Electronic Supplementary Information for:

Chelate-Functionalized Magnetic Micelles for Sequestration of Cisplatin

Kang Du,[a] Pan Liao,[b] Shengsong Yang,[a] Dora von Trentini,[a] Kushal Sharma,[c] Xiaorui Shi,[c] Christopher B. Murray,[a,d] Daqing Li,[b,*] Ivan J. Dmochowski[b,*]

Departments of [a]Chemistry, [b]Otorhinolaryngology, and [d]Materials Science and Engineering, University of Pennsylvania, Philadelphia, PA 19104
[c]Department of Otolaryngology/Head & Neck Surgery, Oregon Health & Science University, Portland, OR 97239

Email: lidaqing@pennmedicine.upenn.edu; ivandmo@sas.upenn.edu

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Experimental Section

General Considerations. Unless otherwise specified, chemicals and solvents were purchased from commercial vendors and used without purification. Deuterated solvents and ^{13}C-labeled CS_2 were purchased from Cambridge Isotope Laboratories. Deionized water was obtained from an EMD Millipore purification system. The block copolymers PCL_{5k}-PEG_{5k}-NH_2 and PCL_{5k}-PEG_{5k}-RhB were purchased from Sigma Aldrich and Nanosoft Polymers, respectively. Pharmaceutical grade cisplatin was supplied by Teva Pharmaceuticals.

Synthesis of 10-nm Superparamagnetic Iron Oxide Nanoparticles (SPIONs). Synthesis of oleate-stabilized 10-nm SPIONs was adopted from reported methods.[1] In a three-neck flask, a mixture of 10 mL 1-octadecene, 1 mL oleylamine and 3 mL oleic acid was stirred under vacuum at 120 °C for 30 min to remove dissolved air. The flask was then purged with N_2 and the temperature was increased to 300 °C and kept for 1 h. After cooling to 150 °C, 50 μL $Fe(CO)_5$ was swiftly injected to the mixture. The resulting dark black solution was cooled to rt, and iPrOH was added to precipitate the SPIONs with the desired size.

Synthesis of Block Copolymer PCL_{3k}-PEG_{5k}-GSH. Dimethylformamide (DMF, 3 mL) was degassed in a 25 mL Schlenk tube by three successive freeze-pump-thaw cycles. With outflowing N_2, PCL_{3k}-PEG_{5k}-NHS (structure see Fig. S1, 100 mg, ca. 13 μmol), diisopropylethylamine (DIPEA, 30 μL, 172 μmol) and glutathione (10 mg, 33 μmol) were added to the Schlenk tube. The resulting solution was stirred under static N_2 atmosphere and at rt for 48 h. The resulting solution was dialyzed against 1 mM tris(2-carboxyethyl)phosphine (TCEP) solutions (2 × 3 L) followed by deionized water (4 × 3 L) over 48 h, using dialysis tubing with molecular weight cutoff of 6000–8000 Da. The resulting cloudy suspension was freeze-dried to afford a white powder (87 mg, 87%). ^{13}C NMR (ppm, $CDCl_3$): 174.13, 71.15, 64.74, 34.71, 28.93, 26.11, 25.16 (Figure S2). Percentage of S (ICP-OES, w/w): 0.4%.

Synthesis of Block Copolymer PCL_{5k}-PEG_{5k}-DTC. To a 100 mL Schlenk tube containing PCL_{5k}-PEG_{5k}-NH_2 (structure see Fig. S1, 50 mg, ca. 5 μmol) was added 30 ml tetrahydrofuran (THF). CS_2 (15 μL, ca. 50 equivalents) and diisopropylethylamine (DIPEA) (44 μL, ca. 50 equivalents) were transferred to the solution via pipettes. The Schlenk tube was sealed, and the resulting homogeneous solution was stirred at 70 °C for 4 days (Figure S1). The resulting lightly yellow solution was dialyzed against deionized water (4 × 3 L) for 48 h, using dialysis tubing with molecular weight cutoff of 6000–8000 Da. The resulting cloudy suspension was freeze-dried to afford a light-yellow powder (42 mg, 84%). ^{13}C NMR (ppm, $CDCl_3$): 173.69, 70.67, 64.28, 34.25, 28.47, 25.65, 24.70 (Figure S2). Percentage of S (ICP-OES, w/w): 1.6%.

Synthesis of PCL_{5k}-PEG_{5k}-^{13}DTC. The procedure was the same as the one for PCL_{5k}-PEG_{5k}-DTC, with the exception that $^{13}CS_2$ was used instead of CS_2. ^{13}C NMR (ppm, $CDCl_3$): 204.30, 173.68, 70.68, 64.27, 34.24, 28.47, 25.65, 24.69 (Figure S2).

Synthesis of GSH-/DTC-Micelle. This preparation was modified from a reported procedure.[2] Block copolymer (4 mg) in toluene (80 μL) was mixed with SPIONs in toluene (80 μL, 25 mg Fe/mL). The resulting dark brown solution was incubated at rt for 1 h. With sonication, the dark brown solution was added to deionized water (4 mL) in a scintillation vial. The capped vial was

sonicated in a water bath for 2 h. After sonication, the vial was uncapped and the emulsion was left exposed to air for 2 days, during which residual toluene was fully evaporated. The resulting solution was filtered by PES membrane (pore size: 0.22 μm) to give a dark brown solution. The elemental concentrations of Fe and S for the synthesized GSH- and DTC-SPION-micelles were determined by ICP-OES.

Syntheses of RhB-GSH-Micelle and RhB-DTC-Micelle. This procedure was the same as the one for GSH-/DTC-SPION-Micelle, except that 1% PCL_{5k}-PEG_{5k}-RhB (w/w) was doped in the synthesis and the synthesis was carried out in dark to prevent potential photo-degradation.

Figure S1. Chemical structures of all relevant polymers.

