

## Chapter 2

# Definition of Terms and Nomenclature

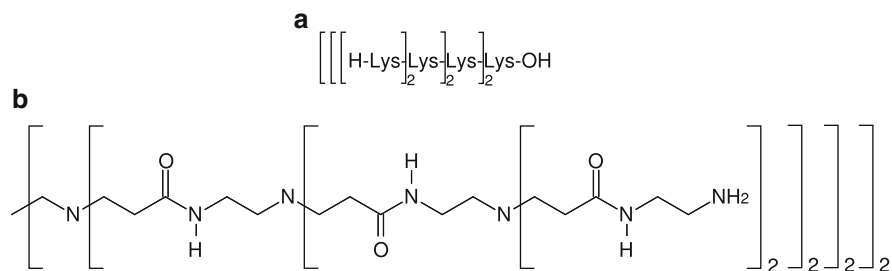
Basic terms and nomenclature of dendrimers have been covered by many excellent reviews [6, 11, 12, 20, 21, 37, 39, 86, 96, 97, 101, 110]. Detailed nomenclature rules for dendritic molecules (“cascadane-nomenclature”) based on the principles of dendrimer terms [73] have been elaborated [33]. Without any doubts, it is not easy to create a nomenclature for dendrimers, like a nomenclature for carbohydrates, and peptides. The topic of dendrimer chemistry is fantastically diverse; therefore, exact classification is very difficult or even impossible. When possible, then the name is complicated, long, or difficult to understand, especially for immunologists. Besides, MAP (multiple antigenic peptide) and MAG (multiple antigenic glycopeptide) dendrimers use their own nomenclature. The figure with chemical formula is still the best information. Other possibility is to use a combination of well-known trivial names like glucose, and lysine. Independently on the above facts, the authors [33] deserve admiration.

A hexadecavalent MAP core can be described simply and clearly as  $R_{16}$ -Lys<sub>8</sub>-Lys<sub>4</sub>-Lys<sub>2</sub>-Lys-OH, where R = peptide antigen. The same MAP with R = H can be represented as {[H-Lys-Lys(&1)-Lys(&2)-Lys(&3)-OH][H-Lys-Lys(&4)-Lys(&5)&3][H-Lys-Lys(&6)&2][H-Lys-Lys(&7)&5][H-Lys&1][H-Lys&4][H-Lys&6][H-Lys&7]} [103].

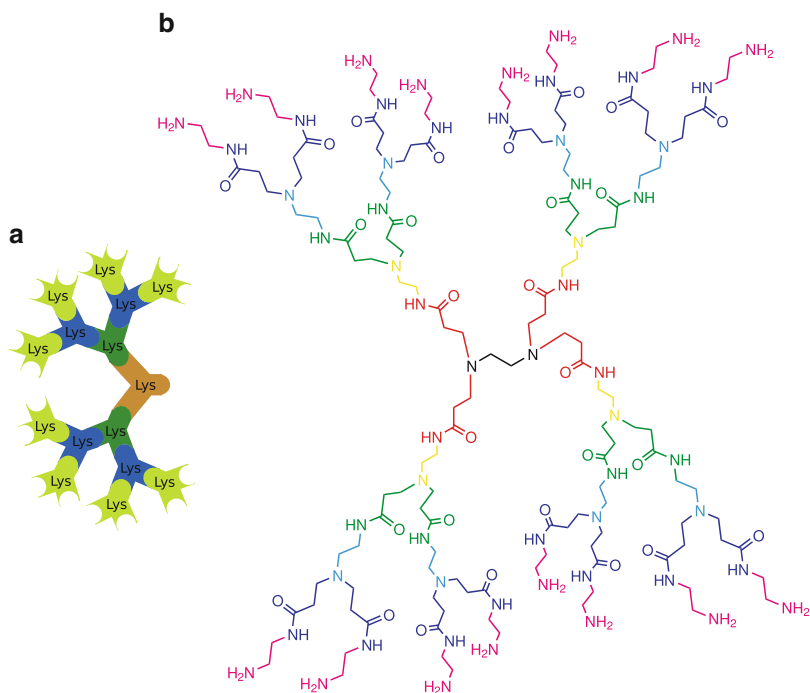
For example, the PAMAM dendrimer can be depicted as linear representation (Fig. 2.1). Another way of PAMAM nomenclature was proposed [23].

Another approach is fractal notation [64], a concise descriptive system for symmetrical dendrimers and other, simple symmetrical molecules. Fractal notation was applied also for nearly symmetrical dendrimers [65]. Fractal notation derives its qualities by taking advantage of the symmetry of dendritic molecules. The integrity of the system can be preserved also in nearly symmetrical dendrimers, which can be described as perturbations of the symmetrical parent molecules (Fig. 2.2).

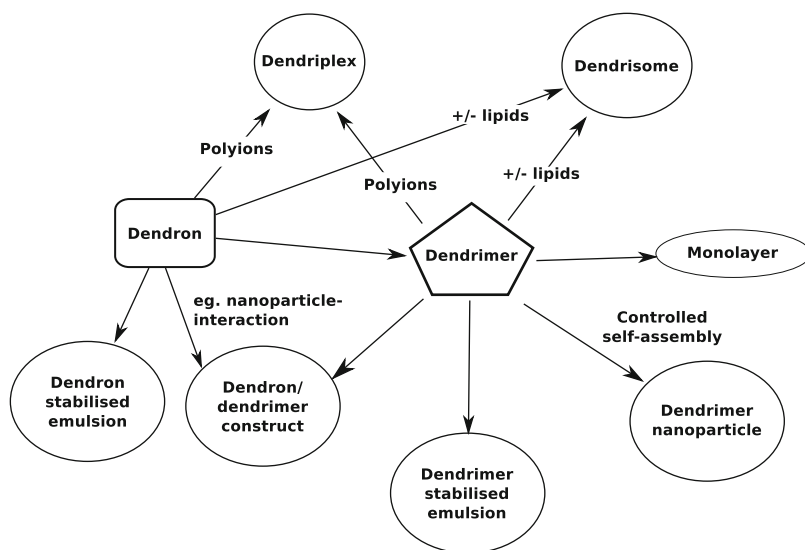
Tomalia [110] proposed a systematic framework in order to unify and define nanoscience on the base of historic first principles and step logic that led to a “central paradigm” (i.e., unifying framework) for chemistry of traditional elemental/small molecules. The proposed “nanomaterials classification road map” divides



**Fig. 2.1** Linear representation of classical MAP (**a**) and G3 PAMAM dendrimer (**b**). The extended structures are depicted in Fig. 2.2



