HBV Forum 4
Paris, 12th April 2018

Effect on combination therapy on achieving cure

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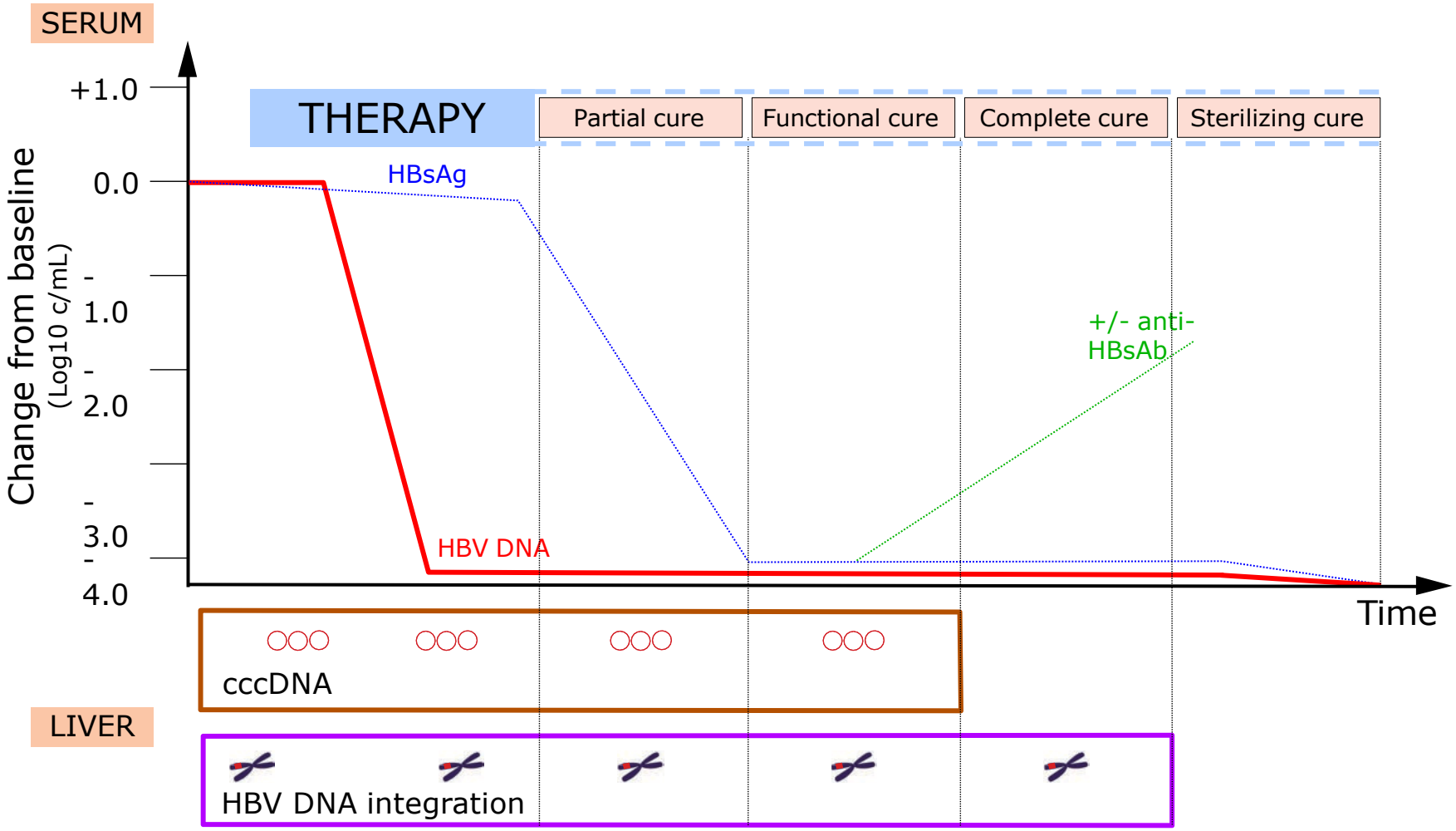
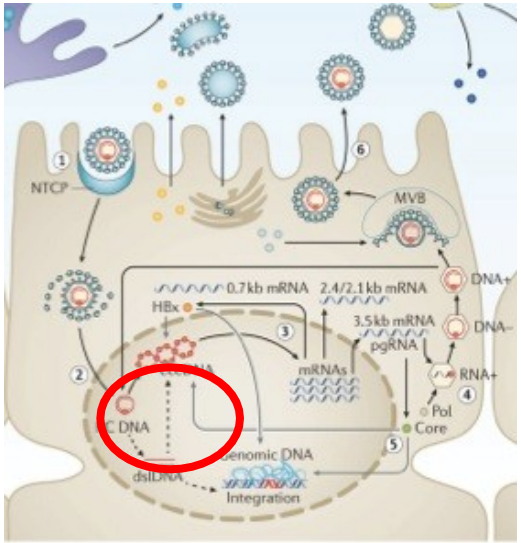
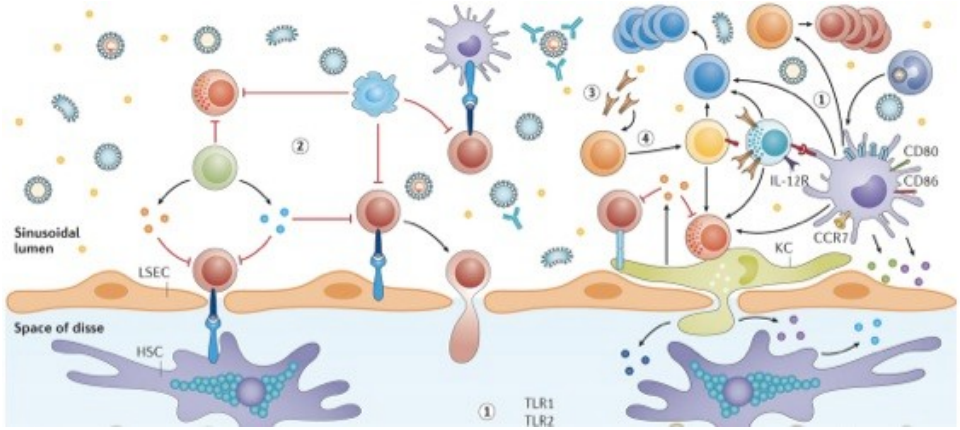
Definition of HBV cure: what do we want to achieve ?



Lok et al, J Hepatol joint publication 2017
Testoni, Levrero, Zoulim, Sem Liv Disease 2017

Barriers to eradicating HBV





cccDNA reservoir
Long t1/2
Continuous replenishment
Not affected by NAs and IFN

Integrated forms

HBV persistence

Defective CD8+ responses

Defective B cell responses

Inefficient innate response

Defective immune responses

Revill, Testoni, Locarnini, S. & Zoulim, F. Nat. Rev. Gastroenterol. Hepatol 2016

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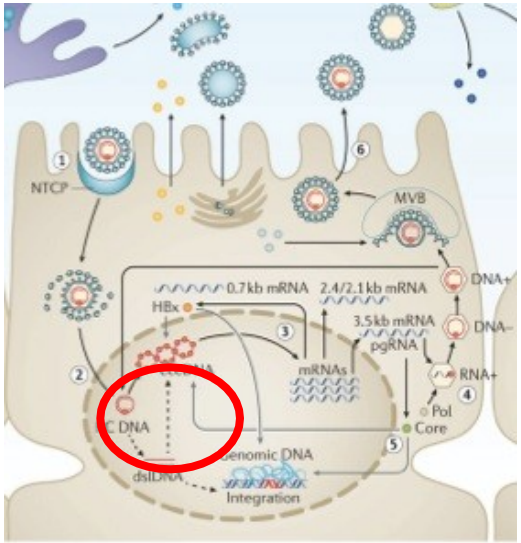

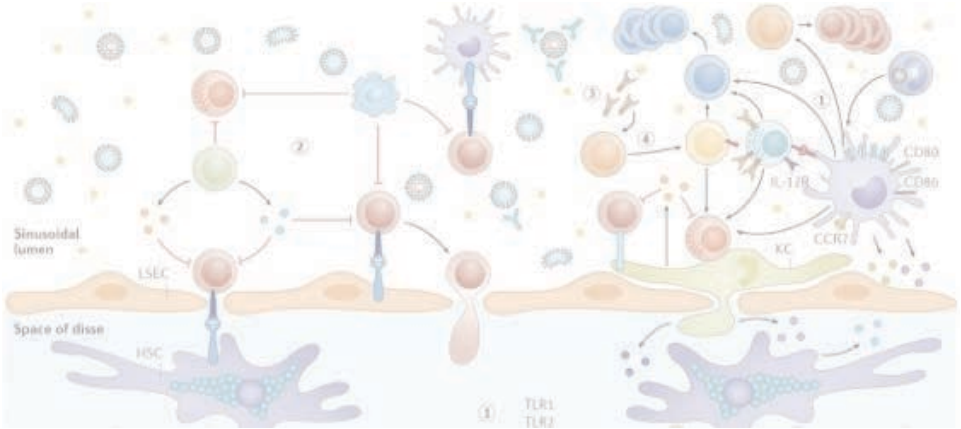

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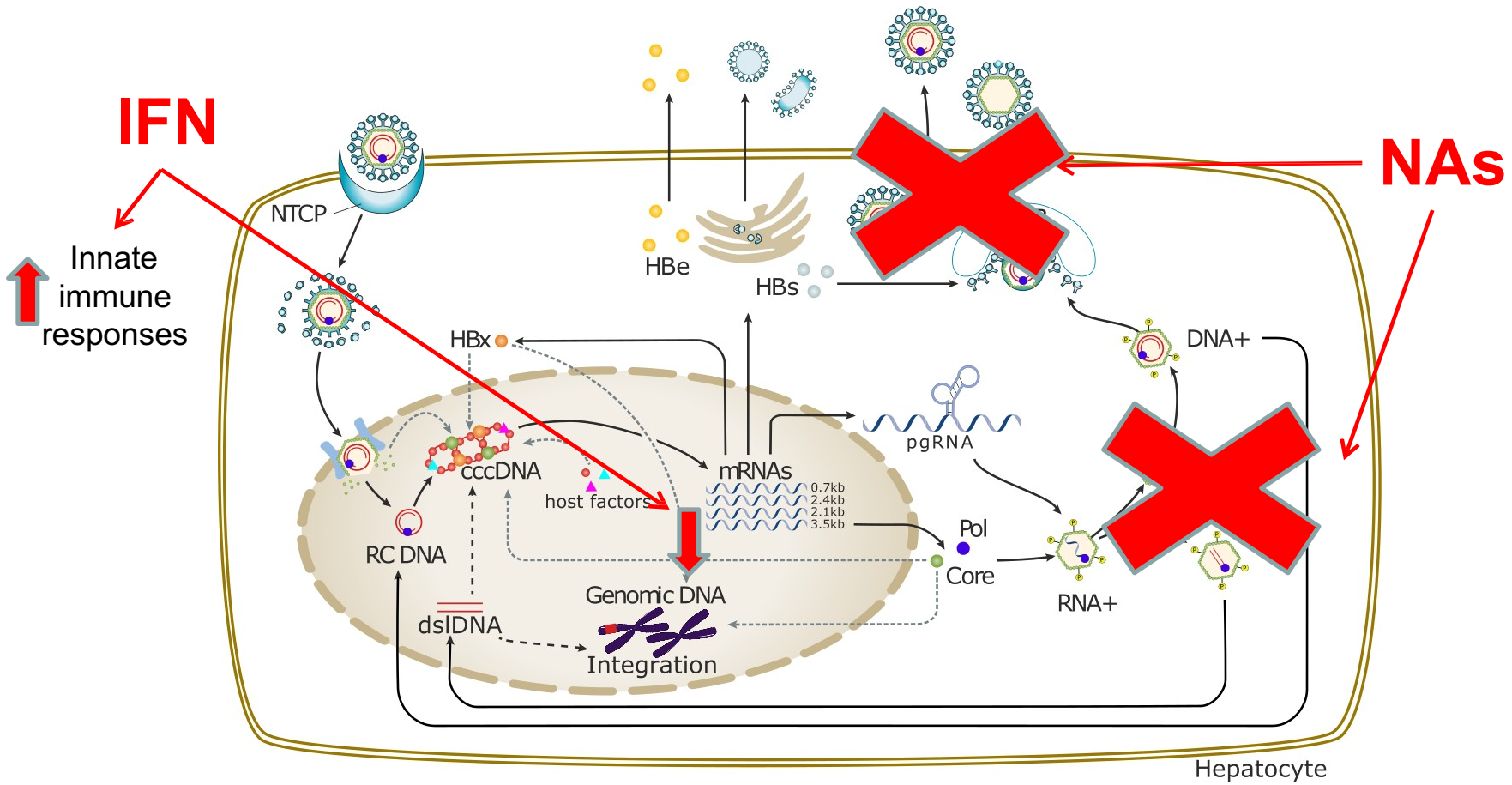
Current treatment options

