REP 2139 has a direct antiviral effect on HDV replication

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Disclosures

No discusures relative to this presentation	
Relations that could be relevant for the meeting	**Company names**
Sponsorship or refund funds	Gilead, , Abbvie, MSD, Inventiva, Roche,
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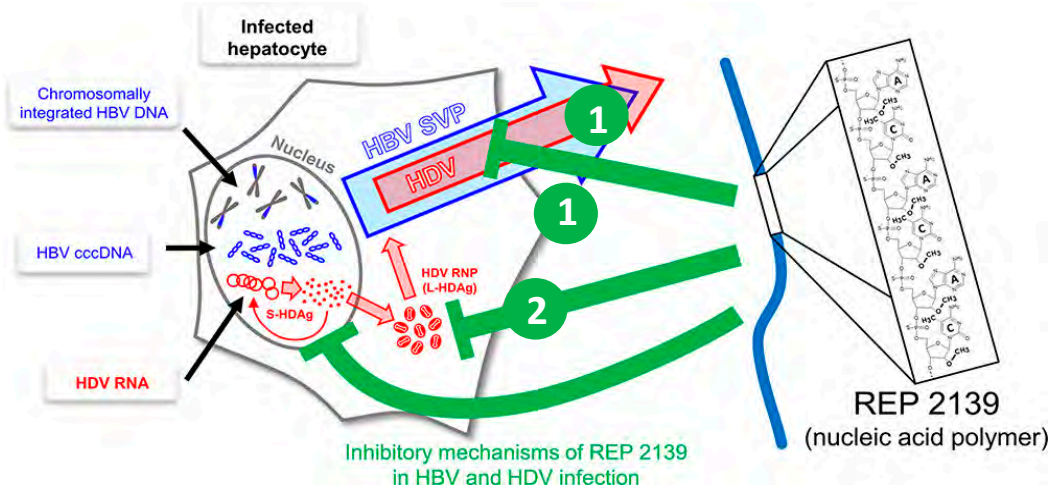
Other relations (Speaking and Teaching)	Gilead, Abbvie, Ipsen

REP 2139 has multiple molecular mechanisms

- REP 2139 blocks HBV subviral particles assembly and secretion, an effect which also blocks HDV ribonuclear protein (RNP) envelopment and HDV secretion from infected cell.



1 Bind HSP40 chaperone DNAJB12 (ERGIC)

Inhibition of HBV SVP assembly

Inhibition of HDV RNP envelopment

2 Bind small and large isoforms of HDAg (nucleus)

Shamur 2017; 2: 877-889

Inhibition of HDV RNP assembly ??

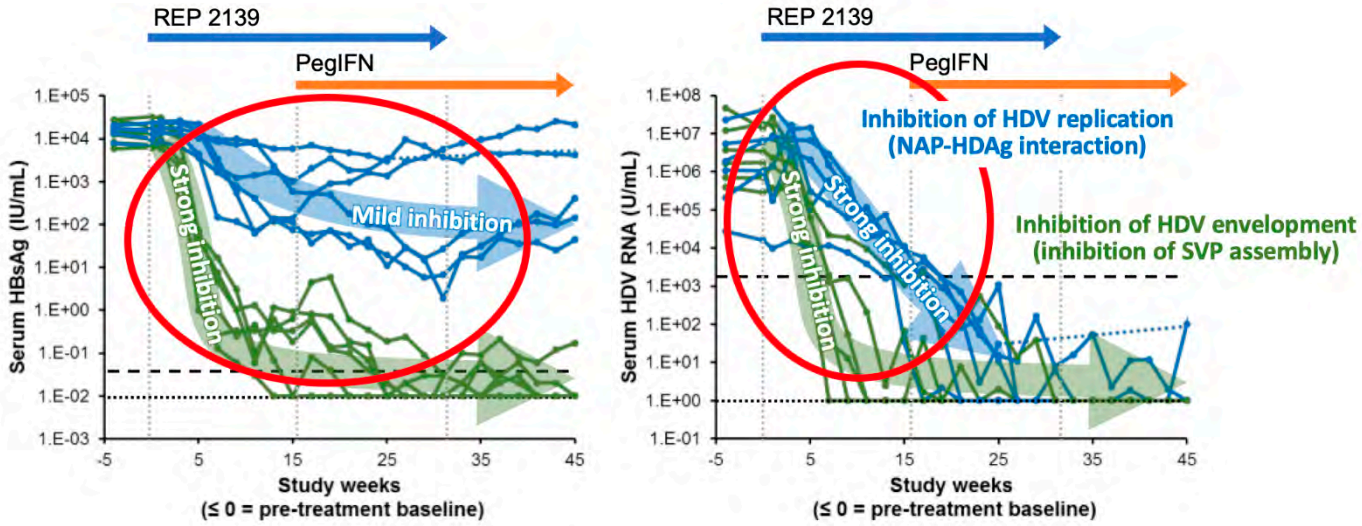
REP2139 in HDV patients

- A phase II study and current compassionate use of REP 2139 in HBV/ HDV infection have shown a robust and early response toward HDV RNA as compared to HBsAg, suggesting a second direct acting antiviral mechanism.

Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial

Lancet Gastroenterol Hepatol 2017; 2: 877–89

Michel Bazinet, Victor Pântea, Valentin Cebotarescu, Lilia Cojuhari, Pavlina Jimbei, Jeffrey Albrecht, Peter Schmid, Frédéric Le Gal, Emmanuel Gordien, Adalbert Krawczyk, Hrvoje Mijočević, Hadi Karimzadeh, Michael Roggendorf, Andrew Vaillant



The effect on HDV RNA before PEG-IFN is started

AIM

- To investigate the direct antiviral activity of HDV in relevant cell infection models *in vitro*.

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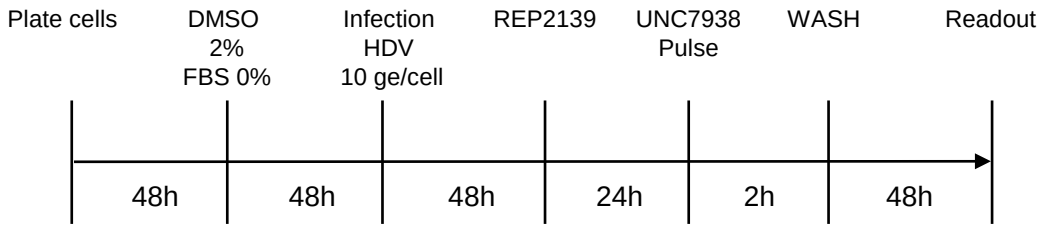
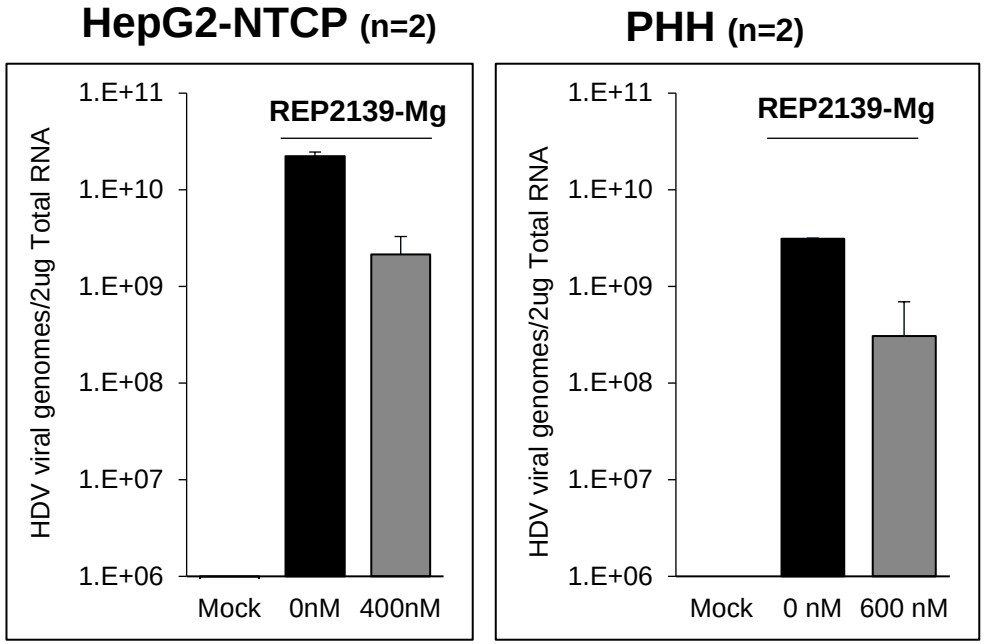
METHODS

- REP 2139 endosomal release in vitro was restored by UNC 7938 (Blanchet, Antiviral Res 2019).
- Clinical supply of REP 2139-Mg (lot FAB-22-0001) was used for dosing in HDV-infected (10 ge/cell) HepG2-NTCP cells and primary human hepatocytes (PHH).
- Intracellular HDV viral genome levels were assessed by qRT-PCR and ddPCR
- HDV RNA and Hepatitis Delta Antigen (HDAg) association to form the HDV ribonucleoprotein (HDV RNP) was monitored by anti-HDAg RNA immunoprecipitation (RIP) followed by HDV qRT-PCR (Abeywickrama-Samarakoon N, Nat Comms 2020).

