

## Supplementary Information

### **Construction of a tumor microenvironment pH-responsive cleavable PEGylated hyaluronic acid nano-drug delivery system for colorectal cancer treatment**

Xinyu Zhang <sup>a, †</sup>, Minyi Zhao <sup>a, †</sup>, Nan Cao <sup>a, †</sup>, Wei Qin <sup>d</sup>, Meng Zhao <sup>a \*</sup>, Jun Wu <sup>abc \*</sup>, Dongjun Lin <sup>a \*</sup>

<sup>a</sup> *Department of Hematology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, 518107, China.*

<sup>b</sup> *Key Laboratory of Sensing Technology and Biomedical Instrument of Guangdong Province, School of Biomedical Engineering, Sun Yat-sen University, Guangzhou, 510006, China.*

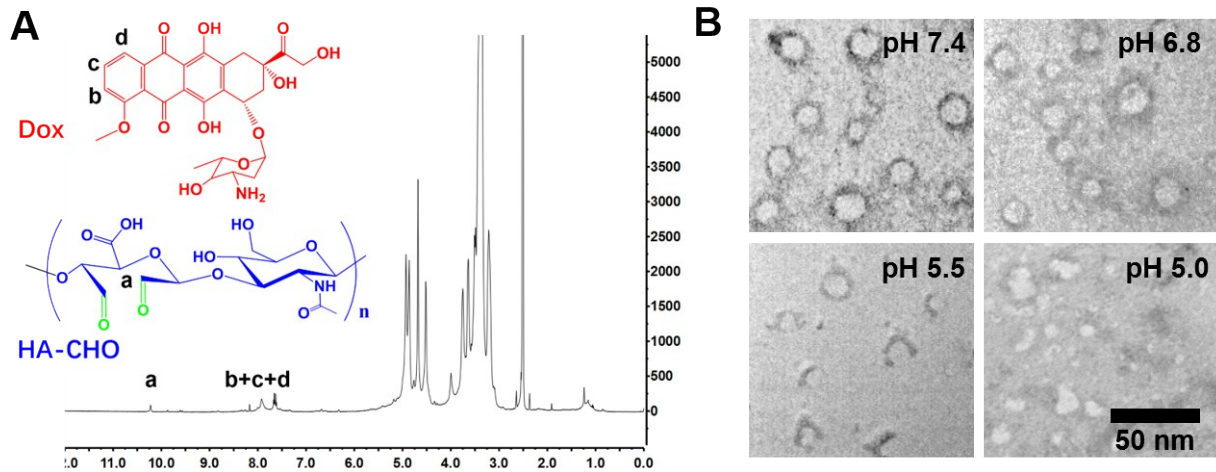
<sup>c</sup> *Research Institute of Sun Yat-sen University in Shenzhen, Shenzhen, 518057, China.*

<sup>d</sup> *Key Laboratory for Stem Cells and Tissue Engineering, Ministry of Education, Sun Yat-sen University, Guangzhou, 510006, China.*

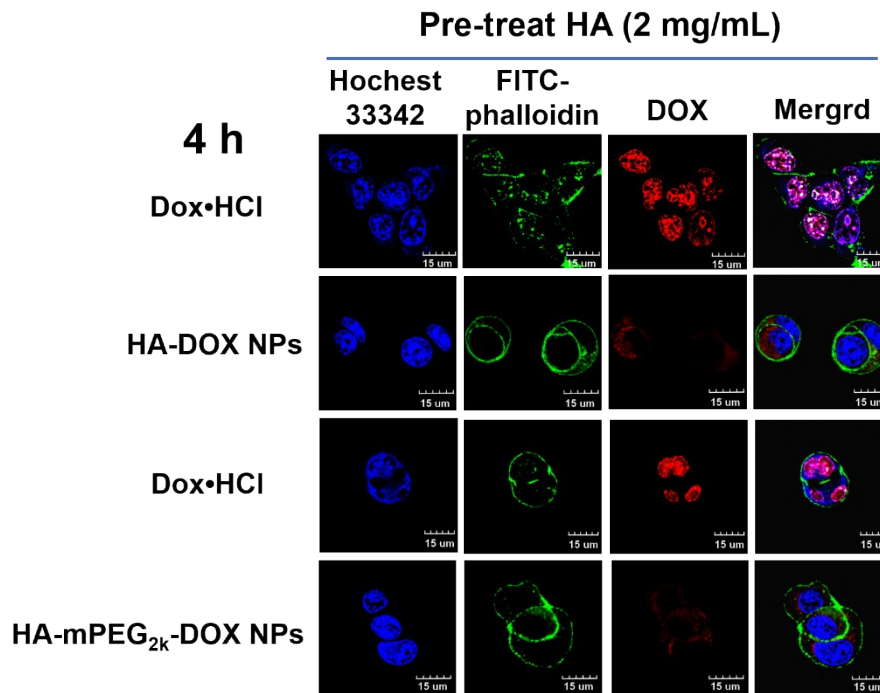
*\*Corresponding Authors: E-mail: zhaom38@mail.sysu.edu.cn (M.Z.),*

*E-mail: wujun29@mail.sysu.edu.cn (J.W.), E-mail: lindj@mail.sysu.edu.cn (DJ. L.)*

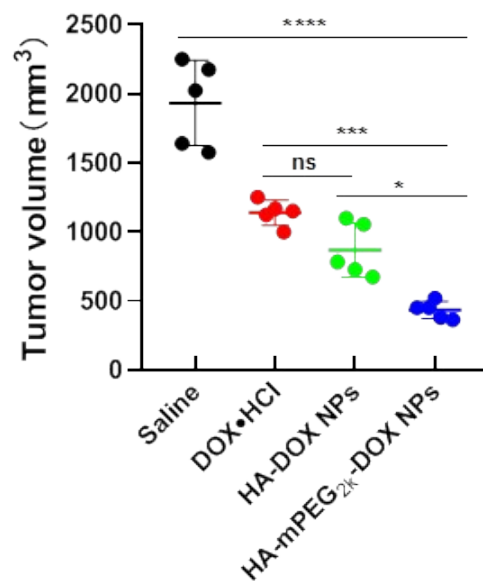
*† These authors contributed equally to this work*



**Fig. S1**  $^1\text{H}$  NMR of HA-DOX incubated at pH 6.8 PBS for 4 h (A) and TEM of HA-DOX NPs when treated under different pH values after 4h incubation (B).



**Fig. S2** Confocal images of CT26 cells pretreated with excess HA for 1 h and followed with DOX·HCl, HA-DOX NPs or HA-mPEG<sub>2k</sub>-DOX NPs after 4 h (scale bar: 15  $\mu\text{m}$ ).



**Fig. S3** The volume of tumors extracted from the mice at the end of the experiment after various administrations. (\*\*\*\* $p < 0.0001$  compared with saline group, \*\*\* $p < 0.001$  compared with DOX·HCl group, \* $p < 0.05$  compared with HA-DOX NPs group)