Published in final edited form as:

Curr Opin Chem Biol. 2009 December ; 13(5-6): 562–564. doi:10.1016/j.cbpa.2009.09.008.

Editorial Overview for Biopolymers (2009, No. 6) By Zhongwu Guo, Guest Editor

Zhongwu Guo

Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202,
United States

Zhongwu Guo: zwguo@chem.wayne.edu

Editorial Overview

This “*Biopolymers*” issue is focused on recent advances in carbohydrate research, particularly in chemical and chemoenzymatic synthesis of carbohydrates and glycoconjugates, glycomics, carbohydrate microarray techniques, and design and development of carbohydrate-based drugs or therapies.

Carbohydrates, including oligosaccharides, polysaccharides and various glycoconjugates, are the most abundant and arguably the most structurally complex and diverse organic molecular species in nature. Compared to DNA, RNA, proteins/peptides and other biopolymers, carbohydrates consist of not only linear oligomers and polymers but also an astronomical number of branched and stereogenic isomers; meanwhile, carbohydrates are also commonly decorated with various functional groups, such as alkyl, acyl, phosphoryl, sulfonic groups, etc. In addition, carbohydrate biosynthesis is not precisely regulated by a rigid template or translating system, which usually results in structurally heterogeneous end products that are difficult to separate. Consequently, the chemical synthesis and structural analysis of carbohydrates and access to homogeneous forms of glycoconjugates represent an important problem in chemistry and biology, which in large part accounts for the relatively slow advancement in carbohydrate research, as compared to protein and nucleotide research.

On the other hand, the high complexity and diversity of carbohydrate structures make them the ideal and the most economical carriers of biological messages in nature, because they can use the shortest sequences to store the richest structural information. Moreover, the relative flexibility of carbohydrate biosynthesis determines that it is easily affected by numerous factors, such as developmental progression, disease states, external chemical and biological stimuli, and the complex interplay between biosynthetic enzymes and activated nucleotide sugar substrates. Therefore, carbohydrates play important roles in various biological events including pathological processes, for example, many diseases are accompanied with unique glycosylation profiles, and carbohydrate research provides excellent opportunities for utilizing small synthetic molecules, including structurally well defined oligosaccharides, to probe biological problems and for the discovery of novel therapeutics.

Metabolic cell glycoengineering, which makes use of the flexibility of glycan biosynthesis machineries to install non-natural sugars into the glycocalyx of mammalian cells by using

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

monosaccharide analogues, is a prime example of “chemical glycobiology” and has undergone a flurry of advances in recent years. As an introduction to this special issue, Yarema and coworkers provide an overview of the capability of this unique technique to endow complex carbohydrates in living cells and animals with interesting functionalities, as well as an overview of how acylated monosaccharides used in metabolic cell glycoengineering have led to the establishment of a set of compounds as a versatile platform for antitumor drug discovery.

Currently, the chemical synthesis of oligosaccharides remains a significant challenge due to a number of issues. First, to realize regioselective coupling reactions between sugar units, the involved hydroxyl groups must be distinguished from other hydroxyl groups within the structure, which can be very tedious and time-consuming. Moreover, to distinguish multiple positions within a monosaccharide or oligosaccharide building block, a number of chemically orthogonal protecting groups must be used and a proper protection-deprotection scheme has to be carefully planned. Second, glycosylation reactions usually give relatively poor yields, which has remarkably affected the synthetic efficiency and made product purification difficult. More importantly, all glycosylation reactions can afford two stereoisomers, that is, α - and β -anomers, and presently there is not a good or universally applicable method to achieve stereoselective glycosylation. Finally, because the majority of biologically important carbohydrates in nature are in conjugated forms with peptides/proteins or lipids, usually synthetic oligosaccharides need to be eventually coupled with peptides or lipids. In this case, the designed reactions, protection tactics and target assembly strategies for carbohydrates must be compatible with peptide and lipid chemistries as well. In the past decades, an enormous number of protecting groups, glycosylation methods and oligosaccharide assembly strategies have been developed to deal with these issues, which has enabled the chemical synthesis of structurally complex carbohydrates and glycoconjugates. Xi Chen and coworkers summarize the recent progress in this area by especially focusing on solid-phase and one-pot carbohydrate syntheses.

