**Supplemental Materials & Methods**

***Sirius-Red and Alcian Blue histological colorations.***

Tissue slides were dewaxed, rehydrated, and stained with Picro-Sirius red (Sigma-Aldrich, #365548), for 1 h. Stained slides were then washed twice in acidified water and dipped into 95%, 100%, and 100% ethanol baths for dehydration. Slides were finally cleared in xylene, prior their mounting in Pertex. Alcian Blue staining were performed on rehydrated formalin-fixed paraffin-embedded (FFPE) sections, using a commercial solution (Sigma-Aldrich, #B8438), and counterstaining with Nuclear Fast Red Solution (Sigma-Aldrich, #N3020).

***Western-Blot Analysis***

For western blots, proteins were extracted using a commercial RIPA buffer (Thermo Fischer, 89900). supplemented with a protease (Complete, Sigma Aldrich 4693159001) and phosphatase (PhosSTOP, Sigma Aldrich 4906845001) inhibitor cocktail, quantified using a Bradford protein assay, and resolved on a 15% acrylamide gel. The antibodies used for detection are as follows: p21WAF1/Cip1 (1/1,000, Sigma-Aldrich, P1484), P-Smad2 (1/1,000, Cell signaling, 3108S), and Tubulin (1/10,000, GeneTex, GTX628802).

**Supplemental Figure Legends**

***Figure S1: Analysis of mouse WT pancreases, exposed to short-term sActRIIB-Fc treatment. (A)*** Monitoring the body weights of WT mice, before (W1) and after (W3) short-term (ST) sActRIIB-Fc treatment. Actual pancreas weights (g) and normalized pancreas weights, relative to body weight (%), are shown. Experimental design of ST sActRIIB-Fc treatment [FC (ST)]: 5 mg/kg of sActRIIB-Fc, or equal volume of PBS (vehicle), was i.p. injected into 2.5-month-old WT animals, twice a week for 3 weeks (n = 3 animals/group). ***(B)*** Representative images ofimmunohistochemical staining against amylase performed on FFPE pancreas sections collected from control or sActRIIB-Fc-treated [(FC (ST)] WT mice. Quantifications of amylase-positive cells in each pancreas are shown for each condition. ***(C)*** Immunohistochemical staining of activin A performed on WT FFPE pancreas sections. A pancreas section collected from Caerulein-treated animals is shown as a positive control for activin A expression. Data are expressed as the mean ± SEM. *ns*: not significant; ∗*P* < 0.05; ∗∗*P* < 0.01*,* Student’s *t*-test.

***Figure S2:* Inactivation of *Acvr1b,* combined with oncogenic Kras, results in the development of enlarged ADM lesions.** ***(A)*** Weights of pancreases from 1.5-2.5-month-old WT (n = 20), KC (n = 24) and 4KC (n = 13) mice. ***(B)*** Quantification of the numbers of individual ADM lesions found in KC (n = 6) and 4KC (n = 9) mice, at 1.5 months of age. ***(C)*** Representative images of H&E, Ck19, and Desmin immunostaining and Alcian Blue- and Sirius-Red collagen staining, performed on pancreas sections obtained from 1.5-month-old KC and 4KC mice. Dashed lines identify individual ADM lesions quantified in *(B)*. Data are presented as the mean ± SEM. ∗*P* < 0.05; ∗∗*P* < 0.01; ∗∗∗*P* < 0.005*,* Student’s *t*-test.

***Figure S3: Smad2 phosphorylation is blunted in 4KC neoplastic pancreatic lesions.*** Representative images of Ck19/P-Smad2 double IF staining performed in pancreatic sections obtained from 1.5-month-old KC and 4KC mice. Note the lack of P-Smad2 in Ck19-positive cells from ALK4 ablated regions of 4KC mice compared with the cells in the stromal compartment.

***Figure S4: Cultures of KC acinar cells, embedded in 3D-collagen, recapitulate ADM. (A, B)*** Quantitative reverse transcription-polymerase chain reaction (RT-PCR) of the indicated Acinar- (*Amy2a, Rbpjl, Cpa1, Ptf1a,* and *Cela1*) and Duct-associated (*Sox9, Rbpj, Pdx1, Hes1,* and *Ck7*) genes. Acinar collagen cell cultures from 1.5-month-old KC mice were analyzed at the indicated time points.Results were obtained from independent cultures, generated from 4 independent isolationsof KC acinar cells. ***(C)*** Representative IHC staining against Ck19 and Sox9, performed on 3-M-thick histological sections of FFPE duct structures, obtained from KC acinar cells cultured for 6 days in 3D-collagen media. Arrowheads indicate Sox9-positive nuclei. Data are expressed as the mean ± SEM. ∗*P* < 0.05; ∗∗*P* < 0.01; ∗∗∗*P* < 0.005*,* Student’s *t*-test.

***Figure S5: Colocalization of ALK4/Activin A in KC pancreatic lesions.*** Representative double IF staining against Ck19/Activin A and Ck19/ALK4performed on serial FFPE pancreatic sections, obtained from 3-month-old KC mice. Right panels show magnified views of the *a, b,* and *c* dashed and annotated areas.

