Supplemental Figure 1. Failed acinar regeneration in mice possessing mutant Kras targeted to developing and adult acini.

(A, B) CK19/Alcian Blue staining in *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* mice 7 and 21 days following caerulein. **(C-F)** H&E staining of pancreas from PBS and caerulein treated *Pdx1-Cre^{Late}; LSL-Kras^{G12D}* mice. Duct like cells develop 2 days following treatment (B), followed by persistent ADM/PanIN at 7 and 21 days (C, D) along a similar timeframe as *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* mice. **(G-J)** CK19 (blue), amylase (red), YFP (green) immunfluorescent labeling in PBS and caerulein treated *Elastase-Cre^{ERT2}*; *R26R-EYFP* mice. Note that YFP, CK19 positive cells are observed 2 days following caerulein, but YFP is restricted from CK19 positive cells in PBS treated mice and following regeneration (7, 21 days after caerulein). Asterisks in G, I, and J denote auto fluorescent erythrocytes found in blood vessels frequently found near ducts. **(K-N)** H&E staining of pancreas from PBS and caerulein treated *Elastase-Cre^{ERT2}*; *LSL-Kras^{G12D}; R26R-EYFP* mice. As in *Pdx1-Cre^{Late}; LSL-Kras^{G12D}* and *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* mice, duct like cells develop at day 2 (L) and persist as ADM/PanIN at 7 and 21 days (M, N) following caerulein. (A-F; K-N, x200 magnification, G-J, scale bar=50μM).

Supplemental Figure 2. Additional characterization of acinar regeneration versus Kras induced ADM/PanIN formation

(A-H) Pdx1 expression in caerulein treated *Pdx1-Cre^{Early}* (A-D) and *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* (E-H) pancreata. (A-D) Pdx1 is strongly expressed in islets

(arrowheads) in PBS treated (A) and post-regeneration pancreata (C, D). (B, inset) Pdx1 is reactivated in duct like cells 2 days following caerulein treatment. (E-H) (E) Pdx1 is expressed in spontaneous PanIN lesions (asterisk) in *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* pancreata. (F, inset) Pdx1 is found in duct like cells 2 days following caerulein and persists in metaplastic ducts and PanINs 7 and 21 days following caerulein (G, H). **(I-P)** Hes1 expression in caerulein treated *Pdx1-Cre^{Early}* (I-L) and *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* (M-P) pancreata. (I-L) Hes1 is expressed in centroacinar cells (arrowheads) in PBS treated (I) and post-regeneration pancreata (K, L). (J, inset) Hes1 is reactivated in regenerating duct like cells 2 days following caerulein treatment. (M-P) (M) Hes1 is expressed in spontaneous PanIN lesions (asterisk) in *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* pancreata. (N, inset) Hes1 is expressed in duct like cells 2 days following caerulein and persists in metaplastic ducts and PanINs 7 and 21 days following caerulein (O, P). (A-P, X400) (insets, original magnification X400).

Supplemental Figure 3. Mutant Kras blocks acinar regeneration in favor of persistently de-differentiated ADM/PanIN.

(A-H) Clusterin (blue) and YFP (green) immunofluoescent labeling in PBS and caerulein treated *Elastase-Cre^{ERT2}; R26R-EYFP and Elastase-Cre^{ERT2}*; *LSL-Kras^{G12D}; R26R-EYFP* mice. Co-expression is indicated by cyan. **(I-P)** Sox9 (blue) and YFP (green) immunofluoescent labeling in PBS and caerulein treated *Elastase-Cre^{ERT2}; R26R-EYFP and Elastase-Cre^{ERT2}*; *LSL-Kras^{G12D}; R26R-EYFP*

mice. Co-expression is indicated by cyan. Strong Sox9 staining marks centroacinar and duct cells in I, K, L, M. (A-P, scale bar=50μM).

Supplemental Figure 4. phospho-p42/p44 is persistently active in Kras induced ADM/PanIN.

