

## Supporting Information

for *Adv. Sci.*, DOI 10.1002/adv.202303872

Sonodynamic Therapy of NRP2 Monoclonal Antibody-Guided MOFs@COF Targeted Disruption of Mitochondrial and Endoplasmic Reticulum Homeostasis to Induce Autophagy-Dependent Ferroptosis

Zhiyu Zhao, Yanjie Wu, Xiaochen Liang, Jiajing Liu, Yi Luo, Yijia Zhang, Tingting Li, Cong Liu, Xian Luo, Jialin Chen, Yunjie Wang, Shengyu Wang, Ting Wu, Shaoliang Zhang, Dong Yang, Wengang Li, Jianghua Yan, Zhihai Ke\* and Fanghong Luo\*

## Supporting Information

**Sonodynamic Therapy of NRP2 Monoclonal Antibody-Guided MOFs@COF Targeted Disruption of Mitochondrial and Endoplasmic Reticulum Homeostasis to Induce Autophagy-Dependent Ferroptosis**

*Zhiyu Zhao<sup>a#</sup>, Yanjie Wu<sup>b#</sup>, Xiaochen Liang<sup>c</sup>, Jiajing Liu<sup>a</sup>, Yi Luo<sup>d</sup>, Yijia Zhang<sup>a</sup>, Tingting Li<sup>a</sup>, Cong Liu<sup>a</sup>, Xian Luo<sup>a</sup>, Jialin Chen<sup>d</sup>, Yunjie Wang<sup>a</sup>, Shengyu Wang<sup>a</sup>, Ting Wu<sup>a</sup>, Shaoliang Zhang<sup>e</sup>, Dong Yang<sup>a</sup>, Wengang Li<sup>a</sup>, Jianghua Yan<sup>a</sup>, Zhihai Ke<sup>b\*</sup>, Fanghong Luo<sup>a\*</sup>*

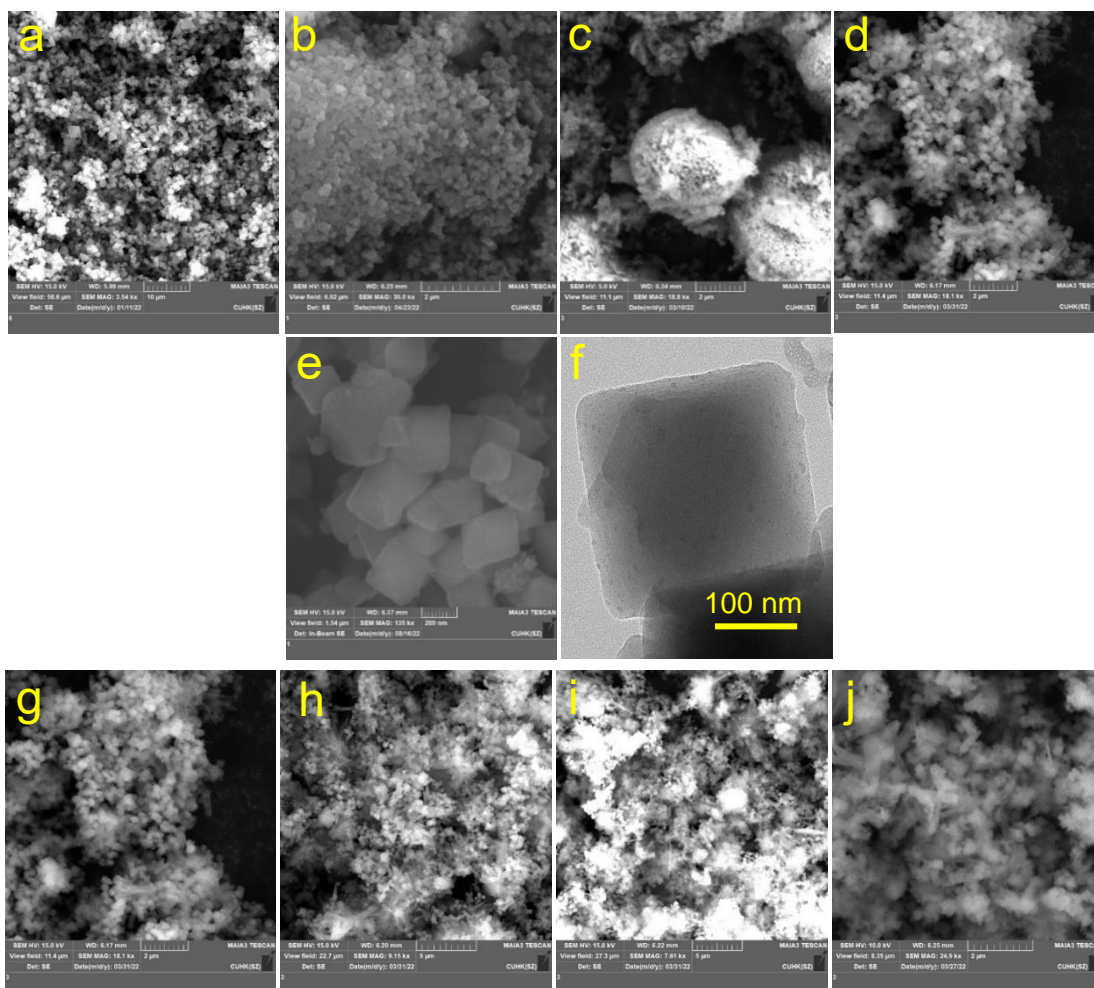
Zhiyu Zhao, Jiajing Liu, Yijia Zhang, Tingting Li, Cong Liu, Xian Luo, Yunjie Wang, Shengyu Wang, Ting Wu, Dong Yang, Wengang Li, Jianghua Yan, Fanghong Luo  
Cancer Research Center, School of Medicine, Xiamen University, Xiamen, 361000, P. R. China  
Fanghong Luo([luofanghong@xmu.edu.cn](mailto:luofanghong@xmu.edu.cn))

