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Glycan arrays: biological and medical applications
Pi-Hui Liang1,2, Chung-Yi Wu2, William A Greenberg1 and Chi-Huey Wong1,2

Carbohydrates and their conjugates are involved in various biological events, including viral and bacterial infection, the immune response, differentiation and development, and the progression of tumor cell metastasis. Glycan arrays are a new technology that has enabled the high-sensitivity and rapid analysis carbohydrate–protein interaction and contribute to significant advances in glycomics. Glycan arrays use a minute amount of materials and can be used for high-throughput profiling and quantitative analysis and provide information for the development of carbohydrate-based vaccines and new drug discovery.

Addresses
1 Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
2 The Genomics Research Center, Academia Sinica, No. 128 Academia Road, Section 2, Nankang District, Taipei 11529, Taiwan

Corresponding author: Wong, Chi-Huey (wong@scripps.edu), (chwong@gate.sinica.edu.tw)

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Introduction
Recent advances in the study of functional glycomics in living organisms have received a great deal of attention [1**]. Carbohydrates, presented in the form of glycoproteins, glycolipids, glycosaminoglycans, or other glyc conjugates, have long been known to play important roles in a variety of biological processes. They participate in molecular recognition events such as cell adhesion, migration, and metastasis; host–pathogen interactions such as bacterial and viral infections; and initiation of the immune response [2]. Despite the increased awareness of the important function of carbohydrates, the study of carbohydrate–protein interactions is difficult. This is largely because of the structure complexity of carbohydrates, and the low affinity of their interactions with glycan-binding proteins (GBPs) — typically the monomeric \( K_D \) values are in the micromolar to millimolar range, thus biological responses are often because of multivalent display and interaction of these glycans [3].

Carbohydrates are generated cotranslationally/post-translationally through a nontemplated synthetic process, which involves over 200 glycosyltransferase genes, whose differential expression and combined specificities contribute to the complexity and diversity of carbohydrate structure.

Glycan arrays have become a powerful platform to map out interactions involving carbohydrates in a high-throughput manner because they were introduced in 2002 [4*,5*]. In general, the chip-based format unites a diverse set of novel technologies: generation of carbohydrate libraries (from natural sources or chemical and enzymatic synthesis); attachment of the saccharides to a surface (covalent or noncovalent bindings); high-throughput expression of carbohydrate-binding proteins; analysis of carbohydrate–protein binding by fluorescence measurements or mass spectrometry (Figure 1).

Till date, most published glycan array reviews have emphasized the methods of fabrication [1**,5*,6,7]. These reviews focus on new applications of glycan arrays in glycomics and drug discovery over the past few years.

Generation of a glycan library
Based on a limited pool of about nine monosaccharides found in mammalian glycans, it has been calculated that \( \sim 10^{12} \) different hexasaccharides are possible [8]. Not all of these possibilities exist in nature, but the current list of known N-linked and O-linked glycans found in proteins contains more than 2000 structures [9]. Therefore, the construction of the complete array of an entire glycome on a single chip is a major challenge. The recent development of new methods for chemical and enzymatic synthesis of oligosaccharides will increase the complexity and utility of carbohydrate arrays [1**,5*]. The discovery of uncharacterized natural glycans is another challenge, typically achieved by the extraction from natural sources of glycoproteins or glycolipids. A novel technology has recently been developed and used to modify sugar for detecting specifically glycosylated structures on cells. Alkynyl sugar analogs were attached to the cellular glycans through biosynthesis, and the modified glycans were detected by click chemistry with an azido fluorogenic probe or biotin handles [10]. Application of proteomic methods to the metabolically engineered cells has allowed for the identification of new glycoproteins and glycans (GIDmap) [11*]. This glycoproteomic method will allow for a complete analysis of a subset of the glycoproteome, and for the differential comparison between cancer and normal cells for differences in glycosylation pattern.
Profiling carbohydrate–lectin interactions

