

# Supporting Information

## Arginine-Rich Manganese Silicate Nanobubbles as a Ferroptosis-Inducing Agent for Tumor-Targeted Theranostics

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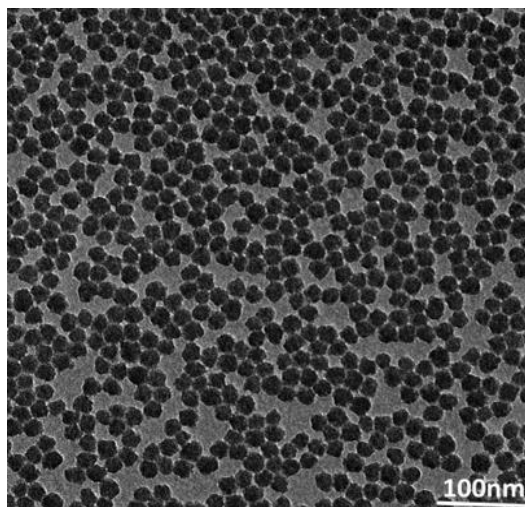
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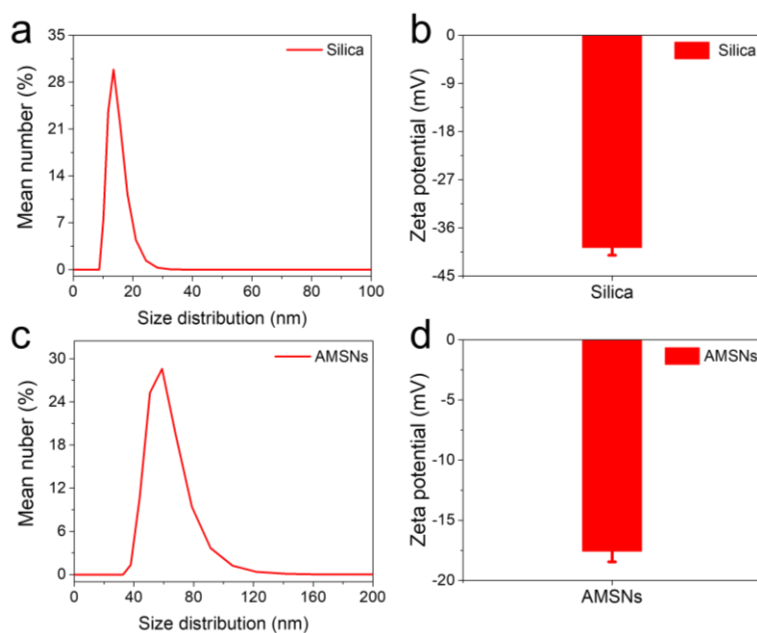
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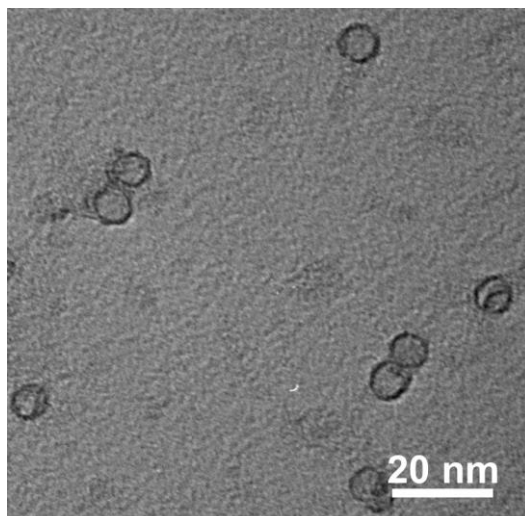
\*E-mail: lingds@zju.edu.cn



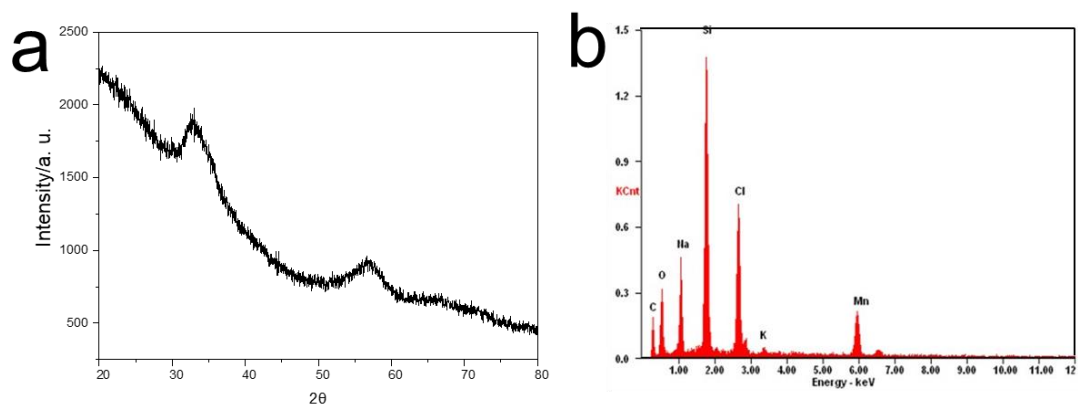
**Figure S1.** TEM image of silica nanoparticles.



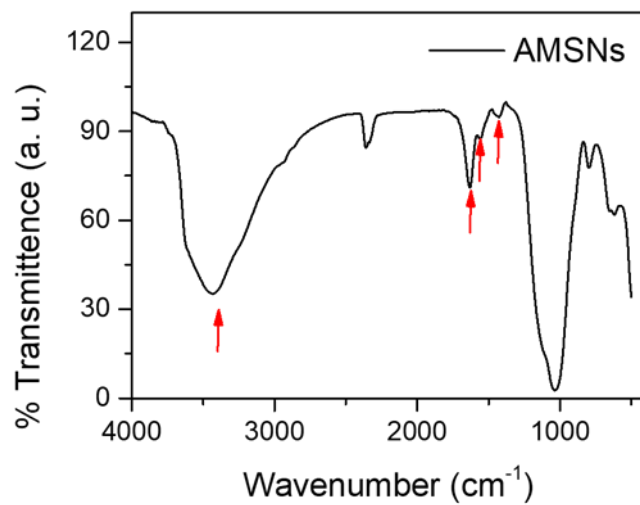
**Figure S2.** Size and zeta potential distributions of silica nanoparticles and AMSNs. Size distributions of silica nanoparticles (a) and AMSNs (c). Zeta potential values of the silica nanoparticles (b) and AMSNs (d).



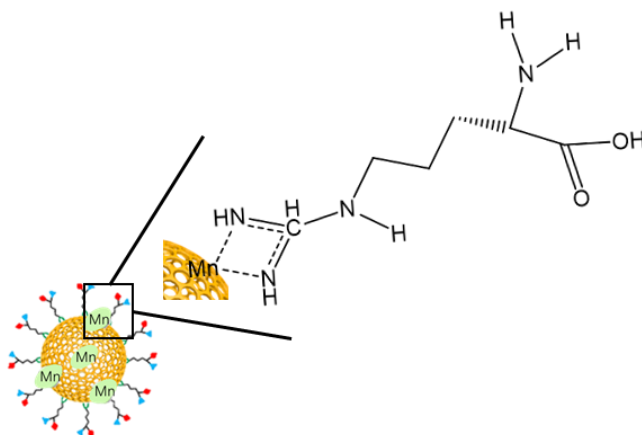
**Figure S3.** TEM image of monodispersed AMSNs.



