Tumor Microenvironment Remodeling-Mediated Sequential Drug Delivery Potentiates Treatment Efficacy

*Yajun Xu and Zhaohui Tang**

5625 Renmin Street
Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry,
Chinese Academy of Sciences
Changchun 130022, China
ztang@ciac.ac.cn

Toll-like receptor 7/8 agonists, such as imidazoquinolines (IMDQs), are promising for the *de novo* priming of antitumor immunity.[1,2] However, their systemic administration is severely limited due to the off-target toxicity. Here, we describe a sequential drug delivery strategy (Figure 1). The formulation is composed of two sequential modules: a tumor microenvironment remodeling nanocarrier (poly(L-glutamic acid)-*graft*-methoxy poly(ethylene glycol)/combretastatin A4, termed CA4-NPs) and an immunotherapy nanocarrier (apcitide peptide-decorated poly(L-glutamic acid)-*graft*-IMDQ-N_3 conjugate, termed apcitide-PLG-IMDQ-N_3). CA4-NPs, as a vascular disrupting agent, are utilized to remodel the tumor microenvironment for enhancing tumor coagulation and hypoxia. Subsequently, the apcitide-PLG-IMDQ-N_3 could identify and target tumor coagulation through the binding of surface apcitide peptide to the GPIIb-IIIa on activated platelets. Afterward, IMDQ was activated selectively through the conversion of "-N_3" to "-NH_2" in the presence of hypoxia. The biodistribution results confirmed their high tumor uptake of activated IMDQ (22.66%ID/g). By augmenting the priming and immunologic memory of tumor-specific $CD8^+$ T cells, 4T1 and CT26 tumors with a size of ~500 mm^3 were eradicated without recurrence in mouse models.

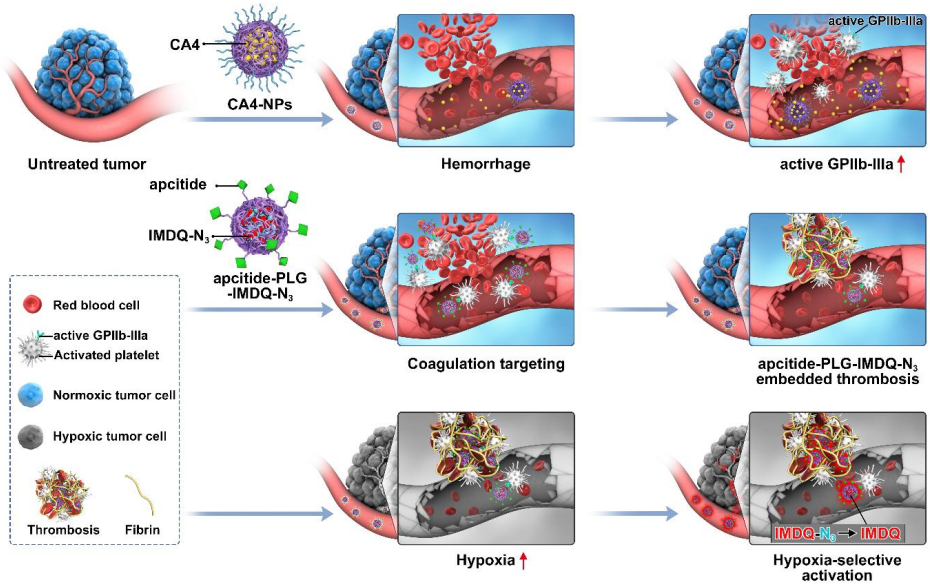

Figure 1: Schematic of the sequential drug delivery strategy with tumor microenvironment remodeling

References:

[1] Huppertsberg, A.; et al. *J. Am. Chem. Soc.* **2021**, *143*, 9872.
[2] Vinod, N.; et al. *Sci. Adv.* **2020**, 6, eaba5542.