Supplementary Figure Legend

Supplementary Figure 1

(A) Scheme of *Ptf1a-Cre; Arid1a*$^{f/f}$ (CA) mice. Exon 8 of *Arid1a* was flanked by two loxP sites and recombination created a frameshift mutation and induced nonsense-mediated decay of the resulting transcript.

(B) Western blots showing loss of ARID1A protein in CA mice.

(C) Serial section of *Ptf1a-Cre; Arid1a*$^{f/f}$*; ROSA26-LSL-tdTomato (Td)* pancreata showing that tomato reporter signal was present in acinar (amylase positive), duct (CK-19 positive), beta cells (insulin positive), and alpha cells (glucagon positive, arrowheads) demonstrating ubiquitous Cre expression driven by the *Ptf1a* transcription factor. However, ARID1A expression was retained in a subset of duct cells and all endocrine cells.

(D) CA mice had acinar ductal metaplasia (arrowheads)

(E) Cysts in CA mice had infiltration by CD45-positive cells and collagen deposition as shown by Sirius red.

(F) 52-week old CA mice can develop massive pancreatic cysts and can have significant pancreatic fatty infiltration.

Supplementary Figure 2

(A) Scheme of *Kras*^{G12D}*; Ptf1a-Cre; Arid1a*$^{f/f}$ (KCA) mice.

Eight-week old KCA mice had

(B) PanIN, infiltration of CD45-positive cells, and fibrosis as shown by Sirius red staining.

(C) The stroma of KCA cysts did not express progesterone receptor (PR) or estrogen receptor (ER), thus ruling out mucinous cystic neoplasm. Mouse uterus was used as positive control.

(D) While KCA mice had mostly gastric subtype IPMN, there were areas mixed gastric (circled) and pancreaticobiliary patterns.

(E) KCA mice did not have intestinal subtype IPMN as demonstrated by the negative CDX2 staining.

(F) Example of the various level of ARID1A staining seen in human IPMN samples.

(G) Human intestinal subtype IPMN have strong ARID1A expression while pancreaticobiliary and gastric subtype IPMN could be mosaic for ARID1A (arrow to ARID1A negative cells and arrowhead to ARID1A positive cells).

(H) $Kras^{G12D}$*;* $Trp53^{f/+}$*; Ptf1a-Cre;* $Arid1a^{f/f}$ mouse with massive pancreatic cyst without associated mass suggestive of pancreatic ductal adenocarcinoma.

Supplementary Figure 3

(A) Scheme of $Kras^{G12D}$*; Sox9-CreER*; $Arid1a^{f/f}$ mice.

After tamoxifen (TAM) induction,

(B) $Kras^{G12D}$*; Sox9-CreER;* $Arid1a^{f/f}$ mice developed occasional PanIN and sporadic significant inflammatory response associated with dilated duct (asterisk) and infiltration of CD45-positive cells.

(C) There was no difference in proliferative rates (measured by Ki-67) in duct cells (CK-19 positive) between $Kras^{G12D}$*; Sox9-CreER;* $Arid1a^{+/+}$ and $Kras^{G12D}$*; Sox9-CreER;* $Arid1a^{f/f}$ mice compared 12 and 52-60 weeks after TAM.

(D) Efficiency of Cre recombinase in *Sox9-CreER* mice was examined in $Kras^{G12D}$*; Sox9-CreER;* $Arid1a^{+/+}$*; ROSA26-LSL-tdTomato (Td)* and $Kras^{G12D}$*; Sox9-CreER;* $Arid1a^{f/f}$*; Td* mice 12 weeks after TAM. Each dot represents one 100X field, each bar represents one mouse. One section from each mouse was examined.

(E) Kaplan-Meier curves of $Kras^{G12D}$*;* $Trp53^{f/+}$*; Sox9-CreER* mice that were $Arid1a^{+/+}$; $Arid1a^{f/+}$; or $Arid1a^{f/f}$.

(F) $Kras^{G12D}$*;* $Trp53^{f/+}$*; Sox9-CreER;* $Arid1a^{f/f}$ mice developed occasional acinar-ductal metaplasia (ADM), PanIN, and cysts.

Supplementary Figure 4

(A) Scheme of *Kras^{G12D}; Ptf1a^{CreER}*; *Arid1a$^{f/f}$* mice.

(B) Two days after tamoxifen induction, the pancreata of *Ptf1a^{CreER}; ROSA26-LSL-tdTomato (Td)* mice were grossly pink.

(C) No difference in proliferative rates seen in PanIN between *Kras^{G12D}; Ptf1a^{CreER}* mice that were *Arid1a$^{+/+}$*; *Arid1a$^{f/+}$*; or *Arid1a$^{f/f}$*, as measured by Ki-67.

Supplementary Figure 5

Acini and islets (asterisk) both had very little c-MYC expression in

(A) Kras^{G12D}; Ptf1a-Cre; Arid1a$^{+/+}$ and *Kras^{G12D}; Ptf1a-Cre*; *Arid1a$^{f/f}$* mice,

and

(B) Kras^{G12D}; Sox9-CreER; Arid1a$^{+/+}$ and *Kras^{G12D}; Sox9-CreER; Arid1a$^{f/f}$* mice.

Supplementary Figure 6

(A) qPCR of RNA from wild-type (n = 5) and *Ptf1a-Cre; Arid1a$^{f/f}$* (n = 4) pancreata validated the findings from RNA-seq. *P < 0.05.

(B) qPCR of RNA from wild-type (n = 5) and *Ptf1a^{CreER}; Arid1a$^{f/f}$* (n = 5) pancreata. *P < 0.05, **P < 0.01.

(C) Representative FACS plot from HPDE cells treated with O-propargyl-puromycin (OPP) and various siRNA.

(D) Western blots showing that *ARID1A* knockdown in HPDE cells had no effect on mTOR signaling.

(E) HPDE cells were treated with OPP and treated with siScramble (n = 8), si*ARID1A* (n = 3), si*MYC* #2 (n = 4), and si*ARID1A* and si*MYC* #2 (n = 3). *P < 0.05, **P < 0.01.

Supplementary Figure 7

Western of HPDE cells that underwent CRISPR/CAS9 gene editing to knock out *ARID1A*. WT: cells that underwent editing process but retained wild-type ARID1A expression. KO: cells that were ARID1A null after editing.

Supplementary Figure 8

There was no difference in number of Ki-67 or cleaved caspase-3 positive cells after EPZ011989 treatment.