ACS Macro Letters

Letter

pubs.acs.org/macroletters

PEG-Polypeptide Dual Brush Block Copolymers: Synthesis and Application in Nanoparticle Surface PEGylation

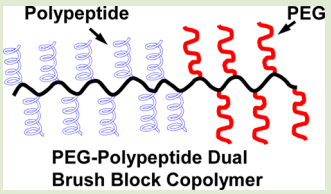
Yanfeng Zhang,[†] Qian Yin,[†] Hua Lu,[†] Hongwei Xia,[‡] Yao Lin,*[,‡] and Jianjun Cheng*[,†]

[†]Department of Materials Science and Engineering, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States

[‡]Polymer Program, Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06269, United States

Supporting Information

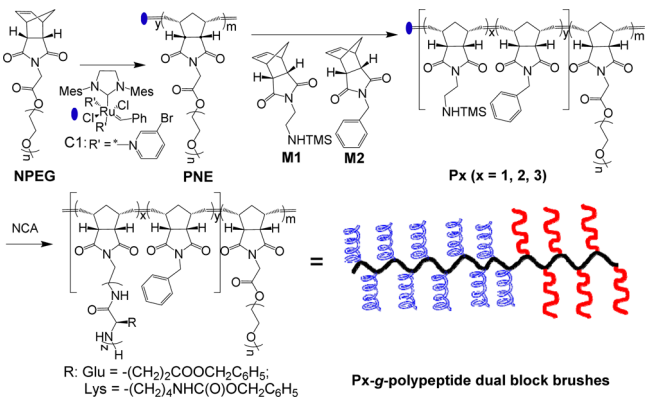
ABSTRACT: Amphiphilic polypeptide-containing hybrid dual brush block copolymers with controlled molecular weights and narrow molecular weight distributions were synthesized in one pot via ring-opening metathesis polymerization of sequentially added norbornyl-PEG and *N*-(2-((trimethylsilyl)amino)ethyl)-5-norbornene-endo-2,3-dicarboximide (M1), followed by ring-opening polymerization of amino acid *N*-carboxyanhydrides. Polylactide nanoparticles coated with these amphiphilic dual brush block copolymers showed significantly improved stability in PBS solution compared to those coated with amphiphilic linear block copolymers such as PEG-polylactide and PEG-polypeptides.



The synthesis and self-assembly of amphiphilic linear block copolymers with well-defined compositions and structures have been an important research topic in polymer science over the past several decades.[1] Numerous well-organized structures have been developed,[2] some of which have been widely adopted for drug delivery and controlled release applications.[3] Block copolymers bearing more complex segments than linear polymers (e.g., dendritic,[4] brush,[5] and cyclic polymers[6]), however, are not as actively reported due in part to their relatively challenging synthesis. Controlled synthesis of these complex block copolymers would significantly expand the library of polymeric materials and make it possible to explore their physicochemical properties for potential applications.

Brush-like polymers are useful materials in nanoscience, either as standalone materials or as building blocks for self-assembly.[7] Brush block copolymers are particularly interesting materials because of their peculiar topological and large domain structures.[8] Most brush polymers developed so far contain flexible brushes made of polyolefins, polyesters, and polyethers.[9] Brush block copolymers containing rigid polymer brushes would yield materials with unique properties, but such materials with controlled molecular weights (MWs) and narrow molecular-weight distributions (MWDs) remain synthetically challenging. Polypeptides have been frequently used as rigid building blocks in the design of homo- and hybrid copolymers for their unique, protein-like conformations (e.g., α-helix).[10] Incorporating polypeptides with intrinsic secondary structures into the brush side chains may significantly expand the horizon of brush-like macromolecules by providing materials with unprecedented properties. We have previously reported the synthesis and self-assembly of a series of polypeptide-brush polymers in the past few years.[11] Here, we report the first synthesis of amphiphilic poly(ethylene glycol)(PEG)-polypeptide dual brush block copolymers with controlled MWs and narrow MWDs via one-pot ring-opening metathesis polymerization (ROMP) of norbornyl-PEG (NPEG) and inimer *N*-(2-((trimethylsilyl)amino)ethyl)-5-norbornene-endo-2,3-dicarboximide (M1), followed by trimethylsilyl amine (*N*-TMS) mediated ring-opening polymerization (ROP) of amino acid *N*-carboxyanhydrides (NCAs) (Scheme 1). We further demonstrated that these amphiphilic polypeptide-containing brush block copolymers were remarkable materials for coating polylactide (PLA) nanoparticles and preventing nanoparticles from aggregation in PBS solution for an extended period of time.

