PRECLINICAL CHARACTERIZATION OF POTENT CORE PROTEIN ASSEMBLY MODIFIERS FOR THE TREATMENT OF CHRONIC HEPATITIS B

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Background

Approximately 240 million people worldwide are chronically infected with Hepatitis B virus (HBV). A significant proportion will develop chronic liver diseases, such as hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Two classes of treatment options are currently approved for chronic HBV: nucleotide analogs (e.g., adefovir, entecavir [ETV], tenofovir disoproxil fumarate, lamivudine, and telbivudine) and interferons (IFN) and pegylated interferons (PEG-IFN). These therapies are effective in inhibiting HBV replication and reducing the risk of chronic liver diseases, however they carry a number of side effects and provide a cure to chronic HBV. Thus, there is a need for a novel class of potent and selective HBV inhibitors. The core protein is a highly conserved viral protein that has no human homolog and is involved in multiple steps of the HBV life cycle. Core Protein Assembly Modifiers (CPAMs) represent a novel class of disease-modifying agents for the treatment of chronic HBV and have been shown to interfere with the HBV capsid assembly process and reduce HBV replication. Here we report the preclinical characterization of a potent series of CPAMs.

Materials and Methods

**HBV DNA Replication and HBAg Production are Reduced in CPAM Treated AD38 Cells**

Cell lines and compounds treated: AD38 cells were treated with DMSO (vehicle) or CPAMs at indicated concentrations. Supernatants and cells were harvested at 48 h post treatment. The addition of CPAMs reduced the production of HBV DNA and HBAg in AD38 cells.

**CpAMs Interfere with HBV RNA Packaging in Induced AD38 Cells**

Encapsidated HBV RNA was reduced in CPAM treated AD38 cells. This indicates that CPAMs interfere with HBV RNA packaging and replication.

**CpAMs Inhibit Establishment of cccDNA in a HepG2-NTC HBV Infection Model**

CpAMs were added to HepG2 cells to inhibit cccDNA formation. The cccDNA levels were significantly reduced in the presence of CpAMs.

**CpAMs Show Activity Specific to HBV and are Generally Non-Cytotoxic**

CpAMs were evaluated for their activity against HBV and other viruses. The selectivity factor (SF) was calculated to determine the non-cytotoxic nature of the CPAMs.

Conclusions

A new series of potent and selective CPAMs have been identified and their effects upon the viral life cycle characterized. CPAMs have shown the potential to modulate and reduce HBV virus assembly, suggesting a potential role for CPAMs in the treatment of chronic hepatitis B. Further studies are needed to fully understand the mechanism of action of CPAMs.