Supporting Information

Multiphoton transition activated iron base-metal organic framework for synergistic therapy of photodynamic therapy/ chemodynamic therapy/chemotherapy for orthotopic gliomas

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1. Materials

The gadolinium chloride hexahydrate ($GdCl_3 \cdot 6H_2O$), ytterbium chloride hexahydrate ($YbCl_3 \cdot 6H_2O$), thulium chloride hexahydrate ($TmCl_3 \cdot 6H_2O$), neodymium oxide (Nd_2O_3), yttrium oxide (Y_2O_3), Ytterbium oxide (Yb_2O_3), oleic acid (OA), 1-octadecene (ODE), doxorubicin hydrochloride (Dox), 2-aminoterephthalic acid, trifluoroacetic acid and iron chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) were all obtained from Shanghai Aladdin Biochemical Technology Co., Ltd. Acetone, sodium hydroxide and ammonium fluoride were purchased from Xilong Scientific Co., Ltd. Cyclohexane was purchased from Tianjin Xinbote Chemical Co., Ltd. N,N-Dimethylformamide (DMF) was purchased from Tianjin Tiantai Chemical Co., Ltd. Polyvinyl pyrrolidone (MW: 40000) was purchased from Beijing Solarbio Technology Co., Ltd. Lactoferrin was purchased from Shanghai Yuanye Biotechnology Co., Ltd. The CCK-8 was bought from Changchun Sanbang Pharmaceutical Technology Co., Ltd. Calcein acetoxymethyl ester (Calcein AM) and propidium iodide (PI) were obtained from Sigma-Aldrich. 4',6- diamidino-2-phenylindole (DAPI) and fluorescein isothiocyanate isomer (FITC) were obtained from Shanghai Biyuntian Biotechnology Co., Ltd. Hydroxyphenyl fluorescein (HPF) was purchased from Shanghai Maokang Bio. Co., Ltd. Dihydroethidium (DHE) was purchased from Beijing Baiaolaibo Technology Co., Ltd. Mitochondrial Membrane Potential Assay Kit with JC-1 was purchased from Beyotime Biotechnology. The trans-well chamber (polycarbonate membrane, 0.4 μm pore size) was obtained from Corning Biotechnology Co., LTD.

2. Experimental section

2.1 Synthesis of OA-stabilized $NaGdF_4$: Yb, Tm core nanoparticles

OA-stabilized $NaGdF_4$: Yb, Tm core nanoparticles were synthesized according to the literature method. Typically, $GdCl_3 \bullet 6H_2O$ (0.5 mmol), $YbCl_3 \bullet 6H_2O$ (0.49 mmol) and $TmCl_3 \bullet 6H_2O$ (0.01 mmol) were mixed in a 100 mL three-necked flask charged with OA (7.0 mL) and ODE (15.0 mL). The mixture solution was heated to 160°C under argon atmosphere and kept for 30 min to obtain clear solution. After the solution was cooled to 50°C, a methanol solution (10 mL) of NH_4F (4.0 mmol) and NaOH (2.5 mmol) was added and stirred at 50°C for 30 min. After methanol was evaporated at 100°C, the solution was heated to 300°C and kept for 60 min. Finally, the products were purified by centrifugation after addition of ethanol, washed several times with cyclohexane and ethanol, and finally re-dispersed in cyclohexane for further experiments.

2.2 Synthesis of $RE(CF_3COO)_3$ (RE= Y, Nd and Yb)

The 10.0 mM RE_2O_3 was dissolved in 5.0 mL deionized water and 5.0 mL trifluoroacetic acid mixed solution and kept stir for 12 h under the 105ºC. After that, the clear solution is kept stirring and exposed to air until it becomes a dry powder. The dried powder was further dried in an oven at 80°C for 48 h, and the $RE(CF_3COO)_3$ was obtained.

