GLYCOMIMETICS: TOOLS FOR INVESTIGATION OF FUNCTIONAL DIVERSITY IN THE CARBOHYDRATE REGIME

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Received: 2nd May 2012/Published: 11th July 2012

This account is dedicated to the memory of Willi von der Lieth

ABSTRACT

Glycomimetics are valuable tools in glycobiology, suited to address the queries of glycomics. Since in glycomimetics the natural structural features of oligosaccharides have been altered in various ways, the nomenclature that is used to systematically describe structures and properties of naturally occurring sugar structures cannot be applied. An appropriate nomenclature is desirable. Moreover, it is necessary to understand the conformational properties that are displayed by – especially – multivalent glycomimetics. Molecular dynamics simulations using explicit solvent molecules are suited to obtain an impression of the conformational space occupied by various multivalent glycomimetics such as the glycodendrimers and so-called octopus glycosides. Unexpected similarities on one hand and discrepancies on the other hand have been shown by extensive modelling and can be correlated with the results of biological testing.

INTRODUCTION

There are three basic classes of biopolymers, the oligonucleotides, the proteins, and the carbohydrates. Among these three, the carbohydrates hold the greatest potential for structural diversity. The number of possible oligosaccharide structures exceeds that of possible peptides and oligonucleotides, respectively, by a nameless order of magnitude [1]. There is a

http://www.beilstein-institut.de/glycobioinf2011/Proceedings/Lindhorst/Lindhorst.pdf
number of principle differences between oligonucleotide, oligopeptide, and oligosaccharide structures. Most importantly, oligosaccharides occur in branched forms, whereas oligonucleotides and oligopeptides can only form linear chains (cf. Figure 1). Moreover, configurational alterations are found frequently in the carbohydrate regime for all stereocenters of the carbohydrate ring including the anomeric linkage. Strikingly, that in case of the sugars, nature alters biochemical function by small configurational changes, whereas the configuration of the stereocentres in oligonucleotides as well as oligopeptides remains untouched in mammalian organisms.

Most of the complexity of the oligosaccharides is found as part of a thick layer of glycoconjugates that covers every eukaryotic cell, called the glyocalyx. The glyocalyx comprises a multitude of glycoproteins, glycolipids, GPI anchors, and proteoglycans, i.a. [2, 3]. The glyocalyx must be considered as a cell organelle that has an essential function in cellular communication. To unravel the secrets of glyocalyx function is the major task of the “glycomics”. As the “omic naming” suggests, the field of the glycosciences deals with large numbers, reminding us of the genomics and the human genome project, as well as the proteomics. While the proteome of an animal is much more difficult to define than its genome, it is even more demanding to handle the glycome of a living organism. Understanding the glycome means considering unknown functional principles and this is supported by a combination of imagination and know-how; and, additionally, it requires clear standards of nomenclature and data processing.

Figure 1. Comparison of homotrimer structures, a trinucleotide (1, comprising three 2’-deoxythymidine monomers), a tripeptide (2, comprising three L-alanine monomers), and a trisaccharide (3, comprising three D-mannose monomers). The red asterisks highlight the potential for configurational variation as it is typical for the oligosaccharides, light red asterisks are highlighting different anomeric configurations, namely α or β, respectively.
CARBOHYDRATES AND COMMUNICATION

A modern statement about the carbohydrates is that they have a key function in cellular communication. Reams of experimental data have given us certainty that the molecular recognition processes happening at the sweet cell surface interface are essential in all cell-cell interactions. A plethora of complex glycoconjugates is participating in this sophisticated control of biological response. There is a large number of parameters that are modified to create structural diversity within this carbohydrate regime. Interestingly, tiny structural variations can make a big difference within this nano-dimensioned network of molecules, such as in the case of blood group differentiation.

Variation of configuration, anomeric linkage, ring modification, hydroxyl group masking, charge, hydrophilicity, branching, and conformational properties are the instrumentation for a fine-tuning of carbohydrate-mediated biological response. How would we ever be able to handle such a complicated matrix of function parameters? How can we deal with the size of the numbers of functional states? How can we communicate about the questions addressed in our experiments and about their results? And how would we, at all, define experiments that allow us to retrieve causalities from specific alterations?