RESULTS .1

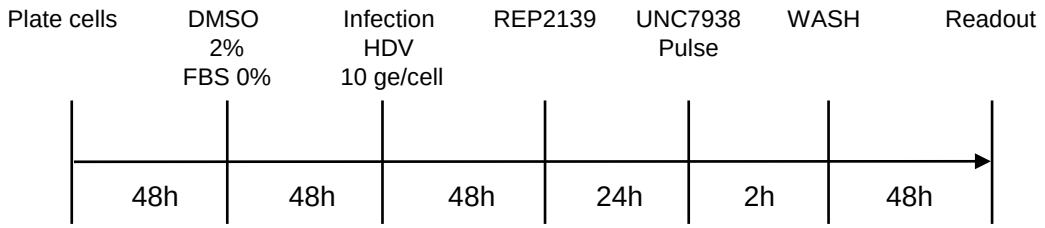
- A single dose of REP 2139-Mg reduced intracellular HDV viral genome levels by ~1 log_{10} in HepG2-NTCP and PHH cells at 400nM and 600nM, respectively.

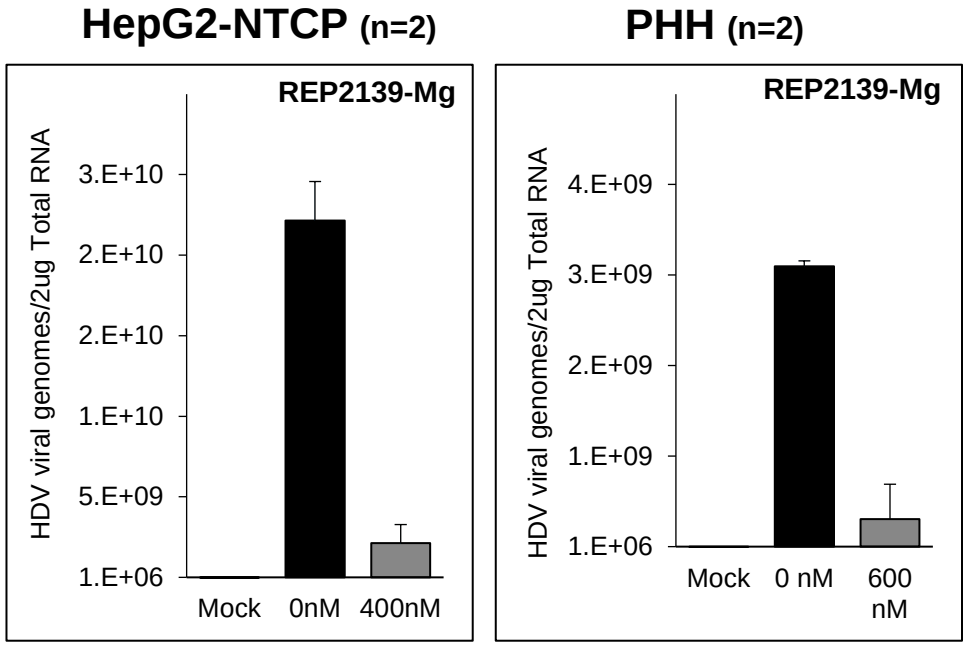




RESULTS .1 (bis)

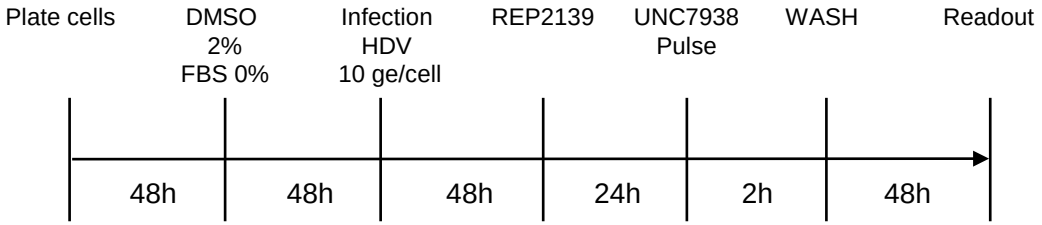
- A single dose of REP 2139-Mg reduced intracellular HDV viral genome levels by ~1 log_{10} in HepG2-NTCP and PHH cells at 400nM and 600nM, respectively.





