Supporting Information

Hyaluronic acid functional amphipathic and redox-responsive polymer particles for co-delivery of doxorubicin and cyclopamine to eradicate breast cancer cells and cancer stem cells

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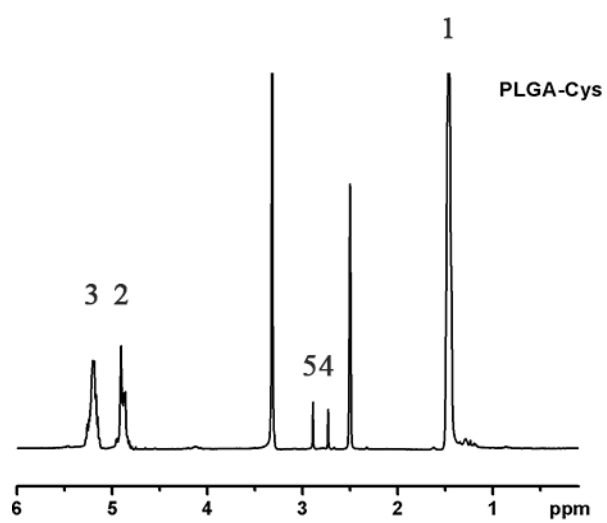E-mail address: liuy@nanoctr.cn (Y. Liu)

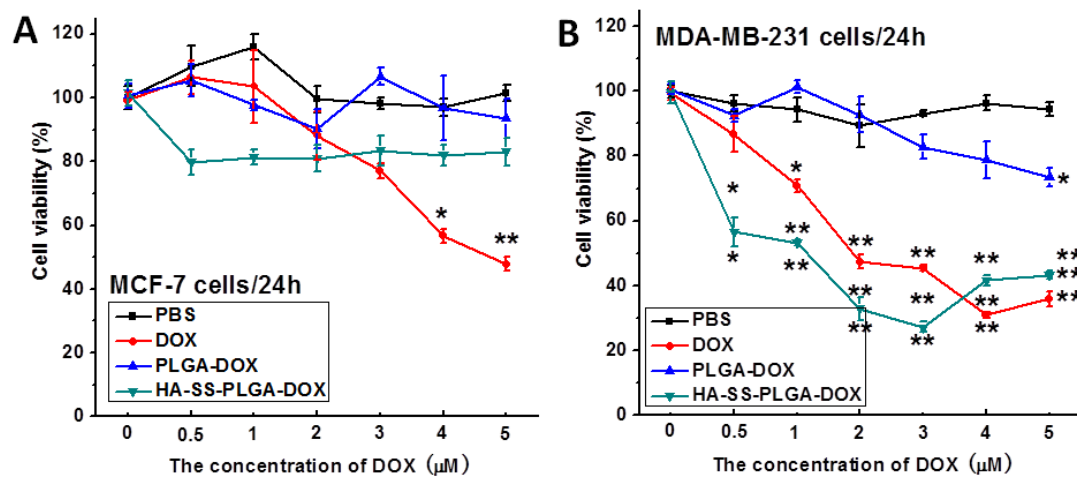**Figure S1. ^{1}H NMR spectrum of PLGA-Cys.**

