201

Influenza Virus-Inhibitory Activity of a Series of Antisense Oligonucleotides. J. H. Huffman[1], R. W. Sidwell[1], A. P. Gessaman[1], B. J. Moscone[1], J. Y. Tang[2] and S. Agrawal[2]. [1]Institute for Antiviral Res., Utah State Univ., Logan, UT, USA and [2]Hybridon, Inc., Worcester, MA, USA.

A series of phosphorothioate oligonucleotides (ODNs), complementary to a conserved region of PB1 RNA of influenza virus, has been evaluated for their inhibitory activity against influenza virus in MDCK cells. Viruses inhibited included influenza A/NWS/33 (H1N1), A/Japan/305/57 (H2N2), A/Victoria/3/75 (H3N2), and A/Washington/897/80 (H3N2). The ODNs carrying modifications to improve their (a) stability, (b) cellular uptake, and (c) affinity to the RNA target showed increased inhibitory activity. Maximal 50% effective doses (ED50) exhibited by these ODNs ranged as low as 6 μg/ml (~1μM). Cytoxicity was not seen at 100 μg/ml, the highest dose studied. Viral inhibitory effects were seen both by inhibition of viral cytopathic effect and by viral yield reduction assays. Certain of these ODNs have been studied earlier for their toxicity[1] and pharmacokinetics[2] in mice and rats. *In vivo* experiments have begun with the most active of these ODNs, utilizing a once daily intraperitoneal treatment regimen in mice infected intranasally with the H1N1 virus. The antiviral efficacy seen to date in these animals has been an inhibition in the decline of arterial oxygen saturation as measured by pulse oximeter, and an increase in mean survival time.

[1]*Agrawal, S. (1991) In, Prospects for Nucleic Acid Therapy for Cancer and AIDS. Wiley Liss, NY, pp 143-150.*

[2]*Agrawal, S. et al. (1991) Proc. Natl Acad Sci USA 88:7595-9.*

Supported by contract NO1-AI-15097 from the Antiviral Research Branch, NIAID, NIH.

202

In Vitro and In Ovo Effects of Various Nucleoside and Non-Nucleoside Analogues on Influenza A and B Virus Replication.

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Six nucleoside analogues, two sulfated polysaccharides, and four protease inhibitors, were evaluated in vitro as inhibitors of influenza virus replication. The guanosine analogues mizoribine, ribavirin, pyrazofurin, and EICAR, the sulfated polysaccharide dextran sulfate (molecular weight: 500,000), and the protease inhibitors camostat mesilate and nafamostat mesilate, were inhibitory to the replication of various strains of influenza viruses type A and type B at concentrations down to 0.3 μg/ml. Of these seven compounds, ribavirin, camostat mesilate, and nafamostat mesilate were efficacious in both reducing the viral titer and increasing the survival rate of influenza virus-infected chick embryos. For camostat mesilate the 50% effective dose (required to improve the survival rate of influenza virus-infected chick embryos by 50%) was 0.80 μg/g, and its selectivity index, based on the ratio of the 50% toxic dose (required to reduce the viability of chick embryos by 50%) to the 50% effective dose was 280. The corresponding values for ribavirin were 4.0 μg/g and 55, respectively. Camostat mesilate deserves further exploration for its potential in the treatment of influenza virus infection.