Electronic Supplementary Information

Covalent organic framework based nanoagent for H_2S-activable phototherapy against colon cancer

Jie Feng,[‡,] Wen-Xiu Ren,[‡] Fei Kong, Yu-Bin Dong**

College of Chemistry, Chemical Engineering and Materials Science, Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Key Laboratory of Molecular and Nano Probes, Ministry of Education, Shandong Normal University, Jinan 250014, P. R. China.

Corresponding author email address: jiefeng@sdnu.edu.cn, yubindong@sdnu.edu.cn

‡J.F. and W.-X.R. contributed equally to this work.

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Experimental Procedures

1. Materials and Instrument

Materials: All reagents are analytically pure and used directly without further purification. N,N-Dimethylformamide (DMF), glacial acetic acid, ethanol, and methanol were purchased from Sinopharm Chemical Reagent Co., Ltd. $CuCl_2 \cdot 2H_2O$, o-dichlorobenzene, dimethyl sulfoxide (DMSO), AOAA and SAM were purchased from Shanghai Macklin Biochemical Co., Ltd., 5,10,15,20-tetra(4-aminophenyl) porphyrin was purchased from Jilin Yanshen Technology Co., Ltd., 2,5- Dihydroxyterephthalaldehyde was purchased from ArK Pharm, Inc (Chicago, USA). Active oxygen detection kit (DCFH-DA) was purchased from Shanghai Biyuntian Biotechnology Co., Ltd. 1,3-diphenylisobenzofuran (DPBF) and NaHS was purchased from Sigma-Aldrich (Shanghai) Trading Co. Ltd. (4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) was purchased from Sigma-Aldrich (Shanghai) Trading Co. Ltd. Living dead cell staining kit (calcein-AM, PI) was purchased from Shanghai Yisheng Biotechnology Co., Ltd. 4% formaldehyde universal tissue fixative was purchased from Biosharp Co., Ltd.Dulbecco's Phosphate-Buffered Saline (DPBS), and Fetal Bovine Serum (FBS) were purchased from Biological Industries USA, RPMI Medium Modified (1640), Penicillin Streptomycin Mixtures (Pen-Strep), and Trypsin-EDTA Solution (0.25%) were purchased from HyClone Laboratories. Human colorectal cancer (HCT116) cells, which were purchased from the Procell Life Science & Technology Co., Ltd.

Instrument : Ultraviolet–visible (UV−vis) absorption spectra were recorded on a Shimadzu UV-2700 Double Beam UV−vis Spectrophotometer. Scanning electron microscopy (SEM) micrographs were recorded on a Hitachi SU8010 Scanning Electron Microscope. Transmission electron microscope (TEM) micrographs were recorded on a Hitachi HT7700 120kV Compact-Digital Transmission Electron Microscope. Powder X-ray diffraction (PXRD) patterns were obtained on a Rigaku Smart Lab SE X-Ray Powder Diffractometer with Cu Kα line focused radiation (λ = 1.5405 Å) from 2θ = 2.00° up to 50.00° with 0.01° increment. Fourier transform infrared (FT-IR) spectra were obtained in the 4000–400 cm^{-1} range using a Thermo Scientific Nicolet iS50 FT-IR Spectrometer equipped with diamond attenuated total reflection (ATR) module. Each spectrum was the average of 16 scans. Nitrogen adsorption isotherms were measured at 77 K with KUBO-X1000 aperture specific surface area analyzer. Hydrodynamic particle size and zeta potential were measured using Malvern Zetasizer Nano ZS90 System. Inductively coupled plasma (ICP) measurements were obtained on Thermo Scientific iCAP 7000 ICP-OES. Laser scanning confocal fluorescence images were captured with a Leica TCS SP8 Confocal Laser Scanning Microscopy with an objective lens (×20). The fluorescence images of the cells

were performed on a confocal laser scanning microscope (TCS SP8, Leica, Wetzlar, Germany) with a pointed excitation wavelength. Cell proliferation data were obtained by Full-wavelength, multi-channel microporous plate detector-SpectraMax 190 optical absorption marker. Thermogravimetric analysis (TGA) was obtained by Mettler Toledo TGA2 thermogravimetric analyzer. All fluorescence measurements were performed on an F-4600 spectrofluorometer (Hitachi, Japan) equipped with a circulating water bath for temperature control. X-ray photoelectron spectroscopy (XPS) was performed using an ESCALAB 250 X-ray photoelectron spectrometer with a monochromatized Al Kα X-ray source (1486.71 eV).

2. Synthesis of CuTph, DhaTph, **Cu-DhaTph**

Synthesis of CuTph. A mixture of porphyrin (93.12 mg, 0.138 mmol) and $CuCl_2 \cdot 2H_2O$ (46.9 mg, 0.275 mmol) in DMF (20 mL) was degassed three times by refrigeration pump thawing technology, sealed under nitrogen, and then heated at 120°C for 4 h. After cooling to room temperature, approximately 80 mL of water was added to the above solution. The resulting precipitate was collected by filtration, then washed with methanol for several times and dried under vacuum at 60°C for 12 hours. The characteristic of the as-prepared CuTph was carried out by FT-IR, UV-vis, XPS and fluorescence spectra. The FT-IR, UV-vis, XPS and fluorescence spectra of Tph and CuTph are shown in Figures S1-S4. FT-IR (ATR, cm^{-1}): 3435 (w),3344 (m), 3208 (w), 3027 (m), 1672 (w), 1615 (s), 1532(w), 1504 (s), 1443 (w), 1425 (w), 1404 (w), 1345 (m), 1280 (m), 1202 (w), 1177 (m), 1118 (w), 1068 (w), 1026 (w), 998 (m), 961 (w), 870 (w), 847 (w), 798 (m), 714 (m), 643 (w), 599 (w), 561 (w), 527 (w), 428 (w).

