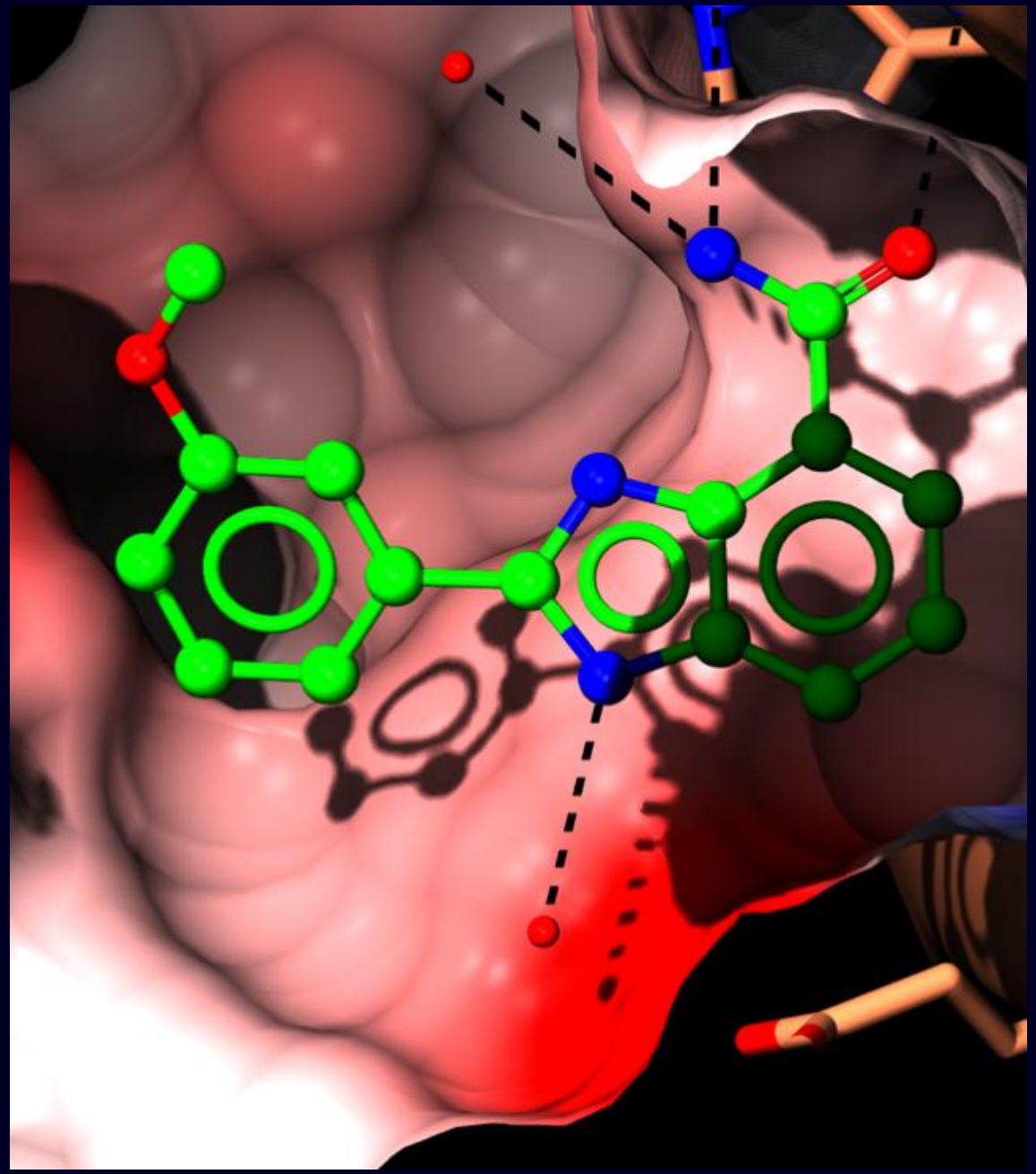


CANCER RESEARCH HORIZONS

Small Molecule CDC7 Kinase Inhibitors

Licensing opportunity

Non-confidential deck

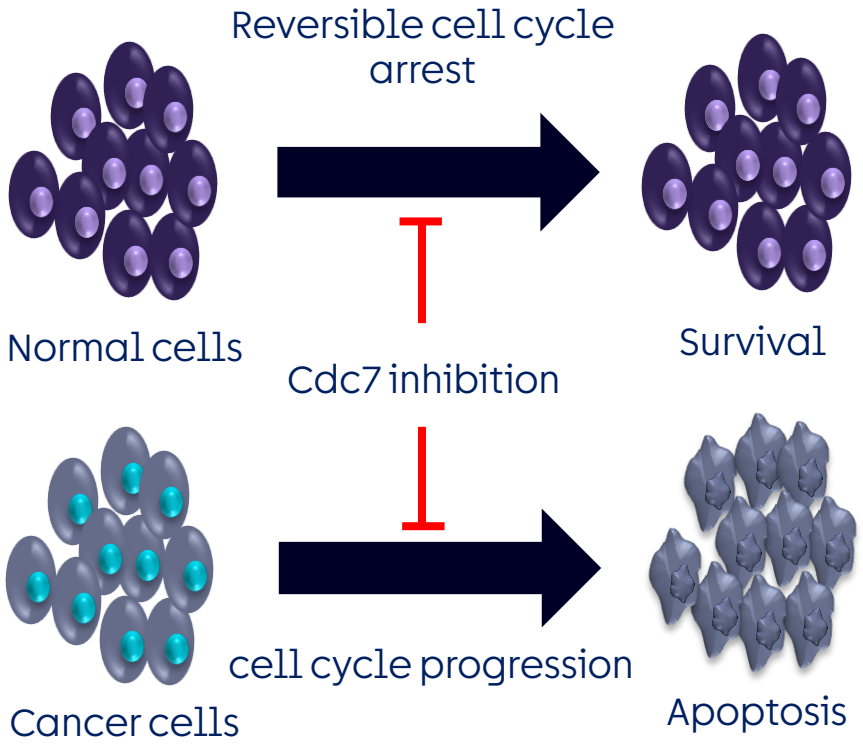
FURTHER FASTER TOGETHER
We are beating cancer

OPPORTUNITY OVERVIEW

- Potent, selective and orally bioavailable CDC7 inhibitors
- Lead pre-candidate chemistry developed in-house at the CRH *Therapeutic Innovation* laboratories
- Demonstrated target engagement in vivo in tumour models
    - Potent tumour inhibition in DLBCL and renal xenograft models
    - Favourable PK
    - Predicted low human efficacious dose
- Collaboration in progress with Turbine AI to identify novel disease positioning hypotheses and patient stratification biomarkers
- Strong IP position – CoM patents filed on chemical cores of interest in major markets
    - Granted in US, GB, DE, FR, IT
- Available for licensing and collaborative partnership

CDC7 kinase – target hypothesis

- Cell division cycle 7-related kinase (CDC7) is a nuclear ser/thr kinase that is essential for initiation of DNA replication via MCM2 phosphorylation.
- CDC7 inhibition may selectively induce apoptotic cell death in cancer cells:
  - In normal/untransformed cells, inhibition of CDC7 leads to checkpoint activation and reversibly halts the cell cycle at G1,
  - In cancer cells, inhibition of CDC7 leads to progression through a defective S-phase and results in p53-independent apoptosis.



