Supporting Information

In Vivo Tumor Vasculature Targeting of CuS@MSN Based Theranostic Nanomedicine

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Supplementary Figures

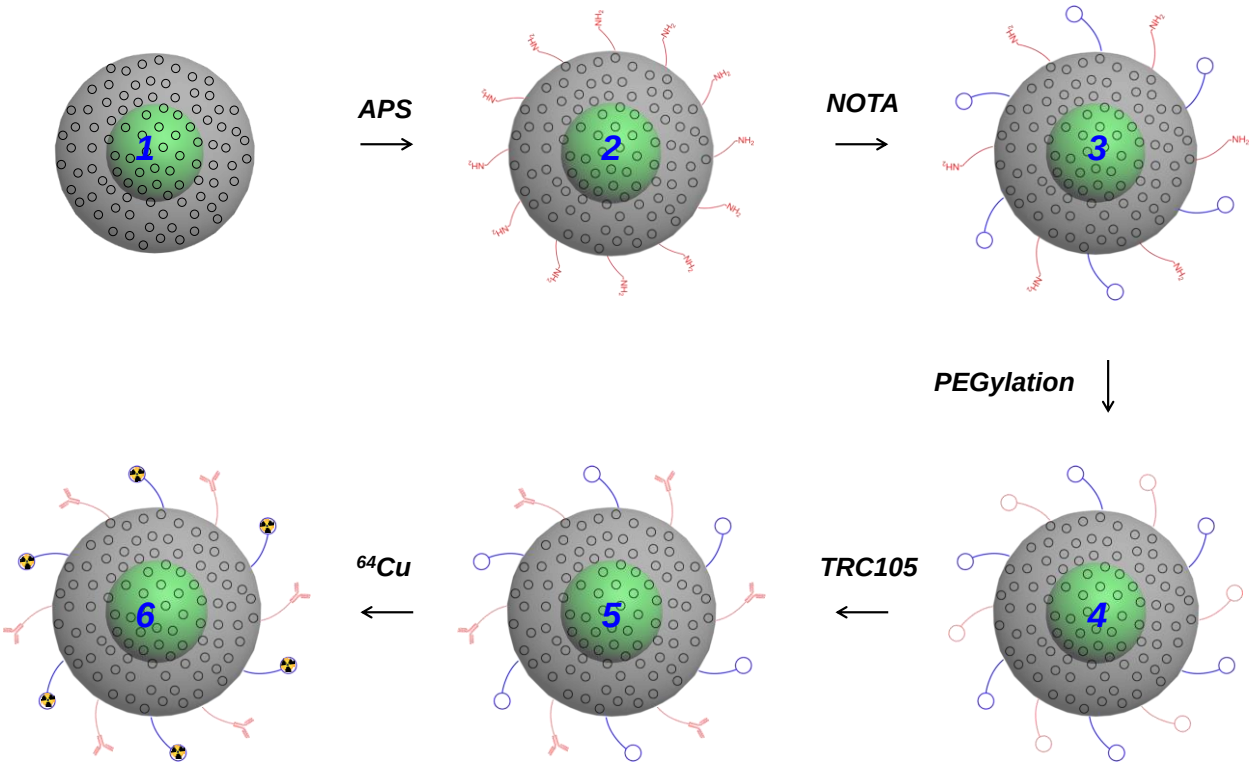

Figure S1. Surface engineering of ^{64}Cu-CuS@MSN-TRC105. As-synthesized CuS@MSN (**1**) was first surface modified with (3-Aminopropyl)triethoxysilane (APS) to form amino groups conjugated CuS@MSN-NH_2 (**2**) before further bio-conjugations. p-SCN-Bn-NOTA, a well-known ^{64}Cu chelator, was then conjugated to form NOTA-CuS@MSN-NH_2 (**3**). Afterward, nanoconjugate was PEGylated with SCM-PEG_{5k}-Mal to render its stability in biological buffers (e.g. PBS), forming NOTA-CuS@MSNPEG_{5k}-Mal (**4**). Then, thiolated anti-CD105 antibody (i.e. TRC105-SH) was conjugated to the nanoparticle to obtain NOTA-CuS@MSN-PEG_{5k}-TRC105 (**5**). Lastly, PET isotope ^{64}Cu ($t_{1/2}$=12.7 h) was used to label the nanoparticle, forming ^{64}Cu-NOTA-CuS@MSN-PEG_{5k}-TRC105 (**6**), or short for ^{64}Cu-CuS@MSN-TRC105 for clarity considerations.

