

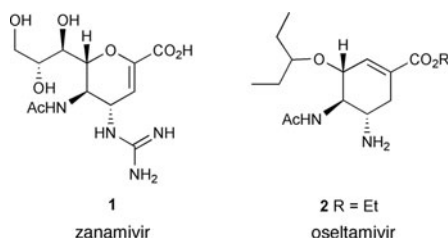
# Preface

Influenza virus remains a significant threat to humanity [1] despite the discovery of novel antiviral therapies and the continuing development of seasonal vaccines. Annual influenza epidemics exact a high toll in morbidity, estimated to be in the range of three to five million cases of severe illness, and mortality, with up to half a million deaths worldwide [2]. The twenty-first century's first influenza pandemic caused by the commonly referred 'swine flu' virus strain (H1N1) 2009 has had major economic impact across the world and accounted for 414,000 confirmed cases and 5,000 deaths worldwide [3]. Human infection with the highly pathogenic avian H5N1 influenza A virus accounted for 552 confirmed cases and 322 deaths worldwide between 2003 and 2011 [4]. A recent study has estimated that a human-to-human transmissible, highly pathogenic, pandemic influenza virus could lead to ~62 million deaths worldwide [5]. The prevalence of oseltamivir-resistant influenza A(H1N1) viruses increased to 99% in many countries during 2008–2009 flu season [6] and recent isolation of oseltamivir-resistant [7] H5N1 *thus necessitate the continued development of alternative antiviral agents.*

In this edited volume, Klenk provides an excellent review on the virology of influenza virus and its pathogenesis. As introduced in this particular contribution influenza virus sialidase (neuraminidase EC 3.2.1.18) is an enzyme (an *exo*-glycosidase) and is a tetrameric glycoprotein that consists of four identical subunits [8] anchored to the viral membrane by a long thin stalk. This enzyme effectively acts as a pair of biological scissors cleaving  $\alpha$ -ketosidically linked sialic acids from glycoconjugates [8]. This enzyme action facilitates both the movement of virus particles through the upper respiratory tract, and, importantly, the escape of virion progeny from the surface of infected cells [8–11]. The essential nature of the influenza virus sialidase in the virus' life cycle makes it an ideal drug discovery target.

In subsequent contributions, Nicholls and colleagues provide an invaluable overview on the characterisation of carbohydrate recognition by influenza virus and a detailed analysis of virus tropism, Chan and Bennet elaborate on sialidase enzymology and Dyason and von Itzstein provide an up-to-date discussion on recent developments in influenza virus sialidase structure-based drug design.

Influenza virus sialidase [8] targeted anti-influenza drug discovery and development has used structure-assisted drug design to discover the first highly potent influenza virus sialidase inhibitor that mimics characteristics of the putative enzyme transition state: zanamivir (Relenza<sup>®</sup>) **1** [12, 13] and subsequently oseltamivir (Tamiflu<sup>®</sup>) **2** [14] are now marketed for treatment and prophylaxis of influenza virus infection. The worldwide stockpiling of these two antiviral drugs as part of pandemic preparedness highlights the overall importance of influenza virus sialidase inhibitors.



Substantial chemical methodologies have been developed in the discovery of both zanamivir [13] and oseltamivir [14]. The recent chemistries associated with carbohydrate-based and non-carbohydrate-based influenza virus sialidase inhibitor discovery are described, in good detail, by Thomson and von Itzstein and Streicher and Stanley, respectively. Both contributions highlight the latest approaches towards the synthesis of influenza virus sialidase inhibitors.

In the clinical setting, both zanamivir and oseltamivir are effective in both the prevention and treatment of influenza A and B infection. Benefit in treatment is typically restricted to patients treated within 48 h of symptom onset [15]. The influenza virus surface glycoproteins haemagglutinin and sialidase continually undergo natural and antibody-induced antigenic drift [16]. However, as the active site residues of influenza virus sialidase that are involved in interactions with the designed sialidase inhibitors are highly conserved, it was hoped the likelihood of variants with uncompromised infectivity and transmissibility would be reduced. The final two contributions by Buchy and Naffakh and colleagues provide excellent insight into the clinical experience of influenza virus sialidase targeting anti-influenza drugs and the complications of resistance development to these drugs respectively.

In summary, in the first part of this edited volume readers are provided with an excellent and comprehensive multi-disciplinary overview of (1) influenza virus sialidase as an essential enzyme in the lifecycle of the virus, (2) the importance of carbohydrate recognition phenomena for successful virus infection of host cells, (3) influenza virus sialidase enzymology and (4) influenza virus sialidase structure-based drug discovery. Furthermore, in the second part the reader is provided with a substantial review of the chemistry associated with influenza virus sialidase inhibitor development, the importance of the lead anti-influenza drugs zanamivir and oseltamivir in a clinical setting and the potential of the virus to develop resistance to the first-line-of-defence anti-influenza drugs.

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