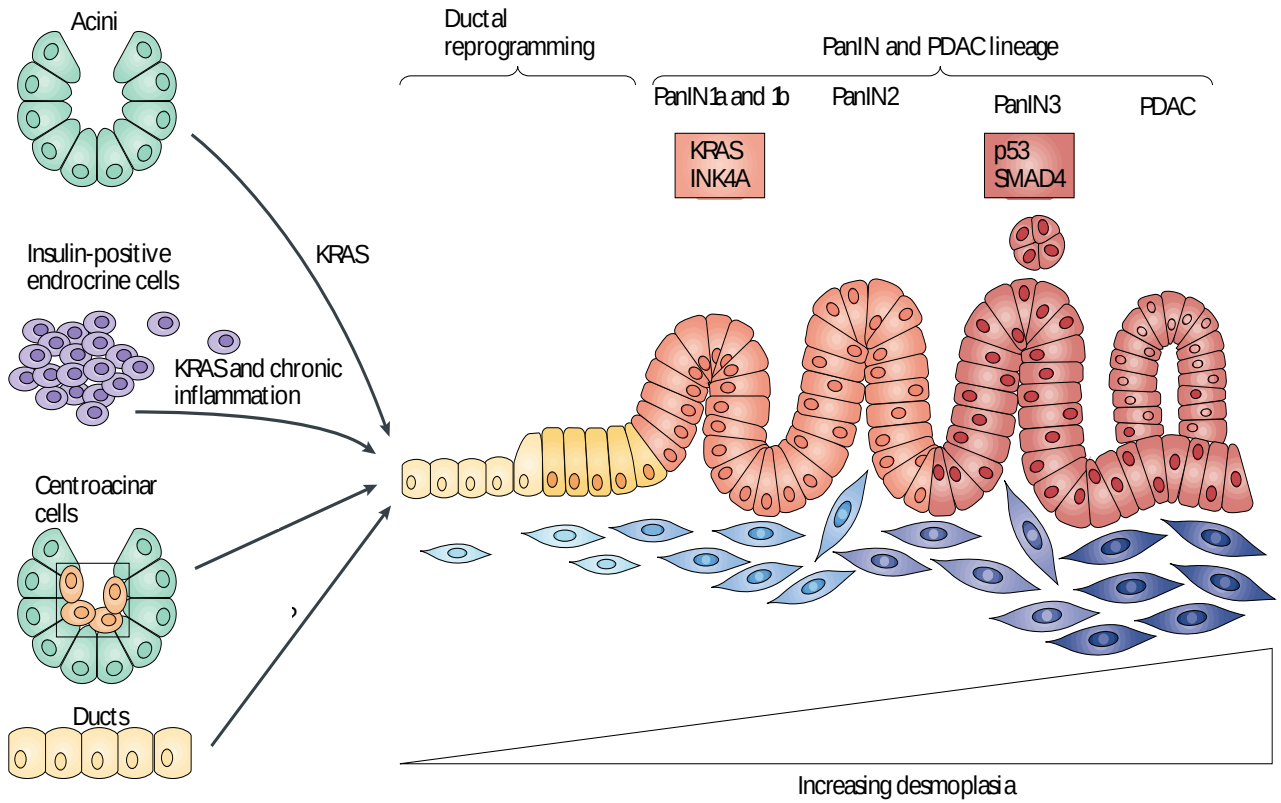
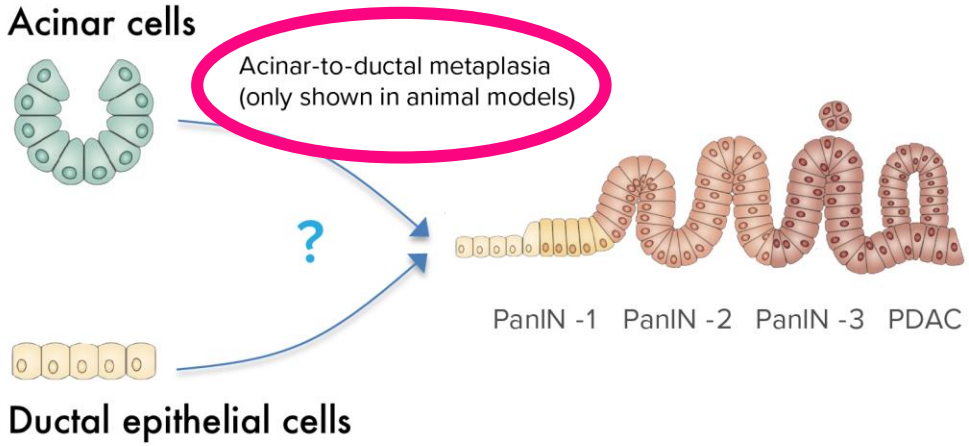
Cell of Origin Studies – Morton Lab

