HBV cure: where do we stand in 2019 ?

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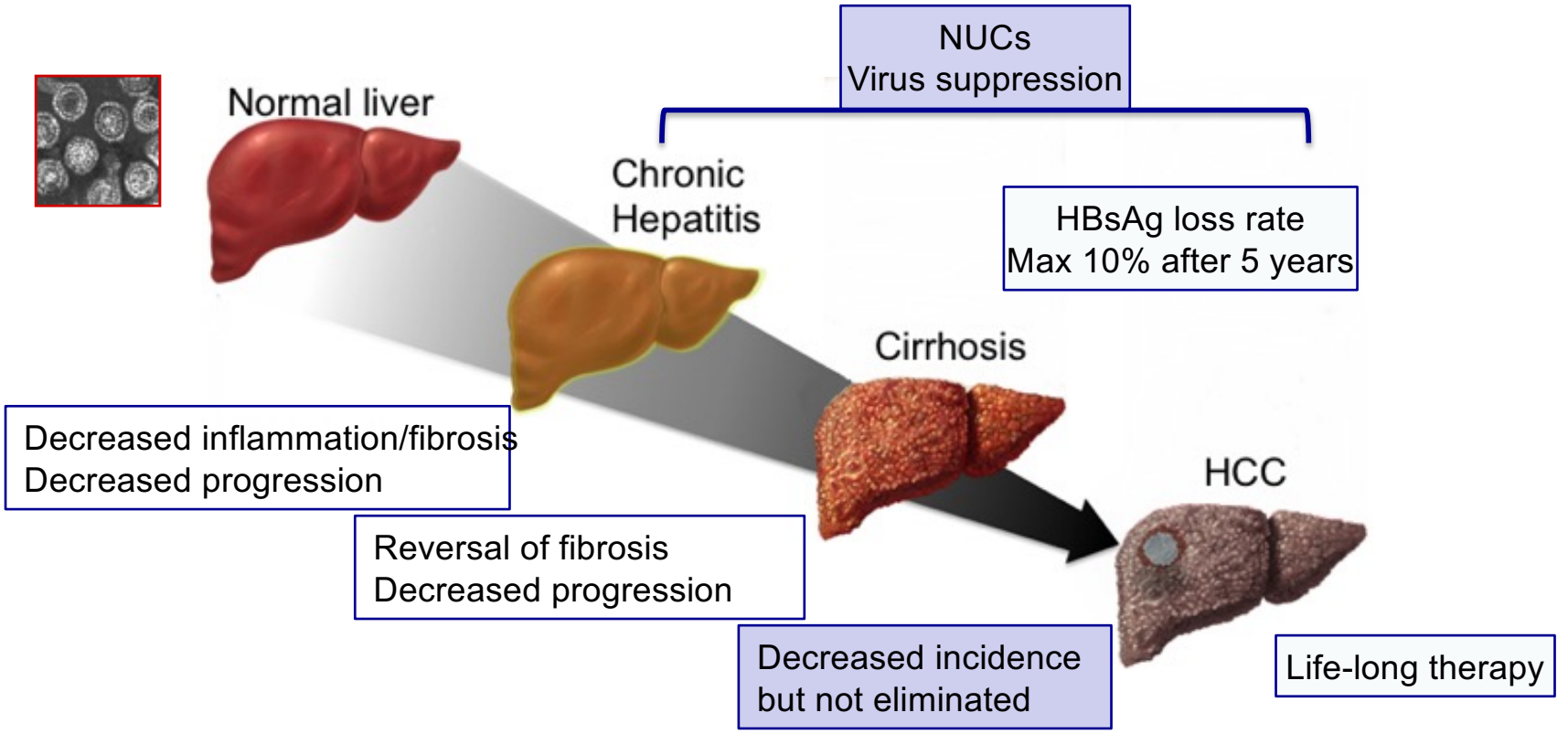
Instituts thématiques Inserm

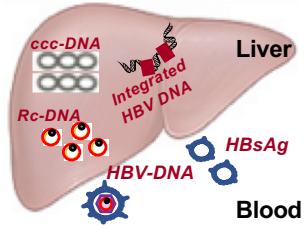
Institut national de la santé et de la recherche médicale

Current treatments: virus suppression and sustained disease control
(Why not treating more patients ?)

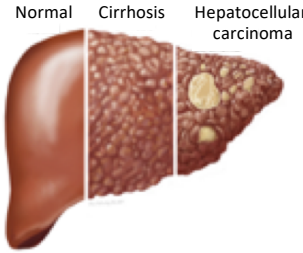


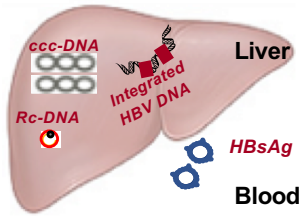
Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015

From viral suppression to cure

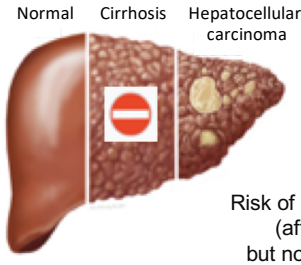


UNTREATED

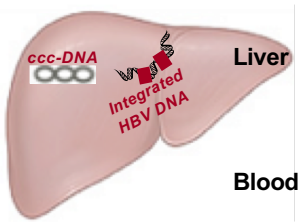


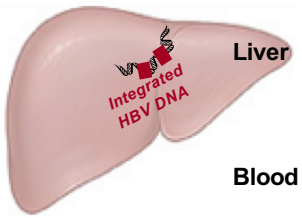


NUCs



Risk of HCC reduced
(after 5 yrs)
but not eliminated

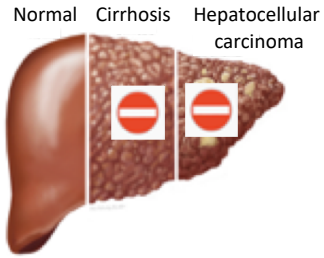




NMEs *"Cure"*

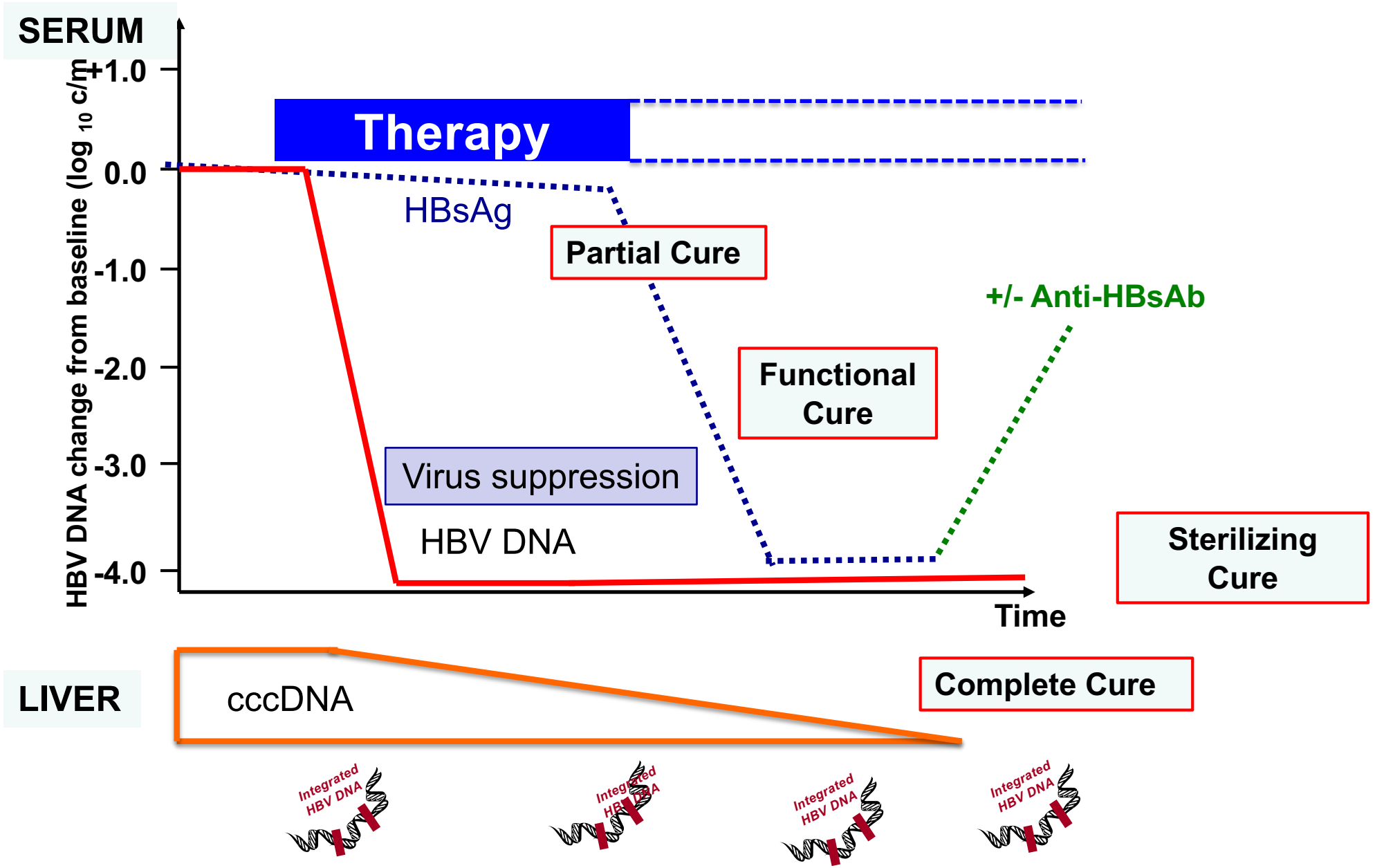
Direct Antiviral Agents

Immunomodulatory strategies



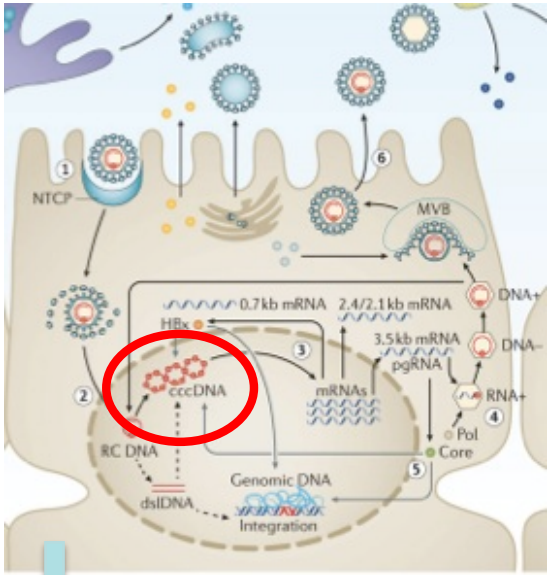
Levrero & Zoulim, Current Opinion Virology 2016

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



Lok et al, Hepatology / J Hepatol joint publication, 2017; Testoni et al, Sem Liver Dis, 2017.

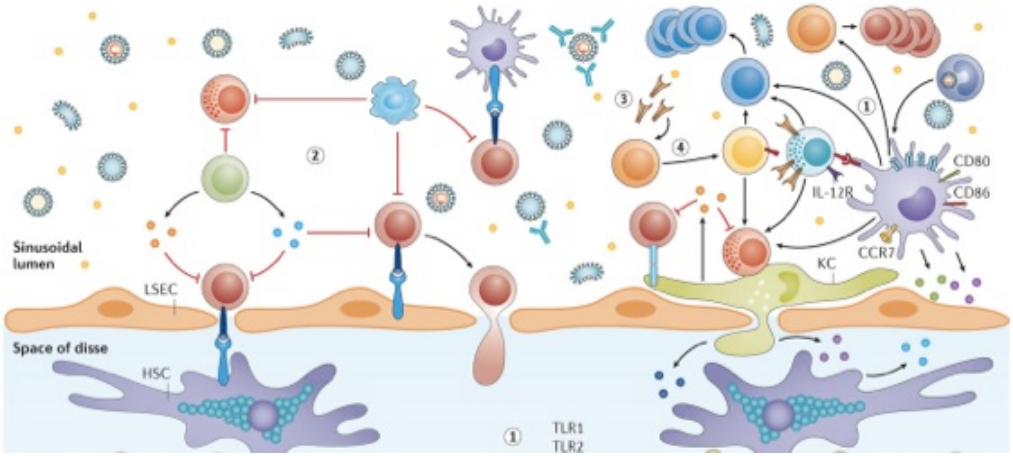
Barriers to eradicating HBV



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

Integrated forms

HBV persistence



Defective CD8+ responses

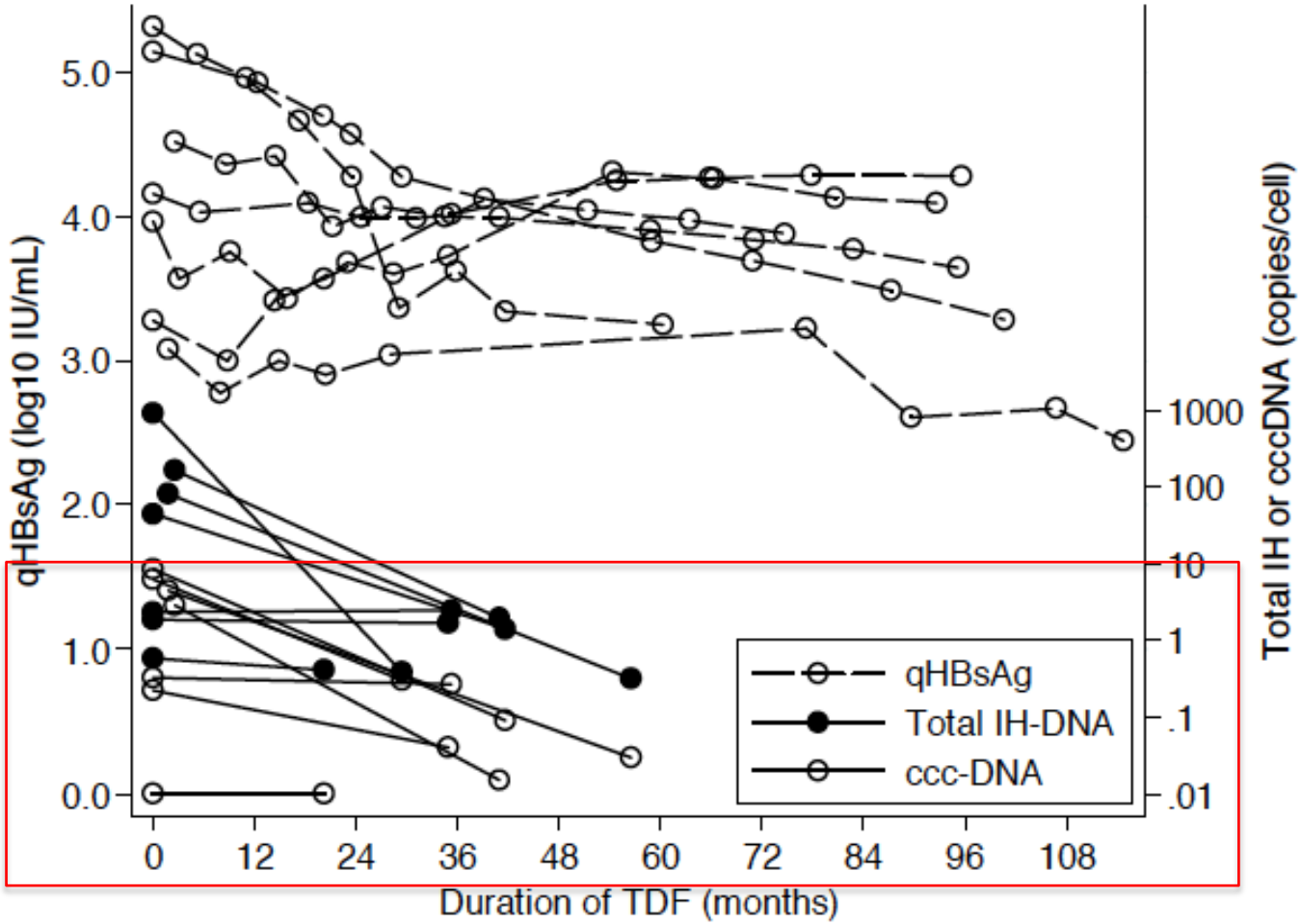
Defective B cell responses

Inefficient innate response

Defective immune responses

Revill, Testoni, Locarnini, S. & Zoulim, F. et al. (2016) Global strategies are required to cure and eliminate HBV infectionNat. Rev. Gastroenterol. Hepatol.

