Electronic Supplementary Information

Endosome/lysosome-detained supramolecular nanogels as an efflux retarder and autophagy inhibitor for repeated photodynamic therapy of multidrug-resistant cancer

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Materials and Experimental Details

Materials. 3-[2-(2-Aminoethylamino)ethylamino]propyl-trimethoxysilane (AEEA) was purchased from Acros Organics. Rose bengal (RB), *cis*-dichlorodiammineplatinum(II) (DDP), and $NaHCO_3$ were obtained from Aladdin (China). Methoxy-poly(ethylene glycol)$_{113}$-*block*-poly(*L*-glutamic acid sodium salt)$_{200}$ (PEG-PLE, MW ~31000 Da) was purchased from Alamanda Polymers. Tetraphenylporphinesulfonate (TPPS) hydrate was obtained from the Tokyo Chemical Industry. 2,2,6,6-Tetramethylpiperidine (TEMP), methylthiazolyldiphenyl-tetrazolium bromide (MTT), chlorpromazine hydrochloride (CPZ), genistein, and 5-(*N*,*N*-dimethyl)-amiloride hydrochloride (amiloride) were bought from Sigma Aldrich. The blue fluorescent lysosome tracker, LysoBlue, was purchased from KeyGen Biotech (China). All solutions were prepared with deionized water (18.2 MΩ·cm) purified by a Milli-Q system (Millipore).

Synthesis of Organosilica Nanodots (OSiNDs). OSiNDs were prepared using a previously reported method.[1] Briefly, 1 mL AEEA was mixed with 4 mL RB aqueous solution (7.5 mg/mL), and the mixture was heated to 160 ^{o}C and incubated at this temperature for 4 h. The OSiND powder was obtained after dialysis (500 Da) and freeze drying, and suspended in water with a final concentration of 20 mg/mL.

Synthesis of SiPT40, SiPT75, and SiPT185. Three solutions (200 μL each) containing 5 mg/mL TPPS and 5 mg/mL PEG-PLE were first prepared by mixing 100 μL of TPPS solution (10 mg/mL) and 100 μL of PEG-PLE solution (10 mg/mL). Then, 800 μL solutions containing different concentrations of OSiNDs (6.25, 10, and 12.5 mg/mL) were separately added into the above-obtained TPPS/PEG-PLE mixtures (with a final TPPS concentration of 1 mg/mL). The final products were obtained after vortex for 30 s and standing at ambient temperature for 30 min.

Characterization. Scanning electron microscopy (SEM) experiments were carried out using a scanning electron microscope (ULTRA Plus, Zeiss). Transmission electron microscopy (TEM) experiments were performed on a transmission electron microscope (JEM-2100, JEOL). The hydrodynamic (HD) diameters and zeta potentials were measured on a zetasizer instrument (Nano ZS, Malvern). Ultraviolet–visible (UV–vis) absorption spectra were collected on a UV−vis spectrophotometer (UV-2600, Shimadzu, Japan). Fluorescence spectra were recorded on a spectrofluorophotometer (RF-5301PC, Shimadzu).

TPPS Release from the Nanogels. SiPT40, SiPT75, and SiPT185 suspensions (1 mL) prepared as described above were centrifugated at 10,000 rpm for 5 min, and the precipitates were resuspended in phosphate-buffered saline (PBS) solutions (1 mL, pH = 7.4). Afterwards, the as-prepared suspensions were kept at 37 ^{o}C. At different time points, the suspensions were centrifugated at 10,000 rpm for 5 min, and the released TPPS concentrations were obtained by analyzing the fluorescence intensities in the supernatants.

Mechanism of the Formation of SiPT75. To investigate whether electrostatic interaction, hydrogen bonding, and hydrophobic interaction could affect the formation of SiPT75, 100 μL of PEG-PLE solution (2 mg/mL) was added into 640 μL solution containing one of the inhibitors including NaCl, urea, and Triton X-100, followed by addition of 100 μL of TPPS solution (2 mg/mL) and 160 μL OSiND suspension (10 mg/mL). The final concentration of the inhibitors was 0.01, 0.02, 0.05, 0.1, or 0.2 M. The HD sizes were measured after incubation for 30 min.

Singlet Oxygen ($^1O_2$) Measurement. The $^1O_2$ generation of different samples was measured using fluorescence spectroscopy and electron paramagnetic resonance (EPR) spectroscopy. For fluorescence spectroscopic measurements, the singlet oxygen sensor green (SOSG) reagent (1 μL, 100 mM) was added to 2 mL of the PBS solution (0.01 M, pH = 4.5 (containing HCl), 6.0, or 7.4) containing SiPT75 (with the TPPS concentration of 10 μg/mL),

or 2 mL of the PBS solution (0.01 M, pH = 7.4) containing OSiNDs (80 μg/mL) or free TPPS (10 μg/mL). The fluorescence intensities at 525 nm of the mixtures were measured at an excitation wavelength of 504 nm before irradiation. Then the mixtures were irradiated by a 532 nm laser at a power density of 20 mW/cm^2, and the $^1O_2$ generation was recorded using a fluorescence spectrometer within the duration of irradiation (30 min).

For EPR spectroscopic measurements, TEMP was used as a $^1O_2$ trapping reagent. Freshly prepared TPPS (100 μg/mL) or SiPT75 (with the TPPS concentration of 100 μg/mL) in a PBS solution (0.01 M, pH = 4.5 or 7.4) was placed at ambient condition for 1 h, and then exposed to a 532 nm laser (20 mW/cm^2) for 5 min. Then the signals of $^1O_2$ were recorded on the EPR equipment EMX-10/12 (Bruker).

Cell Culture. The cisplatin-resistant A549/DDP lung cancer cells were cultured using Roswell Park Memorial Institute (RPMI) 1640 medium plus 10% fetal bovine serum, 100 U/mL of penicillin, and 100 μg/mL streptomycin in a humidified incubator at 37 ^{o}C and 5% CO_2.

