

# CRT Licensing Opportunity



## Novel Dual Inhibitors of FLT3 and Aurora Kinases

- Preclinical development candidate nominated
- Lead Series with low nM biochemical activity (FLT3, Aur A & B) and <math><500\text{nM}</math> cell-based  $\text{EC}_{50}$  (cell viability)
- Orally bioavailable single agent dose dependent growth inhibition in leukaemic and solid tumour xenograft models; mutation-driven resistance to selective FLT3 inhibition overcome in AML *in vivo* model
- Follow-on FLT3 / Aurora A selective programme with x-ray co-crystal structures elucidating binding mode of series
- Capacity and expertise to run first-in-man and paediatric clinical trials with PK/PD support

SMALL MOLECULES | *In Vivo* Proof-of-Principle

August 2011

### Background and Rationale

- Internal tandem duplication of the *fms*-like tyrosine kinase 3 gene (FLT3-ITD) results in constitutive FLT3 kinase activation. FLT3-ITD occurs in 20-35% of adults and 15% of children with AML (AML FLT3-ITD) and confers a poor prognosis in both age groups.
- The clinical impact of FLT3 inhibitors has thus far been limited by transient responses when used as single agents and the emergence of secondary acquired resistance following treatment.
- Aurora kinases A and B play a key role in several stages of mitosis.
- Over-expression of these serine-threonine kinases has been demonstrated in malignancies including leukaemia, colon, breast and ovarian cancers suggesting that a wide range of tumours could respond therapeutically to inhibitors.
- Aurora kinase inhibitors are emerging as promising agents in the treatment of acute myeloid leukaemia (AML) and Philadelphia chromosome-positive leukaemias.
- The strategy of dual FLT3 / Aurora inhibition is predicted to have improved single-agent efficacy and reduced susceptibility to resistance in FLT3-mutated AML (1).

### Potent and Selective Dual FLT3 / Aurora Inhibitors with *In Vivo* Efficacy

Novel compounds with low nM activity against both FLT3 and Aurora (A and B) kinases have been identified; the Lead Series has been protected by patent filings. Compounds from the Lead Series have been shown to be efficacious in both leukaemic (Figure 1) and solid tumours models.

These compounds inhibit the growth of:

- MOLM-13 and MV4-11 human AML xenografts in a dose dependent manner with robust biomarker modulation (Figure 2) as well as overcoming resistance to selective FLT3 inhibition (MOLM-13-MLN518-resistant human tumour xenografts);
- other solid tumours: human colon carcinoma HCT116 and transgenic and primary transplant MYCN-driven neuroblastomas.

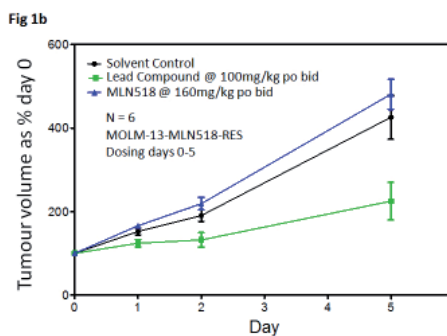
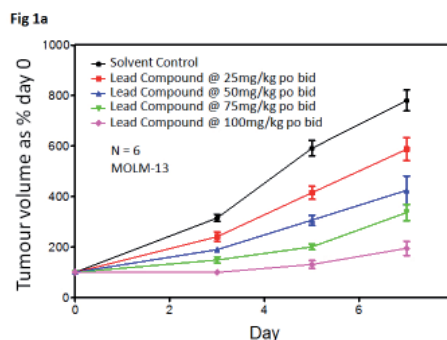


Figure 1a and 1b: Inhibition of growth of human AML xenografts (relative tumour volumes shown) (a) MOLM-13 and (b) MOLM-13-MLN518 resistant

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Mechanism of action and *in vivo* studies featuring an early Lead Series compound have been published by the team (2,3,4). Compounds in the Lead Series are ATP-competitive and have good *in vitro* ADME properties; lead optimisation studies have successfully focused on optimising PK properties while maintaining potency, cell-based and *in vivo* activity.

