Preface

This book presents two important, closely connected and fundamental areas of research: glycobiology and human diseases. The field of glycobiology is focused upon understanding the chemical structure, metabolism and biological function of simple and complex carbohydrates (glycans) and their glycoconjugates: glycoproteins, glycosaminoproteoglycans and glycolipids. The last three groups of biopolymers are final products of post-translational modification of proteins and lipids and play a pivotal role in cellular homeostasis. Protein folding, intercellular communication, development, the immune system, various types of cell and molecular recognition and many others processes are characterized by close involvement of glycoconjugates. Major achievements in glycobiology have been obtained by the combined efforts of multiple investigators with a variety of backgrounds and expertise in carbohydrate chemistry, cell and molecular biology, enzymology and life sciences. Glycomics, younger than genomics and proteomics, deals with the analysis of glycan moieties of glycoconjugates and elucidation of their functional roles. Comprehensive glycomics methods has led to an understanding of not only many unknown earlier glycobiology processes in the normal state, but has also significantly expanded our knowledge of processes related to glycobiology in various human diseases. The contents of this book illustrate the research productivity of these two directions in glycobiology.

Chapter 1 (Wiederschain) presents an introduction to basic data about the peculiarity of simple and complex carbohydrates and glycoconjugates. Consideration of the unique structure, biosynthesis, degradation and function of glycans forms a basis for consideration of critical changes in many of these processes in disease, and lays the ground work for the chapters that follow. The reference list of this chapter includes many recently published reviews, monographs and collective comprehensive editions, and summarizes basic directions in glycobiology that may help readers expand their knowledge and skills in both theoretical and experimental areas of this science.

Methods of structural analysis of glycosaminoglycans (GAG), applications of these methods for identification of lysosomal storage diseases (LSD) and GAG participation in the development of Lyme disease are reviewed in Chapters 2 (Azadi and Heiss), 3 (Bruggink et al.) and 4 (Lin et al.), respectively. Various methodical approaches for GAG analysis are described as well as changes of these biopolymers in different types of LSD, and the role of GAG in tissue tropism for the Lyme disease spirochete.

Chapter 5 (Hartshorn) highlights the role of viral envelope protein glycosylation in pathogenesis of influenza A virus. In collaboration with experts in crystallography, molecular modeling, and molecular dynamics, the author and his colleagues have determined the molecular mechanism of binding of surfactant protein D (SP-D) to the influenza A virus hemagglutinin, and established the basis for increased inhibitory activity of mutant versions of SP-D. These studies provide the first detailed molecular mechanism for viral inhibition by an innate lectin inhibitor based on shared expertise in virology, structural biology, protein chemistry, and glycomics.

Chapter 6 (Alroy et al.) describes the application of lectin histochemistry for the diagnosis of LSD and Chapter 7 (Dingjan et al.) discusses computational approaches for studying carbohydrate-lectin interactions in infection. These two contributions illustrate the significance of lectinology in glycoscience pathology. Chapters 8 (Annunziata and d'Azzo) and 9 (Amith et al.), respectively, review pathogenic effects of altered sialylation (biosynthesis and degradation) of specific glycoconjugates in genetic diseases, as well as the role of Neu1 sialidase in the activation of toll-like receptors, their downstream signaling events,

and effector functions. In both of these reviews various types of mammalian sialidases (neuraminidases) are discussed in the context of specificity and function.

Chapter 10 (Dimitroff) focuses on novel insights on sialyltransferase regulation of cancer-associated O-glycans. The importance and more recognizable roles of Galectin-binding cancer cell O-glycans continue to provide new paradigms for cancer research and development of novel cancer therapies. The future model of glycobiological development for the treatment of cancer is scientific partnership between industrial and academic scientists. Each entity can effectively leverage their scientific expertise, research tools and laboratory infrastructure to develop potent and specific glyco-therapeutics in a cost-efficient manner. This type of collaborative relationship provides an opportune circumstance to rapidly test lead candidates in biologically-relevant screening assays and translate their use *in vivo*—namely to humans.

