Viral Hepatitis
Prevention Board

VHPB Meeting
Hot Topics in Prevention and Control of Viral Hepatitits
Lisbon, 15-16th March 2018

Novel targets for HBV therapy

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Cancer Research Center of Lyon – INSERM UMR1052, CNRS 5286
Lyon, France

CRCL
CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

Inserm
La science pour la santé
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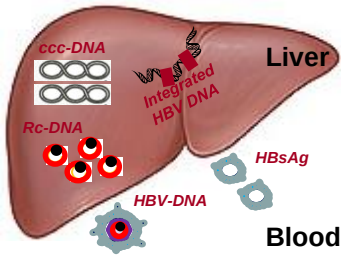
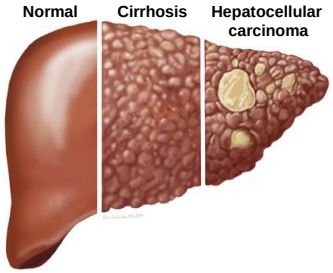
Chronic Hepatitis B (CHB) - a global health problem

*from viral suppression to **cure***

- 240 million CHB worldwide
- 1.7 million CHB treated worldwide
- Hepatocellular Carcinoma (HCC) : 2nd cause of cancer death worldwide



UNTREATED



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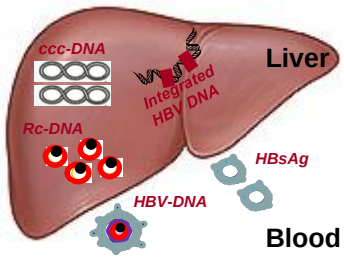

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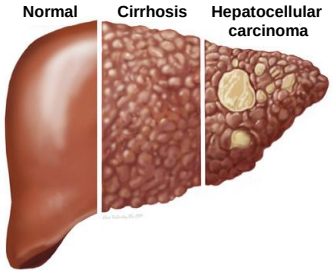
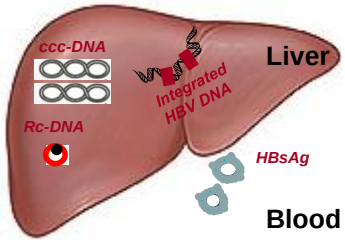
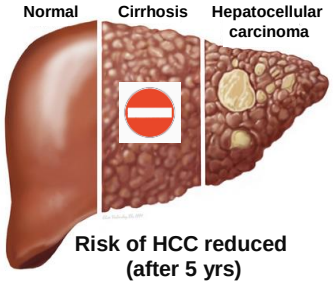




NUCs



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

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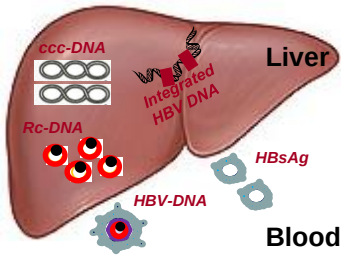

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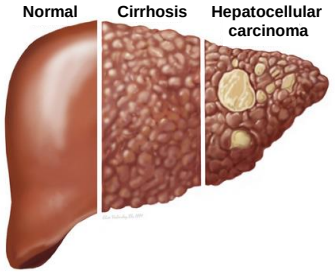

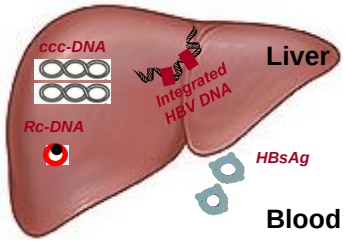

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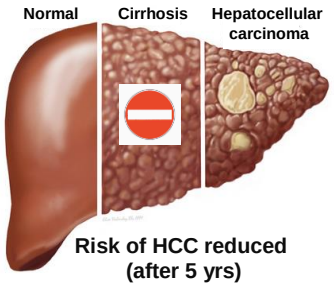

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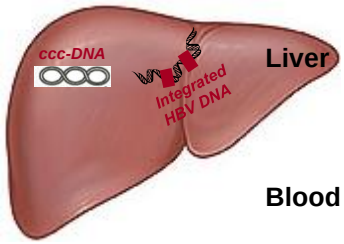
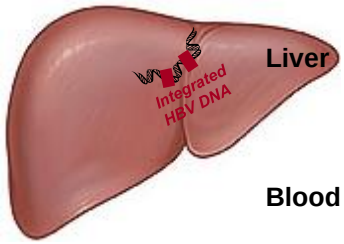
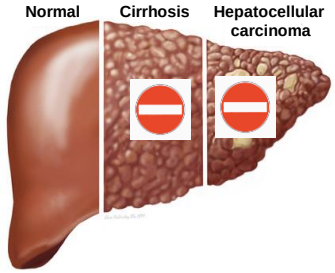




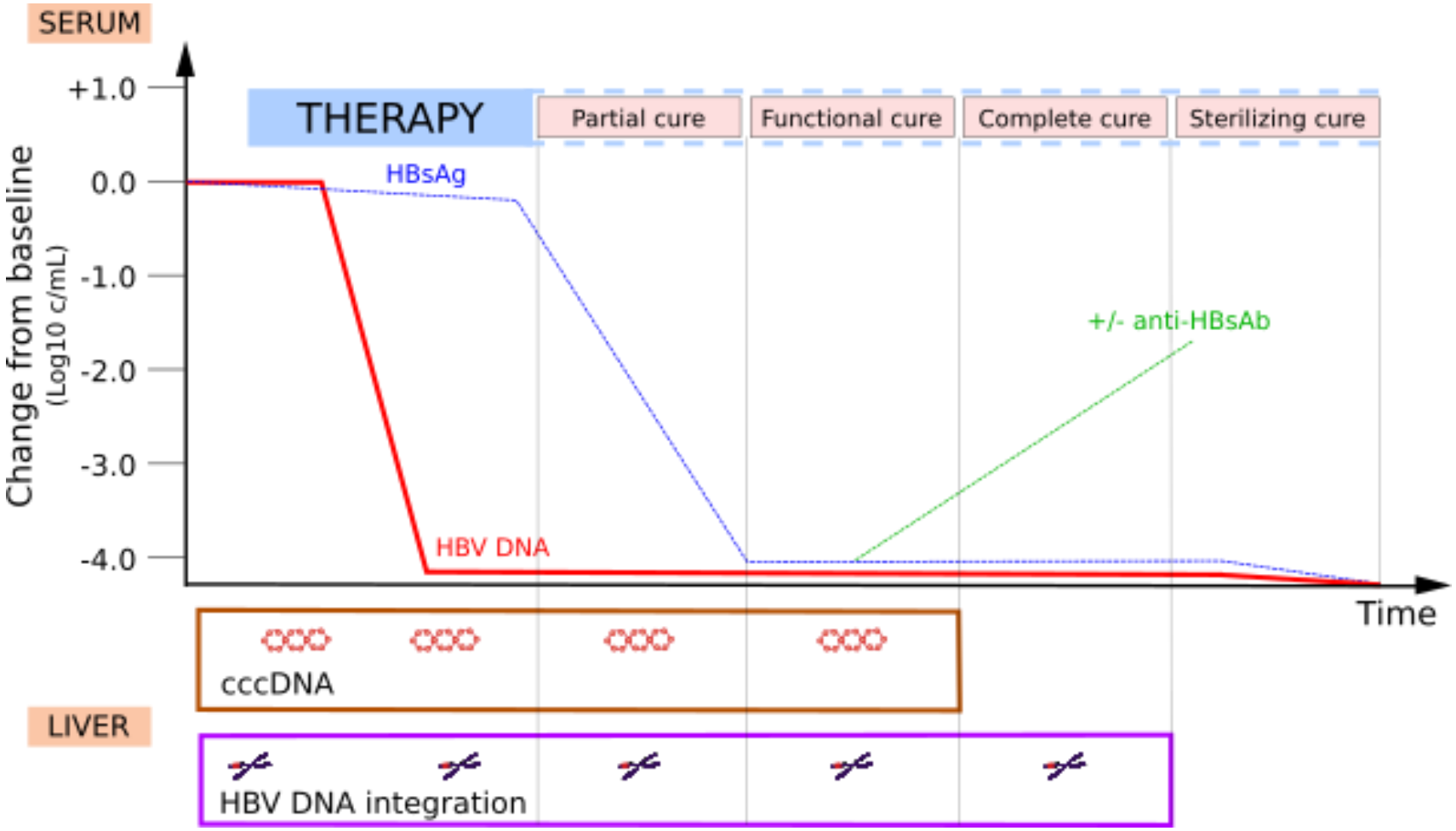
NMEs | ***"Cure"***

Direct Antiviral Agents (DAAs)

Immunomodulatory strategies

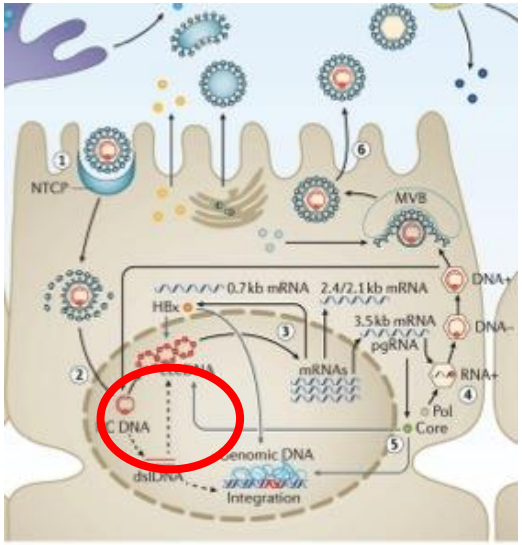


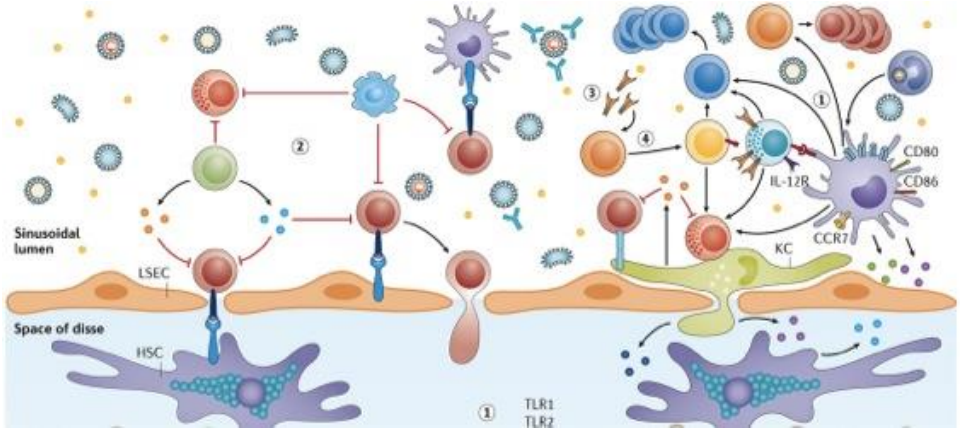
Definition of HBV cure: what do we want to achieve ?



Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 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

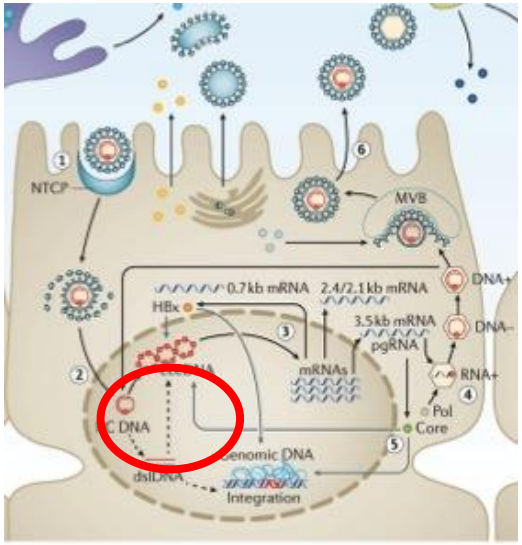
Defective B cell responses

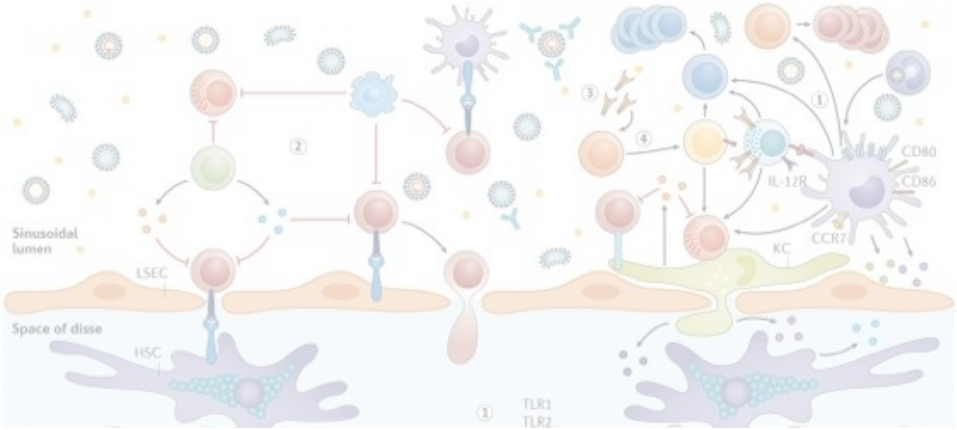
Inefficient innate response

Defective immune responses

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

Barriers to eradicating HBV





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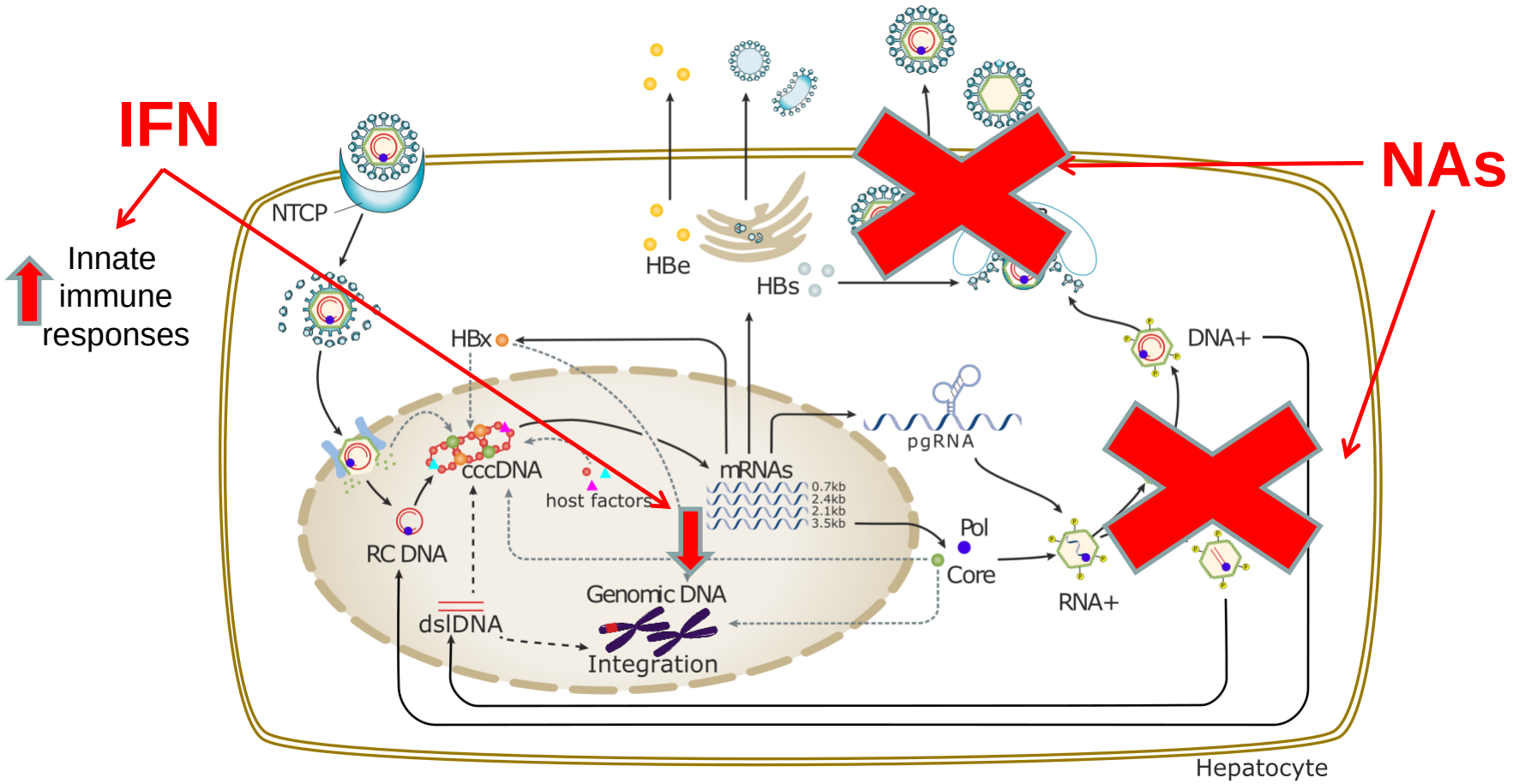
Current treatment options

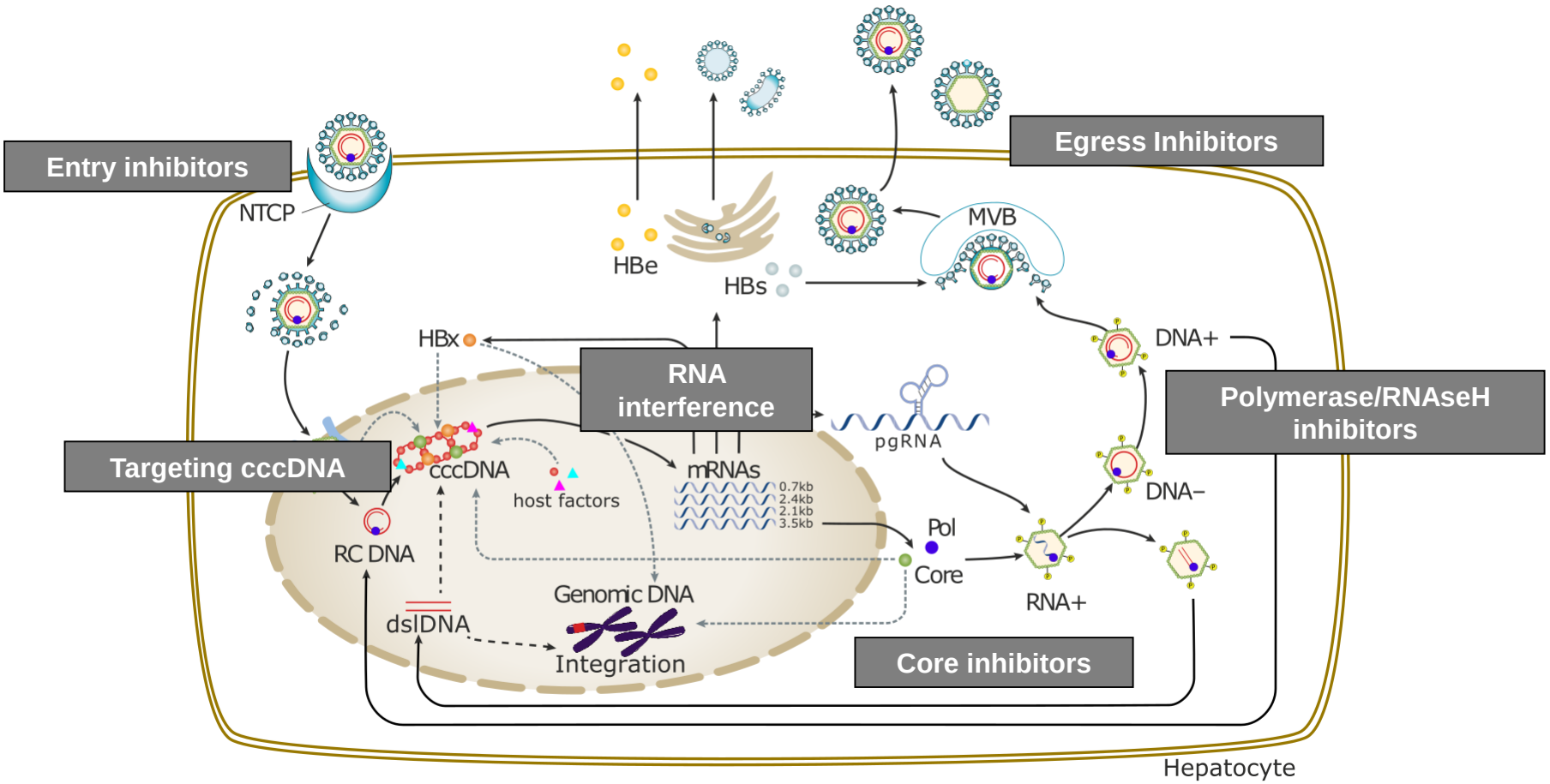


Current available therapies inhibit complete virion formation and release, but are not able to eliminate cccDNA

