Carbohydrate Chemistry: State of the Art and Challenges for Drug Development

by Laura Cipolla

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The circulating glucose serves as a fuel for energy metabolism and as substrate for biosynthesis of polysaccharides, lipids, nucleic acids, and proteins. The growing knowledge about carbohydrate involvement in physiological and pathological states has spurred renewed interest in the chemistry, biology and therapeutic for the potentialities of these natural compounds. Moreover, the need of carbohydrate multivalent activities has led to the synthesis of a plethora of compounds based on different scaffolds. Their language requires, in fact, a huge effort to be learned, but is meant to be one the most spoken in the future of drug development.

This book organized in **V Parts and 19 Chapters**, reports and discusses the key aspects of carbohydrate biology and chemistry, fundamental to design and market novel therapeutics.

Part I: *Structure and Biological Function of Glycoconiugates*, introduces the reader to the fields of glycoproteins, gangliosphingolipids and bacterial lipo-polysaccharides giving a wide report on their chemical structure and biological roles. On **Chapter 1**, *Glycoproteins: Chemical Features and Biological Roles*, the important biological role of glycoproteins is focused. They can serve as structural components, lubrificants, protective agents, transport molecules, inhibitors, hormones, and enzymes. The N-Glycans in glycoproteins, for example, affect the folding, stability, solubility, function, and activity of different proteins, while O-glycosylated mucins form viscous gels functioning as cell chemical signalling and barrier. In addition, the terminal sequences of N-and O-GalNAc-glycans serve as recognition molecules and sites for cell-attachment.

Among glycoprotein therapeutics, antibody-based drugs are the largest and fastest growing category and have a wide range of applications, particularly in cancer, immune disorders, and infectious diseases. Establishing cost-efficient and robust system possibilities to produce humanized therapeutic glycoproteins with improved functions and homogeneous forms at industrial scale is reported and discussed on this chapter.

The lipid moiety of vertebrate glycosphingolipids (GSLs) consists of either a shingoid or a ceramide, which is a sphingoid base linked to a fatty acid through an amide bond. Most of the structural variability of gangliosides and GSLs is born by the carbohydrate domain that exhibits a staggering structural diversity. They are important compounds of the plasma membranes involved in many cellular functions, mainly supported by the glycine moiety of gangliosides.This the topic focused on **Chapter 2** *Gangliosphingolipids: Structure and Biological Roles*.

Chapter 3 reports an overview on the structure, biosynthesis, and immunological activity of the bac-

terial Lipo-polysaccharides (LPSs), also known as *endotoxins*. As the major component of the outer membrane of almost all Gram-negative bacteria and some Cyanobacteria, they have the capability to activate the immune system. LPSs are amphiphilic molecules which contribute to the protection and integrity of the bacterial envelop, organized as a highly ordered structure of a lipid mono layer of low fluidity, stabilized by electrostatic interactions between bivalent cations and negatively charged groups present on LPS molecules. Among all the other activities, LPSs have been shown to be the most potent immunostimulant molecules, playing a key role in the pathogenesis of Gram-negative infections, triggering the immune system in a wide range of organisms ranging from insects to humans.

Part II is focused on the latest techniques used to investigate the structure and biological role of carbohydrates, including their interactions with proteins and receptors; it is comprised by chapters 4-7 reporting the most advanced methods necessary to develop the synthesis of carbohydrate-based therapeutics, such as Mass Spectrometry (**Chapter 4**), where the new methodological and analitical aspects about for example, of the glycols moiety of glycoconjugates is reported and discussed. Due to the high importance of glycoconjugates in biology and medicine, in fact, an entire generation of chemists has been involved in solving the structural intricacies of carbohydrates, developing new methodologies for studying the primary structures of the glycan moieties attached to proteins. Advanced NMR techniques, that provide scientists the possibility to study, in solution and at atomic scale, the structure of carbohydrates, is the topic of **Chapter 5.**

Glycoarrays for Glycomics, i.e. the high-throughput bioanalytical screening to evaluate thousand of individual glycan-receptor binding events in a single experiment and with minimum reagent use, is reported on **Chapter 6**.

Chapter 7, on the other hand, summarizes the current software and databases that have been developed reporting informatics and analytical tools for glycans analysis and biotherapeutics. The chemical synthesis of complex carbohydrates, in fact, has been a challenge for more than a century due to the diversity and complexity of their structures recovered in mammalians and, composed by building blocks of monosaccharide units. Thus, the first step in the assembly of a complex oligosaccharide is its retro synthetic analysis and, afterwards, the choice of the appropriate building blocks.