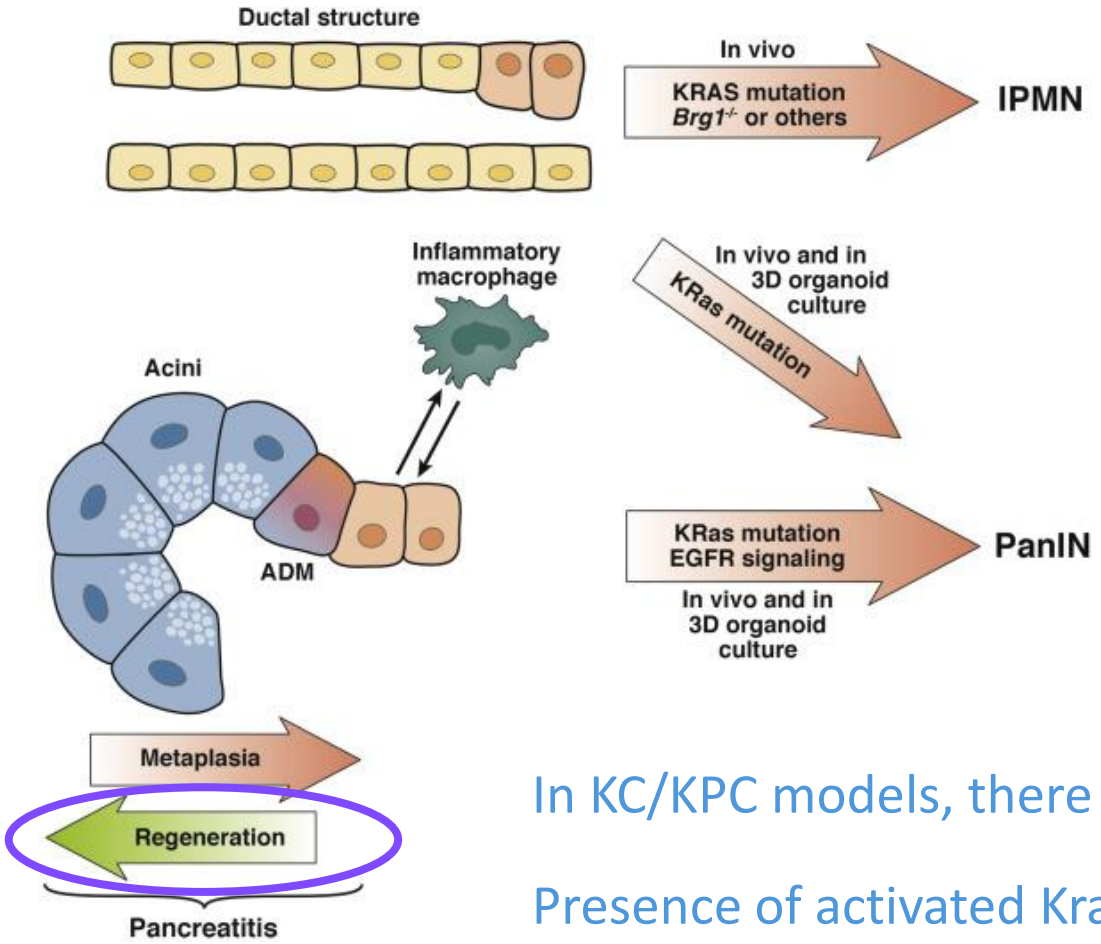
Curtis Rink – CRUK Beatson

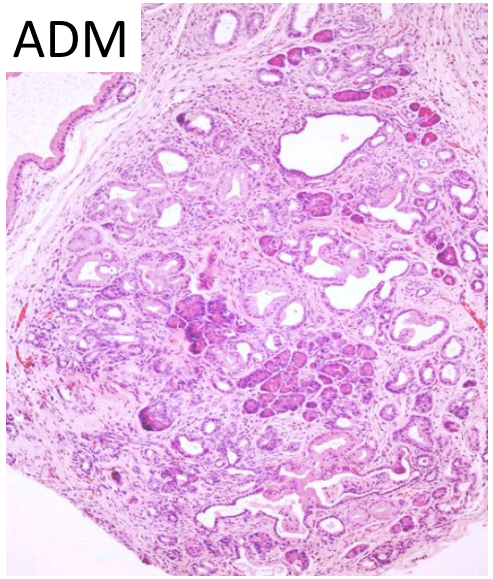
PDAC Progression – multiple cells of origin?

