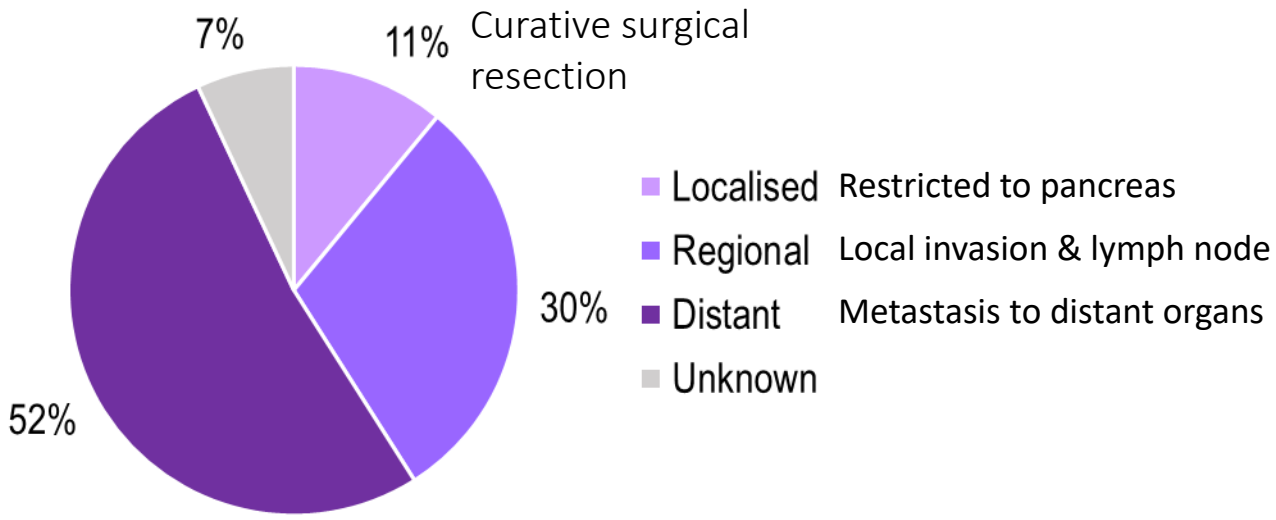
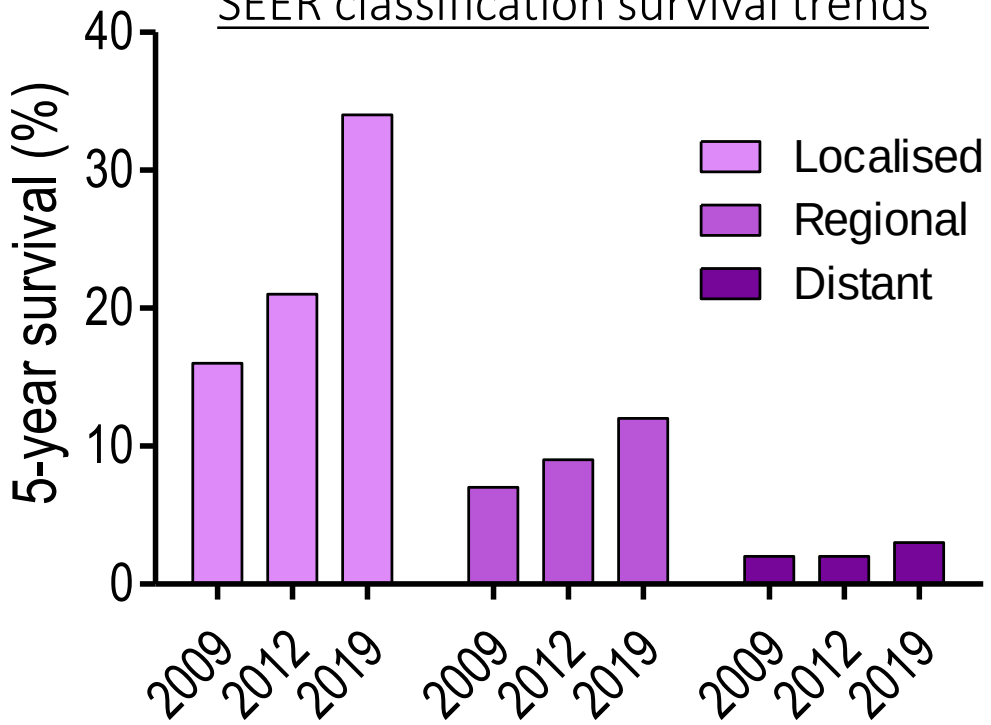
Metastasis markedly reduces PDAC patient survival

The 5-year survival rate for pancreatic cancer has now reached ~11 %.

SEER classification diagnosis stage



SEER classification survival trends



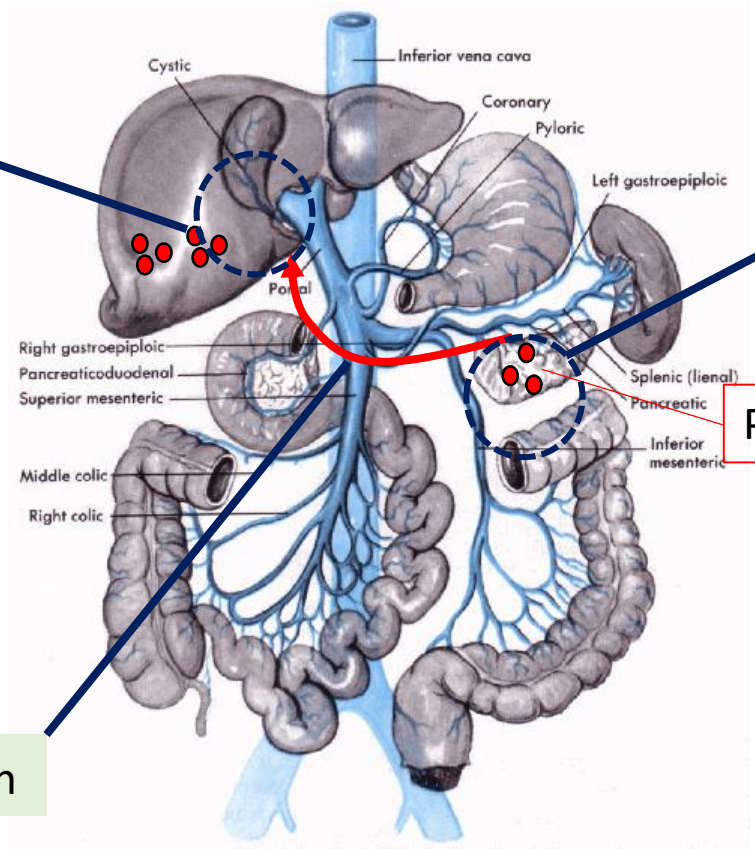
Survival rates for metastatic PDAC patients remain low (~ 3%) despite standard of care chemotherapy treatments.

