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A pH-responsive Pickering Nanoemulsion for specified spatial delivery of Immune Checkpoint Inhibitor and Chemotherapy agent to Tumors

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➢ Abstract

Immune checkpoint (ICP) blockade therapy combined with chemotherapy is a promising treatment strategy for tumors. Chemotherapeutic agents usually function inside the tumor cells, while ICP inhibitors are efficacious out of the tumor cells. It is desirable to effectively co-deliver an ICP inhibitor and a chemotherapy agent to different sites of a tumor. We designed a Pickering nanoemulsion (PNE) using multi-sensitive nanogels with pH-responsive, hydrophilicity-hydrophobicity switch, and redox-responding properties as an oil/water interfacial stabilizer. The D/HY@PNE was employed for specified spatial delivery of the chemotherapy agent doxorubicin (DOX) and ICP inhibitor HY19991 (HY). D/HY@PNE disassembled to release the ICP inhibitor HY and DOX-loaded nanogels due to the hydrophilicity-hydrophobicity reversal of nanogels in the acidic tumor microenvironment. The DOX-loaded nanogels were easily internalized by tumor cells due to their small size and hydrophobicity. DOX was released from nanogels due to the high intracellular GSH concentration, triggering ICD. The released HY blocked the PD-1/PD-L1 connection between T cells and tumor cells, leading to the activation of T cells resulting in the synergistic therapeutic effect.

➢ Results

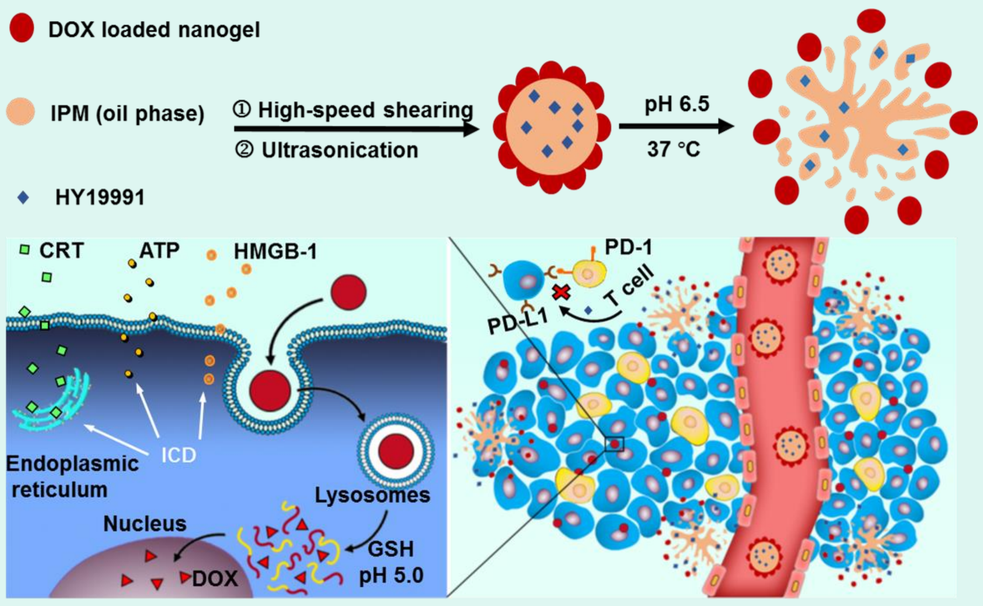

Figure 1. Schematic illustration of the preparation and disassembly of D/HY@PNE. In the tumor microenvironment.

