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.

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

Larryn W. Peterson[1,*], Boris A. Kashemirov[1], Ulrika Eriksson[3], Jae-Seung Kim[2], Stefanie Mitchell[2], Paul Kijek[2], Kyung-Dall Lee[3], John M. Hilfinger[2], Charles E. McKenna[1]

[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 promoieties, 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-CO_2Me dipeptide. Val-Ser-CO_2Me 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-CO_2iPr cHPMPC (**4**) was synthesized and was also found to be a useful synthon for preparation of its acyclic analogue, Val-Ser-CO_2iPr 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.

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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 Evdokimov[1], Evgeniy Belanov[1], Ernst Malygin[1], Sergey Balachnin[1], Olga Serova[1], Viktor Zinoviev[1], Valentina Zarytova[2], Asya Levina[2], Marina Repkova[2], Zinfer Ismagilov[3], Nadegda Shikina[3], Stanislav Zagrebelnyi[4], Sergey Baiborodin[5]

[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 epidemy falled 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 TiO_2-nanoparticles, which helps penetration of complex into mammal cell. Influence of TiO_2-nanoparticles on different cellular enzymes activity was explored and shown possibility of principle protection of antisense oligonucleotides against nucleases. Cytotoxic tests of TiO_2 shown that TiO_2 is non-toxic for cells at concentrations lower than 100 mg/ml. We test antiviral activity of conjugants which based on TiO_2-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.

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