Supplementary Materials

Phosphorylcholine-based stealthy nanocapsules enabling tumor microenvironment-responsive doxorubicin release for tumor suppression

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Synthesis of nBSA-COOH-Dox

First, amine group-containing nBSA (nBSA-NH_2)was synthesis. Briefly, BSA, MPC, Apm and GDA (molar ratio of BSA/MPC/Apm/GDA/Aps/TEMED = 1:4500:500:500:500:2000) were firstly dissolved in deoxygenated and deionized phosphate-buffered saline (PBS) with BSA concentration as 1 mg/mL. Then APS and TEMED was added to initiate the *in-situ* radical polymerization around BSA. The reaction was carried out for 60 min in nitrogen atmosphere. Finally, the impurities including unencapsulated BSA were removed by ultrafiltration [molecular weight cut-off (MWCO): 100 KDa].

Next, nBSA-COOH was synthesized by modification of nBSA-NH_2 with succinic anhydride (SA). SA (10% in DMSO) was added in 1 mg/mL of nBSA-NH_2 (molar ratio of BSA/SA = 1:500) at pH 8 and reacted for 2 h. Then the small molecules were removed by ultrafiltration [molecular weight cut-off (MWCO): 10 KDa].

Finally, nBSA-COOH-Dox was synthesized. A solution of Dox (10 mg/mL in DI water) was added into nBSA-COOH solution (1 mg/mL, in PBS) followed by adding EDC (molar ratio of EDC/Dox/BSA = 400:200:1) and the mixture was stirred overnight at room temperature. The unconjugated Dox and impurities were removed by ultrafiltration [MWCO: 10 KDa].

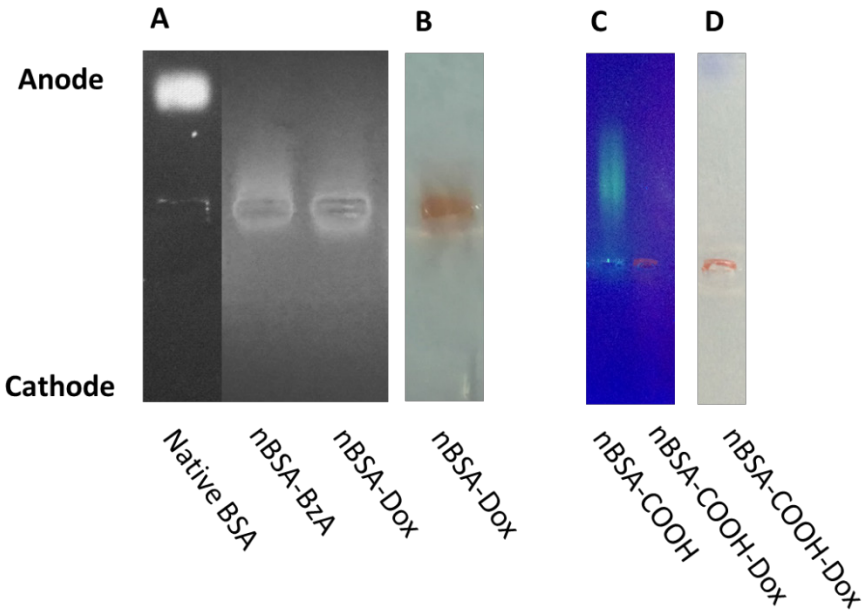

Figure S1. Agarose gel electrophoresis results. (A) FITC-labeled BSA, nBSA-BzA and nBSA-Dox. (B) nBSA-Dox in the light field. (C) FITC-labeled BSA-COOH and nBSA-COOH-Dox. (D) nBSA-COOH-Dox in the light field.

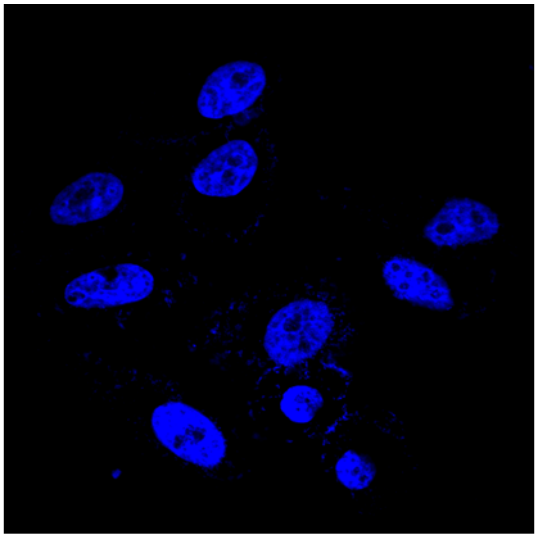

Figure S2. No cellular uptake of nBSA-BzA by HepG2 cells at pH 7.4.

