

Antisense oligonucleotide-based strategy to target hepatitis delta virus infections



Yannick Debing¹, Caroline Pons², Faustine Bernardin², Lars Degrauwe¹, Kellan Passow³, Isabel Heremans¹, Aneerban Bhattacharya³, Antitsa Stoycheva³, Lawrence Blatt⁴, Julian A. Symons³, Andreas Jekle³, Vivek Rajwanshi³, David B. Smith³, Eloi R. Verrier², David Durantel² and Julie Lucifora²



Contact information

julie.lucifora@inserm.fr

ydebing@aligos.com

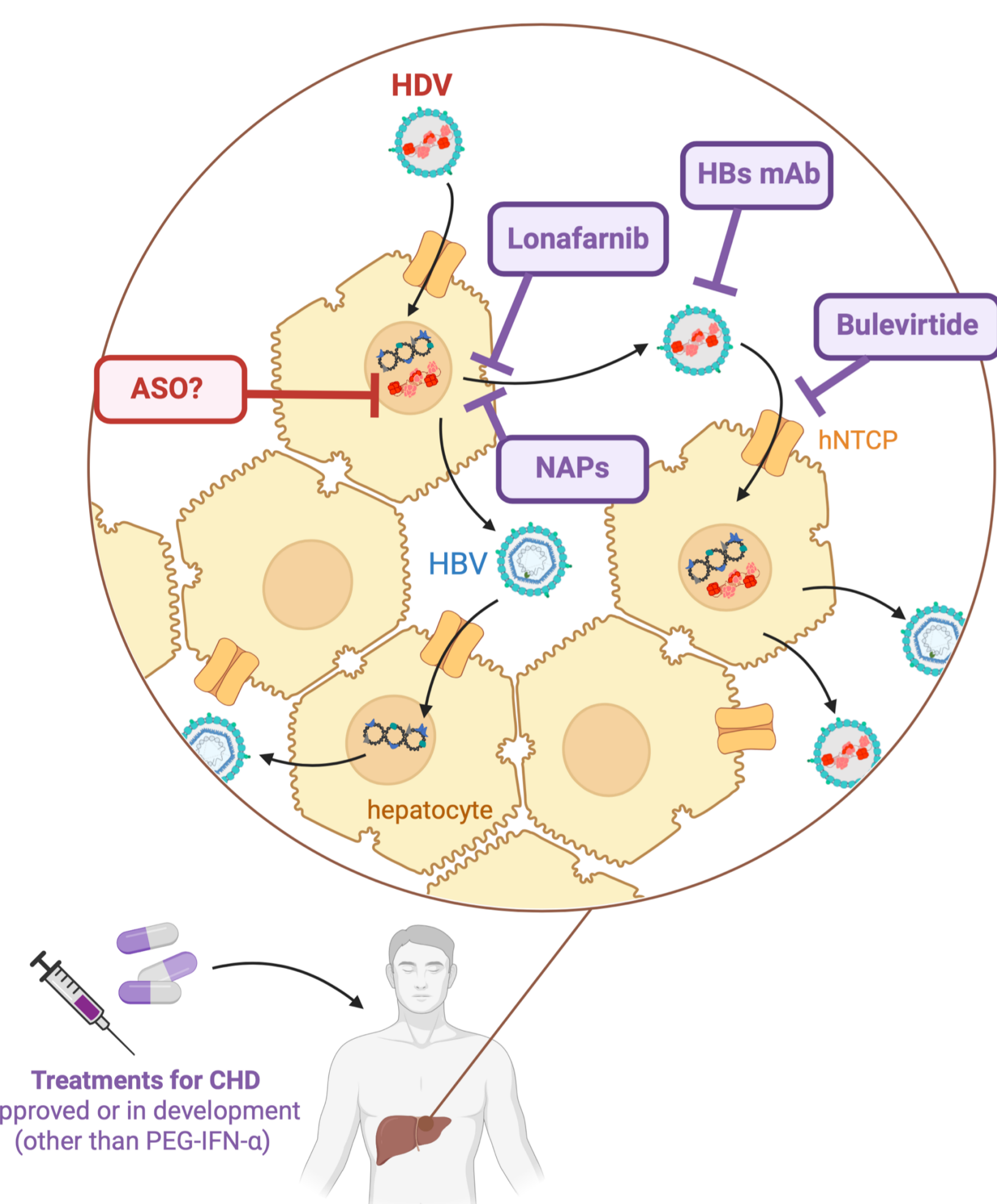
¹Aligos Belgium BV, Gaston Geenslaan 1, 3001 Leuven, Belgium

