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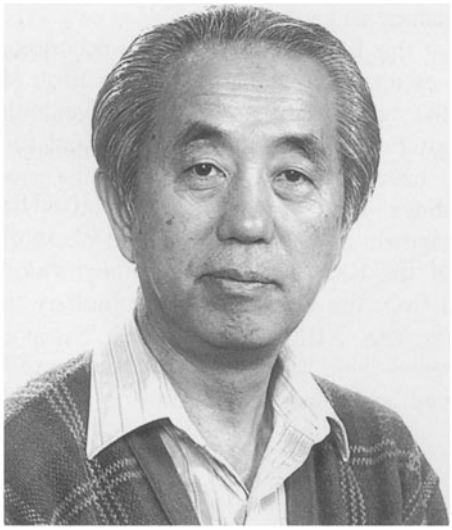
Editorial



Dr Sen-itiroh Hakomori

This issue of the *Glycoconjugate Journal* is dedicated to Dr Sen-itiroh Hakomori, whose 65th birthday was on 13 February 1994. The papers which could not be accomodated in this issue will be published in the next issue.

Dr Sen-itiroh Hakomori was born in Sendai, Japan and obtained his degree as a medical doctor at Tohoku University Medical College, Sendai, in 1951. He started his training in biochemistry the following year in the laboratory of Professor Hajime Masamune, one of the pioneers of glycoconjugate research in Japan, and the chairman of the Department of Biochemistry, Tohoku University School of Medicine. From this early stage of his research career, Dr Hakomori studied glycolipids expressing blood group activity and those present in cancer patients. He went to Dr Roger Jeanloz's laboratory at Massachusetts General Hospital, Harvard Medical School as a Fullbright Scholar in 1956.

After returning to Japan, he became a professor at Tohoku College of Pharmaceutical Science in 1959, where he established a rapid permethylation method for glycolipids (Hakomori's method), published in 1964, and now a 'citation classic'. Despite the fact that Dr Hakomori spent the majority of his research career in the USA, it is obvious that his enormous contributions have their roots in Japan. He rejoined Jeanloz's group in 1964, and held a faculty position at Brandeis University from 1966–68. Since 1968, he has been a faculty member at the University of Washington, Seattle, with joint appointments at Fred Hutchinson Cancer Research Center (1975–87) and The Biomembrane Institute (1987–present).

The first field in which Dr Hakomori made major contributions is the structural analysis of glycolipids from normal and cancer cells. The first critical discovery was made by comparing glycolipid compositions of fibroblasts and their polyoma virus-transformed counterparts. He showed that tumour cells express precursor glycolipids in much greater abundance than their normal counterparts [1]. This line of study was extended to the analysis of glycolipid composition during the cell cycle. Hakomori and Carl Gahmberg established a method that allows specific labelling of cell surface glycoproteins and glycolipids. Using this method, they discovered 'galactoprotein a' (now called fibronectin), which disappears in transformed cells [2].

Hakomori's group was involved in determining anomeric structures of globo-series glycolipids (e.g. globoside, Forssman antigen) and later various lacto-series glycolipids. They carried out studies incorporating exoglycosidase in collaboration with Yu-Teh Li, and release of N-acetyllactosamine by endo-β-galactosidase in collaboration with Michiko Fukuda. This work provided important advances in structural and functional analysis of lacto-series glycolipids. We still remember clearly how their meticulous studies revealed a GalNAcα1 $\rightarrow$ 3GalNAc structure in a Forssman glycolipid, rewriting the method of structural analysis of glycolipids [3–5]. Hakomori and his colleagues, in particular Kiyohiro Watanabe and Roger Laine, established that complex glycolipids contain N-acetyllactosamine branches attached to C-6 of galactose [6]. This led to further discoveries on ontogenic changes in human erythrocytes. First, they found that fetal erythrocytes contain much less of these branched glycolipids than do adult erythrocytes [7]. This led to the discovery that fetal erythrocytes contain i-antigen, composed of linear poly-N-acetyllactosamine, whereas adult erythrocytes express I-antigen, composed of heavily branched poly-N-acetyllactosamine [8, 9]. These studies, done in collaboration with Ten Feizi, K. Watanabe,

Minoru Fukuda and Michiko Fukuda, demonstrated for the first time that carbohydrate structures are responsible for antigenic changes during ontogeny.

