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Nitazoxanide is an Effective Antiviral Agent Against Both HBV and HCV replication in vitro

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Nitazoxanide (NTZ), a thiazolide, is an anti-infective drug marketed in the United States for treating gastroenteritis caused by *Cryptosporidium parvum* and *Giardia lamblia* and is in late stages of development for treating *Clostridium difficile* and rotavirus-associated diseases. NTZ and its active circulating metabolite, tizoxanide (TIZ), were tested against Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) replication in cell culture. NTZ (EC_{50}, 0.2 μM; SI, 462) and TIZ (EC_{50}, 0.03 μM; SI, 300) exhibited potent and selective antiviral effects against HCV sub-genomic, genotypes 1b and 1a replicons. Moderate synergistic interactions against HCV were observed between nitazoxanide and either alpha interferon 2b, or 2′C-methyl cytidine in combination treatments. Activity against NS5b S282T, and NS3 A156S/V/T drug-resistant mutants, as well as a genotype 2a replicon are being investigated. Both compounds also inhibited intracellular HBV replication and virion production by 2.2.15 cells (EC_{50}, 1.5 μM, SI, 172), and NTZ exhibited moderately synergistic anti-HBV interactions with either lamivudine (LAM) or adefovir dipovoxil (ADV). NTZ was equally effective in inhibiting the replication of several LAM and ADV-resistant mutants. Most notably, NTZ induced a reduction in the production of several HBV proteins (HBsAg, HBeAg, HBcAg) without a corresponding reduction in HBV RNA, indicating a post-transcriptional mechanism. NTZ is currently in clinical trials against HBV and HCV infection. Preliminary reports have demonstrated multi-log declines in HBV viremia (and improvement in serum ALT levels) with NTZ monotherapy, and in HCV viremia with both monotherapy and combination therapy with interferon alpha, during 24–48 weeks treatment regimens. Detailed studies of mechanisms against both HBV and HCV are in progress. Nitazoxanide is a promising new antiviral agent that, due to its probable novel mechanism of action, has substantial potential for use as an adjunct to current and future therapies to enhance sustained response rates against chronic hepatitis virus infection and disease.

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Efficacy of Cationic Lipid-DNA Complexes (CLDC) on Hepatitis B Virus in Transgenic Mice

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Cationic lipid-DNA (non-coding) complexes (CLDC) are activators of the innate immune response inducing substantial TH1 cytokine production as well as natural effector mechanisms. CLDC rapidly induces efficacious natural immune responses that increase survival of rodents with some acute viral infections and cancers. CLDC were evaluated in transgenic mice carrying an infectious clone of hepatitis B virus (HBV). Mice used in the studies were restricted as nursing pups from solid food, because the expression of HBV DNA in the liver was increased above background levels in some mice with this restriction. Survival surgery was performed on these mice to obtain liver biopsies from which to determine their pre-experiment HBV DNA levels. Only animals with suitable levels of liver HBV DNA were entered into the experimental protocols. Intravenous administration of 50 μg/mouse of CLDC on days 1, 7 and 13 reduced liver HBV DNA to similar low levels achieved with the positive control, adefovir dipivoxil. In a subsequent experiment, the same treatment schedule was used to determine that the minimal effective dose was between 0.5 and 0.05 μg/mouse. Selective cytokines were increased in the livers of CLDC- compared to placebo-treated mice in a dose-responsive manner. CLDC were effective in reducing liver HBV DNA and could be considered for further evaluation in other hepatitis models.

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Mononuclear Cells as a Transfer Vehicle For Herpes Simplex Virus (HSV) or Vaccinia Virus (VV) Infection of Epithelial Cells Grown in 3D

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We have previously shown that organotypic raft cultures of human keratinocytes isolated from neonatal foreskins can be infected with different dermotropic viruses, including α-herpesviruses [i.e. Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and varicella-zoster virus] and poxviruses [i.e. vaccinia virus (VV), cowpox virus (CPV) and orf virus]. Normal keratinocytes stratify and fully differentiate in a manner similar