Supporting Information

Materials and general methods:
Chemicals and animals: Fmoc-OSu and other Fmoc-amino acid as well as Rapamycin were obtained from GL Biochem (Shanghai), Succinic acid and Folic acid were come from sigma, and Triamcinolone acetonide and rapamycin were come from TCI. Chemical reagents and solvents were used as received from commercial sources. Commercially available reagents and solvents were used without further purification, unless noted otherwise.

General methods: $^1$H NMR (Bruker ARX 400) was used to characterize the synthesized compounds. ESI-MS spectrometric analyses were performed at the Thermo Finnigan LCQ AD System. Drug release profile was carried out by a LCMS-20AD (Shimadzu) system. Rheology test was done on an AR 1500ex (TA instrument) system, 40 mm parallel plates was used during the experiment at the gap of 500 µm.

Preparation of TA-SA: A mixture of TA 0.13 g (0.3 mmol) and succinic anhydride 0.09 g (0.9 mmol) were dissolved in pyridine (2.5 mL). The resulting solution was stirred for 3 h at room temperature. The solution was removed by a rotary evaporator to dryness in vacuo. Water (50 ml) was added into the residue slowly and then the solution was placed on ice statically. Finally, the fine crystals were collected through centrifuging and lyophilized by lyophilizer.

Preparation of rapamycin-SA: To the solution of rapamycin (0.5 g, 0.55 mmol) in toluene (10 mL), succinic anhydride (0.25 g, 0.25 mmol) was added. Novozym SP435 (1.2 g) was then induced and the reaction mixture was stirred at 45 °C for 40 h under N$_2$ atmosphere. The solution was then filtered to remove the enzyme and washed with toluene for 3 times. The combined organic was evaporated in vacuum to give a crude product. The product was finally purified by silica gel column chromatography eluting with CH$_2$Cl$_2$-MeOH (12:1) as a white solid (0.35 g, 64%).

Peptide synthesis: Peptide of FA-K-ss-EE and FA-K(Ac)-ss-EE were prepared by standard Fmoc solid-phase peptide synthesis (SPPS) using 2-chlorotrityl chloride resin and the corresponding N-Fmoc protected amino acids with side chains properly protected by a tert-butyl group. The first amino acid (Fmoc-Glu(OtBu)-OH) was loaded on the resin at the C-terminal with the loading efficiency about 0.92 mmol/g. 20% piperidine in anhydrous N,N’-dimethylformamide (DMF) was used during the deprotection of Fmoc group. Then the next Fmoc-protected amino acid was coupled to the free amino group using O-(Benzotriazol-1-yl)-N,N,N’,N’- tetramethyluronium-hexafluorophosph- ate (HBTU) as the coupling reagent. The growth of the peptide chain was according to the standard Fmoc SPPS protocol. In the last coupling step, Folic acid was used to cap the amine group of the peptide. After the last coupling step,
excessive reagents were removed by a single DMF wash for 5 min (5 ml per gram of resin), followed by five steps of washing using dichloromethane (DCM) for 2 min (5 ml per gram of resin). The peptide derivatives were cleaved from the resin by ice-cold reagent B and the mixture was stirred at room temperature, filtered, and poured into ice-cold diethylether, successively. The resulting precipitate was centrifuged for 10 min at 3 °C at a speed of 10,000 rpm. Afterward the supernatant was decanted and the solid was dried by vacuum pump.

Characterizations of FA-K(Ac)-ss-EE: $^1$H NMR (400MHz, DMSO-d6) $\delta$ 8.185-7.804 (m, 7H), 7.741 (s, 1H), 7.650-7.615 (m, 2H), 6.939 (s, 2H), 6.619 (d, $j=8.278$, 2H), 4.469 (s, 2H), 4.340-4.112 (m, 5H), 3.491 (s, 1H), 2.974-2.913 (m, 2H), 2.746-2.706 (t, 4H), 2.528 (s, 3H), 2.357-2.210 (m, 10H), 2.049-1.412 (m, 12H), 1.354-1.205 (m, 4H), MS:calc. $M^+ = 1103.4$ obsvd. ($M^+$)$^+ = 1104.3870$. 