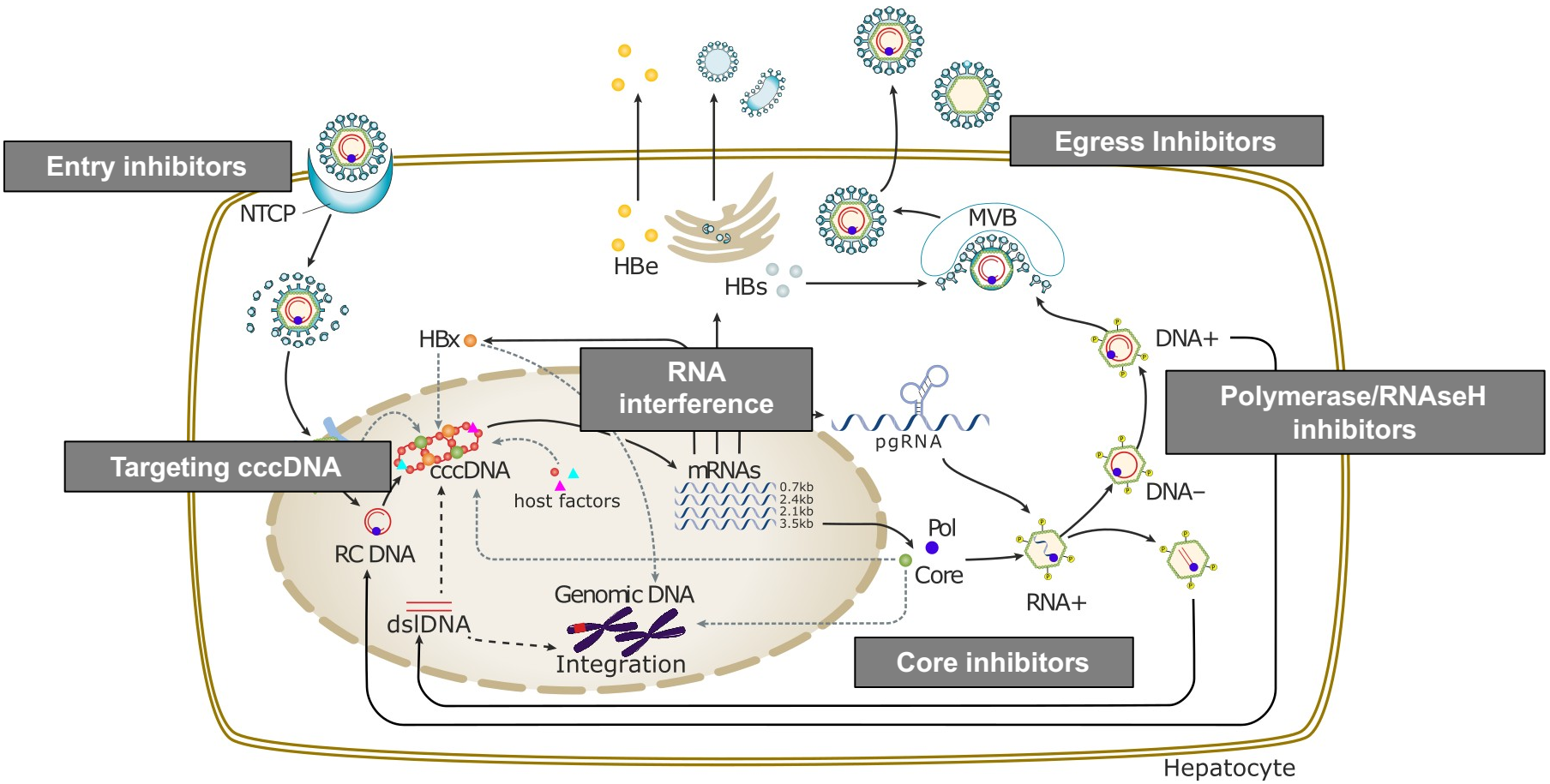


Current available therapies inhibit complete virion formation and release, but are not able to eliminate cccDNA

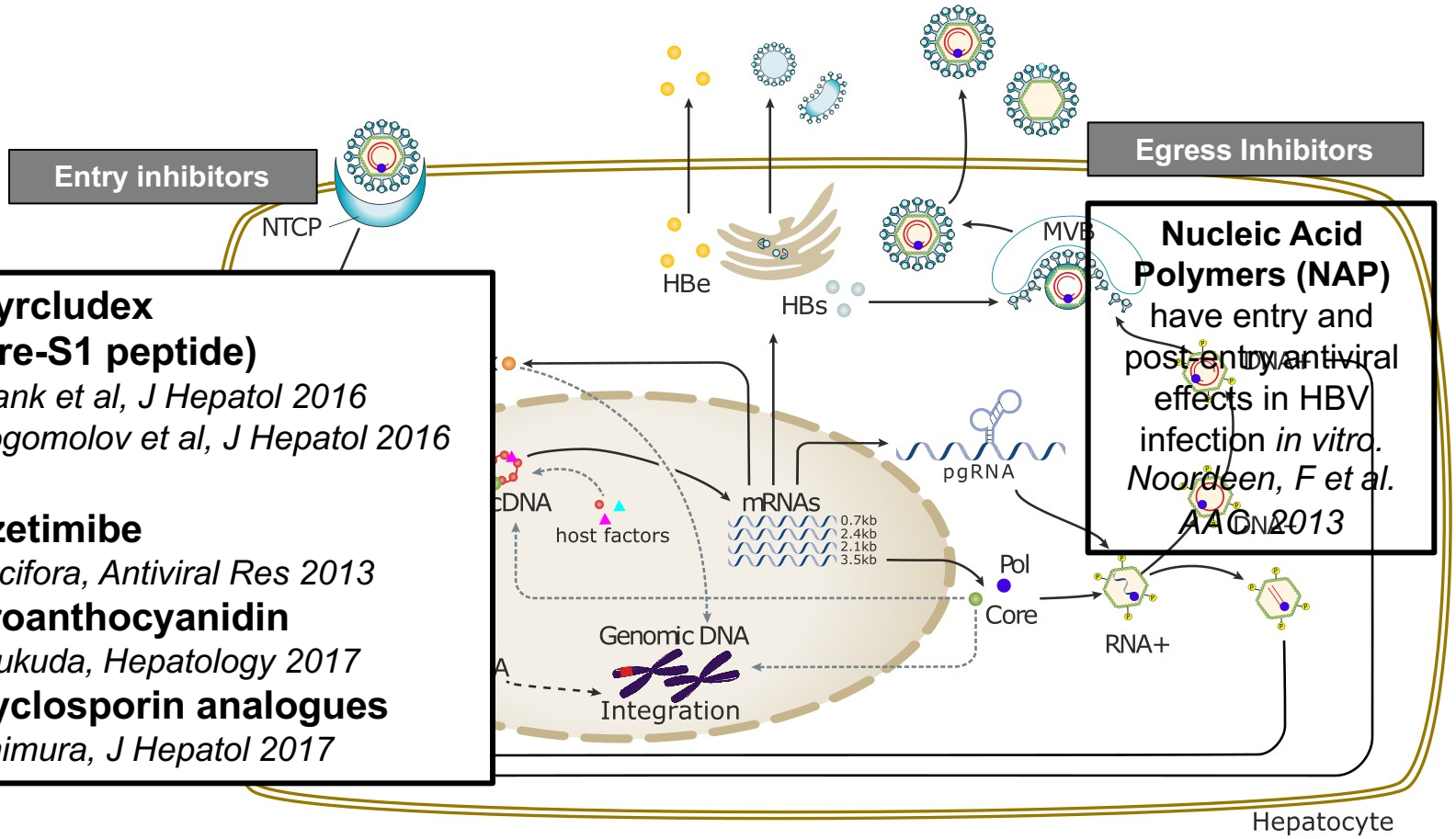
→no real « cure » of the infection

A few copies of cccDNA per liver can (re)initiate a full-blown infection

Viral Targets under investigation



Entry/egress inhibitors



Myrcludex (pre-S1 peptide)
Blank et al, J Hepatol 2016
Bogomolov et al, J Hepatol 2016

Ezetimibe
Lucifora, Antiviral Res 2013

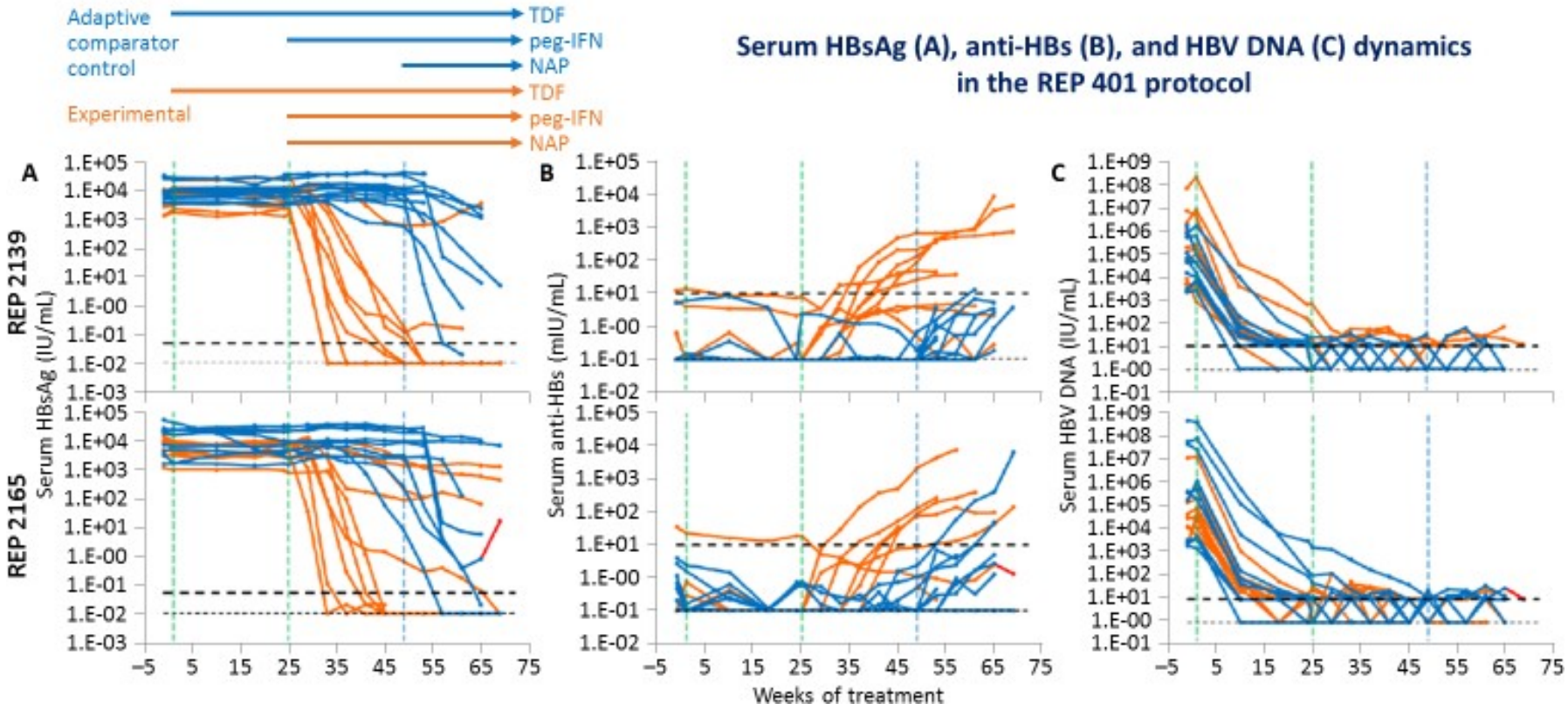
Proanthocyanidin
Tsukuda, Hepatology 2017

Cyclosporin analogues
Shimura, J Hepatol 2017

Effect on HBV/HDV co-infection
Opportunity to combine
Long term effect on cccDNA pool? HBsAg?