2.3 Synthesis of OA-stabilized core-shell structured $NaGdF_4$: Yb, Tm@$NaYF_4$: Yb, Nd nanoparticles

Briefly, as-prepared $NaGdF_4$: Yb, Tm core NPs (1 mmol), CF_3COONa (1.0 mmol), $Y(CF_3COO)_3$ (0.6 mmol), $Yb(CF_3COO)_3$ (0.1 mmol) and $Nd(CF_3COO)_3$ (0.3 mmol)

were added to the mixture of OA (10.0 mL) and ODE (10.0 mL) in a three-necked flask at room temperature. The solution was heated to 100°C with magnetic stirring for 60 min. After that, the temperature was increased to 300°C and kept for 60 min under argon atmosphere. After the solution was cooled to room temperature, the final products were purified by centrifugation, and washed several times with cyclohexane and ethanol and finally re-dispersed in cyclohexane for further experiments.

2.4 Synthesis of OA-stabilized core-shell-shell structured $NaGdF_4$: Yb, Tm@ $NaYF_4$: Yb, Nd @ $NaYF_4$ nanoparticles (UCNPs)

Briefly, as-prepared $NaGdF_4$: Yb, Tm@$NaYF_4$: Yb, Nd NPs, CF_3COONa (1.0 mmol), $Y(CF_3COO)_3$ (1.0 mmol) were added to the mixture of OA (10.0 mL) and ODE (10.0 mL) in a three-necked flask at room temperature. The solution was heated to 100°C with magnetic stirring for 60 min. After that, the temperature was increased to 300°C and kept for 60 min under argon atmosphere. After the solution was cooled to room temperature, the final products were purified by centrifugation, and washed several times with cyclohexane and ethanol and finally re-dispersed in 10.0 mL cyclohexane for further experiments.

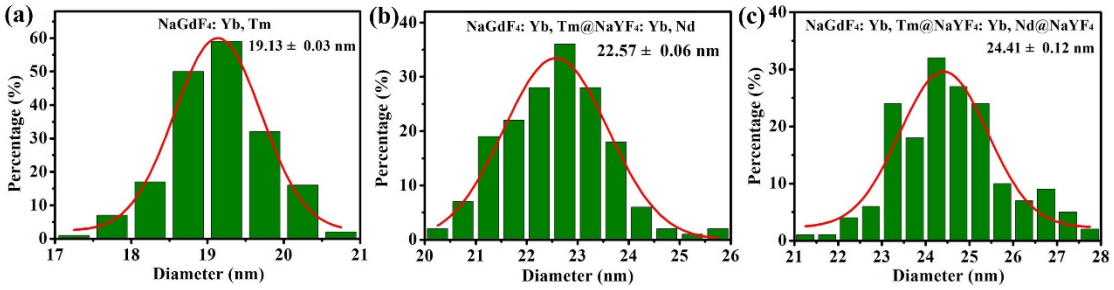

Figure S1. Histogram of particle size distribution of $NaGdF_4$: Yb, Tm nanoparticles (a), $NaGdF_4$: Yb, Tm@$NaYF_4$: Yb, Nd nanoparticles (b) and $NaGdF_4$: Yb, Tm@$NaYF_4$: Yb, Nd@$NaYF_4$ nanoparticles (c).

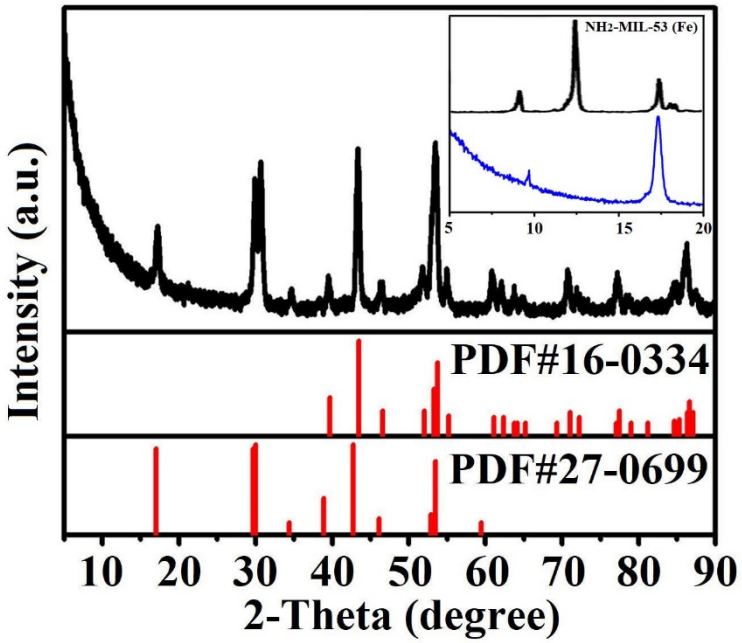

Figure S2. The XRD spectrum of UM (the illustration was a partial enlargement of the spectrum).

