Targets and new drugs for HBV

Tarik Asselah

Paris Hepatology Conference

January 2018

Professor of Medicine
Hepatology, INSERM UMR 1149,
Hôpital Beaujon, Clichy, France.


adidas


10

Disclosures

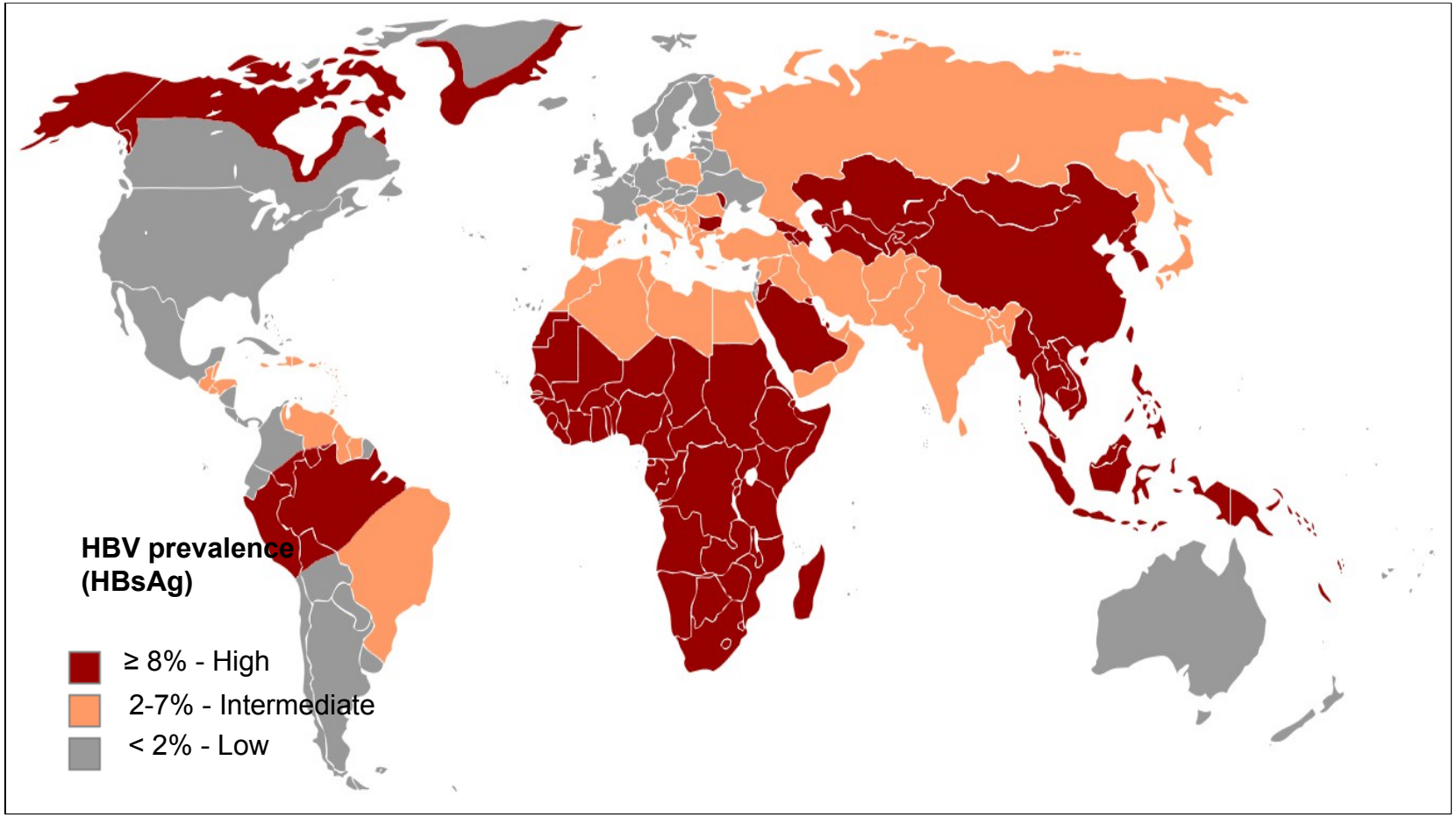
Speaker/consultant:

