making this tissue a primary site of viral infection. Coinfection with human herpesviruses 6 and 7 or measles virus selectively modulates infection by R5 and X4 HIV by changing chemokine release and the expression of HIV receptors and coreceptors. In conclusion, we describe an HIV-triggered complex cycle of infection-activation-infection that creates new targets for HIV as well as for other viruses via cell activation, involving new cells in productive infection, upregulating cytokines and triggering apoptosis. This cycle is greatly affected by coinfecting pathogens, which by these means can determine the course of HIV disease progression. Intervention in the interactions between HIV and other pathogens may provide a new tool for antiviral therapy.

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Oral Session II: Respiratory and West Nile Viruses

8

Identification and Biochemical Characterization of Small Molecule Inhibitors of West Nile Virus Serine Protease by a High Throughput Screen

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West Nile Virus (WNV) and dengue virus (DV) are mosquito-borne members of *Flaviviridae* that cause widespread human disease for which there is no vaccine or chemotherapy. These viruses, like all flaviviruses, encode a serine protease (NS3-pro) that is essential for polyprotein processing, a required step in viral replication. In this study, we report the development and validation of an in vitro, high throughput screening (HTS) assay for WNV protease. Using this assay, more than 32,000 small molecule compounds were screened, from which three core chemical structures were identified among them that inhibit the protease. A secondary screen of seven compounds selected from the three core structure groups, identified two compounds (A and B) as strong WNV protease inhibitors with K_i values as low as ~3 μM. Based on molecular docking of compound B with the recently reported crystal structure of WNV protease, we propose that compound B binds in the vicinity or within the substrate-binding pocket involved in the interaction with the P1 residue of the substrate. Furthermore, we suggest a plausible mechanism of protease inhibition by this group of compounds. This assay will be useful to identify other potent inhibitors of the flaviviral protease and lead the way for development of antiviral therapeutics against WNV and related flaviviruses.

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Discovery of a New Class of Polycyclic RSV Inhibitors

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Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in children under 1 year of age and is a leading cause of severe lower respiratory infections in infants and young children. Prophylactic antibodies such as Synagis® (palivizumab) effectively reduce the incidence and severity of RSV disease in high-risk pediatric populations but the only antiviral treatment available for patients with RSV disease is ribavirin, a nucleoside analog with suboptimal clinical efficacy and safety profile.

We have discovered a new class of imidazoisoindolone RSV inhibitors with general structure as depicted in Fig. 1. The synthesis of this novel series of compounds will be described with the identification of key features important for antiviral activity. Medicinal chemistry has been applied to develop highly active and specific small molecules species that inhibit RSV.

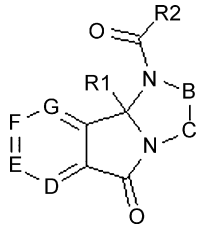

Fig. 1.

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Potent Inhibition of Viral Entry and Replication of SARS-CoV by siRNAs Targeting the Genes Encoding the Cellular ACE2 Receptor or the Viral Nucleocapsid Protein

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Severe acute respiratory syndrome (SARS), which is caused by a newly identified human coronavirus named SARS-associated