UMEÅ UNIVERSITET

Tailored conjugates of *N*-acetylneuraminic acid and small molecules that block virus cell attachment and entry

Emil Johansson

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Glasburen, Kemiskt Biologiskt Centrum,
fredagen den 21 maj, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor, PhD, Gert-Jan Boons,
University of Utrecht, Utrecht, Netherlands.

Department of Chemistry

Organization
Umeå University
Department of Chemistry

Document type
Doctoral thesis

Date of publication
21 May 2021

Author
Emil Johansson

Title
Tailored conjugates of *N*-acetylneuraminic acid and small molecules that block virus cell attachment and entry.

Abstract
Viruses are obligate intracellular parasites, unable to replicate without exploiting machinery and materials from host cells. Pandemics of viral diseases have had large impacts on human socieities and are continued threats to global health. The most efficient means of controlling viral diseases are preventive measures such as immunization of the population, social distancing, and basic hygiene routines. Another mean is development of antiviral drugs that could be used as preventive measures and in treatment of infected individuals. Coxsackievirus A24 variant (CVA24v) is a highly contagious pathogen that cause large outbreaks and pandemics of the eye infection acute hemorrhagic conjunctivitis. Human adenovirus D species type 37 (HAdV-D37) causes epidemics of the severe eye infection epidemic keratoconjunctivitis, that can become life-threatening in immunocompromised individuals. Currently, no specific treatments (vaccine or antivirals) are available to combat the diseases caused by these two pathogens.

CVA24v and HAdV-D37 bind to *N*-acetylneuraminic acid (Neu5Ac) glycans on host cells facilitating attachment and subsequent infection. In this thesis, we explored inhibition of this common recognition motif by development of pentavalent Neu5Ac containing molecules with radial topology to act as decoy receptors. This allowed us to study the potential of development of a general inhibitor targeting both these viruses. The developed compounds inhibited attachment of CVA24v and HAdV-D37 to cells. Furthermore, we developed divalent Neu5Ac tools to validate if targeting the Neu5Ac-mediated attachment of CVA24v to cells were a potential target for antiviral drug discovery and development. The results from these studies indicate that development of a Neu5Ac-based antiviral targeting CVA24v looks bleak as the primary receptor utilized by this virus is ICAM-1. The work with developing Neu5Ac tools led to a side project with synthesis of 4-*O*-alkyl Neu5Ac analogs. In this project we provided a method to synthesize 4-*O*-alkyl analogs of Neu5Ac and gave insights into the scope of the reaction. This work could have have value in drug discovery.
Targeting enterovirus uncoating is a well explored strategy for the inhibition of enterovirus infection. In this thesis, we synthezied novel branched probes of pleconaril (a well-known pocket binding molecule) to study if targeting the unique branched pocket of CVA24v could have potential as a target for antiviral drug discovery. Further experiments are needed to draw conclusions in regards to the future prospects of targeting this unique feature.

At last, two novel classes of trivalent Neu5Ac conjugates were develop using a structure-based approach targeting HAdV-D37, -D36, and -D26. This led to a more potent compound towards HAdV-D37 further validating that targeting the attachment of this virus to cells is a reasonable strategy for antiviral drug development. Towards HAdV-D26 the inhibitory effect was saturated at 50%, likely due to engagement of other receptors. Evaluation towards HAdV-D36 is currently ongoing. Structural biology studies, indicates the compounds bind to the viruses via chelation of their trimeric binding sites. Taken together, these compounds have potential to be used as chemical tools to study the biology of human adenoviruses and perhaps other Neu5Ac binding proteins.

Keywords
N-acetylneuraminic acid, Neu5Ac, sialic acid, multivalency, Coxsackievirus A24v (CVA24v), Human adenovirus D37, D36, D26, (HAdV-D37, HAdV-D26, HAdV-D36), 4-*O*-alkyl Neu5Ac, cryo-EM, branched pleconaril probes, conjunctivitis

Language
English

ISBN
print: 978-91-7855-566-6
PDF: 978-91-7855-567-3

Number of pages
91 + 6 papers