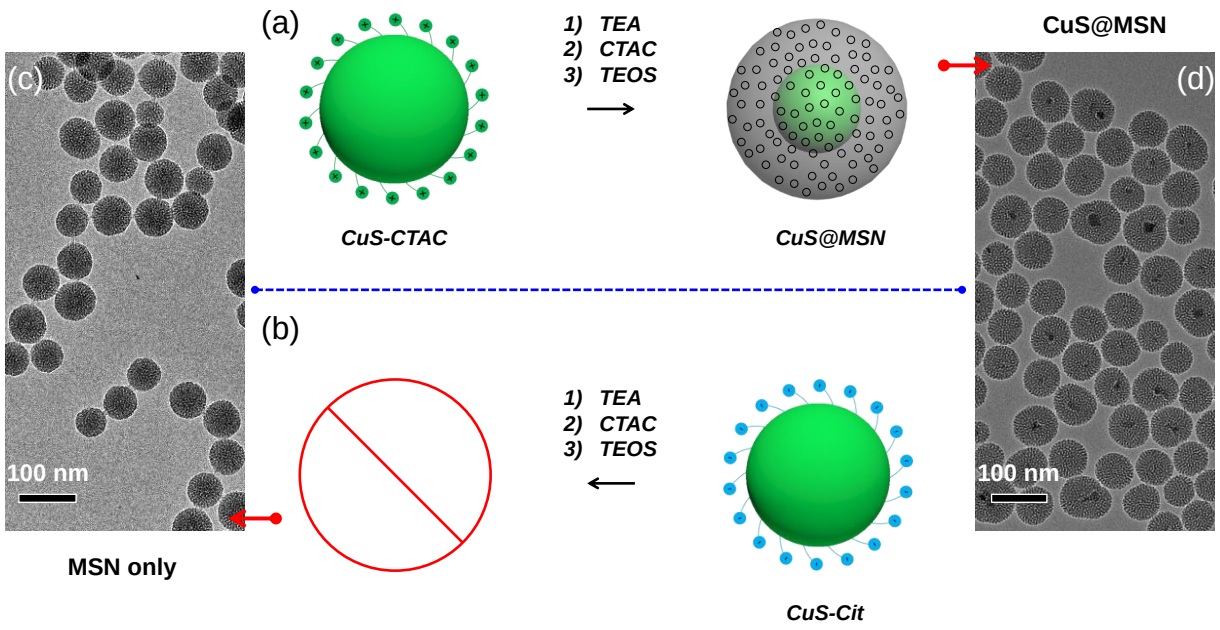

Figure S2. Impact of surface charge on the synthesis of CuS@MSN. Schematic illustrations showing the synthesis of CuS@MSN starting from CTAC-capped CuS nanoparticles (**a**) and sodium citrate capped CuS (**b**). Corresponding TEM images of CuS@MSN synthesized by using two different protocols.

