Materials and Reagents. Fetal bovine serum (FBS), phosphate-buffered saline (PBS), Dulbecco's modified Eagle's medium (DMEM) and 0.25 % (w/v) trypsin-0.03 % (w/v) ethylenediaminetetraacetic acid (EDTA) solution were purchased from Grand Island Biological Co. Doxorubicin hydrochloride (DOX·HCl) (99 %), α-lipoic acid, 4',6-diamidino-2-phenylindole (DAPI) and 2,7-dichlorodihydrofluorescein diacetate (DCFH-DA), dimethylsulfoxide (DMSO), dichloromethane (DCM), N,N-Dimethylformamide (DMF), N,N-Diisopropylethylamine (DIEA), triethylamine (TEA), formaldehyde and poly(γ-glutamic acid) (γ-PGA, M.W. = 3000) were purchased from Sigma-Aldrich (Shanghai, China). Protoporphyrin IX (PpIX) was obtained from Yuanye Bio-Technology Co., Ltd. (Shanghai, China). GGsTOP was purchased from APExBIO Technology LLC (USA). Lyso Tracker Green was purchased from Invitrogen Corporation (USA). Cell counting kit-8 was purchased from Dojindo Molecular Technologies, Inc. (Japan). A terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) kit was provided by Roche Inc. (Switzerland). Dialysis tubes and dialysis bags were supplied by Spectrum (USA). All materials were of analytical grade.

Preparation of NLS-LA-PpIX polymer. NLS-LA-PPIX polymer was synthesized by a solid-phase method. Briefly, 2-chlorotrityl chloride resin was washed with DCM (15 ml/g) and shaken for about 30 min. Once the resin was fully swollen, the solvent was filtered off and the synthesis started. Firstly, the first amino acid of the C-terminal end of the sequence (Fmoc-Gly-OH) was added and dissolved with DMF, then DIEA was added and activated for 2 min. Secondly, the solution was transferred to the drained resin followed by adding 20 % piperidine DMF solution and was then stirred and drained off. Again, 1 ml piperidine solution was added and stirred for 7 min, then the solution was filtered and washed with DMF to remove the Fmoc protecting group. The reaction was confirmed by the ninhydrin test. Thirdly, the solution was drained and washed

with DMF at stirring for three times. The above steps for each amino acid in the sequence were repeated until the last Fmoc protecting group was removed. Fourthly, the peptide resin was washed with MeOH and dried under gentle suction. Then, the cleavage mixture (1 ml/100 mg peptidyl resin) was added to cleave the polymer from the resin. Finally, all the polymers were purified using reversed phase semi preparative HPLC, which were characterized by analytical HPLC and LCMS techniques.

Pharmacokinetic tests. Male Sprague-Dawley rats (250~300 g) were randomly divided into two groups (n=5). For the control group, free DOX solution (3 mg/kg) was intravenously injected and for another group, NLS-LA-PpIX-DOX@cyclo-γ-PGA with the same amount of DOX was also intravenously injected. At predominated time (0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 h), 0.5 mL blood was withdrawn and centrifuged at 14000 rpm for 10 min at 4 ℃ and the plasma was obtained for drug concentration detection using High Performance Liquid Chromatography (HPLC) methods. The data were analyzed using Excel software.

Table S1. Physical characterizations of cyclo-γ-PGA-coated micelles with different polymer/cyclo-γ-PGA ratio

	Polymer/cyclo-γ-PGA (w/w)				
	64:1	32:1	16:1	8:1	4:1
Size (nm)	125.7±4.4	130.3±2.6	143.2±2.8	151.6±3.6	160.2±2.0
PDI	0.27 ± 0.08	0.18 ± 0.06	0.28 ± 0.09	0.34 ± 0.07	0.35 ± 0.09