Infographics generated from the latest Surveillance, Epidemiology, and End Results (SEER) Program statistics available from the NCI

Steps of the metastatic cascade in pancreatic cancer

4. Extravasation
5. Colonization

Dormancy



1. Invasion
2. Intravasation

Pancreas

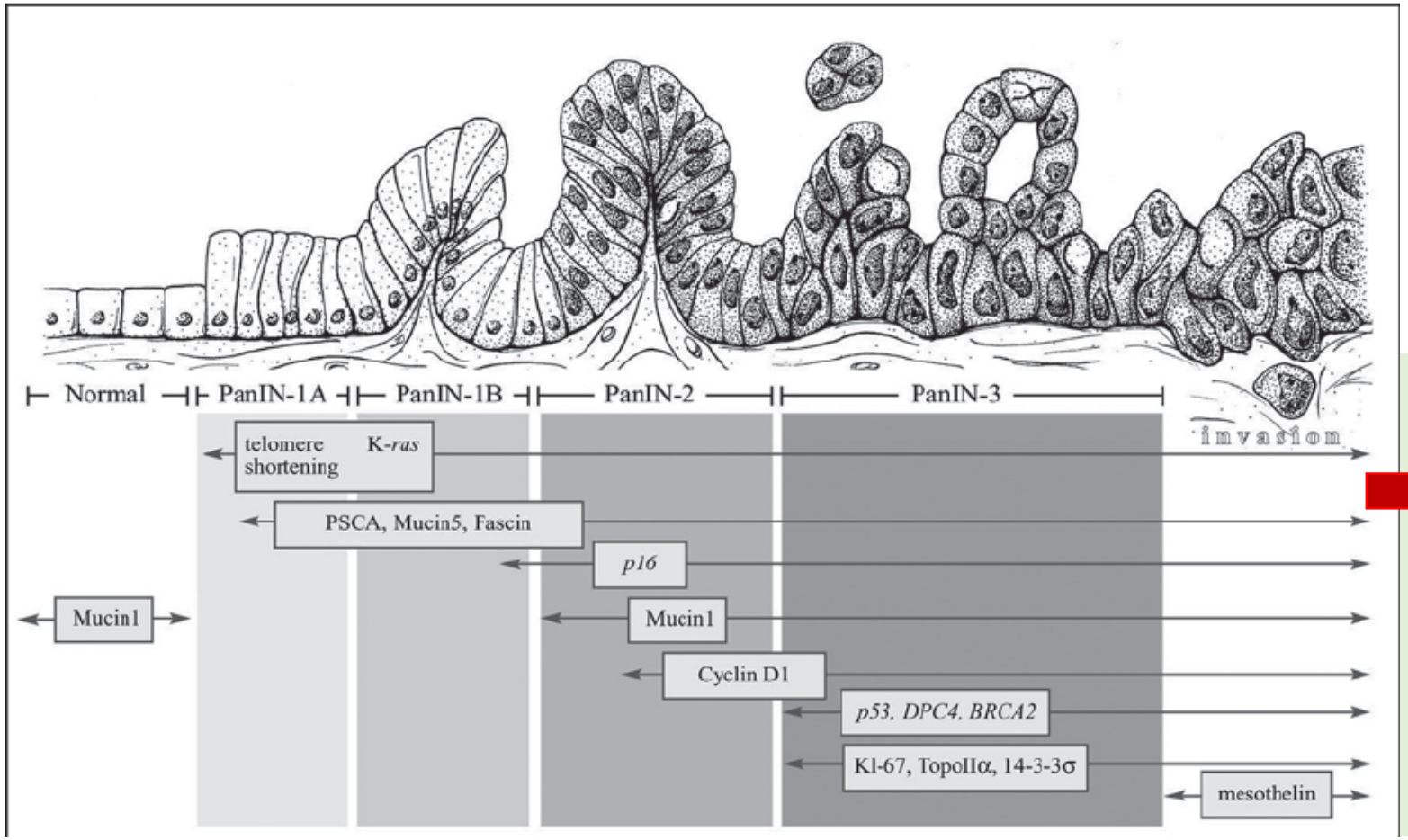
3. Dissemination

Peinado et. Al, Nat Med 2012
Qiang et al., Nature 2011
Acharyya et al., Cell 2012
Ryan, Hong & Bardeesy, NEJM 2014

Time point of metastatic spreading

Time >12 years

Metastasis



Late dissemination model: linear progression

First local progression, then metastatic spreading.

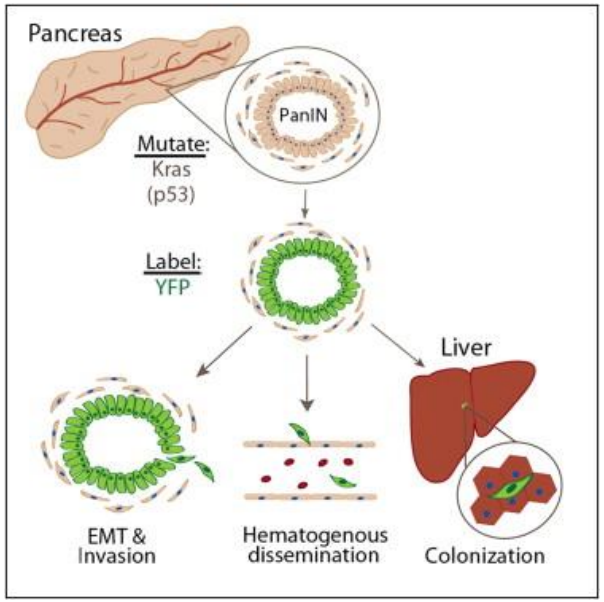
Invasion → **Dissemination** → **Colonisation**

32% **52%**

Patients at diagnosis stage

Klein, Nature Reviews Cancer, 2009
Koorstra et al., Pancreatology, 2008

Metastatic spreading is an early event

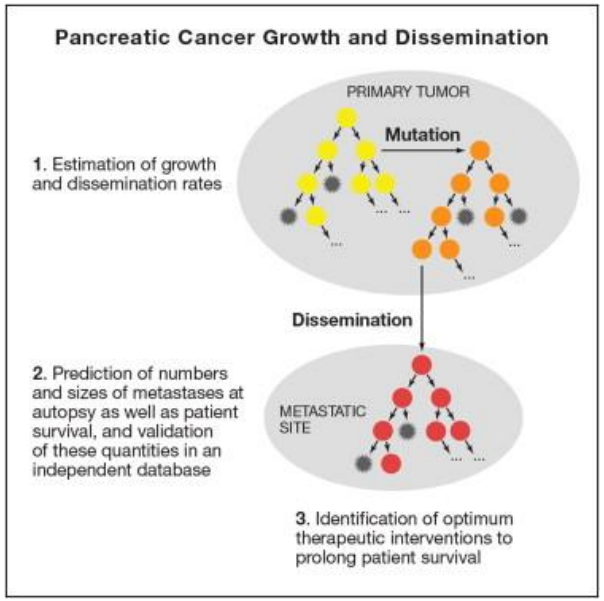


"**EMT and dissemination precede pancreatic tumour formation**"

Approach used:

Pre-clinical mouse models used:
Fluorescence reporter mouse lines
Pdx1-Cre; KrasG12D; p16/p19fl/+; RosaYFP ("IKCY")
Pdx1-Cre; KrasG12D; p53fl/+; RosaYFP ("PKCY")

