# Electronic Supplementary Information

## Controlling blood sugar levels with a glycopolymersome

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## 1. Materials

Polyethylene oxide monomethylether ($PEO_{43}$; $M_n$ = 2000) was purchased from Alfa Aesar. 2-(Dodecylthiocarbonothioylthio)-2-methylpropanoic acid (DDMAT) was synthesized according to our previously reported method.[1] Dicyclohexylcarbodiimide (DCC), azobisisobutyronitrile (AIBN), methacryloyl chloride, 7-hydroxy-4-methylcoumarin, 2-bromoethanol and glucose, were purchased from Aladdin Chemistry. 4-(Dimethylamino)pyridinium 4-toluenesulfonate (DPTS), 3-acrylamidophenylboronic acid monohydrate, and glucosamine hydrochloride were purchased from Sigma-Aldrich. Toluene, potassium carbonate ($K_2CO_3$), sodium

hydroxide (NaOH), sodium chloride (NaCl), magnesium sulfate ($MgSO_4$), triethylamine (TEA), and dimethyl sulfoxide (DMSO) were purchased from Sinopharm Chemical Reagent Co., Ltd. (SCRC, Shanghai, China) and used as received. Dichloromethane (DCM), tetrahydrofuran (THF), sodium bicarbonate ($NaHCO_3$), sodium carbonate ($Na_2CO_3$), hexane, acetic ether, ethanol, and methanol were purchased from Tansoole. $CDCl_3$ and DMSO-$d_6$ were purchased from J&K Scientific Ltd. AIBN was recrystallized from methanol and stored at 4 °C before use.

# 2. Characterization

## 2.1 $^1$H NMR

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded using a Bruker AV 400 MHz spectrometer at room temperature using $D_2O$, $CDCl_3$ or DMSO-$d_6$ as solvent and TMS as standard.

## 2.2 SEC

The molecular weight ($M_n$) and polydispersity ($Đ$) were evaluated by a size exclusion chromatography (SEC) with two different methods: (1) performed at 40 °C with two linear Styragel columns and an Agilent differential refractive index (RI) detector (1200 Infinity Series from Agilent Technologies). HPLC grade DMF was utilized as eluent with flow rate of 0.8 mL•min$^{-1}$. PEO was used as standard; (2) measured on a PL-SEC220 integrated system using refractive index detector and a column set (PLGel MIXED-B × 2, and PLGel MIXED-D × 1). DMF containing 10.0 mM LiBr was used as an eluent at a flow rate of 1.0 mL min$^{-1}$ at 80 °C and the samples were calibrated

with near-monodisperse poly(methyl methacrylate) (PMMA) standard samples (Agilent, 1.95-1048.0 kDa).

**2.3 DLS**

Dynamic light scattering (DLS) was used to determine the hydrodynamic diameter ($D_h$) and polydispersity of glycopolymersomes (0.45 mg $mL^{-1}$) with ZETASIZER Nano series instrument (Malvern Instruments ZS 90) at a fixed scattering angle of 90°. All the aqueous solutions were analyzed using disposable cuvettes. The data were processed by cumulative analysis of the experimental correlation function and the diameters of glycopolymersomes were calculated from the computed diffusion coefficients using the Stokes-Einstein equation. Each reported measurement was conducted for three runs.

**2.4 TEM**

TEM images were obtained using a JEOL JEM-2100F instrument at 200 kV equipped with a Gatan 894 Ultrascan 1k CCD camera. 10 μL of glycopolymersome solution (0.45 mg $mL^{-1}$) was dropped onto a carbon-coated copper grid to prepare TEM samples. Then the TEM samples were dried under ambient conditions to evaporate the water and stained by neutral 1.0% phosphotungstic acid solution for 45 seconds.

**2.5 SEM**

SEM images were recorded by an FEI Quanta FEG 250 electron microscopy operating at 10 kV equipped with a digital camera. To prepare SEM samples, a drop of

glycopolymersome solution (0.45 mg $mL^{-1}$) was dropped onto a silicon wafer and dried at ambient temperature. Subsequently, the samples were coated with gold.

### 2.6 UV-vis spectroscopy

A UV759S spectrophotometer (Shanghai Precision & Scientific Instrument Co., Ltd.) was employed to acquire UV-vis spectroscopy of the photo-cross-linking process of the glycopolymersome (0.45 mg $mL^{-1}$). Both of the absorbance and transmittance spectra of the aqueous glycopolymersome solution were tested in the range of 250-370 nm. DI water served as the control group. All the samples were analyzed with quartz cuvettes.

## 3. EXPERIMENTAL SECTION

### 3.1 Synthesis of macro chain transfer agent (macro-CTA) of PEO-DDMAT

The PEO-DDMAT macro-CTA was synthesized according to a previously reported method.[2] $PEO_{43}$ ($M_n$ = 2000, 20.0 g, 0.010 mol) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 0.244 g, 2.00 mmol) were dried by azeotropic distillation of a toluene solution. Anhydrous DCM (50 mL), DDMAT (7.30 g, 0.020 mol), dicyclohexylcarbodiimide (DCC, 10.35 g, 0.0500 mol) and *N*,*N*-dimethylpyridin-4-amine 4-methylbenzenesulfonate (DPTS, 1.475 g, 5.000 mmol) were added to the above solution. Then the suspension was reacted at room temperature for 20 h. The mixture was filtered off the undissolved solid and precipitated into iced hexane (200 mL) for three times. The crude product was dried under vacuum at room temperature and finally

a yellow crystal was obtained. Yield: ~ 59%.The $^{1}$H NMR spectrum is presented in Fig. S1.

### 3.2 Synthesis of 3-acrylamidophenylboronic acid (AAPBA)

AAPBA was prepared using a previous method.[3] 3-Aminophenylboronic acid monohydrate (5.00 g, 32.2 mmol) and mixed solution (v/v, 2:1) of water and tetrahydrofuran (THF) (45 mL) were added to a flask. When all the 3-acrylamidophenylboronic acid monohydrate was dissolved, sodium bicarbonate (5.00 g, 59.5 mmol) was added and then the mixture was cooled in an ice bath. Acryloyl chloride (5.00 mL, 62.5 mmol) was added dropwise into the mixture solution with stirring over a period of 1 h. The mixture was reacted for another 2 h at room temperature. The resultant solution was washed with acetic ether and the organic phase was concentrated to obtain a dry crude product. The crude product was recrystallized from 100 mL of hot water (90 ºC). The resulting crystals were filtered and dried under vacuum. Yield: ~ 71%. The $^{1}$H NMR spectrum is shown in Fig. S2.

### 3.3 Synthesis of 7-(2-hydroxyethoxy)-4-methylcoumarin (HEMC)

7-Hydroxy-4-methylcoumarin (5.00 g, 0.0300 mol) was dissolved in acetone (250 mL). $K_2CO_3$ (21.14 g, 0.1500 mol) and 2-bromoethanol (17.92 g, 0.1400 mol) were added under stirring. Then the mixture solution was reacted at 60 ºC under protection for 48 h. The reaction mixture was filtered off the undissolved salt and concentrated to obtain a yellow solid. Then the yellow solid was dissolved in DCM (250 mL) and washed with 1.0 M NaOH (2 × 250 mL) and DI water (250 mL). The organic phase was dried over

anhydrous $MgSO_4$ and concentrated to obtain a white solid. Subsequently, the crude product was recrystallized from 100 mL of ethanol. The resulting crystals were filtered and dried under vacuum. Yield: ~ 80%. The $^1H$ NMR spectrum is shown in Fig. S3.

### 3.4 Synthesis of 7-(2-methacryloyloxyethoxy)-4-methylcoumarin (CMA)

7-(2-Hydroxyethoxy)-4-methylcoumarin (2.00 g, 9.08 mmol) and TEA (2.220 g, 21.94 mmol) were dissolved in anhydrous THF (150 mL) in an ice bath. Methacryloyl chloride (1.200 g, 11.48 mmol) was dissolved in anhydrous THF (25 mL) and added dropwise to the above solution over a period of 1 h. Then the reaction was performed at room temperature with stirring for 36 h. The mixture was filtered off the undissolved TEA·HCl salt and evaporated to remove THF. The obtained solid was re-dissolved in DCM (100 mL) and washed with DI water (200 mL), saturated brine (200 mL) successively. The organic phase was dried over anhydrous $MgSO_4$ and evaporated to obtain a yellowish solid. Further purification was carried out with column chromatography (*n*-hexane/EtOAc, 4:1) to obtain the 7-(2-methacryloyloxyethoxy)-4-methylcoumarin monomer. Yield: ~ 50%. The $^1H$ NMR spectrum is presented in Fig. S4.

