Where cancers come from and how to make them go away

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CANCER RESEARCH UK

Pancreatic Cancer UK

STAND UP TO CANCER

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- Ben (Chun Ming) Lam
- Alessandra Perfetto
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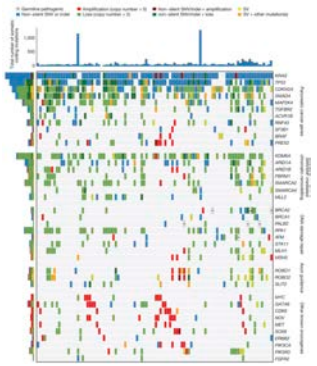
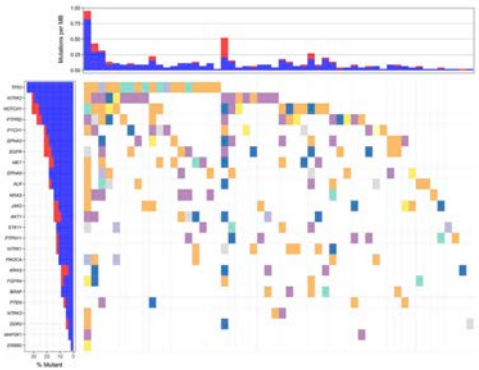
- Jade Newbury
- Trevor Littlewood
- Luca Pellegrinet (→Kymab)
- Nicole Sodir (→Genentech)
- Cathy Wilson (→Dept. Pharmacology)

Human cancers harbour huge numbers of mutations in diverse oncogenes and tumour suppressor genes



Human pancreatic adenocarcinoma (PDAC)



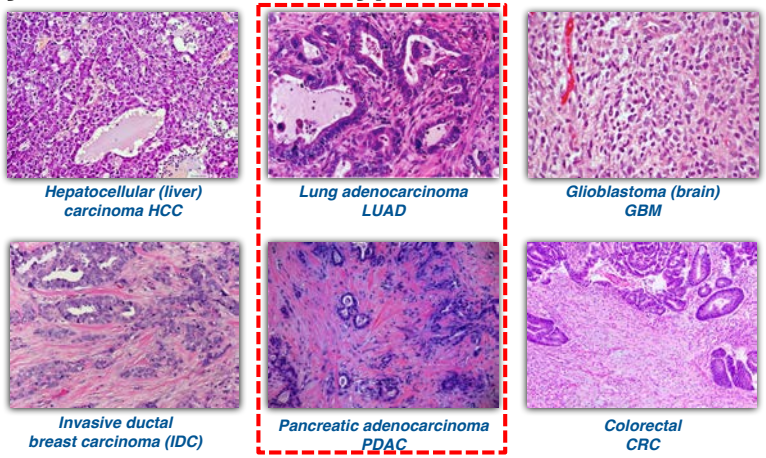
Human lung adenocarcinoma (LUAD)

So, are cancers irreducibly complex?

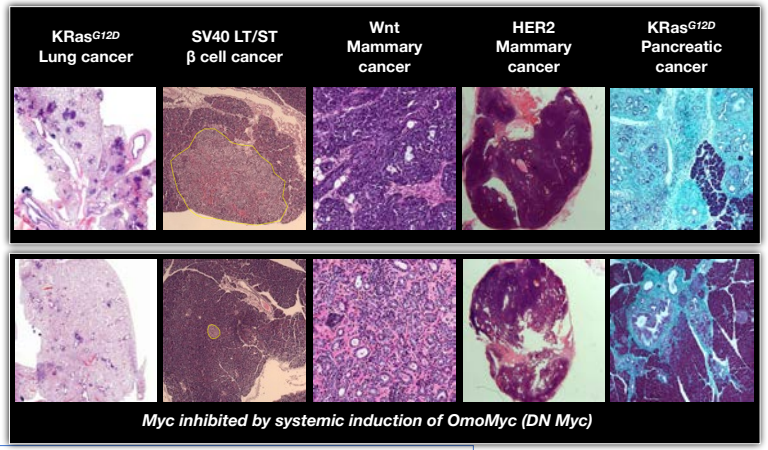
Although there are many differences between tumors…..

there are also many underlying commonalities

Tumor phenotypes: each cancer is different yet cancers of each type look like each other

