

## Supporting Information

# **Enhancement of Ultralow-Intensity NIR Light Triggered Photodynamic Therapy based on Exo- and Endogenous Synergistic effects through Combination of Glutathione-depletion Chemotherapy**

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Author Contributions:

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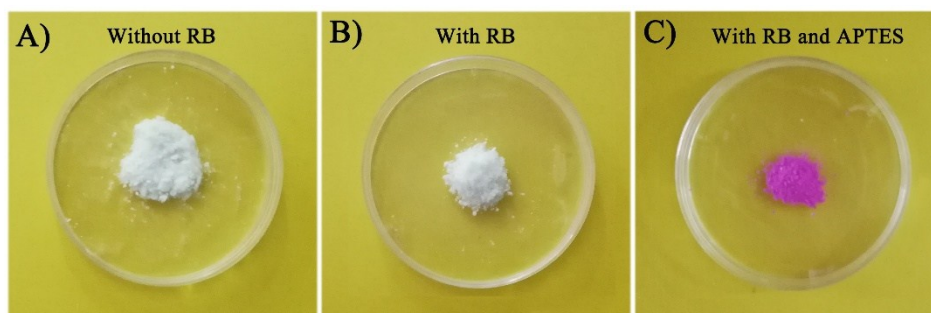
## Experimental details

**Synthesis of NaYF<sub>4</sub>:Yb,Er nanoparticles.** YCl<sub>3</sub>·6H<sub>2</sub>O (3.12 mmol, 946.5 mg), YbCl<sub>3</sub>·6H<sub>2</sub>O (0.80 mmol, 310.7 mg), and ErCl<sub>3</sub>·6H<sub>2</sub>O (0.08 mmol, 30.5 mg) were added to a three necked flask (250 mL) containing OA (24 mL) and ODE (60 mL). The solution was heated to 160 °C and kept 3 h under argon flow and magnetic stirring. The temperature was then cooled to 50 °C, and 40 mL of methanol containing NH<sub>4</sub>F (16 mmol, 592.6 mg) and NaOH (10 mmol, 400.0 mg) was added. The mixture was stirred for another 30 min and heated to 100 °C to evaporate the methanol and then heated to 300 °C and kept 1 h under argon protection. After it was cooled to room temperature, the product was collected by centrifugation and washed three times with ethanol/cyclohexane, and finally re-dispersed in cyclohexane (40 mL) for further use.

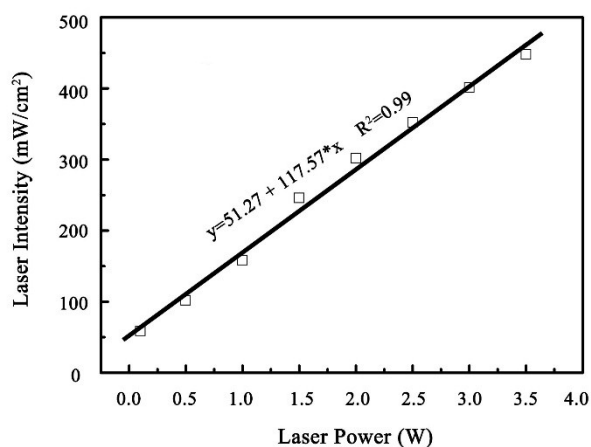
**Synthesis of NaYF<sub>4</sub>:Yb,Er@NaYF<sub>4</sub>:Yb,Nd nanoparticles.** YCl<sub>3</sub>·6H<sub>2</sub>O (1.50 mmol, 455.1 mg), YbCl<sub>3</sub>·6H<sub>2</sub>O (0.30 mmol, 116.5 mg), NdCl<sub>3</sub>·6H<sub>2</sub>O (1.2 mmol, 345.3 mg), and pre-prepared NaYF<sub>4</sub>:Yb,Tm (3.00 mmol, 30 mL) were added to a three necked flask having OA (18 mL) and ODE (45 mL). The solution was heated to 160 °C and kept 3 h under argon protection. After the temperature was cooled to 50 °C, 30 mL of methanol containing of NH<sub>4</sub>F (12 mmol, 444.4 mg) and NaOH (7.5 mmol, 300.0 mg) was added and the mixture was stirred for another 30 min. Subsequently, the solution was heated to 100 °C to evaporate the methanol and then heated to 300 °C and kept 1.5 h under argon protection. The final product was dispersed in cyclohexane (30 mL) for further use.

