

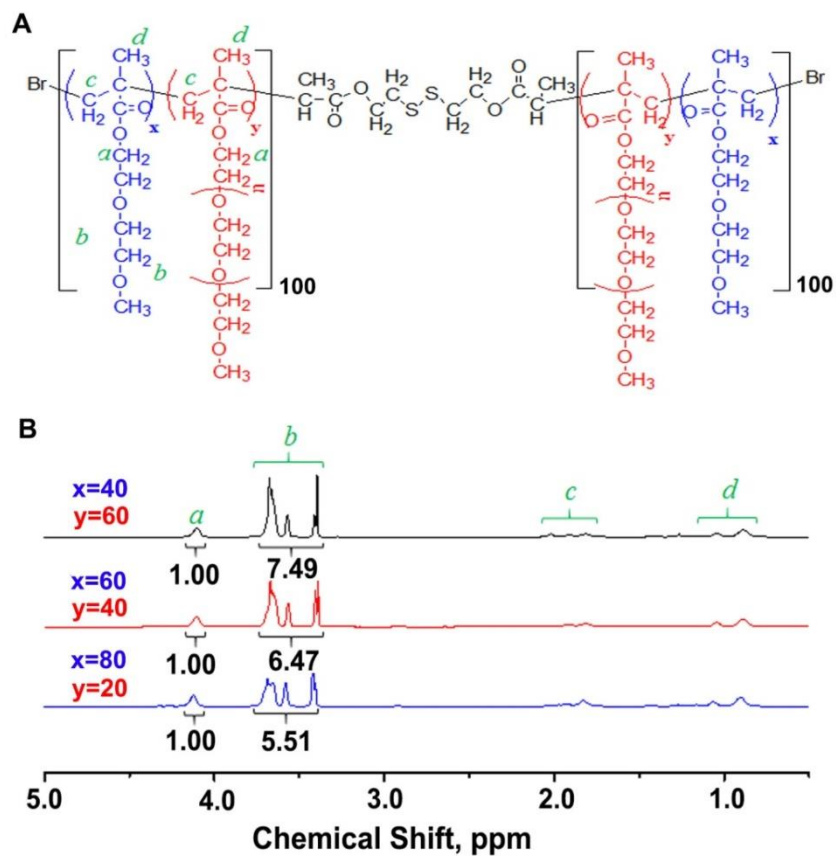
## **pH- and photothermal-driven multistage delivery nanoplatfrom for overcoming cancer drug resistance**

