

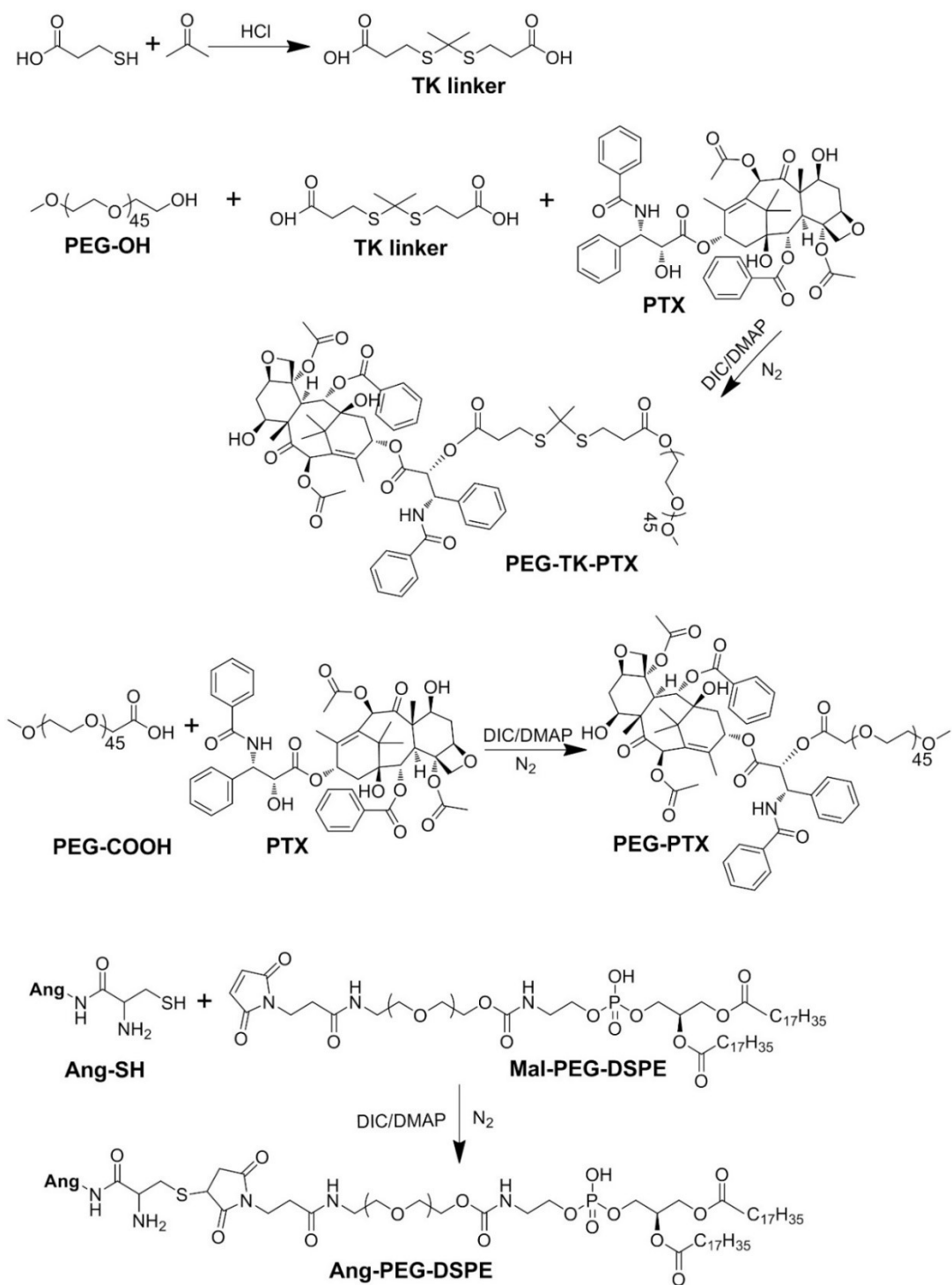
# **Rational Design of ROS-Responsive Nanocarriers for Targeted X-ray-Induced Photodynamic Therapy and Cascaded Chemotherapy of Intracranial Glioblastoma**

