Supporting information

Virus-Inspired Mimics: Dual-pH-Responsive Modular Nanoplatforms for Programmable Gene Delivery without DNA Damage with the Assistance of Light

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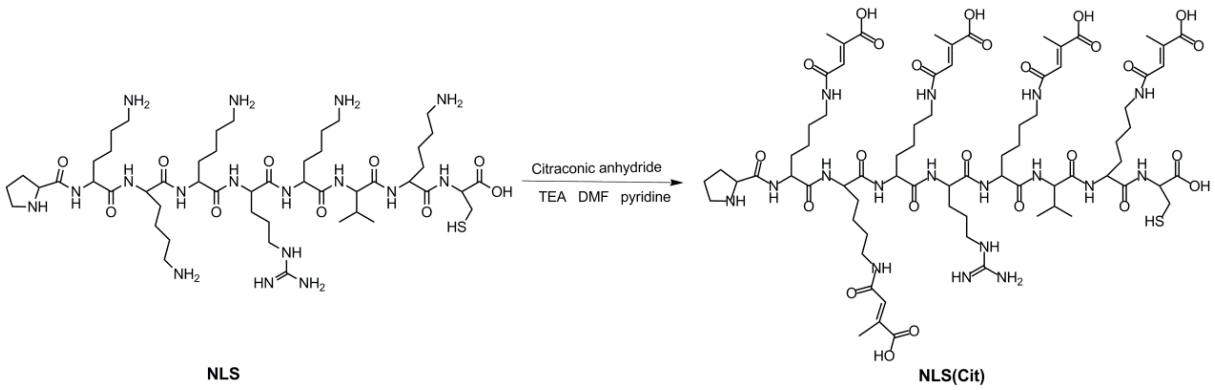

Figure S1. Synthesis routine for NLS(Cit).

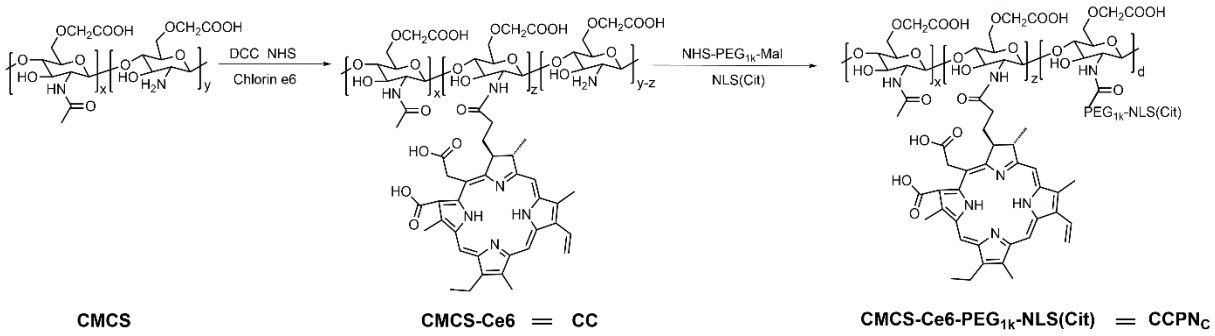

Figure S2. Synthetic routine for CMCS-Ce6-PEG_{1k}-NLS(Cit) ($CCPN_C$).

