What makes a Best in Class Anti-Fibrotic?

Gary Phillips CEO

30 October 2019

Forward looking statement

This document contains forward-looking statements, including statements concerning Pharmaxis' future financial position, plans, and the potential of its products and product candidates, which are based on information and assumptions available to Pharmaxis as of the date of this document. Actual results, performance or achievements could be significantly different from those expressed in, or implied by, these forward-looking statements. All statements, other than statements of historical facts, are forward-looking statements. These forward-looking statements are not guarantees or predictions of future results, levels of performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this document. For example, despite our efforts there is no certainty that we will be successful in partnering our LOXL2 program or any of the other products in our pipeline on commercially acceptable terms, in a timely fashion or at all. Except as required by law we undertake no obligation to update these forward-looking statements as a result of new information, future events or otherwise.

Summary

A global leader in drug development for fibrosis & inflammation

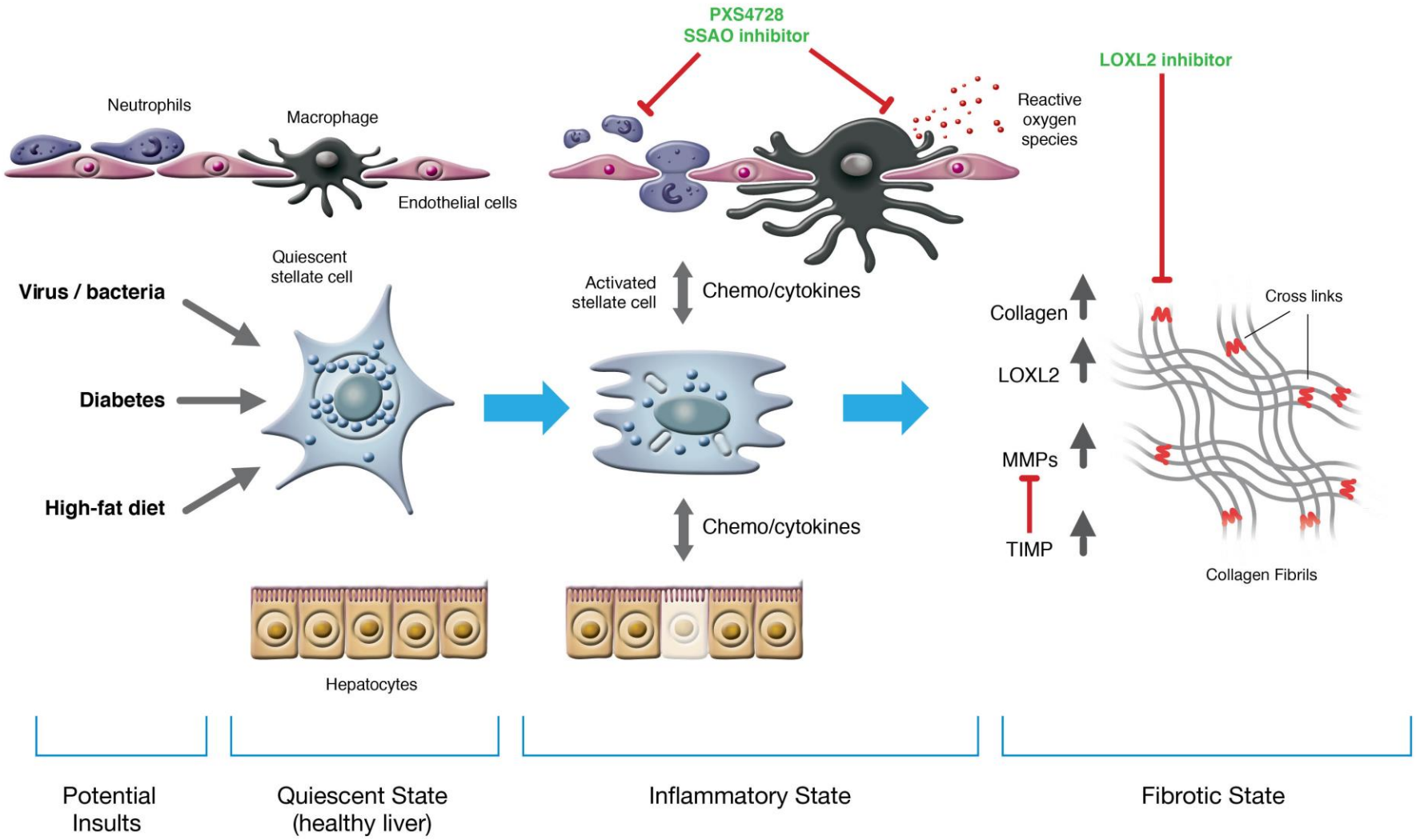
1. **Exciting product pipeline with multiple near term opportunities**
   - Lead drug (BI1467335) sold to Boehringer Ingelheim (BI) in 2015 in development for two disease indications
     - Total deal >$600m+ in development milestones plus royalties; $83m received to date from BI
   - Anti fibrotic LOXL-2 program for the treatment of diseases including NASH and IPF completed phase 1 safety trials
     - Commercial partnering in progress
   - Bronchitol and Aridol (Mannitol business) business unit nearing breakeven revenues
     - US FDA approval expected H1 2020
   - Two further anti fibrotic programs in late stage pre clinical / phase 1
     - Patient proof of clinical efficacy trials due to start in 2020; myelofibrosis & skin scar revision
2. **Management team** with significant international experience in drug development, commercialisation and partnering
   - Big Pharma validation of science and commercial acumen from existing deals with BI and Chiesi
3. **Strong balance sheet**
4. **Specialist** US, UK and Australian institutional **biotech investors** on the share register
5. **Numerous catalysts** over next 12 months including two cash generating events (LOXL2 partnering & Bronchitol US)

Agenda

What makes a Best in Class Anti-Fibrotic?

