Supplementary Figure-1

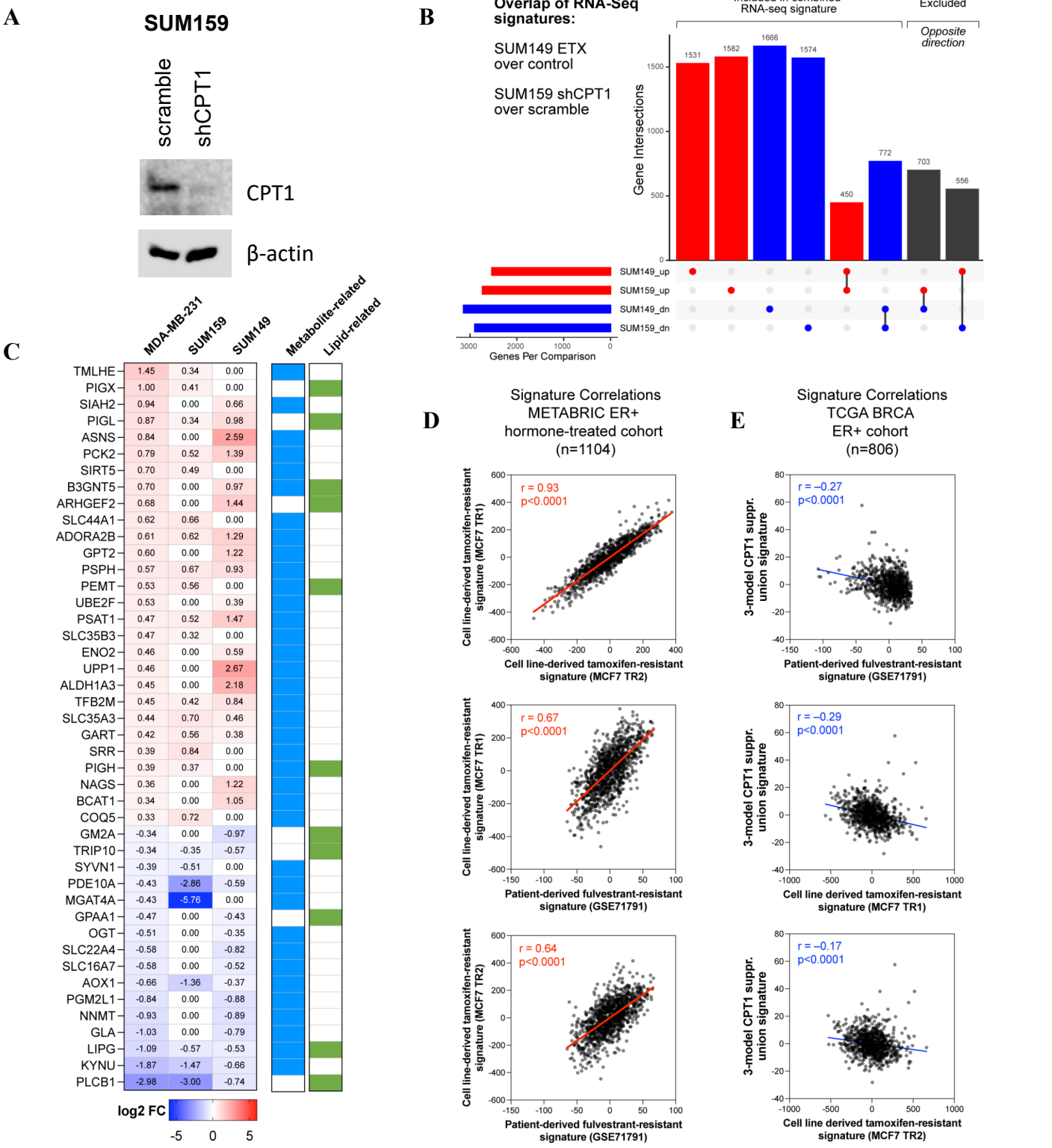

Figure S1. Integration of CPT1 transcriptomic profiles with clinical datasets. (A) Western Blot (WB) analysis confirming CPT1 knockdown in SUM159 cells. **(B)** Strategy of combining CPT1 suppression signatures from SUM149 and SUM159 cells. An upset plot is presented with DEGs stratified by direction of change. **(C)** Gene expression fold change table of the 3-model CPT1 suppression union signature. The genes related to metabolomics and lipidomics are labeled on the right. **(D)** Pairwise activity score correlation for the three endocrine resistance signatures [fulvestrant resistance signature from GSE71791 and tamoxifen resistance signature from tamoxifen-resistant (TR) cells] was computed over the patient tissue biopsies transcriptomic profiles from the METABRIC BC ER+ hormone treated dataset. **(E)** Pairwise activity score correlation for the three endocrine resistance signatures and 3-model union signature was computed over the patient tissue biopsies transcriptomic profiles from the TCGA BC ER+ dataset.

