The BAC technology has the potential to increase bioavailability of a wide range of active compounds using oral administration, thereby increasing the accessibility and potentially improving the safety profile of the drug product.

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Lymphocytic Necrosis in Hamsters Inoculated with Western Equine Encephalitis Virus

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We hypothesized that disease in hamsters inoculated with the California strain of Western Equine Encephalitis virus (WEEV) follows a biphasic pattern, an initial systemic phase and a secondary neurologic phase. Furthermore, we hypothesized that the cause of death during the systemic phase was primarily inflammatory in nature. To test these hypotheses, we inoculated hamsters with WEEV and evaluated clinical, histopathological and virological parameters. Following inoculation animals displayed fever and weight loss, and the majority of animals, which died due to virus infection succumbed by 108 h post-virus inoculation (hpi). Animals developed necrosis in lymphocytic organs by 96 hpi, but, no pathological lesions could be observed in the brain at this time. Animals also developed lymphopenia, the severity of which appeared to be correlated to outcome. Animals that died during the initial phase had significantly decreased lymphocyte counts at 72 and 84 hpi compared to animals, which survived. Administration of the non-steroidal anti-inflammatory drug Flunixin Meglumine (FM) to hamsters inoculated with WEEV significantly improved survival. Over the course of multiple experiments placebo treated animals had an average survival rate of 4% at 120 hpi, while animals treated with FM had a survival rate of 30% ($p < 0.001$). Hamsters, which survived the initial stages of WEEV infection sometimes progressed to a neurological stage of the disease, showing overt signs of nervous system involvement, such as hind limb paralysis. Histopathological analysis of animals dying after 120 hpi revealed inflammation and necrosis within the central nervous system. These data indicate that WEEV in hamsters results in an initial systemic phase with lymphocytic necrosis and death due to an overwhelming inflammatory response, which may be partially blunted by administration of anti-inflammatory agents. Animals that survive the systemic phase may develop an encephalomyelitis.

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Combined Anti-Influenza Virus Effect of a Plant Polyphenol-Rich Extract and Ribavirin

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The anti-influenza virus activity of the extract, obtained from the plant *Geranium sanguineum* L (PC) has been studied intensively. It was shown that its in vitro antiviral effect was strain-dependent, consistent with a selective antiviral action (Serkedjieva and Hay, 1998). In one-cycle experiments of viral growth of A/Germany/34, strain Rostock (A/Rostock) in CEF PC inhibited the synthetic stages of viral replication. PC exhibited a pronounced protective effect in the lethal murine experimental influenza A/Aichi/2/68 (H3N2) virus infection (Serkedjieva and Manolova, 1992). Here, we present the results from the investigation of the combined virus-inhibitory effects of PC with ribavirin (Rib), a selective viral inhibitor. The in vitro combined application resulted in enhancement of the inhibitory effect of PC on the replication of A/Rostock in MDCK cells. The antiviral activity was determined by the difference in the infectious titers of control and treated viruses and the combined effect was defined on the base of infectious viral yields. As a rule the combinations showed increased virus-inhibitory effects with respect to the individual compounds. Most of the combinations proved to be synergistic. Administration of PC in combination with Rib in the course of the experimental influenza infection in mice produced a synergistic protective effect: mortality rate was significantly decreased, MST was markedly prolonged. A pronounced reduction of the lung lesions and of lung virus titres was achieved. The presented results together with the data from others suggest that the combined application of natural and synthetic viral inhibitors may be used successfully to potentate the antiviral efficacy of the plant preparations and may enable dose reduction of their toxic components.

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Anti-Influenza A Synergistic Combination Effect of Rimantadine and Oseltamivir in Mice

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The combination effect of rimantadine hydrochloride and oseltamivir phosphate was examined on infection with 10 and 20 MLD_{50} influenza A/Aichi/2/68 (H3N2) virus in mice. Doses of 2.5, 5.0 and 7.5 mg/kg/day of rimantadine and 0.05, 0.1 and 0.2 mg/kg/day of oseltamivir were selected and combined in a chess-board order, as an initial study. Compounds were administered in 5-day-treatment course, beginning 4 h pre-infection. Significant differences were observed comparing combination-