Supporting Information

808 nm Near-Infrared Light Controlled Dual-Drug Release and Cancer Therapy in vivo by Upconversion Mesoporous Silica Nanostructures

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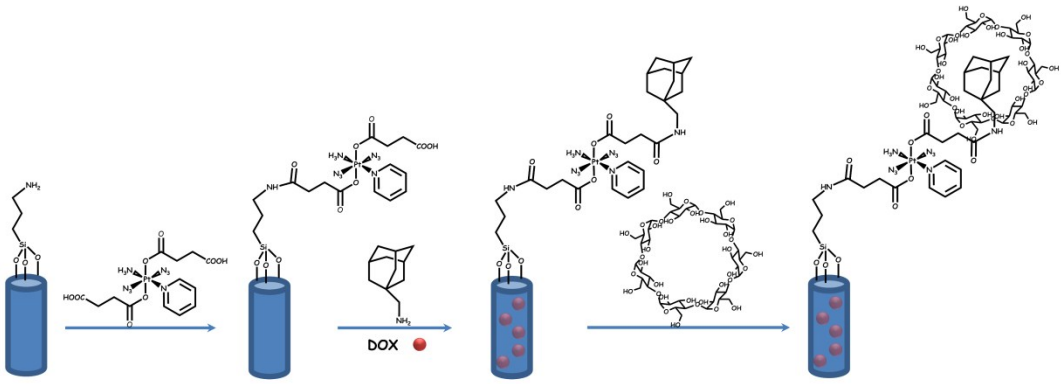
Chemicals and materials: The rare earth oxides of Y_2O_3, Gd_2O_3, Nd_2O_3, Yb_2O_3 and Tm_2O_3 (99.999%) were purchased from Science and Technology Parent Company of Changchun Institute of Applied Chemistry. Aminopropyltriethoxysilane (APTES), octadecene (ODE, 90%, technical grade), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), N-hydroxysuccinimide (NHS), ammonium fluoride, trifluorocaetic acid, hydroxide (H_2O_2) (30% in H_2O), Methanol, $AgNO_3$, oleic acid, cyclohexanone and NaN_3 were purchased from Beijing Chemical Regent Co., Ltd.. Tetraethylorthosilicate (TEOS), cetyltrimethylammonium bromide (CTAB), β-cyclodextrin (CD) and fluorescein isothiocyanate were purchased from Aladdin. Cis-Diamminedichloroplatinum (II) (cisplatin) was purchased from Zibo Aote Fine Chemical Factory (Shandong, China). Doxorubicin hydrochloride (DOX) was obtained from Nanjing Duodian Chemical Limited Company (China). Succinic anhydride was obtained from Sinopharm Chemical Reagent Co. Extra dry toluene, extra dry methyl sulfoxide (DMSO) and 1-adamantanemethylamine was purchased from Thermo Fisher Scientific.

Characterization: The X-ray diffraction (XRD) measurements were operated on a D8 Focus diffractometer (Bruker) with Cu Kα radiation (λ = 0.15405 nm). Transmission electron microscopy (TEM) was obtained using FEI Tecnai G2 S-Twin with a field emission gun operating at 200 kV. Fourier-transform Infrared spectra were performed on a Vertex Perkin–Elmer 580BIR spectrophotometer (Bruker) with the KBr pellet technique. Zeta potential of the mixtures was performed by Zetasizer Nano ZS (Malvern Instruments Ltd., UK). The UC emission spectra were taken on an F-7000 spectrophotometer (Hitachi) equipped using a 980 nm laser as the excitation source. The UV-vis absorption spectrum was obtained by Hitachi U-3100 spectrophotometer. Inductively Coupled Plasma (ICP) results were obtained on an iCAP 6300 of Thermo

scientific. The surface temperature of the tumor site was tested by an infrared thermometer (AR300, Smart Sensor).The conclusions section should come in this section at the end of the article, before the acknowledgements.



Scheme S1. The surface functionalization of UCNPs@$mSiO_2$ nanoparticles.

Fourier-transform Infrared (FTIR) spectra: The FT-IR spectra of UCNPs@$mSiO_2$-NH_2, UCNPs@$mSiO_2$-DPP and UCNPs@$mSiO_2$-DPP-Ad and UCNPs@$mSiO_2$-DPP-Ad@CD were given in Figure S1. The peak appeared at 1620 cm^{-1} can be assigned to N-H vibration. In the case of the pro-drug conjugated UCNPs@$mSiO_2$-DPP, the peak at 2038 cm^{-1} deals with the N_3 group of DPP, which confirms the successful modification of DPP onto the surface of the particles.[1] And the peak at 1644 cm^{-1} is attributed to the coordinated carboxyl group of DPP.[1] After modification with Ad, the obvious peak at 2926 cm^{-1} is attributed to the -CH_2 stretching in the Ad structure. Due to the supramolecular interaction between Ad and β-CD, we modify the surface with β-CD to gain the UCNPs@$mSiO_2$-DPP-Ad@CD. The peak of 1646 can be attributed to the vibration of H-O-H of the H_2O, which is absorbed on the â-CD. Compared with the UCNPs@$mSiO_2$-DPP-Ad, the appeared peaks at 956 cm^{-1} and 1060 cm^{-1} for growth of the peaks of the UCNPs@$mSiO_2$-DPP-Ad@CD are ascribable to β-CD cyclic vibration,

which overlay the vibration bands of Si-OH and Si-O-Si at ~1080 cm^{-1}, respectively.[2] These results demonstrate that we have succeeded in chemically modifying and assembling the nanoparticles.