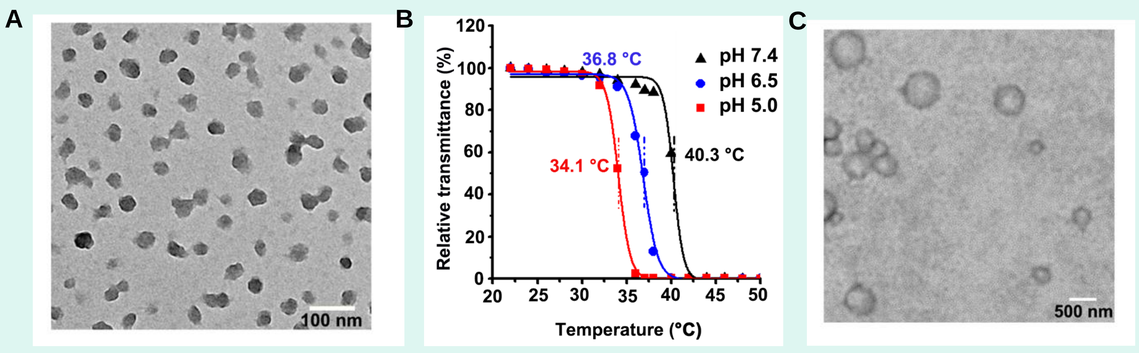

Figure 2. Characterization of SNG, PNE. (**A**) TEM image of SNG. **(B)** LCST measurement of SNG at different pH values by the transmittance analysis. (**C**)TEM image of PNE.

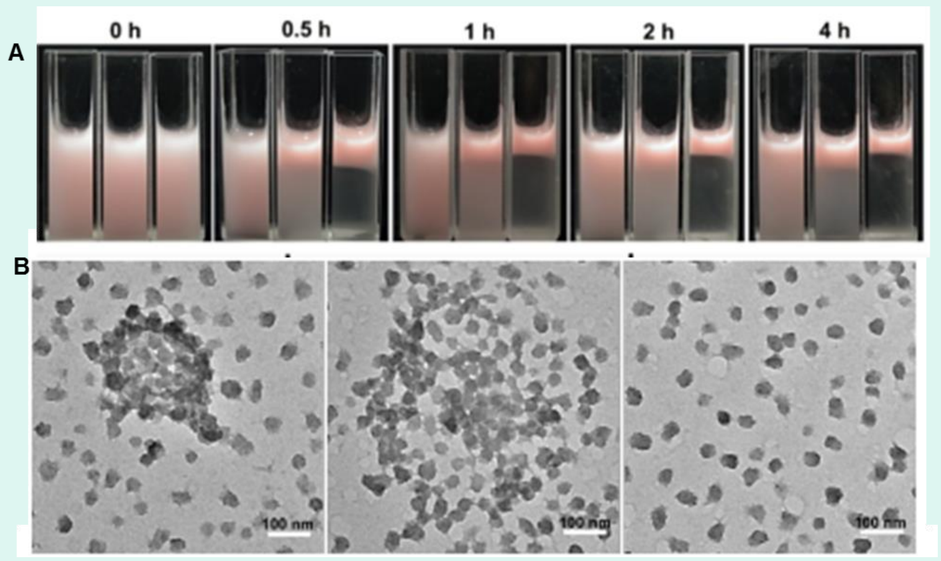

Figure 3.(**A**)Photos of NR@PNE with different pH values and incubated at 37 ℃ for different times. From left to right, the pH value is 7.4, 6.5, and 5.0.(**B**)TEM images of PNE with pH 6.5 warmed at 37 ℃ for 4 h taken at different visual field.