- The role of lysyl oxidase enzymes in fibrosis
- Validation of LOXL2 as an important target in fibrotic disease
- The competition for Best in Class
- Pre clinical and clinical profile of Pharmaxis drug
- Other LOX programs

Drugs targeting NASH → Cirrhosis



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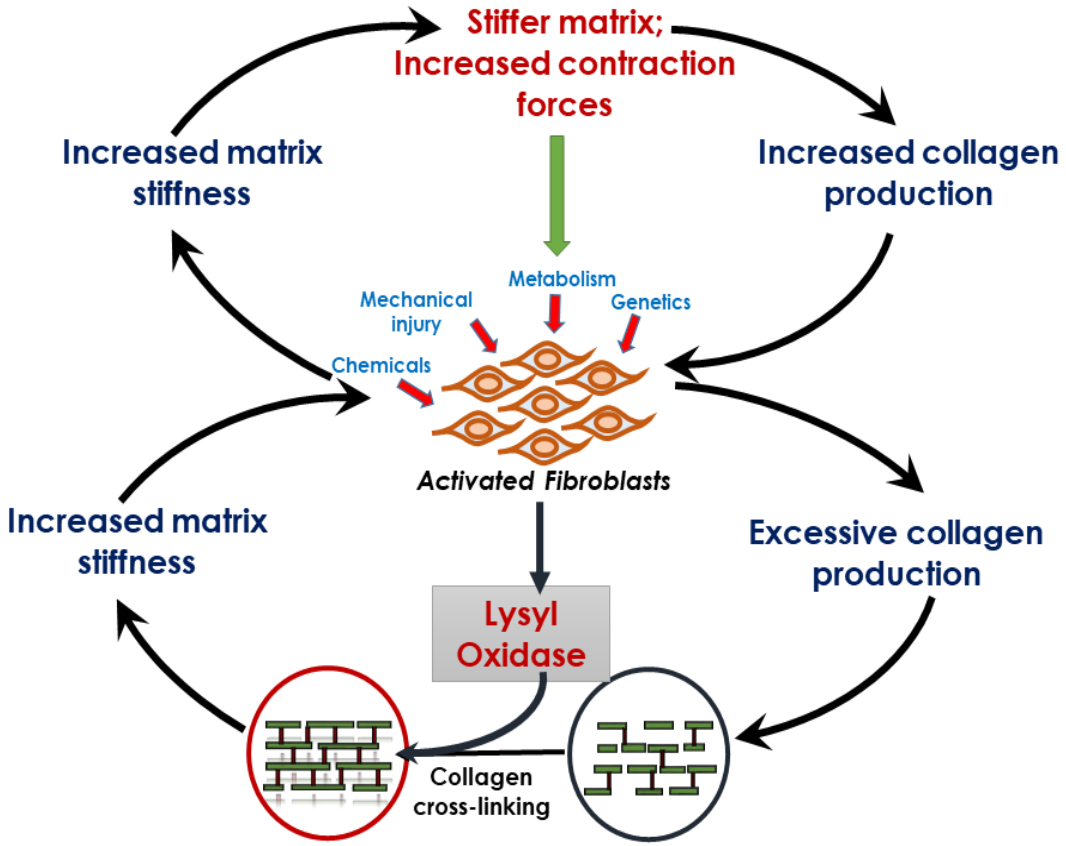
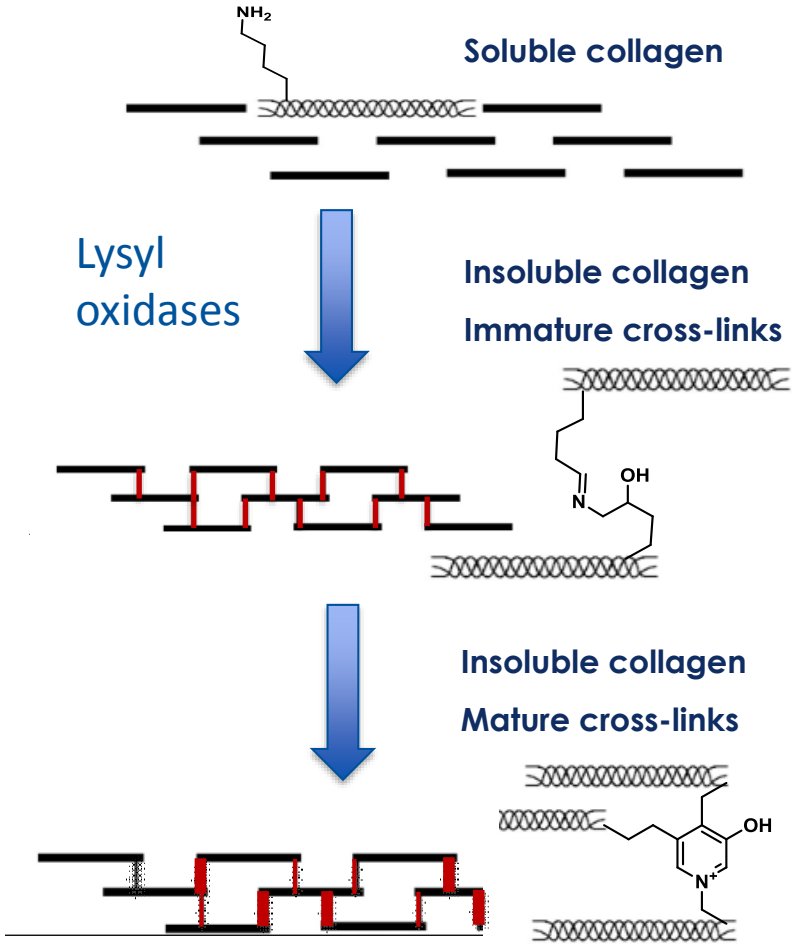
Role of lysyl oxidase enzymes in genesis of fibrotic tissue