It is essential for the advancement in the difficult field of the glycomics, to be able to learn from one another; to interconnect experimental data; to conclude from related findings. An essential prerequisite for this all is a complete as possible survey of data and a precise nomenclature to pave the ground for unequivocal communication.

GLYCOCONJUGATES AND GLYCOMIMETICS

To cope with the structure-function relationships of carbohydrates, a number of different approaches can be chosen. From a synthetic point of view, carbohydrate and glycoconjugate structures can be assembled according to the natural example molecules and interrogated with a library of lectins in solution as well as on surfaces, for example [4, 5]. In another approach, however, only some specific parts of a complex natural molecule are selected and conjugated such that particular functional questions can be addressed. The resulting artificial glycoconjugates have been named “glycomimetics”, regardless of how much they resemble the nature of the original molecule. Thus, a complex glycoconjugate can experience a structural abbreviation until a structure is obtained in which only some essential aspects of the natural prototype are conserved. Such an approach allows the investigation of isolated structure-function relationships with the expectation to receive experimental data which are easy to interpret. In addition, glycomimetics are often much more facile to make than the natural examples [6 – 9]. Thus, it turns out that the glycomimetics offer a variety of advantages for glycomics studies (Figure 2).
Resemblance of natural structure
Ease of synthesis
Stability and biodegradability
Easy functionalization and labelling
Easy and systematic variation of multivalency
Focused study of structure-function relationships

Figure 2. Selected advantages of glycomimetics.

MULTIVALENT GLYCOMIMETICS

A central characteristic of carbohydrate-protein interactions is their multivalency. Multivalency of molecular interactions is an important principle in biochemistry that typically takes place in a supramolecular environment of interaction partners. The biophysical details of multivalent molecular interactions can be very different as well as their structural basis [10, 11]. Multivalency effects can lead to stronger binding as well as more specific binding, and to fine-tuning of biological response such as in the case of receptor signalling [12]. To investigate the details of multivalency effects as well as to find means to utilize multivalency in a medicinal context, for example, multivalent glycomimetics are valuable tools [6 – 9, 13, 14].

Typical multivalent glycomimetics are the glycodendrimers, in which a non-carbohydrate hyperbranched dendrimer core is decorated in its periphery with essential carbohydrate moieties [6]. In addition, also other multivalent molecules have been utilised as scaffolds for the preparation of multivalent glycomimetics, for example carbohydrates themselves. The latter approach has led us to the introduction of various carbohydrate-centred cluster glycosides [15 – 18], which have been named “octopus glycosides” as they resemble the multi-armed look of an octopus (Figure 3) [19].

Figure 3. Structural formula of a trehalose-centered cluster mannose of the octopus type (left, 13 in Figure 5), resembling the look of an octopus as sketched on the right.
There is a favourable potential in designing multivalent glycomimetics. Firstly, their valency can be nicely modified and modulated, and in addition, they can be designed as homo-multivalent glycomimetics, bearing only one type of carbohydrate, and – more difficult to realize – multivalent glycomimetics of a mixed type can be synthesised [20]. Moreover, multivalent glycomimetics, such as the glycodendrons can include a focal point in their structures, which is suited for an orthogonal modification of the multivalent molecule (Figure 4).

**Figure 4.** Structures and architectural potential of multivalent glycomimetics. Glycodendrimers (left) can be constructed as homo-glycodendrimers exposing only one type of carbohydrate, whereas glycodendrimers of a mixed type carry different carbohydrates. In contrary to glycodendrimers, glycodendron molecules (right) include a functional group at the focal point (FP) of the molecule which can be utilised for immobilisation or further functionalisation, for instance. X: Oxygen in case of glycosidic linkages, or another heteroatom or ligating moiety such as a peptide or a thiourea linkage, respectively.