(A-H) phospho-p42/p44 staining in caerulein treated *Pdx1-Cre^{Early}* (A-D) and *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* (E-H) pancreata. (A, C, D) phospho p42/44 staining above background levels is rare in PBS treated *Pdx1-Cre^{Early}* mice and pancreata following regeneration. (B, inset) phospho-p42/p44 is reactivated in some duct like cells 2 days following caerulein treatment. (E) phospho-p42/p44 is found in spontaneous PanIN lesions (asterisk) in *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* pancreata, but is mostly absent in morphologically normal acini. (F, inset) phospho-p42/p44 is strongly displayed in de-differentiated acini 2 days following caerulein and persists in metaplastic ducts and PanINs 7 and 21 days following caerulein (G, H). (A-P), X400) (insets, original magnification X400).

Supplemental Figure 5. E-cadherin accumulates in response to pancreatitis in *Pdx1-Cre^{Early}* and *Pdx1-Cre^{Early}; LSL-Kras^{G12D}* mice.

(A-D) E-cadherin (green) and amylase (red) expression in caerulein treated *Pdx1-Cre^{Early}* mice. E-cadherin is weakly expressed at the acinar membrane in PBS treated (A) and post-regeneration animals (C, D). (B) E-cadherin accumulates in regenerating acini and duct like cells following caerulein. **(E-H)**

E-cadherin (green) and amylase (red) expression in caerulein treated *Pdx1-Cre^{Early};LSL-Kras^{G12D}* mice. E-cadherin is strongly expressed at the membrane of spontaneous PanINs (E, asterisk) but weakly in morphologically normal acini. (F) Duct like cells display E-cadherin accumulation similar to such structures in WT mice (B). Strong E-cadherin expression persists in metaplastic ducts at day 7 (G) and in PanINs (H) at day 21 following caerulein treatment. (A-H, X400).

Supplemental Figure 6. Comparison of acinar regeneration following caerulein in *p48-Cre; LSL-Kras^{G12D}*, *p48-Cre; ß-catenin$^{exon3/+}$*, and *p48-Cre; ß-catenin$^{exon3/+}$; LSL-Kras^{G12D}* mice.

