



R&D Showcase Webinars

Pharmaxis drug PXS-5505  
targeting several cancers

**pharmaxis**

developing breakthrough treatments for fibrosis and inflammation

Investor Presentation | 29 March 2022

## 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 developing or partnering any of the 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.

## Program

11.00	Welcome and introduction to program	Michael Woods
11.05	Introduction to Pharmaxis research and clinical development program	Dr Wolfgang Jarolimek Gary Phillips
11.15	The myelofibrosis landscape and MF-101	Dr Gabriela Hobbs (Massachusetts General Hospital)
11.45	Hepatocellular cancer and Rochester University investigator led study	Dr Paul Burchard (Rochester NY)
12.15	Pancreatic Cancer	Dr Tom Cox (Garvan Sydney)
12.40	Pharmaxis Q&A	Gary Phillips
13.00	Close	

## Pharmaxis' portfolio of compounds in research and development

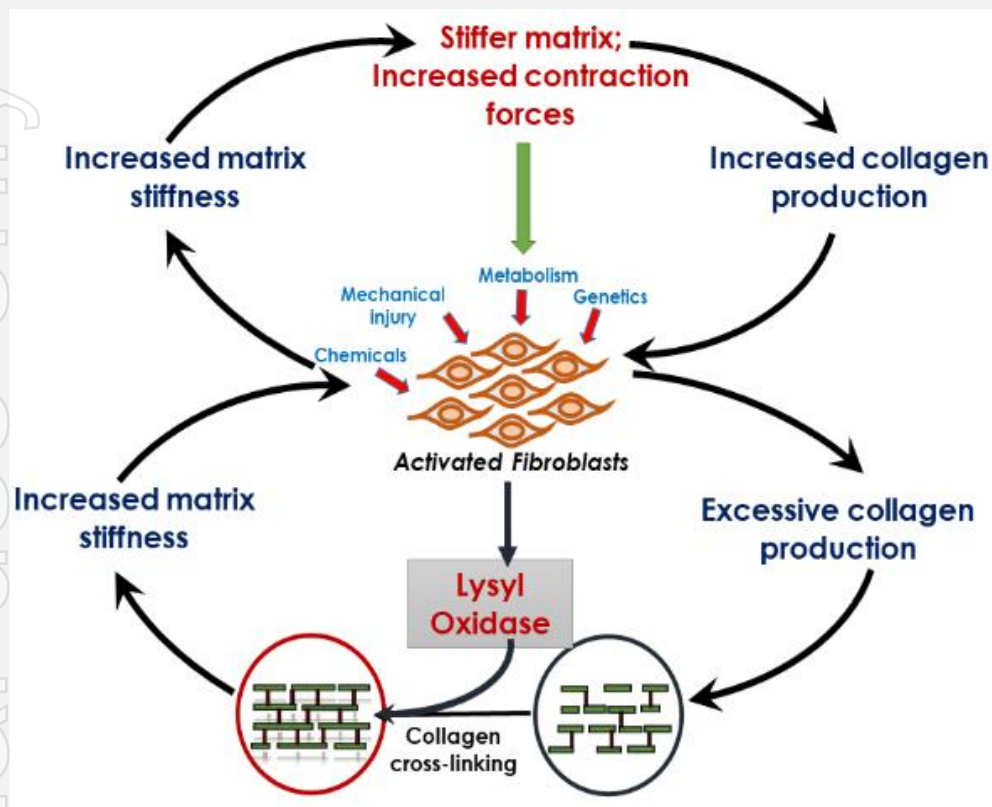
		Pre-clinical	Phase 1	Phase 2
<b>PXS-5505</b> Pan-LOX Inhibitor	Myelofibrosis			
	Myelodysplastic syndrome		Planning	
	Hepatocellular carcinoma			
	Fibrotic diseases/other cancer	Evaluation		
<b>PXS-6302</b> Pan LOX inhibitor	Established scars			
	Post surgical burns scarring	Planning		
<b>PXS-4728</b> SSAO Inhibitor	Neuroinflammation	Planning		
<b>PXS-5382</b> LOXL2 Inhibitor	Idiopathic pulmonary fibrosis Kidney fibrosis	Phase 1c ready		
<b>PXS-5370</b> SSAO/MPO Inhibitor	Lung inflammation	Phase 1 ready		
<b>PXS-4699</b> SSAO/MAO-B Inhibitor	Organ fibrosis and inflammation			
Enzyme Inhibitor	Inflammation			



# Pharmaxis is the global leader in lysyl oxidase chemistry and biology

Multi year research program leveraged with extensive scientific collaborations worldwide has delivered 2 drugs in the clinic

## Lysyl oxidases are the final stage in fibrosis



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

### ■ PXS-5505

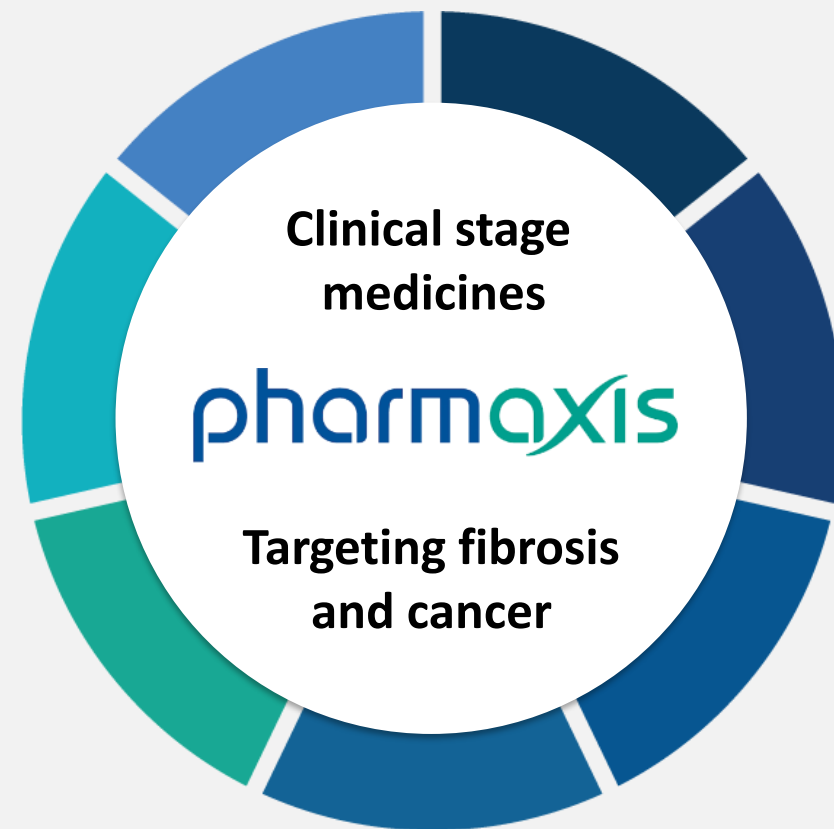
- Oral dosage form – twice a day dosing
- Patent 2018
- Strong pre clinical evidence in models of fibrosis and cancer
- INDs approved for myelofibrosis and hepatocellular carcinoma
- Potential in multiple cancer indications
- Phase 1 data demonstrates a safe, well tolerated drug that gives >90% inhibition of LOX enzymes

### ■ PXS-6302

- Topical dosage form – one application per day
- Patent 2019
- Strong pre clinical evidence in models of skin fibrosis and scarring
- Potential in prevention of scar formation and modification of existing scars
- Phase 1 data demonstrates a safe, well tolerated drug that gives full inhibition of LOX enzymes in the skin with minimal systemic exposure

## Executive Summary

- Pharmaxis is a clinical stage drug development company targeting fibrosis and cancer indications with first in class or best in class small molecule drugs in markets of high value
- Pharmaxis is the global leader in fibrosis driven by lysyl oxidase enzymes having invested in a multi year research program leveraged with extensive external scientific collaborations
- Pharmaxis has 4 studies planned for 2022 that will lead to near term value opportunities
  - Lead asset PXS-5505 is in a multinational phase 2 trial – a breakthrough clinical program with disease modifying potential in Myelofibrosis
  - IND approval to commence US investigator led phase 2 trial in liver cancer with PXS-5505 as first line treatment added to existing chemotherapy.
  - Topical drug PXS-6302 is in a phase 1c trial in patients with potential to improve function and appearance of established scars with a study in burns patients to follow later this year.
- Specific corporate strategy to deliver non-dilutive cash and cost savings from commercial stage mannitol business
- Pharmaxis is well positioned to fund its focused clinical program



# Four trials to deliver near term value

Pipeline creates multiple opportunities in high value markets

	Indication	Addressable market (US\$)	Trial design	# patients	Status	Data
PXS-5505	Myelofibrosis (MF)	\$1 billion	Phase 2 open label 6 month study in JAK intolerant / ineligible myelofibrosis patients	24	Recruiting	Year end 2022
	Hepatocellular Carcinoma (HCC)	\$7 billion	Phase 1c open label dose escalation study in newly diagnosed patients with unresectable HCC on top of standard of care (PD-L1 inhibitor + anti VEGF)	18	First Patient Q2 2022	2H 2023
PXS-6302	Modification of established scars	\$3.5 billion	Phase 1c 3 month placebo controlled study in patients with established scars (>1 year old)	50	Recruiting	Q4 2022
	Scar prevention post surgery	\$3.5 billion	Phase 1c 3 month placebo controlled study in patients with scarring subsequent to a burns injury	50	First patient mid 2022	1H 2023

The myelofibrosis  
landscape and MF-101  
Dr Gabriela Hobbs (MGH)



A Teaching Affiliate  
of Harvard Medical School

Gabriela Hobbs, MD

# MYELOFIBROSIS TREATMENT LANDSCAPE



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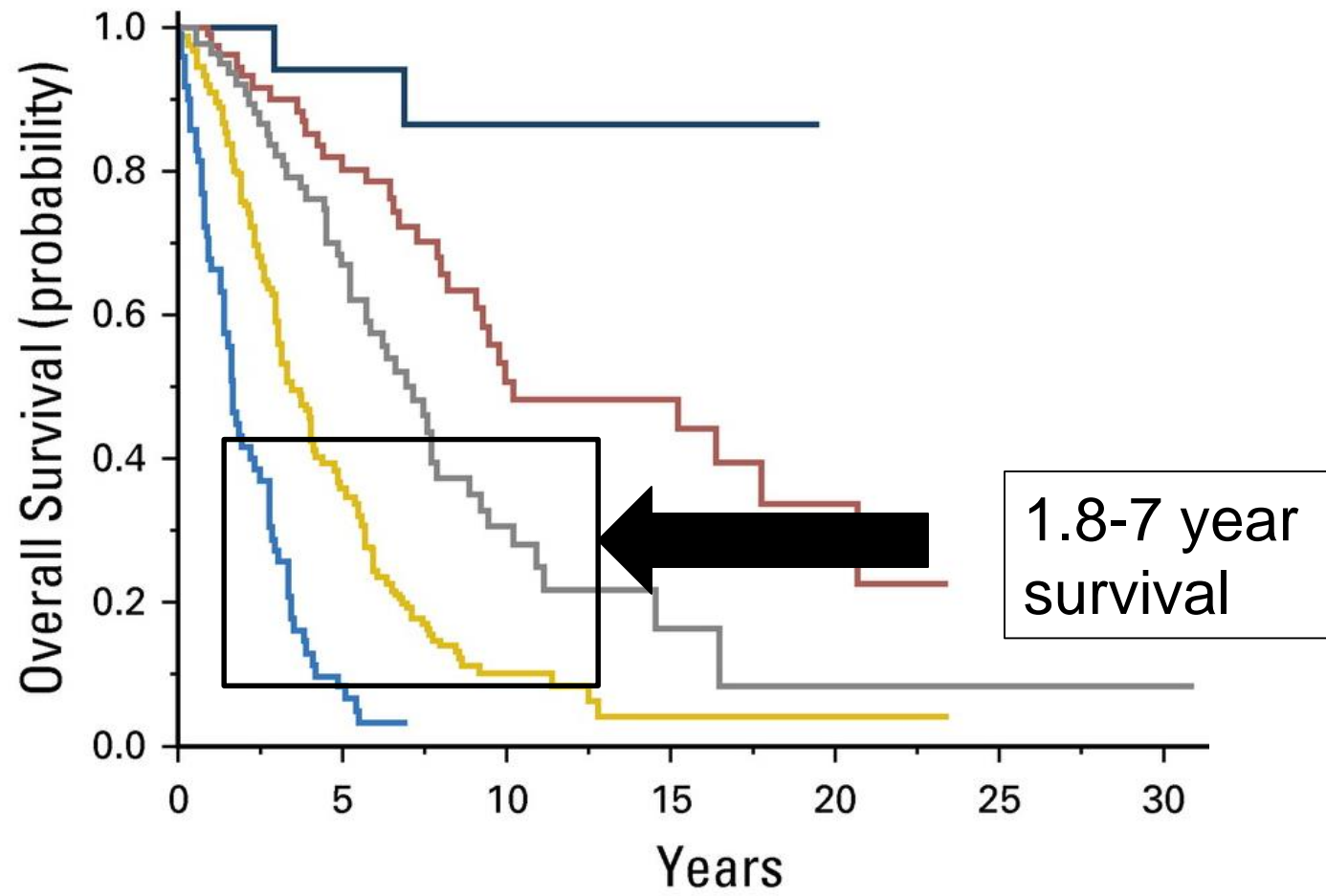
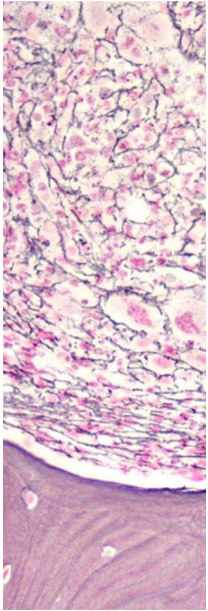
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# Outline

- What is myelofibrosis?
- Current treatment landscape
- Drugs in development
- Rationale for LOX inhibition in MF



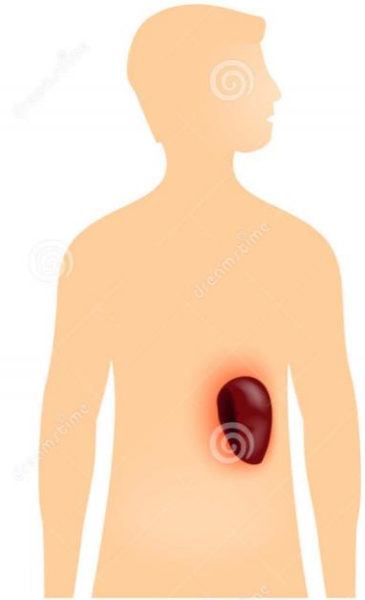
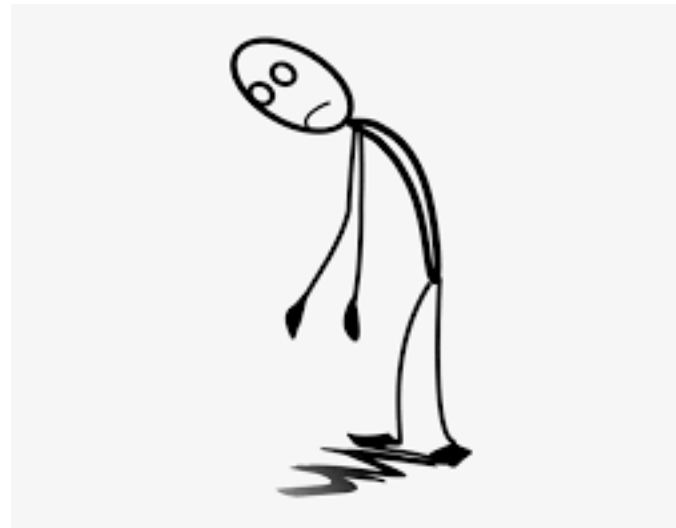
# Myelofibrosis