Phase II: REP 401 protocol interim results

REP 2139-Mg or REP 2165-Mg used in combination with TDF and peg-IFN alpha-2a in treatment-naive Caucasian patients with chronic HBeAg-negative HBV



Clearance of HBsAg uniquely occur with NAP exposure

In the presence of pegIFN, HBsAg clearance is accompanied by an increase in circulating anti-HBs

Functional control of infection persists 48 weeks after treatment has stopped

Bazinet et al, AASLD 2017, HEPDART 2017

Challenges of entry/egress inhibitors

Myrcludex

SC administration

Inhibition of NTCP and increase of bile salts

Slow kinetics of cccDNA decay and slow hepatocyte turn-over; which combination with other DAAs ?

NAPs

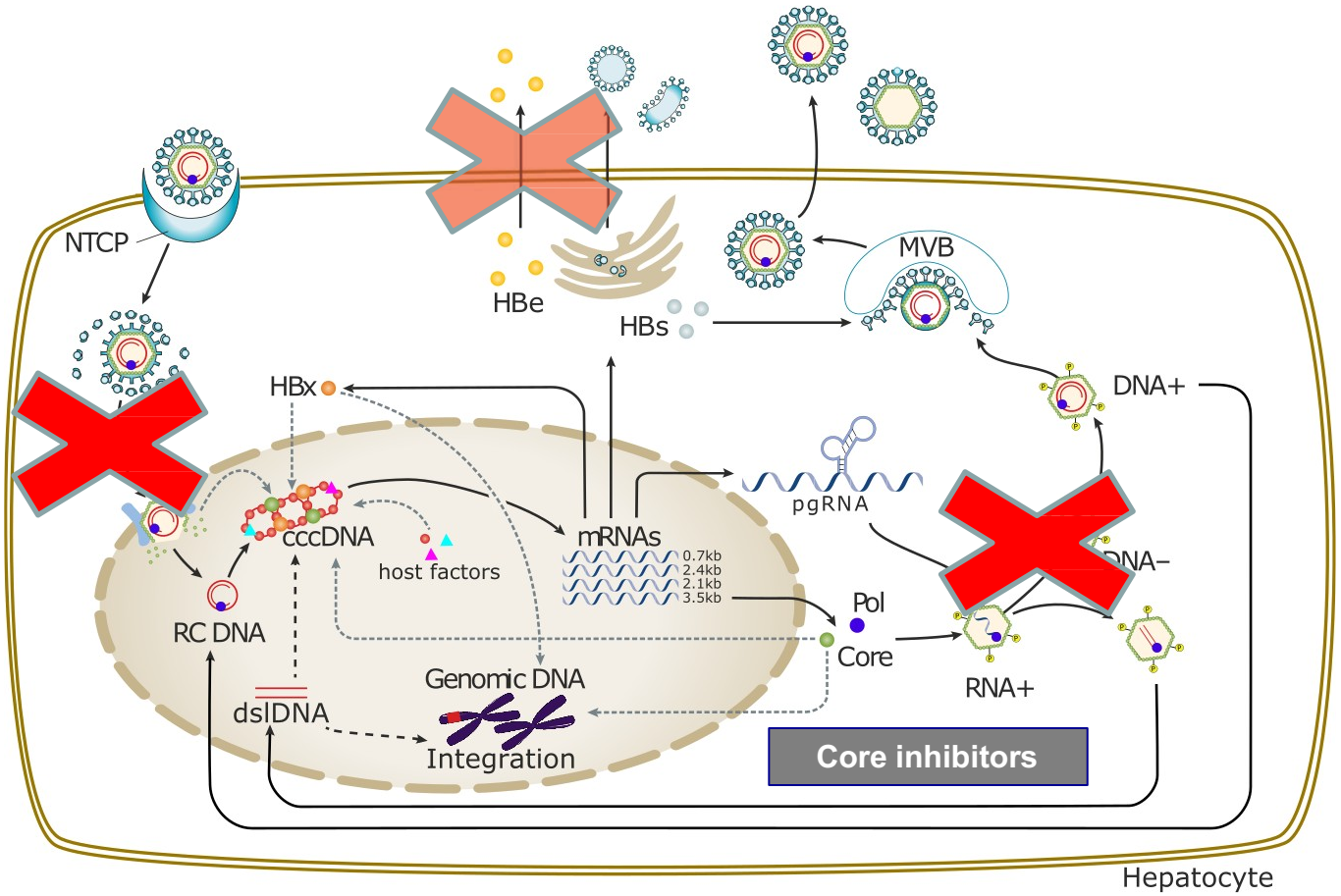
Mode of action still under investigation

IV infusion

ALT exacerbation

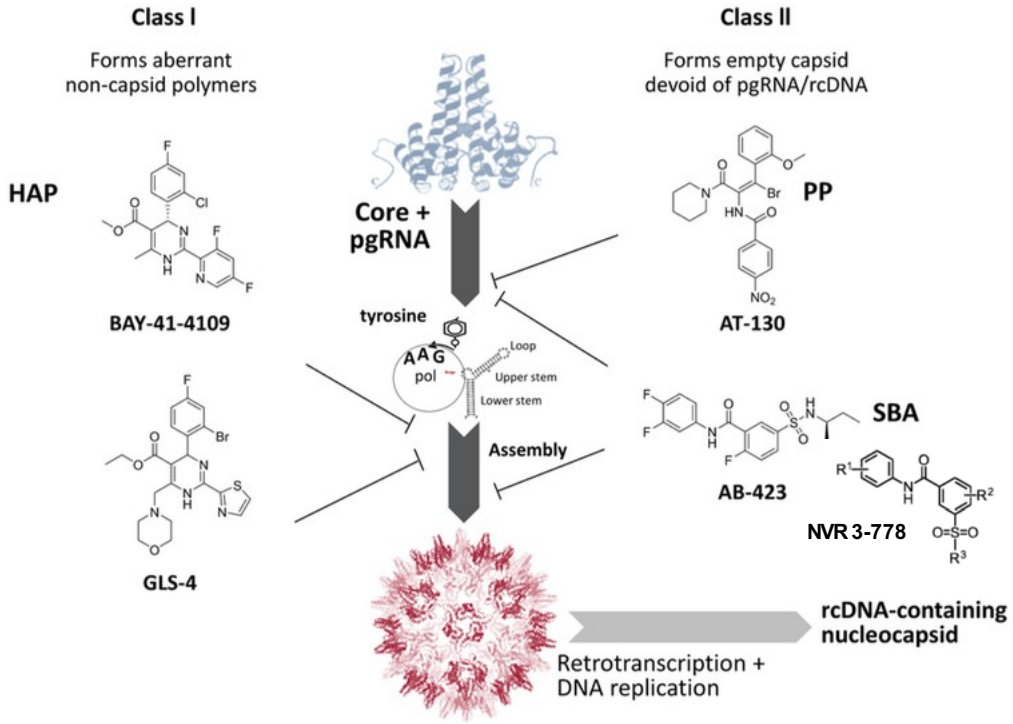
Long-term safety profile

Capsid assembly modulators (CAMs)



Inhibition of nucleocapsid entry into the nucleus
Inhibition of encapsidation
Inhibition of HBeAg secretion?

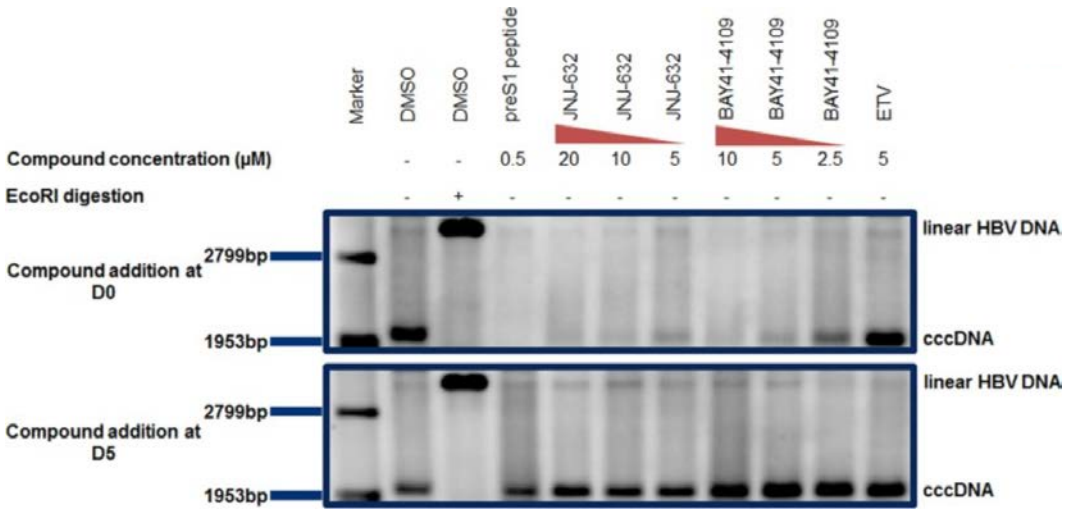
Capsid assembly modulators (CAMs)



CAMs effect on early steps of HBV infection

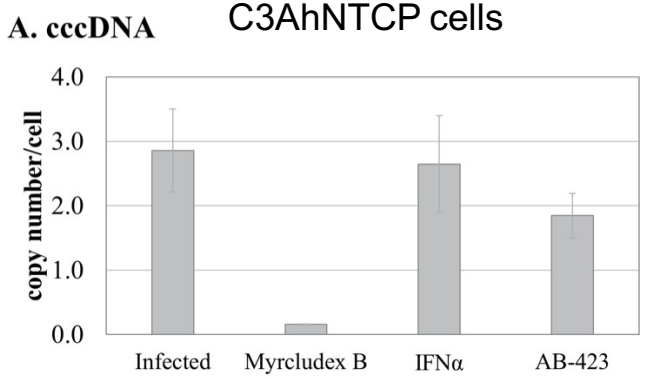
CAM administration before or concomitantly to viral infection

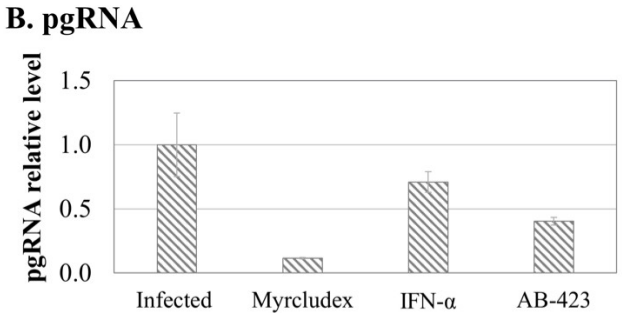
PHH



Berke et al, AAC 2017

C3AhNTCP cells

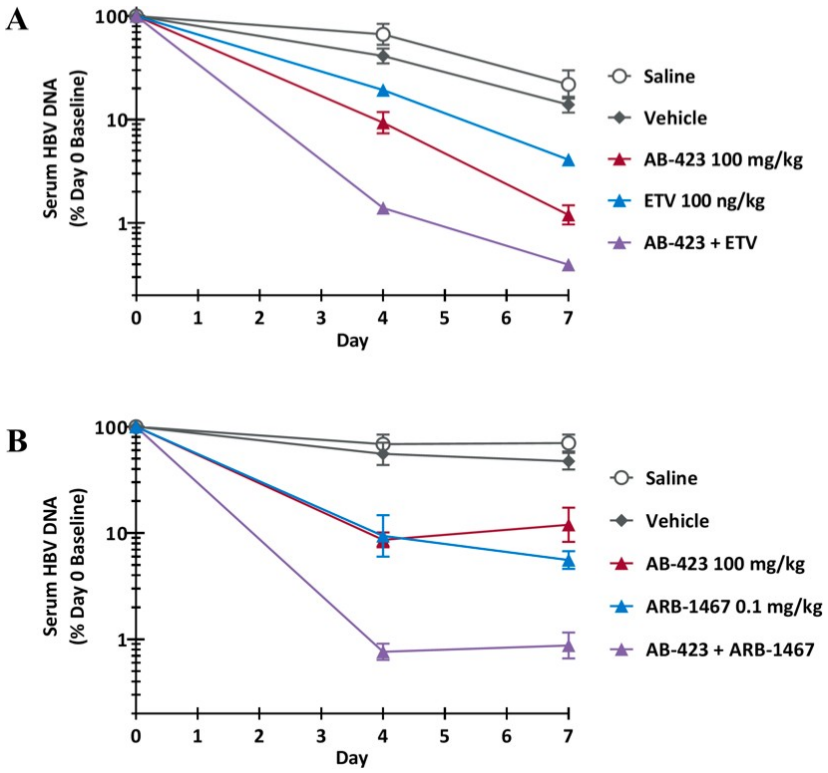


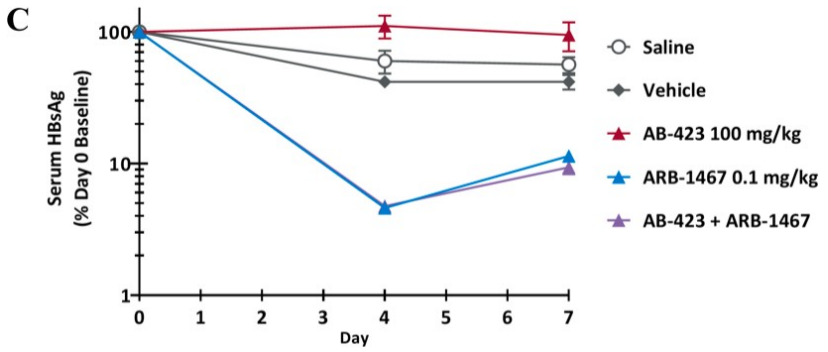


Mani et al, AAC 2018

Preclinical: AB-423

HDI mice: monotherapy or combination with ETV or ARB-1467 (RNAi)