Yanjie Wu, Zhihai Ke  
School of Science and Engineering, Shenzhen Key Laboratory of Innovative Drug Synthesis, The Chinese University of Hong Kong, Shenzhen, 518172, P. R. China  
Zhihai Ke([kezhikai@cuhk.edu.cn](mailto:kezhikai@cuhk.edu.cn))

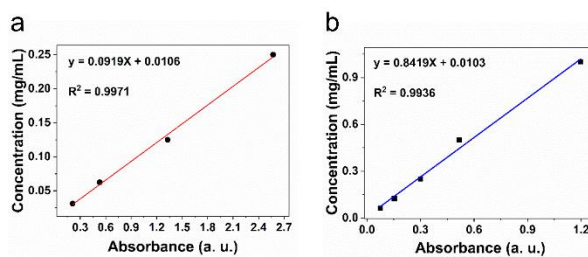
Xiaochen Liang  
Environmental Toxicology, University of California, Riverside, California, 92507, United States

Yi Luo, Jialin Chen  
School of Basic Medicine, School of Clinical Medicine, Fujian Medical University, Fuzhou, 350122, P. R. China

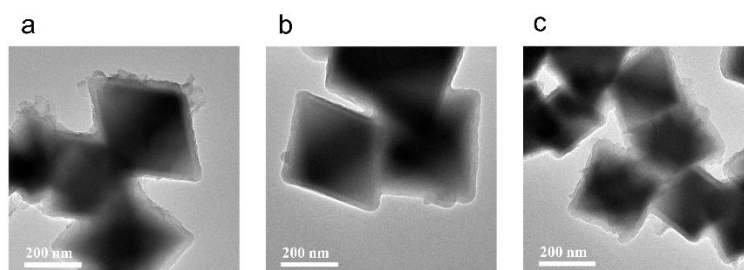
Shaoliang Zhang  
Shanghai Guangsheng Biopharmaceutical Co., Ltd, Shanghai, 200120, P. R. China



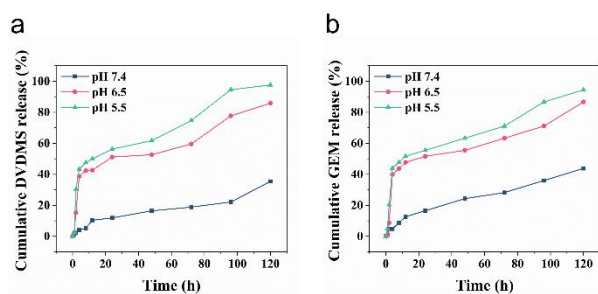
**Fig. S1** SEM images of a)  $\text{NH}_2\text{-MIL-101 (Fe)}$ , b)  $\text{GEM-DVDMS@NH}_2\text{-MIL-101 (Fe)}$ , c)  $\text{TpPa-1}$ , d)  $\text{NH}_2\text{-MIL-101 (Fe)@TpPa-1}$ , e)  $\text{NRP2-GEM-DVDMS/NH}_2\text{-MIL-101 (Fe)@TpPa-1}$ , f) TEM image of  $\text{NH}_2\text{-MIL-101(Fe)}$ . Different weight ratios of  $\text{NH}_2\text{-MIL-101 (Fe)@TpPa-1}$ : (g) 15.75 mg Tp, 12 mg Pa-1, (h) 31.5 mg Tp, 24 mg Pa-1, i) 47.25 mg Tp, 36 mg Pa-1, j) 63mg Tp, 48 mg Pa-1, samples were denoted as  $\text{NH}_2\text{-MIL-101(Fe)@TpPa-1-1}$ ,  $\text{NH}_2\text{-MIL-101(Fe)@TpPa-1-2}$ ,  $\text{NH}_2\text{-MIL-101(Fe)@TpPa-1-3}$ ,  $\text{NH}_2\text{-MIL-101(Fe)@TpPa-1-4}$ , respectively. The weight of  $\text{NH}_2\text{-MIL-101(Fe)}$  was fixed at 30 mg.



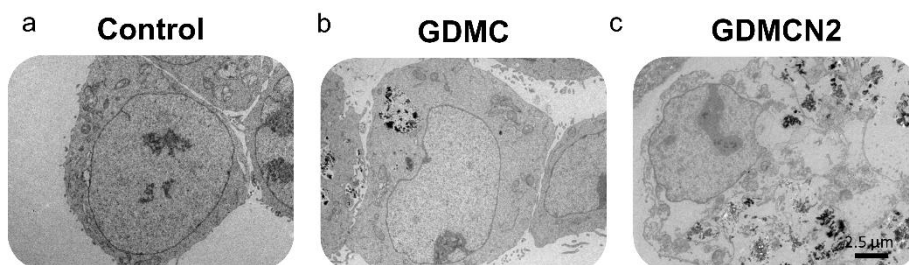
**Fig. S2** a) Standard curve of GEM at different concentrations. b) Standard curve of DVDMS at different concentrations.



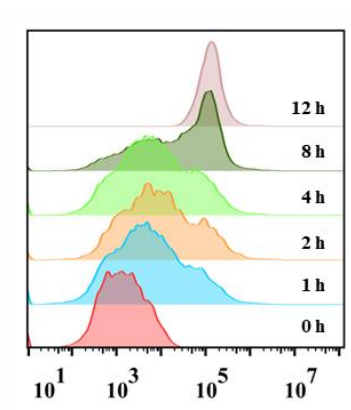
**Fig. S3** TEM image of GDMCN2 stability in PBS. a) 24 h. b) 72h. c) 168 h.



