

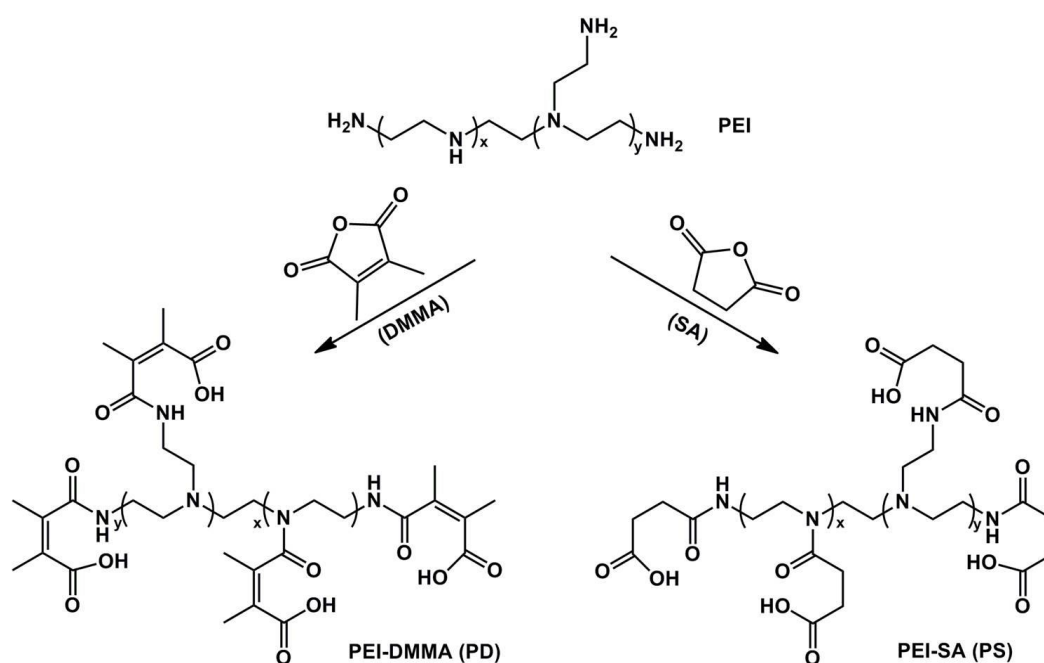
Supporting Information

Tumor acidity activated triphenylphosphonium-based mitochondrial targeting nanocarriers for overcoming drug resistance of cancer therapy

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Scheme S1. Synthesis of PEI-DMMA (PD) and PEI-SA (PS).

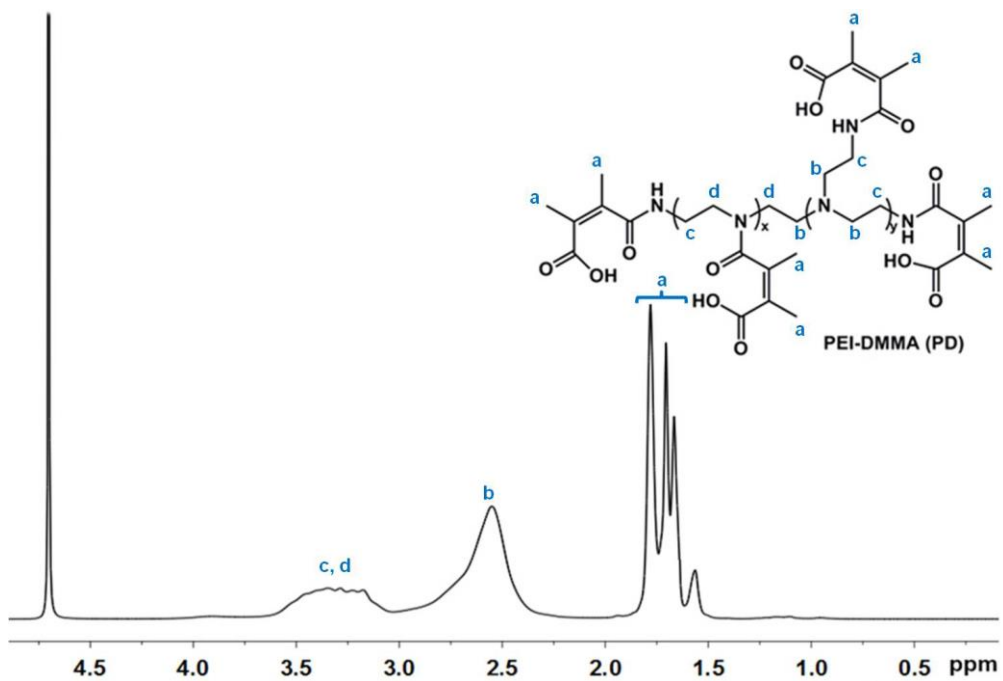


Figure S1. ^1H NMR spectrum (400 MHz, D_2O) of PEI-DMMA (PD).

