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# Towards Biologically Active Self-assemblies: Model Nucleotide Chimeras

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*Abstract:* With this article, we wish to give an overview of our main research activities assessing the potential of a suitable polymer modification of DNA fragments to self-assemble biologically active nanostructures. Specifically, the grafting of a hydrophobic polymer segment on DNA fragments results in amphiphilic nucleotide-based macromolecules, which, owing to both chemical and physical incompatibility, organize in self-assembled structures either on surfaces or in aqueous solution. Through the combination of the existing know-how in polymer chemistry with modern analytical techniques, we are currently focusing on establishing the mechanism of self-assembly of the polymer-modified nucleotide sequences in solution and on surfaces prior to the assessment of their hybridization capacity once involved in the ensemble. With the evaluation of the potential of the functional nanostructures to undergo biological-like adhesion through hybridization one can eventually foresee that the optimal functionality of these bio-inspired systems could be fine-tuned for biological applications such as drug delivery, gene therapy, tissue engineering and the design of either biomedical devices or biosensors.

**Keywords:** Copolymer · DNA · Functional nanostructures · Self-assembly

## 1. Introduction

Nowadays, there is a major interest in the design of bioactive polymeric materials. Some of the prominent examples are the developments of platforms for tissue engineering and the design of medical devices and carriers for drug or gene therapy.[1–3] In this context, soft templates based on self-assembled amphiphilic copolymers present a new class of very promising biologically functional materials.[1,4,5] Self-assembly is a process intrinsic to the amphiphilic character of the constituent molecules. This is a simple and natural design tool to form nanometer to micrometer-sized structures that retain the characteristics of the original components. Since synthetic polymers exhibit no specific biological activity, the design of self-assembled polymeric structures that eventually induce a positive biological response currently remains a challenge.

Recently, synthetic polymers have been conjugated with peptide sequences.[6–23] Block copolymers composed of at least one polypeptide segment are usually referred to as 'polypeptide hybrid polymers' or 'molecular chimeras'. A comprehensive level of knowledge about the mechanism of structure formation of polypeptide hybrid copolymers has been achieved. Similar to their fully synthetic analogues,[24–36] self-assembly in dilute aqueous solution yields nanostructures of various sizes and morphologies. These properties of the resulting self-assembly particularly reflect the occurrence of the polypeptide secondary structure and the sensitivity toward stimuli such as temperature, ionic strength and pH. In thin films, structure formation arises from the competition between micro-phase separation and crystallization of amphiphilic rod-coil polypeptide-based copolymers.[37–46] Recently, a novel approach to the design of self-assembling peptide-based copolymers which induce a positive biological response has been reported.[47] It consists in the modification of a readily self-assembling copolymer with the arginine–glycine–aspartic acid (RGD) cell binding peptide motif. In this specific case, the delicate hydrophobic to hydrophilic balance, which drives self-assembly in aqueous solution, could be preserved upon modification of the copolymer with the peptide sequence.

Besides being the universal carrier of the genetic information, DNA plays a pivotal role in numerous biological mechanisms, such as gene silencing[48] and cell recognition,[49] which constantly directs research efforts toward applications in sensor development, gene therapy or targeted drug delivery. Moreover, various compositions, lengths and structures are synthetically accessible, which makes DNA an attractive model biologically active macromolecule.[50–54] Since the properties of self-assembled structures retain the characteristics of the original components, grafting synthetic polymers to nucleotide sequences to self-assemble biologically active nanostructures recently opened a new research area in the field of polymer science.[55–68] However, the general mechanism of structure formation of these novel nucleotide-based copolymers needs to be established. The inter-molecular interactions between the self-assembled macromolecules are defined by the characteristics of the nanostructures, in particular the morphology, and rule the potential biological activity of the self-assembly. However, nucleotide sequences are charged polyelectrolytes[69,70] and colloidal forces govern the stability of the suspension of the resulting like-charged self-assembled structures.[71–73] In addition, nucleotide sequences interact through several binding modes other than electrostatic interactions.[74,75] Nevertheless, nucleotide sequences possess a unique molecular recognition property, namely the hybridization of complementary sequences according to Watson-Crick base pairing. This property of hybridization enables the assessment of the functionality of self-assembled polymer modified nucleotide sequences using the recent theories and modern tools developed in polymer science prior to any biological assays. Based on this assump-

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tion, we are conducting investigations to establish a general mechanism of the self-assembly of the polymer-modified nucleotide sequences and quantify the degree of functionality of the resulting structures in respect with inter-molecular interactions. With these investigations, we will demonstrate that the polymer modification of nucleotide sequences can eventually be fine-tuned to yield self-assembled nanostructures, which feature optimal biological activity.

