

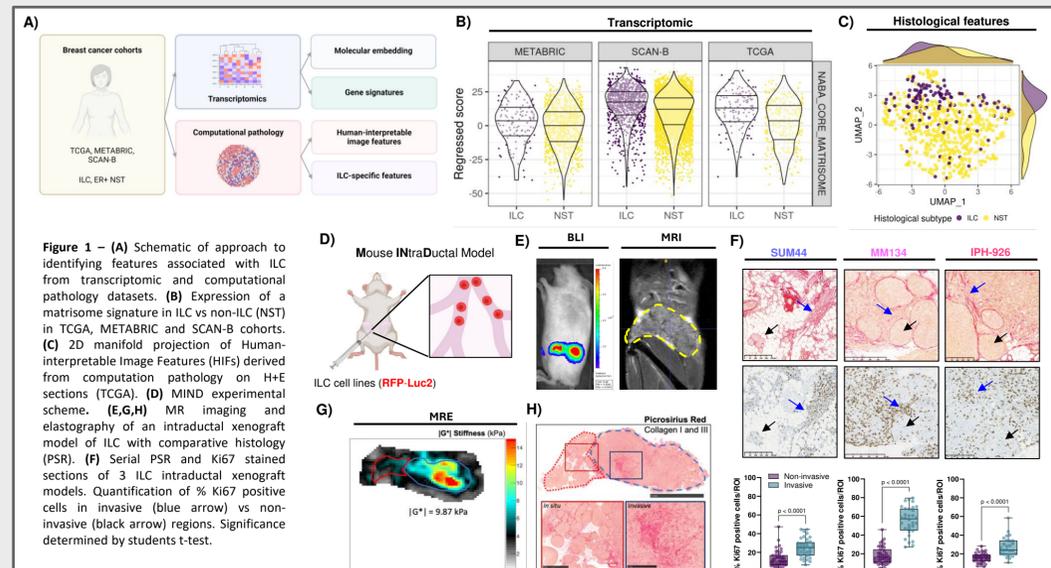
Extracellular matrix remodelling is a targetable feature of invasive lobular carcinoma (ILC)

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1. Background

- Invasive lobular carcinoma (ILC) accounts for 15% of breast cancer cases and is characterised by strong estrogen receptor (ER) positivity, loss of E-cadherin, and a distinctive "single-file" growth pattern.
- Historically, ILC has been understudied due to limited models and poor clinical trial inclusion.
- Despite differences in biology and long-term outcome, ILC is often not treated clinically as a distinct entity
- Previously ILC cells have been shown to overexpress the collagen crosslinking enzyme LOXL1, which promotes tumour cell invasion through remodelling of the extracellular matrix (ECM).
- We therefore propose PXS-5505, a highly selective LOX inhibitor, be investigated as a therapeutic strategy in ILC.

2. Histological features separate ILC from ER+ NST, and matrix remodelling is associated with progression



- Matrisome and morphological features distinguish ILCs from NST within ER+ BC.
- Pre-clinical models of ILC demonstrate invasion and proliferation is associated with increased matrix deposition

3. Pan-LOX inhibition (LOXi) alone or in combination with hormone deprivation inhibits progression of ILC

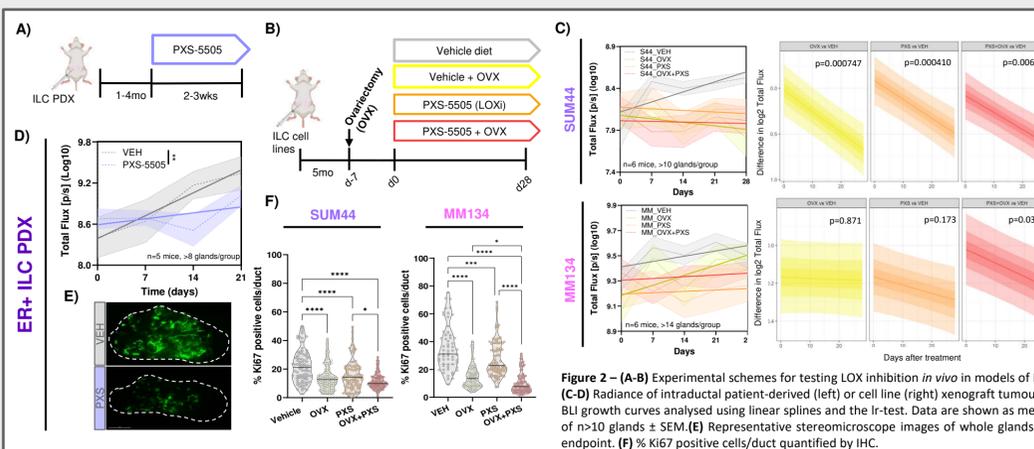


Figure 2 - (A-B) Experimental schemes for testing LOX inhibition *in vivo* in models of ILC (C-D) Radiance of intraductal patient-derived (left) or cell line (right) xenograft tumours. BLI growth curves analysed using linear splines and the Ir-test. Data are shown as mean of >10 glands ± SEM. (E) Representative stereomicroscope images of whole glands at endpoint. (F) % Ki67 positive cells/duct quantified by IHC.

