

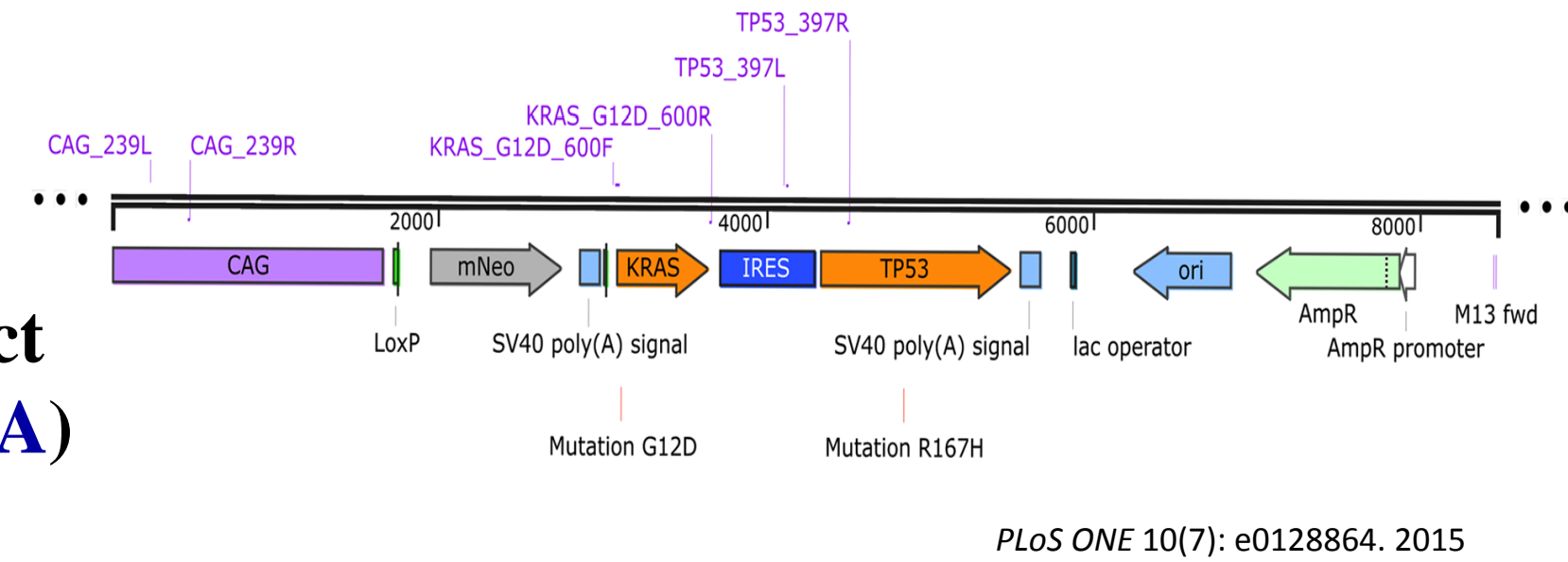
Introduction

- PDAC remains remarkably lethal with a 5-year survival of ~9%.
- Murine models continue to provide outstanding research support despite different anatomy and physiology.
- *Sus Scrofa domestica* (domestic pigs) share more structural and genetic homology to humans and may serve as an improved research platform.
- We developed a KRAS^{G12D}/TP53^{R167H} (KP; **Figure 1**) induced porcine model of PC that mimics two human cancer histotypes.

Methods

- KP Transgenesis to establish OncoPig
- Porcine pancreatic duct cell isolation (**Figure 4A**)
- Cre Induction *in vitro*: transfection of Adeno-Cre-particles *in vivo*: injection of adeno-Cre particles into pancreas (**Figure 4B,C**)
- Subcutaneous or intraperitoneal injection of porcine pancreatic duct cells expressing KP into immunocompromised mice
- Collection, fixation, and histology of porcine pancreatic tumors/tissue
- IF and IHC biomarker staining of *in vitro* and *in vivo* samples: CK19, E-cad, PCNA, pERK, mtRAS, mtp53, αSMA, vimentin, amylase, synaptophysin

Figure 1: Porcine KP transgene



Results

Figure 2: KRAS^{G12D} and TP53^{R167H} mutations lead to self immortalization of Porcine Pancreatic Duct Cells *in vitro*

