Clearing serum HBsAg with nucleic acid polymers: Mechanistic insights and clinical impact

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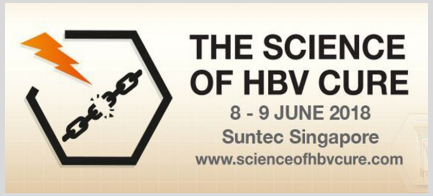
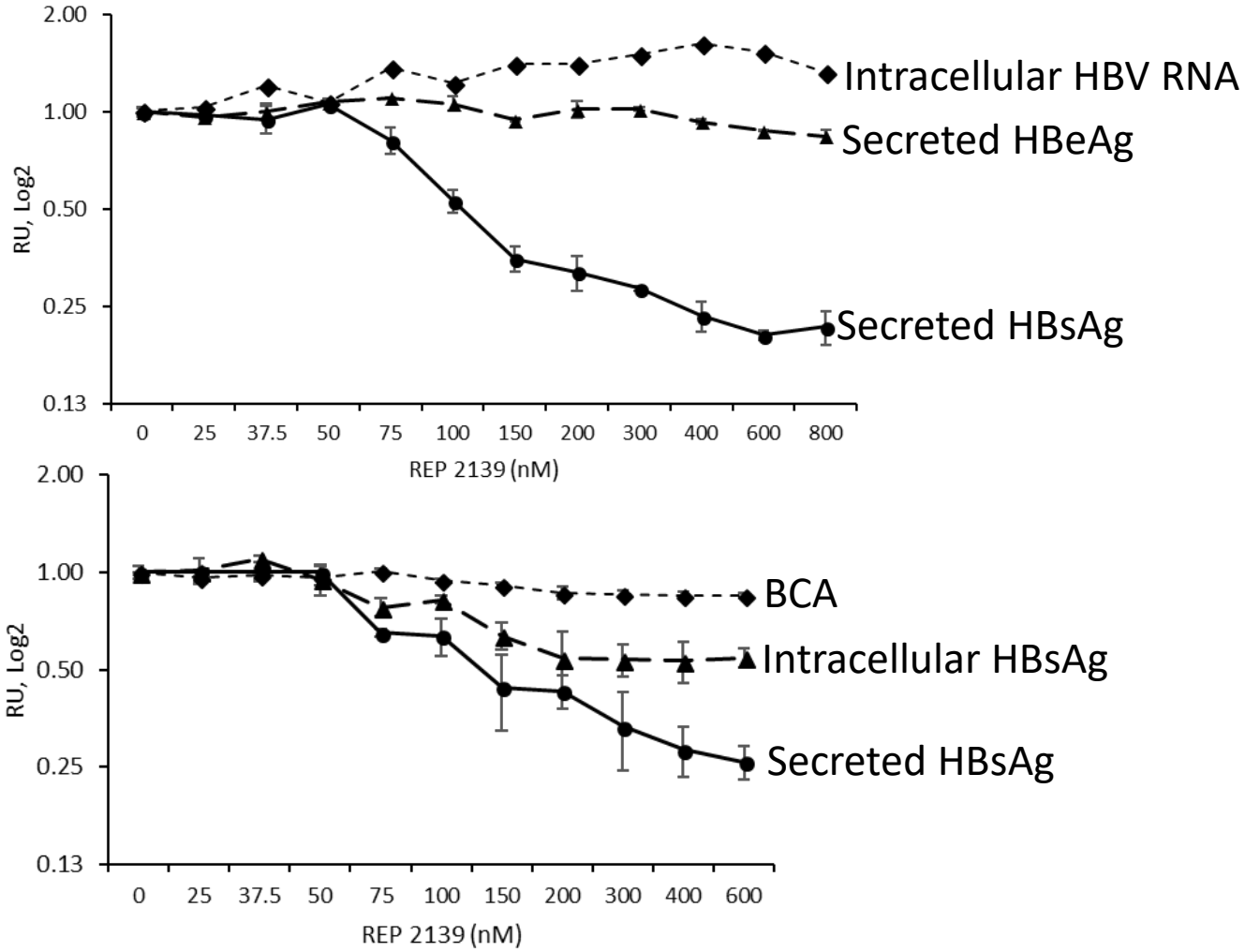


replicor

Mechanism of action of REP 2139 in HBV
(HepG2.2.15 cells)