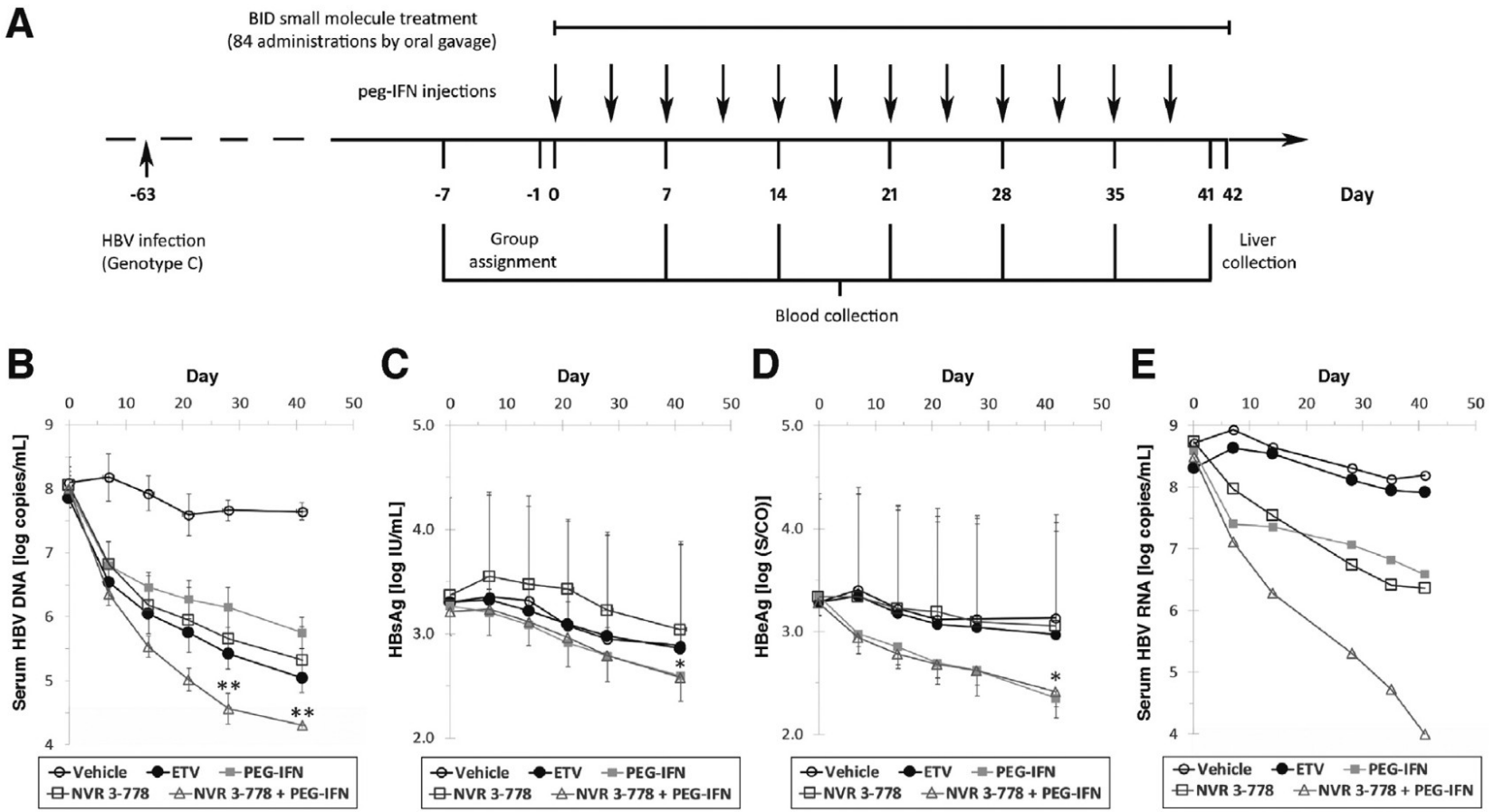




Mani et al, AAC 2018

Preclinical: NVR 3-778

uPA/SCID liver humanized mice



Klumpp, Gastroenterology 2018

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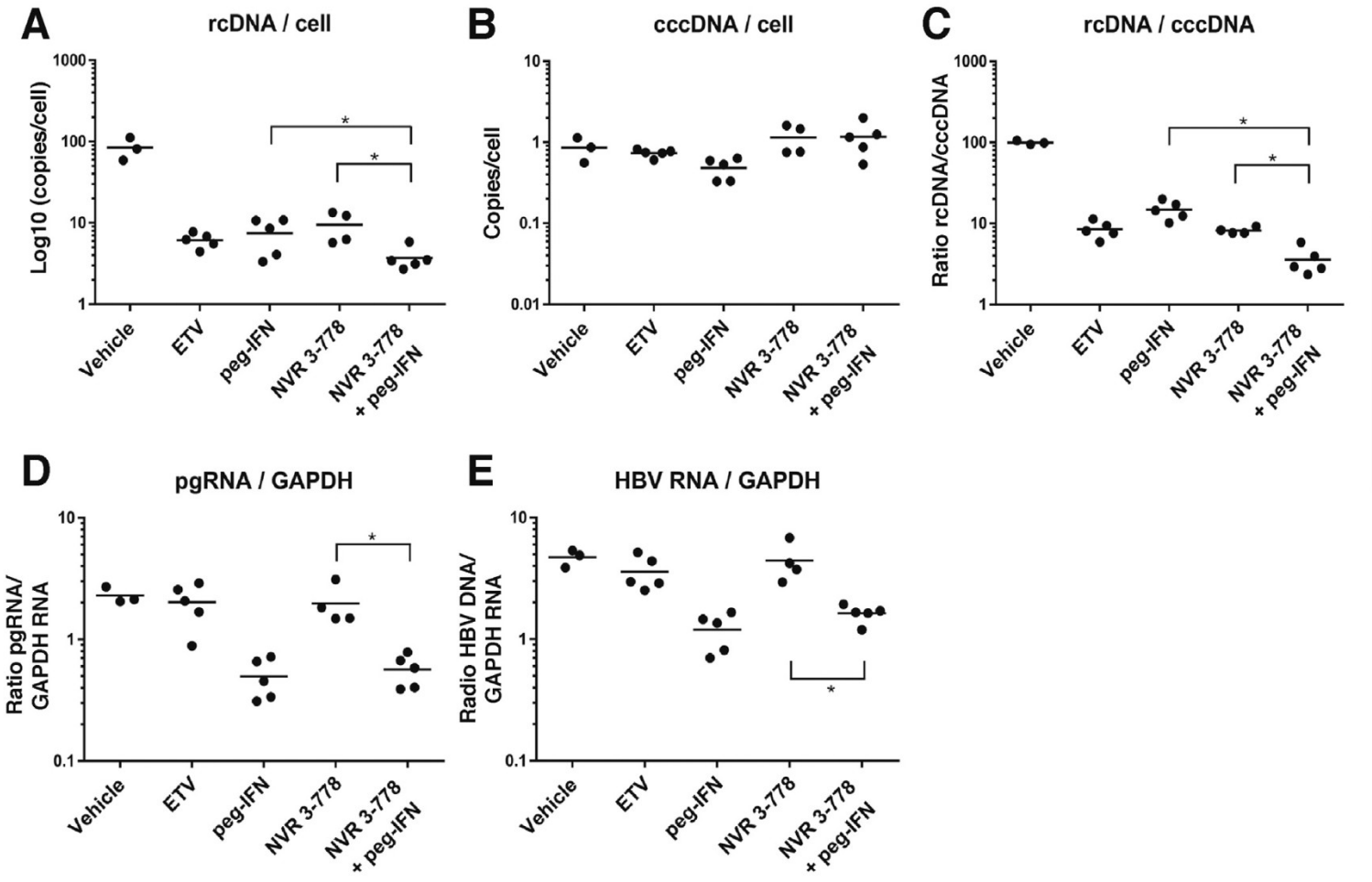
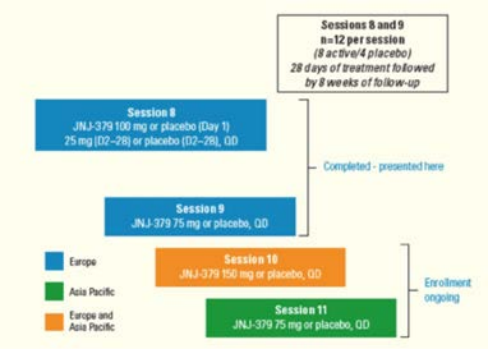
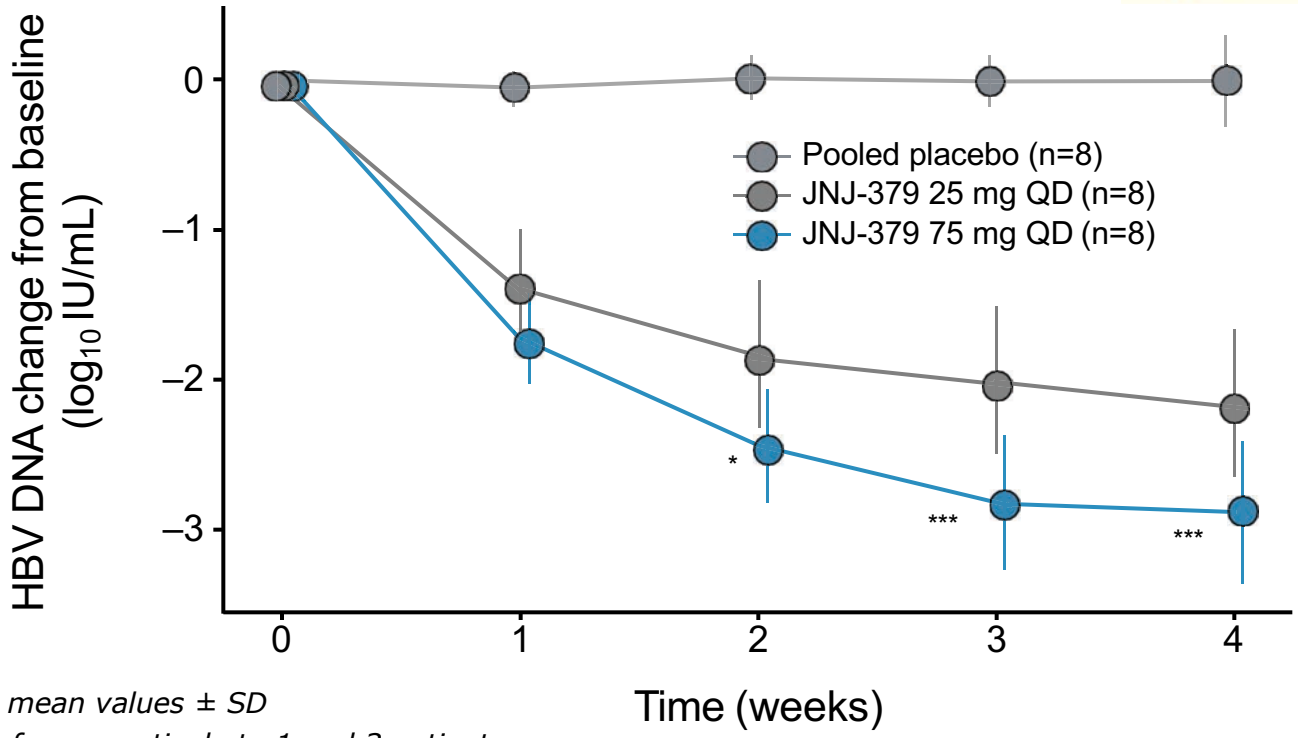


Phase 1b clinical trial of JNJ-379 (Janssen)

treatment naïve, HBeAg(+/-) CHB patients



HBV DNA Change from Baseline



Shown are mean values ± SD

** and *** refer respectively to 1 and 3 patients with HBV DNA <LLOQ of the HBV DNA assay*

Zoulim et al, AASLD 2017

Phase 1b clinical trial of ABI-H0731 (Assembly)

LBP-012, ILC 2018

25 subjects, majority male (≥90%), 76% Asian

Mean baseline HBV DNA levels were 8.0 ± 1.1 log_{10} in HBeAg pos and 3.8 ± 1.5 log_{10}IU/ml in HBeAg neg patients.

