

## Supporting Information (SI)

### **Near-Infrared Light-Induced Dissociation of Zeolitic Imidazole Framework-8 (ZIF-8) with Encapsulated CuS Nanoparticles and Their Application as Therapeutic Nanoplatfom**

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## Experimental Section

**Chemicals.** Zinc nitrate hexahydrate ( $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ ), 2-methylimidazole (2-MeIM), copper(II) chloride dihydrate ( $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ), sodium sulfide nonahydrate ( $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ ), silver nitrate ( $\text{AgNO}_3$ ), sodium borohydride ( $\text{NaBH}_4$ ), polyvinylpyrrolidone (PVP-k30, Molecular weight of 40 KDa), methanol ( $\text{CH}_3\text{OH}$ ), and ascorbic acid (AA) were obtained from Sinopharm Chemical Reagent Co., Ltd. Hexadecyl-trimethylammonium Bromide (CTAB) and  $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$  were purchased from Aldrich. DOX in the form of the hydrochloride salt was purchased from Shanghai Yuanye Biotechnology Company. RPMI-1640 culture medium was supplied by Jiangsu KeyGEN Biotech Limited Corporation. All reagents and solvents were used as received. Water used in experiments was purified by distillation of deionized water.

**Synthesis of PVP-modified CuS nanoparticles (NPs).** In a typical reaction, 10 mL of  $\text{CuCl}_2$  aqueous solution (3.5 mg/mL) and 10 mL of PVP aqueous solution (20 mg/mL) were added into 180 mL of water. The mixture was stirred for 30 min at room temperature. Next, to the above mixture, 800  $\mu\text{L}$  of  $\text{Na}_2\text{S}$  aqueous solution (60.54 mg/mL) was added. The resulting mixture was stirred for another 5 min before being transferred to a 90 °C water bath. The reaction was kept for 15 min. After the reaction, PVP-modified CuS solution was cooled to room temperature, and centrifuged to remove excess free PVP. Finally, PVP-modified CuS NPs were dispersed in methanol with the concentration of 96 mg/L.

**Fabrication of CuS@ZIF-8 NPs.** For the synthesis of CuS@ZIF-8 NPs, 2 mL of 2-methylimidazole methanol solution (8 mg/mL) and 1.5 mL of PVP-modified CuS methanol solution were added into 10 mL of methanol. After gently mixing by inversion, 2 mL of  $\text{Zn}(\text{NO}_3)_2$  methanol solution (27.5 mg/mL) was added into the above mixture at once under gentle stirring. The reaction solution was then left undisturbed at 50 °C for 2.5 h. After the reaction, the color of solution turned from transparent green to yellow-green, indicating the formation of CuS@ZIF-8 NPs. The resulting NPs were centrifuged at 13000 rpm for 8 min, then washed twice by methanol, and finally re-dispersed in 2 mL of methanol.

**Synthesis of ZIF-8.** In a 25 mL flask, 6 mL of 2-methylimidazole (16 mg) methanol solution and 6 mL of  $\text{Zn}(\text{NO}_3)_2$  (55 mg) methanol solution were mixed together. The resulting mixture was then heated at 50 °C for 2.5 h. After the reaction, the as-prepared ZIF-8 were separated by the centrifugation at 13000 rpm for 8 min, washed twice by methanol, and finally re-dispersed in 2 mL of methanol.

**Procedure for DOX encapsulation.** Briefly, 15 mg of CuS@ZIF-8 NPs were added to 3 mL of DOX solution (200  $\mu\text{g}/\text{mL}$ ), and further stirred for 24 h. DOX-loaded CuS@ZIF-8 NPs was collected by the centrifugation, and further washed by methanol for three times. The concentration of DOX before or after interaction with CuS@ZIF-8 NPs was determined at 480 nm by UV-vis absorption spectrum.

