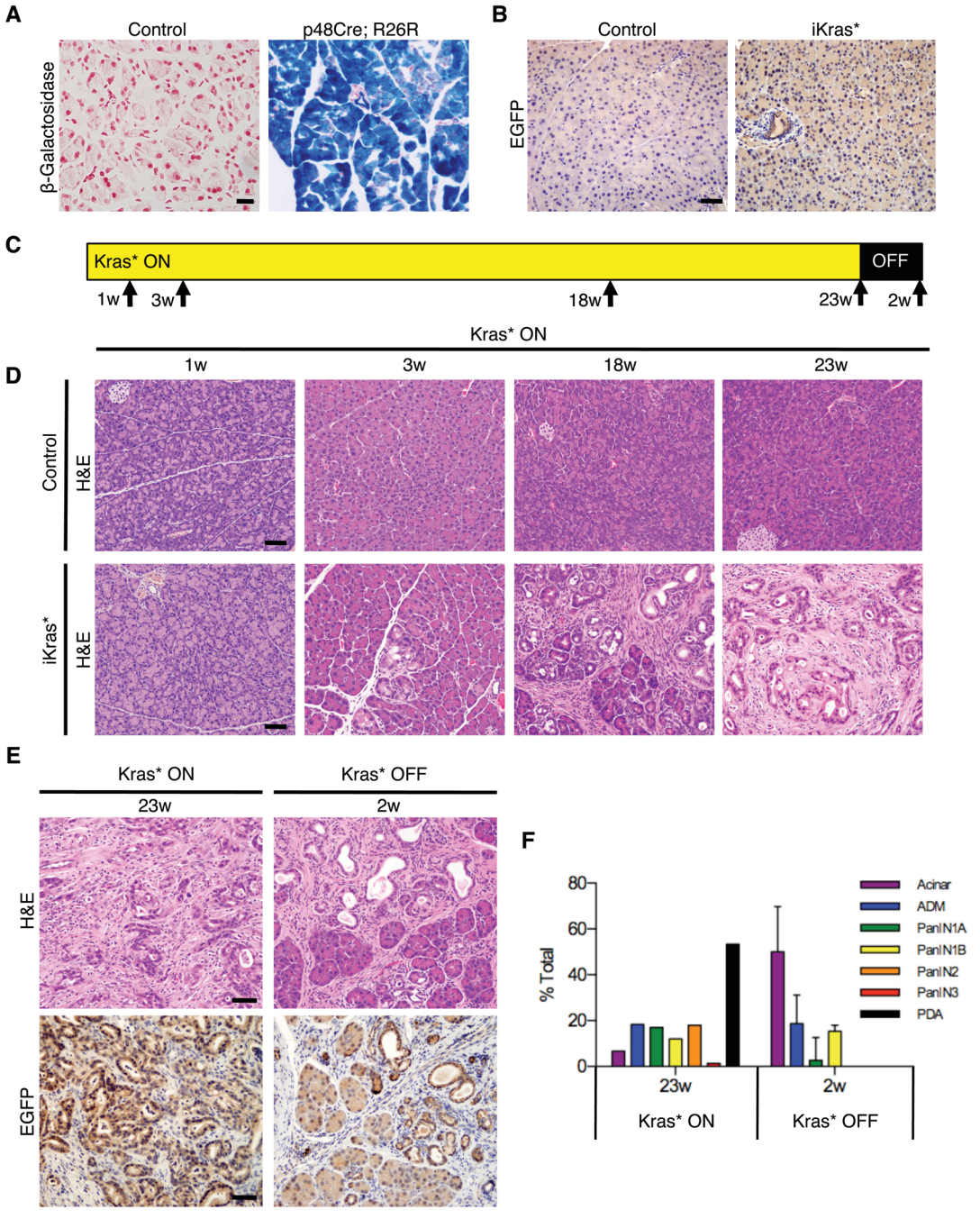
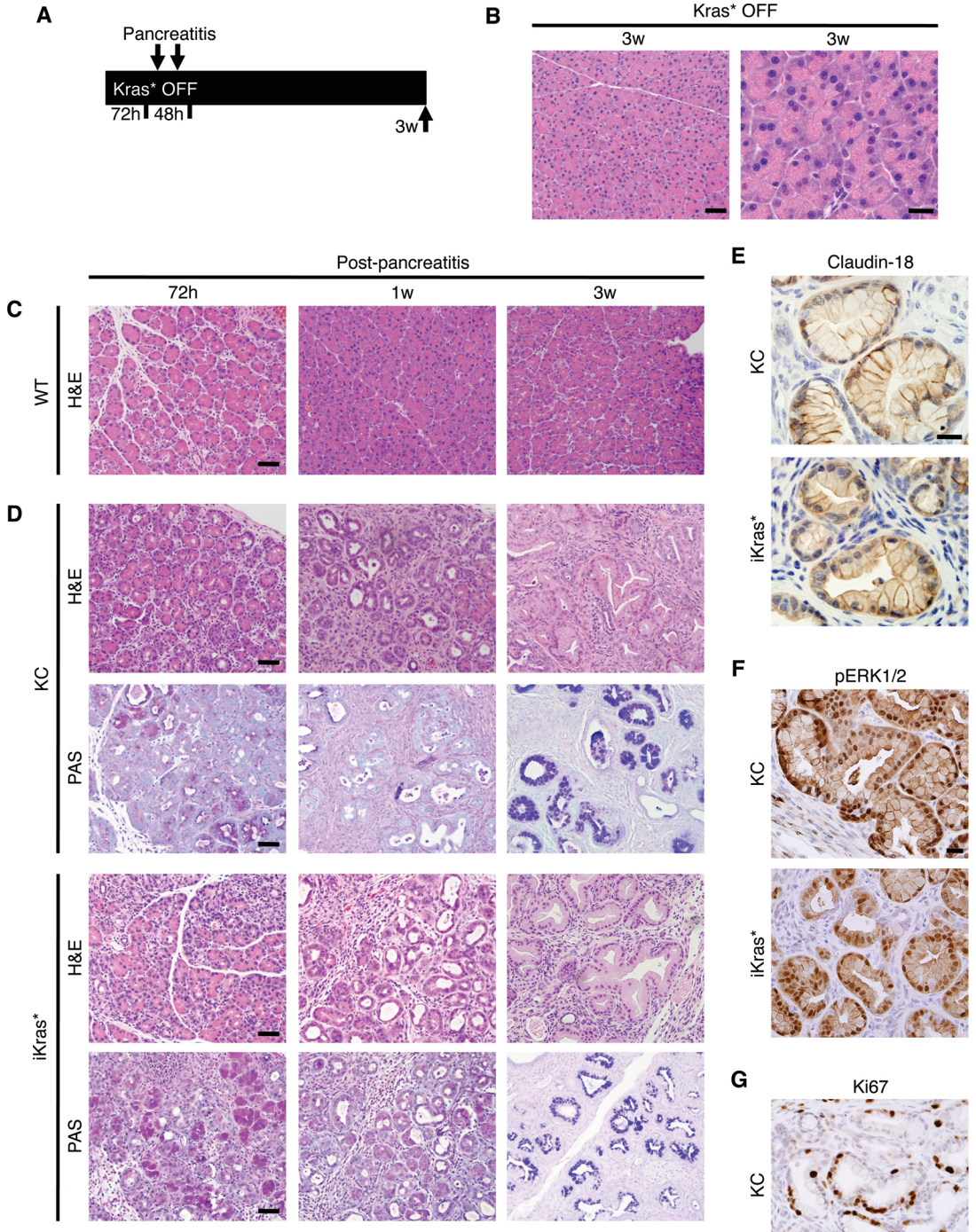


