Electronic Supplementary Material (ESI) for Nanoscale.

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Supporting Information

Hierarchically stimuli-responsive nanovectors for improved tumor penetration and programed tumor therapy

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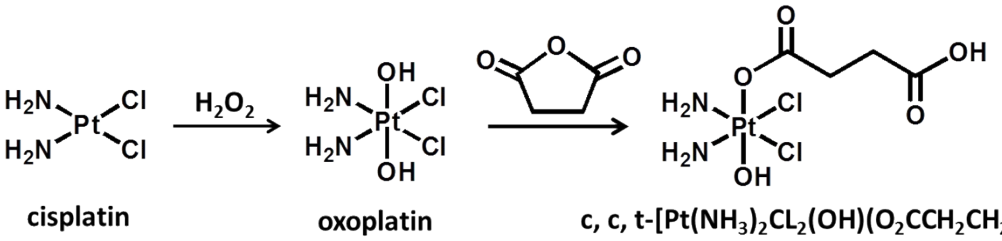

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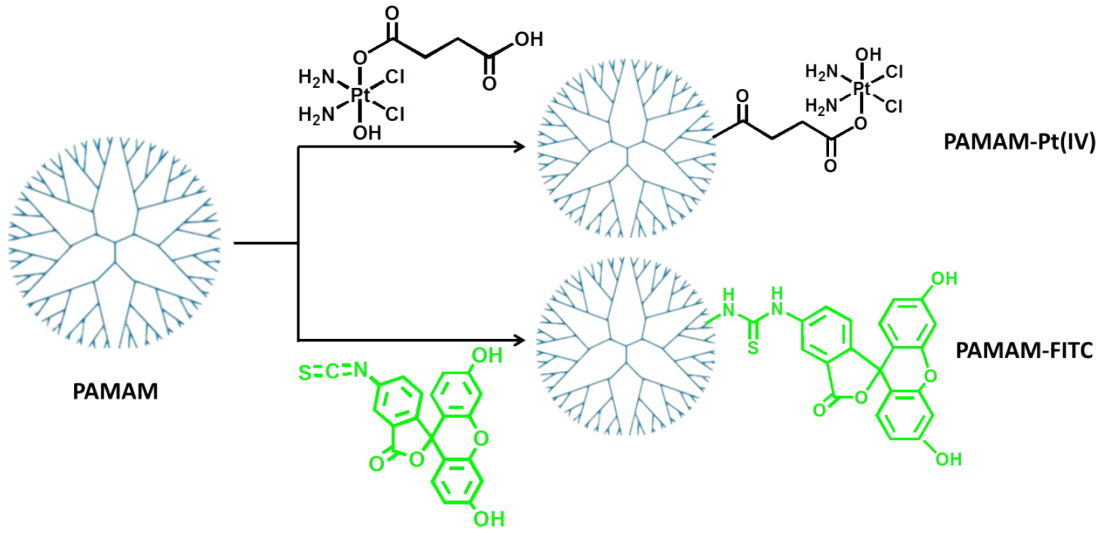

Scheme S1. Synthetic procedures of (**A**) cisplatin prodrug, c, c, t-[$Pt(NH_3)_2CL_2(OH)(O_2CCH_2CH_2CO_2H)$], and (**B**) PAMAM-Pt(IV) or PAMAM-FITC dendrimers.

