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ANTI-INFLUENZAVIRUS-ACTIVITIES OF POLYOXOMETALATES

S. Shigeta[1], S. Mori[1], J. Watanabe[1], T. Yamase[2], C.L. Hill[3] and R.F. Schinazi[3], Fukushima Medical College, Fukushima[1], Tokyo Institute of Technology, Yokohama[2], Japan, Emory University, Decatur GA[3], USA

Polyoxometalates exhibit a broad spectrum antiviral activities against retro, herpes, toga, orthomyxo and paramyxoviruses. We examined 25 compounds of HS-series (Hill and Schinazi) and 61 compounds of PM-series (Yamase) against influenzavirus (FluV)A Ishikawa strain (H3N2) and 24 of HS and 27 of PM compounds showed anti-FluV-A activities in vitro. Among these effective compounds HS-54 ($Na16Fe4(H_2O)_2(P2W15056)_2H_2O$], HS-58 [$K10Fe4(H_2O)_2(PW9034)_2nH_2O$], PM-504[K9H5(G2Ti6W18077)16H_2O, PM523[(Pri NH_3)6H[$PTi_2W10O38(O)_2[H_2O$] showed low EC50 of less than 1.0uM and high CC50 of more than 200uM. All 4 compounds also showed antiviral activities against FluVB, RS-virus, measles virus and parainfluenza virus 2. The mechanism of inhibitory activity of these compounds against FluV was analysed and they did not inhibit adsorption (or hemagglutination) but inhibited penetration (or hemolysis) of virus. Polyoxometalates which inhibit penetration of FluV in to cells and have broad spectrum antimyxovirus activities must be promissive candidate of antiviral drugs of influenza and related repiratory viral diseases.

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Synthetic Peptides from Conserved Regions of RSV, HPIV-3, and MeV Fusion Proteins are Potent Antivirals (Inhibitors of Viral Fusion). **S.R. Petteway, Jr., S. Barney, A.L. Lambert, K. Guthrie, T. Bucy, J. Erickson, G. Merutka, D.M. Lambert. Trimeris, Inc., Durham, NC**

The fusion proteins of enveloped viruses are required for virus-mediated membrane fusion and infection. Inhibitors targeted to these proteins would represent a novel class of antiviral agents that act at the cell surface. Until recently, Mabs have been the only rational approach to the inhibition of fusion protein function. However, recent discoveries by Wild et al. and Carr et al. provide a structural and functional basis for the discovery of antivirals targeted to the viral fusion protein. 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. The antiviral activities of these peptides appear to be related to their structure. The primary amino acid sequences of these peptides are consistent with the propensity to form helical structures. To investigate potential conservation of these domains in other enveloped virus fusion proteins, we developed a computer search strategy to identify regions of viral fusion proteins similar to DP-107 and DP-178. A computer search of viral envelope protein primary amino acid sequences identified regions within the fusion proteins of RSV, HPIV-3, and MeV corresponding to DP-107 and DP-178. Surprisingly, both the DP-107-like and DP-178-like regions were located at the same relative locations within the fusion proteins of RSV, HPIV-3, MeV, and HIV-1. Overlapping 35-mer peptides spanning these regions within the F proteins of RSV, HPIV-3, and MeV were synthesized and assayed for ability to block virus-mediated fusion and infection. Active peptides that block virus-mediated fusion and infection were identified within the F proteins for RSV, HPIV-3, and MeV. These fusion-inhibiting peptides represent a new class of antivirals acting at the cell surface. The conservation of the domains from which these peptides were derived is consistent with structural and functional similarities between retroviral and paramyxovirus fusion proteins.