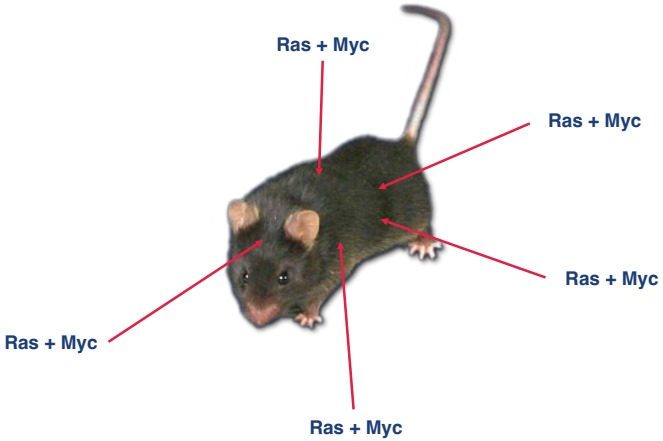


Myc is a common requirement for tumour maintenance in diverse cancers

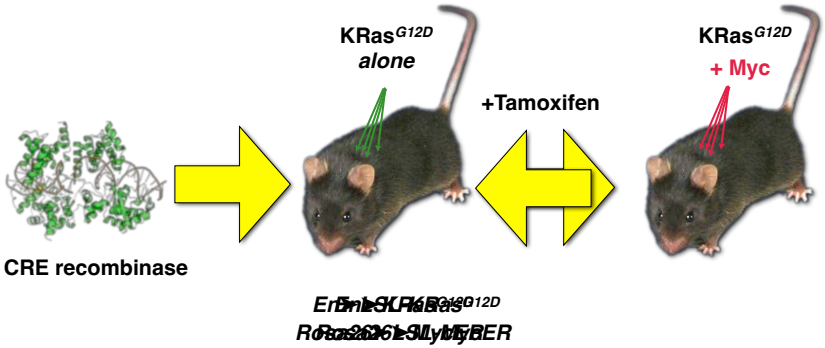


Laura Soucek, Trevor Littlewood, Roderik Kortlever, Nicole Sodir, Luca Pellegrinet, Tania Campos

How does Myc instruct and maintain so many, diverse tumour phenotypes?

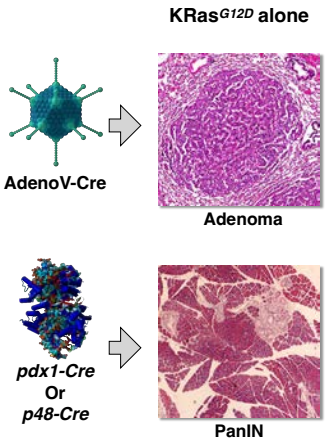


Cause and effect relationships in adenocarcinoma progression

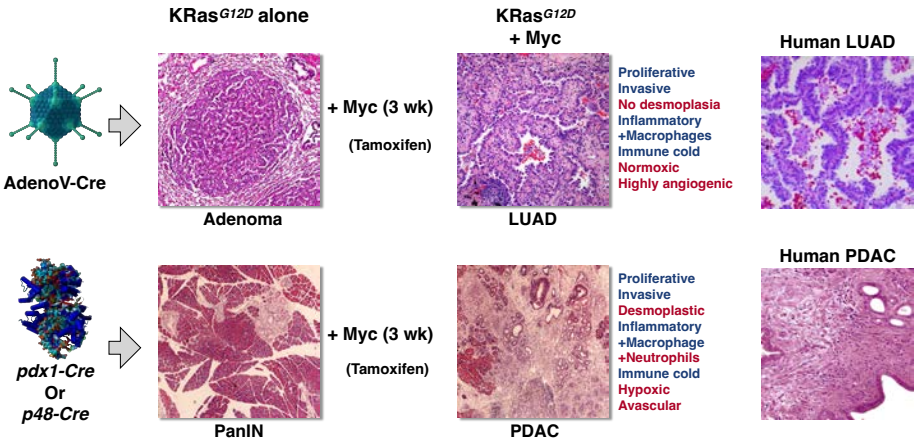


Ras and Myc activated only in the epithelial compartment

On its own, KRas^{G12D} is a feeble oncogene



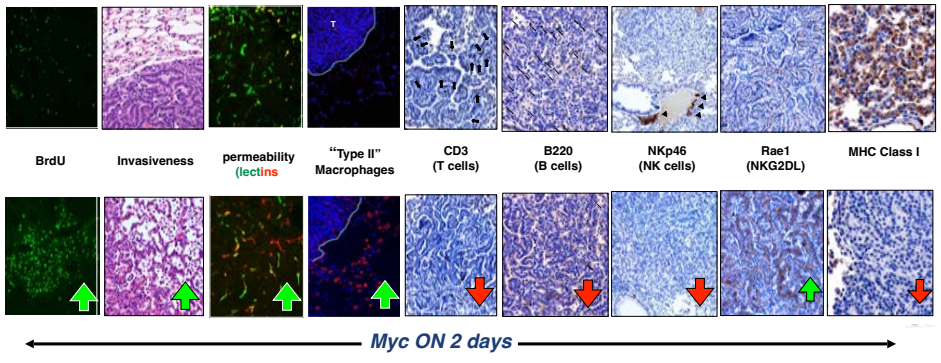
Myc cooperates with KRas to induce rapid tumour progression



The tumour/stromal phenotypes of solid cancers are principally determined by their cell/tissue of origin, not the oncogenes that drive them

Myc

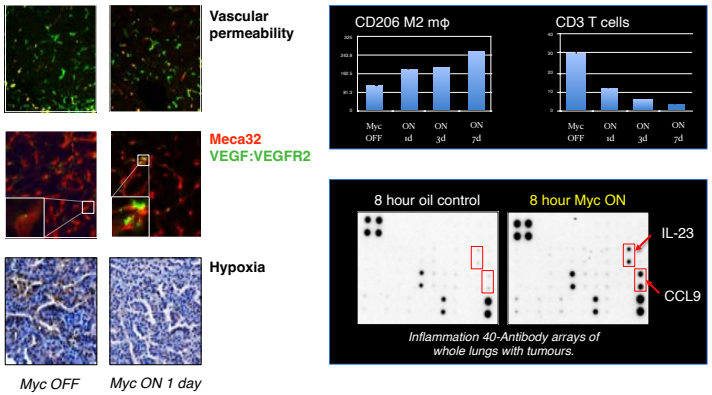
Myc activation in lung adenoma *epithelium* induces immediate transition to adenocarcinoma



