

CRT Licensing Opportunity



Inhibitors of LIMK1 and LIMK2

- Emerging target for therapeutic intervention in cancer and ocular disease
- Inhibition of LIMK leads to reduction in growth of invasive tumours *in vivo*
- Potent and selective late hit-to-lead inhibitors of LIMK1/2 available
- Demonstrated activity in cellular assays for tumour cell invasion and growth

SMALL MOLECULES | Hit-to-Lead

December 2009

Commercial Opportunity

CRT are seeking a commercial partner to undertake further *in vitro* and *in vivo* development of an exciting collection of potent pre-clinical LIMK1/2 inhibitors, with potential application in cancer and ocular disease. In particular, validation data suggests LIMK inhibitors may be effective in breast and prostate cancer indications, as well as ocular hypertension/glaucoma. Two potent chemical series are subject to recent priority patent filings.

Therapeutic Rationale

LIMK1/2 are ser/thr kinases which are upregulated in metastatic breast and prostate tumours (1, 2). Over-expression of LIMK has been demonstrated to increase tumour cell migration and invasion and to increase tumour growth, angiogenesis and metastasis *in vivo* (1). Conversely, abrogation of LIMK function results in decreased breast cancer cell motility and formation of osteolytic bone lesions in an animal model of invasion (3).

By virtue of their role as effectors of Rho and cdc42 pathways involving ROCK, PAK1, PAK4 and MRCK, the LIM kinases are implicated as key regulators of the cytoskeleton (Figure 1). Several reports have also suggested cross-talk between LIMK and the TGF- β superfamily, key mediators of fibrotic responses.

Downregulation of LIMK1 has been demonstrated to reduce inflammation in a mouse model of ocular surgery (4). Furthermore, small molecule inhibition or genetic deletion of

LIMK2 is effective in reducing intraocular pressure in mouse models, a key risk factor in disease progression in glaucoma (5).

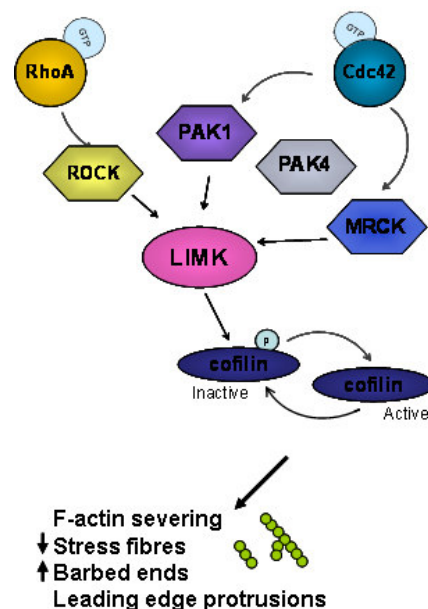


Figure 1: LIMK signalling pathways

Potent and Selective LIMK1/2 Inhibitors

CRT's Discovery Laboratories and the Australian consortium Cancer Therapeutics Pty Ltd. have collaborated to develop two late hit-to-lead compound series with low nM activity against

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LIMK1/2. The compounds were identified through an HTRF-based screen of CRT's fully synthetic compound library. An extensive medicinal chemistry effort has been carried out resulting in impressive potency and selectivity over a wide panel of other kinases. Compounds from the lead series are amongst the most potent LIMK inhibitors reported in the literature to date, some having sub-nM IC_{50} s *in vitro*, and are in novel chemical space.

Cellular Activity

The compounds exhibit low uM potency in breast cancer cells as shown by inhibition of phosphorylation of the LIMK substrate cofilin (Figure 2). Treatment of MDA-MB-231 breast cancer cells with the compounds significantly reduces their ability to invade a matrigel plug in an inverse *in vitro* invasion assay (Figure 3). Furthermore, the inhibitors effectively reduce fibroblast-led collective invasion in a published co-culture organotypic model (6).

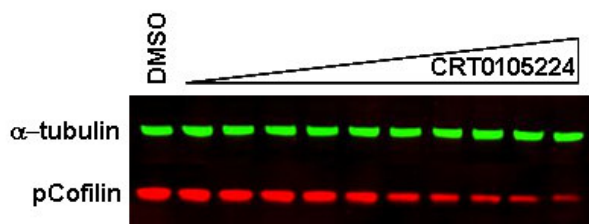


Figure 2: LIMK inhibitors reduce cofilin phosphorylation

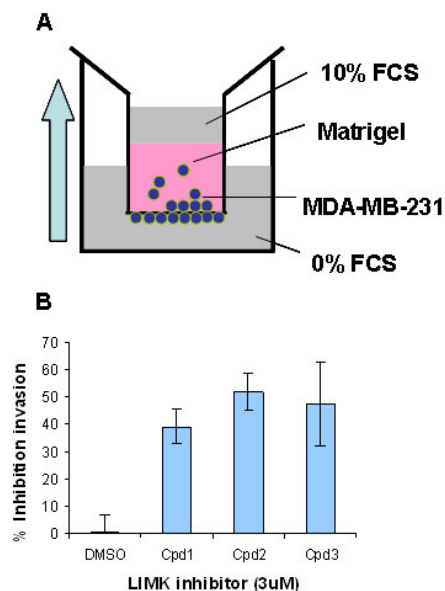


Figure 3: LIMK inhibitors block breast cancer cell invasion

Proprietary target validation data has been established which implicates LIMK in protection against cell death in the presence of certain cancer therapies. Inhibitors of LIMK have

been demonstrated to synergise with such agents to promote apoptosis of tumour cells (Figure 4).

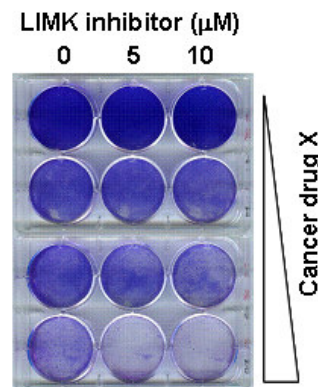


Figure 4: LIMK inhibition synergises with cancer therapy to cause apoptosis

in Vitro ADMET Properties

Compounds from the lead series demonstrate drug-like physicochemical properties including low molecular weight, with high membrane permeability and metabolic stability.

References

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