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Preface

Drs. Harry Schachter and Akira Kobata became 65 years old on 25 February and 17 March, 1999, respectively. This Special Issue is dedicated to these two giants in the field of glycobiology.

KOBATA

During his impressive academic career, Dr. Akira Kobata has given several seminal contributions to structural glycobiology. After receiving his PhD from Tokyo University in 1967, he joined the Section of Biochemistry, Laboratory of Pharmacology, NIH, Bethesda, MD, USA. In the Section of Dr. Victor Ginsburg he carried out fundamental studies on milk oligosaccharides and on the enzymatic basis of blood groups in man. This productive period formed the solid basis for his later work. Upon his appointment in 1971 as Professor and Chairman of the Department of Biochemistry, Kobe University School of Medicine, Japan, Akira Kobata extended his interest to structural studies on the *N*-linked glycans of glycoproteins. At that time, this was a very challenging, but difficult area of research. The methods were not yet sufficiently developed to afford unambiguous results, and it was not surprising when structural investigations on the same glycoprotein by different research groups led to controversial results. This inspired Akira Kobata and his colleagues to improve existing methodology and to develop new methods until reliable results could be obtained on minute amounts of material. A number of foreign scientists came to Kobe to make themselves familiar with the application of these methods.

The appointment of Akira Kobata as Professor and Chairman at the Department of Biochemistry, Institute of Medical Science, Tokyo University, led to an expansion of his research themes. In addition to the structures of *N*-glycans he focused his studies on metabolism, function and pathology of these compounds. He recognised the cell and organ specificity of *N*-glycosylation. He initiated the investigation of rheumatoid arthritis in relation to the structure of the *N*-glycans of IgG. Now a vast amount of data is available, documenting the changes in the IgG-carbohydrate structures of patients suffering from this disease. It is proposed that rheumatoid arthritis is a dysregulated glycosylation disease.

Another fascinating topic concerns alterations in the carbohydrate chains in specific glycoproteins in relation to cancer and metastasis. In this context Akira Kobata studied the glycans of human chorionic gonadotropin (hCG) in a number of patients with trophoblastic diseases like hydatidiform mole, invasive mole and choriocarcinoma. In the case of the malignant transformation in choriocarcinoma, it was concluded that the ectopic expression and alteration of substrate specificity of *N*-acetylglucosaminyltransferase IV in the trophoblast are the decisive features of the altered glycosylation of hCG. For a number of glycoproteins synthesised by the liver, a comparative study was carried out on the structure of their *N*-glycans derived from normal hepatocytes and hepatocellular carcinoma. It could be demonstrated that the altered glycosylation of γ-glutamyltranspeptidase, transferrin and choline esterase from hepatocellular carcinoma is due to enhancement of the *N*-acetylglucosaminyltransferase IV and *N*-acetylglucosaminyltransferase V activities. An important outcome of the comparative studies of normal versus malignant transformed cells lies in the potential use of differences in glycosylation as tools for diagnostic purposes.

In 1993 Akira Kobata was appointed Director of

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the Tokyo Metropolitan Institute of Gerontology and became Professor Emeritus of Tokyo University. This opened new perspectives for glycobiology in the context of gerontology. Since some collaborators joined him in this move, new studies, e.g. aimed at the cerebrospinal system, could quickly start.

Without any doubt, Akira Kobata has profoundly influenced the ideas about structure and function of the glycans of glycoproteins. The solid molecular approach of glycosylation in the framework of normal cell functioning compared to the diseased state has been very fruitful. Many interesting results were obtained and more can be expected. The students he trained in glycobiology will certainly follow the lines of research he has set. It is in this spirit that his 65th birthday can be conceived as another landmark in a great career.

For glycobiology Akira Kobata has also done a lot of additional work in his function as the national representative of Japan in the International Glycoconjugate Organisation and as organiser of the XVth International Glycoconjugate Symposium. In Japan he is a great stimulator of this research area. His editorial activities for various journals are well appreciated. Nationally and internationally his achievements have been recognised with several awards. In particular, the Award from the Japan National Academy of Sciences and the Hudson Award from the American Chemical Society, awarded in 1994, recognised Kobata's outstanding contribution to the glycobiology field.

