

CRT Licensing Opportunity



Oral Inhibitors of Checkpoint Kinase 1 (Chk1)

- *In vivo* potentiation of DNA damaging agent induced tumour growth inhibition in solid tumours
- Single agent efficacy in *in vivo* models of AML and neuroblastoma
- *In vivo* efficacy in combination with radiotherapy in solid tumours is under investigation
- Pre-clinical candidate nominated

SMALL MOLECULES | Selected Pre-clinical Candidate

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In vivo efficacy via oral administration

Orally administered compounds from the Lead Series have been assessed for efficacy in combination with the genotoxic chemotherapies gemcitabine and irinotecan in *in vivo* models. Strong potentiation of the efficacy of these genotoxic agents is observed with once-daily dosing of Chk1 inhibitors, as shown with the preclinical candidate combined with gemcitabine in a colon cancer xenograft study (Figure 1).

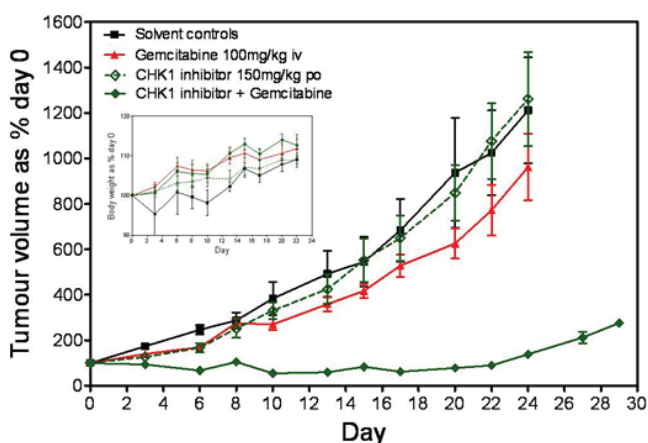


Figure 1: Oral Chk1 pre-clinical candidate potentiates the efficacy of gemcitabine in HT29 colon cancer xenografts (Inset: total body weights as % of day 0).

Sustained (24hr) inhibition of gemcitabine-induced Chk1 signalling is observed following single oral doses of the

pre-clinical candidate and other members of the Lead Series. Potentiation of irinotecan and gemcitabine by earlier Lead Series compounds dosed ip in colon cancer xenografts has also been demonstrated [1].

Additionally, single agent efficacy is observed with Lead Series compounds and once-daily oral dosing in *in vivo* models of AML and neuroblastoma. The efficacy and pharmacodynamics of oral Lead Series compounds are being further investigated in combination with radiotherapy in solid tumour models, and with chemotherapies in AML and other solid tumours.

Potent and Selective inhibitors

Novel competitive inhibitors with pM to nM *in vitro* activity against Chk1 have been developed starting from a combined crystallographic bioassay template screen.

	Oral Chk1 Inhibitors
Chk1 IC ₅₀ (nM)	1 - 30
Selectivity vs Chk2	200x - >500x
Checkpoint abrogation (µM)	0.03 - 0.2
Potentiation of cytotoxicity <i>in vitro</i>	3x - 25x
MW	340 - 410
ALogP	0.5 - 2.0
TPSA	100 - 115

The Lead Series is highly selective over the related checkpoint kinase Chk2 (200- to >500-fold), and against a wider panel of enzymes chosen to represent a spectrum of the kinome. Compounds from the Lead Series abrogate the G2/M checkpoint in cells at sub-micromolar concentrations, and potentiate

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irinotecan and gemcitabine cytotoxicity by 3 to 30 fold in colon tumour cell lines. The Lead Series has good *in vitro* ADME (including low hERG inhibition), good *in vivo* pharmacokinetic properties, and has demonstrated *in vivo* pharmacodynamic modulation of signalling through Chk1. A subset of the Lead Series demonstrates oral bioavailability and sustained tumour levels on oral dosing. Oral bioavailability of between 61% and 100% has been demonstrated in the most advanced compounds.

Therapeutic Rationale

Chk1 inhibitors are anticipated to provide a therapeutic strategy for enhancing the effectiveness of the genotoxic agents currently used in cancer treatment [2]. The most immediate target indications for Chk1 inhibitors in combination therapies are likely to be solid tumours with a high frequency of p53 defects and where genotoxic therapy is currently a preferred clinical option (colon, ovarian, pancreatic and lung in particular).

Chk1 is a serine/threonine kinase that is phosphorylated and activated in response to DNA damage, initiating a signalling cascade culminating in cell cycle arrest in the S and G2/M phases. Inhibition of Chk1 has been shown to abrogate cell cycle arrest leading to enhanced tumour cell death following DNA damage by a range of chemotherapeutics. Cells lacking intact G1 checkpoints through inactivation of p53 are particularly dependent on S and G2/M checkpoints and are therefore expected to be more sensitive to chemotherapeutic treatment in the presence of a Chk1 inhibitor, whereas normal cells with functional G1 checkpoints would be predicted to undergo less cell death [3].

Recent preclinical data has shown the potential for selective Chk1 inhibition alone as a therapy in specific tumour types with activated Chk1 signalling due to constitutive DNA damage or replication stress [4,5].

Biomarkers of Chk1 Inhibition

Lead compounds inhibit cytotoxic drug induced Chk1 autophosphorylation at Ser296 and block phosphorylation of CDK1 at Tyr15 *in vitro* and *in vivo* consistent with Chk1 inhibition and checkpoint abrogation. Sustained inhibition of Chk1 signalling may be important for optimal potentiation of genotoxic therapies. Lead series compounds have demonstrated inhibition of Chk1 autophosphorylation for up to 24h in xenografts following a single oral dose. Compounds increase irinotecan and gemcitabine induced H2AX phosphorylation and PARP cleavage consistent with elevated DNA damage and tumour cell death.

Crystallography

Multiple low MW hits were identified from a combined crystallographic-bioassay template screen [6], followed by iterative ligand-protein co-crystallography on multiple series to define SAR and guide improvements to potency. More than 90 co-crystal structures have been determined.

Commercial Opportunity

CRT is offering prospective commercial partners global rights to the Chk1 programme on an exclusive basis for all fields.

The preclinical pharmacology and therapeutic activity of a representative systemically administered compound from the Lead Series has recently been published [1]. Details of unpublished results relating to more efficacious and orally bioavailable compounds are available under CDA.

Originating Institute

The programme originates from The Institute of Cancer Research (ICR) Cancer Therapeutics Unit (CTU) and is a collaborative discovery programme between the ICR, Sareum Ltd and CRT. CTU has an excellent track record of collaboration, licensing and drug discovery success.



Intellectual Property

There is a strong patent portfolio protecting the Lead Series and surrounding chemical space with both composition of matter and medical use claims to claimed compounds (WO2009004329; WO2009044162; WO2009103966).

References

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