In vivo self-assembled shape-memory polyurethane for minimally invasive delivery and therapy

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Materials

ε-Caprolactone (ε-CL, Aladdin, 99%) was purified with calcium hydride for at least 48 h. The selenocystamine dihydrochloride (SeCy, Bidepharm, 97%) was neutralized to remove hydrochloric acid before use. Poly(ε-caprolactone) diol (PCL, Mn = 2.0 kDa, Macklin), stannous octoate ($Sn(Oct)_2$, Sigma-Aldrich, 95%), calcium hydride (Macklin, 95%), 6-hexamethylene diisocyanate (HDI, Aladdin, 99%), xylene (J&K, 99%), triethylenediamine (TEDA, Sigma-Aldrich, 99%), 1,1,1,3,3,3-hexafluroisopropanol (HFIP, Aladdin, 99.5%), tetrahydrofuran (THF, SCR, 99%), diphenyl diselenide (J&K, 98.5%), dichloromethane (DCM, SCR, 99.5%), sodium sulfate (SCR, 99%), Dulbecco's modified Eagle's medium (DMEM, Gibco) and fetal bovine serum (FBS, Gibco) were used as received. Water was purified via a Milli Q water system (Millipore, USA).

Characterizations of synthesized polyurethanes

The chemical structure was analyzed by ^{1}H nuclear magnetic resonance (^{1}H NMR, Bruker, 500 MHz) spectroscopy and ^{77}Se nuclear magnetic resonance (^{77}Se NMR, Bruker, 600 MHz) spectroscopy by using chloroform-d ($CDCl_3$) as the solvent. Fourier transform infrared (FTIR) spectroscopy was used to verify the characteristic functional groups with a range of 4000-400 cm^{-1} on a Vector 22 spectrophotometer (Bruker optics, Switzerland). The number-average molecular weight (Mn) and molecular weight distribution (polydispersity index, PDI) was characterized by gel permeation chromatography (GPC, Waters 1515-2414) with polystyrene as a standard sample and THF as an eluent at 40 °C.

The crystallization properties of the materials were measured by differential scanning calorimetry (DSC) from the TA Instruments company (USA). All samples were measured by the same conditions. The 8 mg sample was heated from -60 °C to 120 °C with a rate of 10 °C/min, which was maintained for 2 min at 120 °C (circle 1) before cooled from 120 °C to -60 °C and maintained at -60 °C for 2 min (circle 2). The circle 3 was then performed according to the conditions of circle 1. The whole measuring processes were conducted under a nitrogen atmosphere. The final data were obtained from circle 2 and 3. Wide-angle X-ray diffraction (WAXD) (Rigaku Smartlab) was used to confirm the crystalline domain of the PCLUSe films with Cu Kα (λ = 0.154 nm) irradiation at 40 kV and 150 mA. The test was performed using a reflection mode with a scanning 2θ angle ranging from 5° to 60°.

The longitudinal sections of self-healed PCLU, PCLU-PCLUSe and PCLUSe films were evaluated using a S-4800 scanning electron microscope (SEM, Hitachi) with an accelerating voltage of 15 kV. All

specimens were frozen in liquid nitrogen and broken to expose the cross section. SEM observations were performed after sputtering the samples with a thin film of gold for 30 s.

Synthesis and characterization of $(PCLSe)_2$

10.0 g selenocystamine dihydrochloride was dispersed in 500 mL DCM, into which 100 mL sodium hydroxide solution (6 mol/L) was dropped under magnetic stirring, until the mixed solution became transparent with a yellow color. After continuous stirring for 2 h, the selenocystamine/DCM solution was collected by a separatory funnel, and was dried by 10.0 g anhydrous sodium sulfate overnight. After filtering off the sodium sulfate, and removing the DCM by reduced pressure distillation, the pure selenocystamine (SeCy) was obtained. The $(PCLSe)_2$ was synthesized through a ring-opening reaction of ε-CL with SeCy under the catalyzation of stannous octoate. The molecular weight of $(PCLSe)_2$ was adjusted by the mole ratio of SeCy and ε-CL (1:10-1:40). In a typical experiment, SeCy and ε-CL with a mole ratio of 1:20 were added into a Schlenk flask with Sn $(Oct)_2$ (0.5‰ of ε-CL mole) under stirring. The flask was vacuumed and supplied with nitrogen before the polymerization was conducted at 115 °C with a nitrogen atmosphere for 24 h. After 10 mL THF was added to dissolve the polymers, they were precipitated by cold diethyl ether. After vacuum drying, the yellow $(PCLSe)_2$ powder was obtained. The molecular weight of $(PCLSe)_2$ was calculated according to the ^1H NMR spectra and GPC analysis.

Synthesis and characterization of PCLUSe

The PCLUSe was synthesized by $(PCLSe)_2$ and 6-hexamethylene diisocyanate (HDI). Into a two-neck flask 10.0010 g $(PCLSe)_2$ (3.7 mmol, Mn=2700) was added, which was then heated at 100 °C for 1 h under vacuum to remove moisture completely. After 40 mL xylene was added to dissolve the $(PCLSe)_2$ under a nitrogen atmosphere, 0.81 g HDI (4.81 mmol) and 170 mg TEDA were added. The reaction was lasted for 8 h. After10 mL THF was added to reduce the solution viscosity, the obtained solution was dropped into cold absolute ethyl alcohol to harvest the pale-yellow polymer PCLUSe, which was dried under a vacuum oven.

The diselenide bond-free polyurethane PCLU was also synthesized with pure PCL and HDI. In brief, 14.3065 g PCL (7.15 mmol, Mn=2000) was added into a two-neck flask and heated at 100 °C for 1 h, before 56 mL xylene was added to dissolve the PCL, followed by addition of 1.57 g HDI (9.33 mmol) and 238 mg TEDA. 8h later, the same treatment was performed to obtain the PCLU.

The PCLU-PCLUSe copolymers was synthesized by using PCL and $(PCLSe)_2$ with a mass ratio of 1:1 under the same conditions.

Mechanical properties of PCLUSe

1.0 g polyurethane (the mole ratio of SeCy and ε-CL in PCLUSe was 1:20) was dissolved into 10 mL good-solvent HFIP under stirring to form a homogeneous solution, which was then poured into a customized Teflon mold. A home-made cap was covered on the mold to avoid formation of bubbles due to the over-rapid evaporation of the solvent. When the solvent was evaporated, the mold with samples was incubated in a vacuum oven for at least 24 h to obtain the polyurethane films with a final thickness of 200~300 μm.

To study the tensile property of the polyurethane under 40 °C, the samples (20 × 4 × 0.2 mm^3) were stretched by a dynamic thermo-mechanical analyzer (DMA-TAQ 800). The samples were first heated from room temperature to 60 °C and maintained for 2 min, which were then cooled down to 40 °C with a rate of 10 °C/min, and followed by stretching. Five individual testing was performed for each sample, and the average value was reported.

Degradation of PCLUSe

After the polyurethane films (m_0) were incubated in PBS or 100 mM hydrogen peroxide (H_2O_2) at 37 °C under shaking at 100 rpm/min for 3 days, they were taken out, and washed with water for three times to remove any possible residual salts. The remained weight (m_t) was measured after being freeze-dried. To continue the degradation experiment, the films were incubated in fresh PBS or 100 mM H_2O_2 again before the weight was measured on the 7, 14 and 28 days. The mediums were replaced every 3 days. The residual mass was calculated by $(m_0-m_t)/m_0\times100\%$, n=3.