### 3.5 Synthesis of *N*-acryloyl glucosamine (AGA)

Sodium carbonate (8.48 g, 0.0800 mol), sodium bicarbonate (6.72 g, 0.0790 mol) and glucosamine hydrochloride (17.4 g, 0.0800 mol) were dissolved in DI water (40 mL) in an ice bath. Acryloyl chloride (8.00 g, 0.088 mol) was added dropwise to the above solution under stirring within 30 minutes. Then the mixture was reacted in an ice bath

for 2 h and then at room temperature for 1 day. The resulting solution was filtered to remove the undissolved salt and concentrated to 3.0 mL. Purification with column chromatography (methanol/EtOAc, 1:4) to yield a yellow crystal. Yield: ~35%. The $^{1}$H NMR spectrum is shown in Fig. S5.

### 3.6 Synthesis of PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA) by RAFT polymerization

PEO-DDMAT (115 mg, 0.0500 mmol), CMA (295.0 mg, 1.024 mmol), AAPBA (774.0 mg, 1.013 mmol), AIBN (2.2 mg, 0.010 mmol) were dissolved in dimethyl sulfoxide (5.00 mL) in a 25 mL flask. Then AGA (181 mg, 0.776 mmol) and DI water (1.0 mL) were added to the flask. When all the AGA was dissolved, the mixture was flushed with argon for 30 minutes for deoxygenation. The flask was then sealed and polymerized in an oil bath at 70 ºC. After 24 h of polymerization, the mixture was dialyzed against DI water for 48 h to eliminate the unreacted monomer and organic solvent. The dialyzed solution was freeze-dried to obtain purified polymer PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA). Yield: ~40%. The $^{1}$H NMR spectrum is presented in Fig. S6.

### 3.7 Self-assembly of PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA)

PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA) (10.0 mg) was dissolved in DMSO (5.0 mL) to give an initial concentration of 2.0 mg mL$^{-1}$. Then DI water (15 mL) was added dropwise to the above solution through a peristaltic pump under vigorous stirring to form glycopolymersomes. The resulting solution was dialyzed against DI water (5 × 1000 mL) to remove DMSO. When dialysis finished, the PEO-*b*-P(CMA-*stat*-AAPBA-

*stat*-AGA) glycopolymersome solution (0.45 mg $mL^{-1}$) was characterized by DLS to determine the hydrodynamic diameter and polydispersity.

### 3.8 Photo-cross-linking of glycopolymersomes

The PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA) glycopolymersome solution (0.45 mg $mL^{-1}$) was placed under a UV-vis spot curing system (8000 mW $cm^{-2}$) at a λ of 365 nm for 6 minutes to immobilize the structure. Monitored by a UV-vis spectrometer, the cross-linking degree of polymersomes can be calculated from the change of UV absorbance at 330 nm defined as 1 - $A_t/A_0$ according to Fig. S8 A-B (Where $A_0$ is the initial absorbance at 330 nm and $A_t$ is the absorbance when the cross-linking process finished).

### 3.9 Glucose-responsiveness of glycopolymersomes

Glucose solution (1000 mg $dL^{-1}$) was added to 1.0 mL of glycopolymersomes (0.45 mg $mL^{-1}$) to give various glucose concentrations: 25, 50, 75, 100, 125, 150, 260 mg $dL^{-1}$. The sizes of glycopolymersomes at different glucose concentrations were measured by DLS.

### 3.10 Maximum extent of glucose binding of glycopolymersomes

Glucose solution (1000 mg $dL^{-1}$) was added to 1.0 mL of glycopolymersomes (0.45 mg $mL^{-1}$) to give various glucose concentrations: 300, 350, 360, 370, 380, 390, 400, 450, 500 mg $dL^{-1}$. Then the sizes of glycopolymersomes at different glucose concentrations were measured by DLS.

### 3.11 Reversible glucose-responsiveness of glycopolymersomes

Glycopolymersomes solution (0.45 mg $mL^{-1}$) was treated with 150 mg $dL^{-1}$ glucose solution followed with dialysis against DI water (4 × 500 mL). Subsequently, the glycopolymersomes solution after dialysis were further exposed to 150 mg $dL^{-1}$ glucose solution. DLS was employed to measure the hydrodynamic diameter and polydispersity of the glycopolymersomes.

### 3.12 *In vitro* responsive glucose release of glycopolymersomes

The glucose release process was carried out by the following procedures: 1.0 mL of glycopolymersome solution ($c_{\text{polymersome}}$ = 0.45 mg $mL^{-1}$ in $c_{\text{glucose}}$ = 150 mg $dL^{-1}$ solution) and pure glucose (as control) was dialyzed in the dialysis tube (cutoff $M_n$ = 8000-14000) against 2.0 mL of pure water or various concentrations of glucose solution ($c_{\text{ini}}$ = 0, 50, 100 mg $dL^{-1}$) in a centrifuge tube in the constant temperature vibrator at 37 °C with a speed of 140 rpm. During the measurement the volume of the dialysis media was ensured to be 2.0 mL. At desired time intervals (15 min, 30 min, 1 h, 2 h, 8 h, 21 h), 5.0 μL of dialysis media were withdrawn and incubated with glucose kit for UV-vis spectroscopy study (553 nm) to obtain the concentration of glucose in the dialysis media ($c_{\text{media}}$). Each group was carried out for three times.

The cumulative glucose release was calculated by the following equation: $Cumulative\ \ glucose\ \ release = \frac{(C_{media} - C_{ini}) \times 2.0}{1.5} \times 100\%$

### 3.13 *In vitro* responsive glucose uptake of glycopolymersomes

The glucose uptake process was carried out by the following procedures: 1.0 mL of glycopolymersomes ($c_{\text{polymersome}}$ = 0.45 mg mL$^{-1}$ in pure water), glucose-loaded glycopolymersomes ($c_{\text{polymersome}}$ = 0.45 mg mL$^{-1}$ in $c_{\text{glucose}}$ = 150 mg dL$^{-1}$ solution), pure water (as control) and pure glucose (as control) were dialyzed in the dialysis tube (cutoff $M_n$ = 8000-14000) against 2.0 mL of various concentrations of glucose solutions ($c_{\text{ini}}$ = 200, 300, 400 mg dL$^{-1}$) in a centrifuge tube in the constant temperature vibrator at 37 °C with a speed of 140 rpm. During the measurement the volume of dialysis media was ensured to be 2.0 mL. At desired time intervals (15 min, 30 min, 1 h, 2 h, 8 h, 21 h), 5 μL of dialysis media were withdrawn and incubated with glucose kit for UV-vis spectroscopy study (553 nm) to obtain $c_{\text{media}}$. Each group was carried out for three times.

The cumulative glucose uptake was calculated by the following equation:

$$m_{uptake}(\text{mg}) = (c_{ini} - c_{media}) \times 2.0$$

### 3.14 Cytotoxicity tests

The cytotoxicity of PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA) glycopolymersome against human normal liver cells (L02) was tested by measuring the inhibition of cell growth using the Cell Counting Kit-8 (CCK-8) assay, whereby dehydrogenase activities were determined via the reduction of WST-8 (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium sodium salt) to a yellow product (formazan). The amount of the formazan dye generated by the activity of

dehydrogenases in cells is directly proportional to the number of living cells. L02 cells were treated with glycopolymersome at various concentrations from 31.25 μg $mL^{-1}$ to 400 μg $mL^{-1}$. At the beginning, L02 cells were seeded with equal density in each well of 96-well plate (4000 cells/well) in 100 μL of Dulbecco's Modified Eagle medium (DMEM) supplemented with 10 % fetal bovine serum (FBS) for 24 h at 37 ºC in a humidified 5% $CO_2$-containing atmosphere. Then 20 μL of glycopolymersomes at various concentrations were added and incubated with cells for another 48 h. Untreated cells served as a control group. Finally, CCK-8 dye was added to each well, and the plates were incubated for another 1 h at 37 ºC. The absorbance was measured by dual wavelength spectrophotometry at 450 nm and 630 nm using a microplate reader. Each treatment was repeated five times. The relative cell viability (%) was determined by comparing absorbance at 450 nm with control wells containing only cell culture medium.

### 3.15 *In vitro* stability of glycopolymersomes in PBS

Glycopolymersomes was incubated in phosphate buffered saline (PBS; 0.01 M at pH 7.4). At desired intervals (12 h, 24 h, 36 h, 48 h, 60 h, 72 h and 15 months), the hydrodynamic diameter and polydispersity were evaluated by DLS.