Rhim et al., Cell, 2012

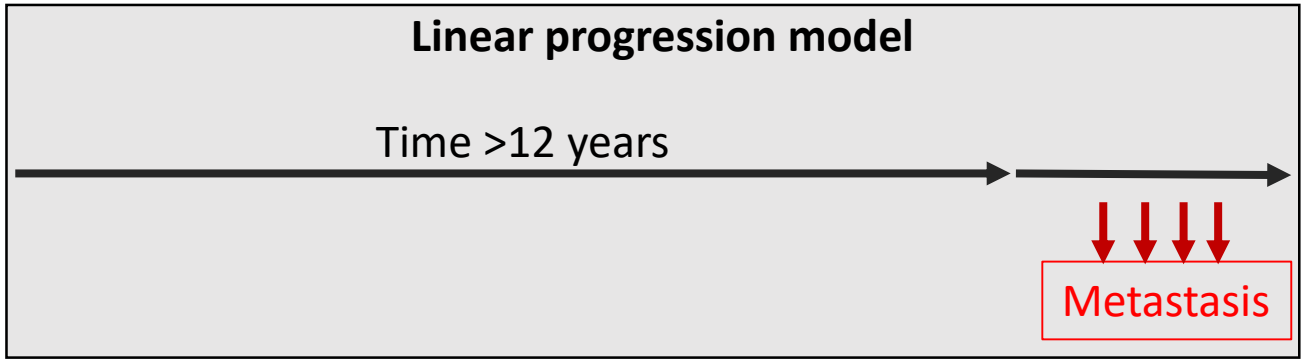


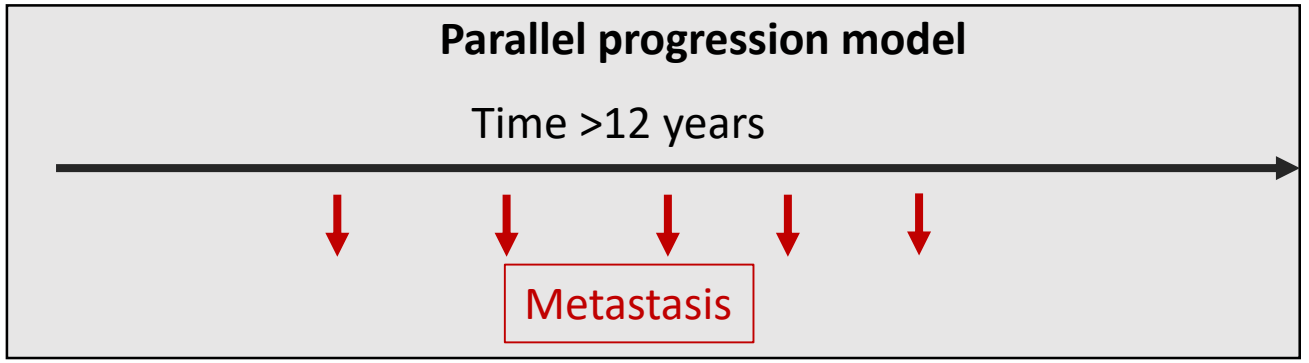
"Model predicated that **even when primary tumours are small**, all patients are expected to harbour cells that are **capable of metastasis** "

Approach used:
Mathematical model based on autopsy data of n= 101 PDAC patients

Haeno et al., Cell, 2012

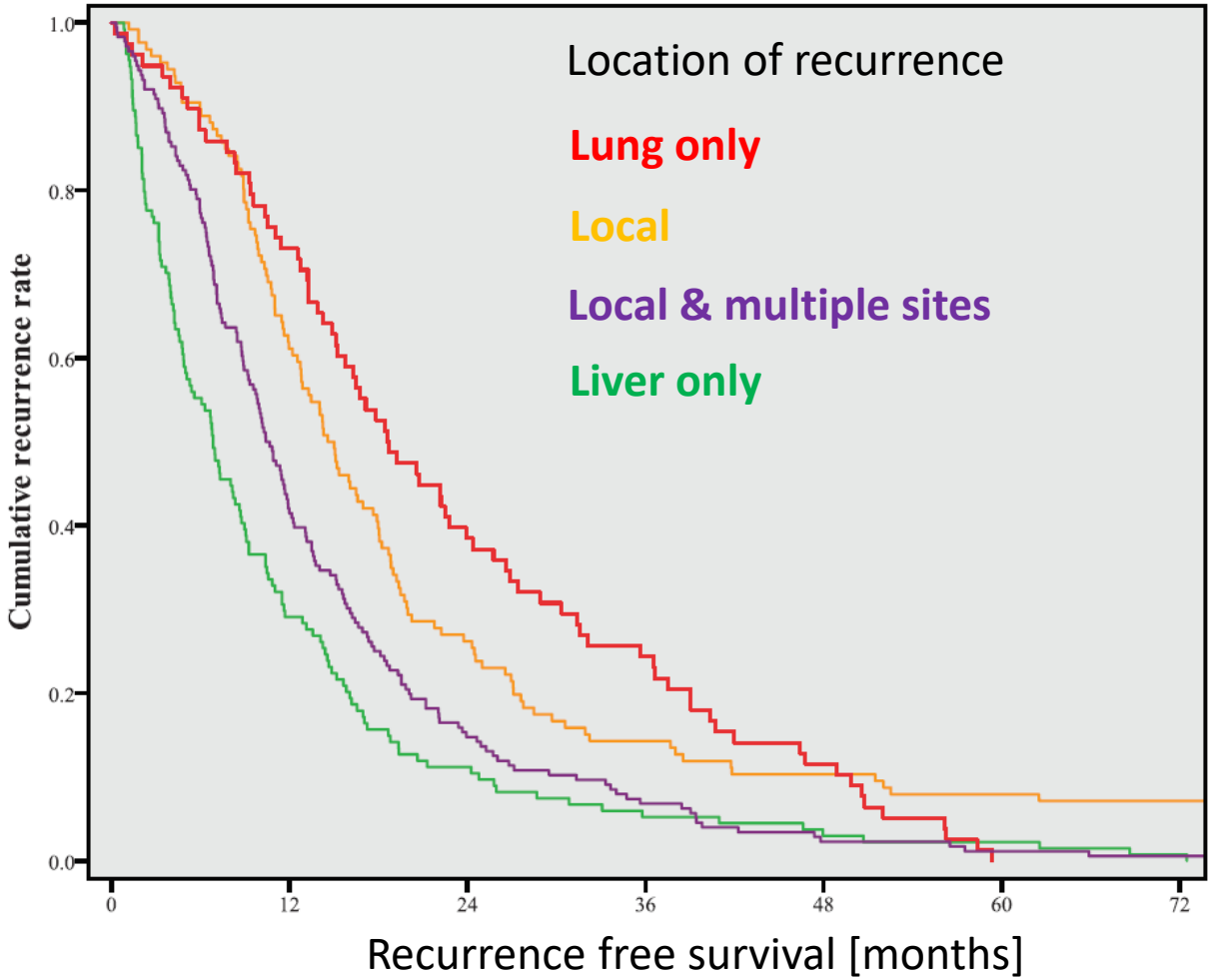
Metastasis progression models





Rapid recurrence after surgical resection of pancreatic cancer

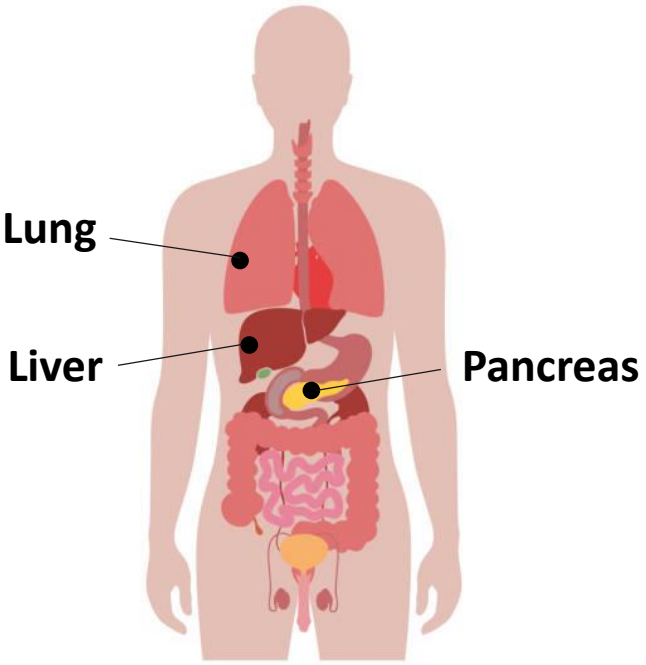
- Despite adjuvant chemotherapy > 70% **relapse** with distant recurrence **within the first 24 months** after surgery.
- **Timing or recurrence strongly correlates with overall survival.**
- Hepatic metastatic relapse occurs earlier and is associated with poor prognosis.



Groot et al., EJSO, 2019

Key points progression

- **By the time pancreatic cancer is diagnosed it is already a systemic disease in most of the cases.**
- **At time of diagnosis, the metastatic cascade is already completed and metastatic tumours are present.**
- **Current treatments are not effective.**



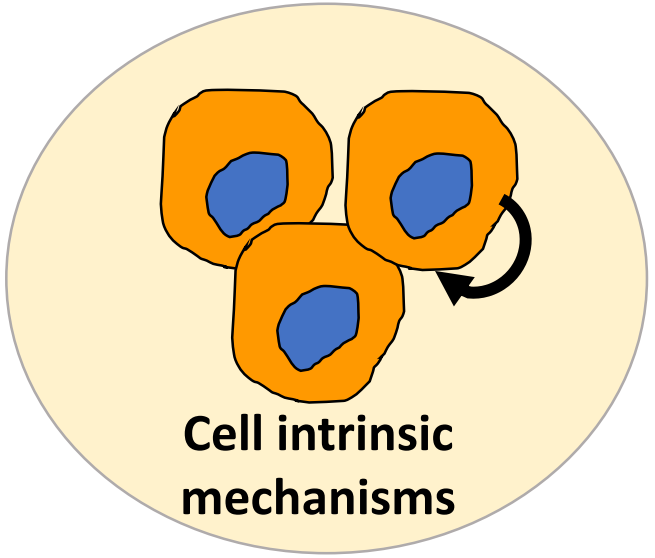
We need to better understand how to restrain metastatic outgrowth or even reverse metastasis?