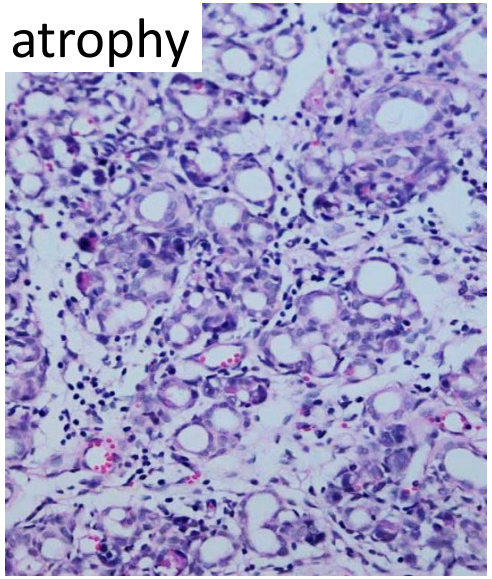




Acinar-Ductal Metaplasia



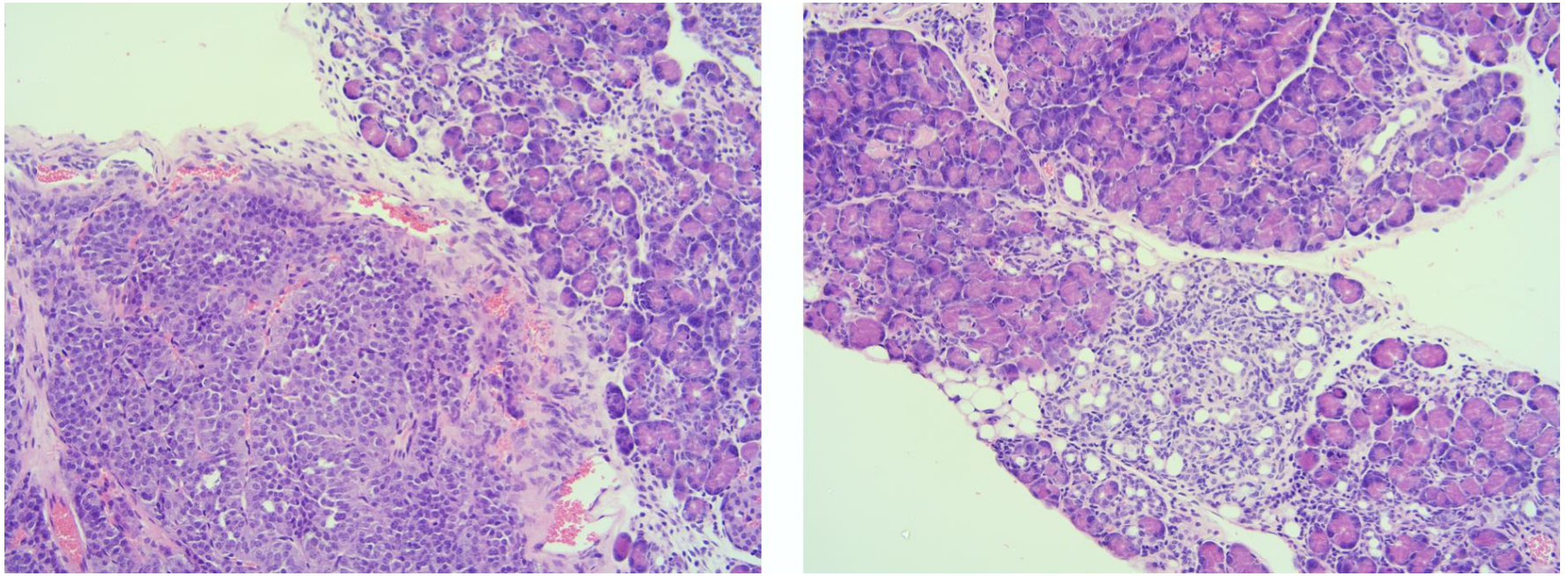




In KC/KPC models, there are multiple lesions leading to inflammation.

Presence of activated Kras in most of the tissue means damage can never resolve.

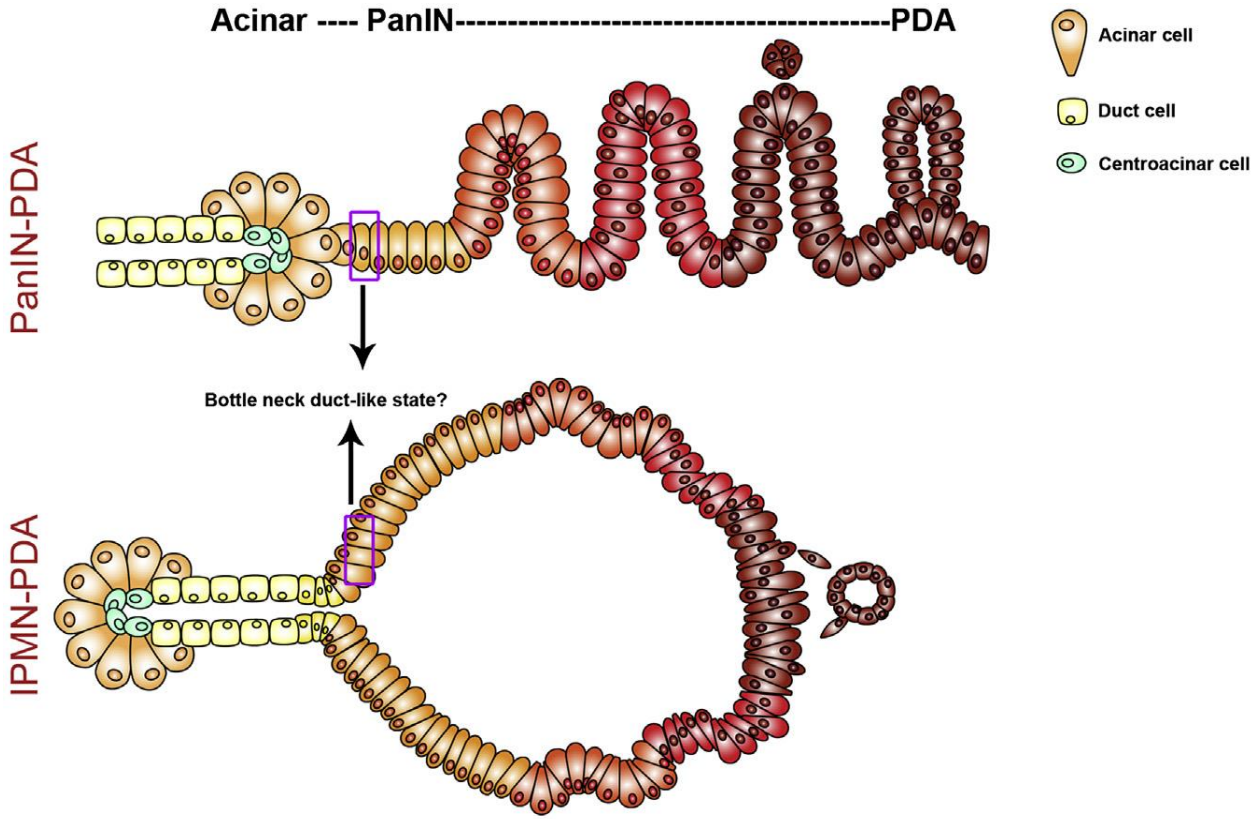
ADM-like acinar atrophy occurs even in absence of PDAC



Acinar atrophy in response to endocrine tumour

PDAC progression – PanIN v IPMN?