## 2. Results and Discussion

### 2.1 *Design and Self-assembly of Nucleotide-based Amphiphilic Diblock Copolymers*

To self-assemble functional nanostructures in aqueous solution, we grafted a synthetic hydrophobic polymer segment to a nucleotide sequence (Fig. 1). A single-point linkage is created between the natural and synthetic polymers, which preserves both the conformational freedom of the synthetic polymer and the right-handed helical configuration of the nucleotide sequence (as assessed through circular dichroism). The ability to engage in specific and directional inter-molecular interactions of the DNA fragment is preserved.

Two synthesis routes of modification of DNA fragments with synthetic polymer segments have been developed so far. Single-stranded nucleotide sequences were modified with low molecular weight polymers through solid phase synthesis.[56] Briefly, solid-phase synthesis is performed in a 2 mL reaction reactor. The 12 nucleotide-long single-stranded sequence (Microsynth AG, Balgach, Switzerland) is functionalized with a carboxylic acid group through a $C_{10}$-linker at the 5'-end whereas the 3'-terminus is bound to the control pore glass resin. Diisopropylcarbodiimide (DIC) is used as initiator and dichloromethane (DCM) as solvent. DIC activates the carboxylic acid group. The resulting ester thus undergoes a nucleophilic attack by the amino-terminated polymer, leading to a stable urea living group. The nucleotide-based amphiphilic diblock copolymer is synthesized at room temperature. In a typical synthesis, the nucleotide sequence (1 equiv.) is added together with DIC (1.2 equiv.) to a solution of polymer (5 equiv.) in 1.5 mL DCM. The solution is shaken overnight and subsequently washed several times with DCM to get rid of the initiator and the non-reacted material. At the cleavage step, 1.5 mL of a 33% $NH_4OH$ solution is added and transferred to an eppendorf tube for overnight shaking at a temperature of 40 °C. The ammonium hydroxide cleaves the polymer-modified nucleotide sequences from the solid support which is filtered away. To separate the nucleotide-based amphiphilic diblock copolymer from the non-reacted nucleotide sequences, size exclusion chromatography (SEC) is carried out using Sephadex©G-50 in a 150 mM NaCl and 0.01% azide buffer. The UV sensitivity of the nucleotide-based copolymer further leads to an accurate concentration determination through UV spectroscopy. The different fractions collected from SEC are therefore lyophilized prior to dialysis ($M_W$ cut off of 3500 Da) to filter out the salt of the buffer as well as the remaining ammonium hydroxide from the cleavage step. The synthesis yield is in average 30%.

The grafting of polymers of larger molecular weight is carried out through heterogeneous biphasic chemistry (unpublished data). The slow diffusion of the polymer chains through the pores of the resin limits the reaction yield achieved through solid-phase synthesis. Therefore, the nucleotide sequences are cleaved from the solid support prior to reaction with the synthetic polymers. The reaction thus takes place at the interface between an aqueous solution of the nucleotide sequences and an organic phase, in which the hydrophobic polymer segments are dissolved (typically dichloromethane, DCM). Nucleotide sequences have been modified with poly(ethylene glycol) (PEG) ($M_w$ = 2000 Da), poly(butadiene) (PB) ($M_w$ = 2000 Da, 5000 Da and 10000 Da) and poly(isobutylene) (PIB) ($M_w$ = 2000 Da). PB and PIB were selected for their low glass transition temperature, Tg, which ensures certain solubility of the polymer-modified nucleotide sequence in aqueous solution as well as self-assembly of non-kinetically frozen structures. A cross-linking polymerization of the vinyl pendant groups along the PB backbones could be performed subsequent to self-assembly in order to stabilize the structure, which is otherwise held together by non-covalent hydrophobic interactions.

The following nucleotide sequences have been modified so far with synthetic polymers (A stands for adenosine, G, guanosine, C, cytidine and T, thymidine):
Sequence I:
5'-GGGGGGGGGGGG-3', $G_{12}$;
sequence II (complementary of I):
5'-CCCCCCCCCCCC-3', $C_{12}$;
sequence III:
5'-AGAGAGAGAGGG-3', $A_5G_7$;
sequence IV (complementary of III):
5'-CCCTCTCTCTCT-3', $C_7T_5$;
sequence V:
5'-TTTCTCTCTCTC-3', $T_7C_5$;
sequence VI:
5'-AGAGAGAGAGGGAGAGAGAGA GGG-3', $A_{10}G_{14}$;
and sequence VII:
5'-GGAAGTAGGCGGTAGAGTCAA-3', siDNA. Several criteria dictate the choice of the nucleotide sequences. Twelve nucleotides is the minimal number required to ensure a thermodynamically stable double helix assembled by Watson-Crick base-pairing. The composition of the sequences is chosen such that the temperature at which the double helix starts to disassemble is much higher than the temperature at which the investigations are carried out (20 °C). The sequences are linear: no secondary structures occur through self-hybridization. Eventually, sequences I, III and VI are readily expected to induce a positive biological response. Poly(guanosine) is recognized by cell-surface receptors[76] whereas sequence VII is the DNA analogue of a small interfering ribonucleic acid, siRNA that silences a gene involved in intracellular trafficking.[77]