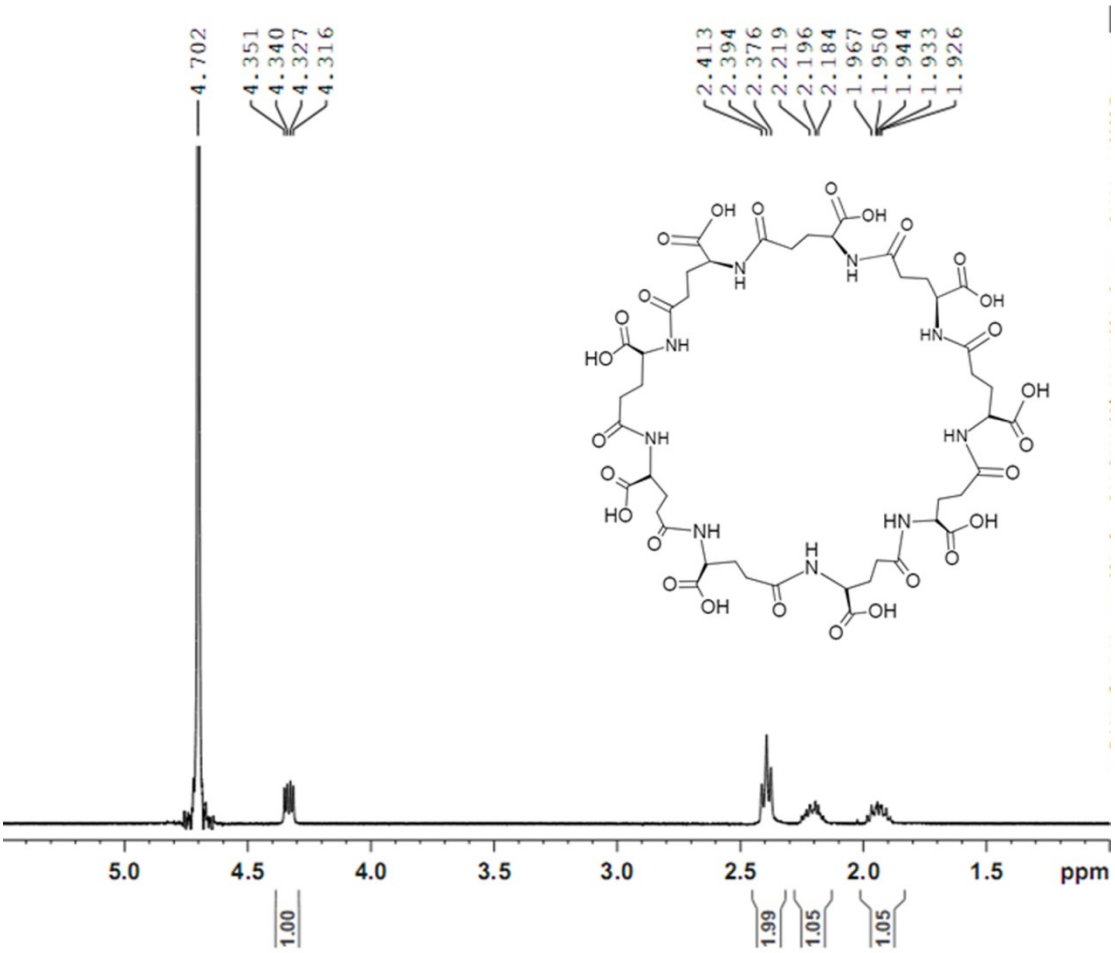

Figure S1. Structure and ^{1}H-NMR analysis of synthetic cyclo-nona-polyglutamic acid

