Supporting Information

NIR-Responsive and Sugar-Targeted Polypeptide Composite Nanomedicine for Intracellular Cancer Therapy

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Experimental Section

Materials. Concanavalin (ConA, Aldrich), copper (I) bromide (99.999%, Aldrich), L-cysteine (97%, Aldrich), 1,6-diphenyl-1,3,5-hexatriene (DPH, Aldrich), lactobionic acid (97%, Aldrich), o-nitrobenzyl bromide (98%, Aldrich), N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA, Aldrich), 2-propynylamine (98%, Aldrich), ricinus communis agglutinin (RCA_{120}, Aldrich), sodium azide (99%, Aldrich), toluene-4-sulfonyl chloride (TsCl, 98.5%, Aldrich), triphenylphosphine (PPh_3, 99%, Adamas), and triphosgene (99%, Aladdin Chemistry Ltd.) were used as received. Dimethylformamide (DMF, 99.5%) was distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves. Tetrahydrofuran (THF, ≥99%) and hexane (≥97%) were distilled from sodium and stored over 4Å molecular sieves. Doxorubicin (DOX) hydrochloride was purchased from Beijing Huafeng United Technology Corp and used as received. $Y(CH_3CO_2)_3•4H_2O$ (99.99%), $Yb(CH_3CO_2)_3•4H_2O$ (99%), $Tm(CH_3CO_2)_3•4H_2O$ (99.9%), NH_4F (98%), octadecene (90%), and oleic acid (90%) were purchased from Alfa Aesar and used as received.

Methylthiazolyldiphenyl-tetrazolium bromide (MTT, Ultra Pure, Aldrich), Hoechst33342 (Ultra Pure, Aldrich), Dulbecco's Modified Eagle Medium (DMEM, PAA Laboratories), fetal bovine serum (FBS , PAA Laboratories) and HeLa cell (a human uterine cervix carcinoma cell line, Shanghai Institute of Biochemistry and Cell Biology) were used as received. Other solvents and reagents were purchased locally and used as received. Poly(ethylene glycol) (PEO, $M_{n,NMR}$ = 2000, Aldrich) was dried overnight at 50 ºC in vacuum before use. *S*-(*o*-nitrobenzyl)-*L*-Cysteine *N*-carboxyanhydride (NBC-NCA) monomer was synthesized from *S*-(*o*-nitrobenzyl)-*L*-cysteine with triphosgene according to our previous publication.[1] The core-shell $NaYF_4$:Tm^{3+} 0.5 mol%, Yb^{3+} 30 mol%/$NaYF_4$ upconversion nanoparticles (UCNPs) were synthesized according to the previous publication,[2] and dispersed in THF (51.9 mg/mL) for subsequent experiments.

Methods. Fourier transform infrared (FT-IR) spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer at frequencies ranging from 400 to 4000 cm^{-1} at room temperature, and powder samples were thoroughly mixed with KBr crystal and pressed into pellet form. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury-400 spectrometer at room temperature, and tetramethylsilane was used as an internal standard. Molecular weights and polydispersities (M_w/M_n) of polymers were determined on a gel permeation chromatograph (GPC, HLC-8320, Tosoh Corporation, Japan) equipped with two HLC-8320 columns (TSKgel Super AWM-H, pore size: 9 μm; 6×150 mm, Tosoh Corporation) and a double-path, double-flow refractive index (RI) detector (Bryce) at

30 °C. The elution phase was DMF-LiBr (0.01 mol.L^{-1}) with an elution rate of 0.6 mL.min^{-1}, and a series of polymethyl methacrylate was used as the calibration standard. The critical aggregation concentration (cac) values of copolymers were determined employing the hydrophobic dye solubilization method using 1,6-diphenyl-1,3,5-hexatriene (DPH) as a probe molecule. Thermogravimetric analysis (TGA) was obtained using a Perkin-Elmer TGA 7 instrument under nitrogen flow (10 mL/min) from 40 ºC to 600 ºC at 10 ºC/min. Fluorescence emission spectra were recorded on a steady-state & time-resolved spectrofluorometer (QM/TM/IM, PTI company). The near infrared (NIR) laser (FC-980-6000-MM; intensity: 5 W/cm^2) with a wavelength of 980 nm was purchased from Shanghai SFOLT Co. Ltd. with a fiber (FC/PC/200UM/1M) and a fiber collimator. UV-vis spectroscopy was recorded in the range of 200-500 nm at room temperature using a Specturmlab54 UV-visible instrument. The mean size of nanoparticles was determined at 25 °C by dynamic light scattering (DLS) using a Malvern ZS90 instrument. All of the measurements were repeated three times, and the average values reported were the mean diameter ± standard deviation. Transmission electron microscopy (TEM) was performed without staining by using a JEM-2010 at 200 kV accelerating voltage. Samples were deposited onto the surface of 300 mesh Formvar-carbon film-coated copper grids, and excess solution was removed in vacuo.

Synthesis of Lactonolactone. Lactonolactone was synthesized according to the previous publication.[3] Lactobionic acid (1.0 g, 2.79 mmol) and trifluoroacetic acid (TFA, 0.2 mL) were added in anhydrous methanol (20 mL). The solution was stirred

at 70 °C for 6 h with reflux. This reaction became clear when the acid precursor was fully converted to the lactone. Methanol, water and TFA were removed under reduced pressure at 40 °C. Finally, white solid was obtained (0.9155 g, 96.4% yield). ^{1}H NMR (DMSO-d_6/CF_3COOD, v:v = 5:1): δ (ppm) = 4.35 (dt, J = 8.2, 3.3 Hz, 1H), 4.23 (d, J = 7.1 Hz, 1H), 3.91 (d, J = 7.1 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.78 – 3.73 (m, 1H), 3.68 (d, J = 2.6 Hz, 2H), 3.61 (d, J = 2.3 Hz, 1H), 3.52 (s, 1H), 3.50 (s, 1H), 3.42 (d, J = 6.4 Hz, 1H), 3.34 – 3.29 (m, 2H). ^{13}C NMR (DMSO-d_6/CF_3COOD, v:v = 5:1): δ (ppm) = 171.90, 104.60, 79.73, 78.78, 76.09, 73.78, 73.33, 71.65, 71.10, 68.76, 61.11, 60.60.