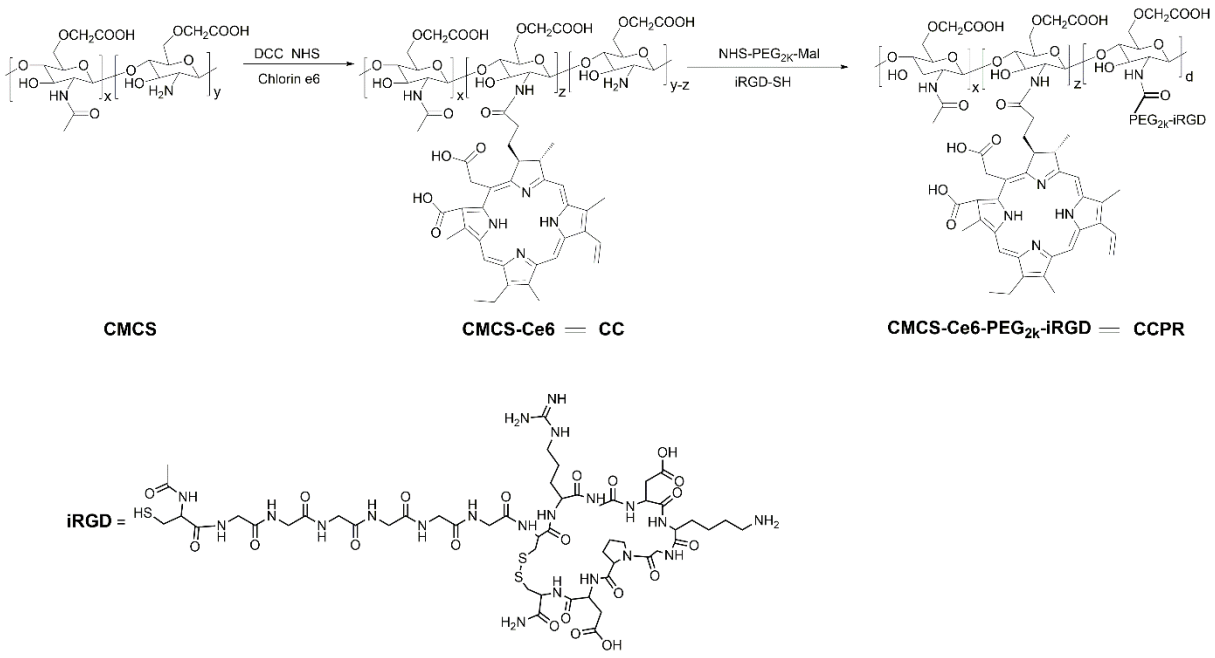

Figure S3. Synthetic routine for CMCS-Ce6-PEG_{2k}-iRGD (CCPR).

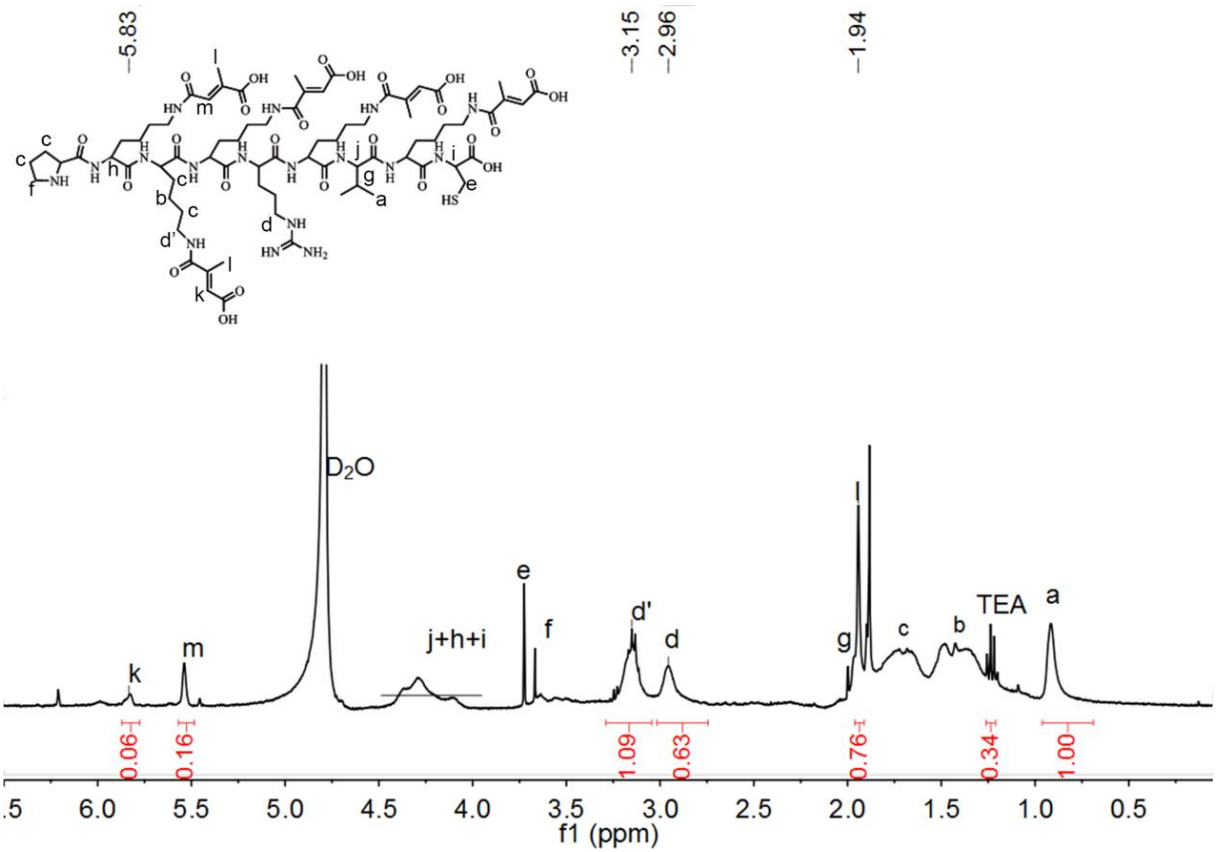

Figure S4. ^{1}H NMR spectrum for NLS(Cit) in D_2O.