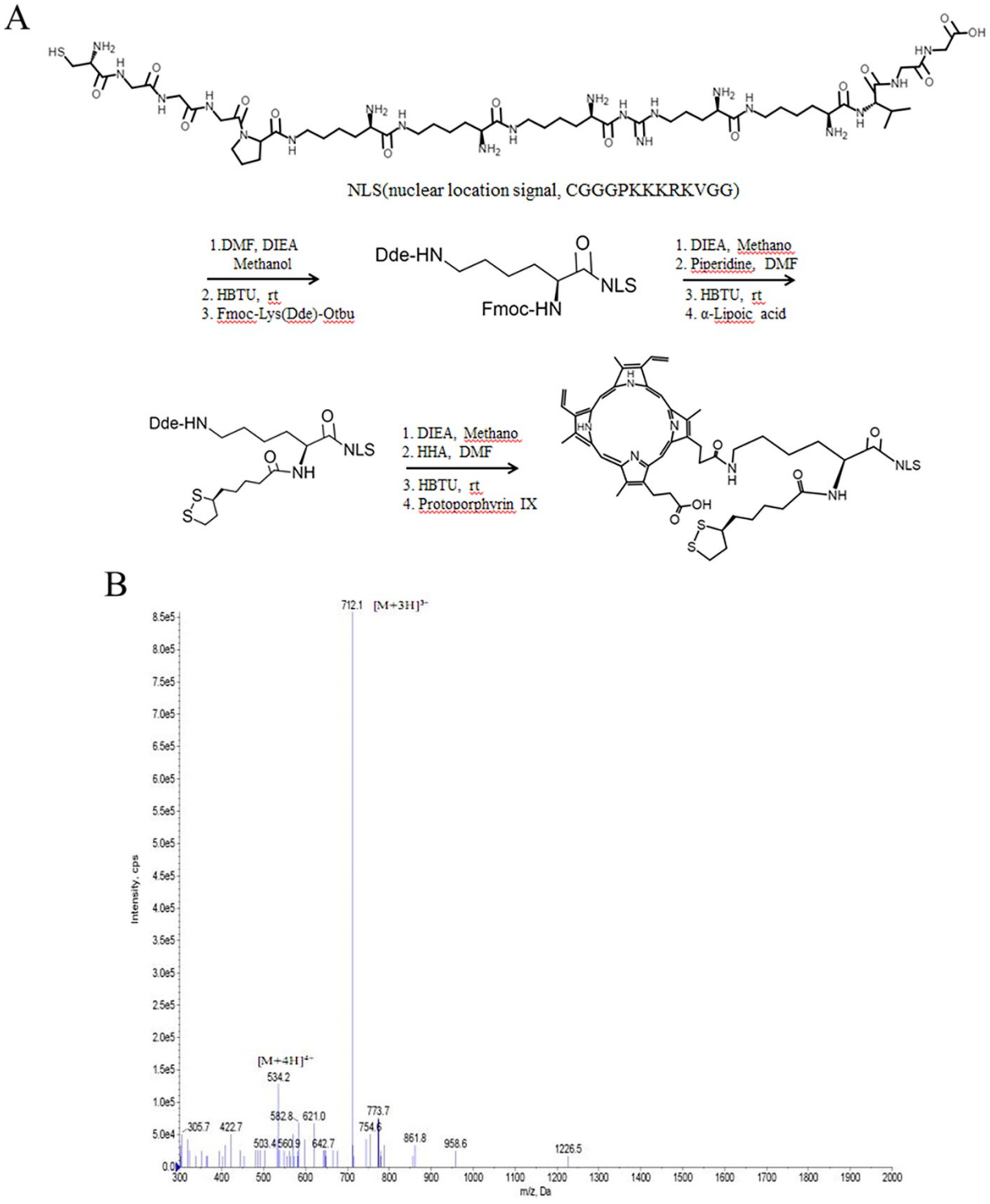

Figure S2. Synthesis and characterization of the NLS-LA-PpIX polymer. (A) Synthetic process and (B) ion scan spectrum of the NLS-LA-PpIX polymer