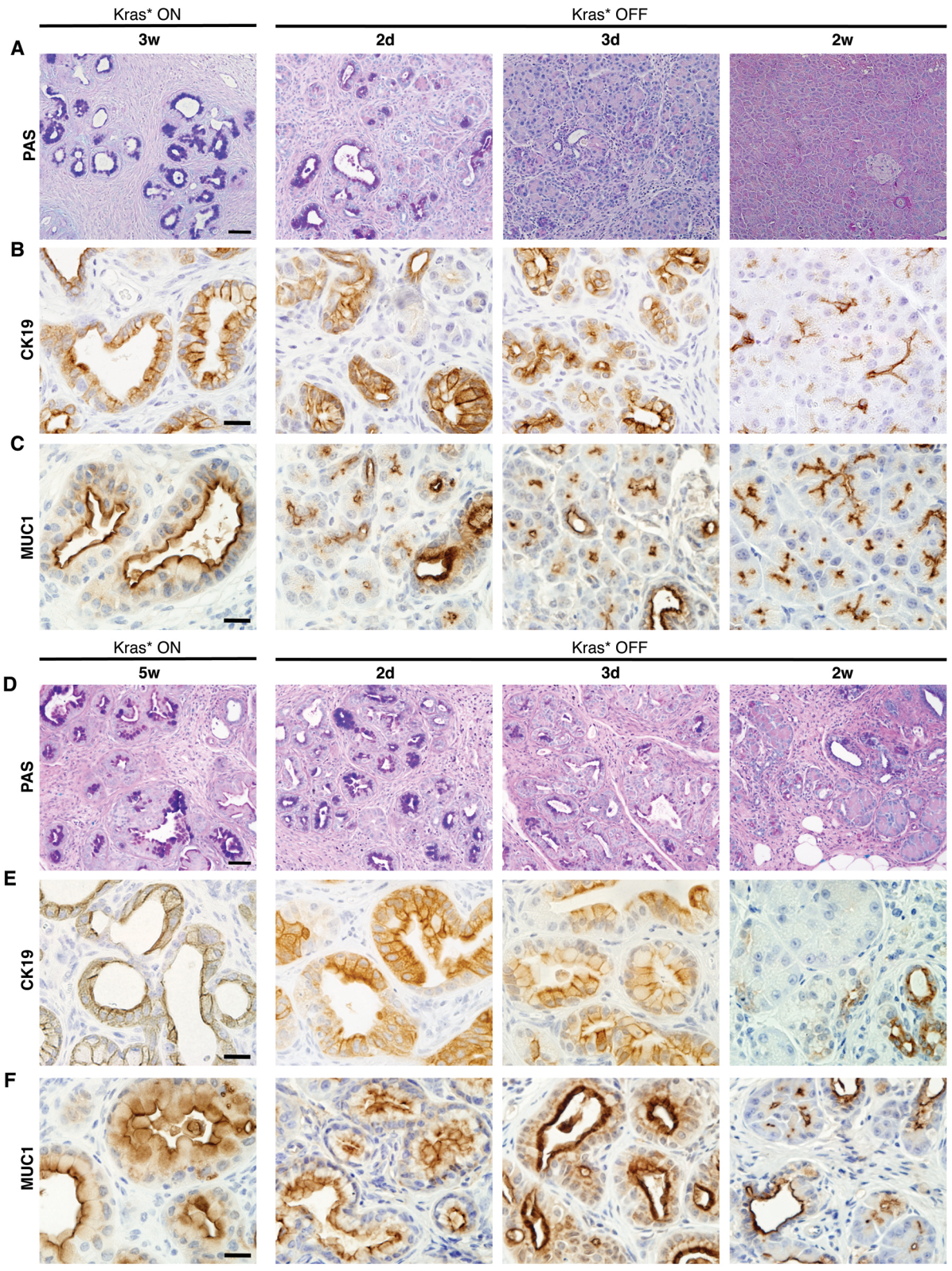

**Supplemental Figure 1**

**Analysis of the induction of Kras* expression.** (**A**) Lineage tracing of p48Cre expression, shown by Beta-galactosidase staining shows exclusinve expression in the epithelial compartment of the pancreas. Scale bar 20um. (**B**) rtTa-*IRES*-EGFP expression is specific to pancreatic epithelium, ducts and acini, shown by EGFP immunohistochemistry. Scale bar 50um. (**C**) Experimental design: Kras* expression was maintained ON and tissue was harvested at the indicated timepoints. Following Kras* activation for 23 weeks, Kras* was turned OFF for 2 weeks. (**D**) Histology of the pancreas of both control and iKras* animals at the indicated timepoints. Scale bar 50um. (**E**) Analysis of tissue histology upon Kras* inactivation (top row) and EGFP immunohistochemistry (bottom row) at the indicated timepoints. Scale bar 50um. (**F**) Quantification of pancreas histology. Data represent mean ± SEM



