Supporting Information

of

Tumor-Triggered Drug Release with Tumor-Targeted Accumulation and Elevated Drug Retention to Overcome Multidrug Resistance

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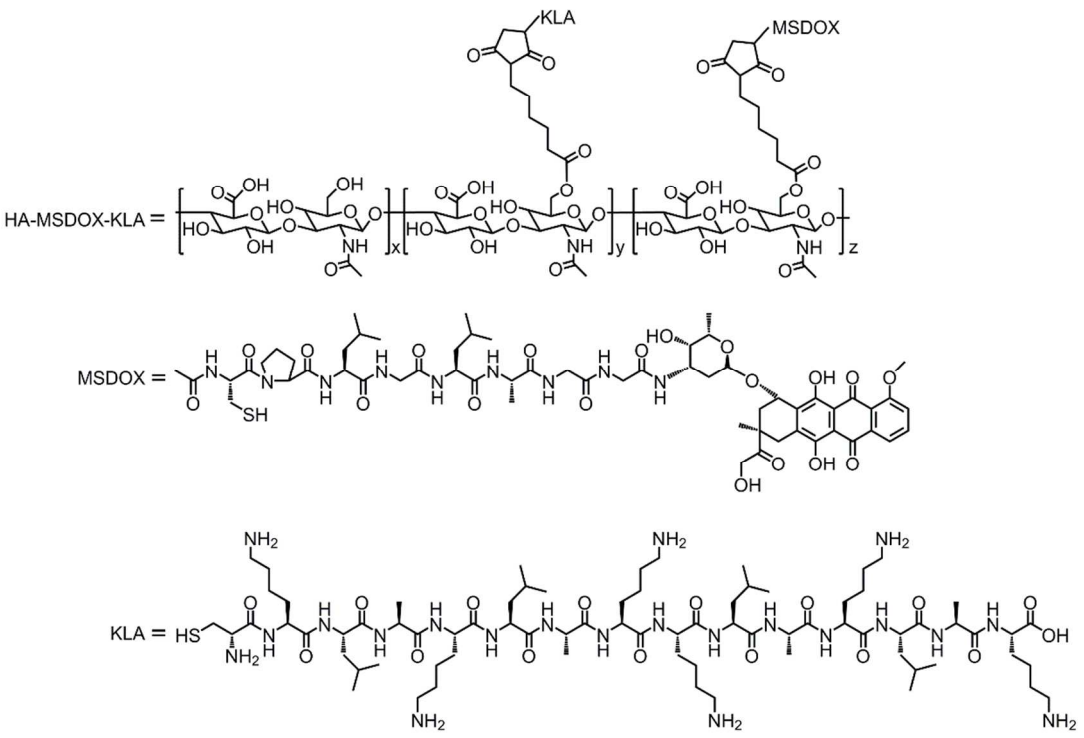

Scheme S1. The chemical structure of HA-MSDOX-KLA.

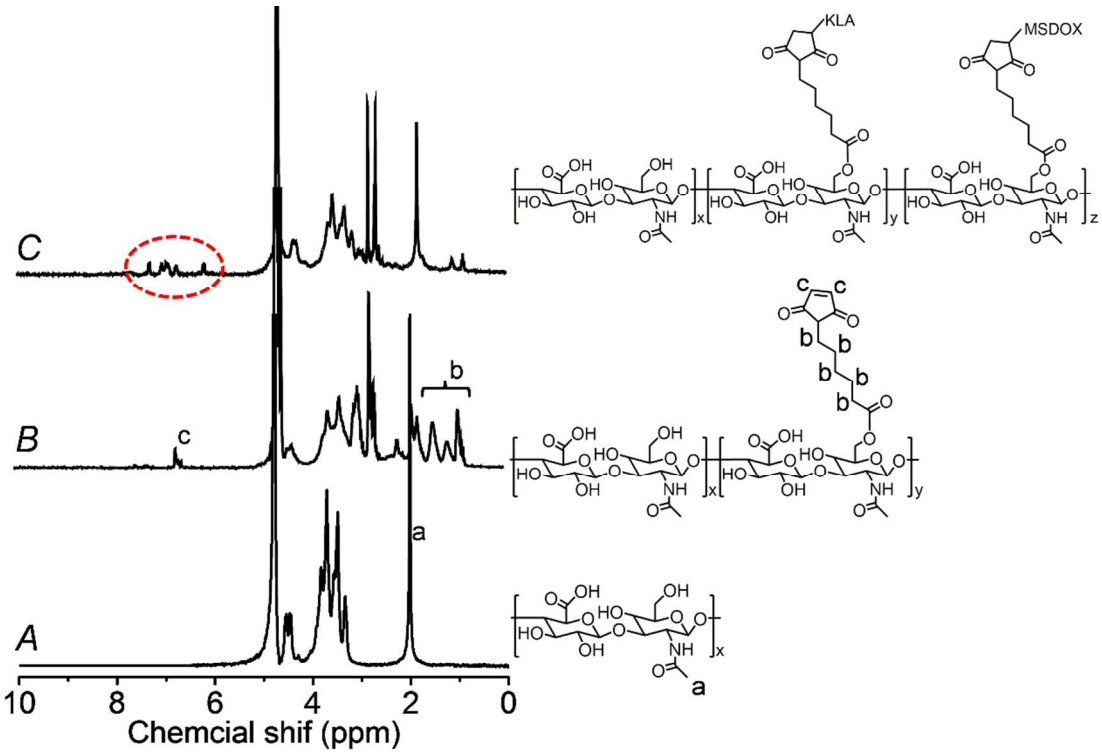

Figure S1. ^{1}H NMR spectra of HA (A), HA-Mal (B), and HA-MSDOX-KLA (C). The red ellipse indicated the typical ^{1}H NMR peaks of benzene rings, which belonged to the DOX in HA-MSDOX-KLA.

