Supporting Information

Dual pH-responsive Shell-cleavable Polycarbonate Micellar Nanoparticles for *In Vivo* Anticancer Drug Delivery

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Monomer Synthesis

Synthesis of MTC-ProtCat. Briefly, in a single-neck 50 mL round bottom flask equipped with a stir bar, MTC-OC_6F_5 (3.1 g, 9.5 mmol) was first dissolved in THF (15 mL) and stirred for 5 minutes under ambient conditions. Subsequently, 2-hydroxyethyl 3,4-bis(benzyloxy)benzoate (3.0 g, 7.9 mmol) was added and allowed to stir at room temperature (~ 22 ºC) for an additional 5 minutes. Lastly, 1.0 M solution of Tetrabutylammonium fluoride (TBAF) in THF (0.4 mL) was added to the stirred solution dropwise via syringe. The reacted mixture was quenched by addition of ammonium acetate (1.1 g, 14.3 mmol), and was allowed to stir for 1.5 h. The reaction mixture was directly loaded on to a silica gel column and was purified by flash column chromatography (eluent: CH_2Cl_2) to yield MTC-ProtCat as a yellow solid. To obtain monomer suitable for polymerization, the crude product was further purified by recrystallization by dissolving the solid in 8 ml of diethyl ether, ethyl acetate, dichloromethane and THF (2 ml each), followed by addition of 50 mL of hexane. The crystals are allowed to form at room temperature for 1 day, and are subsequently obtained by washing the crystals with cold hexane. ^{1}H NMR (400 MHz, $CDCl_3$, 22 ºC): δ 7.65-7.63 (m, 2H, -COOCC*H*-), 7.46-7.28 (m, 10H, -$CH_2C_6H_5$), 6.98-6.96 (m, 1H, -*COOCCHCCHC*-), 5.26-5.23 (d, *J* = 12 Hz, 4H, -$C_2COCH_2C_6H_5$), 4.70-4.67 (m, 2H, -$COOCH_2CH_2$-), 4.54 (m, 4H, $COOCH_2$CC2-), 4.21-4.18 (s, 2H, -$COOCH_2CH_2OH$), 1.32 (s, 3H, -CH_3).

Polymer Synthesis

PEG5k-*a*-poly[(TMC)$_6$-*co*-(MTC-ProtCat)$_{24}$]. The procedure of PEG5k-*a*-poly(MTC-OBn)$_{30}$ (PC3) was followed using mPEG-*a*-OH (200 mg, 0.04 mmol), trimethylene carbonate (TMC) (82 mg, 0.8 mmol, 20 equiv), MTC-ProtCat (536 mg, 1.0 mmol, 26 equiv), 2.2 mL of dry CH_2Cl_2, and DBU (13 mg, 0.09 mmol). The crude mixture was dialyzed (1000 MWCO) against 1:1 v/v 2-propanol:acetonitrile, concentrated, suspended in water (5 mL) and

lyophilized to afford the desired polymer as a white solid (0.575 g, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.60-6.90 (m, 300H), 5.14 (br s, 96H), 4.38 (br s, 100H), 4.21-4.05 (br m, 121H), 3.64 (s, 454H), 3.38 (s, 3H), 2.00 (br, 70H), 1.28 (d, 3H), 1.15 (m, 72H). $M_{n,GPC}$: 12.7 kDa, $Đ$ = 1.13.

PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$]. The procedure of PEG5k-*a*-poly(MTC-OBn)$_{30}$ (PC3) was followed using mPEG-*a*-OH (400 mg, 0.04 mmol), trimethylene carbonate (TMC) (99 mg, 0.97 mmol, 24 equiv), MTC-ProtCat (536 mg, 1.0 mmol, 26 equiv), 2.2 mL of dry CH_2Cl_2, and DBU (13 mg, 0.09 mmol). The crude mixture was dialyzed (1000 MWCO) against 1:1 v/v 2-propanol:acetonitrile, concentrated, suspended in water (5 mL) and lyophilized to afford the desired polymer as a white solid (0.771 g, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.59-6.90 (m, 317H), 5.13 (br s, 94H), 4.75 (q, 1H), 4.37 (br s, 96H), 4.21-4.07 (br m, 128H), 3.64 (s, 910H), 3.37 (s, 3H), 2.17-1.88 (m, 37H), 1.15 (m, 74H). $M_{n,GPC}$: 15.6 kDa, $Đ$ = 1.18.