**Photothermal effect of CuS@ZIF-8 NPs.** For the purpose of investigating the photothermal effect of CuS@ZIF-8 aqueous solution, ZIF-8 or CuS@ZIF-8 aqueous solution with various concentrations ranging from 0 to 100  $\mu\text{g/mL}$ , were irradiated by a 980 nm NIR laser (diode laser, MW-GX-980/1~5000 mW, Chinese) for 7 min. The temperature change of resulting aqueous solution was monitored by an IR thermal imaging (FLUKE) and recorded once every 30s.

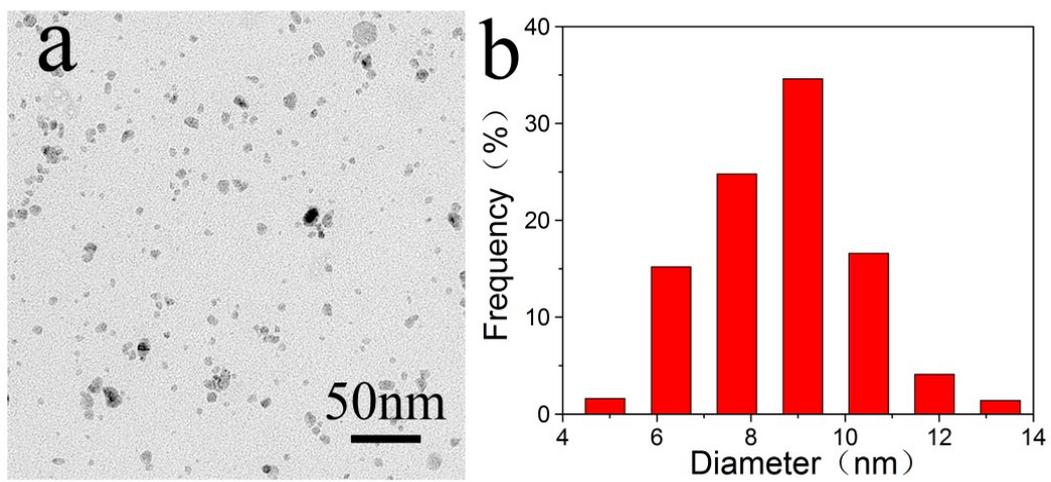
***In vitro* release of DOX from DOX-loaded CuS@ZIF-8 NPs.** The release of DOX triggered by pH, NIR-light or being heated was separately studied according to the literature.<sup>1</sup> To investigate time-dependent cumulative release profiles of DOX loaded CuS@ZIF-8 under various pH, we dispersed 5 mg of NPs in 20 mL of buffer solution (pH 7.4, 6.0 or 5.0, respectively) at 37 °C. The resulting mixture was kept stirring. 1 mL of release medium was sampled at each time point, and the concentration of DOX released into the solution was determined by the UV-vis spectrophotometry. After the measurement, the sample was returned to the original release system. Similar to the above procedure, the release profiles of DOX triggered by 980 nm laser irradiation or being heated at 80 °C under various pH were also measured. In the latter two cases, the mixture solution was exposed to the 980 nm laser (5W) irradiation or heated at 80 °C water bath simultaneously.

***In vitro* Cytotoxicity Assay.** The cell toxicity was analyzed by standard MTT assay using MCF-7 cells. First, MCF-7 cells were seeded in a 96-well plate with a density of  $1 \times 10^4$  cells per well for 24 h. Then, CuS@ZIF-8 NPs (0, 65, 125, 250, 500 and 1000  $\mu\text{g/mL}$ ), DOX (with the equivalent concentration to that loaded inside CuS@ZIF-8) or DOX loaded CuS@ZIF-8- NPs (0, 0.1, 0.5, 1, 5, 10, 20  $\mu\text{g/mL}$ ) was added into the culture medium. After 24 h incubation, the medium was aspirated. The cells were then washed twice with PBS to eliminate the remaining NPs. Next, 100  $\mu\text{L}$  of fresh culture medium was added to each well, followed by the addition of 20  $\mu\text{L}$  of MTT solution (5 mg/mL in PBS). The cells were incubated for another 4 h at 37 °C, and the medium was then carefully aspirated followed by adding 150  $\mu\text{L}$  DMSO each well. Finally, the absorbance value at 570 nm was measured against a background control using a Thermo Scientific Multiskan FC microplate photometer. The cytotoxicity was expressed as the percentage of cell viability compared to the untreated control cells.