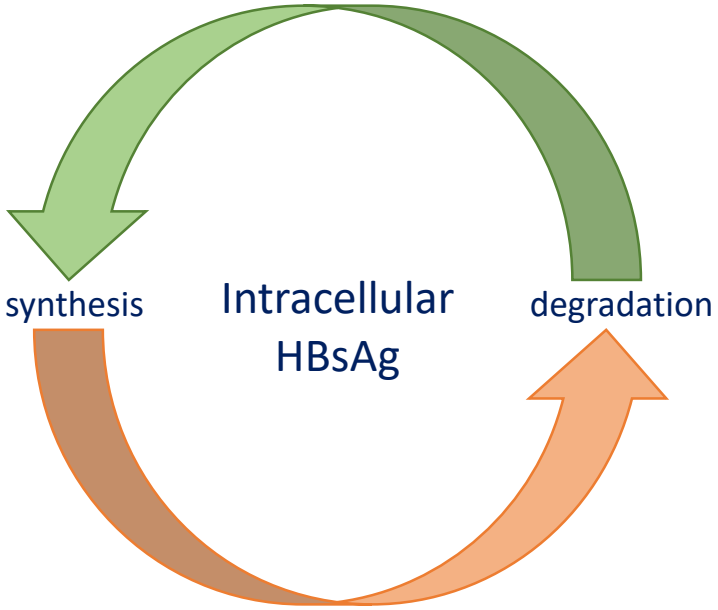


REP 2139 acts post-translationally to selectively inhibit HBsAg release

Inhibition of HBsAg secretion is accompanied by declines in intracellular HBsAg

Blanchet et al., 2017. Hepatol. 66: 512A

Model for intracellular HBsAg dynamics



Intracellular HBsAg turns over continuously (unstable)

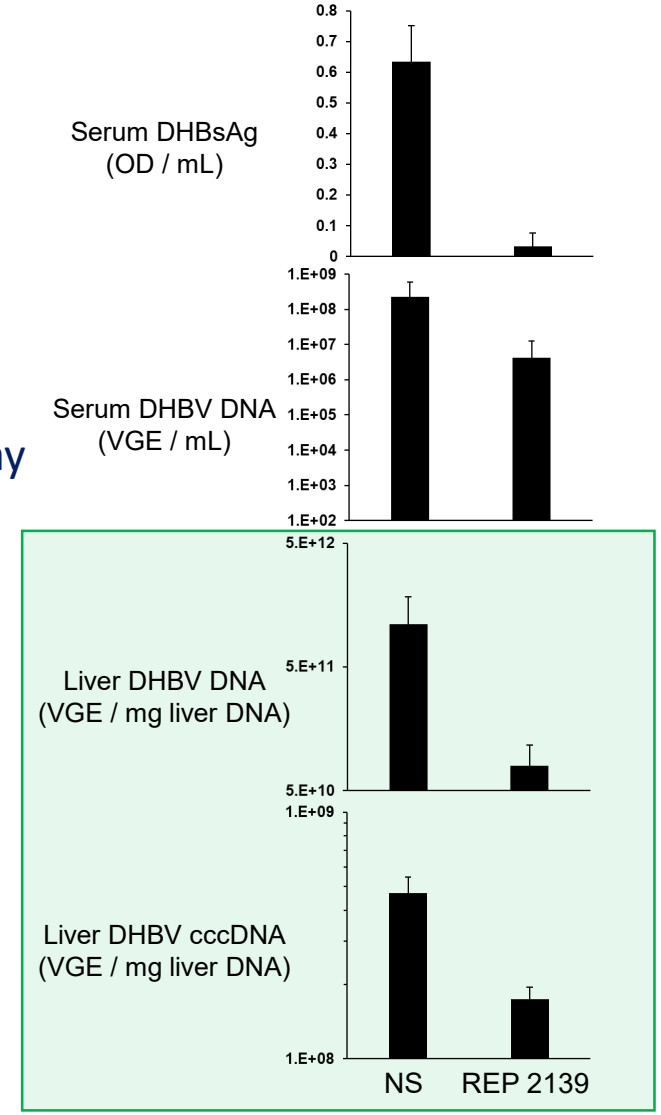
HBsAg is removed from turnover cycle by assembly into virions or SVP

