

Setting the Scene - Stroma

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No Cancer Cell is an Island

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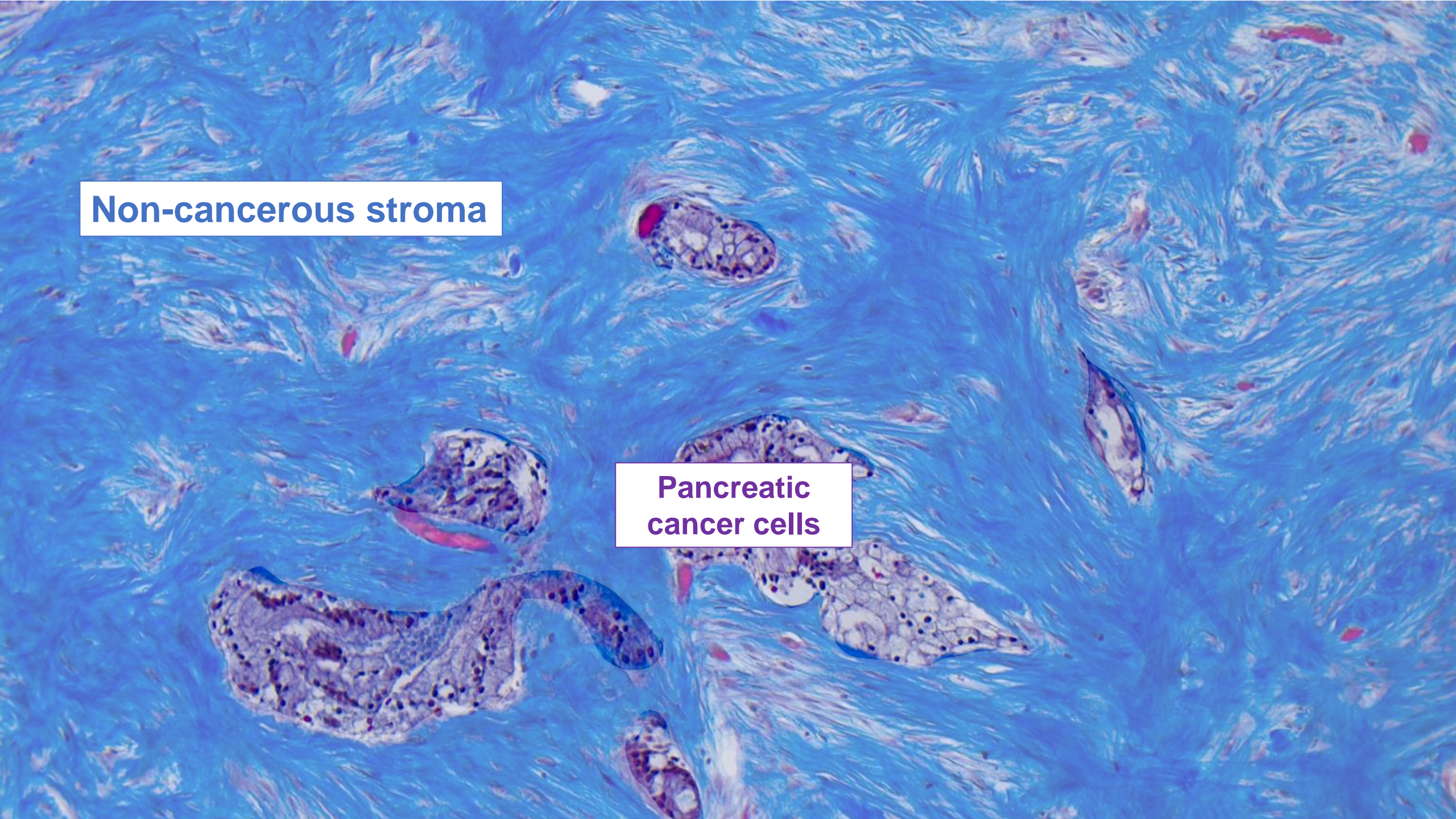
University of Cambridge