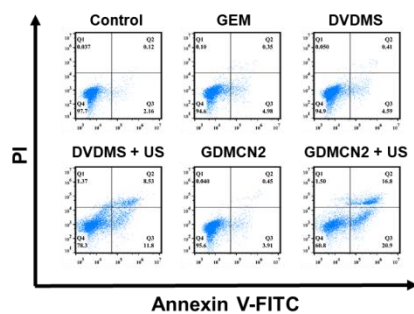
**Fig. S4** *In vitro* cumulative release profiles of a) DVDMS and b) GEM.



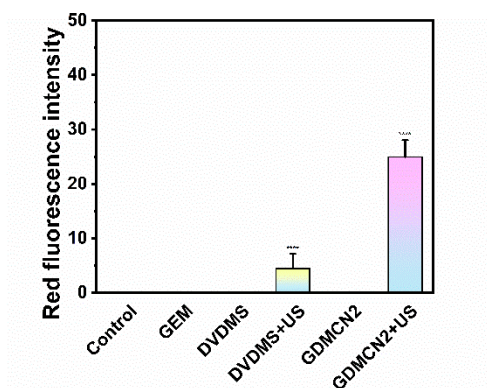
**Fig. S5** Intracellular TEM images of PANC-1/GEM cells incubated with a) PBS b) GDMC, and c) GDMCN2 following 1 h of incubation.



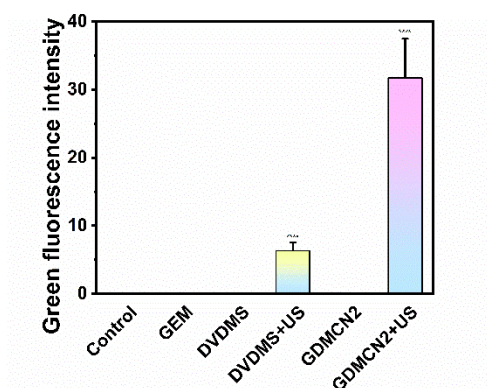
**Fig. S6** Flow cytometric analysis of PANC-1/GEM cells following incubation with GDMCN2 for 0h, 1h, 2h, 4h, 8h, and 12h.



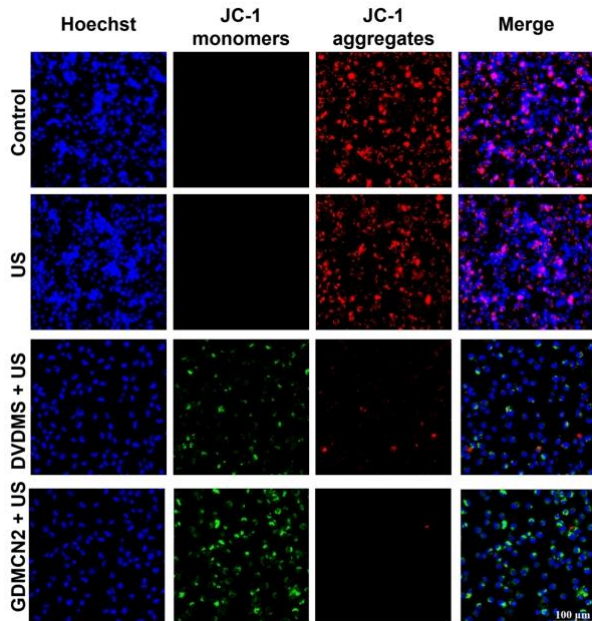
**Fig. S7** Flow cytometer analysis after various treatments.



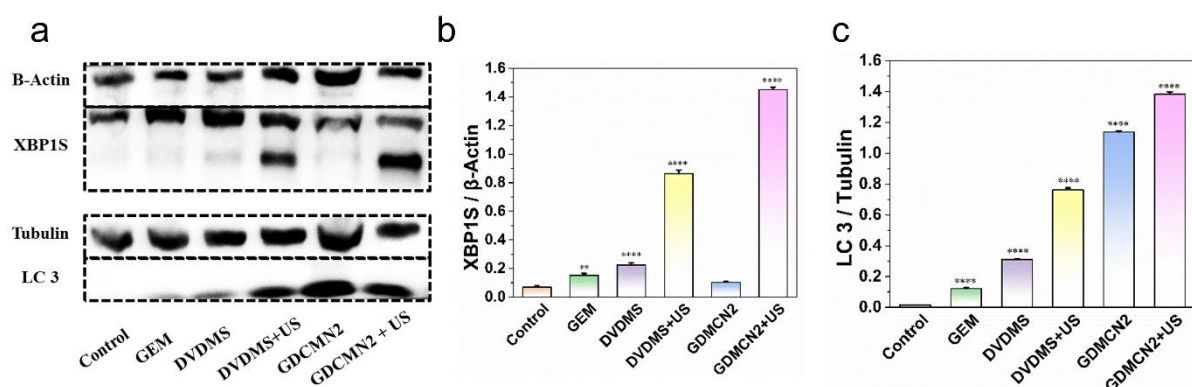
**Fig. S8** Red fluorescence intensity in PANC-1/GEM cells stained with AM-PI under different treatment.



