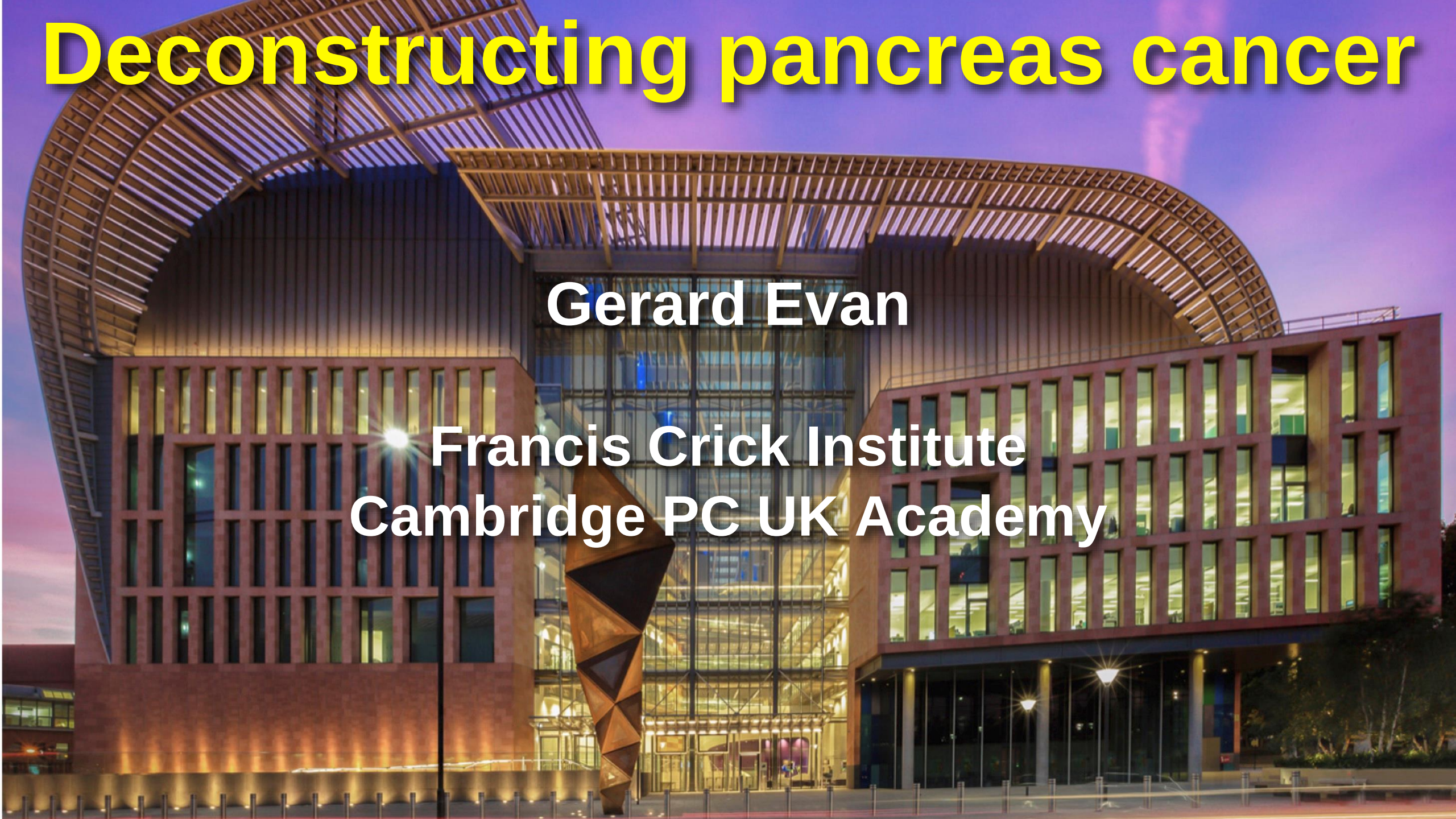
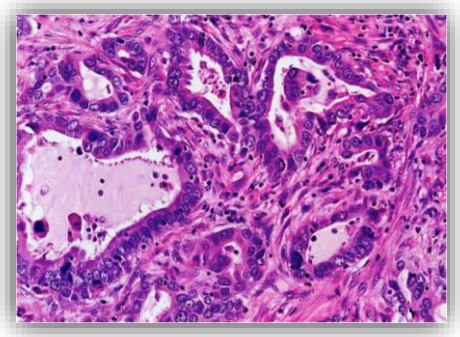
Deconstructing pancreas cancer



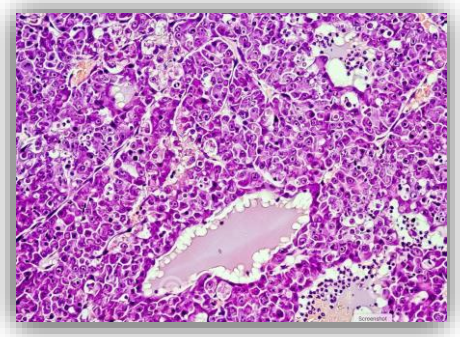
Gerard Evan

Francis Crick Institute
Cambridge PC UK Academy

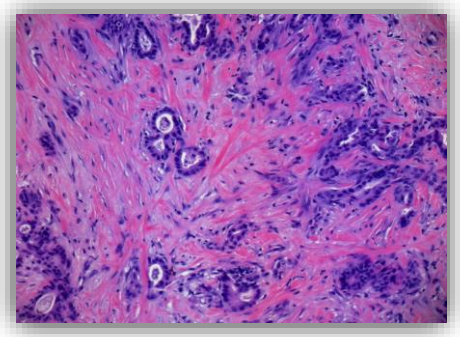
Where do the signature phenotypes of solid tumours come from?