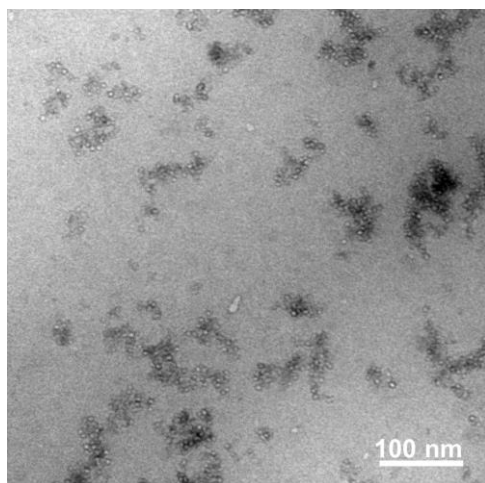
**Figure S4.** a) XRD pattern of AMSNs. b) EDX spectrum of AMSNs.



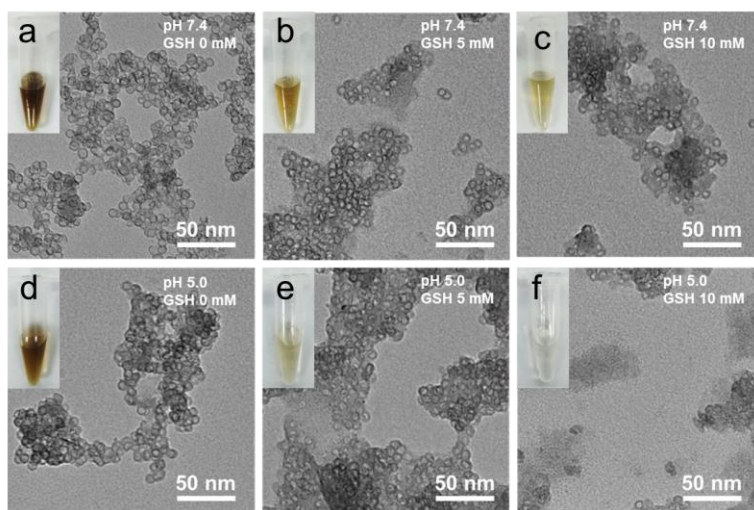
**Figure S5.** FTIR spectrum of AMSNs.



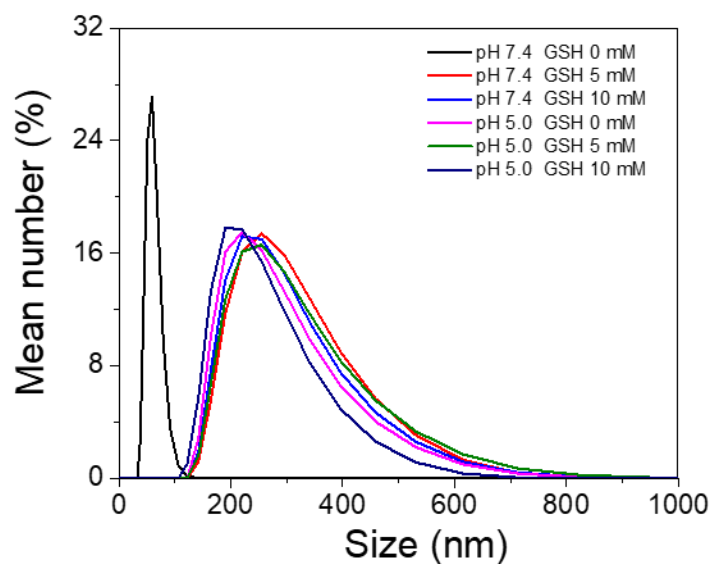
**Figure S6.** Schematic diagram of the chemical structure of arginine and its binding mode on the surface of AMSNs.



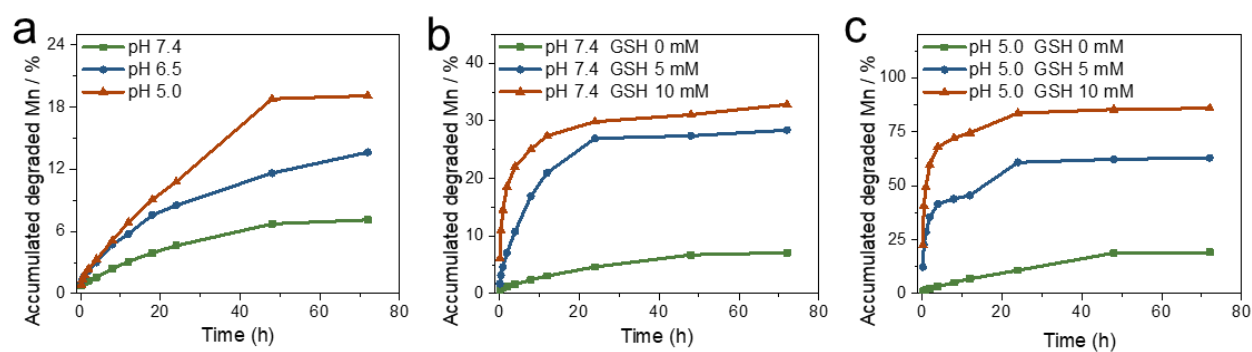
**Figure S7.** TEM image of AMSNs after incubation in blood serum for 24 h at room temperature.



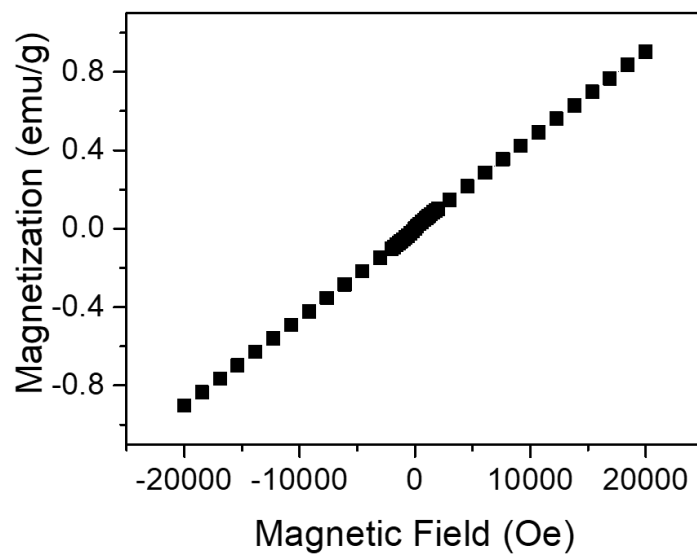
**Figure S8.** Photos and TEM images of AMSNs after incubation in buffers with different GSH concentrations (0, 5, and 10 mM) at pH 7.4 (a–c) and pH 5.0 (d–f).



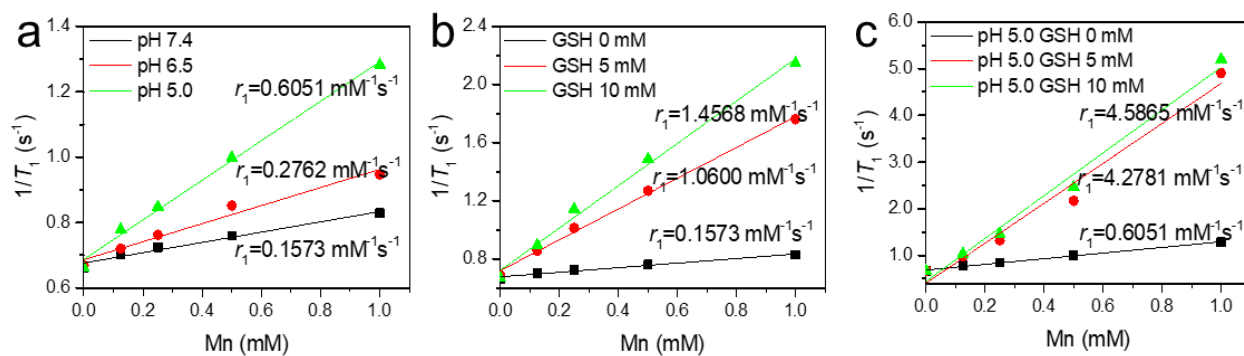
**Figure S9.** Size distribution of degraded AMSNs after incubation in buffers with different GSH concentrations at pH 7.4 and pH 5.0 for 12 h at 37°C.



