Supporting Information

Redox-responsive Nanocarier Based on Heparin End-capped Mesoporous Silica Nanoparticles for Targeted Tumor Therapy *in Vitro* and *in Vivo*

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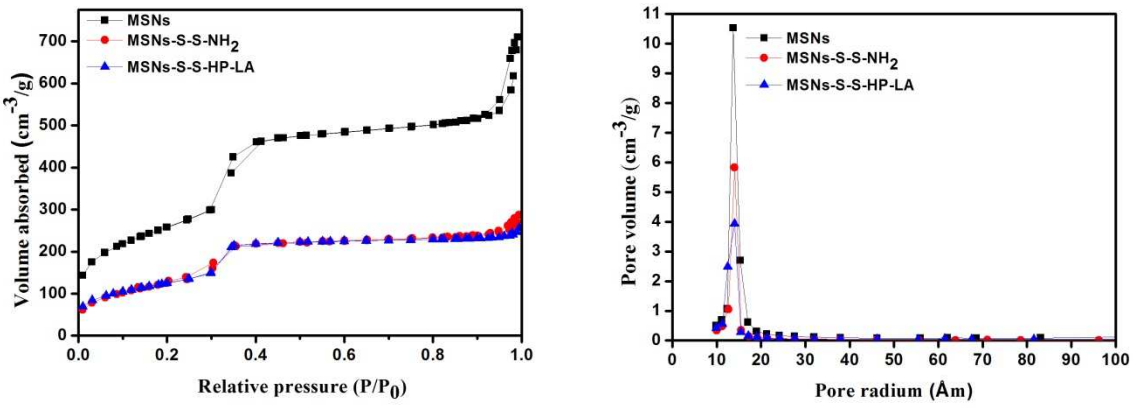


(A) **(B)**

Figure S1. BET N_2 adsorption/desorption isotherms (A) and BJH pore sizes distributions (B) of MSNs, MSNs-S-S-NH_2 and MSNs-S-S-HP-LA, respectively.