Since the resulting polymer-modified nucleotide sequences consist of a flexible, amorphous hydrophobic polymer segment

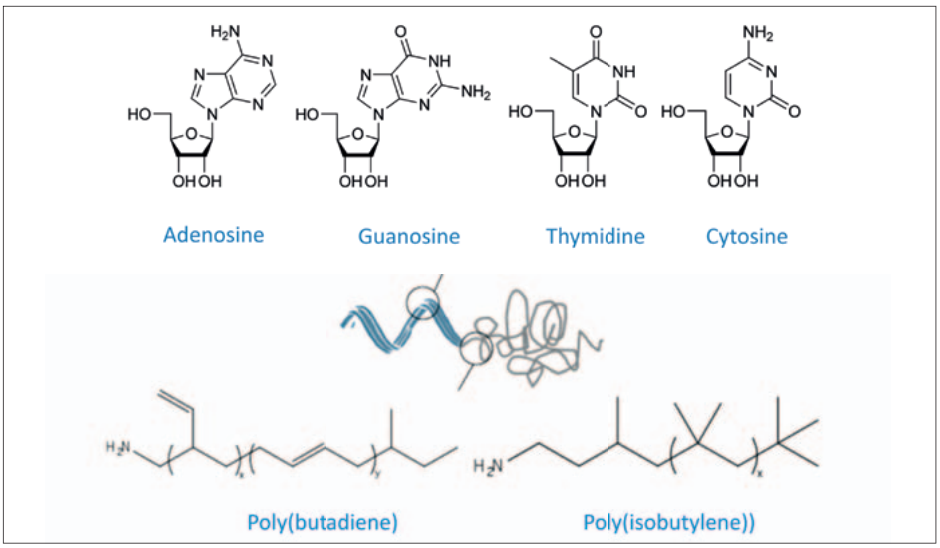


Fig. 1. Schematic representation of the polymer-modified nucleotide sequence.

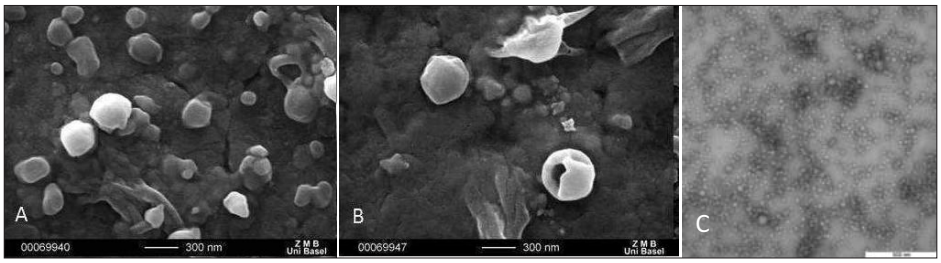


Fig. 2. A) Scanning electron micrographs of UV reticulated self-assembled structures from poly(butadiene)-modified $G_{12}$. B) The hollow sphere morphology of self-assembled structures from poly(butadiene)-modified $G_{12}$ is clearly evidenced through scanning electron microscopy. C) Transmission electron micrograph of 100 nm size vesicles assembled from poly(isobutylene) modified $G_7A_5$

and a stiff, rod-like nucleotide sequence, both chemical and physical incompatibilities between the constituting blocks drive micro-phase separation.[56] While the composition of the nucleotide sequence and the characteristics of the aqueous medium such as ionic strength affect the size of the self-assembly, the composition of the nucleotide-based amphiphilic diblock copolymer defines the morphology. Self-assembly into vesicular structures upon modification with either PIB or PB takes place (Fig. 2). Since nucleotide sequences engage in intermolecular interactions, the formation of a membrane-like structure which closes into hollow spheres is strongly favored.

Preliminary investigations of the self-assembly of polymer-modified nucleotide sequences provide insights into the role of electrostatic interactions in the structure formation of nucleotide-based copolymers. In the absence of counter ions in the aqueous medium, higher order vesicular structures self-assembled from $PB_{38}C_{12}$ are observed by electron microscopy and confocal laser scanning microscopy.[56] These micrometer-size structures disappeared in a 150 mM aqueous solution of NaCl. A high ionic strength induces the disassembly of $PB_{38}A_{10}G_{14}$. Although UV spectroscopy confirmed the presence of $PB_{38}A_{10}G_{14}$, no signal was monitored through light scattering in a 1 M NaCl aqueous solution. However, at lower salt and similar copolymer concentrations, 100 nm size self-assembled vesicular structures were detected. Therefore, the extent of shielding of electrostatic interactions by the counter-ions significantly influence the non-covalent interactions, which in turn induce the self-assembly and stabilize the suspension.

