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Hydrophilic Polymer Driven Crystallization Self-assembly: Inflammation Multi-Drug Combination Nanosystem Against Alzheimer Disease

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SUPPORTING INFORMATION

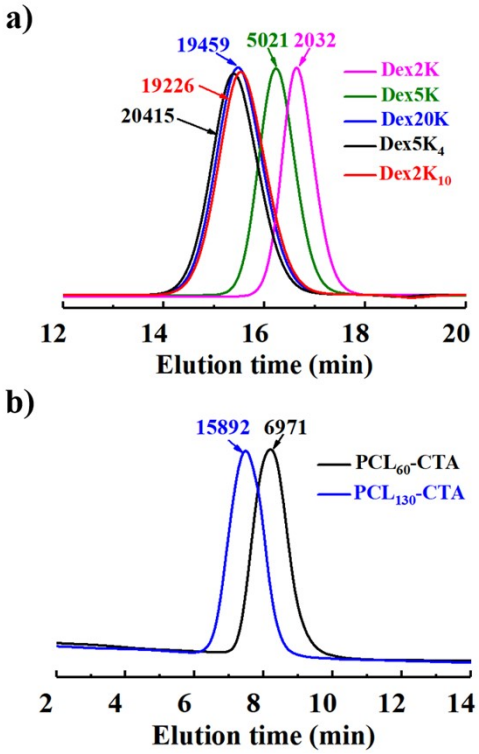

Fig. S1 GPC profiles of dextran and PCL-CTA polymers. (a) Elution time of Dex2K, Dex5K, $Dex2K_{10}$, $Dex5K_4$ and Dex20K with water as an eluent, and the flow rate was 1.0 mL/min. (b) Elution time of PCL_{60}-CTA and PCL_{130}-CTA with THF as an eluent, and the flow rate was 1.0 mL/min.

Table S1 Structural parameters of polymers.

sample	m_{PCL},[a] NMR	p_{PPBA},[b] NMR	n_{Dex},[c] NMR	M_n (g/mol),[d] NMR	M_n (g/mol),[e] GPC	PDI (M_w/M_n),[f] GPC
Dex2K	/	/	1	2000	2032	1.21
Dex5K	/	/	1	5000	5021	1.23
Dex20K	/	/	1	20000	19459	1.31
$Dex5K_4$	/	/	4	20000	20415	1.26
$Dex2K_{10}$	/	/	10	20000	19226	1.28
PCL_{60}-CTA	60	/	/	7067	6971	1.35
PCL_{130}-CTA	130	/	/	15047	15892	1.32
PCL_{60}-*b*-$PPBA_{10}$	60	10	/	8977	/	/
PCL_{130}-*b*-$PPBA_{10}$	130	10	/	16957	/	/
PCL_{130}-*b*-$PPBA_{120}$	130	120	/	37967	/	/
PCL_{130}-*g*-Dex20K	130	/	1	35047	/	/
PCL_{130}-*g*-$Dex5K_4$	130	/	4	35047	/	/
PCL_{130}-*g*-$Dex2K_{10}$	130	/	10	35047	/	/
PCL_{60}-*b*-$PPBA_{10}$-Dex20K	60	10	1	28977	/	/
PCL_{130}-*b*-$PPBA_{10}$-Dex20K	130	10	1	36957	/	/
PCL_{130}-*b*-$PPBA_{10}$-$Dex5K_4$	130	10	4	36957	/	/
PCL_{130}-*b*-$PPBA_{10}$-$Dex2K_{10}$	130	10	10	36957	/	/

[a] m: DP of PCL as determined by ^{1}H-NMR measurement. [b] p: DP of PPBA as determined by ^{1}H-NMR measurement. [c] n: DP of dextran brush as determined by ^{1}H-NMR measurement. [d] M_n: Number-average molecular weight as calculated from DPs determined by ^{1}H-NMR measurement. [e] M_n: Number-average molecular weight as determined by GPC. [f] PDI: The ratio of weight-average molecular weight to number-average molecular weight as determined by GPC.

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b)

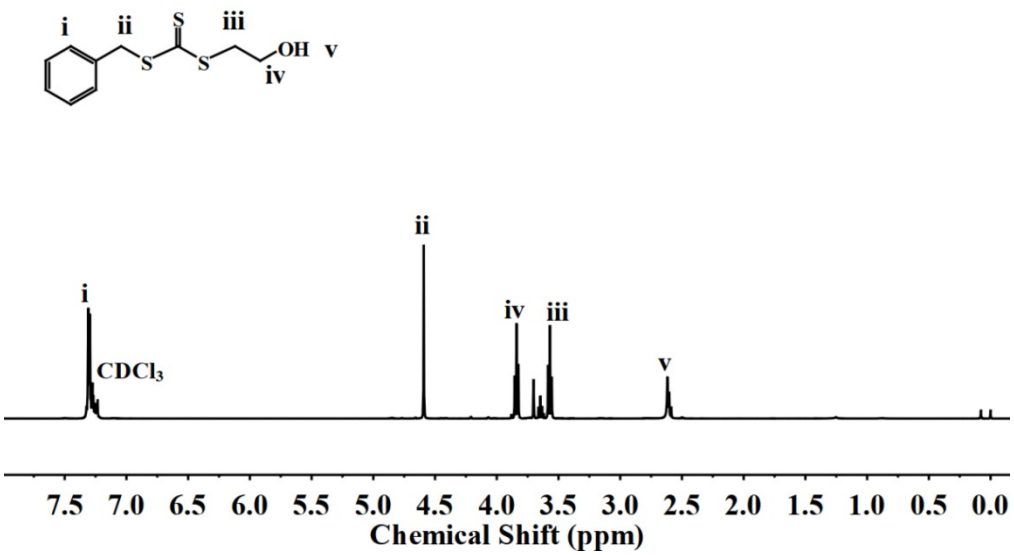

Fig. S2 Synthesis and characterization of polymers. (a) Synthesis Route of BSTSE and (b) ^{1}H-NMR spectra of BSTSE in $CDCl_3$.

b)

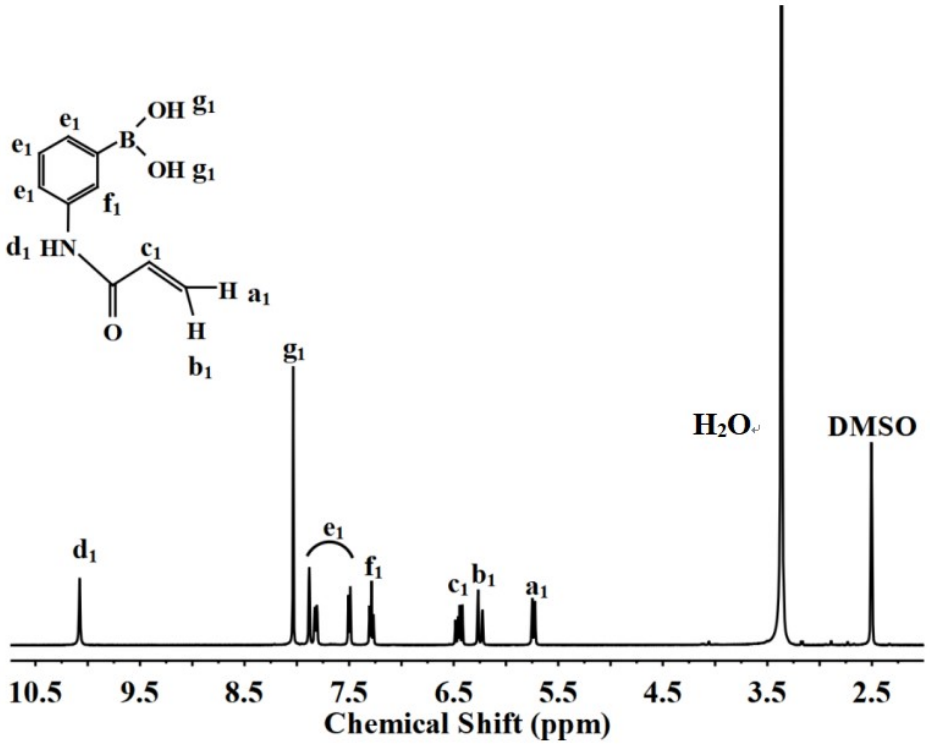

Fig. S3 Synthesis and characterization of polymers. (a) Synthesis Route of PBA and (b) ^{1}H-NMR spectra of PBA in DMSO-d_6.

