Electronic Supplementary Material (ESI) for Nanoscale.

Supporting Information

Cisplatin-Directed Coordination-Crosslinking Nanogels with Thermo/pH-Sensitive Triblock Polymers: Improvement on Chemotherapic Efficacy *via* Sustained Release and Drug Retention

Hao Zhao[†], Jiabao Xu[†], Jiangshan Wan, Shinan Geng, Han Li, Xiaole Peng, Qianwen Fu, Ming He, Yanbing Zhao[*], Xiangliang Yang[*]

National Engineering Research Center for Nanomedicine, College of Life Science and Technology, Huazhong University of Science and Technology, 430074, Wuhan City, P. R. China.

[†] These authors contributed equally to this work.

[*] E-mail: zhaoyb@ hust.edu.cn, yangxl@hust.edu.cn.

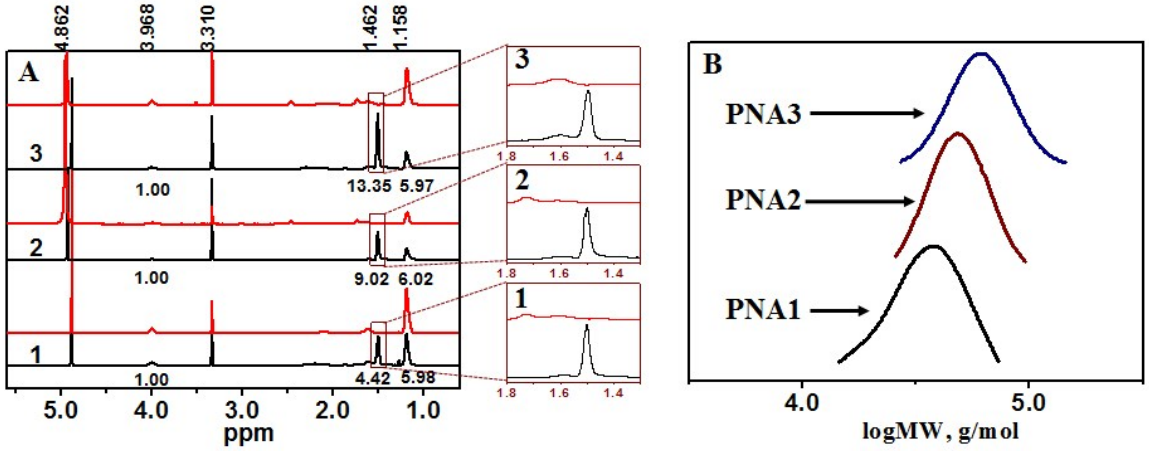

Figure S1. (A) ^{1}H-NMR spectrums: PNA1 (1, red line) and PN*t*B1 (1, black line), PNA2 (2, red line) and PN*t*B2 (2, black line) and PNA3 (3, red line) and PN*t*B3 (3, black line). (B) GPC spectrums: PNA1 (black line), PNA2 (red line) and PNA3 (blue line).