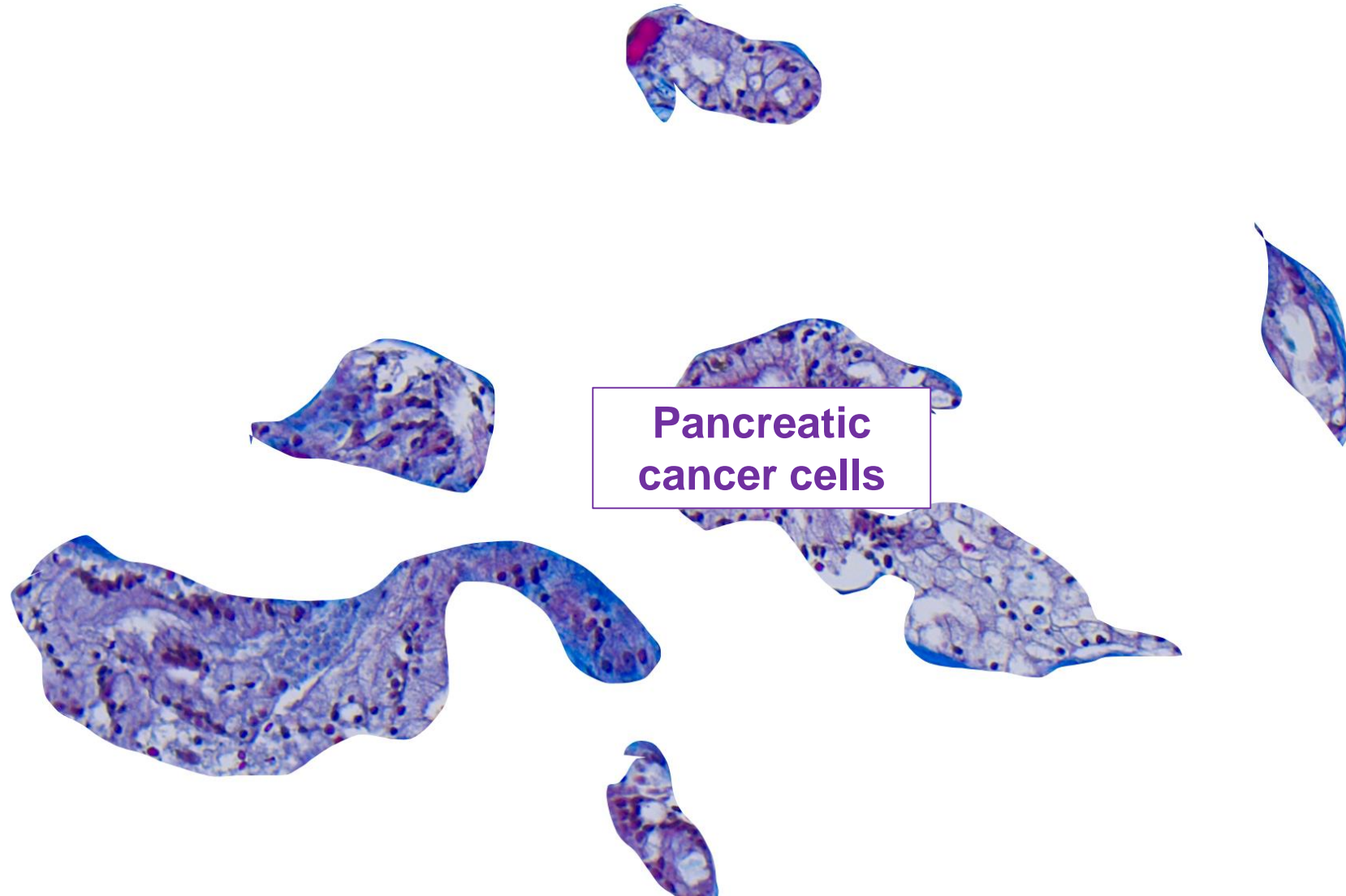
Co-director Pancreatic Cancer Programme

CRUK Cancer Centre

Non-cancerous stroma

**Pancreatic
cancer cells**





**Pancreatic
cancer cells**

Cancer-associated fibroblasts and extracellular matrix play several roles in pancreatic cancer

Metastasis formation promotion

Orimo et al. *Cell* 2005,
Erez et al. *Cancer Cell* 2010, ...

Tumor growth promotion

Immunosuppression

Kraman et al. *Science* 2010, Feig
et al. *PNAS* 2013,
Hutton et al *Cancer Cell* 2021...

T cells

Cancer
cells

Chen, *Cancer Cell* 2021, ...

Tumor restraining

Laklai, *Nat Med* 2016, ...

