AASLD NOV. 5-9, 2026
The Liver Meeting®
Denver, CO
Poster 3224

POTENT IN VITRO INHIBITION OF HEPATITIS DELTA VIRUS REPLICATION BY THE ANTISENSE OLIGONUCLEOTIDE ALG-215007

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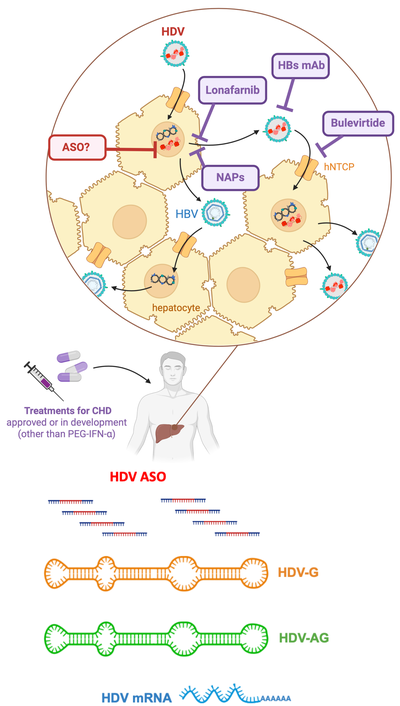
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BACKGROUND AND AIMS

Current treatments for chronic hepatitis delta virus (HDV) infection (Peg-IFN-α and bulevirtide) rarely cure patients. New direct-acting agents targeting HDV replication could therefore be a valuable addition to the current therapeutic arsenal.

Since HDV replicates its RNA genome in the nucleus via a rolling-circle process, and antisense oligonucleotides (ASOs) act in both the cytoplasm and the nucleus, we hypothesized that ASOs targeting HDV RNAs may potently and specifically inhibit intracellular HDV RNA amplification irrespective of helper HBV. In addition, unconjugated ASOs may distribute to Kupffer cells and stimulate Toll-like receptor 8 (TLR8), contributing to the antiviral effect.

We synthesized 112 different 5-10-5 gapmer ASOs targeting conserved regions of HDV and screened them for antiviral activity; the HBV-directed ASO bepirovirsen was used as a non-targeting ASO control. Here we describe the in vitro antiviral activity of the lead candidate ALG-215007.

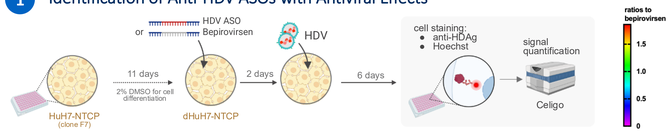


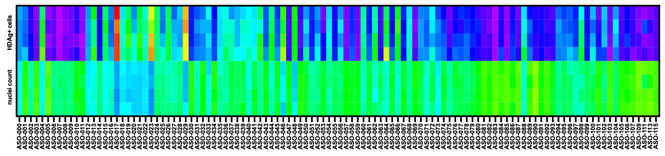
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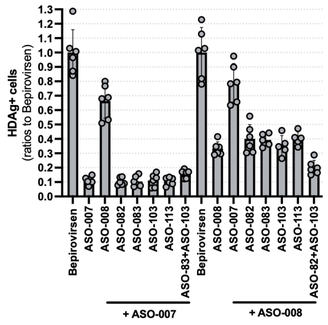
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RESULTS

