

CRT Licensing Opportunity



Novel Inhibitors of Aurora Kinase

- Pan-Aurora Lead Series with low nM biochemical and <math><300\text{nM}</math> cell-based IC_{50}
- Single agent growth inhibition in two human tumour xenografts (colon and ovarian, *p.o.*)
- No *in vivo* toxicity at 200mg/kg (*p.o.*)
- Follow-on Aurora A selective programme benefiting from crystallographic support

SMALL MOLECULES | Lead Optimisation

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Background and Therapeutic Rationale

The Aurora protein kinases, a family of serine/threonine kinases, regulate many processes during cellular division and are involved in the control of the centrosome and nuclear cycles (1). Aurora kinases A and B are each critical for the proper progression of cells through mitosis. Both enzymes are deregulated in many cancers, suggesting that a wide range of tumours could respond therapeutically to inhibitors. Overexpression of either Aurora A or B kinase has been shown to induce cancer-related phenotypes in cell lines and isoform-specific small molecule inhibitors have shown efficacy in multiple tumour cell lines as well as various animal models of cancer.

The rationale behind developing compounds inhibiting Aurora kinases A and B simultaneously, as most compounds currently in development do, is to more efficiently target highly proliferating cells, induce cytokinesis failure and ultimately cell death.

Potent and Selective Pan-Aurora Inhibitors with Efficacy *In Vivo*

Novel compounds with low nM activity against both Aurora kinases have been identified; the Lead Series has been protected by patent filings. Compounds from the Lead Series have been shown to decrease tumour growth significantly in colon and ovarian human xenografts, without noticeable change in body weight (Figure 1).

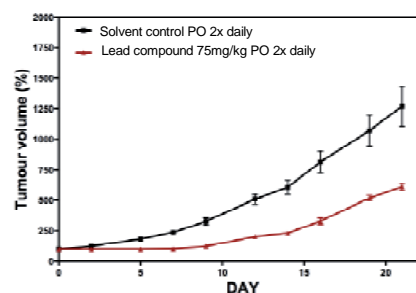


Figure 1: Inhibition of growth of SW620 human colon cancer xenografts in athymic mice. Twice daily oral treatment with lead compound 1 (control: 0.1% DMSO vehicle) with $n = 8$ per group. (% Tumour/Control = 54).

Mechanism of action and *in vivo* studies featuring an early Lead Series compound have been published by the team (2). Compounds in the Lead Series are ATP-competitive and have good *in vitro* ADME properties; lead optimisation studies are focused on optimising PK properties whilst maintaining potency and cell based activity.

Biomarkers of Aurora Kinase Inhibition

Treatment of HCT116 and HeLa cells with compounds from the Lead Series induced the formation of abnormal mitotic spindles and various degrees of chromosome alignment defects, consistent with the phenotype induced by siRNA and other Aurora kinase inhibitors. In addition, p21 induction, hypophosphorylation of Rb, reduction in TK1 protein and histone H3 phosphorylation are observed. Compounds from

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the Lead Series exhibit *in vivo* PD modulation of signalling downstream of Aurora kinases consistent with a mechanism of action via Aurora inhibition (Figure 2). Lead compounds also induce a reduction in tumour [18F]FLT retention detectable by non-invasive PET imaging (2).

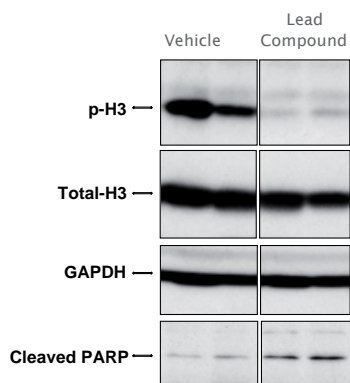


Figure 2: Inhibition of phosphorylation of histone H3 in SW620 human colon cancer xenografts treated with lead compound 1 (4 cycles bid, 75mg/kg).

The ability to identify a signature predictive of response in a patient population would prove very valuable to successful development of Aurora Kinase inhibitors. To this end, initial studies using microarray data and mutational status focusing on a panel of colon cancer cell lines have given promising results.

Summary of Lead Series Data

		Lead Series
Biochemical IC ₅₀ (nM)	Aurora A	6-30
	Aurora B	30-150
	Aurora C	85
Cellular biomarker activity: lead compound 2 IC ₅₀ & IC ₉₀	Inhibition of Aurora-A T288 phosphorylation	IC ₅₀ = 0.06 µM IC ₉₀ = 0.48 µM
	inhibition of Aurora-B H3 phosphorylation	IC ₅₀ = 0.3 µM IC ₉₀ = 1.2 µM
Selectivity (Gini score*)		0.537

Table 1: Aurora Kinase Inhibitors; (*Staurosporine Gini score: 0.150 (non selective inhibitor); PD184352 Gini score: 0.905 (very selective inhibitor of MAPK1) (3).

Aurora A Selective Inhibitors

Despite the historical focus on pan-Aurora kinase inhibitors, it remains an open question whether better clinical outcomes might be achieved by inhibiting Aurora kinase A or B selectively. In addition to the pan-Aurora kinase programme described above, a programme focusing on Aurora A selective inhibitors is on-going. These inhibitors are expected to provide access to anti-tumour efficacy in specific tumour types

as well as reduce bone marrow toxicity compared to general anti-mitotic drugs. Methods have been developed to obtain co-crystals of Aurora A with putative Aurora A selective inhibitors, and it is anticipated that the knowledge gained through the pan-Aurora programme as well as the crystallography capabilities will enable this programme to progress rapidly.

Originating Institute

This ongoing programme, led by Dr Spiros Linardopoulos, originates from the Cancer Research UK Centre for Cancer Therapeutics headed by Professor Paul Workman and the Breakthrough Breast Cancer Research Centre headed by Professor Alan Ashworth at The Institute of Cancer Research. The Institute of Cancer Research, in partnership with The Royal Marsden, is at the forefront of cancer research and has a unique drug discovery and development facility on site. Many drugs discovered or developed at The Institute of Cancer Research have successfully entered the clinic and some have entered the market.



Commercial Opportunity

CRT seeks a commercial partner for collaborative research and/or exclusive licensing for the further development of these novel Aurora kinase inhibitors, which are protected by patent application number WO2007/072017.

Cancer Research Technology

CRT is an oncology focused development and commercialisation company. Novel Inhibitors of Aurora Kinase is one of a robust pipeline of projects currently available from CRT for licensing and co-development.

References

1. Vader G. and Lens S. M., Biochim. Biophys. Acta. 2008 1786(1):60-72.
2. Chan F., *et al.*, Mol. Cancer Ther. 2007 6:3147-3157.
3. Graczyk P.P., J. Med. Chem. 2007 50:5773-5779.

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