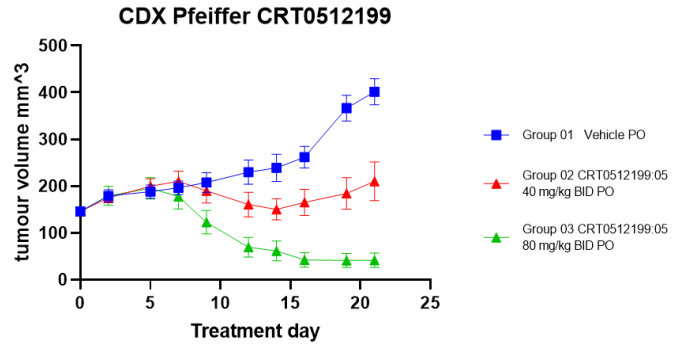
Clinical positioning

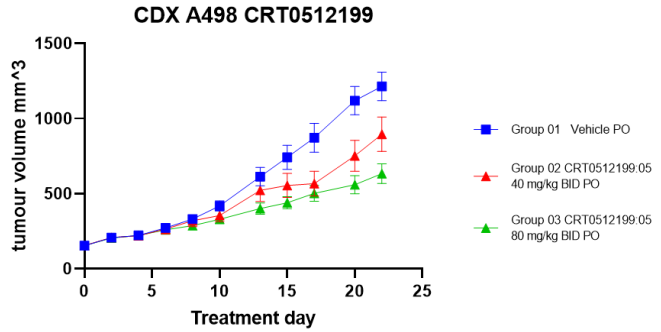
- Over-expression of Cdc7 is broadly correlated with poor clinical outcomes in cancer patients with:
  - Colorectal cancer (Melling N. et al. Diagn Pathol. 2015; 10: 125)
  - Ovarian carcinoma (Kulkarni A. et al. Clin Cancer Res 2009; 15:2417-2425)
  - Breast cancer (Choschzick M. et al. Hum Pathol. 2010; 41(3):358-65)
  - Lung adenocarcinoma (Datta A. et al. EMBO reports,2017; 18:2030-2050)
  - Oral squamous cell carcinoma (Cheng AN. et al. Cancer Lett. 2013; 337(2):218-25)
- In a study of 62 human cancer cell lines, Cdc7 was found to be increased in ~50%, and CDC7 overexpression was found in 90% of mutant p53 cell lines (Bonte *et al.*, 2008, *Neoplasia*).
- CDC7 inhibition as a mechanism of action has been trialled in the clinic in at least 18 indications (source: Informa Pharma Intelligence)
- CRH and Turbine are actively collaborating to position our CDC7 inhibitors (see later slides)

CRH CDC7 inhibitors in cancer models

Lead compounds are CRT'2199 (lead candidate) and CRT'2000 (second candidate) demonstrated potent tumour inhibition (TGI) in in nod/scid mice:

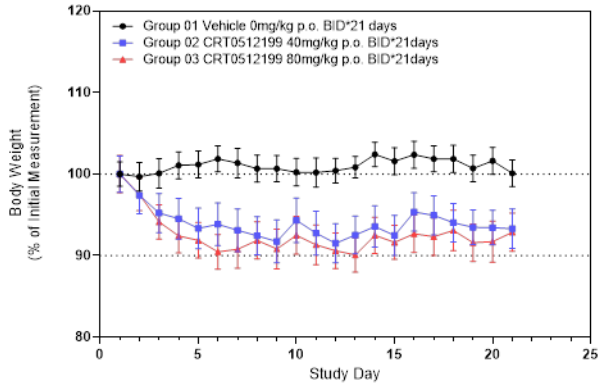
- A498 SC xenograft (renal cancer)
  - 55 TGI after 22 treatment days
- Pfeiffer SC xenograft (DLBCL)
  - 141% TGI after 21 treatment days
- Well tolerated at 40mg/kg and 80mg/kg p.o
  - No treatment related deaths

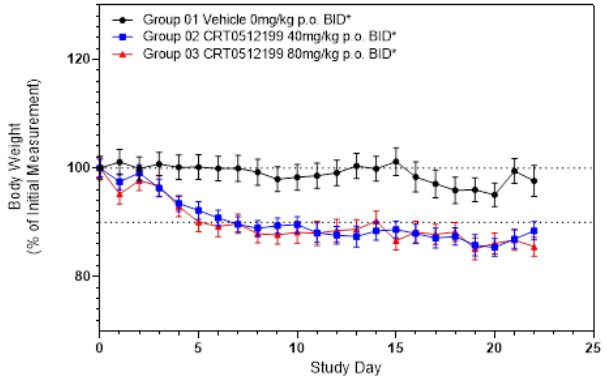




Pfeiffer 21 days	40 mg/kg BID		*p value*	80 mg/kg BID			*p value*
	TGI [1]	TGI [2]		TGI [1]	TGI [2]	PR	
D9	8	29	ns	41	138	16	*<0.05*
D12	30	83	ns	70	191	52	*<0.05*
D14	37	96	ns	74	191	58	*<0.05*
D16	37	83	ns	84	189	71	*<0.05*
D19	50	83	*<0.05*	89	147	71	*<0.05*
D21	48	75	*<0.05*	90	141	71	*<0.05*

