Bioresponsive drug delivery depot for epigenetic modulation and immune checkpoint blockade

With the support by the National Natural Science Foundation of China, the research teams directed by Prof. Lu WeiYue (陆伟跃) at the Department of Pharmaceutics, School of Pharmacy, Key Laboratory of Smart Drug Delivery, Fudan University and Prof. Gu Zhen (顾臻) at the Department of Bioengineering, University of California, Los Angeles (UCLA), recently reported an *in situ* formed bioresponsive depot for combination of epigenetic modulation and immune checkpoint blockade, which was published in *Advanced Materials* as a front cover (2019, 1806957).

Expression of programmed death receptor-ligand 1 (PD-L1) on tumor cells could interact with the co-inhibitory molecule programmed death-1 (PD-1) receptor on the activated $CD8^+$ T cells, leading to T cell anergy and impeding antitumor immune responses. However, patients with advanced melanoma that is of low tumor-associated antigen (TAA) expression often poorly respond to PD-1/PD-L1 blockade therapy. Epigenetic alteration like DNA hypermethylation is a common feature of heterogeneous cancer phenotypes, and has an important role in immune evasion by tumors during tumorigenesis. Epigenetic modulators, such as hypomethylation agents (HMAs), can enhance the antitumor immune response by inducing TAA expression.

The researchers engineered a bioresponsive gel depot that can respond to the acidic pH and reactive oxygen species (ROS) within the tumor microenvironment for codelivery of anti-PD1 antibody (aPD1) and Zebularine (Zeb), an HMA. aPD1 was first loaded in the pH-sensitive CaCO3 nanoparticles (aPD1-NPs), and then the aPD1-NPs and Zeb were encapsulated together into the ROS-responsive hydrogel (Zeb-aPD1-NPs-Gel). Locally sustained release of Zeb increased the tumor immunogenicity via enhancing TAAs expression and decreasing immunosuppression. Furthermore, its combination with anti-PD1 antibody effectively contributed to inhibiting the tumor growth and prolonging the survival time of B16F10 melanoma-bearing mice. Furthermore, local delivery of Zeb-aPD1-NPs-Gel could effectively induce the systemic antitumor immune response.

This delivery strategy integrated with both epigenetic modulators and immune checkpoint blockade treatments has potential for enhancing objective response rates in clinics.

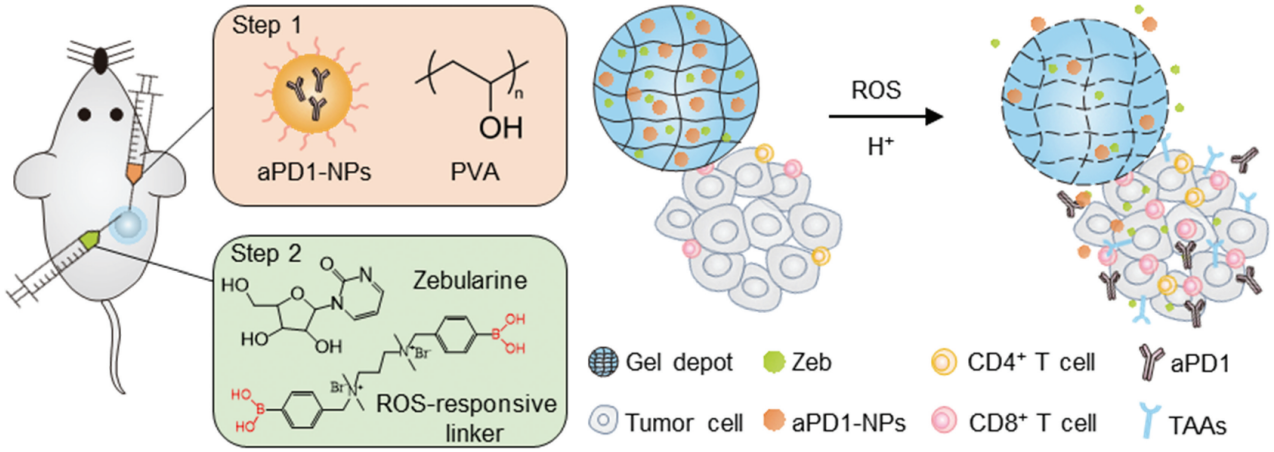

Figure Schematic illustration of the combination strategy of epigenetic modulation and immune checkpoint blockade therapy using ROS/H^+ responsive scaffolds.