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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Experimental details

**Synthesis of NaYF₄:Yb,Er nanoparticles.** YCl₃·6H₂O (3.12 mmol, 946.5 mg), YbCl₃·6H₂O (0.80 mmol, 310.7 mg), and ErCl₃·6H₂O (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 NH₄F (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 NaYF₄:Yb,Er@NaYF₄:Yb,Nd nanoparticles.** YCl₃·6H₂O (1.50 mmol, 455.1 mg), YbCl₃·6H₂O (0.30 mmol, 116.5 mg), NdCl₃·6H₂O (1.2 mmol, 345.3 mg), and pre-prepared NaYF₄: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 NH₄F (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 NaYF₄:Yb,Er@NaYF₄:Yb,Nd@NaYF₄ nanoparticles (UCNP).** YCl₃·6H₂O (1.00 mmol, 303.4 mg), and pre-prepared NaYF₄:Yb,Er@NaYF₄: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 NH₄F (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$_2$ 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 NaYF₄:Yb,Er@NaYF₄:Yb,Nd and UCNP (NaYF₄:Yb,Er@NaYF₄:Yb,Nd@NaYF₄) under 808 nm NIR light irradiation.

**Figure S4.** Step-by-step synthesis protocol of UCNP@SiO₂(RB)-S-S-CPT. a) UCNP@SiO₂(RB); b) UCNP@SiO₂(RB)-SH; c) UCNP@SiO₂(RB)-COOH; d) UCNP@SiO₂(RB)-S-S-OH; e) UCNP@SiO₂(RB)-S-S-CPT.
Figure S5. Leaking of RB molecules from UCNP@SiO$_2$(RB) during 6 days extraction in PBS.

Figure S6. Original UV-Vis data on CPT release for UCNP@SiO$_2$(RB)-S-S-CPT without GSH.
Figure S7. Fluorescence microscopy images of HeLa cells incubated with UCNP@SiO$_2$(RB)-S-S-OH and UCNP@SiO$_2$(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$^2$ 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.