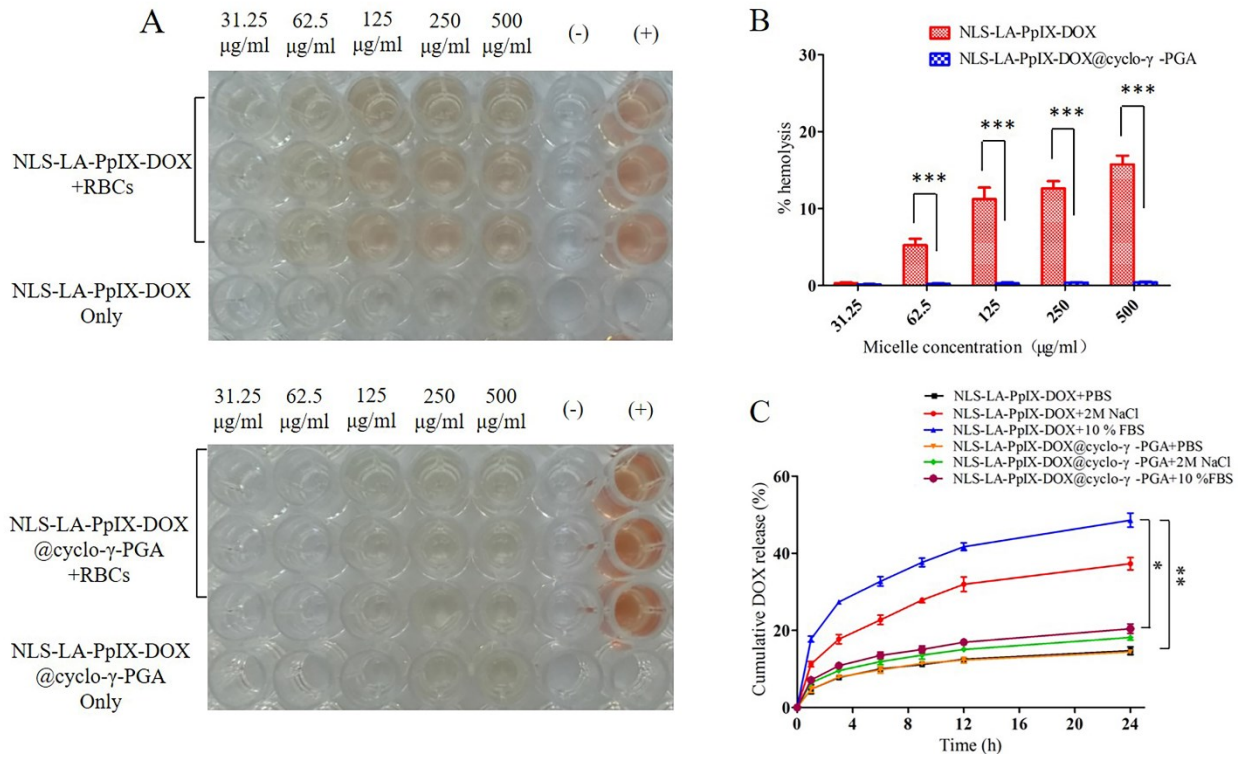

Figure S3. Evaluation of hemolysis and stability *in vitro*. (A) Hemolysis of RBCs incubated with NLS-LA-PpIX-DOX and NLS-LA-PpIX-DOX@cyclo-γ-PGA micelles at different concentrations (31.25, 62.5, 125, 250, and 500 μg/ml). The corresponding micelles (31.25, 62.5, 125, 250, and 500 μg/ml) were used as background controls. PBS and saponin (4 mg/ml) were used as negative (-) and positive (+) controls, respectively. (B) Comparison of the hemolysis activities of NLS-LA-PpIX-DOX and NLS-LA-PpIX-DOX@cyclo-γ-PGA micelles. (C) *In vitro* DOX release profiles of NLS-LA-PpIX-DOX and NLS-LA-PpIX-DOX@cyclo-γ-PGA micelles in PBS, PBS with 2 M NaCl and PBS with 10 % FBS. Data are represented as the mean ± SD (n=3), $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

