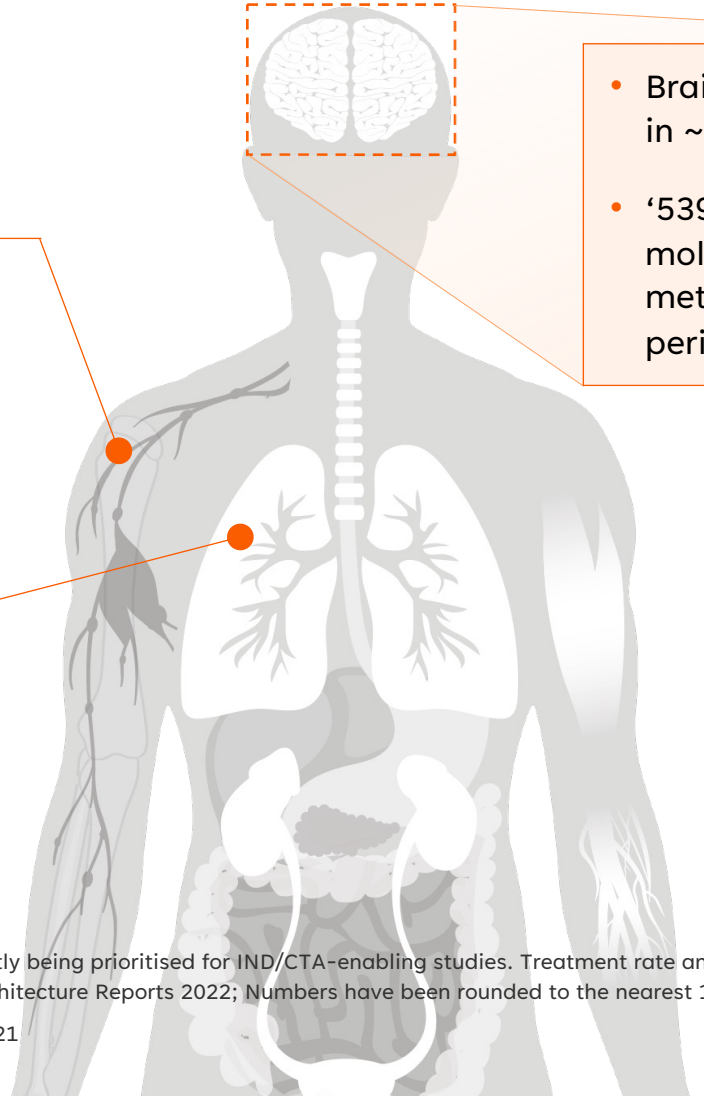
2022 United States incidence for planned patient sub-groups

17K

Acute Myeloid Leukaemia

28K

Small-cell Lung Cancer
Extensive Disease (Stage III / IV)



- Brain metastases develop in ~50% of SCLC patients[1]
- ‘539, a brain penetrant molecule, may target brain metastases as well as peripheral disease

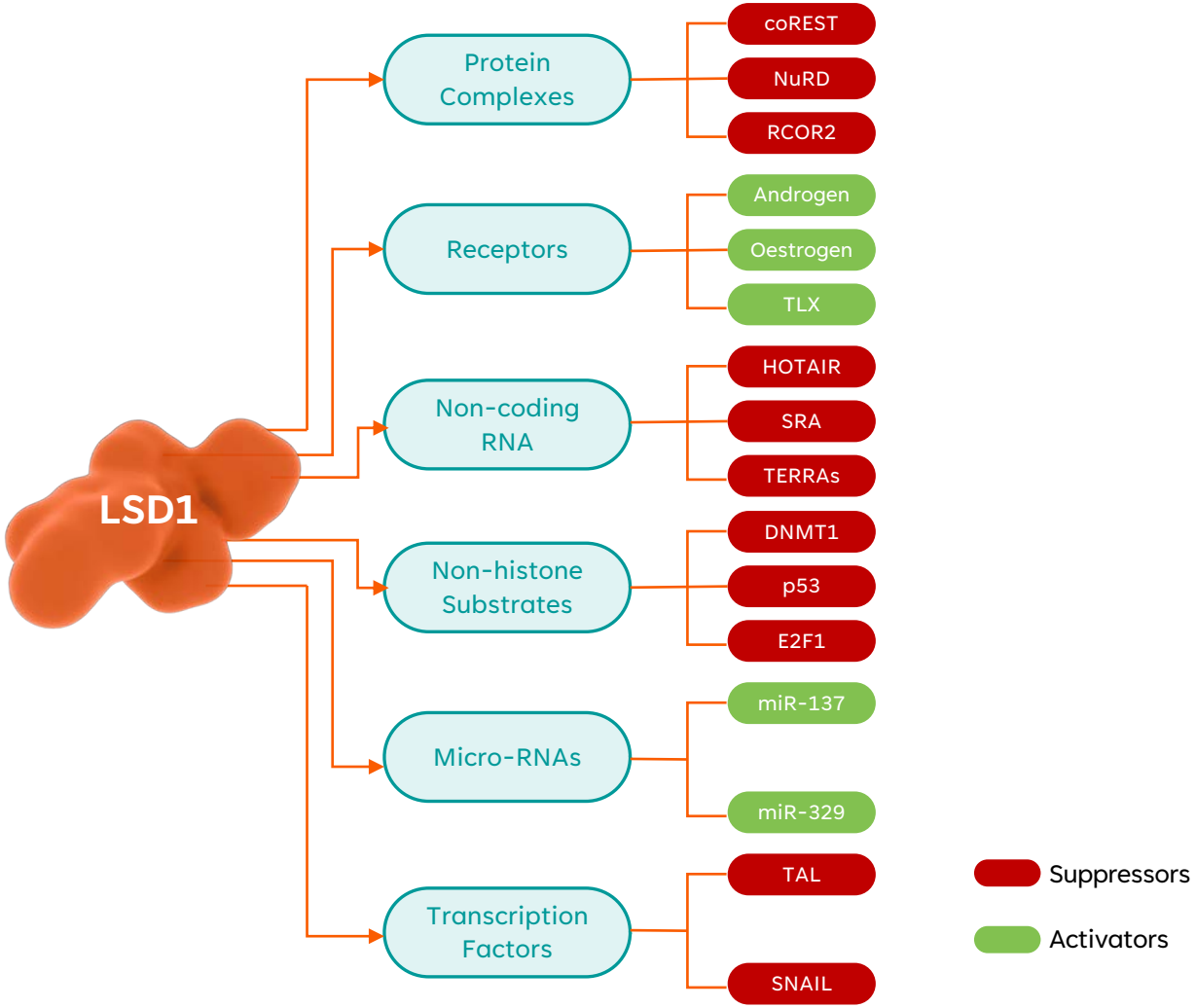
~45K U.S. Patients Lives Annually

Covers all indications currently being prioritised for IND/CTA-enabling studies. Treatment rate and progression rates based on Cerner Enviza Treatment Architecture Reports 2022; Numbers have been rounded to the nearest 1000 patients per year;

1) Li et al. Int J Gen Med, 2021

LSD1 inhibition leads to differentiation of tumour cells

Sensitising stem-cell like tumour cells to combination therapies



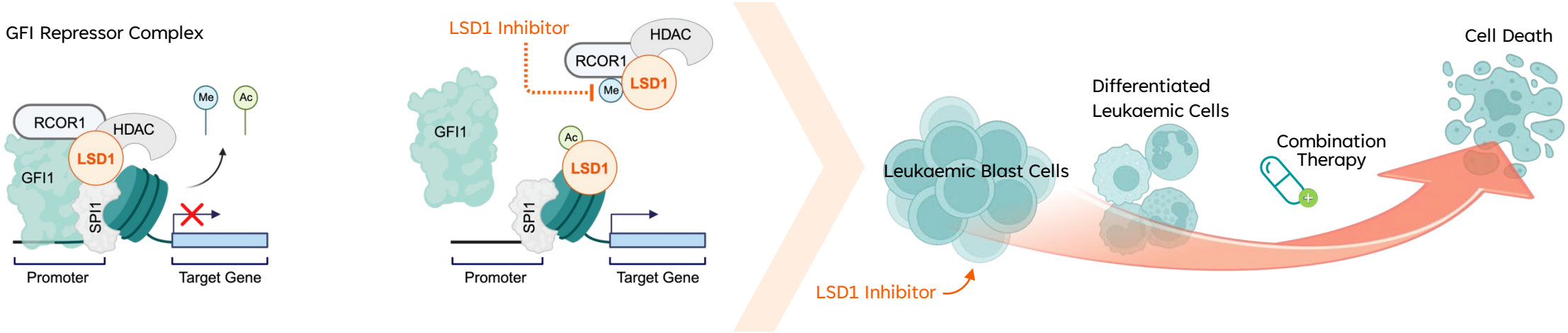
- LSD1 is not only an epigenetic modifier but also forms a variety of complexes with transcription factors, promoters, activators, corepressors and non-coding RNAs
- This variety of functions can drive tumourigenesis and modify the tumour microenvironment to enable enhanced cancer cell proliferation
- LSD1 is overexpressed in many cancer types across haematological and solid tumours and correlates with poor patient survival[1]
  - Literature has shown potential benefit of LSD1 inhibition in indications including AML[2], and neuroendocrine-like cancer types including SCLC[3], pancreatic[4] and prostate[5] cancer

Graphic adapted from Ismail et al. *Epigenetics Chromatin*, 2018.

1) Kim et al. *J Biomed Sci*, 2021; 2) Maes et al. *Cancer Cell*, 2018; 3) Mohammad et al. *Cancer Cell*, 2015; 4) Qin et al. *Cancer Lett*, 2014; 5) Kumaraswamy et al. *JCI Insight*, 2023.