Fig. S-1. $^1$H NMR of FA-K(Ac)-ss-EE
Hydrogelator synthesis and characterizations:

Preparation of FA-K(TA)-ss-EE: TA-SA (53.4 mg, 0.1 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) followed by addition of N-hydroxysuccinimide (12.7 mg, 0.11 mmol) and dicyclohexylcarbodiimide (24.7 mg, 0.12 mmol). The reaction was stirred for 3 h at room temperature and in dark, the precipitation was filtered and washed with CH$_2$Cl$_2$, and the organic solution was removed under reduced pressure to give an intermediate. The intermediate was dissolved in DMF (10 mL), and then FA-K-ss-EE (159.3 mg, 0.15 mmol) and DIEA (99 μL, 0.6 mmol) were added. The mixture was stirred at room temperature and in dark for 24 h. The reaction mixture was purified by preparative HPLC, yield 118 mg of title product (74.9%).

$^1$H NMR (400MHz, DMSO-d$_6$) δ 8.211-7.906 (m, 7H), 7.858-7.801 (m, 2H), 7.652-7.617 (m, 2H), 7.261 (d, j=9.911, 2H), 6.622 (d, j=8.062, 2H), 6.227-6.188 (m, 1H), 5.992 (s, 1H), 5.511-5.408 (m, 1H), 5.143-5.084 (d, 2H), 4.837-4.826 (m, 1H), 4.744 (s, 1H), 4.684 (s, 1H), 4.497 (s, 3H), 4.353-4.077 (m, 8H), 3.010-2.902 (m, 2H), 2.795-2.680 (m, 4H), 2.629-2.579 (t, 3H), 2.417-2.210 (m, 14H), 2.099-1.667 (m, 12H), 1.504-1.7507 (m, 2H), 1.474 (s, 3H), 1.330 (s, 5H), 1.264-1.156 (m, 2H), 1.121 (s, 3H), 0.808 (s, 4H). HR-MS: calc. M$^+$ = 1577.6, obsvd. (M+1)$^+$ = 1578.5915.
Preparation of FA-K(rapamycin)-ss-EE: N-hydroxysuccinimide (12.7 mg, 0.11 mmol) and dicyclohexylcarbodiimide (24.7 mg, 0.12 mmol) was added in the solution of rapamycin-SA (101.4 mg, 0.1 mmol) in CH₂Cl₂ (20 mL), the mixture was stirred 3 h at room temperature and in dark. The precipitation was filtered and the filtrated was concentrated by rotary evaporation. The resulting yellow solid was dissolved in DMF (10 ml), and then FA-K-ss-EE (159.3 mg, 0.15 mmol) was added to the
solution followed by DIEA (99 μL, 0.6mmol). The mixture was stirred overnight at room temperature and in dark. The product was purified by preparative HPLC to give the title product (2) 148 mg (71.9%) as a yellow powder.

$^1$H NMR (400MHz, DMSO-d$_6$): $\delta$ 8.68-8.60 (s, 1H), 8.26-8.15 (m, 2H), 8.11-8.01 (m, 3H), 7.88-7.79 (s, 1H), 7.73-7.62 (m, 2H), 7.07-6.89 (m, 2H), 6.70-6.60 (m, 2H), 6.51-6.32 (m, 2H), 6.24-6.08 (m, 2H), 4.59-4.43 (m, 3H), 4.38-4.23 (m, 3H), 4.20-4.08 (m, 2H), 4.06-3.96 (m, 2H), 3.34-3.25 (m, 8H), 3.21-3.12 (m, 5H), 3.07-2.93 (m, 4H), 2.81-2.69 (m, 5H), 2.41-2.16 (m, 14H), 2.05-1.91 (m, 4H), 1.78-1.45 (m, 20H), 1.40-1.12 (m, 13H), 1.07-0.90 (m, 9H), 0.84-0.66 (m, 9H). HR-MS: calc. M$^+$ = 2057.93, obsvd. (M+1)$^+$ = 2058.9387.

Fig. S-5. $^1$H NMR of FA-K(Rapamycin)-ss-EE
**Fig. S-6.** HR-MS of FA-K(Rapamycin)-ss-EE

**Formation of hydrogels:**

**TAgel:** 2.0 mg of FA-K(TA)-ss-EE (1.27 μmol) was dissolved in 0.15 mL of PBS buffer solution containing 0.7 mg (5.2 equiv. to FA-K(TA)-ss-EE) of Na₂CO₃ (2 equiv. of Na₂CO₃ were used to neutralize the carboxylic acids on FA-K(TA)-ss-EE and the additional 3.2 equiv. of Na₂CO₃ were used to neutralize GSH to make the final pH value to 7.4). 0.05 mL of PBS buffer solution containing 0.6 mg of GSH (5.08 μmol, 4 equiv. to FA-K(TA)-ss-EE) was then added. The hydrogel will form within 5 minutes.