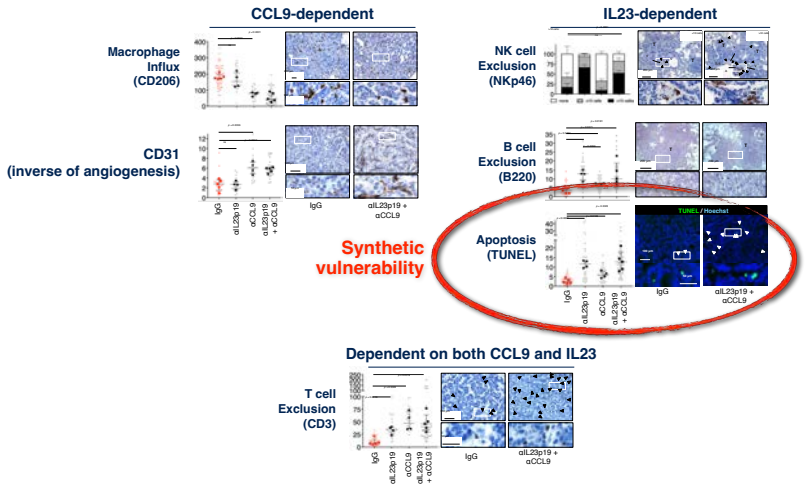
Myc *immediately* instructs the lung adenocarcinoma phenotype

Roderik Kortlever

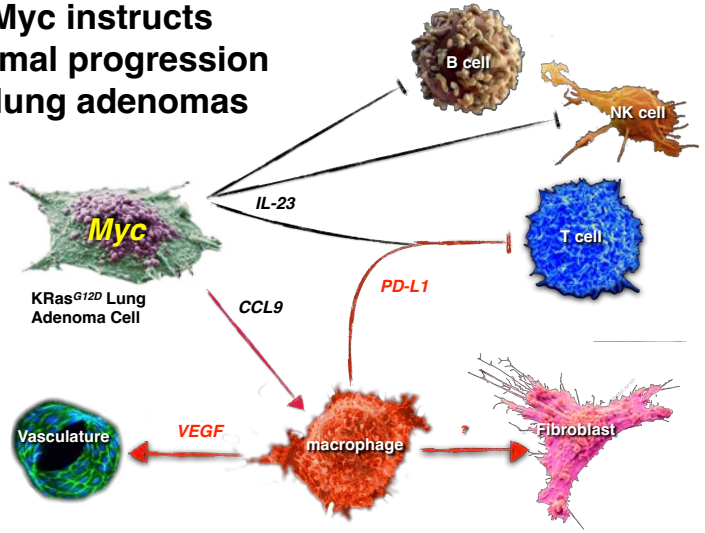
Myc-induced transition from dysplasia to adenocarcinoma is immediate



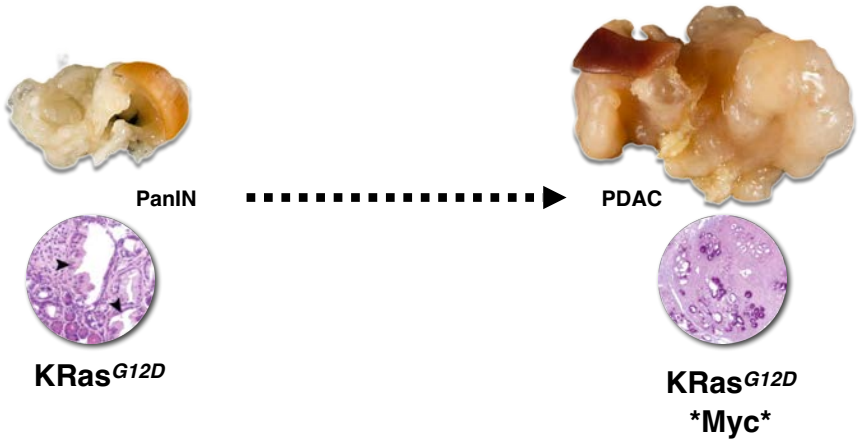
LUAD induction by Myc requires specific signals



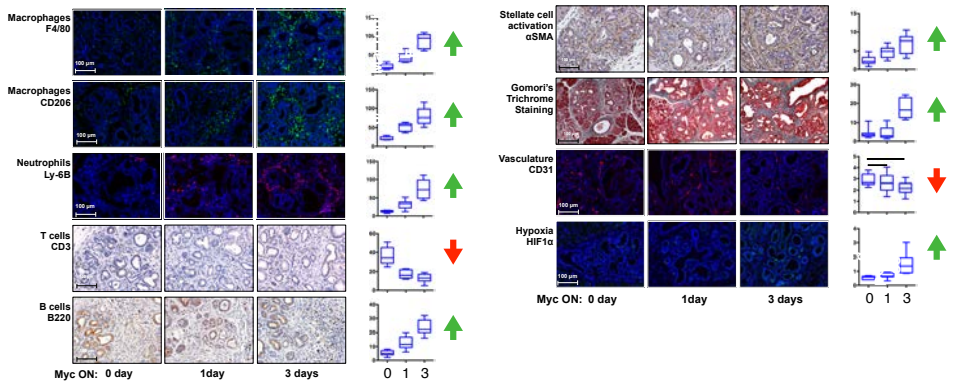
Myc instructs stromal progression in lung adenomas



How does Myc drive PanIN to PDAC?