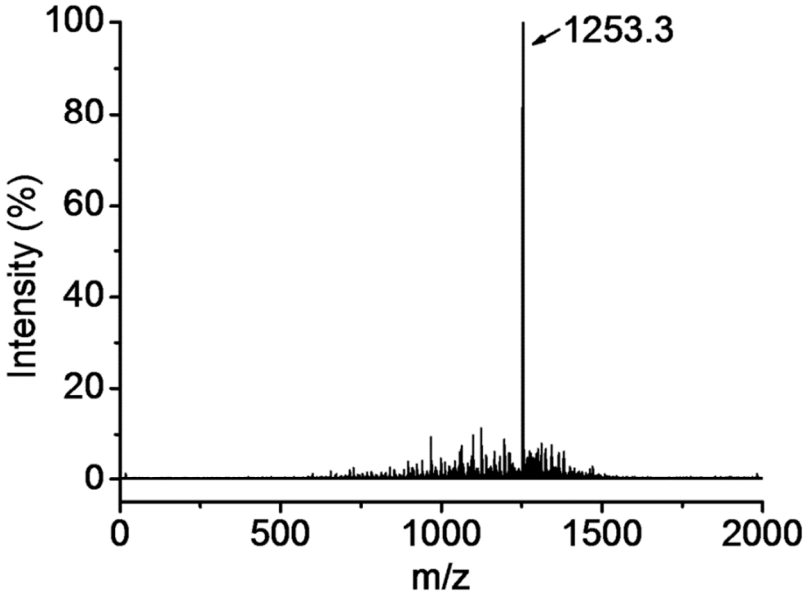

Figure S2. MALDI-TOF-MS of MSDOX.

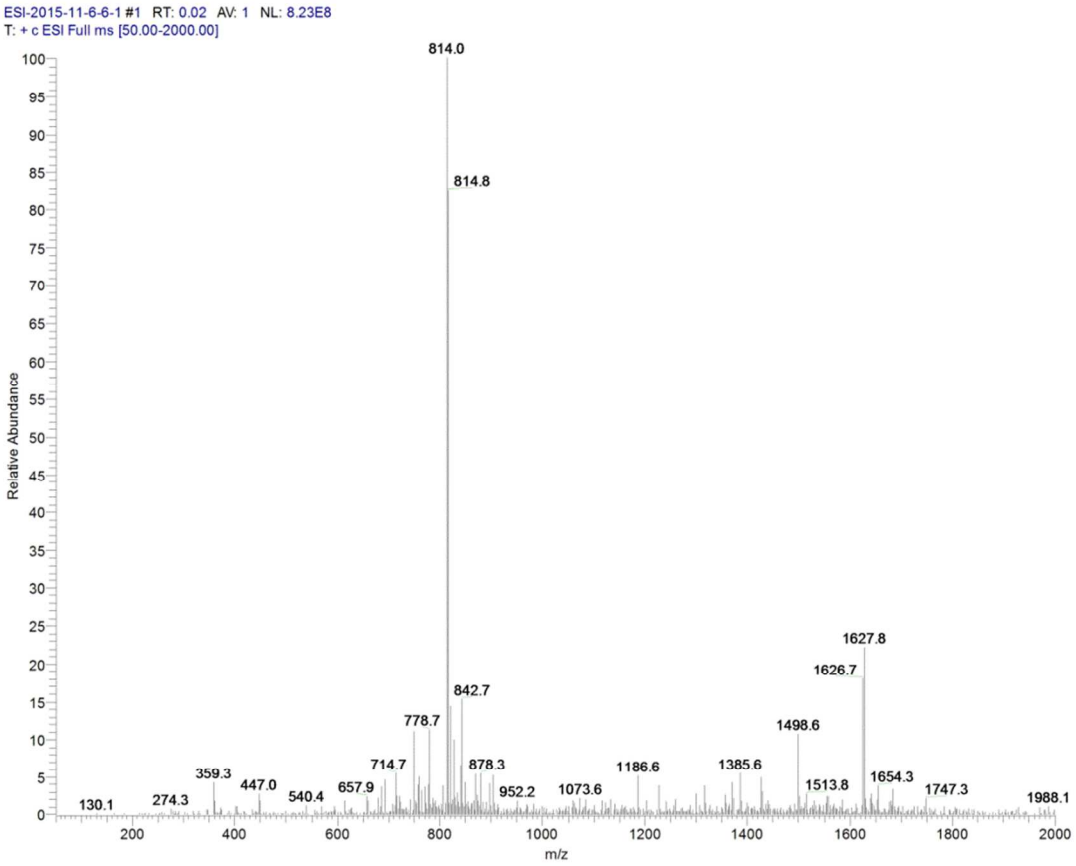

Figure S3. ESI-MS of KLA.