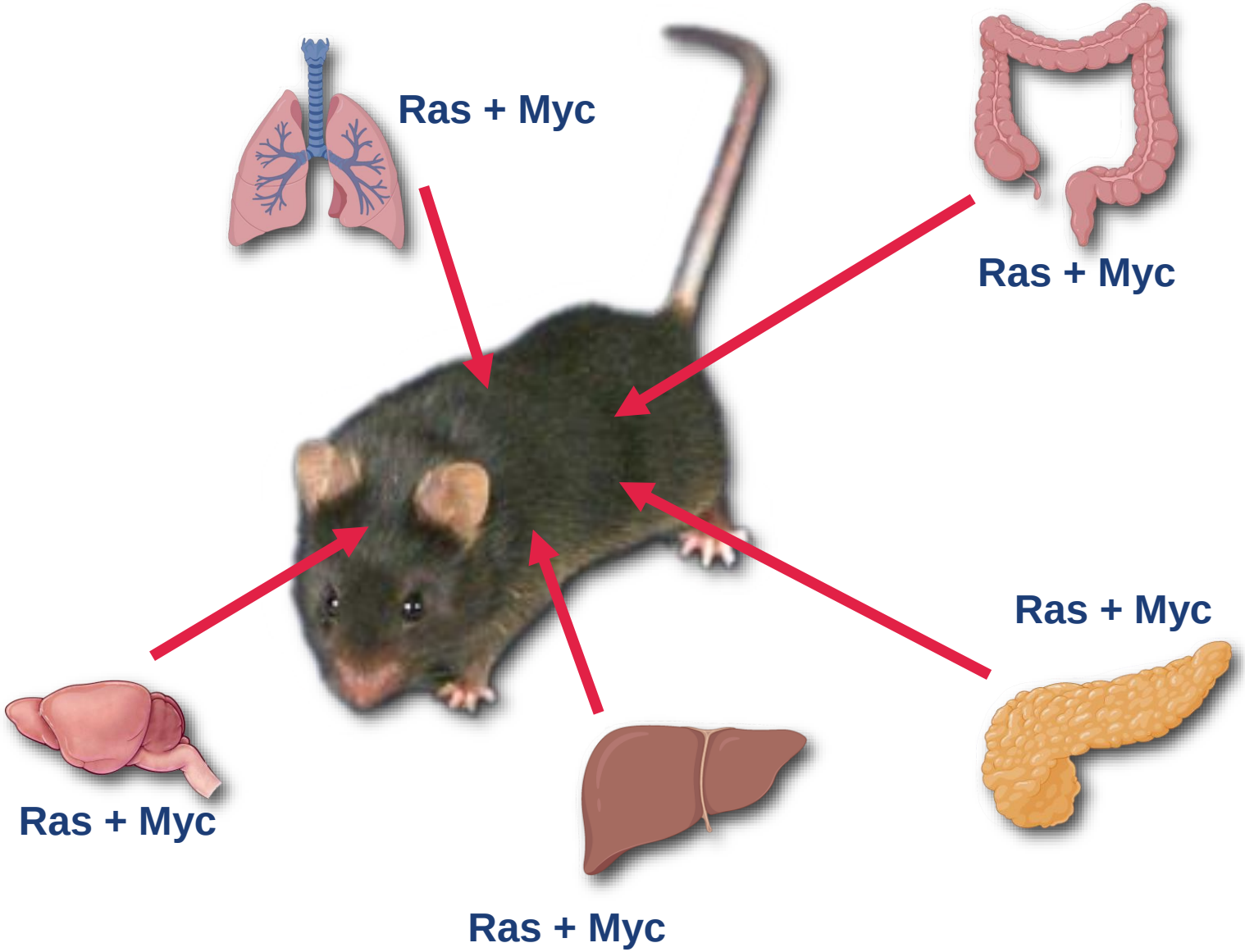
Pancreas
PDAC



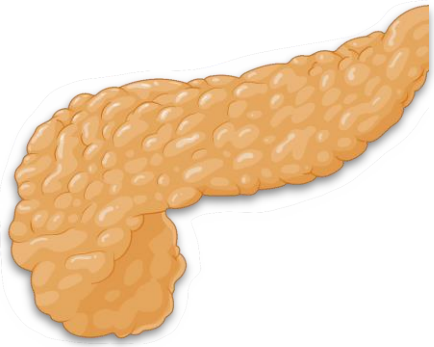
Liver
HCC



Lung
LUAD

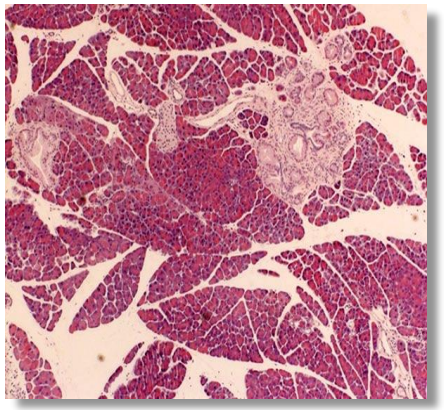


Cancer phenotypes are tissue, not oncogene, specific



pdx1 or *p48*-CRE

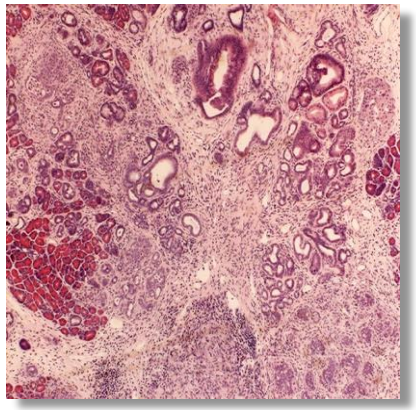
KRas^{G12D} alone



PanIN

+ Myc (3 wk)

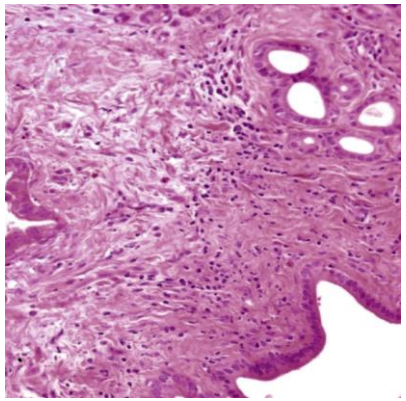
KRas^{G12D} + Myc

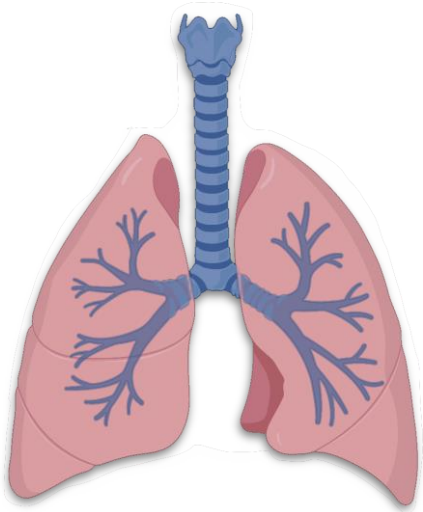


PDAC

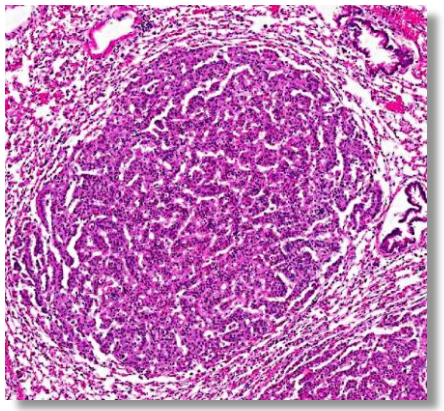
Proliferative
Invasive
Desmoplastic
Inflammatory
+Macrophage
+Neutrophils
Immune cold
Hypoxic
Avascular

Human PDAC



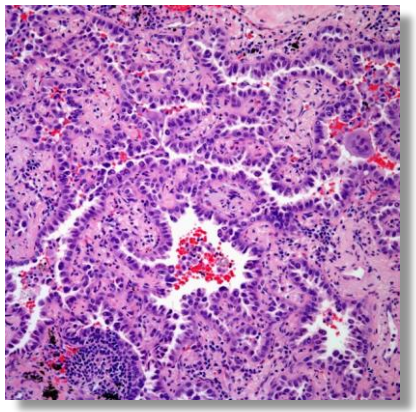


AdenoV-CRE



Adenoma

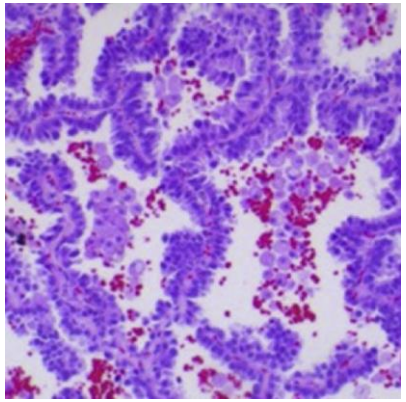
+ Myc (3 wk)