Deprotection of PEG5k-*a*-poly[(TMC)$_6$-*co*-(MTC-ProtCat)$_{24}$] (PC1) and PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$] (PC2). The deprotecture of PEG5k-*a*-poly[(TMC)$_6$-*co*-(MTC-ProtCat)$_{24}$] was described as an example. PEG5k-*a*-poly[(TMC)$_6$-*co*-(MTC-ProtCat)$_{24}$] (0.57 g) was first dissolved in 14 mL of methanol and THF (1:1), followed by addition of 2 spatulas of Pd/C into a 50 ml glass vial. The glass vial was placed under hydrogen at room temperature with overnight stirring. After which, the polymer was filtered using THF/methanol (1:1) solvent mixture, and the collected polymer was dried under vacuum, followed by precitation in cold diethyl ether twice. Finally, the solvents were removed and the polymer was lyophilized to obtain an off-white polymer with a more than 90% yield.

AF-488-conjugated PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$] (AF488-PC2). In a glovebox, PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$] (63.7 mg, 4.07×10^{-3} mmol) was dissolved in 1 mL of dry DMSO, followed by addition of 4-dimethylaminopyridine (DMAP,

0.9 mg, 7.4×10^{-3} mmol) and ALEXA FLUOR 488 free acid (5 mg, 9.1×10^{-3} mmol) in 1 mL of dry DMSO solution. After 36.4 μL of *N*,*N*'-dicyclohexylcarbodiimide solution (DCC, in 1 M DCM solution) was dropped to the above reaction mixture, the resulting solution stirred for 2 days, and then dialyzed against the solvent mixture of MeOH and DCM (volume ratio is 1:1) using a dialysis membrane with the MWCO 1,000 Da (Spectra/Por 7, Spectrum Laboratories Inc.**)** for 2 days. Finally the solution in the dialysis bag was concentrated to dryness and dried in a vacuum oven.

Synthesis of PEG10k-*a*-P(TMC)$_{16}$ (PC3). In a nitrogen filled glovebox, a 4 mL glass vial was charged with mPEG-*a*-OH (404 mg, 0.04 mmol, 1 equiv), TMC (204 mg, 2 mmol, 50 equiv), a Teflon-coated stir bar, and 3 mL of dry CH_2Cl_2. After the solids dissolved, DBU (30 mg, 0.2 mmol) was added to start the polymerization. The reaction mixture was stirred for 3 hours at room temperature, at which point an excess of benzoic acid (37 mg, 0.3 mmol) was added to quench the catalyst. The crude reaction mixture was precipitated into diethyl ether (30 mL). Two cycles of centrifugation/decantation of the supernatant, followed by drying under reduced pressure, afforded the desired block copolymer as a white solid (424 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.23 (t, 64H), 3.64 (s, 909H), 3.37 (s, 3.3H), 2.04 (m, 32H), 1.31 (d, 2H). $M_{n,GPC}$: 13.9 kDa, $Đ$ = 1.08.