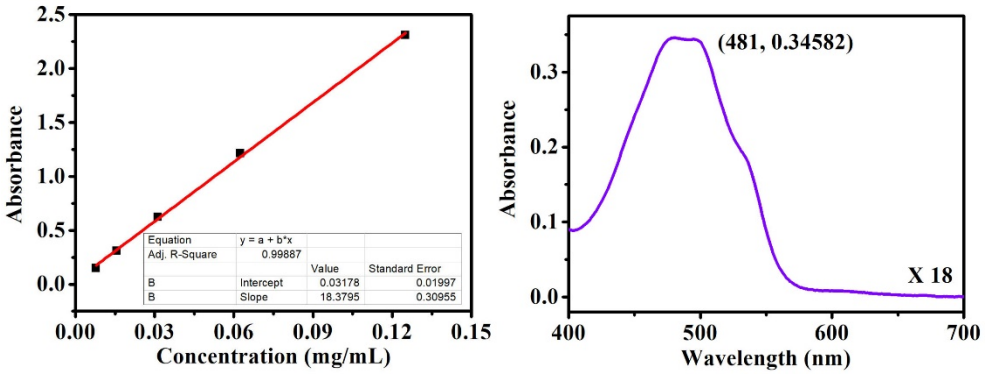

Figure S3. The UV-vis standard curve of Dox. (b) The UV-vis absorbance spectrum of UMD supernatant.

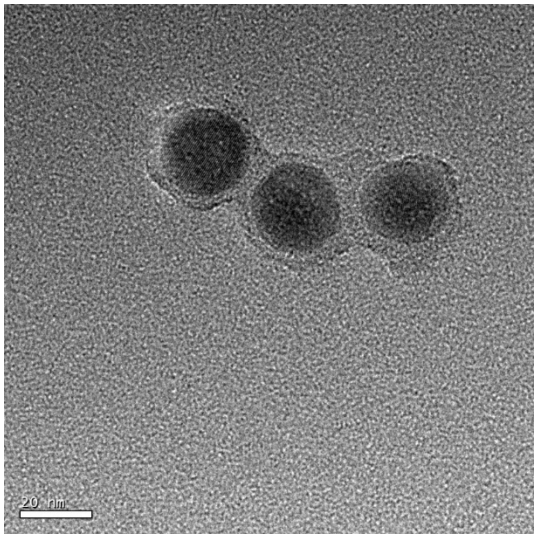

Figure S4. The TEM image of UMDL.