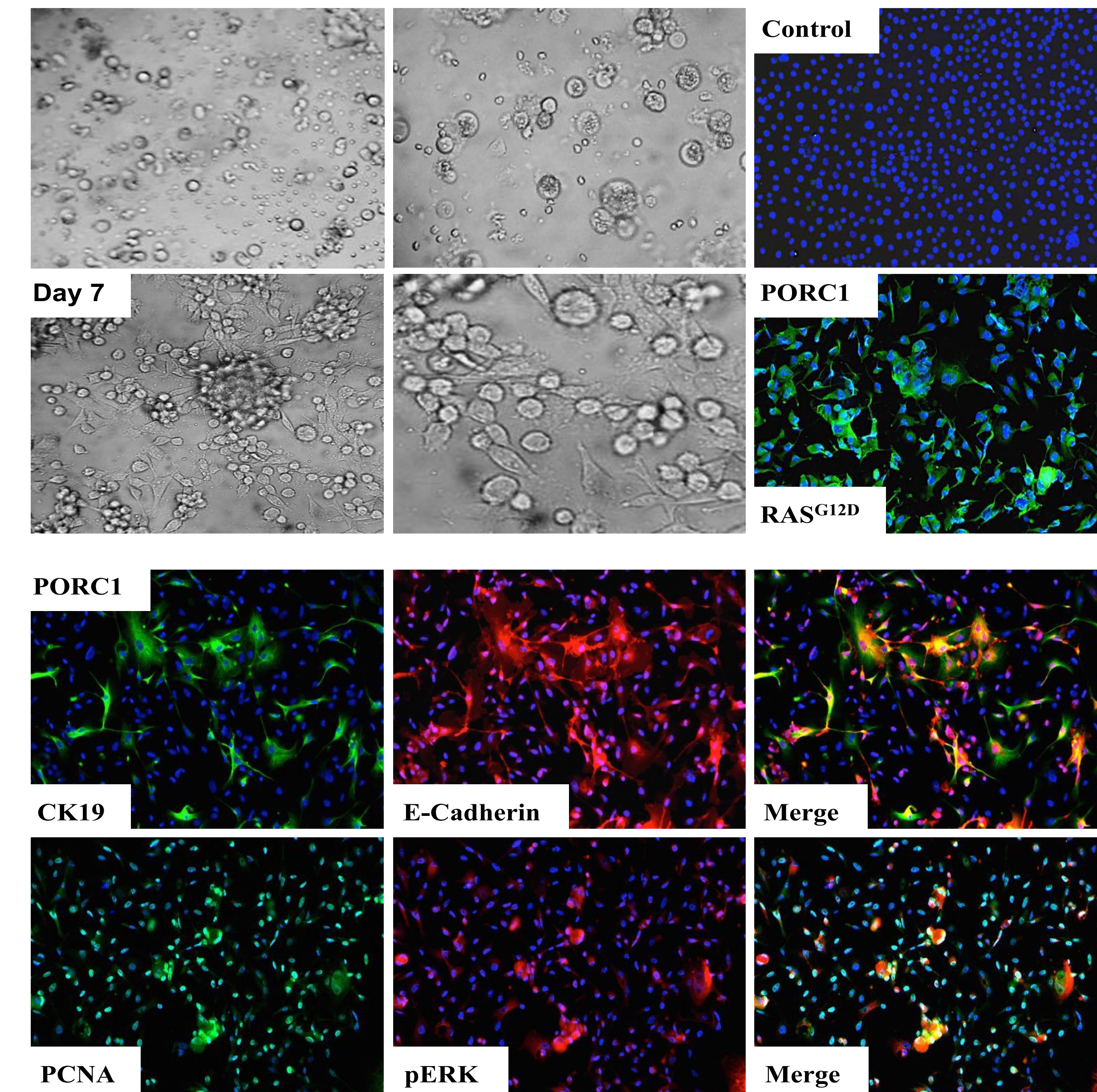


Figure 3: PORC1 cells establish large subcutaneous tumors in immunodeficient mice.