Supplementary Figure-2

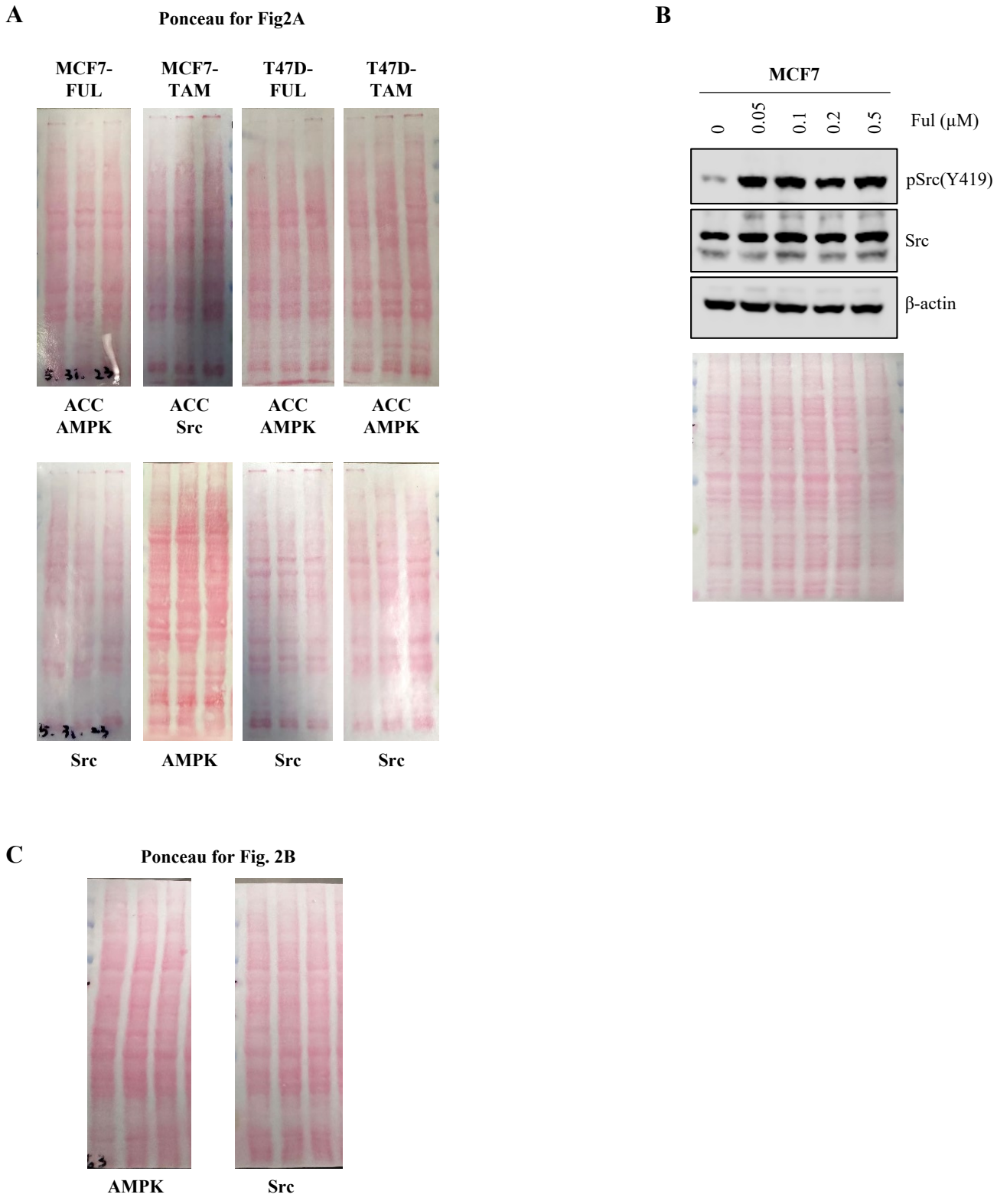

Figure S2. Validation of the WB analysis of Fig 2. (A) Ponceau staining of total proteins on the membrane of Fig. 2A. **(B)** WB (up) and ponceau staining (bottom) of MCF7 cells treated with low-doses of Ful for 24h in DMEM with 5% charcoal-stripped FBS. **(C)** Ponceau staining of total proteins on the membrane of Fig. 2B.