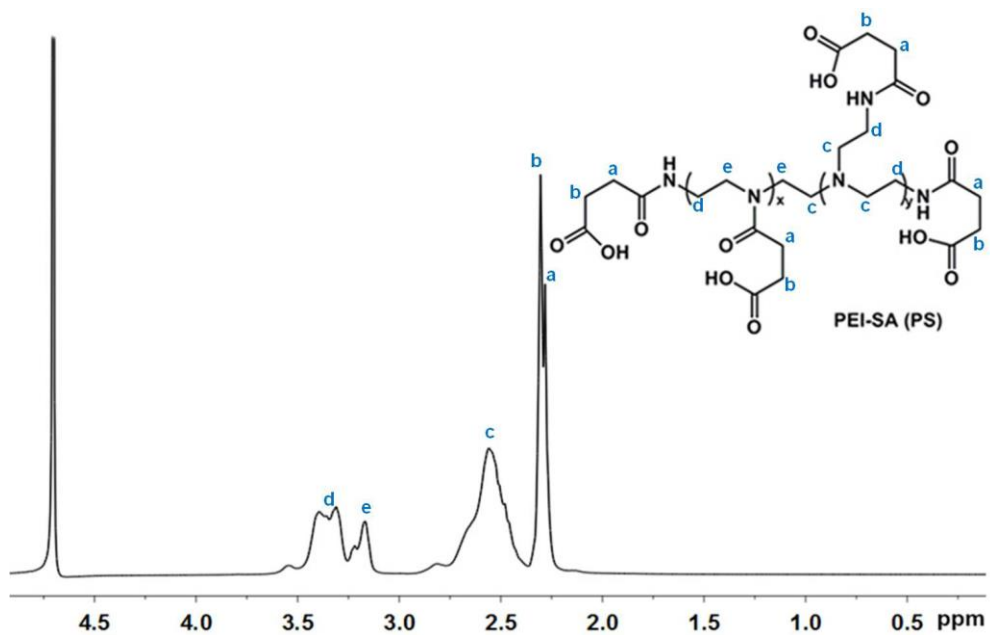


Figure S2. ^1H NMR spectrum (400 MHz, D_2O) of PEI-SA (PS).

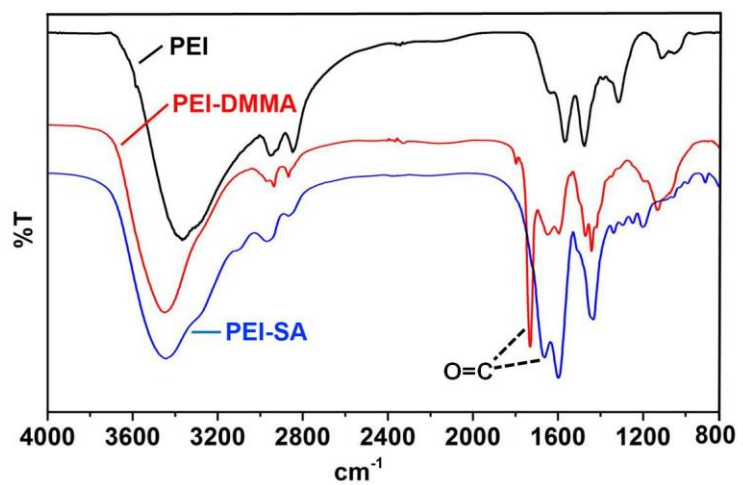


Figure S3. FT-IR spectra of PEI, PEI-DMMA (PD), and PEI-SA (PS).

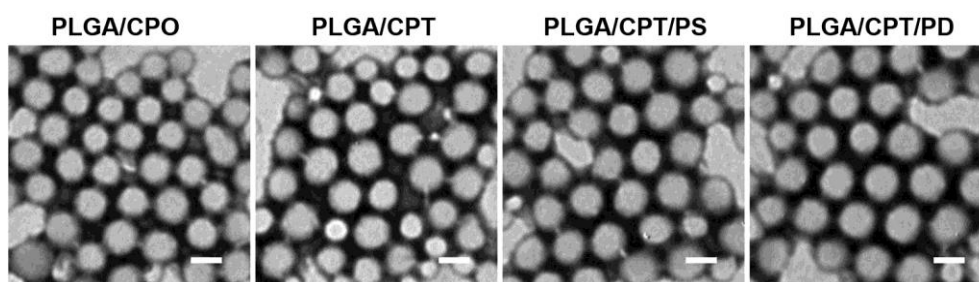


Figure S4 TEM images of LPNPs, scale bar = 100 nm.