**Synthesis of NaYF<sub>4</sub>:Yb,Er@NaYF<sub>4</sub>:Yb,Nd@NaYF<sub>4</sub> nanoparticles (UCNP).** YCl<sub>3</sub>·6H<sub>2</sub>O (1.00 mmol, 303.4 mg), and pre-prepared NaYF<sub>4</sub>:Yb,Er@NaYF<sub>4</sub>:Yb,Nd (2.00 mmol, 20 mL) were added to a three necked flask having OA (12 mL) and ODE (30 mL). The solution was heated to 160 °C and kept 3 h under argon protection. After the temperature was cooled to 50 °C, 30 mL of methanol containing of NH<sub>4</sub>F (8 mmol, 296.3 mg) and NaOH (5 mmol, 200.0 mg) was added and the mixture was stirred for another 30 min. Subsequently, the solution was heated to 100 °C to evaporate the

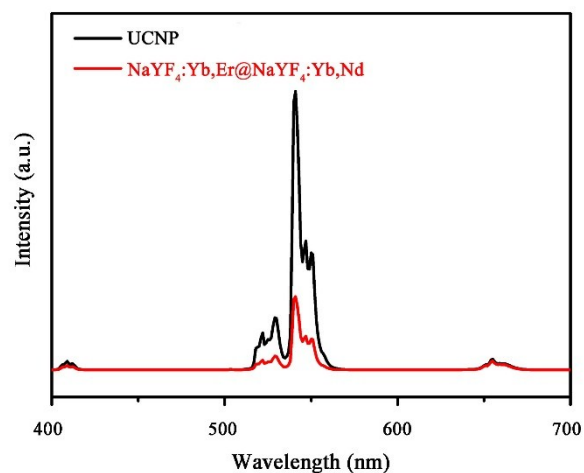
methanol and then heated to 300 °C and kept 2 h under argon protection. The final product was dispersed in cyclohexane (20 mL) for further use.



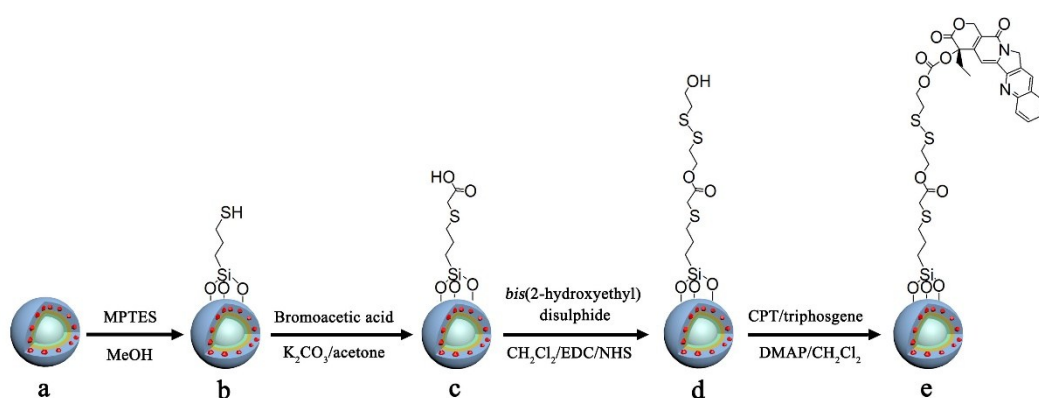
**Figure S1.** Digital photographs of UCNP@SiO<sub>2</sub> nanoparticles: A) loading with APTES only, B) loading with RB only, and C) loading with RB and APTES.



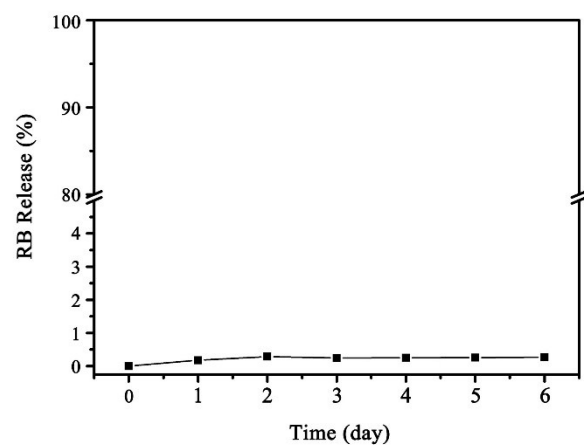
**Figure S2.** The intensity calibration curve of 808 nm laser obtained using laser power density meter (Thorlabs PM100D). The set distance between laser source and sample was 6 cm.



