 *Supplementary Figure 2 -* **Nrh knock-down potentiates Thapsigargin dose-dependent effect in the**

**MDA-MB-231 cell line**

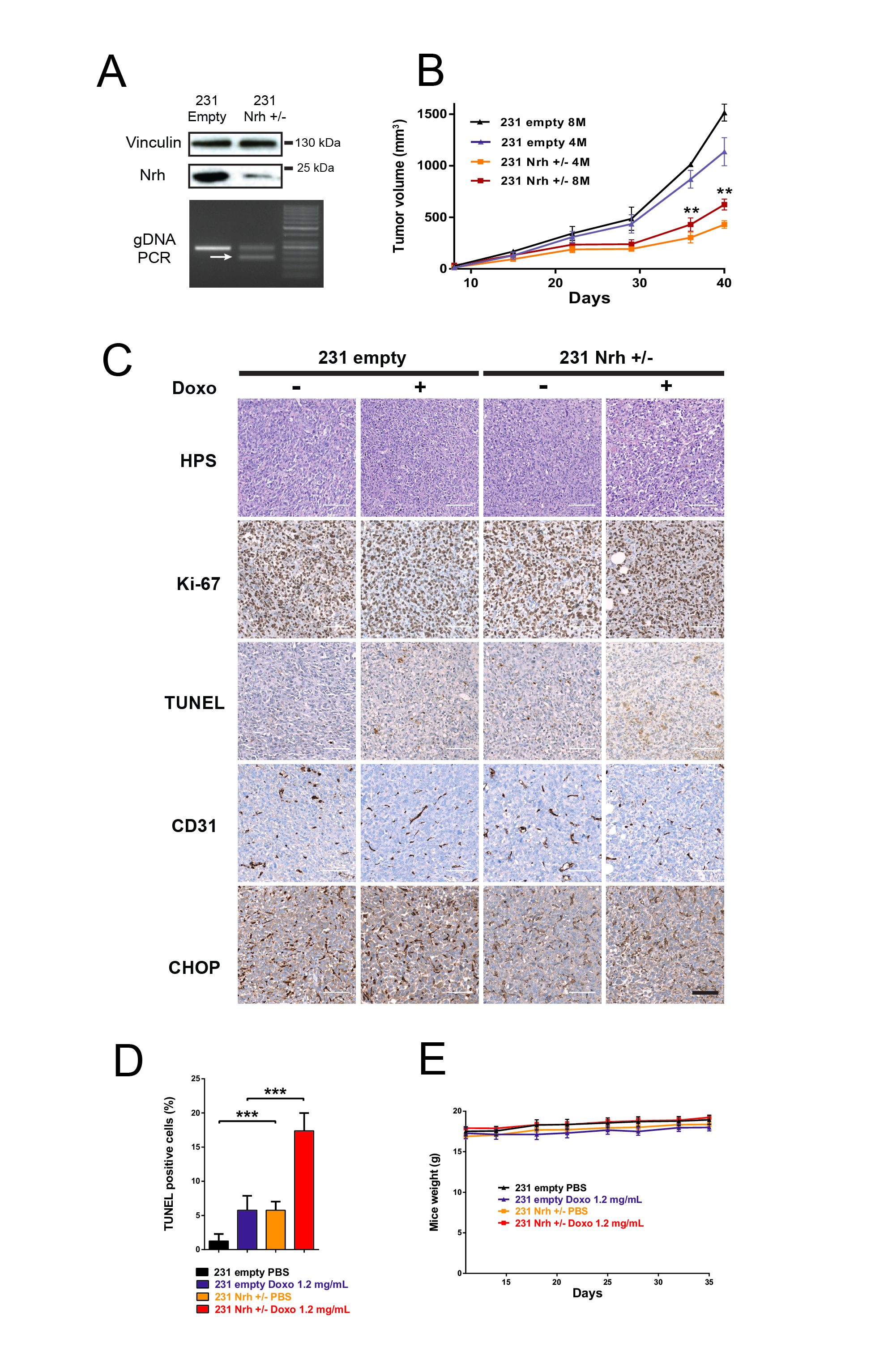
(**A**) Kinetic apoptosis assay (% of cells displaying Caspases 3/7 activity) in MDA-MB-231 cells

transfected with corresponding siRNAs and treated with 10 μM Thapsigargin (THG) for 36 hours, (**B**)

1μM Thapsigargin or (**C**) 100 nM Thapsigargin (mean ± SD; *n* = 3). (**D**) Percentage (%) of cells

displaying Caspases 3/7 activity as a function of log[THG] concentration using two *nrh* siRNA at 36

hours.

 *Supplementary Figure 3 –* **Nrh knock-down is sufficient to impair tumor progression**

(**A**) Characterization of the MDA-MB-231 *nrh*+/- cell line, bearing a mutant *nrh* allele; Top endogenous Nrh expression levels in 231 *nrh* +/- and containing pLentiCRISPRv2 empty vector (231 empty) cell lines (50 μg lysate), detected by Western blot analysis; Bottom: gel electrophoresis validation of the CRISPR-CAS9 engineered genomic DNA deletion in one allele. (**B**) Evaluation of the tumorigenic capacity of MDA-MB-231 heterozygous cells (231 *nrh* +/-), injected into the mammary fat pad of nude mice. MDA-MB-231 containing pLentiCRISPRv2 empty vector were used as a control (231 empty). Four (4M) or eight million (8M) cells from 231 *nrh* +/- or 231 empty cell lines were injected into nude mice. Tumor volume was assessed using calipers (mean ± SEM; *n* = 3 mice per condition; \*\*, P < 0.01). (**C**) Expression of Ki-67, TUNEL-positive apoptotic bodies, CD31- positive blood vessels and CHOP in representative tumor sections of MDA-MB-231 (231 empty) or MDA-MB-231 *nrh* +/- (231 *nrh* +/-) mouse group, with or without chemotherapy treatment (PBS control or Doxorubicin at 1.2 mg/kg). Hematoxylin staining is shown on top panels (HPS)*.* Representative tumor sections in non-necrotic area were processed for immunohistochemical detection of Ki-67 and CHOP to assess cell proliferation and UPR, respectively. Blood vessels were visualized via CD31. Cell death was detected by TUNEL assays. At least five randomly selected non-overlapping fields were examined. TUNEL signal was increased upon *nrh* silencing and Doxorubicin treatment. Mitotic index (Ki-67) and vessel density quantification (CD31/PECAM) showed no significant differences between groups. Scale bars: 100 μm. (**D**) Quantification of TUNEL positive cells in two different mouse tumors per conditions processed as described in (**C**), representing cell death levels (mean ± SD; *n* = 8 microscopic field, at least 100 cells per field; \*\*\*, P < 0.001) (**E**) Measurement of mouse weight over the course of the experiments (see also Figures 1H and I). Mice were weighted twice a week using a precision scale (mean ± SEM; *n* = 8 mice per condition) and did not show significative weight change upon doxorubicin treatment.