**Molecular Dynamics of Multivalent Glycomimetics**

Multivalent glycomimetics often show pronounced multivalency effects in interaction with lectins [10, 14]. We have a long-standing experience in testing multivalent glycomimetics used as inhibitors of bacterial adhesion [21, 22]. Bacterial adhesion to the glycosylated surface of their eukaryotic target cells is mediated by long adhesive organelles called fimbriae. Important virulence factors among the enterobacteriaceae are the type 1 fimbriae, which display the lectin FimH at their tips with specificity for α-d-mannosides. Thus, we have dedicated much of our research to the design and synthesis of multivalent cluster mannosides and other mimetics of high-mannose type oligosaccharides [7, 23–27]. A key criterion for the biological function of all mannose clusters is the conformational availability of the exposed mannose residues for binding to the respective lectin carbohydrate binding sites. Thus, we have performed molecular dynamics (MD) simulations of glycoclusters and glycodendrimers to obtain an impression of their conformational features [28].
A number of 14 synthetic multivalent glycomimetics were investigated in MD simulation studies including explicit water molecules. The studied molecules fall into two groups. In one case, small, basically PAMAM (polyamidoamine)-based glycodendrimers with carbohydrate valencies between 3 and 8 have been selected (compounds 1–9, Figure 5) [29]. These expose either α-β-mannosyl or β-GlcNAc residues [30–33] which are attached to the dendritic core by thiourea-bridging. The second group comprises cluster mannosides, in which α-β-mannosyl residues were O-glycosidically linked to a pentaerythritol scaffold (compound 10, Figure 5) [34] and various carbohydrate scaffolds (octopus glycosides, compounds 11-14, Figure 5) [27], respectively.

Figure 5. Structures of the investigated glycoclusters and glycodendrimers, 1 to 9.
Table 1 provides an overview about the key structural features and differences, respectively, of the multivalent glycomimetics 1–14 (Figure 5), which were computed in MD simulations.

<table>
<thead>
<tr>
<th>Scaffolded carbohydrate unit</th>
<th>Linkage type</th>
<th>Scaffold (core molecule)</th>
<th>Valency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 α-d-mannosyl</td>
<td>thiourea</td>
<td>TRIS*</td>
<td>3</td>
</tr>
<tr>
<td>2 β-d-GlcNAc</td>
<td>thiourea</td>
<td>TRIS*</td>
<td>3</td>
</tr>
<tr>
<td>3 α-d-mannosyl</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>4</td>
</tr>
<tr>
<td>4 β-d-GlcNAc</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>4</td>
</tr>
<tr>
<td>5 α-d-mannosyl</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>6</td>
</tr>
<tr>
<td>6 β-d-GlcNAc</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>6</td>
</tr>
<tr>
<td>7 α-d-mannosyloxyphenyl</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>6</td>
</tr>
<tr>
<td>8 α-d-mannosyl</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>8</td>
</tr>
<tr>
<td>9 β-d-GlcNAc</td>
<td>thiourea</td>
<td>PAMAM#</td>
<td>8</td>
</tr>
<tr>
<td>10 α-d-mannosyl</td>
<td>O-glycosidic</td>
<td>PE+</td>
<td>4</td>
</tr>
<tr>
<td>11 α-d-mannosyl</td>
<td>O-glycosidic</td>
<td>glucose</td>
<td>5</td>
</tr>
<tr>
<td>12 α-d-mannosyl</td>
<td>O-glycosidic</td>
<td>melibiose</td>
<td>8</td>
</tr>
<tr>
<td>13 α-d-mannosyl</td>
<td>O-glycosidic</td>
<td>trehalose</td>
<td>8</td>
</tr>
<tr>
<td>14 α-d-mannosyl</td>
<td>O-glycosidic</td>
<td>raffinose</td>
<td>11</td>
</tr>
</tbody>
</table>

*TRIS: tris(aminomethyl)amine; #PAMAM: different scaffold molecules of the polyamidoamine dendrimer type; +PE: pentareythritol derivative.
For each glyocluster extreme, rather “artificial” structures and typical average conformations were determined (cf. Figure 6). Firstly, maximal elongated structures of the PAMAM-based glycodendrimers were obtained applying additional forces in the simulation. This is of interest in order to estimate the maximal possible distances between carbohydrate moieties as an extreme fit for a multivalent interaction with multiple lectin carbohydrate binding sites. Also the optimally stretched structures with the maximal possible extension of sugar residues was used to define the size of the water box required for the MD simulations. Secondly, closest packing conformations were formed during MD simulations when they were calculated in vacuo (without including explicit solvent molecules). Strikingly, the glycodendrimers adopt a completely different structure in vacuo than in water. In vacuo the structure is dominated by intramolecular interactions, leading to densely packed structures. Finally, conformations were deduced from MD simulations with explicit water molecules and only these can be regarded as realistic structures as present in water.

