Supporting Information

Multiple responsive Nano-Prodrug Combining Chemo-Differentiation-Cancer Stem Cells Inhibition toward Triple-Negative Breast Cancer

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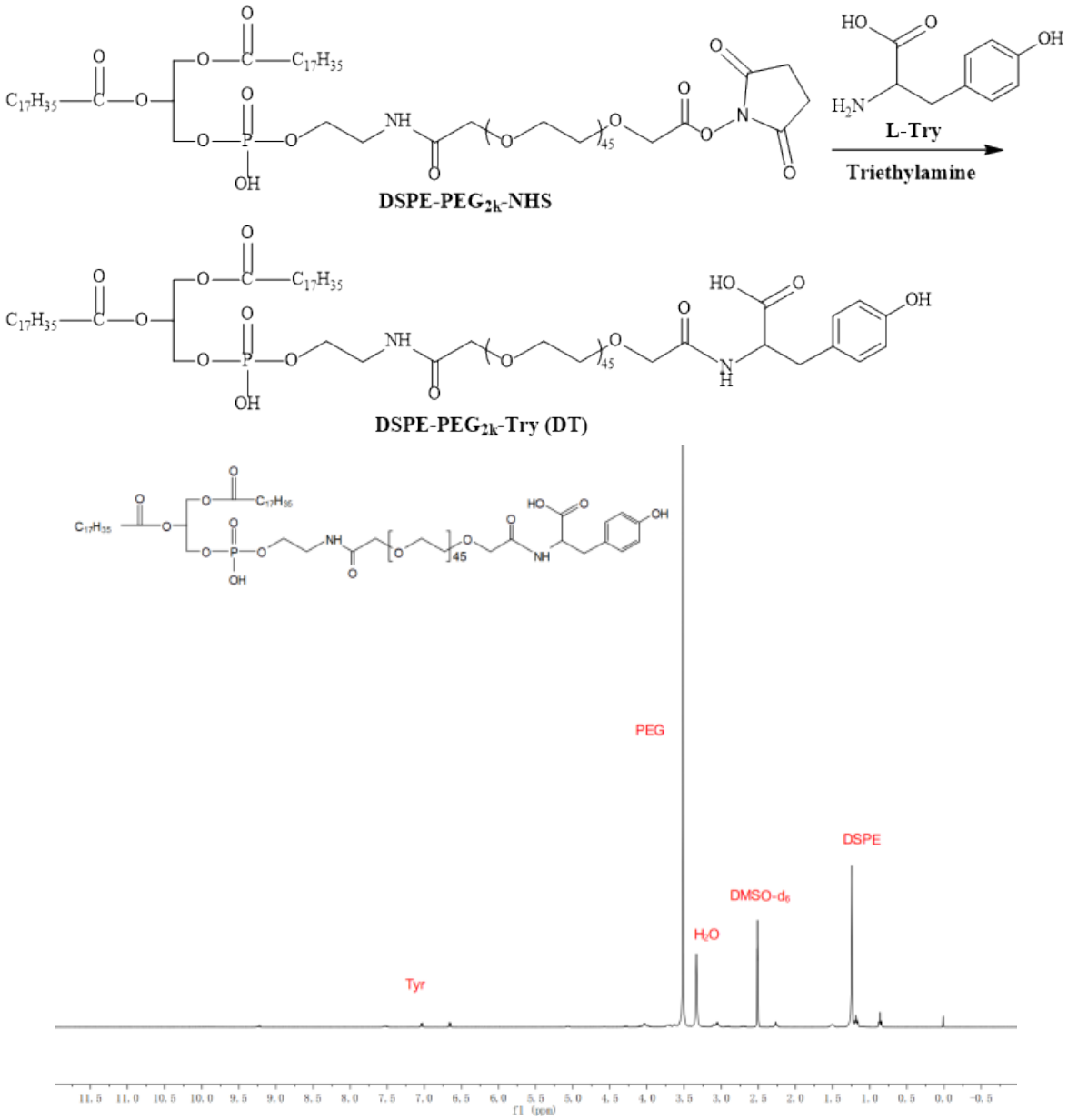


Fig. S1. Synthetic route and ^{1}H-NMR spectra of DT (Deuterated reagents: DMSO-d_6).

