

Chk2 INHIBITOR PROGRAMME

- Chk2 is a cancer target involved in cell cycle arrest, DNA repair and apoptosis
- Patented lead series with good selectivity profile versus Chk1 and other kinases
- Compounds show *in vivo* pharmacodynamic biomarker modulation

THERAPEUTIC RATIONALE

The cell cycle checkpoint kinase Chk2 is a central multifunctional 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 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 (2,6). It has been demonstrated that disruption of the homologous recombination (HR) DNA repair pathway by Chk2 siRNA induces cellular sensitivity to the inhibition of poly (ADP-ribose) polymerase (PARP) activity (3, 5). In addition, transgenic mouse studies have demonstrated that Chk2 abrogation gives rise to protection from radiation, raising the possibility that Chk2 inhibitors may be used as radioprotection agents.

POTENT & SELECTIVE CHK2 INHIBITORS

A compound series with low nanomolar activity against Chk2 has been developed following an IMAP bead-based screen of Cancer Research UK'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* (4).

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 (4,5) (Figure 1).

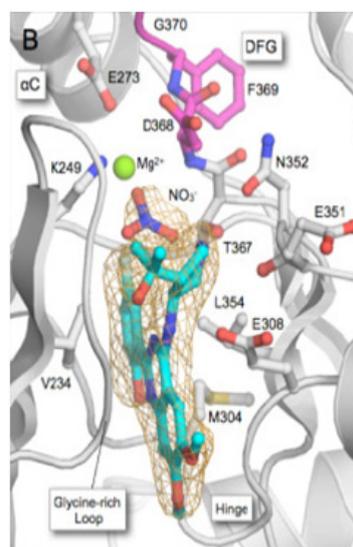


Figure 1. X-Ray crystal structure of CCT241533 bound to the kinase domain of Chk2 (2.3 angstrom).

Genetic and pharmacological abrogation of Chk2 activity has been reported to act synergistically with current cancer therapies to cause apoptosis (1,3). However, we have determined in a small panel of cell lines that Chk2 inhibitors do not synergise with bleomycin, etoposide, gemcitabine or SN38. Studies are ongoing to examine synergy with these and other agents in a wider panel of cell lines.

However, the Chk2 inhibitors were shown to potentiate the cytotoxicity of two structurally distinct PARP inhibitors *in vitro* (7) (Figure 2).

[Read more overleaf](#)

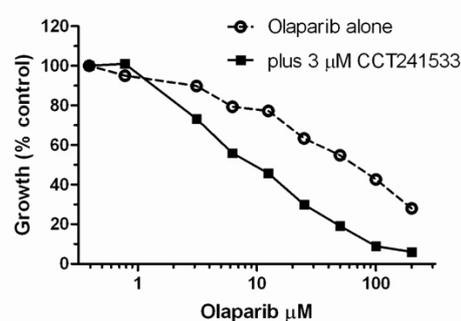
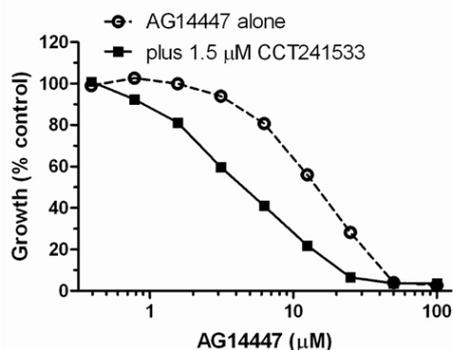


Figure 2. Chk2 inhibitor CCT241533 sensitises to PARP inhibitors. Cytotoxicity was determined by SRB assay. Potentiation index = 1.61 – 3.42 (ratio of GI_{50} :Combination GI_{50})

IN VITRO ADMET PROPERTIES

The lead compounds demonstrate drug-like physicochemical properties, as summarised in Table 1. Some members of the series have oral bioavailability from 38 – 54%. The current lead compound CCT241533 has a 3nM Chk2 biochemical IC_{50} , >80-fold selectivity over Chk1, and at 1µM shows inhibition of only 4 of 85 other kinases tested.

Chk2 IC_{50} (nM)	3 - 60 (ATP comp)
Selectivity vs Chk1	10x - 650x
MW	324 - 487
CLogP	2.9 - 4.1
TPSA	70 - 120 Å ²
Cell activity (µM)	<1 - 10
Mouse liver microsome turnover	0 -45% @ 30 mins
Membrane permeability (PAMPA)	High - Low
CaCo2 efflux ratio	0.1 - 1.6
hERG inhibition	9-90% @ 10 µM
Cyp450 inhibition IC_{50}	>10 µM

Table 1. Properties of Chk2 lead series inhibitors.

IN VIVO STUDIES

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

INTELLECTUAL PROPERTY

Lead series chemistry is protected by a patent application (WO2009/053694) filed on 24th October 2007.

ORIGINATING INSTITUTE

This programme is under development at the Institute of Cancer Research within the Cancer Research UK Cancer Therapeutics Unit.

COMMERCIAL OPPORTUNITY

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

REFERENCES

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