
Exscientia
Precision
Designed.
Personalised
Medicine.
March 2023

# Forward Looking Statements

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

**30+**
Programmes consisting of wholly owned, co-owned and partnered

**4**
Clinical stage compounds*

**>$6.5b**
Potential partnership milestones (over $3.5b of which are pre-commercial)

**10%**
Average royalty rate without co-investment

**$625m**
3Q22 cash with F9M 2022 net cash burn of $15m**

**21%**
Top-end royalty rate with co-investment in Sanofi collaboration

*Includes out-licensed programmes
**On a constant currency basis as of September 30, 2022

# Multiple near-term milestones

## Upcoming Pipeline Progress

- ✓ Phase 1 start for ‘4318 (PKC-theta) programme (BMS)
- Enroll first patient in Phase 1/2 trial for ‘617 (CDK7i) in 1H 2023
- Enroll first patient in IGNITE Phase 1/2 trial for ‘546 ($A_{2A}R$) in 1H 2023
- New patient selection biomarker data on multiple programmes throughout the year
- ✓ At least 3 new targets disclosed by YE 2023

## Upcoming Platform Advancements

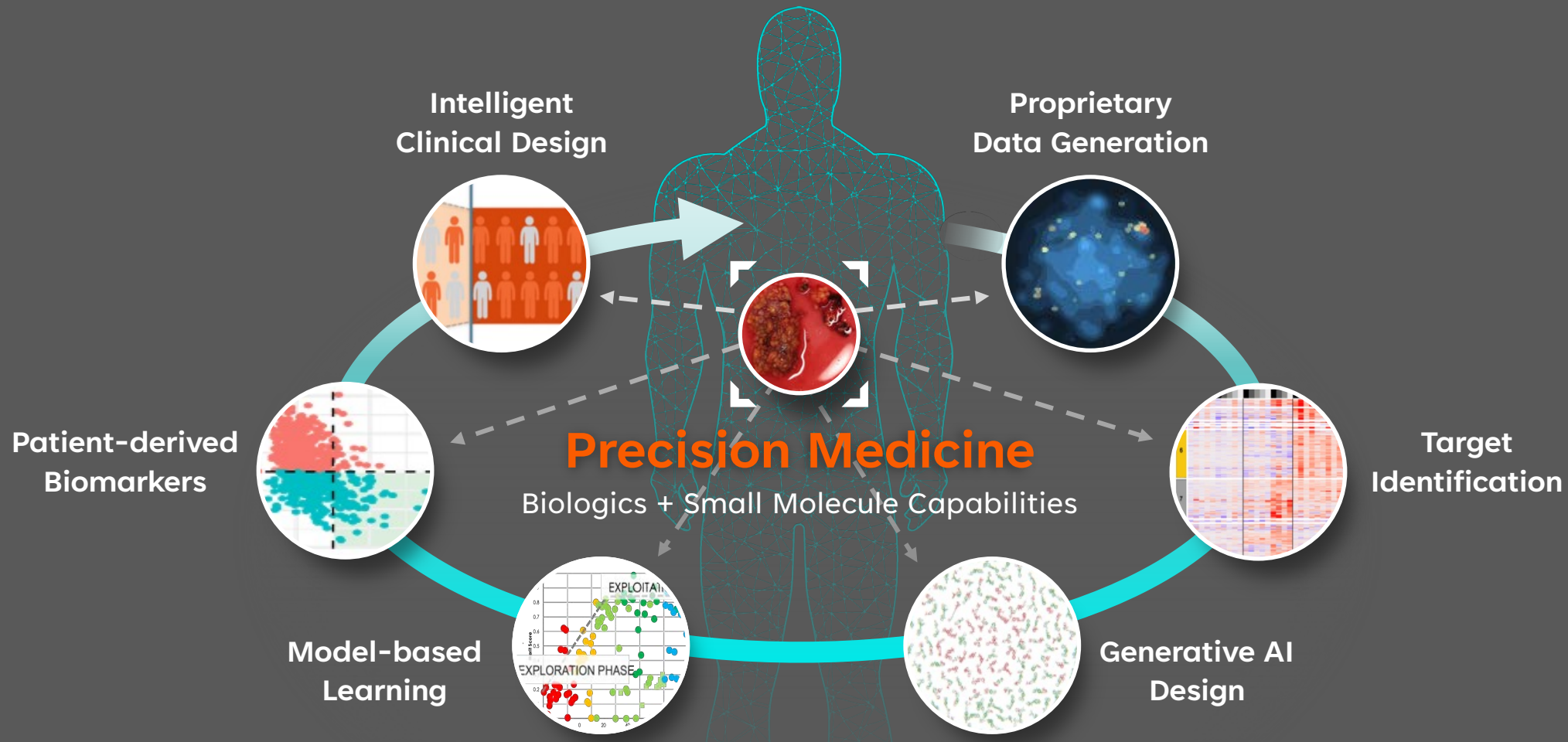
- At least two new partnerships during 2023
- Advancement of first antibody programme from biologics design platform
- Open 50,000 sq ft precision medicine centre of excellence in 1H 2023
- Open 46,000 sq ft of new biologics lab and automation facility by mid-2023
- Additional clinical trials utilising precision medicine platform

**Cash balance and expected partner milestones provide foundation to execute on business plan**

# 4 major reasons clinical trials fail

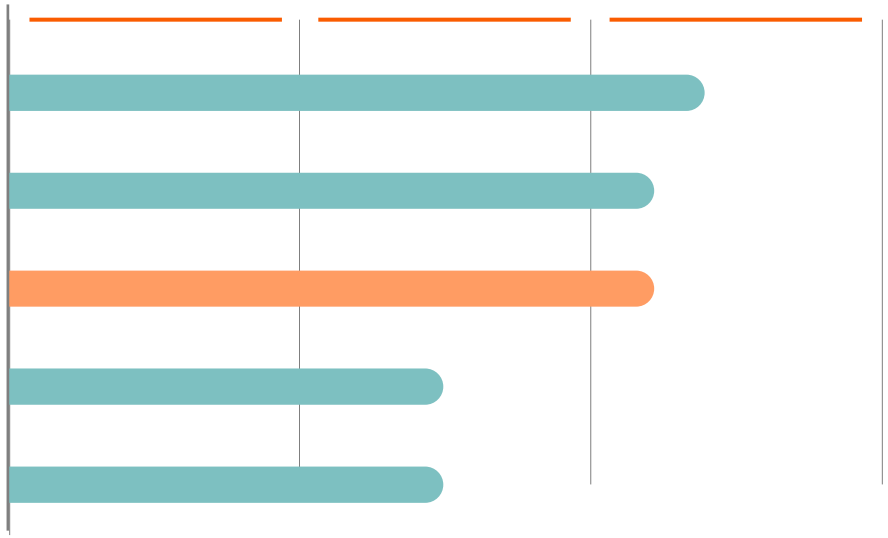
1. **Drug design:** Inadequate safety, potency or bioavailability
2. **Target biology:** Weak target-disease correlation
3. **Patient selection:** Not enrolling patients that are most likely to benefit from the therapy
4. **Clinical trial design:** Biological efficacy was obscured due to protocol issues

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



# Pipeline advancing to the clinic

## Three clinical stage compounds in oncology and I&I




| PROGRAMME | TARGET | PHASE 3/ APPROVED* | INDICATION | EXSCIENTIA RIGHTS |
|---|---|---|---|---|
| **EXS21546** | $A_{2A}$ | | r/r RCC, NSCLC | Majority-owned (Evotec) |
| **GTAEXS617** | CDK7 | | Transcriptionally Addicted Cancers | Co-owned (GTA) |
| **EXS4318** | PKC-theta | | Inflammatory Diseases | Milestones & Royalties (BMS) |
| **EXS73565** | MALT1 | | Haematology | Wholly Owned |
| **EXS74539** | LSD1 | | Haematology and Oncology | Wholly Owned |

**>10 programmes with 50–100% ownership**

**>20 partnered programmes with substantial economics**

**Internal focus on precision oncology**

**Additional clinical programme through DSP collaboration**

*Phase 3 may not be required if Phase 2 is registrational; PKC theta is in a Phase 1 healthy volunteer study

# Why are our clinical candidates different?

## Differentiated through design and personalised medicine

| Target | Phase | Target Market | Key Differentiation |
|---|---|---|---|
| **$A_{2A}$** | Phase 1/2 | ~20-50% of r/r RCC and NSCLC patients estimated to be ABS* high | Novel approach to patient selection allows identification of potential responders |
| **CDK7** | Entering Phase 1/2 | Multiple relapsed/refractory solid tumour indications | Precision designed PK/PD specific for mechanism. Biomarker identification of high-grade responders |
| **PKC-theta** | Phase 1 | Multiple immunology indications | Better selectivity, improvements in whole blood potency and predicted human dose <200mg/day |
| **LSD1** | IND-enabling | Solid tumour and haematology patients | Uniquely combines reversibility with brain penetration, together with PK to optimise therapeutic index |
| **MALT1** | IND-enabling | Multiple haematology indications | Solved potential dose-limiting toxicity issue present in competitor compounds. Precision medicine platform to factor in likely responding groups |

Does not include Exscientia-designed programmes that entered clinical trials through DSP collaboration, *Exscientia's biomarker (adenosine burden score)

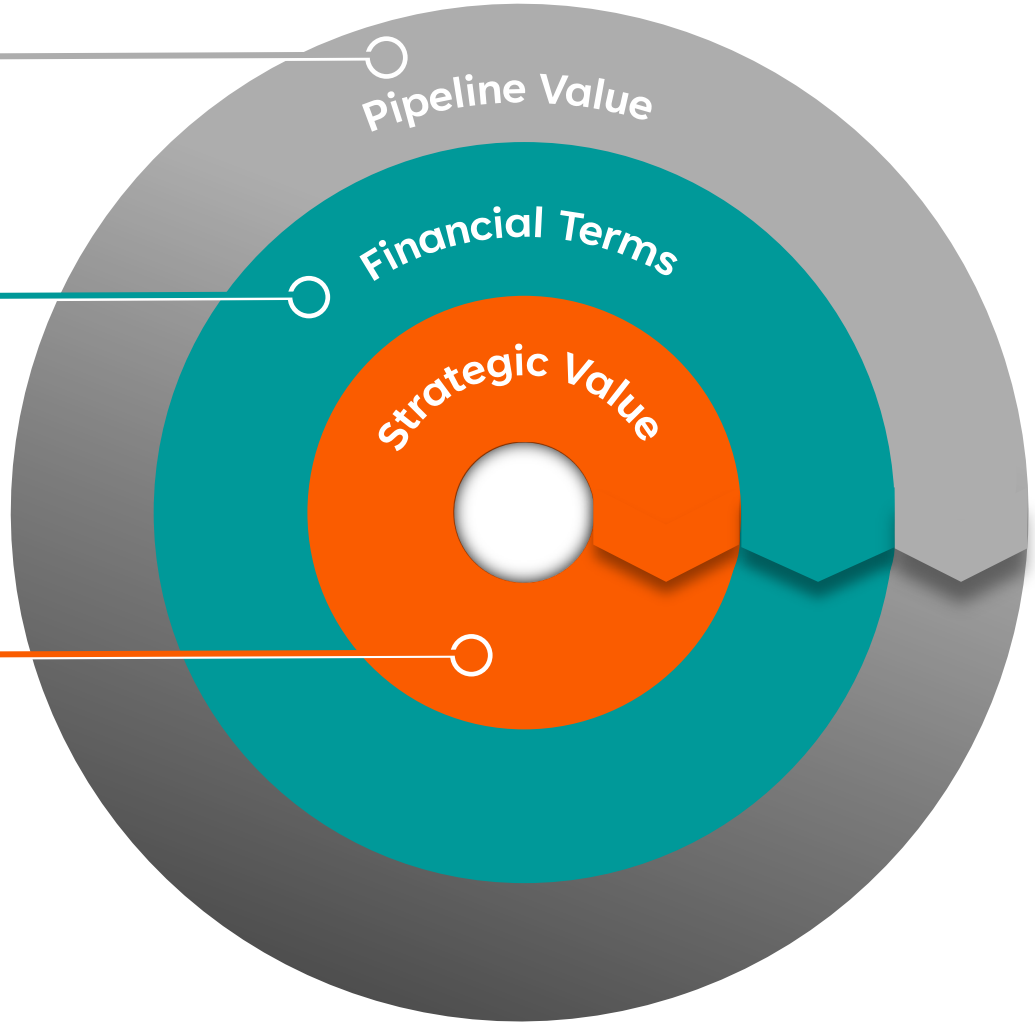
# High value partnerships also create strong foundation

## Potential for partnership structure to fund majority of Exscientia's operations

- >20 programmes between BMS & Sanofi
- NPV of a Sanofi programme estimated at ~50% of a wholly owned programme

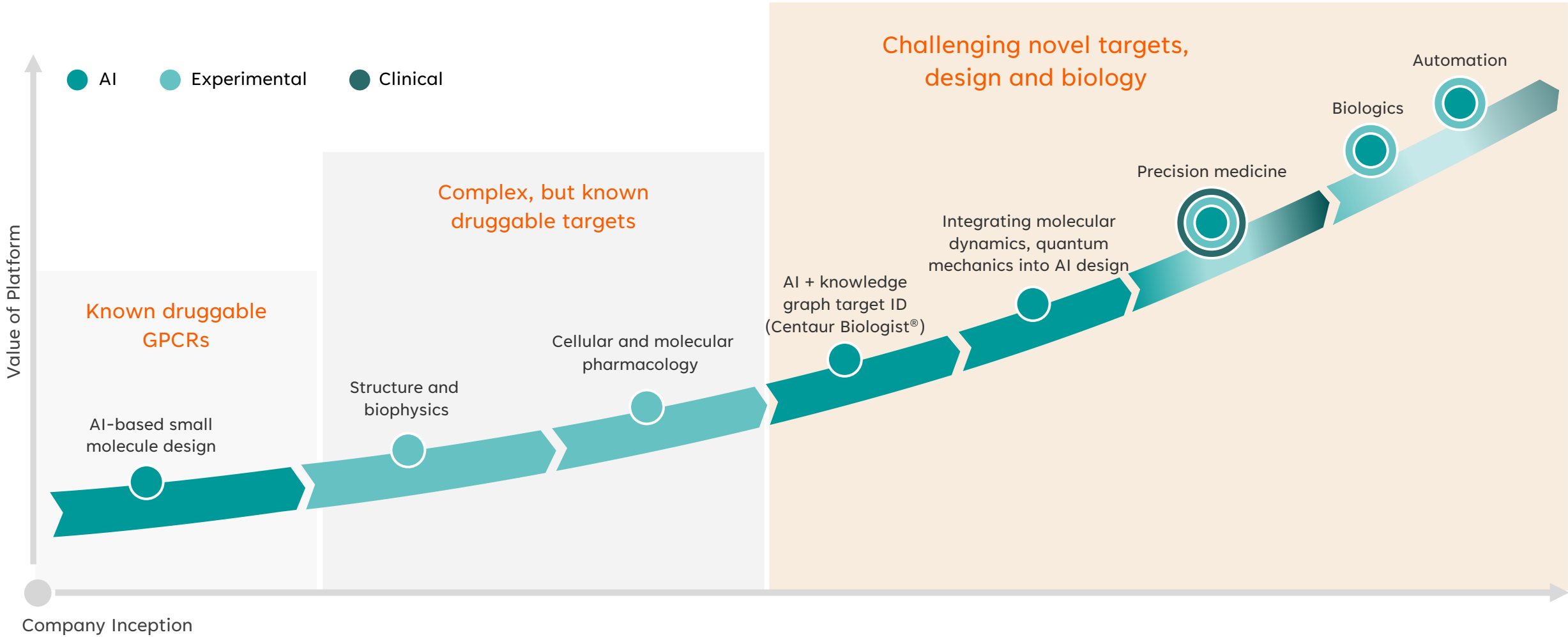
- Upfront payments typically cover operating costs
- >$3.5 billion of potential pre-commercial milestones
- $3.0 billion of potential commercial milestones
- Average royalty rate of 10%
- Co-investment option can take royalties up to 21%

- Strong partners for clinical development and marketing
- Provide therapeutic area expertise for programmes
- Learnings are integrated into broader platform



# Expanding technologies enhance value creation

## Advancements of AI-driven drug design




Timeline for illustrative purposes

# 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

**>$3.5b**

In pre-commercial milestone potential

*Kornauth et al. Cancer Discovery 2021

# Our strategy maintains balance sheet strength

## First Nine Months (F9M) 2022 financial performance

| ($m) | F9M22 | F9M21 | Comments |
|---|---|---|---|
| Cash inflows from collaborations | $117.3 | $67.5 | Expect to remain lumpy around development milestones and business development |
| Net operating cash (outflows)/ inflows | ($15.0) | $8.3 | Continue to make measured investments into pipeline and platform growth |
| Capital expenditures | $18.5 | $4.5 | 2022 CapEx expected to be higher YoY with automation and precision medicine expansion |
| Cash balance* | $624.7 | $253.4 | Project several years of cash runway |

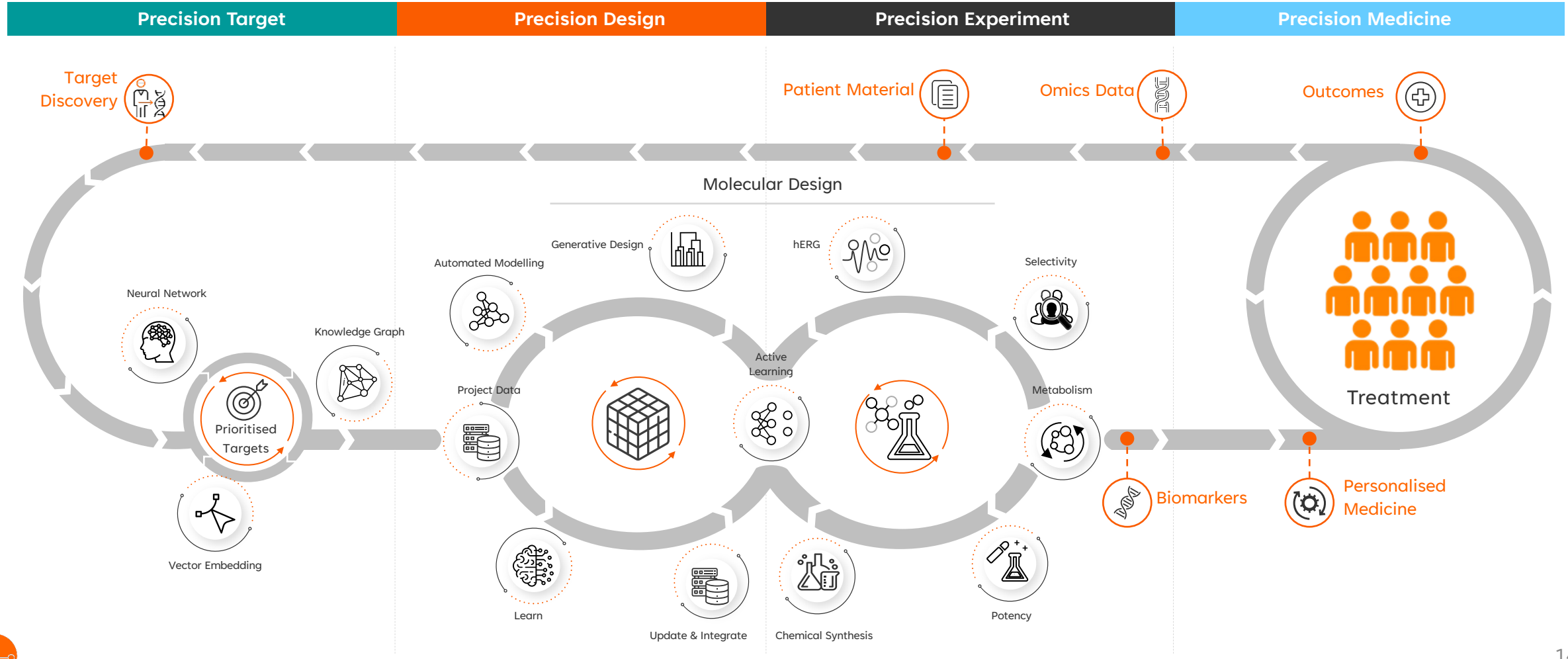
**Expect partnerships to continue to moderate cash burn**