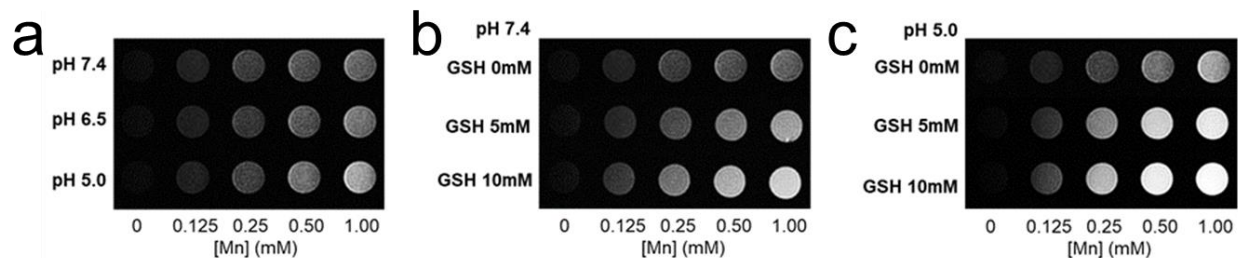
**Figure S10.** Accumulated release profiles of Mn ions in PBS for various pH values (7.4, 6.5, and 5.0) (a), different GSH concentrations (0, 5, and 10 mM) at pH 7.4 (b) and pH 5.0 (c).



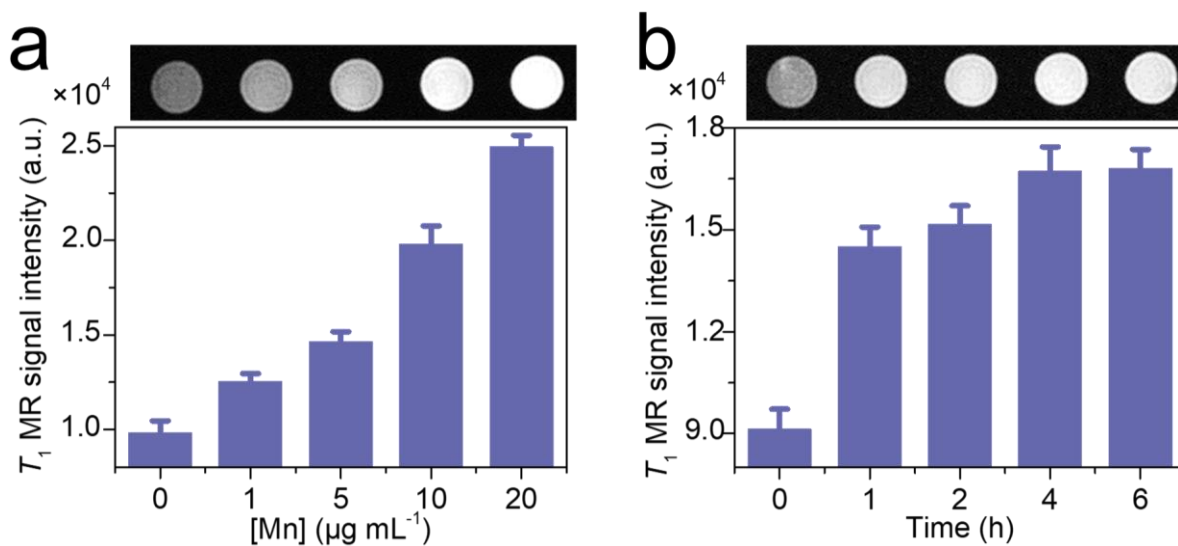
**Figure S11.** Magnetization curve of AMSNs.



**Figure S12.** Curves of  $\Delta 1/T_1$  versus the Mn concentration of AMSNs under different conditions, the slope indicates the specific relaxivity ( $r_1$ ).

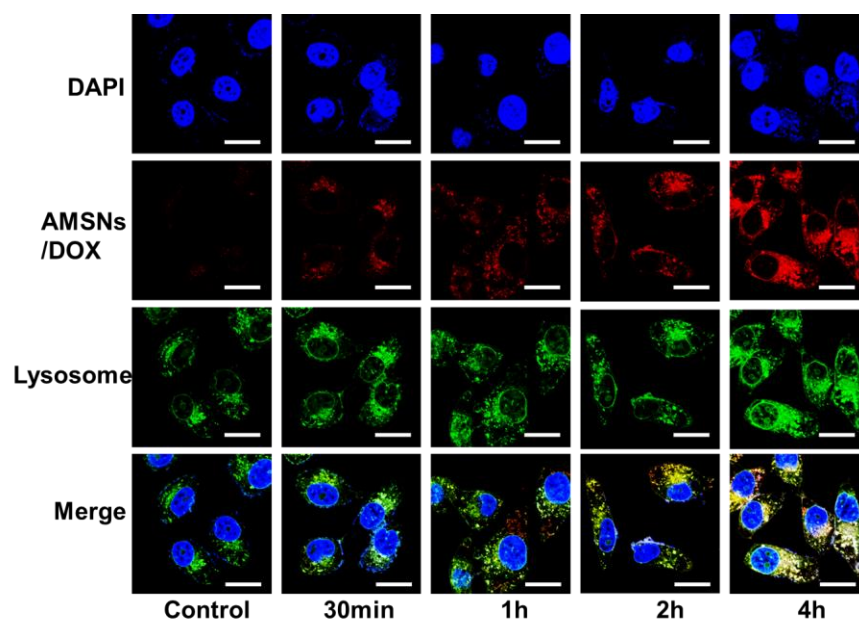


**Figure S13.**  $T_1$ -weighted MRI under different pH (a) and different GSH concentrations (0, 5, 10 mM) at pH 7.4 (b) and pH 5.0 (c).