Supplementary Figure-3

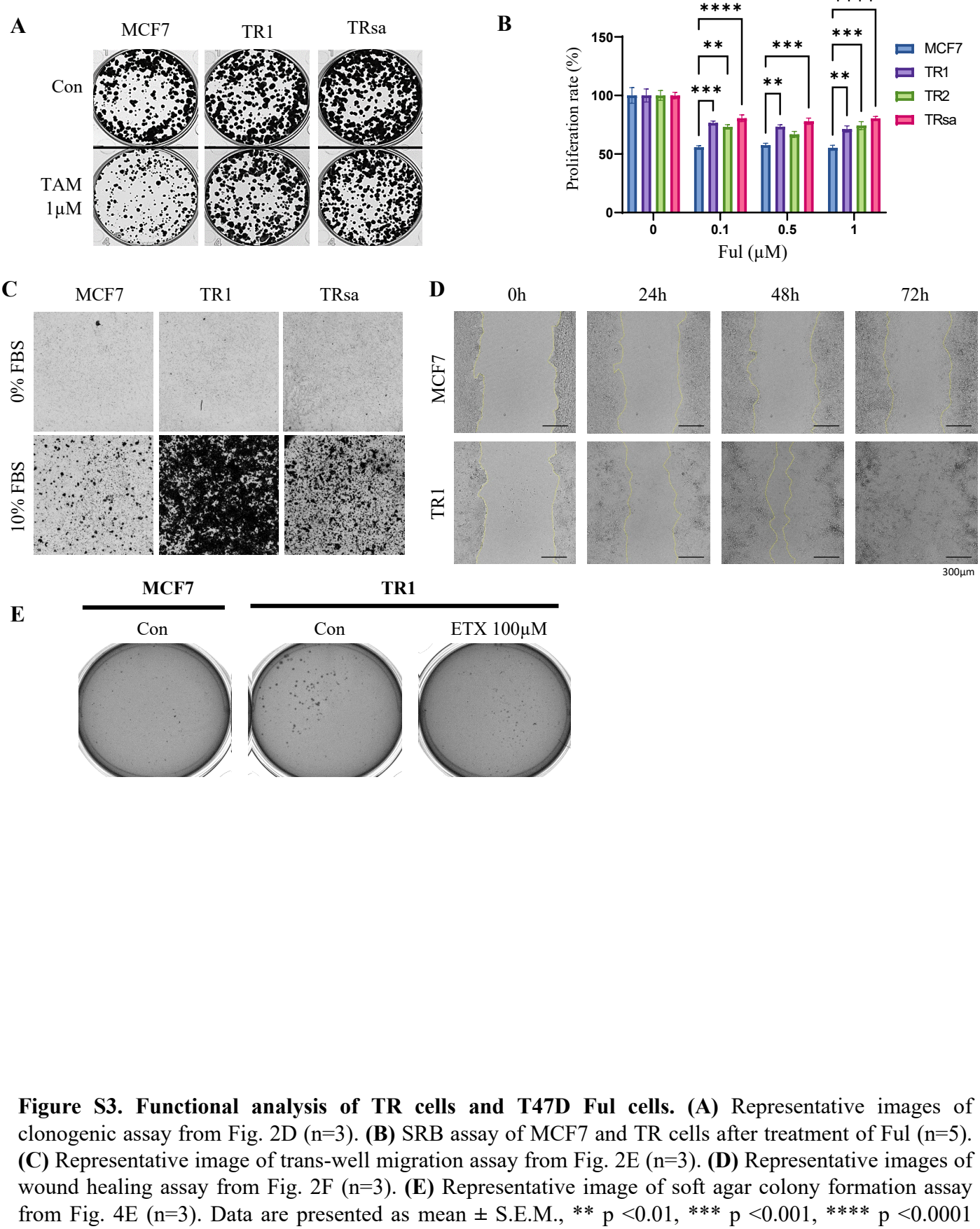

Figure S3. Functional analysis of TR cells and T47D Ful cells. (A) Representative images of clonogenic assay from Fig. 2D (n=3). **(B)** SRB assay of MCF7 and TR cells after treatment of Ful (n=5). **(C)** Representative image of trans-well migration assay from Fig. 2E (n=3). **(D)** Representative images of wound healing assay from Fig. 2F (n=3). **(E)** Representative image of soft agar colony formation assay from Fig. 4E (n=3). Data are presented