Polymer Glycomimetics

International Edition: DOI: 10.1002/anie.201610395
German Edition: DOI: 10.1002/ange.201610395

Polymeric Selectin Ligands Mimicking Complex Carbohydrates: From Selectin Binders to Modifiers of Macrophage Migration

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Abstract: *Novel polymeric cell adhesion inhibitors were developed in which the selectin tetrasaccharide sialyl-Lewis^X (SLe^X) is multivalently presented on a biocompatible poly(2-hydroxypropyl)methacrylamide (PHPMA) backbone either alone (P1) or in combination with O-sulfated tyramine side chains (P2). For comparison, corresponding polymeric glycomimetics were prepared in which the crucial "single carbohydrate" substructures fucose, galactose, and sialic acid side chains were randomly linked to the PHPMA backbone (P3 or P4 (O-sulfated tyramine)). All polymers have an identical degree of polymerization, as they are derived from the same precursor polymer. Binding assays to selectins, to activated endothelial cells, and to macrophages show that polyHPMA with SLe^X is an excellent binder to E-, L-, and P-selectins. However, mimetic P4 can also achieve close to comparable binding affinities in in vitro measurements and surprisingly, it also significantly inhibits the migration of macrophages; this provides new perspectives for the therapy of severe inflammatory diseases.*

The required level of specificity in biological recognition is often achieved by means of the structural diversity of glycoproteins, which play important roles in cell–cell interactions.[1] They bind for example, to cell adhesion molecules (CAMs), like selectins, and are key players in chronic and acute inflammatory processes.[2]

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Supporting information (experimental details) and the ORCID identification number for one author of this article can be found under http://dx.doi.org/10.1002/anie.201610395.

The selectin family consists of three receptors composed of calcium-dependent type I transmembrane glycoproteins with an extracellular lectin domain, which naturally bind to fucosylated and sialylated glycoprotein ligands. P-selectin is present on activated platelets and endothelial cells. E-selectin is exposed on the endothelium after activation by cytokines, while L-selectin is expressed by leukocytes.[3] Therefore, selectins are interesting targets for the therapy of inflammation-related diseases, for example, multiple sclerosis, rheumatoid arthritis, and cancer.[4]

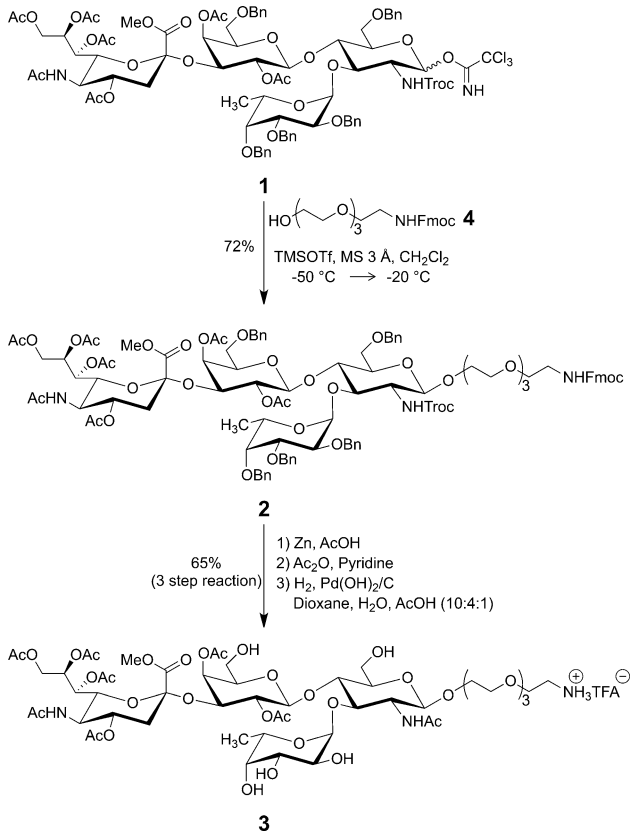
While targeting P- and E-selectin can monitor endothelial cells in the early phases of inflammation,[5] binding to L-selectin offers the opportunity to visualize local concentrations of leukocytes or even modulate their function.[6] Natural ligands of selectins within the inflammatory cascade are glycoproteins: P-selectin glycoprotein ligand-1 (PSGL-1, P-selectin dissociation constant: 0.3 μM) and E-selectin ligand-1 (ESL-1, E-selectin dissociation constant: 62 μM). In such glycoproteins, the sialyl Lewis^X tetrasaccharide (SLe^X) is the common structure required for binding.[1,2] However, the binding affinity is modulated by the peptide part of the respective glycoprotein. In particular, the N-terminal binding site of PSGL-1 is characterized by O-sulfation of tyrosine residues. The carbohydrate moiety SLe^X itself has different, but rather low affinities to all selectin members ($IC_{50} = 0.6$–1 mM).[7]