Beibei Zhang<sup>†</sup>, Rui Xue<sup>†</sup>, Chunyang Sun<sup>†, ‡, \*</sup>

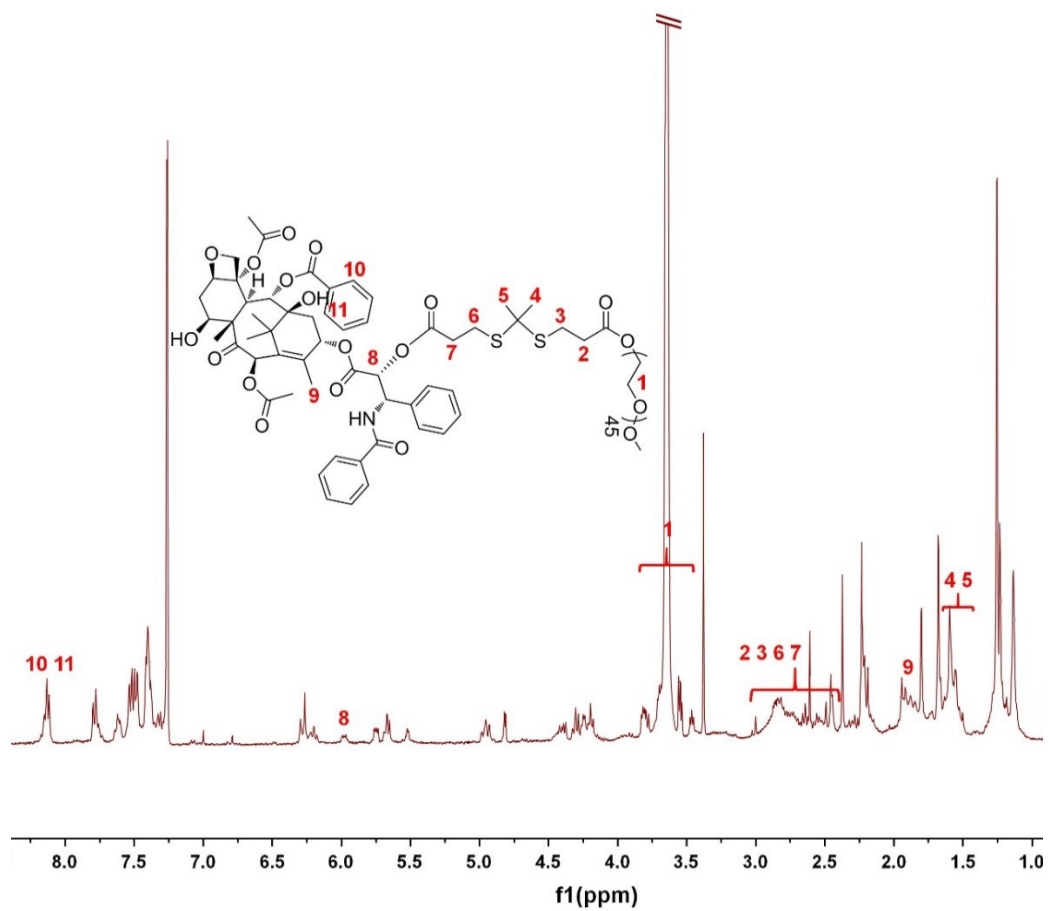
<sup>†</sup> Department of Radiology and Tianjin Key Laboratory of Functional Imaging, Tianjin Medical University General Hospital, Tianjin 300052, P.R. China

<sup>‡</sup> Multimodality Preclinical Molecular Imaging Center, Tianjin Medical University General Hospital, Tianjin 300052, P.R. China