Mechanisms promoting PDAC metastasis

Genetic changes:
MYC amplification in metastatic PDAC patients.
(Maddipati et al, Cancer Discovery, 2022)

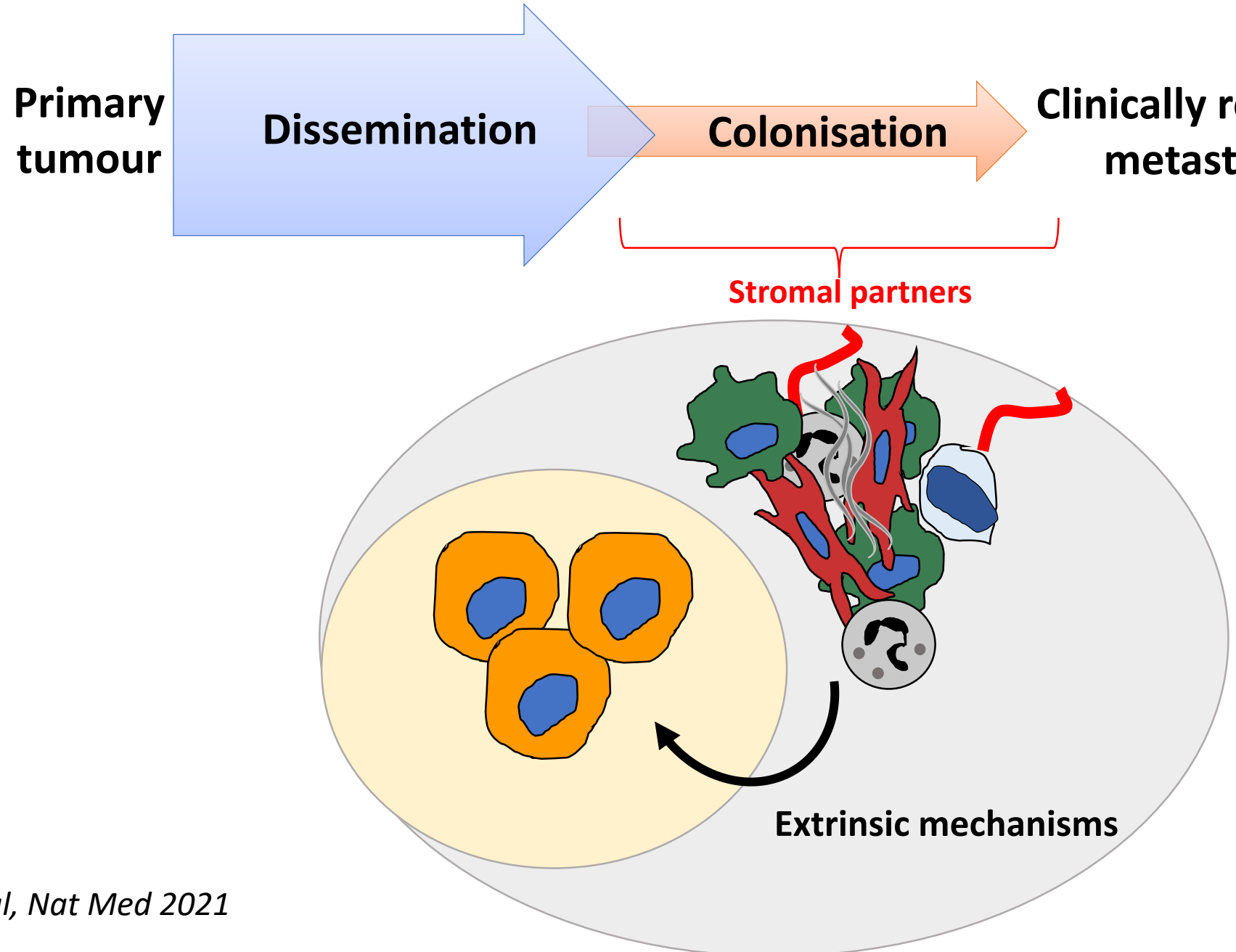
Metabolomic changes
Low glutamine induces Epithelial Mesenchymal Transition (EMT) in PDAC.
(Recouvreux et al., JEM, 2020)

Epigenetic changes:
Enhancer reprogramming (FOXA1-mediated) allowing metastatic PDAC progression.
(Roe et al. Cell, 2017)



>> Enhanced invasiveness, migration, stemness-like phenotype, anchorage-independent growth of cancer cells

Colonisation of distant organs is a rate limiting step



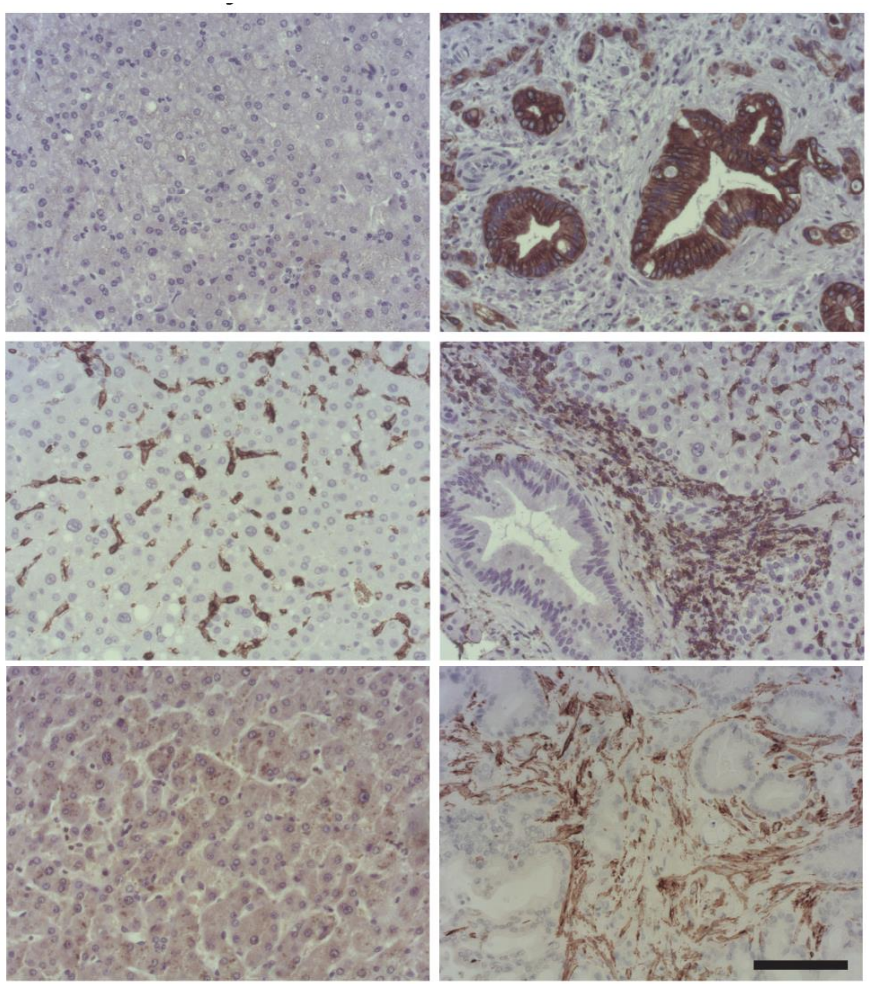
Ganesh et al, Nat Med 2021

Metastatic PDAC cells induce the accumulation of immune/stromal cells in the liver

Cancer cells
(CK19+)