"Stabilized" HBsAg is secreted from hepatocytes in virions or SVP

REP 2139 effect *in vivo*

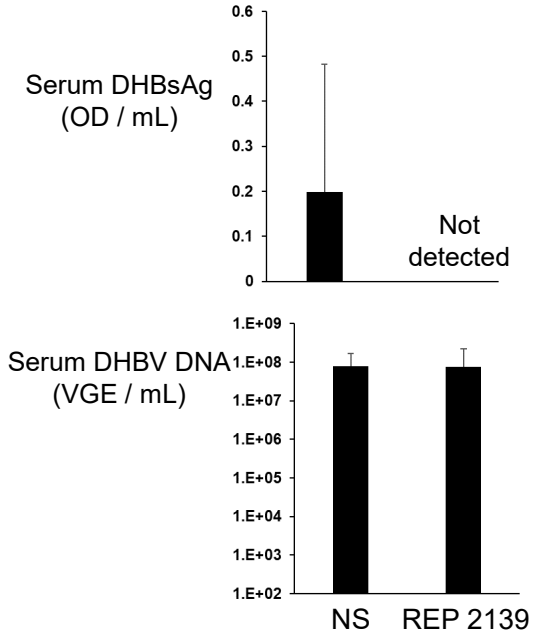
(pekin ducks with established DHBV infection)

10mg/kg/day
2 weeks



Reductions in serum DHBsAg are accompanied by inhibition of viral replication in the liver

10mg/kg/day
2 (of 4) weeks
(repeat study)



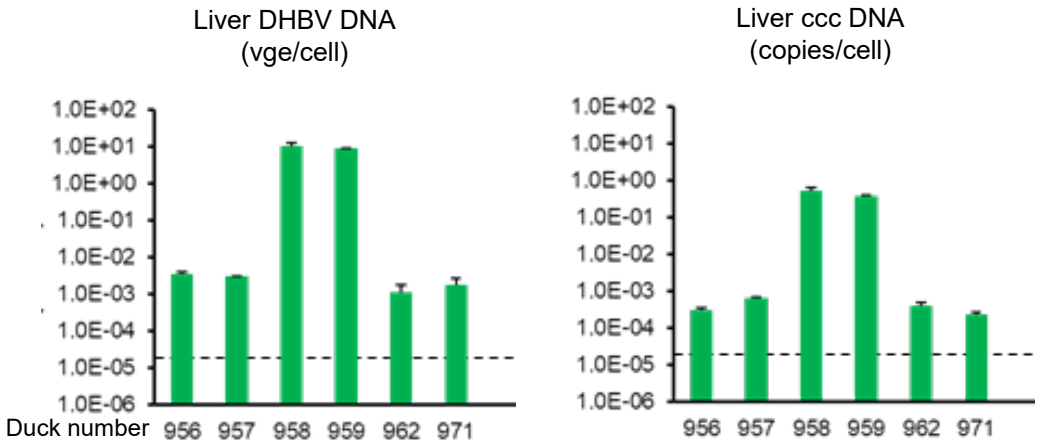
8 weeks follow-up:
DHBsAg and DHBV DNA
< LLOQ in 4/6 animals

DHBsAg appears more efficiently targeted during therapy than DHBV DNA
(consistent with selective targeting of SVP)

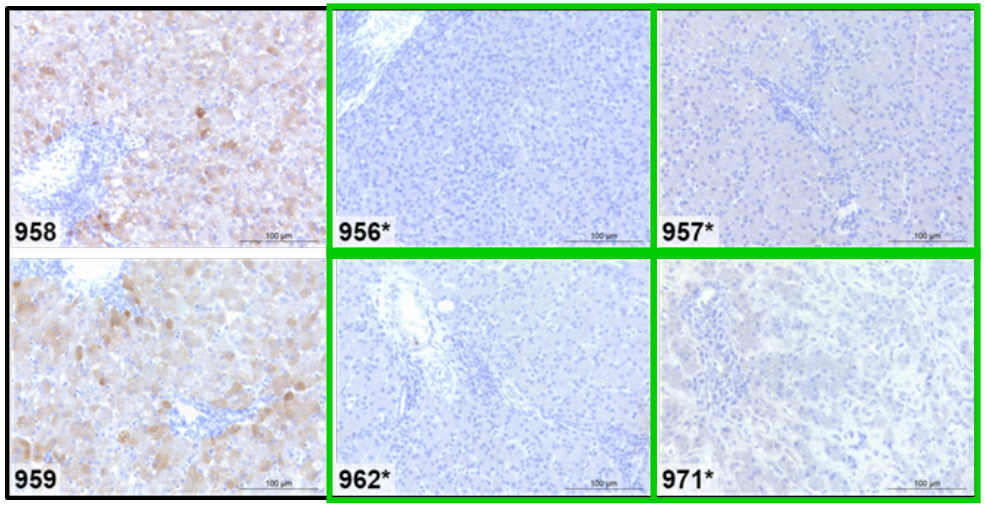
Roehl et al., 2017. Mol. Ther. Nuc. Acids 8: 1-12
Quinet et al., 2018. Hepatol. 67: 2127-2140