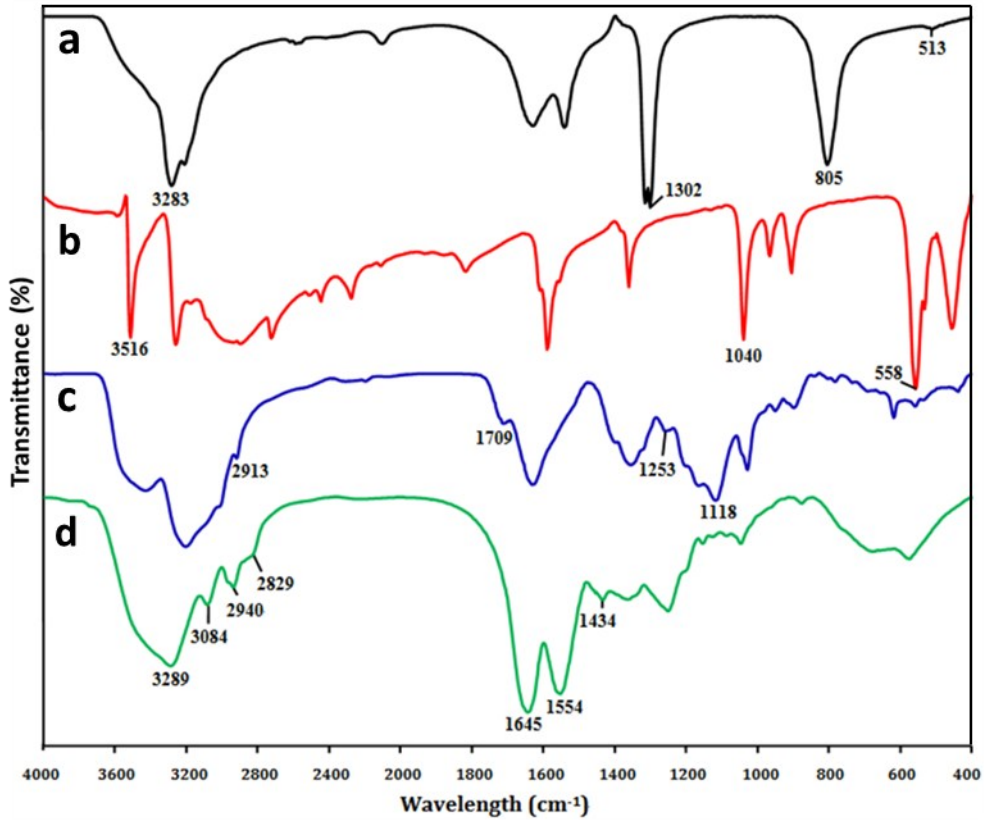

Figure S1. FTIR spectra of cisplatin (**a**), oxoplatin (**b**), c, c, t-$[Pt(NH_3)_2CL_2(OH)(O_2CCH_2CH_2CO_2H)]$ (**c**) and PAMAM-Pt(IV) (**d**), respectively.

The characteristic absorption peaks at 3283 cm^{-1}, 1302 cm^{-1} and 805 cm^{-1} were ascribed to the stretching vibration of N-H bonds from cisplatin. The absorption peak at 513 cm^{-1} was characteristics of $V_{pt\text{-}N,}$ which corresponds to the cis-structure of platinum. After oxidation with hydrogen peroxide, c,c,t-$[Pt(NH_3)_2Cl_2(OH)_2]$ showed a sharp, intense O–H stretching band at 3516 cm^{-1}. Meanwhile, additional absorption peaks at 1040 cm^{-1} and 558 cm^{-1} were ascribed to the Pt-OH bend and Pt–N stretch vibrations, respectively.[S1] The observations imply that cisplatin was successfully

oxidized into oxoplatin. The c,c,t-[$Pt(NH_3)_2Cl_2(OH)(O_2CCH_2CH_2CO_2H)$] showed additional strong absorption peak at 1709 cm^{-1}, which was assigned to the carbonyl (C=O) in carboxyl groups.[S2] New peaks at 1253 cm^{-1} and 1118 cm^{-1} were attributed to stretching vibration of the C-O in ester bonds. Meanwhile, characteristic peak corresponding to the $–CH_2-$ at 2913 cm^{-1} was also observed, indicating the successful preparation of c,c,t-[$Pt(NH_3)_2Cl_2(OH)(O_2CCH_2CH_2CO_2H)$].[S3] The final PAMAM-Pt(IV) prodrug was prepared via amide reaction of between PAMAM and c,c,t-[$Pt(NH_3)_2Cl_2(OH)(O_2CCH_2CH_2CO_2H)$]. The IR spectrum of PAMAM-Pt(IV) displayed a broad absorption peak of N–H bonds at 3289 cm^{-1}. The peaks at 2829, 2940, and 3084 cm^{-1} corresponding to the stretching vibrations of the C–H bonds in PAMAM unit are also observed. The peak at 1434 cm^{-1} was contributed to the bending vibrations of the C–H bonds in dendrimer. Moreover, new peaks at 1645 and 1554 cm^{-1} were attributed to stretching vibration of amide I and amide II of PAMAM dendrimer structure. All results indicate that PAMAM-Pt(IV) prodrug was successfully synthesized.[S4]

