

## Experimental Supporting Information

### General methods.

Fmoc-amino acids were obtained from GL Biochem (Shanghai, China). All the other Starting materials were obtained from Alfa. Chemical reagents and solvents were used as received from commercial sources.

<sup>1</sup>H NMR spectra were obtained on Bruker ARX 400. HR-MS were acquired at VG ZAB-  
HS system (England). HPLC was conducted at LUMTECH HPLC (Germany) system using a C18 RP column with MeOH (0.05% of TFA) and water (0.05% of TFA) as the eluents. LC-MS was conducted at the Shimadzu LCMS-20AD (Japan) system. TEM samples were prepared as following: a copper coated with a thin layer of carbon layer was dipped into the hydrogel, and then it was kept in a desiccator overnight. The dried sample was performed at the Tecnai G2 F20 system, operating at 200 kV. rheology was performed on an ARES 1500ex (TA instrument) system using a parallel plates (40 mm) at the gap of 500µm.

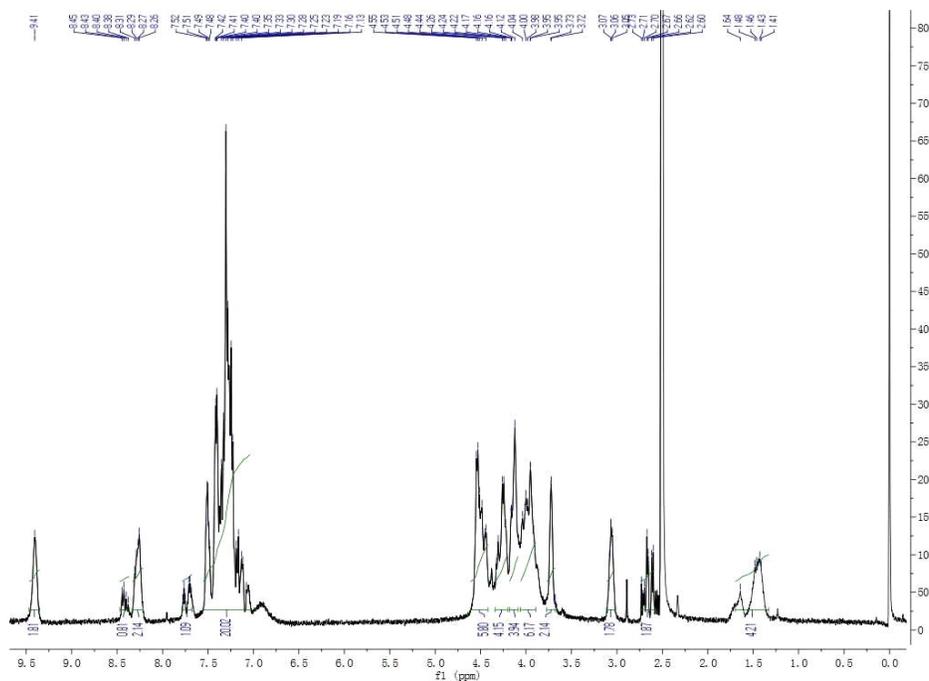
### Peptide Synthesis.

**Preparation of Fmoc-NPhe-OH:** The synthesis of Fmoc-NPhe-OH was described by John et al.<sup>1</sup> We got the white solid of the product in a yield of 84% by using the same method.<sup>2</sup>

