New Drug Research for Chronic Hepatitis B

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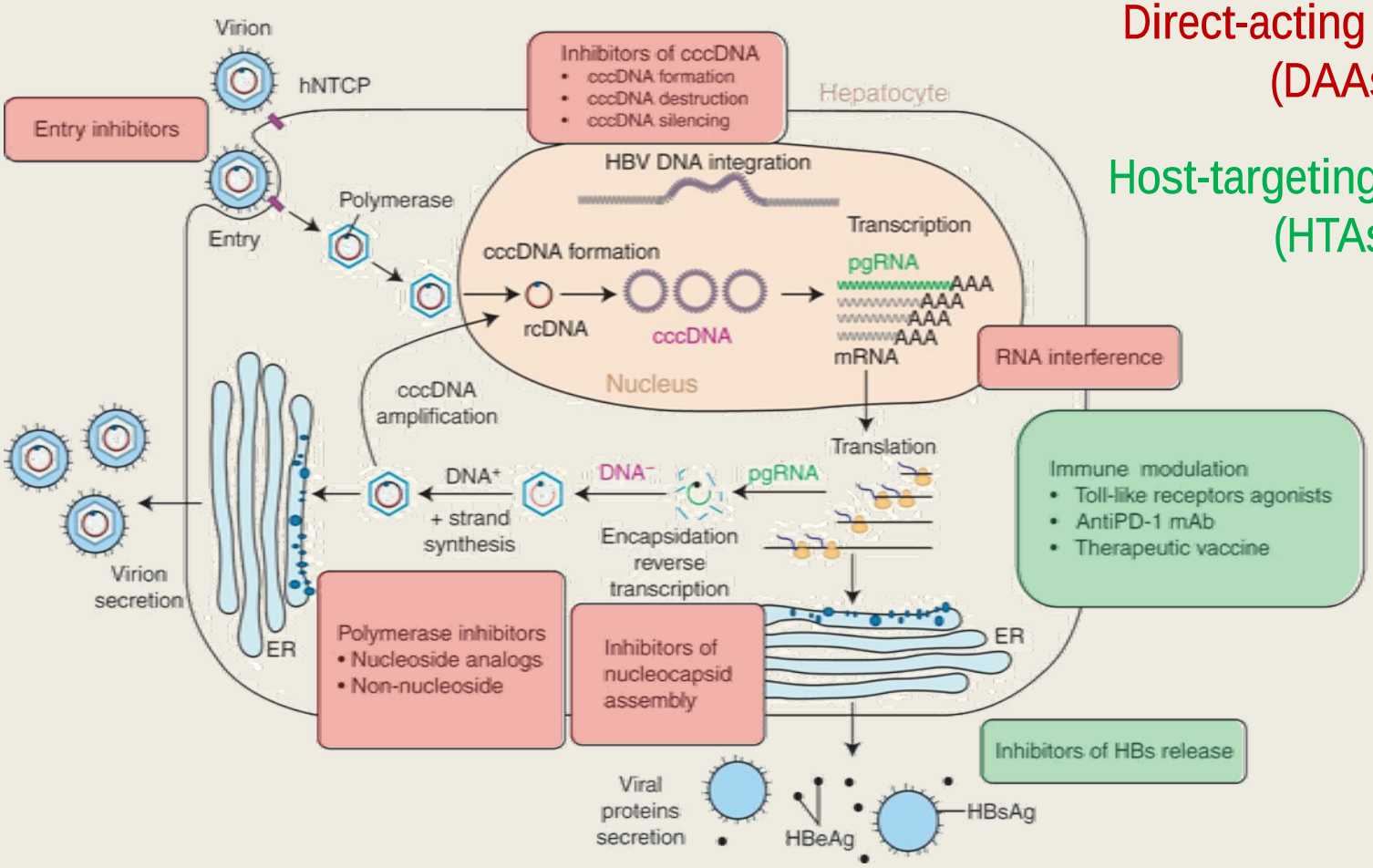
Overview

- Emerging Drugs against HBV
  - Direct-acting antiviral agents (DAAs)
  - Host-targeting antiviral agents (HTAs)
- Conclusions and Future perspectives

Emerging Drugs Against HBV

Hepatitis B virus (HBV) life cycle



Direct-acting antivirals (DAAs)

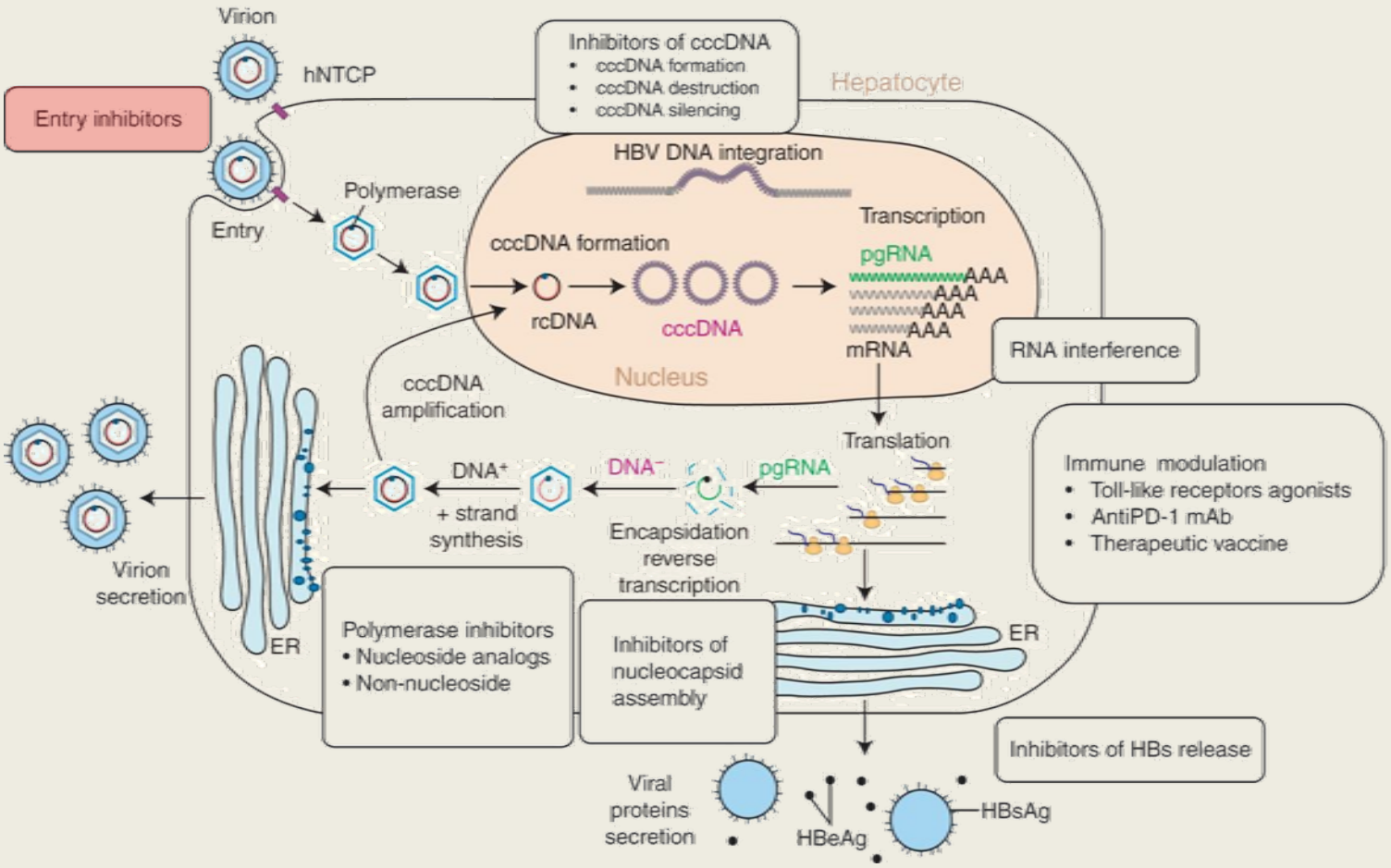
Host-targeting antivirals (HTAs)

Zeisel MB et al. Gut 2015;64:1314-25

Emerging Drugs Against HBV

- Direct-acting antiviral agents (DAAs)
- Host-targeting antiviral agents (HTAs)

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-25

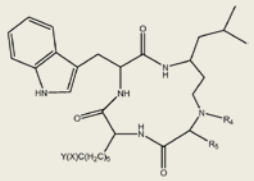
Direct-acting antiviral agents

- Entry inhibitors

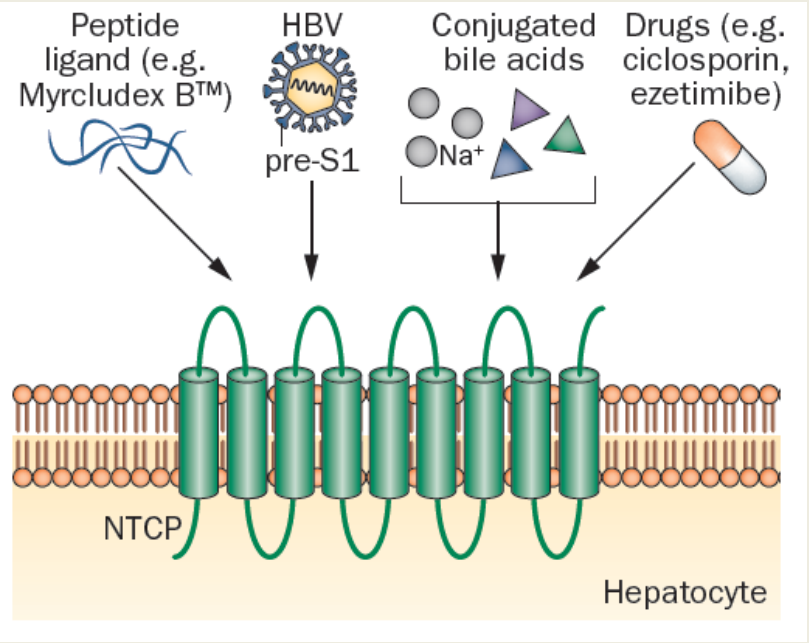
Drug name	Mechanism	Compound	Stage of Development
Myrcludex-B	Competitive inhibition of viral entry via NTCP	HBV preS1-derived lipopeptide	Phase II
Cyclosporin A	Competitive inhibition of viral entry via NTCP	Cyclic nonribosomal peptide	FDA approved, but not tested for HBV
Ezetimibe	Competitive inhibition of viral entry via NTCP	Ezetimibe	FDA approved, but not tested for HBV