REP 2139 effect *in vivo*
(pekin ducks with established DHBV infection)

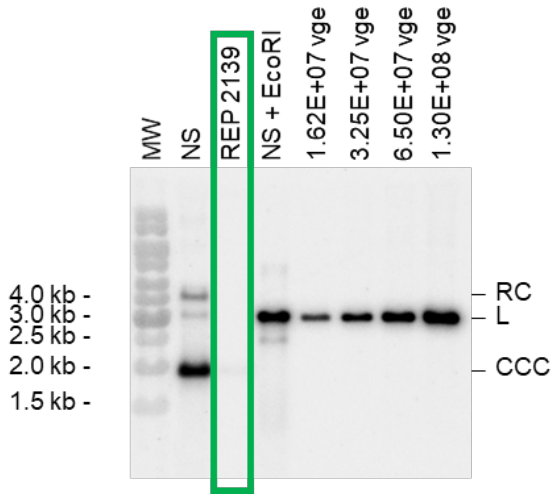
10mg/kg/day, 4 weeks + 8 weeks follow-up



DHBsAg is cleared from the liver



Verification of cccDNA reduction by southern blot



Functional control of infection persists off-treatment

- < LLOQ serum DHBsAg
- < LLOQ serum DHBV DNA
- Control of cccDNA
- Elimination of intrahepatic DHBsAg

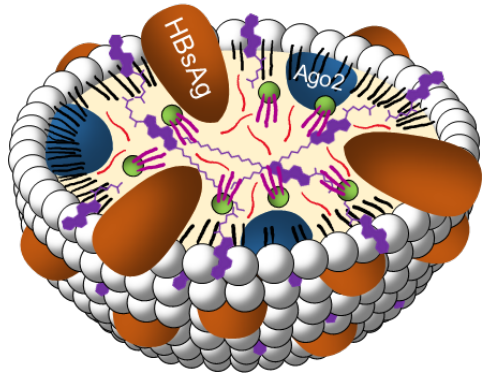
Quinet et al., 2018. Hepatol. 67: 2127-2140

Searching for the target…..

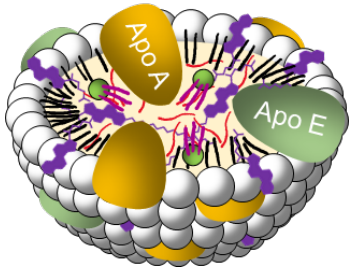
REP 2139 does not interact with HBsAg, HBV or HDV virions, but assembly / release of SVP is clearly targeted

Subviral particles are biochemically similar to HDL

- Buoyant density and % protein content
- Phospholipid content and chain length
- Tg., chol., chol. ester content
- Both contain miRNA



SVP



HDL

(adapted from Grenier et al., 2010. Biochemie. 92: 994-1002)

NAPs are active against hepadnaviral infection in ducks and humans but not in rodents

- HDL maturation in ducks and humans is similar
- HDL maturation in rodents is distinct (no CETP)
- **SVP morphogenesis in rodents may not mirror that in humans.**

Host target of REP 2139 may be involved in HDL morphogenesis in a benign fashion:

Lipid metabolism in pre-clinical and clinical studies with chronic REP 2139 exposure is normal

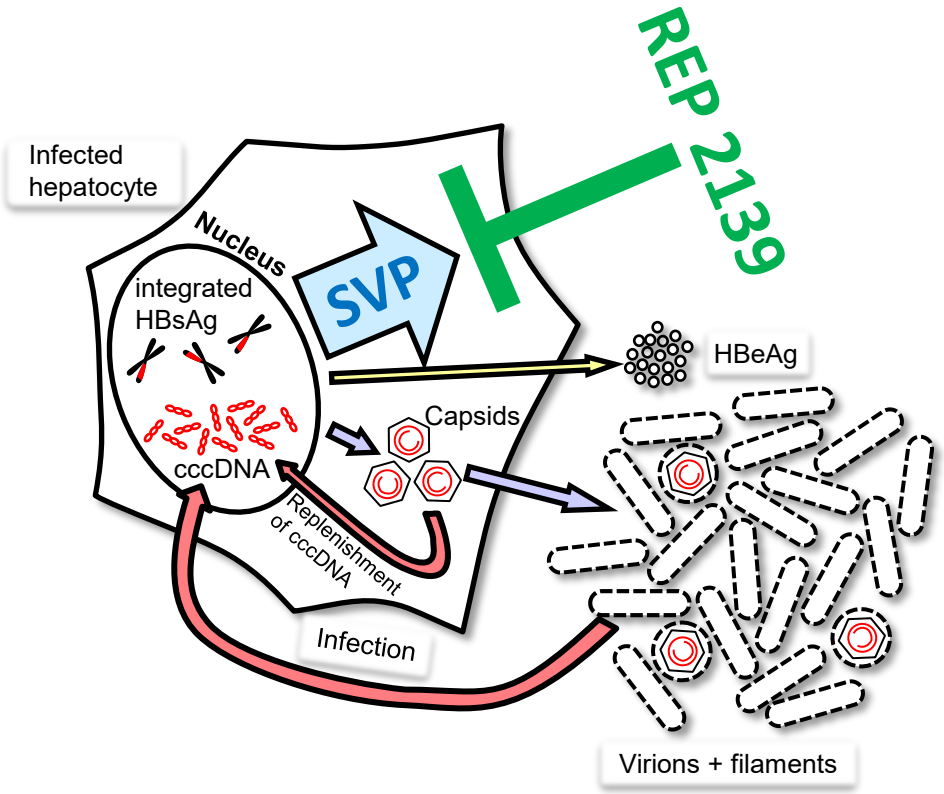
Beilstein et al., 2018. J. Virol. 30: e01416-17
Schöneweis et al., 2018. Antiviral Res. 149: 26-33