The rough calculations process of photons absorbance of UCNPs and the UV photon needed to activate the platinum drug:

For one UCNP, the diameter is 65 nm, the superficial area can be calculated:

$$S = 4\pi r^2 = 4 \times 3.14 \times (65 \times 10^{-9}/2)^2 = 1.33 \times 10^{-14} m^2$$

The pump power is 3 W/cm^2, each UCNP absorbs the energy:

$$E(UCNP) = 3 \times 10^{4W}/_{m^2} \times 1.33 \times 10^{-14} m^2 = 4.0 \times 10^{-10} w = 4.0 \times 10^{-10} J/s$$

One-electron transfers from azide to Pt for platinum prodrug photoactivation process, which needs one UV phonon. We could calculate the energy of each 365 nm phonon:

$$e(365P) = hv = \frac{hc}{\lambda} = \frac{6.63 \times 10^{-34} \times 3 \times 10^8}{365 \times 10^{-9}} = 5.45 \times 10^{-19} J$$

If the UV upconversion quantum yield is as low as 0.001%, each UCNP could produce 4.0×10^{-15} J every second. Therefore, thousands of drug molecules are activated and released from per nanoparticles.

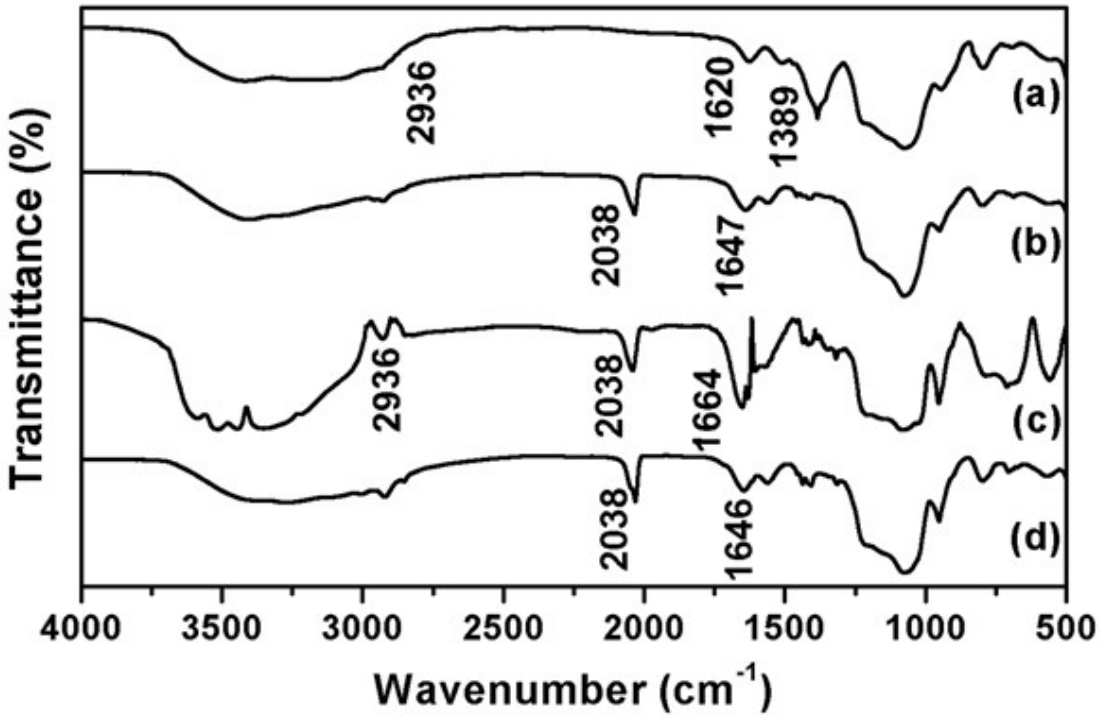


Figure S1. FTIR spectra of (a) UCNPs@mSiO$_2$-NH$_2$, (b) UCNPs@mSiO$_2$-DPP, (c) UCNPs@mSiO$_2$-DPP-Ad and (d) UCNPs@mSiO$_2$-DPP-Ad@CD.