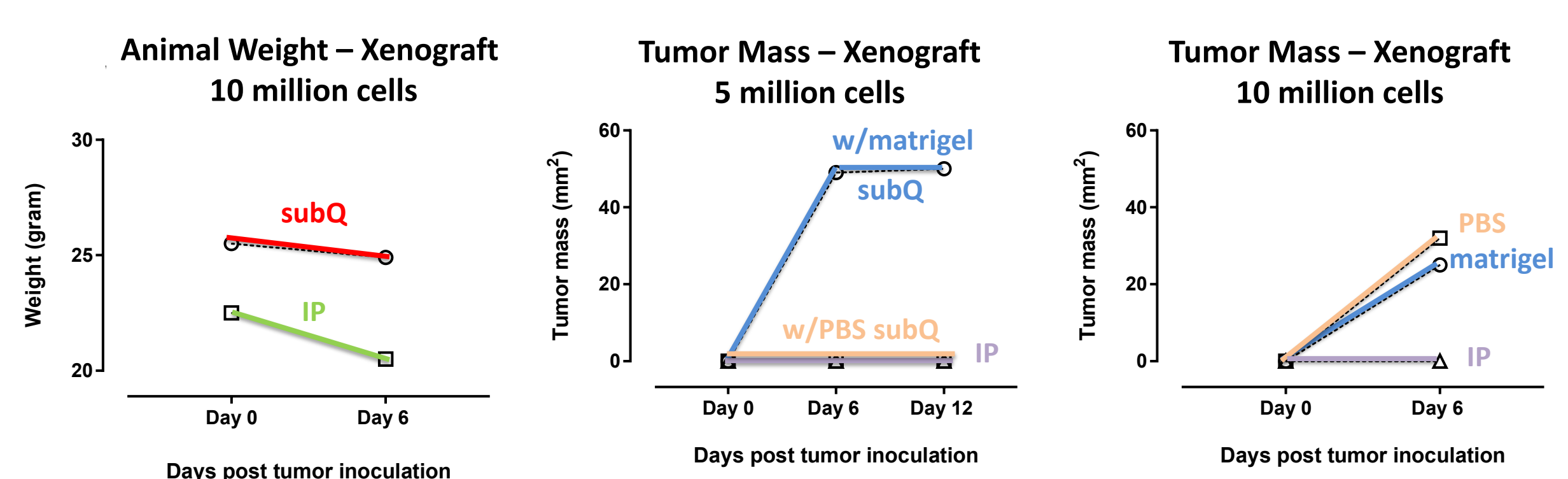
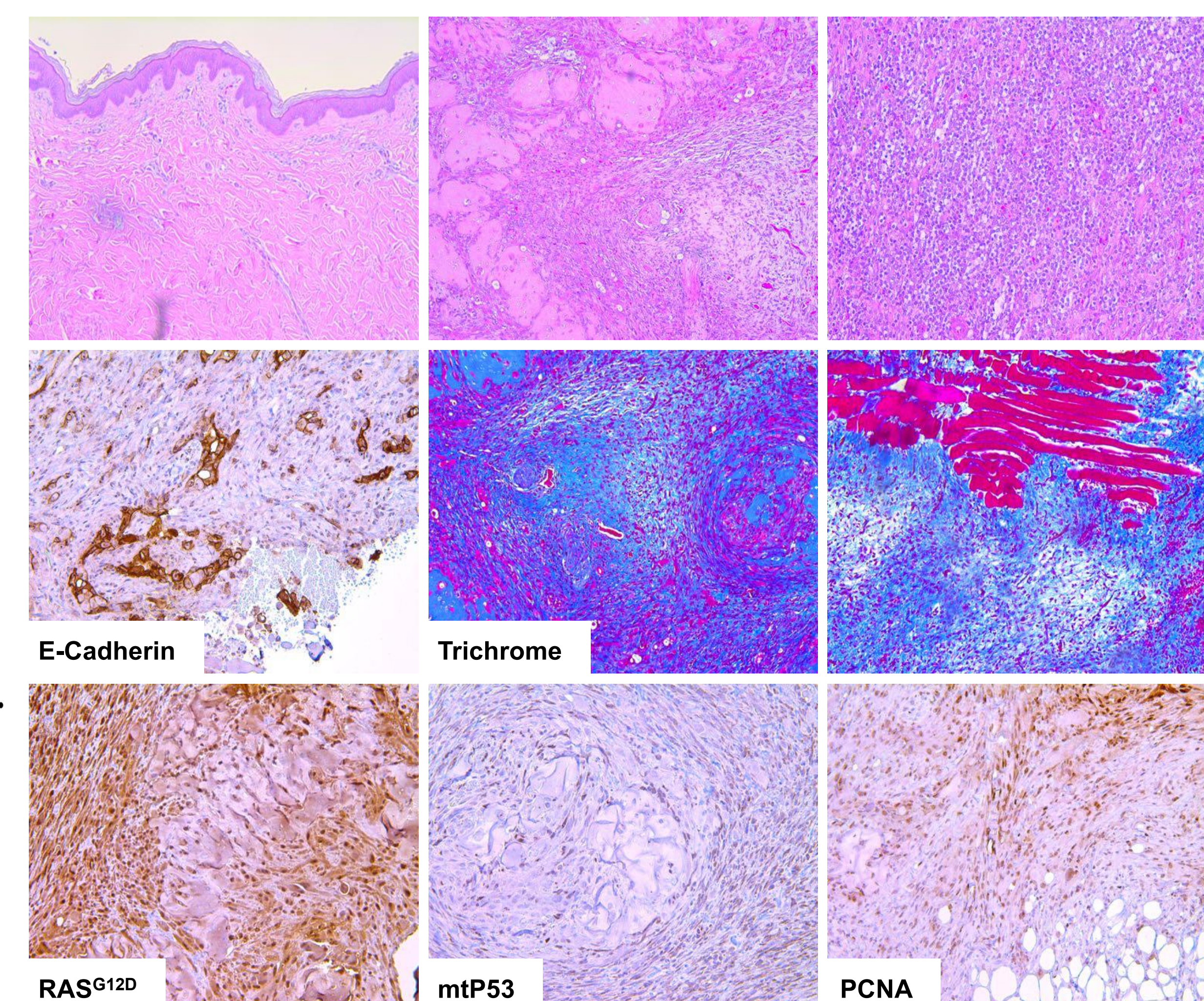


Figure 4: The Primary Technologies for Building Oncopig Mice.