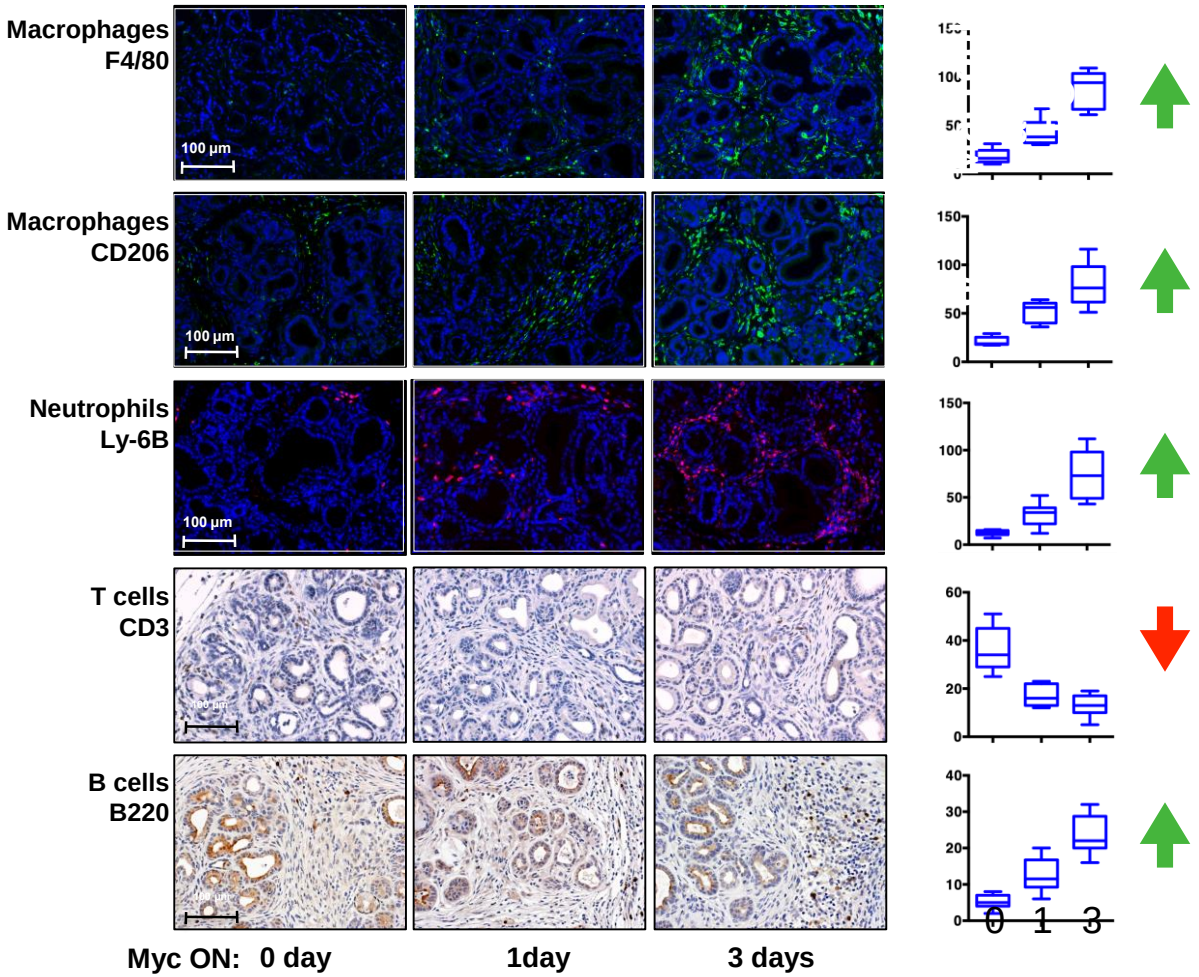
LUAD

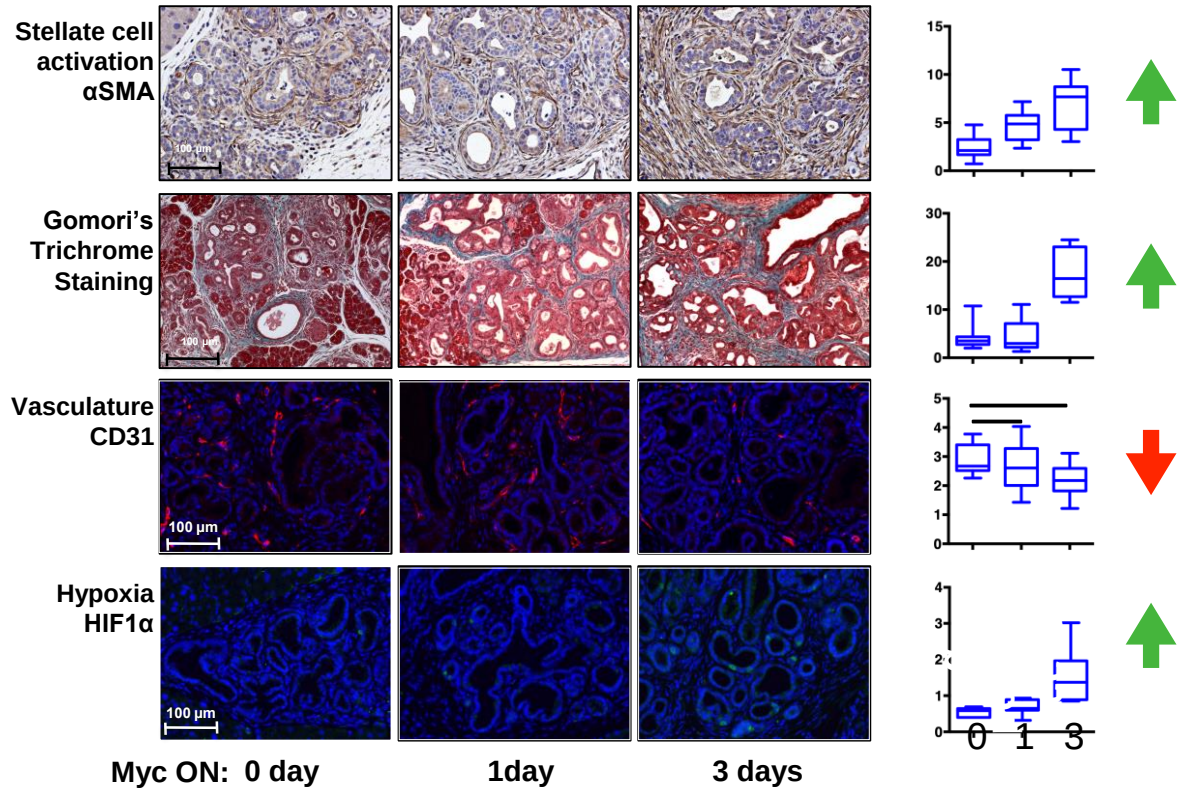
Proliferative
Invasive
No desmoplasia
Inflammatory
+Macrophages
Immune cold
Normoxic
Highly angiogenic

Human LUAD



Myc activation *in the epithelial compartment* of KRas^{G12D}-driven PanIN triggers *immediate* transition to adenocarcinoma