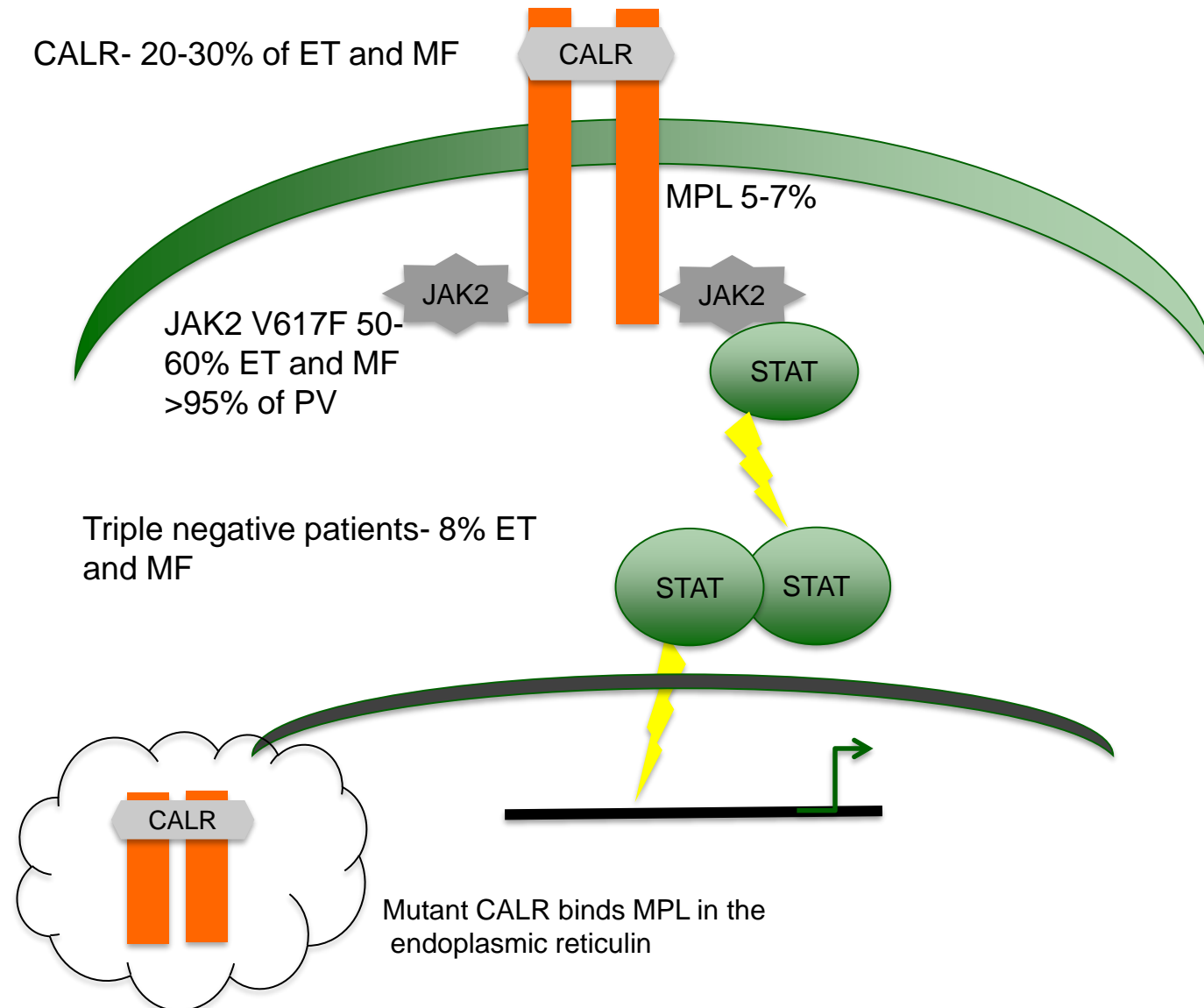
# Myelofibrosis epidemiology in the USA

18,000 people live with MF	Average age at diagnosis- 65	30% transform to leukemia	Most patients live with significant symptoms
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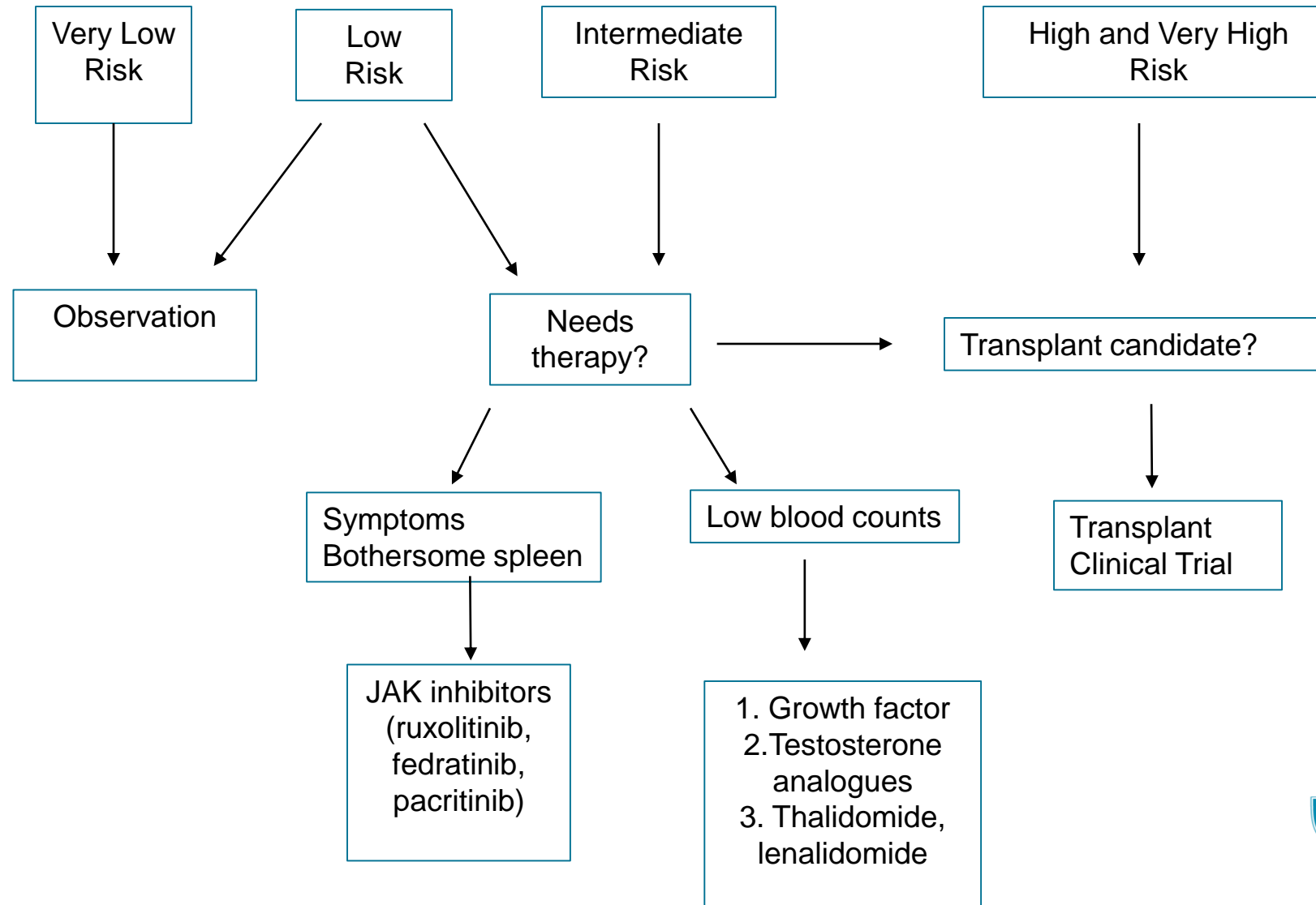


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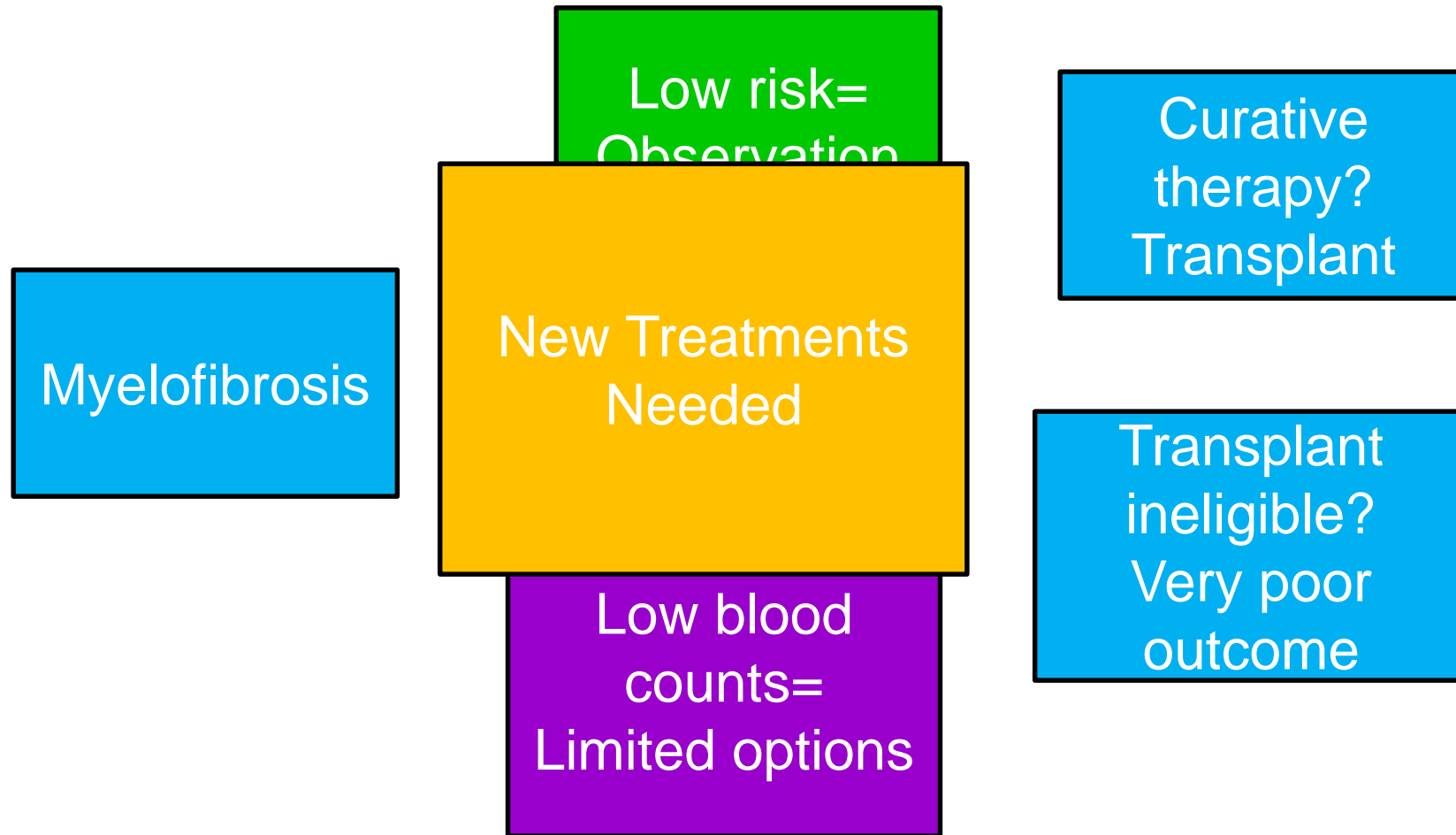
# Mutations in myelofibrosis



# Myelofibrosis Treatment Approach



# Myelofibrosis approach summary



# JAK Inhibitors- Pros and Cons

Pros	Cons
Symptom improvement	Decreased blood counts
Spleen size reduction	Does not alter disease progression
? Survival benefit	Response will eventually be lost
Improved quality of life	Outcome after Jakafi failure is poor



# Therapies in development

Agents	Class of drug	Trial
Palabresib + Rux	BETi	MANIFEST-2
Navitoclax + Rux	BCL2i	TRANSFORM1/2
Parsaclisib + Rux	P13Kd	LIMBER-313/304
Luspatercept + Rux	ActRII ligand trap	INDEPENDENCE
Pacritinib	JAKi/IRAK1	PACIFICA
Jaktinib	JAKi	
Momelotinib	JAKi	MOMENTUM
Fedratinib	JAKi	FREEDOM-2
Imetelstat	Telomerase inh.	IMpactMF

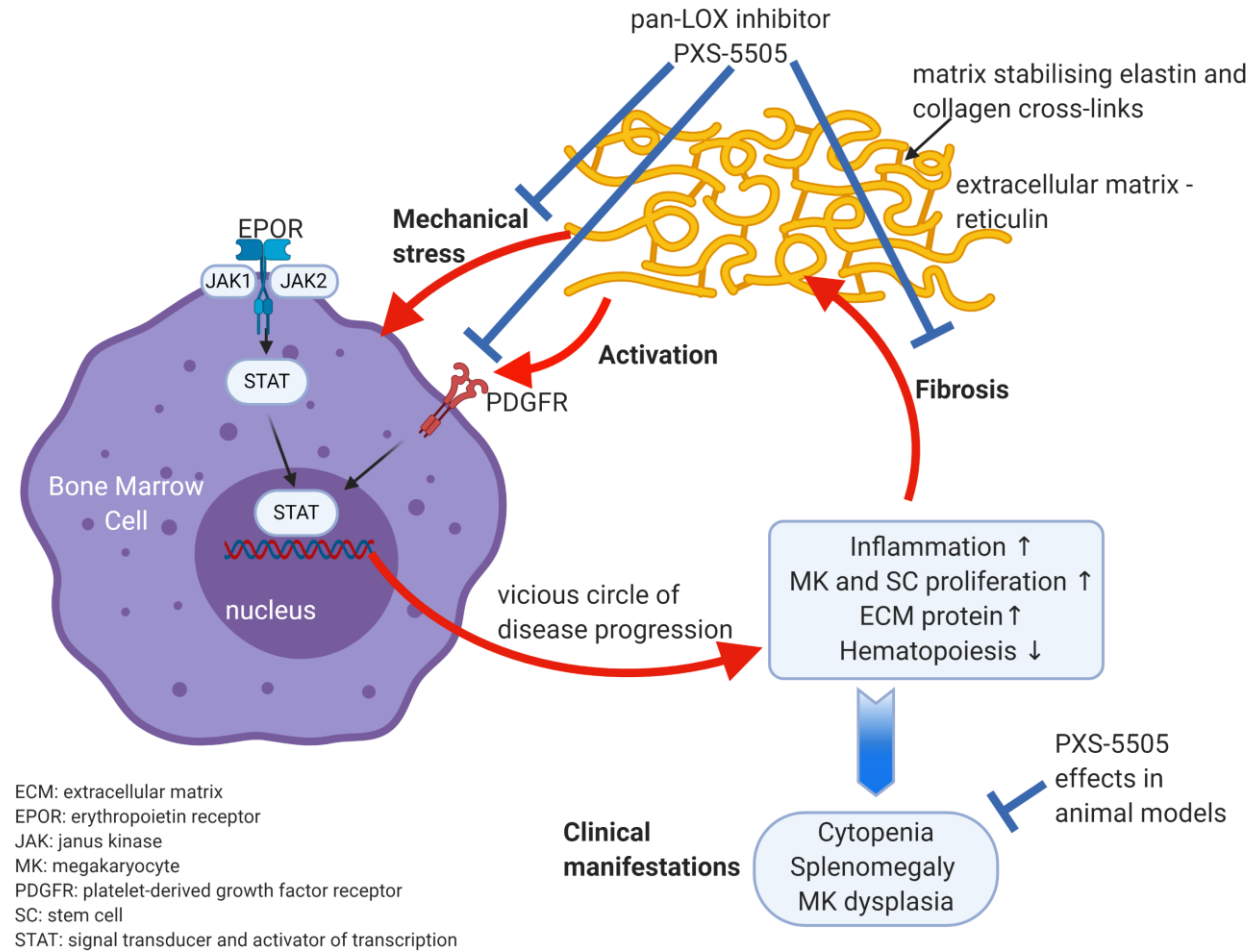


# The role of lysyl oxidase in Myelofibrosis

- Lysyl oxidases- important to making scar tissue
- There are 5 LOX enzymes in mammals
- In MF there is elevated expression of most of the LOX enzymes
- PX5-5505 is a pan-LOX inhibitor that is well tolerated without off-target activities (as seen in other LOX inhibitors)



# LOX in Myelofibrosis



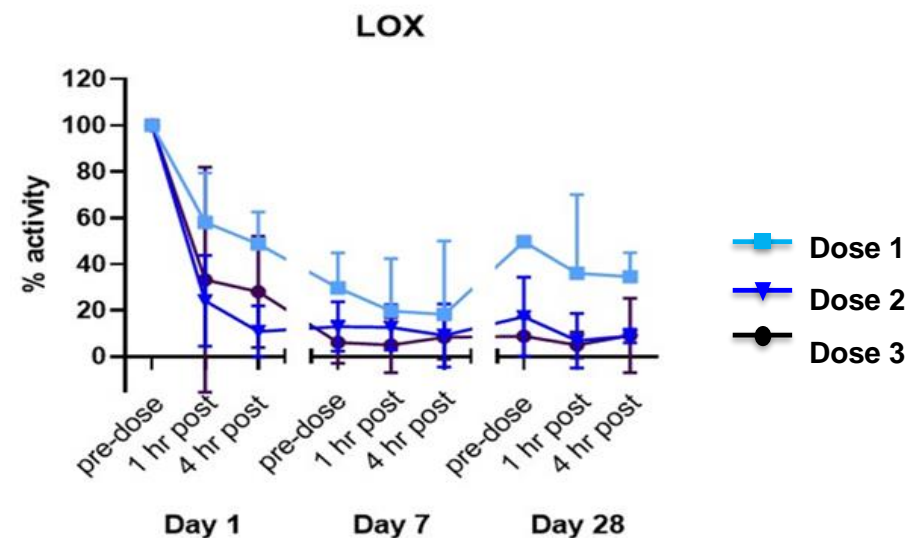
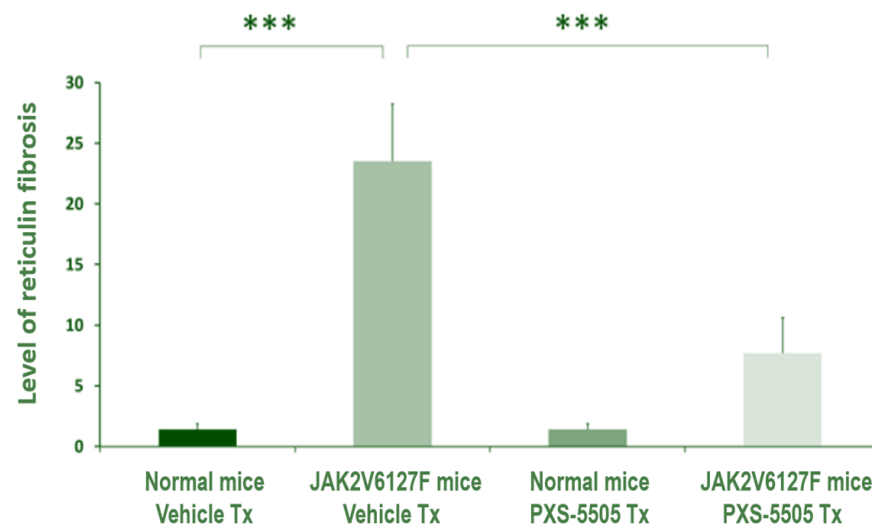
## • The central hypothesis:

Effective inhibition of LOX will prevent collagen cross-linking, reduce marrow fibrosis and allow normal hematopoiesis to resume. Normal hematopoiesis will result in normalization of blood counts and reduction in spleen size.



# PXS-5505 experience- Safe and effective LOX inhibitor

## PXS-5505 attenuates hallmarks of primary myelofibrosis in mice PXS-5505 – Phase 1c dose escalation in MF patients

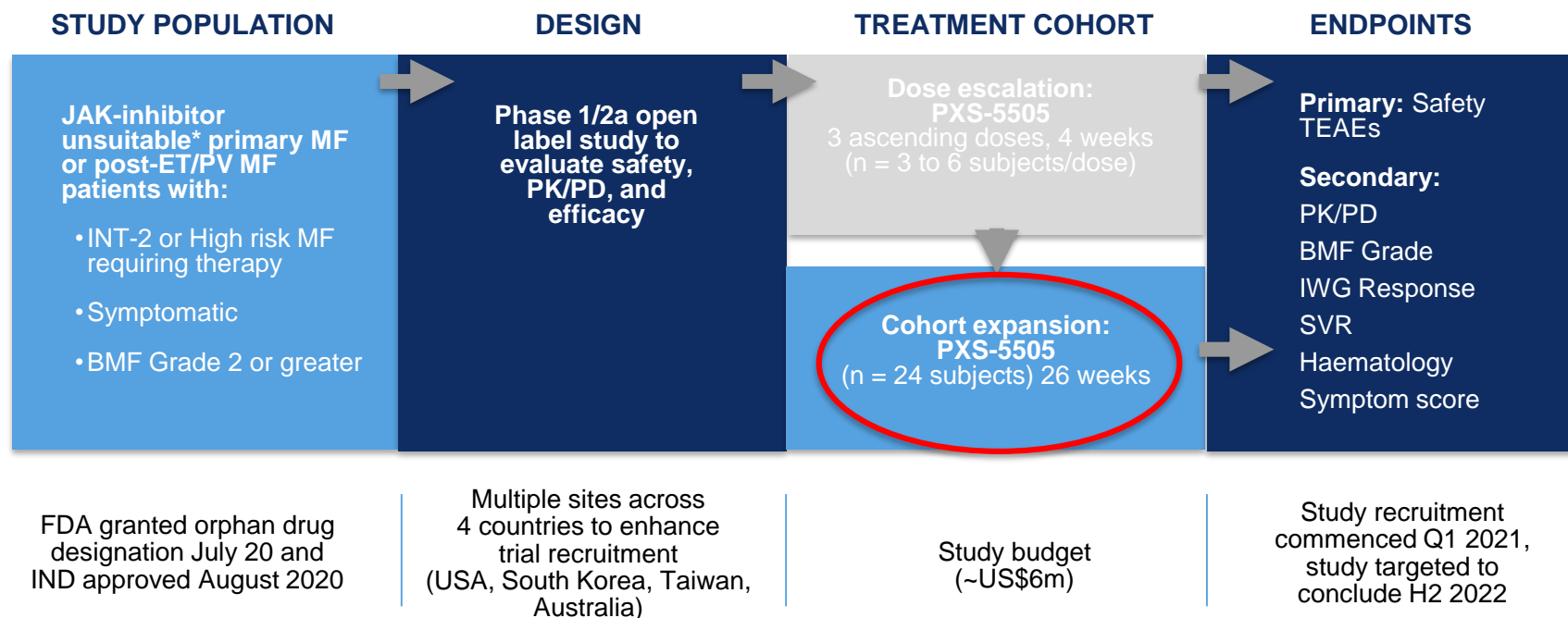


- Open label dose expansion in JAK-inhibitor unsuitable<sup>2</sup> primary MF or post-ET/PV MF patients
- Maximum of 3 patients on each dose for 28 days
- Good safety profile with no adverse events at highest dose
- >90% inhibition of LOX and LOXL2 at trough on highest dose at day 7 and 28



# PXS-5505 Phase 1/2a Trial in myelofibrosis

6 month monotherapy study with meaningful safety and efficacy endpoints (phase 1c complete)



\*Unsuitable = ineligible for JAKi treatment, intolerant of JAKi treatment, relapsed during JAKi treatment, or refractory to JAKi treatment. JAKi – Janus Kinase inhibitor, MF myelofibrosis, ET Essential Thrombocythaemia, PV polycythaemia vera, INT intermediate, BMF bone marrow fibrosis, RP2D recommended phase 2 dose, TEAE treatment emergent adverse event, PK pharmacokinetics, PD pharmacodynamics, SVR spleen volume response, IWG International Working Group Myeloproliferative Neoplasms

Thank you



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Hepatocellular cancer and  
Rochester University IIS  
Dr Paul Burchard  
(Rochester NY)

# **A Phase 1b/2 Trial of PXS-5505 Combined With First Line Atezolizumab plus Bevacizumab For Treating Patients With Unresectable Hepatocellular Carcinoma**

