Supplementary information

Synthesis of Acid-Degradable Hyperbranched Polymers by Chain-Growth CuAAC

Polymerization of an AB₃ Monomer

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1. Experimental

Materials and characterization.

4-Pentynoic acid (Chem-impex, 98.5%), copper(II) sulfate pentahydrate (CuSO₄·5H₂O) (BDH, ACS grade), 4-(dimethylamino) pyridine (DMAP, Aldrich, \geq 99%), sodium ascorbate (Alfa Aesar, 99+%), sodium azide (VWR), 3-(3-dimethylaminopropyl)-1-ethyl-carbodiimide hydrochloride (EDC·HCl) (Chem-impex), *p*-toluenesulfonic acid (Aldrich, \geq 98.5%), poly(ethylene glycol) monomethyl ether (PEG, average M_n 750, Alfa Aesar) and 3-bromo-2,2-bis(bromomethyl)propan-1-ol (Oxchem, 95%) were used as received. 3-Azido-2,2-bis(azidomethyl)propan-1-ol was synthesis according to a previous report.¹ **B**₃ core molecule and 4-(but-3-ynyloxy)-4-oxobutanoic acid were synthesized according to previous literature.² All other chemicals and solvents were analytical grade and purified through appropriate method.

The THF size exclusion chromatography (SEC) was equipped with Polymer Standards Services (PSS) columns (guard, 10^5 , 10^3 , and 10^2 Å SDV columns) at 35 °C with THF flow rate = 1.0 mL/min and a differential refractive index (RI) detector (Wyatt Technology, Optilab T-rEX) using PSS WinGPC 7.5 software. The DMF SEC used Polymer Standards Services (PSS) columns (guard, 10^4 , 10^3 , and 10^2 Å GRAM 10 columns) at 55 °C with flow rate = 1.00 mL/min and connected with a differential refractive index (RI) detector (Waters,2410) using PSS WinGPC 7.5 software. The apparent molecular weights were calculated based on linear poly(methyl methacrylate) (PMMA) standards. The detectors employed to measure the absolute molecular weights of hyperbranched polymers in THF SEC were the RI detector and a multi-angle laser light scattering (MALLS) detector (Wyatt Technology, DAWN HELEOS II) with the light wavelength at 658 nm. Absolute molecular weights were determined using ASTRA software from Wyatt Technology with the pre-measured dn/dc value 0.0896 ml/g for all hyperbranched polymers.

¹H nuclear magnetic resonance (¹H NMR) spectra were acquired on Bruker spectrometers at 25 °C. The hydrodynamic size (D_h) of the samples was determined using dynamic light scattering (DLS) equipped with Zetasizer Nano-ZS (He-Ne laser wavelength at 633 nm, Malvern Instruments, Malvern, UK).

Syntheis of 4-pentynoic acid 2-vinyloxy-ethyl ester.



To a solution of 4-pentynoic acid (9.80 g, 0.1 mol), DMAP (0.65 g, 05 mmol), and 2-vinyloxyethanol (9.68 g, 0.11 mol) in 100 mL of dichloromethane (DCM) was added EDC·HCl powder (21.0 g, 0.11 mol). The reaction mixture was stirred overnight. Then, water (200 mL) was added to quench the reaction and the mixture was extracted with DCM (200 mL) for three times. The DCM extracts were combined and washed with brine (100 mL) for three times, then dried over MgSO₄, and concentrated. The product was purified by column chromatography [petrol ether/ethyl acetate, 10/1 (v/v), 3% TEA] as a clear liquid (15.50 g, yield 91%). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 6.48 (dd, J₁=14.4 Hz, J₂=6.8 Hz, 1H), 4.35 (m, 2H), 4.20 (dd, J₁=14.4 Hz, J₂=2.3 Hz, 1H), 4.05 (dd, J₁=6.8 Hz, J₂=2.3 Hz, 1H), 3.89 (m, 2H), 2.60 (m, 2H), 2.51 (m, 2H), 1.97 (t, J₁=2.6 Hz, 1H).

