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Supporting Information

Dual-Responsive Polyphosphazene as a Common Platform for Highly Efficient Drug Self-Delivery

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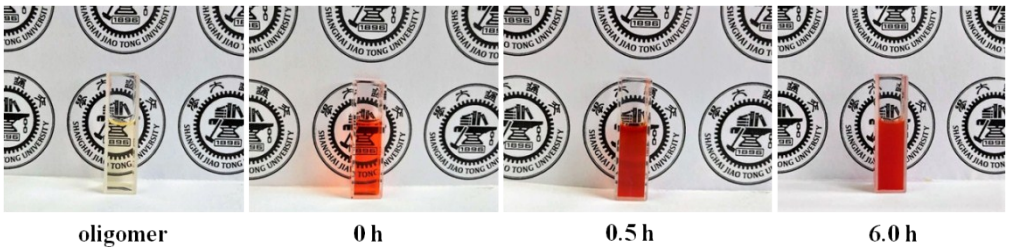

Figure S1. Photographs of HCCP-CysM oligomer solution, and the reaction mixture after 0 h, 0.5 h, and 6.0 h.

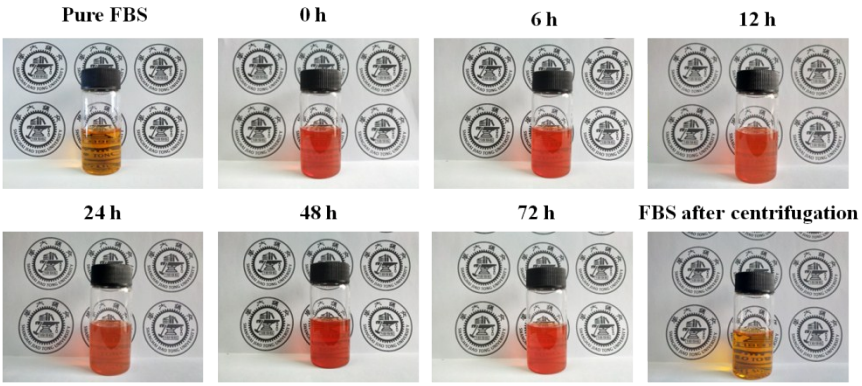

Figure S2.Photographs of pure PBS, DOX-CysM-CPPZ NPs dispersed in FBS for 0 h, 6 h, 12 h, 24 h, 48 h and 72 h and PBS after centrifugation.

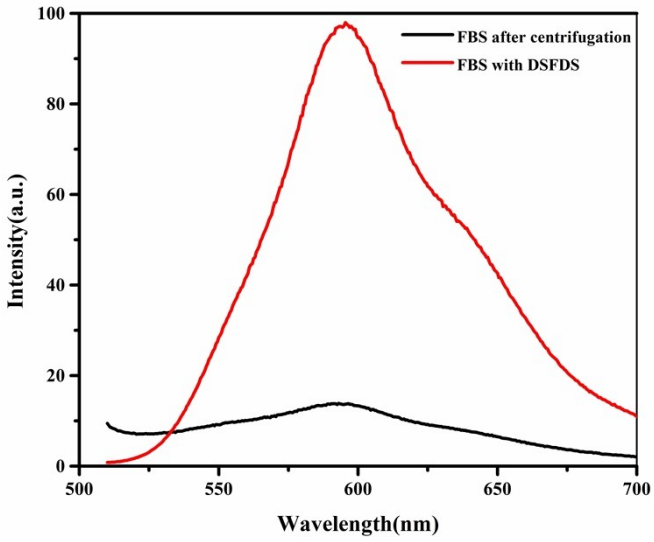

Figure S3. The luminescence spectrum of FBS with DFSDS and FBS after removing DFSDS.

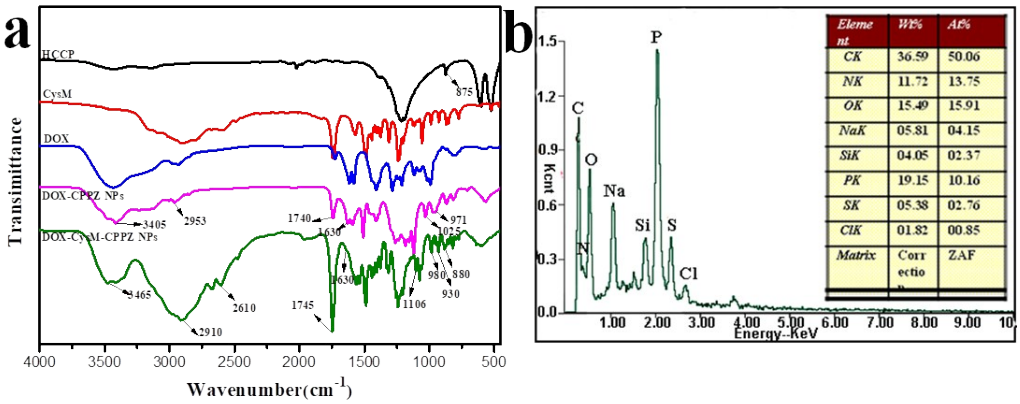

Figure S4. a) FTIR spectra of free DOX, HCCP, DOX-CPPZ NPS, and DOX-CysM-CPPZ NPs. b) EDX spectrum and element contents of the DOX-CysM-CPPZ NPs.