Scheme 1



We first prepared the hydrophilic poly(norbornene diimide) with pendant PEG polymer (denoted as $PNE_{M/I}$, where M/I is the monomer/initiator ratio) by ROMP of NPEG using Grubbs' catalyst C1 in DCM (Scheme 1). The MWs of PNE_{20}

Received: July 13, 2013
Accepted: August 16, 2013

   dx.doi.org/10.1021/mz4003672 | *ACS Macro Lett.* 2013, 2, 809−813

Table 1. PNE-Poly(norbornene diimide) Prepared by ROMP

entry	polymer	initiator	monomer	$[M]_{tot}/[I]$	conv[b] (%)	dn/dc[c] (mL/g)	M_n (M_n*; $\times10^{-4}$)[d]	MWD[d]
1	PNE_{20}		NPEG	20	>98	0.032	2.34 (2.60)	1.19
2	PNE_{40}		NPEG	40	>98	0.032	4.84 (5.20)	1.20
3	P1	PNE_{20}	M1 + M2[a]	80	>98	0.056	6.21 (6.94)	1.12
4	P2	PNE_{20}	M1 + M2[a]	160	>98	0.060	9.85 (11.08)	1.21
5	P3	PNE_{40}	M1 + M2[a]	160	>98	0.052	11.24 (13.68)	1.17

[a]Random copolymerization, M2/M1 molar ratio was fixed at 3/1. [b]The conversion of monomer was determined by ^{1}H NMR in $CDCl_3$. [c]The dn/dc values were calculated offline by using the internal calibration system processed by the ASTRA V software. [d]The MW obtained by GPC (the expected MW).

Table 2. Synthesis of PEG-Polypeptide Dual Brush Block Copolymers

entry	polymer	microinitiator	monomer	$[M]/[I]$	conv[a] (%)	dn/dc[b] (mL/g)	M_n[c] (M_n*; $\times10^{-4}$)	MWD[c]
1	P1-*g*-Glu_{20}	P1	Glu-NCA	20	>95	0.080	14.3 (15.7)	1.05
2	P1-*g*-Glu_{40}	P1	Glu-NCA	40	>95	0.086	20.6 (24.4)	1.04
3	P2-*g*-Glu_{20}	P2	Glu-NCA	20	>95	0.083	25.0 (28.5)	1.08
4	P2-*g*-Glu_{40}	P2	Glu-NCA	40	>95	0.088	38.7 (46.0)	1.09
5	P3-*g*-Glu_{20}	P3	Glu-NCA	20	>95	0.081	26.4 (31.1)	1.06
6	P1-*g*-Lys_{20}	P1	Lys-NCA	20	>95	0.082	13.3 (16.9)	1.09

[a]The conversion of monomer was determined by FT-IR. [b]The dn/dc values were calculated offline by using the internal calibration system processed by the ASTRA V software. [c]The MW obtained by GPC (the expected MW).

and PNE_{40}, obtained through ROMP of NPEG at M/I ratios of 20 and 40, were 2.34×10^4 and 4.84×10^4 g/mol, agreeing well with the expected M_n of 2.60×10^4 and 5.20×10^4 g/mol, respectively (Table 1). The MWDs of both PNE_{20} and PNE_{40} were less than 1.2. The ^{1}H NMR analysis indicated that NPEG monomers were completely consumed in 3 h (Figure S2b).

We next attempted to synthesize polypeptide-containing dual brush block copolymers via a "grafting-from" strategy by growing polypeptide brushes from a ROMP backbone polymer derivatized with the initiation groups for the NCA polymerization. To facilitate controlled NCA polymerization and prevent inactivation of ROMP catalyst by free amine, the polymer backbone derived from ROMP was designed to have *N*-TMS amine groups for the subsequent controlled NCA polymerization.[11e] *N*-(2-((Trimethylsilyl)amino)ethyl)-5-norbornene-endo-2,3-dicarboximide (M1), an inimer containing a ROMP polymerizable *endo*-norbornene functional group and an *N*-TMS amine group, was selected in this study (Scheme 1). M2 was used as a comonomer to tune the density of *N*-TMS group along the polynorbornene backbone. Random block copolynorbornene containing *N*-TMS groups, denoted as P*x* (*x* = 1−3), were prepared by adding a mixture of M1 and M2 (M2/M1 = 3:1) to PNE at a (M1 + M2)/PNE molar ratio ($[M_{tot}]/[I]$) of 80 and 160 (entries 3−5, Table 1 and Scheme 1). The resulting P1−P3 thus contain a hydrophilic PNE block and a hydrophobic random poly(M1/M2) block. As shown in Table 1, the synthesis of P1−P3 was well controlled, with expected MWs and narrow MWDs (entries 3−5).