A498 23 days	40 mg/kg BID		*p value*	80 mg/kg BID		*p value*
	TGI [1]	TGI [2]		TGI [1]	TGI [2]	
D15	25	32	*ns*	41	52	*<0.05*
D17	35	43	*<0.05*	42	52	*<0.05*
D20	33	38	*<0.05*	50	58	*<0.05*
D22	26	30	*ns*	48	55	*<0.05*





[1]- %TGI =(1-T/C)*100
[2] -%TGI = (1-(Tt/T0 / Ct/C0) / 1-(C0/Ct)) X 100
Percent Regression PR = (T0-Tt)/T0 x 100

Pre-candidate molecule profiles

Pharmacodynamics

- Lead compound CRT'2199 and backup CRT'2000 deliver potent, orally bioavailable CDC7 inhibition

Molecule ID	CRT'2199	CRT'2000
Potency		
Enzyme IC_{50}	4 nM	4 nM
CTG Phenotypic (SW48) EC_{50}	371 nM	1.3 µM
CTG Phenotypic (COLO205) EC_{50}	399 nM	1.1 µM
Biomarker (SW48, pMCM2 ELISA, SAP93) EC_{50}	76 nM	202 nM
ADME		
PPB (% Bound)	86.3 (m), 93.8 (h)	20 (m) 50 (h)
Permeability (Caco-2)	P_{A-B}: $7.3x10^{-6}$ cm/s P_{B-A}: $46.7x10^{-6}$ cm/s ER: 6.4	PA-B: 1.2x10-6 cm/s PB-A: 21.4x10-6 cm/s ER: 18.4
CYP450s	$IC_{50} \geq 25$ µM for all isozymes	$IC_{50} \geq 25$ µM for all isozymes

Pre-candidate molecule profiles

Pharmacokinetics

- Lead compound CRT'2199 and backup CRT'2000 deliver potent CDC7 inhibition with favourable PK and low toxicity and a low predicted human dose.
- Low predicted human dose
- In vitro and non-GLP MTD/DRF in rat
  - Favourable tox and tolerability

Molecule Identity	CRT'7461	CRT'2199	CRT'2000	LY3177833
Pharmacokinetics: SD male rats; 1 mg/kg IV, 3 mg/kg PO				
Cl b mL/min/kg	6	3	20	10
T1/2 h	5.6	5.6	5.7	3.7
Vss L/kg	0.9	0.5	1.7	2.7
%F po	53	38	39	174
PD Biomarker				
In vitro potency SW48, pMCM2 ELISA (SAP93) EC_{50}	135 nM	76 nM	202 nM	1.4 µM
PK/PD in mouse xenografts				
In vivo free $EC_{50,}$ nM / 24 h % Inh Colo205 model SW48 model	115 / nd 39 / nd	2 / 83% 67 / 65%	12 / 74% 70 / 84%	nd / 88% 610 / nd
Estimated Human Pharmacokinetics: single species allometry from rat and free concentration ≥ free EC90				
Cl b mL/min/kg	Not testsd	0.7	4.9	2.4
T1/2 h	Not testsd	7.9	4	12.8
Vss L/kg	Not testsd	0.5	1.7	2.7
%F po	Not testsd	38	39	100
Predicted human efficacious dose				
Based on free MEC *ca. in vivo* Colo205 free EC_{90}	Not testsd	**64 mg QD** **17 mg BID**	**120 mg BID**	nd
Based on free MEC *ca. in vivo* SW48 free EC_{90}	Not tested	557 mg BID	690 mg BID	1470 mg BID

