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Supporting Information

Combination of Mitochondrial Targeting Doxorubicin with Bcl-2 Function Converting Peptide NuBCP-9 for Synergistic Breast Cancer Metastasis Inhibition

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Table S1 Characterization of HPMA conjugates

Polymer Conjugate	Mw (kDa)	PDI	Zeta potential (mV)	Dox content (wt%)
P-Dox (PDx)	19.6	1.12	26.7±2.3	7.7
P-Dox-SMP (PDS)	21.7	1.23	-13.5±1.1	9.8

Table S2 IC_{50} value of copolymer for 24 h on 4T1 cells (μg/mL, Dox equiv)

Group	PN9	PDM	PNDM
IC_{50}	--	62.2	41.1

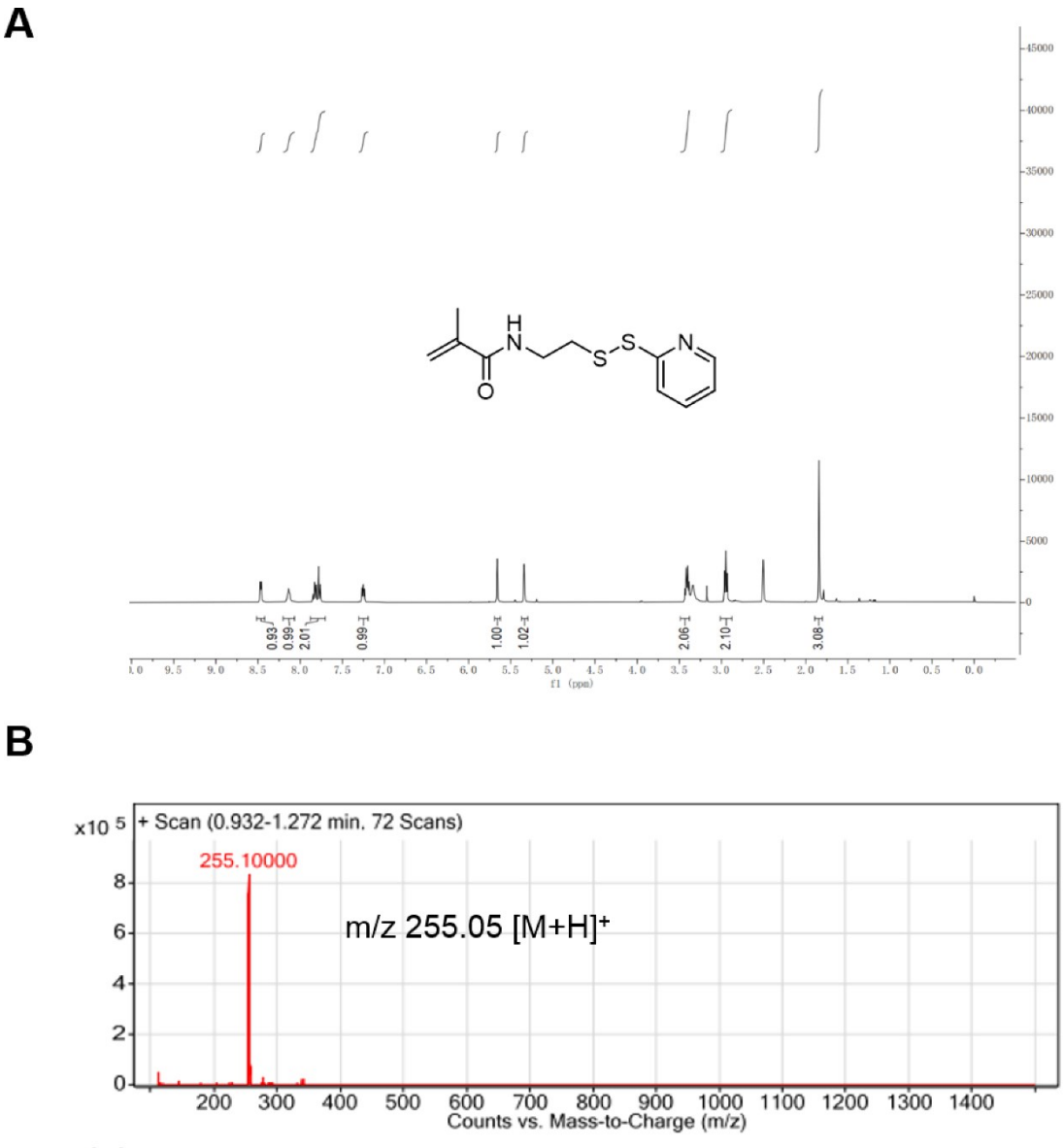

Fig. S1 Characterization of pyridyl disulfide methacryl amide (PDSMA). (A) ^{1}H-NMR spectra in DMSO and (B) mass spectra of PDSMA.

