

Achieving Functional Cure of Chronic HBV Infection with REP 2139-Based Combination Therapy

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Why care about HBV?

- 350 million people have chronic HBV infection worldwide
- Causes fibrosis, cirrhosis and hepatocellular carcinoma (HCC)
- Responsible for 880,000 deaths worldwide annually
- Currently approved therapies are life long (except interferon)
- **Rarely achieve functional cure**

Functional cure

HBV DNA and HBsAg not detectable

Restoration of Immunological control of the virus

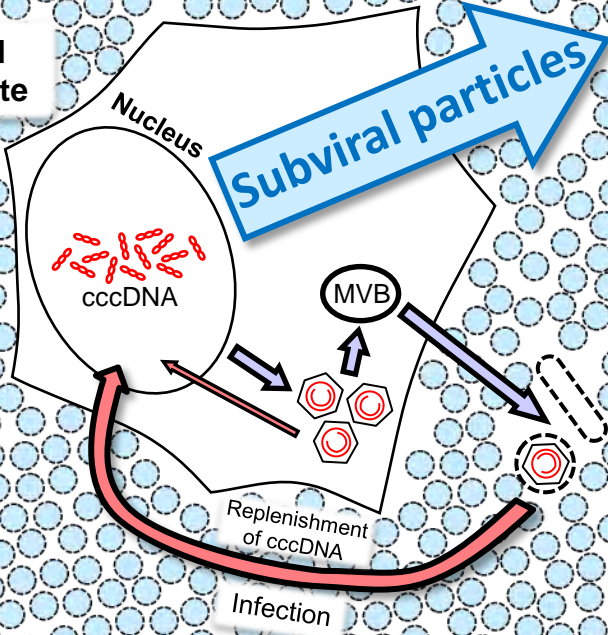
Reversal of liver damage and reduced risk of HCC

Antiviral therapy no longer required

HBsAg production in chronic HBV

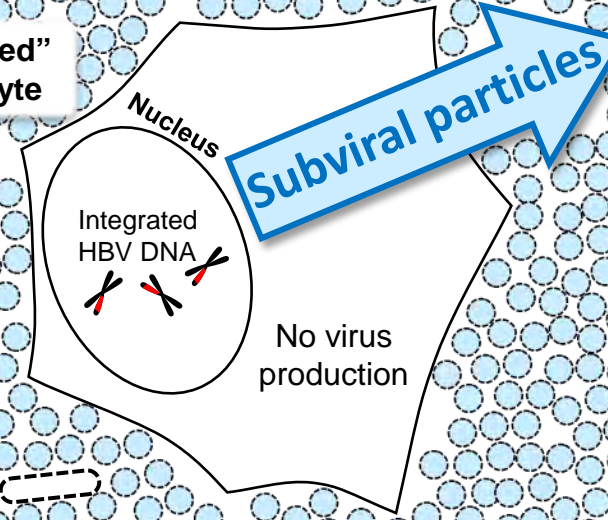
A tiny fraction of HBsAg is derived from virions and filaments

Infected hepatocyte



Almost all HBsAg is derived from subviral particles

"Integrated" hepatocyte



Subviral particles are also produced in hepatocytes with integrated viral DNA independently of cccDNA

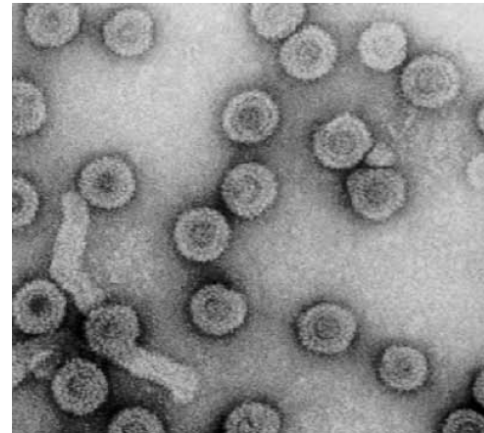
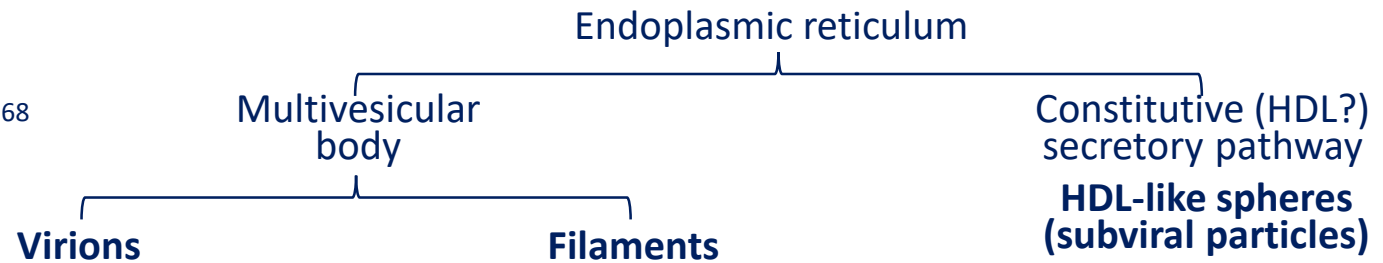
Can direct acting antivirals target HBsAg?

Gavilanes et al., J Biol Chem 1982; 257: 7770-7777
 Heermann et al., J Virol 1984; 52: 396-402
 Ganem and Prince, N Engl J Med 2004; 350: 1118-1129
 Gerlich and Mann, Topley and Wilsons microbiol microb inf 2005; 2: 1226-1268
 Watanabe et al., PNAS 2007; 104: 10205-10210
 Garcia et al., J Virol 2009; 11152-11165
 Gerlich, Virol J 2013; 10: 239
 Jiang et al., J Virol 2016; 90: 3330-3341
 Wooddell et al., Sci Trans Med 2017; 9: eaan0241
 Frietas et al., J Virol 2018 92: e02221-17
 Hu et al., J Gastro Hepatol 2018; 33: 1389-1396

(purified preparations)

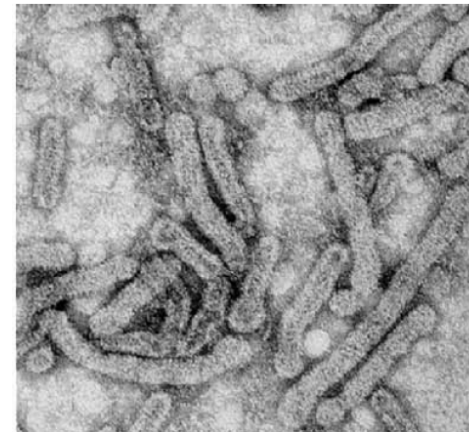
RATIO IN THE BLOOD

Derived from



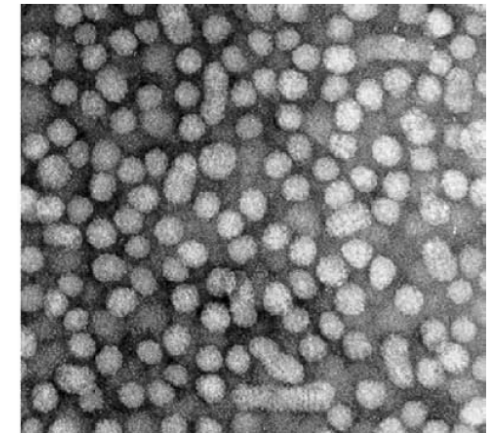
1

cccDNA
**Targeted by
 NUCs and
 CpAMs(?)**



10

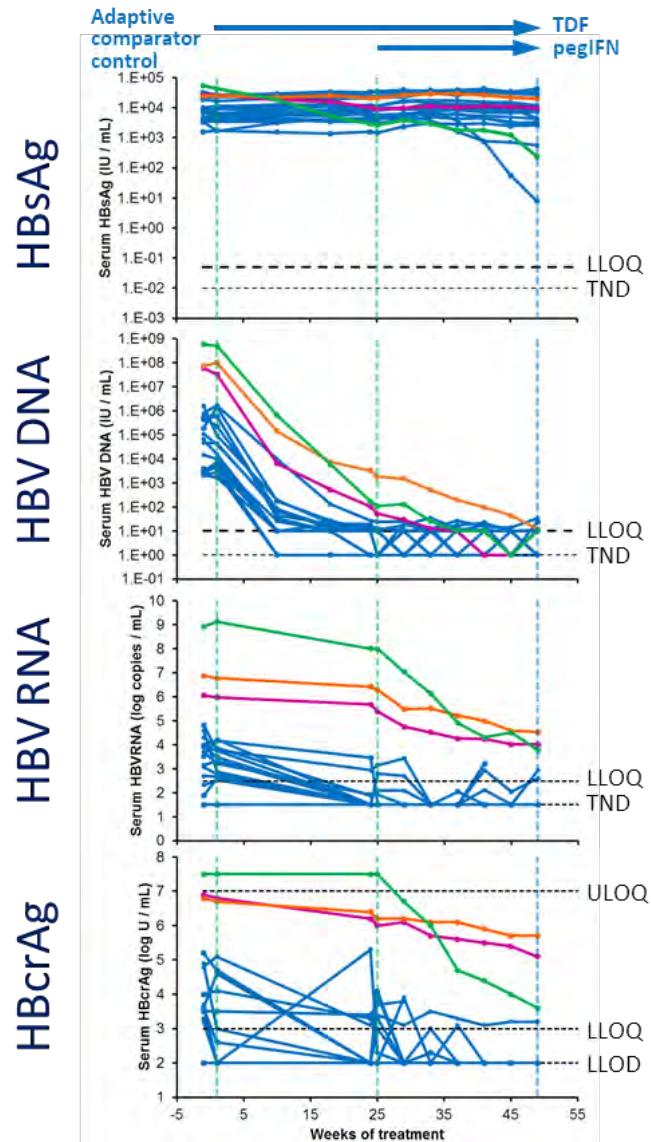
cccDNA (major)
 integrated HBV DNA
 (trace?)