Anti-oxidative capacity of PCLUSe

The biomaterials that can mitigate oxidative stress are advantageous for local antioxidant therapy.[1] Firstly, the total anti-oxidative level of PCLUSe films was estimated by a Total Antioxidant Capacity Assay Kit with an ABTS method (T-AOC Assay Kit, Shanghai yuanye Bio-Technology Co., Ltd., Shanghai, China). Then the scavenging of some specific reactive oxygen species also was measured. 10 mg polyurethane film was incubated in 200 μM 1,1-diphenyl-2-picrylhydrazyl (DPPH)/ethanol solution at 37 °C in dark for different time intervals. The inhibition capacity was characterized by measuring the absorbance at 517 nm, which was used to calculate the elimination degree of DPPH.[2] The ability of PCLUSe films to scavenge superoxide radicals was determined using a superoxide anion assay kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Its potential of scavenging hydroxyl radicals was revealed by the Fenton reaction. In brief, 100 mg of polyurethane film was immersed in 1

mL reactive mixture (5 mM H_2O_2 and 0.5 mM $FeSO_4$ solution) for 10 h at 37 °C. 100 μL of the reactive solution was pipetted into a 96-well plate, into which 100 μL of 3,3″,5,5″-tetramethylbenzidine (TMB)/DMSO solution (10 mM) was added. 10 min later, the absorbance at 650 nm was measured using a microplate reader. Three parallel samples were set for all groups.

Cytotoxicity and cytocompatibility of PCLUSe

The cytotoxicity and cell proliferation were tested by Cell Counting Kit-8 (CCK-8). The PCLUSe and PCLU patches (20 mg/mL) were soaked in Dulbecco's modified Eagle's medium (DMEM) supplemented with 100 U/mL penicillin and 100 μg/mL streptomycin for 24 h at 37 °C to obtain the extracts, respectively. After filtered with 0.22 μm filters, the extracts were used to prepare the complete medium with 10% fetal bovine serum (FBS). H9C2 cells at a density of 5×10^3 were cultured on a 96-well plate with 200 μL DMEM that contained 10% fetal bovine serum, 100 U/mL penicillin and 100 μg/mL streptomycin for 24 h to allow cell adhesion. The culture medium was then replaced by the medium containing the extracts. After continuous culture for another 1 or 3 days, the mediums were removed, and the cells were incubated with a 10% CCK-8 for 2 h. The absorbance of the medium at 450 nm was measured by a microplate reader (Tecan M200 PRO; Tecan Company, Switzerland), and was used to calculate the cell viability.

The PCLUSe and PCLU patches with a diameter of 8 mm were sterilized by UV irradiation for 2 h before they were placed into a 48-well plate, atop which H9C2 cells were cultured with a density of 3×10^4 in 500 μL DMEM. On the 1, 3 and 5 days, the cells were incubated with 10% CCK-8 for 2 h to characterize the cell proliferation, respectively.

Acridine orange/ethidium bromide (AO/EB) staining was used to display the cell viability. The viable cells emitted green fluoresce, and apoptosis or necrosis ones showed orange or red fluoresce. H9C2 cells were seeded on the patches at 3×10^4 cells/well in 48-well plates and cultured for 3 d. The cells were harvested by trypsinization and resuspended in 100 μL AO/EB/PBS solution, which was prepared according to the AO/EB Staining Kit (T-AOC Assay Kit, Shanghai yuanye Bio-Technology Co., Ltd., Shanghai, China). Having been incubated for 10 min, 10 μL of cell suspension was pipetted onto a clean glass slide and observed under a fluorescence microscope with a 10× objective (Axiovert 200, Zeiss, Germany).

Shape-memory property of polyurethane films

The shape memory property can be usually characterized by the cyclic thermomechanical tests.[3] Similarly, our samples were tested by a dynamic thermo-mechanical analyzer (DMA-TAQ 800) with a tensile mold. All the samples were heated to 55 °C and maintained for 2 min, before they were cooled down to -20 °C as soon as possible under 0.4 MPa stress until their strain reached approximately 130% (ε_m). When the temperature was equilibrated at -20 °C, the stress was unloaded, and the samples were undisturbed for 5 min to obtain the strain (ε_n). Next, the samples were heated to 55 °C again with a rate of 5 °C/min, and the recovery shape strain (ε_p) was recorded finally. This process was repeated for 6 times. The shape fixity ratio (R_f) and the shape recovery ratio (R_r) were calculated according to the following equations:[4]

$R_f=\varepsilon_n/\varepsilon_m\times100\%$; $R_r=(\varepsilon_n-\varepsilon_p)/\varepsilon_m\times100\%$.

The shape memory performance was also exemplified by stretching, bending, twisting and flower-booming procedures. After the samples were heated to 45 °C for 5 min and deformed fast under a proper force, they were cooled down to 0 °C to fix their temporary shapes (heating-cooling procedure). The samples were heated again to 37 °C in water to recover their original shapes, and were then placed at room temperature for 5 min at least to examine the shape fixity. The materials with different thickness had a slightly higher or lower transformation temperature.

Self-healing property of polyurethane films

The mechanical property was measured by an Instron 5540 A universal testing machine (USA) with a sample size of 30 × 5 × 0.2 mm^3. All samples were tested under a strain speed of 10 mm/min at room temperature (25 °C).

To investigate the self-healing degree of polyurethanes, the samples (30 × 5 × 0.2 mm^3) were cut off, and placed together again before they were irradiated by a 405 nm laser (500 mW) for 2 min. The mechanical property was measured by an Instron 5540 A universal testing machine (USA). The strength under 40 °C was checked by DMA-TAQ 800 with the same procedure mentioned above.

To verify the dynamic change of double selenium, the selenocystamine and diphenyl diselenide were irradiated by 405 nm light for 5 min and tested by ^{77}Se NMR (Bruker, 600 MHz) with a dimethyl sulfoxide (DMSO) solvent.

A vascular leakage sealing model for the PCLUSe in vitro

The applicability of the PCLUSe film was demonstrated by using an aortaventralis blood leakage model. The PCLUSe tube was firstly manufactured from a film. In brief, the PCLUSe film was wrapped around

the outside of a polytetrafluoroethylene (PTFE) tube (outer diameter 2 mm) in water at 45 °C. The heating was then maintained for at least 4 h to achieve the shape reconstruction, before the PCLUSe tube was harvested. This shape reconstruction was permanent due to the dynamic exchange of diselenide bonds. When reheated to above Tm, the PCLUSe tube, as an original shape, would not be self-recovered to the film. The temporary PCLUSe sheet was obtained from the tube through a heating-cooling procedure. Once triggered at 37 °C, the PCLUSe film began to transform into a tube to seal the leaking site on the vessel. Then the remained gap in the PCLUSe tube was finally healed under 405 nm laser.

The bearing pressure of the leakage site was measured by a self-manufactured manometry set. The set was consisted of a water inlet, a vacuum meter and a measured site. The water was injected from the right inlet by a 20 mL syringe. Along with the increasing amount of injected water, the stress on the leakage site increased. A flexible latex tube was used to mimic the leakage of vessels. The leaking site was encased by a healed PCLUSe tube, and the bearing stress was presented by the vacuum meter. A real vessel was used to evaluate whether the PCLUSe tube could seal the leaking and bear the "blood" pressure.

Minimally invasive implantation of PCLUSe patches in vitro

The minimally invasive implantation procedure of PCLUSe films was simulated *in vitro*. The hearts of pigs were used for this demonstration. The films (40 × 30 × 0.2 mm^3) were rolled up by hand in 45 °C water and cooled to 0 °C to fix their tubular shape. They were delivered to the heart surface via a trocar (10 mm in diameter). The films recovered their shape in 37 °C water, and adhered to the heart surface by pulling with a tweezer. However, this film could not be delivered by a trocar with a dimeter of 5 mm due to its larger size, whereas the smaller one could be.