Access to various oligosaccharides and structurally defined analogues makes their structure-activity relationship (SAR) studies feasible, which helped the understanding of the functions and functional mechanisms of carbohydrates in many biological processes. For example, N-linked high-mannose-type oligosaccharides were demonstrated to play a critical role in glycoprotein quality control, but how these glycans interact with the glycoprotein quality control system precisely has not been clarified. Ito and coworkers summarize the chemical synthesis of a series of high-mannose-type glycans and their functionalized derivatives and the use of these glycans to probe the glycoprotein quality control system via detailed analyses of their interaction with the various proteins and enzymes involved.

Another exciting development in access to carbohydrates is the utilization of enzymes involved in glycan biosynthetic processes to prepare oligosaccharides, polysaccharides and glycoproteins. Enzymatic reactions are typically regio-, stereo- and substrate-specific, thus free sugars and glycoconjugates can be directly used in the synthesis. Moreover, some chemically difficult glycosylation reactions, such as α -sialylation, are easily achievable with enzymes. Xi Chen and coworkers also summarize the recent progress in the application of sugar nucleotide synthases, glycosyltransferases and other enzymes to chemoenzymatic synthesis of carbohydrates. Wang and Huang review the elegant application of transglycosylation reactions catalyzed by glycan-processing enzymes such as glycosidases and glycosynthases to the preparation of structurally defined glycoconjugates, including large glycoproteins. These structures are useful but difficult to access otherwise.

The biosynthesis of glycans has been observed to be highly sensitive to the surrounding biochemical environment, thus many pathological processes are accompanied with changes in cell surface glycosylation profiles. Glycomics, which is the comprehensive analysis of all

glycans expressed in biological systems, can help identify and characterize unusual glycans involved in specific diseases and discover new molecule markers for disease diagnosis and therapy. In this regard, mass spectrometry is emerging as a particularly powerful tool. Lebrilla and coworkers summarize the recent progress in this area as well as the glycan profiling of human serum by mass spectrometry, which has been used to identify promising markers for several types of cancer and other diseases.

Oncogenesis is closely associated with changes in cell surface glycosylation patterns. The unusual glycans expressed by tumors, known as tumor-associated carbohydrate antigens (TACAs), are useful molecular targets for the development of new antitumor strategies. Guo and Wang summarize recent advancements in the design of new TACA-based therapeutic cancer vaccines, including glycoconjugate vaccines containing clustered or multiple TACA epitopes and fully synthetic multi-component conjugate vaccines formed by covalent coupling of TACAs to unique carrier molecules, including immunostimulant epitopes and T cell peptidic epitopes. This review has also described a novel strategy for cancer immunotherapy based on combined treatments with vaccines made of chemically modified TACAs and metabolic glycoengineering of cancer cells to express the corresponding unnatural TACA analogues.

Tam and Lowary's article summarizes recent genetic and biochemical studies leading to the identification and characterization of mycobacterial glycosyltransferases that work in tandem in the assembly of mycobacterial cell wall glycans, such as arabinogalactan (AG) and lipoarabinomannan (LAM). Since these cell wall glycans are essential to the viability and virulence of mycobacteria, such as the causative agents of the human diseases tuberculosis and leprosy, the involved enzymes represent novel targets for drug discovery.

Song and Pohl have reviewed recent developments in the fabrication and detection methods for carbohydrate arrays, especially methods based on surface plasmon resonance (SPR) and mass spectrometry. Carbohydrate arrays can provide facile analyses of carbohydrate-binding proteins, antibodies in serum, and enzyme activities with minimal quantities of sugar samples. The new methods have enabled not only qualitative but in some cases quantitative data analysis in a variety of multivalent display formats, making diagnostic tools based on carbohydrate arrays more promising for infectious disease detection, cancer monitoring, and vaccine development.

