Exscientia

Precision Design for Precision Oncology

March 2023

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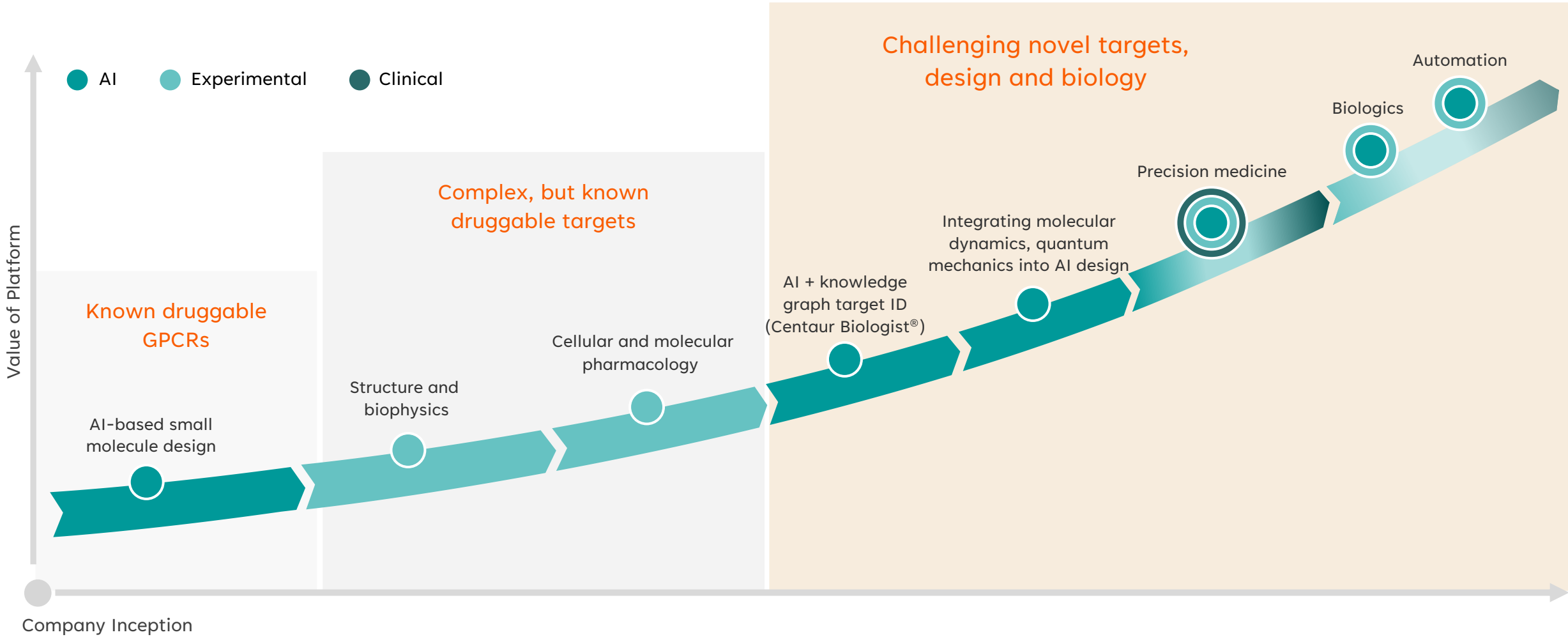
Expanding technologies enhance value creation

Advancements of AI-driven drug design



Timeline for illustrative purposes

Delivering differentiated molecules against challenging criteria

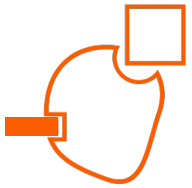
Three new molecules highlighting precision design capabilities

✓ **Kinase Selectivity**

EXS4318 (‘4318)
(PKC-theta inhibitor)

✓ **Reversible MoA & CNS Penetration**

EXS74539 (‘539)
(LSD1 inhibitor)



✓ **Allosteric Inhibition**

EXS73565 (‘565)
(MALT1 protease inhibitor)

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

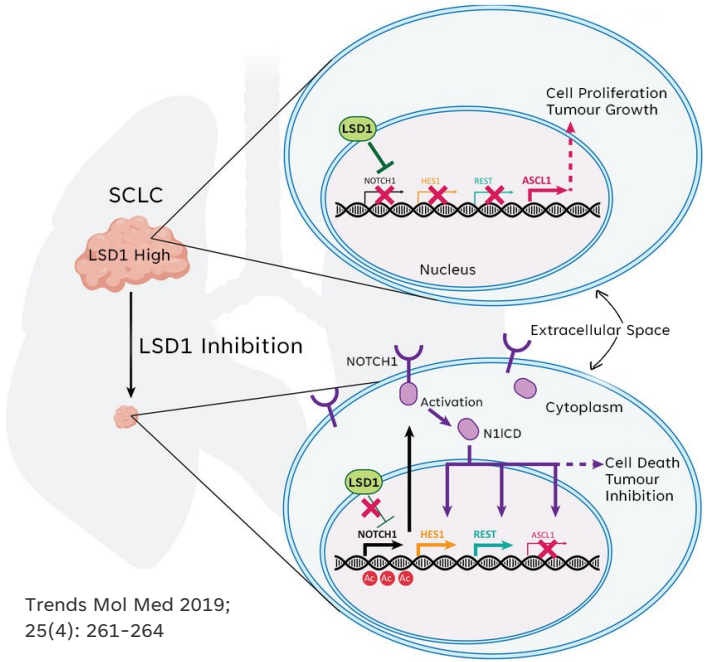
Potential as monotherapy or in combination in range of haematology and oncology indications, including those with brain metastases