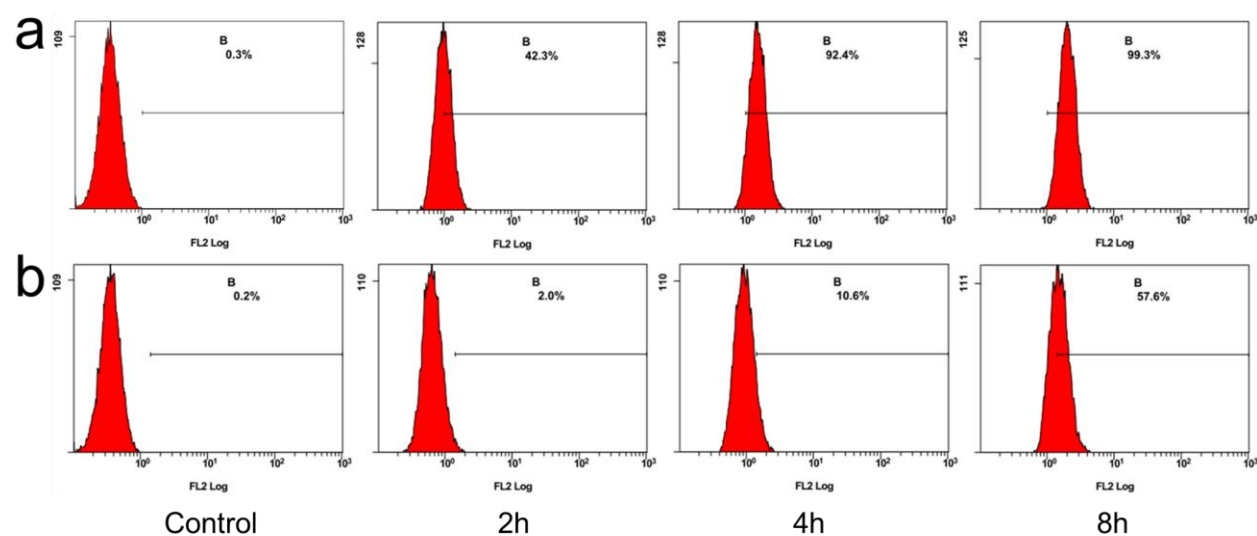


**Figure S14.** *In vitro* cell uptake behavior of AMSNs test by MRI. a)  $T_1$ -weighted MRI of Huh7 cells after incubation with AMSNs at different concentrations for 6 h. b)  $T_1$ -weighted MRI of Huh7 cells after incubation with 10  $\mu\text{g mL}^{-1}$  AMSNs for various time periods.

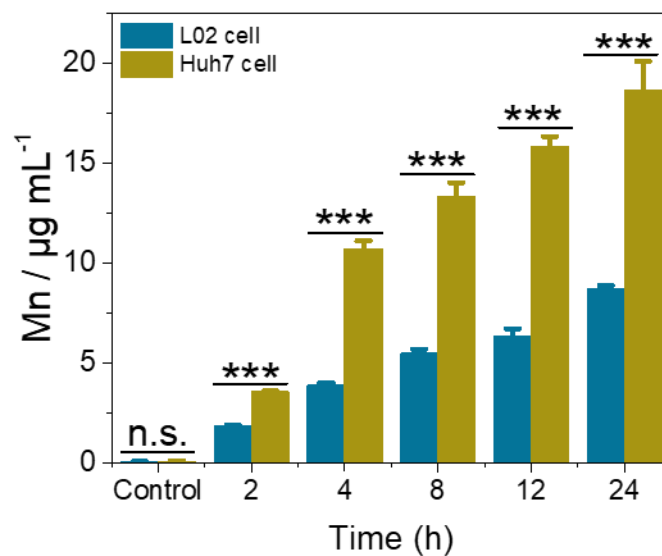




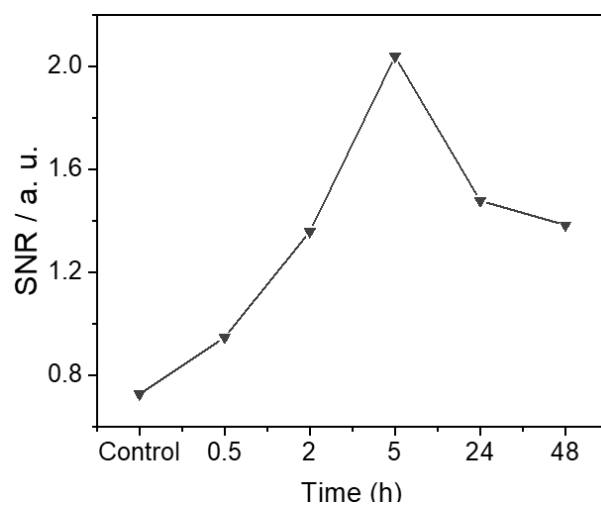
**Figure S15.** CLSM images of AMSNs localized to lysosomal networks in Huh7 cells. Scale bar: 20  $\mu\text{m}$ .



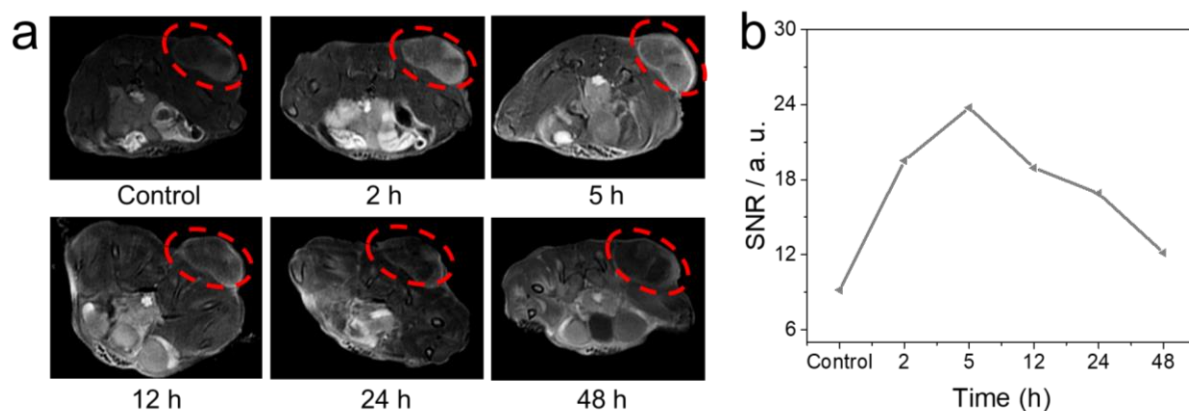
**Figure S16.** Flow cytometry results for cell uptake. Fluorescence intensity percentage of Huh7 cells (a) and L02 cells (b) after incubation with AMSNs/DOX for 0, 2, 4, and 8 h.



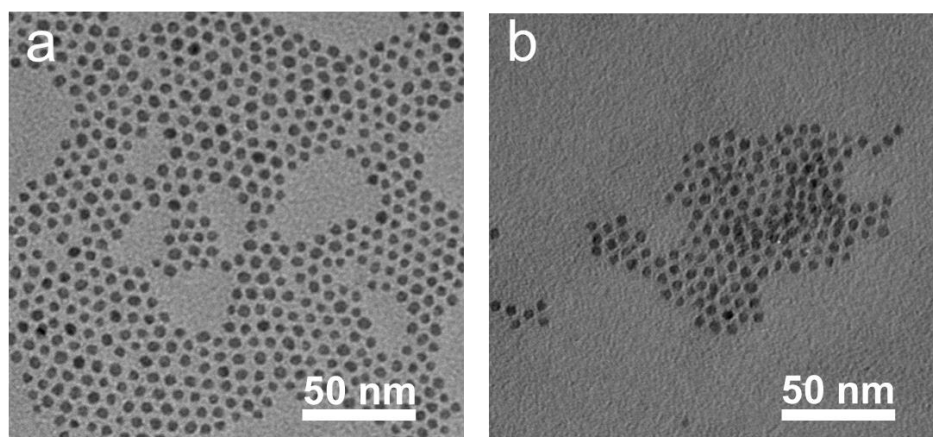
**Figure S17.** Cell uptake analysis by ICP-MS.



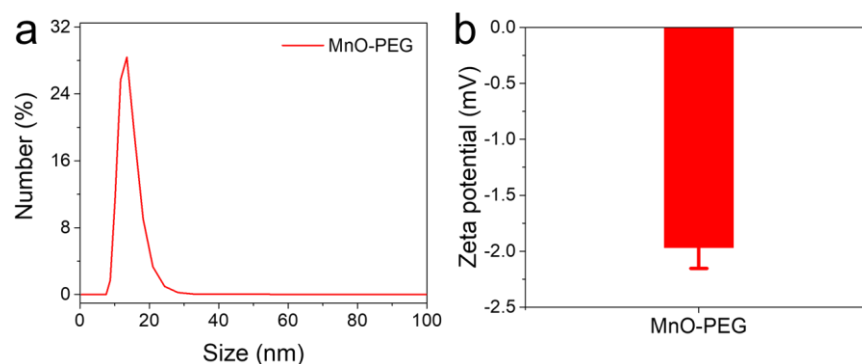
**Figure S18.** Quantitative signal-to-noise ratio (SNR) intensity at the tumor site corresponding to figure 3c.



