Supporting information

Synthesis of Dextran Graft Copolymers

The synthesis route of the dextran graft copolymers is shown in Scheme S1. The details for the synthesis of graft copolymers are as follows.



Scheme S1. The synthesis route of Dex-*g*-PMAGGCONHTyr-NHPEG_{3k} (**II**), Dex-*g*-P(MPEG-*co*-MAGGCONHTyr) (**III**), Dex-*g*-P(HPMA-*co*-MAGGCONHTyr) (**IV**).

Synthesis of Dex-g-P(MPEG-co-MAGGCONHTyr) and Dex-g-P(HPMA-co-MAGGCONHTyr). Dextran (250 mg) was firstly dissolved in 6 mL water and then $K_2S_2O_8$ (2.7 mg, 0.01 mmol), NaHSO₃ (1.4 mg, 0.01 mmol) were added. The solution was bubbled with nitrogen at room temperature for 30 min to remove the oxygen. Then 4 mL MAGGCOOH/MPEG or MAGGCOOH/HPMA mixed aqueous solution was added slowly

under nitrogen atmosphere. The resultant reaction solutions were dialyzed against water, and then were freeze-dried to obtain Dex-*g*-P(MPEG-*co*-MAGGCOOH) or Dex-*g*-P(HPMA-*co*-MAGGCOOH).

The details on the selection of the optimal conditions are listed in Tables S1 and S2. From run 1 to 4 (Table S1), when *n*(-COOH):*n*(MPEG) is kept at 1.95:1, $DS_{-COOH}/DS_{MPEG} \approx 1$, so the graft monomer MAGGCOOH/MPEG reactivity ratio is around 1:2, From run 1 to 3 (Table S2), when *n*(-COOH):*n*(HPMA) is kept at 0.77:1, $DS_{-COOH}/DS_{MPEG} \approx 0.8$, so the graft monomer reactivity ratio MAGGCOOH/HPMA is around 1:1. In order to synthesize graft copolymer with a degree of substitution of -COOH groups around 0.5-0.6, the reaction feeding ratios of the MAGGCOOH were adjusted as those listed in Tables S1 and S2. DS_{HPMA} and DS_{MPEG} increase with the increase of the mass of the added monomer HPMA or MPEG. The influences of MPEG and HPMA mononmer concentrations on the graft ratio (G)are listed in Tables S1 and S2. Grafting ratio (G) was calculated by the following formula. G= $W_2/W_1 \times 100\%$, where W_1 and W_2 the mass of pure graft copolymer and graft chains, respectively. $DS_{\text{HPMA}} = A_2/2A_1$, where A_1 and A_2 are the integrated areas of the protons on dextran backbone ($\delta = 4.95$ ppm) and the methylene of O=C-NH-CH₂- groups of the PHPMA side chains ($\delta = 3.00-3.30$ ppm) on ¹H NMR spectra, respectively. $DS_{MPEG} = A_3/2A_1$, where A_3 is the methylene of O=C-O-CH₂- groups of the PMPEG side chains ($\delta = 4.12-4.28$ ppm) on ¹H NMR spectra, respectively. Molecular weight of Dex-g-P(MPEG-co-MAGGCOOH) graft copolymer was calculated by $M_{w,Dex-g-P(MPEG-co-MAGGCOOH)} = M_{w,Dex} + M_{w,Dex}$ $n(184 \times DS_{-COOH} + 360 \times DS_{MPEG})$, where $M_{w,Dex}$ is the molecular weight of dextran, 184 is the molar mass of MAGGCOOH. Molecular weight of Dex-g-P(HPMA-co-MAGGCOOH) graft copolymer was calculated by $M_{w,\text{Dex-}g-P(\text{HPMA-}co-\text{MAGGCOOH})} = M_{w,\text{Dex}} + n(184 \times DS_{-\text{COOH}} + N)$ $143 \times DS_{\text{HPMA}}$, where 143 is the molar mass of HPMA. *n* is the average numbers of glucose unit per dextran chain. The graft copolymers are characterized by using ¹H NMR, and the

typical ¹H NMR data is shown in Figure S1 and S2. The conjugation of the *L*-Tyrosine is similar to the previous work.¹

Dex-*g*-P(MPEG-*co*-MAGGCONHTyr). Yield 74%. ¹H NMR (400 MHz, D₂O, δ, ppm): 0.87-1.22 (3H, m, -CH₃), 1.62-2.10 (2H, m, -C-CH₂-), 2.70 (2H, s, -CH₂- from L-Tyrosine), 4.13-4.28 (2H, m, O=C-O-CH₂- from PMPEG), 3.40-4.00 (9H, m, dextran), 4.95 (1H, s, H₁ from ring of dextran), 6.70 (2H, s, m-phenyl hydrogen), 7.10 (2H, s, o-phenyl hydrogen).