IND-enabling studies and CMC readiness work ongoing

Additional updates expected in 2H 2023

LSD1 inhibition leads to tumour cell death

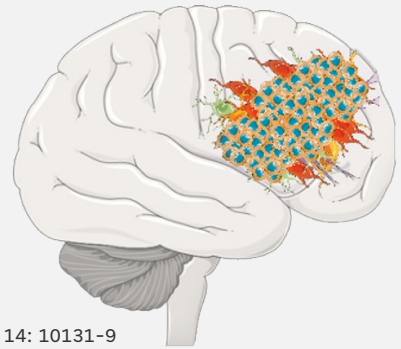
Epigenetic target plays critical role in haematology and oncology indications



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/10^6cells	<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		

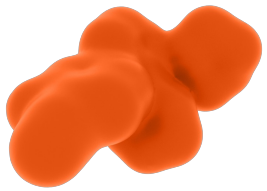
EXS74539

- 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

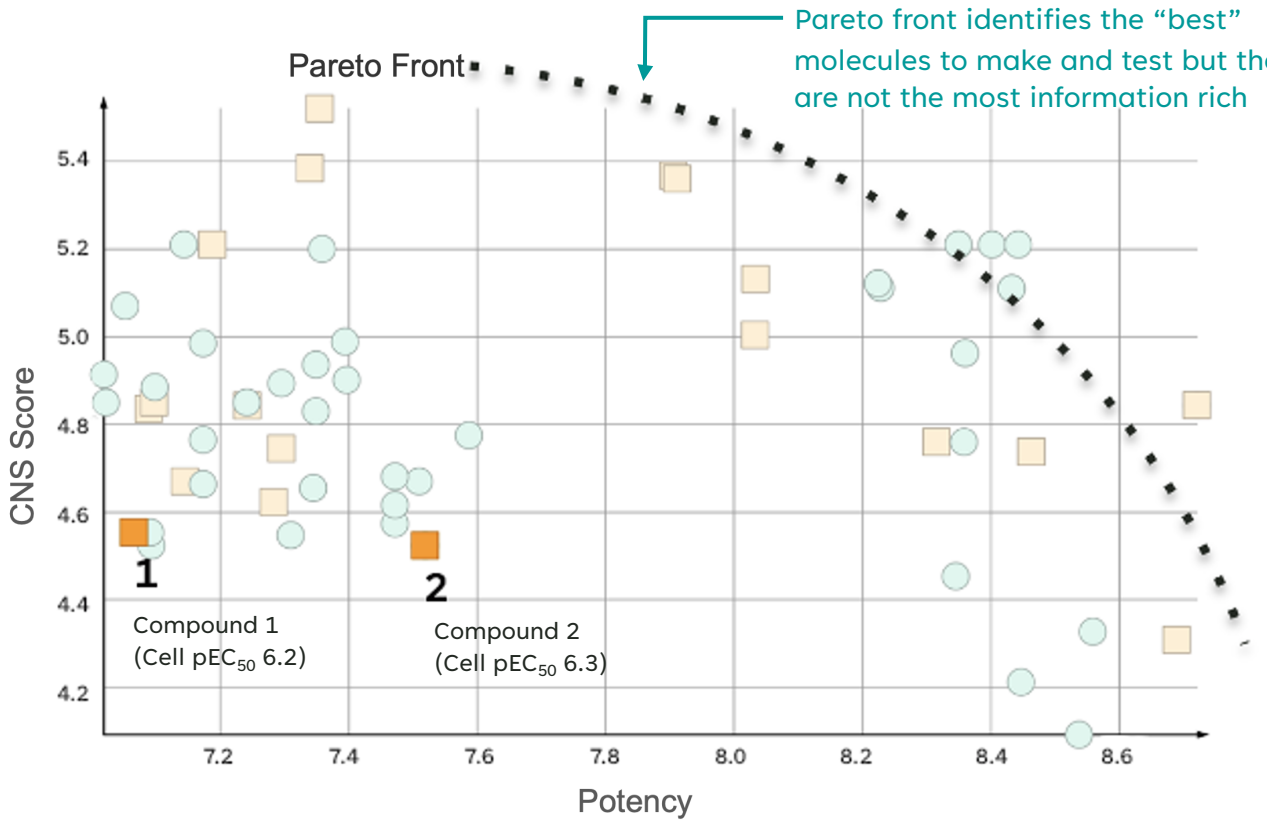
10-20 for Synthesis

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

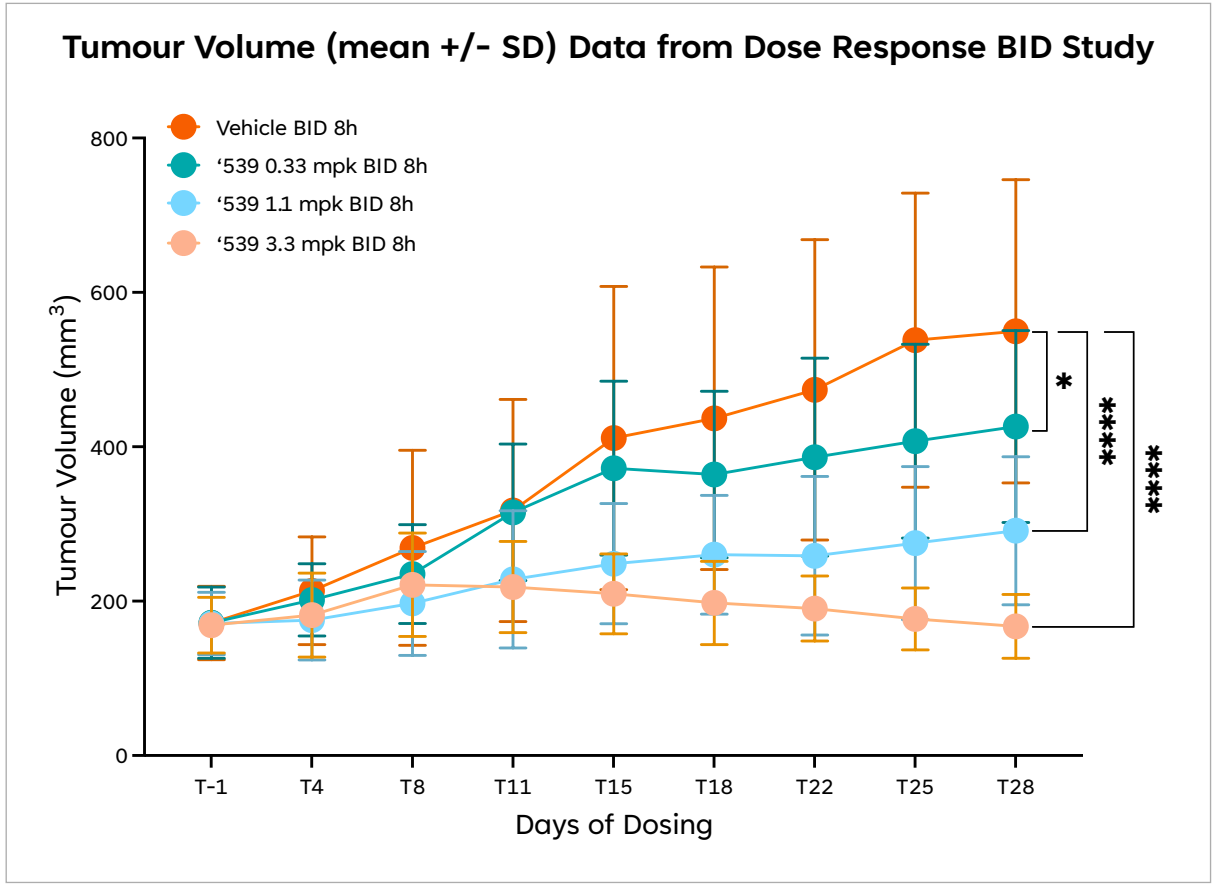


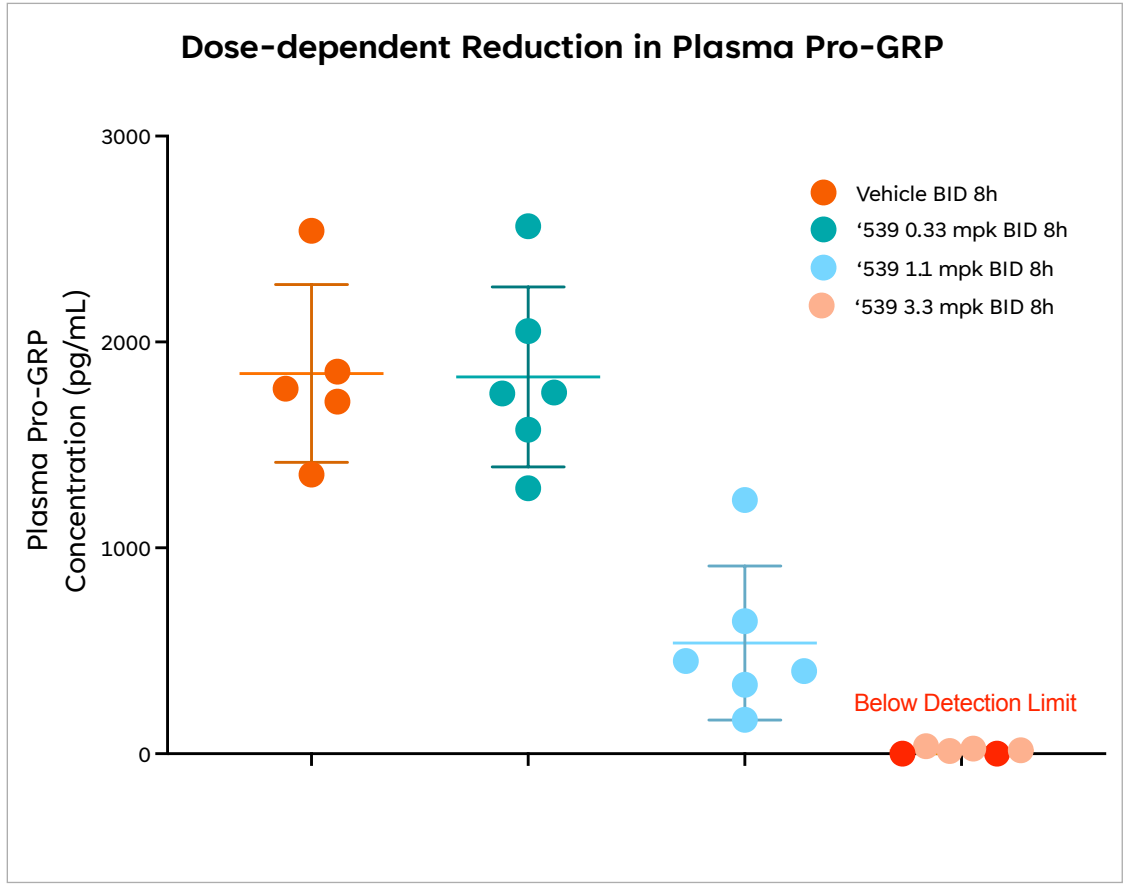
20 compounds (square) are selected by active learning chemical coverage; other compounds (circles) were not selected