REP 2139 mechanism of action in HBV

REP 2139 blocks subviral particle release
from cccDNA and integrated HBV DNA

→

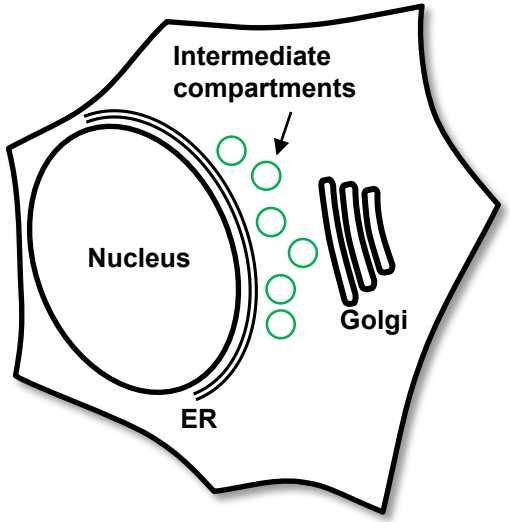
Efficient HBsAg clearance
from the blood



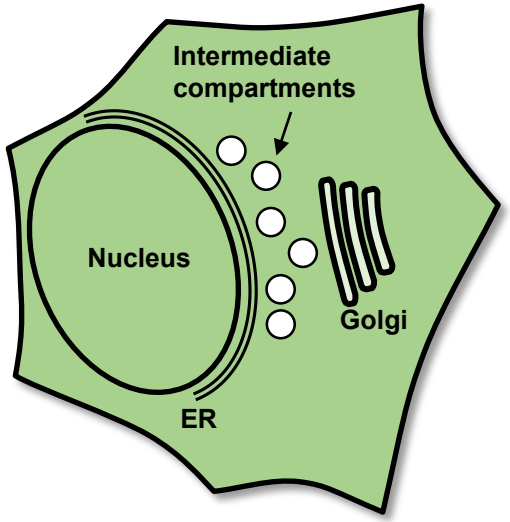
REP 2139 prevents HBsAg replenishment only

HBsAg clearance is dependent on the clearance of SVP by host immune function.