Lectins are carbohydrate-binding proteins, which are highly specific for their sugar ligands, and are the most common detection tool for the characterization of glycan arrays [12–14]. In the landmark studies by researchers at the Consortium for Functional Glycomics (www.functionalglycomics.org), a comprehensive array of more than 200 glycans on a glass slide was used to analyze the specific binding of mammalian, plant, viral, and bacterial lectins [15]. Recently, Gildersleeve and coworkers used a glycan array that contained 73 different glycans to do the high-throughput analysis of 24 lectins [16]. Carbohydrate specificity profiling of the C-type lectin macrophage galactose-type lectin (MGL) revealed that the lectin specifically recognized terminal α-linked and β-linked GalNAc moieties. This result led to the postulation that the expression of Tn antigen (GalNAc-α-Thr) by tumors might modulate the host immune response via the interaction of Tn with C-type lectins, such as MGL [17].

Glycosaminoglycans — growth factor and cytokine interactions

Glycosaminoglycans are complex carbohydrates known to play a key role in regulating growth factors, virus entry, and angiogenesis, but their structure–activity relationship is poorly understood. The first microarrays of heparin-like glycosaminoglycans have been constructed by Seeberger and coworkers to tackle this problem [18]. Heparin oligosaccharides on the arrays were incubated with the acidic and basic fibroblast growth factors (FGF-1 and FGF-2) and it was found that FGF-1 not only interacted with the hexamer and tetramer of heparin oligosaccharides but also with the unusual 2,4-O-sulfated monomer, which may become important for inhibitor design. The Hsieh-Wilson group reported the use of a chondroitin sulfate microarray to probe the specificity of TNF-α [19], as well as midkine-derived and brain-derived neurotrophic factor [20]. The tetrasulfated tetrasaccharide CS-E was found to react strongly with these growth factors within the physiological concentration range. A brain neuron growth experiment confirmed that the CS-E motif stimulated neurite outgrowth by about 50% [20]. It is anticipated that these microarrays will accelerate the understanding of glycosaminoglycan–protein interactions and pinpoint the sulfation patterns responsible for modulating physiological and disease states. These microarrays also provide valuable structure information for the design of inhibitors or antagonists of these therapeutically important cytokines and growth factors.

Carbohydrate–antibody interactions

Pathogen-induced antibody recognition

Most pathogens contain specific polysaccharides on their cell surfaces, which can elicit antibody responses in
infected humans. Microbial polysaccharide microarrays can be used for the diagnosis of pathogen infection by analyzing patient serum samples. Several examples of this application are described below (Figure 2). In an application with relevance to AIDS vaccine development, glycan arrays were used to dissect the glycan-binding specificity of the HIV-1 broadly neutralizing antibody 2G12 [21,22]. An array of oligomannose structures was analyzed against 2G12, and a minimal binding element was identified. Smaller oligomannose structures (Man₄) were found to be as effective as the Man₉-GlcNAc²-high mannose core at binding to 2G12 and inhibiting complexation with HIV gp120. These results may lead to the development of potential HIV vaccines by the synthesis of polyvalent derivatives of these oligomannose core structures. Wang et al. discovered that rabbit IgG antibodies elicited by Bacillus anthracis spores specifically recognize a rhamnose tetrasaccharide chain that decorates the outermost surface of the B. anthracis exosporium [23]. This tetrasaccharides appear to be a key biomarker for the detection of B. anthracis spores and may guide the development of novel anthrax vaccines. The same group used the glycan arrays to characterize the carbohydrate-binding activity of SARS-CoV neutralizing antibodies induced by an inactivated SARS-CoV vaccine and found potential crossreactivity between the immune response to an inactivated SARS-CoV vaccine and a host carbohydrate [24]. Blixt et al. reported an array containing oligosaccharide antigens specifically expressed by serogroups Salmonella enterica sv. Paratyphi, Typhimurium, and Enteritidis [25]. This microarray was used to detect the sera from patients with salmonellosis. Disaccharides (Tva₁-3Man, Abe₁-3Man) and trisaccharide (Manα₁-2Rhaα₁-2Gal) were found to have high-specificity serological recognition. By using the same strategy, a polysaccharide microarray was prepared by immobilizing bacterial polysaccharides to detect bacterial infection by using human or animal serum sample [26,27]. It is obvious that glycan array applications in this field may facilitate the identification of key immunogenic carbohydrates expressed by microbial pathogens.