Available data

Further data packages are available under CDA, including:

- SW48 colon xenograft head-to head: Eli Lily LY3177833 vs CRT'461 (early lead)
- Eurofins Panlabs 210 cell line panel (CRT'461 vs LY3177833) apoptosis and GI_{50}
- Oncolines 102 cell line panel (inc competitor compounds head-to-head)
  - Response profiling
- In-house CRISPR KO drug-gene interaction cell line screen
  - Response profiling and sensitisation profiling in colon cancer lines
- 19 cell line rare cancers IC50 and drug combination screen (inc competitor compounds head-to-head)
- Comprehensive rat tox
- Turbine-CRH collaboration results:
  - In silico-derived patient stratification biomarker hypotheses
  - In vitro validation of biomarker hypotheses

Intellectual property

Composition of matter patents filed on two chemical series.

Structural approach has enabled development of entirely novel chemical classes of CDC7 inhibitors.

- Chemical cores of interest are free from encumbrance
- Lead and backup chemical series covered by composition of matter claims

- First patent family WO 2018/055402
  - PCT filing date 22 September 2017 (US priority application no. US62/398,068)
  - Publication date: 29 March 2018;

- Second patent family WO 2018/087527
  - PCTfiling date: 7 November 2016 (GB priority application no. GB1618845.0)
  - Publication date: 17 May 2018

- Both patent families are granted in USA, Great Britain, Germany, Spain, France, Italy.

CRH-Turbine collaboration to identify novel disease hypotheses

CRH is collaborating with Turbine AI to identify novel disease positioning and patient stratification hypotheses for our CDC7i compounds.

Turbine is leveraging its proprietary Simulated Cell™ platform and drug discovery expertise to undertaking a research program to develop disease positioning hypotheses:

1. In silico modelling (Data to include in silico comparative analysis between CRH leads and competitor compounds): **Complete**
2. AI hypothesis generation: **Complete**
3. Wet lab validation (in vitro/ex vivo via CROs): **Complete**

Research activity is governed by a Joint Project Committee and advised by external CDC7 key opinion leaders.

Turbine's analysis has resulted in several disease positioning hypotheses for CRH's lead CDC7 inhibitor. Data available under CDA.

