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Book Review

Complex Carbohydrates in Drug Research: Structural and Functional Aspects, Edited by K Bock and H. Clausen, Munksgaard, Copenhagen, Denmark, 1994. ISBN 87-16-11229-6, 451 pp plus index, DKK 400.

Some five years ago there was a heady excitement about a new carbohydrate-based paradigm for drug design. It had been discovered that complex carbohydrates of glycoproteins, glycolipids, and bacterial polysaccharides encode information relevant to cell interaction and that the information is decoded by binding to lectins and other proteins. It was soon recognized that this information controls many important biological phenomena such as initiation of the inflammatory process, control of the circulating lifetime of serum glycoproteins, coagulation of blood, and microbial attachment and invasion. Since drugs designed to look like carbohydrates could modulate these functions, a need arose for chemical methods to analyze carbohydrates, for physical methods to determine their shapes and interactions with proteins, and for synthetic methods to prepare suitable analogues. Competition developed between new biotechnology startup companies and established pharmaceutical houses to develop chemical methods along with suitable biological assay systems.

The lack of any immediate payoff from these ventures has dampened enthusiasm. Now many of the startup companies have disappeared and large pharmaceutical companies have turned their attention to other problems. But the basic science on which this enthusiasm was based remains sound. This well-produced type-set book captures a substantial representation of the fundamental science on which that enthusiasm was based. Carbohydrate scientists should read this book and dream that excitement in the field will be resuscitated by some imminent new observations about selectins, about cancer, or about microbial attachment mechanisms in disease. Carbohydrates which are found mostly at the cell surface have an inherent advantage of accessibility over other macromolecular candidates for drug development; delivery to the cell surface involves fewer problems than does transport of drugs acting on cytosolic enzymes or nucleic acids.

The book has 27 chapters ranging in length from 10 to 15 pages contributed by authors on a wide variety of topics. The discussions, which are included at the end of each contribution, are in some cases unrelated to the printed article but in other cases,

where the printed article corresponds more closely to the actual oral presentation, the discussion is quite informative, bringing out various points of view and elaborating ideas of the authors.

The early chapters of the book focus on analysis and structural chemistry. The article by Woods, Edge, Wormald, and Dwek discusses parameters for molecular modelling of complex oligosaccharides, and Vliegenthart reviews NMR data and computerized data bases for structure identification. Ann Dell describes mass spectrometry research in collaboration with a number of research groups in determining carbohydrate structures involving a host of important biological applications. Homans reviews recent technical developments in NMR including 3D and 4D methods for conformational studies. His discussion of the question of rigidity and flexibility of complex carbohydrate epitopes emphasizes that this continues to be an important question and he proposes that new methods promise to provide more definitive answers regarding dynamic structures. As larger and more flexible targets are studied, new methods will be needed for constructing molecular models. K. Bock describes new Metropolis Monte Carlo methods applied to oligosaccharides and glycopeptides, including handsome colour photographs of which there are a number in this book. New supersensitive methods for detecting single molecules of complex oligosaccharides by capillary electrophoresis are described by Hindsgaul.

Oligosaccharide candidates for drug design will require new paradigms for synthetic chemistry to conquer the multiple chiral centers and hydroxyl groups which have intimidated synthetic chemists less adventurous than Ichikawa and Wong who describe innovative approaches combining enzymatic synthesis with chemical methods to prepare selectin ligands and inhibitors of glycosidases. Vasella and coworkers review sophisticated syntheses of glycosidase inhibitors based on transition state analogues. Meldal and Bock summarize an elegant strategy for synthesis of sugar ligands in suitable orientation for lectin binding by use of peptide libraries to provide scaffolds. Paulsen describes results of a collaboration with the group of Schachter in which chemical syntheses of inhibitors of the glycosidases in glycoprotein biosynthesis are used to reveal the role of GlcNAc transferases in the resynthesis of N-linked glycopeptides.