^{1}H NMR analysis showed that the TMS groups on M1 were well preserved in P1−P3 (Figure S2c), similar to what was reported previously.[11e] P1−P3 were then used as initiators for polymerization of NCAs after DCM (solvent for ROMP) was removed under vacuum and replaced with anhydrous DMF. ROP of the (*S*)-γ-benzyl-L-glutamate *N*-carboxyanhydride (Glu-NCA) initiated by P1−P3 proceeded in a similar fashion to those initiated by *N*-TMS amine-containing small molecules,[11f,12] and yielded poly(γ-(benzyl)-L-glutamate) (PBLG)-containing hybrid dual brush block copolymers with controlled MWs and narrow MWDs (Table 2).[11a] The dual brush block copolymers were denoted as P*x*-*g*-Glu_z, where "P*x*" corresponds to the P1−P3 in Table 1 and "*z*" is the Glu-NCA/M1 ratio. When P1 was used as the macroinitiator (containing ∼20 *N*-TMS groups per chain) and the [Glu-NCA]/[*N*-TMS] ratio was controlled at 20, the M_n of the dual brush block copolymer P1-*g*-Glu_{20} was 14.3×10^4 g/mol, agreeing well with the calculated M_n (15.7×10^4 g/mol; entry 1, Table 2). GPC analysis revealed a monomodal peak for P1-*g*-Glu_{20}, the elution time of which shifted to the higher MW region compared to its precursor P1 (Figure 1b,c). The actual DP of the PBLG brush

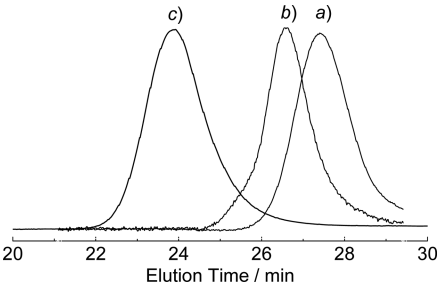


Figure 1. GPC traces (light scattering signal) of PNE_{20} (a), P1 (b), and P1-*g*-Glu_{20} (c).

was determined to be ∼19 by ^{1}H NMR analysis (Figure S3), which agreed well with the expected DP (20). Following the same methods, a series of dual brush block copolymers P*x*-*g*-Glu_z with controlled MWs were prepared (entries 2−5, Table 2). When the polymerization of (*S*)-ε-carbobenzoxy-L-lysine-*N*-carboxyanhydride (Lys-NCA) was mediated by P1 at a Lys-NCA/*N*-TMS ratio of 20, P1-*g*-Lys_{20} with the expected MW was also obtained (entry 6, Table 2). The actual DP of PLys block was determined to be 20 by ^{1}H NMR analysis, which is in perfect agreement with the expected DP of PLys. All P*x*-*g*-Glu(or Lys)$_z$ dual brush block copolymers reported in Table 2 have very narrow MWDs (<1.1), substantiating that both ROMP and NCA ROP were highly controlled. We have previously reported a short ROMP polymer (11mer poly(M1)) grafted with 200mer PBLG (Glu_{200}) with excellent controlled

dx.doi.org/10.1021/mz4003672 | ACS Macro Lett. 2013, 2, 809−813

MW and narrow MWD.[11e] ROMP of functional norbornene monomers to give polymers with DP up to 400 has been reported.[7e] Although dual brush block copolymers with very long backbones or very long brushes are not the focus of this study, dual brush copolymers with a wide range of backbone and brush lengths should be attainable.