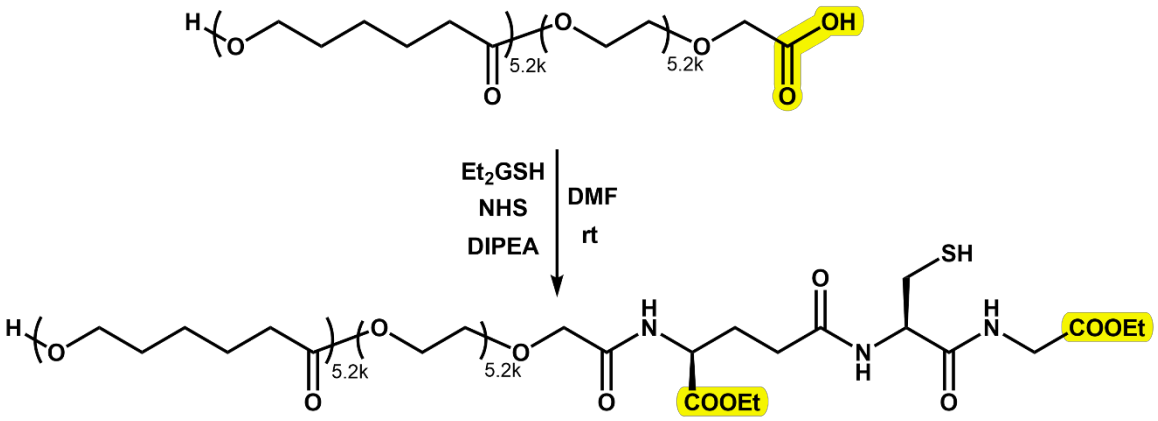

Figure S2. Reported synthetic scheme for $PCL_{5.2k}$-$PEG_{5.2k}$-Et_2GSH. Highlighted areas represent the key differences in functional groups as compared to the synthesis of PCL_{3k}-PEG_{5k}-GSH.

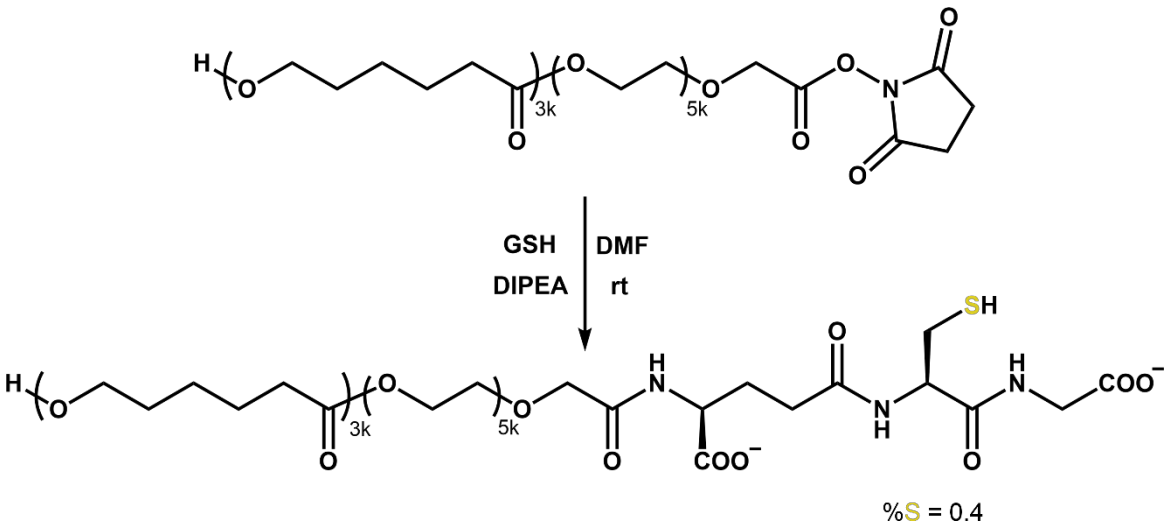

Figure S3. Synthetic scheme for PCL_{3k}-PEG_{5k}-GSH.

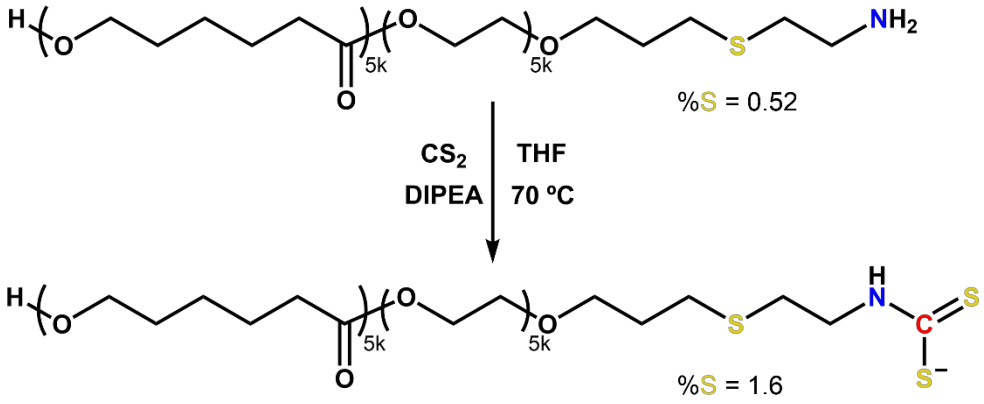

Figure S4. Synthetic scheme for PCL_{5k}-PEG_{5k}-DTC.

