ALG-005398 is a Potent Non-HAP Class I HBV Capsid Assembly Modulator that Strongly Reduces HBsAg Levels in Vivo

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Background
Hepatitis B virus (HBV) capsid assembly is an attractive target for the treatment of chronic hepatitis B. In addition to inhibiting HBV DNA replication and formation of infectious HBV particles, Class I capsid assembly modulators (CAMs) induce HBV core protein (HBc) aggregation and sustained HBsAg reduction in AAV-HBV mice. All known Class I CAMs are heterodimeric proline-rich peptides (HRPs), such as RG7907 and GLS4.1 As a part of our efforts to advance multiple structurally diverse CAMs, we report on ALG-005398, a first representative of a series of non-HAP Class I CAMs, identified using structure-based design and scaffold hopping.

ALG-005398 is a potent HBV DNA inhibitor

The HepG2.117 cell line contains a stably integrated genome D HBV genome. ALG-005398 was highly effective in reducing the amount of produced HBV DNA (EC50 = 3 nM). When additional DnaJ digestion steps2 were performed to determine EC50, EC60, and EC90 values for ALG-005398, confirming its potential to reduce HBV DNA levels by several orders of magnitude. ALG-005398 is an HAP Class I CAM and strongly inhibited when compound was added at the time of infection, as evidenced by reductions in extracellular HBsAg and intracellular HBV RNA. In vivo antiviral efficacy was assessed using a 1x10^6 infectious titer of virus in newborn C57BL/6J mice infected with HBV recombinant AAV. ALG-005398 strongly reduced the amount of detectable HBc; possibly aggregated HBc is not solubilized under the tested conditions or does not migrate during SDS-PAGE due to its large molecular size.

ALG-005398 reduces HBsAg levels in vivo with minimal ALT increase

The AAV-HBV model was used to assess the efficacy of ALG-005398 in vivo. ALG-005398 at 30 mg/kg/dose bio was tested and resulted in a multiphasic reduction in HBV DNA, with a 6.4 log10 IU/mL reduction after 95 days of treatment. A significant decrease in serum HBsAg levels was observed with a 2.24 log10 IU/mL reduction with paced kinetics, the main decline manifesting between day 49 and 95 of ALG-005398 treatment with only a minor change in ALT. This is in contrast to RG7907 for which a pronounced ALT flare was reported.12 Significant decreases in HBsAg levels were also noted but with a slight delay compared to HBsAg decline. Immunohistochemical staining of liver sections from 5 mice showed a dramatic disappearance of intraphasic HBc. In line with serum HBV DNA, liver pgRNA levels were also significantly reduced. Interestingly, quantification of liver total HBV and HBV-HBV livers demonstrated a 10-fold reduction in the amount of AAV-HBV episome in the livers of Class I CAM-treated animals, explaining the reported sustained HBsAg reduction after stopping treatment with a HAP Class I CAM.12

Conclusions
ALG-005398 is the first non-HAP Class I CAM reported to date. It showed excellent in vitro and in vivo antiviral activity, including a pronounced HBsAg reduction in vivo, with a minimal ALT elevation and paused kinetics shown for this lead compound confirm that this is an attractive chemotype for further development. CAMs from other chemical series are also advancing in the Aligos pipeline.

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