Comparison of the Endocytosed Amounts of Free TPPS, SiPT40, SiPT75, and SiPT185. A549/DDP cells were seeded in a 96-well plate at a concentration of 5 × 10^4 cells/mL. After 24 h, the cell culture medium was replaced by fresh cell culture medium containing various drugs with the same TPPS concentration of 10 μg/mL. The cells were washed with PBS at different time points post treatment, and observed using a confocal microscope (TCS SP8, Leica). The endocytosed amounts were quantified by a flow cytometer (NovoCyte 2070R, ACEA Biosciences, Inc., USA).

Co-Localization Analysis. A549/DDP cells were seeded in a 96-well plate at a concentration of 5 × 10^4 cells/mL. After 24 h, the cells were incubated with SiPT75 with the TPPS concentration of 10 μg/mL for 24 h. After washing with PBS solution, the cells were divided into two groups: irradiation group and non-irradiation group. The cells in the non-

irradiation group were placed in the dark, while the ones in the irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 10 min. Afterwards, the cells in both irradiation and non-irradiation groups were incubated with LysoBlue (0.01 mM) for 2 h to stain the lysosomes. Finally, the cells were observed using a confocal microscope. The OSiNDs and TPPS of SiPT75 were excited at 488 and 552 nm, respectively, while the LysoBlue was excited at 405 nm.

Investigation of the Endocytosis Pathways of SiPT75. A549/DDP cells were seeded at a density of 5 ×10^3 cells/well in a 96-well plate and incubated at 37 ^{o}C and 5% CO_2 for 24 h. Then, the cells were washed with PBS solution and pretreated with 50 μg/mL genistein, 5 μg/mL CPZ, 10 μg/mL amiloride, or cultured at 4 ^{o}C for 2 h in serum-free RPMI 1640 medium. Next, the medium was removed and complete RPMI 1640 containing SiPT75 (TPPS concentration: 10 μg/mL) with one of the above different inhibitors at 37 ^{o}C for another 2 h. The cells pretreated at 4 ^{o}C were incubated at 4 ^{o}C after the addition of complete RPMI 1640 with SiPT75. Finally, after washing with PBS solution, the cells were collected and analyzed by flow cytometry. Each group had 3 parallel samples.

Comparison of the Anti-Efflux Abilities of Free TPPS, SiPT40, SiPT75, and SiPT185. A549/DDP cells were seeded in a 96-well plate at a concentration of 5 × 10^4 cells/mL, and incubated for 24 h. Afterwards, the cells were treated with various drugs with the same TPPS concentration of 10 μg/mL for another 24 h. Then the cell culture medium was replaced by serum-free culture medium without drug. The cells were observed using a confocal microscope at different time points. The residual contents of various drugs within the cells were quantified by flow cytometry.

Comparison of the Anti-Efflux Abilities of A549/DDP Cells against SiPT75 with Different Concentrations. A549/DDP cells were seeded in a 96-well plate at a concentration of 5 × 10^4 cells/mL. 24 h later, the cells were treated with different concentrations of SiPT75

for another 24 h. Then the cell culture medium was replaced by the serum-free culture medium without drugs. The residual contents of drugs within the cells were quantified by flow cytometry.

Extraction of the Lysosomes from the SiPT75-Treated A549/DDP Cells. A549/DDP cells were seeded in a 6-well plate at a density of 1×10^5 cells/mL. After 24 h, fresh culture medium containing SiPT75 (TPPS concentration: 20 μg/mL) was added for another 24 h incubation. Then, the lysosomes were extracted using a lysosome extraction kit (BestBio, China) and observed under a transmission electron microscope (JEM-2100, JEOL).

Biological TEM (Bio-TEM) Imaging of the A549/DDP Cells. A549/DDP cells were seeded in a 6-well plate at a density of 1×10^5 cells/mL. After 12 h, the cells were divided into two groups: $NaHCO_3$-treated group and untreated group. The cells in the $NaHCO_3$-treated group were treated with 20 mM $NaHCO_3$, and the cells in the untreated group were cultured in fresh cell culture medium. 12 h later, the cell culture medium in the $NaHCO_3$-treated group was replaced by the fresh cell culture medium containing SiPT75 (TPPS concentration: 10 μg/mL) and 20 mM $NaHCO_3$, and the cell culture medium in the untreated group was replaced by the fresh cell culture medium containing SiPT75 (TPPS concentration: 10 μg/mL). All the cells were incubated for another 24 h. The Bio-TEM images were obtained using a transmission electron microscope (H-7650C, Hitachi).

Comparison of the Anti-Efflux Abilities of $NaHCO_3$-Treated and Untreated Cells against SiPT75. A549/DDP cells were seeded in a 96-well plate at a concentration of 5×10^4 cells/mL. After 12 h, the cells were divided into two groups: $NaHCO_3$-treated group and untreated group. The cells in the $NaHCO_3$-treated group were treated with 20 mM $NaHCO_3$, and the cells in the untreated group were cultured in fresh cell culture medium. 12 h later, the cell culture medium in the $NaHCO_3$-treated group was replaced by the fresh cell culture medium containing SiPT75 (TPPS concentration: 10 μg/mL) and 20 mM $NaHCO_3$, and the

cell culture medium in the untreated group was replaced by the fresh cell culture medium containing SiPT75 (TPPS concentration: 10 μg/mL). All the cells were incubated for another 24 h, and the cell culture medium was replaced by the serum-free culture medium without drugs. The residual contents of drugs within the cells were quantified by flow cytometry.

Dark- and Photo-Cytotoxicities of Free TPPS, SiPT40, SiPT75, and SiPT185. A549/DDP cells were seeded in 96-well plates at a concentration of 5×10^4 cells/mL. After 24 h, the cells were treated with different concentrations of free TPPS, SiPT40, SiPT75, or SiPT185 for another 24 h. Afterwards, the cells were washed twice with PBS, and divided into two groups: irradiation group and non-irradiation group. The cells in the non-irradiation group were placed in the dark, while the cells in the irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 10 min. Afterwards, all the plates were incubated for 4 h. Then, 10 μL of MTT solution (10 mg/mL) was added to each well. After another 4 h, 150 μL of DMSO was added to each well and mixed. The absorbance at 492 nm was measured with a microplate photometer (Multiskan FC, Thermo, USA).