Natural ligands for selectins, for example, SLe^X, have failed to become anti-inflammatory drugs because they are often subject to rapid digestion by glycosidases and peptidases in the blood stream. Synthetic selectin inhibitors representing the binding sites of PSGL-1[8] or E-selectin ligands (ESL-1)[9] exhibit high and selective affinity to the corresponding selectins. The binding of synthetic ligands, however, is often irreversible and causes off-target effects, which limits their potential medical application.

Thus, the original structures are still of interest, since they naturally avoid the adverse effects resulting from long-term or even irreversible blocking of selectins.[10] The therapeutic use of SLe^X derivatives is, however, compromised by their very complex total synthesis.[11] Therefore besides reducing synthetic complexity, it is appealing to evaluate whether the binding affinity and the biological activity of glycoconjugate selectin ligands can be mimicked by synthetic polymers presenting the crucial ligand substructures (known from X-ray crystallography[10c]) in a polyvalent manner. As only three of the substructures (galactose, fucose, and sialic acid) are involved in selectin binding,[10c] synthetic complexity can be reduced even further.

Recently, glycopolymers are at the focus of great interest.[12] For this comparison of SLe^X and its (substructure) mimetics, we choose the stealth-like, clinically evaluated poly(2-hydroxylpropyl methacrylamide) (PHPMA)[13] as the polymer backbone. In order to mimic the multivalency of natural glycoprotein ligands,[14] the synthetic conjugates were designed to contain on average 10 SLe^X groups or ten times the three individual monosaccharides randomized along the polymer chain (Scheme 2). Additionally, 10 tyramine-*O*-sulfate groups per polymer were incorporated, which mimic the O-sulfation of tyrosines in the natural ligands.[5,6]

The tetrasaccharide SLe^X was synthesized following the method of Baumann et al.[8b,c] In order to incorporate an amine function for reaction with the polymer active ester (Scheme 1), a hydrophilic spacer was introduced by reaction of the SLe^X trichloroacetimidate **1** with Fmoc-protected 11-amino-3,6,9-trioxa-undecanol (**4**). The glycosylation was promoted by trimethylsilyl triflate at low temperatures (−50 to −20 °C) to achieve high stereoselectivity[15] (see the Supporting Information (SI)). This coupling selectively yielded the β-anomer **2**. Tetrasaccharide **2** was partially deprotected in three steps. The trichloroethoxycarbonyl (Troc) group was removed with zinc in glacial acetic acid, followed by acetylation. Then, the benzyl ethers were hydrogenolyzed using palladium hydroxide/charcoal (Pearlmann catalyst) in a mixture of dioxane/water/acetic acid (10:4:1) yielding the glycoside **3**. This strategy gave exclusively the β-anomer.



Scheme 1. Last three steps in the 42-step synthesis of SLe^X derivative **3** for polymer conjugation. Bn = Benzyl, Fmoc = fluorenylmethoxycarbonyl, TFA^- = trifluoracetate (purification by semipreparative HPLC with ACN/H_2O (1:1) and 0.1 % TFA, see SI), TMSOTf = trimethylsilyltriflate, Troc = 2,2,2-trichlorethoxycarbonyl. For synthetic details see Ref. [8b,c] and SI.

As the SLe^X derivative **3** (Scheme 1, SI) required a multistep synthesis (42 steps) prior to conjugation, the synthesis of polymer–carbohydrate conjugates separately exposing fucopyranose, galactose, and neuramic acid, each with only a four- or five-step synthesis, appeared promising. To this end, 11-amino-3,6,9-trioxaundecyl-α,β-L-fucopyranoside (**5**), 11-amino-3,6,9-trioxaundecyl-β-D-galactopyranoside (**6**) and 11-amino-3,6,9-trioxaundecyl(4,7,8,9-tetra-*O*-acetyl)-*N*-acetylneuraminic acid methyl ester hydrotrifluoracetate (**7**; see SI) were synthesized. All compounds contained a hydrophilic 11-amino-3,6,9-trioxaundecanyl spacer (see SI) for spatial separation from the polymer after conjugation. Compound **7** was used in protected form to avoid side reactions during postpolymerization modifications. In addition, tyramine-*O*-sulfate **8** was synthesized by sulfation of tyramine (see SI).