HBV declines of 1.3 ± 0.3 and 2.2 ± 1.0 log_{10}IU/ml were seen in HBeAg pos/neg subjects (respectively) at 100 mg/day, the lowest dose tested, with greater declines observed at higher doses.

HBV RNA reductions were generally proportional to reductions of plasma HBV DNA.

Pros & challenges for CAMs

Decrease the pool of cccDNA on the long term

Opportunity to combine with NUCs, pegIFN and other DAAs

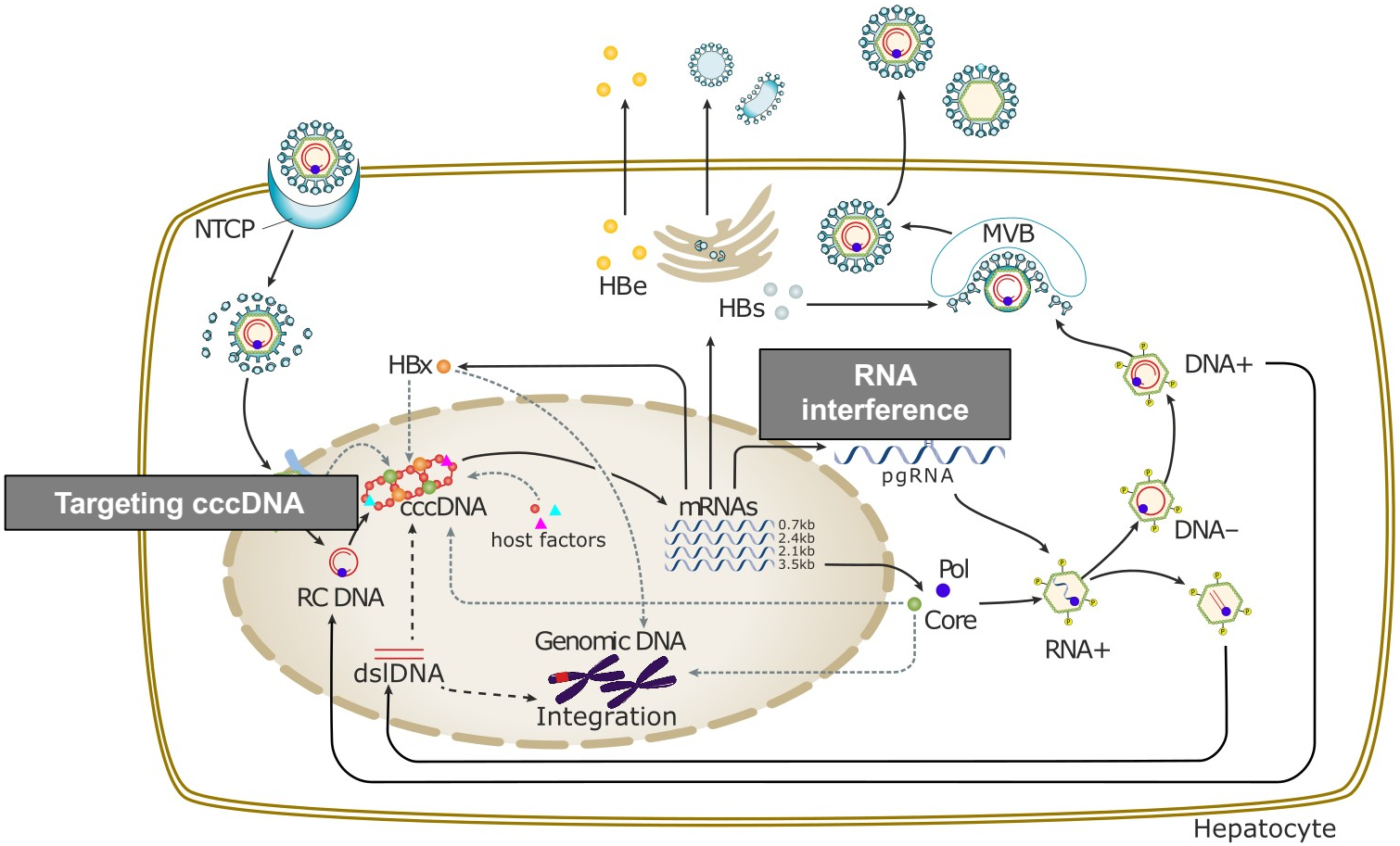
Oral administration

Long-term safety profile

Mainly suppressive

How to combine with other DAAs to be curative ?

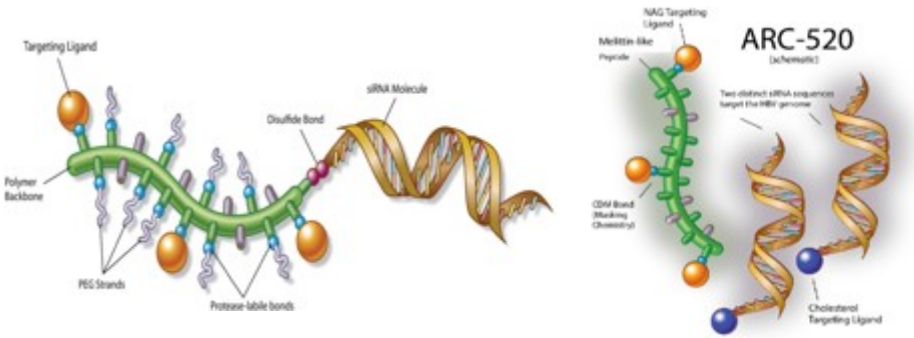
cccDNA targeting or functional silencing



siRNA Candidate Development

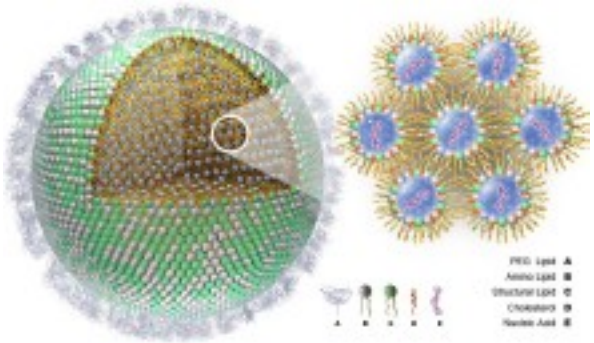
arrowhead pharmaceuticals

- Contains a hepatocyte targeted, reversibly masked membrane active peptide (NAG-MLP)
- Endosomal release of two synthetic siRNAs
- PEG modification to inhibit membranolytic activity



Journal of Controlled Release, Volume 209, 2015, 57–66

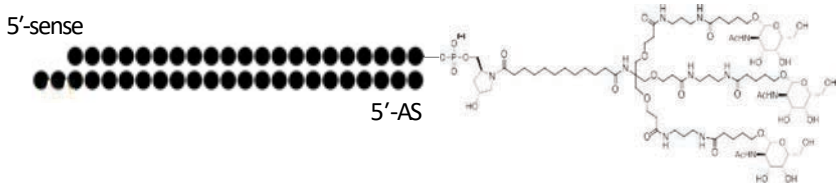
Arbutus BIOPHARMA
Aspiring to Cure Chronic Hepatitis B



Proprietary Lipid Nanoparticles

Alnylam PHARMACEUTICAL

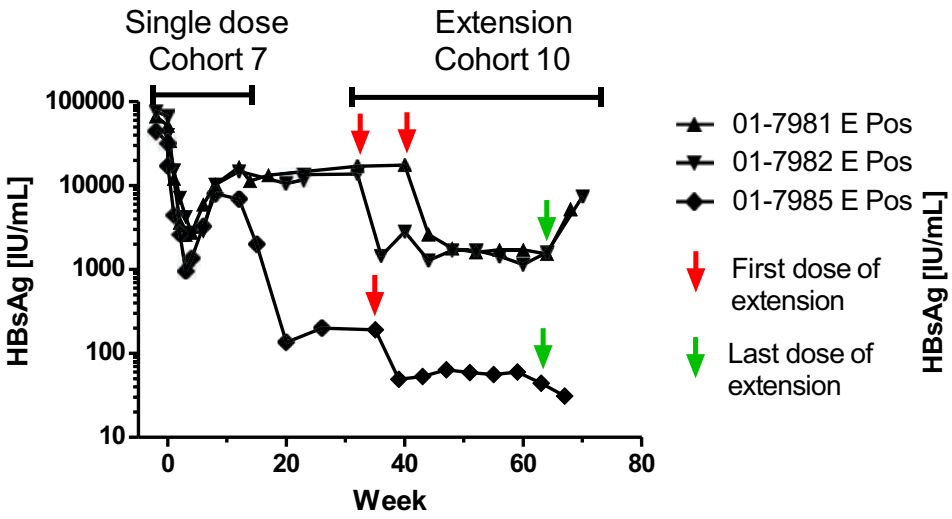
VIR



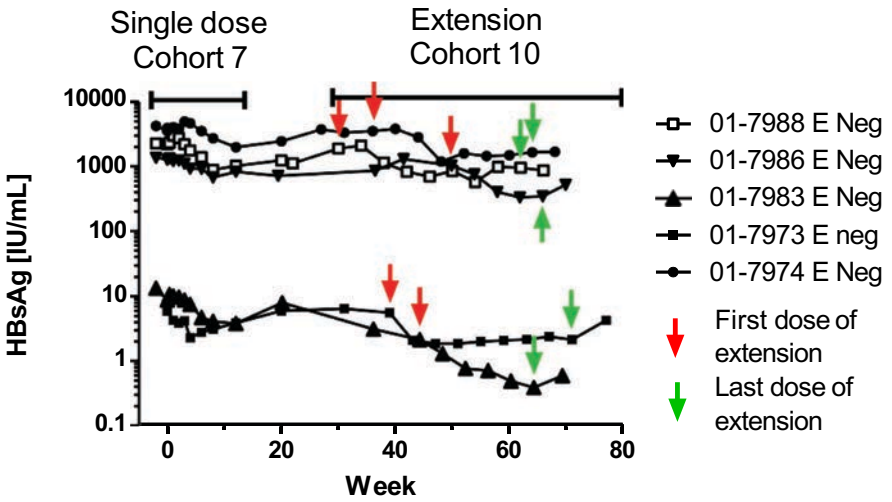
ESC-GalNAc-Conjugate for subcutaneous administration

Decreased serum HBsAg levels in patients receiving ARC-520 every 4 weeks with daily entecavir

HBeAg+ patients



HBeAg- patients

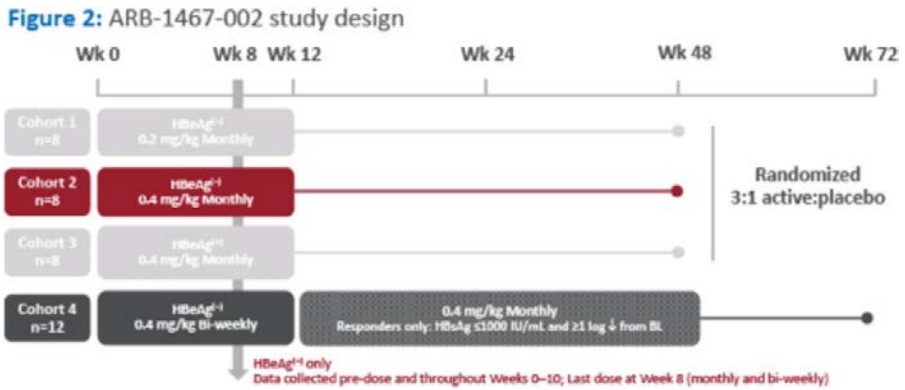


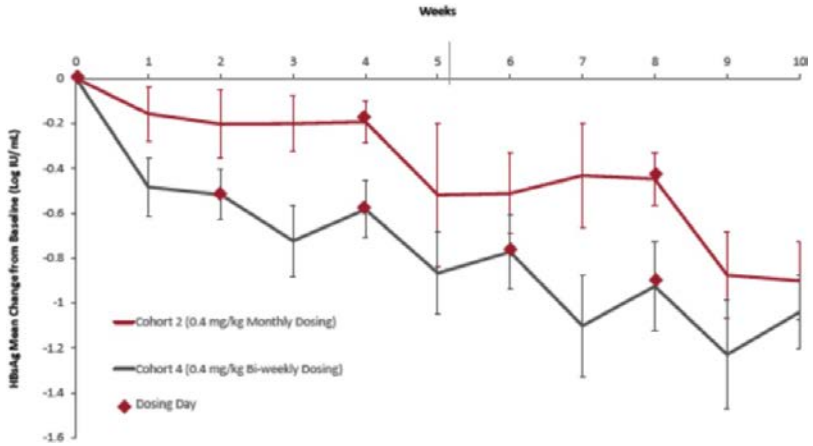
Impact of integrated sequences on siRNA efficacy

Will the decrease of viral antigen load result in restoration of immune responses ?

