Electronic Supplementary Information for

An Ultrasmall PVP-Fe-Cu-Ni-S Nano-agent for Synergistic Cancer Therapy through triggering Ferroptosis and Autophagy

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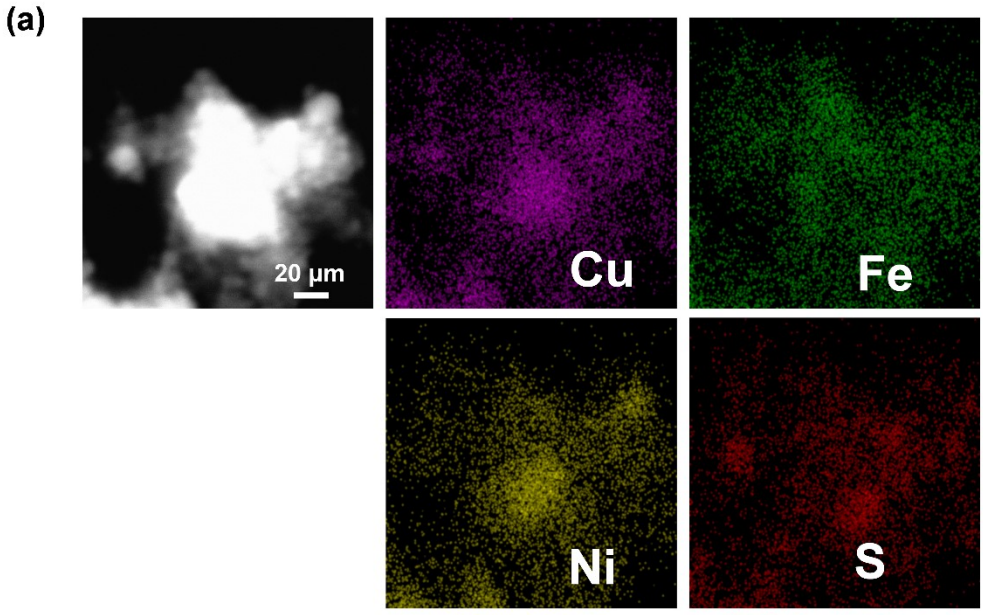
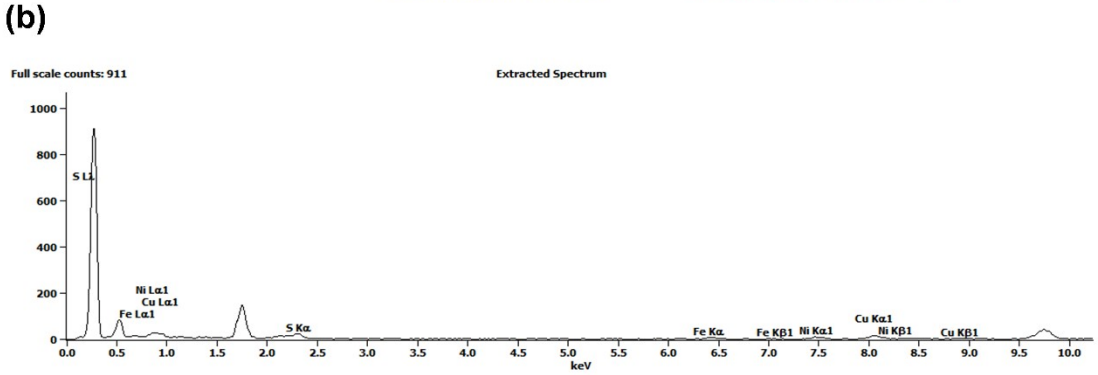
1. TEM-EDS mapping of NPs





Element Line	Net Counts	Int. Cps/nA	Weight %	Weight % Error	Norm. Wt.%	Norm. Wt.% Err	Atom %	Atom % Error	Standard Name
S K	160	11.760	18.98	± 2.61	18.98	± 2.61	30.77	± 4.23	
Fe K	102	7.497	14.37	± 2.39	14.37	± 2.39	13.37	± 2.23	
Ni K	135	9.923	20.35	± 3.01	20.35	± 3.01	18.01	± 2.67	
Cu K	279	20.507	46.30	± 4.65	46.30	± 4.65	37.86	± 3.80	
Total			100.00		100.00		100.00		

Fig. S1. (a) TEM-EDS mapping and (b) compositional analysis of NPs.