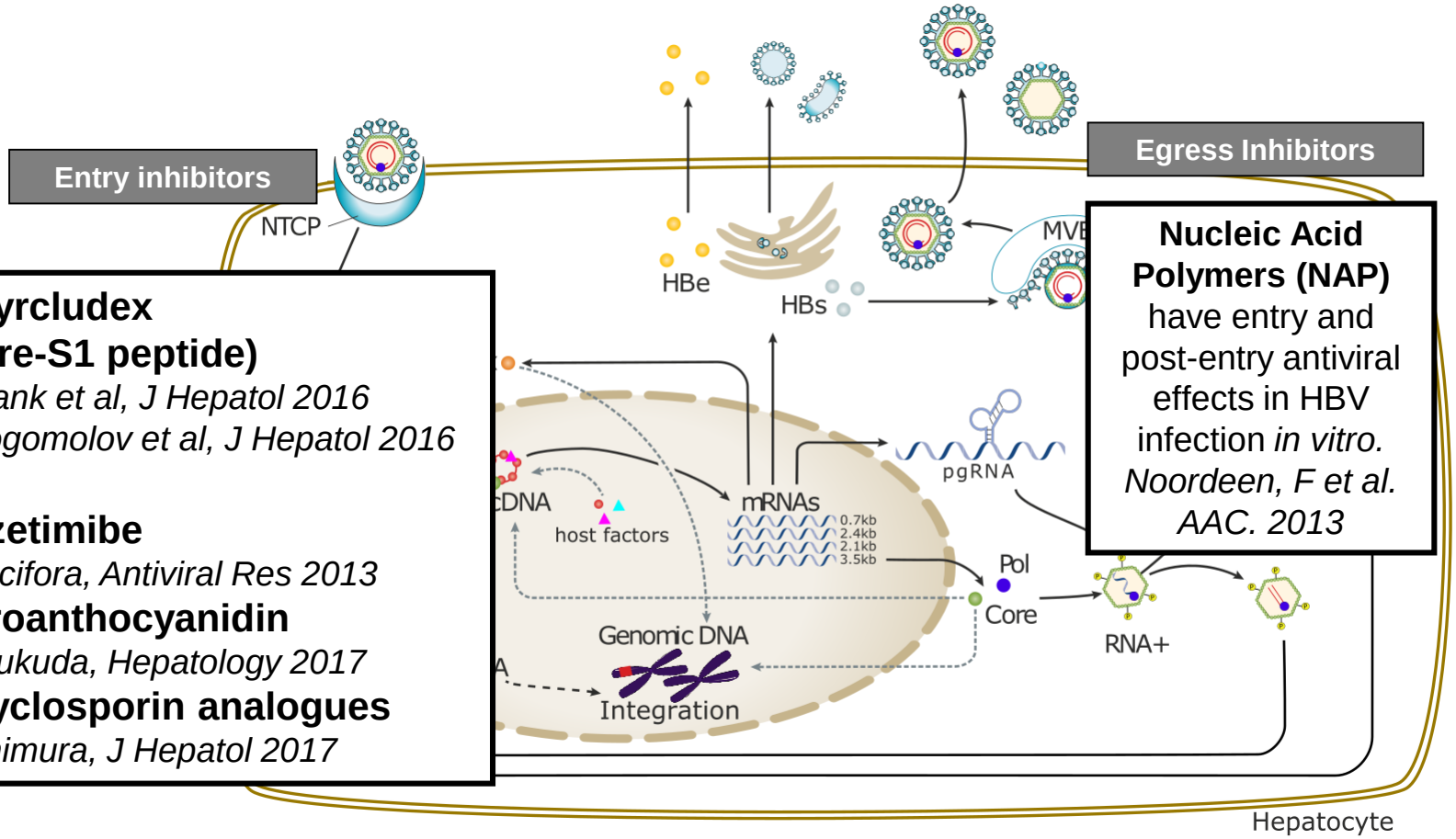
→no real « cure » of the infection

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

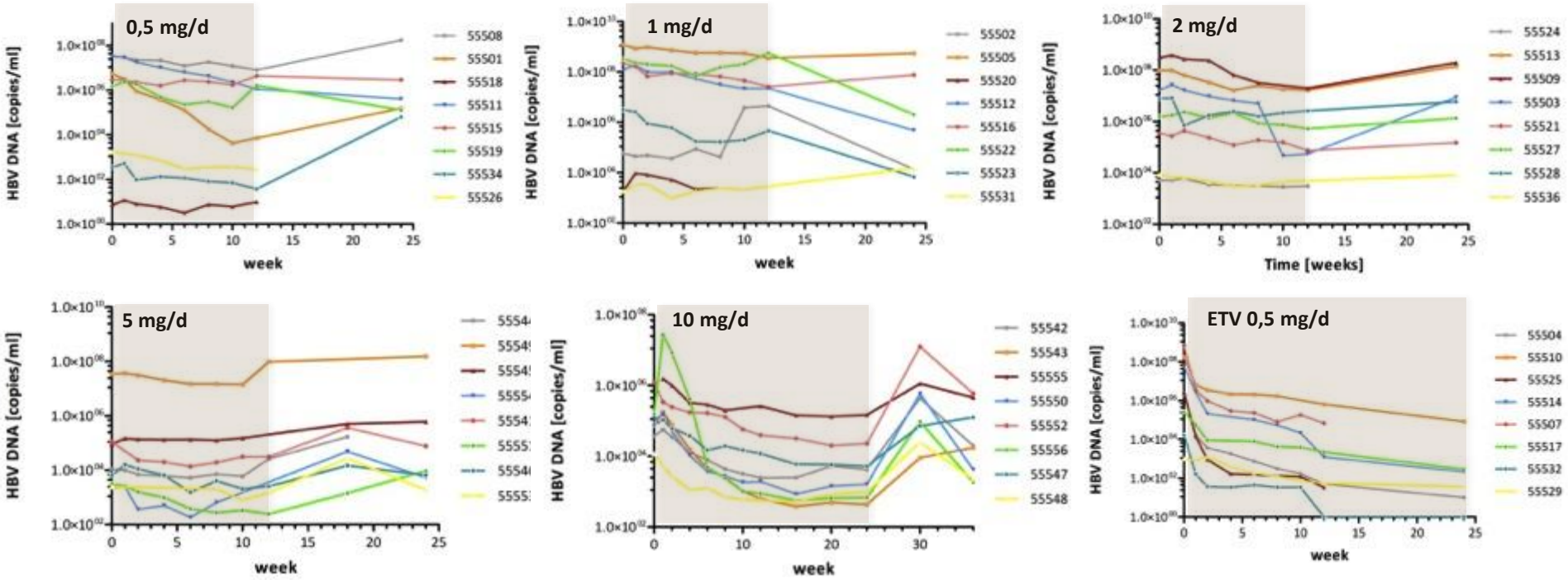
Proanthocyanidin
Tsukuda, Hepatology 2017

Cyclosporin analogues
Shimura, J Hepatol 2017

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

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

HBV Serum DNA-levels decline during Myrcludex B treatment



⇒ **HBV DNA levels decline significantly during Myrcludex B treatment in all groups.**

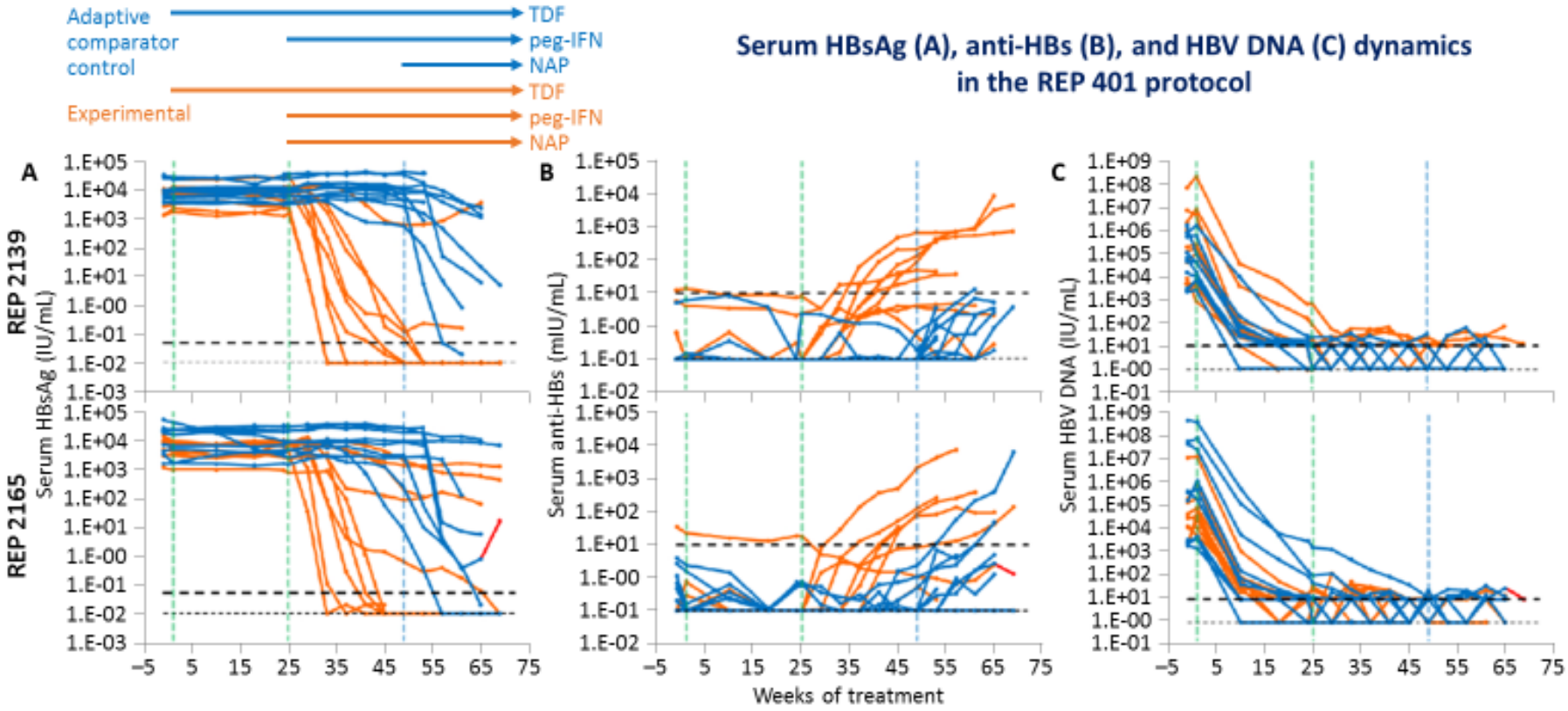
⇒ **Pronounced effects by > 1log in 6/8 patients were observed in the 10 mg dosing group.**