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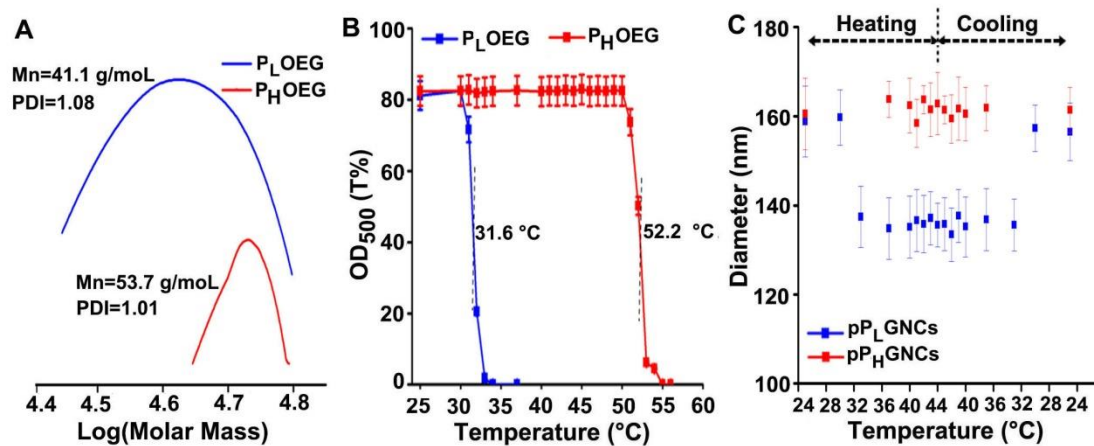
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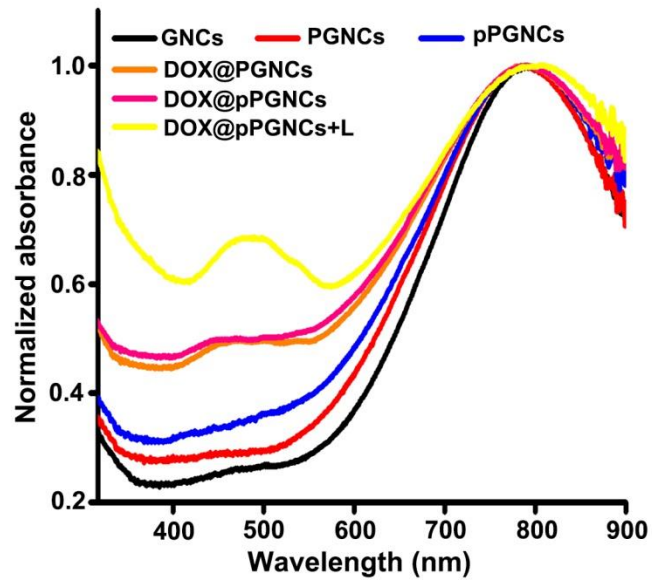
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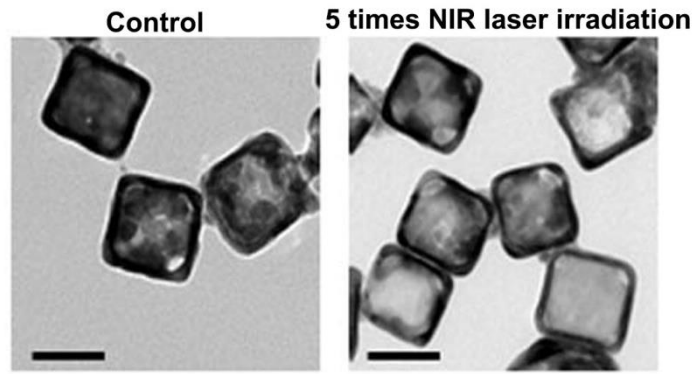
**Figure S1.** Identification of  $\text{PMEO}_2\text{MA}_{80}\text{-OEGMA}_{120}$ ,  $\text{PMEO}_2\text{MA}_{120}\text{-OEGMA}_{80}$  and  $\text{PMEO}_2\text{MA}_{160}\text{-OEGMA}_{40}$ . (A) Chemical structure of  $\text{PMEO}_2\text{MA}_{80}\text{-OEGMA}_{120}$ ,  $\text{PMEO}_2\text{MA}_{120}\text{-OEGMA}_{80}$  and  $\text{PMEO}_2\text{MA}_{160}\text{-OEGMA}_{40}$ . (B)  $^1\text{H-NMR}$  spectra of  $\text{PMEO}_2\text{MA}_{80}\text{-OEGMA}_{120}$ ,  $\text{PMEO}_2\text{MA}_{120}\text{-OEGMA}_{80}$  and  $\text{PMEO}_2\text{MA}_{160}\text{-OEGMA}_{40}$ .



**Figure S2.** Characterization of P<sub>L</sub>OEG and P<sub>H</sub>OEG. (A) GPC spectra of P<sub>L</sub>OEG and P<sub>H</sub>OEG. (B) Transmittance of P<sub>L</sub>OEG and P<sub>H</sub>OEG at 500 nm after incubation in PBS at the indicated temperatures for 5 min. (C) Diameter change of P<sub>L</sub>OEG and P<sub>H</sub>OEG incubating in PBS at the different temperatures. The data are presented as the mean ± SD (n = 3).

