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**Supporting Information**

# In Situ Synthesis of Functional ZIF-8 Nanocomposite for Synergistic Photodynamic-Chemo Therapy and the pH and NIR-Stimulated Drug Release

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## Experimental

**Materials and synthesis**

Tetrabutyl titanate, $NdCl_3 \cdot 6H_2O$, $YbCl_3 \cdot 6H_2O$, $TmCl_3 \cdot 6H_2O$ $GdCl_3 \cdot 6H_2O$, $Zn(NO_3)_2 \cdot 6H_2O$, and curcumin (Cur) were purchased from Sigma-Aldrich (Shanghai, China). Polyvinylpyrrolidone (MW 58,000), 2-methylimidazole, sulfur, NaOH, $NH_4F$, NaCl, urea, oxalic acid and glycol were purchased from Aladdin (Shanghai, China). All purchased chemicals were used directly without further purification.

**Synthesis of $NaGdF_4$: $Yb^{3+}$, $Tm^{3+}$, $Nd^{3+}$ UCNPs**

UCNPs were synthesized by a solvothermal method. 20 mL of ethylene glycol, 6 mmol of KF, 0.05 mmol of $TmCl_3$, 0.2 mmol of $YbCl_3$, 0.5 mmol of $NdCl_3$, 0.8 mmol of $GdCl_3$ and 1 mmol of NaCl were stirred and added into a polytetrafluoroethylene container, which was tightly sealed, and heated at 180 ºC for 12 h. The product was washed with water and ethanol thrice, dried, and stored for further use.

**Synthesis of small size $TiO_2$**

$TiO_2$ NPs were synthesized by a hydrothermal method. Briefly, 60 mL of water, 340 μL of tetrabutyl titanate, 0.9 g of urea and 0.6 g of oxalic acid were added into a polytetrafluoroethylene container which was heated at 180 ºC for 12 h. The obtained product was washed with water and ethanol three times, dried at 60 ºC, and stored for further use.

**Synthesis of UCNPs/$TiO_2$ @ ZIF-8**

20 mg of the UCNPs or $TiO_2$ was mixed with 100 mg of polyvinylpyrrolidone (PVP, Mw 58,000) in chloroform until chloroform was completely volatilized, and the materials were then redispersed in methanol. The products were centrifuged for

10,000 rpm for 15 min, excess PVP was removed.

UCNPs and $TiO_2$ were redispersed in 2 mL of methanol, followed by the addition 25 mM 2-MIM, stirred for 15 min, and finally 25 mM of zinc nitrate was added. The sample solution was incubated at 50 ºC for 2 h, washed three times with methanol for further use.

**Synthesis of UCNPs/ $TiO_2$/ Cur @ ZIF-8 nanocomposites**

10 mg UCNPs/$TiO_2$ @ ZIF-8 and 10 mg $mL^{-1}$ Cur methanol solution were mixed together and stirred for 24 h in the dark, centrifuged to remove the excess unreacted reagent to obtain the final nanocomposite.

## Characterization

**Physicochemical characterization**

The surface morphology and the size of as prepared UTCZ were characterized by scanning electron microscopy (SEM, Hitachi S3S-4800-II) and transmission electron microscopy (TEM, FEI Tecnai F20). The structural features of UTCZ were examined by X-ray diffraction (XRD) on a Bruker D8 Focus diffractometer at a scan rate of 0.02º $min^{-1}$ between 5-50º. Gas adsorption data were obtained by a gas adsorption analyzer (Autosorb iQ Station 2). The luminescence properties of $NaGdF_4$:Yb,Nd,Tm were characterized by using F-4500 fluorescence spectrophotometer (Hitachi, Japan) and 808 nm laser as excitation source. FTIR spectra were obtained on an VERTEX70 spectrometer. Cell viabilities were measured on a SYNERGY H1 microplate reader.

Stained cells were imaged with C2 laser confocal live cell imaging microscope of Nikon Corporation.