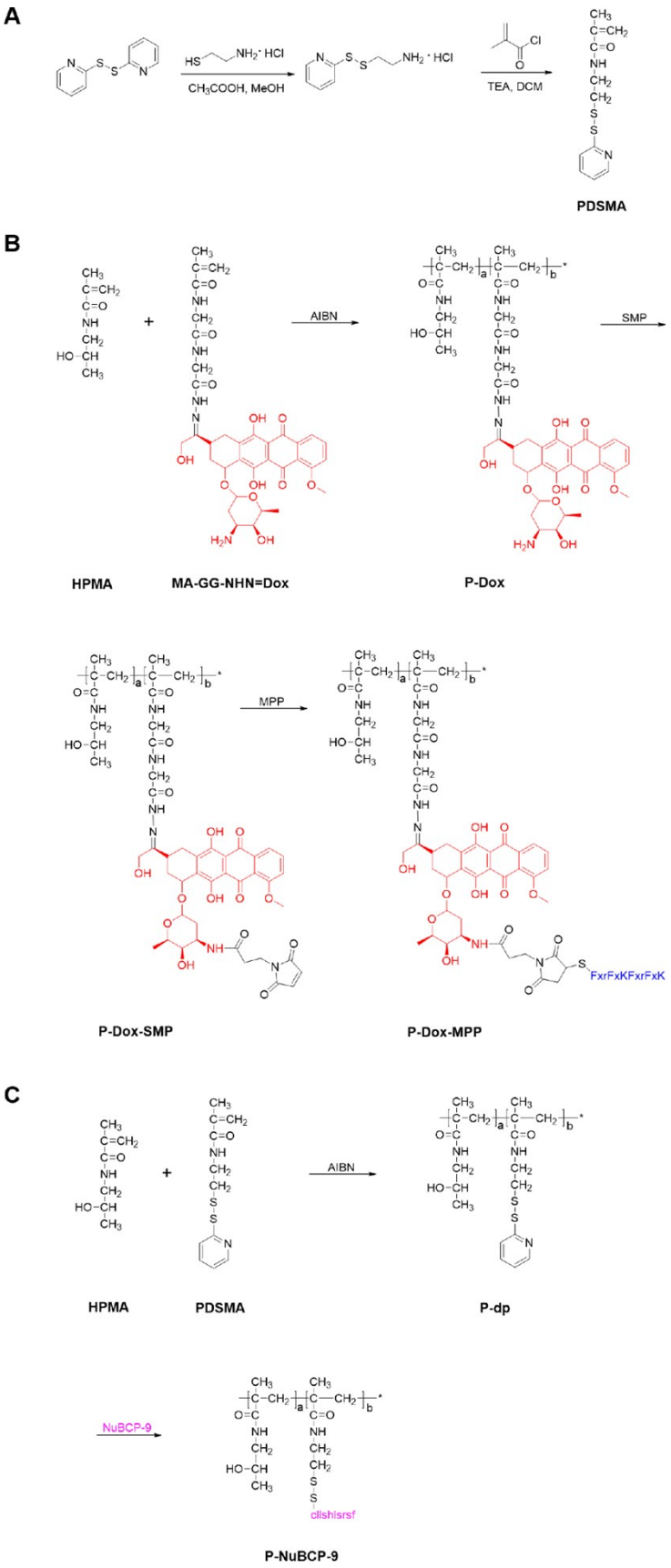

Fig. S2 (A) Synthesis of PDSMA. (B) Synthesis of MPP modified HPMA copolymer Dox conjugates. (C) Synthesis of NuBCP-9 peptide modified HPMA copolymers.