- 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

‘539 inhibits tumour growth *in vivo*

Dose-dependent tumour growth inhibition in SCLC xenograft model





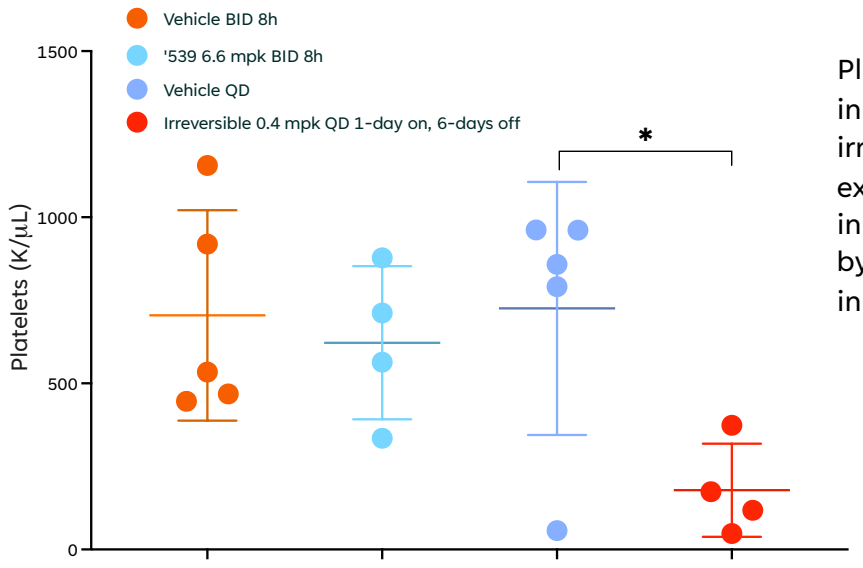
‘539 was well tolerated with body weight maintained in our studies

NCI-H1417 xenograft

Benefit of reversible LSD1 target engagement on platelets

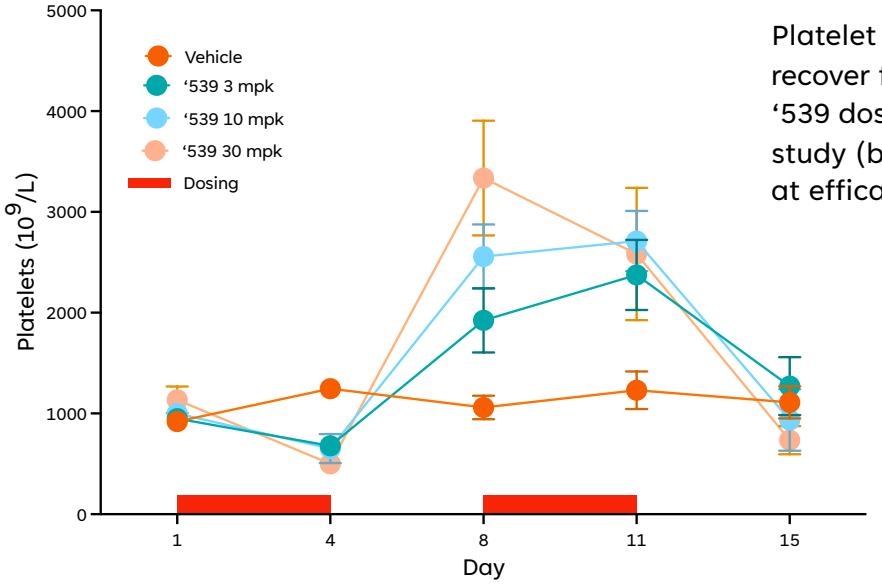
Shorter half-life and reversibility may benefit on-target tox management

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]



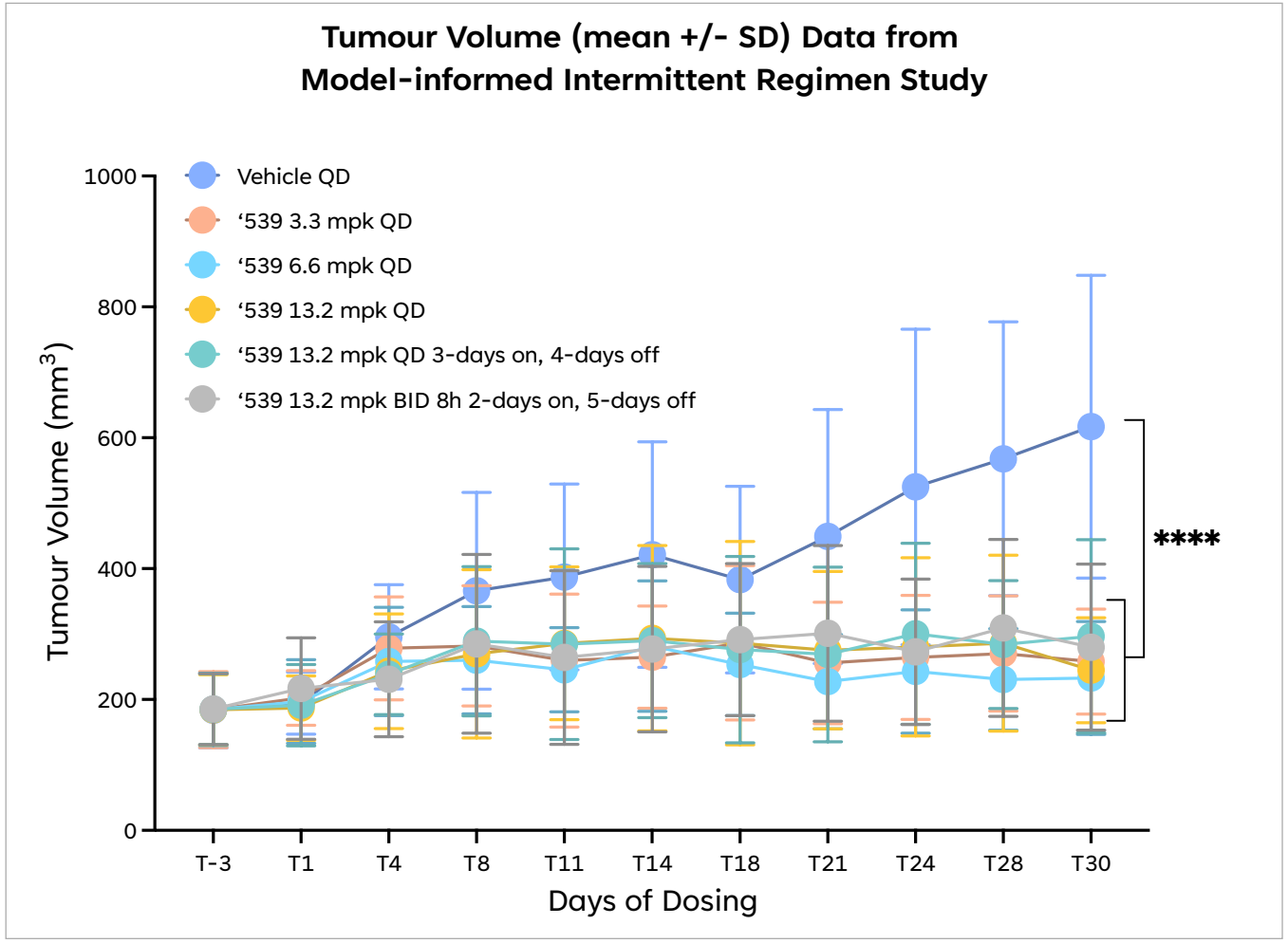
Platelet numbers recover following '539 dosing in rat study (by Day 15) at efficacious doses