- Transgenesis of single-cell fertilized pig egg
- Intraparenchymal injection into pig pancreas
- Endoscopic main pancreatic duct injection (future injections)

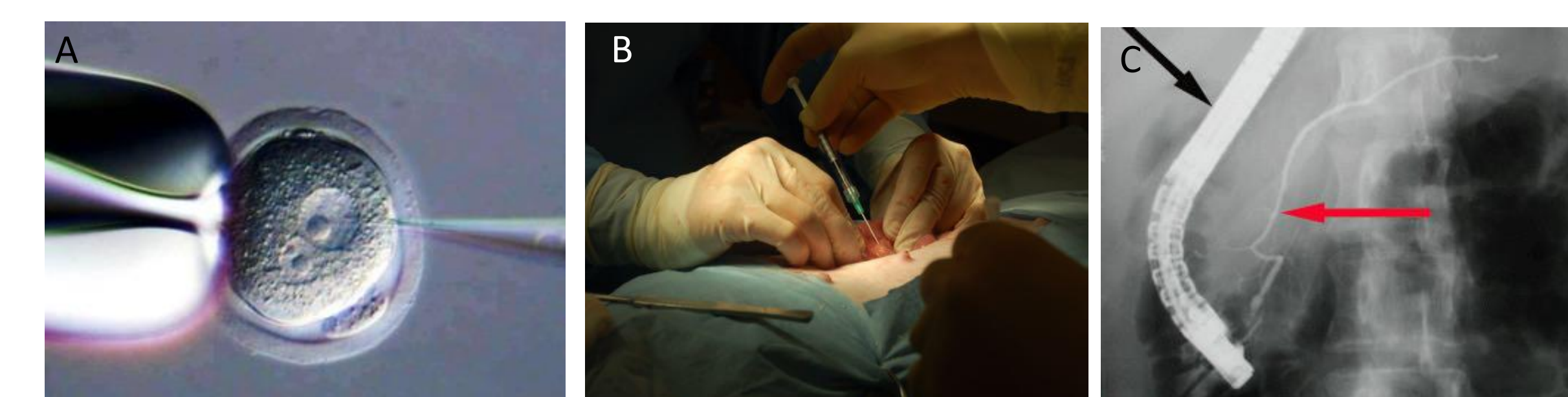


Figure 5: Intraparenchymal injection of Adeno-Cre particles induces metastatic disease involving the greater omentum & spleen

