

## BOOK REVIEW

**Complex Carbohydrates in Drug Research: Structural and Functional Aspects, Alfred Benzon Symposium No. 36, Proceedings of a Symposium held at the Royal Danish Academy of Sciences and Letters, 6-10 June, 1993.**

K. Bock & H. Clausen (eds)  
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The title of this book implies that complex carbohydrates are already in use (or about to be used) as drugs. However, this is far from the truth, and research in this area is still in its infancy. Indeed, the 27 manuscripts which are presented and discussed clearly demonstrate how little is actually known about both the conformation of oligosaccharides in solution and the overall complexity of the oligosaccharide structures (owing to microheterogeneity) which are encountered when cell surfaces are examined.

Over the years many functions for the carbohydrates on proteins have been proposed. These include the control of protein folding, secretion, distribution, heat sensitivity and protection (against proteolysis). It is only recently, however, that the importance of cell-surface carbohydrate (on both lipids and proteins) in the regulation of cellular targeting, development and the immune response has been fully appreciated. This has led to the increasing promotion of oligosaccharides and glycosylation inhibitors as possible therapeutic drugs of the future. This is the main subject matter of this book, in which every aspect of this area is covered, from the analysis, structure and conformation of *O*- and *N*-linked oligosaccharide chains to the regulation of their biological functions.

The book can be divided into two parts. The first 15 articles are more chemically orientated and describe the analysis of oligosaccharide chains, the synthesis of synthetic

carbohydrate substrates and inhibitors and the study of oligosaccharide conformation. Several articles use complex computer modelling programs and nuclear magnetic resonance (NMR) to try to elucidate the conformations of oligosaccharides in solution. A better understanding of this area would allow the development of competitive substrates and inhibitors. Unfortunately, these articles are very technical and are often very difficult to comprehend. They also show how difficult it is to predict the structure of even simple carbohydrate chains. Hence, the conformational analysis of the numerous glycoforms of most naturally occurring glycoproteins and glycolipids would appear to be currently impossible. Two excellent reports describe state-of-the-art analysis of very complex oligosaccharide side chains by one- and two-dimensional NMR (Vliegenthart) and fast atom bombardment mass spectrometry (Dell *et al.*). Even in these studies, the sugar chains have first to be isolated by enzymic digestion, then purified by sequential chromatography, before they can be analysed: a major problem when each molecule has several carbohydrate attachment sites and numerous glycoforms. The synthesis of several substrates and inhibitors of specific glycosyl transferases is also discussed.

The final 12 articles relate to the biological functions of exposed carbohydrates. These are, to the reviewer, the most interesting reports as they discuss the many reactions and biological properties of glycoconjugates with which one can interfere. They also demonstrate the tremendous potential of carbohydrates/glycosylation inhibitors as therapeutic drugs of the future. One very interesting report describes the discovery of a highly conserved *O*-glycosylated region in the strongly antigenic HIV gp120 (Clausen *et al.*). This glycoprotein is 50% glycosylated (mostly via *N*-linked chains), and antibodies that have previously been raised against it have tended to be of no therapeutic use owing to massive heterogeneity (and drift) from patient to patient. However, if antibodies could be raised against this

conserved region they could be of therapeutic use.

The problems involved in producing recombinant proteins with the correct glycosylation are also discussed in the second part of the book. A recombinant protein assumes the glycosylation of the host cell line in which it is being produced, and this is often very different to the naturally occurring human version. One advantage of this is that different glycosylated versions of the same protein can be compared, and the effects on activity of alterations in carbohydrate structure can be deduced.

Most (if not all) cell-surface molecules are glycosylated, and many of these structures are discussed in relation to their effects on cellular adhesion (NCAM- and E-selectin-mediated lymphocyte adhesion and cancer metastasis) and on the immunogenicity of viruses, bacteria, cancer cells and transplants. In theory, if the correct oligosaccharides were available, then their use as drugs to block, for example, the adhesion of cancer cells and metastasis is possible. Immune responses could be similarly controlled, preventing transplant rejection and allowing the treatment of autoimmune diseases. Viral and bacterial infections could also be controlled by preventing their attachment to host cells and/or increasing their immune response by modifying surface antigens. Alternatively, the glycosylation of glycoconjugates or cell-surface molecules could be altered by the addition of competitive synthetic substrates for the glycosyl transferases or specific glycosylation inhibitors. All of these possibilities are examined.

In summary, this book presents an interesting overview of the potential of carbohydrates/glycosylation inhibitors as drugs. It also discusses the limitations of the currently available chemical techniques in both the synthesis and the analysis of the structure and conformation of carbohydrate chains. My main criticism is that, if the book is aimed at biochemists (the largest potential group of readers), then more articles should have been included on the biological aspects of carbohydrate heterogeneity.

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ity. If this was not possible then the order of the articles should have been reversed in order to review the important areas of why glycoconjug-

ates could be used as drugs, before the discussion of the problems involved in the chemical analysis and synthesis of these structures.

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