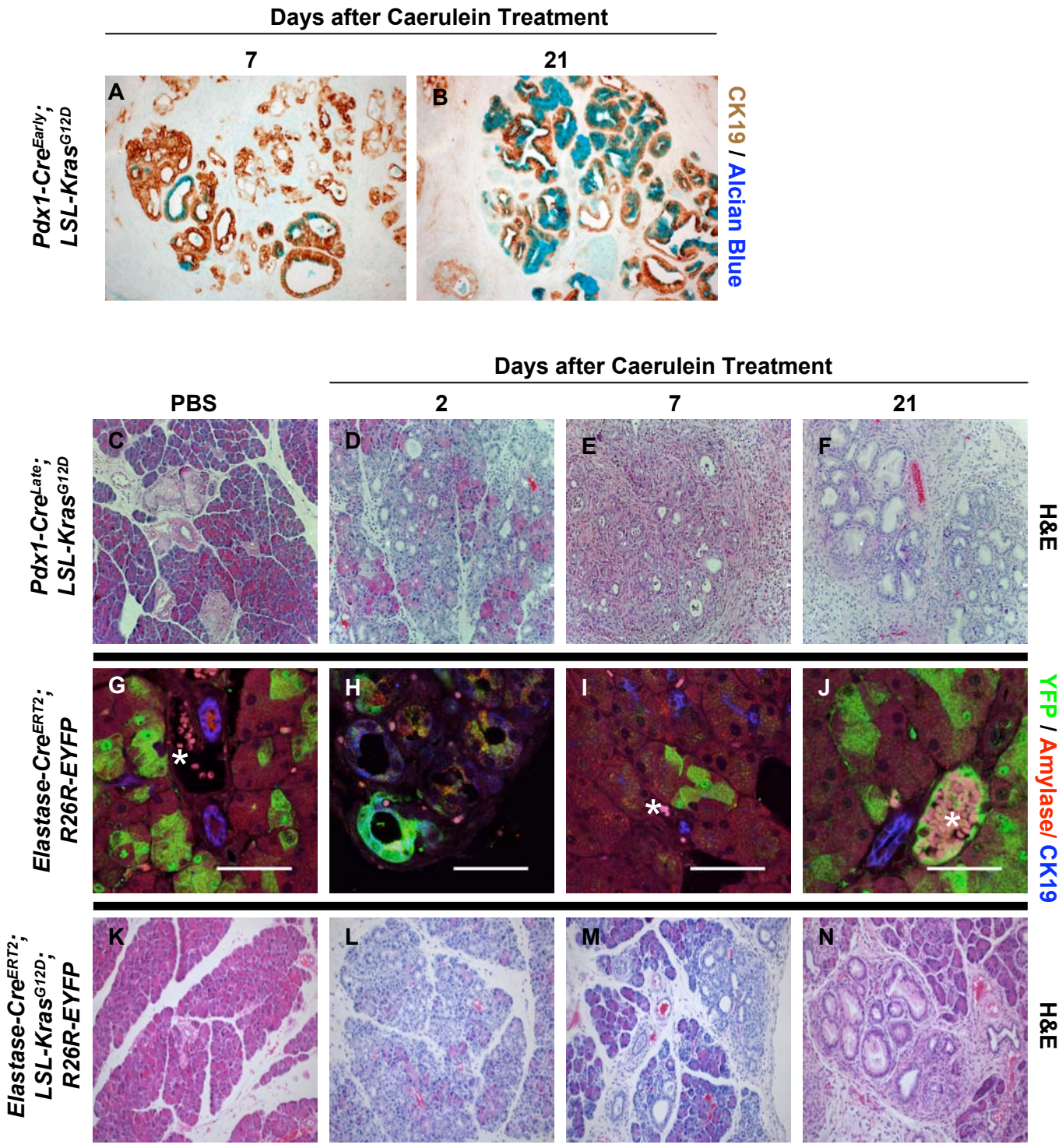
(A-C) PBS treated *p48-Cre; LSL-Kras^{G12D}* display rare spontaneous PanINs (asterisk). Acini assume a duct like state two days following caerulein (B), but undergo ADM and fail to regenerate seven days following treatment (C). **(D-F)** Acini assume a transient ductal state in *p48-Cre; ß-catenin$^{exon3/+}$* mice two days following caerulein (E), but display regeneration 7 days after treatment (F). **(G-I)** Yellow lines outline areas of cells with acinar morphology in PBS treated *p48-Cre; ß-catenin$^{exon3/+}$; LSL-Kras^{G12D}* mice (B) which are maintained at day two and 7 following caerulein treatment (H,I).

Supplemental Figure 7. Additional characterization of antagonized Kras induced ADM by stabilized ß-catenin