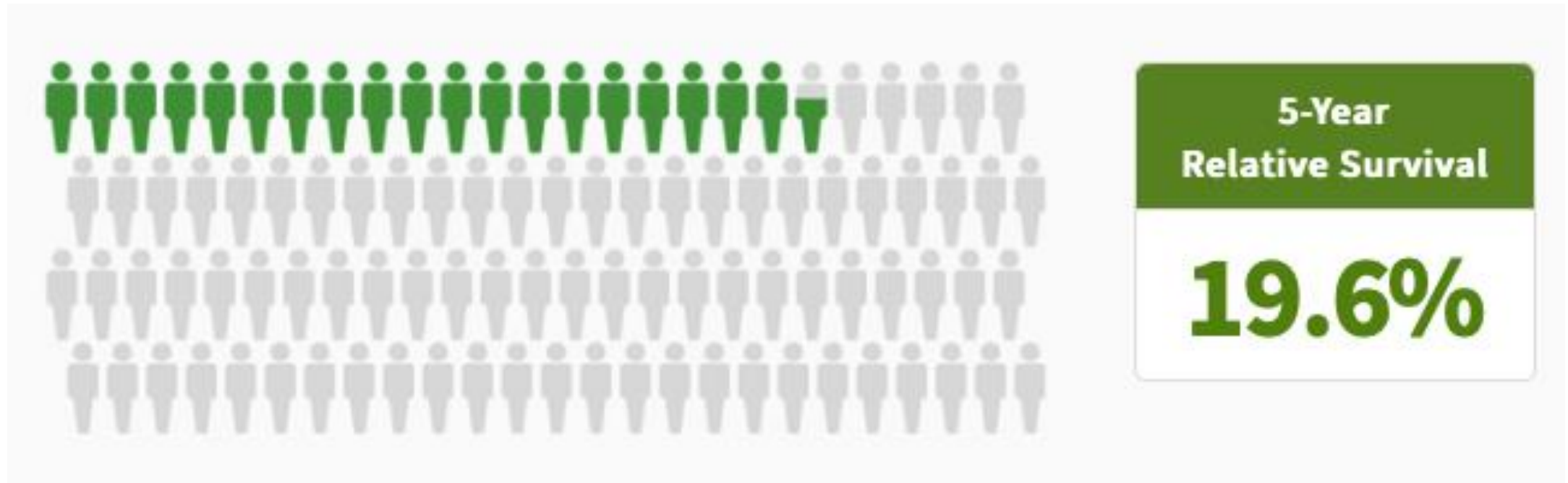
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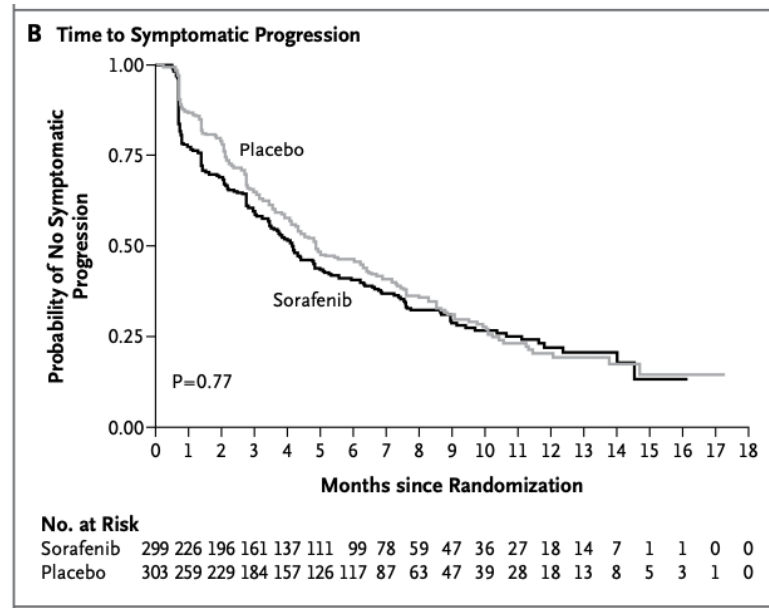
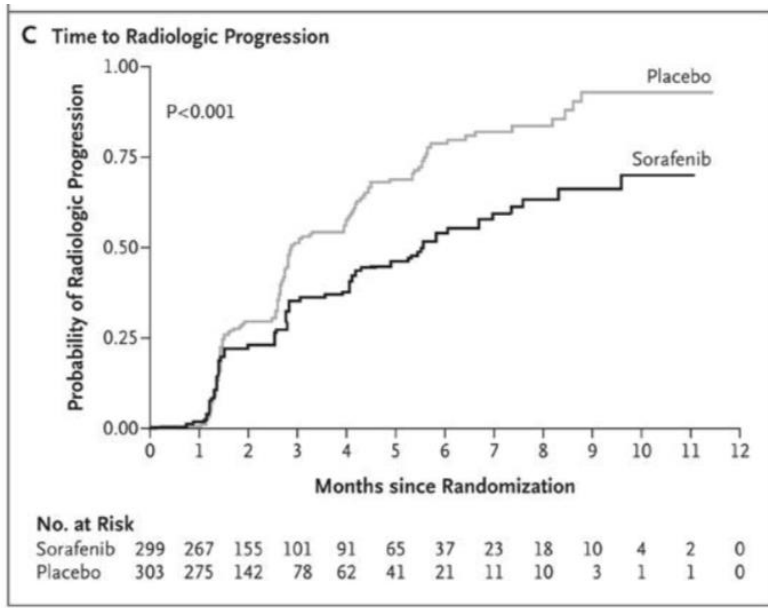
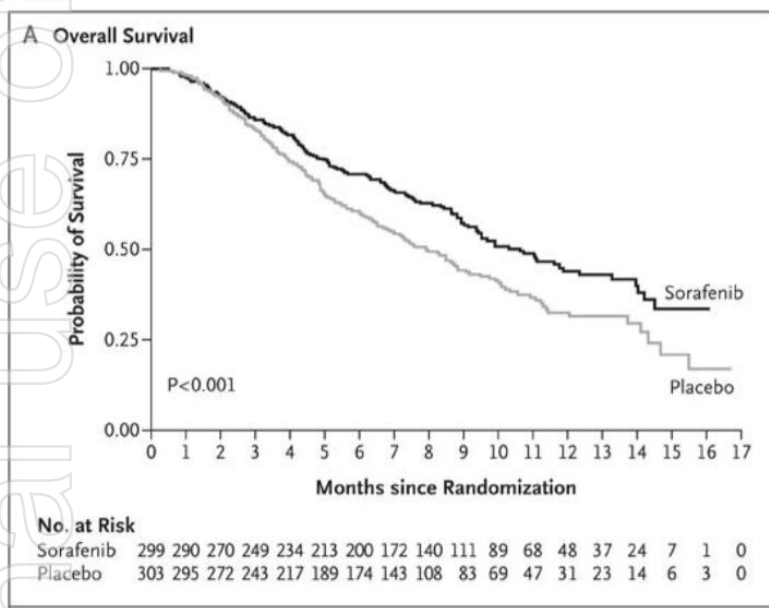
## Primary liver cancer incidence and deaths U.S.



Source: SEER Cancer Statistic Database, U.S. DHHS

# Resectability & Current Treatment Options

- Only 20-30% of cases resectable at presentation
- Sorafenib initial 1<sup>st</sup> line therapy

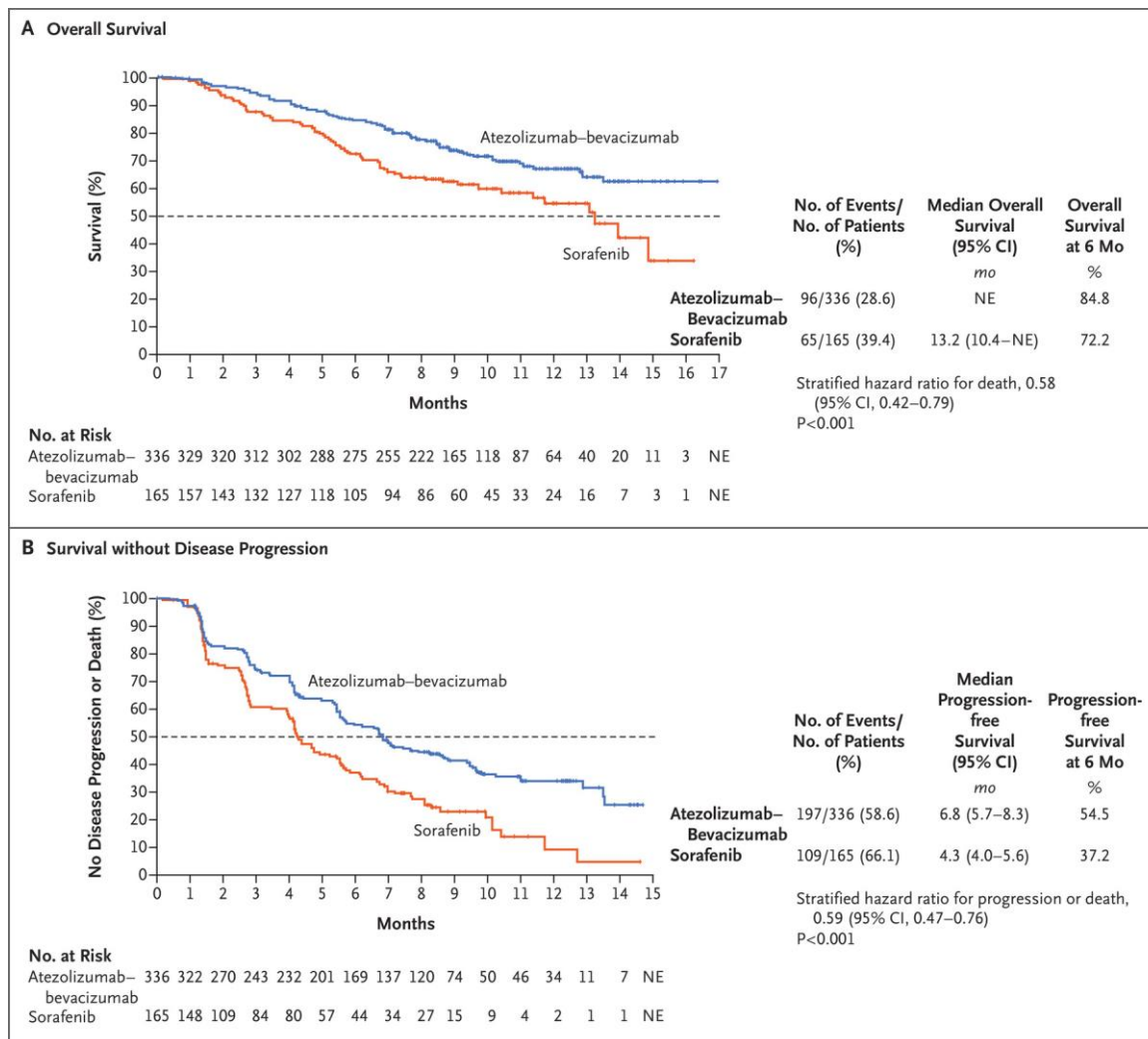


Llovet et al. NEJM 2008

# Resectability & Current Treatment Options

- **HIMALAYA:** Durvalumab (Anti-PDL<sub>1</sub>) & Tremelimumab (Anti-CTLA<sub>4</sub>)
- **IMBRAVE<sub>50</sub>:** Atezolizumab (Anti-PDL<sub>1</sub>) & Bevacizumab (Anti-VEGF) combination therapy now 1<sup>st</sup> line
- Replacing Sorafenib at many institutions

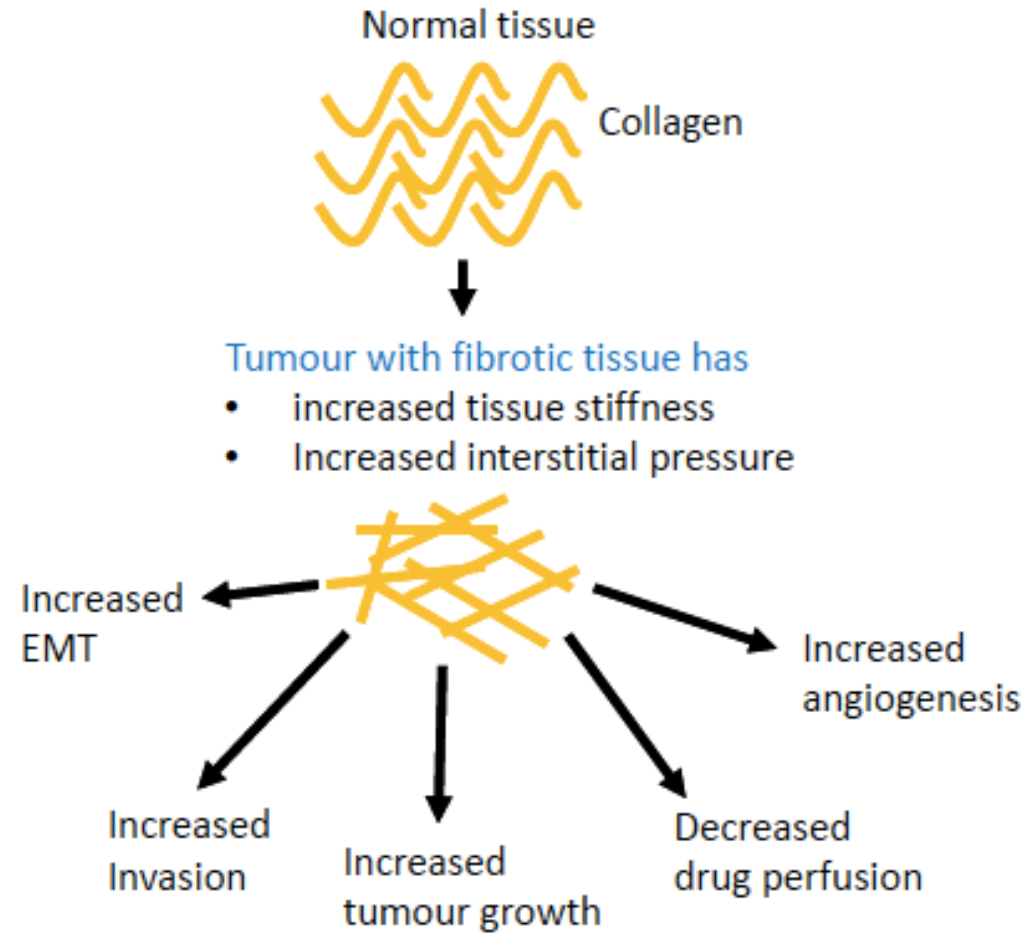
Finn et al. NEJM 2020



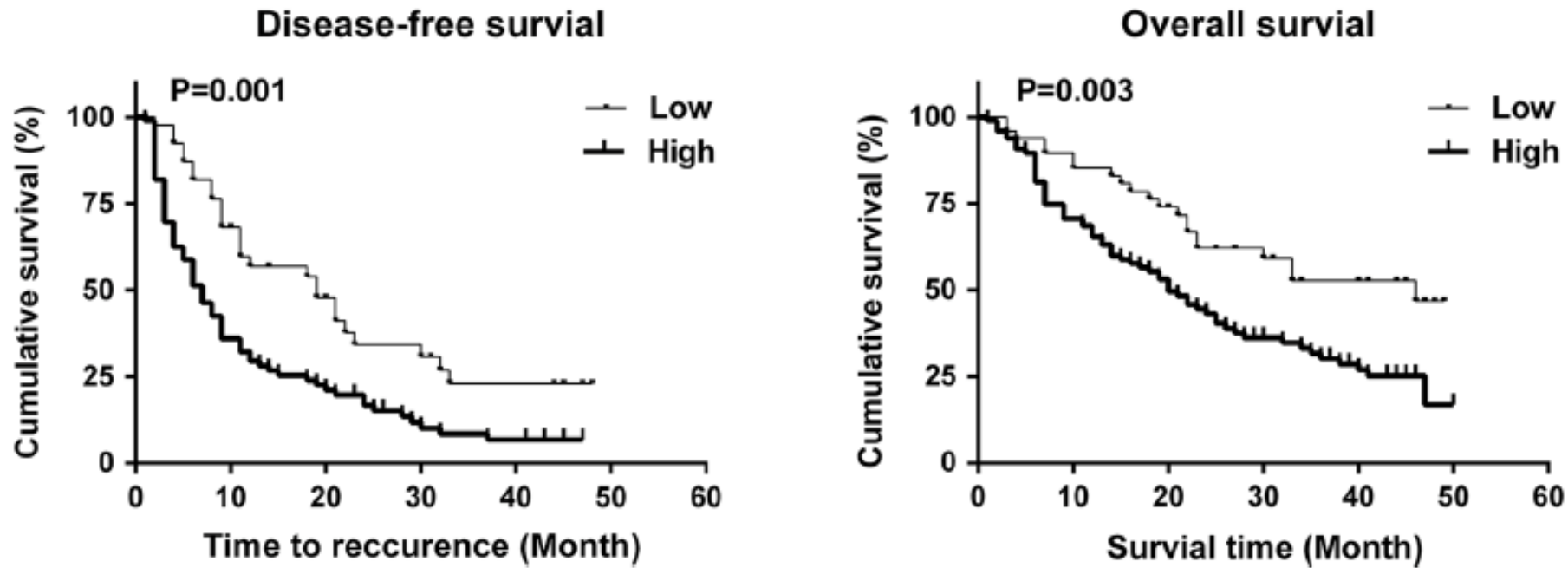
# Lysyl Oxidase (LOX)

## Conventional mechanisms of LOXs

- LOX
- LOXL1
- LOXL2
- LOXL3
- LOXL4



# LOX is associated with poor outcomes in HCC

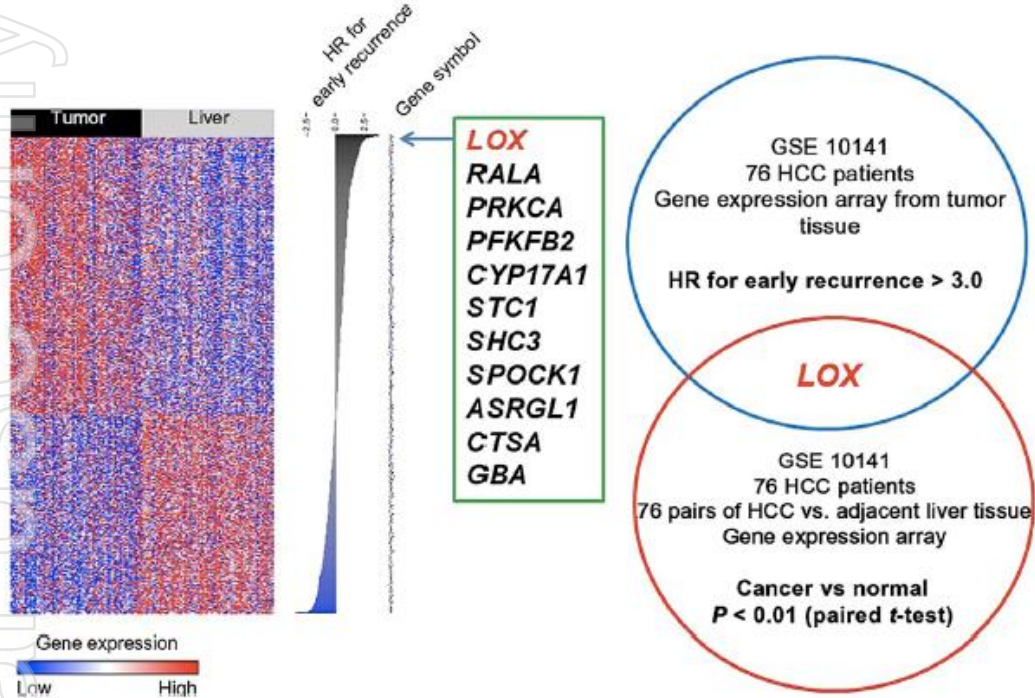


Zhu, et al. *Dig Dis Sci*, 2015

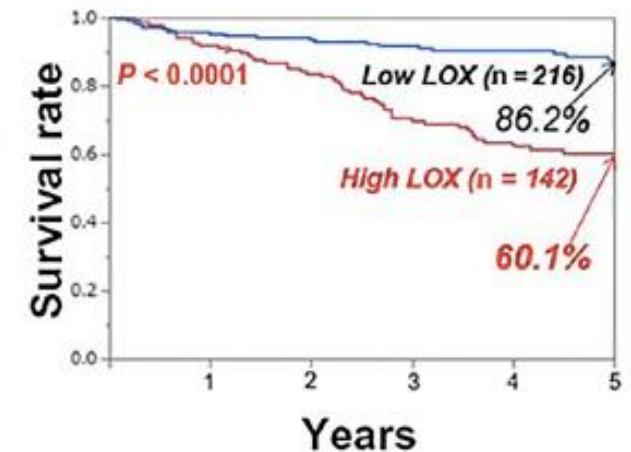
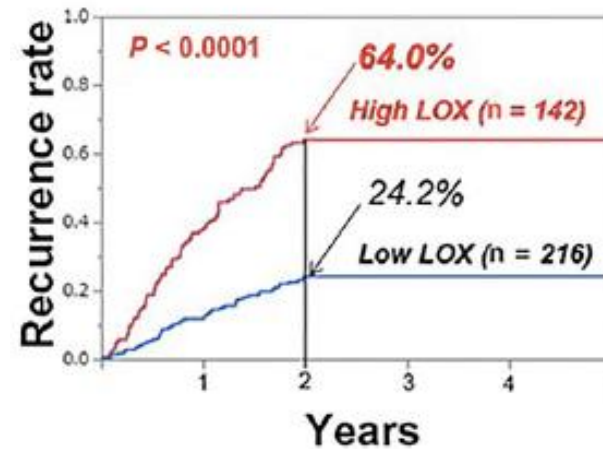


