Supplementary Information

Sieging tumor cells via an amorphous ferric coordination polymer

Yanli Li,‡[a] Ruoqi Zhang,‡[a] Yuanye Dang,‡[a] Yongyu Liang,[a] Lulu Wang,[a] Na Chen,[d] Luwen Zhuang,*[c] Wen Liu, *[b] and Teng Gong*[a]

[a] Guangzhou Municipal and Guangdong Provincial Key Laboratory of Molecular Target & Clinical Pharmacology, the NMPA and State Key Laboratory of Respiratory Disease School of Pharmaceutical Sciences Guangzhou Medical University, Guangzhou 511436, China. E-mail: tgong@gzhmu.edu.cn

[b] School of Public Health Guangzhou Medical University, Guangzhou 511436, China. E-mail: liuwen@gzhmu.edu.cn

[c] Center for Water Resources and Environment, and Guangdong Key Laboratory of Marine Civil Engineering, School of Civil Engineering, Sun Yat-sen University, Guangzhou 510275, China. E-mail: zhuanglw3@mail.sysu.edu.cn

[d] Soochow University Library, Soochow University, Suzhou 215006, China.

‡ These authors contributed equally to this work.

Experimental Procedures

Materials. Iron trichloride hexahydrate ($FeCl_3 \cdot 6H_2O$) and salicylic acid were purchased from Aladdin biochemical Technology Co., Ltd. (Shanghai, China). 2,5-dihydroxyterephthalic acid (DHTA) and 2-aminoterephthalic acid (ATA) were purchased from J&K Scientific Co.,Ltd. (Beijing, China). Polyethylene-polypropylene glycol (F127, Mw ≈13000) was obtained from Macklin Biochemical Co., Ltd. (Shanghai, China). Hoechst 33342 staining solution and calcein-AM/PI double staining kit were purchased from Beyotime Biotechnology. FITC-labeled secondary antibody was purchased from Cell Signaling Technology (CST). Recombinant mouse heparanase (HPSE) was obtained from R&D. Mouse vascular endothelial cell growth factor (VEGF) elisa kit was obtained from cusabio. Biotin-Heparan sulfate-Eu cryptate (Bio-HS-Eu(K)) and streptavidin-XL665 were purchased from Cisbio International. All the reagents were analytical grade and used directly without further purification. Ultrapure water (18.2 MΩ·cm) was used the whole experiments.

Characterization. Morphologies of particles were observed by a JEOL-1400 PLUS transmission electron microscopy (TEM). The hydrodynamic diameter and zeta-potential were collected with a Nano-ZS ZEN 3600 (Malvern). UV-vis absorbance spectra were recorded by UV–vis spectrophotometry UV-2600 (Shimadzu). Fluorescence analysis of singlet oxygen was carried out by using a Synergy H1 multifunctional microplate reader (BioTek). CCK-8 assay was conducted with a microplate reader (Bio-Rad). Confocal laser scanning microscopy (CLSM) images were collected with a Leics SP8 confocal microscope (Leica). Flow cytometry analysis was performed by a CytoFLEX flow cytometry (Beckman). *In vivo* luminescence imaging of mice was detected and analyzed by a IVIS AniView100 imager. H&E and immunohistochemical stainings of sacrificed tissues were imaged by a Leica CS2 Slide scanner (Leica).

Synthesis of FeCPs and MIL-88-Fe. FeCPs was synthesized via a one-pot synthesis method. First, 198.12 mg DHTA, 138.12 mg SA and 1 mg pluronic F127were dissolved in 20 mL ethanol and stirred for 30 min. Then, 270.3 mg $FeCl_3 \cdot 6H_2O$ dissolved in 30 mL ultrapure water were added to the above-mentioned mixture for 12 h at room temperature under continuous mechanical stirring. After that, the product was washed sequentially with ethanol for three times, and finally dispersed in ethanol.

MIL-88-Fe was synthesized according to the previous method.[1] 450 mg of ATA were dissolved in 95 mL ethanol. 675 mg $FeCl_3 \cdot 6H_2O$ was dissolved in 5 mL ethanol. To ensure thorough dissolution, proper ultrasound was required. Under vigorous stirring, the two solutions were mixed. After that, the solution was transferred into an oil bath at 80 °C to react for 6 h with vigorously stirring. After cooling to room temperature, the product was collected by centrifugation and washed three times with ethanol. Finally, the obtained nanoparticles were redispersed in ethanol.

Ion release. Regarding pH-responsive degradation property of the coordination polymer, the release of ion was investigated by using inductively coupled plasma mass spectrometry (ICP-MS). FeCPs (Fe, 720 μg) or MIL-88-Fe (Fe, 630 μg) was dispersed in 500 mL of 50 mM HEPES buffer (pH = 7.4, pH = 6.5 and pH = 5.4) in a dialysis bag (MWCO: 5000 Da) and incubated for a series of different times. And then, the obtained solution was diluted using ultrapure water before ICP-MS determination. HCl was added to completely dissolve FeCPs or MIL-88-Fe to calculate the 100% releasing efficiency.

SA and DHTA release. The release of SA and DHTA were investigated by using UV-vis spectrophotometry. First, FeCPs (Fe, 720 μg) or MIL-88-Fe (Fe, 630 μg) was dispersed in 500 mL of 50 mM HEPES buffer (pH = 7.4 and pH = 5.4) in a dialysis bag (MWCO: 5000 Da) and incubated for a series of different times. Then, the mixture was centrifuged, and the supernatant was mixed with excessive NaOH to remove the Fe^{3+}. To eliminate the influence of NaOH on SA and DHTA, the pH of the supernatant collected after centrifugation was readjusted back to 5.4. Afterward, the UV absorbance of the samples was measured at 305 nm and 368 nm. Finally, the content of SA and DHTA was calculated by standard calibration curve of UV-vis spectroscopy with different concentrations of SA (λ = 305 nm) and DHTA (λ = 368 nm). In order to further calculate the mass ratio of SA and DHTA in the FeCPs, HCl was added to completely dissolve FeCPs. The content of SA and DHTA was carried out as the same procedure above.

General dosage of nanoparticles in subsequent research. The concentration of FeCPs and MIL-88-Fe used for following utilization were quantified by the concentration of Fe. The specific dosage of nanoparticles would be provided in different experimental details.

•OH detection. The •OH-induced Methylene blue (MB) degradation were employed to evaluate the quantitation analysis of the generation of •OH by ultraviolet-visible absorbance change respectively. Briefly, The UV absorbance at λ = 664 nm of MB solution (10 mg L^{-1},) at different pH solutions (pH = 7.4, pH = 6.5 and pH = 5.4) with H_2O_2 (1 mM) was measured before and after the addition of FeCPs (Fe, 0, 10, 20, 40, 60, 80, 100 ppm) or MIL-88-Fe (Fe, 100 ppm). Additionally, the electron spin resonance (ESR) spectroscopy was used to investigate the generation of •OH with radical trap agent 5, 5-dimethyl-1-pyrroline-N-oxide (DMPO). 60 μl of DMPO buffer solution (100 mM) was added into pH phosphate buffered solution in a dark Eppendorf tube with following supplements including: H_2O_2 (1 mM) at pH =7.4, FeCPs (Fe, 100 ppm) at pH = 7.4, H_2O_2 (1 mM) + FeCPs (Fe, 100 ppm) at pH = 7.4, H_2O_2 (1 mM) + FeCPs (Fe, 100 ppm) at pH =6.5, H_2O_2 (1 mM) + MIL-88-Fe (Fe, 100 ppm) at pH = 5.4. and H_2O_2 (1 mM) + FeCPs (Fe, 100 ppm) at pH = 5.4. Afterward, the mixture was transported into a quartz capillary, and then X-band EPR spectra were acquired by Bruker EMX-8/2.7 spectrometer at room temperature (microwave frequency = 9.872 GHz, microwave power = 6.375 mW, modulation frequency = 100.00 kHz and modulation amplitude = 1.00 G).

Homogeneous time-resolved fluorescence-based heparanase activity assay. 1.0 μL different concentrations of SA and 4.0 μL of heparanase solution (20 μg/mL) or heparanase dilution buffer (as a delta Fmax % and Blank) consisting of 20 mM Tris-HCl pH 7.5, 0.15 M NaCl and 0.1% CHAPS were added into 384-well plate. After 10 minutes pre-incubation at 37 °C, an enzyme reaction was initiated by adding 5 μL of Bio-HS-Eu(K) (0.7 μg/mL in 0.2 M $NaCH_3CO_2$ pH 5.5) and the 384-well plate was incubated for 150 minutes at 37 °C. To stop the enzyme reaction and detect the remaining substrate, either 10 μL of a 1.0 mg/mL XL665-labeled streptavidin (0.1 M NaPO4 pH 7.5, 0.8 M KF, 0.1 % BSA, 2.0 mg/ml heparin) solution or dilution buffer was added into plate. After a 30-minute incubation at RT, the HTRF signal was measured using an Envision plate reader using the following setup: excitation 337 nm, emissions 620 nm and 665 nm.

Specific HTRF signal was expressed as a percentage of delta F, and calculated as follows:

Delta F (%) = {[(665/620) sample-(665/620) blank] / (665/620) blank}x100

Percent of substrate degradation was calculated as follows:

[1-Delta F / Delta Fmax] x100

Cell culture. The 4T1 cells were incubated in RPMI-1640 culture medium supplemented with 10% fetal bovine serum and 1% antibiotics (100 U/mL penicillin and 100 mg/mL streptomycin) at 37 °C in 5% CO_2 atmosphere. All the cell lines were obtained from Shanghai Institute of cells (Chinese Academy of Science).

Synthesis of FITC-labeled FeCPs. FITC-labeled FeCPs was prepared through non covalent bonding forms such as electrostatic or π-π interactions. First, 2 mgFeCPs were dissolved in 5 mL ultrapure water and stirred for 30 min. Then, 1 mg FITC dissolved in 5 mL ultrapure water were added to the above-mentioned mixture for 12 h at room temperature under continuous mechanical stirring. After that, the product was washed sequentially with ultrapure water for three-five times, and finally dispersed in ultrapure water.

Cellular uptake of the nanoparticle. The cellular uptake of the nanoparticle using the 4T1 cells was studied. 4T1 cells (1×10^5 cells/mL) were seeded in confocal dishes and incubated for 24 h. After that, FITC-labeled FeCPs were incubated with 4T1 cells for 6 h, followed by nuclear staining (Hoechst 33342). After that, cells were washed twice with PBS and subjected to confocal microscope imaging using the confocal laser scanning microscopy (CLSM).

Cell cytotoxicity assay. 4T1 cells (5×10^3 cells/well) were seeded in 96-well plates. After incubation for 24 h, the culture medium was replaced by fresh medium containing FeCPs or MIL-88-Fe at different Fe concentration and incubate. Then, 10 μL of CCK-8 solution was added to each well and incubated for another 2 h. The amount of the orange formazan dye is directly proportional to the quantity of live cells in the well. In addition, Cell viability was then calculated from measuring the absorbance at 450 nm using a microplate reader. In order to further evaluate the cytotoxicity of H_2O_2 for 4T1 cells, Cell Counting

Kit-8 (CCK-8) assays in 4T1 cells with different concentration of H_2O_2 were measured. After 24 h incubation, CCK-8 assays were carried out as the same procedure above.

Cell viability assays. To evaluate the inhibitory effect of nanomaterials on 4T1 cells. Tumor cells (5×10^3 cells/well) were plated in 96-well plates and further attached for 24 h. To simulate the slightly acidic (pH = 6.5~6.9) extracellular microenvironment in solid tumor, the RPMI-1640 (pH = 7.4) was acidized to pH = 6.5 by adding 12 mM hydrochloric acid, which shows negligible influence on the cell growth. The culture medium was then replaced by fresh medium (pH = 7.4 and pH = 6.5) containing 100 and 200 μM H_2O_2 with FeCPs or MIL-88-Fe at Fe concentration of 0, 12.5, 25, 50 and 100 ppm, respectively. The cells were incubated at 37 °C in 5% CO_2. After 24 h of incubation, cells were washed with PBS three times, CCK-8 assays were carried out as the same procedure above.

