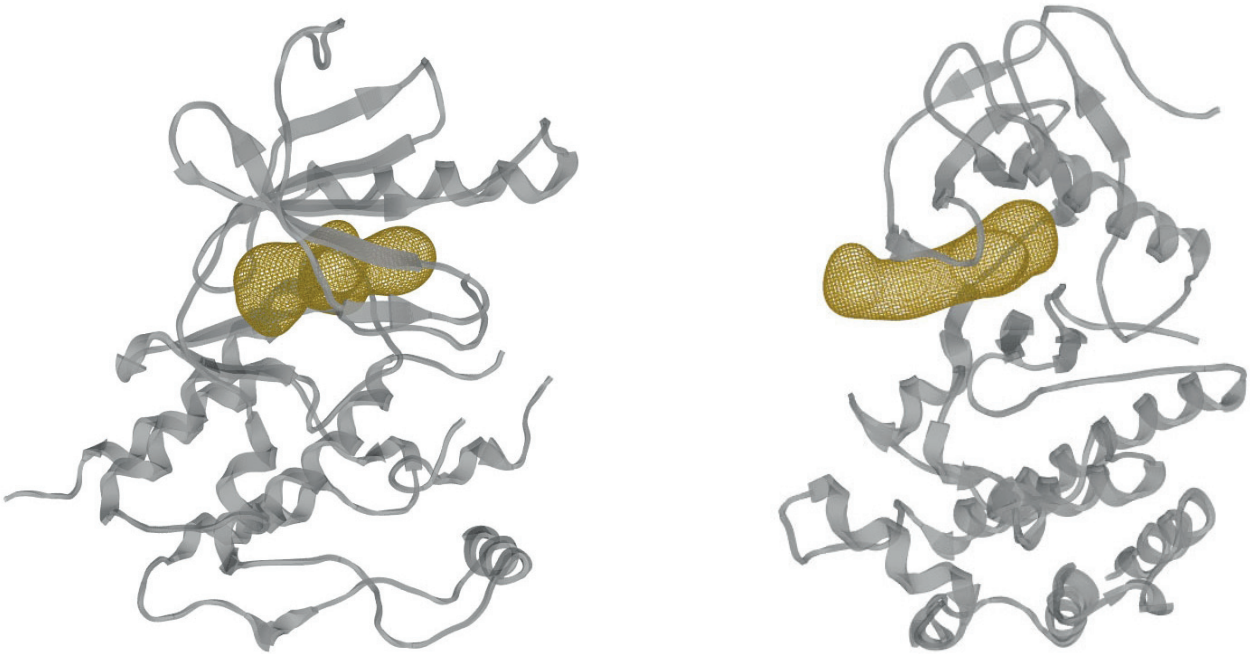
Lead optimisation of potent LOX inhibitors for the treatment of pancreatic cancer



Opportunity

Pancreatic cancer is the tenth most common type of new cancer but the fourth leading cause of cancer deaths. In the UK, there are over 8000 new cases per year. It is extremely difficult to diagnose in its early stages. The relative one-year survival rate for pancreatic cancer is 24% and the overall five-year survival rate is only 5%. There are currently no effective treatments for metastases in patients with pancreatic cancer. Thus, despite the number of different oncology treatments approved, there remains an unmet need for the effective treatment of metastatic pancreatic cancer.

The Wellcome Trust has funded a drug discovery programme at the Institute of Cancer Research (ICR) that has identified lead candidate inhibitors of lysyl oxidase (LOX) for treatment of both primary and metastatic pancreatic cancer.

The team

The LOX drug discovery programme is led by Professor Caroline Springer (Institute of Cancer Research, ICR) and Professor Richard Marais (Paterson Institute). The ICR, together with its partner institution, the Royal Marsden NHS Foundation Trust, forms the largest comprehensive cancer centre in Europe and one of the largest in the world. The ICR and the Marsden together conduct research across the whole spectrum of cancer studies from basic biology to clinical trials. Professor Springer is part of the Cancer Research UK Centre for Cancer Therapeutics at the ICR, a renowned drug discovery unit that has developed many novel anticancer drugs. Professor Marais is director of the Paterson Institute in Manchester.

Project information is provided overleaf.

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Image above: Co-crystal inhibitor–BRAF structures. *Institute of Cancer Research*

Lysyl oxidase
The enzyme lysyl oxidase (LOX) regulates cross-linking of structural proteins in the extracellular matrix. LOX is produced and secreted into the circulation by cancer cells in response to hypoxia and is a critical mediator of invasion and metastatic tumour spread. High levels of LOX expression have been described in patients with breast, head and neck, colorectal and lung cancers. LOX is highly expressed in aggressive metastatic melanoma and pancreatic cancer cell lines. Importantly, elevated LOX expression is associated with metastasis and decreased patient survival. Inhibition of tumour-secreted LOX by genetic, antibody or chemical means significantly reduces invasion and metastasis of human breast tumours in mice.