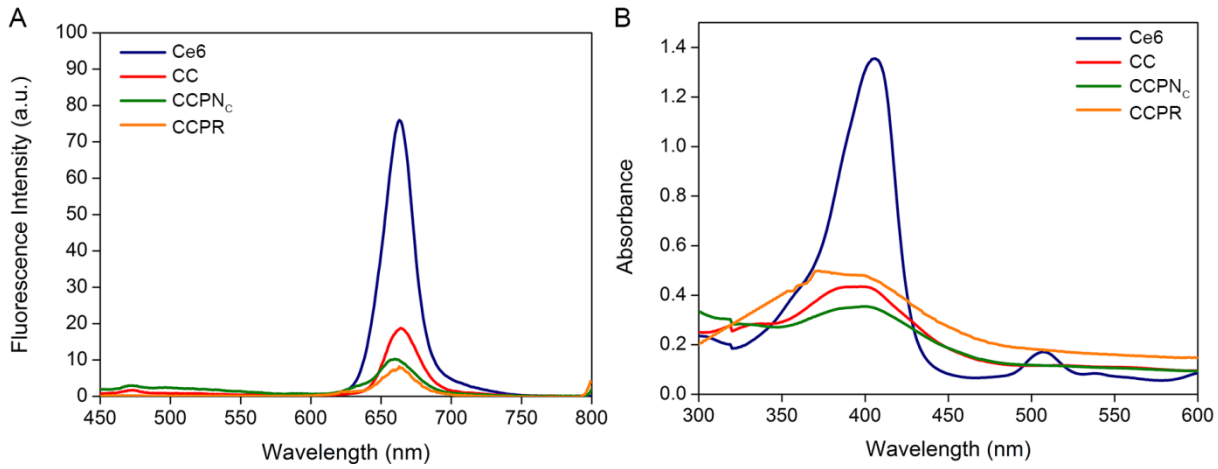

Figure S5. (A) Fluorescence spectra and (B) UV−vis absorption spectra of different polymers in the PBS buffer at pH 7.4 (Ce6 0.01 mg/mL, CC 0.15 mg/mL, $CCPN_C$, and CCPR 1 mg/mL). The excitation wavelength of fluorescence emission spectra was fixed at 405 nm.