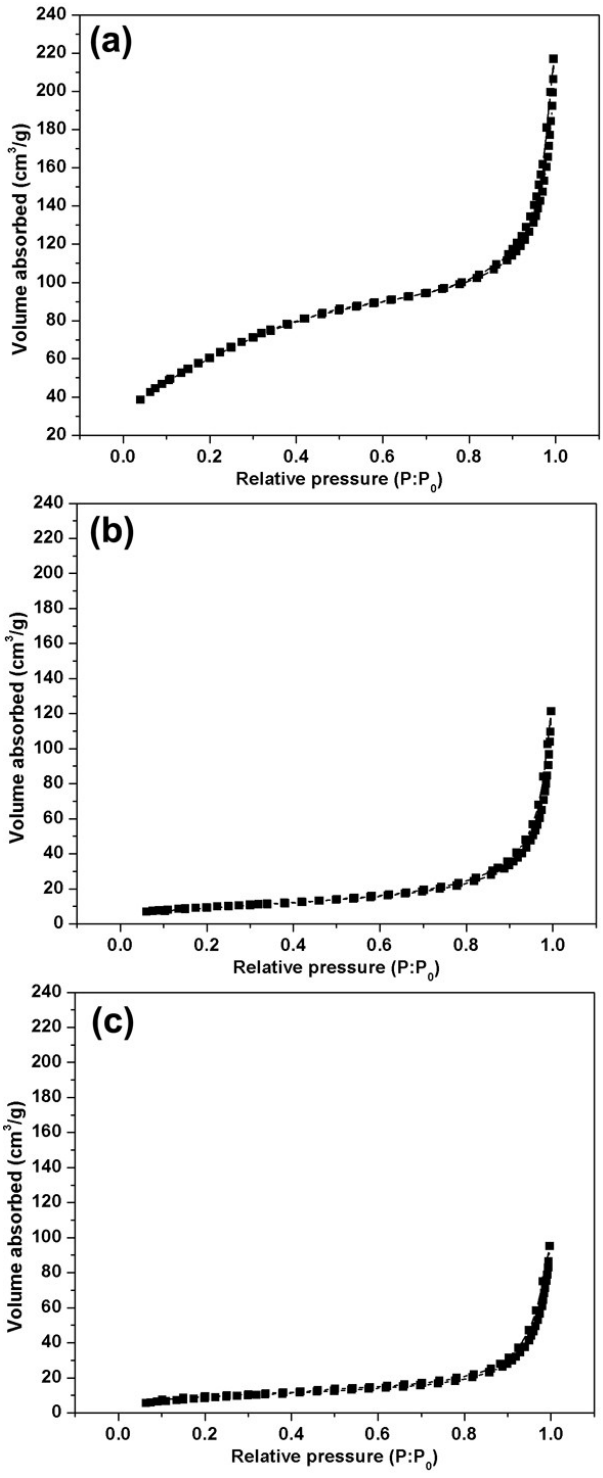


Figure S2. N_2 absorption/desorption isotherm of the UCNPs@$mSiO_2$ (a), UCNPs@$mSiO_2$-DPP-DOX (b) and UCNPs@$mSiO_2$-DPP-DOX@CD (c).

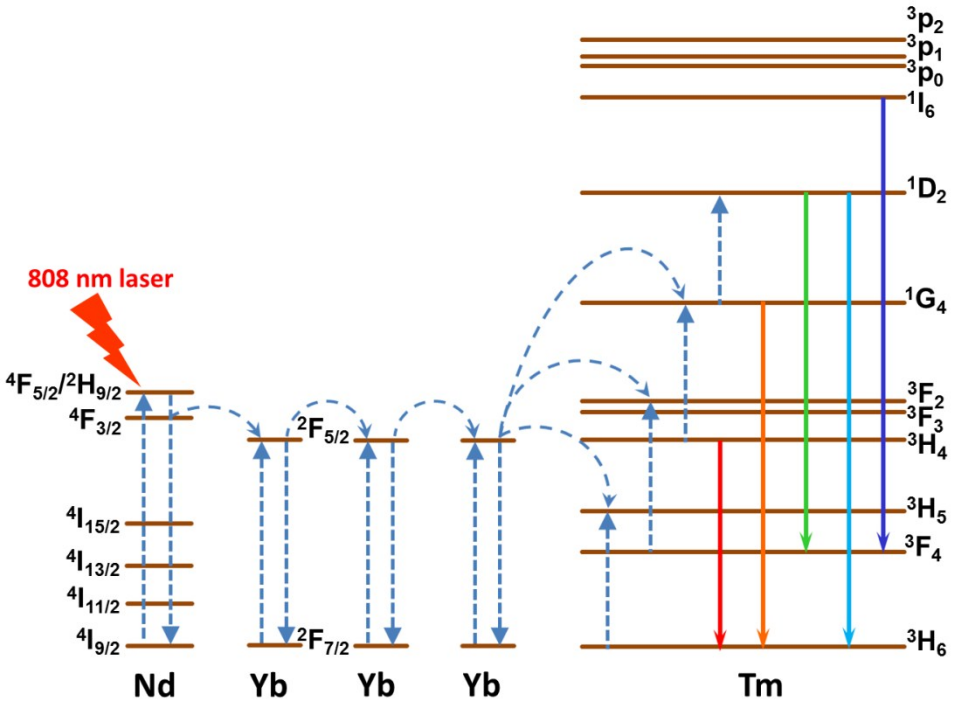


Figure S3. Energy-transfer mechanisms in the core-shell-shell $NaYF_4:Yb_{0.4}/Tm_{0.02}$ @$NaGdF_4:Yb_{0.1}$@$NaNdF_4:Yb_{0.1}$_upconversion nanoparticle upon 808 nm diode-laser excitation.