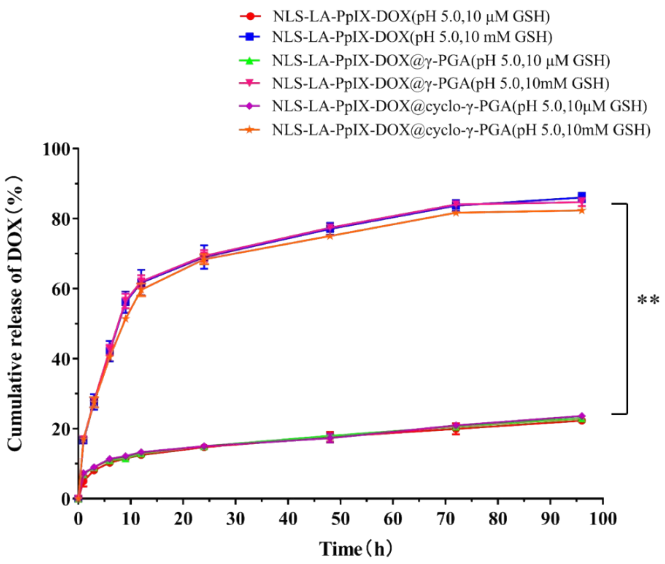

Figure S4. Cumulative DOX release from the DOX-loaded NLS-LA-PpIX-DOX, NLS-LA-PpIX-DOX@γ-PGA and NLS-LA-PpIX-DOX@cyclo-γ-PGA micelles in PBS (pH 5.0, GSH 10 μM or pH 5.0, GSH 10 mM). The results are expressed as the mean ± SD (n = 3), $^{**}P < 0.01$