To deliver the same size film by a smaller channel (5 mm in diameter), the film was cut into two parts. Each of them was rolled up into a tubular structure by hand in 45 °C water and cooled to 0 °C to fix their shape. The two tubular structures were delivered onto the porcine heart surface through a 5 mm diameter trocar, respectively. The films were then irradiated by 405 nm laser for 2 min to self-heal into a larger one with the original size.

Minimally invasive implantation of PCLUSe patches in vivo

To illustrate the potential of shape-memory PCLUSe films in MIS *in vivo*, the patches (20 × 10 × 0.2 mm^3) were cut into two parts (10 × 10 × 0.2 mm^3), which were rolled up by hand in 45 °C water and cooled to 0 °C to form a temporary tubular shape in advance. The MIS operation in canine was approved

by the Laboratory Animal Welfare and Ethics Committee of Zhejiang University (Approval Code: ZJU20220035). The anesthesia of male beagles was performed by intravenous injection of propofol (3 mg/kg) until the dog had no swallowing reflex behaviors. The anesthesia machine was connected to the dog to deliver air with 3% isoflurane, ensuring surgical anesthesia. On the ventilator, tidal volume was set to 75 mL, and the breathing ratio was 1:2. Then, the local anesthesia was performed by multi-point subcutaneous injection of lidocaine (4 mg/mL) for the surgical area. There were three circular holes impaled between the 8^{th} and 9^{th}, the 9^{th} and 10^{th}, and the 10^{th} and 11^{th} ribs, respectively, which were supplied for endoscope and minimally invasive devices.

The rolled-up patch was delivered onto the heart surface by a 10 mm trocar, and recovered to the original shape by the heating of body temperature. Because the surrounding temperature was not high enough to make the patch transformation completely, the auxiliary heating by some hot wind was used. The 405 nm laser was irradiated through a 5 mm invasive channel to assemble the two patches. In 5 min, the two patches were self-healed into a larger one. The whole procedure was observed through the endoscope.

A rat myocardial infarction model and implantation of patches in vivo

The rat myocardial infarction model experiments in this study were approved by the guidelines of the Institutional Animal and Use Committee (Approval No: ZJCLA-IACUC-20030034). Male Sprague-Dawley rats (200 ± 20 g, supplied by the Zhejiang Academy of Medical Sciences) were anesthetized with 1.7 mL/250 g 1% sodium pentobarbital by intraperitoneal injection. After endotracheal intubation and assisted ventilation, the heart was exposed through a left thoracotomy and excised pericardium. The left anterior descending (LAD) coronary artery was ligated with a 6-0 silk suture to create left ventricular (LV) infarction. The pale discoloration appearance suggested that the MI model was successfully established. Then, 3 stitches were performed to fix the polyurethane patch (8×8 mm^2) on the infarcted region. Finally, 3–0 silk sutures were used to close the chest cavity, muscles and skin. The rats were divided into four groups at random: (1) sham group (underwent thoracotomy only without LAD ligation); (2) MI group (without patch); (3) PCLU patches; (4) PCLUSe patches.

Echocardiography test

28 days post-operation, the rats (n=5) were anesthetized with inhaled isoflurane and underwent the 2D transthoracic echocardiography. The heart function was assessed by the ultrasound system (VEVO 2100 ultrasound system, Visual Sonics, Canada) and quantitatively characterized by LVEF (left ventricular

ejection fraction), LVFS (left ventricular fractional shortening), LVEDV (left ventricular end-diastolic) and LVESV (left ventricular end-systolic volume).

Electron paramagnetic resonance (EPR) test

The intrinsic antioxidant capacity *in vivo* was evaluated by the residual free radical levels of infarction tissue (n=3). Briefly, the whole infarcted region obtained on the 1st day after MI surgery was ground to powder in liquid nitrogen, which was then detected by an EPR spectrometer (Bruker 300) at the 3372 G magnetic field.[5] The double integral of the main signal peaks (3350-3370 G g^{-1}) calculated by Bruker BioSpin WinEPR Acquisition software represents the level of the ROS-related free radical signal.

Immunohistochemical evaluation

On the 28th day after MI surgery, the infarction tissue was taken out by opening the chest, which was preserved with paraformaldehyde solution. The degree of tissue fibrosis was characterized by Masson's trichrome staining. The infarction area was calculated by the area ratio of the fibrotic tissue (blue) and the normal tissue (red) through Image J software.

On the 28th and 7th day after MI surgery, the infarction tissues were harvested and immersed fully into a paraformaldehyde solution. The inflammatory cell infiltration and tissue repairment were estimated by the hematoxylin and eosin (H&E) staining.

To evaluate the inhibition of cell apoptosis of the polyurethane patches, the infarction tissue of each group (n=3) was removed with opening chest on the 1st day post-operation and fixed with paraformaldehyde solution for TdT-mediated dUTP Nick-End Labeling (TUNEL) staining. The ratio of positive cells (brown) and normal cells (blue) was calculated by Image J software.

Immunofluorescence evaluation

On the 3rd day post MI surgery, the infarction tissue (n=3) was obtained by opening the chest and fixed with paraformaldehyde solution. The immunofluorescence staining was applied to reveal the differentiation of macrophages. The pro-inflammatory phenotype macrophages (M1) and anti-inflammatory phenotype macrophages (M2) were marked by CD86 and CD163, respectively. The cell nuclei were counterstained by DAPI. The ratio of $CD163^+$ cells to DAPI counts was calculated by Image J software.

Statistical tests

IBM SPSS Statistics 26 was applied to the data statistical analysis. The data were plotted by GraphPad Prism 8 and Origin 2021 with mean ± standard deviation (SD), $n \geq 3$. The data statistical difference was

performed by using one-way Analysis of Variance (ANOVA) with the least significance difference (LSD) test. There is statistically significant difference when *p < 0.05 and **p < 0.01.

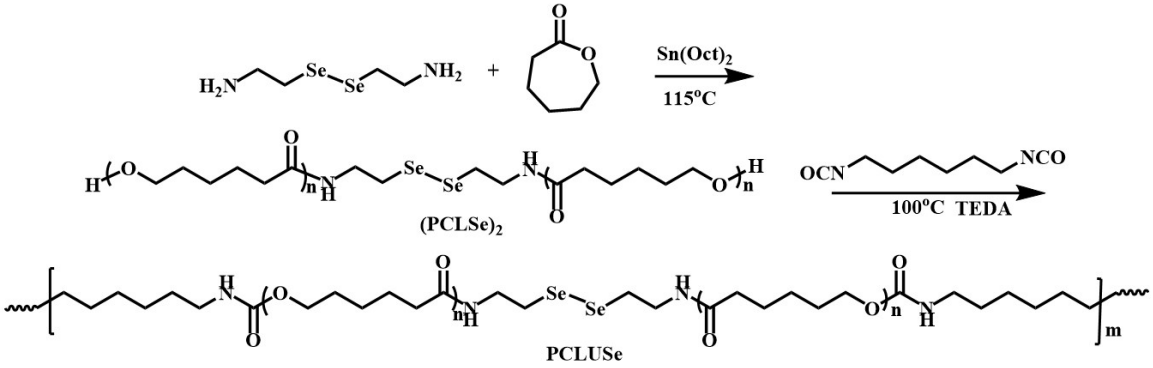

Figure S1. Synthesis route of PCLUSe. Synthesis route of diselenide-containing shape memory polyurethane by a two-step process. The molecular structures of semi-crystallized PCL segment, diselenide group and 1,6-hexamethylene diisocyanate (HDI) are also shown.