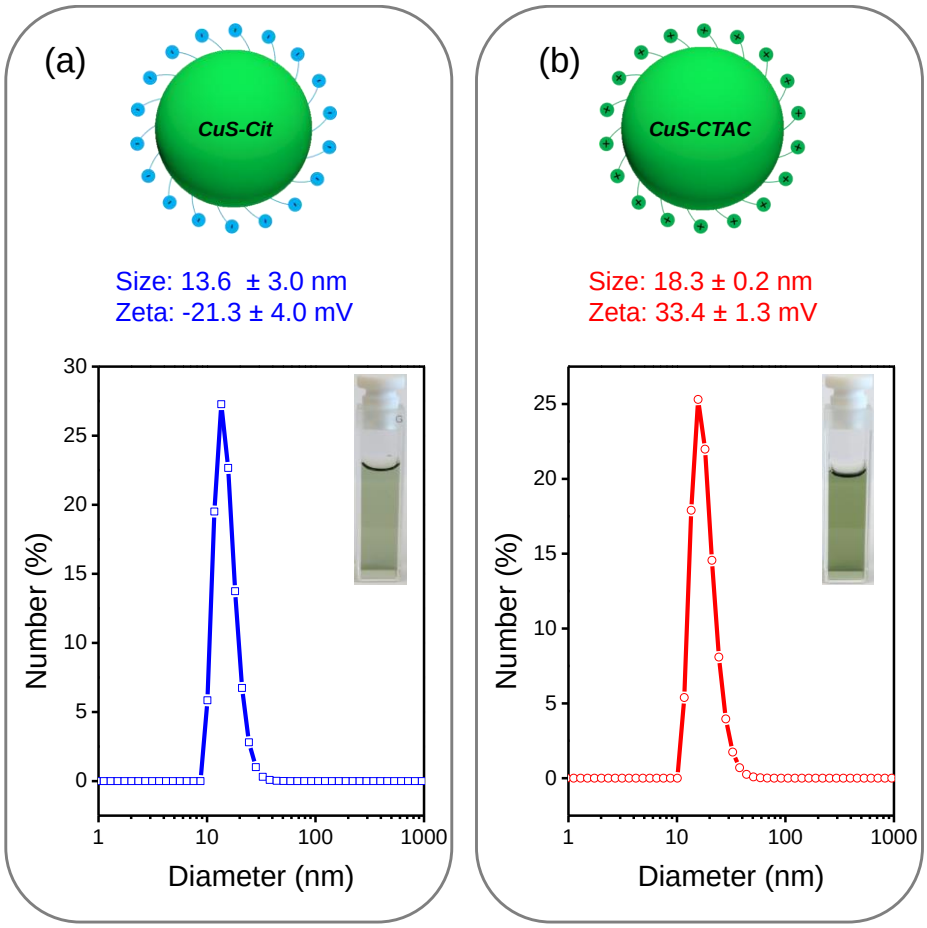

Figure S3. Dynamic light scattering (DLS) and zeta potential measurements of CuS-Cit (**a**) abd CuS-CTAC (**b**).

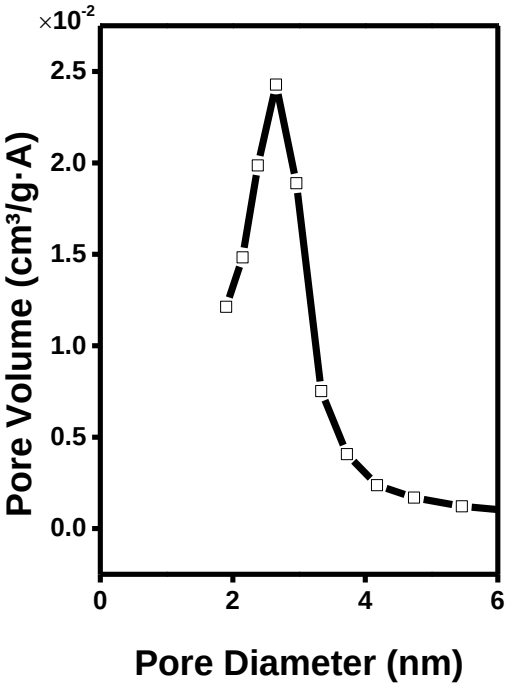

Figure S4. Corresponding pore size distribution of CuS@MSN.

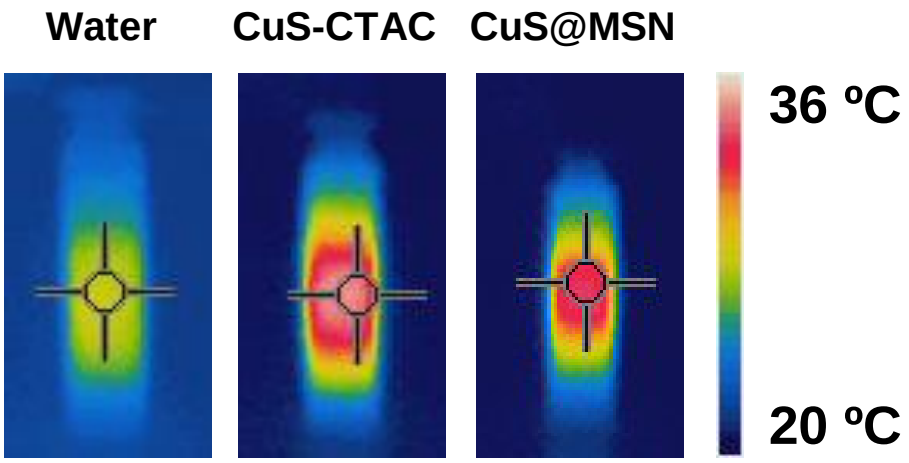

Figure S5. Photothermal images of water, CuS-CTAC and CuS@MSN (from left to right).