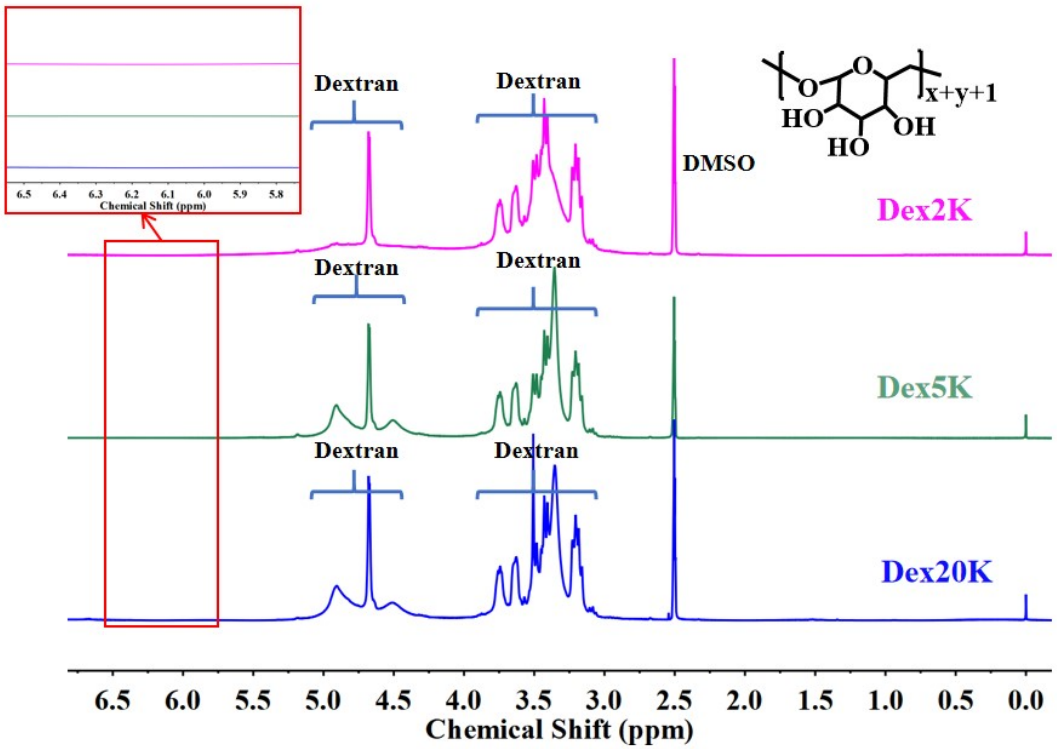

Fig. S4 ^{1}H-NMR spectra of Dex2K, Dex5K and Dex20K in DMSO-d_6.

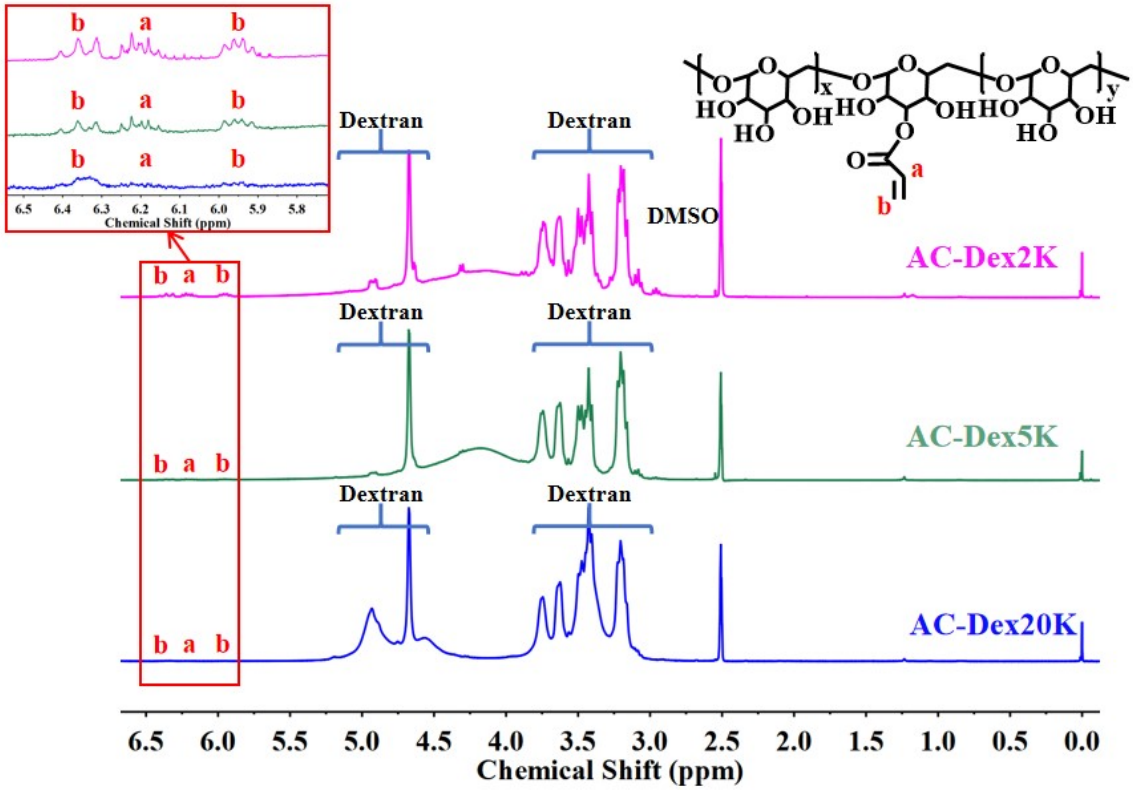

Fig. S5 ^{1}H-NMR spectra of AC-Dex2K, AC-Dex5K and AC-Dex20K in DMSO-d_6.