Taken together, this data demonstrates a critical requirement for tumour-secreted LOX in invasive migration, pre-metastatic niche formation and sustenance of tumour growth at newly formed metastatic sites.

Small-molecule LOX inhibitors
The Wellcome Trust-funded drug discovery research has led to the discovery of two distinct chemical series that are now in lead optimisation. The intellectual property (IP) space of the two series is non-overlapping, offering better IP protection.

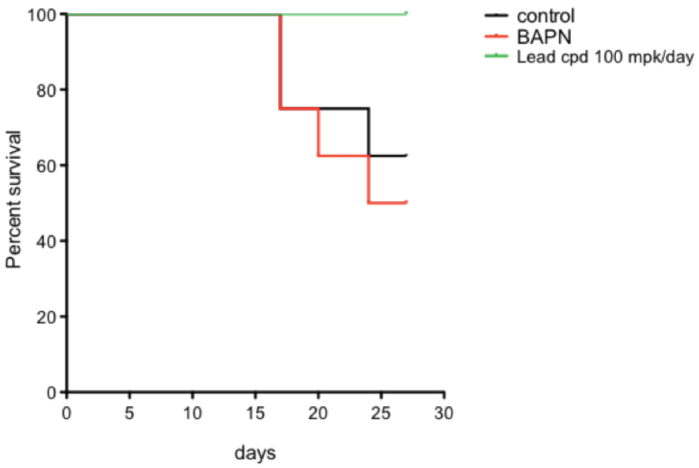
***In vivo* profile**
Inhibitors from both series demonstrate cell potency in the low µM range with excellent physiochemical properties. Compounds from both show no inhibition of common CYP isoforms or the hERG channel and have an excellent toxicological profile in rodent species.

***In vivo* efficacy**
The oral therapeutic efficacy of a selected inhibitor has been compared to the published non-selective LOX inhibitor, BAPN (100 mg/kg/day), in a pancreatic ductal adenocarcinoma cancer (PDAC) LOX-dependent tumour model, at 100 mg/kg/day qd for 28 days. The LOX inhibitor treatment group (see figure 1) exhibits a clear survival advantage compared with the vehicle-treated controls and over the BAPN-treated group, which has no effect in this model (figure 2).

DMPK
Compounds from both series exhibit good metabolic stability in both mouse and human liver microsomes. They have good permeability and high solubility, demonstrate high bioavailability, and are well tolerated on repeat dosing.

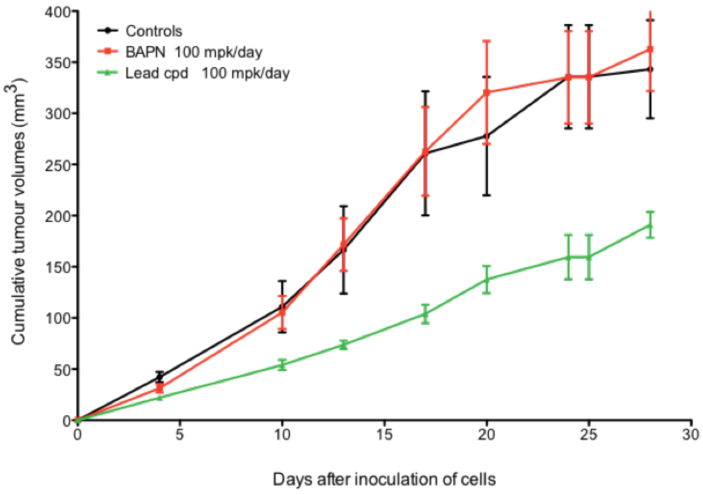
Preclinical development of selective LOX inhibitors
The programme is currently in lead optimisation towards the selection of pre-clinical development candidates. This will be followed by demonstration of proof of concept in accepted pre-clinical animal models.

Figure 1
Survival of Kaplan: survival proportions



Unpublished data showing Kaplan-Meier per cent survival of one lead series inhibitor compared to the vehicle-treated control and to the BAPN-treated group in a LOX-driven PDAC allograft model.

Figure 2
Tumour regression



Unpublished data showing therapeutic efficacy of one orally dosed lead series inhibitor compared to vehicle-treated control or to a BAPN-treated group in a LOX-driven PDAC allograft model.

Commercial partnership

The Wellcome Trust and the Institute of Cancer Research are now seeking a commercial partner on this exciting programme in order to undertake the development of these compounds through proof-of-concept studies. Importantly, partnering of this programme affords the advantage of working with Professors Martin Gore and Stan Kaye at the Royal Marsden Hospital, both of whom are leading cancer specialists.

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