Synthesis of PA-Lactose. PA-Lactose (PA-Lac) was synthesized according to the previous publication.[4] Lactobionolactone (0.6408 g, 2 mmol) was first dissolved in methanol at 40 °C and then cooled to room temperature before the addition of propargylamine (PA, 0.2203 g, 4 mmol) and triethylamine (0.56 mL). The mixture was stirred for 24 h, concentrated by rotary evaporation and precipitated into a large excess of ether to obtain yellow solid (0.5807 mg, 81.6% yield). ^{1}H NMR (DMSO-d_6/CF_3COOD, v:v = 5:1): δ (ppm) = 4.26 (d, J = 7.1 Hz, 1H), 4.14 (d, J = 2.5 Hz, 1H), 4.02 (dd, J = 4.1, 2.5 Hz, 1H), 3.85 (dd, J = 23.7, 2.5 Hz, 2H), 3.68 (d, J = 2.1 Hz, 2H), 3.59 (d, J = 3.0 Hz, 1H), 3.58 (d, J = 3.4 Hz, 1H), 3.54 (s, 1H), 3.51 (d, J = 7.2 Hz, 1H), 3.49 (d, J = 5.1 Hz, 1H), 3.40 (dd, J = 6.9, 5.5 Hz, 1H), 3.31 (dd, J = 7.6, 5.1 Hz, 2H), 2.85 (s, 1H). ^{13}C NMR (DMSO-d_6/CF_3COOD, v:v = 5:1): δ (ppm) = 172.97, 105.01, 83.11, 81.53, 76.16, 73.68, 72.65, 72.38, 71.82, 71.70, 70.98, 68.91, 62.75, 61.41, 28.31.

Synthesis of Difunctional Poly(ethylene glycol) Macroinitiator (N_3-PEO-NH_2). According to our previous publication,[5] azide-terminated poly(ethylene oxide) (N_3-PEO-N_3) was prepared via the tosylation of poly(ethylene glycol) methyl ether ($M_{n,NMR}$ = 2000) followed by azidation reaction. ^{1}H NMR ((DMSO-d_6): δ (ppm) = 3.48 (s, 180H), 3.39 – 3.35 (t, 4H). FT-IR (KBr, cm^{-1}): 2879 ($\nu_{C–H}$), 2110 (azide), 1105 ($\nu_{C–O–C}$). The N_3-PEO-NH_2 macroinitiator was then synthesized according to the previous publication.[6] N_3-PEG-N_3 (2 g, 0.9769 mmol) was dissolved in 10 mL of THF in a flask, followed by addition of PPh_3 (0.0268 g, 1.0244 mmol) and H_2O (18.4 μL, 1.0244 mmol). The mixture was stirred at room temperature for 24 h. Afterward, the solution was precipitated into a large excess of ether to obtain crude product. Then the crude product was purified by flash column chromatography (methanol/chloroform = 1/12.5, v/v) to afford N_3-PEO-NH_2 as a white solid. The white solid was dissolved completely in chloroform (250 mL), then the solution was washed sequentially with saturated sodium bicarbonate aqueous solution twice (2 ×25 mL) and distilled water once (25 mL). The organic phase was collected, dried over sodium sulfate, and then dropwise poured into a large excess of cold ether. The powder was dried in vacuo to give N_3-PEO-NH_2 (0.76 g, 38% yield). ^{1}H NMR ($CDCl_3$): δ(ppm) = 3.62 (s, 180H), 3.41 – 3.35 (t, J = 5.2 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 1.90 (s). ^{13}C NMR ($CDCl_3$): δ(ppm) = 73.49, 70.74, 70.47, 70.22, 50.87, 41.94. FT-IR (KBr, cm^{-1}): 3407 ($\nu_{N–H}$), 2873 ($\nu_{C–H}$), 2108 (azide), 1641 ($\beta_{N–H}$), 1109 ($\nu_{C–O–C}$), 852 ($\gamma_{N–H}$). $M_{n,GPC}$ = 2010, M_w/M_n = 1.58.

Preparation of Azide-Terminated Poly(ethylene glycol)-b-Poly(*S*-(*o*-nitrobenzyl) -*L*-cysteine) Block Copolymers (N_3-PEO-b-PNBC). In a representative polymerization reaction, N_3-PEO-NH_2 (107.6 mg, 53.1 μmol) was dissolved completely in 1 mL DMF under nitrogen atmosphere, and then a degassed solution of NBC-NCA (150 mg, 0.53 mmol) in 2 mL DMF was added via a syringe. The resulting solution was stirred vigorously at room temperature for 48 h, and then precipitated dropwise into a large excess of ether (30 mL). The white precipitate was filtered and dried in vacuo at 40 ºC to give 201.4 mg of N_3-PEO-b-$PNBC_9$ (86% yield). ^{1}H NMR of N_3-PEO-b-$PNBC_9$ ($CDCl_3$/CF_3COOD, v:v = 1:1): δ (ppm) = 8.02 – 7.93 (m, 9H), 7.66 – 7.35 (m, 27H), 4.82 – 4.67 (m, 9H), 4.18 – 4.05 (m, 18H), 3.78 (s, 180H), 3.53 – 3.50 (m, 2H), 2.99 – 2.92 (m, 18H). FT-IR (KBr, cm^{-1}): 3274 ($\nu_{N\text{-}H}$, PNBC), 2908 ($\nu_{C\text{-}H}$), 2105 (azide), 1631 ($\nu_{C=O,}$ amide I), 1526 ($\delta_{N–H,}$ amide II), 1346 ($\nu_{s\ NO2}$), 1111 ($\nu_{C–O–C}$), 860 ($\nu_{C–NO2}$), 712 ($\nu_{C–S}$). $M_{n,\ GPC}$ = 3790, M_w/M_n = 1.52.