In order to further assess synergistic effect between SA and DHTA on sensitizing Fe-mediated CDT. 4T1 cells were seeded into the 96-well plates (5×10^3 cells/well) to attach overnight and then exposed to hypoxic condition for 24 h. Then, 4T1 cells were incubated with $FeCl_3 \cdot 6H_2O$ (Fe, 50 ppm) and different concentrations of SA (25, 50, 100 ppm), DHTA (22.53, 45.06, 90.12 ppm) or SA + DHTA (25/22.53, 50/45.06, 100/90.12) at 37 °C for 24 h under pH 7.4 or 6.5 (100 μM H_2O_2). In addition, 100 μL MTT solutions (0.6 mg/mL in PBS) were added to each well and incubated for 4 h. The formazan crystals formed by viable cells were solubilized in 100 μL dimethylsulfoxide and then the absorbance value was measured at 490 nm with microplate reader. Combination index (CI) values were calculated using Chou-Talalay methods by CalcuSyn software.[2] CI values of <1, =1, and >1 indicate synergism, additive, and antagonism, respectively.[3]

Live/dead cell analysis. 4T1 cells were seeded and cultured in 6-well plates for 24 h. The culture medium was then replaced by fresh medium (pH = 7.4 and pH = 6.5) containing 200 μM H_2O_2 with FeCPs or MIL-88-Fe at Fe concentration of 100 ppm, respectively. With 24 h more incubation, the cells were treated with Calcein-AM/PI Double Stain Kit (Yeasen) according to the manufacturer's instruction and measured by CLSM.

Intracellular •OH staining. To further determine the ability of FeCPs or MIL-88-Fe mediated conversion of H_2O_2 to • OH, intracellular •OH detection was performed using a hydroxyphenyl fluorescein (HPF) indicator. 4T1 cells were seeded on confocal dishes (1×10^5 cells/mL) for 24 h. The culture medium was then replaced by fresh medium (pH = 7.4 and pH = 6.5) containing 200 μM H_2O_2 with FeCPs or MIL-88-Fe at Fe concentration of 50 ppm, respectively. After 12 h more incubation, the cells were incubated with hydroxyphenyl fluorescein (HPF), according to the manufacture's introductions. The cells were stained with Hoechst 33342 for 10 min and viewed under the CLSM.

Cell apoptosis assessment. 4T1 cells were seeded in a 6-well plate overnight. The medium was replaced, followed by addition of fresh medium containing 100 μM H_2O_2 and FeCPs or MIL-88-Fe (Fe, 50 ppm). After 12 h of incubation, the cell culture medium was sucked out into a suitable centrifuge tube, the

adherent cells were washed once with PBS. And then, the cells were collected by trypsin (no EDTA) and suspended gently with PBS. After adding it to the centrifuge tube mentioned above, the suspension of the cells was incubated with Annexin V-FITC for 15 min in dark and PI was added to the above solution for 5 min at 4 °C. Finally, the apoptosis levels of the cells were analyzed by flow cytometer, Annexin V-FITC (green) and PI (red).

Cell migration and invasion assay. 4T1 cells were seeded in a 6-well plate for 12 h. Then, the cells were incubated with PBS, MIL-88-Fe and FeCPs (Fe, 50 ppm) for 24 h at 37 °C. Vertical scratches were made using a 200 μL pipette tip. To clear displaced cells, culture medium was removed, and the cells were washed with PBS. The cellular wound was observed, and images were taken at time 0 h, 12 h and 24 h post-wounding. Transwell assay was used to examine cell migration ability and conducted using Matrigel-coated invasion chambers. 4T-1 cells (1.0×10^5 cells/well) were placed into the upper chambers containing free FBS. RPMI-1640 with 10% FBS was added to the lower chambers. After incubation for 12 h and 24 h at 37˚C, cells on the lower surface of the membranes were fixed and stained with 0.1% crystal violet, and the random fields of vision were selected and counted under optical microscope.

The effect of FeCPs on heparanase activity. 4T1 cells were seeded in a 6-well plate. After the cells adhered to the plate, the cells were incubated with different concentrations of FeCPs (Fe, 25, 50 and 100 ppm) at 37 °C. After 24 h, cells were washed with PBS three times. Cells were lysed in 150 μL of lysis buffer and collected. The total protein was determined using Enhanced BCA Protein Assay Kit. Afterward, the inhibition of heparanase activity by FeCPs was carried out as the same procedure above homogeneous time-resolved fluorescence-based heparanase activity assay.

Immunofluorescence Assays. HPA immunofluorescence analysis was exploited to characterize the level of HPA. 4T1 cells were seeded in confocal dishes for 24 h. All cells were incubated with PBS, MIL-88-Fe and FeCPs (Fe, 100 ppm) for 24 h. Then, the cells were fixed in 4% paraformaldehyde for 10 min at room temperature. By three washing with PBS buffer, the cells were permeabilized with 0.2% Triton X-100 in PBS for 10 min. Next, the cells were incubated with primary antibodies (Anti-heparanases 1 antibody) overnight at 4 °C. The cells were rinsed with PBS, incubated with secondary antibodies conjugated with FITC for 1 h at room temperature. At last, the cells were stained with Hoechst 33342 for 10 min to visualize the nuclei. Subsequently, the cells were washed with ice-cold PBS for three times and imaged under CLSM.

Western Blot Analysis. The expression level of HPA in 4T1 cells were measured by Western blot. In brief, 4T1 cells were seeded in a 6-well plate. After the cells adhered to the plate, the cells were incubated with PBS, MIL-88-Fe and FeCPs (Fe, 100 ppm) for 24 h. Subsequently, cells were collected and lysed in 150 μL of lysis buffer. The total protein was determined using Enhanced BCA Protein Assay Kit. Cellular proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride membranes (PVDF). After blocking in 5% skim milk, the

membranes were incubated with specific primary antibodies (HPA1) overnight at 4 °C, followed by HRP-goat anti-rabbit immunoglobulin G (IgG) diluted 2500 times for 1 h. Finally, protein detection was performed using the enhanced chemiluminescence solution reaction.

Assaying the release of VEGF. 4T1 cells were seeded in a 6-well plate for 12 h. After adherence, the cells were incubated with PBS, MIL-88-Fe and FeCPs (Fe, 50 ppm) at 37 °C. After 24 h, conditional media were collected, and elisa was performed to measure the release of VEGF in the media according to the instruction of kit.

Tube formation assay. 96-well plates were precoated with 60 μL liquid Matrigel per well. After incubated at 37 °C for 1 h, HUVECs (1.5×10^5 cells/well), suspended in RPMI-1640 medium with PBS, MIL-88-Fe and FeCPs (Fe, 100 ppm), were seeded and further cultured for 8 h. Tubes were imaged by an inverted phase contrast microscope and the enclosed networks of complete tubes from five randomly chosen fields were photographed and counted.

Gel electrophoresis of adsorbed proteins. FeCPs was dispersed in fetal bovine serum for 30 min under mild vibration. The solutions were then centrifugated for 10 min at 10000 g to collect the nanoparticles. After that, the particles were digested for 4 h in 1 M hydrochloric acid to erode the FeCPs. The proteins adsorbed were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and stained with coomassie brilliant blue to quantify the proteins.

***In vivo* PA imaging of tumor.** 4T1 tumor xenografted nude mice were anesthetized using 2% isoflurane in oxygen, and placed with prone position. Before FeCPs injection, the PA and US images of the tumor area were obtained first as control using the AR-PAM system. The PA and US images of the tumor area were captured before and 6, 12, and 24 h after i.v. injection of FeCPs.

Hemolytic test. The hemolytic effect of the FeCPs was evaluated using New Zealand rabbit erythrocytes. In brief, different concentrations of FeCPs were incubated with 2% (w/v) erythrocytes diluent at 37 ℃ for 6 h. After centrifugation, 100 μL of the supernatant was added to a 96-microwell plate, and the absorbance was measured at 540 nm by microplate reader. The results were calculated as percentage hemolysis with the assumption that deionized water caused 100% hemolysis and saline 0% hemolysis.

Biosafety evaluation of FeCPs *in vivo*. All animal experiments were carried out coinciding with the guidelines of Institutional Animal Care and Use Committee (IACUC) of Animal Experiment Center of Guangzhou Medical University (Guangzhou, China) as well as the Regulations for the Administration of Affairs Concerning Experimental Animals, and the accreditation number was GY2022-088. ICR mice (female, ~30 g) and balb/c nude mice (female, ~20 g) were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. ICR mice were randomly divided into three groups (n = 5). Then, the mice were administered PBS or FeCPs (10 mg/kg of Fe) by intravenous (*i.v.*) injection and their body weight was monitored every two days. After the mice were killed on 3 days and 30 days, blood samples and

major organs were collected for routine blood analysis and biochemical analysis, and H&E section staining, respectively.

Blood circulation study. To explore the blood circulation half-life of FeCPs, the mice (n = 3) were intravenously injected with FeCPs (10 mg/kg of Fe). Then, 10 μL blood was acquired from the mice at different time points (10 min, 20 min, 30 min, 40 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h) and diluted with 10 mM ethylenediaminetetraacetic acid disodium salt (EDTA-2Na) as anticoagulant. The concentration of Fe was determined by ICP-MS.

***In vivo* anticancer efficacy analysis.** 4T1 xenograft models were generated by the subcutaneous injection of 1×10^6 cells in RPMI 1640 medium (150 μl) into the flank of female balb/c nude mice (4-6 weeks old, ~20 g). When the tumor volume reached about 50-70 mm^3, tumor-bearing mice were randomly divided into 3 groups (n = 6/group) and injected three times on day 0, 3, and 5 including control group (injected with PBS); intravenous (*i.v.*) injection group (injected with the dosage of 100 μL 10 mg/kg Fe of MIL-88-Fe and FeCPs). Subsequently, the tumor sizes and body weights of each mouse were monitored every three days. The tumor sizes were calculated as equation volume = (length × $width^2$)/2 and the relative tumor volume = V/V_0 (V_0 was the original tumor volume). Six days after the treatments, one of the mice in each group was sacrificed. The tumors were excised for haematoxylin and eosin (H&E) staining analysis, immunofluorescence staining analysis (terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), immunofluorescence (IF) analysis (HSPG) and immunohistochemical (IHC) analysis (HPA and VEGF). Ultimately, mice were euthanized at the end of the treatments and the weight of the tumors was further tested.

Tumor inhibition rate = (tumor weight of control group - tumor weight of treatment group) / tumor weight of control group * 100%

***In vivo* anti-metastatic efficacy evaluation.** To evaluate the anti-metastatic efficacy against orthotopic breast tumor, 4T1-Luc breast cells (5×10^6 cells) were seeded into the mammary fat pad of the balb/c mice (4-6 weeks old, ~20 g) and caused the construction of orthotopic breast tumors with 75~100 mm^3. MIL-88-Fe or FeCPs (10 mg/kg of Fe, 100 μL) was intravenously injected into the orthotopic tumor-bearing mice on day 0, 2, 4, 6 and 8. Biofluorescence at the tumor and lung sites was monitored for 21 days post-treatment. Briefly, the mice were intraperitoneally injected with fluorescein sodium solution (200 μL, 15.0 mg/mL), followed by bioluminescence imaging. At day 21 post-treatment, five mice in each group were sacrificed, and the lungs of the mice were harvested, photographed and imaged for *ex vivo* bioluminescence analysis. Furthermore, the number of macroscopic metastatic nodules per lung was recorded and counted. For histological analysis, the lung tissues were sliced for H&E staining to detect the metastatic foci. During this experiment, the mean survival time and survival rate were recorded

Statistical analysis. Data was analyzed by GraphPad Prism (version 6.02) using Student's *t*-tests to make two group comparisons. Each experiment was conducted with chemical or biological replicates and

repeated multiple times. Data were expressed as mean ± SD. No significant difference was denoted n.s., and statistical significance was denoted as *P < 0.05, **P < 0.01, ***P < 0.001, and ****P<0.0001.

