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Multivalent glycocyclopeptides: toward nano-sized glycostructures

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ABSTRACT

Cyclopeptides have recently emerged as attractive molecular scaffolds for the multivalent presentation of carbohydrates in a well-defined constrained spatial orientation. This *mini-review* describes the last advances on the synthesis and the biological applications of these particular structures, going from low molecular weight glycoclusters to fully synthetic nano-sized glycodendrimers.

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1. Introduction

Synthetic multivalent glycoconjugates that mimic the cell surface glycocalyx are being the object of intense investigations due to their fascinating biological properties.[1] In contrast to weak and poorly specific interactions that occur between individual carbohydrates and proteins, the multivalent presentation of carbohydrates at the surface of a molecular scaffold is indeed currently used to enhance binding avidity and selectivity toward a target protein.[2] This phenomenon known as the *cluster-glycoside effect*[3] is at the heart of the design of bioactive glycostructures. However, if the nature, the size, the valency and the geometry of scaffolds are important parameters, no valuable rule has emerged so far to rationalize the design of high affinity ligands.[4] For this reason a large variety of structures have been explored to inhibit and detect infectious agents or to stimulate immunity against cancers or pathogens.[5]

Among linear (e.g., peptides,[6] oligonucleotides,[7] polymers,[8] nanotubes,[9] etc.), dendritic (e.g., peptide,[10] polyamidoamine,[11] carbohydrates,[12] carbosilane,[13] etc.), cyclic (e.g., cyclodextrins,[14] calixarenes,[15] glycophanes,[16] aromatics,[17] etc.) or spheric (e.g., fullerenes,[18] quantum dots,[19] metal nanoparticles,[20] etc.) scaffolds, Regioselectively Addressable Functionalized Templates[21] (commonly known by its acronym 'RAFT') and analog cyclopeptide[22,6] have shown interesting structural properties to construct multivalent glycostructures. Besides their straightforward access and their resistance against proteolysis, the presence of either Gly-Pro β-turns or alternate D- and L-amino acid is one of their most interesting features. It indeed allows high conformational stability in solution, thus providing two independent addressable domains to display clusters of carbohydrates for recognition and other functional units in well-defined spatial orientation with minimum risk of steric clashes (Fig. 1).

This mini-review gives an overview of the last advances on the synthesis of these particular structures by starting from the first generation of low molecular weight glycoclusters until the third generation of nano-sized glycodendrimers. Their recognition properties toward diverse carbohydrates-binding proteins, namely lectins, are also discussed through competitive enzyme-linked lectin assays (ELLA), surface plasmon resonance (SPR), and isothermal calorimetric titration (ITC) experiments. Scaffolds decorated with other functional units at the second addressable domain have already been reviewed recently[6] and are therefore not covered in this manuscript.

2. First generation

The utilization of cyclopeptide scaffolds was pioneered by the group of Kunz in 1996 who has attached three copies of sialyl Lewis^X, a well-known ligand of E-selectin involved in cell-adhesion processes, to aspartic acid units of topologically oriented cyclic

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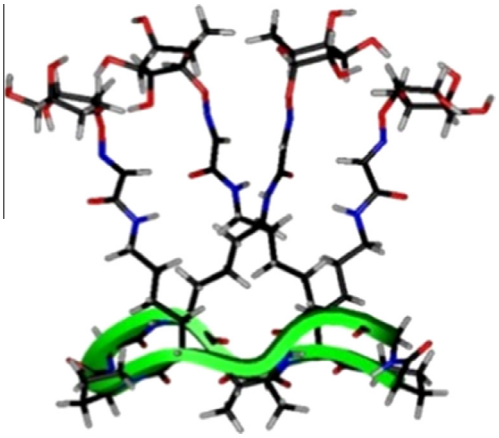

Figure 1. Molecular model of a tetravalent glycocluster showing the two separated addressable domains with glycans pointing at the upper face. The cycle size is approximately 10 Å length and 5 Å width.

heptapeptides using the amide coupling strategy.[23] Cell adhesion assay against recombinant human E-selectin and immunoglobulin fusion proteins revealed that glycocluster **1** (Fig. 2) exhibited highest inhibition (IC_{50} of 0.35–0.6 mM) than the monovalent control. The authors hypothesized that such ligands are promising anti-inflammatory candidates against selectin promoted leukocyte adhesion.

In 2000, Bundle and co-workers have made the impressive demonstration that nanomolar affinity for Shiga-like toxins can be achieved with multivalent ligands with appropriate size and well-defined geometry.[24] Studying a similar family of bacterial toxins namely, the cholera toxin which comprised five galactoside-recognition subunits, Fan and co-workers have designed cyclodecapeptides alternating flexible amino acids (e.g., glycine, γ-aminobutyric acid, ε-aminohexanoic acid) and L-lysine residues and displaying variable ring size and linkers[25] to explore the geometric requirement of galactose units for binding improvement (Fig. 3). Interestingly, inhibitory experiments with cholera toxin B pentamer and ganglioside have revealed that derivative **2** containing shorter flexible linkers with $n = 2$ exhibited a 100,000-fold increase in inhibitory potency (IC_{50} below 1 μM) than the corresponding monovalent control (IC_{50} of 100 mM). From this observation, it could be concluded that both the size and geometry of the glycocluster need to be considered for achieving optimal binding efficiency.

