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Multivalent scaffolds in glycoscience: an overview†

Olivier Renaudet[ab] and René Roy[c]

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The seminal contributions of Y. C. Lee and co-workers since the early 1980s in the field of glycobiology and multivalent carbohydrate–protein interactions have culminated into the concept of "Glycoside cluster effect". These pioneering observations led to the foundation of glycodendrimer chemistry initiated more than two decades ago.

It became progressively evident that the interplay of complex multivalent interactions was similarly applicable to a wide range of other biomolecular relationships valuable in new drug design. Although tremendous progress has been accomplished in our understanding of the "glycocodes" through multivalency, it is also becoming increasingly obvious that the detailed mechanisms underlying multiple ligand–protein interactions are far more complicated than initially perceived.

On the other hand, numerous useful applications of multivalent glycoarchitectures have emerged through this exciting activity. They encompass several therapeutic opportunities that include antimicrobial strategies, vaccines, and targeted drug delivery, together with diagnostic applications and cell and tissue imaging.

The quest to overcome the weakness of natural glycan binding interactions

[a] *Département de Chimie Moléculaire, UMR-CNRS 5250 & ICMG FR 2607, Université Joseph Fourier, BP 53, 570 rue de la chimie, 38041 Grenoble Cedex 9, France. E-mail: olivier.renaudet@ujf-grenoble.fr; Fax: +33 4 56 52 08 03; Tel: +33 4 56 52 08 33*

[b] *Institut Universitaire de France, 103 boulevard Saint-Michel, 75005 Paris, France*

[c] *Pharmaqam – Department of Chemistry, Université du Québec à Montréal, P.O. Box 8888, Succ. Centre-ville, Montréal, Québec, Canada H3C 3P8. E-mail: roy.rene@uqam.ca; Fax: +1 514 987 4054; Tel: +1 514 987 3000 ext 2546*

† Part of the multivalent scaffolds in glycosciences themed issue.

Olivier Renaudet

Olivier Renaudet received his PhD in 2002 in the field of peptide and carbohydrate chemistry at the Université Joseph Fourier, Grenoble (France). Thereafter, he pursued postdoctoral research in the group of Prof. J.-L. Reymond at the University of Berne (Switzerland) then he returned to Grenoble to obtain an Assistant Professor position in 2004 in the group of Prof. P. Dumy at the Department of Molecular Chemistry. He was appointed as a junior member at the Institut Universitaire de France in 2011, then full Professor in 2012. He has co-edited a book on the synthesis and biological applications of glycoconjugates in 2011. His current research activities focus on the development of polyfunctional homo- and heteroglycoclusters as antitumoral synthetic vaccines, nanovectors or anti-pathogenic agents.

René Roy

René Roy was born in Québec (Canada). He holds a Canadian Research Chair in Therapeutic Chemistry in the Department of Chemistry of the Université du Québec à Montréal (Qc, Canada) since 2004. After his PhD, obtained in 1980 from the Université de Montréal in carbohydrate chemistry under Prof. Stephen Hanessian, he joined the National Research Council of Canada in Ottawa (Canada) from 1980–1985. He was then professor in the Department of Chemistry at the University of Ottawa from 1985–2002. He was the recipient of the 2003 Melville L. Wolfrom Award from the ACS Division of Carbohydrate Chemistry for his contributions in the design of vaccines and glycodendrimers. He has published over 290 publications and has contributed to the development of two commercial carbohydrate-based vaccines. His actual interests are in multivalent carbohydrate–protein interactions and in nanomedicines.

has triggered the use of several families of molecular scaffolds that this themed issue critically and tutorially reviews. Each such scaffold has its own advantage in terms of mimicking the usual display of multivalent glycans. They allow for the precise controls of geometry, topology and valency. Adding the arsenal of sophisticated synthetic methodologies to increasingly creative scaffolds and building blocks offers great potential towards novel glyconanomaterials of interest. Moreover, the need for rationally designed glycoclusters that conspicuously address the precise architectural needs of both ligands and receptor partners constitutes the biggest challenge of the next decades ahead.