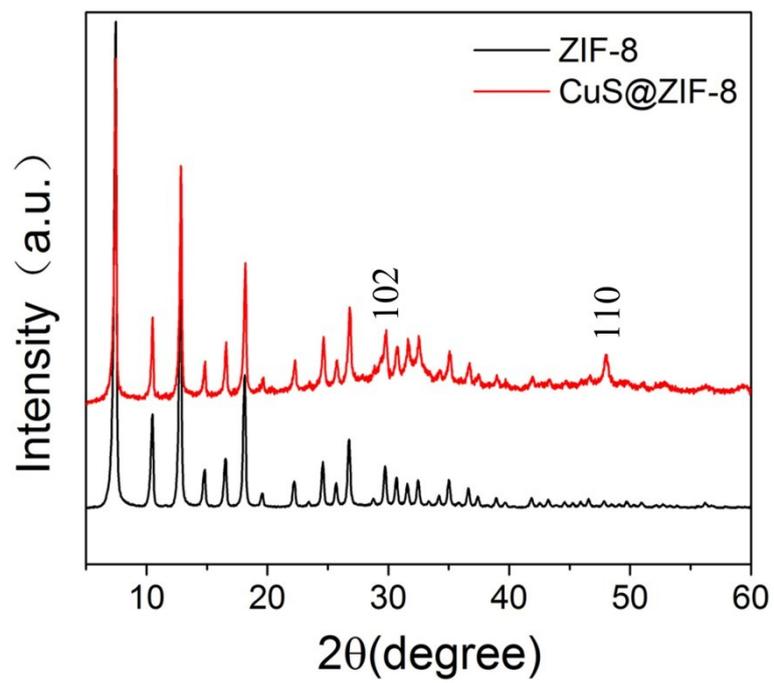
***In vitro* synergistic chemo- and photothermic therapy.** MCF-7 cells were seeded in 96-well culture plate at a density of  $1 \times 10^4$  cells per well for 24 h in 5%  $\text{CO}_2$  at 37 °C. And the resulting Cells were then incubated with CuS@ZIF-8 (25  $\mu\text{g/mL}$ ), DOX (1  $\mu\text{g/mL}$ ) or DOX loaded CuS@ZIF-8 (25  $\mu\text{g/mL}$ ) for 12 h, respectively. After that, they were washed twice by PBS solution, and 100  $\mu\text{L}$  of cell medium was then added to each well. Next, MCF-7 cells were irradiated with NIR laser (980 nm, 5W) for 0, 1, 2, 4 or 6 min, respectively. After another 2 h incubation, 20  $\mu\text{L}$  of 5 mg/mL MTT solution were added into each well, followed by the incubation for an additional 4 h at 37°C. Afterwards, each well was treated with 150  $\mu\text{L}$  of DMSO in order to solubilize the blue formazan precipitate before measuring the absorbance at 570 in a Thermo Scientific Multiskan FC microplate photometer.

***In vivo* Photothermal Treatment.** Nine nude mice (body weights of 18~20 g) with breast-cancer tumor were acquired from the Center of Experimental Animals of Southeast University, and randomized into three groups (n=3 per group). All animal experiments were approved and performed in accordance with the Animal Management Rules of the Ministry of Health of the People's Republic of China and the guidelines for the care and use of the Southeast University Laboratory Animal Center. These breast tumor-bearing mice were intratumorally injected with saline (group I), free DOX (group II) (40  $\mu$ L, 200  $\mu$ g /mL), or DOX loaded CuS@ZIF-8 NPs (40  $\mu$ L, 5 mg/mL), separately. Afterwards, these mice were exposed to 980 nm laser (5 W) irradiation. Thermal images were taken every minute using an Infrared camera of FLUKE. The morphology of tumor in each mouse was comparatively observed every two days for up to 9 days.