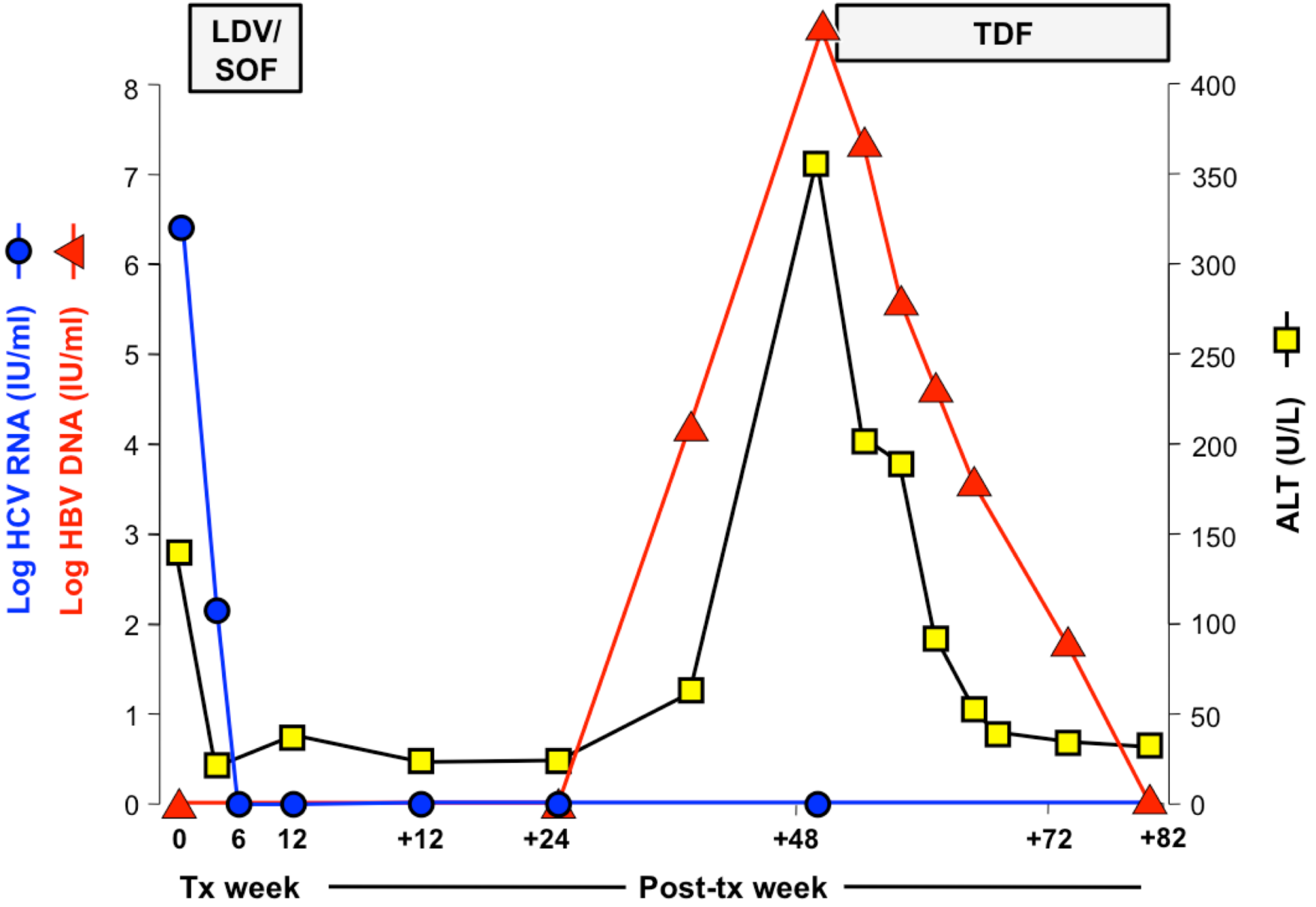
Persistence of intrahepatic viral DNA synthesis during Tenofovir therapy (HIV-HBV cohort)



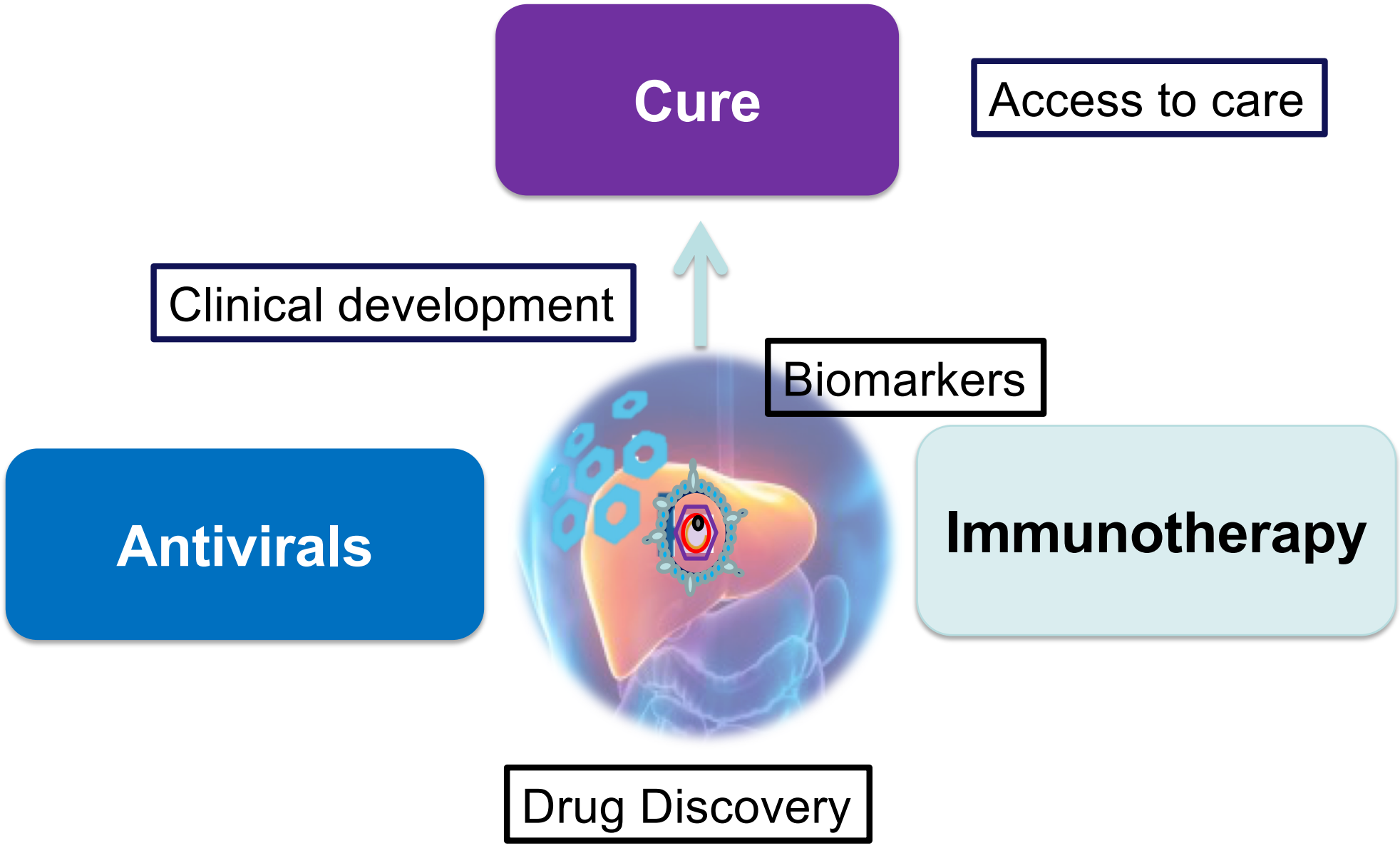
New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »

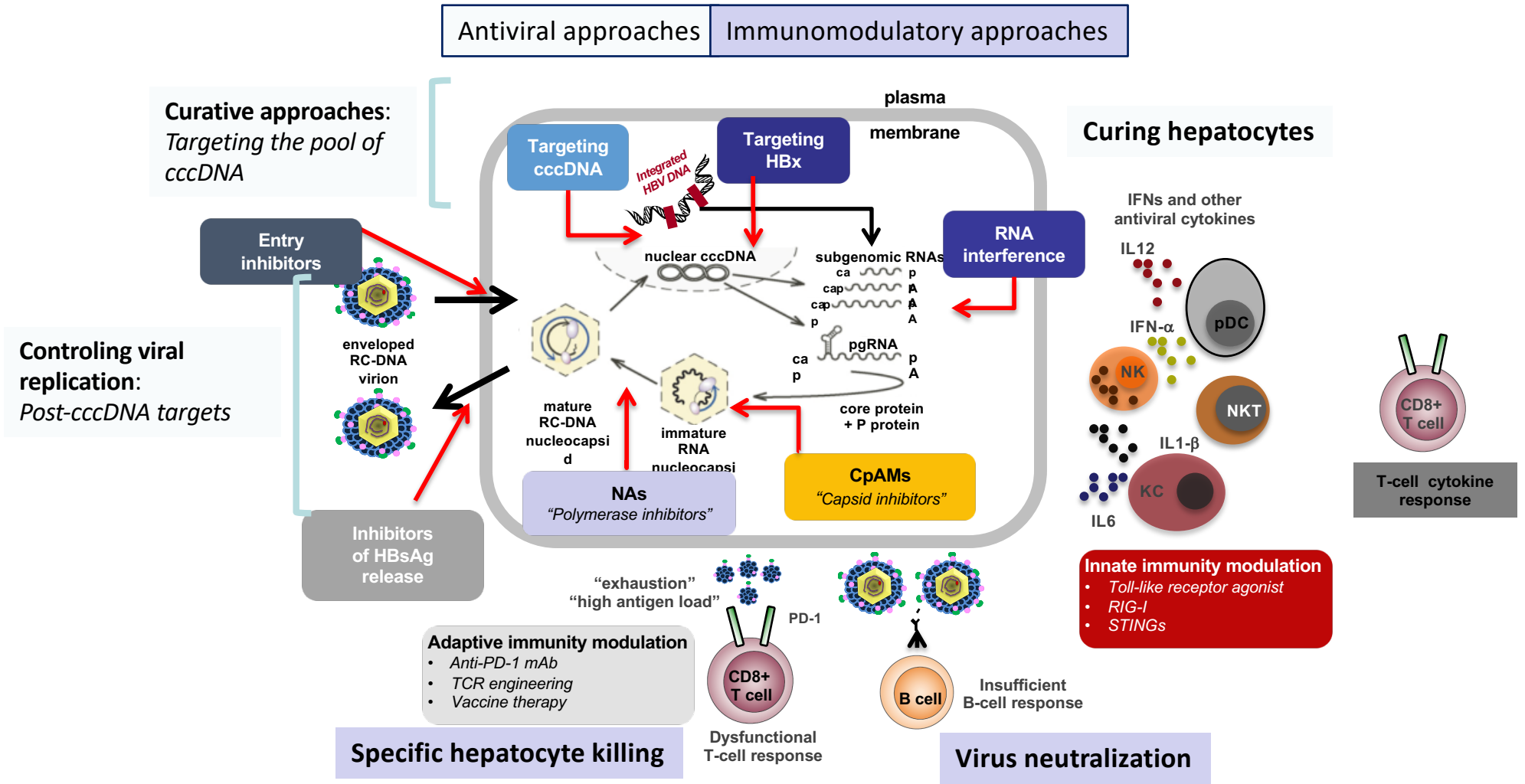
Boyd et al, J Hepatol 2016

Late hepatitis B reactivation following DAA-based treatment of recurrent hepatitis C in an anti-HBc-positive liver transplant recipient