AbbVie
Gilead Sciences
Janssen
Merck Sharp & Dohme
Roche

Targets and new drugs for HBV

1. **Is an HBV cure a priority ?**
2. What are the objectives (endpoints) ?
3. HBV virology, viral cycle and targets
4. Direct-acting antivirals
5. Host antivirals
6. Conclusion

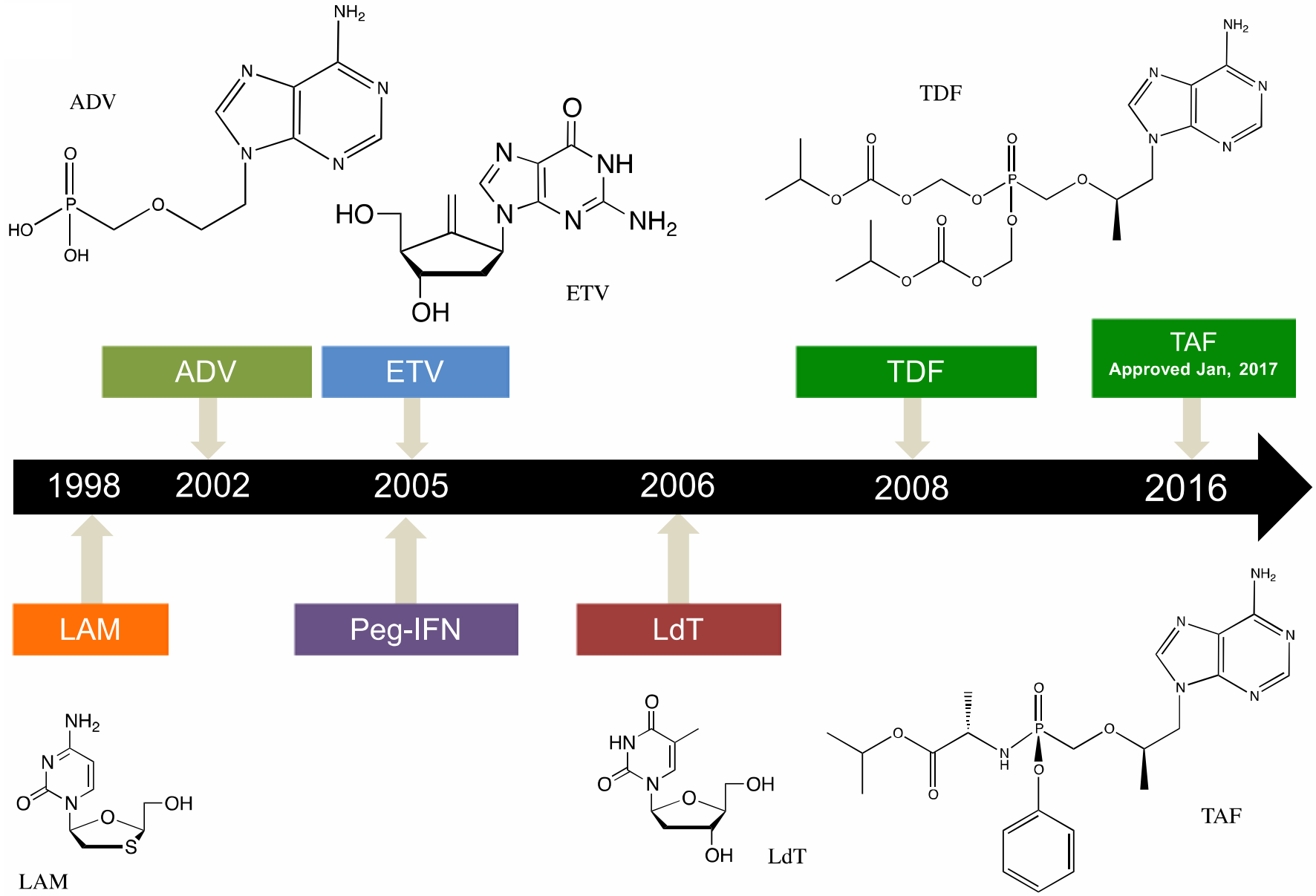
HBV infection is a major medical need



- **~ One third of individuals** exposed to HBV infection.
- **~ 257 million people** are living with HBV infection.
- **Main cause** of Cirrhosis, Hepatocellular carcinoma (HCC), Transplantation
- HCC, one of leading cancer worlwide, **~ 1 million deaths / year**

World Health Organization Global hepatitis report. 2017.