*Includes fixed term bank deposit, based on constant currency as of September 30, 2022
Shares outstanding: 122.8 million as of September 30, 2022

# Technologies

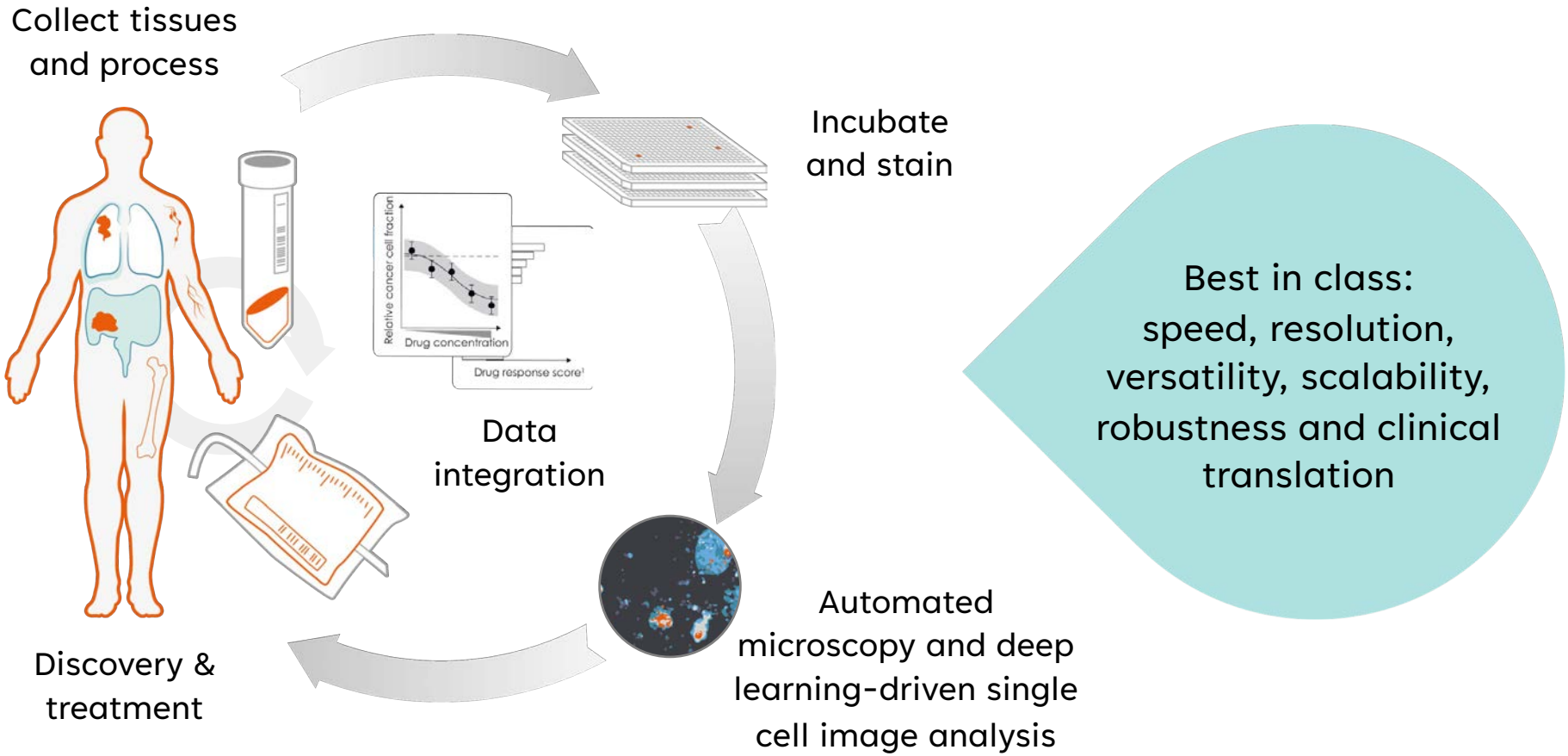
# Patient-first AI is a learning process

## Our end-to-end architecture brings the patient into every stage of drug creation



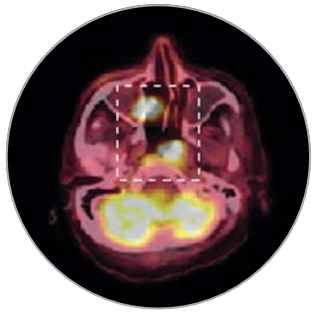
# Our differentiated process

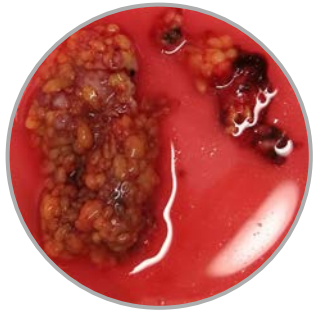
## Interrogating drug action in complex primary tissues at the single cell level

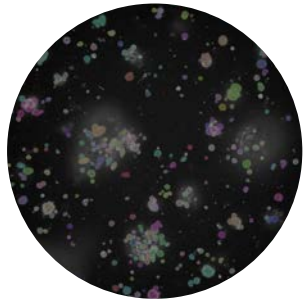



Vladimer et al. *Lancet Hematol*. 2017; Vladimer, Snijder et al. *NCB* 2017; Schmidl, Vladimer et al. *NCB* 2019; Kornauth et al. *Cancer Discovery* 2021

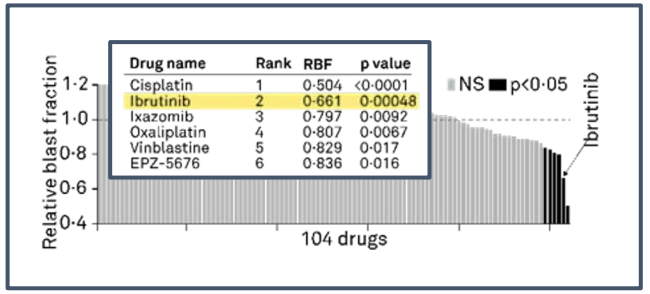
# **EXALT-1 study:** First AI-driven functional precision medicine platform to directly improve cancer treatment & patient outcomes

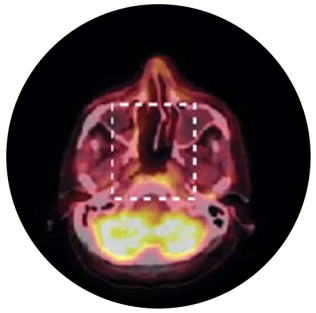






Select the best tolerable treatment in the tumour board



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 & single cell image analysis

Measure drug response using image-based screening

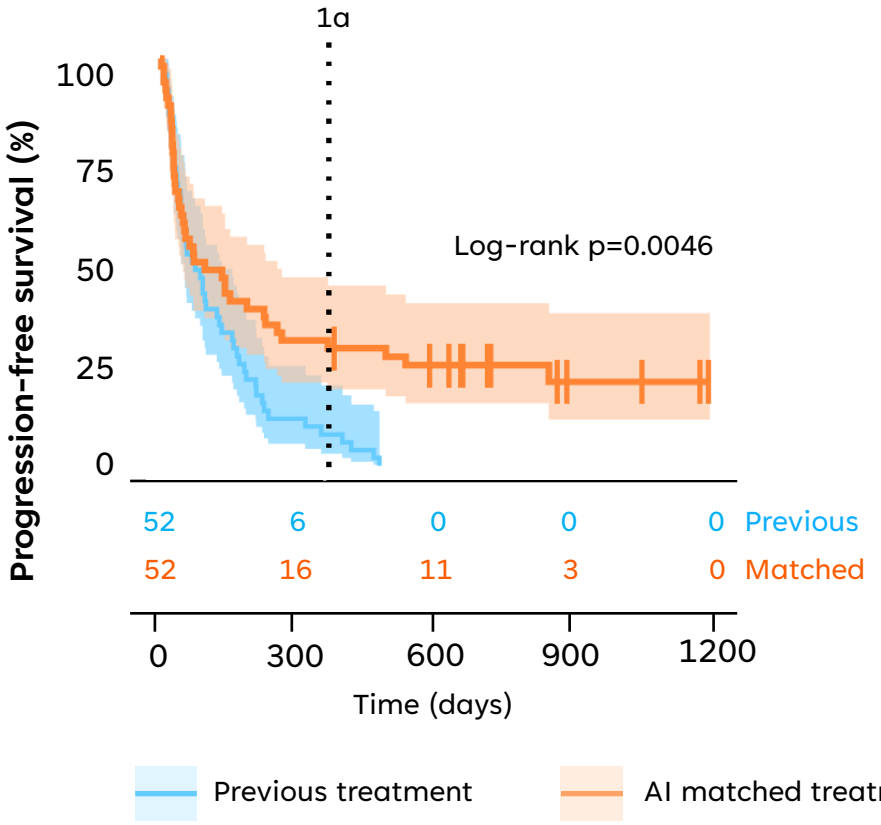
Complete remission 2-years survival at fraction of cost of CAR-T

DLBCL = diffuse large B-cell lymphoma

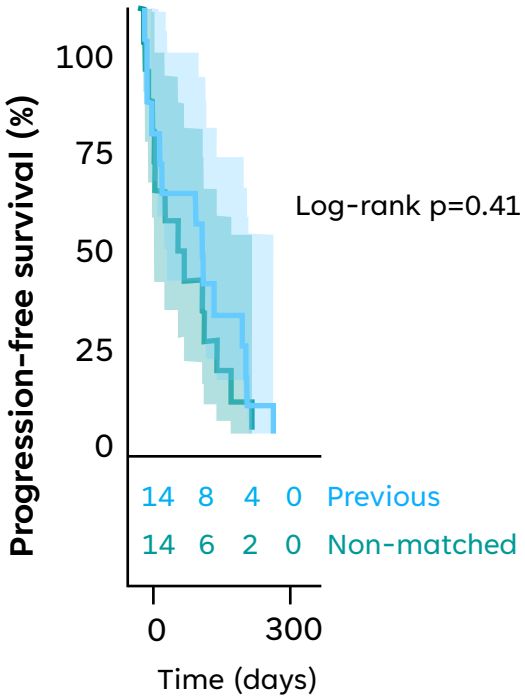
# EXALT-1 study results

## Patients receiving drugs prioritised by platform had significantly better outcomes

**Patients receiving treatment prioritised by platform had improved PFS**

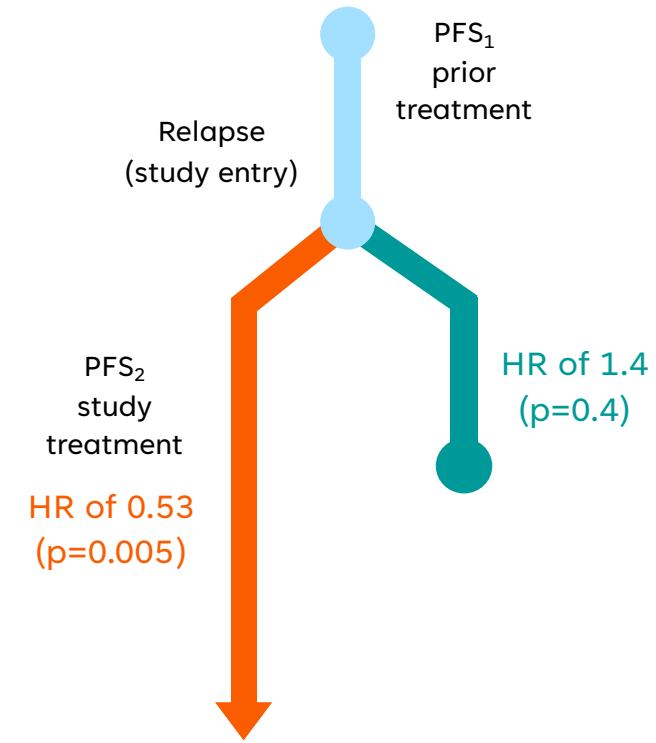



**Patients receiving treatment not prioritised by platform did not have improved PFS**




Previous treatment | AI matched treatment | Non-matched treatment

**CANCER DISCOVERY**

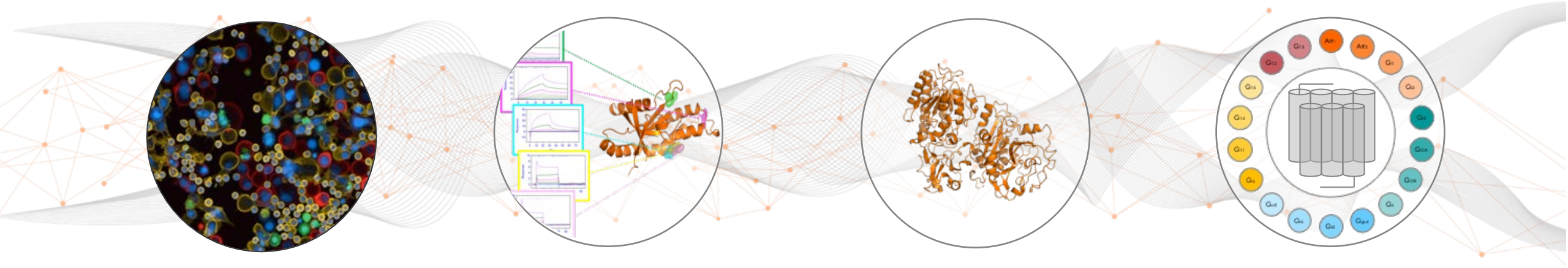



54% of patients demonstrated clinical benefit of >1.3-fold enhanced PFS compared to prior therapy

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

# Extensive proprietary data generation capabilities

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



**Primary tissue disease models**

Live patient tissues

Single cell resolution

Deep learning AI

Biobanked samples

**World-class biosensors**

Proprietary seed data

GPCRs in native state

Label free and automated

**High throughput crystallography**

Proprietary seed data

Automated Hotspot binding site analysis

**Extensive pharmacology**

Transducerome mapping

Automated assay development

Polypharmacological profiling

# Creating a consistent flow of high-quality targets

## Integrated capabilities drive new discoveries

**>35%**

of pipeline generated using Exscientia target ID platforms

### AI

CENTAUR BIOLOGIST®

Applies deep learning to genome-scale datasets to identify connections and predict target-disease associations

Global knowledge graphs

### Experimental

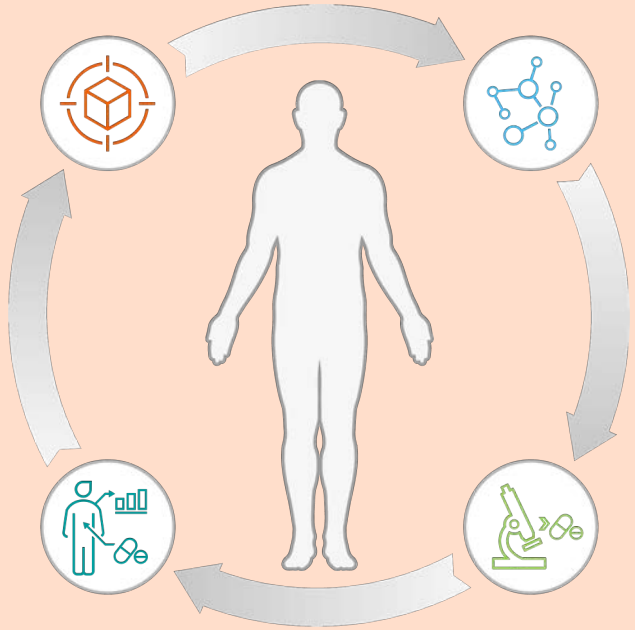
CELLOMICS™

Launched 2022, open-source programme in collaboration with the University of Oxford

Focus on phenotypic assays

### Experimental + AI

PRECISION MEDICINE



Proprietary human tissue platform

Single cell phenotypic screening to ID novel targets

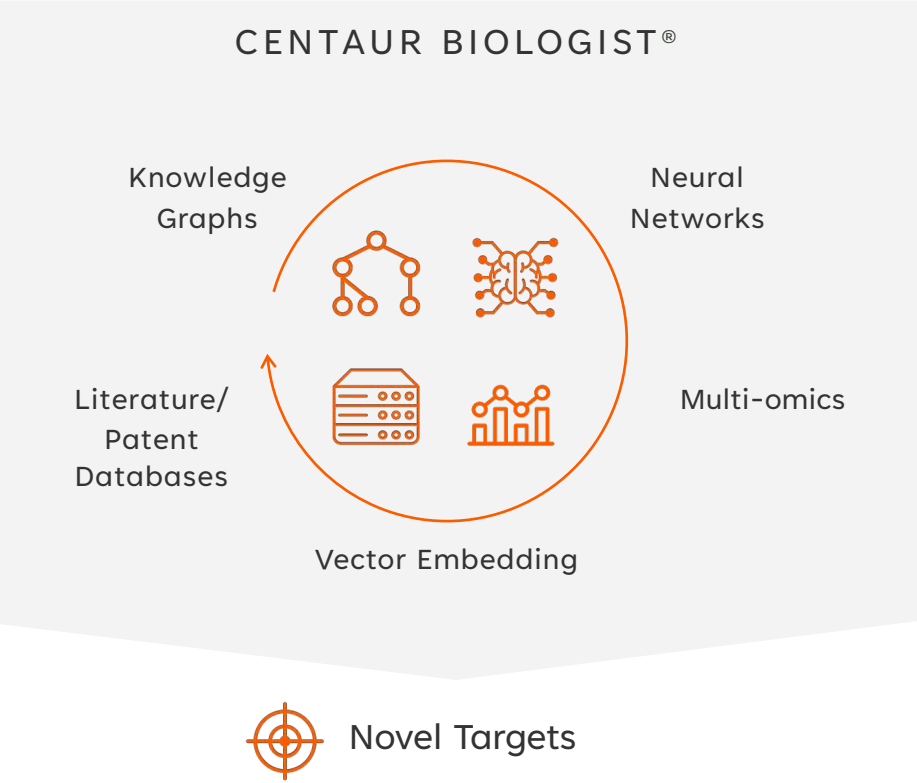
**70%**

of oncology targets tested on platform

Percentages as of YE 2022

# Prioritising and validating targets with Centaur Biologist

## AI-driven target identification through deep learning algorithms

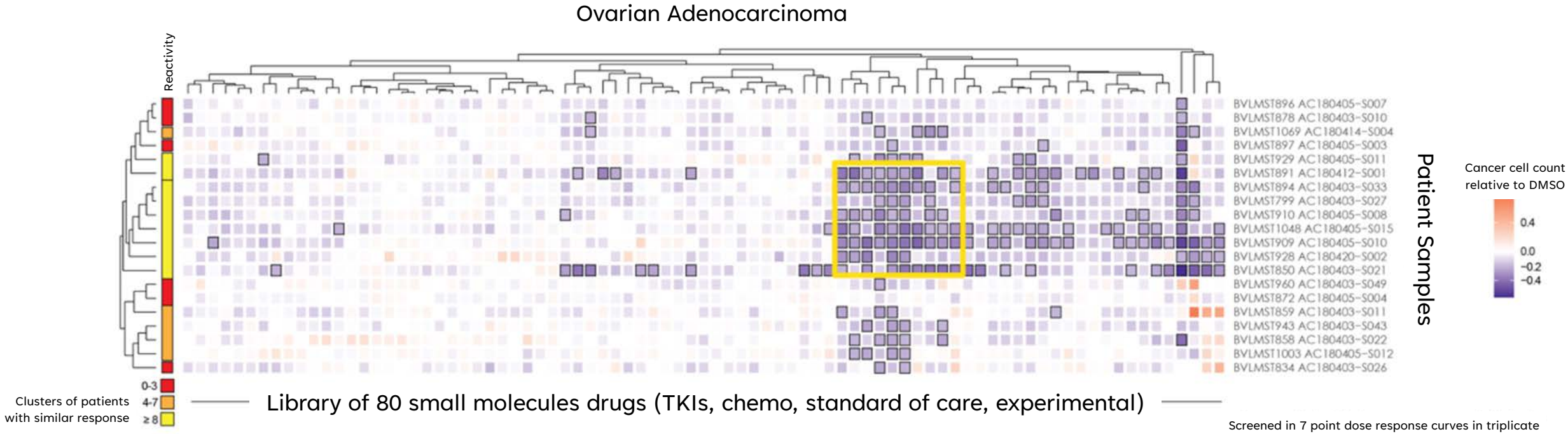



- Applies deep learning to genome-scale datasets to identify connections and predict target-disease associations
- Builds insights from constructing global knowledge graphs
- TrendyGenes algorithm generates graphic representation of literature identifying trends from over 30 million publications
- Disease area agnostic with application to date across oncology, immuno-oncology, immunology and rare disease