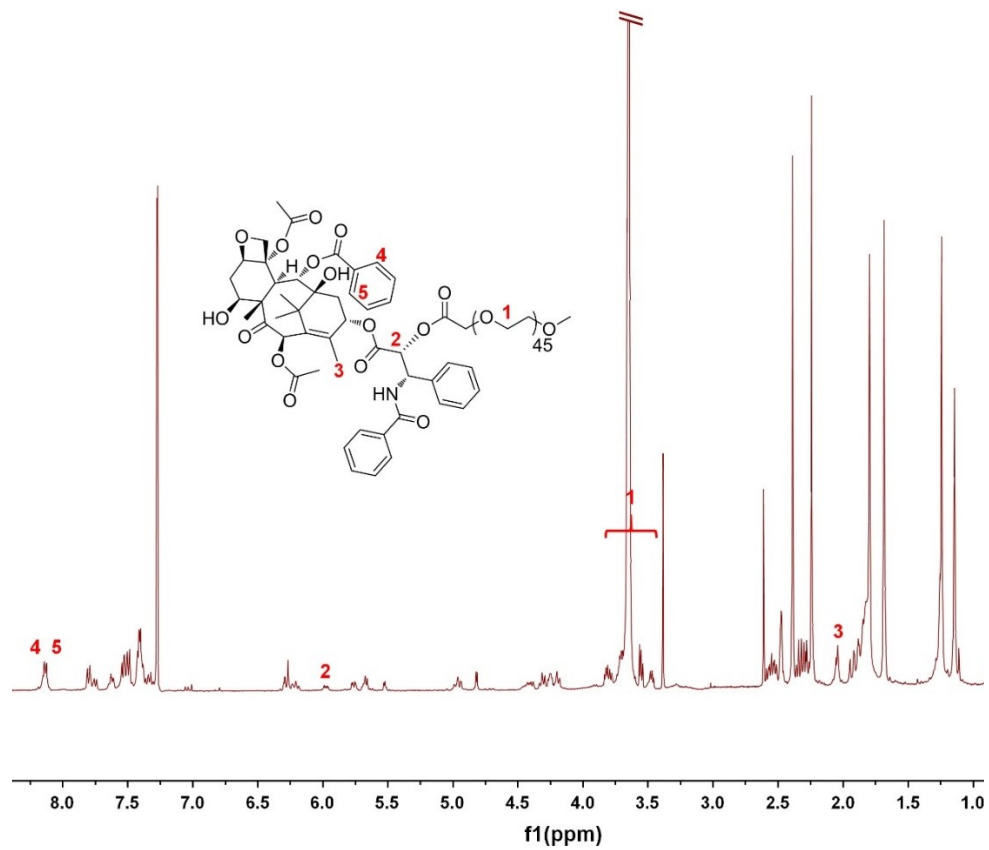
E-mail: chysunshine@gmail.com (C. Y. Sun)



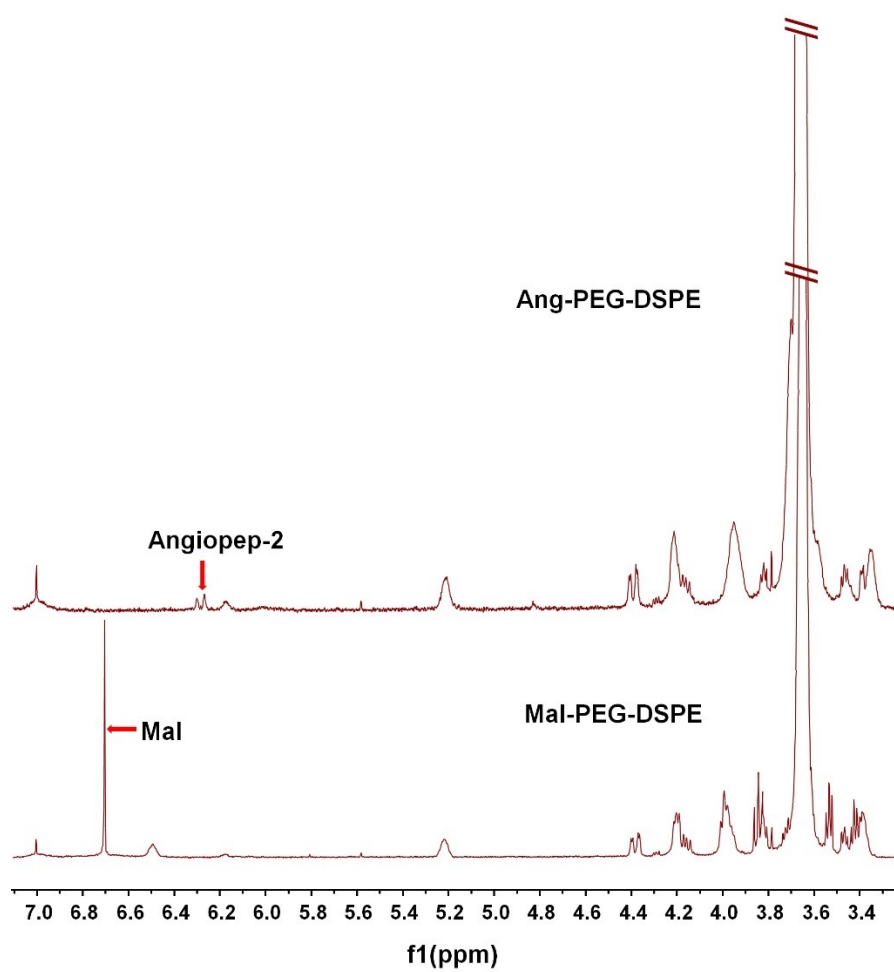
**Figure S1.** Synthetic routes for TK linker, PEG-TK-PTX, PEG-PTX and Ang-PEG-DSPE, respectively.