**Fig. 2.2** Example of generation definition for G3-MAP (**a**) [92, 105] and G3-PAMAM (**b**) [10]. In the case of MAP (dendron), every generation is defined with color code starting from *brown* Lys (G0) leading through *dark green* (G1), *blue* (G2), and *light green* (G3) Lys residues. For PAMAM case (dendrimer), even halves of generations are depicted. *Black core* (G0) is surrounded by *red branches* (G0.5) which continue to *yellow ones* (G1). Next half generation is *green* (G1.5) and whole generation is *cyan* (G2). Finally, *dark blue* and *magenta* colors stand for G2.5 and G3, respectively



**Fig. 2.3** A schematic depiction of the variety of relationships between the primary dendron and dendrimer structures and their aggregated states. Adapted and extended from [1, 75]

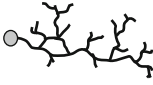
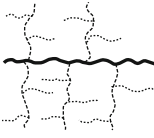

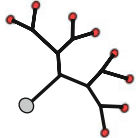
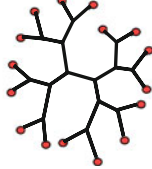
all nanomatter (including dendrimers) into Category I: discrete, well-defined and Category II: statistical, undefined nanoparticles. The proposed nanoparaperiodic table(s) is a milestone, like the Mendeleev table of elements, and can be used for predicting important risk/benefit borders in the nanoscience and dendrimer-based field. This predictive ability represents a breakthrough in theoretic approach to dendrimers.

For other nomenclature approaches in the area of nanoparticle and dendrimer classification see [50, 69, 85, 93, 103, 107]. Till now, there is not one simple, unambiguous, generally applicable, and worldwide acceptable dendrimer nomenclature, like IUPAC-IUB rules, which must be respected in every journal.

## 2.1 Dendriplexes and Dendrisomes

DNA can form nanostructures with cationic dendrons and dendrimers. These complexes have been termed dendriplexes [1, 82, 84]. However, similar structures can be probably formed from anionic dendrimers and linear polycations. Schematic interrelationships between dendrons, dendrimers, and their aggregated states (monolayers, dendrisomes, dendriplexes, nanoparticles, etc.) are shown in Fig. 2.3.

Small vesicular aggregates that are formed in water from cationic lipidic lysine MAP dendron with the appropriate hydrophile–lipophile balance were termed dendrisomes. Dendrisomes are resembling cationic liposomes and are able to

Statistical Structure	Semicontrolled Structures		Controlled Structures	
Random Hyperbranched	Dendrigrrafts	Megamers	Dendrons	Dendrimers
				
MW 1 - 100 kDa Mw/Mn = 2 - 10	MW 1 - 10 <sup>4</sup> kDa Mw/Mn = 1.1 - 1.5	MW 5 - 10 <sup>6</sup> kDa Mw/Mn = 1.05 - 1.5	MW 1 - 10 <sup>3</sup> kDa Mw/Mn = 1.0000 - 1.05	MW 1 - 10 <sup>3</sup> kDa Mw/Mn = 1.0000 - 1.05

**Fig. 2.4** Schematic representation of random hyperbranched polymers, dendrigrrafts, megamers, dendrons, and dendrimers. Adapted from [7, 53, 54, 75, 104, 108–111, 114]

encapsulate water-soluble, negatively charged compounds [1]. Both dendriplexes and dendrisomes are used as drug delivery systems and vectors [67].

## 2.2 Dendrigrraft

For dendrimer synthesis, traditional monomers are generally employed. Dendrigrrafts are prepared from reactive oligomers or polymers. Therefore, dendrigrrafts are generally much larger (Fig. 2.4) than dendrimers [25, 31, 108, 109, 111–113]. Some authors use the term “dendronized polymer” [51, 58].

## 2.3 Glycotope

The term “epitope” is used often in immunology, peptide, and protein chemistry. Epitopes are sites on an antigen that interact with specific antibodies. They can be either conformational or sequential. In the area of glycopeptides, glycodendrimers, MAGs, and glycobiology, the term “glycotope” is used. Glycotope is a three-dimensional carbohydrate (or glycopeptide) epitope in which carbohydrates play a decisive role in basic immunological recognition processes (antibodies, self–nonself, interaction with T and B cells, etc.). Its activity is governed not only by the carbohydrate part but depends also on the peptide or protein backbone and also on the amino acid, to which the glycotope is bound (Ser, Thr) [27, 56, 59, 81, 88, 97, 99, 120, 121, 127–130, 133]. Some respected authors [15, 29, 41, 43, 58, 77] do not use the term anyway. Many terms, e.g., glycotope, sugar epitope, carbohydrate epitope, glycopeptide epitope, polyvalent glycotope, glycocluster, and glycodomain more or less coincide. We will use the term glycotope.

## 2.4 Glycocluster

Sterical arrangement of two or more glycotopes, which can be in the form of dendron or dendrimer, is called glycocluster. The clustering leads to the amplification of the given biological or physicochemical activity. The amplification factor (activity increase overcalculated to one active unit, e.g., Glc) is a few orders of magnitude higher in comparison with the sum of the individual contributions. For more details see Sect. 2.6; [2–5, 14, 16, 18–20, 22, 24, 36, 38, 40, 42, 44, 45, 49, 52, 55, 58, 60, 61, 66, 71, 72, 75, 79, 80, 87–90, 94, 95, 98, 100, 102, 115, 119, 124, 125, 132, 134].

## 2.5 Glycocluster–Cluster

Complex glycoclusters are sometimes called as “glycocluster–cluster” [95]. The transformation of a simple sugar unit to a glycocluster unit in order to synthesize a novel “glycocluster–cluster” is accomplished using a glycocluster–cluster unit (cluster) in which a condensed glycocluster unit is connected with a cluster chain unit. By other words, e.g., dendrimers with valences 3,4, etc. are grouped in 3,4,5, etc. copies to a common core, shell, or backbone. On the other hand, other authors do not use designation “glycocluster–cluster” [20]. They prefer using the term glycoclusters also for complex molecules, e.g., with six branches having three carbohydrates on each branch, bearing together 18  $\alpha$ -mannopyranoside residues.

## 2.6 Cluster Effect and Multivalency

In general, interactions between saccharides and peptides or proteins are weak. Isolated carbohydrate–protein interactions are typically very weak with  $K_D$  values in the range of  $10^{-3}$ – $10^{-6}$  M. The nature compensates for the weakness of these isolated interactions by tending to cluster together multiple copies of carbohydrate ligands and their receptors [30, 97] (Fig. 19.1).