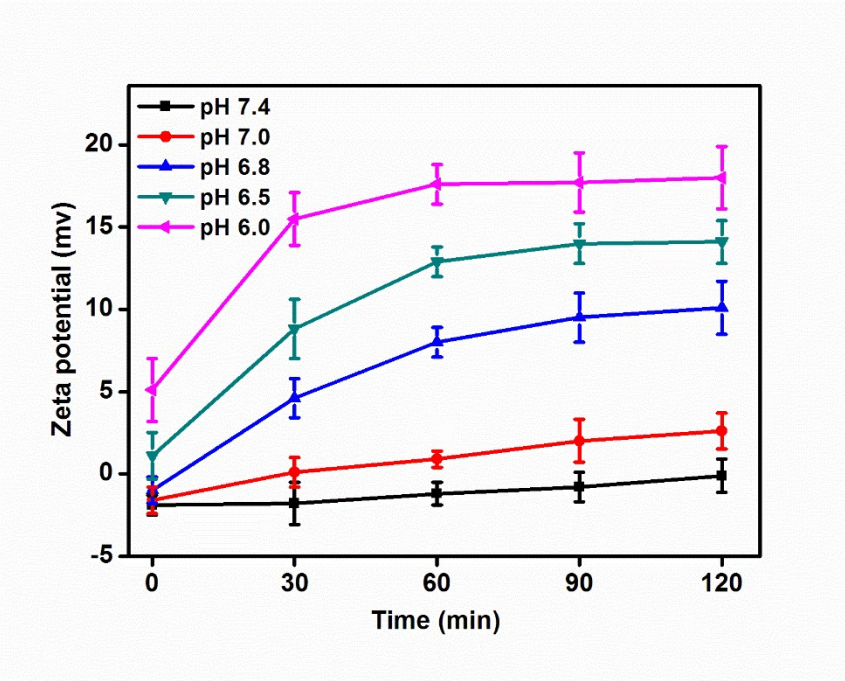

Figure S2. Relationship between pH and zeta potential: changes of zeta potentials of HMSN-CS(DMA)/PAMAM-Pt at different pH points.

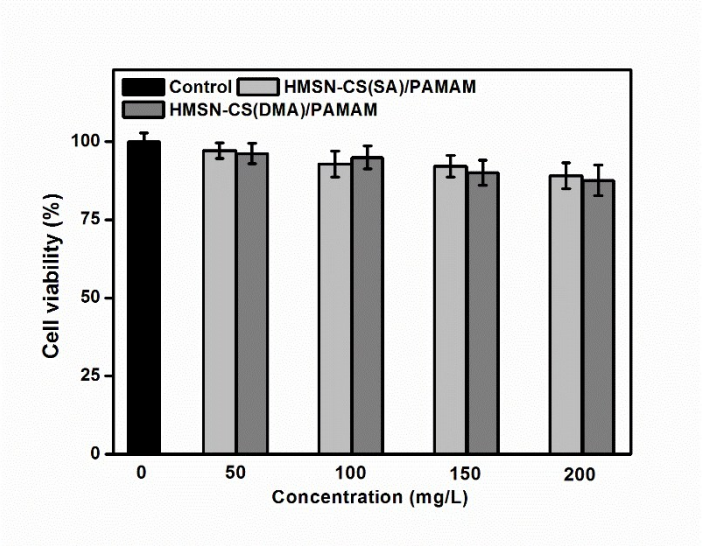

Figure S3. Concentration-dependent cytotoxicity of drug-freed nanosystems.

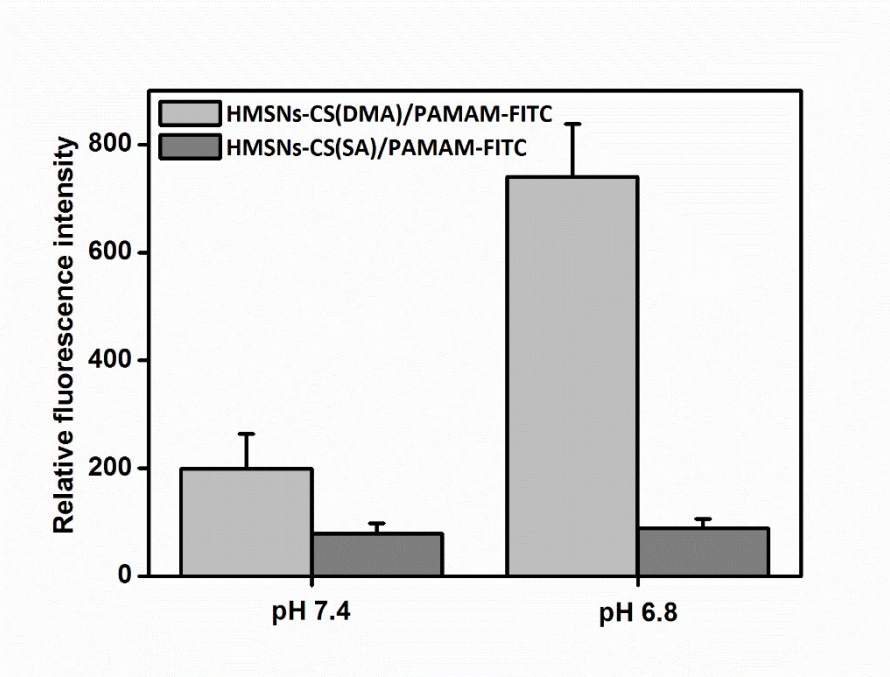

Figure S4. Quantitative fluorescence intensity analysis after cells with HMSNs-CS(DMA)/ PAMAM-FITC or HMSNs-CS(SA)/PAMAM-FITC treatments at different pH.