²CIRI, Centre International de Recherche en Infectiologie, Univ Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, Lyon, France

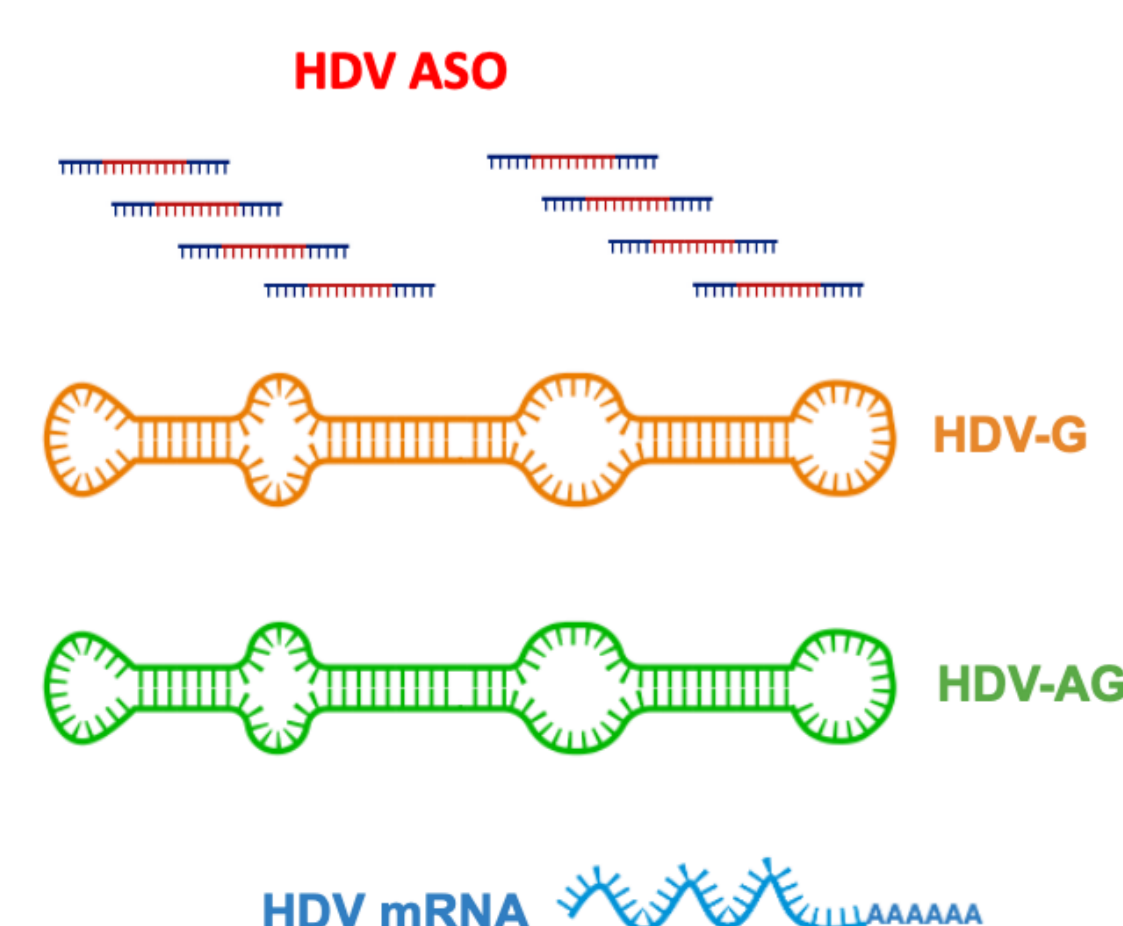
³Aligos Therapeutics, Inc., 1 Corporate Drive, South San Francisco, CA 94080