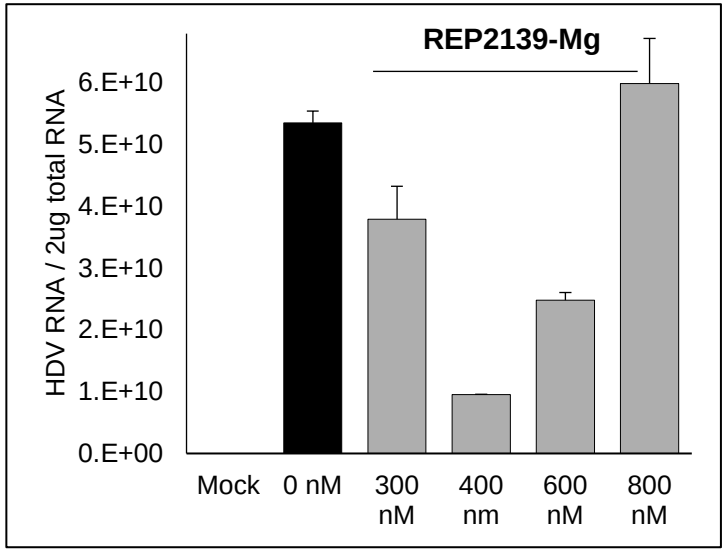
RESULTS .2

- REP2139-Mg inhibits the HDV replication in a dose-dependent manner
- Higher dosage of REP2139-Mg determine its accumulation in the endosomes and require higher concentration of UN7938 to be released



PHH (n=2)

5 uM UNC 7938



RESULTS .3

- REP2139-Mg inhibits the HDV replication in a dose-dependent manner
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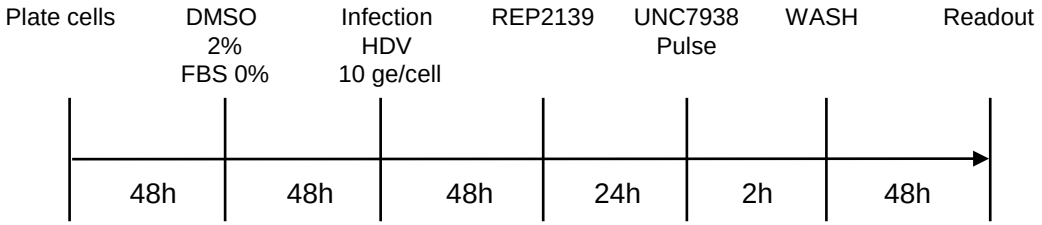
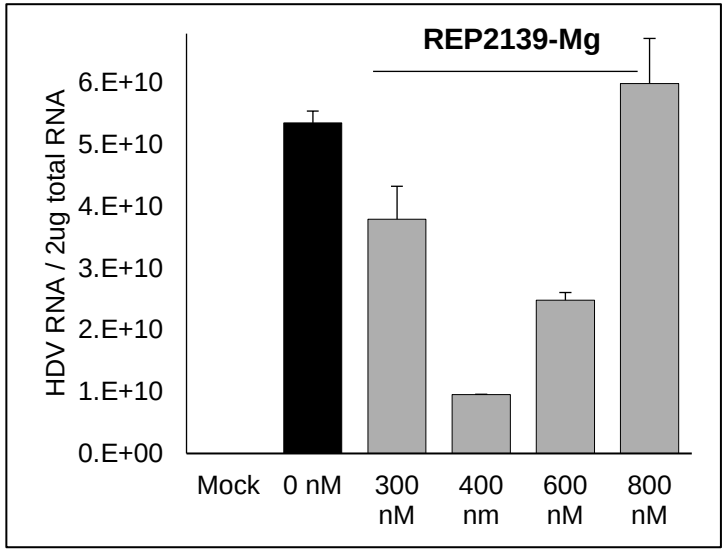


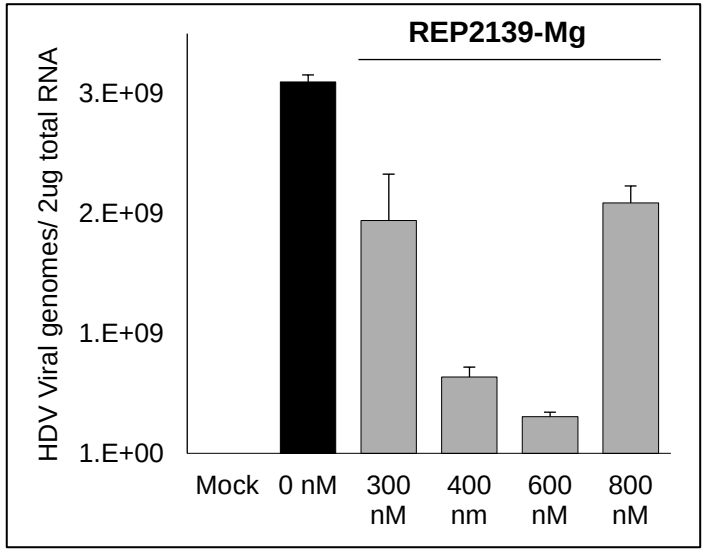
PHH (n=2)