**Drug loading experiment**

The drug loading experiment has been added to explain the loading of curcumin. The standard curve of curcumin was made by measuring the OD value of curcumin with the microplate reader. Then UTCZ was dispersed at a concentration of 1mg $mL^{-1}$ and centrifuged at 8000 rpm for 3 minutes. The supernatant was detected by ultraviolet spectrophotometer. The OD value of the collected supernatant was measured with the microplate reader and calculated by the standard curve to obtain the quality of free curcumin. The loading rate of curcumin was calculated to be 33% by the following formula. Encapsulation efficiency (%) = (Total amount of curcumin -Free curcumin)/ Total amount of curcumin ×100%.

**Release of UTCZ at different pH values**

UTCZ (3 mg) was suspended in 2 mL of phosphate buffer saline solutions (PBS, pH 7.4, pH 6.8 and pH 5.4) containing 2.0 wt % Tween-80. Sample solutions were sealed in dialysis bag (Mw 3.5 kDa) and incubated in the release medium (8 mL) at 37 ºC under the stirring condition. At different time periods, 1 mL of buffer solution was replaced by 1 mL of fresh buffer solution outside the dialysis bag for UV-vis analysis. The 427 nm wavelength was used for Cur quantification and accumulative weight and relative percentage of the released Cur were calculated as a function of incubation time.

**The generations of extracellular and intracellular ROS**

The generation of extracellular ROS was measured with 1,3-diphenylisobenzofuran (DPBF) probe. In a typical process, 50 μg $mL^{-1}$ of UTCZ was dispersed in 1 mL EtOH : PBS (pH 5.4) = 1 : 4 in the presence of DPBF. The sample mixtures were illuminated with 808 nm laser light (0.5W $cm^{-2}$) for various time periods. The generation of ROS was characterized by UV-vis absorption changes of DPBF. SOSG (5 μM, methanol) was mixed with UCNPs, $TiO_2$, UZ, TZ, UTZ and UTCZ in PBS (pH 5.4) respectively. Under the illumination of 808 nm, their fluorescence spectra were recorded by microplate reader every 2 min to detect the fluorescence change of SOSG at 525 nm.

NIR light triggered ROS generation. 2,7-dichlorofluorescein diacetate (DCFH-DA) was used to record the generation of intracellular ROS. 1.6 x $10^5$ 4T1 cells were seeded into six well plates, and incubated with 100 μg $mL^{-1}$ PBS, UCNPs, $TiO_2$, UZ, TZ, UTZ and UTCZ for 4 hours. Then irradiated by 808 nm light at 0.5 W $cm^{-2}$ for 10 min, and incubated for another 2 h. After that, the cells were treated with DCFH-DA solution in the cell incubator for 20 min. And the generation of ROS were observed by a confocal fluorescence microscope (CLSM, Nikon, ECLIPSE Ti, Japan).

**In vitro cytotoxicity of UTCZ**

$10^5$ 4T1 cells were spread in a 96-well plate, cultured in Roswell Park Memorial Institute 1640 medium in a cell incubator at 37 ºC for 12 h. UCNPs, $TiO_2$, UZ(UCNPs@ZIF-8), TZ($TiO_2$@ZIF-8), UTZ (UCNPs/$TiO_2$@ZIF-8) and UTCZ were added at 100, 50, 25, 12.5 and 0 μg $mL^{-1}$. Cells were treated with or without light 808 nm laser light. The no light group was cultured for 24 h. The group with NIR light

was first cultured for 6 h, then irradiated by 808 nm laser light (0.5W $cm^{-2}$), and cultured for another 18 h. Then, 100 μL of 10% MTS was added and incubated for 120 min, the absorption at 490 nm was recorded with a microplate reader. For the live/dead assay, 4T1 cells were washed with PBS four times, and stained with propidium iodide (PI, 2 μM) and calcein AM (2 μM) for 0.5 h, then washed with PBS, and the fluorescence images were captured using a confocal microscope (Nikon, ECLIPSE Ti, Japan) with a 10× objective.