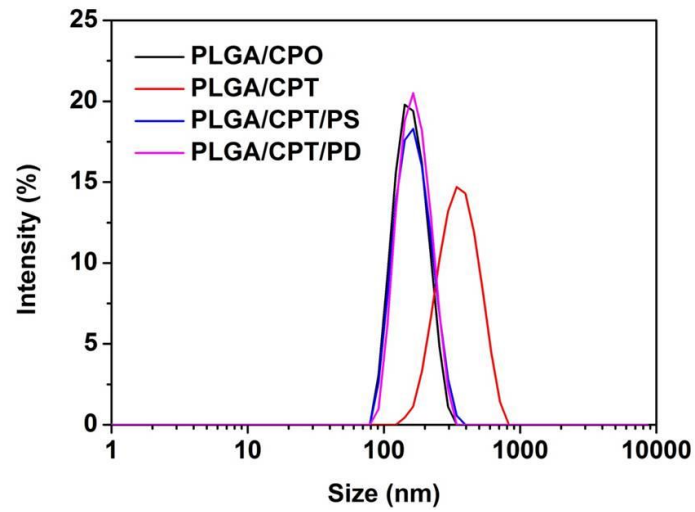


Figure S5. Hydrodynamic sizes of LPNPs in RPMI 1640 medium containing 10% fetal bovine serum (FBS).

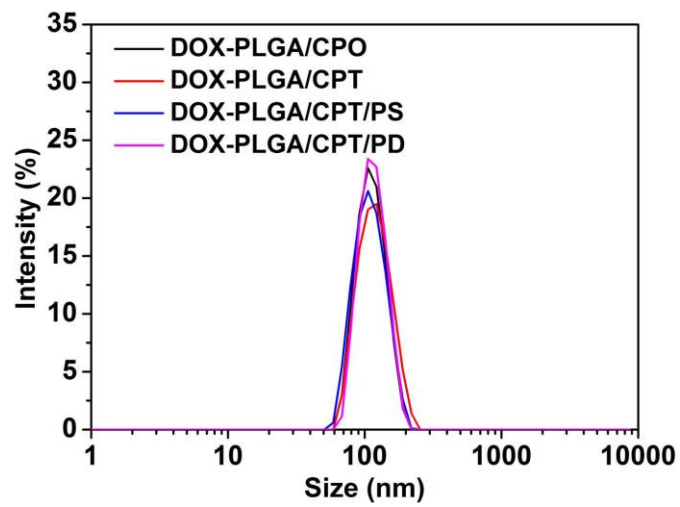
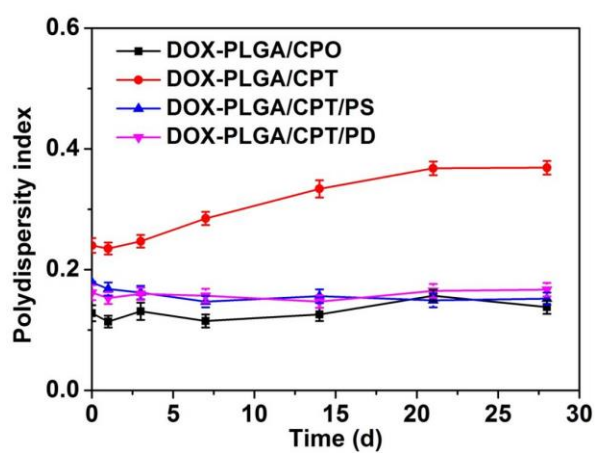


Figure S6. Hydrodynamic sizes of DOX loaded LPNPs in PBS.

Table S1. Characterization of LPNPs and DOX-LPNPs

Samples	LPNPs in PBS			LPNPs in RPMI 1640 medium			DOX-LPNPs in PBS			
	Size (nm)	PDI	Zeta potential (mV)	Size (nm)	PDI	Zeta potential (mV)	Size (nm)	PDI	Zeta potential (mV)	DLC (%)
PLGA/CPO	146.2	0.095	-18.3	151.7	0.132	-21.7	154.5	0.128	-16.6	6.10
PLGA/CPT	149.3	0.233	19.6	319.2	0.381	7.45	164.1	0.240	21.8	5.82
PLGA/CPT/PS	159.7	0.169	-31.2	164.9	0.152	-35.1	161.8	0.179	-32.8	5.39
PLGA/CPT/PD	156.6	0.124	-24.2	166.6	0.154	-29.6	162.7	0.162	-18.9	5.66

