## Supplementary Figures

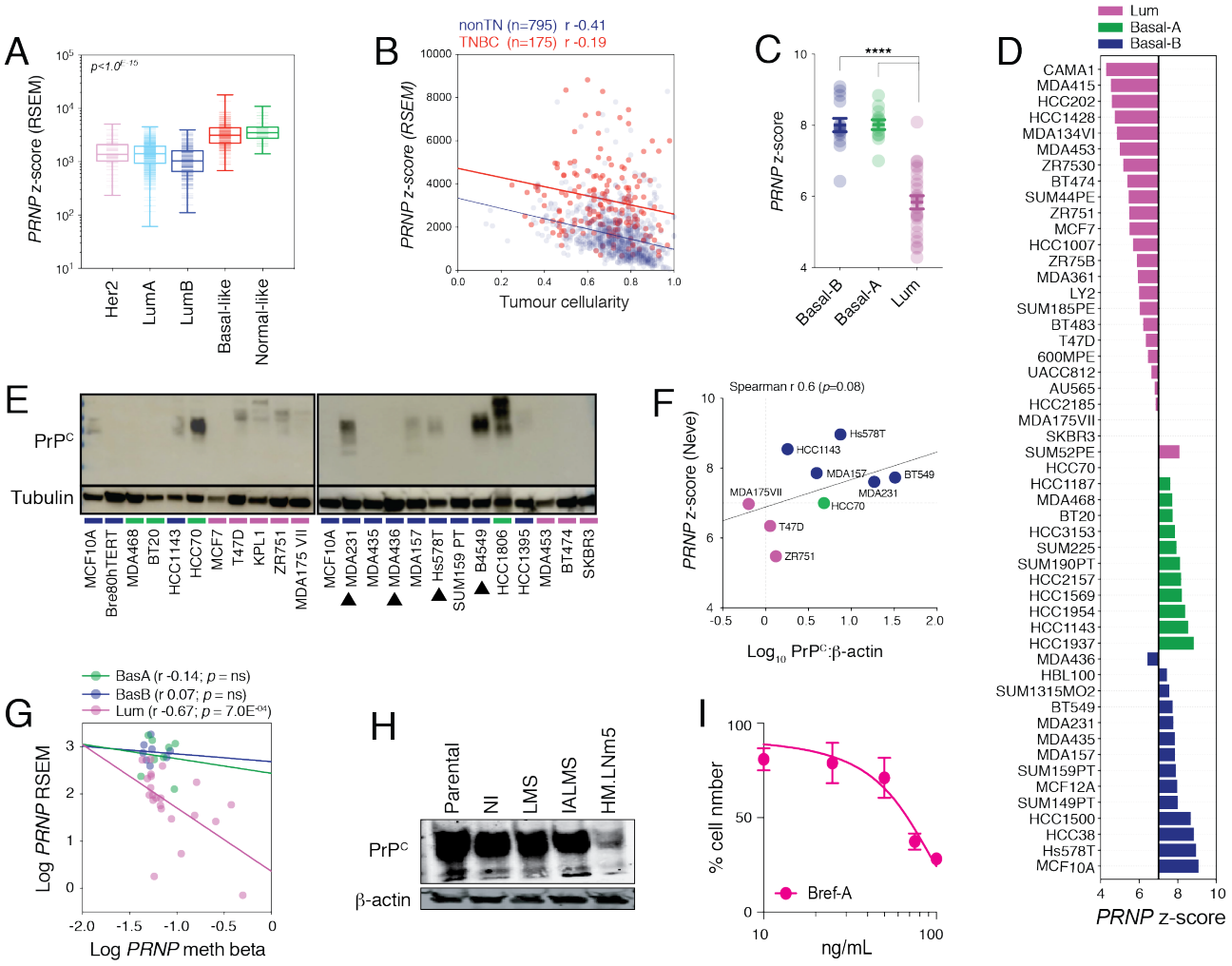


**Figure-S1. PrP$^C$ expression in breast tumors and cell lines. [A]** Analysis of *PRNP* mRNA expression in the TCGA dataset. *PRNP* is more highly expressed in basal-like and normal-like breast cancers compared to Her2-enriched or luminal A/B types (*p*-value indicated from non-parametric Kruskal-Wallis test). **[B]** Relationship between PRNP mRNA expression and tumor purity (*r*, correlation coefficient) (25). **[C/D]** *PRNP* mRNA levels in breast cancer cell lines according to cell line molecular subtype (26). **[E]** Western analysis of intracellular PrP$^C$ in selected cell lines (relative to Tubulin), arrows mark cell lines used for doxorubicin mechanistic studies. **[F]** Relationship between published *PRNP* z-scores and PrP$^C$ protein level (determined by densitometry of S1E). Spearman correlation coefficient (*r*) and *p*-value indicated. **[G]** Relationship between *PRNP* expression and methylation at the *PRNP* genomic locus (average of probes) in breast cancer cell lines from the Daemen et al. dataset (27). **[H]** PrP$^C$ protein expression relative to β-actin across MDA231 clonal derivatives with increasing metastatic potential. **[I]** Brefeldin A dose curve for cellular toxicity.

