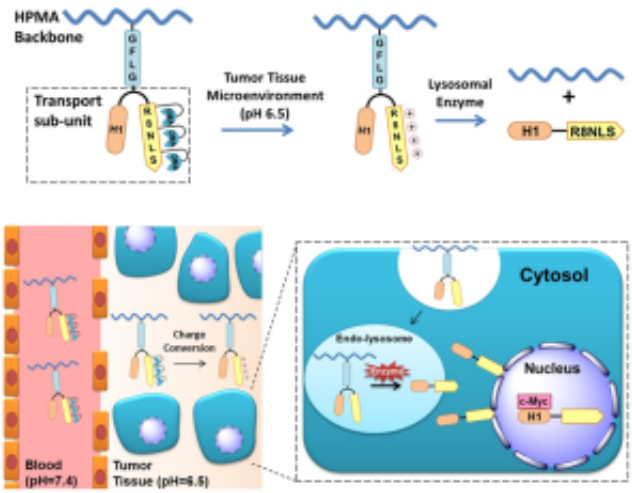
Nucleus-targeted anticancer drug delivery

Tumor cell nucleus-targeted delivery of antitumor agents is of great interest in cancer therapy, since the nucleus is one of the most frequent targets of drug action. However, efficient nuclear drug delivery upon systemic administration remains a challenge due to existence of the multiple physiological barriers, including escaping rapid elimination through renal excretion and the mononuclear phagocyte system (MPS), enhancing cellular uptake and endosomal escape, and penetrating through the double-layered nuclear membrane. Here we report a polymeric conjugate platform, which utilizes a novel strategy to achieve nuclear drug delivery upon systemic administration (Scheme 1).



Scheme 1. Illustration of the multistage nuclear targeting drug delivery process of dual-responsive HPMA copolymer conjugates with H1 peptide and nuclear targeting peptide (R8NLS) decorated sub-units (P-GFLG-R8NLS-DMA-H1).

The conjugates composed of a backbone based on HPMA copolymer, and detachable nucleus transport sub-units that sensitive to lysosomal enzyme. The sub-units possess a biforked structure with one end conjugated with the model drug, H1 peptide, and the other end conjugated with a novel tumor microenvironment pH-responsive targeting peptide (R8NLS) that combining the strength of cell penetrating peptide and nuclear localization sequence. Due to the rational design, the conjugates exhibited long-circulating property and excellent tumor homing, the AUC and tumor accumulation of the Cy5.5 labbled conjugate (P-GFLG-R8NLS-DMA-Cy5.5) were 2-fold higher than P-GFLG-R8NLS-Cy5.5 (Fig. 1 A-D). The acidic tomor microenvironment (pH6.5) resulted in the activation of the targeting peptide, which enhanced the tumor penentation and cellular uptake (Fig. 1 E). Once internalized into the cell, the sub-units were unleashed by lysosomal cathepsin B for nuclear transport through nuclear pore complex. The unique features resulted in 50-fold increase of nuclear drug accumulation relative to the original polymer-drug conjugates in vitro, and excellent in

vivo nuclear drug delivery efficiency (Fig. 1 F).