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. 2015;64:1314-25

Entry inhibitor: Myrcludex-B



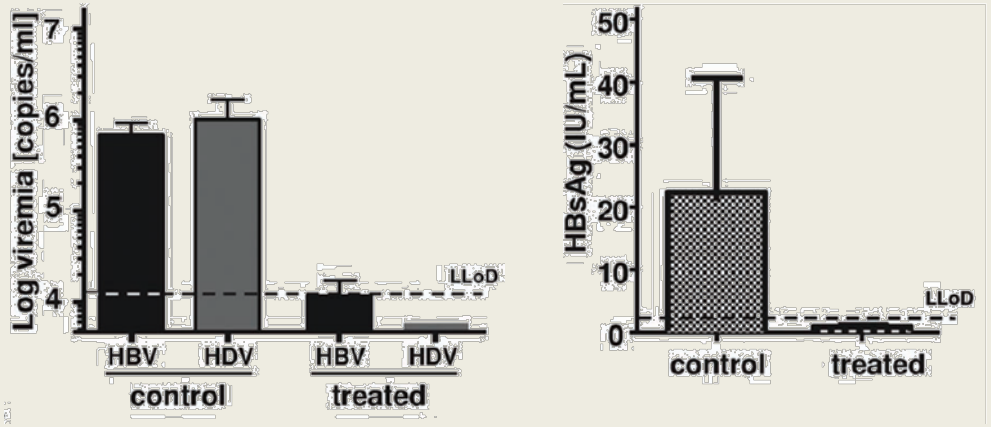
- Synthetic lipopeptide derived from pre-S1 domain of HBV envelope protein
- Specifically targets NTCP, the functional receptor for HBV

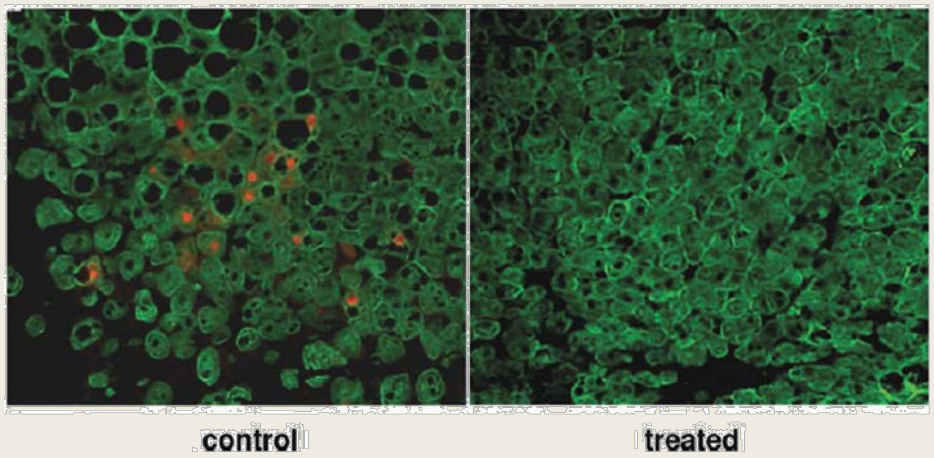


Yuen et al. Nat Rev Gastroenterol Hepatol 2015;12:70-72

Entry inhibitor: Myrcludex-B

- Pre-clinical results





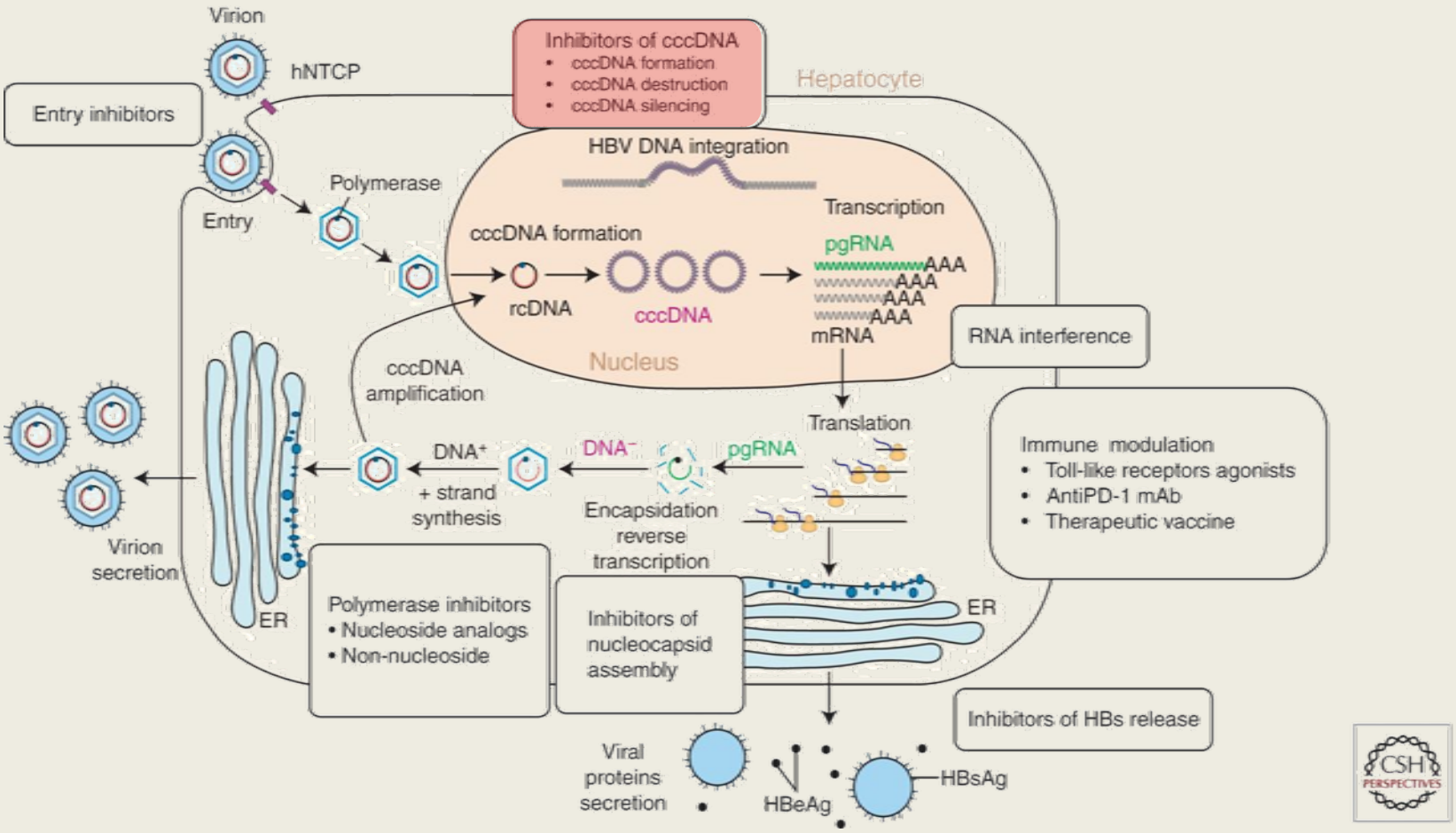
Lutgehetmann M et al. Hepatology 2012

Entry inhibitor: Myrcludex-B

- Phase IIa clinical trial
  - Safety, tolerability and efficacy of multiple doses of Myrcludex B (0.5mg, 1mg, 2mg, 5mg and 10mg Myrcludex-B SC QD) in comparison with the control group receiving standard therapy with NAs is recently completed
  - Results:
    - Very well tolerated; injection site dermatitis in 3/40 patients
    - HBV DNA decline > 1 $\log_{10}$ at Wk 12: 6/8 (75%) patients receiving 10 mg Myrcludex-B
    - ALT normalization: 22/40 (55%) patients
    - HBsAg levels: no significant changes

Urban S et al. AASLD 2014 (LB-20)