- IPMN has been proposed as the progression route from duct

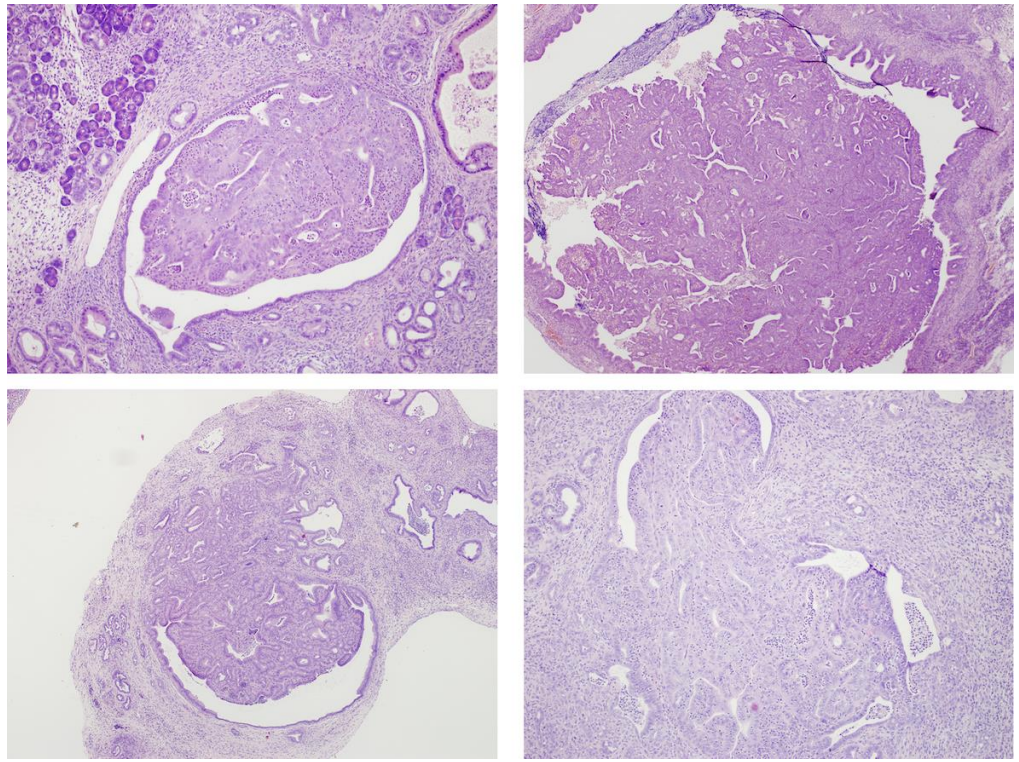


IMPN = intraductal papillary mucinous neoplasm

What if we use ductal Cres instead?

- Ductal Cres?
  - CK19-CreER
  - Sox9-CreER
    - + KrasG12D etc.

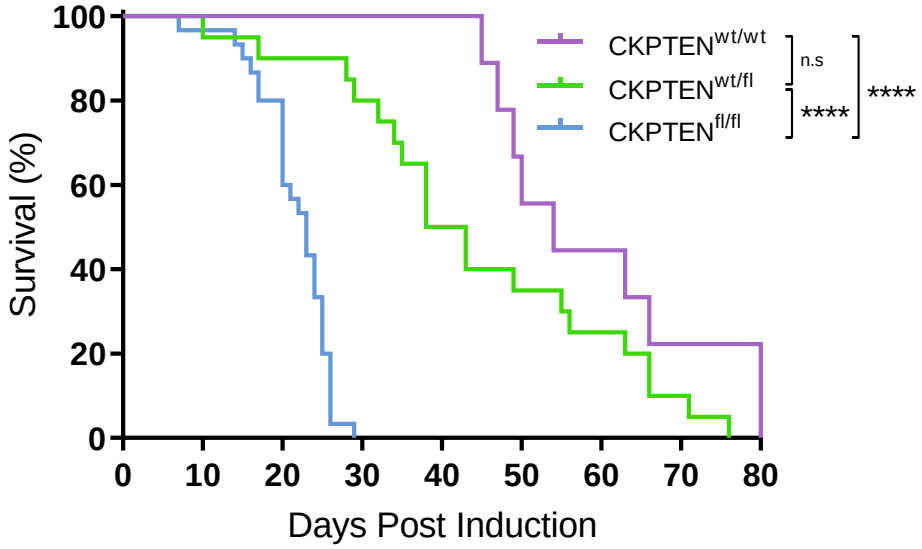
- Pten deletion is our best driver on the regular KC model, and tumours looked of ductal origin
- So we developed ductal-cre driven models of Pten deletion first….