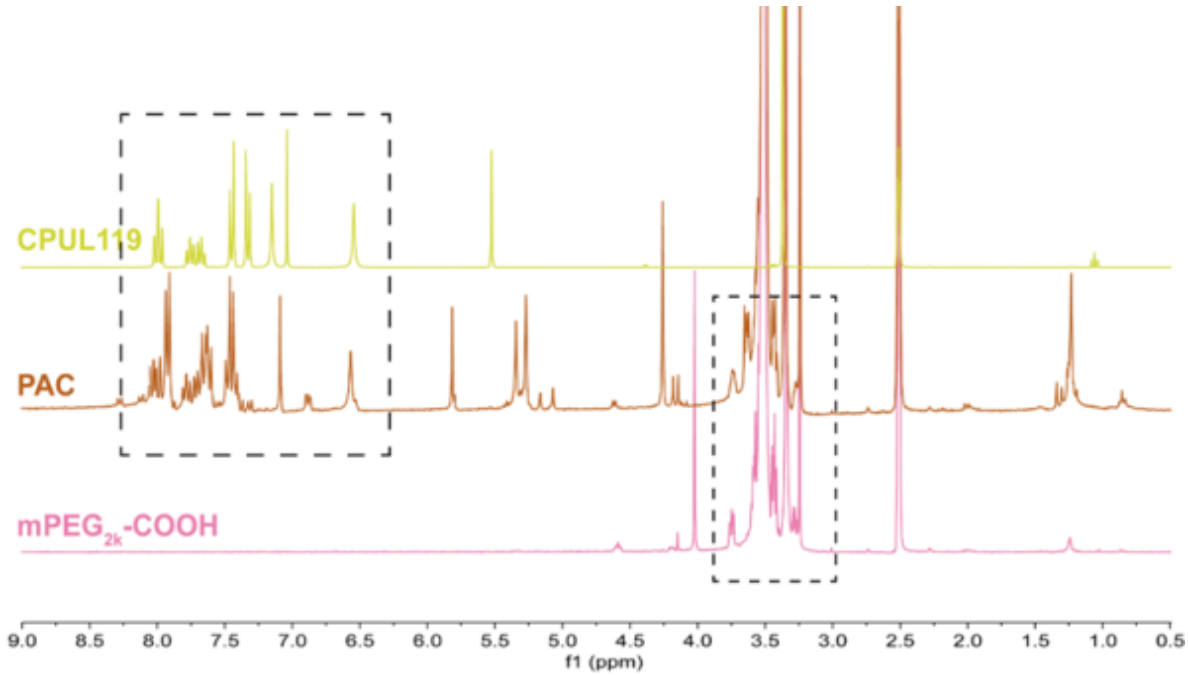


Fig. S2. ^{1}H-NMR spectra of CPUL119, PAC and $mPEG_{2k}$-COOH in DMSO-d_6.