Background and aims

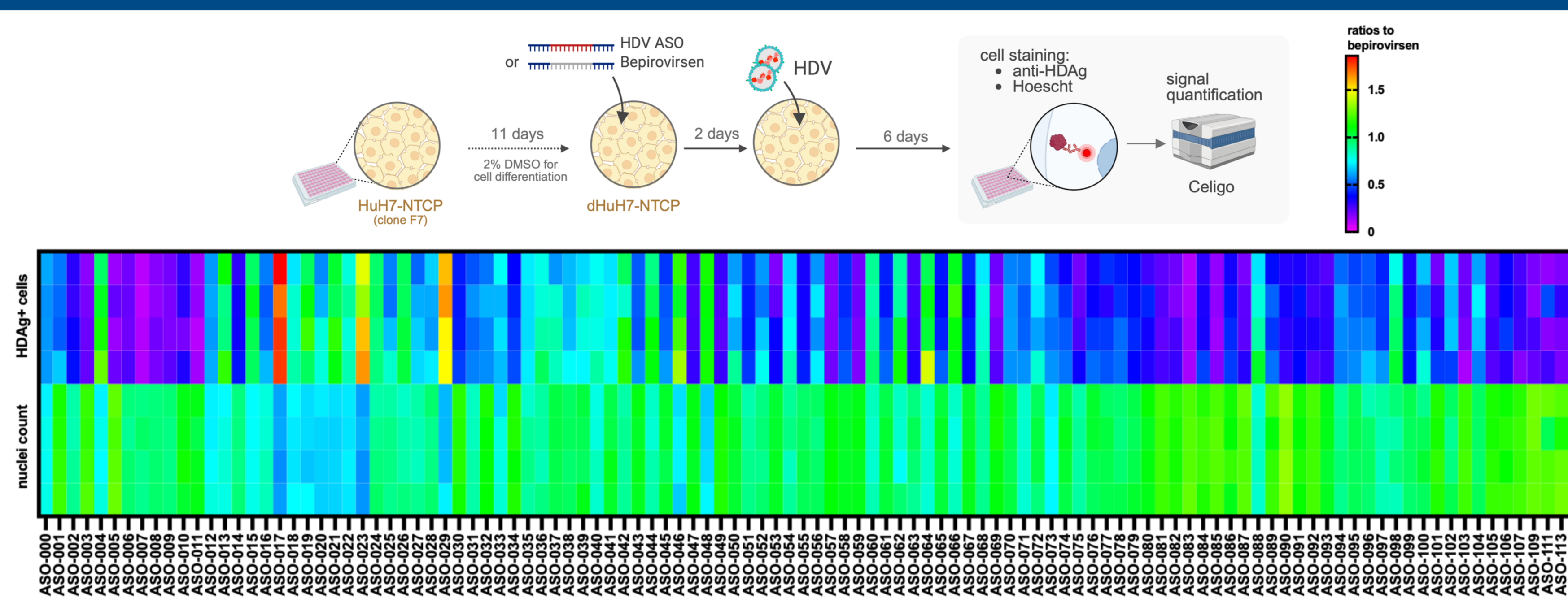
Currently approved treatments for chronic hepatitis delta virus (HDV) infection (Peg-IFN- α and bulevirtide) rarely cure patients in a finite treatment regimen. New direct-acting agents (DAA), targeting HDV replication, could therefore be a valuable addition to the current therapeutic arsenal.