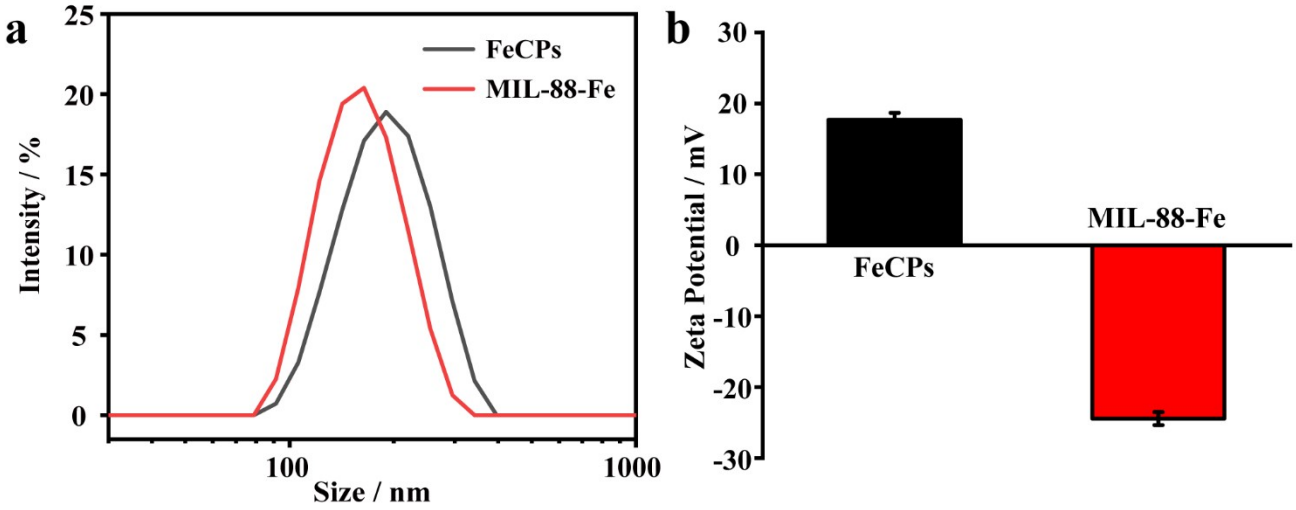


Figure S1. a) Particle size distributions of FeCPs and MIL-88-Fe. b) Zeta potentials of FeCPs and MIL-88-Fe.

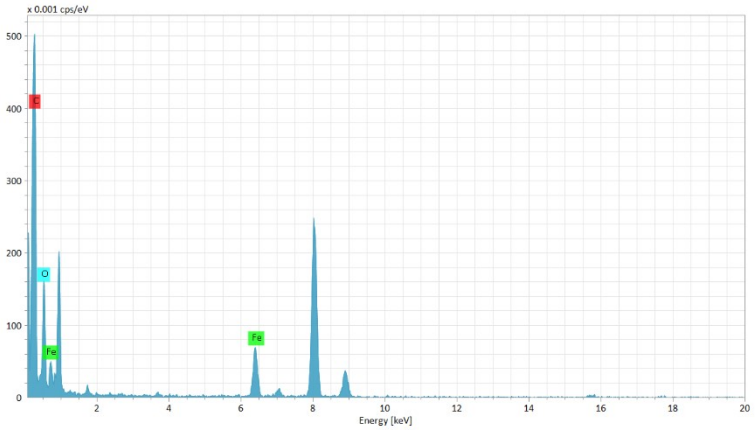


Figure S2. The energy dispersive spectrum of FeCPs. Displaying the existence of every part in FeCPs.

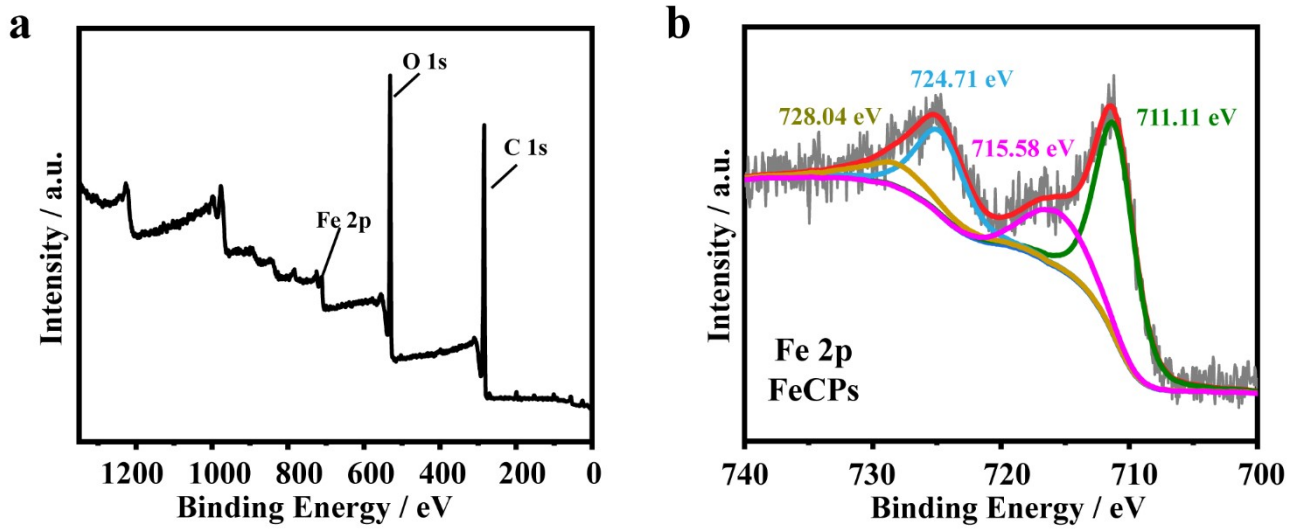


Figure S3. a) XPS survey spectra of FeCPs. b) XPS spectra of Fe 2p for the FeCPs.

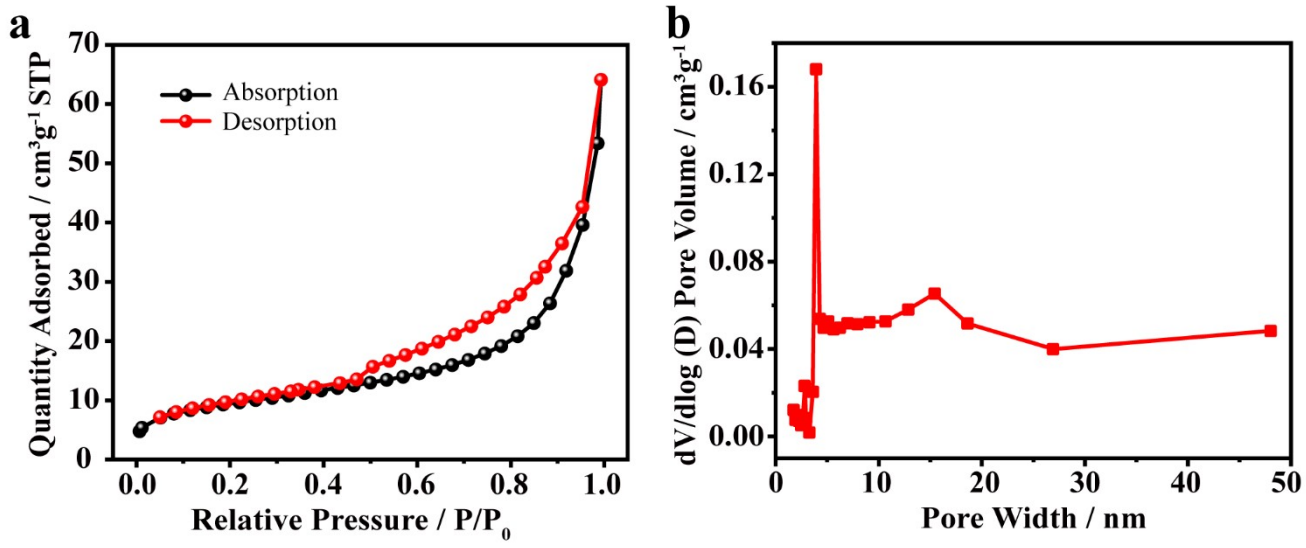


Figure S4. a) N_2 adsorption-desorption isotherms and b) corresponding pore size distribution of FeCPs.

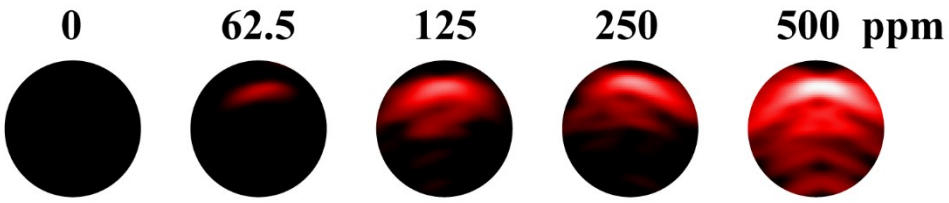


Figure S5. PA images of FeCPs at different concentrations under 715 nm laser irradiation.

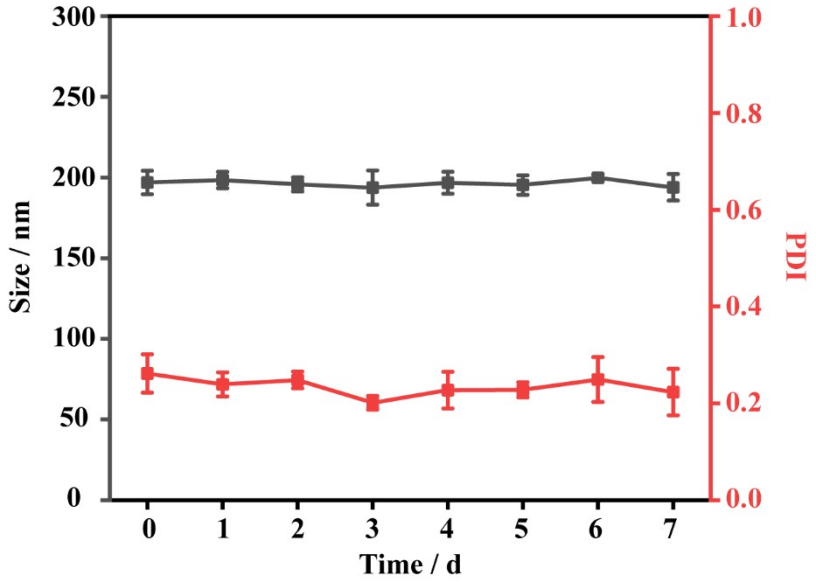


Figure S6. The hydrodynamic size and polydispersity index (PDI) changes of FeCPs in aqueous solution for 7 days.

