

## Supplementary information

### **Engineering thermo-pH dual responsive hydrogel for enhanced tumor accumulation, penetration, and chemo-protein combination therapy**

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**Table S1.** Reproducibility of 3 batches CDM.

	Size (Num. nm)	PdI	Zeta potential(mV)	EE of DTX (%)	DL of DTX (%)	EE of CC (%)
1	28.04	0.281	-15.2	70.75	2.93	95.79
2	26.21	0.165	-14.3	72.41	2.90	95.77
3	26.45	0.209	-14.1	69.36	2.67	96.56
AVE ± SD	26.90±0.99	0.218±0.058	-14.53±0.58	70.84±1.53	2.84±0.13	96.04±0.45

**Table S2.** Characterizations of CyC6M and GDM including particle size and zeta potential.

Formulations	Size (Num. nm)	PdI	Zeta potential (mV)
GDM	23.23±1.02	0.539±0.003	-9.03±0.28
CyC6M	25.40±0.32	0.611±0.116	-14.13±1.62

**Table S3.** IC<sub>50</sub> and CI values of GrB/DTX at different mass ratios in B16 cells. \**p*<0.05, GDM versus GM, GDM versus DM

Formulation	IC <sub>50</sub> (GrB)	IC <sub>50</sub> (DTX)	CI
Free DTX	/	9.95±2.05	/
DM	/	9.77±0.58	/
GM	0.40±0.11	/	/
GDM (1:50)	0.15±0.01	7.62±0.40*	1.15±0.06
GDM (1:100)	0.07±0.01*	6.81±0.41*	0.87±0.06
GDM (1:200)	0.17±0.12	6.02±0.63*	1.03±0.35

