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Supplementary Information

Polycarbonate-based core-crosslinked redox-responsive nanoparticles for targeted delivery of anticancer drug

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Synthesis of α-lipoic acid, 2-azidoethyl ester (LA-N_3)

LA-N_3 was synthesized by a two-step method, namely esterification of α-lipoic acid (LA) with 2-bromoethanol and substitution reaction with sodium azide.[1] Typically, LA (1.500 g, 7.3 mmol) and DCC (1.648 g, 8.0 mmol) were dissolved in anhydrous DCM (20 mL). The mixture was kept stirring at 0 °C for 30 min. A solution of 2-bromoethanol (0.863 g, 6.9 mmol) and DMAP (0.089g, 0.73 mmol) in DCM (20 mL) was added dropwise. After dispersing with vigorous stirring and incubation for 1 h, the resulting mixture was then stirred at room temperature for 24 h. The insoluble salts were removed by filtration, and the filtrate was washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica column chromatography using petroleum ether/ethyl acetate as eluent. α-Lipoic acid, 2-bromoethyl ester was obtained as a yellow oil. Yield:1.530 g (70.8%).

α-Lipoic acid, 2-bromoethyl ester (1.500 g, 4.8 mmol) and sodium azide (0.960 g, 14.8 mmol) were dissolved in DMF (15 mL). The mixture was stirred at 80 °C overnight. Then, the resulting mixture was diluted with DCM, filtered, washed with deionized water and saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated. LA-N_3 was obtained as a yellow oil. Yield:1.121 g (84.8%).

Synthesis of 6-azido-hexanoic acid ethyl ester (AHE-N_3)

AHE-N_3 was also prepared by a similar two-step procedure as the synthesis of LA-N_3. Briefly, 6-bromohexanoic acid (1.950 g, 10 mmol) and p-toluenesulfonic acid (0.172 g, 1.0 mmol) were dissolved in ethanol (30 mL). The mixture was stirred and heated to reflux. After 24 h, the unreacted ethanol was removed by rotary evaporation. The crude product was then diluted with DCM, washed with saturated NaCl and saturated Na_2CO_3, dried over $MgSO_4$. When the solution was evaporated to dryness, 6-bromohexanoic acid ethyl ester was obtained. Yield: 1.975 g (89.7%).

In a 50 mL round-bottomed flask, DMF (20 mL) was poured into the mixture of 6-bromohexanoic acid ethyl ester (1.970 g, 8.8 mmol) and NaN_3 (0.861 g, 13.3 mmol). The reaction solution was stirred at 80 °C for 24 h. Residual NaN_3 was removed by filtration. The filtrate was diluted with DCM, washed with deionized water as well as saturated $NaHCO_3$, and then dried over $MgSO_4$. After being concentrated by rotary evaporation, the crude product was further purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent. AHE-N_3 was obtained as colorless oil. Yield:1.543 g (94.8%).

Table S1. Summary of the sizes change under different conditions.

Sample	NCNs		CC-RRNs		CC-RRNs treated with GSH		CC-RRNs diluted by 10-fold DMF		CC-RRNs diluted by 100-fold H_2O	
	Size(nm)	PDI	Size(nm)	PDI	Size(nm)	PDI	Size (nm)	PDI	Size (nm)	PDI
P1	75.2	0.12	73.2	0.056	80.1	0.086	251.3	0.350	170.3	0.430
P2	69.8	0.08	74.6	0.009	80.9	0.193	253.5	0.416	112.3	0.394
P3	64.9	0.13	/	/	/	/	/	/	/	/
P4	80.7	0.21	77.0	0.176	80.6	0.310	310.4	0.370	109.6	0.477
P5	64.4	0.17	62.4	0.172	66.0	0.156	--	--	173.4	0.373
P6	80.8	0.19	/	/	/	/	/	/	/	/

