Supporting information

Reversibly disulfide cross-linked micelles improve the pharmacokinetics and facilitate the targeted, on-demand delivery of doxorubicin in the treatment of B-cell lymphoma

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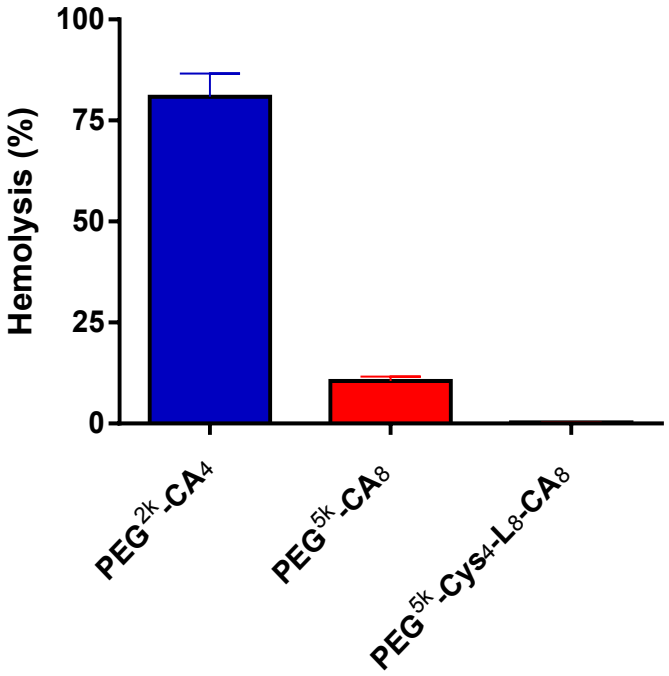

Figure S-1. Hemolytic activities of different PEG-oligocholic acid telodendrimer based micelles. PEG^{2k}-CA_4 micelles, PEG^{5k}-CA8 micelles, and PEG^{5k}-Cys_4-L_8-CA_8 DCMs were incubated with human erythrocyte suspension for 4 h at 37 °C at the final concentration of 0.2 mg/mL. Red blood cell lysis was determined spectrophotometrically (Ab = 540 nm) based on hemoglobin level. PBS was used as negative control, and Triton-100 was used as positive control. Data represent mean ± SEM (n = 3).

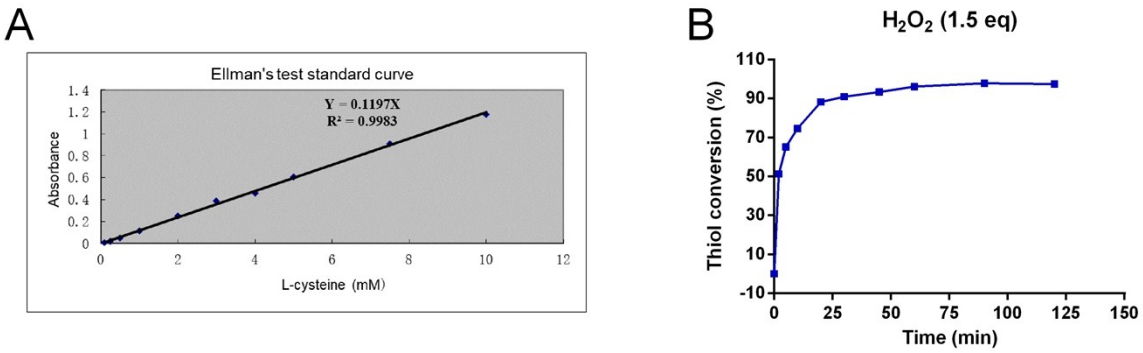

Figure S-2. The formation of disulfide bonds in the micelles was monitored by Ellman's test. (A) The free cysteine concentration standard curve was measured by Ellman's test; (B) Thiol conversion (%) in the micelles was monitored by Ellman's test after the addition of 1.5 equivalent H_2O_2 at different time points.