We sincerely hope that Akira Kobata will continue stimulating and encouraging the advancement of our field.

SCHACHTER

Dr. Harry Schachter's research career spans almost four decades, of which three decades were dedicated to his research in the biosynthesis of complex carbohydrates, in particular glycoproteins. His major contribution can be divided into three different aspects of glycoprotein biosynthesis.

The first aspect mainly deals with the identification of glycosyltransferases that form the core structures of *N*-glycans and *O*-glycans. By using a purified enzyme preparation for each step and rigorously determining the acceptor specificity and the enzymatic products, Harry Schachter demonstrated many critical steps in *N*-glycan biosynthesis. He determined the order of the addition of different *N*-acetylglucosamine residues which will elongate to form side chains or antennas in *N*-glycans. One of these studies dealt with the relationship between *N*-acetylglucosaminyltransferase I and α-mannosidase II, and to other scientists his findings have become a basis for understanding *N*-glycan processing.

One of the other important discoveries by Schachter is the mutually exclusive relationship between two different enzymatic reactions. This is exemplified by his finding that the addition by *N*-acetylglucosaminyltransferase III precludes the reaction by *N*-acetylglucosaminyltransferase V, findings which are important for the understanding of *N*-glycosylation in tumour cells. This pioneering work formed the basis of our understanding of *N*-glycan biosynthesis, as now described in textbooks. This critical contribution extends to the biosynthesis of mucin-type *O*-glycans. Harry Schachter formulated different core structures and their biosyntheses based on his studies. Again, all of us adopted his nomenclature, such as core 1 and core 2, in describing the biosynthesis of *O*-glycans.

The second major contribution by Harry Schachter lies in the identification of the glycosyltransferases that are important in pathophysiological conditions. In the early stages of his career, Schachter developed assays for various serum glycosyltransferases. Using his assays he discovered that the difference between A1 and A2 blood group antigens is due to the difference in the amount of α-*N*-acetylgalactosaminyltransferase. This has been extended to measure various glycosyltransferases in cancer cells. Moreover, Harry Schachter discovered that carbohydrate-deficient glycoprotein syndrome type II is due to a defective *N*-acetylglucosaminyltransferase II gene.

A third, but not least important, aspect of Harry Schachter's contributions is that he is constantly driving the glycobiology field into new directions. This is evident in various studies. In particular, Harry Schachter collaborated with Pamela Stanley to elucidate the glycosylation defect in mutants of Chinese hamster ovary cells. This initial collaboration with and input from Schachter eventually led

Pamela Stanley to obtain many mutant CHO cell lines with a defect in carbohydrate metabolism, which now have become one of the most frequently used resources in our field.

The next important contribution by Harry Schachter is the isolation of cDNA encoding *N*-acetylglucosaminyltransferase I and II. Considering that this was carried out in the late 1980s and early 1990s, his efforts to overcome the obstacles are beyond our imagination. Scientists now know that it is possible to clone a cDNA encoding a glycosyltransferase in low quantity by purification and sequencing the polypeptide. Schachter made pioneering efforts in this regard, which have now been followed by many scientists who have cloned various sulfotransferases and *N*-acetylglucosaminyltransferase III and V, and others. More recently, Harry Schachter together with Jamey Marth was one of the first to knock-out glycosyltransferases and through this process brought Marth into our field. Knocking-out *N*-acetylglucosaminyltransferase II also provides an animal model for studying carbohydrate-deficient glycoprotein syndrome II.

We believe that his most recent work on *Caenorhabditis elegans* glycosylation also comes into this category. His explosive energy in exploring a new frontier is unquestionably demonstrated here.

Harry Schachter has been a kind mentor to the members of our field. Despite his many tireless efforts in research, he also served as President of the Society for Glycobiology, was a board member and even served as a pinch-hitter board member of the Society for Glycobiology. He continues to nurture many of his associates long after they leave his laboratory. In 1997, Harry Schachter was awarded the Karl Meyer Award by the Society for Glycobiology, recognising his excellence and life-time contributions to the field of glycobiology.

Writing this, we cannot help but realise that Akira Kobata and Harry Schachter are living models for our research life. We sincerely hope that both will continue their prosperous research for many years to come.

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Guest Editors