Figure 6. Three extreme conformations of the tetravalent PAMAM-based GlcNAc glycodendrimer 4. Top left: closest packing; bottom left: maximal elongated structure; bottom right: realistic conformation in water. Green: carbon; red: oxygen; blue: nitrogen; yellow: sulfur; (hydrogen atoms not shown). Copyright (2002), with permission from Elsevier.

The investigated multivalent glycomimetics are highly flexible molecules mainly due to their spacer moieties. The rotational barriers of the spacer bonds are sufficiently low so that many different conformations can be adopted. A number of structural features were deduced based on statistics (cf. Table 2), and evaluation of the statistics of the defined descriptors was accomplished with the conformational analysis tool (CAT) program developed by Martin Frank [35]. For example, in order to get an estimate about the size of the computed molecules, the radius of gyration was determined in each case. The $R_g$ values of all 14 investigated glyoclusters range between 6.9 and 13.5 Å. The comparison of the two
different classes of investigated glycoclusters reveals interesting differences. The $R_g$ values of the carbohydrate-centred clusters 11-14 range from 7.1 to 9.4 indicating rather compact structures in comparison to the PAMAM-based glycodendrimers, which have a considerably larger radius of gyration (Table 2). Length of carbohydrate-equipped spacers can be estimated in each case by the mean distances between the centre of the cluster and the centre of the respective pyranose ring (Table 2). These values range from 7.5 to 19.1 Å and largely depend on the chemical nature of the spacer moieties.

Table 2. Structural properties of the investigated multivalent glycomimetics based on statistics.

<table>
<thead>
<tr>
<th>Scaffolded carbohydrate unit (number of branches)</th>
<th>Number of bonds per branch</th>
<th>$R_g$* [Å]</th>
<th>Mean value center-sugar distance [Å]+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 α-ᴅ-mannosyl (3)</td>
<td>6</td>
<td>7.4</td>
<td>8.5</td>
</tr>
<tr>
<td>2 β-ᴅ-GlcNAc (3)</td>
<td>6</td>
<td>6.9</td>
<td>7.6</td>
</tr>
<tr>
<td>3 α-ᴅ-mannosyl (4)</td>
<td>10</td>
<td>10.6</td>
<td>13.1</td>
</tr>
<tr>
<td>4 β-ᴅ-GlcNAc (4)</td>
<td>10</td>
<td>11.0</td>
<td>12.9</td>
</tr>
<tr>
<td>5 α-ᴅ-mannosyl (6)</td>
<td>13</td>
<td>11.4</td>
<td>13.8</td>
</tr>
<tr>
<td>6 β-ᴅ-GlcNAc (6)</td>
<td>13</td>
<td>11.7</td>
<td>13.5</td>
</tr>
<tr>
<td>7 α-ᴅ-mannosylxylophenyl (6)</td>
<td>18</td>
<td>13.5</td>
<td>19.1</td>
</tr>
<tr>
<td>8 α-ᴅ-mannosyl (8)</td>
<td>17</td>
<td>12.0</td>
<td>17.2</td>
</tr>
<tr>
<td>9 β-ᴅ-GlcNAc (8)</td>
<td>17</td>
<td>10.7</td>
<td>13.6</td>
</tr>
<tr>
<td>10 α-ᴅ-mannosyl (4)</td>
<td>6</td>
<td>7.1</td>
<td>7.5</td>
</tr>
<tr>
<td>11 α-ᴅ-mannosyl (5)</td>
<td>6 (7)#</td>
<td>7.1</td>
<td>7.8</td>
</tr>
<tr>
<td>12 α-ᴅ-mannosyl (8)</td>
<td>6 (7)#</td>
<td>8.7</td>
<td>9.4</td>
</tr>
<tr>
<td>13 α-ᴅ-mannosyl (8)</td>
<td>6 (7)#</td>
<td>8.7</td>
<td>9.2</td>
</tr>
<tr>
<td>14 α-ᴅ-mannosyl (11)</td>
<td>6 (7)#</td>
<td>9.4</td>
<td>9.7</td>
</tr>
</tbody>
</table>

* For the spacers branching out from C5 of the core sugar ring, the C5-C6 bond is counted in and this number is given in brackets.
* Radius of gyration.
+ Mean distances of n branches of the respective multivalent glycomimetic between the center of the cluster and the center of the respective pyranose ring (Man or GlcNAc, respectively).