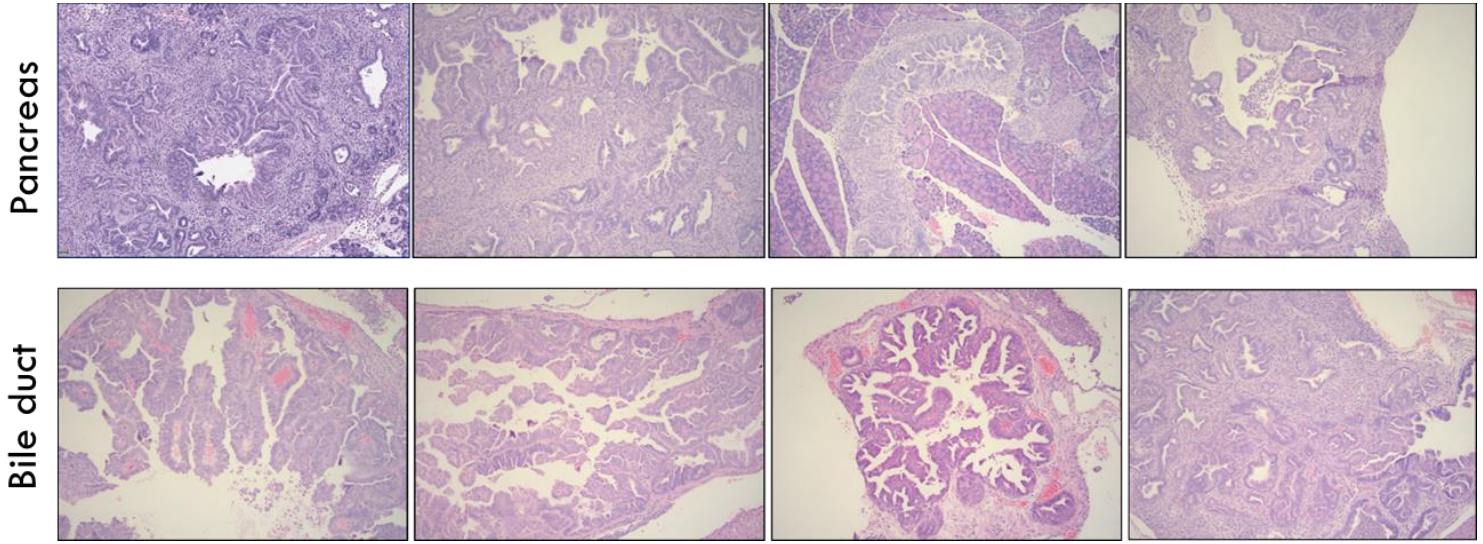


IPMN common in KC Pten model

Bad news:

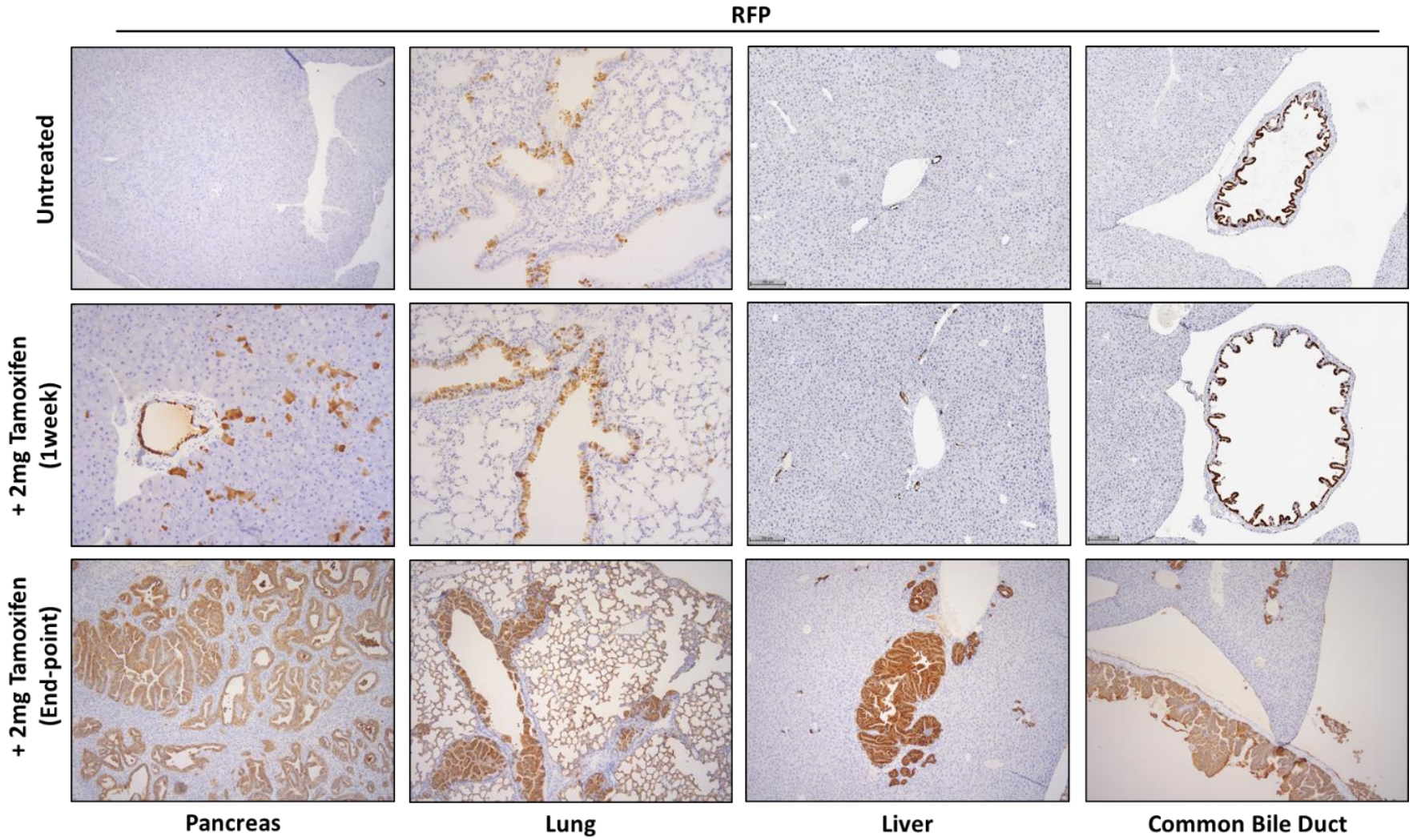
CK19-CreER; $Kras^{G12D/+}$; $Pten^{fl/fl}$