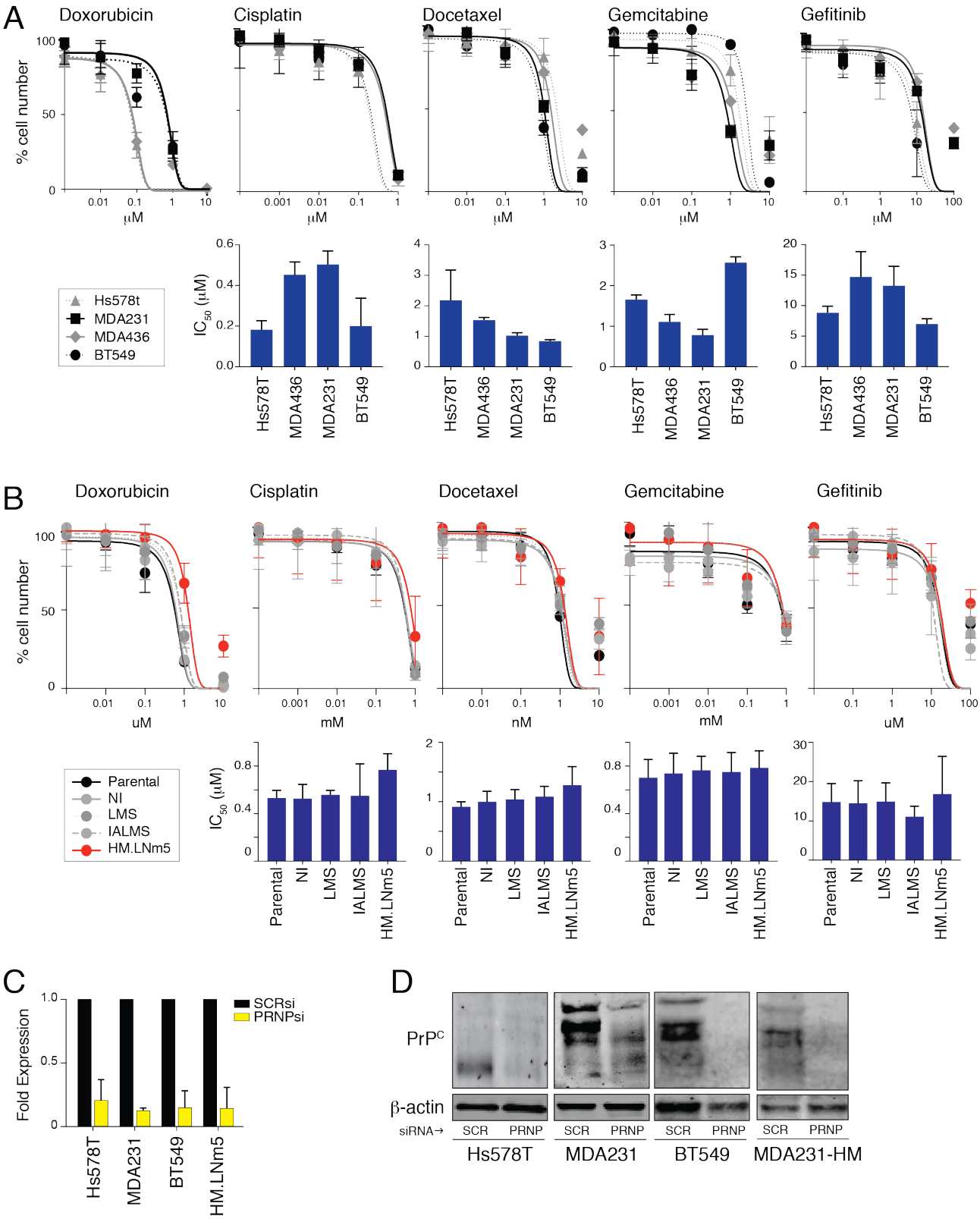


**Figure-S2. Soluble PrP$^C$ can mediate resistance to doxorubicin. [A/B]** Logarithmic dose-response curves for a set of standard chemotherapeutics in a range of cell lines expressing and secreting different levels of PrP$^C$. Data shown are the means +/- SEM of triplicate experiments, with non-linear regression lines of best fit. **[C]** Analysis of *PRNP* mRNA expression by qRT-PCR 48h after transiently transfecting scrambled or *PRNP*-directed