## Injectable and pH-responsive self-assembly peptide hydrogel for promoted tumor cell uptake and enhanced cancer chemotherapy

Jiamin Zhang<sup>1</sup>, Wenjing Lin<sup>1</sup>, Lijun Yang, Aijie Zhang, Yumin Zhang\*, Jinjian Liu\*, Jianfeng Liu\*

Key Laboratory of Radiopharmacokinetics for Innovative Drugs, Chinese Academy of Medical Sciences, and Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical

College, Tianjin

\*Corresponding author:

Dr. Yumin Zhang, E-mail: zhangyumin@irm-cams.ac.cn;

Dr. Jinjian Liu, E-mail: liujinjian@irm-cams.ac.cn;

Prof. Jianfeng Liu, E-mail: liujianfeng@irm-cams.ac.cn

## **Supplementary Figures**



Figure S1. The LC-MS of KKFKFEFEF peptide



Figure S2. The high-resolution mass spectrometry of MTX-KKFKFEFEF peptide



Figure S3. (A) The synthetic process of DA conjugated KKFKFEFEF peptide. (B-D) <sup>1</sup>H NMR results of (B) KKFKFEFEF peptide, (C) DA conjugated KKFKFEFEF peptide and (D) the DA conjugated KKFKFEFEF peptide after being incubated with TFA at pH 6.5.



Figure S4. ThT assay of different MTX conjugated peptides. The fluorescence measurements were performed at ex. 450 nm and em. 485 nm.



Figure S5. The relevant fluorescence intensity of cells incubated with different FITC-labelled peptides after 2 h incubation.



Figure S6. In vitro bioluminescent images of major organs and tumor after 72 h injection.



Figure S7. *In vivo* biosafety of the MTX-peptide hydrogel after 21 days treatment. H&E images of the main organs including heart, liver, spleen, lung, and kidney of 4T1-tumor-bearing BALB/c mice. Scale bar =  $100 \mu m$ .



Figure S8. Hematology analysis of mice treated with different drug-peptide samples, (A) WBC, (B)

RBC, (C) platelet and (D) hemoglobin.



Figure S9. Hemolysis analysis of MTX, MTX-KKFKFEFEF and MTX-KKFKFEFEF(DA) at predetermined concentrations. Red blood cells incubated with PBS and 0.1% Triton X-100 (diluted with PBS) were used as negative (–) and positive (+) control, respectively. The data are shown as mean  $\pm$  SD (n = 3).