### 3.16 *In vivo* antidiabetic results

***Declaration for use of animals.*** We declare that we complied with guidelines for use of animals in bioscience research of China. All ethical considerations have been undertaken to appropriate standards for China. Research involving scientific process

which may bring mice about pain, suffering, distress or lasting harm followed the provisions of Regulations for the Administration of Affairs Concerning Experimental Animals (Approved by the China State Council on October 31, 1988 and amended on March 1, 2017). Besides, all the animal experiments were approved by the Laboratory Animal Ethics Committee of Shanghai Tenth People's Hospital. We used the simplest and the least conscious species of animals to conduct these experiments and made the utmost efforts to avoid the distress and pain. Furthermore, on the basis of ensuring repeatability of treatments within error, we employed an appropriate experimental design and used the minimum number of animals.

***Diabetes model.*** To develop the Type 2 diabetes model, firstly streptozocin (STZ; dissolved in 0.1 M citrate buffer solution, 10 mg $mL^{-1}$) were injected intraperitoneally into 20 male KM mice of 8 weeks with a dose of 50 mg $kg^{-1}$ after fasting 12 h but allowing free access to water for three times every other day. Each time after injection the mice were fed with high-sugar and high-fat diet. Then after all of the injection finished, the mice were continually raising with high-sugar and high-fat diet. One week later, the weight and the blood glucose level were measured. Mice with a blood glucose level between 324 and 468 mg $dL^{-1}$ were considered to be diabetic.

***Treatment.*** The diabetic mice were randomly divided into two groups, 6 for each group. The mice of the experimental group were treated with glycopolymersome (0.45 mg $mL^{-1}$, in 0.01 M PBS buffer) while the mice of the control group were treated with PBS buffer (0.01 M at pH 7.4) *via* tail vein injection with the same dose of 4.0 mg $kg^{-}$

[1]. To measure the blood glucose level, the blood was drawn from the mice tail. The blood glucose levels were tested at 0, 2, 6, 10, 19, 27, 47, 72 h after the tail vein injection. Each time before the measurement the mice were fasted with food for 2 h but access to water.

***Procedures for monitoring glucose levels.*** A glucose estimation kit (Applygen Technologies Inc., Beijing, China) accompanied with an Epoch2 Microplate Spectrophotometer (BioTek Instruments, Inc., USA) was used to test the blood glucose levels. Firstly, the working solution was prepared by mixing Regent 1 (R1) and Regent 2 (R2) of the kit (R1:R2 = 4:1). Then, 195 μL of working solution was mixed with 5 μL of the following solutions: (1) DI water (blank sample); (2) glucose standard solution (10 mM); or (3) blood samples. After incubating for 20 min at 37 °C, the optical density (OD) at 553 nm of wavelength was measured by the Spectrophotometer. The blood glucose levels were calculated using the following equation (where C represents the concentration):

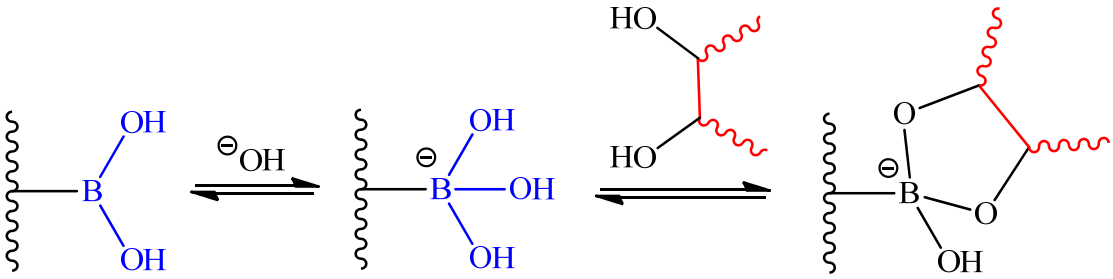
$$\text{Glucose level (mM)} = C_2 \times \frac{OD_3 - OD_1}{OD_2 - OD_1}$$

***Intraperitoneal glucose tolerance test (IPGTT).*** db/db mice were received a single SC injection of glycopolymersomes or equivalent volume PBS. At 10 h post-injection, mice were fasted for 6 h and then challenged with an intraperitoneal (IP) injection of 1.00 g $kg^{-1}$ 10 w/v% sterile glucose. At 16 h post-injection, the blood glucose levels were measured at 0, 10, 20, 40, 60, 90, 120 min after glucose administration.

***Statistical analysis.*** Data are expressed as means ± SD. Comparisons were performed

via one-way analysis of variance (ANOVA) for multiple groups using Microsoft Excel.

# 4. Discussions, tables, figures and schemes




Scheme S1. Mechanism of dynamic interaction between boric acid (e.g., AAPBA) and cis-diol compounds (e.g., glucose).

### 4.1 Calculation procedures of $^1$H NMR spectrum

The procedures for determining the compositions of PEO-*b*-P(CMA-*stat*-AAPBA-*stat*-AGA) diblock copolymer are listed below:

**Table S1. Integral areas and calculation of degrees of polymerization**

| Polymer | $A_j$ | $A_k$ | $A_{n+s+f+f'}$ | $A_r$ | $x$ | $y$ | $z$ |
|---|---|---|---|---|---|---|---|
| PEO-*b*-P(CMA$_x$-*stat*-AAPBA$_y$-*stat*-AGA$_z$) | 6 | 10 | 50 | 168 | 6 | 10 | 6 |

In table S1, $A_j$, $A_k$, $A_{n+s+f+f'}$, $A_r$ are the integral areas of peaks j (CMA pendent group, $x$ H), k (AAPBA pendent group, $y$ H), n (AGA pendent group, 4$z$ H), s (PEO-DDDMAT pendent group, 2 H), f + f' (CMA pendent group, 2$x$ H), r (PEO block, 168 H) in **Table S1**.

The integral area of peak r is set to be 168 as the internal reference, which corresponds to the amount of H in PEO block. Then the value of $x$, $y$, $z$ is obtained as following process according to the integral areas of peak j, k, n listed in **Table S1**.

$$x = \frac{A_j}{A_b} \times \frac{168}{1} \approx 6$$

$$y = \frac{A_k}{A_b} \times \frac{168}{1} \approx 10$$

$$z = (\frac{A_{n+s+f+f'}}{A_b} \times \frac{168}{1} - 2 - 4 \times 6)/4 \approx 6$$

**4.2 SEC analysis of $PEO_{43}$-*b*-P($CMA_6$-*stat*-$AAPBA_{10}$-*stat*-$AGA_6$) glycopolymer**

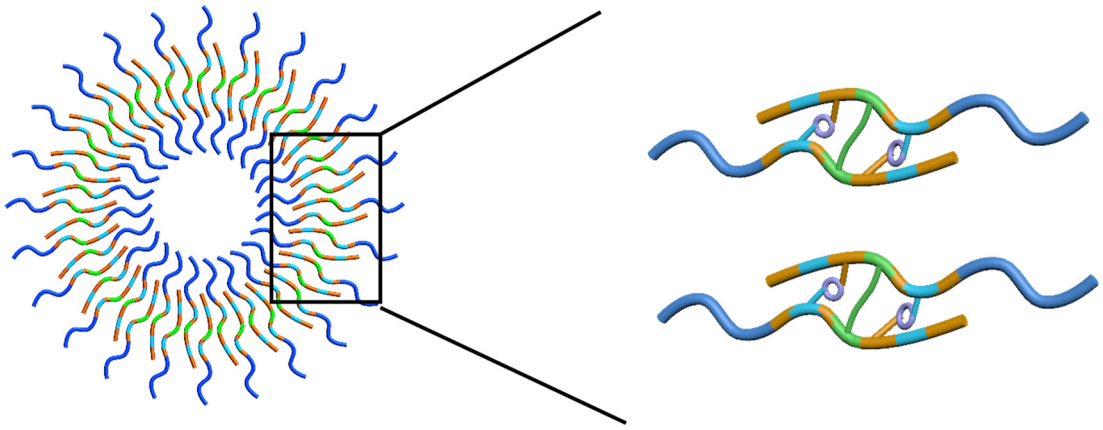
It is difficult to determine the molecular weight and molecular weight distribution of this copolymer by SEC as there are no suitable solvents for this copolymer except DMSO as used in $^1$H NMR analysis. After trying different solvents, we found that DMF is a relatively good choice for the SEC analysis. However, it should be pointed out that the DMF SEC data are only for reference not for evidence, compared with other polymers which can be completely dissolved in the SEC solvents.

In the first SEC measurement performed at 40 ºC in DMF, the $M_n$ was 117980 and the $Đ$ was 1.07, showing a narrow molecular weight distribution but much higher molecular weight (Fig. S7A) than that determined by $^1$H NMR (7340 Da, Fig. S6). The higher $M_n$ of the glycopolymer was due to the weak aggregation and the binding effects of AAPBA and AGA, which formed an inter-cross-linking interaction between the glycopolymers.