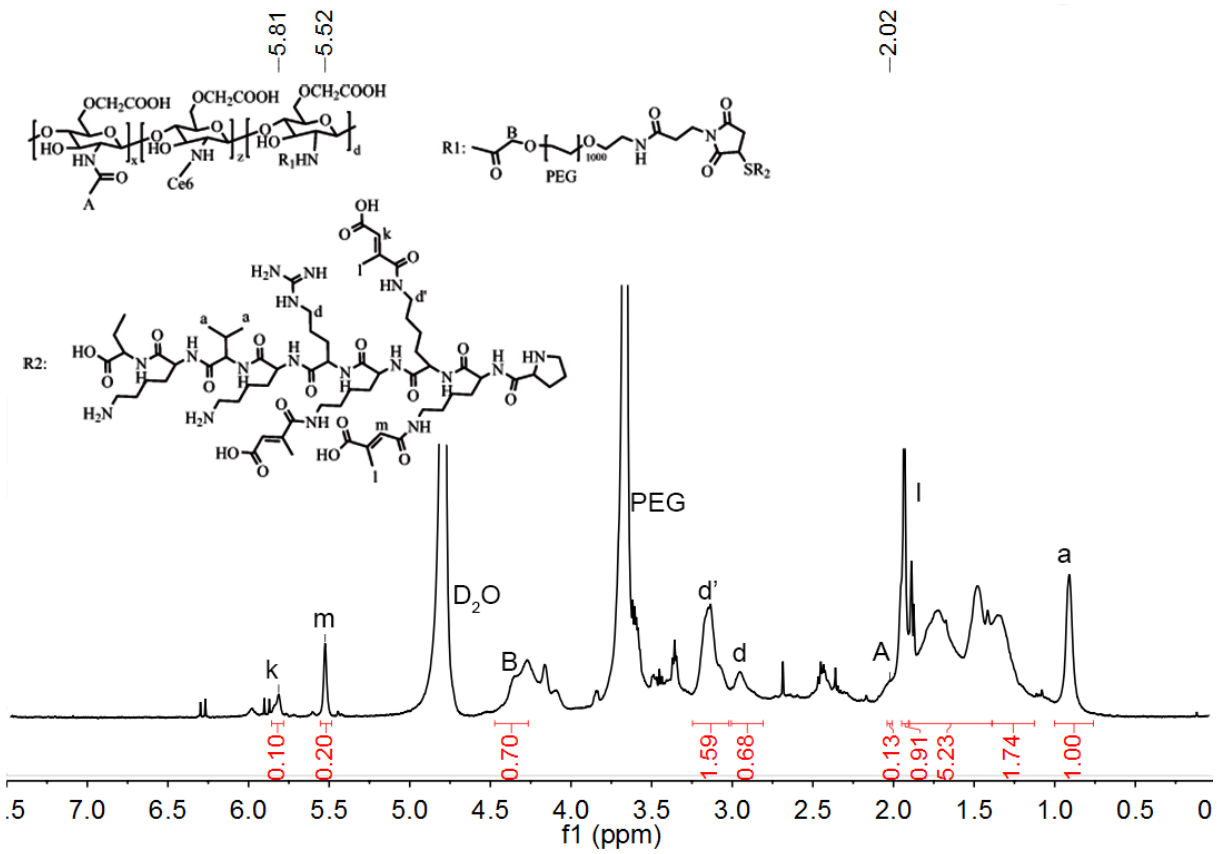

Figure S6. ^{1}H NMR spectrum for $CCPN_C$ in D_2O.

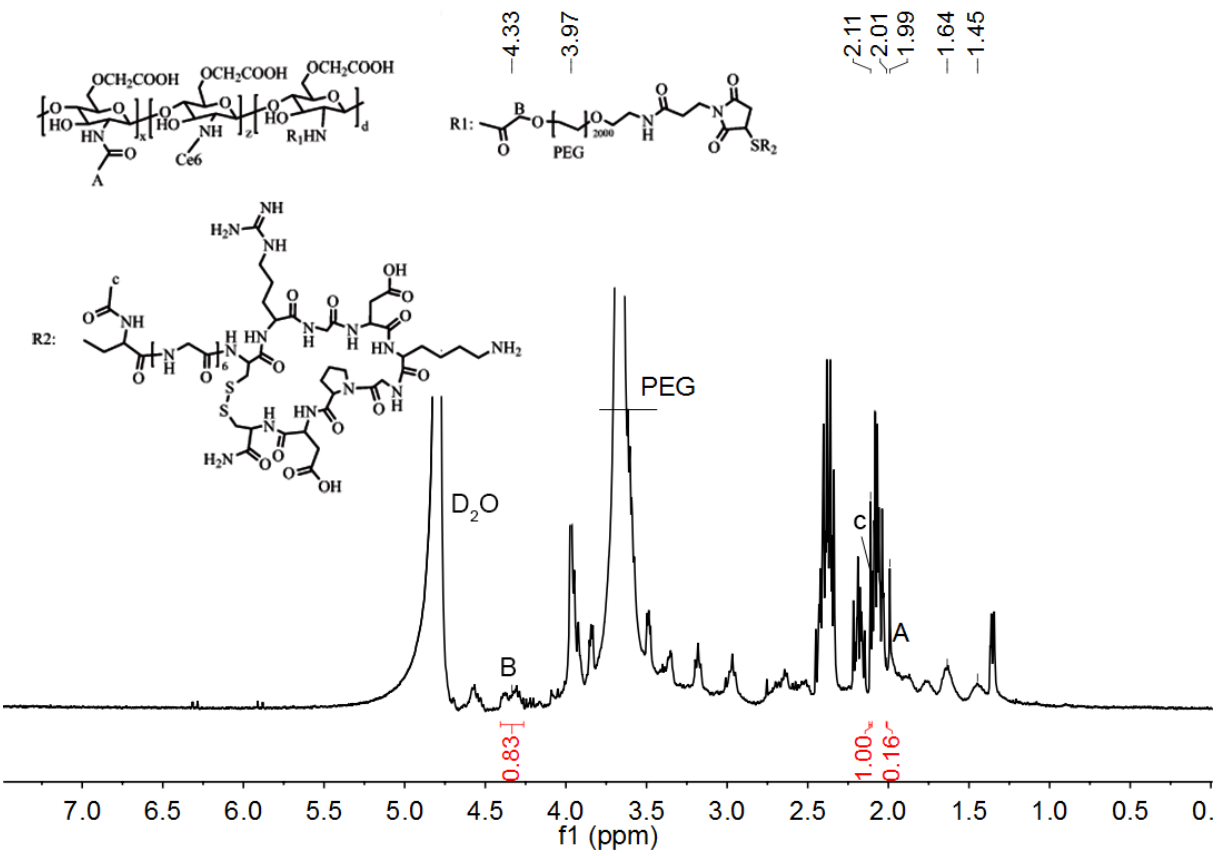

Figure S7. ^{1}H NMR spectrum for CCPR in D_2O.