⇒ **7/40 showed > 1log HBV reduction in lower dosing groups.**

S Urban Heidelberg U & MyrGmbH, AASLD 2014

NAPs ± TDF and pegIFNa2a in treatment naïve HBeAg(-) CHB patients

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



Bazinet M, et al. EASL 2017, Amsterdam. #THU-154

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

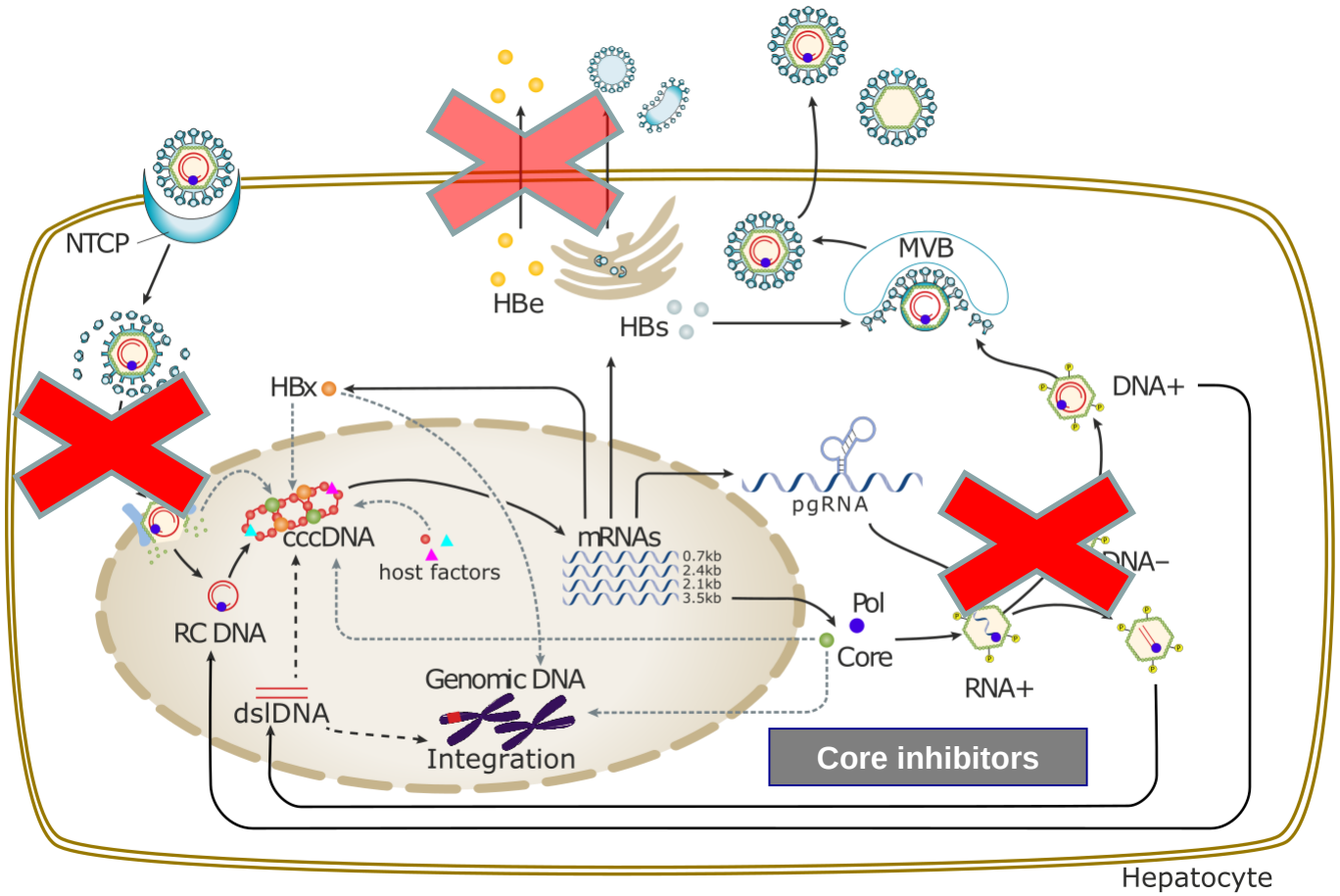
Mode of action still under investigation

IV infusion

ALT exacerbation

Long-term safety profile

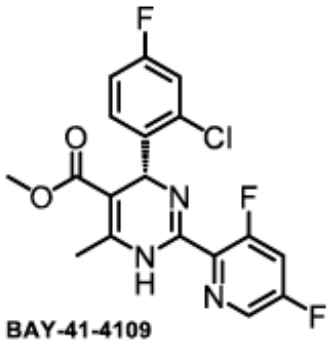
Capsid assembly modulators (CAMs)



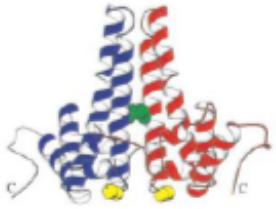
Inhibition of nucleocapsid entry into the nucleus
Inhibition of encapsidation
Inhibition of HBeAg secretion?

Different classes of CAMs

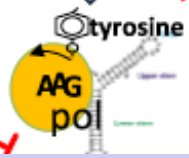
Heteroaryldipyrimidine derivatives (HAP)



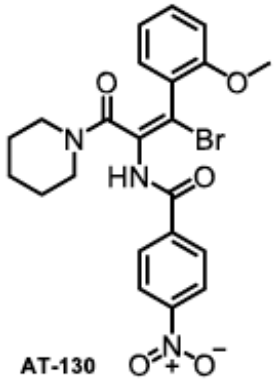
BAY-41-4109



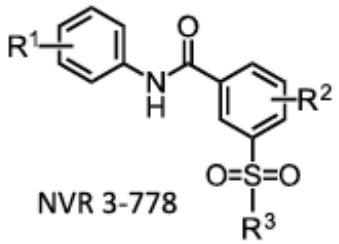
Core + pgRNA



Phenylpropenamide derivatives (A*T series)*

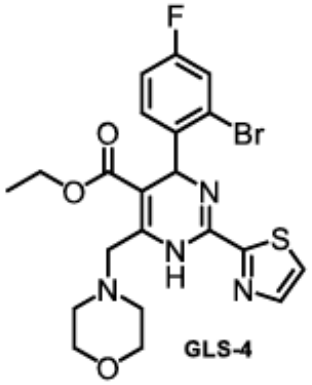


AT-130



NVR 3-778

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



GLS-4

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

Compounds in evaluation

BAY41-4109
HAP-12
AT-130
NVR3-778
JNJ-379
ABI-H0731
ABI-H0808
GLS4JHS
HAP_R01
SBA_R01
AB-423

scription
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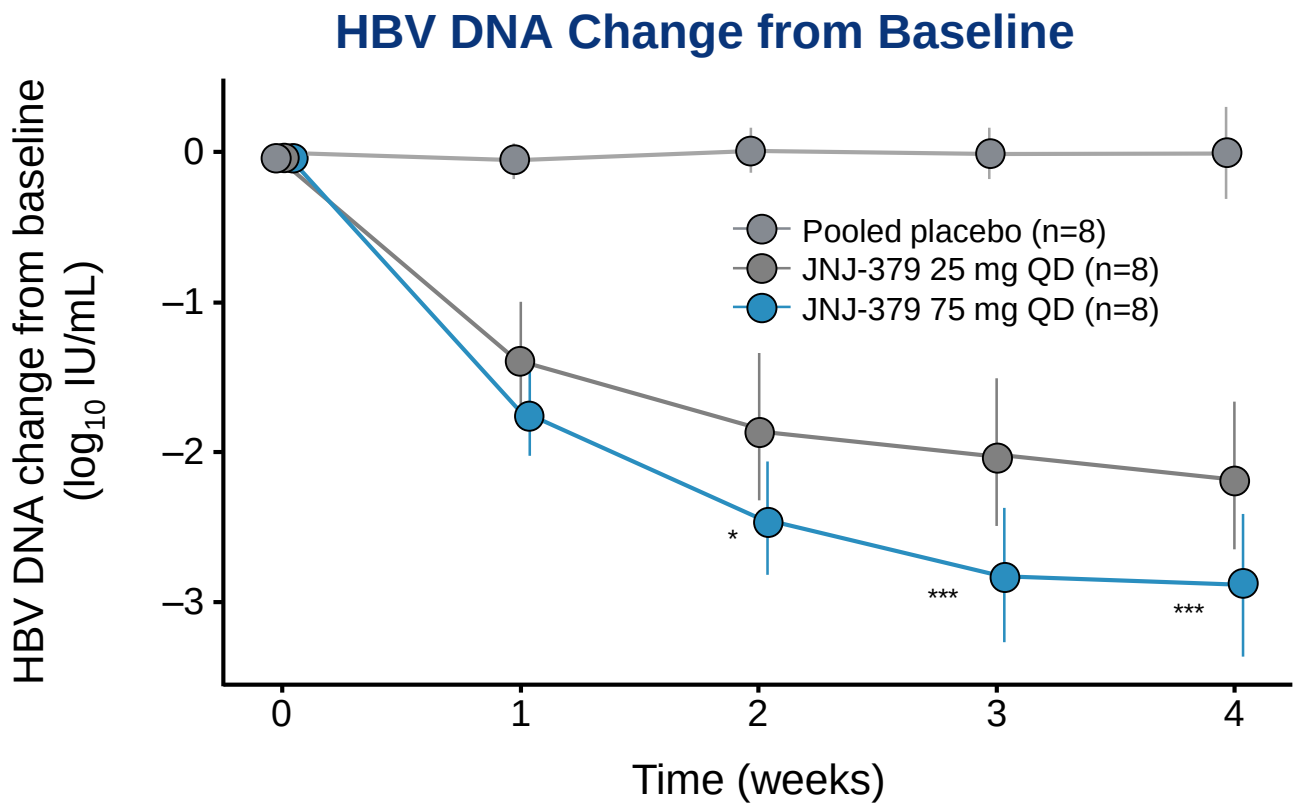
rcDNA-containing nucleocapsid