# LOX expression is associated with HCC metastases and recurrence

Gene expression HCC

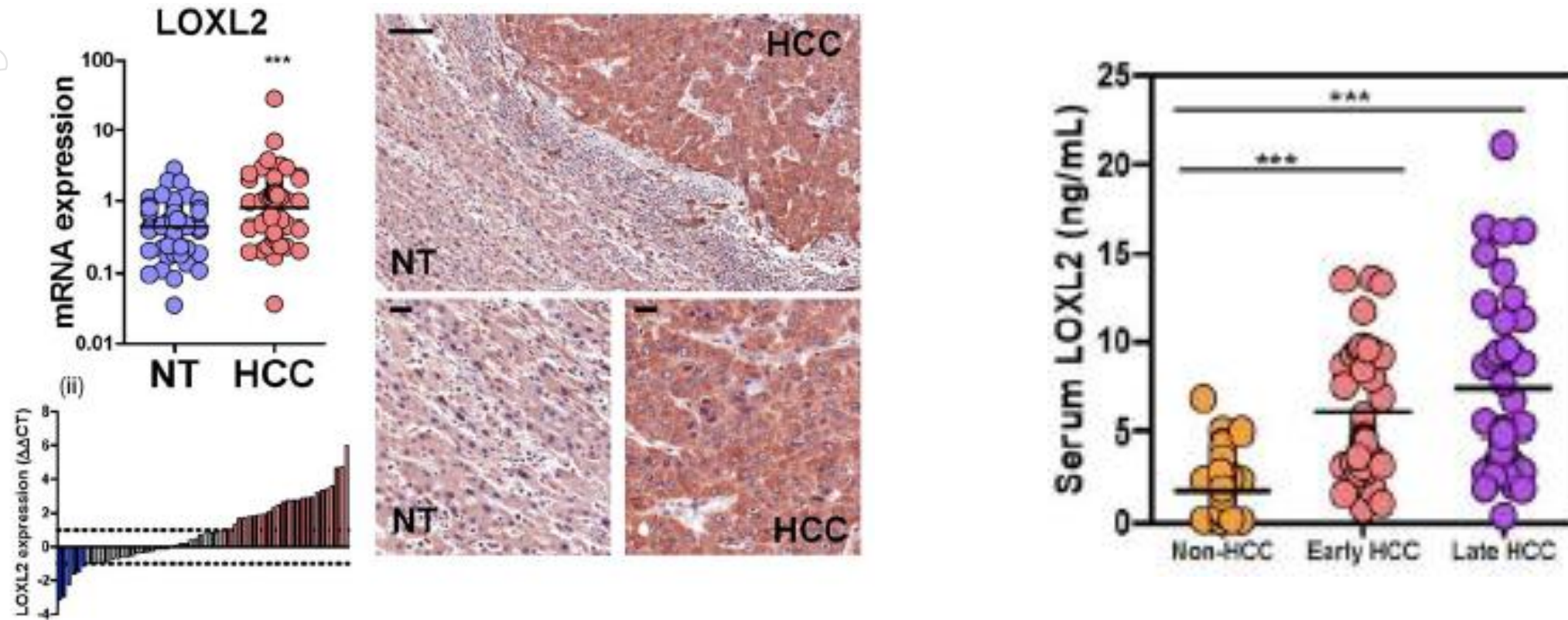


Recurrence & Survival



Umezaki et al. *Cancer Science*, 2019

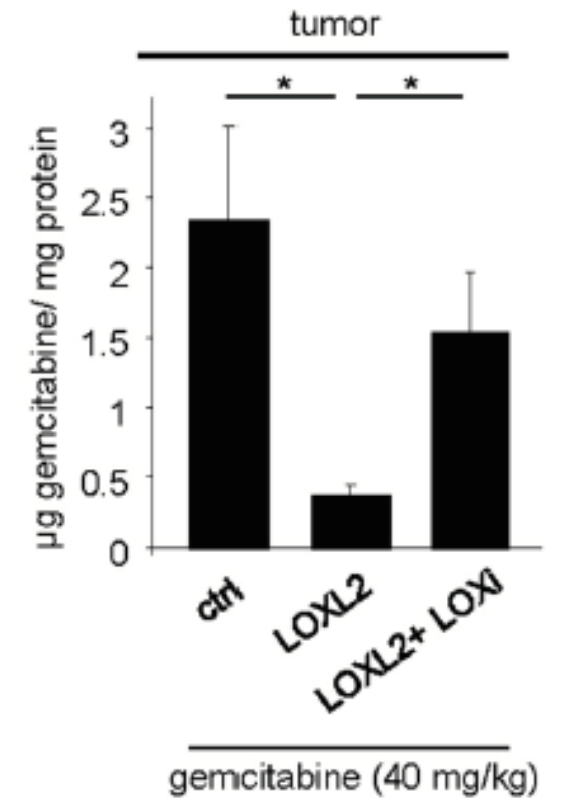
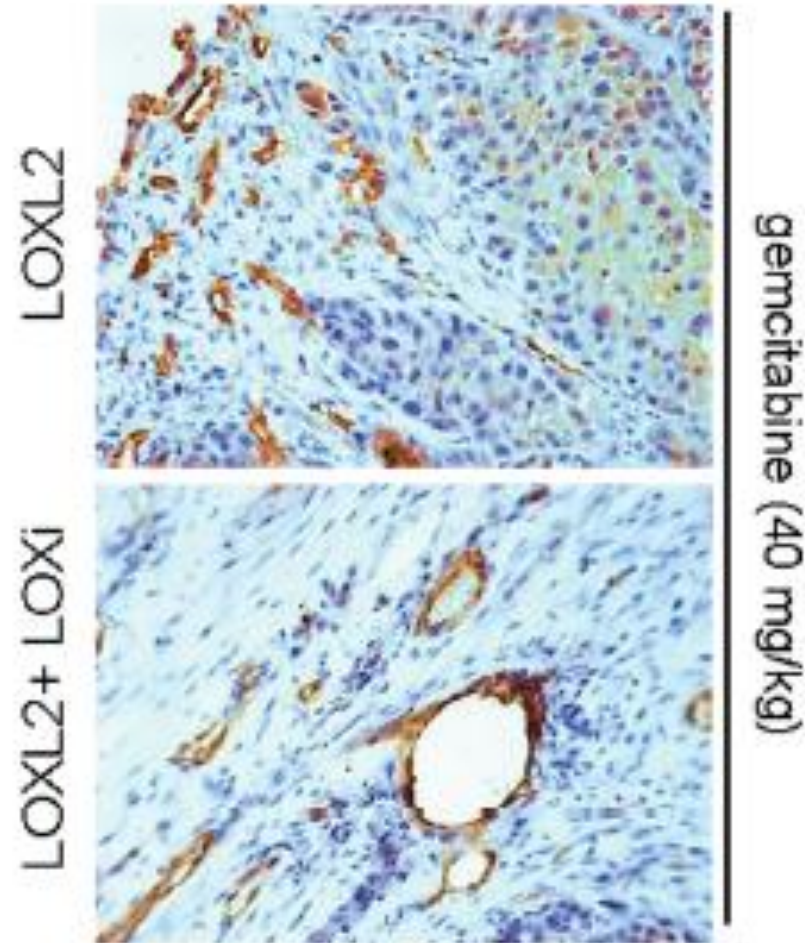
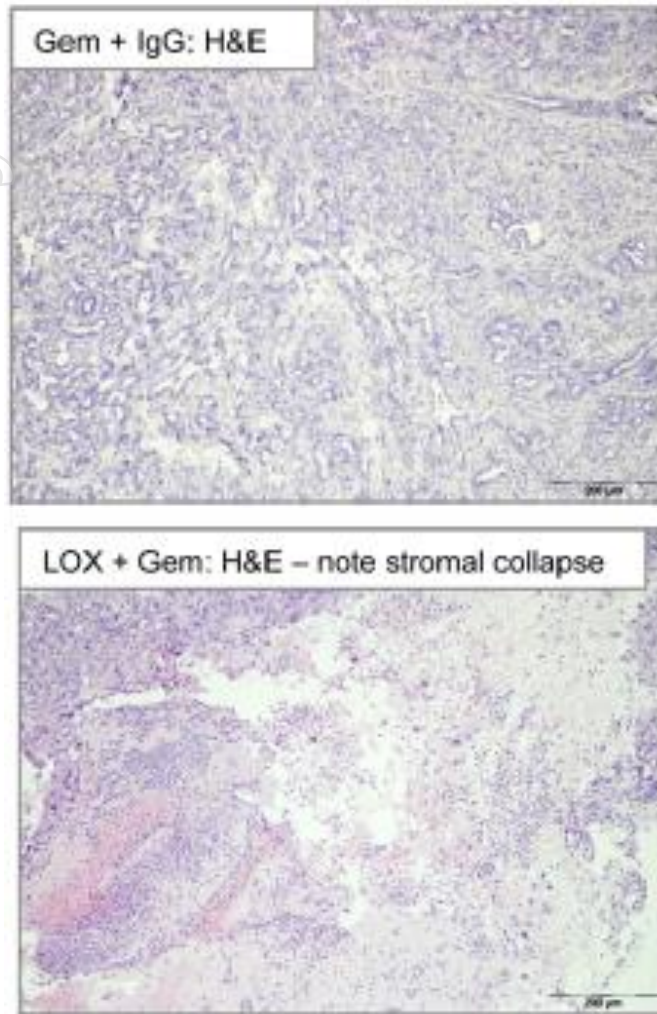
# LOXL2 promotes HCC intrahepatic metastases and local invasion



Wong, et al. *Hepatology*, 2014

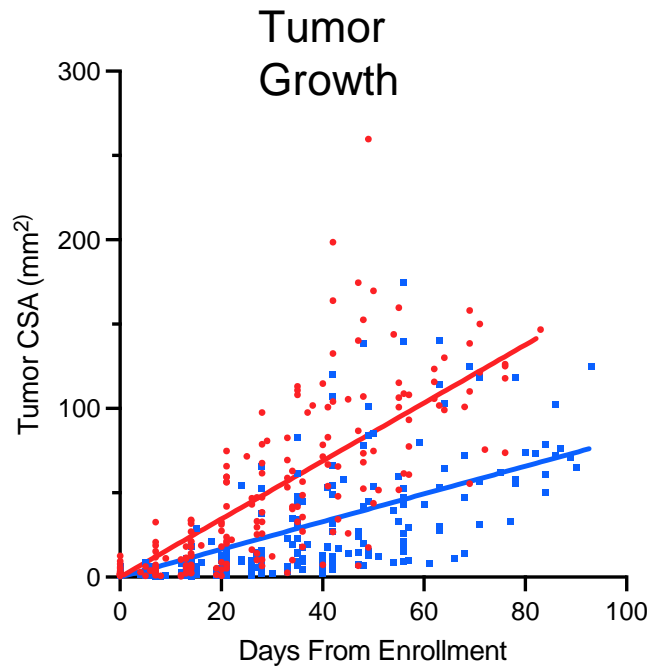
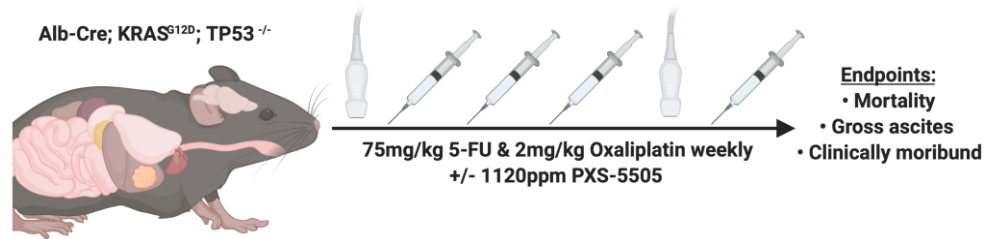


# LOX inhibition disrupts tumor stroma & improves drug delivery:

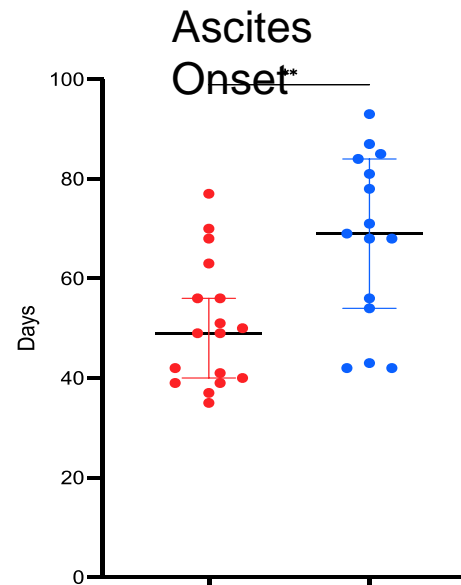


Le Calve et al., *Oncotarget* 2015, Miller et al., *EMBO Mol Med* 2018

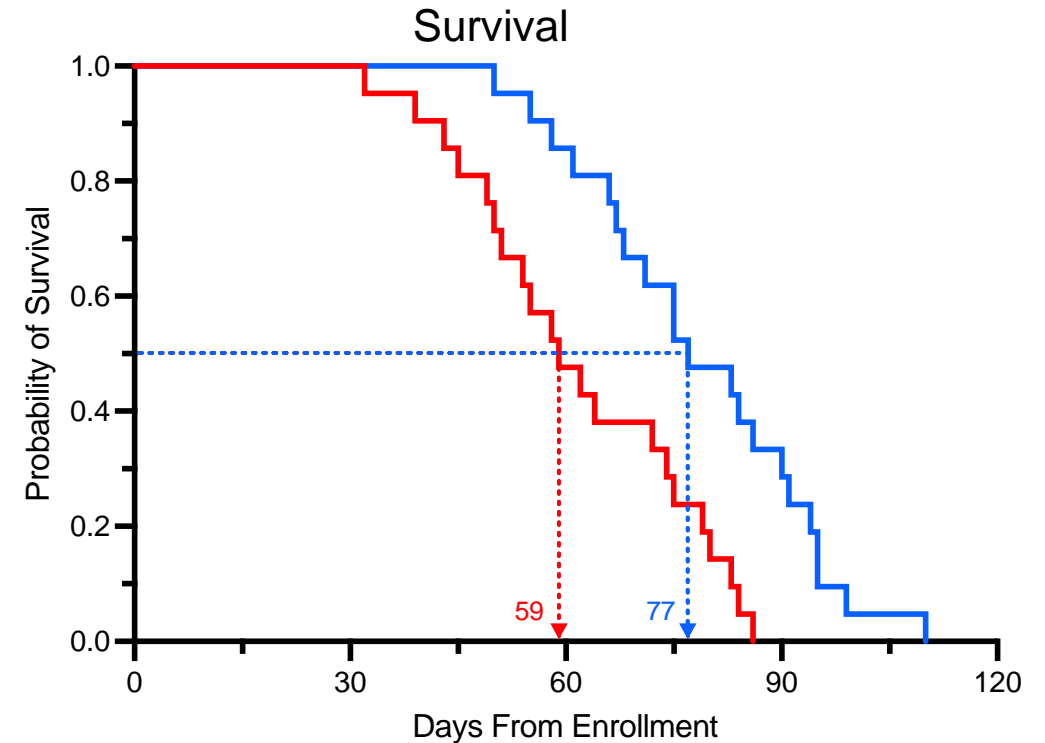
# Combination Therapy with PXS-5505 Delays Tumor Progression and Improves Survival in a Murine Model of Primary Liver Malignancy



$p < 0.000$   
1



$p = 0.0026$



$p = 0.001$   
1

— 5-FU + Oxaliplatin

— 5-FU + Oxaliplatin + PXS-5505

# PXS-5505 in Primary Liver Malignancy

## Oral Presentations

- Americas Hepato-Pancreatico-Biliary Association, 2021
- Society of Surgical Oncology, 2022
- International Hepato-Pancreatico-Biliary Association, World Congress, 2022

## Poster Presentations

- American Association for the Study of Liver Diseases, 2021
- American Association for Cancer Research, Advances in Pathogenesis and Molecular Therapies of Liver Cancer, 2022

# Phase 1b/II Trial Design: Unresectable &/or Non-Transplantable HCC

**FDA Approval of IND** – September 2021

**Anticipated Enrollment** – May/June 2022

## **Phase Ib Cohort**

18 Patients

### **Timeline**

1. 43-day total interphase
2. Assessment of dose tolerability at 3 week intervals
3. Biopsy for correlative science prior to treatment initiation and at conclusion
4. CT imaging per routine guidelines to assess response (2-3mo)
5. pK lab draws for analysis days 1, 22, 43

## **Phase II Cohort**

1. Designed for objective response rate of 45%
2. Anticipate 12 patients at MTD in Phase Ib to determine rationale for expansion to Phase II study
3. Would require 4 patients at MTD to demonstrate response in order to proceed
4. Phase II expansion for total of 42 patients at MTD

# Phase 1 Trial Design: Unresectable &/or Non-Transplantable HCC

## Inclusion Criteria

- Unresectable, not transplant candidate (incl. metastatic)
- $\leq$  Child A cirrhosis
- ECOG 0 or 1
- Meets criteria for 1<sup>st</sup> line therapy
- Cross-sectional imaging prior to enrollment

## Exclusion Criteria

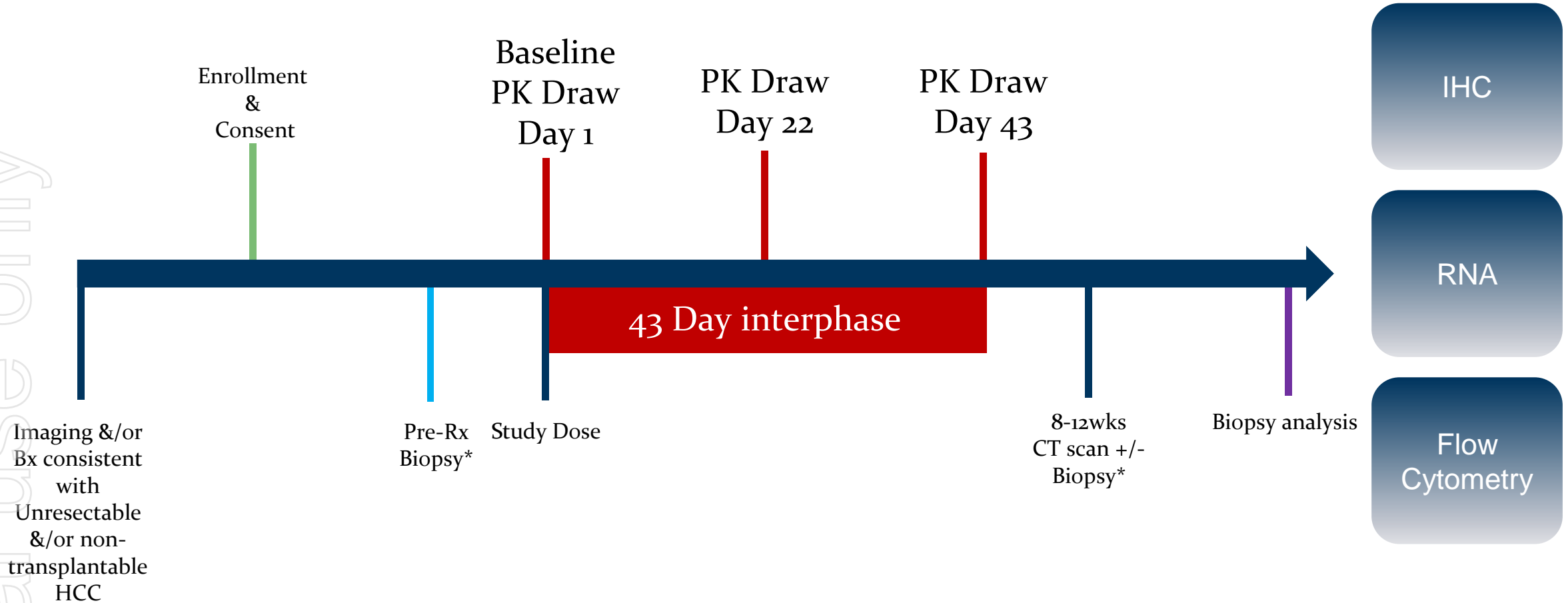
- Connective tissue disorder
- Evidence of aneurysmal disease
- Known or suspected autoimmune disease
- History of myelodysplastic or myeloproliferative disorders
- Major surgery within 4 weeks of enrollment