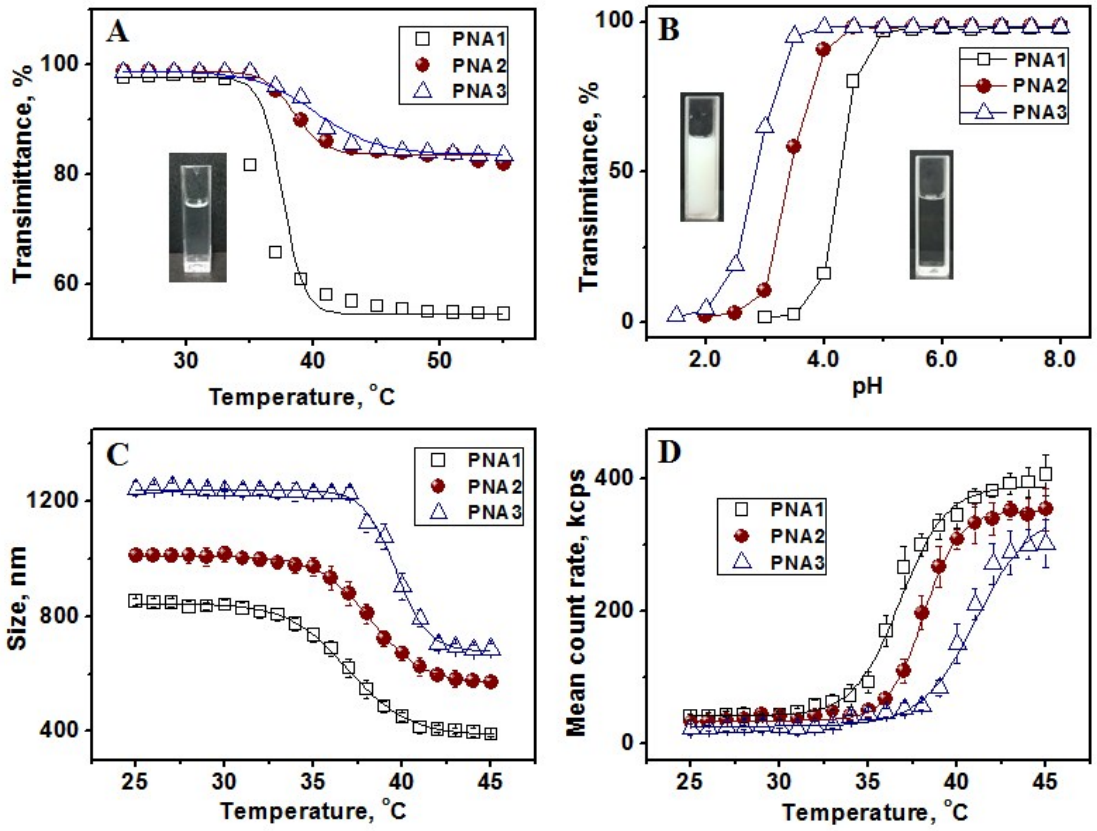

Figure S2. Dual temperature/pH sensitivity of PNA1, PNA2 and PNA3: The transmittance curves of three PNA dispersions with temperature (A) and pH at room temperature (B). Hydrodynamic diameters (C) and scattering light intensity (count rate, kcps) (D) curves of three PNA dispersions with temperature. The pH of the solutions is 7.4 expect for (B).