**Fig. S9** Green fluorescence intensity in PANC-1/GEM cells stained with DCFH-DA under different treatment.

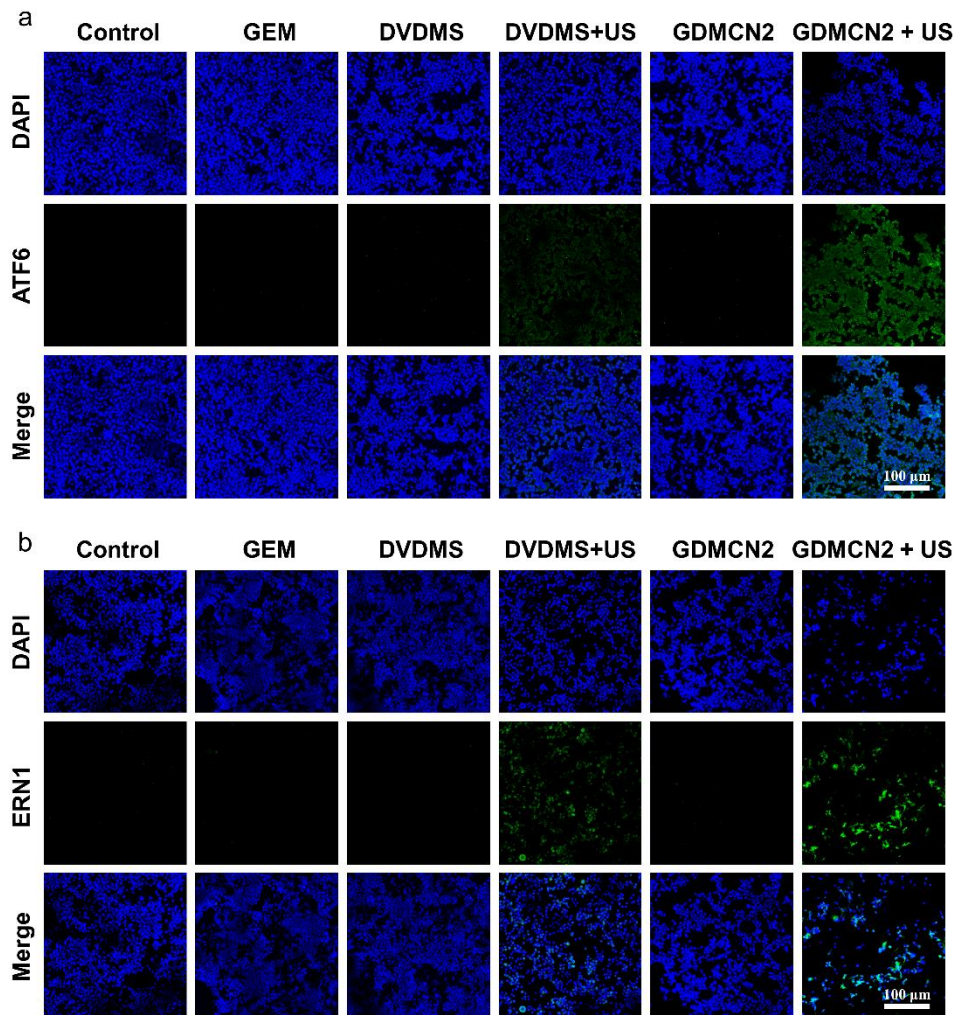


**Fig. S10** CLSM images of PANC-1/GEM cells stained with JC-1 following Control, US, DVDMS+US, and GDMCN2+US group.

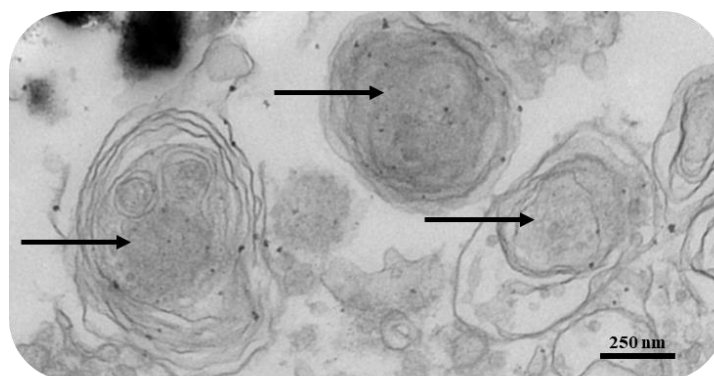


**Fig. S11** a) Protein expression levels of XBP1S and LC3 in PANC-1/GEM cells with different treatments. b and c) Quantitative analysis of XBP1S and LC3 proteins

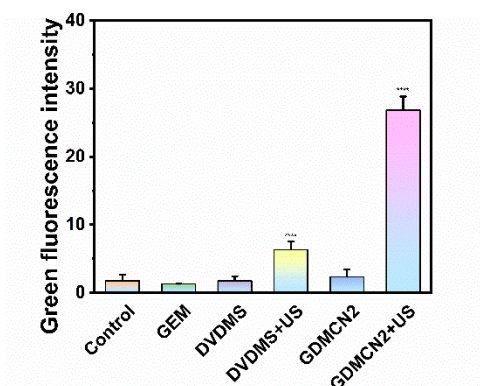




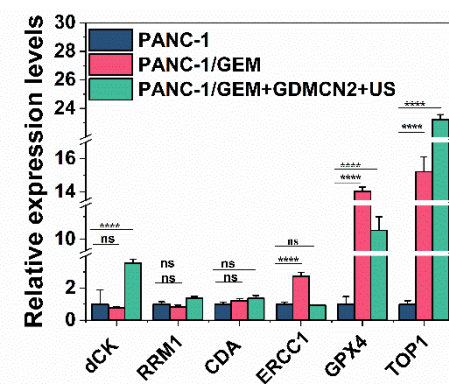
**Fig. S12** CLSM image of cell immunofluorescence in PANC-1/GEM cells treated with various treatments. a) ATF6 protein, b) ERN1 protein.



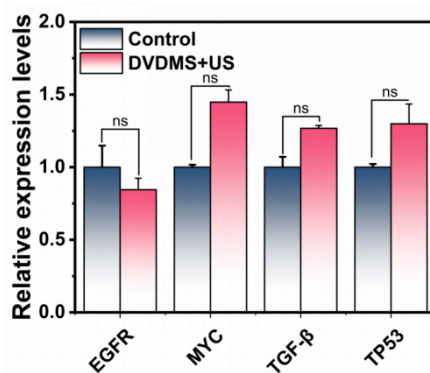
**Fig. S13** Autophagy-lysosomes in TEM images of PANC-1/GEM cells after GDMCN2 combined with US treatment.



**Fig. S14** Green fluorescence intensity in PANC-1/GEM cells stained with  $\gamma$ -H2A.X antibody under different treatment.