Synthesis of DhaTph. The synthesis of DhaTph was synthesized according to the reported literature**.**[1] Typically, 2,5-dihydroxyterephthalaldehyde (**Dha**) (13.3 mg, 0.08 mmol) and tetra(*p*amino-phenyl)porphyrin (**Tph**) (27.0 mg, 0.04 mmol) were added to a combination solution of dichlorobenzene and ethanol (2 mL, 1:1) in acetic acid (0.2 mL, 6 M). The mixture was ultrasonically treated for 10-15 minutes to obtain a uniform dispersion solution. Then the test tube was quickly frozen at 77K (liquid N_2 tank), degassed through three freeze-pump-thaw cycles, sealed and heated at 120°C for 3 days. Finally, the DhaTph powders were filtered out, washed with ethanol for several times, and dried under vacuum at 150°C for 12 hours. FT-IR (ATR, cm^{-1}): 3463 (w), 3372 (w), 3314(w), 3208(w), 3099(w), 3031(w), 2967 (w), 2870 (w), 2700 (w), 1665(m), 1613 (s), 1589 (m), 1510 (w), 1493 (m), 1471 (m), 1400 (w), 1336 (m), 1310 (m), 1213 (m), 1178 (w), 1152 (s), 1109 (w), 1018 (w), 983 (w), 966 (m), 889 (w), 872 (w), 851 (w), 796 (m), 734 (m), 681 (w), 639 (w), 563(w), 529(w), 492(w).

Synthesis of Cu-DhaTph. The synthesis of **Cu-DhaTph** was carried out by utilizing the same protocol with a mixture of 2,5-dihydroxyterephthalaldehyde (Dha) (13.3 mg, 0.08 mmol) and CuTph (29.5 mg, 0.04 mmol) in presence of acetic acid (0.2 mL, 6M) using a solvent mixture of dichlorobenzene and ethanol (2 mL) in 1:1 of volume ratio. The mixture was ultrasonically treated for 10-15 minutes to obtain a uniform dispersion solution. Then the test tube was quickly frozen at 77K (liquid N_2 tank), degassed through three freeze-pump-thaw cycles, sealed and heated at 120°C for 5 days. Finally, the **Cu-DhaTph** powders were filtered out, washed with ethanol for several times, and dried under vacuum at 150°C for 12 hours. The H_2S-activated the **Cu-DhaTph** has been confirmed by the fluorescence spectra. Yield: 69%. FT-IR (ATR, cm^{-1}): 3376 (w), 3209 (w), 2976 (w), 2927 (w), 2855 (w), 1666(w), 1614 (s), 1592 (m), 1493 (m), 1395 (w), 1344 (m), 1305 (m), 1207 (m), 1154 (s), 1111 (w), 1085 (w), 1001 (m), 963 (w), 891 (w), 872 (w), 854 (w), 812 (w), 797 (m), 780 (w), 716 (m), 683 (w), 656 (w), 574 (w), 540(w), 486(w), 458(w).

3. Photodynamic and photothermal performance of H_2S-activated **Cu-DhaTph**

Singlet Oxygen ($^1O_2$) detection. The $^1O_2$ generation ability of H_2S-activated **Cu-DhaTph** was examined by 1,3-diphenylisobenzofuran (DPBF). DPBF was a commercial $^1O_2$ probe whose absorption intensity can be obvious decreased when reacted with $^1O_2$.[2] The experimental groups, **Cu-DhaTph** (100 μg/mL), was firstly incubated with NaHS (70 μM) in phosphate buffer saline buffers (PBS, pH = 7.4) for 120 min. Then 10 mM of DPBF was added into the resulted solution, and irradiated with a 660 nm laser irradiation (50 mW/cm^2) for 1 min. Every ten seconds recorded the absorption intensity by UV-vis spectrum. In addition, the group of **Cu-DhaTph** without H_2S-pretreated but under irradiation was used as control to evaluate the $^1O_2$ controlled release by H_2S. The generation of $^1O_2$ ability was also investigated in group of DPBF, DPBF with irradiation and **Cu-DhaTph** pretreated H_2S but without irradiation, which was carried out under the similar condition with above.

Photothermal performance testing. A thermoelectric thermometer was carried out to measure the temperature change in the **Cu-DhaTph** dispersions in the presence of NaHS upon 808 nm laser (2 W/cm^2) irradiation. Typically, **Cu-DhaTph** solution (200 μg/mL) was first incubated with NaHS (70 μM) for 2 h, and then irradiated with 808 nm laser for 10 min with different power density (0.5, 1, 1.5, 2, 2.5 W/cm^2). In addition, the homogenized dispersed solution of **Cu-DhaTph** without NaHS initiator was used as a control to further evaluate the ability of local heat generation for H_2S-activated **Cu-DhaTph**. This control experiment is carried out under the similar condition with above, except for the absence of NaHS initiator. The temperature various of different concentration of **Cu-DhaTph** (0, 50, 100, 200, 400, 800 μg/mL) pretreated with NaHS (70 μM) for 2 h was also studied, followed a similar

procedure described above. The photothermal stability of **Cu-DhaTph** was evaluated by irradiated the NaHS-treated **Cu-DhaTph** (200 μg/mL) to the max temperature and then turn off the laser and cooled to room temperature naturally. Repeated this operation for at least five cycles. The photothermal conversion efficiency (η) was calculated by the precious reported method and equation.[3]

4. Confocal imaging

Cell uptake. HCT116 cells were seeded in a 6-well plate and incubated at a humidified incubator in 5% CO_2/95% air at 37 °C for 24 h. Then, the cell medium was replaced by the fresh cell medium containing **Cu-DhaTph** (200 μg/mL), and incubated for the pointed time, including 0, 1, 2, 4, 8, and 24 h. After removed the cell medium and washed with cold PBS for three times, the resulted cells were collected, digested by aqua regia and then diluted to 10 mL for ICP-MS analysis. The cell uptake efficiency can be calculated according the measured content of copper ions in cells.

