cost less since 1 or 2 g of ribavirin can be used daily instead of 6 g.

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Therapy of Advanced Arenaviral Infection in Hamsters with T-705

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Severe arenaviral diseases such as Lassa fever are insidious in their progression and generally do not present with distinguishing symptoms, making them difficult to clinically diagnose at early stages. Consequently, it is of utmost importance to identify antiviral therapies that can be effective when given at later times during the course of infection, which is consistent with the time whereby patients would actually seek medical attention due to illness. T-705 has proven to be efficacious in the Pichinde virus (PICV) hamster infection model of severe arenaviral disease when treatment is initiated within 3 days of viral challenge with a highly lethal viral inoculum. Here we present efficacy data based on the initiation of therapy as late as 7 days post-PICV challenge and compare the antiviral activity of T-705 with that of ribavirin. Both drugs offered significant protection when given as late as day 6 of infection, but hamsters receiving ribavirin lost considerably more weight and those that survived recovered at a much slower rate. At equitoxic doses, T-705 was found to be more effective than ribavirin when treatment was started on day 5 of infection, but comparable when started on day 6. T-705 activity was also compared to the related pyrazine analog, T-1106, reported to be highly active in the hamster model of yellow fever. In contrast to T-705, only limited protection was seen with T-1106 in the PICV infection model when treatment was begun 4 days after viral challenge. Determining the efficacy of T-705 when treatment is started at later stages of infection and in the face of substantial viral burden is important from a practical standpoint, as therapy in human cases would most likely start when patients are viremic. In this regard, the significant protection of PICV-challenged hamsters by therapy with T-705 initiated 2 days prior to the time when animals begin to succumb to the infection is encouraging. Moreover, T-705 appears to be as effective as ribavirin at treating PICV infection in hamsters and considerably less toxic.

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Virucidal Activity of Extracts from Four Algae Species Against Herpes Simplex Virus

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Herpes simplex virus types 1 and 2 (HSV-1, HSV-2) are the cause of a wide variety of human diseases. These viruses are opportunistic and their infection can result in major problems in immunocompromised individuals. The drugs currently used to treat cutaneous or genital HSV infections are effective in limiting disease, although the emergence of drug resistant viruses is observed after prolonged therapy. Prophylactic systemic treatment with antiviral drugs reduces transmission but there is continuing need for topical microbicides with virucidal activity that have the potential to limit transmission of the virus. Previous reports demonstrated the antiviral activity of complex carbohydrates extracted from some seaweed species and suggested that they interfered with the attachment of virions to host cells. Here, we evaluated the antiviral activity of extracts from *Undaria pinnatifida*, *Splachnidium rugosum*, *Gigartina atropurpurea*, and *Plocamium cartilagineum* against HSV-1 and HSV-2 in standard laboratory assays. This series of compounds exhibited good activity when added during viral infection, but were ineffective if they were added after the first hour of infection. Pretreatment plaque reduction assays with these compounds yielded EC_{50} values that ranged from (1.9–45 μg/ml) for HSV-1, (0.8–7.4 μg/ml) for HSV-2. None of the compounds exhibited significant toxicity in a neutral red uptake assay ($IC_{50} > 100$ μg/ml). Subsequent assays revealed that the compounds possessed virucidal activity and were capable of inactivating virus at very low concentrations. We conclude that these extracts are nontoxic and effective virucidal agents that warrant further investigation to determine their potential role in the treatment of HSV infections of humans.