Nicole Sodir, Tania Campos

De-activating Myc triggers rapid PDAC regression

Myc ON

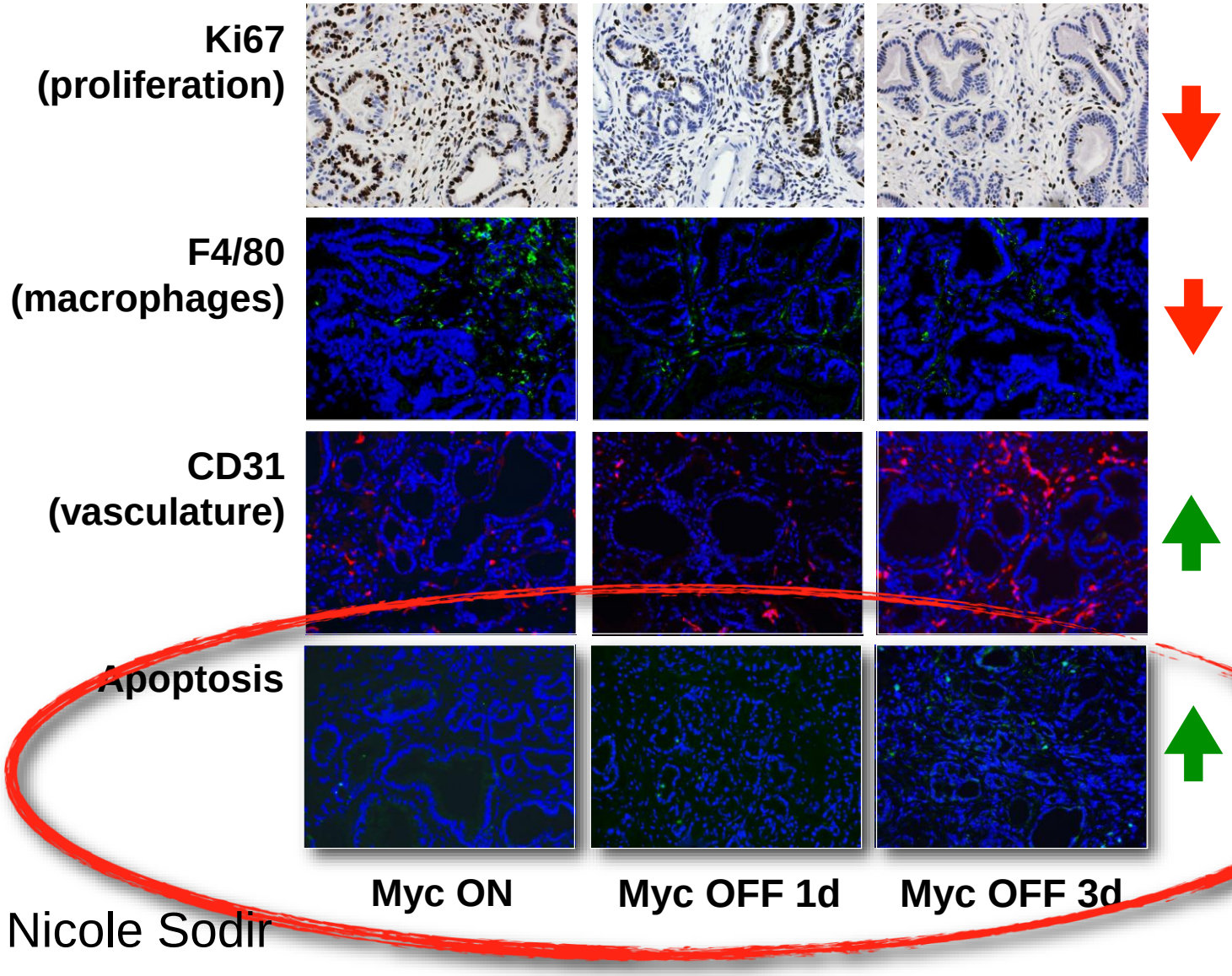
4 weeks

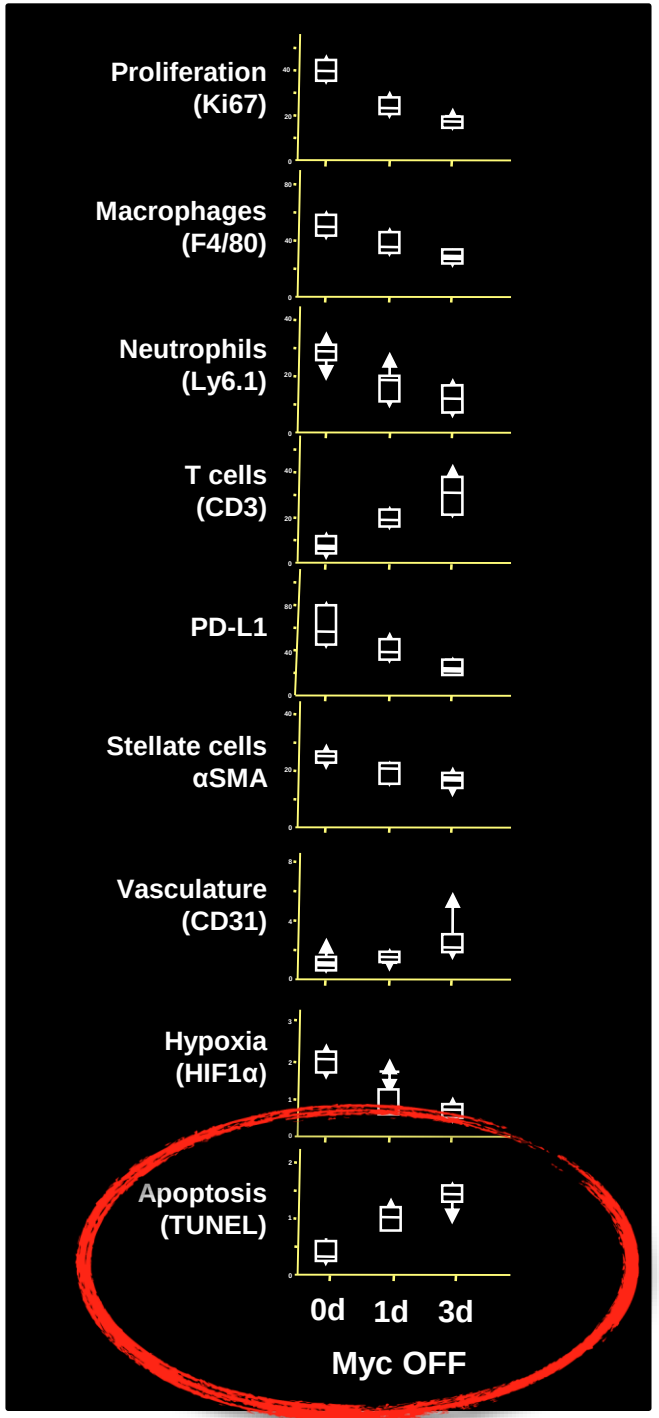
Myc ON 4 weeks

Then Off 4 weeks

Pancreas

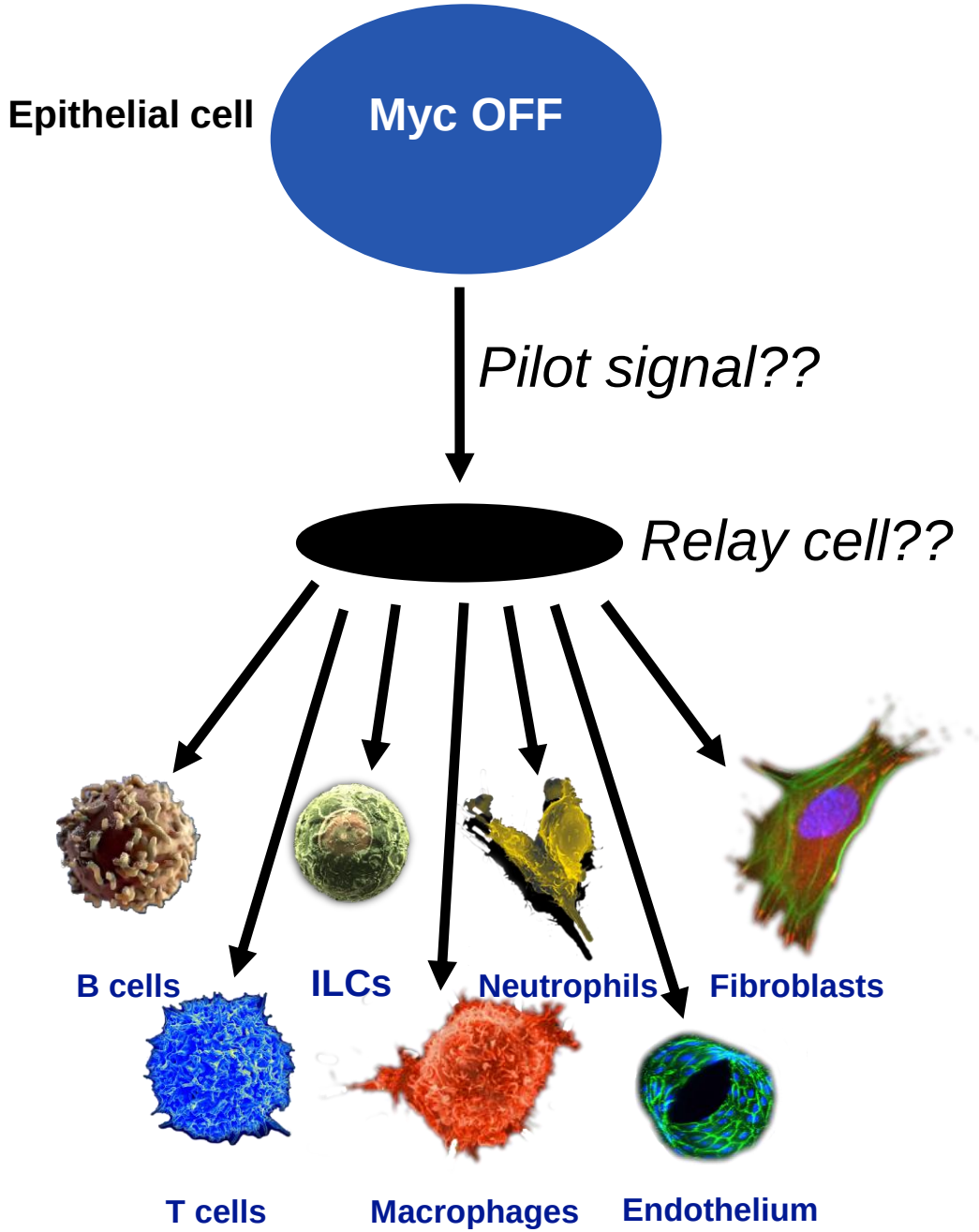