Intracellular production of reactive oxygen species (ROS). HCT116 cells were seeded in a confocal dish and incubation at a humidified incubator in 5% CO_2/95% air at 37 °C for 24 h. Then, the cell medium was replaced by the fresh 1640 medium containing **Cu-DhaTph** (200 μg/mL), and incubated for another 4 h. After removed the cell medium containing **Cu-DhaTph**, the cells were incubated with a ROS probe, 2,7-Dichlorodihydrofluorescein diacetate (DCFH-DA), for another half hours at 37 °C. Then the resulted cells were under 660 nm laser irradiation (50 mW/cm^2) for 1 min. Afterwards, the cells were imaged by the confocal laser microscope at 488 nm excitation. In addition, the cells without any treatment, the cells under 660 nm laser irradiation, treated with **Cu-DhaTph**, treated with DhaTph under 660 nm laser irradiation (50 mW/cm^2) for 1 min were used as a control to further evaluate the ability of ROS generation for H_2S-activated **Cu-DhaTph**. This control experiment is carried out under the similar condition with above.

Live/dead cells staining assays. Six groups of HCT116 cells were seeded in confocal dishes and incubation at a humidified incubator in 5% CO_2/95% air at 37 °C for 24 h. Then, the six groups of cells were treated differently: group 1, PBS, without any treatment and cultured for another 24 h in the dark only; group 2, PBS + Laser, without any treatment and cultured for another 24 h after being irradiated with 660 nm (50 mW/cm^2) for 5 min and 808 nm laser for (2 mW/cm^2) for 10 min; group 3, **Cu-DhaTph**, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h; group 4, **Cu-DhaTph** + PTT, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 808 nm (2 W/cm^2) for 10 min; group 5, **Cu-DhaTph** + PDT,

pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 660 nm (50 mW/cm^2) for 5 min; group 6, **Cu-DhaTph** + PDT + PTT, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 660 nm (50 mW/cm^2) for 5 min and 808 nm laser for (2 mW/cm^2) for 10 min. Afterwards, the six groups of cells were stained by the Calcein-AM (AM) (2 μM) and PI (4.5 μM) at 37 °C for half an hour. After being washed by PBS for three times, the cells were imaged by the confocal laser microscope at 488 nm excitation and 543 nm excitation, respectively.

5. MTT assays

Biocompatibility. To evaluate the biocompatible of **Cu-DhaTph**, HCT116 cells were seeded into 96-well plates and incubation at a humidified incubator in 5% CO_2/95% air at 37 °C for 24 h. Then the cells medium was replaced by the fresh cell medium containing different concentrations of **Cu-DhaTph** (0, 25, 50, 75, 100, 150, 200, 400 μg/mL), and incubated for another 24 h. Afterwards, removed the cells medium and washed with PBS for three times. Then MTT (100 μL, 0.5 mg/mL) solution was added and incubated at 37 °C. After four hours, removed the remaining MTT solution and added the DMSO (150 μL) into each well to dissolve the formazan crystals. Microplate reader was carried out to record the absorbance at 490 nm.

In vitro phototherapy effect. To investigate the phototherapy effect of the **Cu-DhaTph**, HCT116 cells were seeded into 96-well plates and incubation at a humidified incubator in 5% CO_2/95% air at 37 °C for 24 h. Then the cells medium was removed and treated differently: group 1, **Cu-DhaTph**, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h; group 2, **Cu-DhaTph** + PTT, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 808 nm (2 W/cm^2) for 10 min; group 3, **Cu-DhaTph** + PDT, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 660 nm (50 mW/cm^2) for 5 min; group 4, **Cu-DhaTph** + PDT + PTT, pre-incubated with **Cu-DhaTph** (200 μg/mL) for another 4 h and washed with fresh 1640 medium, and then cultured for another 24 h after being irradiated with 660 nm (50 mW/cm^2) for 5 min and 808 nm laser for (2 W/cm^2) for 10 min. Afterwards, the cell viability of the six groups was investigated by MTT assay using the method described in above.

6. Animal assays

Animal tumor xenograft models. Female BALB/c nude mice (aged 5~6 weeks, and 15~20 g body weight) purchased from the Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China) were used for tumor xenograft establishment. Animal experiments were reviewed and approved by the Ethics Committee of Shandong Normal University, Jinan, P. R. China (approval number AEECSDNU2021041). All the animal experiments complied with relevant guidelines of the Chinese government and regulations for the care and use of experimental animals. Typically, each mouse was subcutaneous injected with 1×10^6 of living HCT116 cells dispersed in 60 μL of PBS. The injection sites were under the armpit of nude mice. When the tumor volume reached to approximately 100 mm^3, the following experiments were carried out.

In vivo NIR-thermal imaging. The HCT116 subcutaneous xenograft nude mice was randomly split into four groups, and referred to as the phosphate-buffered saline (PBS), **Cu-DhaTph**, aminooxyacetic acid (AOAA, CBS inhibitor) + **Cu-DhaTph**, and S-adenosyl-L-methionine (SAM, CBS activator) + **Cu-DhaTph** groups. Specifically speaking, for the PBS and **Cu-DhaTph** groups, the NIR-thermal images of the HCT116 tumor-bearing nude mice were obtained after intravenous injection of only PBS (100 μL) and **Cu-DhaTph** (100 μL, 2 mg/mL), whereas in the other groups, the mice were pretreated with AOAA (2 mg/kg) and SAM (20 mg/kg) via intraperitoneal injection 12 h prior to intravenous injection of **Cu-DhaTph** (100 μL, 2 mg/mL). Afterwards, the tumor sites were irradiated with 808 nm laser (1.5 W/ cm^2) for 10 min, and the NIR-thermal imaging was captured by an IR thermal camera.

In vivo antitumor photothermal treatment. The HCT116 subcutaneous xenograft nude mice was randomly divided into six groups, each group and referred to as the PBS, PBS + Laser, **Cu-DhaTph**, **Cu-DhaTph** + PTT, **Cu-DhaTph** + PDT, and **Cu-DhaTph** + PDT + PTT. More concretely, the mice were intravenous injected with **Cu-DhaTph** (100 μL, 2 mg/mL). After 12 hours of administration, 808 nm laser (1.5 W/ cm^2, 10 min) and 660 nm laser (50 mW/cm^2, 5 min) were performed on the specified group. Afterwards, one of each of the mice from the five groups was sacrificed and the tumor was dissected for hematoxylin and eosin (H&E) staining assay. The other mice in the groups were used for long-term observations, in which the tumor volume and the weight of the nude mice were recorded every day for 14 days. At the end of the treatment process, the mice were sacrificed and the major organs (heart, liver, spleen, lung and kidney) were collected for histological analysis. Specifically, these organs were fixed in 10% paraformaldehyde solution, and prepared to slices in process routinely. Then the slices were stained with hematoxylin and eosin, and observed by a confocal laser microscope.