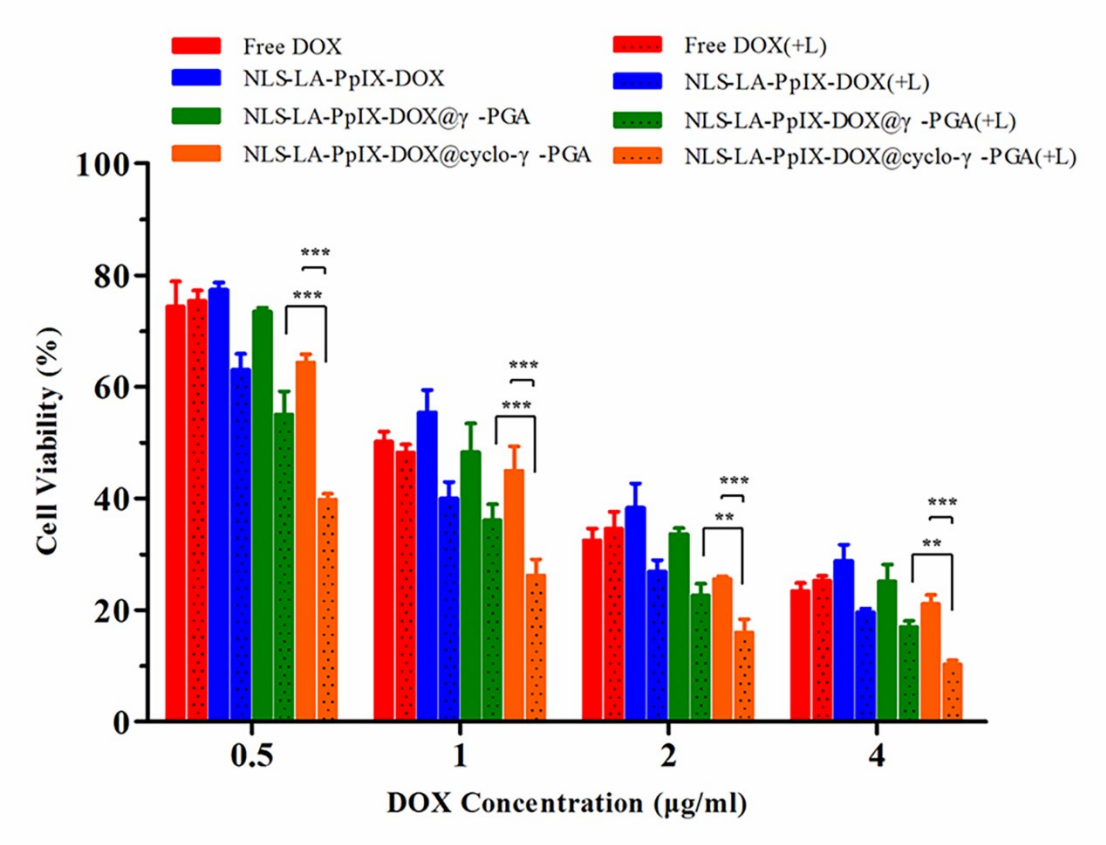

Figure S5. The viabilities of HCT-116 cells after incubation with DOX, NLS-LA-PpIX-DOX, NLS-LA-PpIX-DOX@γ-PGA and NLS-LA-PpIX-DOX@cyclo-γ-PGA with different concentrations of DOX (0.5, 1, 2, and 4 μg/ml) for 24 h. The laser irradiation groups (+L) were exposed to laser irradiation (635 nm, 5 mW/cm^2) for 20 min at the selected time points (1, 3, 6, and 12 h). $^{**}P < 0.01$, $^{***}P < 0.001$

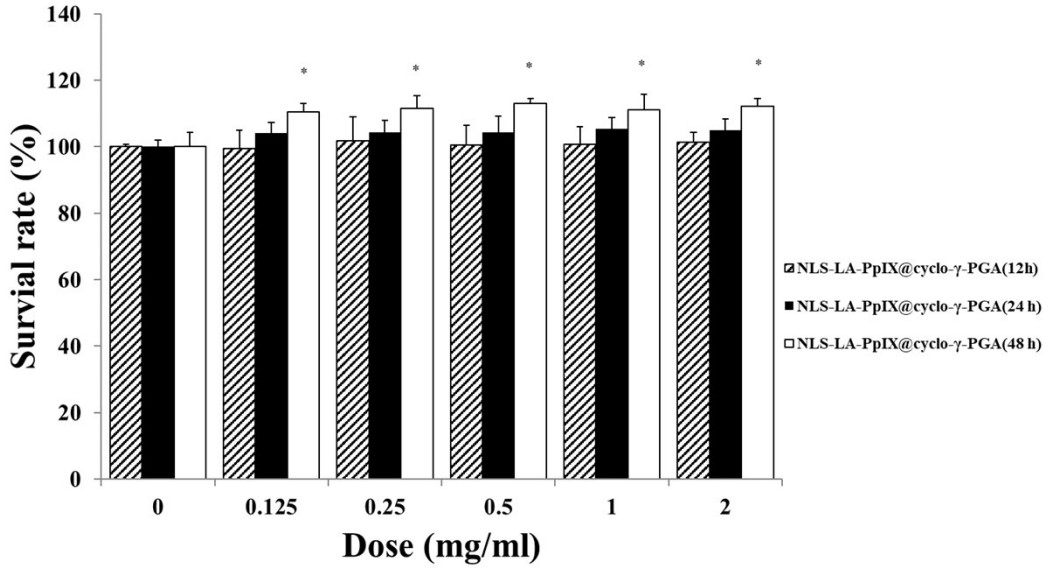

Figure S6. Effects of NLS-LA-PpIX@cyclo-γ-PGA on L929 cell viability. The L929 cells were stimulated with different doses of NLS-LA-PpIX@cyclo-γ-PGA (0-2 mg/ml) for different time durations. $^{*}P< 0.05$ vs. Control.