Myc de-activation in PDAC triggers immediate onset of tumour regression



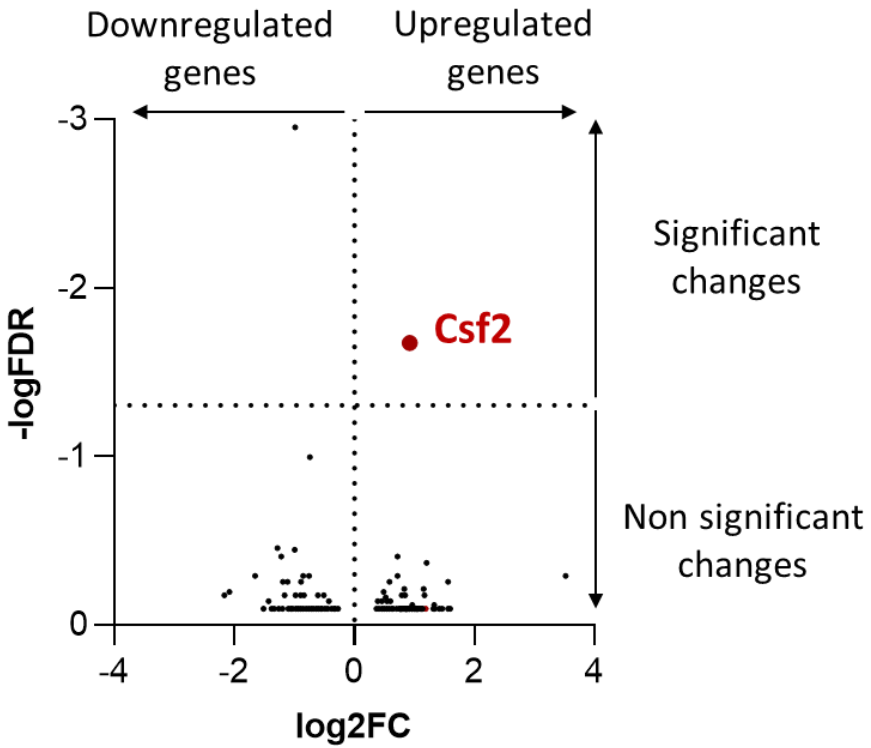


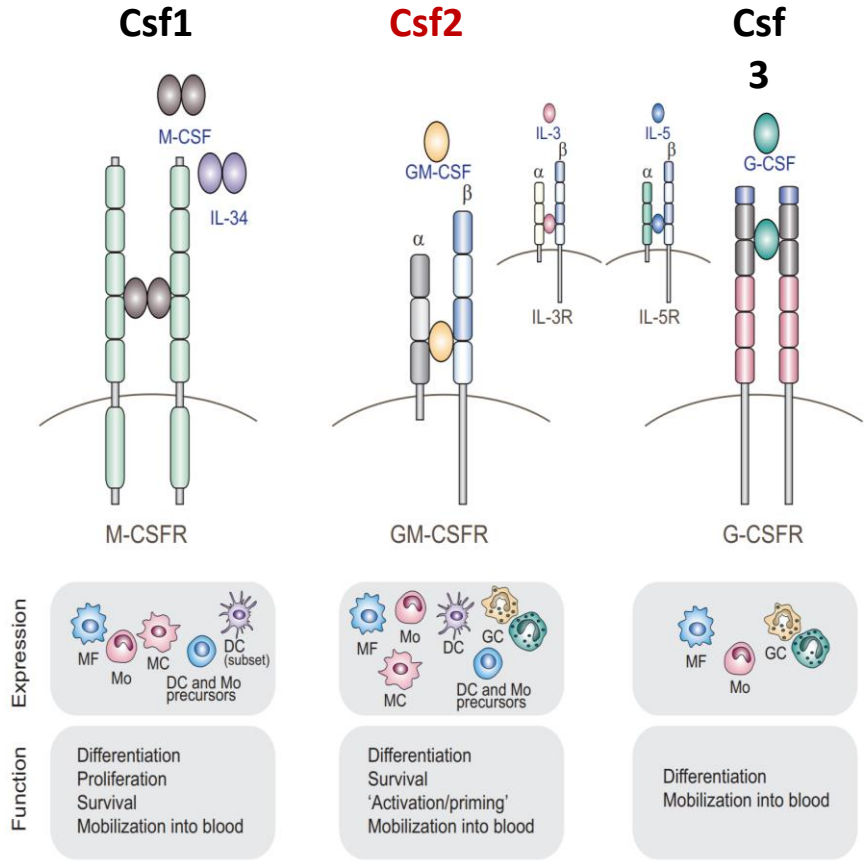
Nicole Sodir

PDAC


Epithelial cell
Myc OFF
Pilot signal??
Relay cell??
B cells
ILCs
Neutrophils
Fibroblasts
T cells
Macrophages
Endothelium