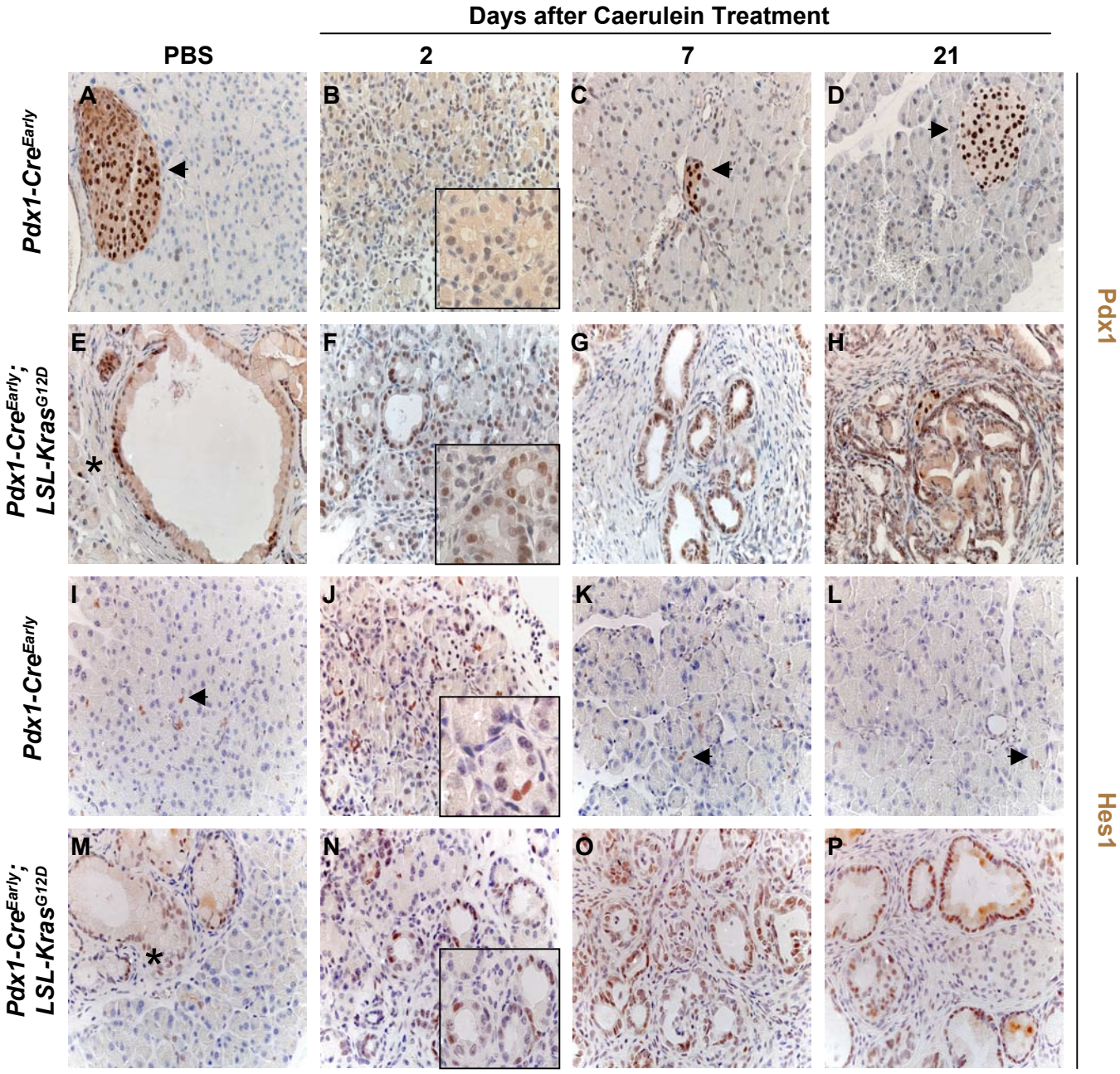
(A, E) Hes1 is widely expressed in ADM seven days after caerulein treatment in *p48-Cre; LSL-Kras^{G12D}* mice, but mainly restricted to abnormal ducts in caerulein

treated *p48-Cre; ß-catenin$^{exon3/+}$; LSL-Kras^{G12D}* mice. **(B,F)** Similarly, phospho p42/p44 staining is displayed in ADM seven days after caerulein treatment in *p48-Cre; LSL-Kras^{G12D}* mice, but mainly restricted to abnormal ducts in caerulein treated *p48-Cre; ß-catenin$^{exon3/+}$; LSL-Kras^{G12D}* mice. **(C, D; G, H)** (C) Merge of CK-19 (green) and amylase (red) indicating widespread ADM 7 days following caerulein treatment in *p48-Cre; LSL-Kras^{G12D}* mice. (D) ß-catenin (green) and DAPI (blue, marking nuclei) labeling of the same section shown in 'C'. (G) Merge of CK-19 (green) and amylase (red) indicating retained cells with acinar morphology and acinar marker expression 7 days following caerulein treatment in *p48-Cre; ß-catenin$^{exon3/+}$; LSL-Kras^{G12D}* mice. (H) ß-Catenin (green) and DAPI (blue, marking nuclei) labeling of the field shown in (G), displaying ß-catenin accumulation throughout the transgenic exocrine compartment. Arrowheads mark areas of nuclear accumulation indicated by cyan (blue/green overlap).