- 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

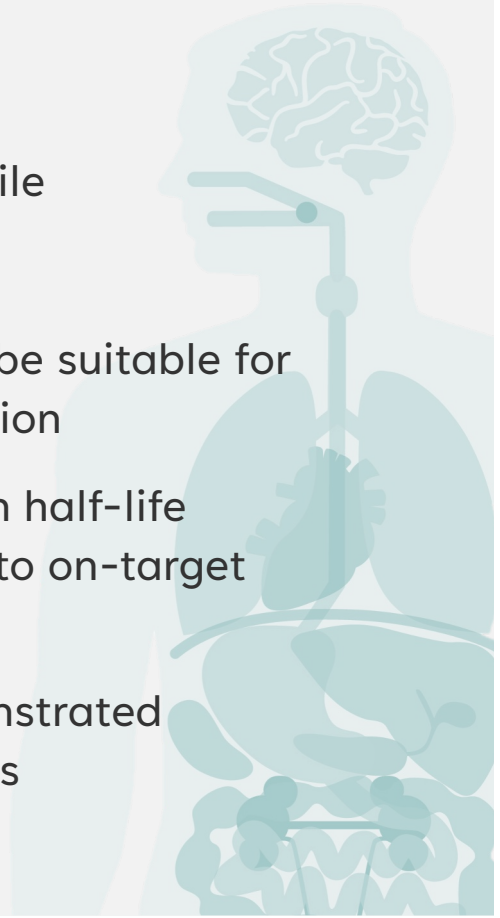
NCI-H1417 xenograft model

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

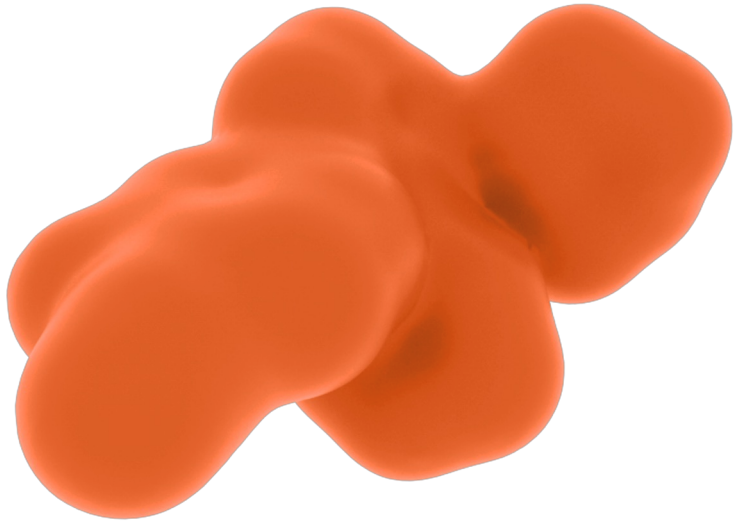


Toxicology & Safety Pharmacology

- 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

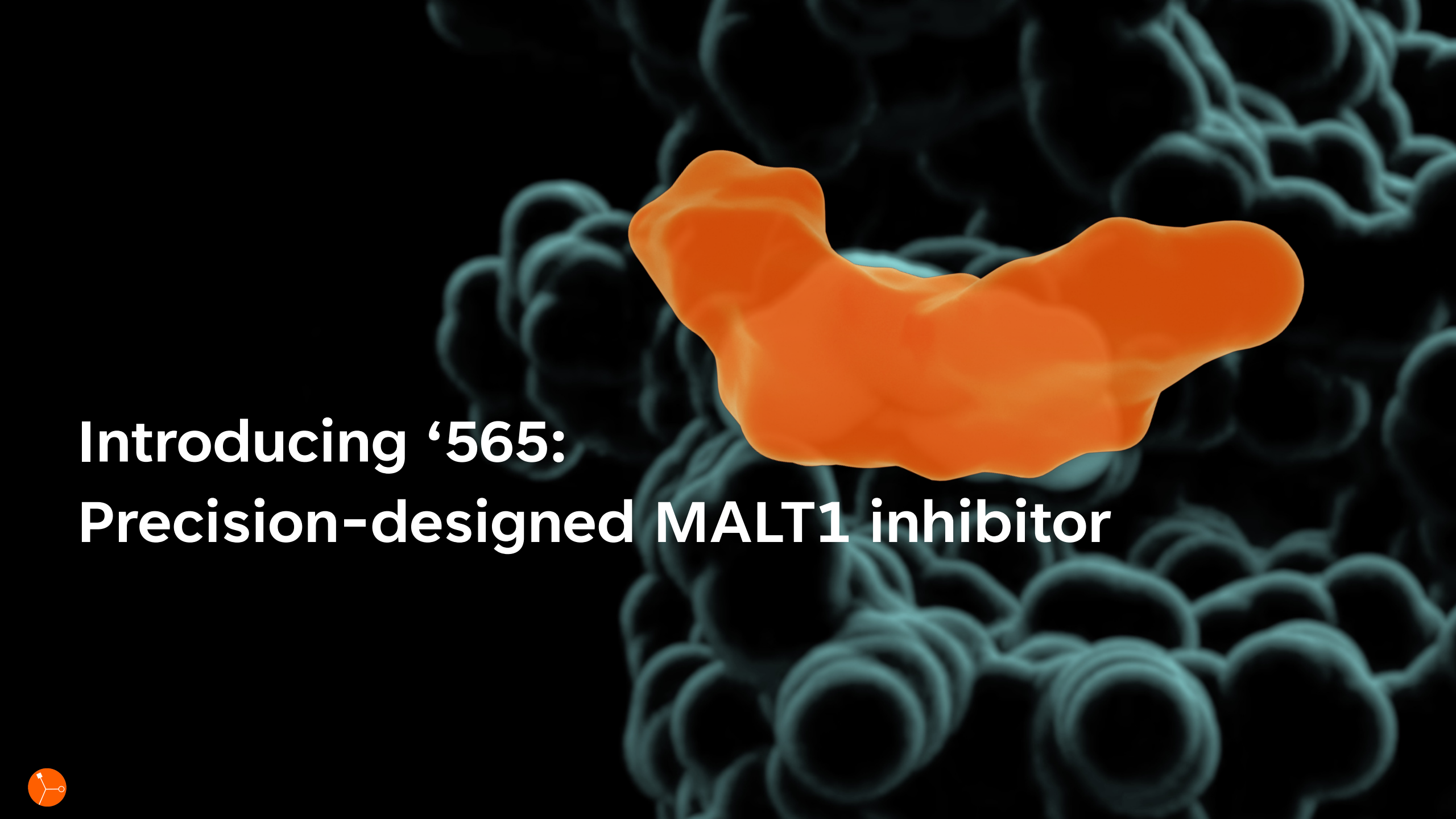
- GLP-tox studies ongoing
- CMC work underway
- MIDD to define best dose and dosing regimen



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

MIDD = Model-informed Drug Development



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 inhibitor

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