Preparation of Lac-terminated Poly(ethylene glycol)-b-Poly(*S*-(*o*-nitrobenzyl) -*L*-cysteine) Block Copolymers (Lac-PEO-b-PNBC). The obtained N_3-PEO-b-PNBC was click conjugated with PA-Lac to produce the Lac-PEO-b-PNBC block copolymers. A representative procedure for the click conjugation is as follows: N_3-PEO-b-$PNBC_9$ (200 mg, 0.048 mmol) and PA-Lac (22.8 mg, 0.058 mmol) were completely dissolved in DMF (2 mL). The solution was bubbled with N_2 for 10 min, and both CuBr (6.9 mg, 0.048 mmol) and PMDETA (10 μL, 0.048 mmol) were added to the solution. The reaction mixture was stirred vigorously under N_2 at 35 ºC for 48 h, and then precipitated into cold diethyl ether (20 mL), the centrifugalized product was

then washed with cold methanol (2 mL) for three times to remove the excess PA-Lac. The precipitate was dried in vacuo to give the Lac-PEO-b-PNBC$_9$ of 205.9 mg (94% yield). ^{1}H NMR (DMSO-d_6/CF_3COOD, v:v = 5:1): δ (ppm) = 8.45 (s, 1H), 7.94 – 7.89 (m, 9H), 7.55 – 7.41 (m, 27H), 4.63 – 4.59 (m, 9H), 4.02 – 3.94 (m, 18H), 3.47 (s, 180H), 2.70 – 2.53 (m, 18H). FT-IR (KBr, cm^{-1}): 3292 ($\nu_{N\text{-}H}$, PNBC), 2919 ($\nu_{C\text{-}H}$), 1631 ($\nu_{C=O,}$ amide I), 1525 ($\delta_{N–H,}$ amide II), 1349 ($\nu_{s\ NO2}$), 1111 ($\nu_{C–O–C}$), 1035 ($\nu_{C\text{-}OH}$, Lac), 860 ($\nu_{C–NO2}$), 706 ($\nu_{C–S}$). $M_{n,\ GPC}$ = 4270, M_w/M_n = 1.56.

The Micelles Fabricated from Lac-PEO-b-PNBC. The blank and UCNPs-loaded micelles were fabricated from Lac-PEO-b-PNBC by using a film rehydration method.[7] Typically, 10 mg of Lac-PEO-b-PNBC$_9$ was completely dissovled in mixed solvents of chloroform and trifluoroacetic acid (10 mL, v:v = 9:1) and stirred for 2 h, and the polymer solution was in vacuum dried to form a homogeneous film in a 25 mL flask. The film was hydrated by 5 mL distilled water at 70 °C for 24 h to generate the micelles and the precipitate was filtered off. The UCNPs-loaded micelles (UCNPs/Lac-PEO-b-PNBC$_9$ = 67/33 wt% in feed) was prepared similarly and stored at 4 °C for DLS and TEM analyses. The DOX-loaded micelles (DOX/Lac-PEO-b-PNBC$_9$ = 33/67 wt% in feed) and the DOX-loaded composite micelles (UCNPs/DOX/Lac-PEO-b-PNBC$_9$ = 57/14/29 wt% in feed) were prepared similarly and then put into a dialysis bag (MWCO = 3500) and subjected to dialysis against 4×1 L of distilled water for 24 h. Analyzed by UV-vis at 500 nm, the drug loading capacity is calculated as the weight ratio of actual drug to drug-loaded nanoparticles,

and the drug loading efficiency is calculated as the weight ratio of actual and added drug content.

UV and NIR-Sensitivity of the Nanoparticles Solution. The sample solution (about 2 mL) was placed vertically under a high-pressure mercury lamp (wavelength: 365 nm; power: 150 W, intensity: 3.5 mW/cm^2) or NIR laser (980 nm, 5 W/cm^2). After irradiation for different periods, the irradiated samples were analyzed by means of UV-vis, DLS, and TEM.

In Vitro DOX Release. The pulsatile "on-off" drug release experiments are carried out as follows. The nanoparticles solution (5 mL) was irradiated at 365 nm for 3 min and/or at 980 nm for 5 min every two hours, and the irradiated sample in dialysis bag was then put in 15 mL of PBS (10 mM) at 37 °C. The drug-released solution was changed periodically, and the amount of DOX released from nanoparticles was determined at 500 nm by UV-vis. All release experiments were carried out in duplicate.

