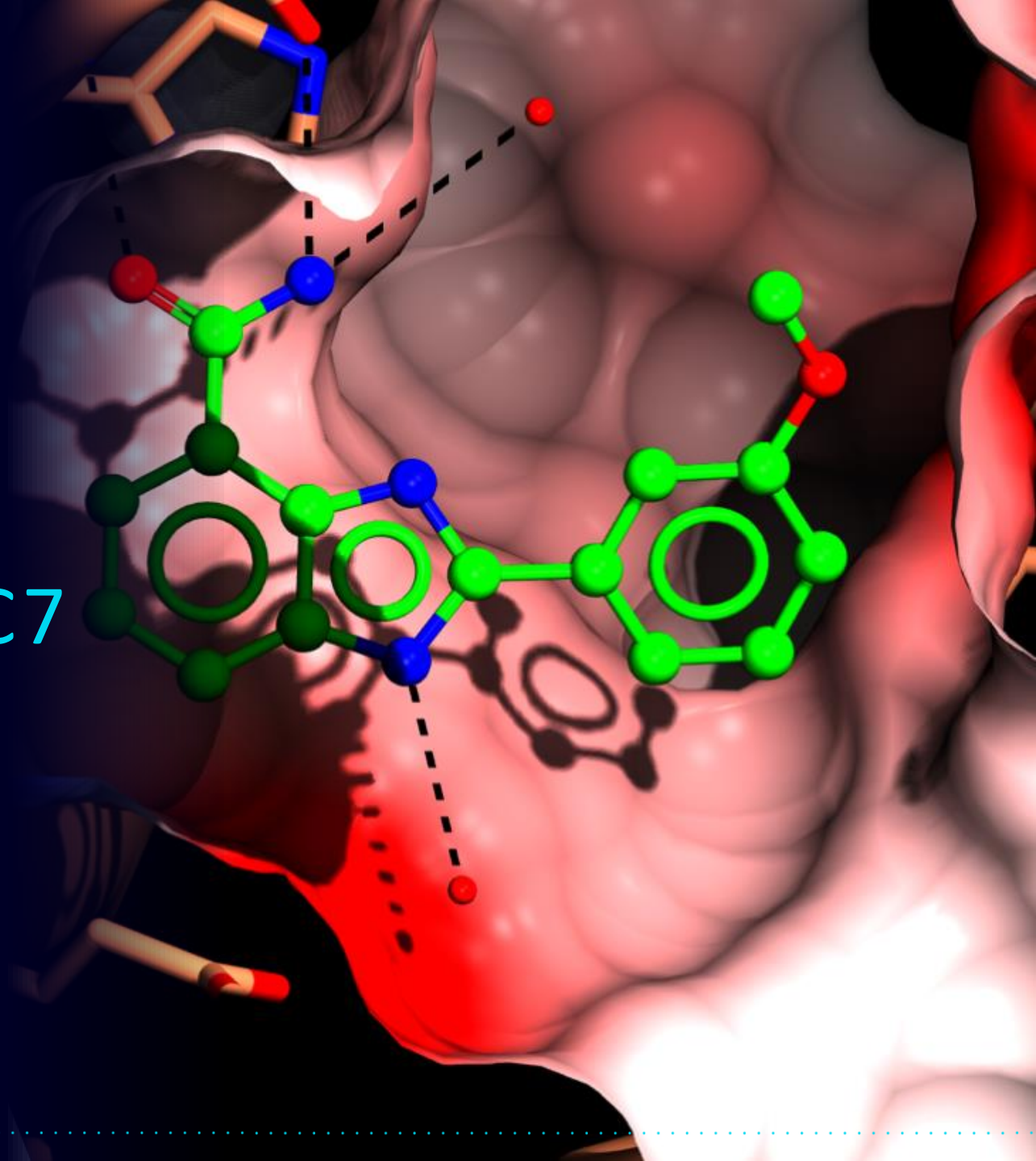
CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