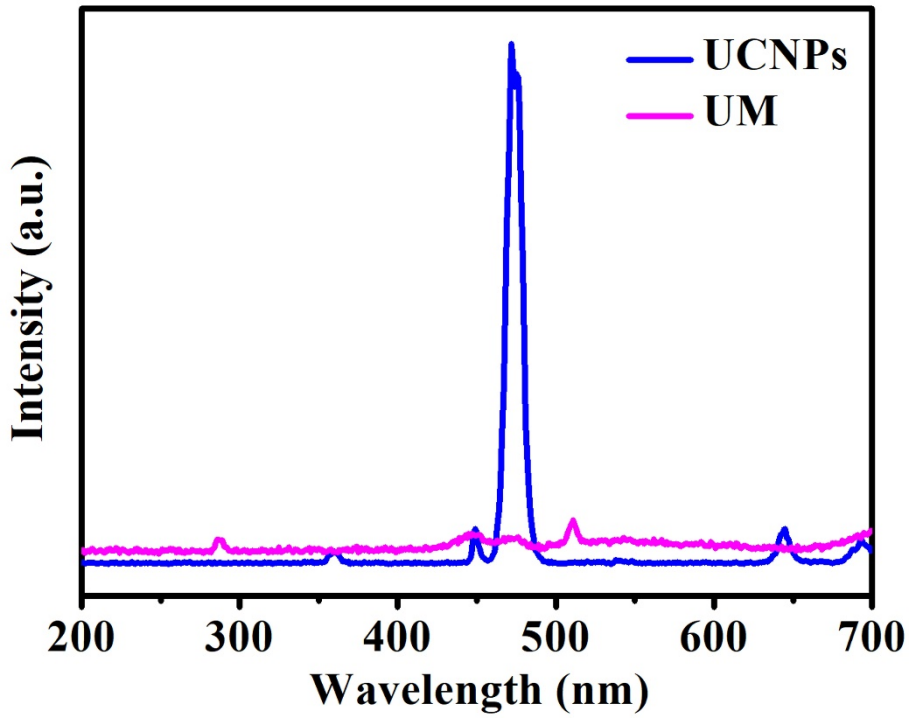

Figure S5. Up-conversion fluorescence spectra of UCNPs and UM, respectively.

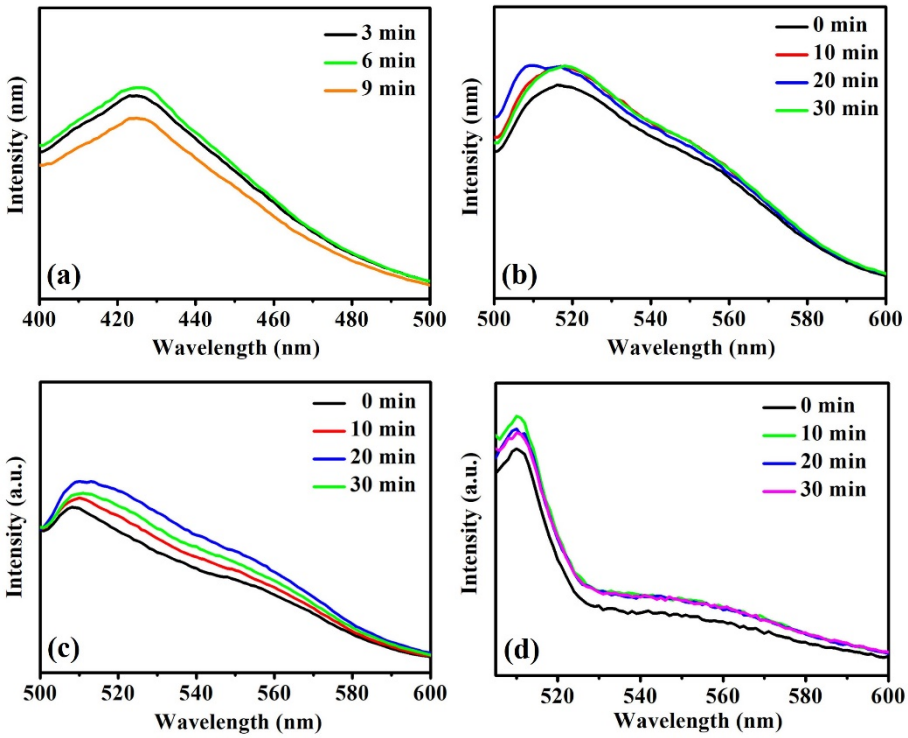

Figure S6. (a) The fluorescence spectra of 200 ppm UCNPs by DHE probe to detect the generation of $\cdot O_2^-$ under the 808 nm laser (1.0 W cm^{-2}). (b) The fluorescence spectra of 200 ppm UCNPs by HPF probe to detect the generation of ·OH in the simulate TME solution without GSH. (c) The fluorescence spectra of 200 ppm UCNPs by HPF probe to detect the generation of ·OH in the simulate TME solution. (d) Fluorescence spectra of 200 ppm UM by HPF probe in the simulate TME without GSH.