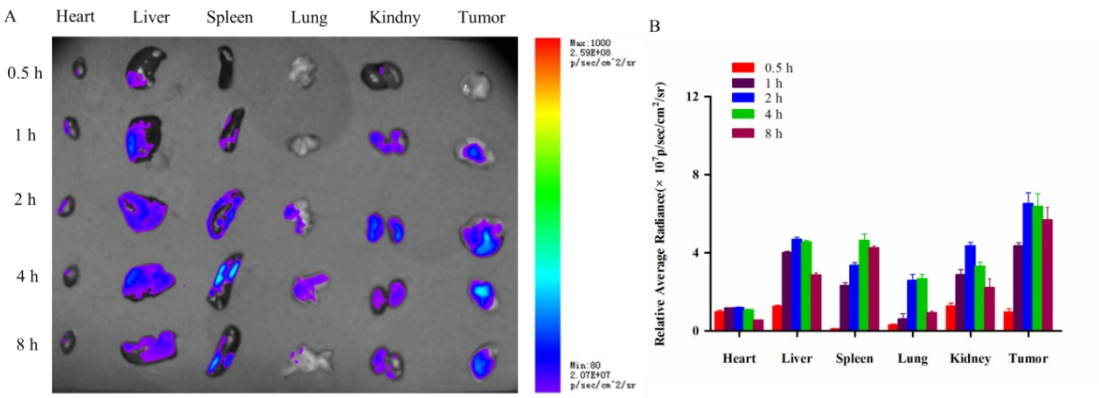

Figure S7. Biodistribution of DOX after intravenous injection of NLS-LA-PpIX-DOX@cyclo-γ-PGA (n=5).

Table S2. Parameters of pharmacokinetic tests of free DOX and NLS-LA-PpIX-DOX@cyclo-γ-PGA

Parameter	Free DOX	NLS-LA-PpIx-DOX@cyclo-γ-PGA
$t_{1/2\alpha}$/h	1.28±0.18	1.59±0.47
$t_{1/2\beta}$/h	25.32±3.85	40.46±10.11
$AUC_{0-\infty}$/h·μg·L^{-1}	1715.13±133.52	55715.04±4820.11
C_{max}/μg·L^{-1}	256.3±57.8	3751±952.6
CL/L·h^{-1}	1.75±0.13	0.05±0.001

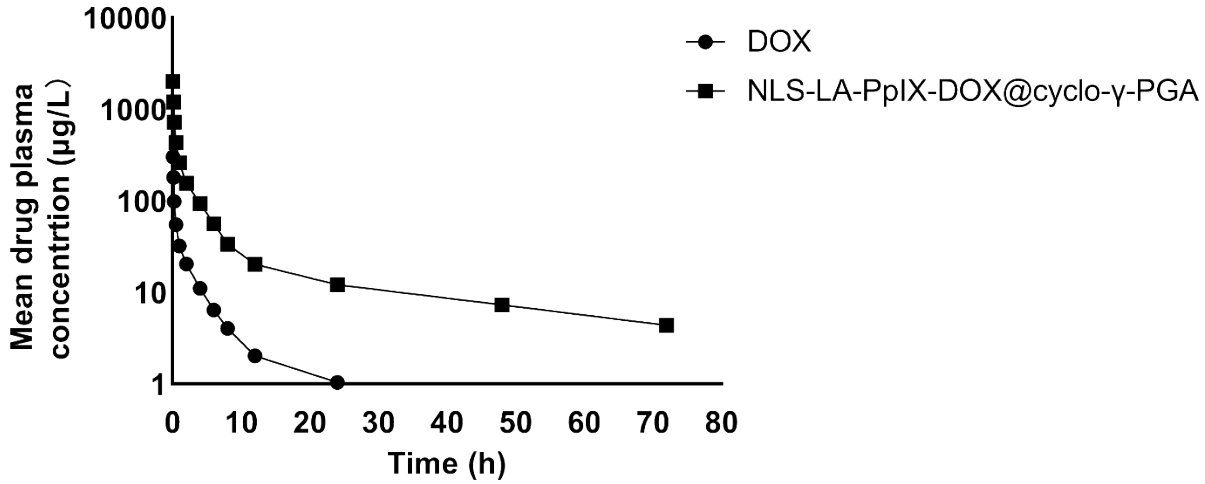

Figure S8. Mean plasma concentration-time curves of free DOX and NLS-LA-PpIX-DOX@cyclo-γ-PGA. (n=5)