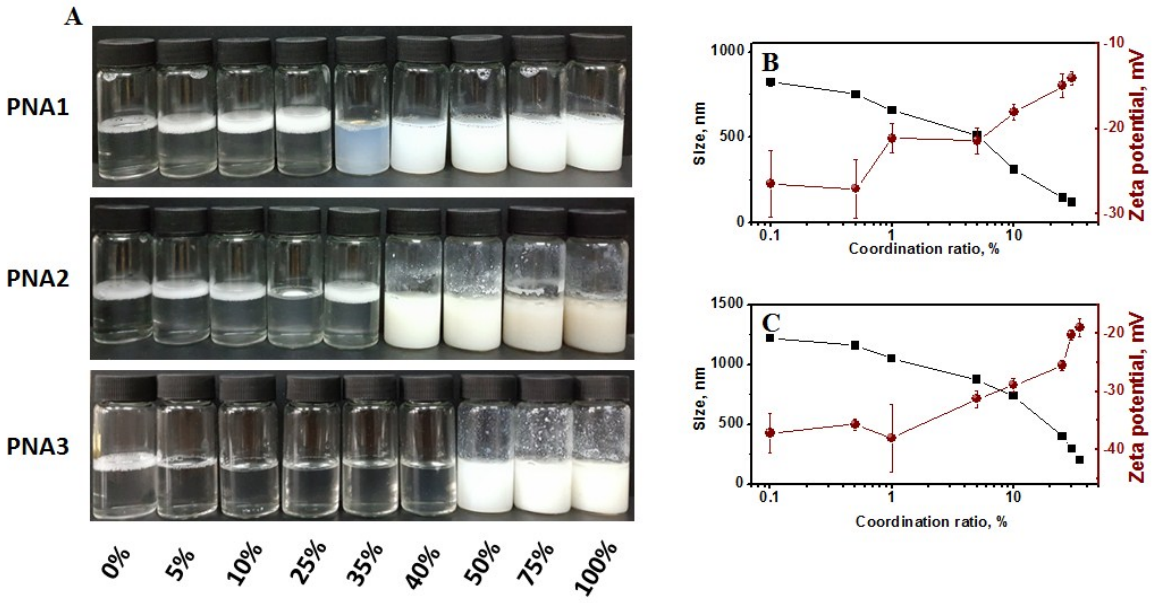

Figure S3. (A) The appearance change of three Pt-PNA nanogel dispersions when cisplatin was added dropwise to PNA dispersions at 30 °C. Hydrodynamic diameters (black solid square) and zeta potentials (red solid sphere) carves of Pt-PNA1 nanogels (B) and Pt-PNA3 nanogels (C) in water when cisplatin was added dropwise to PNA dispersions at 30 °C.

