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Supporting information

A tumor-sensitive biological metal-organic complex for drug delivery and cancer therapy

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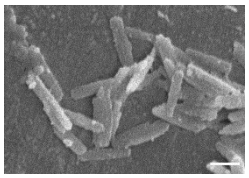
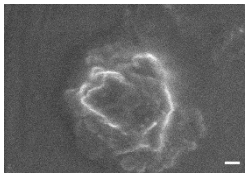
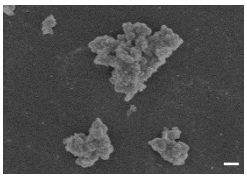
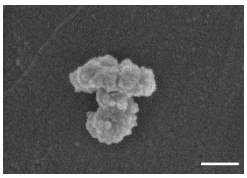
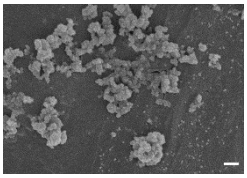
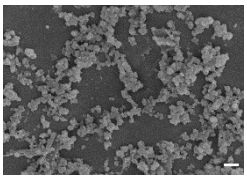
Table S1. bioMOC-Fe(Cys) synthesized at different temperatures

Temperature (°C)	SEM/TEM [a]	Morphology	Average Size (nm)
40		nanorod	L=380 ± 7.8 W=60~100 [b]
60		amorphous cluster	1400 ± 15.5 [c]
80	N.D.	N.D.	N.D.
120	N.D.	N.D.	N.D.
150	N.D.	N.D.	N.D.

[a] Scale bars = 200 nm. [b] Statistical analysis of TEM/SEM images, L: length, W: width.
[c] Measured using DLS.

Table S2. bioMOC-Zr(Cys) synthesized at different temperatures

Temperature (°C)	SEM/TEM [a]	Morphology	Average Size (nm)
40		amorphous cluster	695 ± 9.8 [b]
60		amorphous cluster	689 ± 8.7 [b]
80		amorphous cluster	567 ± 4.5 [b]
120		amorphous cluster	301 ± 3.9 [b]
150	N.D.	N.D.	N.D.

[a] Scale bars = 200 nm. [b] Measured using DLS.

Table S3. Comparison of the cumulative amount of drug released from some GSH-sensitive NDDSs

NDDSs	Cumulative release (%)		Release time (h)	Reference
	No GSH (pH 7.4)	10 mM GSH (pH 7.4)		
TTMOF	16.5	78.5	140	Wang *et al.*[1]
ZDOS NPs	17.5	38.5	48	Ren *et al.*[2]
Mn-SS/DOX@PDA-PEG	18.5	45.5	24	Zhao *et al.*[3]
MSN-ss-GHA	11.77	51.1	60	Chen *et al.*[4]
MOF-Zr(DTBA)	50	87.4	22	Lei *et al.*[5]
bioMOC-Zn(Cys)	8.25	83.3	48	**This study**

Table S4. Comparison of the cytotoxicity of MOF-based drug carriers

Carriers	Cells	Concentration (μg/mL)	Incubation time (h)	Cell viability (%)	Reference
ZJU-101	PC12	200	24	80.0	Yang *et al.*[6]
PCN-221	PC12	100	24	90.0	Lin *et al.*[7]
Fe-MIL-53-NH_2 -FA-5-FAM	HASMC	200	24	84.5	Gao *et al.*[8]
	MGC-803	200	24	78.5	
ZIF-8	HeLa	100	48	83.5	Ren *et al.*[2]
	MCF-7	100	48	82.5	
MOF-Zr(DTBA)	HeLa	200	24	70.5	Lei *et al.*[5]
	MDA-MB-231	200	24	80.5	
bioMOC-Zn(Cys)	A549	200	24	97.7	**This study**
	BEAS-2B	200	24	93.9	

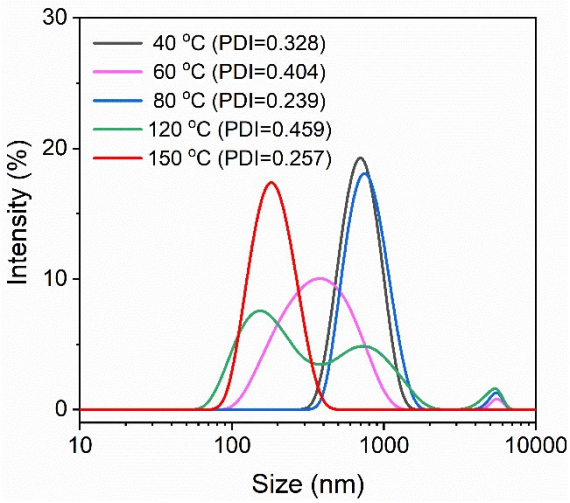


Figure S1. The DLS analysis of bioMOC-Zn(Cys) synthesized at different temperatures.