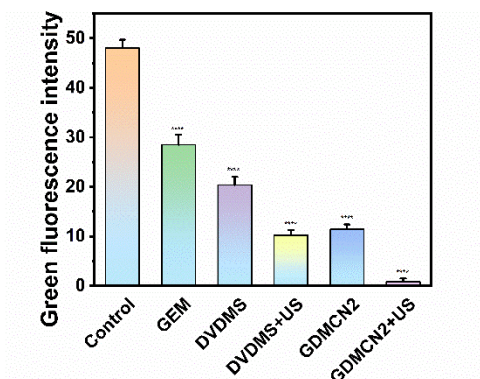


**Fig. S15** RT-qPCR relative expression levels of DNA repair-related genes.

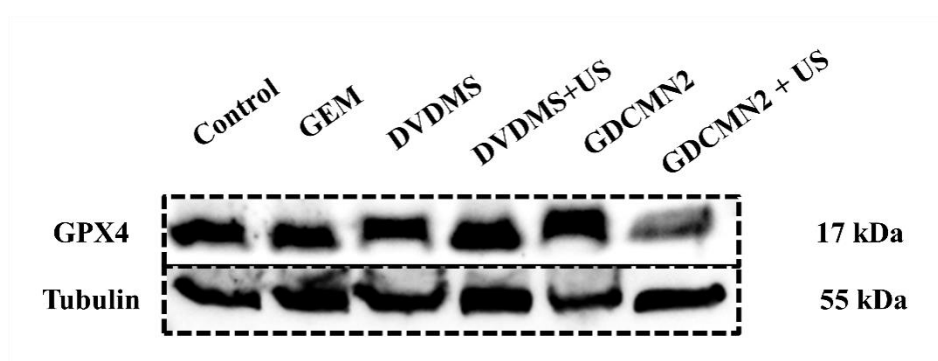


**Fig. S16** RT-qPCR relative expression levels of cell proliferation-related genes.

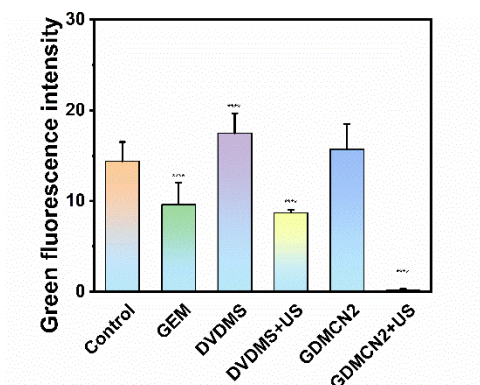




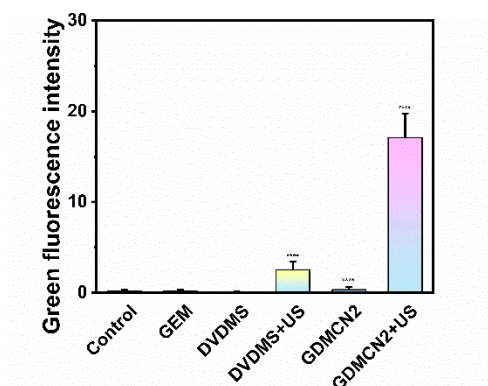
**Fig. S17** Green fluorescence intensity in PANC-1/GEM cells stained with ThiolTracker Violet under different treatment.



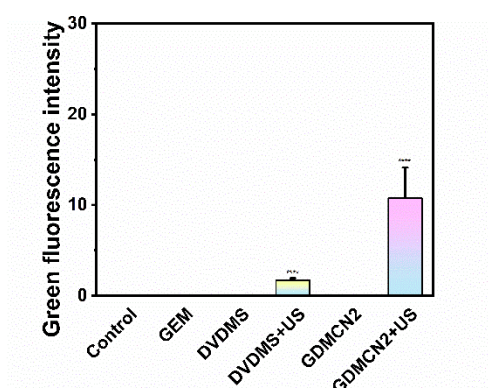
**Fig. S18** Ferroptosis-associated Western Blot results.



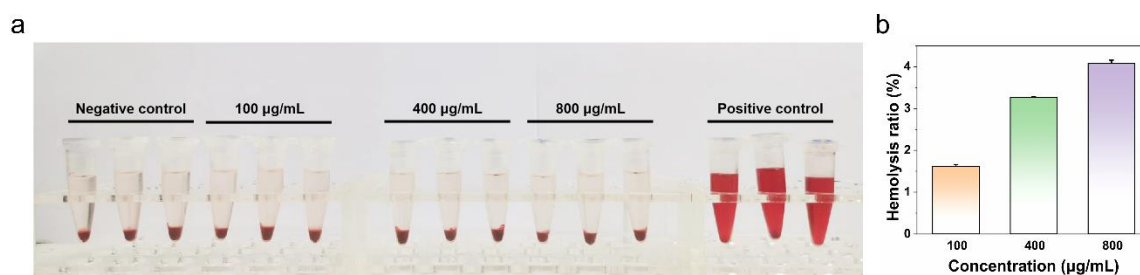
**Fig. S19** Green fluorescence intensity in PANC-1/GEM cells stained with GPX4 antibody under different treatment.