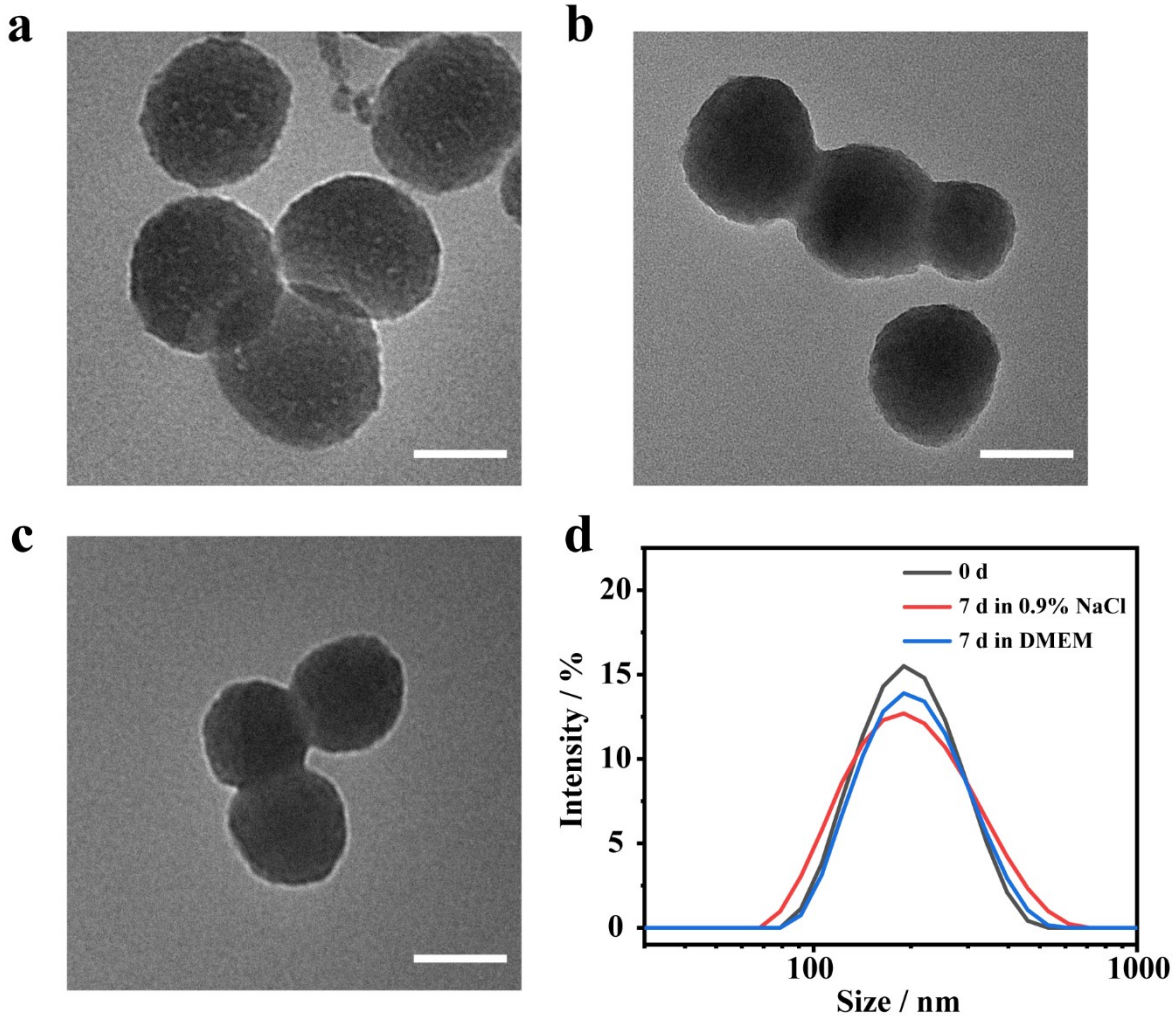


Figure S7. The stability of FeCPs. TEM images of FeCPs a) as-synthesized, b) in 0.9% NaCl at 7 days and c) in DMEM cell culture medium at 7 days. (d) Particle size distributions of FeCPs with different treatments.

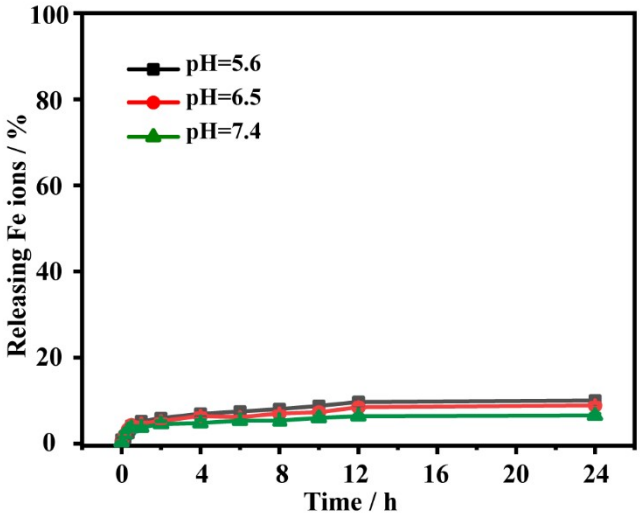


Figure S8. Time-dependent Fe^{3+} release of MIL-88-Fe at different pH values. Slight leakage of Fe^{3+} were observed, indicating the favorable crystallinity of MIL-88-Fe prevents its further degradation.

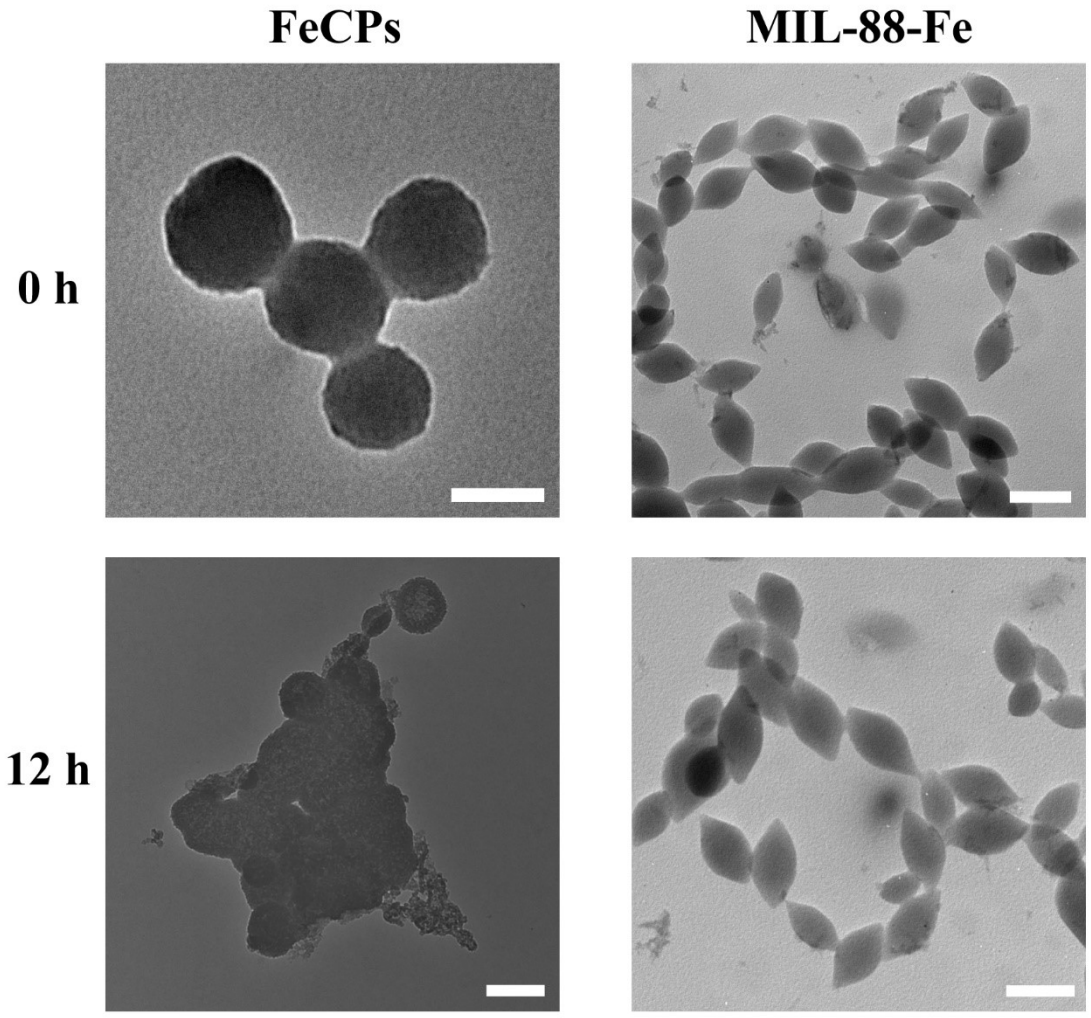


Figure S9. TEM images of FeCPs and MIL-88-Fe at pH 5.4 after different treatment time. Scale bar = 100 nm.

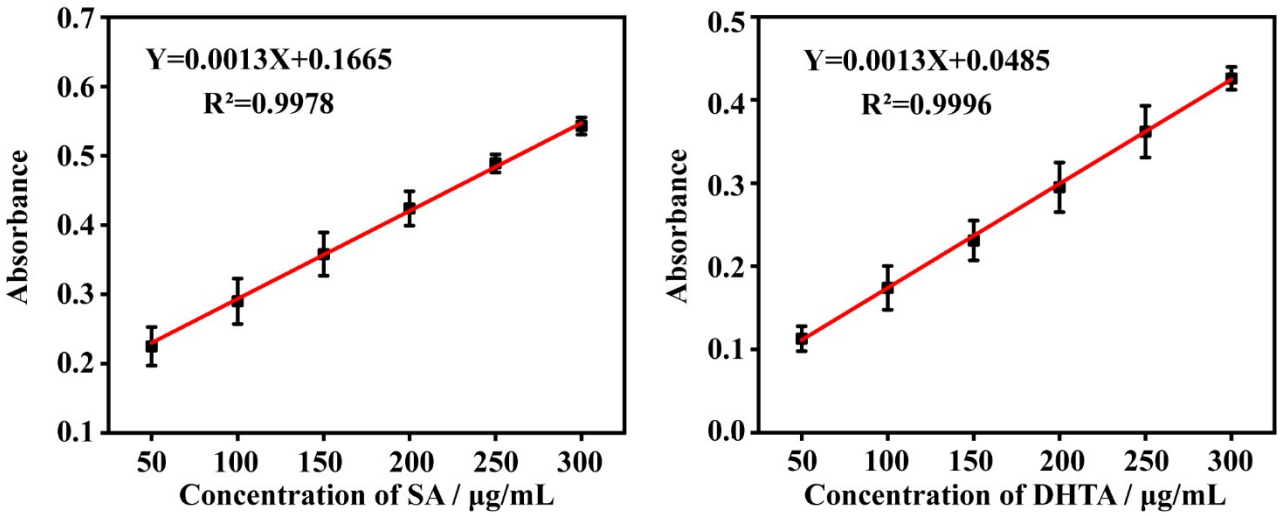


Figure S10. Calibration curve of UV-vis spectroscopy with different concentrations of SA (λ = 305 nm) and DHTA (λ = 368 nm) for calculating the content of DHTA and SA.

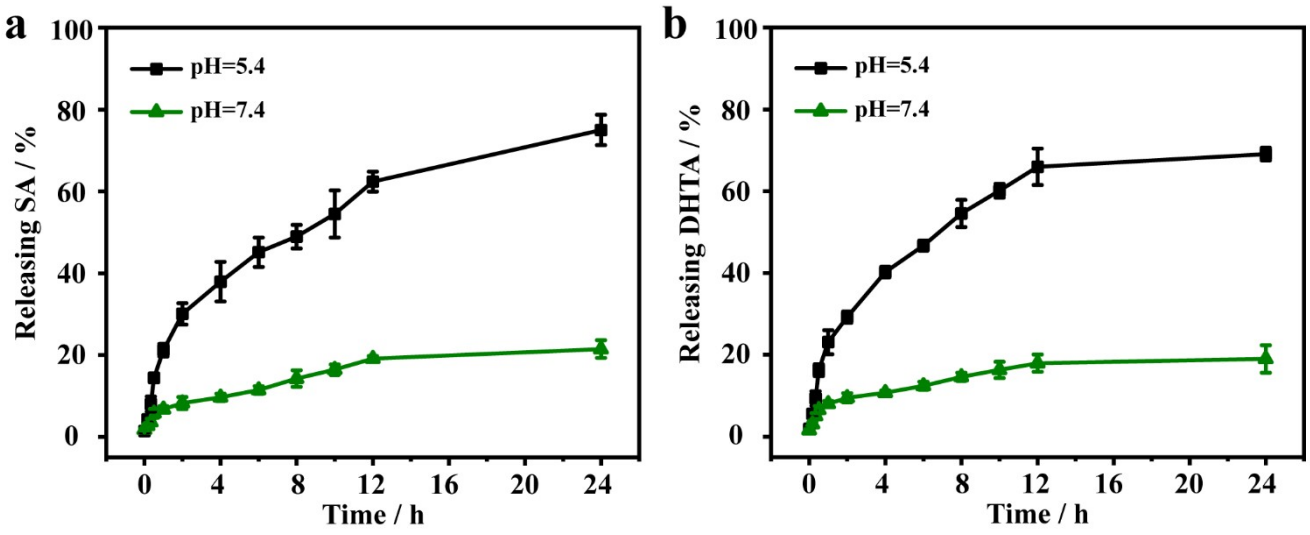


Figure S11. The release of a) SA and b) DHTA over time at different pH values.

