Self-Assembled Nucleotide/Saccharide-Tethering Polycation-Based Nanoparticle for Targeted Tumor Therapy

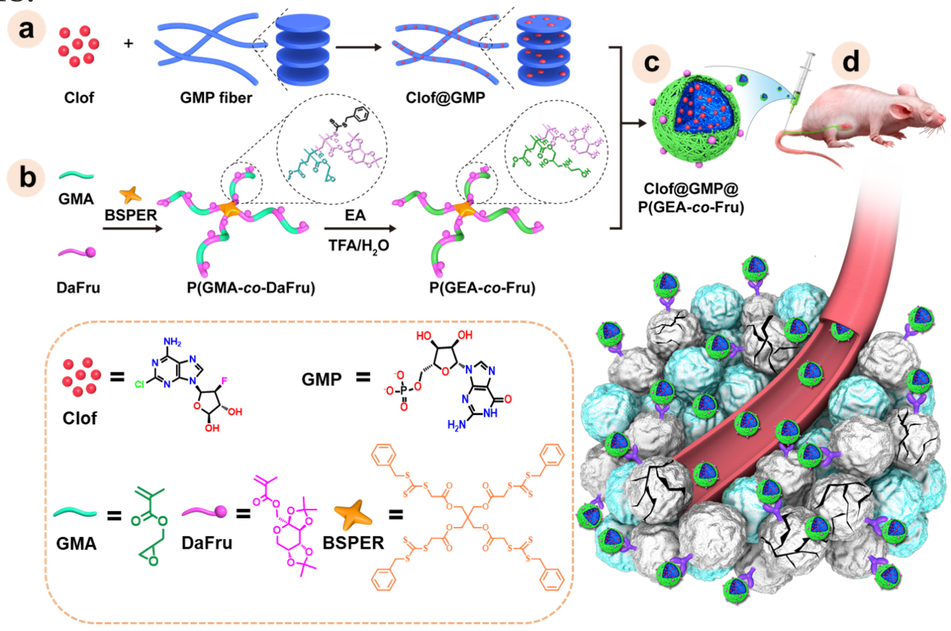
Dan Yu, Bingran Yu*, Zhen-Gang Wang* and Fu-Jian Xu*

Beijing University of Chemical Technology

*Corresponding author: xufj@mail.buct.edu.cn; yubr@mail.buct.edu.cn; wangzg@mail.buct.edu.cn;

Hydrophobic drugs, as a vast majority of the chemotherapeutics, have suffered from low biosafety, bioavailability and the anticancer effect, due to poor solubility and short half-life and low specificity. The therapeutic effects of the hydrophobic drugs can be improved by physical or chemical inclusion in the drug vehicles, including liposomes, vesicles, polymer micelles, and multifunctional copolymers. In recent years, supramolecular systems derived from endogenous materials have been considered promising for the fabrication of drug vehicles, due to their full biocompatibility. A variety of self-assembled DNA-based drug vectors, which loaded the anticancer drugs through intercalation interactions, have been fabricated to deliver drugs *in vivo*. However, the specific interactions between the carrier materials and the drug molecules limited the type of chemotherapeutics.

Hence, development of novel concepts to construct drug vehicles for efficient encapsulation of hydrophobic drugs and targeted therapy is highly desirable to biomedical science. It remains a challenge to create effective noncovalent linkage between the components within the drug vectors.



Scheme 1. Schematic illustration of the self-assembled Clof@GMP@P(GEA-*co*-Fru) nanoparticle for targeted tumor therapy.

In this manuscript, we employed self-associating guanosine monophosphate (GMP, a monomeric nucleotide in RNA) as the carrier to load a FDA (Food and Drug Administration)-approved second-generation adenosine analogue, clofarabine (Clof), as a model hydrophobic anticancer drug (**Scheme 1a**). Then we designed and synthesized P(GEA-*co*-Fru), a fructose/ethanolamine-functionalized star-like poly(glycidyl methacrylate) (PGMA)-based cationic polymer (**Scheme 1b**). We assembled the Clof@GMP complex with P(GEA-*co*-Fru) into nanoscale particles (**Scheme 1c**), namely Clof@GMP@P(GEA-*co*-Fru), to investigate the treatment of breast cancer *in vitro* and *in vivo* (**Scheme 1d**).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant numbers 51733001, 21875014 and 21872044), Fundamental Research Funds for the Central Universities (XK1806, XK1802-2 and buctrc201902), Beijing Outstanding Young Scientist Program (BJJWZYJH01201910010024) and China Postdoctoral Science Foundation (Grant No. 2019M650452).