Furthermore, the sample was tested at 80 ºC in DMF, affording an $M_n$ of 14167 and a $Đ$ of 2.24, as shown in Fig. S7B. During the experimental process, it was found that the sample of the glycopolymer tended to be denatured including being insoluble or discolored at higher temperatures, which may be responsible for the apparent $Đ$ of 2.24. Based on the measurements at two temperatures, we can conclude that the molecular weight determined at higher temperature is more reliable than that at lower temperature as it is closer to the theoretical value. However, the molecular weight distributions at

both 40 and 80 °C are not the real one due to the reasons mentioned above.

### 4.3 Calculation of the contour length of P(CMA$_6$-*stat*-AAPBA$_{10}$-*stat*-AGA$_6$) block in PEO$_{43}$-*b*-P(CMA$_6$-*stat*-AAPBA$_{10}$-*stat*-AGA$_6$) glycopolymer



Scheme S2. Interdigitated Membrane Structure of Glycopolymersomes.

The contour length of the P(CMA$_6$-*stat*-AAPBA$_{10}$-*stat*-AGA$_6$) block is calculated by accumulating the length of carbon-carbon covalent bonds at a specific angle (109° 28′).

$$l = l_a \times DP \times 2 \times \cos((180° - 109°28') \div 2) = 0.154\ \ nm \times 2 \times 22 \times \cos(35°16') \approx 5.51\ \ nm$$

$l_a$: the length of *C*-*C*

DP: degree of polymerization

The thickness of the glycopolymersome membrane is 6.2 nm from TEM images (Fig. S10), which is comparable to the contour length of the P(CMA$_6$-*stat*-AAPBA$_{10}$-*stat*-AGA$_6$) block, suggesting an interdigitated structure of the glycopolymersome membrane.

### 4.4 Calculation of glucose uptake by per glycopolymersome

The number of glucose molecules taken up by per glycopolymersome (vesicle) is estimated by the following equations (*ca.* $3.0 \times 10^7$) according to a modified protocol.[4]

$$N_{agg} = n_{\mathrm{P(CMA-AAPBA-AGA)}} \times N_{\mathrm{A}} = \frac{M_{\mathrm{membrane}} \times N_A}{M_{\mathrm{n,P(CMA-AAPBA-AGA)}}}$$

$$= \frac{\rho_{\mathrm{P(CMA-AAPBA-AGA)}} \times V_{\mathrm{membrane}} \times N_A}{M_{\mathrm{n,P(CMA-AAPBA-AGA)}}}$$

$$= \frac{\rho_{\mathrm{P(CMA-AAPBA-AGA)}} \times \frac{\pi}{6} \times ({D_{\mathrm{outer}}}^3 - {D_{\mathrm{inner}}}^3) \times N_A}{M_{\mathrm{n,P(CMA-AAPBA-AGA)}}} = 8.7 \times 10^4$$

$$M_{v,n} = M_n \times N_{agg} = 6.4 \times 10^8$$

$$N_v = \frac{m_v}{M_{v,n}} \times N_A = 4.24 \times 10^{11}$$

$$N_{glucose} = \frac{m_{glucose}}{M_{glucose}} \times N_A = 1.27 \times 10^{19}$$

$$N_{uptake} = \frac{N_{glucose}}{N_v} = 3.0 \times 10^7$$

$N_{\mathrm{agg}}$: mean vesicle aggregation number;

$n_{\mathrm{P(CMA-AAPBA-AGA)}}$: Number of moles of $PEO_{43}$-*b*-P($CMA_6$-*stat*-$AAPBA_{10}$-*stat*-$AGA_6$) chains in one vesicle;

$N_A$: Avogadro's constant ($6.02\times10^{23}$);

$M_{\mathrm{membrane}}$: mass of one vesicle membrane;

$M_{\mathrm{n,\ P(CMA-AAPBA-AGA)}}$: number-average molecular weight of P($CMA_6$-*stat*-$AAPBA_{10}$-*stat*-$AGA_6$) block ($^1$H NMR; 5039);

$\rho_{\mathrm{P(CMA-AAPBA-AGA)}}$: density of P($CMA_6$-*stat*-$AAPBA_{10}$-*stat*-$AGA_6$) block (~$1.1\times10^{-21}$ g $nm^{-3}$);

$V_{\mathrm{membrane}}$: volume of the vesicle membrane;

$D_{\mathrm{outer}}$: the diameter of vesicle (TEM; 268 nm);

$D_{\mathrm{inner}}$: the diameter of the inner sphere (TEM; 262 nm);

$M_{v,n}$: number-average molar mass of one vesicle;

$M_n$: number-average molecular weight of one copolymer chain ($^1$H NMR; 7342);

$N_v$: number of vesicles in 1 mL of solution ($c_{vesicles}$ = 0.45 mg mL$^{-1}$)

$m_v$: mass of copolymer in 1 mL solution (0.45 mg)

$N_{glucose}$: number of glucose molecules in 1 mL solution ($c_{glucose}$ =3.8 mg mL$^{-1}$, maximum extent of glucose binding of glycopolymersomes)

$m_{glucose}$: mass of glucose in 1 mL solution (3.8 mg)

$N_{uptake}$: number of glucose taken up by per vesicle

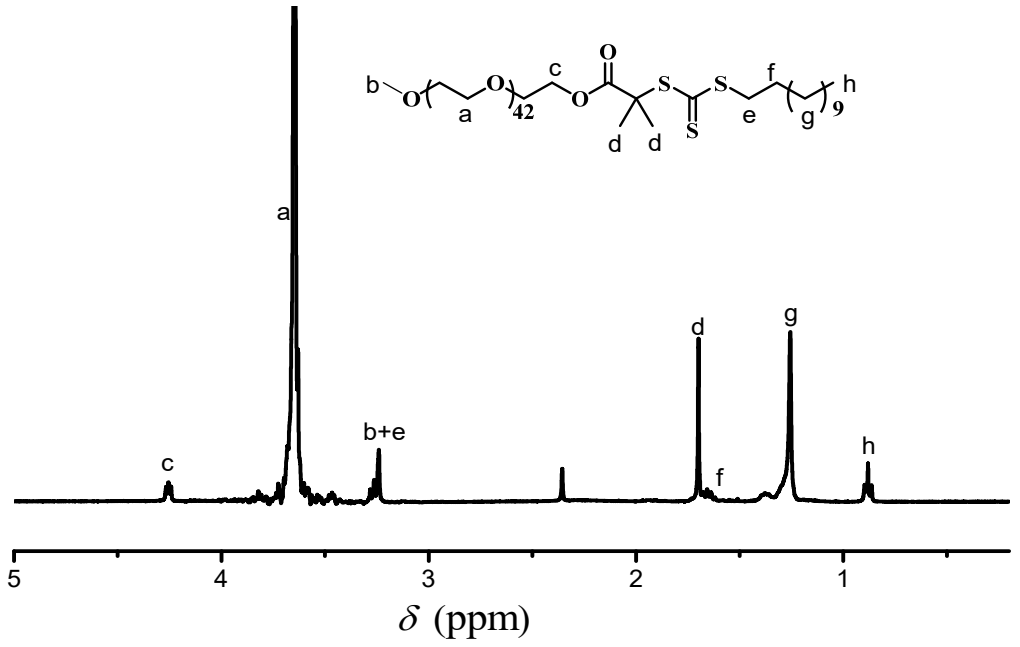



Fig. S1. $^1$H NMR spectrum of PEO-DDMAT macro-CTA in $CDCl_3$.

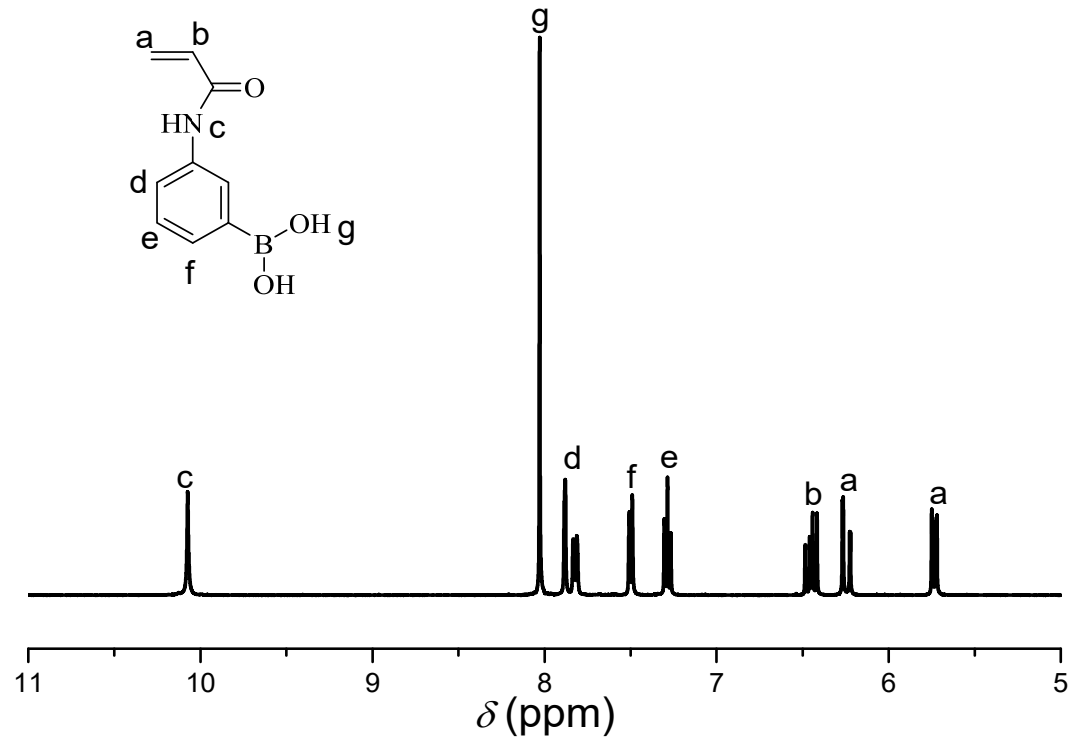



Fig. S2. $^{1}$H NMR spectrum of AAPBA in DMSO-$d_6$.