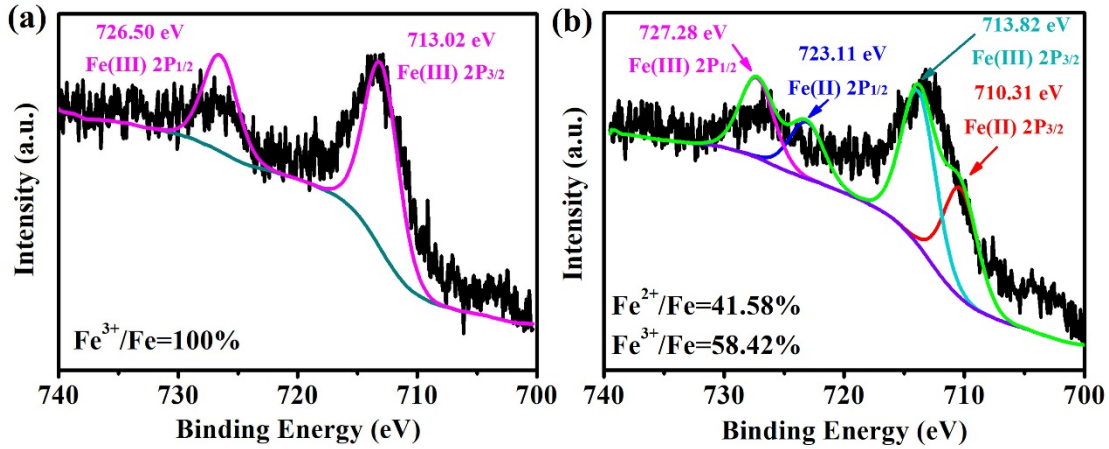

Figure S7. The XPS high-resolution spectra for Fe 2p characteristic peaks of UM (a) and UM reacted with 3 mM GSH for 4 h (b).

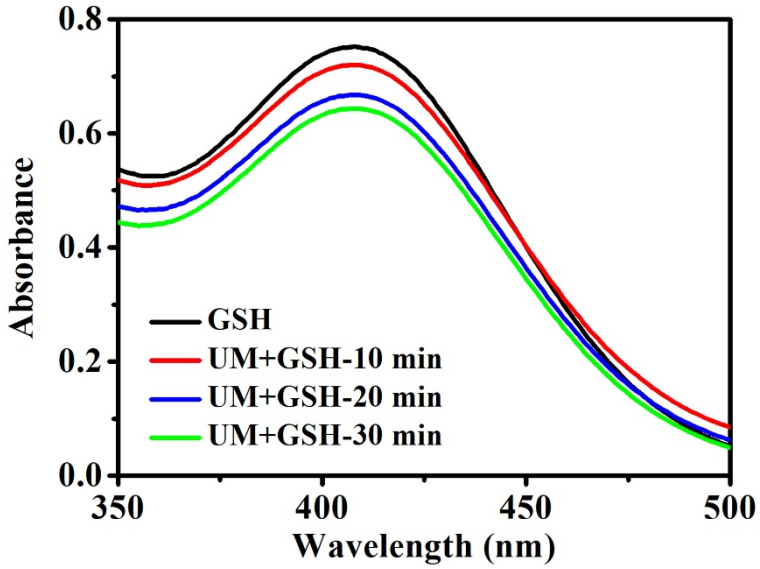

Figure S8. GSH residue detected by DTNB probe after 150 ppm UM consumed GSH for different times.