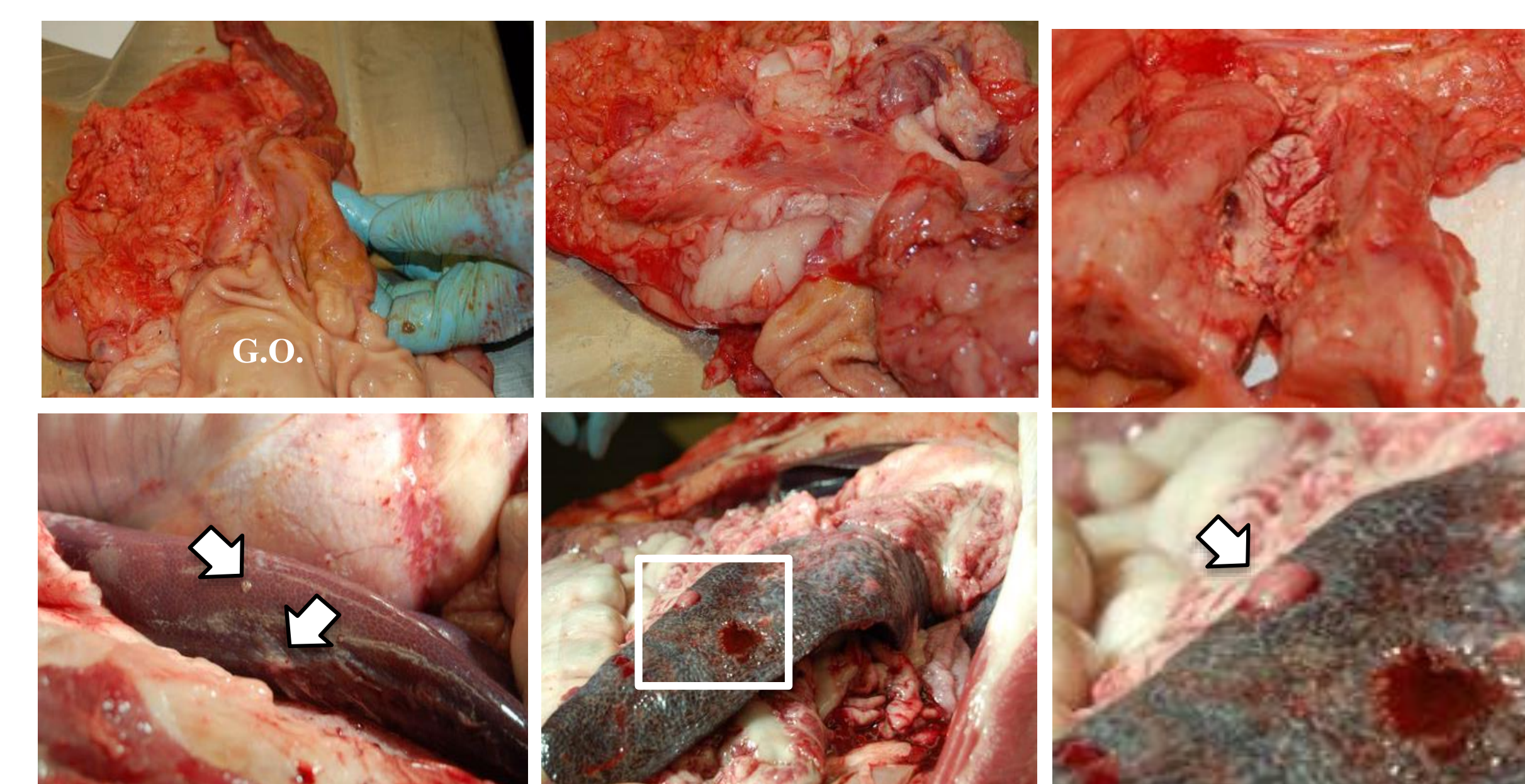


Figure 6: Tumors established via intraparenchymal injection often share histologic features of leiomyosarcoma