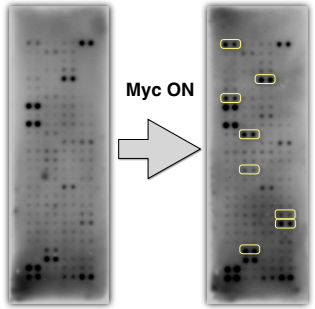


Myc activation *in the epithelial compartment* of KRas^{G12D}-driven PanIN triggers *immediate* transition to adenocarcinoma



Identifying candidate PDAC drivers

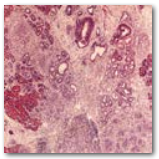
Cytokine/chemokine array



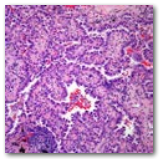
Ligand		Receptor	Target cell	Impact
PDGF	→	PDGFR	Stellate cells	↑
EGF	→	EGFR	Stellate cells	↑
GAS6	→	AXL kinase	Epithelial	↑
CCL2	→	CCR2	"M2" Macrophages	↑
CCL9	→	CCR1	"M2" Macrophages	↑
CXCL5	→	CXCR2	Neutrophils	↑
PD-L1	→	PD1	T cells	↓
sTNFR1	→	TNF	Monocytes?	↓
IL1-Ra	→	IL-1R	Adaptive T&B	↓

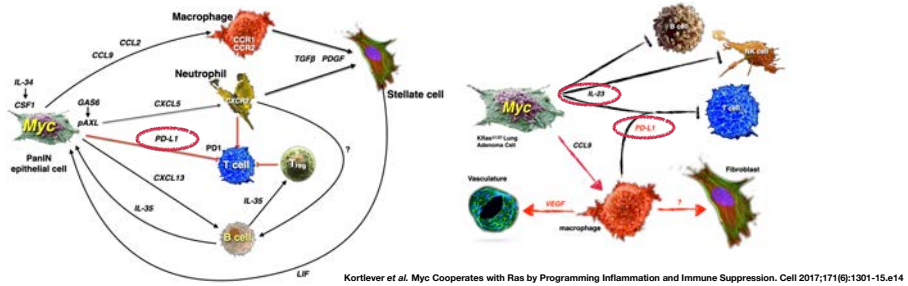
Myc-induced tumour phenotypes are instructed by tissue-specific signals - *organ-specific codes*

Pancreas



Lung

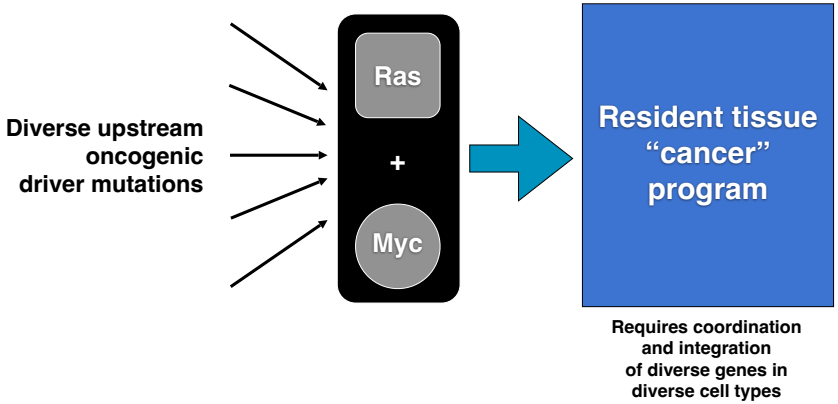




Kortlever *et al.* Myc Cooperates with Ras by Programming Inflammation and Immune Suppression. Cell 2017;171(6):1301-15.e14

Sodir NM *et al.* Myc Instructs and Maintains Pancreatic Adenocarcinoma Phenotype. Cancer Discovery 2020;10(4):588-607

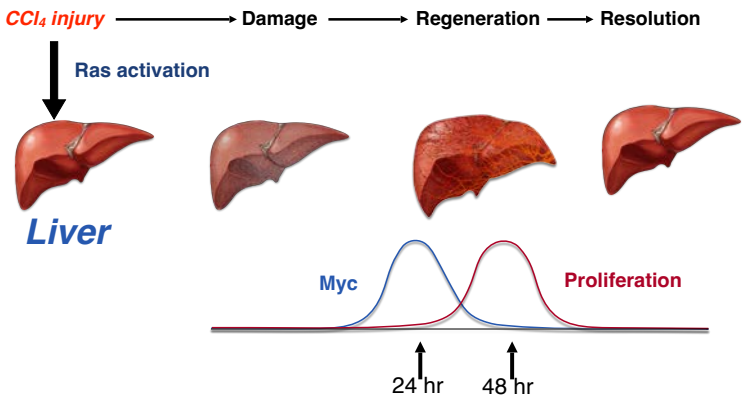
Ras and Myc in cooperation serve as a common combinatorial interface that engages resident tissue-specific "cancer" programmes



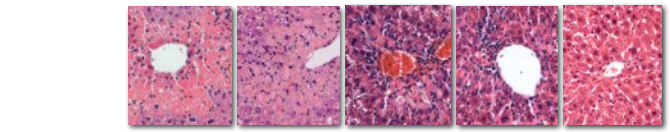
So where do these elaborate, tissue-specific cancer programmes come from?

And why are they there?