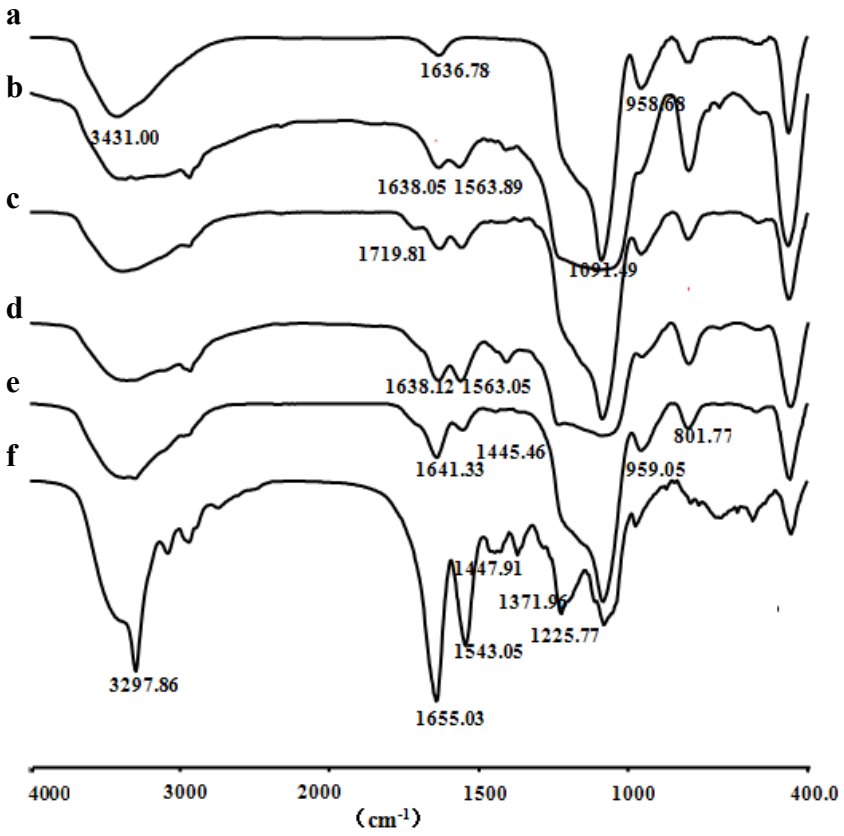


Figure S2. FTIR spectra of (a) MSNs, (b) MSNs-NH_2, (c) MSNs-COOH, (d) MSNs-S-S-NH_2, (e) MSNs-S-S-HP and (f) MSNs-S-S-HP-LA, respectively.

MSNs displayed strong absorption signals at 962 cm^{-1} and 1092 cm^{-1}, which were assigned to skeletal vibration of the C-O bonds, stretching and asymmetric stretching of Si-O-Si bridges, respectively. Peaks at 3431 cm^{-1} and 1636 cm^{-1} were attributed to physically adsorbed water molecules in MSNs (Figure S2 a). Compared to MSNs, MSNs-NH_2 displayed additional peaks at 1638 cm^{-1} and 1563 cm^{-1} (Figure S1 b), which were assigned to the stretching vibration of amide Ⅰ and -NH_2 bending, respectively. The result suggests that amino-functionalization of MSNs

was successfully achieved. Following modification with succinic anhydride, distinctive absorption peak at 1719 cm^{-1} (C=O) was observed (Figure S1 c). The intensity of the peak at 3400 cm^{-1} increased due to the introduction of carboxyl groups deriving from succinic anhydride (MSNs-COOH). After modification with cystamine dihydrochloride, no carboxyl groups signals (around 1719 cm^{-1}) were observed in the spectrum of disulfide bond-linked MSNs-COOH (MSNs-S-S-NH_2) (Figure S1 d). The intensities of peaks at 1638 cm^{-1} and 1556 cm^{-1} increased since more amide Ⅰ and amide Ⅱ groups were introduced after reacting with cystamine. The results indicate that disulfide bonds were covalently formed on MSNs. After covalently coupling with heparin, the distinctive characteristic absorption peaks at 959 cm^{-1}, 801 cm^{-1} and 1445 cm^{-1} were observed from the spectrum of MSNs-S-S-HP (Figure S1 e). The peak at 1445 cm^{-1} was assigned to SO_3^{2-} stretching vibration. Compared to MSNs-S-S-HP, the intensities of amide Ⅰ (1655 cm^{-1}) and OH (3297 cm^{-1}) increased after LA coupling to MSNs-S-S-HP. Moreover, the amide Ⅰ peak of MSNs-S-S-HP-LA slightly shifted from 1655 cm^{-1} to 1641 cm^{-1} (Figure S1 f), which was consistent with a previous study. [1] All results suggest that MSNs-S-S-HP-LA was successfully synthesized.

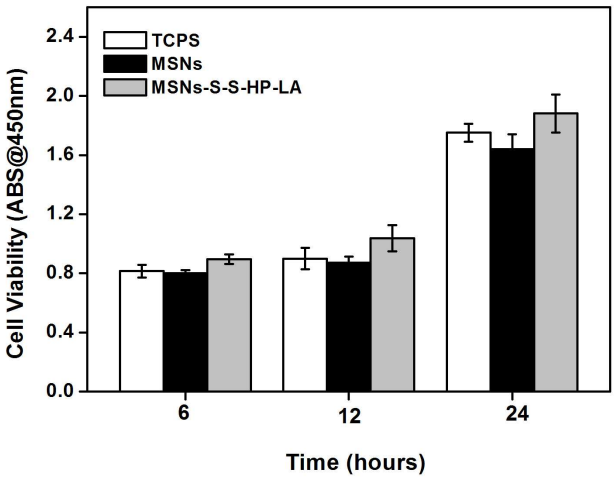


Figure S3. Cell viability of HepG2 treated with MSNs and MSNs-S-S-HP-LA (0.4 mg/mL) as comparing with TCPS (control).