Intracellular trafficking of REP 2139 may govern its potency in the clinic



Intermediate compartments are the sites of SVP assembly

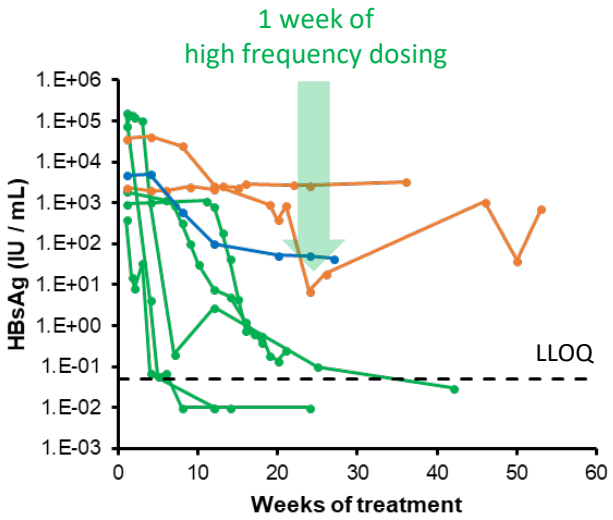


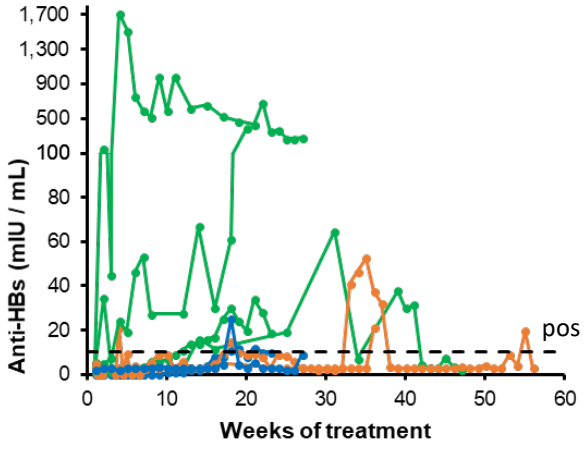
In hepatocytes, active phosphorothioate oligonucleotides (and NAPs) are found at their highest concentrations in the cytoplasm and nucleus (unknown for intermediate compartments)

Patient et al., 2007. J. Virol. 81: 3841-3851
Juliano, 2016. Nuc. Acids Res. 44: 6518-6548

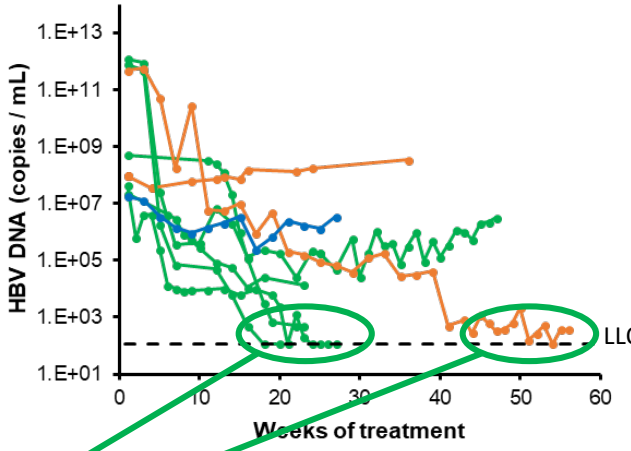
Clinical effects of REP 2139 monotherapy

REP 101 study: HBeAg positive HBV mono-infection (REP 2055)

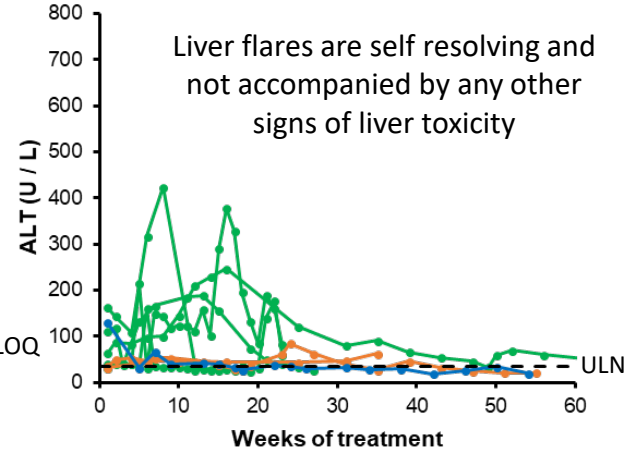




Low levels of anti-HBs in most patients unmasked by removal of SVP



HBsAg response is decoupled from HBV DNA response (selectivity for SVP)



Flares restricted to patients with HBsAg decline to < 1 IU/mL

HBsAg decline < 1 log
(inefficient REP 2139 transit to the IC)

overcome with high frequency dosing

HBsAg decline > 1 log but < 1 IU/mL
(efficient REP 2139 transit to the IC
but attenuated host SVP clearance)

HBsAg decline to < 1 IU/mL
(efficient REP 2139 transit to the IC
and efficient host SVP clearance)

Follow-up:

4/8 patients with functional control on therapy (HBV DNA < 1000 IU/mL)

Poor responder patient -> immediate rebound

3 responder patients -> all with persistent functional control for 1 year

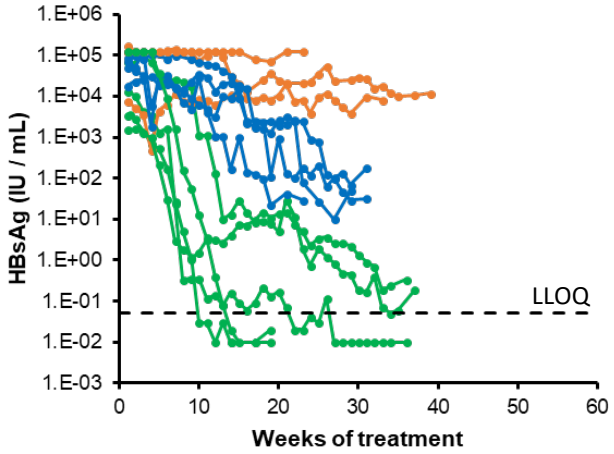
2 patients with persistent functional control for 5 years

