Supporting Information

Single-Stimulus Dual-Drug Sensitive Nanoplatfom for Enhanced Photoactivated Therapy

Shasha He,^{†,‡} Yanxin Qi,[†] Gaizhen Kuang,[§] Dongfang Zhou,^{*,†} Jizhen Li,[⊥] Zhigang Xie,[†] Xuesi Chen,[†] Xiabin Jing,[†] and Yubin Huang^{*,†}

[†] State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun–130022, PR China

[‡] University of Chinese Academy of Sciences, Beijing 100049, PR China

[§] Department of Gastroenterology, The Second Affiliated Hospital, Medical School of Xi'an Jiaotong University, Xi'an–710048, PR China

[⊥] College of Chemistry, Jilin University, Changchun–130023, PR China

Synthesis of *c,c,t*-[Pt(NH₃)₂Cl₂(N₃)₂(OH)₂]

c,c,t-[Pt(NH₃)₂Cl₂(N₃)₂(OH)₂] was synthesized according to reference. To a suspension of cisplatin (1 g) in H₂O (5 mL), 2eq AgNO₃ (1.13 g) was added and stirred for 6 h in the dark. Then the resultant AgCl was filtered and NaN₃ (1 g) was added to the filtrate and stirred at room temperature for another 4 h in the dark. The yellow precipitate was oxidized by H₂O₂.¹

Synthesis of Pt(N₃)

Pt(N₃) was synthesized according to the reference. Succinic anhydride (100 mg) was added to a suspension of *c,c,t*-[Pt(NH₃)₂Cl₂(N₃)₂(OH)₂] (347 mg) in anhydrous DMSO (5 mL) and the reaction mixture was stirred at room temperature for 24 hours away from light. Then diethyl ether (50 mL) was added to precipitate the product for three times.¹ The obtained bright yellow solid was dried in 85% yield (380 mg). Pt(N₃) was characterized by ¹H NMR, IR and ESI-MS. ¹H NMR (Fig. S1a), IR (Fig. S2a) and ESI-MS (Fig. S3); ¹H NMR: (400 MHz, d₆-DMSO, 25 °C): δH 2.33-2.39 (4H, m, -OCH₂CH₂C-), 5.12-5.71 (6H, m, NH₃); IR: cm⁻¹ 2061 (sh, N₃), 1689 (sh, CO-OH), 1648 (sh, -PtOOC-C-), 557 (sh, Pt-OH). ESI-MS: (negative mode) m/z 446.2 [M-H]⁻ (100%).

Synthesis of Dex-Pt(N₃) conjugate

Dextran (50 mg, 0.005 mmol) and Pt(N₃) (112 mg, 0.25 mmol) were added into a round-bottomed flask. DMAP (1 eq. per carboxyl group each) and EDC·HCl (4 eq. per carboxyl group each) in DMSO (5 mL) were added and stirred at room temperature for 24 h. Then, the reaction solution was dialyzed (M_wCO = 3500) against water to remove the DMSO and the unreacted Pt(N₃) for 72 h and finally freeze-dried to obtain the Dex-Pt(N₃) conjugate for storage.² The Pt content on the obtained Dex-Pt(N₃) conjugate was measured by ICP-MS.

SUPPLEMENTARY FIGURES

Scheme S1 Synthesis and photo-reduction reaction of Dex-Pt(N₃) conjugate.

Figure S1. ¹H NMR spectra of (A) Pt(N₃) complex, (B) Dextran and (C) Dex-Pt(N₃) conjugate in DMSO-d₆.

Figure S2. FT-IR spectra of (A) Pt(N₃) complex, (B) Dextran and (C) Dex-Pt(N₃) conjugate.

Figure S3. ESI-MS of Pt(N₃) complex.

Figure S4. Platinum content of Dex-Pt(N₃) conjugates as a function of the molar ratio of Pt(N₃) to dextran.

Figure S5. TEM images of DPNs with different Pt contents: (A) 2.1 wt%, (B) 5.7 wt%, (C) 7.8 wt%, (D) 10.1 wt% and (E) 14.2 wt%.

Figure S6. Average hydrodynamic diameter and PDI stability of Cur@DPNs in 10% blood serum solution.

Figure S7. In-dark stability of Cur and Cur@DPNs in term of Cur in PBS (pH =7.4).

Figure S8. (A) In-dark stability of Pt(N₃) and Cur@DPNs in term of Pt(N₃) in water; UV-vis spectra changes of (B) Pt(N₃), (C) DPNs and (D) Cur upon UVA irradiation (365 nm, 10 mW/cm²) for the indicated intervals of time; (E) Relative UV absorbance of Cur and DPNs at 258 nm with irradiation time.

Figure S9. TEM images of DPNs in response to irradiation (365 nm, 10 mW/cm²) for (A) 10 min, (B) 20 min, (C) 30 min and (D) 40 min.

Figure S10. Average hydrodynamic diameter change of DPNs and Cur@DPNs in response to UVA irradiation (365nm, 10 mW/cm²).

Figure S11. Feasibility of ICG to the detection of $^1\text{O}_2$. (A) ICG and Cur@DPNs under irradiation; (B) ICG under irradiation; (C) Relative absorbance of ICG, ICG and Cur@DPNs under irradiation.

Figure S12. Platinum contents in HeLa cells after different treatments: (a) Cur@DPNs and (b) DCF-DA + Cur@DPNs in the dark, (c) Cur@DPNs and (d) DCF-DA + Cur@DPNs upon irradiation for 4 h.

Figure S13. In vitro cytotoxicity of cisplatin, Pt(N₃), DPNs, Cur@DPNs and Cur against L929 normal fibroblasts for (A) 24 h and (B) 48 h.

Figure S14. Cell viability of HeLa cells after UVA irradiation for different time.

Figure S15. In vitro cytotoxicity curves of cisplatin, $\text{Pt}(\text{N}_3)$, Cur, DPNs and Cur@DPNs against HeLa cells in the dark for (A) 24 h, (B) 48 h, (C) 72 h and in the presence of irradiation for (D) 24 h, (E) 48 h, (F) 72 h.

Figure S16. In vitro cytotoxicity curves of Cur and Cur@DPNs against HeLa cells for (A) 2 h, (B) 4 h after UVA irradiation; (C) In vitro cytotoxicity curves of DPNs against HeLa cells for 2 h, 4 h and 12 h after UVA irradiation.

Figure S17. Survival rates of KM mice treated with saline, cisplatin, Cur, DPNs and Cur@DPNs (A) in the dark, and (B) after UVA irradiation.

Figure S18. Biodistribution of Pt in heart, liver, spleen, lung, kidney and tumor after cisplatin and Cur@DPNs were intravenously injected for 2 h and 24 h.

- (1) Xiao, H.; Noble, G. T.; Stefanick, J. F.; Qi, R.; Kiziltepe, T.; Jing, X. *J. Controlled Release* **2014**, *173*, 11–17.
- (2) He, S.; Cong, Y.; Zhou, D.; Li, J.; Xie, Z.; Chen, X.; Jing, X.; Huang, Y. *J. Mater. Chem. B* **2015**, *3*, 8203–8211.