as mean ± S.E.M., ** p <0.01, *** p <0.001, **** p <0.0001 using two-way ANOVA

Supplementary Figure-4

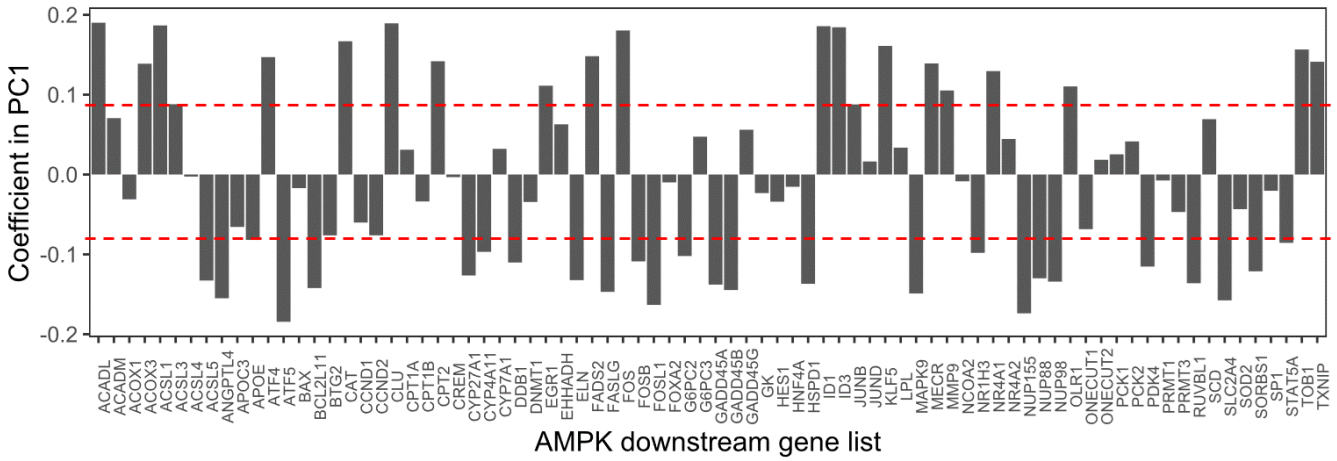

Figure S4. Coefficient of PC1 of AMPK downstream genes from MCF7 and TR cell microarray. Coefficient of each downstream gene of AMPK in the PC1 eigenvectors are plotted from the microarray data. Top 45% of genes were selected according to the absolute values of the corresponding components in the PC1 eigenvector (cutoff values indicated by the read dotted lines).