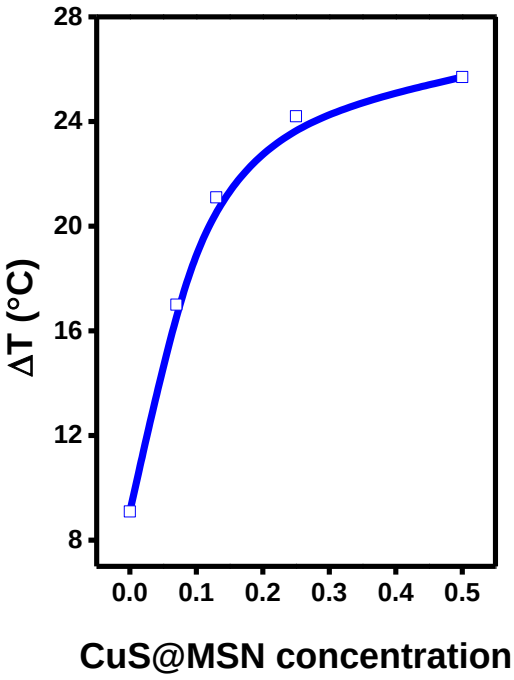

Figure S6. Increased temperature for samples with varied CuS@MSN concentrations.

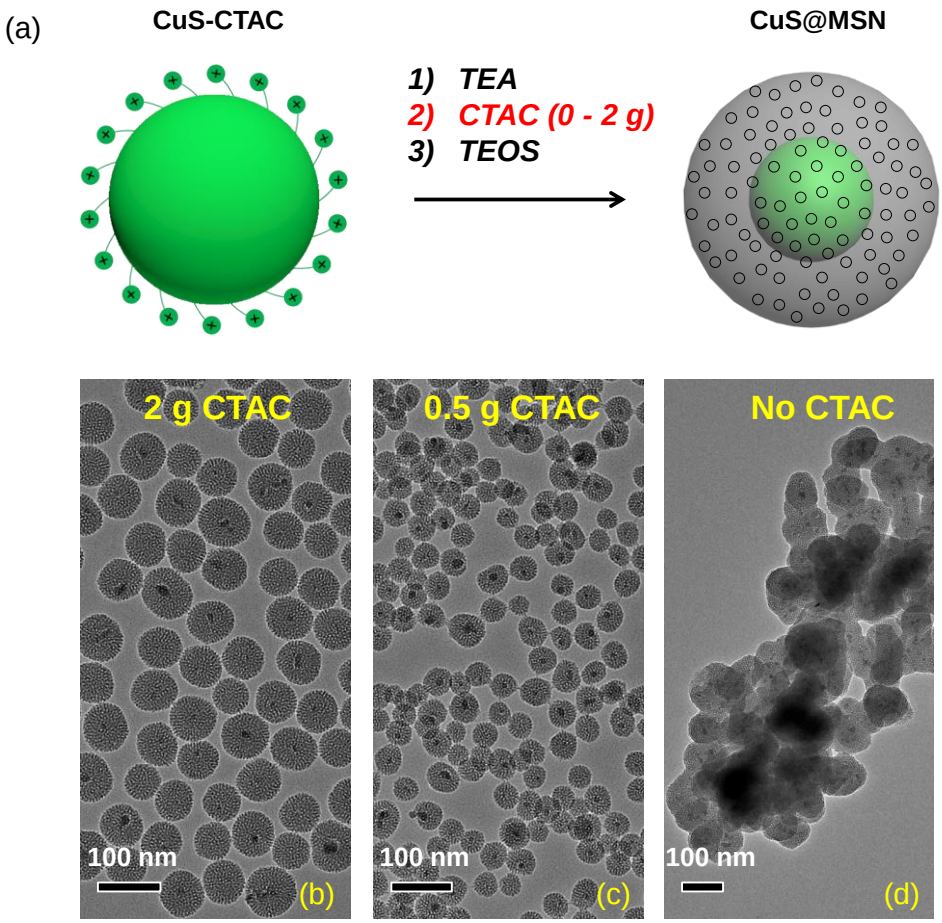

Figure S7. Impact of extra CTAC amount on the morphology, size, yield and monodispersity of CuS@MSN. (**a**) A schematic illustration showing the synthesis of CuS@MSN. TEM images of CuS@MSN synthesized by additionally adding 2 g CTAC (**b**), 0.5 g CTAC (**c**) and no extra CTAC (**d**).