Dark- and Photo-Toxicities of SiPT75 to $NaHCO_3$-Treated A549/DDP Cells. A549/DDP cells were seeded in 96-well plates at a concentration of 5×10^4 cells/mL. After 12 h, the cells were treated with 20 mM $NaHCO_3$. 12 h later, the cells were co-treated with SiPT75 (TPPS concentration: 10 μg/mL) and 20 mM $NaHCO_3$ for 24 h, Afterwards, the cells were washed twice with PBS, and divided into two groups: irradiation group and non-irradiation group. The cells in the non-irradiation group were placed in the dark, while the cells in the irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 10 min. Afterwards, all the plates were incubated for 4 h. Then, 10 μL of MTT solution (10 mg/mL) was added to each well. After another 4 h, 150 μL of DMSO was added to each well and mixed. The absorbance at 492 nm was measured with the microplate photometer.

Apoptosis Assay. An annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) apoptosis detection kit (KeyGen Biotech, Nanjing, China) was used to detect the apoptotic cells. The cell suspension (100 μL per well) at a density of 5×10^4 cells/mL was added in 96-well plates and incubated for 24 h. Then culture media, or TPPS- or SiPT75-containing culture media (with the same TPPS concentration of 10 μg/mL) were added by replacing the original culture media. After another 24 h, the plates were divided into two groups: irradiation group and non-irradiation group. The cells in the non-irradiation group were placed in the dark, while the cells in the irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 10 min. 4 h later, the cells were stained with annexin V-FITC/PI at ambient condition for 10 min, and analyzed by flow cytometry. Each group had three parallel samples.

Reactive Oxygen Species (ROS) Generation. 2',7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) (KeyGen Biotech, Nanjing, China) was used to quantify the ROS generated in the untreated (control) and treated A549/DDP cells. DCFH-DA is a non-fluorescent probe which diffuses through the cell membrane and is then hydrolyzed by intracellular esterases to form 2',7'-dichlorodihydrofluorescein (DCFH). The formed DCFH reacts with intracellular ROS to form green fluorescent 2',7'-dichlorofluorescein (DCF). Briefly, the cell suspension (100 μL per well) at a density of 5×10^4 cells/mL was added in 96-well plates and incubated for 24 h. Then the original culture media were replaced by the TPPS- or SiPT75-containing cell culture media (with the same TPPS concentration of 10 μg/mL). After being incubated for another 24 h, the cells in each well were treated with DCFH-DA (10 μM), and were then divided into two groups: irradiation group and non-irradiation group. The cells in the non-irradiation group were placed in the dark, while the cells in the irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 10 min. The

cells without treatment were set as the control group. The fluorescence intensities of the cells were quantified using flow cytometry.

Western Blot Analysis. A549/DDP cells were lysed in radioimmunoprecipitation assay buffer with 1 mM phenylmethanesulfonyl fluoride on ice, and were centrifuged at 12,000 rpm at 4 ^{o}C for 30 min. The protein supernatant was transferred into precooled tubes, and the concentration of the samples was determined with a bicinchoninic acid kit (Pierce, Rockford, USA). A 40 μg sample was resolved using 13% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred onto polyvinylidene fluoride membranes. The membranes were then blocked in Tris-buffered saline containing 1% bovine serum albumin and Tween 20 at room temperature for 4 h. Primary antibodies to detect LC3 (1: 1000, Cell Signaling Technology, USA) and p62 (1: 1000, Proteintech Group, China) were incubated overnight with the membranes at 4 ^{o}C, extensively washed, and incubated with horseradish peroxidase-conjugated secondary antibody (1: 5000 dilution) for 2 h. After that, proteins were detected by enhanced chemiluminescence kit (KeyGen Biotech, Nanjing, China). β-Actin was used as the internal control.

***In Vivo* Fluorescence Imaging.** Female BALB/c nude mice (16 ± 2 g) aged 4 weeks were purchased from Yangzhou University Medical Center (Yangzhou, China) and all animal experiments were approved by the Animal Ethics Committee of Southeast University and were conducted in compliance with the Regulations for the Administration of Affairs Concerning Experimental Animals of China. After being acclimatized for at least 7 d, A549/DDP tumors were inoculated by subcutaneous injection of 1 × 10^8 A549/DDP cells (suspended in the mixture containing 50 μL PBS and 50 μL Matrigel) onto the dorsal side of each nude mouse. When the tumors grew to about 20 mm^3 in volume, the mice were divided into two groups: $NaHCO_3$-treated group and untreated group. The mice in the $NaHCO_3$-treated group were intratumorally injected with $NaHCO_3$ solution (50 μL, 0.2 M). Then, the

mice in the two groups were intravenously injected with 200 μL of free TPPS or SiPT75 with the same TPPS concentration of 1 mg/mL. The *in vivo* fluorescence imaging was performed on a PerkinElmer *in vivo* imaging system (IVIS Lumina XRMS Series III). The TPPS channel (*ex:* 560 nm, *em:* 670 nm) was used to monitor the drug distribution. The major organs and tumors of the mice were collected at various time points postinjection, and imaged using the *in vivo* imaging system. Bio-TEM images of the tumor slices excised from the mice on the 3rd day postinjection were observed by a transmission electron microscope (H-7650C, Hitachi).

***In Vivo* Cancer Therapy.** When the A549/DDP tumors grew up to about 20 mm^3, the mice were intravenously injected with 200 μL of free TPPS or SiPT75 with the same TPPS concentration of 1 mg/mL. After 24 h, the mice were divided into three groups: non-irradiation group, one-irradiation group, and two-irradiation group. The mice in the non-irradiation group were placed in the dark, while the mice in the one-irradiation group and two-irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 20 min. After another 24 h, the mice in the two-irradiation group were exposed to a 532 nm laser (20 mW/cm^2) for 20 min again. After 14 d, all the mice were sacrificed and the tumors were stained with hematoxylin and eosin (H&E).

