

CRT Licensing Opportunity



Inhibitors of CDK7

- First in class selective CDK7 inhibitors
- Series (CDK7 selective and multi-CDK exemplars) with low nM biochemical and sub- μ M PD biomarker activities
- Selective inhibition of CDK7 leads to tumour cell-specific apoptotic response *in vitro*
- Drug-like molecules with excellent selectivity and *in vitro* ADME profiles

SMALL MOLECULES | Hit-to-Lead

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Commercial Opportunity

CRT seeks a commercial partner for collaborative research and/or exclusive licensing for the further development of these CDK7 inhibitors. There is potential for "first in class" (CDK7-specific) therapies.

Background and Rationale

Cyclin-dependent kinases (CDKs) control two major biological processes in cells; cell cycle progression and gene transcription. Progression from the G1 to S phases of the cell cycle involves sequential phosphorylation of the Rb protein by cyclin D- and cyclin E-dependent kinases, CDK4, CDK6 and CDK2, which disrupts the Rb-mediated repression of the E2F-1 transcription factor to allow expression of genes required for S-phase transit. S-phase and G2-phase progression also requires CDK2 and CDK1 controls G2/M transition. CDK7 and CDK9 phosphorylate the C-terminal domain of the largest subunit of RNA polymerase II (PolII), a modification required for promoter release and transcription initiation by PolII. Moreover, phosphorylation of the cell cycle CDKs (including by CDK7) at a threonine residue in the activation segment (T-loop) is a key component of CDK activation. This phosphorylation is mediated by the CDK activating kinase (CAK), comprised of CDK7, cyclin H and the so-called accessory protein MAT1. It has been proposed that the activity of CDK7 in regulating cell cycle progression through phosphorylation of CDKs and its regulation of PolII activity helps to ensure that mRNAs encoding effectors of cell division are expressed at the right time in the cell cycle (1).

Deregulation of cell cycle progression is a universal characteristic of cancer, and the majority of human cancers have abnormalities

in some component of CDK activity, frequently through elevated and/or inappropriate CDK activation. Hence there is considerable interest in the identification of CDK inhibitors as cancer therapeutics. Inhibition of the catalytic activity of CDK7 would be expected to inhibit cell cycle progression by blocking the phosphorylation of cell cycle CDKs, and would additionally inhibit transcription of effectors of cell division. CDK7 inhibition therefore represents an attractive strategy for an anti-tumour therapeutic. Small molecule inhibitors of CDK7 are anticipated to result in anti-proliferative and pro-apoptotic response.

Potent and Selective CDK7 Inhibitors

The Imperial College Cancer Drug Design and Development Group, together with CRT, have identified several distinct CDK7 inhibitors. Two of these series have been progressed to lead optimization, including a CDK7 selective. Current data establish CDK7 selective compounds that inhibit CDK7 activity with sub-nM potency (Table 1), show excellent selectivity against a diverse panel of kinases and display drug-like physicochemical properties. *In vitro* ADME properties and *in vivo* pharmacokinetic profiles have been established for several of the compounds (Table 2). These assays show:

- That several lead compounds inhibit the growth of a wide range of cancer cell lines (NCI60 panel) (Table 1)
- Growth inhibition is mediated by cell cycle arrest and apoptosis
- Inhibition of cell cycle by CDK7, PolII and Rb phosphorylation

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Table 1: *In vitro* kinase inhibition and cell growth activities of Series Exemplifiers.

Kinase (IC ₅₀ nM)	Series Representative A (Multi-CDK)	Series Representative B (CDK7 Selective)
CDK1	250	1,521
CDK2	3	578
CDK4	20,000	42,000
CDK5	30	9,000
CDK6	35,000	32,100
CDK7	250	41
CDK9	90	1,100
NCI60 Cancer Cell Line Panel		
Mean (GI ₅₀ μM)	0.28	0.31

Table 2: Key properties of CDK7 specific lead series inhibitors (Series Representative B).

CDK7 chemical matter	Range
Selectivity vs CDK2	x9 - x112
Solubility (μM)	>100
Cell Activity (μM)	0.15 - 10
Plasma protein binding (%)	85 - 98
Bioavailability (% murine. S.C.)	84 - 110
Cytochrome P450 IC ₅₀ (μM)	7 - >25
hERG inhibition IC ₅₀ (μM)	8 - >25

Animal *In Vivo* Studies using Multi-CDK Inhibitor

Preliminary studies have been carried out using a multi-CDK inhibitor (Series Representative A) and demonstrate that said compound is well tolerated in mice and can achieve significant tumour reduction (Figure 1). Oral administration results in inhibition of breast (MCF-7) and colorectal (HCT116) xenograft tumours, associated with inhibition of Rb phosphorylation in tumours (Figure 1, results obtained using a multi-CDK inhibitor).

In vivo studies in relevant murine models are ongoing with the CDK7-specific series.

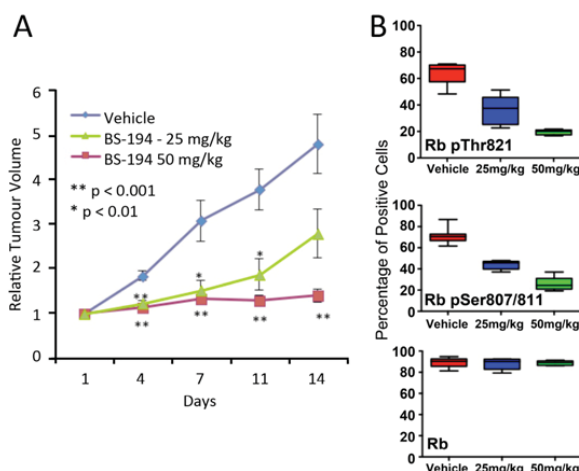


Figure 1: Series Representative A BS-194 (multi CDK inhibitor) inhibits the growth of a colorectal (HCT116) xenograft tumour in a dose dependent manner (A). The inhibitor was administered PO. Scoring of tumours based on levels of Rb phosphorylation following 14-day administration using immunostaining for Rb (B) (see ref. 2).

Academic Collaborators

The project is run by Prof Simak Ali, Prof Tony Barrett FRS FMedSci, Prof Charles Coombes FMedSci and Dr Matt Fuchter from the Imperial College Cancer Drug Design and Development Group and the Imperial College CRUK Cancer Centre and Dr Cathy Tralau-Stewart of the Imperial College Drug Development Centre. The project has progressed through collaboration with Prof Dennis Liotta and Prof Jim Snyder from Emory University.

Cancer Research Technology

CRT is an oncology-focused development and commercialisation company. Identification of small molecule inhibitors of CDK7 is one of a robust pipeline of projects currently underway in CRT.

References

- Ali S, *et al*, (2009) *Cancer Res.* 69: 6208–6215
- Heathcote DM, *et al*, (2010) *J. Med. Chem.* 53: 8508–8522

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