10,000 – 100,000
> 99.9% of HBsAg is SVP

cccDNA (minor)
 integrated HBV DNA (major)
**HBsAg cannot be targeted by
 NUCs and CpAMs**

Gauging the proportion of HBsAg from integration



(from REP 401 protocol)

Treatment response to TDF + pegIFN (n=20)

- 14/20: HBV RNA becomes TND
- 15/20: HBcrAg becomes < LLOD
- 3/20: HBsAg reduction > 1 log
- weak or absent HBsAg response even in patients with continuous declines from high pre-treatment HBV RNA and HBcrAg (green, pink and orange lines)

**TDF + pegIFN efficiently control cccDNA
(but have little effect on HBsAg)**

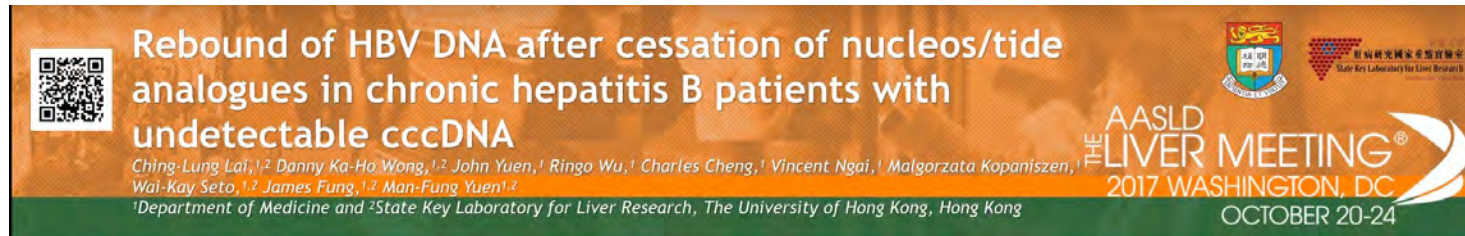
**Bulk of HBsAg in HBeAg negative patients
appears to be derived from integration**

HBsAg clearance is essential for functional cure

While circulating HBsAg persists:

- Anti-HBs will be continually neutralized
Rydell et al., Virology 2017; 509: 67-70
- T-cells will remain in a functionally exhausted state
Kruse et al., Cytotherapy 2018; 20: 697-705
Boni et al., J Virol 2007; 81: 4215-4225
Bertoletti and Gehring, J Gen Virol 2006; 87: 1439-1449
- Innate immunity will be suppressed
Lebossé et al., J Hepatol 2017; 66: 897-909
- Vaccination / immunotherapy will be ineffective
Dembeck et al., Virology 2018; 30: 58-67
Al-Mahtab et al., PLoS ONE 2016; 11: e0156667
Bazinet et al., Lancet Gastro Hepatol. 2017; 2: 877-889
- **Risk for reactivation of infection or re-infection remains!**

Reactivation of infection with efficient removal of cccDNA



Lai et al. Hepatol 2017; 66: 512A (AASLD 2017)

Long term study of 43 NUC treated patients:

- Median treatment of 126 months
- **99.89% (~3 log) reduction of cccDNA (liver biopsy)**
- 21/43 (49%) had no detectable cccDNA by liver biopsy (all with persistent HBsAg)

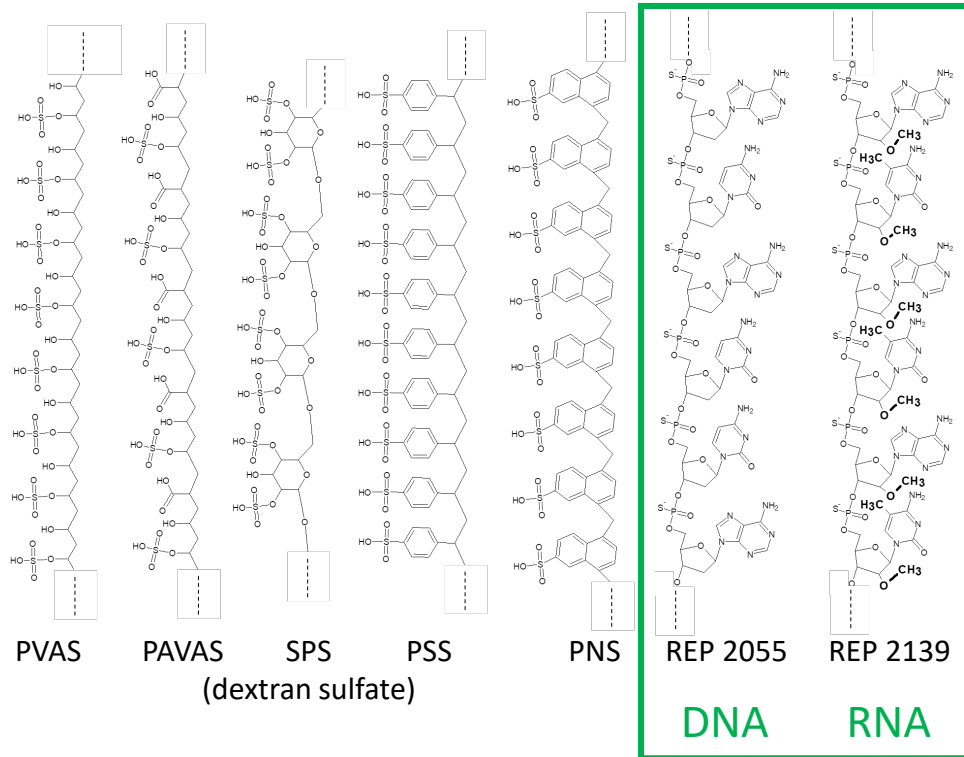
NUC therapy was removed in 13 of 21 patients with undetectable cccDNA

viral rebound observed in all 13 patients requiring return to NUC therapy

Highly efficient clearance / control of cccDNA will likely not be effective in achieving functional cure unless HBsAg is also controlled

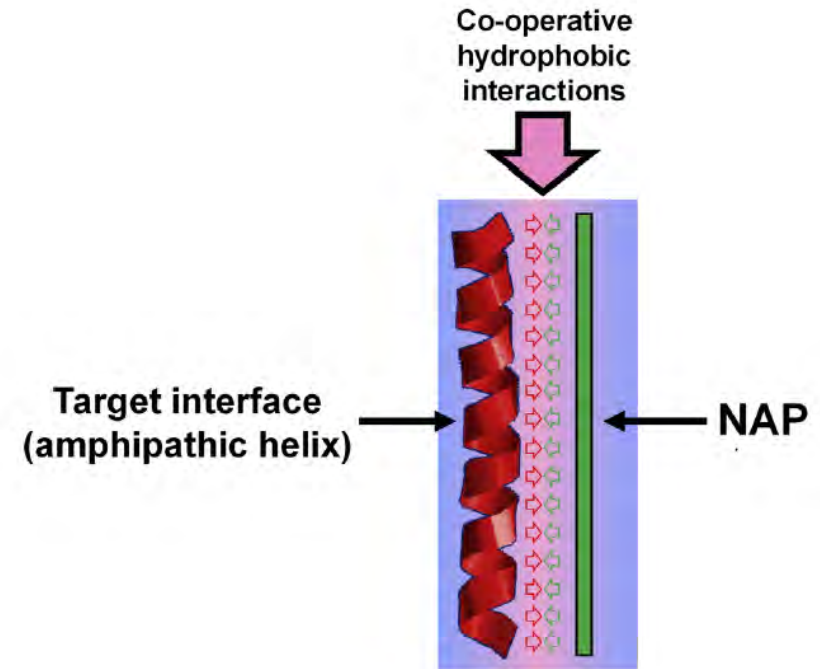
What are NAPs?

NAPs are the latest generation of antiviral polymers with broad spectrum activity



Built from nucleic acids (activity is sequence independent)
Requires phosphorothioation (increased hydrophobicity)
Requires oligonucleotide length >30mer (40mer is optimal)

The NAP – target interface



Uncomplexed amphipathic alpha helices are rare:

Viral / malarial surface glycoproteins

Prion proteins

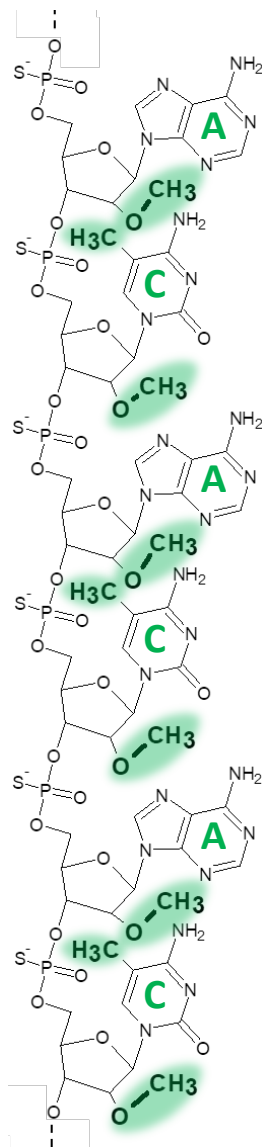
Apolipoproteins (B, E and H)

All verified interactors with NAPs

Vaillant. Antiviral Res 2016;133:32-40

Vaillant 2018, ACS Inf Dis 2018; epub Sept 10

REP 2139: the lead NAP candidate



Safety optimizations only possible with NAPs:

Repetitive adenosine / cytidine sequence

- Blocks recognition by TLR 9 (no CpG motifs present)
- Eliminates secondary structure formation and off target interaction

2'O-methylation of all ribose sugars in backbone

- Blocks recognition by TLR 3, 7, 8 and 9
- Improves compound solubility

5-methylation of cytosine

- Blocks recognition by TLRs and RIG-I / NOD in cytoplasm
- Identifies NAP as a “self” nucleic acid

All modifications are naturally occurring
(no mitochondrial toxicity)

Vaillant. Antiviral Res 2016;133:32-40
Real et al., Sci Reports 2017; 7: 43838
Roehl et al., Mol Ther Nuc Acids 2017; 8: 1-12
Vaillant. ACS Inf Dis 2018; epub Sept 10

In vitro effects of REP 2139 in infectious models of HBV

Post-entry inhibition of DHBV in duck liver primary cultures

Similar hydrophobic target interface identified as in other viral infections

Noordeen et al., Antimicrob Agents Chemother 2013; 57: 5291-5298

No entry or post-entry inhibition of HBV (HepaRG and PHH)

Guillot et al., PLoS ONE 2017; 12: e0179697

No entry or post-entry inhibition of HDV (Huh-106)

Beilstein et al., J Virol 2018; 92: e01416-17

No interaction with HBsAg, HBeAg, HBcAg, HBV or HDV

Beilstein et al., J Virol 2018; 92: 001416-17

Shamur et al., Hepatol 2017; 66: 504A

Bazinet et al., Lancet Gastro Hepatol 2017; 2: 877-889

(!)

REP 2139 is active in humans

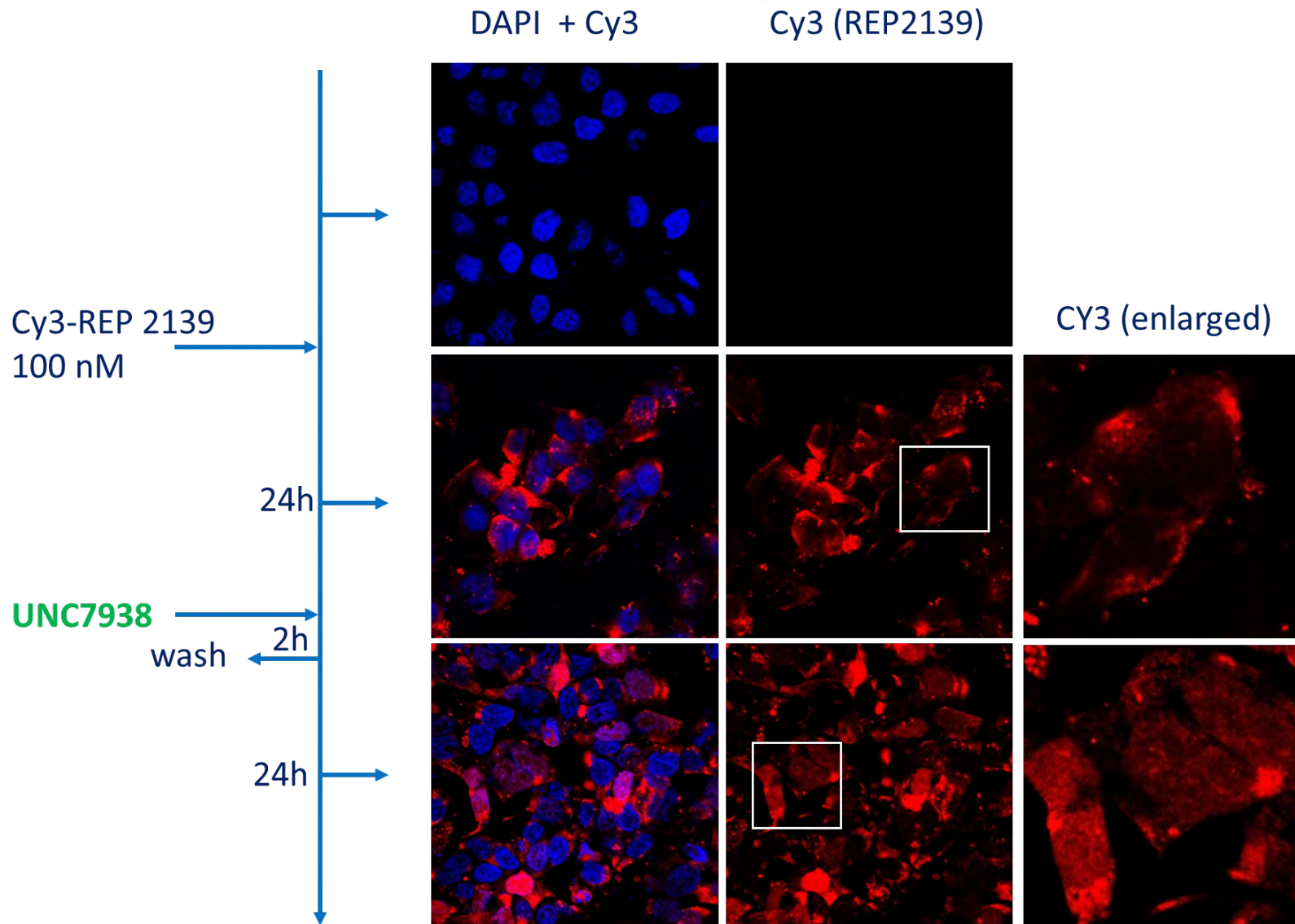
Endosomal release of PS-ONs (including NAPs) into cytoplasm occurs *in vivo* but is blocked *in vitro* in PHH or hepatocyte derived cell lines