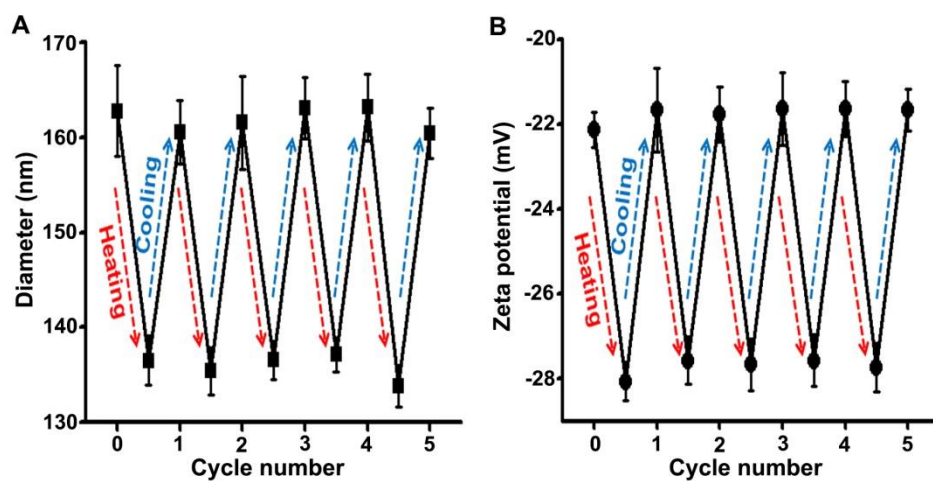


**Figure S3.** UV-Vis-NIR spectra of GNCs, pGNCs, pPGNCs, DOX@PGNCs, DOX@pPGNCs and DOX@pPGNCs undergoing five cycles of 808 nm laser irradiation ( $0.7 \text{ W/cm}^2$ , 10 min) and then cooling to room temperature (10 min).

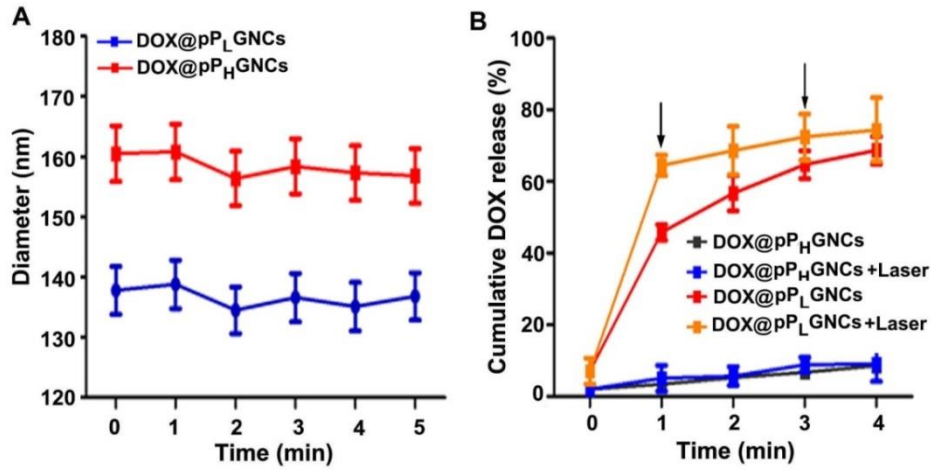


**Figure S4.** TEM images of DOX@pPGNCs after undergoing five cycles of 808 nm laser irradiation ( $0.7 \text{ W/cm}^2$ , 10 min) and then cooling to room temperature (10 min).