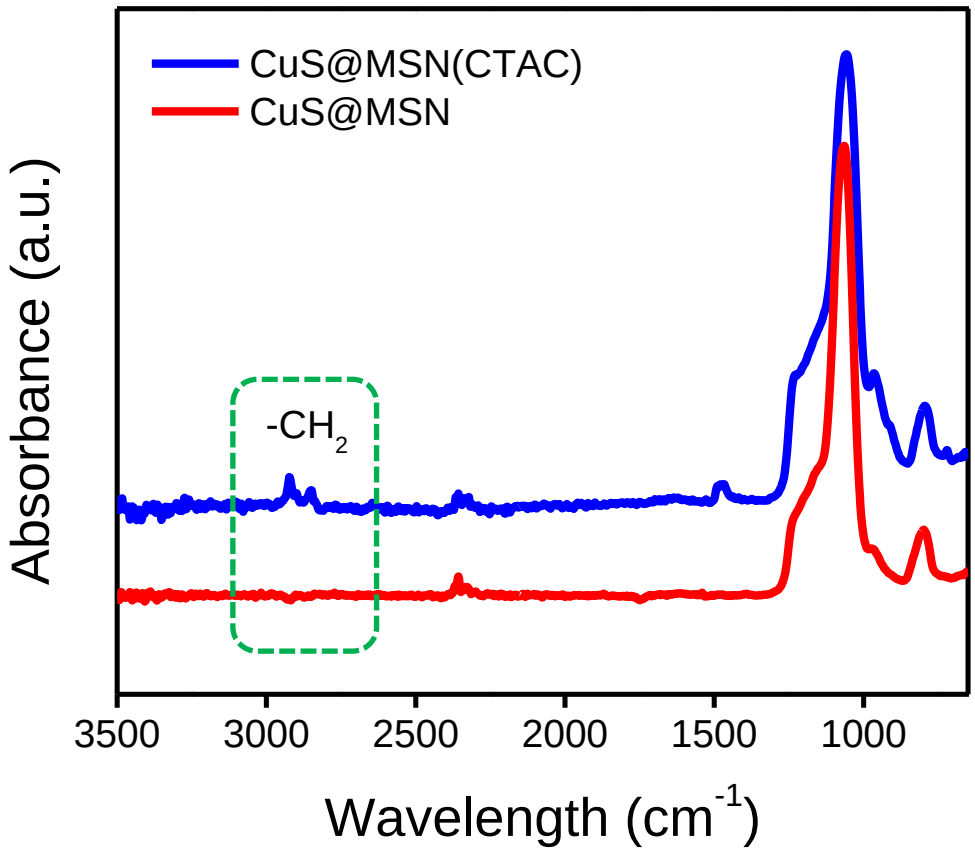

Figure S8. Fourier transform infrared spectroscopy spectra of CuS@MSN before (*blue line*) and after (*red line*) the removal of surfactant CTAC. The successful removal of CTAC was evidenced by the absence of characteristic C-H peak in the 3000 ~ 2800 cm^{-1} wavelength range for surfactant-extracted sample.

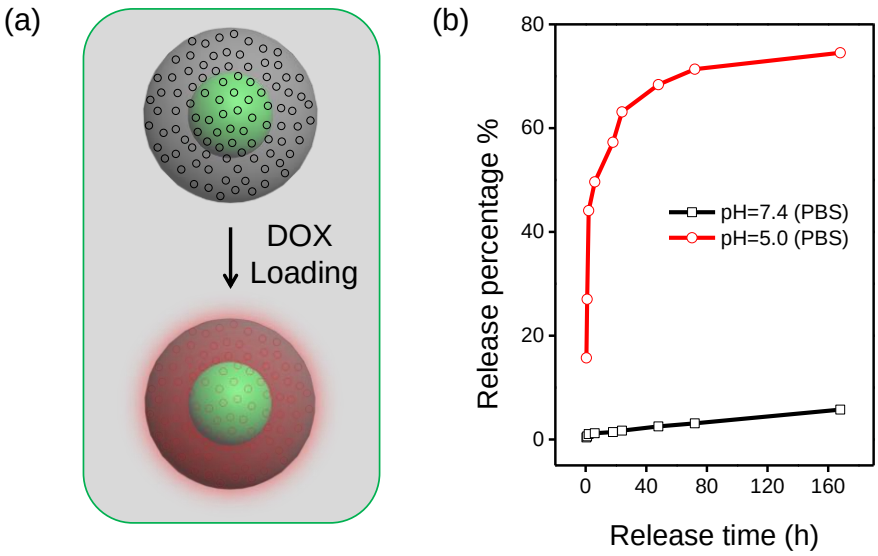

Figure S9. Anti-cancer drug loading and releasing of CuS@MSN. (**a**) A schematic illustration showing the loading of DOX in CuS@MSN. CuS@MSN with a known mass (0.6 mg) was re-suspended in 0.5 mg/mL of DOX-PBS solution (total amount of DOX was 0.3 mg). The mixture was kept under constant shaking for 24 h at room temperature. The DOX loading capacity was found to be 465.1 mg/g. (**b**) The DOX releasing profiles of CuS@MSN(DOX) under different pH conditions (pH 5.0 and pH 7.4) over 7 days in PBS.