Multivalency plays a major role in the relationship between pathogenic microorganisms and their host. Protein–carbohydrate interactions occur during the first steps of infection, for specific recognition between host and bacteria, but also at different stages of the immune response. Imberty and co-workers (DOI: 10.1039/C2CS35408J) demonstrate how high affinity multivalent glycoconjugates can serve as an alternative to antibiotic treatments by interfering with pathogen adhesion or by stimulating the innate and adaptive immune systems. This review also provides an outlook on the exploitation and targeting of bacterial lipopolysaccharides and S-layers in anti-infectious strategies.

Branson and Turnbull (DOI: 10.1039/C2CS35430F) focus on protein toxins released by intestinal bacteria that cause diarrhoeal diseases such as cholera and present solutions to prevent them from reaching their site of action. Multivalent inhibitors based on glycopolymers, glycodendrimers, tailored glycoclusters and inhibitors exploiting templated assembly are described. It is concluded that if spacers connecting the sugar to the scaffold are important to achieve optimal binding, better inhibition is not necessarily achieved by maximizing the number of ligand groups.

Peri (DOI: 10.1039/C2CS35422E) reviews the most recent results in the field of semi and fully synthetic carbohydrate vaccines against viruses, bacteria and cancers. In particular the author explains how the understanding of the immunological processes allows the rational design of potent carbohydrate vaccines.

Galan, Dumy and Renaudet (DOI: 10.1039/C2CS35413F) highlight the most recent advances in the preparation and the biological applications of glycopeptides and glycocyclopeptides. While linear glycopeptides are flexible and mimic native glycoprotein fragments, glycocyclopeptides are conformationally stable and non-immunogenic carriers with improved resistance against proteolytic degradation, and allow the carbohydrate presentation in a well-defined orientation. Both glycopeptides and glycocyclopeptides are currently used as antitumoral vaccines, inhibitors against pathogens and ligands for carbohydrate-binding proteins.

In order to mimic more accurately the inherent heterogeneity of biological systems, novel molecular and supramolecular scaffolds displaying different saccharide motifs have been designed recently. Jiménez Blanco, Ortiz Mellet and García Fernández (DOI: 10.1039/C2CS35219B) review for the first time the synthesis of such hetero-glycoclusters, -glycopolymers and -supramolecular glycoassemblies and discuss the influence of glycoheterogeneity on carbohydrate–protein and carbohydrate–antibody recognition events. In particular, this review highlights the existence of new binding mechanisms, also referred to as the 'heterocluster effect' or 'carbohydrate module effect', that are dramatically depending on the total and relative densities of the exposed glycotopes.

Hatano, Matsuoka and Terunuma (DOI: 10.1039/C2CS35421G) present methodologies for synthesizing carbosilane glycodendrimers. Their structure–activity relationships toward diverse pathogens such as Shiga toxins, dengue and influenza viruses and their utilization as new lectin sensors and drug delivery systems are also addressed.

Conjugation of oligonucleotides (ONs) is of great interest to improve the poor cellular uptake or tissue specific delivery of ONs, as well as to prepare carbohydrate biochips using the DNA-directed immobilization strategy. In their review Spinelli, Defrancq and Morvan (DOI: 10.1039/C2CS35406C) give an overview of the recent advances in this field. The synthetic approaches available to conjugate oligonucleotides and peptide nucleic acids to carbohydrates or glycosylated scaffolds, and their recognition properties are presented.

Nano-sized metallic nanoparticles such as gold, iron oxide or semiconductor are currently used as scaffolds to attach carbohydrates (glycoclusters) in a controlled manner, thus providing multivalent glyconanoparticles (GNPs) with special geometry and chemico-physical properties. Marradi, Chiodo, García and Penadés (DOI: 10.1039/C2CS35420A) review the current state of this research field. They first focus on multifunctional GNPs that contain different types of carbohydrates and luminescent probes, peptides, and magnetic chelates on the same gold nanoparticles. The second part of the review concerns the modification of the metallic core to provide multimodal GNPs with magnetic or fluorescence properties for studying protein–carbohydrate interactions and for applications in molecular imaging.