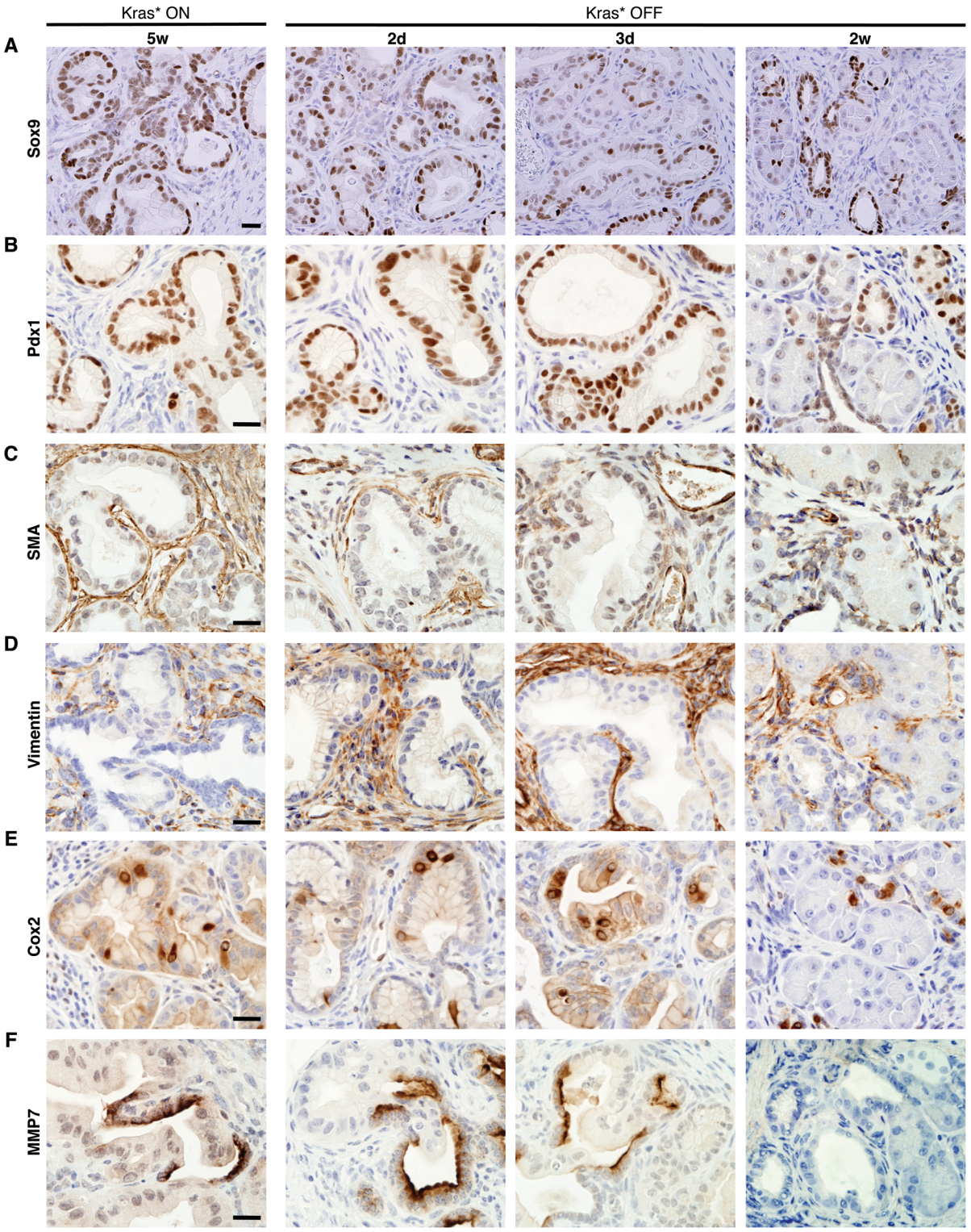

**Supplemental Figure 2**

**Evaluation of the iKras* and KC models following the induction of pancreatitis.** (**A**) Experimental design: pancreatitis was induced in iKras* animals in the absence of doxycycline (Kras* OFF) and tissues were harvested 3 weeks following treatment. (**B**) Histology of the pancreata in the absence of Kras* expression following pancreatitis shows no lesions. (**C**) Histology of WT pancreas following pancreatitis at the timepoints indicated. Scale bar 50um. (**D**) Histology (top rows) and mucin accumulation (Periodic Acid Schiff staining - bottom rows) show development of dysplastic changes in KC and iKras* models after the induction of pancreatitis. Scale bars 50um. (**E-G**) Analysis of KC and iKras* pancreata 3 weeks after the induction of pancreatitis: (**E**) Claudin-18, a PanIN marker. Scale bar 20um. (**F**) phospho-ERK1/2, a measure of MAP/ERK pathway activity. Scale bar 20um. (**G**) Ki67, marker of proliferation. Scale bar 20um.