Tissue stiffening due to increases in collagen and number of cross-links is preventable through lysyl oxidase inhibition → at the heart of a true anti-fibrotic therapy

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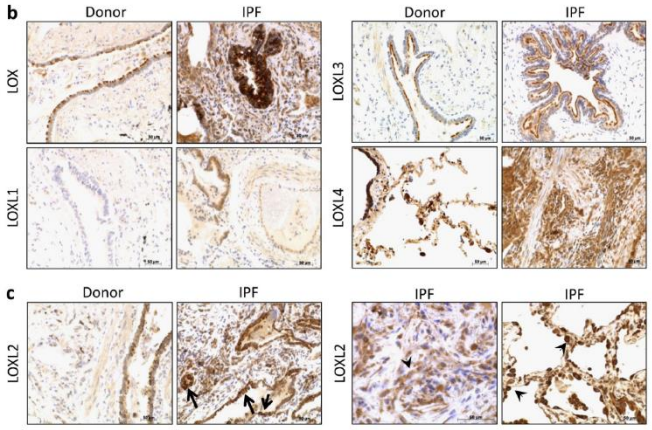
Expression of LOX family members in IPF

Comparative analysis of lysyl oxidase (like) family members in pulmonary fibrosis

Verena Aumiller[1], Benjamin Strobel[2], Merrit Romeike[1], Michael Schuler[2], Birgit E. Stierstorfer[2] & Sebastian Kreuz[1]

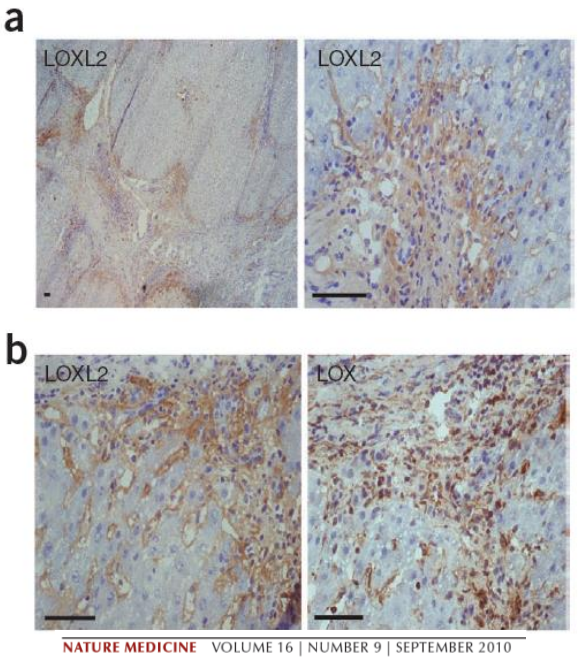


SCIENTIFIC REPORTS | 7: 149 | DOI:10.1038/s41598-017-00270-0

"In summary, we provide the first systematic comparison of lysyl oxidase expression in experimental and clinical pulmonary fibrosis and their functional involvement in fibroblast to myofibroblast transition in vitro.

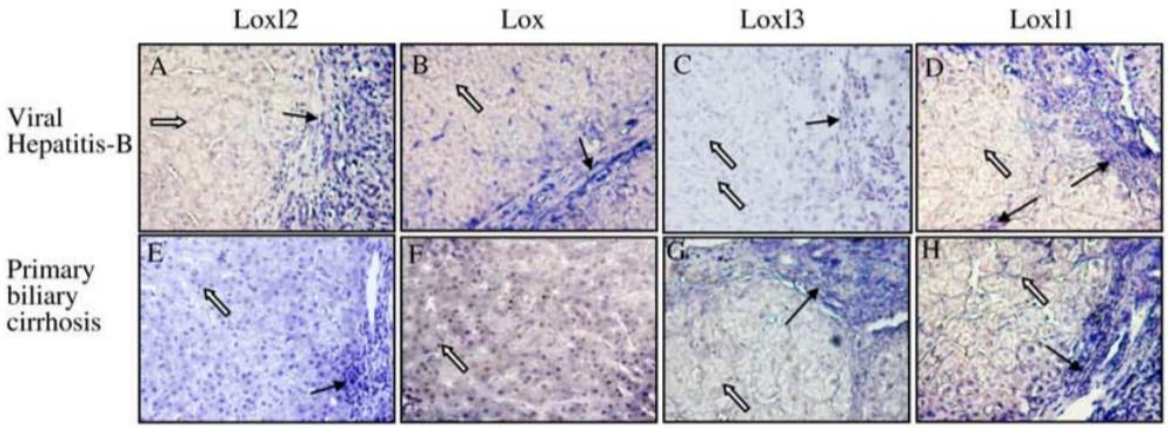
Our results point towards an outstanding role of LOXL2 among the other lysyl oxidase family members, which seem to have partial redundancy in fibrotic tissue remodelling."