Hemolytic test. Blood cells were obtained from the mice and incubated with different concentrations of **Cu-DhaTph** (0, 6.25, 12.5, 25, 50, 75, 100, 150, 200, 400 μg/mL) for 4 h, where the PBS and pure

water were separately used as negative and positive controls. Then, the samples were centrifuged at 4000 rpm for 5 min, and the supernatant were used for absorbance measurement by a Microplate reader.

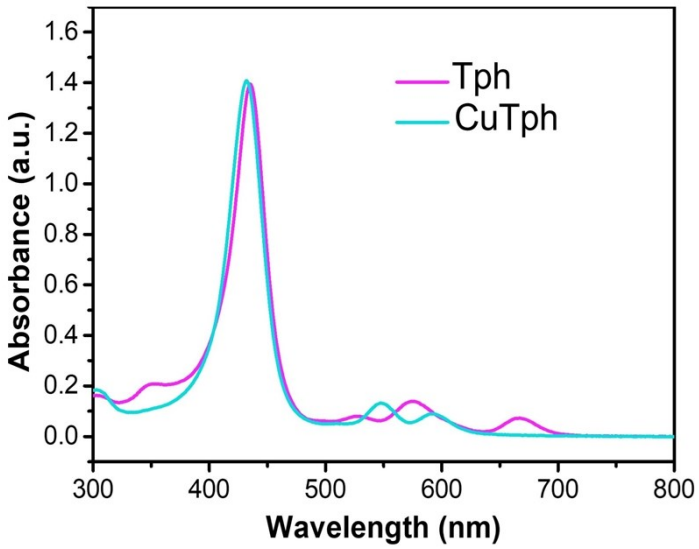


Fig. S1 UV-Vis spectra of Tph and CuTph.

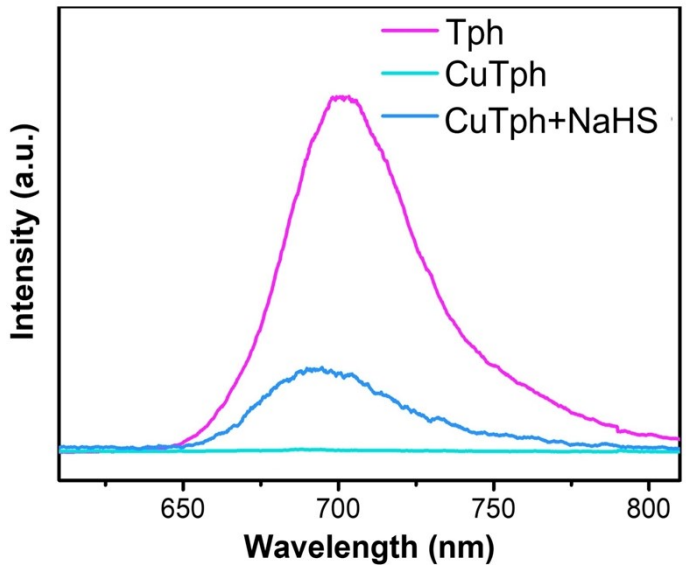


Fig. S2 Fluorescence spectra of Tph (purple) and CuTph in the presence (green curve) and absence (blue curve) of NaHS.

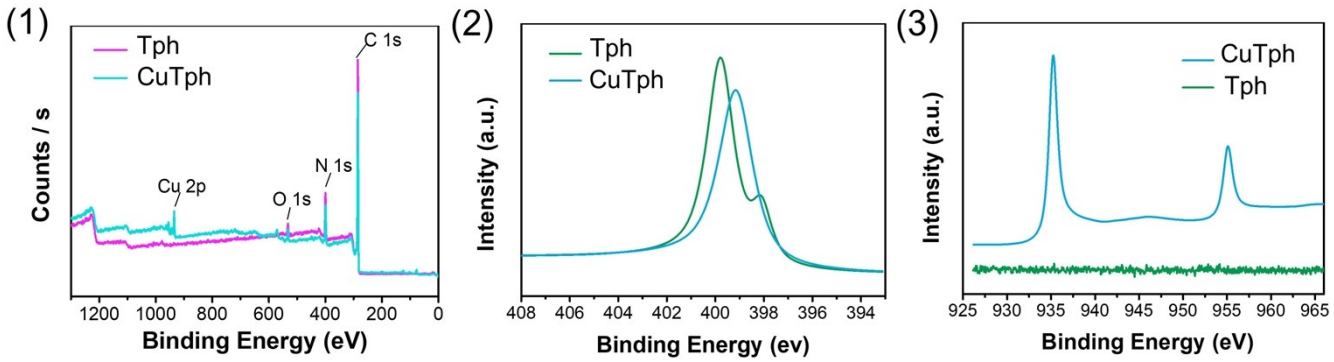


Fig. S3 The XPS spectra of total spectrum of Tph and CuTph (1). The XPS spectra showing the binding energy of N1s (2) and Cu 2p (3) of Tph and CuTph.

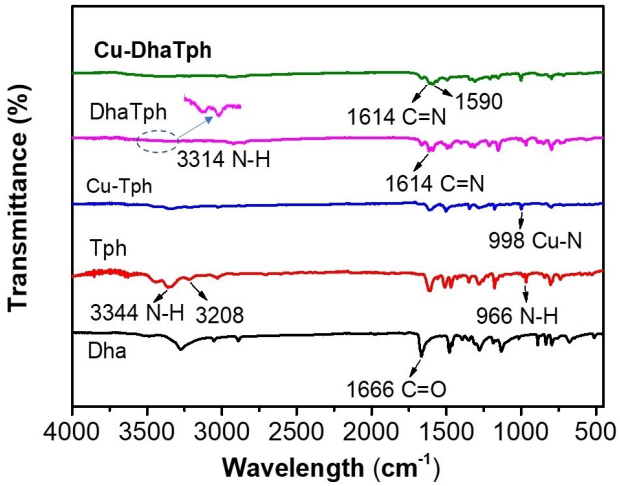
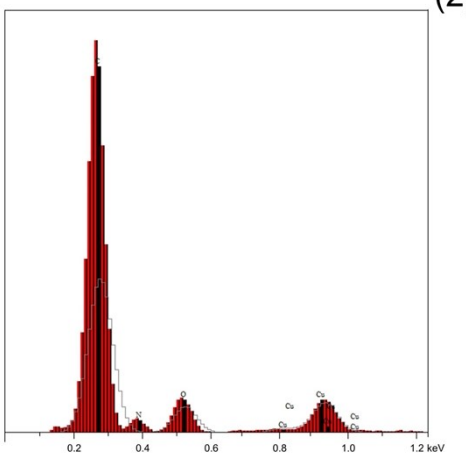


Fig. S4 FT-IR spectra of Dha, Tph, CuTph, DhaTph and **Cu-DhaTph**.