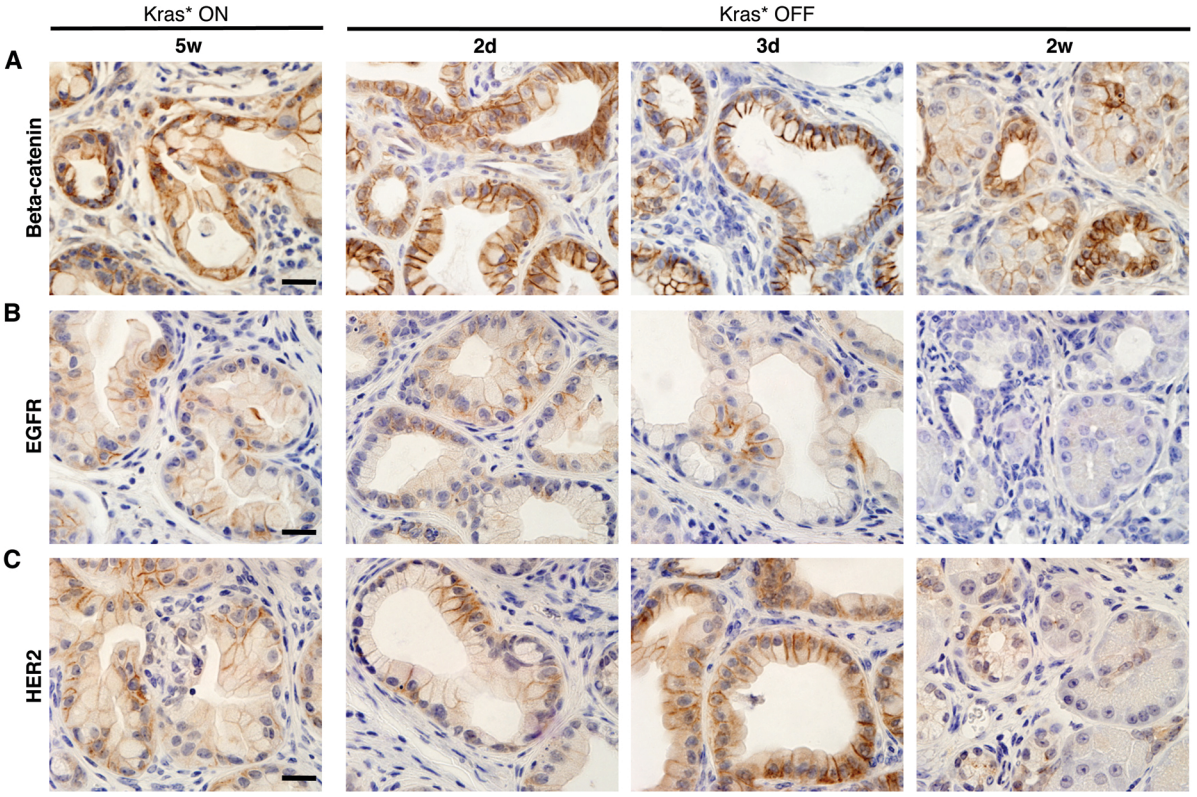

**Supplemental Figure 3**

**Regression of early and established PanINs.** Kras* expression was maintained ON for either 3 or 5 weeks following pancreatitis, then turned OFF for 2 days, 3 days, and 2 weeks. n=3-5 mice/timepoint (**A, D**) Reduction in mucin positive cells shown by Periodic Acid Schiff (PAS) staining of the pancreata at the indicated timepoints. Scale bars 20um. Regression of ductal-like cells as indicated by (**B, E**) CK19 and (**C, F**) MUC1 immunohistochemistry at the indicated timepoints. Scale bars 20um.



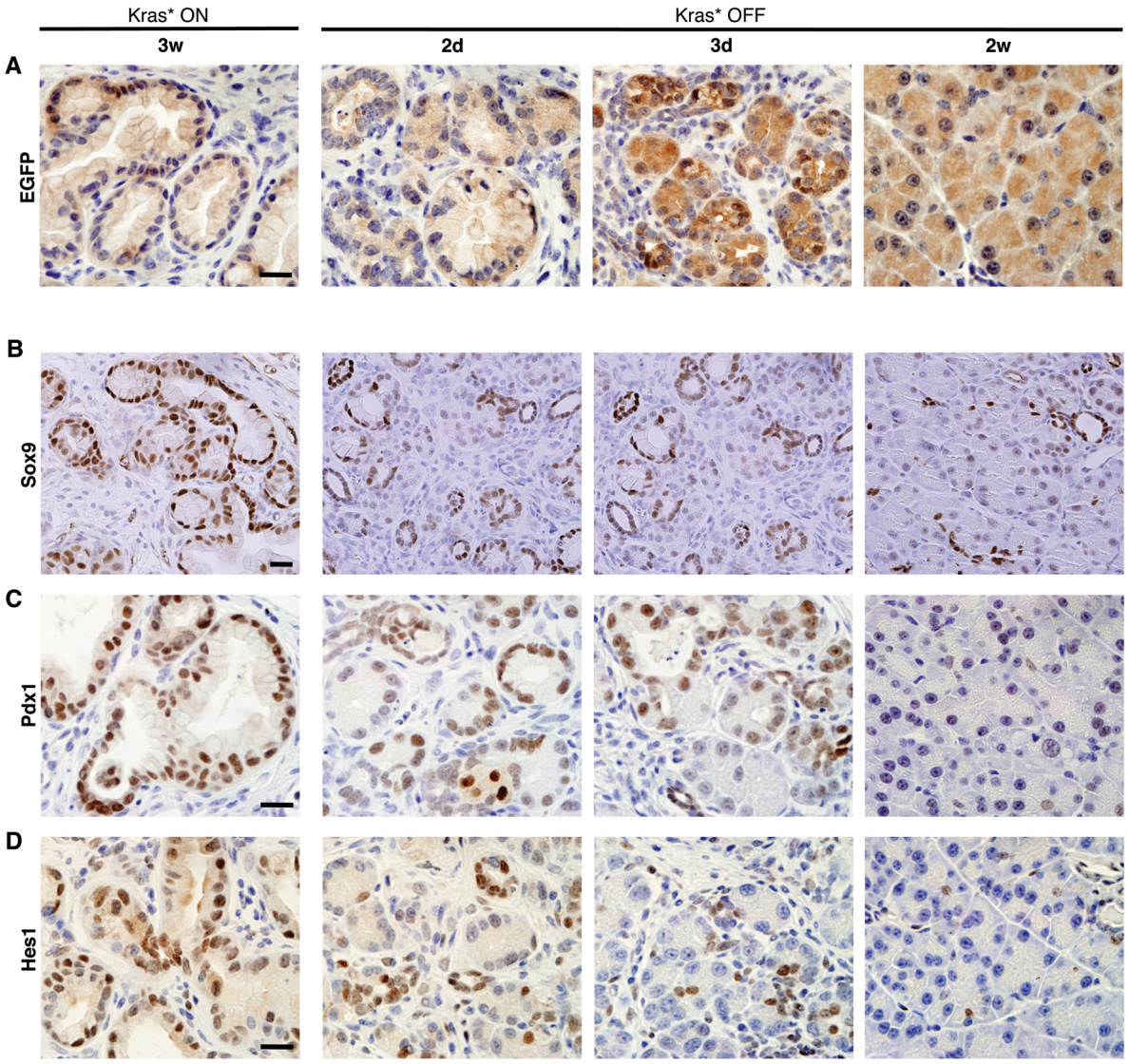

**Supplemental Figure 4**

**Established PanINs have a delayed recovery process.** Kras* expression was maintained ON for 5 weeks following pancreatitis, then turned OFF for 2 days, 3 days, and 2 weeks. n=3-5 mice/timepoint. (**A-F**) Immunohistochemistry for (**A**) Sox-9 and (**B**) Pdx1, both progenitor markers, (**C**) alpha-Smooth muscle actin and (**D**) Vimentin, markers of reactive fibroblasts, and (**E**) Cox2 and (**F**) MMP7. Scale bars 20um.