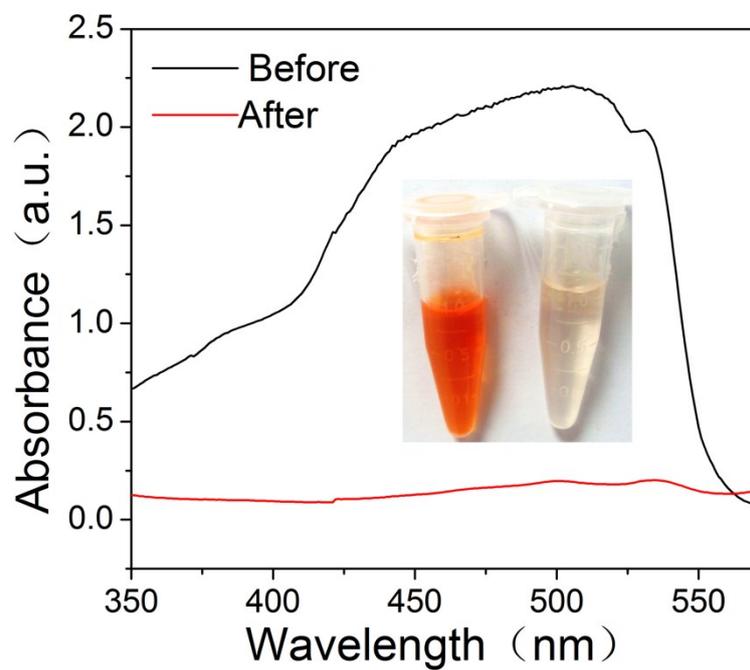
***Characterization.*** UV-vis absorption spectra were recorded on a Helios Gamma spectrophotometer between 400 and 1100 nm. The morphology and size of the NPs were characterized by transmission electron microscopy (TEM, a JEOL JEM 2100 F electron microscope operated at 200 kV) and scanning electron microscopy (SEM, a Zeiss Ultra Plus field emission SEM). X-ray diffraction (XRD) patterns were acquired by using an X-ray diffraction system (Ultima IV, Japan). Nitrogen adsorption/desorption isotherms were measured at 77 K on a nitrogen adsorption apparatus (Micromeritics ASAP 2010 volumetric adsorption apparatus) after degassing of the sample at 120  $^{\circ}$ C for 3 h.



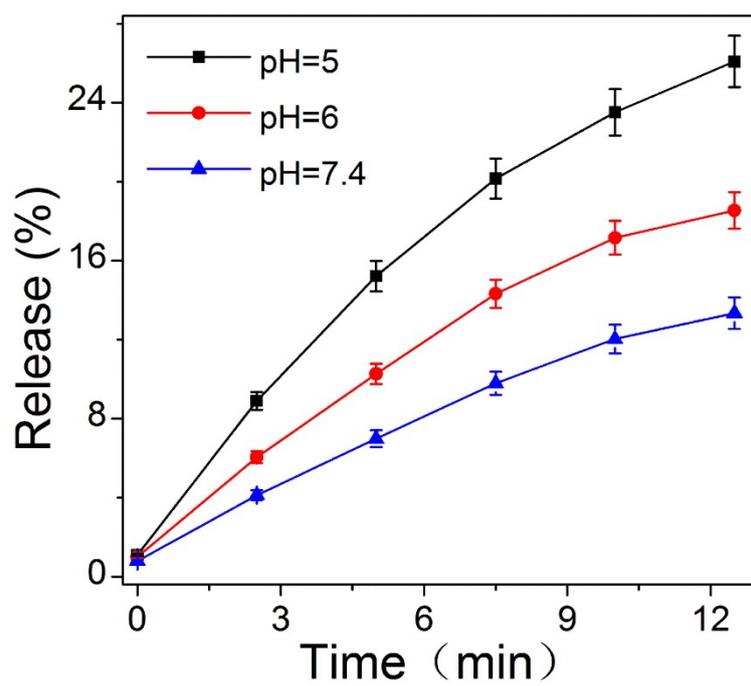
**Figure S1.** TEM image (a) and the corresponding size distribution of PVP-stabilized CuS NPs (b).