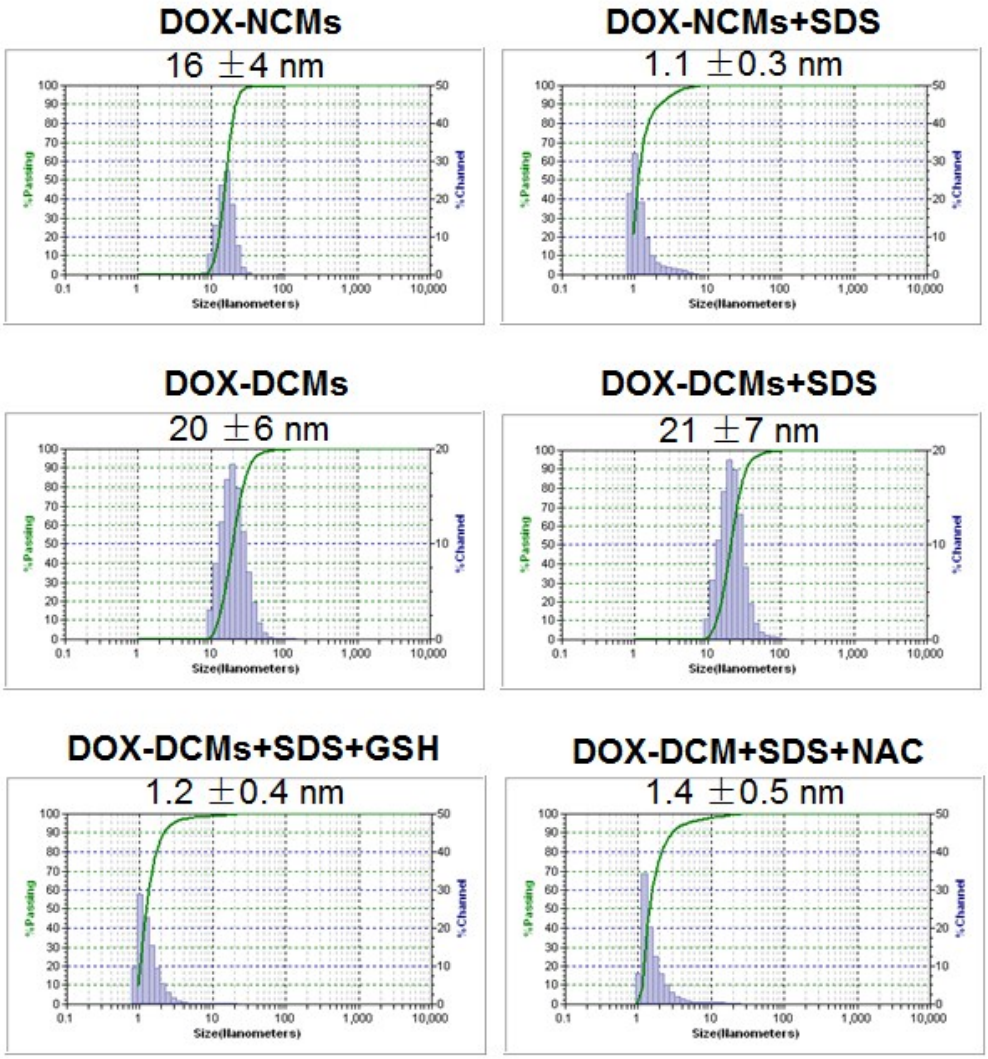

Figure S-3. Representative DLS particle size of DOX-NCMs and DOX-DCMs in the presence of SDS with or without the addition of reducing agent GSH (10 mM) or NAC (10 mM).