**Enables Exscientia to identify targets with a higher probability of translating into the clinic**

# Cancer is a heterogenous disease

## Our platform is designed to better understand differential response




**Evaluating an array of drugs and primary tissues** at single cell resolution to quantify cancer cell cytotoxicity uncovers **potential novel target space in ovarian cancer**

Gutierrez-Perez et al, AACR (2022)

# Precision objectives for precision design

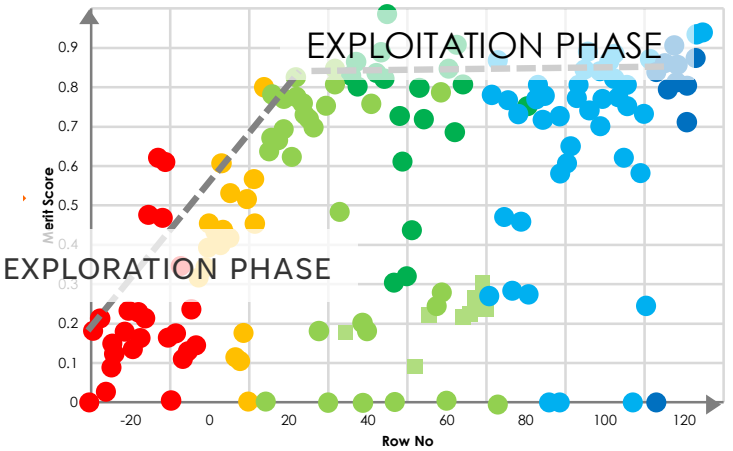
## Dozens of endpoints can be optimised in parallel

### 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

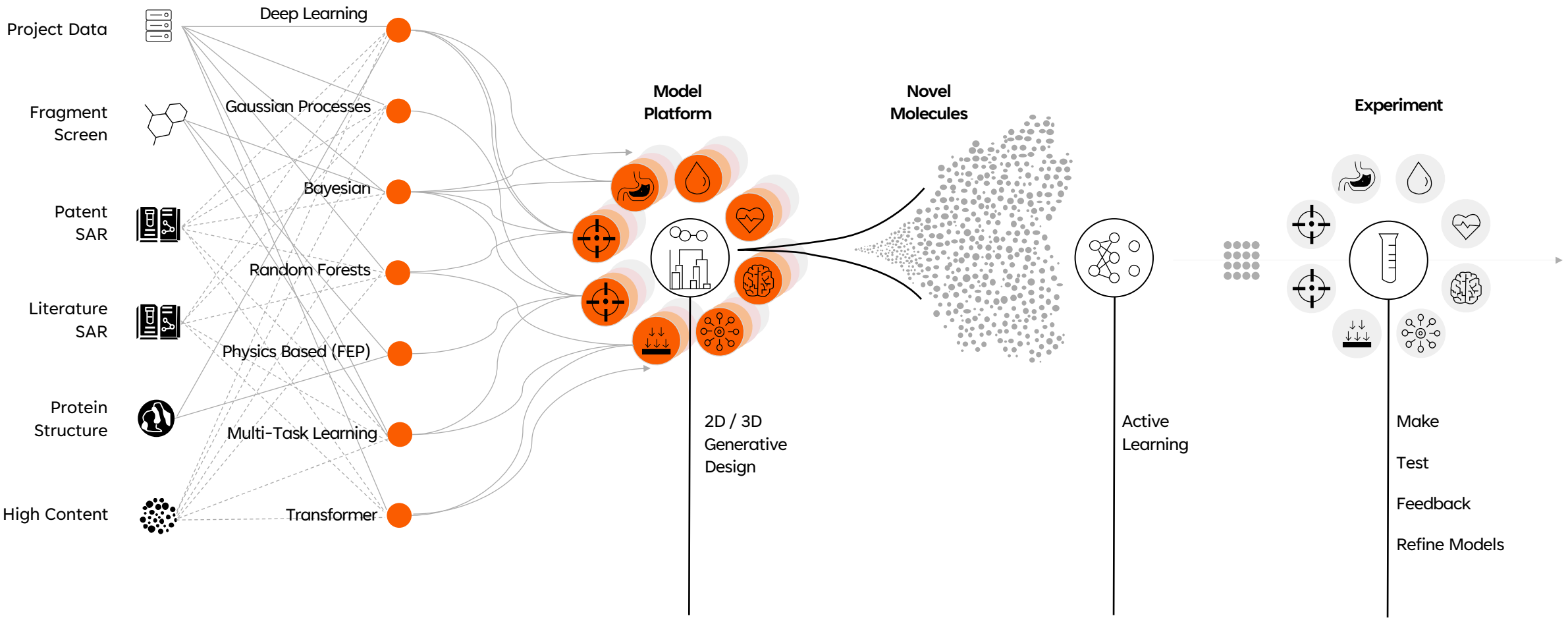
### Merit: Project Telemetry

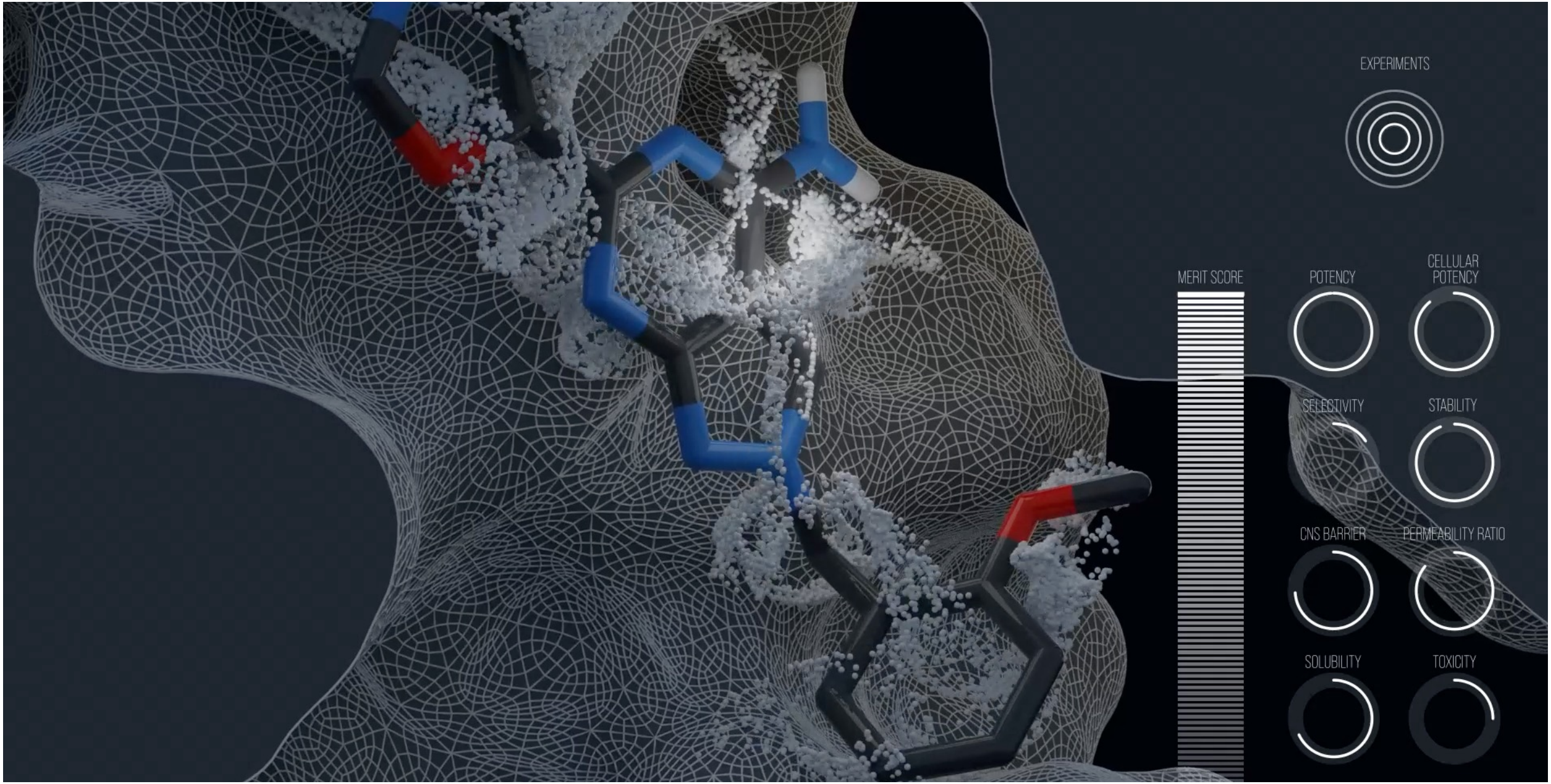



For illustrative purposes

# Data and model agnostic

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



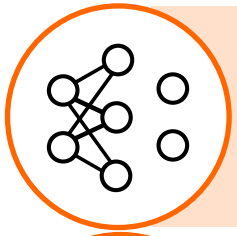



Watch video at: https://bit.ly/EXAIvideo

# Active learning AI leads to creative breakthroughs

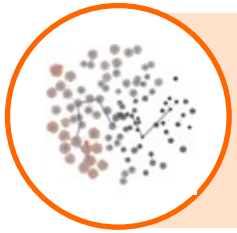
## Counterintuitive selection goes against preconceptions and breaks dogma

**AI system to maximise information gain**



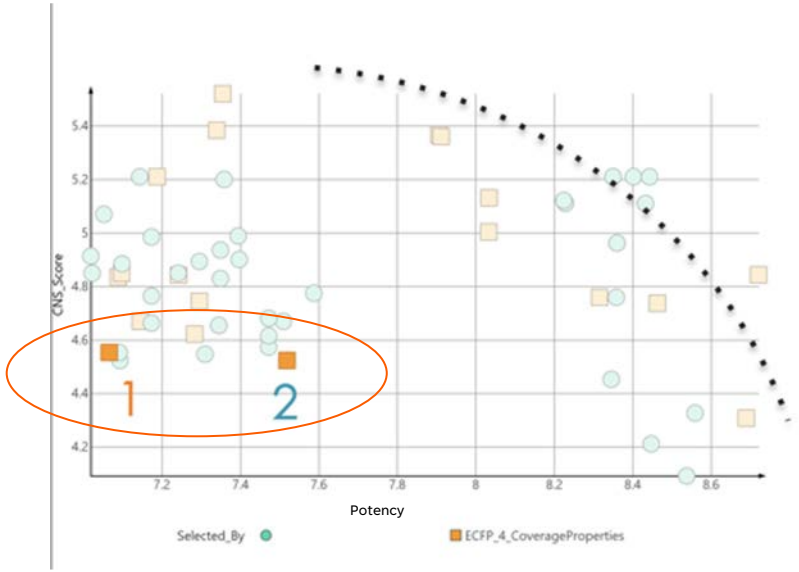
Chooses which compounds to synthesise from output of generative design and predictive models

Mathematically evaluates how much can be learned from each compound



Efficiently explores the available structural and property space

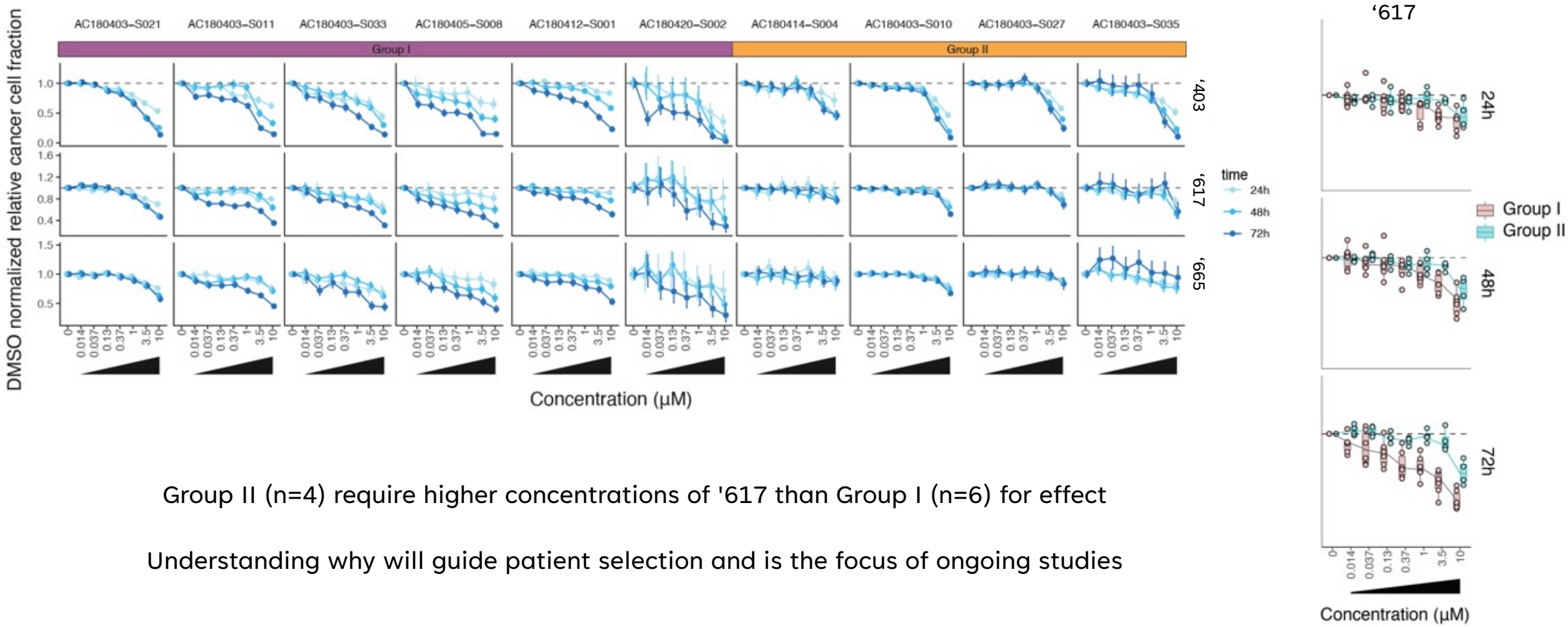
Example of our AI choosing unexpected candidates that led to a design breakthrough and development candidate




20 compounds (square) are selected by active learning

# 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


‘546
IGNITE Phase 1/2 initiated
FPI expected in 1H 2023

# **IGNITE:** ‘546 Phase 1/2 initiated in RCC & NSCLC

## Exscientia’s biomarker signature for patient selection to be tested during trial

**Two-part trial assessing safety, PK, PD and efficacy of EXS21546:**

**EXS21456 + PD-1 inhibitor**

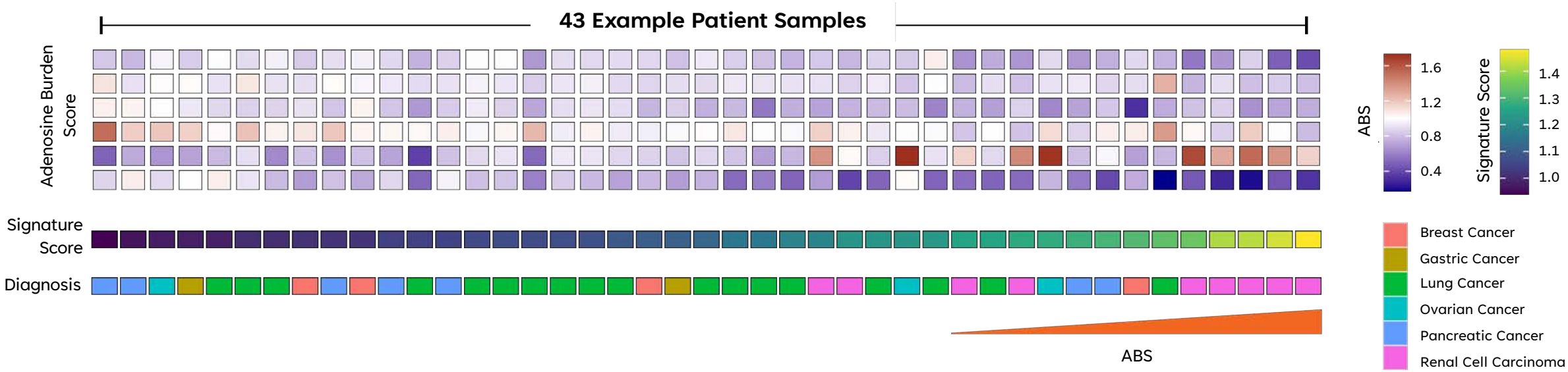
| Part 1: Dose Escalation | Part 2: Dose Expansion |
|---|---|
| n=up to 30 relapsed/refractory RCC and NSCLC patients<br><br>Across up to 7 dose levels to establish MTD | MTD<br><br>n=up to 80 relapsed/refractory RCC and NSCLC patients<br><br>Primary efficacy endpoint: ORR |

Biomarker signature, adenosine burden score (ABS) to be evaluated

IGNITE is multicentre, open-label, two-stage clinical trial to evaluate safety, pharmacokinetics, pharmacodynamics and efficacy of EXS21546 in combination with PD-1 inhibition. Study to enroll patients who have progressed after checkpoint inhibition

# Enriching for patients that will benefit most from ‘546

## Developed novel adenosine-pathway activity signature




Exscientia's ‘546 response signature, the adenosine burden score (ABS), was developed using single cell transcriptomics of primary samples after *ex vivo* perturbation with stabilised adenosine