Supplementary Figure-5

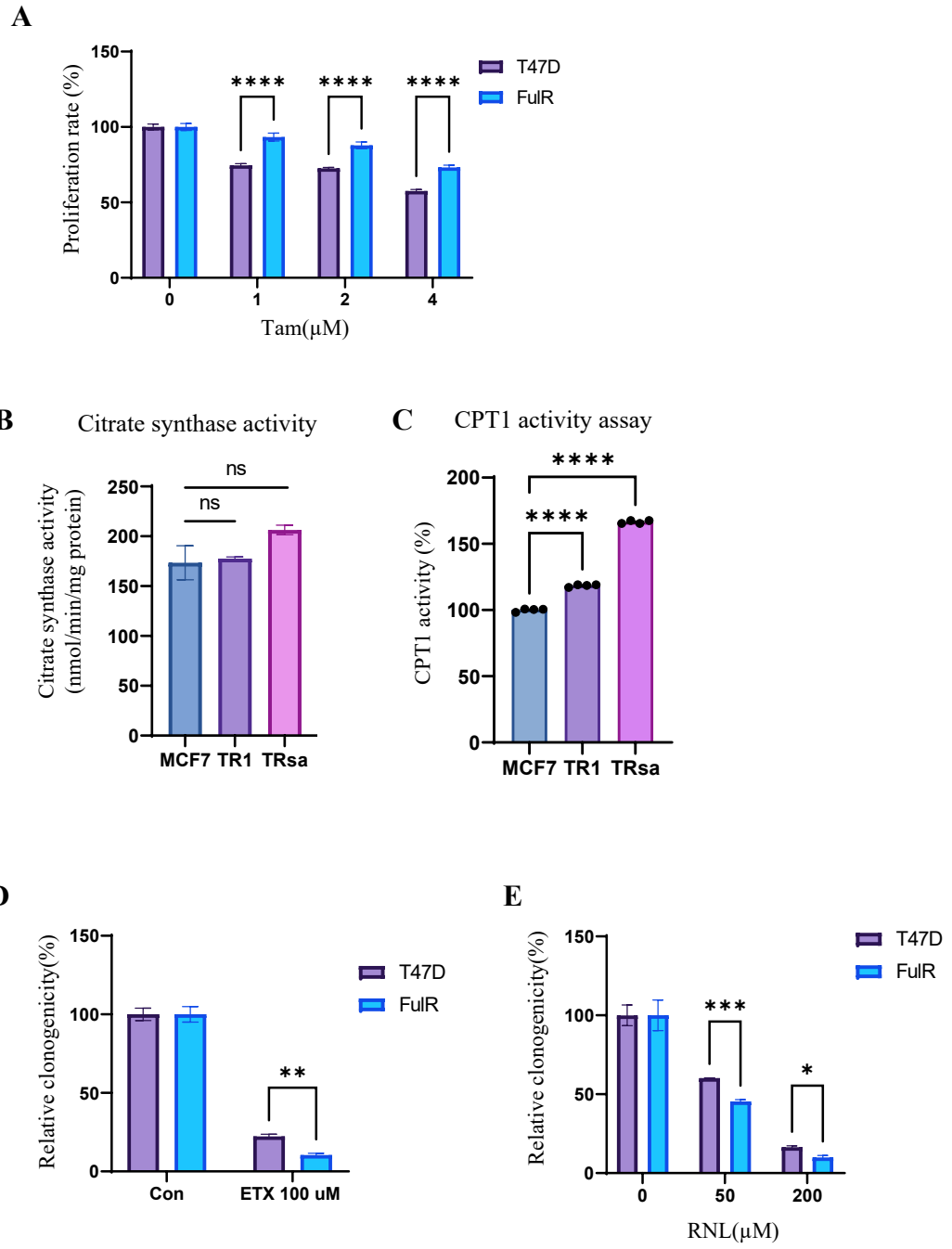

Figure S5. Analysis of fulvestrant-resistant (FulR) T47D cells and MCF7 TR cells. (A) Quantification of the SRB assay in T47D and FulR cells after Tam treatment (n=6). **(B)** Citrate synthase activity of MCF7 and TR cells from Fig. 3C (n=3) **(C)** CPT1 activity assay of MCF7 and TR cells in complete media (n=4). **(D-E)** Quantification of the clonogenic potential of T47D and FulR cells after treatment with ETX **(D),** RNL **(E)** (n=3). Data are presented as mean ± S.E.M., *p < 0.05, ** p <0.01, *** p <0.001, **** p <0.0001, A,D and E: two-tailed student t-test. B and C: one-way ANOVA

Supplementary Figure-6

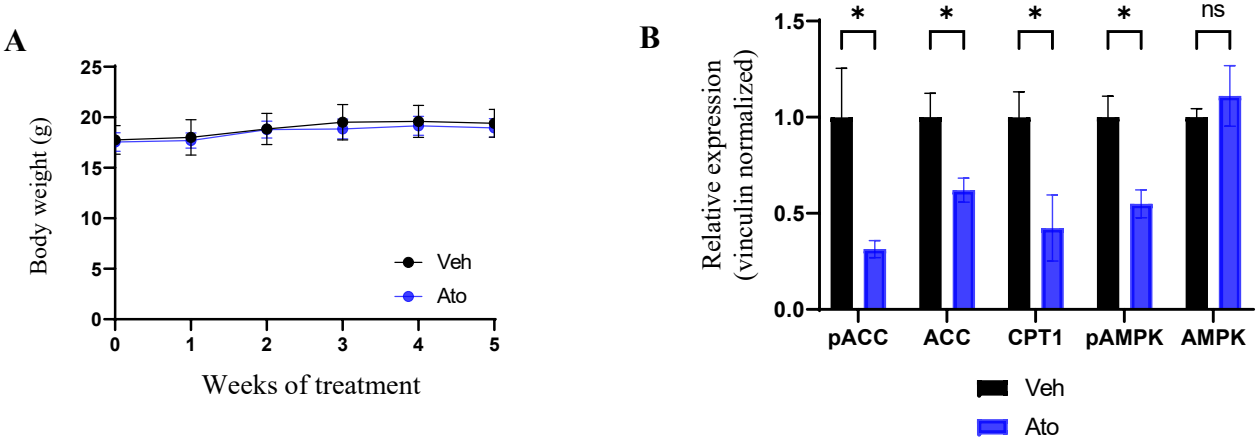

Figure S6. *In vivo* experiments using TRsa cells. (A) Average body weight of the mice from the tumor growth curve shown in Fig. 5F (n=6 mice/group). **(B)** Quantification of WB from Fig. 5I (n=6 tumors). Data are presented as mean ± S.E.M., *p < 0.05, two-way ANOVA.