The HPMA polymer was synthesized by the active ester approach employing the reversible addition–fragmentation chain-transfer (RAFT) polymerization of pentafluorophenyl methacrylate according to Barz et al.[13d,16] The RAFT polymerization proceeds in a well-controlled manner, yielding reactive ester polymers (PPFPMA) with a dispersity index (ĐI) of 1.2. In agreement with recent results,[17] hydrolysis of activated esters was avoided. Active ester groups remaining after the coupling of the carbohydrates were aminolyzed with 2-hydroxylpropylamine, yielding the functionalized PHPMA polymer. The polymer–carbohydrate conjugates were synthesized by stepwise aminolysis of the polypentafluorophenyl methacrylates (PPFPMA) with the amine-functionalized carbohydrates. This ensures the same number of repeating units along the polymer chain (identical degree of polymerization P_n independent of the molecular weight which depends on functionalization) for all polymers, as they are all derived from the same parent PPFPMA. Quantitative ligation of the functionalized carbohydrates **3**, **5**, **6**,and **7** and tyramine-*O*-sulfate **8** was ensured by letting the mixture react for 15–36 h and monitoring the extent of the reaction by thin-layer chromatography (see SI). The next conversion (e.g. aminolysis with 2-hydroxypropylamine to prepare PHPMA) was started only when no free carbohydrate could be detected. Acetyl groups were removed using Zemplén deacetylation, while the sialic acid methyl ester was hydrolyzed in aqueous sodium hydroxide at pH 10.5.[18] For model reactions and a thorough analysis of conjugates see the Supporting Information. Data of the polymers are listed in Table 1 and structures are displayed in Scheme 2.

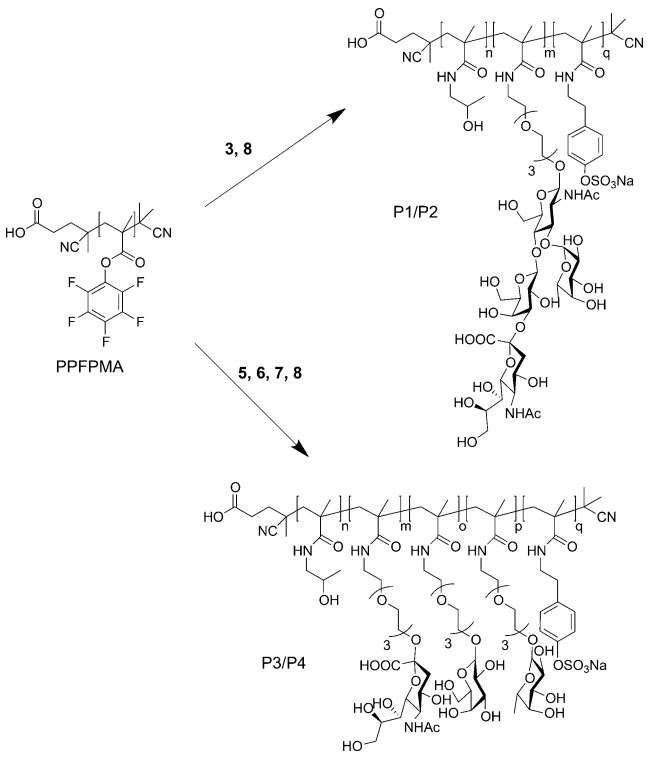
Next, the biological activities of SLe^X conjugates P1 and P2 were investigated and compared to those of the tetrasaccharide SLe^X **3** and of the mimetic polymers P3 and P4, which present the fucopyranose, galactose and neuramic acid randomly along the polymer backbone.

First, in vitro binding affinities towards the selectins were determined in competition studies applying a surface plasmon resonance (SPR) setup (see SI).[19] The IC_{50} values for SLe^X **3**, P1, P2, P3, and P4 (lower IC_{50}, higher binding affinity) are displayed in Table 2.

Table 1: Characteristics of SLe^X **3** and polymer–carbohydrate conjugates P1–P4 labeled with 1 mol% of the fluorophore Oregon Green 488 (see Scheme 2).

