(Revised Supporting Information for *Biomacromolecules*)

Bioreducible Shell-Crosslinked Hyaluronic Acid Nanoparticles for Tumor-Targeted Drug Delivery

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EXPERIMENTAL PROCEDURES

Preparation of PCL-N_3

PCL-N_3 was synthesized according to a previously reported procedure.[1] Hydroxyl-terminated PCL (PCL-OH) was first synthesized by the ring-opening polymerization of ε-caprolactone (5 g, 43.8 mmol) in the presence of n-butanol (32.46 mg, 0.438 mmol) and stannous octoate (52.23 mg, 0.101 mmol) at 110 ºC. In the second step, the PCL-OH was tosylated using p-toluenesulfonyl chloride. For this reaction, PCL-OH (2 g, 0.180 mmol) and p-toluenesulfonyl chloride (343 mg, 1.80 mmol) were dissolved in dichloromethane under nitrogen atmosphere. The resulting solution was cooled in an ice water bath, followed by the addition of triethylamine (182 mg, 1.80 mmol). Thereafter, the solution was stirred at room temperature for 24 h. Tosylated PCL (PCL-OTs) was obtained by precipitation in an excess of cold methanol and dried at room temperature under vacuum. Sodium azide (235 mg, 3.6 mmol) was added to a solution of PCL-OTs (850 mg, 0.18 mmol) in dry DMF under nitrogen atmosphere (Caution: NaN_3 is highly toxic and can explode on heating. Extreme care should be taken when handling NaN_3). The reaction mixture was stirred at room temperature for 24 h. After the solution was concentrated under vacuum, the mixture was diluted with dichloromethane and passed through a short basic alumina column to remove excess salt. Then, PCL-N_3 was obtained by precipitation in cold methanol.

REFERENCE

(1) Kim, S. H.; Kim, J. H.; You, D. G.; Saravanakumar, G.; Yoon, H. Y.; Choi, K. Y.; Thambi, T.; Deepagan, V. G.; Jo, D. G.; Park, J. H. *Chem. Commun.* **2013,** *49*, 10349-10351.

Table S1. Physicochemical characteristics of HA-*b*-PCL copolymer.

Block copolymer	Feed molar ratio[a]	X[b]	M_n[c]
HA-*b*-PCL	1.5:1	32	17740

[a]Molar feed ratio of alkyne HA to PCL-N_3.
[b]Weight percentage of PCL in the block copolymer.
[c]Number-average molecular weight calculated using ^{1}H NMR.

Table S2. Physicochemical characteristics of HA nanoparticles.

Sample name	Size (nm) [a]
HA-NPs	198.1±2.95
HA-ss-NPs	162.1±0.81

[a]Determined using the particles analyzer.

Table S3. Physicochemical characteristics of DOX-loaded HA nanoparticles.

Sample name	DS of PDA	DOX feed ratio	Loading effieciency (%)[a]	Loading content (%)[a]	Size (nm)[b]
DOX-HA-ss-NPs (3)	3.74	10	75.35±0.48	7.5	190.5±0.38
DOX-HA-ss-NPs (6)	6.38	10	79.48±2.70	7.9	178.5±1.76
DOX-HA-ss-NPs (10)	10.61	10	90.93±1.74	9.0	159.2±0.14
DOX-HA-NPs (10)	10.61	10	74.4±3.15	7.4	181.63±1.33

[a]Determined using UV-visible spectrophotometer. [b]Determined using the particles analyzer.