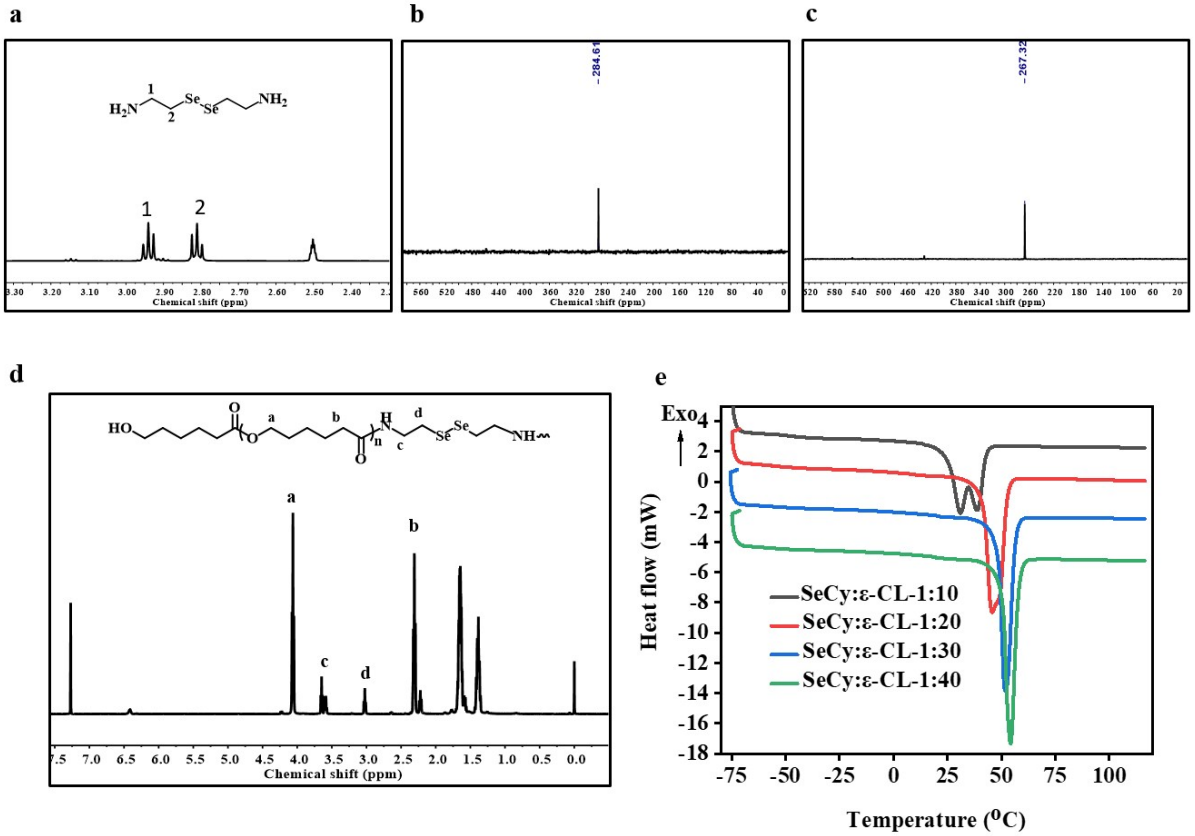

Figure S2. Synthesis of $(PCLSe)_2$. **a**, ^1H NMR spectrum of selenocystamine after neutralization of hydrochloride. **b**, ^{77}Se NMR spectrum of selenocystamine dihydrochloride. **c**, ^{77}Se NMR spectrum of selenocystamine. **d**, ^1H NMR spectrum of $(PCLSe)_2$. **e**, DSC thermograms of $(PCLSe)_2$ with different SeCy: ε-CL ratios by heating from -60~120 °C at 10 °C/min under nitrogen atmosphere.

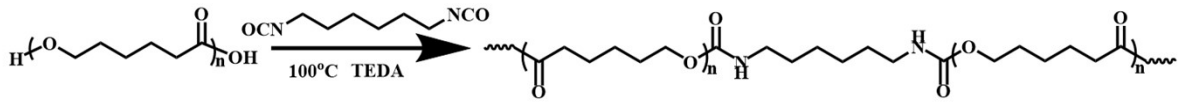

Figure S3. Synthesis route of the non-responsive PCLU.

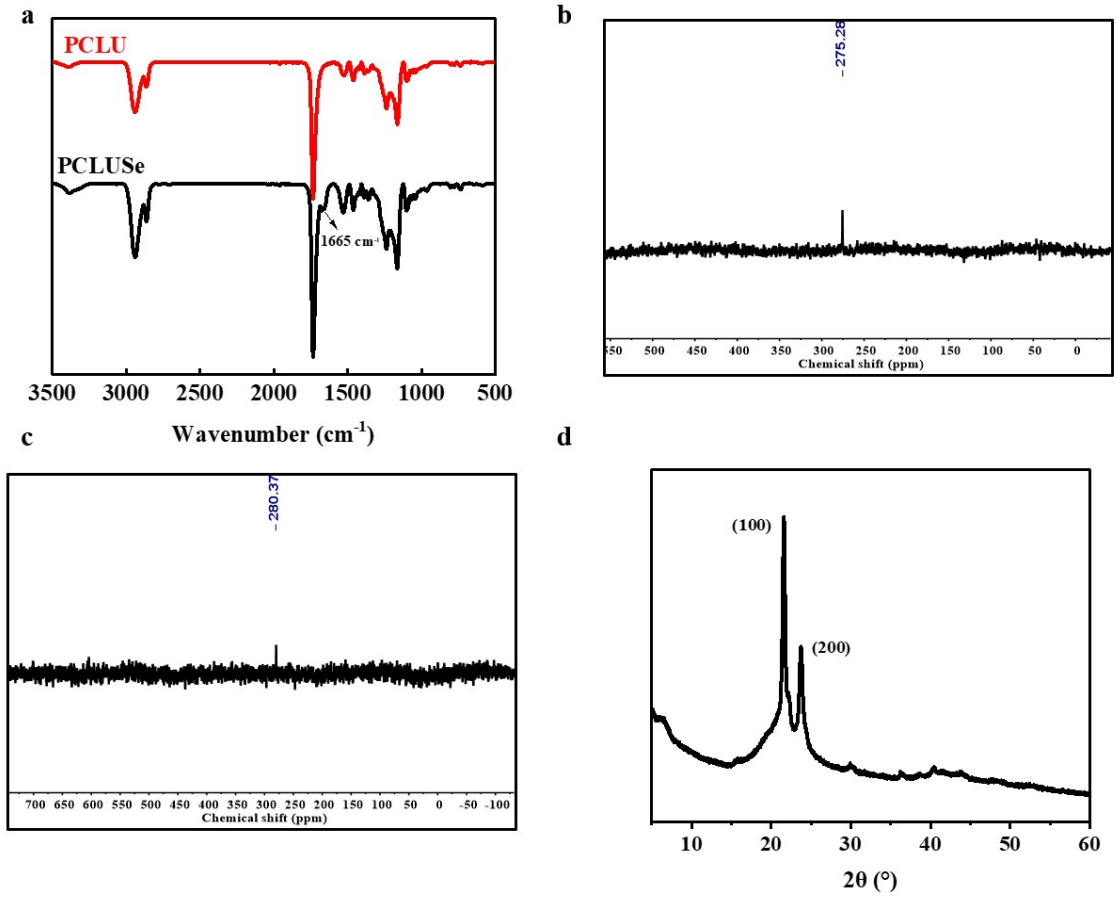

Figure S4. Characterization of chemical structure of PCLUSe. **a**, Fourier transform infrared (FTIR) spectra of PCLUSe and PCLU. **b,** ^{77}Se NMR spectra of $(PCLSe)_2$ and (**c)** PCLUSe. **d**, Wide-angle X-ray diffraction (WAXD) spectrum of PCLUSe.