Subsequent studies with Reiji Kannagi and Bruce Fenderson in his laboratory revealed that the earliest antigen expressed during ontogeny was a novel type of extended globo-series structure [10], and that this was subsequently replaced by lacto-series and then ganglio-series structures [11].

Further studies on blood group antigens (involving Henrik Clausen and Steven Levery) established a novel 'repetitive A' structure as A_1 antigen [12], and 'A-associated H' as A_2 antigen. The research on ABO antigens culminated in the cloning of cDNAs encoding A and B transferases. This work, by Fumi Yamamoto and Henrik Clausen, showed that A and B enzymes have almost identical sequences, whereas the corresponding gene in O individuals has a frame shift resulting in synthesis of a non-functional protein [13].

The concept that some glycolipids found at high levels in tumours could be 'tumour-associated antigens' was originally based on the observed accumulation of Le^x glycolipid in various types of human cancer [15] and accumulation of asialo-GM2 in mouse sarcoma [14]. These early studies utilized polyclonal antibodies for detection of antigen; the monoclonal antibody approach was not yet commonly available. William Young and Hakomori reported the first isolation of monoclonal antibodies (mAbs) specific to tumour-associated glycolipids [15], and showed eradication of mouse tumours by IgG_3 but not IgM mAbs directed to Gg3Cer [16]. During the 1980s, Hakomori's group produced a variety of human and mouse mAbs specific to tumour-associated glycolipid antigens. Some of the mouse mAbs established by Yasuo Fukushi [17] were used to define sialyl-Le^x, dimeric Le^x, Le^y and extended Le^y as tumour-associated antigens, in collaborative studies with Paul Terasaki and Young Kim [18, 19]. For the series of studies on the role of glycolipids in tumour development, Hakomori received the prestigious Asahi Prize (Japan) in 1991.

Hakomori's group has pioneered research of glycolipid function, a field still in its infancy. They published a paper entitled 'Possible role of ceramide in defining structure and function of membrane glycolipids' in 1982 [20]. This very original and insightful concept was developed extensively in later years. Hakomori, in collaboration with Eric Bremer and Russell Ross, reported that gangliosides are involved in modulation of tyrosine kinase associated with growth factor receptor [21]. This principle was applied to other kinases, leading to the conclusion that glycolipids in general function as modulators of various kinases involved in transmembrane signalling.

In other glycolipid function studies, Hakomori, Naoyo Kojima and Ivan Eggens introduced the concept of carbohydrate–carbohydrate interaction of glycolipids on the surfaces of two adjacent cells [22, 23] as a basis for cell–cell recognition, adhesion, etc. This attractive hypothesis has been slow to catch on among cell biologists, but has been supported by several recent studies from other laboratories.

The roles of sphingosine and its derivatives in control of signalling associated with cell proliferation, differentiation, motility and apoptosis have been explored in a series of collaborative studies with Yasuyuki Igarashi, Yoshito Sadahira and others e.g. [24].

Looking at this brief summary of his accomplishments, one cannot escape from feeling that Sen-itiroh Hakomori is one of the 'giants' in the field of glycobiology. His systematic studies on structure, synthesis and function of glycolipids have provided an astonishing variety of crucial findings, long before other scientists have been able to recognize or appreciate them. Hakomori is well deserving of the Karl Meyer International Award which he received from the Society of Glycobiology in August 1995 during the XIIIth International Symposium on Glycoconjugates held in Seattle, Washington. We wish him continued health and productivity in the years ahead.

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On behalf of the Editorial Board and publishers of Glycoconjugate Journal, I wish to thank Drs. Minoru Fukuda and Yu-Teh Li for their expert help in organizing the special issue in honour of Dr Sen-Itiroh Hakomori. I also would like to add my own personal congratulations to Dr Hakomori for his many superb contributions to our discipline and to wish him many more years of health and productive work. The respect we all have for Dr Hakomori is clearly reflected in the large number of manuscripts we received for this special issue. Unfortunately, we cannot publish all of them in a single volume. The remaining papers will appear in issue number 3, 1996, of Glycoconjugate Journal.

Harry Schacter
Chief Editor

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