Vionnet et al, Hepatology 2017

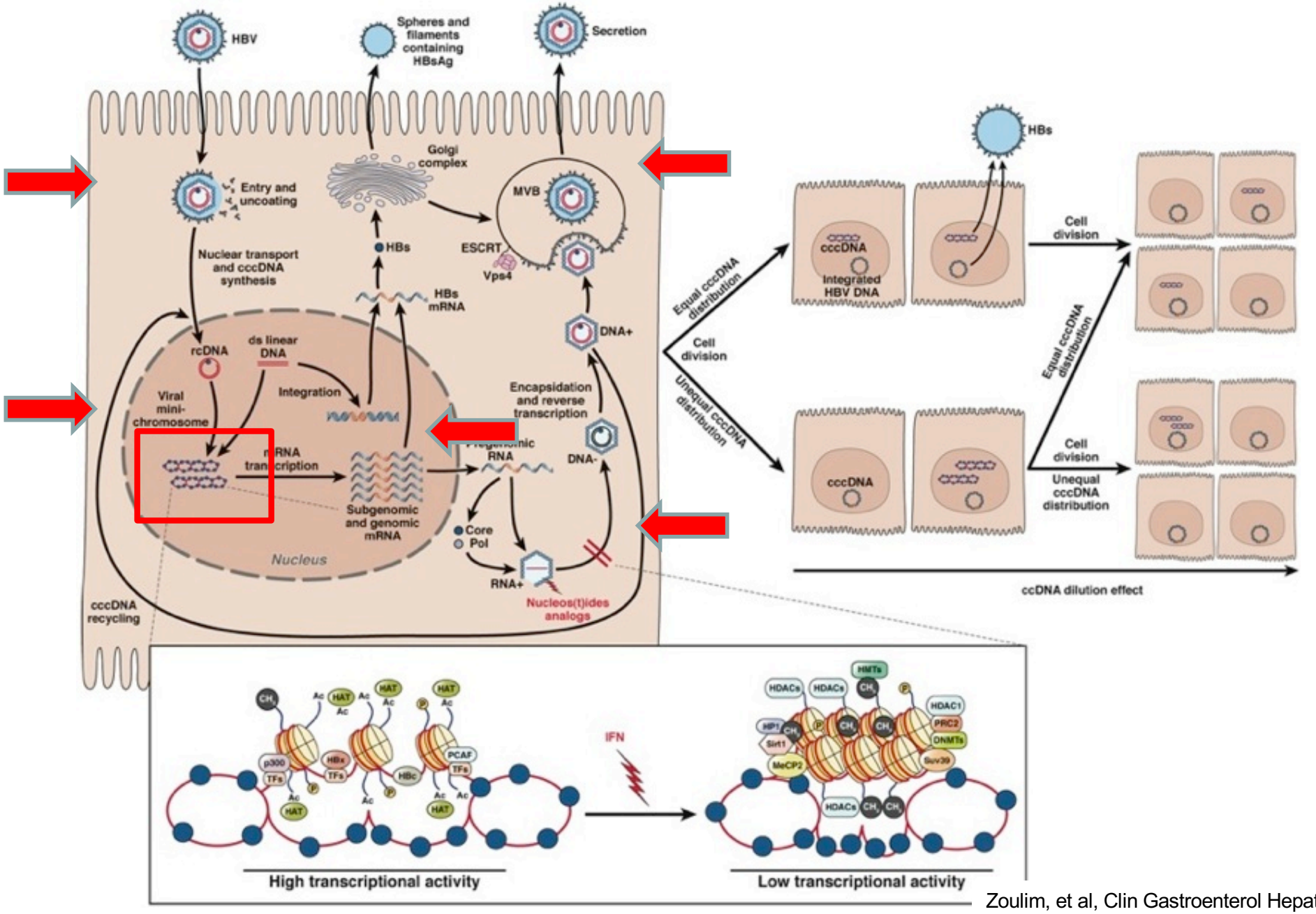

Cure
Access to care
Clinical development
Biomarkers
Antivirals
Immunotherapy
Drug Discovery



Adapted from: Levrero M, et al. Curr Opin Virol 2016;18:135–43

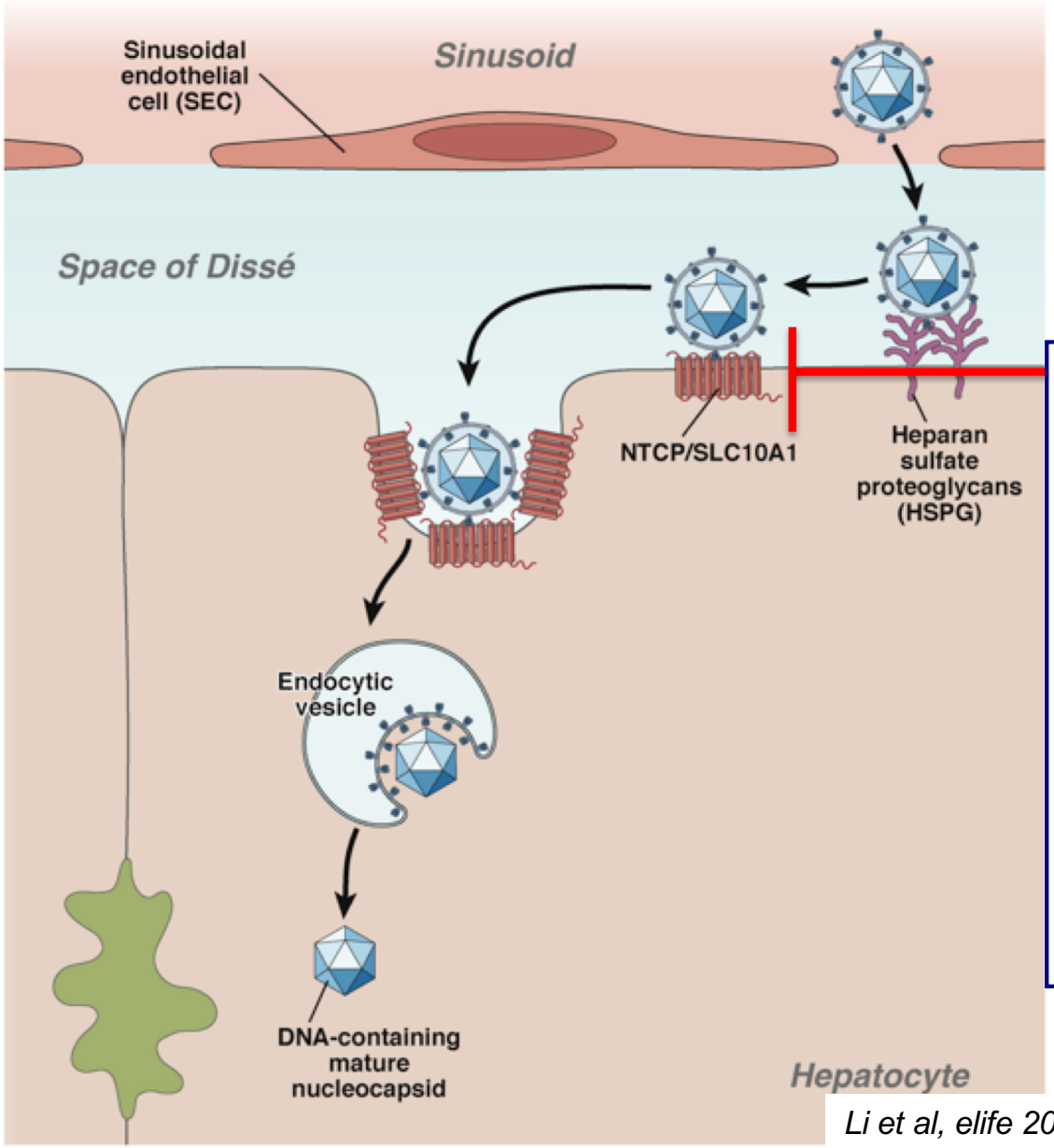
CpAM: core protein allosteric modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK: natural killer; NKT: natural killer T cell; pDC: plasmocytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor

cccDNA the ultimate target…
Up- and/or Down- stream of cccDNA ? Potential to be curative ?



Zoulim, et al, Clin Gastroenterol Hepatol 2013

Model for HBV entry in hepatocytes and development of entry inhibitors



Entry 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

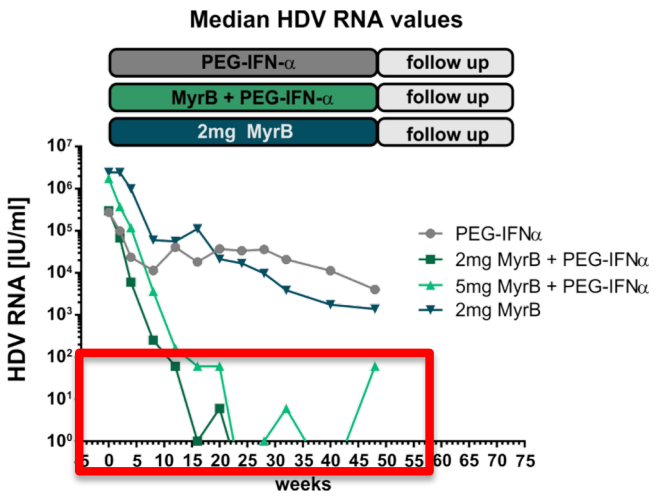
HBV conference, Taormina 2018

Li et al, elife 2012; Urban et al, Gastroenterology 2014

Myrcludex B for chronic HDV infection

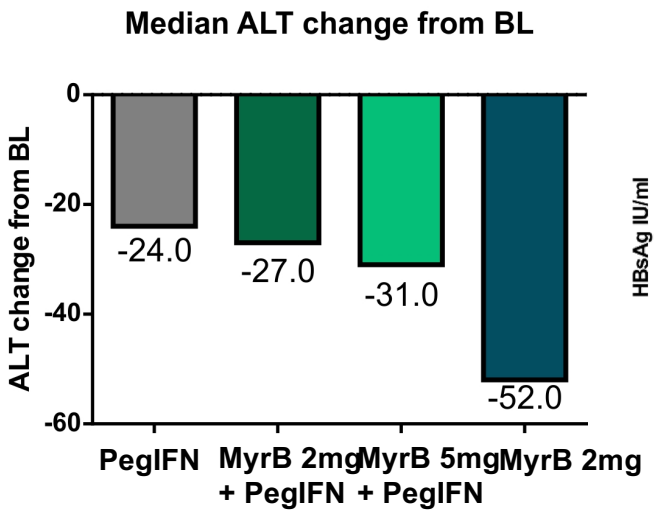
Chronic HBV/HDV co-infection (n=60) **Myrcludex B (2 or 5 mg) +/- PegIFN** x 48 weeks

HDV serum RNA

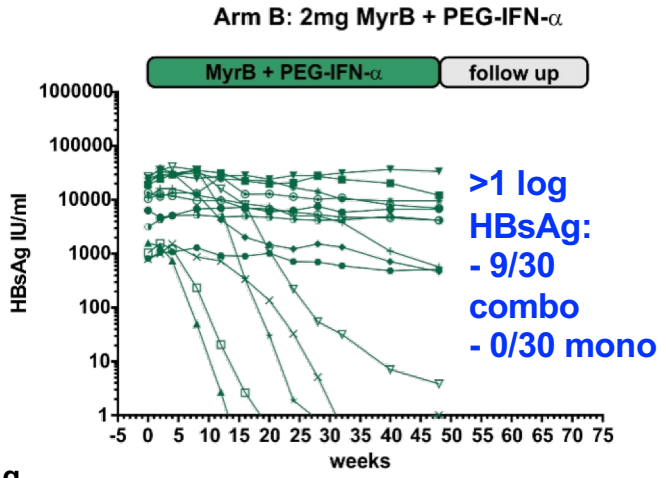


	Combo	Mono
>2 log HDV RNA:	29/30	15/30
Undetectable:	15/30	4/30

ALT



HBsAg



>1 log HBsAg:
- 9/30 combo
- 0/30 mono

Promising Phase 2 result showing **synergistic effect** of **entry inhibition (MyrB) + PegIFN** on HDV RNA & HBsAg raising the possibility of ***curative potential for HDV/HBV co-infection***

Wedemeyer et al., AASLD 2018, Abstract 18

Pros & Challenges for entry inhibitors

Inhibition of new rounds of infection

Decrease the pool of cccDNA on the long term

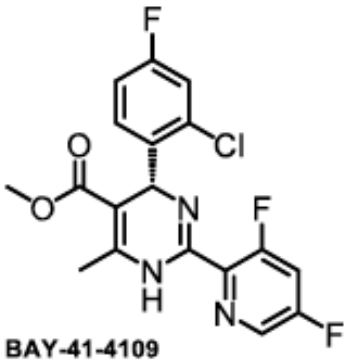
Opportunity to treat HBV/HDV co-infections

Effect on NTCP and elevation of bile salts

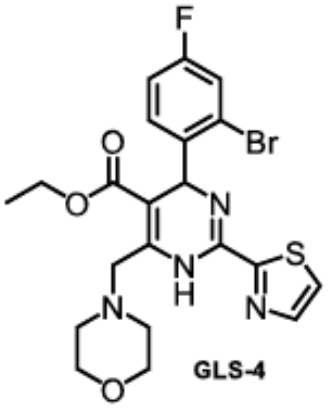
Slow kinetics of cccDNA decay and slow hepatocyte turn-over; which combination with other DAAs ?