## 2.2 *Surface Immobilization of Polymer-modified Nucleotide Sequences*

Ongoing studies focus on the surface immobilization of polymer-modified nucleotide sequences and self-assembled nanostructures (Fig. 3) to prepare patterned surfaces that influence cell-growth.

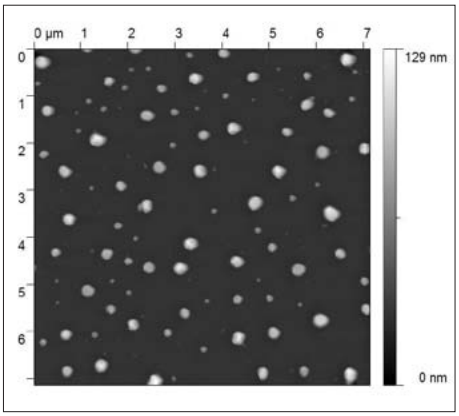


Fig. 3. Atomic force micrograph of model surfaces to study cell response to the topography, which were designed by immobilizing poly(butadiene)-modified nucleotide sequences self-assembled into vesicular structures onto a substrate functionalized with nucleotide sequences of the same composition than those involved in the self-assembly. Copyright: Wiley, *Macromol. Biosci.* **2008**, *8*, 1161, doi: 10.1002/mabi.200800081.

Despite no known recognition process, a positive response of bacteria was found on surfaces coated with nucleotide sequences through the over expression of curli, which are organelles produced by *Escherichia Coli* in response to substrate adhesion.[55]

Initial work on the immobilization of polymer-modified nucleotide sequences on hydrophobic surfaces by dip coating revealed several limitations of the process. For instance, immobilization by this process at concentrations below the critical micelle concentration (cmc) led to adsorption below the detection limit of conventional surface characterization techniques, such as Fourier transform infrared spectroscopy (FTIR) and photoelectron spectroscopy (XPS). However, in contrary to lipid vesicles, which open to form a lipid bilayer on a solid support,[78] vesicular structures assembled from polymer-modified nucleotide sequences retain their morphology as assessed by atomic force microscopy as well as frequency and dissipation shifts monitoring with the quartz crystal microbalance (Q-Sense, Göteborg, Sweden). As can be observed in Fig. 4, over the time course of the experiment, mass adsorption takes place as monitored through a decrease of the oscillation frequency of the quartz crystal. Nevertheless, no dissipation decrease could be detected, indicating conformal immobilization of the vesicular structures. Their mechanical stability is not affected by strong interactions with the substrate. Intact PIB-$C_7T_5$ vesicular structures could be deposited on aminopropyltriethoxysilane-, APTES-modified silicon wafers. An alternative strategy could be to deposit $PB_{38}$-$A_{10}G_{14}$ at high ionic strength (1 M NaCl) on a gold substrate modified with a hydrophobic self-assembled monolayer of 1-octadecanothiol ($C_{18}H_{38}S$). The high ionic strength disassembles the structures and individual molecules could thus be immobilized.

## 2.3 *Functionality of Self-assembled Polymer-modified Nucleotide Sequences*

The next stage in our research focused primarily on the assessment of the func-

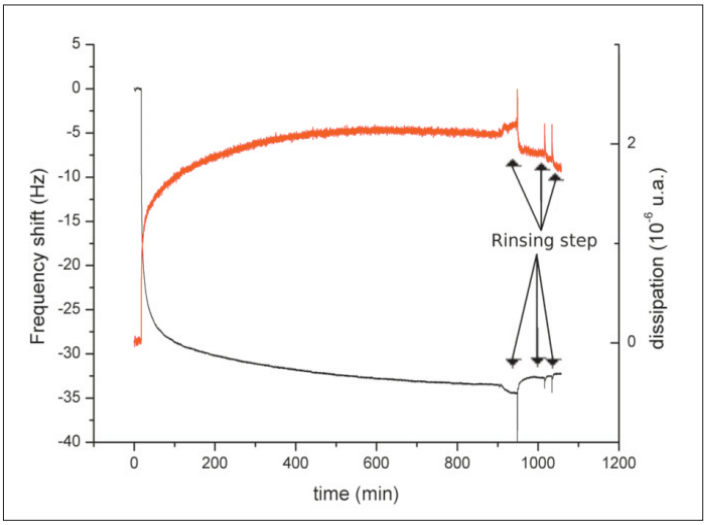


Fig. 4. Time course of both the frequency and dissipation shifts monitored with the quartz crystal microbalance with dissipation monitoring (Q-Sense, Göteborg, Sweden) upon immobilization of vesicles self-assembled from poly(isobutylene)-modified nucleotide sequences ($G_7A_5$) on surfaces modified with their complementary sequence.