Expression of LOXL2 in liver fibrosis



NATURE MEDICINE VOLUME 16 | NUMBER 9 | SEPTEMBER 2010

a Hepatatitis C
b steatohepatitis



Z. Vadasz et al. / Journal of Hepatology 43 (2005) 499–507

Serum lysyl oxidase-like-2 (sLOXL2) levels correlate with fibrosis stage in patients with nonalcoholic steatohepatitis (NASH)

Author(s): Stephen A. Harrison, Zachary D. Goodman, Vlad Ratziu, Rohit Loomba, Anna Mae Diehl, Eric Lawitz, Holger Hinrichsen, Kiran Bambha, Manal F. Abdelmalek, Robert Paul Myers, Raul Eduardo Aguilar Schall, Mani Subramanian, John G McHutchison, Nezam H. Afdhal, Andrew J Muir

Strong rationale for role of LOXL2 and LOXL3 in liver fibrosis.
Serum LOXL2 is a biomarker.

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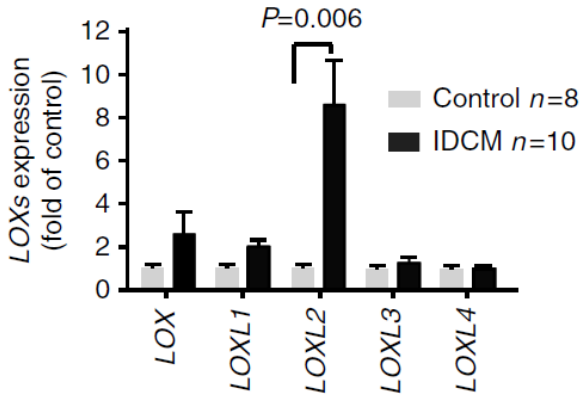
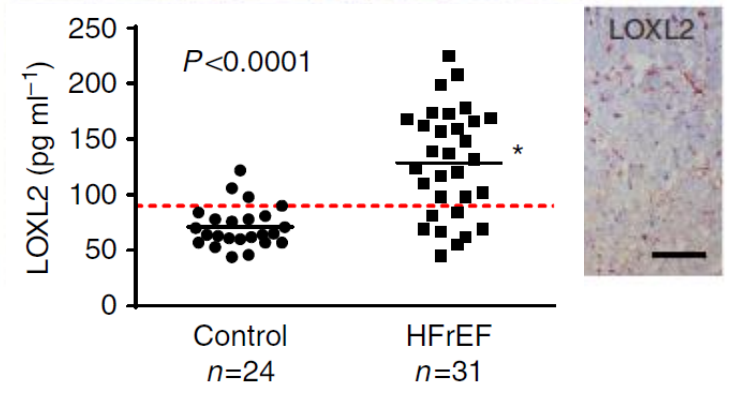
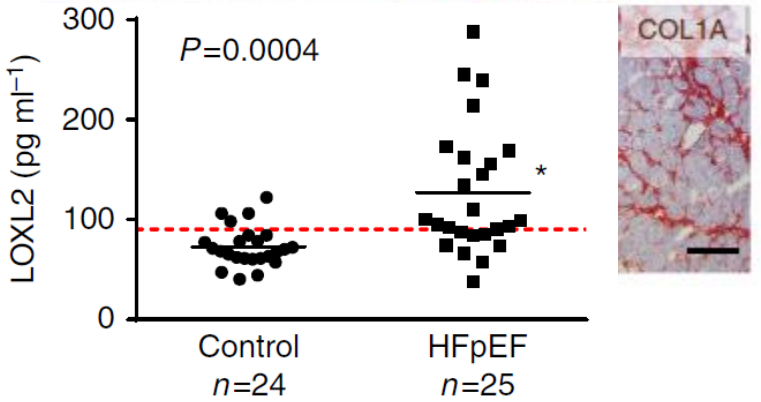
Expression of LOX family members in cardiac fibrosis







Yang et al, NATURE COMMUNICATIONS | 7:13710 | DOI: 10.1038/ncomms13710

Strong rationale for role of LOXL2 in cardiac failure.
Serum LOXL2 is a biomarker.

HFr(p)EF: Heart Failure with Reduced (Persistent) Ejection Fraction
IDCM: Idiopathic Dilated Cardiomyopathy

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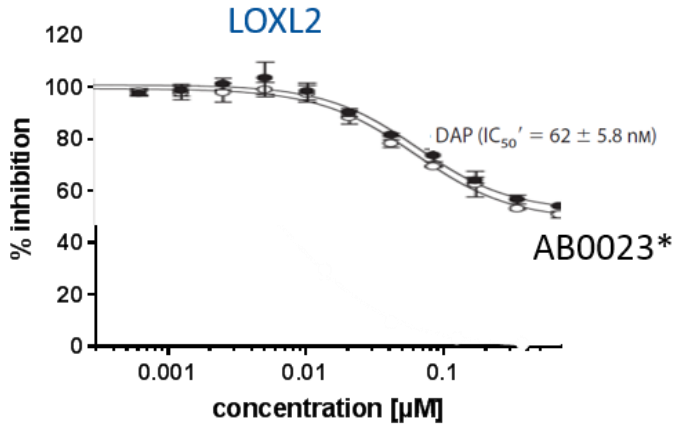
The Competition for "Best in Class" LOXL2 inhibitor

- Gilead
  - Acquired Arresto 2010 for LOXL2 antibody; simtuzumab
  - Completed 5 phase 2 studies
- Pharmakea
  - Celgene spin out
  - Phase 1 complete
  - 6/9 month tox



*Arresto data (*J Biol Chem* **2010**, *285*, 20964)

Table 3. Average human plasma drug concentrations and percent target engagement (TE) after a single oral dose of Compound **1-13a**.