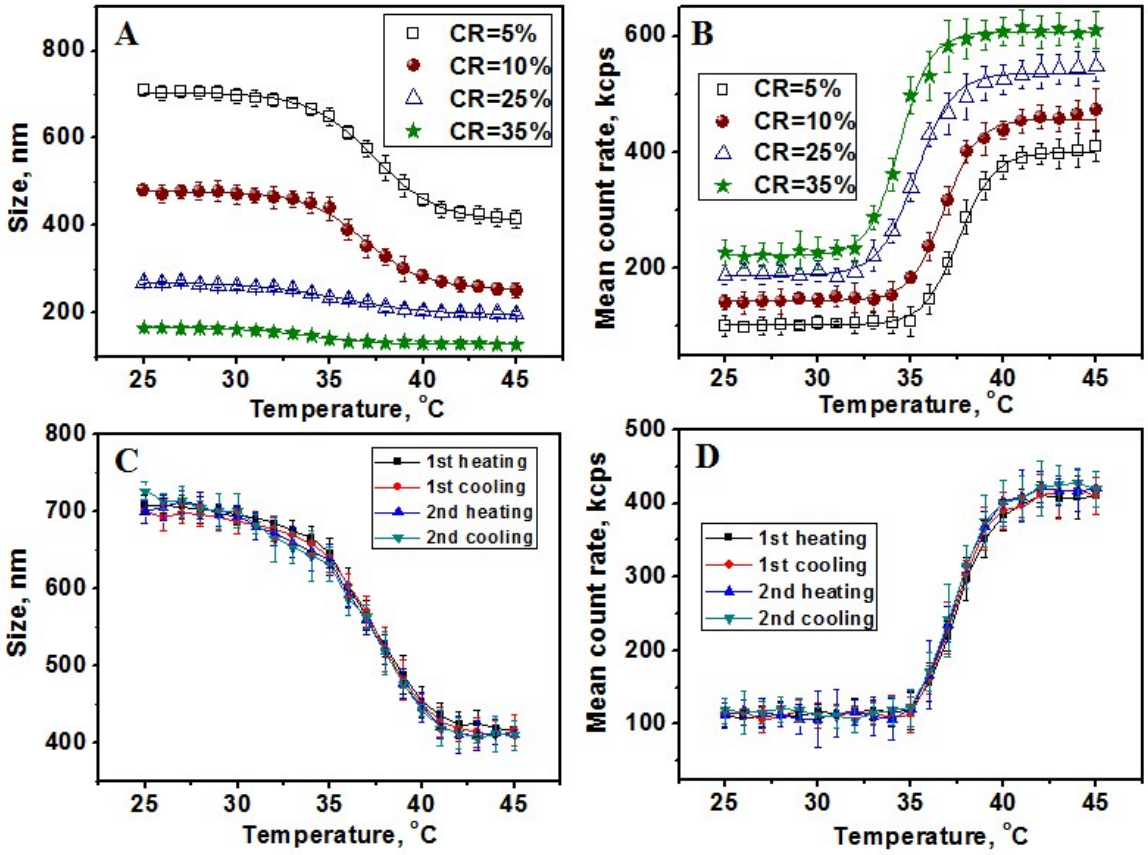

Figure S4. Temperature sensitivity of Pt-PNA nanogels: Hydrodynamic diameters (A) and scattering light intensity (count rate, kcps) (B) curves of Pt-PNA nanogels with temperature at the coordination ratios (CRs) of 5%, 10%, 25% and 35%. PNA2 was used in the nanogels. The size (C) and mean count rate (D) reversibility of Pt-PNA2 at the CR of 5% during heating and cooling procedures.

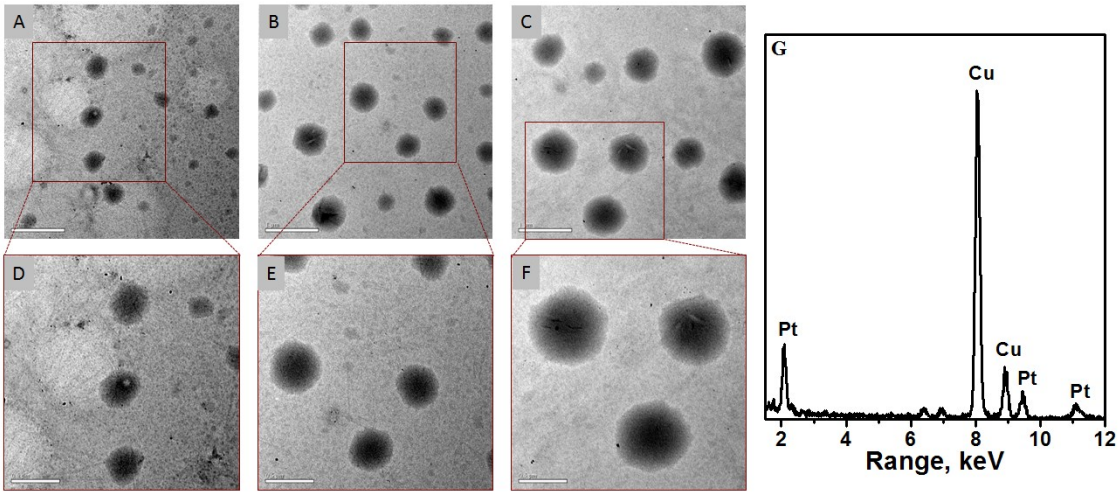

Figure S5. The micromorphologys (TEM photographs) of Pt-PNA nanogels with the same coordination ratio (CR) of cisplatin: (A) Pt-PNA1, (B) Pt-PNA2 and (C) Pt-PNA3 nanogels. The scale bar was 1μm. (D), (E), (F) were the partial enlarged diagrams of (A), (B), (C), respectively. The scale bar was 0.5μm. (G) The Energy Dispersive Spectrometer (EDS) of Pt-PNA2 nanogels with CR of 5% (Cu signals were related to the copper grid).

