Non-HAP class I capsid assembly modulators have distinct profiles and a differentiated mechanism of action

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Abstract 1208

Background

Hepatitis B virus (HBV) capsid assembly is an attractive target for the treatment of chronic hepatitis B. In addition to inhibiting HBV RNA encapsidation and formation of infectious HBV particles, class I capsid assembly modulators (CAM1s), also called CAM-A s, induce HBV core protein aggregation and subsequent HBV DNA reduction in AAV-HBV mice.7,8 Most known CAM1s are heterosubunit hydrophodiprins (HAPs), such as RG7907 and RG7907Cgl,1 which have several drawbacks including suboptimal PK profiles and potential for drug-drug interactions. We recently reported on ALG-005398, the first non-HAP CAM1. Here we present a characterization of two CAM1 profiles distinct from the typical HAP profile and explore their differentiation vs. HAP RG7907.

Methods

Antiviral activity on HBV DNA was determined in HepG2.117 cells using qPCR. Further characterization was performed using electron microscopy visualization and immunofluorescent HBc staining. HBc-dependent CAM1-induced cell death (CCD) was investigated by prolonged treatment of HepG2.117 cells. In vivo antiviral efficacy was assessed in the AAV-HBV mouse model.7

HAPs, profile A, and profile B CAM1s induce different HBC aggregate types

To overcome the drawbacks associated with the CAM1 HAP chemotype, we initiated a drug discovery effort to identify and optimize Non-HAP class I capsid assembly modulators that have distinct profiles and a differentiated mechanism of action. We recently reported on ALG-005398, the first non-HAP CAM1. Here we present a characterization of two CAM1 profiles distinct from the typical HAP profile and explore their differentiation vs. HAP RG7907.

Profile CAM1s have distinct HBV DNA inhibition characteristics

All three tested compounds inhibited intracellular HBV DNA to a similar extent. Interestingly, profile B reference ALG-005863 displayed a considerably steeper slope (2.5) compared to RG7907 and ALG-005398 (slopes of 1.4 and 1.5 respectively), suggesting different HBV binding kinetics. When comparing EC50 values for HBV DNA and HBc spotting, ALG-005398 again behaved differently with only a 2-fold difference between the EC50 values for both phenomena, compared to a 10-fold ratio for the other compounds. These trends were observed for many more molecules categorized into HAP, profile A, and profile B, based on their chemotype and spotting phenotype (data not shown).

HBC-dependent CAM1-induced cell death kinetics differ between profiles

As described in the accompanying poster by Kum et al (abstract 1202), RG7907 induces an HBC-dependent cytotoxicity (CCD) upon prolonged treatment that may help explain the observed loss of HBV-infected hepatocytes in the AAV-HBV mouse model. To investigate whether the different CAM1 profiles translate to different CCD phenotypes, HepG2.117 cells were incubated with different compound concentrations for prolonged periods of time, in the absence or presence of doxycycline (with or without HBC incubation). Profile B ALG-005863 did show CCD, but displayed delayed kinetics compared to RG7907 with the effect only seen at low dose (50 nM) and 7 days of incubation. Conversely, profile A ALG-005398 did not show any CCD at all, with virtually identical curves in the presence or absence of doxycycline. Profile A ALG-005398 did show CCD, but displayed delayed kinetics compared to RG7907 with the effect only becoming apparent after 7 days of incubation.

Conclusions

Non-HAP CAM1s have profiles that are clearly distinct from known HAP CAM1s such as RG7907. The reported data provides in vitro evidence that CAM1s induced by optimal non-HAP CAM1s have suitable ADME and PK profiles, and their representation may offer new options to address some of the limitations observed with the HAP class of compounds. In particular, profile A CAM1s such as ALG-006162 display a sustained HBsAg reduction in AAV-HBV mice, demonstrating promising in vivo potential.

References