2. Synthesis process of NPs and PVP NPs.

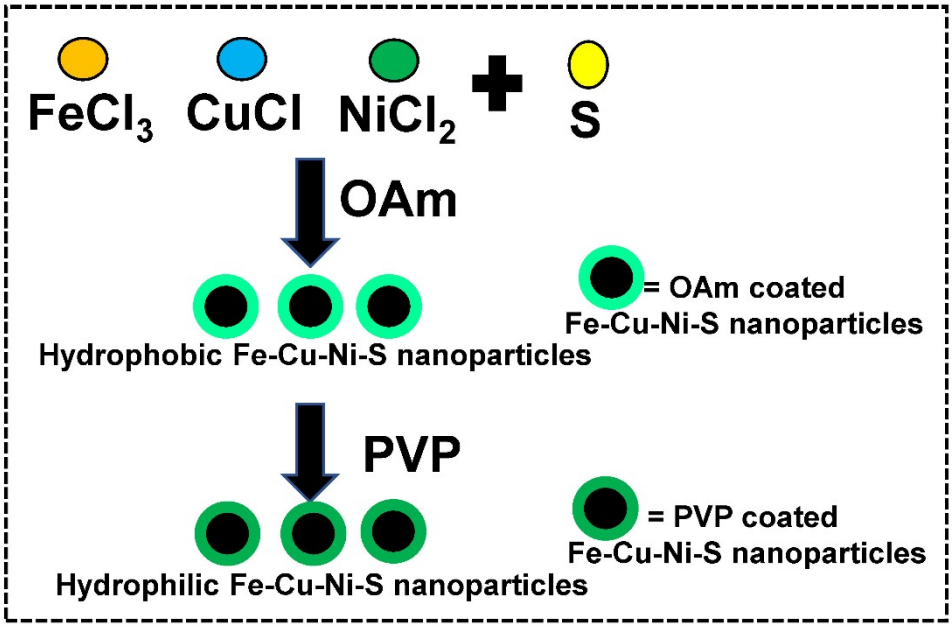


Fig. S2. A scheme of the synthesis process of NPs and PVP NPs.

3. The water solubility of PVP-NPs.

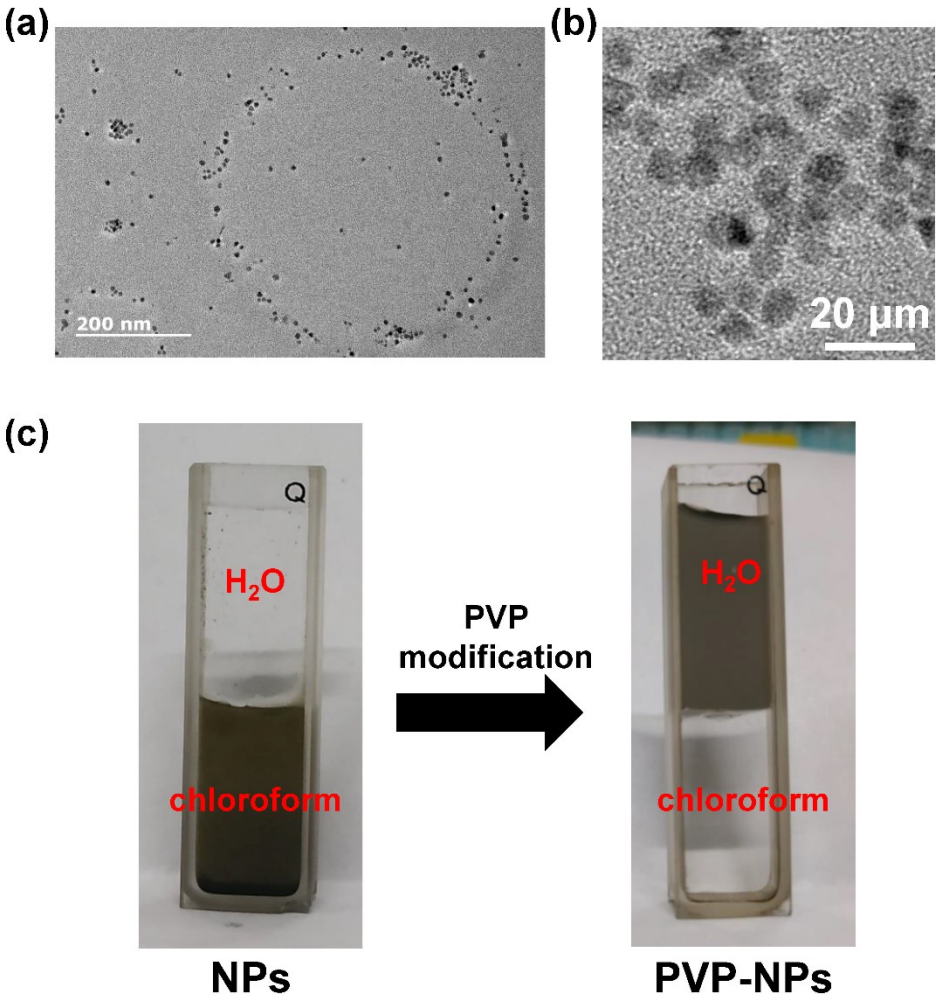


Fig. S3. (a, b) TEM of PVP-NPs. (c) Photograph of NPs dispersed in chloroform (left) and in pure water (right) before and after PVP modification.