Biochemical/mechanical cues

ECM deposition

Nutrients

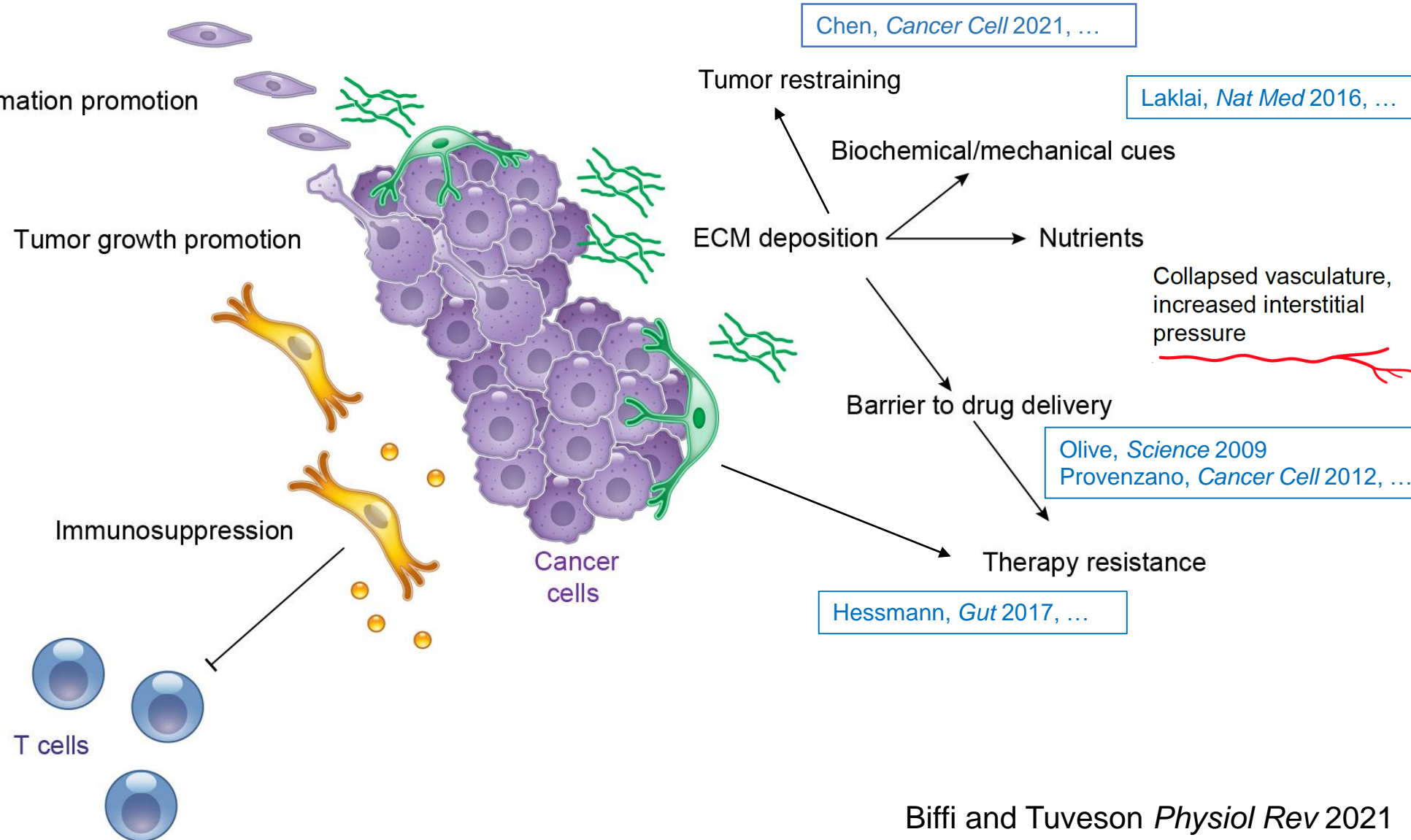
Collapsed vasculature,
increased interstitial
pressure