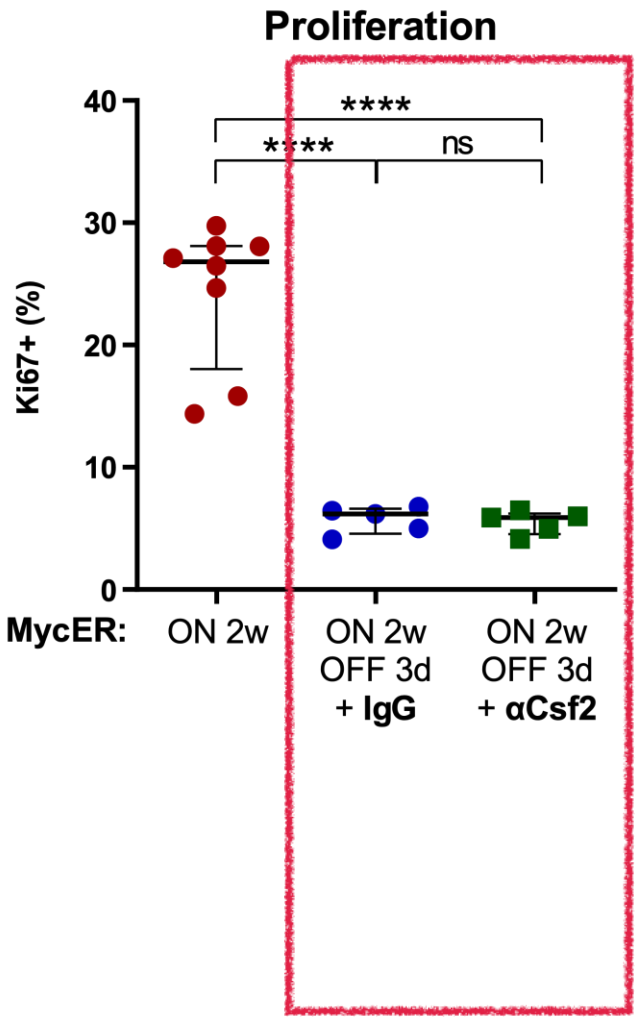
Myc de-activation drives CSF2 expression in MycER+ PDAC cells

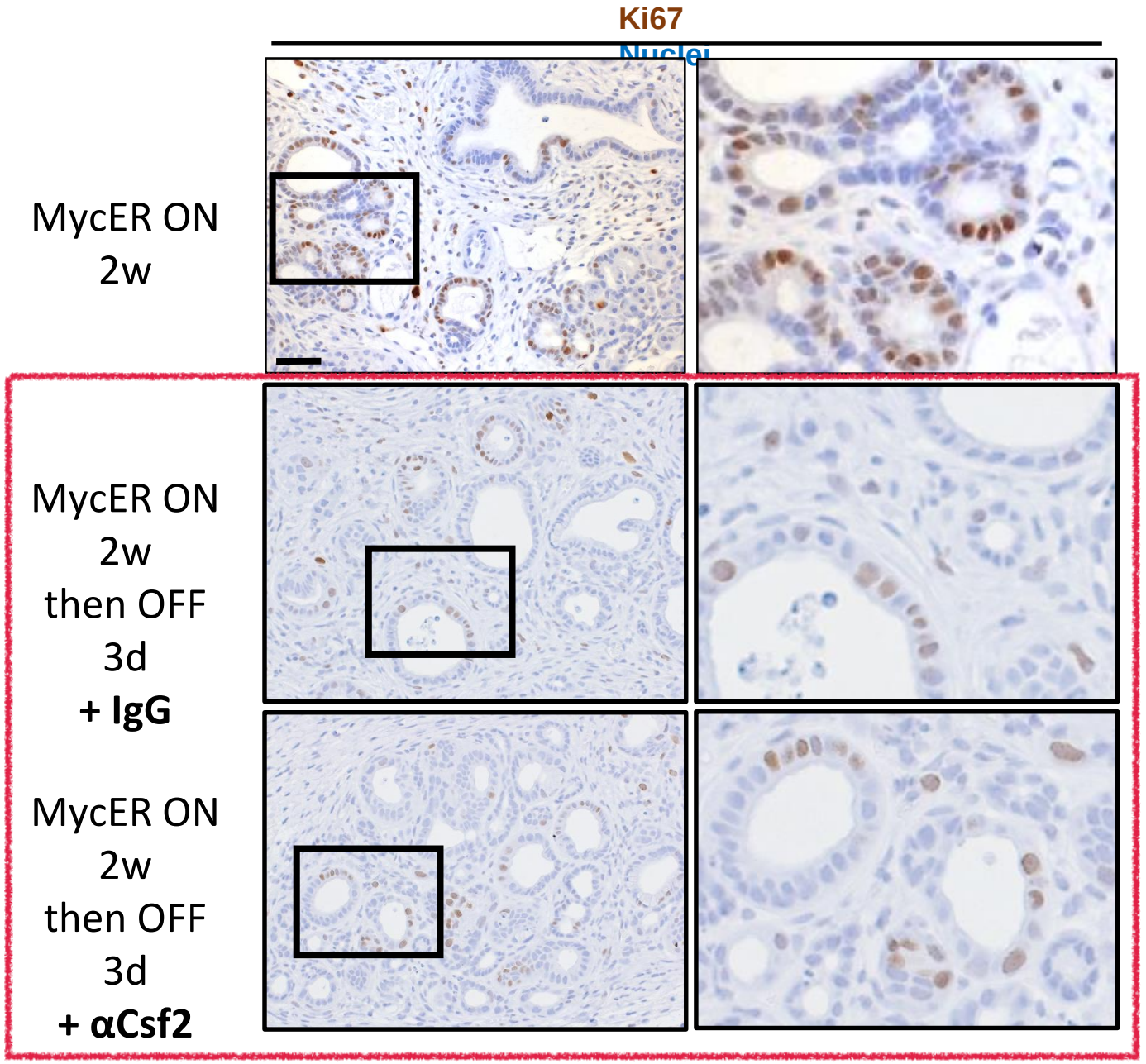




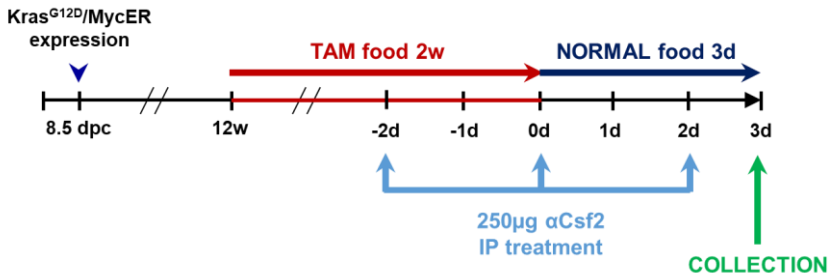
Becher B. *et al*. Immunity. 45(5):963-973. 2016.