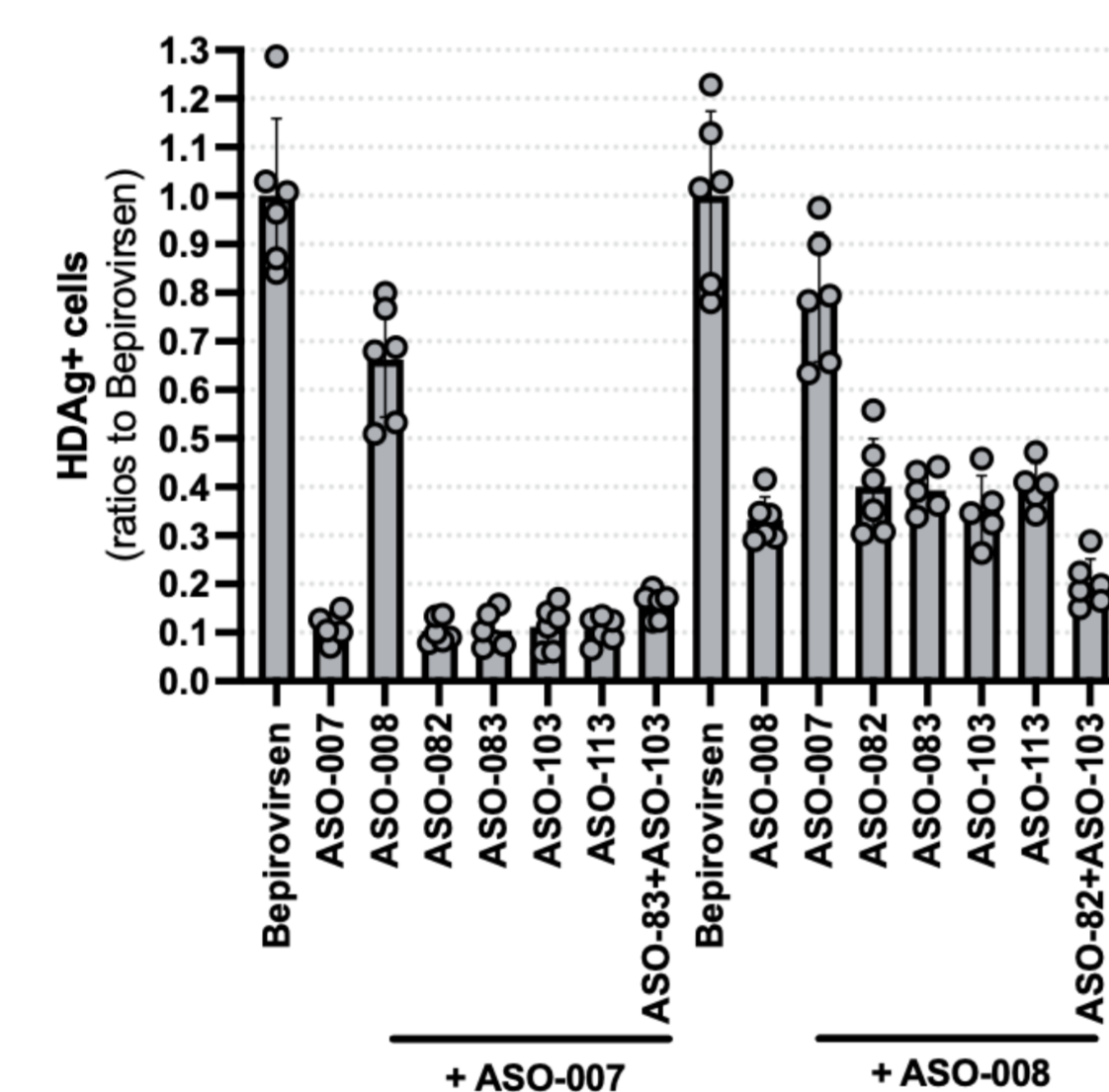
Since HDV is an RNA virus replicating its genome via a rolling-circle process in the nucleus, and antisense oligonucleotides (ASOs) are known to act both in the cytoplasm and the nucleus, we hypothesized that ASOs targeting HDV RNAs may potently and specifically inhibit intracellular HDV RNA amplification irrespective of helper HBV. We synthesized 112 different 5-10-5 gapmer ASOs targeting conserved regions of HDV and screened them for their antiviral effect on HDV. The HBV-directed ASO, bepirovirsen, was used as a non-targeting ASO control.



