**Supplemental Figure Legends:**

**Fig. S1.** Conditioned media does not affect growth of PDAC cells except at 100% supplementation but does protect human PDAC cell lines regardless of P53 status. (**A-E**) Arbitrary units of resazurin fluorescence representing growth of PDAC cells after 3 days in culture are shown for cells cultured with the indicated supplement of media conditioned for the indicated number of days. Data show three biological replicates ± SEM. \*\*\*, P ≤ 0.001, ns, not significant (one-way ANOVA with Bonferroni post-tests). (**G**) Viability of PDAC organoids after the indicated treatment with 0.05 μM gemcitabine, 20% CM, and/or 20 μM dC. Data show three biological replicates ± SEM. Mean and SEM are indicated on the plot. One-way ANOVA with Bonferroni post-tests reveals no significant difference between gemcitabine treatment and gemcitabine + CM treatment, or gemcitabine + dC treatment. (**F**) Viability of the indicated cell lines at the indicated doses of gemcitabine with or without CM supplementation. Data show three biological replicates ± SEM. \*, P ≤ 0.05, \*\*, P ≤ 0.01, ns, not significant (two-tailed one sample t-test).

**Fig. S2.** N-acetyl alanine does not protect from gemcitabine toxicity and nucleoside levels in PDAC cells are not effected by treatment with gemcitabine or conditioned media (**A**) Dose response curves with N-acetyl-alanine without (solid lines) or with (dashed lines) 0.025 μM gemcitabine. The viability after treatment with PSC2 CM is also shown. Data show three biological replicates ± SEM. (**B-E**) Absolute quantification of the indicated species in within PDAC cells after the indicated treatment. Data show 3 biological replicates ± SEM.

**Fig. S3.** Absolute quantification of the indicated species in 3 day CM. (**A-D**) 8-MDP and dipyridamole were applied to PSC2s conditioning the media at 6.67 μM. A83 was applied to PSC2s conditioning the media at 5 μM. Data show 3 biological replicates ± SEM except for 293T data which shows one biological replicate. \*\*\*, P ≤ 0.001, ns, not significant (one-way ANOVA with Bonferroni post-tests).

**Fig. S4.** Boiling does not inactivate ENT inhibitors 8-MDP and dipyridamole. Dose response curves with gemcitabine supplemented with boiled or untreated media containing 6.67 μM of ENT inhibitors 8-MDP or dipyridamole. Data represent the mean of three biological replicates ± SEM. \*, ns, not significant, \*\*, P ≤ 0.01 (one-way ANOVA with Bonferroni post-tests).

**Fig. S5.** PSC lines exhibit heterogeneity in expression of fibroblast activation markers (**A**) Staining of the indicated PSCs lines with DAPI and αSMA and PDGFRβ antibodies. Scale bars are indicated in the bottom right corner of each image. (**B-C**) Histogram of pixel intensity in the images in part **A**. (**D**) Staining of the indicated PSCs lines with DAPI and a fibronectin antibody. Scale bars are indicated in the bottom right corner of each image. (**E**) Histogram of pixel intensity in the images in part **D**. (**F**) Quantification of pixel intensity in αSMA and PDGFRβ channels over a horizontal slice of each image in part **A**.