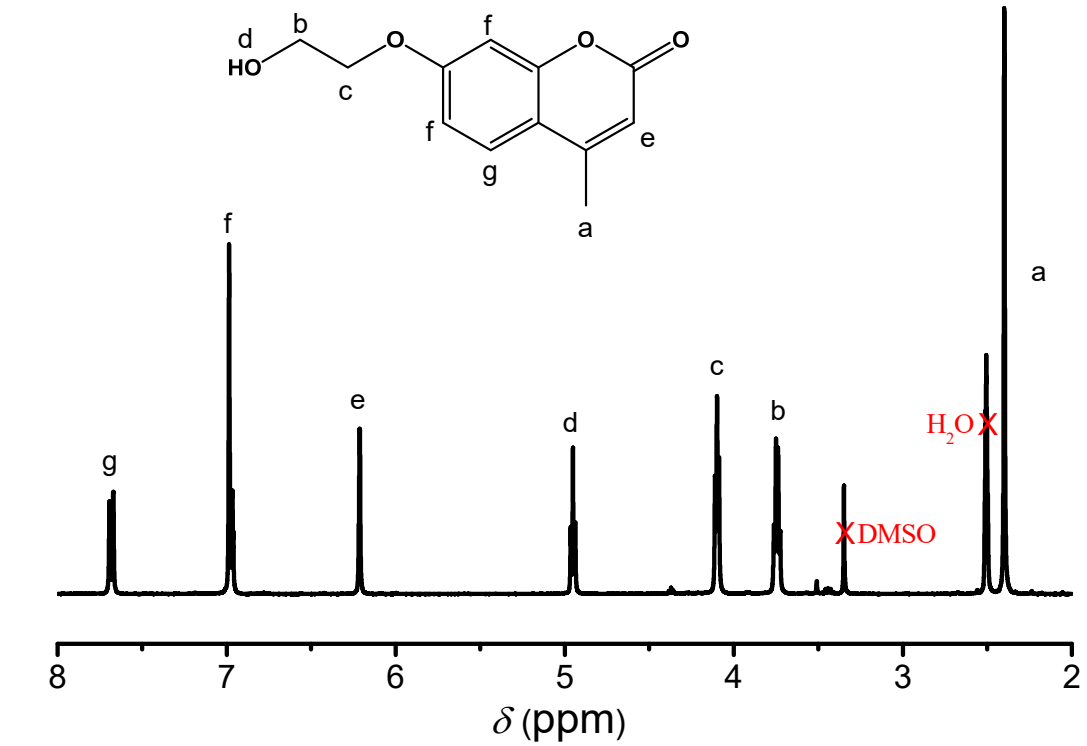



Fig. S3. $^{1}$H NMR spectrum of HEMC in DMSO-$d_6$.

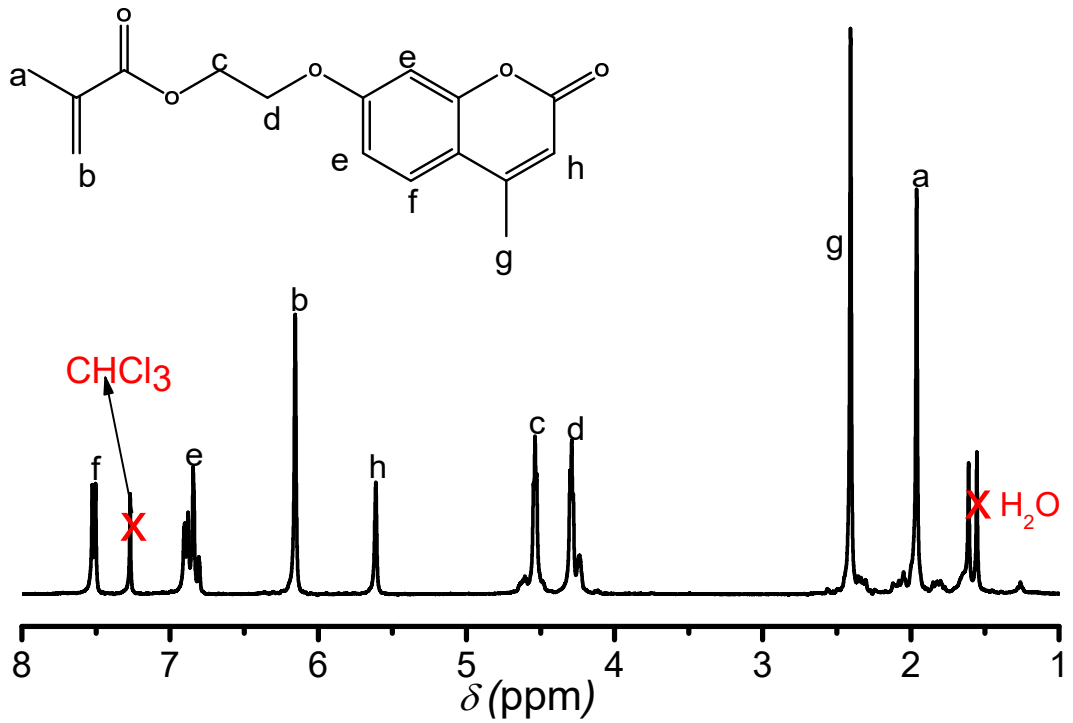



Fig. S4. $^{1}H$ NMR spectrum of CMA in $CDCl_3$.

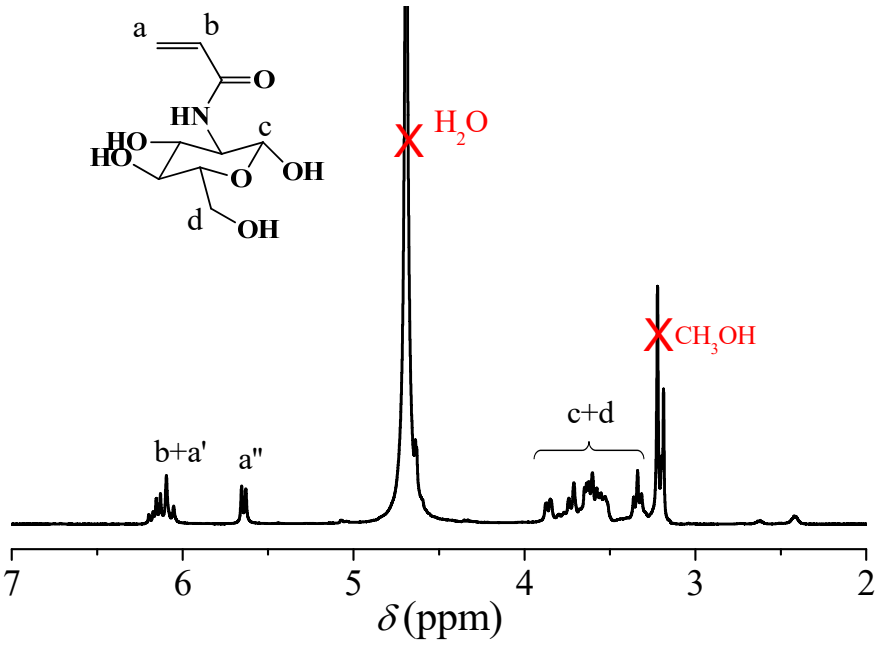



Fig. S5. $^{1}H$ NMR spectrum of AGA in $D_2O$.