4. Zeta potential analysis of NPs and PVP-NPs.

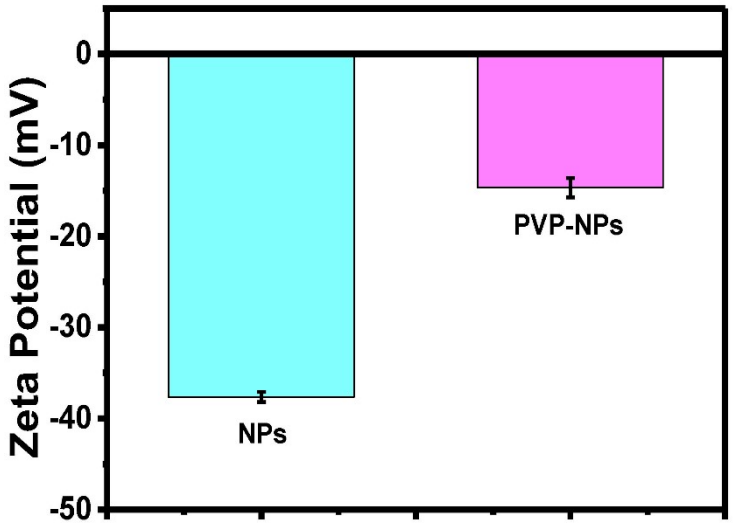


Fig. S4. Zeta potential analysis of NPs and PVP-NPs.

5. Photothermal ability of NPs.

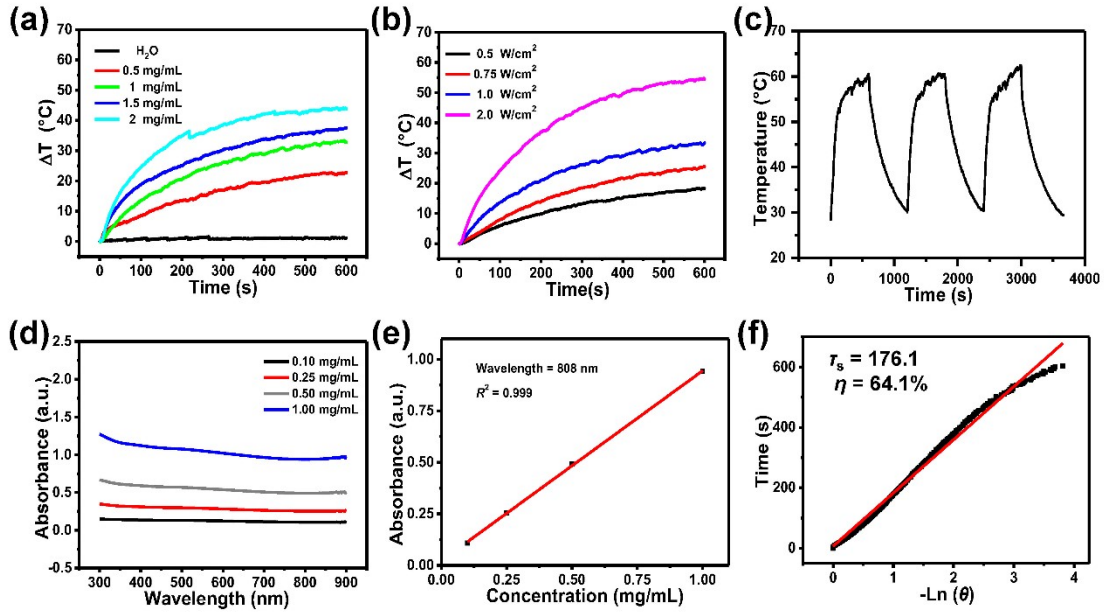


Fig. S5. Photothermal ability of NPs. (a) The relationship of the photothermal conversion with different concentrations of NPs under NIR irradiation (1 W/cm^2) for 10 min. (b) The relationship of photothermal conversion and the different power densities (0.5-2 W/cm2) of NPs (1 mg/mL). (c) Temperature variations of NPs (1 mg/mL) over 3 heating-cooling cycles under NIR irradiation. (d) UV-vis-NIR absorbance spectrum with different concentrations of NPs. (e) The relationship of absorbance and different concentrations of NPs. (f) The relationship between the first cooling time and negative natural logarithm of the temperature driving force calculated from (c). The η of PVP-NPs was estimated to be ~ 64.1%.