Supplemental Figure 1_Morris *et al*



Supplemental Figure 2_Morris *et al*



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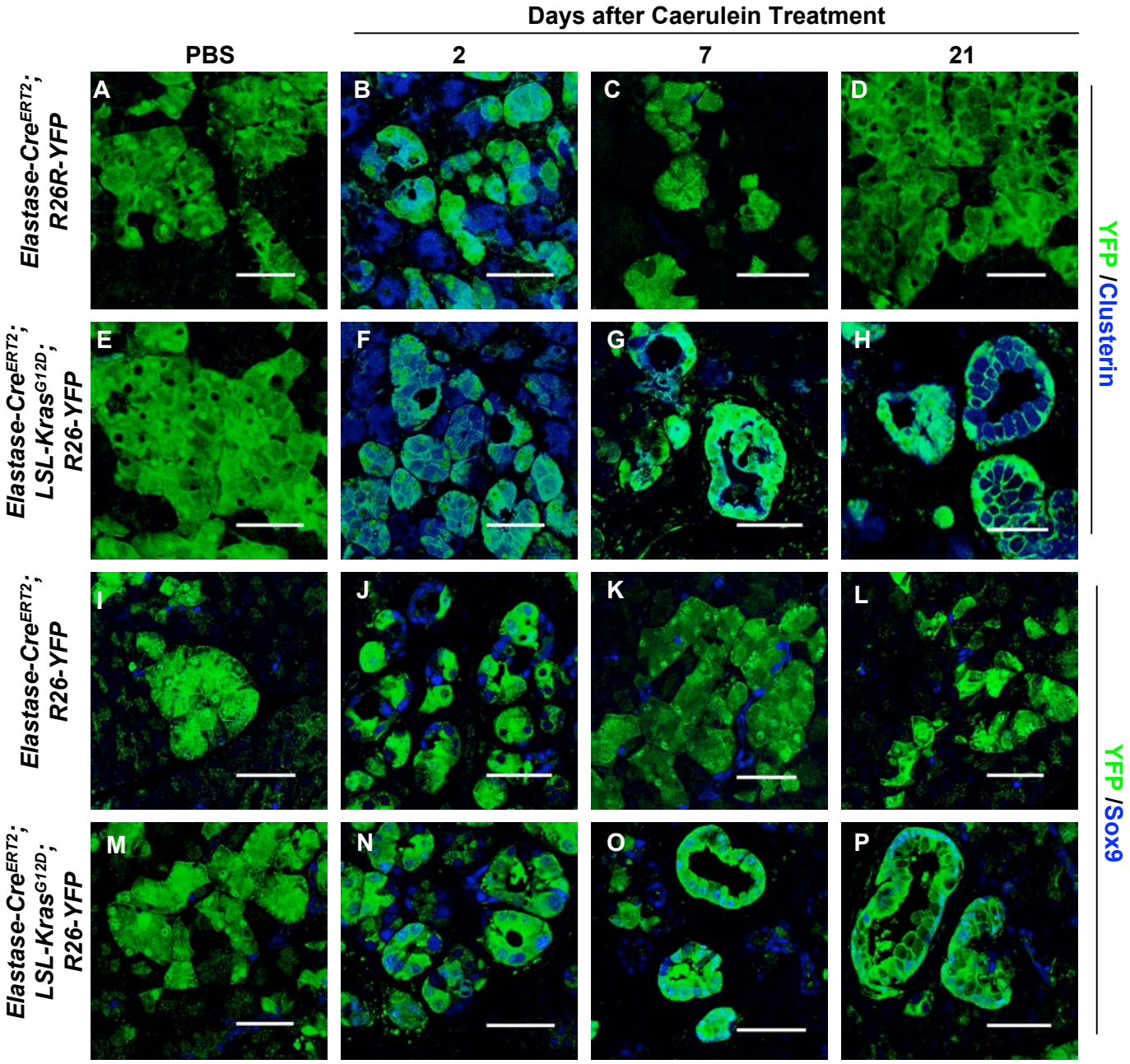
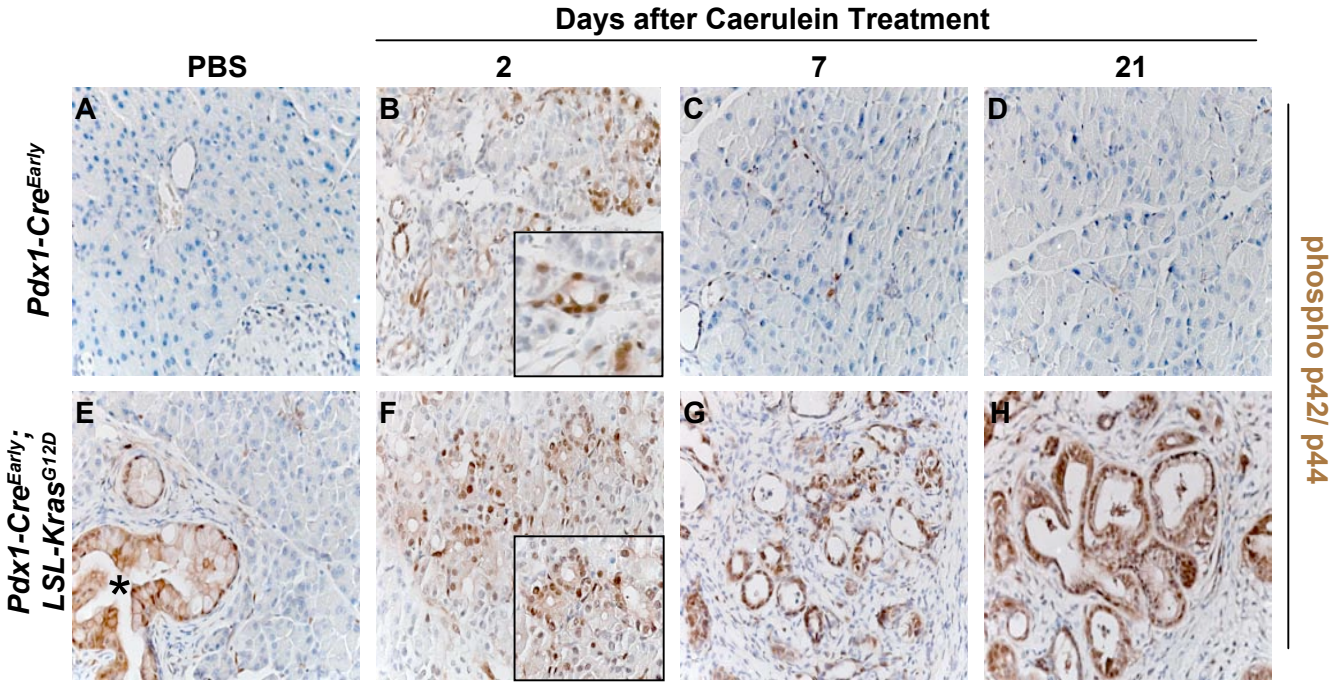
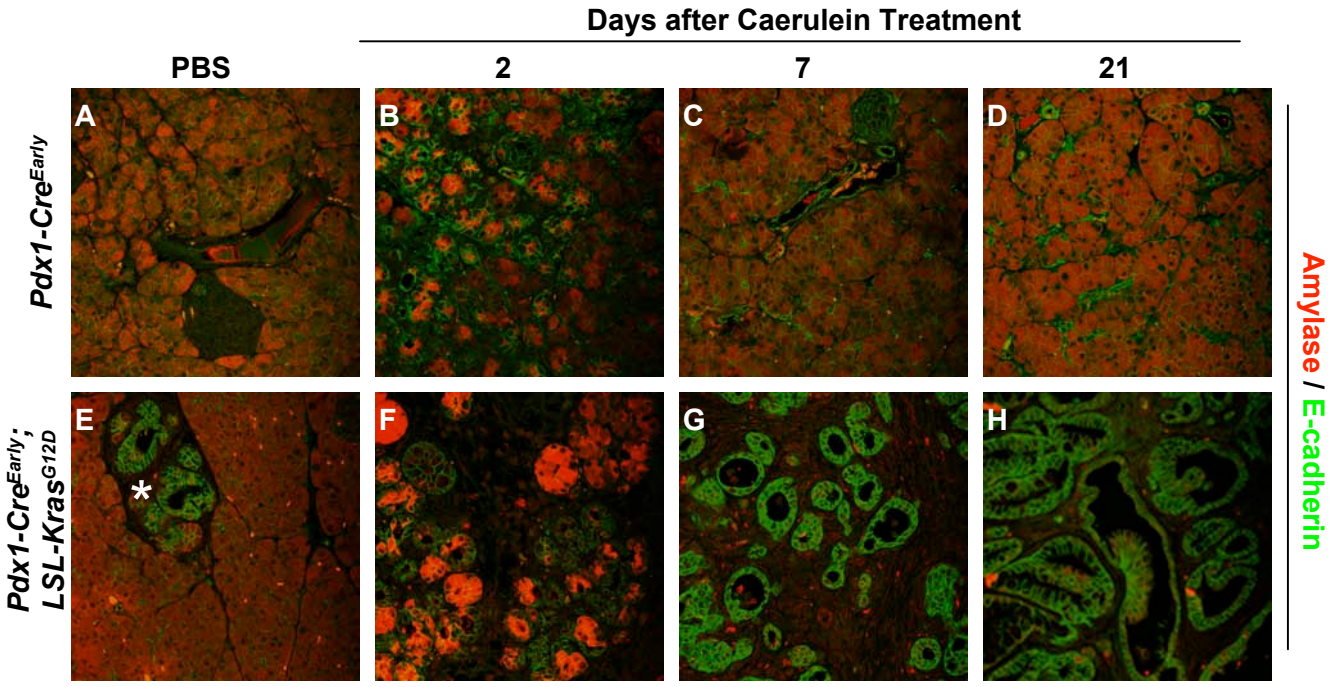