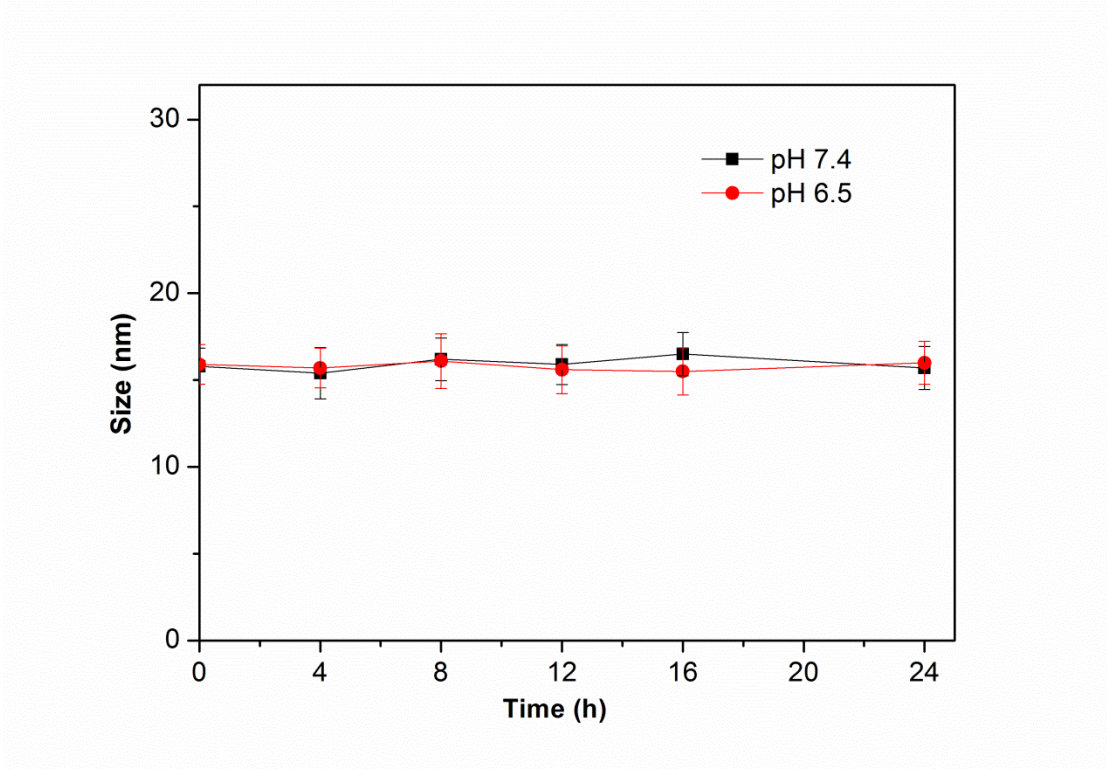

Figure S3. Stability of nBSA-BzA over 24 h (n = 3) at pH 7.4 and 6.5, respectively.

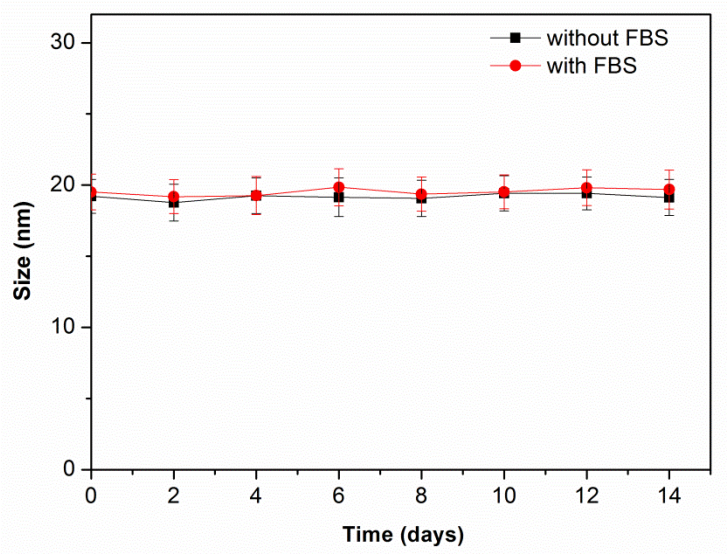

Figure S4. Stability of nBSA-COOH-Dox in PBS without and with 10% FBS over two weeks.