HBV drug development



Schinazi RF, Ehteshami M, Bassit L, Asselah T. Liver Int. 2018;38 S1:102-114.

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

30 millions of new HBV infection per year

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

  30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

  30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy

  Problems of implementation for vaccination campaigns

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

  30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy

  Problems of implementation for vaccination campaigns

- **Nuclesos(t)ides analogues** have high efficacy and favorable tolerability

Do we need an HBV cure ?

- A major public health problem , **257 million people** are living with HBV infection.

  30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy

  Problems of implementation for vaccination campaigns

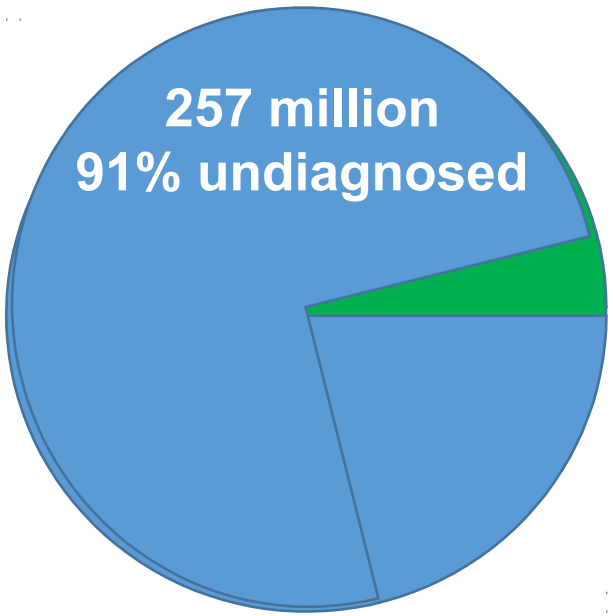
- **Nuclesos(t)ides analogues** have high efficacy and favorable tolerability

  Nucs does not affect cccDNA and HBs seroconversion is rare;

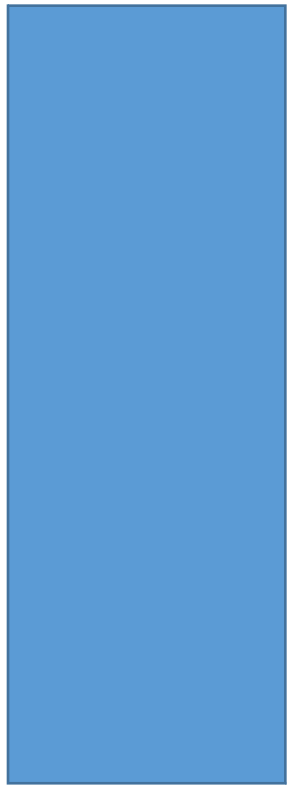
  HCC risk is reduced but remains

  Long-life duration, costs, compliance, discrimination.