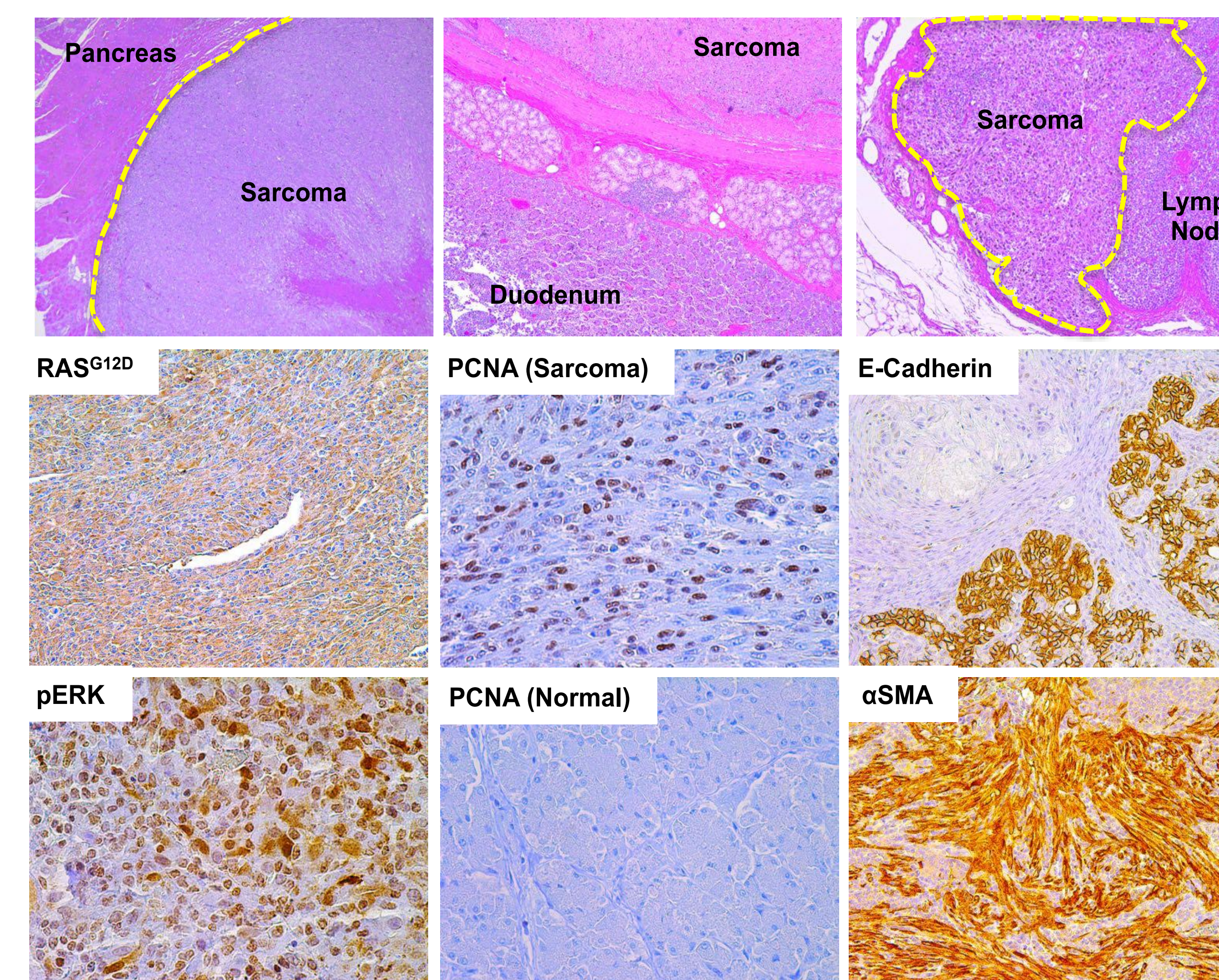


Figure 7: Pig Pancreas Diagram and following necropsy

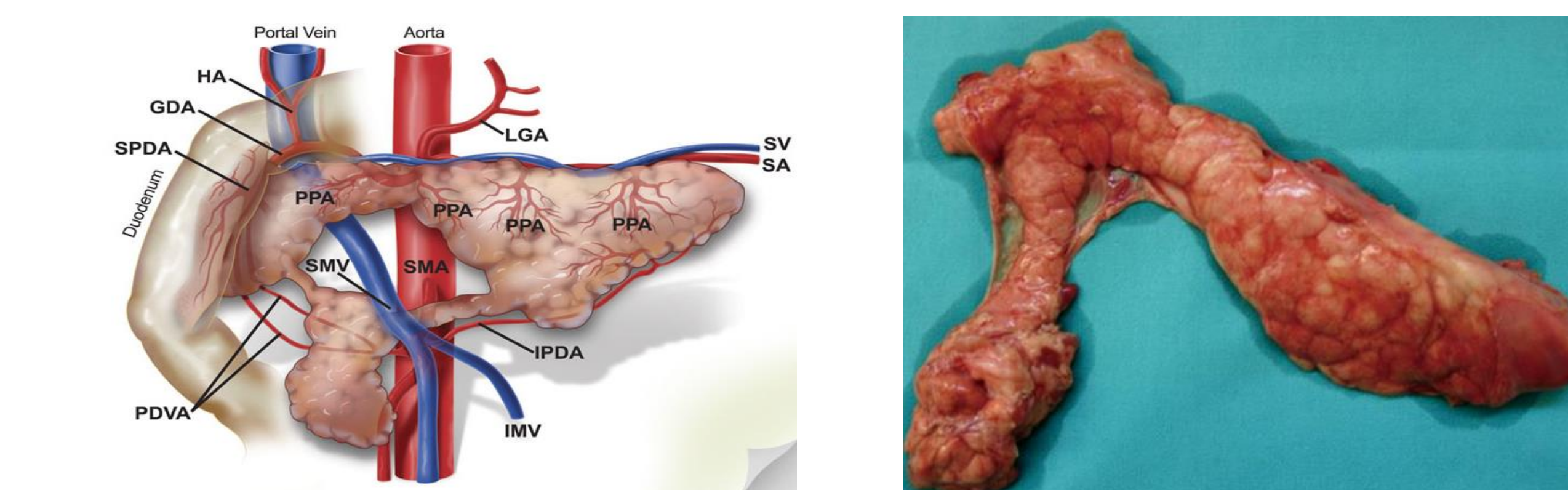


Figure 8: Pancreatic tumors also display acinar to ductal metaplasia (ADM) and PanIN disease

