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Introduction to the special issue 'Glycobiology of cancer'

This special issue "Glycobiology of cancer" has been dedicated to Professor Hans Paulsen, University of Hamburg, Institute of Organic Chemistry, Hamburg, Germany, in appreciation for his tireless work to provide the basic tools for studies of the glycobiology of cancer, and to Professor Joyce Taylor-Papadimitriou, Cell Biology, Imperial Cancer Research Fund, London, England, for her pioneering work on cancer cell surface glycoproteins. Both have been my respected teachers, valued colleagues, wonderful friends and mentors.

As a carbohydrate chemist always interested in new avenues and applications of his work, Hans Paulsen has developed synthetic methods and produced hundreds of unique novel carbohydrate derivatives. Some of these compounds have been identified as glycosidase inhibitors, or have been used to study cancer cell enzymes, the properties and structures of cancer cell surfaces, functions of the immune system or were used to develop cancer vaccines. A short overview of the eminent contributions of the Paulsen laboratory to glyco-chemistry is found in the minireview 'From iminosugars to cancer glycoproteins' of this issue.

Hans Paulsen became professor at the Department of Organic Chemistry and Biochemistry at the University of Hamburg in 1968. Since then, he has received many prestigious honours and awards, including the Emil Fischer Award of the German Chemical Society, the Haworth Memorial Medal of the Royal Chemical Society and the Claude Hudson Award of the American Chemical Society. As a carbohydrate chemist, Professor Paulsen has published about 500 scientific papers and has been invited to many Universities as a guest professor where he helped to develop carbohydrate chemistry and glycobiology with his knowledge, solid expertise and practical ideas. He has the ability with patience and perseverance to find a solution to most seemingly insoluble problems. Perhaps the most important achievement of Hans Paulsen has been the rigorous training of PhD students. Many of these are now in prominent positions at Universities and in the chemical industry, working on all aspects of carbohydrate science. Although carbohydrate chemistry has guided Hans Paulsen's life, he has also found great pleasure in ancient cultures, history, travels and music. Those that know him well have thoroughly enjoyed his lectures and slide shows of travels to foreign countries.

Hans Paulsen has established a broad base of expertise that is invaluable for the acquisition of knowledge on the glycobiology of cancer. The methods developed in the Paulsen lab led to the synthesis of carbohydrates that we have used as substrates and standards for product identification in our studies of enzymes altered in cancer cells. These enzymes include polypeptide GalNAc-transferase, core 1 β3-Gal-transferase, core 2 β6-GlcNAc-transferase and α3-sialyltransferase involved in the synthesis of mucin-type O-glycans, and GlcNAc-transferases I to V required for the synthesis of complex N-glycan antennary structures. Many of Paulsen's synthetic oligosaccharides or glycopeptides have been used to map the detailed substrate recognition of glycosyltransferases, to detect novel enzyme activities, or to synthesize affinity reagents for enzyme purification. In addition, synthetic substrate analogs have the potential to inhibit enzymes in cancer cells with the possibility of changing cell surface glycosylation and biological properties of the cell, either as glycosyltransferase inhibitors or as competitive substrates (primers).

A series of glycopeptides derived from mucin tandem repeat regions helped to show that O-glycosylation is a complex process where the addition of individual sugars to glycopeptide substrates depends on the structure of the peptide moiety at each O-glycosylation site, as well as on neighbouring glycan structures. Thus the individual enzymes involved in the processing of O-glycans are directed differently by the glycopeptide structure near the sugar attachment site. In cancer cells expressing a different spectrum of glycoproteins, this 'site directed processing' of O-glycan chains can thus result in novel cancer-associated glycosylation patterns.

The Paulsen lab was the first to study sugars by temperature-dependent NMR spectroscopy, and has been instrumental in promoting research of the glycopeptide conformations by NMR and theoretical calculations. This field of science is most important in obtaining knowledge of the mechanisms of biosynthetic regulation and functions of cancer cell surfaces. Immune surveillance is considered an important defence against cancer. Paulsen's group has synthesized oligosaccharides and glycopeptides which mimic mucin structures; such compounds have potential use as cancer vaccines and stimulators of T cell responses. This and other projects have brought Hans Paulsen and Joyce Taylor-Papadimitriou together as collaborators.

The group headed by Joyce Taylor-Papadimitriou cloned the first cell surface mucin MUC1, and has since worked on the mechanism and functions of cancer cell surface glycosylation. Her accomplishments have been acknowledged with several prestigious awards and prominent positions. As a scientist, J. Papadimitriou has had extensive experience in areas ranging from peptide

chemistry and enzymology to molecular and cell biology and immunology. We share an interest in the control of enzymes that assemble cancer mucin glycoproteins.

Joyce Taylor graduated from the Biochemistry Department in Cambridge, and then moved to Toronto, Canada, where she completed her PhD work in microbiology and gained experience in making vaccines and working with viruses. Back in England in the 1960s, Joyce, elegantly and importantly, showed that interferon (IFN) affected RNA and protein expression which led to protection against viral disease. Not surprisingly, she maintained a life long interest in IFN and cytokine responses.

After a boat trip in Greece, a special Greek by the name Papadimitriou received her full attention which resulted in an intensive search for science and research in Greece. She found a research position and was able to add peptide synthesis to her already broad expertise. In addition, she started her own virology lab in Thessaloniki and pursued her previous research interests, for example, the synthesis of IFN.

These years were an important preparation for Joyce Taylor-Papadimitriou's position at the ICRF in London where she found her niche as a breast cancer researcher. Joyce has made fundamental contributions to our understanding of the role of mucin glycosylation on breast cancer cell surfaces. She has been able to combine the fields of biochemistry, enzymology, molecular biology, immunology and structural analysis of glycans to characterize the phenotypes of cancer cell surfaces, their mucins and the antibodies directed against them. Of particular value were the findings that cancer patients carried antibodies against specific breast cancer mucin epitopes, with the likelihood of a therapeutic immune response to cancer cell surface mucins. We now know that specific enzymes regulate the appearance of cancer cell surface mucin epitopes recognized by antibodies. Elegantly, the Taylor-Papadimitriou team showed by transfection and other studies that branching reactions compete with sialylation to shape the cancer-associated phenotype. Joyce's lab has also studied patient samples and concluded that the α3-sialyltransferase expression is also elevated in vivo which corresponded to the in vitro results. These observations have been the basis for immunological studies in animal models, for clinical studies, and the development of immunotherapy for breast cancer. Glycopeptide mimics of breast cancer antigens have been synthesized and tested in vitro and in vivo as stimulators of immunity such as T cell responses. Current and future work will hopefully show how these cancer epitopes influence cell-cell interactions of cancer cells, their ability to survive and metastasize in the breast cancer patient, and to trigger intracellular signaling and induction of growth and apoptosis.

Thus carbohydrate chemistry and cancer biology are two complementary areas of research that are pillars of the glycobiology of cancer. This issue shows a diversity of approaches all contributing to our understanding of the biological roles of cancer glycoproteins. We highly value the contributions of Hans Paulsen and Joyce Taylor-Papadimitriou. We wish them the very best for future health and success, and hope that they will never retire from research.

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