Akhtar et al., Nuc Acids Res 1991; 19:5551-5559

Koller et al., Nuc Acids Res 2011; 39:4795-4807

Yang et al., Nuc Acids Res 2015; 43:1987-1996

Restoring endosomal release of REP 2139 (HepG2.2.15 cells)



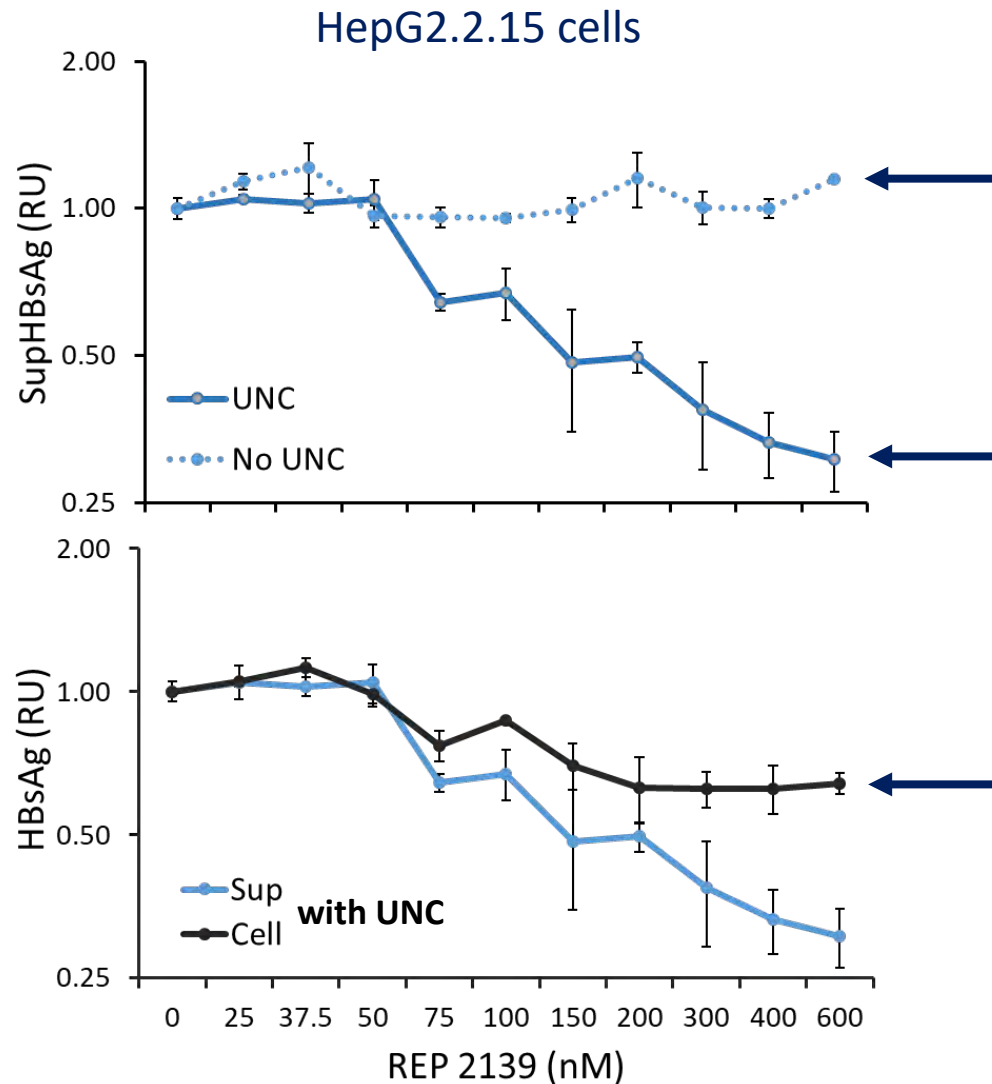
UNC 7938 – specific agent restoring
endosomal release of PS-ONs *in vitro*
Yang et al., Nuc Acids Res 2015; 43:1987-1996

REP 2139 sequestered in endosomes

REP 2139 released into
cytoplasm / nucleus

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

Antiviral effects of REP 2139 with normal endosomal release

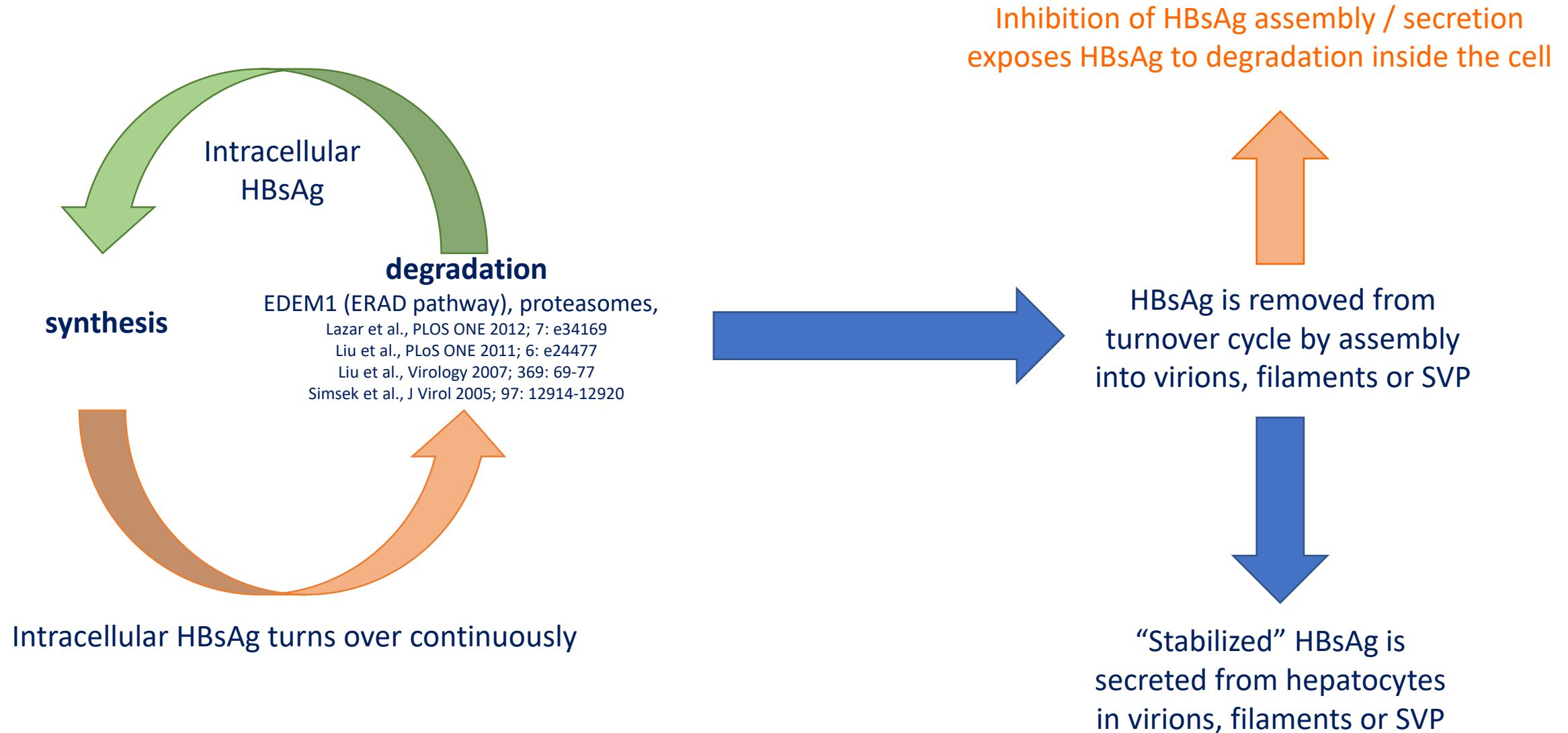


No effect on HBsAg release with endosomal sequestration of REP 2139

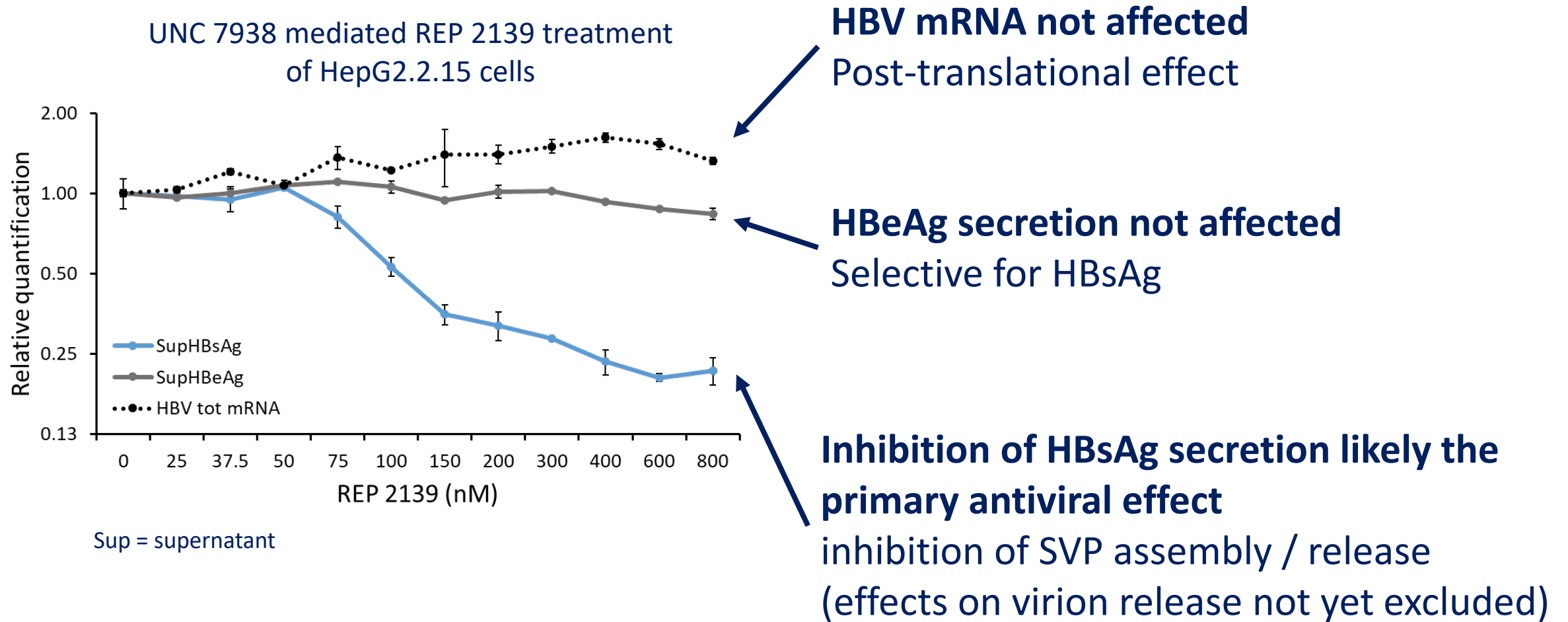
Release of REP 2139 into cytoplasm results in inhibition of HBsAg release