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

Direct-acting antiviral agents

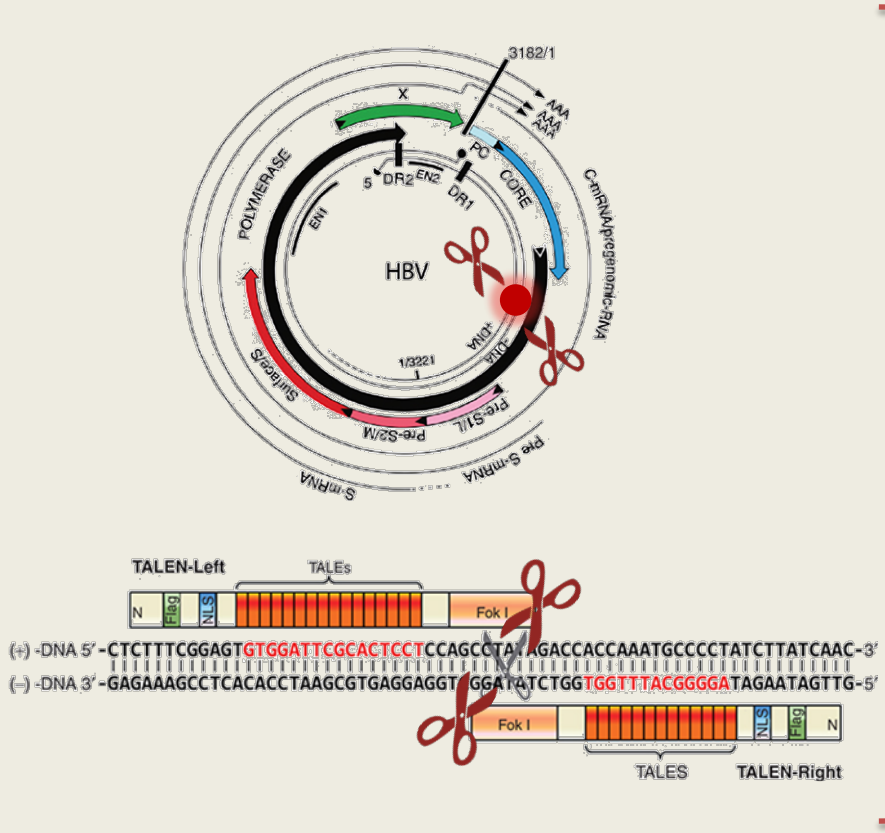
- Inhibitors of cccDNA

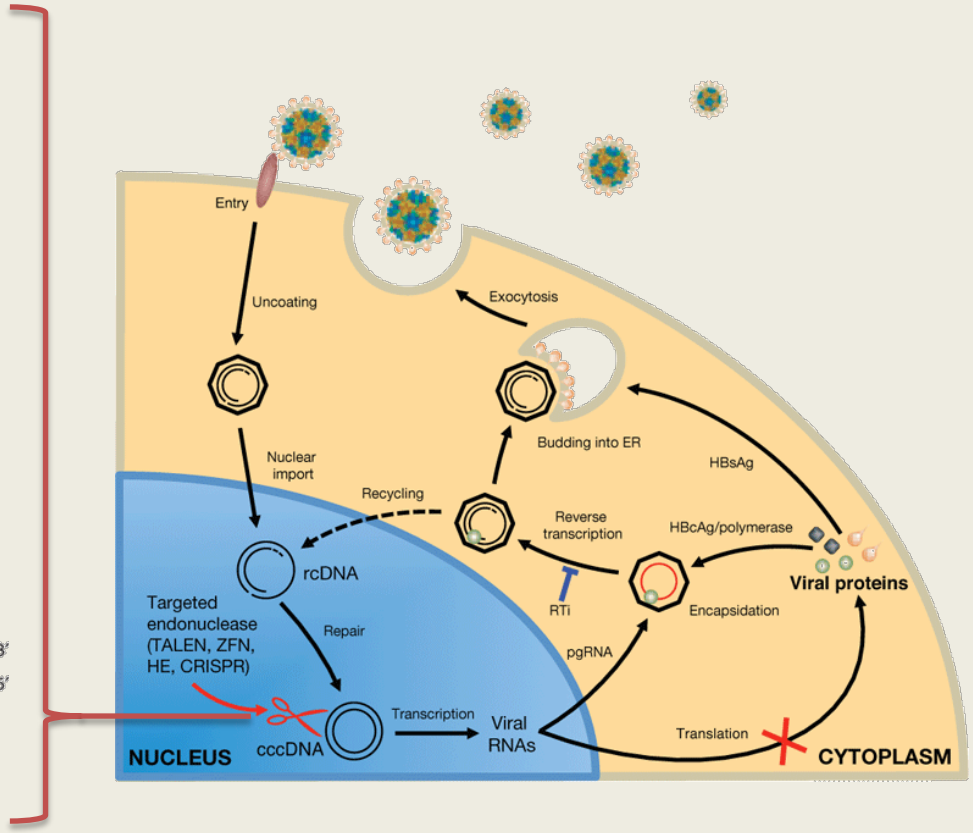
Drug name	Mechanism	Compound	Stage of Development
BSBI-25	cccDNA inhibitor	N/A	Preclinical
CCC-0975	Inhibition of rcDNA-cccDNA conversion	Disubstituted sulfonamide (DSS)	Preclinical
Zinc-finger nucleases	cccDNA-targeted endonuclease	Zinc-finger nucleases	Preclinical
TALENs	cccDNA-targeted endonuclease	Transcription activator-like effector nucleases	Preclinical
CRISPR/Cas9	cccDNA-targeted endonuclease	CRISPR/Cas9 system	Preclinical

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

cccDNA targeted endonucleases

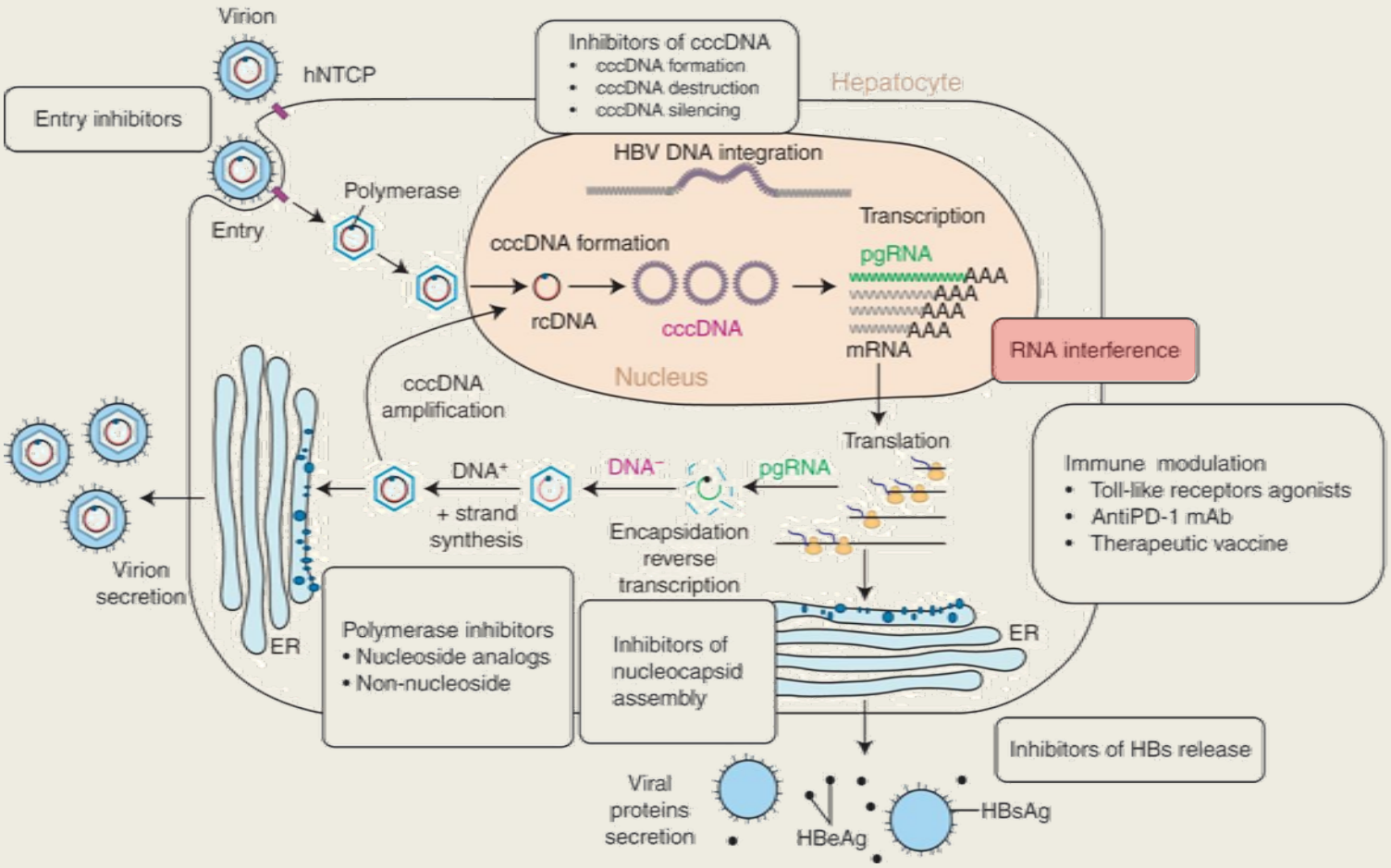
- cccDNA-targeting TALENs





Bloom K et al. Molecular Therapy 2013; Weber ND et al. Molecular Therapy 2013; Chen J et al. Molecular Therapy 2014; Seeger C et al. Molecular Therapy Nucleic Acids 2014

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

Direct-acting antiviral agents

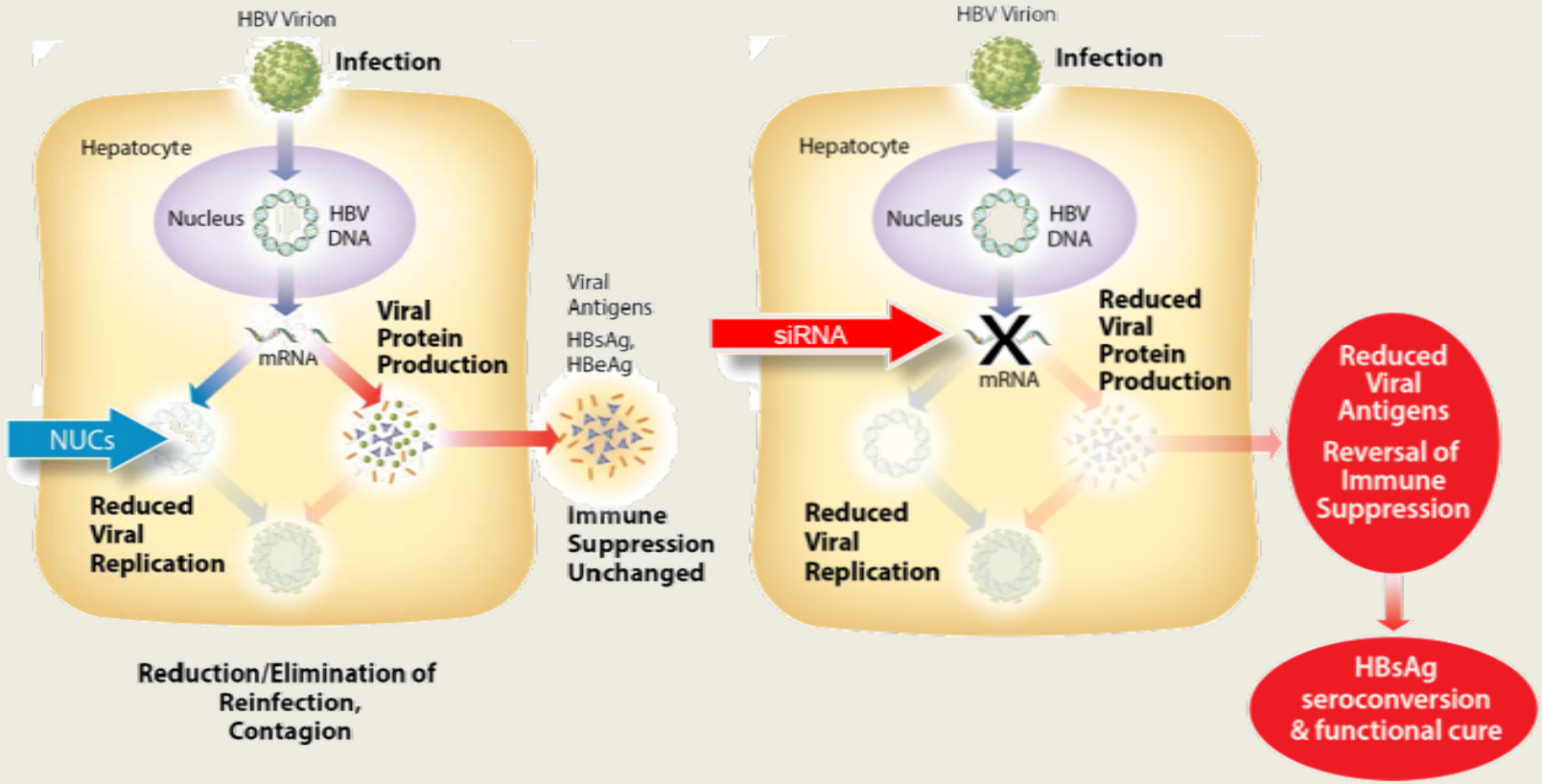
- RNA interference

Drug name	Target	Compound	Stage of Development
ARC-520	HBV mRNA	siRNA	Phase II / III
TKM-HBV	HBV mRNA	siRNA	Phase I
ISIS-HBVRx	HBV mRNA	Anti-sense RNA	Phase I
dd-RNAi compound	HBV mRNA (Pol)	shRNA	Preclinical
ALN-HBV	HBV mRNA	siRNA - LNP	Preclinical