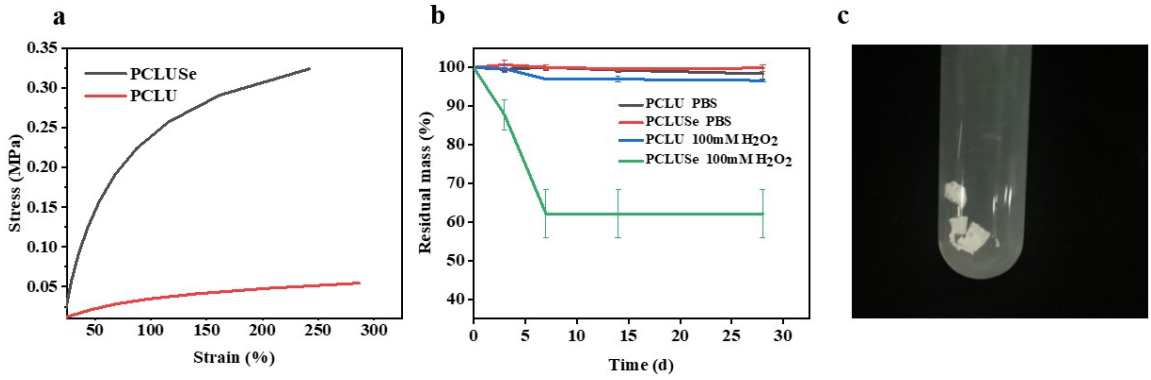

Figure S5. Physiochemical properties and biocompatibility of PCLUSe. **a**, Stress-strain curves of PCLUSe and PCLU films measured by DMA at 40 °C. **b**, Weight remaining of PCLUSe and PCLU films after being incubated in PBS and 100 mM H_2O_2 at 37 °C under 100 rpm/min shaking for different time, respectively. **c**, A photo of the degraded PCLUSe film in 100 mM H_2O_2 for 3 days, respectively. $n \geq 3$, mean ± SD.

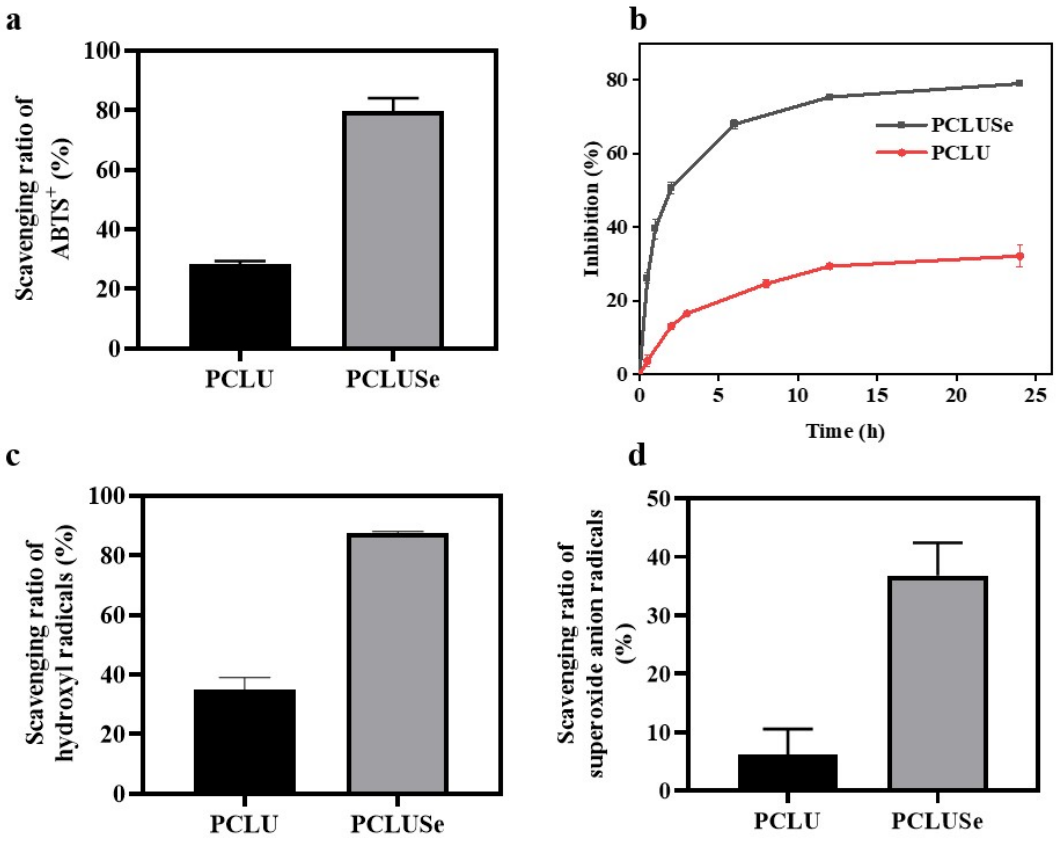

Figure S6. ROS-scavenging ability of PCLUSe. **a**, A total anti-oxidative capacity of PCLUSe and PCLU films. **b**, Inhibition of free radicals by PCLUSe and PCLU films after being incubated in 200 μM DPPH/ethanol solution at 37 °C for different time. Scavenging capacity of PCLUSe and PCLU films against (**c**) hydroxyl radicals and (**d**) superoxide anion radicals, respectively. $n \geq 3$, mean ± SD.

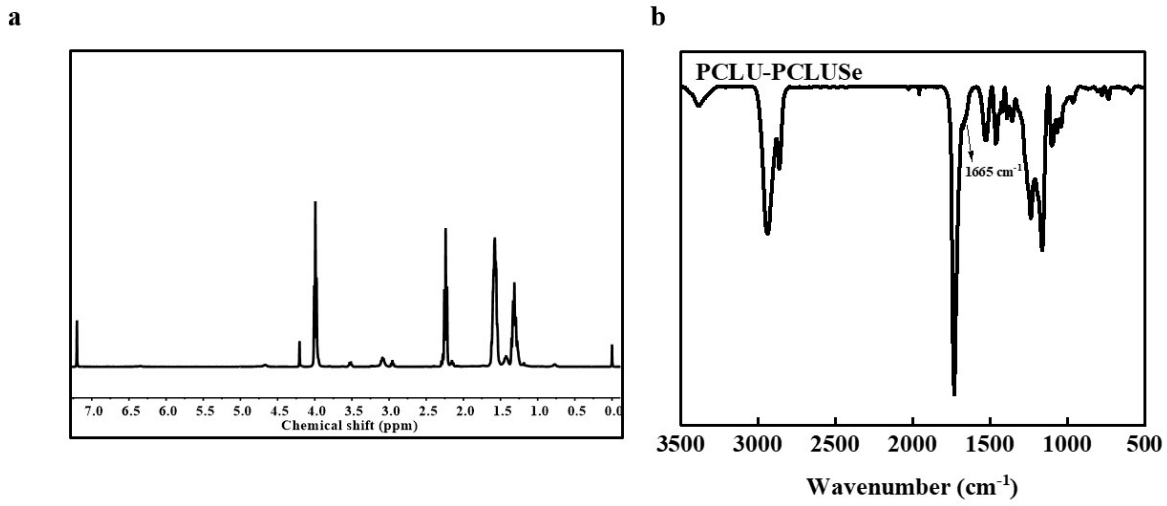

Figure S7. Characterization of PCLU-PCLUSe. ^{1}H NMR (**a**) and (**b**) FTIR spectra of PCLU-PCLUSe.