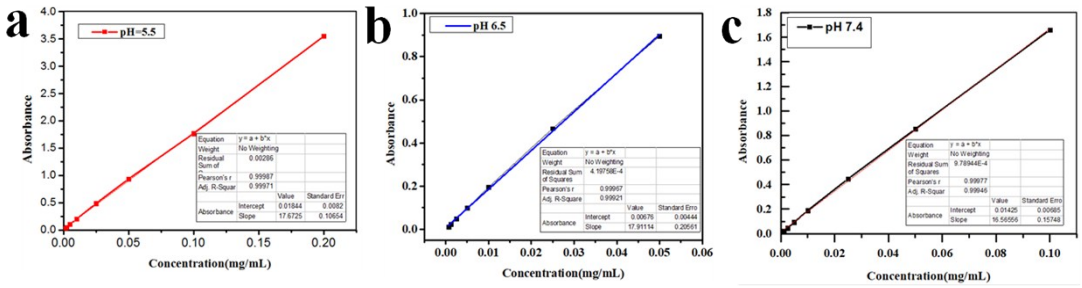

Figure S5. Standard curves of UV absorbance at 480 nm versus concentration of free DOX at pH 5.5 (a), 6.5 (b), and 7.0 (c).

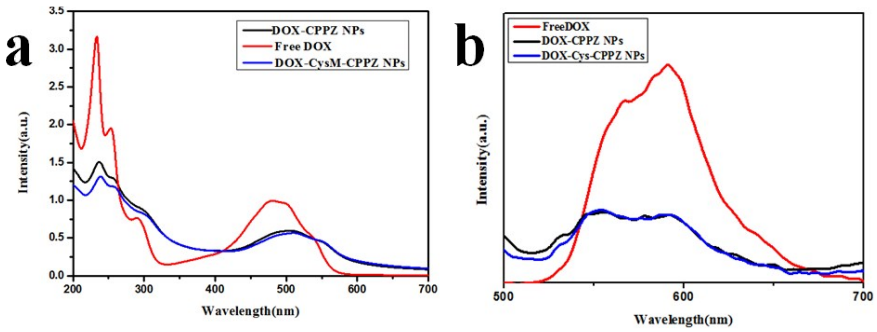

Figure S6. UV/Vis spectra (a) and luminescence spectra (b) of free DOX, DOX-CPPZ NPs, and DOX-CysM-CPPZ NPs.

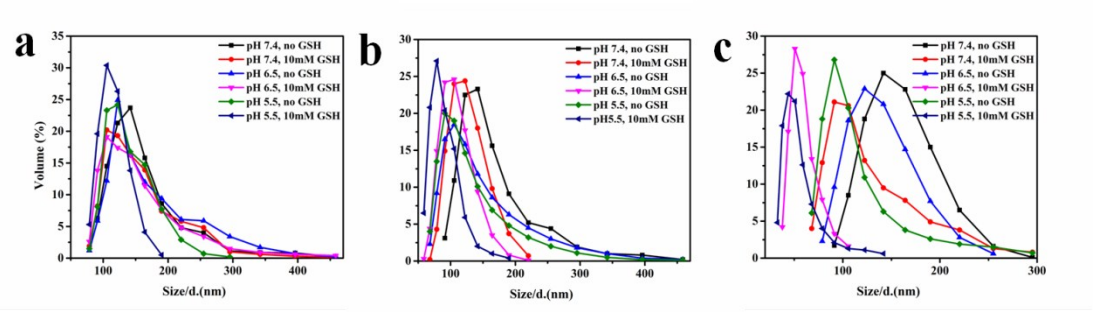

Figure S7. DLS data of DOX-CysM-CPPZ NPs during degradation processes in pH 7.4, 6.5 and 5.5 PBS with 10 mM GSH or not after a) 1 day, b) 2 days, and c) 3 days.

Table S1. DLS data of DOX-CysM-CPPZ NPs during degradation processes in DI water, pH 7.4, 6.5, 5.5, and 4.0 PBS after 1 day, 2 days, and 3 days. Drug release rates calculated from particle size change.