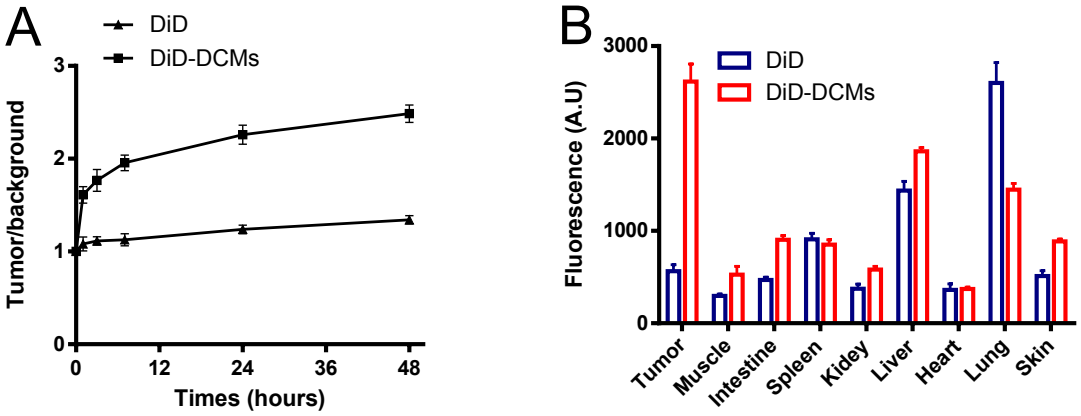

Figure S-4. (A) Time-dependent tumor accumulation profile of DiD-DCMs. It was semi-quantified as the tumor/background (normal skin) ratio of fluorenscence intensity (n=3). (B) Quantitative fluorescence intensities of tumors and organs from *ex vivo* images (n=3).

Table S-1. Pharmacokinetic parameters of free DOX and DOX micellar formulations

Parameters	Free DOX	DOX-NCMs	DOX-DCMs
$T_{1/2\alpha}$ (min)	1.8 ± 0.8	3.2 ± 2.9	2.4 ± 0.6
$T_{1/2\beta}$ (h)	1.4 ± 1.0	5.0 ± 1.7*	7.7 ± 2.1**
K_{10} (1/h)	2.8 ± 2.5	1.5 ± 1.6	0.3 ± 0.1
AUC (h*ug/mL)	31.6 ± 24.6	192.3 ± 38.0*	391.8 ± 79.9**
CL (mL/h/kg)	525.0 ± 371.2	53.4 ± 10.3	26.4 ± 5.6*
MRT (h)	3.0 ± 2.5	6.9 ± 2.2	11.0 ± 3.0**
V_{ss} (mL/kg)	2222.5 ± 1630.3	355.8 ± 54.4	277.8 ± 33.7*

Note: K_{10}: Elimination rate constant from central compartment; $T_{1/2\alpha}$: Distribution half-life; $T_{1/2\beta}$: Elimination half-life; AUC: Area under curve; Cl: Clearance from the blood; MRT: Mean residence time; V_{ss}: Steady-state volume of distribution. Data presented as mean ± SD. * $P < 0.05$, ** $P < 0.01$.

Table S-2. Blood cell counts on day 4 after last dosage in the therapeutic study

Groups	WBC (K/ul)	RBC (M/ul)	Hemoglobin (g/dL)	Platelets (K/uL)
PBS	8.9 ± 0.6	8.4 ± 1.0	12.9 ± 1.5	1063.0 ± 166.4
DOX	4.6 ± 1.3*	7.5 ± 0.9	10.9 ± 1.2	997.4 ± 305.8
DOX-NCMs	9.1 ± 1.0	5.8 ± 0.7*	9.5 ± 1.0*	1143.2 ± 281.5
DOX-DCMs	8.9 ± 1.6	7.4 ± 1.4	11.2 ± 1.3	1205.7 ± 249.3
DOX-DCMs + NAC	7.8 ± 2.4	7.9 ± 1.1	12.0 ± 1.8	1129.5 ± 229.7

Table S-3. Serum chemistry on day 4 after last dosage in the therapeutic study

Groups	ALT (U/L)	AST (U/L)	BUN (mg/dL)
PBS	39.4 ± 14.9	225.0 ± 69.1	29.2 ± 5.2
DOX	45.8 ± 12.5	215.9 ± 44.4	26.6 ± 4.9
DOX-NCMs	48.8 ± 20.6	181.5 ± 80.7	25.4 ± 7.6
DOX-DCMs	42.8 ± 9.4	217.5 ± 65.4	27.9 ± 4.2
DOX-DCMs + NAC	41.3 ± 8.7	232.0 ± 43.2	26.7 ± 4.9