6. Chemo-Dynamic ability of PVP-NPs.

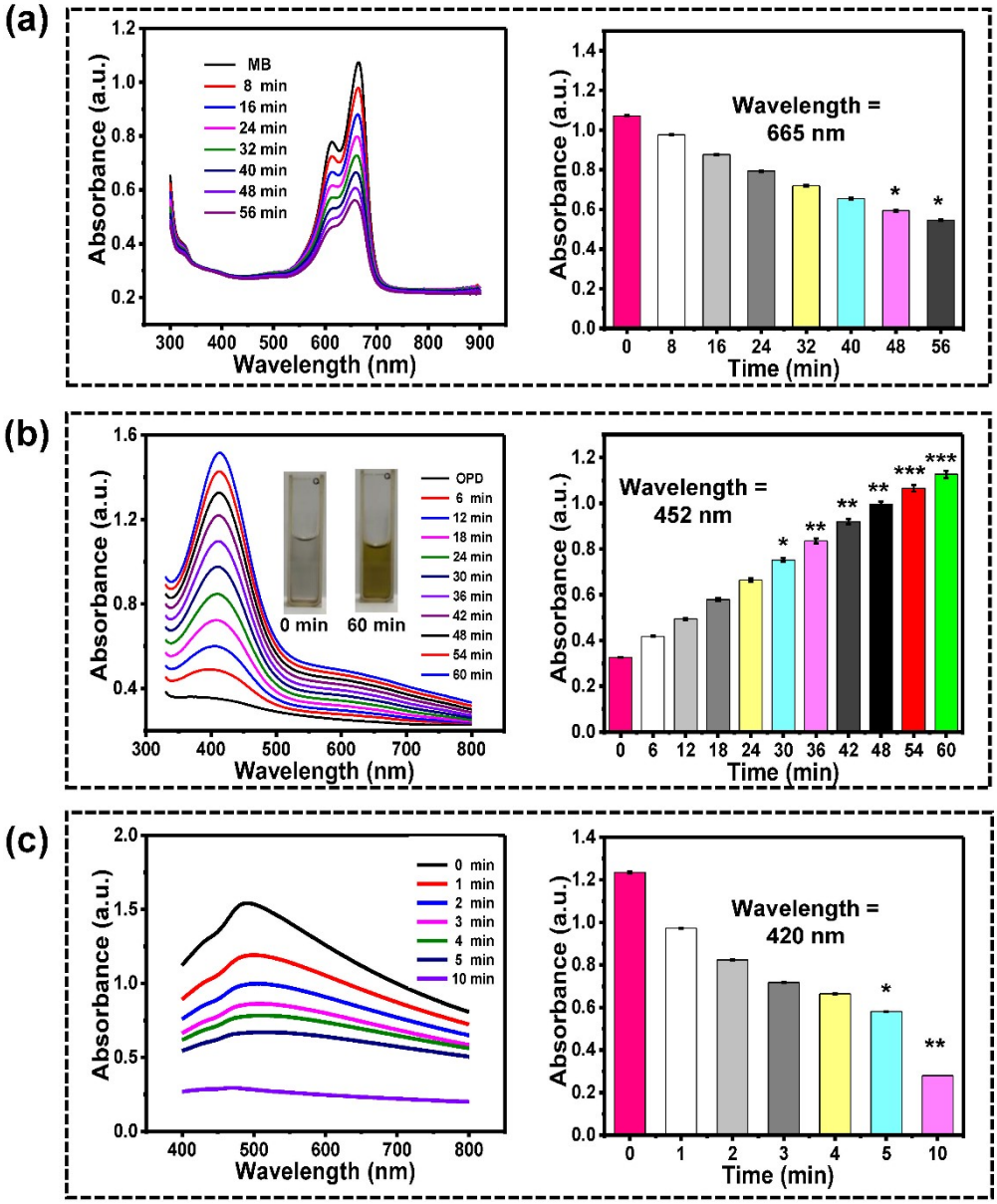


Fig. S6. Chemo-Dynamic ability of PVP-NPs. (a) The degradation of MB with PVP-NPs (0.1 mg/mL) in different treatment time. (b) The degradation of OPD with PVP-NPs (0.1 mg/mL) in different treatment time. (c) Extracellular singlet oxygen ($_1O^2$) generation of PVP-NPs (0.1 mg/mL) with different NIR treatment. Data are presented as mean value ± SD. **p<0.05, **p<0.01, ***p<0.001*.

7. Electron paramagnetic resonance analysis of PVP-NPs.

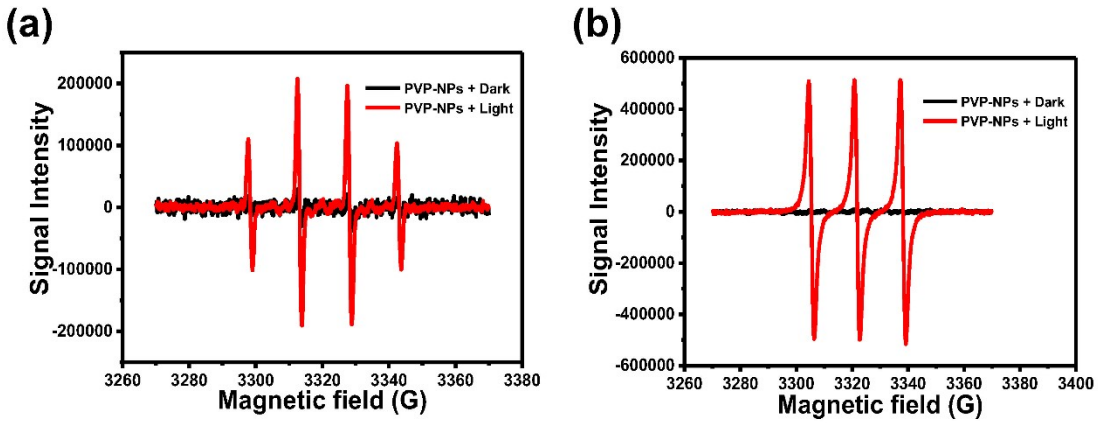


Fig. S7. (a) Electron paramagnetic resonance spectra of PVP-NPs after white light irradiation or not in the presence of DMPO. (b) Electron paramagnetic resonance spectra of PVP-NPs after white light irradiation or not in the presence of TEMP.