Figure S2. *In vitro* **cytotoxicity after 24h treatment.** The cytotoxicity of DOX, PLGA-DOX and HA-SS-PLGA-DOX towards breast cancer cells was evaluated by CCK-8 assay. (A) MCF-7 cells. (B) MDA-MB-231 cells. $*p < 0.05$ and $**p < 0.01$ compared to the PBS control group (one-way ANOVA, Tukey's post-hoc test).
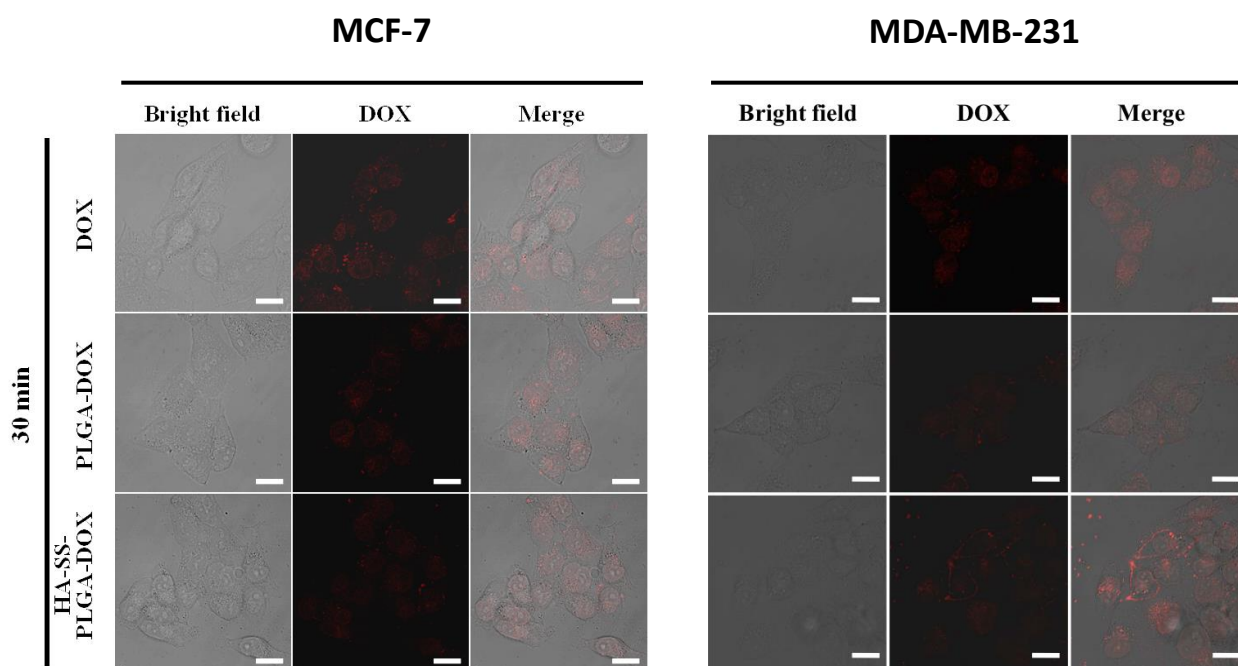
Figure S3. The cell uptake of particles by confocal microscopic study. The MCF-7 and MDA-MB-231 cells were treated with free