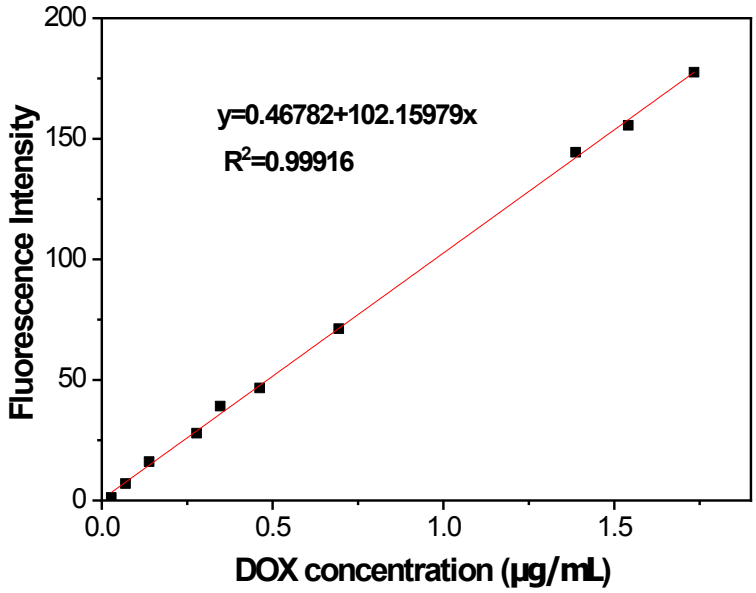

Figure S1. Standard curve of DOX in PBS.

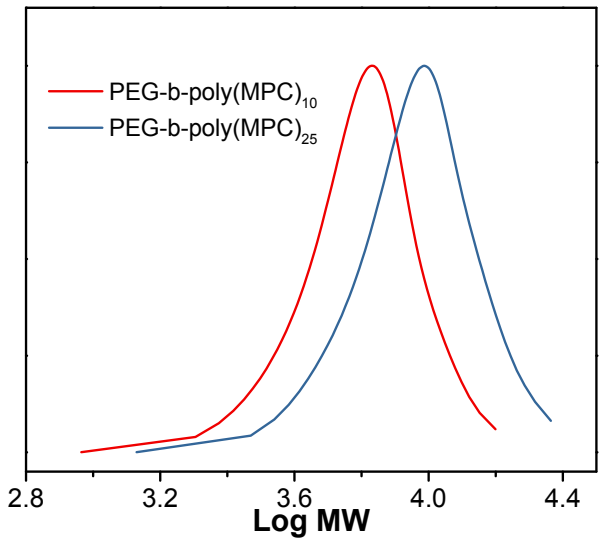

Figure S2. GPC curves of PEG-b-poly(MPC)n.