Phase 1b clinical trial of JNJ-379



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

Pros & challenges for CAMs

Decrease the pool of cccDNA on the long term

Opportunity to combine with NUCs, pegIFN and other DAAs

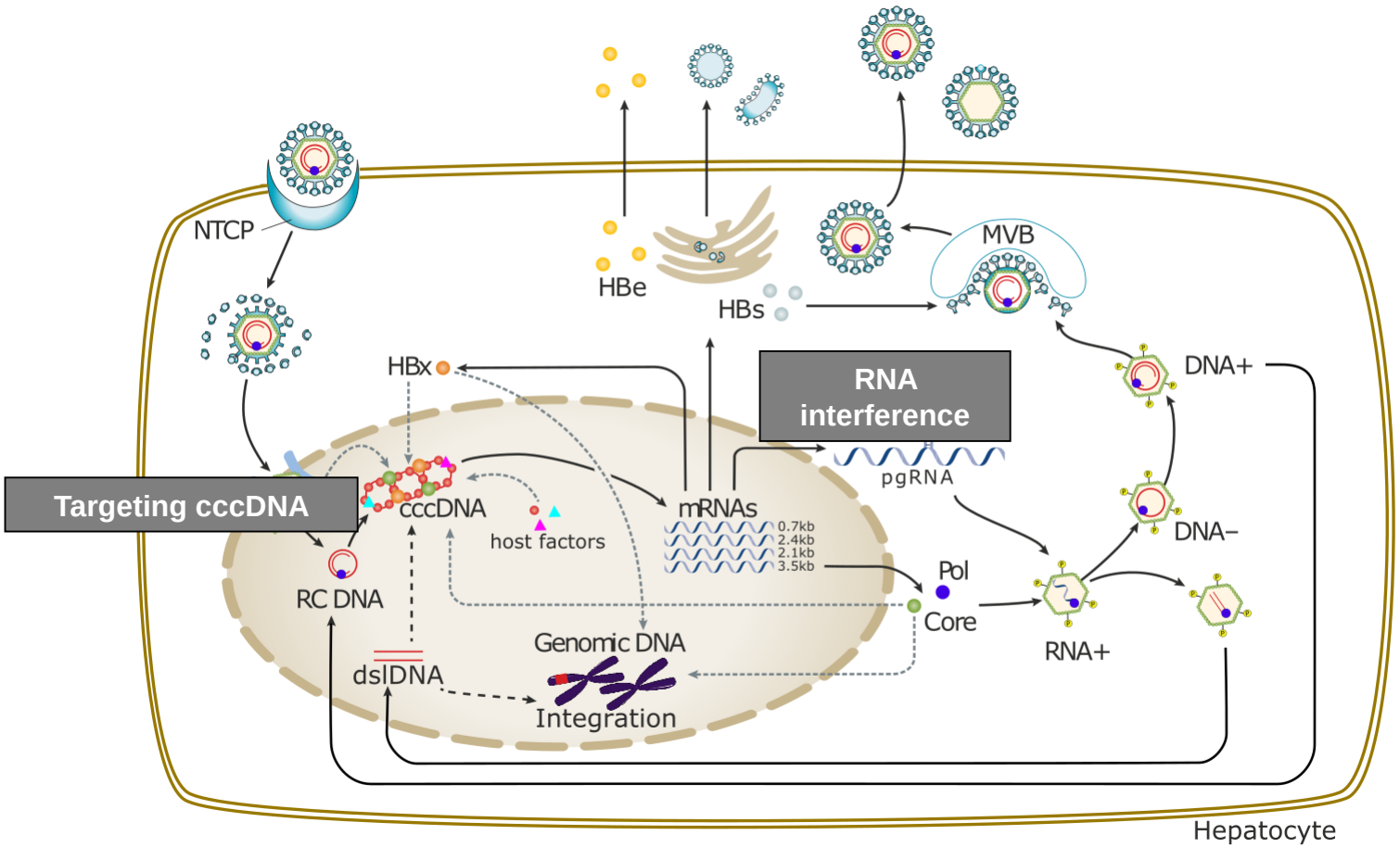
Oral administration

Long-term safety profile

Mainly suppressive

How to combine with other DAAs to be curative ?

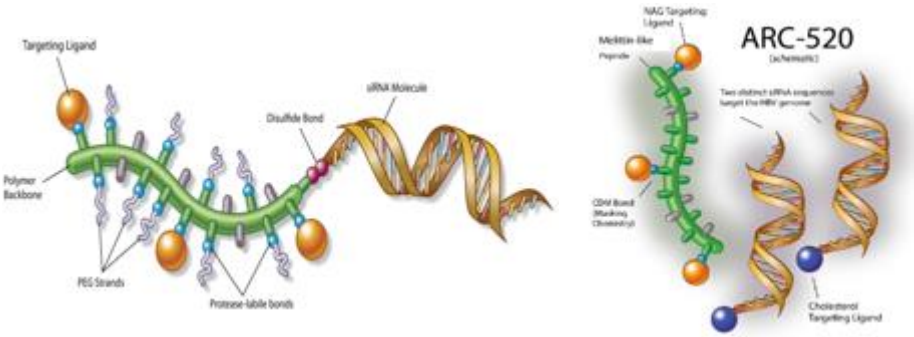
cccDNA targeting or functional silencing



siRNA Candidate Development

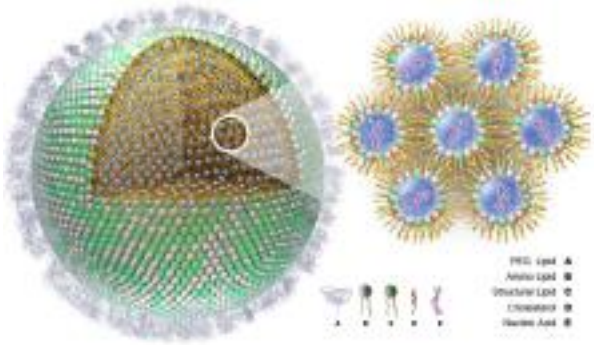
arrowhead pharmaceuticals

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



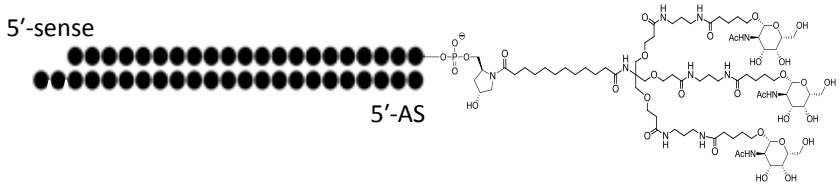
Journal of Controlled Release, Volume 209, 2015, 57–66

Arbutus BIOPHARMA
Aspiring to Cure Chronic Hepatitis B



Proprietary Lipid Nanoparticles

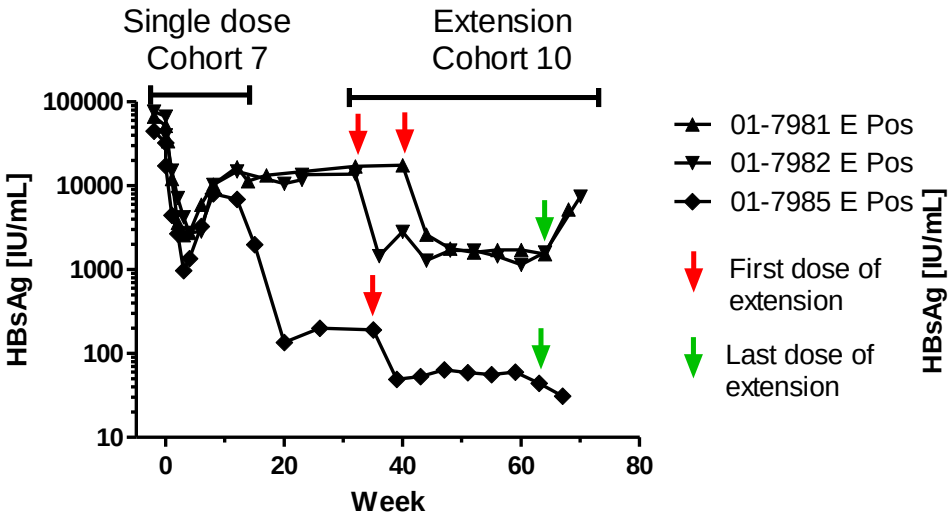
Alnylam PHARMACEUTICALS



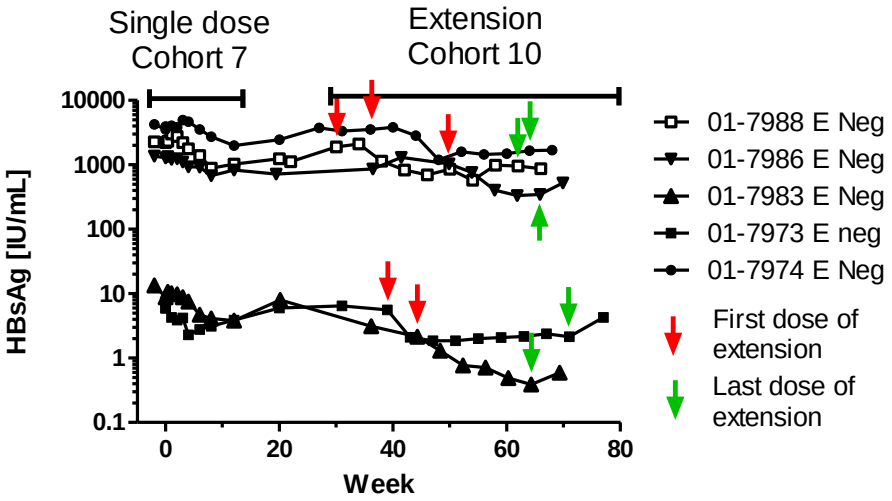
ESC-GalNAc-Conjugate for subcutaneous administration