HBV : Limited access to treatment



22 million
9% diagnosed

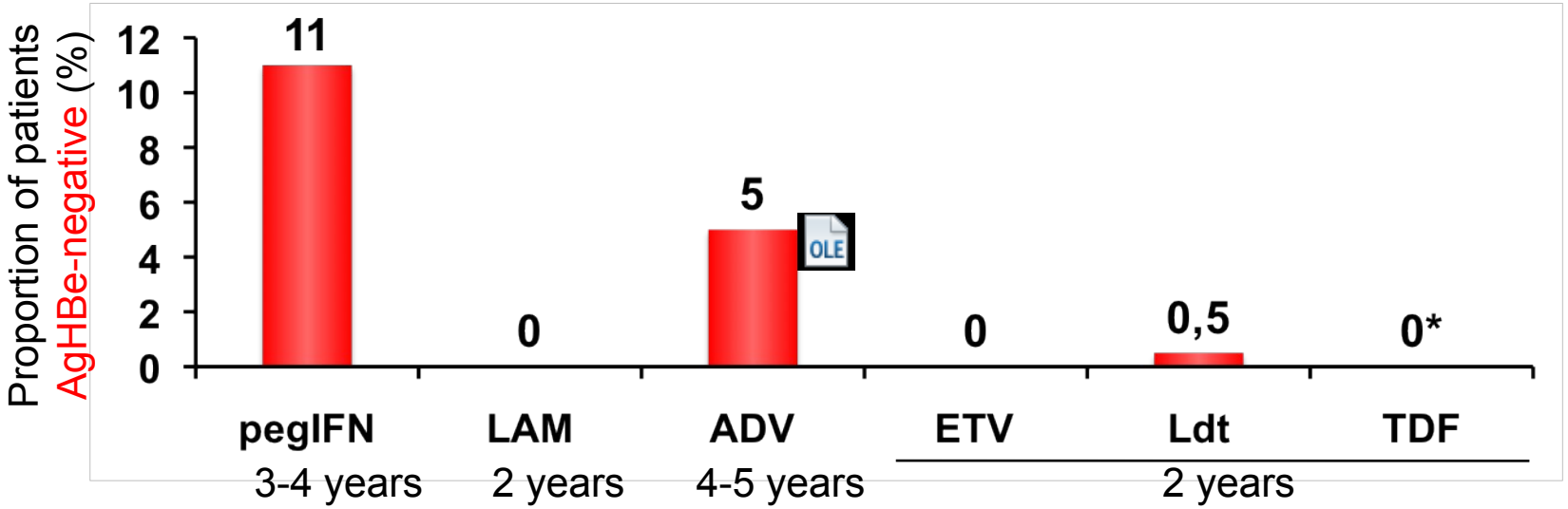


257 million
HBsAg +

22 million
Diagnosed (9%)

1.7 million
Treated (8%)

HBsAg loss



Schinazi RF, Ehteshami M, Bassit L, Asselah T. Liver Int. 2018;38 S1:102-114.

Targets and new drugs for HBV

1. HBV cure is a priority
2. **What are the objectives (endpoints) ?**
3. HBV virology, viral cycle and targets
4. Direct-acting antivirals
5. Host antivirals
6. Conclusion

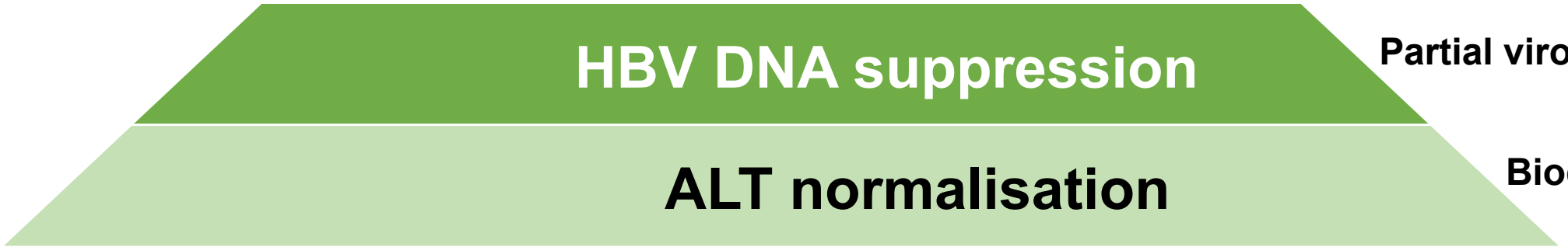
Clinical endpoints of therapy (Goals)
Sustained (after a finite course of treatment)