1. Identification of anti-HDV ASOs with antiviral effects

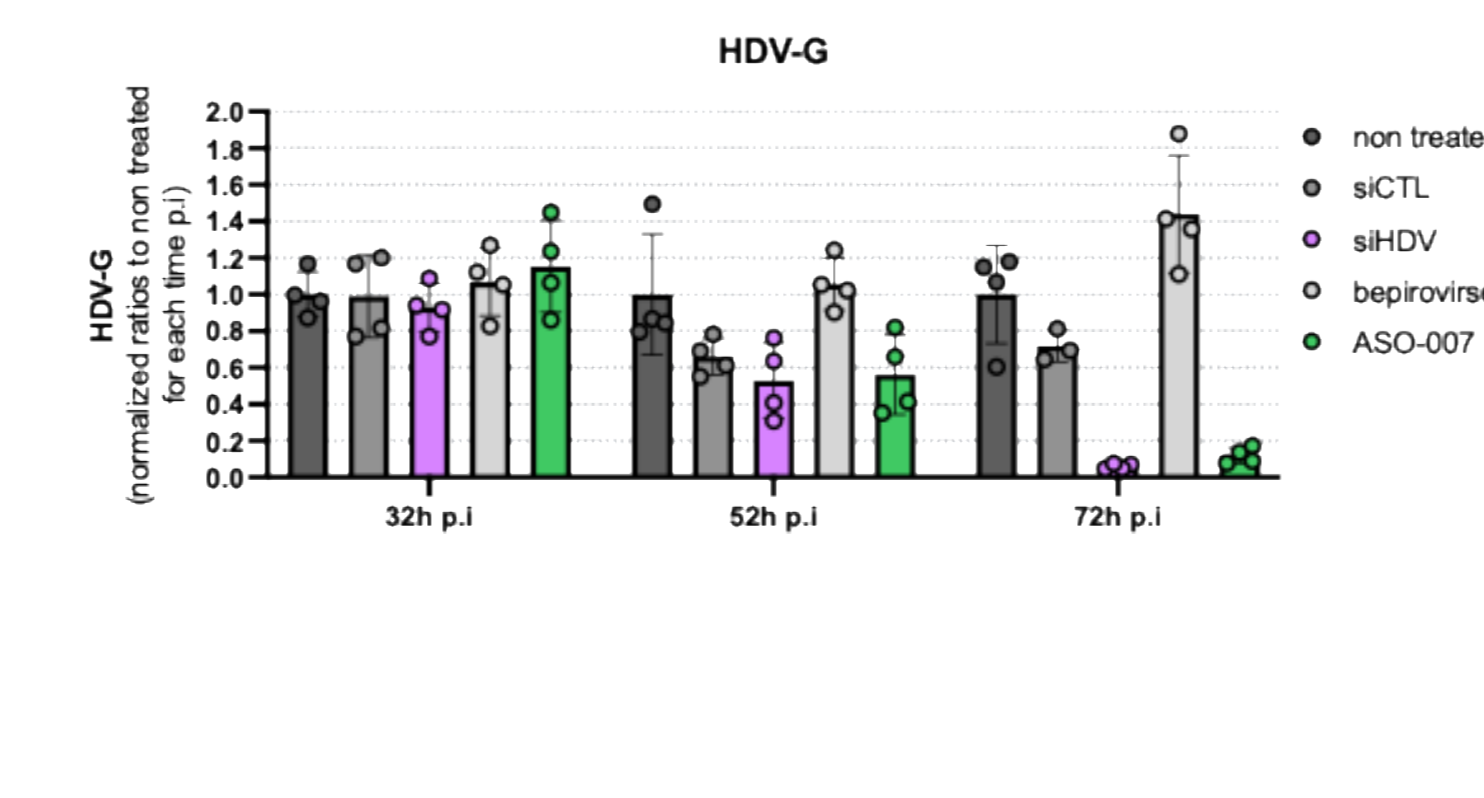
