Glycoconj J (2006) 23: 3–4
DOI 10.1007/s10719-006-5432-1

Editorial

Prof. José Antonio Cabezas Fernández del Campo's 75th birthday and his seminal contributions to the field of glycobiology and especially to the sialidases and esterases, as well as the awareness of the growing importance of our need to understand the host-parasite interactions for coping with the possible dangers of infections by these microorganisms prompted us to gather first-hand articles for this special issue of *Glycoconjugate Journal* on "Viruses and Sialic Acids". We dedicate this special issue to Prof. Cabezas, who by his recent contribution "Nuevos datos acerca del virus causante de la pandemia de gripe de 1918–19 y su relación con los de la gripe aviar. Datos recientes relatives a èstos" (Anales de la Real Academia Nacional de Farmacia 71:83–110 (2005)) shows the timeliness of the publication of these papers. Pablo Hueso and Enrique Villar Ledesma report on Prof. Cabezas' personal history.

To initiate an infection, viruses have to come into close contact with their target cells. Depending on the route of infection, viruses must cross barriers like the skin, the extracellular matrix or mucosal membranes. On that way, viruses encounter numerous carbohydrates, and even the target cells themselves are covered with glycoproteins and glycolipids. Especially among those viruses which use the oro-nasal route of infection many have been found to specifically interact with sialic acids.

Sialic acids are a large family with about 50 members of C-9 sugars in most cases representing *N*- and *O*-acyl derivatives of neuraminic acid. In 1955 Ernst Klenk and coworkers identified sialic acid as receptor for influenza A viruses, which had been observed on chicken erythrocytes by George Hirst in 1942. This led to the discovery of the receptor-destroying enzyme (RDE) of these viruses, denominated first neuraminidase and later sialidase, in 1946 by Frank Macfarlane Burnett (for a review of earlier work see A. Gottschalk (ed.) "The Chemistry and Biology of Sialic Acids and Related Substances", Cambridge University Press, 1960).

Over the years sialic acids were found to represent receptors or co-receptors for many other viruses. In the laboratory of Prof. José Antonio Cabezas Fernández del Campo at the University of Salamanca (Spain) several scientists were involved in research on viruses and sialic acids. Among those, Enrique Villar Ledesma and Isabel Munoz Barroso spent much of their time for investigations on the hemagglutinin-neuraminidases (HN) of paramyxoviruses. Their detailed review on the "Role of sialic acid-containing molecules in paramyxovirus entry into the host cell" is a strong indicator that "Glycovirology" became a well established field in Salamanca. In the review by Gee *et al*. we learn that the human polyomavirus JC virus uses the serotonergic receptor 5-HT_{2A}R and α2,6-linked sialic acid for initiation of infection. JC virus and BK virus infect approximately 85% of the human population. Under normal conditions, they are not associated with disease. However, a fatal demyelinating disease caused by destruction of oligodendrocytes in the brain by JC virus is a major concern for immunocompromised patients like HIV-infected persons. BK virus is involved in the loss of graft function in renal transplant recipients. Rotaviruses, the major cause of gastrointestinal infections in young children, also adopted strategies to use sialic acids for infection. In the review by Isa *et al*. the current knowledge on the interactions between viral proteins and sialic acids is discussed.

The ability of the cardiovirus Theileŕs murine encephalomyelitis virus (TMEV) to cause a demyelinating disease made it a model virus to study human multiple sclerosis. TMEV strains are known for their ability to use either heparan sulfate or sialic acid as receptor determinants. In the review by Lipton *et al*. it is described how "low neurovirulence strains" use α2,3-linked sialic acids.