DOX, PLGA-DOX, HA-SS-PLGA-DOX for 30 min. The red fluorescence of DOX was observed by a confocal microscope.
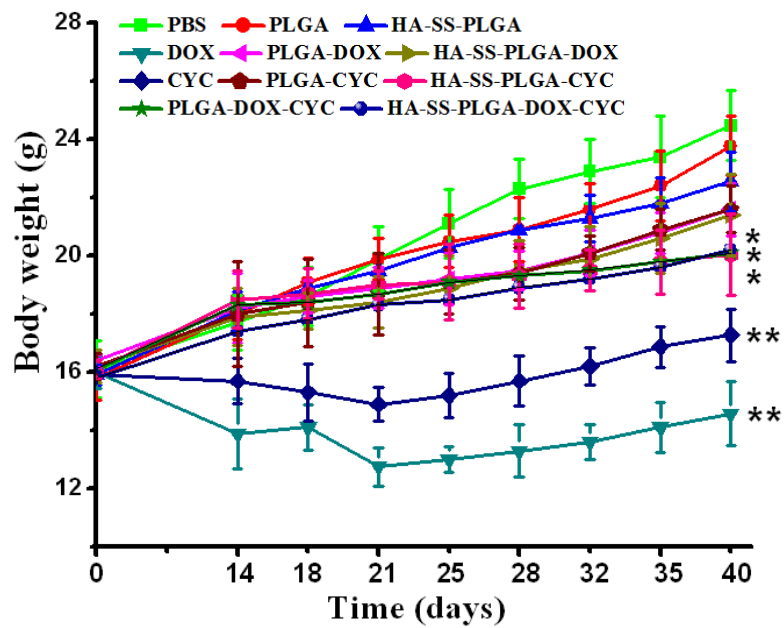
Figure S4. The body weights of mice. Data are expressed as mean ± SD. At the end of treatment, the average body weight between groups was compared by Student's t test. *$p < 0.05$ and **$p < 0.01$, vs. PBS group.
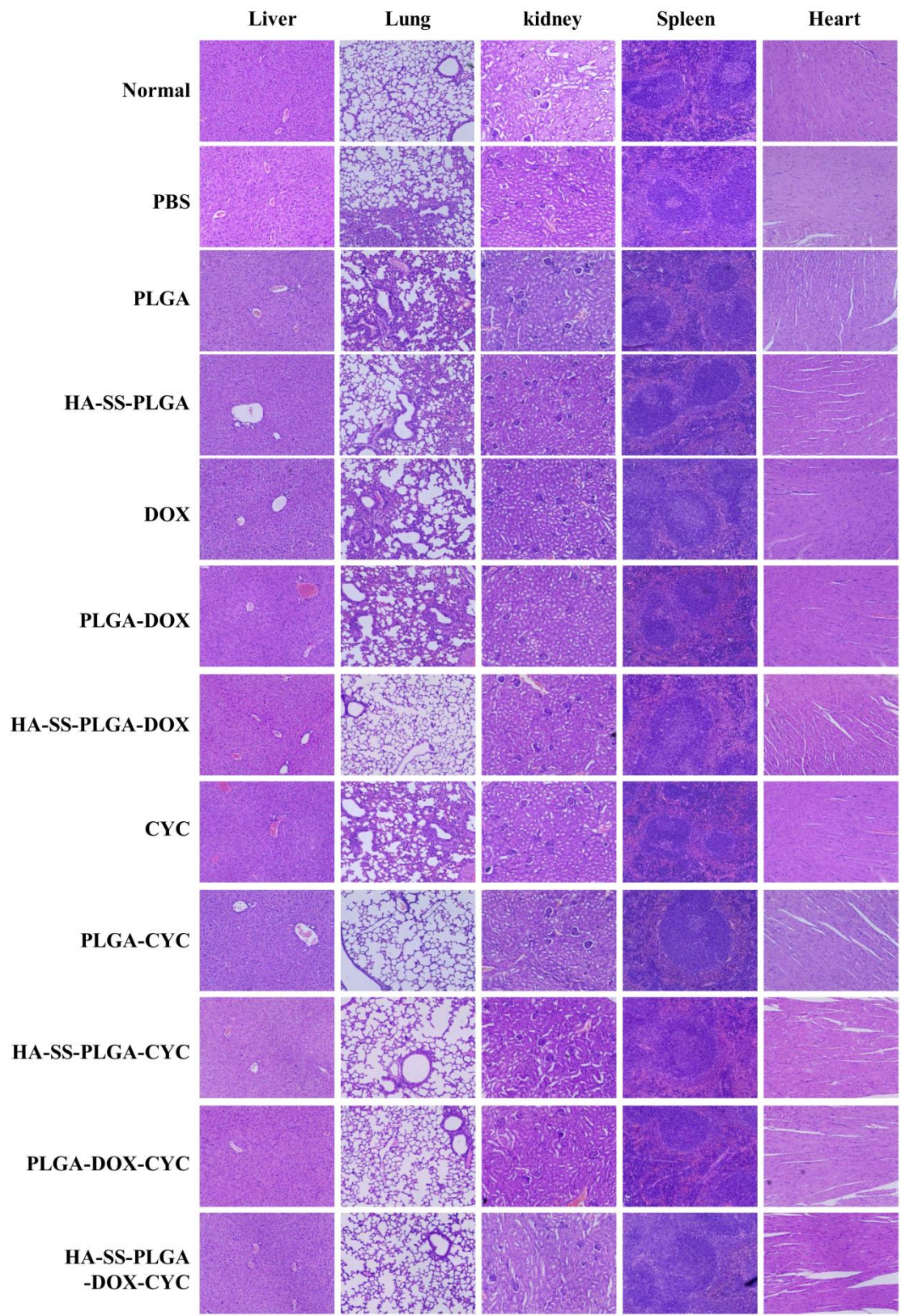
Figure S5. Histological examinations of liver, spleen, lung and kidney.