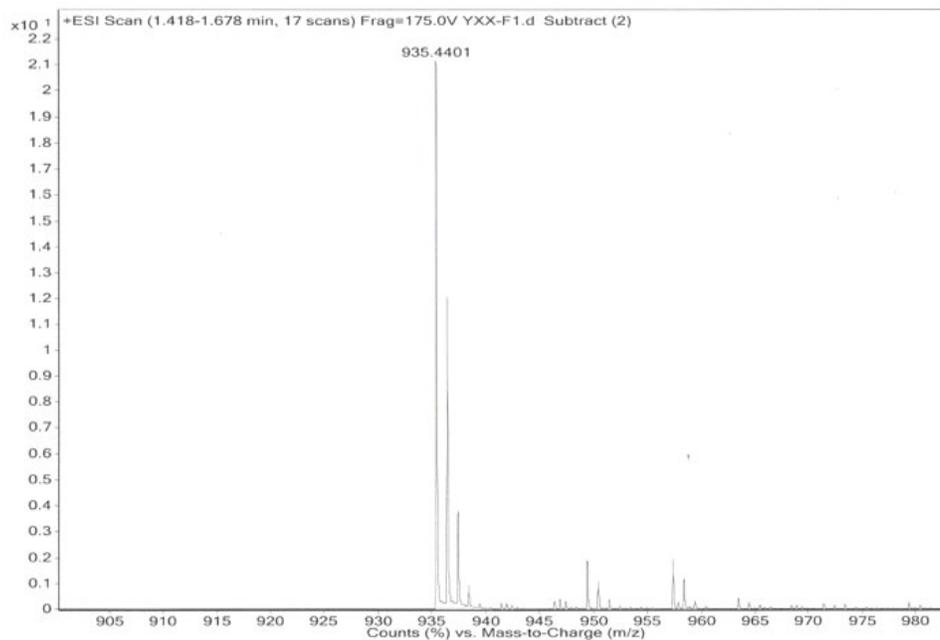
**Preparation of F<sub>4</sub>RGD:** The F<sub>4</sub>RGD was prepared by solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride resin, the corresponding N-Fmoc protected amino acids with side chains properly protected by a tert-butyl group, Fmoc-succinated cystamine and Fmoc-protected N-substituted amino acids. The first amino acid was loaded on the resin at the C-terminal with the loading efficiency of about 0.6 mmol/g in anhydrous dichloromethane (DCM). After 2 hours, the reaction solution was drained and the resin was washed by dimethyl Formamide (DMF) for 5 minutes. Afterwards, 20% piperidine in DMF was used to de-protect Fmoc group. Then the next Fmoc-protected amino acid was coupled to the free amino group on the resin using HBTU as the coupling reagent and DIPEA as the catalytic agent. The growth of the peptoid-peptide chain was according to the established Fmoc SPPS protocol. After the last coupling step, excessive

reagents were removed by DMF washing one time for 5 minutes (5 mL per gram of resin), followed by five steps of washing using DCM for 2 min (5 mL per gram of resin). The peptoid-peptide conjugates were cleaved from resin using 95% of TFA with 2.5% of TIS and 2.5% of H<sub>2</sub>O for 30 minutes, then washed the resin 5 times with DCM. After combining these solutions together and concentrated by the rotary evaporator, diethyl ether was then added to concentrate the solution. The resulting precipitate was centrifuged for 10 min at room temperature at 10,000 rpm and further purified by reverse phase HPLC.

<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 9.41 (s, 2H), 8.37-8.47 (m, 1H), 8.21-8.33 (m, 2H), 7.68-7.79 (m, 1H), 7.03-7.56 (m, 20H), 4.42-4.61 (m, 6H), 4.20-4.34 (m, 4H), 4.09-4.18 (m, 4H), 3.89-4.06 (m, 6H), 3.68-3.78 (m, 2H), 3.02-3.11 (m, 2H), 2.59-2.74 (m, 2H), 1.33-1.70 (m, 4H).



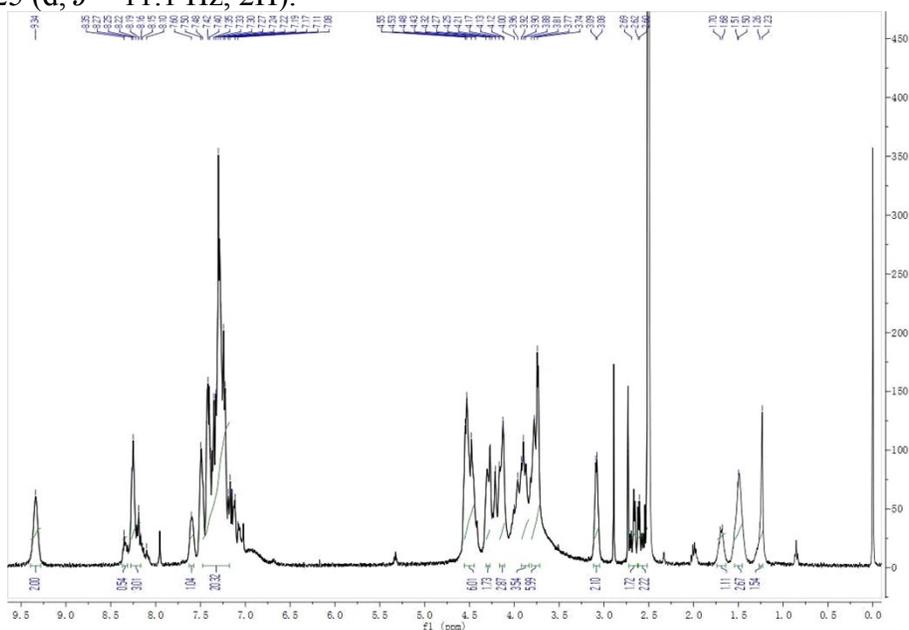
**Fig. S-1.** <sup>1</sup>H NMR of F<sup>24</sup>RGD