Inhibition of HBsAg release is not accompanied by intracellular HBsAg accumulation (intracellular HBsAg may actually also decrease)

Model for intracellular HBsAg dynamics

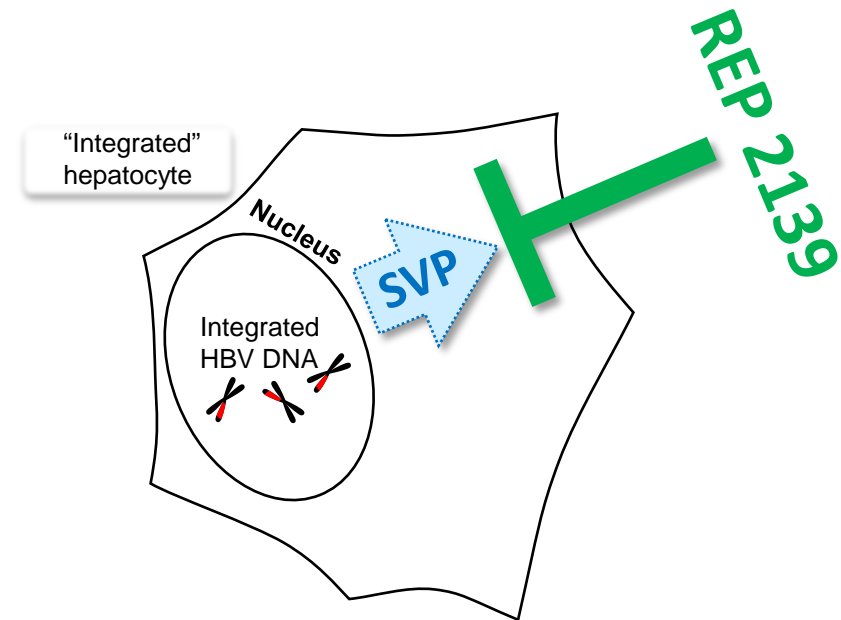
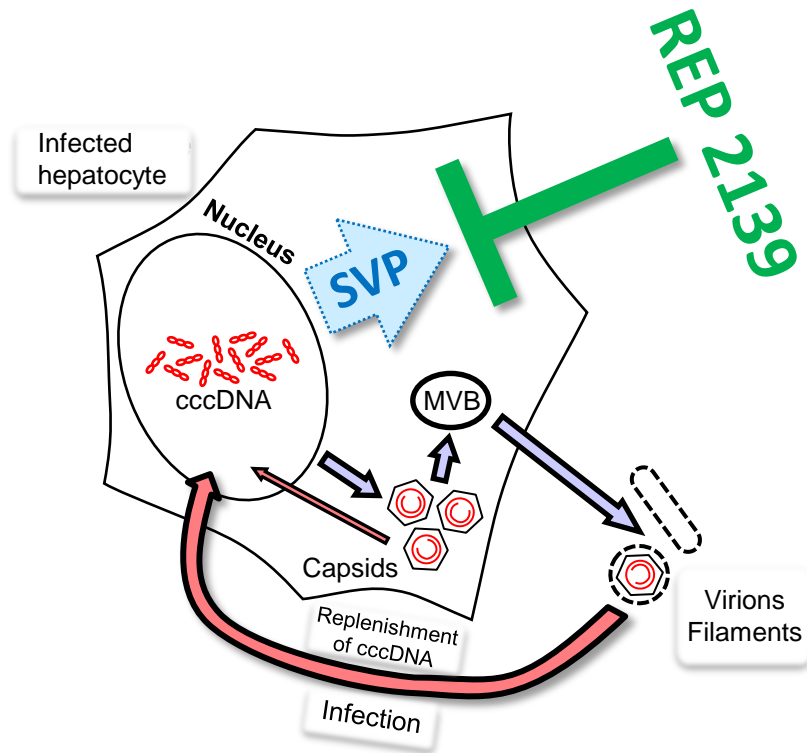


Selectivity of REP 2139 effect



Antiviral mechanism of NAPs

NAPs block the release of subviral particles from infected or “integrated” hepatocytes



Circulating HBsAg can now be cleared by existing immune function
Critical elimination of HBsAg mediated immunosuppression
Functional cure can be established

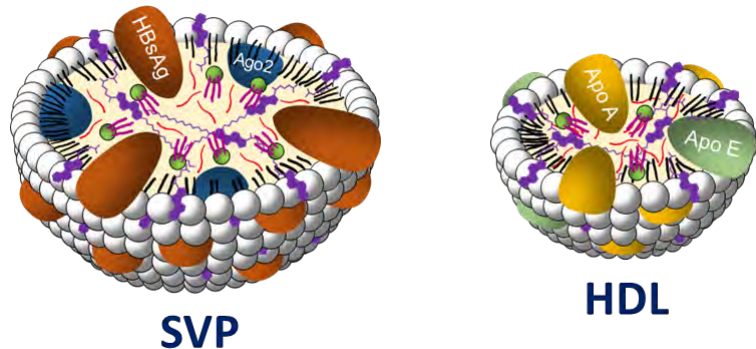
Evaluation of NAPs *in vivo*

NAPs are inactive in rodent models!

- Chisari and PAMF HBV transgenic mice
- HBV infected SCID-Hu mice
- WHV infected woodchucks

Liver accumulation with NAPs occurs in all these species but

HDL metabolism is different from humans.....



SVP in humans is very similar to HDL

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

Duck HBV (DHBV) infection of Pekin ducks:

HDL metabolism is similar to humans!

DHBV infection is similar to HBV infection:

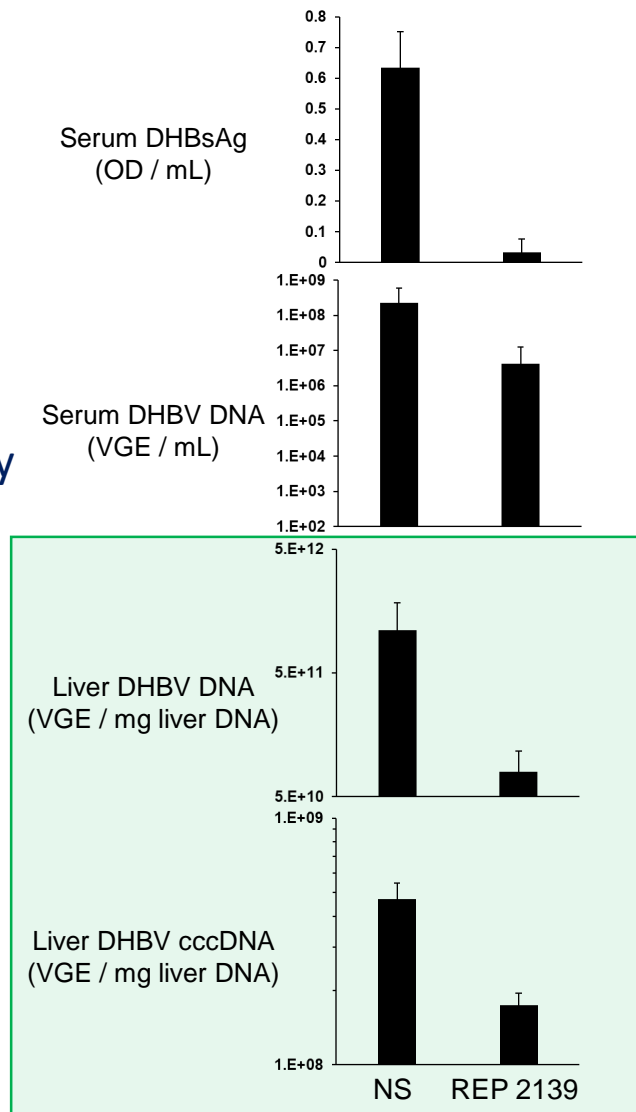
- hepatotropic
- SVPs form the bulk of surface antigen
- reservoir of cccDNA is established
- respond to NUCs (ETV, ADV, TDF)

Liver inflammation and cirrhosis is largely absent
Immunological assessment hampered by lack of reagents

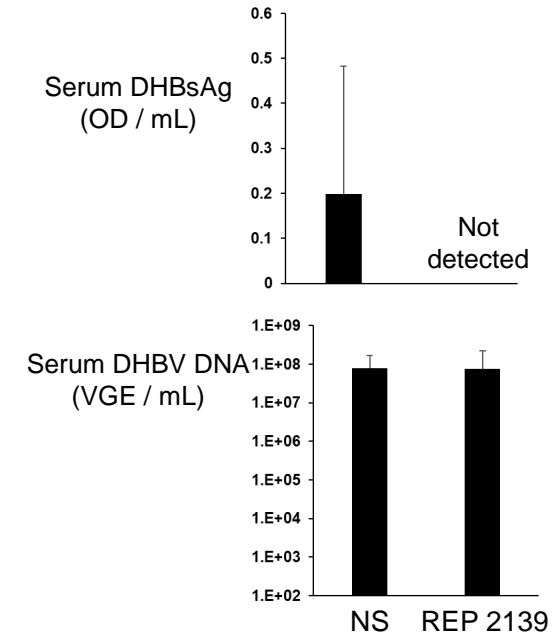
REP 2139 effect *in vivo*

(Pekin ducks with established DHBV infection)

10mg/kg/day
2 weeks



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



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

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

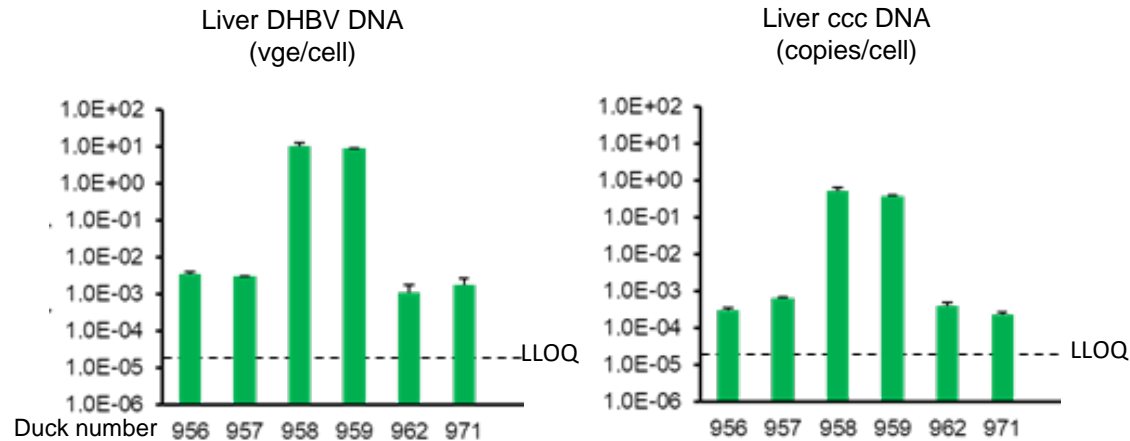
DHBsAg appears more efficiently targeted
during therapy than DHBV DNA
(consistent with selective targeting of SVP)

