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Furthermore, prediction with NPV=100% and specificity=28% can be obtained already at 1 week. Combining both criteria allows to increase specificity up to 50%. Moreover, by selecting more strict thresholds for the above criteria one obtains PPV=94%.

For HBV two major patterns were identified during weeks 4-48: a flat second phase (RF) or a slow second phase decline (RS) in 35% and 65% of patients, respectively. This slow second phase was then followed by three different third phases: HBV DNA became undetectable (<400copies/ml) (RSBD) in 37%, or reached a flat third phase (RSF) in 35%, or had a staircase pattern (RSFS) in 28% of RF patients. No patients with RF pattern as identified at 48 weeks lost HBeAg during that same period, compared to 28%, 43% and 77% of the RSF, RSFS and RSBD groups. However, when the RF pattern was identified at 16 weeks we find that 10% of early RF patients had HBeAg loss at 16-48 weeks.

CONCLUSIONS: HCV sustained viral response to treatment with peginterferon-alfa and ribavirin can be predicted, independent of genotype, as early as 1 or 4 weeks of treatment. On the other hand, the earliest HBV kinetics can predict HBeAg loss is at 16 weeks. Moreover, changes in HBV kinetic patterns occur even after that time making the prediction of end-point less accurate. This may indicate that HBV has more dynamical viral dynamics as compared to HCV, and that processes triggered later on during HBV treatment can influence response to treatment, while the fate of HCV treatment is determined by early kinetic events.

ABSTRACT 030

Synthesis of a New Series of Nucleoside Analogs with Antiflaviviridae Activity and Their Interaction with RNA-Dependent RNA-Polymerase

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BACKGROUND: The inability of current therapies to achieve a high sustained viral response with all HCV infections highlights the necessity of developing more potent and broad-spectrum inhibitors of all the HCV genotypes. The most promising antivirals target viral proteins or processes that are not endogenous to host cells. Close structural homologs of the HCV RNA-dependent RNA polymerase (RdRp) do not exist within the uninfected host cell; thus, this protein represents an excellent target for antiviral therapy. Under these perspectives, a new series of nucleoside analogs was designed, synthesized and tested for biological activity on cell cultures infected by different *Flaviviridae*, and their interaction with RdRp was investigated by means of molecular modeling.

METHODS: All compounds were obtained by 1) adapting well-known synthetic strategies for the derivatization of hydroxyl moieties in sugar-modified analogs and 2) resorting to standard organic chemistry for base-modified analogs. The derivatives were tested for biological activity and cytotoxicity on virus/cell systems such as MT4, YFV/BHK and BVDV/MDBK. Molecular modeling studies were conducted on a model of the BVDV RdRp, obtained by homology study from the corresponding human enzyme.

RESULTS: Among the plethora of synthesized compounds, a number of different analogs have shown interesting activity data, at least comparable to

Ribavirin, the unique nucleoside analogue currently approved for HCV therapy. We have discovered that the presence of bulky, apolar substituents in the glycosidic portion of the molecule results in derivatives endowed with interesting *Flaviviridae* inhibitory activity. Based on these encouraging results, an explorative molecular modeling study has been undertaken to explore the interactions between the most probable molecular target (RdRp) and the most promising drug candidates, in order to derive a structure-activity relationship, aimed at designing a second generation of derivatives with enhanced potency.

CONCLUSIONS: 1) A series of new nucleotide analogs have been designed and obtained by means of simple synthetic routes. 2) Several of these compounds revealed good activity/cytotoxicity data, at least comparable to Ribavirin. 3) The molecular modeling studies on the interaction between RdRp and the most active compounds allowed for the derivation of a structure-activity relationship, upon which the design of a new series of inhibitors has subsequently been based.

ABSTRACT 031

Inhibition of Authentic Hepatitis C Virus Replication by Arsenic Trioxide and Sodium Stibogluconate

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BACKGROUND: Using a hepatitis C virus (HCV) subgenomic RNA replicon system, drugs currently being used to treat other human diseases were examined for their antiviral activities against HCV. Several drugs including arsenic trioxide (ATO), a compound used to treat acute promyelocytic leukemia, and sodium stibogluconate (SSG), a compound used to treat leishmaniasis, were capable of suppressing replication of HCV replicon. It is pivotal to know whether these drugs inhibit HCV replication in authentic HCV replication systems.

METHODS: The antiviral effect of ATO and SSG was examined using a cell line (293EBNA-Sip-L) proved to be permissive for HCV infection/replication. An *ex-vivo* assay using fresh human liver slices was established and a panel of human liver slices obtained from biopsy samples of patients infected with HCV were used to examine the antiviral activities of these drugs.

RESULTS: Both ATO and SSG suppressed authentic HCV replication in HCV-infected 293EBNA-Sip-L cells. Partial and complete suppression effect was achieved in 2 and 1 of 5 human liver slices, respectively, at 300 nM of ATO. A nearly complete suppression effect was achieved in 4 of 6 human liver slices at 100 μg/ml of SSG, much lower than what was required to treat leishmaniasis.

CONCLUSION: Both ATO and SSG suppressed authentic HCV replication. A human trial is mandatory to evaluate the roles of these drugs in treating HCV infection.

ABSTRACT 032

Characterization of Hepatitis C RNA-Dependent RNA Polymerase Inhibitors that are Competitors of RNA Template Binding

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BACKGROUND: The RNA-dependent RNA polymerase (NS5b) of hepatitis C virus is an essential enzyme in the replication of viral RNA and a primary target for drug discovery programs. We have bacterially overexpressed a truncated form of NS5b and purified it to homogeneity in support of our efforts to identify novel NS5b inhibitors. A series of non-nucleoside compounds was synthesized, including a number of potent inhibitors of NS5b. An initial lead compound, GL49174, was found to inhibit the *de novo* (primer-independent) synthesis of HCV RNA with an IC_{50} of 0.26 uM and was chosen for comparison to several known inhibitors. These include representative inhibitors disclosed by Shire Pharmaceuticals (Compound B), GlaxoSmithKline (Compound C), and Japan Tobacco (Compound D).