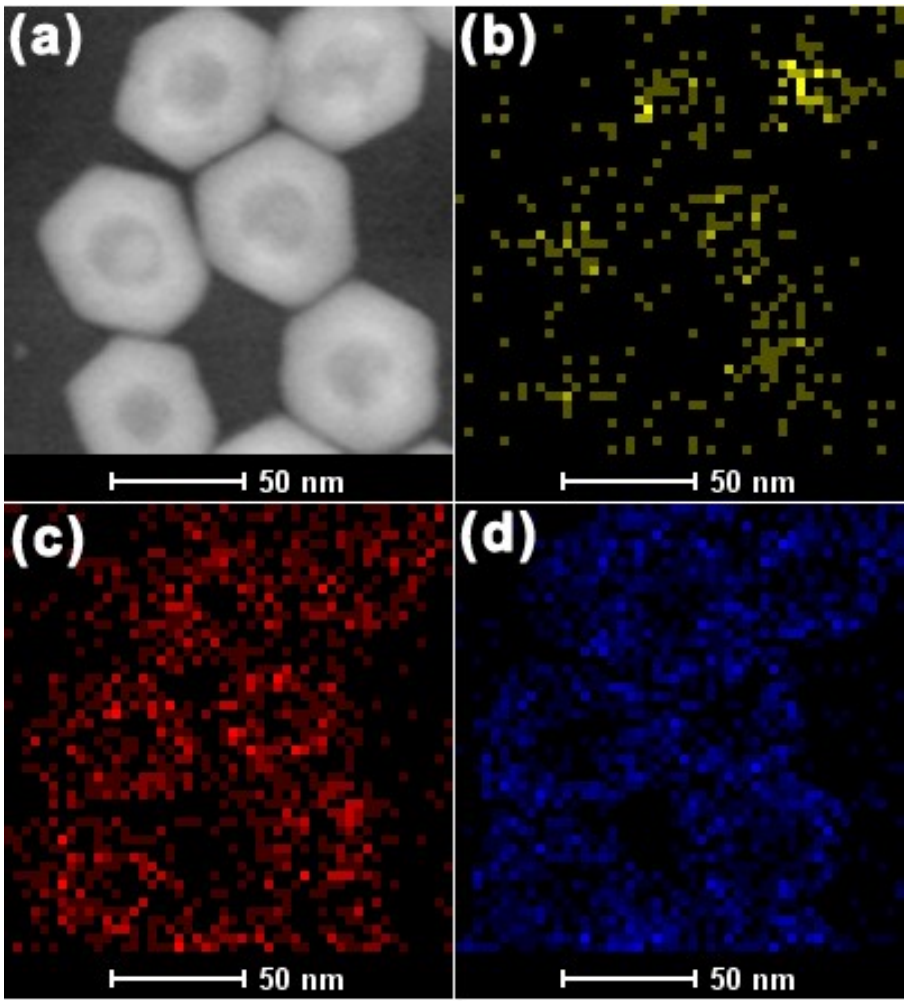


Figure S4. (a) High angle annular dark field scanning transmission electron microscopy (HAADF-STEM) of $NaYF_4$:$Yb_{0.4}$/$Tm_{0.02}$@$NaGdF_4$:$Yb_{0.1}$@$NaNdF_4$:$Yb_{0.1}$ nanoparticles and HAAD-STEM-EDX elemental distribution maps of (b) Y, (c) Gd and (d) Nd.