Yuen MF et al, EASL ILC 2017; Wooddell, Science Trans Med 2017

Phase II: ARB-1467+ETV or TDF





significant reductions in serum HBsAg levels, demonstrating a dose-response with repeat dosing

Nagarwal, AASLD 2017

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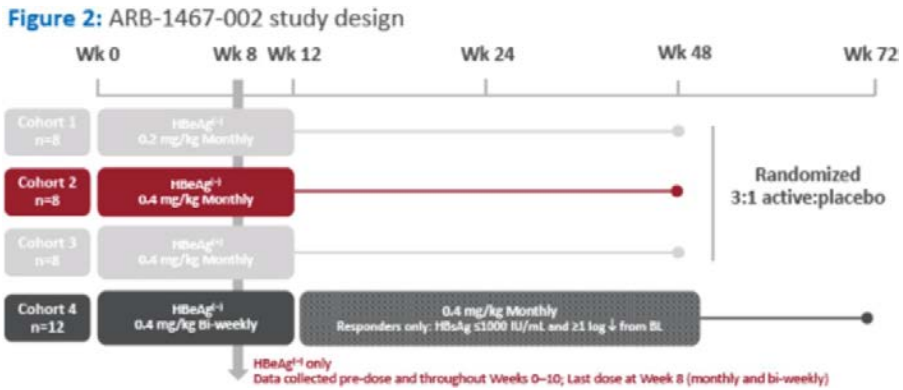

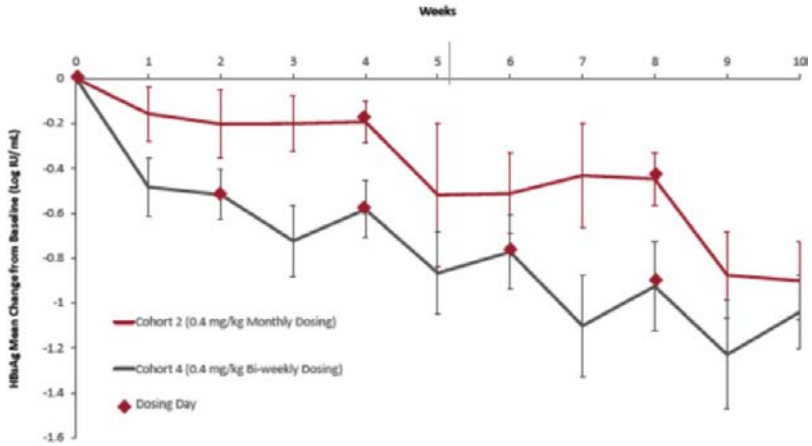

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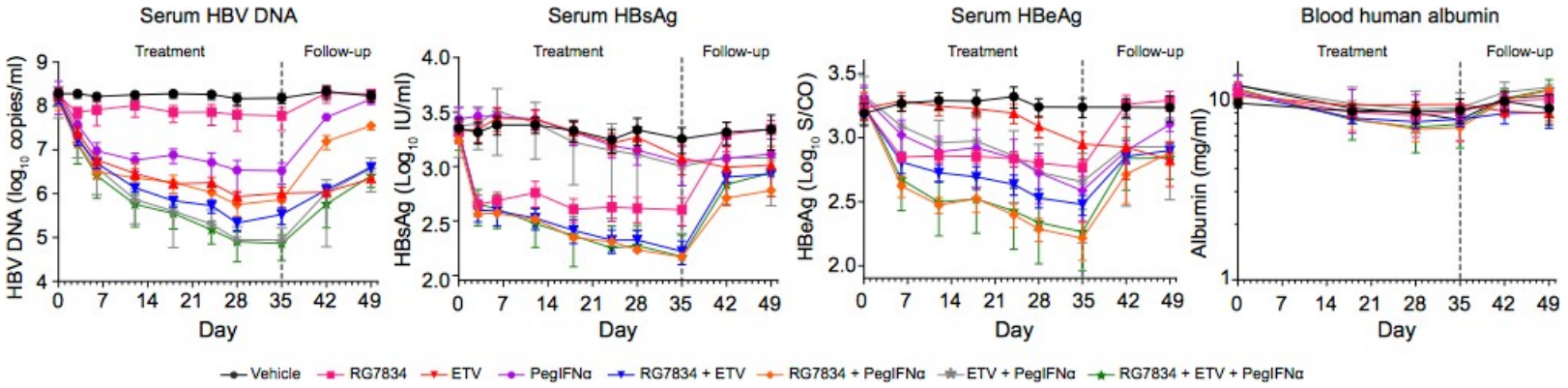
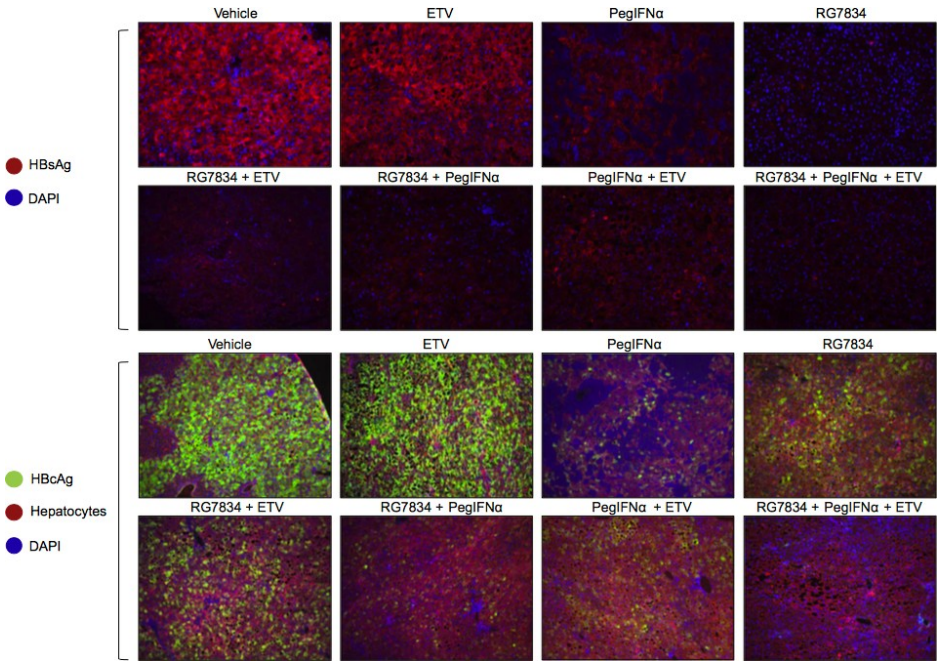
Nagarwal, AASLD 2017

Safety, tolerability, and pharmacokinetics of **BMS-986263/ND- L02-s0201**, a novel targeted **lipid nanoparticle delivering HSP47 siRNA**, in healthy participants: A randomised, placebo-controlled, double-blind, phase 1 study
B. Soule, Bristol-Myers Squibb, LBP-015, ILC 2018

Preclinical: Roche RG7834 (small molecule)





uPA/SCID mice

fast and selective reduction in HBV mRNAs

significantly reduced levels of viral proteins (including HBsAg), as well as viremia

Mueller, J Hepatol 2017

Pros & challenges for siRNAs

Decrease of HBsAg

Possibility of immune restoration ?

Opportunity to combine with NUCs, pegIFN and other DAAs

Combination with immunotherapeutic approaches ?

IV infusion

Long-term safety profile

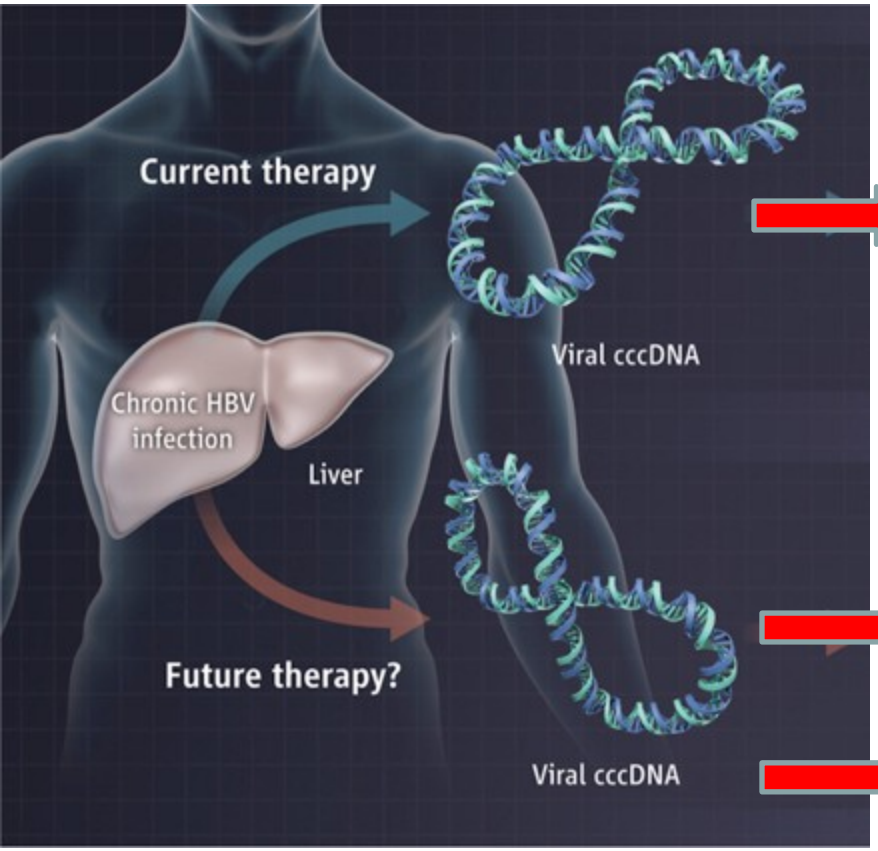
Mainly suppressive

Impact of integrated sequences

How to combine with other DAAs to be curative ?

•As of November 2016, the NAG-MLP containing drug platform was discontinued due to animal toxicology findings, not due to safety signals in humans. New formulations are being evaluated (TRIM™ Platform)

Direct cccDNA targeting



IFNalpha /Lymphotoxin beta induced APOBEC3A/B dependent degradation; other cytokines