(1)



(2)

Element	Weight%
C	63.788
N	0.248
O	24.768
Cu	11.195
Totals: 100.00	

Fig. S5 EDS spectra of **Cu-DhaTph**.

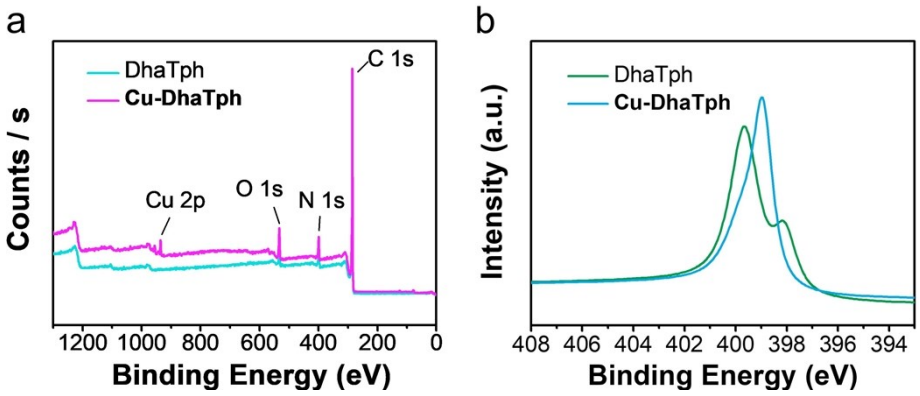


Fig. S6 The XPS spectrum of DhaTph and **Cu-DhaTph** (a) and N in DhaTph and **Cu-DhaTph** (b). The single N1s peak at 398.9 eV in **Cu-DhaTph** and two peaks at 399.9 and 398.1 eV in DhaTph indicated that the coordinated N existed in **Cu-DhaTph** and uncoordinated =N- and -NH- existed in DhaTph.

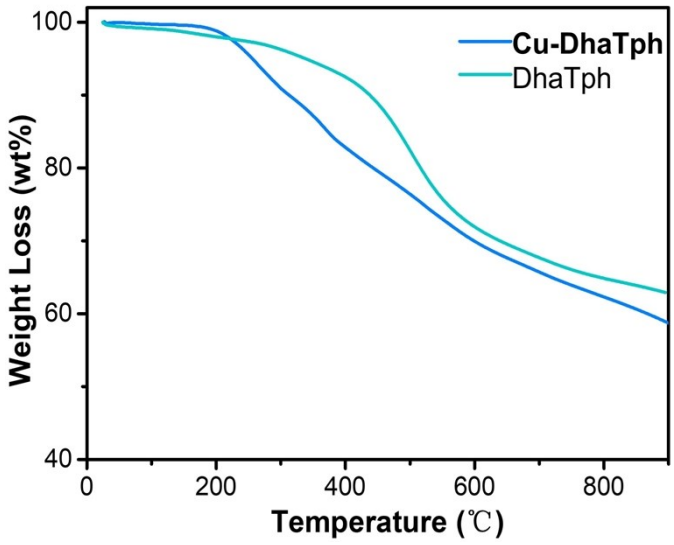


Fig. S7 TGA datas of DhaTph and **Cu-DhaTph** under N_2 atmosphere.

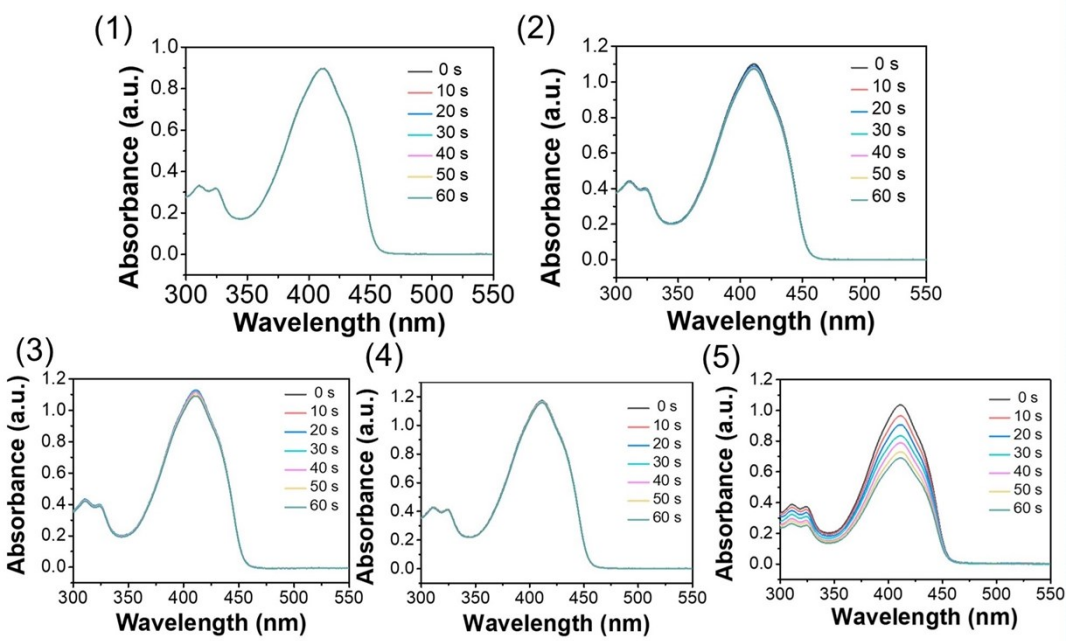


Fig. S8 DPBF absorption spectra of different groups. (1) DPBF only; (2) DPBF + Laser; (3) **Cu-DhaTph** + DPBF + Laser; (4) **Cu-DhaTph** + DPBF + NaHS; (5) **Cu-DhaTph** + NaHS + DPBF + Laser. Laser represents 660 nm irradiation for 60 s (50 mW/cm^2).

