1 Synthesis of the block copolymer PEG_{114}-b-PLys_{44}^{[1]}

Synthesis of ε-(benzyloxycarbonyl)-L-lysine N-carboxyanhydride (Lys(Z)-NCA): The Lys(Z)-NCA were synthesized according to scheme 1. Firstly, 8.00 g N(ε)-(benzyloxycarbonyl)-L-lysine was dissolved in 100mL redistilled THF, 4.00g bis(trichloromethyl)carbonate was also dispersed in THF and then added into the N(ε)-(benzyloxycarbonyl)-L-lysine solution slowly under the temperature of 50-60°C with slightly shaking. After the solution turned into transparent, remove the unreacted bis(trichloromethyl)carbonate with argon. Then the solution was concentrated with reduced pressure distillation and was precipitated into excess cold n-hexane. Finally, the product was purified by dissolving into the mixture of hot ethyl acetate and n-hexane (1:1) and filtering to obtain the saturated solution. The product was separated out under static
condition and finally we obtain 5.98 g of the dry product.

Scheme S1. Synthesis route of Lys(Z)-NCA.

**Synthesis of poly(ethylene glycol)-block-poly(L-lysine) (PEG$_{114}$-b-PLys$_{44}$):** Firstly, poly(ethylene glycol)-b-poly(ε-(benzyloxy carbonyl)-L-lysine) (PEG-b-PLys(Z)) block copolymer was prepared by the polymerization of Lys(Z)-NCA initiated by the terminal amino group of PEG-NH$_2$. Briefly, a total of 2.68 g (8.8 mmol) of Lys(Z)-NCA was dispersed in 40 mL of DMF followed by the addition of 1.0 g (0.2 mmol) of PEG$_{114}$-NH$_2$. The reaction mixture was stirred for 72 h at 40 °C under a dry argon atmosphere. Then the solution was diluted with CHCl$_3$. Subsequently, the mixture was precipitated into excess cold diethyl ether to obtain 2.68 g (yield 81.4%) PEG-b-PLys(Z) (Mn = 15 kDa by $^1$H NMR, Mw/Mn = 1.13 by GPC). To obtain PEG-b-PLys, 2.6 g PEG-b-PLys(Z) was dissolved in 40 mL of trifluoroacetic acid and stirred for 0.5 h. Then, 4mL hydrogen bromide (HBr) (45% in acetic acid) was added into the solution and stirred for further 24 h at room temperature. The reaction mixture was diluted with 60 mL of distilled water and vigorously shaken with 400 mL of diethyl ether. The water phase was neutralized by sodium hydroxide and dialyzed against distilled water using a dialysis membrane (molecular weight cutoff = 3.5 kDa). The aqueous solution of purified product was lyophilized to obtain 1.08 g PEG$_{114}$-b-PLys$_{44}$ (yield 64.8%).
2 Characterization of block polymers

The $^1$H NMR spectra of the block polymers PEG-$b$-PLys(Z) in CDCl$_3$ and PEG-$b$-PLys in D$_2$O were recorded using a Varian UNITY-plus 400 spectrometer and chemical shifts were given in ppm relative to TMS. The $^1$H NMR spectra of PEG-$b$-PLys(Z) in CDCl$_3$ and PEG-$b$-PLys in D$_2$O are shown as Fig. S1A and S1B. The signal at about 5.0 ppm in the $^1$H NMR spectrum of PEG-$b$-PLys(Z) in Fig. S1A is attributed to the $\alpha$-methylene protons of carboxybenzyl. It is disappeared in the $^1$H NMR spectrum of PEG-$b$-PLys in Fig. S1B, indicating the complete removal of the protection group carboxybenzyl. The composition of PEG-$b$-PLys is determined by the ratio of the integrated area of peak “a” corresponding to methylene protons of PEG block to that of peak “d” corresponding to $\alpha$-methylene protons of the $\omega$-amino group on PLys block. Gel permeation chromatography (GPC) analysis of PEG-$b$-PLys(Z) was performed on a Waters 600E system, where N,N-dimethylformamide (DMF) with 0.05 M LiBr was used as the eluent and narrowly distributed poly(methyl methacrylate) was used as the calibration standard. The GPC trace showed in Fig. S1C gives a polydispersity index (PDI) of 1.13 for the block copolymer precursor PEG-$b$-PLys(Z).
3 Determination of the standard curve of CAPE.

The concentration of capecitabine released was determined by UV-Vis by measuring absorbance at 310 nm. To obtain the standard curve of CAPE, we prepared an array of CAPE aqueous solution (1.95, 3.91, 7.81, 15.63, 31.25, 62.50, and 125 µg/mL) and measured the absorbance at 310 nm. The absorbance at 310 nm shows linear relationship with the concentration of CAPE, as shown in Fig. S2.
Fig. S2 Standard curve for CAPE in pH 7.4 PBS buffer solution determined by UV-vis absorbance at 310 nm.

4 Characterization of 2-FPBA binding to PEG-b-PLys by $^1$H NMR spectra.
Fig. S3 Calculation of the ratios of integrated areas from the signal of aldehyde protons at 9.9 ppm to those of aromatic protons in the range of 7.2 – 8.0 ppm based on the $^1$H NMR spectra of 2-FPBA without and with PEG-b-PLys.

5 Characterization of loading of CAPE into micelles by UV-vis spectra.

Fig. S4 UV-vis absorbance of the capecitabine (CAPE), polymer complex PEG-b-PLys/2-FPBA, and drug-loaded polymer complex PEG-b-PLys/2-FPBA/CAPE.

References