Chemical glycochemistry drives the discovery of carbohydrate-based drugs

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As one of the four major classes of biomolecules (carbohydrate, protein, nucleotide, and lipid), carbohydrates are the most prominent features of the cell’s exterior. Carbohydrates and their conjugates (glycoproteins, glycolipids) play important roles in various biological processes, including inflammation and immune response, angiogenesis and tumor cell metastasis, viral and bacterial infection, and many other cell-cell communications. Glycoscience has gained significant interest in biomedical research owing to their critical physiological functions. Through vast effort devoted by glycoscientists in recent decades, carbohydrate drugs pave the way to a non-ignorable area of the therapeutics world. Among the recorded carbohydrate drugs, natural polysaccharides represent the largest percentage of more than 75%, followed by oligosaccharides, monosaccharides and their derivatives, contributing an equal occupation of about 10%. Several types of carbohydrate-based antibiotics, such as aminoglycosides, macrolides, and glycosylated aromatic structures, have been used in the treatment of pathogenic bacterial infections. Clinical antitumor adjuvants benefited from their immunomodulatory effects and low cytotoxicity account for about 30% of the marketed carbohydrate drugs. Notably, approximately all of the adjuvants are first marketed in China as polysaccharides extracted from traditional Chinese medicinal plants or fungi. About 20% of the marketed carbohydrate drugs are exploited to treat blood and cardiovascular diseases. Heparin, a well-known highly sulfated glucosaminoglycan, has been widely used as injectable anticoagulant since 1940s. Additionally, the physiological properties of carbohydrates and glycomimetic drugs are also exploited for the treatment of gastro-intestinal diseases, virus infections and diabetes. The unique carbohydrate structures on the surface of invasive pathogens and the aberrant glycosylation on malignant cells make such carbohydrate moieties attractive immunotherapy targets. The carbohydrate-based vaccines against Streptococcus pneumonia, Neisseria meningitides, Haemophilus influenzae type b and Salmonella typhi Vi have been used successfully to prevent such bacterial infections. Inspired by the success of antibacterial glycoconjugate vaccines, carbohydrate-based conjugate vaccines for cancer, viruses, protozoans and fungi are currently under development.

Notably, the applications of most polysaccharide-derived drugs such as the antitumor adjuvants are regional restricted due to their mixed compositions, ambiguous mechanisms, and the difficulties in quality control. Thus, chemical glycochemistry is emerging as a powerful sub-discipline of chemical biology, aiming at structure characterization, artificial synthesis, pharmacological mechanism investigation, and quality control of carbohydrate drugs. Tremendous efforts have been devoted to the structure characterization of polysaccharides derived from traditional Chinese medical plants and fungi possessing diverse bioactivities. GV-971, a mixture of oligosaccharides derived from brown algae, was structurally elucidated as oligomannate with the degree of polymerization from 2 to 10. In 2019, the oligomannate sodium GV-971 had received conditional marketing approval in China to improve cognitive function in mild to moderate Alzheimer’s disease. Furthermore, various efficient methods (sulfation, selenylation, phosphorylation, acetylation, and alkylation) have been developed for the modification of polysaccharides to generate novel bioactivities or enhance the original activities. The complexity of carbohydrates has hampered investigations of their pharmacological mechanisms which require homogeneous and well-defined carbohydrates. To deal with this challenge, glycochemists continuously explore carbohydrate chemistry and develop versatile methods to streamline the synthesis of complex carbohydrates, such as gold (I)-catalyzed glycosylation (Yu glycosylation), preactivation-based one-pot glycosylation and automated glycan assembly. Efficient synthesis of well-defined carbohydrates has significantly promoted the development of carbohydrate-based therapeutic agents.
omponents of carbohydrate drugs. Compare to isolated polysaccharide-based vaccines, the advantages of synthetic oligosaccharide-based vaccines include well-defined antigen structure, homogeneity, highly reproducibility and better safety profile. A Haemophilus influenzae type b vaccine Quimi-Hib®[6], the first commercialized synthetic carbohydrate-based vaccine, is comprised of a synthetic carbohydrate antigen [10]. Fondaparinux, a fully synthetic analog according to the pentasaccharide domain of heparin, has been widely used for the treatment of deep vein thrombosis in clinic. Synthetic glycomimetics have been potential alternatives to enhance the activities of corresponding natural carbohydrates [11]. Additionally, the specific recognition between carbohydrates and their receptors on the corresponding cells have been extensively exploited to develop targeted drug delivery systems [12].

In this issue, we are pleased to publish four original articles covered a specific range of chemical glycochemistry topics including the investigation of carbohydrate reaction characteristics, synthesis of carbohydrate analogues, and discovery of pharmaceutical active polysaccharides. The issue begins with a paper reported the influence of protecting group patterns on the transformation efficiency of D-glucose derivatives into synthetically useful D-alloses and D-allomaltoses via the Lattrell-Dax epimerization [13]. Zhang ZP et al. describe the synthesis and bioactivity of novel carbohydrate-triazole derivatives [14]. Ding HM et al. provide a study on effect of Sargassum fusiforme polysaccharide on apoptosis and its possible mechanism in human erythrooleukemia cells [15]. Kim JY et al. study on the phytyglycoprotein isolated from Dioscorea batatas Decne [16].

Despite the structural complexity of carbohydrates, chemical glycochemistry based on rapidly developed carbohydrate chemistry has driven the discovery of a vast array of carbohydrate-based drugs for the treatment of a variety range of human diseases. However, more efforts should be put on the study of precise mechanisms and active domains, as well as automated synthesis of complex carbohydrates. Additionally, modification and simulation of natural carbohydrates, targeted drug delivery based on recognitions of carbohydrates by receptors, and synthetic carbohydrate-based vaccines are all highly potential approaches for the future development of carbohydrate-based drugs. It’s anticipated that chemical glycochemistry will be one of the most successful fields of novel drug development and play a key role in the treatment of human diseases.

References


Dr. YIN Jian is now a Professor of Glycoscience at Jiangnan University. His research interests cover chemical synthesis of complex oligo/polysaccharides, development of carbohydrate-based vaccines, drugs, and drug delivery systems. In the past five years, he has published 34 peer-reviewed articles as a corresponding author including J Am Chem Soc, Angew Chem Int Ed, Adv Funct Mater, Chem Sci, Chem Commun, etc. He has applied for 23 Chinese patents of invention with eight already authorized. In addition, nine PCT patents were claimed, and two U.S. patents have been issued. He won the 3rd China “Zhang Shuzheng Glycoscience Award” in 2019.