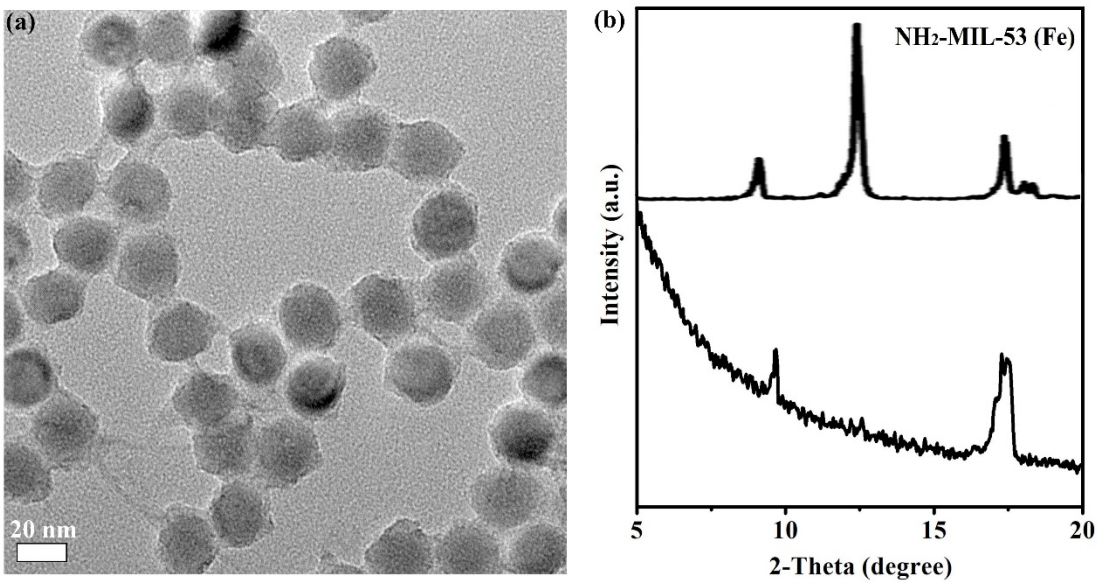

Figure S9. The TEM image and XRD pattern of UMDL dissolved in TME solution for 24 h.

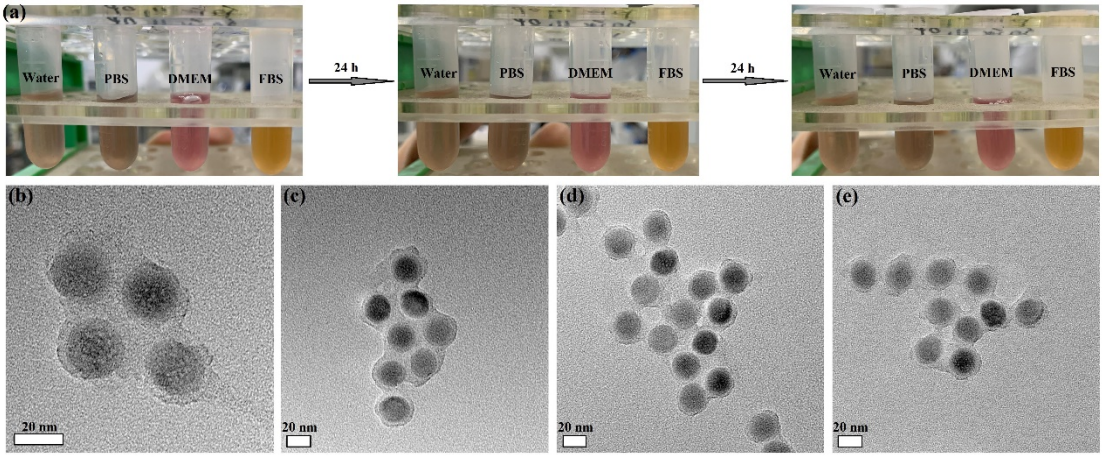

Figure S10. (a) The digital photographs of UMDL dispersed in water, PBS, dulbecco's modified eagle medium (DMEM) and fetal bovine serum (FBS) for 24 h and 48 h. The TEM images of UMDL nanoparticles after immersed in each solvent for 48 h, (b) water, (c) PBS, (d) DMEM and (e) FBS.