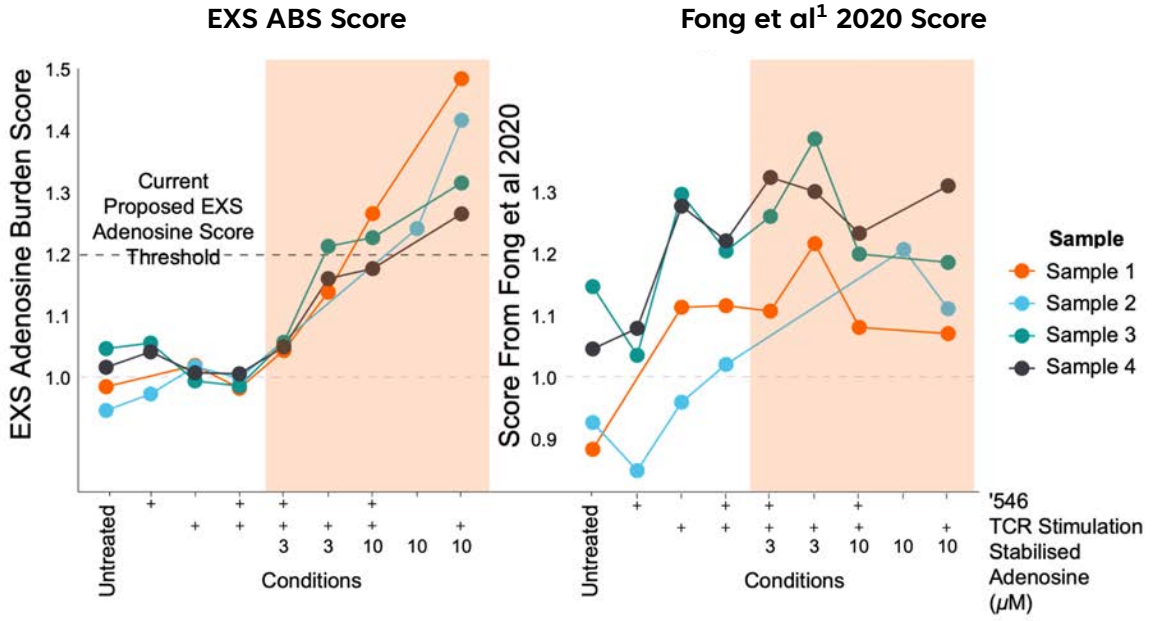
- Expected to enrich patients more likely to respond to adenosine-pathway inhibition
- Supported with biological validation including soluble factor data
- Exscientia’s ABS is differentiated from other published “adenosine signatures”

Vladimer et al, ESMO I-O (2022)

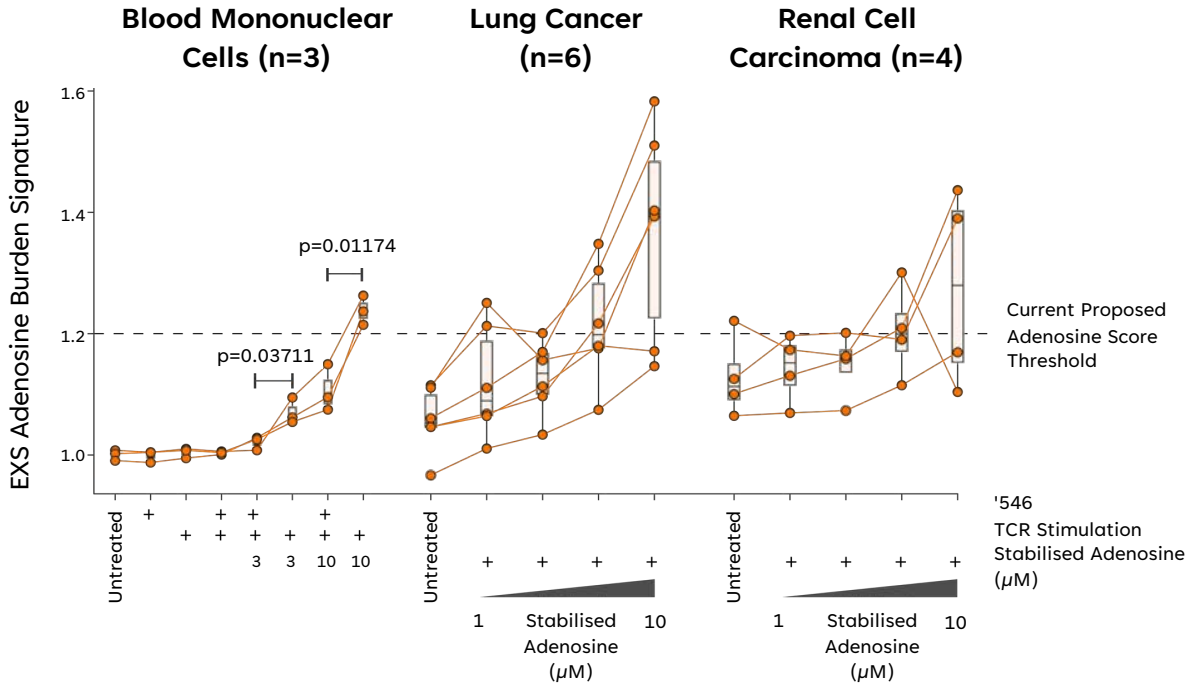
# Biological validation of the ABS in various models

## Ensuring the signature performs as expected *ex vivo* in the presence of adenosine

### Exscientia's ABS outperforms published signature in the presence of stabilised adenosine




### ABS also behaves well in cancer patient samples exposed to stabilised adenosine *ex vivo*



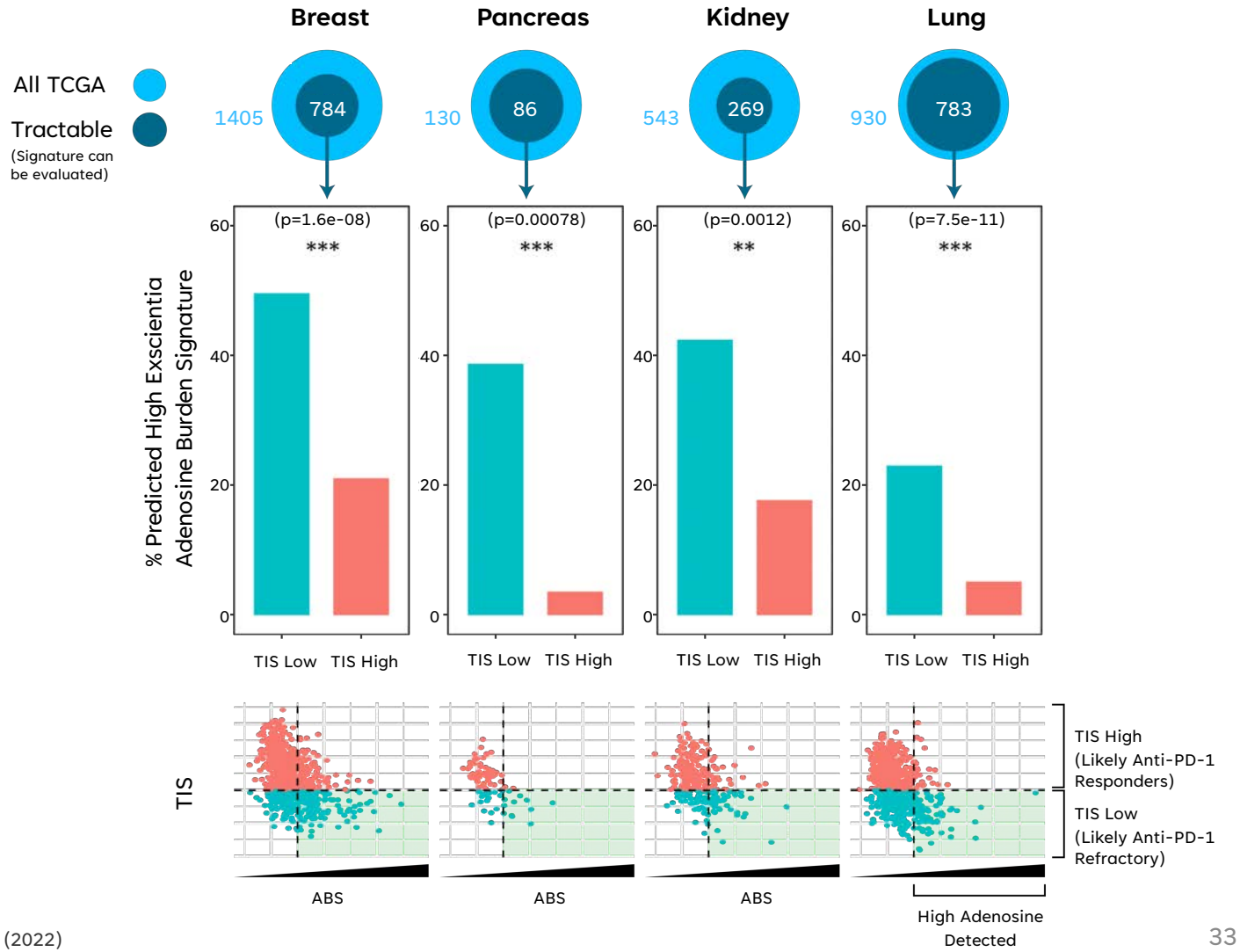

1. Fong et al, Cancer Discovery (2020); ABS = adenosine burden score, stabilised adenosine = 2-chloroadenosine (CADO); Vladimer et al, ESMO I-O (2022)

# Connection between high adenosine and inflammation

## High ABS correlates with weakened local immune response in microenvironment

**Biological validation of ABS in a larger sample cohort (TCGA[1]):**

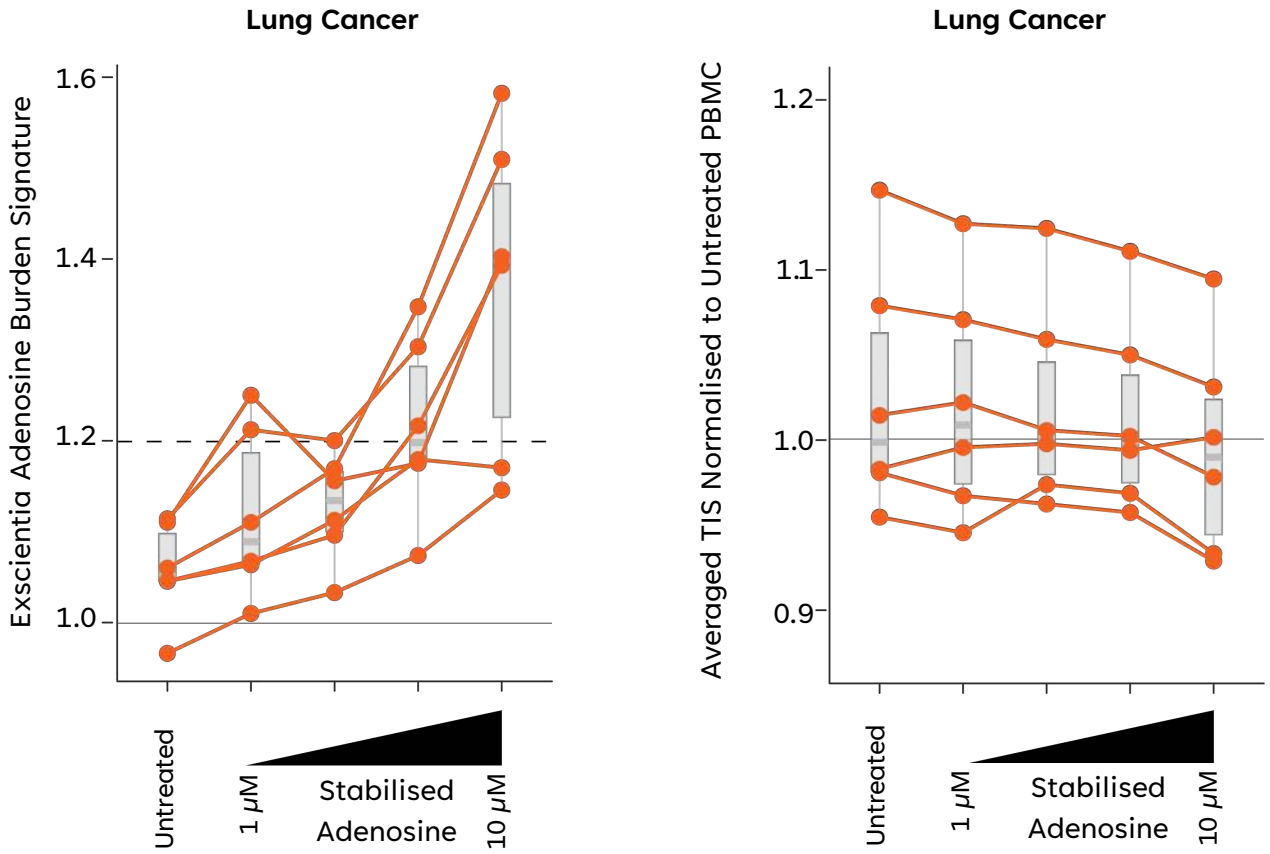
- Higher adenosine as determined by ABS correlates to lower inflammation in the tumour as determined by the tumour inflammation signature (TIS)
- Patients who have high ABS have a low TIS score
- TIS is a predictive signature for anti-PD-1 response[2]




1. The Cancer Genome Atlas Project (TCGA) dataset, NCI
2. Damotte et al, Journal of Translational Medicine (2019); Vladimer et al, ESMO I-O (2022)

# Findings from ABS inform ‘546 clinical strategy

## Correlation between higher ABS and lower TIS[1] *ex vivo* with stabilised adenosine



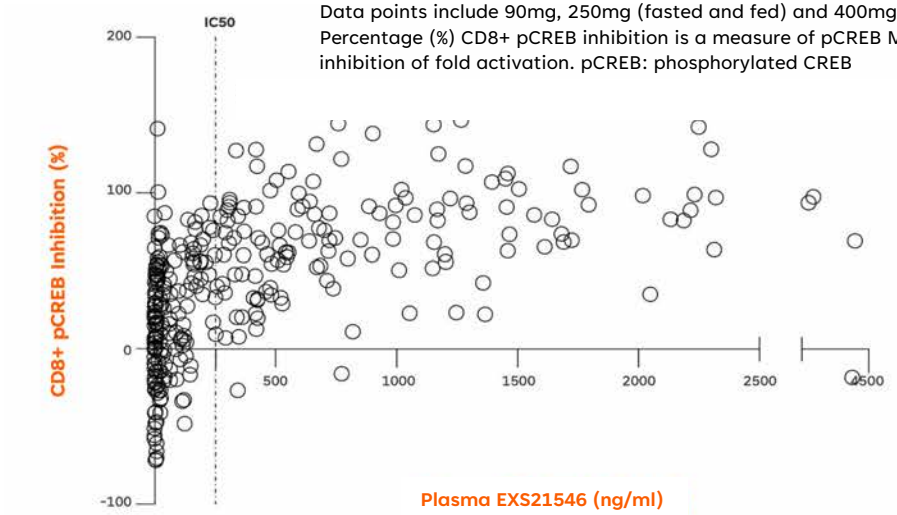

- ‘546 may be able to reverse immuno-suppression
- Potential to increase the likelihood of responding to checkpoint inhibitors in patients who relapse or did not respond originally

Damotte et al, Journal of Translational Medicine (2019) Vladimer et al, ESMO I-O (2022)

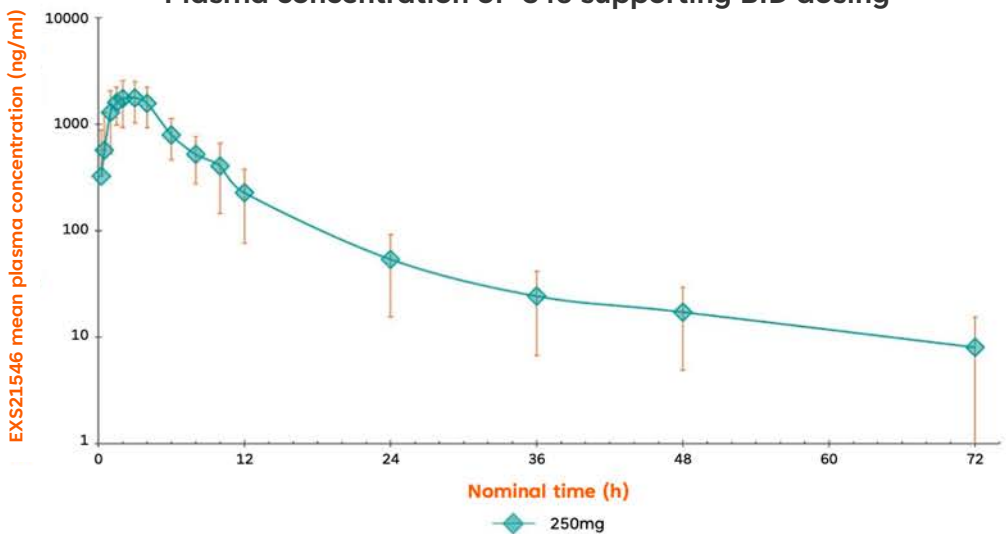
# ‘546 achieved targeted objectives in Phase 1a study

## Potency, selectivity, PK, low expected brain exposure achieved

**Correlation of ‘546 plasma exposure to inhibition of $A_{2A}R$ signalling**




**Plasma concentration of ‘546 supporting BID dosing**

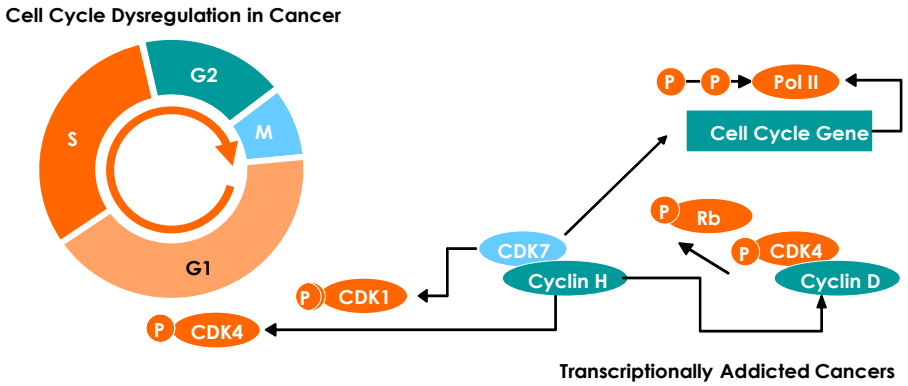



- Observed human PK for ‘546 in line with predictions from preclinical modelling
  - Supports BID dose for continuous $A_{2A}$ receptor inhibition over a dosing interval
- ‘546 showed dose-dependent inhibition of CREB phosphorylation in CD8-positive cells
  - PD profile mirrored plasma exposure
- Level of lasting target engagement identified
  - Inhibition of $A_{2A}$ receptor signalling sustained over BID dosing period

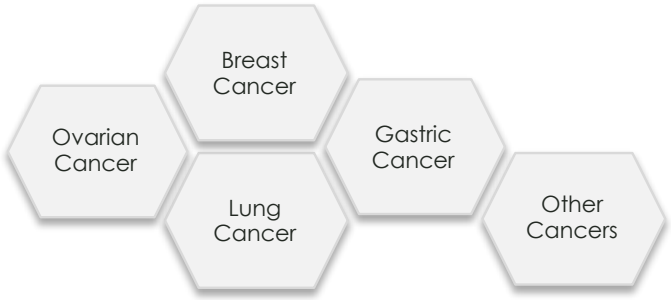

‘617
CTA filed for Phase 1/2
FPI expected in 1H 2023

# 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
  - Ibrance (palbociclib) generated $5.4b sales in 2021
  - 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 increased 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 6-8 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