4. LOXi disrupts collagen remodelling and downregulates matrisome-associated proteins

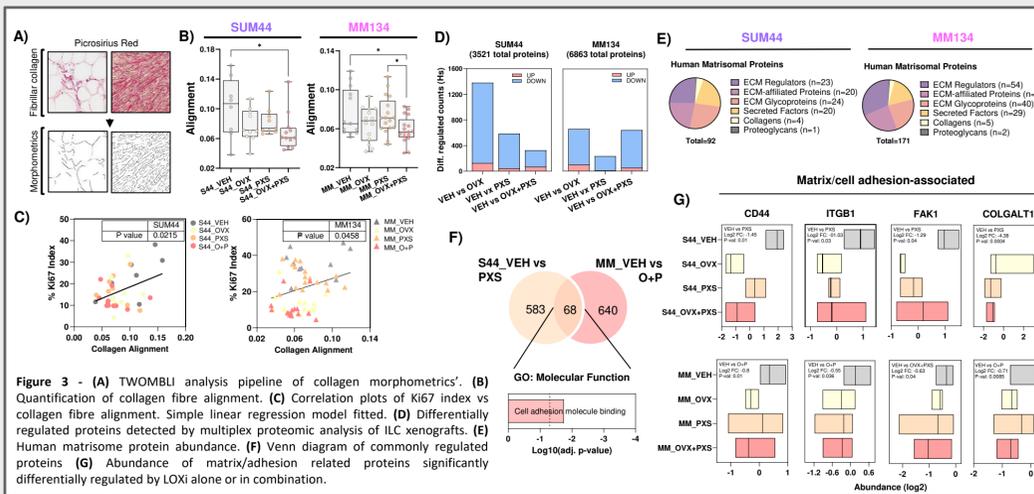
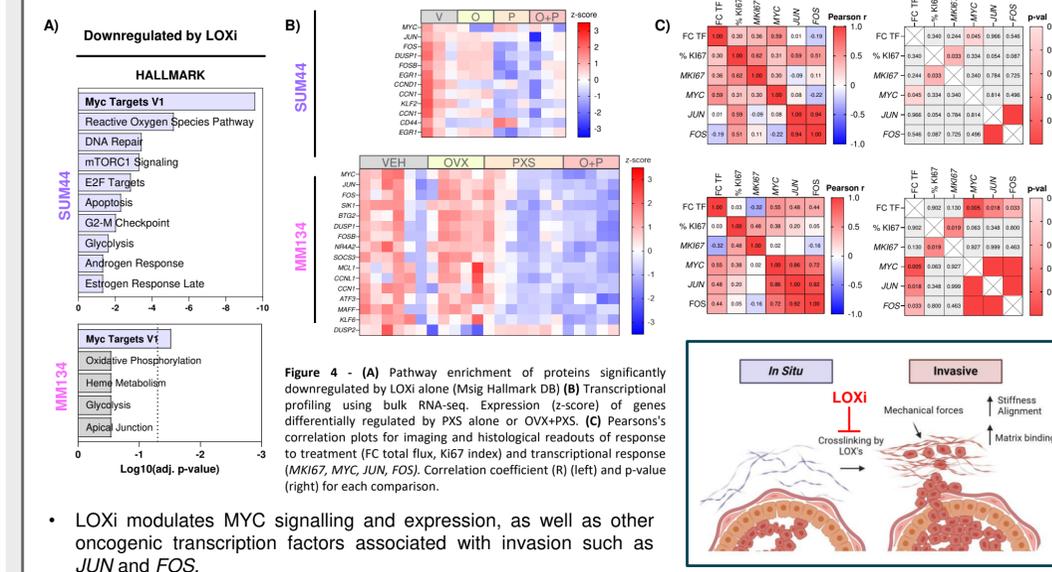


Figure 3 - (A) TWOMBU analysis pipeline of collagen morphometrics. (B) Quantification of collagen fibre alignment. (C) Correlation plots of Ki67 index vs collagen fibre alignment. Simple linear regression model fitted. (D) Differentially regulated proteins detected by multiplex proteomic analysis of ILC xenografts. (E) Human matrisome protein abundance. (F) Venn diagram of commonly regulated proteins (G) Abundance of matrix/adhesion related proteins significantly differentially regulated by LOXi alone or in combination.

5. LOXi alone or in combination modulates MYC signalling



- LOXi modulates MYC signalling and expression, as well as other oncogenic transcription factors associated with invasion such as JUN and FOS.

6. Conclusions

- Invasion of ILC cells relies on tumour cell-mediated extracellular matrix remodelling
- Collagen matrix alignment is associated with increased proliferation
- Inhibition of collagen remodelling through targeting LOX downmodulates matrix-associated proteins and oncogenic transcription factor signalling
- Therapeutically, addition of LOXi to standard of care therapy effectively limits ILC progression

Lay Summary

We use innovative mouse models of ILC to test a new therapy which prevents collagen remodelling. By combining this new drug with the standard of care therapy for ILC, we can reduce tumour progression.