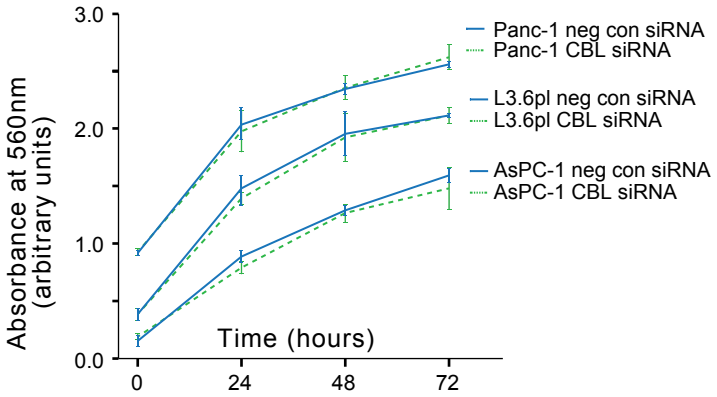


Figure S1. CBL knockdown does not enhance baseline cell viability. Knockdown of CBL in Panc-1, L3.6pl and AsPC-1 cell lines versus their respective parental isogenic line showed no difference in cell viability as assessed by MTT assays. The results for serum-supplemented media (10% FBS) are shown, but were no different when grown in serum-free culture. Error bars ± SD.

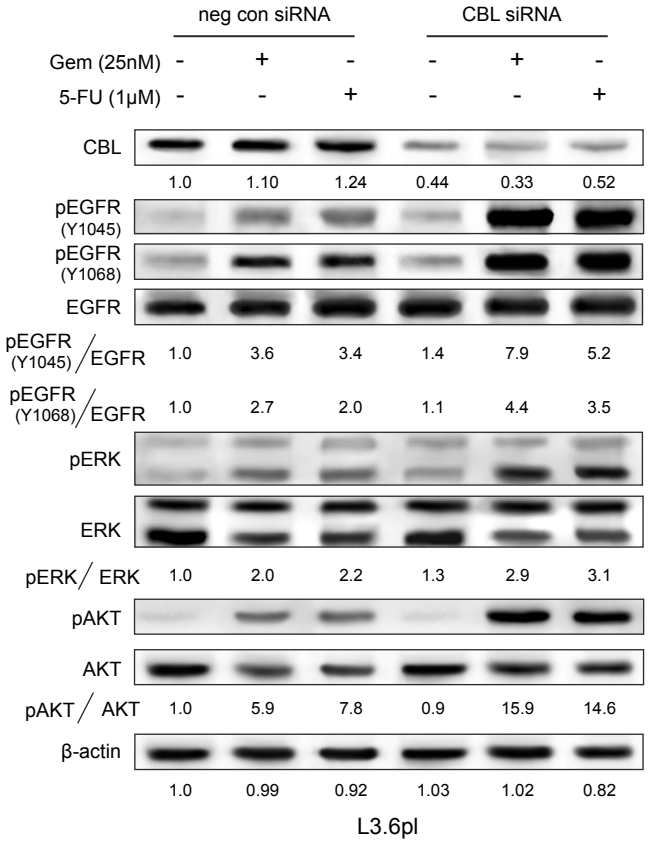
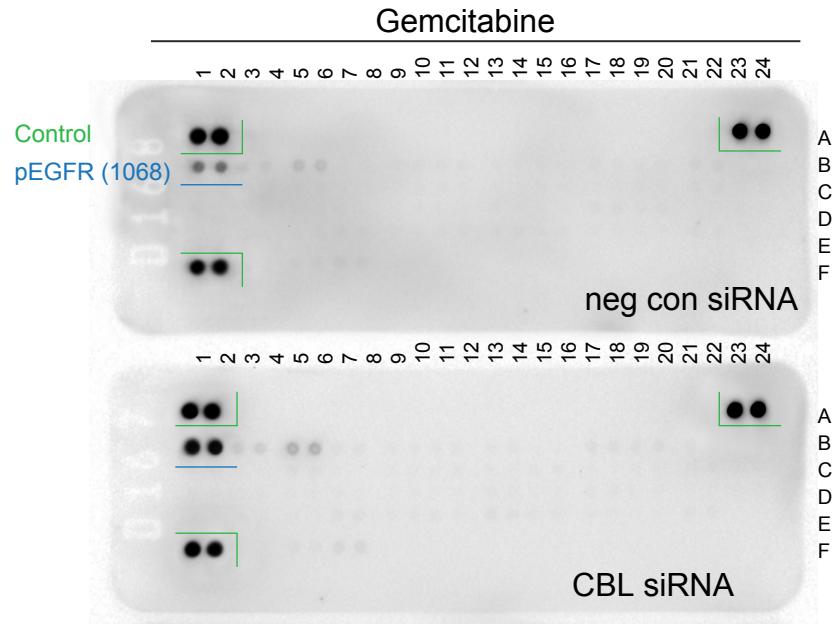