# LICENSING OPPORTUNITY:

# SMALL MOLECULE CDC7 KINASE INHIBITORS



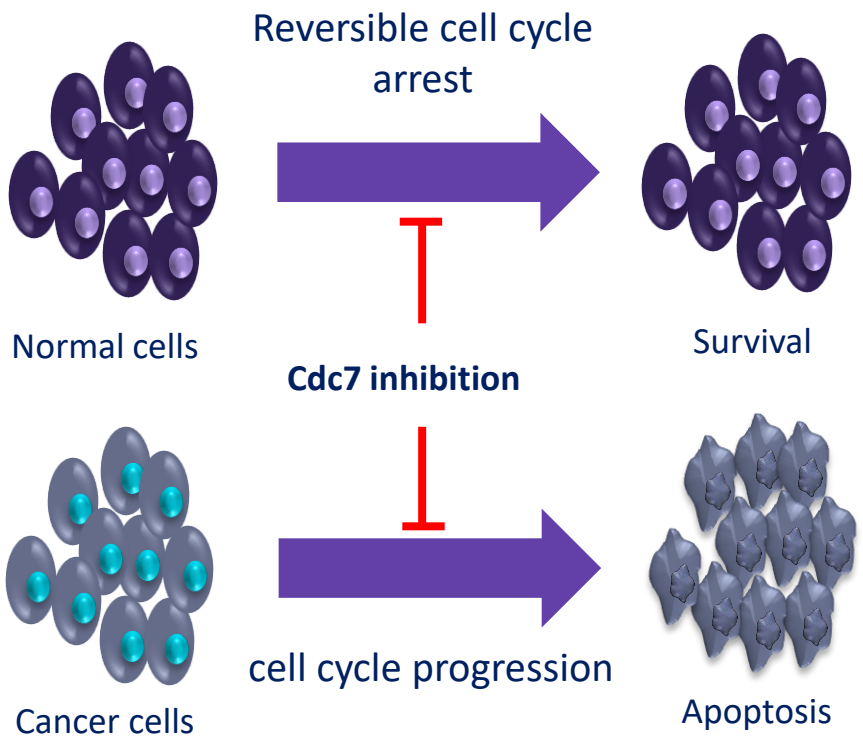
July 2022

# 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
- 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 rationale

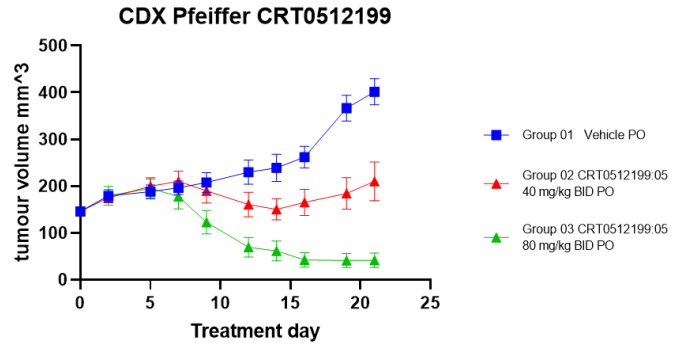
- Over-expression of Cdc7 is broadly correlated with poor clinical outcomes in cancer patients with:
  - colorectal cancer (Melling N. et al. Diagn Pathol. 2015; 10: 125)
  - ovarian carcinoma (Kulkarni A. et al. Clin Cancer Res 2009; 15:2417-2425)
  - breast cancer (Choschzick M. et al. Hum Pathol. 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)

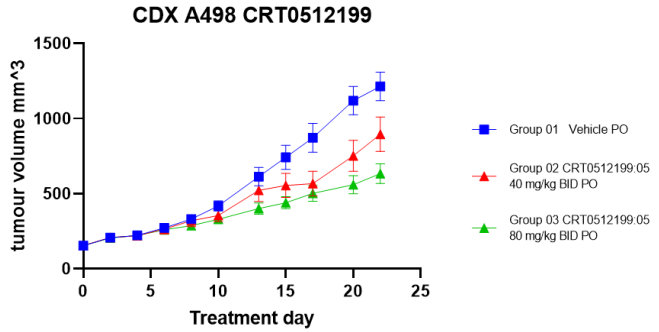
- In a study of 62 human cancer cell lines, Cdc7 was found to be increased in ~50%, and CDC7 overexpression was found in 90% of mutant p53 cell lines (Bonte *et al*., 2008, *Neoplasia*).
- CDC7 inhibition as a mechanism of action has been trialed in the clinic in at least 18 indications as of 2021 (source: Informa Pharma Intelligence)

# 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:

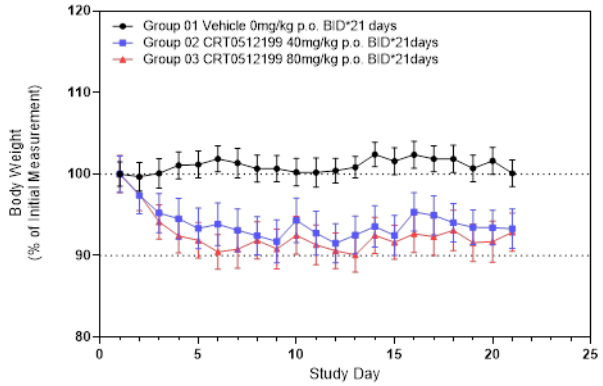
- A498 SC xenograft (renal cancer)
  - 55 TGI after 22 treatment days
- Pfeiffer SC xenograft (DLBCL)
  - 141% TGI after 21 treatment days
- Well tolerated at 40mg/kg and 80mg/kg p.o
  - No treatment related deaths