**Figure S7.** Polydispersity index (PDI) of DOX-LPNPs stored at 4 °C.

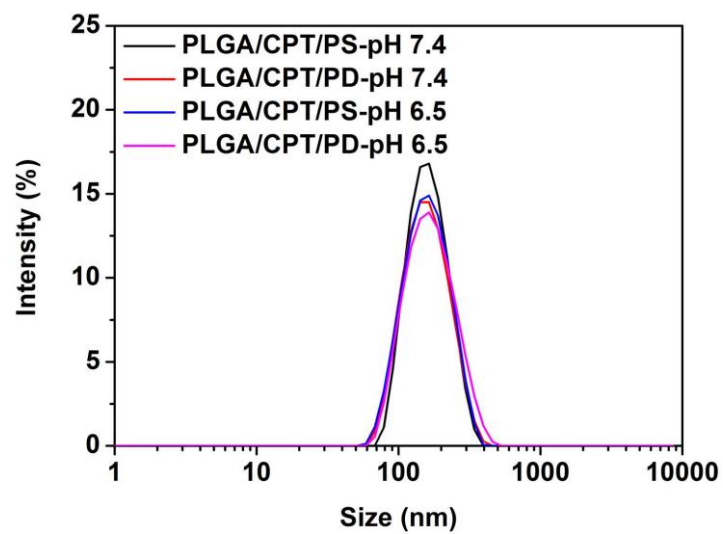


Figure S8. Sizes of PLGA/CPT/PS and PLGA/CPT/PD after separate treatment at pH 7.4 and pH 6.5 for 4 h.

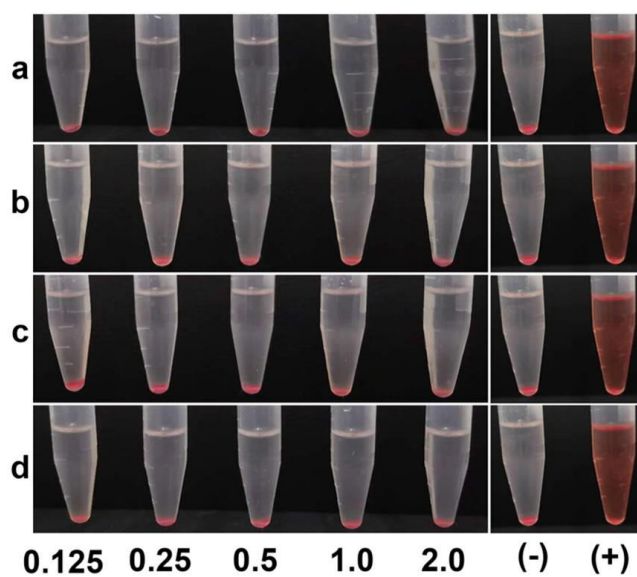


Figure S9. Photographs of hemolysis assay. a, PLGA/CPO; b, PLGA/CPT; c, PLGA/CPT/PS; d, PLGA/CPT/PD; (-), saline; (+), ultrapure water.

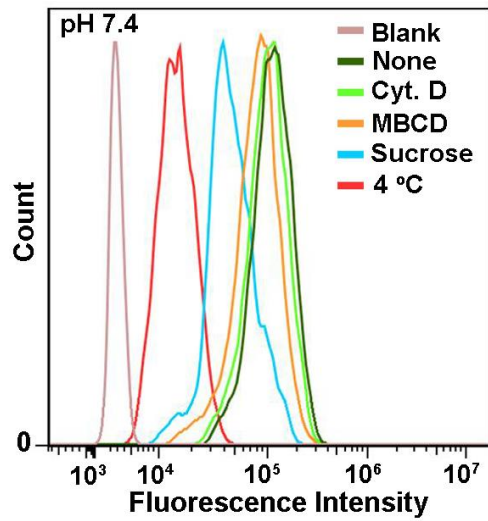


Figure S10. Cellular uptake mechanism analysis of DOX-PLGA/CPT/PD in MCF-7/ADR cells at pH 7.4.