To obtain an impression of the globular shape and dynamic properties of the investigated multivalent glycomimetics, 1000 snapshots of 1 ns long MD simulations including explicit water molecules were overlaid. Three atoms in the core region of each molecule were used to orient all archived conformations in space in the same way. The centres of the pyranose rings were defined as “pseudo atoms” and a distinct colour was assigned for each pyranose moiety of the respective cluster. The calculated positions of the pseudo atoms were converted into a PDB format which can be visualised using RASMOL [36], for example. The core of each computed molecule was positioned in the middle of a cube with an edge length
of 40 Å and thus, size, orientation and conformational flexibility of the investigated glycodendrimers and glycoclusters can be compared (cf. Figures 7, 8, and 9). MD simulations of the PAMAM-based glycodendrimers 1–9 led to unexpected results. It turned out that glycoclusters with higher valency do not necessarily occupy much more conformational space than smaller glycoclusters. In particular, tetravalent, hexa-, and octavalent analogues appear not to be too different from each other (Figure 7). The octavalent GlcNAc glycocluster 9 occupies even less conformational space than its hexavalent analogue 6 (cf. Table 2). This situation is, again unexpectedly, different in case of the hexa- and octavalent mannose glycoclusters 5 and 8. Cluster 8 expands further in space than 5, however, interestingly, separates one mannose residues, that is split from the core conformational space and does not interact with the rest of the molecule.

The difference between mannose and GlcNAc clusters can be explained by comparison of the exposed sugar residues. GlcNAc has six atoms more than mannose, namely an additional N-acetyl group. The water accessible surface increases from 162 Å² for α-mannose to 217 Å² for β-GlcNAc. This leads to considerable differences in the conformational behaviour of the respective glycoclusters, which can best be demonstrated by the trivalent clusters 1 and 2. Whereas the α-mannosyl-terminated compound exhibits a rather torus-like distribution of conformations, the β-GlcNAc cluster populates an almost perfect spherical distribution.

Figure 7. Accessible conformational space of PAMAM-based glycodendrimers decorated with α-β-mannosyl residues (1, 3, 5, and 8) or β-β-GlcNAc residues (2, 4, 6, and 9), respectively. 1000 snapshots from 1 ns long MD simulations including explicit water molecules are overlayed in each case. The core region of each conformation is consistently fixed in space and the centers of the carbohydrate residues are displayed as differently coloured spheres. Results are displayed in 40 × 40 Å squares and thus the occupied conformational space can be visualized and compared. Copyright (2002), with permission from Elsevier.
Overall, it turned out that the three-dimensional shape of the investigated molecules is significantly influenced by inter- and intramolecular interactions. Often, two or more carbohydrate units may form short-lived clusters of two or more terminating sugar units. The tendency to form sugar clusters within one molecule is more pronounced in the higher branched glycodendrimers, mainly in the case of the octavalent glycodendrimers 8 and 9, as well as for the carbohydrate-centred glycoclusters 11–14 (cf. Figure 9). The possibility of establishing intramolecular interactions favours the occurrence of intramolecular sugar clusters and moreover, it generally supports the tendency to form more packed than elongated structures.

It was especially interesting to see the difference between the two hexavalent mannose clusters 5 and 7. While in case of 5 α-D-mannosyl residues are linked to the PAMAM core via thiourea bridging, in case of 7 p-(α-D-mannosyloxy)phenyl units are attached to exactly the same core via the same linkage type. In spite of this, the two clusters occupy very different conformational space (Figure 8). The conformational space that is occupied by 5 is rather globular, whereas 7 leaves out large areas in space. In the latter case, the conformational behaviour is apparently dominated by intramolecular interactions between branch pairs of the multivalent molecule, triggered by ππ interactions of the phenyl residues.