Parameter	Phase 1/2 (Large pharma)	Phase 1 (Large pharma, patent examples)	Phase 1 (Mid-size pharma, patent examples)	Phase 1 (Biotech, patent examples)	EXS73565
Biochemical pIC_{50} >7					
OCI-Ly3 IL-10 pIC_{50} >7					
OCI-Ly3 proliferation IC_{50} (<400 nM)					
TMD8 IL-10 IC_{50} (<200 nM)					
TMD8 proliferation IC_{50} (<300 nM)					
UGT1A1 IC_{50} (>10 µM)					
Hu heps Clu calc (ml/min/kg) <20					
Caco-2 A-B (ER) 10^{-6} cm/s [>5(<3)]					
Solubility pH 7.4 (>250 µg/mL)					
Cerep / full kinase panel					

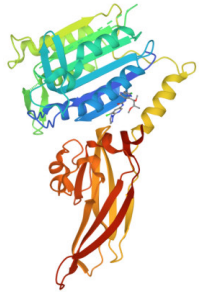
Meets or exceeds criteria | Minor deviation | Major deviation | Not tested

Technology in action: Precision design of ‘565

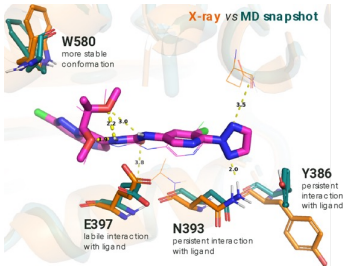
Designing and selecting the right molecules to synthesise