MPEG10k-poly[(TMC)$_8$-*co*-(MTC-Cat)$_{24}$] (PC4). The polymerization procedure of PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$] was followed using MPEG10k (Mn 10,595, PDI 1.03) as a macroinitiator. MPEG10k-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$], 81% yield, ^{1}H NMR (400 MHz, $CDCl_3$): 7.63-6.85 (m, 317H), 5.15 (br s, 94H), 4.38 (br s, 96H), 4.33-4.02 (br m, 128H), 3.64 (s, 910H), 2.07-1.64 (m, 37H), 1.15 (m, 74H). $M_{n,GPC}$: 16.8 kDa, $Đ$ = 1.19. The polymer was then subject to hydrogenolysis following the above deprotection ptocotol of PEG10k-*a*-poly[(TMC)$_8$-*co*-(MTC-ProtCat)$_{24}$] to achieve MPEG10k-poly[(TMC)$_8$-*co*-(MTC-Cat)$_{24}$].

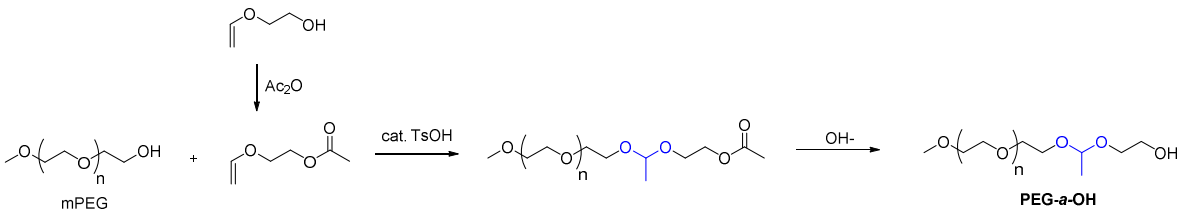


Figure S-1. Synthesis of acetal end-functionalized PEG.

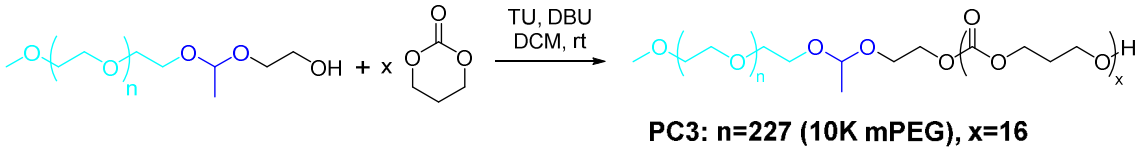


Figure S-2. Synthesis of PEG10k-*a*-poly(TMC)$_{16}$ *via* organocatalytic ROP.