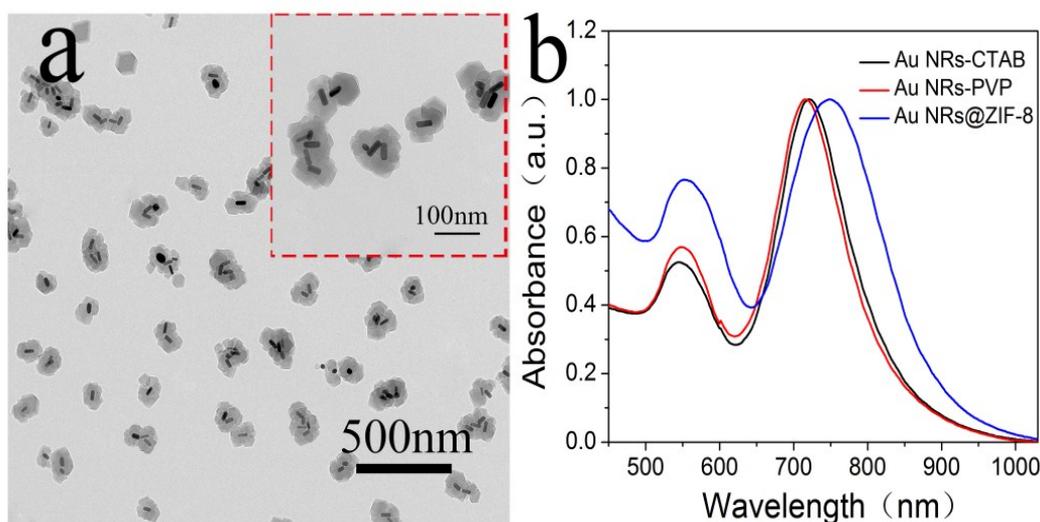
**Figure S2.** XRD spectra of ZIF-8 and CuS@ZIF-8 NPs.



**Figure S3** UV-vis absorption spectra of DOX solutions before and after interaction with CuS@ZIF-8 NPs.



**Figure S4** DOX-release profiles of DOX loaded CuS@ZIF-8 NPs when being heated at 80 °C.



**Figure S5.** TEM image of Au NRs@ZIF-8 NPs (a), and UV-vis absorbance spectra of Au NRs-CTAB, Au NRs-PVP and Au NRs@ZIF-8 (b).

**Synthesis and surface modification of Au nanorods (Au NRs).** Au NRs were synthesized according to the literature.<sup>2</sup> To facilitate the *in situ* formation of the ZIF-8 around Au NRs, the CTAB ligands on Au NRs were further replaced by PVP in advance. In the typical procedure, 20 mL of CTAB stabilized Au NRs was first centrifuged to remove the excess CTAB. The resulting CTAB stabilized Au NRs was then re-dispersed in 10 mL of water with the concentration of 0.8 mM, followed by the addition of 35 mg of PVP (K-30). The resulting mixture was stirred for 24 h at room temperature. Finally, PVP stabilized Au NRs were obtained by the centrifugation, and further dispersed in water again.