**Fig. S-2.** HR-MS of F'<sub>4</sub>RGD

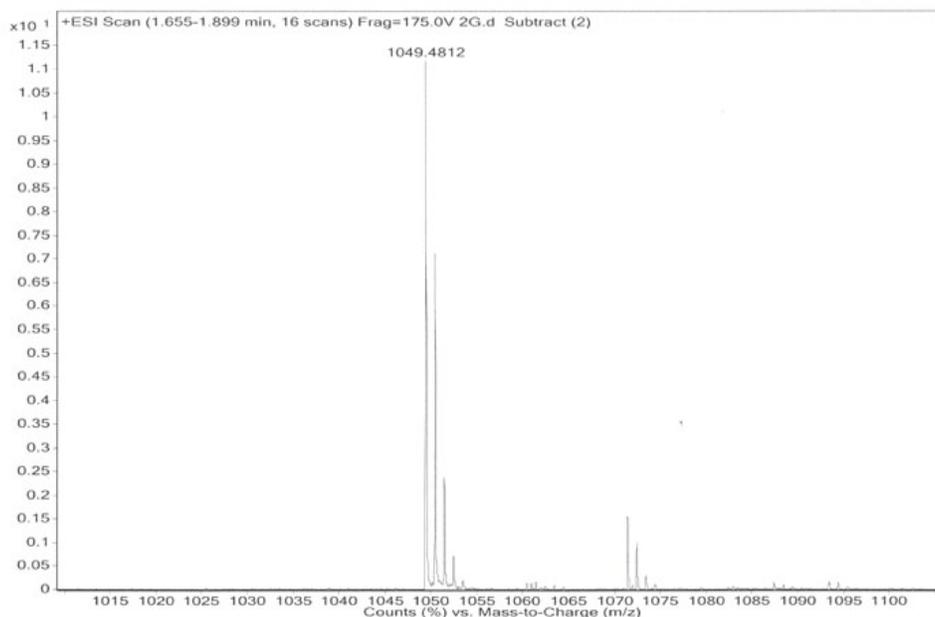
**Preparation of F'<sub>4</sub>GRGD:** The same procedure for preparation of F'<sub>4</sub>RGD was used.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 9.34 (s, 2H), 8.35 (s, 1H), 8.23 (dd, *J* = 21.6, 9.7 Hz, 3H), 7.60 (s, 1H), 7.47 – 7.18 (m, 20H), 4.56 – 4.45 (m, 6H), 4.27 (s, 2H), 4.12 (d, *J* = 4.2 Hz, 3H), 3.89 (d, *J* = 8.3 Hz, 4H), 3.76 (d, *J* = 12.9 Hz, 6H), 3.08 (d, *J* = 5.8 Hz, 2H), 2.65 (d, *J* = 28.5 Hz, 2H), 2.61 (d, *J* = 6.4 Hz, 2H), 1.69 (d, *J* = 9.5 Hz, 1H), 1.50 (d, *J* = 4.1 Hz, 3H), 1.25 (d, *J* = 11.1 Hz, 2H).