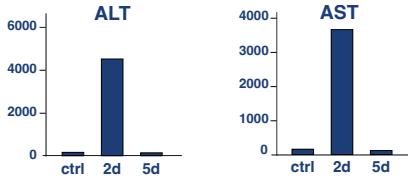
The kinetics of liver injury



Liver rapidly repairs after hepatoxic injury

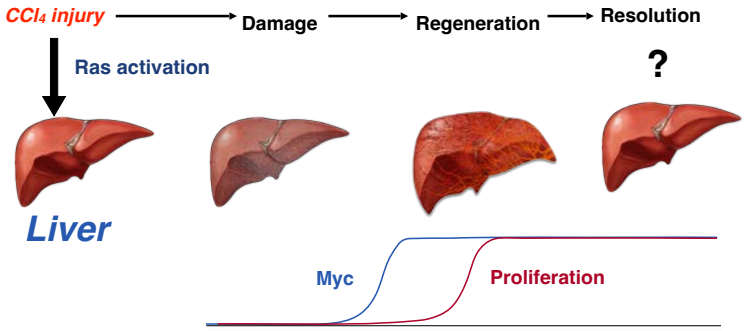


Liver damage biomarkers

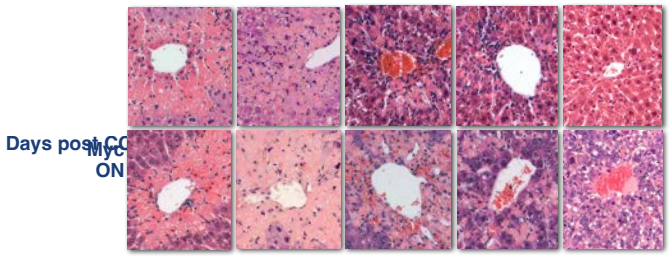


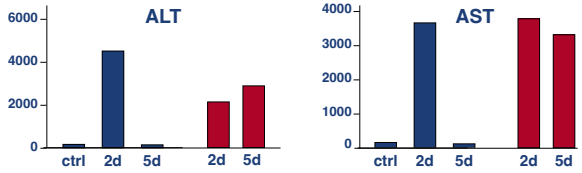
Luca Pellegrinet

The kinetics of liver injury



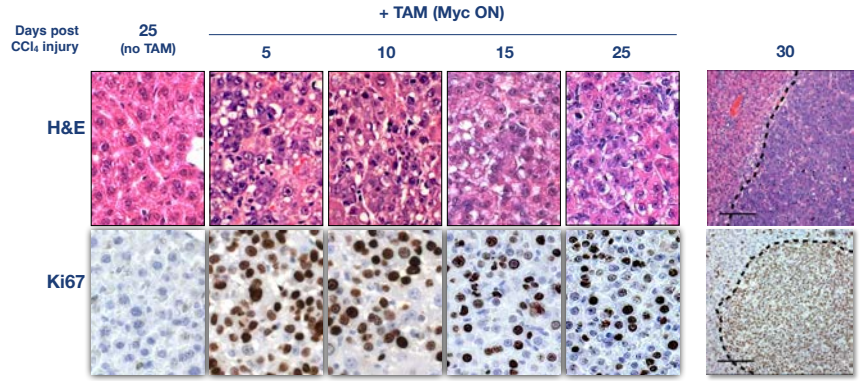
Persistent Myc drives sustained liver regeneration



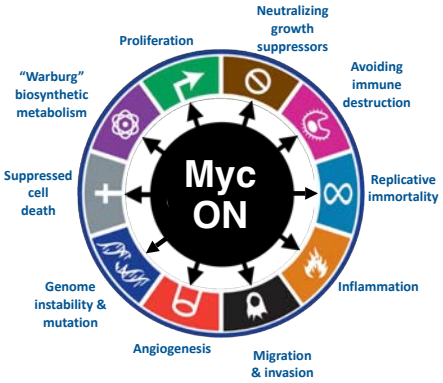


Luca Pellegrinet

Persistent Myc activity sustains the injury response, blocks exit of liver from its regenerating state and phenocopies HCC

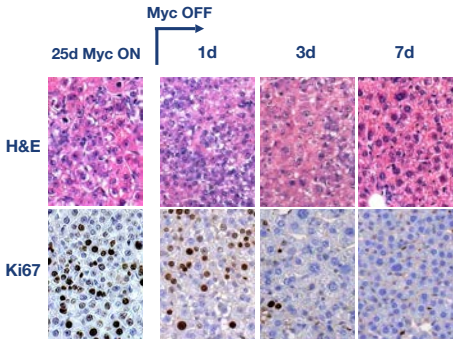


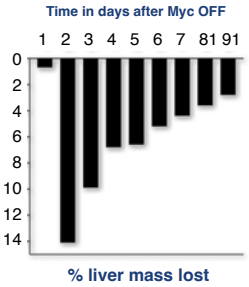
Most cancer "hallmarks" are features of normal tissue regeneration



Myc

Subsequent Myc de-activation triggers immediate injury resolution and regression of excess liver mass





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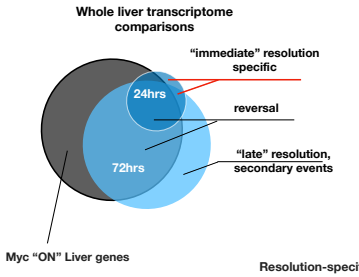
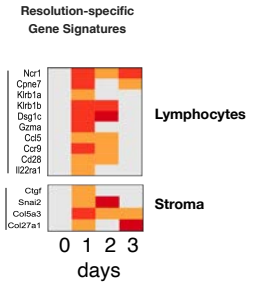
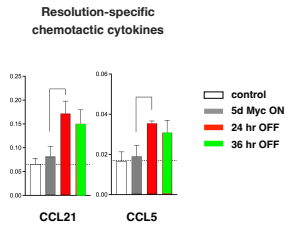
A liver-specific transcriptional resolution/regression programme