5 uM UNC 7938



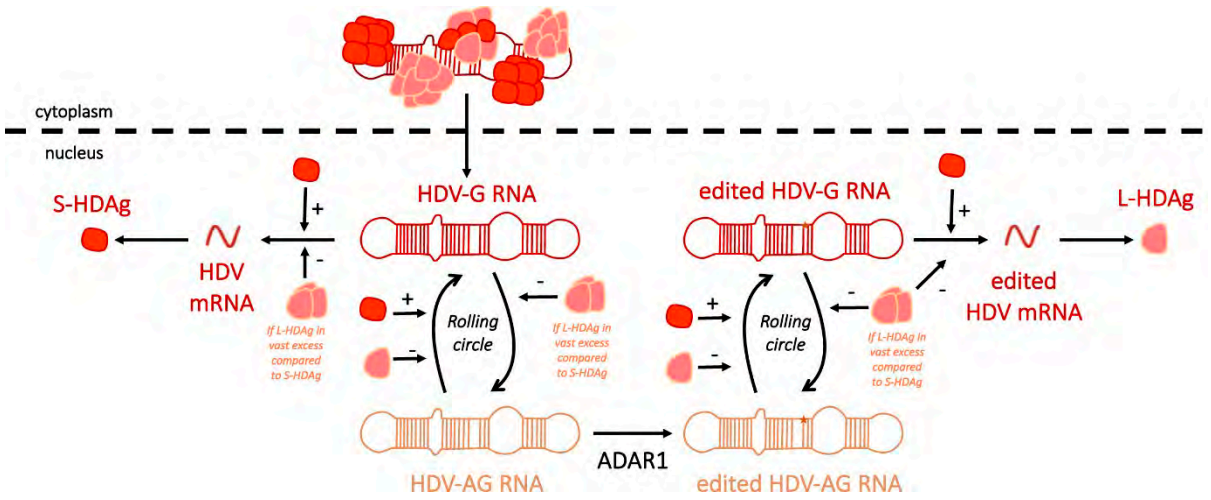
PHH (n=2)