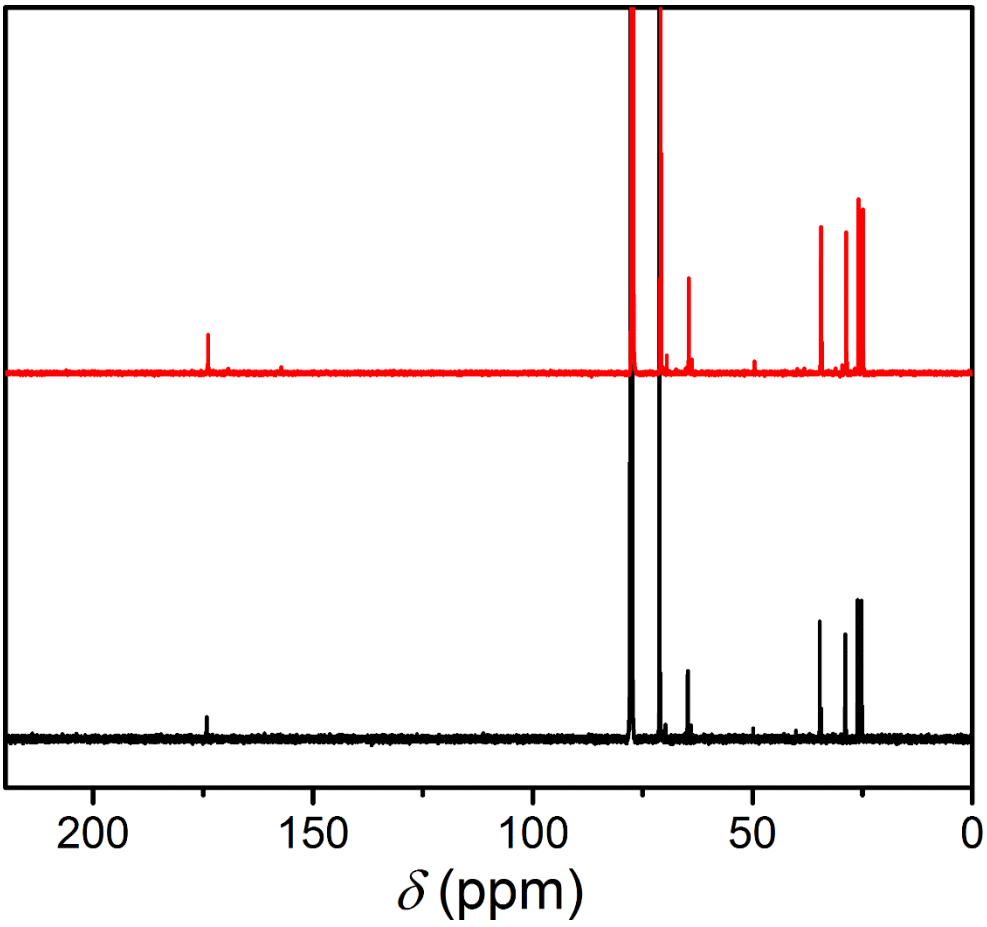

Figure S5. Stacked ^{13}C NMR spectra of block copolymers PCL_{3k}-PEG_{5k}-NHS (bottom) and PCL_{3k}-PEG_{5k}-GSH (top).

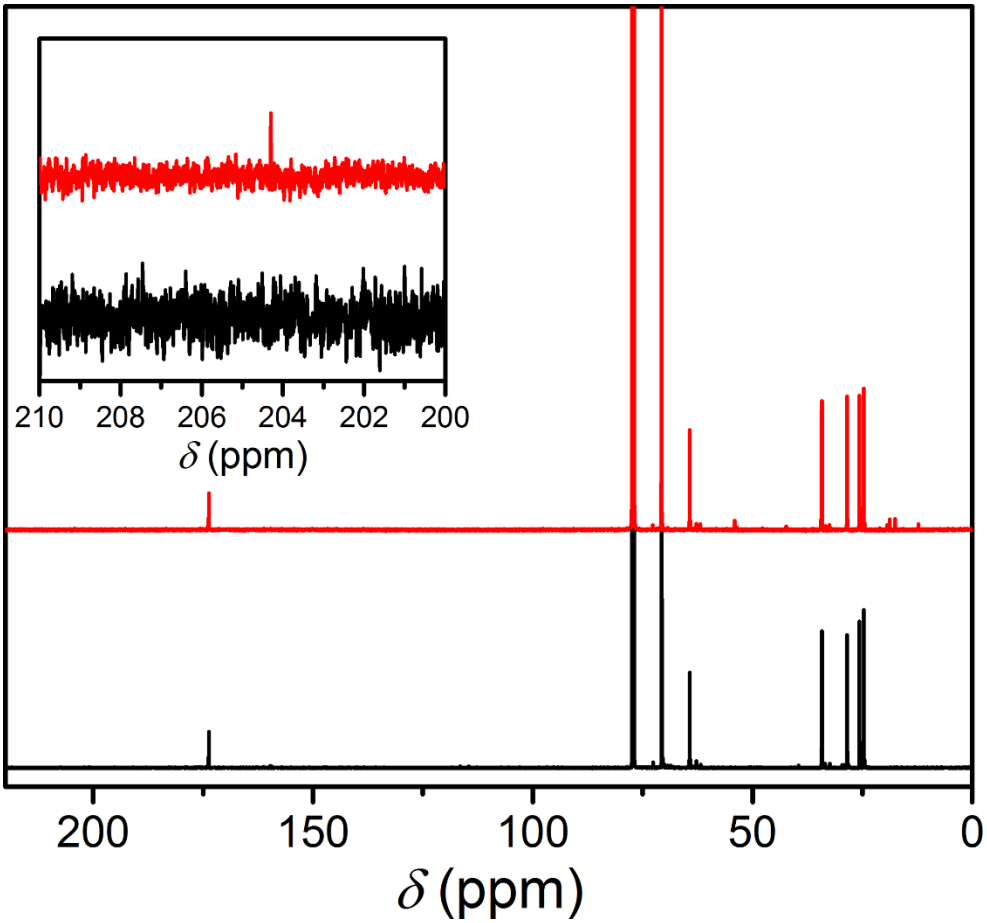

Figure S6. Stacked ^{13}C NMR spectra of block copolymers PCL_{5k}-PEG_{5k}-NH_2 (bottom) and PCL_{5k}-PEG_{5k}-DTC (top). Inset: selected region for block copolymers PCL_{5k}-PEG_{5k}-NH_2 (bottom) and PCL_{5k}-PEG_{5k}-^{13}DTC (top).

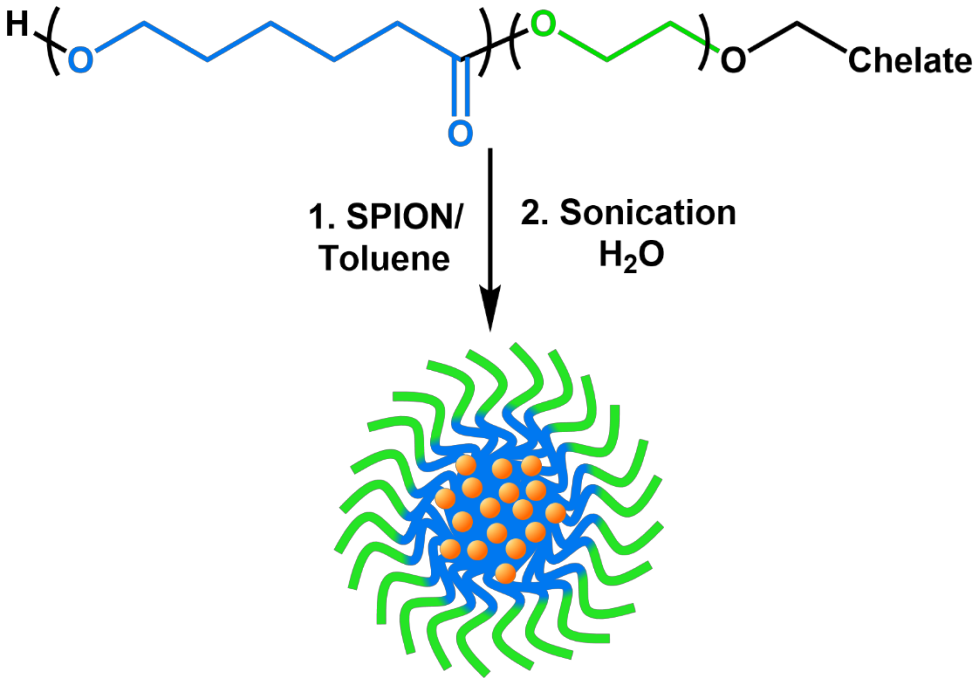

Figure S7. Synthetic scheme and illustration of magnetic micelles.