LSD1 inhibition promotes cell differentiation in AML

‘539 reversibility and dosing schedule may provide safety benefits



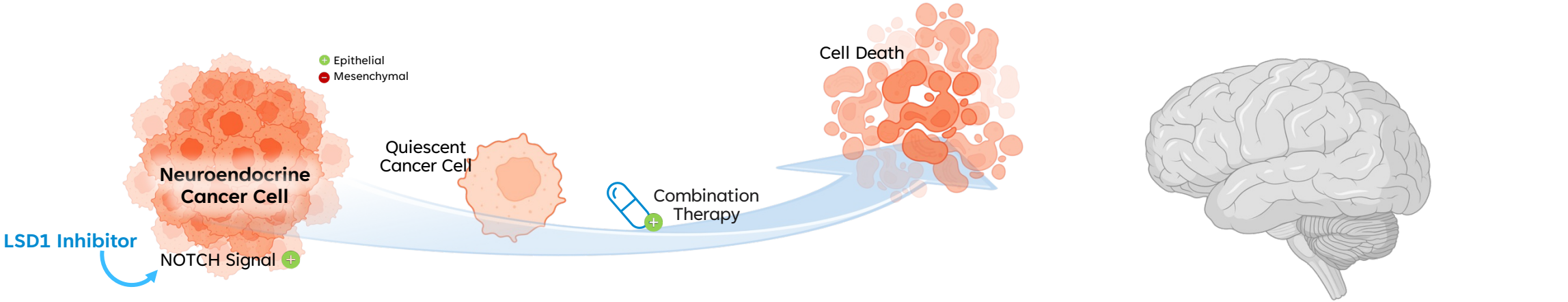
- LSD1 has key scaffolding function in GFI repressor complex that blocks differentiation
- Inhibiting LSD1 blocks the repressor complex and leads to increased acetylation of key promoters
- Results in the induction of leukaemic blast differentiation, which in turn stops cancer cell proliferation

- LSD1 inhibition has shown reduction of tumour growth in AML xenograft models[1]
- ‘539’s reversibility coupled with planned intermittent dosing is expected to reduce on target toxicity in AML

1) Maes et al. *Cancer Cell*, 2018

LSD1 inhibition drives neuroendocrine SCLC to quiescence

‘539 CNS penetrance may provide competitive differentiation



NE to Quiescence

Inhibiting LSD1 upregulates NOTCH signalling which promotes differentiation of neuroendocrine cancer cells into quiescent cancer cells

LSD1i + Cytotoxic

Quiescent cells treated with an LSD1 inhibitor and cytotoxic agent combination undergo apoptosis

‘539 Brain Penetrance

Brain metastases develop in ~50% of SCLC patients[1]

‘539, a brain penetrant molecule, may target brain metastases as well as peripheral disease

Patient selection strategies underway to identify patients most likely to respond

1) Li et al. *Int J Gen Med*, 2021

‘539: Highly differentiated LSD1 inhibitor

First precision designed molecule to tackle reversibility and brain penetrance

Better Design

Improved therapeutic index from low projected human dose, predicted human PK and reversible mechanism. Highly selective. Brain penetrant.

Mechanistic Rationale

Promotes differentiation pathways leading to tumour cell growth inhibition/death and/or higher sensitivity to standard of care in oncology indications

Target Population

Potential as monotherapy or in combination in range of haematology and oncology indications, including those with brain metastases

Phase 1 expected to start in 2024

Precision design to maximise therapeutic window

Mechanism requires tight control of duration of inhibition

Reversible, Selective

- LSD1 has important functions (e.g., influencing formation of blood cells)
- Most inhibitors are irreversible and/or have long human half-lives. Protein is inactivated for long periods of time
- Reversible inhibition and controlled human PK allow the key functions of the protein to be spared

Design needs to achieve potency and selectivity non-covalently

Pharmacokinetics

- Innovator lead (**irreversible**) has a human terminal half-life >40 hours. Most advanced **reversible** asset has half-life >70 hours and is dosed weekly. Both are known to deplete platelets in humans
- Design needs to deliver a compound with an **improved** therapeutic window. Maximise efficacy at the expense of side effects through better control of "time on target"

Goal is to minimise on-target toxicity (through dose and schedule)

CNS Penetrant

- Brain metastases are a major cause of mortality in SCLC patients
- Having a compound with meaningful CNS exposure would allow exploration in this area of high unmet need

Candidate needs to be brain penetrant to access brain metastases

LSD1: Delivering quality candidate against a novel TPP

EXS74539 offers potential best-in-class asset with unique property profile

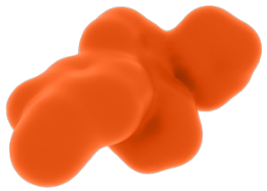
	Assay	Candidate Properties	Competing Irreversible Ph 1/2 Candidate	Competing Reversible Candidate	Exscientia Candidate '539
CNS penetration	Brain:plasma ratio	>0.5			
Target affinity and mechanism	LSD1 IC_{50} (nM)	<10			
	Surface plasmon resonance	Reversible			
Cell potency and *in vivo* efficacy	SCLC cell line proliferation (nM)	<100			
	Efficacy in 2x SCLC models *in vivo*	TVR >65%			
Safety and metabolism	CV safety margin				
	Human microsome Clint µL/min/mg	<15			
	Human hep Clint µLmin/10^6 cells	<15			
Permeability / transporter liability	MDCK-MDR1 efflux ratio (Pgp inhibition)	<2			
	Solubility pH 7.4 µg/ml	>50			
PK properties	F % (p.o.)	>30%			
	Half-life	Suitable for QD administration			

- CNS penetrant
- Potent and reversible
- Highly selective (including related amine oxidases)
- Efficacious *in vivo*
- Excellent metabolic stability, bioavailability and efflux
- Shorter predicted half-life than competitors

Meets or exceeds criteria | Minor deviation | Major deviation | Not tested

Technology in action: Precision design of ‘539

Designing and selecting the right molecules to synthesise



Generative Design | Machine Learning | Structure | Selection Criteria | Active Learning

Initiate | **Evolve** | **2D Models** | **3D Models** | **Prioritise** | **Synthesis**

Knowledge-based Evolutions Using 2D and 3D Data

Improve properties of compounds from knowledge-based starting points

Evolutionary Algorithm

Gambit

Evolve into 3D binding pocket and shape of known ligands

2D generative approaches

2D Models **ML Models**

Use known LSD1 amine groups

Good physchem properties

CNS MPO

Good predictions against models

Interaction Filter

Prioritise on key interactions with the protein

Coverage Score **Active Learning Exploitation**

hERG and CNS constraints

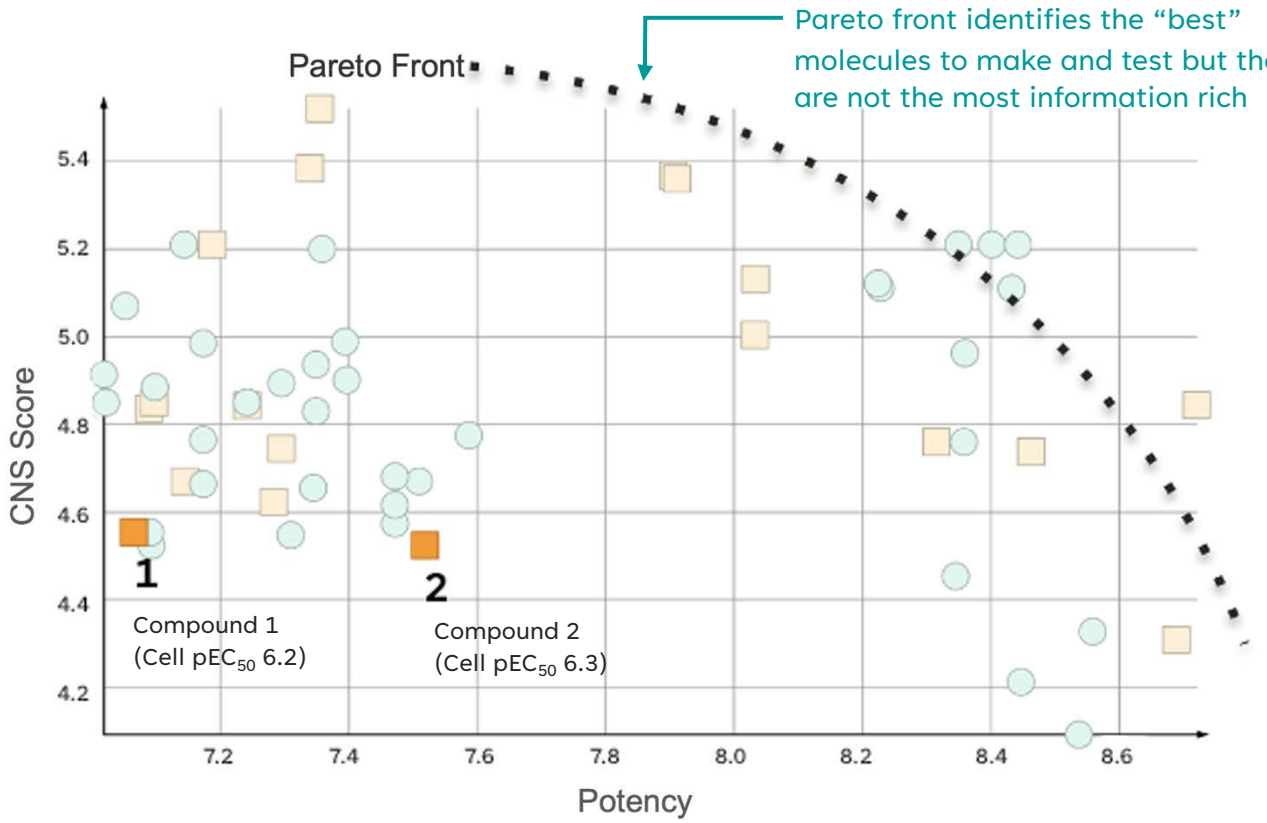
10–20 for Synthesis

AL pushes design into novel chemical space

Key example of active learning exploring chemical space

Active learning enabled breakthrough for ‘539

Counterintuitive selection went against preconceptions to break dogma



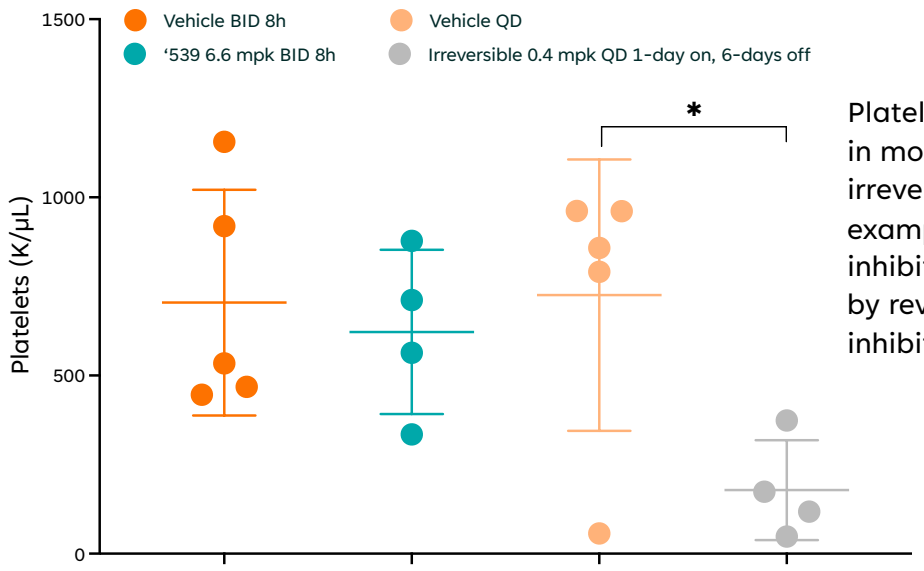
20 compounds (square) are selected by active learning chemical coverage; other compounds (circles) were not selected

