

CRT Licensing Opportunity



Chk2 Inhibitor Programme

- Exciting cancer target for therapeutic intervention
- Patented potent lead series with high selectivity over Chk1
- Chk2 co-crystal solved with multiple compounds
- Opportunity to optimise compounds for preclinical and clinical development

SMALL MOLECULES | Lead Optimisation

October 2009

Therapeutic Rationale

The cell cycle checkpoint kinase Chk2 is a central multi-functional player in the induction of cell cycle arrest, DNA repair and apoptosis. The current understanding of Chk2 function in tumour cells, in both a biological and genetic context, suggests that targeted modulation of Chk2 could prove to be an effective anti-cancer strategy (2,5).

Intriguingly, data on Chk2 suggest inhibition of the kinase may be able to both sensitise tumour cells to certain damaging agents, whilst also protecting normal cells from damage, thus widening the therapeutic window.

Potent & Selective Chk2 Inhibitors with Cellular Activity

A compound series with low nanomolar activity against Chk2 has been developed following an IMAP bead-based screen of CRT's fully synthetic compound library. An extensive medicinal chemistry effort has been carried out to optimise potency against Chk2, whilst retaining selectivity over Chk1 and other kinases.

A number of the lead compounds show sub 10nM potency against Chk2 *in vitro*, and are able to inhibit the activation of Chk2 induced by DNA damaging agents in cultured tumour cells (Figure 1). Genetic and pharmacological abrogation of Chk2 activity has been reported to act synergistically with current cancer therapies to cause apoptosis (1,3).

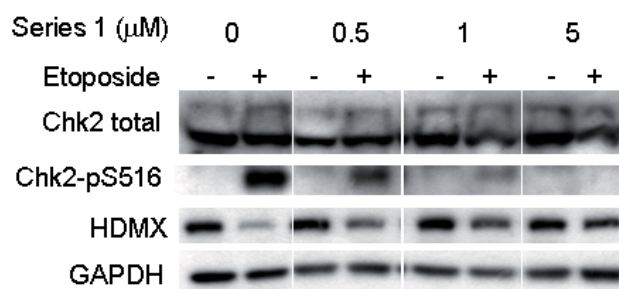


Figure 1. Inhibition of etoposide-induced Chk2 autophosphorylation (S516) and HDMX loss by Chk2 inhibitors in MCF7 breast cancer cells.

Crystallography

Medicinal chemistry efforts have been significantly accelerated with the aid of structural biology information. Methods to obtain the crystal structure of inhibitors bound to the ATP-binding pocket of the Chk2 catalytic domain have been developed, and the co-crystal structures of number of compounds from the series have been solved (Figure 2) (4).

In-vitro ADMET Properties

The lead compounds demonstrate drug-like physiochemical properties with high membrane permeability and metabolic stability (Table 1)

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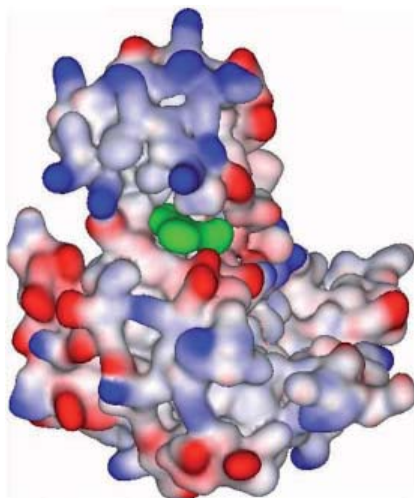


Figure 2 - X-ray of Series 1 bound to Chk2

Chk2 IC ₅₀ (nM)	<5 - 20
Selectivity vs Chk1	30x - 600x
MW	350 - 450
CLogP	3.0 - 4.0
Chk2 cellular inhibition (μM)	<1 - 10
Metabolic stability (mouse liver microsomes)	70 - 100%
Membrane permeability (PAMPA)	moderate - high
HERG	>10 μM

TABLE 1 - Chk2 inhibitors

In-vivo studies

Preliminary PK/PD studies have been carried out and demonstrate that compounds from the lead series have good oral availability and are well tolerated in mice. Furthermore, the compounds demonstrate significant inhibition of Chk2 activity induced by a DNA damaging agent in a tumour xenograft model.

Intellectual Property

CRT has filed US provisional and PCT patent applications to protect the lead compound series.

Originating Institute

This programme is under development at the Institute of Cancer Research under the direction of Professor Paul Workman, within the Cancer Research UK Centre for Cancer Therapeutics with crystallographic input from Professor Laurence Pearl.

Commercial Opportunity

CRT is now seeking a commercial partner interested in pursuing a co-development or direct licensing arrangement.

Target Validation

Pharmacological inhibition of Chk2 has been shown to have a radioprotective effect on normal human cells, and targeted disruption of Chk2 also allows the increased survival of mice exposed to radiation (through resistance to apoptosis). Importantly these animals do not show an increase in spontaneous tumour development thereby confirming the viability of this therapeutic strategy. Inhibition of Chk2 may also allow tumour cells with limited checkpoint activity to remain in the proliferative cycle, sensitising them to genotoxic DNA-damaging agents.

Chk2 has also been shown to be a negative regulator of mitotic catastrophe, and recent evidence suggests that inhibition of Chk2 may cause cancer cells to override mitotic checkpoints, leading to cell death. Chk2 has been shown to protect cancer cells from apoptosis under hypoxic growth conditions, whilst Chk2^{-/-} cancer cells exhibit an attenuated G2 arrest, increased apoptosis, reduced clonogenic survival, and deficient phosphorylation of downstream targets. In summary, a Chk2 inhibitor combined with a genotoxic cancer treatment may increase tumour cell efficacy by both protecting normal cells from apoptosis, and allowing tumour cells to be more sensitive to genotoxic agents and potentially tumour hypoxia.

References

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