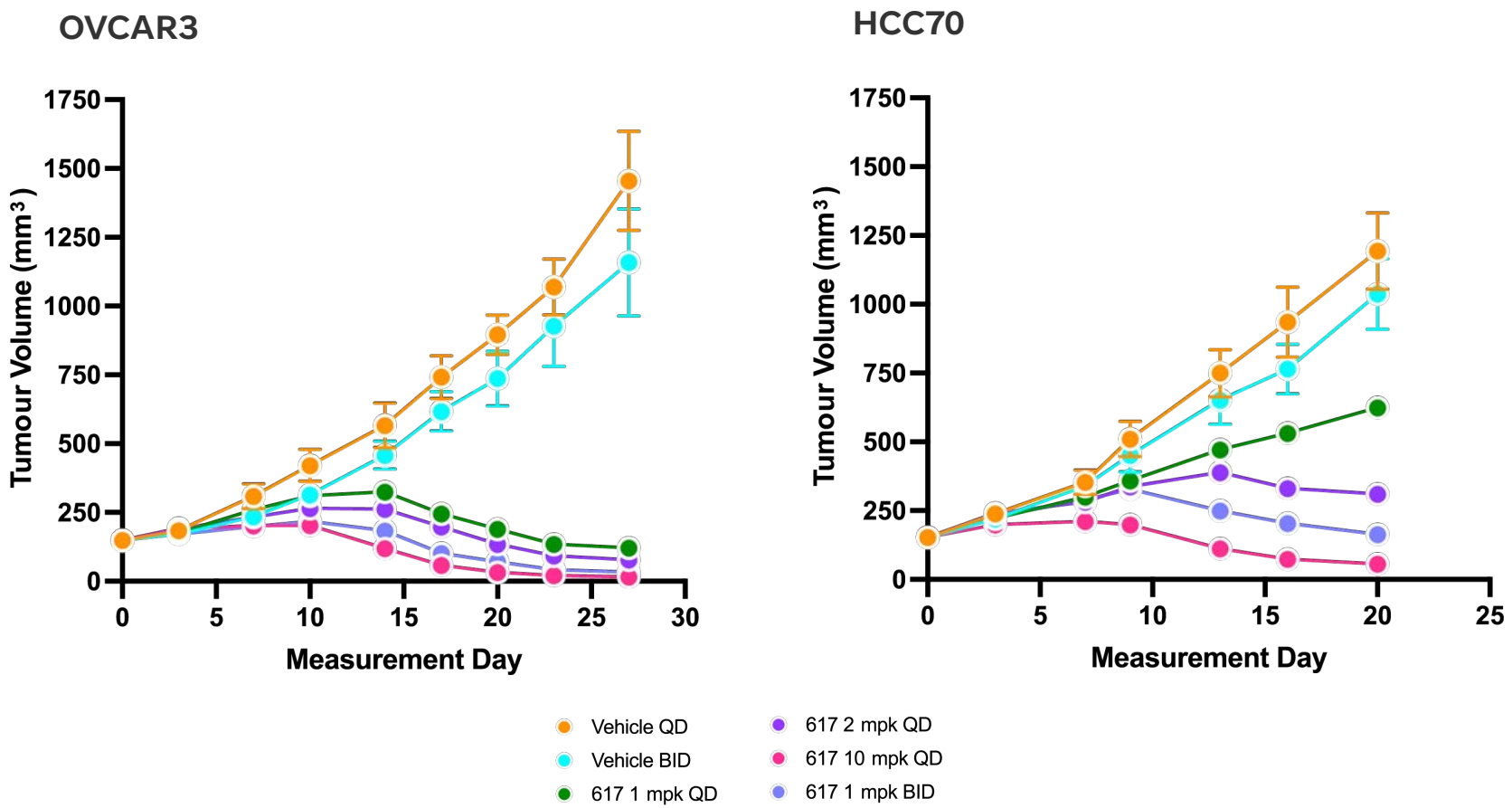
| | Assay | Candidate Criteria | Competing Phase 1 Candidate | Competing Phase 1/2 Candidate | ‘617 |
|---|---|---|---|---|---|
| Target affinity and selectivity | CDK7 $IC_{50}$ (nM) | <10 | 6 | 30 | 2 |
| | CDK family selectivity | >100 fold | | <20 | |
| Cell potency | HCC70 (breast cancer) $IC_{50}$ (nM) | <100 | 2.5 | 500 | 4.2 |
| | OVCAR-3 (ovarian cancer) $IC_{50}$ (nM) | <100 | 0.8 | | 0.8 |
| Safety and metabolism | hERG $IC_{50}$ (µM) | >5 | 5 | 24 | >30 |
| | Human microsome Clint µL/min/mg | <15 | 9 | 3.6 | <3 |
| | Human hep Clint µL/min/$10^6$ cells | <15 | 7 | <15 | 2 |
| Permeability / transporter liability General properties | Caco-2 A2B (efflux) $10^{-6}$ cm/s | >3 (<5) | 0.55 (51) | 0.14 (107) | 5.3 (4) |
| | pH 7.4 µg/ml | >50 | 132 | >100 | 120 |
| | F % (p.o.) | >30% | 100% | 30 % | 77% |

Meets or exceeds criteria  Minor deviation  Major deviation

- Potent biochemical and cellular activity
- High selectivity
- Excellent bioavailability and efflux

# ‘617 is highly effective in classical models

## Potent anti-tumour activity demonstrated in multiple solid tumour types



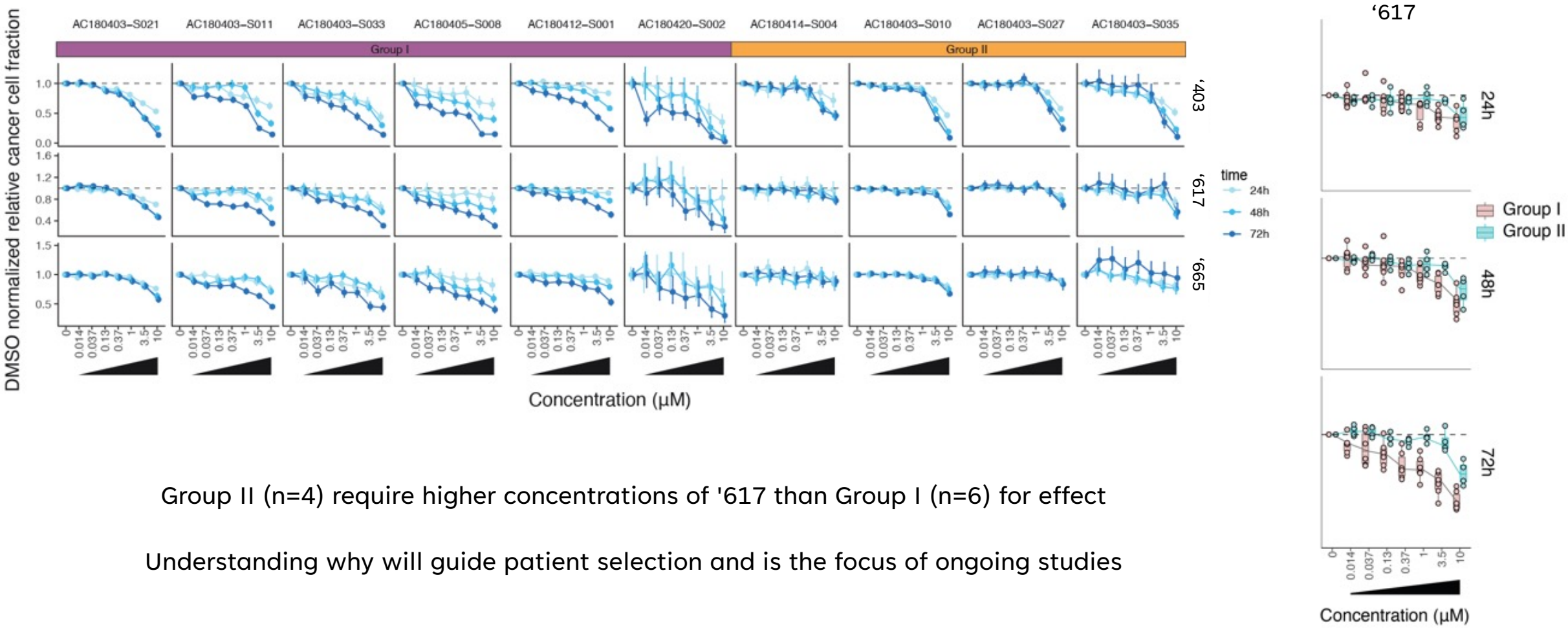

**‘617: Differentiated CDK7i**

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

Besnard et al, AACR (2022)

# 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

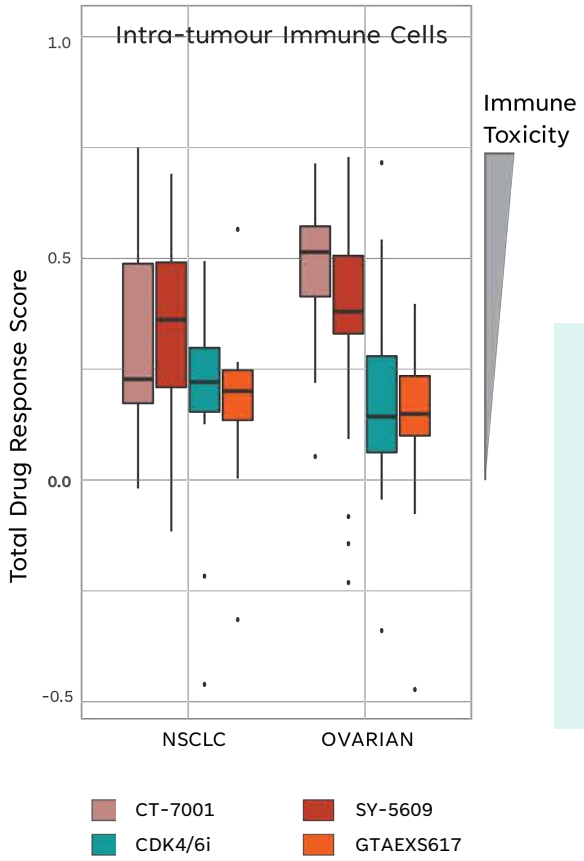
Understanding why will guide patient selection and is the focus of ongoing studies

Besnard et al, AACR (2022)

# Identifying MOA-specific patient selection marker for CDK7

## Functional drug assessment using a platform with proven translation

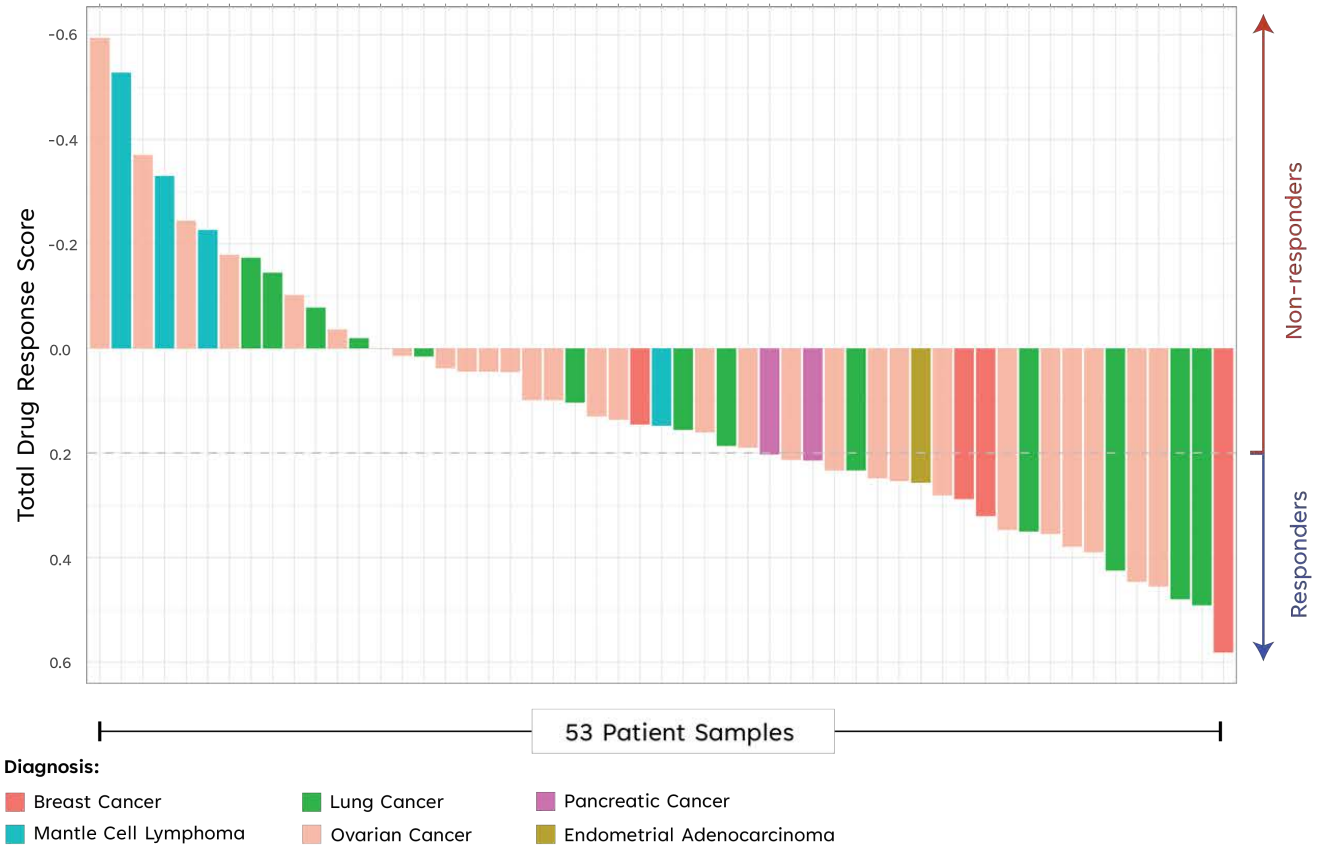
### Reduced immune toxicity endpoints




**'617 Driven Inhibition:**

Lower immune cell mediated toxicity compared to other CDK7 clinical candidates

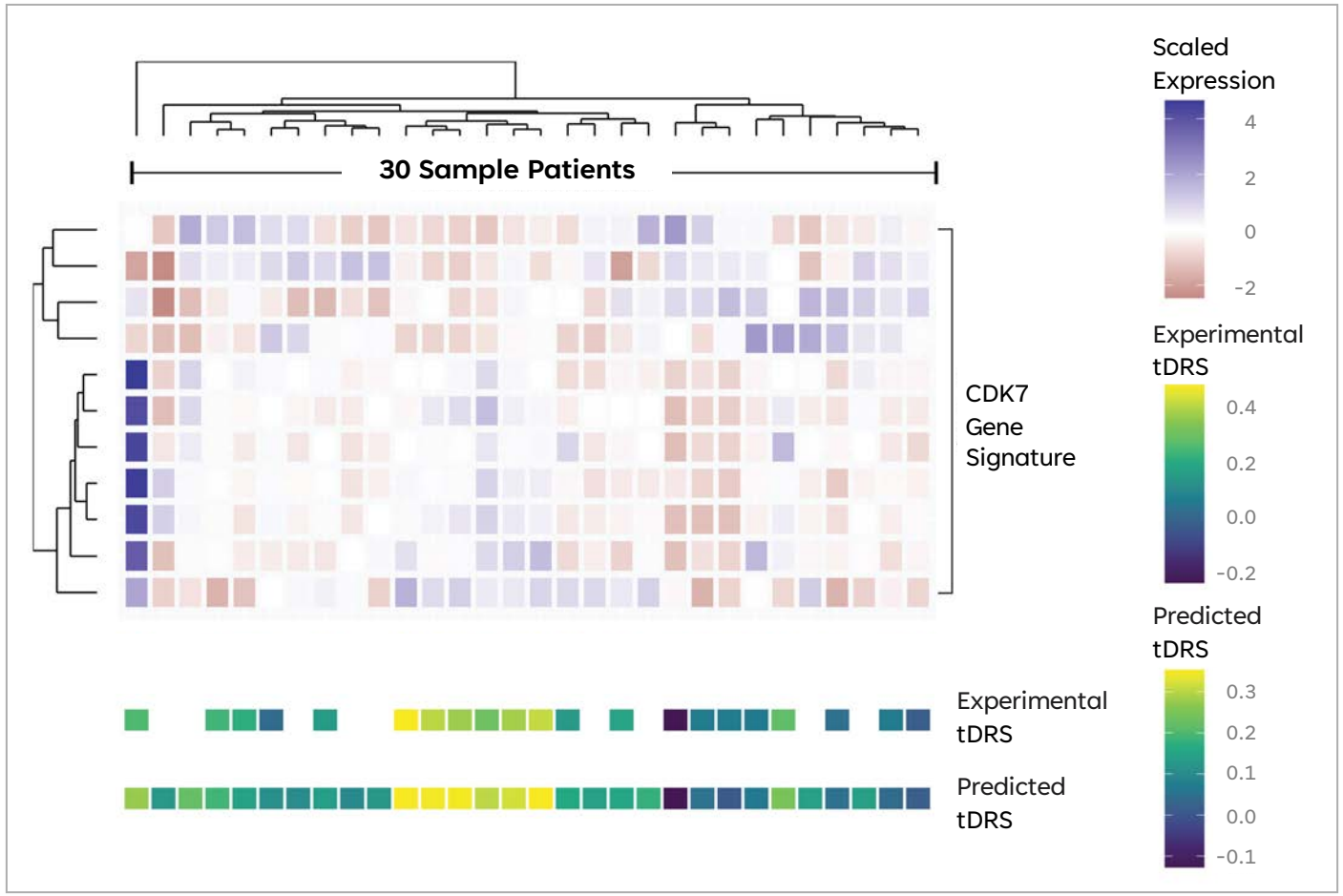
### Platform can identify responders and non-responders across tumour types

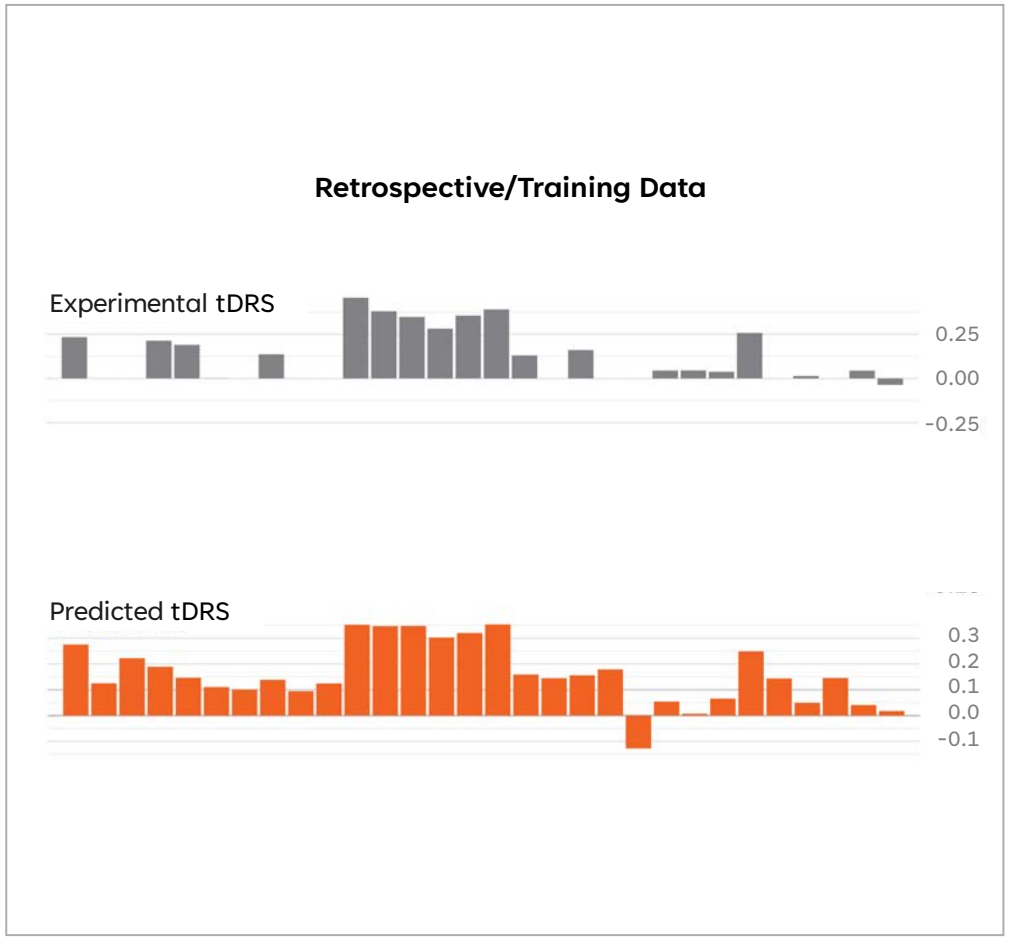



Durinikova et al, ENA (2022)