tionality of the nucleotide sequences after polymer modification and self-assembly. The biological activity of the DNA fragment is primarily encoded in its ability to assemble a double helix with its complementary nucleotide sequence through hybridization. Since a polymer–polynucleotide interface is created through polymer modification and subsequent self-assembly, the functionality of the self-assembled nucleotide-based copolymers encounters hindrances similar to those in the context of surface tethering of nucleotide sequences.[79–83] The main limitations are molecular crowding, impenetrable wall effect, and sensitivity towards ionic strength. However, using the existing theory and tools developed in polymer science we demonstrated that the main hindrance to hybridization of short, surface-tethered nucleotide sequences is macromolecular crowding.[84] Recent advances in the design of surface sensors enable real-time tracking of label-free biochemical events. In collaboration with Dynetix AG and CSEM (Landquart, Switzerland), we validated the use of a prototype of a newly developed wave-guide interrogated optical sensor (Bright-Reader®). With this technique in combination with the quartz crystal microbalance with dissipation monitoring (QCM-D), the kinetics and the efficiency of the hybridization process on surfaces could be accurately quantified. To counter macromolecular crowding, immobilization of the double helix was performed prior to de- and re-hybridization. The resulting grafting density enabled the achievement of 100% hybridization efficiency.[84] Further, this highly efficient immobilization of double helices was tailored to design bioactive micro-patterned surfaces through micro-contact printing.[85] We are currently further adapting this methodology to the immobilization of nucleotide sequences on a conducting polymer thin film. This approach is particularly attractive for the design of miniaturized surface sensors for the *in situ* detection of hybridization with electrochemical characterization techniques, which are not mandatorily dependant on the electrochemical properties of the polymer.

Investigations of the interaction between self-assembled polymer-modified nucleotide sequences and surfaces modified with their complementary sequences have been instigated. Vesicular structures could be immobilized and observed by atomic force microscopy (see Fig. 4). However, the specificity and strength of interaction are difficult to address with sub-micrometer size structures and a methodology is currently being assessed. To demonstrate that the self-assembled functional nanostructures will successfully undergo recognition through ligand-receptor interaction we will quantify the specificity and efficiency of recognition between the self-assembled polymer-modified nucleotide sequences and their complementary sequences bound to a surface through the determination of the kinetics and adhesion strength. Toward this end, giant unilamellar vesicles will be assembled through electro-formation.[86,87] Optical microscopy will be used to assess the formation of these micrometer-sized structures. Compared to sub-micrometer sized structures self-assembled in dilute aqueous solution, these micrometer-sized vesicles have several advantages. Their size range allows the use of light microscopy for the investigations. Their reduced curvature will enable the comparison of the functionality of the nucleotide sequences assembled either in giant vesicular structures or in brushes on a solid support. The kinetics of adhesion of polymer-modified giant vesicles to surfaces modified with the complementary nucleotide sequence of the one involved in the self-assembly will be then studied. To modify the substrate with the complementary sequence, we will make use of the approach that we established to immobilize nucleotide sequences on a solid support to achieve optimal hybridization efficiency.[84] Optical microscopy will thus enable the indirect observation of the specific interaction driven by hybridization between self-assembled polymer-modified DNA fragments and a substrate modified with the complementary nucleotide sequence. Moreover, reflection interference contrast microscopy (RICM) will provide further information on the specificity of the interaction between the two interfaces.[88] The average membrane-surface distance will scale with the length of the rigid double helix (8 nm for a 24 nucleotide-long sequence). In parallel, micromanipulations will enable to correlate the hybridization efficiency with the strength of adhesion between giant vesicles and either microspheres or surfaces modified with the nucleotide sequence complementary to the one involved in the self-assembly. The strength of interaction will be characterized by the disengagement of the vesicular structure from the microsphere and/or substrate. Combining RICM and micromanipulations, we will therefore demonstrate that the nanostructures undergo ligand-receptor-like ligation, which is a prominent biological interaction. These investigations will further prove that the functionality of the nucleotide sequence is retained in the ensemble. These results are of primary importance, since they assess that a positive biological response will arise through bioadhesion between cell surface receptors and the functional nanostructures.