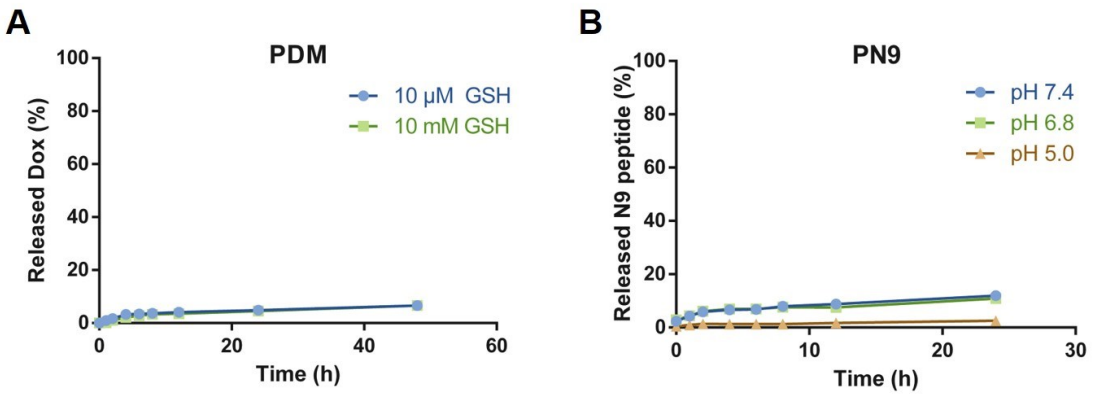

Fig. S3 (A) *In vitro* release profile of PDM in GSH solution (10 μM GSH and 10 mM GSH). (B) *In vitro* release profile of PN9 in phosphate buffer saline (pH 7.4, pH 6.5 and pH 5.0).

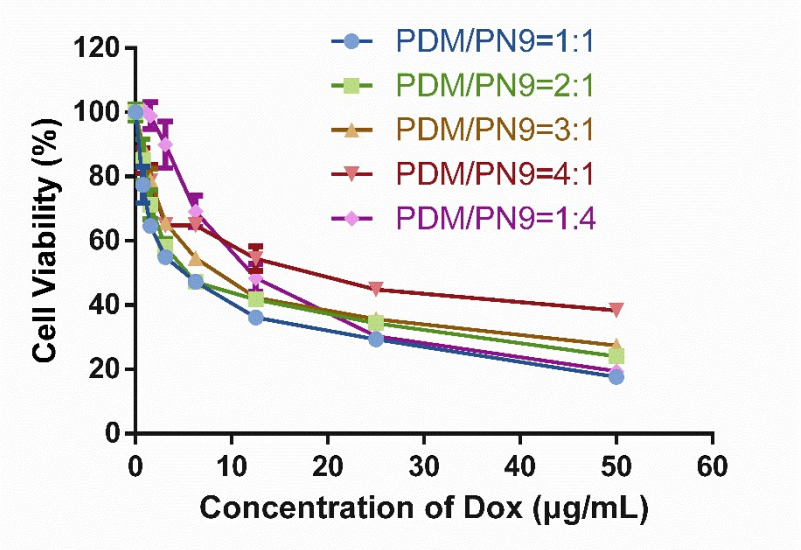

Fig. S4 Cell viability with combination therapy of PDM and PN9 at different ratio against 4T1 cells for 48 h.(n=3)

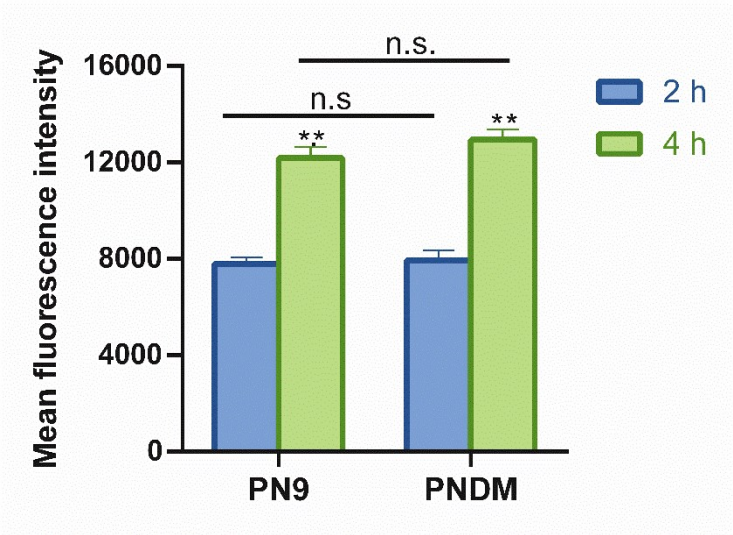

Fig. S5 Cell uptake of PN9 determined by flow cytometry after 2 h or 4 h treatment (n=3, **: P < 0.01**).**

