

protein from an HTLV-1 carrying human T-cell line in insect cells of *Mamestra brassicae*. We further purified the enzyme under native conditions using affinity chromatography. The purified IN carried out activities characteristic of retroviral integrases when it was evaluated for processing and strand-transfer reactions. The extracted 3,5-DCQA inhibited the recombinant IN activities in biochemical assays at 20 nM. Additionally, docking studies supported the hypothesis of an enzyme induced allosteric change by interaction with the caffeoyl groups of 3,5-DCQA and a lysine in position 159 (K159) in the domain outside the active site of IN. Thus, dicaffeoylquinic acids represent an important class of antiviral agents that may contribute to the understanding of the molecular mechanism of viral integration and the design of HTLV therapeutics.

doi:10.1016/j.antiviral.2008.01.090

77

Serine Side-Chain-linked Peptidomimetic Prodrugs of Cidofovir and Cyclic Cidofovir: C-Ester Effects on Transport and Activation

Larryn W. Peterson^{1,*}, Boris A. Kashemirov¹, Ulrika Eriksson³, Jae-Seung Kim², Stefanie Mitchell², Paul Kijek², Kyung-Dall Lee³, John M. Hilfinger², Charles E. McKenna¹

¹ Department of Chemistry, University of Southern California, Los Angeles, USA; ² TSRL, Inc., Ann Arbor, USA;

³ Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, USA

Cidofovir (HPMPC, **1**) and its equivalently potent cyclic form (cHPMPC, **2**) are active against orthopox virus infections, but are limited in this role by low oral bioavailability. In contrast to some alternative prodrugs, peptides offer low toxicity together with versatility in tuning transport and activation pharmacology. We previously reported the synthesis and biological evaluation of several prodrugs of cyclic cidofovir in which the phosphonic acid group of **2** was esterified by the free serine side-chain hydroxyl group of an X-Ser-CO₂Me dipeptide. Val-Ser-CO₂Me cHPMPC (**3**) was stable at pH 3–5, but rapidly released the active drug in cell and tissue homogenates, while exhibiting enhanced transport versus the parent drug in a rat model. Incorporation of D-amino acids, especially at the N-terminus, resulted in increased stability and improved transport, consistent with our present finding that co-dosing with the aminopeptidase inhibitor, bestatin, results in enhanced transport of **3**. Seeking an optimal balance of transport and efficient activation, we are exploring the influence of the carboxyl ester group in these prodrugs. Val-Ser-CO₂iPr cHPMPC (**4**) was synthesized and was also found to be a useful synthon for preparation of its acyclic analogue, Val-Ser-CO₂iPr HPMPC (**5**). LC and LC–MS analysis of **3**–**5** stability in buffer and in cell and tissue homogenates provides evidence that the activation efficiency and pathway are strongly dependent on the ester structure. The results further demonstrate the potential of this peptidization approach in the development of an orally effective form of cidofovir.

Acknowledgements: This work was supported by NIH grants U01 AI061457 and R44 AI056864.

doi:10.1016/j.antiviral.2008.01.091

78

Check of Antiviral Activity of Nanocomposites with Active Check of Antiviral Activity of Drugs Based on Nanocomposites, Which Contained Oligonucleotides for Direct Splitting Viral Genome of Influenza Virus Type A

Dmitriy Pletnev^{1,*}, Aleksei Evdokimov¹, Evgeniy Belanov¹, Ernst Malygin¹, Sergey Balachnin¹, Olga Serova¹, Viktor Zinoviev¹, Valentina Zarytova², Asya Levina², Marina Repkova², Zinifer Ismagilov³, Nadezda Shikina³, Stanislav Zagrebelnyi⁴, Sergey Baiborodin⁵

¹ FSRI SRC VB “Vector”, Novosibirsk, Russia; ² Institute of Biochemistry and Fundamental Medicine SB RAS, Novosibirsk, Russia; ³ Institute of Catalysis SB RAN, Novosibirsk, Russia; ⁴ Novosibirsk State University, Novosibirsk, Russia; ⁵ Institute of Citology SB RAN, Novosibirsk, Russia

Influenza is a mass infection, which yearly registered at different countries and inflict huge economic damage. Main characteristics of influenza virus type A are rapid spreading and high sickness rate. During epidemic fell ill about 20–30% of children and about 5–10% of adult people, during pandemic they are up to 40–60%. Yearly influenza virus and its complications causes death of 250,000–500,000 people in developed countries [Reichert, T.A., Sharma, A., 2001. WER, 2005]. For research new antiviral drug we used nanocomposites. They contain antisense oligonucleotides (as immunostimulating components and facilities for inhibition of NP gene expression of birds' influenza virus) and TiO₂-nanoparticles, which helps penetration of complex into mammal cell. Influence of TiO₂-nanoparticles on different cellular enzymes activity was explored and shown possibility of principle protection of antisense oligonucleotides against nucleases. Cytotoxic tests of TiO₂ shown that TiO₂ is non-toxic for cells at concentrations lower than 100 mg/ml. We test antiviral activity of conjugants which based on TiO₂-nanoparticles. To do this we infected MDSK cells and used nanocomposites. We discovered that conjugants have definitely antiviral activity. When we used nanocomposites amount of survived cells increased by 3.5 times. Thus we show obvious antiviral activity of conjugants against influenza virus type A (H5N1). In perspective, methods we developed can be used to make antiviral drugs against influenza virus type A for humans. **Acknowledgement:** The work is supported by Programme FCSTP 2007-2-1.2-05-02 (lot no. 3).

doi:10.1016/j.antiviral.2008.01.092