***Figure S6: Disruption of ALK4-expression reduces Kras-OIS in ADM, in vitro. (A)*** Representative FFPE 3-M sections from whole-mount SA--Gal staining, performed on KC and 4KC acinar cells, cultured in 3D-collagen media for 6 days***.*** Note that all experiments were performed with acinar cells isolated from 1–1.5-month-old animals. Quantification of the percentage SA--Gal-positive cells in each field is shown (KC: n = 3, 4KC: n = 3). ***(B, C)*** Representative double IF staining against Ck19/Sox9 *(B)*, Ck19/p21, and Ck19/H2AX *(C),* performed on FFPE duct structures, obtained from KC and 4KC acinar cells, cultured in 3D-collagen media for 6 days. Quantifications of the percentage Sox9-, p21-, and H2AX-positive cells in each duct are shown (B and C). A total of 16 and 14 independent duct structures were Supplemental Material & Figure legends\_Rev evaluated from independent KC and 4KC Supplemental Material & Figure legends\_Rev Supplemental Material & Figure legends\_Rev acinar cell culture Supplemental Material & Figure legends\_Rev Supplemental Material & Figure legends\_Rev ± SEM. ∗*P* < 0.05; ∗∗∗*P* < 0.005; *ns: non-significant,* Student’s *t*-test.

***Figure S7: inhibition of Activin A signaling blocks Smad2 phosphorylation and inhibits the subsequent induction of p21. (A)*** Western blot analysis of P-Smad2 in cultured Panc-1, Mia Paca-2, and Capan-1 cell lines. Cells were treated for 24 h with Activin A (25 g/mL) or TGF(5 g/mL) ligands, combined with the sActRIIB-Fc (0.5 µg/mL) or SB431542 (10 M) inhibitors, as indicated. ***(B)*** Analysis of*Cdkn1a* expression, performed by quantitative RT-PCR in Panc-1 cells, following 24-h stimulation with the indicated molecules.***(C)*** Western blot analysis of P-Samd2 and p21 expression levels in cultured Panc-1 cell, subjected to 24-h stimulation with the indicated compounds [Activin A (25 g/mL), TGF-(5 g/mL), and SB431542 (10 M)].

***Figure S8: Disruption of ALK4 expression reduces Kras-OIS in ADM, in vivo.*** ***(A)*** FFPE sections from whole-mount SA--Gal staining, performed on the pancreases of 1.5-month-old KC and 4KC mice. Representative images of SA--Gal reactivity in PanIN lesions and the quantification of ADM/PanIN SA-β-gal-positive surfaces are shown (KC, n = 9; 4KC, n = 7). ***(B, C)*** Images of p21 and H2AX IHC staining performed on pancreatic sections obtained from 1.5-month-old KC and 4KC mice. Quantifications are shown in the right panels (n = 4 animals/group).Data are presented as the mean ± SEM. ∗∗*P* < 0.01; ∗∗∗*P* < 0.005*,* Student’s *t*-test.

***Figure S9: Disruption of ALK4 expression promotes the proliferation of ADM lesions. (A, B)*** IHC and IF staining, performed on 3-M sections ofFFPE duct structures, obtained from KC and 4KC acinar cells cultured in 3D-collagen media for 6 days. Note that all experiments were performed with acinar cells isolated from 1-1.5-month-old animals. ***(A)*** Representative Ck19 IHC staining, showing the enlarged diameters of duct structures formed from 4KC acinar cell cultures compared with KC cell cultures. Quantifications are shown. ***(B)*** Representative Ck19/Ki67 IF staining, showing the increased proliferation observed in 4KC cells. Quantification of the percentage of Ki67-positive cells in each duct structure is shown (KC: n = 3, 4KC: n = 10). ***(C)*** Representative images of Ck19/Ki67 double IF staining performed on ADM sections, obtained from 1.5-month-old KC and 4KC mice. Quantifications are shown in the right panels (n = 3 animals/group). Scale bars are indicated.Data are presented as the mean ± SEM. ∗∗*P* < 0.01; ∗∗∗*P* < 0.005*,* Student’s *t*-test.

***Figure S10: Analysis of mouse 4KC pancreases exposed to short-term sActRIIB-Fc treatment. (A)*** Monitoring of 1-month-old 4KC mouse body weights before (W1) and after (W3) sActRIIB-Fc treatment. Actual pancreas weights (g) and normalized pancreas weights, relative to body weights (%), are shown. Experimental design of short-term sActRIIB-Fc treatment [FC (ST)]: 5 mg/kg sActRIIB-Fc, or equal volume of PBS (vehicle), were i.p. injected into 1-month-old 4KC animals, twice a week for 3 weeks (n = 3 animals/group). ***(B)*** Immunohistochemical staining against Activin A, performed on FFPE pancreatic sections, collected from control and FC-treated 4KC mice. ***(C*** and ***D)*** Representative images ofimmunohistochemical staining against Ck19 or Ki67, performed on FFPE pancreatic sections, collected from control or sActRIIB-Fc-treated [FC (ST)] 4KC mice. Quantifications of the percentage of Ck19-positive cells in each pancreas and the Ki67-positive cells in each ADM/PanIN lesion are shown for each condition. Data are presented as the mean ± SEM. *ns*: not significant; ∗*P* < 0.05; ∗\*∗*P* < 0.001*,* Student’s *t*-test.

***Figure S11: Ki67 expression in ALK4-expressing KC lesions, following sActRIIB-Fc treatment.*** Representative images of Ck19/Ki67 and Alk4/Ki67double IF staining, performed on serial pancreatic sections, showing ADMs/PanINs obtained from KC mice subjected to short-term sActRIIB-Fc [KC + sActRIIB-Fc (ST)] or vehicle (KC-Control) treatments. Right panels show magnified views of the dashed areas for each condition.

***Figure S12: Disruption of ALK4-expression promotes the formation of pancreatic cystic lesions. (A)*** Macroscopic pictures of a 30-week-old, age-matched WT, KC, and 4KC pancreases. Right panels show magnified views of the dashed areas. ***(B)*** Immunohistochemical staining against ALK4 performed on KC and 4KC FFPE pancreatic sections. Loss of ALK4 expression is shown in PanIN and pancreatic cystic lesions in 4KC animals. ***(C)*** Representative images of Alcian-blue staining performed on FFPE pancreatic sections from age-matched KC and 4KC animals.