Modification of the surface of nanoparticles (NPs) with PEG, termed "PEGylation", is a well-established approach to reduce the non-specific protein/tissue binding to NPs and to enhance NP stability under physiological condition.[13] The PEG density on the NP surface plays a significant role in enhancing the stability of NPs.[14] PEGylating NPs with hydrophobic surface can be achieved via precipitation of amphiphilic PEG-containing block copolymers, such as PEG-polylactide (PEG-PLA), taking advantage of the hydrophobic interaction between NP and PLA. While this approach is simple and effective, several drawbacks are also noted.[15] For instance, linear PEG may not provide enough surface coating and thus often cannot offer sufficient stealth effect and render completely inert surface. PEGylated NPs, especially those with low MW PEG, can still be subject to aggregation in biological media, nonspecific protein binding, and undesirable recognition by the reticuloendothelial system.[16] Moreover, a single block of hydrophobic polymer may not provide sufficient force to hold PEG, in particular, high MW PEG, on the NP surface via its hydrophobic interaction with the hydrophobic NP surface. Specially designed block copolymers, such as PLA-PEG-PLA, need to be used to provide more stable NP surface PEGylation by increasing hydrophobic interaction with NP surface.[15] It has been reported that branched PEG[17] and brush PEG[18] can provide more surface stealth effect. To this end, an amphiphile that could give rise to a stronger hydrophobic interaction and better stealth effect than conventional linear PEG-PLA is of great value. We reason that P*x*-*g*-Glu$_z$, with its ordered packing of the rigid rod-like hydrophobic polypeptide domains[19] and the bottle brush-like PEG,[20] may offer strong hydrophobic interaction and sufficient surface stealth simultaneously.

To examine the stabilization effect of P*x*-*g*-Glu$_z$ on NPs, we prepared paclitaxel-polylactide (Ptxl-PLA) conjugates through paclitaxel-initiated lactide polymerization at M/I (lactide/paclitaxel) ratio of 100 in the presence of (β-diimine)ZnN(TMS)$_2$ (TMS = trimethylsilyl) as the catalyst.[21] The resulting Ptxl-PLA has a M_n of 12.7 × 10^3 g/mol and MWD (M_w/M_n) of 1.03. It was then used to prepare NPs to evaluate various surface PEGylation methods.[22] As expected, coprecipitation of Ptxl-PLA and mPEG5k (PEG) in phosphate buffered saline (PBS) solution could not provide sufficient surface PEGylation, and therefore, Ptxl-PLA NP aggregation was observed almost instantaneously (Figure 2a). Ptxl-PLA/PEG-PLA coprecipitation formed stable NP in water, as reported previously.[15] However, when a 1:1 mixture of mPEG$_{113}$-PLA$_{194}$ (PEG-PLA) and Ptxl-PLA was precipitated directly in PBS solution, effective NP surface PEGylation could not be achieved. NP size increased from 101 to 195 nm within 4 min based on dynamic light scattering (DLS) analysis. Large aggregates (~870 nm) were also observed (Figure 2b). As large aggregates would have substantially changed pharmacological profiles as compared to original NPs and the presence of large aggregates with micrometer diameter sizes would result in undesired death of animals based on our previous studies,[22] therefore the NPs prepared via coprecipitation of Ptxl-PLA/PEG-PLA in PBS solution cannot be used for in vivo systemic drug delivery. On the contrary, P1-*g*-Glu$_{20}$ provided excellent coating and surface

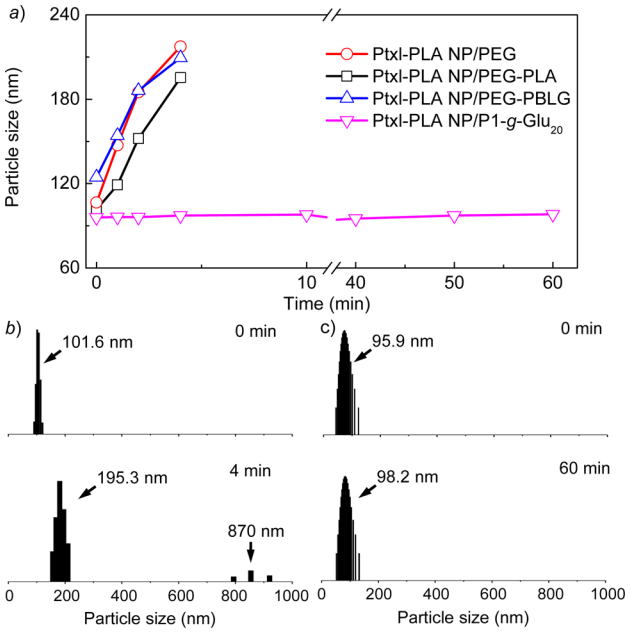


Figure 2. (a) Stability of Ptxl-LA NPs in PBS (1×) after coated with mPEG5k (PEG), mPEG5k-PLA (PEG-PLA), PEG-PBLG, or P1-*g*-Glu$_{20}$; (b) DLS spectra of Ptxl-LA/PEG-PLA NP in PBS buffer after 0 and 4 min; (c) DLS spectra of Ptxl-LA/P1-*g*-Glu$_{20}$ NP in PBS buffer after 0 and 60 min.