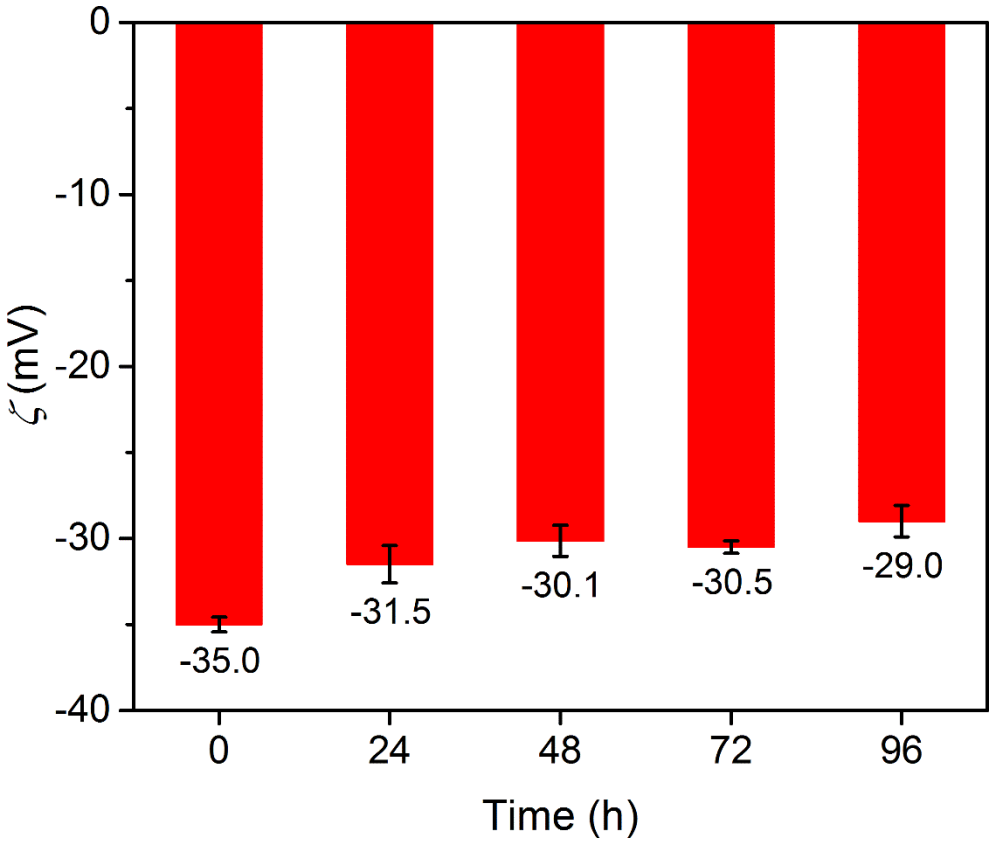

Figure S8. Progression of surface potentials (ζ) of GSH-micelle (containing 150 μM GSH) over 96 h, in the presence of 10 μM cisplatin in H_2O, incubated at 37 °C and pH 7.

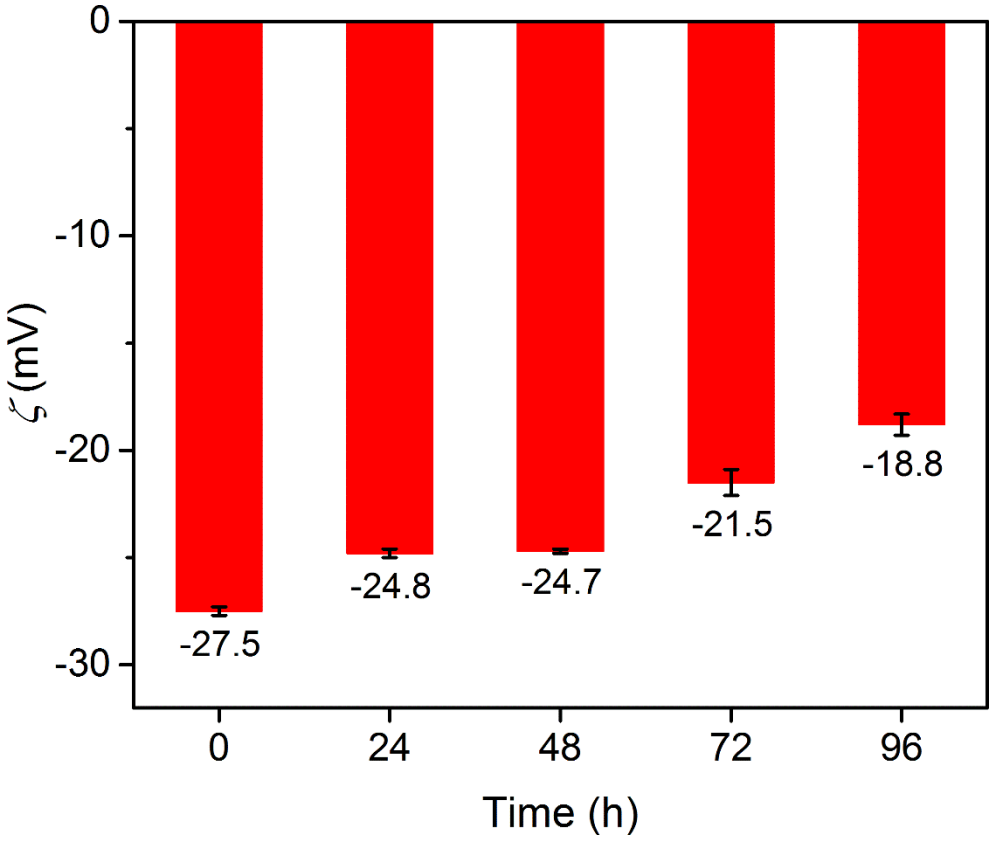

Figure S9. Progression of surface potentials (ζ) of DTC-micelle (containing 150 μM DTC) over 96 h, in the presence of 10 μM cisplatin in H_2O, incubated at 37 °C and pH 7.