Lucifora et al, Science 2014; Xia et al, Gastroenterology 2015

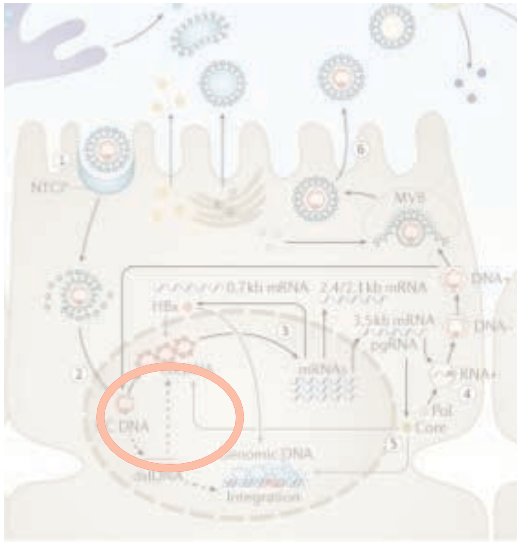
CRISPR/cas9 cleavage

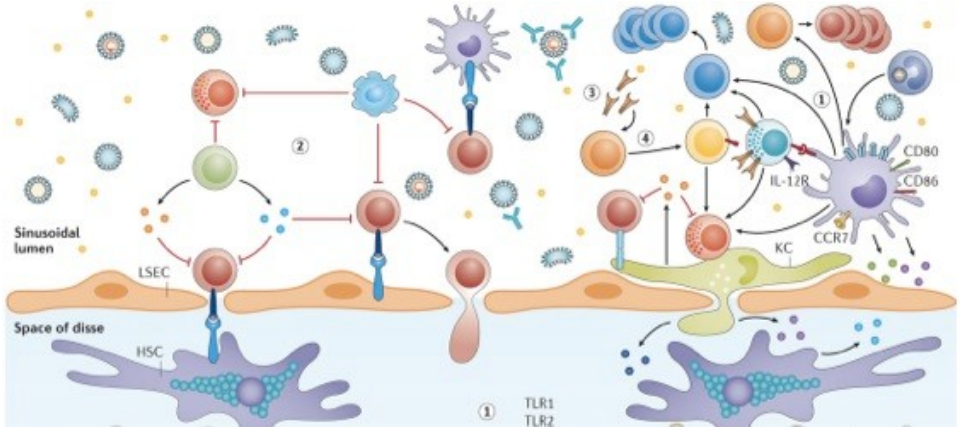
Seeger et al, Mol Ther Nucleic Acids. 2014 & 2016

cccDNA silencing through virus specific mechanims

Belloni et al, JCI 2012; Liu et al, Plos Path 2013; Tropberger et al, PNAS 2015

Barriers to eradicating HBV





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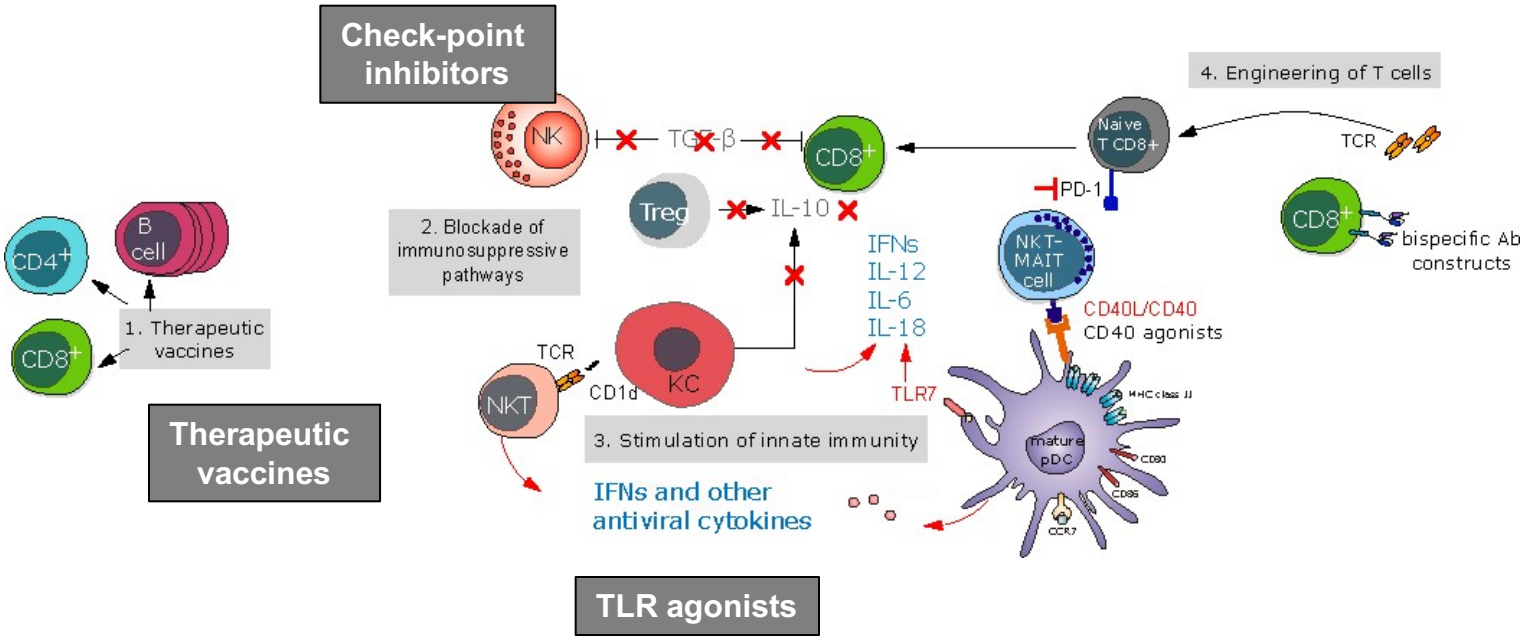
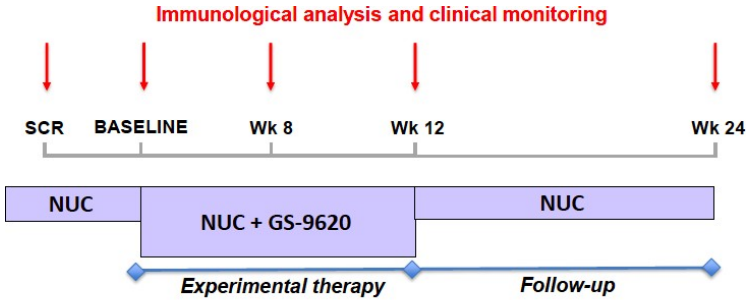
Immune Targets under investigation



TLR-7 agonist GS-9620 improves HBV-specific T and NK cell responses in NAs-treated CHB patients

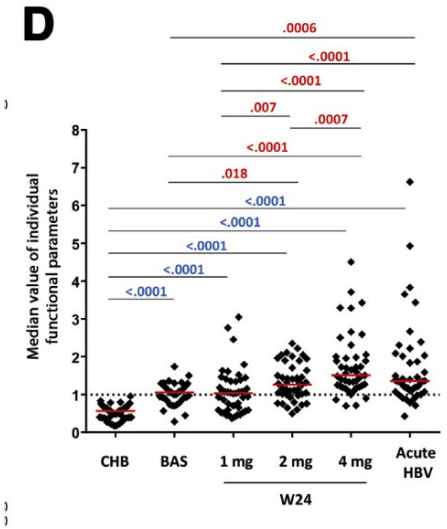


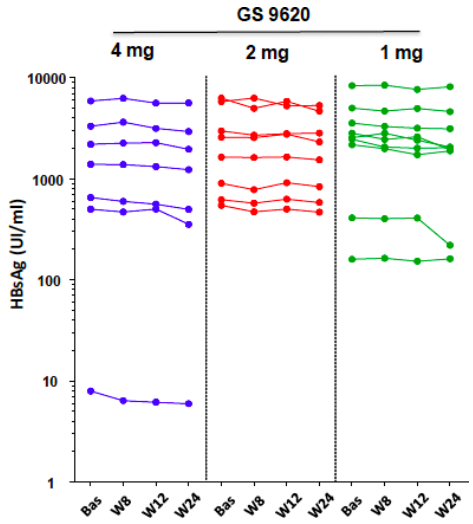
NUC + GS-9620 (n=26)

- 1 mg GS-9620 PO weekly (n=9)
- 2 mg GS-9620 PO weekly (n=8)
- 4 mg GS-9620 PO weekly (n=9)

Chronic naive patients (eligible for therapy, n=13) — Viremic, HBeAg neg, Genotype D

T-cell Functional parameters





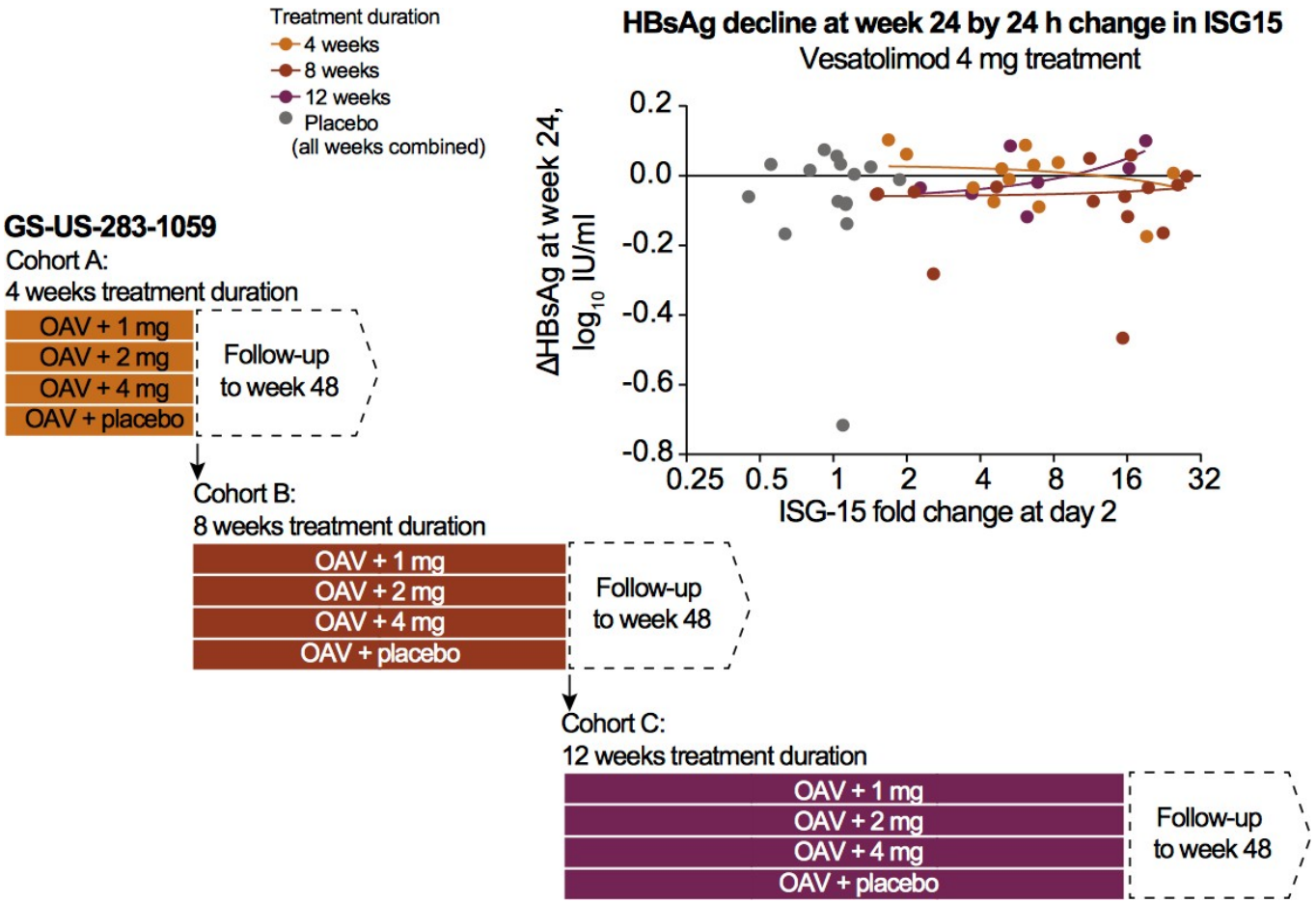
Recovery of CD8 and CD4

Recovery of NK cells (no inhibition of T cells)

No effect on HBsAg levels

Boni, Gastroenterology 2018

Phase II: Oral TLR-7 Agonist GS-9620



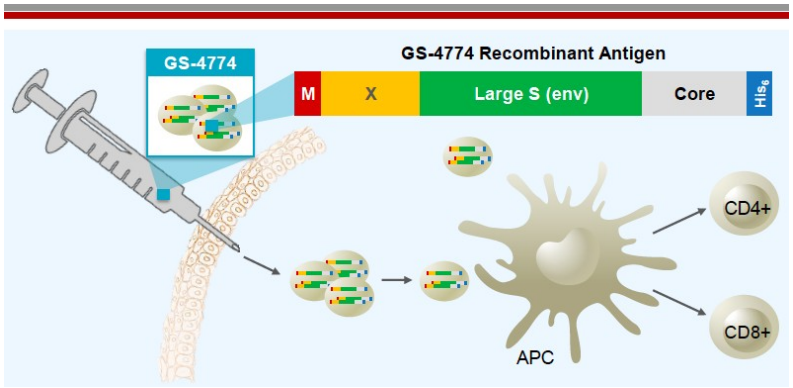
ISG15 induction was dose-dependent and consistent after repeat dosing