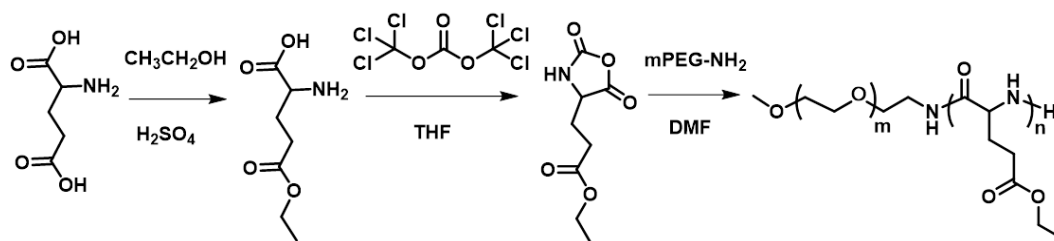


Figure S1. Synthesis route of mPEG-PELG

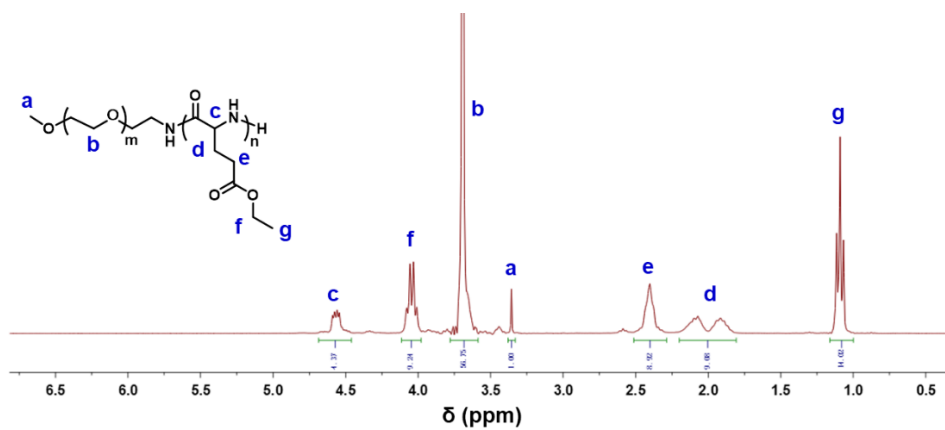


Figure S2. <sup>1</sup>H NMR of mPEG-*b*-PELG

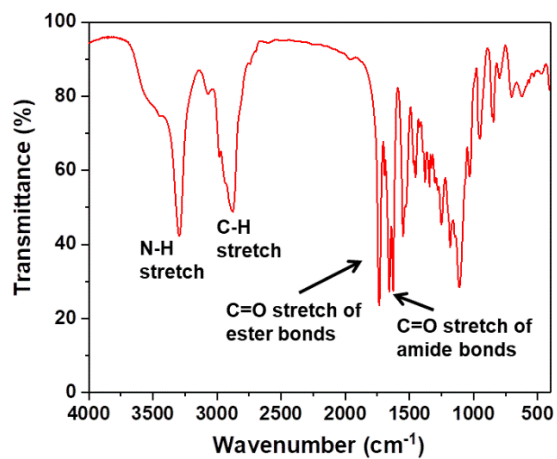


Figure S3. FTIR spectrum of mPEG-*b*-PELG

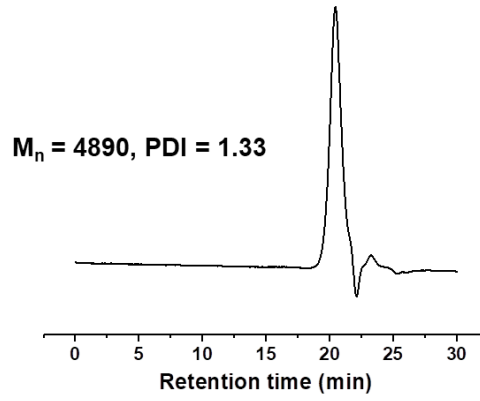


Figure S4. GPC result of mPEG-*b*-PELG

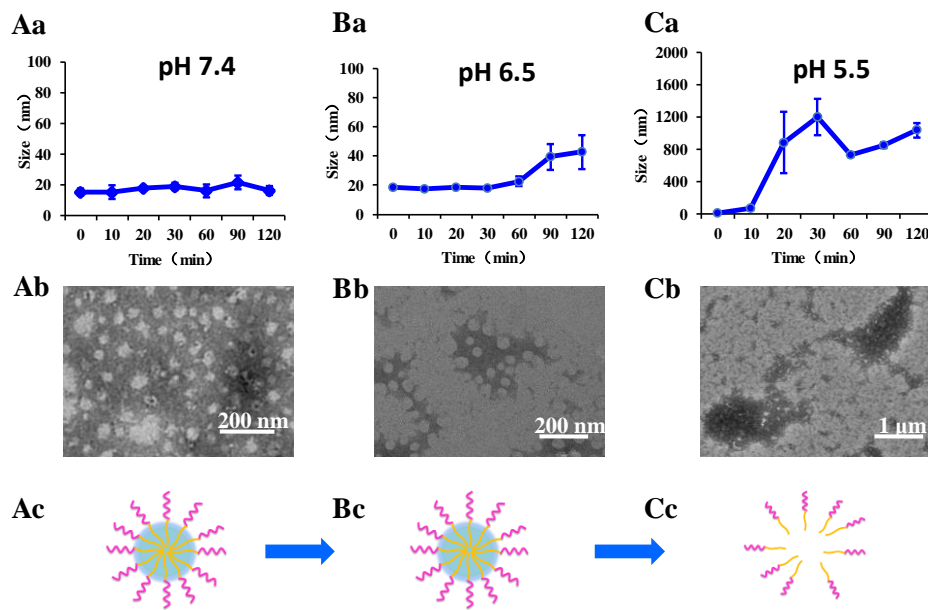


Figure S5. Size change of blank micelles at different pH values (7.4, 6.5, 5.5).