The activity of a tested compound (glycodendrimer, glycocluster, peptide dendrimer, etc.) can be generally expressed in three ways [18]: (1) Minimum concentration [e.g., in  $\mu$ M] required to inhibit the studied activity (e.g., agglutination of erythrocytes). (2) Relative potency, which is calculated as the ratio of the monovalent reference value to the ligands value. (3) Relative potency per carbohydrate (peptide), calculated as the ratio of the relative potency to the dendrimer (cluster) valency. By other words relative potency =  $IC_{50}$  (monosaccharide)/ $IC_{50}$  (inhibitor) and relative potency/sugar = relative potency/n [13]. The third way, relative potency per 1 carbohydrate (peptide), seems to be the most exact and explanative [18].

A bacterial lectin (PA-IL) from the opportunistic pathogen *Pseudomonas aeruginosa*, which is involved in recognition processes of glycoconjugates on human

tissues, was studied [18]. The dodecavalent fullerene glycoclusters obtained were tested as ligands of PA-IL and for their competing potential with its binding to glycosylated surfaces. The affinities tested by hemagglutination inhibition assay (HIA), surface plasmon resonance (SPR), and enzyme-linked lectin assay (ELLA) displayed a significant “glycoside cluster effect” with up to a 12,800-fold increase in binding (relative potency compared to Gal) and nearly 1100-fold increase of relative potency per carbohydrate. Both values are classical example of cluster effect, i.e., with growing valency of the cluster (dendrimer) the activity of the multivalent compound grows exponentially. This has some limits, given by the sterical demands of the surface groups on the dendrimer and also by the shape and dimensions of the counterpart (lectin, etc.).

Another convincing example for a cluster effect in FimH binding was shown by employing mannosylated lysine-based MAGs [70]. The relative inhibitory potencies of the di-, tetra-, octa-, and hexadecavalent mannosylated MAGs increased with growing generations from 455 over 2000 and 3571 to 11111, respectively [44]. In spite of the fact that the avidity did not grow logarithmically, it rose to a much greater extent than it would by a linear increase with respect to the increasing valency. This increase of activity is called “cluster effect” or “multivalent effect” [10, 20, 34, 60, 63, 75, 87, 90, 91, 97, 116, 117, 126, 134].

Roy’s team [91] prepared sialosyl MAGs with valencies of 2, 4, 8, and 16. Sialic acid was bound to the lysine branches by  $\text{SCH}_2\text{-CO-Gly-Gly}$  spacer. Binding properties of these MAGs with the plant lectin wheat germ agglutinin (WGA) were studied in a direct ELLA using horseradish peroxidase (HRPO)-labeled WGA. The octa- and hexadecavalent MAG had best binding properties. In an inhibition test using sialylated MAGs as coating antigen and HRPOWGA, all MAGs performed excellent inhibitory capacities ( $10^6$  times better than a monosialoside). The most powerful inhibitor was the hexadecavalent MAG.

Dramatical enhancement of dissociation constant between folate-binding protein and folate-G5 PAMAM dendrimer was described [47]. The binding avidity was improved by cluster effect up to 170,000 times.

The terms “cluster glycoside effect” [60] or “glycoside cluster effect” [18, 48], multivalent effect [46], multivalent glycotope [99], and clustering effect [9] are used only seldom and we will therefore use the most common term cluster effect [8, 18, 32, 44, 46].

We have not found exactly defined quantitative limits above which the activity increase can be called “cluster effect.” For more information about cluster effect and multivalency see [1, 6, 17, 20, 26, 35, 39, 46, 48, 57, 68, 74, 75, 83, 96, 97, 99, 101, 106, 118, 122, 131].

## 2.7 Macromolecular Effect

Multivalency or cluster effect is not able to explain all interactions. To solve this problem, Lindhorst and her team proposed that comprehension of fimbriae-mediated bacterial adhesion might require at least two different approaches [28]. One attitude

deals with results obtained from ELISA or hemagglutination inhibition assays. The observed inhibition of bacterial adhesion could be neither rationalized on the basis of the known crystal structure of FimH nor interpreted in the sense of a classical “cluster effect.” Instead, the inhibition of bacterial adhesion to the glycocalyx or a glycocalyx mimetic should be more likely explained by a “macromolecular effect” [28]. The inhibitory potencies can be correlated to features which are typical for macromolecules and the interactions they form, rather than for distinct molecular epitopes [28]. The macromolecular effect was discussed also in connection with fucosylated pentaerythrityl phosphodiester oligomers (PePOs) and their binding to *Pseudomonas aeruginosa* lectin (PA-IIL) [66]. Positive macromolecular effect during enhanced gelation of a dendritic gelator was described [135]. The macromolecular effect during NMR analysis of Gd(III)-based contrast agent influenced T1 relaxivity [62].

## 2.8 Sugar Ball

“Sugar balls” provide a spherical platform for a globular multivalent presentation of ligands with many carbohydrate residues in the peripheral region of the dendrimer [76, 78, 123]. It is based on fullerenes, quantum dots, or other spherical nanoparticles, wrapped to sugar shell.

## 2.9 “Smart” Glycodendrimers

Glyco- and glycopeptide dendrimers containing labile functionalities which can easily interconvert in solutions (disulfides, imines, hydrazones, metal coordination, etc.) are left to equilibrate in order to select one another to best fit to the binding site of interest [87]. This strategy was called “dynamic combinatorial chemistry” and was used in the preparation of dynamic combinatorial libraries (see Chap. 8).

## References

1. Al-Jamal, K., Ramaswamy, C., Florence, A.: Supramolecular structures from dendrons and dendrimers. *Adv. Drug. Deliv. Rev.* **57**(15), 2238–2270 (2005)
2. Andre, S., Kaltner, H., Furuike, T., Nishimura, S.I., Gabius, H.J.: Persubstituted cyclodextrin-based glycoclusters as inhibitors of protein-carbohydrate recognition using purified plant and mammalian lectins and wild-type and lectin-gene-transfected tumor cells as targets. *Bioconjug. Chem.* **15**(1), 87–98 (2004)
3. Andre, S., Lahmann, M., Gabius, H.J., Oscarson, S.: Glycocluster design for improved avidity and selectivity in blocking human lectin/plant toxin binding to glycoproteins and cells. *Mol. Pharmaceut.* **7**(6), 2270–2279 (2010)

