A drug targeting scar-like 'fibrotic' tissue within tumours shows promise for treating pancreatic ductal adenocarcinoma (PDAC). In the study, reported online in *Nature Cancer*, 28 August, Australian investigators showed in mouse and human models of PDAC that, when the drug PXS-5505 was given in combination with chemotherapy, survival time was significantly increased and metastasis significantly reduced in comparison to chemotherapy alone.

"The preclinical validation of this first-in-class anti-fibrotic drug marks a major milestone in our quest to overcome the significant challenges in treating pancreatic cancer and brings hope to patients and their families," says Thomas Cox, the senior author from the Garvan Institute of Medical Research, Sydney, Australia. "Importantly, we showed efficacy in both primary PDAC and metastatic disease settings."

PDAC, which has a five-year survival of less than 10%, is known for marked resistance to chemotherapy, radiotherapy, and immunotherapy. Activation of tumour associated stromal cells and increased deposition of extracellular matrix in the tumour microenvironment have been associated with its aggressive nature. "What happens is a vicious cycle where we see increasing fibrosis that feeds back onto the cancer cells making the cancer more aggressive leading to more fibrosis," explains Cox. "Our hypothesis was that if we can target the deposition of the matrix and block this fibrotic response, we can break that cycle and improve the efficacy of already approved standard of care therapies."

The lysyl oxidase family of enzymes is known to play a critical role in the biogenesis of fibrillar collagens, with mammals having five family homologs: lysyl oxidase (LOX) and lysyl oxidase-like 1 to 4 (LOXL1, LOXL2, LOXL3 and LOXL4). The lysyl oxidase family exhibits aberrant gene and protein expression in several solid tumours, with activity closely associated with development of tumour desmoplasia (collagen deposition in fibrotic tissue).

However, *in vivo* preclinical studies targeting LOX and LOXL2 using antibody-based approaches have yielded mixed result. For example, work developing an allosteric LOXL2-specific monoclonal antibody (AB0023) showed promise in preclinical studies, but the humanised version yielded limited success during translation into phase II clinical trials in metastatic pancreatic cancer. "This was likely a result of the critical involvement of other lysyl oxidase family members in PDAC, and that the antibody did not provide complete inhibition of enzymatic activity in patients," Cox tells *Cancerworld*.

PXS-5505, developed by Sydney-based pharmaceutical company Pharmaxis, is a first-in-class small-molecule selective mechanistic inhibitor irreversibly targeting the entire lysyl oxidase family (including LOX and LOXL1, LOXL2, LOXL3 and LOXL4). "PXS-5505 returns the tumour microenvironment to a more 'normal' state by reducing fibrosis and decreasing tumour stiffness," explains Jessica Chitty, the first author of the study. "This allows chemotherapy drugs to penetrate the tumours more easily, work more effectively, and destroy more cancer cells."

For the current study, the team used two models of pancreatic cancer:

- In the KPC mouse model (genetically modified to spontaneously grow pancreatic tumours), cre-lox technology was used to introduce the $Kras^{G12D}$ and mutant $p53R^{172H}$ mutations (the most common mutations in PDAC) into the mouse pancreas via the Pdx1 promoter. This results in the mice developing pancreatic intraepithelial neoplasia at around six weeks, and significant malignant disease at around 10 weeks, and then experiencing progression to metastatic disease within 15 to 20 weeks. Once tumours had developed, mice were treated with PXS-5505 plus gemcitabine chemotherapy to evaluate efficacy.
- Patient-derived xenografts were used, that were taken from patients in the Australian Pancreatic Cancer Matrix Atlas (APMA) and Australian Pancreatic Genome Initiative (APGI), and were surgically implanted into mice, which were then treated with PXS-5505 plus gemcitabine.

Evaluation of tumour desmoplasia (using picrosirius red staining and multiphoton microscopy imaging) showed PXS-5505 decreases chemotherapy-induced pancreatic tumour desmoplasia.

Examination of tumour stiffness (by unconfined compression analysis) showed that PXS-5505 decreases chemotherapy-induced stiffness.

Measurement of cancer cell invasion using a 3D organotypic invasion assay showed that the invaded field of view was significantly reduced for cells exposed to PXS-5505 plus gemcitabine compared to those exposed to gemcitabine alone (P=0.0019). Results in the KPC mouse model showed that the combination of PXS-5505 plus gemcitabine increased median survival from 125 days with gemcitabine alone to 171 days for the combination treatment (P=0.0338).

Preclinical data showed that PXS-5505 had excellent tolerability, no safety signals and no off-target activity on other amine oxidases. Furthermore, the oral pharmacokinetic profile of PXS-5505 showed fast absorption and clearance with a sufficiently long half-life to achieve significant inhibition of the lysyl oxidase family activity.

“These data strongly support the addition of PXS-5505 to gemcitabine potentiates the efficacy of chemotherapy and this study provides evidence that a pan-lysyl oxidase small-molecular-targeting approach can significantly improve gemcitabine efficacy,” write the authors.

Discussions are currently underway with clinical partners, says Cox, for a clinical trial of PXS-5505 in pancreatic cancer patients. “But we don’t have a start date yet,” he adds.

Undoubtedly, pancreatic cancer is not the only cancer that could benefit from PXS-5505. “Although not all cancers involve fibrotic tissue, many solid tumours do, and importantly, many therapies given to patients exacerbate the fibrotic nature of tumours,” says Cox. “Any tumour that is considered highly desmoplastic would potentially benefit from combination therapy (with PXS-5505). However, more work is needed before a definitive list can be drawn-up.”

Currently, a phase 1c/2a trial (MF-101) is underway in Australia, South Korea, Taiwan and the USA using PXS-5505 as monotherapy for myelofibrosis. This is a rare bone cancer where normal bone marrow is replaced with fibrous scar-like material (restricting the production of blood cells), and where lysyl oxidase is known to be upregulated. “Our preclinical trials show pan lysyl oxidase inhibitors slow the disease progression in primary myelofibrosis providing the rationale for initiating our first clinical trials as an anti-fibrotic monotherapy in myelofibrosis patients,” says Lara Perryman, a senior research scientist at Pharmaxis.