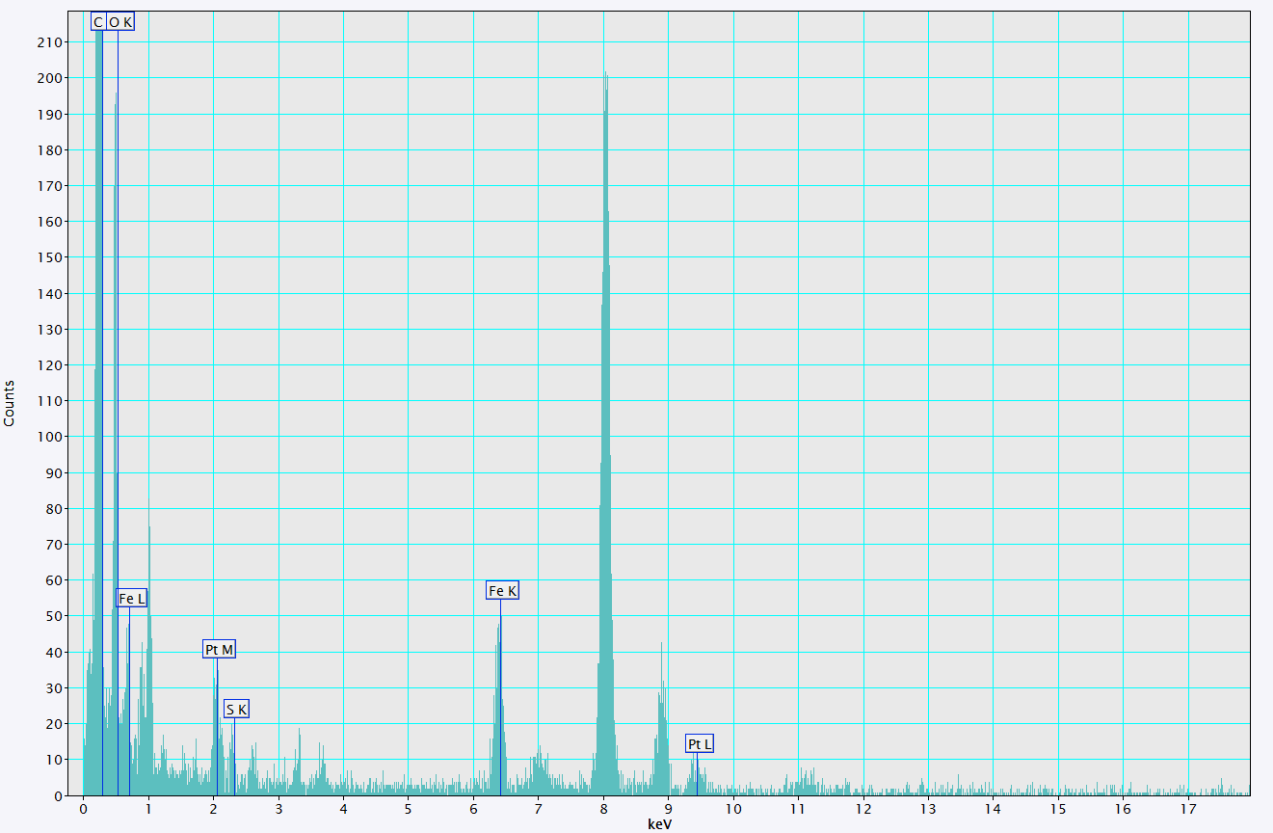

Figure S10. EDS spectrum for a DTC-micelle after incubating with excess cisplatin. Elements relevant to micelles, C, O, Fe, S, Pt are identified in the figure. Unlabeled peaks are attributed to impurities on the sample grid, such as Cu and Co.

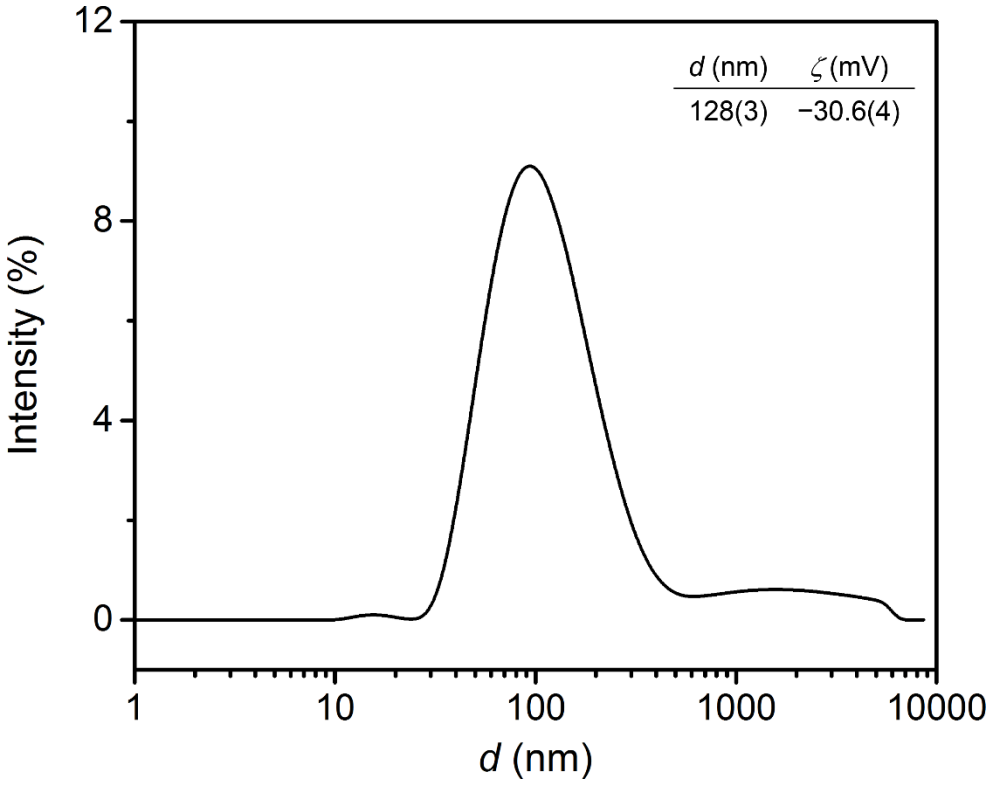

Figure S11. Size distribution of RhB-GSH-micelle in neutral H_2O at 25 °C. Inset indicates the averaged diameter and ζ potential of the particles.