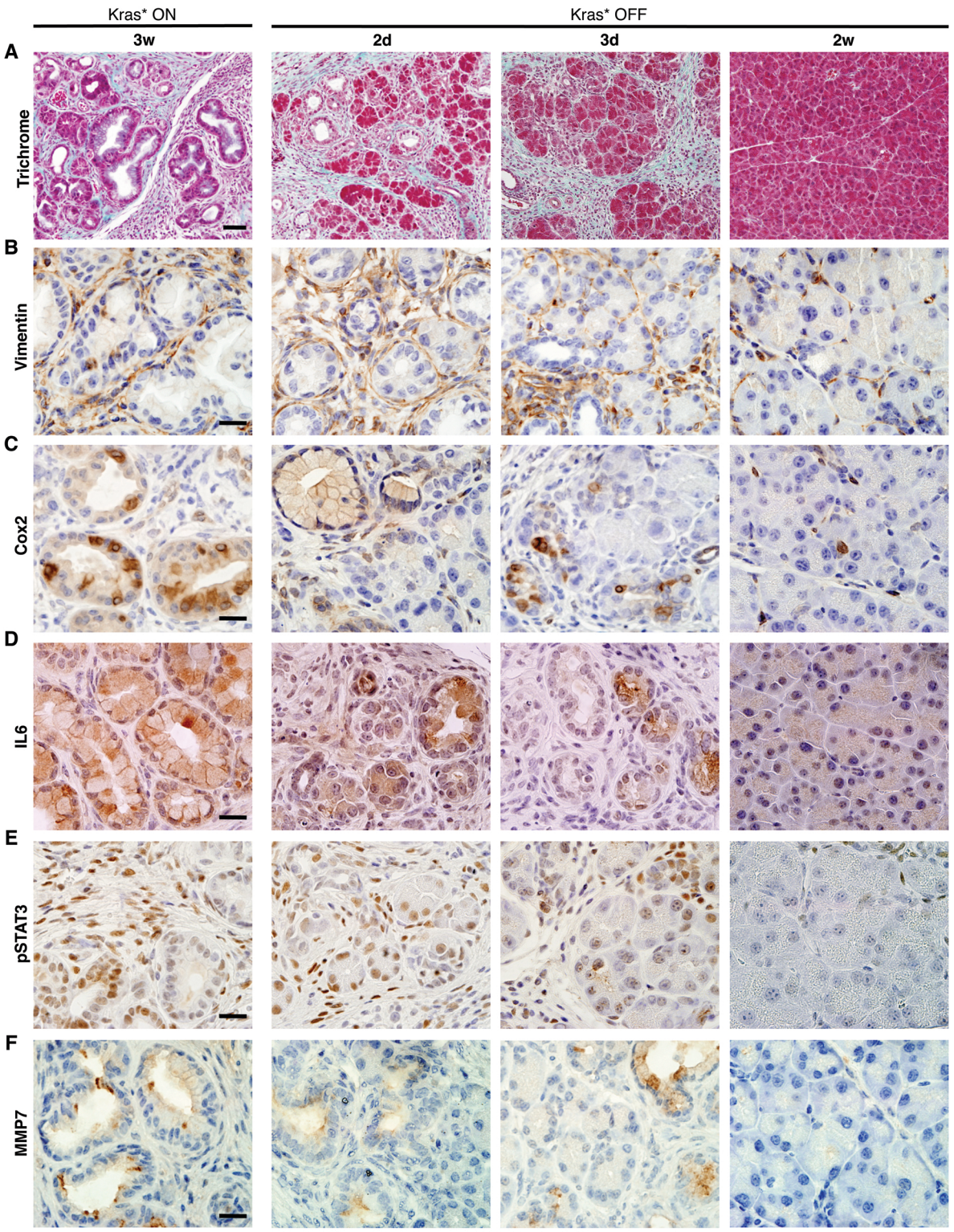

**Supplemental Figure 5**

**Regression of pathway components upon the inactivation of Kras*.** Kras* expression was maintained ON for 5 weeks following pancreatitis, then turned OFF for 2 days, 3 days, and 2 weeks. n=3-5 mice/timepoint Immunohistochemistry for (**A**) Beta-catenin and the EGFR family members (**B**) EGFR, and (**C**) HER2. Scale bars 20um.



