Supporting Information

Polypeptide synthesis

*Synthesis of γ-propargyl-L-glutamate(**2a**) and γ-propargyl-D-glutamate (**2b**).* Briefly, L-glutamate monomers were synthesized from re-crystallized starting material as follows: L-glutamic acid was suspended in hot H_2O and stirred until all solids dissolved. The solution was stored at 4 °C for 18 – 24 hours and the resulting crystals were filtered, rinsed, and dried under high vacuum to remove all residual water. The crystals (**1a**, 19.6 g, 133 mmol) were suspended in propargyl alcohol (500 mL) and chilled to 0 °C under argon. Next, trimethylsilyl chloride (36.2 mL, 333 mmol) was added dropwise (over the course of 1 hour) and then the reaction was stirred at 20 °C for 36 hours. The crude mixture was filtered to remove un-dissolved starting material, and then precipitated into a 10x volume of room-temperature diethyl ether. The precipitate was filtered, re-dissolved in a 10:1 mixture of acetonitrile/dimethylformamide (DMF) at 50 °C, and stored at 2 °C for 18 hours. The resulting fine crystals were filtered, rinsed with cold acetonitrile, and dried to afford the product (**2a**, 21.8 g, 76%

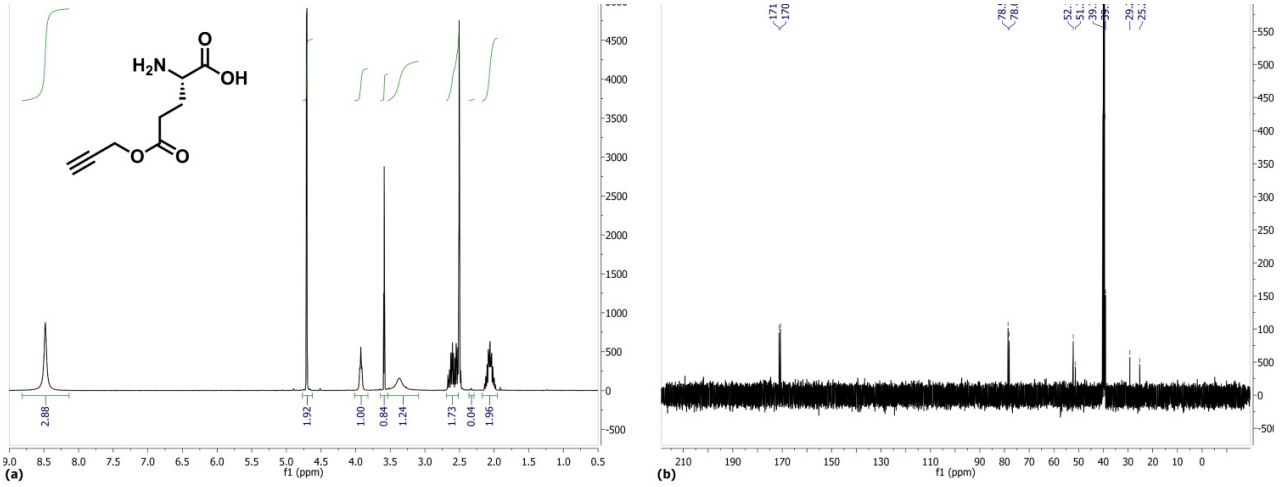

Figure S1. NMR spectra of γ-propargyl-L-glutamate (**2a**) in DMSO-d_6: (a) ^{1}H spectrum, (b) ^{13}C spectrum.

yield). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 8.48 (s, 3H, NH_3^+), 4.70 (s, 2H, CH_2O), 3.93 (m, 1H, CH), 3.59 (s, 1H, CCH), 2.6 (m, 2H, CH_2), 2.1 (m, 2H, CH_2CH). ^{13}C NMR (400 MHz, DMSO, δ, ppm): 171.2 (C(O)OH), 170.7 ($C(O)OCH_2$), 78.6 (CCH), 78.1 (CCH), 52.2 (OCH_2), 51.3 (CH), 29.2 (CH_2CH), 25.3 (CH_2CH_2). The D-glutamate monomer (**2b**) was produced from the starting material D-glutamic acid (**1b**) using a protocol identical to that described above.