Dex-*g*-P(HPMA-*co*-PMAGGCONHTyr). Yield 79.6%. ¹H NMR (400 MHz, D₂O, δ, ppm): 0.87-1.22 (3H, m, -CH₃), 1.62-2.10 (2H, m, -C-CH₂-), 2.70 (2H, s, -CH₂- from L-Tyrosine), 3.00-3.30 (2H, m, -CH₂- from HPMA), 3.40-4.00 (9H, m, dextran), 4.95 (1H, s, H₁ from ring of dextran), 6.70 (2H, s, m-phenyl hydrogen), 7.10 (2H, s, o-phenyl hydrogen).

Table S1. Details of synthesis and information for Dex-g-P(MPEG-co-MAGGCOOH).^a

Run	<i>m</i> _{Dex}	$m_{\text{Dex}}:m_{\text{[-COOH]}}$	<i>n</i> _[-COOH] :	DS-cooh ^b	$DS_{\rm MPEG}^{b}$	DS-COOH/	G_{MAGGCOOH}	G_{MPE}	$M_{ m w}$
		:m _[MPEG]	$n_{[MPEG]}$			DS_{MPEG}	%	_G %	$(kDa)^c$
1	250	1:0.25:0.25	2:1	0.15	0.12	1.08	11.8	18.5	141
2	250	1:0.5:0.5	2:1	0.2	0.21	0.95	13.4	27.6	169
3	250	1:1:1	2:1	0.44	0.4	1.10	20.9	37.2	239
4	250	1:1.5:1.5	2:1	0.52	0.54	0.96	21.1	43.1	279
5	250	1: 1.5: 0.25	-	0.60	0.12	-	34.9	13.6	195

^{*a*} $c[K_2S_2O_8] = c[NaHSO_3] = 1 \text{ mmol/L}$. All the reactions were carried out at 30°C for 9 h.

^b The degree of substitution of the MAGGCOOH ($DS_{MAGGCOOH}$) and MPEG (DS_{MPEG}) per glucose unit were calculated by ¹H NMR.

^c $M_{\rm w}$ is the molecular weight of Dex-g-P(MPEG-co-MAGGCOOH), and is calculated by ¹H NMR.

Table S2. Details of synthesis and information for for Dex-g-P(HPMA-co-MAGGCOOH).^a

Run	m _{Dex}	$m_{[\text{Dex}]}:m_{[\text{-COOH}]}$	<i>n</i> _[-COOH] :	DS-cooh ^b	$DS_{\rm HPMA}^{\ \ b}$	DS-cooh/	G-COOH	G_{HPMA}	$M_{ m w}$
	(mg)	$m_{[\text{HPMA}]}$	n _[MPEG]			DS_{HPMA}	%	%	(kDa) ^c
1	250	1:0.25:0.25	0.8:1	0.12	0.17	0.71	10.6	11.7	129
2	250	1:0.5:0.5	0.8:1	0.27	0.35	0.77	19.0	19.1	162
3	250	1:1:1	0.8:1	0.5	0.62	0.80	26.8	25.9	211
4	250	1:1:0.5	-	0.58	0.44	-	30.7	21.2	205

^{*a*} $c[K_2S_2O_8] = c[NaHSO_3] = 1 \text{ mmol/L}$. All the reactions were carried out at 30°C for 9 h.

^b The degree of substitution of the MAGGCOOH ($DS_{MAGGCOOH}$) and HPMA (DS_{HPMA}) per glucose unit were calculated by ¹H NMR.

^c M_w is the molecular weight of Dex-g-P(HPMA-co-MAGGCOOH), and is calculated by ¹H NMR.



Figure S1. ¹H NMR spectra of Dextran, Dex-*g*-P(MPEG-*co*-MAGGCOOH) and Dex-*g*-P(MPEG-*co*-MAGGCONHTyr) at 400 MHz in D₂O.



Figure S2. ¹H NMR spectra of Dextran, Dex-*g*-P(HPMA-*co*-MAGGCOOH) and

Dex-g-P(HPMA-co-MAGGCONHTyr) at 400 MHz in D₂O.