4. Aoyama, Y.: Macrocyclic glycoclusters: From amphiphiles through nanoparticles to glycoviruses. *Chem. Eur. J.* **10**(3), 588–593 (2004)
5. Aoyama, Y., Kanamori, T., Nakai, T., Sasaki, T., Horiuchi, S., Sando, S., Niidome, T.: Artificial viruses and their application to gene delivery. Size-controlled gene coating with glycocluster nanoparticles. *J. Am. Chem. Soc.* **125**(12), 3455–3457 (2003)
6. Astruc, D., Boisselier, E., Ornelas, C.: Dendrimers designed for functions: From physical, photophysical, and supramolecular properties to applications in sensing, catalysis, molecular electronics, photonics, and nanomedicine. *Chem. Rev.* **110**(4), 1857–1959 (2010)
7. Atapour, M.H., Mojarad, M., Raoofian, R., Baghebani, F., Louie, O., Massoudi, A., Soukhtanloo, M., Hooshang, V.: PAMAM megamer (G2–G2) as a versatile tool in gene delivery. *Clinic. Biochem.* **44**(13, Supplement), S281–S282 (2011)
8. Ballut, S., Naud-Martin, D., Looock, B., Maillard, P.: A strategy for the targeting of photosensitizers. Synthesis, characterization, and photobiological property of porphyrins bearing glycodendrimeric moieties. *J. Org. Chem.* **76**(7), 2010–2028 (2011)
9. Bezouska, K.: Design, functional evaluation and biomedical applications of carbohydrate dendrimers (glycodendrimers). *Rev. Mol. Biotechnol.* **90**(3–4), 269–290 (2002)
10. Boas, U., Heegaard, P.: Dendrimers in drug research. *Chem. Soc. Rev.* **33**(1), 43–63 (2004)
11. Boas, U., Christensen, J., Heegaard, P.: Dendrimers: design, synthesis and chemical properties. *J. Mater. Chem.* **16**, 3785–3798 (2006)
12. Boas, U., Christensen, J., Heegaard, P.: Dendrimers in medicine and biotechnology. New molecular tools. Dendrimers: design, synthesis and chemical properties, pp. 1–27. RSC Publishing, Cambridge (2006)
13. Bossu, I., Berthet, N., Dumy, P., Renaudet, O.: Synthesis of glycocyclopeptides by click chemistry and inhibition assays with lectins. *J. Carbohydr. Chem.* **30**(7–9), 458–468 (2011)
14. Branderhorst, H., Ruijtenbeek, R., Liskamp, R., Pieters, R.: Multivalent carbohydrate recognition on a glycodendrimer-functionalized flow-through chip. *ChemBioChem.* **9**(11), 1836–1844 (2008)
15. Brocke, C., Kunz, H.: Synthesis of tumor-associated glycopeptide antigens. *Bioorg. Med. Chem.* **10**(10), 3085–3112 (2002)
16. Cecioni, S., Lalor, R., Blanchard, B., Praly, J.P., Imbert, A., Matthews, S.E., Vidal, S.: Achieving high affinity towards a bacterial lectin through multivalent topological isomers of calix[4]arene glycoconjugates. *Chem. Eur. J.* **15**(47), 13232–13240 (2009)
17. Cecioni, S., Faure, S., Darbost, U., Bonnamour, I., Parrot-Lopez, H., Roy, O., Taillefumier, C., Wimmerova, M., Praly, J.P., Imbert, A., Vidal, S.: Selectivity among two lectins: Probing the effect of topology, multivalency and flexibility of “clicked” multivalent glycoclusters. *Chem. Eur. J.* **17**(7), 2146–2159 (2011)
18. Cecioni, S., Oerthel, V., Iehl, J., Holler, M., Goyard, D., Praly, J.P., Imbert, A., Nierengarten, J.F., Vidal, S.: Synthesis of dodecavalent fullerene-based glycoclusters and evaluation of their binding properties towards a bacterial lectin. *Chem. Eur. J.* **17**(11), 3252–3261 (2011)
19. Chabre, Y., Roy, R.: Recent trends in glycodendrimer syntheses and applications. *Curr. Top. Med. Chem.* **8**(14), 1237–1285 (2008)
20. Chabre, Y., Roy, R.: Design and creativity in synthesis of multivalent neoglycoconjugates. *Adv. Carbohydr. Chem. Biochem.* **63**, 165–393 (2010)
21. Chabre, Y.M., Roy, R.: Dendrimer-Based Drug Delivery Systems: From Theory to Practice. Dendrimer-Coated Carbohydrate Residues as Drug Delivery Trojan Horses in Glycoscience, 1st edn., pp. 405–436. Wiley, New York (2012)
22. Chabre, Y., Contino-Pepin, C., Placide, V., Tze, C., Roy, R.: Expeditive synthesis of glycodendrimer scaffolds based on versatile TRIS and mannoside derivatives. *J. Org. Chem.* **73**(14), 5602–5605 (2008)
23. Chauhan, A.S., Diwan, P.V., Jain, N.K., Tomalia, D.A.: Unexpected in vivo anti-inflammatory activity observed for simple, surface functionalized poly(amidoamine) dendrimers. *Biomacromolecules* **10**(5), 1195–1202 (2009)
24. Chen, Q., Cui, Y., Cao, J., Han, B.H.: Water-soluble conjugated polyelectrolyte with pendant glycocluster: synthesis and its interaction with heparin. *Polymer* **52**(2), 383–390 (2011)