The exhaustive review by Chabre and Roy (DOI: 10.1039/C3CS35483K) on the use of aromatic scaffolds contains an impressive list of reactions leading to the covalent attachment of varied sugar derivatives onto aromatic functionalities. The scaffolds are presented in increasing order of complexity ending with nanotubes and fullerenes, thus preparing the field for other reviews in this themed issue. A particular emphasis was given to organometallic chemistry.

The unique physicochemical properties of carbon nanotubes and graphene have stimulated the utilization of these scaffolds in many fields of biomedical research. Chen, Star and Vidal (DOI: 10.1039/C2CS35396B) highlight the synthetic strategies for their covalent and noncovalent functionalization with carbohydrates, which both improve their water solubility and provide selective binding properties to biological systems for applications in biosensing and biomedicine.

The glycoconjugation to cyclodextrin scaffolds has been the topic of several

applications toward site-directed glycan binding. This field has matured to the point where in the biophysical properties of the resulting neoglycoconjugates could be controlled to a high degree. In their review, Martínez, Ortiz Mellet and García Fernández (DOI: 10.1039/C2CS35424a) convincingly described several original architectures based on supramolecular assembly of dendronized CDs using versatile inclusion strategies. The syntheses of multivalent "heterotopic" glycotopes have been compiled for the first time.

Similarly, Bojarová, Rosencrantz, Elling and Křen (DOI: 10.1039/C2CS35395D) elegantly presented the notion that, irrespective of the multivalent scaffolds utilized, complex multiantennary *N*- and *O*-linked glycans could be assembled using a wide arsenal of glycosyltransferases. By using glycoengineering, they illustrated a few examples toward the efficient expression of eukaryotic *N*-glycation patterns in bacterial hosts.

In a second review by Imberty and co-workers, Arnaud, Audfray, and Imberty (DOI: 10.1039/C2CS35435G) discussed the possibility of engineering neolectins to be used as improved and more specific sensors in glycosensor microarrays. Given the ubiquitous presence of a large diversity and complexity of glycan structures and paradoxically, the limited number of different mammalian glycosides, the search for more specific glycotope binders represents a formidable challenge. By using synthetic organic chemistry, aptamers, and peptides together with site directed mutagenesis, it is feasible to achieve greatly improved binding systems.

In their review, Reymond, Bergmann and Darbre (DOI: 10.1039/C3CS35504G) further developed the notion that combinatorially designed glycopeptide dendrimers can be effective biofilm inhibitors against bacterial infection. A particular emphasis was placed on *Pseudomonas aeruginosa*, a Gram-negative bacterium often leading to the death of cystic fibrosis patients.

In an excellent tutorial review on calixarenes, Sansone and Casnati (DOI: 10.1039/C2CS35437C) carefully revisited the biophysical parameters endowed in multivalent binding interactions. A useful discussion on the various conformers of calixarenes was also included. This aspect represents a net advantage over cyclodextrins as the carbohydrate ligands can be exposed on two different faces of these aromatic scaffolds, a property inherently critical for supramolecular assembly with lectins.

Supramolecular self-assemblies through liposomes and micelles represent another active area in the field of multivalent carbohydrate–protein interactions. The review by Jayaraman, Maiti and Naresh (DOI: 10.1039/C3CS00001J) also discussed the roles played by carbohydrate–carbohydrate interactions. They included a section on glycopolymersomes, a more recent active area of activity. They illustrated several examples and stressed the fact that, as opposed to other more complex structures, the building blocks leading to liposomes and micelles are simpler.

Gingras and co-workers (DOI: 10.1039/C3CS60090D) nicely compiled the chemical structures and linking methodologies leading to multivalent carbohydrate scaffolds that incorporate sulfur atoms. The goals of this section were to review the basic principles through which the sulfur atom can provide advantageous electrochemical and photophysical properties. The discussion on the relative positioning of the sulfur atom into the architectures is useful in offering clear opportunities for well-designed target molecules while the chemistry involved behind its introduction widens the scope of future chemical design.