10 uM UNC 7938

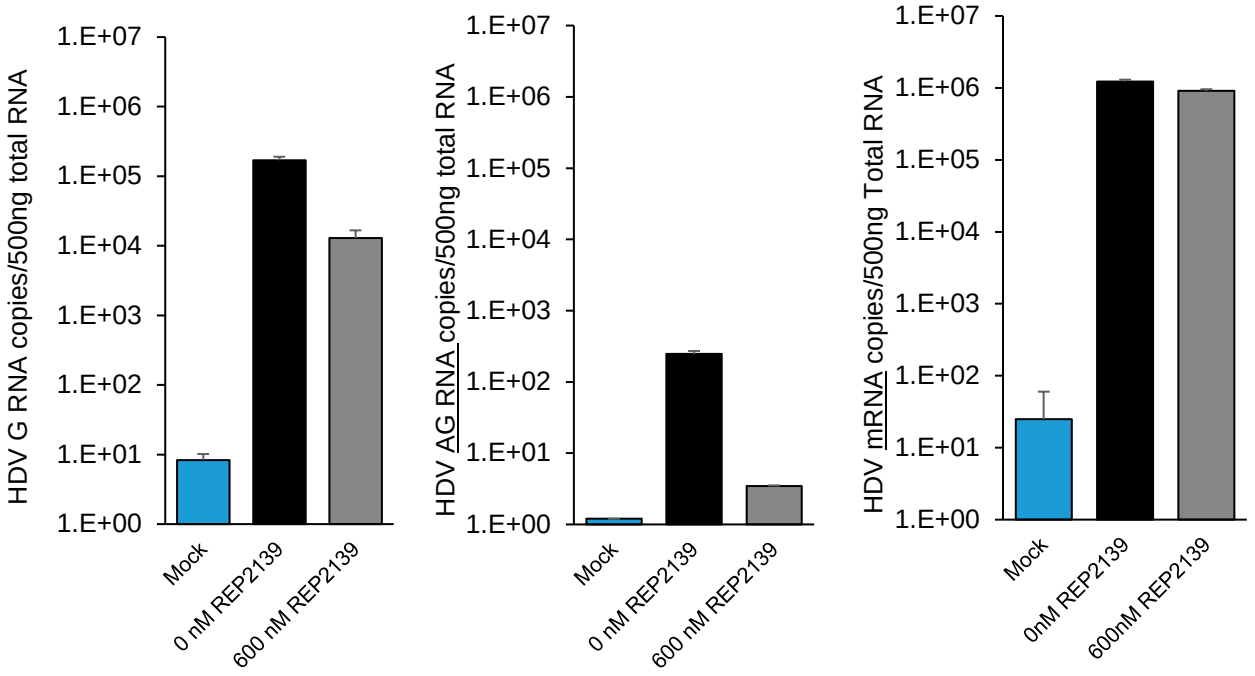


RESULTS .4

- REP 2139-Mg reduces both genomic (≈1Log) and antigenomic (≈1.5Log) HDV RNA

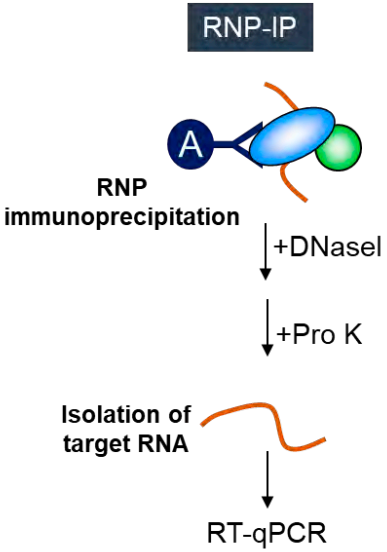


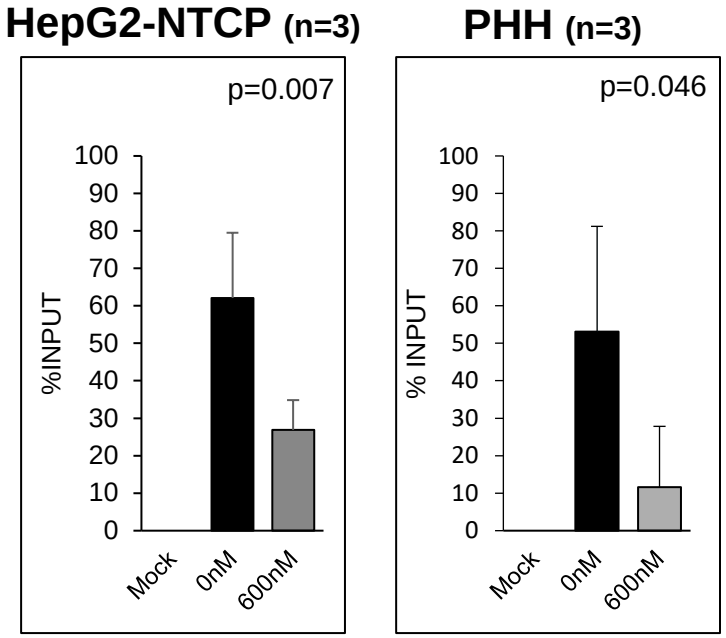
Lucifora J. and Delphin M. 2020



RESULTS .5

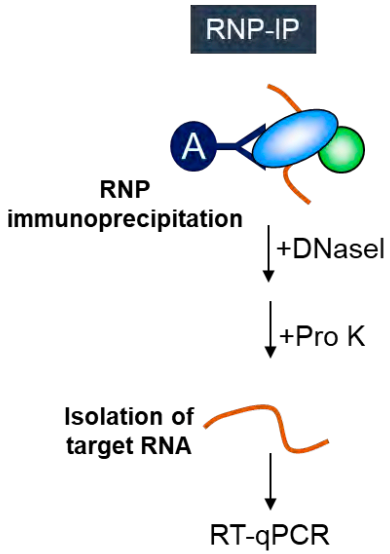
- A single REP 2139-Mg dose also reduced the intranuclear association of HDV RNA with HDAg by ~60% in HepG2-NTCP and by 80% in PHH