*Synthesis of γ-propargyl-L-glutamate N-carboxy anhydride (**3a**) and γ-propargyl-D-glutamate N-carboxy anhydride (**3b**).* The anhydride monomer (**3a**) was produced by reacting **2a** (5.5 g, 24.6 mmol) in anhydrous ethyl acetate (150 mL) with triphosgene (2.4 g, 8.1 mmol) for 6 hours at 85 °C in a flask fitted with a cooling condenser; argon was bubbled directly into the reaction and the gas outlet was fitted with a drying chamber containing potassium hydroxide pellets in order to safely neutralize any residual phosgene gas (CAUTION: phosgene gas is dangerous – this reaction should only be conducted by experienced individuals following appropriate safety measures). The crude product was

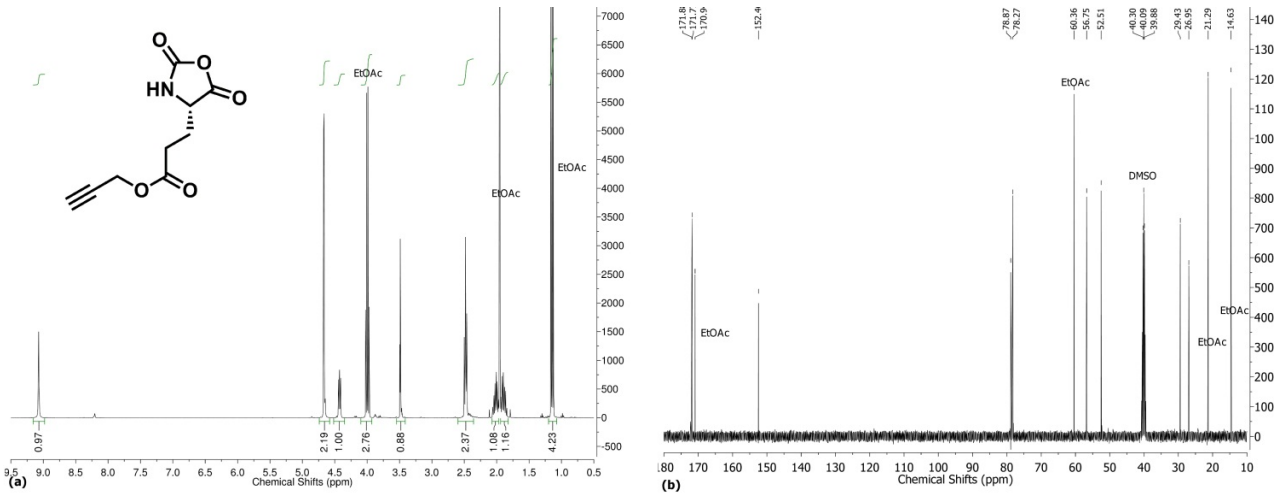

Figure S2. NMR spectra of γ-propargyl-L-glutamate NCA (**3a**) in DMSO-d_6: (a) ^{1}H spectrum, (b) ^{13}C spectrum.

filtered, quickly washed with chilled water, chilled aqueous sodium bicarbonate (5%), and chilled saturated NaCl solution, then dried with magnesium sulfate, filtered, and concentrated under vacuum to yield the product (**3a**) as a colorless oil (3.4 g, 66% yield). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 9.1 (s, 1H, NH), 4.7 (s, 2H, CH_2O), 4.4 (m, 1H, CH), 3.5 (s, 1H, CCH), 2.5 (m, 2H, CH_2), 2.0 (m, 2H, CH_2CH). ^{13}C NMR (400 MHz, DMSO, δ, ppm): 171.8 (C(O)OH), 170.9 ($C(O)OCH_2$), 152.5 (OC(O)NH), 78.9 (CCH), 78.3 (CCH), 56.8 (CH), 52.5 (OCH_2), 29.2 (CH_2CH_2), 27.0 (CH_2CH).

