of Gram-negative bacterial species and the infection sites. The PK/PD analysis for 3
indicators of respiratory syncytial virus (RSV) replication

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Background. RSV can cause severe respiratory tract infections in infants and the elderly. New antiviral therapies including polymerase and fusion inhibitors, but their clinical use may be limited by toxicity or rapid emergence of viral resistance. Here we report new nucleotide prodrugs that are selective for and highly active against RSV replication in vitro.

Methods. Novel nucleotide prodrugs were synthesized and tested for their ability to inhibit RSV replication in 3-dimensional preparations of differentiated normal human bronchial epithelial (dNHBE) cells. Drug selectivity was assessed in the anti-viral efficacy of AB and KPC in vitro and in vivo.

Results. The most potent nucleotide prodrugs inhibited RSV replication by 90% at concentrations (EC₀) as low as 0.021 µM. None of the prodrugs tested showed significant cytotoxicity with dNHBE cells, bone marrow stem cells or cardiomyocytes at concentrations up to 100 µg/mL. The half-life of fT>MIC required for 1 log₀CFU reduction was 5.34 h for the reduction from 10⁻³ to 10⁻⁴, 3.38 h for the reduction from 10⁻⁴ to 10⁻⁵, and 1.55 h for the reduction from 10⁻⁵ to 10⁻⁶.

Conclusion. The data indicate that these potent new nucleotide prodrugs are metabolized to TP’s that prevent RSV replication likely by inhibition of the viral RNA polymerase. Additionally, the long t₁₀₀ observed for many of the TPs suggest that it might be possible to cure RSV infections with a single dose. IND enabling studies are ongoing, targeting clinical evaluation in early 2018.

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1527. Novel Immunization Strategies Against Multi-drug-resistant Gram-negative Bacteria

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Background. Healthcare-related infections due to multi-drug-resistant (MDR) Gram-negative bacteria (GNB) such as Acinetobacter baumannii (AB) and carbapenemase producing Klebsiella pneumoniae (KPC) are associated with high mortality rates. New methods to prevent or treat these infections are needed. Candishantigen Hyr1p is predicted to share structural and sequence homology with the hemagglutinin/hemolysin protein (Fb) and siderophore-binding protein of GNB including AB and KPC, respectively. Indeed, active and passive immunization using Hyr1p as a target protect against AB infections in mice. Thus, we attempted to develop protective monocolonal antibodies (mAb) and test their efficacy against AB and KPC in vitro and in vivo.

Methods. Murine hydramatins were generated from Bab/lc mice after vaccination with recombinant Hyr1p. The concentration and identification of the collected mAbs were determined using Bradford and SDS-PAGE. Binding ability of mAb was tested against AB and KPC by in-vitro studies on the ability of these mAbs to protect KPC and AB were tested by quantitative culturing. The ability of these mAbs to protect from AB- or KPC-mediated alveolar epithelial cell (A549) damage was studied with 12-Cr-release assay. The efficacy of mAb in protecting against AB- or KPC-induced pneumonia was studied in neutrophilic or immunocompetent CD1 mice by administering 30 µg of mAb (i.p.), on Day +1 and +4, relative to infection, respectively. Survival of mice served as an endpoint.

Results. Different AB-producing hydramatin cells generated IgM that bound both AB and KPC. 40-80% of mAb reduced survival of AB or KPC in vitro. Two of these mAbs were selected for further studies.

Conclusion. We used Candida Hyr1p to generate cross protective mAb against MDR AB and KPC. Our results warrant the further development of these mAbs as novel immunotherapeutics against MDR GNB.

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