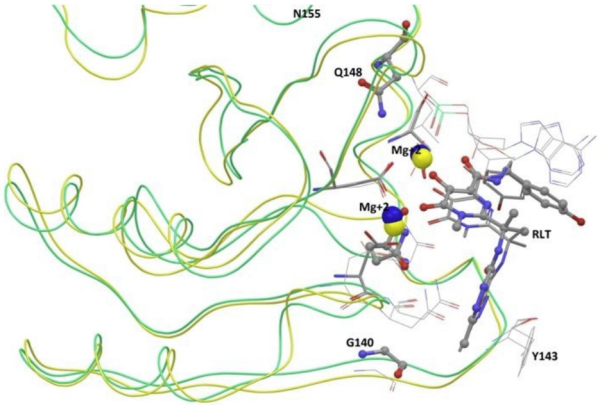

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Susceptibility to Neuraminidase Inhibitors and M2 Blockers of Some Seasonal Influenza Strains Isolated in Bulgaria 2004–2007

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M2 blockers and neuraminidase inhibitors are two classes of drugs currently approved for prophylaxis and treatment of seasonal influenza A virus infections. The frequency of antiviral drug resistance has increased dramatically over the last 10 years and therefore monitoring of susceptibility to licensed inhibitors is an essential component of influenza surveillance and therapy in Bulgaria and worldwide. Phenotypic and molecular techniques were applied for detection of resistance of influenza viruses (H1N1) and (H3N2) strains isolated in Bulgaria 2004–2007 to neuraminidase inhibitors and M2 blockers. IC_{50} values of rimantadine were determined by CPE inhibition in cell cultures. IC_{50} values of oseltamivir were evaluated fluorimetrically by neuraminidase susceptibility assay with MUNANA substrate. RT-PCR and sequencing were carried out for evaluation of gene segments coding HA, NA and M2 proteins with subsequent phylogenetic analysis. From overall 26 influenza strains (H1N1) and (H3N2) 22 were sensitive and 4 (two H1N1 and two H3N2) were resistant to rimantadine hydrochloride in CPE inhibition assay. 17 isolates were subjected to fluorescent assay and their susceptibility to oseltamivir and zanamivir were determined. IC_{50} of zanamivir varied from 1.05 nM to 5.28 nM and osletamivir IC_{50} were from 0.28 nM to 1.31 nM. Sequencing revealed S31N and V27T mutations in transmembrane region of M2 protein conferring resistance to adamantanes in A/Sofia/1250 (H3N2) strain. The virus remained susceptible to neuraminidase inhibitors. In all other viruses no mutations associated with either to M2 blockers or neuraminidase inhibitors were found. The HA, NA, and M sequence data of the H1N1 and H3N2 viruses were assembled and clustered and phylogenetic trees were constructed using the neighbor-joining method and bootstrap analysis.

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Prophylactic Activity of mDEF201 Against Vaccinia Virus Respiratory Infections in Mice

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An attenuated adenovirus type 5 vector containing an interferon alpha gene has been developed for the treatment of viral infections. We investigated mDEF201 (the vector containing mouse interferon) for the treatment of lethal respiratory infections in mice caused by vaccinia virus (WR strain). In the first experiment, mDEF201 was administered intranasally at 100 thousand, 1 million, or 10 million PFU/mouse one time only at 24 h prior to virus exposure. This afforded 90–100% protection from death and reduced day 5 lung virus titers approximately 8-, 80-, and 800-fold, respectively. Lung weights and lung hemorrhage scores, which increase during infection, were also significantly reduced by the treatments. Cidofovir (100 mg/kg/day i.p., once-daily for 2 days starting at +24 h) reduced viral titers 40-fold. A dose-responsive protection from body weight loss was afforded by mDEF-201 treatments, with minimal weight loss seen in groups receiving the two highest doses. This protection was superior to the effect of cidofovir. An empty adenovirus vector was similar to placebo in its activity. High doses (10 or 100 million PFU/mouse) of mDEF201 were required to prevent death when the vector was given 6 h after virus exposure. Extended prophylaxis was performed with a single mDEF201 administration one time only at 28, 21, 14, 7, or 3 days pre-virus challenge. All of these treatments protected mice from the lethal infection. None of the mice treated at these times exhibited weight loss during the infection but showed steady weight gain. Surviving animals from this infection were subjected to re-challenge with vaccinia virus. They all lost minimal body weight and survived, whereas naïve infected animals died. These results demonstrate the potent prophylactic activity of mDEF201 against this orthopoxvirus infection.

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Novel Derivatives of Abacavir – Synthesis and Activity Against Human Immunodeficiency Virus-Type 1 in Cell Culture

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Abacavir (ABC) is clinically associated with hypersensitivity reactions, risk for cardiovascular disease, etc. A possible way to minimize side effects is by modifying chemical structure. Three abacavir (ABC) esters and dipeptides (Gly-ABC, Z-Gly-ABC and