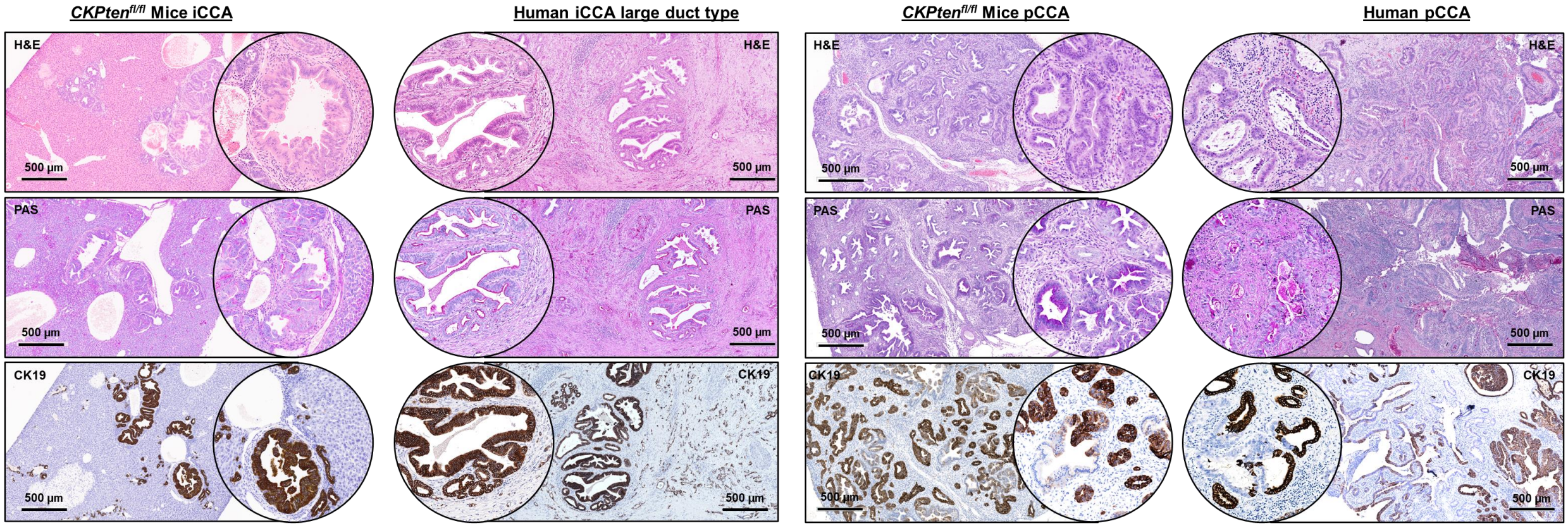


Lung tumours also major issue in Pten WT or Het

…not surprising



Aside…Mouse CCA strongly resemble human CCA

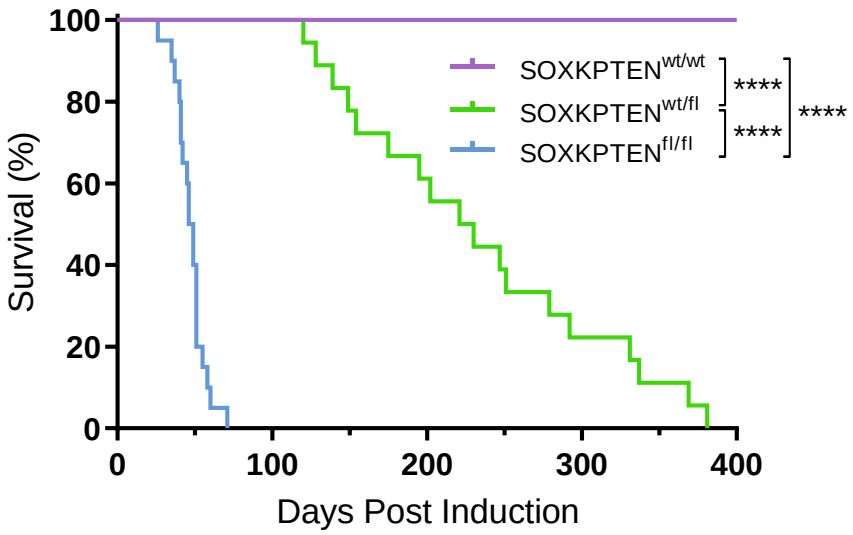


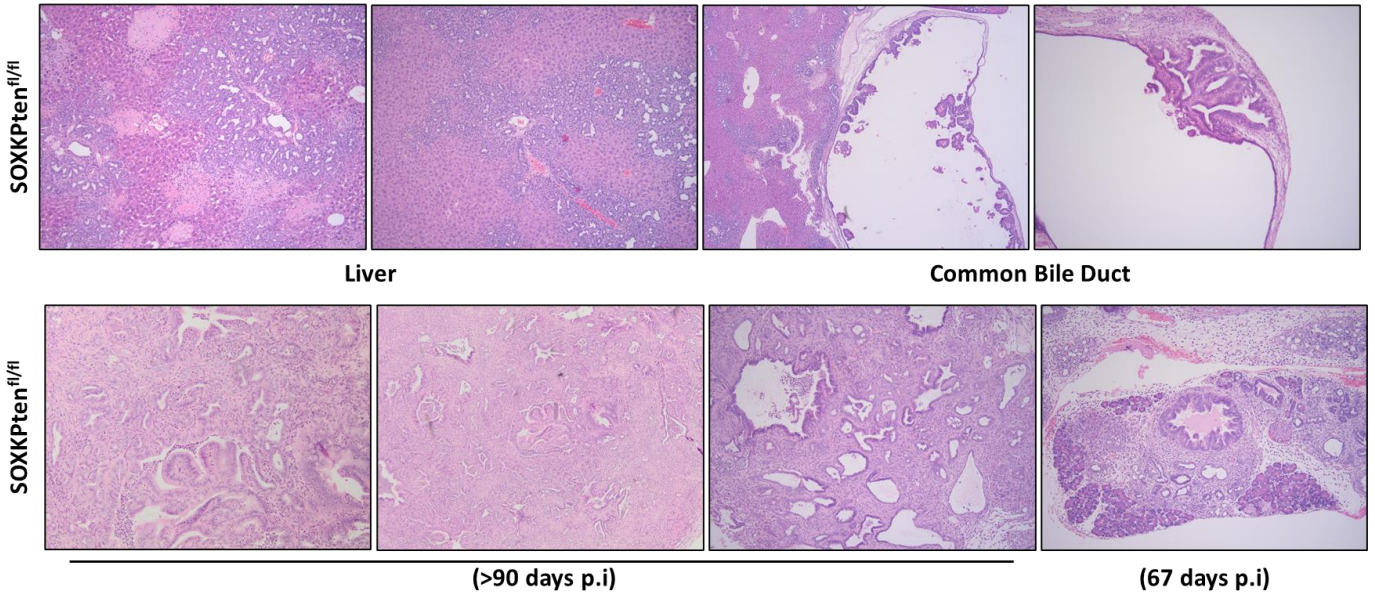