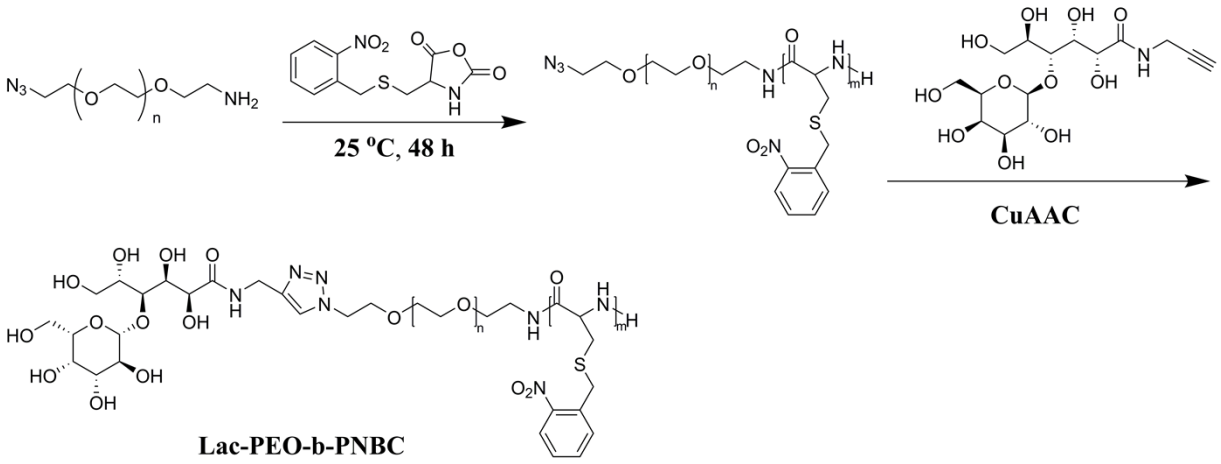
Lectin-Binding Properties of Lac-PEO-b-PNBC and Its Lac-Coated Micelles. The lectin-binding activity of Lac-PEO-b-PNBC unimer (15 μg/mL) or its Lac-coated micelles (30 μg/mL) was analyzed by changes in the turbidity of solution at 360 nm and at room temperature after the copolymer or micelles solution was mixed homogeneously with RCA_{120} or Con A lectins (0.5 mg/mL). Moreover, the mixed solution was online monitored by DLS.

In Vitro Cytotoxicity. HeLa and HepG2 cell lines were used for studying the cytotoxicity and the targeting properties of the blank nanoparticles, the DOX-loaded

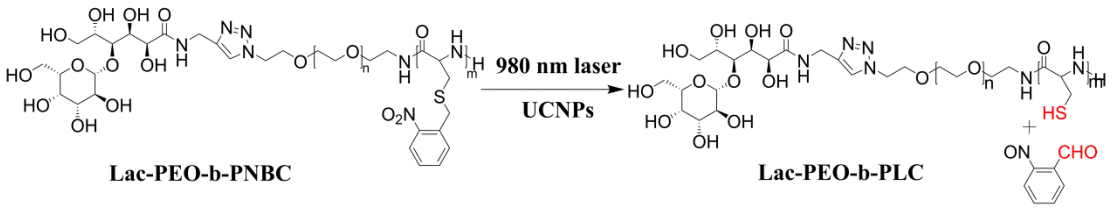
nanoparticles, the triggered cytotoxicity of the DOX-loaded nanoparticles, and the DOX/UCNPs-loaded composite nanoparticles, as exemplified in our previous publication. Briefly, HeLa cells were cultivated in DMEM containing 10% FBS and antibiotics (50 units/mL penicillin and 50 units/mL streptomycin). The conditions of the incubator were set at 37 °C under a humidified atmosphere containing 5% CO_2. 200 μL HeLa cell suspension (1×10^5 cells/mL) in DMEM was added to each well in a 96-well plate. After incubation for 24 h in incubator, the blank nanoparticles, the DOX-loaded nanoparticles, and the DOX/UCNPs-loaded composite nanoparticles solution with a series of concentrations were put in the wells (50 μL per well), and the mixture was further incubated for 48 h; otherwise, the DOX/UCNPs-loaded composite nanoparticles were put into Hela cell suspension in DMEM and irradiated using 980 nm laser for the predetermined time (5 min and 10 min), and then incubated for 48 h. All HeLa cells were washed with 150 μL of PBS and 20 μL of MTT was added in each well and incubated for another 4 h. The solution in each well was removed and 200 μL of DMSO was added with low-speed oscillation. The OD (optical density) value was measured at 490 nm by Microplate Reader (Elx800, BioTek Company). Cell viabilility = $OD_{treated}/OD_{control}$, where $OD_{control}$ and $OD_{treated}$ were obtained in the absence or the presence of micelles/nanomedicines, respectively. Half maximal inhibitory concentration (IC_{50}) was calculated from GraphPad Prism 6 software using 6 samples.

Cell Internalization. Cell internalization was characterized by flow cytometry (BD Accuri C6, US BD Corporation) and confocal laser scanning microscopy (CLSM,

Leica TCS SP5-II). Flow cytomety was used to provide statistics on the uptake of the DOX/UCNPs-loaded composite nanoparticles into HeLa cells. HeLa cells (5.0×10^5 cells per well) were seeded in a 6-well tissue culture plate. After 24 h culture, the DOX/UCNPs-loaded composite nanoparticles (equivalent DOX concentration: 20 μg/mL) and free DOX (20 μg/mL) were added to different wells, and the cells were incubated at 37 °C for predetermined time intervals. After the incubation, samples were prepared for flow cytometry analysis by removing the cell growth media, rinsing with PBS buffer, and treating with trypsin. Data for 1.0×10^4 gated events were collected, and analysis was performed by means of a BD Accuri C6 flow cytometer and FlowJo software. For CLSM, HeLa cells (1.0×10^5 cells per well) were seeded on coverslips in a 6-well tissue culture plate. After 24 h culture, the DOX/UCNPs-loaded composite nanoparticles (equivalent DOX concentration: 20 μg/mL) and free DOX (20 μg/mL) were added to different wells, and the cells were incubated at 37 °C for predetermined time intervals. After being washed with PBS, the cells were fixed by 4% formaldehyde for 30 min at room temperature, and the slides were rinsed with PBS for three times. The cells were then dyed by Hoechst33342 for 5 min and the slides were rinsed with PBS for three times, and finally the slides were mounted and observed by CLSM.



Scheme S1. Synthesis of the lactose-terminated and photoresponsive block copolymer Lac-PEO-b-PNBC by the combination of ROP and copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) click chemistry.



Scheme S2. The NIR-triggered photocleavage reaction of Lac-PEO-b-PNBC with the help of UCNPs and then decaging into Lac-PEO-b-poly(L-cysteine) (PLC) photoproduct. Note that the photoclevage reaction has been confirmed by FT-IR and ^{1}H NMR as shown in Figure S1 and Figure S3.

