v3xUL97, which had similar levels of sensitivity to GCV as wild type GPCMV. These studies indicate the feasibility of using a UL97 humanized GPCMV for antiviral pathogenicity studies in the guinea pig model.

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## Oral Session 5: Respiratory Viruses, Emerging Viruses and Biodefense

**Chairs: Graciela Andrei, Ph.D. and Peter Silvera, Ph.D., 1:00–5:30 pm, Grand A**

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### ST-246, a Therapeutic for Smallpox

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**Background:** ST-246, a small-molecule inhibitor of poxviruses has demonstrated safety and efficacy profiles in various animal model systems. ST-246 is being developed as a promising antiviral for smallpox and is currently in Phase I clinical trials. Here, we evaluated the optimal post-exposure dose of ST-246 to effectively treat rabbits using the intranasal RPXV challenge model.

**Methods:** Two sets of thirty 9-week-old NZW rabbits divided into 5 groups of 6 rabbits each were challenged intranasally with $1 \times 10^5$ PFU of RPXV, Utrecht strain. At 48 or 72 h post-infection (hpi) once daily oral treatment was initiated in each set of 4 groups at doses of 40, 20, 10 and 5 mg/kg, respectively for 14 days. The remaining group received vehicle only. Animals were monitored daily for clinical signs, body weight and temperature. Viral load in the blood and tissue was measured by quantitative PCR.

**Results:** ST-246 at a dose of 40 mg/kg given at 48 and 72 hpi provided 100 and 83% protection, respectively, despite a transient increase in temperature and moderate initial weight loss. Treatment doses of 20 mg/kg or 10 mg/kg ST-246 when given 48 hpi provided 50% protection against severe RPXV disease, whereas, only 17% protection was achieved when the same doses were given a day later. Protection conferred by ST-246 was associated with suppression of viremia in a dose-dependent manner and suppression or clearance of RPXV in the lung, liver and spleen. By contrast, all non-survivors developed typical signs of rabbitpox disease including nasal and ocular discharges, respiratory distress, pyrexia, and anorexia. Finally, viral loads in non-survivors ranged between 6 and 9 logs genome copies/mL with mean time-to-death of 6.5 days.

**Conclusions:** ST-246 demonstrated dose and time dependent protection against lethal RPXV disease. These data further support the advancement of ST-246 as a promising therapeutic for smallpox. This work was funded by NIAID-DMID contract N01-AI-30063.

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### Evidence for Host Drug Targets Essential for Dengue Virus Capsid Formation

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By analogy to previous studies for hepatitis B virus, HIV, and hepatitis C virus, we established a cell-free system involving *de novo* protein biogenesis that appears to faithfully carry out critical steps in the assembly of Dengue virus capsids. The protein synthesis-linked capsid assembly system was converted into an ELISA-based screening platform for identification of small molecules that interfere with proper Dengue virus capsid formation. This screen potentially can identify molecules acting either directly or indirectly, via interference with essential host factors, anywhere in the assembly pathway. A number of small molecules conforming to Lipinski's rules were identified as hits likely acting at diverse steps in the capsid assembly pathway and by different mechanisms. This hypothesis is based on evidence to be presented that the activity of some of these molecules results in aberrant capsids by several different criteria including resistance to digestion by proteases and changes in buoyant density, compared to non drug-treated controls. When tested against live Dengue virus in cell culture, a number of these compounds were found to be robustly active, resulting in multilog drop in plaque forming unit (pfu) titer in the nanomolar to low micromolar range. These active molecules were sorted by chemical class, activity, and toxicity. A total of 11 chemical classes (pharmacophores) were found to be potent ($EC_{50} < 7.5\ \mu M$) and non-toxic (TI > 10). These findings provide strong support for the hypothesis that critical steps in Dengue virus capsid formation are faithfully re-created in the cell-free system. The targets of those drugs not acting directly on the capsid protein are promising candidates for essential host factors in the Dengue virus life cycle.

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### An Adenosine Nucleoside Inhibitor of Dengue Virus

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Dengue virus (DENV), a mosquito-borne flavivirus, is a major public health threat. The virus poses risk to 2.5 billion people world-wide and causes 50–100 million human infections each year. Neither vaccine nor antiviral therapy is currently available for prevention and treatment of DENV infection. We have developed a novel nucleoside NITD008, (2R,3R,4R,5R)-2-(4-amino-pyrrolo[2,3-d]pyrimidin-7-yl)-3-ethynyl-5-hydroxymethyl-tetrahydro-furan-3,4-diol, that potently inhibits DENV both in vitro and in vivo. Besides the four serotypes of DENV, NITD008 inhibits other flaviviruses, including West Nile virus (WNV), yellow fever virus (YFV), and powassan virus (PWV). The compound also suppresses hepatitis C virus (HCV), but it does not inhibit nonflaviviridae, such as Western equine encephalitis virus (WEEV) and Vesicular stomatitis virus (VSV). A triphosphate form of NITD008 directly inhibits the RNA-dependent RNA polymerase (RdRp) activity of DENV, indicating