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

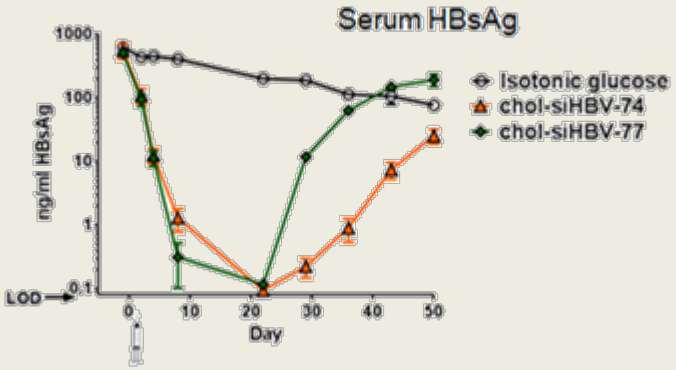
HBV mRNA-targeting siRNA: ARC-520

- siRNAs in ARC-520 intervene at the mRNA level

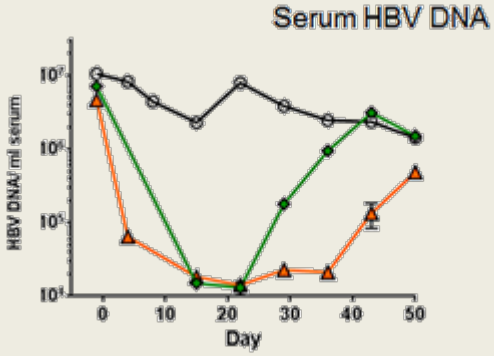


HBV mRNA-targeting siRNA: ARC-520

- Pre-clinical results: mouse model of HBV infection
  - Decreased HBsAg
    - 3-4 log reduction with the most potent chol-siHBVs
    - > 2 log_{10} reduction for 1 month



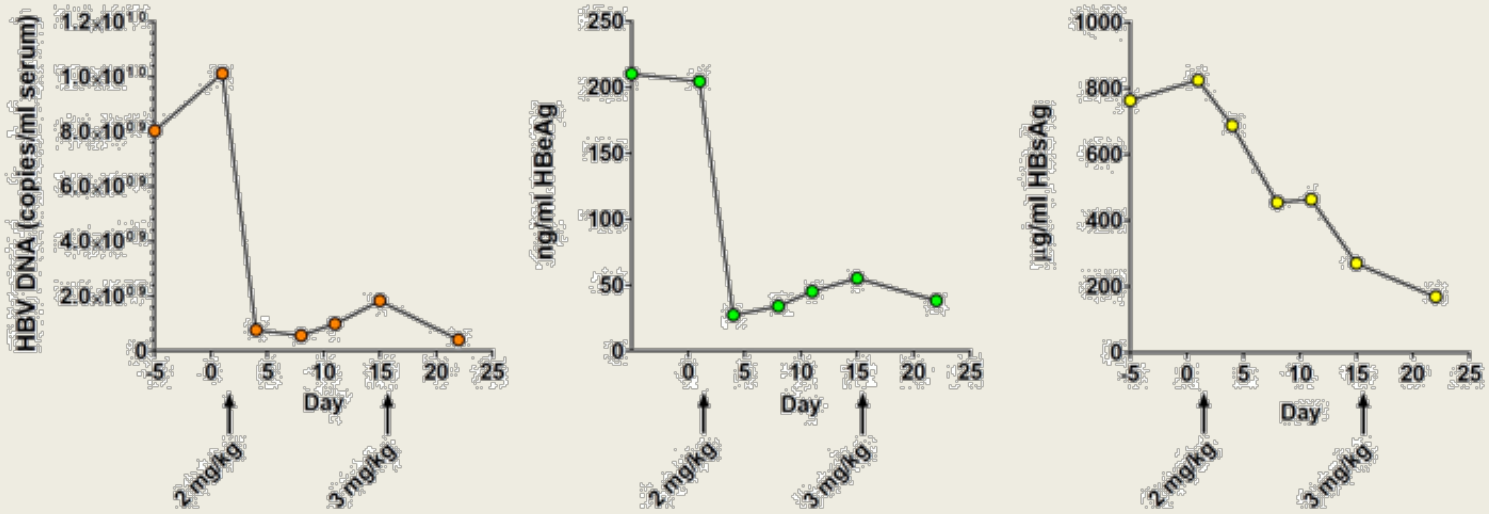
  - Decreased HBV DNA
    - approximately 3 log_{10} reduction for 1 month



Wooddell CI et al. Molecular Therapy 2013

HBV mRNA-targeting siRNA: ARC-520

- Pre-clinical results: HBV-infected chimpanzee
  - Decreased HBV DNA, HBeAg and HBsAg



Lanford R et al. AASLD 2013

HBV mRNA-targeting siRNA: ARC-520

- Phase IIa clinical trial (Heparc-2001)
  - A multicenter, randomized, double-blind, placebo-controlled, multi-dose study of ARC-520 (1-4 mg/kg) administered intravenously to patients with chronic immune active HBV infection maintained on entecavir or tenofovir therapy
  - Results:
    - When given as a single, IV administration, ARC-520 was well tolerated up to and including a dose of 3 mg/kg in CHB patients, who were also receiving entecavir, and up to 4 mg/kg in normal volunteers
    - A single injection of ARC-520 resulted in significant reduction in HBsAg for up to 43 days

Yuen MF et al. AASLD 2014

HBV mRNA-targeting siRNA: ARC-520

Figure 1. Log reduction in HBsAg and HBV core related antigen (HbcrAg) in cohorts 1-4

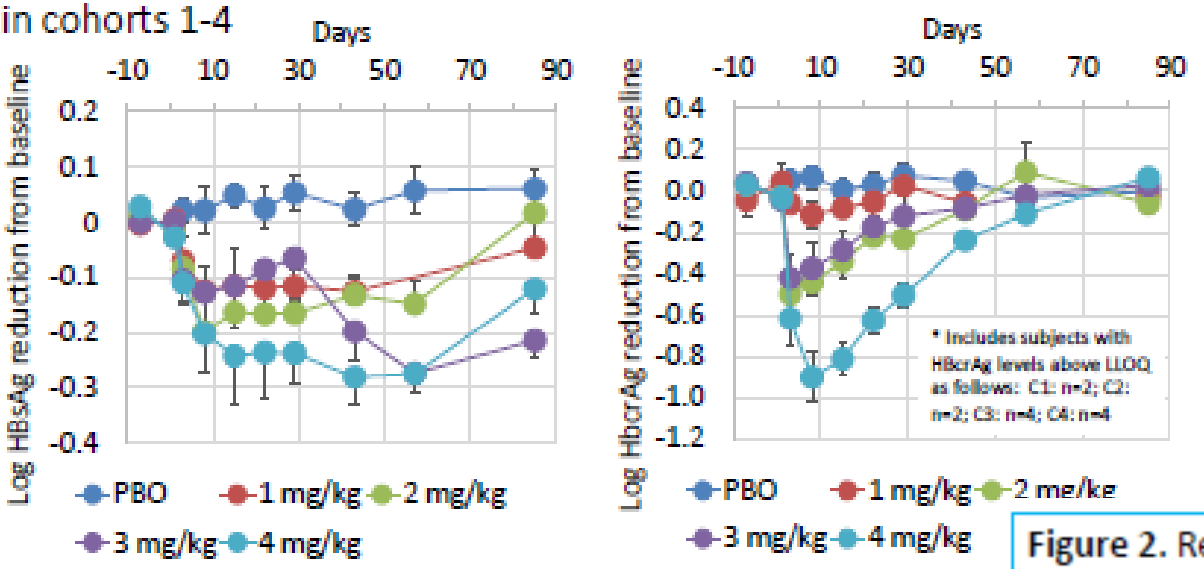
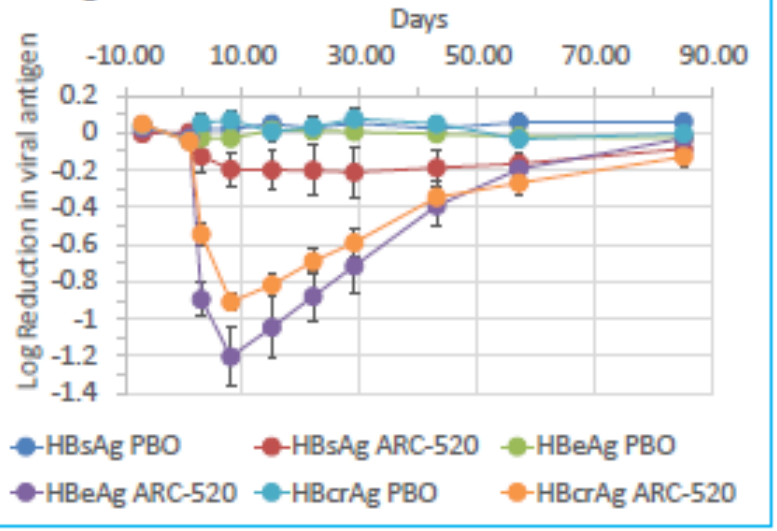
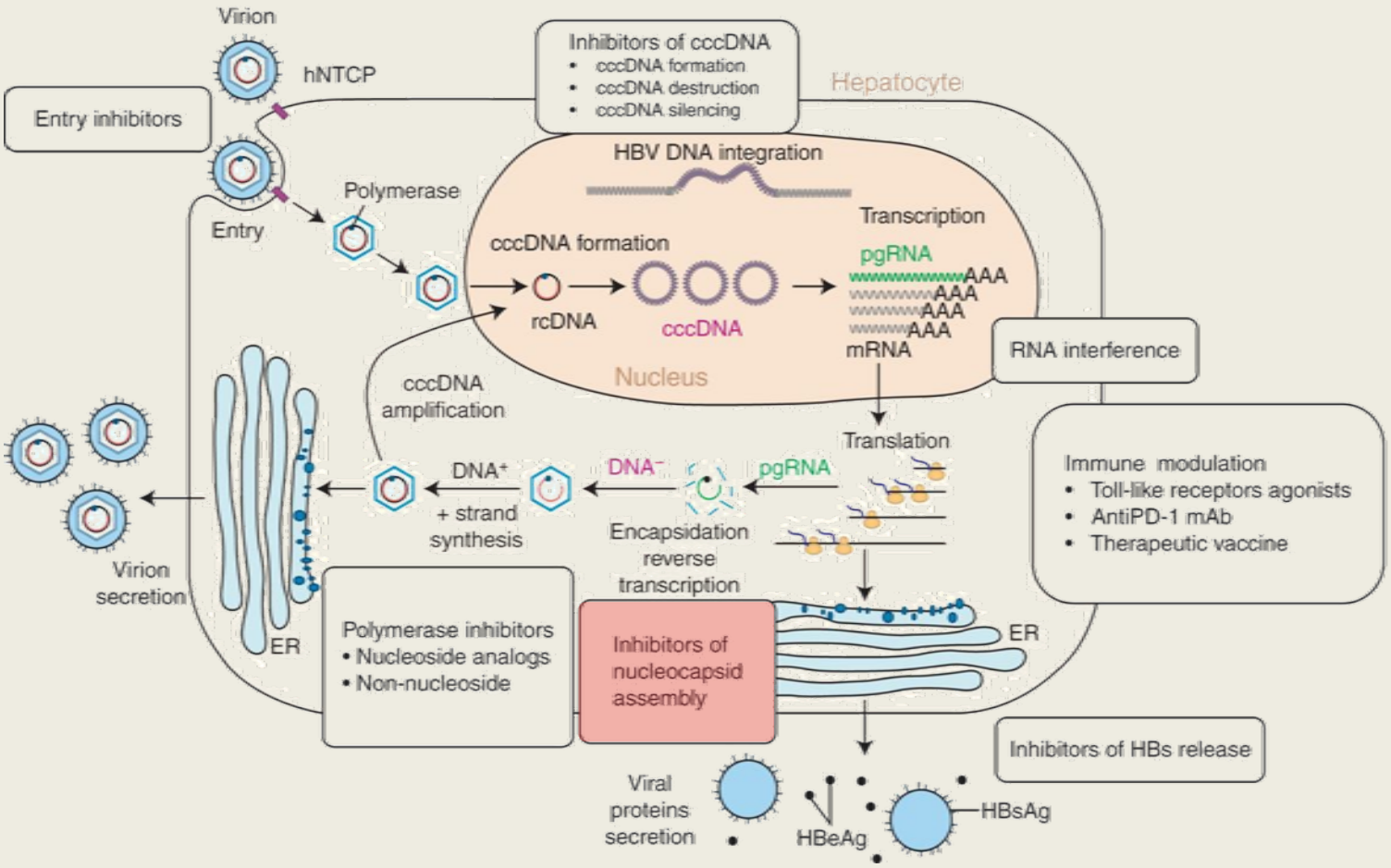


Figure 2. Reduction in HBsAg, HBeAg and HBcrAg in cohort 5.