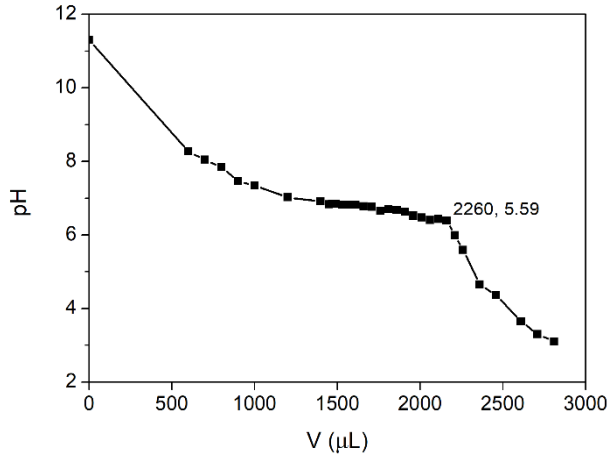

Figure S8. Isoelectric point of CMCS determined by acid-base titration.

Table S1. Size and zeta potential of different polyplexes prepared at a weight ratio of PEI/DNA/envelope (1.33/1/5) recorded using dynamic light scattering (DLS).

Sample name	Abbreviation	Size (nm)	Zeta potential (mV)
PEI/DNA	PD	119.7 ± 3.5	14.0 ± 0.1
PEI/DNA/$CCPN_C$	PD@$CCPN_C$	2146.3 ± 71.5	−3.0 ± 0.8
PEI/DNA/$CCPN_C$-CCPR	PD@CCPNR	211.3 ± 12.3	3.4 ± 0.4

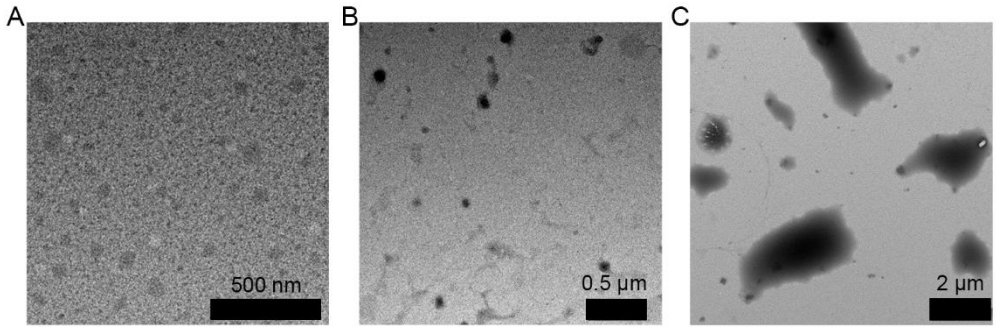

Figure S9. The morphology of (A) PD polyplexes, (B) PD@CCPNR at pH 7.4 and (C) PD@CCPNR at pH 5.0.

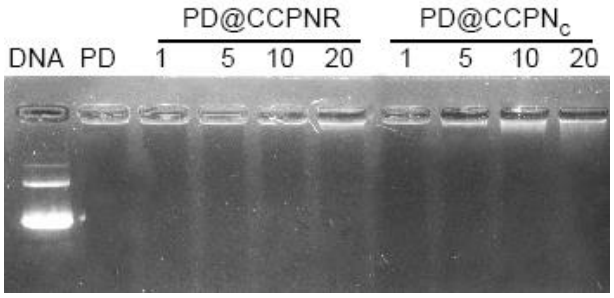

Figure S10. The effect of different envelopes on the stability of PD@CCPNR and PD@CCPN$_C$ prepared at different weight ratios (envelope/DNA in PD).

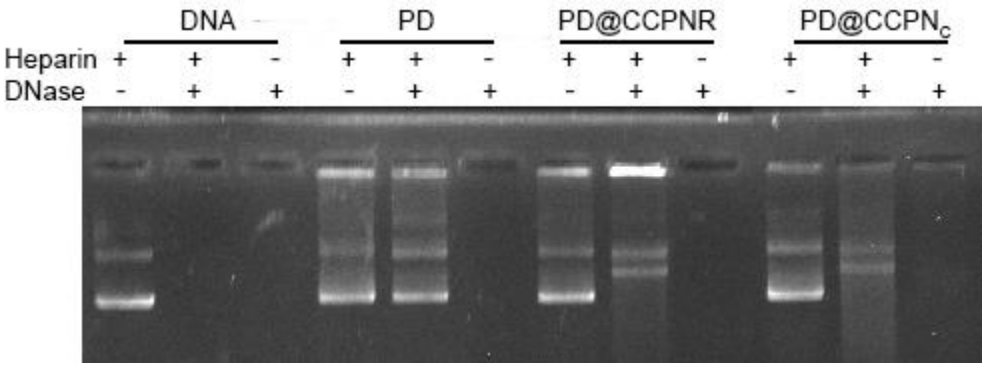

Figure S11. Stability of polyplexes followed by incubation with DNase I and/or heparin analyzed by agarose gel electrophoresis.