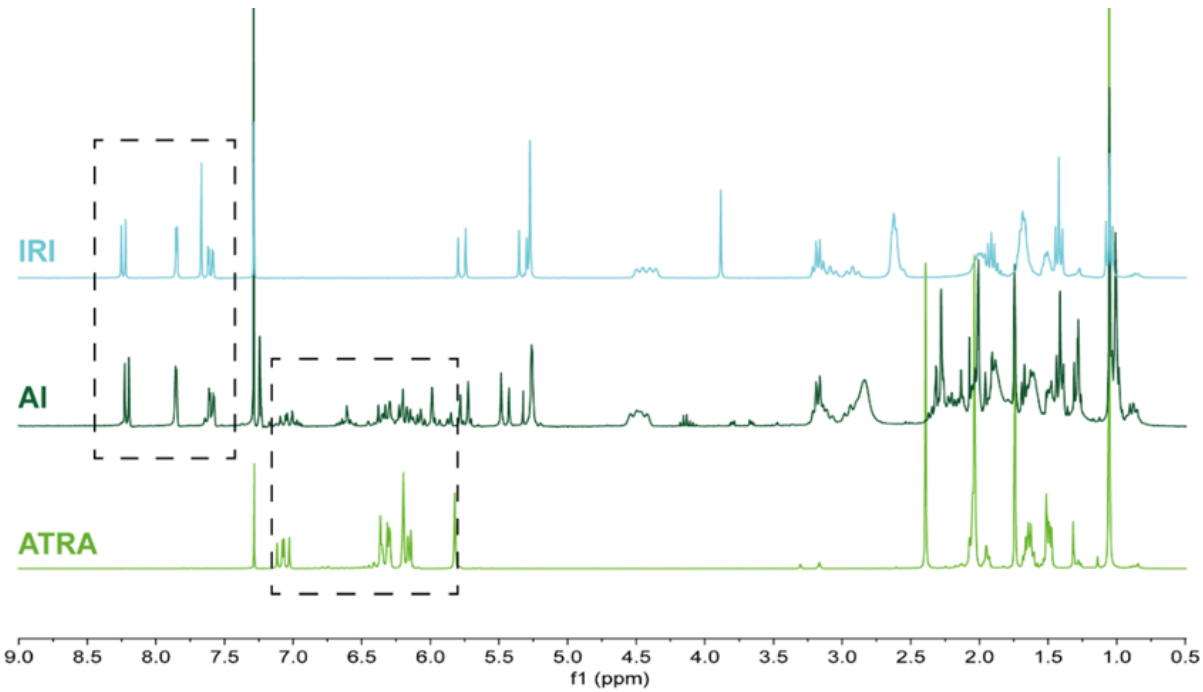


Fig. S3. ^{1}H-NMR spectra of ATRA, AI and IRI in $CDCl_3$.

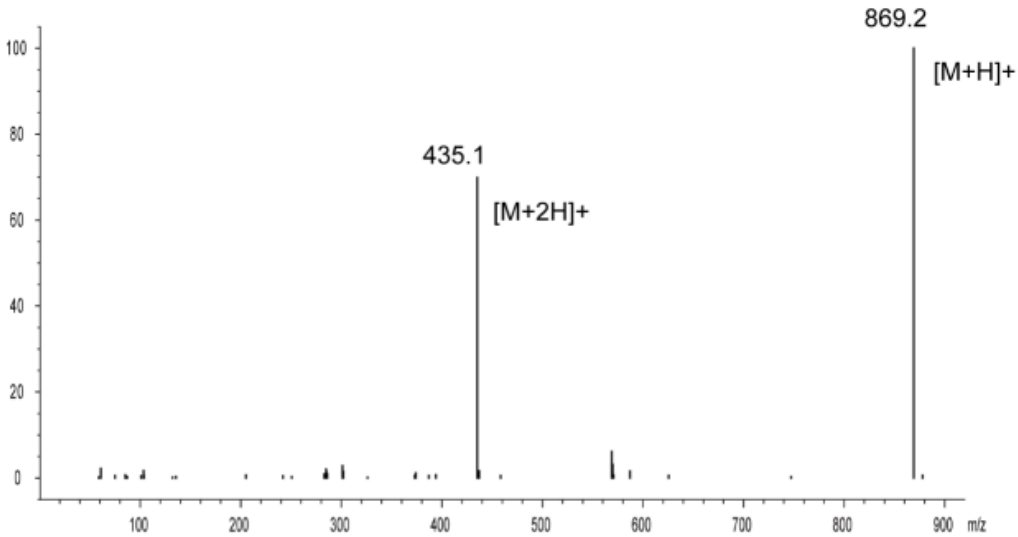


Fig. S4. Mass spectrometry of AI.

