**Supplemental Figure 1: Structures of APE1/Ref-1 and CA9 inhibitors**

APX3330 is a small molecule inhibitor of APE1/Ref-1 redox signaling activity (IND 125360). SLC-0111 is a small molecule inhibitor of CA9 activity (clinicaltrials.gov ID: NCT02215850). FC13-555A is an analog of SLC-0111 that is under development (see supplemental methods).

**Supplemental Figure 2: Confirmation of HIF-1 deletion in MEF cells**

2-loxP/1-loxP PCR was performed using DNA collected from HIF-1-floxed mouse embryonic fibroblast (MEF) cells transduced with either Ad-CMV-Cre (Cre adenovirus) or Ad-GFP (control) vector.

**Supplemental Figure 3: APE1/Ref-1 interactions with STAT3 and NFκB are stimulated by IL-6 and TNFα (respectively) under normoxic conditions**

Stable Panc10.05 cell lines overexpressing APE1/Ref-1 (wt-APE/Lenti-CMV-GFP vs. Lenti-CMV-GFP, “vector”) were exposed to IL-6 (A) or TNF (B) for the times indicated, and APE1/Ref-1 was immunoprecipitated. Western analyses of the IPs with STAT3, APE1/Ref-1, and NFB antibodies were performed.

**Supplemental Figure 4: APE1/Ref-1 interactions with HIF1α and STAT3 are stimulated by hypoxia in Cancer-Associated Fibroblast (CAF) cells**

A. UH1303-02 hTERT (CAF) cells were incubated under normoxic or hypoxic conditions (0.2% oxygen) for 24 hr prior to collection and immunoprecipitation of endogenously expressed APE1/Ref-1. B-C. Stable cell lines overexpressing APE1/Ref-1 were generated using wt-APE/Lenti-CMV-GFP (vs. Lenti-CMV-GFP, “vector”), and APE1/Ref-1 immunoprecipitation was performed following incubation in normoxia (B) or 0.2% oxygen (C) for 24 hr. Western analyses of the IPs with HIF1, STAT3, APE1/Ref-1, and NFB antibodies were performed.

**Supplemental Figure 5: APE1/Ref-1 protein expression affects CA9 mRNA levels in additional PDAC cell lines**

CA9 mRNA levels were evaluated via qPCR in the Panc10.05 (A) and Pa02C (B) cells using samples collected following transfection with SC or APE1/Ref-1-directed siRNA and 24 hr in hypoxic conditions as shown. n=3 per experiment \*\*p<0.01 & #p<0.001 (ANCOVA).

**Supplemental Figure 6: CA9 protein levels are increased under hypoxia, but APE1 levels are not**

PDAC cells were exposed to 0.2% oxygen for the times indicated, and CA9 (A) and APE1/Ref-1 (B) protein levels were evaluated via western blot.

**Supplemental Figure 7: Cell viability analysis used for normalization of pH data**

Panc10.05 cells were treated with APX3330 and SLC-0111 and exposed to hypoxia (0.2% O2) for 48 hrs prior to analysis of intracellular pH and subsequent analysis of viability.

**Supplemental Figure 8: APE1 expression correlates with decreased survival in PDAC & CA9 is upregulated in PDAC**

A. Comparison of overall survival in PDAC patients with low (blue) vs. high (red) expression of APE1/Ref-1 mRNA was obtained from The Cancer Genome Atlas (TCGA) database. B-D. Comparison of CA9 mRNA levels in normal pancreas vs. PDAC (B & D) or pancreatic cancer precursor vs. PDAC (C) was obtained from Oncomine using data provided by Logsdon et al (Ref #62) (B & C) or Pei et al (Ref #63) (D).