Barrier to drug delivery

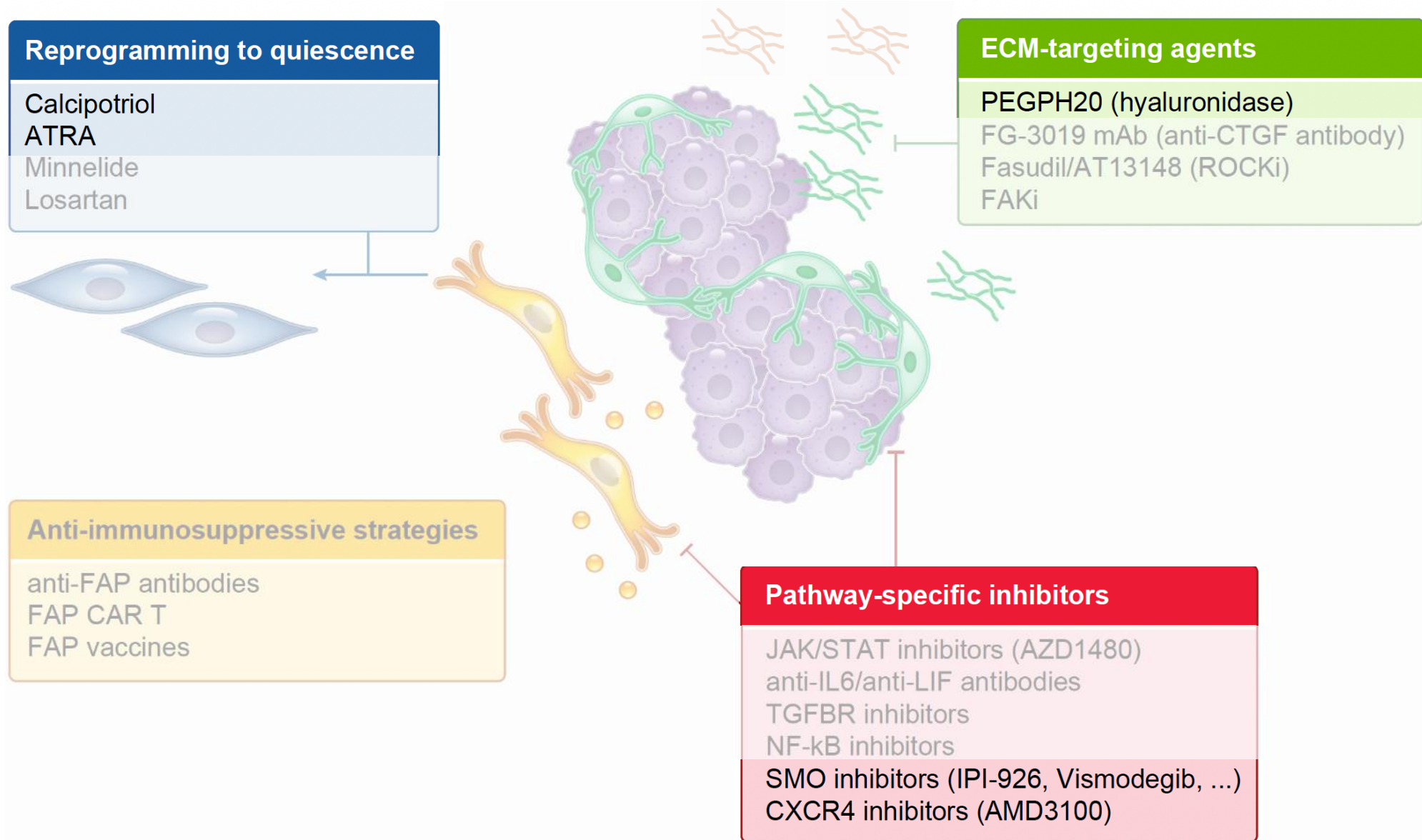
Olive, *Science* 2009
Provenzano, *Cancer Cell* 2012, ...

