**SUPPLEMENTAL DATA**

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**Supplementary figure 1**: *In vivo* experimental plan for NPs, NPs-siRNAs, NPs-Dox or NPs-Dox-siRNAs. (A) Tumor induction and treatment of mice, (B) number of administration of a dose.

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**Supplementary figure 2**: *In vivo* experimental plan for separate treatment of NPs-siRNAs and NPs-Dox. (A) Tumor induction and treatment of mice, (B) number of administrations of a dose.

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**Supplementary figure 3**: Standard curve of fluorescent siRNA vs fluorescent intensity. Each experiment was done in duplicate and repeated for two times to check reproducibility.

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**Supplementary figure 4:** Cell viability assessment in 4T1 and MDA-MB-231 cells for the NPs-Dox-siRNA carrying single siRNA against multidrug transporter genes. Cells were treated with media (untreated), NPs-Dox formed with 3 mM of CaCl2 and 1 nM to 100 nM of Dox, NPs-Dox-siRNA formed with 3 mM CaCl2, 1 nM to 100 nM of Dox and 1 nM of siRNA for a consecutive period of two days (4T1 cells) or one day (MDA-MB-231 cells). After 44 hours, cell viability was measured by MTT assay. Values are represented as % of cell viability compared to untreated cells. siRNAs against (A, B) *ABCB1* (C, D) *ABCG2* and (E, F) *ABCC1* gene in 4T1 and MDA-MB-231 cells respectively.

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**Supplementary figure 5**: Cell viability assessment in 4T1 cells for NPs-siRNAs and NPs-Dox-siRNAs carrying siRNAs against transporter genes in different combinations. 3 mM of CaCl2, 1 nM of each siRNA and 10 nM od Dox were used to form the complex. After 44 hours of treatment cell viability was measured and values are represented as % of cell viability compared to untreated cells. (A) Free siRNAs and NPs-siRNAs without Dox, and (B) with Dox in 4T1 cells.

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**Supplementary figure 6**: (A) Cell viability assessment in three cells for the NPs-neg. siRNA. 3 mM of CaCl2 and 1 nM of allstars negative siRNA were used to form NPs-neg.siRNA. After 44 hours, cell viability was measured and values are represented as % of cell viability compared to untreated cells. (B) Caspase-7-mediated luminescence signal in MCF-7 cells following exposure to NPs and NPs-neg.siRNA formed with 3 mM of CaCl2 and 1 nM of neg.siRNA. After 44 hr of treatment, Caspase 3/7-mediated luminescence signal was measured. Data were presented as mean±SD for duplicate samples.

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**Supplementary figure 7**: Tumor outgrowth in mice treated with NPs carrying Dox and siRNAs targeting three transporter genes (*ABCB1, ABCG2* and *ABCC1*). Mice were treated with 100 µL regimen. 70 mM of CaCl2, 0.34 mg/Kg Dox and 50 nM of each three siRNA against transporter genes were used to make the complexes. Six mice/group were used and data were presented as mean±SD.

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**Supplementary figure 8**: Tumor outgrowth in mice treated with of NPs-neg. siRNA. Mice were treated with 100 µL regimen. 40mM of CaCl2 and 50 nM of allstars neg. siRNA were used. Six mice/group were used and data were presented as mean±SD.