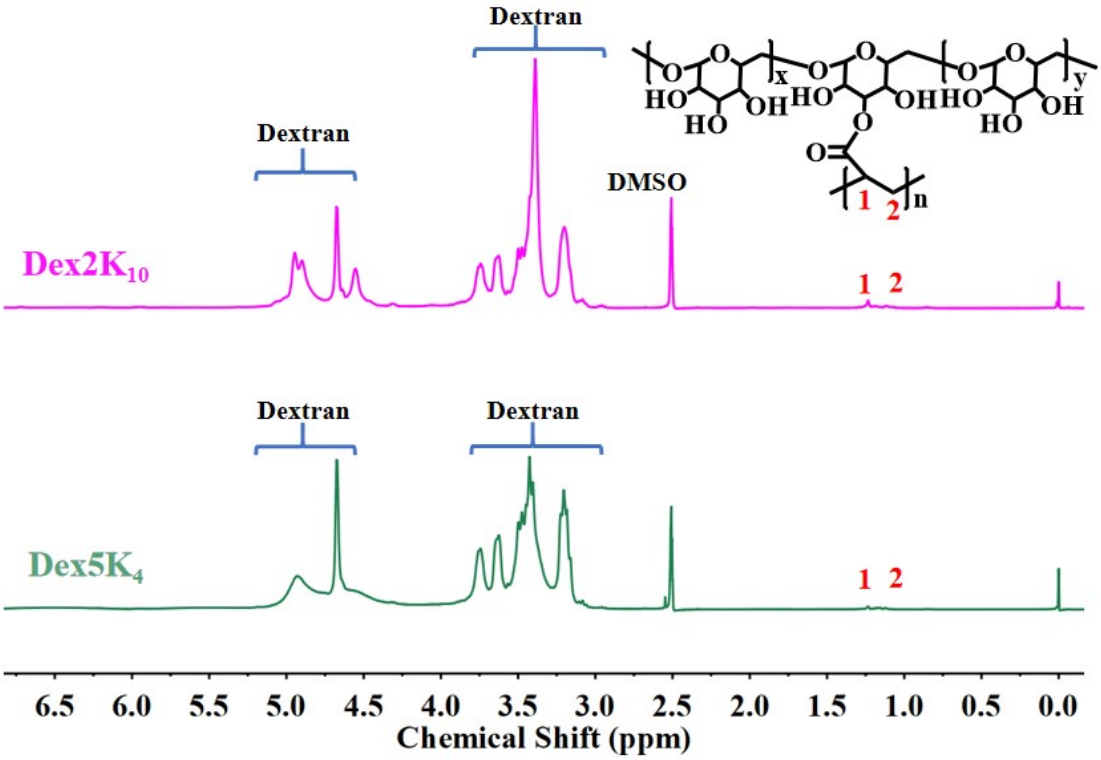

Fig. S6 ^{1}H-NMR spectra of $Dex2K_{10}$ and $Dex5K_4$ in DMSO-d_6.

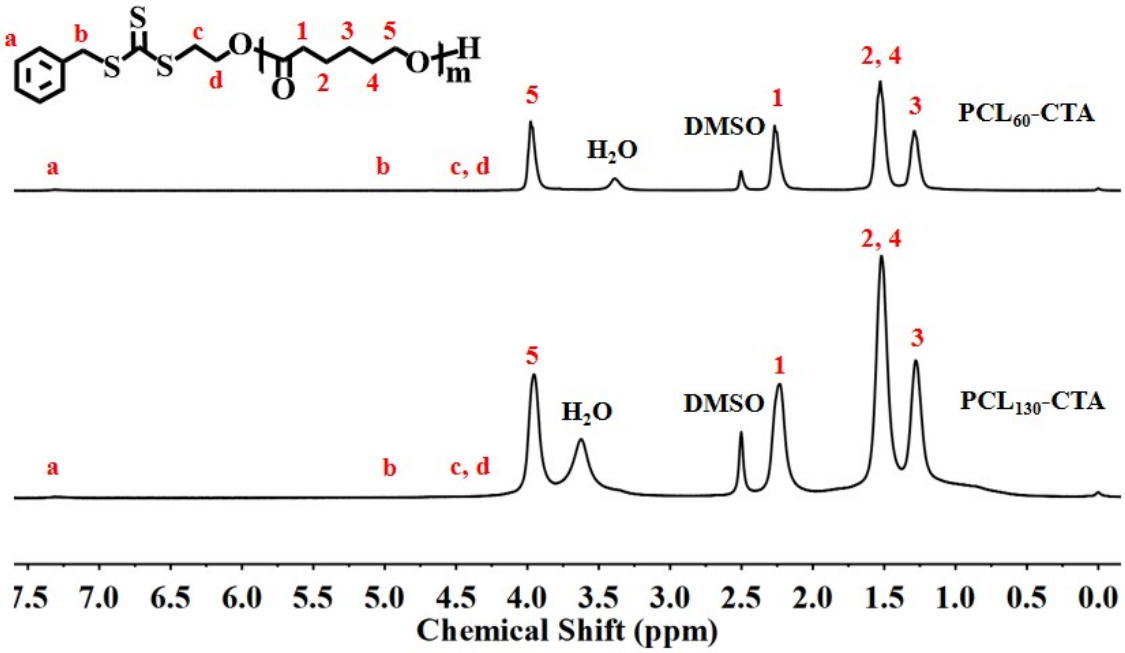

Fig. S7 ^{1}H-NMR spectra of PCL_{60}-CTA and PCL_{130}-CTA in DMSO-d_6.