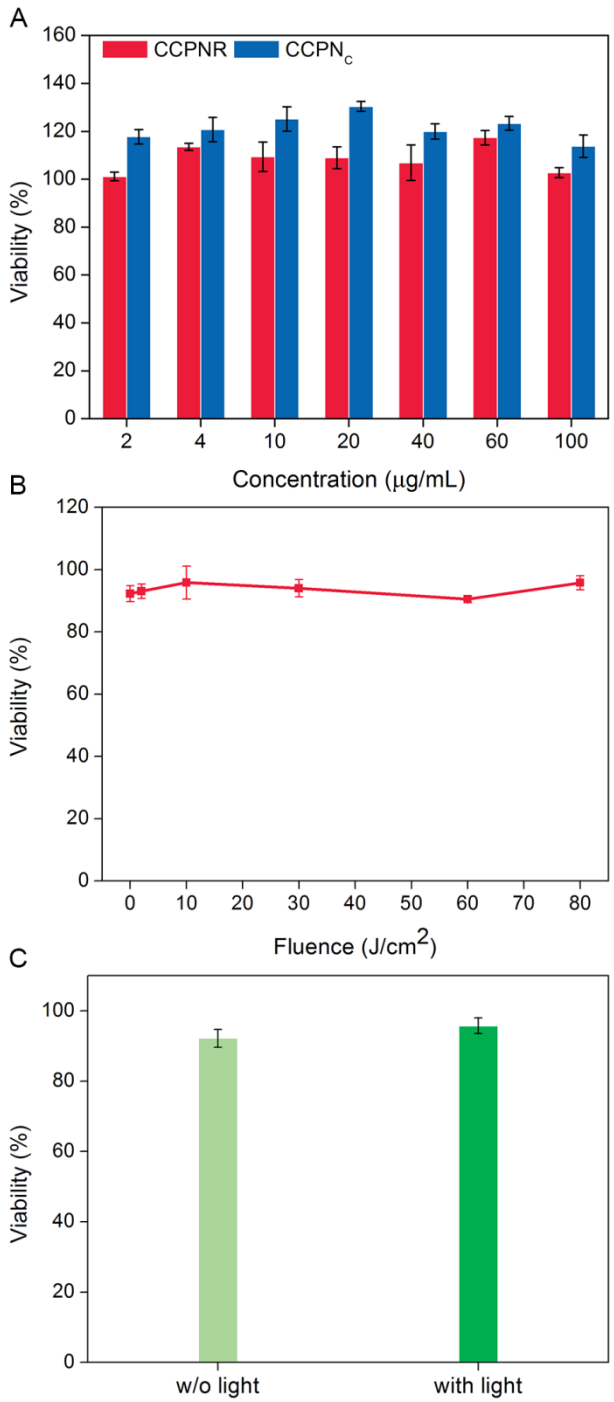

Figure S12. (A) Cell viability of B16 cells after an exposure to envelops at different concentrations. (B) The effect of light fluences on the photocytotoxicity of PD@CCPNR against B16 cells. The light irradiation was performed after incubation with PD@CCPNR for 4 h,

followed by 48 h of incubation in a fresh medium. (C) Viability of B16 cells transfected with PD@CCPNR in the presence or absence of light.