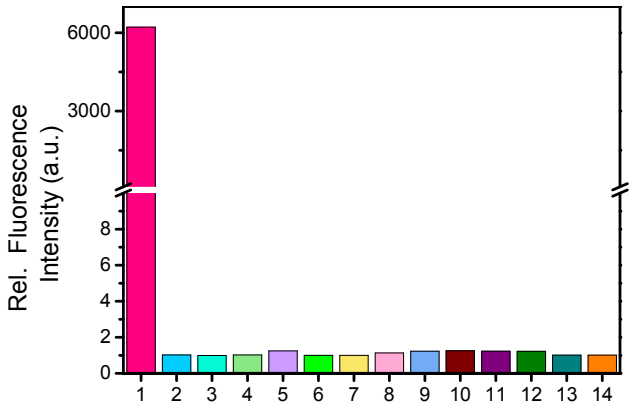


Fig. S9 Fluorescence response of **Cu-DhaTph** toward various reactive species. Relative fluorescence intensity (F-F0) on addition of 1) NaHS (70 μM); 2) F^- (70 μM); 3) Cl^- (70 μM); 4) Br^- (70 μM); 5) I^- (70 μM); 6) SCN^- (70 μM); 7) HCO_3^- (70 μM); 8) HSO_3^- (70 μM); 9) NO_3^- (70 μM); 10) NO_2^- (70 μM); 11) CH_3COO^- (70 μM); 12) SO_4^{2-} (70 μM); 13) GSH (70 μM); 14) Cys (70 μM). Data were obtained in PBS buffer (pH = 7.4) with excitation at ex = 420 nm.

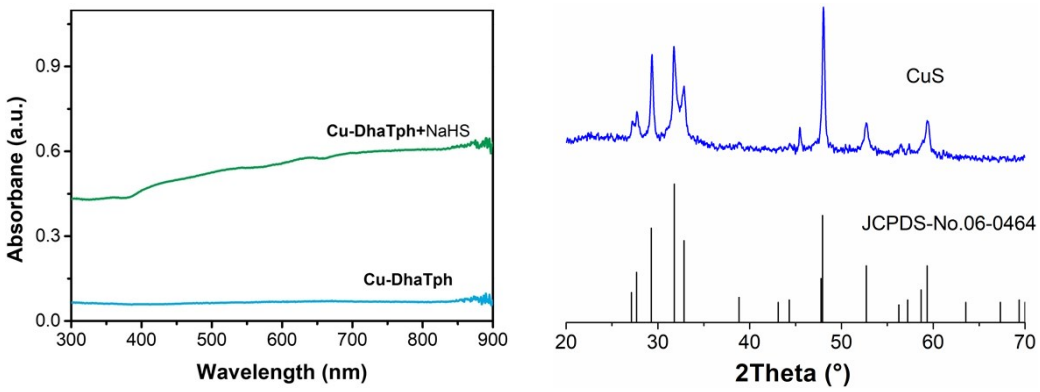


Fig. S10 Left: the Vis-NIR absorption spectrum of **Cu-DhaTph** in the presence (green curve) and absence (blue curve) of NaHS (70 μM). Right: PXRD pattern of the CuS obtained from CuTph (0.1 M) with NaHS (60 mM) in PBS buffer at pH = 7.4, and it is identical to that of the standard CuS pattern.

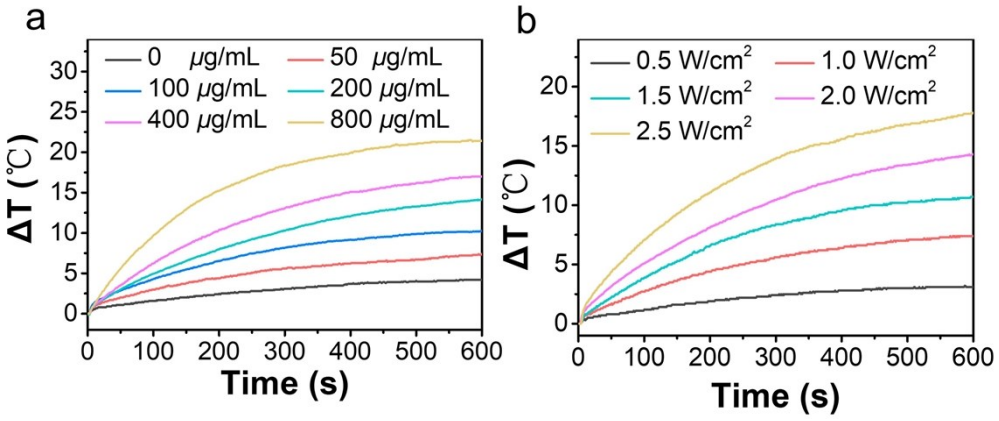


Fig. S11 (a) Temperature versus time curves of different concentrations of aqueous **Cu-DhaTph** solutions in the presence of NaHS (70 μM) under 808 nm laser irradiation (2 W/cm^2, 10 min). (b) Temperature *versus* time curves of aqueous **Cu-DhaTph** solutions (200 μg/mL) in the presence of NaHS (70 μM) under 808 nm laser irradiation at different power density.