Therapy resistance

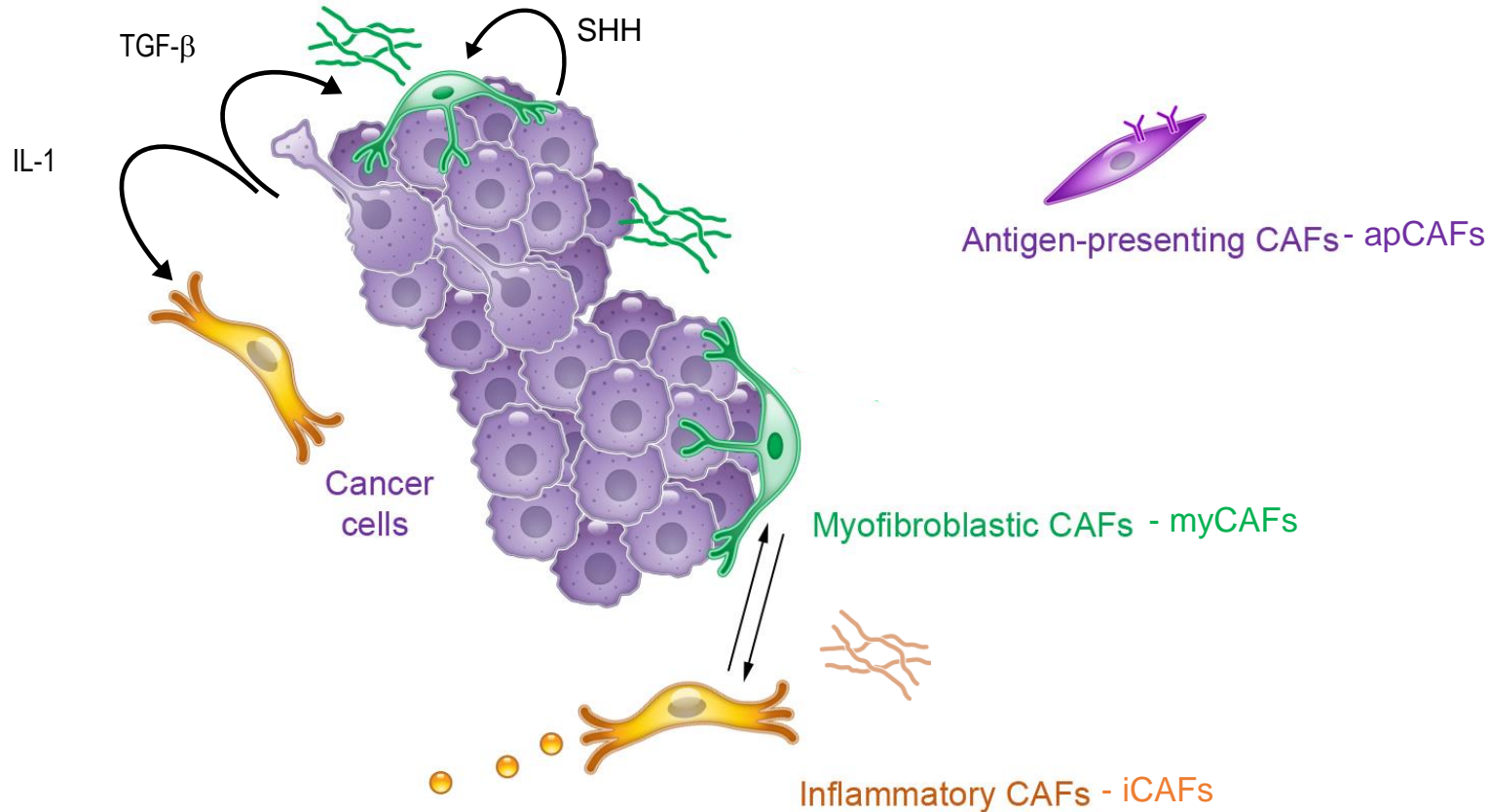
Hessmann, *Gut* 2017, ...



Targeting CAFs and ECM has proven challenging



Pancreatic cancer CAFs are heterogeneous and dynamic



Heterogeneity/Plasticity:

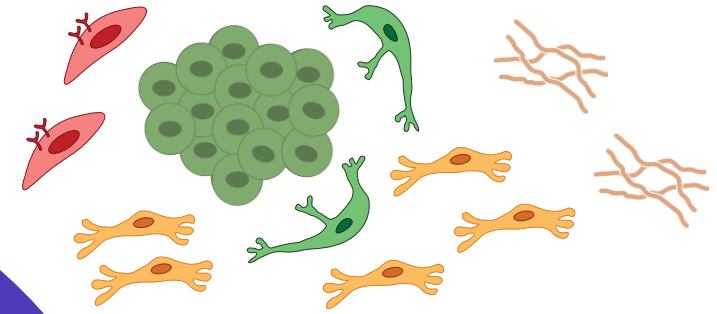
Öhlund, Handly-Santana, Biffi and Elyada, *JEM* 2017
Elyada, *Cancer Discov* 2019
Biffi, *Cancer Discov* 2019
Steele and Biffi, *Clinical Cancer Res* 2021
Dominguez, *Cancer Discov* 2019
Hutton, *Cancer Cell* 2021
Grünwald, *Cell* 2021,
Vennin, *Nat Comm* 2019
Somerville, *Elife* 2020
...