25. Cheng, J., Ling, X., Zhong, Z., Zhuo, R.: Synthesis of dendrigraft poly( $\epsilon$ -caprolactone)s using side hydroxyl groups for the grafting of branch chains. *Macromol. Rapid. Commun.* **32**(22), 1839–1845 (2011)
26. Deniaud, D., Julienne, K., Gouin, S.G.: Insights in the rational design of synthetic multivalent glycoconjugates as lectin ligands. *Org. Biomol. Chem.* **9**(4), 966–979 (2011)
27. Dinglasan, R., Valenzuela, J., Azad, A.: Sugar epitopes as potential universal disease transmission blocking targets. *Insect. Biochem. Mol. Biol.* **35**(1), 1–10 (2005)
28. Dubber, M., Sperling, O., Lindhorst, T.: Oligomannoside mimetics by glycosylation of “octopus glycosides” and their investigation as inhibitors of type 1 fimbriae-mediated adhesion of *Escherichia coli*. *Org. Biomol. Chem.* **4**(21), 3901–3912 (2006)
29. Dziadek, S., Kunz, H.: Synthesis of tumor-associated glycopeptide antigens for the development of tumor-selective vaccines. *Chem. Record.* **3**(6), 308–321 (2004)
30. El-Boubbou, K., Huang, X.: Glyco-nanomaterials: translating insights from the “sugar-code” to biomedical applications. *Curr. Med. Chem.* **18**(14), 2060–2078 (2011)
31. Esfand, R., Tomalia, D.A.: Poly(amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. *Drug Discov. Today* **6**(8), 427–436 (2001)
32. Euzen, R., Reymond, J.L.: Glycopeptide dendrimers: tuning carbohydrate-lectin interactions with amino acids. *Mol. BioSyst.* **7**(2), 411–421 (2011)
33. Friedhofen, J., Vogtle, F.: Detailed nomenclature for dendritic molecules. *New J. Chem.* **30**(1), 32–43 (2006)
34. Gabius, H.J.: Glycans: Bioactive signals decoded by lectins. *Biochem. Soc. Trans.* **36**(6), 1491–1496 (2008)
35. Gabius, H.J., Andre, S., Jimenez-Barbero, J., Romero, A., Solis, D.: From lectin structure to functional glycomics: principles of the sugar code. *Trends Biochem. Sci.* **36**(6), 298–313 (2011)
36. Galante, E., Geraci, C., Sciuto, S., Campo, V.L., Carvalho, I., Sesti-Costa, R., Guedes, P.M., Silva, J.S., Hill, L., Nepogodiev, S.A., Field, R.A.: Glycoclusters presenting lactose on calix[4]arene cores display trypanocidal activity. *Tetrahedron* **67**(33), 5902–5912 (2011)
37. Gao, C., Yan, D.: Hyperbranched polymers: From synthesis to applications. *Prog. Polym. Sci.* **29**(3), 183–275 (2004)
38. Gao, Y., Eguchi, A., Kakehi, K., Lee, Y.: Efficient preparation of glycoclusters from silsesquioxanes. *Org. Lett.* **6**(20), 3457–3460 (2004)
39. Gao, C., Yan, D., Frey, H.: Hyperbranched polymers. *Promising Dendritic Materials: An Introduction to Hyperbranched Polymers*, pp. 1–26. Wiley, New York (2011)
40. Grandjean, C., Santraine, V., Fruchart, J.S., Melnyk, O., Gras-Masse, H.: Combined thioether/hydrazone chemoselective ligation reactions for the synthesis of glycocluster-antigen peptide conjugates. *Bioconjug. Chem.* **13**(4), 887–892 (2002)
41. Guo, Z., Shao, N.: Glycopeptide and glycoprotein synthesis involving unprotected carbohydrate building blocks. *Med. Res. Rev.* **25**(6), 655–678 (2005)
42. Hada, N., Sato, K., Jin, Y., Takeda, T.: Synthesis of new peptidic glycoclusters derived from  $\beta$ -alanine. Part 2: Optionally modulated distance between side-chain branched points. *Chem. Pharm. Bull.* **53**(9), 1131–1135 (2005)
43. Haltiwanger, R., Lowe, J.: Role of glycosylation in development. *Ann. Rev. Biochem.* **73**, 491–537 (2004)
44. Hartmann, M., Lindhorst, T.K.: The bacterial lectin FimH, a target for drug discovery—carbohydrate inhibitors of type 1 fimbriae-mediated bacterial adhesion. *Eur. J. Org. Chem.* **2011**(20–21), 3583–3609 (2011)
45. Hayashida, O., Mizuki, K., Akagi, K., Matsuo, A., Kanamori, T., Nakai, T., Sando, S., Aoyama, Y.: Macrocyclic glycoclusters. Self-aggregation and phosphate-induced agglutination behaviors of calix[4]resorcarene-based quadruple-chain amphiphiles with a huge oligosaccharide pool. *J. Am. Chem. Soc.* **125**(2), 594–601 (2003)
46. Hoai, N.T., Sasaki, A., Sasaki, M., Kaga, H., Kakuchi, T., Satoh, T.: Synthesis, characterization, and lectin recognition of hyperbranched polysaccharide obtained from 1,6-anhydro-D-hexofuranose. *Biomacromolecules* **12**(5), 1891–1899 (2011)