Different classes of capsid assembly modulators

Heteroaryldipyrimidine derivatives (HAP)

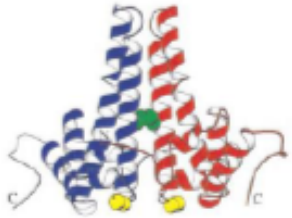


BAY-41-4109



GLS-4

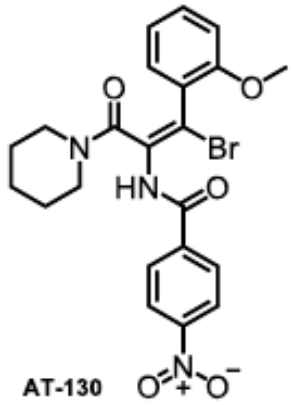
Hu et al., Ann. Rep. in Med. Chem. 2013



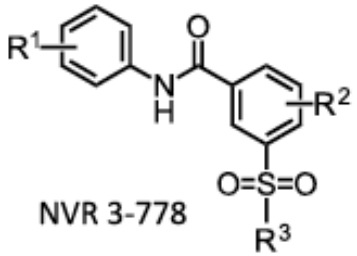
Compounds in evaluation

BAY41-4109
HAP-12
AT-130
NVR3-778
JNJ-6379
RO7049389
ABI-H0731
ABI-H0808
GLS4
GLP26
HAP_R01
SBA_R01
AB-423
AB-506
EP-027367

Phenylpropenamide derivatives (A*T series)*



AT-130



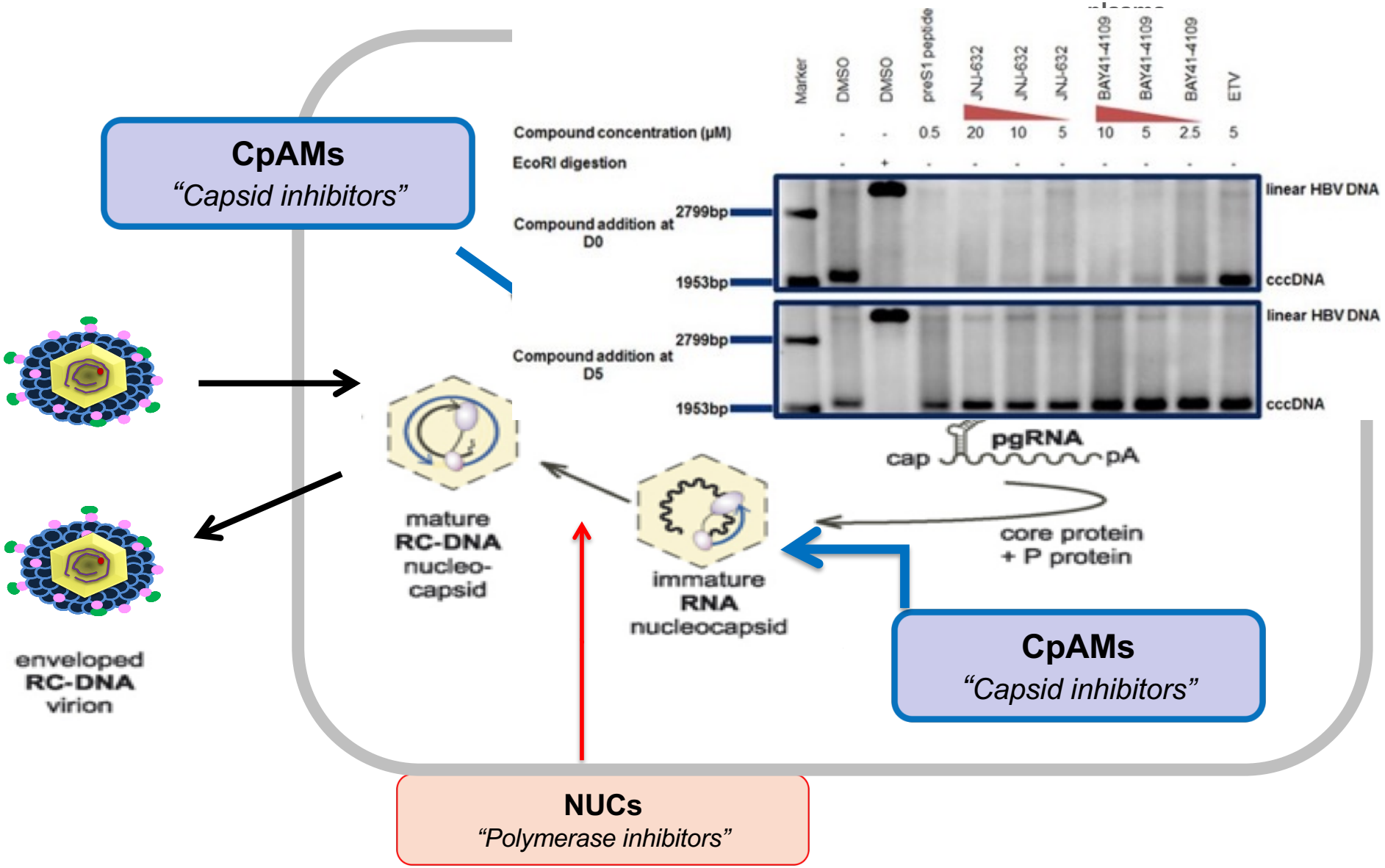
NVR 3-778

(*cf.* Campagna et al J.Virol. 2013)

ranscription
replication

rcDNA-containing
nucleocapsid

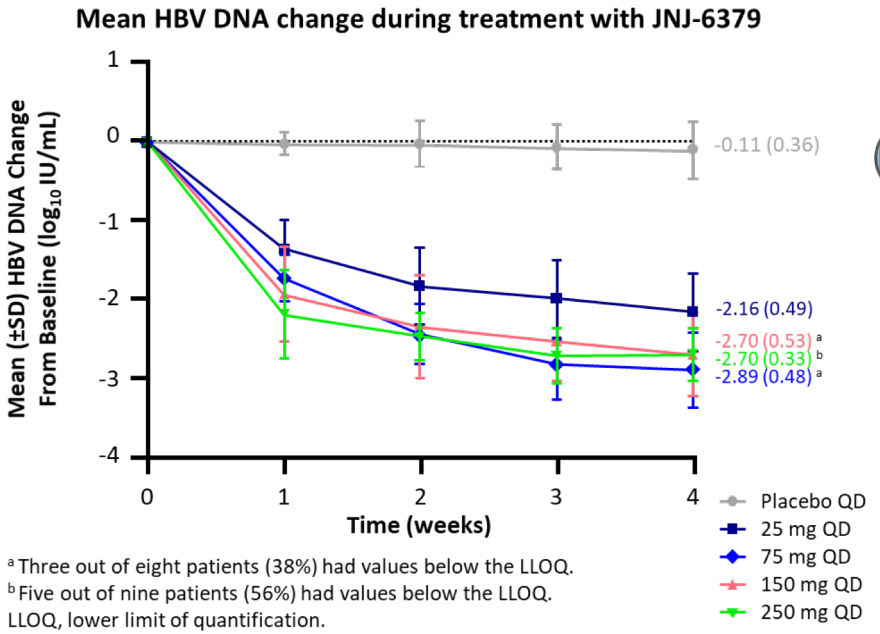
CpAMs inhibit viral genome replication and prevent cccDNA formation when administered prior to HBV inoculation



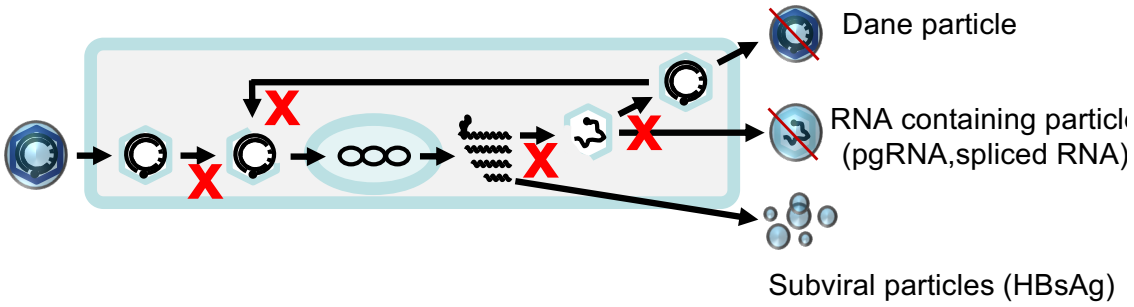
Berke et al. Antimicrob. Agents Chemother. 2017; Lam et al AAC 2017; Mani et al AAC 2018; Zhou et al Sci Report 2017

Capsid Assembly Modulators (CAMs)

JNJ-6379 PO OD x 28 d in non-cirrhotic HBeAg+ and HBeAg- CHB



[a] Three out of eight patients (38%) had values below the LLOQ.
[b] Five out of nine patients (56%) had values below the LLOQ.
LLOQ, lower limit of quantification.



No effect on HBeAg or HBsAg levels

- Well tolerated at increased dose
- Potent HBV DNA suppression with ***limited dose response at higher dose***
- Higher dose may be required ***to prevent cccDNA replenishment***
- **Ongoing Phase 2 trial**

Zoulim et al AASDL 2018, Abstract 74

Pros & challenges for CpAM

Decrease the pool of cccDNA on the long term

Other MoA ?

Opportunity to combine with NUCs, pegIFN, other DAAs and immune interventions

Oral administration

Long-term safety profile

Mainly suppressive

How to combine with other approaches to be curative ?

siRNA Candidate Development

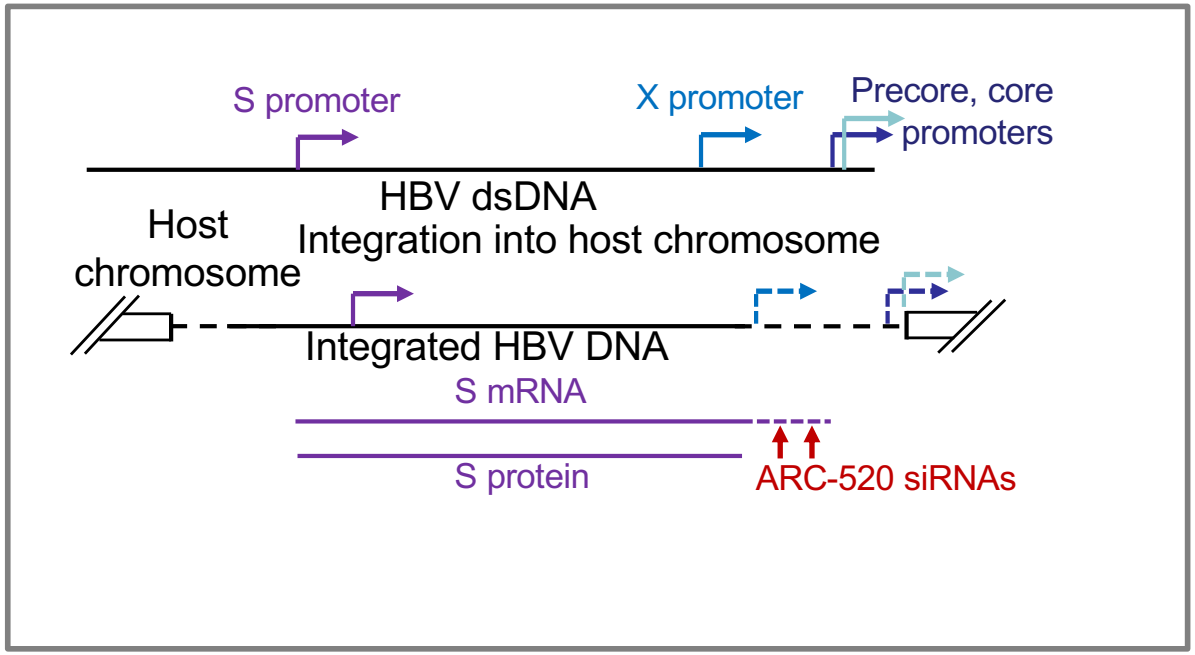
arrowhead pharmaceuticals

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Arbutus BIOPHARMA
Aspiring to Cure Chronic Hepatitis B

Alnylam

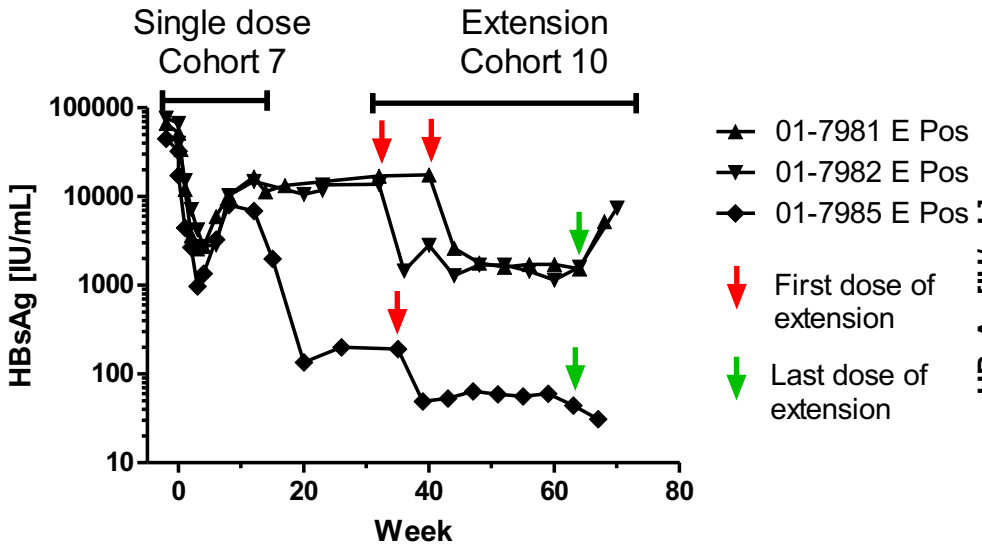
VIR



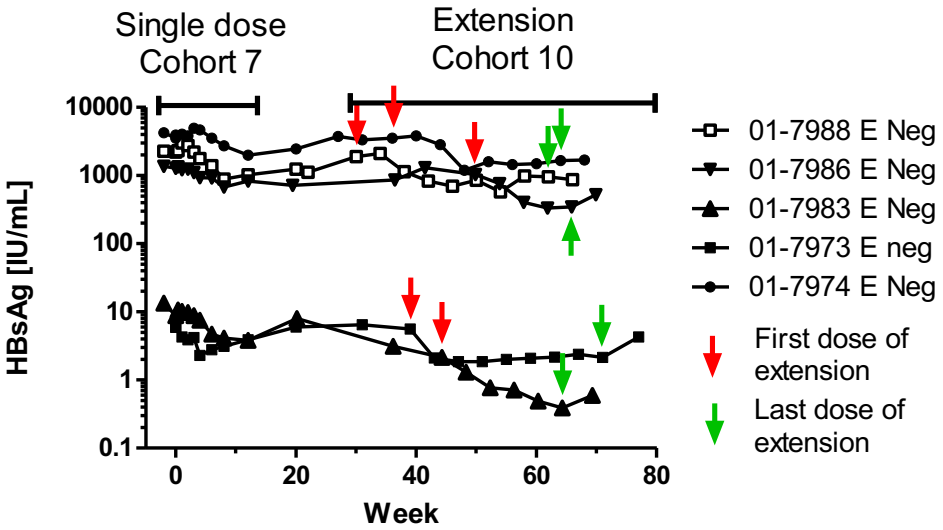
Lipid Nanpparticles for IV infusion
GalNAc-Conjugate for subcutaneous administration

