been attributed to hPepT1-mediated transport. In electrophysiology experiments on *Xenopus laevis* oocytes over-expressing hPepT1, we have not detected a significant signal with Val-Ser-OMe cHPMPC amino acid L/D stereoisomers, although stereoisomers having an L-configuration at the N-terminal amino acid potently inhibited Gly-Sar binding. Single side-chain ester-linked amino acid conjugates of cHPMPC have now been synthesized and investigated for transport and affinity in the oocyte model. An L-Val L-Val dipeptide analogue of acyclovir was also evaluated. The 'monopeptide' conjugates exhibited little or no hPepT1-mediated transport in the model, and had reduced affinity compared to dipeptide analogs. In some cases, TFA salts of the analogues produced weak positive signals in the model, whereas the HCl salts gave no signals, indicating the importance of using the latter form of the prodrug in these assays. The results suggest that one or more alternative mechanisms play a role *in vivo* to facilitate transport of the cHPMPC dipeptide prodrugs.

Acknowledgements: This work was supported by NIH grants U01 AI061457 and R44 AI056864. L.W.P. is a 2008–2009 WiSE Merit Fellow.

doi:10.1016/j.antiviral.2009.02.124

120

Compounds Designed to Bind Conserved Regions of Human Papillomavirus (HPV) DNA show Broad-spectrum Activity Against High-risk Genotypes

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Cervical infections by the "high-risk" human papillomaviruses (HPVs), including HPV16 and 18, are usually not treated upon their discovery, but are flagged for later "follow-up." Traditional approaches to antiviral design for HPV have failed for a variety of reasons including the lack of traditional antiviral targets. Therefore, novel antivirals designed to specifically reduce viral persistence are needed. A series of pyrrole-imidazole polyamides was optimized via medicinal chemistry based on an original lead compound designed against a sequence within the ori of HPV16. A set of improved polyamides was prepared, including compounds that potently reduced both HPV16 and HPV31 copy number (compared with vehicle-control) in cells maintaining these genomes as episomes. Keratinocytes maintaining either HPV16 or HPV31 episomes were treated with increasing concentrations of polyamide or vehicle-control for 48 h in order to study dose–response behavior. Loss of episomal DNA was measured by Q-PCR. Of the 46 polyamides tested, including 16 control polyamides not derived from our core lead structure, 12 gave pseudo-IC50s 200 nM against both genotypes, while 4 reduced HPV16 and HPV31 episomal DNA copy number to undetectable levels. Southern blot analysis confirmed these decreases. Broad-spectrum activity is likely achieved due to high conservation in A-T rich regions among high-risk HPV genotypes and the binding degeneracy of polyamides. Treatment of cells with a lead polyamide, followed by removal of compound and passage of cells, resulted in a moderate rebound of viral DNA that did not return to control levels after 6 additional days in culture. Extension of the polyamide treatment period resulted in a remarkably effective delay and inhibition of episomal DNA rebound. These results illustrate that targeting of the HPV ori with polyamides has the potential for potent and long-lasting effects on HPV DNA load.

doi:10.1016/j.antiviral.2009.02.125

121

Synthesis and Biological Studies of Mutagenic Ribonucleoside Analogues as Potential Inducers of *Error Catastrophe* of Riboviruses

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The development of effective treatments against riboviruses (causing many human diseases, i.e. common cold, haemorrhagic fever, AIDS, Hepatitis C, and SARS) is hampered by their ability to rapidly adapt by mutation and to acquire resistance to antiviral drugs. Riboviruses exhibited an extremely high mutation frequency, and this suggests that the viral population exists near the threshold for viral viability. Maintaining such a high mutation frequency is dangerous for the virus. An increase in mutation could result in a lethal increase in the already high proportion of defective viruses.

An antiviral strategy called *lethal mutagenesis* attempts to exploit this high mutation frequency by increasing the mutation rate even further and driving the virus population into "error catastrophe" (lethal accumulation of errors). This new strategy was validated with the demonstration that virus extinction can be achieved with the mutagenic nucleoside analogue ribavirin. Therefore, RNA virus mutagens may represent a promising new class of antiviral drugs.

We describe here the synthesis and biological studies of potential mutagenic ribonucleosides that may be incorporated into the viral genome during replication and, by mispairing, induce lethal mutagenesis. These ribonucleosides bear universal bases with ambiguous hydrogen bonding properties. We have documented various degrees of inhibition of the replication of foot-and-mouth disease virus (FMDV), encephalomyocarditis virus and lymphocytic choriomeningitis virus in BHK-21 cells by several base and ribonucleoside analogues.

VPg uridylylation (initiation of FMDV RNA synthesis) is inhibited by halogenated pyrimidine-triphosphates. The inhibitory activities cannot be accounted for by the toxicity of the drugs on BHK-21 cells. We are currently carrying out experiments to identify the steps in the life cycle of these viruses that may be affected by the drugs.

Acknowledgement: CSIC is acknowledged for financial support (PIF08-019).

doi:10.1016/j.antiviral.2009.02.126

122

Antiflogistics as Viral Inhibitors

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Virus infection of cells induces cytokines production. Inflammatory cytokines increase a permeability of cell membranes and promote virus penetration. Antiflogistics hamper a synthesis of proinflammatory interleukines and therefore may show antiviral properties. (Iso)nicotinic acids derivatives such structure: C_5H_4N–3(4)-$CONH(CH_2)_m$–$(NHCO)_n$–Ar, where m, $n = 0$ or 1 are known as antiflogistics. In this series we found that compounds display antiviral activity against several viruses if they inhibit carrageneen oedema not less than 30%. Weak antiflogistics does not