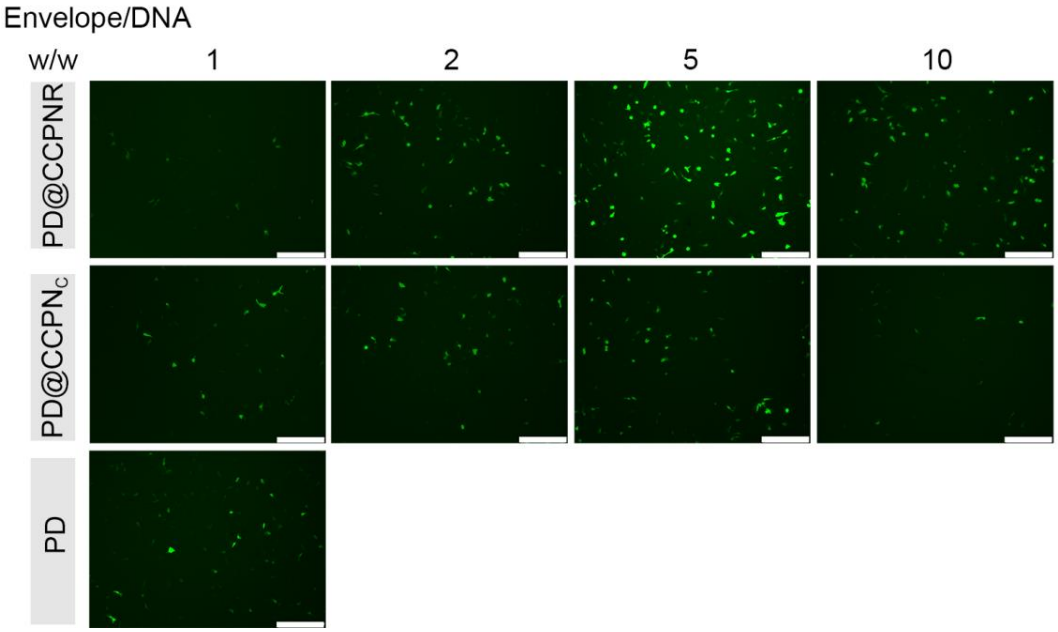

Figure S13. The enhanced green fluorescent protein (EGFP) expression of PD@CCPNR, PD@CCPN$_C$ and PD at various envelope/DNA weight ratios against B16 cells in the presence of serum. All the scale bars are 250 μm.

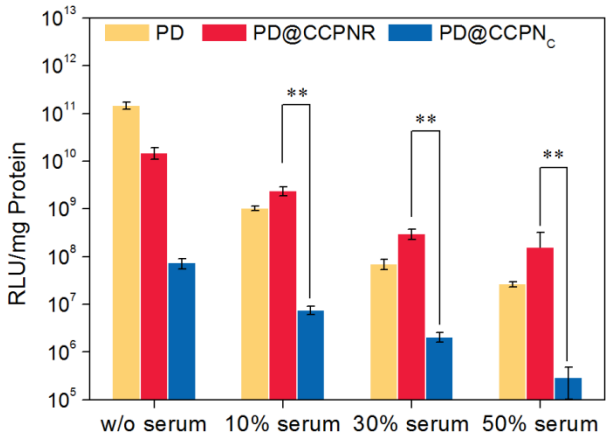

Figure S14. Luciferase expression of PD, PD@CCPNR and PD@CCPN$_C$ against B16 cells in the presence of serum at different concentrations (**$p < 0.01$).

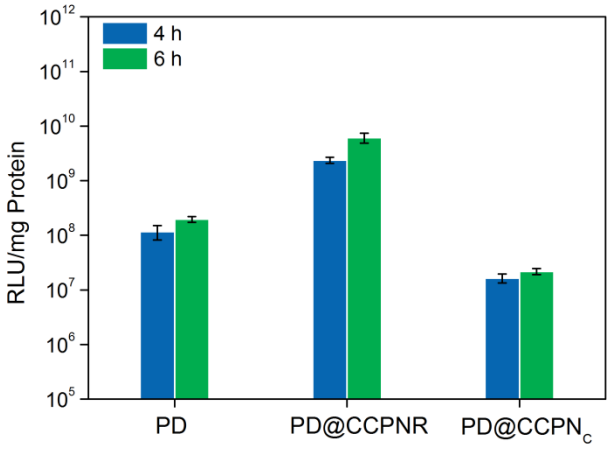

Figure S15. Luciferase activities against B16 cells transfected with PD, PD@CCPNR and PD@CCPN$_C$ for two incubation durations.