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

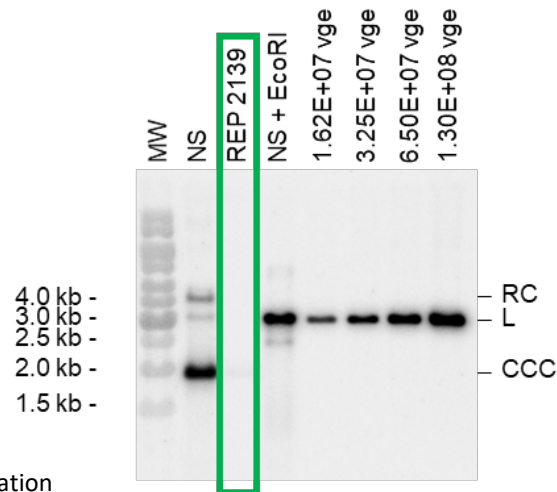
REP 2139 effect *in vivo*

(Pekin ducks with established DHBV infection)

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

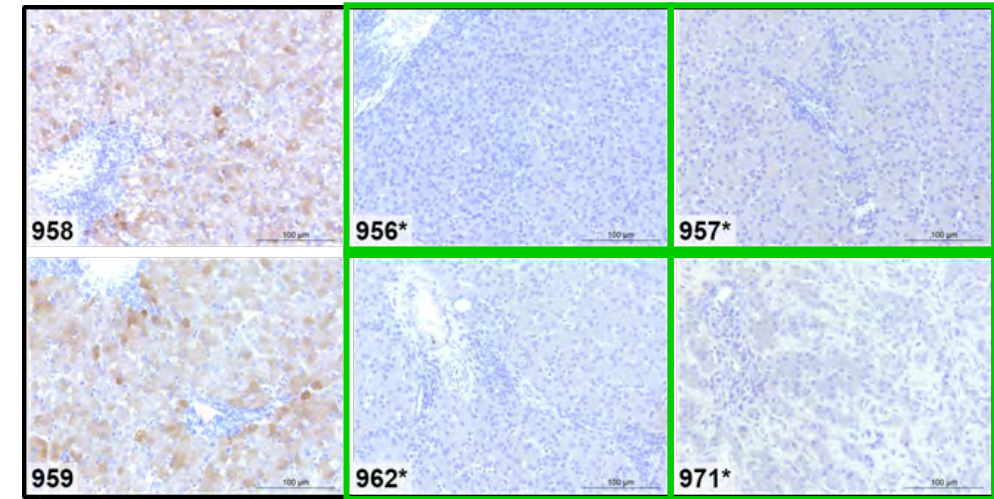


Verification of cccDNA reduction by southern blot



LLOQ= lower limit of quantification

DHBsAg is cleared from the liver



Normal liver histology throughout treatment

Functional control of infection persists off-treatment

- < LLOQ serum DHBsAg
- < LLOQ serum DHBV DNA
- Control of cccDNA
- Elimination of intrahepatic surface and core antigens

Quinet et al., Hepatol 2018; 67: 2127-2140
Noordeen et al., PLoS ONE 2015; 11: e0140909

REP 2139 preclinical safety

Safety pharmacology (cynomolgus monkey):

- NOAEL: 54mg/kg (~15x clinical dose) (due in part to chelate complex formulation)
- Minimal cardiovascular / respiratory / neurologic alterations at 108mg/kg (~30x clinical dose)

No genotox (Ames, *in vitro* / *in vivo* micronucleus)

No genome interactions

6 months chronic tox / TK studies in mice:

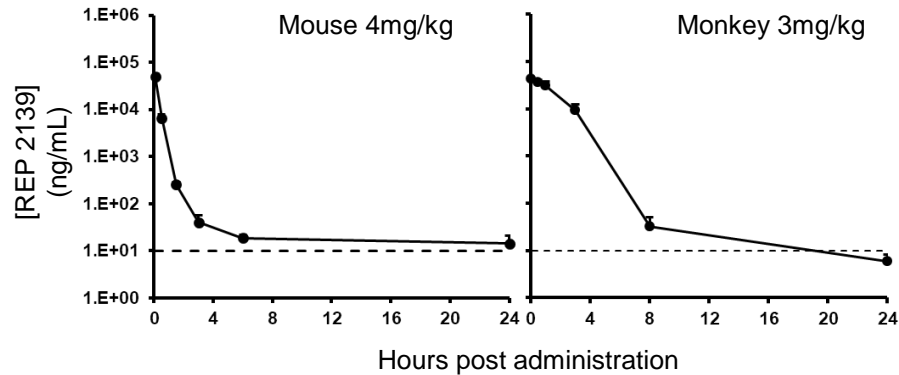
- NOAEL 16 mg/kg
- mild alterations in liver and kidney function at 48 and 96mg/kg

6 months chronic tox / TK in cynomolgus monkeys:

- NOAEL 3mg/kg
- Only significant AEs at 9 and 27mg/kg: complement activation and accompanying vasculitis
- **Common with PS-ONs in this species but absent in humans**
- No significant changes in liver, kidney or hematologic function at 9 or 27mg/kg
- Remarkably minimal organ immune infiltration in organs for a PS-ON

REP 2139 pharmacokinetics

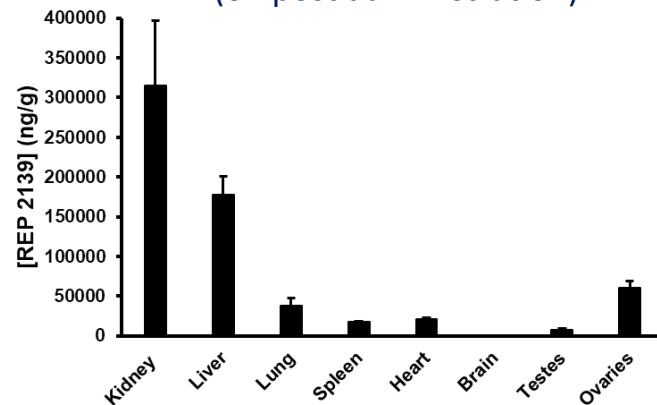
Plasma kinetics



REP 2139 is rapidly cleared from the blood

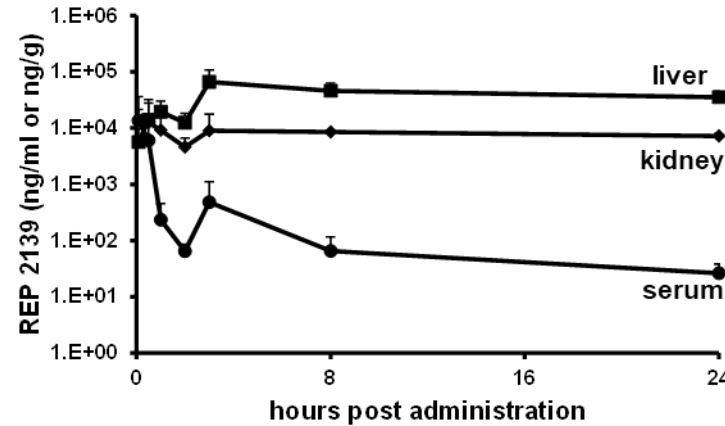
Mouse tissue accumulation

(6h post administration)

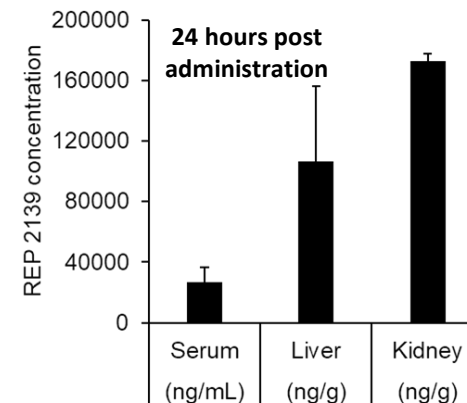


REP 2139 accumulates in the kidney and liver

Well conserved liver accumulation
amongst all species evaluated

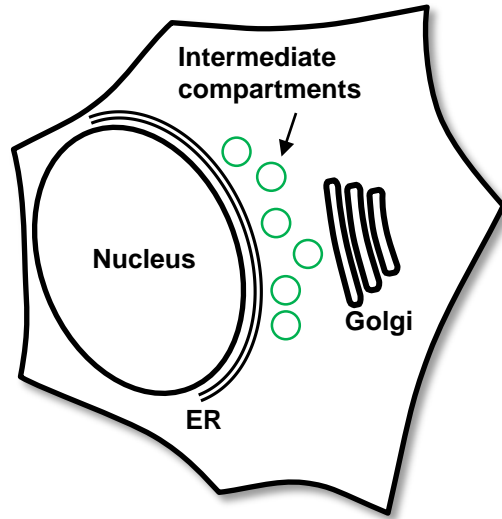


Including ducks

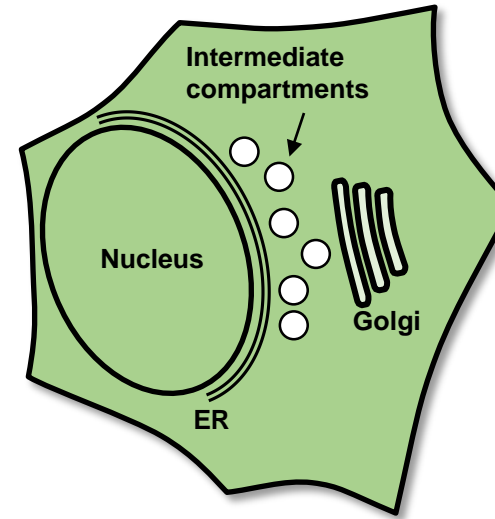


and woodchucks

Intracellular trafficking of REP 2139 governs its potency in humans



Intermediate compartments are the sites of SVP assembly

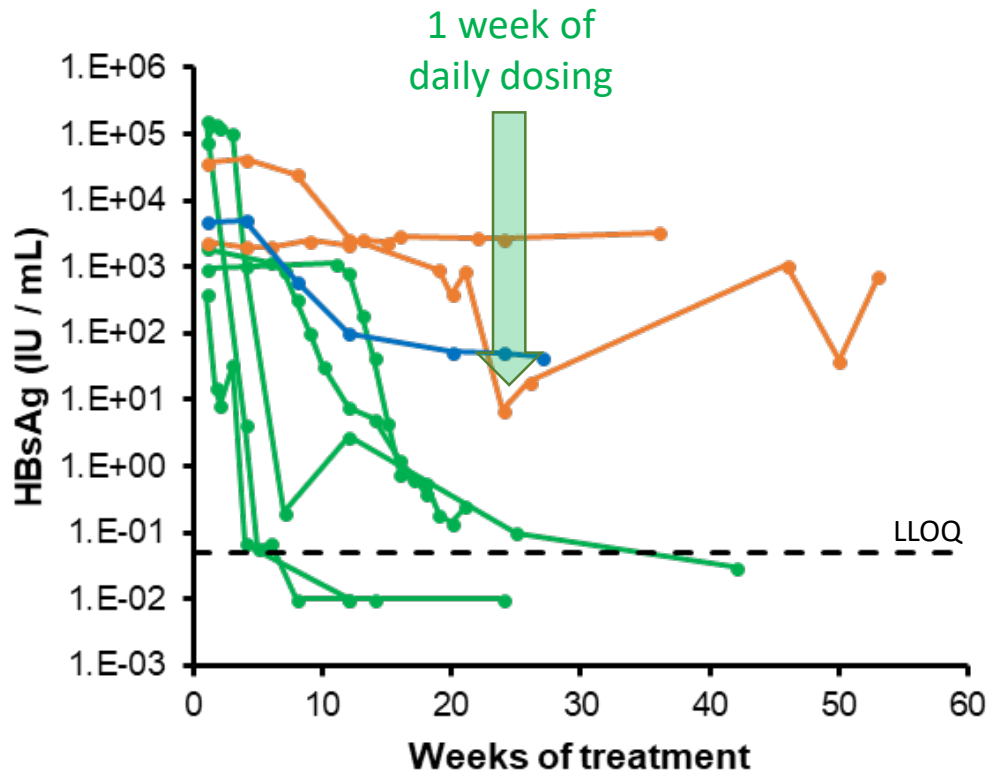


In hepatocytes, active phosphorothioate oligonucleotides (and NAPs) are found at their highest concentrations in the cytoplasm and nucleus (unknown for intermediate compartments)