Cells of origin:

Helms, *Cancer Discov* 2021
Garcia, *CMGH* 2020
Huang, *Cancer Cell* 2022

How does cancer genetics affect the stroma?

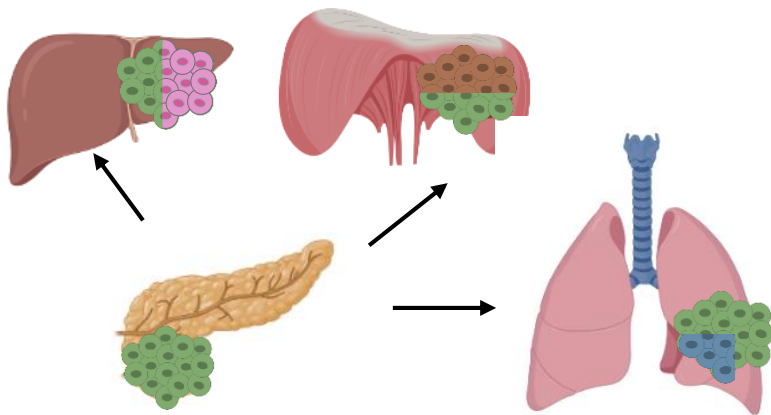
Phenotypic \neq Functional
Heterogeneity



Challenge #1 — Heterogeneity



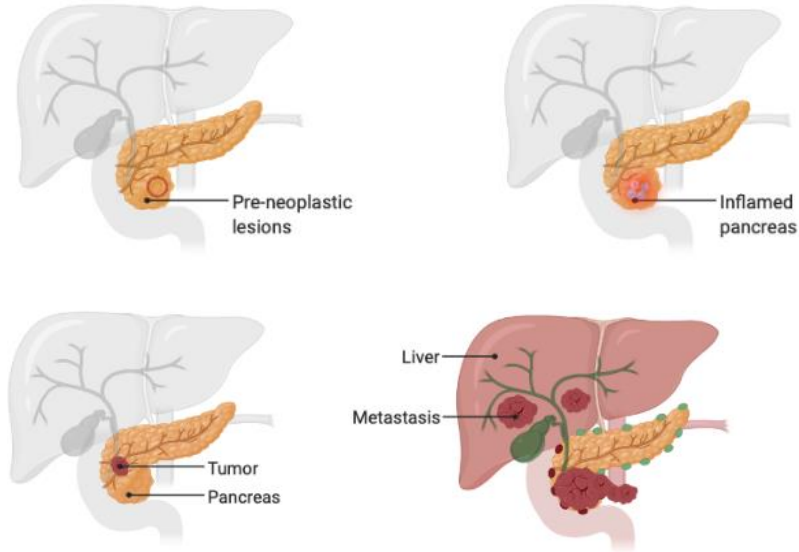
How is the stroma at
metastatic sites?



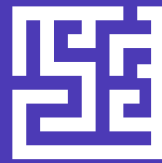
How well
are we capturing this?



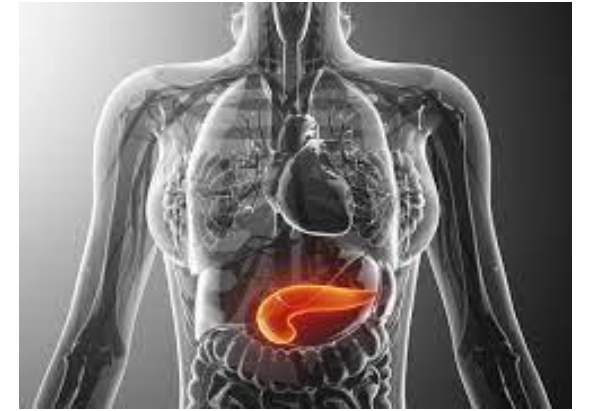
How does the stroma change during cancer progression?



