Supplementary Information

A Biodegradable Block Copolymer-Tannic Acid Glue

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Additional Methods

Scheme S1

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Table S1
Additional Methods

Characterization

$^1$H nuclear magnetic resonance (NMR) was obtained using a Bruker Advance 400 MHz spectrometer (Billerica, MA, USA) using the residual NMR solvent signal as an internal reference. Size exclusion chromatography (SEC) was performed in a 0.05 M LiBr solution in N,N-dimethylformamide (DMF) at 40 °C with a flow rate of 1 mL min$^{-1}$ on an Agilent 1260 Infinity system (Santa Clara, CA, USA). The instrument was equipped with a 1260 refractive index detector, one PSS GRAM analytical 100Å column with a molar mass range 300 – 60,000 g mol$^{-1}$, and two PSS GRAM analytical 10,000Å columns in series with a molar mass range 10,000 – 50,000,000 g mol$^{-1}$. The molar masses of the polymers were calculated relative to linear polystyrene standards obtained from Agilent Technologies. Fourier transform infrared (FTIR) spectra were obtained on a Bruker Alpha FTIR spectrometer using a Platinum attenuation total reflection (ATR) single reflection module. Dynamic light scattering (DLS) measurements were performed on a Brookhaven 90Plus/BI-MAS particle size analyzer (Holtsville, NY) at wavelength of 658 nm with scattering angle of 90°.

Synchrotron small-angle X-ray scattering (SAXS) experiments were performed at the 9A beamline in Pohang Accelerator Laboratory (PAL). A monochromatized X-ray radiation source of 20.01 keV with the sample-to-detector distance of 6.455 m was used. Scattering intensity was monitored by a Mar 165 mm diameter CCD detector with 2048×2048 pixels. The two-dimensional scattering pattern were azimuthally integrated to afford one-dimensional profiles presented as scattering vector ($q$) versus scattering intensity, where the magnitude of scattering vector is calculated with $q = 4\pi/\lambda \sin \theta$. Domain spacing ($d$) was estimated from the position of the principal peak at $q^*$ following the relationship $d = 2/q^*$. Full width at half maximum (FWHM) values of the principal scattering peaks were calculated based on the literature procedure.$^1$ The scattering intensity was subtracted by a constant baseline and plotted
versus \( q \) in a log–log fashion. From the \( q \) regime smaller than \( q^* \), the background scattering intensity was estimated by linear fitting and subtracted from the data. The slope of the background fitting function was in the range of 0.2 and 0.9 (i.e., \( q = 0.2–0.9 \text{ nm}^{-1} \)). By normalizing the resulting peak intensity and fitting with a Lorentzian function, the FWHM values were obtained and shown in Figure S15 along with other parameters.

Rheological properties were measured using an Anton Paar rheometer Model MCR 302 (Graz, Austria) with a parallel plate geometry. The volume of the loaded sample was 0.8 mL, and the gap between the plates was 0.5 mm. Heating and cooling during the oscillatory measurement were conducted in situ. To minimize the effect of water loss via evaporation, we covered the exposed side of the loaded sample between the parallel plates with silicone oil. In the frequency sweep mode, shear moduli were measured at fixed strain amplitude (0.1%) with varying angular frequencies from 0.1 to 100 rad s\(^{-1}\) while in the amplitude sweep mode, shear moduli at a fixed frequency (10 rad s\(^{-1}\)) were measured with strain amplitudes ranging from 0.01\% to 100\% (0.0001 to 1).