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

HBeAg+ patients

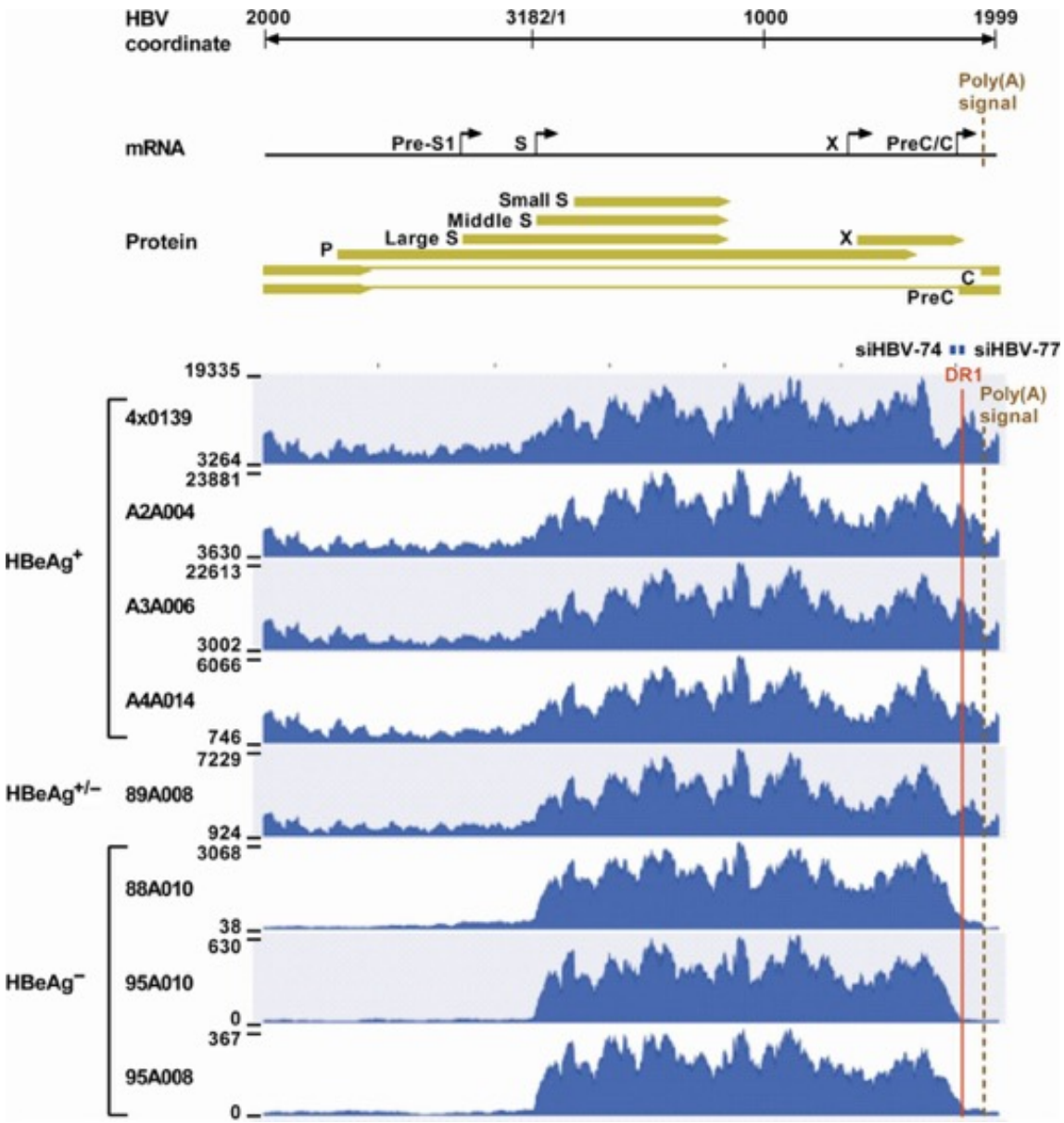


HBeAg- patients



Yuen MF et al, EASL ILC 2017

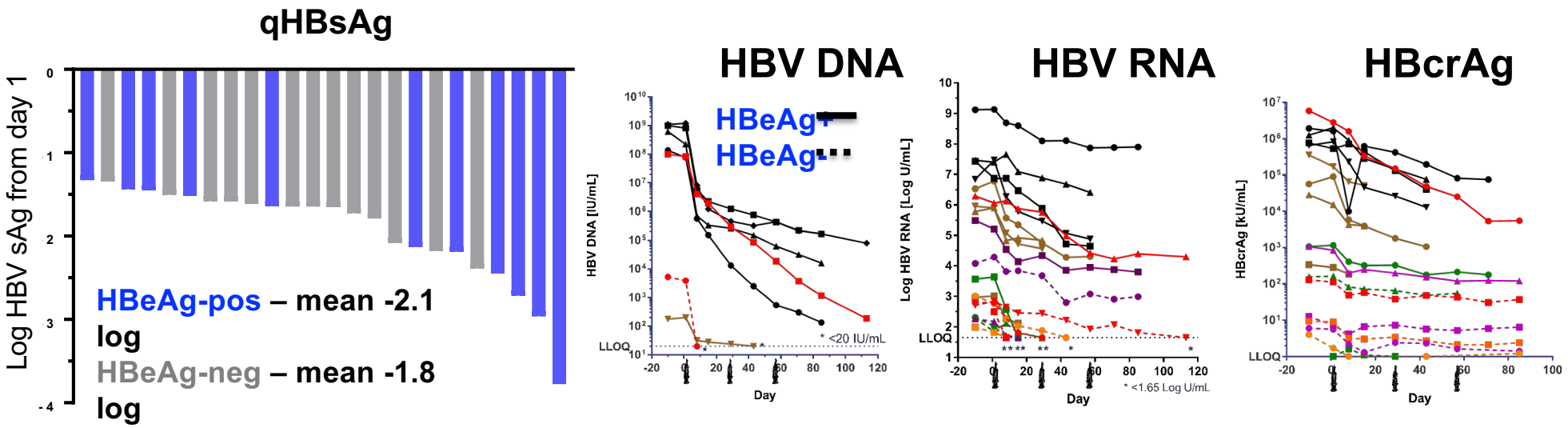
Liver HBV mRNA paired-end sequencing reads in HBeAg-positive and HBeAg-negative chimpanzees reveal truncated viral transcripts associated with integration



Christine I. Wooddell et al., Sci Transl Med 2017

Improved RNAi – ARO-HBV

CHB mix of HBeAg-pos (n=11) and HBeAg-neg (n=13) **monthly ARO-ABV RNAi SC x 3 doses**



- Similar effect in HBeAg-pos and HBeAg-neg without a clear dose-response → ***suggests targets both cccDNA & integrated HBV DNA***
- Mild injection site reactions but otherwise well tolerated with no safety signals

Gane et al, AASLD 2018, Abstract LB-25

Pros & challenges for siRNA

Decrease of HBsAg

Potential for immune restoration ?

Opportunity to combine with NUCs, pegIFN and other DAAs or immunotherapeutic approaches ?

Parenteral administration

Long-term safety profile

Mainly suppressive

Impact of integrated sequences

How to combine with other approaches to be curative ?

Other technologies under investigation

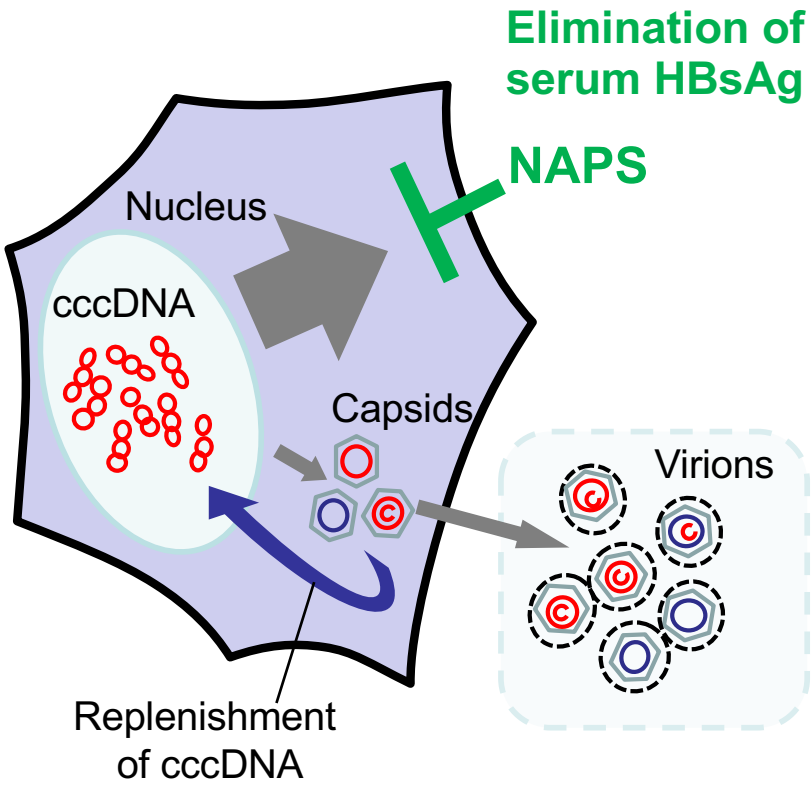
Antisense OGN: Billioud et al, J Hepatol 2016

Locked Nucleic Acids: Javanbakht et al, Mol Ther Nucleic Acids. 2018

RNA destabilizers: Mueller er al, J Hepatol 2018, Zhou et al, Antiviral Res 2018

Nucleic acid polymers (NAPs)

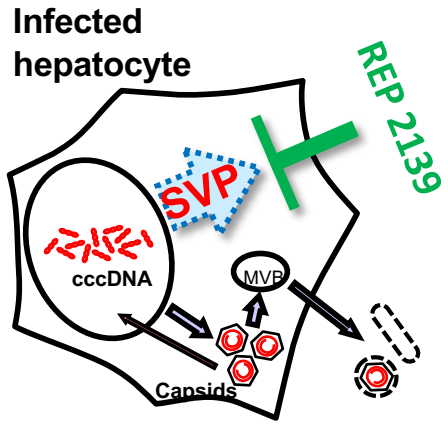
- **Nucleic Acid Polymers (NAP)** have entry and post-entry antiviral effects in HBV infection *in vitro.*
  Noordeen, F et al. AAC. 2013

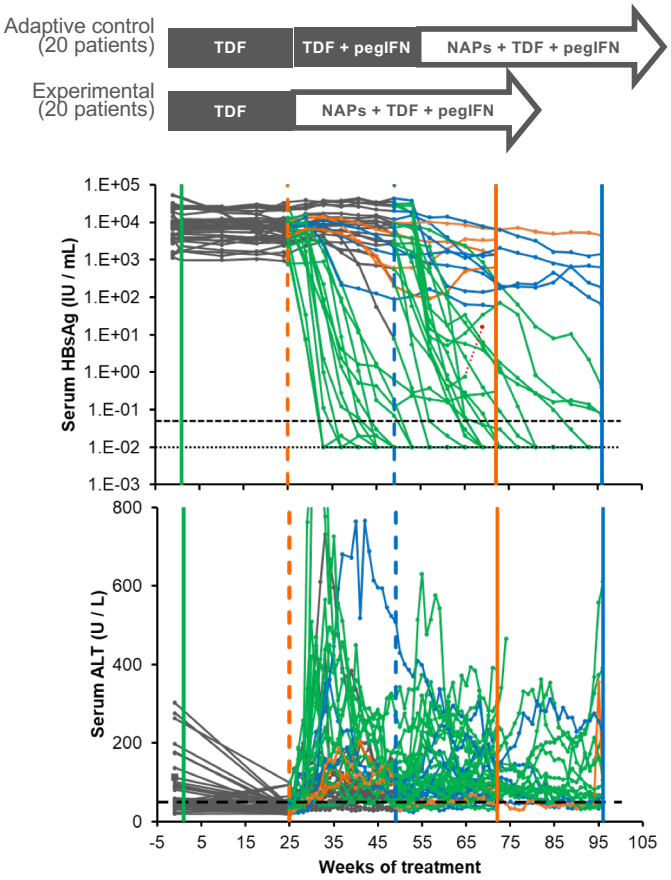


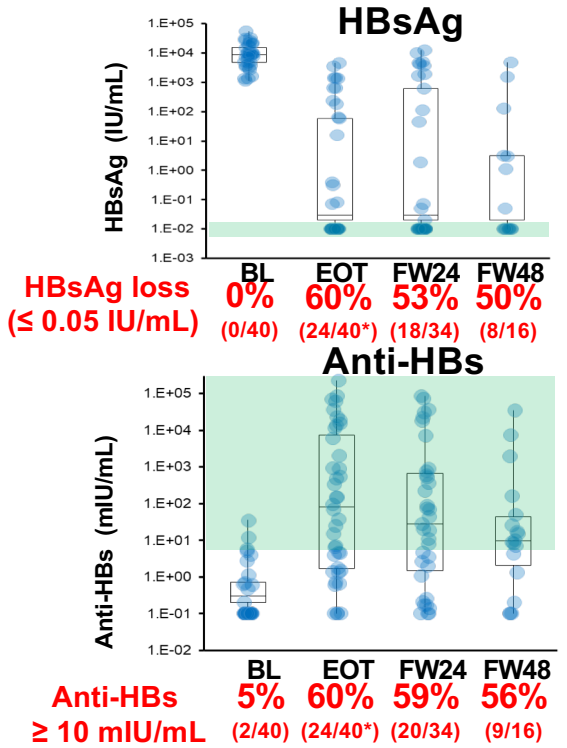
Inhibition of HDV entry by preventing attachment of the virus to cell surface glycosaminoglycans
Belstein et al, J Virol 2018; Quinet et al, Hepatology 2018

Nucleic Acid Polymers (NAPs) – Reducing HBsAg

- NAPs block assembly/release of **subviral particles**
- Aim to restore immune response → viral control







- Marked and seemingly durable HBsAg loss & gain of anti-HBs
- Interesting…need to confirm ALT flares due to immune activation → plan for Phase 2 ACTG trial to clarify

Bazinet et al, AASLD 2018, Abstract 393

Pros & challenges for NAPs

Decrease of HBsAg

Immune restoration ?