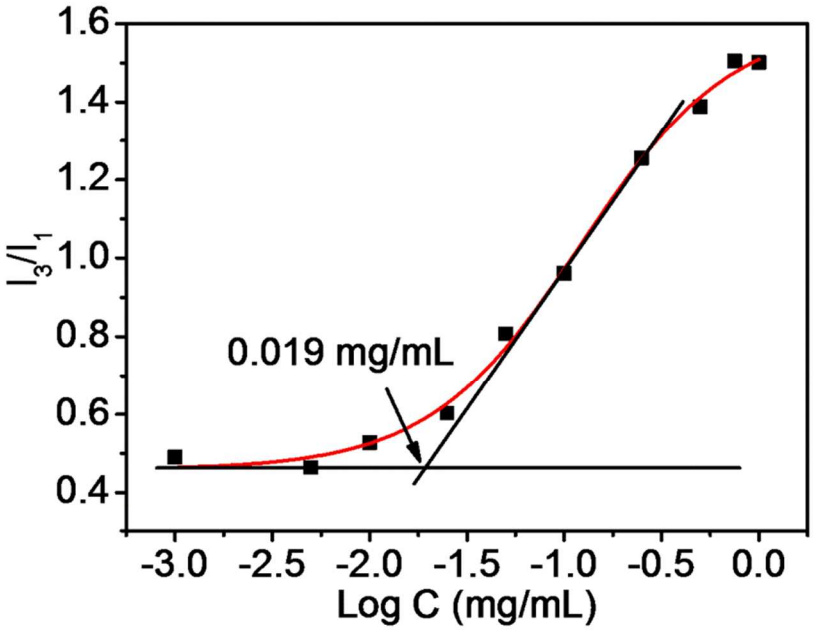

Figure S4. The CMC of HA-MSDOX-KLA micelles determined by fluorescence spectra and using pyrene as a hydrophobic fluorescent probe. Plot of the intensity ratio I_3/I_1 vs log C, the measured CMC value was 0.019 mg/mL.

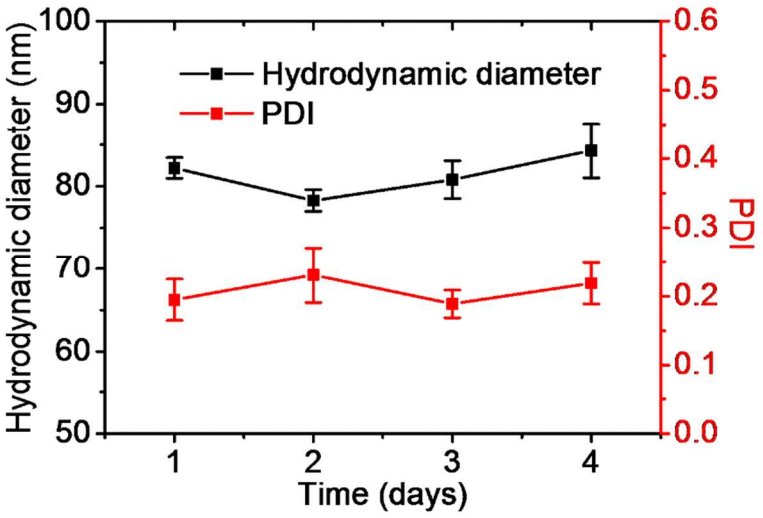

Figure S5. The hydrodynamic diameter and polydispersity index (PDI) of the HA-MSDOX-KLA micelles in PBS with 10% serum proteins (FBS) investigated for four days by DLS.

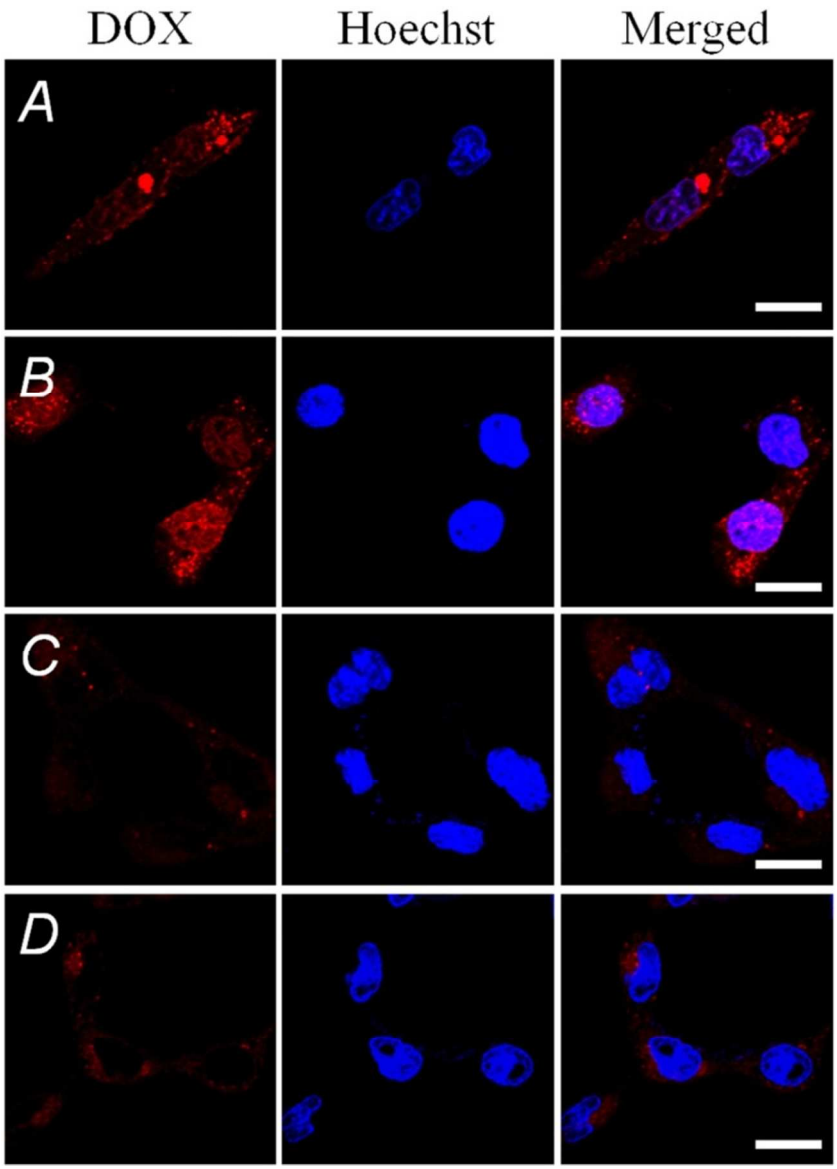

Figure S6. A) and B) Confocal laser scanning microscopy (CLSM) images of COS7 cells treated with free DOX for 6 h or 12 h, respectively. C) and D) CLSM images of COS7 cells treated with HA-MSDOX-KLA for 6 h or 12 h, respectively. The nuclei are stained by Hoechst 33342. Scale bar: 20 μm.