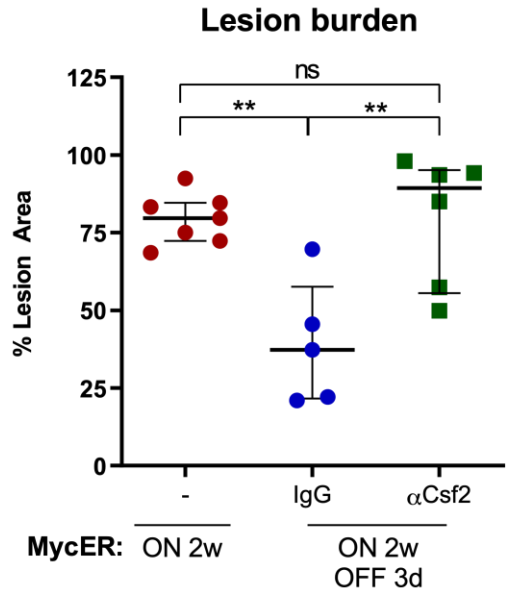
GM-CSF blocking does not impair proliferation decrease during pancreatic tumour regression





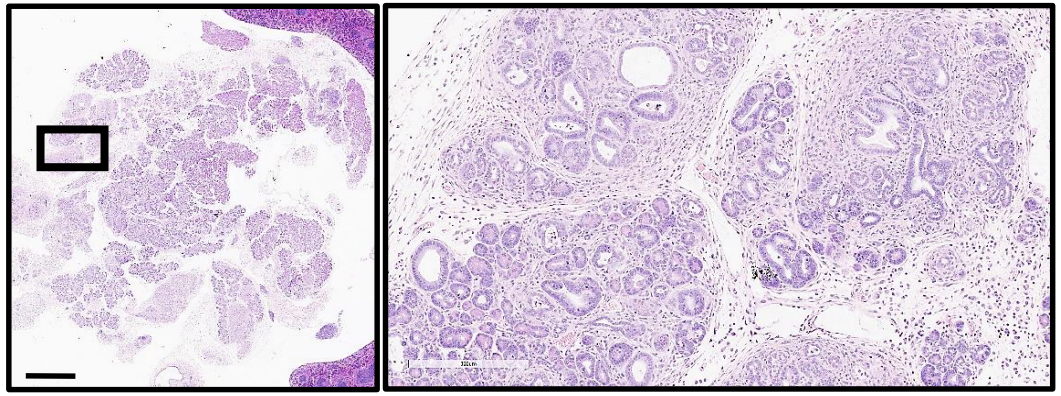
GM-CSF blockade impairs Myc OFF-dependent regression