## Escalation/De-escalation Schema

Group	Atezolizumab	Bevacizumab	PXS-5505
1	1200mg every 3 weeks	15mg/kg every 3 weeks	100mg BID
2	1200mg every 3 weeks	15mg/kg every 3 weeks	150mg BID
3	1200mg every 3 weeks	15mg/kg every 3 weeks	200mg BID

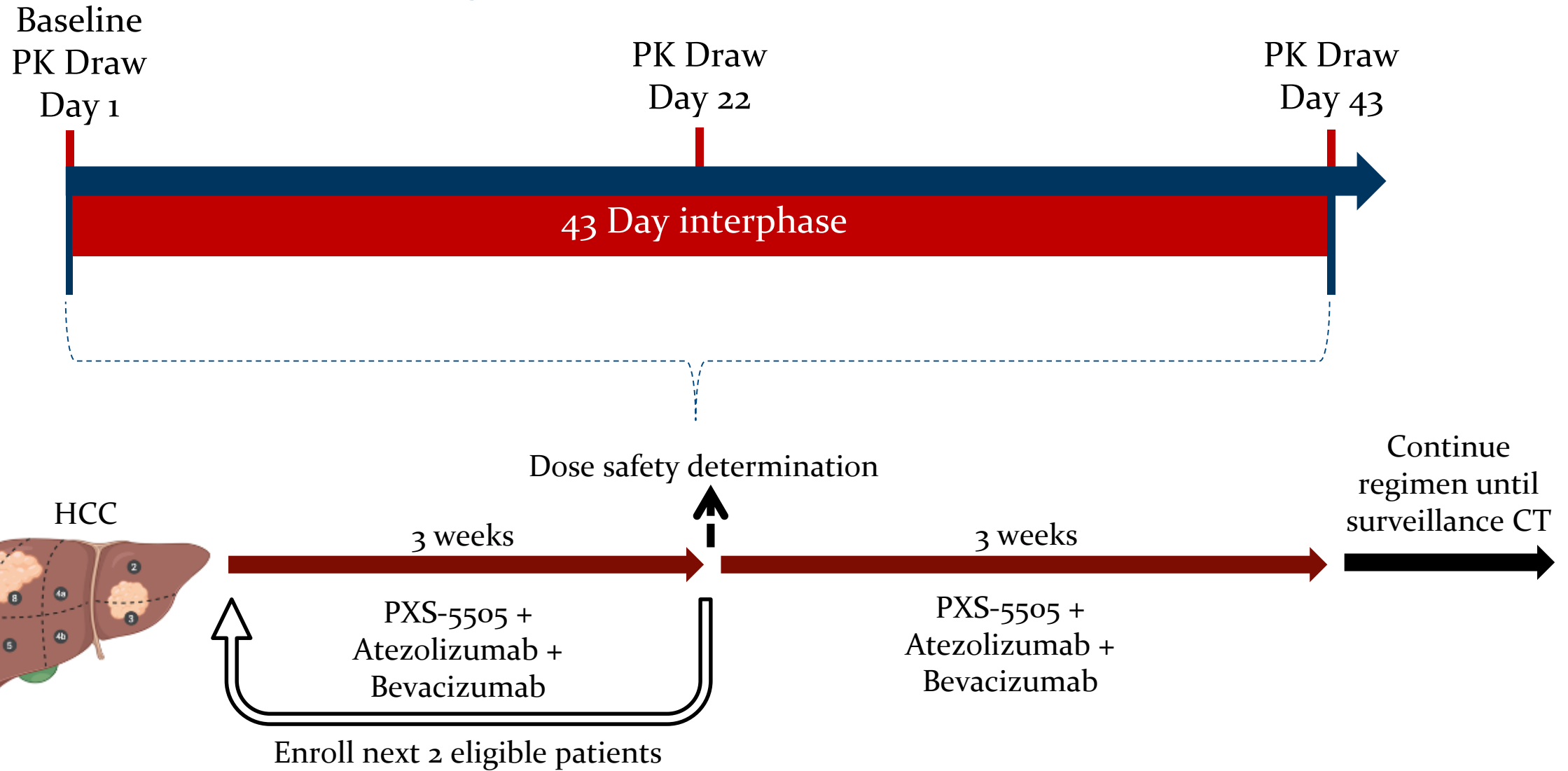


# Phase 1 Trial Design: Unresectable &/or Non-Transplantable HCC



\*Biopsy not standard of care

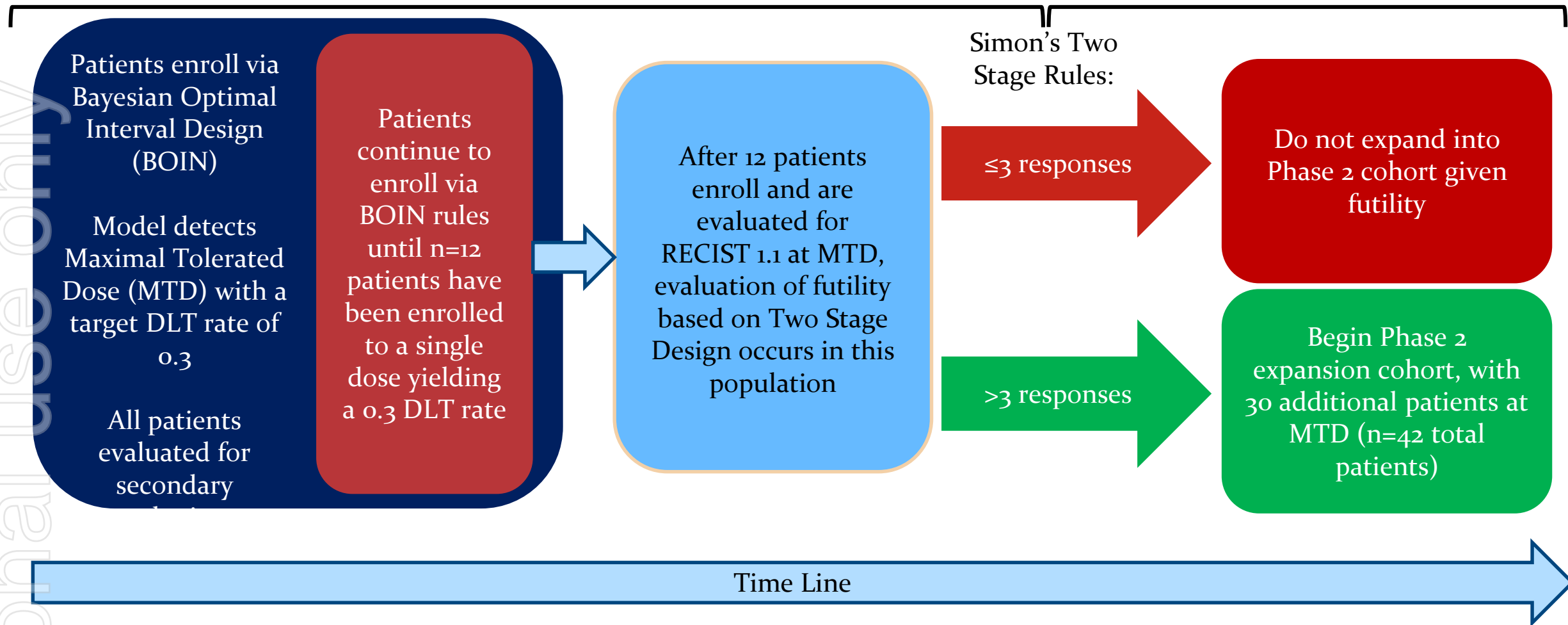
# Phase 1 Trial Design: Unresectable &/or Non-Transplantable HCC



## Phase 1b/2 Design Integrating Evaluation of Safety and Efficacy

Phase 1b (n=18)

Phase 2 (n=30)



Phase 1b: Enrollment begins at dose 0, and proceeds by BION rules dependent on observed rates of DLT, target DLT rate 0.3.

Phase 2: Accrual continues in Phase 1b until the 12th patient is evaluated for RECIST 1.1. Phase 2 Enrollment begins once 12th evaluation passes Simon's Two Stage Rule. Total number of patients between Phase 1b/2; n= 42-48, but expected to be 48.



**Thank You**

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Pancreatic Cancer  
Dr Tom Cox  
Garvan Institute (Sydney)





**Garvan Institute**  
of Medical Research

## *Targeting the Lysyl Oxidases in Pancreatic Cancer*

*R&D Briefing; PXS-5505 - 29<sup>th</sup> March 2022*

**A/Prof Thomas R. Cox**





Laboratory Head - Matrix and Metastasis, Garvan Institute of Medical Research



## Our Mission:

To make discoveries that enhance human health and society,  
leading to longer, healthier lives for everyone

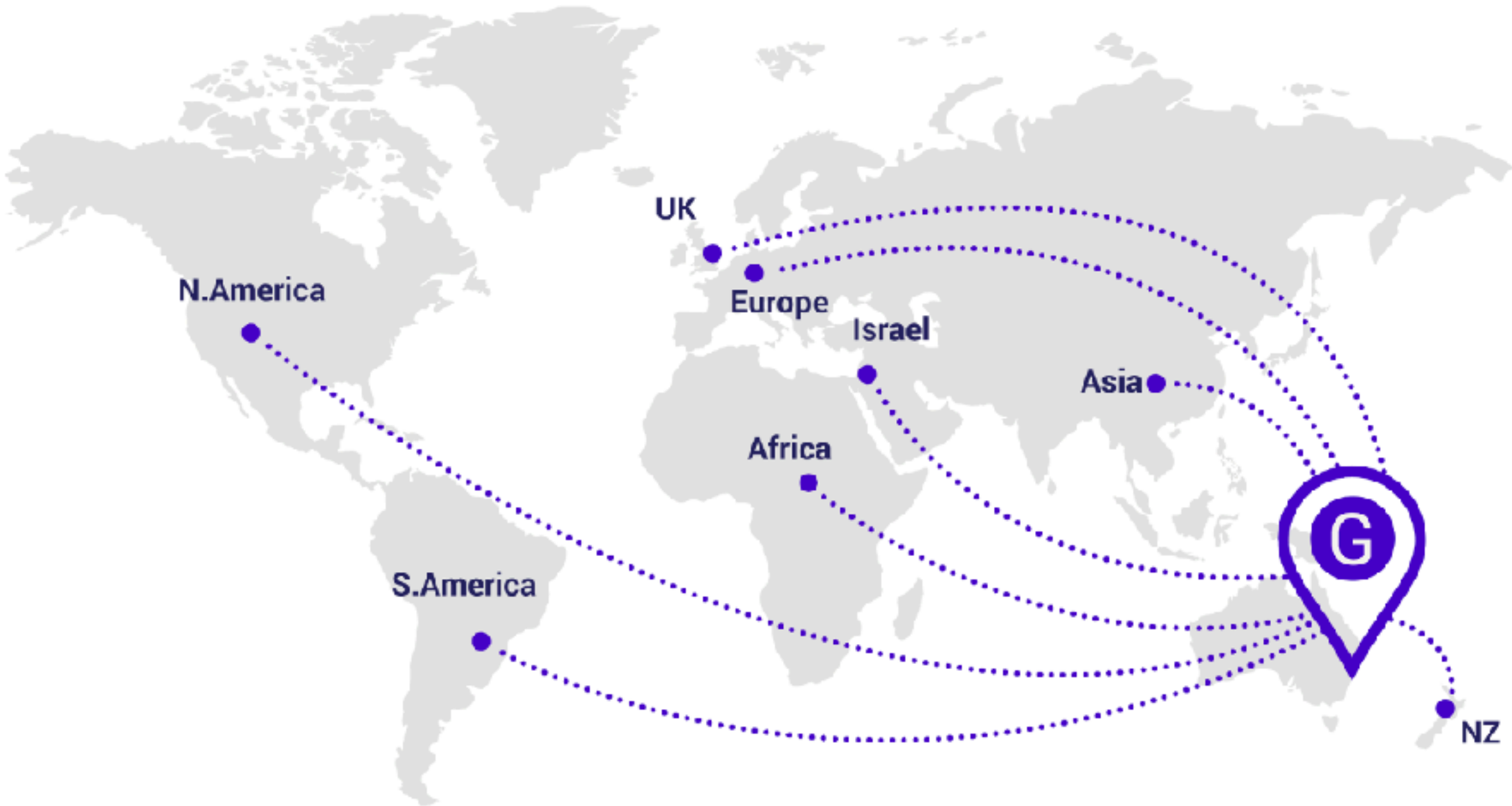
Garvan works across all majors diseases with  
research programs in:

-  Cellular Science
-  Genomic Science
-  Translational Science
-  Data Science

1963  
Garvan  
established

600+

50+

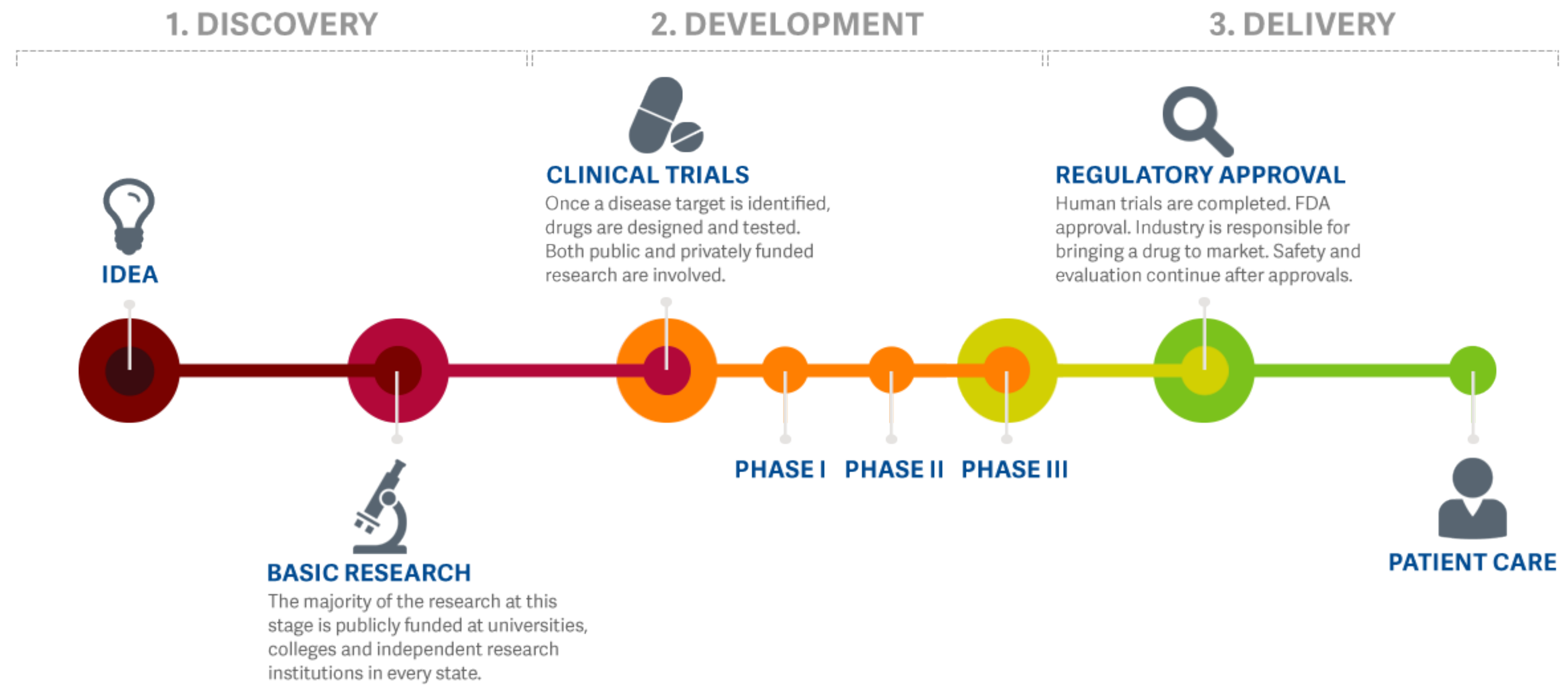


700 research partners and collaborators globally



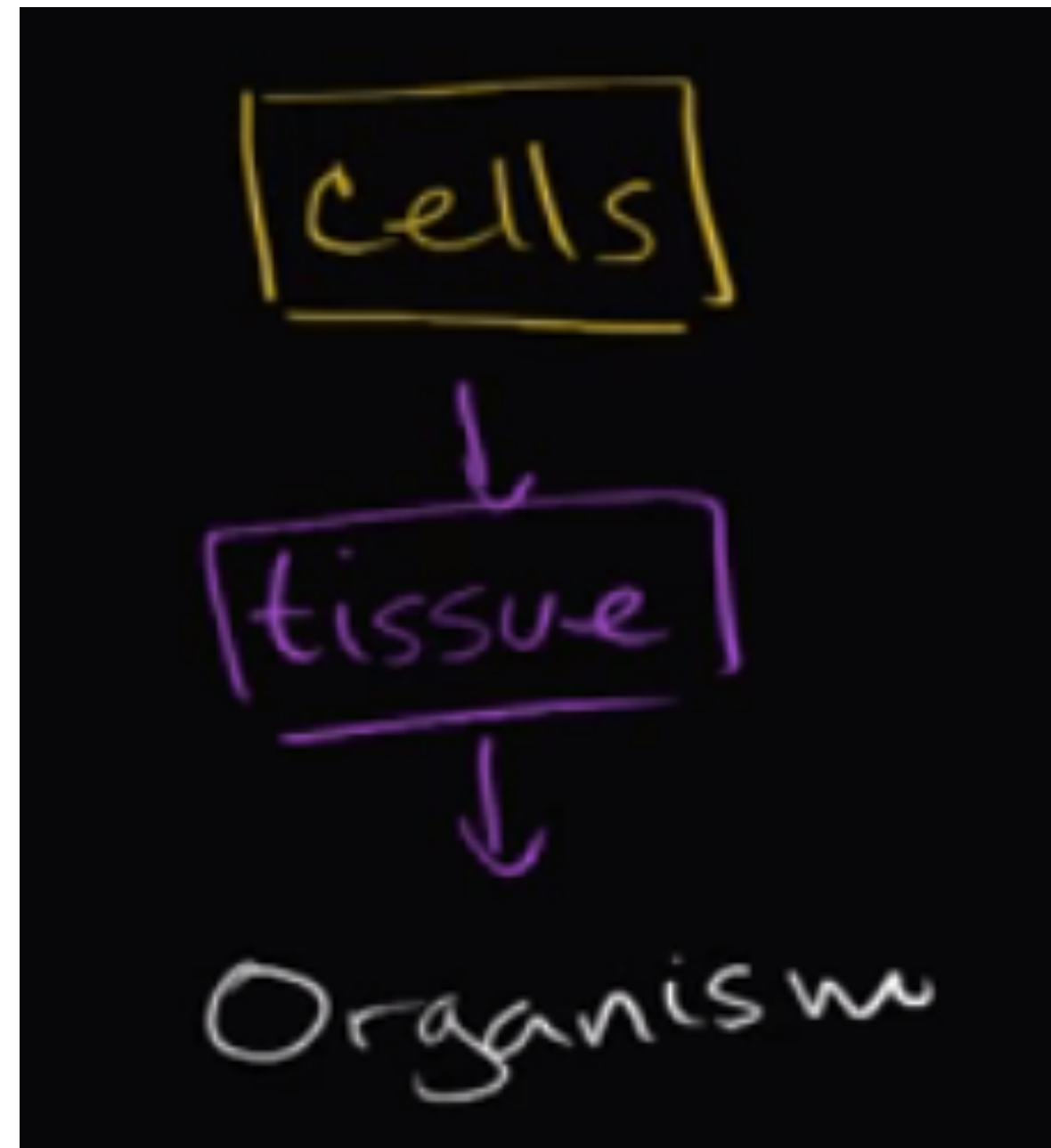
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Garvan through its integration with St Vincents Hospital Precinct has the unique capability to progress research all the way through to the patient in many diseases, especially cancer



