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POSTER #2

AN ANTISENSE OLIGONUCLEOTIDE STRATEGY TARGETING THE HEPATITIS DELTA VIRUS

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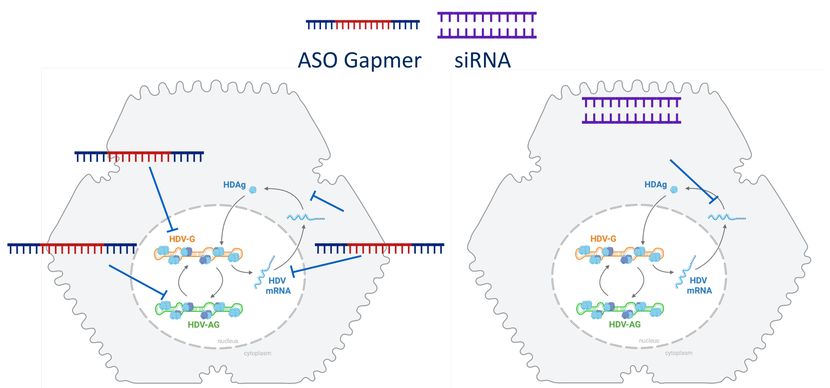
INTRODUCTION

- Hepatitis D virus (HDV) is a satellite virus of Hepatitis B virus (HBV)
- Estimated 12-15M chronically co-infected HBV/HDV patients worldwide[1]
- Co-infection results in more rapid progression of severe hepatitis, cirrhosis, and HCC[2]
- EMA approved entry inhibitor Bulevirtide suggests that there is potential for curative regimens[3]
- No known HDV-targeted RNA-based therapeutics are in development
- HDV replication in nucleus may be vulnerable to ASO slicing of genome, antigenome, or mRNA
- Anti-HDV ASOs may also inhibit HDV mRNA in the cytoplasm



OBJECTIVES

- Identify accessible HDV target regions in the genome, antigenome, or mRNA
- Evaluate the hypothesis that ASOs are superior to siRNAs in HDV inhibition due to their ability to access nuclear and cytoplasmic HDV RNA (genome, antigenome and mRNA) relative to siRNA's sole access to cytoplasmic mRNA
- Generate data to support progression of ASO into animal models for the treatment of HDV

IN SILICO SCREENING AND IDENTIFICATION OF ASO TARGETS

Scanned HDV genome
- Used **HDV_GT1_GENOME_PSVLD3** as starting reference sequence
- Enumerated all 20-mer positions

→ **1678** 20-mer ASO target genome
1678 20-mer ASO target antigenome

Determined oligo positional conservation across HDV genotypes
- Requiring **≥95% conservation** in alignment of **genotype 1**

→ **58** 20-mer ASO target genome
58 20-mer ASO target antigenome
→ **13** also target mRNA

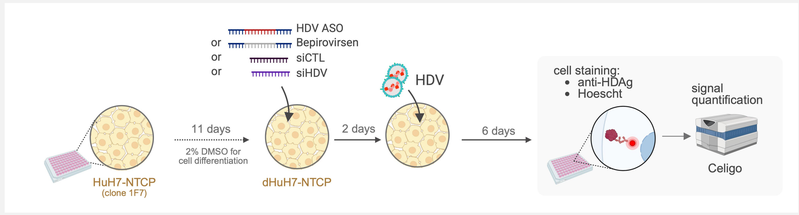
Determined off-target gene hits for human and other non-clinical species on spliced mRNA hits as 1st filter
- No **human** hits with ≤2 mismatches

→ **36** 20-mer ASO target genome
36 20-mer ASO target antigenome

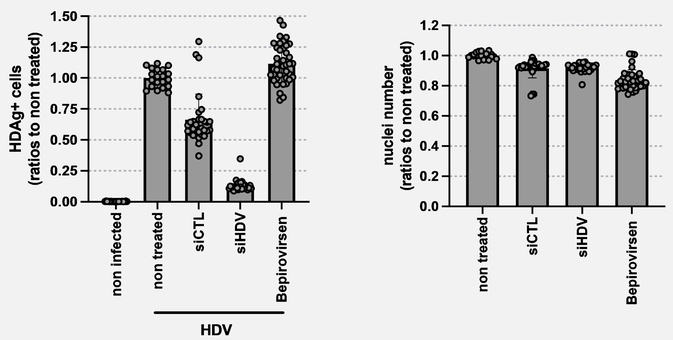
Determined off-target gene hits for human and other non-clinical species on unspliced pre-mRNA hits as 2nd filter
- No **human** hits with ≤2 mismatches