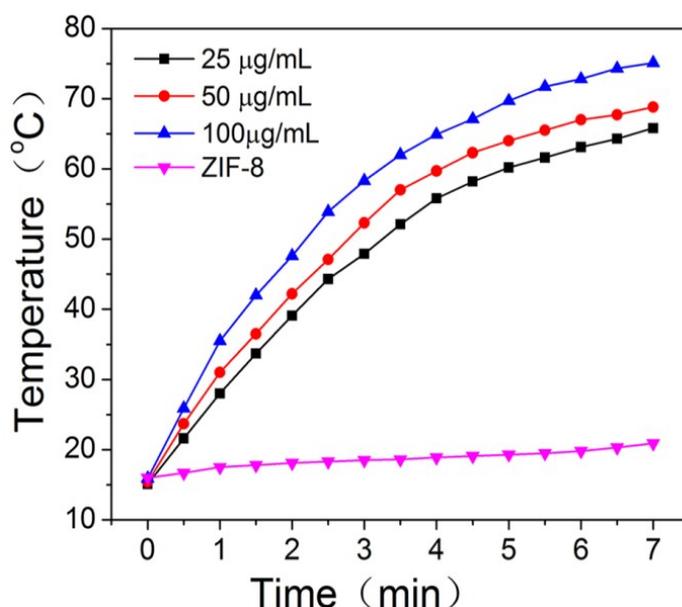
**Fabrication of Au NRs@ZIF-8.** 2.4 mL of  $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  methanol solution (24 mM) was added into 0.8 mL of 2-methylimidazole aqueous solution (1.32 M), and the resulting mixture was gently mixed by inversion. To the above mixture, 0.8 mL of PVP stabilized Au NRs solution was added. The resulting mixture solution was stirred for another 5 minutes. Afterwards, the solution was left undisturbed at 30 °C for 3 h. With the proceeding of the reaction, the color of solution turned from semi-transparent claret to opaque cardinal, indicating the formation of Au NRs@ZIF-8 NPs. After the reaction, the resulting NPs were centrifuged at 13000 rpm for 8 min, washed twice by methanol, and finally re-dispersed in 2 mL of methanol.

As shown in Figure S5a, most of Au NRs are encapsulated in ZIF-8 matrix with the core-shell structure, where there is generally one or two Au NRs in every single nanocomposite. From UV-vis-NIR absorption spectra (Figure S5b), it can be found that for CTAB stabilized Au NRs there are the broad absorption between 600 and 900 nm, and the plasmon peak is centered near 725 nm. After the

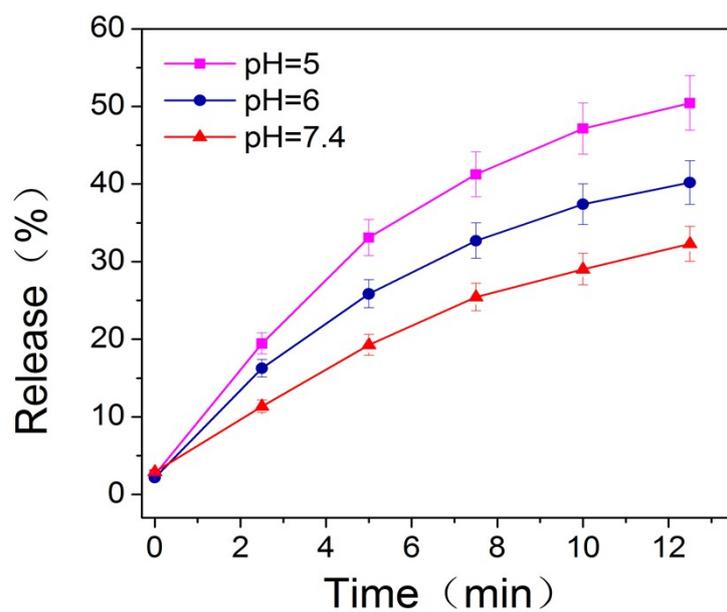
coating of ZIF-8, the peak of Au NRs@ZIF-8 shifts to 765 nm. Therefore, for Au NRs@ZIF-8, 808 nm laser instead of 980 nm laser was used in the experiment.