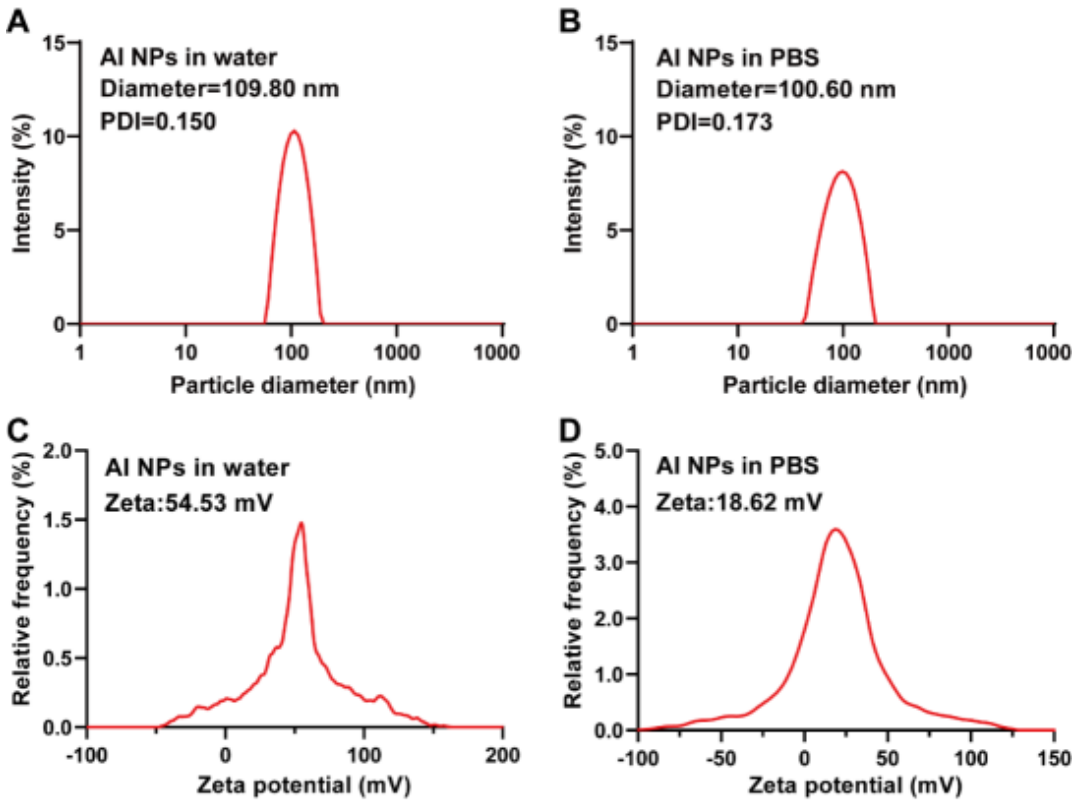


Fig. S5. Particle size distribution of AI NPs (A) in water and (B) PBS. Zeta potential of AI NPs (C) in water and (D) PBS. Data are presented as mean ± SD (n = 3).

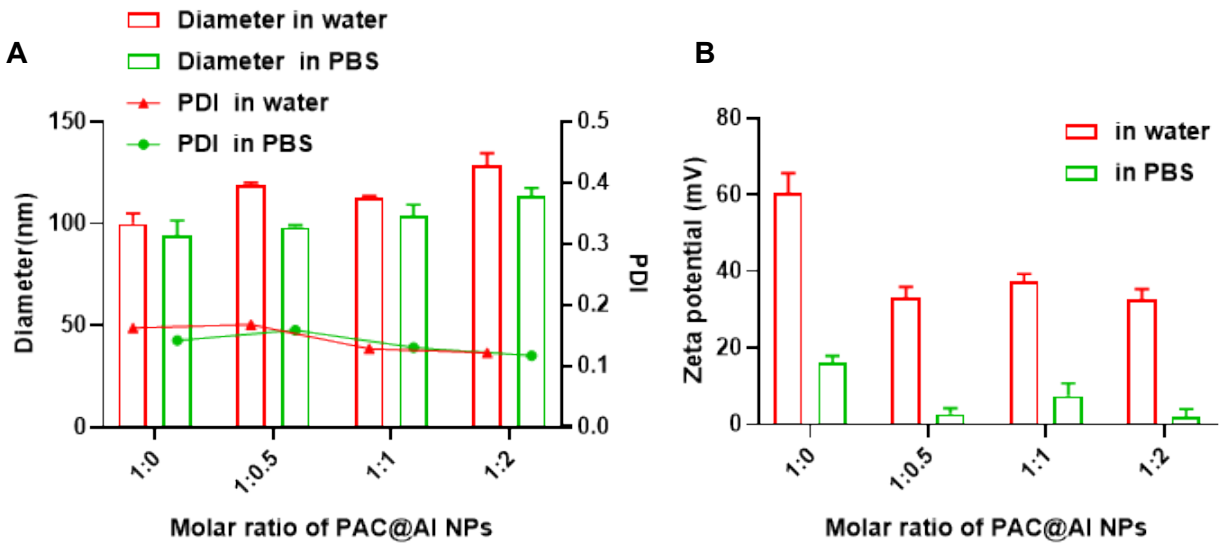


Fig. S6. (A) Particle size and PDI and (B) potentials of different ratios of PAC@AI NPs in water and PBS. Data are presented as mean ± SD (n = 3).