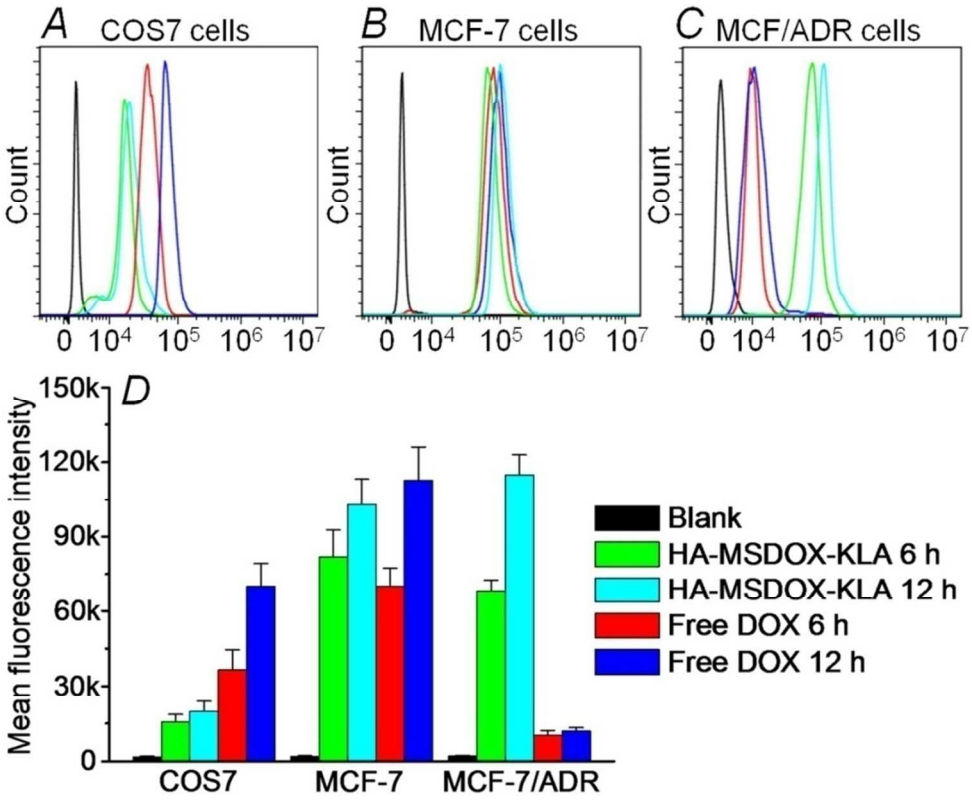

Figure S7. Flow cytometry analysis of intracellular uptake of DOX in COS7 cells in COS7 cells (A), MCF-7 cells (B), and MCF/ADR-7 cells (C), respectively. D) The corresponding mean fluorescence intensity displayed in Figure S7A-7C. The cells treated with HA-MSDOX-KLA for 6 h (green) and 12 h (cyan), the cells treated with free DOX for 6 h (red) and 12 h (blue), and the cells without treatment were used as the control (black).