Table S1. The effects of formulation parameters on drug loading content and encapsulation efficiency

Sample number	PVA&F68 (W/V %)	Copolymer : DOX : CYC (mass ratio)	EE（%）of DOX&CYC	Size(nm) (By DLS)	PDI (By DLS)	Zeta Potential (mv)
1	0.5&0	50:1:2	65.3±2.1&43.3±2.1	327.4±3.2	0.116±0.016	-40.2±5.2
2	1&0	50:1:2	72.2±1.2&48.5±1.1	298.4±2.4	0.176±0.021	-42.1±4.5
3	2&0	50:1:2	76.1±1.9&66.0±1.4	270.6±4.5	0.181±0.006	-36.2±7.1
4	1&1	50:1:2	70.6±0.9&58.2±1.2	245.3±6.1	0.091±0.012	-38.5±2.3
5	1&1	100:1:2	80.3±0.6&71.2±2.4	264.2±2.1	0.114±0.042	-41.1±7.4
6	1&1	200:1:2	85.1±1.1&75.1±1.3	283.1±7.1	0.211±0.012	-32.8±4.7
7	1&1	50:0:2	----- & 68.5±2.5	223.1±4.3	0.164±0.024	-32.1±5.2
8	1&1	50:1:0	77.2±2.4 & ----	210.1±1.2	0.087±0.047	-34.5±2.4

Table S2. The body weights and coefficients of various tissues to body weight at the end of treatment

Group	Body weight (g)	Organ coefficients (mg/g)			
		Liver	Spleen	Lung	Kidneys
PBS	24.48 ±1.20	71.88 ±8.16	7.12 ±0.97	7.11 ±0.98	14.99 ±4.09
PLGA	23.78 ±1.02	72.12 ±9.65	6.97 ±0.63	7.09 ±1.31	15.16 ±5.11
HA-SS-PLGA	22.55 ±1.01	71.09 ±7.67	6.88 ±0.59	7.12 ±0.77	15.21 ±3.98
DOX	14.57±1.11**	74.88 ±6.98	7.54 ±0.33	7.32 ±0.56	15.48 ±3.12
PLGA-DOX	21.60 ±0.94	69.65 ±7.22	7.28 ±1.28	6.99 ±0.87	14.87 ±4.61
HA-SS-PLGA-DOX	21.42 ±1.45	71.32 ±6.45	6.86 ±0.73	7.10 ±0.59	15.23 ±5.32
CYC	17.28 ±0.98**	73.34 ±9.51	7.37 ±1.14	7.24 ±1.23	15.34 ±5.43
PLGA-CYC	21.61 ±0.87	70.11 ±10.43	7.20 ±0.63	6.89 ±0.96	15.32 ±3.46
HA-SS-PLGA-CYC	20.03 ±1.41*	69.62 ±6.47	7.04 ±0.77	7.21 ±1.72	15.21 ±4.13
PLGA-DOX-CYC	20.10 ±1.62*	73.12 ±5.41	6.91 ±0.83	7.17 ±1.14	15.44 ±4.32
HA-SS-PLGA-DOX-CYC	20.19 ±1.08*	68.95 ±8.34	7.10 ±0.29	7.14 ±1.21	15.35 ±4.09

* and ** represent significant difference compared to the control group, *$p < 0.05$ and **$p < 0.05$.