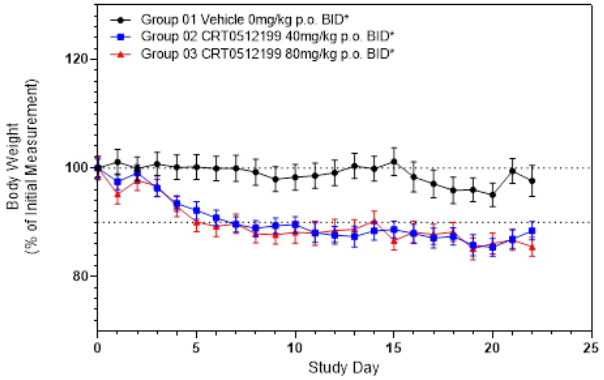



| Pfeiffer 21 days | 40 mg/kg BID | | p value | 80 mg/kg BID | | | p value |
|---|---|---|---|---|---|---|---|
| | TGI [1] | TGI [2] | | TGI [1] | TGI [2] | PR | |
| D9 | 8 | 29 | ns | 41 | 138 | 16 | <0.05 |
| D12 | 30 | 83 | ns | 70 | 191 | 52 | <0.05 |
| D14 | 37 | 96 | ns | 74 | 191 | 58 | <0.05 |
| 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<br>$P_{B-A}$: $46.7x10^{-6}$ cm/s<br>ER: 6.4 | PA-B: 1.2x10-6 cm/s<br>PB-A: 21.4x10-6 cm/s<br>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<br>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<br>Colo205 model<br>SW48 model | 115 / nd<br>39 / nd | 2 / 83%<br>67 / 65% | 12 / 74%<br>70 / 84% | nd / 88%<br>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*<br>Colo205 free $EC_{90}$ | Not testsd | **64 mg QD**<br>**17 mg BID** | **120 mg BID** | nd |
| Based on free MEC *ca. in vivo* SW48<br>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

# Competitor landscape

- 11 CDC7 inhibitor compounds have entered the clinic; none has progressed to phase III
  - First Phase I entry: 2009; most recent Phase I entry: 2021 – more planned
- Trailed indications vary within oncology – there is a lack of clear disease positioning for CDC7 as a target

| Trial Phase | Trial Status | Sponsor | Oncology Indication | Trial ID | Last Modified |
|---|---|---|---|---|---|
| I/II | Terminated | Sierra Oncology {ProNAi Therapeutics} | Colorectal | 282965 | 2021 |
| I | Terminated | Nerviano Medical Sciences | Unspecified Solid Tumor | 124689 | 2012 |
| I | Terminated | Nerviano Medical Sciences | Unspecified Solid Tumor | 118903 | 2012 |
| I/II | Terminated | Bristol-Myers Squibb<br>Exelixis | Unspecified Solid Tumor | 107633 | 2018 |
| I/II | Terminated | Bristol-Myers Squibb<br>Exelixis | Leukemia, Acute Lymphocytic; Leukemia, Acute Myelogenous; Leukemia, Chronic Myelogenous; Myelodysplastic Syndrome | 102286 | 2012 |
| II | Planned | Zai Lab | Unspecified Cancer | 417813 | 2022 |
| I | Planned | Lin BioScience | Leukemia, Acute Lymphocytic; Leukemia, Acute Myelogenous; Leukemia, Chronic Myelogenous; Myelodysplastic Syndrome | 297560 | 2021 |
| I | Open | Sino Biopharm/Chia Tai Tianqing Pharma | Unspecified Solid Tumor | 408880 | 2021 |
| I | Open | Zai Lab | Unspecified Cancer | 395004 | 2021 |
| I | Open | Carna Biosciences | Unspecified Solid Tumor | 378012 | 2021 |
| I | Open | Cancer Research UK | Bladder; Breast; Colorectal; Esophageal; Head/Neck; Lung, Non-Small Cell; Ovarian; Pancreas; Renal | 298491 | 2021 |
| I | Completed | Takeda/Takeda Oncology | Colorectal; Endometrial; Esophageal; Lung, Non-Small Cell; Ovarian; Unspecified Solid Tumor | 334678 | 2021 |
| II | Completed | Takeda/Takeda Oncology | Colorectal; Esophageal; Lung, Non-Small Cell; Pancreas; Unspecified Solid Tumor | 307792 | 2022 |
| I | Completed | Takeda/Takeda Oncology | Bile Duct (Cholangiocarcinoma); Bladder; Cervical; Esophageal; Gallbladder; Liver; Pancreas | 274253 | 2021 |
| I | Completed | Nerviano Medical Sciences | Unspecified Cancer | 104319 | 2014 |

Source: Informa Pharma Intelligence

# Intellectual Property

**Composition of matter patents filed on two chemical series**

**Structural approach 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.

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**Summary**

- Potent pre-candidate chemistry – back up compounds available
- Sub-10nM enzyme $IC_{50}$
- Favourable PK and toxicity
- Patents filed on CoM of chemical cores of interest
    - granted in US, GB, DE, FR, IT
- Available for licensing and collaborative partnerships
- Further data is available

# THANK YOU

For further information, please contact:
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