Figure S2. Low CBL enhances EGFR autoactivation when treated with chemotherapy. In serum-free conditions, addition of gemcitabine (Gem) or 5-fluorouracil (5-FU) results in autoactivation of EGFR with corresponding increased signaling through downstream ERK and AKT (column 1 vs. 2 and 3). This chemotherapy-induced autoactivation of EGFR at Y1068, a major autophosphorylation site, and Y1045, the CBL binding residue, is further enhanced in L3.6pl$^{CBL\text{-}low}$ cells (columns 3 and 4 vs. 5 and 6). This is a similar pattern to Panc-1$^{CBL\text{-}low}$ cells treated under the same conditions suggesting a generalizability of this chemoresistance mechanism in PDAC. Relative densitometry values using β-actin as a loading control are reported below each band.



Coordinate	RTK/Control
A1, A2	Reference Spots
A23, A24	Reference Spots
B1, B2	EGFR
B3, B4	ErbB2
B5, B6	ErbB3
F1, F2	Reference Spots
F7, F8	RYK

Figure S3. A human phospho-receptor tyrosine kinase (pRTK) array reveals that EGFR is highly activated when L3.6pl CBL knockdown cells are treated with gemcitabine. L3.6pl$^{CBL\text{-}low}$ versus their isogenic parental cell line were incubated in serum-free media containing gemcitabine for 48 hours and then cell lysates were analyzed by immunoblot on a human pRTK array. pEGFR (B1,B2) was increased by greater than 2-fold. The table on the right identifies those pRTKs that had significant signal above background at 60 seconds chemiluminescent exposure.