Table S3. Complete blood counts

Group	WBC (10^9/L)	RBC (10^{12}/L)	HGB (g/L)	PLT (10^9/L)	NEUT (%)	LY (%)	MONO (%)
Normal	3.22 ±0.28	10.61 ±1.31	157.76 ±9.74	894.34 ±52.11	1.28 ±0.07	85.47 ±7.26	3.51 ±0.99
PBS	4.23 ±0.54	11.02 ±2.21	160.65 ±9.28	842.98 ±49.67	2.08 ±0.03	90.52 ±7.84	3.90 ±1.11
PLGA	3.97 ±0.26	9.84 ±1.45	153.97 ±6.18	910.75 ±57.31	1.91 ±0.11	90.10 ±8.95	3.55 ±0.65
HA-SS-PLGA	3.84 ±0.61	10.06 ±2.07	151.98 ±7.09	891.56 ±46.78	1.57 ±0.31	91.23 ±8.31	4.07 ±1.23
DOX	3.52 ±0.76	9.88 ±1.98	151.36 ±9.77	735.57 ±32.46*	1.51 ±0.14	92.10 ±9.11*	1.81 ±0.33*
PLGA-DOX	3.47 ±0.76	9.99 ±2.31	149.53 ±10.16	791.09 ±41.98	2.11 ±0.24	91.53 ±7.27	3.60 ±1.63
HA-SS-PLGA-DOX	3.31 ±0.57	9.96 ±1.78	158.09 ±10.31	906.22 ±54.13	1.65 ±0.41	90.06 ±8.03	3.78 ±0.36
CYC	3.23 ±0.56	10.11 ±1.69	151.57 ±7.08	769.53 ±65.32*	1.83 ±0.65	90.43 ±7.22	1.27 ±0.87*
PLGA-CYC	3.07 ±0.41	9.90 ±2.17	152.75 ±9.87	896.11 ±45.78	1.78 ±0.97	88.95 ±8.05	4.08 ±0.07
HA-SS-PLGA-CYC	3.49 ±0.77	10.03 ±1.99	159.31 ±10.22	900.56 ±51.43	2.09 ±0.19	91.32 ±6.45	3.82 ±0.95
PLGA-DOX-CYC	3.74 ±0.24	9.81 ±2.06	152.87 ±9.34	861.75 ±53.13	1.93 ±0.31	88.97 ±3.96	3.64 ±1.02
HA-SS-PLGA-DOX-CYC	3.44 ±0.64	9.95 ±1.98	156.43 ±10.54	891.09 ±45.65	2.07 ±0.54	92.43 ±7.54	4.33 ±1.65

* represents significant difference compared to the normal control group, *$p < 0.05$.

Table S4. Blood biochemical analyses

Group	BUN (mmol/L)	CR (mmol/L)	ALT(U/L)	AST(U/L)	LDH(U/L)	CK(U/L)
Normal	11.71 ±1.23	12.09 ±2.13	60.77 ±9.88	127.38 ±10.94	597.65 ±77.35	673.77 ±54.12
PBS	12.22 ±0.97	11.34 ±1.76	58.54 ±10.05	166.19 ±9.65*	1943.09 ±324.98**	1270.52 ±34.87**
PLGA	11.93 ±2.43	11.79 ±1.98	53.77 ±7.64	153.87 ±8.21	991.26 ±76.56**	1025.43 ±85.12**
HA-SS-PLGA	11.21 ±2.08	10.87 ±2.01	58.34 ±6.15	131.44 ±6.94	1064.34 ±127.43**	877.45 ±43.09*
DOX	7.65 ±1.94*	7.49 ±1.46*	43.67 ±6.23*	137.81 ±5.09	1144.58 ±109.87**	687.45 ±34.21
PLGA-DOX	7.89 ±0.69*	8.03 ±2.41*	44.81 ±9.76*	132.09 ±6.83	721.73 ±43.71*	598.35 ±19.65
HA-SS-PLGA-DOX	10.95 ±2.06	11.12 ±1.97	62.54 ±5.16	129.65 ±7.87	607.67 ±10.76	631.56 ±26.77
CYC	7.18 ±1.94*	6.62 ±0.67*	50.31 ±4.76*	133.45 ±6.15	599.98 ±12.78	909.54 ±43.67*
PLGA-CYC	10.23 ±1.87	7.26 ±2.01*	56.43 ±3.95	130.26 ±4.22	578.53 ±63.84	694.39 ±32.08
HA-SS-PLGA-CYC	11.67 ±1.94	11.89 ±1.09	58.93 ±7.25	129.27 ±8.41	626.87 ±51.65	701.65 ±31.93
PLGA-DOX-CYC	10.99 ±0.52	13.17 ±3.07	68.42 ±6.22	134.12 ±7.87	641.04 ±91.82	688.63 ±46.01
HA-SS-PLGA-DOX-CYC	11.06 ±2.11	11.98 ±2.07	63.74 ±5.24	132.76 ±8.43	609.45 ±87.31	704.87 ±54.22

* and ** represent significant difference compared to the normal control group, *$p < 0.05$ and **$p < 0.05$.