**Fig. S20** Green fluorescence intensity in PANC-1/GEM cells stained with BODIPY C11 under different treatment.



**Fig. S21** Green fluorescence intensity in PANC-1/GEM cells stained with LiperFluo under different treatment.



**Fig. S22** a and b) Hemolysis assay of GDMCN2 in different concentration.

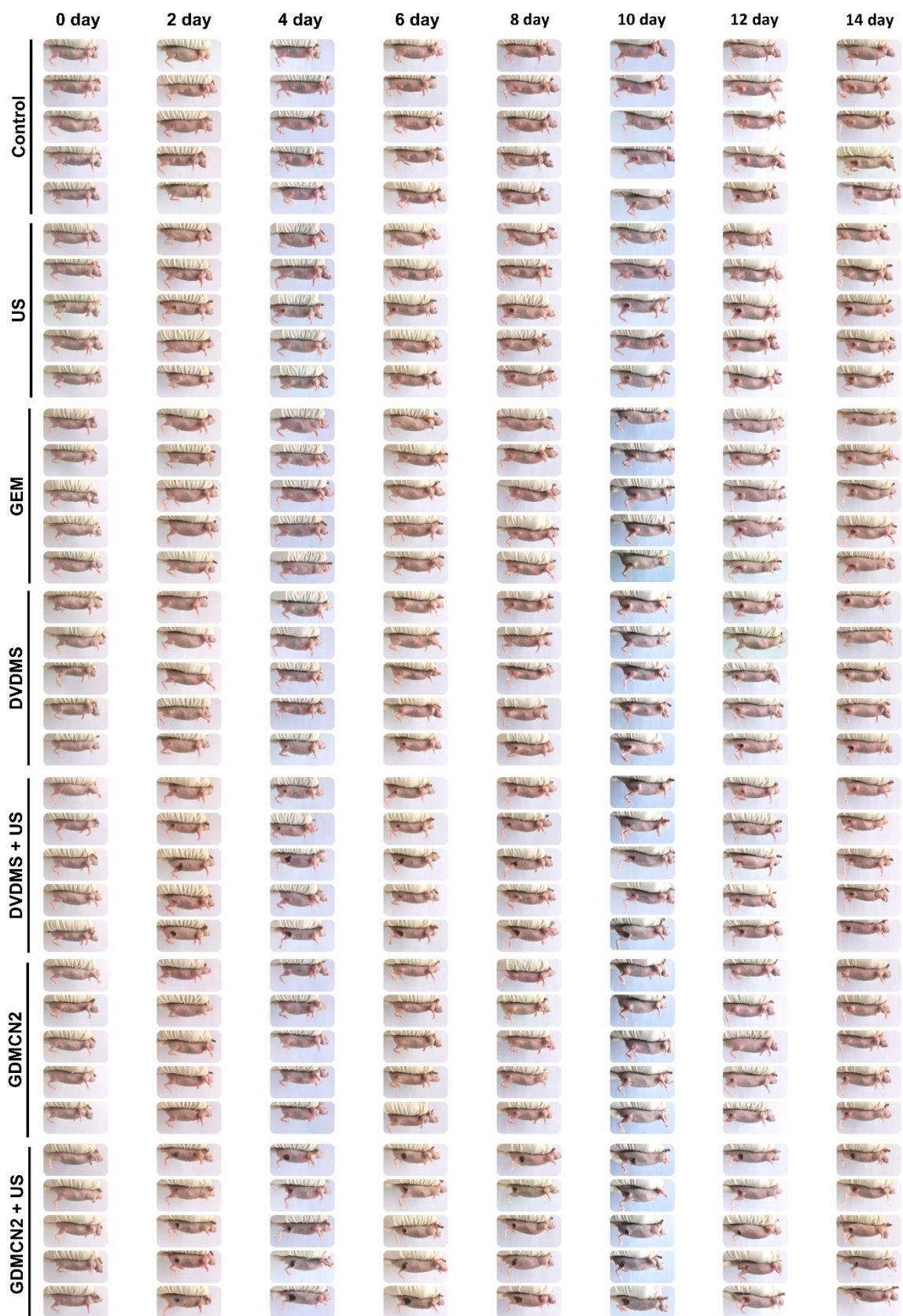
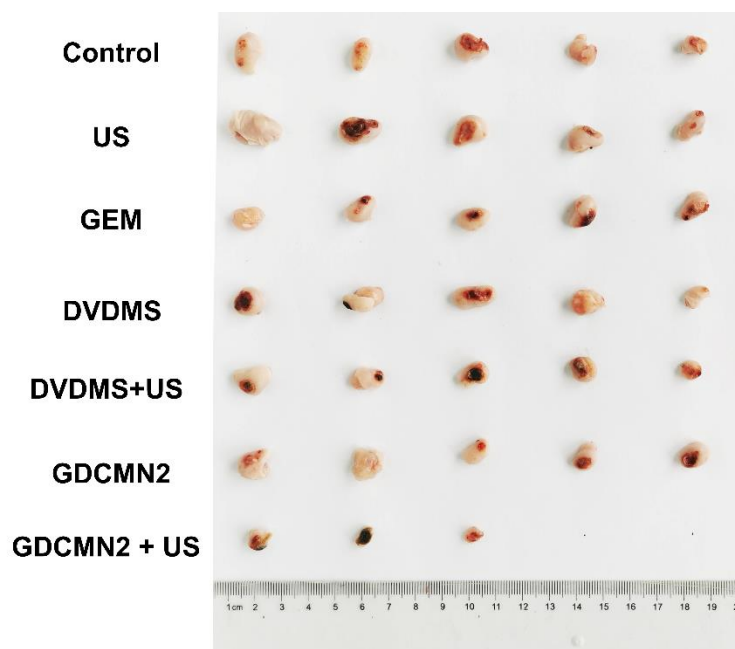
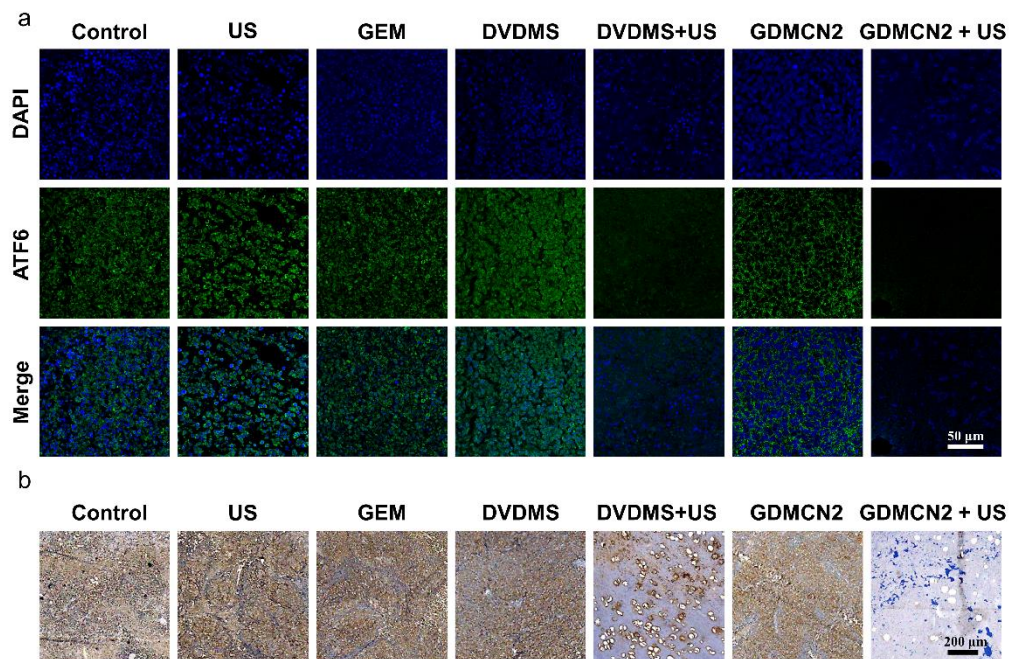