Table S1. Synthesis of Lac-PEO-b-PNBC copolymers.

Samples	M_w/M_n	$M_{n,,GPC}$	$M_{n,NMR}$
N_3-PEO-NH_2	1.58	2010	2020
N_3-PEO-b-$PNBC_9$	1.52	3790	4170
N_3-PEO-b-$PNBC_{23}$	1.56	4680	7500
Lac-PEO-b-$PNBC_9$	1.56	4270	4570
Lac-PEO-b-$PNBC_{23}$	1.50	5210	7900

Table S2. The DLS and TEM results of the self-assembled Lac-PEO-b-PNBC nanoparticles and their DOX-loaded nanoparticles.

Nanoparticles	Morphology	TEM size (nm)	DLS size (nm)	PDI
Lac-PEO-b-$PNBC_9$	spherical micelle	36 ± 7	64 ± 5	0.47 ± 0.05
Lac-PEO-b-$PNBC_{23}$	spherical micelle	65 ± 10	84 ± 11	0.34 ± 0.06
N_3-PEO-b-$PNBC_{23}$	spherical micelle	59 ± 8	77 ± 2	0.45 ± 0.11
Lac-PEO-b-$PNBC_9$/DOX	spherical micelle	42 ± 10	75 ± 11	0.43 ± 0.05
Lac-PEO-b-$PNBC_9$-70%/DOX[a]	spherical micelle	42 ± 7	74 ± 9	0.42 ± 0.06
Lac-PEO-b-$PNBC_9$-30%/DOX[b]	spherical micelle	40 ± 7	72 ± 8	0.41 ± 0.05
N_3-PEO-b-$PNBC_9$/DOX	spherical micelle	40 ± 6	71 ± 7	0.39 ± 0.05

a: Lac-PEO-b-$PNBC_9$-70% denotes the weight percentage of Lac-PEO-b-$PNBC_9$, i.e., the weight ratio of Lac-PEO-b-$PNBC_9$ to N_3-PEO-b-$PNBC_9$ is 7:3 in sample; b: Lac-PEO-b-$PNBC_9$-30% denotes the weight ratio of Lac-PEO-b-$PNBC_9$ to N_3-PEO-b-$PNBC_9$ is 3:7 in sample.

Table S3. The optical density at 360 nm of Lac-PEO-b-$PNBC_9$ unimer (15μg/mL) and its Lac-coated micelles (30 μg/mL) after addition of 0.5 mg/mL RCA_{120} in aqueous solution.

Samples	The increment of OD_{360}	
	15 μg/mL	30 μg/mL
Lac-PEO-b-$PNBC_9$	0.193	0.247
Lac-PEO-b-$PNBC_9$-70%	0.121	0.155
Lac-PEO-b-$PNBC_9$-30%	0.057	0.074

Table S4. The DLS results of the cross-linking aggregates of Lac-PEO-b-$PNBC_9$ (15μg/mL) or its Lac-coated micelles (30 μg/mL) with addition of 0.5 mg/mL RCA_{120}.

Samples	The diameter of the cross-linked aggregates	
	15 μg/mL	30 μg/mL
Lac-PEO-b-$PNBC_9$	1117 ± 31 nm	1193 ± 36 nm
Lac-PEO-b-$PNBC_9$-70%	834 ± 23 nm	951 ± 19 nm
Lac-PEO-b-$PNBC_9$-30%	559 ± 14 nm	640 ± 16 nm

Table S5. The cell viability and half maximal inhibitory concentration (IC_{50}) of DOX-loaded nanoparticles with different Lac densities when being incubated with HeLa or HepG2 cells for 48 h.[a]

DOX-loaded nanoparticles	HeLa cell viability (10μg/mL)	IC_{50} of HeLa (μg DOX equiv/mL)	HepG2 cell viability (10μg/mL)	IC_{50} of HepG2 (μg DOX equiv/mL)
free DOX	10.6%	0.58	21.7%	1.36
N_3-PEO-b-$PNBC_9$	40.0%	6.82	50.1%	10.07
Lac-PEO-b-$PNBC_9$-30%	40.7%	7.02	38.6%	5.3
Lac-PEO-b-$PNBC_9$-70%	42.7%	7.08	28.8%	2.14
Lac-PEO-b-$PNBC_9$	40.4%	6.82	29.8%	2.93

a: IC_{50} values were calculated from Figure 2C and 2D by using a GraphPad Prism 6 software.

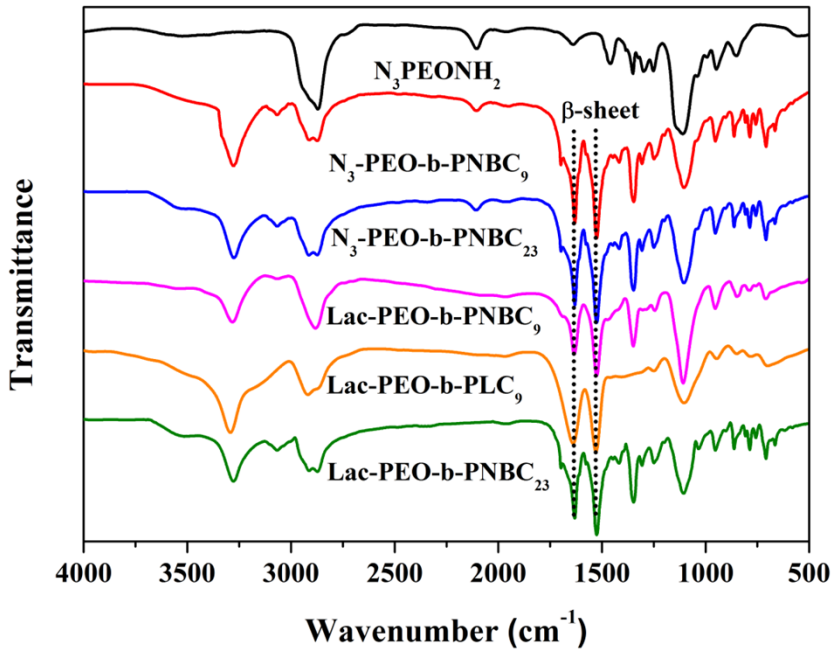


Figure S1. FT-IR of the PEO macroinitiator, N_3-PEO-b-PNBC, Lac-PEO-b-PNBC, and the photo-decaged Lac-PEO-b-PLC$_9$. Note that the characteristic peak of NO_2 at 1347 cm^{-1} disappeared after the full photocleavage reaction for Lac-PEO-b-PNBC$_9$.