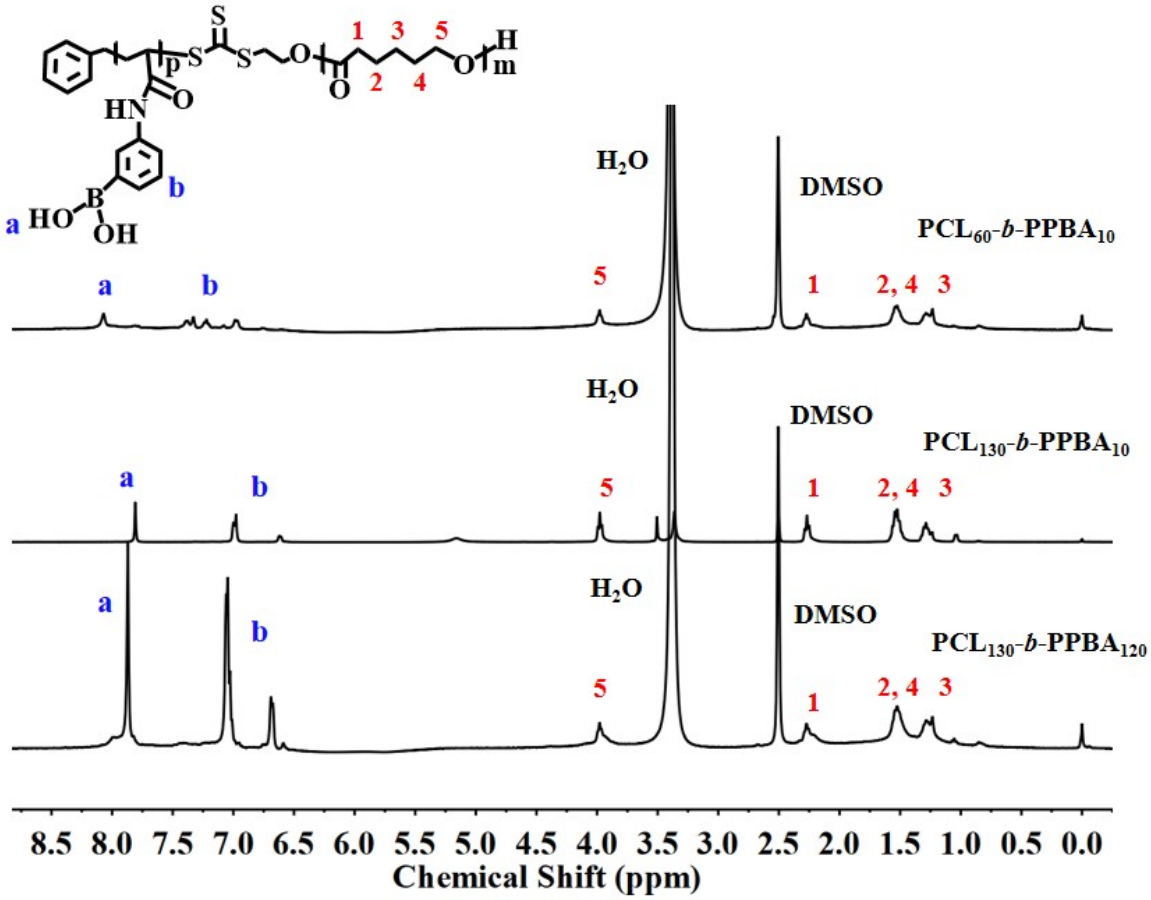

Fig. S8 ^{1}H-NMR spectra of PCL_{60}-*b*-$PPBA_{10}$, PCL_{130}-*b*-$PPBA_{10}$ and PCL_{130}-*b*-$PPBA_{120}$ in DMSO-d_6.

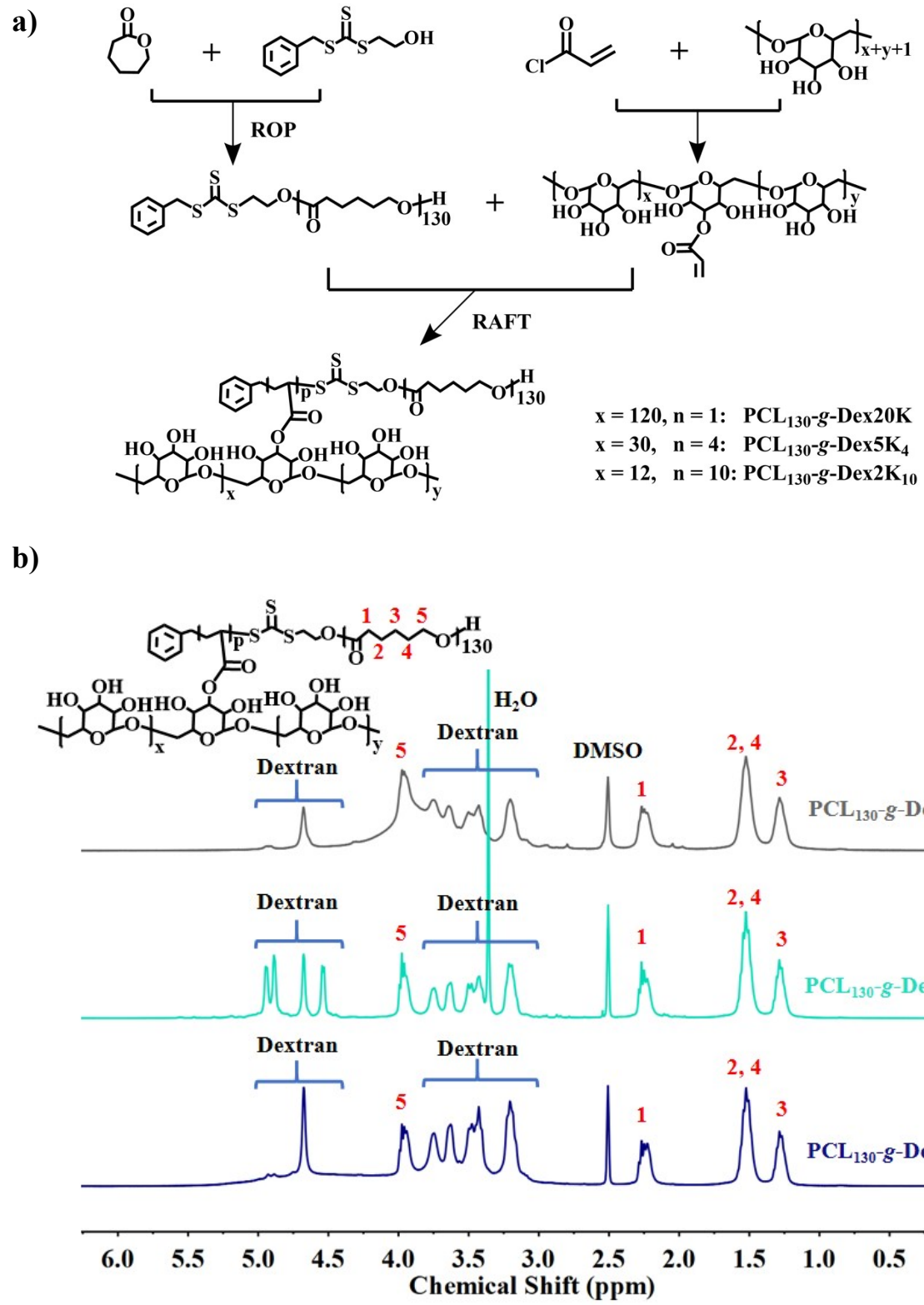

Fig. S9 Synthesis and characterization of polymers. (a)Synthesis routes and (b) ^{1}H-NMR spectra of PCL_{130}-*g*-Dex20K, PCL_{130}-*g*-$Dex5K_4$ and PCL_{130}-*g*-$Dex2K_{10}$ in DMSO-d_6.