- Our active learning approach selected compounds both close to and away from the pareto front (dotted arch) using a combination of MPO and coverage score
- “Seemingly unattractive” compounds, 1&2, were identified, away from the pareto front
- 1&2 were non-optimal on any predicted property but were structurally different
- Structures were synthesised and tested – this new scaffold providing a better starting point to achieve the TPP
- Further cycles of design refined hits to produce ‘539

Benefit of reversible LSD1 target engagement on platelets

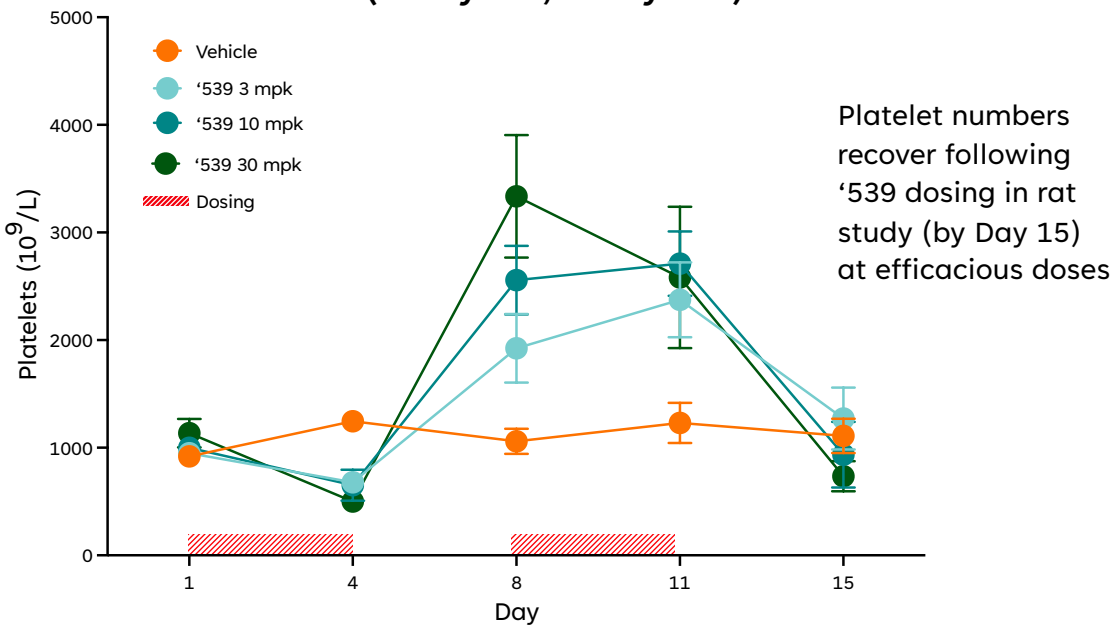
Shorter half-life and reversibility may benefit on-target tox management

Platelet Count in Mouse Efficacy Study[1]



Platelets depleted in mouse *in vivo* by irreversible clinical example LSD1 inhibitor, but not by reversible inhibition by '539

Reversible Platelet Modulation in Rat Study (3-days on, 4-days off)[2]



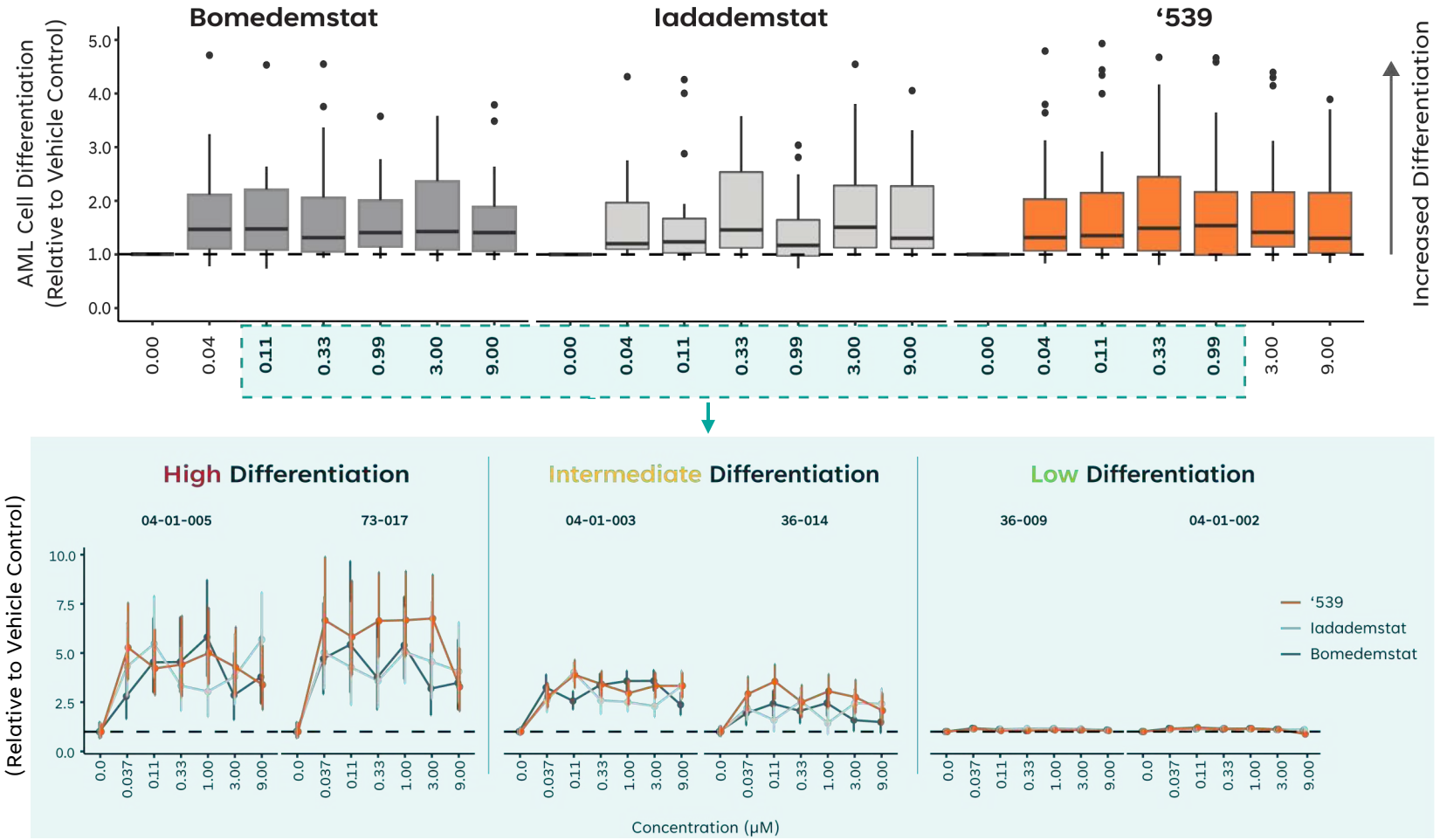
Platelet numbers recover following '539 dosing in rat study (by Day 15) at efficacious doses

- Platelets are **depleted** with a **once-weekly** dosed **irreversible** inhibitor in mouse efficacy study
- Even at supra-efficacious doses, rat platelets recover following dosing with **reversible inhibitor, '539**

1) Mouse SCLC NCI-H69 xenograft model, 20-days dosing; 2) Rat, 2-week study

‘539 induces *ex vivo* myeloid differentiation

Preclinical activity comparable to irreversible LSD1 inhibitors



‘539 has potent *ex vivo* activity against primary human AML samples

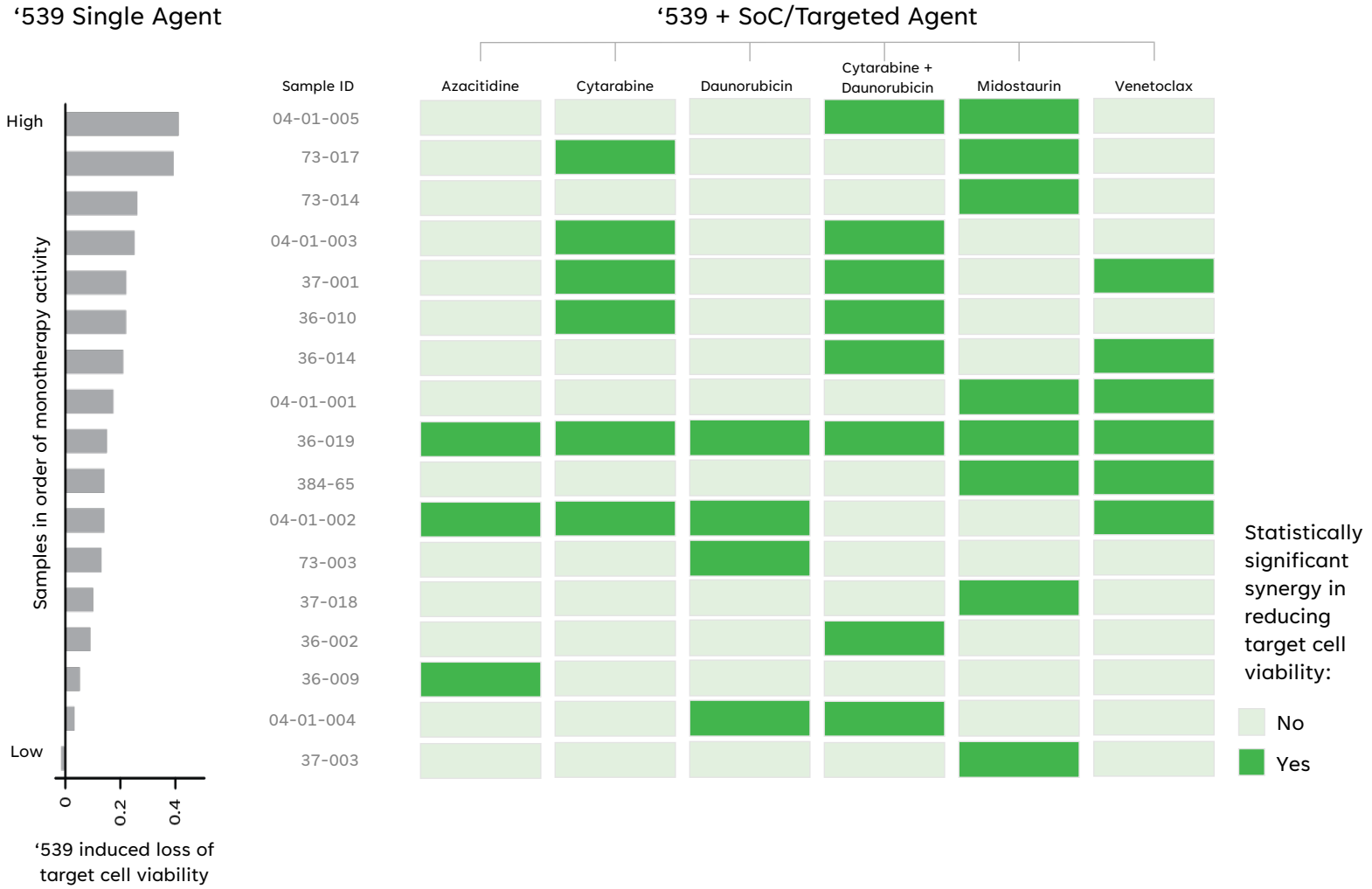
‘539, a reversible inhibitor, has comparable *ex vivo* efficacy to clinical stage irreversible inhibitors