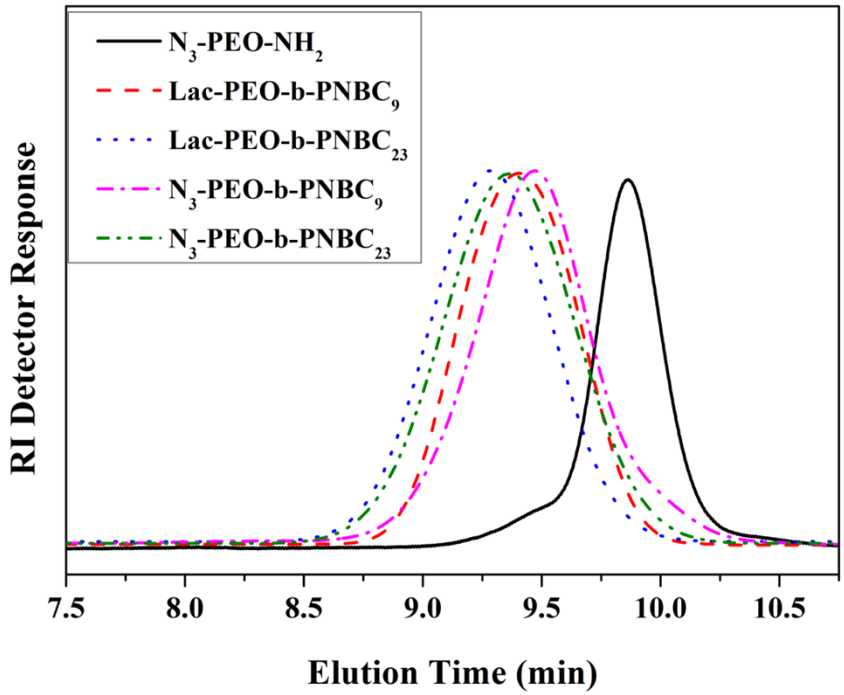


Figure S2. The GPC traces of the PEO macroinitiator, N_3-PEO-b-PNBC and the final products Lac-PEO-b-PNBC.

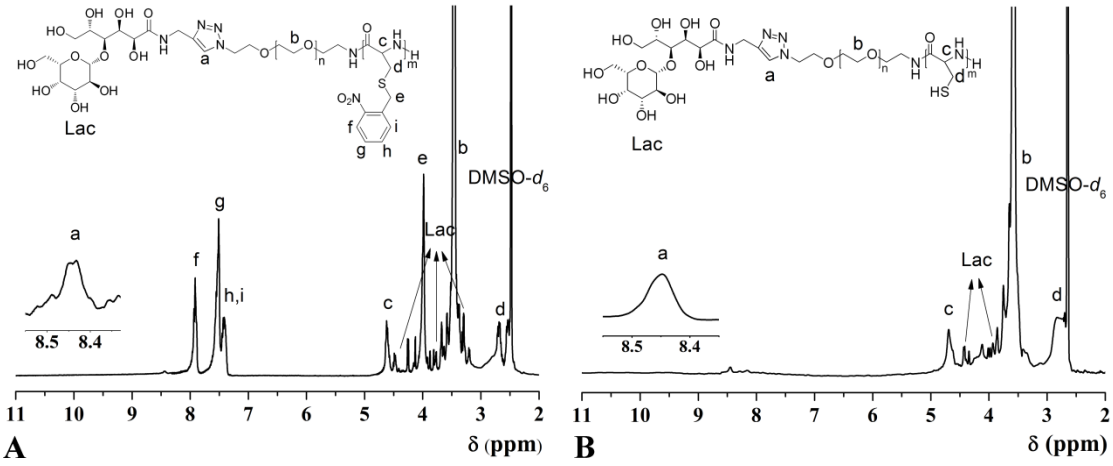


Figure S3. ^{1}H NMR spectra (DMSO-d_6/CF_3COOD, V:V = 5:1) of Lac-PEO-b-$PNBC_9$ (A) and the photo-decaged Lac-PEO-b-PLC_9 (B). Note that the peak signals of NB groups disappeared after the full photocleavage reaction and Lac-PEO-b-$PNBC_9$ was photo-decaged into Lac-PEO-b-PLC_9.