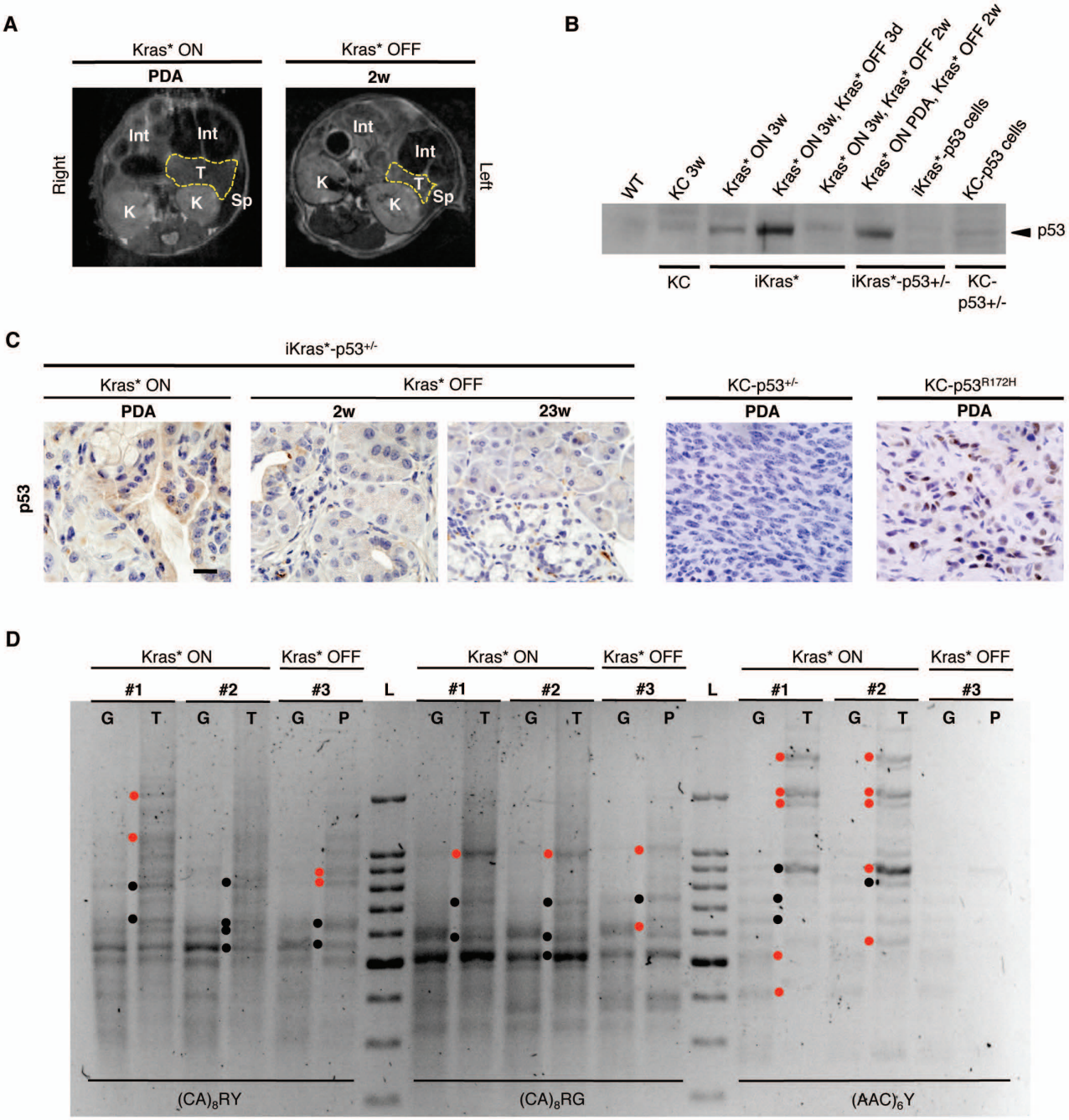

**Supplemental Figure 6**

**Analysis of the mechanism of tissue recover from early PanIN lesions.** Kras* expression was maintained ON for 3 weeks following pancreatitis, then turned OFF for 2 days, 3 days, and 2 weeks. n=3-5 mice/timepoint. (**A**) Lineage tracing, shown by EGFP immunohistochemistry, shows cells that make up the recovered tissue arose from those having previously expressed oncogenic Kras*. Scale bar 20um. Analysis of pancreatic progenitor markers during tissue recovery (**B**) Sox9, (**C**) Pdx1, and (**D**) Hes1. Scale bars 20um.




**Supplemental Figure 7**

**Oncogenic Kras* regulates the microenvironment.** Kras* expression was maintained ON for 3 weeks following pancreatitis, then turned OFF for 2 days, 3 days, and 2 weeks. n=3-5 mice/timepoint. (**A**) Gomori's Trichrome staining for collagen (green) shows a reduction in fibrotic stroma upon the inactivation of Kras*. Scale bar 50um. Immunohistochemistry of fibrotic marker (**B**) Vimentin, inflammatory markers (**C**) Cox2, (**D**) IL6, and (**E**) phospho-STAT3, and the metalloproteinase (**F**) MMP7. Scale bars 20um.