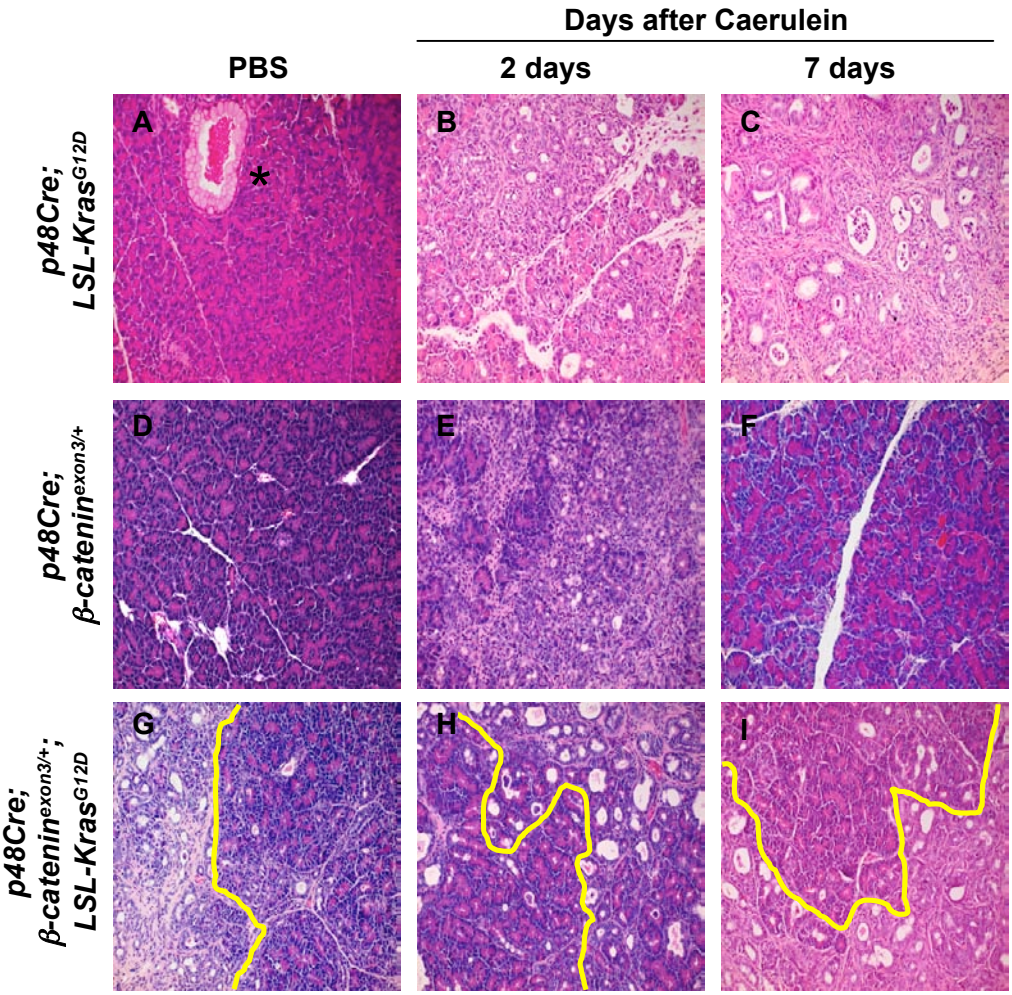
Supplemental Figure 4_Morris *et al*



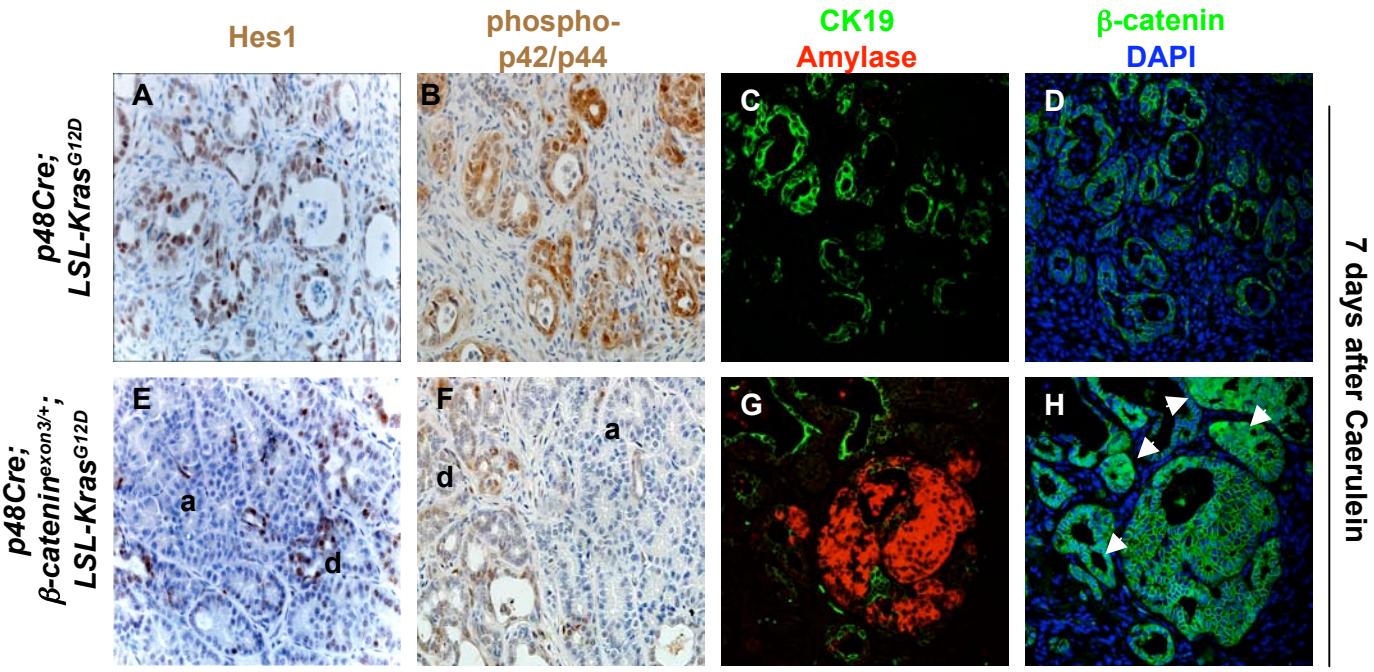
Supplemental Figure 5_Morris *et al*



Supplemental Figure 6_Morris *et al*



Supplemental Figure 7_Morris *et al*



Supplemental Table 1: Gapdh Taqman primer/probe sequences

Gapdh	
Forward primer	TGCACCACCAACTGCTTAG
Reverse primer	GGATGCAGGGATGATGTTC
Probe	CAGAAGACTGTGGATGGCCCCTC