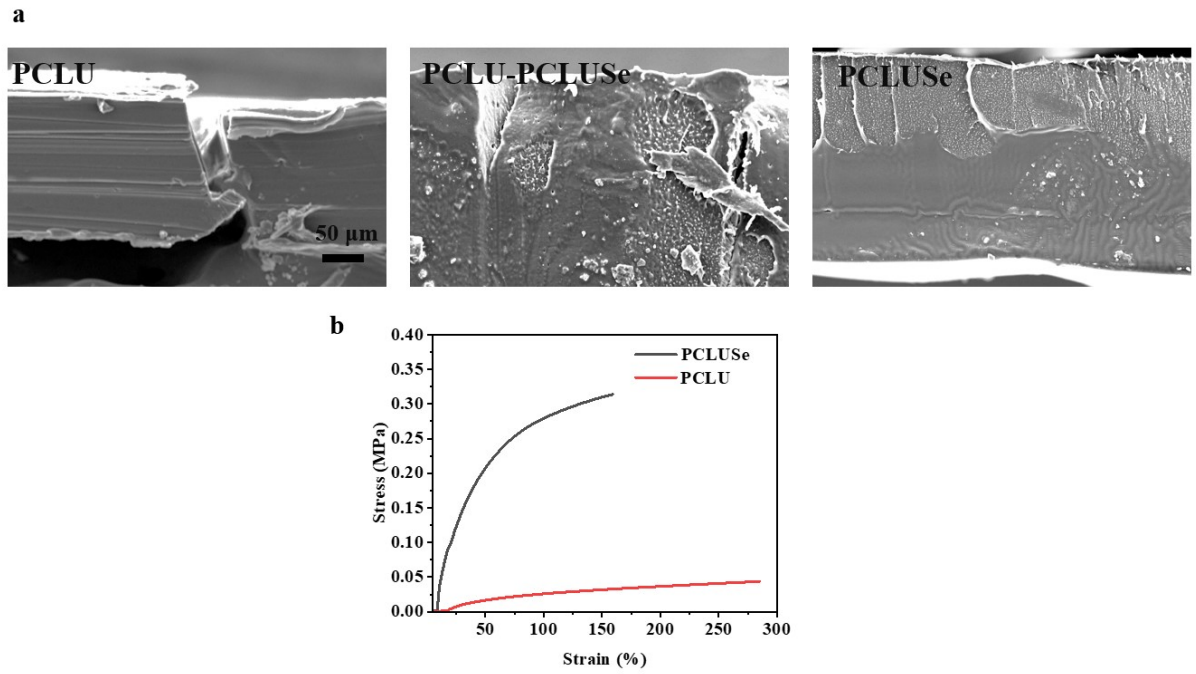

Figure S8. Self-healing ability of PCLUSe. **a**, The longitudinal SEM images of polyurethane films after self-healing. **b**, Stress-strain curves of PCLUSe and PCLU films after self-healing measured by DMA at 40 °C.

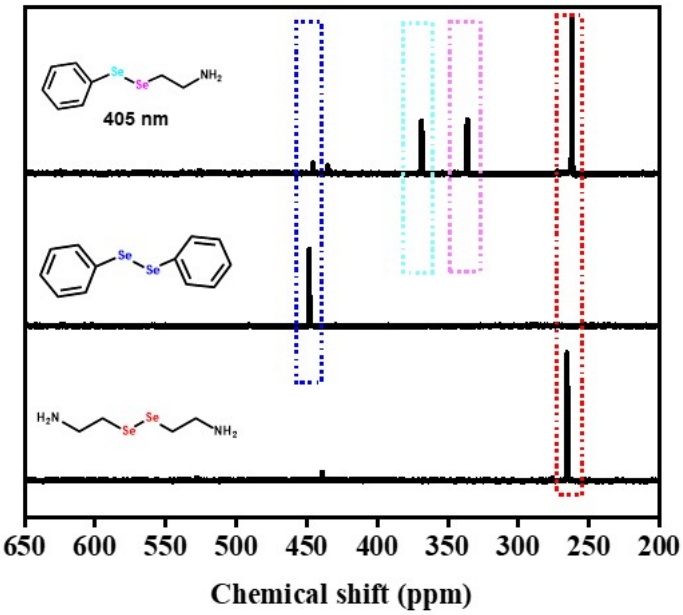

Figure S9. Characterization of dynamic exchange of SeCy and $(PhSe)_2$. ^{77}Se NMR spectra of selenocystamine (SeCy), diphenyl diselenide ($(PhSe)_2$) and their compound after being irradiated by 405 nm laser. The red dot rectangle points out the peak of the SeCy (δ=262 ppm); the blue dot rectangle points out the peak of the $(PhSe)_2$ (δ=448 ppm); the dot nattier blue (δ=368 ppm) and pink rectangles (δ=336 ppm) reveal the formation of a new compound.

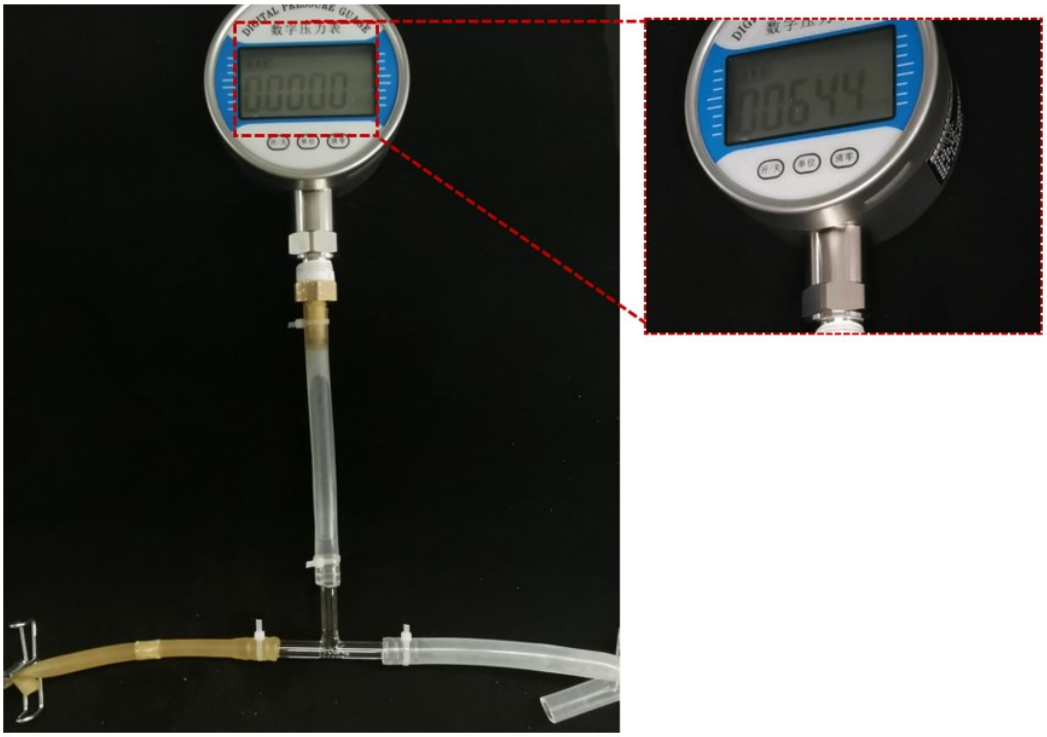

Figure S10. Bearing pressure of healed PCLUSe tube on a latex tube. Performance of the self-manufacture manometry set to measure the bearing pressure of the leaking site in a flexible latex tube and the maximum pressure as shown in the red dot rectangle.