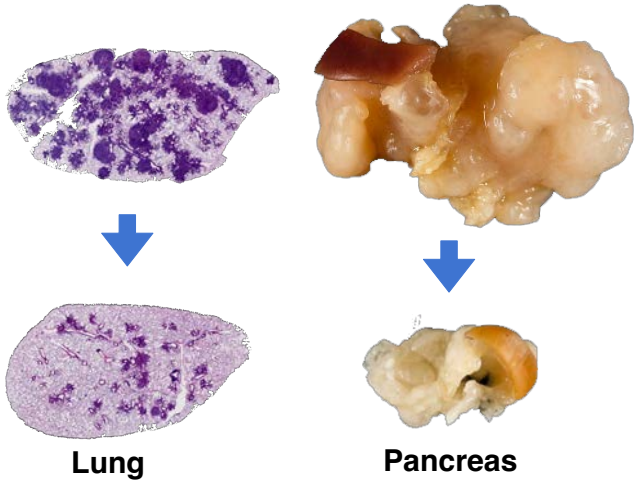
Luca Pellegrinet

The hallmarks of liver injury resolution

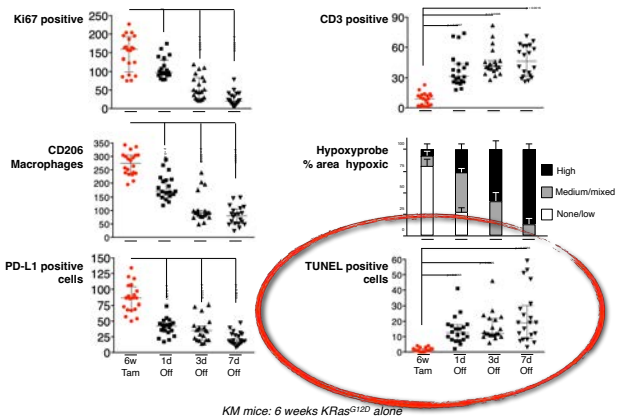
Liver injury resolution

So what happens to a tumor when Myc is turned off?

De-activating Myc triggers profound tumour regression

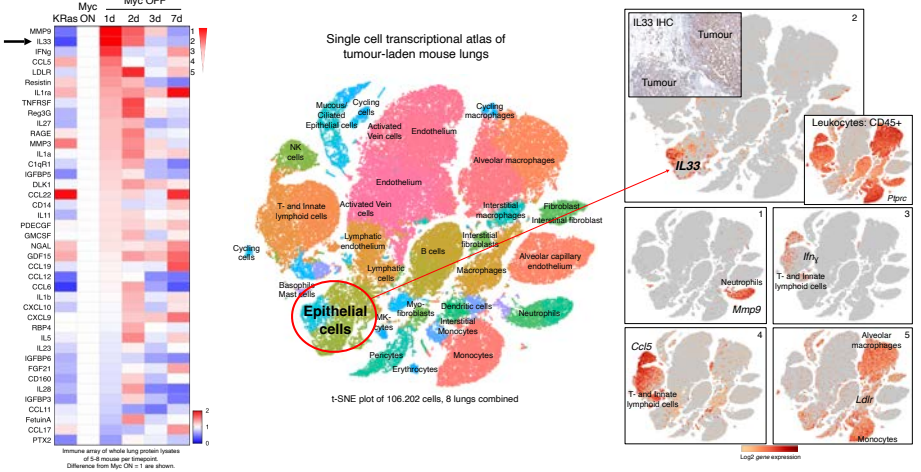


Myc de-activation triggers *immediate* regression of Myc-dependent lung tumours and stroma

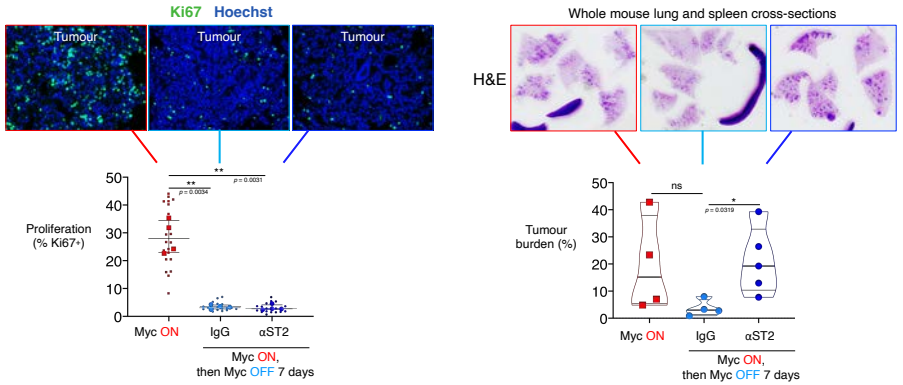


KM mice: 6 weeks KRas^{G12D} alone
then + 6 weeks Tamoxifen
then Tamoxifen withdrawn

Immediate induction of immune signaling components when Myc is turned OFF in lung adenocarcinomas