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

Intracellular trafficking of REP 2139 governs its potency in the clinic

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



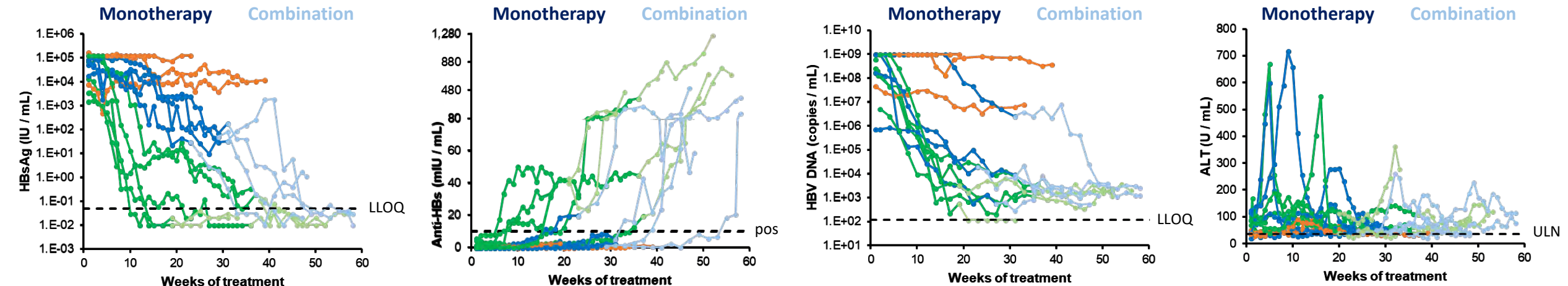
- HBsAg decline < 1 log
(poor NAP transit to the intermediate compartment [IC])
Can be overcome with higher frequency dosing
- HBsAg decline > 1 log but > 1 IU/mL
(efficient NAP transit to the IC but poor host HBsAg clearance)
- HBsAg decline to < 1 IU/mL
(efficient NAP transit to the IC and efficient host HBsAg clearance)

Building a combination regimen with HBsAg loss

Step 1: is the antiviral effect of immunotherapy improved with HBsAg reduction / loss?

REP 102 study - HBeAg positive chronic HBV infection

9 responder patients to REP 2139-Ca monotherapy transitioned to combination therapy: 13-26 weeks of thymosin alpha 1 (n=4) or pegylated interferon alpha 2a (n=5)



HBsAg decline continues / accelerates

Anti-HBs dramatically increased

HBV DNA decline brought to a low threshold in all responder patients

Additional but weaker flares observed during immunotherapy
(all otherwise asymptomatic)

< 1 log reduction in HBsAg

HBsAg > 1 log reduction but > 1 IU/mL

HBsAg < 1 IU/mL

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

Building on functional control rates...

Antiviral response	In vivo (DHBV infected Pekin ducks)	HBeAg positive chronic HBV infection (REP 101 study)	HBeAg positive chronic HBV infection with immunotherapy (REP 102 study)	
Blood	HBsAg reduction to < LLOQ HBV DNA reduction to < LLOQ (decoupled from HBsAg clearance)	HBsAg reduction to < 1 IU/mL HBsAg seroconversion HBeAg seroconversion HBV DNA and RNA reduction (decoupled from HBsAg clearance)		
Liver	Clearance of HBsAg and HBcAg Transcriptional inactivation of cccDNA 2-3 log ₁₀ reduction in cccDNA	Strong, self resolving, asymptomatic transaminase flares (when HBsAg becomes < 1 IU/mL)		
Functional control after removal of therapy Clinical benefit without further need for therapy	55-66% blood and liver (functional cure)*	25% 5 years of follow-up (inactive HBV)**	44% 2 years of follow-up (inactive HBV)**	

*HBsAg and HBV DNA or HDV RNA target not detected

**HBV DNA < 2000 IU/mL with normal ALT

Why care about HDV?

- A co-infection in 15-20 million+ people with chronic HBV infection worldwide (HDV uses HBsAg for its envelope)
- Most aggressive form of viral hepatitis (80% of patients become cirrhotic within 10 years)
- **No approved therapy**

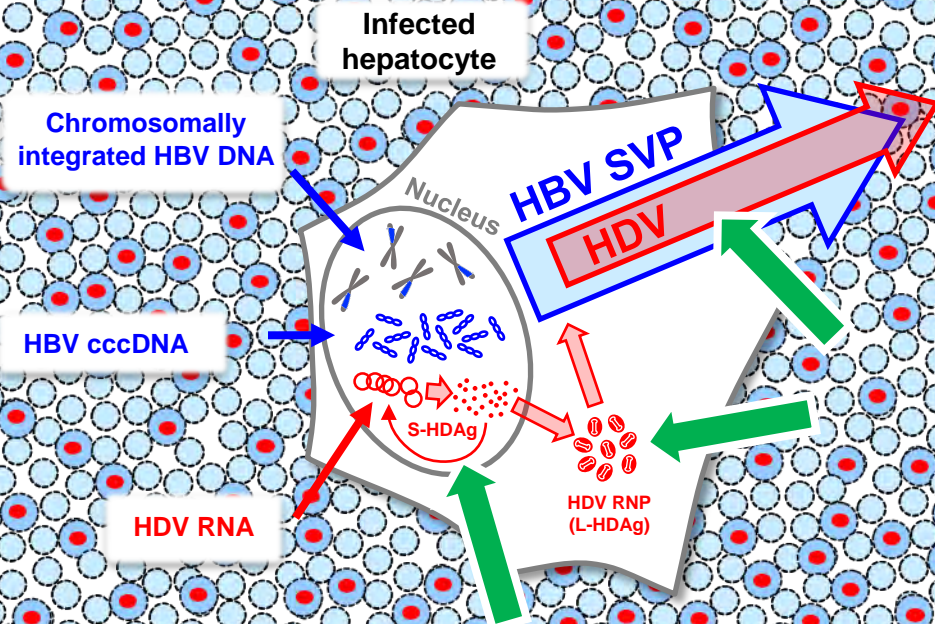
Functional cure:

Eradication of HDV virus from the liver

Antiviral therapy no longer required

Potential for reversal of liver damage

REP 2139 in HBV / HDV infection



HDV exits the hepatocyte using the same secretory machinery as **HBV subviral particles (SVP)**

REP 2139 exerts multiple antiviral effects in HDV:

**Blocks release of HDV
(via indirect effect on blocking assembly / release of SVP)**

Interferes with HDV RNA replication and HDV RNP assembly via REP 2139 interaction with S- and L-HDAg

Shamur et al., Hepatol 2017; 66: 504A

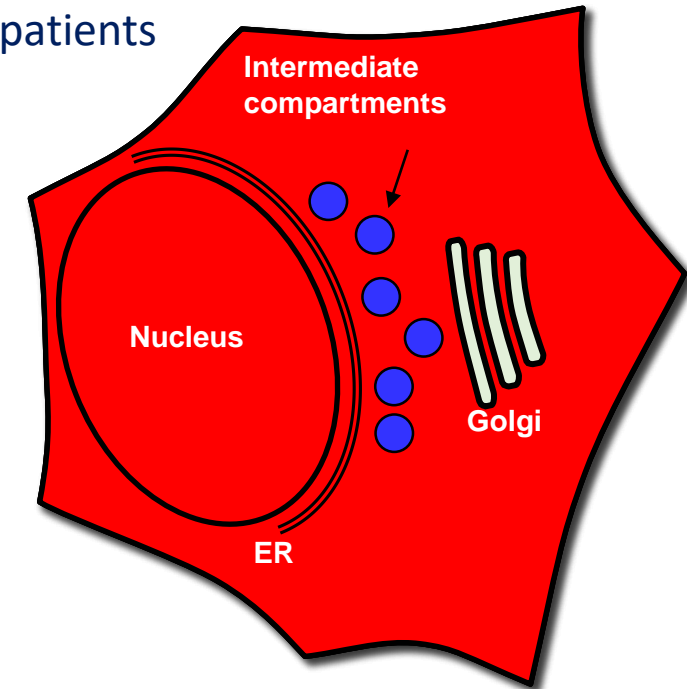
Intracellular trafficking of REP 2139 governs its potency in HBV and HDV

HBsAg

SVP assembly in intermediate compartments

Pharmacological activity not easily achieved in a small proportion of patients
(requires higher frequency dosing)

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



HDV

HDAg activity in nucleus and cytoplasm

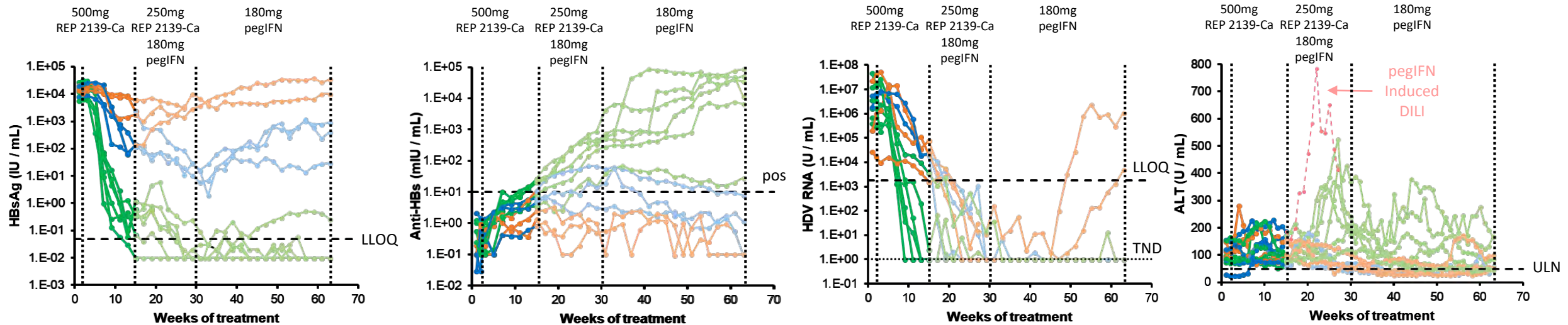
Pharmacological activity easily achieved in all patients

Building a combination regimen in HBV/HDV co-infection

Combination effect in HBeAg negative HBV / HDV co-infection?

