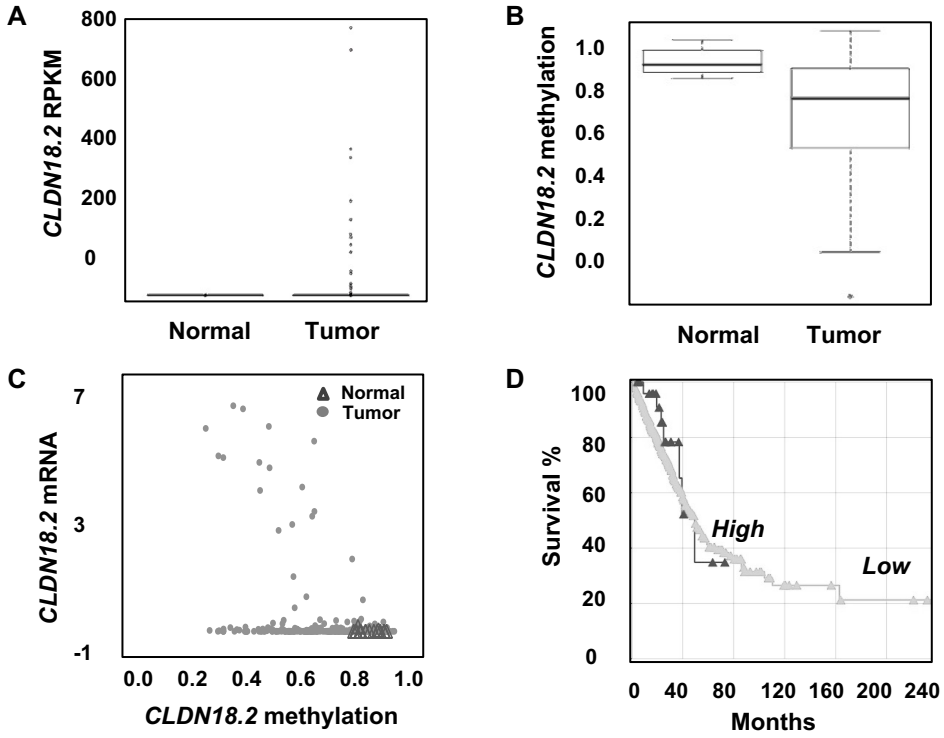
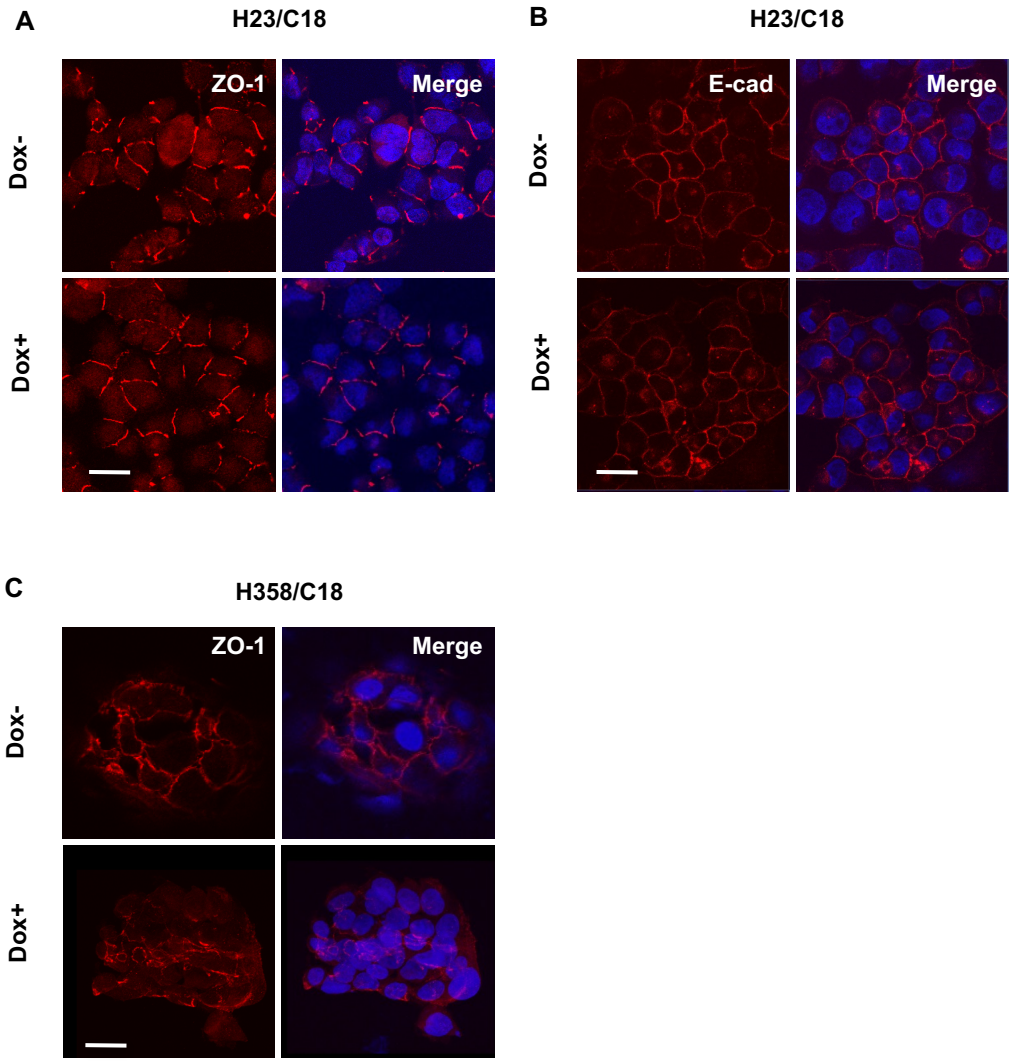
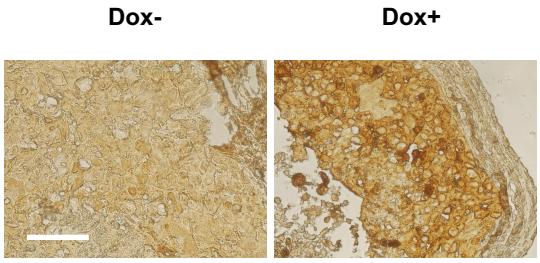