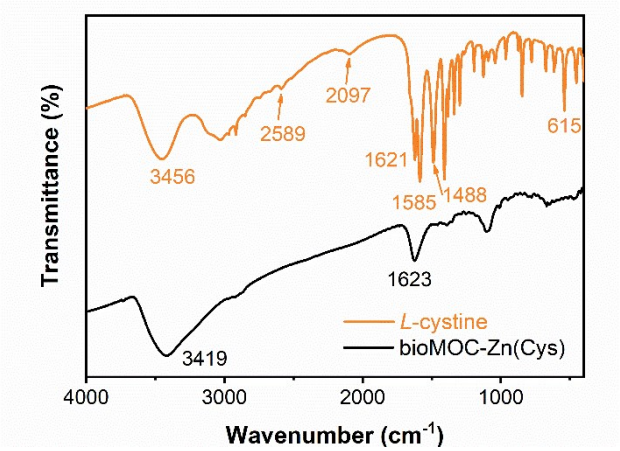


Figure S2. FTIR spectra of *L*-cystine and the bioMOC-Zn(Cys) nanocarrier synthesized at 150 °C.

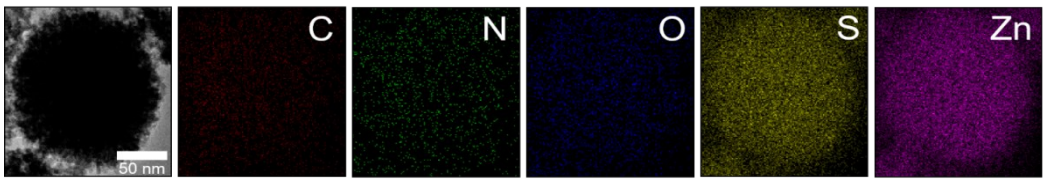


Figure S3. Elemental mapping images of a bioMOC-Zn(Cys) nanoparticle.

Figure S4. Photographs of lyophilized bioMOC-Zn(Cys) and DOX@bioMOC-Zn(Cys) powders.

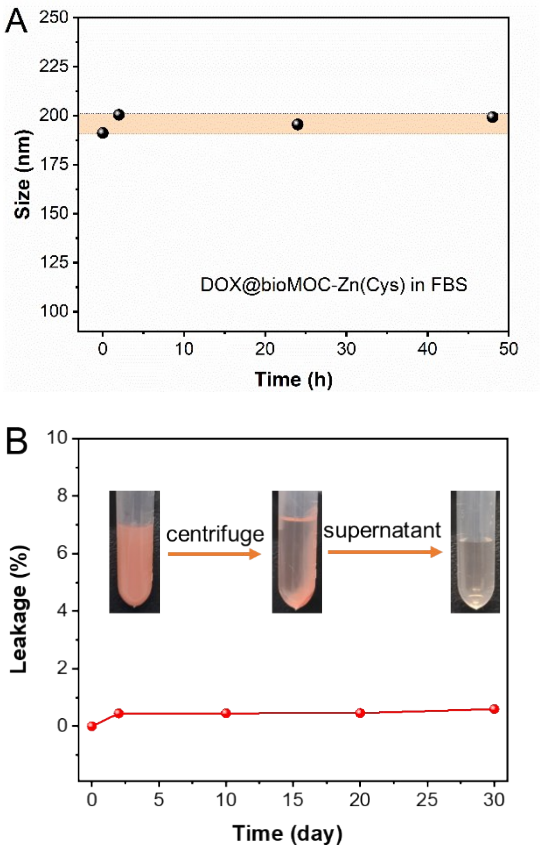


Figure S5. Hydrodynamic diameters of DOX@bioMOC-Zn(Cys) incubated in 20% FBS (A). Drug leakage from DOX@bioMOC-Zn(Cys) during 30 days of storage in deionized water at 4 °C (B).

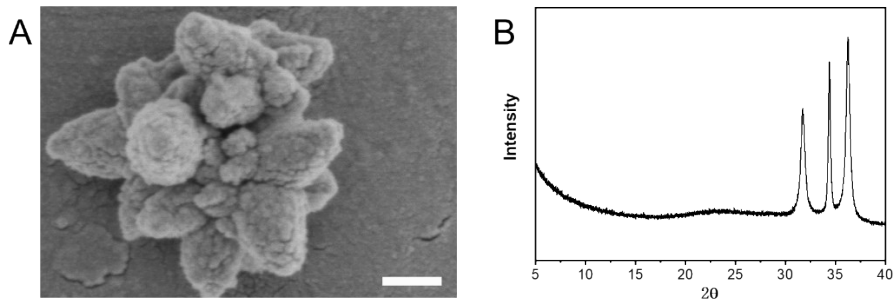


Figure S6. (A) SEM image of a bioMOC-Zn(Lys) particle. Scale bar =200 nm. (B) PXRD analysis of bioMOC-Zn(Lys).