ALT normalisation

Biochemical response

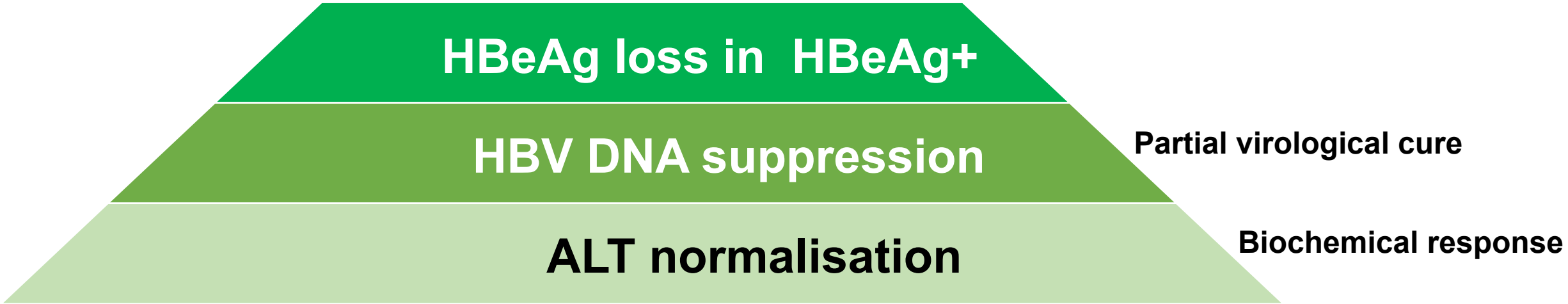
ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

Clinical endpoints of therapy (Goals)



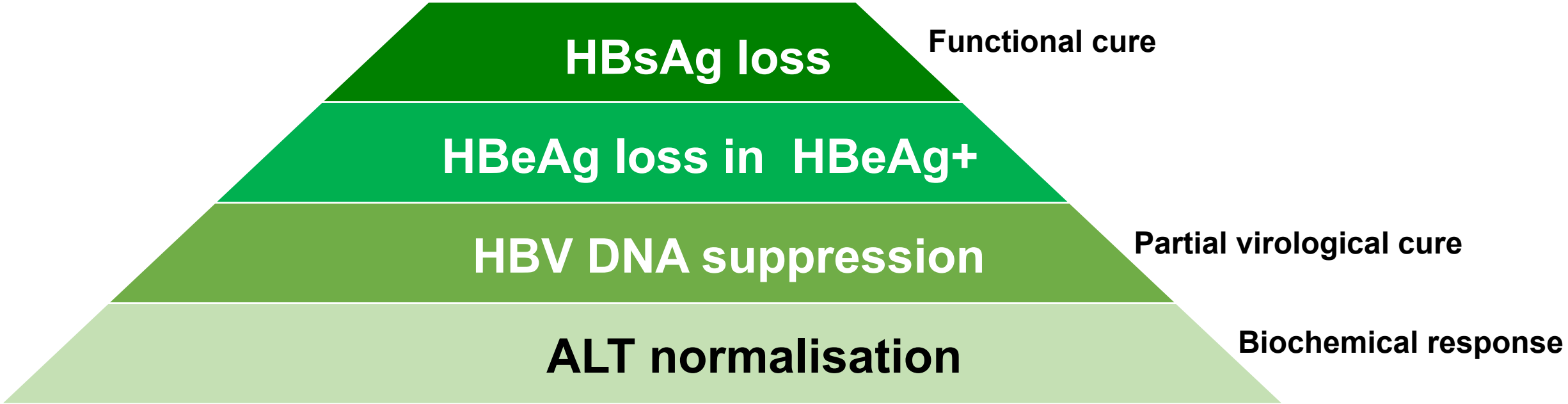
ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

Clinical endpoints of therapy (Goals)