Generative Design | Machine Learning | Structure

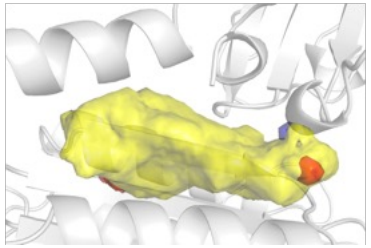
Initiate



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

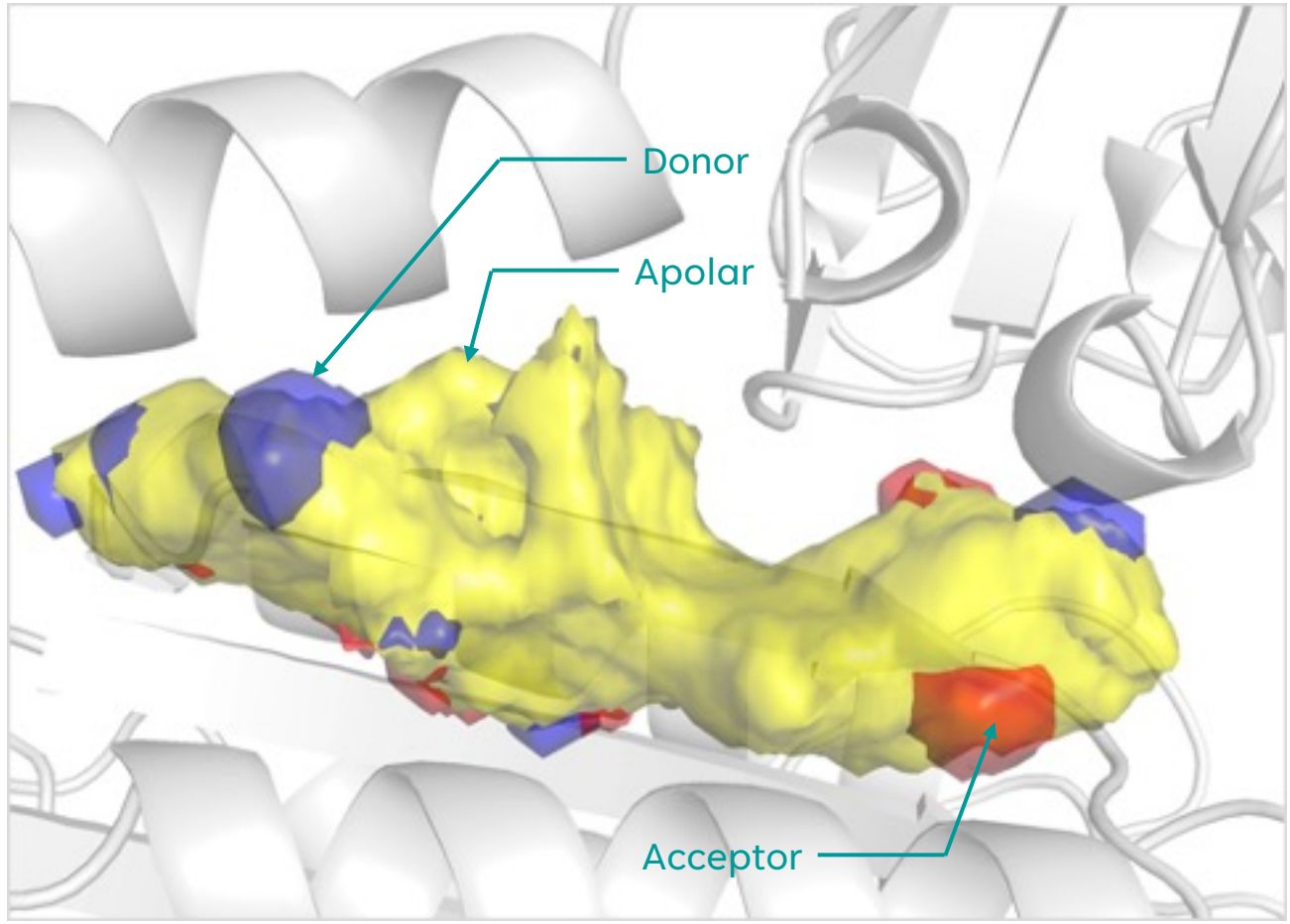
Solubility Potency

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

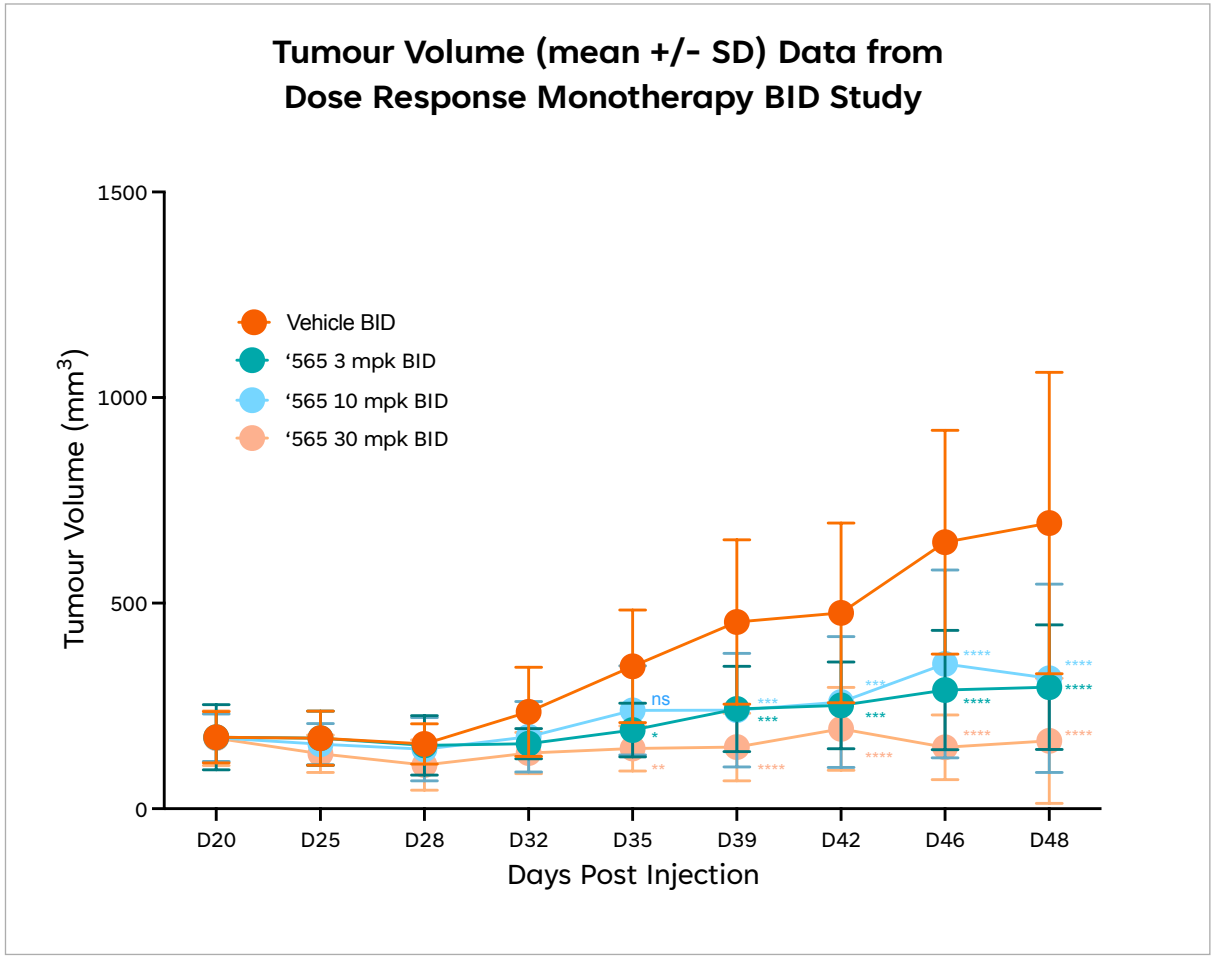
Understanding protein flexibility using molecular dynamics