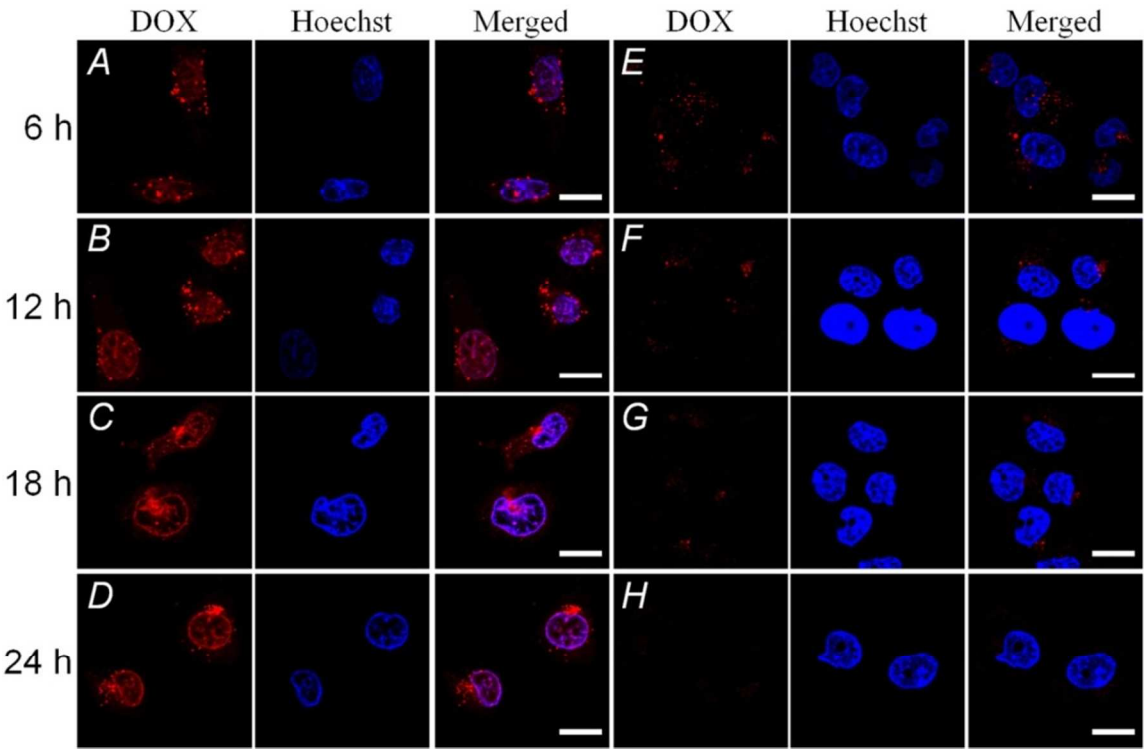

Figure S8. A-D) CLSM images of MCF-7 cells (the cells were pre-treated with free DOX for 6 h) for additional incubation with fresh culture medium of 6 h, 12 h, 18 h and 24 h, respectively. E-H) CLSM images of MCF-7/ADR cells (the cells were pre-treated with free DOX for 6 h) for additional incubation with fresh culture medium of 6 h, 12 h, 18 h and 24 h, respectively. The nuclei are stained by Hoechst 33342. Scale bar: 20 μm.

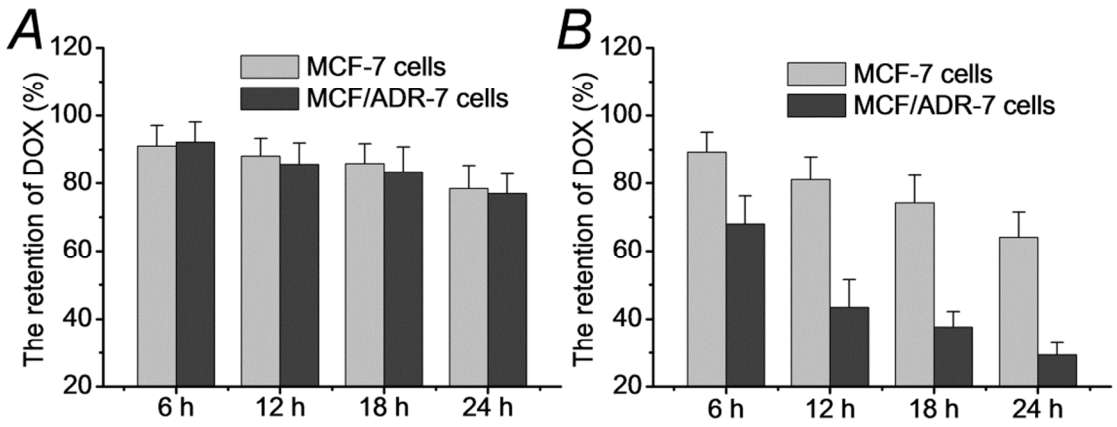

Figure S9. Statistical quantification of corresponding intracellular retention DOX via software Image-J. A) MCF-7 and MCF-7/ADR cells treated with HA-MSDOX-KLA. B) MCF-7 and MCF-7/ADR cells treated with free DOX.

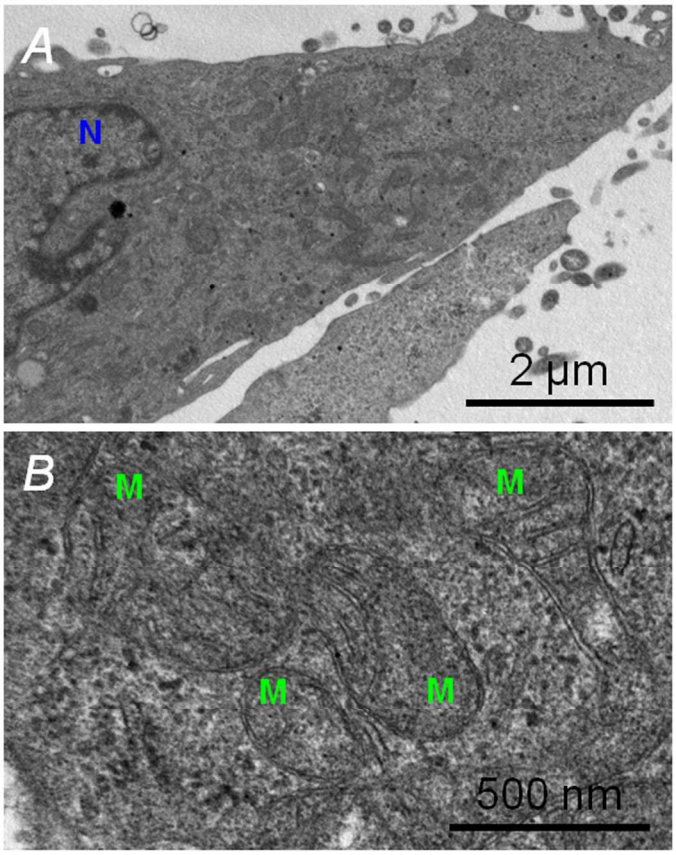

Figure S10. A) and B) Bio-TEM images of MCF-7/ADR cells without HA-MSDOX-KLA treatment. The blue "N" represents nuclei and the green "M" represents mitochondria.