**Animal experiments and ex vivo histological staining**

Female BALB/c mice (18-21g, 4-6 weeks old, purchased from Center for Experimental Animals, Jilin University) were selected to establish the xenograft mice model. All animal studies were performed in the Center for Experimental Animals, Jilin University, and the procedures were in accordance with the protocols approved by the Committee for Animal Research of Jilin University, China. All the mice were implanted with 4T-1 tumor cells. When the tumor grew to about 200 $mm^3$, the 4T1 BALB/C mice were randomly divided into eight groups, with 6 mice in each group. The experimental conditions were as follows: (a) PBS + NIR (b) UCNPs + NIR; (c) $TiO_2$ + NIR; (d) UZ + NIR; (e) TZ + NIR; (f) UTZ + NIR; (g) UTCZ + NIR and (h) UTCZ without NIR. Mice were injected with 100μL of PBS, UCNPs, $TiO_2$, UZ, TZ, UTZ and UTCZ (10 mg Cur $kg^{-1}$ mouse), respectively.

To examine the in vivo therapeutic effect, the tumor region of the mice was intravenously injected with PBS, UCNPs, $TiO_2$, UZ, TZ, UTZ, or UTCZ, and was

irradiated once with 808 nm laser (0.5 W $cm^{-2}$, 10 min) after 24 h post-injection. The tumor volume was examined every day with a digital caliper, and tumor volume was calculated according to the following formula: $width^2$ x length/2. The body weight was measured using a laboratory balance every day within 14 days of treatment. The tumors as well as major organs (heart, liver, spleen, lung and kidney) were dissected from the mice after the phototherapeutic treatment, and fixed in a 4% formaldehyde solution overnight. The various tissues were frozen and cut into slices with a thickness of 10 μm. The slices were stained with haematoxylin & eosin (H & E) staining, and examined by a digital microscope [Nikon ECLIPSE Ui (Japan)].