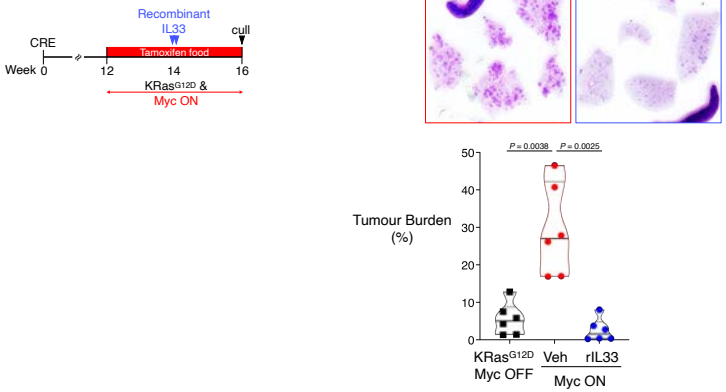


IL-33/ST2 blockade inhibits Myc-OFF-induced physical regression of lung tumours

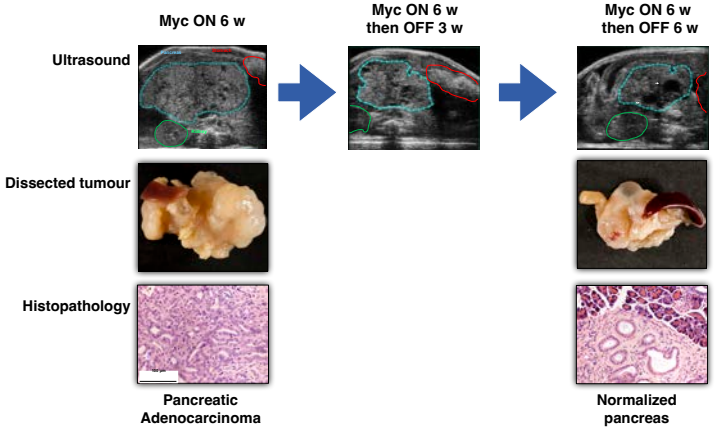


Myc ON 2 weeks, then OFF 7 days ± blocking ST2 (aka IL1RL1)

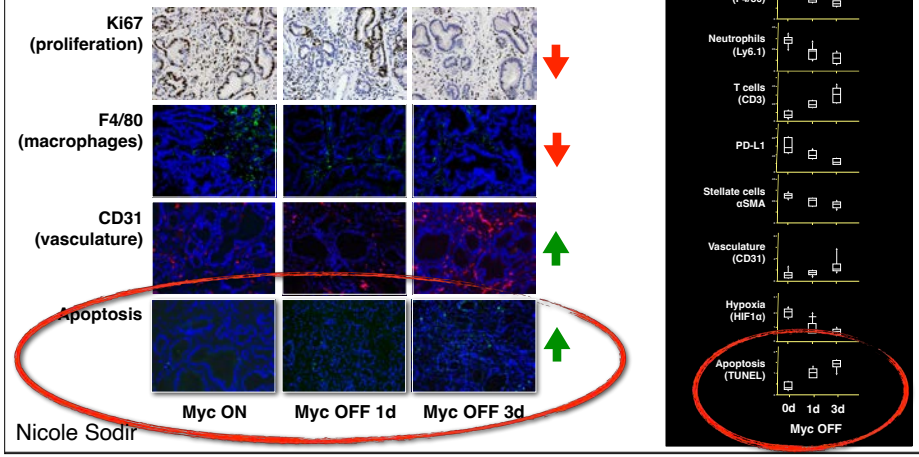
Imposed cell-extrinsic IL33 expression enforces near-complete tumour regression



Myc driven PDACs, along with their attendant complex stroma, are rapidly and completely reversible

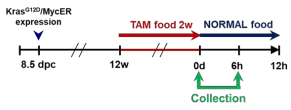


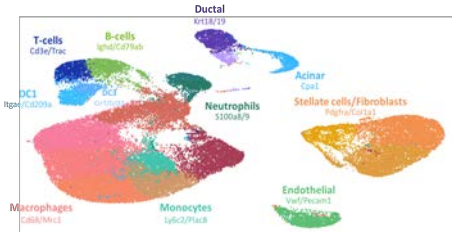
Myc de-activation in PDAC triggers immediate onset of tumour regression

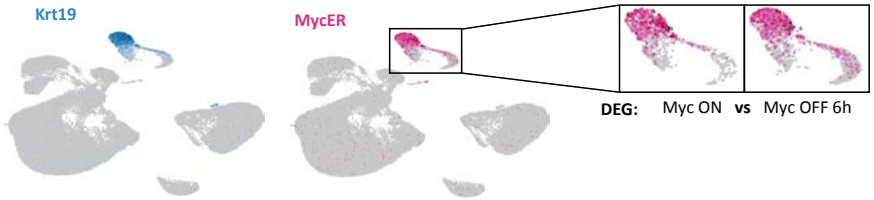


Nicole Sodir

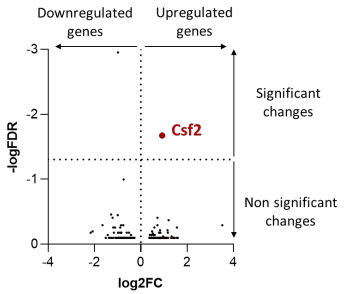
Searching for the PDAC regression signal