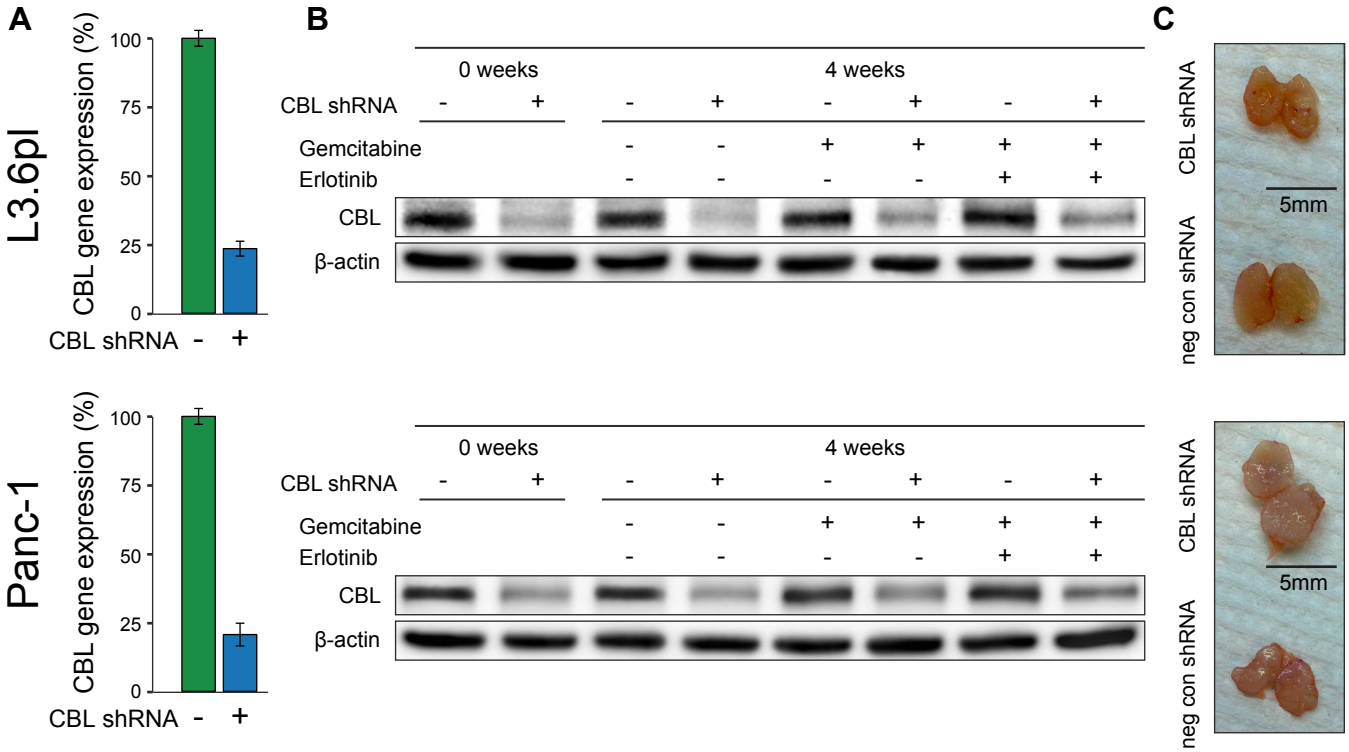


Figure S4. shRNA knockdown of CBL in PDAC cells. A, qRT-PCR of PDAC cells (L3.6pl and Panc-1) transduced with CBL shRNA versus neg control shRNA lentivirus revealed a ≈75% knockdown efficiency. Error bars ± SD. B, Western blot analysis of cells at the time of injection in NOD-*scid-IL2γ^{null}* mice and again ex vivo at 4 weeks confirmed stable CBL knockdown and no difference in expression profiles between treatment groups. C, Subcutaneous tumors excised at the start of chemotherapy are grossly similar.

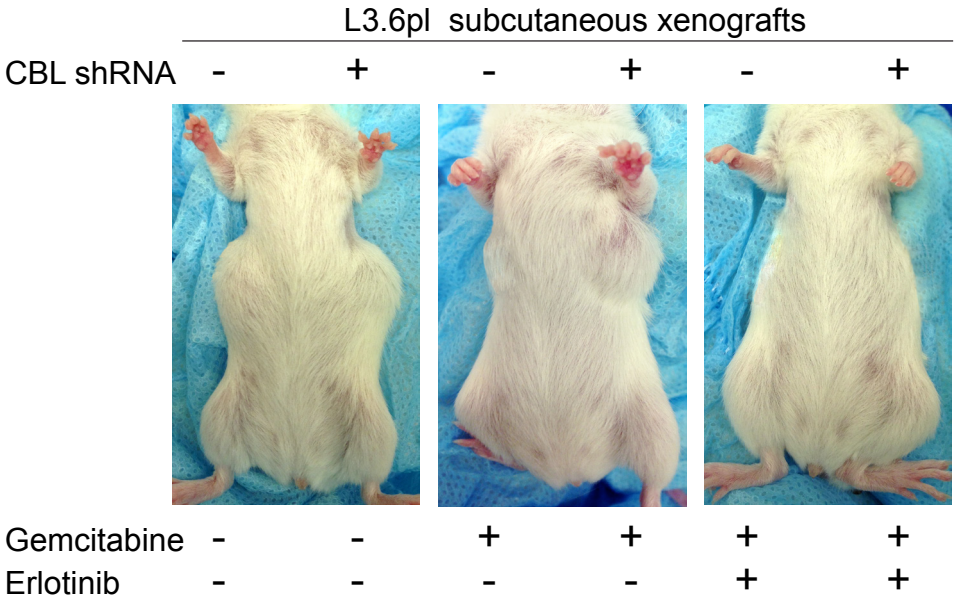


Figure S5. Erlotinib and gemcitabine have synergistic effects on the growth of CBL-low tumors. Necropsy of NOD-*scid*-*IL2γ*^{null} mice at 4 weeks after injection reveals that while CBL shRNA knockdown tumors are Gemcitabine resistant (middle photograph, picture right > left) this resistance is targeted by the addition of an EGFR inhibitor (right photograph, picture right = left). As in the MTT assays, there was no difference in baseline cell viability in the absence of chemotherapy treatment (left photograph, picture right = left).