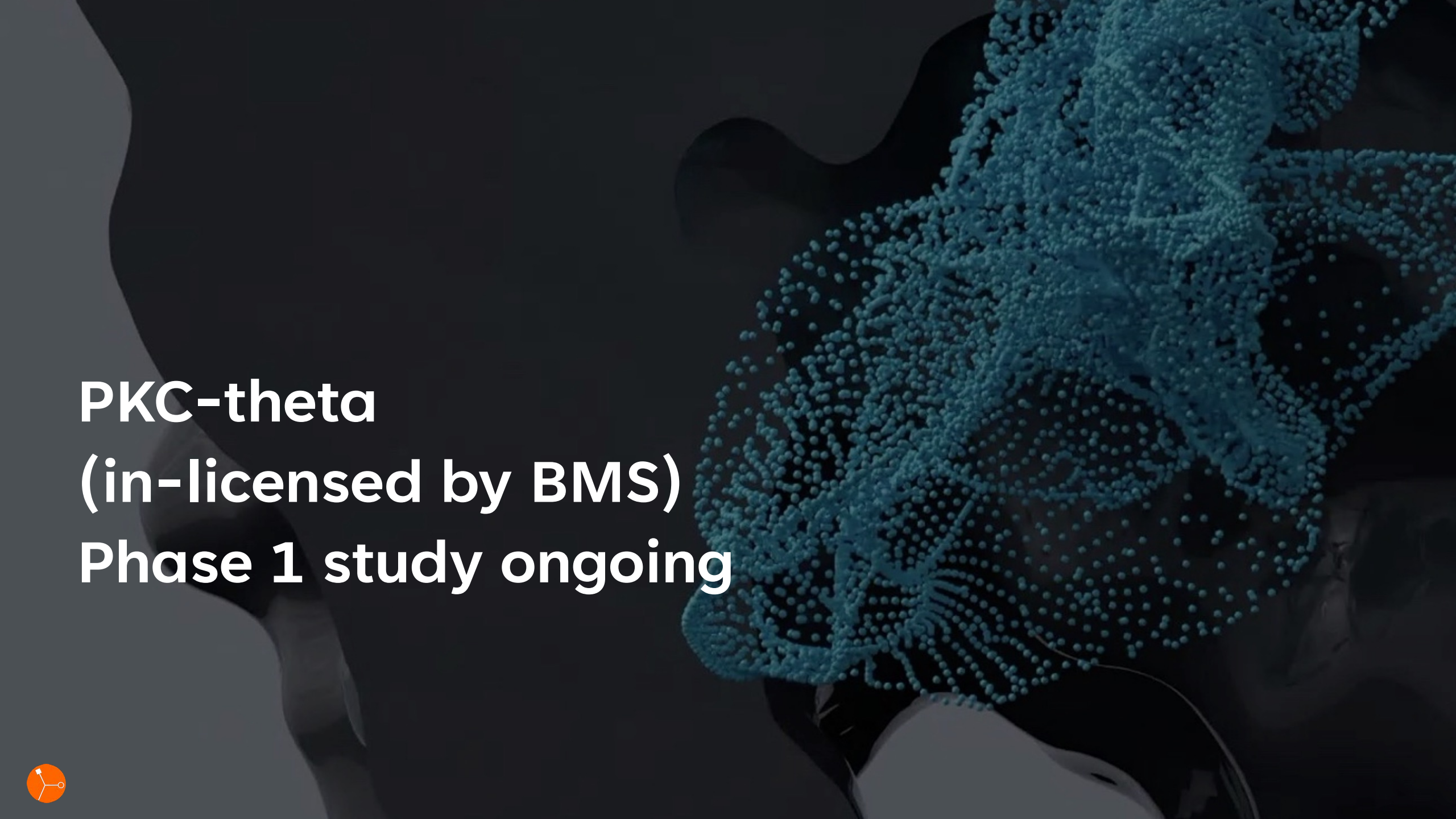
# Establishing ‘617 response predictor model

## Multimodal analysis of functional and matched transcriptomics data




tDRS = Total Drug Response Score; Durinikova et al, ENA (2022)


PKC-theta
(in-licensed by BMS)
Phase 1 study ongoing

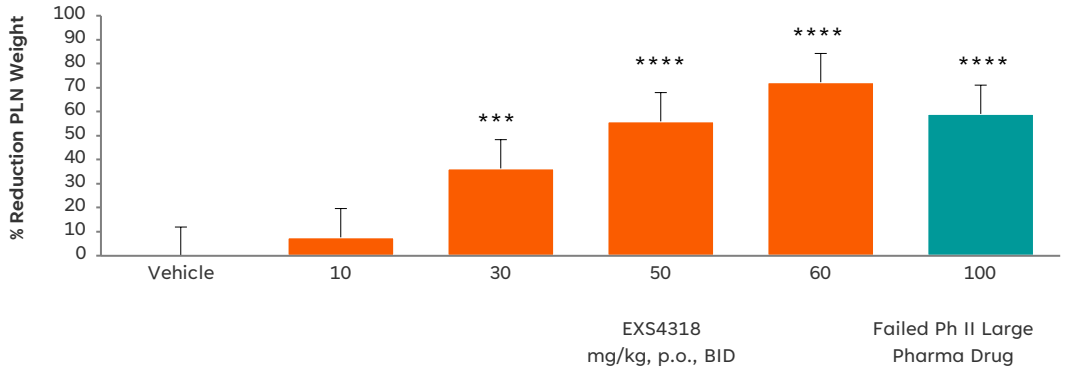
# **PKC-theta:** In-licensed by BMS in August 2021

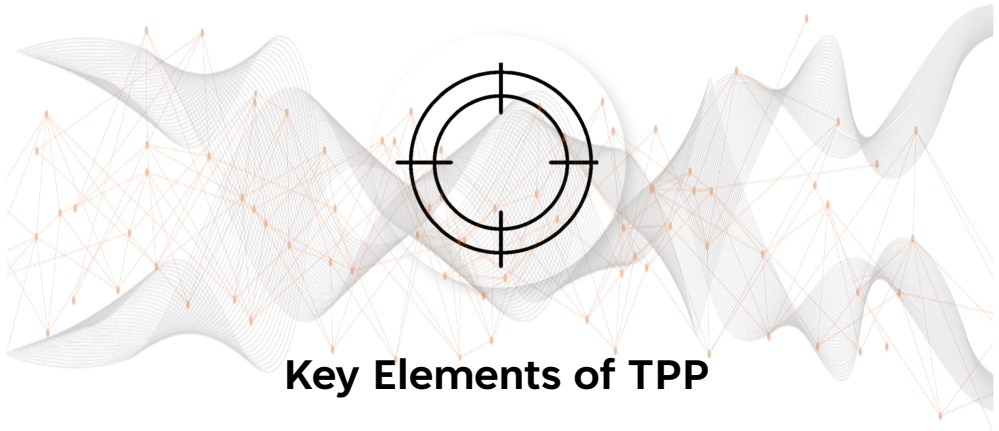
## Expert led AI-design to deliver against a high-value target

### 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 <200mg/day
- **Excellent selectivity** versus near neighbours and broad kinome

### Better Efficacy at Approximately Half the Dose



### Key Elements of TPP

- 24h coverage of $IC_{80}$ required to drive efficacy
- Predicted human dose <200mg/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

### Differentiated PKC-theta inhibitor profile

| Characteristic | Assay | EXS4318 | Failed mid-clinical large pharma drug candidate | Failed early clinical large pharma drug candidate |
|---|---|---|---|---|
| Target potency and selectivity | Biochemical | | | |
| | Near neighbours | | | |
| | Full kinome | | | |
| Cellular potency | T-cell | | | |
| | Human whole blood | | | |
| Safety and metabolic stability | hERG | | | |
| | Microsomal stability | | | |
| | Hepatocyte stability | | | |
| General properties | Permeability | | | |
| | Unbound drug | | | |
| | Solubility | | | |

Meets or exceeds criteria  Minor deviation  Major deviation

# 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 **150$^{th}$ novel compound** prepared
- Demonstrates close relationship at Exscientia of AI and experiment
- Elegant solution to a challenging problem. Nominated candidate <400 MW

# Introducing ‘539: Precision-designed LSD1 inhibitor

# ‘539: Highly differentiated LSD1 inhibitor

## First precision designed molecule to tackle reversibility and brain penetrance

### Better Design

Brain penetrant, reversible LSD1 inhibitor, with good PK and low projected human dose

### Mechanistic Rationale

Promotes differentiation pathways leading to tumour cell death in oncology indications

### Target Population

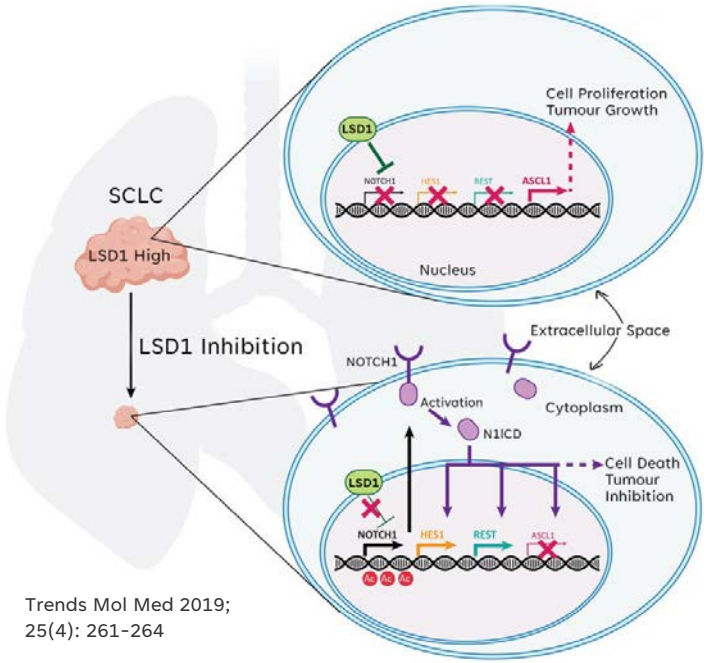
Potential as monotherapy or in combination in range of haematology and oncology indications, including those with brain metastases

IND-enabling studies and CMC readiness work ongoing

Additional updates expected in 2H 2023

# LSD1 inhibition leads to tumour cell death

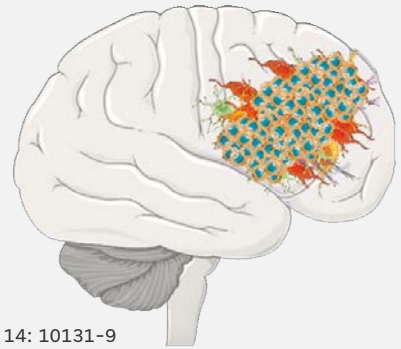
## Epigenetic target plays critical role in haematology and oncology indications




Trends Mol Med 2019; 25(4): 261-264

- LSD1 demethylates histones, playing a critical role in suppressing the expression of genes required for cellular differentiation
  - Drives the proliferation and survival of several tumour types
- LSD1 is overexpressed in many cancer types across haematology and oncology
  - e.g., in SCLC, high LSD1 expression is associated with downregulated differentiation pathways
- Inhibiting LSD1 reactivates expression of genes driving differentiation; can inhibit cell growth and sensitise any remaining cells to other agents

Mol Cell Oncol 2018; 5(4) e1481813



A brain penetrant LSD1 inhibitor can target peripheral disease as well as the brain metastases that develop in ~50% of SCLC patients*

*Int J Gen Med 2021; 14: 10131-9

# Precision design to maximise therapeutic window

## Mechanism requires tight control of duration of inhibition

### Reversible, Selective

- LSD1 has important functions (e.g., formation of red blood cells)
- Most inhibitors are irreversible and based on the antidepressant tranylcypromine. Protein needs to be resynthesised before function recovers (≥1 day)
- Reversible inhibition allows the key functions of the protein to recover more rapidly

Design needs to achieve potency and selectivity non-covalently

### CNS Penetrant

- Brain metastases are a major cause of mortality in cancer 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

### Pharmacokinetics

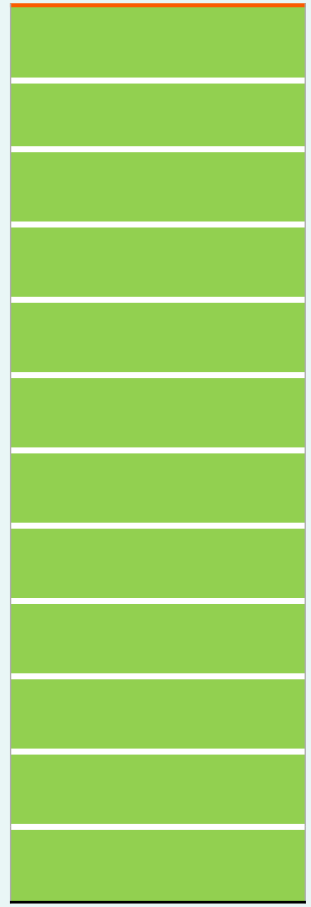
- A mid-stage reversible LSD1 inhibitor has a human terminal half-life of over 70 hours and is dosed weekly, which can cause safety concerns given the MoA
- Design needs to deliver a compound that could flexibly allow once-a-day or intermittent dosing to maximise efficacy whilst still enabling the broader functions of this protein

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

# **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 |
|---|---|---|---|---|
| **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 | | |

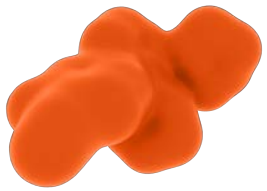



- CNS penetrant
- Potent and reversible
- Highly selective (including related amine oxidases)
- Efficacious *in vivo*
- Excellent metabolic stability, bioavailability and efflux
- Shorter predicted half-life than competitors

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

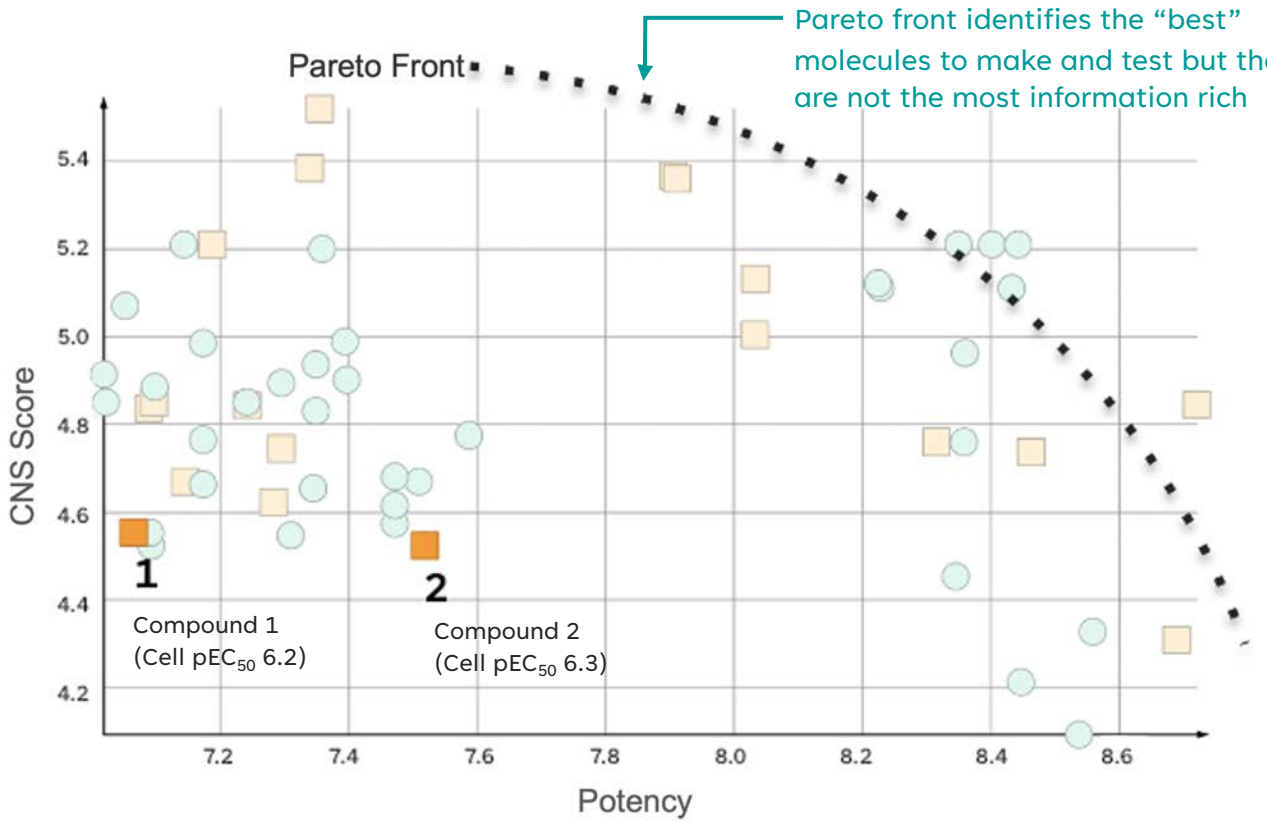
Active Learning

| Initiate | Evolve | 2D Models | 3D Models | Prioritise | Synthesis |
|---|---|---|---|---|---|
| **Knowledge based evolutions using 2D and 3D data** | **Evolutionary Algorithm** | **2D Models** **ML Models** | **Interaction Filter** | **Coverage Score** **Active Learning Exploitation** | **10-20 for Synthesis** |
| Improve properties of compounds from knowledge based starting points | **Gambit**<br>Evolve into 3D binding pocket and shape of known ligands<br>2D generative approaches | Use known LSD1 amine groups<br>Good physchem properties<br>CNS MPO<br>Good predictions against models | Prioritise on key interactions with the protein | hERG and CNS constraints | 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