*Synthesis of poly(γ-propargyl-L-glutamate) (**4a**) and poly(γ-propargyl-D,L-glutamate) (**4b**).* Polypeptides were synthesized by amine-initiated ring-opening polymerization of the N-carboxy anhydride monomers. For example, a polypeptide with a degree of polymerization of 100 was produced by dissolving **3a** (3.4 g, 16 mmol) in anhydrous DMF (20 mL) and adding the resulting solution to 1-aminohexane (21 µL, 0.16 mmol) in anhydrous DMF (5 mL) with stirring under argon. After a reaction time of approximately 72 hours, the DMF was removed under vacuum to yield the crude product, which was then re-dissolved in a minimal amount of dichloromethane (DCM) and precipitated into a 10x volume of diethyl ether. The resulting precipitate was filtered, rinsed with diethyl ether, and dried to yield the pure polymer (**4a**) as a white powder (1.9 g, 70% yield). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 8.15 (s, 68H, NH), 4.7 (s, 142H, CH_2O), 4.3 (m, 71H, CH), 3.5 (s, 71H, CCH), 2.4 (m, 142H, CH_2), 1.9 (m, 142H, CH_2CH), 1.2 (m, 6H, CH_2), 0.8 (m, 3H, CH_3).

*Synthesis of azidoethoxyethanol (**7**).* Azide-functionalized grafting groups were synthesized by reacting chloroethoxyethanol (**6**, 10 g, 80 mmol) with sodium azide (15.7 g, 241 mmol) in a 50:50 mixture of water and ethanol (200 mL) at 80 °C with stirring under N_2 in a flask fitted with a reflux condenser for 36 hours. The crude mixture was cooled to room temperature, concentrated by half *via* rotary evaporation, and extracted into diethyl ether (3x 100 mL aliquots). The organic phase was dried over $MgSO_4$, filtered, and dried under vacuum to yield the product (**7**) as a clear liquid (6.3 g, 60% yield). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 4.6 (t, 1H, $HOCH_2$), 3.6 (m, 2H, CH_2CH), 3.5 (m, 2H, CH_2CH_2), 3.45 (m, 2H, CH_2CH_2), 3.38 (m, 2H, CH_2N_3). ^{13}C NMR (400 MHz, DMSO, δ, ppm): 72.2 (OCH_2), 69.2 (OCH_2), 60.2 ($HOCH_2$), 50.0 (N_3CH_2).

*Synthesis of poly(γ-propargyl-L-glutamate)-g-ethyloxyethanol (**5a**) and poly(γ-propargyl-D,L-glutamate)-g-ethyloxyethanol (**5b**).* The polypeptides were functionalized by 1,3-dipolar cycloaddition