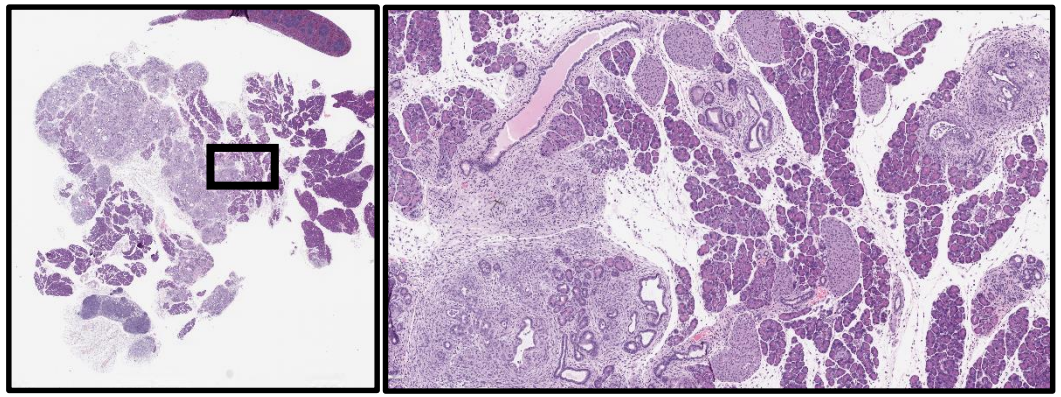


H&E

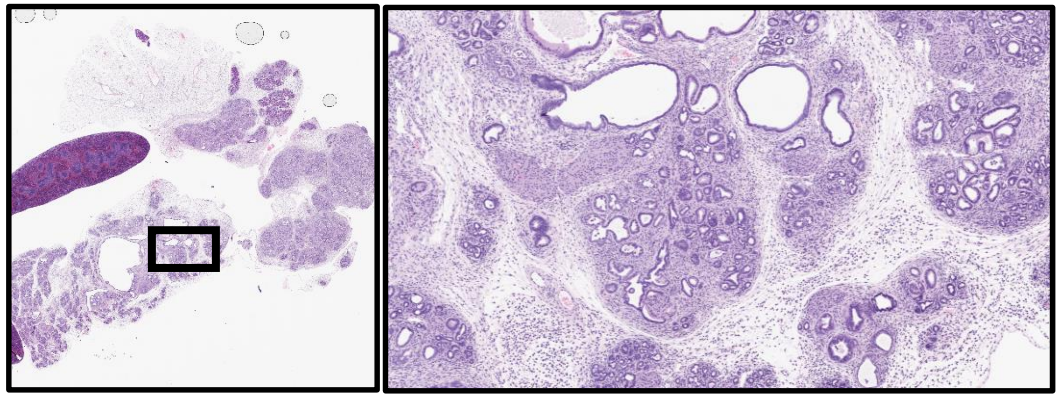
MycER ON
2w



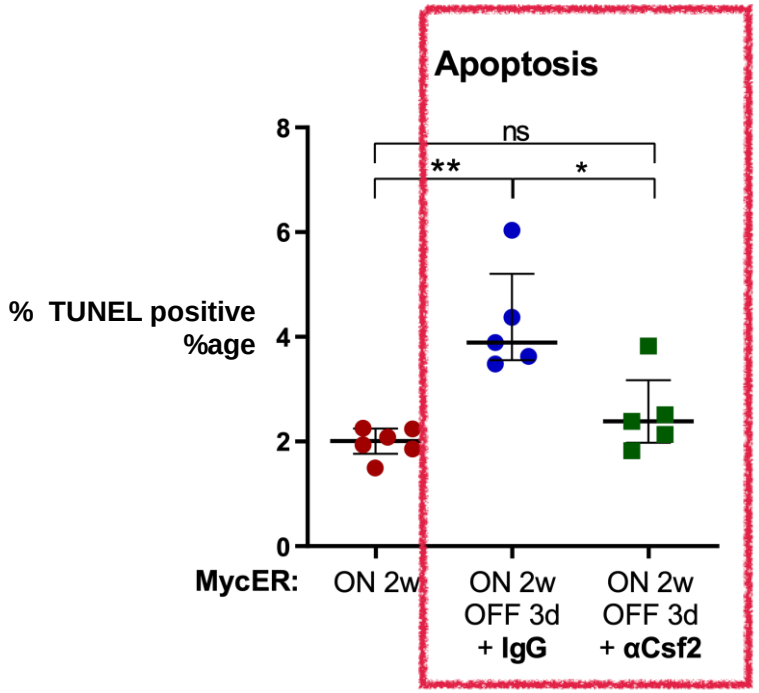
MycER ON
2w
then OFF 3d
+ IgG

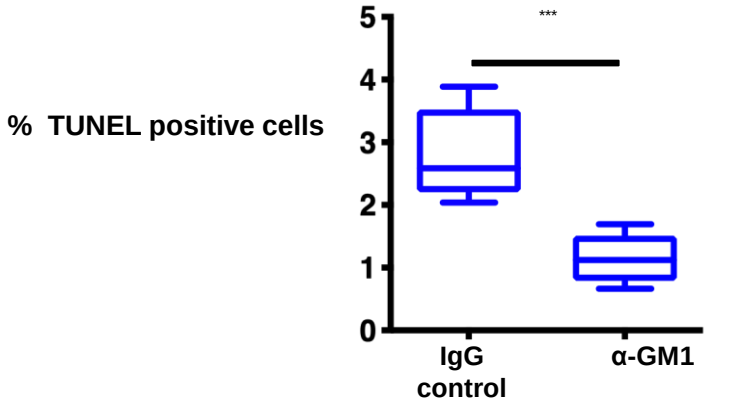


MycER ON
2w
then OFF 3d
+ αCsf2

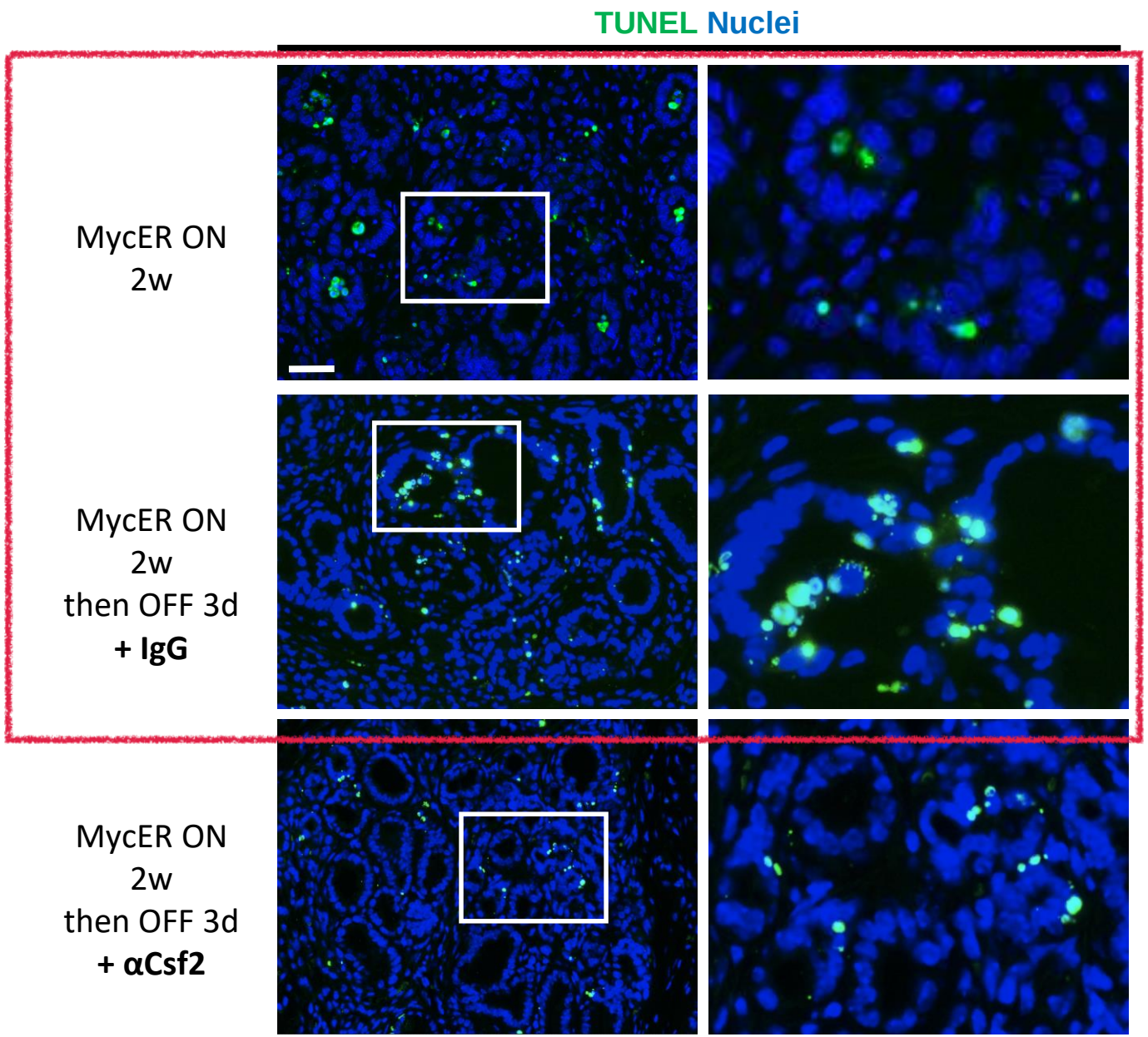


GM-CSF blocking impairs apoptosis during pancreatic tumour regression





Myc OFF-induced apoptosis is NK cell dependent



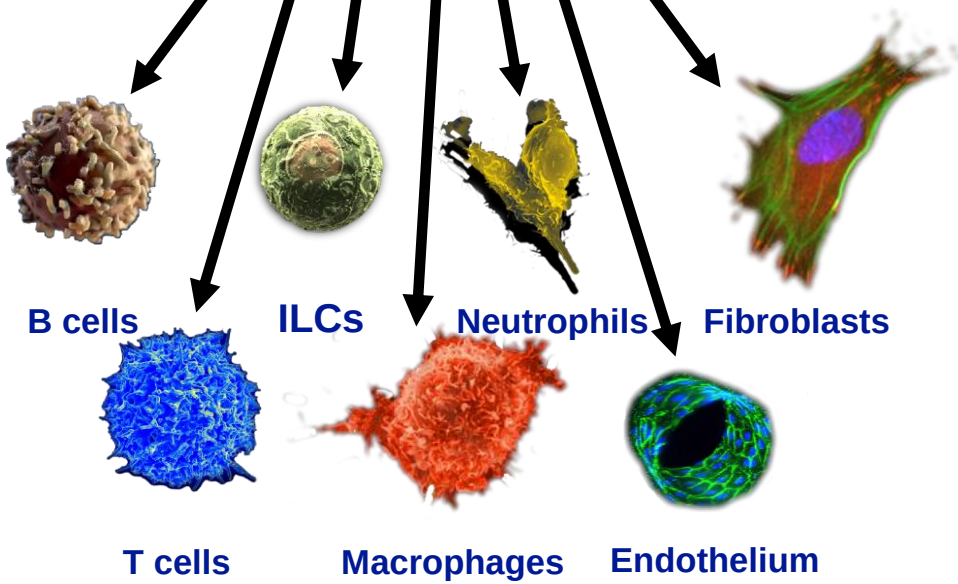
PDAC

Epithelial cell

Myc OFF

CSF2 Pilot signal

Relay cell??



REGRESSION