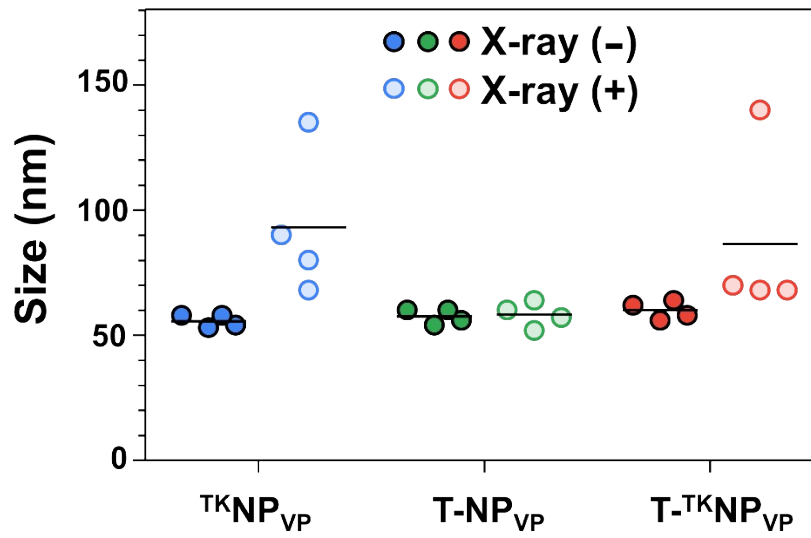
**Figure S2.** <sup>1</sup>H NMR spectrum of PEG-TK-PTX.



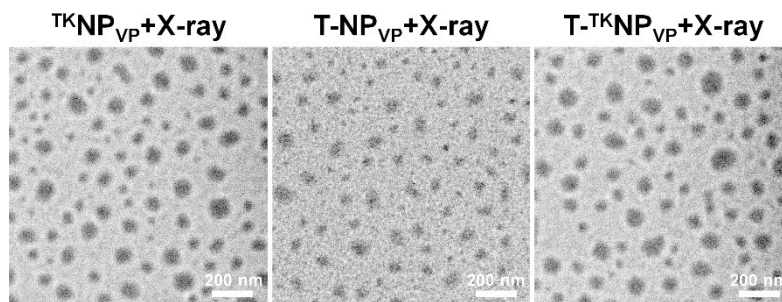
**Figure S3.** <sup>1</sup>H NMR spectrum of PEG-PTX.