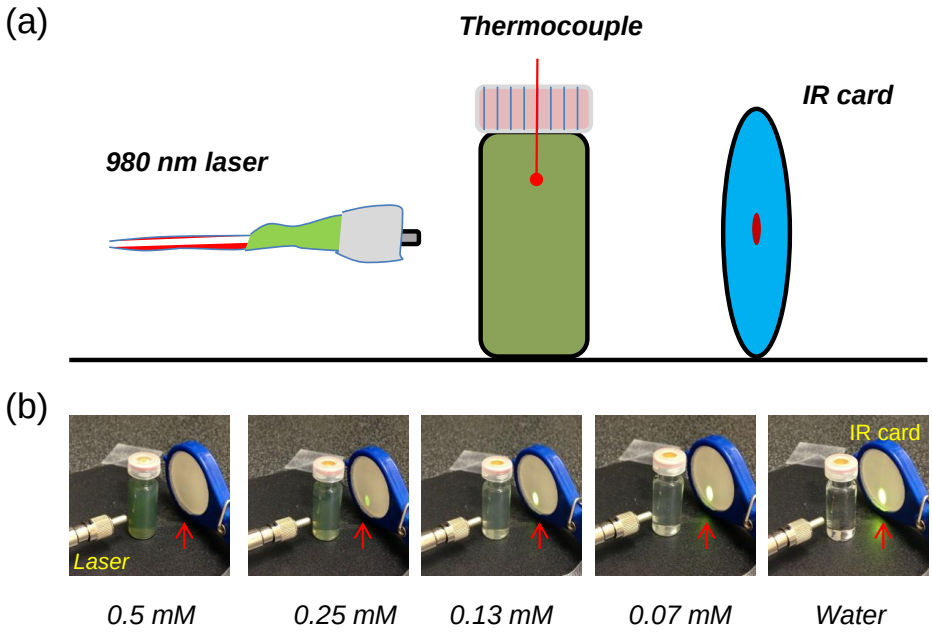

Figure S10. ***In vitro*** **photothermal effect study.** (**a**) A schematic illustration showing the setup for quantitative photothermal effect study. (**b**) Digital photos showing the absorbance of 980 nm light by CuS@MSN nanoparticles with varied concentrations ranging from zero to 0.5 mM.