**Cancer-induced antibody recognition**

Aberrant glycosylation is one of the hallmarks of cancer; tracking differences in cell surface glycan expression may therefore be useful for diagnosing cancer, and provide a solution for specifically targeting drugs to cancerous cells (Figure 2). The Globo H hexasaccharide cancer marker and nine structural analogs were arrayed and used to test monoclonal antibodies raised against Globo H (MBR-1 and VK-9), as well as patient sera [28]. A commercially available array of 37 different carbohydrates microarray was used to profiling of Hodgkin’s lymphoma sera and showed marked deviation in glycan-binding specificity compared to normal samples [29]. Another strategy that used lectin-affinity purification and natural glycoprotein microarrays to screen different glycosylation patterns between healthy and different disease stages of the pancreas was developed [30]. Glycan array profiling is expected to facilitate the identification of more specific
biomarkers, adding to currently used DNA and protein biomarker for improved cancer diagnosis and early detection.

**Carbohydrates for passive immunization**

The unique glycan structures from pathogens and aberrantly glycosylated antigens of cancer cells have guided the development of carbohydrate-based vaccines. Specific carbohydrates were conjugated to carrier proteins or virus particles for passive immunization in animals to induce antibodies against these carbohydrates. The glycan array serves as a rapid and convenient method to validate the specificity of antibodies generated by these potential vaccines. Anticarbohydrate antibodies elicited by the polyvalent display of glycans on a virus scaffold were detected by glycan array to validate the immunogenic scaffold design [31]. Using a glycoprotein array to assay the anti-Tn antibodies, Gildersleeve and coworkers evaluated the potential of Tn antigen as a cancer biomarker [32**].

**Carbohydrate–virus and carbohydrate–bacterial interactions**

Carbohydrates on the cell surface of human cells are used by viruses and bacteria as initial recognition and attachment sites [33]. The specificity of hemagglutinin (HA) from avian and human influenza sources, including those reconstructed from past pandemic strains, was examined [34**,35,36]. Virus entry into host cells is initiated by HA binding to cell surface sialic acid-containing glycans, which vary in structure based on the host species and anatomical location. Binding of HA variants recovered from pandemic and circulating strains on a 260-member glycan array demonstrated differences in the recognition of carbohydrate linkages (α2,3 or α2,6 sialic acid, characteristic of avian or human virus, respectively), sulfation and fucosylation. Remarkably, pandemic 1918 HA switched specificity to human epithelial cells, a change from α-2,3 to α-2,6 NeuAc-Gal-binding preference with only two amino acid substitutions. These findings provide information to assess the host–virus interactions associated with different influenza strains and to understand their evolution. Binding of intact influenza virus to a glycan array surface is also possible [15**].

A microarray displaying monosaccharides was also explored for binding to *Escherichia coli* ORN178. It was found that *E. coli* adhere specifically to mannose-containing slides [37]. By using glycoconjugate arrays, the Ruhl group has demonstrated for the characterization of unknown adhesion specificities of *Helicobacter pylori* and other bacteria [38]. These findings introduce the possibility of using carbohydrate microarrays as a detection system for pathogens.

**Glycan microarray in drug discovery**

High-throughput screening of new inhibitors of carbohydrate-processing enzymes has been performed with

![Figure 3](www.sciencedirect.com)