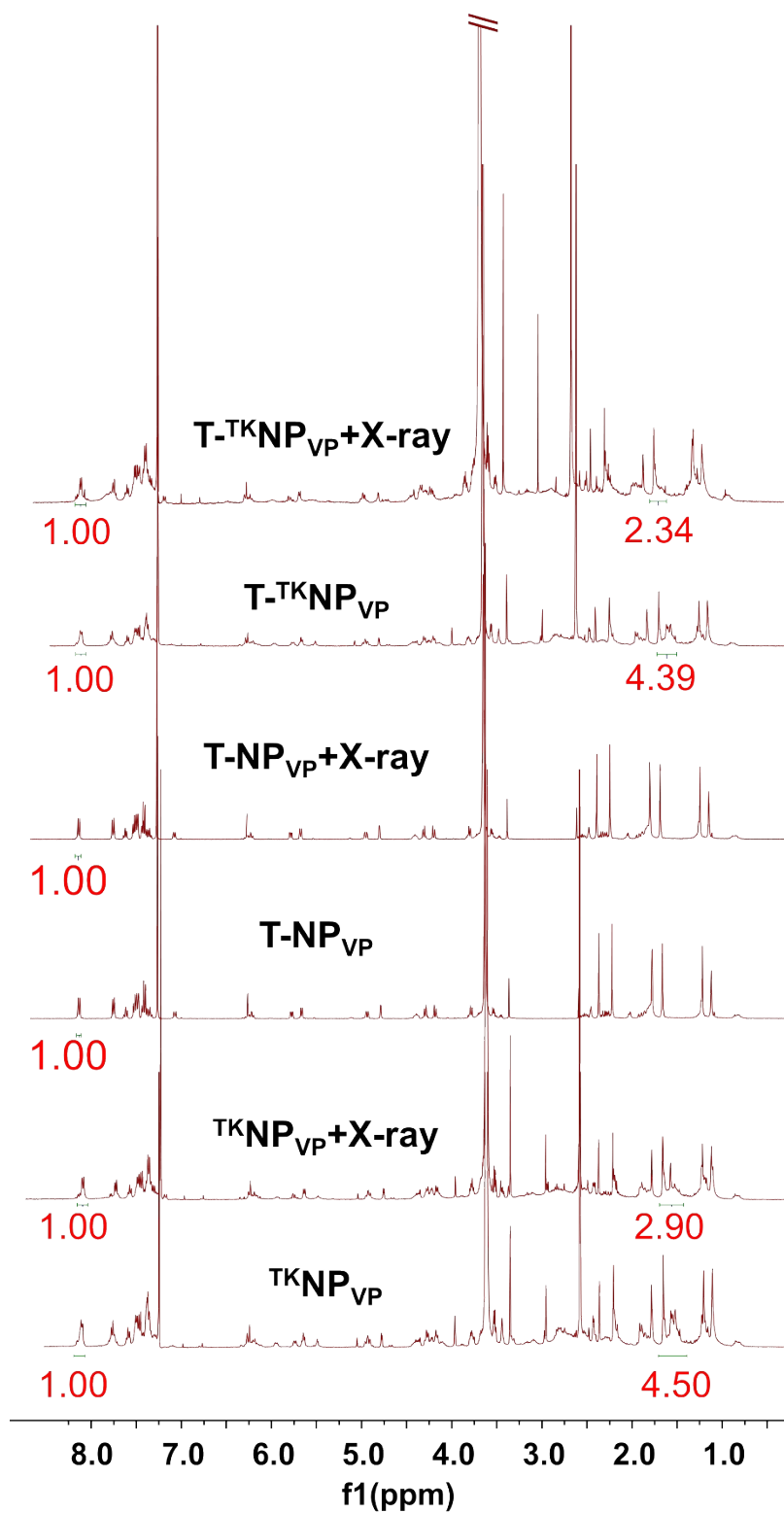
**Figure S4.** <sup>1</sup>H NMR spectrum of Mal-PEG-DSPE and Ang-PEG-DSPE.



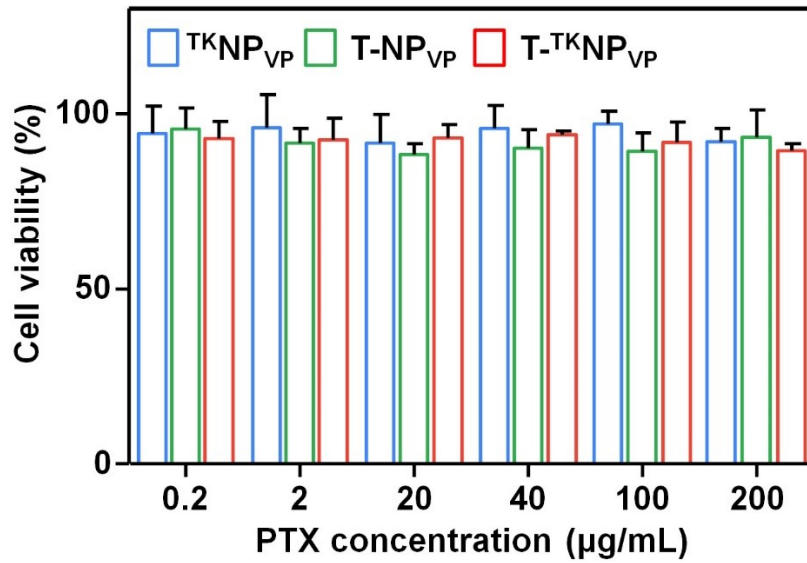
**Figure S5.** Particle size changes before and after 4 Gy of X-ray exposure.