	Carbohydrate[a] content [% of repeating units]	Tyramine sulfate content [% of repeating units]	P_n or M_n [kg mol^{-1}]
SLe^X **3**	100	–	1.95[a]
PPFPMA			100 or 25.2[b]
PHPMA	–	–	100 or 14.1[c]
P1	SLe^X10 (**3**)[d]	–	100 or 24.1[c]
P2	SLe^X10 (**3**)[d]	10[d]	100 or 25.4[c]
P3	Gal10, Fuc10, Neu10[d]	–	100 or 24.8[c]
P4	Gal10, Fuc10, Neu10[d]	10[d]	100 or 26.1[c]

Values determined by [a] ESI-MS or [b] GPC. [c] M_n recalculated from the P_n of PPFPMA for the new molecular structure. [d] The degree of functionalization was obtained proving full conversion of the reactive amines **3, 5, 6, 7**, and **8** with PPFPMA.



Scheme 2. Polymer–carbohydrate conjugates P1–P4 with SLe^X (P1/P2) and carbohydrate mimetics (P3/P4) (see Scheme 1). P1 and P3 are not sulfated ($q = 0\%$), while P2 and P4 are ($q = 10\%$).

The IC_{50} values for binding of P1–P4 to L- and P-selectins were in the nM to μM range and are a factor of 10–100 lower than those to E-selectin. In line with results reported for nature-inspired synthetic ligands[8] and polyglycidol-based ligands,[19] the affinity to L- and P-selectins is enhanced, when sulfate groups are present in the macromolecule (see Haag et al.; describing highly sulfated polyglycidols without any special carbohydrate structure as ligands for L- and P-selectins (30–90 nM)[19c]). Binding to E-selectin, however, requires a carbohydrate structure.[9] The polymer–carbohydrate mimetics P3 and P4 generally display higher IC_{50} values (lower binding affinities) compared to those bearing SLe^X derivatives. After sulfation, the IC_{50} values of P4 showed two orders of magnitude better binding for P-selectin than for its non-sulfated counterpart P3 and reached a comparable (L-selectin) or even lower (P-selectin) level than P1. The conjugate P2 (10% SLe^X and 10% tyramine-*O*-sulfate) had the highest binding affinity of all investigated compounds. In this case, IC_{50} values of 70 nM for P-selectin, 900 nM for L-selectin, and 11 μM for E-selectin were achieved. In comparison to E-selectin, the affinities of P1 and P2 are slightly lower than the natural ligand, with IC_{50} values of 39 and 11 μM (compared to $IC_{50} = 62$ μM for the monovalent glycoprotein ESL-1). Altogether, these data show that sulfated carbohydrate mimetics like P4 can achieve binding affinities that are very similar to those of sulfated polymers with SLe^X, which constitute excellent binders to E-, L-, and P-selectins.

Table 2: IC_{50} values of polymer–carbohydrate conjugates towards binding of E-, L-, and P-selectins.[a]

	E-selectin[b] [nM]	L-selectin[b] [nM]	P-selectin[b] [nM]
SLe^X-S	170000	N.I.	N.I.
PHPMA	N.I.	N.I.	N.I.
P1	39000	7000	26000
P2	11000	900	70
P3	N.I.	85000	200000
P4	298000	10000	6000

[a] N.I.: no inhibition up to 1 mM concentrations; low IC_{50} values correspond to strong binding affinities. [b] Determined by competitive SPR-based binding assay (see SI); IC_{50} values display the concentration, which causes reduction of binding of 50% compared to the control.

After the determination of binding affinities by an SPR assay, the question remains whether polymer–SLe^X conjugates P1 and P2 as well as their glycomimetics P3 and P4 also bind efficiently to selectins expressed on different cells. To address this question, first two-photon laser scanning microscopy (TPLSM) studies of binding and cellular uptake of the fluorescent-labeled conjugates P1–P4 in human umbilical vein endothelial cells (HUVEC) with and without TNF-α stimulation were conducted in a flow chamber setup. This experimental setup (flow rate of 0.25 mL min^{-1}) mimics the blood flow in vivo (see Figure 1, upper line). The cytokine TNF-α induces the expression of P-selectin and E-selectin by HUVEC.[20] Logically, in the absence of TNF-α, polymer–carbohydrate conjugates P1–P4 should not bind to HUVECs. And as shown in Figure 1 (middle line), cell-associated fluorescence is not detectable without endothelial cell stimulation with TNF-α. Neither the control polymer PHPMA nor the polymer–carbohydrate conjugates showed cellular binding or internalization into HUVEC. This excludes unspecific binding in continous flow at the applied conjugate concentration of 1 μM.