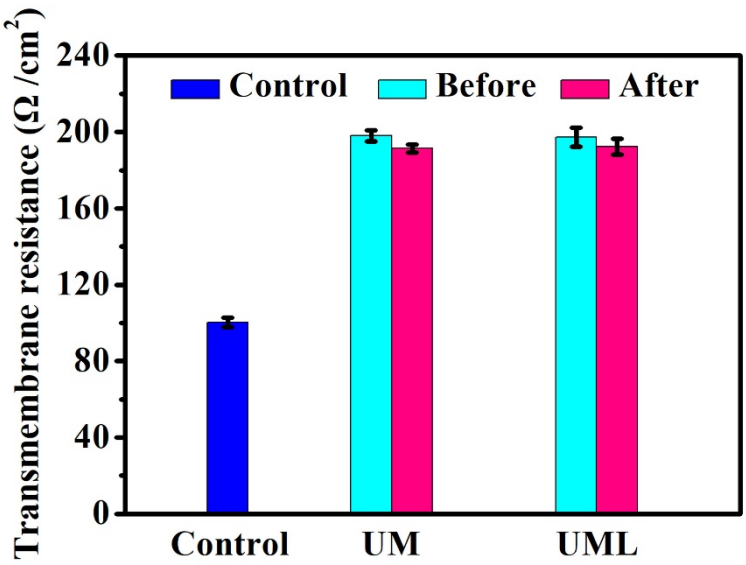

Figure S11. Trans-endothelial electrical resistance value before and after UM and UML NPs traversed the BBB model.

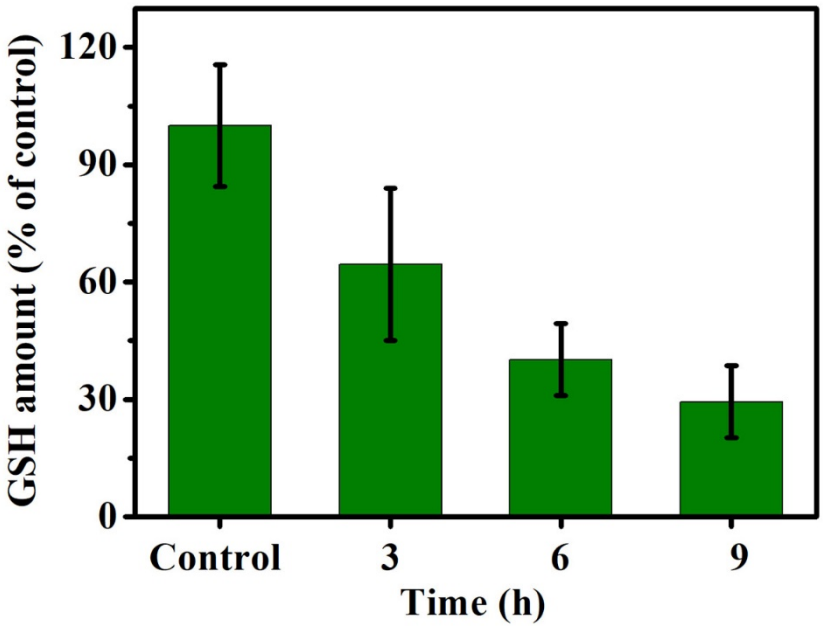

Figure S12. GSH content in GL261 cells after incubating with UML for different times.