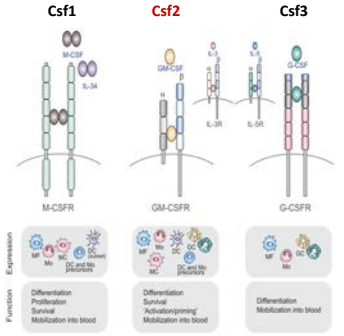






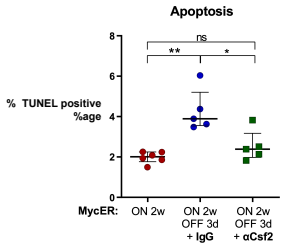
Myc de-activation drives Csf2 expression in MycER+ epithelial cells

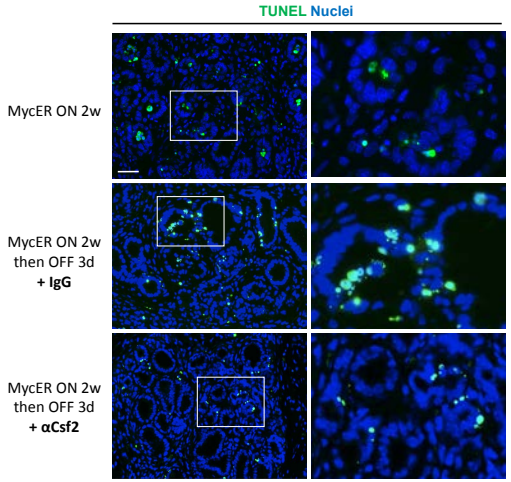




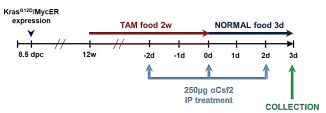
Becher B. *et al.* Immunity. 45(5):963-973. 2016.

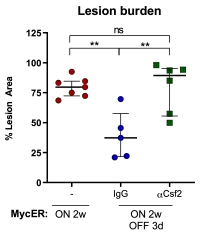
GM-CSF blockade impairs apoptosis during pancreatic tumour regression

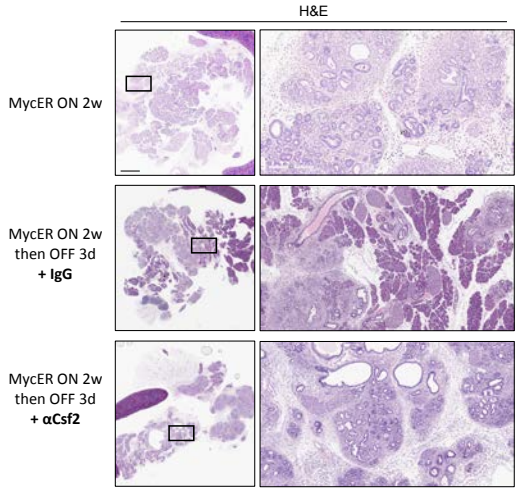




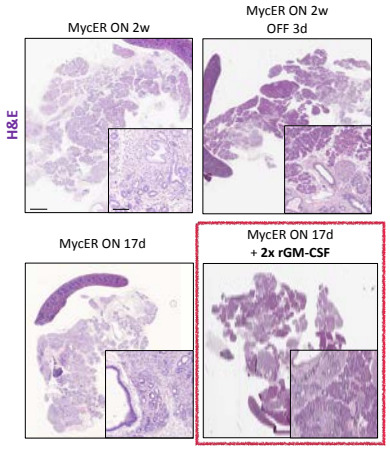
GM-CSF blockade blocks Myc OFF-dependent regression





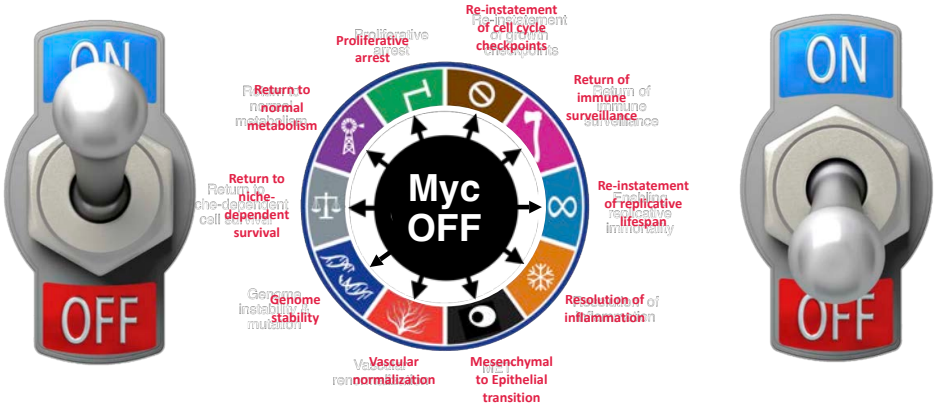


Recombinant CSF2 imposes regression despite sustained Myc activity

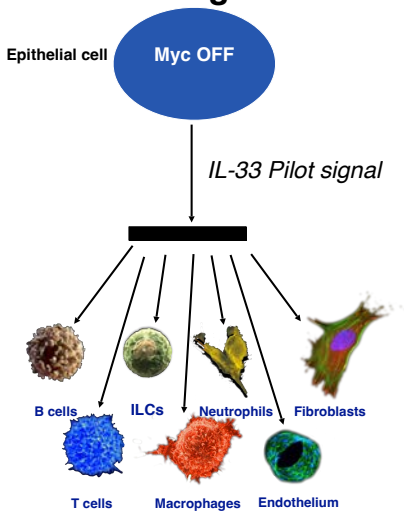


Tania Campos

Hallmarks of Resolution/Regression



Lung



Pancreas