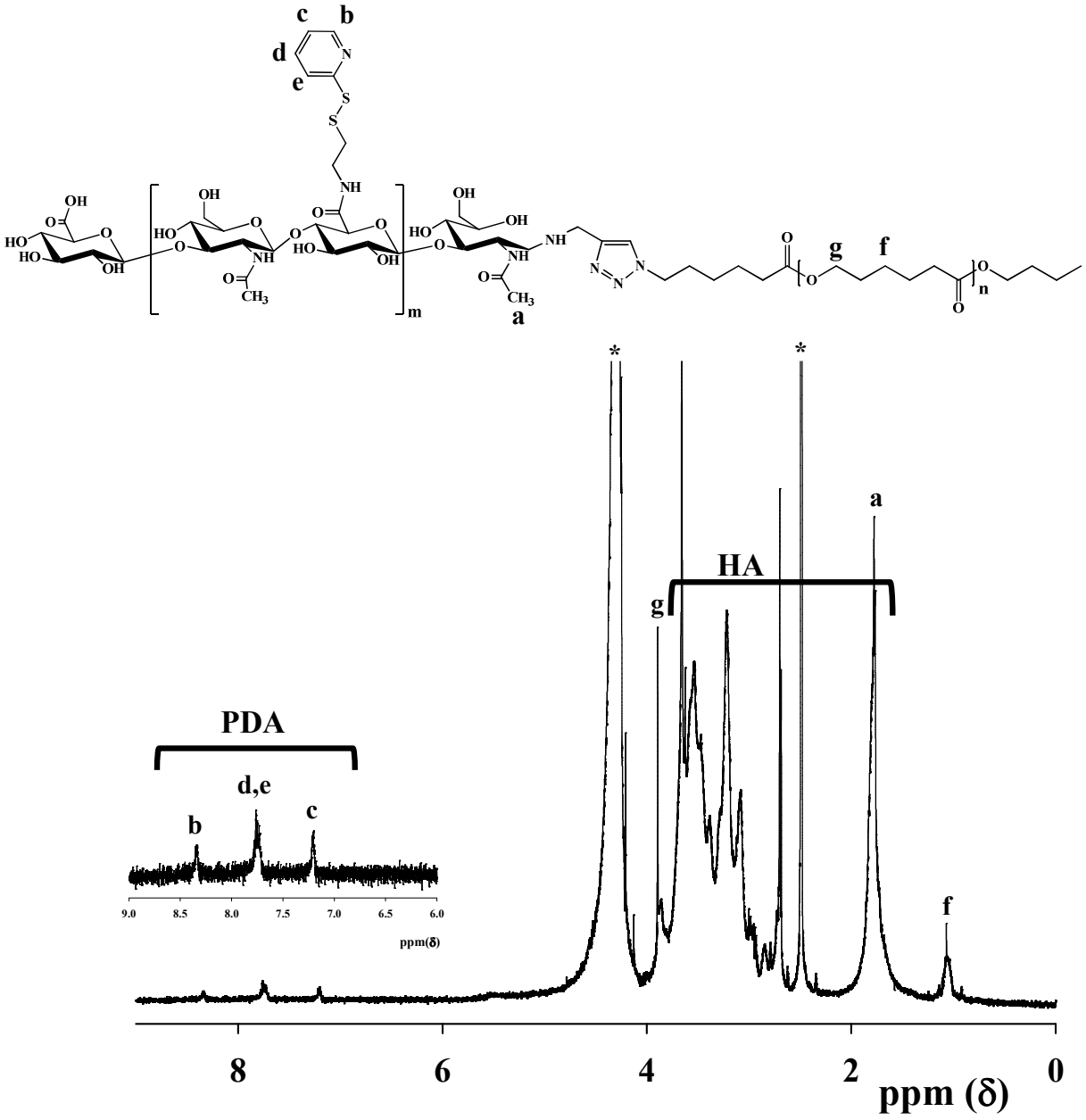

Figure S1. ^{1}H NMR spectra of PDA-conjugated HA-*b*-PCL.