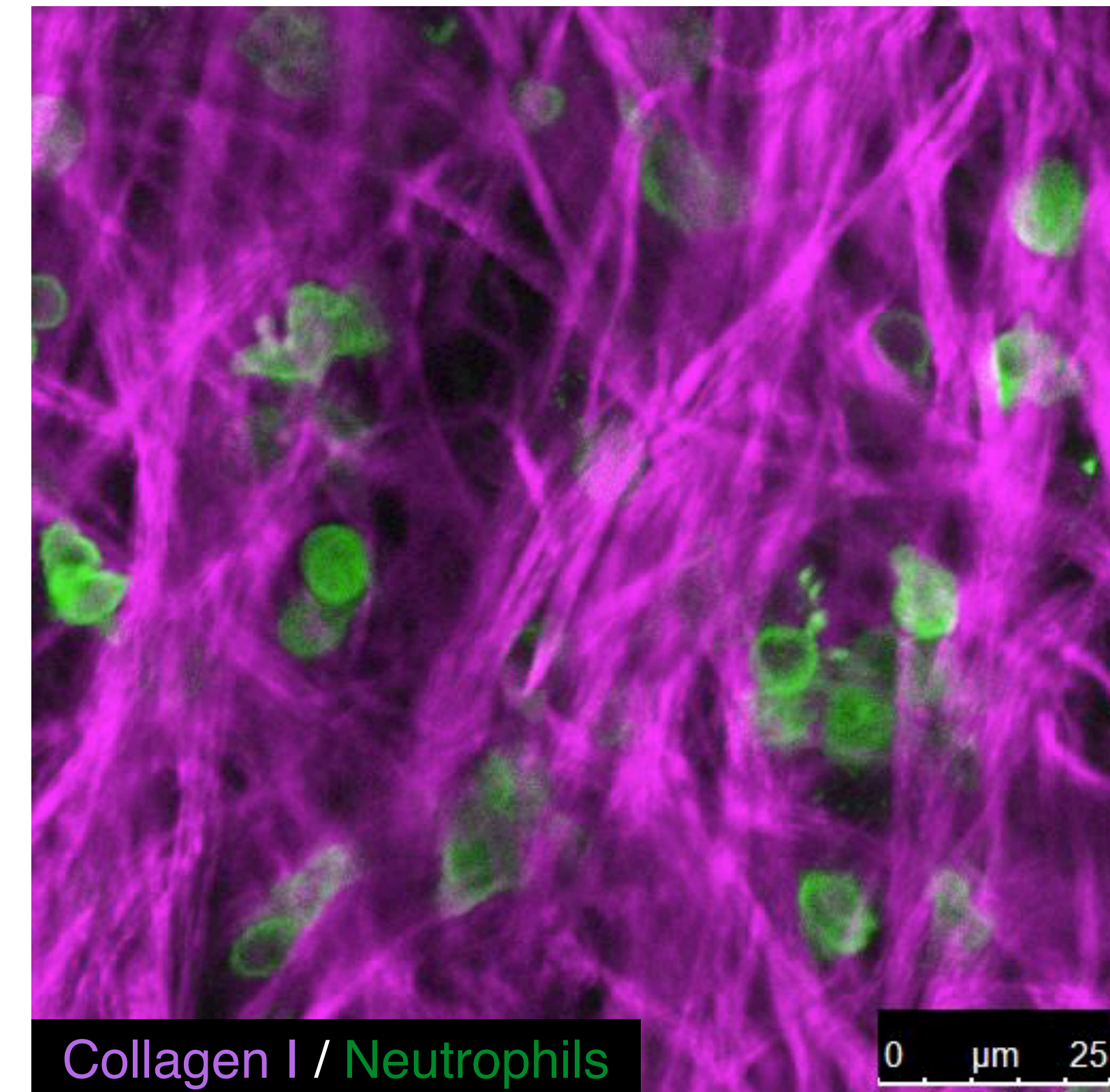
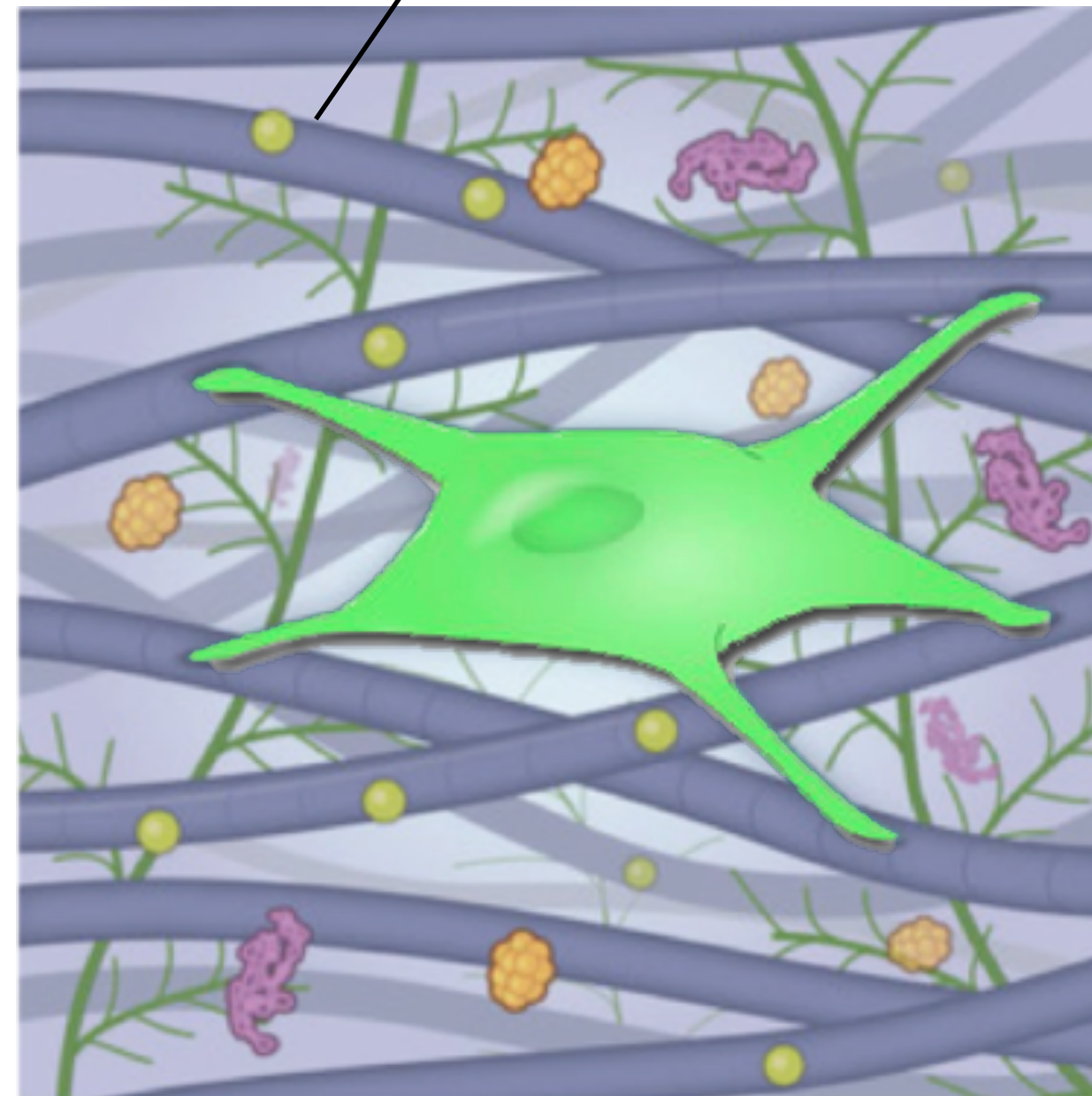


# The Extracellular Matrix (ECM) or 'matrix'



Cells are the basic building block of life

Extracellular Matrix



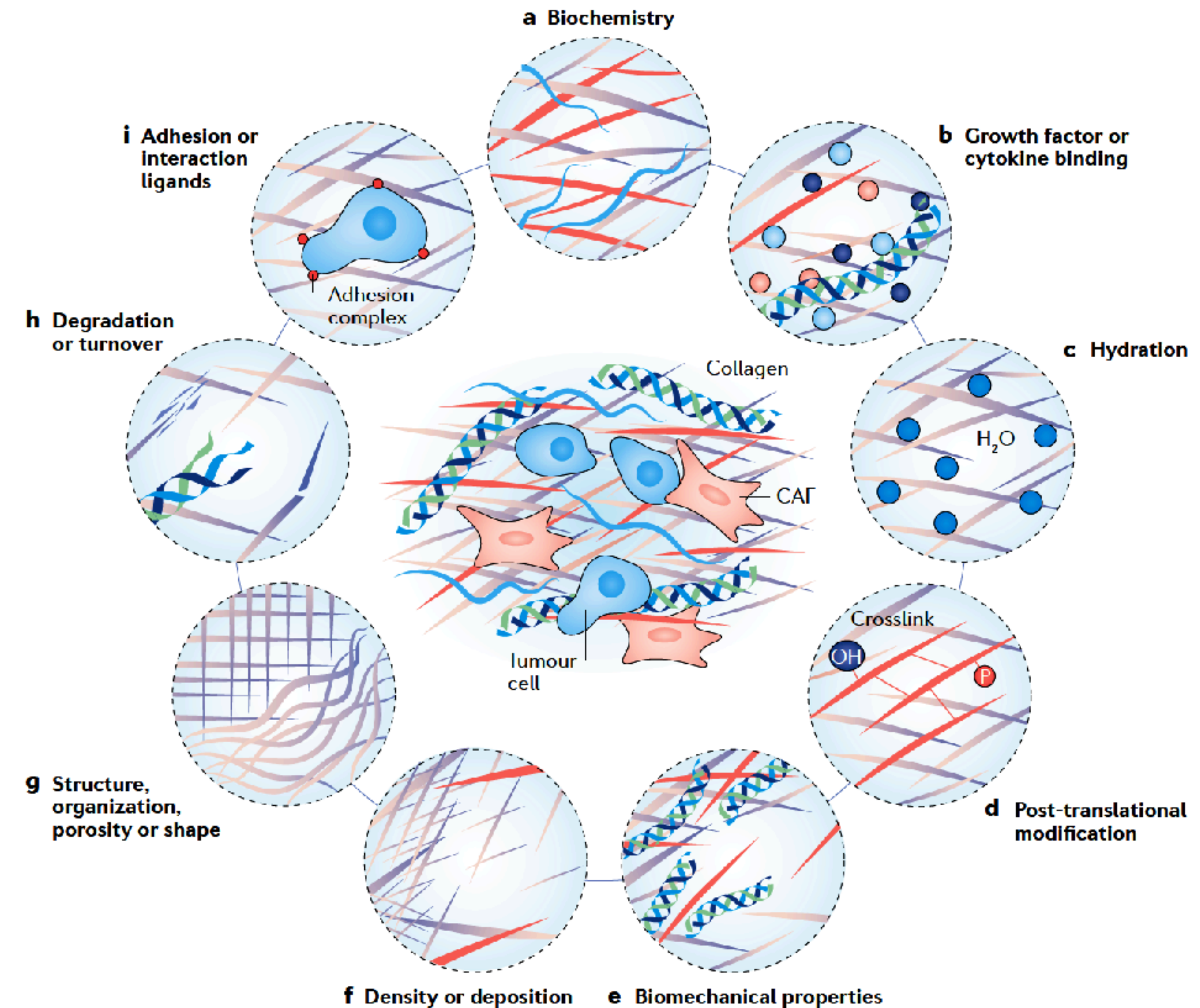


# The matrix perspective in solid tumours

The extracellular matrix plays a fundamental role in all tissues to maintain normal function

The vast complexity of the extracellular matrix contributes across a variety of time and length scales to modulate cell behaviour on an ongoing basis

It is typically highly dysregulated in cancer and is important in the progression of solid tumours as well as the modulation of tumour response to therapy