**Fig. S-3.** <sup>1</sup>H NMR of F'<sub>4</sub>GRGD

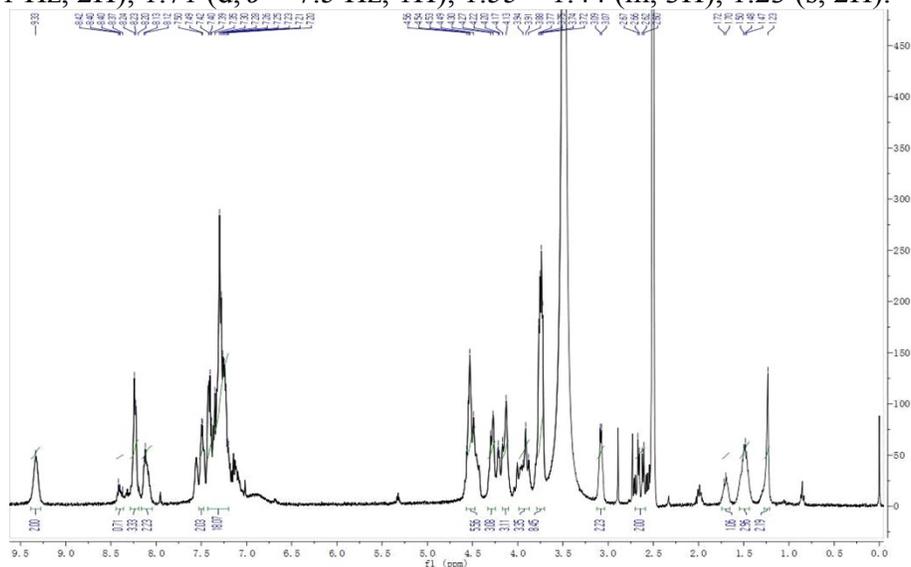




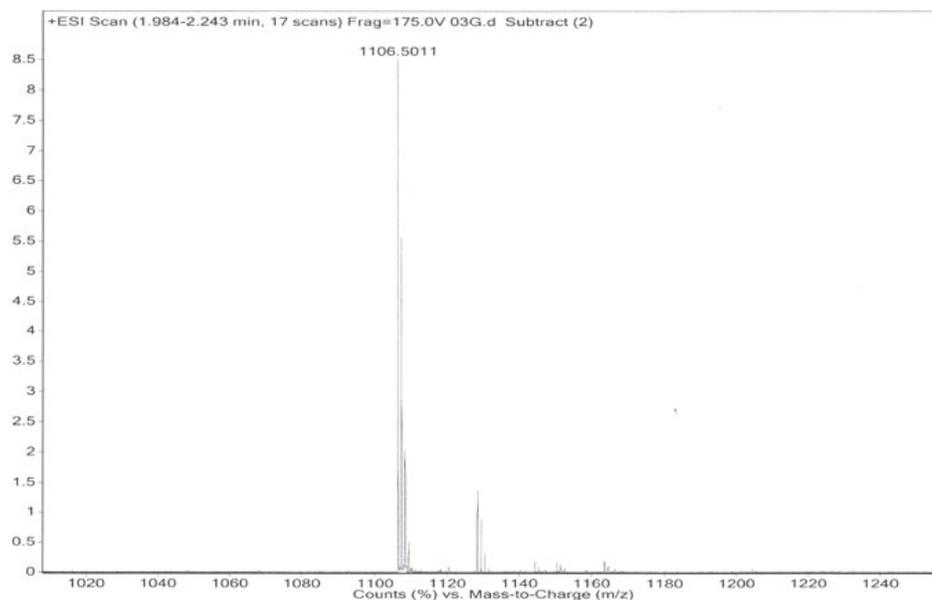
**Fig. S-6.** HR-MS of F'4GGRGD

**Preparation of F'4GGGRGD:** The same procedure for preparation of F'4RGD was used.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 9.33 (s, 2H), 8.40 (dd, *J* = 9.7, 7.5 Hz, 1H), 8.29 – 8.19 (m, 3H), 8.13 (d, *J* = 6.1 Hz, 2H), 7.49 (d, *J* = 3.6 Hz, 2H), 7.43 – 7.20 (m, 18H), 4.53 (dd, *J* = 17.8, 12.0 Hz, 6H), 4.29 (d, *J* = 10.0 Hz, 3H), 4.15 (d, *J* = 16.0 Hz, 3H), 3.91 (t, *J* = 12.6 Hz, 3H), 3.75 (dd, *J* = 11.4, 5.4 Hz, 8H), 3.08 (d, *J* = 5.2 Hz, 2H), 2.64 (dd, *J* = 20.1, 6.1 Hz, 2H), 1.71 (d, *J* = 7.5 Hz, 1H), 1.55 – 1.44 (m, 3H), 1.23 (s, 2H).