Heterogeneity of response supports further exploration of patient selection strategies in the clinic

Okumura et al. ESMO, 2023; Differentiation measured by CD86 marker expression induction

‘539 synergises with first line SoC and targeted therapies

Combination potential established preclinically in primary AML samples



Azacitidine + ‘539
SoC nucleoside analogue
Synergy in 3/17 patients

Cytarabine + ‘539
SoC nucleoside analogue
Synergy in 6/17 patients

Daunorubicin + ‘539
SoC anthracycline/DNA intercalating agent
Synergy in 4/17 patients

Cyta + Dauno + ‘539
Combination SoC
Synergy in 8/17 patients

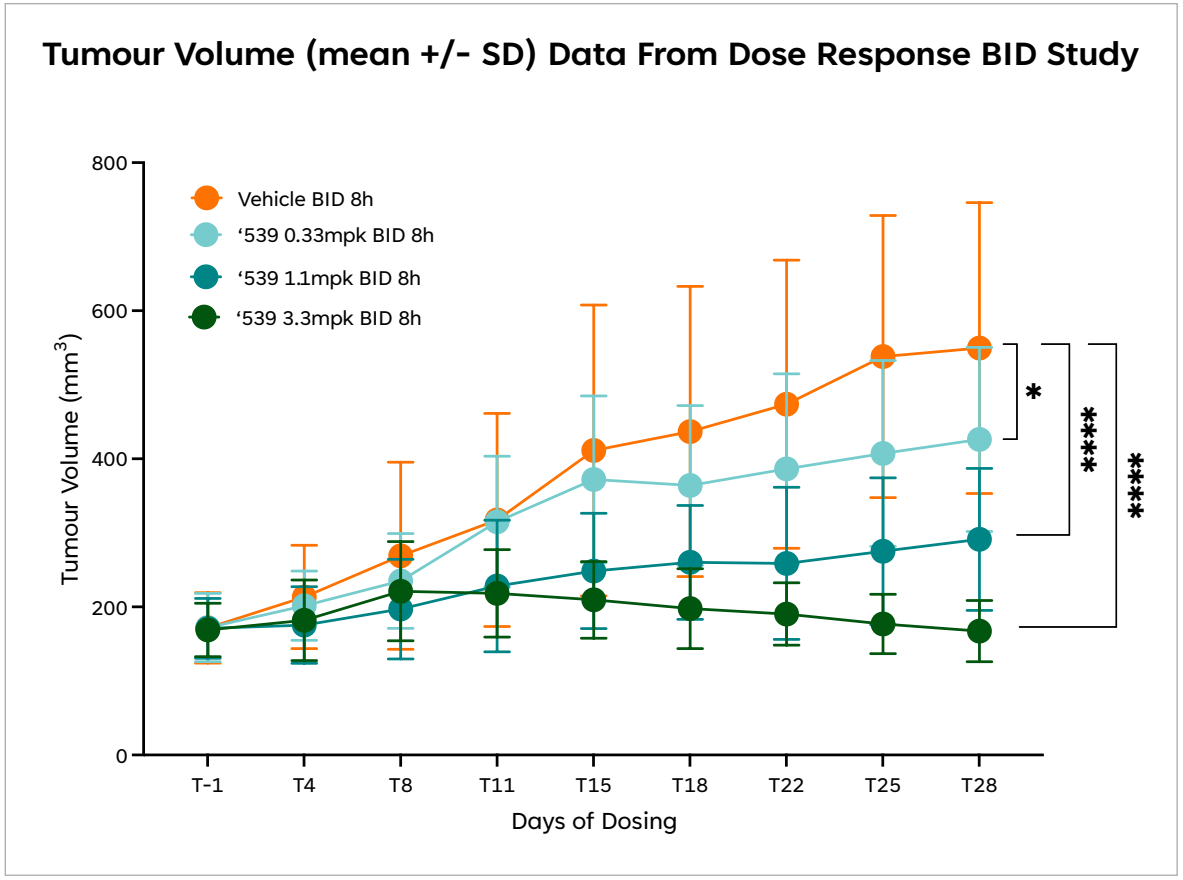
Midostaurin + ‘539
FLT3 inhibitor
Synergy in 8/17 patients

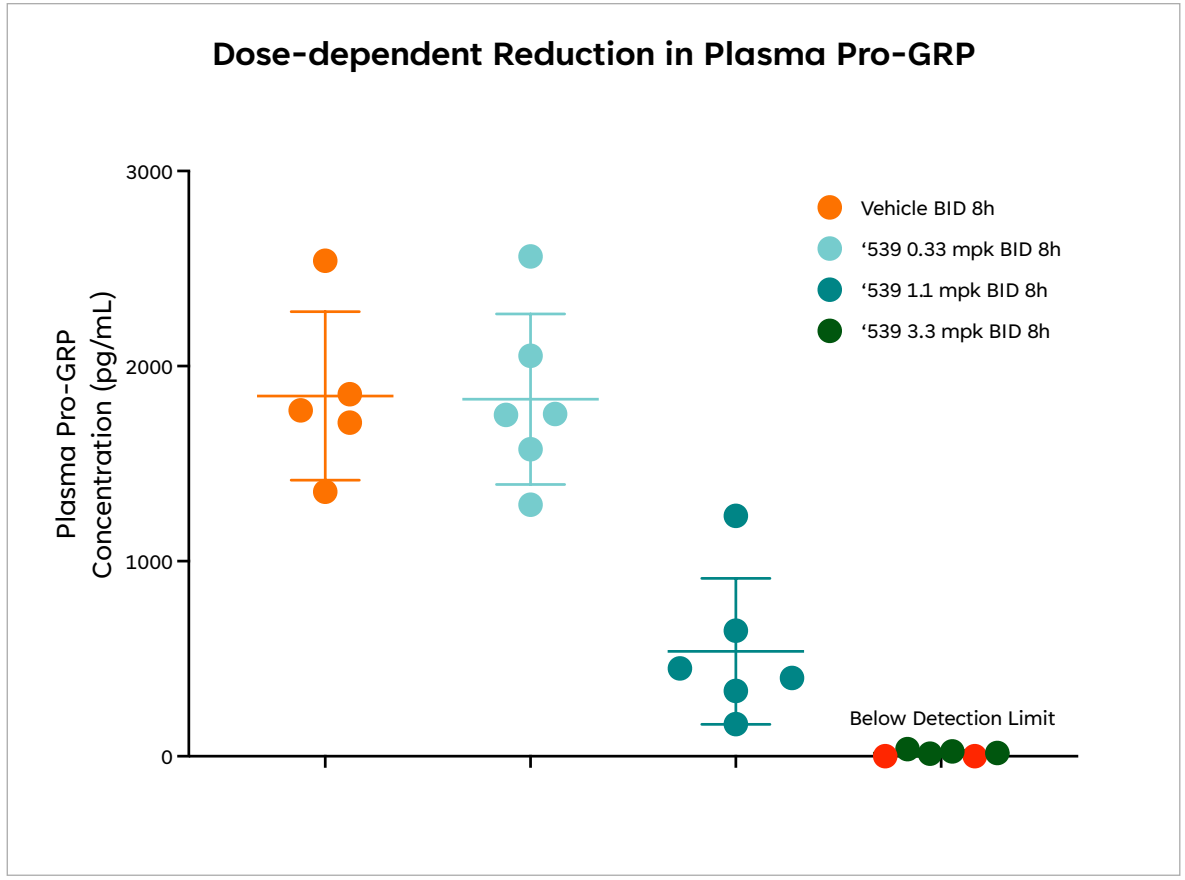
Venetoclax + ‘539
Bcl-2 inhibitor
Synergy in 6/17 patients

Okumura et al. ESMO, 2023; synergy calculated using highest single agent (HSA) index. Significant synergy = p<0.05, (tested with multiple hypothesis correction); SoC = standard of care

‘539 inhibits tumour growth *in vivo*

Dose-dependent tumour growth inhibition in SCLC xenograft model





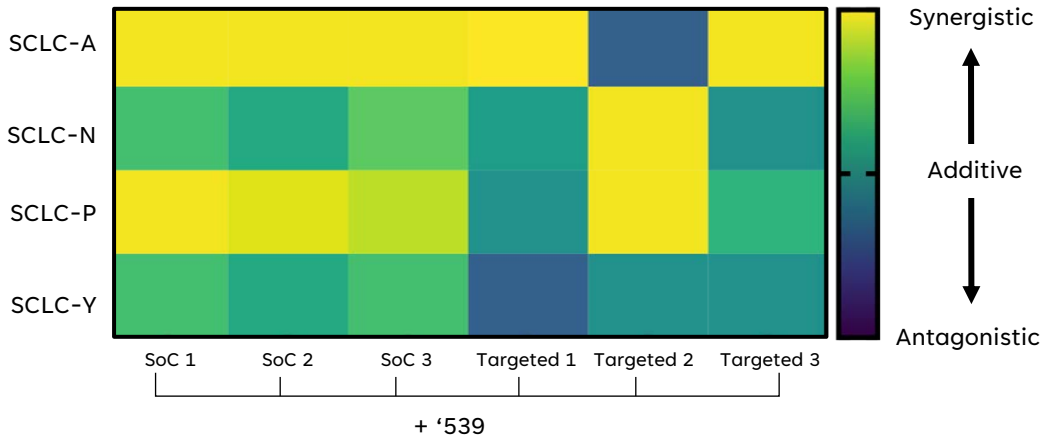
‘539 was well tolerated with body weight maintained in our studies