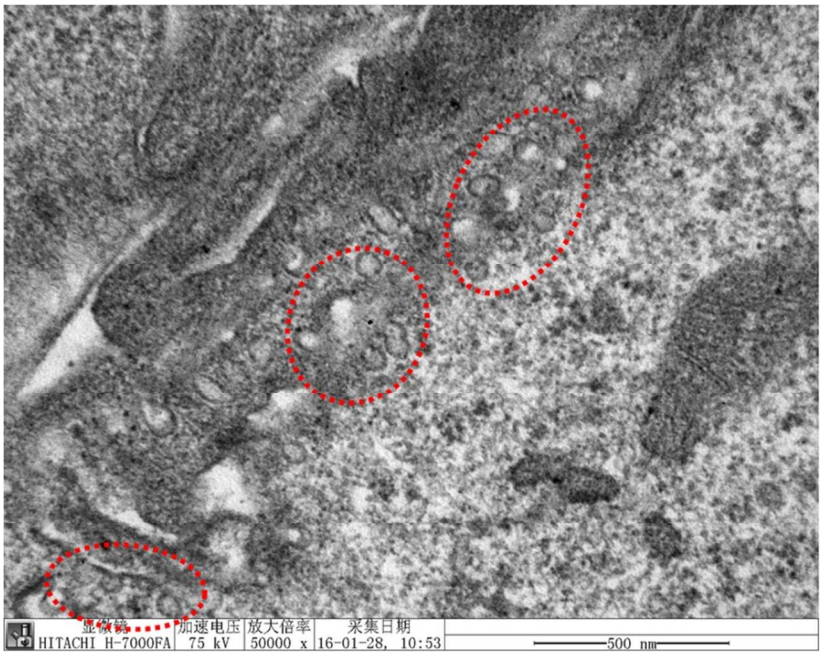

Figure S11. Bio-TEM images of MCF-7/ADR cells treated with HA-MSDOX-KLA for 6 h. HA-MSDOX-KLA nanoparticles are highlighted by red circles.

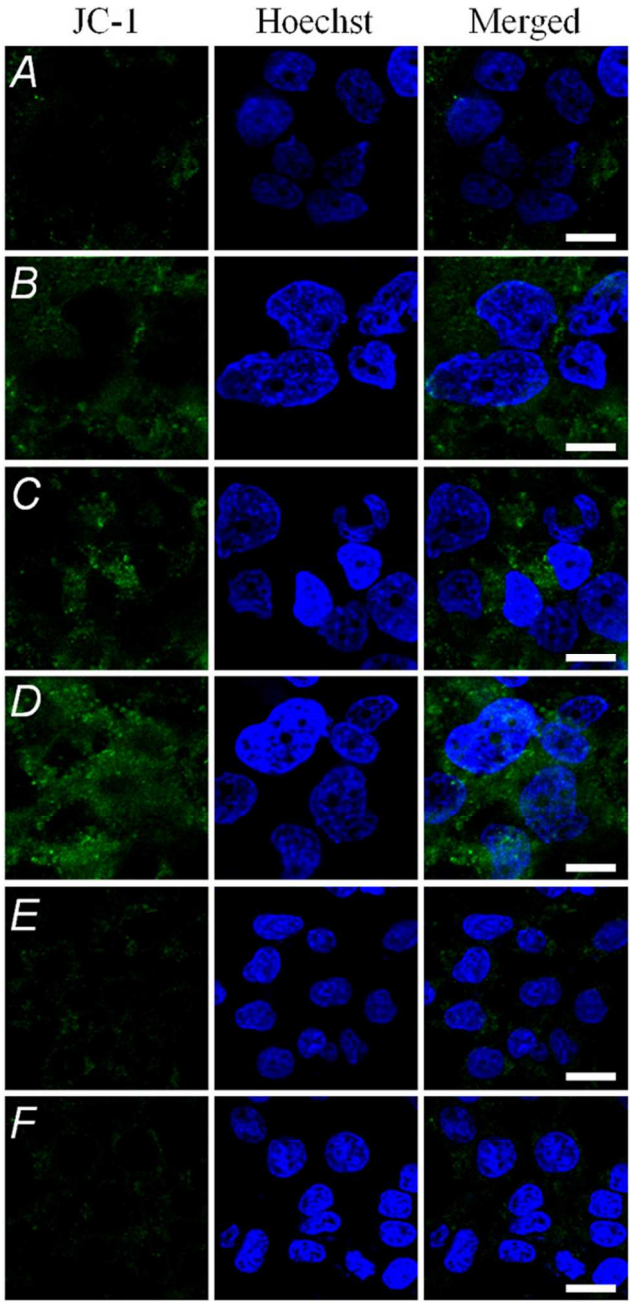

Figure S12. Analysis of mitochondrial membrane potential by JC-1 assay. A) MCF-7/ADR cells without any treatment. B-D) MCF-7/ADR cells treated with HA-MSDOX-KLA for 12 h, 24 h and 48 h, respectively. E) COS7 cells without any treatment. F) COS7 cells treated with HA-MSDOX-KLA for 48 h. The nuclei are stained by Hoechst 33342. Scale bar: 20 μm. The increased green fluorescence (JC-1 monomer in the cytoplasm) can be observed in MCF-7/ADR cells incubated with HA-MSDOX-KLA (Figure S12B-S12D), indicating that the mitochondria of MCF-7/ADR cells are destroyed seriously, leading to a relatively low $\Delta\Psi m$.