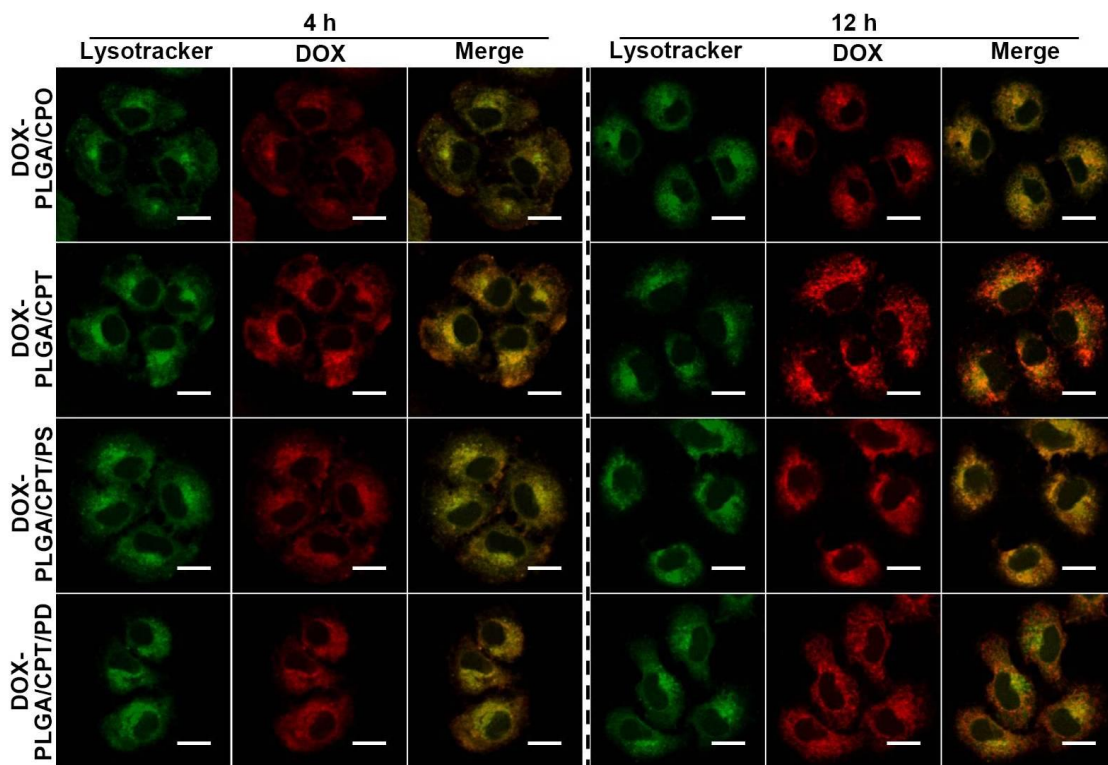


Figure S11. CLSM images of MCF-7/ADR cells after incubation with DOX-LPNPs for 4 h or 12 h at pH 7.4, scale bar = 20 μm .

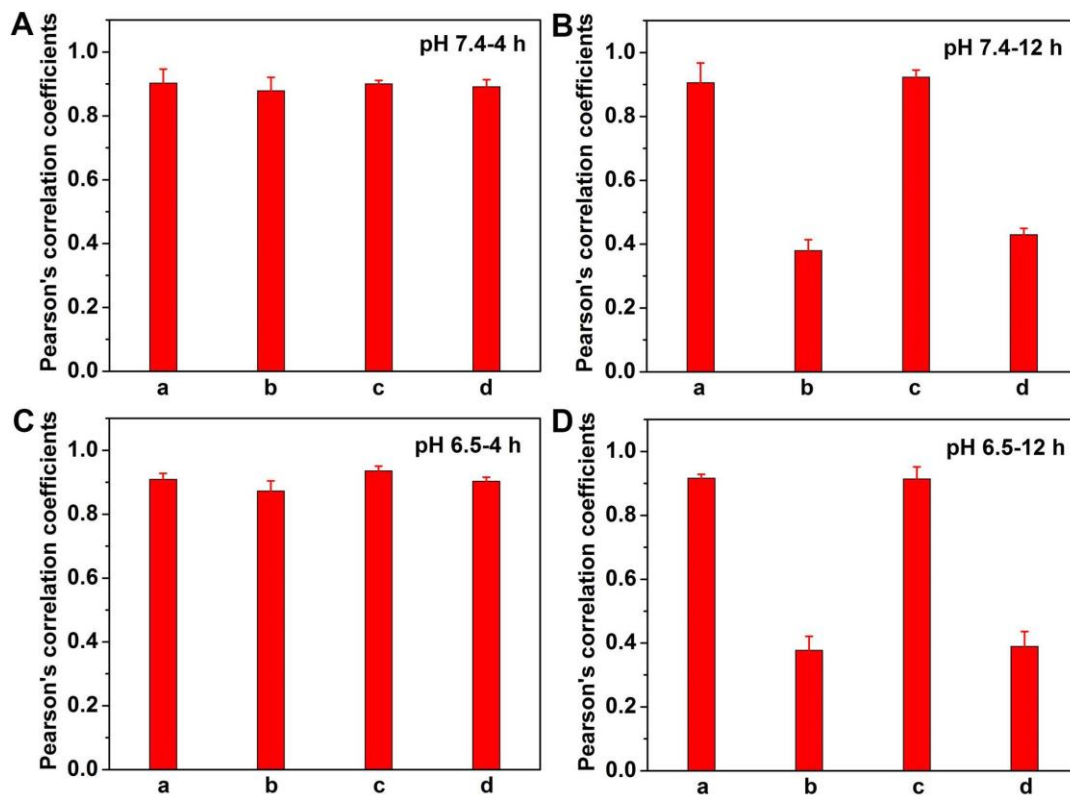


Figure S12. Pearson's correlation coefficients of green fluorescence from LysoTracker Green and red fluorescence from DOX. a, DOX-PLGA/CPO; b, DOX-PLGA/CPT; c, DOX-PLGA/CPT/PS; d, DOX-PLGA/CPT/PD.