The photothermal conversion ability of resulting Au NRs@ZIF-8 under 808 nm laser irradiation was also studied. As shown in Figure S6, the Au NRs@ZIF-8 solution with the concentration of 0.1 mg/mL can be heated up to 75 °C in 7 min.

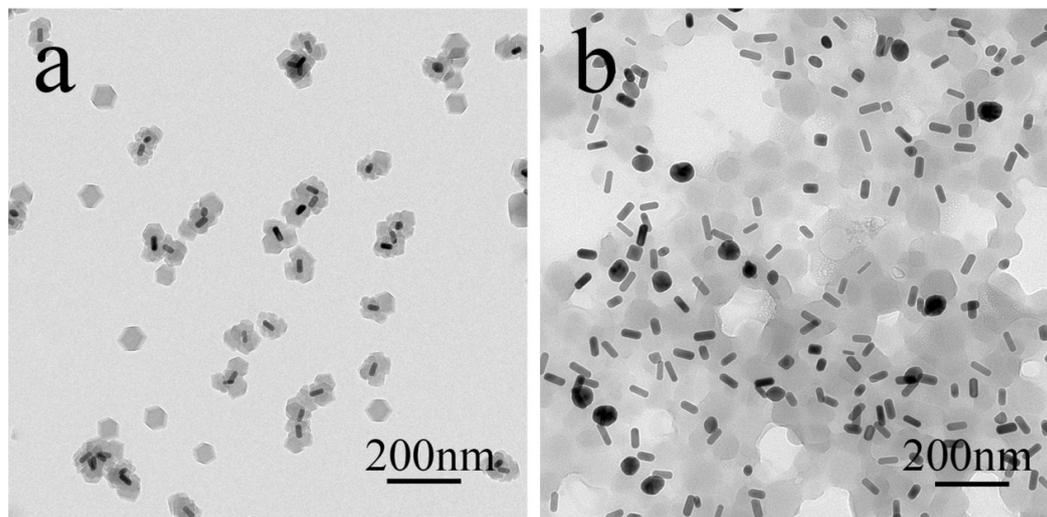
Figure S7 gives the NIR light-responsive DOX release profile of DOX loaded Au NRs@ZIF-8 NPs at various pH. It can be found that the release of DOX is obviously accelerated in comparison with that obtained by CuS@ZIF-8 NPs. Similar to CuS@ZIF-8 NPs, nearly 31 % of the DOX is released in 12 min when irradiated at 808 nm, which is also higher than 15 % obtained when DOX-loaded CuS@ZIF-8 is heated at 80°C.



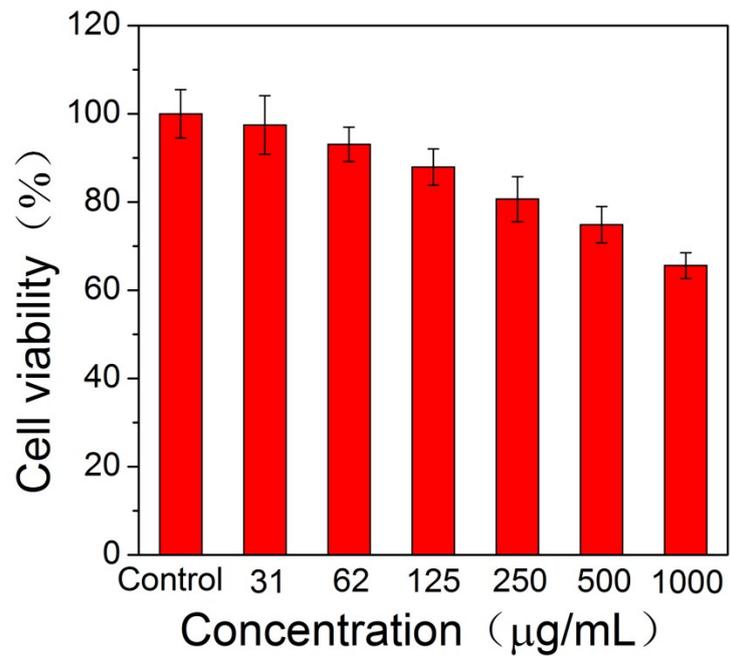
**Figure S6.** Temperature elevation of Au NRs@ZIF-8 with different concentrations (0, 25, 50, 100 µg/mL) as a function of irradiation time (808 nm, 5W).