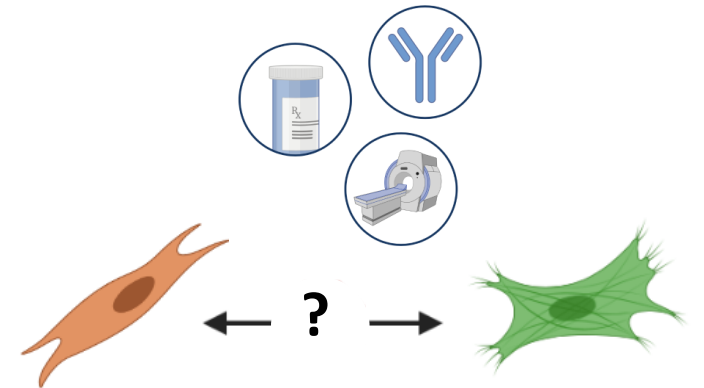
Challenge #2 — Plasticity



How does the host affect the stroma?



How do treatments affect the stroma?





Orthotopic models (3D)



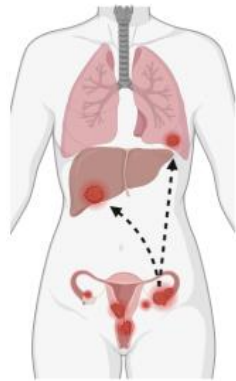
Orthotopic models (2D)



GEMMs

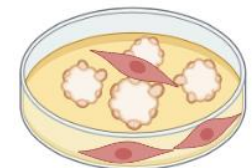


Subcuta ~~STOP~~ models

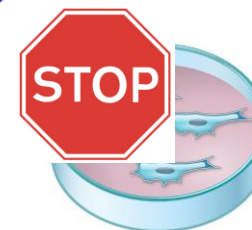


Patient samples

Challenge #3 — Adequate models

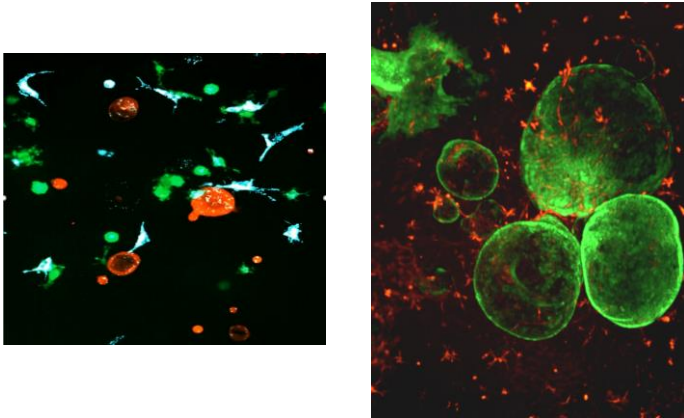


Organoid (co)cultures

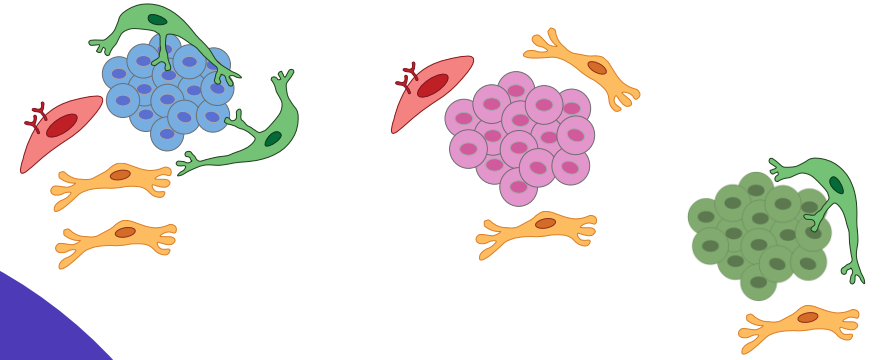


~~STOP~~ 2D (co)cultures

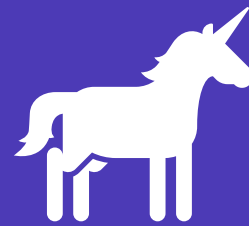
Heterotypic *in vitro* models



Models with different cancer genetics



Strategy #1
—
New
ideas & models



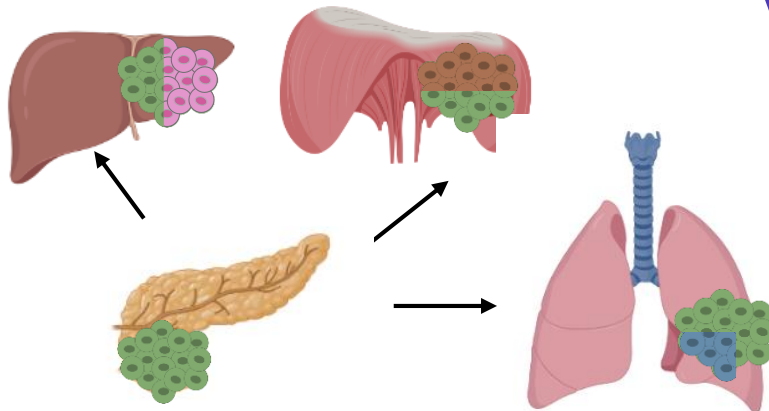
Models to genetically dissect the stroma



