

CRT Licensing Opportunity



New Selective Metabolic Agent for Cancer Therapy

- New Hypoxic Response Inhibitors
- Novel patented compounds with anti-cancer activity
- *In vivo* proof-of-concept efficacy demonstrated with prototype compounds
- Rationale for a US and EU Orphan Designation application (paraganglioma, pheochromocytoma)

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

October 2009

Background

Under normal oxygen levels (normoxia), the half-life of HIF-1 α is very short as it is marked for ubiquitylation by the VHL gene product (pVHL). The binding of VHL to HIF-1 α is enabled by the hydroxylation of specific residues by prolyl hydroxylases (PHD). PHD requires α -Ketoglutarate (α -KG) as substrate, catalysing the conversion of α -KG to succinate. Succinate is subsequently converted to fumarate by succinate dehydrogenase (SDH), a Krebs cycle enzyme and reported tumour suppressor.

It is well established that solid tumours develop hypoxic areas as they grow, resulting in the stabilisation of HIF-1 α and activation of a stress response that is crucial for tumour survival, development and treatment-refractory state.

Pseudo-hypoxia is a cellular metabolic state relying on the activation of HIF-1 α and related stress responses even under conditions of normoxia. This state can lead to angiogenesis, increased energy production through glycolysis and induction of survival and proliferation mechanisms. Mutations in the mitochondrial SDH and fumarate hydratase (FH) genes also leads to pseudo-hypoxia which has been shown to play an important role in rare diseases such as renal cell carcinoma and pheochromocytomas.

Technology

The investigators have shown that inactivation of SDH in tumours leads to an increase in succinic acid levels and results in a pseudo-hypoxic state. Increasing succinate levels inhibited α -KG-dependent PHD metabolism which leads to HIF-1 α stabilisation and increases HIF transcription (Fig 1).

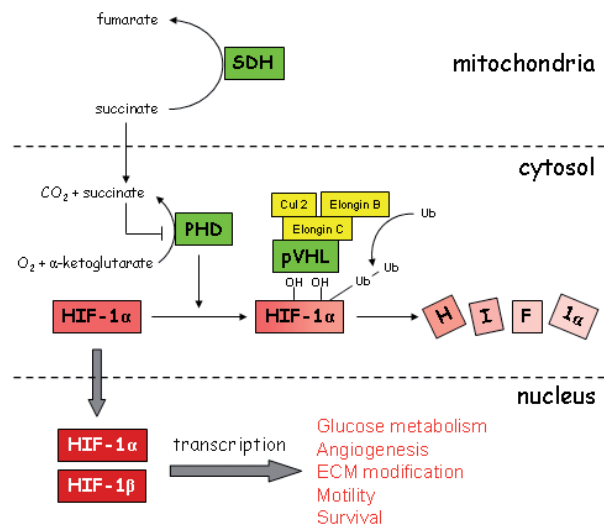


Figure 1 Succinate signalling: from SDH dysfunction to HIF activation. Accumulated mitochondrial succinate (due to inhibition of SDH) can inhibit PHD activity in the cytosol. Consequently, HIF-1 α is not degraded even in normoxic conditions. HIF-1 α induces expression of genes supporting tumour growth and spreading. This process can be inhibited by increasing cellular levels of α -KG.

α -KG can overcome succinate-mediated inhibition of PHD *in vitro* and re-establish HIF-1 degradation. Novel cell permeable and stable derivatives of α -KG have been developed that overcome HIF-1 α stabilisation by succinate or fumarate thereby reversing the pseudo-hypoxic state (Fig 2).

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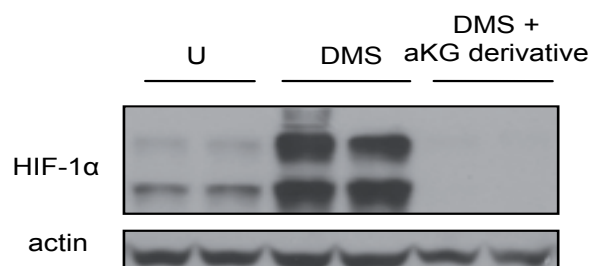


Figure 2 Treatment with α -KG overcomes HIF-1 α stabilisation by succinate. Cells were treated with or without dimethyl succinate (DMS; U=untreated) and with or without a cell permeable α -KG derivative. Endogenous levels of HIF-1 were reduced with the α -KG derivative.

The mechanism by which the novel α -KG derivatives have their biological effect is via a destabilisation of HIF-1 α under hypoxic conditions (Fig 3).

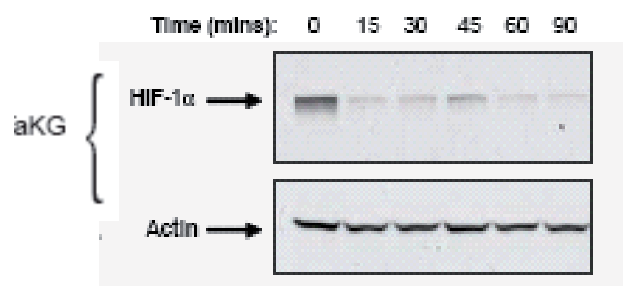


Figure 3 α -KG derivatives promoted destabilisation of HIF-1 α under hypoxia Hypoxic cells were treated with α -KG derivatives and endogenous HIF-1 α levels were reduced.

In vivo proof-of-concept studies show that cell-permeating prototype α -KG derivatives reduce tumour growth (Fig 4) and therefore have therapeutic potential in the treatment of tumours with dysfunctional oxidative phosphorylation by reducing HIF-1 levels.

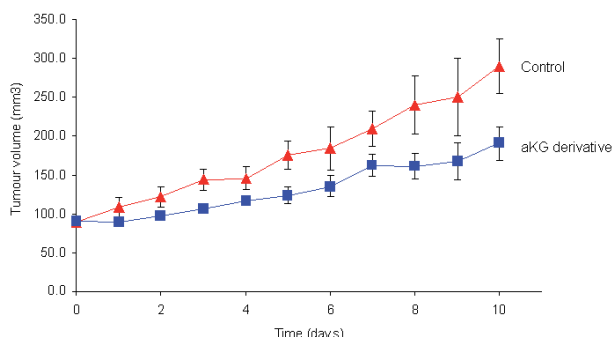


Figure 4 α -KG prototype molecules reduces growth of a hypoxic tumour xenograft in mice. Hypoxic xenografts were generated in nude mice. Tumours of 100mm³ were treated orally with 750mg/Kg of α -KG derivative daily for 10 days.

α -KG derivatives also promote metabolic crisis in hypoxic cancer cells highlighting their potential application in adjuvant chemotherapy in combination with glycolysis inhibitors, hypoxic-dependent cytotoxins and angiogenesis inhibitors.

Intellectual Property

PCT patent application filed in August 2005 (WO 06016143) claiming use of hydrophobic α -KG ester compounds and their use for treatment of HIF-associated disease and SDH mutated cancers. Patent is pending in all major territories.

Commercial Opportunity

CRT are seeking a commercial partner to further develop the α -KG derivatives as novel anti-cancer agents for hypoxic and pseudo-hypoxic tumours. Additional confidential information is available on request.

References

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