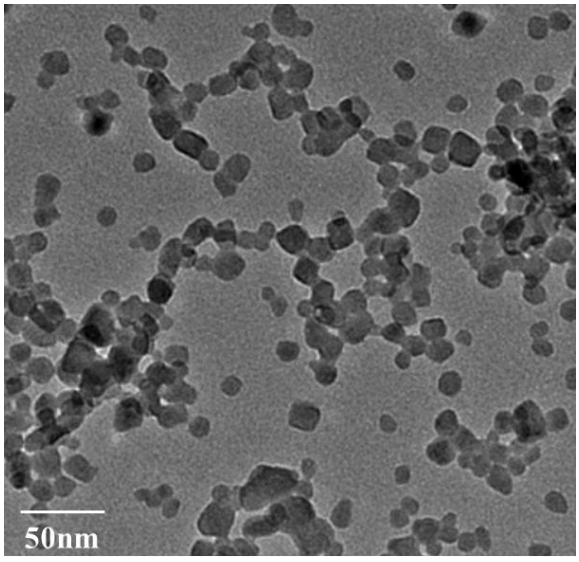


**Fig. S1.** TEM of UCNPs.

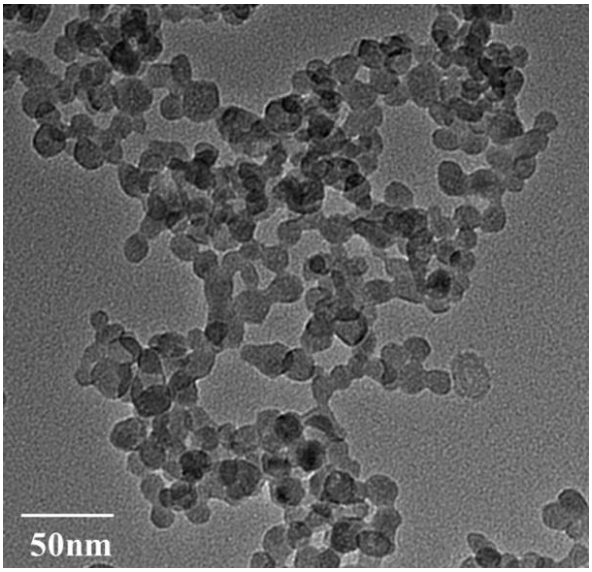


**Fig. S2.** TEM of $TiO_2$.

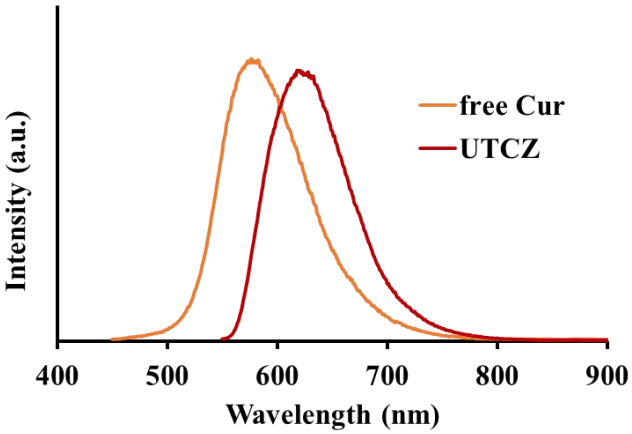


**Fig. S3.** The PL spectra of free Cur and UTCZ.

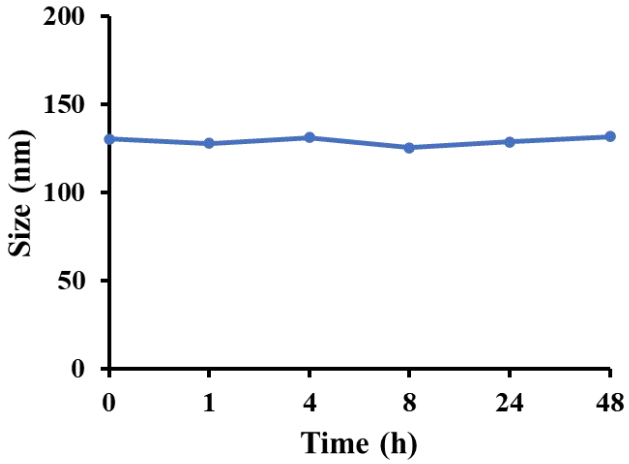


**Fig. S4.** DLS of UTCZ under physiological conditions.

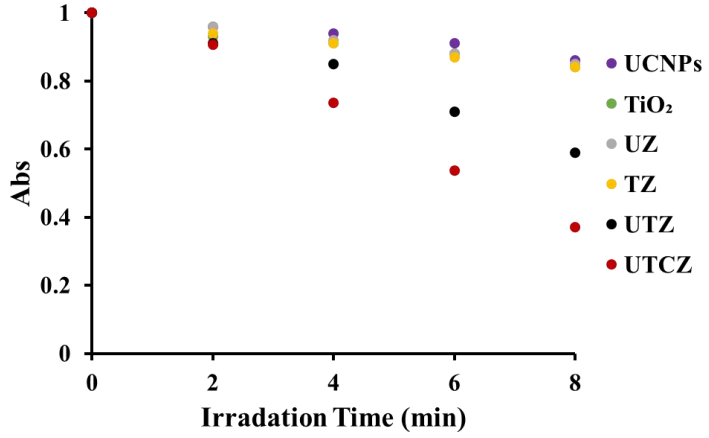


**Fig. S5.** DPBF UV-vis intensity changes at 416 nm in the presence of UCNPs, $TiO_2$, UZ, TZ, UTZ, UTCZ.

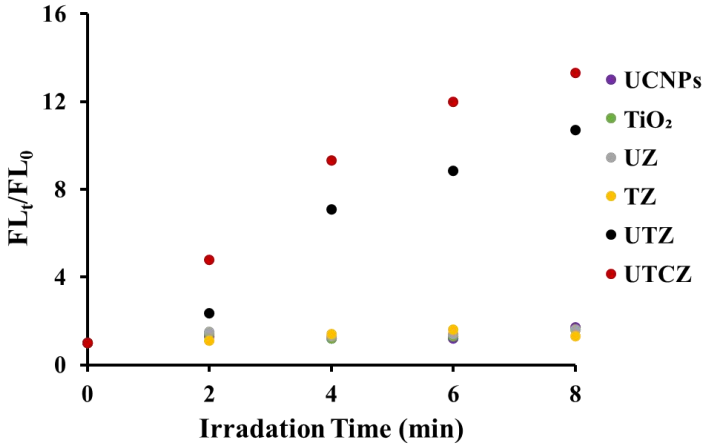