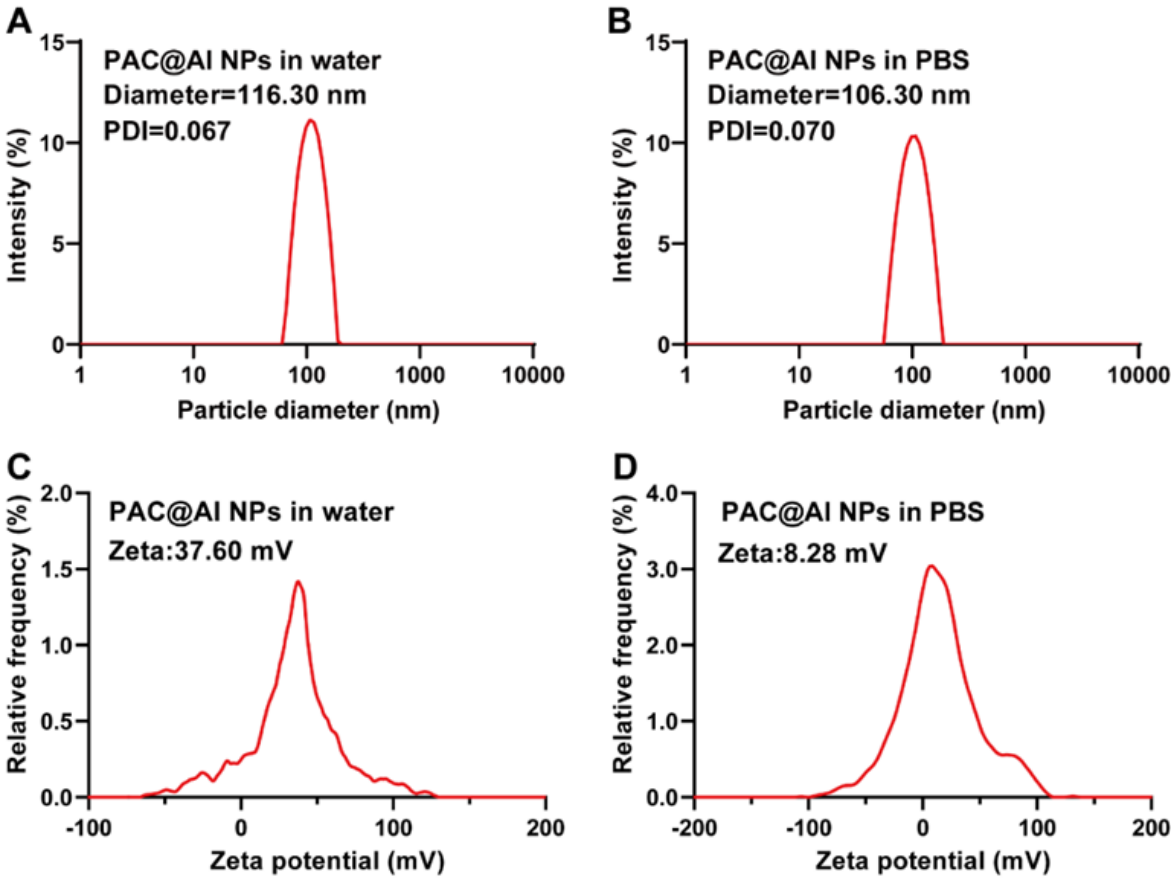


Fig. S7. Particle size distribution of PAC@AI NPs (A) in water and (B) PBS. Zeta potential of PAC@AI NPs (C) in water and (D) PBS. Data are presented as mean ± SD (n = 3).

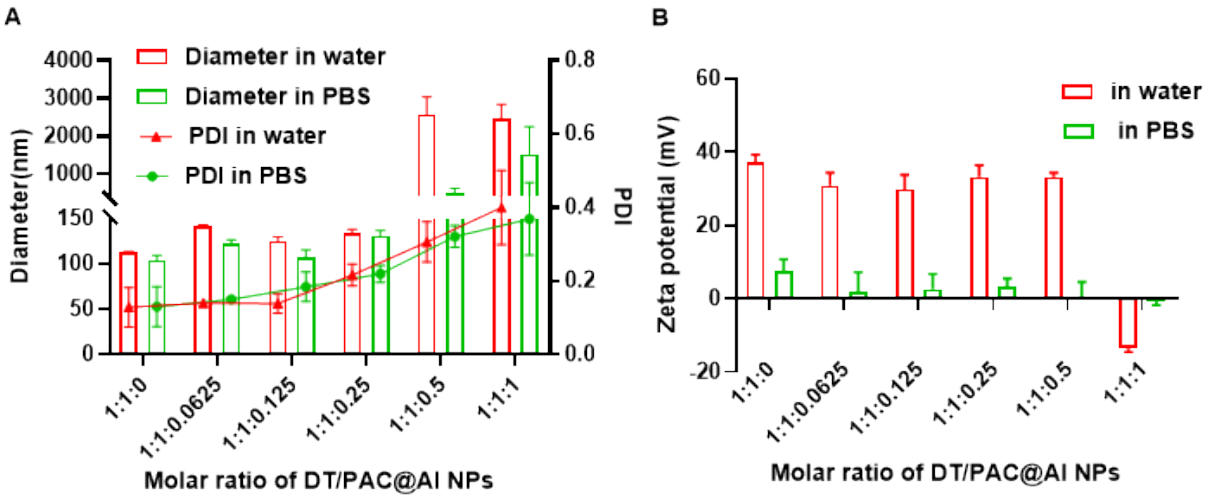


Fig. S8. (A) Particle size and PDI and (B) potentials of different ratios of DT/PAC@AI NPs in water and PBS. Data are presented as mean ± SD (n = 3).