Opportunity to combine with NUCs, pegIFN and other DAAs

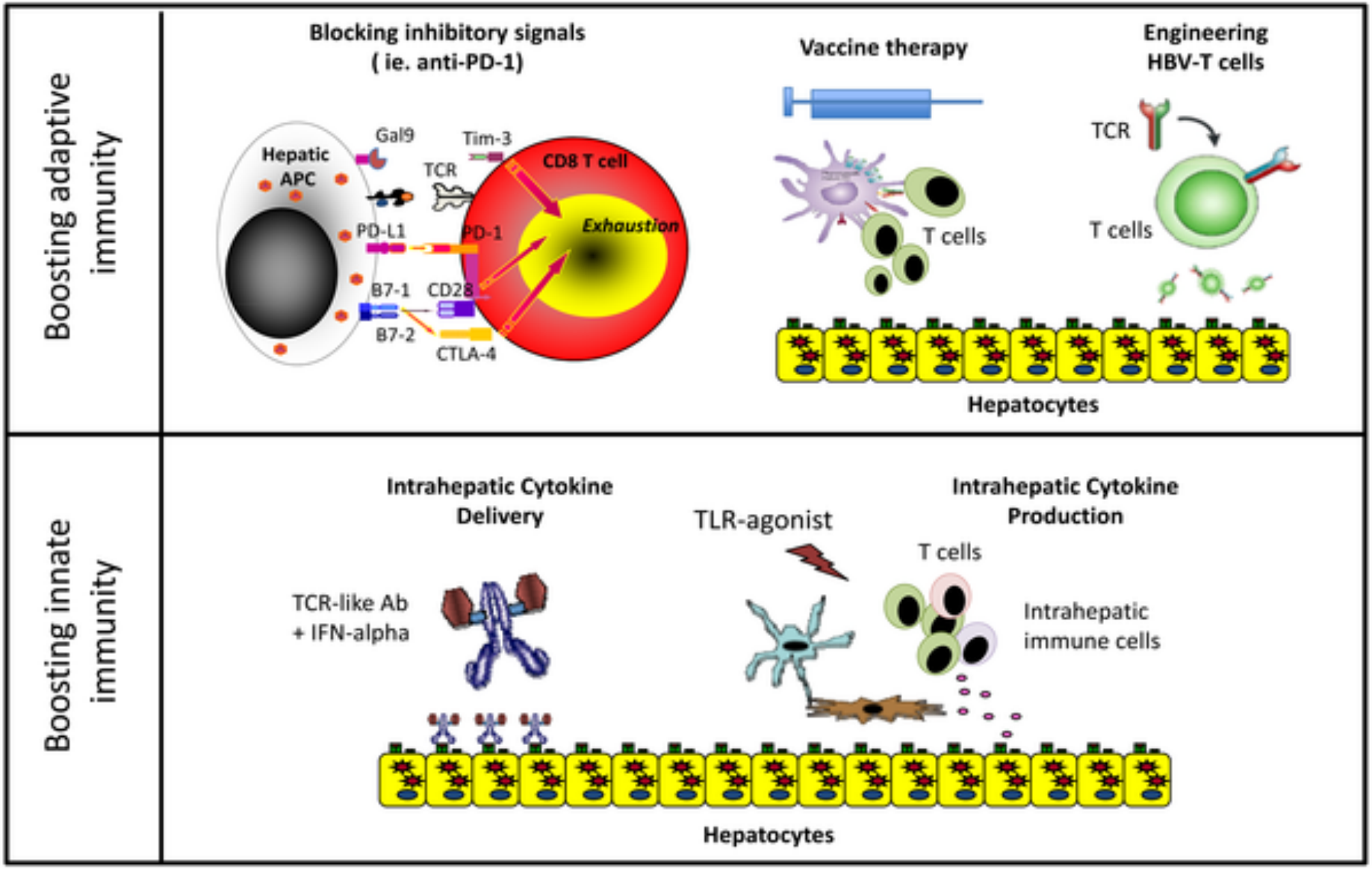
Mode of action under investigation

IV infusion

ALT exacerbation

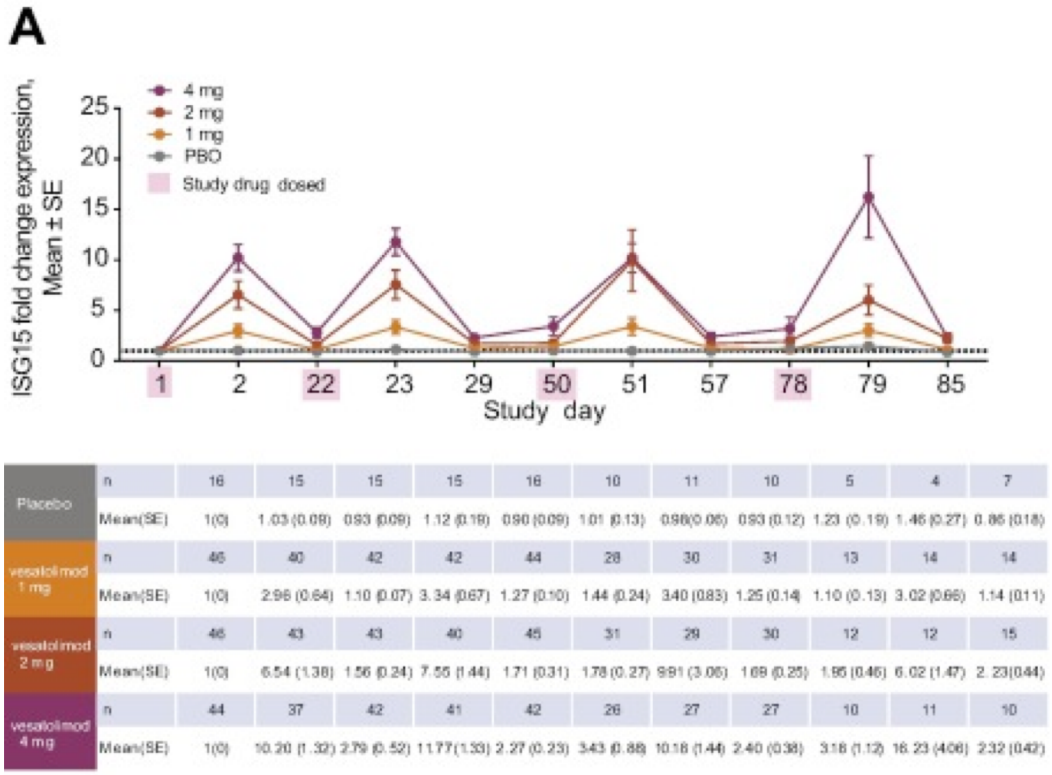
Long-term safety profile

Restoration of antiviral immunity

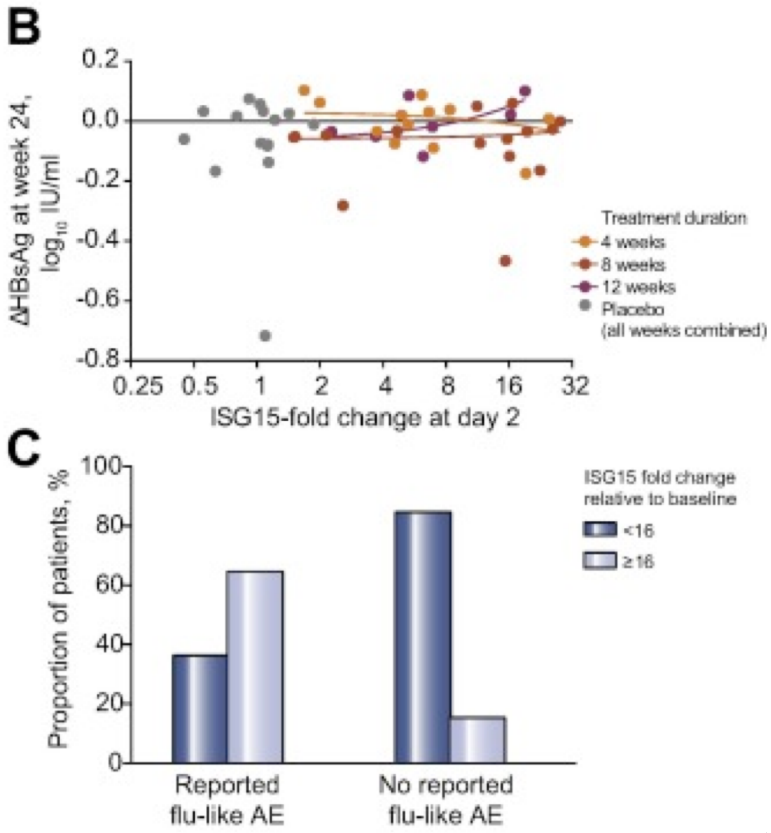


Bertoletti A, Gehring AJ (2013) Immune Therapeutic Strategies in Chronic Hepatitis B Virus Infection: Virus or Inflammation Control?. PLoS Pathog

The Oral Toll-Like Receptor-7 Agonist GS-9620 in Virally suppressed Patients with Chronic HBV Infection

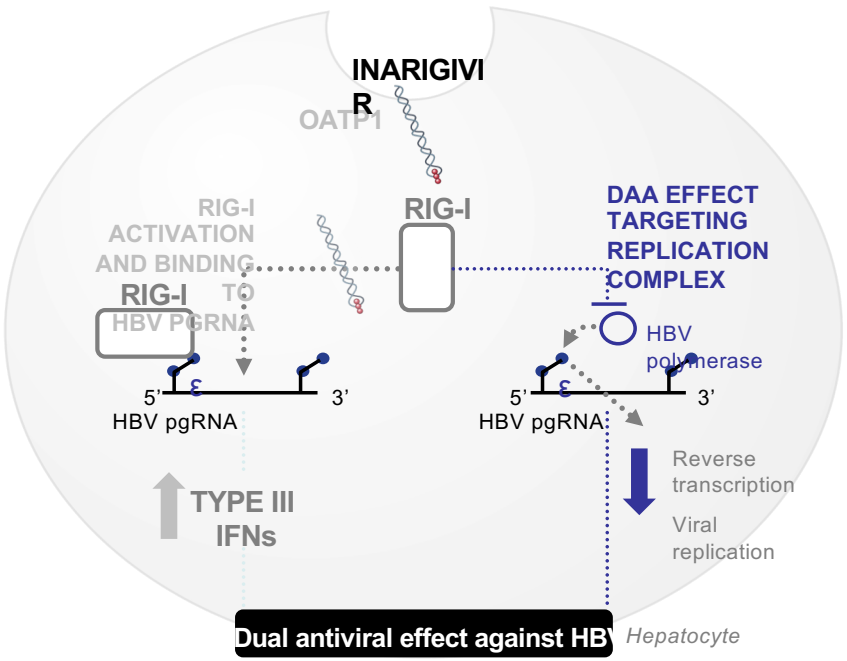


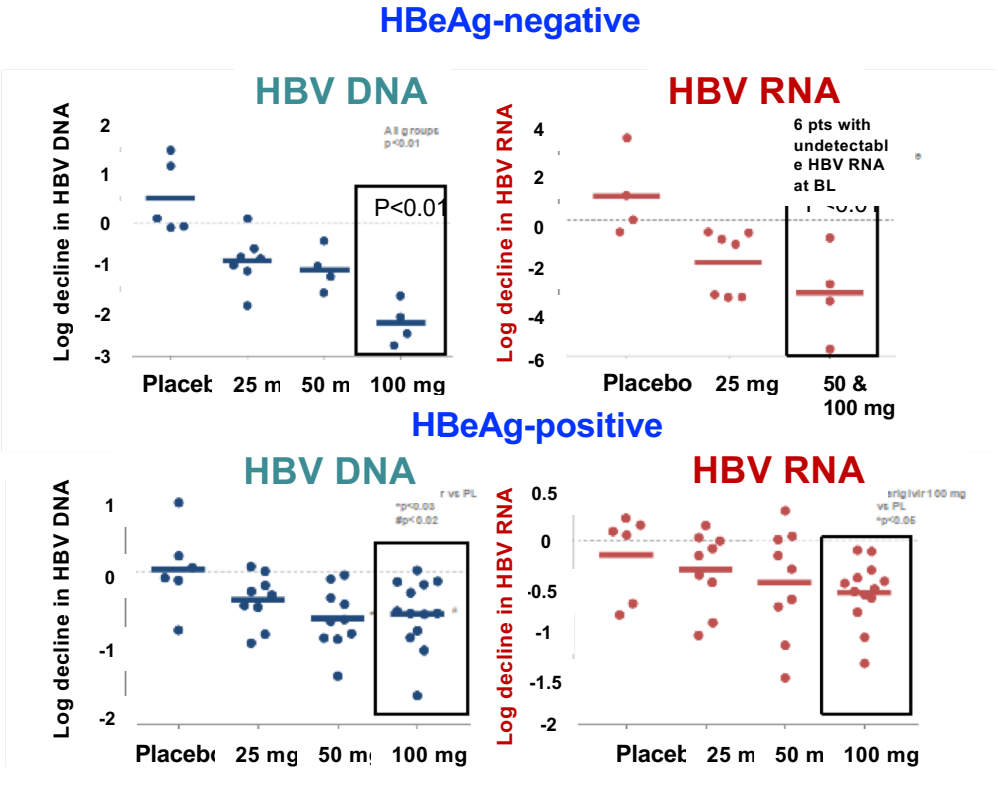
Placebo	n	16	15	15	15	16	10	11	10	5	4	7
	Mean(SE)	1(0)	1.03 (0.09)	0.93 (0.09)	1.12 (0.19)	0.90 (0.09)	1.01 (0.13)	0.98(0.06)	0.93 (0.12)	1.23 (0.19)	1.46 (0.27)	0.86 (0.18)
vesatolimod 1 mg	n	46	40	42	42	44	28	30	31	13	14	14
	Mean(SE)	1(0)	2.96 (0.64)	1.10 (0.07)	3.34 (0.67)	1.27 (0.10)	1.44 (0.24)	3.40 (0.83)	1.25 (0.14)	1.10 (0.13)	3.02 (0.66)	1.14 (0.11)
vesatolimod 2 mg	n	46	43	43	40	45	31	29	30	12	12	15
	Mean(SE)	1(0)	6.54 (1.38)	1.56 (0.24)	7.55 (1.44)	1.71 (0.31)	1.78 (0.27)	9.91 (3.05)	1.69 (0.25)	1.85 (0.46)	6.02 (1.47)	2.23(0.44)
vesatolimod 4 mg	n	44	37	42	41	42	26	27	27	10	11	10
	Mean(SE)	1(0)	10.20 (1.32)	2.79 (0.52)	11.77 (1.33)	2.27 (0.23)	3.43 (0.88)	10.18 (1.44)	2.40 (0.38)	3.18 (1.12)	16.23 (4.06)	2.32 (0.42)