47. Hong, S., Leroueil, P.R., Majoros, I.J., Orr, B.G. Jr., J.R.B., Holl, M.M.B.: The binding avidity of a nanoparticle-based multivalent targeted drug delivery platform. *Chem. Biol.* **14**(1), 107–115 (2007)
48. Hu, M.X., Xu, Z.K.: Carbohydrate decoration of microporous polypropylene membranes for lectin affinity adsorption: comparison of mono- and disaccharides. *Colloids Surf. B* **85**(1), 19–25 (2011)
49. Imberty, A., Chabre, Y., Roy, R.: Glycomimetics and glycodendrimers as high affinity microbial anti-adhesins. *Chem. Eur. J.* **14**(25), 7490–7499 (2008)
50. Jones, J.H.: Abbreviations and symbols in peptide science: a revised guide and commentary. *J. Pept. Sci.* **12**(1), 1–12 (2006)
51. Jung, H., Carberry, T.P., Weck, M.: Synthesis of first- and second-generation poly(amide)-dendronized polymers via ring-opening metathesis polymerization. *Macromolecules* **44**(23), 9075–9083 (2011)
52. Kalovidouris, S., Blixt, O., Nelson, A., Vidal, S., Turnbull, W., Paulson, J., Stoddart, J.: Chemically defined sialoside scaffolds for investigation of multivalent interactions with sialic acid binding proteins. *J. Org. Chem.* **68**(22), 8485–8493 (2003)
53. Khopade, A.J., Mohwald, H.: Statistical megamer morphologies and materials from PAMAM dendrimers. *Macromol. Rapid. Commun.* **26**(6), 445–449 (2005)
54. Kiran, B.M., Jayaraman, N.: Thiol–disulfide interchange mediated reversible dendritic megamer formation and dissociation. *Macromolecules* **42**(19), 7353–7359 (2009)
55. Kohn, M., Benito, J., Mellet, C., Lindhorst, T., Garcia Fernandez, J.: Functional evaluation of carbohydrate-centred glycoclusters by enzyme-linked lectin assay: ligands for concanavalin A. *ChemBioChem.* **5**(6), 771–777 (2004)
56. Korchagina, E., Pochechueva, T., Obukhova, P., Formanovsky, A., Imberty, A., Rieben, R., Bovin, N.: Design of the blood group AB glycotope. *Glycoconj. J.* **22**(3), 127–133 (2005)
57. Lahmann, M.: Glycoscience and microbial adhesion. *Architectures of Multivalent Glycomimetics for Probing Carbohydrate–Lectin Interactions*, pp. 17–65. Springer, Berlin (2009)
58. Lindhorst, T.: Artificial multivalent sugar ligands to understand and manipulate carbohydrate-protein interactions. *Top Curr. Chem.* **218**, 201–235 (2002)
59. Lo-Man, R., Vichier-Guerre, S., Bay, S., Deriaud, E., Cantacuzene, D., Leclerc, C.: Anti-tumor immunity provided by a synthetic multiple antigenic glycopeptide displaying a tri-Tn glycotope. *J. Immunol.* **166**(4), 2849–2854 (2001)
60. Lundquist, J., Toone, E.: The cluster glycoside effect. *Chem. Rev.* **102**(2), 555–578 (2002)
61. MacPherson, I.S., Temme, J.S., Habeshian, S., Felczak, K., Pankiewicz, K., Hedstrom, L., Krauss, I.J.: Multivalent glycocluster design through directed evolution. *Angew. Chem. Int. Ed.* **50**(47), 11238–11242 (2011)
62. Makino, A., Harada, H., Okada, T., Kimura, H., Amano, H., Saji, H., Hiraoka, M., Kimura, S.: Effective encapsulation of a new cationic gadolinium chelate into apoferritin and its evaluation as an MRI contrast agent. *Nanomedicine* **7**(5), 638–646 (2011)
63. Matsuura, K., Kobayashi, K.: Analysis of GM3-Gg3 interaction using clustered glycoconjugate models constructed from glycolipid monolayers and artificial glycoconjugate polymers. *Glycoconj. J.* **21**(3–4), 139–148 (2004)
64. Mendenhall, G.D.: Mesomolecules from molecules to materials. *Fractal Index and Fractal Nomenclature*, pp. 181–194. Chapman & Hall, New York (1995)
65. Mendenhall, G.D.: Fractal notation for nearly-symmetrical dendrimers. *J. Polym. Sci. A* **36**(16), 2979–2983 (1998)
66. Morvan, F., Meyer, A., Jochum, A., Sabin, C., Chevolut, Y., Imberty, A., Praly, J.P., Vasseur, J.J., Souteyrand, E., Vidal, S.: Fucosylated pentaerythrityl phosphodiester oligomers (PePOs): Automated synthesis of DNA-based glycoclusters and binding to *Pseudomonas aeruginosa* lectin (PA-III). *Bioconjug. Chem.* **18**(5), 1637–1643 (2007)
67. Movassaghian, S., Moghimi, H.R., Shirazi, F.H., Torchilin, V.P.: Dendrosome-dendriplex inside liposomes: as a gene delivery system. *J. Drug. Target.* **19**(10), 925–932 (2011)
68. Munoz, E.M., Correa, J., Fernandez-Megia, E., Riguera, R.: Probing the relevance of lectin clustering for the reliable evaluation of multivalent carbohydrate recognition. *J. Am. Chem. Soc.* **131**(49), 17765–17767 (2009)

69. Murer, P.K., Lapiere, J.M., Greiveldinger, G., Seebach, D.: Synthesis and properties of first and second generation chiral dendrimers with triply branched units: A spectacular case of diastereoselectivity. *Helv. Chim. Acta.* **80**(5), 1648–1681 (1997)
70. Nagahori, N., Lee, R., Nishimura, S., Page, D., Roy, R., Lee, Y.: Inhibition of adhesion of type 1 fimbriated *Escherichia coli* to highly mannosylated ligands. *ChemBioChem.* **3**(9), 836–844 (2002)
71. Nakai, T., Kanamori, T., Sando, S., Aoyama, Y.: Remarkably size-regulated cell invasion by artificial viruses. Saccharide-dependent self-aggregation of glycoviruses and its consequences in glycoviral gene delivery. *J. Am. Chem. Soc.* **125**(28), 8465–8475 (2003)
72. Newkome, G.R., Shreiner, C.: Dendrimers derived from 1 → 3 branching motifs. *Chem. Rev.* **110**(10), 6338–6442 (2010)
73. Newkome, G.R., Baker, G.R., Young, J.K., Traynham, J.G.: A systematic nomenclature for cascade polymers. *J. Polym. Sci. A* **31**(3), 641–651 (1993)
74. Nicotra, F., Cipolla, L., Peri, F., La Ferla, B., Redaelli, C.: Chemoselective neoglycosylation. *Adv. Carb. Chem. Biochem.* **61**, 353–398 (2008)
75. Niederhafner, P., Sebestik, J., Jezek, J.: Glycopeptide dendrimers. Part I. *J. Pept. Sci.* **14**(1), 2–43 (2008)
76. Nierengarten, J.F., Iehl, J., Oerthel, V., Holler, M., Illescas, B.M., Munoz, A., Martin, N., Rojo, J., Sanchez-Navarro, M., Cecioni, S., Vidal, S., Buffet, K., Durka, M., Vincent, S.P.: Fullerene sugar balls. *Chem. Commun.* **46**, 3860–3862 (2010)
77. Okada, M.: Molecular design and syntheses of glycopolymers. *Prog. Polym. Sci.* **26**(1), 67–104 (2001)
78. Osaki, F., Kanamori, T., Sando, S., Sera, T., Aoyama, Y.: A quantum dot conjugated sugar ball and its cellular uptake. On the size effects of endocytosis in the subviral region. *J. Am. Chem. Soc.* **126**(21), 6520–6521 (2004)
79. Oshovsky, G., Verboom, W., Fokkens, R., Reinhoudt, D.: Anion complexation by glycocluster thioureamethyl cavities: Novel ESI-MS-based methods for the determination of  $K_a$  values. *Chem. Eur. J.* **10**(11), 2739–2748 (2004)
80. Patel, A., Lindhorst, T.: Multivalent glycomimetics: synthesis of nonavalent mannoside clusters with variation of spacer properties. *Carbohydr. Res.* **341**(10), 1657–1668 (2006)
81. Peterson, N.A., Hokke, C.H., Deelder, A.M., Yoshino, T.P.: Glycotope analysis in miracidia and primary sporocysts of schistosoma mansoni: Differential expression during the miracidium-to-sporocyst transformation. *Int. J. Parasitol.* **39**(12), 1331–1344 (2009)
82. Ramaswamy, C., Sakthivel, T., Wilderspin, A., Florence, A.: Dendriplexes and their characterisation. *Int. J. Pharmaceut.* **254**(1), 17–21 (2003)
83. Reynolds, M., Perez, S.: Thermodynamics and chemical characterization of protein-carbohydrate interactions: the multivalency issue. *Compt. Rend. Chim.* **14**(1), 74–95 (2011)
84. Ribeiro, S., Hussain, N., Florence, A.: Release of DNA from dendriplexes encapsulated in PLGA nanoparticles. *Int. J. Pharmaceut.* **298**(2), 354–360 (2005)
85. Roberts, B.P., Scanlon, M.J., Krippner, G.Y., Chalmers, D.K.: The dotted cap notation: a concise notation for describing variegated dendrimers RID A-4967-2010. *New J. Chem.* **32**(9), 1543–1554 (2008)
86. Roglin, L., Lempens, E.H.M., Meijer, E.W.: A synthetic “tour de force”: Well-defined multivalent and multimodal dendritic structures for biomedical applications. *Angew. Chem. Int. Ed.* **50**(1), 102–112 (2011)
87. Roy, R.: A decade of glycodendrimer chemistry. *Trends Glycosci. Glycotechnol.* **15**(85), 291–310 (2003)
88. Roy, R., Baek, M.G.: Glycodendrimers: Novel glycotope isosteres unmasking sugar coding. Case study with T-antigen markers from breast cancer MUC1 glycoprotein. *Rev. Mol. Biotechnol.* **90**(3–4), 291–309 (2002)
89. Roy, R., Kim, J.: Cu(II)-self-assembling bipyridyl-glycoclusters and dendrimers bearing the Tn-antigen cancer marker: Syntheses and lectin binding properties. *Tetrahedron* **59**(22), 3881–3893 (2003)