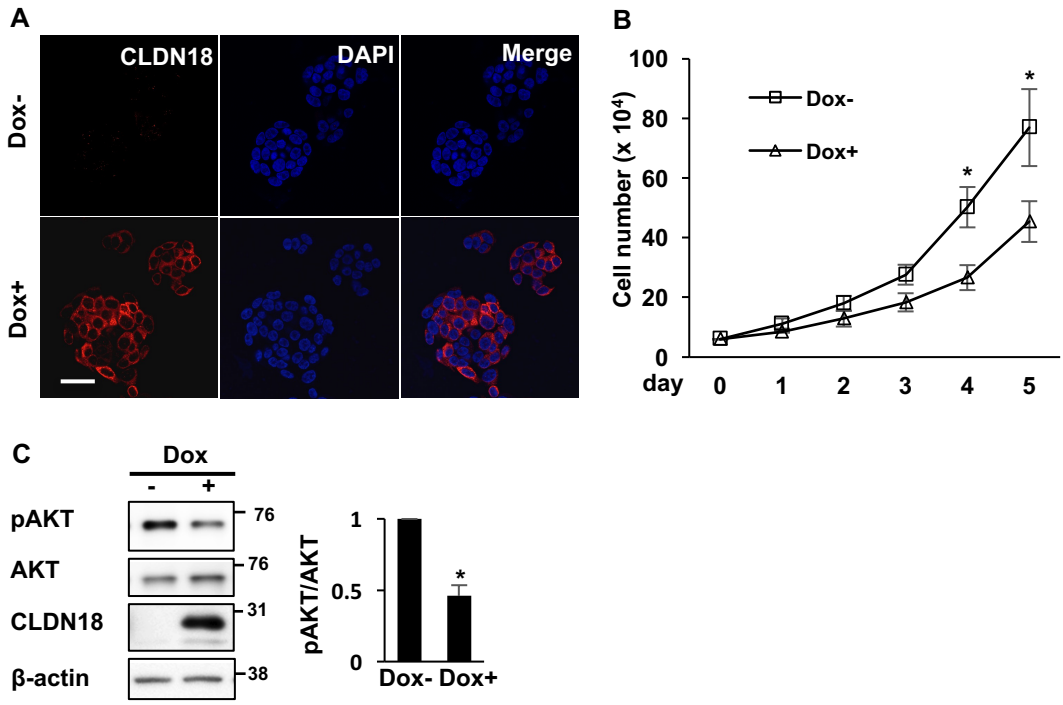
Supplementary Figure 1. A small fraction of LuAd patients express *CLDN18.2* which is associated with decreased promoter methylation but not with patient mortality. A. *CLDN18.2* mRNA expression in normal and LuAd tumor samples. RNA-seq data are from 286 LuAd samples and 19 adjacent non-tumor tissues (*, $p < 0.05$, unpaired two-tailed t-test). Reads per kilobase of transcript (RPKM) is used as expression unit. **B.** Methylation of the *CLDN18.2* promoter in the TCGA LuAd patient cohort. Data are from 286 LuAd samples and 19 adjacent non-tumor tissues, with boxes representing the 25% to 75% quartiles and lines within the boxes depicting median values. Data are for probe cg17298704 (*, $p < 0.0001$, unpaired two-tailed t-test). **C**. Analysis of the correlation between *CLDN18.2* mRNA expression and methylation of CpGs in the promoter region (r = -0.335875, $p < 0.0001$). **D**. Kaplan-Meier curves for 502 patients in the TCGA LuAd cohort of CLDN18.2 ($p = 0.05$, log-rank test).