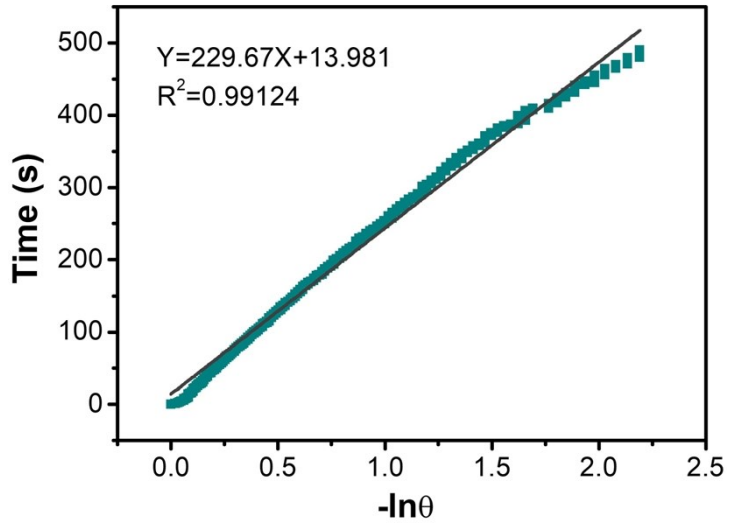


Fig. S12 Time constants of **Cu-DhaTph** solution (200 μg/mL) in the presence of NaHS (70 μM) for heating transfer.

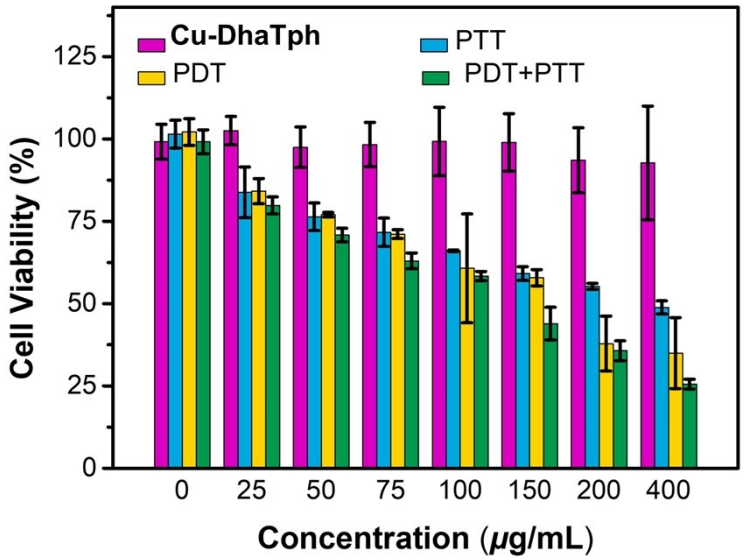


Fig. S13 MTT assay of HCT116 cells in the presence of different concentrations of **Cu-DhaTph** with different treatments: **Cu-DhaTph**-treated cells (1), **Cu-DhaTph** + PTT (808 nm, 2 W/cm^2, 10 min) (2), **Cu-DhaTph** +PDT (660 nm, 50 mW/cm^2, 5 min) (3), and **Cu-DhaTph** + PDT (660 nm, 50 mW/cm^2, 5 min) + PTT (808 nm, 2 W/cm^2, 10 min) (4).

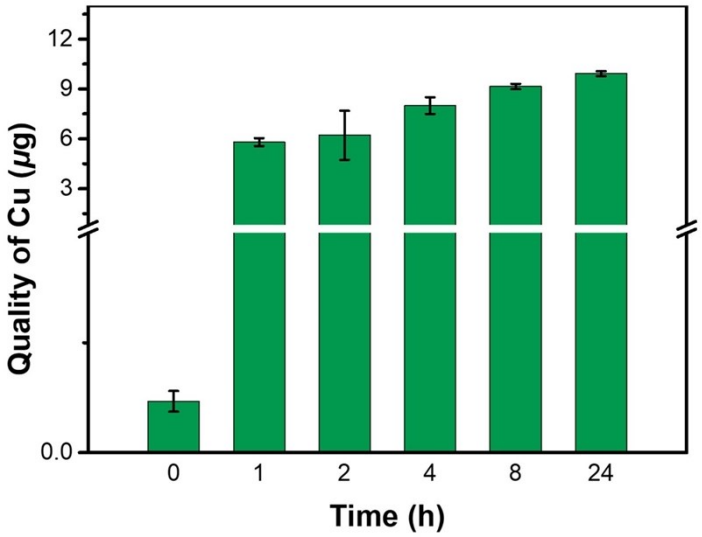


Fig. S14 Relative quantitative analysis of the cellular uptake efficiency of **Cu-DhaTph** (200 μg/mL)-treated HCT 116 cells at different times by ICP-MS.

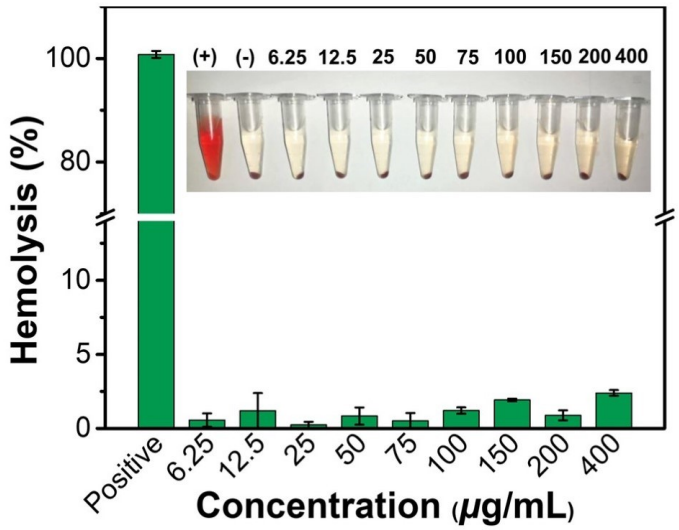


Fig. S15 Hemolytic activity of **Cu-DhaTph** as a function of concentration.