- 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

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

Monotherapy efficacy in a DLBCL xenograft model



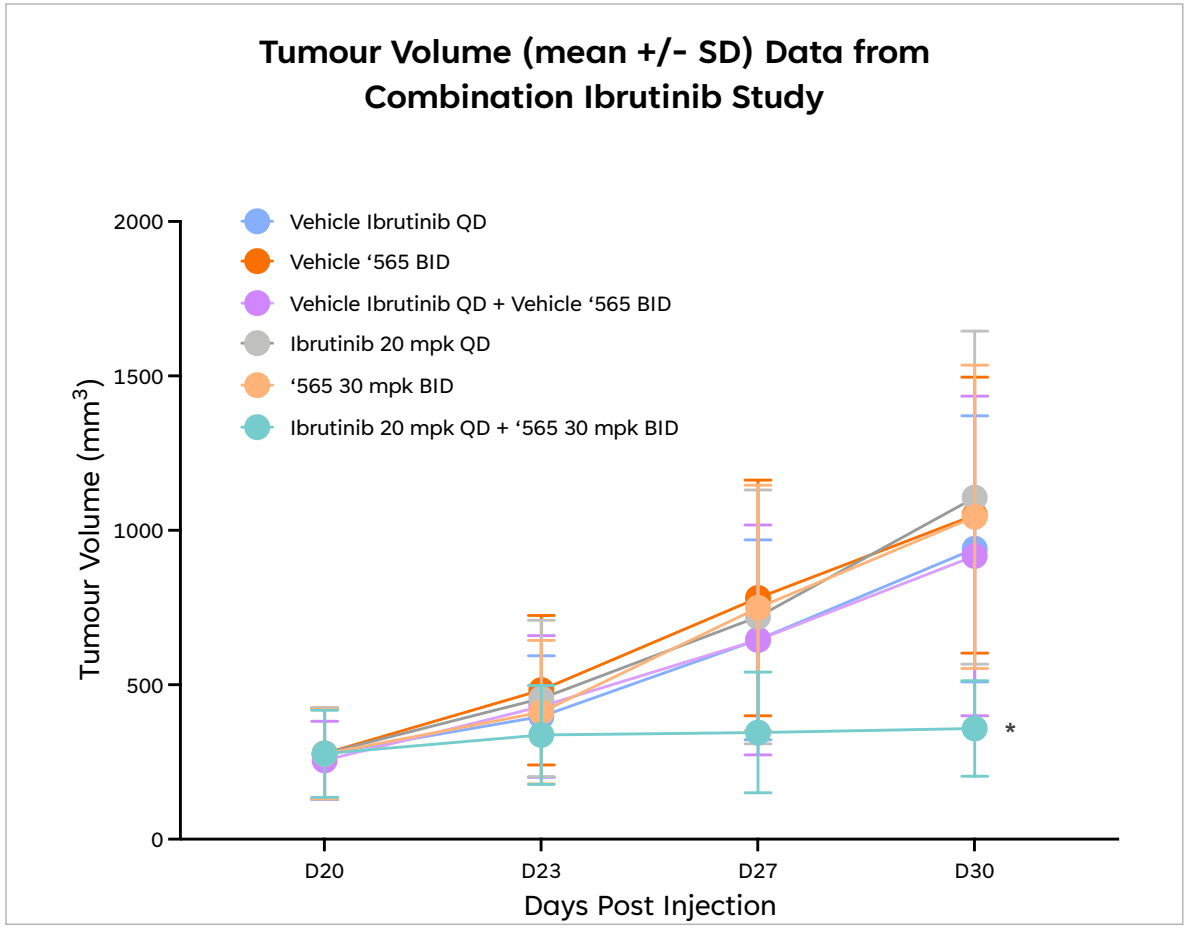
- OCI-Ly3 cells are insensitive to the BTKi inhibitor, ibrutinib, both *in vitro* and *in vivo*
- Oral administration of ‘565 showed statistically significant tumour growth inhibition at all tested doses
- ‘565 was well-tolerated with body weight maintained

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



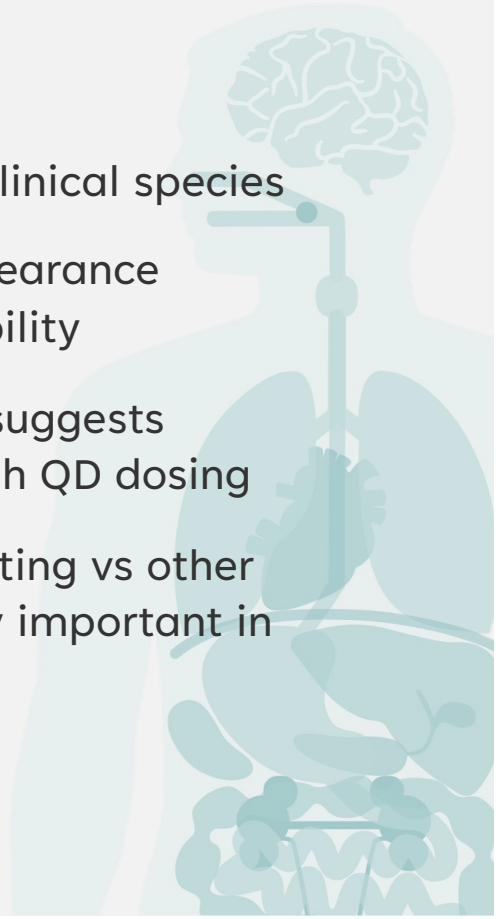
TMD8 xenograft model: CD79B mutant

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

Exscientia plc

OXFORD HEADQUARTERS
The Schrödinger Building
Oxford Science Park
Oxford OX4 4GE

investors@exscientia.ai

Registered address: The Schrödinger Building,
Oxford Science Park, Oxford, OX4 4GE, United Kingdom

Registered number: 13483814