**Supplemental Figure 8**

**Characterization of iKras*-p53+/- tumors.** Kras* expression was maintained ON until the mice developed frank adenocarcinoma, then inactivated for 2 or 23 weeks. (**A**) In vivo imaging of one iKras*-p53+/- mouse using magneticresonance. T: tumor (outlined in yellow), Sp: spleen, K: kidney, Int: intestine. Note the tumor in the tail of the pancreas in the image on the left, and regression after two weeks off doxy. (**B**) Western blot for p53 expression in the indicated samples. (**C**) Immunohistochemistry for p53 in iKras*-p53+/- tumors, and at two time-points following Kras* inactivation, as well as in KC-p53+/- and KC-p53R172H tumors. Note the lack of expression in iKras*-p53+/- and KC-p53+/- tissues, and accumulation of nuclear p53 in p53R172H tissues that express a dominant negative p53 allele. Scale bars 20um. (**D**) Representative example of DNA fingerprints obtained with 3 different sets of primers. DNA was extracted from PDA tissue, T, from two different animals, and matched genomic, G, and from pancreatic tissue, P, of a third animal following Kras* inactivation. Red dots represent absence of bands in either the tumor or corresponding genomic, black dots represent changes in intensity. L: 100bp ladder.

**Supplementary Tables**

**Supplementary Table 1**: Antibodies

| Antibody | Supplier | Catalog Number | IHC dilution | IF Dilution | WB dilution |
|---|---|---|---|---|---|
| Amylase | Sigma-Aldrich | A8273 | - | 1:100 | - |
| Beta-Catenin | Cell Signaling | 9587 | 1:100 | - | - |
| Beta-galactosidase (LacZ) | Abcam | Ab9361 | - | 1:200 | - |
| CK19 (TromaIII) | Iowa Developmental Hybridoma Bank | - | 1:100 | 1:100 | - |
| Claudin-18 | Invitrogen | 700178 | 1:150 | - | - |
| Cleaved Caspase-3 | Cell Signaling | 9661 | 1:100 | - | - |
| Cox 2 | Lab Vision | RM9121S0 | 1:200 | - | - |
| E-Cadherin | Cell Signaling | 4065 | - | - | 1:1000 |
| EGFP | Invitrogen | A11122 | 1:100 | - | - |
| EGFR | Cell Signaling | 4267 | 1:50 | - | - |
| ERK1/2 (p44/42) | Cell Signaling | 4695 | - | - | 1:1000 |
| Gamma-H2AX | Millipore | 05636 | 1:400 | - | - |
| HER2/ErbB2 | Cell Signaling | 2165 | 1:400 | - | - |
| Hes1 | Ben Stanger (UPenn) | - | 1:1500 | - | - |
| IL6 | Abcam | Ab6672 | 1:500 | - | - |
| Ki67 | Vector Laboratories | VP-RM04 | 1:100 | 1:100 | - |
| MMP7 | R&D Systems | AF2967 | 1:100 | - | - |
| MUC1 | Thermo Scientific | HM1630-P | 1:100 | - | - |
| P53 | Abcam | Ab26 | 1:200 | - | - |
| P53 | Cell Signaling | 2524 | - | - | 1:1000 |
| Pdx1 | Chris Wright (Vanderbilt) | - | 1:5000 | - | - |
| p-ERK1/2 (phospho-p44/42) | Cell Signaling | 4370 | 1:100 | - | 1:1000 |
| Shh | R&D Systems | AF445 | 1:100 | - | - |
| Alpha-Smooth Muscle Actin | Sigma | A2547 | 1:1000 | 1:1000 | - |
| Sox9 | Millipore | AB5535 | 1:500 | - | - |
| p-STAT3 | Cell Signaling | 9145 | 1:100 | - | - |
| Vimentin | Cell Siganling | 5741 | 1:100 | - | - |

**Supplementary Table 2**: Primer sequences for quantitative RT-PCR

| Gene | Primer Name | Primer Sequence | Reference |
|---|---|---|---|
| Transgenic Kras | qTRE-Kras-F | CAAGGACAAGGTGTACAGTTATGTGACT | (2) |
| | qTRE-Kras-mp1-R | GCCTGCGACGGCGGCATCTGC | |
| Shh | qShh-F | CAAAGCTCACATCCACTGTTCTG | (1) |
| | qShh-R | GAAACAGCCGCCGGATTT | |
| Ptch1 | qPtch1-F | TTGTGGAAGCCACAGAAAACC | (1) |
| | qPtch1-R | TGTCTGGAGTCCGGATGGA | |
| Gli1 | qGli1-F | GCAGTGGGTAACATGAGTGTCT | (3) |
| | qGli1-R | AGGCACTAGAGTTGAGGAATTTGT | |
| Gli2 | qGli2-F | GTGCACAGCAGCCCCACACTCTC | |
| | qGli2-R | GGTAATAGTCTGAAGGGTTGGTGCCTGG | |

**Supplemental References**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2. Fisher, G.H., Wellen, S.L., Klimstra, D., Lenczowski, J.M., Tichelaar, J.W., Lizak, M.J., Whitsett, J.A., Koretsky, A., and Varmus, H.E. 2001. Induction and apoptotic regression of lung adenocarcinomas by regulation of a K-Ras transgene in the presence and absence of tumor suppressor genes. *Genes Dev* 15:3249-3262.
3. Yauch, R.L., Gould, S.E., Scales, S.J., Tang, T., Tian, H., Ahn, C.P., Marshall, D., Fu, L., Januario, T., Kallop, D., et al. 2008. A paracrine requirement for hedgehog signalling in cancer. *Nature* 455:406-410.