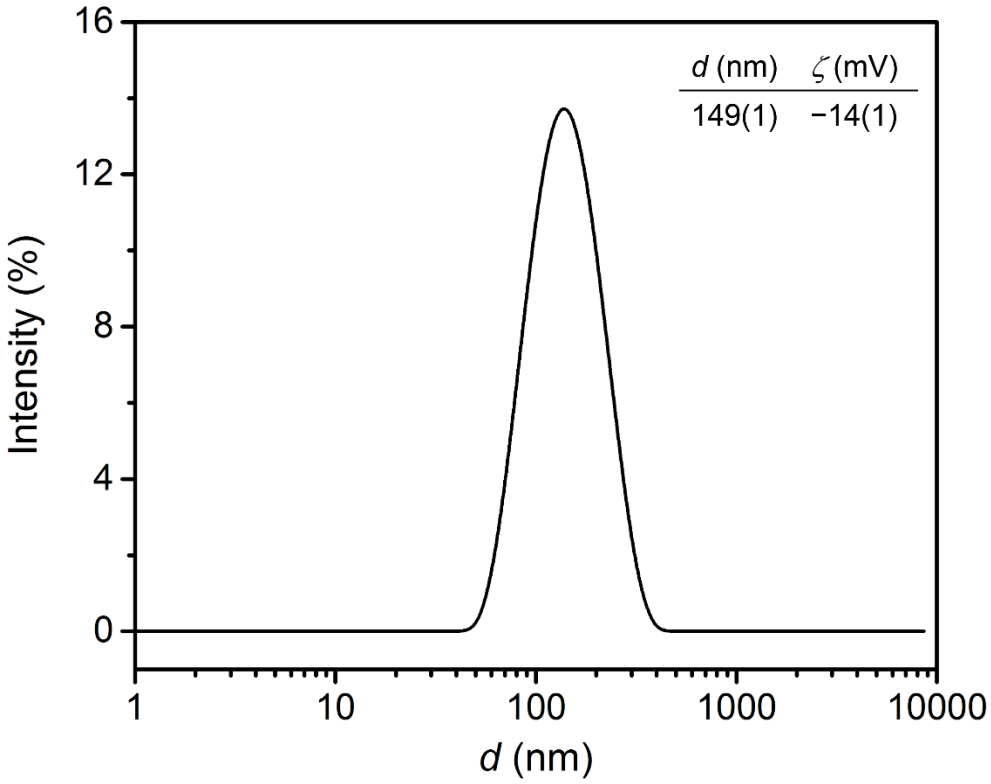

Figure S12. Size distribution of RhB-DTC-micelle in neutral H_2O at 25 °C. Inset indicates the averaged diameter and ζ potential of the particles.

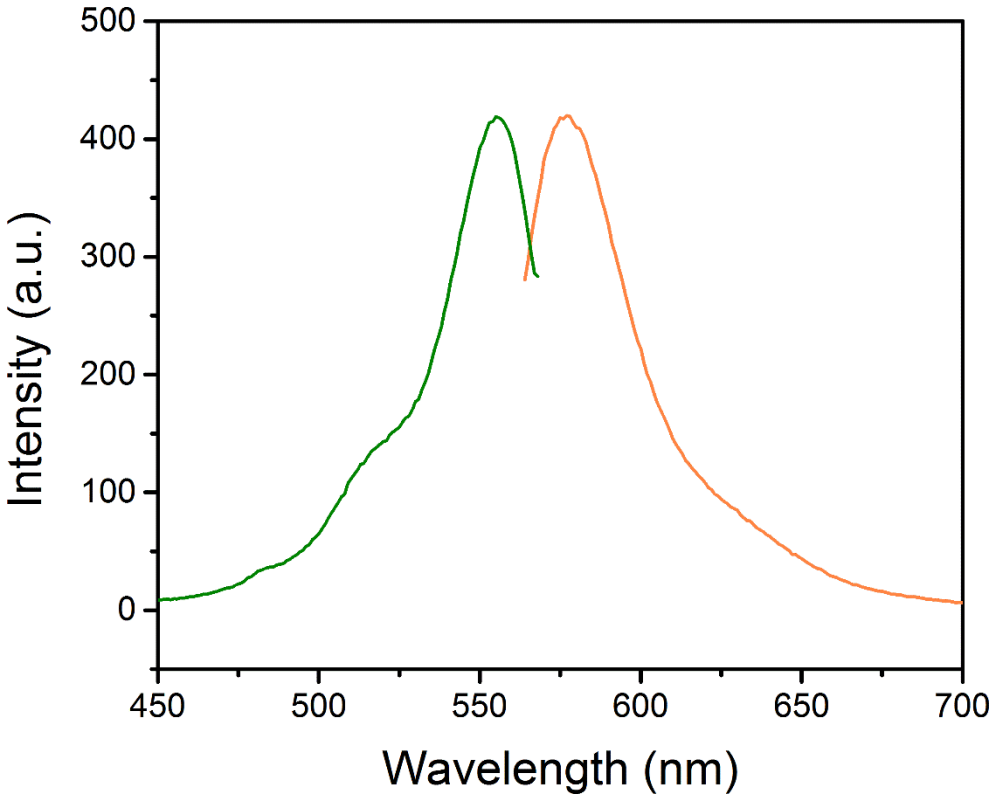

Figure S13. Excitation (monitoring emission at 577 nm, green) and emission (excited at 555 nm, orange) spectra of RhB-GSH-SPION-micelle in water at pH 7 and rt.

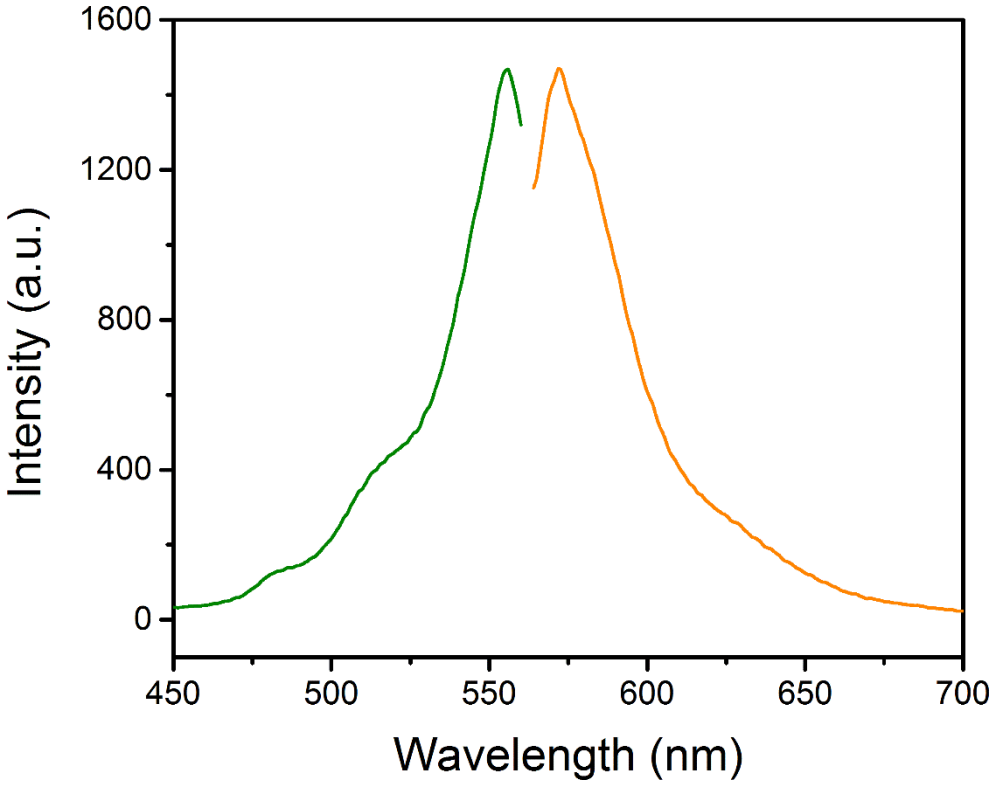

Figure S14. Excitation (monitoring emission at 572 nm, green) and emission (excited at 555 nm, orange) spectra of RhB-DTC-SPION-micelle in water at pH 7 and rt.