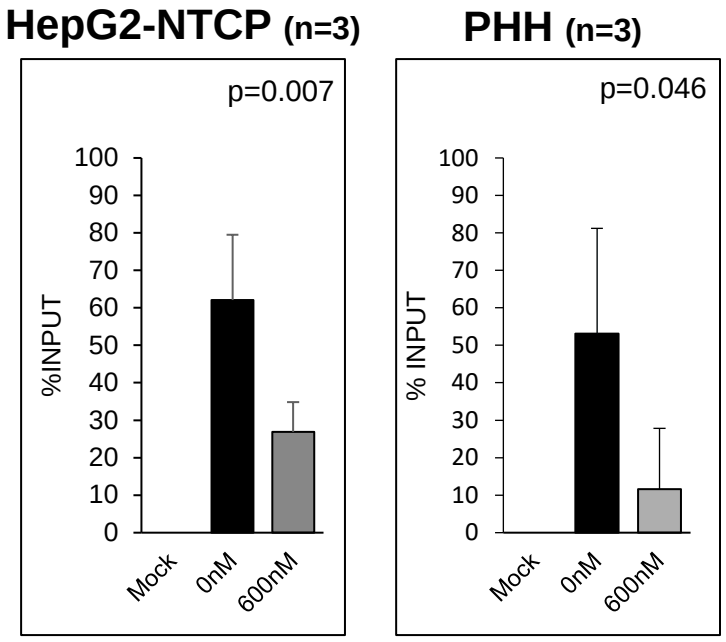


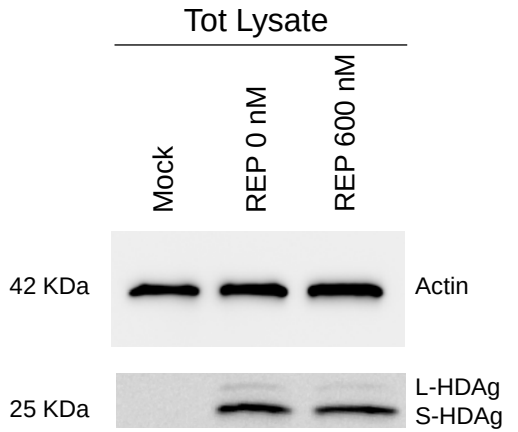


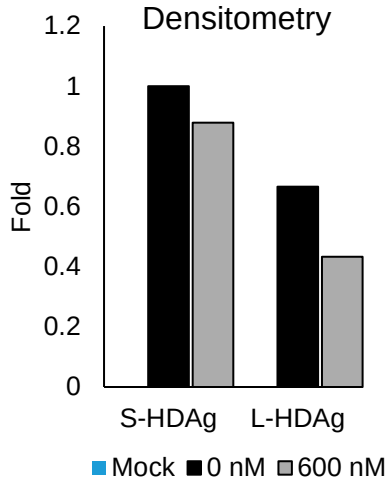
RESULTS .5

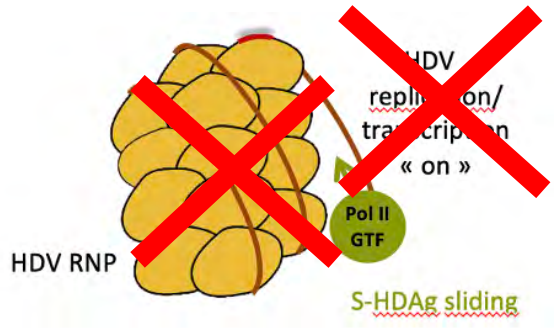
- A single REP 2139-Mg dose also reduced the intranuclear association of HDV RNA with HDAg by ~60% in HepG2-NTCP and by 80% in PHH, **without changing the HDAg protein levels**.







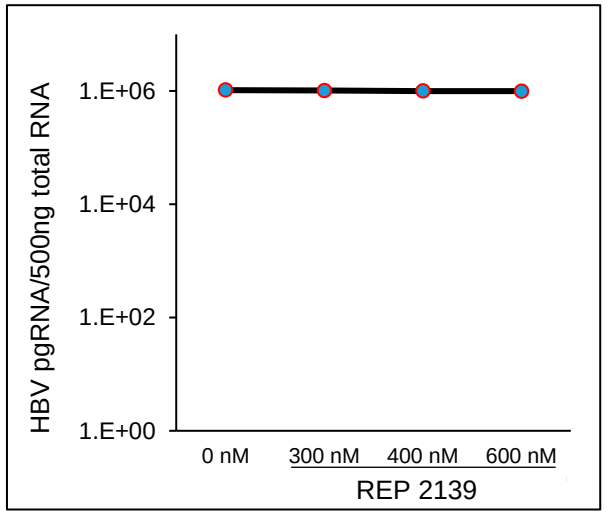




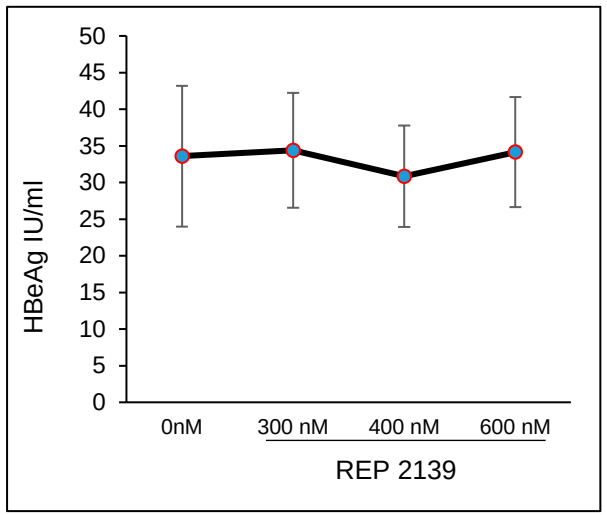
RESULTS .6

- REP 2139-Mg inhibits HDV replication in HBV-HDV coinfected PHHs
- We confirm in HBV-HDV coinfected PHHs that REP 2139 inhibits HBsAg secretion without affecting intracellular pgRNA levels or HBeAg secretion