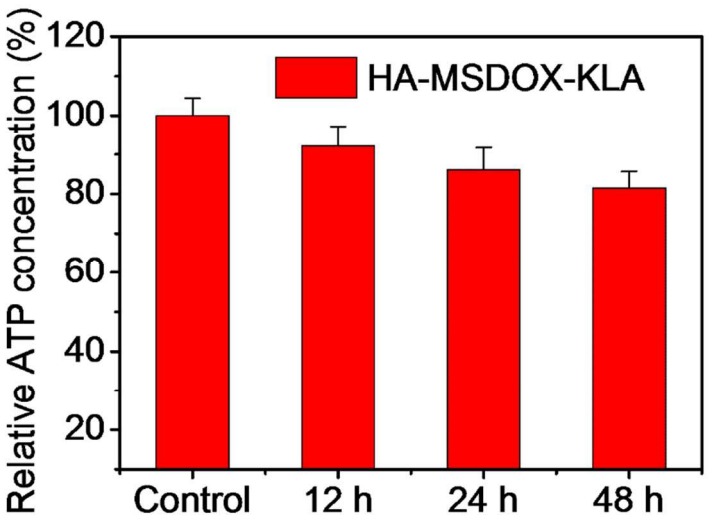

Figure S13. Relative ATP levels of COS7 cells after treatment with HA-MSDOX-KLA.

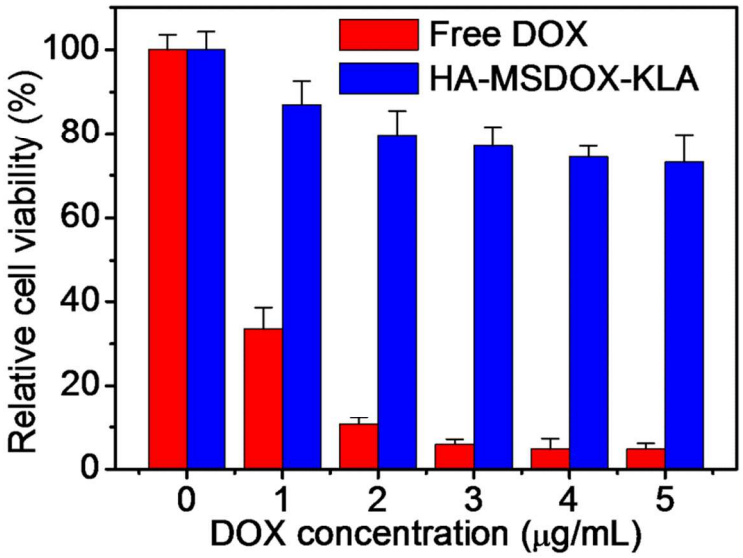

Figure S14. Cytotoxicity of free DOX and HA-MSDOX-KLA against COS7 cells.

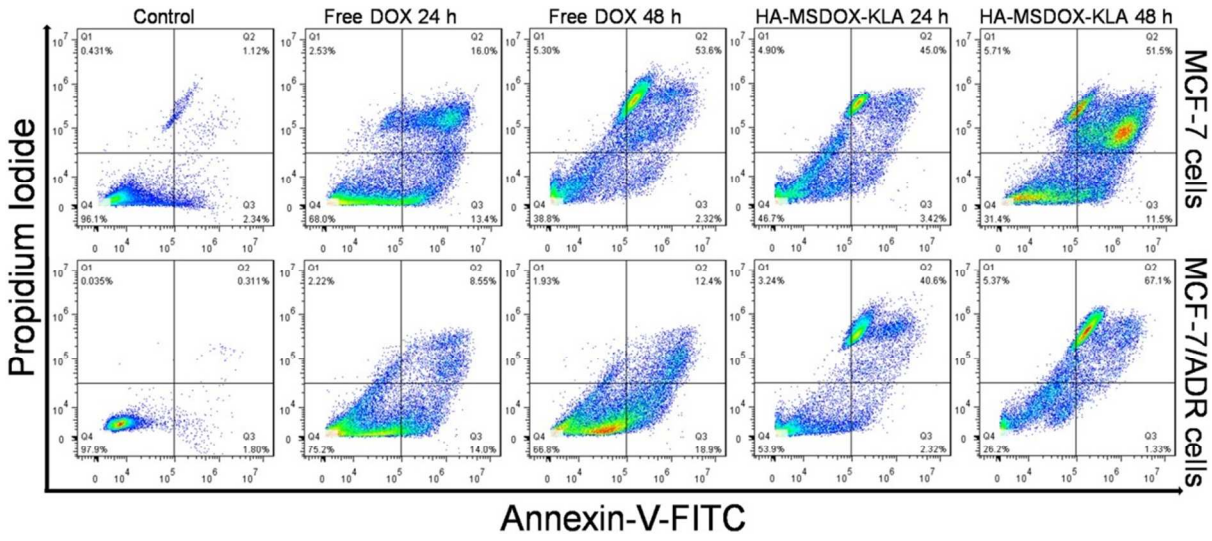

Figure S15. Evaluation of apoptosis in MCF-7 cells and MCF-7/ADR cells with different treatments.

Figure S16. Representative images of the MCF-7/ADR xenograft tumors of the mice after treatment with PBS, free DOX, HA-MSDOX, and HA-MSDOX-KLA at day of 16. Red circles indicate the site of tumors.

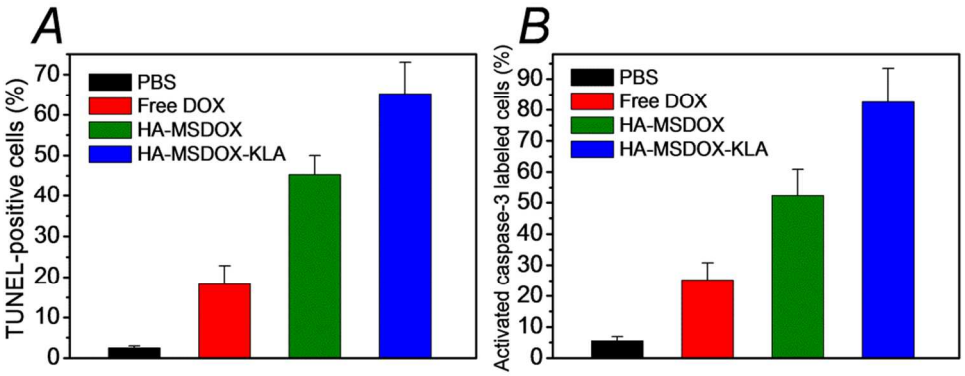

Figure S17. A) Quantification of the percentage of TUNEL-positive apoptotic cells in tumors treated with different DOX formulations. B) Quantification of the percentage of activated caspase-3 labeled cells in tumors treated with different DOX formulations.