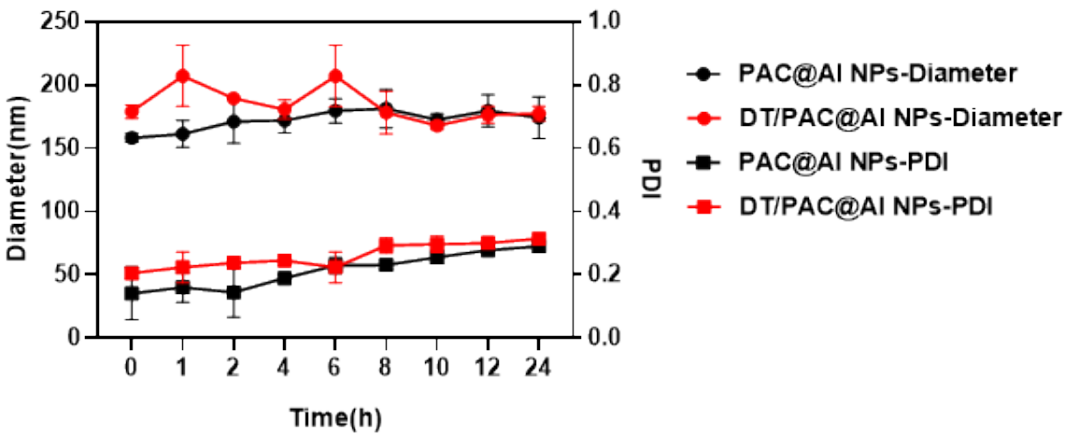


Fig. S9. Stability assessment of nanoparticles in 10% FBS/PBS over 24 h. Data are presented as mean ± SD (n = 3).

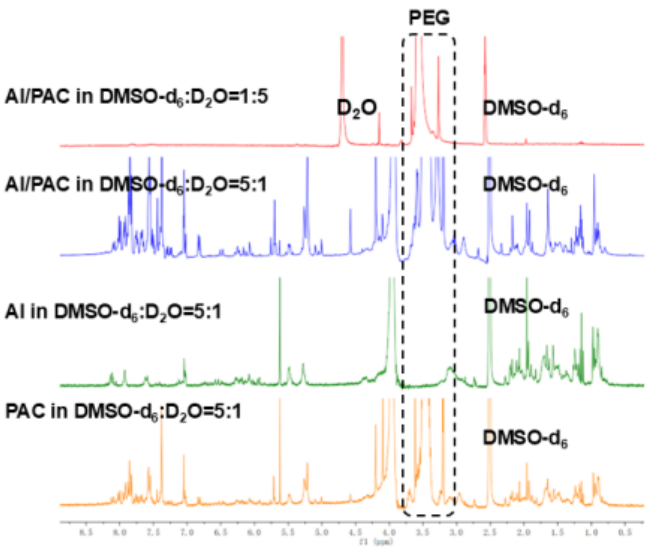


Fig. S10. Characterization of PAC@AI NPs . ^{1}H NMR spectra of AI/PAC in DMSO-d_6/D_2O (1:5)(red line), AI/PAC in DMSO-d_6/D_2O (5:1) (blue line), AI in DMSO-d_6/D_2O (5:1) (green line), and PAC in DMSO-d_6/D_2O (5:1) (orange line).