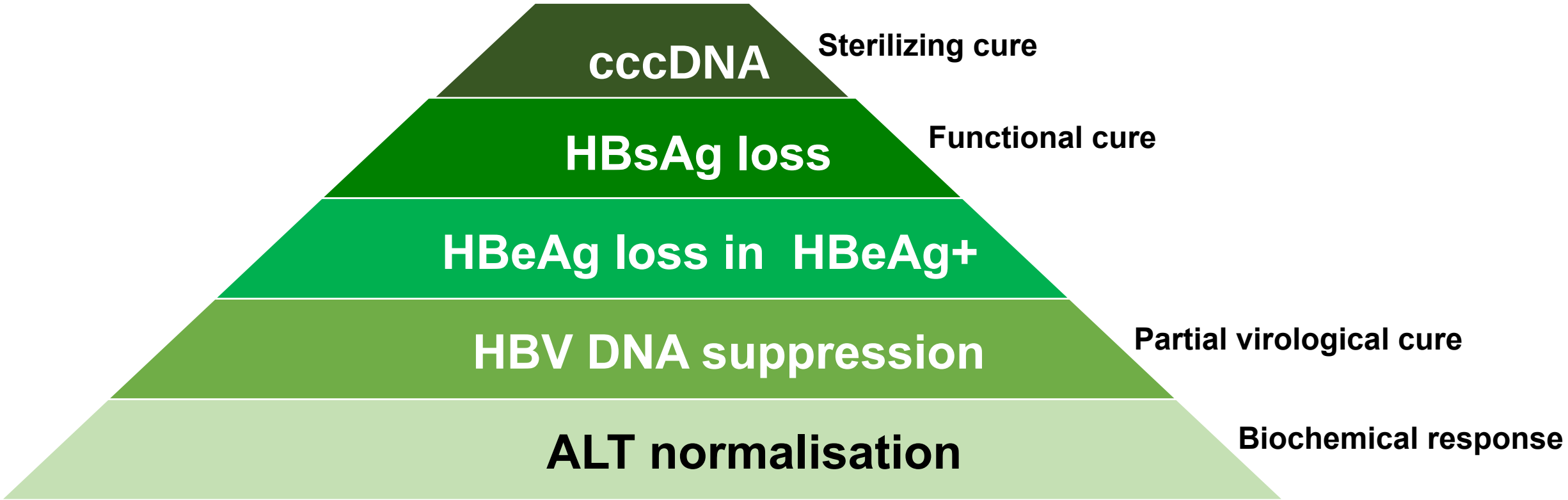
ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

Clinical endpoints of therapy (Goals)



ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

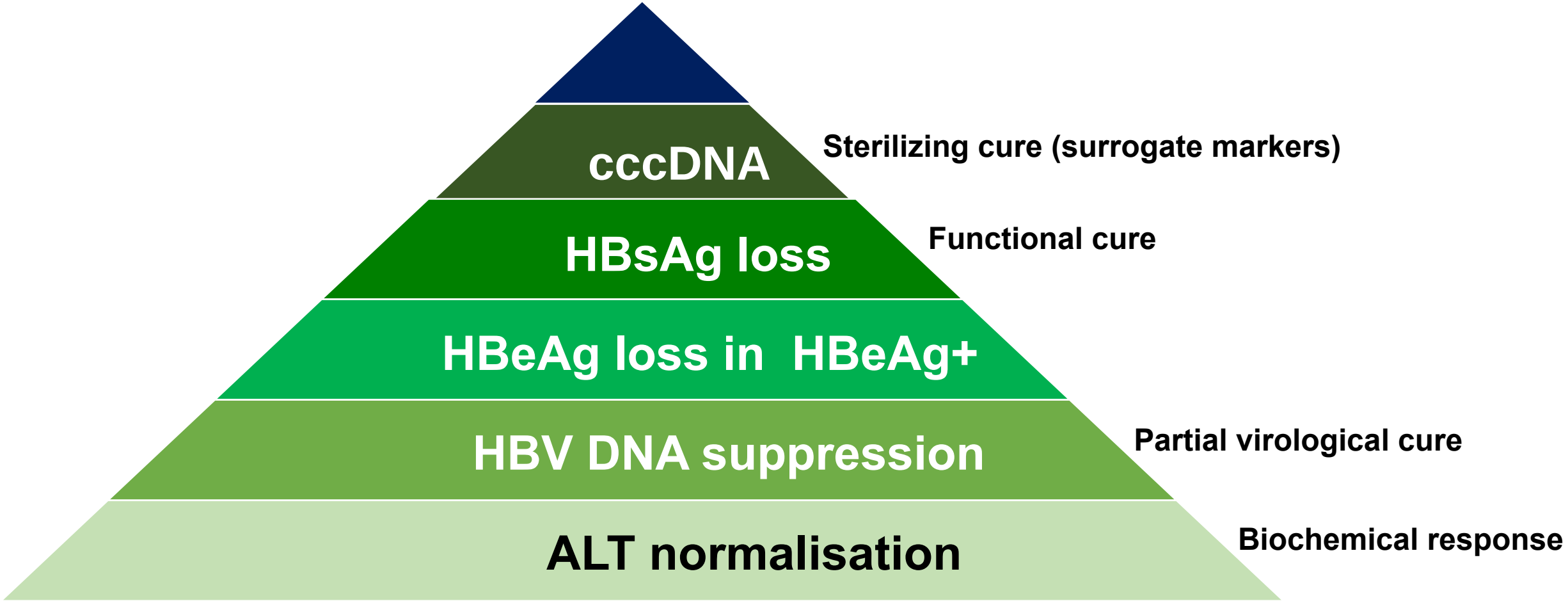
Clinical endpoints of therapy (Goals)



ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

Clinical endpoints of therapy (Goals)

HCC decrease, Fibrosis regression, Increased Survival & Quality of life

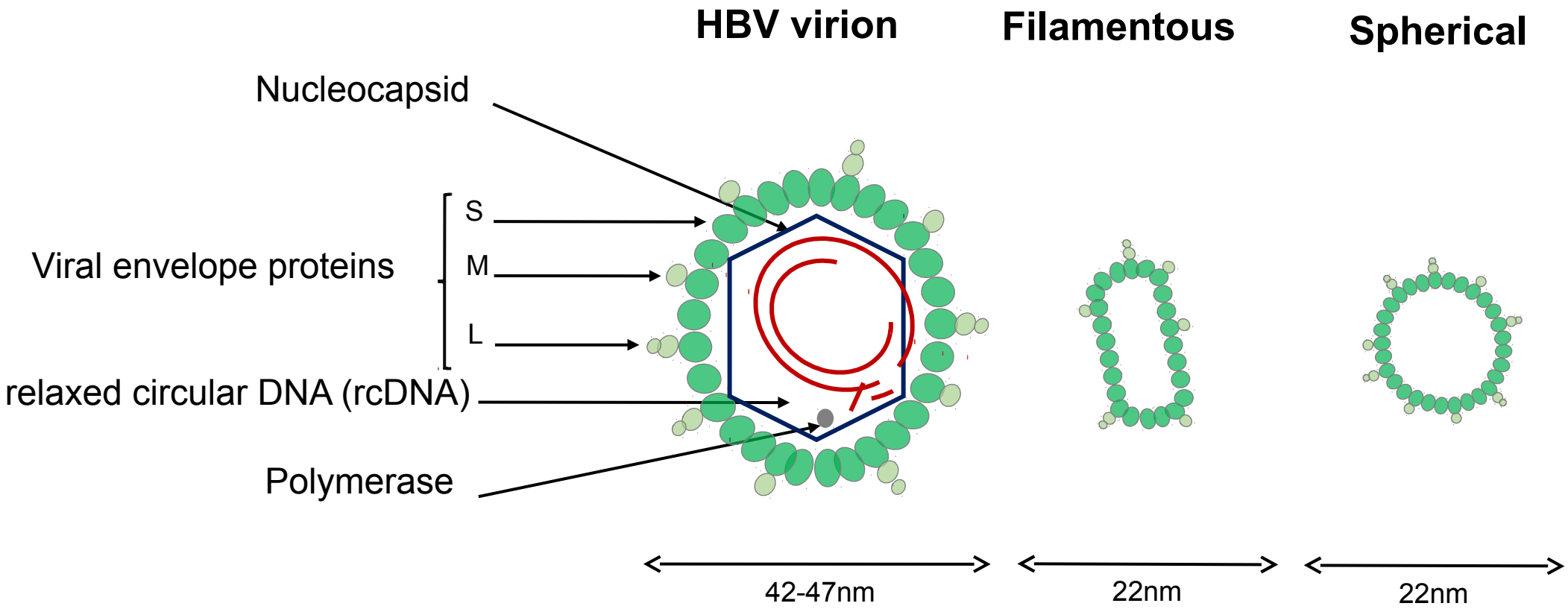


ALT: alanine aminotransferase; CHB: chronic hepatitis B;
anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen;
HBsAg: hepatitis B surface antigen