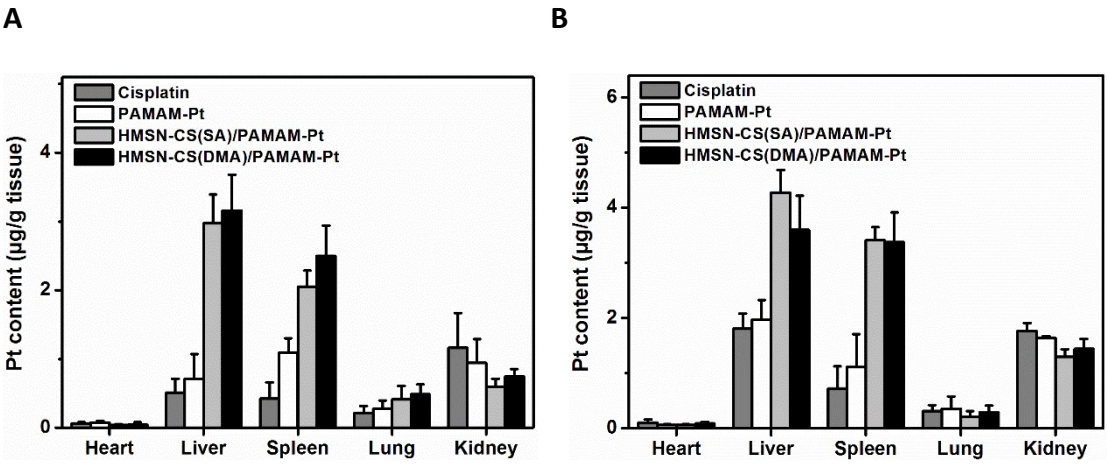

Figure S5. Biodistributions of different platinum formulations (free cisplatin, PAMAM-Pt, HMSN-CS(SA)/PAMAM-Pt and HMSN-CS(DMA)/PAMAM-Pt) in the major organs of nude mice at 12 h (**A**) and 24 h (**B**). Data are presented as mean ± SD, n = 3.

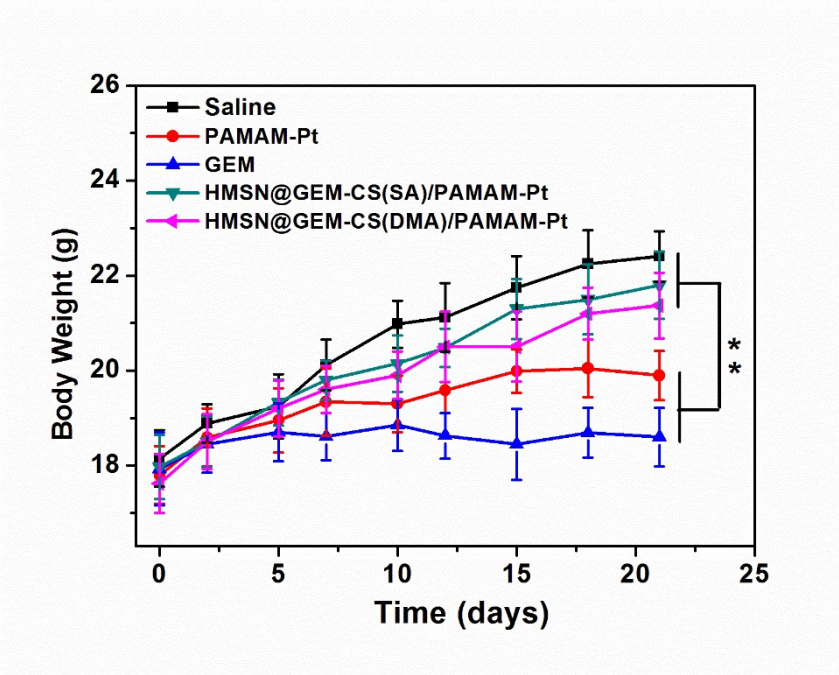

Figure S6. Real-time measurements of average tumor-bearing mice weights after each treatment.