Many of the proposals for carbohydrate-based drugs involve interaction with specific antibodies. Bundle provides a summary of X-ray crystallographic studies revealing the molecular nature of the interaction of carbohydrates with antibodies along with studies aimed at increasing the binding strength of protein–carbohydrate interaction. Samuelsson and Carins propose to use carbohydrate antigens as immune adsorbents to facilitate the use of pig xenografts as a source of organ transplants. Magnusson and coworkers describe the use of oligosaccharides from gangliosides as inhibitors of antibody binding. Lemieux presents a wide ranging overview of studies from his group to dissect the interactions of oligosaccharides with antibodies as well as with lectins at the molecular level.

Although carbohydrate-based vaccines including protein conjugates with bacterial polysaccharides have been a major focus of commercial ventures, this topic received only limited coverage in this volume. But Hansen and Clausen describe possibilities for carbohydrate-based vaccines for HIV.

A huge potential for carbohydrate-based drug development exists in the difficult problem of design of inhibitors of glycosyl transferases and in the somewhat more practical matter of design of glycosidase inhibitors. Johnson and Watson present crystallographic studies of glucose analogues as inhibitors of the allosterically regulated enzyme, glycogen phosphorylase as a potential route for diabetes therapy in an excellent example of rational drug design in the carbohydrate field. Svensson and coworkers summarize a very thoughtful study of amylase inhibitors involving mutation of the catalytic site and extensive crystallographic and kinetic analysis.

The significance of the carbohydrate moiety of recombinant glycoproteins has been emphasized by discoveries of the role of sugars in targeting and clearance of glycoproteins from serum. This important topic in pharmaceutical research is represented in this volume by a paper of Kobata who reviews the biosynthesis of N-linked glycopeptides and their targeting dictated by lectin binding.

For some years, Troy has studied biosynthesis and transport of polysialic acids in bacteria. His article reviews the many tools arising from this research and their applications to newly discovered roles of polysialic acids in animal systems. A paper presented by E. Bock describes the carbohydrate epitopes of neural cell adhesion molecules in which polysialic acids play an important role.

Glycoprotein research has been directed primarily toward N-linked glycopeptides with somewhat less attention devoted to O-linked sugars of the mucin type. This may be due to the confusing peptide structure of mucins with tandem repeating sequences as described by Taylor-Papadimitriou and coworkers in a review which covers structure, biological occurrence, and importance in tumor and developmental biology. O-linked oligosaccharides may be important carriers of the Sialyl-Le^X ligand for selectins as described by Fukuda in a theory of tumor cell metastasis in which lectins specific for blood group related epitopes are responsible for tumor cell attachment to epithelial tissue in a manner parallel to the mechanism of granulocyte adhesion observed in the initial steps in the inflammatory process. On this latter topic, Hakomori reviews the selectin ligands and the role of glycolipids in influencing integrin-mediated cell adhesion. The O-glycosidic linkage of GlcNAc to intracellular glycoproteins of the cytosol and nuclear membrane was first discovered in the laboratory of Hart. His paper reviews this field and discusses the proposed function of these proteins in regulation of transcription.

Karlsson reviews the data on microbial adhesion by lectins which bind to host carbohydrates, especially glycolipids. He discusses experiments intended to prevent infection by use of carbohydrates to inhibit bacterial binding to epithelial tissue. The volume closes with an excellent article by van Boeckel concerning efforts at rational design of oligosaccharides which inhibit blood coagulation by antithrombin-III binding. He summarizes a serious commercial effort involving X-ray crystallography, molecular modelling, and the design and synthesis of analogues of the heparin pentasaccharide to provide a basis for rational design of anticoagulants.

Although this book is ostensibly a report on The 36th Alfred Benzon Symposium, it has some of the features one would hope to see in a comprehensive survey of an important field at a crucial juncture in its history. The articles include a cross section of the most significant contributions to carbohydrate-based drug design and the volume represents most if not quite all the important topics in the field.

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