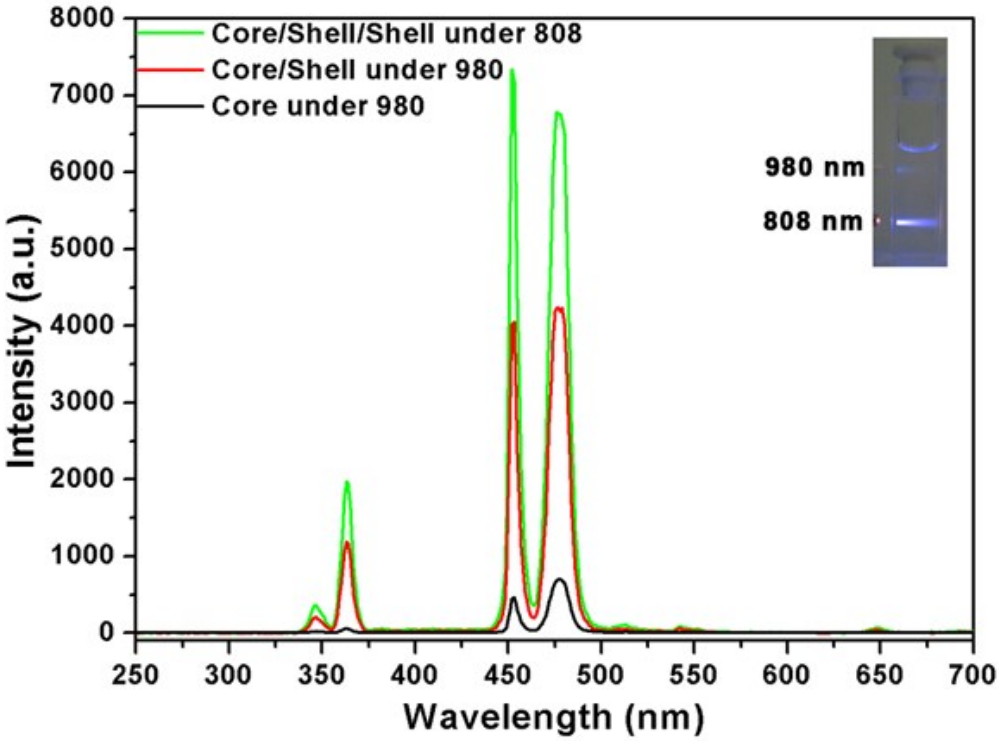


Figure S5. UC emission spectra of the $NaYF_4:Yb_{0.4}/Tm_{0.02}$ (excitation at 980 nm, black line), $NaYF_4:Yb_{0.4}/Tm_{0.02}@NaGdF_4:Yb_{0.1}$ (excitation at 980 nm, red line) and $NaYF_4:Yb_{0.4}/Tm_{0.02}@NaGdF_4:Yb_{0.1}@NaNdF_4:Yb_{0.1}$ (UCNPs) (excitation at 808 nm, green line). The luminescence photograph of UCNPs under 980 nm and 808 nm laser in the dark is given in the inset. After growth of the $NaNdF_4:Gd^{3+}$ shell, the upconversion luminescence intensity of the $NaNdF^4:Gd^{3+}$ coated nanoparticles under 808 nm excitation can be enhanced remarkably compared to the $NaYF_4:Yb^{3+}/Tm^{3+}@NaGdF_4:Yb^{3+}$ nanoparticles under 980 nm excited

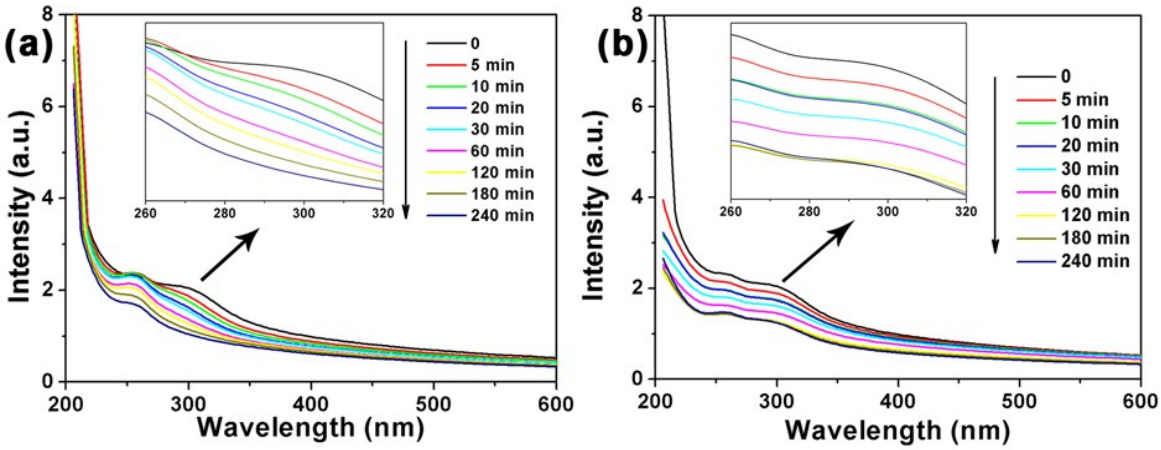


Figure S6. The absorption spectra of UCNPs@mSiO$_2$-DPP after exposed to (a) 365 nm UV and (b) 980 nm laser for different time.