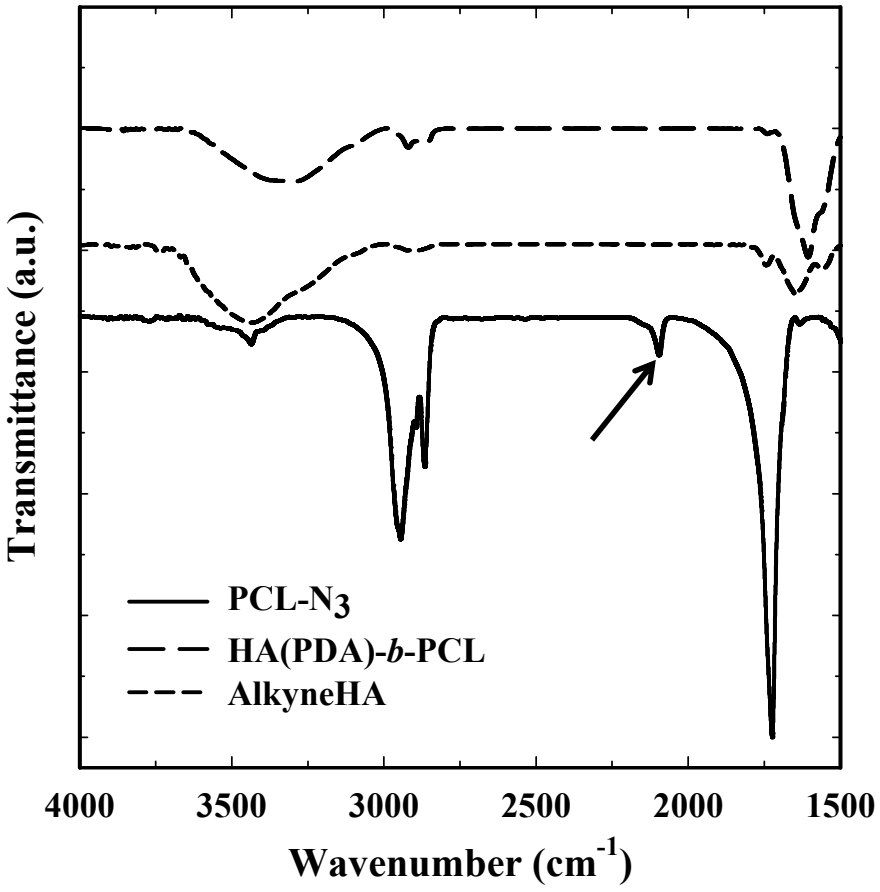

Figure S2. FT-IR spectra of copolymers.

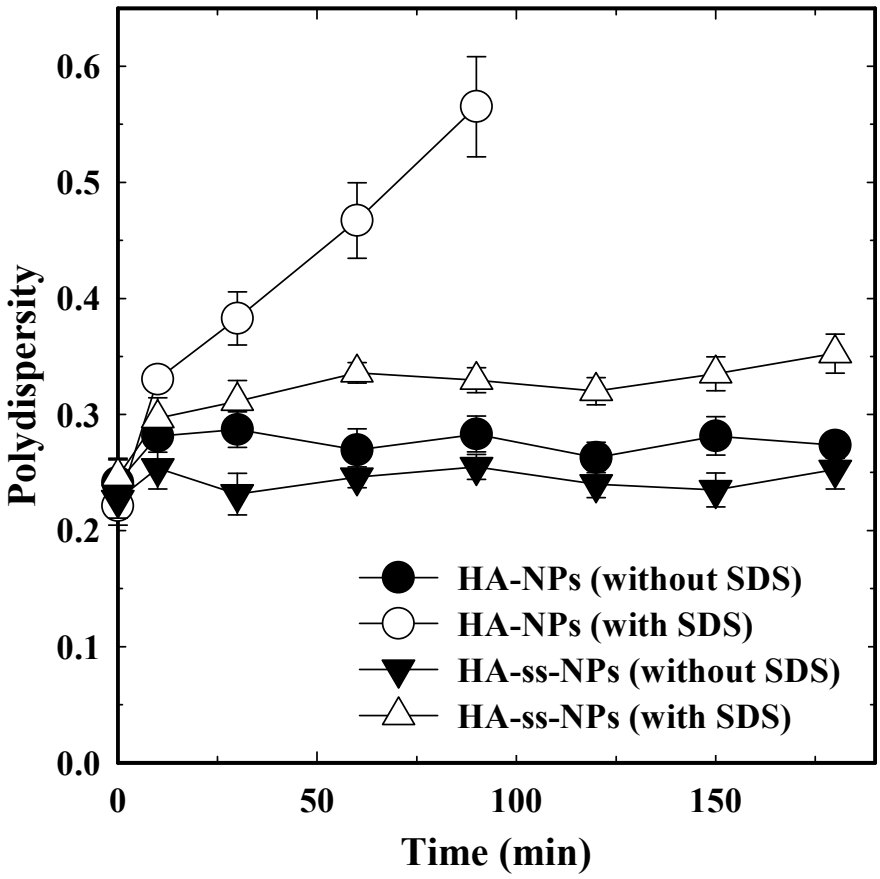

Figure S3. Changes in polydispersity as a function of time. The error bars in the graph represent standard deviations (n= 3).