PEGylation to Ptxl-PLA NPs in PBS. When P1-*g*-Glu$_{20}$ and Ptxl-PLA (1:1, wt/wt) were coprecipitated directly in PBS solution, the obtained particle was 95.9 nm and its size remained unchanged for at least 24 h (Figure 2c and entry 11, Table S1). Other dual brush block copolymer reported in Table 2 could also stably coat Ptxl-PLA NP surface and prevent NPs from aggregation in PBS solution for at least 24 h (entries 12–22, Table S1). To determine whether the bottle brush structure is crucial to the observed NP stabilization effect, we synthesized a linear PEG-PBLG (mPEG$_{226}$-PBLG$_{215}$) with an M_n of 57.1 × 10^3 g/mol (M_w/M_n of 1.18) and a PEG weight percent (17%) similar to that of P1-*g*-Glu$_{20}$ (14%). PEG-PBLG was used for the surface coating of the Ptxl-PLA NPs via coprecipitation method. We found that the size of PEG-PBLG coated Ptxl-PLA NPs increased from 124 to 209 nm within just 4 min (Figure 2a). Very large aggregates (~7.5 μm) were observed 24 h later (entry 8, Table S1), demonstrating that linear PEG-PBLG could not afford a high density of PEG on the surface of NPs and provide excellent stealth effect.

In conclusion, a series of amphiphilic PEG-polypeptide dual brush block copolymers with controlled molecular weights and narrow molecular weights distributions were synthesized via a one-pot reaction of ring-opening metathesis polymerization and ring-opening polymerization of amino acid *N*-carboxyanhydrides. This novel polymerization technique allows easy access to hybrid bottlebrush-like polymeric materials with some unprecedented properties and functions, such as offering excellent surface PEGylation for the formulation of polymeric NPs for drug delivery applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, including monomers synthesis and characterizations, polymerization, and polymer characteriza-

dx.doi.org/10.1021/mz4003672 | ACS Macro Lett. 2013, 2, 809–813

tions. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jianjunc@illinois.edu; ylin@ims.uconn.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

J.C. acknowledges the support from the NSF (CHE-1153122) and the NIH Director's New Innovator Award (1DP2OD007246). Y.L. acknowledges the support of NSF (DMR-1150742).

REFERENCES

(1) Zhou, J. F.; Wang, L.; Chen, T.; Wang, W. *Prog. Chem.* **2005**, *17*, 1102.

(2) (a) Robb, M. J.; Connal, L. A.; Lee, B. F.; Lynd, N. A.; Hawker, C. J. *Polym. Chem.* **2012**, *3*, 1618. (b) Al-Badri, Z. M.; Maddikeri, R. R.; Zha, Y. P.; Thaker, H. D.; Dobriyal, P.; Shunmugam, R.; Russell, T. P.; Tew, G. N. *Nat. Commun.* **2011**, *2*, 482. (c) Bates, F. S.; Hillmyer, M. A.; Lodge, T. P.; Bates, C. M.; Delaney, K. T.; Fredrickson, G. H. *Science* **2012**, *336*, 434. (d) Cui, H. G.; Chen, Z. Y.; Zhong, S.; Wooley, K. L.; Pochan, D. J. *Science* **2007**, *317*, 647.

(3) (a) Yu, Y. S.; Eisenberg, A. *J. Am. Chem. Soc.* **1997**, *119*, 8383. (b) Wang, H. B.; Wang, H. H.; Urban, V. S.; Littrell, K. C.; Thiyagarajan, P.; Yu, L. P. *J. Am. Chem. Soc.* **2000**, *122*, 6855. (c) Hickey, R. J.; Haynes, A. S.; Kikkawa, J. M.; Park, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 1517. (d) Elsabahy, M.; Wooley, K. L. *Chem. Soc. Rev.* **2012**, *41*, 2545.