**Rgel:** 4.0 mg of FA-K(rapamycin)-ss-EE (1.94 μmol) were dissolved in 0.15 mL of PBS buffer solution containing 0.41 mg (2 equiv. to FA-K(TA)-ss-EE) of Na₂CO₃. 0.05 mL of PBS buffer solution containing 4 equiv. of GSH (pH 7.4) was then added. The hydrogel will form within 5 minutes.

**Compound FA-K(Ac)-ss-EE:** 20.0 mg of it (18.1 μmol) were dissolved in 0.15 mL of PBS buffer solution containing 9.98 mg (5.2 equiv. to it) of Na₂CO₃ (2 equiv. of Na₂CO₃ were used to neutralize the carboxylic acids on it and the additional 3.2 equiv. of Na₂CO₃ were used to neutralize GSH to make the final pH value to 7.4). 0.05 mL of PBS buffer solution containing 22.23 mg of GSH (2 μmol, 4 equiv. to it) was then added. Gels can not form after being kept at room temperature (22-25°C) for about 24 hs.
Fig. S-7. A) Solution of FA-K(Ac)-ss-EE with 4 equiv. of GSH after 24hs

Rheology of hydrogel: Rheology test was done on an AR 1500ex (TA instrument) system, 40 mm parallel plates was used during the experiment at the gap of 500μm. For the dynamic time sweep, the solution of FA-K(TA)-ss-EE or FA-K(rapamycin)-ss-EE after the addition of 4 equiv. of GSH was directly transferred to the rheometer and it was conducted at the frequency of 2 rad/s and the strain of 1%. The gels were also characterized by the mode of dynamic strain in the region of 0.1%-10% at the frequency of 2 rad/s. The experiments were performed at 37 °C.

Fig. S-8. Dynamic time sweep of solutions containing 1.0 wt% of FA-K(TA)-ss-EE with 4 equiv. of GSH at the strain of 1% and the frequency of 2 rad/s (the experiment was performed at 37 °C)
**Fig. S-9.** Dynamic strain sweep of solutions containing 1 wt% of FA-K(TA)-ss-EE with 4 equiv. of GSH by the mode of dynamic strain in the region of 0.1%-10% at the frequency of 2 rad/s (the experiment was performed at 37 °C).

**Fig. S-10.** Dynamic strain sweep of solutions containing 2 wt% of FA-K(rapamycin)-ss-EE with 4 equiv. of GSH by the mode of dynamic strain in the region of 0.1%-10% at the frequency of 2 rad/s (the experiment was performed at 37 °C).
**Fig. S-11.** Recovery property of TAgel: the gel was firstly subjected to a large external stress of 50% of strain for 600 seconds, and then recovery property of the gel was measured at the strain of 1% and the frequency of 2 rad/s for another 3,600 seconds (the experiment was performed at 37 °C).

**Fig. S-12.** Temperature sweep of TAgel at the strain of 1% and frequency of 1 rad/s

**Drug release determination:** 0.20 mL of gels (1.0 wt%, 24 hours after the addition of GSH) was treated with 0.25 mL of fresh PBS buffer solutions (pH = 7.4). 0.2 mL of the upper buffer solution was taken out to run LC-MS and 0.2 mL of fresh PBS buffer solution was added back at each time. The areas of peaks in LC-MS spectra were used to determine the percentage of TA or rapamycin derivative from the gels. The experiment was conducted in 3 parallel experiments. The experiment was conducted at 37 °C.
**Scheme S-1.** Chemical structure of dimer of FA-rapamycin conjugate released from Rgel

**In vivo biocompatibility study:** Six adult male rabbits weighing 1.8-3.0kg were used for test. All experimental protocols and animal care were compiled with the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, and were approved by the Institutional Animal Care and Use Committee of Wenzhou medical college. Sub-Tenon’s injection of 400 μl of TAgel (1%; w/v) to rabbit eyes (n=6) was carried out by using a 20-G needles under general anesthesia. At specific time schedule (1, 3, 7, 14, 21, 40 and 60 day), the appearance of hydrogel in rabbit eye was observed and the observation of ocular tissue (corneal, iris and etc) condition were evaluated. At 21 days after administration, three rabbits were sacrificed and its eyes were enucleated, followed by fixation at 10% formaldehyde aqueous solution for 24h. After that, the tissue were embedded, sectioned and stained with hematoxylin-eosin (H&E) to examine the histological structure of injected tissues, conjunctiva, retina and etc.

**Fig. S-13.** The observation of hydrogel after sub-Tenon’s injection with time evolution (Red arrow represent the gel)