Yuen MF et al. AASLD 2015

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

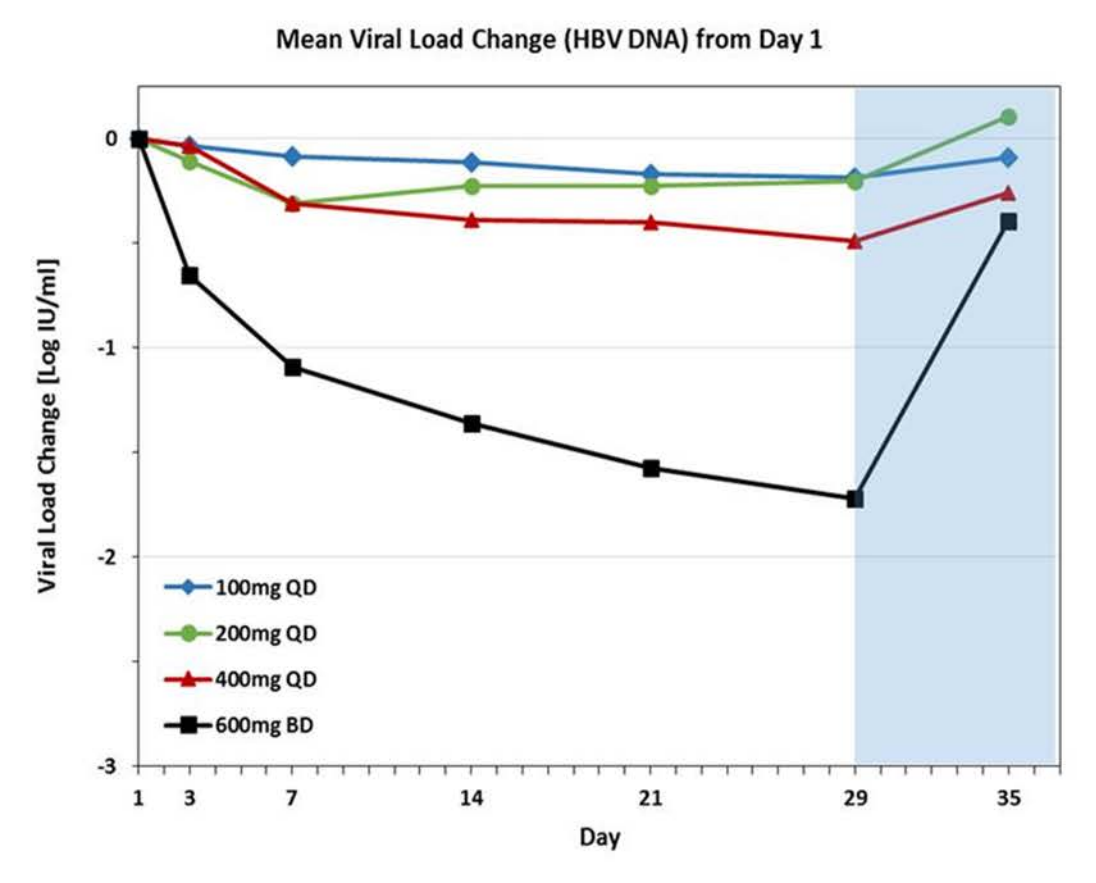
Direct-acting antiviral agents

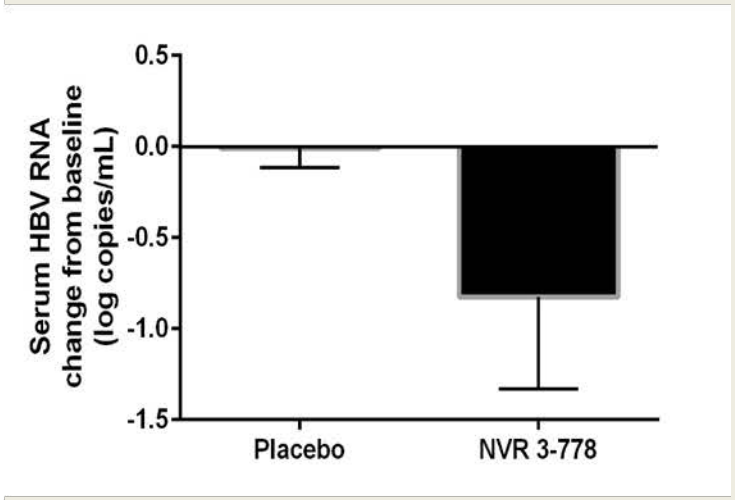
- Inhibitors of nucleocapsid assembly

Drug name	Target	Compound	Stage of Development
GLS4	Interfere with capsid formation/ stability	Heteroaryldihydropyrimidine (HAPs)	Phase II
Bay 41-4109	Viral nucleocapsid inhibitor	HAPs	Phase I
AT-130	Inhibition of HBV capsid assembly	Phenylpropenamide derivatives	Preclinical and early clinical phase
NVR-3-778 (NVR1221)	Inhibition of HBV capsid assembly	Small molecule	Phase Ib

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

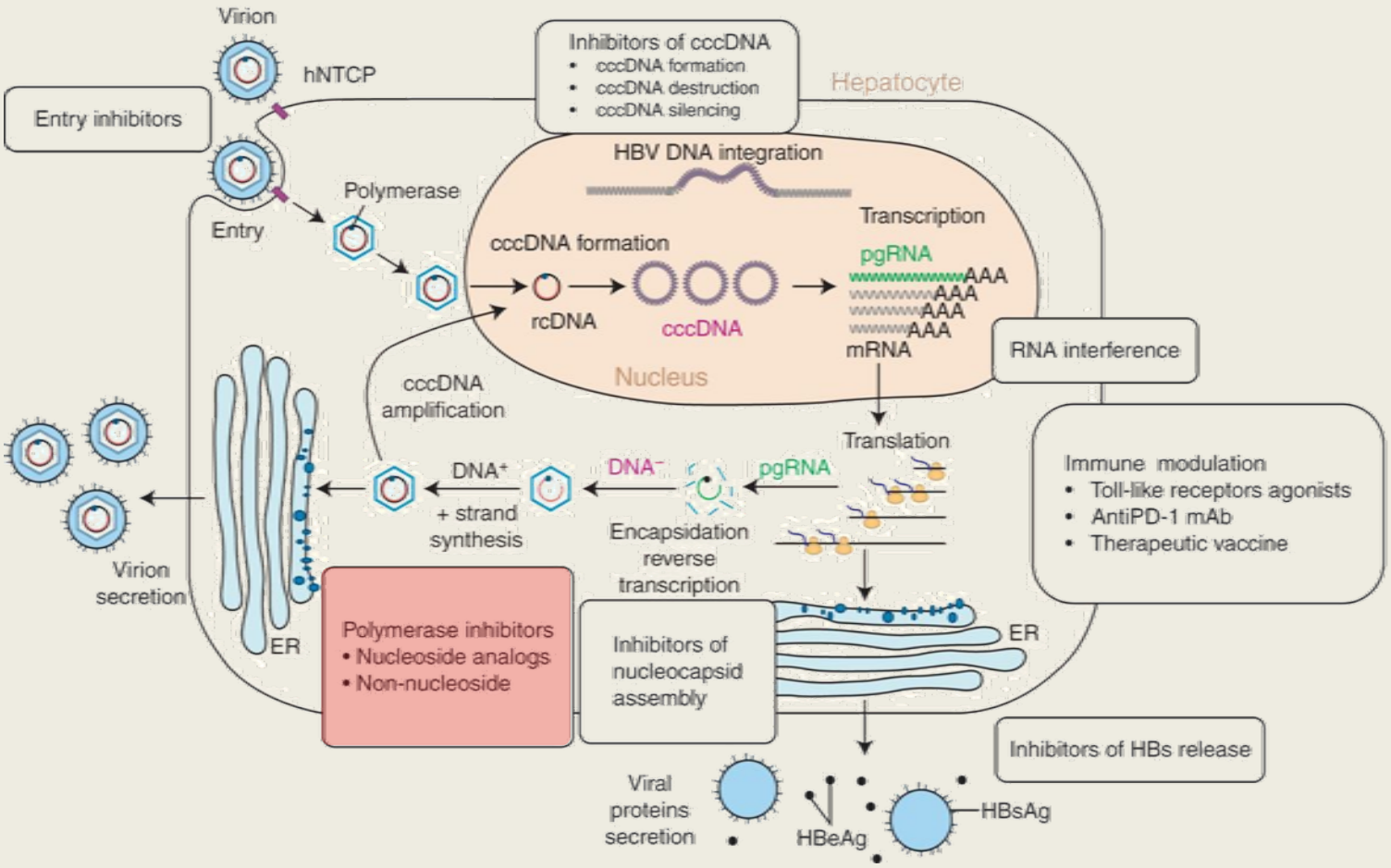
HBV nucleocapsid inhibitor





Yuen MF et al. AASLD 2015

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

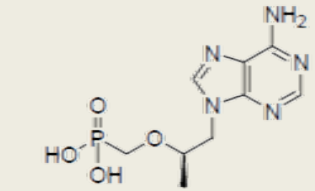
Direct-acting antiviral agents

- Polymerase inhibitors

Drug name	Target	Compound	State of Development
Tenofovir alafenamide (TAF)	HBV polymerase	Prodrug of Tenofovir	Phase III
CMX157	HBV polymerase	Prodrug of Tenofovir	Phase II
AGX-1009	HBV polymerase	Prodrug of Tenofovir	Phase I, China
Besifovir	HBV polymerase	Acyclic nucleotide phosphonate	Phase III, Korea

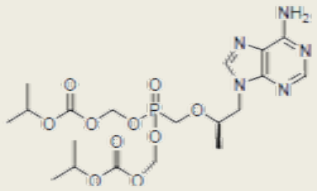
Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

Tenofovir alafenamide (TAF)