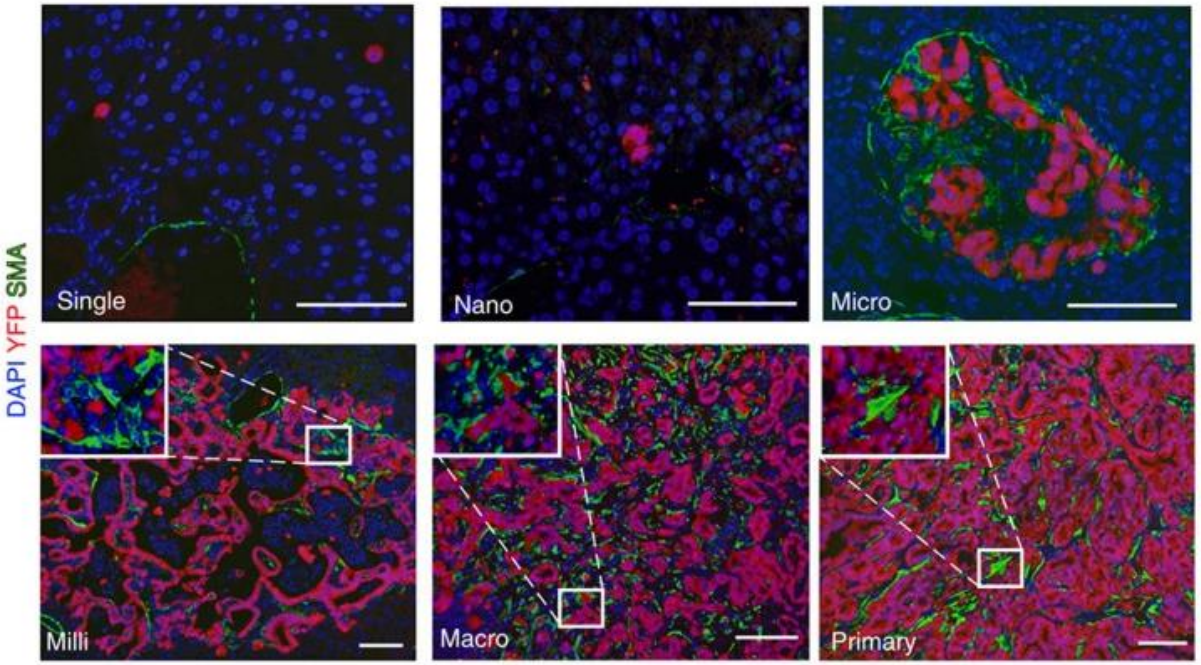
Hematopoietic cells
(CD45+)

Myofibroblasts
(αSMA+)



