tive inhibition at concentrations of 0.1 nM. Experiments varying features of the shRNA design showed that, for 25 bp shRNAs, neither the size of the loop (4–10 nt) nor the sequence or pairing status of the ends affects activity, whereas in the case of 19-bp shRNAs, larger loops and the presence of a 3′-UU overhang increase efficacy. A comparison of shRNAs and siRNAs targeting the same sequence revealed that shRNAs were of comparable or greater potency than the corresponding siRNAs. Anti-HCV activity was confirmed with HCV subgenomic replicons in a human hepatocyte line. The results indicate that shRNAs, which can be prepared by either transcription or chemical synthesis, may be effective agents for the control of HCV.

[a] TransDerm, Inc., Santa Cruz, CA, USA.

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Synthesis and Anti-HBV Activity of 7-Deaza-Neplanocin A Analogs

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Four anti-HBV nucleosides (Lamivudine, Adefovir dipivoxil, Entecavir and Telbivudine) have been approved by the US FDA for the treatment of chronic HBV infection. In addition to these drugs, several other nucleosides such as Clevudine (L-FMAU), Valtorcitabine (LdC) and Tenofovir are currently under various stages of clinical evaluation. However, a significant number of patients develop drug resistance during the long-term use of these agents. Thus, there is a critical need to continue discovering and developing safe and effective novel anti-HBV agents to cope with the drawbacks of the current agents.

As part of our antiviral drug discovery program, it was of interest to synthesize less toxic neplanocin A analogs as potential anti-HBV agents. For the synthesis of the analogs, we utilized a key cyclopentenyl carbocyclic intermediate, which was previously developed in our laboratory. From the synthesis, we prepared 10 7-deaza-neplanocin analogs.

Among the 7-deaza naplanocin A analogs, two analogs exhibited significant anti-HBV activity with EC_{50} values of 0.43 and 0.32 μM, respectively based on extracellular HBV virions with negligible cytotoxicity ($CC_{50} > 300$ μM). In addition, these analogues also showed significant anti-HBV activity against variety of clinically relevant Lamivudine-resistant mutants.

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A Novel Class of Amphipathic DNA Polymers Inhibits Hepatitis C Virus Infection by Blocking Viral Entry

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Long (>30 base) phosphorothioate oligonucleotides (PS-ONs) are novel amphipathic polymers that display a sequence-independent antiviral activity against numerous type 1 enveloped viruses. The amphipathic nature of these long PS-ONs targets them to the amphipathic alpha helical "hinge" domains of fusion proteins and inhibits viral entry by blocking virus-cell fusion. The antiviral activity of these molecules in viruses with type I or II fusion mechanisms suggest that structural similarities exist between type I and type II fusion proteins. The aim of this study was to assess the ability of long PS-ONs to inhibit HCV infection by blocking viral entry. Huh7.5 cells were infected with the HCV-containing culture medium (HCVcc) and treated with various PS-ON analogs to assess their inhibitory activity. The antiviral mechanism of action of these compounds was further examined in viral binding and entry assays with HCV-like particles (HCV-LPs) and HCV pseudovirus (HCVpp), respectively and in HCV replicon systems. PS-ONs displayed a similar size dependent antiviral activity, plateauing with 40mer and longer PS-ONs. These compounds potently inhibited HCV infection in both the HCVcc and HCVpp systems with IC_{50} in the range of 10–100 nM and were equally active against HCVpp of various genotypes. Several chemical modifications of these polymers which eliminated their amphipathic character also rendered them ineffective against HCV infection. Active PS-ONs had no effect on viral replication in the NK5.1 and JFH-1 replicon systems or binding of HCV-LPs to Hep3B or Huh7.5 cells but did prevent internalization of HCVpp virions into Hep3B cells, indicating that the target of inhibition by PS-ONs is at the post-binding, cell entry step. Thus PS-ONs (amphipathic DNA polymers) are a promising new class of antiviral compounds that inhibit HCV fusion and entry. The similar chemical requirements on the PS-ON structure (size and amphipathic character) for antiviral activity in both HIV-1 and HCV suggest that the entry mechanisms of HIV-1 and HCV are similar.

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