## 3. Conclusion and Outlook

To demonstrate that polymer-modified DNA fragments can be self-assembled in stable, functional nanostructures, the realization of the following three objectives is currently in focus: i) design and characterization of stable self-assembled nanostructures in solution and on surfaces; ii) demonstrate the hybridization capacity of the self-assembled polymer-modified nucleotide sequences with their complementary sequences; ii) eventually, assess the strength and kinetics of interaction between the self-assembled polymer-modified nucleotide sequences and their complementary strands bound to a surface. We will have then explored the utility of the self-assembly process to develop novel biologically active systems with substantial potential for application in gene therapy, sustained, targeted drug delivery, tissue engineering and the design of medical devices. Advances in the development of sensors for genomics and proteomics are equally foreseen.

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[1] S. Liu, R. Maheshwari, K. L. Kiick, L. *Macromol.* **2009**, *42*, 3.
[2] R. R. Maddikeri, S. Tosatti, M. Schuler, S. Chessari, M. Textor, R. G. Richards, L. G. J. Harris, *Biomed. Mater. Res., Part A* **2007**, *84A*, 425.
[3] M. Schuler, G. R. Owen, D. W. Hamilton, M. de Wild, M. Textor, D. M. Brunette, S. G. P. Tosatti, *Biomater.* **2006**, *27*, 4003.
[4] J. K. Kim, J. I. Lee, D. H. Lee, *Macromol. Res*. **2008**, *16*, 267.
[5] S. Minko, M. Motornov, Y. Roiter, I. P. E. Tokarev, in 'From Polymeric Nanostructures and Their Applications', Ed. H. S. Nalwa, **2007**, p. 61.
[6] W. Agut, R. Agnaou, S. Lecommandoux, D. Taton, *Macromol. Rapid Commun*. **2008**, *29*, 1147.
[7] J. Babin, D. Taton, M. Brinkmann, S. Lecommandoux, *Macromol.* **2008**, *41*, 1384.
[8] A. Carlsen, S. Lecommandoux, *Curr. Opin. Colloid Interface Sci.* **2009**, *14*, 329.
[9] C. Houga, J. Giermanska, S. Lecommandoux, R. Borsali, D. Taton, Y. Gnanou, J.-F. Le Meins, *Biomacromol.* **2009**, *10*, 32.
[10] M. Le Hellaye, N. Fortin, J. Guilloteau, A. Soum, S. Lecommandoux, S. M. Guillaume, *Biomacromol.* **2008**, *9*, 1924.
[11] S. Lecommandoux, H.-A. Klok, H. Schlaad, *Nanosci*. **2006**, 117.
[12] C. Schatz, S. Louguet, J.-F. Le Meins, S. Lecommandoux, *Angew. Chem. Int. Ed.* **2009**, *48*, 2572.
[13] K. K. Upadhyay, J. F. Le Meins, A. Misra, P. Voisin, V. Bouchaud, E. Ibarboure, C. Schatz, S. Lecommandoux, *Biomacromol.* **2009**, *10*, 2802.
[14] H. Schlaad, *Adv. Polym. Sci*. **2006**, *202*, 53.
[15] R. Sigel, M. Losik, H. Schlaad, *Langmuir* **2007**, *23*, 7196.