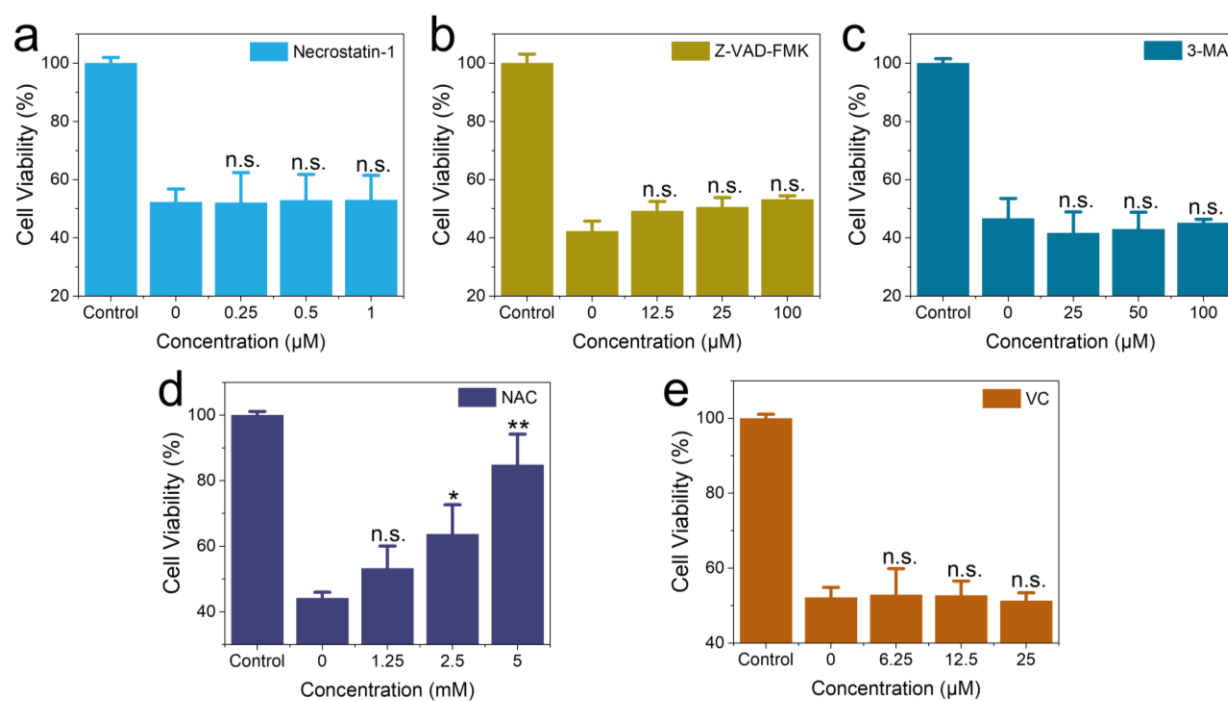
**Figure S19.** *In vivo*  $T_1$ -weighted MRI of Huh7 tumor-bearing mice after the intravenous administration of AMSNs for different time periods (a) and the quantitative signal-to-noise ratio (SNR) intensity at the tumor site (b) ( $B_0=3.0T$ ).



**Figure S20.** TEM images of MnO nanoparticles before (a) and after (b) being transferred to aqueous solutions.



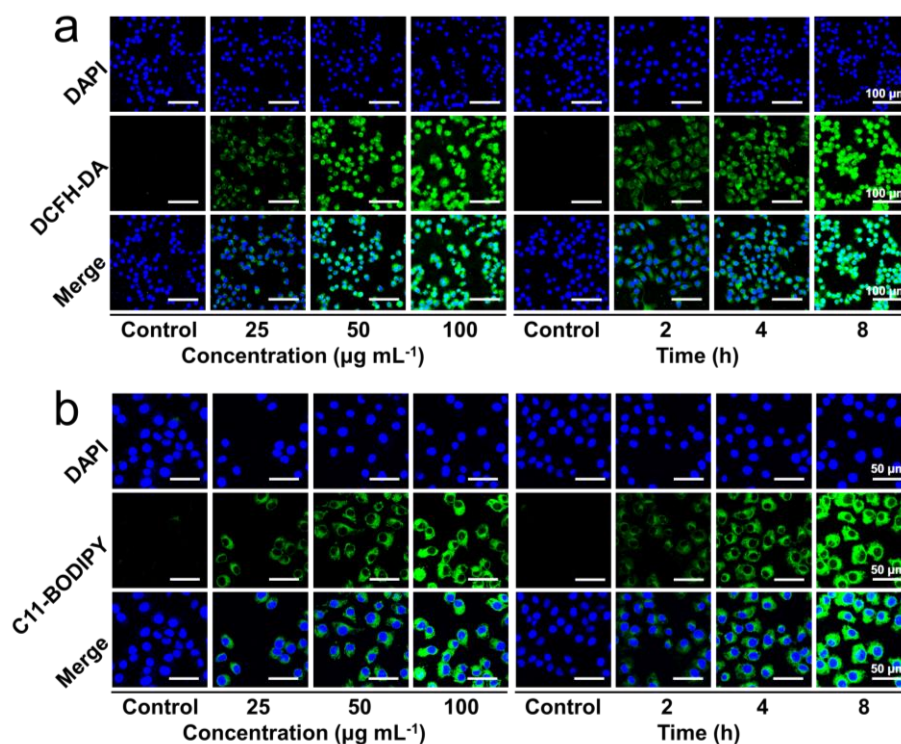
**Figure S21.** Size distribution (a) and zeta potential (b) of 5 nm MnO-PEG dispersed in aqueous solution.



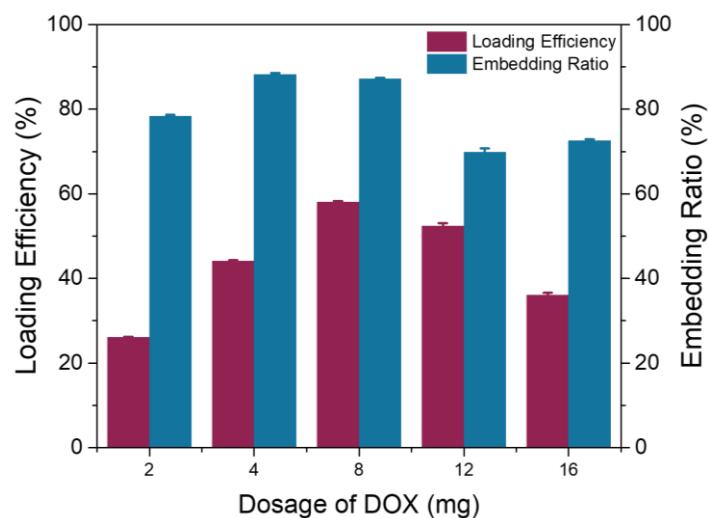
**Figure S22.** The cell viability of Huh7 cells treated with AMSNs and a) Necrostatin-1, b) Z-VAD-FMK, c) 3-MA, d) NAC, and e) VC.