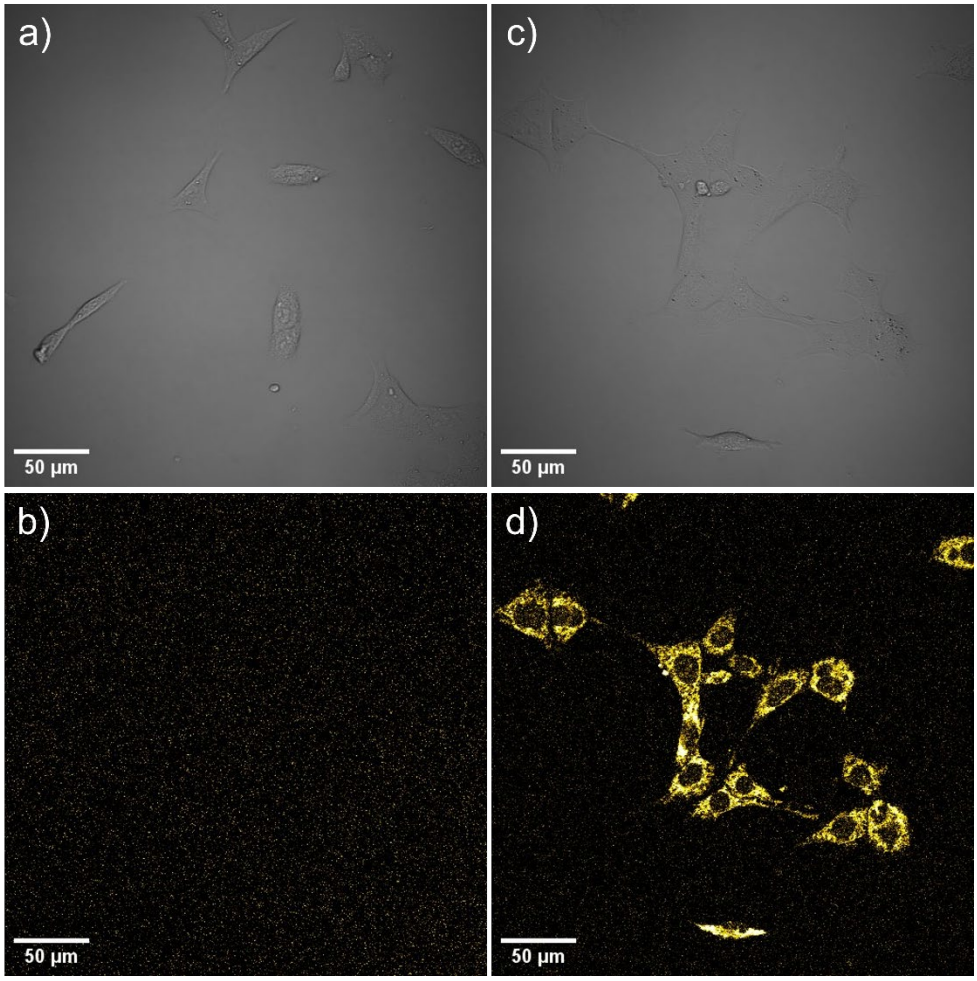

Figure S15. Confocal micrographs of HEI-OC1 cells incubated in the absence (panels a–b)/ presence (panels c–d) of GSH-micelles.

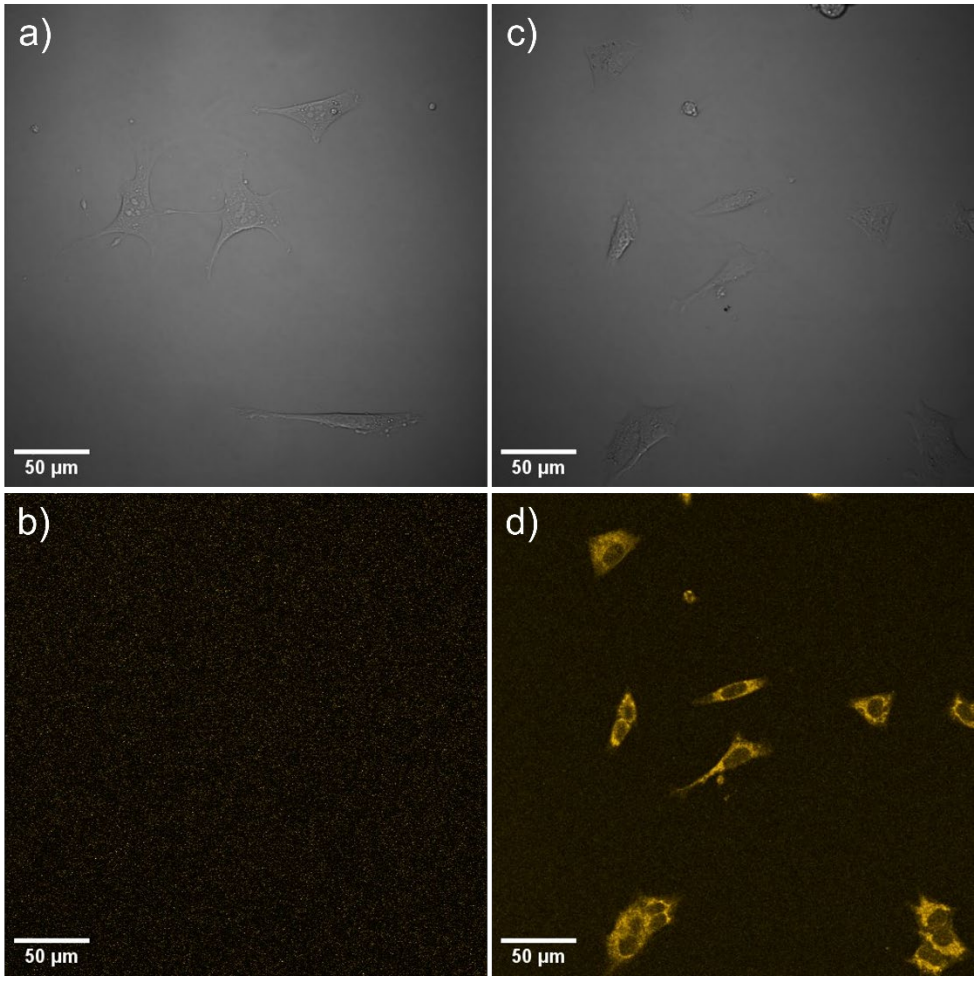

Figure S16. Confocal micrographs of HEI-OC1 cells incubated in the absence (panels a–b)/ presence (panels c–d) of DTC-micelles.

