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Supplementary Information

Enhanced of nuclear delivery of anti-cancer drugs using micelles containing releasable membrane fusion peptide and nuclear-targeting retinoic acid

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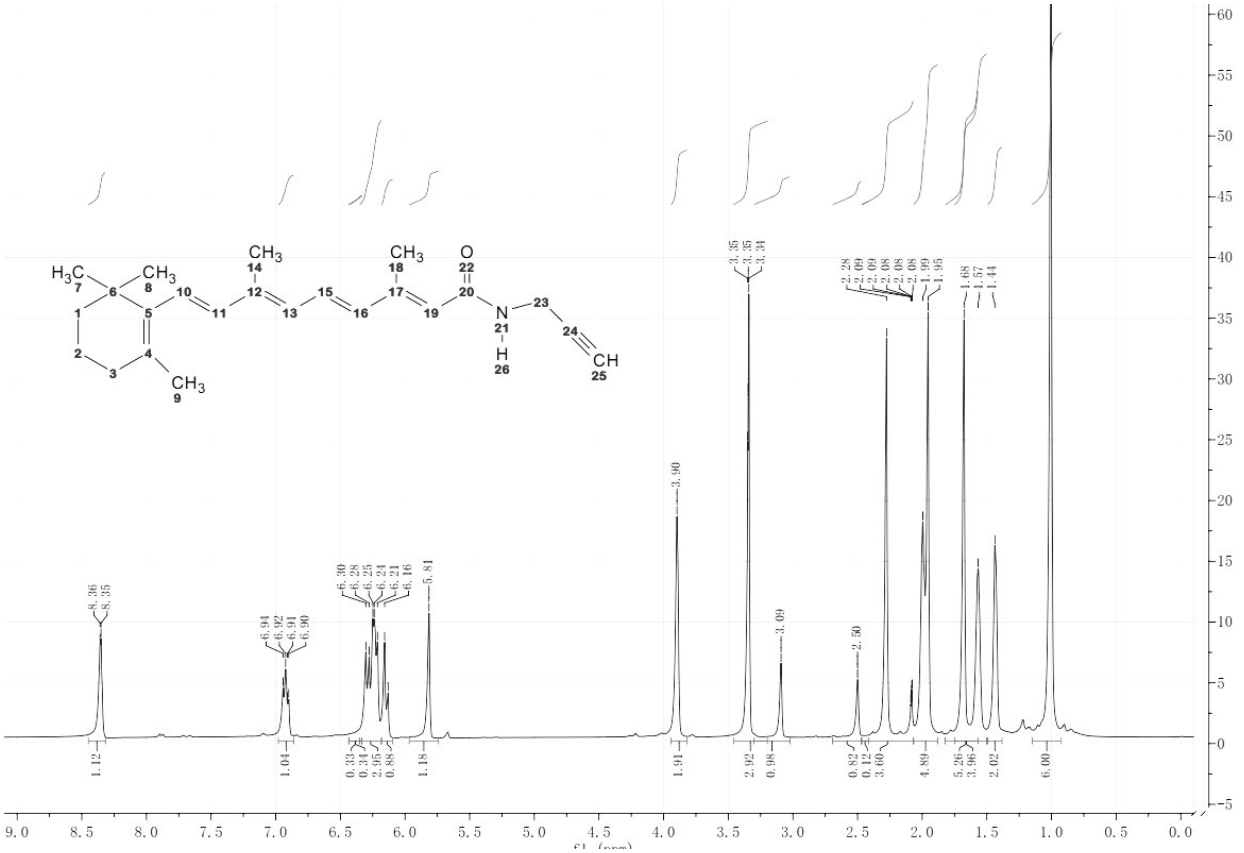

Fig.S1. ^{1}H NMR spectra of N-propargyl all-trans retinoic acid amide in [D6] DMSO. 1H NMR (600 MHz, [D6] DMSO) δ 8.36 (d, J = 4.4 Hz, 1H), 6.92 (dd, *J* = 17.2, 8.8 Hz, 1H), 6.34 (s, 1H), 6.33 (s, 1H), 6.35 – 6.18 (m, 3H), 6.14 (d, *J* = 16.0 Hz, 1H), 5.81 (s, 1H), 3.90 (s, 2H), 3.46 – 3.28 (m, 3H), 3.09 (s, 1H), 2.50 (s, 1H), 2.42 (s, 1H), 2.47 – 2.07 (m, 4H), 1.97 (d, *J* = 24.4 Hz, 5H), 1.68 (s, 4H), 1.62 (d, *J* = 65.0 Hz, 5H), 1.44 (s, 2H), 1.00 (s, 6H).