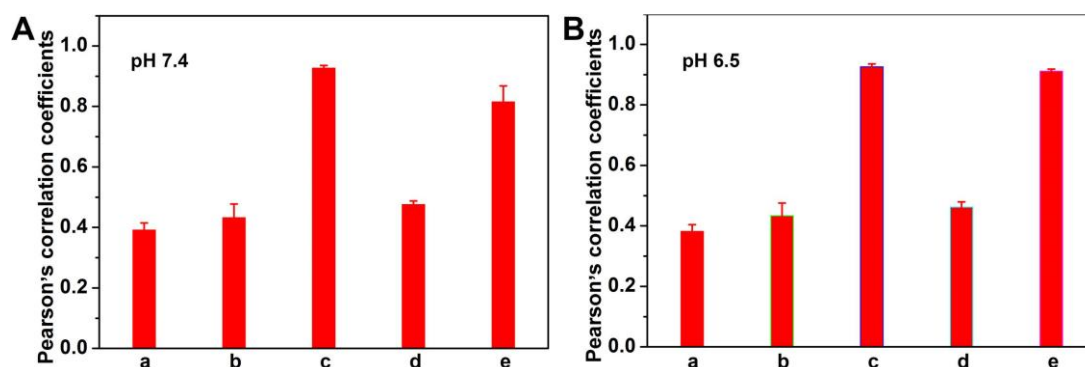


Figure S13. Pearson's correlation coefficients of green fluorescence from Mitotracker Green and red fluorescence from DOX. a, free DOX; b, DOX-PLGA/CPO; c, DOX-PLGA/CPT; d, DOX-PLGA/CPT/PS; e, DOX-PLGA/CPT/PD.

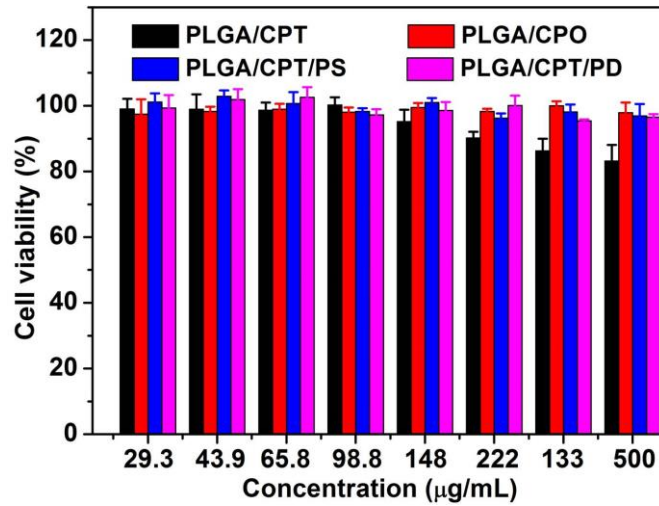


Figure S14. Cytotoxicity of LNPVs against COS 7 cells.