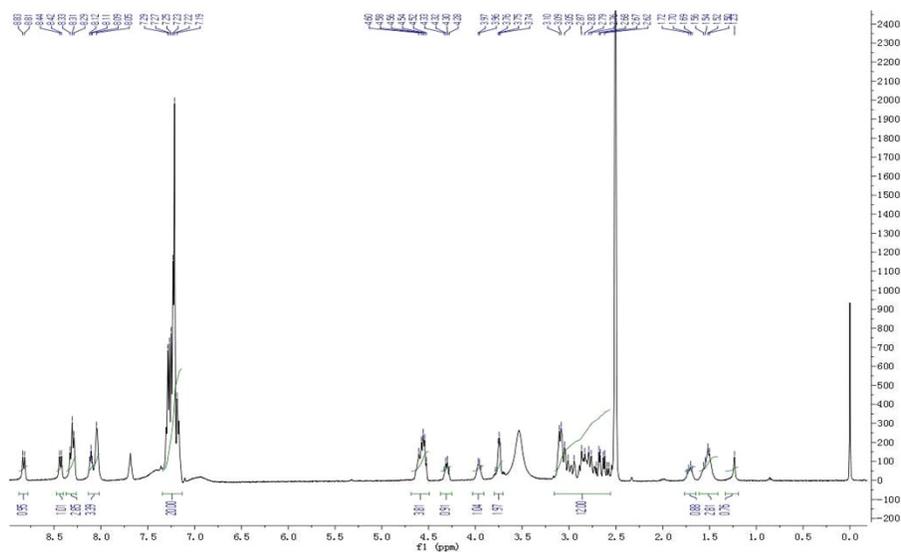
**Fig. S-7.** <sup>1</sup>H NMR of F'4GGGRGD



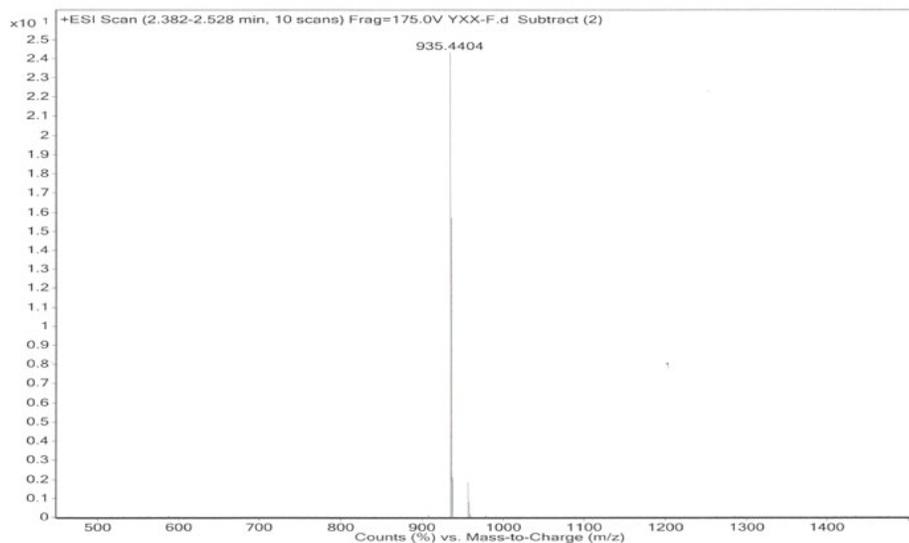
**Fig. S-8.** HR-MS of F<sub>4</sub>GGGRGD

**Preparation of F<sub>4</sub>RGD:** The same procedure for preparation of F<sub>4</sub>RGD was used.

<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 8.78-8.88 (d, J=8.10Hz, 1H), 8.40-8.48 (d, J=7.62Hz, 1H), 8.26-8.37 (t, 3H), 8.02-8.14 (m, 3H), 7.13-7.35 (m, 20H), 4.49-4.69 (m, 4H), 4.25-4.37 (m, 1H), 3.91-4.03 (m, 1H), 3.71-3.80 (m, 2H), 2.56-3.16 (m, 12H), 1.65-1.77 (m, 1H), 1.41-1.61 (m, 3H), 1.23 (s, 1H).