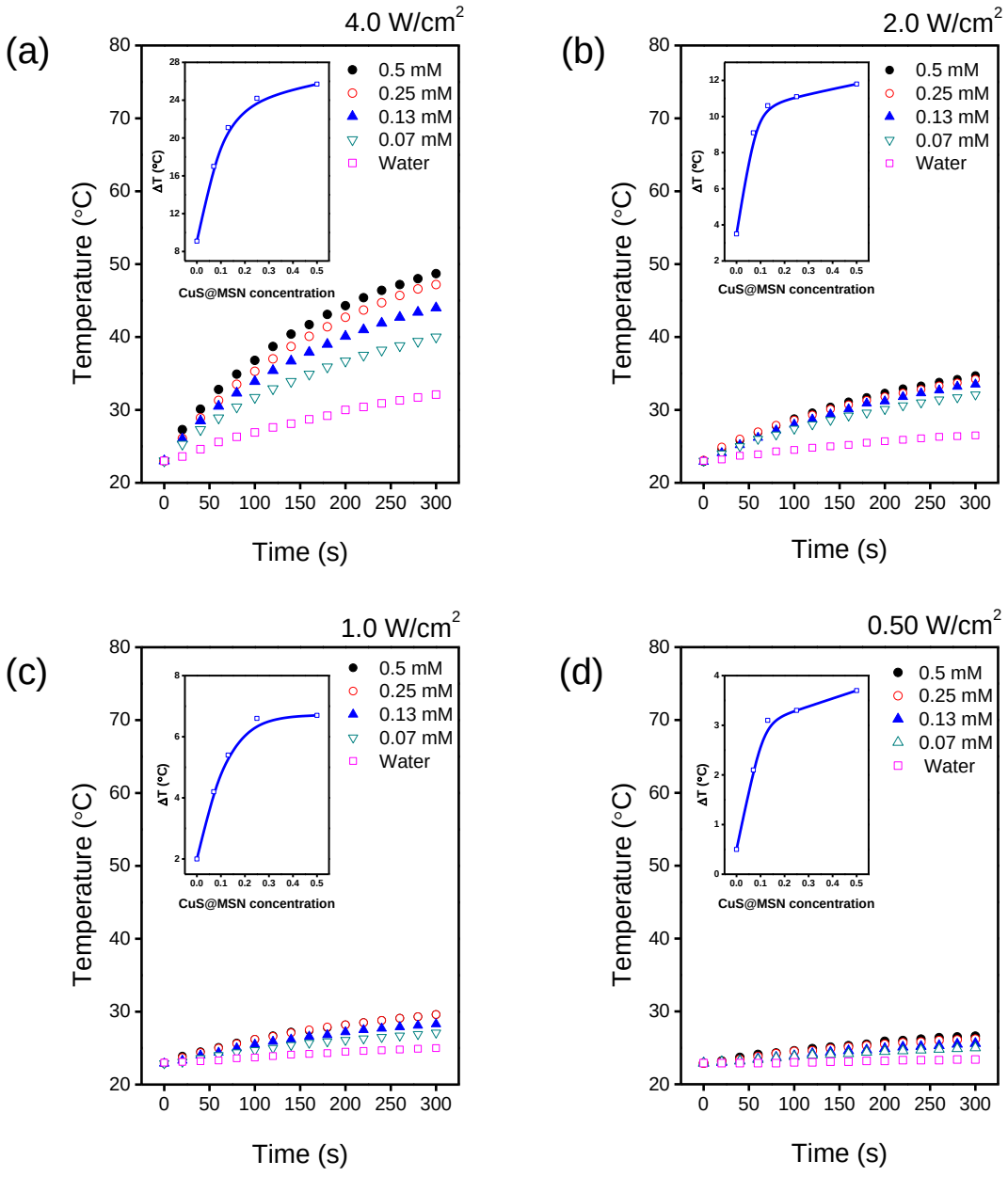

Figure S11. Photothermal effect study. Quantitative temperature change of CuS@MSN aqueous solution as a function of 980 nm laser exposure time with varied laser power density (from 0.5 to 4.0 W/cm^2). Inset shows the increased temperature for samples with varied CuS@MSN concentrations.