“Humanized” mouse models



Models of metastatic disease



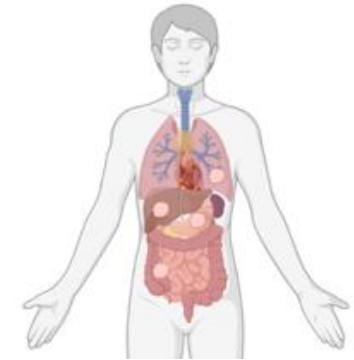
**Not only fibroblasts, not only ECM,
not only immune cells, ...**



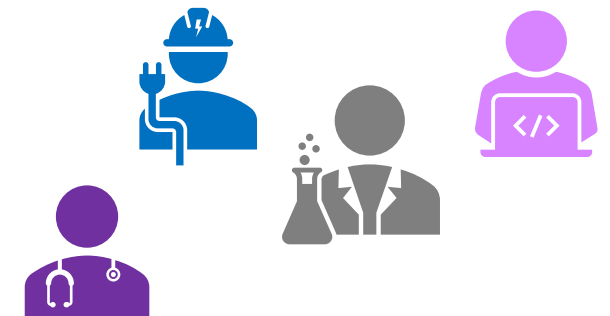
**Strategy #2
—
New
collaborations**



Not only pancreatic cancer



Not only cancer biologists

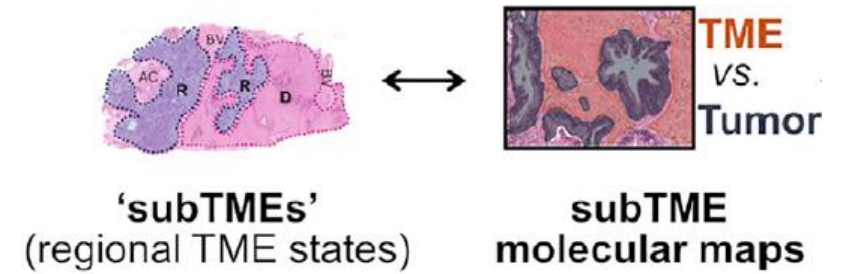


Single-cell transcriptomics/proteomics



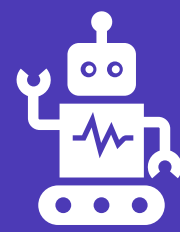
Hutton, *Cancer Cell* 2021

Spatial transcriptomics/proteomics

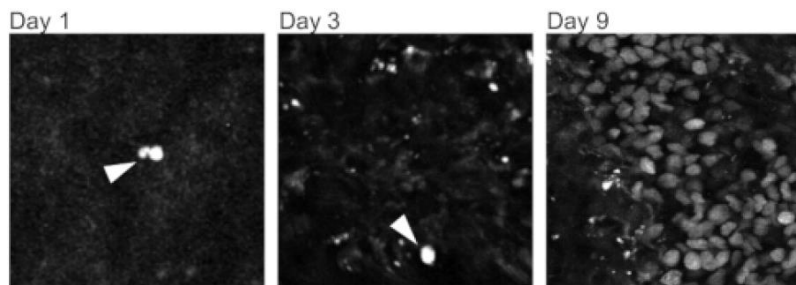


Grünwald, *Cell* 2021

Strategy #3
—
Adequate
technologies

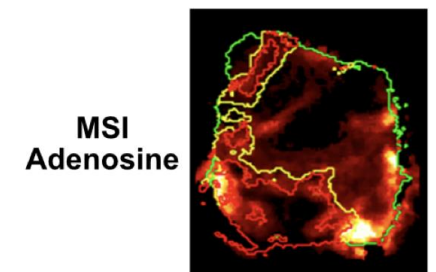


Intravital imaging



Maiorino, *JOVE* 2022

Spatial metabolomics/MSI



Graziano, *BioRxiv* 2022

To sum up





Pancrea_tive Lab

(The Pancreas Initiative)