**Computational Details**

Molecular dynamics (MD) simulations were carried out using the Large-scale Atomistic Modeling Massively Parallelized Simulation (LAMMPS)\(^2\) code. For the canonical (NVT) ensemble simulations, Nosé–Hoover thermostat\(^3\) was used with a damping constant of 100 fs. For the isothermal-isobaric (NPT) ensemble simulations, Parrinello-Rahman barostat\(^4\) was used with a damping constant of 2000 fs. Grand Canonical Monte Carlo (GCMC) simulations were performed using Cerius\(^3\) program (Accelrys Software Inc.). Density functional theory (DFT) calculations were performed using the B3LYP\(^5\)-D3\(^6\) functional and the 6-31G** basis set\(^7\) as implemented in the Jaguar software package\(^8\) to determine quantum mechanical partial charge distributions.
We used the modified force field parameter of DREIDING\textsuperscript{9} generic force field (FF). The partial charges of PEO and TA were determined using the electrostatic potential (ESP) charges derived from DFT calculations. For water, we used the TIP3P\textsuperscript{11} water model with a -0.83\textit{e} partial charge on the oxygen and a 0.415\textit{e} partial charge on the hydrogen. PEO chain was modeled as a linear polymer consisting of 100 repeating monomers (terminating one end with hydroxyl, -OH and the other one with methyl, -CH\textsubscript{3}), and the structure in a good solvent was sampled using NVT simulations, where scaled-effective solvent (SES)\textsuperscript{9} technique was applied. By analyzing the distribution of radius of gyration ($R_g$), two characteristic structures, of which mean and variance reproduce those of entire distribution, were sampled. After placing two characteristic structures in the large enough simulation cell with a periodic boundary condition (PBC), PEO chains were hydrated using GCMC simulation, where the external pressure ($P_{\text{ext}}$) was set to be same as the water vapor pressure at 298 K, i.e., 3.17 kPa. After constructing hydrated PEO chains, TA molecules were included in between the polymer chains and the system was equilibrated with an NPT ensemble for 3 ns at ambient condition (300 K and 1 atm), which was followed by a subsequent NVT dynamics for 3 ns. The final structure was considered to model the PEO/TA system. We then dehydrated the structure by randomly deleting two water molecules at every picosecond during 250 ps NPT dynamics, and then rehydrated the system using GCMC simulation.

For the calculation of stress-strain curves, a uniaxial strain was applied along the $z$-direction. Here the strain was applied in a staircase manner by repeating an 1\% elongation for 1 ps followed by an equilibration for 5 ps. The simulation cell was elongated until 30\% of strain was applied. The number of hydrogen bonds were quantified using geometric criteria – the distance between the donor and the acceptor is less than 3.5 Å, and the angle of donor-H-acceptor is less than 30°.
**Adhesion Test**

The adhesion tests performed in this study are schematically illustrated in Scheme S1. Polyethylene terephthalate (PET) films were used to measure the adhesive strength of PEO/TA gel and OL/TA gels. For the shear test, 20 μL of adhesive gels were applied to the $15 \times 15 \text{ mm}^2$ areas of a PET sheet ($15 \text{ mm} \times 30 \text{ mm}$) and another same-sized PET sheet covered the glue-applied area in the opposite direction. After 2 h, the shear adhesive strength was measured using a universal testing machine (UTM, Instron 5583, USA) with a 50 N load cell at speed of 5 mm/min until the sample was detached. For the detachment test, a PET sheet ($11 \text{ mm} \times 11 \text{ mm}$) was attached to an aluminum holder by cyanoacrylate glue. The adhesive gels (10 μL) were applied to the face of the PET sheet and another PET sheet with aluminum holder covered the glue-applied area for 1h. The detachment adhesive strength was measured using the UTM with a 50 N load cell at speed of 1 mm min$^{-1}$. The adhesive strength at each test was obtained by dividing the maximum load ($N$) into the overlapped area ($\text{mm}^2$, gel-applied area). For the T-peel test, the adhesives (20 μL) were applied to the half area ($10 \times 20 \text{ mm}^2$) of a PET film ($10 \times 40 \text{ mm}^2$), and the other same-sized PET film was overlapped onto it. After 2 h, tests were performed using the UTM with a 50 N load cell at a constant speed of 20 mm min$^{-1}$. The peel test data was presented as the load divided by the sample width as a function of time. Statistical $P$-value is calculated by one-way analysis of variance (ANOVA) followed by Tukey’s test. To confirm the effect of heating/cooling cycles, the sample was prepared in the same manner as the tensile-shear test sample above. Next, the attached portion of the PET sheets was continuously held with bulldog clips. Control groups were kept for 1 h 40 m at room temperature (RT). The other groups were kept RT and subjected to several cycles of heating (20 min, 85 °C)/cooling (20 min, 25 °C) cycles (The number of cycles: 1, 3, and 5). The shear adhesive strength was measured by UTM with a 500 N load cell at speed of 5 mm min$^{-1}$.
Intradermal Reaction Test