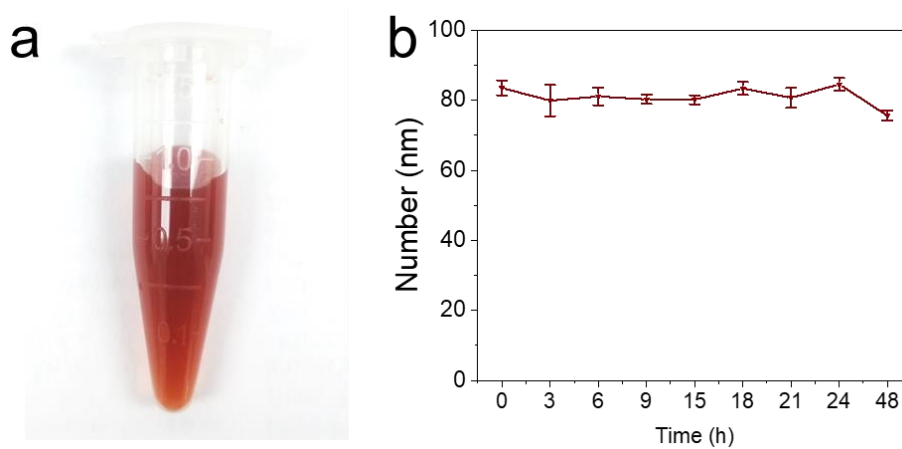
**Figure S23.** Knockdown and overexpression of GPX4 in Huh7 cells. Scr: Scramble siRNA; EV: Empty vector; GPX4-OE: GPX4 over-expression.



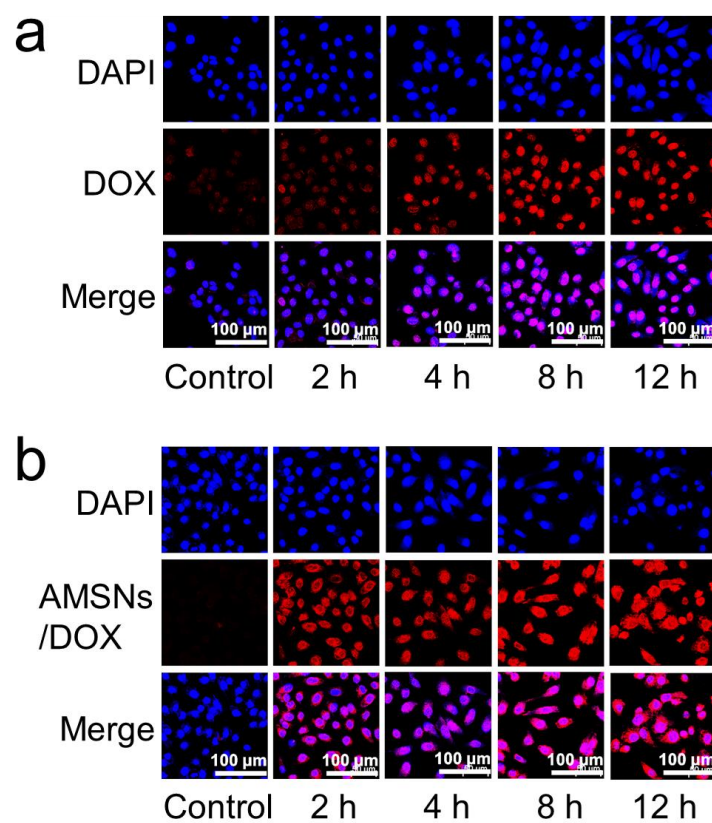
**Figure S24.** a) DCFH-DA assay of Huh7 cells treated with AMSNs. Scale bar: 100 μm. b) Lipid peroxides of Huh7 cells stained with C11-BODIPY<sup>581/591</sup> after co-incubation with AMSNs. Scale bar: 50 μm.



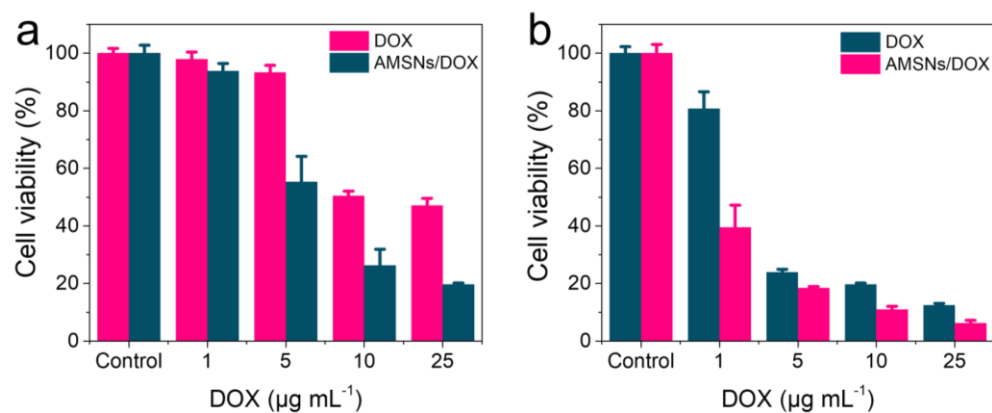
**Figure S25.** DOX loading efficiency and embedding ratio of AMSNs.



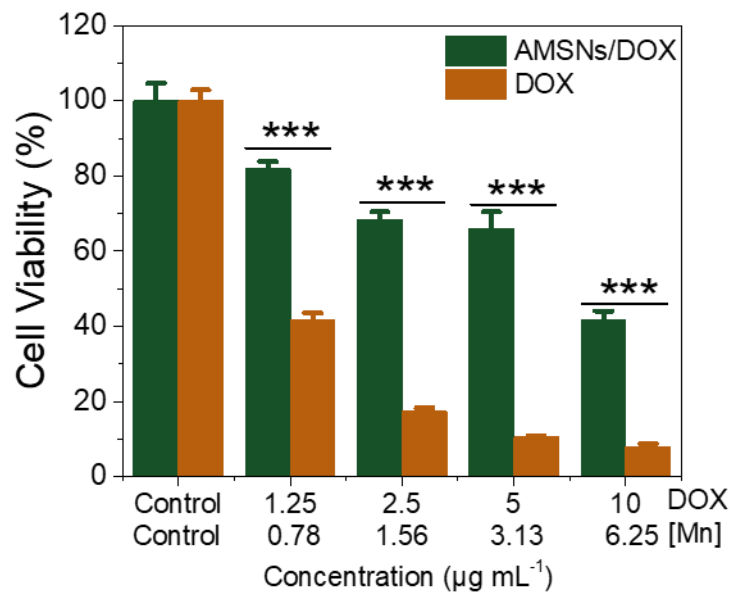
**Figure S26.** The stability of AMSNs/DOX in aqueous solution. a) Photo of AMSNs/DOX disperse in aqueous solution with a DOX concentration of  $0.5 \text{ mg mL}^{-1}$ . b) DLS profile of AMSNs/DOX in aqueous solutions for 2 days.



**Figure S27.** CLSM images of Huh7 cells after incubation with free DOX (a) and AMSNs/DOX (b) for various times periods.

