Copper-Free Click Reaction for Synthesis of Redox-Responsive Water-soluble Core Cross-Linked Nanoparticles for Drug Delivery in Cancer Therapy

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Figure S1. $^1$H NMR (in CDCl$_3$) of 4-formylphenyl acrylate (FPA).
Figure S2. $^1$H NMR (in CDCl$_3$) of $N,N'$-Bis (acyloyl)cystamine (BAC).

Figure S3. $^1$H NMR (in CDCl$_3$) of poly(FPA-co-PEGMEA) (P2a).
**Figure S4.** $^1$H NMR (in CDCl$_3$) of poly(FOPA-co-PEGMEA) (P2b).

**Figure S5.** $^1$H NMR (in DMSO-d$_6$) of core cross-linked nanoparticle CCNP2.
**Figure S6.** FT-IR spectra of cross-linker BAC, oxime functionalized copolymer P2b and CCNP2.

*Synthesis of click product P3 by P2b and acrylic acid:* P3 was synthesized in a similar way of CCNPs. Shortly, aqueous NaOCl (0.084 ml, 0.135 mmol) was added to dissolved P2b (0.05 mg, 0.054 mmol) in 1.5 ml H$_2$O-THF (1:1.5) at 5 °C. After 20 min stirring, acrylic acid (3.9 mg, 0.054 mmol) was added slowly to the mixture and kept it in a stirring condition for 24 h at room temperature. Excess NaOCl and acrylic acid were removed by dialysis with water and product was dried by lyophilisation. $^1$H NMR (CDCl$_3$, 400MHz) (Figure S7, Supplementary Information): $\delta$ (ppm) 1.59 (polymer backbone), 1.76 (polymer backbone), 2.31 (polymer backbone), 4.08 (CH$_2$-CH$_2$-O- of PEGMEA), 4.83 (CH of isoxazoline ring), 7.12 (Ar protons), 7.32 (Ar protons), 7.70 (Ar protons), 7.96 (unreacted oxime CH).
Figure S7. $^1$H NMR (in DMSO-d$_6$) of model isoxazoline formation from P2b and acrylic acid.

Figure S8. FESEM images after 4 days of 10 mM GSH treatment - (a) CCNP1 and (c) CCNP2; corresponding AFM image of (b) CCNP1 and (d) CCNP2.
**Figure S9.** DLS data of oxime functionalized copolymers and CCNPs before and after DOX loading: a) P1b, b) P2b, c) CCNP1 and d) CCNP2.
Figure S10. Fluorescent images of breast cancer cell line MDA MB 468 over a time span of 1-4 h. DOX emits red fluorescence whereas nuclei stained with DAPI produces blue fluorescence. The top 9 panels are for DOX loaded CCNP1 and bottom 9 panels are for free DOX samples done at same time.
Figure S11. Phase contrast microscopy images of MDA MB 468 treated with DOX loaded CCNP1 in dose (top, after 48 h) and time (bottom, for 4 μg/ml) dependent manner.