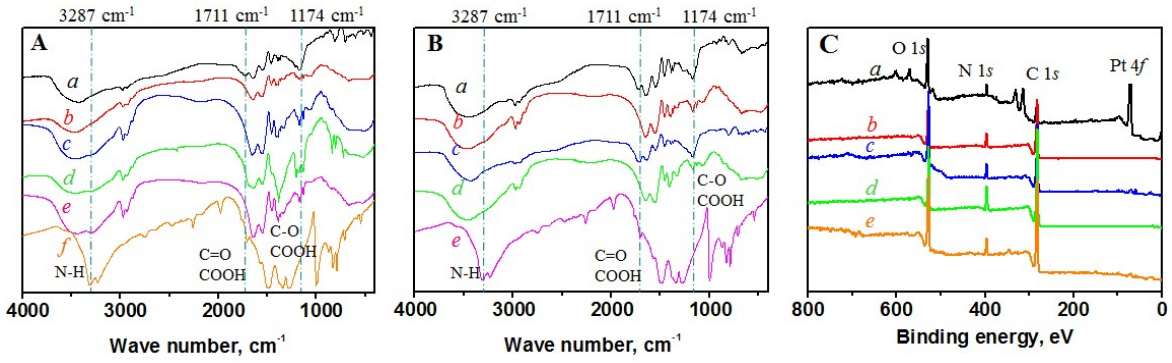

Figure S6. (A) FTIR spectrums: PNA2 (*a*, black), Pt-PNA nanogels with 5% (*b*, red), 10% (*c*, blue), 25% (*d*, green), 35% (*e*, magenta) of CR and free cisplatin (*f*, orange). (B) FTIR spectrums: PNA1 (*a*, black), Pt-PNA1 nanogels with 5% of CR (*b*, red), PNA3 (*c*, blue), Pt-PNA3 nanogels with 5% of CR (*d*, green) and free cisplatin (*e*, magenta). (C) XPS spectrums: free cisplatin (*a*, black), PNA1 (*b*, red), Pt-PNA1 nanogels with 5% of CR (*c*, blue), PNA3 (*d*, green) and Pt-PNA3 nanogels with 5% of CR (*e*, orange)

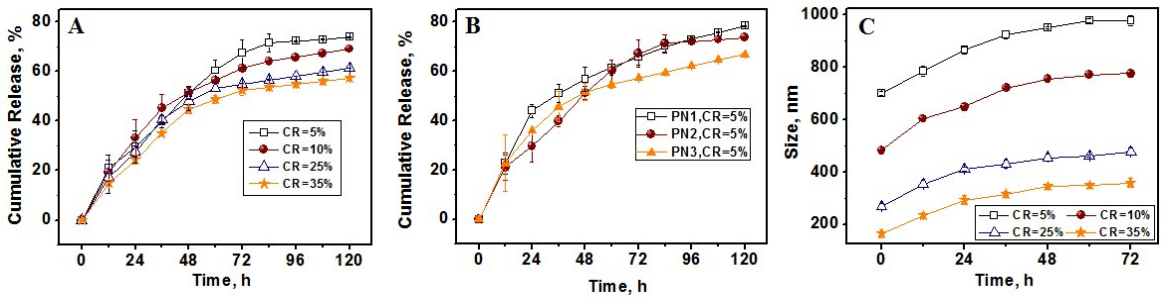

Figure S7. In *vitro* releasing behavior: (A) The cumulative release carves in *vitro* of Pt-PNA2 nanogels with various coordination ratios (CR) of cisplatin: 5%, 10%, 25% and 35% in the condition of 37 ^{o}C and pH 7.4. (B) The cumulative release carves in *vitro* of Pt-PNA1, Pt-PNA2 and Pt-PNA3 with 5% of CR in the condition of 37 ^{o}C and pH 7.4. (C) The change of size during cisplatin release of the Pt-PNA2 nanogels with various CRs at 25^{o}C.