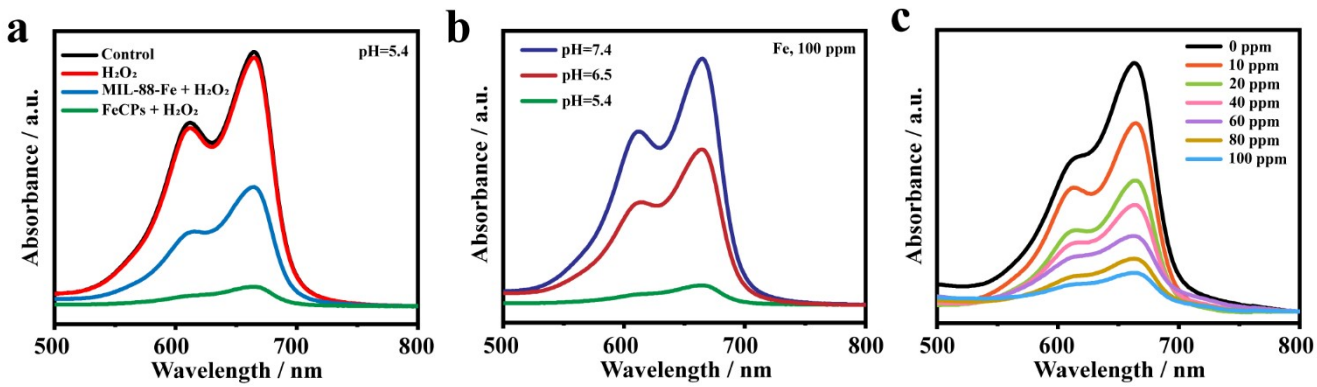


Figure S12. a) UV-vis absorption spectra of MB after different treatments. UV-vis absorption spectra of MB under different b) pH values and c) FeCPs concentrations. The dosage of H_2O_2 was 1 mM.

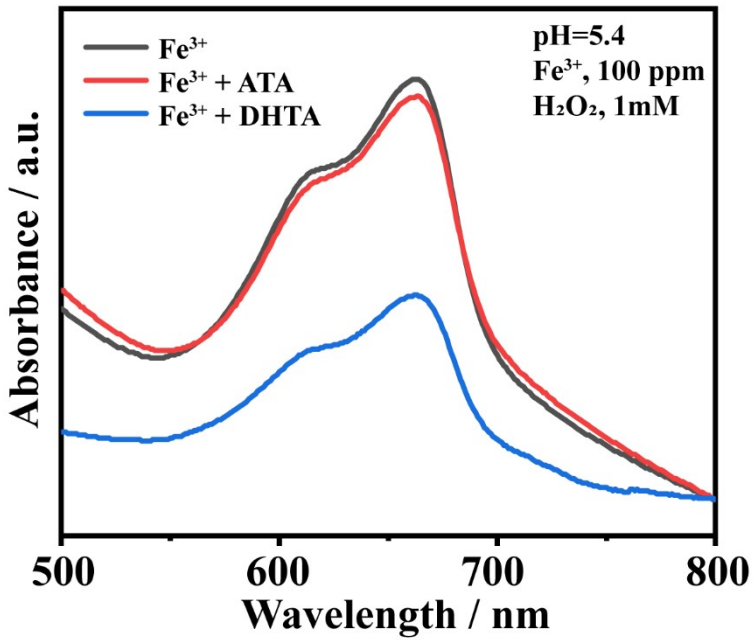


Figure S13. UV-vis absorption spectra of MB after different treatments.

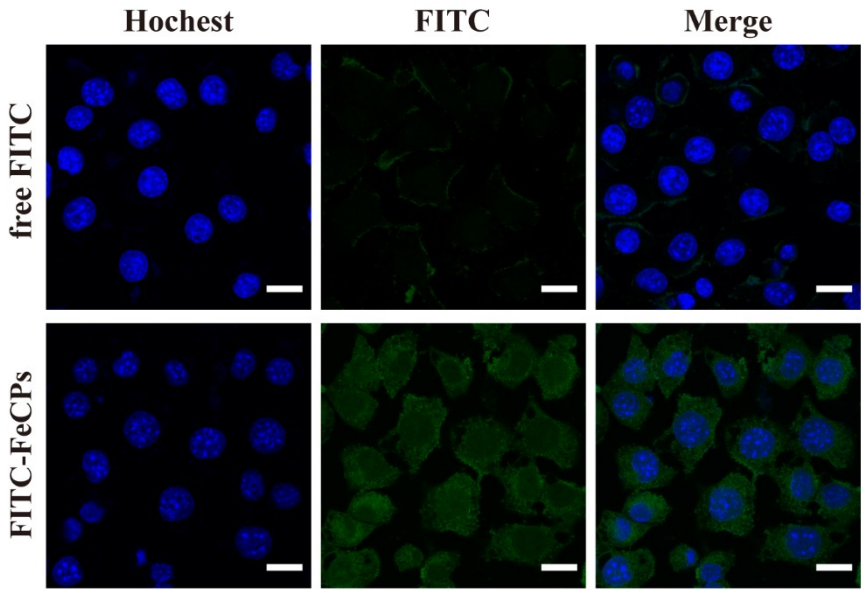


Figure S14. The cellular uptake of FeCPs. 4T1 cells treated with FITC-labeled FeCPs showed remarkable green fluorescence. Scale bar = 20 μm.

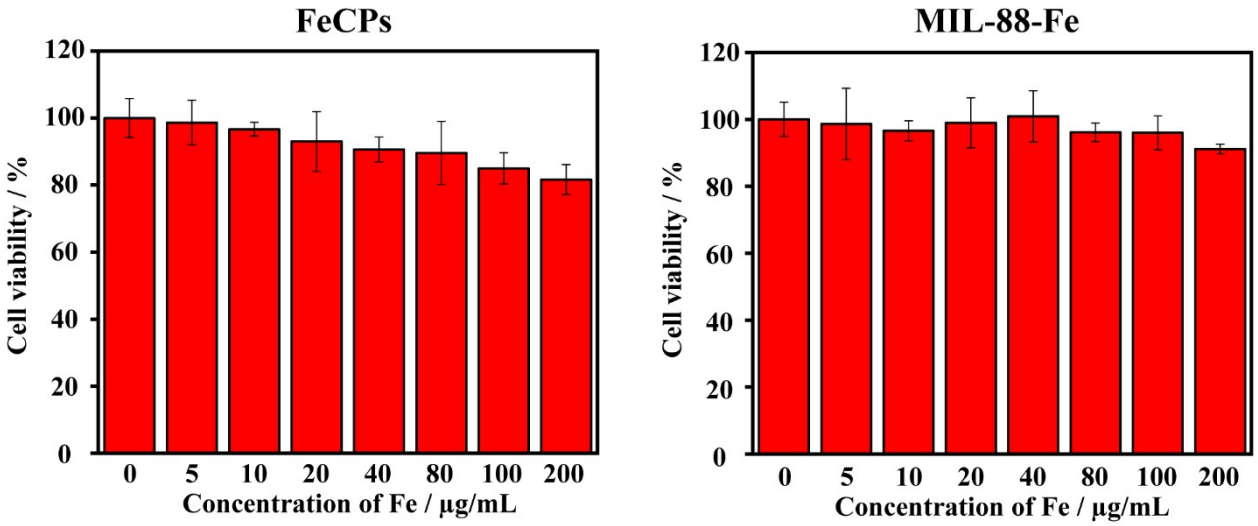


Figure S15. Cell viability of 4T1 cells after incubated with different concentrations of FeCPs and MIL-88-Fe for 48 h.

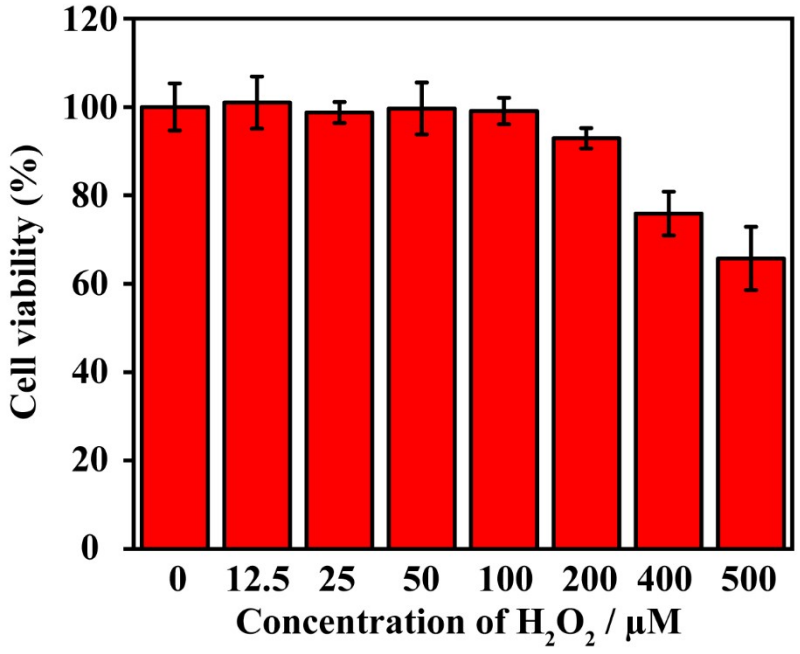


Figure S16. Cell viability of 4T1 cells after incubated with different concentrations of H_2O_2. Showing no obvious decrease of cell viability was observed (more than 90%) if treated with H_2O_2 less than 200μM.

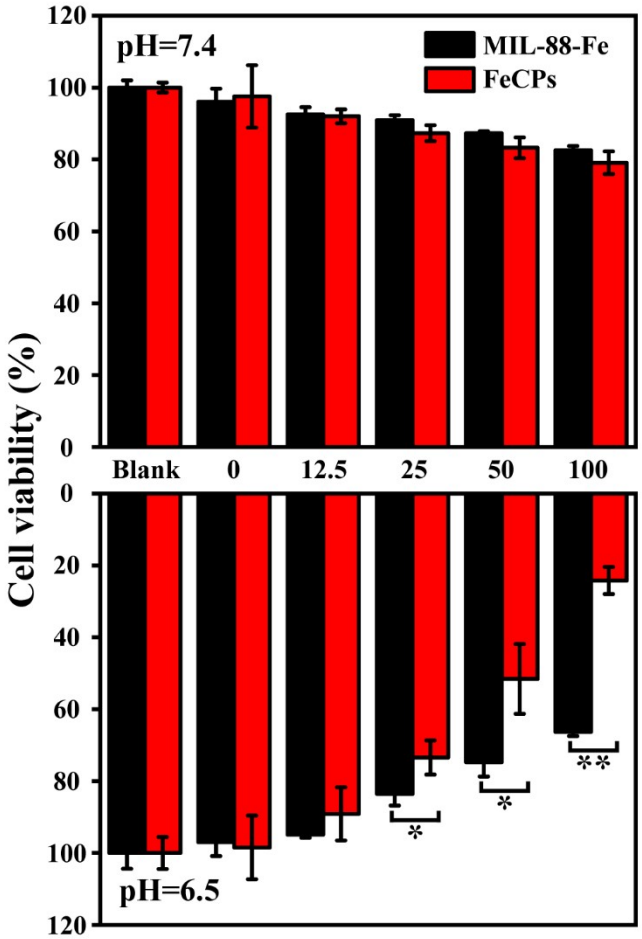
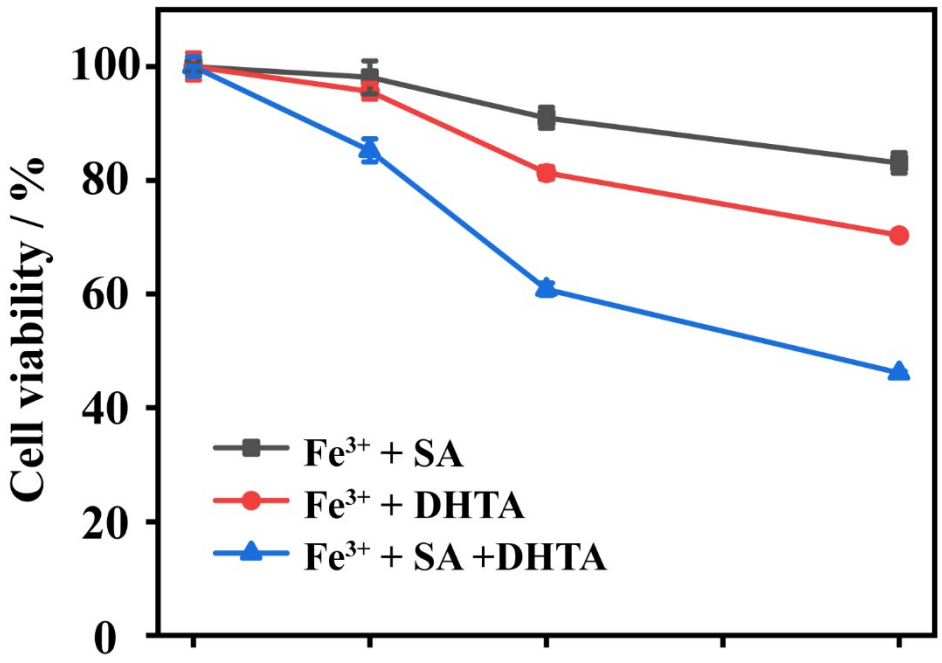


Figure S17. The cell viability of 4T1 cells after different treatments (Fe concentration of 0, 12.5, 25, 50 and 100 ppm) at the concentration of 100 μM H_2O_2. Statistical analysis was calculated by Student's t-test: *P < 0.05, **P < 0.01 and ***P < 0.001.