REP 301 study – 12 patients - HBeAg negative chronic HBV / HDV co-infection

Strong HDV RNA response even in patients with attenuated HBsAg response



HBsAg decline continues / accelerates

(but not in non-responders)
(slow rebound after removal of REP 2139)

Anti-HBs dramatically increased

(only in patients where
HBsAg < 1 IU/mL before
pegIFN)

HBV RNA TND in 11/12 patients during therapy

(rebound in non-responders
after removal of REP 2139)

ALT flares observed during immunotherapy

(all otherwise asymptomatic)
(only in patients where
HBsAg < 1 IU/mL before pegIFN)

< 1 log reduction in HBsAg

HBsAg > 1 log reduction but > 1 IU/mL

HBsAg < 1 IU/mL

Bazinet et al., Lancet Gastro. Hepatol. 2018; 2: 877-889

Building on functional control rates...

Antiviral response	In vivo (DHBV infected Pekin ducks)	HBeAg positive chronic HBV infection (REP 101 study)	HBeAg positive chronic HBV infection with immunotherapy (REP 102 study)	HBeAg negative chronic HBV/HDV co-infection with immunotherapy (REP 301 study)
Blood	HBsAg reduction to < LLOQ HBV DNA reduction to < LLOQ (decoupled from HBsAg clearance)	HBsAg reduction to < 1 IU/mL HBsAg seroconversion HBeAg seroconversion HBV DNA and RNA reduction (decoupled from HBsAg clearance)		HBsAg reduction to < 1 IU/mL HBsAg seroconversion HDV RNA clearance (target not detected)
Liver	Clearance of HBsAg and HBcAg Transcriptional inactivation of cccDNA 2-3 log ₁₀ reduction in cccDNA	Strong, self resolving, asymptomatic transaminase flares (when HBsAg becomes < 1 IU/mL)		Weak transaminase flares (strong following pegIFN add-on when HBsAg < 1 IU/mL)
Functional control after removal of therapy Clinical benefit without further need for therapy	55-66% blood and liver (functional cure)*	25% 5 years of follow-up (inactive HBV)**	44% 2 years of follow-up (inactive HBV)**	36% (HBsAg)* 55% (HBV DNA)* 64% (HDV RNA)* (functional cure) 2 years of follow-up

*HBsAg and HBV DNA or HDV RNA target not detected

**HBV DNA < 2000 IU/mL with normal ALT

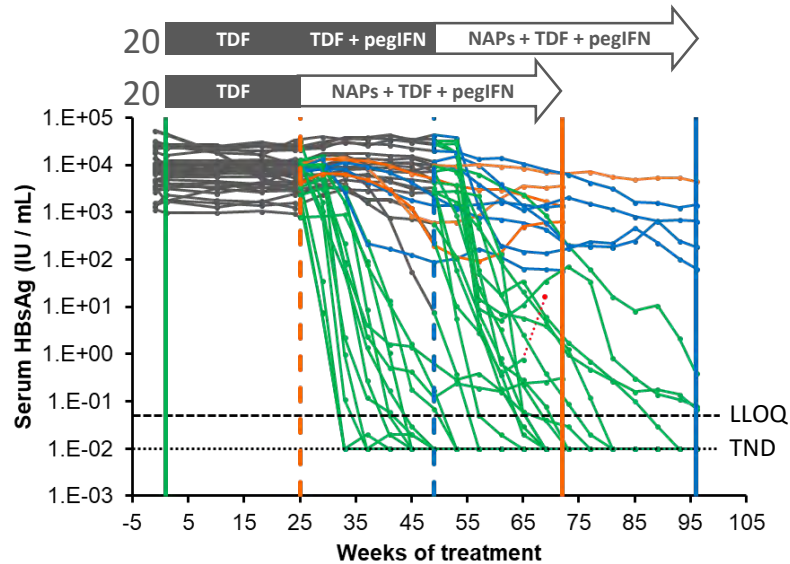
Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

REP 401 study - HBeAg negative chronic HBV mono-infection

40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN

Interim analysis from July 7, 2018



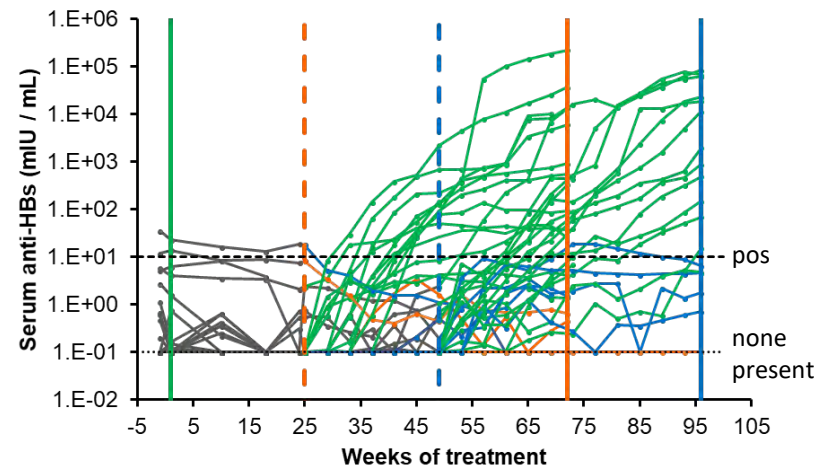
REP 2139-Mg = REP 2165-Mg

4/40 non-responders

8/40 HBsAg > 1 log reduction but > 1 IU/mL

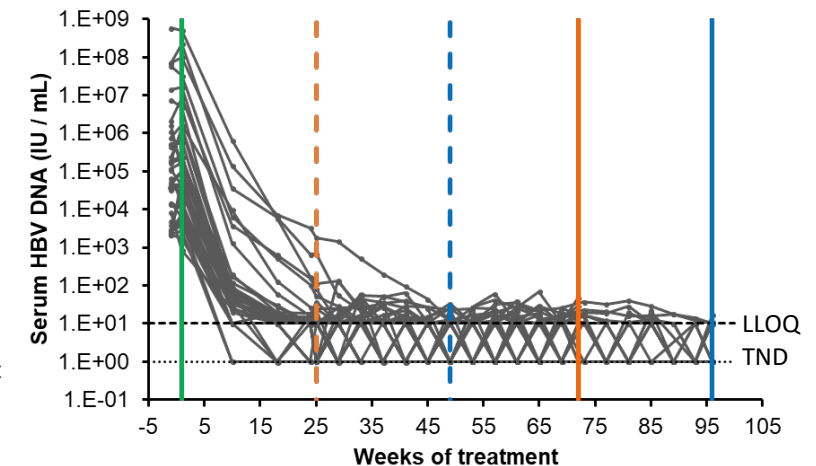
28/40 HBsAg < 1 IU/mL

24/40 HBsAg loss (≤ 0.05 IU/mL)



Anti-HBs dramatically increased with the introduction of pegIFN

(but only in patients with HBsAg declines to < 1 IU/mL)



TDF-induced HBV DNA declines unaffected during therapy

Standard of care only

< 1 log reduction in HBsAg

HBsAg > 1 log reduction but > 1 IU/mL

HBsAg < 1 IU/mL

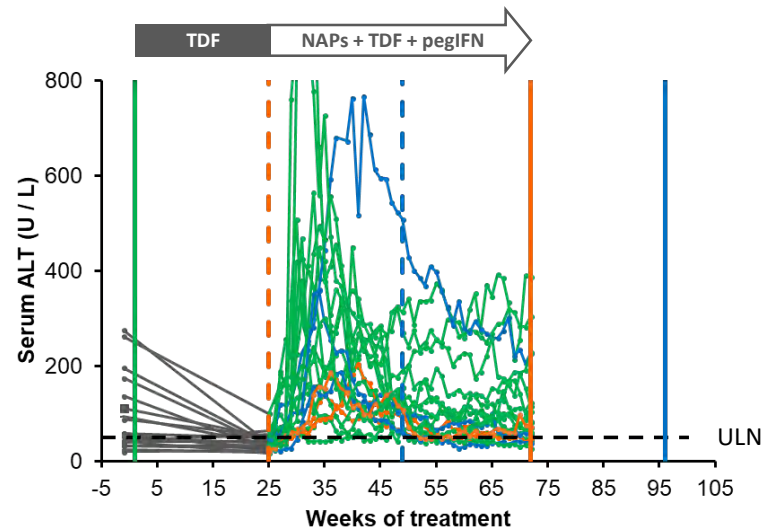
Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

REP 401 study - HBeAg negative chronic HBV mono-infection

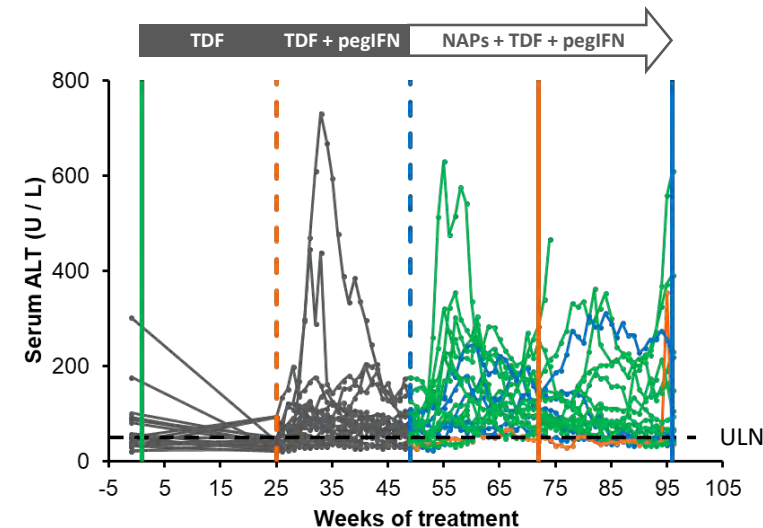
40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN

Interim analysis from July 7, 2018



ALT flares observed during immunotherapy
(all otherwise asymptomatic)

(increased intensity in patients with HBsAg declines to < 1 IU/mL)



Flares attenuated when NAPs introduced
following 24 weeks of pegIFN

Loss of T-cell function with pegIFN(?)