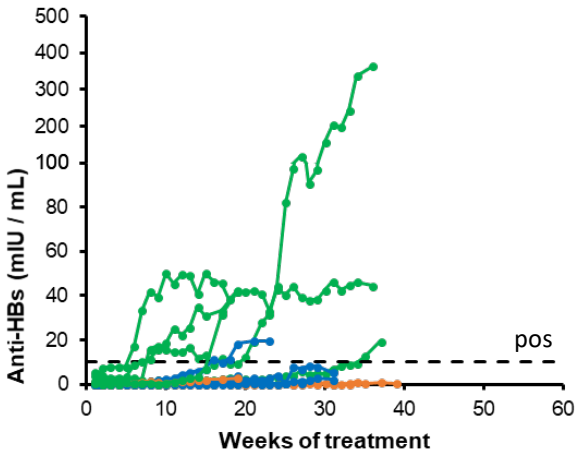
All rebound patients successfully treated with ETV

Al-Mahtab et al., 2016 PLoS One 11: e0156667

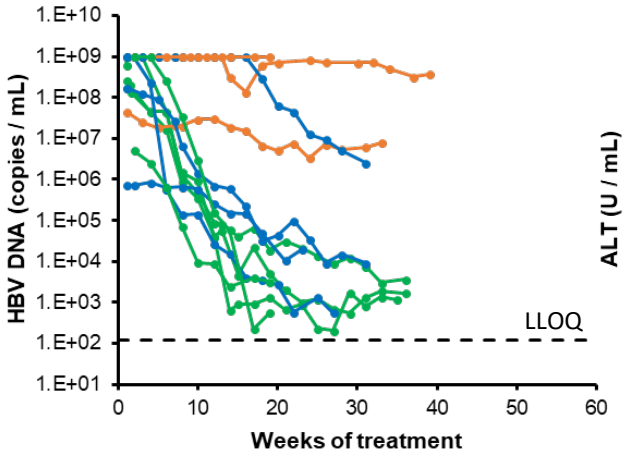
Clinical effects of REP 2139 monotherapy

REP 102 study: HBeAg positive HBV mono-infection (REP 2139-Ca)

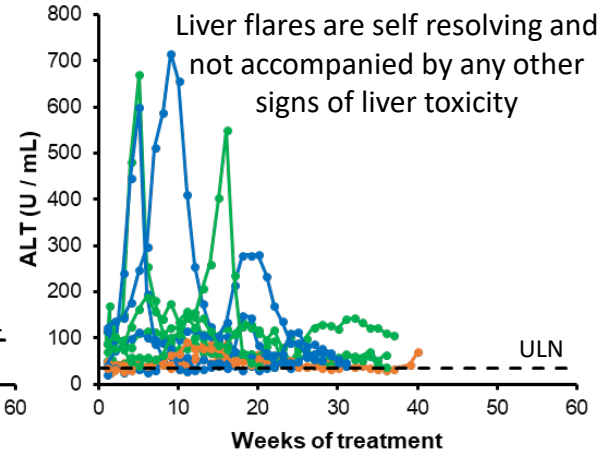




Low levels of anti-HBs in most patients unmasked by removal of SVP



HBsAg response in several patients is decoupled from HBV DNA response (selectivity for SVP)



Flares restricted to patients with HBsAg decline close to or < 1 IU/mL

HBsAd decline < 1 log

HBsAg decline > 1 log but > 1 IU/mL

HBsAg decline to < 1 IU/mL

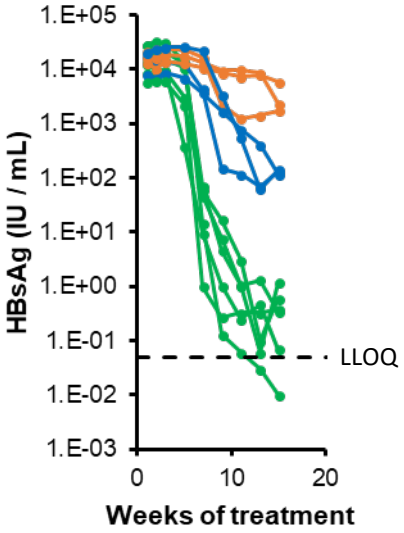
3/12 non-responder patients -> rebound controlled with ETV or TDF