Supplementary Figure-7

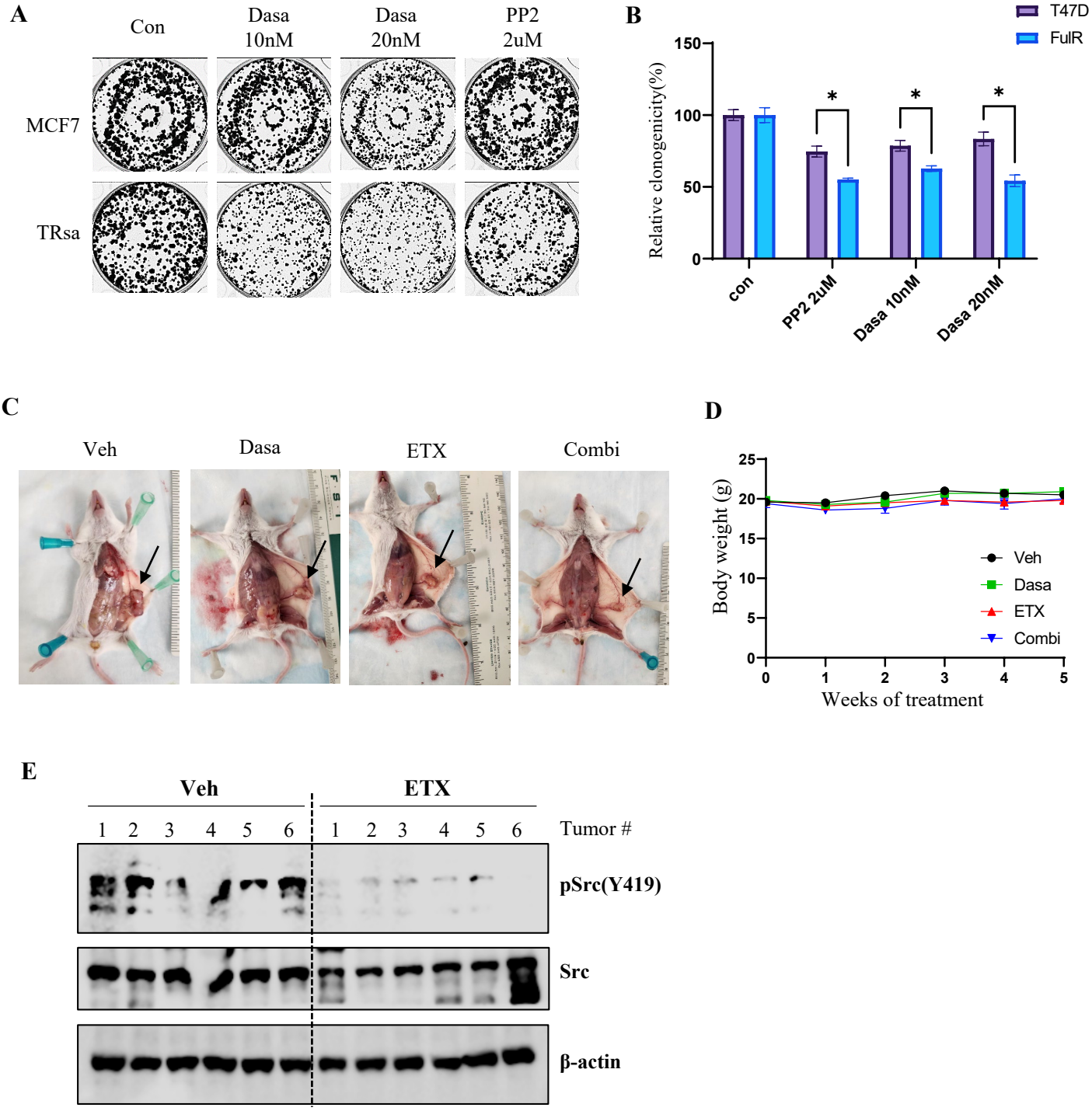

Figure S7. ***In vitro and in vivo*** **experiments using treatment of Src inhibitors in MCF7, TRsa, T47D and T47D FulR cells. (A)** Representative images of Fig. 6E illustrating the clonogenic assay of MCF7 and TRsa cells treated with Src inhibitors (n=3). **(B)** Quantification of the clonogenic potential of T47D and FulR cells after treatment with Src inhibitor (n=3). **(C)** Representative mouse pictures of Fig. 6G. **(D)** Average body weight of the mice from the tumor growth curve shown in Fig. 6G (n=6 mice/group). **(E)** WB of individual tumors (n=6) of vehicle or ETX-treated mice from Fig. 6G**.** Data are presented as mean ± S.E.M., *$p < 0.05$, two-tailed student t-test.