8. Synthesis process of NPs and PVP NPs.

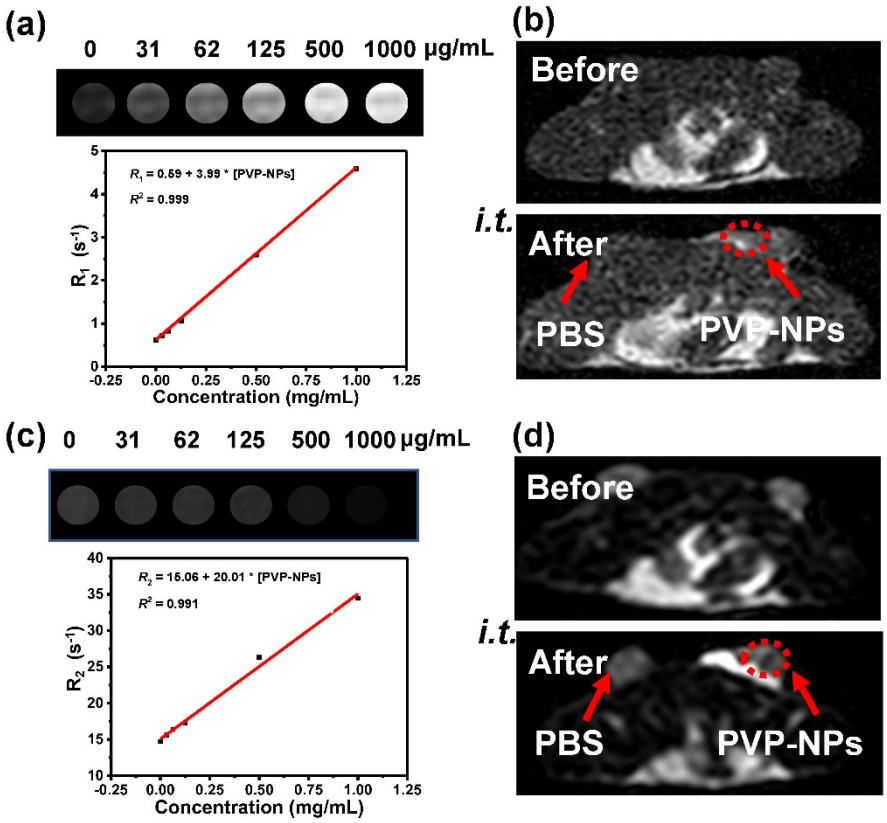


Fig. S8. MRI signal detection of PVP-NPs. (a) The relationship of T1-weighted MRI signal and concentration of PVP-NPs *in vitro*. (b) T1-weighted MRI signal intensity of mice collected pre- and post-intratumorally injected of PBS and 2 mg/kg of PVP-NPs. (c) The relationship of T2-weighted MRI signal and concentration of PVP-NPs in vitro. (d) T2-weighted MRI signal intensity of mice collected pre- and post-intratumorally injected of PBS and 2 mg/kg of PVP-NPs.

9. Pearson's correlation analysis of Fig. 3.

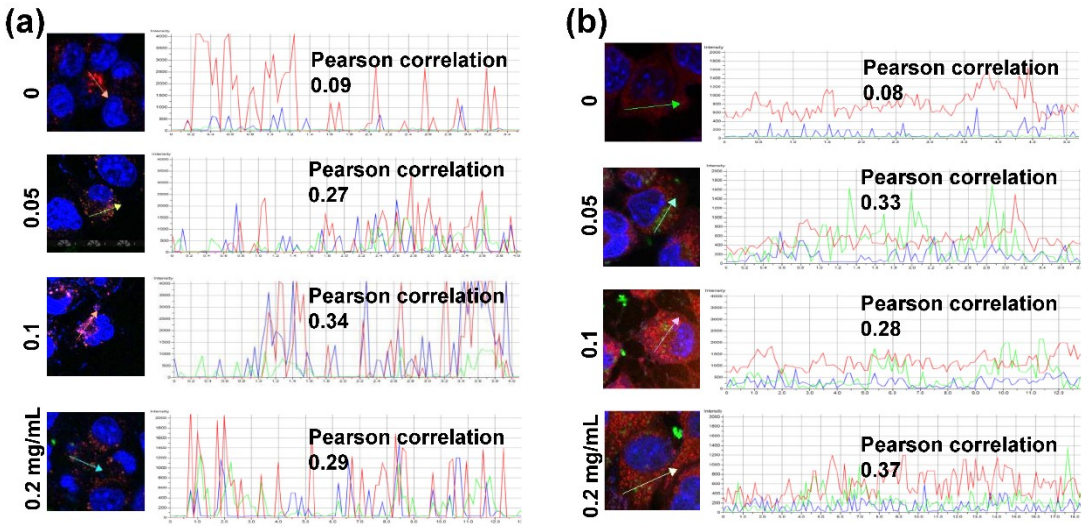


Fig. S9. (a) Pearson's correlation of Fig. 3c. (b) Pearson's correlation of Fig. 3d.