	GSH (mM)	pH 7.4			pH 6.5			pH 5.5		
		VRR(%)[a]	PZ(nm)[b]	PDI [c]	VRR (%)	PZ(nm)	PDI	VRR (%)	PZ(nm)	PDI
1D	0	5.8	129.9	0.201	27.1	119.2	0.210	38.6	112.6	0.155
	10	52.5	103.4	0.268	59.2	98.3	0.263	68.6	90.1	0.094
2D	0	NA	137.2	0.217	29.6	117.9	0.297	41.0	111.1	0.264
	10	59.2	98.5	0.152	63.7	94.5	0.127	77.3	80.888	0.075
3D	0	NA	148.3	0.144	31.9	116.2	0.241	43.2	109.7	0.199
	10	58.9	95.4	0.208	63.7	89.4	0.108	86.4	66.5	0.118

[a)] (Volume Release Rate); [b)] (Particle Size); [c)] (Polydispersity Index)

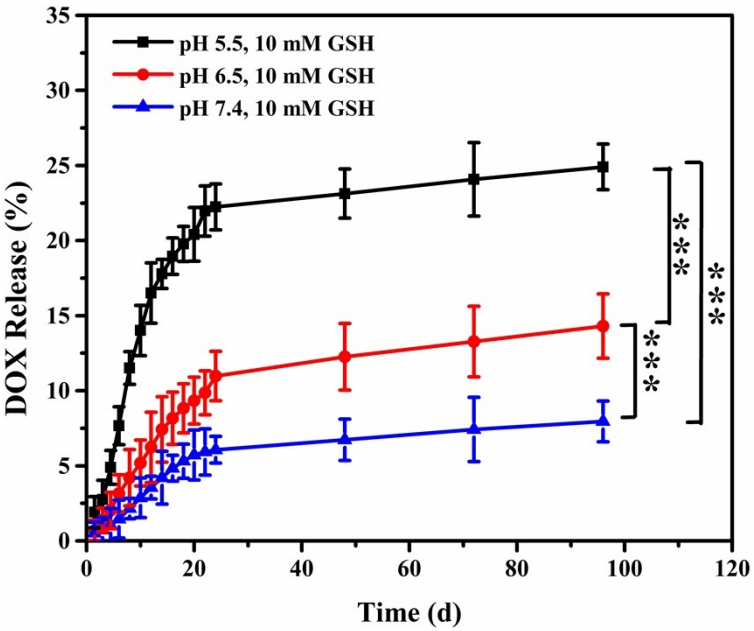

Figure S8. DOX release from DOX-CPPZ NPs triggered at different pH values and 10 mM GSH.

TEM characterization of DSFDs in cells: HeLa cells were seeded in a culture dish of diameter 60 mm (Corning) and cultured overnight for cell attachment. They were then incubated with DOX-CysM-CPPZ NPs (2.56 μg mL^{-1}) in FBS-free culture medium for 12 h. For TEM analysis, HeLa cells were washed with PBS and then fixed with 2% glutaraldehyde and 1% osmium tetroxide for 2 h at 48 °C. They were then dehydrated in a graded series of ethanolic media (30, 50, 70% with 3% uranyl acetate, 80, 95, and 100%) for 10 min at each concentration, followed by two replacements of the medium with 100% propylene oxide. After infiltration and embedding in epoxy resin at 60 °C for 48 h, the sections were stained with lead citrate and investigated by TEM.

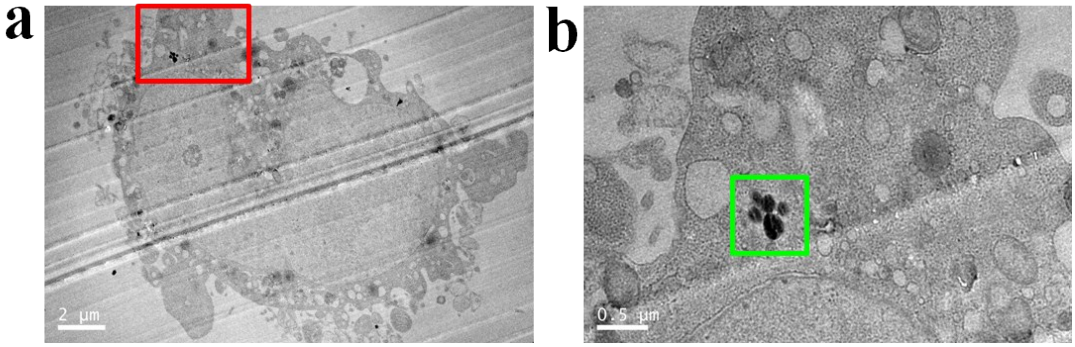

Figure S9. TEM images of an HeLa cell after incubation with DOX-CysM-CPPZ NPs (2.56 μg mL−1) in FBS-free culture medium for 12 h. a) TEM image of a single HeLa cell, b) high magnification image of the area within the red box in a). Scale bars: a) 2 μm, b) 0.5 μm.