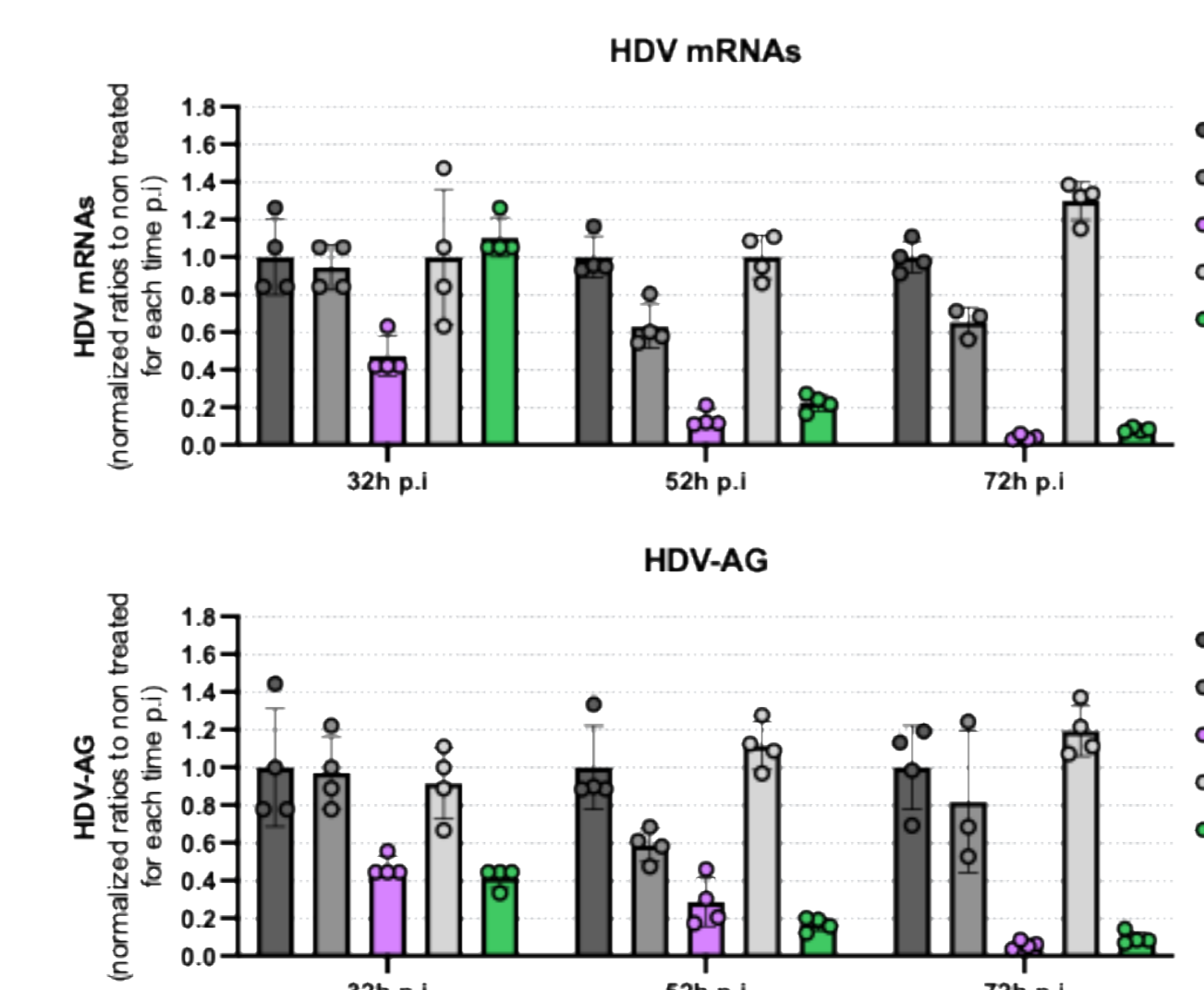
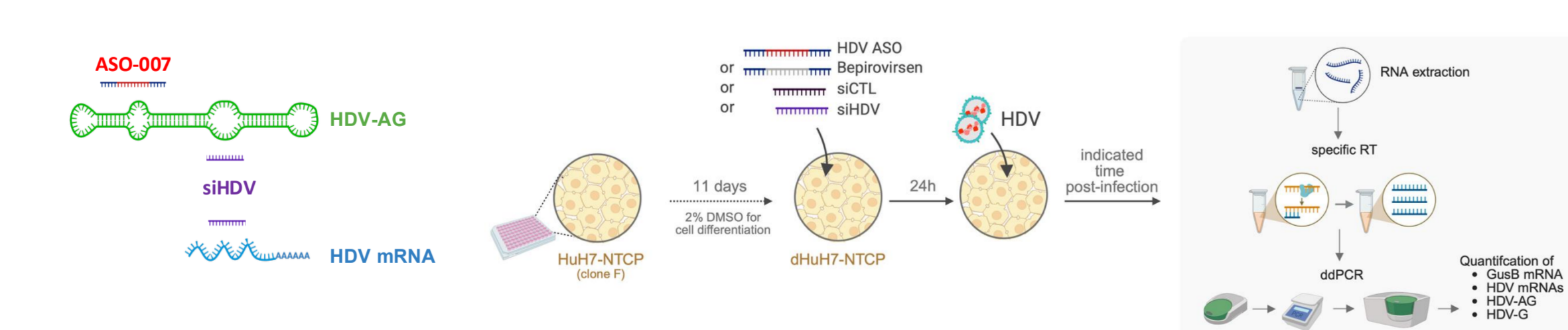