NCI-H1417 xenograft (SCLC); Pro-GRP: Progastrin-releasing peptide is a commonly used biomarker for SCLC malignancies

‘539 synergises with approved SoC and targeted therapies

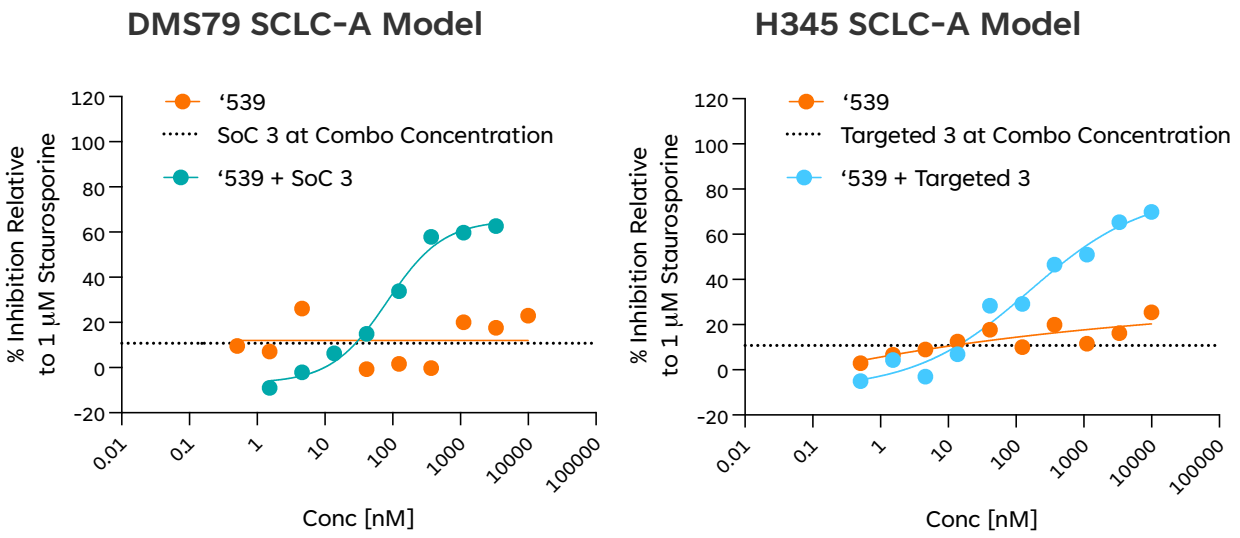
Combinations enhance anti-proliferative effects in ‘539 unresponsive SCLC cell lines

‘539 Combination Synergy
(Calculated Using Bliss Independence Model)



SCLC molecular subtypes[1]	SCLC-A	SCLC-N	SCLC-P	SCLC-Y
Percentage (%)	70	11	17	2

‘539 + SoC/targeted Agent in SCLC-A Cell Lines
Non-responsive to ‘539

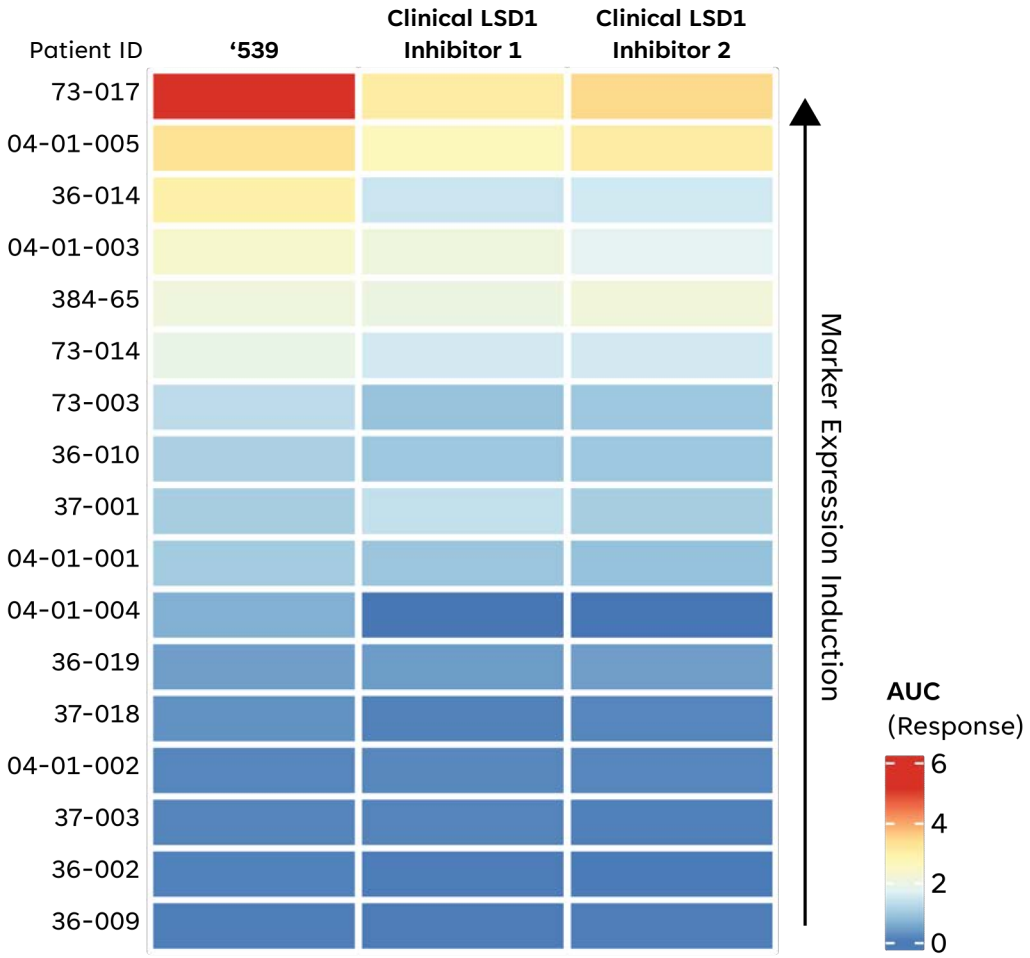


‘539 in combination with SoC has potential in most common SCLC patient sub-types even for those that are not responsive to LSD1i as a single agent

1) Rudin et al. *Nat Rev Cancer*, 2019

Variability observed in ‘539-induced AML cell differentiation

Patient enrichment is critical to clinical success



- High patient-to-patient variability in LSD1-induced myeloid cell differentiation *ex vivo* in primary AML patient samples
- Crucial to identify AML patients more likely to respond to ‘539 in the clinic
- Currently generating patient enrichment hypotheses leveraging our single cell omics capabilities to detail ‘539-induced gene expression on AML cell subpopulations

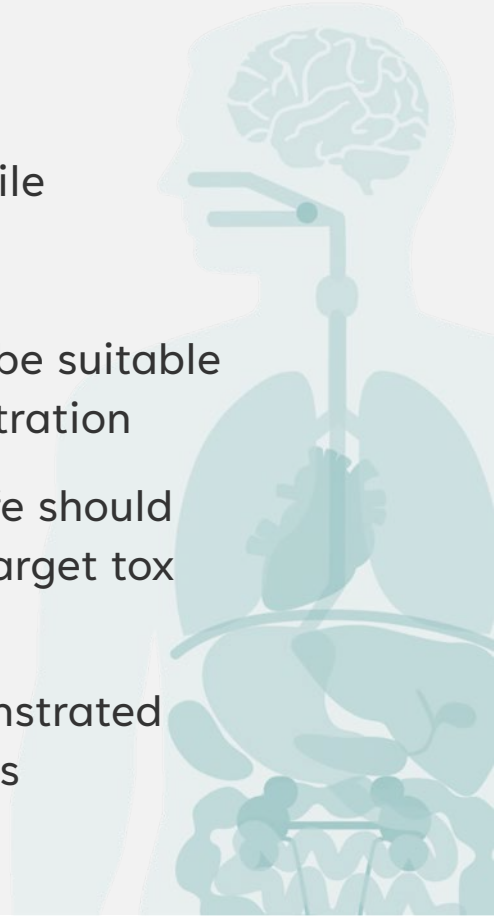
Okumura et al. ESMO, 2023; Variability observed across all diagnoses, age groups and subtypes

LSD1

Favourable PK, tox and safety profile supports ongoing development

Pharmacokinetics (PK)

- Good preclinical PK profile
- High oral bioavailability
- Human PK predicted to be suitable for once-a-day administration
- Predicted human half-life should provide benefits to on-target tox management
- Brain penetration demonstrated across preclinical species

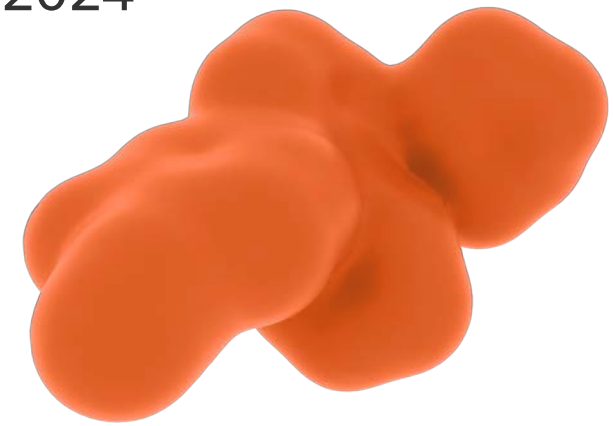


Toxicology & Safety Pharmacology

- No unexpected *in vitro* or *in vivo* safety concerns identified
- No changes recorded in dog CV telemetry study
- Tolerated in rat/dog 28-day GLP tox studies with expected effects on haematology parameters
- Margins suitable for progression to clinical trial