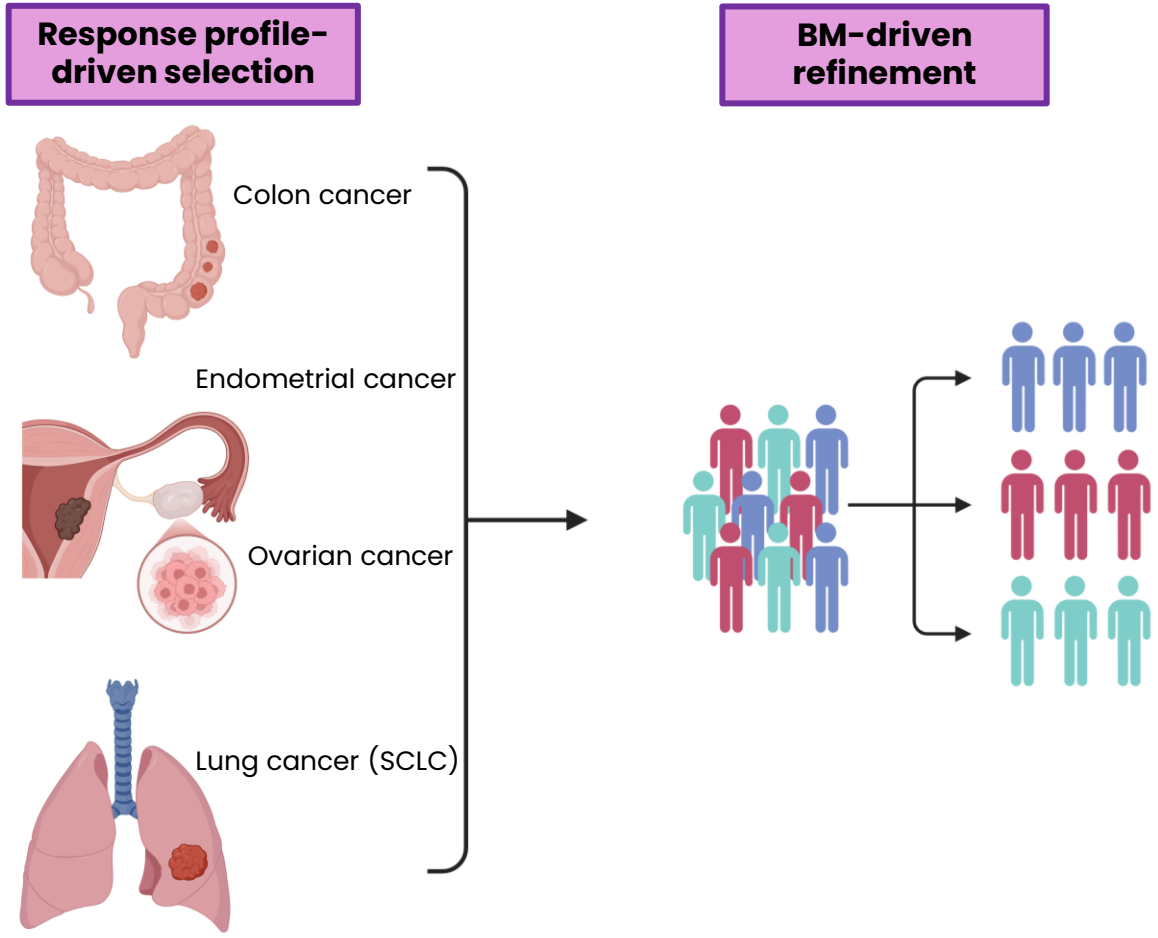
CANCER RESEARCH HORIZONS

turbine.

Turbine's indication recommendations for CRH-Lead1 compound positioning

CRH-Lead1 indication positioning recommendations were based on:

1. **Better response to CRH-Lead1 in indications which are generally sensitive to SoC chemotherapeutics** based on *in vitro* and *ex vivo* (patient-derived organoids) screens.
2. Alterations of the **CRH-Lead1-specific Loss-of-Function (LoF) biomarker (BM)** identified for further patient stratification.
   - BM1: deleted in 8% ovarian cancer*, low expression# in 4% endometrial cancer and 2% colorectal cancer.
   - BM2: low expression# in 25% colorectal cancer, 13% endometrial cancer.
   - BM3: deleted in 4% endometrial cancer*, low expression# in 11% endometrial cancer, 6.5% colorectal cancer.
   - BM4: deleted in 3.9% ovarian cancer*, low expression# in 6.7% colorectal cancer.
3. **Better toxicity profile of CRH-Lead1** compared to other CDC7i compounds.