Intrahepatic

Perihilar

Thanks to Guido Carpino

Similar phenotype in Sox9-CreER model

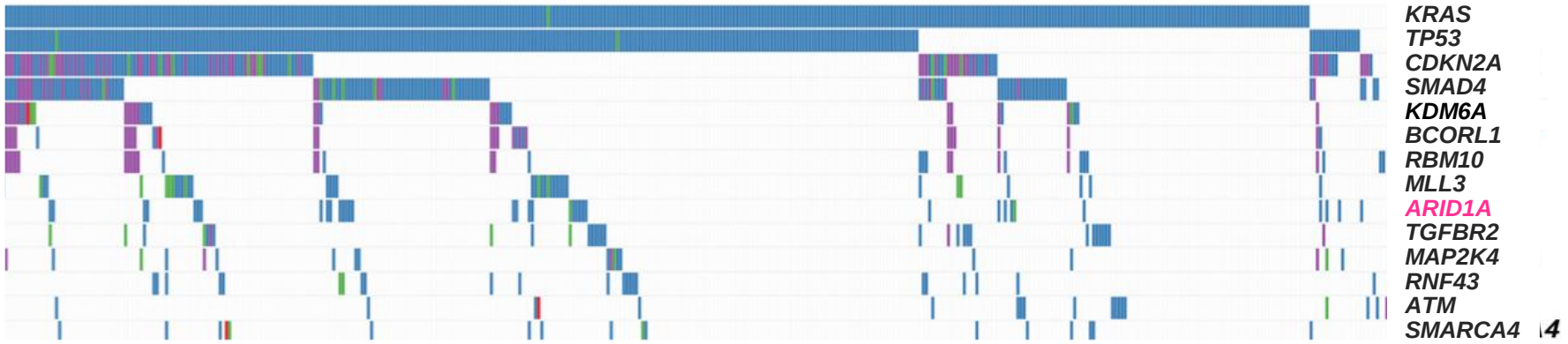




(although iCCA resemble human small duct type, rather than large duct type in the CK19 model)