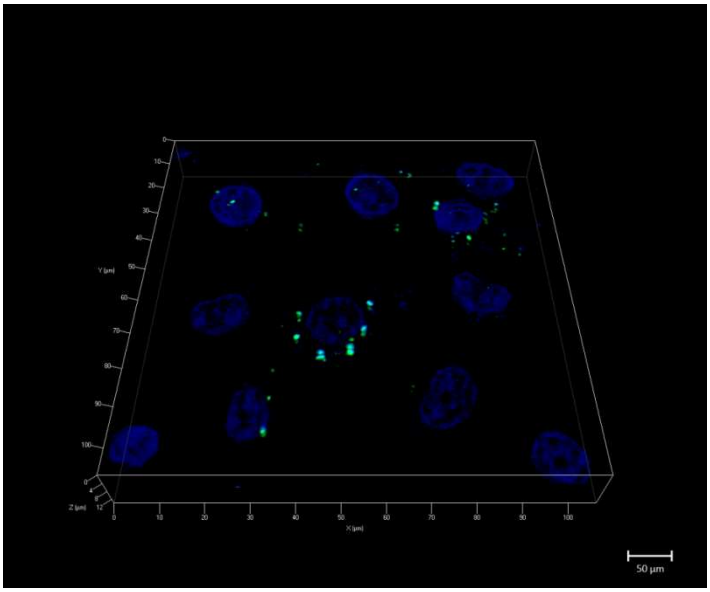


Figure S4. 3D reconstructed image of MSNs-S-S-HP-LA@FITC within HepG2 cells. Scar bar: 50 µm.

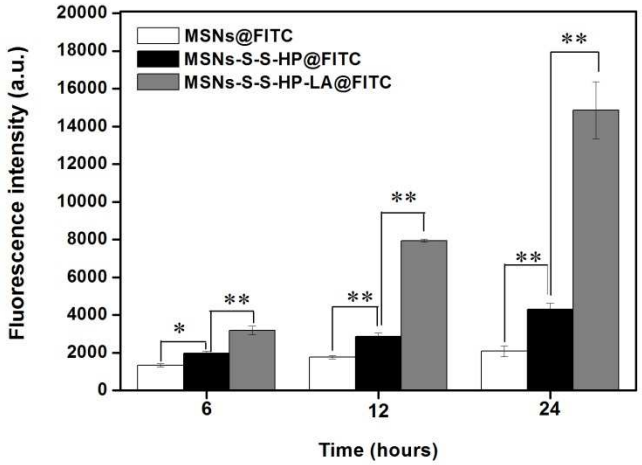


Figure S5. Fluorescence intensity analysis of FITC in HepG2 cells after treating with MSNs@FITC, MSNs-S-S-HP@FITC, and MSNs-S-S-HP@FITC for 6, 12 and 24 h, respectively. Error bars represent means ± SD (n=3), *$p < 0.05$, **$p < 0.01$.