Fig. S23 Representative digital images of mice from each group within 14 days.

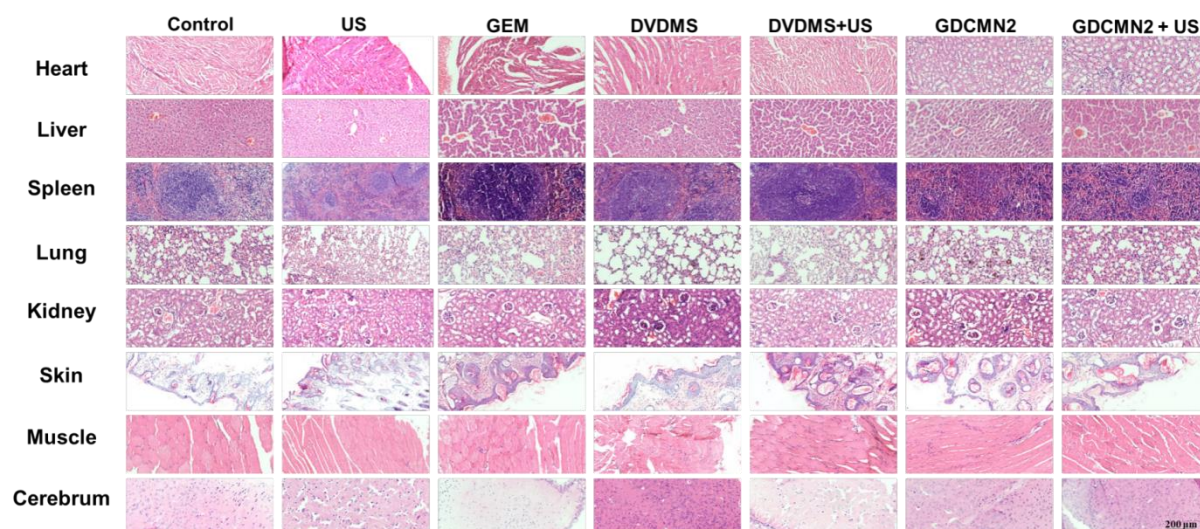




**Fig. S24** Tumor tissue isolated from different treatment groups.



**Fig. S25** Images demonstrate TOM20 a) immunofluorescence and b) immunohistochemistry of tumors collected on day 14 of different therapies.



**Fig. S26** H&E staining of normal tissues from different treatment group.

**Table S1.** The EDS element analysis of different samples.

Element	Fe Weight (%)	Fe Atom (%)
NH <sub>2</sub> -MIL-101 Fe	31.66	10.11
NH <sub>2</sub> -MIL-101(Fe)@TpPa-1-1	9.22	2.37
NH <sub>2</sub> -MIL-101(Fe)@TpPa-1-2	5.70	1.41
NH <sub>2</sub> -MIL-101(Fe)@TpPa-1-3	2.79	0.67
NH <sub>2</sub> -MIL-101(Fe)@TpPa-1-4	2.00	0.48

**Table S2.** The weight of the nude mice

Markers	DAY 0	DAY 2	DAY 4	DAY 6	DAY 8	DAY 10	DAY 12	DAY 14
Weight (g)								
Time								
(I)-1	17.8	17.9	17.9	16.3	17.8	18.6	18.5	18.6
(I)-2	19.7	19.7	20.1	19.9	19.3	19.7	20.1	20
(I)-3	19.3	19.3	16	17.3	19.2	20	19.9	19.8
(I)-4	21.3	21.2	21.2	19	20.2	20.2	20	19.8
(I)-5	20.9	20.9	21.2	20.9	20.8	21.5	21.3	21.2
(II)-1	20.4	20.7	21.2	22.4	22.1	19.6	19.7	19.5