SA / ppm	0	25	50	100
DHTA / ppm	0	22.53	45.06	90.12
Fa		0.15	0.39	0.54
CI		0.78	0.70	0.98

Figure S18. Synergistic effect between SA and DHTA on sensitizing Fe-mediated CDT. The combination index (CI) values were calculated using the Chou-Talalay equation. The data was presented by the fraction affected by the dose-CI (Fa-CI). CI values <1, =1, and >1 represent synergism, additive, and antagonism, respectively.

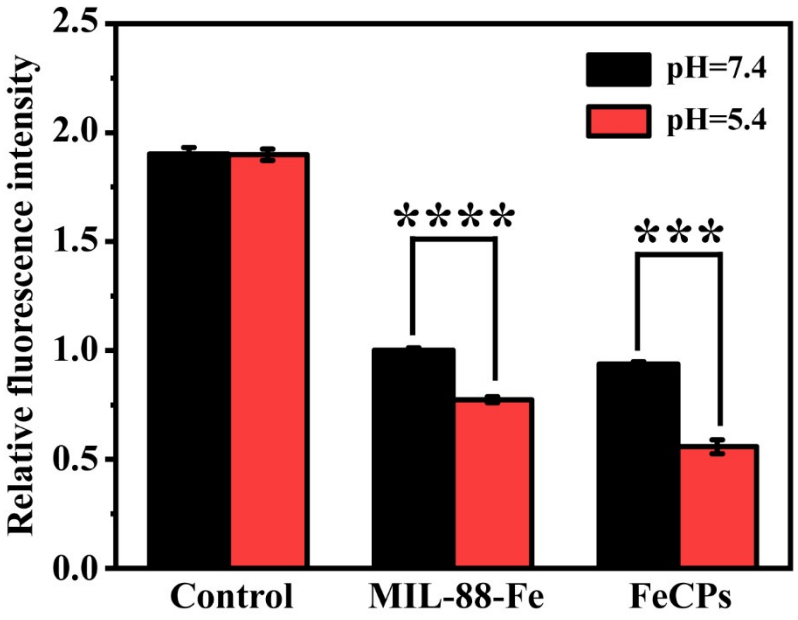


Figure S19. Relative fluorescence intensities of viable cells versus dead 4T1 cells with various treatments. Statistical analysis was calculated by Student's t-test: ***P < 0.001 and ****P<0.0001.

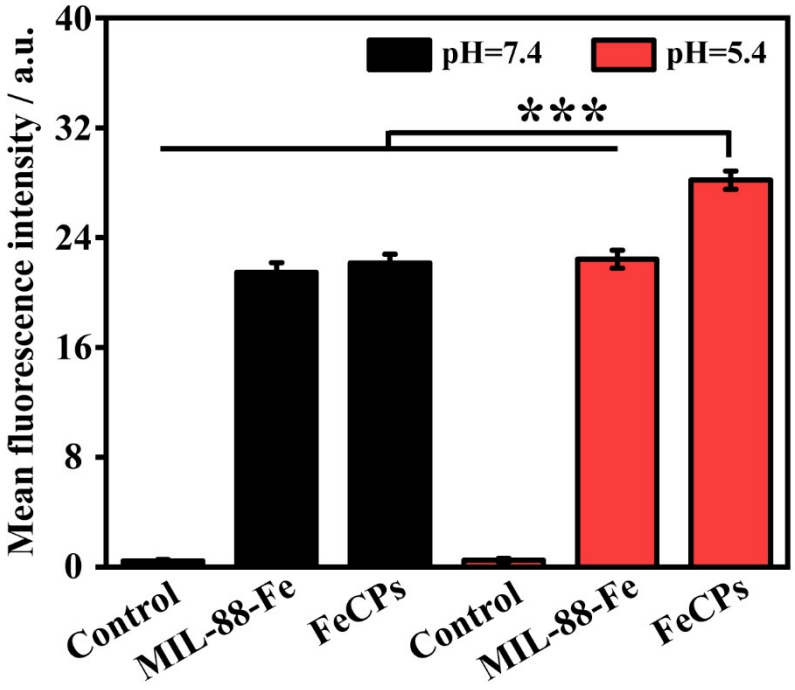


Figure S20. The quantitative analysis of HPF-stained 4T1 cells with different treatments. Statistical analysis was calculated by Student's t-test: ***P < 0.001.

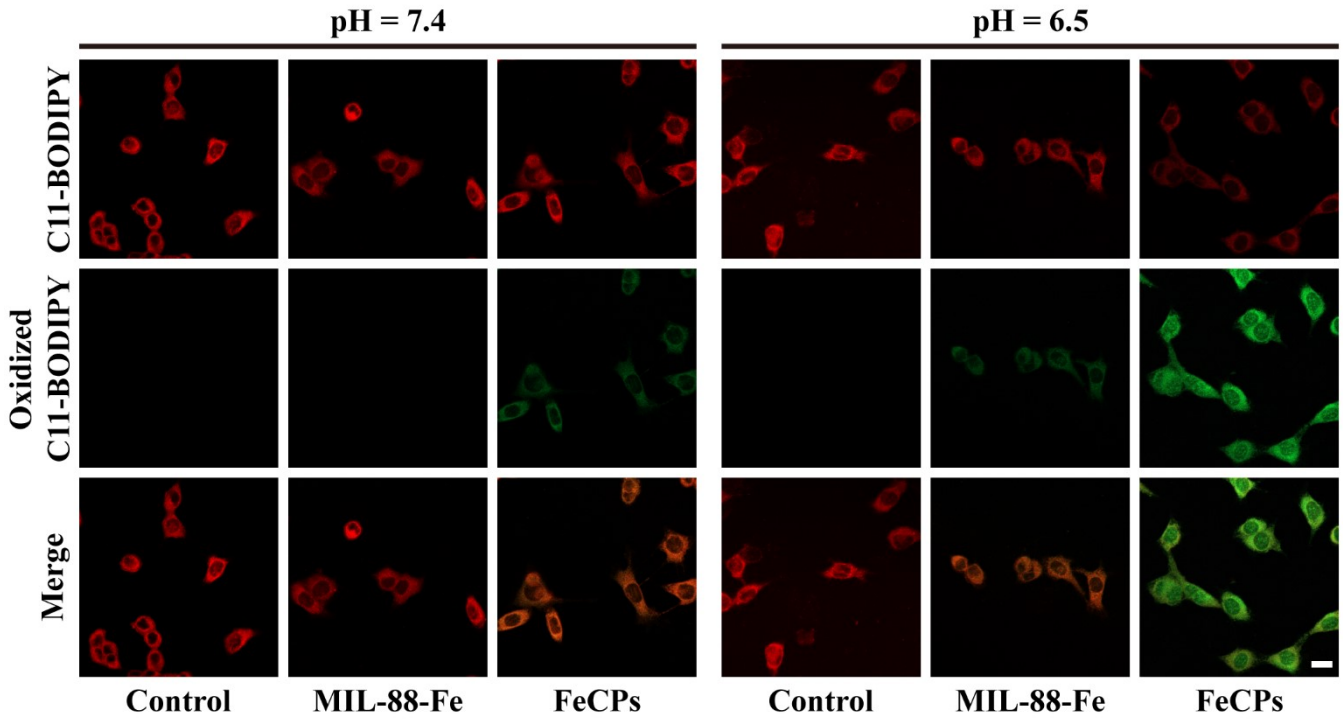


Figure S21. CLSM analysis of lipid peroxidation in BODIPY581/591-C11-stained 4T1 cells after different treatments. Scale bar = 20 μm.

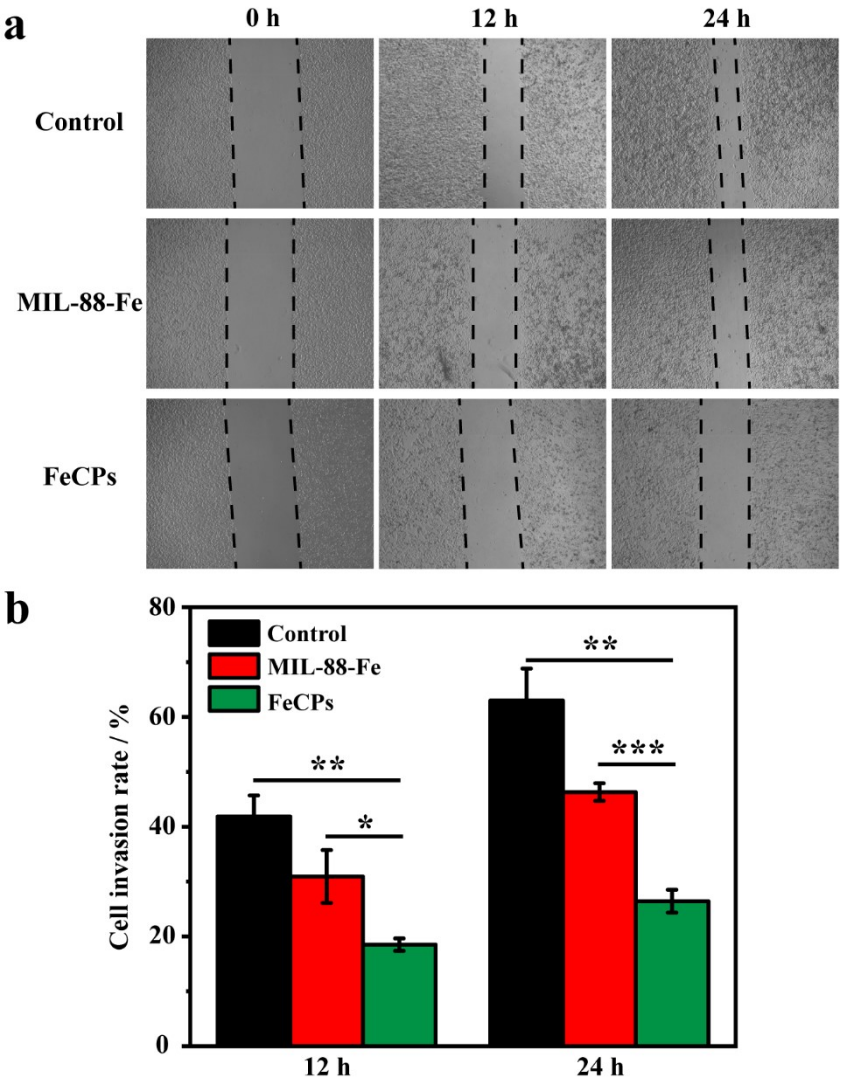


Figure S22. a) Wound-healing assay of 4T cells treated with PBS, MIL-88-Fe and FeCPs (100 μg/mL) at different time points after wounding. The black lines indicate the wound edge. b) The quantitative analysis of cell invasion. Statistical analysis was calculated by Student's t-test compared to the FeCPs group: *P<0.05, **P<0.01 and ***P<0.001.