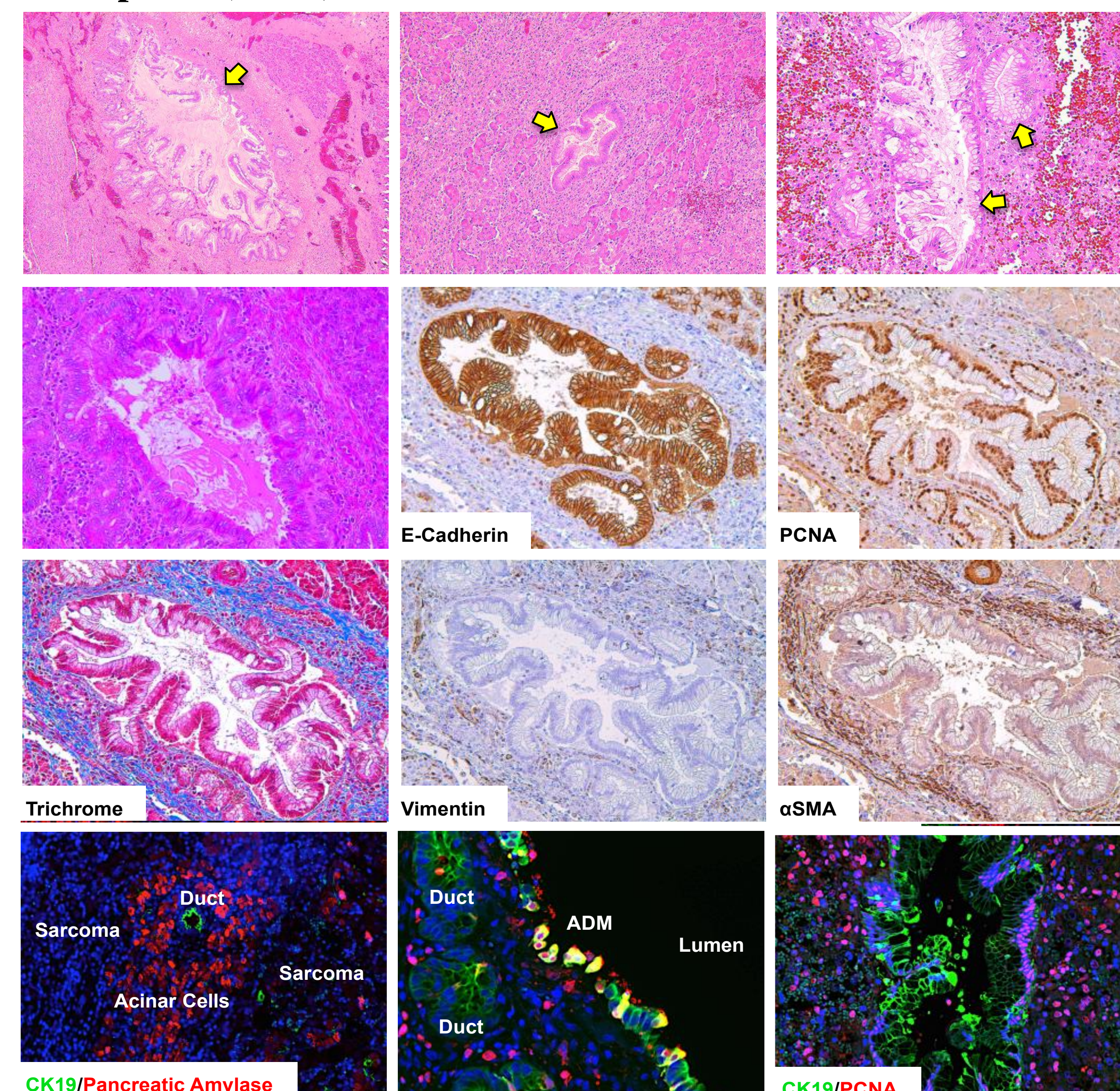


Figure 9: Pancreatic Intraductal injection of Adeno-Cre Particles leads to disease restricted to the pancreas