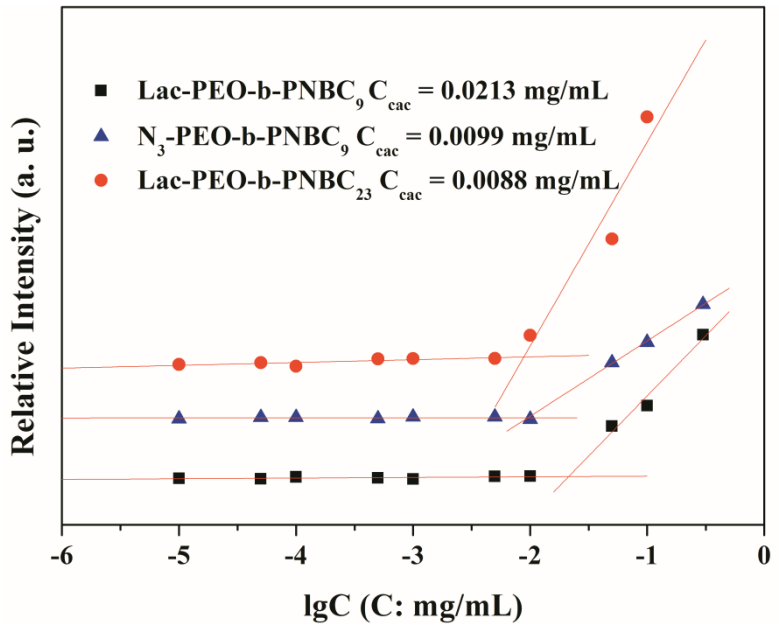


Figure S4. The relationship of the absorbance intensity of DPH as a function of Lac-PEO-b-PNBC concentration in aqueous solution. Based on the critical aggregation concentration (cac) of Lac-PEO-b-$PNBC_9$, it can be concluded that Lac-PEO-b-$PNBC_9$ mainly exists in a unimer state at 15 μg/mL or self-assembles into the Lac-coated micelles at 30 μg/mL, which has also been characterized by DLS and TEM (**Table S2**).

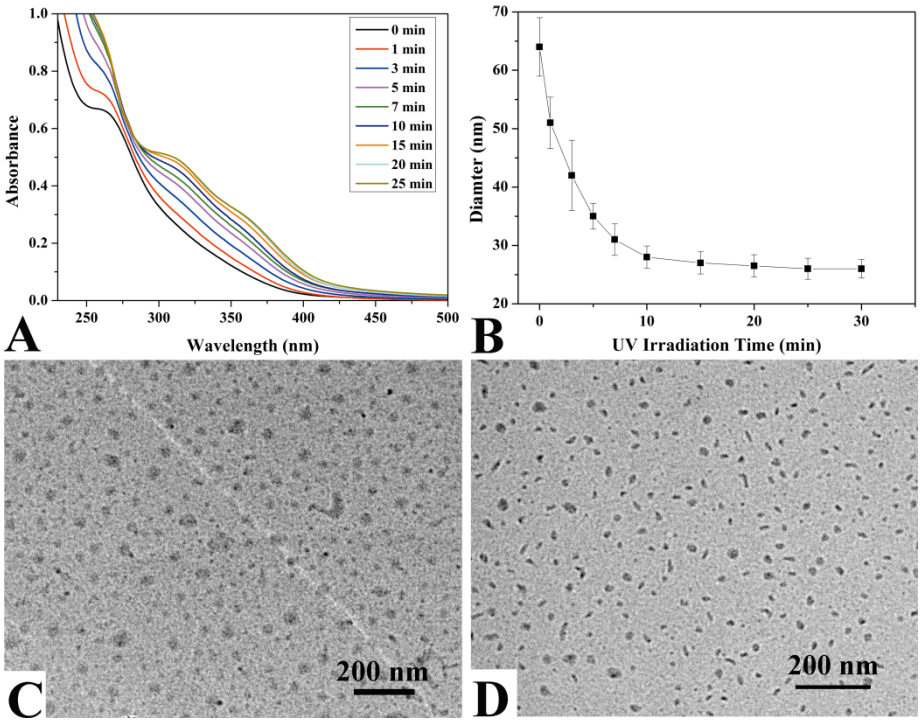


Figure S5. UV-vis time-resolved spectra of the Lac-PEO-b-PNBC$_9$ nanoparticles solution after 365 nm UV irradiation at different times (A); the dependence of DLS-determined diameter of the nanoparticles on UV irradiation time (B); TEM photographs of the Lac-PEO-b-PNBC$_9$ nanoparticles before (C) and after 20 min of UV irradiation (D). Note that Lac-PEO-b-PNBC$_9$ was photo-decaged into Lac-PEO-b-PLC$_9$ and reassembled into smaller micelles with PLC core and PEO corona.

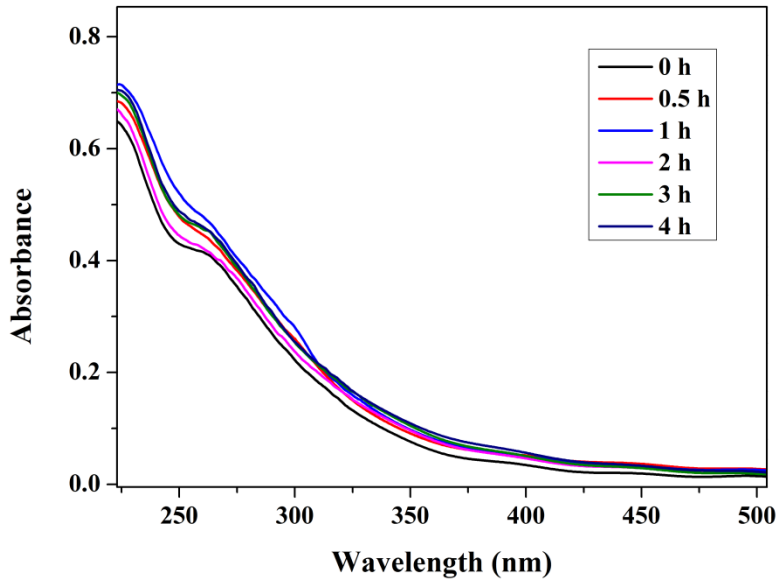


Figure S6. UV−vis spectrum of the PEO-b-PNBC nanoparticles solution after 800 nm NIR irradiation of a pulsed laser (800 nm, 50 fs, 80 kHz, 8 W) at different time.