**Fig. S6.** The SOSG fluorescence changes at 525nm after treatment with UCNPs, $TiO_2$, UZ, TZ, UTZ, UTCZ.

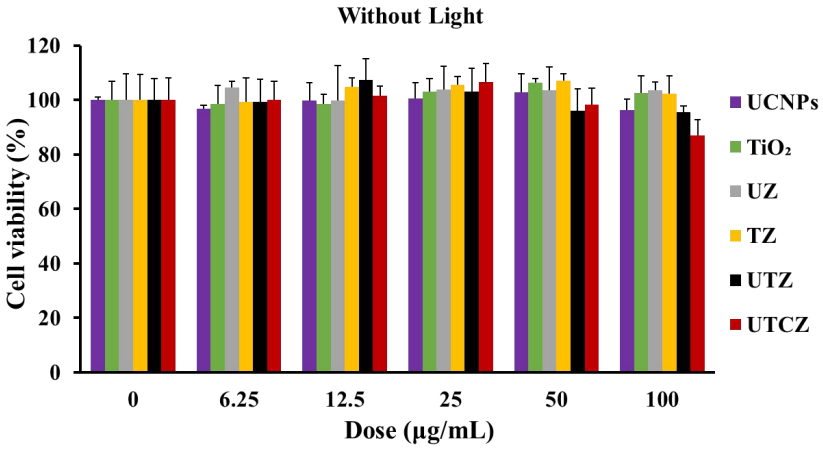

**Fig. S7.** Cytotoxicity of different materials without laser light illumination.

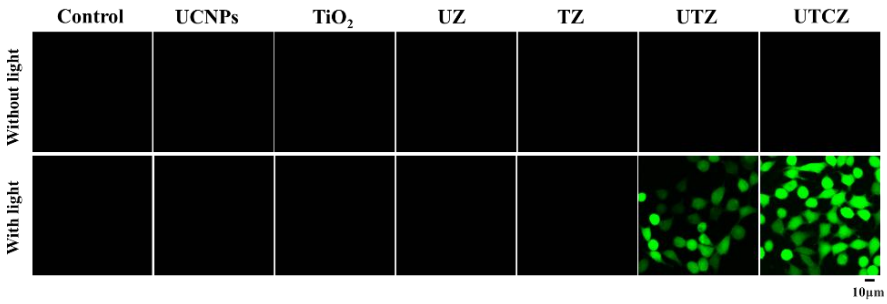


**Fig. S8.** Detection of ROS in 4T1 cells.

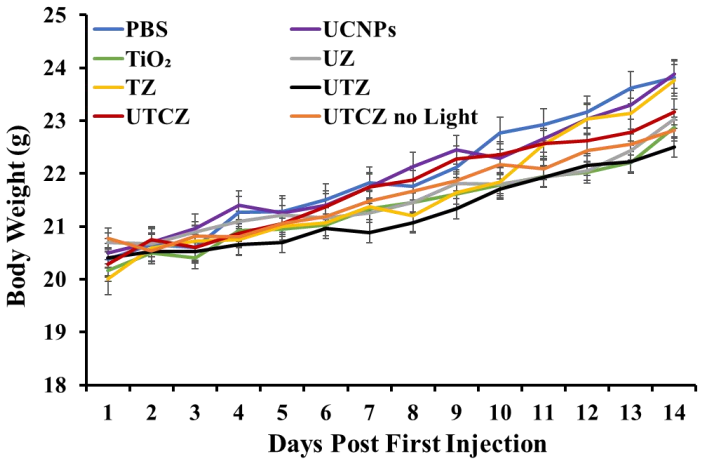


**Fig. S9.** Body weight changes of mice treated with different materials and for different periods of time.