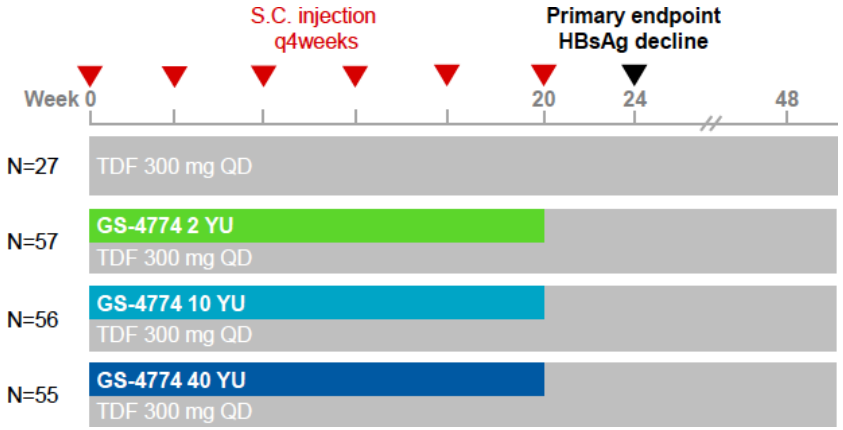
no patient demonstrated significant serum interferon alpha (IFNa) expression at any timepoint evaluated

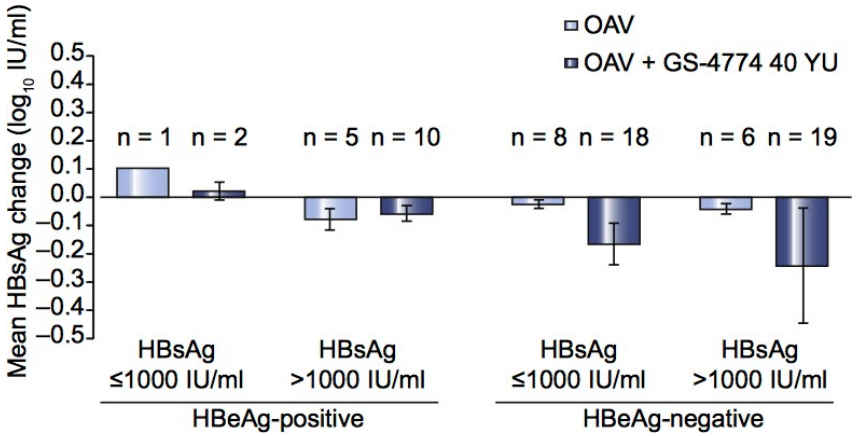
No significant declines in HBsAg were observed at the primary or secondary endpoints

Janssen et al, JHepatol 2018

Phase II: GS-4774 therapeutic vaccine + NAs





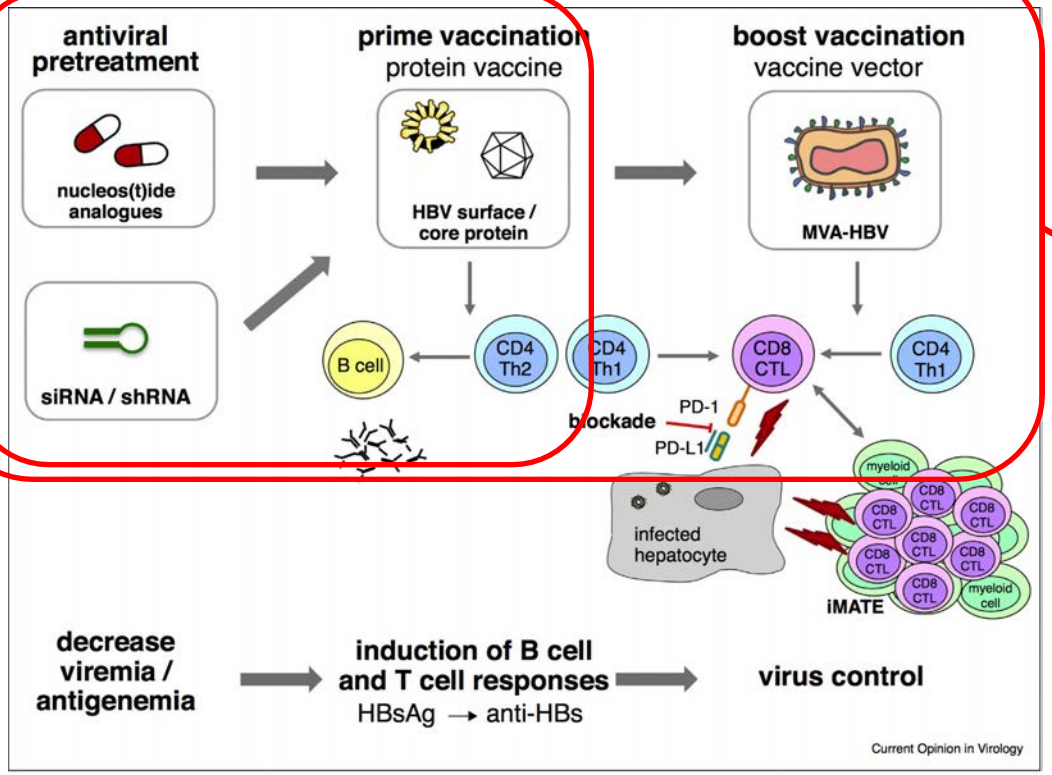


GS-4774 was well tolerated, but did not provide significant reductions in serum HBsAg in virally suppressed patients with chronic hepatitis B

Lok, JHepatol 2016

Preclinical: TherVac B strategy

Transgenic or AAV-HBV infected mice



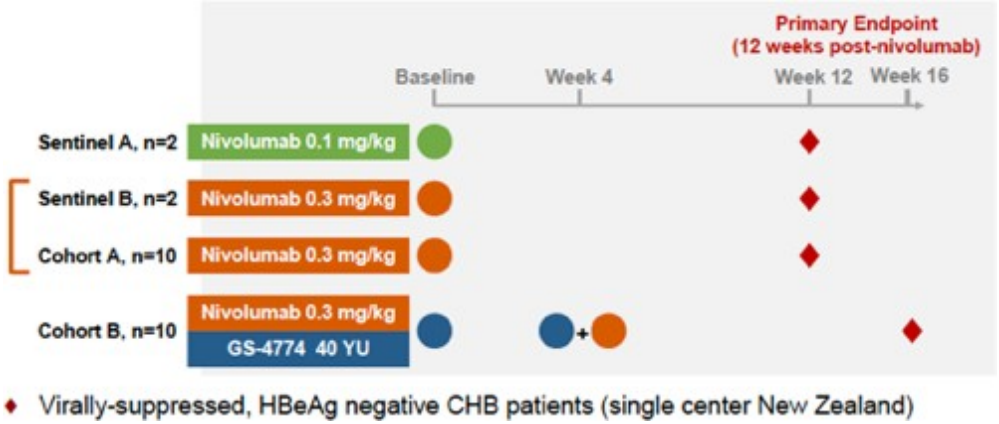
Boost B-cell immunity and induce anti-HBs seroconversion in all animals

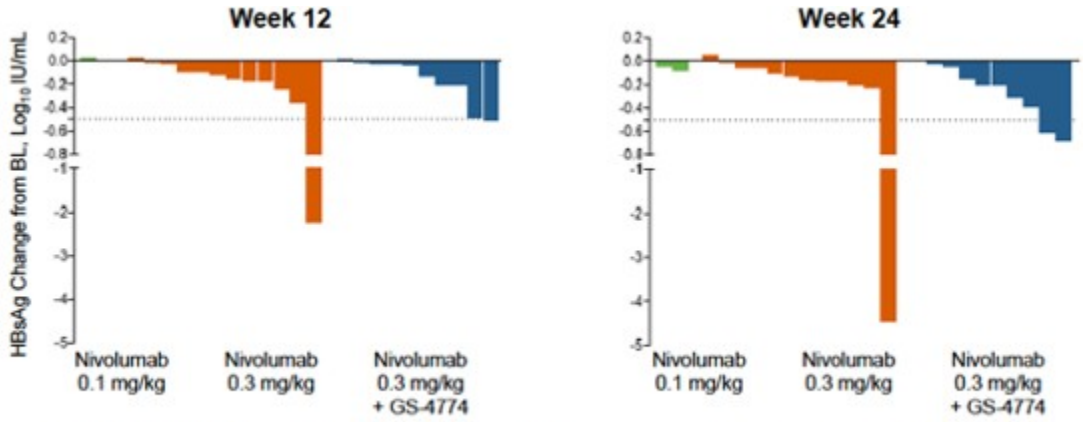
HBsAg and serum HBV DNA decline to <LLOD
HBV-specific T-cell response

Michler, ILC 2017, ILC 2018 PS-025

Phase I anti-PD-1 with or without GS-4774 in CHB patients

PD-1 blockade enhances HBV-specific T cell response
(Fisicaro, Gastroenterology 2010; Park, Gastroenterology 2016)





Gane et al, EASL ILC 2017 PS-044

Pros & challenges for immune-modulators

Induction of ISGs

Restoration of adaptive immunity

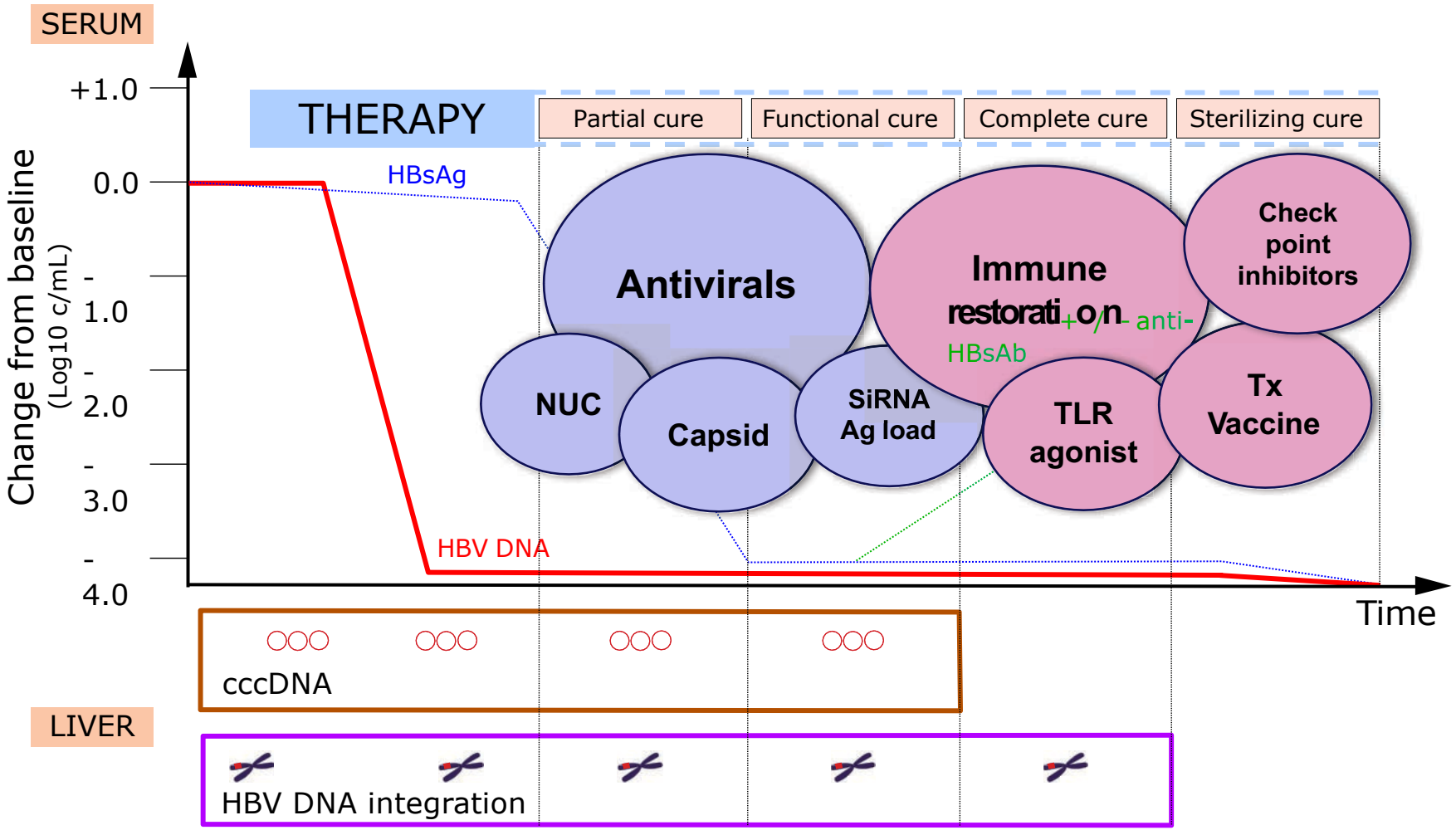
Combination with other DAAs or other immunotherapeutics

Not effective in humans (vs animal models)

Side effects: potential for cytokine storm/autoimmunity

Hepatitis flares

Conclusions



Combination therapies required
Direct cccDNA targeting remains a priority