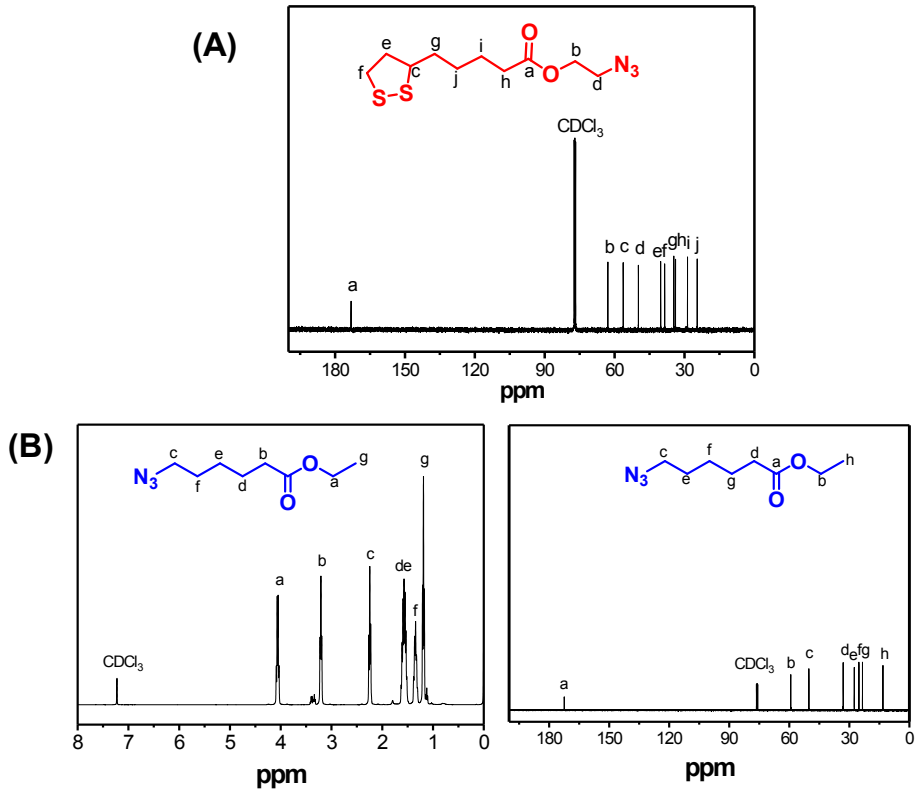

Figure S3. The NMR spectra of LA-N_3 (A) and AHE-N_3 (B).

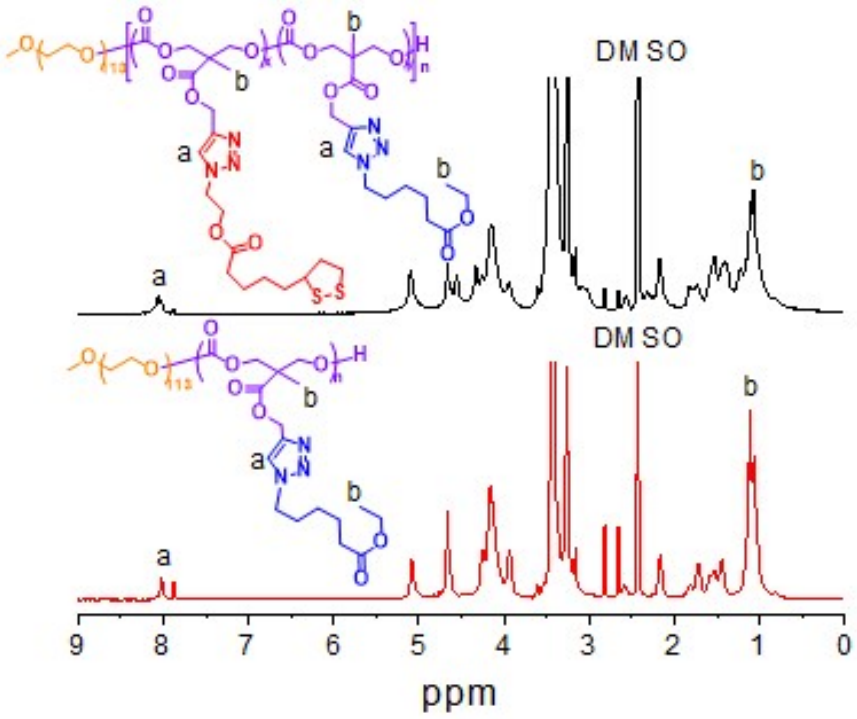

Figure S4. ^{1}H NMR spectra of PEG-b-poly(MPC-LA/AHE)$_{25}$ and PEG-b-poly(MPC- AHE)$_{25}$ obtained after click reaction.