19 anti-HDV ASO candidates allowed a $\geq 75\%$ reduction of the levels of HDAg+ cells without toxicity

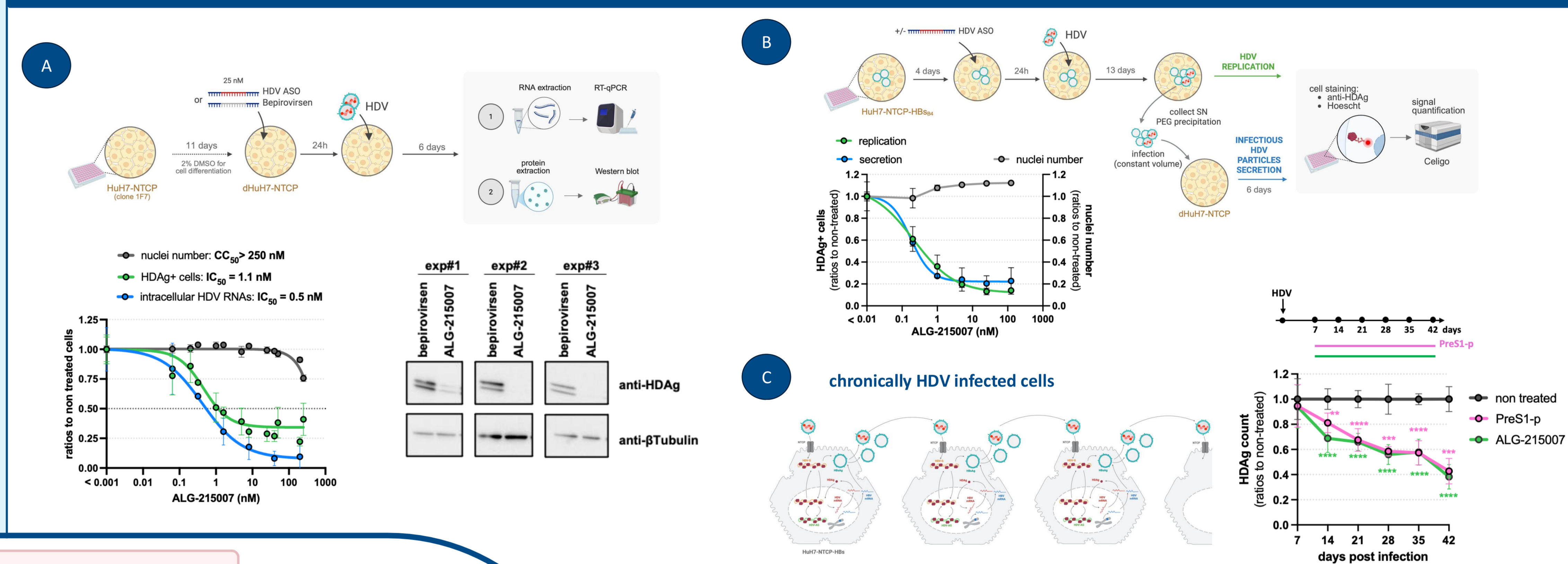


Combination of active anti-HDV ASOs did not increase the antiviral effects and complementary ASO (007 and 008) are antagonists