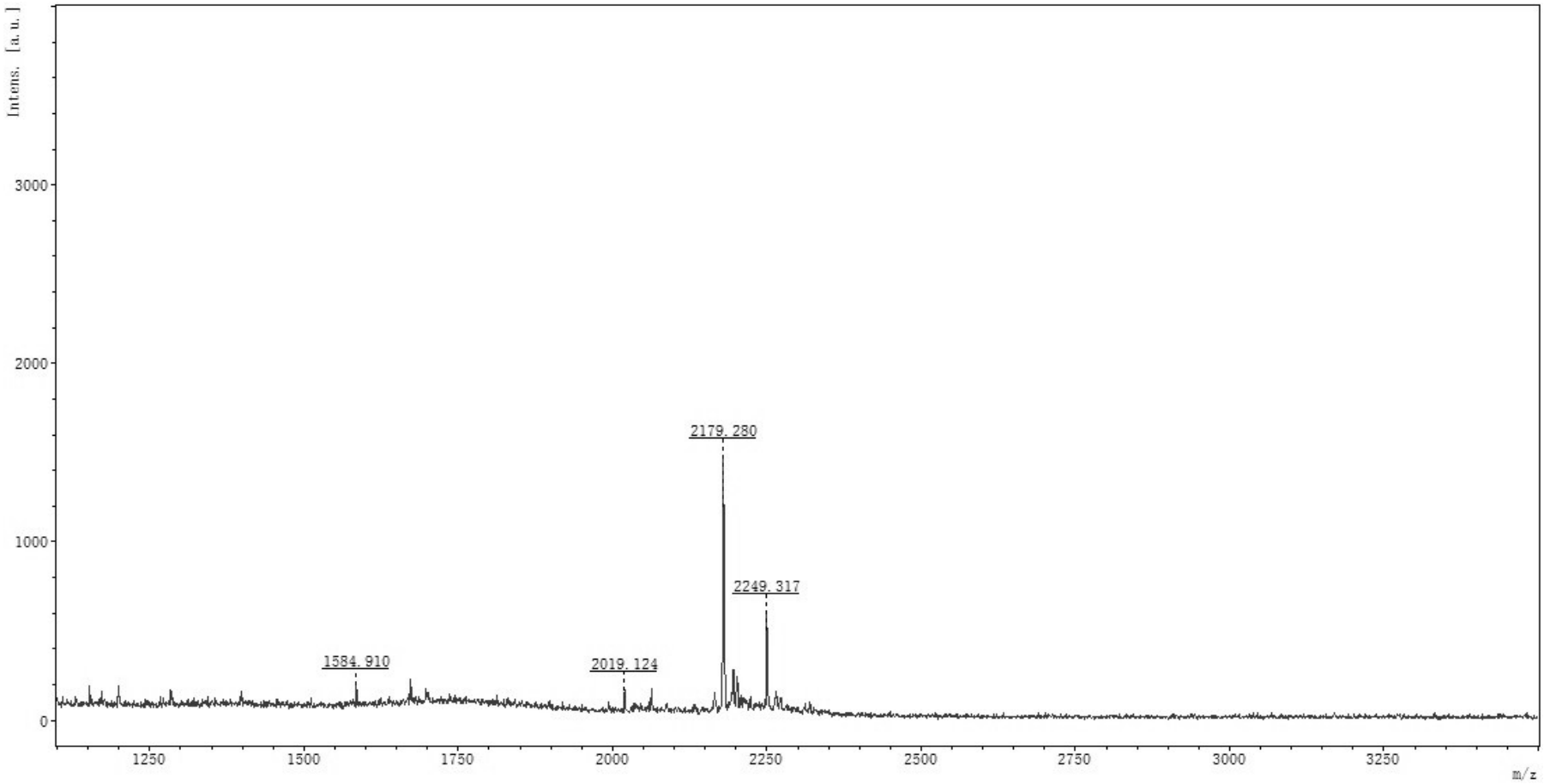

Fig.S2. MALDI-TOF mass spectra of H1-retinoic acid conjugate (H1RA, Mw: 2179.28).