When endothelial cells were, however, stimulated with TNF-α, enhanced cell-associated fluorescence and accumulation of polymer–carbohydrate conjugates inside HUVEC became visible (Figure 1, lower line) for the sulfated polymers P2 and P4. In contrast, neither non-sulfated polymers P1 and P3 displayed cell-associated fluorescence (see SI). Appa-

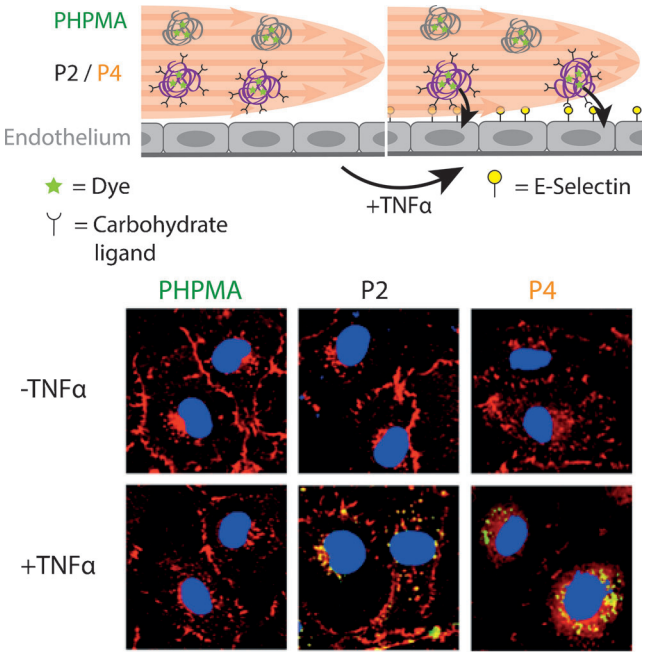


Figure 1. Schematic depiction and two-photon microscopy analyses of the binding of polymer–carbohydrate conjugates P2, P4, and PHPMA to human umbilical vein endothelial cells (HUVEC) depending on TNF-α stimulation. The images show DAPI staining of the nucleus (blue), WGA-AF562 staining of the cell membrane (red), and OG488-labeled polymers (green) after 1 h of incubation. Yellow color indicates colocalization of the polymers with the cell membrane.

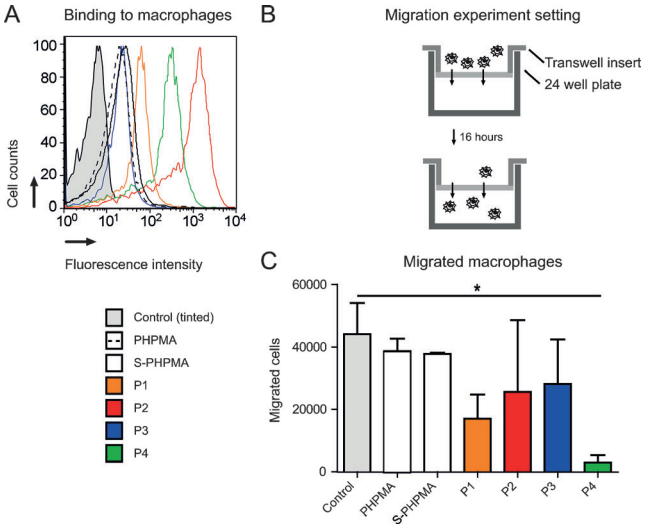


Figure 2. Binding of polymeric selectin ligand mimetics to macrophages and effects on macrophage migration. Primary human macrophages were generated by monocyte culture in RPMI1640 supplemented with 5% serum for seven days. A) Flow cytometry based quantification of conjugate-associated fluorescence after 60 min of incubation at a concentration of 3 μM. Histogram overlays reflect the fluorescent signal of selectin-directed constructs and their binding to macrophages. B) Scheme of transwell assay before (top) and after (bottom) macrophage migration. C) Quantification of macrophage migration after 16 h. Prior to the experiment, cells were preincubated for 1 h with the conjugates. Mean data of $n = 5$. *$P < 0.05$ (StDev).

rently, sulfate-dependent electrostatic interactions of the ligands with P-selectin enhance cell adhesion and uptake. Since we observed no pronounced difference between the sulfated SLe^X-HPMA polymer P2 and the sulfated Sia-Fuc-Gal-HPMA copolymer P4, it seems that even the mimetic polymer P4 bears significant potential to bind to endothelial cells already in the early stages of inflammation when P-selectin is expressed.