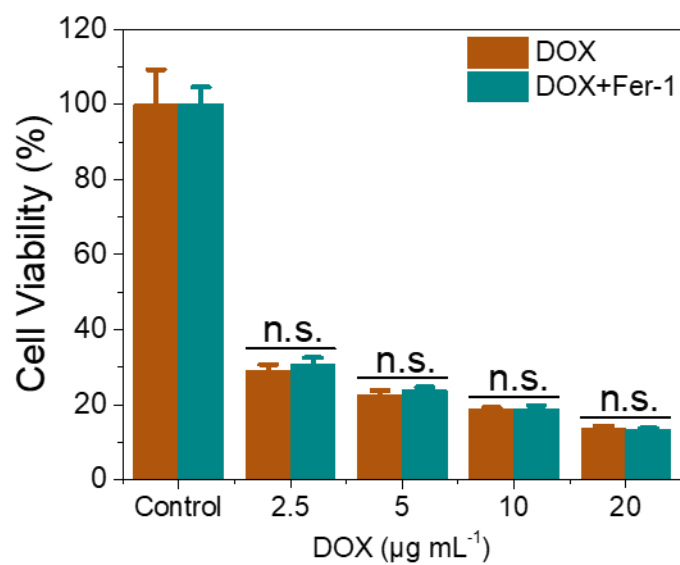


**Figure S28.** Cytotoxicity of AMSNs/DOX and free DOX against Huh7 cells after incubation for 24 (a) and 48 h (b).

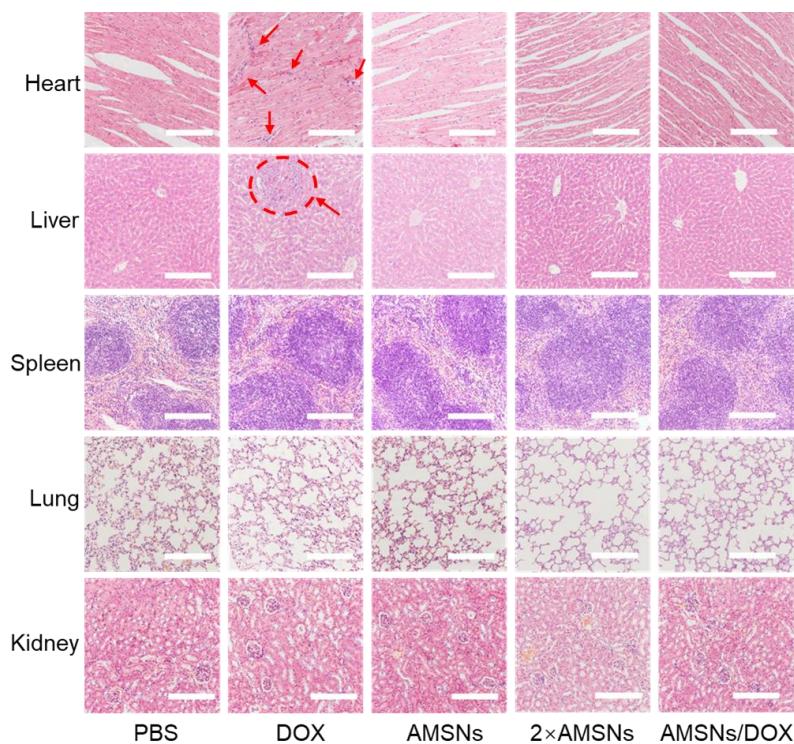


**Figure S29.** Cytotoxicity of free DOX and AMSNs/DOX.

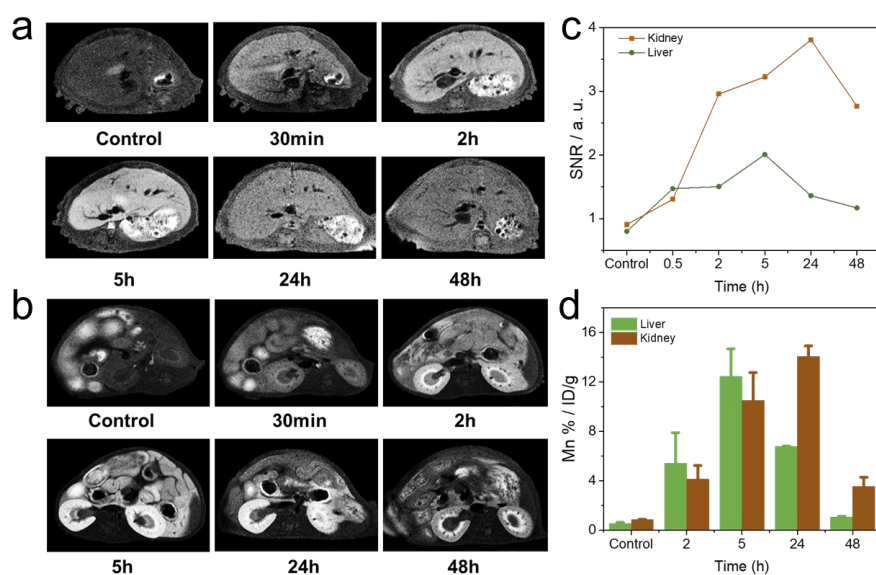




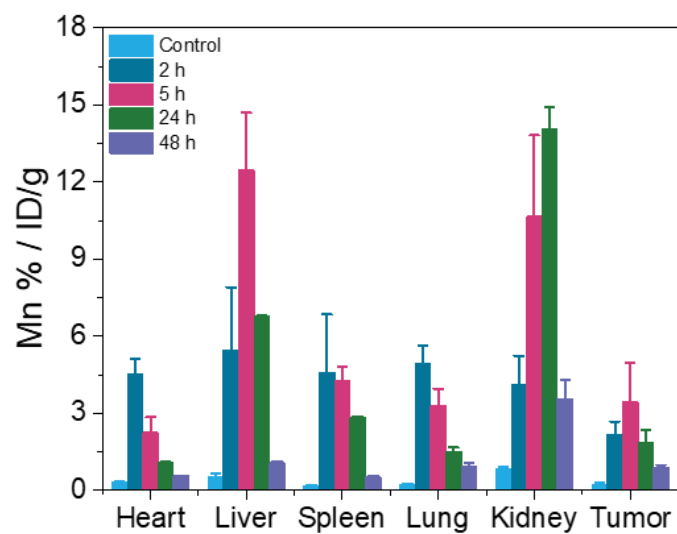
**Figure S30.** Cytotoxicity of free DOX and DOX+Fer-1.



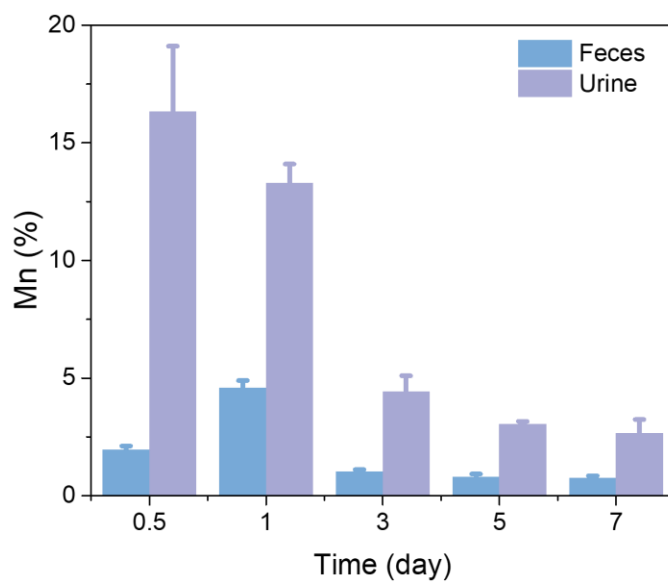
**Figure S31.** Histopathological examination of the main organs after various treatments (scale bar: 200 µm).