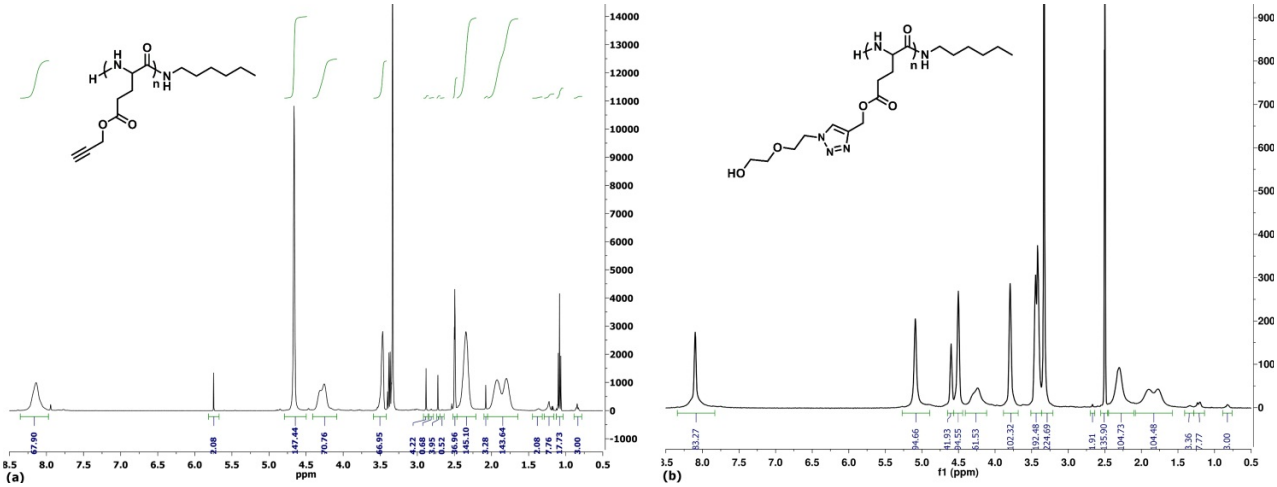

Figure S3. ^{1}H NMR spectra: (a) poly(γ-propargyl-D,L-glutamate) (**4a**) and (b) poly(D,L-glutamate)-*g*-(hydroxyethylene glycol) (**5a**) in DMSO-d_6.

reactions as described below with stoichiometry tabulated on a per-monomer basis. For example, the polymer **4a** (0.4 g, 2.4 mmol monomer) was dissolved in anhydrous DMF (10 mL) and reacted with azidoethyloxyethanol (**7**) (0.47 g, 3.6 mmol), N,N,N',N",N"-pentamethyldiethylenetriamine (PMDETA, 250 μL, 1.2 mmol) and Cu(I)Br (0.17 g, 1.2 mmol) under argon for 8 hours at 20 °C. The solvent was then removed under vacuum to yield the crude polymer, which was dissolved in water (10 mL), incubated with approximately Dowex M4195 ion exchange resin (approximately 1g of resin) for 20 minutes at 20 °C. The resin was removed by filtration and the filtrate was further purified by dialysis in pure water for 72 hours (3500 molecular weight cut-off dialysis tubing). The polymer solution was then removed from the tubing and lyophilized to yield the product (**5a**) as a white powder (0.7 g, 93% yield). ^{1}H NMR (400 MHz, DMSO, δ, ppm, n = degree of polymerization): 8.2 (s, 2H*n, NH, CCH), 5.15 (s, 2H*n, CH_2O), 4.6 (m, 1H*n, $HOCH_2$), 4.5 (m, 2H*n, CH_2N), 4.2 (m, 1H*n, CH), 3.8 (m, 2H*n, CH_2O), 3.4 (m, 4H*n, CH_2O), 2.3 (m, 2H*n, CH_2CH_2), 1.8 (m, 2H*n, CH_2CH) 1.3 (m, 8H/n, CH_2CH_2), 0.8 (t, 3H/n, CH_3CH_2).