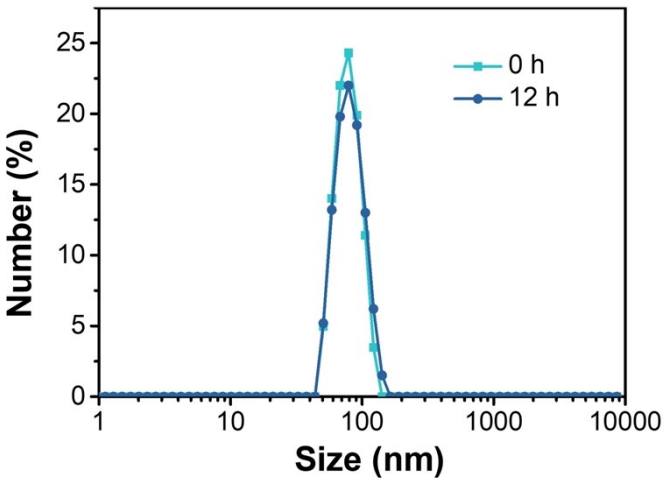


Fig. S16 DLS size profiles of **Cu-DhaTph** in the blood for 12 h.

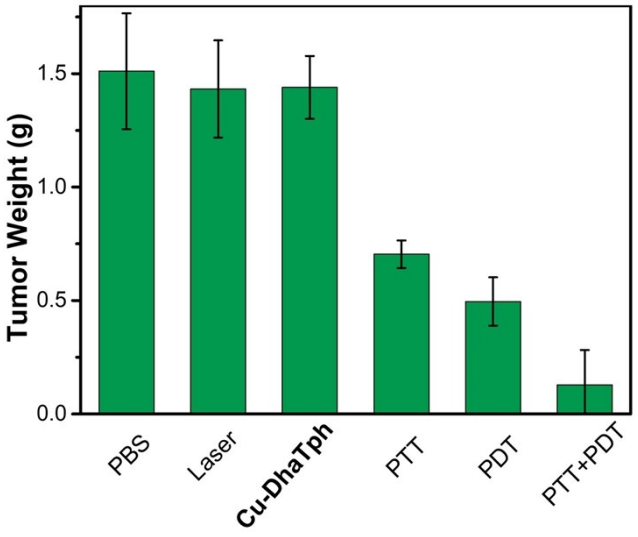


Fig. S17 Excised tumors weights of the different groups on the 14th day.

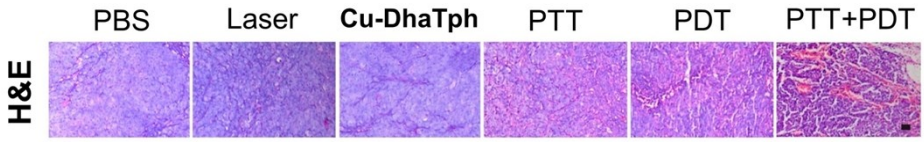


Fig. S18 Sections of tumor stained with H&E for the different groups, Scale bar, 100 μm.

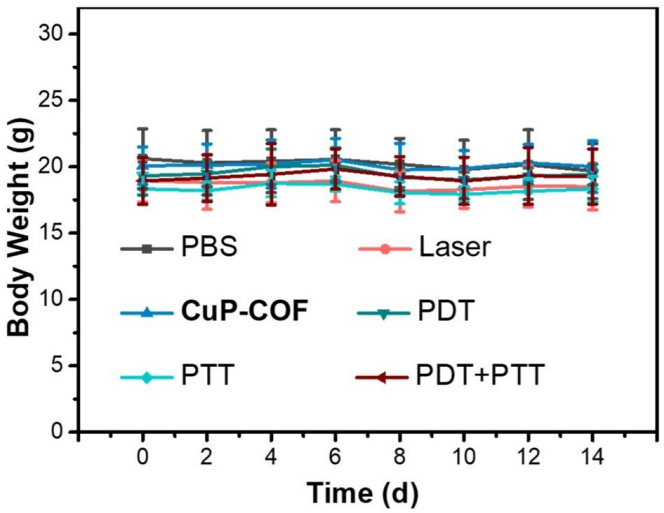


Fig. S19 Body weights of mice in the different groups.

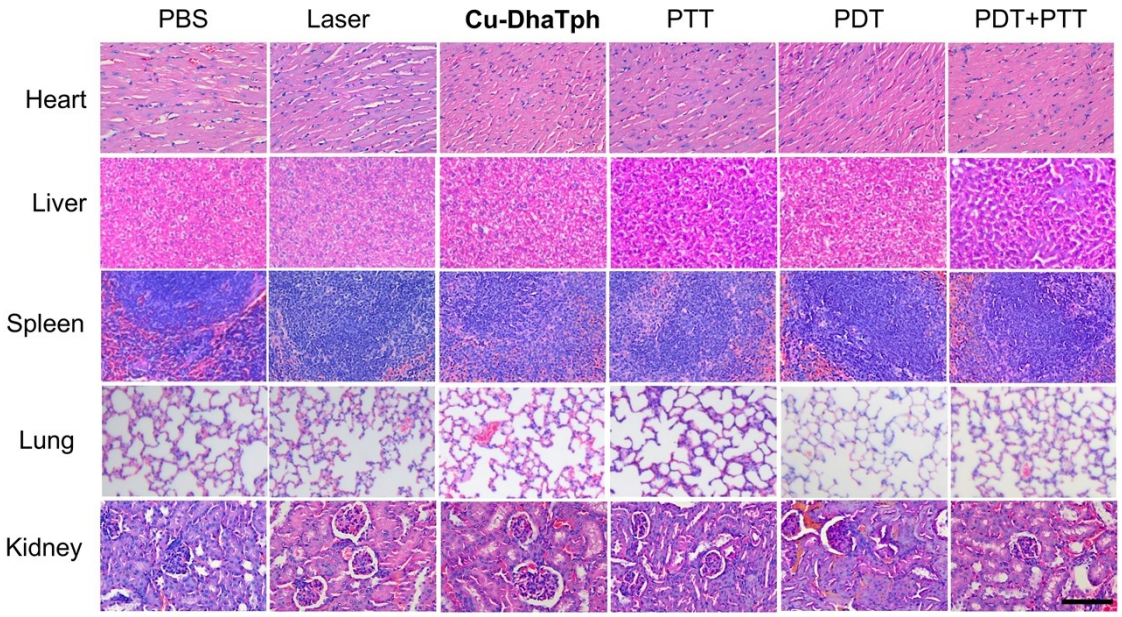


Fig. S20 Sections of major organs stained with H&E for the different groups, Scale bar, 100 μm.

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