‘539: Summary

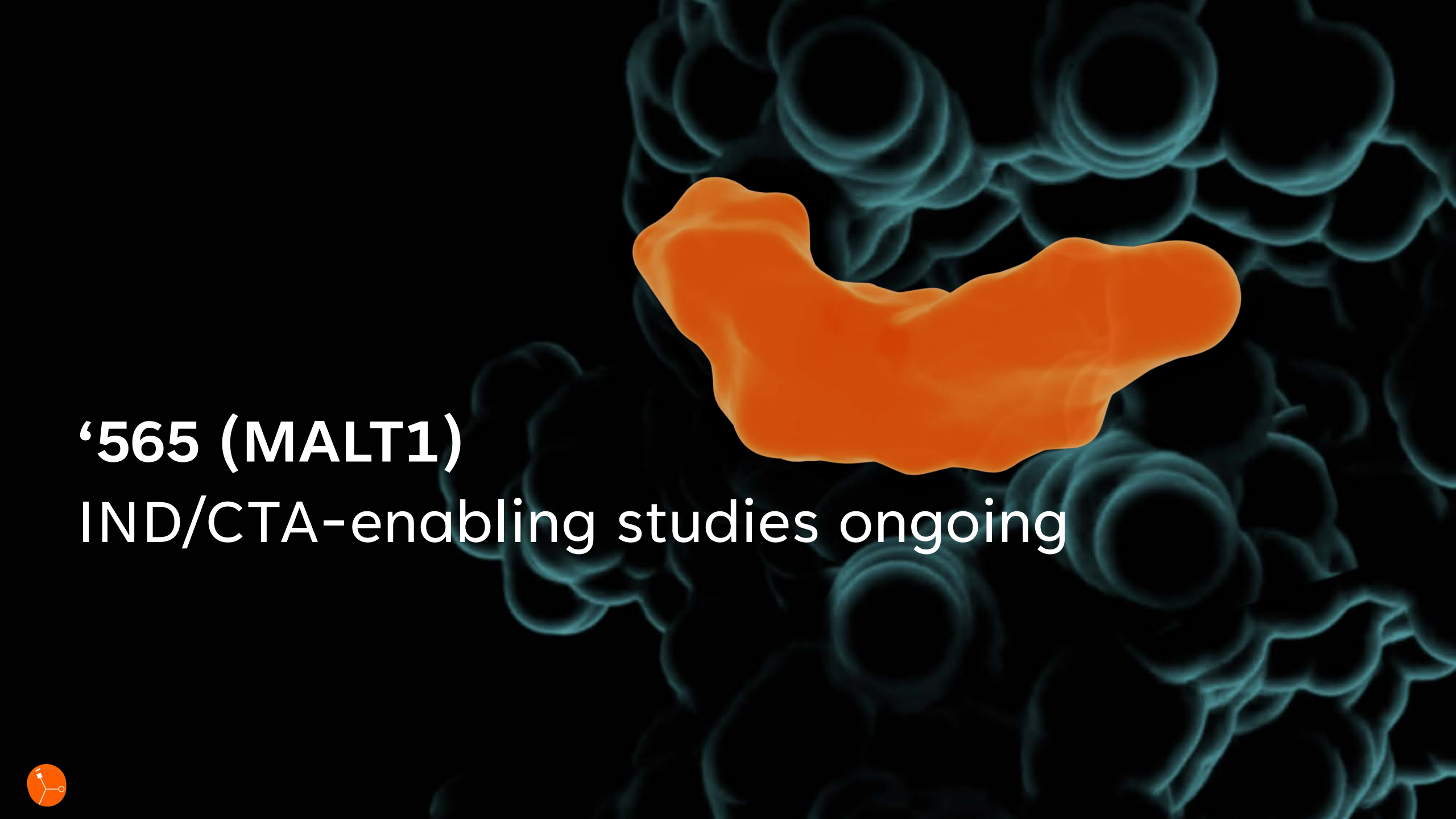
- GLP-tox studies completed
- Secondary formulation development ongoing
- MIDD to define best dose and dosing regimen
- Phase 1 expected to start in 2024



MIDD = Model-informed Drug Development

Programme Highlights:

- Potent, highly selective, reversible and brain penetrant LSD1 inhibitor
- Suitable therapeutic index established with no unexpected toxicity in GLP tox studies
- Potential in broad range of haematologic and oncologic diseases
- Potential as monotherapy or combination therapy
- Translational work ongoing to define optimal patient populations and validation of PD biomarkers



‘565 (MALT1)

IND/CTA-enabling studies ongoing

‘565: Potential to avoid key class-wide safety concern

Allosteric MALT1 protease inhibitor shows significant anti-proliferative activity

Better Design

MALT1 protease inhibitor with significantly reduced UGT1A1 inhibition risk combined with potency and selectivity

Mechanistic Rationale

MALT1 is required for oncogenic signalling in B-cell and T-cell lymphomas

Target Population

May expand therapeutic options for patients with B-cell lymphomas

Confirmed activity in B-cell lymphomas with PM platform

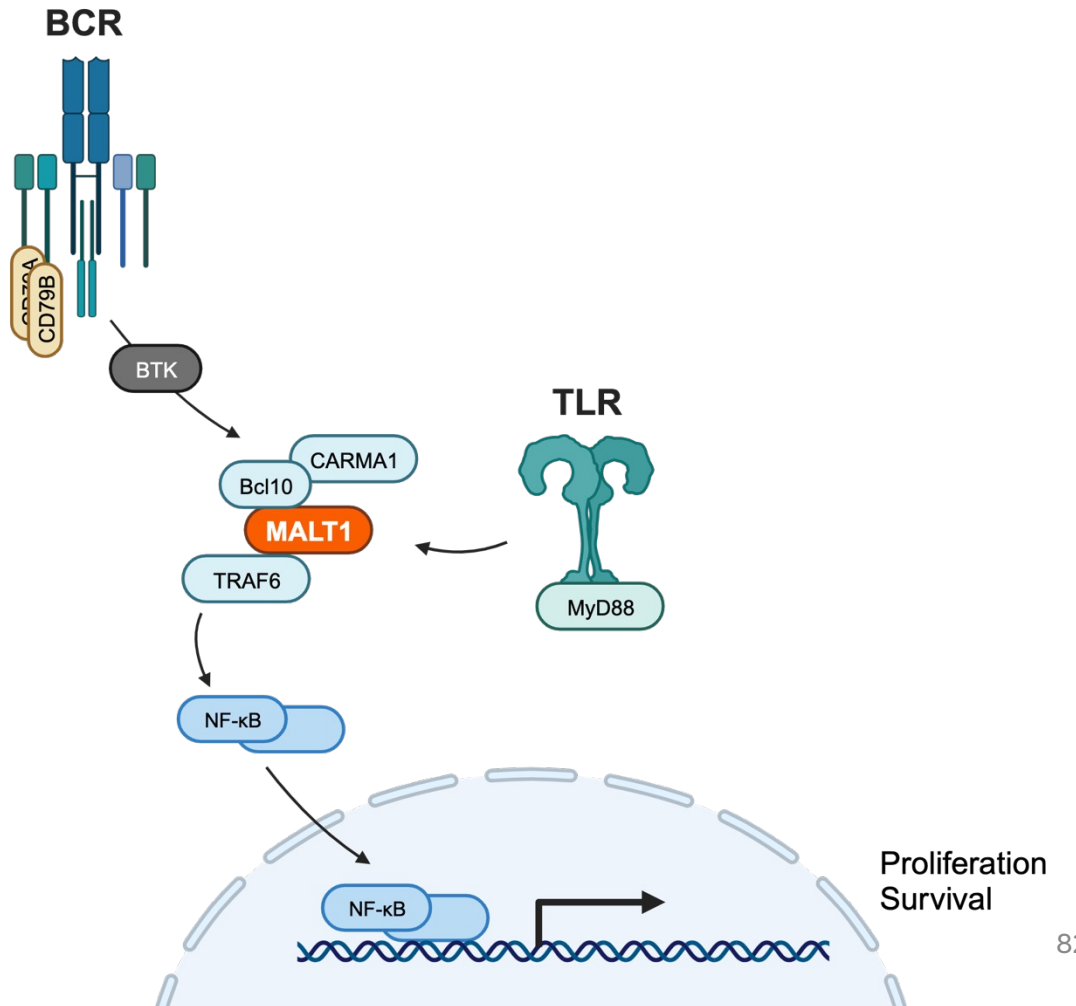
IND-enabling studies ongoing

Additional updates expected in 1H 2024

MALT1: Inhibiting malignant cell signaling in B-cell lymphomas

Important mechanism in haematologic malignancies

- Chronic activation of the B-cell receptor (BCR) in malignant B-cells can lead to inappropriate NF-κB signalling, driving uncontrolled tumour cell proliferation and survival
- MALT1 functions downstream of the BCR and also the therapeutic target, BTK, and is a critical component of tumourogenic signalling pathways in these tumour cells
- Inhibition of MALT1 protease activity blocks the pathogenic signals from the BCR and, in a subset of NF-κB-addicted tumours, inhibits tumour cell proliferation
- Combining MALT1 and BTK inhibitors could provide additional efficacy in these lymphomas by stronger inhibition of the pathway and by maintaining activity in tumours with target-mediated BTK inhibitor resistance



Precision designed to maximise therapeutic index

Developing a differentiated and selective inhibitor

Selective and Potent

- Design a potent and highly selective MALT1 inhibitor with an allosteric mechanism of action
- Clean protease panel selectivity profile

Goal was to invent a potent and highly selective allosteric MALT1 inhibitor

Therapeutic Index

- Demonstrate adequate therapeutic index over potential on mechanism toxicity
- Minimise potential drug-drug interactions with combination agents

Addresses a combination issue common to most MALT1 inhibitors

Efficacy and Dosing

- Shown to be effective as both a monotherapy and in combination with ibrutinib (BTKi)
- Anti-proliferative against primary B-cell lymphoma samples
- Predicted half-life suitable for QD administration

Synergistic efficacy

Avoiding uridine glucuronyl transferase (UGT1A1)

‘565 offers potential competitive differentiation

- Bilirubin is made during the natural degradation of red blood cells. It is rapidly cleared from the body, mainly through liver metabolism and subsequent biliary elimination
  - Uptake of unconjugated bilirubin into the liver occurs in part *via* OATP transport
  - Once in the liver, bilirubin is exclusively glucuronidated by UGT1A1, and then effluxed into the bile by MRP2

- UGT1A1 inhibition can cause elevated bilirubin (hyperbilirubinaemia) and can lead to metabolic disorder
  - Jaundice, nausea, vomiting and potentially encephalopathy can occur

- UGT1A1 pathway has an active role in triggering potential drug-drug interactions in the clinic
  - This is particularly relevant to BTKi given the many reports of drug-induced liver injury with these agents