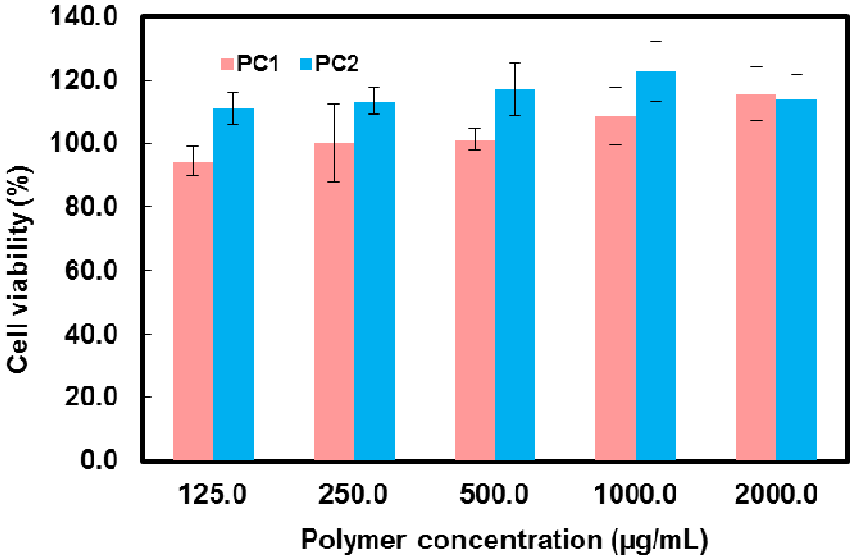
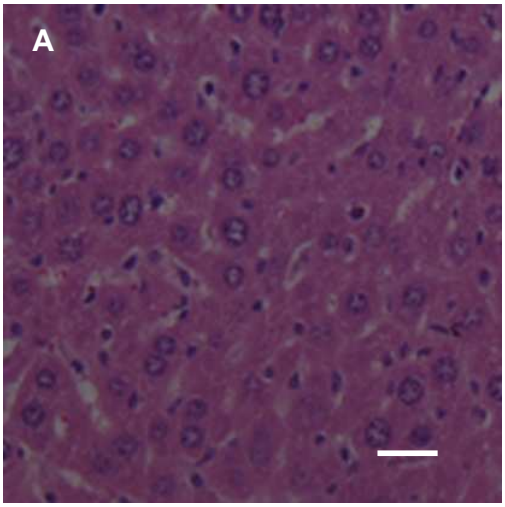
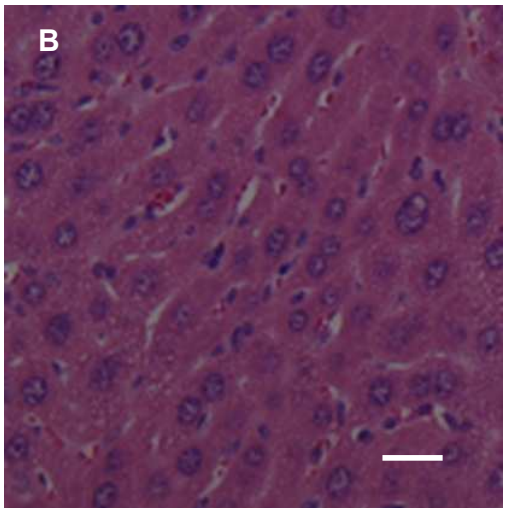


Figure S-3. Viability of BT-474 cells after 48-h incubation with blank polymers.


A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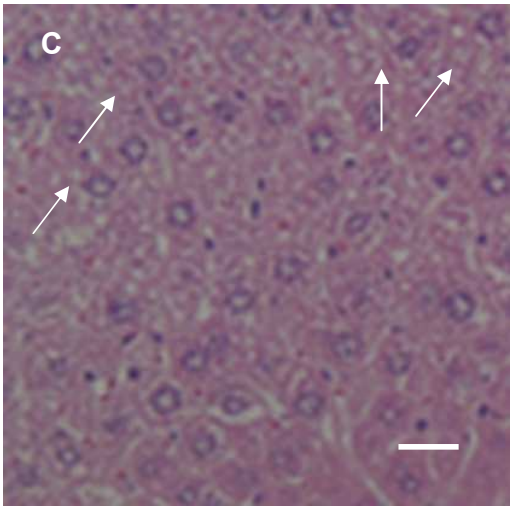
C

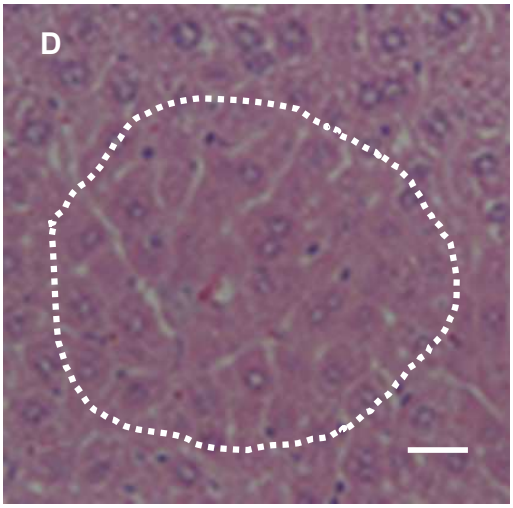

Figure S-4. High magnification of H&E staining of liver sections from control mouse (A), mice treated with BTZ-PC2 (B) and BTZ (C, D), where cytoplasmic vacuolation is seen in C and hydrop degeneration of hepatocytes is observed in D. Scale bar: 50 μm.