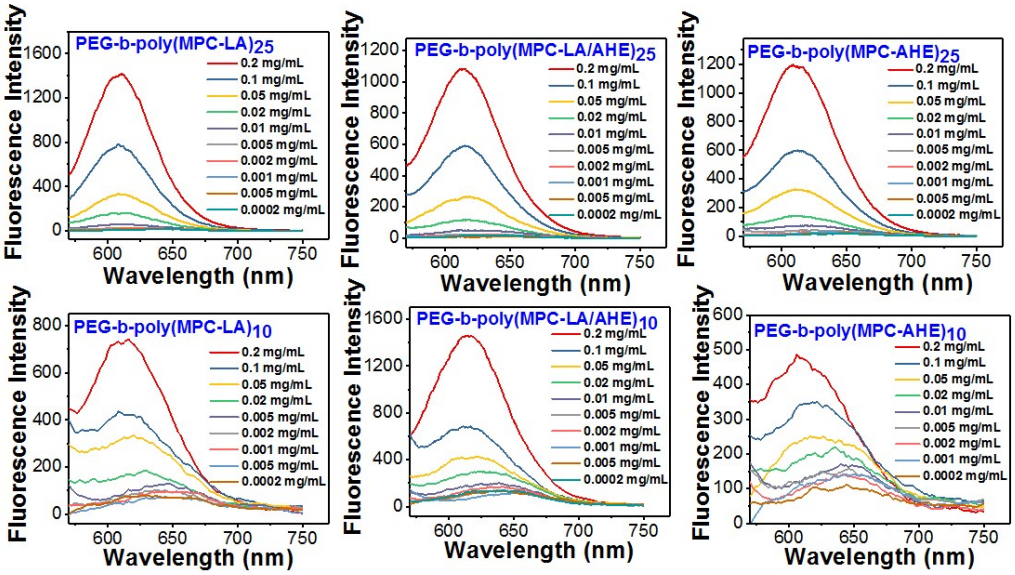

Figure S5. Fluorescence emission spectra of Nile Red in PMPC-based polymers of varying concentrations.

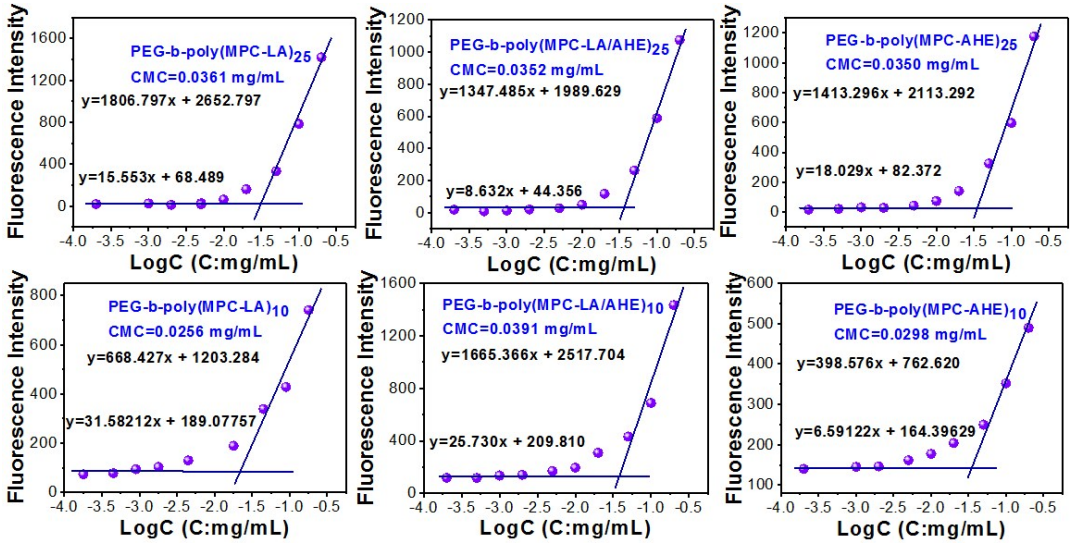

Figure S6. Determination of CMC using Nile Red as a fluorescent probe. The fluorescence intensity at the maximum emission wavelength is plotted against the log of concentration and the CMC was estimated as the cross-point when extrapolating the fluorescence intensity at the low and high concentration regime.

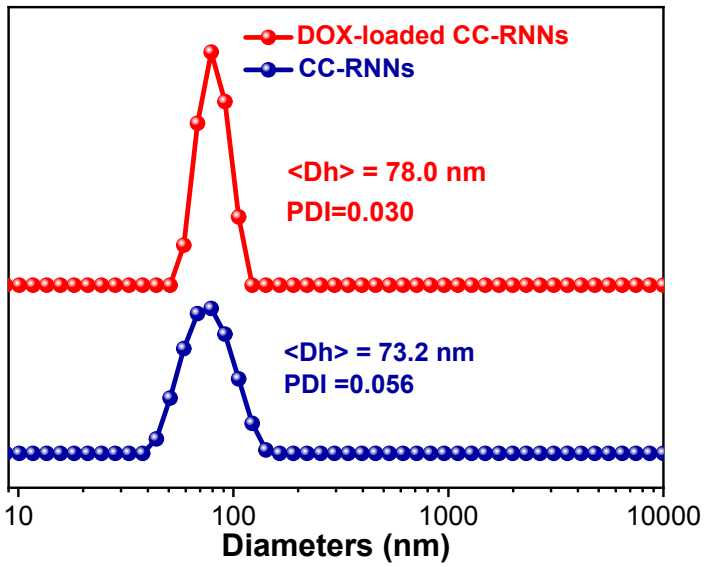

Figure S7. Distributions of hydrodynamic diameters of CC-RNNs-1 and DOX-loaded CC-RRNs-1.