Biosafety Evaluation. The healthy mice injected with 200 μL of PBS solution (control) or SiPT75 suspension (TPPS concentration: 1 mg/mL) were sacrificed on the 15th day postinjection. Then, the biocompatibility of the drugs was assessed by: (1) routine blood analysis using an automatic hematology analyzer (BC-2800Vet, Mindray, China), (2) some organ function-related biomarkers such as the alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (CRE) using a chemistry analyzer (Catalyst One, IDEXX), and (3) H&E staining of the organs including hearts, livers, spleens, lungs, and kidneys.

Statistical Analysis. All statistical results were presented as the mean ± standard deviation. The differences between two groups were calculated using unpaired Student's *t*-test.

Supplementary Figures

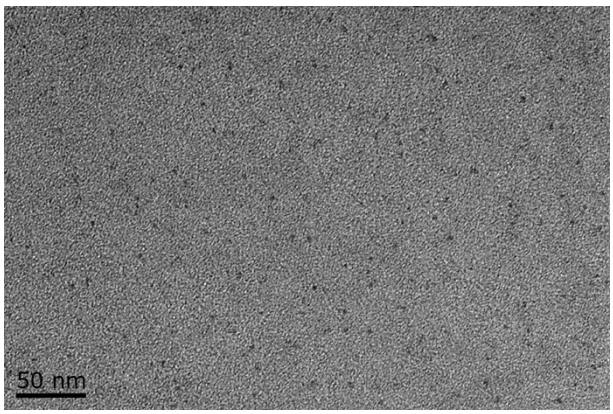

Fig. S1 TEM image of OSiNDs.

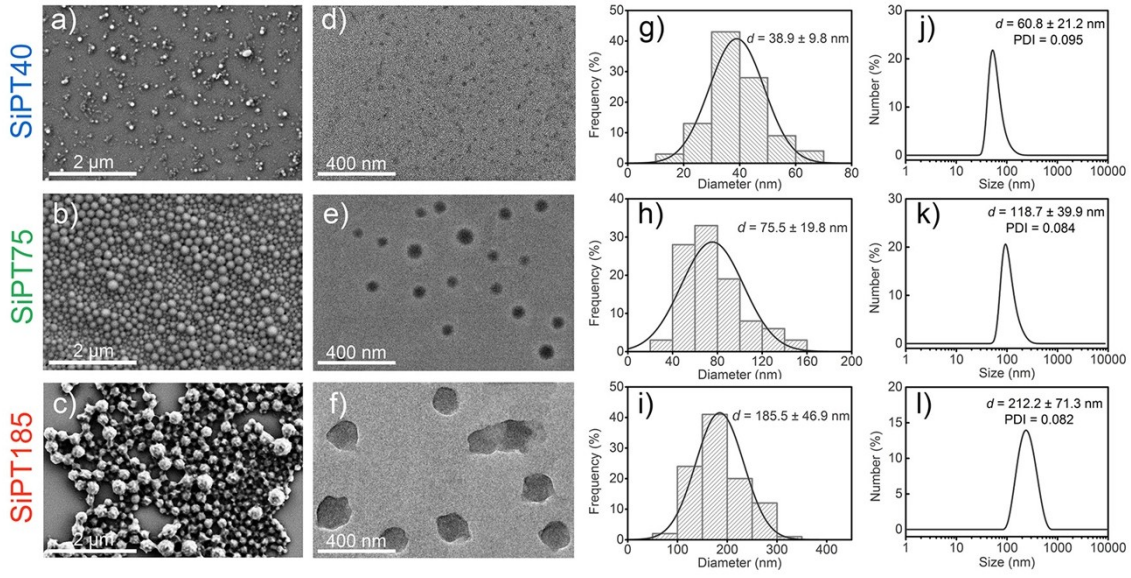

Fig. S2 (a–c) SEM images, (d–f) TEM images, (g–i) size distribution histograms (from TEM results in d–f), and (j–l) DLS results of SiPT40, SiPT75, and SiPT185 dispersed in the PBS solutions (pH = 7.4).

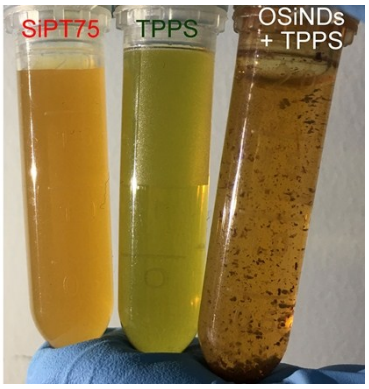

Fig. S3 Digital image of SiPT75 suspension, free TPPS solution, and the aqueous mixture of OSiNDs and TPPS. The freshly prepared mixture of OSiNDs and TPPS was placed at ambient condition for several seconds and photographed.

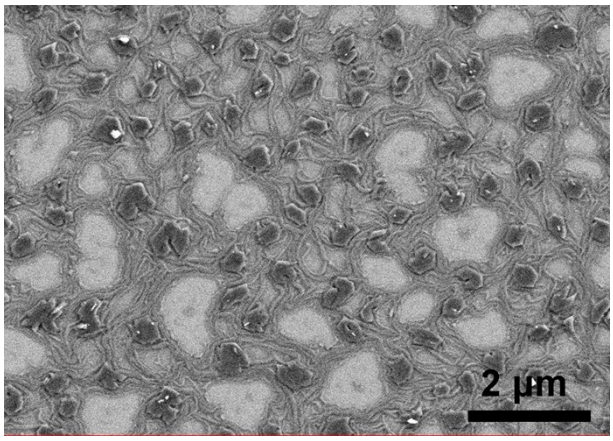

Fig. S4 SEM image of the mixture of TPPS (100 μg/mL) and PEG-PLE (100 μg/mL).

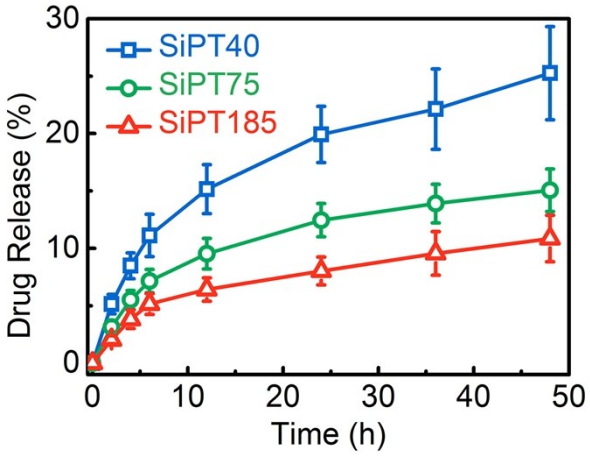

Fig. S5 Profiles of the release of TPPS from SiPT40, SiPT75, and SiPT185 in PBS solutions (pH = 7.4).