## Biomarkers of inhibition of FLT3 and Aurora kinases

Compounds from the Lead Series exhibit *in vitro* and *in vivo* modulation of signalling downstream of FLT3 and Aurora kinases consistent with a mechanism of action via dual inhibition in leukaemic models (Figure 2).

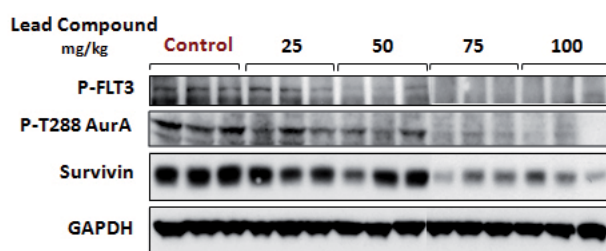


Figure 2: Immunoblot analysis of xenograft tumour lysates (MOLM-13 FLT3-ITD) demonstrating dose-dependent biomarker modulation.

Compounds from the Lead series show *in vivo* PD modulation of signalling downstream of Aurora in human colon carcinoma xenografts (HCT116) and also induce a reduction in tumour [18F]FLT retention detectable by non-invasive PET imaging (2).

## Summary of Lead Compound Data

		Lead Compound
Biochemical IC <sub>50</sub> (nM)	FLT3	35
	FLT3 (D835)	100
	Aurora A	15
	Aurora B	117
Cellular efficacy EC <sub>50</sub> (MTS, nM)		MOLM-13: 104 MV4-11: 270 MOLM-13 RES:180 HCT116: 300 SW620: 300
Cellular biomarker activity IC <sub>50</sub> (µM)	Inhibition of Aurora-A T288 phosphorylation	0.038
	inhibition of Aurora-B H3 phosphorylation	0.148
No gross <i>in vivo</i> toxicity (e.g. bodyweight loss) observed up to 200mg/kg		
Selectivity		Gini score: 0.56 <sup>11</sup> S(10) = 0.057 <sup>22</sup>
Bioavailability		%F = 100

Table 1: Lead Compound; \*1Staurosporine Gini score: 0.150 (non selective inhibitor); PD184352 Gini score: 0.905 (very selective inhibitor of MAPK1) (5). <sup>2</sup>Panel of 442 kinases tested at 1 µM (KINOMEScan™ technology).

## FLT3 / Aurora A selective inhibitors

Despite the historical focus on pan-Aurora kinase inhibitors, it remains an open question as to whether better clinical outcomes might be achieved by inhibiting Aurora kinase A or B selectively. In addition to the dual FLT3 / pan-Aurora kinase inhibitor programme described overleaf, inhibitors with a FLT3 / Aurora A selective inhibition profile are also available. These inhibitors are expected to provide access to anti-tumour efficacy in specific tumour types as well as reducing bone marrow toxicity compared with general anti-mitotic drugs. The most advanced compound exhibits 480 fold cellular selectivity for Aurora A versus Aurora B with good oral bioavailability in the mouse. In addition, methods have been developed to obtain co-crystals of Aurora A with putative Aurora A selective inhibitors.

## Originating Institute

This ongoing programme, led by Dr Spiros Linardopoulos, originates from the Cancer Research UK Cancer Therapeutics Unit 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. Capacity and expertise to run first-in-man and paediatric clinical trials with PK/PD support would be available through The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research. Many drugs discovered or developed at The Institute of Cancer Research have successfully entered the clinic and several have entered the market.

## Commercial Opportunity

CRT seeks a commercial partner for exclusive licensing and/or collaborative research for the further development of these novel dual inhibitors of FLT3 and Aurora kinases, which are protected by patent application number WO2007/072017 granted in US.

## Cancer Research Technology

CRT is an oncology focused development and commercialisation company. Novel Dual Inhibitors of FLT3 and Aurora Kinases is one of a robust pipeline of projects currently available from CRT for licensing and co-development.

## References

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2. Chan F., *et al.*, Mol. Cancer Ther. 2007 6:3147-3157.
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4. Moore A.S., *et al.*, abstract & poster 3289, 52nd ASH Annual Meeting and Exposition (publ. Nov 7 2010) and abstract & poster 3554, 102nd AACR Annual Meeting.
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