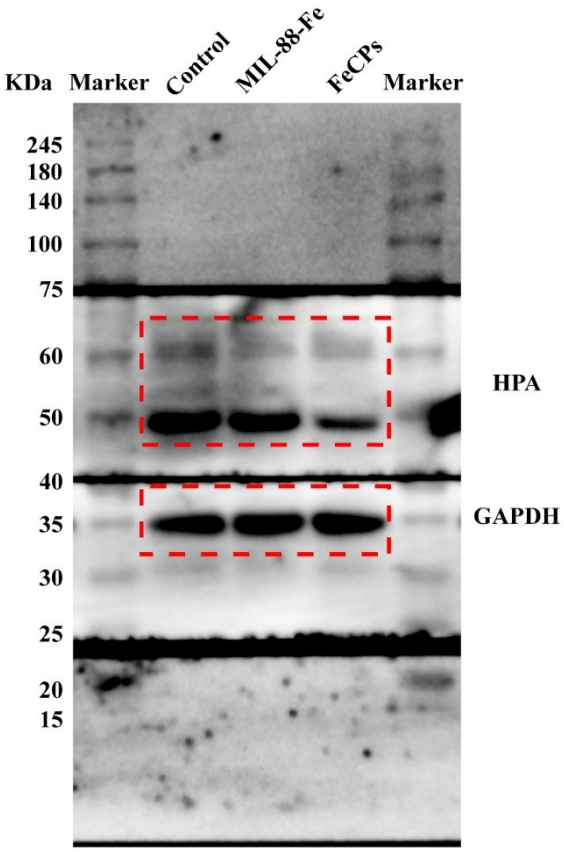


Figure S23. The full western blot analysis of HPA protein in 4T1 cells treated with PBS, MIL-88-Fe, FeCPs. Red dashed boxes indicate the target protein.

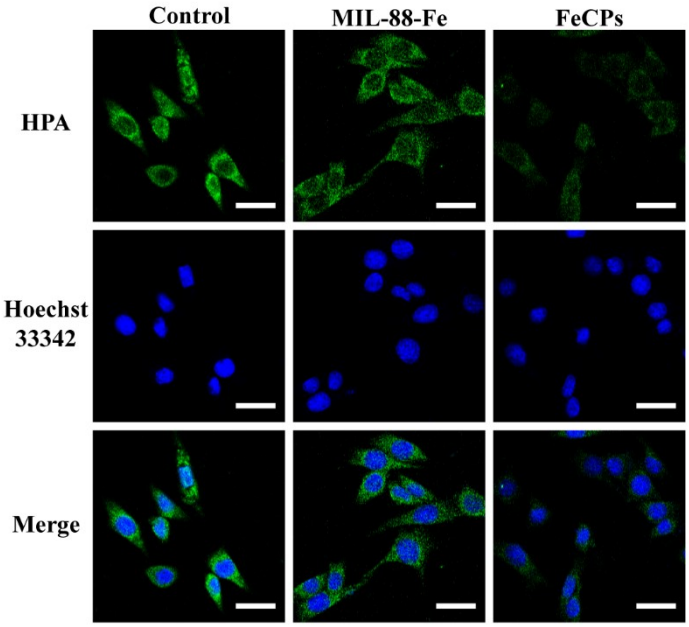


Figure S24. Immunofluorescence staining for HPA in 4T1 cells after various treatments. Scale bar = 30 μm.

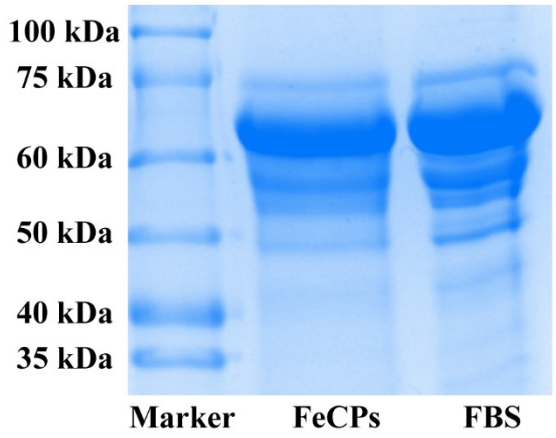


Figure S25. Gel electrophoresis of proteins adsorbed on FeCPs.

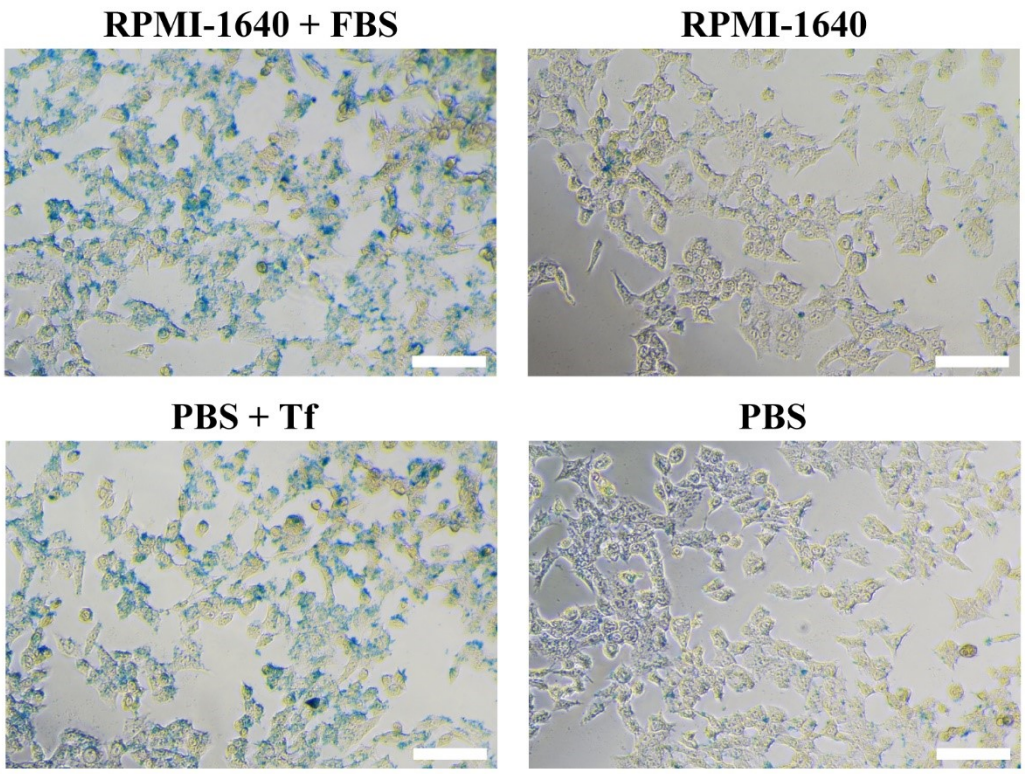


Figure S26. The chlorophosphonazo III stained 4T1 cells obtained after incubation with FeCPs for 4 h in RPMI-1640 with or without FBS and in PBS buffer with or without transferrin, respectively. Scale bars = 200 μm.

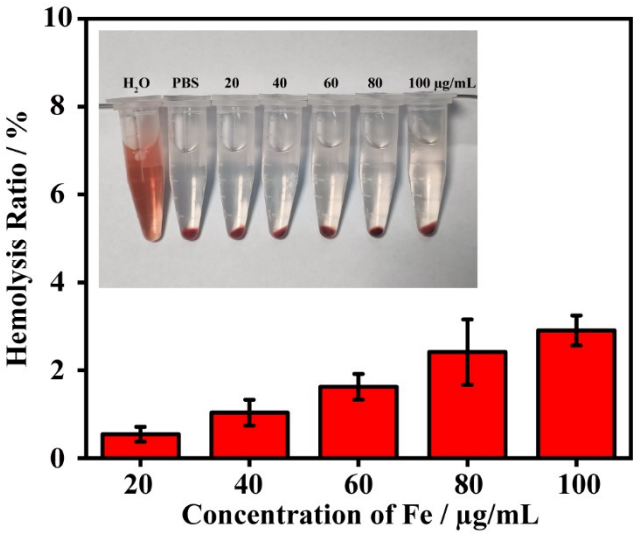


Figure S27. Hemolytic activity of FeCPs with different concentrations, The inset shows digital photograph of hemolysis test.

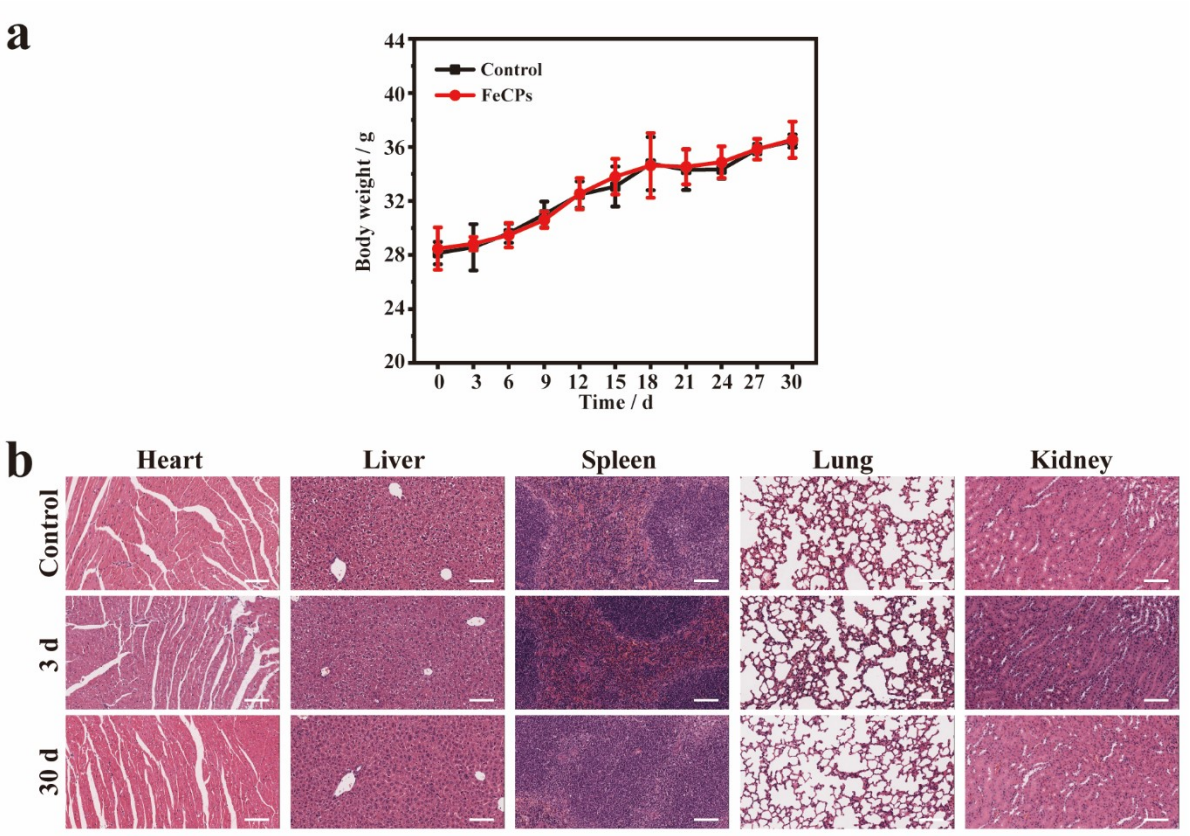


Figure S28. a) Time-dependent body-weight in the PBS and FeCPs groups after *i.v.* injection during a month. b) Images of H&E-stained tumor sections from heart, liver, spleen, lung and kidney of the mice treated with FeCPs (Fe, 10 mg/kg, n = 5). The tissue sections were harvested in 3 and 30 days, showing no significant change of H&E tissue sections. Scale bars = 100 μm.