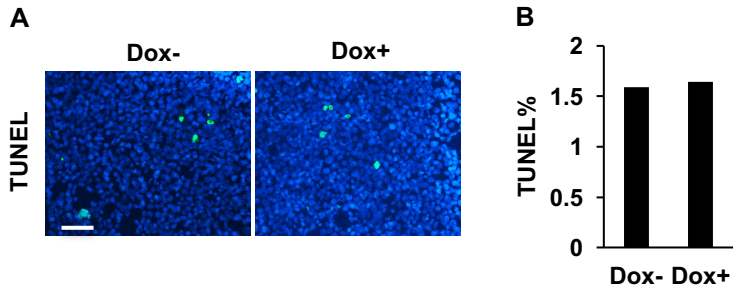
Supplementary Figure 2. Expression of CLDN18.1 does not change intracellular distribution of junctional proteins in H23 and H358 cells. A-B. Immunofluorescence staining of ZO-1 and E-cadherin in H23/C18 cell cultures treated with Dox or vehicle. Bar = 5 μm, n = 1. **C.** Immunofluorescence staining of ZO-1 in H358/C18 cells treated with Dox (1 μg/ml) or vehicle. Bar = 5 μm, n = 1.



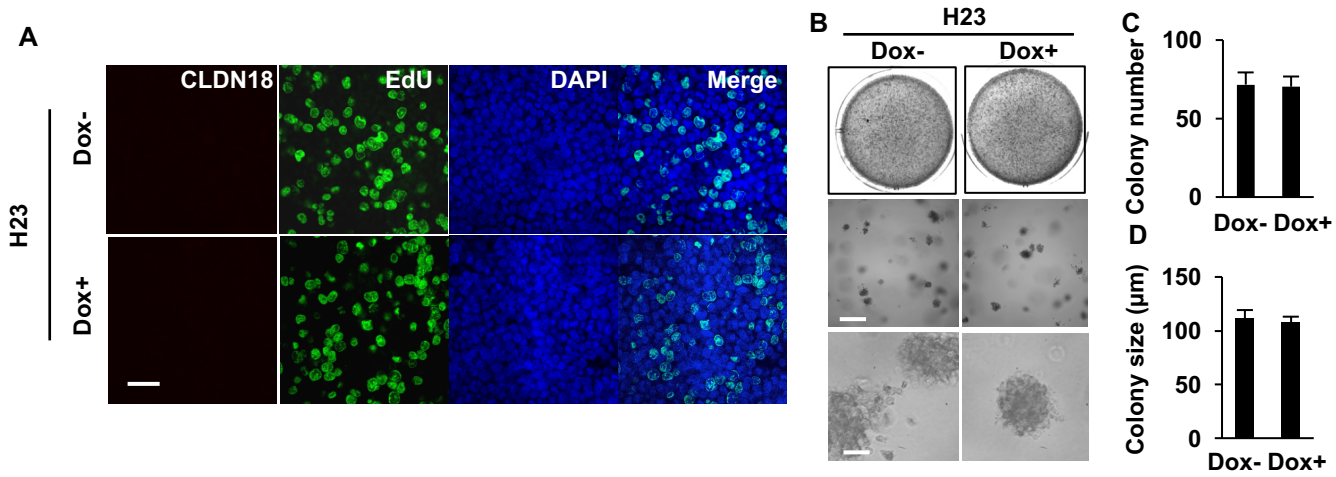
Supplementary Figure 3. Immunohistochemical (IHC) staining of CLDN18 in the isolated H23/C18 xenografted tumor. Bar = 200 μm, n = 1.



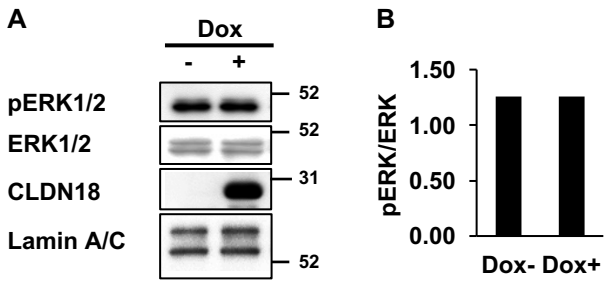
Supplementary Figure 4. *CLDN18.1* inhibits proliferation and AKT phosphorylation in H358/C18 cell cultures. A. Immunofluorescence staining of CLDN18 in H358/C18 cell cultures treated with Dox (1 μg/ml) or vehicle. Bar = 10 μm. **B**. Cell number was counted on days 1-5. * indicates $p < 0.05$ compared to no Dox treatment at the same time point, n = 3, two-way ANOVA. **C**. Representative western analysis and quantitation of AKT phosphorylation in Dox-treated H358/C18 cells, n = 4.



Supplementary Figure 5. *CLDN18.1* does not affect apoptosis. TUNEL staining (A) and quantitation (B) in H23/C18 cells treated with Dox or vehicle. Bar = 50 μm, n =1.



Supplementary Figure 6. Dox does not affect proliferation or soft agar colony formation by parental H23 cells. A. Fluorescence images of EdU$^+$ (green) labeling of H23 cells treated with Dox or vehicle. Bar = 20 μm, n =1. **B-D.** Colonies formed in soft agar by H23 cells in the presence or absence of Dox are shown at low (top, whole well), medium (middle, bar = 200 μm) and high magnification (bottom, bar = 50 μm). Results are quantitated for colony number (C) and size (D). n = 3, unpaired two-tailed t-test.



Supplementary Figure 7. Western (A) and quantitative analysis (B) demonstrate that Dox-induced CLDN18.1 expression in H23/C18 cells does not affect ERK1/2 phosphorylation. n = 1. Western blot data shown in figures 4D, 5B and S7A of the manuscript are from the same experiment.