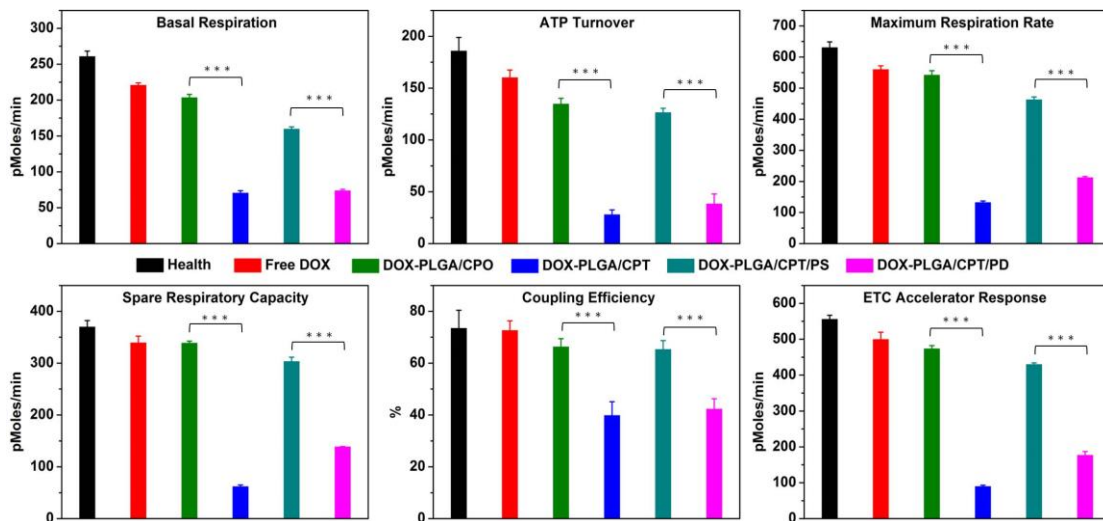


Figure S15. Comparison of basal respiration, ATP turnover, maximum respiration rate, spare respiratory capacity, coupling efficiency, and electron transport chain (ETC) accelerator response of MCF-7/ADR cells after treatment with or without DOX formulations at pH 6.5 for 24 h (mean \pm S.D, n=3), ***P < 0.001.

Table S2. Pharmacokinetic parameters of free DOX and DOX-LPNPs after intravenous injection at a dose of 5 mg DOX per kg body weight (n = 3).

Parameters	Free DOX	DOX-PLGA/CPT	DOX-PLGA/CPO	DOX-PLGA/CPT/PS	DOX-PLGA/CPT/PD
$t_{1/2Z}$	2.71	4.13	16.92	18.82	15.84
$AUC_{0-\infty}$	25.09	35.90	112.79	122.35	109.60
$MRT_{0-\infty}$	3.81	4.24	16.59	17.02	10.06
CL_Z	223.69	199.25	55.80	44.33	65.88

Parameters and units: half-life ($t_{1/2Z}$, h); area under the curve ($AUC_{0-\infty}$, mg/L×h); mean residence time ($MRT_{0-\infty}$, h); total body clearance (CL_Z , L/h/kg).

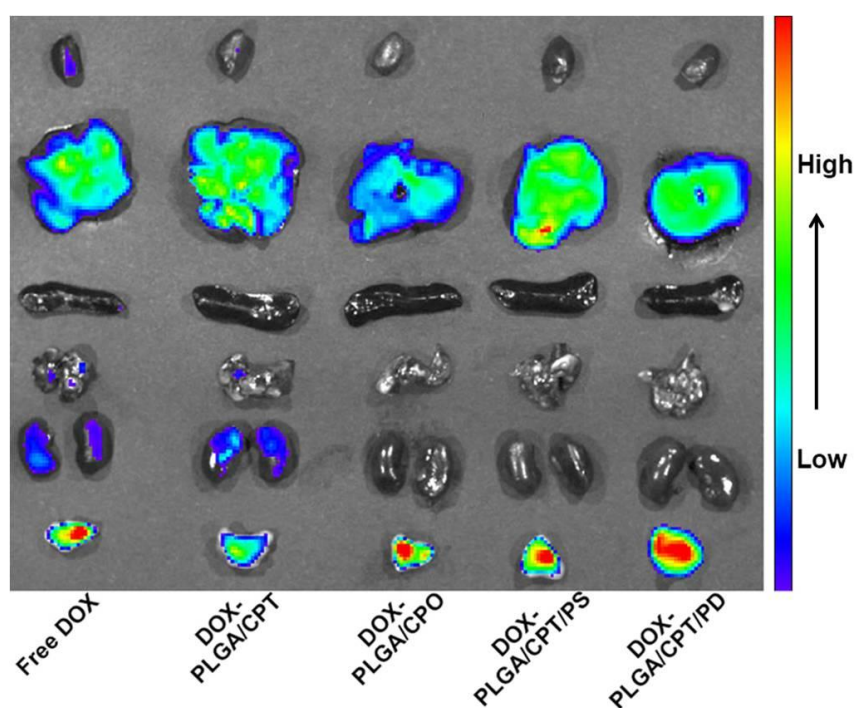


Figure S16. Fluorescence image of heart, liver, spleen, lung, kidney, and tumor of MCF-7/ADR tumor-bearing mice after intravenous injection for 24 h.

