Supporting Information for

A Dual-response Drug Delivery System with X-ray and ROS to Boost the Anti-Tumor Efficiency of TPZ via Enhancement of Tumor Hypoxia Level

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1. Synthesis procedures.

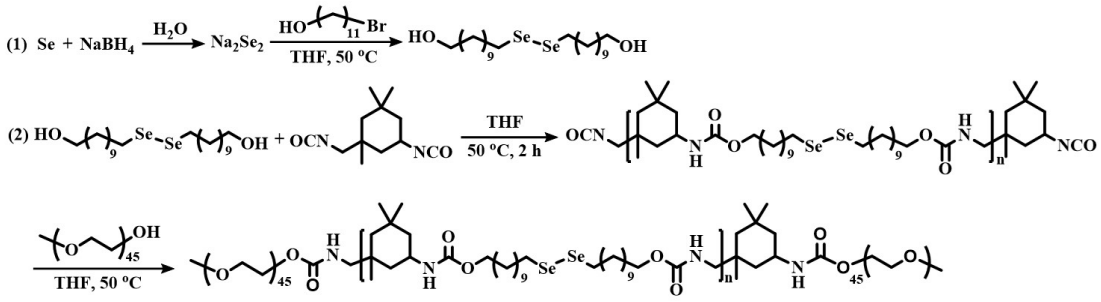

Figure S1. The synthesis routes of di(1-hydroxylundecyl) diselenide and PEG-PUSeSe-PEG (Se-polymer) block copolymer.

1.1 Synthesis of di(1-hydroxylundecyl) diselenide.

Firstly, Sodium borohydride (1.0 g, 26.4 mmol) was dissolved in 10 mL water and slowly added to selenium powder (1.0 g, 12.6 mmol) suspended in 15 mL water under N_2 flow at room temperature. Secondly, 1.0 g selenium powder was added after 10 minutes of reaction. The solution was stirred for 15 min and warmed by the steam bath to 50 °C. Next, 11-bromoethanol (6.33 g, 25.2 mmol) dissolved in 25 mL anhydrous THF was slowly added into it. The reaction was performed at 50 °C for 24 h and the reaction solution was extracted three times by CH_2Cl_2 and dried with anhydrous Na_2SO_4 for 12 h. Then, the product was steamed by evaporator to remove the solvent and purified by column chromatography with CH_2Cl_2 and ethyl acetate (volume ratio: 4:1) as eluent. A yellow transparent liquid was obtained. Finally, the liquid was steamed by evaporator to obtain di(1-hydroxylundecyl) diselenide ($HOC_{11}SeSeC_{11}OH$). ^{1}H-NMR (300 MHz, $CDCl_3$, δ) (ppm): 3.63 (4H, t, $HOCH_2$), 2.90 (4H, t, $SeSeCH_2$) 1.72-1.28 (36H, m, $HOCH_2$ $(CH2)_9CH_2SeSe$); LC-MS: calculated 500.53, found 500.16.

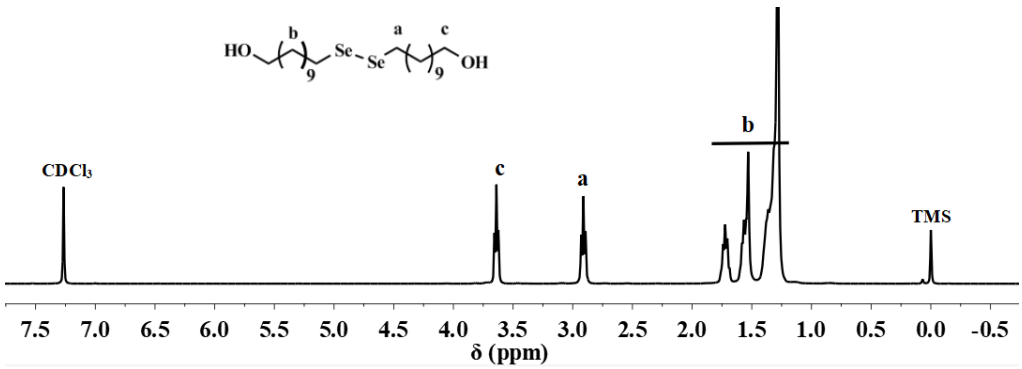

Figure S2. ^{1}H NMR spectrum of di(1-hydroxylundecyl) diselenide in $CDCl_3$.