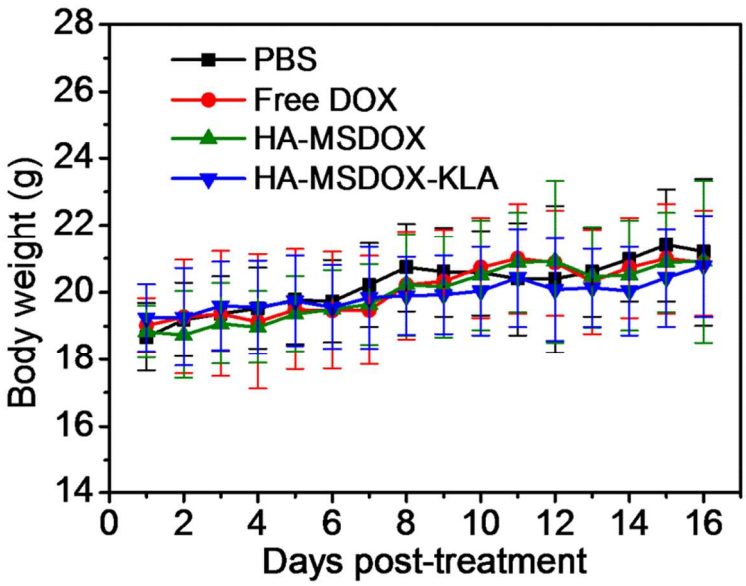

Figure S18. The body weight alteration of MCF-7/ADR tumor-bearing mice after different treatments.

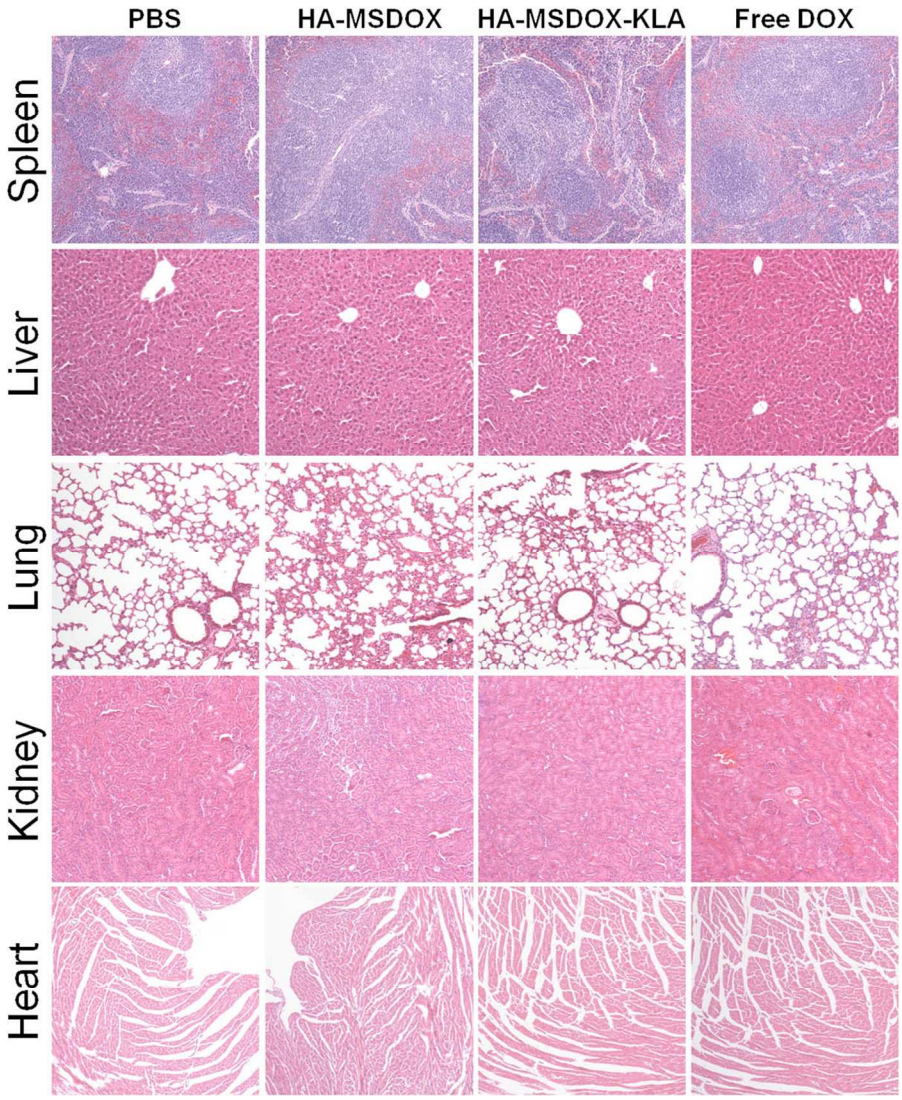

Figure S19. Major organs (spleen, liver, lung, kidney, and heart) stained with H&E after different treatments. Compared with PBS control group, no appreciable physiological morphology changes and undetectable adverse effects were observed after HA-MSDOX-KLA treatment, suggesting that almost no damage of HA-MSDOX-KLA to organs in the *in vivo* assessments.