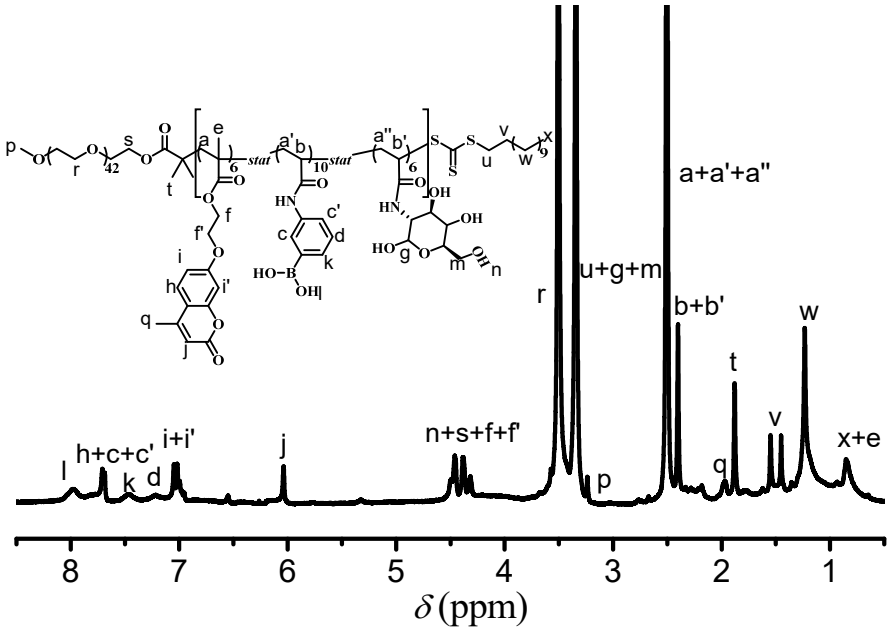



Fig. S6. $^{1}$H NMR spectrum of PEO$_{43}$-*b*-P(CMA$_{6}$-*stat*-AAPBA$_{10}$-*stat*-AGA$_{6}$) glycopolymer in DMSO-*d*$_{6}$.

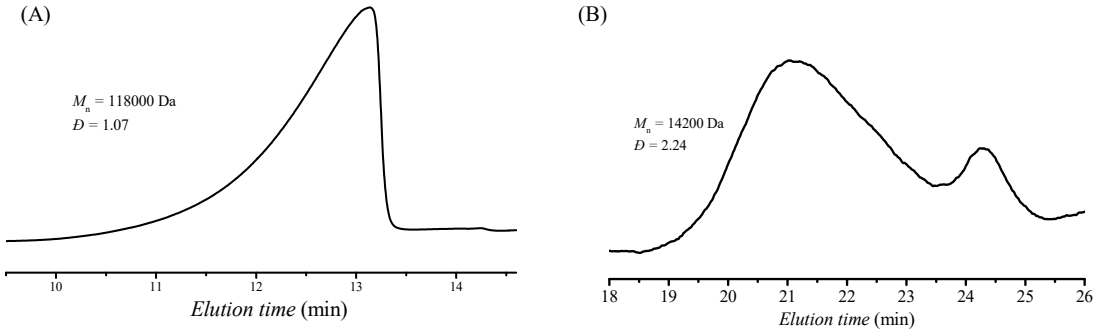



Fig. S7. Apparent SEC analysis of PEO$_{43}$-*b*-P(CMA$_{6}$-*stat*-AAPBA$_{10}$-*stat*-AGA$_{6}$) glycopolymer in DMF. (A) 40 °C; (B) 80 °C. The detailed analysis is presented in Section 4.2 in the ESI.

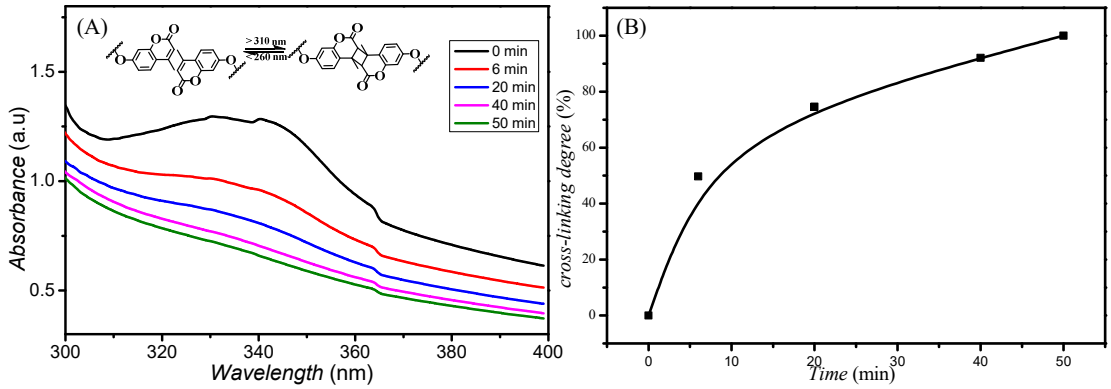



Fig. S8. (A) UV-vis spectra of photo-cross-linked glycopolymersomes with different degrees of cross-linking; (B) The relationship between the cross-linking degrees of glycopolymersomes with UV irradiation time.

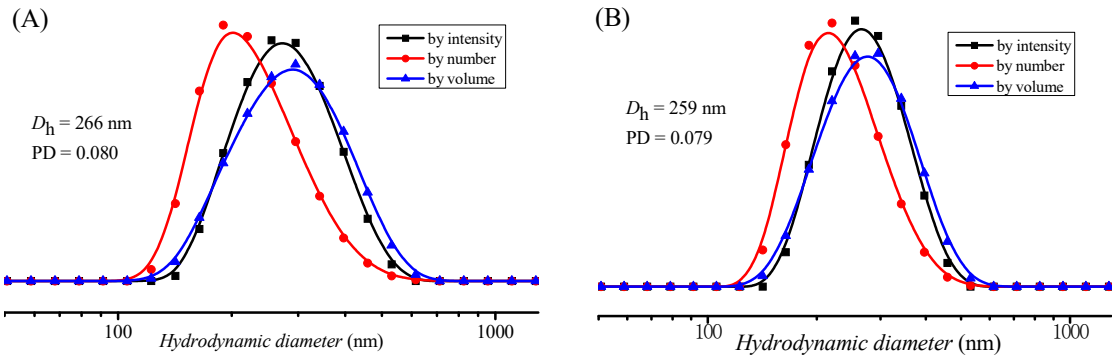



Fig. S9. DLS studies of cross-linked (A) and un-cross-linked (B) glycopolymersomes.

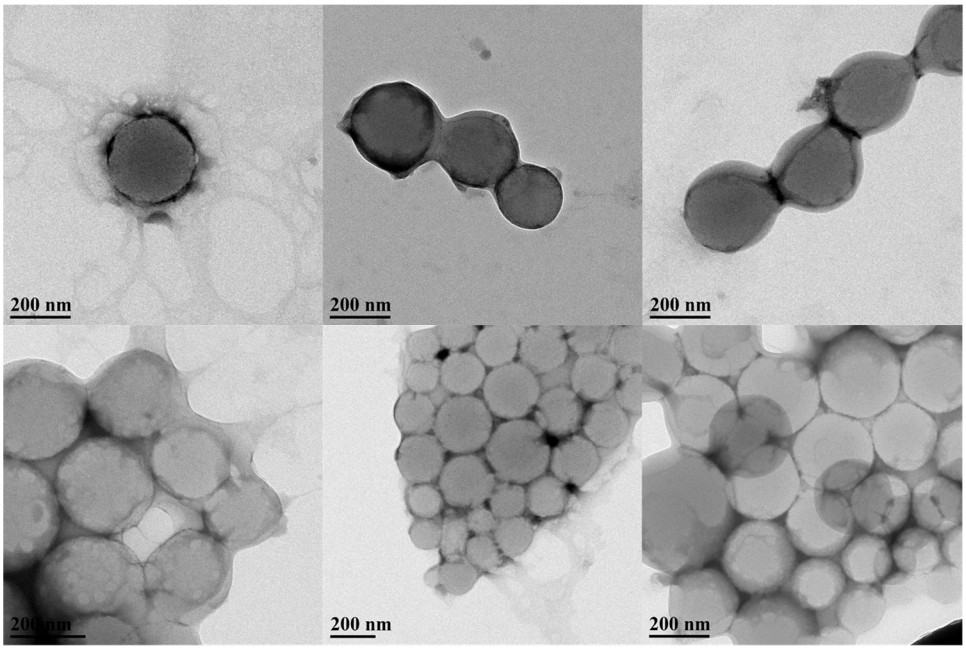



Fig. S10. TEM images of cross-linked glycopolymersomes (0.45 mg $mL^{-1}$) in the absence of glucose.