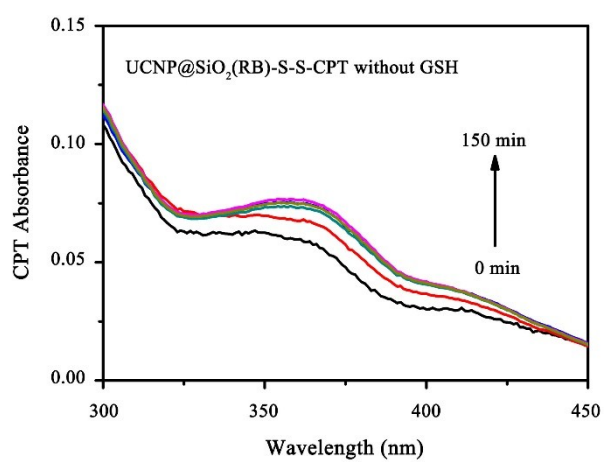
**Figure S3.** The upconversion emission spectrum of  $\text{NaYF}_4:\text{Yb,Er}@\text{NaYF}_4:\text{Yb,Nd}$  and UCNP ( $\text{NaYF}_4:\text{Yb,Er}@\text{NaYF}_4:\text{Yb,Nd}@\text{NaYF}_4$ ) under 808 nm NIR light irradiation.



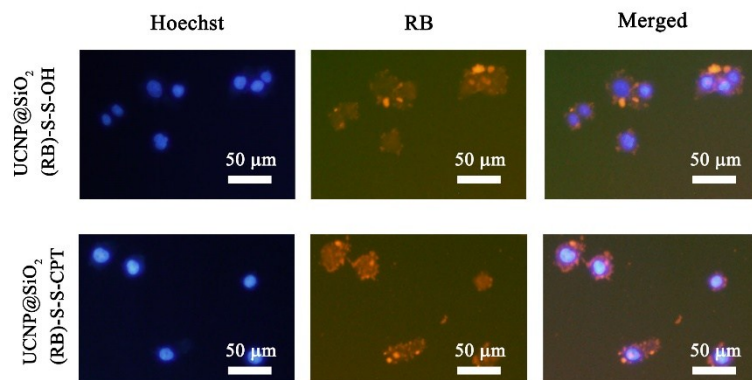
**Figure S4.** Step-by-step synthesis protocol of  $\text{UCNP}@\text{SiO}_2(\text{RB})\text{-S-S-CPT}$ . a)  $\text{UCNP}@\text{SiO}_2(\text{RB})$ ; b)  $\text{UCNP}@\text{SiO}_2(\text{RB})\text{-SH}$ ; c)  $\text{UCNP}@\text{SiO}_2(\text{RB})\text{-COOH}$ ; d)  $\text{UCNP}@\text{SiO}_2(\text{RB})\text{-S-S-OH}$ ; e)  $\text{UCNP}@\text{SiO}_2(\text{RB})\text{-S-S-CPT}$ .



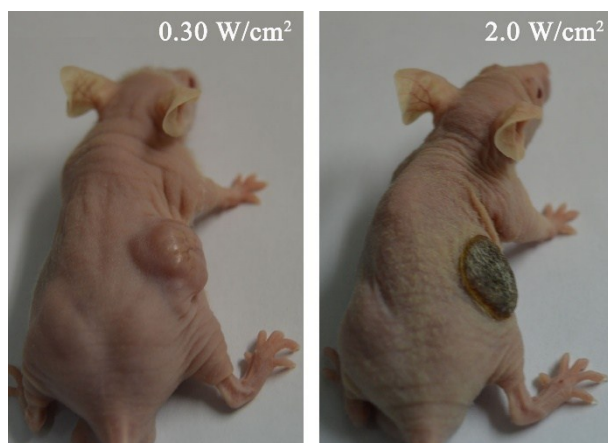
**Figure S5.** Leaking of RB molecules from UCNP@SiO<sub>2</sub>(RB) during 6 days extraction in PBS.



**Figure S6.** Original UV-Vis data on CPT release for UCNP@SiO<sub>2</sub>(RB)-S-S-CPT without GSH.

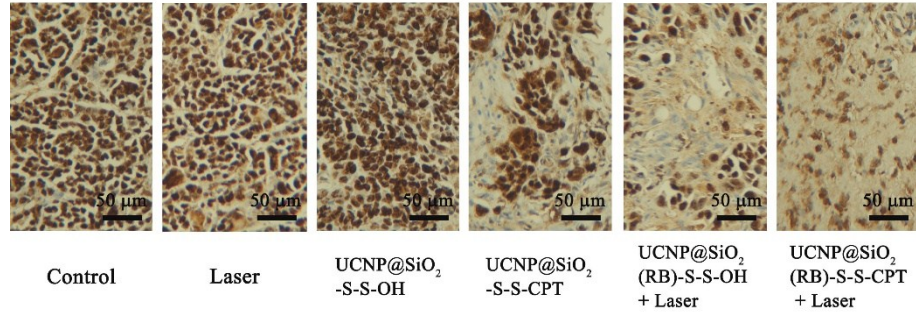


**Figure S7.** Fluorescence microscopy images of HeLa cells incubated with UCNP@SiO<sub>2</sub>(RB)-S-S-OH and UCNP@SiO<sub>2</sub>(RB)-S-S-CPT nanoparticles respectively, suggesting as-synthesized nanoparticles can be effectively uptake by HeLa cells.