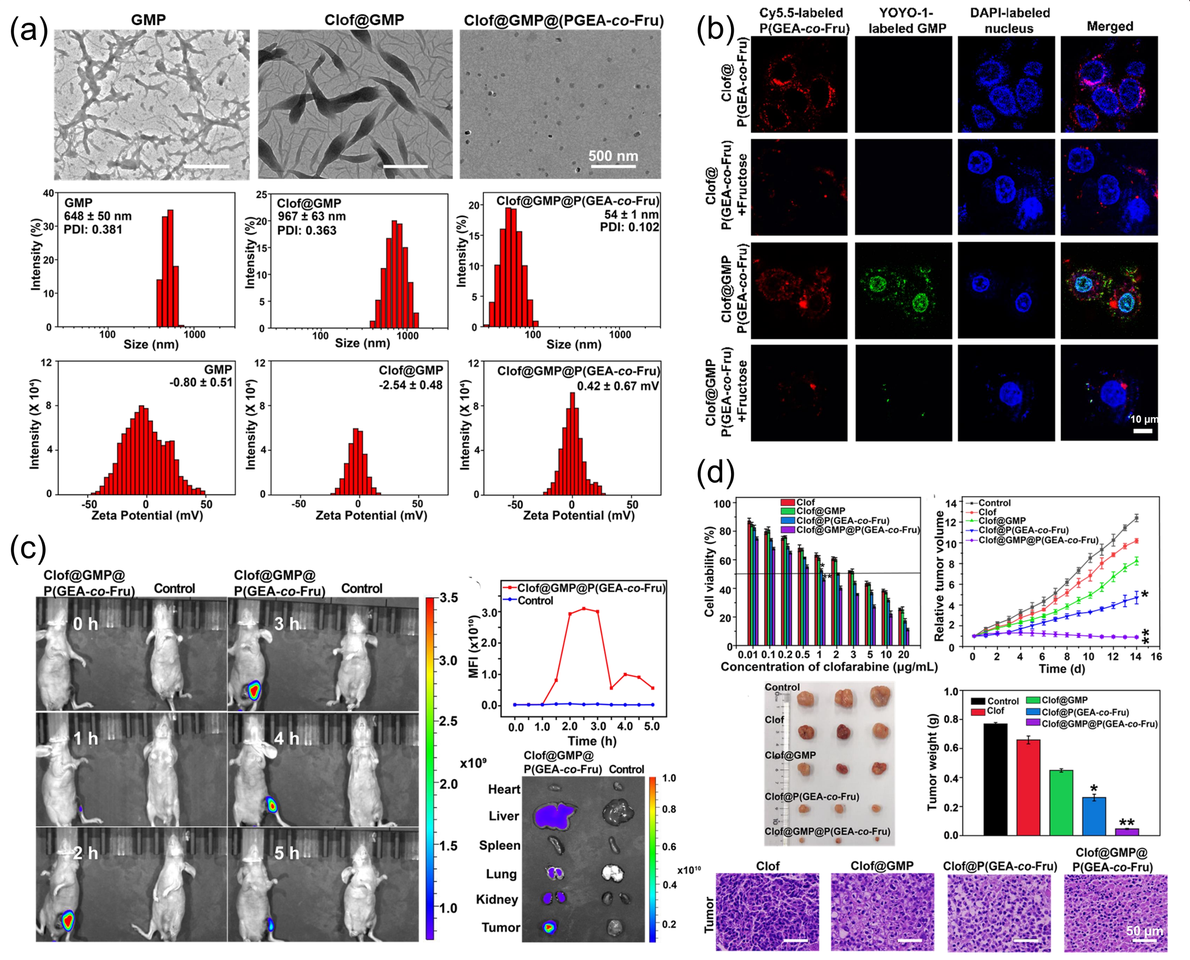


Figure 1. The pivotal datas of Clof@GMP@P(GEA-*co*-Fru) *in vitro* and *in vivo*.

In **Figure 1a**, the DLS results indicated that practical size of Clof@GMP@P(GEA-*co*-Fru) was about 50 nm, which is consistent with TEM images. The zeta potential of Clof@GMP@P(GEA-*co*-Fru) was close to neutral, which would be beneficial to long circulation. Excessive fructose is able to saturate the GLUT5 receptors expressed on the cells through specific recognition and inhibit the binding of P(GEA-*co*-Fru) to the cell surfaces. In **Figure 1b**, the red fluorescence of Clof@GMP@P(GEA-*co*-Fru) was significantly weaker in the presence of fructose than in the absence of fructose, which indicated Clof@GMP@P(GEA-*co*-Fru) was beneficial to be recognized and to be uptaken by the MCF-7 cancer cells. As shown in **Figure 1c**, the whole-body imaging results revealed tumor-targeting capabilities of the Clof@GMP@P(GEA-*co*-Fru) nanoparticles, promising therapeutic effects of clofarabine to the tumor site. In **Figure 1d,** *in vitro* cytotoxicity experiments indicated an excellent cancer cells-killing effect of Clof@GMP@P(GEA-*co*-Fru). The animal experiments showed that Clof@GMP@P(GEA-*co*-Fru) inhibited the tumor growth most effectively, which is matched well with *in vitro* cytotoxicity tests.

In summary, abundant fructose units in P(GEA-*co*-Fru) enabled the self-assembled nanoparticles to target MCF-7 cancer cells, which facilitated the accumulation of Clof@GMP@P(GEA-*co*-Fru) at the tumor site to suppress the tumor growth. This work provides a novel and effective avenue for the design and construction of vehicles for targeted delivery of hydrophobic drugs and tumor therapy.

Publications

Yu, D.; Zhang, N.; Liu, S.; Hu, W.; Nie, J.-J.; Zhang, K.; Yu, B.; Wang, Z.-G.; Xu. F.-J. Self-Assembled Nucleotide/Saccharide-Tethering Polycation-Based Nanoparticle for Targeted Tumor Therapy. *ACS Materials Lett*. **2020**, *2*, 550−556.