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Luciferase-based Assay for Rapid Screening of Antivirals against Human Cytomegalovirus

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Human cytomegalovirus (HCMV) infections continue to be a problem in the immunocompromised host. There is a growing need for new classes of compounds that are effective against nucleoside-resistant mutants and are also less toxic than the currently available compounds. A recombinant virus was described previously that expresses luciferase from an immediate early promoter (McVoy and Mocarski, 1999). An assay was developed using this virus to facilitate the evaluation of large numbers of new compounds for potential antiviral activity. In this assay,

96-well plates containing monolayers of primary human fibroblasts were infected at an MOI of 0.01 PFU/cell and the infection was allowed to proceed for 7 days. The level of luciferase activity expressed by the virus was assayed and used as a surrogate marker for viral replication. The assay yielded EC_{50} values that were comparable to those generated in standard assays for several compounds that are currently licensed for use against HCMV, but appears to offer significant advantages. Chief among them were reduced processing time, reduced incubation time (7 days instead of 14 days) and reduced sensitivity to colored compounds. This assay, paired with the CellTiter Glo® toxicity assay, promises to provide a rapid means to assess cytotoxicity as well as antiviral activity against HCMV.

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Carbocyclic L-Nucleoside Analogues as Potential Antiviral Agents

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The application of nucleosides in antiviral therapy has grown to a common process over the last three decades. There exists a huge variety of nucleosides, which show several modifications on the nucleobase or the sugar moiety. Due to these changes in nucleoside structure new antiviral activities were found. Beside the commonly used D-configurated natural nucleosides there is the important class of L-nucleosides which are the mirror-images of the natural ones. L-Nucleosides are known for their significant bioactivity, especially their antiviral activity towards Hepatitis B. There are several FDA-approved L-nucleoside analogues, e.g. lamivudinde (3TC), telbivudine (L-thymidine) and clevudine (L-FMAU). With regard to these derivatives we decided to connected the concept of carbocyclic and L-nucleosides within this work to obtain similar carbocyclic L-nucleoside analogues as potential antitumor and antiviral agents. As starting material, we chose a chiral cyclopentenol, which can be prepared from cyclopentadiene by alkylation and a subsequent asymmetric hydroboration. After protection of the formed hydroxy group, the remaining double bond can easily be hydroxylated by different methods, yielding a chiral cyclopentanol. Using a modified Mitsunobu protocol, heterocycles were condensed to this precursor leading to L-configurated pyrimidine und purine carbocyclic nucleosides, e.g.: L-*carba*-dT, L-*carba*-dA, L-*carba*-BVDU or L-*carba*-d4T. The obtained enantiomerically pure carbocyclic nucleosides can simply be converted into the corresponding *cyclo*Sal-pronucleotides or their monophosphate esters (nucleotides) with the aim to improve their activity.

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Immunoprophylaxis of Phleboviral Infection in Hamsters with Recombinant Eimeria Protozoan Surface Antigen

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Recombinant *Eimeria* antigen (rEA) has been shown to have potent anticancer and antiviral activity in respective mouse disease models, presumably through robust immune stimulation that occurs via TLR11, a pattern recognition receptor that recognizes profilin-like proteins expressed on apicomplexan protozoans. Comparable immunostimulatory activity in other species has yet to be demonstrated. Since rEA is known to be highly effective in treating Punta Toro virus (PTV) infection in mice, its ability to elicit protective immunity in the hamster PTV infection model was investigated. rEA was given alone, or in combination with IL-18 or IL-2, and virally challenged hamsters were observed for mortality. A dose of 100 μg of rEA, given once 4 h prior to viral challenge, and a second time on day 3 of the infection, was found to be the most effective prophylactic therapy protecting 60% of treated hamsters from mortality, compared to only 5–10% observed in animals receiving placebo. In addition, splenic cytokine transcript profiles for IL-12, IL-21, IFN-γ and TNF-α were assessed at various times after a single 100-μg dose treatment of rEA. Only IFN-γ and IL-12 were found to have remarkably increased expression following exposure. The data suggest that rEA does induce host antiviral responses in hamsters that result in significant protection from death, although determining the most appropriate dose for intervention in other species, including humans, will likely be very challenging.

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Novel Inhibitors of Orthopoxvirus Replication Target Vaccinia Virus P37 Envelope Protein

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Three compounds with antiviral activity against orthopoxviruses were identified through routine in vitro screening of over 1800 compounds from a chemical library utilizing cytopathic effect assays. Plaque reduction assays in human foreskin fibroblast cells confirmed the activity of three compounds against both vaccinia (VV) and cowpox (CV)