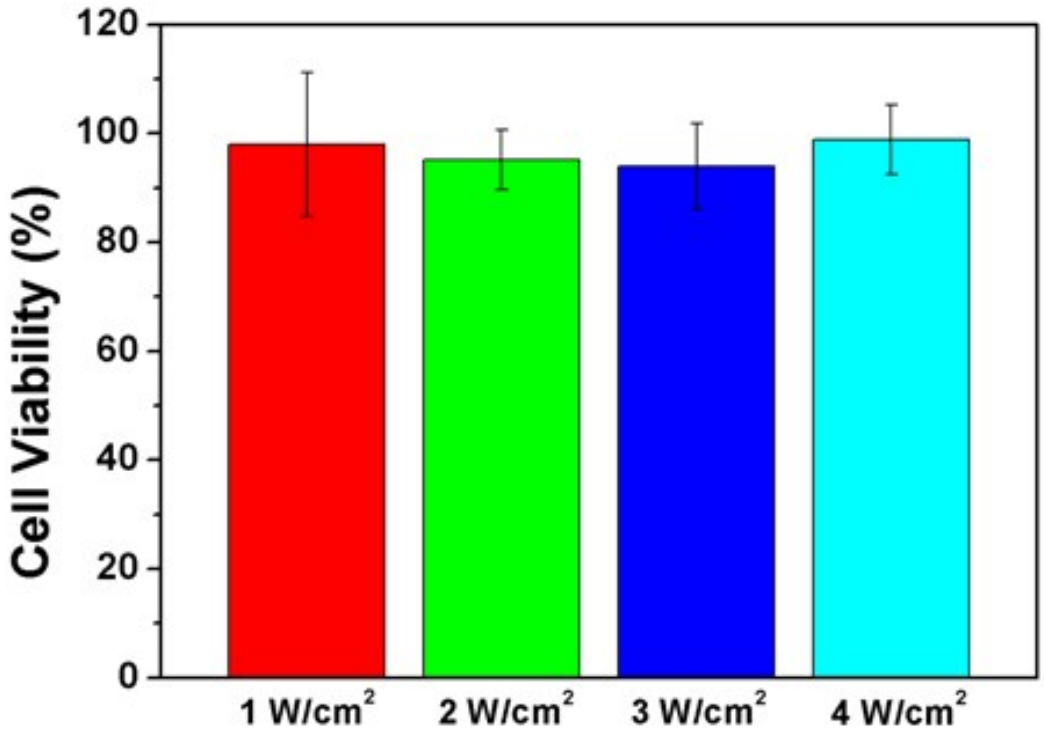


Figure S7. Cell viability after being irradiated with 808 nm laser under different intensities for 30 min (10 min break after 10 min irradiation).

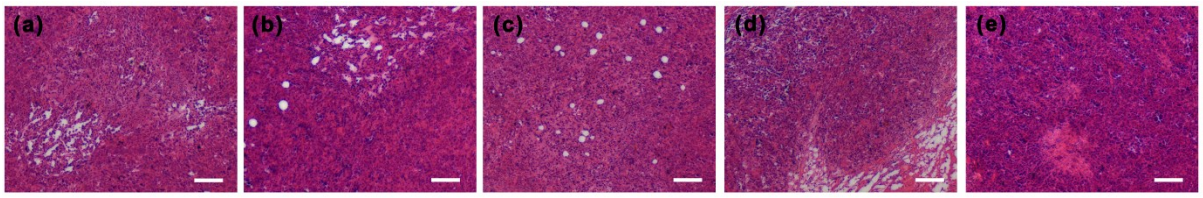


Figure S8. Images of digital photos of H&E stained tumor sections after 15 day treatment from different groups. UCNPs@mSiO$_2$-DPP-DOX@CD + 808 nm laser irradiation (a), UCNPs@mSiO$_2$-DPP-DOX@CD + UV irradiation (b), UCNPs-DPP-PEG in the dark (c), 808 nm laser irradiation (d) and saline (e). All the scale bars are 100 μm

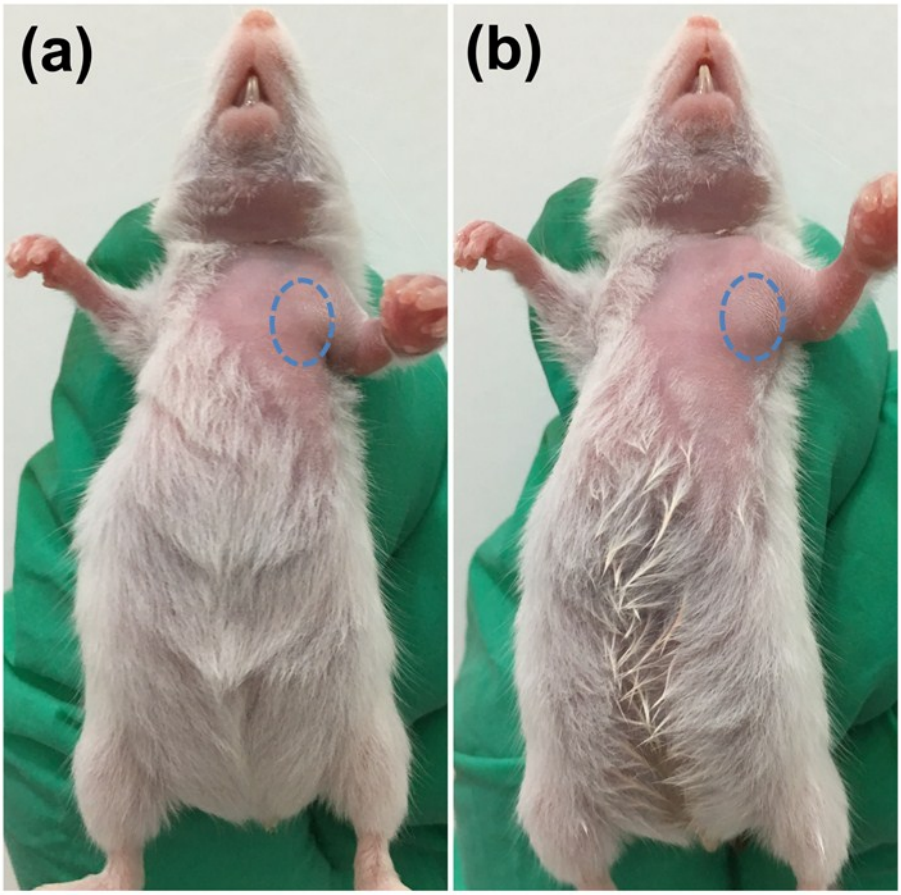


Figure S9. The images of control mouse (a) and the mouse with 808 nm laser irradiation at 3 W/cm^2 on the surface of skin for 30 min (10 min break after 10 min irradiation).