Quantitative analysis of protein–carbohydrate interactions to obtain surface and solution dissociation constants from glycan arrays.
glycan arrays. For example, α-(1,3)-fucosyltransferase (FucT) is an enzyme which mediates the final reaction in the biosynthesis of SLe\(^a\) by transferring the fucose from GDP-Fucose (GDP-Fuc) to sialyl lactosamine to form SLe\(^a\) and is therefore a target for the identification of inhibitors to block the inflammation cascade. Eighty-five synthetic compounds were incubated with FucT and GDP-Fuc on a LacNAc-coated microtiter-type microarray and then detected by peroxidase-coupled T. paraparus lectin. Four inhibitors with nanomolar \(K_i\) were discovered [39]. The technique was further improved by using a glass slide glycan array to test several monosaccharides to inhibit the binding of surface-coated mannose with Con A [40\textsuperscript{**}]. Recently, an aminoglycoside microarray platform has been developed for directly monitoring and studying antibiotic resistance [41,42]. This type of array will be a useful tool for the discovery of new antibiotics that evade resistance. Inhibition or disruption of the biosynthesis of disease-related glycans may be an effective approach for the treatment of various diseases.

**Quantitative carbohydrate–protein interaction using glycan array**

Most reported glycan arrays binding experiments have been performed at one or two concentrations of proteins to globally profile carbohydrate–protein interactions. Although qualitative assessment of binding by this method is useful, using fluorescence intensities to quantify binding affinities might be misleading. Values are highly variable from batch to batch because the spot intensities depend on immobilization efficiency. Recently, the Wong lab has developed a quantitative method to assess the binding affinities between carbohydrates and proteins (Figure 3) [40\textsuperscript{**}]. A series of protein concentrations were incubated with repeated subarrays which contained several monosaccharides to get surface dissociations (\(K_{D,surf}\)). A similar strategy was also reported to determine the dissociation constant of α-LacNAc and β-LacNAc for RCA120 [43]. By varying the printing concentration of glycans, multivalent interactions were probed. Higher density printing generally led to lower observed \(K_{D,surf}\), indicating a multivalency effect which mimics the multivalent display of glycans on cell surfaces. Furthermore, solution dissociation constants (\(K_D\)) were determined by the competition between carbohydrates and inhibitors in solution-bound and surface-bound glycans. It is envisioned that this method will be useful for the quantitative characterization of sugar-binding specificities of proteins and for the high-throughput discovery of inhibitors of carbohydrate-binding proteins of therapeutic interest.

**Glycan array for measuring enzyme specificities**

Glycan microarrays can be utilized to rapidly determine the substrate specificity or activity of carbohydrate-processing enzymes. In a model study reported by Shin and coworkers, a microarray containing GlcNAc and fucose was treated with β-1,4-galactosyltransferase (GalT) and UDP-Gal and then probed with fluorophore-labeled lectins [44\textsuperscript{**}]. Enzymatic conversion of GlcNAc to LacNAc by GalT was detected by fluorescence lectin. Recently, the method was extended to profile 20 carbohydrates as GalT acceptors [43]. Maltose derivatives were covalently conjugated on the microtiter-type glycan array and glycosylation products were detected by FITC-labeled Con A. New acceptor substrate specificities of glycosyltransferase were observed [45]. Owing to the limitation of lectins as detection tool (low-binding specificities and weak affinities), a broad spectrum of detection method was developed to study various recombinant sialyltransferase specificities. The donor substrate cytidine-5’-monophospho-N-acetylneuraminic acid (CMP-Neu5Ac) was biotinylated at the 9-position of Neu5Ac. After screening of a series of sialyltransferase against a +200 member glycans microarray, the sialylation products were observed with fluorescein-streptavidin to determine acceptor substrate specificities [46]. Similarly, GDP-\(^{[14C]}\)Fuc was transferred to surface carbohydrates on an array using plant cell wall glycosyltransferase [47]. Arrays have proven to be powerful tools for high-throughput profiling of the substrate specificities of carbohydrate-processing enzymes.

**Conclusions**

Glycan arrays are powerful tools for screening the specificity of GBPs, including profiling of lectins, growth factors, cytokines, antibodies, and microbial toxins, and have demonstrated their utility in the identification and the characterization of glycan–protein interactions. More detailed quantitative analysis and enzyme characterization have also shown that arrays can be used in inhibitor and drug discovery. Glycan arrays continue to be an important tool in the evolving field of glycomics, and new applications will be developed in the future.

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