The creation of the corresponding building blocks is, therefore, the most time-consuming part of the complete synthesis performed and generated by numerous steps. The different methodologies used have been reported in **Chapter 8**, first chapter of **Part III**, where the chemical synthetic problems solved by the use of enzymes are focused. Enzymatic strategies are an open field of research, with significant applications in glycosciences and industrial biotechnology, addressing the need for simple end efficient methodologies to access structurally defined oligosaccharides, polysaccharides, and glycoconjugates.

The screening of new enzymes and engineered methods is the topic reported and discussed on **Chapter 9**, and the novel technologies for the automation of oligosaccharides synthesis have been discussed on **Chapter 10**. However, until today further development of existing automated synthesis remains a significant area of research and the manual synthesis still remains an important tool to obtain complex oligosaccharides of particularly challenging sequences.

Part IV, developed in 8 chapters, is entirely dedicated to the carbohydrate-based compounds used for medical applications.

On **Chapter 11** are summarized the potential possibilities the iminosugers have to mimic some bio-

logical activities, acting as immune modulators and pharmacological chaperons of misfolded proteins. Iminosugers, in particular, are sugar analogs with nitrogen in place of the ring oxygen of the corresponding sugar, while naturally occurring iminosugers are one of the most interesting discoveries and the most fascinating nature arts in the fields of natural product chemistry. The first interest for these compounds was based on their properties as glycosidase inhibitors, while today scientists are also studying their ability for other potential activities.

Chapters 12, 13, and **14** are all dedicated to the routine production and use of vaccines, characterized for their high diversity. From the list of 15 vaccines ranked by sales and representing the 15 top-selling of 2012, for example, six are carbohydrate-based vaccines. However, despite the advent of antibiotics, implementation of national vaccination campaigns and intensive care support, bacterial meningitis continues to be an important cause of morbility and mortality among high-risk groups. The common feature of the organisms that cause most of the bacterial meningitis is a carbohydrate capsule with different oligosaccharide patterns that act as both a virulence determinant and target of protective antibody. Therefore, antibodies specifically against bacterial surface polysaccharides may enhance the elimination of pathogenic bacteria. This the reason of cancer immunotherapy, based on tumour-associated carbohydrate antigens (TACAs), as promising alternative to antitumoral treatments, such as surgery, chemo-and/or radiotherapies, often cause of undesired side effects. However, the presence of TACAs in vaccine formulation is indeed necessary to activate B lymphocytes, but are not sufficient to produce high titers of antibodies and to induce reproducible and long-lasting immunity against tumors. In any way, new generations of structures associating 3 and 4 components and unimolecular multiantigenic constructions, represent author bases for further optimization of future vaccine candidates.

Chapters 15-18 are focused respectively to specific inter cellular adhesion molecule-3 graffing non-integrin (DC-SIGN) that play a key role in human immunodeficiency virus (HIV) transmission, biomaterials and tissue engineering applications, carbohydrate multivalent systems, and antitubercular drugs based on carbohydrate-derived.

On one hand, much work remains to allow the selection of polyvalent scaffolds, ligands and biomaterials optimal in size, shape, and valency, tuned to the supramolecular architecture for antagonizing the majority of pathogens structures that infect humans. On the other hand, early research and fortuitous accidents, linking material chemistry to biological responses, have provided a rationale basis for developing new biomaterials, significantly affected by the biology revolution and the advanced knowledge in genomics, proteomics, and glycomics. At this purpose, it is interesting to underline that carbohydrate structures encode information that modulates interceptions between cells and the extracellular matrix (ECM). Thus, saccharidic motifs are undoubtedly interesting cues to be used for the upgrading of synthetic or natural polymers to smart biomaterials with the ability to cross-talk with their biological environment.

In any way, despite the increasing development of glycomics and methods at disposal for the oligosaccharide synthesis, the application of glycoscience is still scarce and remain a difficult challenge.Glycans are, in fact, not only an important source of metabolic energy, but play also a key role in many relevant biological processes, expressed as glycoconjugates on the surface of the cells. In recent years, there has been an increasing amount of research on the utilization of natural polymeric materials as drug, covering several therapeutic niches, or as drug delivery vehicles due to their high biocompatibility and biodegradability. Their potential uses have not been completely under-

stood yet and probably the future will hold new and challenging opportunities to create many other structures and drugs with interesting biological and therapeutic potential. While the exploration of polysaccharides for their multifaced roles is still in its infancy, the introduction of targeting moieties carbohydrate-based will certainly improve their therapeutic efficacy, reducing also undesired side effects.

This interesting book offers an ample overview of all the fundamental chemical and biological aspects of carbohydrates. Its intelligent editorial organization represents an indispensable guide for the academic and industrial researchers of the medical and chemical communities who wish to be introduced or to understand in a better way the fascinating structural chemical and therapeutic activity of these natural compounds. Moreover its reading may be of great help for students in chemistry or medicine who wish to enter into the mechanisms regulating the cell life in healthy or pathological state.

P. Morganti
Editor in Chief