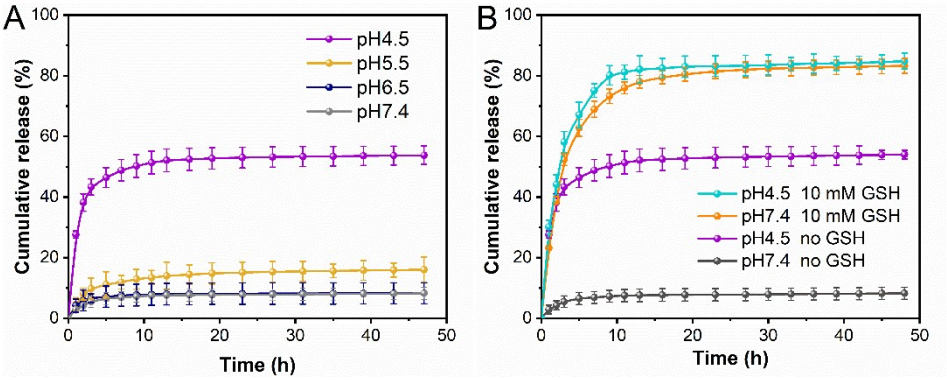


Figure S7. Drug release from DOX@bioMOC-Zn(Cys) in PBS at different pH values (A). Drug release from DOX@bioMOC-Zn(Cys) in PBS (pH 7.4 or pH 5.5) with and without GSH (B).

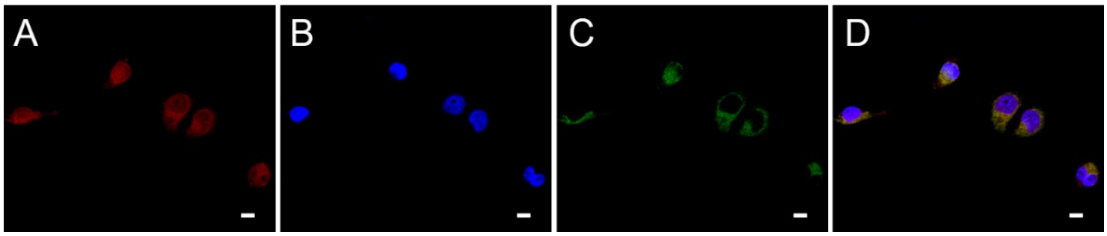


Figure S8. CLSM images of A549 cells after a 4 h incubation with DOX@bioMOC-Zn(Cys). (A) Red fluorescence of DOX, (B) cell nuclei stained with DAPI, (C) late endosomes and lysosomes stained with LysoTracker Green and (D) merged image (scale bars: 10 μm)

Confocal laser scanning microscopy (CLSM) analyses were used to investigate the endocytosis of DOX@bioMOC-Zn(Cys) in human lung cancer cells (A549 cells). The intrinsic red fluorescence of DOX was used to monitor the intracellular distribution of DOX@bioMOC-Zn(Cys). The blue fluorescence indicated the cell nuclei stained with DAPI. Late endosomes and lysosomes were stained with LysoTracker Green. As shown in **Figure S8**, the red fluorescence overlapped with both the green (endosomes and lysosomes) and blue areas (nuclei) in cells that had been exposed to DOX@bioMOC-Zn(Cys) for 4 h. Thus, DOX@bioMOC-Zn(Cys) was taken up by A549 cells via endocytosis, and the drug that accumulated in endosome/lysosomal compartments was further delivered to the cell nucleus.

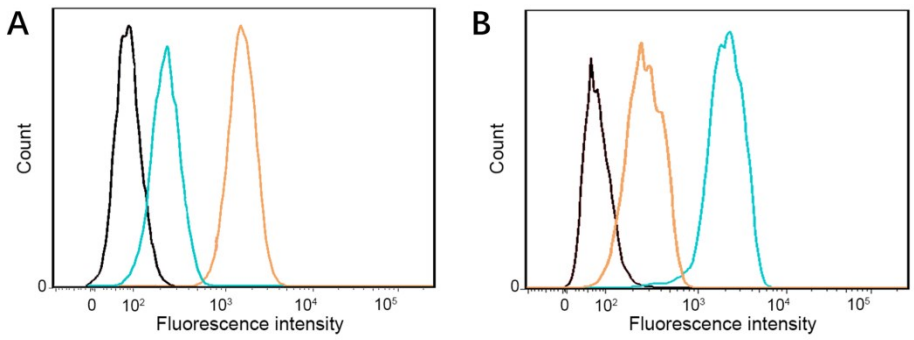


Figure S9. Flow cytometry analysis of A549 cells (A) and BEAS-2B cells (B) after a 0.5-h treatment with free DOX (cyan), DOX@bioMOC-Zn(Cys) (orange) or the blank (black).

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