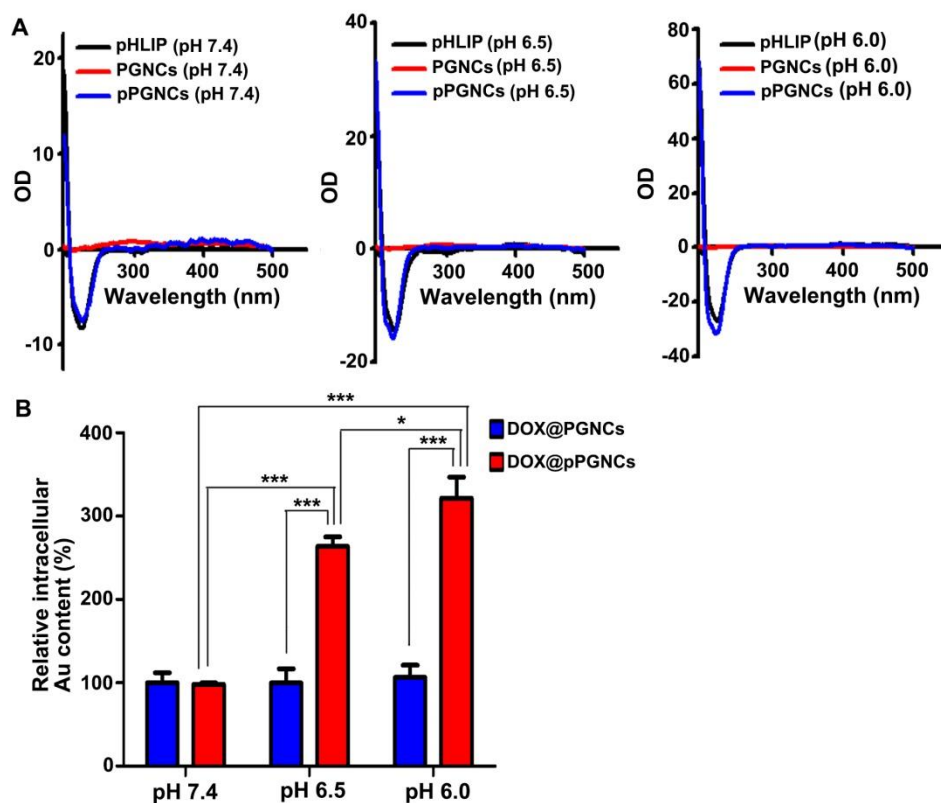
Scale bar: 50 nm.



**Figure S5.** Change in size (A) and zeta potential (B) of DOX@pPGNCs undergoing five cycles of 808 nm laser irradiation ( $0.7 \text{ W/cm}^2$ , 10 min) and then cooling to room temperature (10 min).

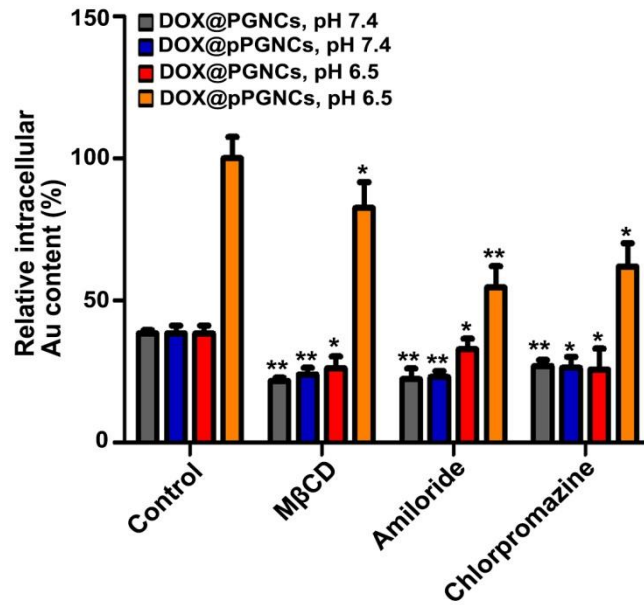


**Figure S6.** Characterization of DOX@pP<sub>L</sub>OEG and DOX@pP<sub>H</sub>OEG upon NIR laser irradiation. (A) Diameter of DOX@pP<sub>L</sub>OEG and DOX@pP<sub>H</sub>OEG upon 808 nm laser irradiation ( $0.7 \text{ W/cm}^2$ ) for different time intervals. (B) *In vitro* DOX release profiles from DOX@pP<sub>L</sub>OEG and DOX@pP<sub>H</sub>OEG in PBS with or without 808 nm laser irradiation ( $0.7 \text{ W/cm}^2$ ) for 5 min. Black arrows indicate the irradiation points. The data are presented as the mean  $\pm$ SD ( $n = 3$ ).