siRNA. **[D]** Western analysis of PrPC relative to β-actin 48h after transiently transfecting scrambled or *PRNP*-directed siRNA.

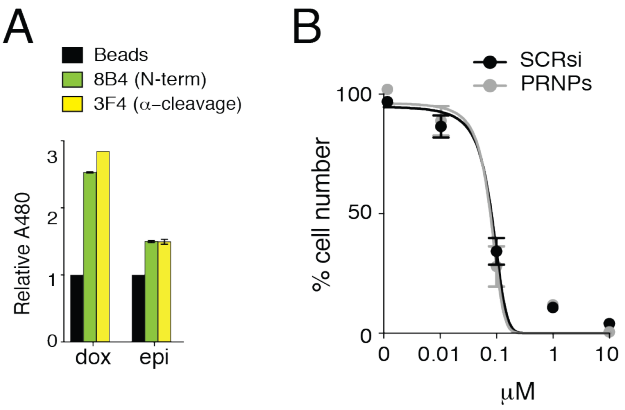


**Figure-S3. Effect of PrP$^C$+ serum on doxorubicin efficacy *in vitro*. [A]** Co-immunoprecipitation of doxorubicin and epirubicin with PrP$^C$ using two different antibodies (mean +/- SEM is shown for three experiments). **[B]** Epirubicin dose-response assay in HM.LNm5 cells with and without siRNA-mediated depletion of *PRNP*.