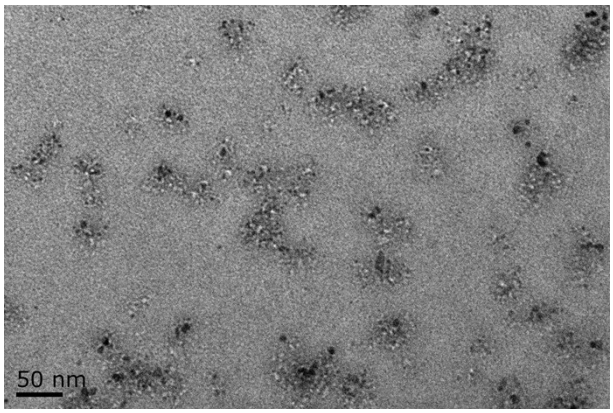

Fig. S6 TEM image of SiPT40 dispersed in an acidic solution (pH = 4.5).

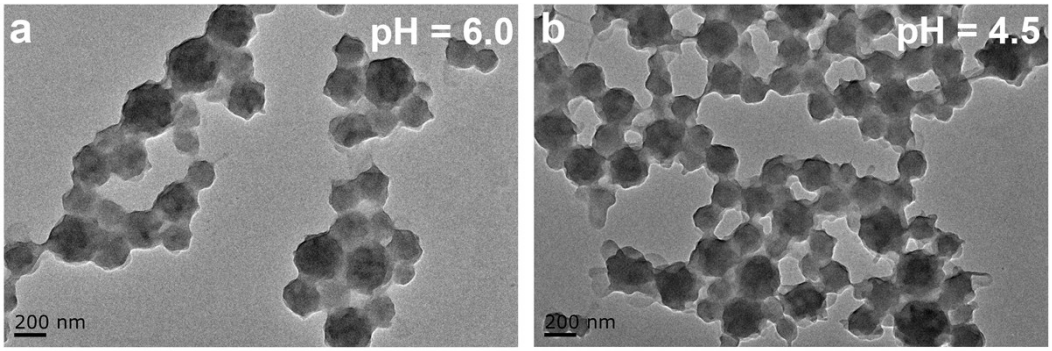

Fig. S7 TEM images of SiPT185 dispersed in acidic solutions with the pH values of (a) 6.0 and (b) 4.5.

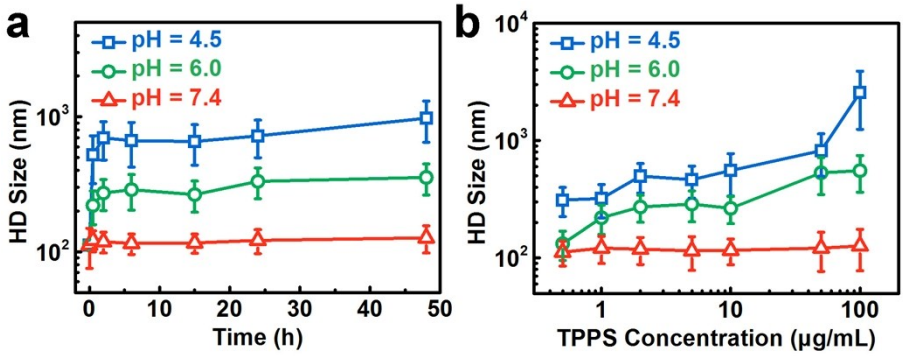

Fig. S8 (a) Time-dependent HD sizes of SiPT75 in solutions with different pH values. The TPPS concentration in SiPT75 was 10 μg/mL. (b) Concentration (based on TPPS)-dependent HD sizes of SiPT75 in solutions with different pH values. Before measurements, the nanogels were dispersed in solutions with different pH values for 24 h.

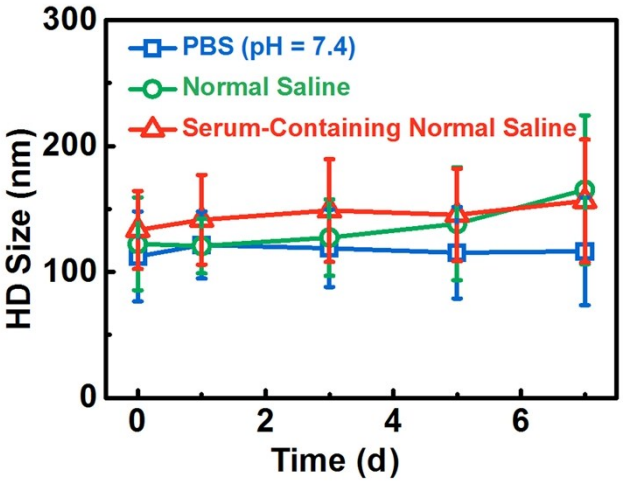

Fig. S9 Time-dependent HD sizes of SiPT75 (TPPS concentration: 100 μg/mL) in various solutions including PBS (ionic strength: 150 mM, pH = 7.4), normal saline (0.9% NaCl), and serum (1% FBS)-containing normal saline.

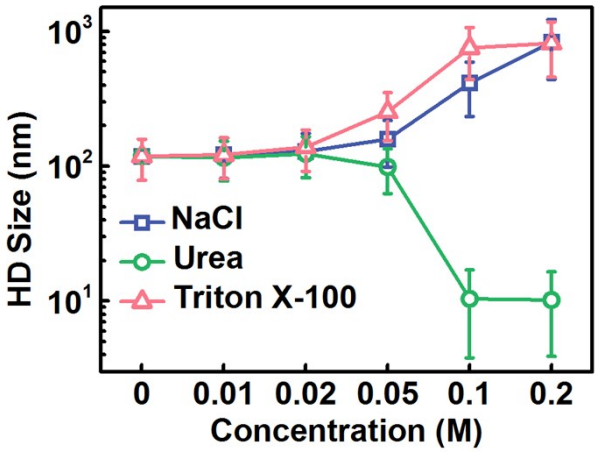

Fig. S10 HD sizes of the mixtures formed by OSiNDs, PEG-PLE, TPPS, and various concentrations of one of the three inhibitors (NaCl, urea, and Triton X-100). The weight ratio of OSiNDs/PEG-PLE/TPPS is 8:1:1.