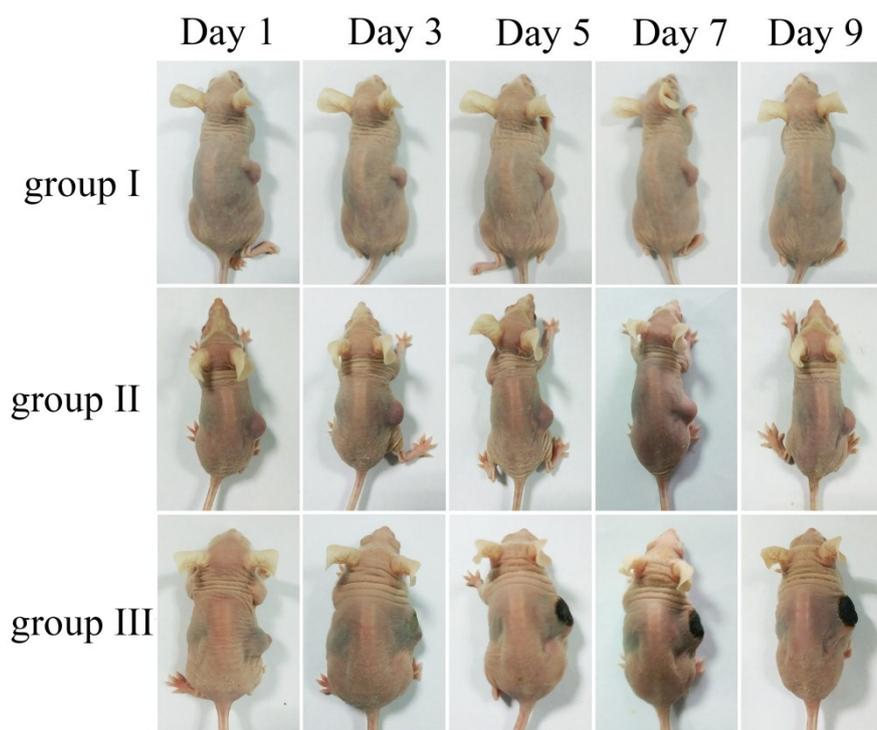
**Figure S7.** DOX-release profiles of DOX loaded Au NRs@ZIF-8 NPs when exposed to NIR laser irradiation (808 nm, 5W).



**Figure S8.** TEM images of DOX loaded Au NRs@ZIF-8 NPs exposed to NIR laser irradiation for 0 min (a), and 12 min (b).



**Figure S9.** Cell viability of MCF-7 cells after 24 h incubation in presence of CuS@ZIF-8 NPs with different concentrations.



**Figure S10.** Photos of breast cancer-bearing mice at different time after the treatments: saline (control, group I), DOX (group II) and DOX loaded CuS@ZIF-8 NPs (group III) during 3 min irradiation of 5 W NIR every day.

## References

1. H. Q. Zheng, Y.N. Zhang, L. F. Liu, W. Wan, P. Guo, A. M. Nystrom, and X. D Zou, *J. Am. Chem. Soc.*, 2016, **138**, 962–968.
2. L.M. Zhang, K. Xia, Z. X. Lu, G. P. Li, J. Chen, Y. Deng, S. Li, F. M. Zhou and N.Y. He, *Chem. Mate*, 2014, **26**, 1794–1798.