

# CRT Licensing Opportunity



## Inhibitors of Atypical Protein Kinase C (aPKC)

- Two lead series with low nM biochemical and sub-200nM cellular activities
- Potent inhibitors of cancer cell proliferation and anchorage-independent growth
- Direct mode of action PKC $\alpha$  biomarker assay allowing cellular readout of PKC $\alpha$  activity
- Drug-like molecules with good selectivity and *in vitro* ADME profiles

SMALL MOLECULES | Lead Optimisation

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## Background and Therapeutic Rationale

PKC $\alpha$  and PKC $\zeta$  together define the atypical sub-class of the Protein Kinase C (aPKC) family. The aPKCs are structurally and functionally distinct from the classic and novel PKC isoforms, and have been implicated in diverse cellular processes including regulation of cell polarity, and the control of cellular migration and growth. Recent clinical and genetic evidence has suggested that the aPKCs play a key role in driving tumourigenesis (reviewed in [1]).

PKC $\alpha$  acts as an oncogene in non-small cell lung cancer (NSCLC, [2]), and has been strongly implicated in the progression of many other solid tumours including ovarian and colon cancers ([3,4]). A common feature of these tumours is the overexpression of PKC $\alpha$  (commonly arising through amplification of the PRKCI gene on 3q26), which strongly correlates with poor prognosis and loss of cellular polarity. PKC $\zeta$  has been shown to sensitise cancer cells to a number of chemotherapeutic agents routinely used in the clinic ([5]), and together with PKC $\alpha$  is thought to play an important role in cancer cell invasion.

Inhibition of the catalytic activity of the aPKC isoenzymes represents an attractive strategy for an anti-tumour therapeutic. Inhibitors of aPKC are anticipated to act as direct anti-proliferative, anti-metastatic and chemopotentiating agents in tumours driven by high levels of aPKC expression and activity.

## First-In-Class Potent and Selective aPKC Inhibitors

Two series of ATP-competitive inhibitors exhibiting low nM activity against aPKCs have been developed. Compounds show improved potency compared to a recently published aPKC inhibitor from Pfizer (Table 1, [6]), and demonstrate excellent selectivity profiles when screened against a broad panel of protein kinases. In contrast to known inhibitors of the PKC super-family, CRT compounds are highly selective for the aPKCs, and do not inhibit the classic or novel PKC isoforms. In addition, inhibitors display good *in vitro* ADME properties, and are being profiled in pharmacokinetic studies.

Table 1: Biochemical and cellular activities of CRT's aPKC inhibitors and Pfizer aPKC inhibitor

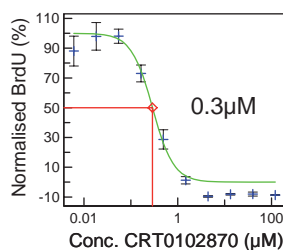
	CRT0066854	CRT0099431	Pfizer
Series	A	B	
MW	< 450	<450	<450
PKC $\alpha$ IC $_{50}$ ( $\mu$ M)	0.161	0.025	0.398
PKC $\zeta$ IC $_{50}$ ( $\mu$ M)	0.388	0.129	0.217
A549 proliferation IC $_{50}$ ( $\mu$ M)	15.6	4.2	9.3

## Cellular Activity

CRT has developed a direct mode of action pharmacodynamic assay allowing cellular readout of PKC $\alpha$  activity. aPKC inhibitors are highly efficacious in this assay, exhibiting improved inhibition of aPKC catalytic activity compared to the Pfizer compound. In phenotypic assays, aPKC inhibition leads to i) a pronounced decrease in proliferation of NSCLC and ovarian cancer cells (Table 1), and ii) blocks the anchorage-independent growth of NSCLC cell lines.

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CRT has further characterised a large number of compounds which show significantly improved cellular activities. These compounds have maintained their drug-like physicochemical and *in vitro* ADME properties, and are potent (low nM) inhibitors in pharmacodynamic and phenotypic assays (Figure 1). Compounds show strong structure-activity relationships (SAR), and highly significant enzyme:cell activity correlations throughout the two series.



PKC $\alpha$  IC<sub>50</sub> = 0.002µM  
PKC $\zeta$  IC<sub>50</sub> = 0.006µM  
A549 prolifer. IC<sub>50</sub> = 0.3µM

Figure 1: Effects of CRT0102870 on A549 proliferation (% inhibition)

## Structural Biology

Crystals have been obtained for ATP-competitive compounds bound to PKC $\alpha$  and PKC $\zeta$  that diffract beyond 3.0Å. Crystallography and *in silico* modelling has been instrumental in driving improvements in potency and selectivity.

## Academic Collaborators

The project is run in collaboration with Professors Peter Parker and Neil McDonald from CRUK's London Research Institute. Each brings extensive experience and expertise to the programme in their respective fields of signalling pathway phosphorylation events, and structural biology. Both have ongoing research interests in the molecular function of members of the PKC superfamily, including both aPKC isoforms.

## Cancer Research Technology

Cancer Research Technology (CRT) is an oncology focused development and commercialisation company. Identification of small molecule inhibitors of aPKC is one of a robust pipeline of projects currently underway in our Discovery Laboratories (CRTDL). CRTDL bridges the gap between academia and industry by working in collaboration with the originating academic laboratories and enabling their discoveries to be turned into projects that are readily recognisable and valued by the pharmaceutical industry.

## Commercial Opportunity

CRT seeks a commercial partner for collaborative research and/or exclusive licensing for the further development of these aPKC inhibitors. Patent applications with composition of matter and medical use claims are in preparation. Details of unpublished results relating to more recent compounds are available under CDA.

## References

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Contact: Phil Masterson, [pmasterson@CancerTechnology.com](mailto:pmasterson@CancerTechnology.com)

Ph: +44 (0)207 269 3640