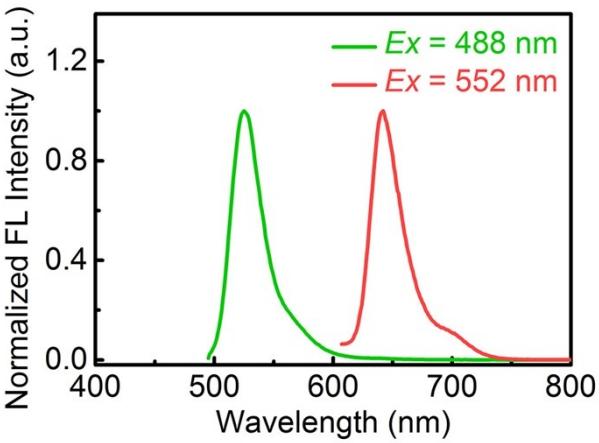

Fig. S11 Fluorescence (FL) emission spectra of SiPT75 suspensions excited by 488 or 552 nm.

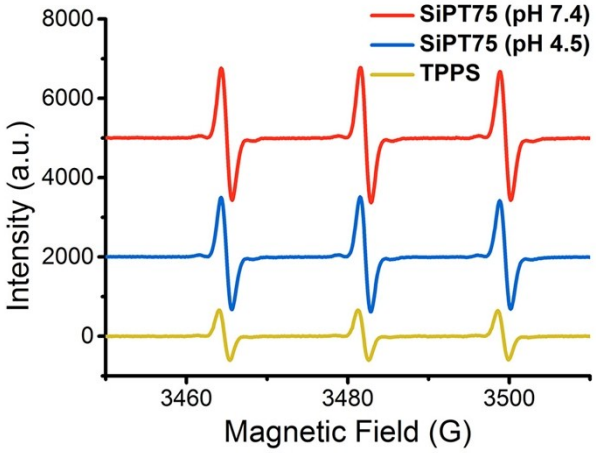

Fig. S12 EPR spectra of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) formed by the reaction between TEMP and the $^1O_2$ generated by TPPS solution (pH = 7.4), SiPT75 suspension (pH = 7.4), or SiPT75 suspension (pH = 4.5) after irradiation for 5 min. All the freshly prepared solutions/suspensions were placed at room temperature for 1 h before the EPR experiments.

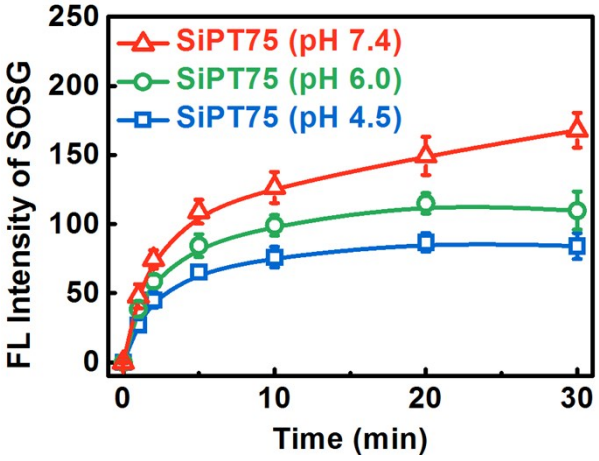

Fig. S13 FL intensities of SOSG showing the $^1O_2$ generation of SiPT75 dispersed in various solutions with different pH values for 24 h after irradiation by a 532 nm laser (20 mW/cm^2) for different time periods. The concentration of TPPS in the nanogels was 10 μg/mL.

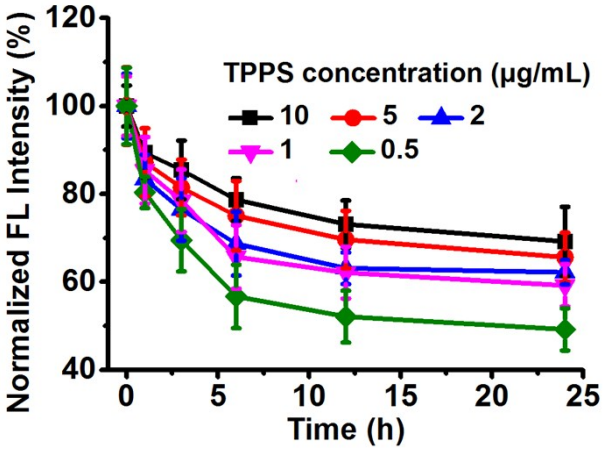

Fig. S14 Flow cytometric results showing the anti-efflux performance of different concentrations (based on TPPS) of SiPT75 in A549/DDP cells.

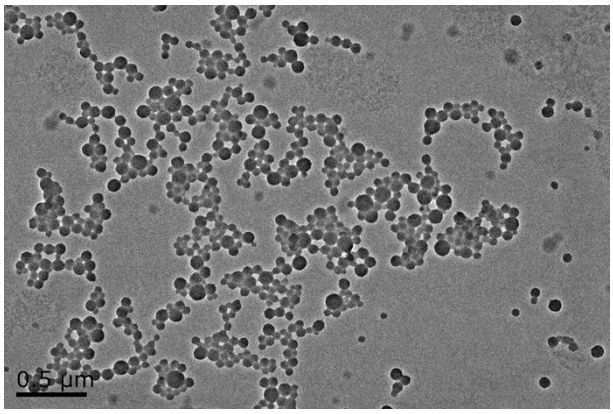

Fig. S15 TEM image showing the formation of SiPT75 aggregates in the lysosomes extracted from the SiPT75-treated A549/DDP cells.