(4) (a) Wurm, F.; Frey, H. *Prog. Polym. Sci.* **2011**, *36*, 1. (b) Zhou, Z. Y.; D'Emanuele, A.; Lennon, K.; Attwood, D. *Macromolecules* **2009**, *42*, 7936. (c) Xie, C.; Ju, Z. H.; Zhang, C.; Yang, Y. L.; He, J. P. *Macromolecules* **2013**, *46*, 1437. (d) Urbani, C. N.; Bell, C. A.; Lonsdale, D.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2008**, *41*, 76. (e) Klok, H. A.; Rodriguez-Hernandez, J. *Macromolecules* **2002**, *35*, 8718. (f) Gillies, E. R.; Jonsson, T. B.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11936. (g) Wong, A. D.; DeWit, M. A.; Gillies, E. R. *Adv. Drug Delivery Rev.* **2012**, *64*, 1031. (h) Wang, Y.; Grayson, S. M. *Adv. Drug Delivery Rev.* **2012**, *64*, 852.

(5) (a) Miyake, G. M.; Weitekamp, R. A.; Piunova, V. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 14249. (b) Du, J. Z.; Chen, D. P.; Wang, Y. C.; Xiao, C. S.; Lu, Y. J.; Wang, J.; Zhang, G. Z. *Biomacromolecules* **2006**, *7*, 1898. (c) Berezkin, A. V.; Guseva, D. V.; Kudryavtsev, Y. V. *Macromolecules* **2012**, *45*, 8910. (d) Cheng, Z. P.; Zhu, X. L.; Fu, G. D.; Kang, E. T.; Neoh, K. G. *Macromolecules* **2005**, *38*, 7187. (e) Stepanyan, R.; Subbotin, A.; ten Brinke, G. *Macromolecules* **2002**, *35*, 5640.

(6) (a) Baba, E.; Honda, S.; Yamamoto, T.; Tezuka, Y. *Polym. Chem.* **2012**, *3*, 1903. (b) Zhu, Y. Q.; Gido, S. P.; Latrou, H.; Hadjichristidis, N.; Mays, J. W. *Macromolecules* **2003**, *36*, 148. (c) Touris, A.; Hadjichristidis, N. *Macromolecules* **2011**, *44*, 1969. (d) Pitet, L. M.; Hillmyer, M. A. *Macromolecules* **2009**, *42*, 3674. (e) Poelma, J. E.; Ono, K.; Miyajima, D.; Aida, T.; Satoh, K.; Hawker, C. J. *ACS Nano* **2012**, *6*, 10845.

(7) (a) Li, C. M.; Gunari, N.; Fischer, K.; Janshoff, A.; Schmidt, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1101. (b) Djalali, R.; Li, S. Y.; Schmidt, M. *Macromolecules* **2002**, *35*, 4282. (c) Mullner, M.; Yuan, J. Y.; Weiss, S.; Walther, A.; Fortsch, M.; Drechsler, M.; Muller, A. H. E. *J. Am. Chem. Soc.* **2010**, *132*, 16587. (d) Yuan, J. Y.; Xu, Y. Y.; Walther, A.; Bolisetty, S.; Schumacher, M.; Schmalz, H.; Ballauff, M.; Muller, A. H. E. *Nat. Mater.* **2008**, *7*, 718. (e) Johnson, J. A.; Lu, Y. Y.; Burts, A. O.; Lim, Y. H.; Finn, M. G.; Koberstein, J. T.; Turro, N. J.; Tirrell, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 559. (f) Zhang, M. F.; Muller, A. H. E. *J. Polym. Sci., Polym. Chem.* **2005**, *43*, 3461. (g) Ruhe, J.; Ballauff, M.; Biesalski, M.; Dziezok, P.; Grohn, F.; Johannsmann, D.; Houbenov, N.; Hugenberg, N.; Konradi, R.; Minko, S.; Motornov, M.; Netz, R. R.; Schmidt, M.; Seidel, C.; Stamm, M.; Stephan, T.; Usov, D.; Zhang, H. N. *Adv. Polym. Sci.* **2004**, *165*, 79. (h) Yuan, W. Z.; Zhang, J. C.; Wei, J. R. *Prog. Chem.* **2011**, *23*, 760. (i) Lee, H. I.; Pietrasik, J.; Sheiko, S. S.; Matyjaszewski, K. *Prog. Polym. Sci.* **2010**, *35*, 24. (j) Neiser, M. W.; Okuda, J.; Schmidt, M. *Macromolecules* **2003**, *36*, 5437. (k) Rzayev, J. *ACS Macro Lett.* **2012**, *1*, 1146.