Janssen et al, Journal of Hepatology, 2017

Inarigivir (RIG-I agonist) – a novel approach with dual antiviral activity



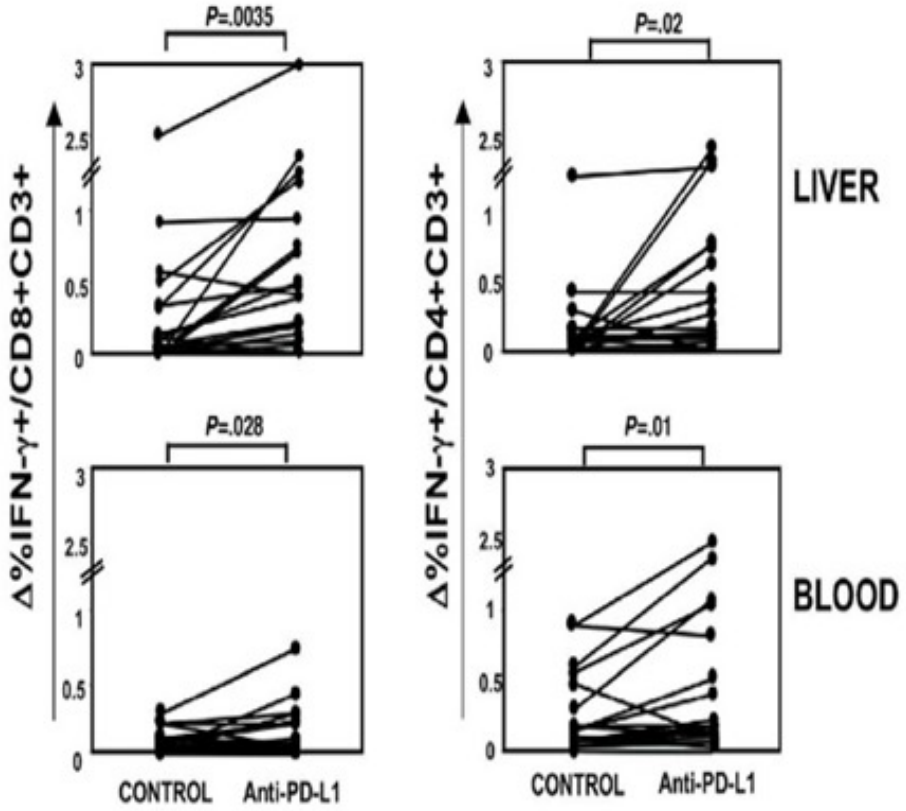


- Dose-dependent decline in HBV DNA & HBV RNA **> in HBeAg-neg patients and those with low qHBsAg levels**
- HBV RNA effects persisted after cross-over to tenofovir – 'new set-point'? ***Interesting proof-of-concept***

Yuen et al, AASLD 2018, Abstract 75

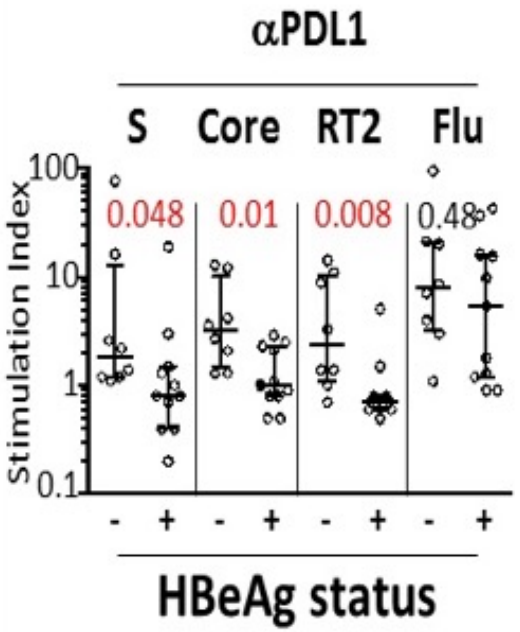
PD-1 blockade enhances HBV-specific T cell function

In liver and blood



Fisicaro P, Gastroenterol 2010; 138: 682

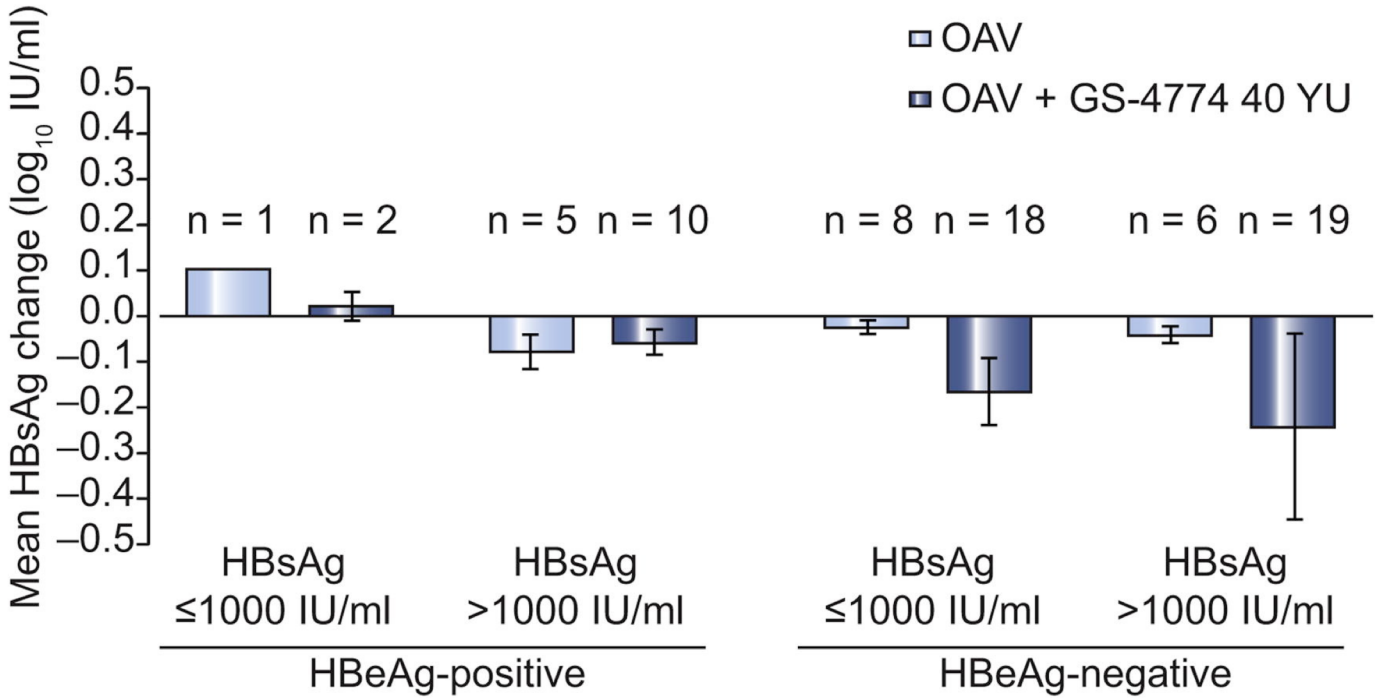
With differential impact based on HBeAg status



Park J, Gastroenterol 2016; 150: 684

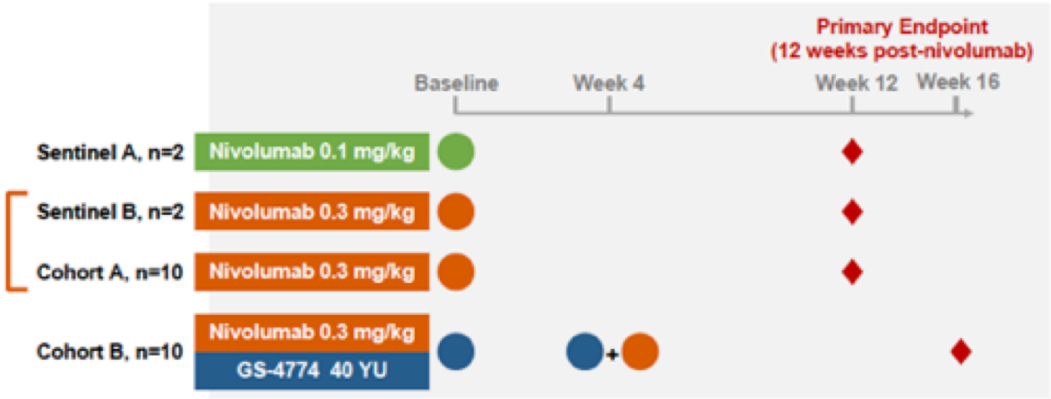
Randomized phase II study of GS-4774 as a therapeutic vaccine in virally suppressed patients with chronic hepatitis B

GS-4774 is a heat-inactivated, yeast-based, T-cell vaccine designed to elicit HBV-specific T-cell responses

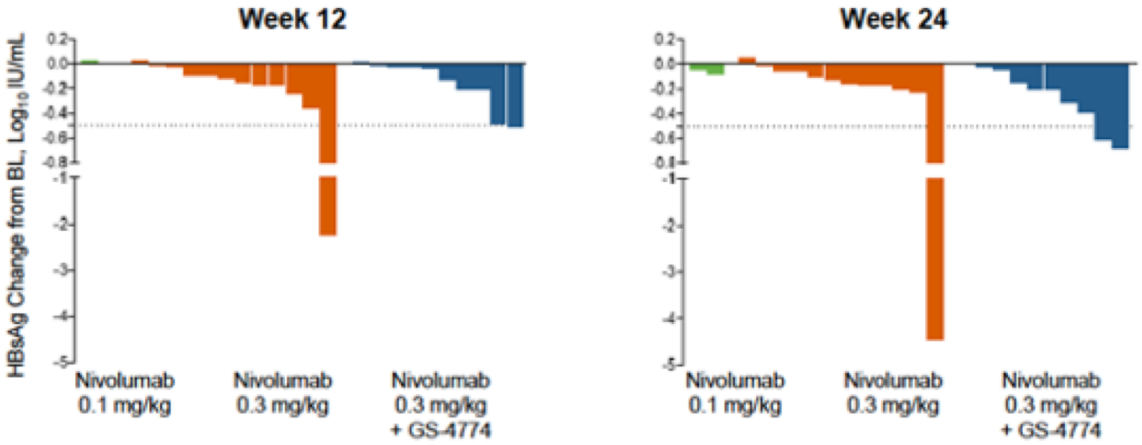


Lok et al, J Hepatol 2016

A Phase 1 Study Evaluating Anti-PD-1 Treatment With or Without GS-4774 in HBeAg Negative Chronic Hepatitis B Patients

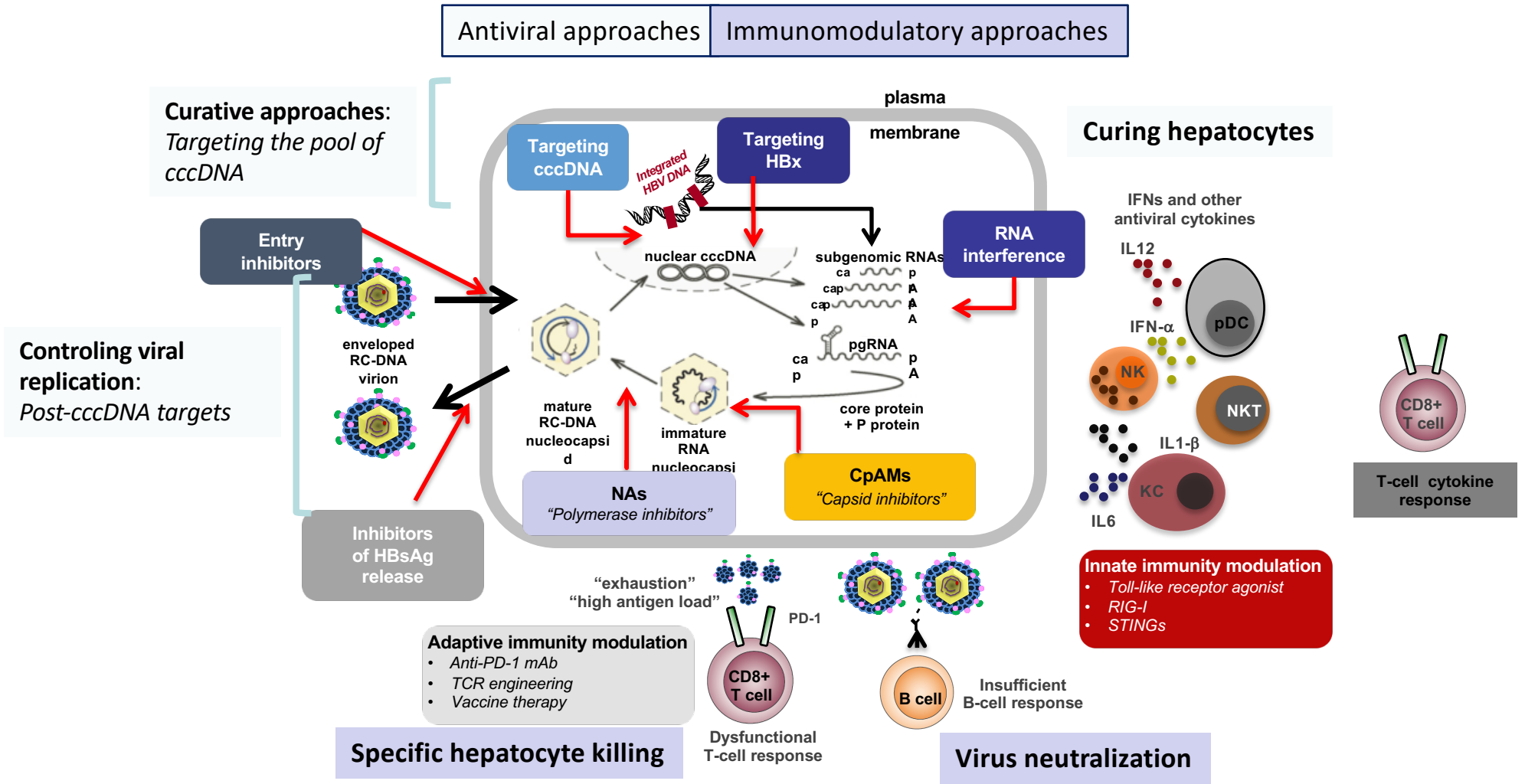


- Virally-suppressed, HBeAg negative CHB patients (single center New Zealand)



- 2/22 (9%) at Week 12 and 3/22 (14%) at Week 24 with a >0.5 log_{10} reduction in HBsAg

Gane et al, EASL ILC 2017 PS-044



Adapted from: Levrero M, et al. Curr Opin Virol 2016;18:135–43

CpAM: core protein allosteric modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK: natural killer; NKT: natural killer T cell; pDC: plasmocytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor

Towards combined therapies

- **Combination of CpAm + RNA destabilizer + NUC**

  HDI mouse model

  Gindin Y, et al. ILC 2018, #3503 (PS-027)

- **Combination of CpAM and TLR-7 agonist**

  AAV-HBV mouse model

  Gao L, et al. ILC 2018, #4008 (PS-028)