10. Cloning formation ability of PVP-NPs.

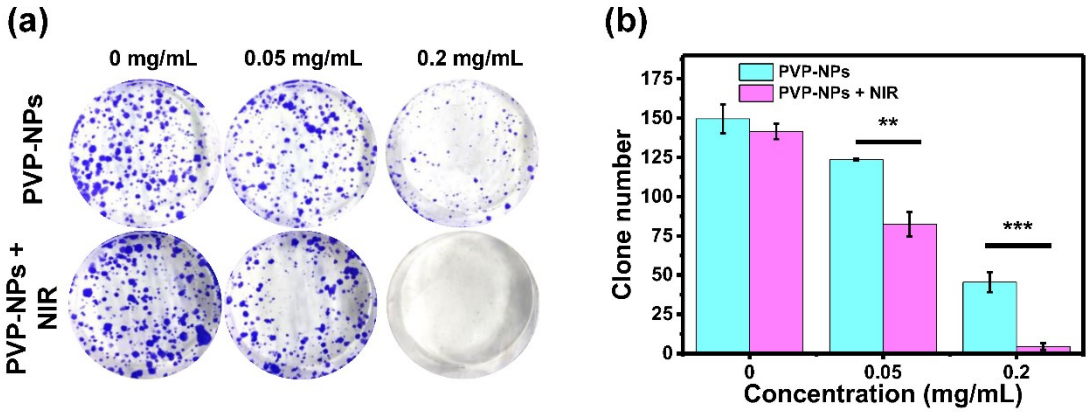


Fig. S10. (a, b) The photo and statistical analysis of cloning formation ability of PVP-NPs with NIR treatment. Data are presented as mean value ± SD. **p<0.05, **p<0.01, ***p<0.001*.

11. Gating strategies for the flow cytometry experiment.

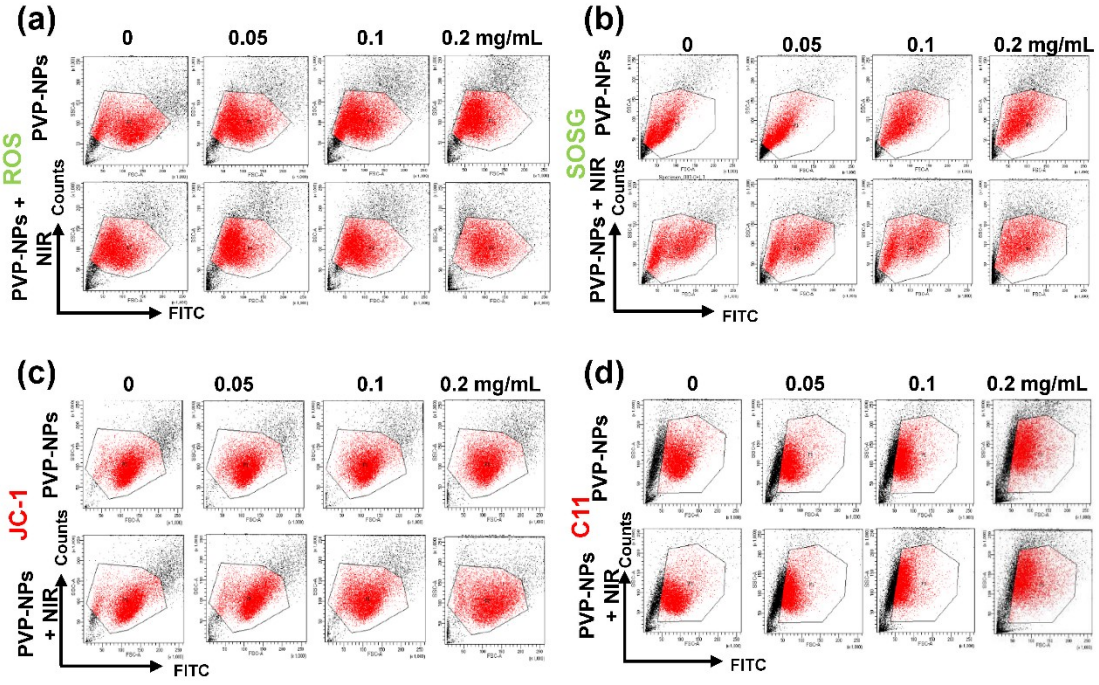


Fig. S11. (a) Gating strategies for the flow cytometry experiment of ROS assay. (b) Gating strategies for the flow cytometry experiment of SOSG assay. (c) Gating strategies for the flow cytometry experiment of JC-1 assay. (d) Gating strategies for the flow cytometry experiment of membrane lipid peroxidation assay.