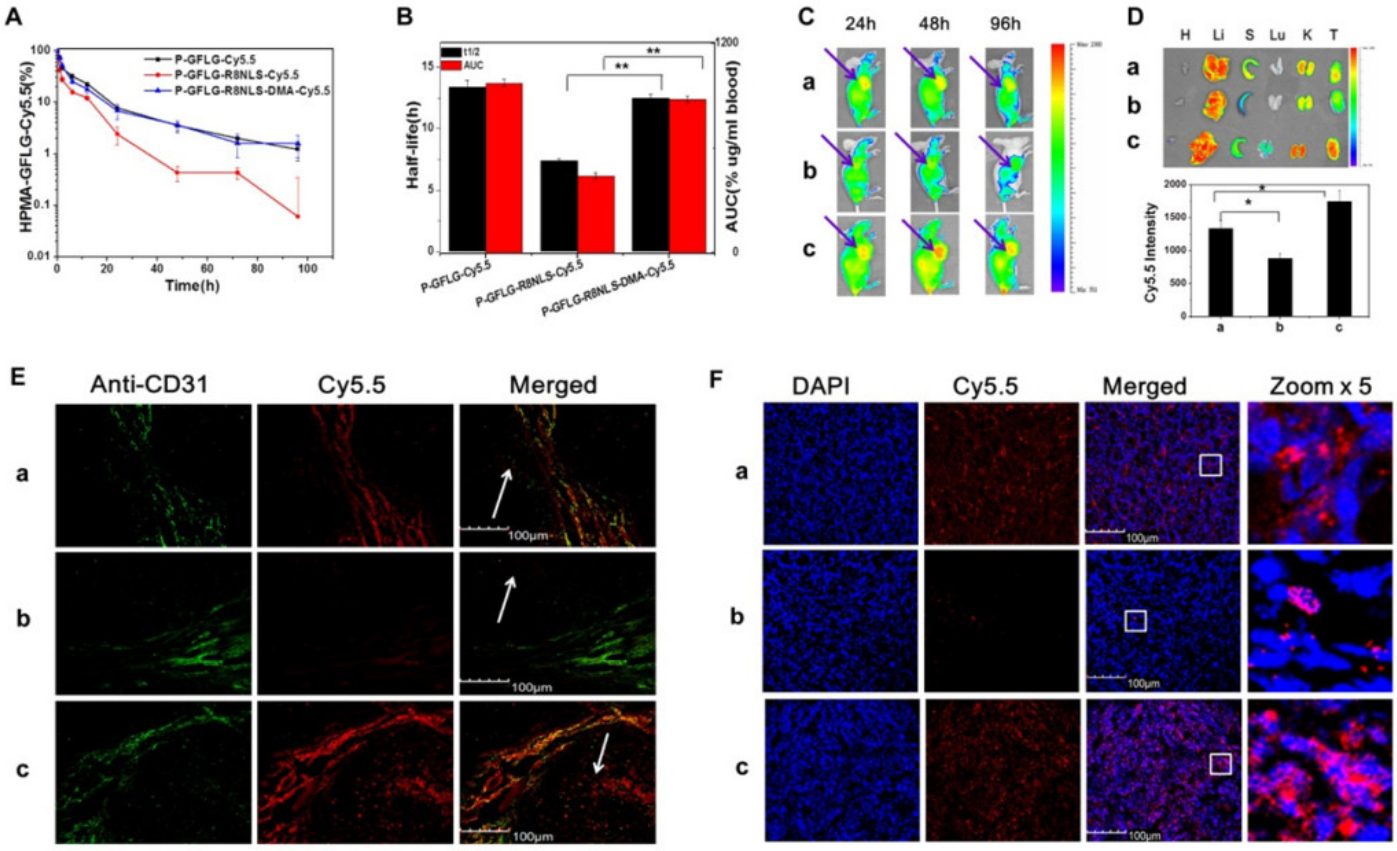


Fig. 1. (A) Pharmacokinetic profiles in BALB/c mice. (B) The pharmacokinetic parameter (C) In vivo fluorescence imaging of the HeLa tumor-bearing nude mice at 24, 48 and 96 h after intravenous injection of Cy5.5-labeled polymer conjugates. (D) Ex vivo fluorescence imaging of the tumor and normal tissues (heart, liver, spleen, lung and kidney) at 48 h post-injection. (E and F) Frozen sections of tumor (20×) removed 48 h after treatment with different Cy5.5-labeled polymeric conjugates (red). Vessel labeling with FITC-tagged CD31 (green) and nucleus staining with DAPI (blue). a: P-GFLG-Cy5.5, b: P-GFLG-R8NLS-Cy5.5 ,c: P-GFLG-R8NLS-DMA-Cy5.5.Results are means ± SD, n=5, **p less than 0.01.

The conjugates also significantly improved the in vivo antitumor efficacy of H1 peptide, a drug that requires nucleus accumulation for its action. Our report provides a novel strategy in systemic nuclear drug delivery by combination the microenvironment–responsive structure and detachable sub-units. This system might also offer a means for rapid in vivo validation of other potential anti-tumor agents that requires nuclear specific delivery. Importantly, HPMA copolymer-based therapeutics has progressed into clinical trials, which might suggest the potential of this platform for clinic translation.

Publication

A smart polymeric platform for multistage nucleus-targeted anticancer drug delivery.
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