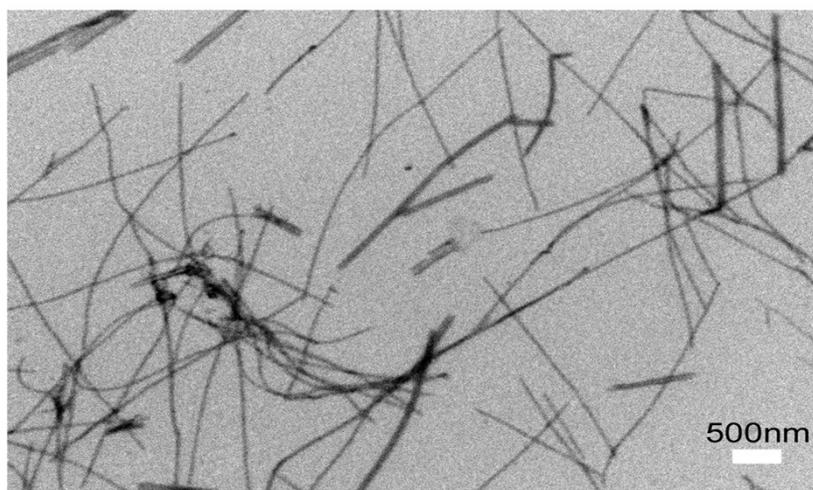
**Fig. S-9.** <sup>1</sup>H NMR of F<sub>4</sub>RGD



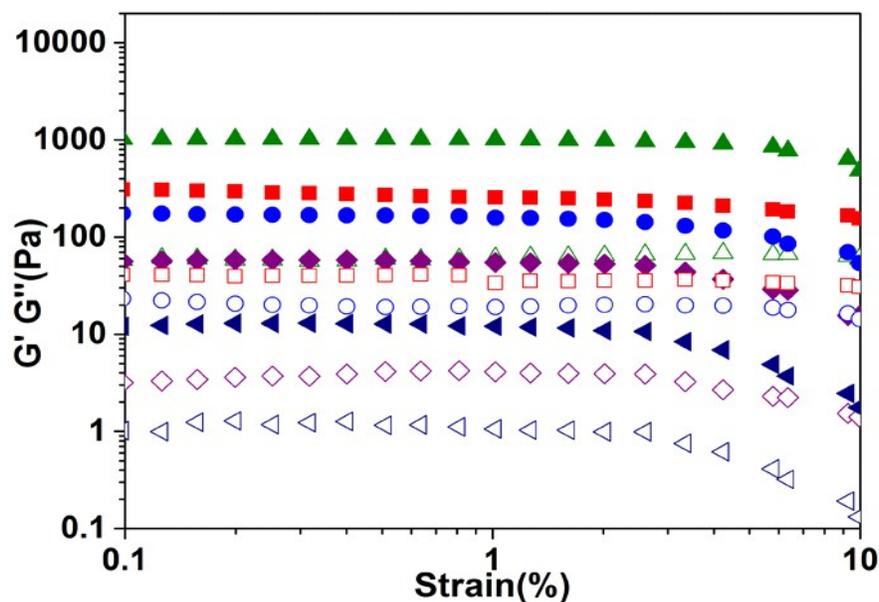
**Fig. S-10.** HR-MS of F<sub>4</sub>RGD

**Preparation of the hydrogels (1.0 wt%):**

2 mg of pepoid-peptide conjugates was dissolved in 0.19 mL of PBS buffer solution (pH = 7.4). Na<sub>2</sub>CO<sub>3</sub> (0.4 M) was then added to the above solution to make the final pH=7.4. The solution was heated to dissolve the powders completely and gel was formed after the hot solution being kept at room temperature (22-25°C) for less than 15 minutes. The minimum gelation concentration was about 0.40, 0.40, 0.40, 0.35 and 0.35 wt% for G<sub>0</sub>gel, G<sub>1</sub>gel, G<sub>2</sub>gel, and G<sub>3</sub>gel, and Fgel, respectively.