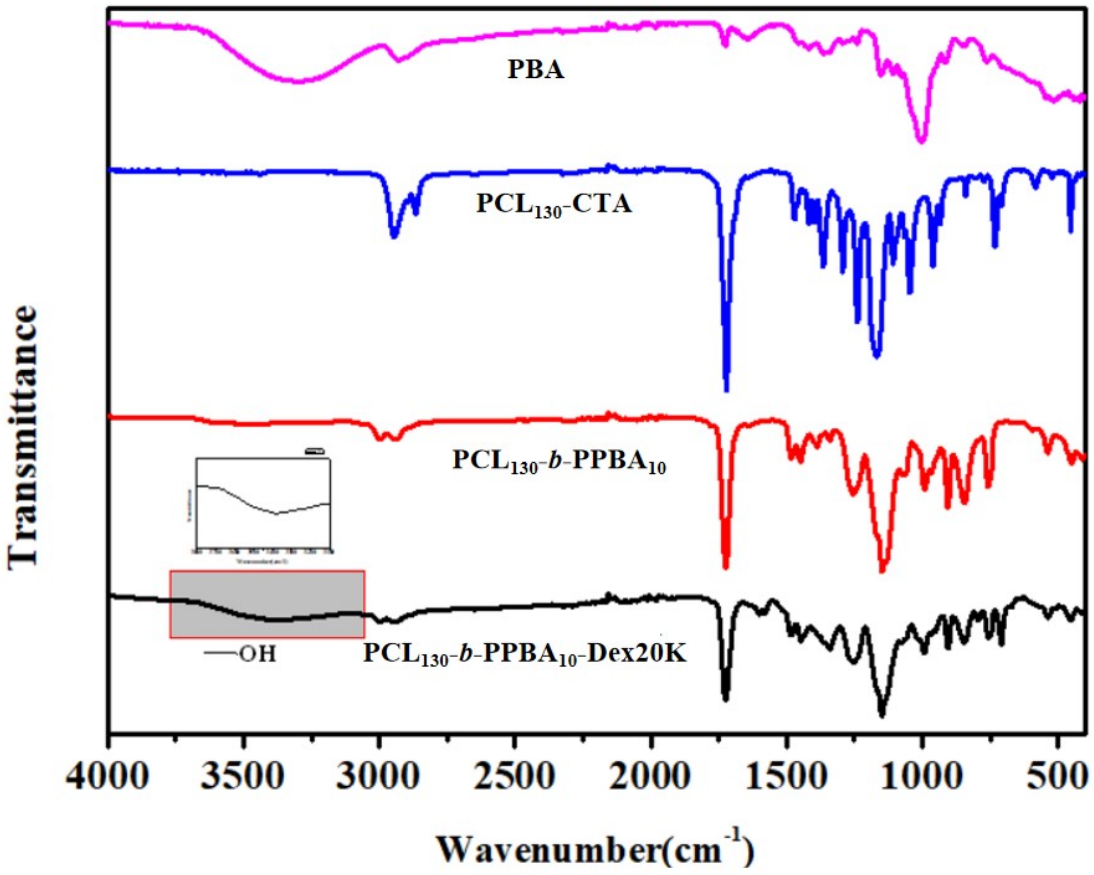

Fig. S10 FT-IR spectra of PBA, PCL_{130}-CTA, PCL_{130}-*b*-$PPBA_{10}$ and PCL_{130}-*b*-$PPBA_{10}$-Dex20K.

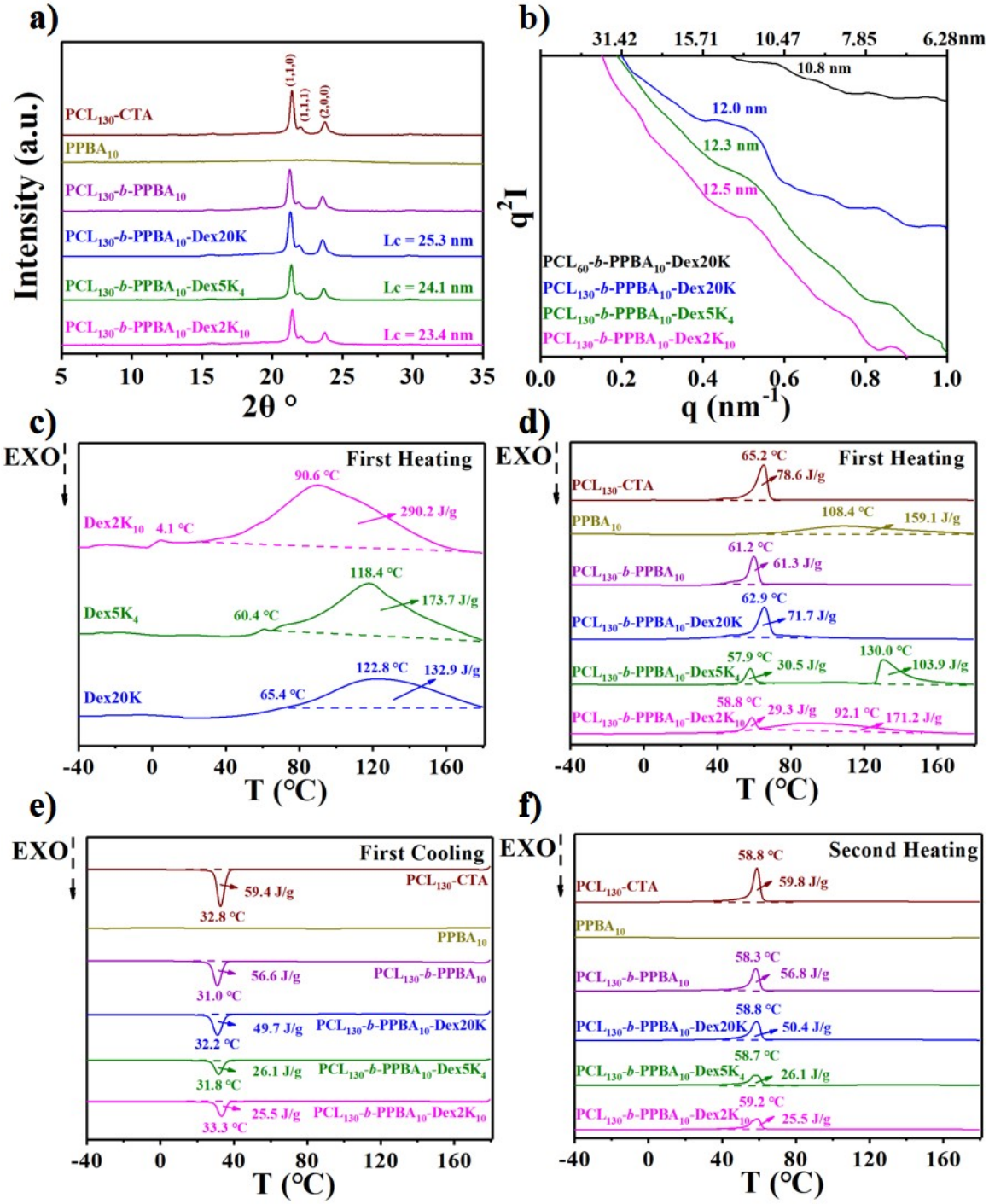

Fig. S11 Crystallization behavior and thermodynamic characterization of copolymers and nanoparticles. (a) WAXD patterns of PCL_{130}-CTA, $PPBA_{10}$, PCL_{130}-*b*-$PPBA_{10}$, PCL_{130}-*b*-$PPBA_{10}$-Dex20K, PCL_{130}-*b*-$PPBA_{10}$-Dex5K$_4$ and PCL_{130}-*b*-$PPBA_{10}$-Dex2K$_{10}$. (b) SAXS patterns of PCL_{60}-*b*-$PPBA_{10}$-Dex20K, PCL_{130}-*b*-$PPBA_{10}$-Dex20K, PCL_{130}-*b*-$PPBA_{10}$-Dex5K$_4$ and PCL_{130}-*b*-$PPBA_{10}$-Dex2K$_{10}$. (c) DSC curves of Dex2K$_{10}$ and Dex5K$_4$. (d-f) DSC curves of PCL_{130}-CTA, $PPBA_{10}$, PCL_{130}-*b*-$PPBA_{10}$, PCL_{130}-*b*-$PPBA_{10}$-Dex20K, PCL_{130}-*b*-$PPBA_{10}$-Dex5K$_4$ and PCL_{130}-*b*-$PPBA_{10}$-Dex2K$_{10}$.