- **RIG-I agonist (Inarigivir) and NUCs**

  Clinical trial

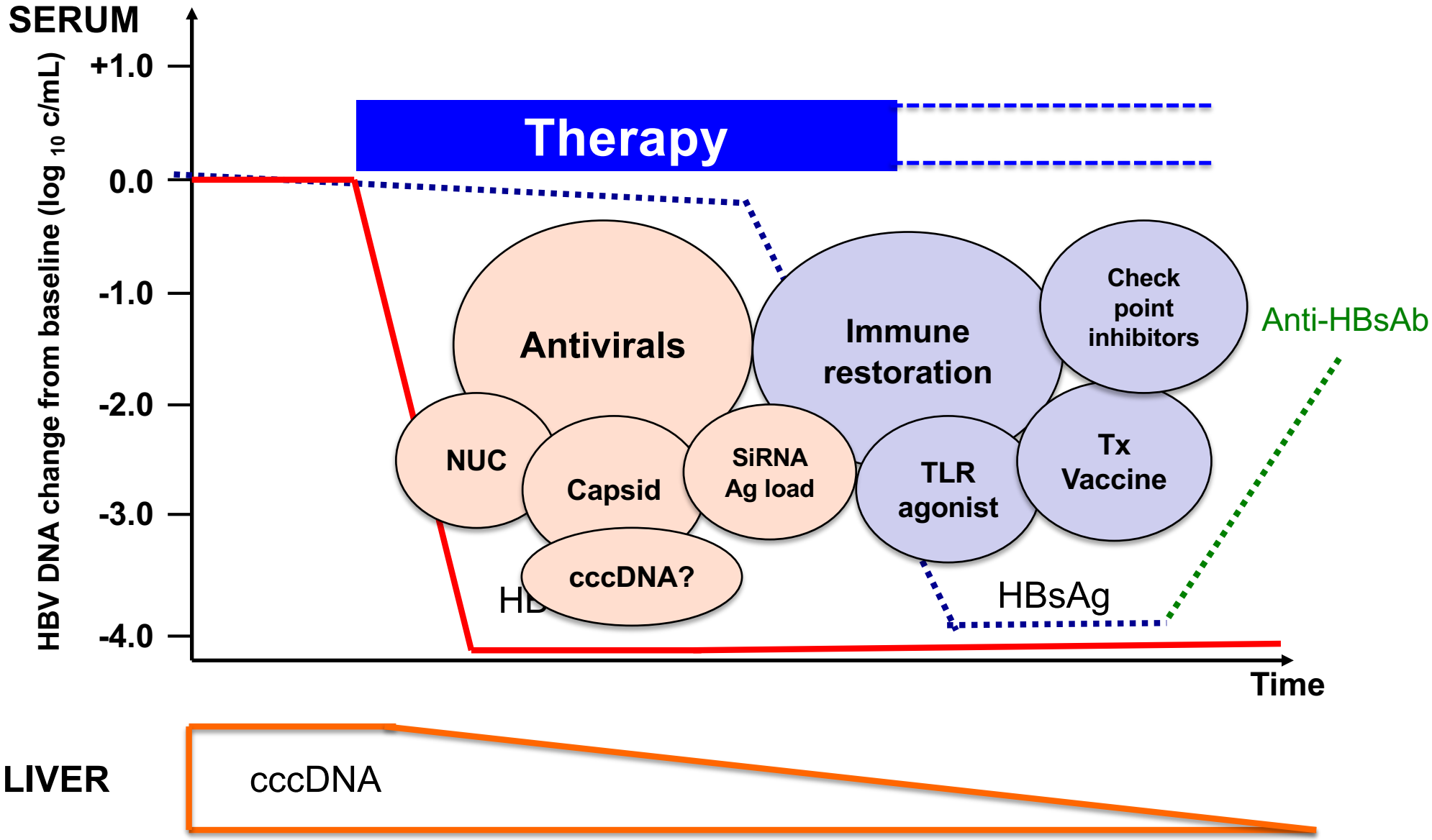
  Walsh R, et al. ILC 2018, #2694 (PS-160)

- **SiRNA followed by therapeutic vaccination**

  AAV-HBV mouse model

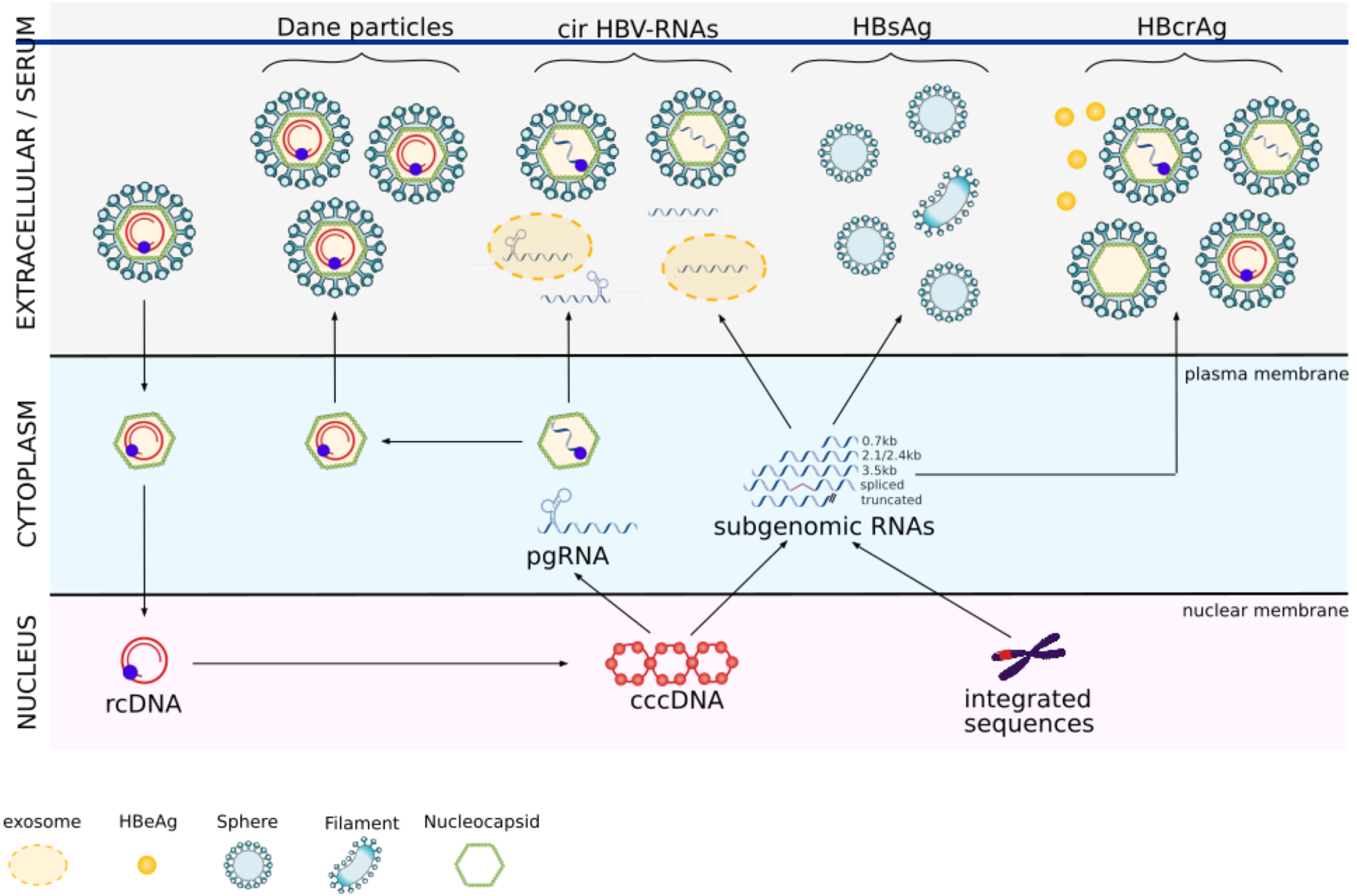
  Michler T, et al. ILC 2018, #1044 (PS-025)

HBV cure - New treatment concepts – Will we need combination of DAA and immune therapy ?



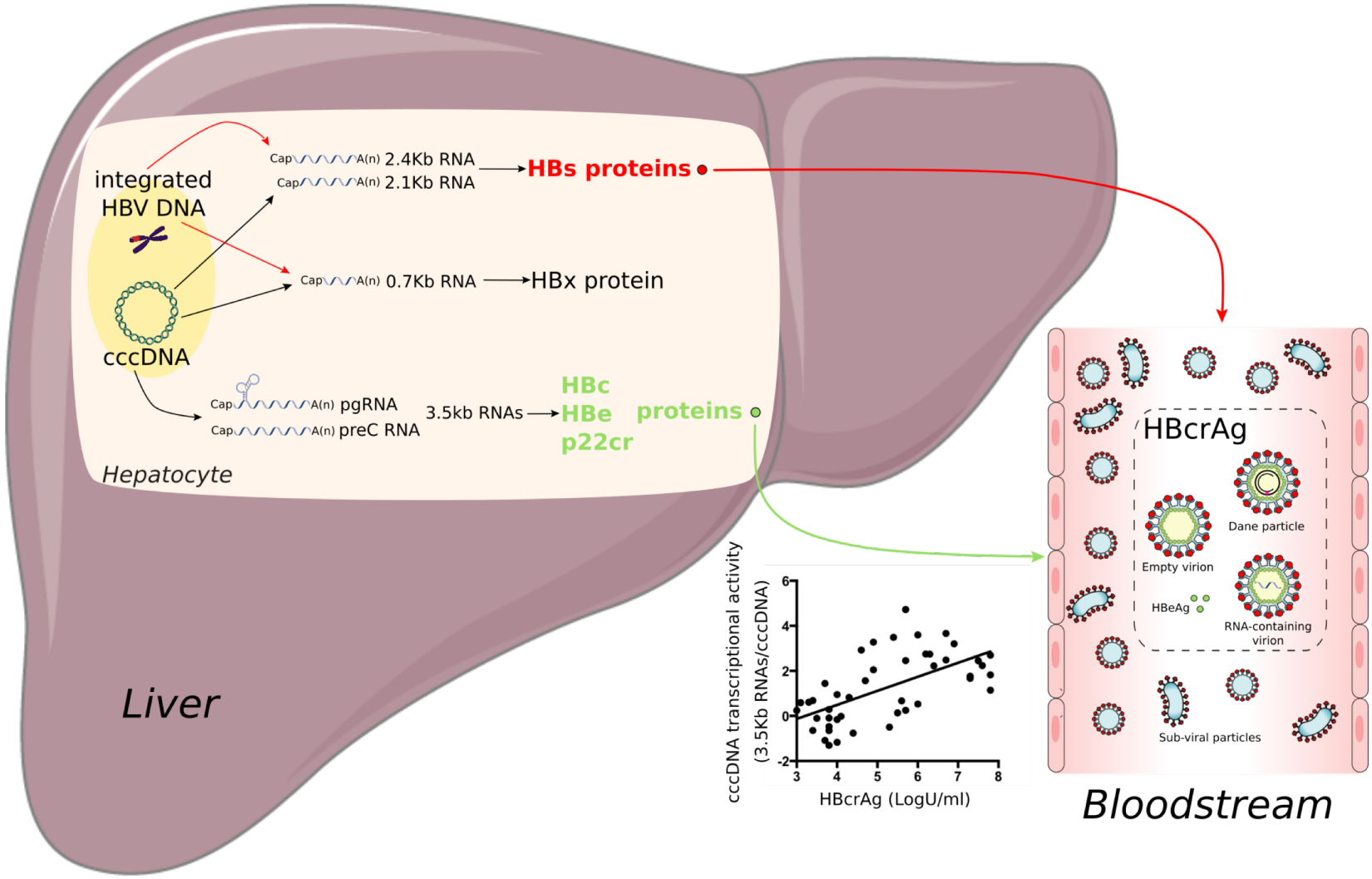
Testoni et al, Liver International 2017

Need for Novel Biomarkers to Assess Target Engagement and Treatment Endpoints



Testoni et al, Sem Liver Dis, 2017 & J Hepatol 2019; Liu et al, Hepatology 2019

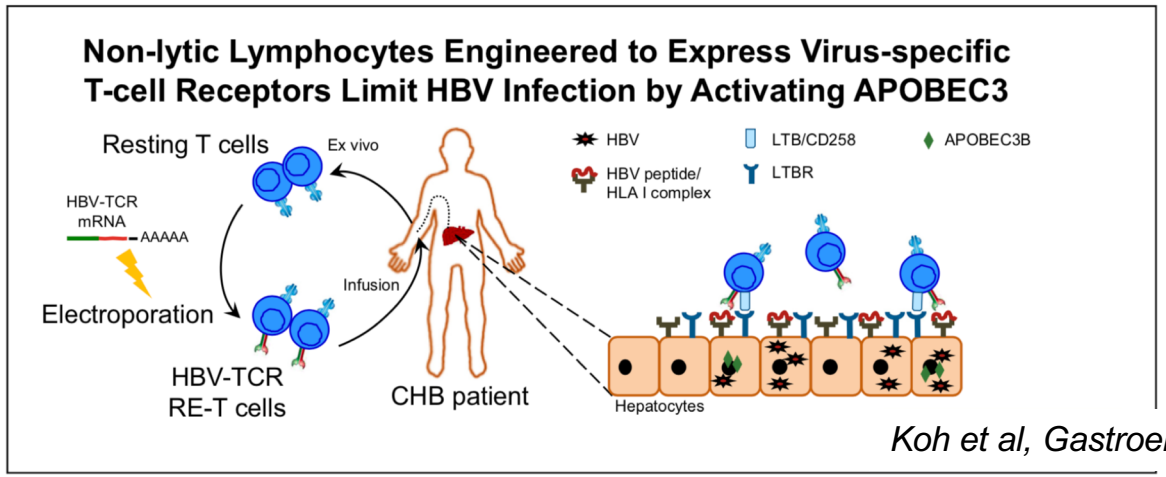
Serum HBcrAg levels are correlated with intrahepatic cccDNA transcriptional activity



Testoni et al, J Hepatol, in press.

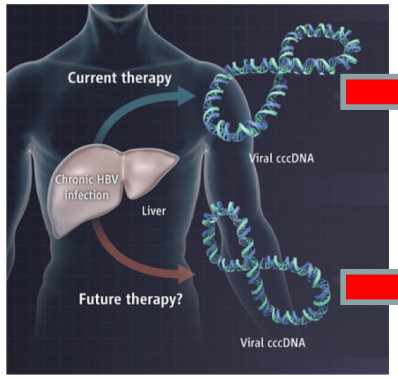
Innovations and novel perspectives for cure

- **T cell engineering and immunotherapy**



Koh et al, Gastroenterology 2018

- **cccDNA biology and targeting strategies**



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

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

Gene editing: CRISPR/cas9 and others

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

HBV cure: An attainable goal within the next decade !

- Collaboration between Academia, Industry and Stakeholders

National health programs

World Health Organization

EASL European Association for the Study of the Liver

AASLD American Association for the Study of Liver Diseases

- International HBV cure programs

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

DZIF

Doherty Institute

ICE-HBV International Coalition to Eliminate HBV

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