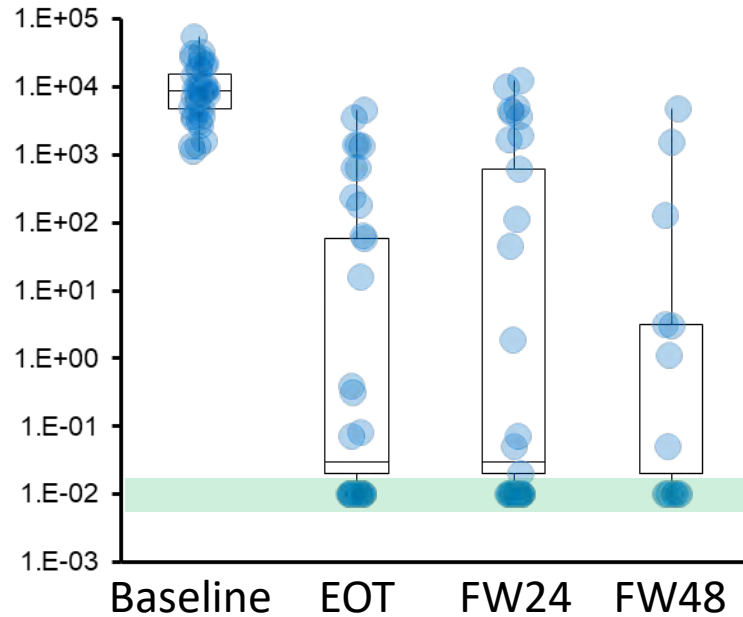
Standard of care only < 1 log reduction in HBsAg HBsAg > 1 log reduction but > 1 IU/mL HBsAg < 1 IU/mL

REP 401

Antiviral performance during therapy and follow-up

34/40 patients have completed treatment and ≥ 24 weeks of treatment-free follow-up as of July 7, 2018

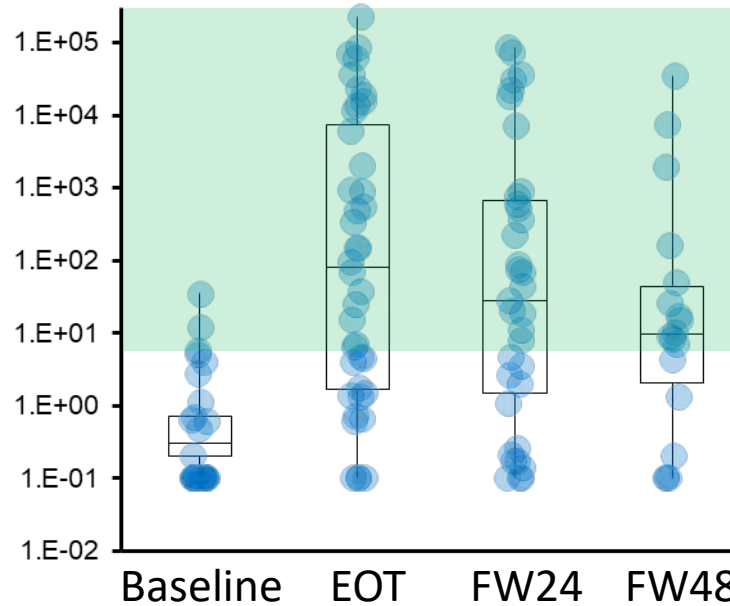
HBsAg (IU/mL)



0% **60%** **53%** **50%**
(0/40) (24/40*) (18/34) (8/16)

HBsAg loss
(≤ 0.05 IU/mL)

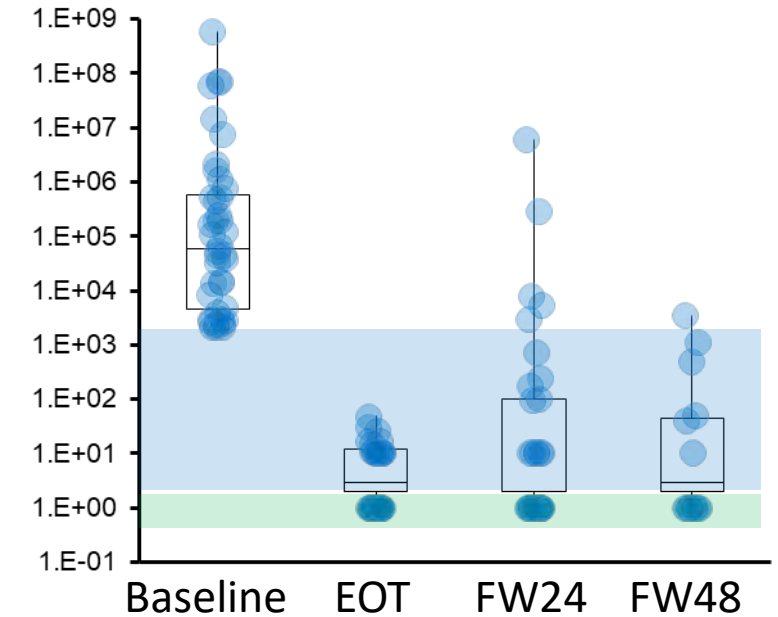
Anti-HBs (mIU/mL)



0% **60%** **59%** **56%**
(0/40) (24/40*) (20/34) (9/16)

HBsAg seroconversion
(Anti-HBs ≥ 10 mIU/mL)

HBV DNA (IU/mL)



0% **55%** **50%** **62%**
(0/40) (22/40*) (17/34) (10/16)

HBV DNA target not detected

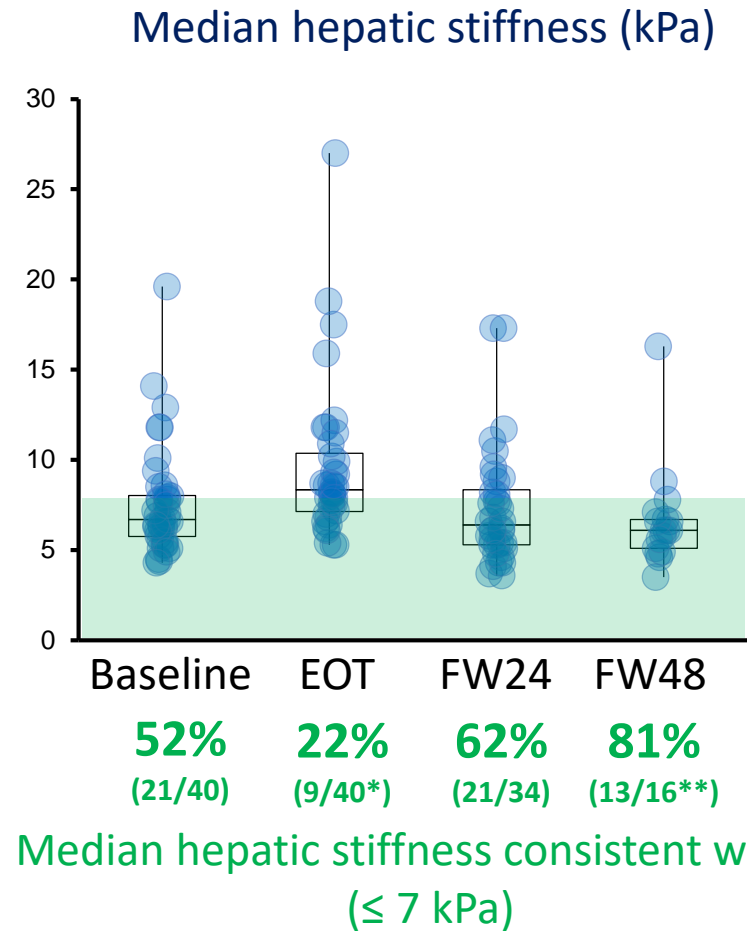
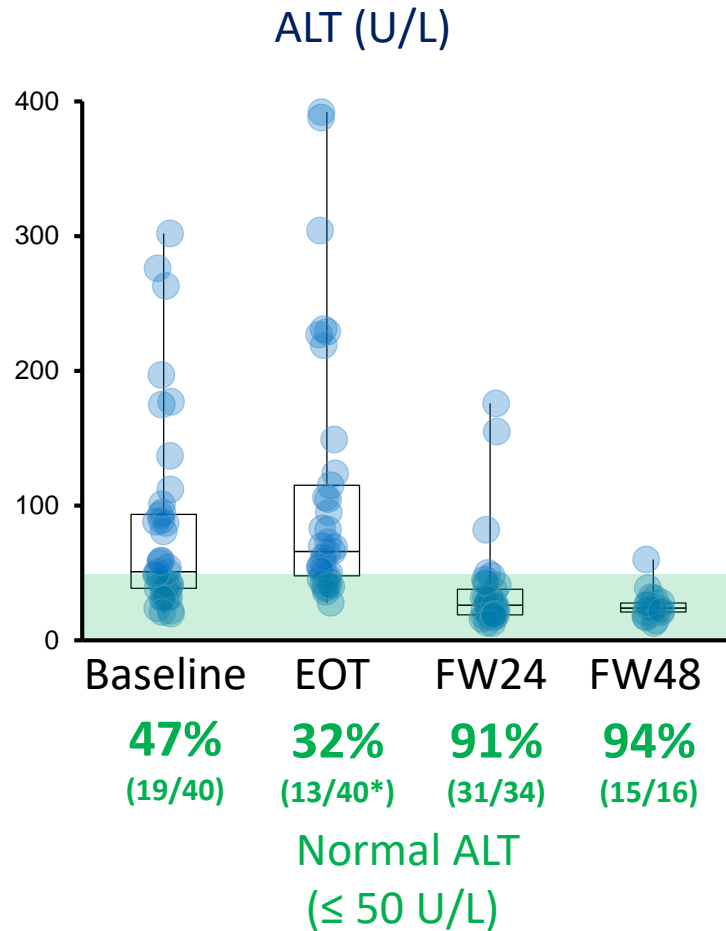
0% **45%** **38%** **31%**
(0/40) (18/40*) (13/34) (5/16)

HBV DNA LLOQ to 2000 IU/mL

* 3 patients withdrew from therapy early for personal reasons

REP 401

Liver status during treatment and follow-up



Improvement in liver function
during follow-up

**Significant improvement
compared to baseline**

* 3 patients withdrew from therapy early for personal reasons

** 2 FW48 fibroscan results still pending

REP 401 response summary (as of July 7, 2018)

Patients entered into trial		40
End of treatment HBsAg response	> 1 log from baseline	36
	< 1 IU/mL	27
	≤ 0.05 IU/mL	24
Patients currently completed treatment and ≥ 24 weeks of follow-up		34
Inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		44%
Functional cure (HBsAg and HBV DNA target not detected)		41%
Clinical benefit (Low risk of progression, reduced risk of HCC)		85%

Summary

HBsAg loss is essential for restoration of immune control (functional cure) of HBV infection

- **Cannot be achieved by direct acting antivirals due to HBV DNA integration**

REP 2139 uniquely achieves rapid HBsAg loss in most patients

- Blocks release of HBsAg derived from cccDNA and integrated HBV DNA
- Accompanied by clearance of HBsAg and control of cccDNA in the liver that persists after therapy

REP 2139 eliminates HDV RNA and establishes functional cure of HDV infection

- Likely driven by direct interaction with HDAg

REP 2139-mediated HBsAg loss dramatically potentiates the effects of immunotherapy

- Requires HBsAg to be < 1 IU/mL
- High rates of HBsAg seroconversion
- Occurrence of asymptomatic (likely therapeutic) transaminase flares are stronger and more prevalent
- Improved rates of functional control of HBV and HDV infection observed after removal of all therapy

Currently 85% of patients have control of infection with clinical benefit

Interferon therapy is easily managed and safe when combined with TDF and REP 2139-Mg

- REP 2139-Mg will also improve the effects of other immunotherapies

Next steps

Transition of REP 2139-Mg to subcutaneous dosing

- REP 2139-Mg is already optimized for SC administration

Initiation of phase IIA triple combination trial in the US

- In collaboration with the ACTG (DAIDS / NIH)
- Will use same regimen as in the REP 401 trial (NUCs + pegIFN + REP 2139-Mg)

Assessing other immunotherapies

- PegIFN is much better tolerated in HBV than in HCV but results in loss of T-cells during therapy
Marcellin et al., Liv Int 2008; 28: 477-485
Micco et al., J Hepatol 2013; 58: 225-233
- Functional cure rates may improve with other immunotherapies
 - Thymosin alpha 1 (T-cell agonist)
 - TLR / RIG-I agonists
 - Therapeutic vaccines

Development of REP 2165-Mg to salvage poor HBsAg response to REP 2139-Mg (~ 10% of patients)

- REP 2165 can be safely dosed at higher frequency to ensure HBsAg response
- Predictive markers for patients having poor HBsAg response to REP 2139 under investigation

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