Cox TR (2021) *Nature Reviews Cancer*

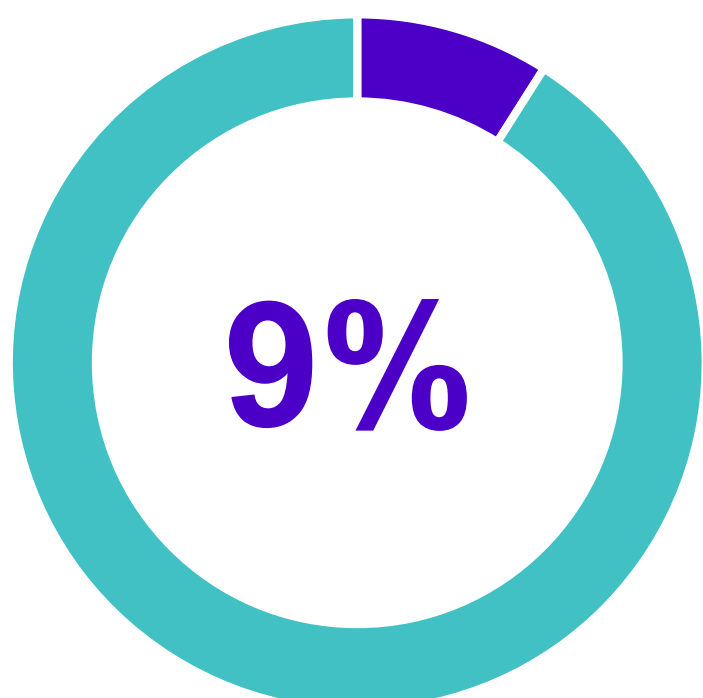


# Pancreatic Ductal Adenocarcinoma as a highly aggressive disease



**3,000** deaths in  
Australia in 2019

**5-year** probability  
of survival



**Chemotherapy**  
is the mainstay of  
patient treatment

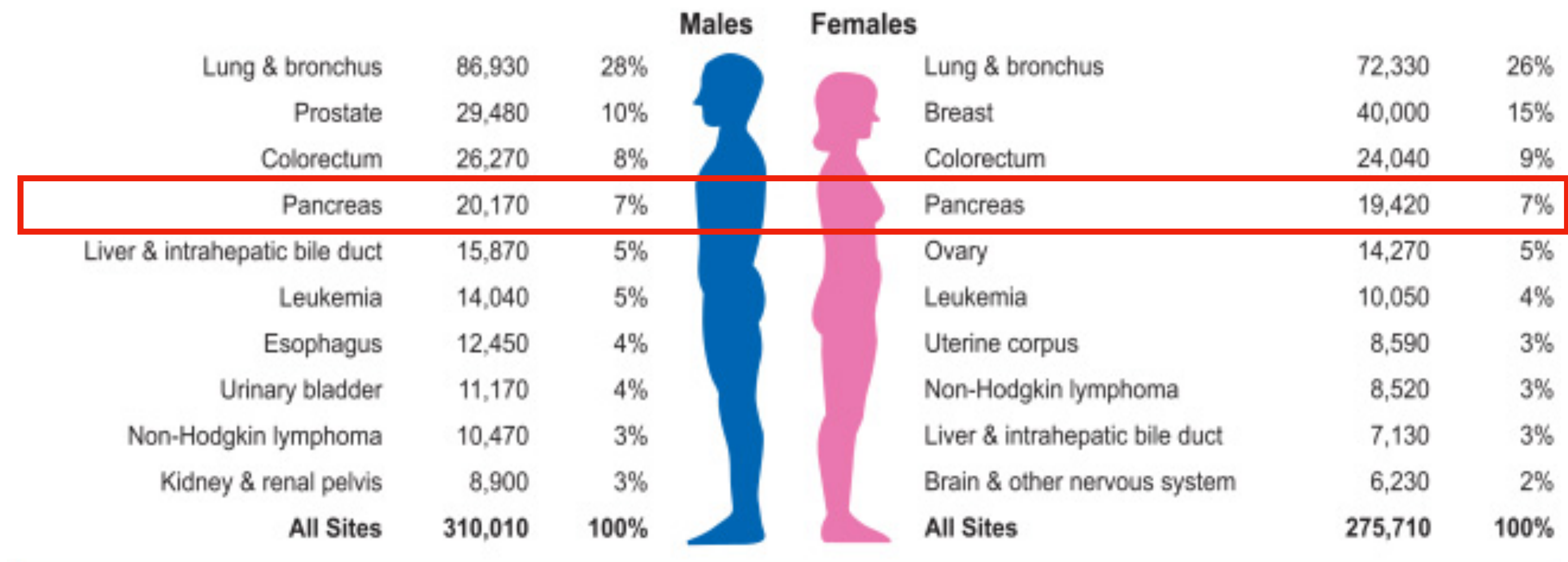
Highly **Fibrotic**  
nature





# Pancreatic Ductal Adenocarcinoma as a highly aggressive disease

Estimated Deaths 4th most common cancer related death in men and women



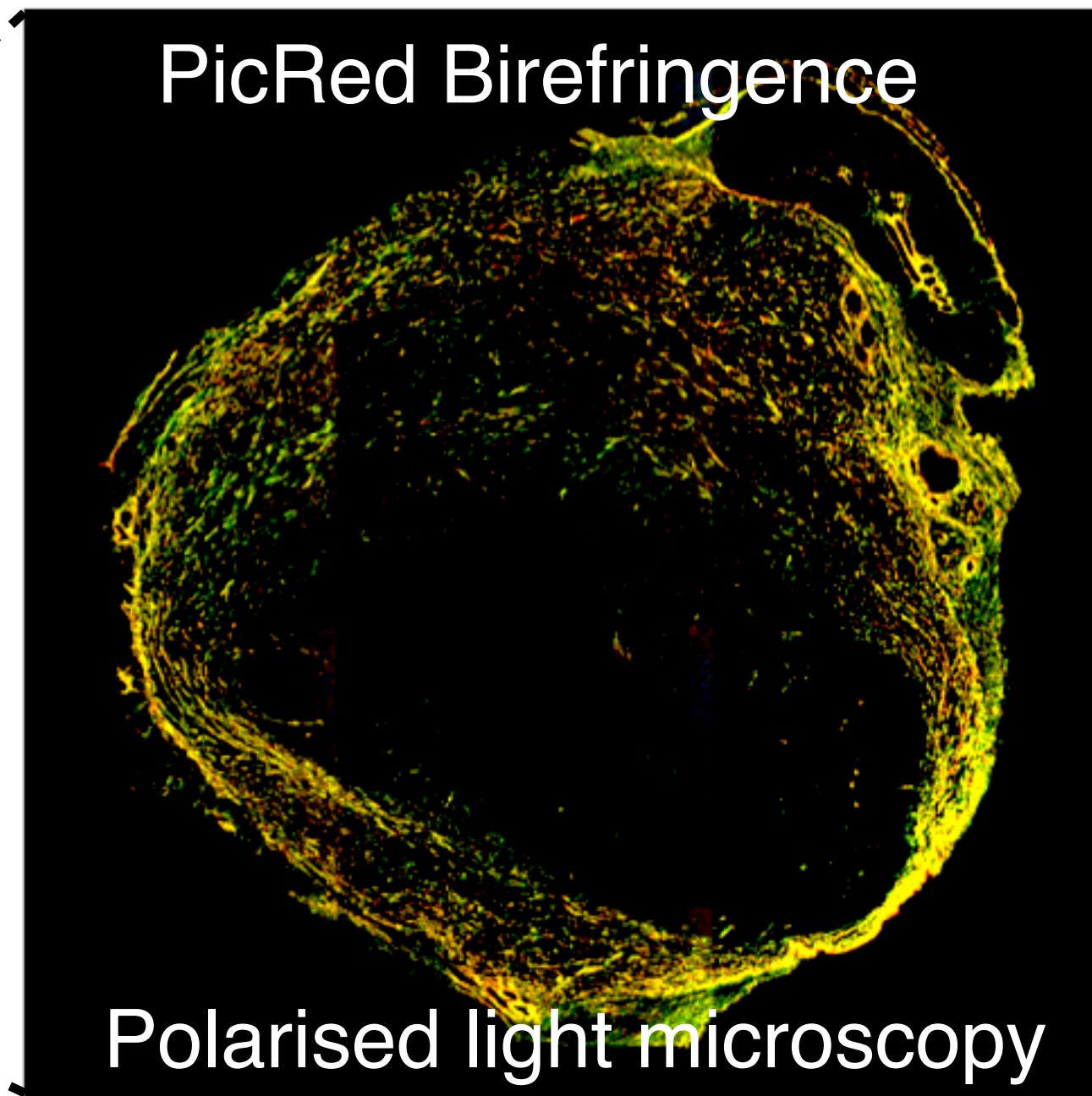
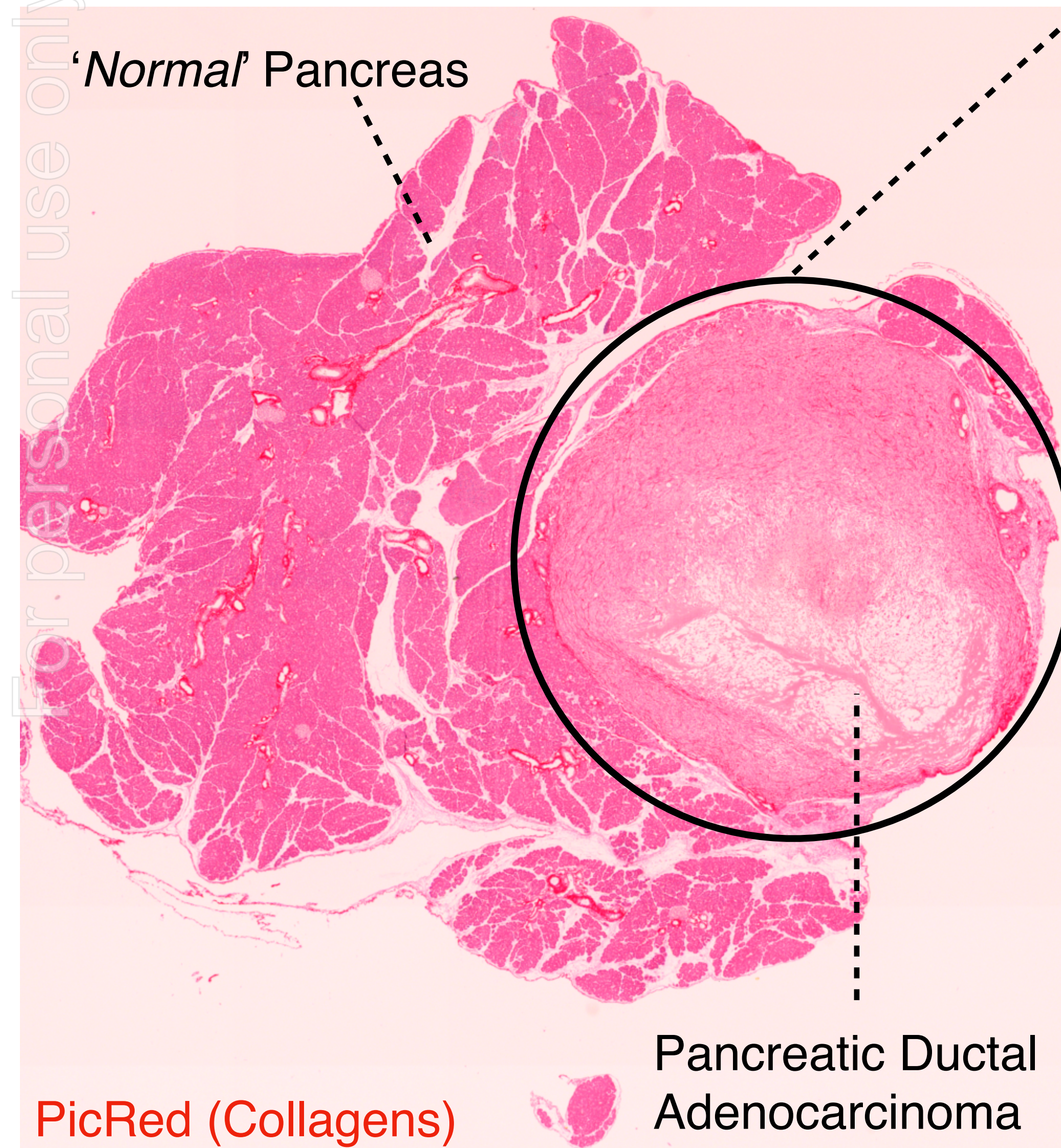
- ~ The median survival for untreated advanced pancreatic cancer is approximately 3-4 months
- ~ The median survival for advanced pancreatic cancer treated **with our best therapeutics** is 6-8 months
- ~ This statistic has barely improved in the last 2-3 decades
- ~ Pancreatic cancer therefore represents a significant economic burden of disease
- ~ **New treatments to improve outcome are seen as an urgent unmet clinical need**





# Pancreatic tumours contain high levels of fibrosis (desmoplasia)

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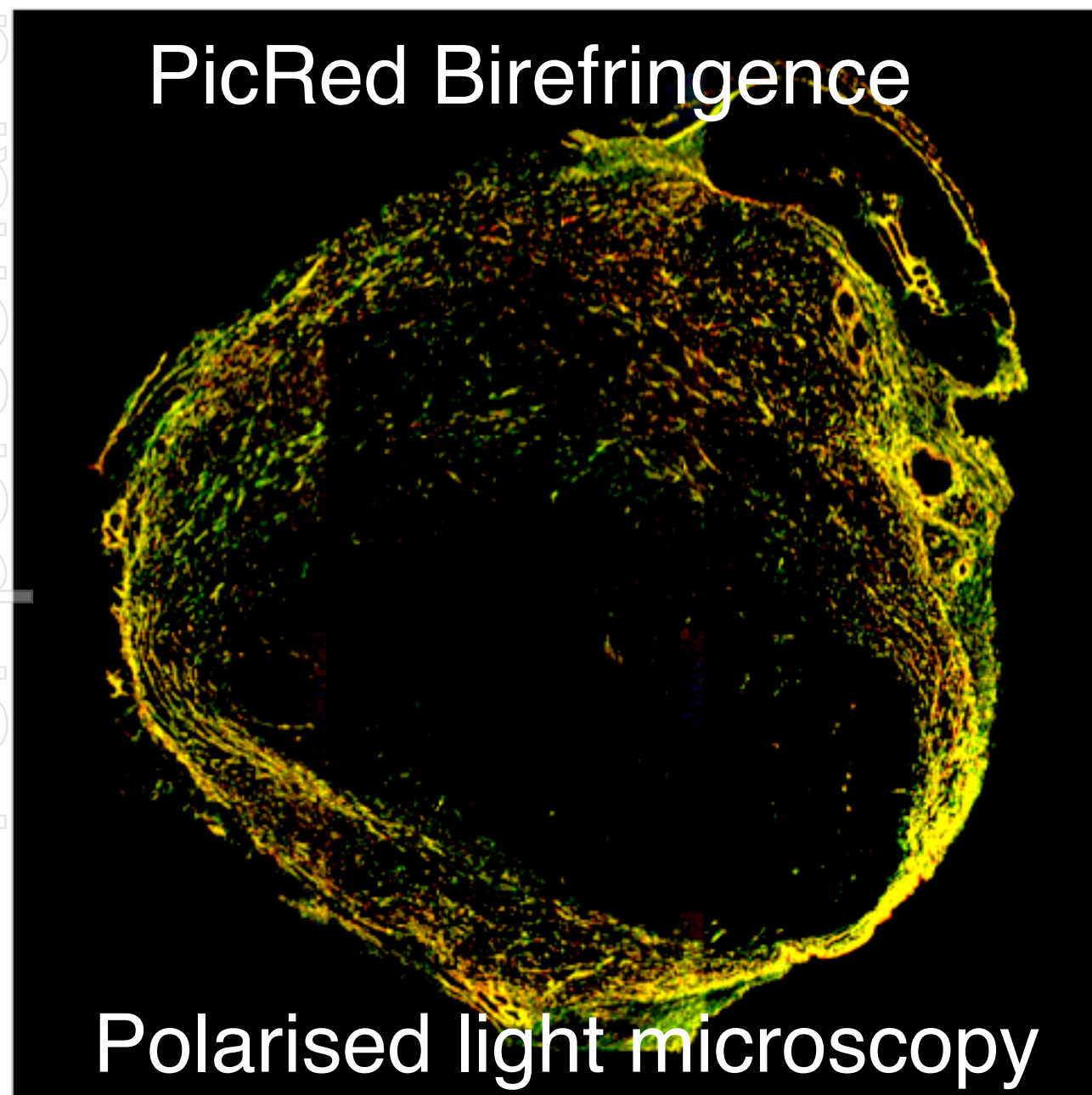
*Polarised light microscopy allows visualisation of fibrillar collagens, the major component of tissue fibrosis*

As pancreatic cancer progresses, an accompanying fibrotic response (*desmoplasia*) evolves within and around the developing tumour

As this scar-like tissue builds up, it decreases the efficacy of our standard-of-care therapies







Tumour fibrosis drives disease progression by...

- ~ Altering cancer cell behaviour including making them more aggressive
- ~ Directly and indirectly altering cancer cell sensitivity to therapies
- ~ Acting as a physical barrier to the delivery of our adjuvant therapies
- ~ Providing a physical highway for cancer cells to spread (metastasise) to other parts of the body



# Drivers of tumour fibrosis (desmoplasia)

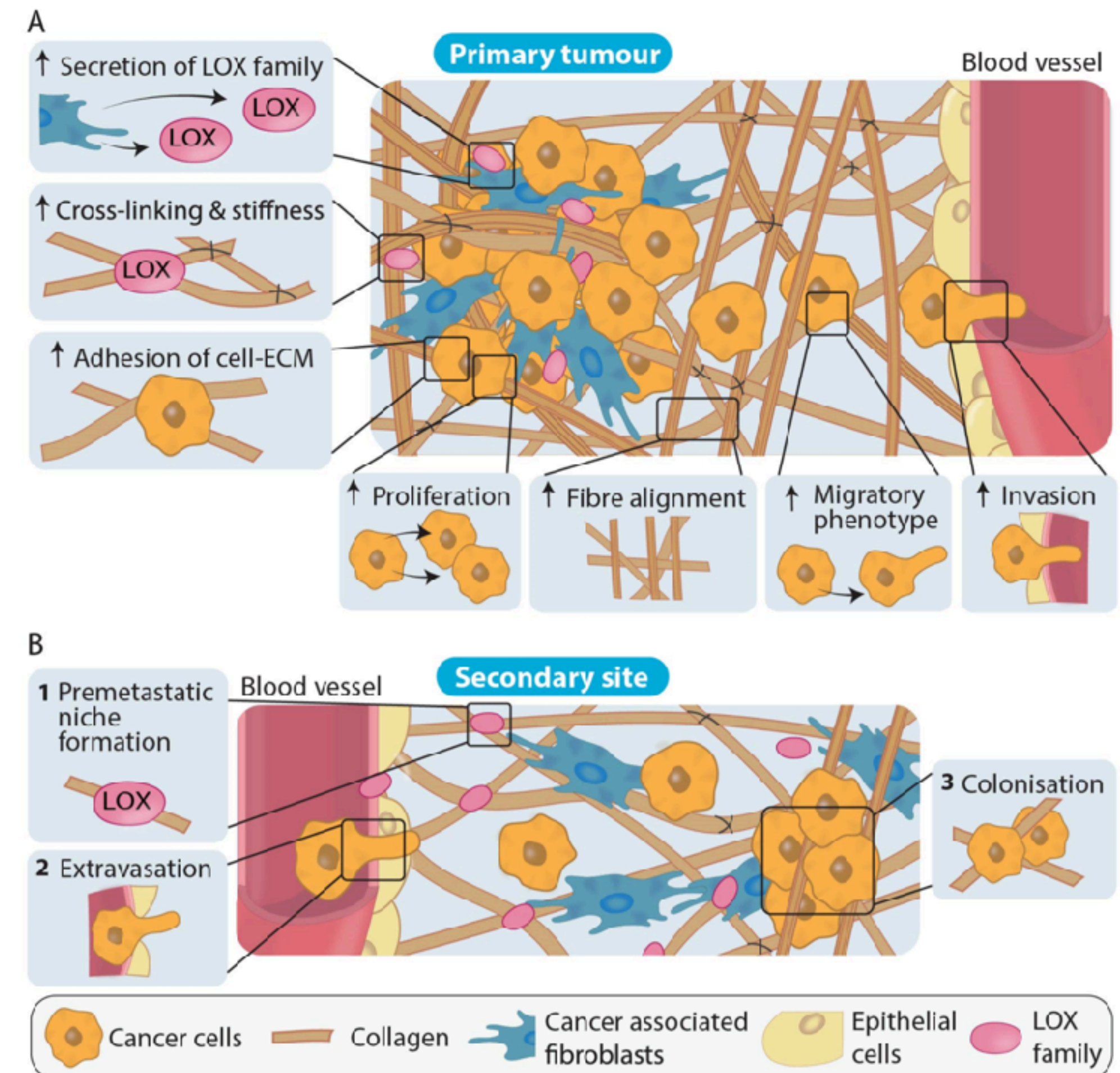
Prominent pathological characteristic of pancreatic cancer, marked by a significant overproduction of extracellular matrix and extensive proliferation of “Cancer Associated Fibroblasts” (CAFs)

Occurs at primary and secondary sites

Driven by multiple intercellular and intracellular biological signalling events (including, but not limited to, growth factors such as PDGF, TGF $\beta$ , FGFs, TNF- $\alpha$ , CTGF, IL-1 $\beta$ )

Desmoplasia feeds back to activate intracellular signalling programs inside cancer cells driving progression in a process known as “**Dynamic Reciprocity**”

Therefore, targeting the deposition of matrix offers a powerful approach to break this cycle



Setargew YSI, Wyllie K, Grant RD, Chitty JL & Cox TR (2021) *Cancers*

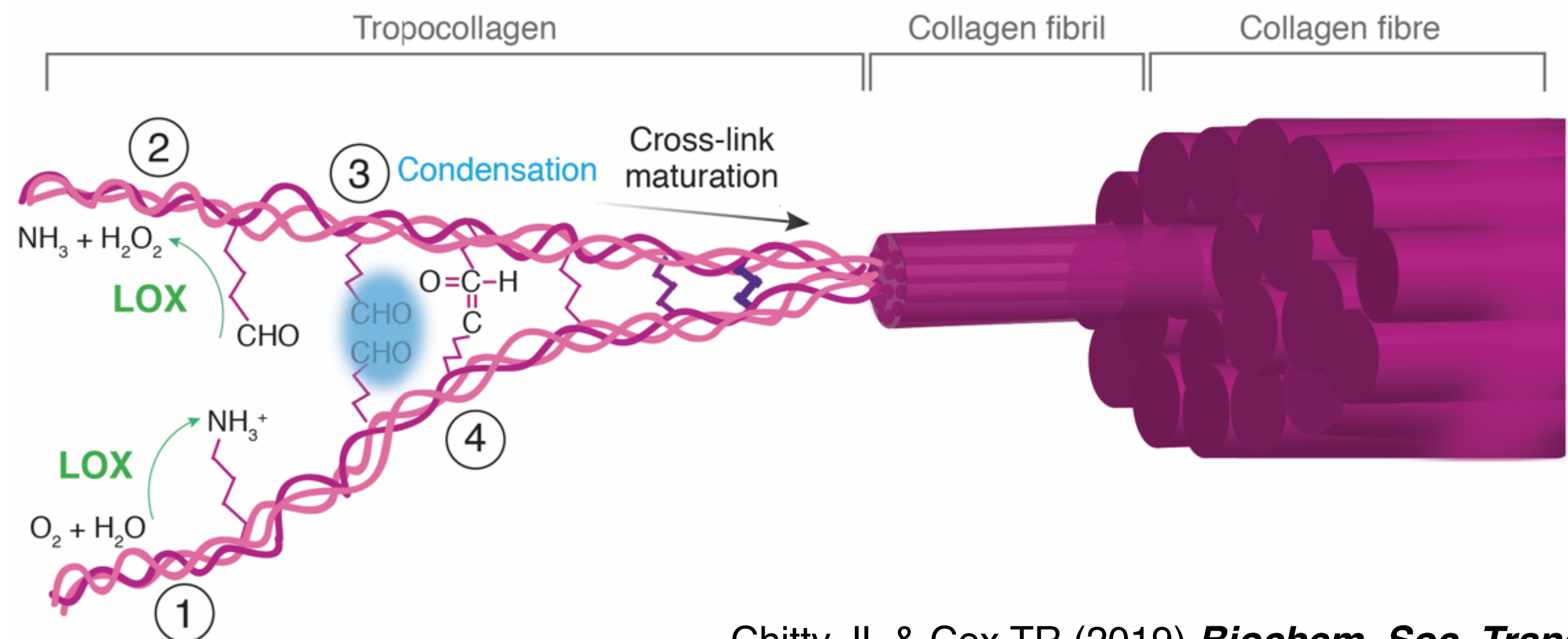


# The Lysyl Oxidase (LOX) family in tumour fibrosis

One of the major components of tumour desmoplasia is fibrillar collagens

The lysyl oxidase enzymes (LOX, LOXL1, LOXL2, LOXL3 and LOXL4) are the critical linchpin in the production of fibrillar collagens through enabling their assembly and cross linking

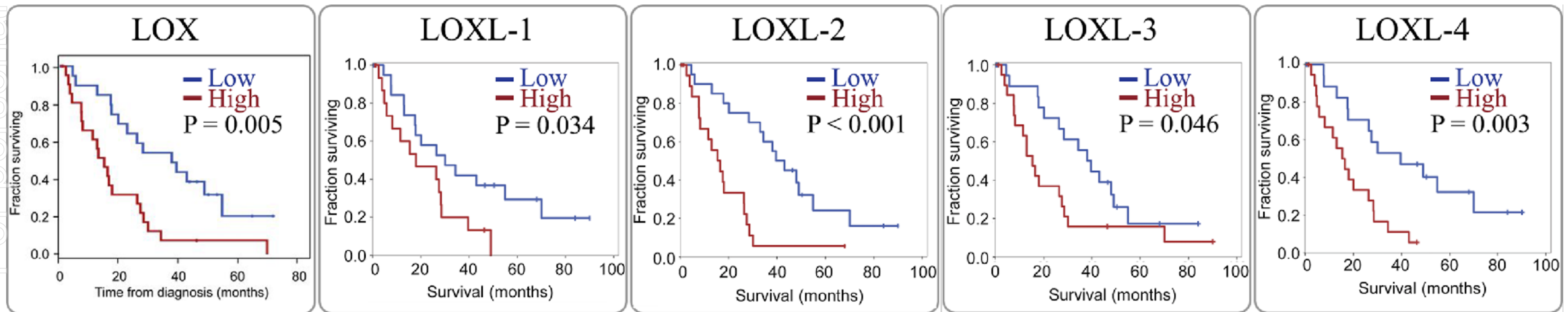
Opportunity to develop and deploy new therapeutic approaches to co-target the development of this scar-like tissue in order to improve the efficacy of our already approved standard-of-care treatments



Chitty JL & Cox TR (2019) *Biochem. Soc. Trans.*

# The lysyl oxidase family in pancreatic cancer

Each of the lysyl oxidase family members are up-regulated in pancreatic ductal adenocarcinoma (PDAC) and individually associated with poor survival