All animal experiments were performed with approval from the Animal Care Committee of Korea Advanced Institute of Science and Technology (KA2021-076). For intradermal irritation reaction, normal SD rats (7 weeks, male) were used. The skin irritation test was conducted by implanting extract solutions from OL/TA gel and OL/TA\textsuperscript{Q} gel (heat cycle = 3, heating temperature = 85 °C). The extraction solutions from OL/TA gel and OL/TA\textsuperscript{Q} gel were prepared by incubating 0.2 g of OL/TA gels in 1 mL of PBS at 37 °C for 3 days. Fifty microliters of the extraction solution were injected into the intradermal skin of rats after shaving (n = 5). A TA aqueous solution was used as a control group. The amount of TA included in the 0.2 g of OL/TA gel used above was calculated, and incubated in 1 mL of PBS under the same conditions. The erythema and edema of immune reaction in the injection sites were observed every 24 h for 3 days.

Biodegradation Test

For the biodegradability test of OL-M/TA gel, hairless mice (7 weeks, male) were used. The gel (15 µL) was implanted subcutaneously and it was reopened after 14 days (n = 3). The photos were taken to monitor its degradation.
**In Vivo Hair Transplantation**

First, 7-week-old male BALB/c nude mice (CAnN.Cg-Foxn1nu/CrlOri) were anesthetized. Human hairs were collected by cutting off the tips of the donor’s hair. The collection procedure was approved by the Institutional Review Board of Korea Advanced Institute of Science and Technology (KH2021-182). We prepared two sets of as-synthesized OL-M/TA glues. One group (denoted as OL-M/TA) was kept at room temperature in the gel state. Another group (denoted as OL-M/TAQ) was heated to 75 °C to make it into a sol. A single hair strand was passed through a needle (31 G) and exposed at the tip with about 1 cm in length. Each type of glue was applied to the exposed hair part only enough to coat thin. The OL-M/TAQ-applied strands were kept at 75 °C to avoid gelation prior to injection. The needle with the glue applied single strand was injected into the dorsal subcutaneous tissue of the mouse and removed leaving the hair strand. In the case of the OL-M/TAQ-applied strands, we found that the final temperature of the glue was 40 – 50 °C as they were exposed to ambient air about 5 s before injection. The number of remaining strands was counted in the next day. We also prepared a control group where the hair strands were injected without applying the glue.
Table S1. Characterization of OLs

| Entry | $M_n, \text{PEO}$ (kg mol$^{-1}$) | $M_n, \text{PLA}$ (kg mol$^{-1}$) | $M_n, \text{SEC}$ (kg mol$^{-1}$) | $D$ | $f_{\text{PLA}}$ | $D_{h, \text{H}_2\text{O}}$ (nm) |
|-------|------------------|------------------|------------------|-----|-------------|------------------|
| PEO   | 20               | -                | 39.5             | 1.23| 0           | -                |
| OL-L  | 20               | 1.4              | 39.9             | 1.19| 0.06        | 228.2            |
| OL-M  | 20               | 3.2              | 43.7             | 1.16| 0.13        | 180.6            |
| OL-H  | 20               | 5.5              | 47.4             | 1.15| 0.20        | 141.0            |