MALT1 allosteric competitor profiles

Most competitor compounds have a high UGT1A1 inhibition risk

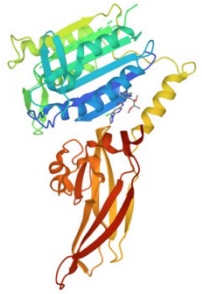
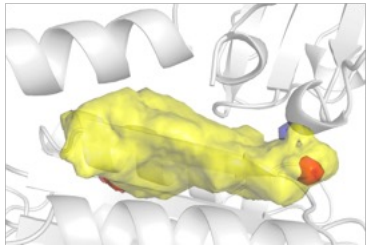
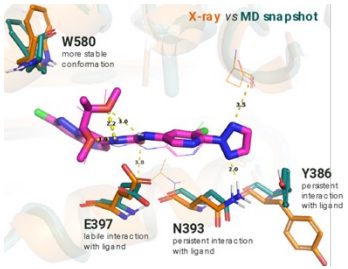
Parameter	Phase 1/2 (Large pharma)	Phase 1 (Large pharma, patent examples)	Phase 1 (Mid-size pharma, patent examples)	Phase 1 (Biotech, patent examples)	Exscientia Candidate '565
Biochemical pIC_{50} >7	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria
OCI-Ly3 IL-10 pIC_{50} >7	Meets or exceeds criteria	Meets or exceeds criteria	Not tested	Meets or exceeds criteria	Meets or exceeds criteria
OCI-Ly3 proliferation IC_{50} (<400 nM)	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Minor deviation	Meets or exceeds criteria
TMD8 IL-10 IC_{50} (<200 nM)	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Minor deviation	Meets or exceeds criteria
TMD8 proliferation IC_{50} (<300 nM)	Minor deviation	Meets or exceeds criteria	Not tested	Not tested	Meets or exceeds criteria
UGT1A1 IC_{50} (>10 µM)	Major deviation	Minor deviation	Major deviation	Major deviation	Meets or exceeds criteria
Hu heps Clu calc (ml/min/kg) <20	Meets or exceeds criteria	Not tested	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria
Caco-2 A-B (ER) 10^{-6} cm/s [>5(<3)]	Meets or exceeds criteria	Major deviation	Major deviation	Minor deviation	Meets or exceeds criteria
Solubility pH 7.4 (>250 µg/mL)	Minor deviation	Major deviation	Major deviation	Major deviation	Minor deviation
Cerep / full kinase panel	Meets or exceeds criteria	Meets or exceeds criteria	Not tested	Not tested	Meets or exceeds criteria

Meets or exceeds criteria Minor deviation Major deviation Not tested

Technology in action: Precision design of ‘565

Designing and selecting the right molecules to synthesise

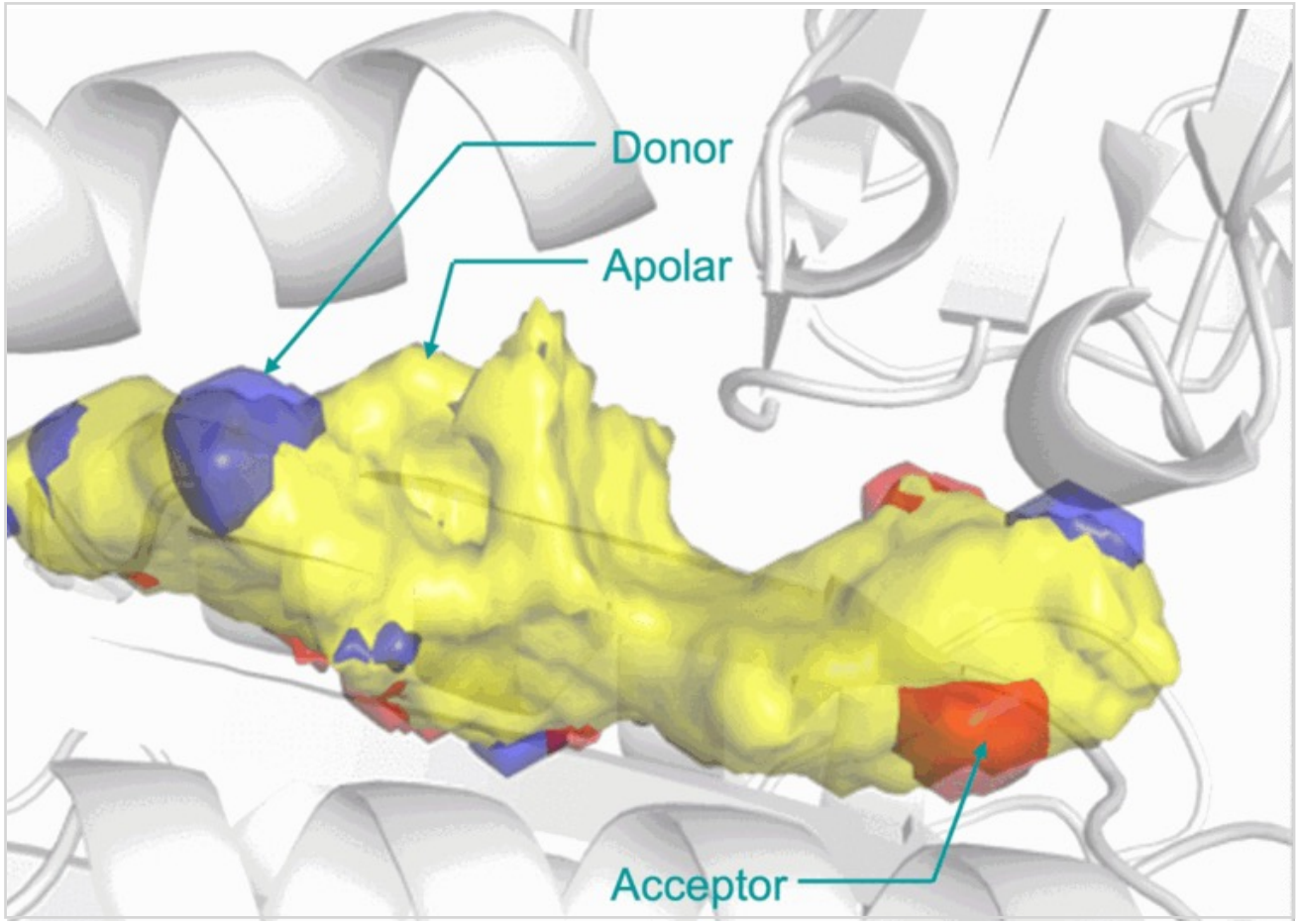
Generative Design | Machine Learning | Structure

Initiate	Analyse	Evolve	2D Models	3D Models	Active Learning
					**10-20 for Synthesis**
Use of MD to define dynamic pocket	Hotspot analysis to find key interactions and drive generative algorithms	**Evolutionary Algorithm**	**2D Models** **ML Models**	**Interaction Filter**	**Coverage Score** **Active Learning Exploitation**
		Automated structural informatics Evolve in 3D directed towards Hotspot interaction (Gambit) Hybridisations	Good physchem properties MPO Good predictions against models	**Compatibility with key Hotspots**	**Solubility Potency** AL pushes design into novel chemical space

Proof of concept to use MD with our end-to-end AI-driven platform

‘565 leveraged physics-based predictive modelling

Understanding protein flexibility using molecular dynamics

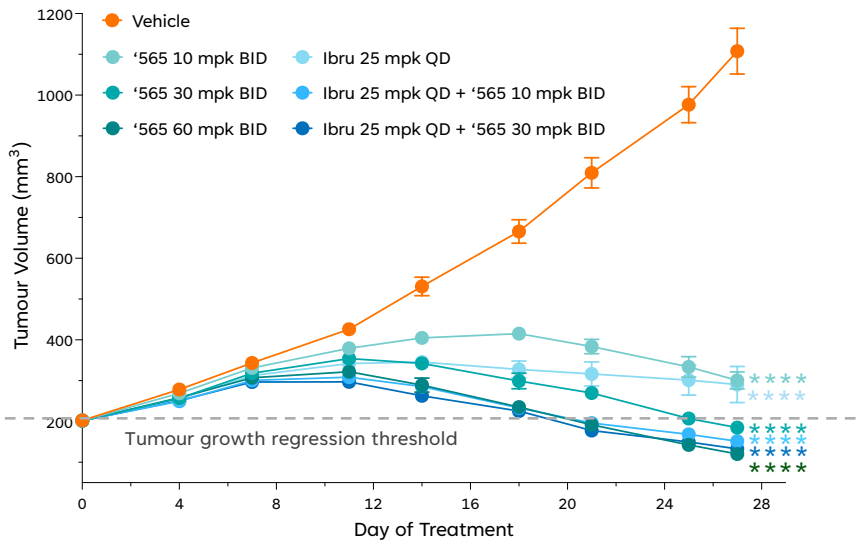


- Simulated binding site movements and integrated with Hotspots for automated definition
- Design of ‘565 expanded our approach onto complex dynamic targets and into novel chemical space
- Drove our generate constraints towards delivering improvement in permeability
- ‘565 candidate delivered using physics-based constraints in allosteric site

‘565 inhibits DLBCL tumour model growth *in vivo*

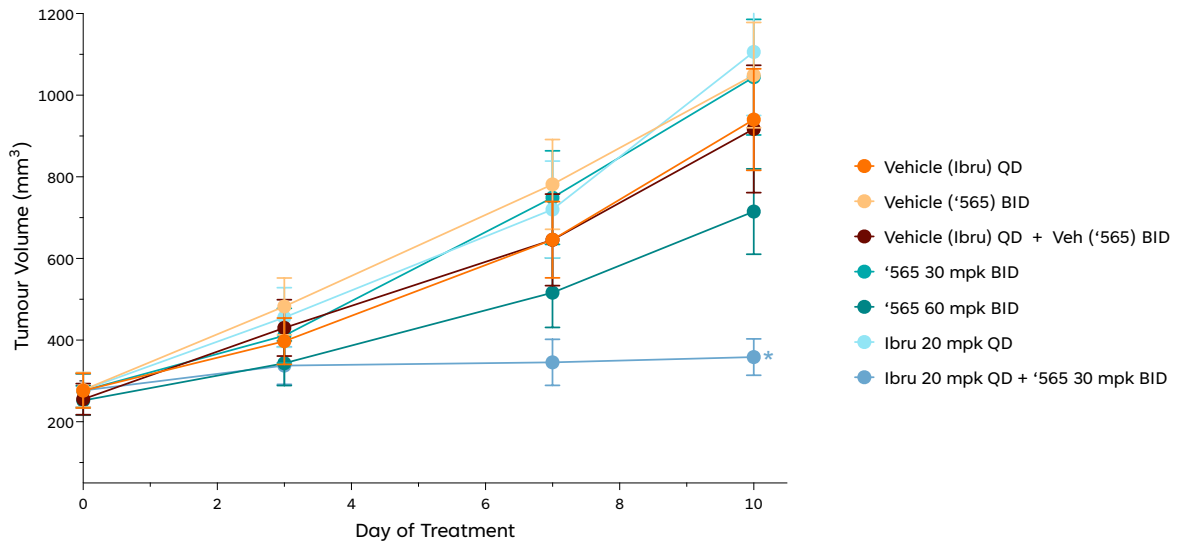
Single agent and synergistic effects seen in DLBCL xenograft models