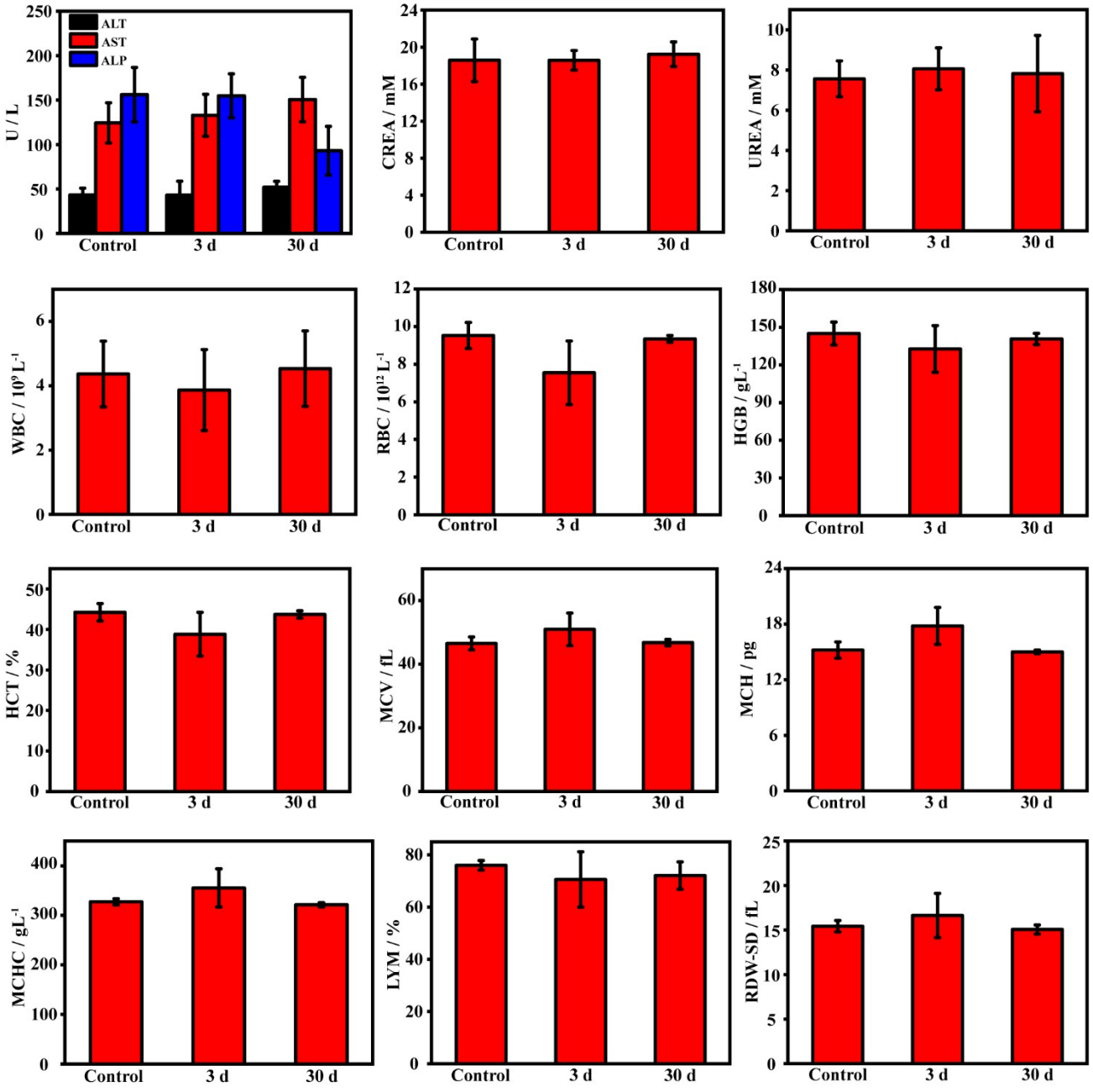


Figure S29. Blood biochemical indexes and hematology parameters of the mice after *i.v.* injection of FeCPs (Fe, 10 mg/kg, n = 5, mean ± s.d.) for 3 days and 30 days with equivalent injection of saline as control. No difference between the FeCPs-injected group and the control group, indicating the good biosafety of the nano-platform for tumor therapy *in vivo*.

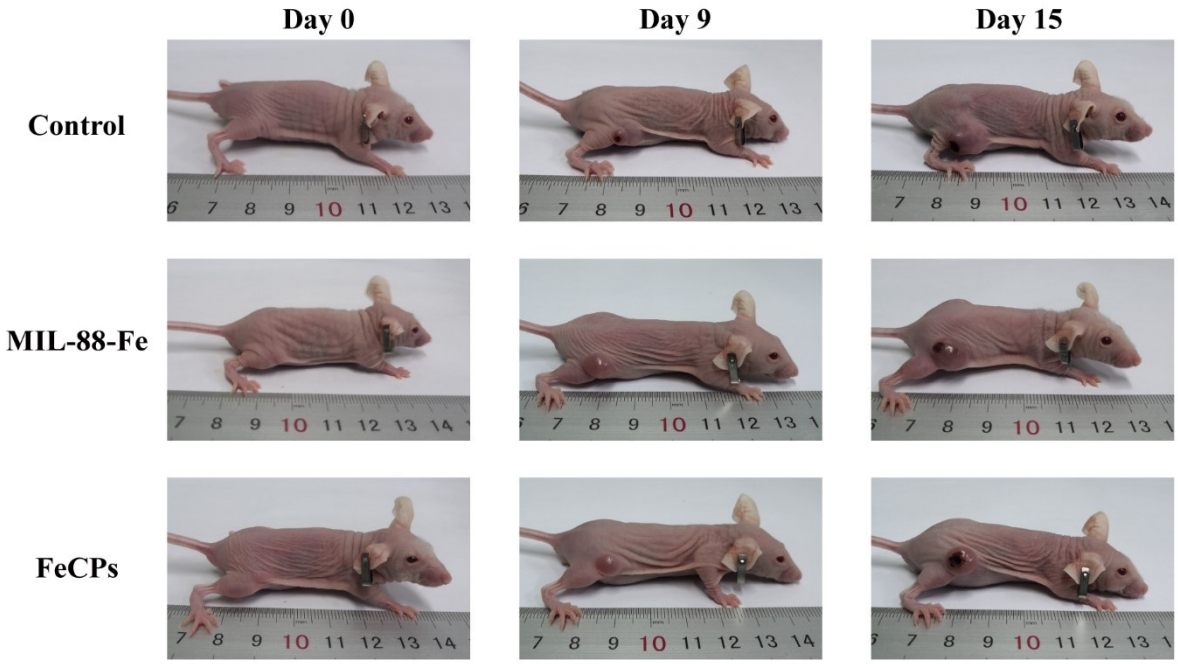


Figure S30. Representative photographs of tumors after *i.v.* injection with PBS, MIL-88-Fe, and FeCPs at different times.

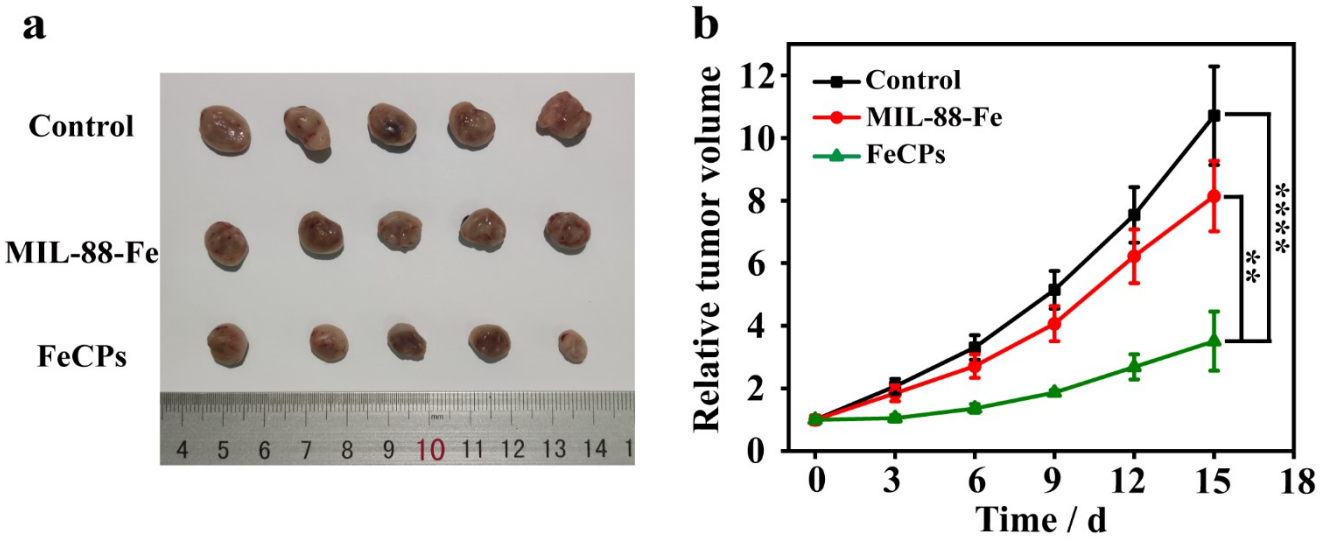


Figure S31. a) Photo of tumors harvested at the end of the experiments. b) Relative tumor volume curves of different treatment groups at different times. Statistical analysis was calculated by Student's t-test: **P<0.01 and ****P<0.0001.

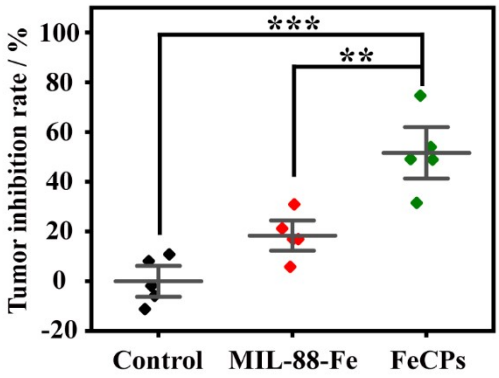


Figure S32. Calculated tumor-inhibition rates of different groups after the treatment period. Statistical analysis was calculated by Student's t-test: **P<0.01 and ***P<0.001.

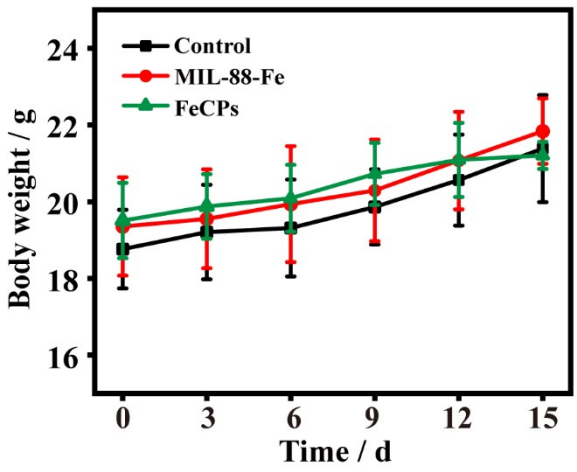


Figure S33. The change of body weight in different treatment groups.

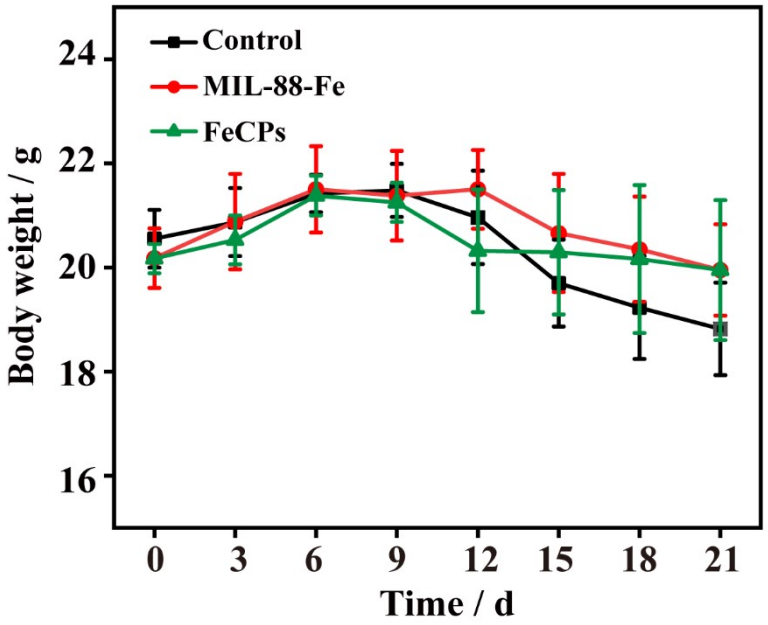


Figure S34. Time-dependent body-weight of orthotopic 4T1-Luc breast tumor model after *i.v.* injection PBS and FeCPs.

References

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