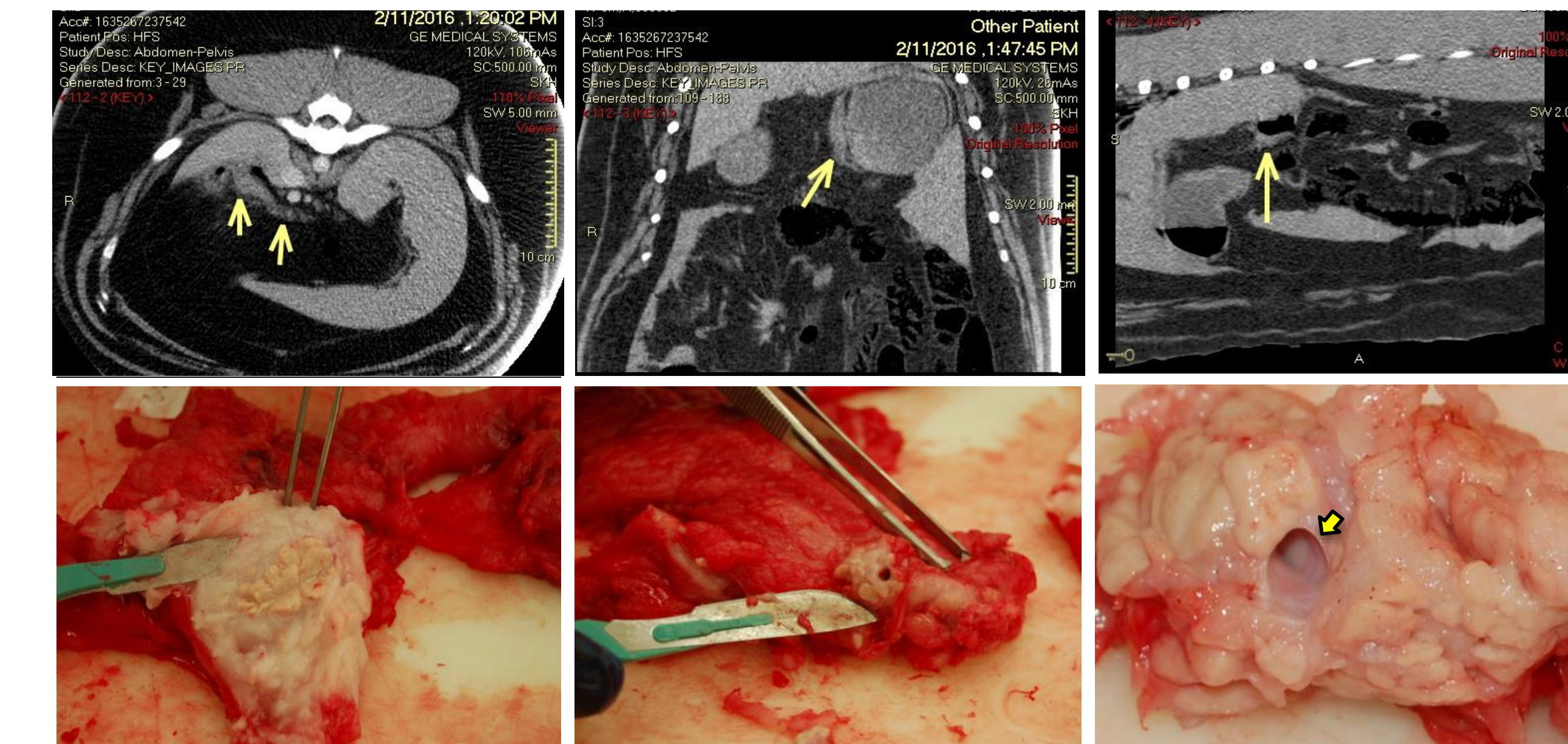
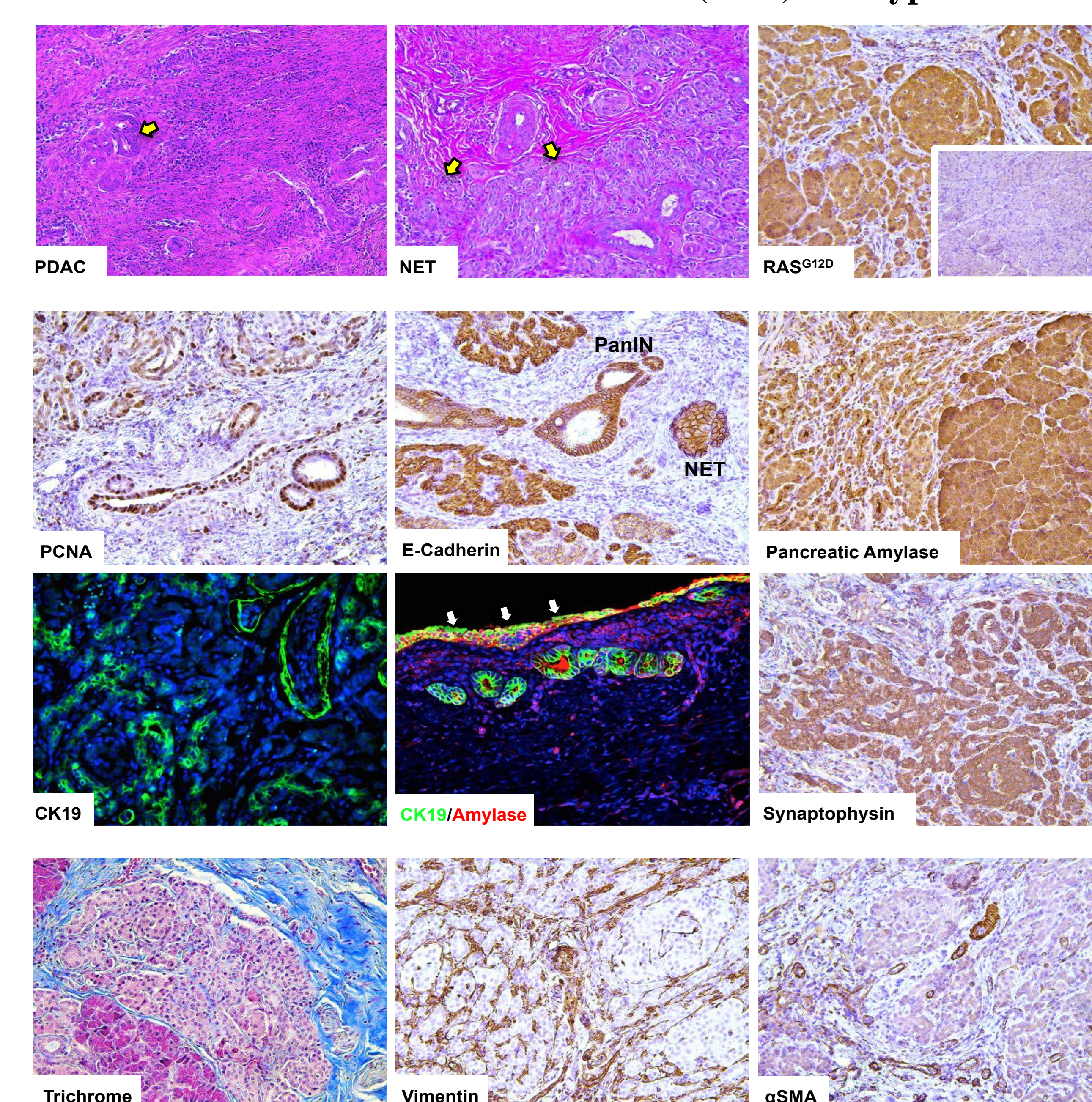


Figure 10: Tumors induced by pancreatic intraductal injection have a mixed PDAC and neuroendocrine tumor (NET) histotype



Summary

- Expression of LSL-KRAS^{G12D}/TP53^{R167H} can generate:
 - pancreatic neoplasia (& sarcoma) - ectopic Adeno-Cre administration
 - both local PDAC & neuroendocrine cancers - intraductal Adeno-Cre
- Porcine pancreatic carcinogenesis resembles human pancreatic cancer as evident by neoplasia development & biomarker expression.

Future Directions

- Restrict transgene expression via pancreatic duct cell Cre expression.
- Employ Porcine PDAC model for:
 - Therapy evaluations: chemotherapy, immunotherapy, etc.
 - Surgical, interventional radiology, and training model
 - Epigenetic studies including diet manipulation