(8) (a) Xia, Y.; Olsen, B. D.; Kornfield, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 18525. (b) Rzayev, J. *Macromolecules* **2009**, *42*, 2135. (c) Sun, G. R.; Cho, S. H.; Clark, C.; Verkhoturov, S. V.; Eller, M. J.; Li, A.; Pavia-Jimenez, A.; Schweikert, E. A.; Thackeray, J. W.; Trefonas, P.; Wooley, K. L. *J. Am. Chem. Soc.* **2013**, *135*, 4203. (d) Bolton, J.; Bailey, T. S.; Rzayev, J. *Nano Lett.* **2011**, *11*, 998. (e) Zhang, X. J.; Zhong, Z. L.; Zhuo, R. X. *J. Controlled Release* **2011**, *152*, E118. (f) Chang, Y.; Kwon, Y. C.; Lee, S. C.; Kim, C. *Macromolecules* **2000**, *33*, 4496.

(9) (a) Li, L.; Zheng, S. X. *J. Polym. Sci., Polym. Phys.* **2008**, *46*, 2296. (b) Vivek, A. V.; Dhamodharan, R. *J. Polym. Sci., Polym. Chem.* **2007**, *45*, 3818. (c) Cerit, N.; Cakir, N.; Dag, A.; Sirkecioglu, O.; Durmaz, H.; Hizal, G.; Tunca, U. *J. Polym. Sci., Polym. Chem.* **2011**, *49*, 2850. (d) Chen, J. K.; Hsieh, C. Y.; Huang, C. F.; Li, P. M. *J. Colloid Interface Sci.* **2009**, *338*, 428. (e) Ishizu, K.; Takano, S.; Ochi, K. *J. Appl. Polym. Sci.* **2007**, *104*, 3994. (f) Shi, Y.; Zhu, W.; Chen, Y. M. *Macromolecules* **2013**, *46*, 2391. (g) Teuchert, C.; Michel, C.; Hansen, F.; Park, D. Y.; Beckham, H. W.; Wenz, G. *Macromolecules* **2013**, *46*, 2. (h) Li, C. H.; Ge, Z. S.; Fang, J.; Liu, S. Y. *Macromolecules* **2009**, *42*, 2916. (i) Kang, E. H.; Lee, I. H.; Choi, T. L. *ACS Macro Lett.* **2012**, *1*, 1098. (j) Han, D. H.; Tong, X.; Zhao, Y. *Macromolecules* **2011**, *44*, 5531. (k) Tang, H. Y.; Li, Y. C.; Lahasky, S. H.; Sheiko, S. S.; Zhang, D. H. *Macromolecules* **2011**, *44*, 1491. (l) Li, Z.; Ma, J.; Lee, N. S.; Wooley, K. L. *J. Am. Chem. Soc.* **2011**, *133*, 1228. (m) Le, D.; Montembault, V.; Soutif, J. C.; Rutnakornpituk, M.; Fontaine, L. *Macromolecules* **2010**, *43*, 5611. (n) Liu, Y.; Chen, P.; Li, Z. B. *Macromol. Rapid Commun.* **2012**, *33*, 287.

(10) (a) Blasco, E.; del Barrio, J.; Sanchez-Somolinos, C.; Pinol, M.; Oriol, L. *Polym. Chem.* **2013**, *4*, 2246. (b) Shi, Z. H.; Lu, H. J.; Chen, Z. C.; Cheng, R. S.; Chen, D. Z. *Polymer* **2012**, *53*, 359. (c) Yun, J. P.; Faust, R.; Szilagyi, L. S.; Keki, S.; Zsuga, M. *Macromolecules* **2003**, *36*, 1717. (d) Chang, Y. K.; Kim, C. H. *Abstr. Pap. Am. Chem. Soc.* **2001**, *221*, U411. (e) Zhu, L. Y.; Toug, X. F.; Li, M. Z.; Wang, E. *J. Phys. Chem. B* **2001**, *105*, 2461. (f) Chang, Y. Y.; Kim, C. *J. Polym. Sci., Polym. Chem.* **2001**, *39*, 918.