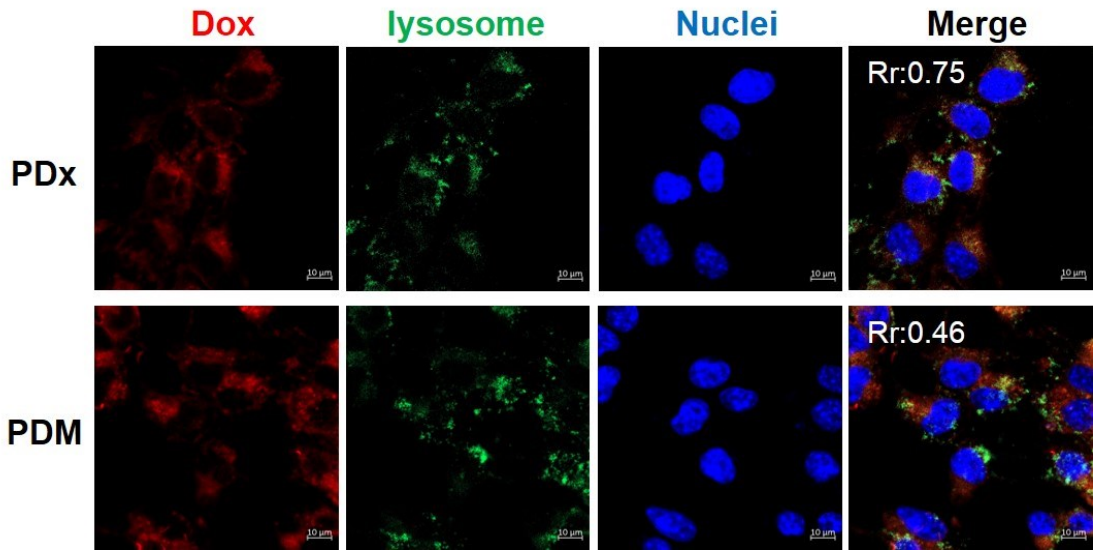

Fig. S6 Qualitative analysis of PDx and PDM in 4T1 cells lysosome distribution for 4 h. Red: Dox. Green: Lysosome. Blue: nuclei. The equivalent of Dox was 10 μg/mL. Scale bar: 10 μm.

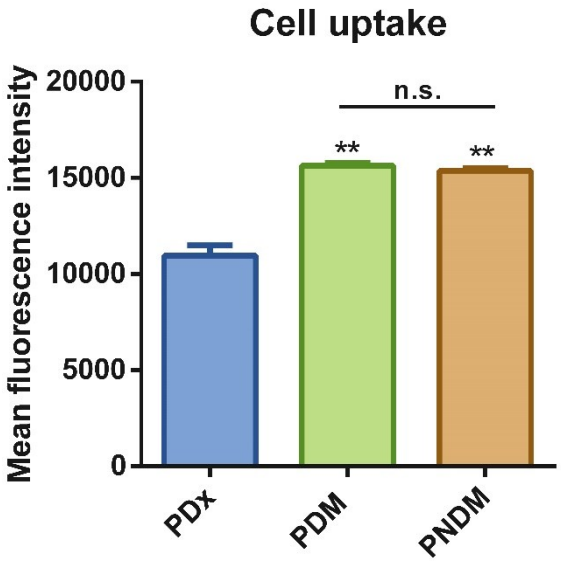

Fig. S7 Cell uptake of PDx, PDM and PNDM determined by flow cytometry after 12 h treatment (n=3, **: $P < 0.01$).

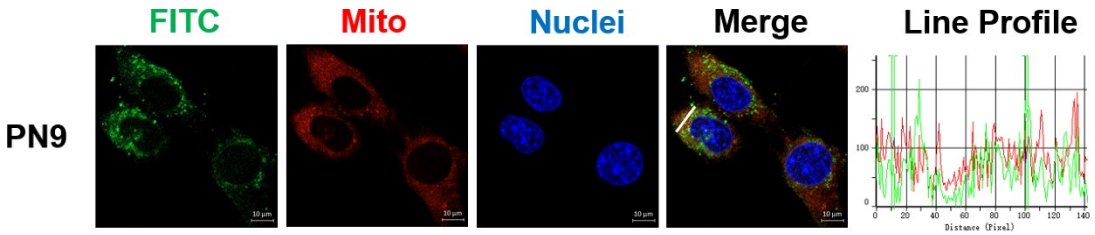

Fig. S8 Mitochondrial distribution of PN9 in 4T1 cells. (Scale bar: 10 μm).