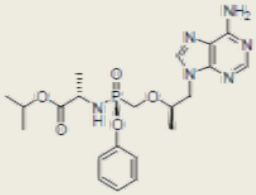
TFV

Tenofovir



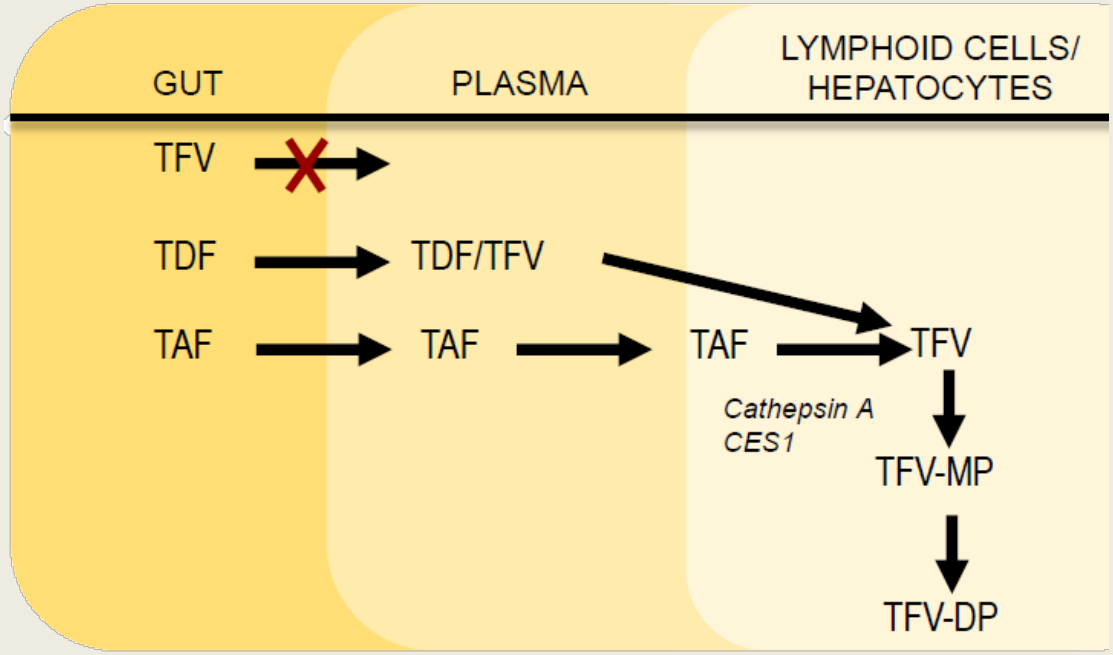
TDF

Tenofovir
Disoproxil Fumarate



TAF

Tenofovir
Alafenamide



CES1 = Carboxylesterase 1

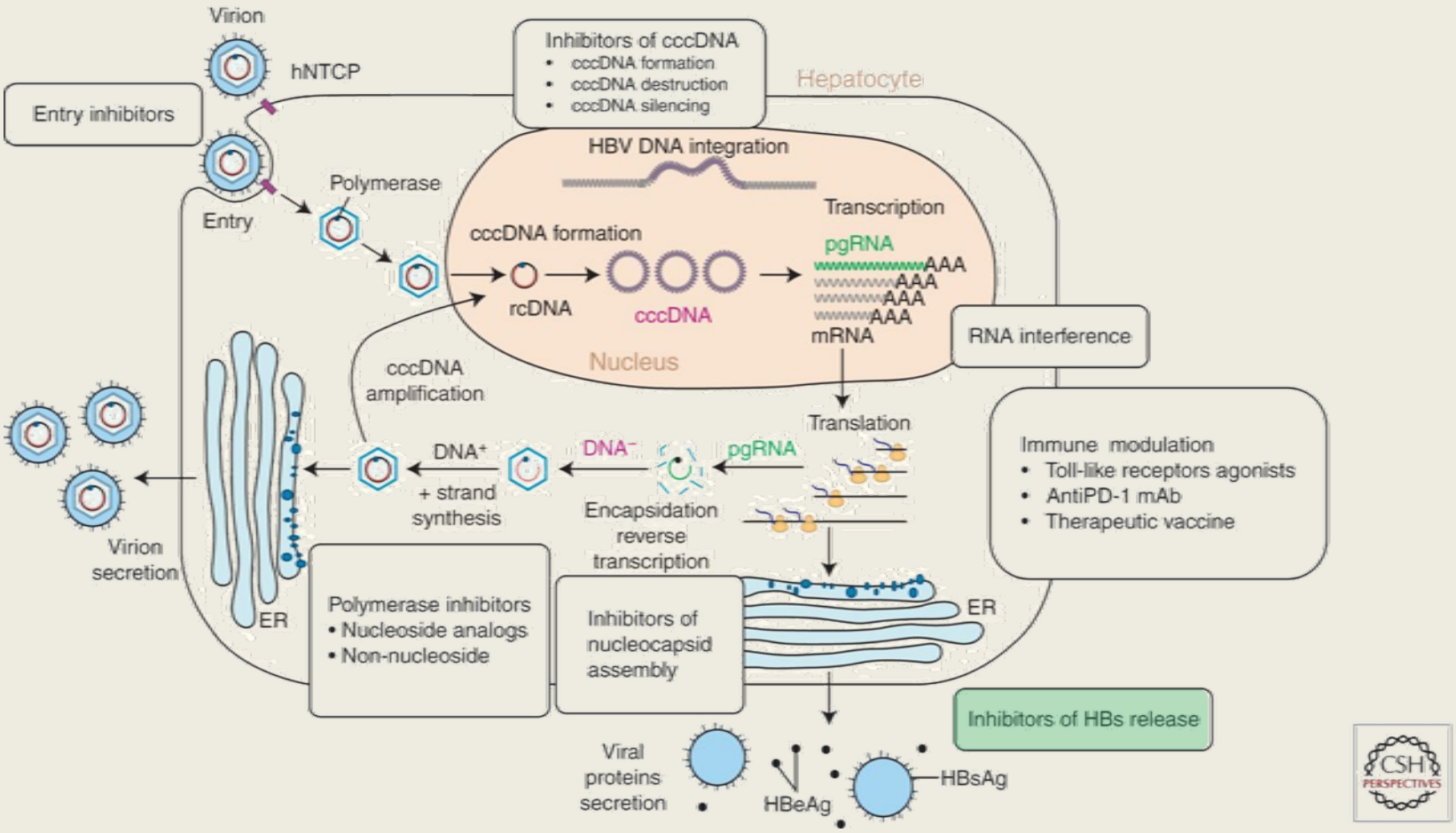
- ↑ **stability in plasma**
- ↑ delivery to hepatocytes
- ↓ doses with TAF
- ↓ **systemic exposures of TFV**

Argarwal K et al. AASLD 2013

Emerging Drugs Against HBV

- Direct-acting antiviral agents (DAAs)
- Host-targeting antiviral agents (HTAs)

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

Host-targeting agents

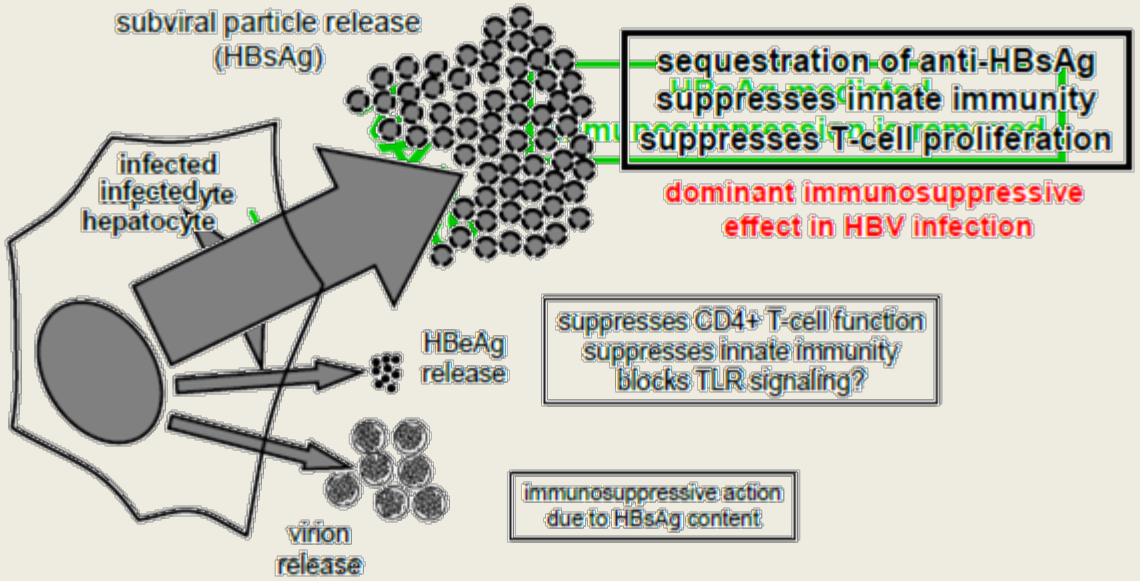
- Inhibitors of HBsAg release

Drug name	Target	Compound	Stage of Development
REP-2139 (REP 9AC)	Subviral particle formation	Phosphorothioated oligonucleotides	Phase II
BM601	Inhibits HBsAg secretion	Benzimidazole derivative	Preclinical
NVPO18	Inhibits HBsAg secretion	Cyclophilin inhibitor	Preclinical
CPI-431-32	Inhibits HBsAg secretion	Cyclophilin inhibitor	Preclinical
PBHBV-001 PBHBV-2-15	Inhibits HBsAg secretion	Triazolo-pyrimidine derivatives	Preclinical
DNJ	Inhibits HBsAg secretion	α-glucosidase inhibitors / Iminosugar derivatives of butyldeoxynojirimycin	Preclinical
GC1102	Neutralizing HBsAg	Recombinant Hepatitis B Human Immunoglobulin	Phase I

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

REP-2139 (REP 9AC, Replicor), i.v qw

- REP-2139 prevents subviral particle (SVP) formation in HBV-infected hepatocytes and inhibits HBsAg release



