

CRT Licensing Opportunity



Potent Inhibitors of Protein Kinase D (PKD)

- PKD is required for tumour growth, VEGF driven angiogenesis and cardiac hypertrophy
- Two potent and selective series of patented inhibitors of PKD with good *in vitro* ADME profile.
- Lead compound has excellent oral bioavailability and shown to inhibit tumour growth in xenograft model

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

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Scientific Rationale

Protein Kinase D (PKD), also known as Protein Kinase C mu (PKC μ), is a serine/threonine protein kinase that was originally identified as a member of the PKC superfamily. Recently PKD has been reclassified as a member of the calcium/calmodulin dependent protein kinase (CAMK) family, based on sequence similarities of the kinase domain. PKD is an integral part of signalling cascades that are aberrantly activated during a number of pathological conditions. PKD is known to be required for a number of cellular processes that have been demonstrated to be suitable points of therapeutic intervention. In particular, PKD plays a key role in promotion of cancer:

- Proliferation
- Invasion
- Inhibition of apoptosis in response to oxidative stress
- Signalling downstream of VEGF in endothelial cell proliferation.

PKD is an attractive target for development of anti-cancer and anti-angiogenesis therapeutics. A growing body of evidence implicates PKD in the pathogenesis of:

- Oncology: Pancreatic; CML; Colon; Breast; Prostate; Small cell lung; Basal cell carcinoma
- Cardiac hypertrophy
- Hyper-proliferative skin disorders
- Pathologies involving aberrantly activated immune response.

In summary, potent and specific drug-like inhibitors of PKD would have significant clinical and commercial potential.

First-In-Class Potent and Cell Active PKD Inhibitors

Two series of compounds were identified and developed from an IMAP bead based screen of CRT's fully synthetic compound library. The lead series has been the subject of an intense hit-to-lead and lead optimisation programme that has improved the potency of the original hits by over 500 fold. As a result, the most potent compounds inhibit PKD with IC₅₀ of <1 nM. These compounds show good selectivity against a panel of known kinases.

ADME Characteristics and Cellular Activity

Investigation of *in vitro* ADME properties of the compounds has indicated that they are soluble, cell permeable and have promising CYP450 inhibition and microsomal stability profiles.

Cell based studies have shown that the lead compounds not only inhibit PKD auto-phosphorylation, a useful biomarker for activated PKD, but also inhibit the proliferation of pancreatic cancer cells in response to growth factors with sub- μ M potency.

In vivo Proof of Concept

The lead compound from Series 1, CRT0066101, exhibits excellent oral bioavailability and inhibits tumour growth in Panc-1 (Pancreatic) and A549 (Lung) subcutaneous xenograft

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models without any sign of overt toxicity (Figure 1). In addition, a collaborative study carried out by Prof. S. Guha's laboratory (MD Anderson) showed that CRT0066101 inhibits growth of Panc-1 tumour in an orthotopic tumour model (poster presented at AACR Annual Conference 2009; manuscript in preparation)

Lead compounds of a structurally distinct second series have sub-nM biochemical activity and excellent selectivity profile.

More detailed non-confidential and confidential packs are available for further review.

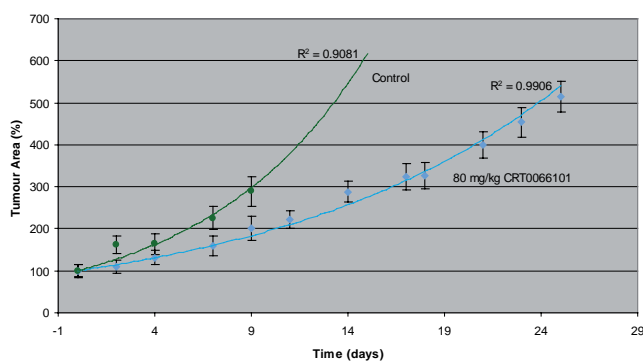


Figure 1: Proof of efficacy in vivo

Intellectual Property

Patent applications with composition of matter and medical use claims to Series 1 (WO27125331) and Series 2 (WO2008074997) are available for partnering.

Commercial Opportunity

CRT is seeking a commercial partner to facilitate further development of PKD inhibitors for oncology and other potential applications under an exclusive license or via collaboration.

Selected References

Pancreatic Cancer

Guha *et al.* 2003 Neurotensin stimulates PKC-dependent mitogenic signaling in human pancreatic carcinoma cell line PANC-1. *Cancer Research*. 63: 2379-2387

Basal Cell Carcinoma

Ristich *et al.* 2006 Protein kinase D distribution in normal human epidermis, basal cell carcinoma and psoriasis. *Br J Dermatol*. 154: 586-93

Chronic Myeloid Leukaemia

Mihailovic *et al.* 2004 Protein kinase D2 mediates activation of NfκB by Bcr-Abl in Bcr-Abl+ human myeloid leukemia cells. *Cancer Research*. 64: 8939-8944

Small Cell Lung Cancer

Paolucci and Rozengurt 1999 Protein Kinase D in small cell lung cancer cells: Rapid activation through Protein Kinase C. *Cancer Research*. 59: 572-577

Oxidative Stress

Storz and Toker 2003 Protein kinase D mediates a stress-induced NF-κB activation and survival pathway. *EMBO J*. 22: 109-120

Angiogenesis

Wong and Jin 2005 Protein kinase C-dependent protein kinase D activation modulates ERK signal pathway and endothelial cell proliferation by vascular endothelial growth factor. *J Biol Chem*. 280: 33262-9

Cardiac Hypertrophy

Fieltz *et al.* 2008 Requirement of protein kinase D1 for pathological cardiac remodelling. *PNAS* 105(8):3059-3063

A comprehensive list of references and full text articles are available on request.

CRT

Cancer Research Technology is an oncology focused development company. Identification of small molecule inhibitors of Protein Kinase D, an exciting target for anti-cancer drug discovery, is one of a robust pipeline of projects currently underway in our Discovery Laboratories.

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