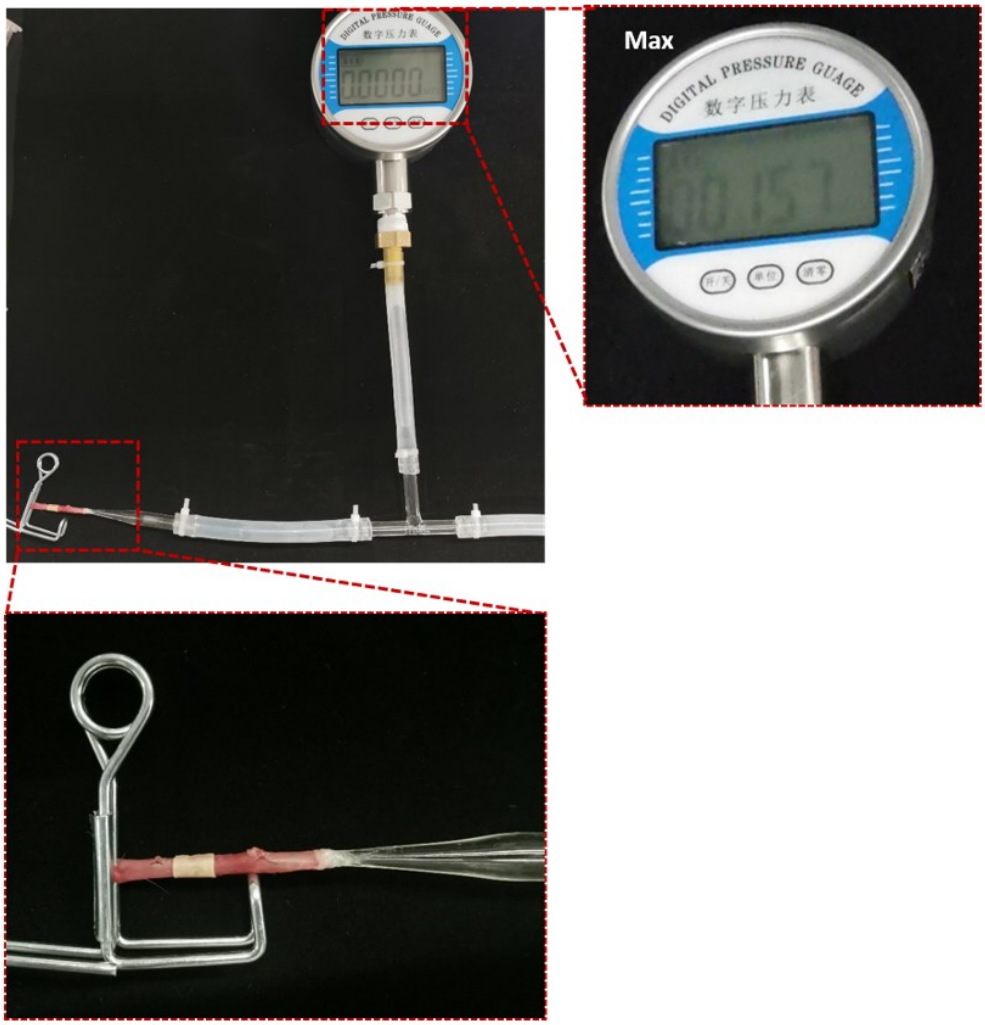

Figure S11. Bearing pressure of healed PCLUSe tube on an aortaventralis. Performance of the self-manufacture manometry set to measure the bearing pressure of the leaking site in aortaventralis of rabbit and the maximum pressure as shown in the red dot rectangle.

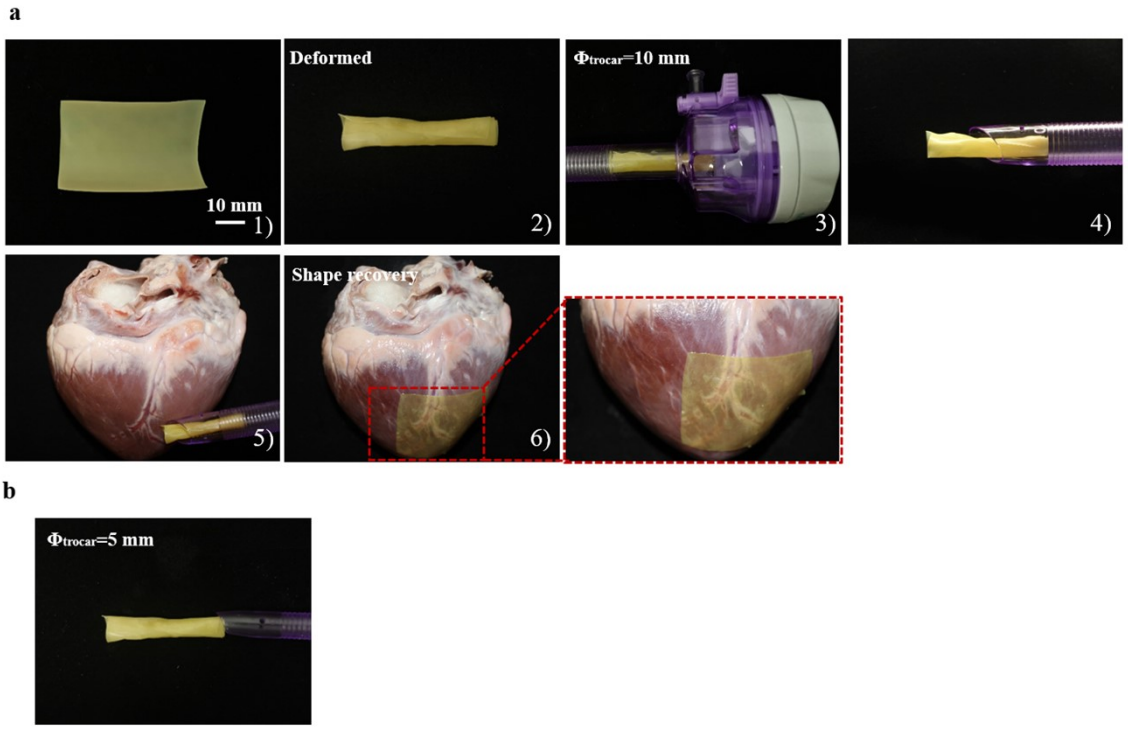

Figure S12. Minimally invasive implantation of PCLUSe cardiac patch *in vitro*. **a**, Performance of PCLUSe patch to unfold and self-heal on the pig heart surface *in vitro*: 1) the original shape of PCLUSe patch; 2) the temporary tubular shape of PCLUSe patch by heating at 45 °C, curving quickly and cooling down to 0 °C; 3-5) the tubular patch was delivered through a trocar (10 mm in diameter) to the heart surface; 6) the tubular patch was unfolded at 37 °C and attached on the heart surface. **b**, the tubular PCLUSe patch was delivered through a trocar of 5 mm in diameter.