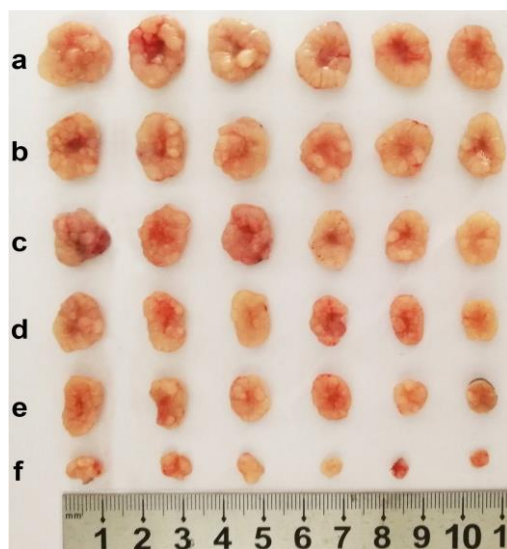


Figure S17. Tumor images on the 18th day after various treatments. a, PBS; b, free DOX; c, DOX-PLGA/CPT; d, DOX-PLGA/CPO; e, DOX-PLGA/CPT/PS; f, DOX-PLGA/CPT/PD.

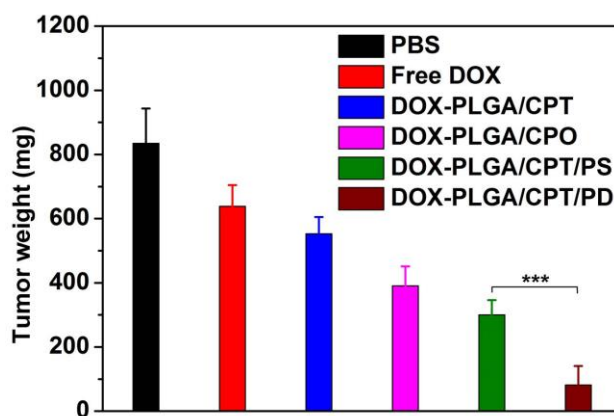


Figure S18. Weights of MCF-7/ADR tumors after various treatments for 18 days (mean \pm S.D, n=3), ***P < 0.001.

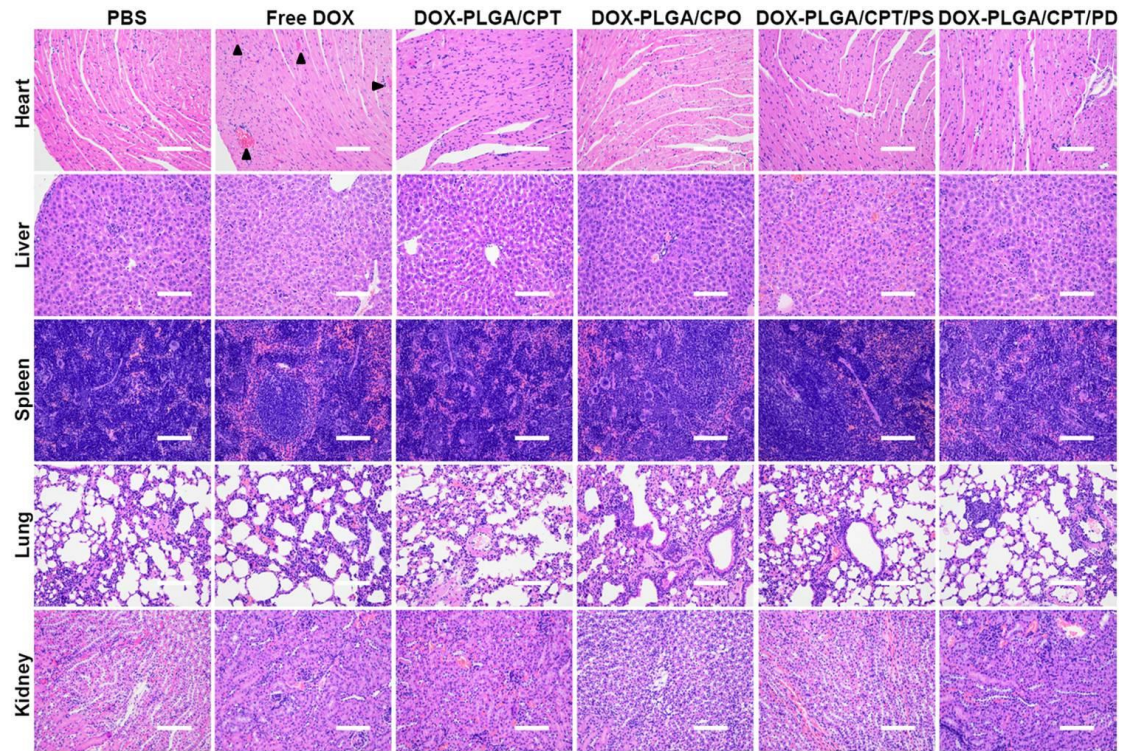


Figure S19. H&E staining analysis of main organs after treatment with PBS, free DOX, DOX-PLGA/CPT, DOX-PLGA/CPO, DOX-PLGA/CPT/PS, and DOX-PLGA/CPT/PD for 18 days, scale bar = 100 μ m.