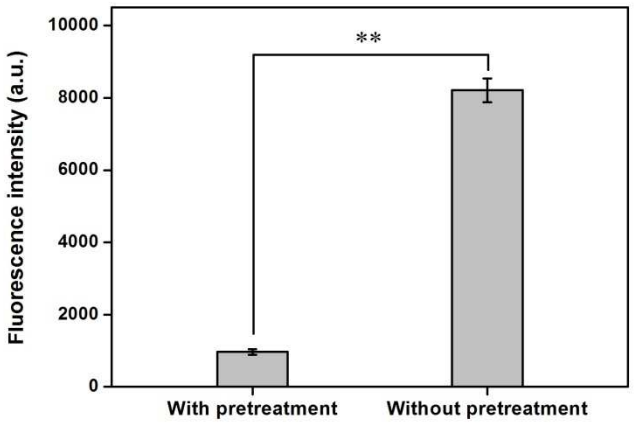
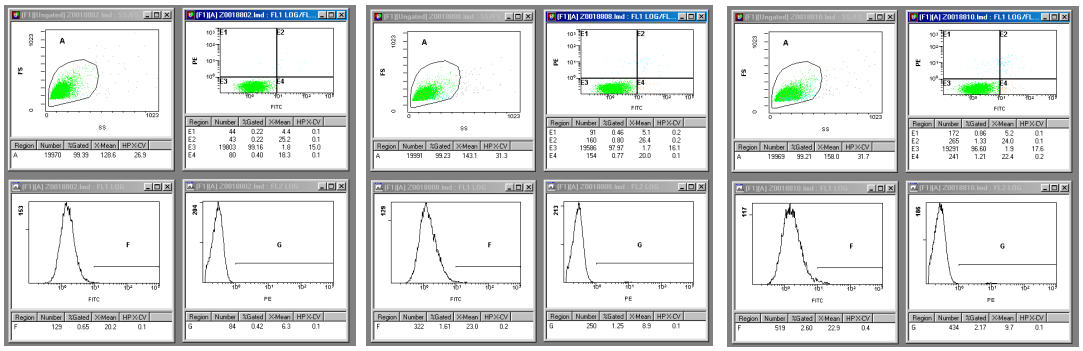
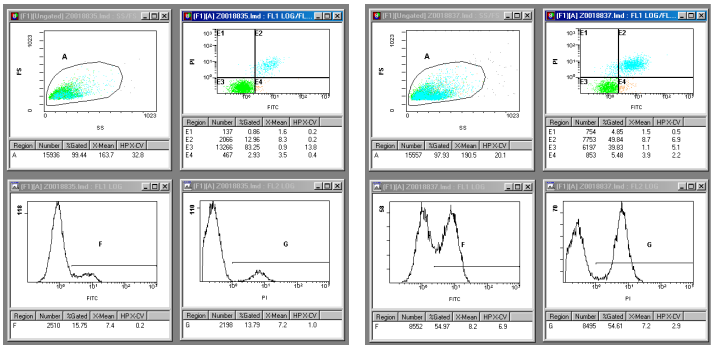


Figure S6. Fluorescence intensity analysis of FITC in HepG2 cells pretreated with or without galactose for 2 h and then incubated with 0.4 mg/mL MSNs-S-S-HP-LA@FITC at 37 °C for 24 h. Error bars represent means ± SD (n=3), **p < 0.01.



(a) (b) (c)



(d) (e)

Figure S7. Flow cytometry analysis of HepG2 cells after culture with TCPS (control, a) and 0.4 mg/mL of MSNs (b), 20 μg/mL of HP (c) and DOX(d), and the same amount of DOX loaded MSNs-S-S-HP-LA@DOX (e) (0.4 mg/mL) at 37°C for 24 h.