Dose	**150 mg**		**450 mg**		**1000 mg**		**Placebo**	
Time post-dose	2 hour	24 hour	2 hour	24 hour	2 hour	24 hour	2 hour	24 hour
Ave plasma Cmpd **2** conc (nM)	966	BLOQ	4382	3.5	12855	8.0	0	0
Ave plasma %TE	62%	20%	78%	-13%	92%	1%	15%	5%

Healthy human subjects (male and female) were dosed with compound 2 in solution. Blood samples were drawn at regular intervals and the plasma isolated and analyzed for compound **1-13a** concentration as well as LOXL2 target engagement. Placebo data is the average of all the placebo subjects in the single dose study (n=10).

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Pharmaxis has developed a very sensitive (LLOQ 1 pg/mL) LOXL2 protein concentration assay for human serum and plasma

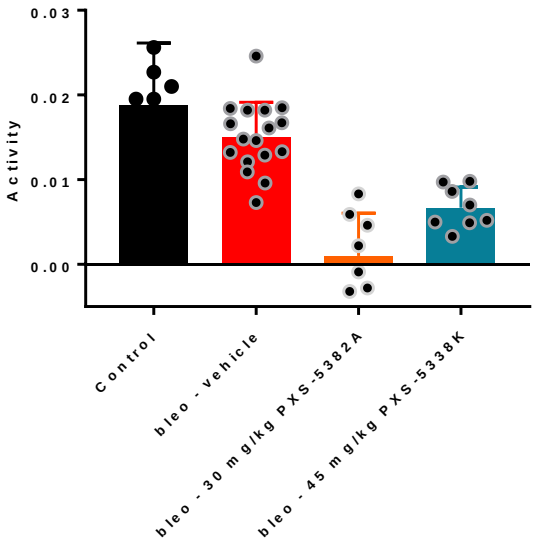
This assay can be also applied to rodent plasma, serum and some tissues

The quantifiably best in class LOXL2 inhibitor

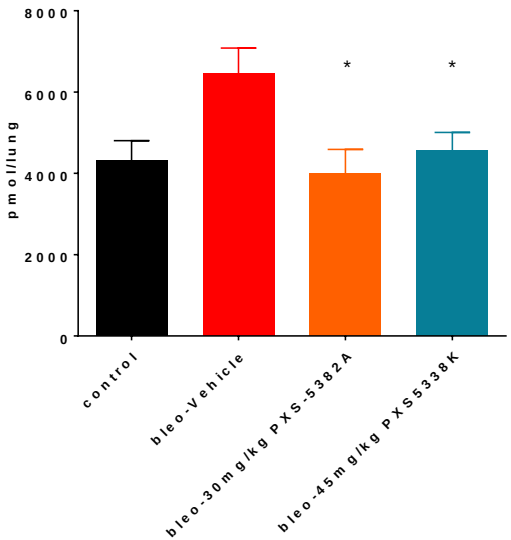
Bleomycin-induced lung fibrosis

Bleomycin-induced mouse lung fibrosis, prophylactic once a day oral gavage
Western blots confirmed LOXL2 upregulation in lung (data not shown).

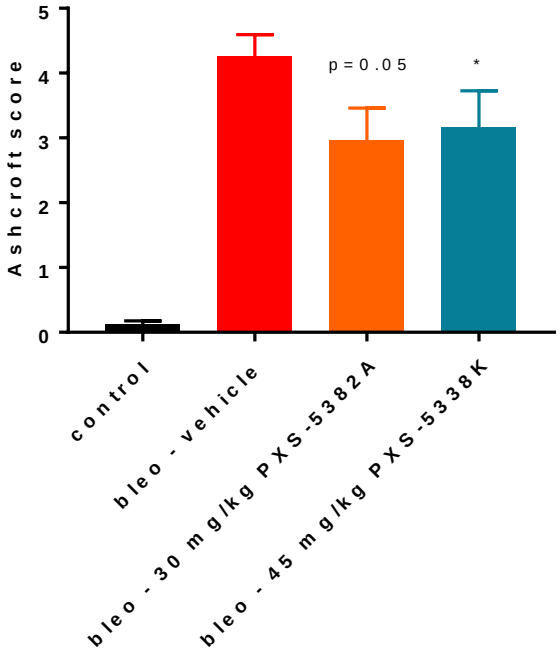
LOXL2/3 inhibitors reduce LOXL2 activity in serum