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

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

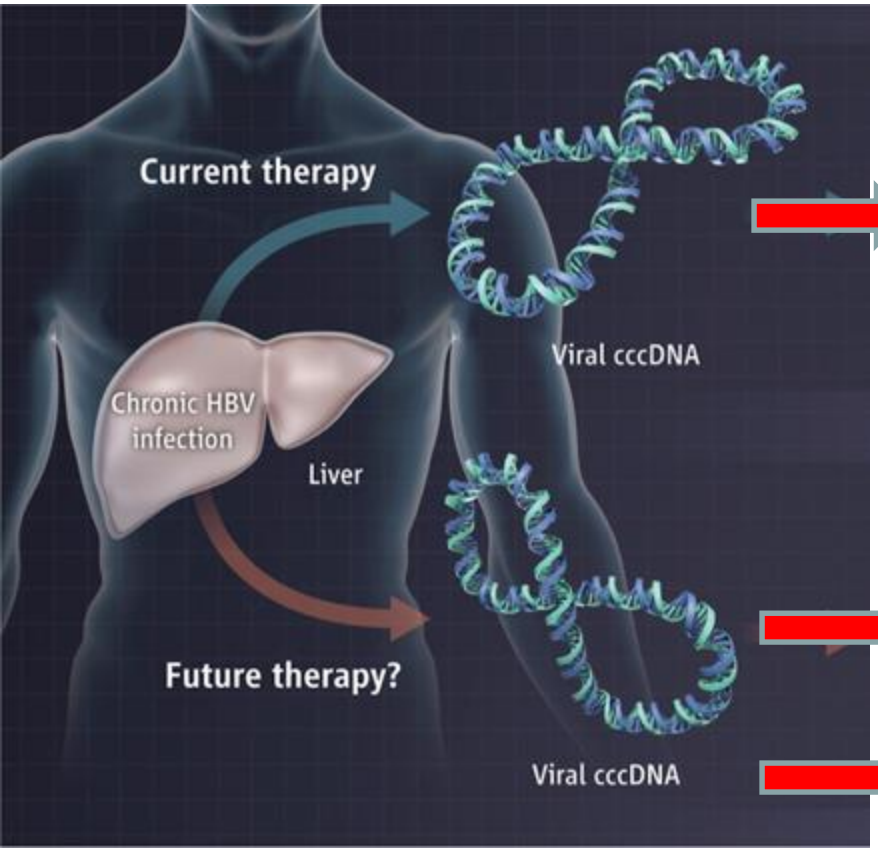
Mainly suppressive

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.

Direct cccDNA targeting



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

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

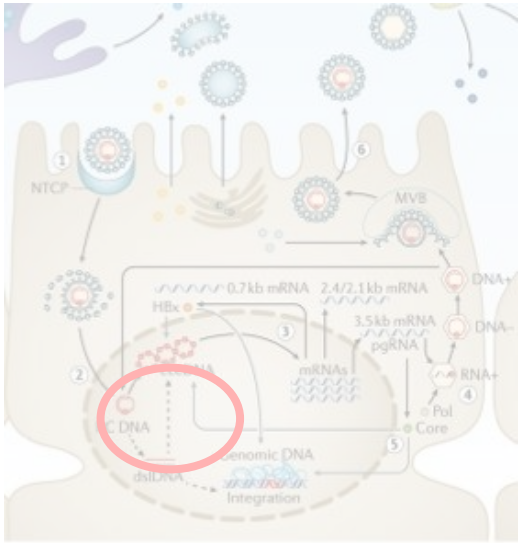
CRISPR/cas9 cleavage

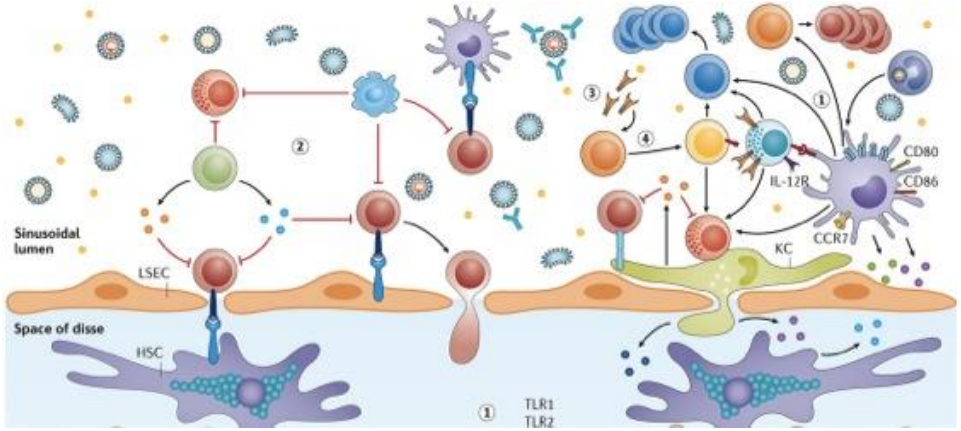
Seeger et al, Mol Ther Nucleic Acids. 2014 & 2016

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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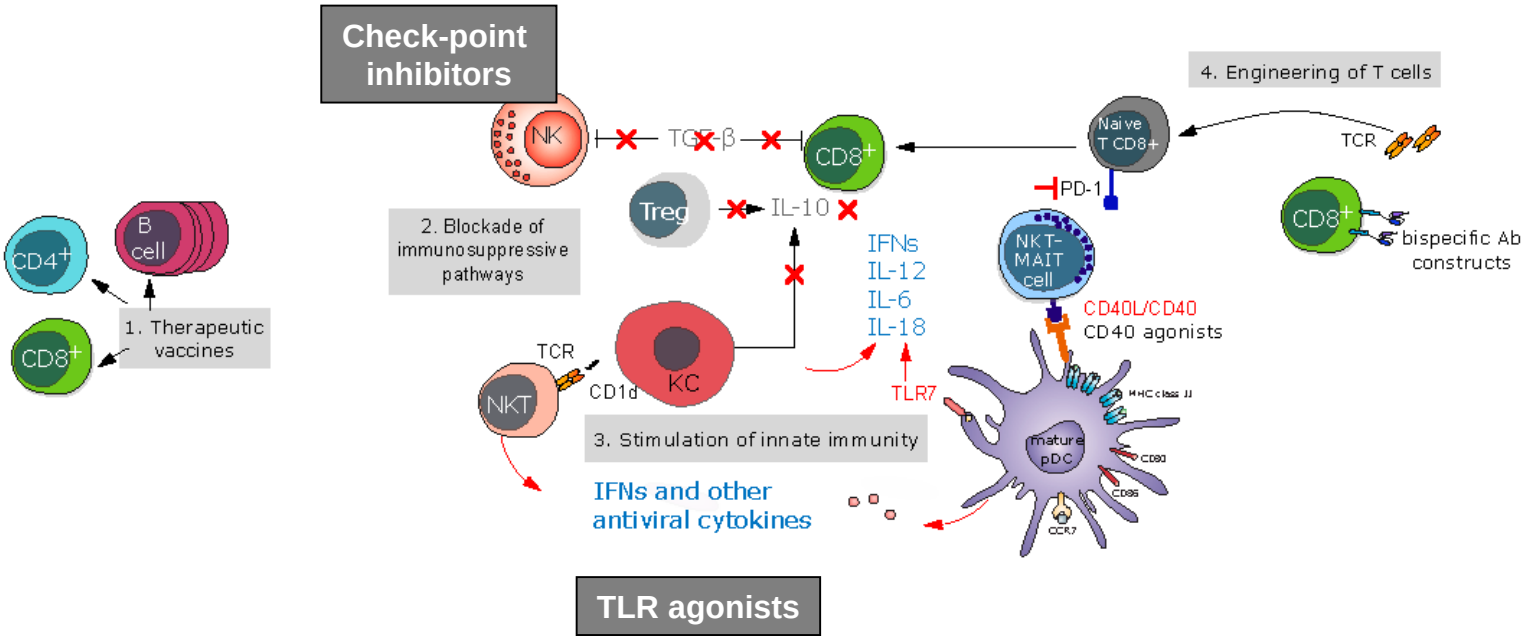
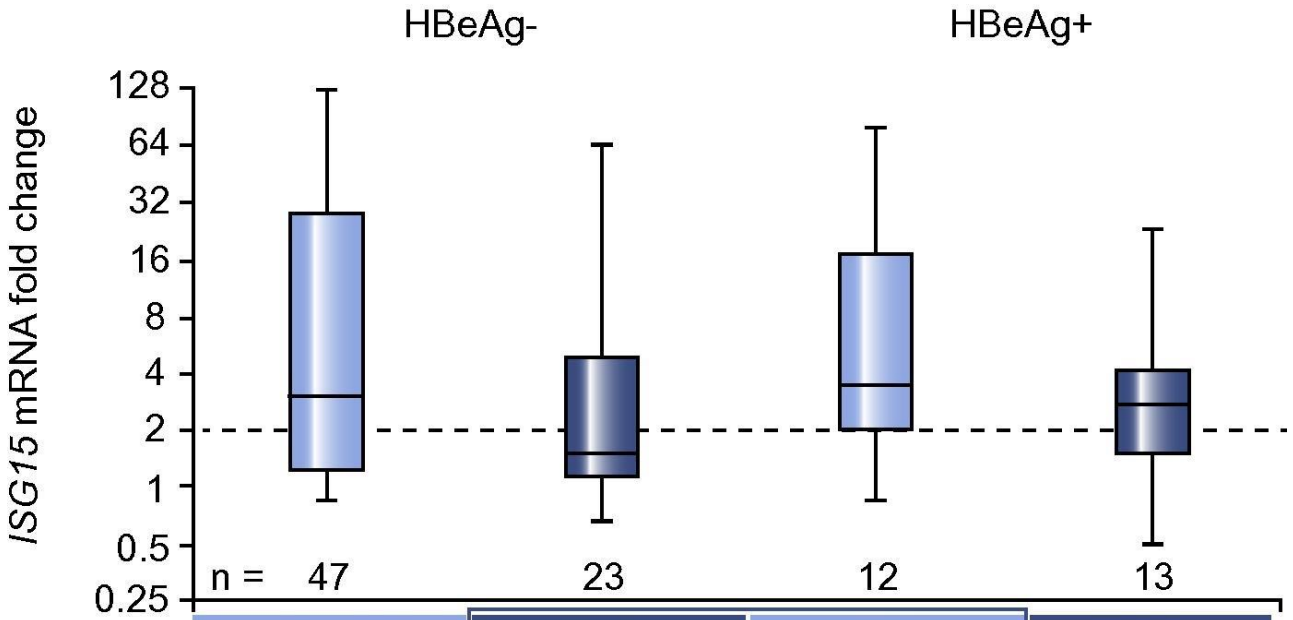
Immune Targets under investigation