Synthesis of Dex-g-PMAGGCONHPEG_{3k}-NHTyr Copolymers. Dex-g-PMAGGCOOH $(DS_{-COOH} = 0.57)$ (50 mg) was dissolved in water to obtain a solution with pH of 3.5-4.5. Then certain amounts of EDC/NHS were added and stirred for 10 min for pre-activation, after which L-Tyrosine, NH₂PEG_{3k} and Na₂CO₃ mixed solution was added dropwise. The reaction mixture was kept in water bath at 25 °C and stirred for 3 h. Dex-g-PMAGGCONHPEG_{3k}-NHTyr was obtained by the previous purified method. The optimism of the reaction conditions are listed in Table S3. Dex-g-PMAGGCOOH with 0.57 of DS_{-COOH} was chosen for amide reaction according to our previous work, $DS_{NHPEG3k}$ is determined by the mass of the added NH₂PEG_{3k}. The content of NH₂PEG_{3k} in the side chain PMAGGCOOH of graft copolymers, which was defined as the average NH₂PEG_{3k} groups per glucopyranose unit (DS_{NHPEG3k}) , can be estimated by $DS_{\text{NHPEG3k}} = (A_4 - A_5)/280$, where A_4 : the integrated from δ 3.45 4.12 areas to ppm of graft copolymer Dex-g-PMAGGCONHPEG_{3k}-NHTyr, A_5 : the integrated areas from δ 3.45 to 4.12 ppm of graft copolymer Dex-g-PMAGGCOOH, 280: all the numbers of hydrogen atom per PEG chain. Molecular weight of Dex-g-PMAGGCONHPEG_{3k}-NHTyr graft copolymers were calculated by $M_{\rm w, Dex-g-PMAGGCONHPEG3k} = M_{\rm w,Dex} + n(184 \times (0.57 - DS_{\rm NHPEG3k}) + 3166$ $\times DS_{\text{NHPEG3k}}$) where $M_{\text{w,Dex}}$ is the molecular weight of dextran, n is the average numbers of glucose unit per dextran chain. 184 is the molar mass of MAGGCOOH, 0.57 is the DS_{-COOH} of the Dex-g-PMAGGCOOH graft copolymers that used for the amide formation

Dex-*g*-PMAGGCONHPEG_{3k}-NHTyr. Yield 71%. ¹H NMR (400 MHz, D₂O, δ, ppm): 0.87-1.22 (3H, m, -CH₃), 1.62-2.10 (2H, m, -C-CH₂-), 2.70 (2H, s, -CH₂- from L-Tyrosine), 3.40-4.00 (m, dextran and -CH₂-CH₂- from NH₂PEG_{3k}), 4.95 (1H, s, H₁ from ring of dextran), 6.70 (2H, s, m-phenyl hydrogen), 7.10 (2H, s, o-phenyl hydrogen).

Run	<i>m</i> _{Dex-g-PMAGGCOOH}	$m_{\rm PEG}$	<i>m</i> _{Tyr}	$n_{[\text{COOH}]}:n_{[\text{PEG}]}:n_{[}$	DS _{PEG3k}	N_{Tyr}	$M_{\rm w}({\rm kDa})^c$
	$(mg)^{b}$	(mg)	(mg)	$_{\text{Tyr}]}:n_{[\text{EDC}]}:n_{[\text{NHS}]}$			
1	50	7.5	18.1	1 :0.025 :1:1:0.5	0.009	0.014	181
2	50	15	0	1: 0.05 :0:1:0.5	0.019	0	200
3	50	30	18.1	1:0.1:1:1:0.5	0.028	0.004	213
4	50	60	0	1: 0.2 :0:1:0.5	0.077	0	306
5	50	90	0	1: 0.3 :0:1:0.5	0.114	0	374

Fable S3. Details of	synthesis and	l information	for Dex-	g-PMAGGCONHPEG _{3k}	-NHTyr. ^a
-----------------------------	---------------	---------------	----------	------------------------------	----------------------

^{*a*} Reaction at pH = 10-11, adjusted by Na₂CO₃, pre-activited for 10 min, All the reactions were carried out at 25°C for 3 h.

^b The average numbers of MAGGCOOH per glucose ring is 0.57.

^c M_w is the molecular weight of Dex-g-PMAGGCONHPEG_{3k}-NHTyr, and is calculated by ¹H NMR.



Figure S3. Representative ITLC chromatograms of ¹²⁵I labeled

Dex-g-PMAGGCONHPEG_{3k}-NHTyr. (a) the original kit and (b) after purification.



Figure S4. Representative ITLC chromatograms of ¹²⁵I labeled

Dex-g-P(MPEG-co-MAGGCONHTyr). (a) the original kit and (b) after purification.

Reference

1. D. Wang, J. Shi, J. Tan, X. Jin, Q. Li, H. Kang, R. Liu, B. Jia and Y. Huang, *Biomacromolecules*, 2011, **12**, 1851-1859.