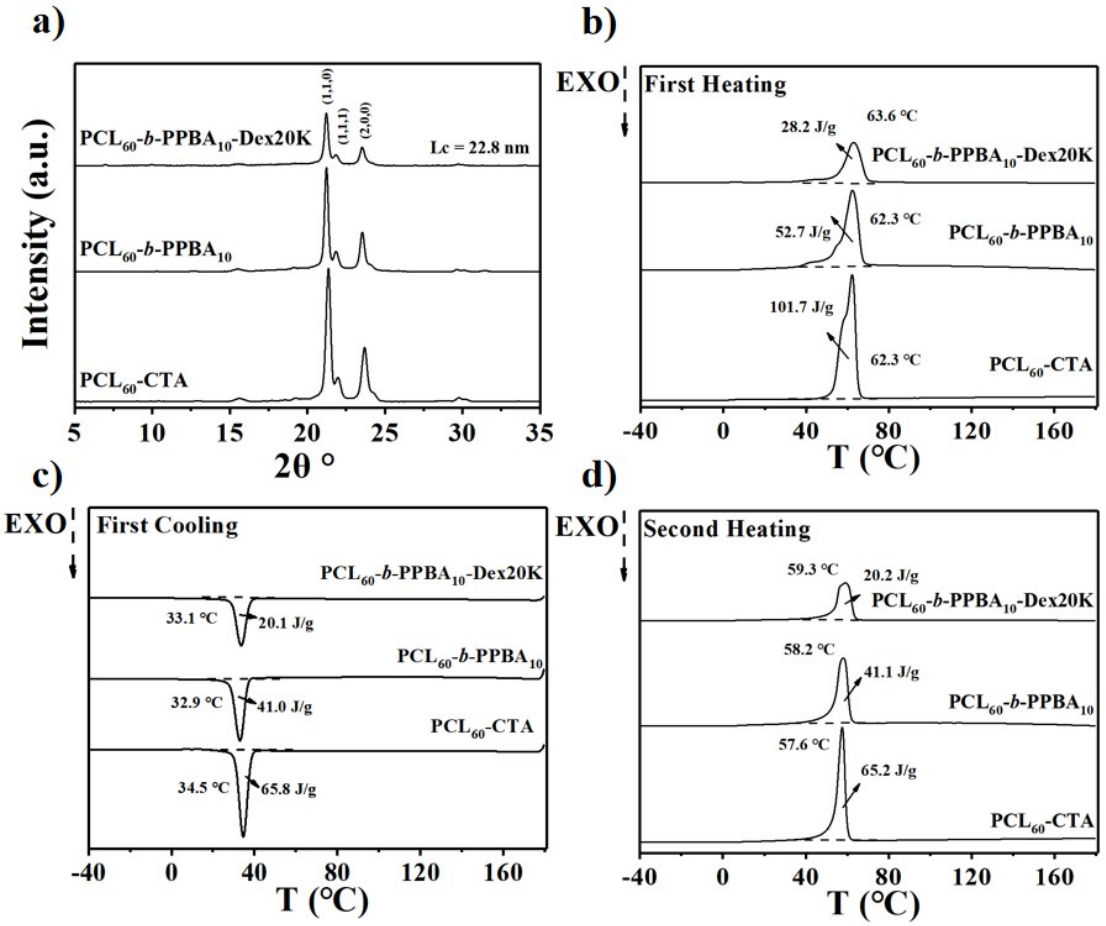

Fig. S12 Crystallization behavior and thermodynamic characterization of copolymers. (a) WAXD spectrum and (b-d) DSC curves of PCL_{60}-CTA, PCL_{60}-*b*-$PPBA_{10}$ and PCL_{60}-*b*-$PPBA_{10}$-Dex20K.

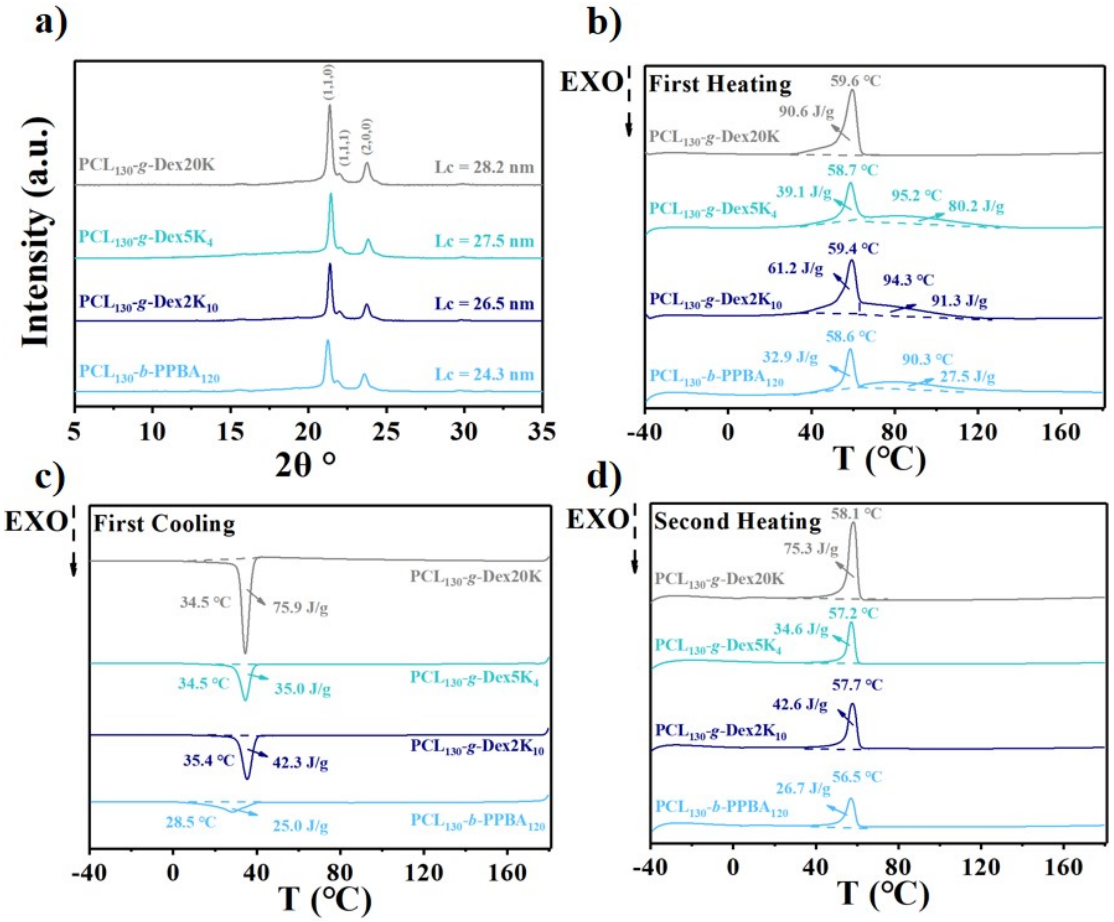

Fig. S13 Crystallization behavior and thermodynamic characterization of copolymers. (a) WAXD spectrum and (b-d) DSC curves of PCL_{130}-*g*-Dex20K, PCL_{130}-*g*-Dex5K_4, PCL_{130}-*g*-Dex2K_{10}, PCL_{130}-*b*-$PPBA_{120}$.

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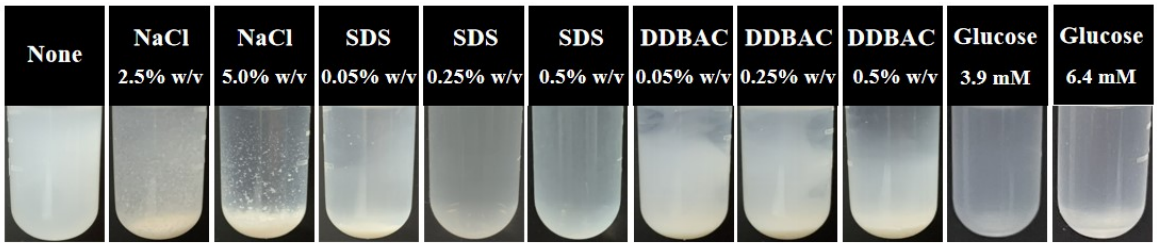

Fig. S14 Stability test of PCL_{130}-*b*-$PPBA_{120}$ vesicle dispersions. Photographs before and after NaCl (the final concentration: 2.5% w/v, 5% w/v), SDS (the final concentration: 0.05% w/v, 0.25% w/v, 0.5% w/v), DDBAC (the final concentration: 0.05% w/v, 0.25% w/v, 0.5% w/v) and glucose (the final concentration: 3.9 mM, 6.4 mM) treatments (the final concentration of PCL_{130}-*b*-$PPBA_{120}$ vesicle is 0.5% w/v).

