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New Strategy to Control Viral Infection

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Field of Invention: Anti-viral Therapy, Homeland Security, and Biodefense
Inventors: B. He. M. Sun and S. Fuentes
Penn State Invention Disclosure No. 2006-3255

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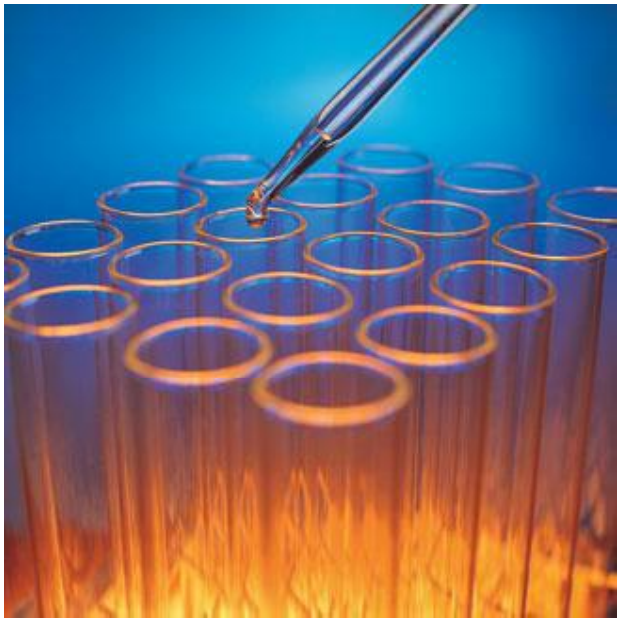
New Strategy to Control Viral Infection



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Background

The paramyxovirus family of non-segmented negative sense RNA viruses (NNSV) is classified in the order Mononegavirale, which contains many important human and animal pathogens such as rabies virus, vesicular stomatitis virus (VSV), human parainfluenza virus, Sendai virus, mumps virus, Newcastle disease virus (NDV), measles virus (MeV), rinderpest virus and human respiratory syncytial virus (hRSV) as well as emerging viruses such as Ebola virus, Nipah and Hendra virus. The single stranded RNA genomes of the Mononegavirale range from ~11,000-16,000 nucleotides in length and contain a series of tandemly linked genes separated by non-transcribed sequences. The viral RNA-dependent RNA polymerase (vRNAP) that transcribes the nucleocapsid protein (NP)-encapsidated RNA into 5' capped and 3' polyadenylated mRNAs minimally consists of two proteins, phosphoprotein (P) and the large (L) polymerase protein. While the vRNAP is essential, it is not sufficient for viral RNA synthesis. For instance, purified vRNAP (P and L complex) of Sendai virus has no activity on purified NP-encapsidated RNA template, unless cell lysate is added to the reaction mixture, indicating that host proteins are required for viral RNA synthesis. The same vRNAP also replicates viral RNA genome. Regulation of the switch between viral RNA transcription and replication is not well understood. It is thought that one or more unidentified host proteins play an essential role in regulating the viral RNA synthesis.

Invention Description

The subject invention represents a novel method of controlling viral replication, especially for NNSV

as well as positive-stranded RNA virus. Parainfluenza virus 5 (PIV5), formerly known as simian virus 5 (SV5) is a prototypical member of the Rubulavirus genus of the family Paramyxoviridae. The Penn State researchers have identified a host protein that is critical to PIV5 replication. Furthermore, the Penn State researchers have identified several lead compounds that block PIV5 replication at low concentration without causing cytopathic effect (CPE). They have further demonstrated that these compounds inhibit the replication of other negative stranded RNA viruses including but not limited to hRSV, MeV and VSV (the best compound can inhibit at least 99.9% viral replication in tissue culture cells, i.e., about 1,000-fold reduction of viral replication). Further testing of these compounds in tissue cultutre cells has demonstrated that they are effective against replication of Bovine Viral Diarrhea Virus (BVDV), a major bovine pathogen as well as a model system for human hepatitis C virus (HCV).

⊟ Applications

The subject invention offers the possibility of new drugs that target host proteins and pathways essential for RNA virus replication and could provide an effective means to control virus infection with lower probability of developing drug resistant viruses. The lead compounds target many viruses that are of great threat to human health but there is not an effective anti-viral strategy against these viruses. Mumps virus and measles virus are paramyxovirus that have reemerged in Europe and in the United States, due in part to poor efficacy of the vaccine, gaps in vaccination participation, and possible mutated viruses due to selection pressure of vaccination. In the developing world, mumps virus and measles virus are still a major health threat. In the US, it is estimated that over 90% infant hospitalization is caused by hRSV infection. VSV is a bovine pathogen as well as a model for rabies virus. BVDV infection causes major economic consequences for cattle industry. What is more, BVDV is often used as a model for human HCV, with which in the US alone over three million people are infected (CDC, 2005).

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