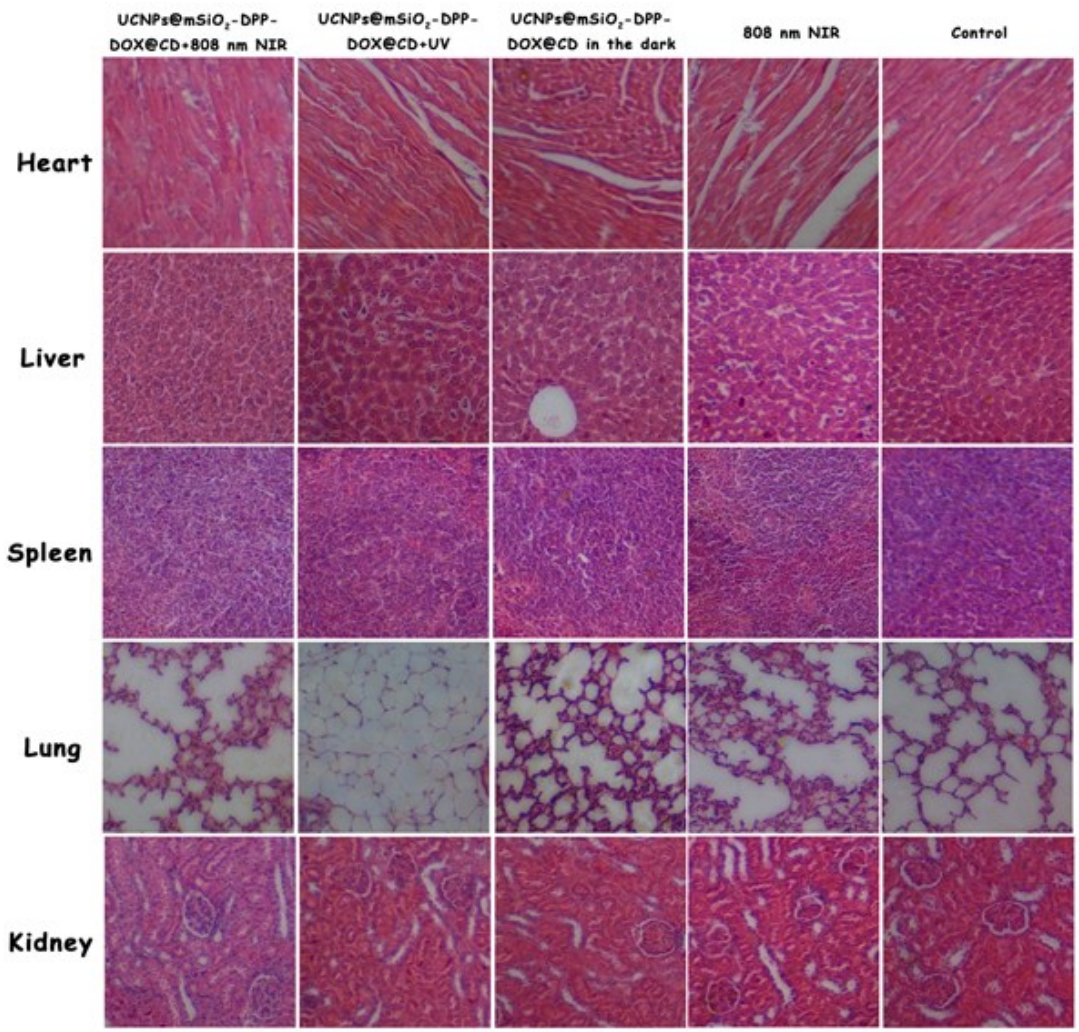


Figure S10. H&E stained images of heart, liver, spleen, lung, kidney of mice after 14 day treatment from different groups.