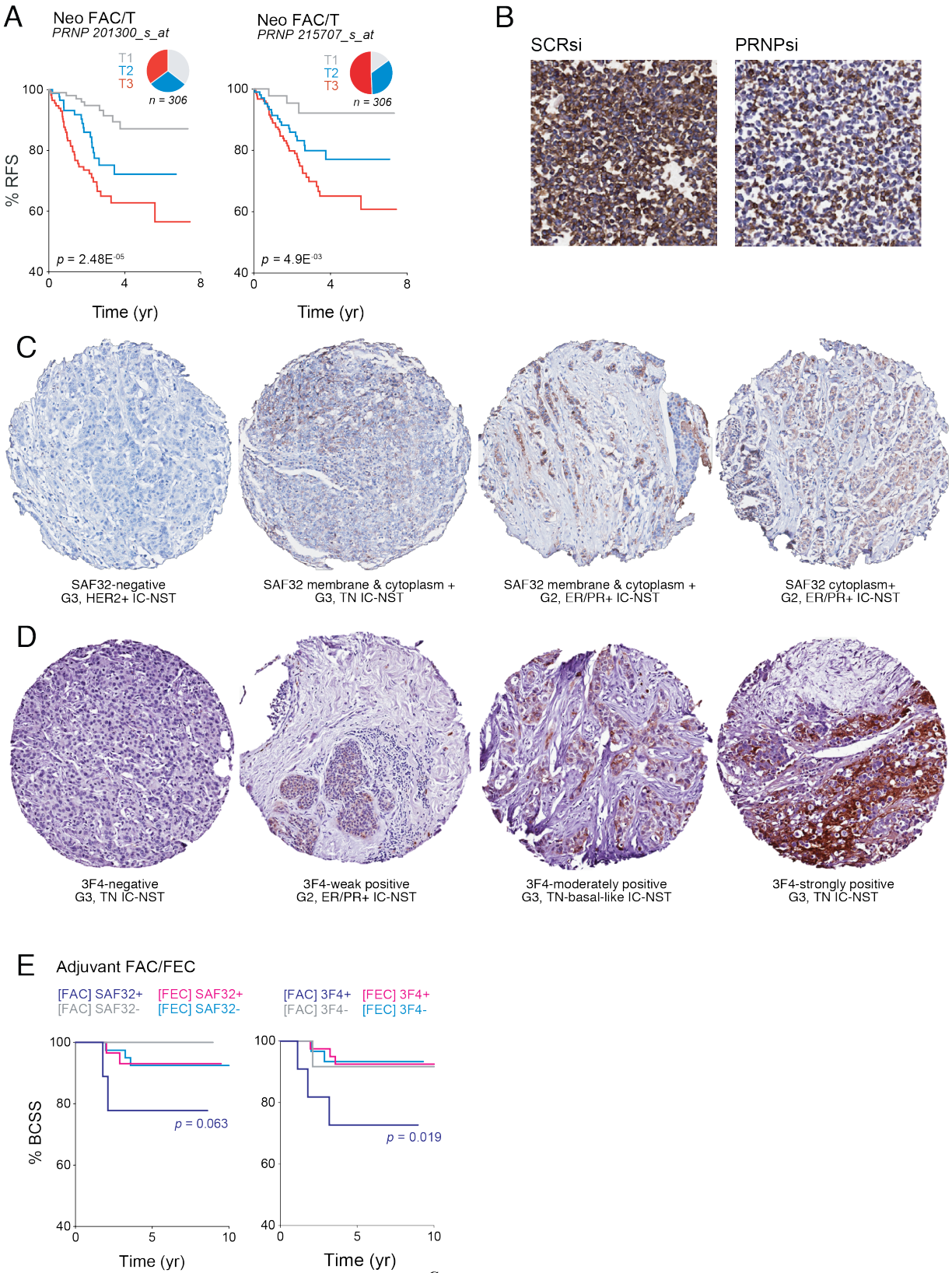


**Figure-S4. Relationships between tumor PrP$^C$ expression and clinical outcomes of breast cancer patients treated with anthracycline-based chemotherapy. [A]** Similar trends between *PRNP* expression and relapse-free survival (RFS) were observed with two different *PRNP* expression array probes. *PRNP T1-3*, RNA expression tertiles. [B] SAF32 antibody validation by IHC analysis of paraformaldehyde-fixed, pelleted and paraffin embedded MDA231 cells transiently transfected with control (SCR) or *PRNP*-specific siRNAs. **[C-D]** Additional examples of PrP$^C$ IHC staining with the SAF32 and 3F4 antibodies. **[E]** Kaplan Meier analysis of the relationships between PrP$^C$ protein isoforms and breast cancer specific survival (BCSS).