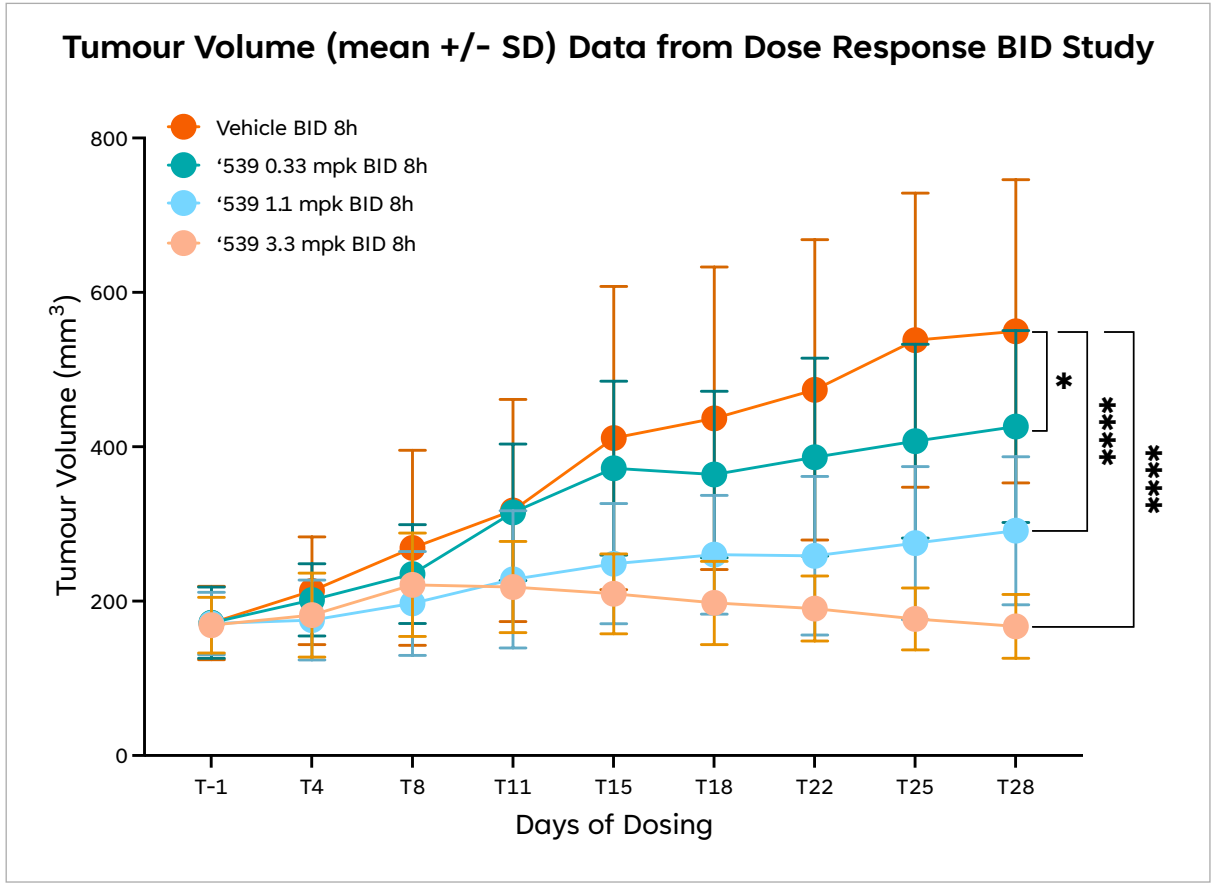


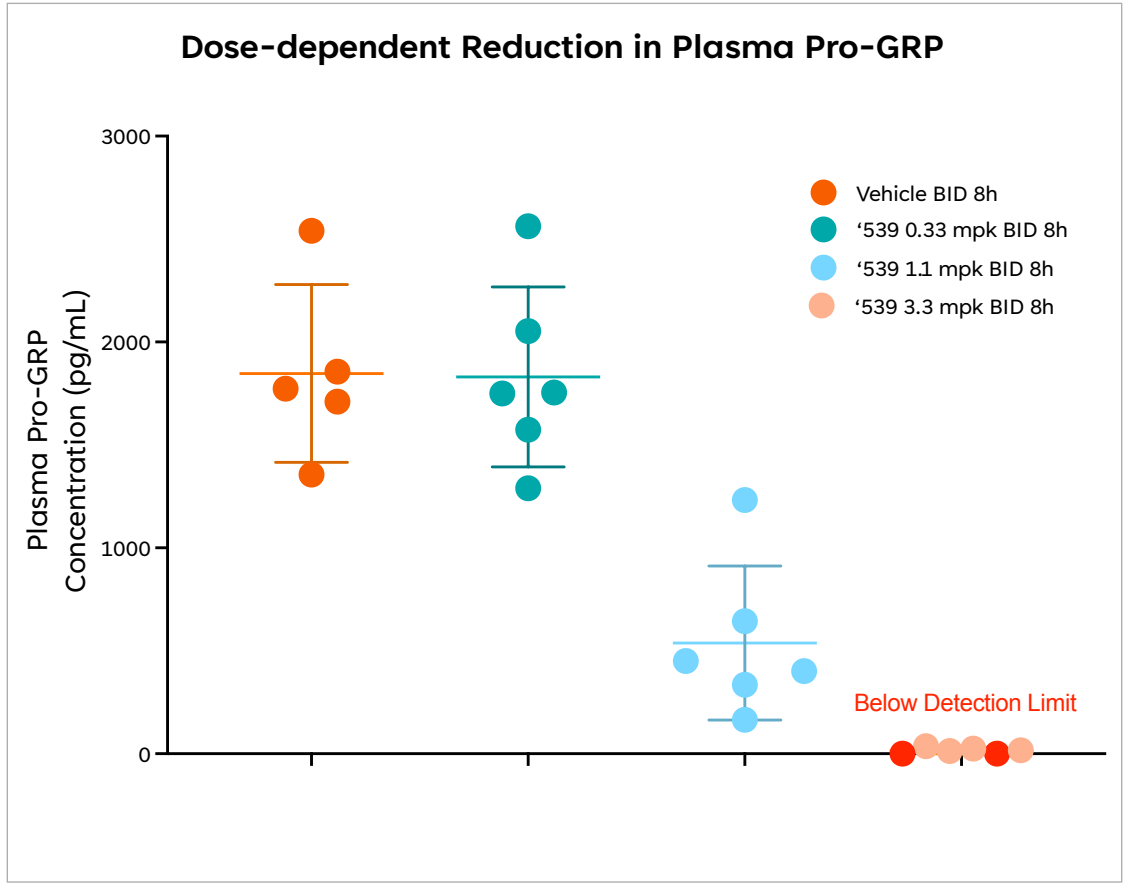

**20 compounds (square) are selected by active learning chemical coverage; other compounds (circles) were not selected**

- 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

# ‘539 inhibits tumour growth *in vivo*

## Dose-dependent tumour growth inhibition in SCLC xenograft model



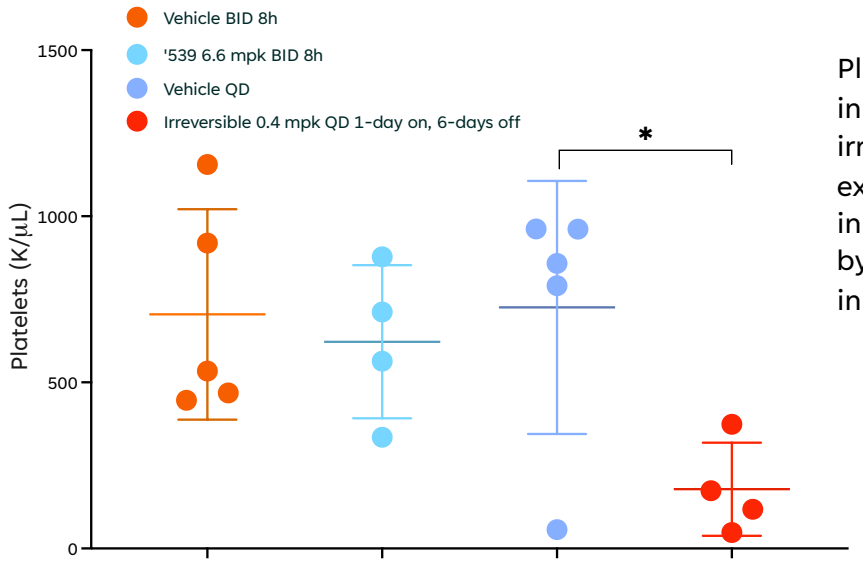

‘539 was well tolerated with body weight maintained in our studies

NCI-H1417 xenograft

# Benefit of reversible LSD1 target engagement on platelets

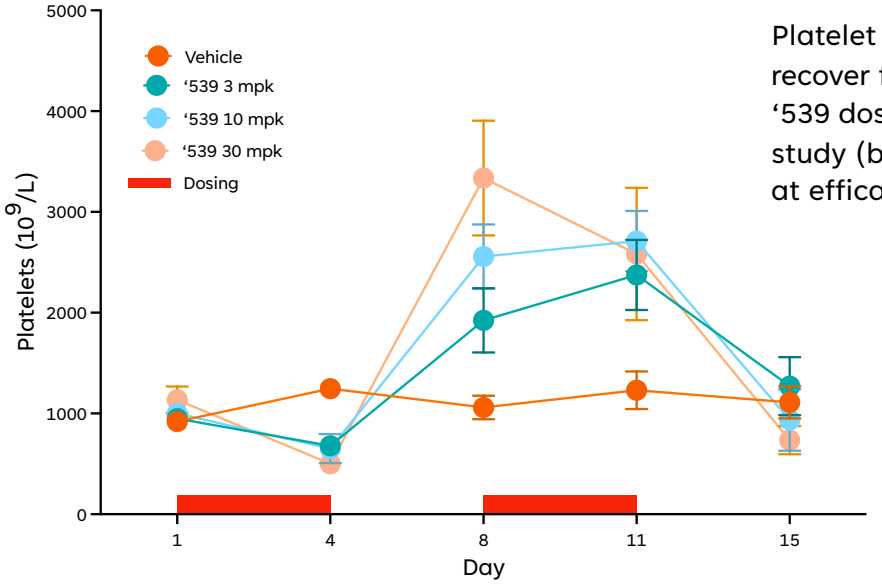
## Shorter half-life and reversibility may benefit on-target tox management

**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]**



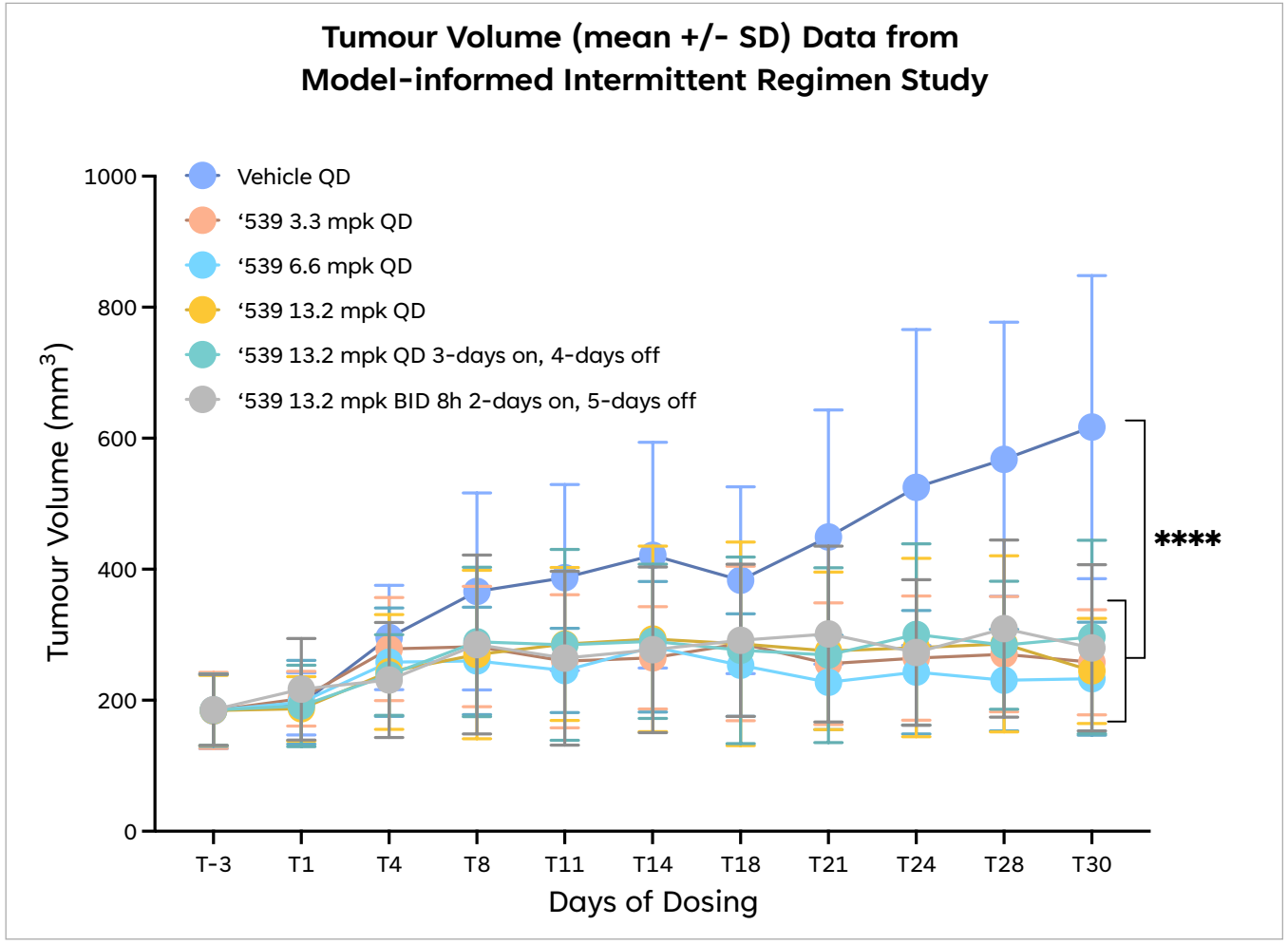

Platelet numbers recover following '539 dosing in rat study (by Day 15) at efficacious doses

- 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

# Efficacy maintained with intermittent dosing

## Shorter half-life and reversibility enables exploration of different dosing schedules




- Dose regimens were selected based on model-based predictions of anti-tumour efficacy with minimal impact on platelets
- Achieving this balance is anticipated to be more challenging with irreversible inhibitors, protein degraders and even reversible inhibitors with long human half-lives
- The anti-tumour efficacy predictions were strongly correlated with outcomes

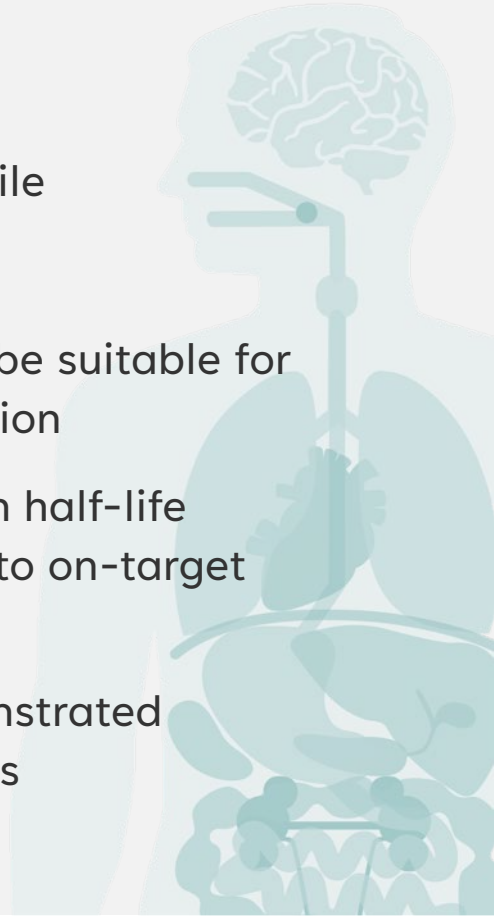
NCI-H1417 xenograft model

# 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
- Shorter 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 DRF studies with expected effects on haematology parameters
- Margins suitable for progression to GLP safety
- GLP-tox studies ongoing

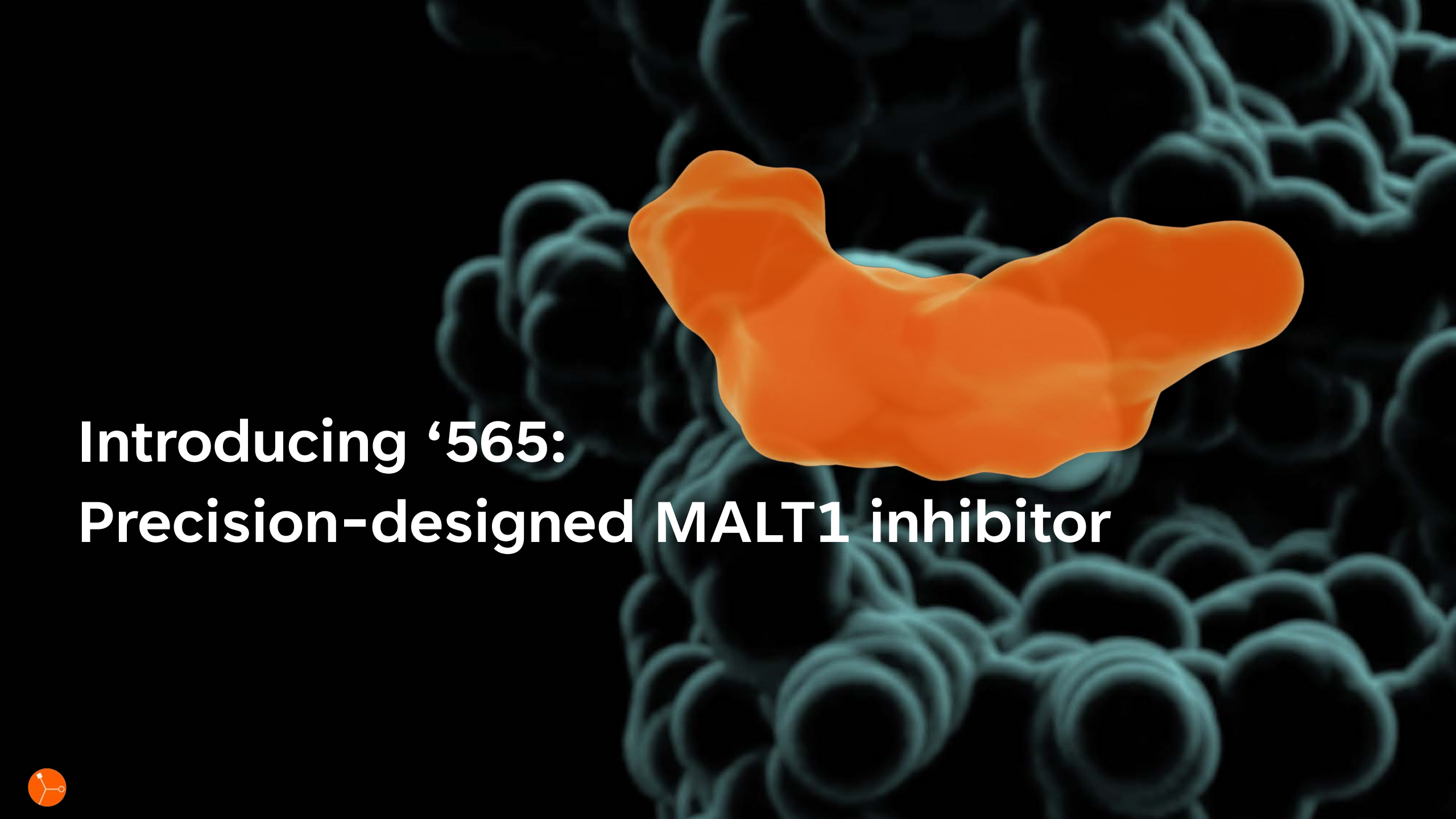
# ‘539: Summary

- GLP-tox studies ongoing
- CMC work underway
- MIDD to define best dose and dosing regimen

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 non-GLP 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



# Introducing ‘565:
# Precision-designed MALT1 inhibitor

# ‘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 and CMC readiness work ongoing

Additional updates expected in 2H 2023

# **MALT1:** Inhibition of immune cell signalling

## Important mechanism in haematologic malignancies

- BCR signalling pathway is chronically activated in some haematologic indications through multiple mechanisms
- MALT1 is a key component of dysregulated antigen signalling pathways in T- and B-cell malignancies
  - Protease activity crucial for activation of the NF-κB pathway
  - Supports uncontrolled proliferation of malignant T- and B-cells in haematological cancers
- MALT1 inhibition can block/dampen NF-κB signalling which is activated in DLBCL subtypes
- Single agent treatments currently used in a subtype of DLBCL are generally not curative/drive resistance
- Combining MALT1 inhibition with BTK inhibitors (or BCL2 inhibitors) may achieve deep and long duration of response and enable treatment cessation upon attainment of undetectable minimal residual disease in CLL