Synthesis of acid-degradable monomer.



4-Pentynoic acid, 2-vinyloxy-ethyl ester (0.84 g, 5 mmol) and 3-azido-2,2-bis(azidomethyl)propan-1-ol (1.05 g, 5 mmol) were dissolved in 10 mL of DCM. A catalytic amount of *p*-toluenesulfonic acid (42.0 mg, 0.25 mmol) was added to start the reaction. The reaction was allowed to stir for 1 h and then neutralized with a few drops of TEA. The solvent was removed under reduced pressure, and the product was purified by column chromatography [petrol ether/ethyl acetate, 10/1 (v/v), 3% TEA] as clear oil (0.7 g, 35% yield). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 4.74 (q, J = 5.4 Hz, 1H), 4.27 (m, 2H), 3.75 (m, 1H), 3.64 (m, 1H), 3.48 (d, J=4.7 Hz, 1H), 3.35 (s, 6H), 3.24 (d, J=4.7 Hz, 1H), 2.60 (m, 2H), 2.52 (m, 2H), 1.98 (t, J=2.6 Hz, 1H) , 1.32 (d, J=5.4 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 171.8, 100.3, 82.6, 69.3, 63.9, 63.8, 63.0, 51.8, 44.4, 33.5, 19.4, 14.5.

Synthesis of ay-PEG.



To a mixture of 4-(but-3-ynyloxy)-4-oxobutanoic acid (2.04 g, 0.012 mol), poly(ethylene glycol)

monomethyl ether (7.50 g, 0.01 mol), and DMAP (73.2 mg, 0.6 mmol) in 200 mL of dry dichloromethane was added EDC·HCl (4.6 g, 0.024 mol) and the reaction mixture was stirred for 48 hours. Then, the reaction mixture was washed with 100 mL brine for five times. The dichloromethane phase was dried over MgSO₄ and concentrated. The residue was subjected to column chromatography [dichloromethane/methanol, 20/1 (v/v)] and **ay-PEG** was obtained as sticky liquid. ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 4.22 (m, 2H), 4.18 (t, J = 6.8 Hz, 2H), 3.68-3.51 (m, 66H), 3.35 (s, 3H), 2.64 (m, 4H), 2.51 (td, J₁=6.8 Hz, J₂=2.7 Hz, 2H), 1.99 (t, J=2.7 Hz, 1H).

Polymerization of AB₃ monomer.

AB₃ monomer (0.38 g, 1 mmol), **B**₃ core (0.0508 mg, 1 µmol), and CuSO₄·5H₂O (2.5 mg, 0.01mmol) were dissolved in 2 mL of DMF in a schlenk flask. The flask was degassed by three freeze-pump-thaw cycles. At the last cycle, the flask was opened when everything was frozen to quickly add sodium ascorbate (20 mg, 0.1 mmol) into the flask before re-capping the flask. The flask was vacuumed and backfilled with N₂ for more than 5 cycles before immersed in a thermostatic oil bath at 45 °C to thaw the mixture solution and initiate the polymerization. At timed intervals, samples were collected using deoxygenated syringes and quenched by exposure to air for characterization of conversions and molecular weights. The polymerization was stopped at 90 minutes and the reaction mixture was diluted with 10 mL THF. Copper catalyst was removed by adding two equivalents of PMDETA followed by passing through a neutral alumina column. The copper-free HBP were then purified by dissolving small amount of THF and precipitating into large amount of methanol for three times. The final product was freeze-dried with benzene as sticky material.

Synthesis of PEGylated HBPs.