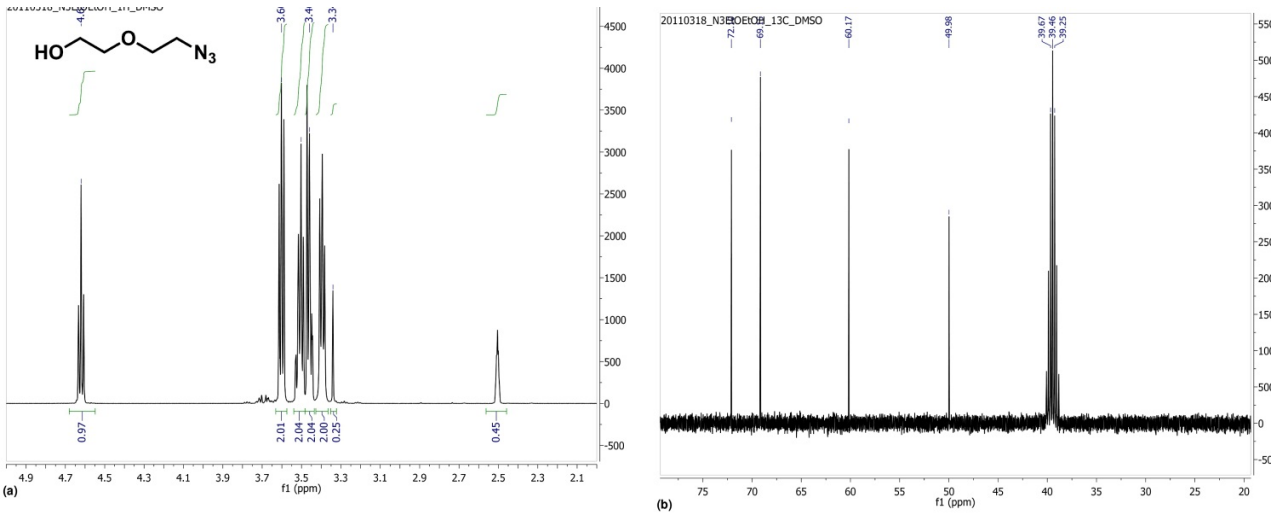

Figure S4. NMR spectra of azidoethoxyethanol (**7**) in DMSO-d_6: (a) ^{1}H spectrum, (b) ^{13}C spectrum.

Polypeptide characterization

Secondary structure and hydrogen bonding of grafted polypeptides. The comparison between helical and random coil grafted propargyl-glutamate polypeptides is shown in more detail in **Figure S5**. In this figure, we display previously published FTIR spectra of poly(L-glutamic acid) from Doty *et al*.[53] above a re-sized image of the FTIR spectra of PPLG*g*EG$_2$OH and PPDLG*g*EG$_2$OH from this manuscript. Although the poly(L-glutamic acid) and grafted poly(propargyl-glutamate) macromers have slightly different chemical identities, the peak shifts between helical and random coil polymers is still insightful. Specifically, the shift between helical and random coil polypeptides for the amide I peak was an identical 6 cm^{-1} for both the Doty *et al.* poly(L-glutamic acid) and our grafted poly(propargyl-glutamate). The amide II peak shift was slightly more pronounced at 10 cm-1 for Doty *et al.* in comparison to the 7.8 cm^{-1} measured for our grafted poly(propargyl-glutamate) (20% less). Part of this discrepancy may be due to the more complicated nature of the poly(L-glutamic acid) spectra in this region, which makes it difficult to assign the exact peak for amide II. Image from Doty *et al.* reprinted with permission (John Wiley and Sons, license # 2967120947702, August 13, 2012).

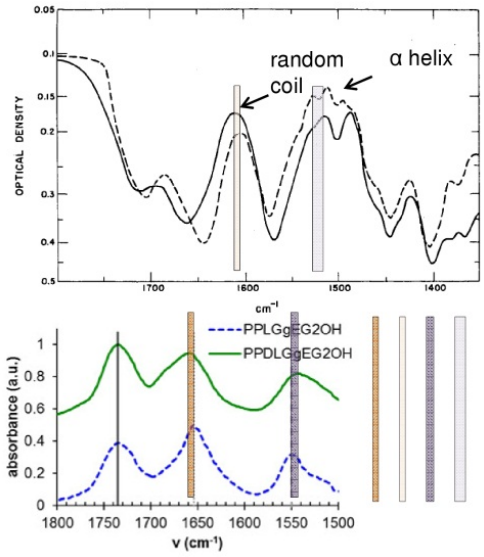

Figure S5. Enhanced comparison of FTIR spectral differences between helical and random coil polypeptides. Upper spectra are of poly(L-glutamic acid) at different pH conditions as adapted from Doty *et al.*[53] Lower spectra are of PPLG*g*EG$_2$OH and PPDLG*g*EG$_2$OH and are re-sized from this manuscript such that the x-axes of the two data sets are identical. Bars represent differences in shifts between helix and coil polypeptides, they are also offset together at right for better comparison.