[16] H. G. Boerner, H. Schlaad, *Soft Matter* **2007**, *3*, 394.
[17] Y. Geng, D. E. Discher, J. Justynska, H. Schlaad, *Angew. Chem. Int. Ed*. **2006**, *45*, 7578.
[18] H. Schlaad, M. Antonietti, *Eur. Phys. J. E* **2003**, *10*, 17.
[19] H. Kukula, H. Schlaad, M. Antonietti, S. Foerster, *J. Am. Chem. Soc*. **2002**, *124*, 1658.
[20] A. Ribeiro, F. J. Arias, J. Reguera, M. Alonso, J. C. Rodriguez-Cabello, *Biophys. J*. **2009**, *97*, 312.
[21] J. C. Rodriguez-Cabello, J. Reguera, S. Prieto, M. Alonso, *Smart Polym*. **2008**, 177.
[22] F. J. Arias, V. Reboto, S. Martin, I. Lopez, J. C. Rodriguez-Cabello, *Biotechnol. Lett.* **2006**, *28*, 687.
[23] R. Herrero-Vanrell, A. C. Rincon, M. Alonso, V. Reboto, I. T. Molina-Martinez, J. C. J. Rodriguez-Cabello, *Controlled Release* **2005**, *102*, 113.
[24] M. Burkhardt, N. Martinez-Castro, S. Tea, M. Drechsler, I. Babin, I. Grishagin, R. Schweins, D. V. Pergushov, M. Gradzielski, A. B. Zezin, A. H. E. Mueller, *Langmuir* **2007**, *23*, 12864.
[25] O. Colombani, M. Ruppel, M. Burkhardt, M. Drechsler, M. Schumacher, M. Gradzielski, R. Schweins, A. H. E. Mueller, *Macromol.* **2007**, *40*, 4351.
[26] O. Colombani, M. Ruppel, F. Schubert, H. Zettl, D. V. Pergushov, A. H. E. Mueller, *Macromol.* **2007**, *40*, 4338.
[27] E. Eghbali, O. Colombani, M. Drechsler, A. H. E. Mueller, H. Hoffmann, *Langmuir* **2006**, *22*, 4766.
[28] X. Andre, M. Zhang, A. H. E. Mueller, *Macromol. Rapid Commun*. **2005**, *26*, 558.
[29] C. M. Schilli, M. Zhang, E. Rizzardo, S. H. Thang, Y. K. Chong, K. Edwards, G. Karlsson, A. H. E. Mueller, *Macromolecules* **2004**, *37*, 7861.
[30] S. U. Egelhaaf, P. Schurtenberger, *Phys. Rev. Lett.* **1999**, *82*, 2804.
[31] C. G. Palivan, C. Vebert, F. Axthelm, W. Meier, in 'From Nanotechnology in Biology and Medicine', Ed. T. Vo-Dinh, **2007**, 1.
[32] C. Nardin, D. Bolikal, J. Kohn, *Langmuir* **2004**, *20*, 11721.
[33] L. Sheihet, D. Bolikal, A. Seyda, C. Nardin, J. Kohn, *Mater. Res. Soc. Symp. Proc.* **2004**, 445.
[34] C. Nardin, W. Meier, *Chimia* **2001**, *55*, 142.
[35] V. Schaedler, C. Nardin, U. Wiesner, E. Mendes, *J. Phys. Chem. B* **2000**, *104*, 5049.
[36] C. Nardin, T. Hirt, J. Leukel, W. Meier, *Langmuir* **2000**, *16*, 1035.
[37] I. Botiz, N. Grozev, H. Schlaad, G. Reiter, *Soft Matter* **2008**, *4*, 993.
[38] S. Ludwigs, G. Krausch, G. Reiter, M. Losik, M. Antonietti, H. Schlaad, *Macromol.* **2005**, *38*, 7532.
[39] H. Schlaad, B. Smarsly, M. Losik, *Macromol.* **2004**, *37*, 2210.
[40] H. Schlaad, H. Kukula, B. Smarsly, M. Antonietti, T. Pakula, *Polymer* **2002**, *43*, 5321.
[41] A. Boschetti-de-Fierro, L. Spindler, G. Reiter, D. Olmos, S. Magonov, V. Abetz, *Macromol.* **2007**, *40*, 5487.
[42] D. M. Lambreva, R. Opitz, G. Reiter, P. M. Frederik, W. H. de Jeu, *Polymer* **2005**, *46*, 4868.
[43] C. Vasilev, H. Heinzelmann, G. Reiter, *J. Polym. Sci., Part B: Polym. Phys*. **2004**, *42*, 1312.
[44] G. Reiter, L. Vidal, *Eur. Phys. J. E* **2003**, *12*, 497.
[45] G. Reiter, G. Castelein, P. Hoerner, G. Riess, J. U. Sommer, G. Floudas, *Eur. Phys. J. E* **2000**, *2*, 319.
[46] G. Reiter, G. Castelein, P. Hoerner, G. Riess, A. Blumen, J.-U. Sommer, *Phys. Rev. Lett.* **1999**, *83*, 3844.
[47] J. A. Zupancich, F. S. Bates, M. A. Hillmyer, *Biomacromolecules* **2009**, *10*, 1554.
[48] J. Kurreck, *Angew. Chem. Int. Ed.* **2009**, *48*, 1378.
[49] S.-H. Chou, K.-H. Chin, A. H. Wang, *J. Trends Biochem. Sci*. **2005**, *30*, 231.
[50] C. Leumann, *J. Bioorg. Med. Chem*. **2002**, *10*, 841.
[51] C. J. Leumann, *Nucleic Acids Symp. Ser*. **2006**, 55.