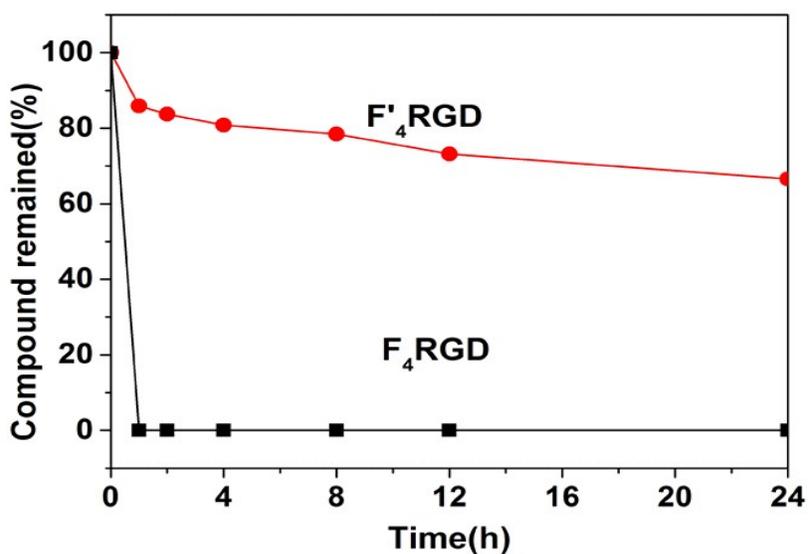
**Fig. S-11.** The transmission electron microscopy (TEM) image of the Fgel.



**Fig. S-12.** Dynamic frequency sweep at the strain of 1% of five hydrogels at 1.0 wt% (Triangles:  $G_0$ gel, squares:  $G_1$ gel, rhombuses:  $G_2$ gel, left triangles:  $G_3$ gel, and circles: Fgel. filled symbols:  $G'$  and open symbols:  $G''$ )

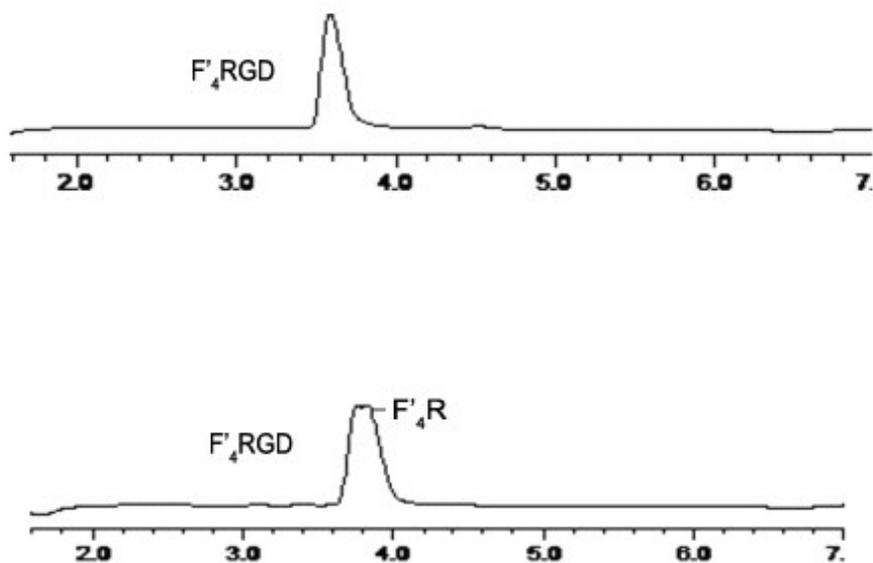
#### Biostability test with proteinase K:

1 mg of each compound was dissolved in 5 mL PBS buffer solution and adjusted it to a final pH at 7.5. Then proteinase K were added in the concentration of 3.2 units/mL and incubated at 37°C for 24 hours. Afterwards 500  $\mu$ l of sample were taken out each time and analyzed by LC-MS.