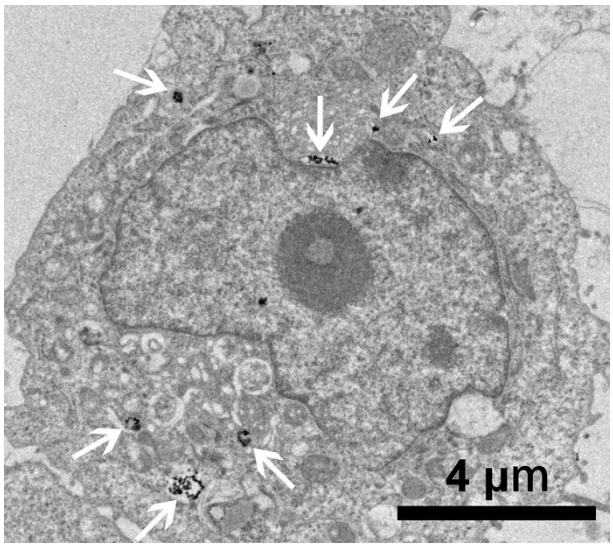

Fig. S16 Representative Bio-TEM image of A549/DDP cells treated with $NaHCO_3$ (20 mM) and SiPT75 (TPPS concentration: 10 μg/mL) for 24 h.

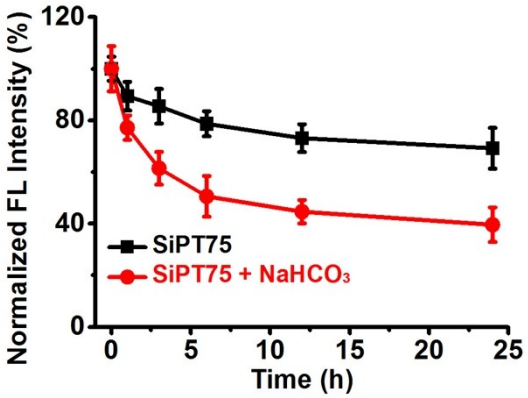

Fig. S17 Flow cytometric results showing the anti-efflux performance of SiPT75 (TPPS concentration: 10 μg/mL) without and with $NaHCO_3$ (20 mM).

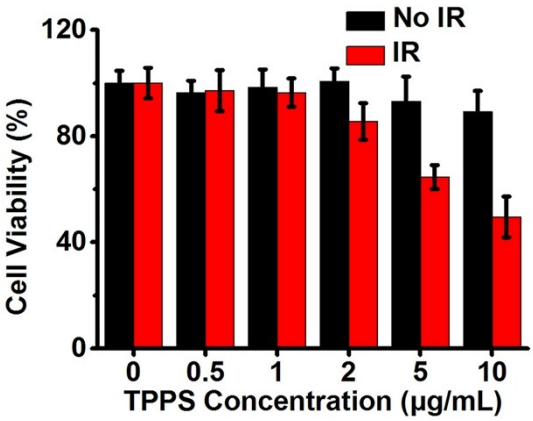

Fig. S18 Dark toxicity and phototoxicity of various concentrations (based on TPPS) of SiPT75 against $NaHCO_3$-treated A549/DDP cells. The $NaHCO_3$ concentration was 20 mM.

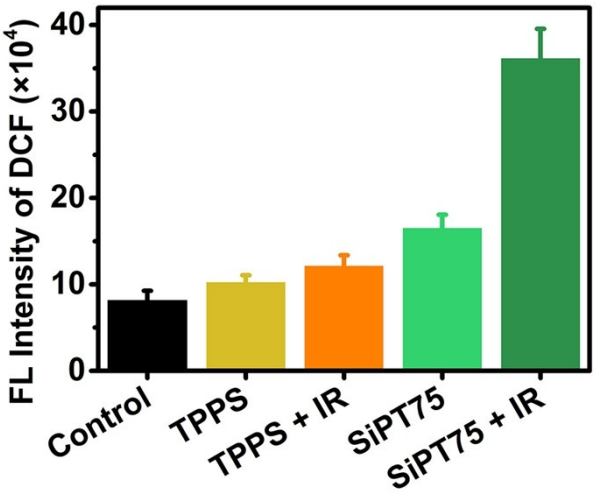

Fig. S19 ROS levels (measured *via* the fluorescence intensities of DCF) of A549/DDP cells after various treatments.

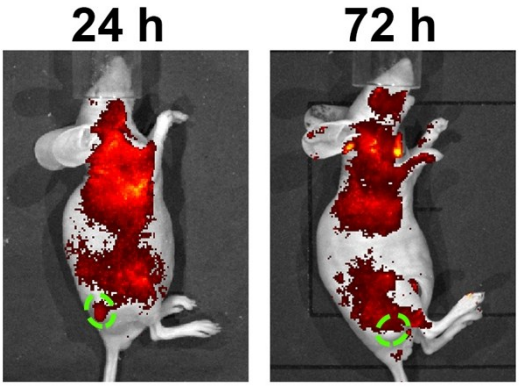

Fig. S20 *In vivo* fluorescence images of A549/DDP tumor-bearing mice after intravenous injection of SiPT75 (TPPS concentration: 1 mg/mL, 200 μL) and intratumoral injection of $NaHCO_3$ (0.2 M, 50 μL).

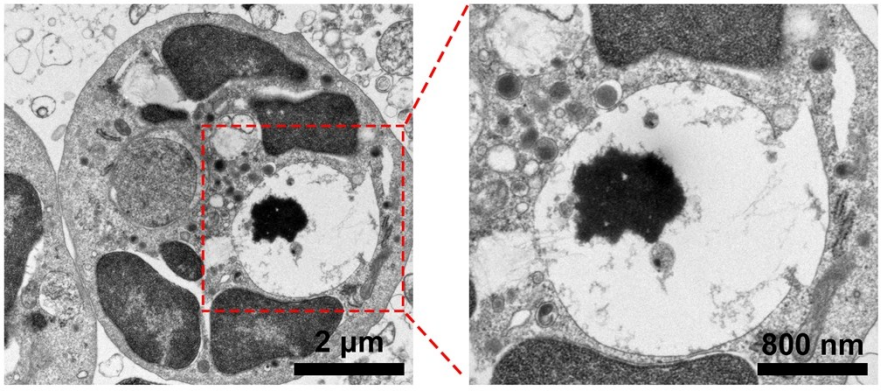

Fig. S21 Bio-TEM images of the tumor cell slice from the A549/DDP tumor-bearing mouse sacrificed on the 3rd day after intravenous injection of SiPT75 (TPPS concentration: 1 mg/mL, 200 μL) and intratumoral injection of $NaHCO_3$ (0.2 M, 50 μL).