Table S2 Summary of PCL_{130}-*b*-$PPBA_{10}$-Dex20K micelle's stability test.

type of added surfactant or glucose	concentration (w/v %)	D_h[a] (nm)	PDI[a]	T[b] (%)
none (i.e., pristine PCL_{130}-*b*-$PPBA_{10}$-Dex20K micelle)	0.0	132.4	0.053	12.2
NaCl	2.5	133.6	0.062	12.5
	5.0	132.5	0.065	12.3
SDS	0.05	133.7	0.081	12.7
	0.25	134.6	0.076	11.9
	0.5	137.2	0.091	12.6
DDBAC	0.05	136.5	0.065	12.4
	0.25	138.2	0.063	12.7
	0.5	137.3	0.057	12.5
glucose	0.07	136.5	0.056	12.3
	0.12	137.4	0.058	12.6

a: Hydrodynamic diameter (D_h) and polydispersity (PDI) measured by DLS. b: Transmittance measured at 600 nm by UV−vis spectroscopy.

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Table S3 Summary of PCL_{130}-*b*-$PPBA_{10}$-$Dex5K_4$ vesicle's stability test.

type of added surfactant or glucose	concentration (w/v %)	D_h[a] (nm)	PDI[a]	T[b] (%)
none (i.e., pristine PCL_{130}-*b*-$PPBA_{10}$-$Dex5K_4$ vesicle)	0.0	173.8	0.062	13.1
NaCl	2.5	174.7	0.064	13.4
	5.0	173.5	0.086	13.6
SDS	0.05	176.2	0.053	12.9
	0.25	177.5	0.066	13.5
	0.5	176.8	0.062	13.2
DDBAC	0.05	179.2	0.095	13.7
	0.25	175.3	0.062	13.5
	0.5	169.5	0.057	12.9
glucose	0.07	173.2	0.057	13.2
	0.12	174.6	0.064	13.1

a: Hydrodynamic diameter (D_h) and polydispersity (PDI) measured by DLS. b: Transmittance measured at 600 nm by UV−vis spectroscopy.

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Table S4 Summary of PCL_{130}-*b*-$PPBA_{10}$-$Dex2K_{10}$ vesicle's stability test.

type of added surfactant or glucose	concentration (w/v %)	D_h[a] (nm)	PDI[a]	T[b] (%)
none (i.e., pristine PCL_{130}-*b*-$PPBA_{10}$-$Dex2K_{10}$ vesicle)	0.0	156.8	0.071	12.6
NaCl	2.5	157.3	0.065	12.8
	5.0	158.3	0.061	13.2
SDS	0.05	154.6	0.057	12.5
	0.25	155.8	0.064	12.6
	0.5	157.3	0.092	12.8
DDBAC	0.05	156.3	0.110	12.5
	0.25	158.3	0.066	12.7
	0.5	157.6	0.085	13.2
glucose	0.07	157.3	0.065	12.3
	0.12	157.8	0.071	12.2

a: Hydrodynamic diameter (D_h) and polydispersity (PDI) measured by DLS. b: Transmittance measured at 600 nm by UV−vis spectroscopy.

Table S5 Summary of PCL_{130}-*b*-$PPBA_{120}$ vesicle's stability test.

type of added surfactant or glucose	concentration (w/v %)	D_h[a] (nm)	PDI[a]	T[b] (%)
none (i.e., pristine PCL_{130}-*b*-$PPBA_{120}$ vesicle)	0.0	121.3	0.053	12.6
NaCl	2.5	814.3	0.252	35.2
	5.0	1151.2	0.731	82.3
SDS	0.05	752.3	0.364	34.2
	0.25	892.1	0.536	46.2
	0.5	1021.6	0.643	56.3
DDBAC	0.05	101.3	0.151	10.2
	0.25	75.3	0.216	8.3
	0.5	42.1	0.263	6.4
glucose	0.07	834.2	0.342	42.1
	0.12	1022.5	0.642	65.2

a: Hydrodynamic diameter (D_h) and polydispersity (PDI) measured by DLS. b: Transmittance measured at 600 nm by UV−vis spectroscopy.

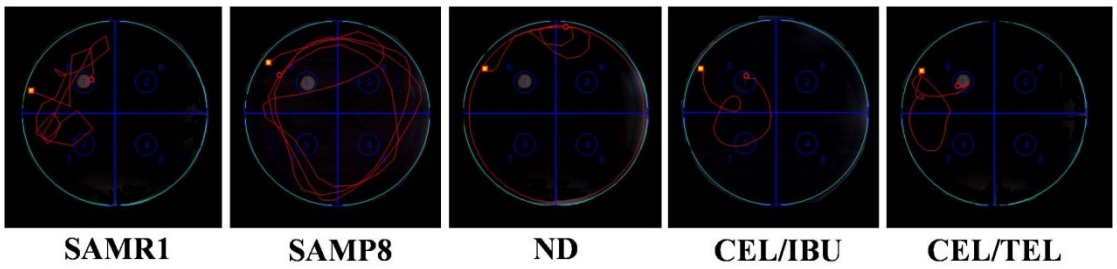

Fig. S15 The typical escape routes of each group mice in the morris water maze on the fifth day.

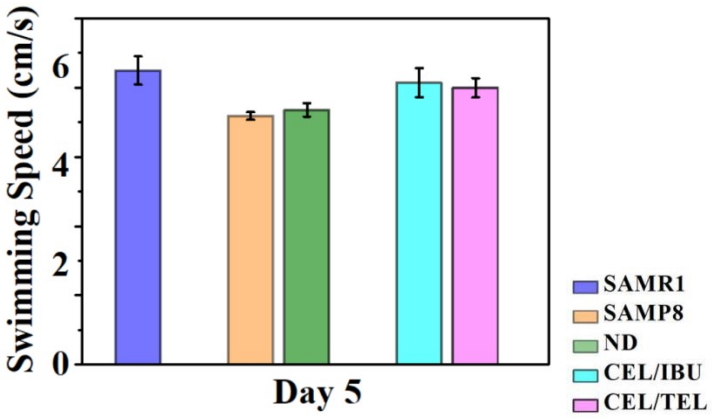

Fig. S16 The swimming speed of each group on the fifth day.