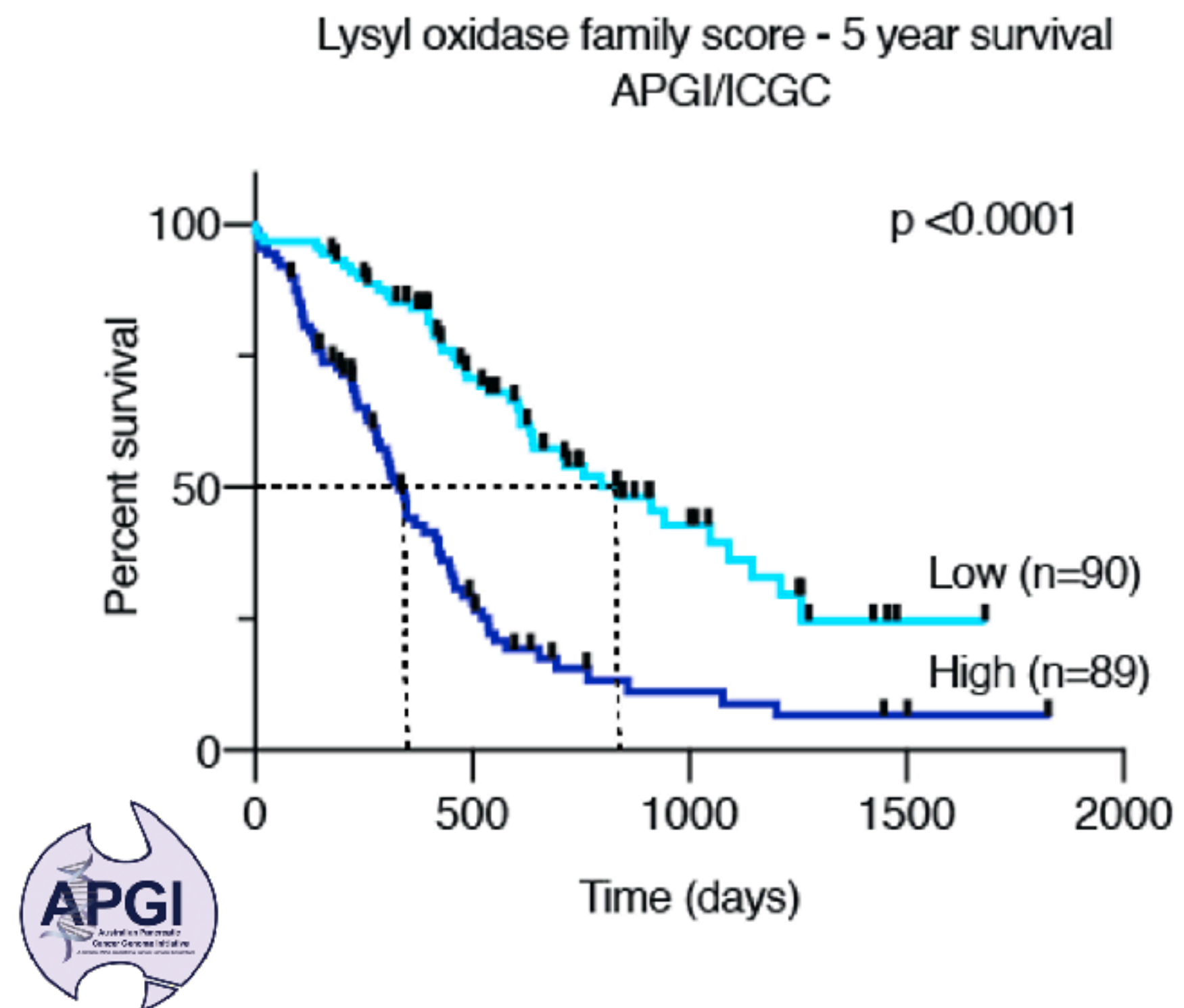
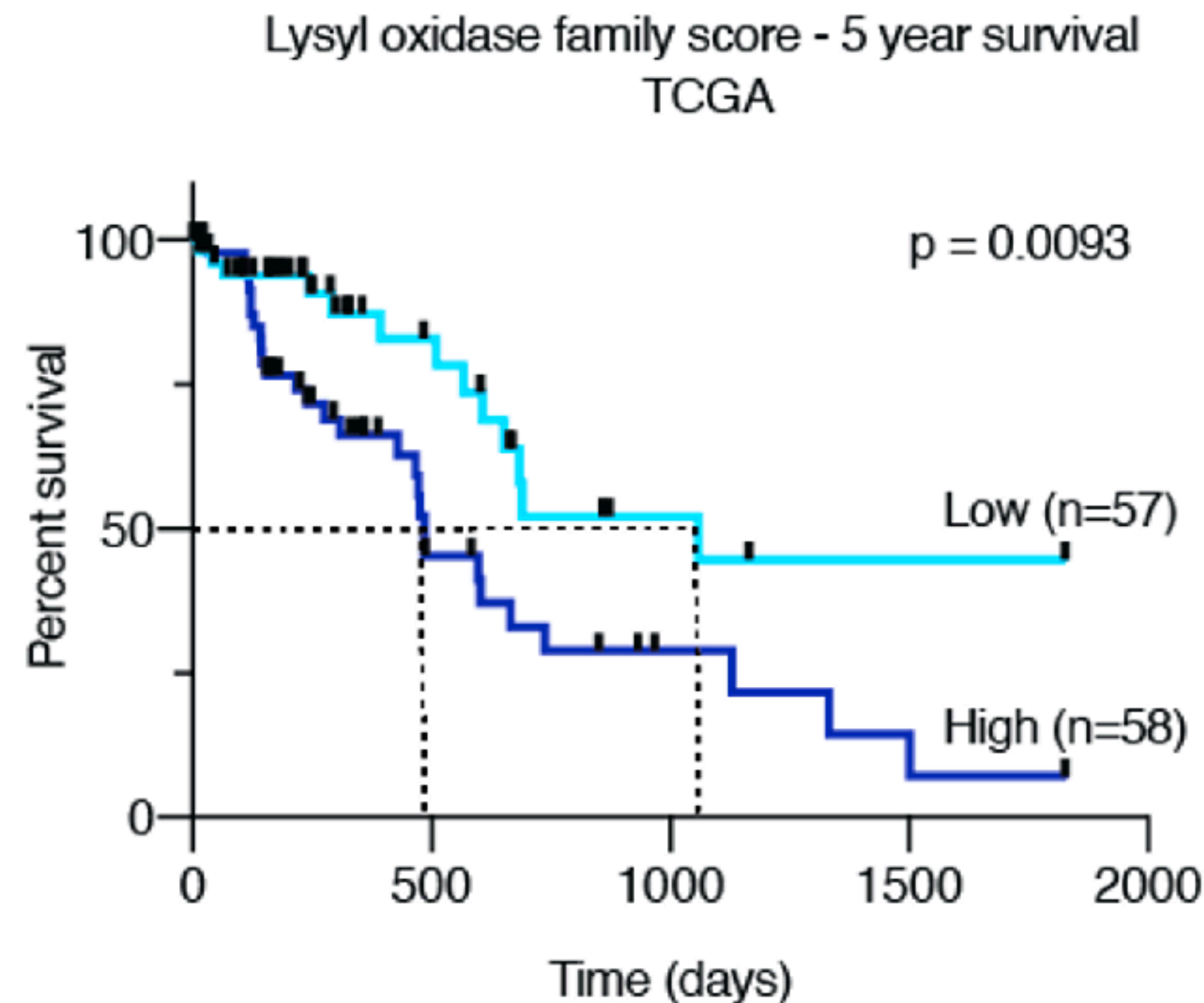
Kaplan-Meier analyses showing correlation of LOX family member expression and survival in the Glasgow patient cohort (microarray analysis of 400 cores from a total of 80 PDAC resections) - *Miller et al. EMBO Mol Med.*



# The lysyl oxidase family in pancreatic cancer

Further analysis in two additional patient cohorts (*TCGA* and *APGI/ICGC*) reveals that a combination score encompassing expression of all 5 family members is significantly associated with survival

A low family score (*light blue*) is associated with an approximately 2 fold increase in patient median survival



Chitty *et al.* ***Nature Cancer*** (in revision)

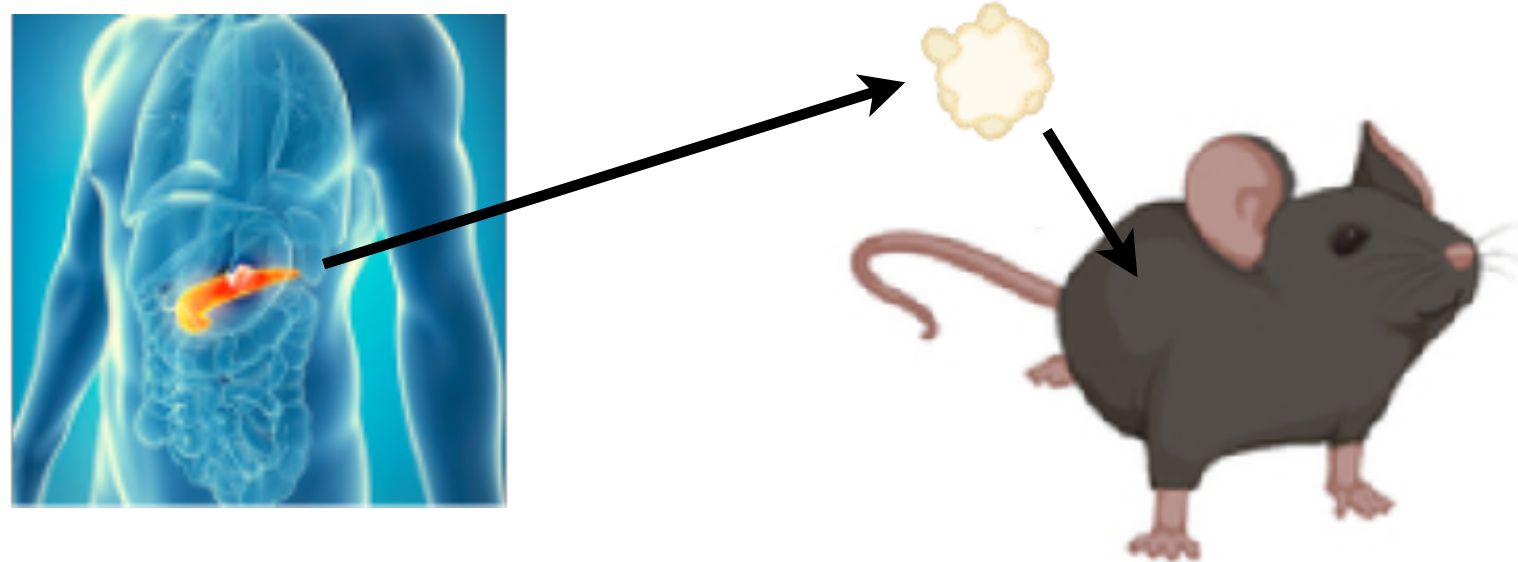


# Pre-clinical models of pancreatic ductal adenocarcinoma

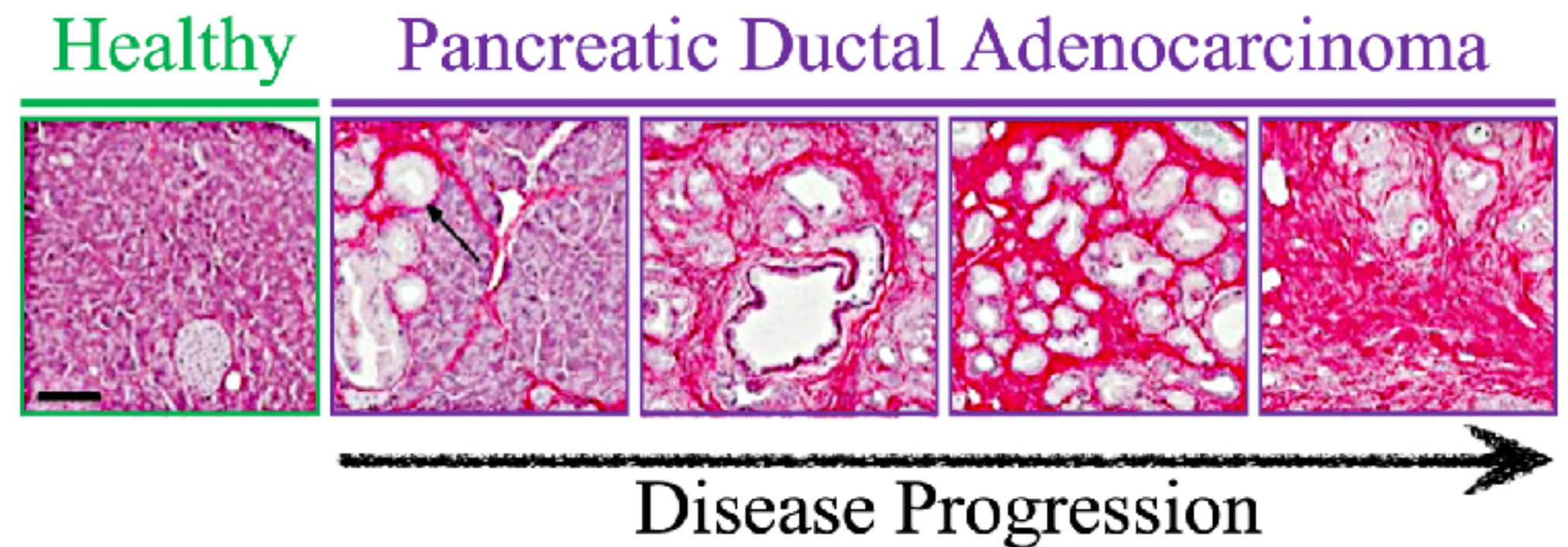
The “KPC” mouse model of spontaneous pancreatic cancer, along with human patient derived xenograft (PDX) models (*part of the Australian APGI and APMA programs*) develop robust tumour desmoplasia allowing for detailed characterisation of novel anti-fibrotic compounds



*Pdx-1-Cre LSL-Kras<sup>G12D/+</sup> LSL-tp53<sup>R172H/+</sup> (KPC)*



*Patient derived xenograft (PDX) models*



Australian Pancreatic Cancer Genome Initiative

<https://www.pancreaticcancer.net.au>



Avner Australian  
Pancreatic Cancer  
Matrix  
Atlas

<https://www.pancreaticcancer.net.au/apma/>

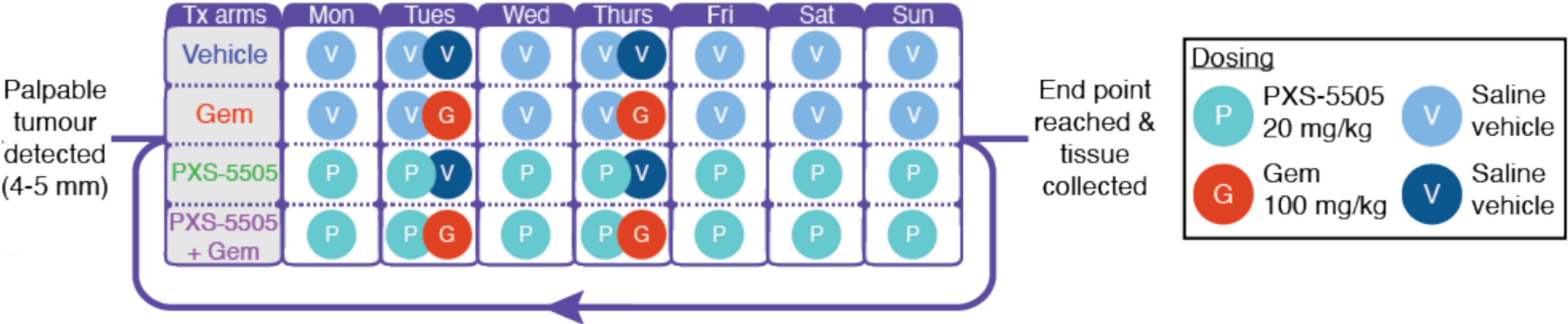




Pre-clinical evaluation of PXS-5505 in combination with standard-of-care chemotherapy (gemcitabine) in genetically engineered mouse (KPC), and human patient derived xenograft (PDX) models of pancreatic cancer.

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Treatment  
arms

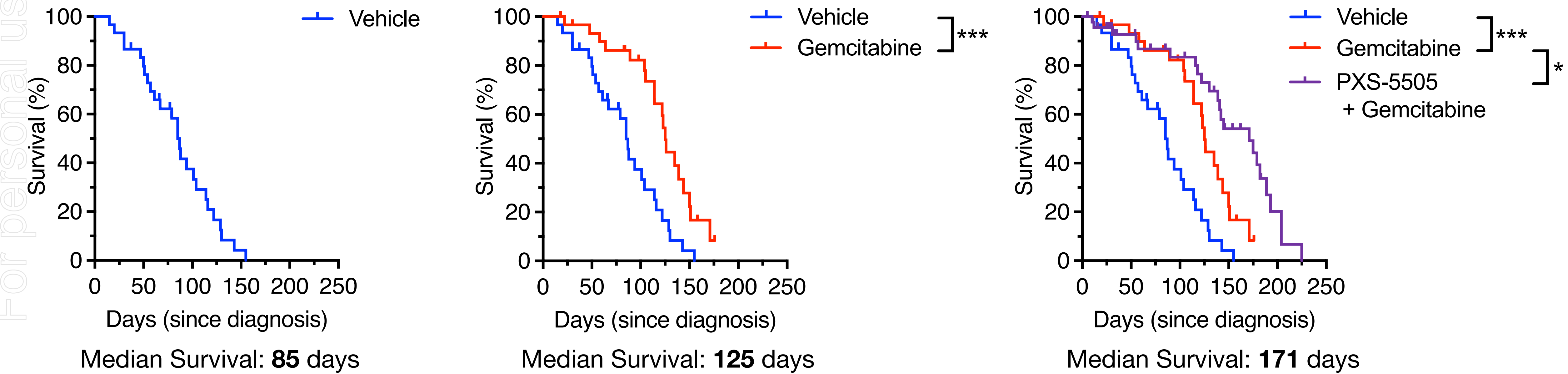


Chitty *et al.* **Nature Cancer** (in revision)



## PXS-5505 in combination with standard-of-care gemcitabine

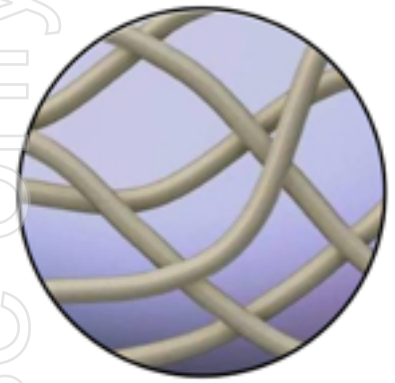
Decreased tumour growth leading to increased median survival over chemotherapy alone



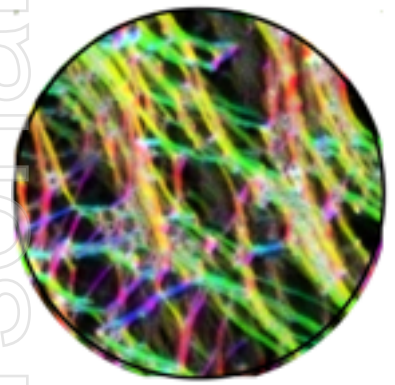
- ~ Decreased tumour desmoplasia (fibrosis)
- ~ Decreased metastatic burden in the liver

Chitty *et al.* **Nature Cancer** (in revision)

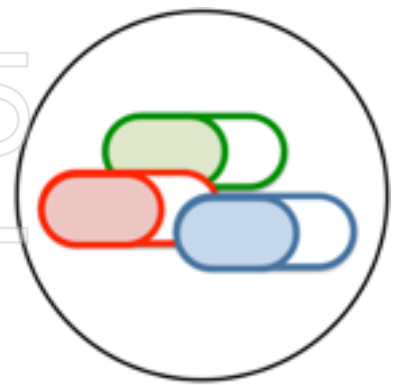




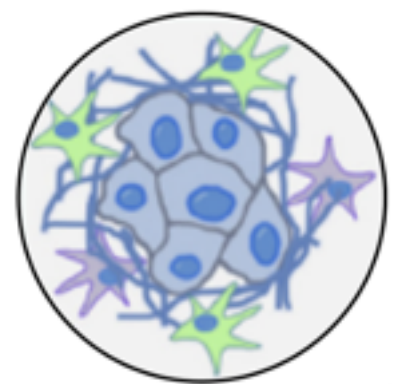
The deposition of scar-like (fibrotic) tissue that accompanies pancreatic tumour development is known to play a significant role in the poor outcome and poor survival of patients



Lysyl oxidases are crucial to the deposition of this scar-like (fibrotic) tissue



Therapies that target this deposition, such as through targeting the lysyl oxidases, offer a way to block cumulative tumour desmoplasia, and augment the efficacy of current standard-of-care therapies



Our pre-clinical data using PXS-5505 in combination with standard of care chemotherapy in mouse and human models of pancreatic cancer demonstrate improved survival supporting future translation into Phase II clinical trials

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## Pharmaxis Q&A





developing breakthrough treatments for fibrosis and inflammation

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