Supplementary Figure-8

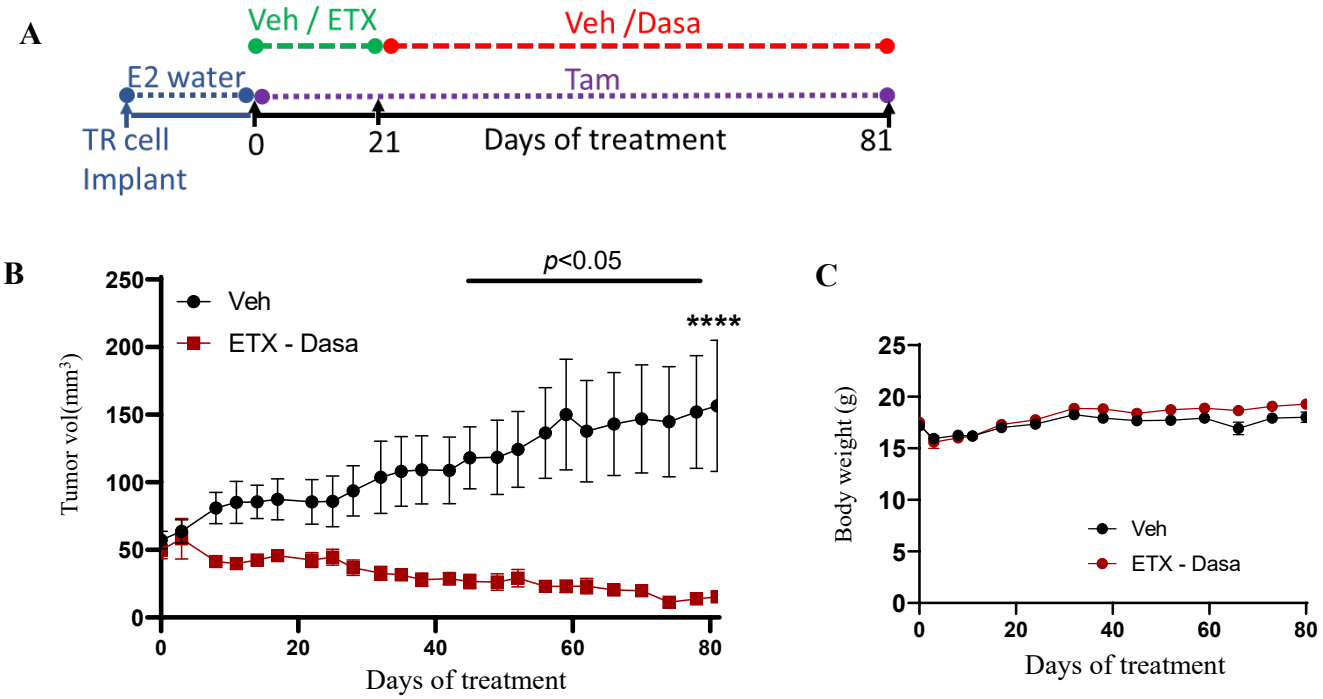

Figure S8. *In vivo* experiment using TR1 cells. (A) Schematic diagram of the *in vivo* treatment timeline of TR1 cells. **(B)** Tumor growth curve of TR1 cells after sequential treatment with ETX and Dasa. After initial tumor formation in the presence of drinking water containing 8µg/mL 17β-estradiol, during the treatment phase, mice in the ETX-Dasa group were treated with ETX (50mg/kg, 3 times/week, i.p.) for 21 days and continued with Dasa (20mg/kg, 5 times/week, p.o.) for 60 days (n=6). All mice received Tam (2mg/kg, 5 times/week, p.o.) during the treatment phase. **(C)** Average body weight of the mice from the tumor growth curve shown in Fig. S8B. Data are presented as mean ± S.E.M., *p < 0.05, ** p <0.01, *** p <0.001, **** p <0.0001, two-way ANOVA.