1.2 Synthesis of PEG-PUSeSe-PEG (Se-polymer) block copolymer.

Firstly, the anhydrous flask was degassed by N_2 for 20 min. Secondly, 0.2 g $HOC_{11}SeSeC_{11}OH$ (0.40 mmol), 10 mg of dibutyltin dilaurate (DBTDL) (0.016 mmol) and 3 mL of anhydrous tetrahydrofuran (THF) were added into the flask. Next, a solution of isophorone diisocyanate (IPDI) (97.8 mg, 0.44 mmol) was injected into the flask. Then, the sealed flask was transferred into an oil bath at 50 °C and reacted for 2 h. 1.3 g $mPEG_{2000}$ (0.65 mmol) dissolved in 2 mL of anhydrous THF was injected into the flask and carried out for 12 h. The final solvent was concentrated by rotary evaporation. The residual viscous solvent was dropped in cold methanol thrice. Finally, the powder of amphiphilic diselenium-inserted copolymer (Se-polymer) was obtained after vacuum drying at room temperature (0.76 g, yield: 45%).

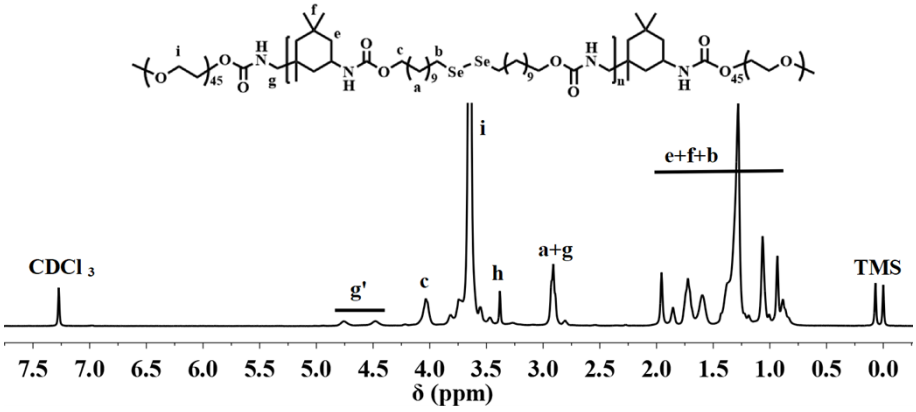

Figure S3. ^{1}H NMR spectrum of Se-polymer in $CDCl_3$.

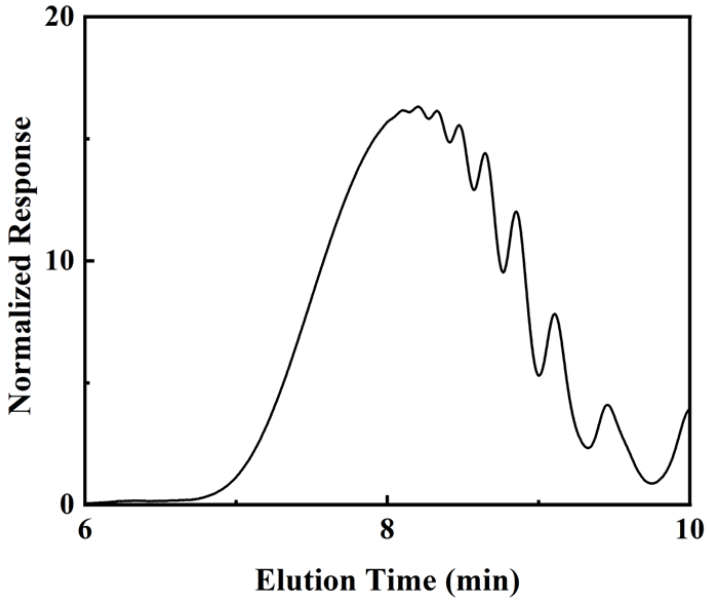

Figure S4. GPC plot of Se-polymer in DMF.