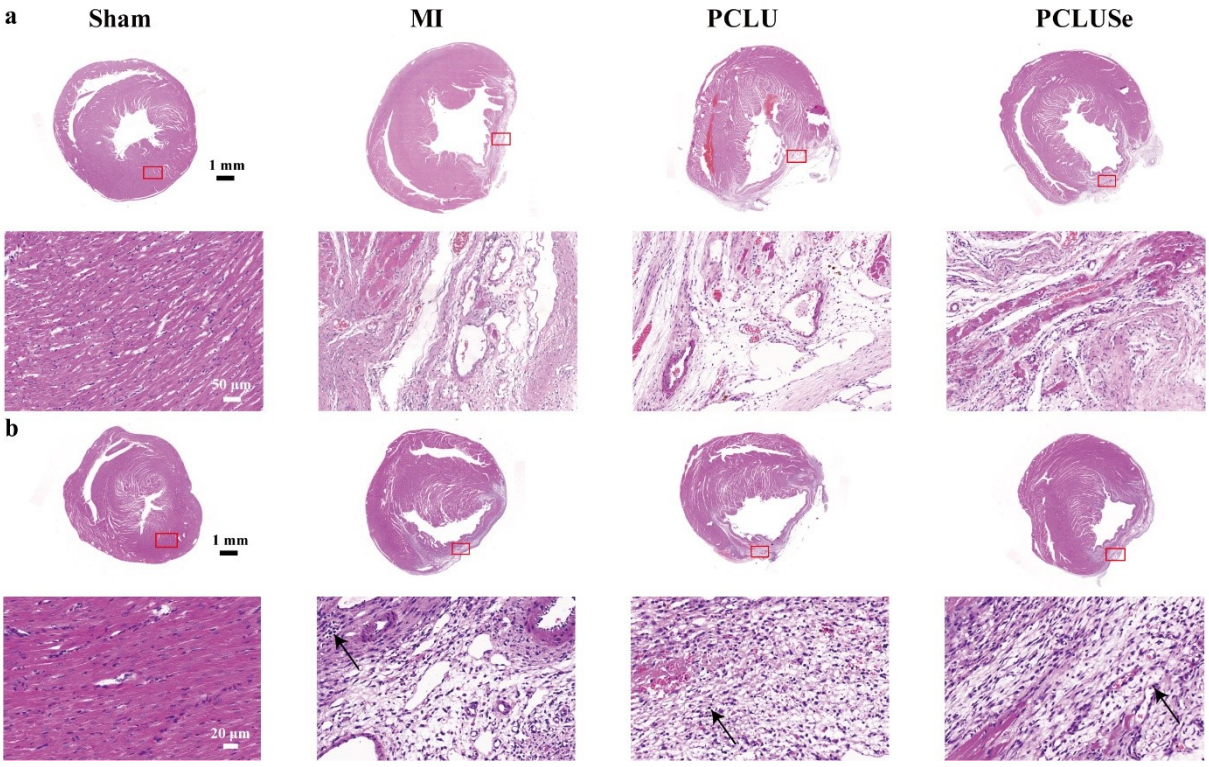

Figure S13. H&E staining to show improved heart function and less inflammatory cell infiltration of PCLUSe cardiac patch in rats. **a**, tissue restoration post-MI for 28 d. **b**, black arrows indicate the inflammatory cells post-MI for 7 d.

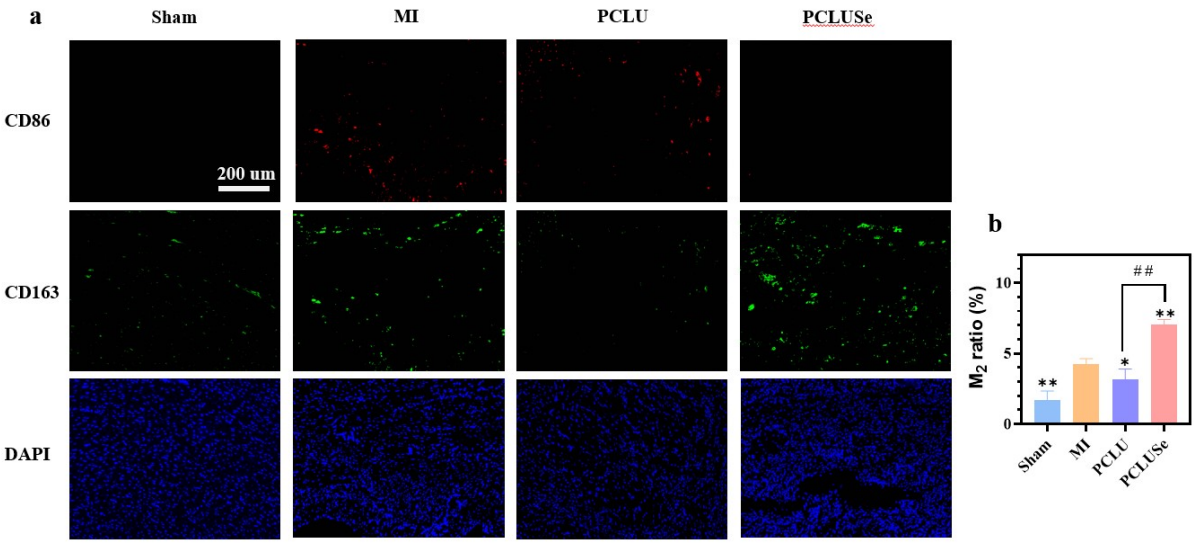

Figure S14. Promoted M2 phenotype polarization of PCLUSe cardiac patch in rats. **a**, Immunofluorescence staining of CD86 (M1 macrophage marker, red) and CD163 (M2 macrophage marker, green) post-operation for 3 days. Cell nuclei (blue) were counter stained with DAPI. **b**, Quantitative analysis of the ratio of M2 macrophages /cells based on (**a**). Data are expressed as means ± SD. n=3. *P < 0.05, **P < 0.01 vs MI group. ## represent P < 0.01 between the selected group.

Table S1. GPC analysis of the $(PCLSe)_2$ with different ratios of SeCy and ε-CL.

Ratio of SeCy and ε-CL	Mn	Mw	PDI
1:10	1708	2317	1.35
1:15	2280	2954	1.29
1:20	3193	4330	1.35
1:30	4905	7147	1.45
1:40	7727	10683	1.38

Table S2. GPC analysis of the PCLUSe (SeCy:ε-CL = 1:20) and PCLU.

Sample	Mn	PDI
PCLUSe	71382	1.69
PCLU	51532	1.52

Table S3. Quantitative analysis of the cyclic curve on the shape fixity ratio (R_f) and shape recovery ratio (R_r) based on DMA measurement.

Recycle	1	2	3	4	5	6	7
Shape fixity ratio (R_f, %)	99.29	99.22	99.76	99.84	99.24	99.93	99.42
Shape recovery ratio (R_r, %)	86.52	93.80	94.54	95.38	95.33	96.44	98.67

Table S4. Quantitative analysis of the stress-strain curves of the PCLUSe, PCLU-PCLUSe and PCLU before and after healing.

Sample	Tensile strength (MPa)	Young's modulus (MPa)	Breaking strain (%)
PCLU	6.22 ± 1.34	36.83 ± 9.07	646.86 ± 88.71
PCLU-PCLUSe	7.68 ± 0.81	64.86 ± 17.68	152.23 ± 32.53
PCLUSe	11.28 ± 1.41	188.08 ± 21.28	7.04 ± 0.43
PCLU-healed	4.67 ± 1.49	160.02 ± 32.30	19.16 ± 7.6
PCLU-PCLUSe-healed	8.86 ± 7.02	180.06 ± 70.76	43.27 ± 14.96
PCLUSe-healed	11.79 ± 3.88	301.36 ± 26.87	4.46 ± 1.19

Video S1. Transformation of a sheet-like PCLUSe film to a tube-like structure in 37 °C water (speed multiply at 4).

Video S2. The self-healed PCLUSe tube was used to bear water pressure on a leaking latex tube measured by a vacuum meter (speed multiply at 3).

Video S3. The self-healed PCLUSe tube was used to bear water pressure on a leaking aortaventralis (rabbit) measured by a vacuum meter.

Video S4. The rolled-up PCLUSe film was recovered to a film in 37 °C water (speed multiply at 3).

Video S5. The unfolding process of the PCLUSe patch on the heart surface in dog observed by an endoscope (speed multiply at 2.8).

Video S6. The self-healing process of the PCLUSe patch on the heart surface in dog under irradiation of 405 nm laser observed by an endoscope (speed multiply at 2.8).

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