90. Roy, R., Touaibia, M.: Carbohydrate-protein and carbohydrate-carbohydrate interactions; comprehensive glycoscience. Application of multivalent mannosylated dendrimers in glyco-biology, pp. 821–870. Elsevier, Utrecht (2007)
91. Roy, R., Zanini, D., Meunier, S., Romanowska, A.: Solid-phase synthesis of dendritic sialoside inhibitors of influenza A virus haemagglutinin. *Chem. Commun.* (24), 1869–1872 (1993)
92. Sadler, K., Tam, J.: Peptide dendrimers: applications and synthesis. *Rev. Mol. Biotechnol.* **90**(3–4), 195–229 (2002)
93. Safarowsky, O., Windisch, B., Mohry, A., Vogtle, F.: Nomenclature for catenanes, rotaxanes, molecular knots, and assemblies derived from these structural elements. *J. Prakt. Chem.* **342**(5), 437–444 (2000)
94. Sato, K., Hada, N., Takeda, T.: Synthesis of new peptidic glycoclusters derived from  $\beta$ -alanine. *Tetrahedron Lett.* **44**(52), 9331–9335 (2003)
95. Sato, K., Hada, N., Takeda, T.: Syntheses of new peptidic glycoclusters derived from  $\beta$ -alanine: di- and trimerized glycoclusters and glycocluster-clusters. *Carbohydr. Res.* **341**(7), 836–845 (2006)
96. Scholl, M., Kadlecova, Z., Klok, H.A.: Dendritic and hyperbranched polyamides. *Prog. Polym. Sci.* **34**(1), 24–61 (2009)
97. Sebestik, J., Niederhafner, P., Jezek, J.: Peptide and glycopeptide dendrimers and analogous dendrimeric structures and their biomedical applications. *Amino Acids* **40**(2), 301–370 (2011)
98. Sicard, D., Cecioni, S., Iazykov, M., Chevolot, Y., Matthews, S.E., Praly, J.P., Souteyrand, E., Imbert, A., Vidal, S., Phaner-Goutorbe, M.: AFM investigation of *Pseudomonas aeruginosa* lectin LecA (PA-IL) filaments induced by multivalent glycoclusters. *Chem. Commun.* **47**, 9483–9485 (2011)
99. Singh, T., Wu, J., Peumans, W., Rouge, P., Van Damme, E., Alvarez, R., Blixt, O., Wu, A.: Carbohydrate specificity of an insecticidal lectin isolated from the leaves of *Glechoma hederacea* (ground ivy) towards mammalian glycoconjugates. *Biochem. J.* **393**(1), 331–341 (2006)
100. Singh, Y., Renaudet, O., Defrancq, E., Dumy, P.: Preparation of a multitopic glycopeptide-oligonucleotide conjugate. *Org. Lett.* **7**(7), 1359–1362 (2005)
101. Smet, M.: Hyperbranched polymers. Biological and Medical Applications of Hyperbranched Polymers, pp. 387–413. Wiley, New York (2011)
102. Soomro, Z.H., Cecioni, S., Blanchard, H., Praly, J.P., Imbert, A., Vidal, S., Matthews, S.E.: CuAAC synthesis of resorcin[4]arene-based glycoclusters as multivalent ligands of lectins. *Org. Biomol. Chem.* **9**, 6587–6597 (2011)
103. Spengler, J., Jimenez, J.C., Burger, K., Giralt, E., Albericio, F.: Abbreviated nomenclature for cyclic and branched homo- and hetero-detic peptides. *J. Pept. Res.* **65**(6), 550–555 (2005)
104. Svenson, S.: Dendrimers. *Kirk-Othmer Encyclop. Chem. Technol.* **26**, 786–812 (2007)
105. Tam, J.: Houben-Weyl, Methods of Organic Chemistry. Synthesis of Peptides and Peptidomimetics, vol. E22d. Macropeptide structures. Synthesis of Peptide Dendrimers and Protein Mimetics, pp. 129–168. Georg Thieme Verlag, Stuttgart (2004)
106. Tanaka, K., Siwu, E.R.O., Minami, K., Hasegawa, K., Nozaki, S., Kanayama, Y., Koyama, K., Chen, W.C., Paulson, J.C., Watanabe, Y., Fukase, K.: Noninvasive imaging of dendrimer-type *N*-glycan clusters: *In vivo* dynamics dependence on oligosaccharide structure. *Angew. Chem. Int. Ed.* **49**(44), 8195–8200 (2010)
107. Teo, B.K., Sun, X.H.: Classification and representations of low-dimensional nanomaterials: terms and symbols. *J. Clust. Sci.* **18**(2), 346–357 (2007)
108. Tomalia, D.: Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry. *Prog. Polym. Sci.* **30**(3–4), 294–324 (2005)
109. Tomalia, D.: Dendrons/dendrimers. The convergence of quantized dendritic building blocks/architectures for applications in nanotechnology. *Chim. Oggi.* **23**(6), 41–45 (2005)
110. Tomalia, D.: In quest of a systematic framework for unifying and defining nanoscience. *J. Nanoparticle Res.* **11**(6), 1251–1310 (2009)

