



HEALTH RESEARCH  
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## Anti-Flavivirus Therapeutic

### Background:

Although flaviviruses cause significant human diseases, no antiviral therapy is currently available for clinical treatment of these pathogens. Discovery of new cellular pathways is crucial to enabling innate or acquired resistance to overcoming this infectious disease. Our method involves use of the complex nature of the compound, lycorine and its analogues, to inhibit antiviral activity by suppression of viral RNA replication. Lycorine is an alkaloid compound naturally occurring in the bulbs of the common daffodil and several other plants in the amaryllis (Amaryllidaceae) family. In the past century, the biological activities of lycorine have been successfully documented to interfere with replication of the polio, small pox and SARS viruses, as well as having anti-fungal and anti-parasitic activities. The biodiversity and unique and challenging chemistry of lycorine has led to its successes as a natural choice for synthetic compound production.

The flavivirus genome is a plus-sense, single-stranded RNA of about 11,000 nucleotides. The genomic RNA consists of a 5' untranslated region (UTR), a single open reading frame (ORF), and a 3' (UTR). The single ORF encodes a long polyprotein that is co-translationally processed by viral and host proteases into ten mature viral proteins. The N-terminus of the polyprotein contains three structural proteins: capsid (C), premembrane (prM/M), and envelope (E). The C-terminus of the polyprotein contains seven nonstructural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. During viral replication, complete polyprotein cleavage generates a 2K peptide between NS4A and NS4B.

In our study, structural modifications of the two hydroxyl groups of the lycorine compound increased its potency while decreasing its cytotoxicity. Furthermore, we found that a single amino acid (Val-Met) substitution at the 9<sup>th</sup> amino acid position in West Nile viruses 2K peptide between NS4A and NS4B proteins yielded resistance to lycorine. Therefore, taken together these results establish lycorine's continuing significance in antiviral activity and as an excellent candidate for flavivirus inhibition.

### Applications:

Utility as a prophylactic or as a therapeutic for flavivirus infection

Advantages:

- This two-pronged approach simultaneously suppresses viral RNA synthesis of the flavivirus and allows for the detection of the 2K peptide in flavivirus RNA replication.
- No effective antiviral therapy has been approved for treatment of flavivirus infections.

State of Development:

Prototypes of compound available – early stage of development



Licensing Potential:

HRI seeks commercial partners to evaluate and develop applications for licensing.

Patents:

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Pei-Yong Shi is currently Head of the Dengue Unit at Novartis Institute for Tropical Diseases. He received his Ph.D. in flavivirus replication in 1995 from Georgia State University, USA. After postdoctoral training at Yale University, he joined Bristol-Myers Squibb as a Principal Scientist from 1998 to 2000. He then moved to the Wadsworth Center, New York State Department of Health. His group at the Wadsworth Center developed the first infectious clone of the epidemic strain of West Nile virus, discovered two cap methylation activities of flavivirus NS5 protein, identified essential RNA elements for flavivirus replication, and established various novel platforms that have been used to screen and study inhibitors of flaviviruses. He is an Editor for Journal of General Virology and a member of the Editorial Board for Journal of Virology. He joined Novartis in August 2008.

Publications:

Puig-Basagoiti F, Tilgner M, Forshey BM, Philpott SM, Espina NG, Wentworth DE, Goebel SJ, Masters PS, Falgout B, Ren P, Ferguson DM, Shi PY. [Triaryl Pyrazoline Compound Inhibits Flavivirus RNA Replication](#). Antimicrobial Agents and Chemotherapy, Apr. 2006, p. 1320–1329 Vol. 50, No. 40066-4804/06/\$08.000 doi:10.1128/AAC.50.4.1320–1329.2006

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