Having demonstrated efficient binding to P- and E-selectins on stimulated endothelial cells, we studied L-selectin binding in more detail. L-selectin is expressed on leukocytes, for example, macrophages. Binding to L-selectin is of particular interest since the local accumulation of macrophages is a hallmark of chronic inflammation and cancer.[21] Depending on their specific properties, nanoparticle-based L-selectin inhibitors may, however, also alter the activation state of macrophages and their functions in inflammation.[22] As macrophages are sensitive to anionic charges in polymers, like sulfation in P2 and P4, we also prepared a sulfated carbohydrate-free reference polymer (S-PHPMA, see SI), in which 10% of the repeating units are functionalized with tyramine-*O*-sulfate.

At first, the binding of conjugates to primary human macrophages after 60 min of incubation at a concentration of 3 μM was investigated by flow cytometry. As displayed in Figure 2A, conjugate P2 displayed the highest cell-associated fluorescence, followed by P4, P1, and P3. This result is in line with the binding affinity to L-selectins obtained from the SPR assay (Table 2). In this case, the cell-associated fluorescence caused by P2 is an order of magnitude higher than that of the mimetic carbohydrate–polymer P4.

More importantly, the binding of the corresponding ligands to selectins may also affect macrophage functions, for instance, their migratory properties. Therefore, we pre-incubated macrophages for 60 min with the different polymer–carbohydrate conjugates at a concentration of 3 μM to allow for binding. Then, the migration of macrophages was assessed for 16 h in a standardized chemotaxis assay (Figure 2B).[23] Interestingly, P4 now led to a significant inhibition of macrophage migration (Figure 2C), while the SLe^X-containing conjugates P1 and P2 reduced macrophage migration only moderately (Figure 2C). PHPMA and S-PHPMA had hardly any effect. The relatively high standard deviations observed for some of the groups treated with mimetics can be explained by intradonor differences in the expression of surface molecules on primary human cells,[24] as well as by variability in the induced biological response (which is absent in the case of controls). In spite of this variability, it is clear that polymer P4—mimicking the SLe^X binding motif—modifies macrophage migration substantially, while P2 with the natural SLe^X ligand binds more efficiently, but has only a minor effect on macrophage migration. Although the exact reasons for these findings need to be investigated in more detail in future experiments, they provide a first indication that even simple glycopolymers mimicking complex carbohydrates may be used to modulate macrophage migration and/or activation.

In this context, the unexpected efficiency of the rather simple sulfonated glycomimetic polymer P4 is particularly

exciting, since the inhibition of macrophage migration may enable novel therapeutic approaches for the treatment of several different inflammatory disorders.[25] Therefore, this study shows that even simple glycomimetics may provide pharmacologically useful properties, and further exploration is needed to reveal the full potential of multivalent polymer–carbohydrate conjugates.

Acknowledgements

Support by the German Research Foundation (SFB 1066) and the European Research Council (ERC-StG-309495) is gratefully acknowledged. We thank Martin Scherer for resynthesizing S-PHPMA and Regina Holm for help with preparing the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Keywords: glycopolymers · nanomedicine · PHPMA · polymer–carbohydrate conjugates · sialyl-Lewis^x mimetics

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Manuscript received: October 24, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Polymer Glycomimetics

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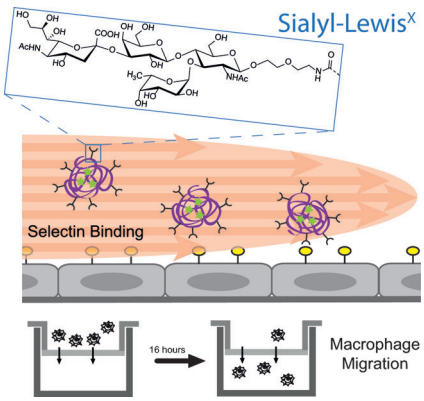
Polymeric Selectin Ligands Mimicking Complex Carbohydrates: From Selectin Binders to Modifiers of Macrophage Migration



Complex carbohydrates like sialyl-Lewis^X (SLe^X) play a role in cell–cell recognition and inflammatory processes. A biocompatible polymer that presents SLe^X multivalently was compared with corresponding polymeric glycomimetics. For one of the mimetics the selectin binding affinity is similar to that of the SLe^X–polymer system. It inhibits macrophage migration and offers new perspectives for therapy of severe inflammatory diseases.