Figure 8. Accessible conformational space of PAMAM-based glycodendrimers 5 and 7 (displayed in 40×40 Å squares). The conformational availability of the p-(α-D-mannosyloxy)phenyl residues (PheMan) in the periphery of 7 is clearly restricted due to intramolecular ππ interactions. Copyright (2002), with permission from Elsevier.

The conformational features of mannose clusters 5 and 7 are reflected in their properties as inhibitors of mannose-specific bacterial adhesion. It is known that p-phenyl α-D-mannoside is a much more potent inhibitor of mannose-specific bacterial adhesion than methyl α-D-mannoside that is in the range of two orders of magnitude less potent [37]. Thus it was expected that clustering of p-(α-D-mannosyloxy)phenyl residues would lead to a very potent...
inhibitor of bacterial adhesion as this compound combines the favourable effects of multi-valency with the high affinity displayed by the \( p-(\alpha-D\text{-mannosyloxy})\text{phenyl unit. However, these expectations were never fulfilled [22] and this finding was only understood after the conformational properties of cluster 7 were elucidated. The MD simulations with this mannose cluster clearly demonstrated that due to the predominant intramolecular interactions ruling the conformational space of the molecule, the \( p-(\alpha-D\text{-mannosyloxy})\text{phenyl units are not well available for lectin binding.} \)

None of the molecules 1–14 forms an ideal sphere. The shape of the populated conformational space of the PAMAM-based glycodendrimers rather has significant aspects of an ellipsoid. However, in case of the carbohydrate-centred octopus-glycosides spherical distributions can be favoured over ellipsoidal ones (Figure 9).

![Figure 9](https://example.com/figure9.png)

**Figure 9.** Accessible conformational space of the PE-based cluster mannoside 10 and octopus mannosides 11–14 as displayed in 40 × 40 Å squares. Copyright (2002), with permission from Elsevier.

The comparison of the carbohydrate-based octopus mannose 11–14 shows that they occupy very similar conformational space and show quite similar sizes (cf. Table 2), which is rather unexpected. In addition, regardless of how many sugar residues are branching out from the glycodendrimers, MD simulations have shown that a closed outer shell of carbohydrate units does not exist. Structural similarities among the octopus glycosides are again reflected
in biological testing. When evaluated as inhibitors of type 1 fimbriae-mediated bacterial adhesion to a surface of immobilized polysaccharide mannan, their inhibitory potential proved very similar, but reflecting the different valency of the various cluster glycosides not at all (Figure 10) [27]. We had originally expected that the nature of the scaffolding carbohydrate would make a significant difference in the biological properties of these glyoclusters, which is not the case. MD simulations have shown that this can be understood based on the similarities of the occupied conformational space in all cases.

![Figure 10](image)

**Figure 10.** Relative inhibitory potencies (RIP) of octopus glycosides 11–14 when tested as inhibitors of type 1 fimbriae-mediated bacterial adhesion. Values are referenced to the inhibitory potency of the standard inhibitor methyl α-d-mannoside [27].

**Conclusions**

Multivalent glycomimetics such as glycodendrimers and octopus glycosides are valuable tools in glycobiology. They can be used to probe and manipulate multivalent interactions of carbohydrates with lectins, such as in inhibition of saccharide-specific bacterial adhesion. Typically, when the structures of multivalent glycomimetics are altered, biological consequences are expected. Often, quantitative structure-activity relationships can be deduced and understood conclusively; in other circumstances, however, this was not the case. In any case, it is essential to consider the conformational space that can be occupied by a particular multivalent glycomimetic in order to understand its interactions with multiple carbohydrate binding sites. For the highly symmetrical and flexible structures of typical hyperbranched glycomimetics, as discussed in this account, NMR analysis does not provide means for
conformational analysis. Also X-ray analysis would not reveal such information. Thus, MD simulations are extremely important and useful in this important area of glycobiological research. MD simulations have allowed understanding how scaffolding units as well as the nature of spacers influence the conformational features of a respective multivalent glycomimetic. This can assist our understanding of structure-activity relationships and can eventually lead us to a better target-oriented design of multivalent lectin ligands.

ACKNOWLEDGEMENT

I am grateful to my colleagues and co-workers for their continual contributions and support. Additionally, I acknowledge financial support by the DFG and the BMBF.

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