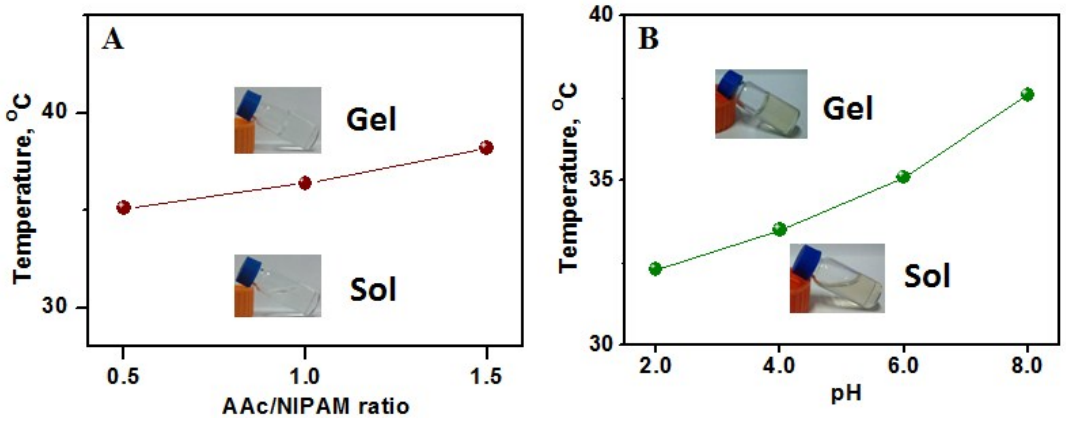

Figure S8. The thermo-sensitive sol-gel phase transition of three PNA dispersions and Pt-PNA nanogels: (A) AAc/NIPAM ratio *vs* temperature diagram of three PNA dispersions; (B) pH *vs* temperature diagram of Pt-PNA2 nanogels with 5% of CR.

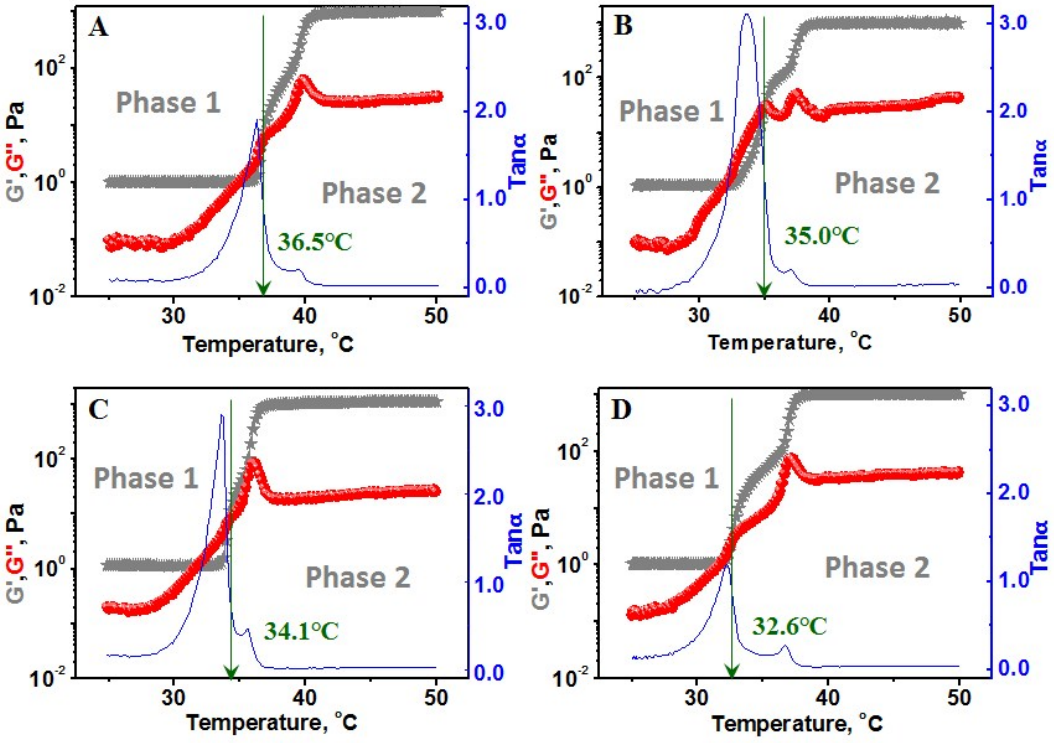

Figure S9. Rheologic properties of Pt-PNA2 nanogels with various coordination ratios (CR) of cisplatin: (A) 5%, (B) 10%, (C) 25% and (D) 35%, respectively.