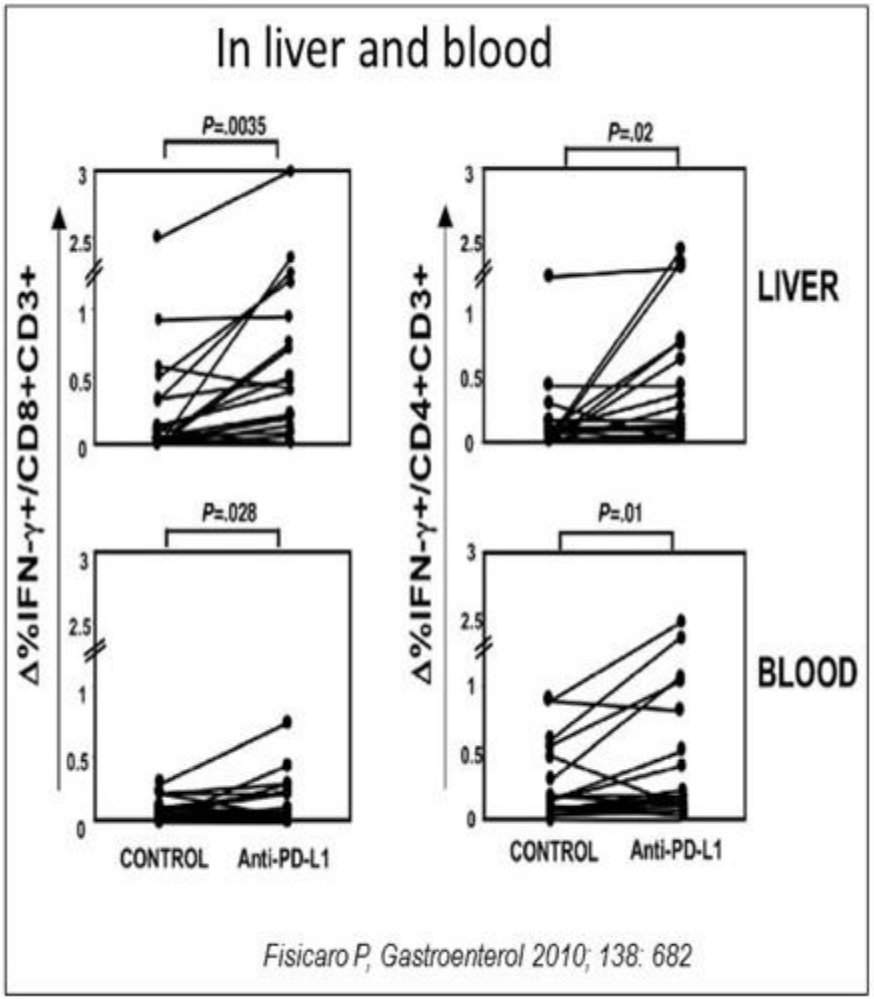
The Oral TLR-7 Agonist GS-9620 in CHB patients

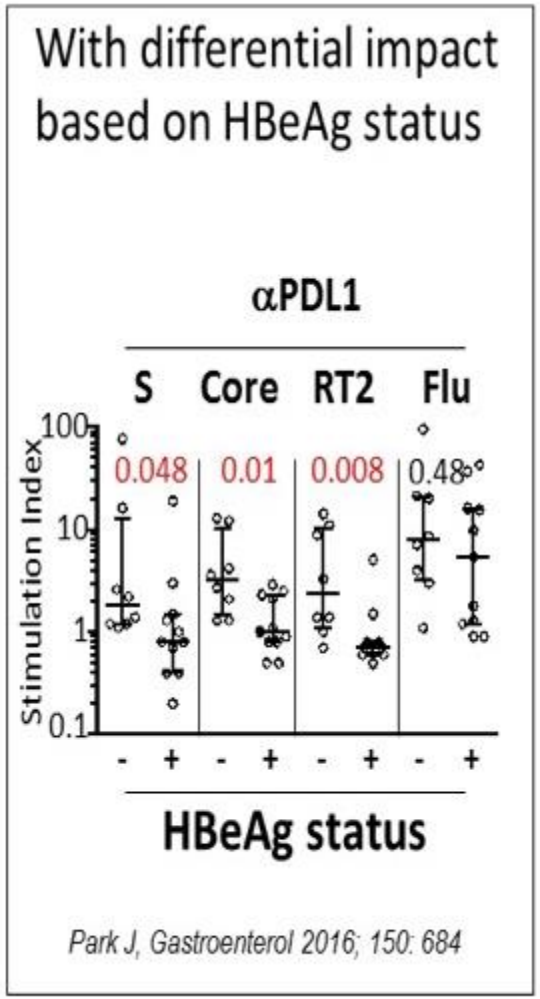


n (%)	HBsAg ≤5000 IU/ml	HBsAg >5000 IU/ml	HBsAg ≤5000 IU/ml	HBsAg >5000 IU/ml
Responders (ISG15 >2-fold change)	28 (60)	8 (35)	10 (83)	8 (62)
Non responders (ISG15 ≤2-fold change)	19 (40)	15 (65)	2 (17)	5 (38)

Gane et al, Journal of Hepatology, 2015

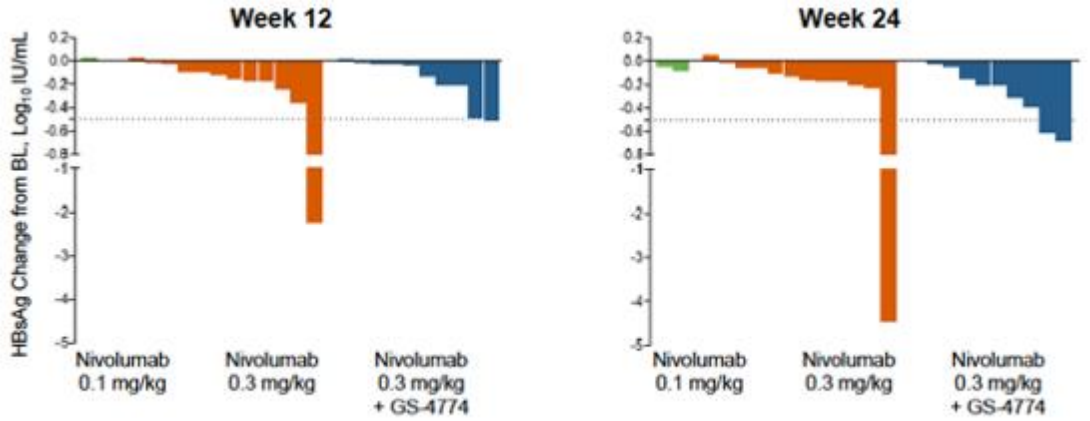
PD-1 blockade enhances HBV-specific Tcell response





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

Pros & challenges for immunemodulators

Induction of ISG

Restoration of adaptive immunity

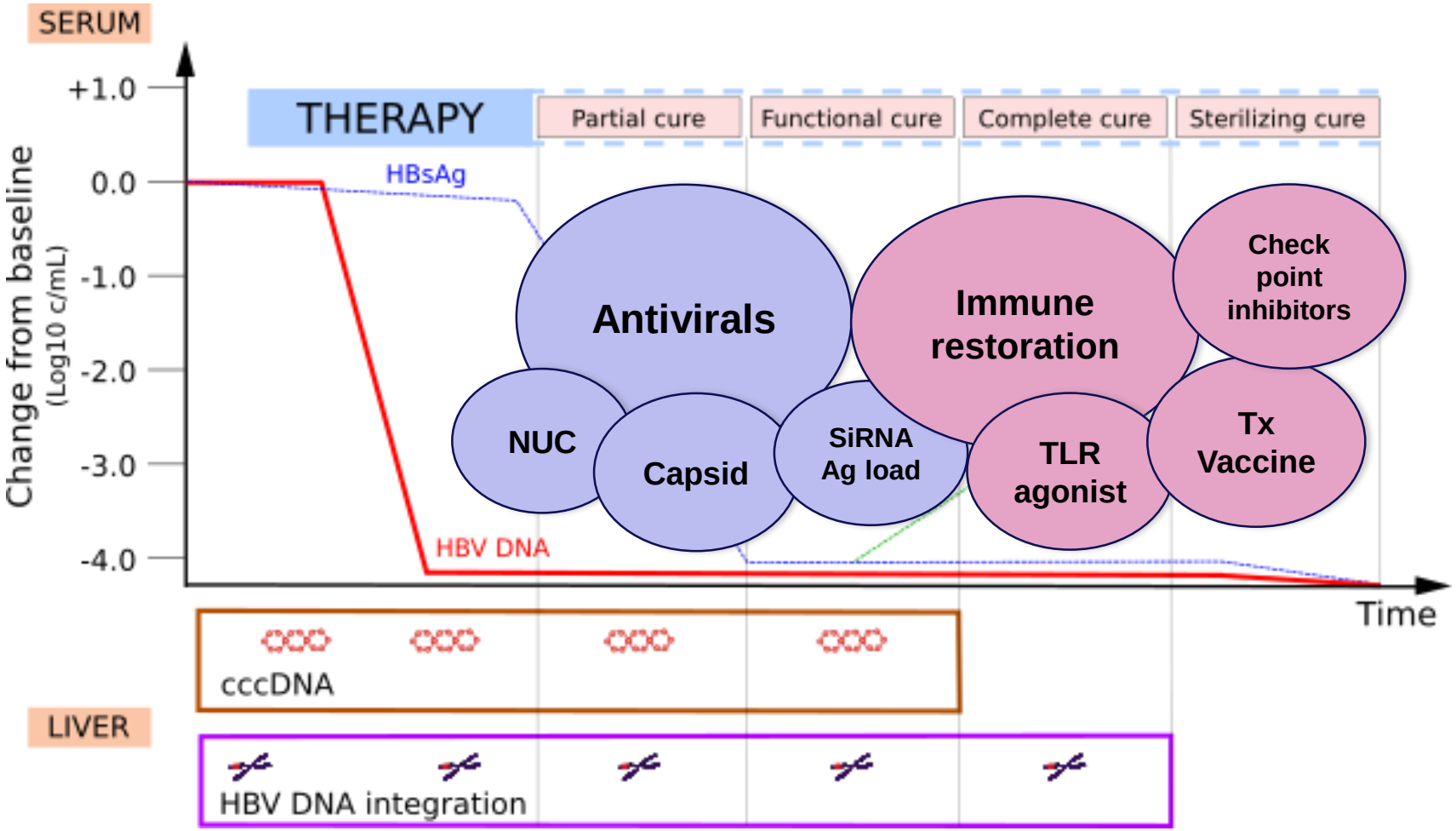
Possibility of combination with NUCs, pegIFN