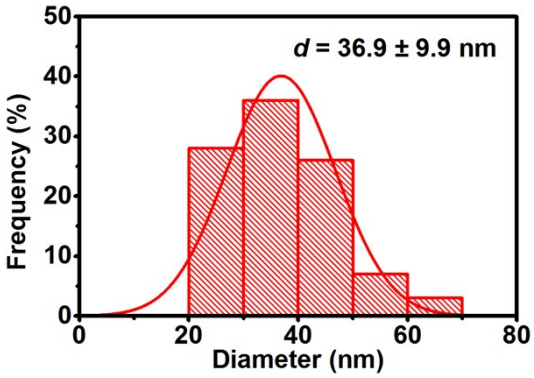

Fig. S22 Size distribution histogram of the nanogels in the red dotted region of Fig. 4d.

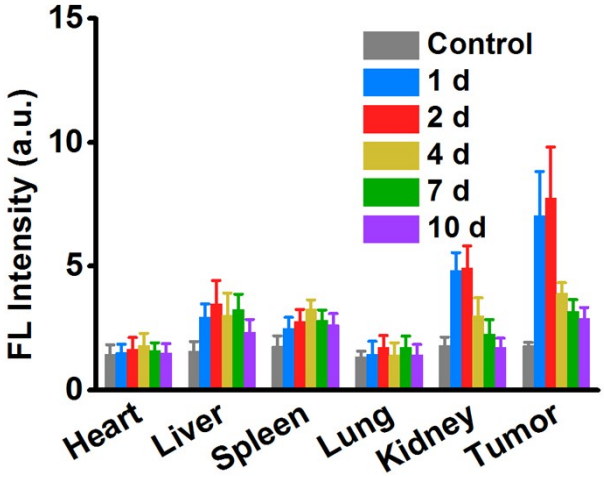

Fig. S23 *Ex vivo* FL imaging results of the major organs and tumors collected from the mice sacrificed at various time points after the injection of SiPT75 suspension (200 μL, TPPS concentration: 1 mg/mL). "Control" in the figure indicates the mice without treatment.

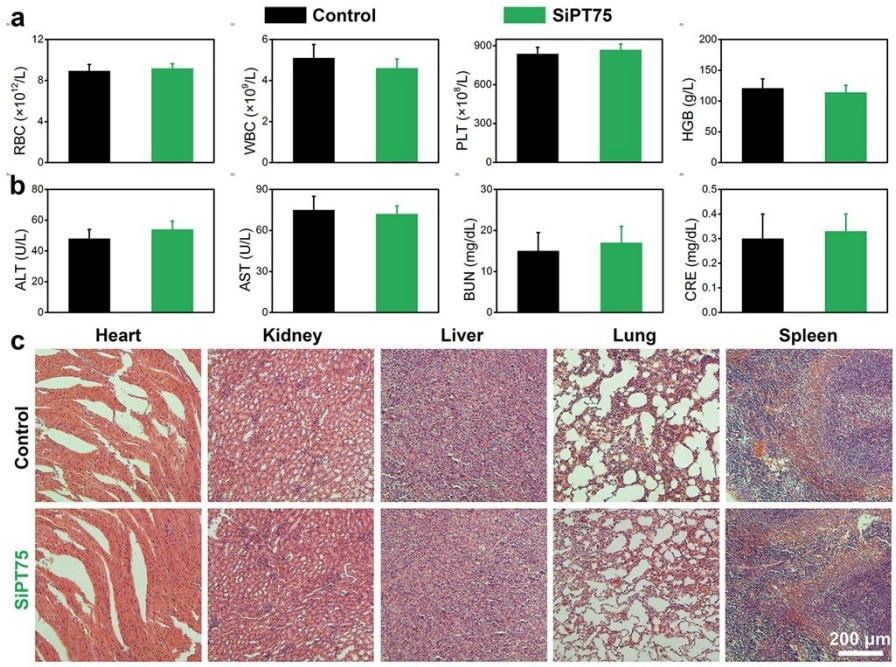

Fig. S24 Routine blood analysis results (a), serum biochemical analysis results (b), and histological images of different organs (c) obtained from the healthy mice sacrificed on the 15th day after treatment with 200 μL of PBS solution (control) or SiPT75 suspension (TPPS concentration: 1 mg/mL). RBC: red blood cells, WBC: white blood cells, PLT: platelets, HGB: hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, and CRE: creatinine.

Supplementary Table

Table S1 Apoptosis results (measured by flow cytometry) of A549/DDP cells after various treatments (n = 3).

	Live cells (%)	Early apoptotic cells (%)	Late apoptotic and dead cells (%)	Other cells (%)
Control	97.5 ± 1.1	0.9 ± 0.3	0.2 ± 0.1	1.4 ± 0.8
Control + IR	97.4 ± 0.5	1.3 ± 0.7	0.5 ± 0.4	0.8 ± 0.4
TPPS	96.9 ± 0.8	1.3 ± 0.2	0.5 ± 0.3	1.4 ± 0.9
TPPS + IR	88.1 ± 2.6	5.9 ± 0.9	4.2 ± 0.8	1.8 ± 1.2
SiPT75	91.8 ± 1.8	2.2 ± 1.1	1.5 ± 1.3	4.5 ± 1.2
SiPT75 + IR	11.1 ± 4.2	75.2 ± 6.9	7.9 ± 1.4	1.1 ± 0.8

Reference

1 X. K. Chen, X. D. Zhang, L. Y. Xia, H. Y. Wang, Z. Chen and F. G. Wu. *Nano Lett.*, 2018, **18**, 1159–1167.