# MALT1 (EXS73565)

## 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 BTKi
- Anti-proliferative against primary B-cell lymphoma samples
- Predicted half-life suitable for QD administration

Synergistic efficacy

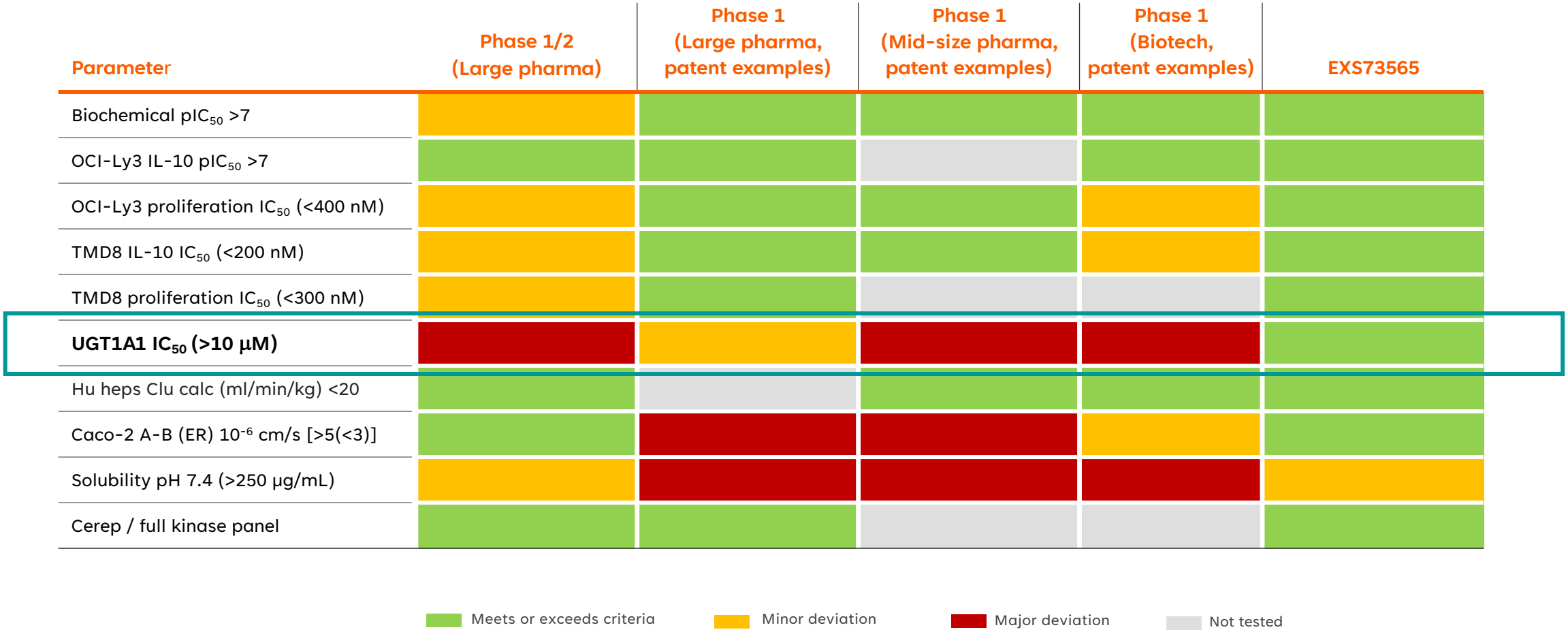
# Avoiding uridine glucuronyl transferase (UGT1A1)

## ‘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 (hyperbilirubinemia) and can lead to metabolic disorder
  - Jaundice, nausea, vomiting and potentially encephalopathy can occur
- The 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

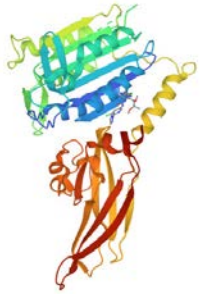


# Technology in action: Precision design of ‘565

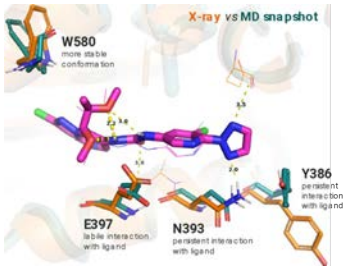
## Designing and selecting the right molecules to synthesise

Generative Design | Machine Learning | Structure

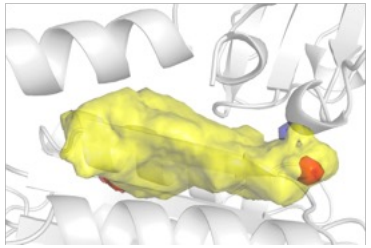
**Initiate**



Use of MD to define dynamic pocket




**Analyse**



Hotspot analysis to find key interactions and drive generative algorithms

**Evolve**

**Evolutionary Algorithm**

Automated structural informatics

Evolve in 3D directed towards Hotspot interaction (Gambit)

Hybridisations

**2D Models**

**2D Models** **ML Models**

Good physchem properties

MPO

Good predictions against models

**3D Models**

**Interaction Filter**

**Compatibility with key Hotspots**

**Active Learning**

**10-20 for Synthesis**

**Coverage Score**

**Active Learning Exploitation**

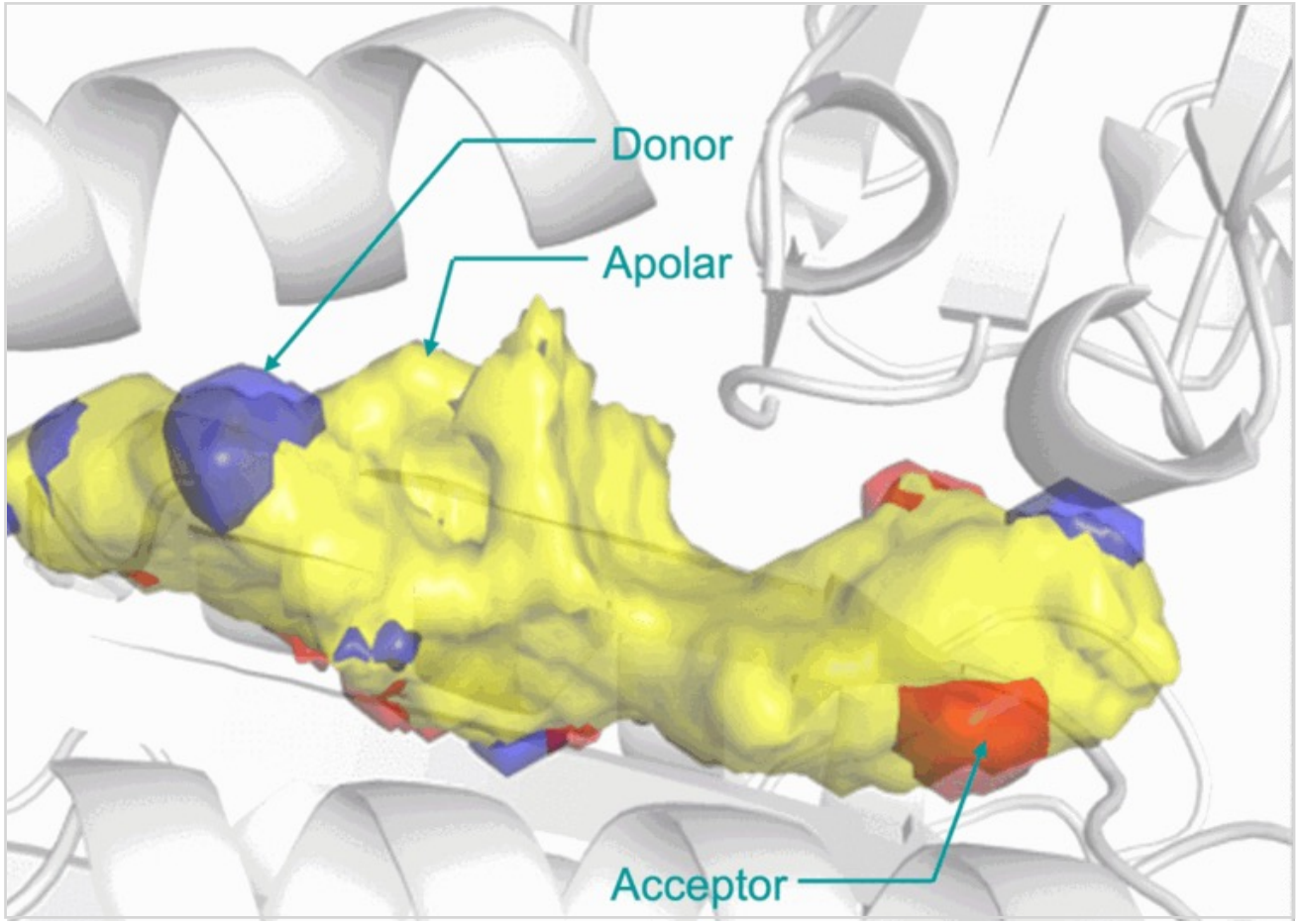
**Solubility Potency**

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

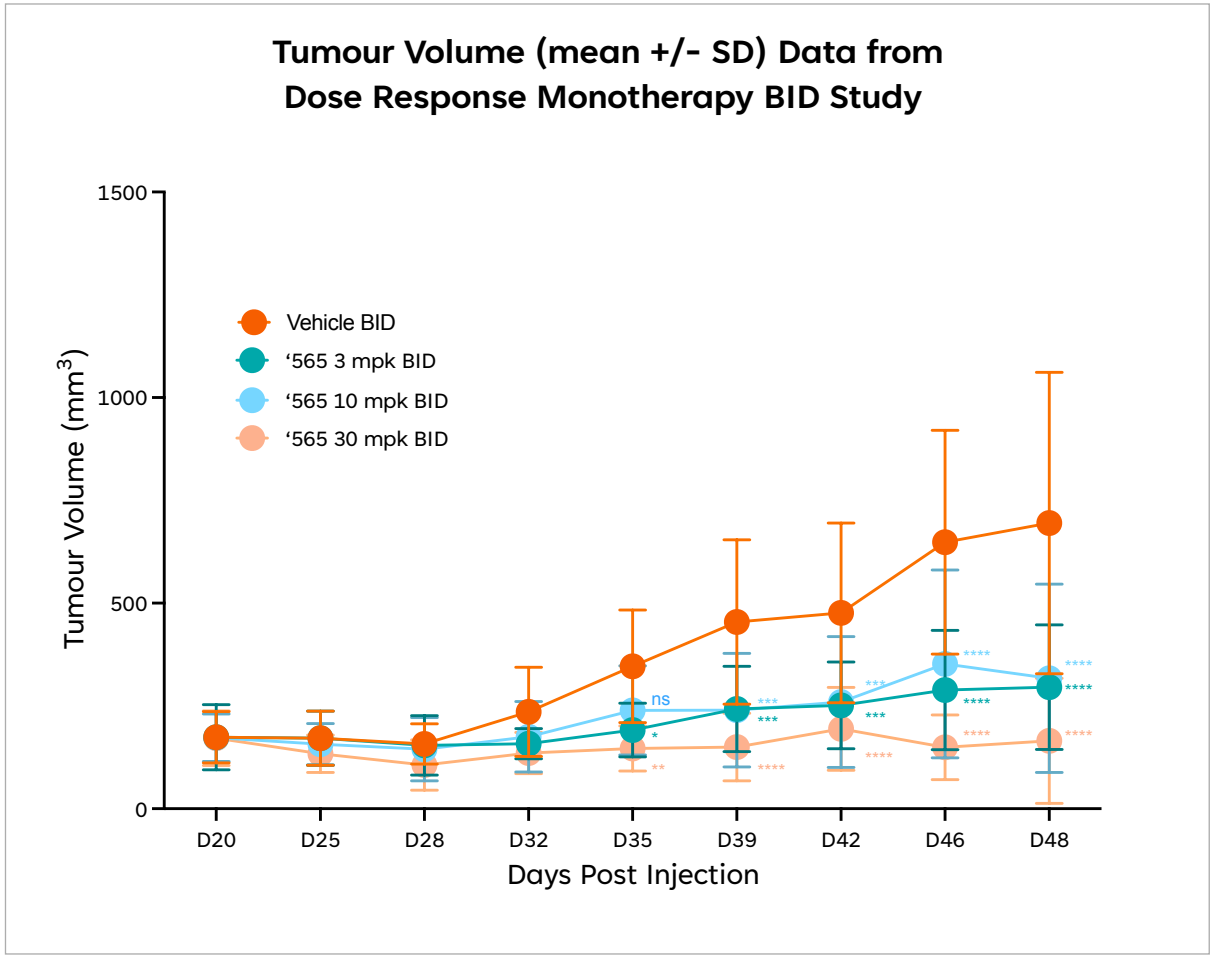



- Simulated binding site movements and integrated with Hotspots for automated definition
- Design of ‘565 expanded our approach onto complex dynamic targets and into novel chemical space
- Drove our generate constraints towards delivering improvement in permeability
- ‘565 candidate delivered using physics-based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

Watch video at: https://bit.ly/565HotSpots

# ‘565 inhibits ibrutinib-insensitive tumour model growth *in vivo*

## Monotherapy efficacy in a DLBCL xenograft model



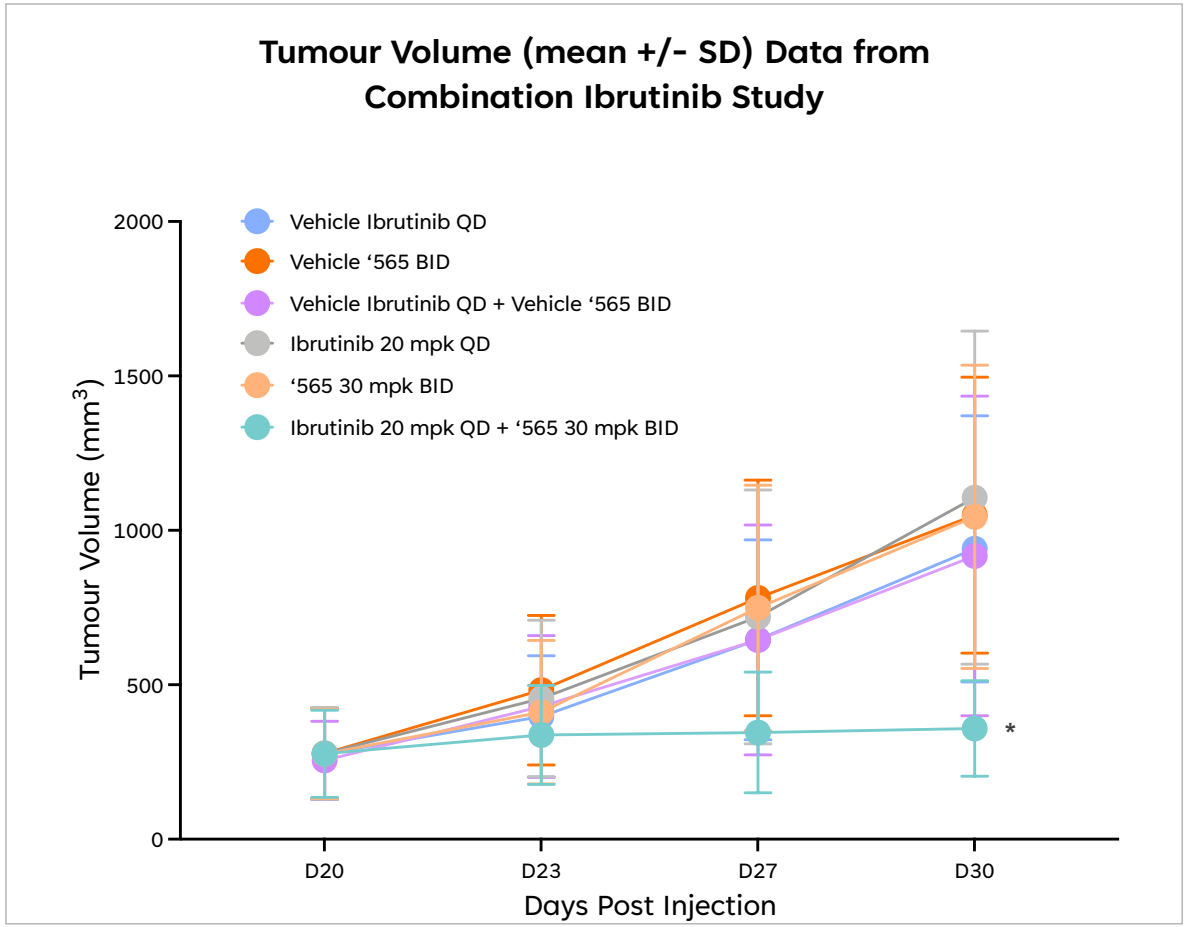

- OCI-Ly3 cells are insensitive to the BTKi inhibitor, ibrutinib, both *in vitro* and *in vivo*
- Oral administration of ‘565 showed statistically significant tumour growth inhibition at all tested doses
- ‘565 was well-tolerated with body weight maintained

OCI-LY3 xenograft model: CARD11 mutant

# ‘565 deepens response to ibrutinib *in vivo*

## Synergistic efficacy of '565 in combination with ibrutinib

- TMD8 DLBCL cells are sensitive to both MALT1 and ibrutinib *in vitro*
- However, administration of ibrutinib or ‘565 (30 mg/kg BID) showed no activity in the TMD8 model *in vivo* when administered alone
- Notably, 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



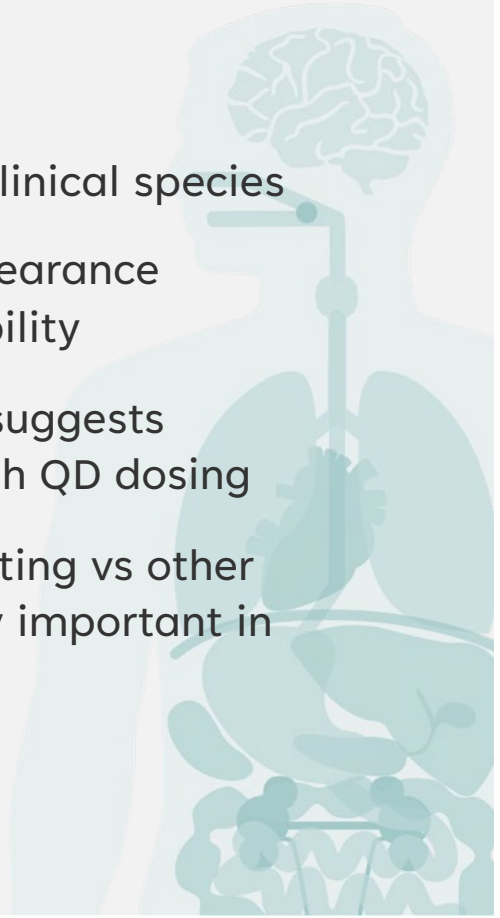

TMD8 xenograft model: CD79B mutant

# 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 DDI risk, differentiating vs other compounds (particularly important in combination with BTKi)



### Toxicology & Safety Pharmacology

- No unexpected *in vitro* or *in vivo* safety concerns identified
- Well tolerated in rat/dog DRF studies
- Dose levels in GLP toxicology studies chosen to establish safety margins to predicted human efficacious dose
- GLP-tox and telemetry studies in reporting phase

# **‘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

Exscientia

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