Cross-links in the lung are reduced by LOXL2/3 inhibitors



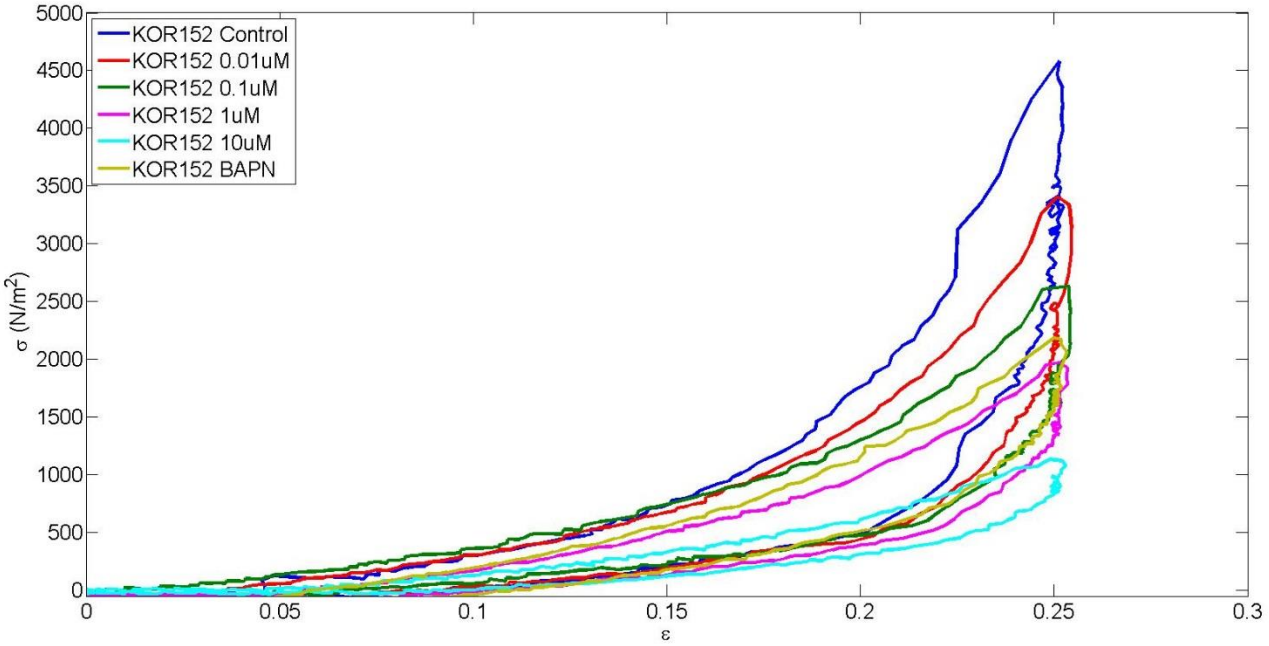
Ashcroft score is reduced by LOXL2/3 inhibitors

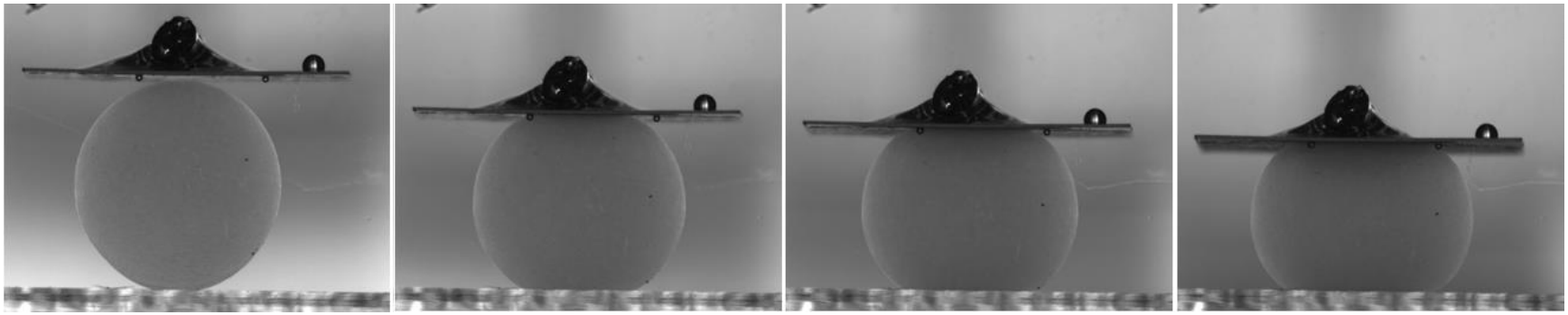


Biomarker shows target engagement → **Proof of mechanism in target tissue** → **Disease modification**

Treatment of *in vitro* cultures using cells from IPF patients reduces tissue stiffness

Tissue stiffness was assessed using a parallel plate compression system (CellScale Microsquisher)





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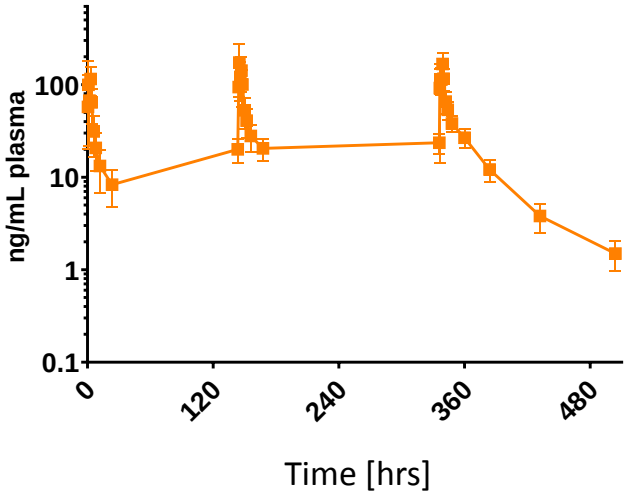
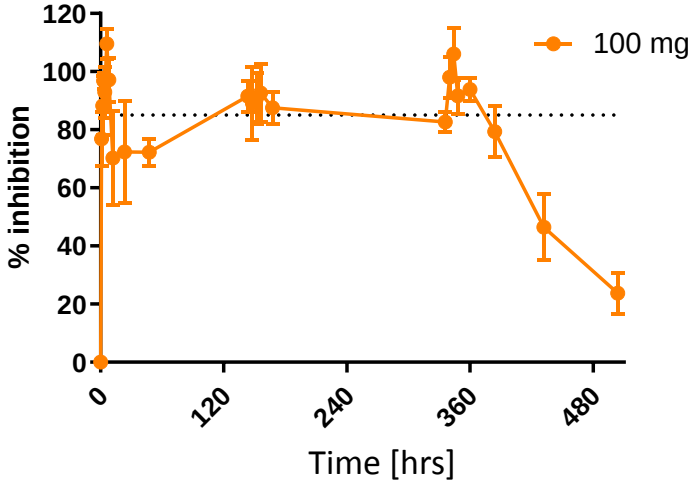
PXS-5382 - Target engagement in human phase 1b

Inhibition of LOXL2 enzyme was measured with bioprobe assay in serum





Pharmacokinetic shows long half-life good exposure
Repeated dosing resulted in >85% enzyme inhibition 24 hrs after last dose from Day 7 onwards.