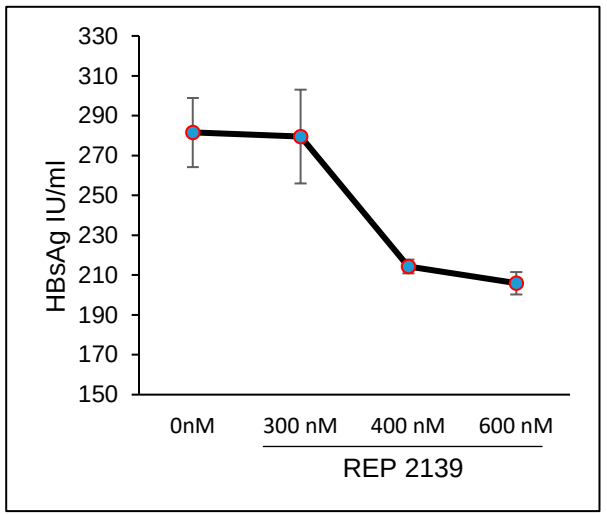
pgRNA (ddPCR)



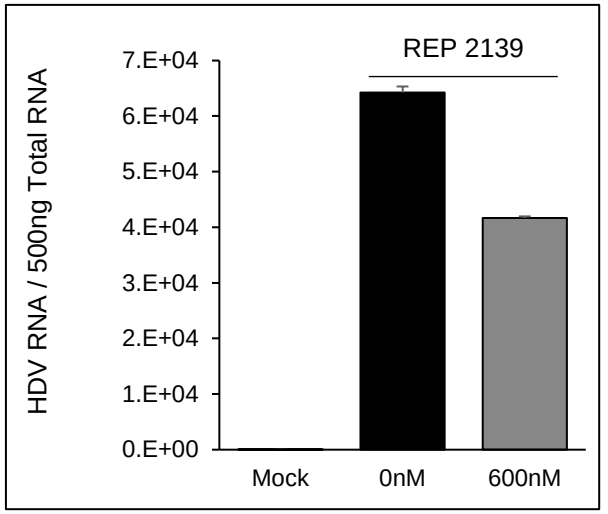
HBeAg (ELISA)



HBsAg (ELISA)

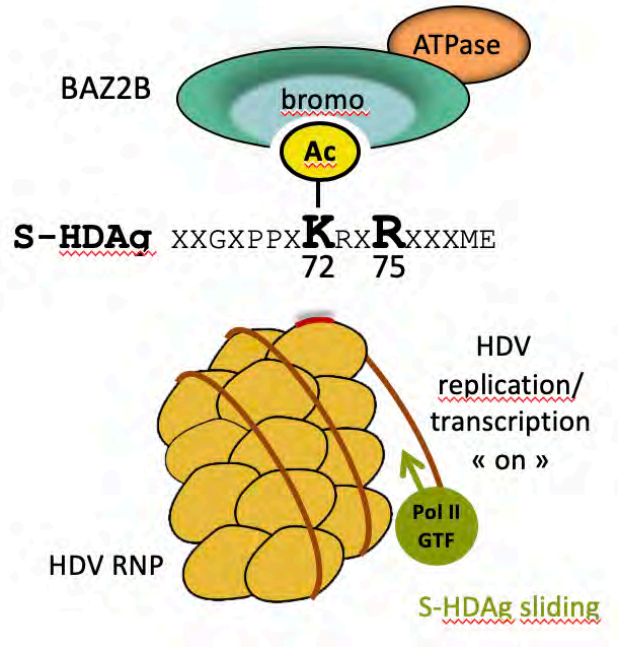


HDV RNA (ddPCR)



Conclusions

- REP 2139 has a direct acting antiviral effect against HDV RNA replication which may involve blocking HDV RNA interaction with HDAg during HDV RNP morphogenesis.
- These antiviral effects may explain the more rapid decline of HDV RNA versus HBsAg in human studies.
- Ongoing experiments include the characterization of the direct antiviral effect of REP 2139 (e.g., HDV secretion; impact on S-HDAg histone mimicry and HDV RNP interactome, HDV infectivity).



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