Synthetic multivalent ligands analogous to naturally occurring sialylated conjugates such as GM3 sialotrisaccharide are promising candidates to inhibit influenza virus infection by interacting with the trimeric viral receptor hemagglutinin (HA). Based on X-ray crystallography, Nishimura and co-workers have synthesized a series of 'glycotentacles' as ligands for HA using chemoenzymatic attachment of GM3 onto cyclopeptides displaying neutral or positive and negatively charged amino acids and mono- to trivalent anchoring sites (Fig. 4).[26] Hemagglutination and SPR assays against the influenza virus H1N1 and chicken erythrocytes have shown that di- and trivalent presentation of GM3 is required to ensure a potent inhibitory effect. In particular derivative **3** is the strongest inhibitor (K_d of 0.63 mM) compared to the other ligands including ligands comprising neutral amino acids. Moreover, it was demonstrated by NMR and molecular modeling that the nature of amino acid into the peptide scaffold influences the spatial orientation of GM3, thereby modulating its biological activity.

Over the last two decades, several reports highlighted that a broad range of HIV strains could be efficiently neutralized by the human 2G12 antibody via multivalent interactions with the high-mannose glycan epitope $Man_9GlcNAc_2$ expressed in the silent region of the gp120 glycoprotein. In this context, Danishefsky and co-workers have synthesized several macrocyclopeptide-based glycoclusters (e.g., **4**, Fig. 5) displaying two and three copies of $Man_9GlcNAc_2$ by using the Lansbury aspartylation strategy.[27] They designed a cyclopeptide scaffold having 14-amino acid residues including aspartic acid residues for anchoring glycan functionalities and stabilized by two D-Pro-L-Pro as β-turns. SPR measurement of binding affinity with 2G12 has confirmed significant binding enhancement for **4** than the monovalent control thereby suggesting requirement of multivalent ligands architecture for optimal design of carbohydrate vaccine candidates against HIV.

In 2003, Renaudet and Dumy reported an efficient chemoselective strategy based on oxime ligation to construct tetravalent glycoclusters (Fig. 6A).[28] The interest of this strategy is that it requires neither protection–deprotection nor activation steps, moreover the coupling reaction occurs in aqueous medium with excellent yields. The synthetic process consists in the condensation of aminooxy carbohydrates (**6**) that are prepared from *N*-hydroxyphthalimido-glycosides having pre-defined anomeric configuration[29] and a cyclopeptide (**5**) displaying four copies of glyoxo-aldehydes generated from oxidative cleavage of serines linked to the lysine side chain. Both compounds are mixed in mild acidic conditions such as sodium acetate buffer or water containing 0.1% of trifluoroacetic acid (TFA) to provide tetravalent glycoclusters **7** with similar efficiency. Fluorescence anisotropy competition experiments with mannosylated clusters and the lectin from *Canavalia ensiformis* (ConA) specific for α-D-mannose have indicated a 20-fold binding improvement (IC_{50} 62 μM) compared to methyl-α-D-mannopyranoside used as reference.

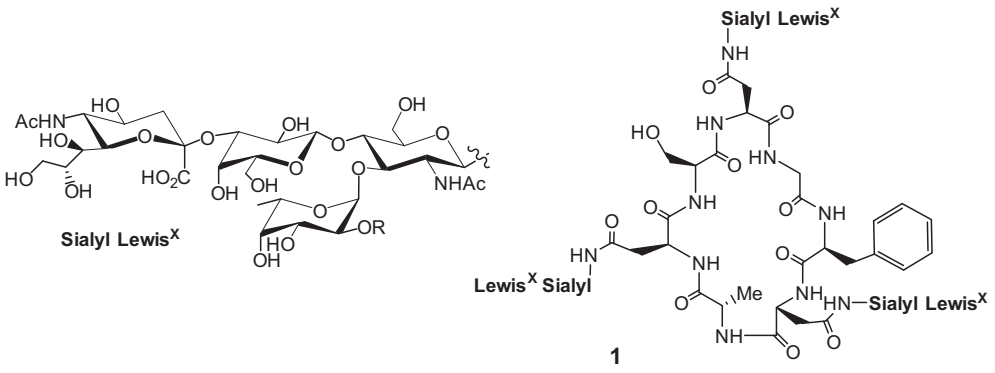

Figure 2. Structure of the first glycosylated cyclopeptide designed by Kunz and co-workers.

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