111. Tomalia, D.A.: Dendrons/dendrimers: quantized, nano-element like building blocks for soft-soft and soft-hard nano-compound synthesis. *Soft Matter* **6**, 456–474 (2010)
112. Tomalia, D.A.: Dendritic effects: dependency of dendritic nano-periodic property patterns on critical nanoscale design parameters (CNDPs). *New. J. Chem.* **36**, 264–281 (2012)
113. Tomalia, D., Frechet, J.: Discovery of dendrimers and dendritic polymers: a brief historical perspective. *J. Polym. Sci. A* **40**(16), 2719–2728 (2002)
114. Tomalia, D.A., Uppuluri, S., Swanson, D.R., Li, J.: Dendrimers as reactive modules for the synthesis of new structure-controlled, higher-complexity megamers. *Pure Appl. Chem.* **72**(12), 2343–2358 (2000)
115. Touaibia, M., Roy, R.: Glycodendrimers as anti-adhesion drugs against type 1 fimbriated *E. coli* uropathogenic infections. *Mini Rev. Med. Chem.* **7**(12), 1270–1283 (2007)
116. Tsvetkov, D., Nifantiev, N.: Dendritic polymers in glycobiology. *Russ. Chem. Bull.* **54**(5), 1065–1083 (2005)
117. Turnbull, W., Stoddart, J.: Design and synthesis of glycodendrimers. *Rev. Mol. Biotechnol.* **90**(3–4), 231–255 (2002)
118. Uhlich, N.A., Darbre, T., Reymond, J.L.: Peptide dendrimer enzyme models for ester hydrolysis and aldolization prepared by convergent thioether ligation. *Org. Biomol. Chem.* **9**, 7071–7084 (2011)
119. Vedala, H., Chen, Y., Cecioni, S., Imberty, A., Vidal, S., Star, A.: Nanoelectronic detection of lectin-carbohydrate interactions using carbon nanotubes. *Nano Lett.* **11**(1), 170–175 (2011)
120. Vichier-Guerre, S., Lo-Man, R., BenMohamed, L., Driaud, E., Kovats, S., Leclerc, C., Bay, S.: Induction of carbohydrate-specific antibodies in HLA-DR transgenic mice by a synthetic glycopeptide: A potential anti cancer vaccine for human use. *J. Pept. Res.* **62**(3), 117–124 (2003)
121. Vichier-Guerre, S., Lo-Man, R., Huteau, V., Driaud, E., Leclerc, C., Bay, S.: Synthesis and immunological evaluation of an antitumor neoglycopeptide vaccine bearing a novel homoserine Tn antigen. *Bioorg. Med. Chem. Lett.* **14**(13), 3567–3570 (2004)
122. Voit, B., Appelhans, D.: Glycopolymers of various architectures-more than mimicking nature. *Macromol. Chem. Phys.* **211**(7), 727–735 (2010)
123. Watanabe, S., Iwamura, M.: Dendritic caged compounds. *J. Photochem. Photobiol. A* **155**(1–3), 57–62 (2003)
124. Wehner, J.W., Lindhorst, T.K.: Glycocluster synthesis by native chemical ligation. *Synthesis* (18), 3070–3082 (2010)
125. Westermann, B., Dorner, S.: Synthesis of multivalent aminoglycoside mimics via the Ugi multicomponent reaction. *Chem. Commun.* (16), 2116–2118 (2005)
126. Wolfenden, M., Cloninger, M.: Mannose/glucose-functionalized dendrimers to investigate the predictable tunability of multivalent interactions. *J. Am. Chem. Soc.* **127**(35), 12168–12169 (2005)
127. Wu, A.: Expression of binding properties of Gal/GalNAc reactive lectins by mammalian glycotopes. *Adv. Exp. Med. Biol.* **491**, 55–64 (2001)
128. Wu, A.: Polyvalent GalNAc $\alpha$ 1  $\rightarrow$  Ser/Thr (Tn) and Gal $\beta$ 1  $\rightarrow$  3GalNAc $\alpha$ 1  $\rightarrow$  Ser/Thr (T $\alpha$ ) as the most potent recognition factors involved in *Maclura pomifera* agglutinin-glycan interactions. *J. Biomed. Sci.* **12**(1), 135–152 (2005)
129. Wu, A., Wu, J., Herp, A., Liu, J.H.: Effect of polyvalencies of glycotopes on the binding of a lectin from the edible mushroom, *Agaricus bisporus*. *Biochem. J.* **371**(2), 311–320 (2003)
130. Wu, A., Wu, J., Liu, J.H., Singh, T., Andre, S., Kaltner, H., Gabius, H.J.: Effects of polyvalency of glycotopes and natural modifications of human blood group ABH/Lewis sugars at the Gal $\beta$ 1-terminated core saccharides on the binding of domain-I of recombinant tandem-repeat-type galectin-4 from rat gastrointestinal tract (G4-N). *Biochimie.* **86**(4–5), 317–326 (2004)
131. Wurm, F., Frey, H.: Linear-dendritic block copolymers: The state of the art and exciting perspectives. *Prog. Polym. Sci.* **36**(1), 1–52 (2011)
132. Yang, L.Y., Haraguchi, T., Inazawa, T., Kajiwar, S., Yuasa, H.: Synthesis of a novel class of glycocluster with a cyclic  $\alpha$ -(1  $\rightarrow$  6)-octaglucoside as a scaffold and their binding abilities to concanavalin A. *Carbohydr. Res.* **345**(15), 2124–2132 (2010)

133. Yen, M.H., Wu, A.M., Yang, Z., Gong, Y.P., Chang, E.T.: Recognition roles of the carbohydrate glycotopes of human and bovine lactoferrins in lectin–N-glycan interactions. *Biochim. Biophys. Acta* **1810**(2), 139–149 (2011)
134. Zhang, J., Pourceau, G., Meyer, A., Vidal, S., Praly, J.P., Souteyrand, E., Vasseur, J.J., Morvan, F., Chevolot, Y.: DNA-directed immobilisation of glycomimetics for glycoarrays application: comparison with covalent immobilisation, and development of an on-chip IC<sub>50</sub> measurement assay. *Biosens. Bioelectron.* **24**(8), 2515–2521 (2009)
135. Zhang, Z., Yang, M., Zhang, X., Zhang, L., Liu, B., Zheng, P., Wang, W.: Enhancing gelation ability of a dendritic gelator through complexation with a polyelectrolyte. *Chem. Eur. J.* **15**(10), 2352–2361 (2009)

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