(II)-2	22.6	22.5	22.5	22.2	21.6	21.7	21.5	21.3
(II)-3	20.8	21.4	21.3	21.1	20.7	20.2	21.1	20
(II)-4	19.5	19.7	21.2	20	19.7	19.2	19.6	19.5
(II)-5	19.9	20.2	20.4	20.6	21.6	21.9	21.6	21.4
(III)-1	20.1	20.2	19.9	19.9	20.5	20.3	20.4	20.3
(III)-2	20.2	20.7	20.9	21.4	21.6	21.2	21.2	21.2
(III)-3	21.3	21.4	20.7	20.9	21.3	20.7	20.8	20.7
(III)-4	19.9	19.6	20.1	20.5	20.5	20.4	20.3	20.4
(III)-5	21.1	21.2	21	21.6	21.2	20.9	20.8	20.7
(IV)-1	20.6	21.1	21	21.1	21.3	21.4	21.3	21.2
(IV)-2	19.9	20.5	19.6	19.9	19.3	18.8	18.6	18.6
(IV)-3	16.1	16.5	17	16.8	16.8	16.8	16.8	17
(IV)-4	21.2	21.2	21.3	21.1	20.8	20.7	20.8	20.7
(IV)-5	19	19.3	19.3	19.2	19	19	19.2	19.5
(V)-1	20.1	19.5	19.3	19.2	19.3	19.4	19.6	19.7
(V)-2	19	19.1	18.7	18.6	19	19	18.6	18.5
(V)-3	19.8	19.6	18.6	18.4	20	19.7	19.6	19.6
(V)-4	20	20.1	19.4	19.4	18.2	16.9	16.5	16.4
(V)-5	17.9	20	19.5	18.9	17.8	17.6	17.5	17.4
(VI)-1	19.1	19.6	19.8	18.4	18.8	18.5	18.4	18.3
(VI)-2	19.2	19.7	20.2	19.2	19.3	19.8	19.7	19.5
(VI)-3	18.5	18.4	19.4	19.2	19.9	20.2	20.1	20.2
(VI)-4	20.2	20.3	20.2	20.7	20.7	20.8	20.7	20.6
(VI)-5	17.5	17.8	18.2	18.5	19.1	19.1	19.2	19.2
(VII)-1	19.4	19.5	18.4	17.6	17.7	17.5	17.4	17.5
(VII)-2	21.6	20.3	19.8	19.2	18.8	18.7	18.5	18.6
(VII)-3	20.4	20.5	19.7	19.4	18.6	18.6	18.6	18.5
(VII)-4	20.3	20.7	20.5	20.2	20.8	20.5	20.3	20.1
(VII)-5	18.9	18.9	18.8	18.2	18.8	18.6	18.7	18.7

PANC-1/GEM tumor-bearing nude mice were randomly divided into seven groups: (i) PBS, (ii) US, (iii) GEM, (iv) DVDMS, (v) DVDMS+US, (vi) GDMCN2, (vii) GDMCN2+US.

**Table S3.** Biochemical blood analysis of the mice treated after different treatments

Markers	WBC (10 <sup>9</sup> /L)	RBC (10 <sup>12</sup> /L)	HGB (g/L)	PLT (10 <sup>11</sup> /L)	MCV (fL)	MCH (pg)	MCHC (g/L)
(I)-1	6.5	7.5	9.5	17.53	4.84	12.6	26.1
(I)-2	6.5	6.21	7.9	18.01	4.78	12.7	26.6
(I)-3	5	6.73	9	25.01	5.1	13.3	26.2
(I)-4	9.7	7.36	9.7	16.53	4.77	13.1	27.6
(I)-5	6.1	7.66	10.2	12.71	4.86	13.3	27.4
(II)-1	10.9	8.03	10.6	11.22	4.85	13.2	27.2
(II)-2	6.5	6.98	9.7	26.12	5.14	13.8	27
(II)-3	6.4	8.41	12.3	32.41	5.26	14.6	27.8
(II)-4	4.5	6.98	9.5	15.03	5.05	13.6	26.9
(II)-5	4.5	7.95	11.2	16.41	5.2	14	27.1
(III)-1	4.5	7.69	11.2	23.71	5.11	14.5	28.5
(III)-2	10	7.18	10	15.44	4.97	13.9	28
(III)-3	5.4	7.91	10.3	29.21	4.83	13	26.9
(III)-4	36	9.53	12.4	7.24	4.48	13	29.1
(III)-5	2.5	8.8	13.2	12.14	5.11	15	29.3
(IV)-1	3	6.81	9.7	5.78	4.98	14.2	28.6
(IV)-2	7.4	8.58	11.9	8.09	4.87	13.8	28.5
(IV)-3	4.4	8.9	13.5	26.46	5.04	15.1	30.1
(IV)-4	5.5	10.58	15	17.22	4.66	14.1	30.4
(IV)-5	4.1	9.52	14.7	12.13	4.99	15.4	30.9
(V)-1	4	8.35	13.5	12.29	5.23	16.1	30.9
(V)-2	3.3	9	13.7	8.45	4.91	15.2	31
(V)-3	5.3	9.53	14	10.09	4.77	14.6	30.8
(V)-4	2.4	9.27	13.4	9.19	4.69	14.4	30.8
(V)-5	4.2	9.1	14.4	8.58	5.27	15.8	30
(VI)-1	3.5	9.33	14.3	18.06	5.06	15.3	30.2
(VI)-2	6	8.43	12.8	16.25	4.93	15.1	30.8
(VI)-3	3.2	8.94	13.2	10.78	4.86	14.7	30.4
(VI)-4	5.4	9.31	13.7	13.01	4.88	14.7	30.1
(VI)-5	3.8	9.12	13.8	10.89	4.97	15.1	30.4
(VII)-1	3.8	9.12	13.8	10.89	4.97	15.1	30.4

---

(VII)-2	7.2	9.16	13.5	28.03	4.92	14.7	30
(VII)-3	3.4	8.7	13.3	15.45	5.05	15.2	30.2
(VII)-4	2.5	9.08	13.7	21.12	4.93	15	30.6
(VII)-5	7.1	7.28	13.5	12.89	5.84	18.5	31.7

---

PANC-1/GEM tumor-bearing nude mice were randomly divided into seven groups: (i) PBS, (ii) US, (iii) GEM, (iv) DVDMS, (v) DVDMS+US, (vi) GDMCN2, (vii) GDMCN2+US.