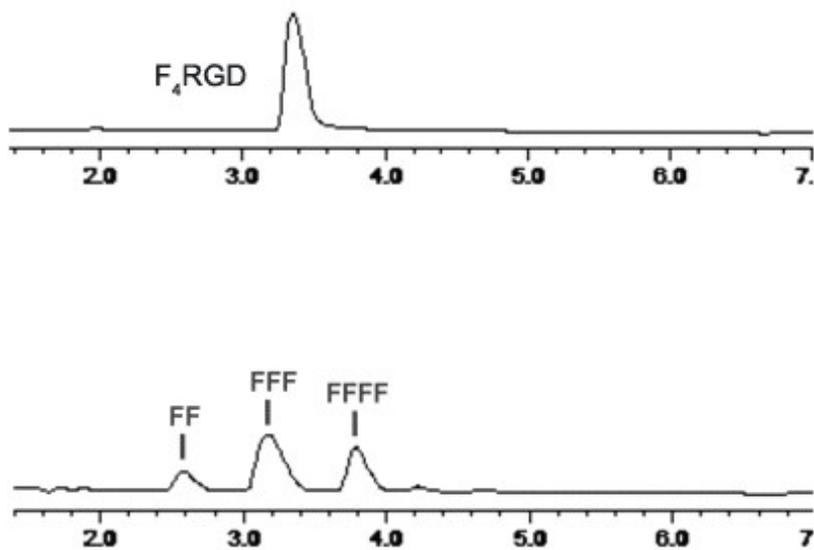


**Fig. S-13.** The stability of F'<sub>4</sub>RGD, and F<sub>4</sub>RGD against proteinase K digestion in PBS

buffer solution (pH=7.4) (compound concentration=0.2 mg mL<sup>-1</sup>, enzyme concentration=0.128 mg mL<sup>-1</sup>, the arrows indicate the cleavage sites).



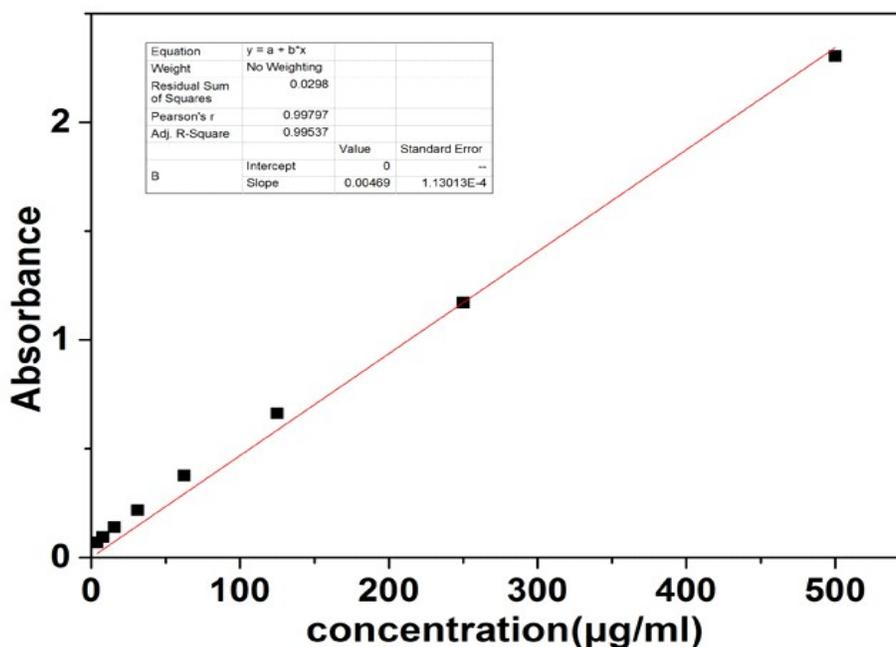
*Fig. S-14.* HPLC traces of F<sub>4</sub>'RGD digested by proteinase K (top: no proteinase K, bottom: 24 hours after added proteinase K)



*Fig. S-15.* HPLC traces of F<sub>4</sub>RGD digested by proteinase K (top: no proteinase K, bottom: 24 hours after added proteinase K).

### Controlled drug release

Hydrogels in PBS solution containing 1.0 wt% of compound and 50 $\mu$ g of doxorubicin (0.05 wt%) were formed in an Eppendorf tube at 25°C. After 24 h, we added 0.25 mL of PBS (containing 0.5%(v/v)Tween 20)on the surface of the hydrogels, 0.2 mL of solution was taken out at the desired time point and 0.2 mL of PBS was added back. For the following time points, 0.2 mL of PBS was taken out and 0.2 mL of PBS was added back at each point. We then monitored and calculated the release profile of doxorubicin from the gels by measuring the absorbance of doxorubicin at wavelength of 490nm. The experiment was performed at 37°C in 3 parallel.



**Fig. S-16.** The standard curve of the absorbance of doxorubicin at wavelength of 490nm.

### Reference:

1. J. A. W. Kruijtzter, L. J. F. Hofmeyer, W. Heerma, C. Versluis, R. M. J. Liskamp, *Chem-Eur J.* 1998, 4, 1570-1580.
2. Zhidan Wu, Ming Tan, Xuemei Chen, Zhimou Yang, Ling Wang, *Nanoscale.* 2012, 4, 3644.