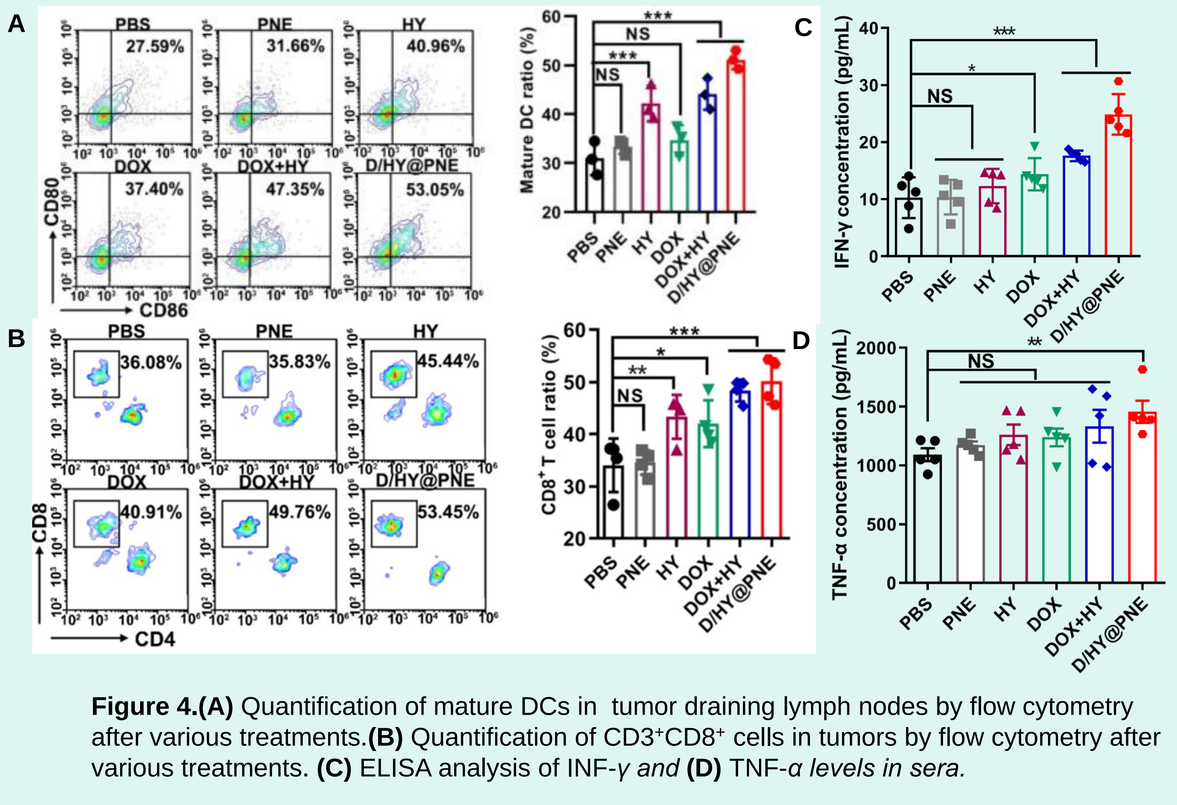

Figure 4.(A) Quantification of mature DCs in tumor draining lymph nodes by flow cytometry after various treatments.**(B)** Quantification of $CD3^+CD8^+$ cells in tumors by flow cytometry after various treatments. **(C)** ELISA analysis of INF-*γ and* **(D)** TNF-*α levels in sera.*

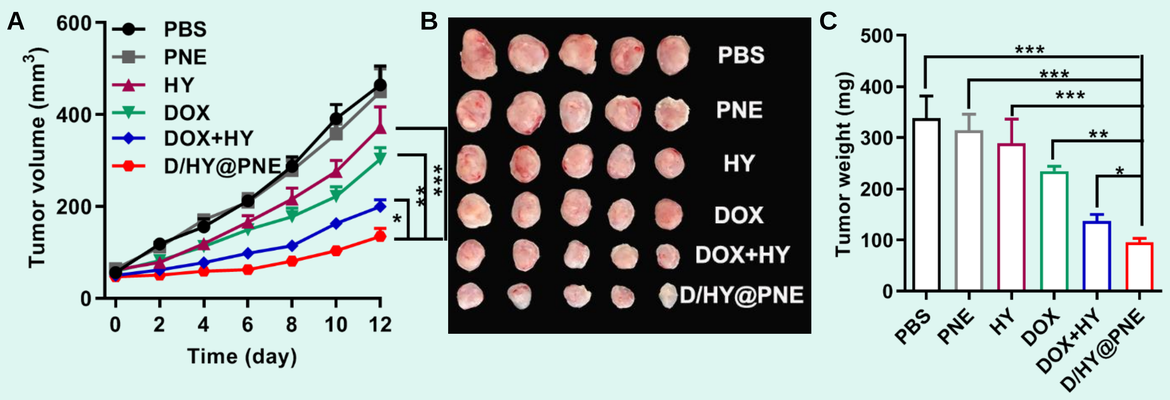

Figure 5. Antitumor efficacy of D/HY@PNE *in vivo*. (A) Tumor growth curves in 4T1 tumor-bearing mice after various treatments. (**B**) Images of the tumors at the end of antitumor studies. (**C**) Tumor weight at the end of various treatments.

➢ Conclusion

This novel strategy highlights the promising potential of a universal platform to co-deliver different therapeutic or diagnostic reagents with spatial regulation to improve the anti-tumor effect.

➢ Acknowledgments

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➢ Reference

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