(11) (a) Wang, J.; Lu, H.; Ren, Y.; Zhang, Y. F.; Morton, M.; Cheng, J. J.; Lin, Y. *Macromolecules* **2011**, *44*, 8699. (b) Zhang, Y. F.; Lu, H.; Lin, Y.; Cheng, J. J. *Macromolecules* **2011**, *44*, 6641. (c) Lu, H.; Wang, J.; Bai, Y. G.; Lang, J. W.; Liu, S. Y.; Lin, Y.; Cheng, J. J. *Nat. Commun.* **2011**, 2. (d) Lu, H.; Cheng, J. J. *J. Am. Chem. Soc.* **2008**, *130*, 12562. (e) Lu, H.; Wang, J.; Lin, Y.; Cheng, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 13582. (f) Lu, H.; Cheng, J. J. *J. Am. Chem. Soc.* **2007**, *129*, 14114.

(12) Lemmouchi, Y.; Perry, M. C.; Amass, A. J.; Chakraborty, K.; Schacht, E. *J. Polym. Sci., Polym. Chem.* **2007**, *45*, 3975.

(13) Stokes, K. K.; Hammond, P. T. *Abstr. Pap. Am. Chem. Soc.* **2004**, *227*, U358.

(14) (a) Han, C. C.; Yao, Y. H.; Dong, X. *Abstr. Pap. Am. Chem. Soc.* **2006**, *232*, 88. (b) Yun, J. P.; Faust, R.; Szilagyi, L. S.; Keki, S.; Zsuga, M. *J. Macromol. Sci.* **2004**, *A41*, 613.

(15) Tong, R.; Yala, L. D.; Fan, T. M.; Cheng, J. J. *Biomaterials* **2010**, *31*, 3043.

(16) Jokerst, J. V.; Lobovkina, T.; Zare, R. N.; Gambhir, S. S. *Nanomedicine* **2011**, *6*, 715.

(17) Prencipe, G.; Tabakman, S. M.; Welsher, K.; Liu, Z.; Goodwin, A. P.; Zhang, L.; Henry, J.; Dai, H. J. *J. Am. Chem. Soc.* **2009**, *131*, 4783.

(18) Lutz, J. F. *J. Polym. Sci., Polym. Chem.* **2008**, *46*, 3459.

(19) (a) Holowka, E. P.; Pochan, D. J.; Deming, T. J. *J. Am. Chem. Soc.* **2005**, *127*, 12423. (b) Bellomo, E. G.; Wyrsta, M. D.; Pakstis, L.; Pochan, D. J.; Deming, T. J. *Nat. Mater.* **2004**, *3*, 244.

(20) (a) Gillich, T.; Acikgoz, C.; Isa, L.; Schluter, A. D.; Spencer, N. D.; Textor, M. *ACS Nano* **2013**, *7*, 316. (b) Imbesi, P. M.; Gohad, N.

V.; Eller, M. J.; Orihuela, B.; Rittschof, D.; Schweikert, E. A.; Mount, A. S.; Wooley, K. L. *ACS Nano* **2012**, *6*, 1503. (c) Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6288. (d) Obermeier, B.; Wurm, F.; Mangold, C.; Frey, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7988. (e) Kainthan, R. K.; Brooks, D. E. *Bioconjugate Chem.* **2008**, *19*, 2231. (f) Pang, Y.; Liu, J. Y.; Wu, J. L.; Li, G. L.; Wang, R. B.; Su, Y.; He, P.; Zhu, X. Y.; Yan, D. Y.; Zhu, B. S. *Bioconjugate Chem.* **2010**, *21*, 2093. (g) Hussain, H.; Mya, K. Y.; He, C. B. *Langmuir* **2012**, *28*, 12690. (h) Chen, C. C.; Borden, M. A. *Biomaterials* **2011**, *32*, 6579. (i) Du, J. Z.; Tang, L. Y.; Song, W. J.; Shi, Y.; Wang, J. *Biomacromolecules* **2009**, *10*, 2169.

(21) (a) Tong, R.; Cheng, J. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4830. (b) Tong, R.; Cheng, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 4744. (c) Tong, R.; Cheng, J. J. *Bioconjugate Chem.* **2010**, *21*, 111. (d) Tong, R.; Cheng, J. J. *Chem. Sci.* **2012**, *3*, 2234.

(22) (a) Farokhzad, O. C.; Cheng, J.; Teply, B. A.; Sherifi, I.; Jon, S.; Kantoff, P. W.; Richie, J. P.; Langer, R. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 6315. (b) Cheng, J.; Teply, B. A.; Sherifi, I.; Sung, J.; Luther, G.; Gu, F. X.; Levy-Nissenbaum, E.; Radovic-Moreno, A. F.; Langer, R.; Farokhzad, O. C. *Biomaterials* **2007**, *28*, 869.