HBP1 (0.25 g, containing 1.32 mmol N₃ group) and **ay-PEG** (1.41 g, containing 1.56 mmol alkynyl group) were dissolved with 6.5 mL of DMF in a schlenk flask. After an aliquot was taken for SEC tests, the flask was degassed by three free-pump-thaw cycles. At the last cycle, the flask was opened when everything was frozen to quickly add CuSO₄·5H₂O (16.5 mg, 0.066mmol) and ascorbic acid (58.1 mg, 0.33 mmol) into the flask before re-capping the flask. The flask was vacuumed and backfilled with N₂ for more than 5 cycles before immersed in a thermostatic oil bath at 45 °C to thaw the mixture solution and initiate the polymerization. After 60 minutes, the flask was opened and reaction mixture was exposed to air to stop the reaction. After another aliquot for SEC was taken, the solution was subjected to a basic Al₂O₃ column to remove copper catalyst. The PEGylated HBP (**HBP1-PEG**) was purified by dissolving small amount of THF and precipitating into large amount of diethyl ether for three times and freeze dried with benzene as white powder.

2. Table and Figures



Fig. S1 ¹H NMR spectra of AB₃ monomer and the precursors in CDCl₃.



Fig. S2 ¹³C NMR spectrum of AB₃ monomer in CDCl₃.

$[AB_3]_0: [B_3]_0:$	Conversion	M _{w,MALLS} ^a	M _{n,MALLS} ^a	$M_{\rm w}/M_{\rm n}^{\rm a}$	M _{n,RI} ^b	$M_{\rm w}/M_{\rm n}^{\rm b}$
$[CuSO_4 \cdot 5H_2O]_0$	(%)	-			-	
1000:1:10	23.2	41.5×10 ³	38.8×10 ³	1.07	18.7×10^{3}	1.07
	28.9	65.8×10 ³	61.5×10 ³	1.07	29.1×10 ³	1.05
	35.7	84.6×10 ³	79.1×10 ³	1.07	34.0×10^{3}	1.07
	51.5	108.4×10^{3}	103.2×10^{3}	1.05	45.7×10 ³	1.07
	68.0	135.7×10 ³	129.3×10 ³	1.05	57.5×10^{3}	1.07
	99.0	177.9×10 ³	172.8×10 ³	1.03	74.3×10 ³	1.06
500:1:5	40.8	24.7×10 ³	23.3×10 ³	1.06	14.3×10^{3}	1.06
	45.2	31.8×10^{3}	30×10 ³	1.06	18.2×10^{3}	1.07
	50.2	38.7×10 ³	36.2×10 ³	1.07	21.4×10^{3}	1.07
	59.7	48.9×10 ³	47.4×10 ³	1.03	27.9×10 ³	1.07
	73.3	64.3×10 ³	62.4×10 ³	1.03	35.7×10^{3}	1.06
	96.7	95.3×10 ³	90.8×10 ³	1.05	49.4×10 ³	1.06
200:1:2	55.4	26.9×10 ³	25.2×10 ³	1.07	12.8×10^{3}	1.05
	60.5	30.7×10 ³	29×10 ³	1.06	15.2×10^{3}	1.07
	67.3	36.7×10 ³	34.6×10 ³	1.06	19.1×10 ³	1.07
	81.2	44.0×10 ³	41.5×10^{3}	1.06	25.4×10 ³	1.07
	92.1	51.8×10 ³	49.4×10^{3}	1.05	31.8×10^{3}	1.06
	100	56.4×10^3	54.2×10^3	1.04	35.1×10^3	1.07

Table S1. Detailed information in the CuAAC polymerization of the AB_3 monomer

^a Measured by THF SEC with MALLS detector. ^b Measured by THF SEC with RI detector, calibrated

with linear PMMA standards.







Fig. S4 Evolution of number-average molecular weights ($M_{n,Rl}$) of polymerization of at different feed ratios of $[AB_3]_0$: $[B_3]_0$: $[CuSO_4 \cdot 5H_2O]_0 = 1000 : 1: 10, 500 : 1: 5 and 200 : 1: 2.$

3. References

- 1. B. G. Davis, K. Khumtaveeporn, R. R. Bott and J. B. Jones, *Bioorg. Med. Chem.*, 1999, **7**, 2303-2311.
- 2. X. Cao, Y. Shi, X. Wang, R. W. Graff and H. Gao, *Macromolecules*, 2016, **49**, 760-766.