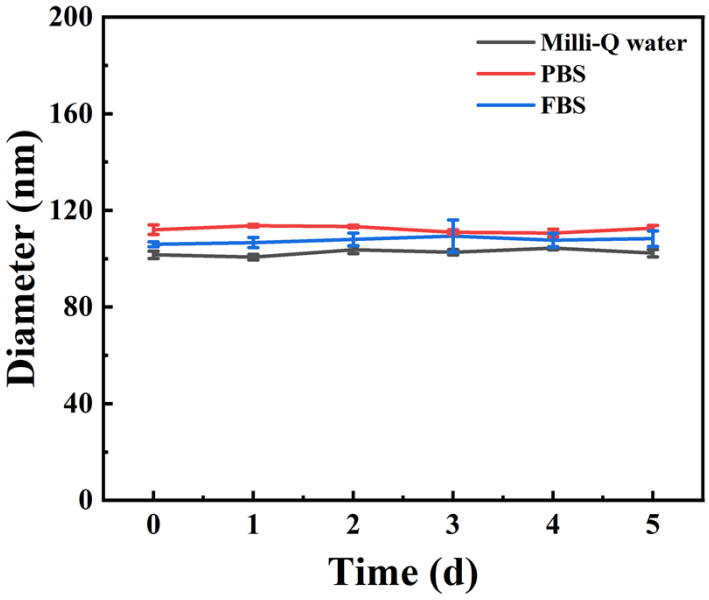

Figure S5. Particle size change of P-NPs at different incubation times and in three different media: Milli-Q water, PBS, and FBS (10%).

2. The stability of Nile red (NR) under H_2O_2 and X-ray irradiation condition.

The stability of the NR (THF: H_2O = 4: 1, 0.1 mg/mL) was tested under five different experimental conditions by fluorometer: (a) control, (b)10 Gy X-ray, (c) 20

Gy X-ray, (d) 100 μM H_2O_2, (e) 10 Gy X-ray and 100 μM H_2O_2. The experiments were carried out in three repeats.

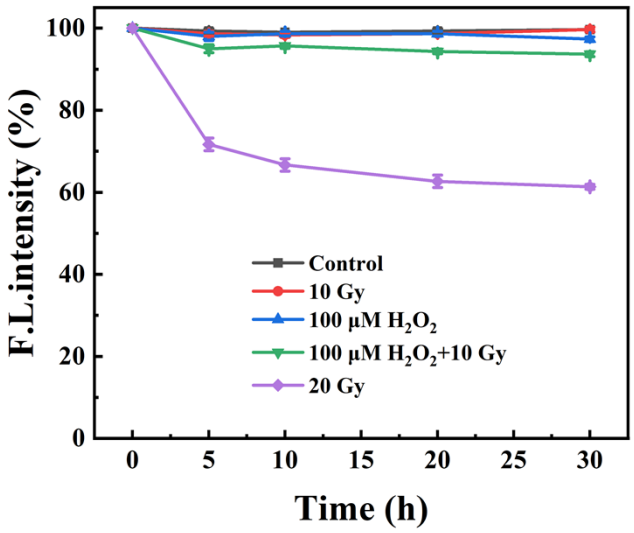

Figure S6. The fluorescence intensity of NR under different conditions.

3. Size distribution of PTX-loaded NPs (P-NPs) and DOX-loaded NPs (D-NPs).

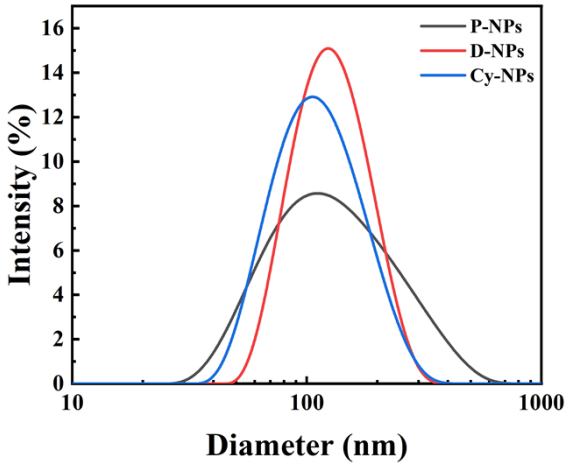

Figure S7. Size distribution of P-NPs, Cy-NPs and D-NPs.

Table S1. Liver and kidney functional marker test.

	Control	P-NPs	F-PTX

ALT (U/L)	43.37 ± 2.83	43.87 ± 5.97	46.73 ± 4.27
AST (U/L)	139.01 ± 18.24	126.40 ± 11.16	159.17 ± 17.17
ALP (U/L)	152.33 ± 12.12	144.67 ± 13.25	169.01 ± 13.53
Bun (mmol/L)	6.37 ± 0.67	6.83 ± 0.55	8.73 ± 0.78
CREA (μmol/L)	16.33 ± 1.89	16.67 ± 1.06	17.67 ± 1.15