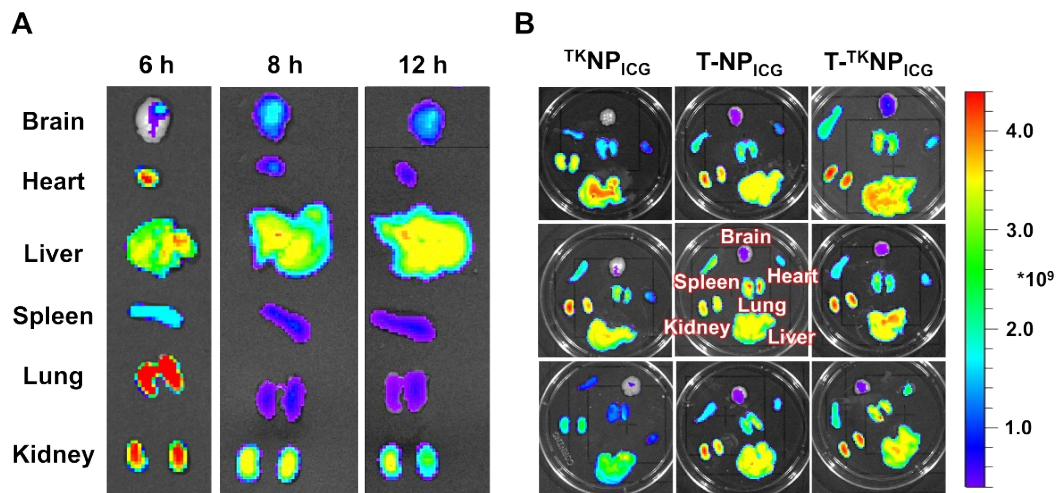
**Figure S6.** TEM images of  $^{\text{TK}}\text{NP}_{\text{VP}}$ ,  $\text{T-NP}_{\text{VP}}$  and  $\text{T-}^{\text{TK}}\text{NP}_{\text{VP}}$  after 4 Gy of X-ray irradiation.



**Figure S7.** <sup>1</sup>H NMR spectra of TKNP<sub>VP</sub>, T-NP<sub>VP</sub> and T-TKNP<sub>VP</sub> before and after 4 Gy of X-ray exposure.

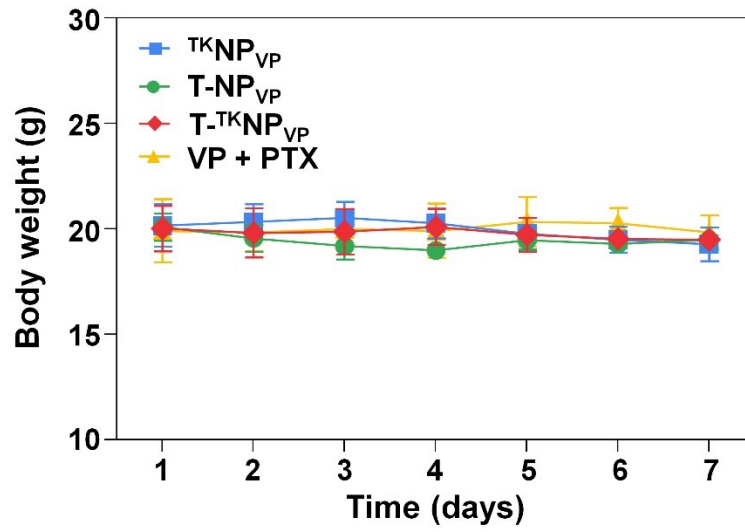


**Figure S8.** The viabilities of bEnd.3 cells after incubation with  $TKNP_{VP}$ ,  $T-NP_{VP}$  or  $T-TKNP_{VP}$  at different PTX concentrations for 24 h.



**Figure S9.** (A) Fluorescence distribution of  $T-TKNP_{ICG}$  in isolated organs at 6, 8 and 12 h post-injection. (B) Fluorescence distribution of  $TKNP_{ICG}$ ,  $T-NP_{ICG}$  or  $T-TKNP_{ICG}$  in major organs at 24 h post-injection (n = 3).