1 Identification of Anti-HDV ASOs with Antiviral Effects

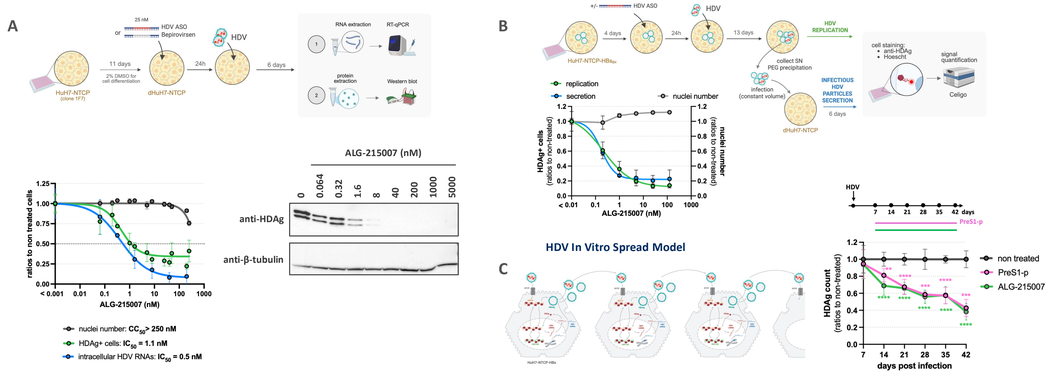






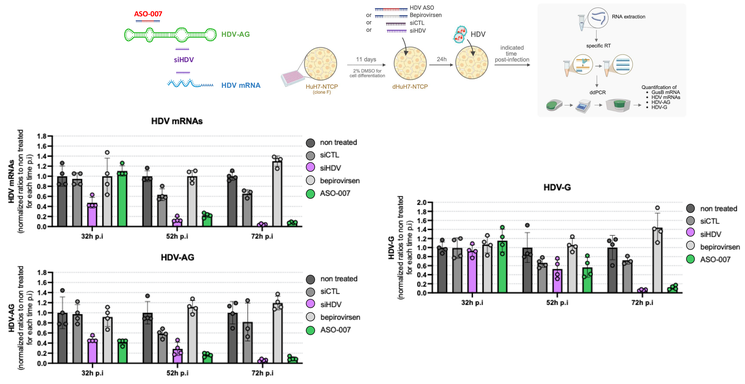
- Screening 112 anti-HDV ASO candidates identified 19 hits that gave a ≥ 75 % reduction in HDAg+ cells without toxicity.
- Combining active anti-HDV ASOs did not increase the antiviral effect, while complementary ASOs (ASO-007 and -008) acted as antagonists.

2 ALG-215007 Decreases All HDV Replication Markers



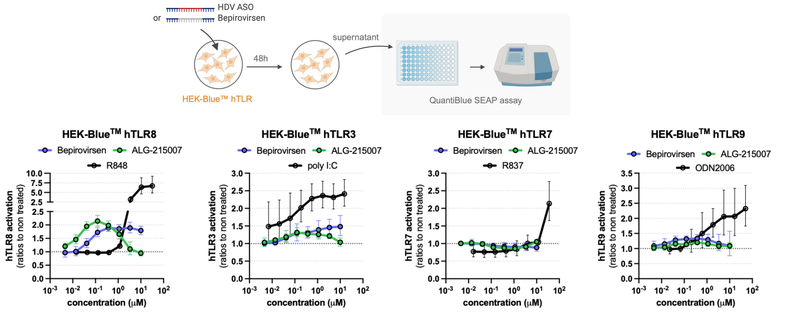
- ALG-215007 inhibited intracellular HDV RNA and HDAg production (A), release of infectious virus (B) and viral spread (C).

3 ALG-215007 Targeting of the HDV Antigenome



- ALG-215007 first inhibited antigenome (AG), followed by mRNA and genome (G).

4 Mild Induction of hTLR8 by ALG-215007



- ALG-215007 showed mild induction of hTLR8, but not 3, 7 or 9, similar to bepirovirsen.

CONCLUSIONS – ALG-215007:

- **Potently inhibits HDV replication in multiple cellular systems and across all read-outs, with IC_{50} values around or below 1 nM, considerably more potent than most other ASOs.**
- **Decreases HDV genome, antigenome and mRNA levels and strongly impairs HDV propagation in vitro, slightly faster than a preS1 peptide equivalent to bulevirtide.**
- **Stimulates hTLR8, but not hTLR3, hTLR7 or hTLR9, with an in vitro profile similar to bepirovirsen.**
- **Is a highly potent ASO in vitro, directly targeting HDV replication in the hepatocyte and possibly also inducing antiviral cytokines, making it a promising candidate for further exploration.**

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Financial disclosures: YD, JH, LD, IH, KP, LB, JAS, VR and DBS are Aligos employees and may own Aligos stock. Figures created with BioRender.com