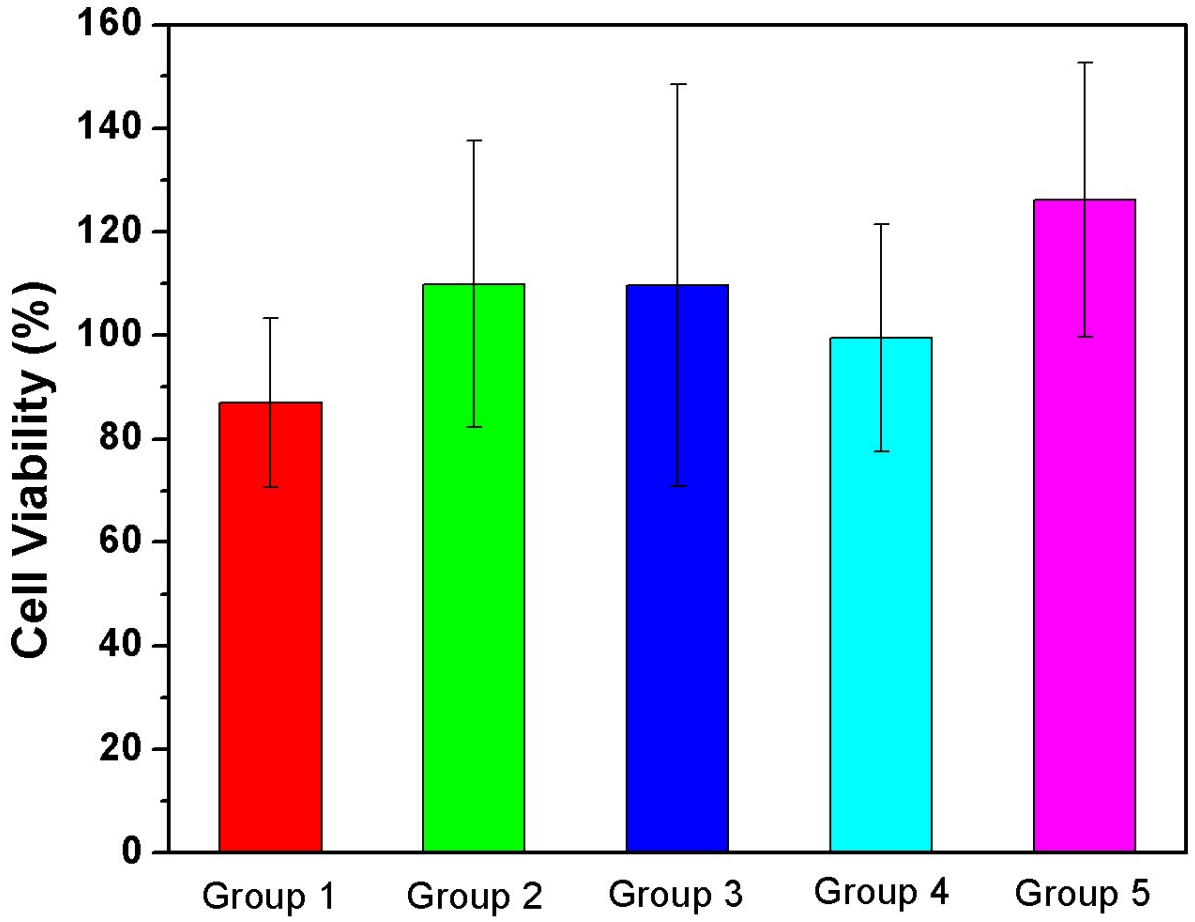


Figure S11. In vitro HeLa cells' relative viabilities after incubation for 24 h with free DOX and platinum prodrug at different concentrations. Group 1: 2 μg/mL of DOX and 0.88 μg/mL of platinum, Group 2: 1 μg/mL of DOX and 0.44 μg/mL of platinum, Group 3: 0.5 μg/mL of DOX and 0.22 μg/mL of platinum, Group 4: 0.25 μg/mL of DOX and 0.11 μg/mL of platinum, Group 5: 0.125 μg/mL of DOX and 0.055 μg/mL of platinum, respectively.

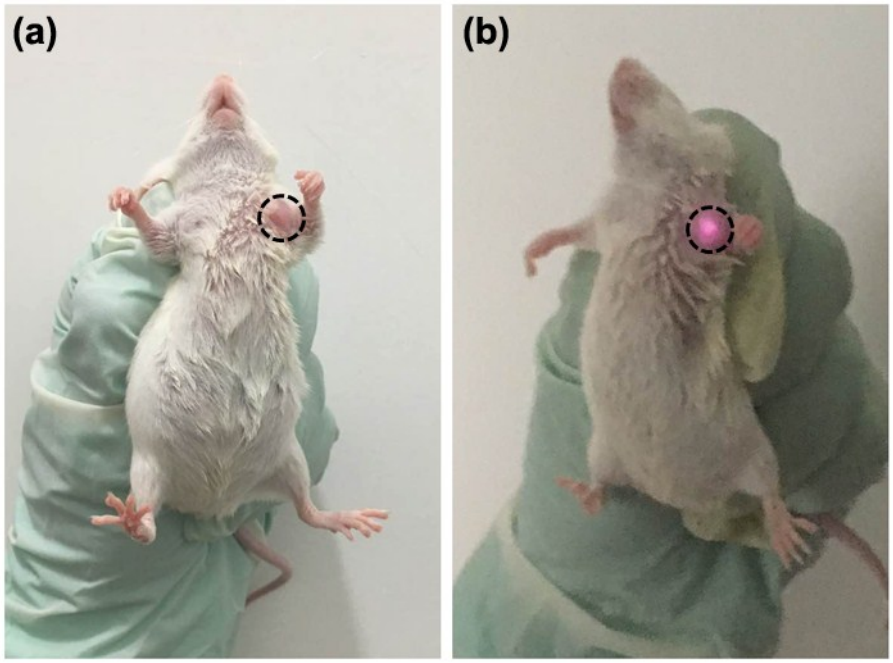


Figure S12. The upconversion luminescence imaging of UCNPs@mSiO$_2$-DPP-DOX@CD in the tumor site before (a) and after (b) 808 nm laser irradiation.

References:

[1] H. Xiao, G. T. Noble, J. F. Stefanick, R. Qi, T. Kiziltepe, X. Jing, B. Bilgicer, *J. Control. Release* **2014**, *173*, 11-17.

[2] P. Díez, A. Sánchez, M. Gamella, P. Martínez-Ruíz, E. Aznar, C. de la Torre, J. R. Murguía, R. Martínez-Máñez, R. Villalonga, J. M. Pingarrón, *J. Am. Chem. Soc.* **2014**, *136*, 9116-9123.