study suggests that these novel imino sugar derivatives may offer realistic candidates for the development of antiviral therapeutics against human dengue virus infection.

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Using the C57BL/6 and SKH1 Strains to Evaluate the Efficacy of CMX001 Following Lethal Respiratory Infections with Ectromelia Virus

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We are currently faced with the potential use of variola and monkeypox viruses as biological weapons, as well as the natural emergence of human MPXV. Such outbreaks would require therapeutic and prophylactic intervention with antivirals. Cidofovir, an antiviral approved for the treatment of cytomegalovirus retinitis in AIDS patients, has activity against poxviruses, but must be administered intravenously and is associated with nephrotoxicity. An ether lipid analogue of CDV, CMX001 (HDP-CDV), has excellent oral bioavailability, minimal nephrotoxicity, and potent in vitro and in vivo antiviral activity against poxviruses. Furthermore, the ST-246 antiviral has also been shown to be efficacious at preventing lethal respiratory infections in mice. Using the A/Ncr and C57Bl/6 mousepox model we have evaluated the optimal, delayed, dosing regimen of CMX001 required for providing protection following a lethal intranasal challenge. Furthermore, we have evaluated biomarkers to stage disease progression and monitor the efficacy of a single dose treatment with CMX001. Ectromelia virus infections of the A/Ncr and C57BL/6 mice result in a highly fulminant diseases with rapid mortality before the onset of rash, whereas human respiratory infections with variola and monkeypox viruses typically result in death after onset of rash. Here we describe a mousepox model using the SKH1 mouse strain that results in an extended disease course with the majority of deaths occurring after the onset of rash. To our knowledge this is the first description of a lesion model of mousepox following a respiratory infection. We also show that rash development in this model can be used to initiate efficacious CMX001 treatment.

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Novel 9-Arylpurines, as Selective Inhibitors of *In Vitro* Enterovirus Replication

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Enteroviruses (family of the Picornaviridae) are implicated in a wide spectrum of illnesses ranging from mild respiratory syndromes, herpangina, hand-foot-mouth-syndrome and common cold to potentially life-threatening disorders such as pancreatitis, myocarditis, meningitis, encephalitis and exacerbations of COPD and asthma. A number of 9-arylpurines have been identified as selective inhibitors of the replication of various enteroviruses. A representative example of this series of compounds is 9-(3-acetylphenyl)-6-chloropurine [TP219] that emerged as one of the most potent congeners in this series. The antiviral activity against Coxsackievirus B3 of TP219 was further assessed by (i) MTS-based CPE assays, (ii) virus yield reduction assays, (iii) real-time quantitative PCR and (iv) antigen detection. Also potential effects of the compound on the accumulation of viral (+)ssRNA and on polyprotein processing were determined. Drug-resistant variant were selected that were at least a 10-fold less susceptible to TP219 than the wild-type virus. TP219 did not prove cross-resistant to other classes of enterovirus inhibitors (including 3A, 2C and a 3D inhibitor). Genotyping of the drug-resistant variants revealed that 2–3 mutations, both in genes encoding for structural and non-structural proteins, may be responsible for the drug-resistant phenotype. To study whether or not individual mutations are sufficient to confer resistance, either single mutations or multiple mutations are being introduced in the wild-type genome. Further genotypic and phenotypic characterization of drug-resistant mutants will help to understand the mechanism by which TP219 exerts its anti-enterovirus activity.

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Oral Session 6: Mini-Symposium: Perspectives and Challenges in the Development of Topical Microbicides

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A Microbicide Perspective: Past, Present, and Future

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Microbicide Product Development: What Is A Microbicide?

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Formulation of Compounds for Vaginal and Rectal Delivery

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Development of Microbicides with Broad Based Anti-Infective Action

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