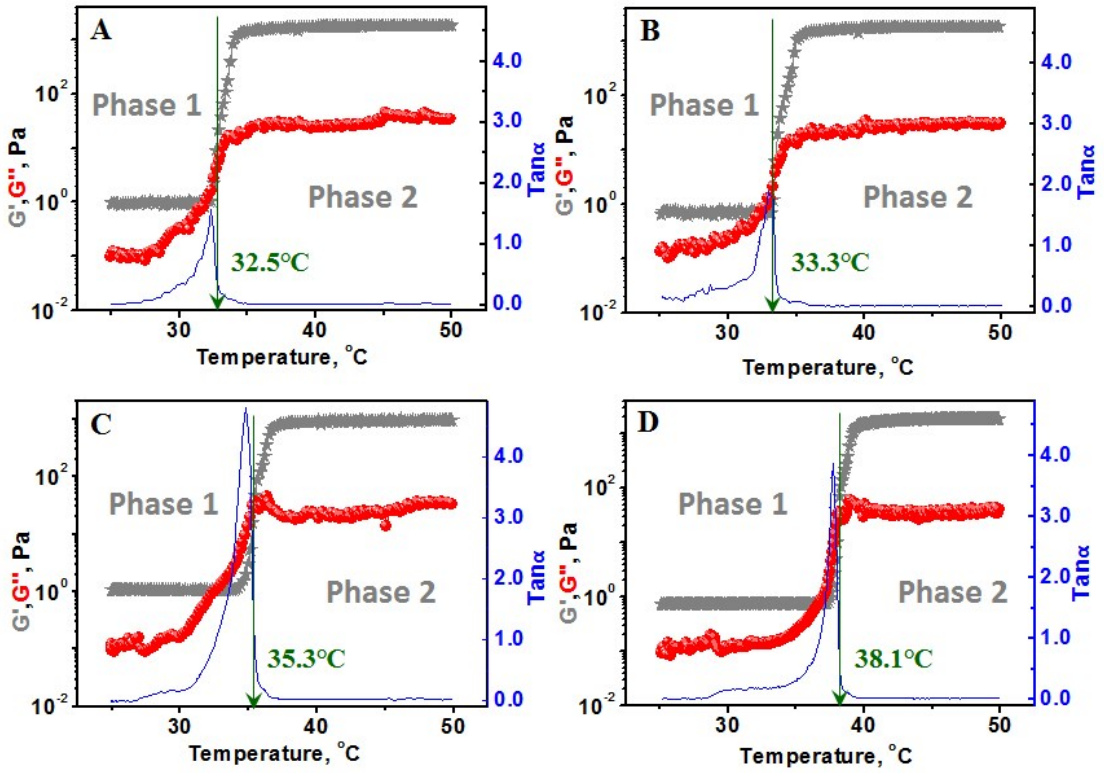

Figure S10. Rheologic properties of Pt-PNA2 nanogels with 5% of CR at various pHs: (A) pH 2.0, (B) pH 4.0, (C) pH 6.0 and (D) pH 8.0, respectively.