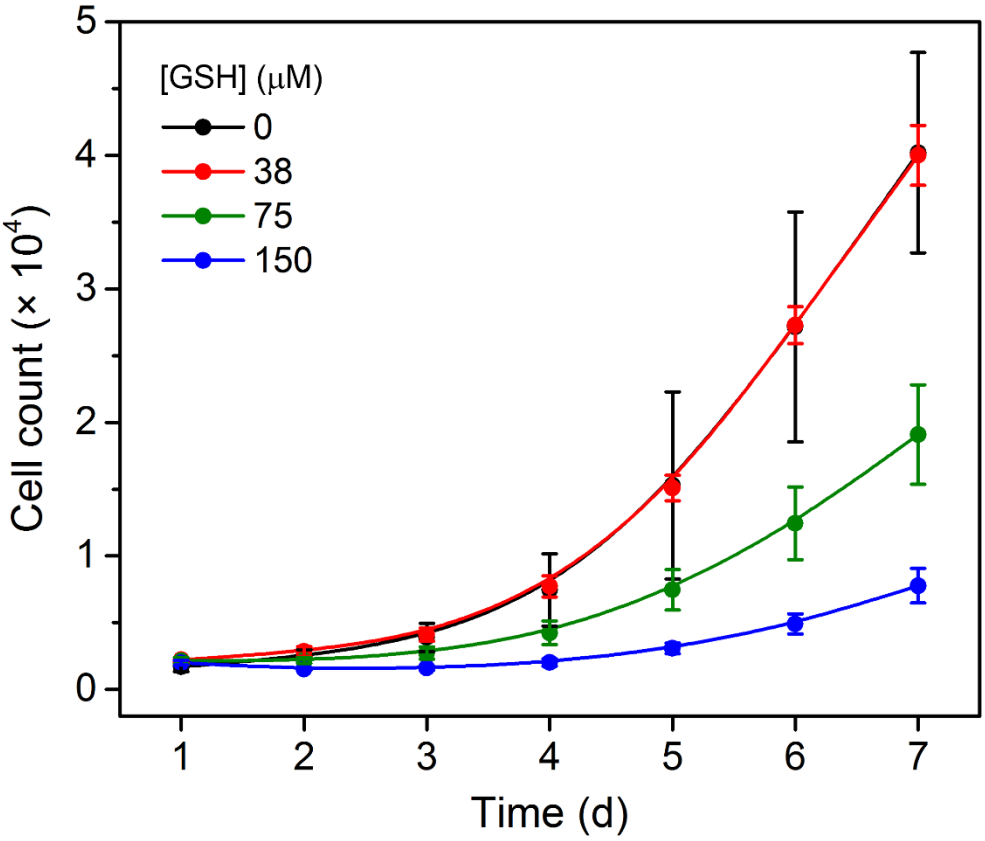

Figure S17. The proliferation of HEI-OC1 cells over 7 days in the presence of GSH-micelles. The legend indicates the concentrations of surface GSH groups.

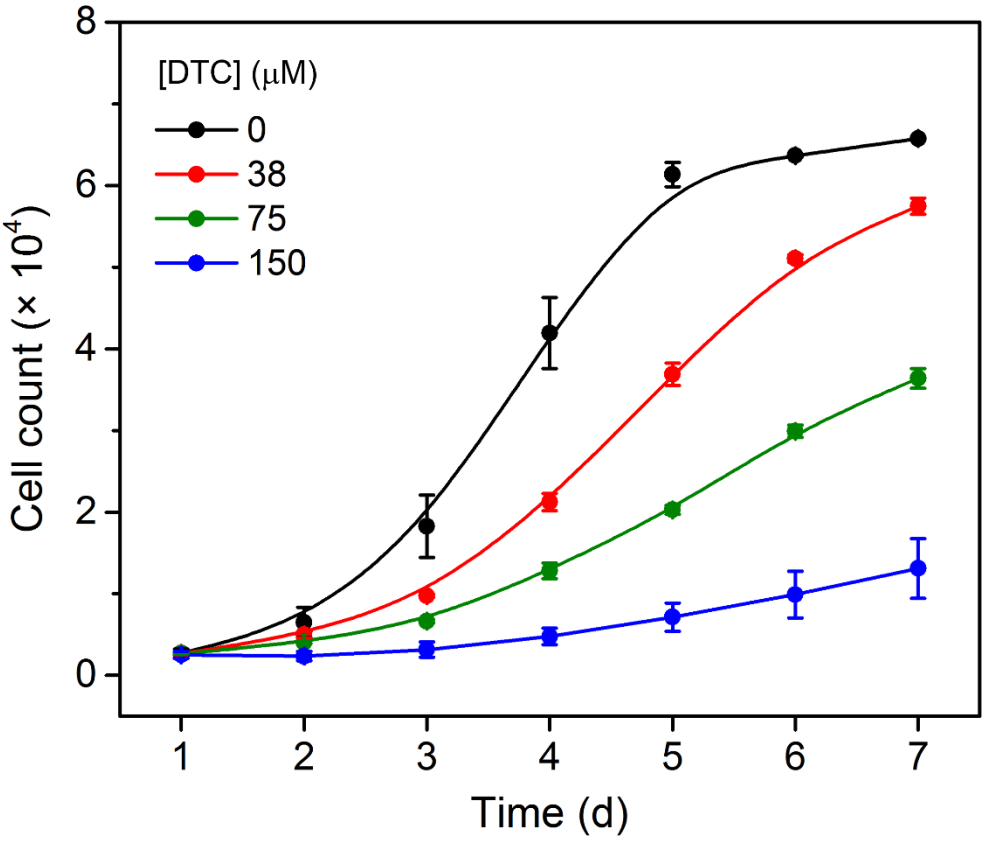

Figure S18. The proliferation of HEI-OC1 cells over 7 days in the presence of DTC-micelles. The legend indicates the concentrations of surface DTC groups.

References

(1) L. Qiao, Z. Fu, J. Li, J. Ghosen, M. Zeng, J. Stebbins, P. N. Prasad and M. T. Swihart, *ACS Nano*, 2017, **11**, 6370–6381.

(2) M. N. Kayyali, A. J. Ramsey, E. M. Higbee-Dempsey, L. Yan, B. W. O'Malley Jr., A. Tsourkas and D. Li, *J. Assoc. Res. Otolaryngol.*, 2018, **19**, 123–132.