‘565 ± Ibrutinib in OCI-Ly10 Xenograft Model



- OCI-Ly10 cells are sensitive to both MALT1i and ibrutinib *in vitro*
- Administration of ‘565 as a single agent showed tumour growth regression
- Synergistic tumour growth regression observed when 10 mpk ‘565 was combined with ibrutinib

‘565 ± Ibrutinib in TMD8 Xenograft Model

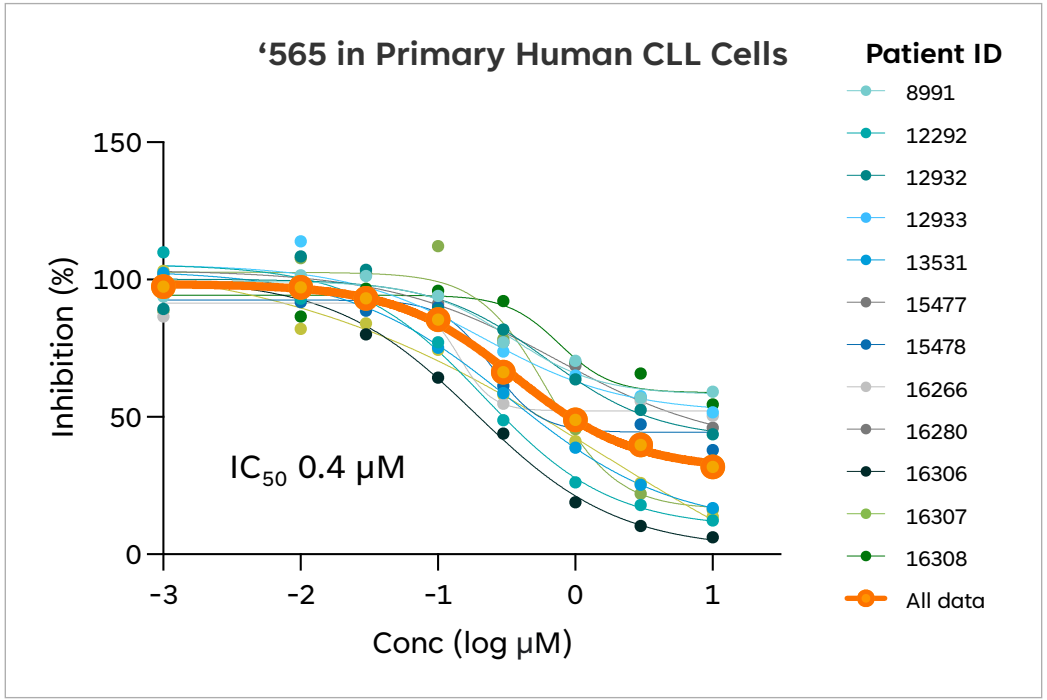


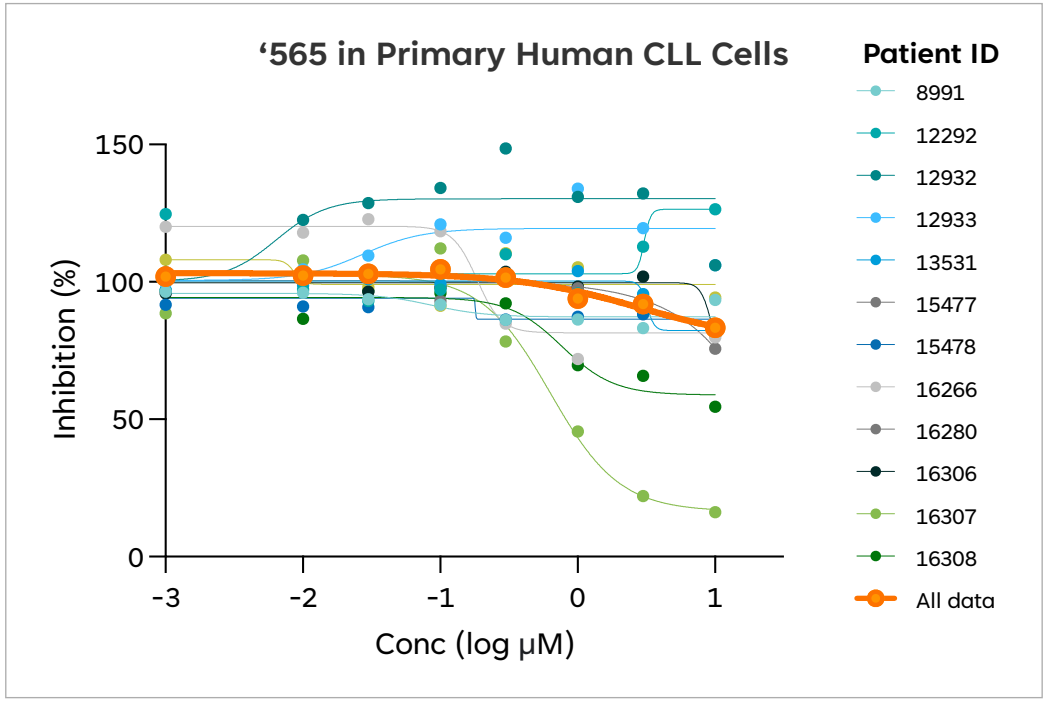
- TMD8 DLBCL cells are sensitive to both MALT1i and ibrutinib *in vitro,* however, standalone administration of ibrutinib showed no activity *in vivo*
- Significant synergistic efficacy was observed when ‘565 was combined with ibrutinib in the study
- ‘565 was well tolerated with body weight maintained in both monotherapy and combination groups

Payne et al. ESMO, 2023; OCI-Ly10 xenograft model: CD79A mutant; TMD8 xenograft model: CD79B mutant

‘565 inhibits primary human CLL cell proliferation

Efficacy in primary human tissues without impacting T-cell viability





- CLL samples from both treatment naïve patients and patients exposed to previous lines of therapy
- ‘565 selectively inhibited the proliferation of primary human CLL cells
- Limited impact of ‘565 observed on T-cell viability

Payne et al. ESMO, 2023

‘565 has a low predicted risk of hyperbilirubinaemia

Potential safety benefit compared with clinical MALT1i in development

- We predict that selectivity over UGT1A1 could be an issue for some clinical stage MALT1 inhibitors
- Inhibition of UGT1A1 mediates bilirubin glucuronidation, potentially leading to hyperbilirubinaemia
- ‘565 has a low risk of potential DDI/ hyperbilirubinaemia at predicted human efficacious doses
- Potential for safer dose escalation for ‘565 to reach the level of target engagement necessary to achieve clinical efficacy

			UGT1A1					
Compound	**Best-estimate Scenario**	**$C_{max,u}$ ($I_{max,u,inlet}$)**	**IC_{50} (μM)**	**$IC_{50}/I_{max,u,inlet}$**	**R_{free}**	**$R_{in,free}$**	**F_i**	**Prediction**
Pharma Phase 1b[1]	$t_{½}$: 127 hr (230 mg QD)	0.28 (0.32) μM	0.76	2.4	1.37	1.42	0.27	Hyperbilirubinaemia Risk
‘565	$t_{½}$: 39 hr	0.30 (0.42) μM	>10	34	1.02	1.03	0.02	Low Risk

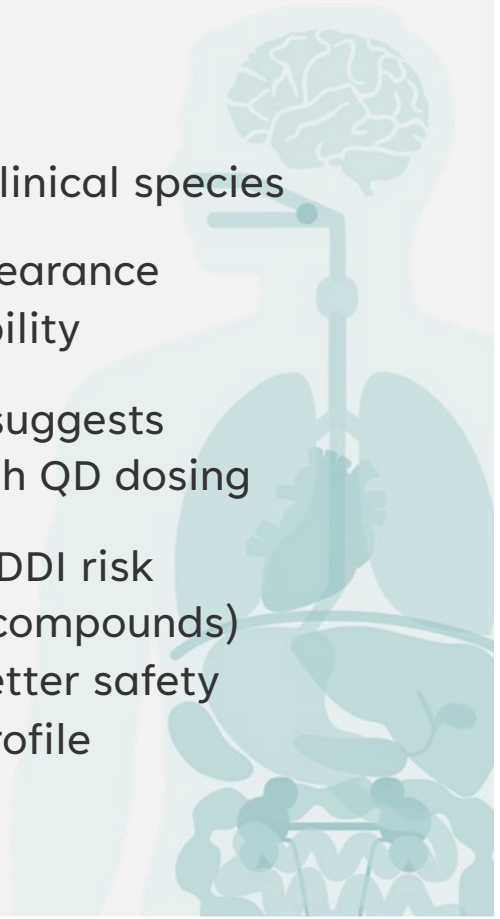
Payne et al. ESMO, 2023. 1) Hertzberg et al. *Hematol Oncol*, 2023; Cmax,u: Predicted maximum free plasma; Imax,u,inlet: free liver inlet concentration

MALT1

Favourable PK, toxicology & safety pharm in preclinical species

Pharmacokinetics (PK)

- Excellent PK across preclinical species
- Low predicted human clearance and high oral bioavailability
- Human clearance data suggests a half-life consistent with QD dosing
- Low UGT1A1-mediated DDI risk (differentiated vs other compounds) leading to potentially better safety (hyperbilirubinaemia) profile



Toxicology & Safety Pharmacology

- No unexpected *in vitro* or *in vivo* safety concerns identified for a patient trial
- Well tolerated in rat/dog dose range finding (DRF) studies
- GLP toxicology studies completed and identified a suitable NOAEL enabling clinical trials

‘565: Summary

- GLP-tox studies in progress
- CMC work underway

Programme Highlights:

- Potent and highly selective MALT1 allosteric inhibitor with low UGT1A1 inhibition risk
- Suitable therapeutic index established
- Potential in broad range of haematologic malignancies
- Potential in combination with BTKi for the prevention and treatment of BTKi-resistant disease
- Potent activity on primary human B-cell lymphoma patient cells; ongoing studies in other indications

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