* NAPs: nucleic acid polymers

REP-2139-Ca, significantly reduces HBV RNA levels in CHB

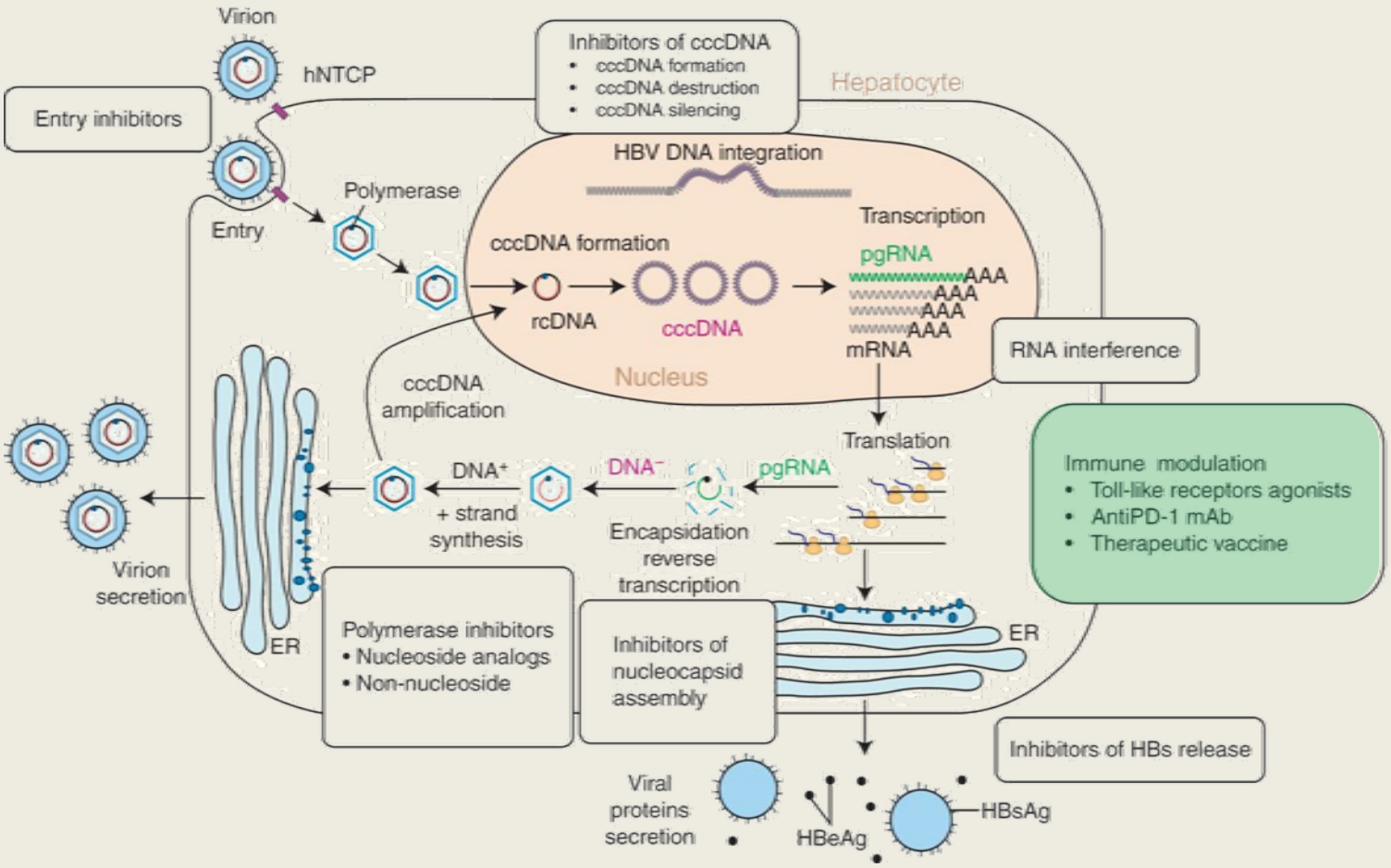
- Phase 2 study in 12 HBeAg-positive patients
  - REP-2139-Ca for 20–38 weeks
  - Patients with HBsAg decline subsequently treated with PEG-IFN and/or thymosin alpha-1

	Response
HBV RNA decline at Weeks 20–24	-2.54 log copies/mL (P<0.001)
HBV DNA decline at Weeks 20–24	-3.34 log copies/mL (P<0.001)
HBsAg decline at Weeks 20–24	-3.12 IU/mL (P<0.001)
Undetectable HBV RNA	
At Weeks 20–24	67% (8/12)
Treatment-free follow-up	88% (7/8)
HBsAg loss/seroconversion during treatment-free follow-up	50% (4/8)

This slide includes investigational agents that are not approved for use in CHB by the EMA;
Additional data presented at ILC 2015 as a late breaker

Jansen L, et al. EASL 2015; Abstract #113.

Hepatitis B virus (HBV) life cycle



Zeisel MB et al. Gut 2015;64:1314-26

Host-targeting agents

- Immune modulation

Drug name	Targets	Compounds	Stage of Development
INO-1800	Therapeutic vaccine	DNA plasmids encoding HBsAg and HBcAg	Phase I
SB-9200	Induction of host immune responses via activation of RIG-I and NOD2	Small molecule nucleic acid hybrids (SMNH)	Phase II
Birinapant (TL32711)	Cellular inhibitor of apoptosis proteins (cIAPs)	SMAC inhibitor	Phase I / IIa
Alinia	Activation of Protein kinase R (PKR)	Nitazoxanide	Preclinical

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

Host-targeting agents

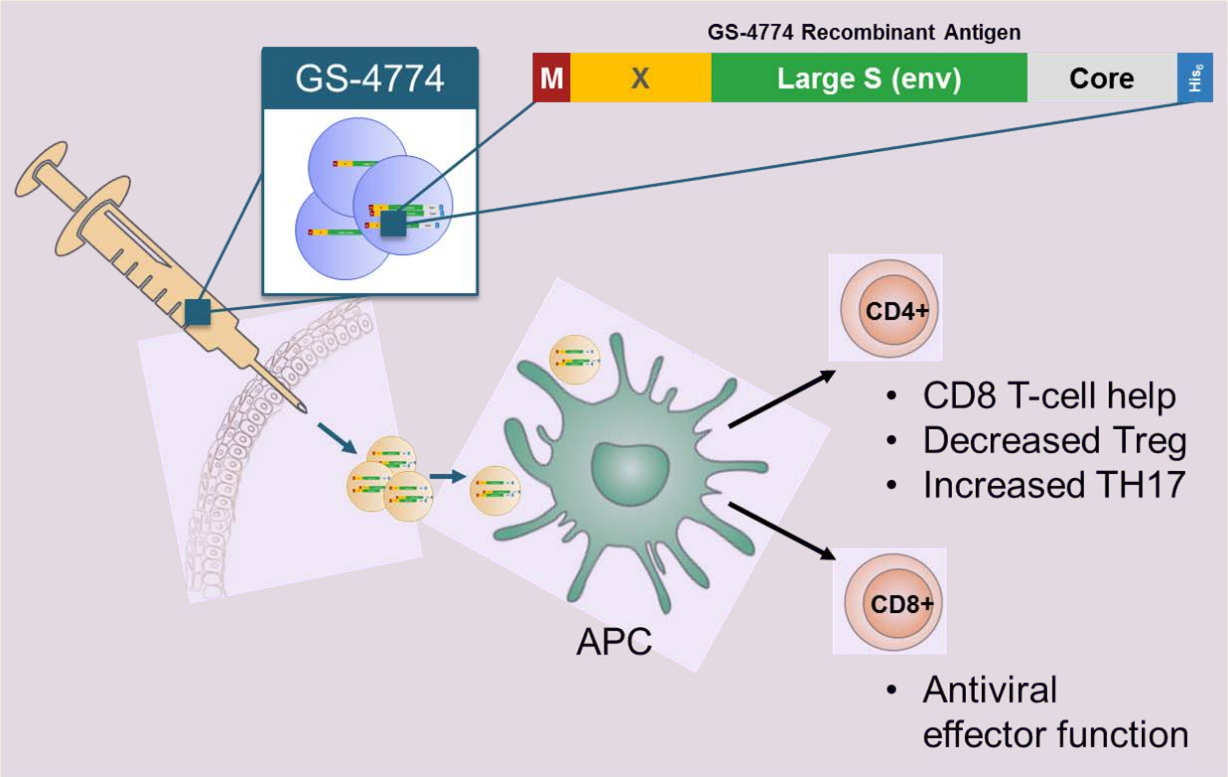
- Immune modulation

Drug name	Targets	Compounds	Stage of Development
ABX-203	Therapeutic vaccine	Recombinant antigen containing HBsAg and HBcAg	Phase IIb / III
GS-4774	Therapeutic vaccine	Recombinant antigen containing X, Env, Core epitopes	Phase II
GS-9620	TLR7 agonist	Oral TLR7 agonist	Phase II
CYT107	Immune-modulator	Recombinant human IL-7	Phase I / IIa
TG-1050	Immunotherapeutic	Non-replicative adenovirus serotype 5 encoding a large fusion protein (truncated Core, modified Pol and two Env domains)	Phase I

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26

Therapeutic vaccine: GS-4774

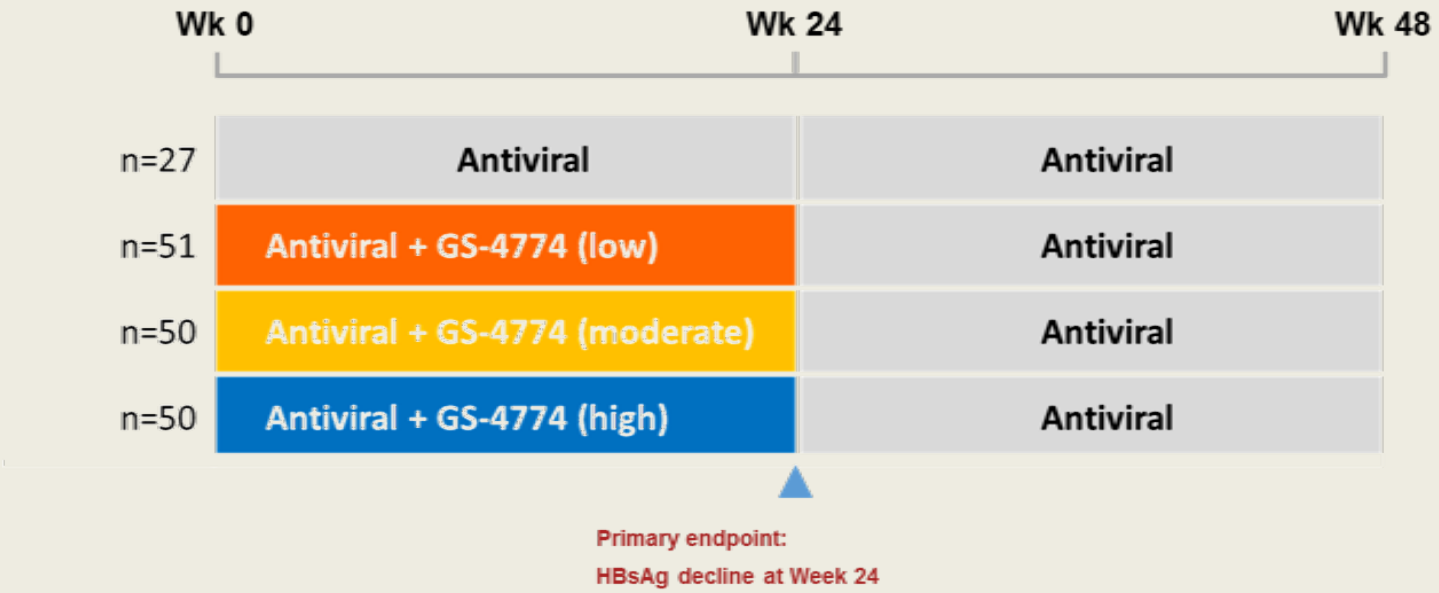
- Recombinant antigen containing X, Large S (env) and Core epitopes
- GS-4774 activates dendritic cells after phagocytosis
- Recombinant antigen epitopes are displayed via MHC class I and II and stimulate $CD4^+$ and $CD8^+$ T cells