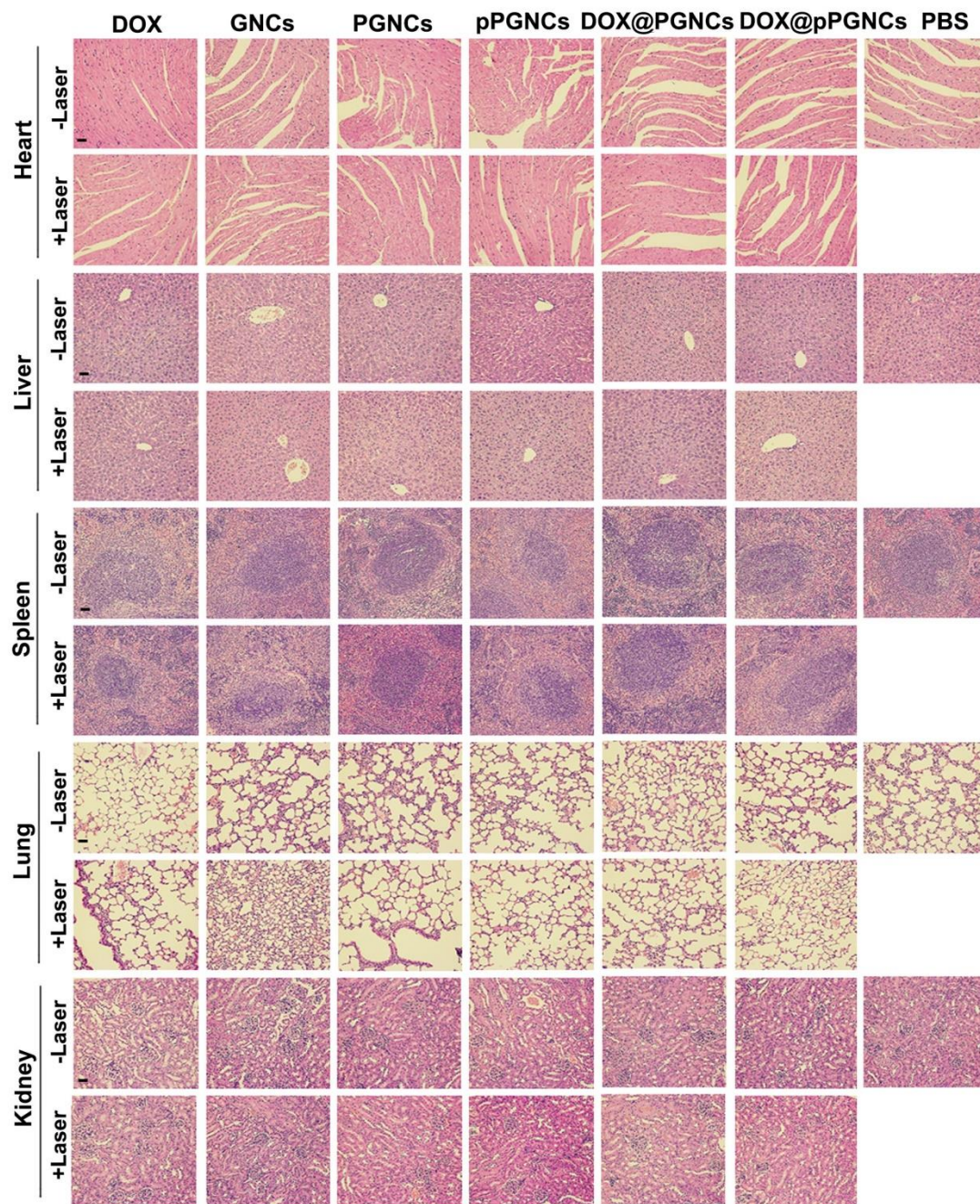


**Figure S7.** Conformation and cellular internalization of pPGNCs at different pH values. (A) CD spectra of pHLIP, PGNCs and pPGNCs at different pH values. (B) Cellular uptake of DOX@PGNCs and DOX@pPGNCs by MCF-7/ADR cells at different pH values. The data are presented as the mean  $\pm$  SD (n = 3). \* $P$ <0.05, \*\*\* $P$ <0.001.