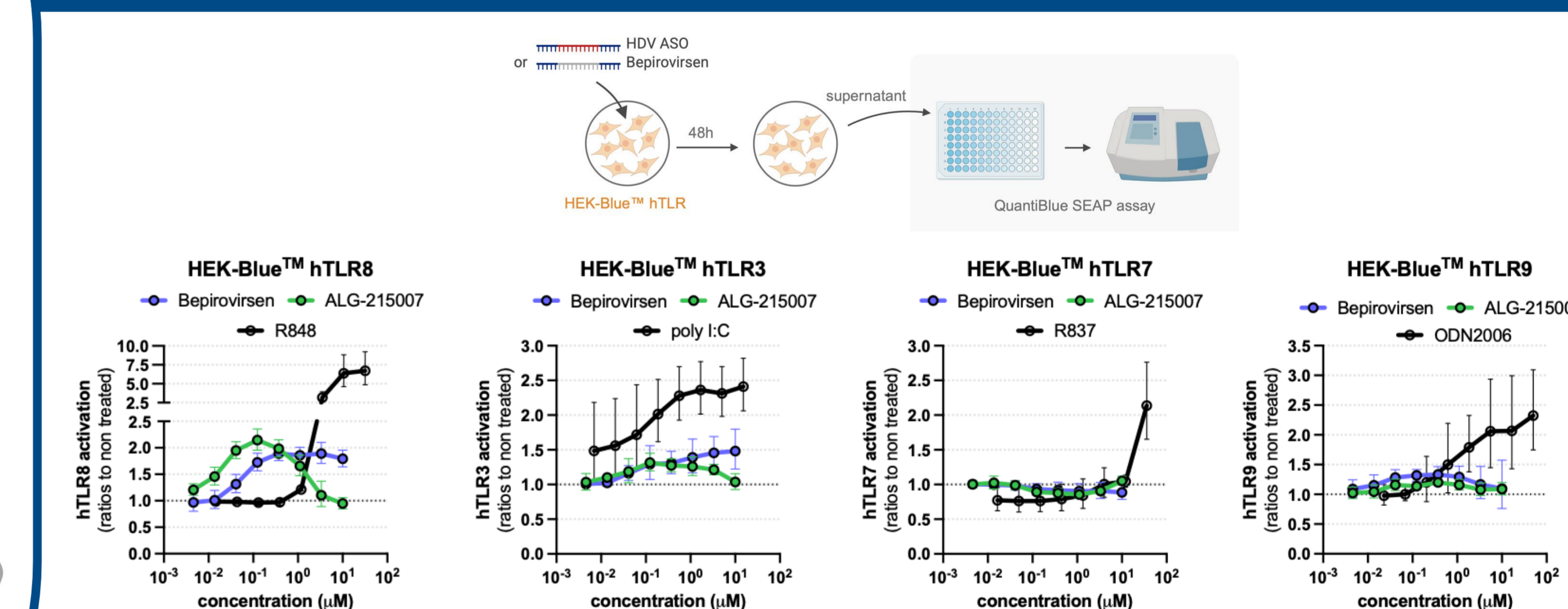
3. ALG-215007 targeting of HDV-AG



2. Anti-HDV ASO ALG-215007 decreases all HDV replication markers



4. Slight induction of hTLR8 by ALG-215007



5. Design for in vivo evaluation of ALG-215007