[52] G. Ivanova, S. Reigadas, D. Ittig, A. Arzumanov, M.-L. Andreola, C. Leumann, J.-J. Toulme, M. J. Gait, *Oligonucleotides* **2007**, *17*, 54.
[53] S. Buchini, C. Leumann, *J. Eur. J. Org. Chem*. **2006**, 3152.
[54] B. M. Keller, C. Leumann, *J. Synthesis* **2002**, 789.
[55] N. Cottenye, F. Jr. Teixeira, A. Ponche, G. Reiter, K. Anselme, W. Meier, L. Ploux, C. Vebert-Nardin, *Macromol. Biosci*. **2008**, *8*, 1161.
[56] F. Jr. Teixeira, P. Rigler, C. Vebert-Nardin, *Chem. Commun*. **2007**, 1130.
[57] F. E. Alemdaroglu, N. C. Alemdaroglu, P. Langguth, A. Herrmann, *Adv. Mater*. **2008**, *20*, 899.
[58] J. Wang, F. E. Alemdaroglu, D. K. Prusty, A. Herrmann, R. Berger, *Macromolecules* **2008**, *41*, 2914.
[59] F. E. Alemdaroglu, N. C. Alemdaroglu, P. Langguth, A. Herrmann, *Macromol. Rapid Commun.* **2008**, *29*, 326.
[60] F. E. Alemdaroglu, J. Wang, M. Boersch, R. Berger, A. Herrmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 974.
[61] F. E. Alemdaroglu, A. Herrmann, *PMSE Prepr.* **2007**, *97*, 968.
[62] F. E. Alemdaroglu, N. C.Alemdaroglu, P. Langguth, A. Herrmann, *Polym. Prepr*. **2007**, *48*, 1033.
[63] A. Herrmann, F. E. Alemdaroglu, M. Safak, E. Ergen, *Polym. Prepr*. **2007**, *48*, 994.
[64] F. E. Alemdaroglu, M. Safak, J. Wang, R. Berger, A. Herrmann, *Chem. Commun*. **2007**, 1358.
[65] F. E. Alemdaroglu, K. Ding, R. Berger, A. Herrmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 4206.
[66] F. E. Alemdaroglu, A. Herrmann, *Org. Biomol. Chem*. **2007**, *5*, 1311.
[67] F. E. Alemdaroglu, M. Safak, A. Herrmann, Abstracts of Papers, 234th ACS National Meeting, Boston, MA, United States, August 19-23, **2007**, 355.
[68] K. Ding, E. Alemdaroglu Fikri, M. Borsch, R. Berger, A. Herrmann, *Angew. Chem. Int. Ed.* **2007**, *46*, 1172.
[69] M. O. Khan, B. Jonsson, *Biopolymers* **1999**, *49*, 121.
[70] M. O. Khan, S. M. Mel'nikov, B. Joensson, *Macromol.* **1999**, *32*, 8836.
[71] M. Borkovec, G. J. M. Koper, C. Piguet, *Curr. Opin. Colloid Interface Sci*. **2006**, *11*, 280.
[72] M. Borkovec, G. Papastavrou, *Curr. Opin. Colloid Interface Sci*. **2008**, *13*, 429.
[73] A. Stradner, H. Sedgwick, F. Cardinaux, W. C. K. Poon, S. U. Egelhaaf, P. Schurtenberger, *Nature* **2004**, *432*, 492.
[74] A. A. Kornyshev, A. Wynveen, *Proc. Natl. Acad. Sci*. **2009**, *106*, 4683.
[75] Y. Li, U. H. Yildiz, K. Muellen, F. Groehn, *Biomacromol.* **2009**, *10*, 530.
[76] M. Franceschin, *Eur. J. Org. Chem*. **2009**, 2225.
[77] P.-P. Luyet, T. Falguieres, V. Pons, A. K. Pattnaik, J. Gruenberg, *Traffic* **2008**, *9*, 2279.
[78] C. Scomparin, S. Lecuyer, M. Ferreira, T. Charitat, B. Tinland, *Eur. Phys. J. E: Soft Matter Biol. Phys.* **2009**, *28*, 211.
[79] S. M. De Paul, D. Falconnet, S. Pasche, M. Textor, A. P. Abel, E. Kauffmann, R. Liedtke, M. Ehrat, *Anal. Chem.* **2005**, *77*, 5831.
[80] A. Halperin, A. Buhot, E. B. Zhulina, *Biophys. J.* **2004**, *86*, 718.
[81] A. Halperin, A. Buhot, E. B. Zhulina, *Biophys. J.* **2005**, *89*, 796.
[82] A. Halperin, A. Buhot, E. B. Zhulina, *Langmuir* **2006**, *22*, 11290.
[83] A. Halperin, A. Buhot, E. B. Zhulina, *J. Phys.: Condens. Matter* **2006**, *18*, S463.
[84] J. Razumovitch, K. de Franca, F. Kehl, M. Wiki, W. Meier, C. Vebert, *J. Phys. Chem. B* **2009**, *113*, 8383.
[85] J. Razumovitch, W. Meier, C. Vebert, *Biophys. Chem*. **2009**, *139*, 70.
[86] C. K. Haluska, A. P. Schroder, P. Didier, D. Heissler, G. Duportail, Y. Mely, C. Marques, *Biophys. J*. **2008**, *95*, 5737.
[87] O. Mertins, N. P. da Silveira, A. R. Pohlmann, A. P. Schroder, C. M. Marques, *Biophys. J.* **2009**, *96*, 2719.
[88] M.-L. Hisette, P. Haddad, T. Gisler, C. M. Marques, A. P. Schroeder, *Soft Matter* **2008**, *4*, 828.