Oral Session 6: Other Viruses, Veterinary Viruses and Late Breaker Presentations

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Use of Antivirals for Control of High Consequence Animal Diseases

Daniel L. Rock

University of Illinois at Urbana-Champaign, Urbana, USA

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Design, Synthesis and Evaluation of 3-Ethynyl-Azole Nucleosides with Antiviral Activity Against Hantaviruses

Jeffrey Arterburn[1,*], Sidath Kumarapperuma[1], Marjan Jeselnik[1], Dong-Hoon Chung[2], Yangie Sun[2], Willaim Parker[2], Yong Kyu Chu[2], Colleen Jonsson[2]

[1] New Mexico State University, Las Cruces, USA; [2] Southern Research Institute, Birmingham, USA

Hantaviruses are negative stranded RNA viruses that cause two acute febrile diseases in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Currently there are no FDA approved drugs for the treatment of HFRS and HPS caused by hantaviruses. Clinical studies with HFRS patients have indicated improved prognosis from early treatment with the broad-spectrum antiviral drug ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), however, limited trials for HPS have not shown efficacy. We have explored chemical modifications of the 1,2,4-triazole scaffold in attempts to increase selectivity and activity for the viral L protein. We recently synthesized a new nucleoside analog with antiviral activity, 1-β-D-ribofuranosyl-3-ethynyl-[1,2,4]triazole (ETAR). ETAR showed an EC_{50} value of 10 and 4.4 mM for Hantaan virus (HTNV) and Andes virus, respectively. In order to define the structure–activity relationship and mechanism of action we designed, modeled and synthesized a series of isosteres, homologated analogs, and substituted derivatives that possess altered steric and hydrogen-bonding profiles. The antiviral activity of these compounds was evaluated in vitro against Hantaan virus and Andes virus. The potential for metabolic conversion of these compounds to the monophosphate by human adenosine kinase (hADK) was determined using an in vitro biochemical assay. Computational docking studies were used to characterize the binding of this series with hADK, and these results correlated with experimental values for hADK activity. These results provide a structural basis for the antiviral activity of this promising class of compounds against hantaviruses.

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A Derivate of the Antibiotic Doxorubicin Inhibits Dengue and Yellow Fever Virus Replication *In Vitro*

Suzanne Kaptein[1,*], Michael Jacobs[2], Andrea Gamarnik[3], Erik De Clercq[1], Ferenc Sztaricskai[4], Johan Neyts[1]

[1] Rega Institute, Leuven, Belgium; [2] Royal Free and University College Medical School, London, United Kingdom; [3] Fundacion Instituto Leloir, Buenos Aires, Argentina; [4] University of Debrecen, Debrecen, Hungary

Doxorubicin is an antineoplastic antibiotic obtained from *Streptomyces peucetius*. We report that doxorubicin exhibits *in vitro* antiviral activity against flaviviruses, i.e. the yellow fever virus (17D strain) ($EC_{50} < 0.78$ μg/ml) and dengue virus (type 2 NG strain) ($EC_{50} = 0.9$ μg/ml). However, doxorubicin proved also cytotoxic in the uninfected host cells and is thus not very selective as an antiviral agent. We identified a novel derivate of doxorubicin, SA-17 with excellent antiviral activity against DENV ($EC_{50} = 0.2$ μg/ml) and that was markedly less cytostatic than the parent compound. SA-17 also inhibited YFV-17D replication, although less efficiently than DENV replication. SA-17 proved inactive against viruses other than flaviviruses (bovine viral diarrhea virus, Coxsackie virus B3, HIV, and HSV-1: $EC_{50} > 100$ μg/ml). A dose-dependent anti-DENV activity was confirmed using a dengue reporter virus, i.e. infectious full-length dengue virus that expresses *Renilla* luciferase. Time-of-drug addition studies indicated that SA-17 acts at an early stage of the replication cycle. This hypothesis was confirmed in experiments using BHK cells harboring the DENV subgenomic replicon that only consists of the non-structural genes of the virus (NS1–NS5). SA-17 was unable to inhibit the replication of the replicon and thus, does not work at the level of the viral replication machinery. Further studies revealed that SA-17 exerts it activity *via* a virucidal effect, even when using very high titers of the virus as the inoculum. Likewise, doxorubicin was also shown to inhibit DENV replication by a virucidal mechanism, but the virucidal effect of the parent compound was less pronounced than that of SA-17. Further studies are ongoing to unravel the precise mechanism by which SA-17 exerts its virucidal effect on flaviviruses.

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One-third of the Surface of the Adenovirus Proteinase Contains Potential Drug Targets via a New Paradigm for Virion Maturation

Walter Mangel

Brookhaven National Laboratory, Upton, USA

Late in adenovirus infection, inside young virions, the adenovirus proteinase (AVP) becomes activated by two viral cofactors enabling it to cleave virion precursor proteins thereby rendering the virus particle infectious. How this occurs reveals that more than one-third of the surface of AVP contains potential therapeutic targets. AVP is activated in part upon the binding