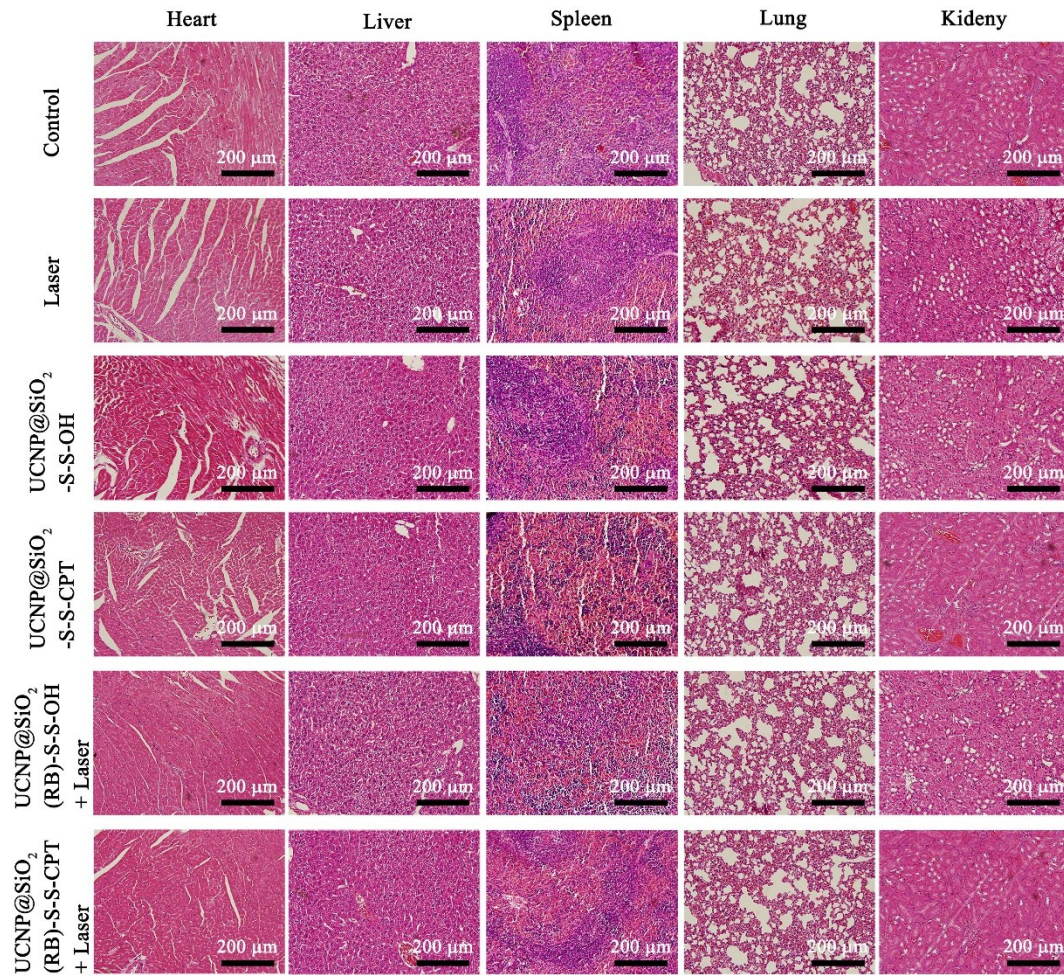


**Figure S8.** Photodamage of the mice in Laser group after 808 nm laser irradiation with 0.30 and 2.0 W/cm<sup>2</sup> intensity for 10 min. This result strongly suggests that the necessity of using ultralow-intensity NIR light for phototherapy to avoid photodamage.





**Figure S9.** Ki-67-stained cellular proliferation in tumor tissues sections after two-week treatment.



**Figure S10.** Representative histological H&E stained tissue sections from mice to monitor the histological changes in heart, liver, spleen, lung, and kidney were collected from different groups followed by dissections at 14 days post injection.