Gilead's LOXL2 Antibody Simtuzumab

A problem or an opportunity?

- Great expectations in the scientific and medical community
- Subsequently, simtuzumab failed in 5 clinical trials

Gastroenterology 2018;155:1140–1153

Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis

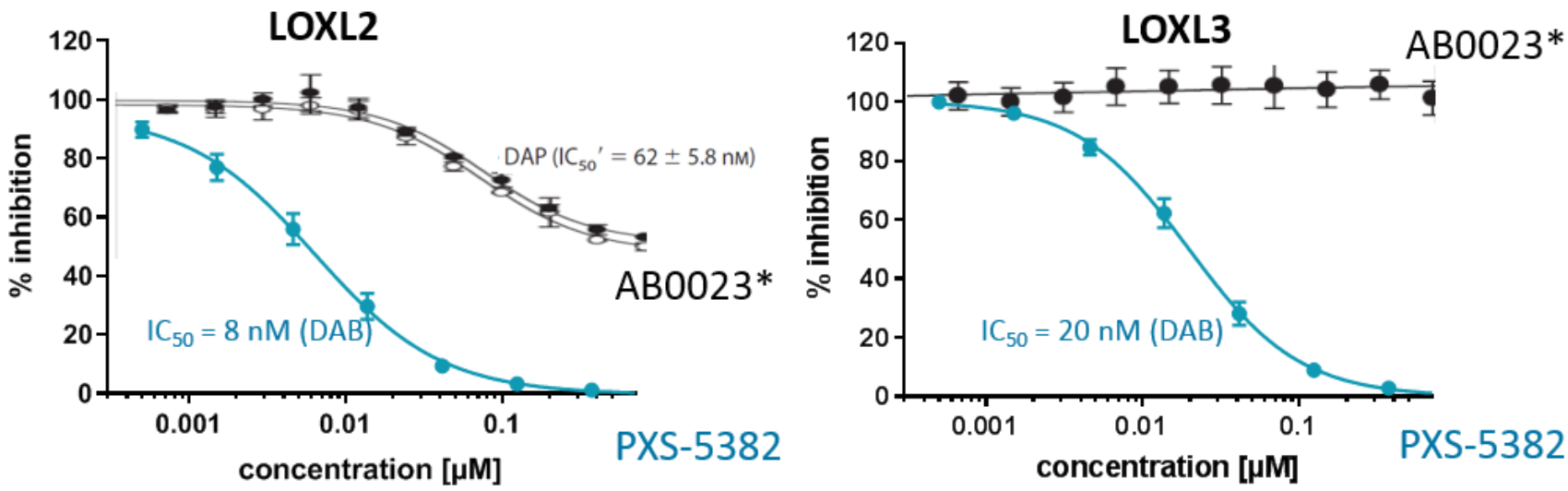
Lancet Respir Med 2017; 5: 22–32

Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial

- However: The study has potential limitations. The absence of a human pharmacokinetic or pharmacodynamic assay for LOXL2 inhibition limited our ability to confirm adequate target inhibition with this dosing regimen.

Pharmaxis has pharmacokinetic AND pharmacodynamic assays for LOXL2 inhibition AND we have confirmed target inhibition in humans as well as animal models

Comparison of Simtuzumab and PXS-5382



*Arresto data (*J Biol Chem* **2010**, *285*, 20964)

Relative to simtuzumab PXS-5382 shows;

- **significant potency, achieving complete enzyme inhibition**
- **efficacy against LOXL3**
- **good tissue/cell penetration**

Inhibition has been measured in a standard Amplex Red (H_2O_2 production measurement) assay using similar conditions.

Pharmakea drug has short half life

Applicant: PHARMAKEA, INC.

(10) International Publication Number
WO 2018/048928 A1

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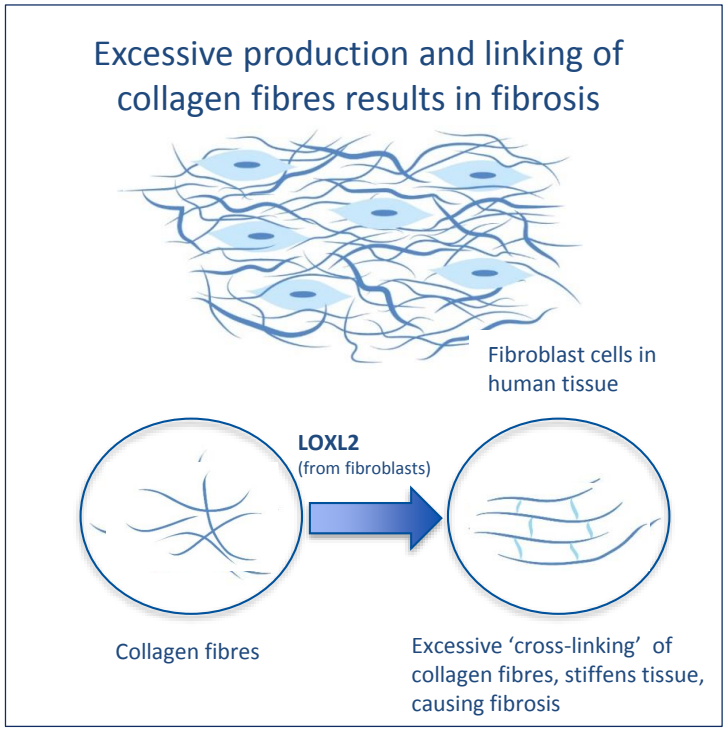
Pharmakea's compound does not show long lasting inhibition of LOXL2