12. Pearson's correlation of Fig. 5.

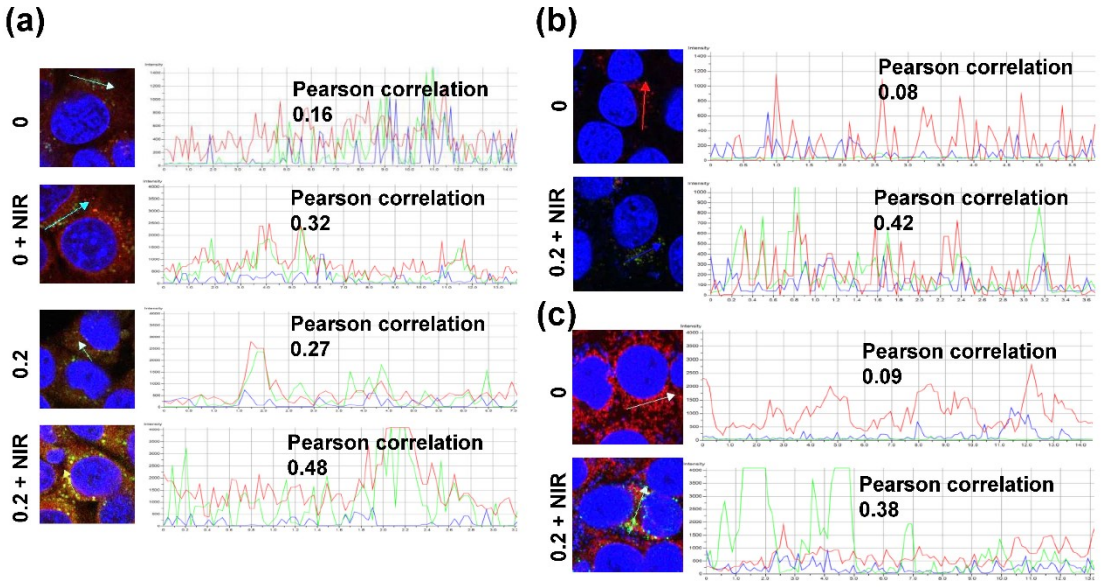


Fig. S12. (a) Pearson's correlation of Fig. 5e. (b) Pearson's correlation of Fig. 5f. (c) Pearson's correlation of Fig. 5g.