Stubbs AC, et al. Nat Med 2001; Cereda V, et al. Vaccine 2011

Therapeutic vaccine: GS-4774

- Phase II clinical trial: *in progress*



- CHB patients without cirrhosis on oral antiviral treatment for >1 year
- Randomization stratified by HBeAg status and HBsAg level
- GS-4774 administered SC every 4 weeks x 6 doses

Host-targeting agents

- Immune modulation

Drug name	Targets	Compounds	Stage of Development
ABX-203	Therapeutic vaccine	Recombinant antigen containing HBsAg and HBcAg	Phase IIb / III
GS-4774	Therapeutic vaccine	Recombinant antigen containing X, Env, Core epitopes	Phase II
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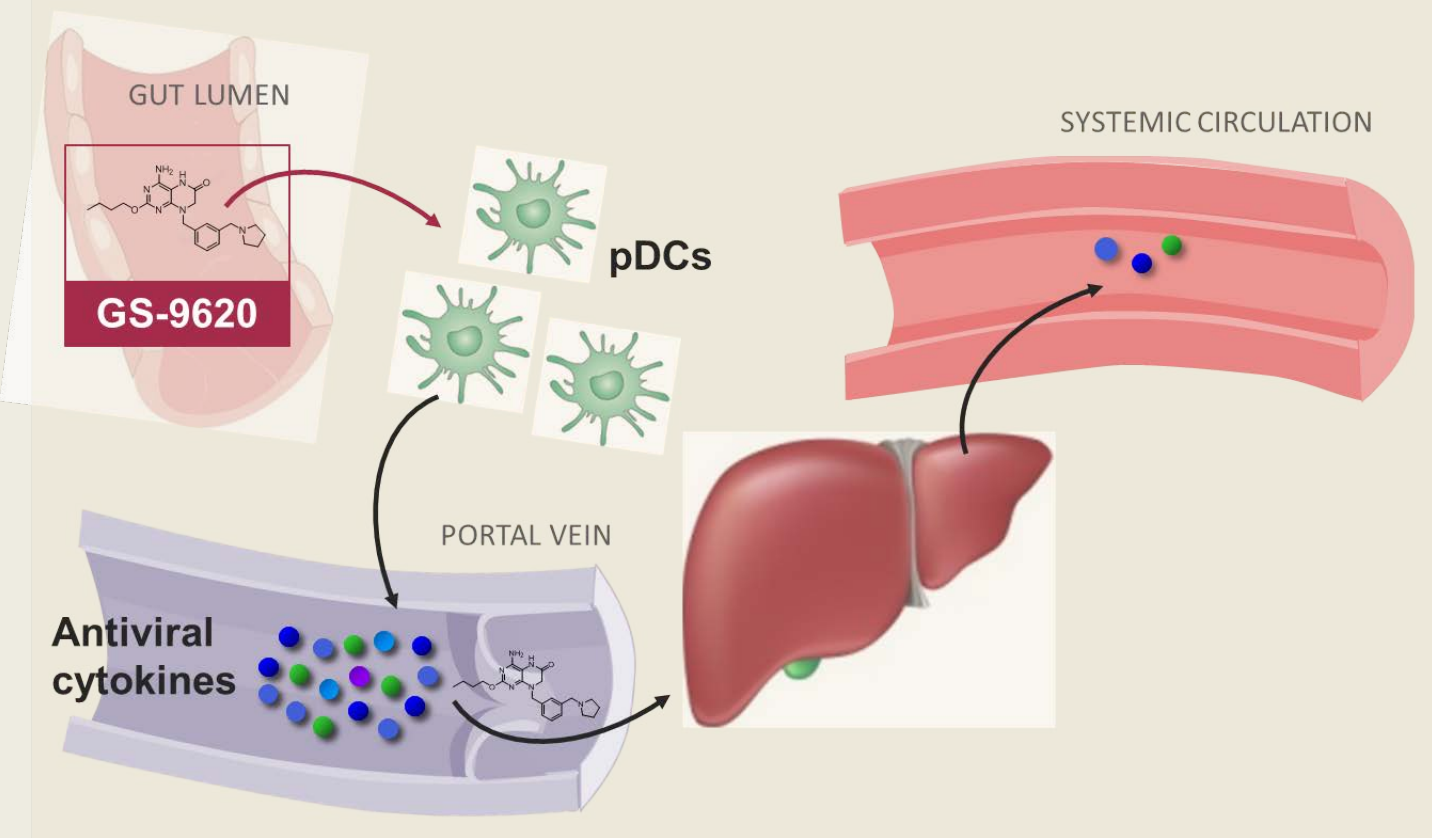
Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015 (*in press*)

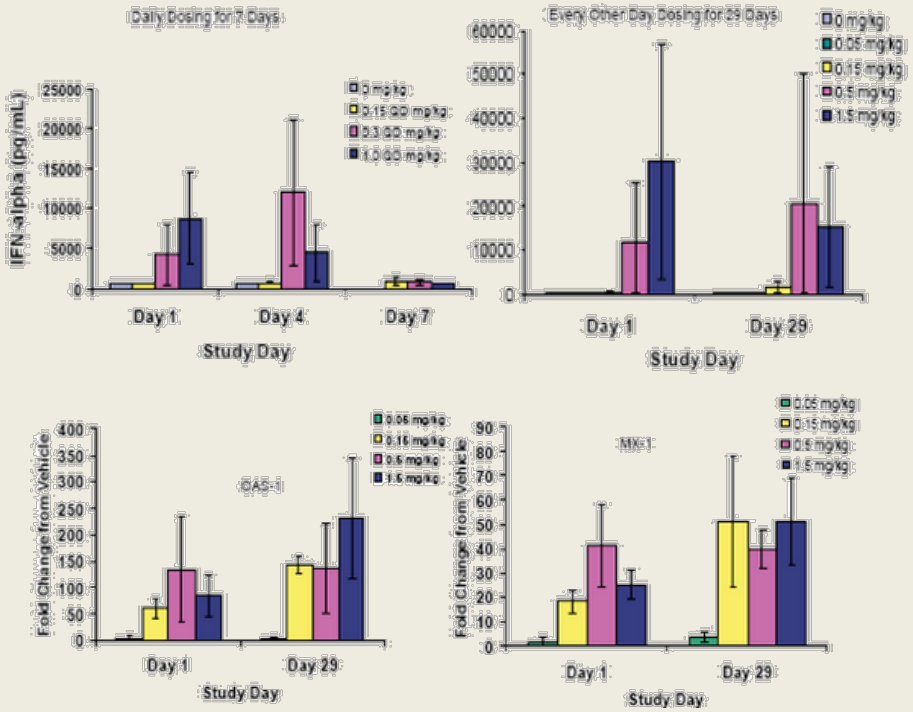
TLR7 agonist: GS-9620

- Potent and selective oral TLR7 agonist
- Activates plasmacytoid DCs and induce antiviral cytokines



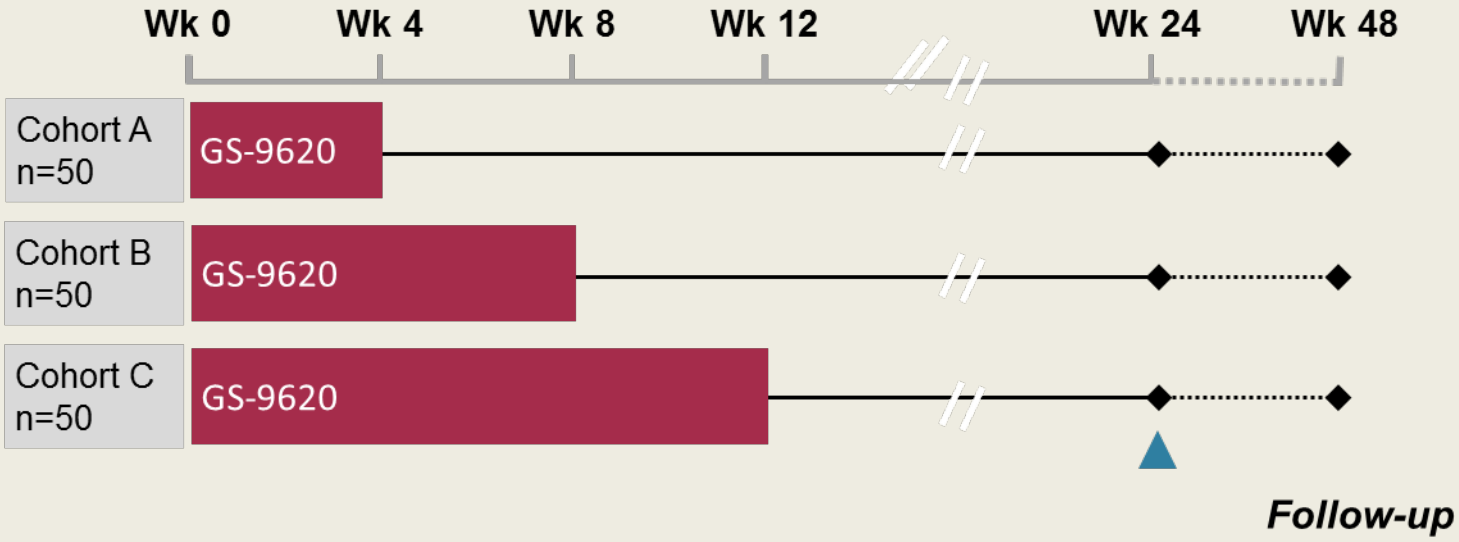
TLR7 agonist: GS-9620

- Pre-clinical results: Male Cynomolgus Monkeys
  - Low oral doses induced serum IFN-α, immunomodulatory cytokines , chemokines and ISGs in blood cells
    - IFN-α induction with GS-9620
    - ISG induction with GS-9620



TLR7 agonist: GS-9620

- Phase II clinical trial: *in progress*



- CHB patients without cirrhosis on oral antiviral treatment for >1 year
- 50 patients per cohort, stratified by HBeAg status and HBsAg level
  - Placebo (n=5); 1 / 2 / 4 mg GS-9620 PO QOW (n=15, respectively)

Conclusions

- Current treatments can only control disease and cannot lead to substantial HBsAg seroclearance, the benchmark of successful therapy
- Two types of new drugs are developed
  - Direct-acting antiviral agents (DAAs)
  - Host-targeting antiviral agents (HTAs)
- Clinical trial results of new therapeutic agents are awaited

Future perspectives: Future HBV curative regimen?

Potent NA

Agent to prevent viral spread and cccDNA re-amplification

+

Immune modulator

Agents to activate specific antiviral immunity or relieve repression/exhaustion of the system

+

cccDNA inhibitor

Safe and selective agent to reduce or silence cccDNA

+

HBV antigen inhibition

Agents to inhibit other components in the HBV life cycle (i.e. entry, cell-spread, capsid assembly, HBx, HBeAg, HBsAg)

Thank you