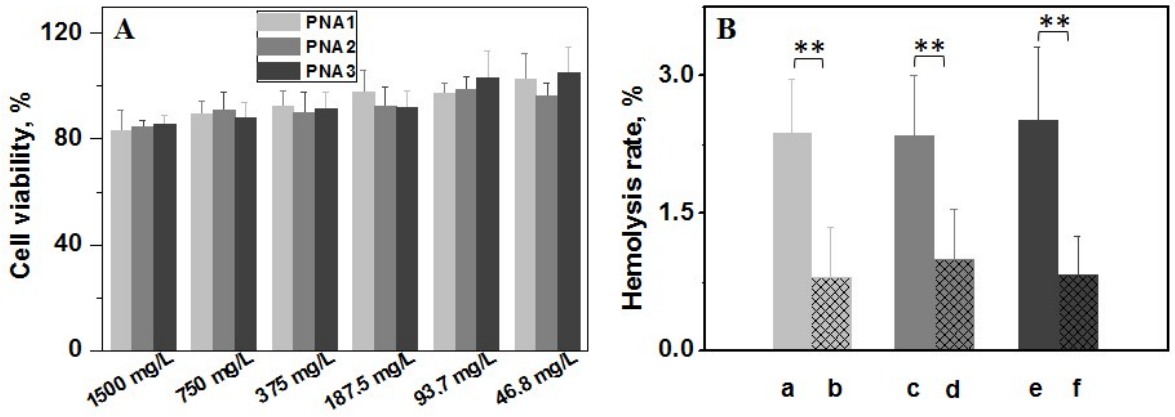

Figure S11. Biocompability of three PNAs and Pt-PNA nanogels: (A) The cytotoxicity comparison of three PNAs in the PNA concentration range of 46.8-1500 mg/L with HepG2 cells after incubation for 24 h; (B) The hemolysis rate of red blood cells after incubation for 1 h with various of materials at 37 ^{o}C: (*a*) (*c*) (*e*) cisplatin, (*b*) Pt-PNA nanogels, CR=10%, (*d*) Pt-PNA nanogels, CR=25%, (*f*) Pt-PNA nanogels, CR=35%, PNA. (*a*) and (*b*), (*c*) and (*d*), (*e*) and (*f*) were with the same amount of Pt, respectively. PNA2 was used in the nanogels.

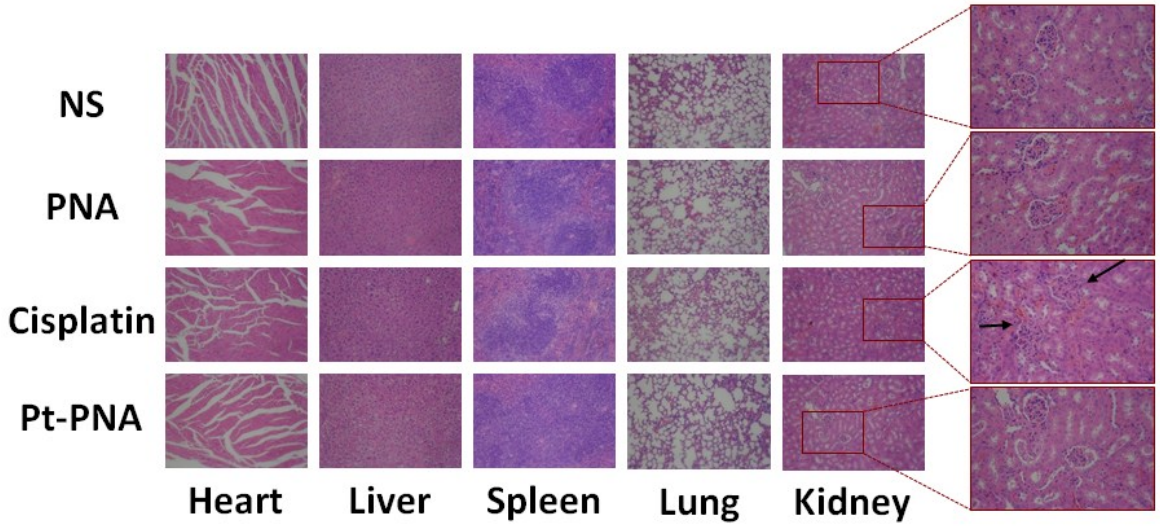

Figure S12. Biocompability of Pt-PNA2 with 5% of CR: histological sections of heart, liver, spleen, lung and kidney stained using H&E after 14 days of treatment by normal saline, PNA, free Cisplatin and Pt-PNA2 nanogel dispersions (x200). The partial enlarged diagrams was the appearance of glomerulus (x400).