Chapter 11 (Popov) summarizes the history of pectin study, chemistry and medicinal uses of pectin, including physiological effects of individual pectins in human studies, processes that underlay the action of pectins, and the beneficial effects of pectin consumption on human health.

Chapter 12 (He and Newburg) discuss the glycobiology of human milk in health and disease. New data presented in this review strongly support the unique properties of human milk glycans and glycoconjugates in various infant defense mechanisms against bacterial and virus infections, including interaction with gut microbiota and effects on human intestinal cells.

Chapter 13 (Maor and Horowitz) considers molecular mechanisms underlying the association between Gaucher's disease (GD) and Parkinson's disease (PD). Since carriers of GD mutations develop PD, a dominant effect of the GBA mutation should be considered to be mediated by either gain of function or haploinsufficiency. The data show that expression of a mutant GBA allele is enough to cause ER stress and ER stress response, which leads to degeneration of dopaminergic cells.

Chapter 14 (Schwarting) highlights expression and function of poly-N-acetyllactosamine (PLNs) glycans in the nervous system. PLNs interact with a large family of endogenous lectins, the galectins. A great deal of what we know about lactosamine function comes from studies of galectin-1, which preferentially binds to lactosamine on N- and O-glycans; PLNs can affect biological systems in two ways: by directly modulating properties of the proteins to which they are attached, and by interacting with galectins and other glycan binding proteins.

Chapter 15 (Conroy and Anthony) reviews the role of glycosylation in various types of immunoglobulins in health and disease. The authors analyze 5 major subtypes of immunoglobulins in mammals, namely IgG, IgA, IgM, IgD, and IgE, all of which are glycoproteins produced by B cells and responsible for protection against a wide spectrum of threats. There is evidence that the peculiarity of glycosylation, the number of glycosylation sites and the types of glycans attached play an important role in antibody function. Many autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, thyroid disease and others, are triggered by antibodies erroneously targeted against host proteins. The intrinsic variable nature of antibodies, including their glycan parts, allow for specificity that can be engineered to meet a clinical need. The therapeutic role of antibodies through engineering modification methods is discussed. Antibody mediated immunotherapy is very promising for a wide range of diseases including cancer.

Chapter 16 (Sparks) highlights basic biochemical, genetic and clinical features of congenital disorders of glycosylation (CDG). Knowledge of glycosylation defects has been rapidly expanding due to improved clinical awareness and biochemical diagnostic techniques. This chapter deals with classification and modern nomenclature of known types of CDG, mechanisms of development of these diseases as a result of direct or indirect deficiency of enzymes involved in glycosylation processes, characterization of analytical techniques for CDG diagnosis, and possible approaches for treatment of these diseases. The clinical spectrum for defects in both N- and O-linked glycosylation is extremely broad, creating a challenge for clinicians to screen for these defects in a variety of settings and disciplines. Since there are some 500 genes involved in the synthesis and function of glycoproteins, it is likely that many more CDG defects will be identified in the future.

Chapter 17 (Ziganshina et al.) focuses on the immune response by human antibodies to hyaluronic acid in preeclampsia, one of the main causes of maternal and perinatal morbidity and mortality worldwide. The

authors hypothesize a role for the glycocalyx in the pathogenesis of the disease and discuss the significance of autoantibodies directed against hyaluronic acid as a marker for diagnostics and clinical disease prognosis.

I wish to thank all the authors for their contributions, which made this book possible. I also express my gratitude to the Editorial staff of CRC/Taylor&Francis Group for their helpful support in book preparation and publication. We anticipate that a variety of readers, including glycobiologists, carbohydrate chemists, immunologists, cell- and molecular biologists as well as clinical physicians, will find this book as a useful source of information, ideas and productive speculation to take further steps forward in understanding the impact of glycobiology in human health and disease.

The book is dedicated to my wife Lyudmila (Mila) in appreciation of her loyal support, understanding, patience and generous love during all my years working in science.

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