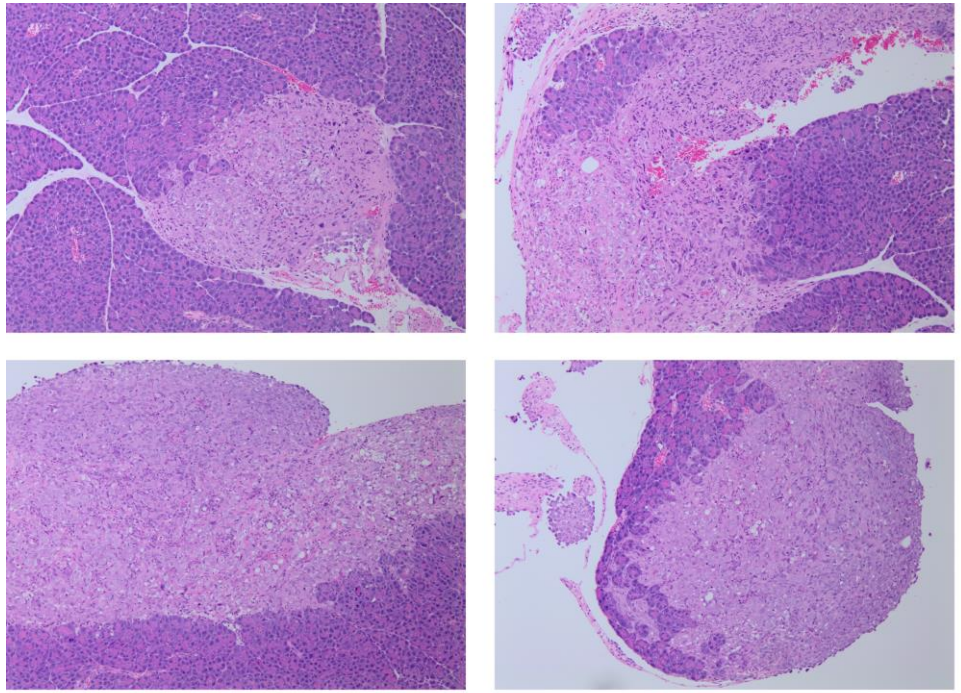
Arid1a

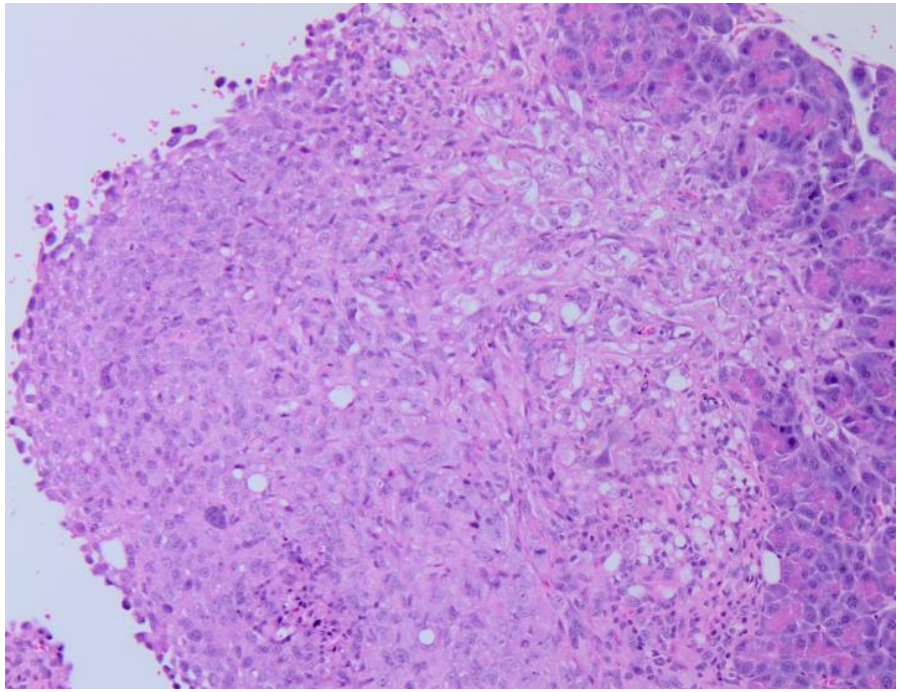
- Commonly mutated in cancer, including pancreatic cancer
- On a p48-Cre, KrasG12D background, Arid1a deletion drives IPMN and PDAC



Arid1a deletion from in CK19-CreER model

- Very undifferentiated carcinomas
- Centro-acinar origin??????



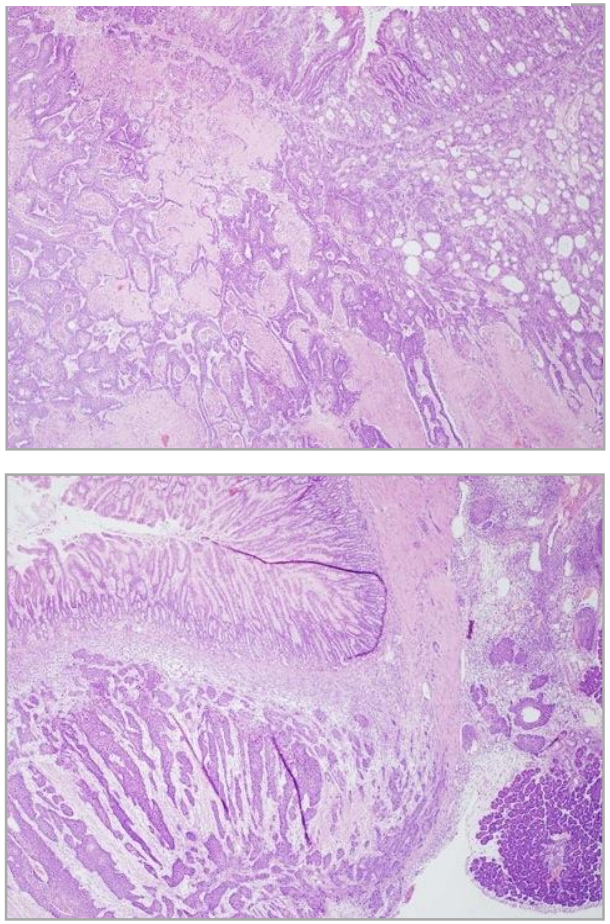


But no phenotype so far on Sox9-CreER model

TGFβR1 / Smad4 deletion

- Pancreatic tumourigenesis is dramatically accelerated in KC and KPC mice
  - Some very glandular looking
- But stomach tumors too (and frequent SCCs)
  - Deletion expands pool of cells of origin?

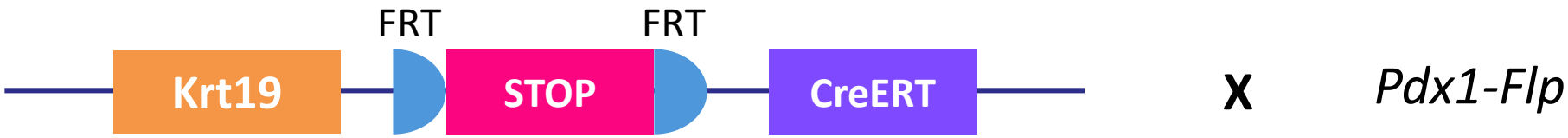
KC TGFβR1$^{fl/fl}$ stomach tumours



But no PDAC so far on ductal models after 1yr

What next?

Krt19-FSF-Cre^{ERT2}



X *Pdx1-Flp*

- Duct-specific inducible Cre specifically in the pancreas (tuneable with 4OHT?)
- Cross with *LSL-Kras*$^{G12D/+}$
- and *Trp53*$^{R172H/+}$ and *Smad4*$^{fl/+}$ and *Cdkn2a*$^{fl/+}$??
- Can we allow loss of 2nd copies of TSGs spontaneously and get somewhere close to physiologically relevant evolution/progression?

Team Pancreas