**Figure S10.** Body weight changes after treatment with various formulations.

**Table S1.** Diameter and zeta potential of  $^{TK}NP_{VP}$ ,  $T-NP_{VP}$  and  $T-^{TK}NP_{VP}$ .

	diameter (nm)	polydispersity	zeta potential (mV)
$^{TK}NP_{VP}$	50.17±2.90	0.124	-11.8
$T-NP_{VP}$	52.83±2.72	0.133	-13.9
$T-^{TK}NP_{VP}$	52.33±4.12	0.147	-13.5

**Table S2.** Drug loading content (DLC) and encapsulation efficiency (EE) of  $^{TK}NP_{VP}$ ,  $T-NP_{VP}$  and  $T-^{TK}NP_{VP}$ .

	DLC (%)		EE (%)	
	PTX	VP	PTX	VP
$^{TK}NP_{VP}$	20.34±1.36	8.46±0.62	78.10±5.24	81.17±5.95
$T-NP_{VP}$	21.04±1.77	8.79±0.39	76.01±6.40	79.33±3.52
$T-^{TK}NP_{VP}$	19.25±1.12	9.25±0.43	68.99±4.01	82.86±3.88

**Table S3.** Animal number and their body weight (unit: g) during treatment.

Days	16	20	24	28	32	36
PBS	7(19.46±0.7)8	7(18.54±1.89)	6(17.53±1.38)	3(15.46±1.30)	1(14.5)	0
PTX+VP	7(20.24±0.38)	7(19.54±0.79)	6(18.75±0.97)	4(17.02±0.60)	2(14.95±0.65)	0
T- <sup>TK</sup> NP <sub>VP</sub>	7(18.54±0.8)	7(18.54±0.48)	7(18.24±0.40)	6(16.74±0.39)	0	0
PBS(+)	7(19.33±0.42)	7(18.54±0.73)	7(18.33±0.43)	7(17.33±0.42)	6(16.25±0.95)	4(15.5±0.35)
<sup>TK</sup> NP <sub>VP</sub> (+)	7(19.49±0.78)	7(19.24±1.19)	7(19.24±0.73)	7(19.74±0.75)	7(19.16±0.47)	6(15.5±0.71)
T-NP <sub>VP</sub> (+)	7(19.56±1.81)	7(20.84±1.97)	7(21.17±2.15)	7(20.56±1.24)	7(20.43±0.42)	7(19.79±0.88)
T- <sup>TK</sup> NP <sub>VP</sub> (+)	7(19.64±0.85)	7(19.54±1.38)	7(20.44±1.11)	7(20.44±0.83)	7(20.21±0.59)	7(19.5±0.76)

Days	40	44	48	52	56	60
PBS						
PTX+VP						
T- <sup>TK</sup> NP <sub>VP</sub>						
PBS(+)	0					
<sup>TK</sup> NP <sub>VP</sub> (+)	2(14±0.71)	0				
T-NP <sub>VP</sub> (+)	7(19.43±0.68)	7(20.63±0.88)	2(15.17±0.62)	1(14)	0	
T- <sup>TK</sup> NP <sub>VP</sub> (+)	7(19.36±0.64)	7(18.36±0.91)	6(17.75±1.18)	3(15.38±0.65)	1(15)	0

**Table S4.** Routine blood test of <sup>TK</sup>NP<sub>VP</sub>, T-NP<sub>VP</sub> and T-<sup>TK</sup>NP<sub>VP</sub>.

	PTX+VP	<sup>TK</sup> NP <sub>VP</sub>	T-NP <sub>VP</sub>	T- <sup>TK</sup> NP <sub>VP</sub>	Unit
WBC	3.86±0.94	5.12±0.38	6.4±0.88	7.01±0.81	10 <sup>9</sup> /L
RBC	11.3±0.58	11.18±0.36	11.5±0.52	11.83±0.38	10 <sup>12</sup> /L
Hb	155.25±6.1	152.75±4.21	156.75±4.76	158.25±4.55	g/L
HCT	38.93±1.22	38.3±0.61	38.98±1.06	39.9±1.42	L/L
MCV	34.45±1	34.3±0.86	33.93±0.54	33.85±1.31	fL
MCH	13.75±0.32	13.68±0.36	13.68±0.25	13.43±0.55	pg
MCHC	398.75±6.98	398.75±5.4	402.25±4.82	396.75±13.94	g/L