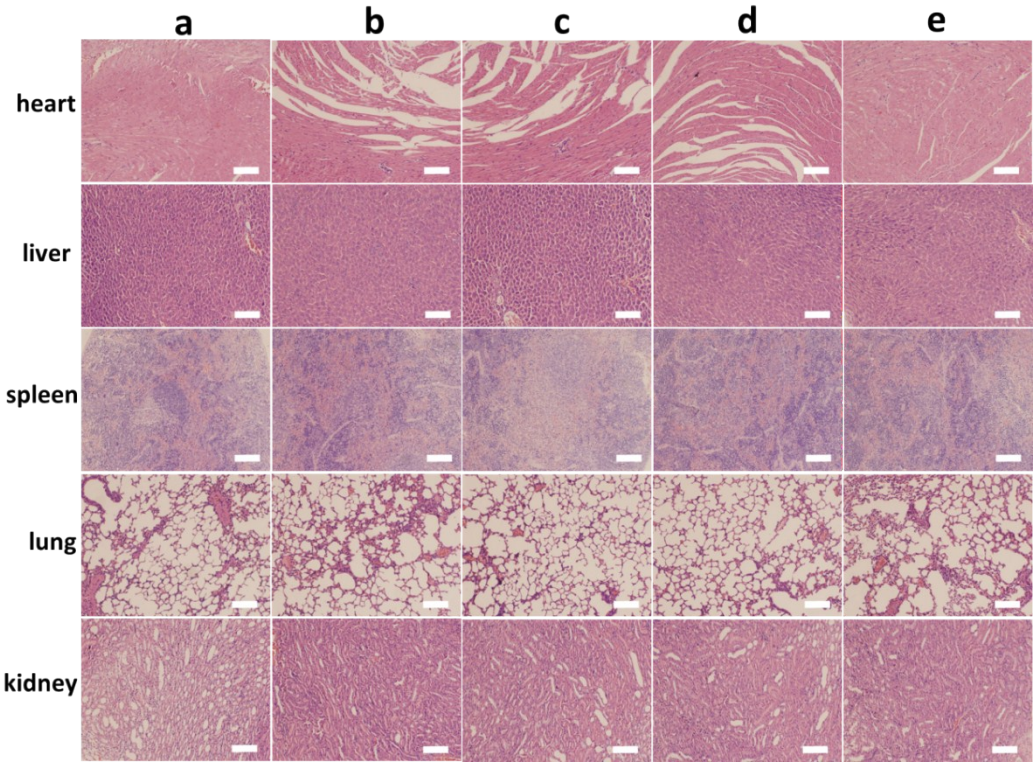

Figure S7. Histologic assessments of main organs of tumor bearing mice treated with saline (a), PAMAM-Pt (b), free GEM (c), HMSN@GEM-CS(SA)/PAMAM-Pt (d) and HMSN@GEM-CS(DMA)/PAMAM-Pt (e), respectively. The scale bar is 200 μm.

Table S1. Survival of tumor-bearing mice after treatment with saline, PAMAM-Pt, GEM, HMSN@GEM-CS(SA)/PAMAM-Pt and HMSN@GEM-CS(DMA)/PAMAM-Pt.

Treatment	MST (days)	ILS (%)	Log-rank P value
saline	32.7	/	/
PAMAM-Pt	38.5	17.7	0.088
GEM	34	4	0.503
HMSN@GEM-CS(SA)/PAMAM-Pt	46.2	41.3	0.003
HMSN@GEM-CS(DMA)/PAMAM-Pt	56.7	73.4	0.001
			$0.009^{[P2]}$

Notes: n =6 for each treatment group; MST, mean survival time; ILS, increased life span; P2 value was calculated in comparison between HMSN@GEM-CS(DMA)/PAMAM-Pt with HMSN@GEM-CS(SA)/PAMAM-Pt.

References

[S1] Y. Shi, S. A. Liu, D. J. Kerwood, J. Goodisman and J. C. Dabrowiak, *J. Inorg. Biochem.*, 2012, **107**, 6-14.

[S2] S. G. Shi, X. L. Chen, J. P. Wei, Y. Z. Huang, J. Weng and N. F. Zheng, *Nanoscale*, 2016, **8**, 5706-5713.

[S3] A. S. Ndamase, B. A. Aderibigbe, E. R. Sadiku, P. Labuschagne, Y. Lemmer, S. S. Ray and M. Nwamadi, *J. Drug Deliv. Sci. Tec.*, 2018, **43**, 267-273.

[S4] J. Zong, X. L. Yang, A. Trinchi, S. Hardin, I. Cole, Y. H. Zhu, C. Z. Li, T. Muster and G. Wei, *Nanoscale,* 2013, **5**, 11200-11206.