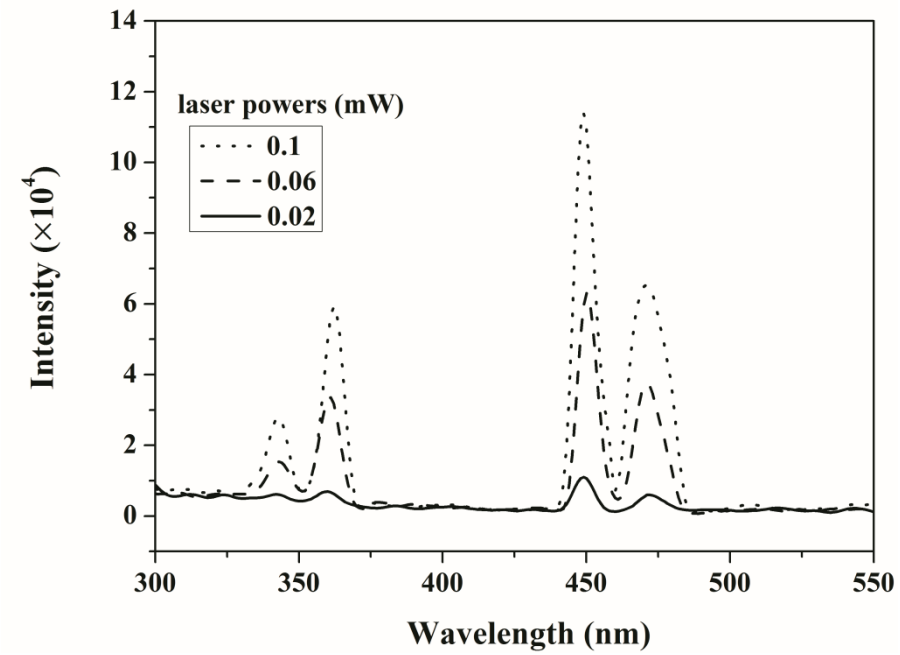


Figure S7. Emission spectra of the composite nanoparticles Lac-PEO-b-$PNBC_9$/UCNPs upon 980 nm laser light excitation. Note that these spectra convincingly confirmed that UCNPs within the composite nanoparticles converted 980 nm NIR light into UV and visible light.

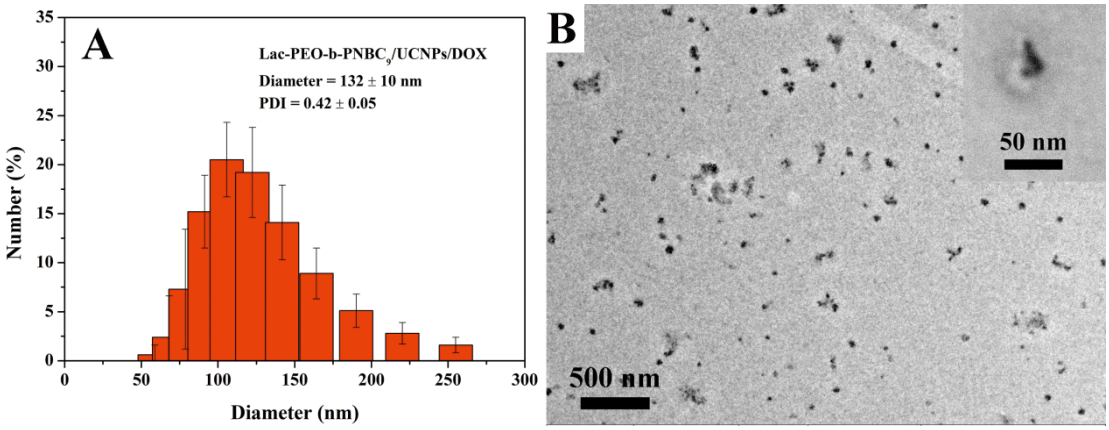


Figure 8. Mean size and distribution (A) and TEM photograph (B) of the DOX-loaded composite nanoparticles of Lac-PEO-b-$PNBC_9$/UCNPs/DOX.

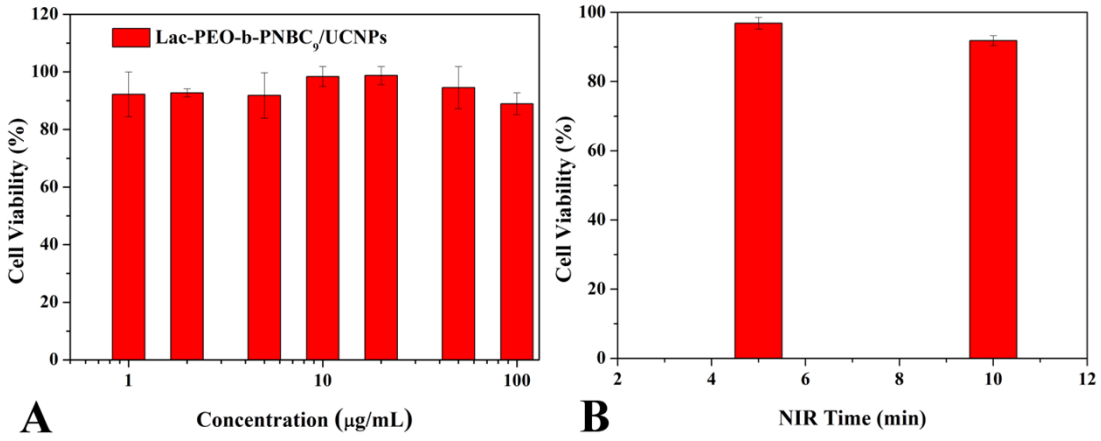


Figure S9. A) Cell viability of HeLa cell line against the composite nanoparticles of Lac-PEO-b-PNBC$_9$/UCNPs after being cultured for 48 h; B) Cell viability of HeLa cell line upon 980 nm irradiation for 5 min or 10 min.

Notes and Reference

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