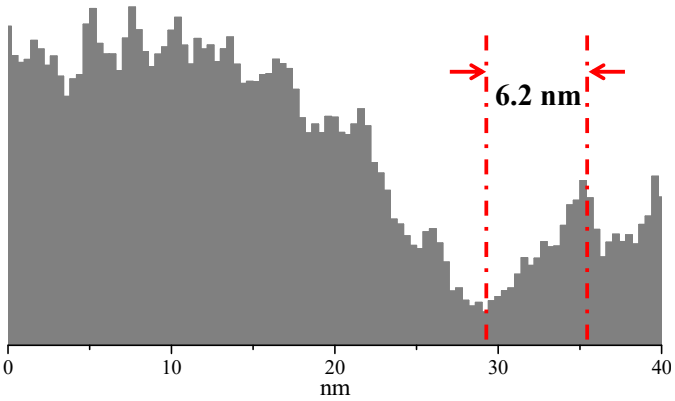



Fig. S11. The electron transmittance chart of one glycopolymersome in Fig. 1A and B (red line) in the main text, suggesting that the actual membrane thickness is the width (6.2 nm) between the first inflection point and the peak point.

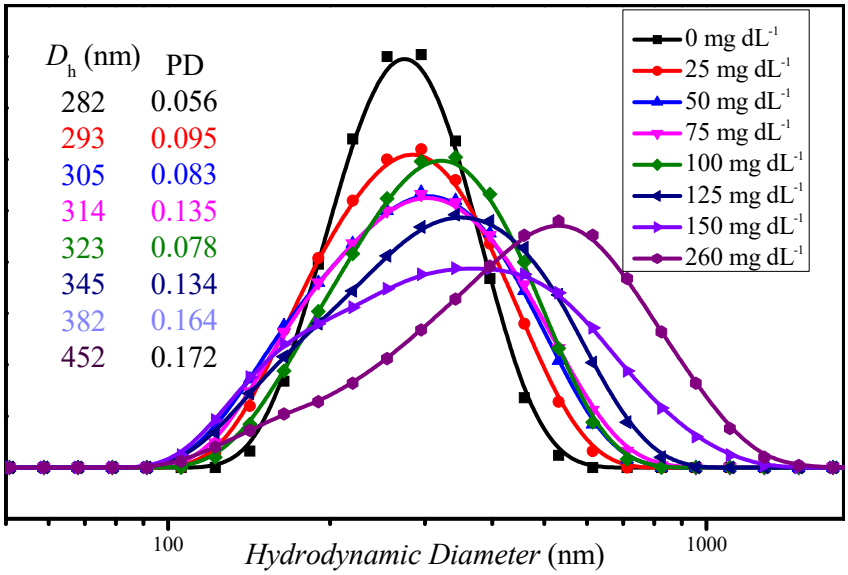



Fig. S12. DLS studies of cross-linked glycopolymersomes (0.45 mg mL$^{-1}$) at different glucose concentrations.

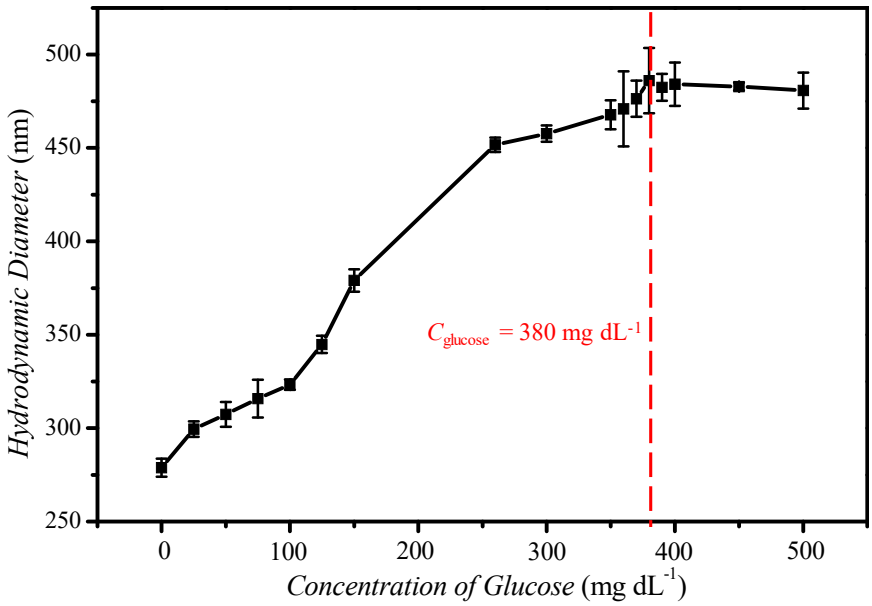



Fig. S13. The changes of hydrodynamic diameter of the cross-linked glycopolymersome treated by various concentrations of glucose solution.

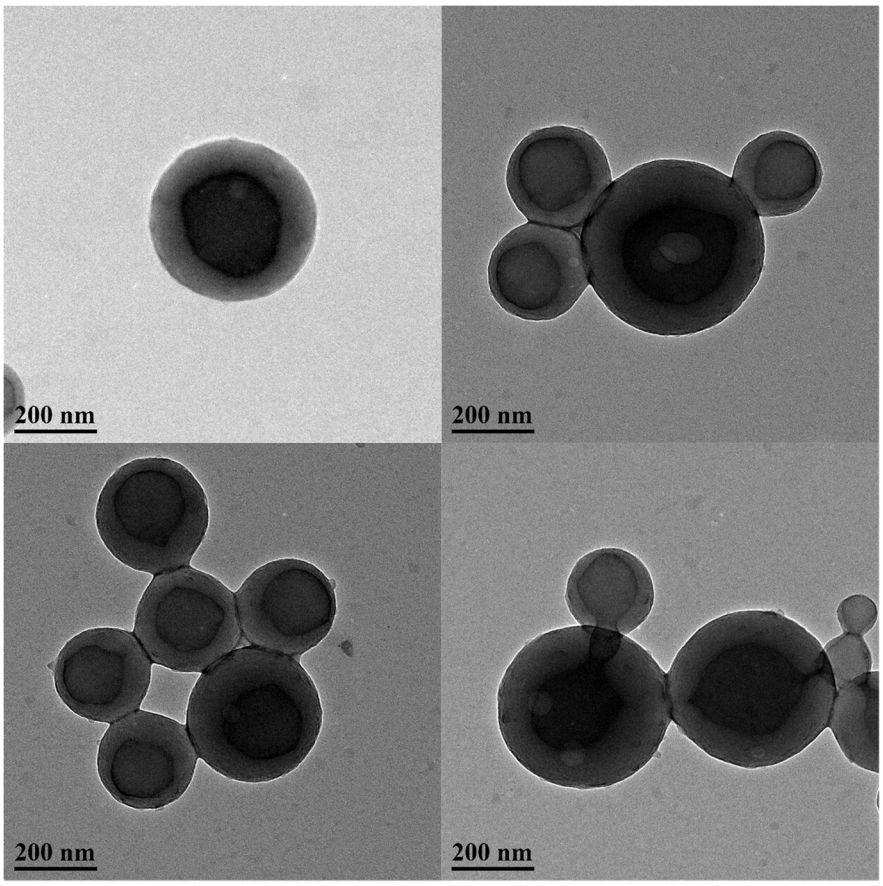



Fig. S14. TEM images of cross-linked glycopolymersomes (0.45 mg $mL^{-1}$) in the presence of glucose.

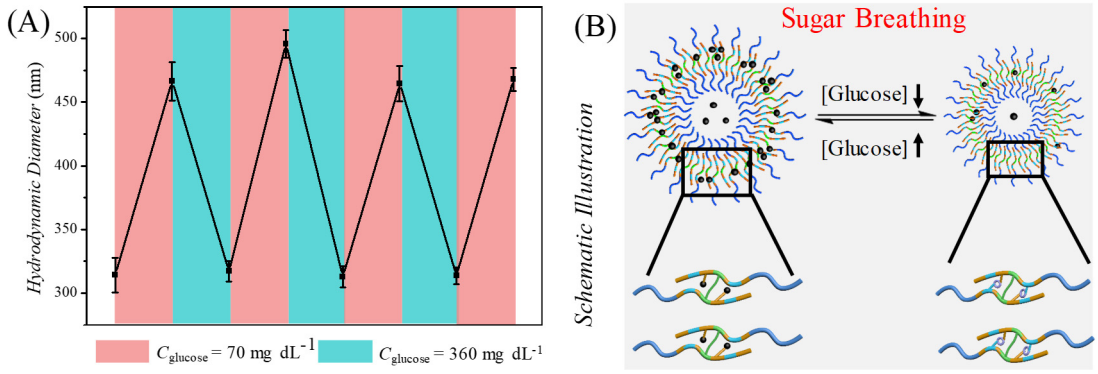



Fig. S15. (A) Reversible glucose binding study of the glycopolymersomes determined by the changes of hydrodynamic diameter when the glucose concentrations were switched between 70 and 360 mg $dL^{-1}$; (B) Corresponding schematic illustration of sugar-breathing behavior of glycopolymersomes.