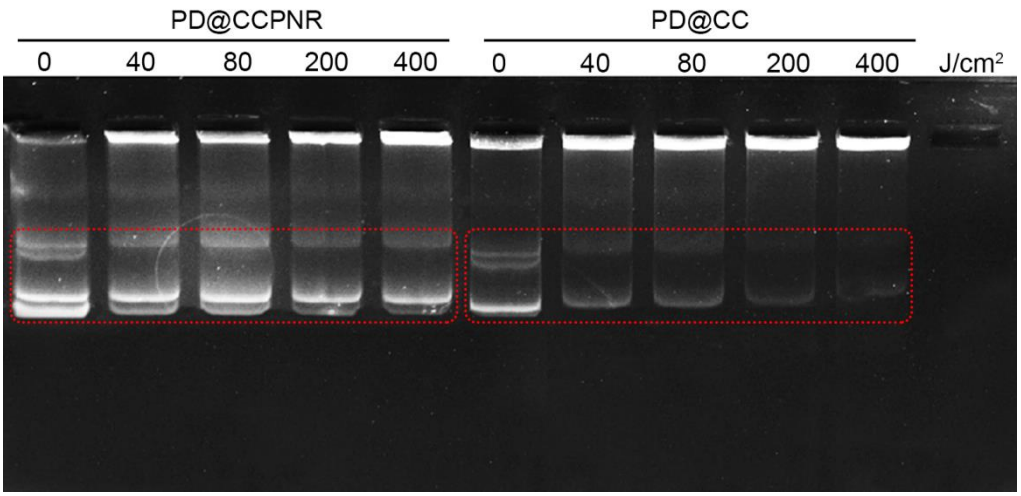

Figure S16. Agarose gel electrophoresis of pDNA released from PD@CCPNR and PD@CC which were both treated by light irradiation at different light fluences (660 nm) and heparin. PD@CCPNR without photoirradiation and PD@CC were set as controls.

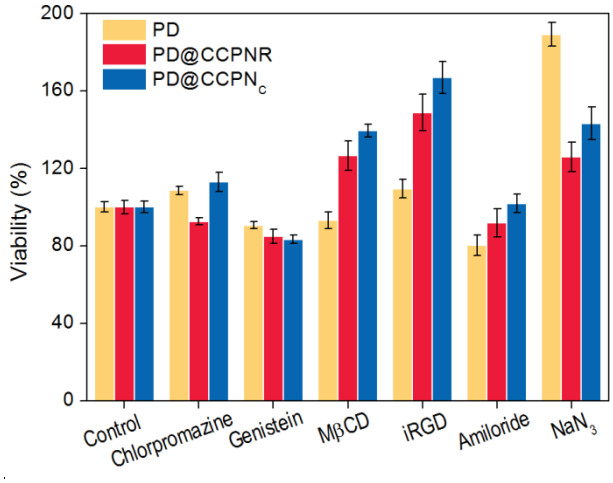

Figure S17. The effects of endocytic inhibitors on the cell viability of B16 cells determined by CCK-8 assay. Cells without any inhibitors treatment were used as a control.

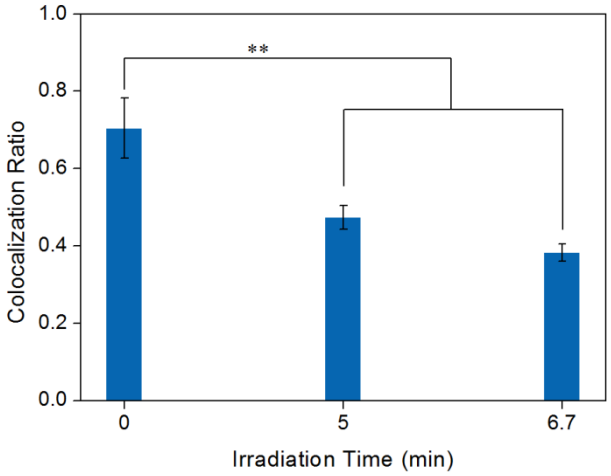

Figure S18. Colocalization ratio between the fluorescence of Cy3-labeled pDNA and endo/lysosomes stained by LysoTracker Green DND-26 as calculated from the confocal images in **Figure 6** (**$p < 0.01$).

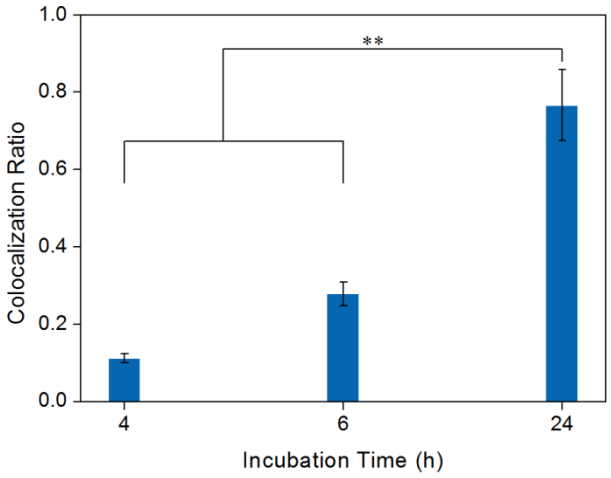

Figure S19. Colocalization ratio between the fluorescence of Hoechst 33342-labeled nuclei and Ce6 from CCPNR as calculated from the confocal images in **Figure 7** (**$p < 0.01$).