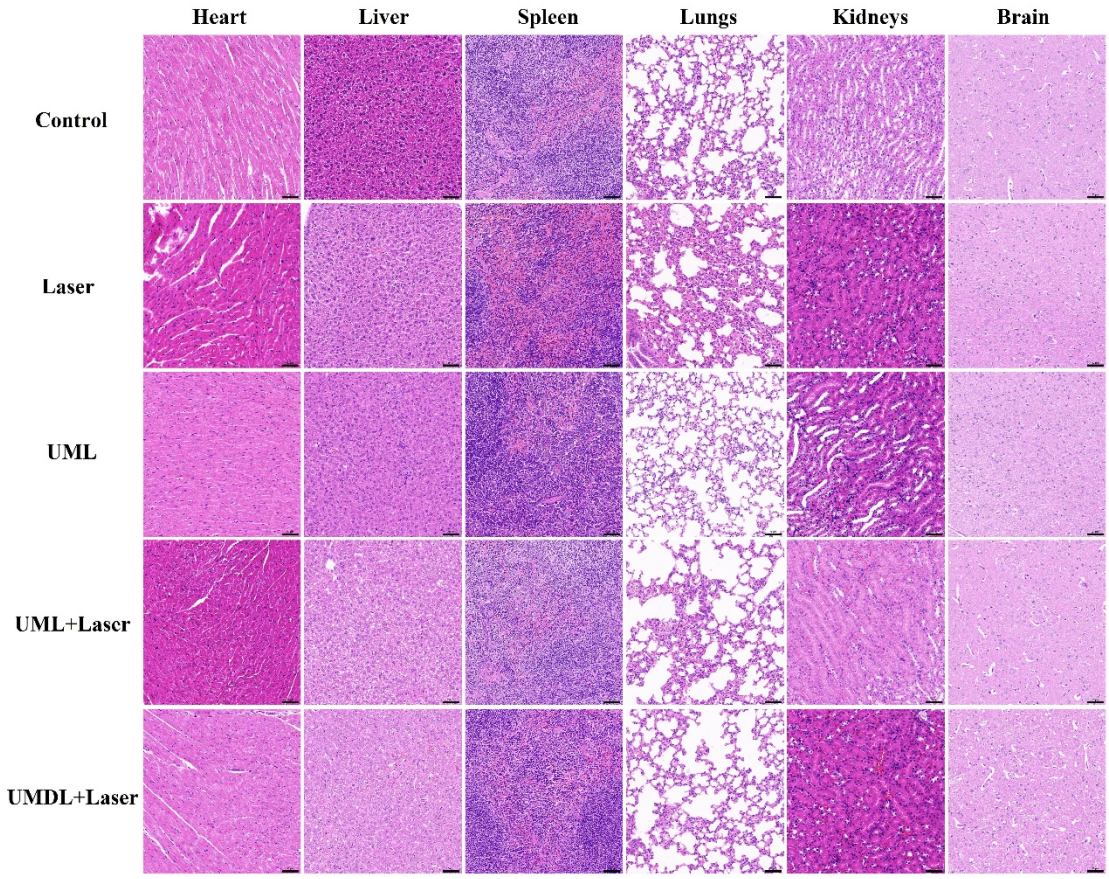

Figure. S13 Hematoxylin-eosin (H&E) staining of the major organs (heart, liver, spleen, lung, kidney and brain) from different groups, scale bar: 50 μm.

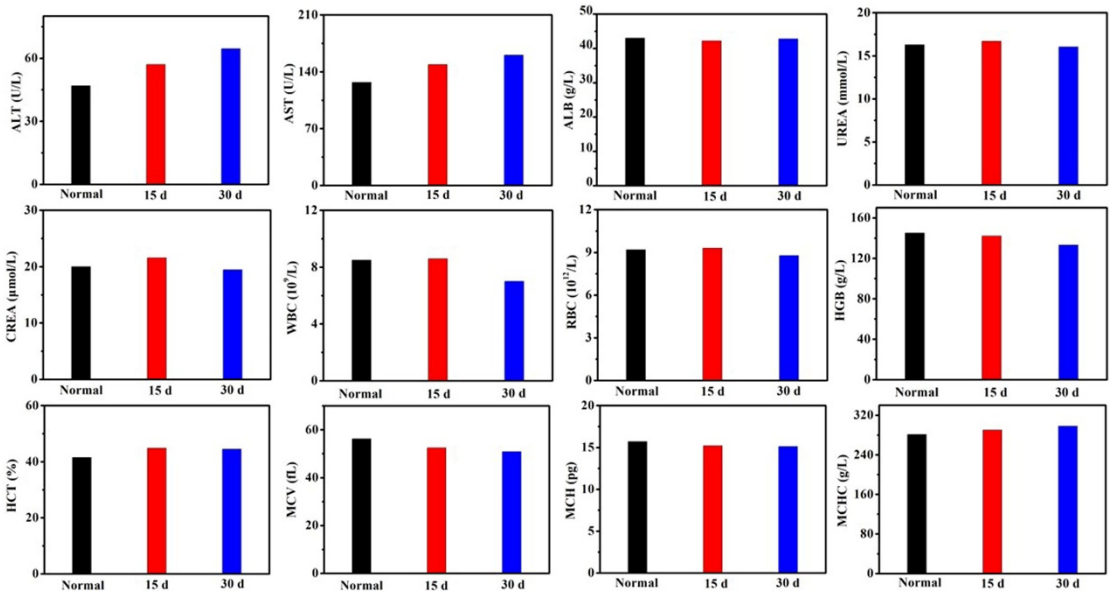

Figure. S14 Blood biochemistry/complete blood panel analysis data after intravenous injected UMDL and collected at normal, 15 and 30 days post-injection C57BL/6J mice (alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), urea (UREA), creatinine (CREA), white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)).