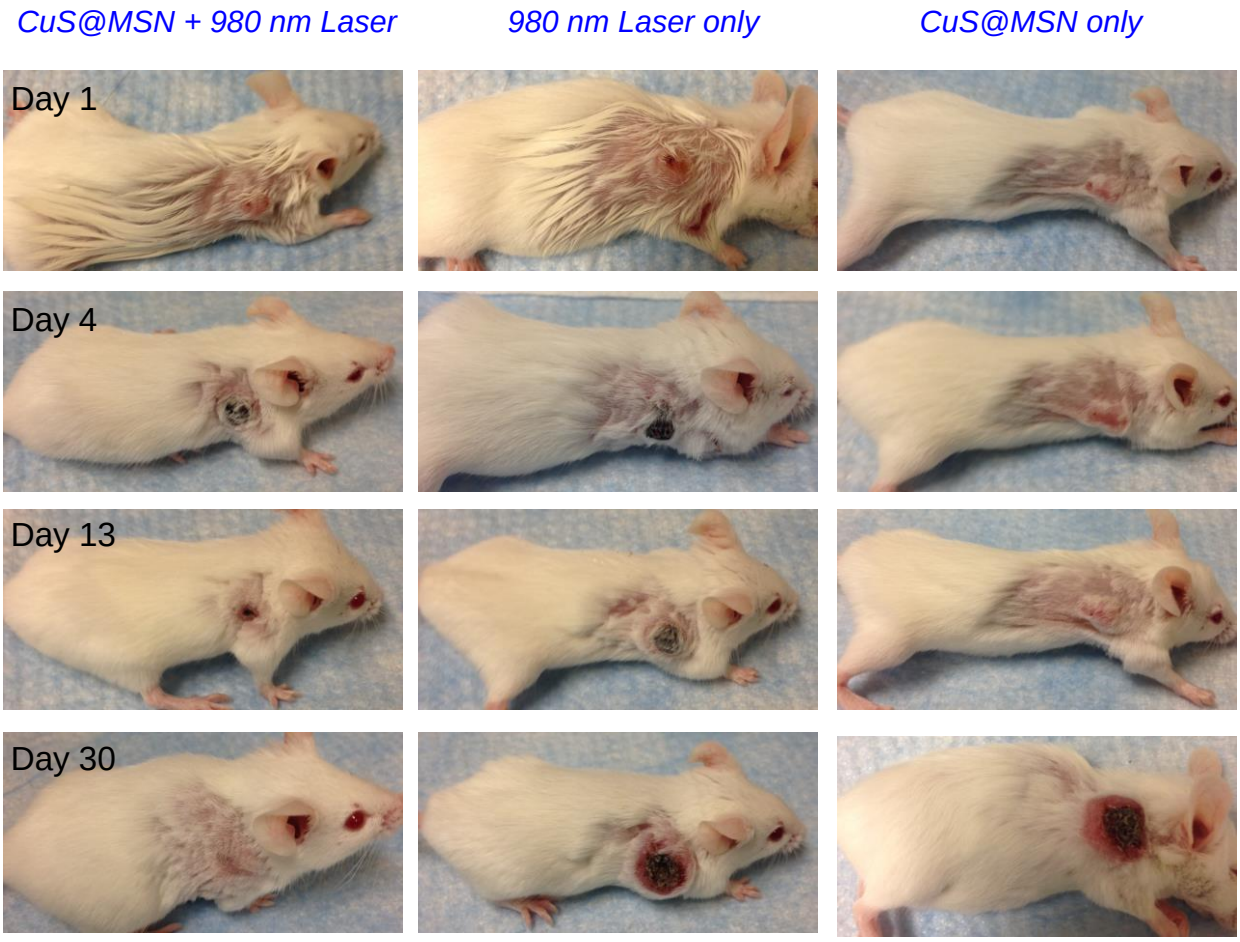

Figure S12. *In vivo* photothermal ablation evaluation. Digital photos of mice from 3 different groups after treatment. Left: *(CuS@MSN+980 nm laser)* group; Middle: *(980 nm laser only)* group; Right: *(CuS@MSN only)* group. CuS@MSN nanoparticles were intra-tumorally injected into 4T1 tumor-bearing mice at a dose of 33 mg/kg (n=5/group). Laser dose: 4.0 W/cm^2, 15 min (every 5 min a break).

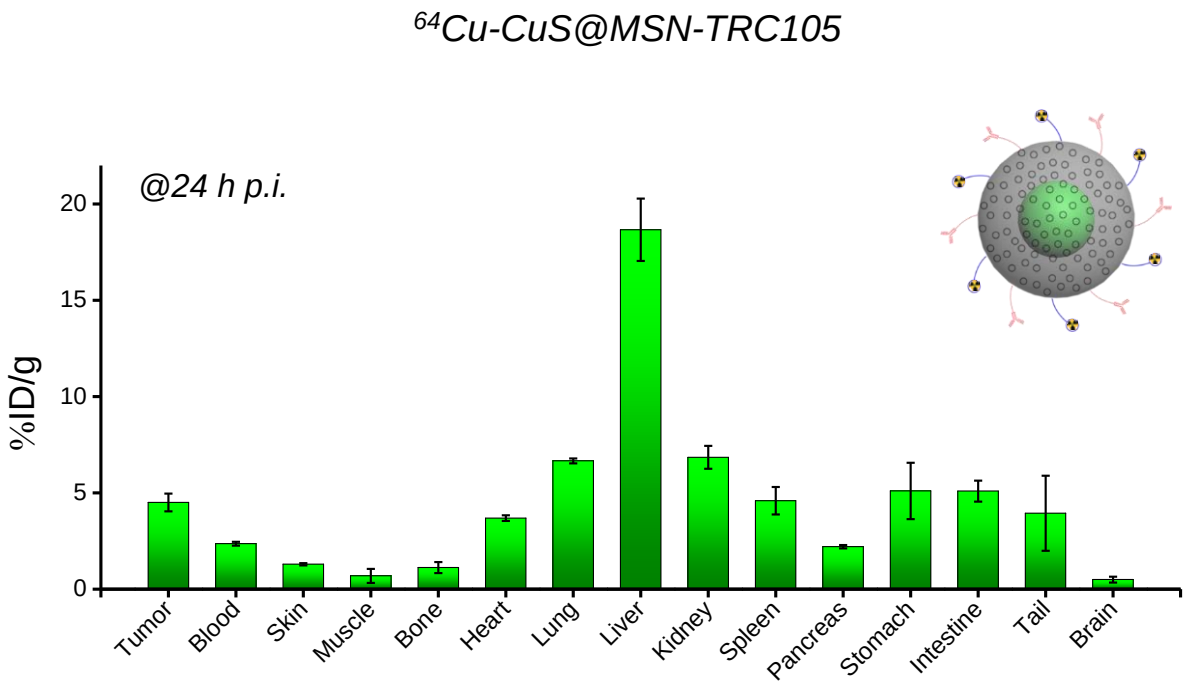

Figure S13. Biodistribution of ^{64}Cu-CuS@MSN-TRC105 at 24 h post-injection (dose: ~1 mg/kg; n=3).