that the compound functions as a chain terminator during viral RNA synthesis. NITD008 has good in vivo pharmacokinetic properties, and is biologically available through oral administration. Treatment of DENV-infected mice with NITD008 suppressed peak viremia, reduced cytokine elevation, and completely prevented infected mice from death. Our results have proved the concept, for the first time, that a small molecular inhibitor could be developed for clinical treatment of flavivirus infections.

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Small Molecule Agonists of the RIG-I Pathway and their Potent Antiviral Actions

Kristin Bedard[1,*], Nicholas Pointinger[1], Eric Tarcha[1], Michael Katze[2], Michael Gale Jr.[2], Shawn Iadonato[1]

[1] *Kineta, Inc., Seattle, USA;* [2] *University of Washington, Seattle, USA*

We report on the identification of five potent, drug-like small molecule agonists of the RIG-I innate immune pathway that demonstrate effective antiviral activity against both the hepatitis C and influenza viruses. Hepatitis C virus is a highly successful virus infecting nearly 200 million people worldwide and causing a chronic lifelong infection in approximately 75% of acutely infected subjects. Influenza A virus continues to be a major health concern despite seasonal vaccination programs, with 5–20% of the U.S. population contracting the infection every year leading to an average of 200,000 hospitalizations. Recent drug development efforts have focused on antiviral products that directly target key viral enzymes, but major improvements to the immune-modulating therapeutic backbone have received scant attention. Drugs that modulate and enhance innate immunity would display broad antiviral activity, immune-enhancing efficacy and an ability to overcome virus countermeasures, while remaining insensitive to the rapid evolution of drug resistance that plagues conventional small molecule therapies. A key pathway that is responsible for mediating the innate immune response to RNA virus infection involves activation of RIG-I and targeting this pathway has successfully lead to the identification of agonist molecules that are highly potent and broadly active antiviral molecules. We have identified five lead compound candidates that specifically agonize the RIG-I pathway, a key mediator of the innate immune response to virus infection. The compounds activate RIG-I responsive promoters by mediating nuclear translocation of IRF-3 and display highly potent antiviral activity against hepatitis C virus and influenza A virus. These molecules efficiently decrease the synthesis of viral proteins, the accumulation and spread of viral RNA, as well as the production of infectious virus. Ongoing studies will further define the mechanism of action of these RIG-I agonist molecules and utilize QSAR studies to optimize their antiviral and drug-like properties.

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The NF-κB-Inhibitor SC75741 Efficiently Blocks Influenza Virus Propagation by Retention of the Viral RNP Complexes in the Nucleus without the Tendency to Induce Resistant Virus Variants

Christina Erhardt[1,*], Andrea Rückle[1], Karoline Droebner[2], Eike Hrincius[1], Oliver Planz[2], Stephan Ludwig[1]

[1] *FLI, Tuebingen, Germany;* [2] *IMV/ZMBE, Muenster, Germany*

Influenza is still one of the major plagues worldwide. The appearance of highly pathogenic avian H5N1 viruses or swine-origin H1N1v influenza viruses in humans and increasing incidence of resistance to the currently available medication highlight the need for new and amply available antiviral drugs. We and others have demonstrated that influenza virus misuses the cellular IKK/NF-κB signalling pathway for efficient replication suggesting that this module may be a suitable target for antiviral intervention. Here we show that the novel NF-κB inhibitor SC75741 efficiently blocks replication of influenza A and B viruses, including A/H5N1 isolates and H1N1v strains in concentration that do not affect cell viability or metabolism. The underlying molecular mechanism of SC75741 action involves impaired expression of proapoptotic factors, subsequent inhibition of caspase activation as well as block of caspase-mediated nuclear export of viral ribonucleoproteins (RNPs). Besides this direct antiviral effect the drug also suppresses virus-induced overproduction of cytokines and chemokines, suggesting that it might prevent the so-called cytokine burst that is an important pathogenicity determinant of infections with highly pathogenic influenza viruses, such as the A/H5N1 strains. Most importantly the drug did not shown any tendency to induce resistant virus variants. Thus, a SC75741-based drug may serve as a broadly active non-toxic anti-influenza agent.

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The Triple Combination Antiviral Drug (TCAD) Regimen of Amantadine, Ribavirin, and Oseltamivir is Highly Efficacious Against Susceptible and Resistant Influenza Virus Strains in Mouse Treatment Models

Matthew Gross[1,*], Minh Le[1], Donald Smee[2], Dale Barnard[2], Amy Patick[1], Jack Nguyen[1]

[1] *Adamas Pharmaceuticals, Emeryville, USA;* [2] *Utah State University, Logan, USA*

The triple combination antiviral drug (TCAD) regimen composed of amantadine (AMT), ribavirin (RBV), and oseltamivir (OSL) has been previously shown to be highly active *in vitro* and synergistic against a range of susceptible and resistant influenza viruses. Here we evaluated the TCAD regimen in mouse models of influenza A infection and compared the efficacy to monotherapy and double combinations using factorial design. In two separate studies, mice were infected with lethal doses of susceptible influenza A/Duck/MN/1525/81 (H5N1) or AMT-resistant novel influenza A/CA/04/09 (H1N1) virus. Treatments were initiated 24 h after infection via oral gavage and continued TID for 5-days. The dosing regimens (OSL 25 mg/kg/day; AMT 46 mg/kg/day; RBV 27 mg/kg/day) were selected to produce drug exposures in mice that approximate those in humans. Survival and body-weights were monitored for 21-days. TCAD was highly effective at treating mice infected with a lethal dose of A/H5N1 and novel A/H1N1 influenza viruses, producing survival rates of 90 and 95%, respectively. In contrast, monotherapy with OSL produced 0 and 20%