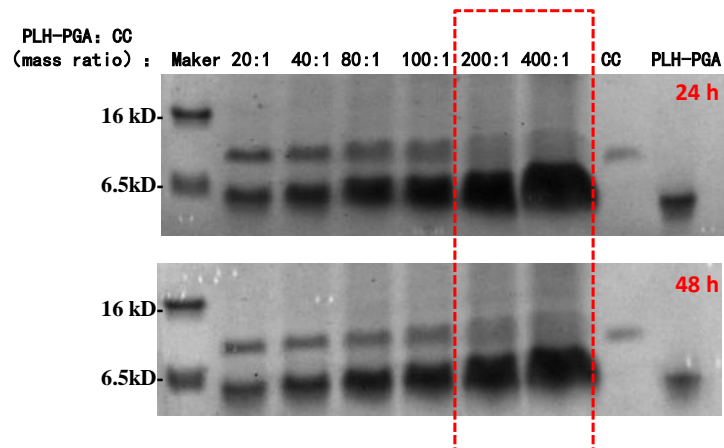
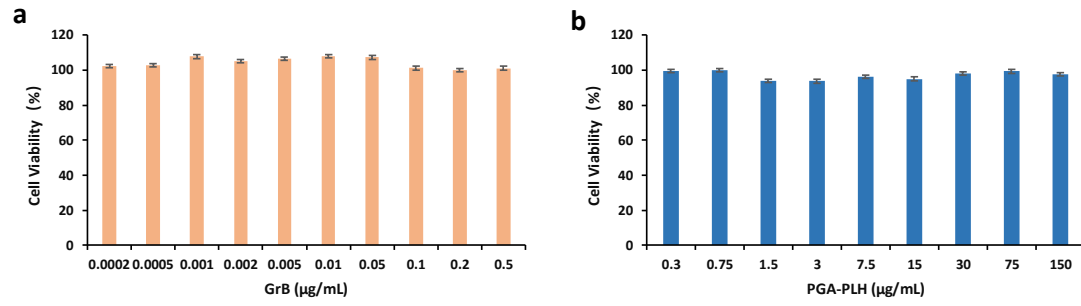
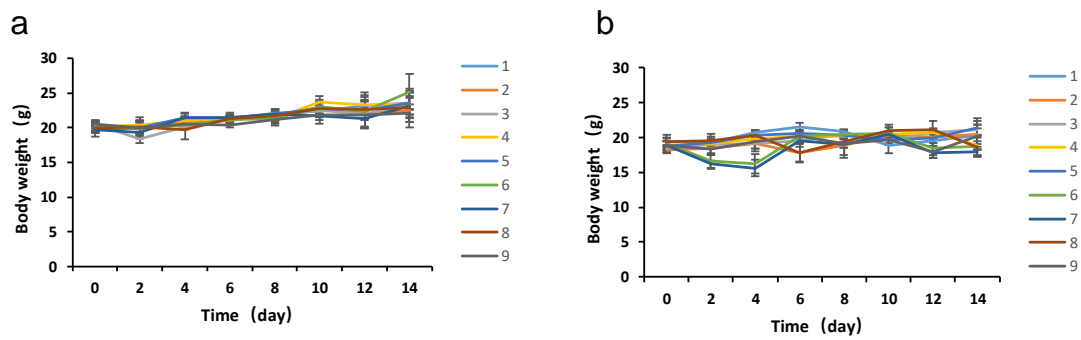


Figure S6. Preparation and formulation investigation of CC-PIC micelles, for which different mass ratios (PLH-PGA:CC) were tested.



**Figure S7.** Cell viabilities of free GrB (a) and PGA-PLH(b) at different concentrations in B16 cells



**Figure S8.** Body weight changes on B16 bearing female C57BL/6 mice after peritumoral injection with different formulations. a: without surgery after tumor bearing; b: with surgery after tumor bearing. Data were given as mean  $\pm$  SD (n=5). ① Normal Solution; ② Free DTX; ③ DM; ④ GM; ⑤ GDM; ⑥ Blank hydrogel; ⑦ DMH; ⑧ GMH; ⑨ GDMH