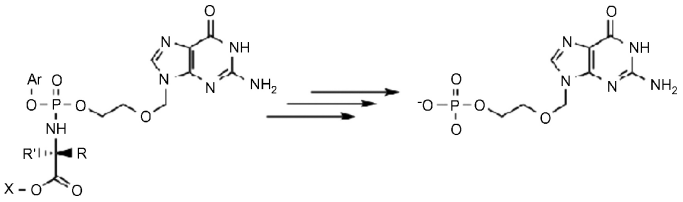

Fig. 1. Bioactivation of acyclovir ProTides.

cant improvement in antiviral activity was observed (McGuigan et al., 2000). In the present work, a new series of optimised acyclovir ProTides with an enhanced biological profile is reported (Fig. 1).

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## 103
## Vidarabine Prodrugs as Potential Inhibitors of Adenosine Deaminase

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Vidarabine (9-(β-D-arabinofuranosyl)adenine or ara-A) is active against herpes simplex virus (HSV) types 1 and 2, cytomegalovirus, and chronic hepatitis B virus (HBV) infections through inhibition of viral DNA synthesis. Although supplanted by acyclovir and other analogs for most applications, vidarabine is still an alternative therapy for acyclovir-resistant HSV and varicella-zoster virus infections. We recently reported that vidarabine was three- to fivefold more active than cidofovir against cow pox and vaccinia viruses in plaque reduction assays [Antiviral Res. 70 (2006) A14]. However, despite the proven efficacy against a variety of viruses, vidarabine suffers some limitations. First and most importantly, it is readily metabolized by adenosine deaminase (ADA) to 9-(β-D-arabinofuranosyl)hypoxanthine (ara-H), which has very low antiviral activity. Secondly, as a nucleoside, vidarabine has low lipophilicity and thus has low intestinal membrane permeability. Finally, it is also poorly soluble in aqueous solutions, thereby limiting options for both parenteral and peroral formulations. To address these concerns, vidarabine 5′-amino acid prodrugs were synthesized and, when perfused intestinally, resulted in increased plasma concentrations. Since it was previously discovered that vidarabine 5′-valerate inhibits metabolism of ara-A to ara-H by ADA [Mol. Pharm. 14 (1978) 366], we confirmed this inhibition ($K_i = 9.5$ μM) and demonstrated that this prodrug was more active verses vaccinia virus in vitro. In contrast, unlike its fatty acid counterpart, the vidarabine 5′-amino acid prodrugs did not inhibit the metabolism of ara-A to ara-H. We conclude that despite certain advantages over vidarabine, the amino acid prodrugs do not inhibit the deamination of the active compound.

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## Megaribavirin Aerosol for the Treatment of Influenza A Virus Infections in Mice

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Clinical efficacy of ribavirin aerosol treatment in mice translated well to natural influenza infections in college students. While newer neuraminidase inhibitors have been developed to treat influenza A and B infections, emergence of drug resistance poses potential problems. Because of this resistance, combination drug treatments have been evaluated. Ribavirin alone or in combination would be an ideal antiviral since it inhibits both influenza A and B viruses and drug resistance has not occurred in the clinical setting. To make ribavirin aerosol treatment a quicker process, limited to once or twice daily treatments, and be more cost effective, a MegaRibavirin formulation (reservoir concentration, 100 mg of ribavirin/mL) was developed that when used with the more efficient nebulizer, the Aerotech II nebulizer, was effective in preventing death in a lethal influenza A/HK/8/68 (H3N2) virus-mouse model. Aerosol generated with the MegaRibavirin formulation using the Aerotech II nebulizer flowing at 10 L of air/min produced aerosol droplets that contained 2.3 mg of ribavirin/L with a mass median aerodynamic diameter of 1.8 μm and a geometric standard deviation of 2.6. Thus, compared to the standard (20 mg/mL) or "high dose" (60 mg/mL) ribavirin concentrations used with the SPAG2-6000 nebulizer that has been used for both influenza and RSV infections, ribavirin aerosol generation was twice as efficient with the Aerotech II nebulizer while maintaining the same aerosol characteristics. Using this system for treatment, a single daily 30-min exposure on days 1–4 produced a survival rate of greater than 90% compared to 0% of animals without treatment. In addition, delaying the start of aerosol treatment for 48 or 72 h and treating just once daily for 30 min for only 2 days (days 2–3 and 3–4, respectively) still significantly increased the rate of survival and mean time to death. For the treatment of influenza in general and specially for pandemic avian influenza, the MegaRibavirin-Aerotech II method of aerosol treatment allows for short treatment periods (30 min once or twice daily), minimizes environmental issues and should

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,