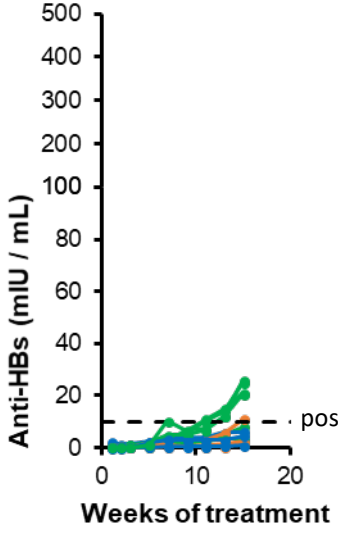
9/12 responder patients -> transitioned to add-on immunotherapy (to be discussed tomorrow)

Al-Mahtab et al., 2016 PLoS One 11: e0156667

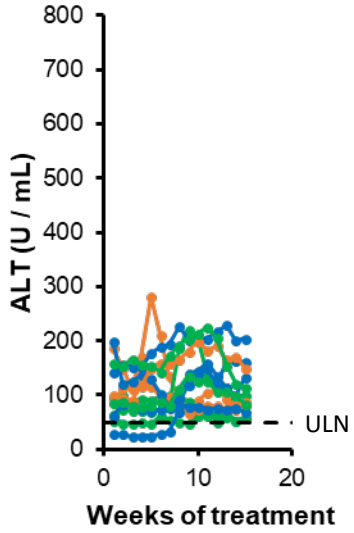
Clinical effects of REP 2139 monotherapy

REP 301 study: HBeAg negative HBV / HDV co-infection (REP 2139-Ca)

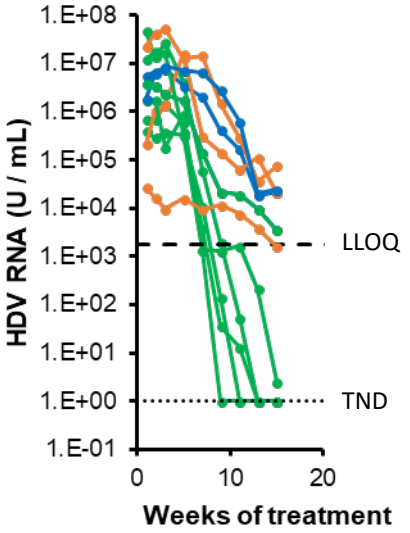




Anti-HBs unmaksing reduced



ALT elevations substantially reduced



HDV RNA declines observed even in HBsAg non-responders

NAPs also target S- and L-HDAg (in cytoplasm and nucleus)

Efficient trafficking of NAPs to these compartments likely underlies the universal effect against HDV RNA even with poor HBsAg response

HBsAg decline < 1 log

HBsAg decline > 1 log but > 1 IU/mL

HBsAg decline to < 1 IU/mL

All patients transitioned to add-on immunotherapy (to be discussed tomorrow)

Bazinet et al., Lancet Gastro. Hepatol. 2: 877-889
Wang et al. Nuc Acids Res. 2003; 31: 6841-6492
Shamur et al., Hepatol. 2017; 66: 504A
Alves et al., World J Virol. 2017; 6: 26-35

Summary

REP 2139 blocks release of HBsAg

- Assembly and secretion of SVPs, accompanied by declines in intracellular HBsAg
- Functional control of HBV infection established in the blood and liver *in vivo*
- Target is host-derived and may be involved in HDL metabolism
- REP 2139 also targets S- and L-HDAg, giving multiple distinct effects against HDV infection.

A small subset of patients experience a poor (< 1 log reduction) HBsAg response

- Likely due to reduced transport into the intermediate compartment -> can be recovered by higher frequency dosing
- REP 2165 is an alternative therapy for these patents (suitable for high frequency dosing)
- Host factor identifying these patients will be investigated

REP 2139-mediated HBsAg clearance has additional clinical benefits

- More profound in HBeAg positive patients and includes:
  - Unmasking of anti-HBs (low levels)
  - HBeAg seroconversion
  - Reduction / clearance of HBV DNA
  - Transaminase flares (likely therapeutic in nature)
  - Inhibition of viral replication in the liver

In monotherapy, HBsAg clearance can restore host immune control (functional control of HBV infection)

- But only occurs in a small subset of patients
- Combination therapy (especially immunotherapy) will be essential to establish high rates of functional control

Acknowledgments

A collaborative effort!

Clinical evaluations:

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