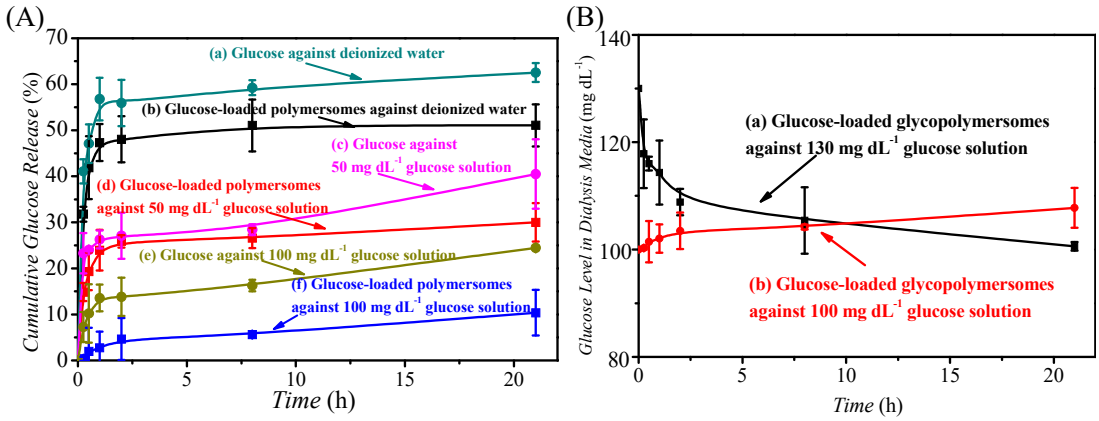



Fig. S16. (A) Cumulative glucose release curves of glycopolymersomes ($c_{polymersome}$ = 0.45 mg mL$^{-1}$ in $c_{glucose}$ = 150 mg dL$^{-1}$ solution) and pure glucose (as control) against pure water and various concentrations of glucose solution in 21 h; (B) Cumulative curves of glucose concentrations in dialysis media in 21 h. The glycopolymersomes ($c_{polymersome}$ = 0.45 mg mL$^{-1}$ in $c_{glucose}$ = 150 mg dL$^{-1}$ solution) were dialyzed against (a) 130 and (b) 100 mg dL$^{-1}$ glucose solution. The glycopolymersomes can release or absorb glucose, depending on the concentration of the glucose in the dialysis media: they release glucose to the dialysis media ($c_{glucose}$ = 100 mg dL$^{-1}$), while absorb glucose from the dialysis media ($c_{glucose}$ = 130 mg dL$^{-1}$).

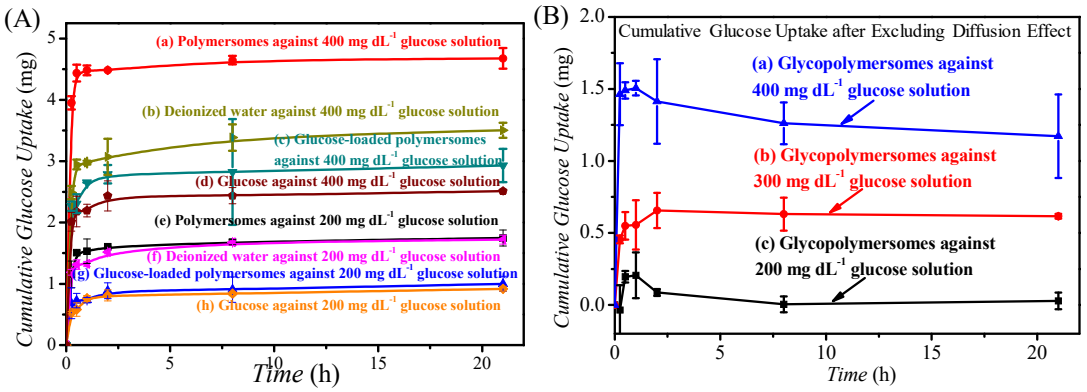



Fig. S17. (A) Cumulative glucose uptake curves of glycopolymersomes ($c_{polymersome}$ = 0.45 mg mL$^{-1}$ in pure water or $c_{glucose}$ = 150 mg dL$^{-1}$ solution) and pure water (as control) against various concentrations of glucose solution in 21 h; (B) Cumulative glucose uptake curves of glycopolymersomes ($c_{polymersome}$ = 0.45 mg mL$^{-1}$ in pure water) against various concentrations of glucose solutions after excluding diffusion effect.

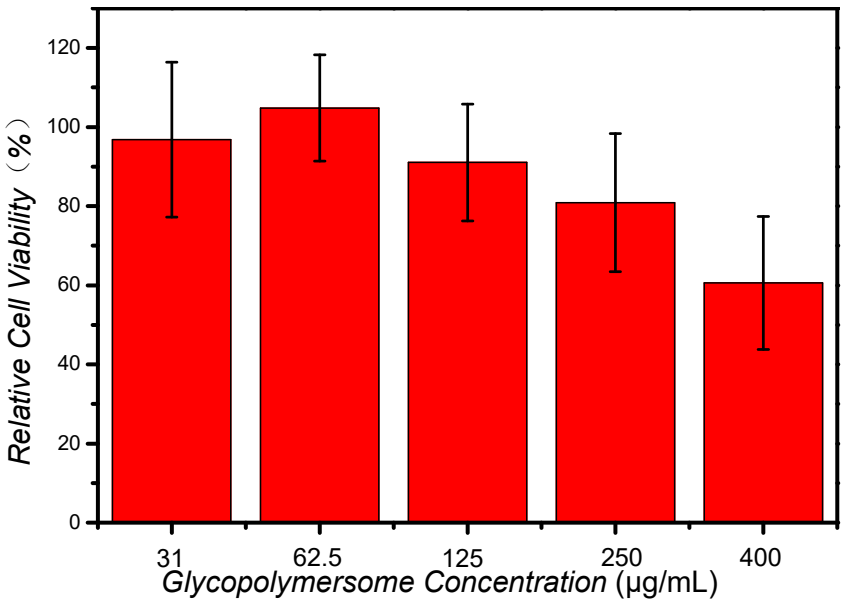



Fig. S18. Cytotoxicity study of cross-linked glycopolymersomes against normal liver L02 cells at various concentrations. L02 cells were incubated with glycopolymersomes for 48 h. The relative cell viabilities were determined by CCK-8 assay (n = 5).

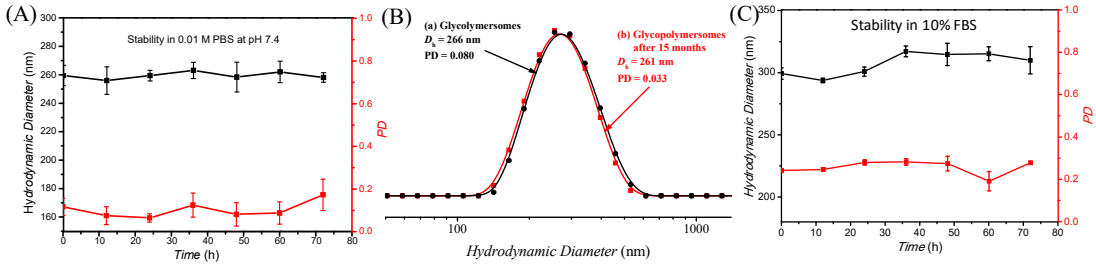



Fig. S19. *In vitro* stability of glycopolymersomes in PBS (0.01 M; pH 7.4) within 72 h (A), 15 months (B) and in 10% FBS (C).

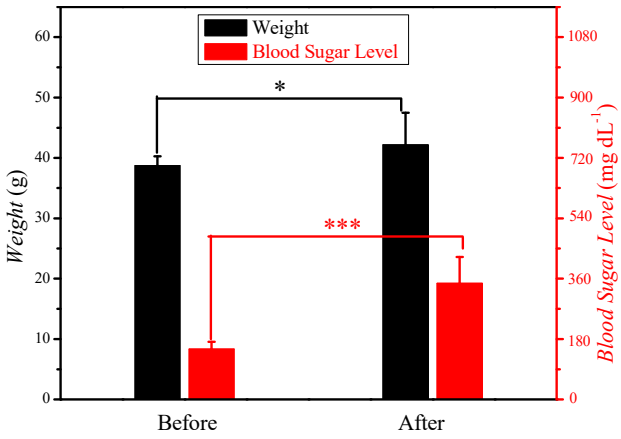



Fig. S20. Diabetes modeling: The weight and blood sugar level of mice before and after the streptozocin-induced modeling process. * $p < 0.05$, *** $p < 0.001$

# References

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