LOXL2 inhibition program in partnering process

for NASH, IPF & other high value fibrotic diseases



Potential indications / market size:

- NASH / Liver Fibrosis; $35b[1]
- Pulmonary fibrosis (IPF); $3.5b[2]
- Kidney fibrosis
- Cardiac fibrosis

Significant market opportunity

- LOXL2 and fibrosis
  - LOX family of enzymes catalyse the final step in the fibrotic disease process
  - Clear association of increased levels of serum LOXL2 with disease progression in IPF, NASH and cardiac fibrosis
- Competitive profile
  - Novel target and mechanism of action
  - Once daily oral drug
  - Best in class drug with high level inhibition of LOXL2 enzyme for 24 hours from one dose in phase 1 studies
  - 13 week tox studies (2 species) for both compounds
  - Only known drug in clinical development to also inhibit LOXL3
  - Place of LOXL2 at the end of the fibrotic cascade provides opportunity to treat various fibrotic diseases and use in combination with other Pharma pipeline drugs

1. Deutsche Bank market forecast for 2025
2. iHealthcareanalyst. Inc market forecast for 2021

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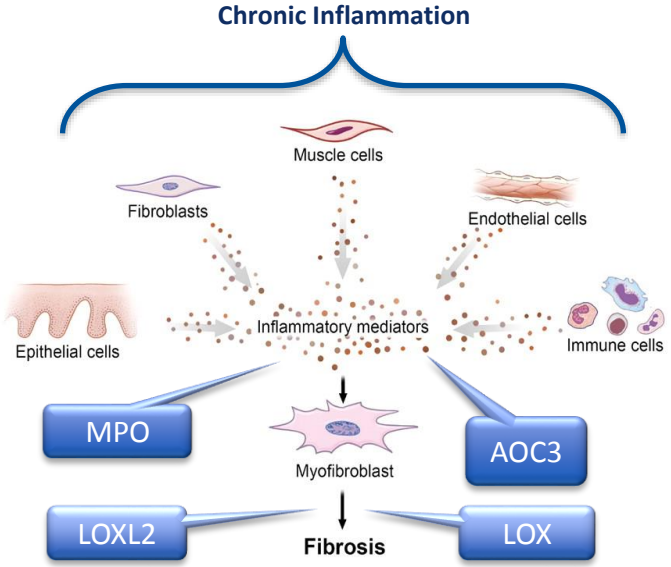
Global leaders in amine oxidase enzyme inhibition

Two new drugs expected to start proof of efficacy studies in 2020

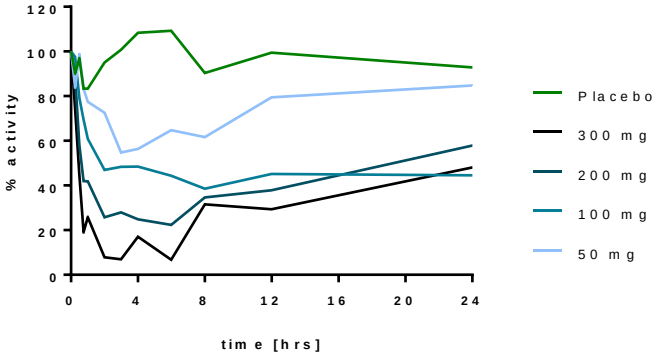
Targeting multiple different pathways



- **Highly productive;**
  - 1 compound partnered (AOC3)
  - 2 compounds partner ready (LOXL2)
  - 2 compounds phase 2 ready in 2020 (Systemic and topical LOX)
- R&D tax credit funds a significant share of expenditure (43.5% of eligible expenditure subject to $20m total revenue cap)

Systemic LOX Inhibitor

- Completed phase 1a – excellent PK/PD profile
- Predicted 24 hour inhibition of LOX with single daily dose
- Two indications with strong academic and clinical advocacy; Myelofibrosis and Pancreatic Cancer
- Phase 1b to report in Q1 2020
- Proof of efficacy studies to commence in H2 2020



Dose dependent reduction in LOX activity in plasma (phase 1a)

Topical LOX Inhibitor

- Compelling pre clinical efficacy in skin fibrosis / scarring models
- Limited competition and strong clinical advocacy
- Pre clinical tox studies to complete in Q1 2020
- Proof of efficacy studies to commence in H2 2020

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Key catalysts targeted for 2019/2020

Pharmaxis value driving events

1. **Boehringer Ingelheim acquired AOC3 inhibitor to report clinical proof of concept**
   - Phase 2a NASH study in 114 patients for 3 months - last patient last visit complete. Phase 2a clinical trial result and commercial assessment to progress to Phase 2b due from BI - Q4 2019
   - Phase 2a diabetic retinopathy study in 100 patients for 3 months - >50% recruited Clinical and commercial assessment due from BI - mid 2020
2. **LOXL2 anti fibrotic program**
   - Partnering process to conclude - H2 2019
3. **Mannitol Business (Aridol & Bronchitol) to turn profitable in 2020**
   - US - FDA to complete review H1 2020; if approved - launch milestone US$10m
   - Sales growth in existing and new territories expected to continue

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