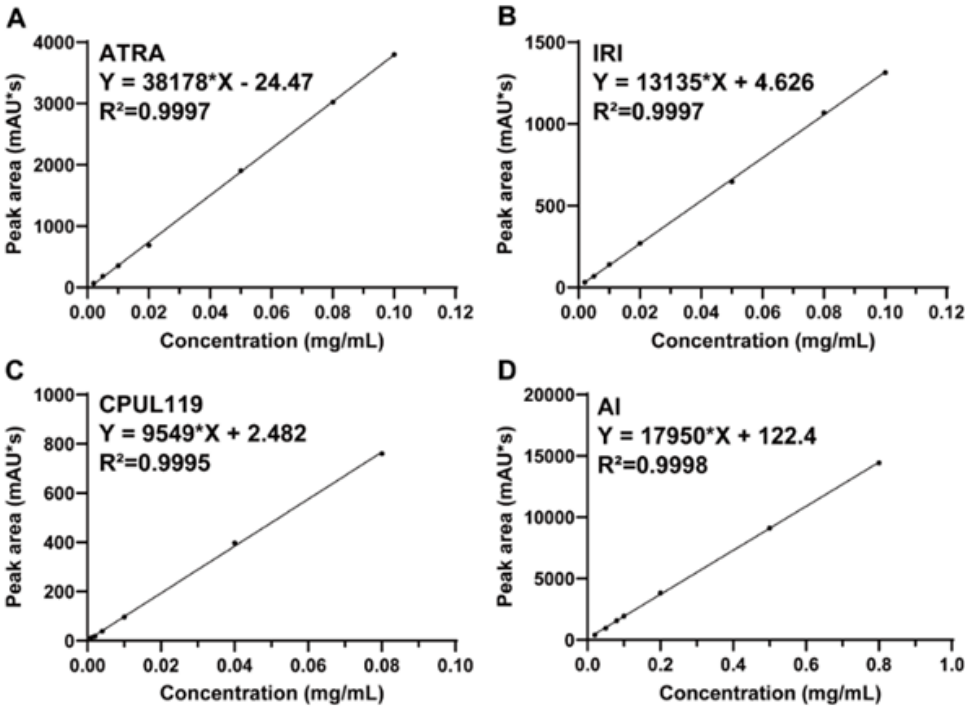


Fig. 11. Standard curve of (A) ATRA, (B) IRI, (C) CPUL119, (D) AI.

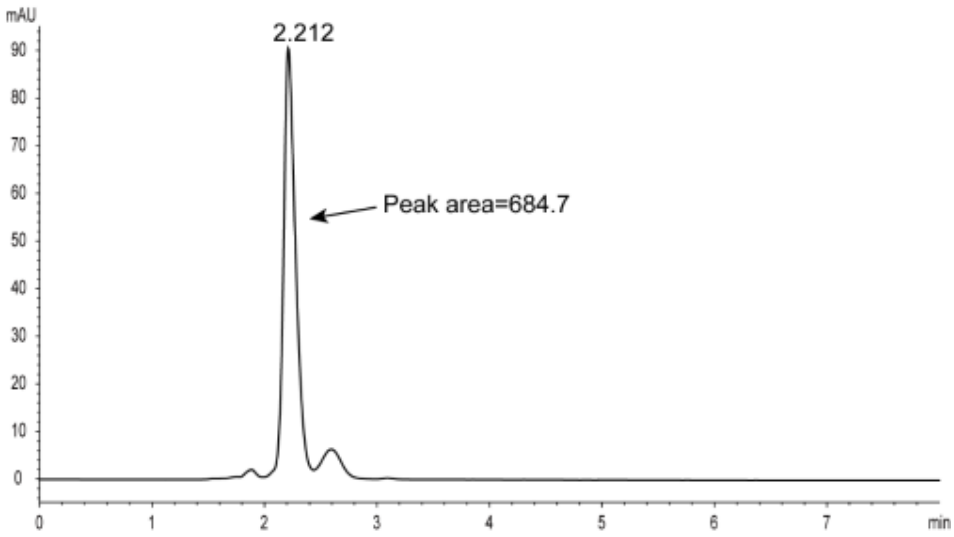
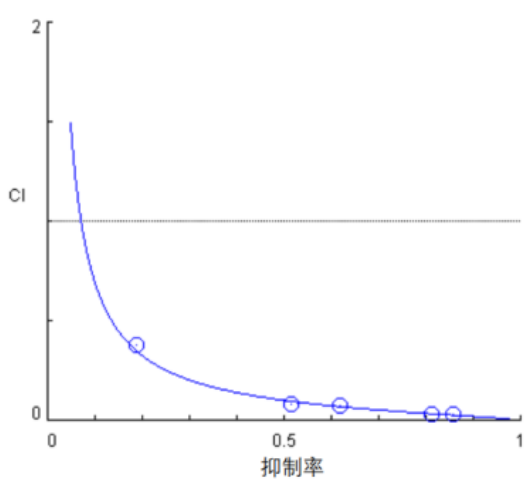


Fig. S12. HPLC of DT/PAC@AI.



	0.37695
	0.08509
	0.07554
	0.02962
	0.03254

Fig. S13. IRI, ATRA and PAC combined index (CI) at different concentration ratios.