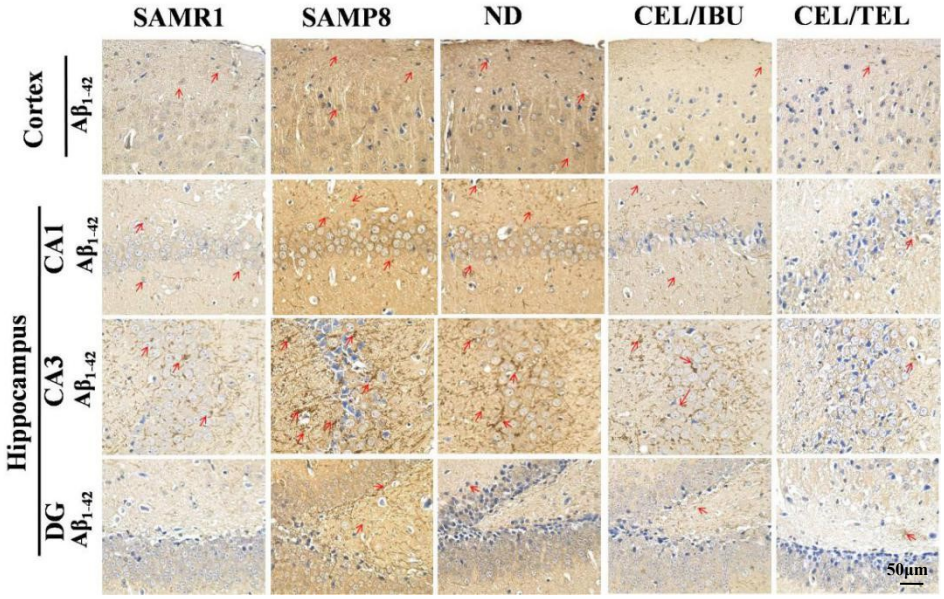

Fig. S17 The immunohistochemical analysis of $A\beta_{1\text{-}42}$ deposition in the hippocampus and cortex of mice. Scale bars = 50 μm.

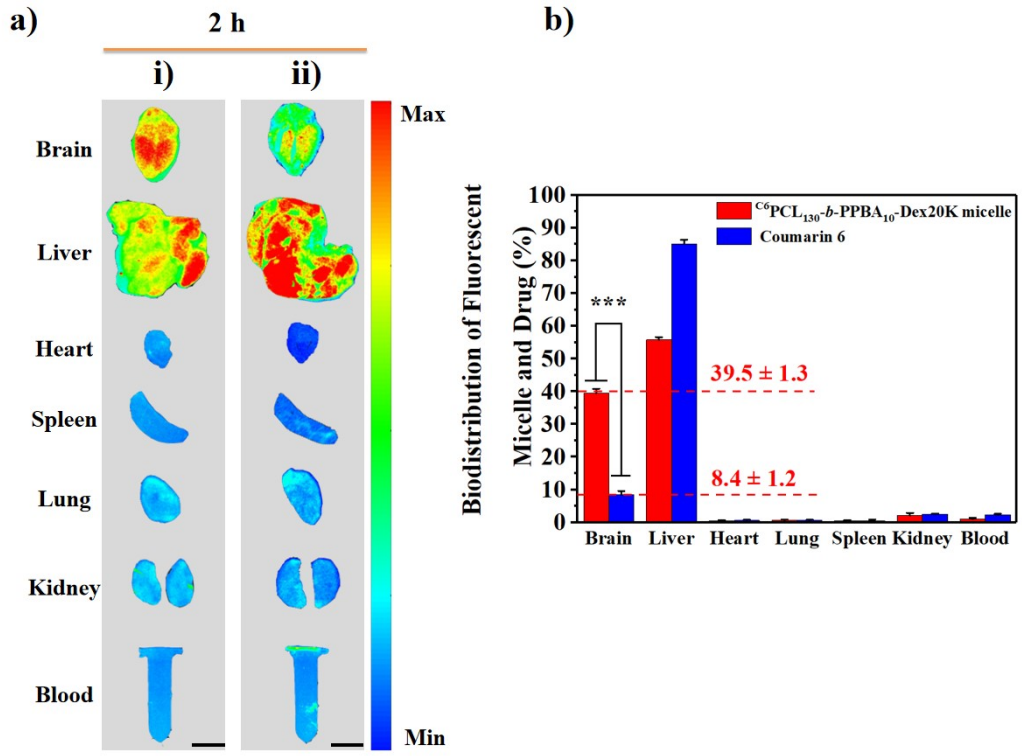

Fig. S18 The delivery efficiency and biodistribution data of micelle. (a) Ex vivo fluorescence tissue images of SAMP8 mice after treated with (i) $^{C6}PCL_{130}$-*b*-$PPBA_{10}$-Dex20K micelle or (ii) coumarin 6 (C6). (b) The biodistribution of $^{C6}PCL_{130}$-*b*-$PPBA_{10}$-Dex20K micelle and coumarin 6 2 hours after nasal administration. Scale bars = 5 mm.

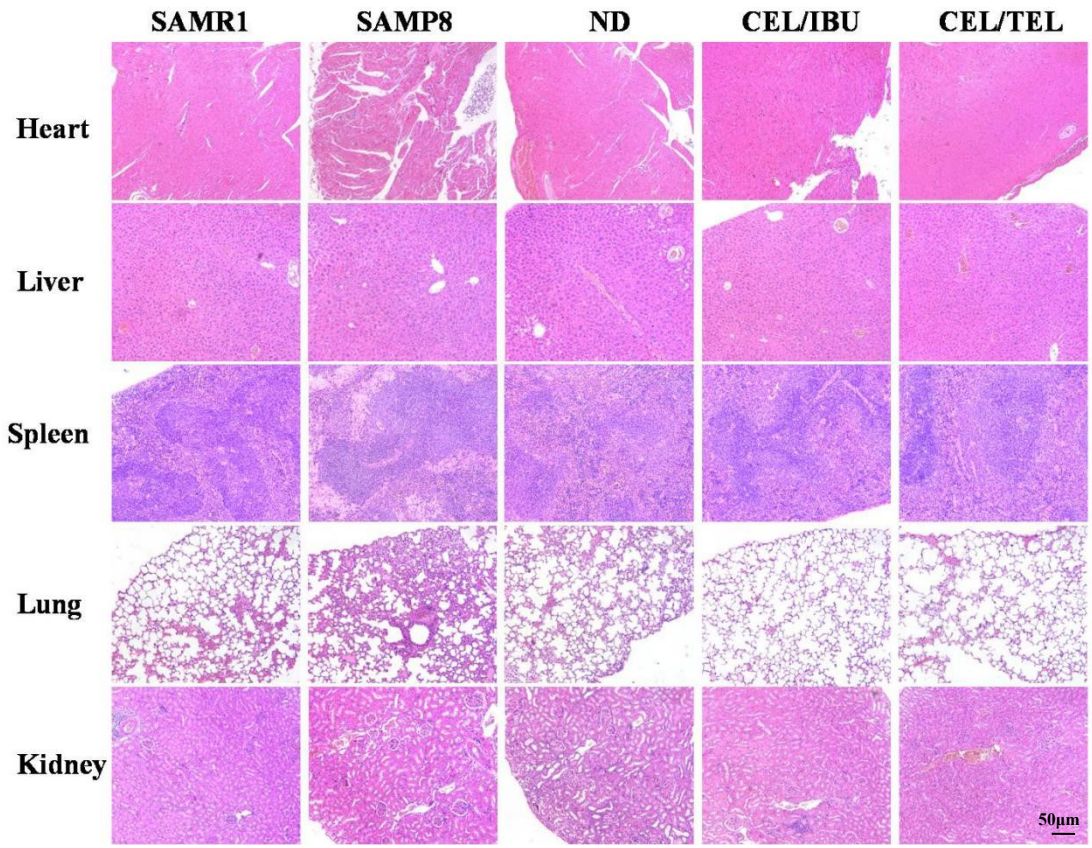

Fig. S19 H&E staining pictures of heart, liver, spleen and lung in each group of mice (100X). Scale bars = 50 μm.