The last article of this issue by Linhardt and coworkers is focused on heparin, a highly acidic polysaccharide that is an important and clinically widely used anticoagulant drug. Current state-of-the-art chemical and chemoenzymatic synthesis of heparin and new approaches for its metabolic engineering are described. New technologies, including microarrays and digital microfluidics, were employed for high-throughput synthesis and screening of heparin and for the fabrication of an artificial Golgi. These advances have significantly facilitated access to heparin and analogues, as well as their structural analysis and biological evaluation, providing new information and opportunity for the design of safer heparin-based therapeutics.

In conclusion, this "*Biopolymers*" issue provides a sampling of topics that exemplify how carbohydrate research, or glycoscience, which includes all aspects of chemical, biochemical, and biological studies of carbohydrates and glycoconjugates, has grown into a flourishing field in the past three decades. During this time, glycoscience has witnessed an accelerating rate of progress, especially in overcoming longstanding (but still incompletely solved) obstacles in carbohydrate synthesis and structural analysis. While advances in carbohydrate synthesis and structural analysis remain cornerstones of glycoscience, progress in these two specific areas will play an even more important role in the future by helping basic researchers gain insight into structure and function and by assisting applied scientists in launching novel applications of carbohydrates. For example, while carbohydrates and glycoconjugates have been used in

biomedical, pharmaceutical, and other industries for decades, nowadays interest in carbohydrate-based diagnostics and therapeutics for diseases is fast growing, thanks to the increased understanding and appreciation of the functions of carbohydrates and an ever increasing number of novel glyco technologies, such as metabolic cell surface glycoengineering, glycoprotein engineering, glycomics, and carbohydrate microarrays. While these, and other areas of the multidisciplinary research field of glycoscience, are currently experiencing exciting progress, major challenges remain, and carbohydrate research will remain a hot topic for years to come.

Appendix: The list and the sequence of appearance of articles in the Biopolymers issue

1. "Hexosamine Analogs: From Metabolic Glycoengineering to Drug Discovery" by Kevin Yarema and coworkers
2. "Recent Progress in Chemical and Chemoenzymatic Synthesis of Carbohydrates" by Xi Chen and coworkers
3. "Chemical approaches toward understanding glycan-mediated protein quality control" by Yukishigo Ito and coworkers
4. "Enzymatic transglycosylation for glycoconjugate synthesis" by Dr. Lai-Xi Wang and coworkers
5. "Glycomics and Disease Markers" by Carlito Lebrilla and coworkers
6. "Recent Development in Carbohydrate-Based Cancer Vaccines" by Zhongwu Guo and coworkers
7. "Recent Advances in Mycobacterial Cell Wall Glycan Biosynthesis" by Todd Lowary and coworkers
8. "Carbohydrate arrays: Recent developments in fabrication and detection methods with applications" by Nicola Pohl and coworkers
9. "Recent progress and applications in glycosaminoglycan and heparin research" by Robert Linhardt and coworkers

About the issue editor

Zhongwu Guo is a professor in the Department of Chemistry at Wayne State University. He received his PharmD from the Second Military Medical University (China) and PhD from Polish Academy of Sciences (Poland) with Aleksander Zamojski. After conducting postdoctoral research with Yongzheng Hui, he joined the faculty of Shanghai Institute of Organic Chemistry in 1994. He was a RIKEN Fellow working with Tomoya Ogawa from 1996 to 1997 and then an Assistant Research Officer at the Institute for Biological Sciences, National Research Council of Canada from 1997 to 1999. He joined the chemistry faculty at Case Western Reserve University in 1999 and Wayne State University in 2005. His research interests include the development of novel synthetic methodologies for carbohydrates and glycoconjugates, total synthesis of natural products, and the development of carbohydrate-based therapies for human diseases such as cancer.