Coronaviruses also use sialic acids as receptor determinants. Schwegmann-Weßels and Herrler focus in their review on the receptor usage of sialic acids of two swine viruses, the transmissible gastroenteritis virus (TGEV) and the porcine respiratory coronavirus. Both viruses are closely related. By gaining additional amino acids, the spike protein of TGEV acquired the ability to use sialic acids, which presumably resulted in a more dangerous virus causing lethal infections in piglets. Moreover, this review also covers new findings on the ability of the highly lethal avian infectious bronchitis virus to use sialic acids. In addition, Herrler's group was among the first to find sialate-*O*-acetylesterases as a new type of receptor-destroying enzymes in group 2 coronaviruses. Raoul de Groot provides a comprehensive review on nidoviral receptor-destroying enzymes. In this paper the newly discovered sialate-*O*-acetylesterases of toroviruses are presented. These enzymes specifically use either *N*-acetyl-9-*O*-acetylneuraminic acid (Neu5,9Ac_2), *N*-acetyl-4-*O*-acetylneuraminic acid (Neu4,5Ac_2) or *N*-acetyl-7(8),9-di-*O*-acetylneuraminic acid (Neu5,7(8),9Ac_3) as substrates. Thus, the number of receptor-destroying enzymes increased to four. Moreover, the genetic basis for horizontal gene transfer of the viral genes encoding sialic acid binding and destroying proteins and the consequences for host- and tissue tropism are discussed. In the first of a series of original research papers of this special issue, Rinninger *et al.* investigated the occurrence and distribution of sialic acids in mice. Using a new mass spectrometric technology developed by J.-P. Zanetta, 13 different neuraminic acid derivatives were found in murine tissues, which are infected by murine coronaviruses.

The newly emerging avian influenza viruses are a major concern for public health. While avian viruses preferentially use α2,3-linked sialic acids, human influenza A viruses specifically bind to α2,6-linked sialic acids. A change in their host specificity might result in the onset of a forthcoming influenza virus pandemic. In the manuscript by Russell *et al*. the structural basis for the receptor specificity towards specific glycosidic linkages is shown. The authors determined the crystal structure of the H7 hemagglutinin of influenza A/turkey/Italy/02 virus complexed with a receptor analogue and compared it with the structures of H1, H3, an H5 hemagglutinins. Their manuscript provides the structural basis for the specificity of avian hemagglutinins for α2,3-linked sialic acids. Adolfo Garcia-Sastre, who formerly also worked with Prof. Cabezas, provides a manuscript on the receptor specificity for α2,3-linked sialic acids of an influenza H2N2 virus recently isolated from chicken in North America. In the manuscript by Kogure *et al.* it is described that the laboratory of Yasuo Suzuki investigated the reasons why avian influenza viruses sporadically infect humans. They found, in extension to an earlier work from Matrosovich, that undifferentiated human bronchial epithelial cells express both α2,3-linked and α2,6-linked sialic acids, thereby further explaining the susceptibility of humans to infections by avian influenza A viruses. Matrosovich *et al.* contribute a manuscript with important new data on the discussion whether gangliosides are essential or dispensable for infection by influenza A viruses. The laboratory of Nicolai Bovin presents results indicating that influenza A and B viruses do not completely rely on sialic acids as receptors. The manuscript by Rapoport *et al.* suggests that 6-sulfated *N*-acetyllactosamine may represent an alternative receptor determinant.

Inhibitors against infections by influenza A and B viruses are already available: the sialic acid-based Relenza^{TM} and the *pseudo*-carbohydrate Tamiflu^{TM} are clinically effective anti-influenza drugs. In order to be prepared for potential forthcoming resistance of influenza viruses to these medicaments, the laboratory of Mark von Itzstein is already preparing new antivirals based on modified *N*-acetylglucosamine. In the manuscript by Mann *et al.,* several sialidase inhibitors are shown to be effective *in vitro*. Last, but not least, the laboratory of Garry Taylor investigated the 3D structure of the HN of the paramyxovirus Newcastle disease virus with a designed inhibitor, which contains a benzyl group added to the O4 position of the naturally occuring inhibitor 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (Neu5Ac2en). The manuscript by Ryan *et al*. discusses the structural differences in the sialic acid binding sites of influenza virus neuraminidases and paramyxovirus HN proteins and shows new ways to develop inhibitors against human paramyxoviruses.

Roland Schauer
Biochemisches Institut,
Christian-Albrechts-Universität, Olshausenstr. 40,
D-24098 Kiel,
Germany
E-mail: schauer@biochem.uni-kiel.de
Reinhard Vlasak
Applied Biotechnology,
Department of Cell Biology, University Salzburg,
A-5020 Salzburg,
Austria
E-mail: rvlasak@applied-biotech.at