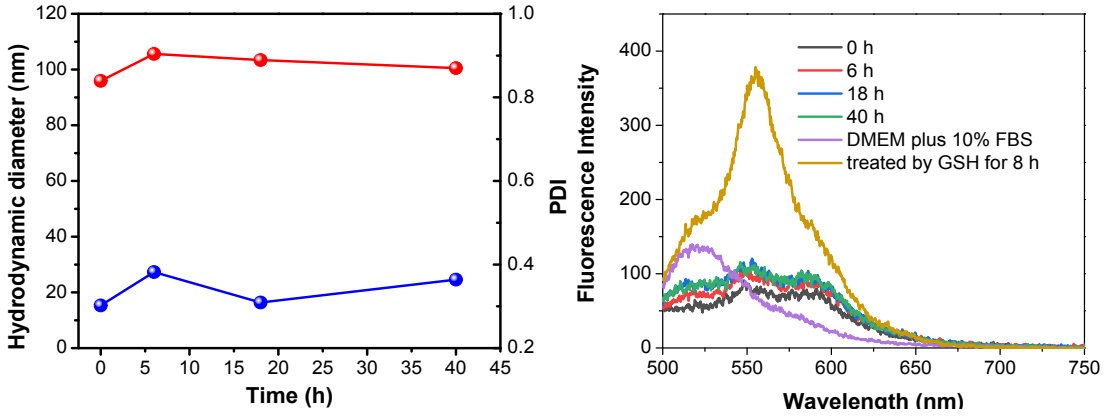

Figure S8. The diameters change of CC-RRNs-2 incubated in DMEM plus 10% FBS at specific time-points (left); the fluorescence spectra of DMEM plus 10% FBS, DOX-loaded CC-RRNs-2 incubated for 0, 6, 18, and 40 h at 37 °C and after 40 h incubation treated by 10 mM GSH for 8 h. (C= 0.2 mg/mL).

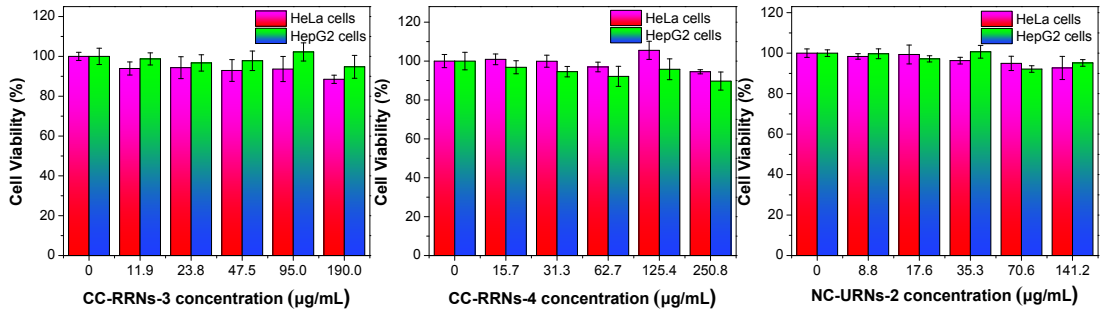

Figure S9. Cytotoxicity of blank CC-RRNs-3, CC-RRNs-4, and NC-URNs-2 in HeLa cells and HepG2 cells. The cells were incubated with NPs for 36 h. Data are presented as the average ± standard deviation (n= 3).

References

1 A. Martí, A. M. Costero, P. Gaviña, M. Parra, *Chem. Commun.*, 2015, **51**, 3077-3079.