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Synthetic Peptides from Conserved Regions of Measles Virus Fusion Proteins are Potent Inhibitors of Viral Fusion. K. Guthrie, S. Barney, D.E. Davis-Rhodes, A.L. Lambert, R. Medinas, T. Bucy, J. Erickson, G. Merutka, S.R. Petteway, Jr., D.M. Lambert. Trimeris, Inc., Durham, NC

The fusion proteins of Measles virus (MeV) are required for virus-mediated membrane fusion and infection. Inhibitors targeted to these essential proteins would represent a novel class of antiviral agents that act at the cell surface. Recent discoveries by Wild et al. and Carr et al. provide a structural and functional basis for the discovery of antivirals targeted to viral fusion proteins. In particular, two synthetic peptides derived from distinct domains of the HIV-1 gp41 fusion protein, DP-107 and DP-178, have been shown to be potent inhibitors of HIV-1 fusion and infection. In an effort to investigate the potential conservation of these domains in other enveloped virus fusion proteins, we developed a computer search strategy designed to identify regions of viral fusion proteins similiar to those represented by DP-107 and DP-178. A subsequent computer search of MeV fusion protein F_1 primary amino acid sequence resulted in the identification of regions corresponding to DP-107 and DP-178. Overlapping 35-mer synthetic peptides spanning these regions within the F_1 protein of MeV were synthesized and assayed for their ability to block virus-mediated fusion and infection. Active peptides that block Measles virus- mediated fusion and infection at sub-micromolar concentrations *in vitro* were identified and three lead peptides were chosen for additional study. These fusion-inhibiting Measles virus peptides represent a new class of antivirals acting at the cell surface.

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Synthetic Peptides from Conserved Regions of Human Parainfluenza Type 3 Virus Fusion Protein are Potent Inhibitors of Viral Fusion. S. Barney, A.L. Lambert, K. Guthrie, R. Medinas, D.E. Davis-Rhodes, T. Bucy, J. Erickson, G. Merutka, S.R. Petteway, Jr., D.M. Lambert. Trimeris, Inc., Durham, NC

Human parainfluenza virus type 3 (HPIV-3) is an important agent of severe lower respiratory illness in infants and is second only to RSV in importance in causing disease. There are no vaccines to prevent infection and current therapies are limited. Although Ribavirin is active against HPIV-3 *in vitro* and has shown some efficacy in the clinic, it is not approved for HPIV-3 infections. Therefore, safe and effective treatments for HPIV-3 infections represent a significant unmet medical need. The surface attachment and fusion glycoproteins of enveloped viruses are intimately involved in the adsorption and penetration steps of the infectious process. In HPIV-3, F_0 (the 60 kDa uncleaved, inactive form) is cleaved into two active disulfide-bonded subunits, F_1 (51 kDa) and F_2 (9 kDa). Inhibition of the function of the F proteins blocks infection as demonstrated by neutralizing antibodies. Inhibitors targeted to these proteins would represent a novel class of antiviral agents that act at the cell surface. Recent discoveries by Wild et al. and Carr et al. provide a structural and functional basis for the discovery of antivirals targeted to viral fusion proteins. In particular, two synthetic peptides derived from distinct domains of the HIV-1 gp41 fusion protein, DP-107 and DP-178, have been shown to be potent inhibitors of HIV-1 fusion and infection. Structural similarities to the HIV gp41 site were identified in several regions of HPIV-3 F protein, using computer algorithms. Overlapping 35-mer peptides spanning these regions were synthesized and assayed for their ability to block virus-mediated fusion and infection. Active peptides that block virus-mediated fusion and infection at sub-micromolar concentrations *in vitro* were identified and three chosen as leads for further study. These fusion-inhibiting peptides represent a new class of HPIV-3 antivirals acting at the cell surface. There is significant potential for exploiting these peptides as therapeutic agents and as a basis for new drugs.