Figure S1. (a) Chemical structure and representative $^1$H NMR spectrum of OL-M (400 MHz, CDCl$_3$, 20 °C). (b) SEC traces of PEO and OLs used in this study (1 mL min$^{-1}$, DMF containing 0.05 M LiBr, 45 °C).
Figure S2. DLS correlation curve of OL aqueous solutions at a 0.01 wt% concentration. (a) OL-L. (b) OL-M. (c) OL-H. (d) Particle size distributions.
Figure S3. $^1$H NMR spectra of TA (grey), OL-M (blue), and OL-M/TA (orange) in D$_2$O (400 MHz, 20 °C).
Figure S4. FT-IR spectra of TA (grey), OL-M (blue), as-prepared OL-M/TA (orange), and OL-M/TA after 5 cycles of the heat treatment (olive). The spectra were obtained after drying the materials under vacuum overnight at RT.
Figure S5. Strain amplitude sweep (a – d) and frequency sweep (e – h) data of PEO and OL 50 wt% aqueous solutions obtained by oscillatory shear measurements. (a, e) PEO. (b, f) OL-L with $f_{PLA} = 0.06$. (c, g) OL-M with $f_{PLA} = 0.13$. (d, h) OL-H with $f_{PLA} = 0.20$. 
Figure S6. Strain amplitude sweep (a – d) and frequency sweep (e – h) data of PEO/TA and OL/TAs obtained by oscillatory shear measurements. (a, e) PEO/TA. (b, f) OL-L/TA. (c, g) OL-M/TA. (d, h) OL-H/TA. The data shown in e – f are the same shown in Figure 2a – d.
Figure S7. Strain amplitude sweep (a – d) and frequency sweep (e – h) data of OL-M/TA which were prepared with different ratios of [EO]:[TA] = 100:0, 30:1, 20:1, and 10:1. The data shown in a and c are identical to Figure 2c.
Figure S8. Frequency sweep measurements of OL-H/TA over five heating-cooling cycles. In each cycle, the temperature was raised to 85 °C at a rate of 20 °C/min and maintained for 5 min. Then the sample was cooled back to 25 °C and rested for 5 min. (a) Data at 25 °C. (b) Data at 85 °C.
Figure S9. Frequency sweep measurement of OL-M/TA with repeating temperature cycles from 25 to 85 °C. (a) and (b) obtained at 25 and 85 °C, respectively. (c) Mechanical enhancement of OL-M/TA by successive heating cycles. The moduli obtained at $\omega = 1 \text{ rad s}^{-1}$ and $\gamma = 0.1 \%$ are presented.
Figure S10. (a-b) Frequency sweep measurements of PEO/TA over five heating-cooling cycles. In each cycle, the temperature was raised to 85 °C at a rate of 20 °C/min and maintained for 5 min. Then the sample was cooled back to 25 °C and rested for 5 min. (a) Data at 25 °C. (b) Data at 85 °C. (c) $G'$ and $G''$ obtained at $\omega = 1$ rad s$^{-1}$ and $\gamma = 0.1$ % over the heating-cooling cycles.
Figure S11. (a-d) Temperature-dependent frequency sweep data of OL-M (a-b) and OL-M/TA (c-d) with raising temperature from 15 to 85 °C. (e-f) Temperature versus $G'$ and $G''$ of OL-M (e) and OL-M/TA (f) obtained at $\omega = 1$ rad s$^{-1}$. 
Figure S12. One-dimensional SAXS profiles of as-prepared PEO and OL aqueous solutions (50 wt%, dashed line) and their coacervates formed with TA (solid line).
Figure S13. One-dimensional SAXS profiles of OLs (dashed line) and OL/TAs (solid line) upon heating to 85 °C and then cooling to 25 °C. (a) OL-L and OL-L/TA. (b) OL-M and OL-M/TA. (c) OL-H and OL-H/TA. The data of OL-H/TA shown in c are the same in Figure 3c.
Figure S14. Lorentzian fitting of the SAXS principal peak of (a,c,e) OL-H and (b,d,f) OL-H/TA upon heating to 85 °C and then cooling to 25 °C. The fitted principal peak is shown as a red solid line.
Figure S15. Change of the intermicellar spacing ($d_{\text{SAXS}}$, gray) and full width at half maximum (FWHM) (blue) values of OL-H and OL-H/TA during the first heating-cooling cycle.
Figure S16. GCMC simulation trajectory during initial hydration step of PEO chains.

Figure S17. GCMC simulation trajectory during rehydration step of dehydrated PEO/TA system.
Figure S18. Peel force of OL-TAs compared to PEO/TA as a function of time estimated by the T-peeling test.
Figure S19. Weight loss of OL-M/TA during the heat-treated strengthening process.
Figure S20. Photographs of the remaining hair strands 1 day post-operation (15 strands of hair) using OL-M/TA (top) and OL-M/TAQ (bottom). Red arrowheads indicate the remaining strands in the OL-M/TA case.
Figure S21. Photographs of the remaining hair strands 1 day after hair transplantation without any glue.
Figure S22. Photographs showing erythema and edema of intradermal immune reactions to extracts of tannic acid, OL-M/TA, and OL-M/TA\textsuperscript{Q} (after 1 heating-cooling cycle) for 1, 2, and 3 days.
Figure S23. Photographs of the OL-M/TA gel 0 day and 14 days after subcutaneous injection.
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