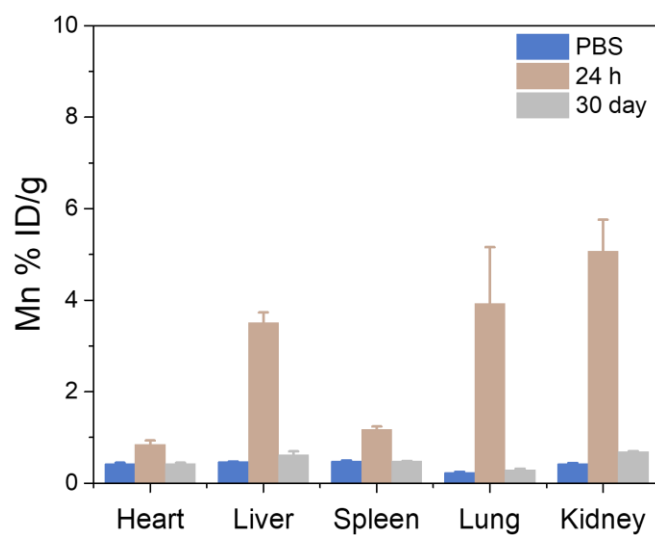
**Figure S32.** *In vivo*  $T_1$ -weighted MRI and bio-distribution of AMSNs after intravenous injection. a-b) *In vivo*  $T_1$ -weighted MRI of mouse liver (a) and kidney (b) obtained at different time points after intravenous administration of AMSNs. c) Temporal change of SNR at liver and kidney sites corresponding to (a) and (b). d) Bio-distribution of AMSNs after intravenous administration of AMSNs for different time points.



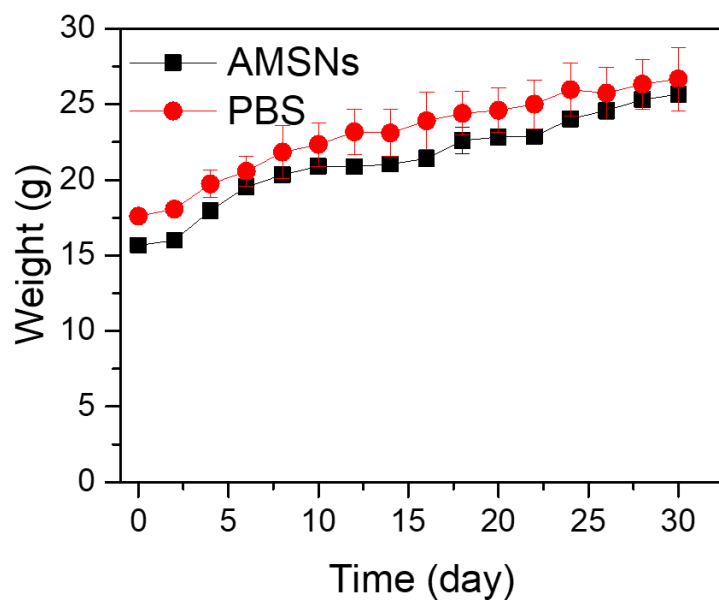
**Figure S33.** *In vivo* distributions of Mn ions after intravenous administration of AMSNs into tumor-bearing mice for different time points.



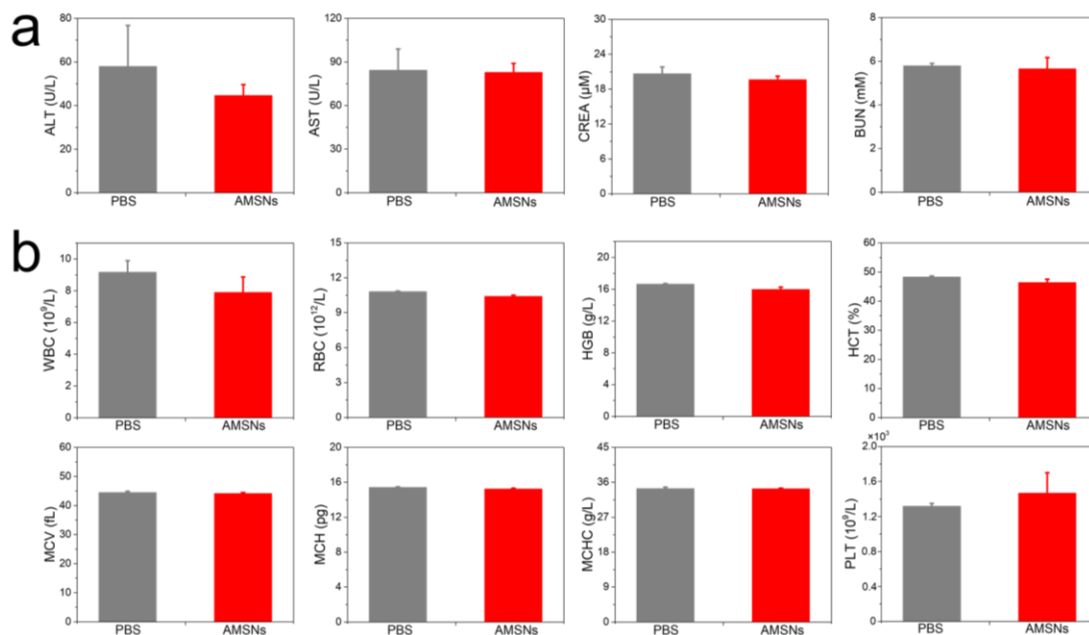
**Figure S34.** Mn excreted *via* urine and feces of the mice after intravenous injection of AMSNs measured at different time points.



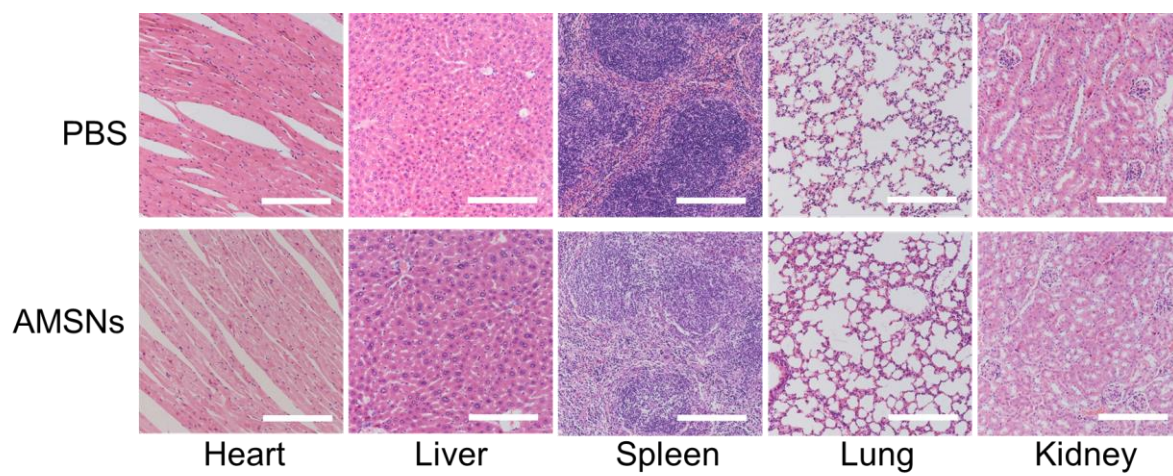
**Figure S35.** *In vivo* distributions of Mn ions 1 d and 30 d after intravenous administration of AMSNs or PBS.



**Figure S36.** Body-weight changes of the mice during 30 d after injection of PBS or AMSNs.



**Figure S37.** Hematology analysis of AMSNs and PBS treated for 30 d after the treatment. a) Biochemical blood analysis of PBS- and AMSNs-treated mice at 30 d post-injection. The terms include alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urine nitrogen (BUN), and creatinine (CREA). b) Hematological indices of mice following intravenous administration of PBS or AMSNs at 30 d post-injection. The results show the means and standard deviations of white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets (PLT).



**Figure S38.** Histopathological examination of the main organs 30 d after intravenous injection of AMSNs (scale bar: 200  $\mu\text{m}$ ).