**Figure S8.** Cellular internalization of DOX@PGNCs and DOX@pPGNCs in MCF-7/ADR cells pretreated with 5 mM MβCD, 10 μg/mL chlorpromazine or 2 mM amiloride for 1 h, followed by treatment with DOX@PGNCs or DOX@pPGNCs at Au concentration of 10 μg/mL at pH 7.4 or 6.5 for 12 h. The data are presented as the mean ± SD (n = 3). \* $P < 0.05$ , \*\* $P < 0.001$  compared with the corresponding control group.



**Figure S9.** Histological observation of major organs, including heart, liver, spleen, lung and kidney after treatment by H&E staining. Scale bar is 200  $\mu\text{m}$ .

**Table S1.** Molecular weight and composition characterization of the PMEO<sub>2</sub>MA<sub>x</sub>-OEGMA<sub>200-x</sub> polymers

| PMEO <sub>2</sub> MA <sub>x</sub> -OEGMA <sub>200-x</sub> |       | $M_n^a$ , kDa      |                    |                  | MEO <sub>2</sub> MA/OEGMA <sup>b</sup> |                  |
|---|-------|--------------------|--------------------|------------------|--|------------------|
|   |       | $M_n(\text{theo})$ | $M_n(\text{meas})$ | PDI <sup>a</sup> | $R(\text{theo})$                       | $R(\text{meas})$ |
| P <sub>L</sub> OEG  | x=160 | 42.6               | 41.1               | 1.08             | 0.67                                   | 0.67             |
| POEG  | x=120 | 47.0               | 48.8               | 1.06             | 1.50                                   | 1.54             |
| P <sub>H</sub> OEG  | x=80  | 51.5               | 53.7               | 1.01             | 4.00                                   | 3.95             |

<sup>a</sup>  $M_n(\text{theo})$  represents the theoretic values of number-average molecular weight ( $M_n$ ), which was calculated according to the feeding ratio between monomer and initiator.  $M_n(\text{meas})$  represents the measured values of  $M_n$  with the polydispersitivity index (PDI) measured by GPC.

<sup>b</sup> The molar ratio of both monomers (MEO<sub>2</sub>MA and OEGMA).  $R(\text{theo})$  represents the feeding ratio of MEO<sub>2</sub>MA and OEGMA, and  $R(\text{meas})$  represents the measured value of MEO<sub>2</sub>MA and OEGMA amount in polymers by <sup>1</sup>H-NMR.

**Table S2.** Secondary conformation of pHLIP and pPGNCs at different pH values by CD analysis

| <b>Sample</b>   | <b><math>\alpha</math>-helix</b> | <b><math>\beta</math>-sheet</b> | <b><math>\beta</math>-turn</b> | <b>random coil</b> |
|-----------------|----------------------------------|---------------------------------|--------------------------------|--------------------|
| pHLIP (pH 7.4)  | 8.9%                             | 65.9%                           | 6.5%                           | 18.7%              |
| pHLIP (pH 6.5)  | 26.9%                            | 34.1%                           | 20.2%                          | 18.8%              |
| pHLIP (pH 6.0)  | 51.2%                            | 20.6%                           | 22.9%                          | 5.3%               |
| pPGNCs (pH 7.4) | 13.0%                            | 56.9%                           | 10.8%                          | 19.3%              |
| pPGNCs (pH 6.5) | 27.0%                            | 42.7%                           | 16.0%                          | 14.4%              |
| pPGNCs (pH 6.0) | 52.8%                            | 10.8%                           | 22.7%                          | 13.7%              |