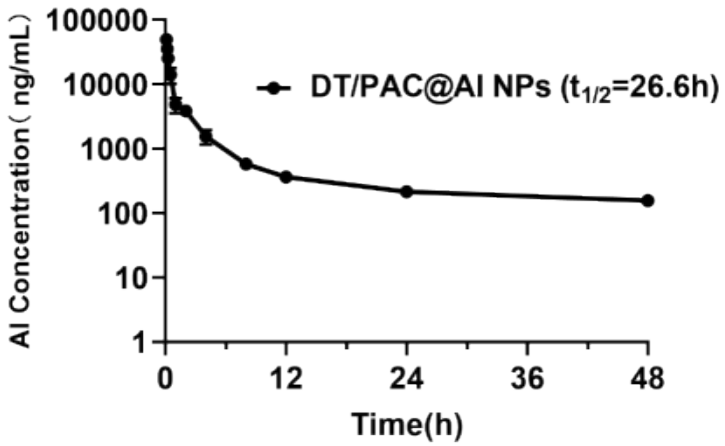


Fig. S14. *In vivo* pharmacokinetics in male SD rats following administration of DT/PAC@AI NPs (74.8 mg/kg; equiv. DT 7 mg/kg + PAC 53 mg/kg + AI 14.8 mg/kg). Data are mean ± SD (n = 3).

Table S1. Proportion of material used to prepare PAC@AI NPs.

	100 μL	-
	100 μL	25 μL
	100 μL	50 μL
	100 μL	100 μL

Table S2. Proportion of material used to prepare DT/PAC@AI NPs.

100 μL	50 μL	-
100 μL	50 μL	12.5 μL
100 μL	50 μL	25 μL
100 μL	50 μL	50 μL
100 μL	50 μL	100 μL
100 μL	50 μL	200 μL

Table S3. Particle size, PDI and potential of different ratios of PAC@AI NPs in water and PBS. Data are presented as mean ± SD. (n = 3).

		PDI in water	PDI in PBS		
99.95±5.16	94.06±7.46	0.1626±0.0352	0.1421±0.0327	60.63±5.09	16.11±1.80
119.0±1.19	98.23±1.11	0.1681±0.0170	0.1592±0.0182	33.10±2.86	2.737±1.51
112.9±0.85	104.1±5.17	0.1287±0.0539	0.1305±0.0545	37.39±1.94	7.507±3.24
128.8±5.92	113.6±3.95	0.1219±0.0334	0.1174±0.0354	32.77±2.59	1.980±1.98

Table S4. Particle size, PDI and potential of different ratios of DT/PAC@AI NPs in water and PBS. Data are presented as mean ± SD (n = 3).

		PDI in water	PDI in PBS		
112.9±0.85	104.1±5.17	0.1287±0.0539	0.1305±0.0545	37.39±1.94	7.507±3.24
142.3±0.96	123.1±3.51	0.1405±0.0093	0.1503±0.0053	30.89±3.47	2.013±5.23
125.5±4.42	108.1±7.57	0.1390±0.0267	0.1846±0.0398	29.90±3.94	2.627±4.11
134.0±4.07	131.5±5.38	0.2165±0.0296	0.2195±0.0226	33.30±3.16	3.303±2.27
2586±448.90	500.5±120.30	0.3064±0.0551	0.3212±0.0295	33.23±1.14	0.6300±3.92
2479±359.10	1526±721.20	0.4001±0.1009	0.3692±0.0989	-13.60±0.97	-0.6567±1.14

Table S5. IC_{50} values of the different drugs in MDA-MB-231 cells under normoxic and hypoxic conditions. Data are presented as mean ± SD (n = 3).

>50	23.17 ±3.19	9.27±0.62	>50	>50	7.70 ±1.07	6.02±0.10	5.08±0.40	3.93±0.20
-	-	9.62±0.46	11.27 ±0.44	-	-	5.32±0.26	4.77±0.32	-

Table S6. Liver function (ALT, AST) and kidney function (BUN, CRE) markers from mouse serum. Data are presented as mean ± SD (n = 3).

SampleId	Range	G1	G2	G3	G4	G5	G6	G7
ALT（U/L）	10.06-96.47	45.33 ±2.89	43.33 ±11.72	39.33 ±5.86	60.00 ±8.19	46.00 ±1.73	29.33 ±2.31	66.67 ±3.51
AST（U/L）	36.31-235.48	131.33 ±10.97	112.67 ±10.69	87.33 ±13.2	181.67 ±18.82	140.67 ±19.6	90.67 ±14.57	130.67 ±9.61
BUN（mmol/L）	10.81-34.74	8.73 ±0.8	12.32 ±0.95	7.86 ±0.22	5.28 ±0.97	14.86 ±2.71	6.64 ±0.87	14.4 ±0.47
CRE（umol/L）	10.91-85.09	16.45 ±1.37	16.52 ±1.41	16.67 ±1.34	13.98 ±0.6	16.01 ±2.72	16.26 ±0.73	19.41 ±2.27