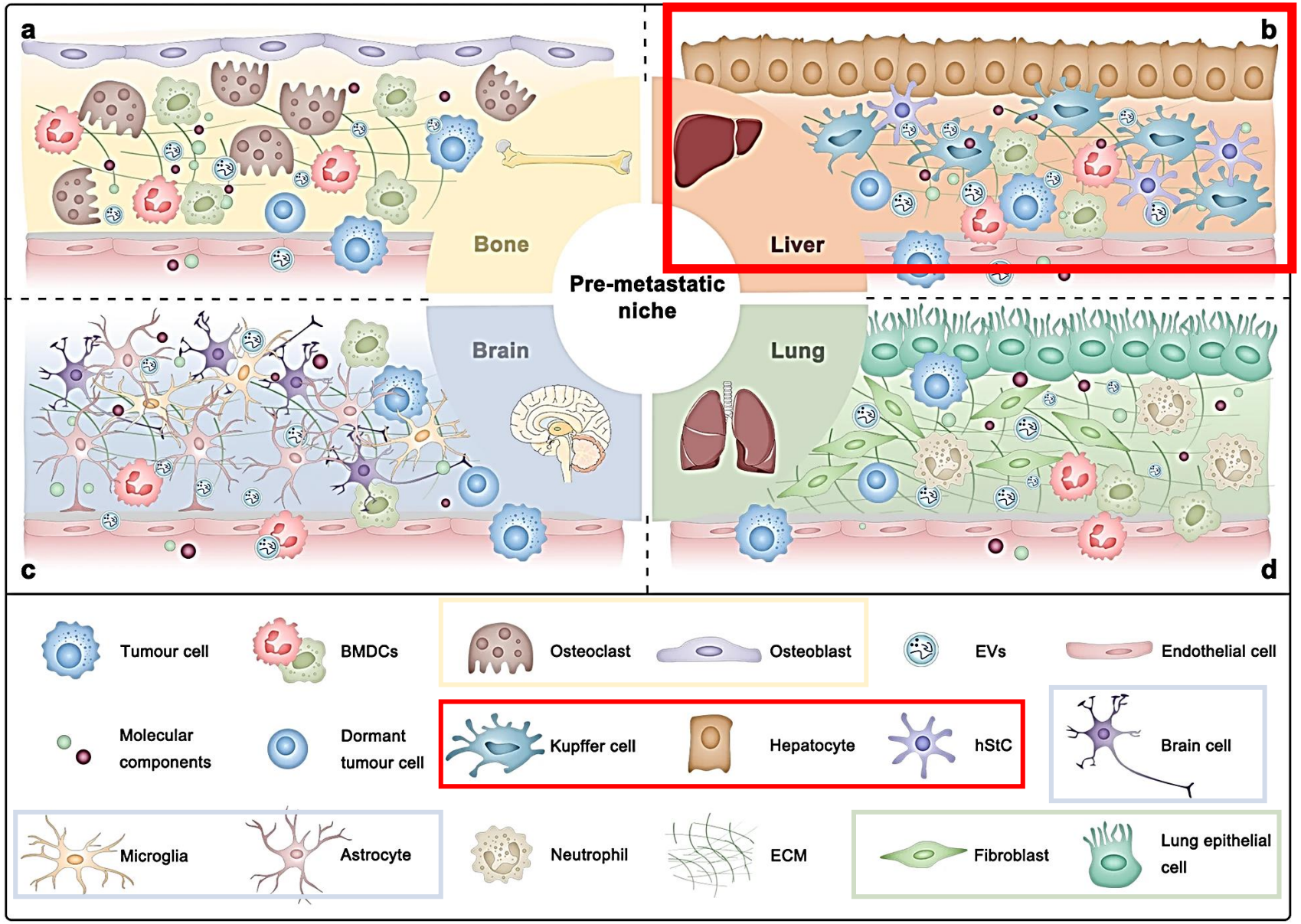
Scale bar = 100 um

Nielsen et al., NCB, 2016
Quaranta et al, Cancer Research, 2018



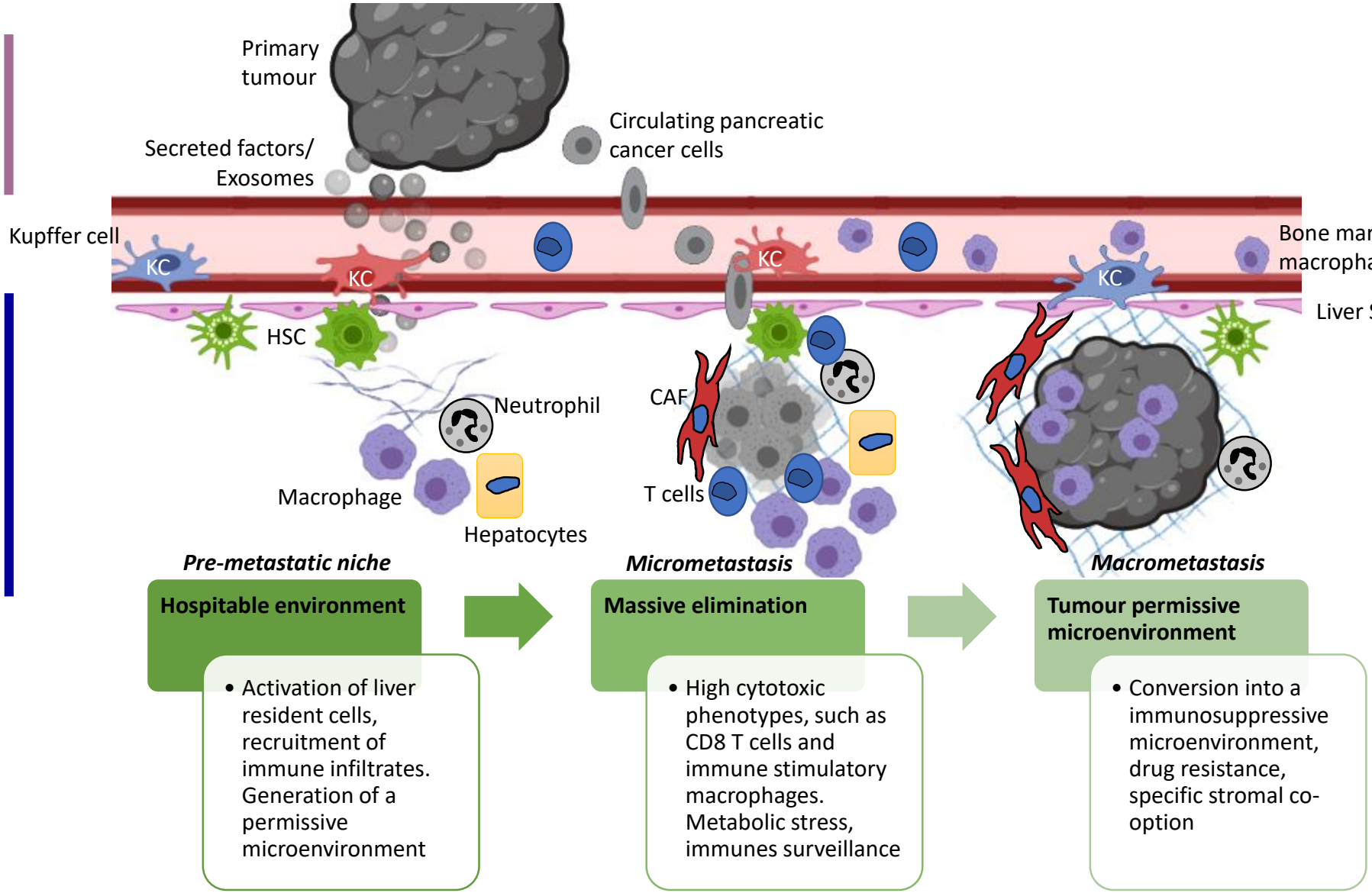
Aiello et al., Nature Commun, 2016

Metastatic niches are organ specific and multi-cellular



Wang *et al*, Molecular Biomedicine, 2021

Distinct stomal partners promote PDAC liver metastasis



Neutrophils:
Steele et al., Cancer Cell 2016
Gorden-Weeks et al., Hepatology, 2017

Macrophages:
Nielsen et al, Nat Cell Biology, 2016,
Griesmann et al., Gut, 2017

Exosomes:
Costa-Silva et al., Nat Cell Biology, 2016

Hepatocytes:
Lee et al., Nature 2019

Fibroblasts:
Bhattacharjee et al., JCI, 2021

Adapted from Ganesh at al., Nature Med, 2021

Cancer Associated Fibroblasts

- Different CAF subtypes (myCAF, iCAF, apCAF): Tumour-supportive and tumour suppressive roles in PDAC.

(*Elyada et al, Cancer Discovery 2019)*

- CAFs show **fibroblast-like** gene signature in the pancreas, while hepatic fibroblasts show a **pericyte-like** signature
  (Raghaven et al., Cell, 2021)

- Distinct cellular origin (PSC vs HSC vs mesenchymal stem cells)
  (*Helms et al., Cancer Discovery, 2022*)

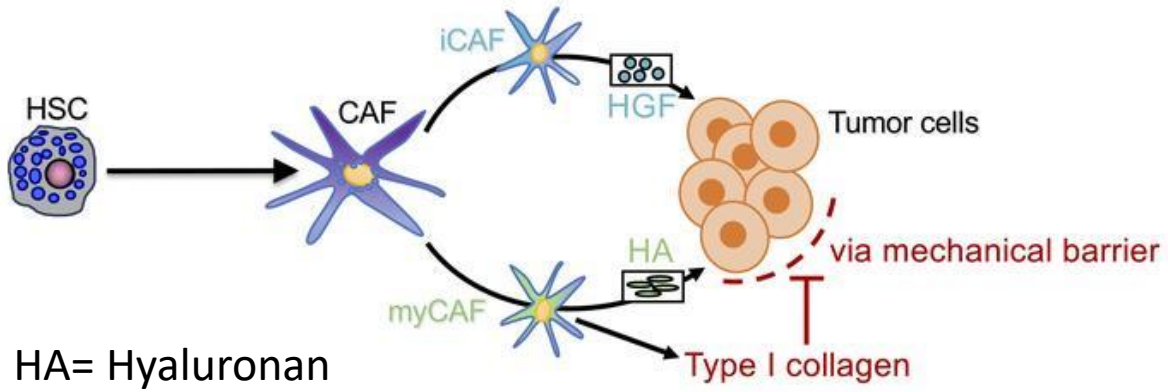
Different organs – different functions:

Pancreas

MyCAF: Depletion of **αSMA+** CAFs accelerates tumour progression at primary site because loss of Type I collagen.
Ozdemir et al., Cancer Cell, 2014

Liver

MyCAF: Depletion of **αSMA+** CAFs reduces liver metastasis
Bhattacharjee et al., JCI, 2021

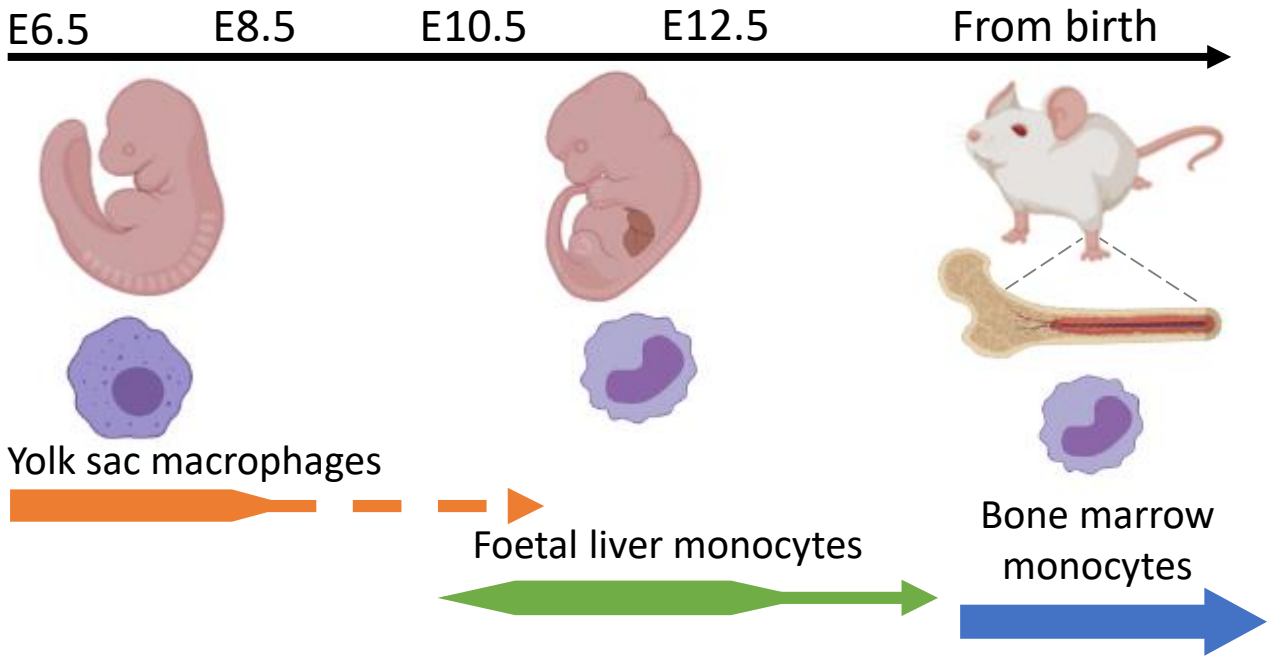


HA= Hyaluronan

Tumour associated macrophages

- **Monocyte derived macrophages versus tissue resident macrophages (Kupffer cells).**
- **Macrophage heterogeneity in PDAC liver metastasis.**
- **Macrophage conversion (immune stimulatory vs immunosuppressive)**