Synthesis of CysM-CPPZ NPs: CysM-CPPZ NPs was prepared according to a previously published procedure.[1] HCCP (0.5 g), CysM (0.48 g), and TEA (3 mL) were dissolved in MeCN (30 mL), and the solution was stirred for 6 h at room temperature. When the reaction was complete, the mixture was centrifuged (10,280 rpm for 2 min) and the supernatant was removed and collected. 10 mL of each of the PN-CysM oligomer solution was injected into a 50 mL round-bottom flask. 12 mL deionized water was added dropwise to reach the LCSP over 5 min under stirring conditions. The white solid was collected by centrifugation and washed three times with deionized water and alcohol successively

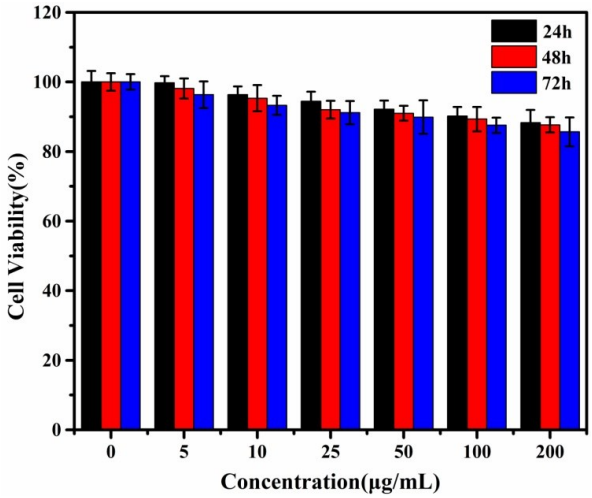

Figure S10. Clone 8 fibroblasts viability after 24, 48, and 72 h incubation with different concentrations of CysM-CPPZ NPs.

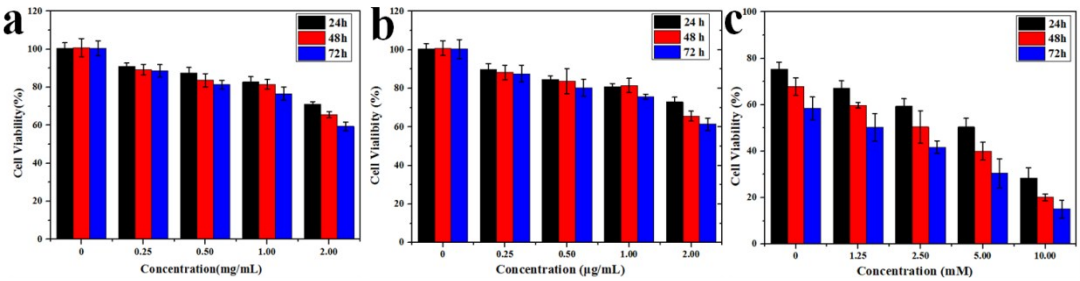

Figure S11. Killing efficiencies of (a) DOX-CPPZ NPs and (b) DOX-CysM-CPPZ NPs towards NEM-treated HeLa cells after 24, 48, and 72 h incubation with different equivalent concentrations of DOX). c) Killing efficiencies of DOX-CysM-CPPZ NPs (illustrated using 2 μg mL^{-1} DOX) towards HeLa cells treated with different concentrations of GSH-OEt, after 24, 48, and 72 h of incubation.

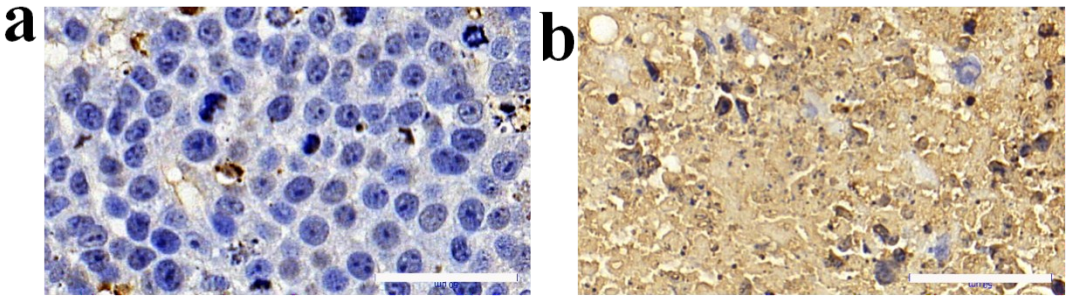

Figure S12. Enlarged immunohistochemical images of tumor issue. Tumor biopsies for TUNEL assay from a) the PBS treatment group and b) the DOX-CysM-CPPZ NPs treatment group. Scale bar is 50 µm.

1. Z. Huang, S. Chen, X. Lu and Q. Lu, *Chem Commun* **2015,** *51*, 8373-8376.