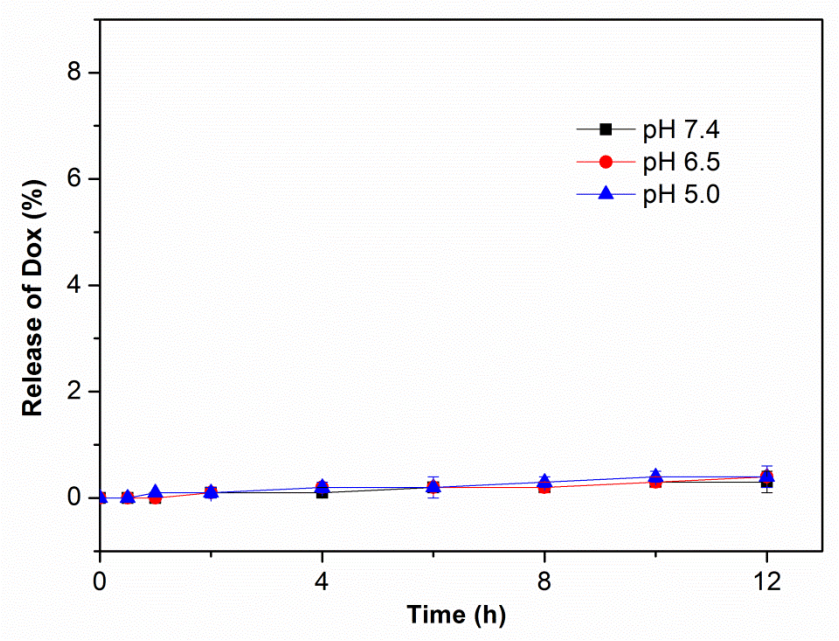

Figure S5. *In vitro* Dox release profiles of nBSA-COOH-Dox in media at different pH.

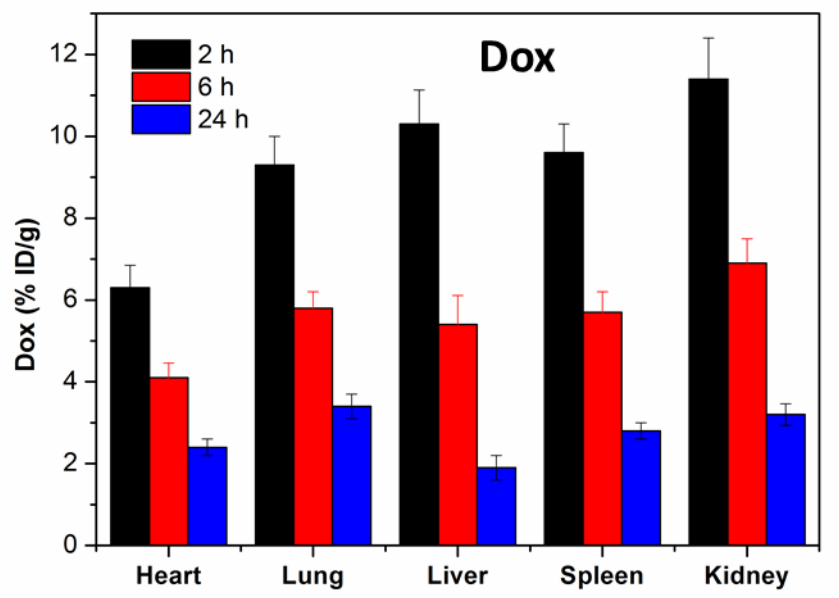

Figure S6. The Dox concentration in organs at 2, 6 and 24 h after the tail vein injection of free Dox.

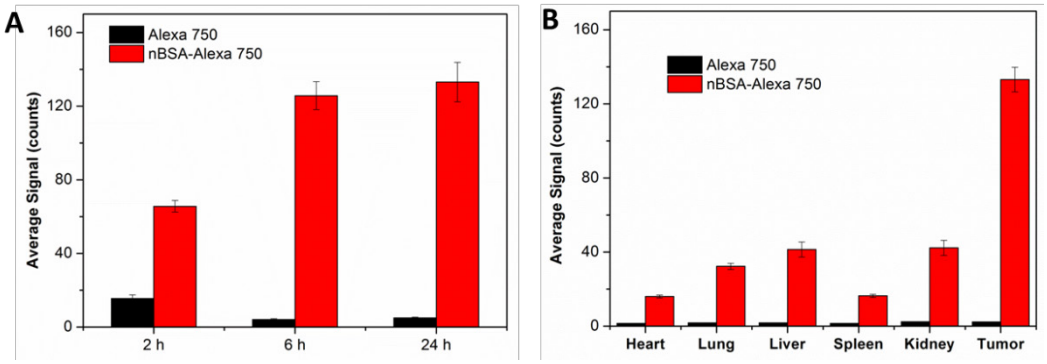

Figure S7. (A) Quantified NIR fluorescence intensity of tumors at the indicated time points after the tail vein injection of nBSA-Alexa 750. (B) Semiquantitative biodistribution of nBSA-Alexa 750 in nude mice as determined by the fluorescence intensity of the organs and tumors.