Combination with other DAAs or other immunotherapeutics

Not effective in humans (vs animal models)

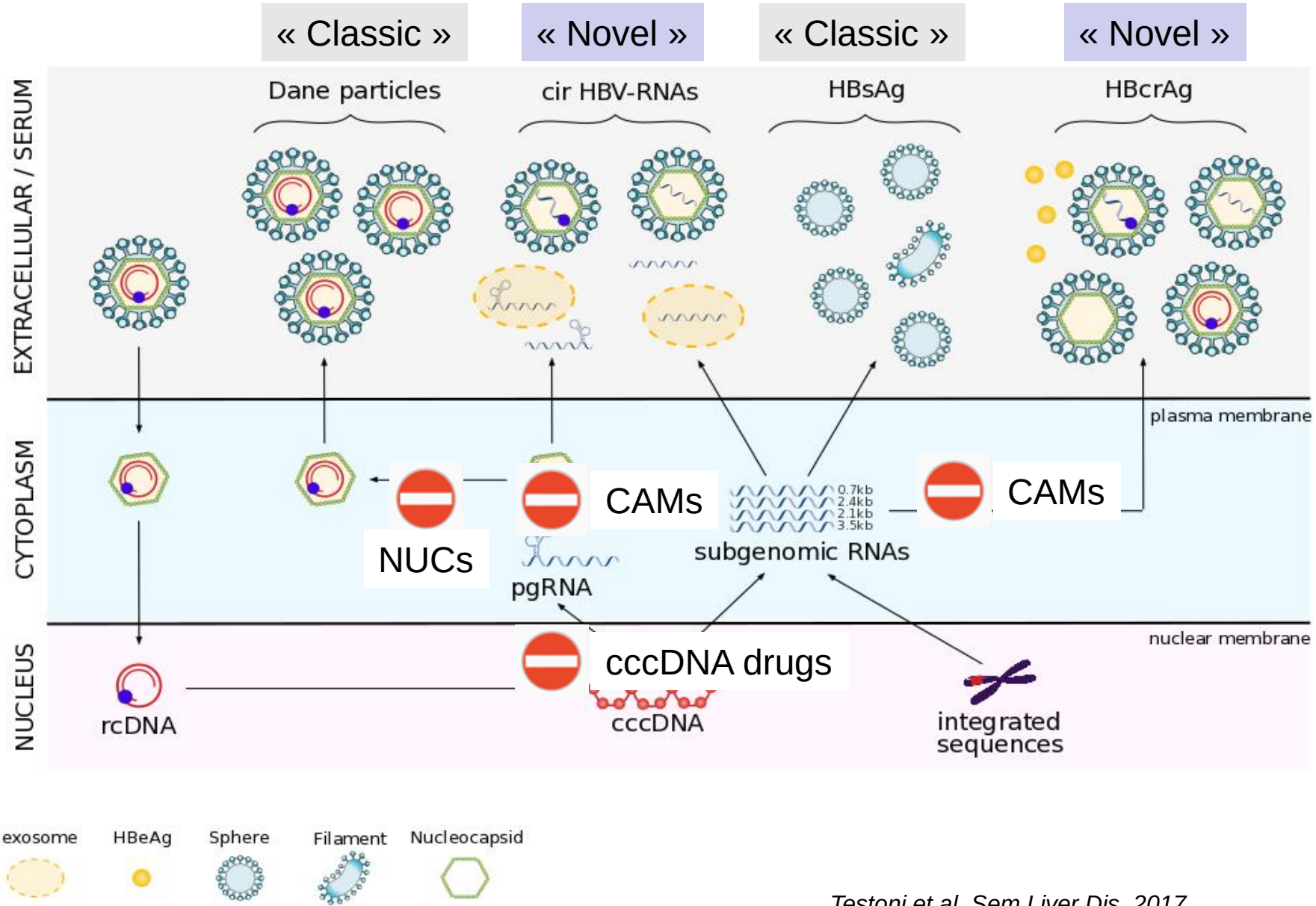
Side effects: potential for cytokine storm/autoimmunity

Conclusions



Combination therapies required
Direct cccDNA targeting remains a priority

Biomarkers in evaluation to assist drug development



Testoni et al, Sem Liver Dis, 2017

Open questions

HBsAg clearance is an **endpoint of therapy**

Decline in HBsAg levels may **restore the antiviral activity of exhausted T cells? Other factors?** *(Fisicaro et al, Nat Med 2017; Schurich, Cell Rep 2016)*

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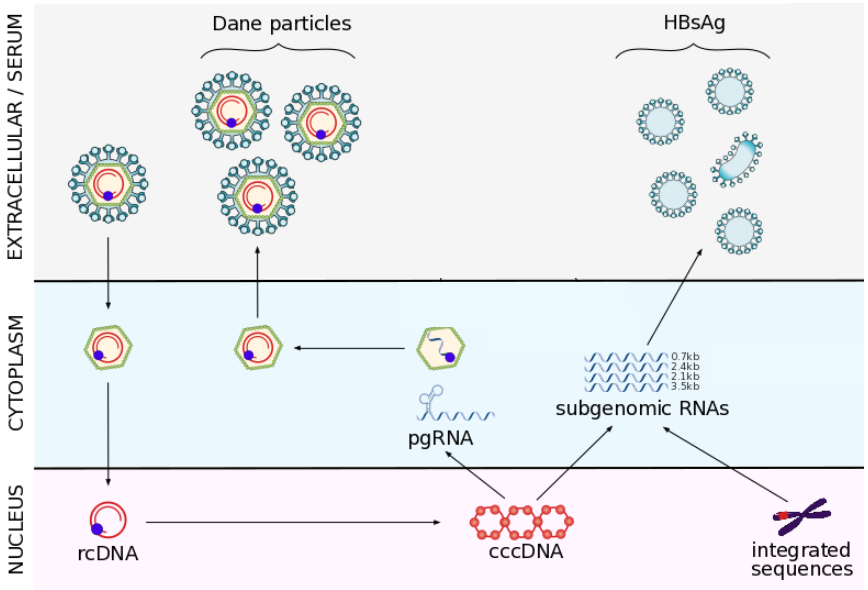
HBV integration?



In HBeAg(-) patients, HBsAg mainly comes from integrated sequences

Lebossé, Testoni et al J Hep 2017
Wooddell et al., Sci Transl Med 2017

HBV integration and clonal expansion of hepatocytes found in all CHB phases (major risk factor for HCC)

Mason et al, Gastroenterology 2016

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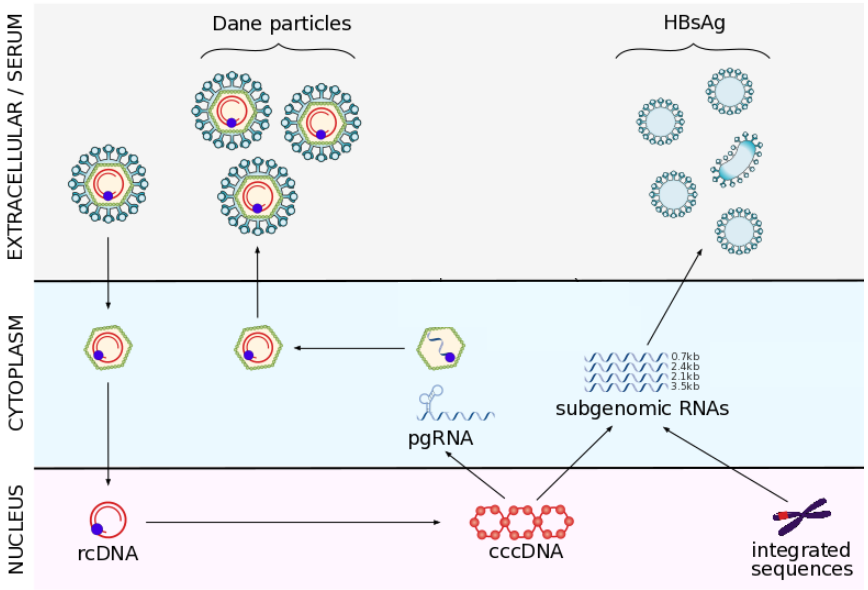

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Early treatment intervention?

Acknowledgements

Prof. Fabien Zoulim

Hepatology Unit
Hôspices Civils de Lyon

Viral pathogenesis team
CRCL-INSERM U1052

François Bailly
Samir Benmaklouf
Marie Ecochard
Kerstin Hartig
Fanny Lebossé
Massimo Levrero
Marianne Maynard
Sylvie Radenne
Caroline Scholtes
Christian Trépo

Barbara Testoni
Julie Lucifora
David Durantel
Bernd Stadelmeyer
Guada Martinez
Maelle Locatelli
Fleur Chapus
Aurore Inchauspé
Maud Michelet
Judith Fresquet

Marc Bonin
Thomas Lahlali
Caroline Charre
Romain Parent
Anna Salvetti
Birke Bartosch
Eve Pecheur
Boyan Grigorov
Christophe Combet

C. Caux, Lyon CRCL
FL. Cosset, Lyon CIRI
A. Boyd, Paris
F Carrat, Paris
C Ferrari, Parma
P Lampertico, Milan
A Craxi, Palermo
JP Quivy, Institut Curie
G Almouzni, Institut Curie
M Dandri, Hamburg
XX Zhang, Shanghai

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

ICE-HBV International Coalition to Eliminate HBV

Inserm Institut national de la santé et de la recherche médicale

Université de Lyon

DEVweCAN UNIVERSITE DE LYON

5th ANRS HBV CURE WORKSHOP

APRIL 10th, 2018 - PARIS

Chair: F. Zoulim

Faculty: H Janssen, P Revill, M Levrero, P Soussan, M Dandri, T Berg, A Balagopal, S Urban, R Schinazi, S Locarnini, M Bourliere, H Strick-Marchand, A Gehring, A Bertoletti, U Protzer

- **Website:** http://www.anrs.fr/