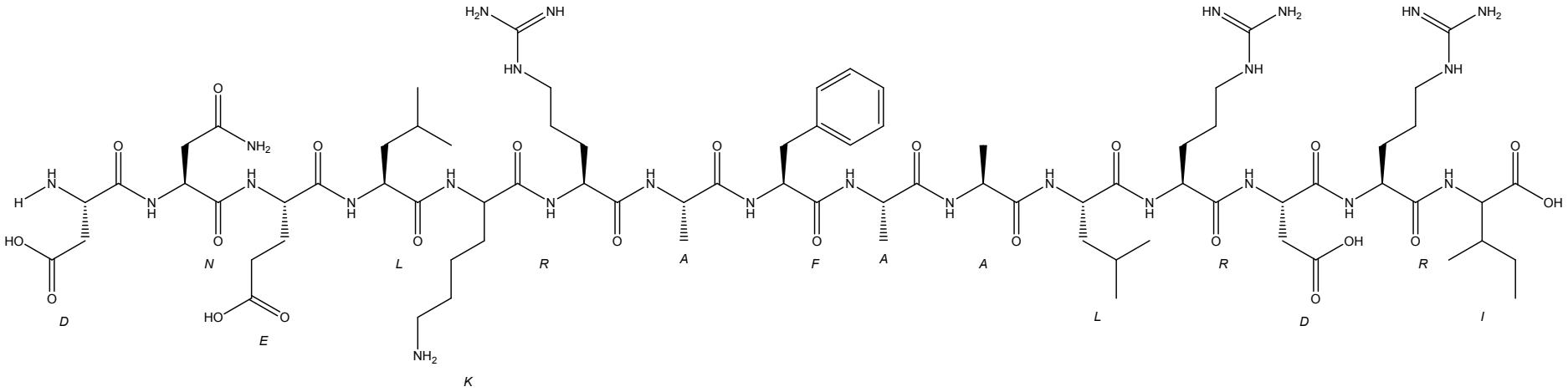

Fig.S3. The structure of non-azide-modified H1-S6A, F8A peptide (DNELKRAFAALRDQI).

The stability of micelles and the enzymatic hydrolysis

The stability of the three cross-linked micelles was performed in phosphate buffer at pH 7.4, 37 °C, while the enzymatic hydrolysis were performed in McIlvaine's buffer (50 mM citrate) at pH 6.0, 37 °C using papain as model enzyme. 5 mg Papain was dissolved in 4.5 mL buffer containing 5 mM reduced glutathione (GSH) and the mixture was pre-incubated for 5 min at 37 °C. The final concentration of cross-linked micelles in these two buffers were both 1 mg/ml. At predetermined intervals, hydrodynamic radii of polymeric micelles were measured using dynamic light scattering (Nano-ZS90, Malvern).

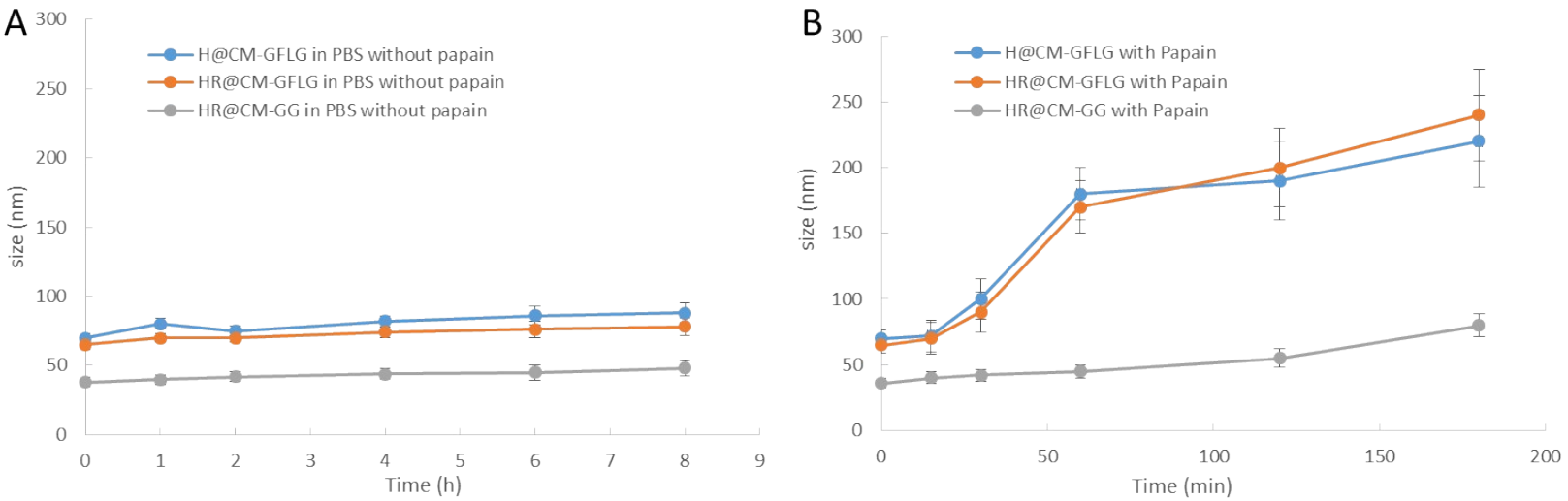

Figure.S4. The size changes of cross-linked micelles (H@CM-GFLR, HR@CM-GFLG, HR@CM-GG) with or without the present of papain which can hydrolyze the spacer GFLG (n=3).

Table S1

Key characteristics of synthesized HPMA copolymer precursors containing different functional groups.

HPMA copolymer precursors	ONp （mmol/g）	-$NHNH_2$ （mol%）
pHPMA-GFLG-ONp	0.52	4.13
pHPMA-GG-ONp	0.61	3.85