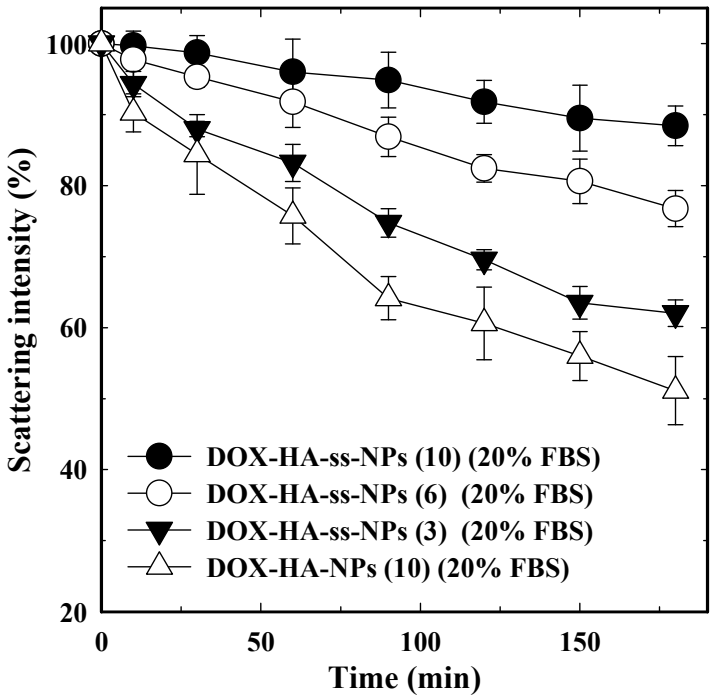

Figure S4. The change in light scattering intensities of DOX-loaded HA nanoparticles with various DSs in the presence of FBS as a function of time. The error bars in the graph represent standard deviations (n= 3).

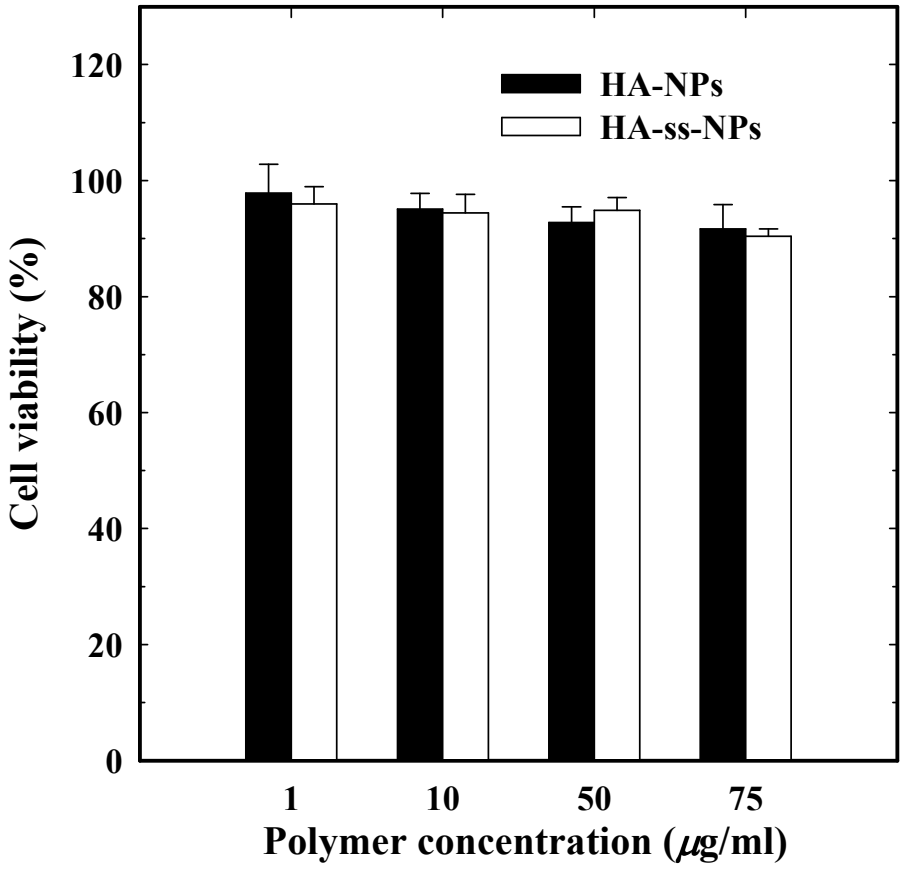

Figure S5. *In vitro* cytotoxicity of bare nanoparticles. The error bars in the graph represent standard deviations (n=3).