**Supplemental figure 1**. ***AGRN*, *SERPINB5*, and *CSTB* gene expression in a panel of PDAC cell lines.** Expression data come from the Cancer Cell Line Encyclopedia (

<https://portals.broadinstitute.org/ccle>). Among all the cell lines, AsPC1 expresses intermediate levels of *AGRN* (A), *SERPINB5* (B), and *CSTB* (C), while BxPC3 expresses high levels of *AGRN* (A), *SERPINB5* (B), and *CSTB* (C). These differences in expression by the two cell lines were exploited in subsequent experiments allowing tests for increased expression (in AsPC1) or decreased expression (in BxPC3).

**Supplemental Figure 2. In vitro proliferation assay for the overexpression and knockdown sets of cells.**

In vitro proliferation curves of the knockdown (A) and overexpression (B) set of cells. P values were individually calculated by student t test for the last 12 hours (last four time points), and then were corrected for the multiple testing using the Benjamini-Hochberg method. The highest adjusted p value among the four points for each cell line were represented by star(s). \*, p<0.05; \*\*, p<0.01; \*\*\*, p<0.001; \*\*\*\*, p<0.0001. ns, not significant.

**Supplemental figure 3. Xenograft tumors knocked down and overexpressing AGRN, SERPINB5, and CSTB show expected protein expression changes.**

A,B, kd1 (A) and oe1 (B) of AGRN, SERPINB5, and CSTB xenograft tumors have the expected knockdown and overexpression, respectively, of the protein expression detected by IHC.

C, human-specific qPCR primers only amplified AGRN, CSTB, and SERPINB5 in human cDNA (BxPC3) but not in mouse cDNA (KPC PDACs). ACTB\_1 is a control that can amplify in both species. ACTB\_2 only amplifies the human gene/cDNA.

D,E, qPCR on xenograft tumor lysates shows expected knockdown (D) and overexpression (E) of AGRN, SERPINB5, and CSTB transcripts. Human-specific qPCR primers for AGRN, CSTB, and SERPINB5 were used; ACTB\_2 was used as an internal loading control.

**Supplemental figure 4. QPCR with human-specific primers shows that AGRN promotes EMT in primary tumors.**

A, human-specific qPCR primers only amplified from human cDNA (BxPC3, hT1CAF) but not from mouse cDNA (KPC PDACs). ACTB\_1 is a control that can amplify in both species. ACTB\_2 only amplifies the human gene.

B, qPCR shows that AGRN kd cancer cells have significantly reduced TWIST1, SNAI1, and FN1 expression. To quantify changes specifically in cancer cells (that are human), human-specific qPCR primers for TWIST1, SNAI1, and FN1 were used, and ACTB\_2 was used as an internal loading control. FN1 primers could not amplify in AsPC1 sets of oe cells because AsPC1 cells express very little FN.

**Supplemental figure 5. Example images for lungs after tail-vein injection and cells with TKS5 immunofluorescence staining.**

A,B, example lung images for mice that were injected with BxPC3 G1.1 cells knocked down for each of the three genes (A) and AsPC1 cells that overexpressed the three genes (B). Scale bar is 2mm.

C, in vivo extravasation assay showed that BxPC3 cells clustered in the blood vessels. Scale bar is 10m.

D, example images showing the colocalization of TKS5+ invadopodia and the degradation spots in AsPC1 cells that degraded (arrows) or did not degrade (arrowheads) gelatin 20 hours post- plating. DAPI signal is also shown on the merged images. Scale bar is 10m.

E, example images showing the TKS5 staining in the Zsgreen positive AsPC1 cells. Closed and open arrows show cells that are negative and positive for TKS5+ invadopodia, respectively. Scale bar is 10m.

**Supplemental figure 6.** **Epithelial SERPINB5 staining is not prognostic.**

A,B. representative images for epithelial SERPINB5 staining scoring system on a human patient tissue microarray. In contrast with Figure 6, which shows regions with IHC signal over extracellular stromal regions, this figure shows regions where the SERPINB5 signal remains within the epithelial cells. Arrows indicate epithelial region and panel B illustrates the scoring system.

C, survival curves from patients categorized into two populations based on high and low epithelial cell staining for SERPINB5 showed that high and low epithelial signal did not have significantly different prognostic value. Scale bars are 50m.

D, immunoblotting on conditioned media from BxPC3 G1.1 cells that do and do not overexpress SERPINB5 or CSTB (see Materials and Methods). Same volume fraction of conditioned media was loaded for each cell line. Comparable levels of GAPDH indicated similar numbers of cells in culture. BxPC3 G1.1 cells overexpressed SERPINB5 and CSTB about 20-fold.