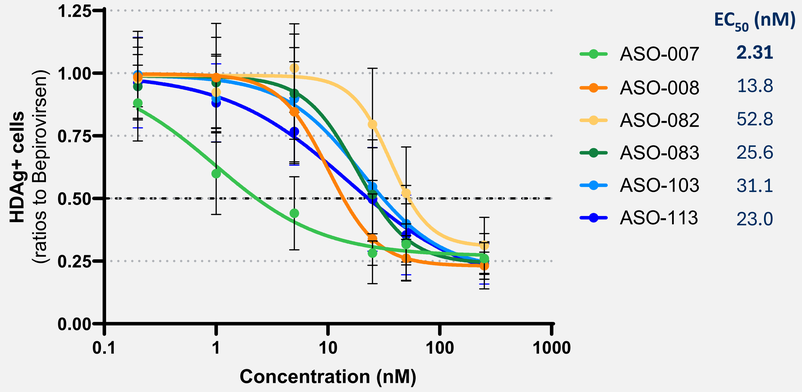
→ **23** 20-mer ASO target genome
15 20-mer ASO target antigenome

RESULTS

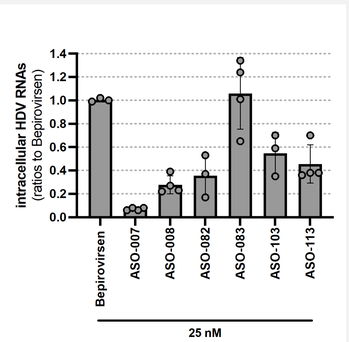


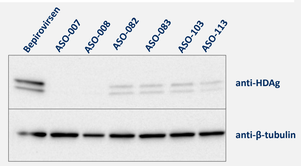
- 116 ASOs (5-10-5 MOE-DNA-MOE gapmers) targeting the genome or antigenome of 58 identified regions of interest were synthesized
- These ASOs were evaluated in a single point dose (1 µM) screen in HDV mono-infected differentiated HUH7-NTCP cells (dHUH7-NTCP)
- Non-targeted controls (Bepirovirsen, and siCTL) and HDV mRNA ORF targeting siRNAs (siHDV) were screened in parallel
- Cell staining readout used for both presence of HDAg and cell viability (HDAg or Nucleus)
- 19 ASOs were able to reduce HDAg >75% with no observable toxicity

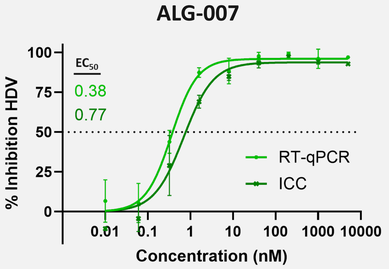




- Follow-up dose response identified 6 ASOs with EC_{50} <53 nM, including ALG-007 with an EC_{50} of 2.31 nM
- Corresponding protein reduction is also observed by western blot
- Hit ASOs reduce HDAg by immunofluorescent staining (ICC) and RNA levels by RT-qPCR
- Slight reduction in EC_{50} if dosing occurs after HDV infection







CONCLUSIONS

- **Scan of the >3000 20-mer targets on HDV genome revealed 58 potential target sites with high conservation across HDV genotypes**
- **116 ASOs MOE-DNA gapmers were synthesized to target the 58 sites' genome or antigenome sequences**
- **Screening identified 19 ASOs that were able to reduce HDsAg levels by >75% at 1 µM**
- **6 ASOs evaluated by dose response; the most active compound was ALG-007 with an EC_{50} of 2.34 nM**
- **Screen reconfirmed 6 hits by western blot, ICC, and RT-qPCR; all results correlated with previously observed activity**
- **Ongoing efforts are evaluating the mechanism of action (impact on genome, antigenome, mRNA levels; impact on HDV replication and viral particle production)**

REFERENCES
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