13. Representative images and tumor weight after different time.

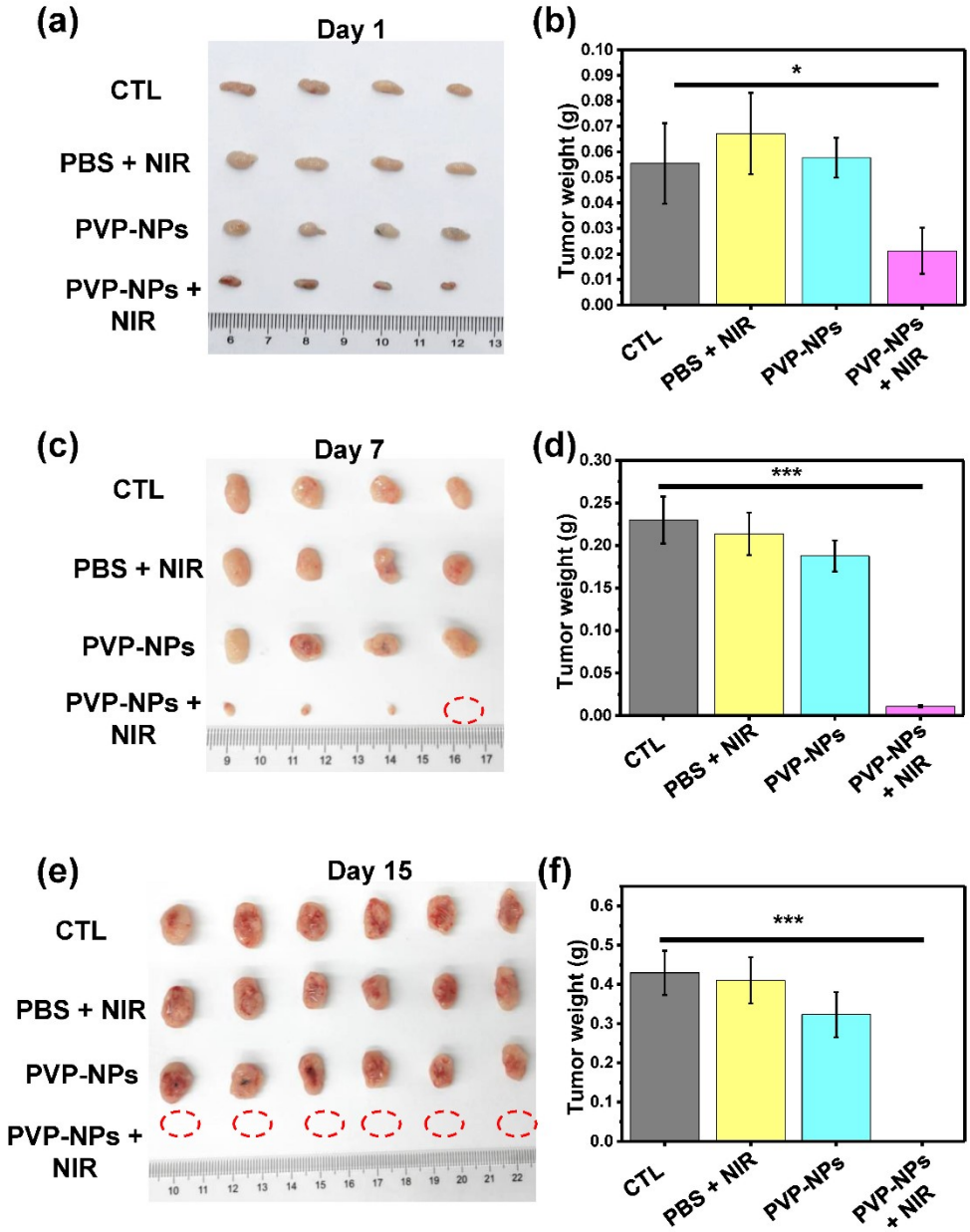


Fig. S13. (a, b) Representative images and tumor weight of harvested 4T1 tumors after different treatments in day 1. (c, d) Representative images and tumor weight of harvested 4T1 tumors after different treatments in day 7. (e, f) Representative images and tumor weight of harvested 4T1 tumors after different treatments in day 15. Data are presented as mean value ± SD. **p<0.05, **p<0.01, ***p<0.001*.

14. Toxicity assessment of PVP-NPs.

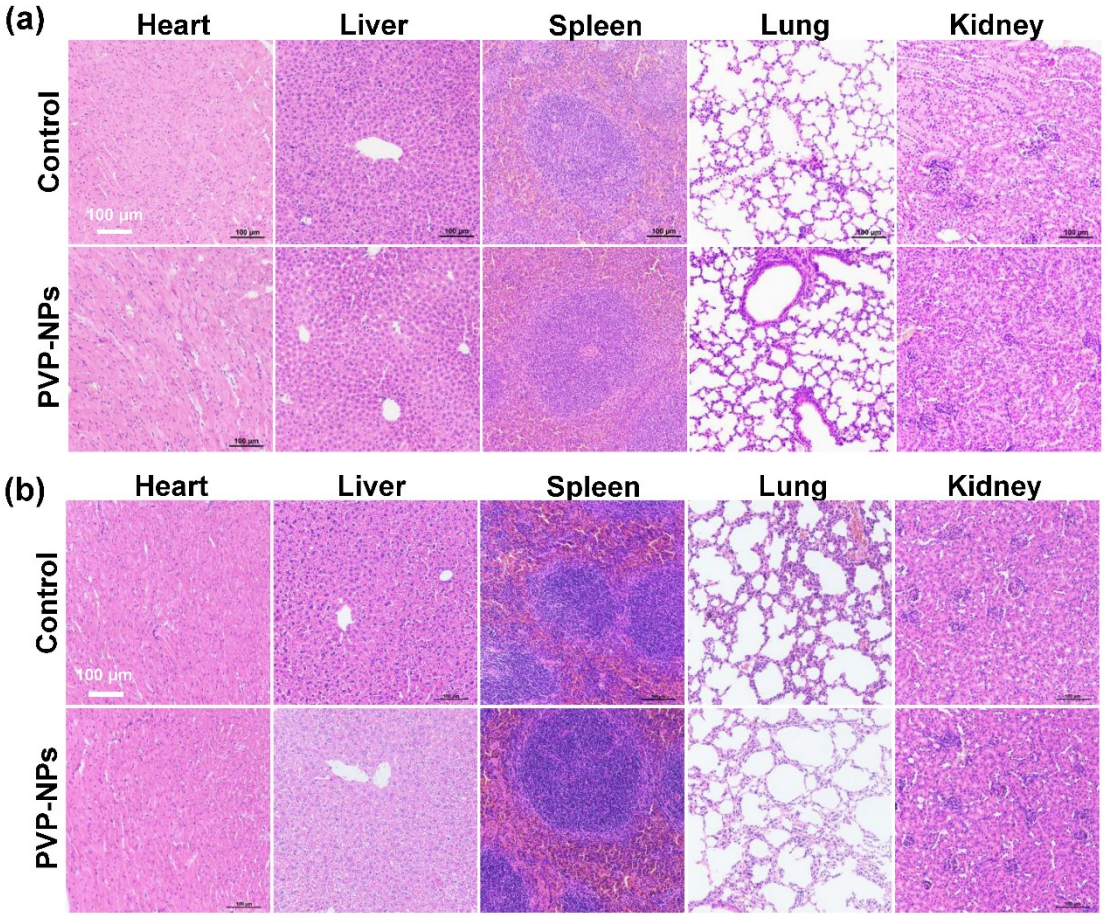


Fig. S14. Toxicity assessment of PVP-NPs. (a, b) H&E images of the major organs (Heart, Liver, Spleen, Lung, and Kidney) of mice received different treatments in day 7 and 30 after intravenous injection of PVP-NPs (200 μL, 2 mg/mL).