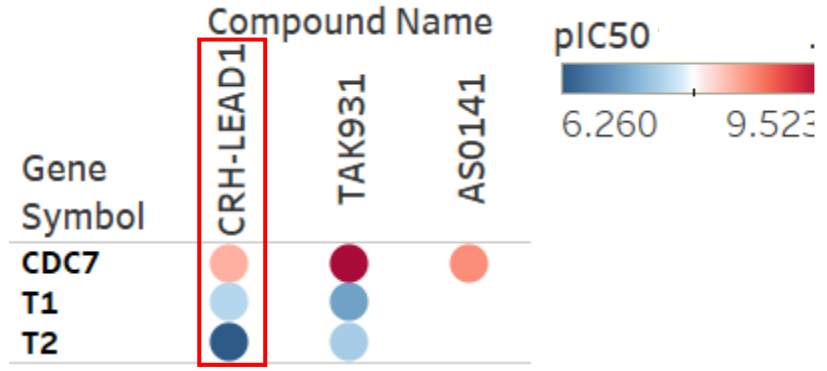


GLDS: General level of drug sensitivity
BM: Biomarkers
SoC: Standard-of-Care

*: curated set of non-redundant TCGA and non-TCGA studies.
#: TCGA studies

Executive summary of the results of the CRH-LEAD1 disease positioning project

- Turbine's analysis demonstrates that **response to CRH-LEAD1** in both cell lines and patient-derived organoids **is driven by general level of drug sensitivity (GLDS), similarly to SoC chemos**.
- By regressing out GLDS effect**, Turbine identified 6 CRH-LEAD1-specific Loss-of-Function (LoF) biomarkers (BM),** further refining the indication selection and patients' population.
- The off-target profile of CRH-LEAD1 **contributes to its enhanced efficacy and reduced toxicity** compared to other CDC7i compounds.
- **CRH-LEAD1 exerts stronger inhibition of off-target 1 (T1)** compared to other CDC7i leading to enhanced efficiency.
    - Dual **inhibition of CDC7 and T1 has a synergetic killing effect** on cancer cells (Patent 1, Patent 2)
- **CRH-LEAD1 has a weaker inhibition effect on off-target 2 (T2)** compared to other CDC7i, contributing to better toxicity profile.
    - Inhibition of T2 leads to hematological toxicity of bone marrow (Paper 1).
    - Degradation of T2 causes severe gastrointestinal disorders due to the high expression of T2 in the gastrointestinal epithelium (Paper 2).
    - Several trials with T2 inhibitors were terminated due to drug-related toxicities (Paper 3, Paper 4, Paper 5, Paper 6, Clinical trial 1, Clinical trial 2).



Target profile overview of different CDC7i compounds

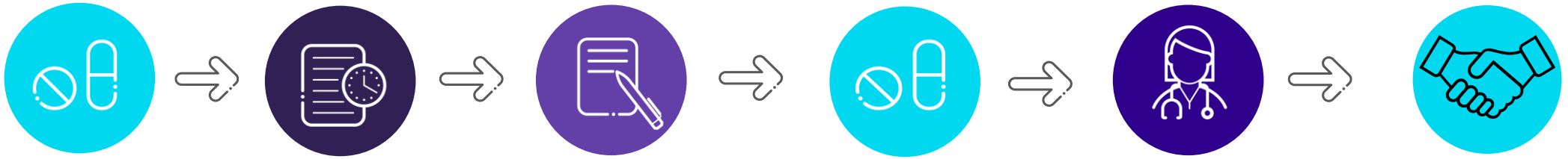
- **CRH-LEAD1**: Eurofins assay
- AS0141: PMID: 34607435
- TAK931: PMID: 31131319

ROUTE TO PRE-CANDIDATE MOLECULES

In-house drug discovery program at CRH
Novel lineage of small molecules developed targeting CDC7
Cell line analyses
PD Biomarkers explored

Two Composition of Matter patents filed in 2017
Broad coverage of chemical cores of interest
Candidate lineages well covered by claims

2022 Collaboration with Turbine to explore disease positioning
Turbine is leveraging AI and wet-lab experiments in collaboration with CRH to identify disease positions.
ETA for pivotal data is mid-April 2024



Early chemistry

Lead optimisation

CoM patents filed

Further target patient identification

Turbine AI collaboration

Seeking Partnership

CANCER RESEARCH UK | THERAPEUTIC DISCOVERY LABORATORIES

Lead optimisation and cancer model studies
CRT'461 identified as early lead - **CRT'2199** later chosen with **CRT'2000** as backup
In vivo and cell line panel studies to identify target indications

In-house disease positioning studies
CRISPR cell line screens at The AZ-CRUK Functional Genomics Centre

Seeking a partner with funding and expertise to provide support for in vivo validation of novel disease hypotheses and drive the therapy into the clinic

12-18 months from IND with partner on board

Further data available under CDA

- Potent pre-candidate chemistry – back up compounds available
- Sub-10nM enzyme IC50
- Favourable PK and toxicity
- Patents filed on CoM of chemical cores of interest
  - granted in US, GB, DE, FR, IT
- Novel disease positioning hypotheses being validated in collaboration with Turbine AI
- Further data is available under CDA
- Available for licensing and collaborative partnerships



CANCER RESEARCH HORIZONS

Thank you

For further information please contact:

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