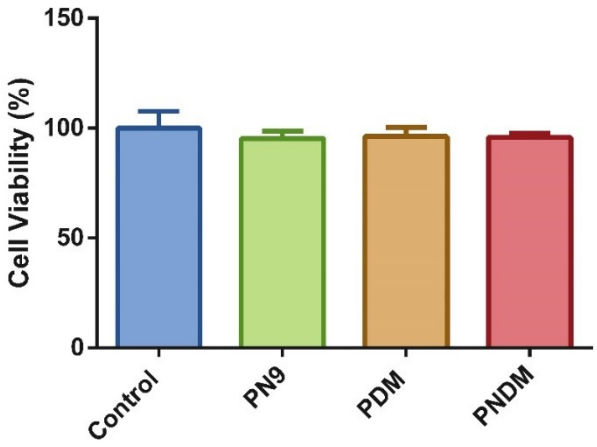

Fig. S9 Cell viability of HPMA copolymer against 4T1 cells for 24 h. The equivalent of Dox/N9 was 2 μg/mL. (n=3).

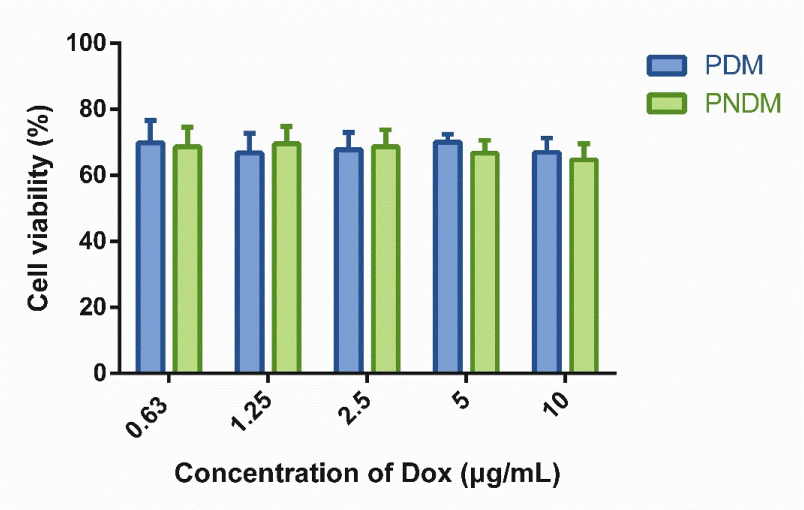

Fig. S10 Cell viability of HPMA copolymer against human umbilical vein endothelial cell (HUVEC) cells for 24 h (n=3).

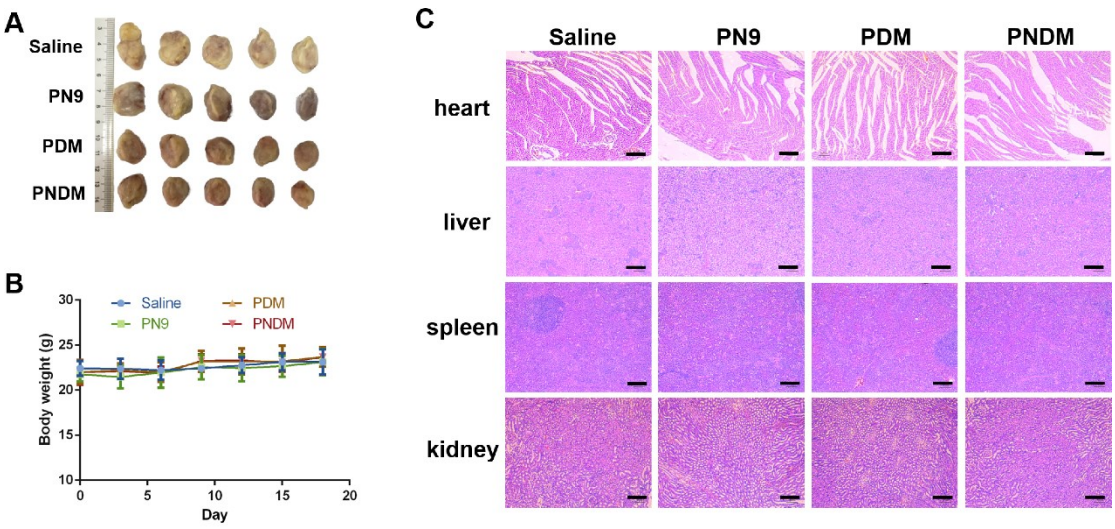

Fig. S11 (A) Images of the excised tumors post-treatment. (B) Changes of body weight during the treatment. (C) H&E staining of major organs (scale bar: 100 μm).