combinations is important since ST-246 and CMX001 are the most advanced candidates under development for the treatment of orthopoxvirus infections and potentially could be used together in the clinic to increase efficacy or minimize the emergence of drug resistance. Combination assays were performed in human foreskin fibroblast cells using the Western Reserve (WR) strain of vaccinia virus. Results from these studies revealed robust synergistic inhibition of viral replication with combinations of 4′-thioIDU and ST-246. Combinations of 4′-thioIDU and CMX001 also exhibited modest, but significant synergistic inhibition of vaccinia virus replication. Simultaneous cytotoxicity controls did not reveal any increased toxicity and suggested that the synergistic effects were not the result of increased toxicity. The use of drug combinations with different mechanisms of action is advantageous because the combinations can offer improved efficacy at lower dosages and minimize the development of drug resistance. The results of these experiments indicate that combinations of 4′-thioIDU with ST-246 or CMX001 are particularly effective in the treatment of orthopoxvirus infections in vitro and suggest that combined therapy may be useful in the treatment of these infections in animals and humans.

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Induction of Interferon Gamma Inducible Protein 10 by SARS-CoV Infection, Interferon Alfacon 1 and Interferon Inducer in Human Bronchial Epithelial Calu-3 Cells and BALB/c Mice

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SARS-CoV has been identified as the causative agent of an emerging human infectious disease, SARS. Its immunopathological mechanisms have not been fully characterized. One hypothesis is that the pathogenesis of SARS-CoV is caused by a disproportionate immune response, illustrated by elevated levels of inflammatory cytokines and chemokines, such as IP-10, MCP-1, IL-6 and IL-8. SARS-CoV has been shown in vitro to induce changes of cytokines and chemokines in various human and animal cells. We previously reported that interferon (IFN)-alfacon 1 was more active against SARS-CoV infection in Calu-3 cells than in African green monkey epithelial cells on day 3 post-infection. In the current study, we evaluated its efficacy of IFN-alfacon 1 in Calu-3 cells during the first 7 days of virus infection compared to its efficacy in Vero 76 cells, in which a more productive virus infection occurs. Calu-3 cells appeared to be more responsive to the antiviral effects induced by exogenous IFN than did Vero 76 cells. Furthermore, IP-10, an IFN-inducible white cell chemoattractant, was detected in Calu-3 cells after SARS-CoV infection. Interestingly, IP-10 expression was shown to be significantly elevated when SARS-CoV-infected Calu-3 cells were treated with IFN-alfacon 1. To our knowledge, this is the first time that the IP-10 expression has been clearly demonstrated in Calu-3 cells after SARS-CoV infection. Since IP-10 seems to be coordinated with a protective response in cells, we evaluated the efficacy of antivirals directed against SARS-CoV infection in BALB/c mice. IP-10 expression was detected in the lungs of SARS-CoV-infected BALB/c mice. Significantly high levels of mouse IP-10 in BALB/c mice was also detected when SARS-CoV-infected mice were treated with the interferon inducer, poly IC:LC. Our data might provide an important insight into the mechanism of pathogenesis of SARS-CoV and these properties might be therapeutically advantageous.

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Anti-influenza Efficacy of Combination Apply of Proteolytic Inhibitor E-aminocaproic Acid with Neuraminidase Inhibitor Tamiflu

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Our investigations have shown antiviral activity of proteolysis inhibitor E-aminocaproic acid (E-ACA). Tamiflu (Tm) is neuraminidase inhibitor and the most popular anti-influenza (AI) agents. But its toxicity is higher than E-ACA. We investigate efficacy of E-ACA and Tm combine action for optimization of AI therapy. AI activity in vitro was studied in tissue culture of chorioallantoic membranes chick embryos. Influenza virus strains A/HK/1/68 (H3N2), A/PR/8/34 (H1N1) and avian influenza H5N3 were used. Both Tm in doses 2 mkM/ml and 1 mkM/ml and E-ACA in doses 10 mg/ml and 15 mg/ml have displayed regular AI activity to A/PR/8/34 and H5N3 accordingly if the preparations were used separately. Combination action of these preparations was more effective. Combination action of Tm (1 mkM/ml) and E-ACA (10 mg/ml) has demonstrated synergistic effect on inhibition of reproduction A/HK/1/68 virus. Synergistic effect took place during experimental infection with influenza virus A/PR/8/34 in mice too. Only combination using of Tm and E-ACA have shown strongly protected effect. The results of this study have demonstrated the expediency of combination using of proteolytic and neuraminidase inhibitors for AI protection and therapy.

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Structure–Activity Relationship of a Novel Class of Aglycoristocetin Derivatives with Potent and Broad Activity Against Influenza Viruses

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Attachment of a hydrophobic substituent to a glycopeptide backbone structure was previously reported to offer favorable pharmacological (i.e. antibacterial and antiviral) properties. We here report on the in vitro anti-influenza virus activity of aglycoristocetin derivatives containing hydrophobic side chain-substituted cyclobutenedione. In Madin-Darby canine kidney (MDCK) cells, the lead compound 8e displayed an antivirally effective concentration (EC_{50}) of 0.4 μM, which was consistent amongst influenza A/H1N1, A/H3N2 and B viruses. The concentration producing 50% inhibition of cell proliferation was 67 μM, yielding an antiviral selectivity index (SI) of 167. Structural analogues derived from aglycovancomycin were completely inactive. The hydrophobic side chain