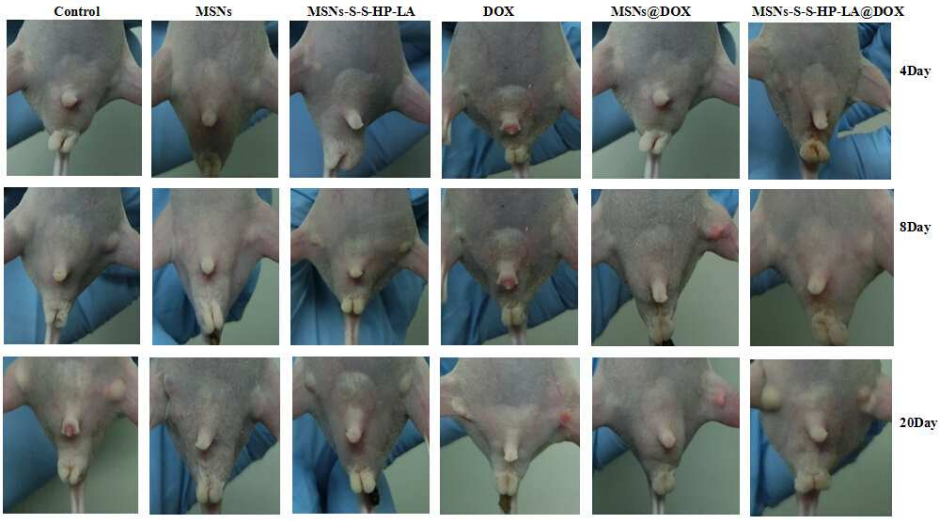


Figure S8. Representative photos of tumor-bearing mice after treatment for 20 days. The tumor was bore at groin both side of mice. The tumors at right side of mice were treated with different methods, while the tumors at left side of mice was only treated with PBS.

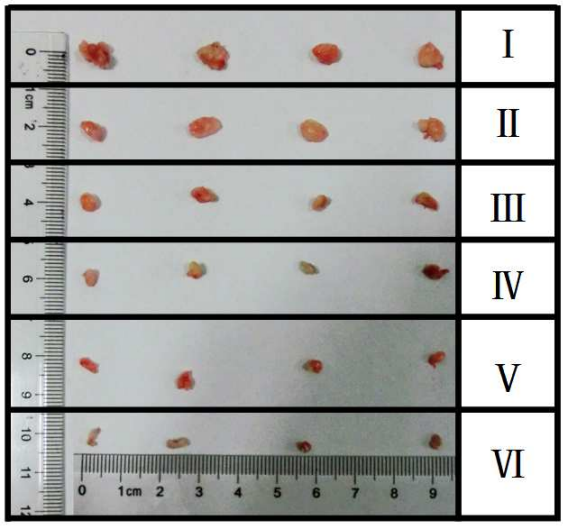


Figure S9. Representative images of the substantial tumors treated with PBS as control (Ⅰ), MSNs(Ⅱ), MSNs-S-S-HP-LA (Ⅲ), DOX (Ⅳ), MSNs@DOX (Ⅴ), and MSNs-S-S-HP-LA@DOX (Ⅵ), respectively. Scale bar: 1cm.

Table S1. BET and BJH parameters of MSNs, MSNs-S-NH_2 and MSNs-S-S-HP-LA.

Materials	S_{BET} (m^2/g)	V_P (cm^3/g)	BJH W_{BJH} (Å)
MSNs	933.6754	0.903569	38.7102
MSNs-S-S-NH_2	463.4716	0.390173	33.6739
MSNs-S-S-HP-LA	435.7575	0.367462	32.2369

Table S2. Zeta potentials variation recorded at various stages of MSNs-S-S-HP-LA fabrication.

Materials	Zeta potential (mV)
MSNs	-23.5±4.73
MSNs-NH_2	35.6±6.74
MSNs-COOH	-30.3±7.7
MSNs-S-S-NH_2	18±7.85
MSNs-S-S-HP	-20.5±6.17
MSNs-S-S-HP-LA	-25.1±6.69

Table S3. The apoptosis percentage of HepG2 cells with different treatments (control, MSNs, HP, DOX, and MSNs-S-S-HP-LA@DOX) calculated from flow cytometry analysis.

Materials	Apoptosis percentage (%)
TCPS	0.65
MSNs	1.61
HP	2.6
DOX	13
MSNs-S-S-HP-LA@DOX	56

Reference

[1]Cai, K. Y.; Hu, Y.; Luo, Z.; Kong, T.; Lai, M.; Sui, X. J.; Wang, Y. L.; Yang, L.; Deng, L. H. Cell-Specific Gene Transfection from a Gene-Functionalized Poly(d,l-lactic acid) Substrate Fabricated by the Layer-by-Layer Assembly Technique. *Angew. Chem. Int. Ed.* **2008**, *47*, 7479-7481.