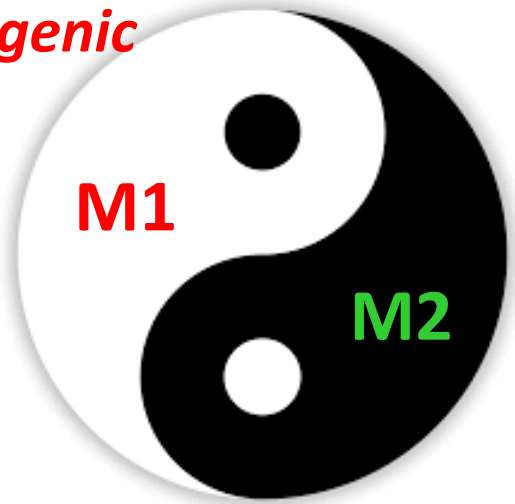
Origin



Pollard et al., Nature Rev Immunol, 2009
Ruffel et al., Trends Immunol, 2012
Noy et al., Immunity, 2014

Activation / Conversion

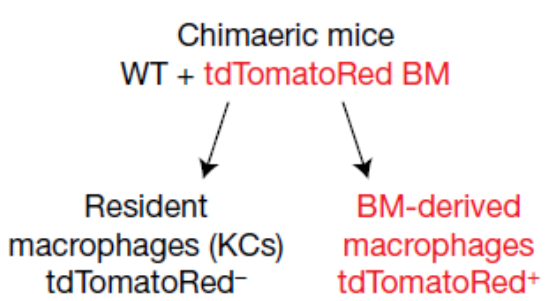
Immune stimulatory
Anti-tumorigenic

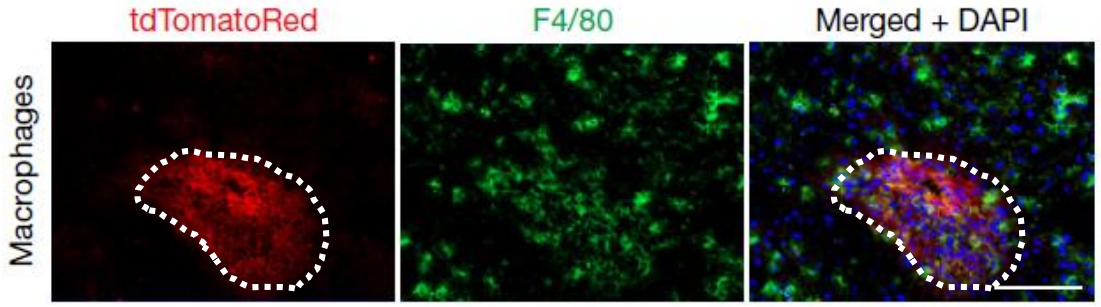


Immune suppressive
Pro-tumorigenic

Mielgo & Schmid, BMP reports, 2013
Bronte & Murray, Nat. Med. 2015
Klemm & Joyce, Trends in Cell. Biol, 2014

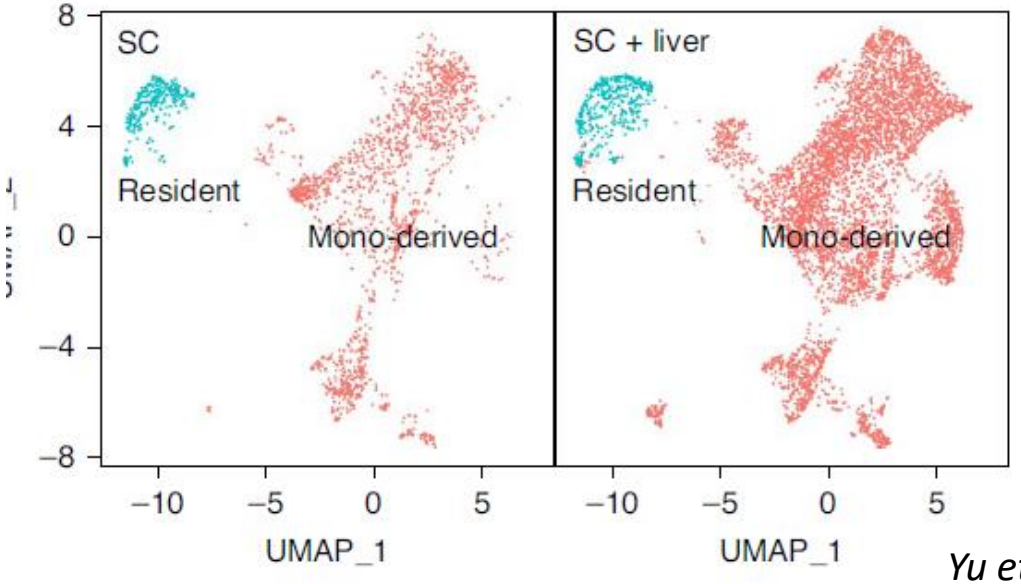
Monocyte-derived macrophage populations expand during liver metastasis

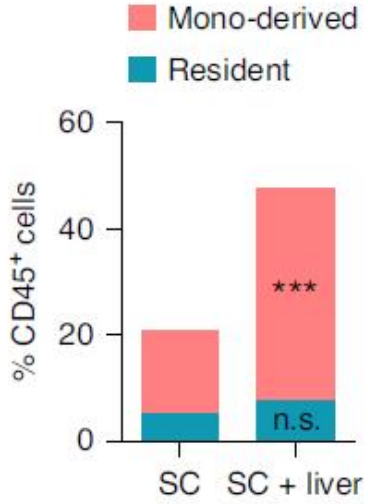




Nielsen et al., Nat Cell Biology, 2016

Tumour free liver **Tumour bearing liver**



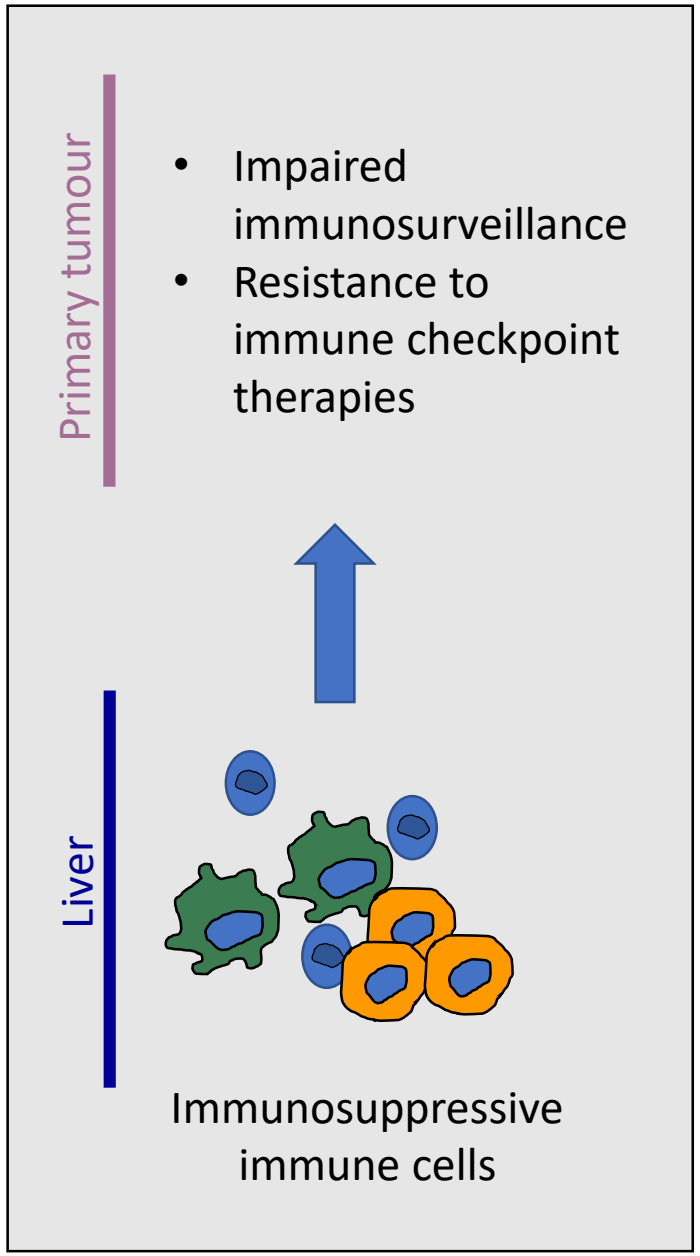


Yu et al., Nature Med, 2021

Functional characterisation:

- Macrophage heterogeneity
- Immune regulation
- Shaping fibrotic response

Systemic immunosuppressive effects mediated by liver metastasis



Melanoma, Non Small Cell Lung Cancer, Colorectal cancer models:

- Systemic "immune desert"
- Metastasis associataed macrophages mediated depletion of activated CD8+ T cells
- Resistance to immunotherapy
- Radiotherapy stimulates anti-tumour immunity and blunts macrophage immunosuppressive effects

Yu et al., Nature Med, 2021

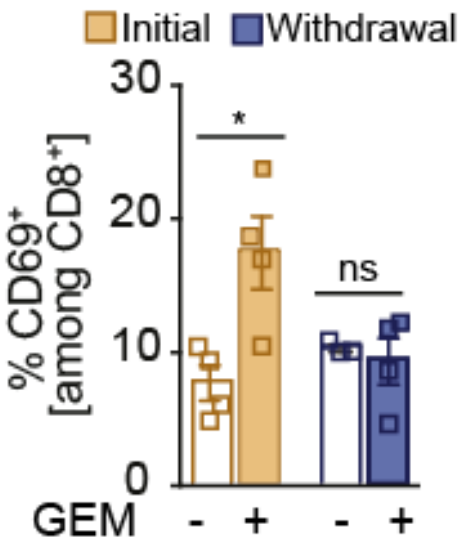
Colorectal cancer model:

- Tumour antigen presence within the liver leads to systemic immunity
- Regulatory T cells and intratumoral CD11b+ monocytes
- Resistance to immunotherapy
- Depletion of Treg cells restored response to anti-PD-1 therapy

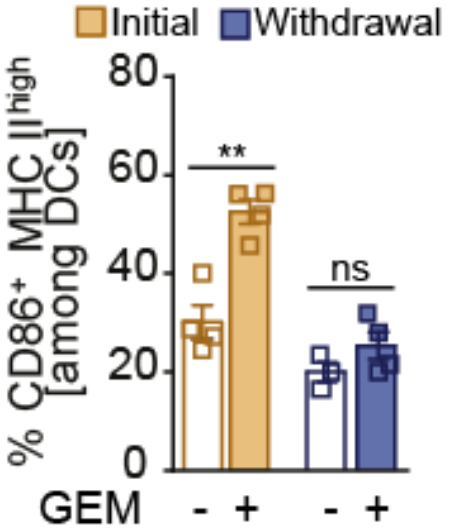
Lee et al., Science Immunology, 2020

Chemotherapy induces a temporary activation of immune cells in metastatic tumours in PDAC

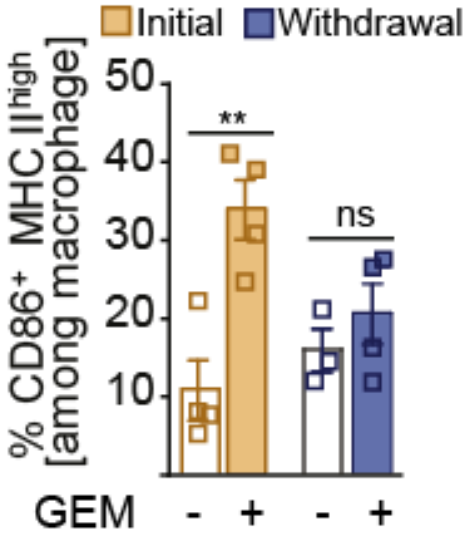
CD8+ T cell



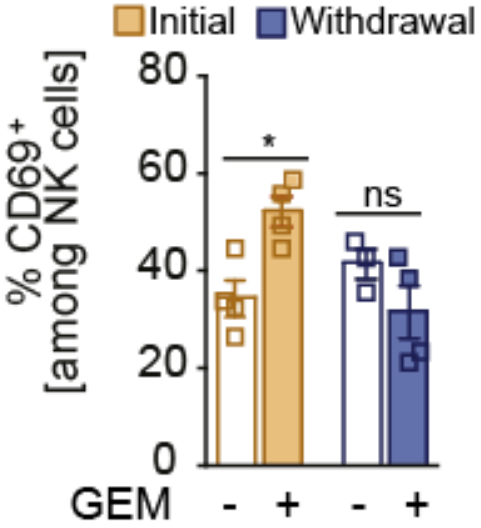
Dendritic cells

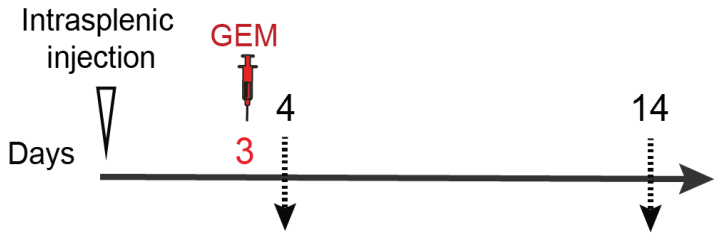


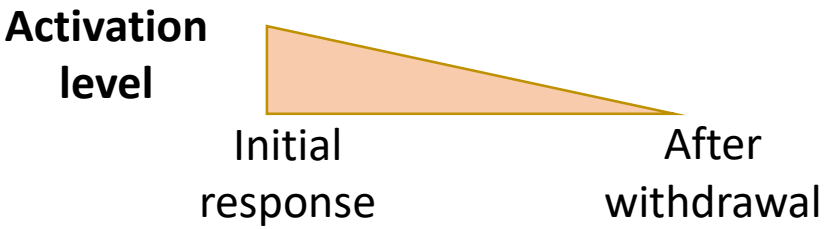
Macrophages



NK cells







Bellomo et al., Gut, 2022

Emerging areas

- **The same, but different?** Decipher stroma heterogeneity, cell origin, and functions of different stroma cells at metastatic sites. Are there conserved molecular targets between the primary and the metastatic tumour site?

- **Who regulates who and how?** Reciprocal interactions among different stromal cells and implication of emerging stroma-targeted therapies.

- **Metastatic niches and therapies**: Impact of adjuvant and neo-adjuvant therapies on the metastatic sites. New opportunities for treatments?

- **Genomics and stroma:** Whether and how mutational changes in cancer cells affect tumour-stroma-immune interactions and could this be exploited for personalised therapies?

- **Keep it local:** Non-invasive markers to detect early disease initiation prior metastatic dissemination.

Challenges and gaps

- We need to **study tumour cells in relation to other cells**. Primary non-cancerous cells loose their propensity in culture? Can we get better ex-vivo models?

- Patients: **Integration of metastatic patient samples**. Matched samples (primary/metastasis, pre/post treatment)

- **Multidisciplinary teams/Collaborative working**: scientists with expertise in different areas, medical oncologists, surgeons, pathologists, technologists, research nurses.

- Current **pre-clinical mouse models for PDAC metastasis have limitations** (biologically and financially). Subsidized centre(s) (charity/UKRI) maintaining larger mouse colonies of metastatic PDAC models accessible for UK scientists?

- **Omics web app for PDAC specific data sets** allowing an uncomplicated access to and sharing of large data sets among pancreatic cancer researchers.