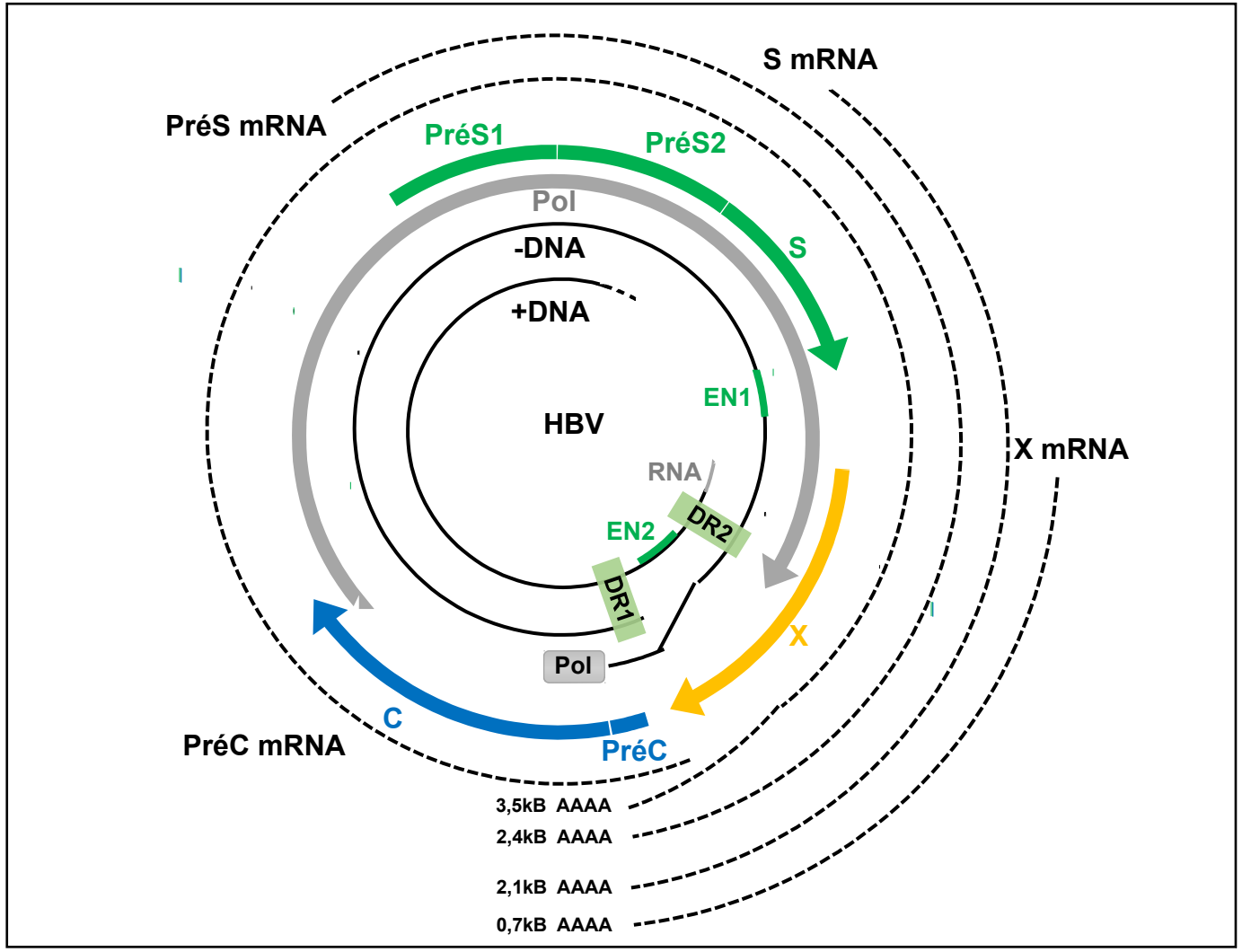
Targets and new drugs for HBV

1. HBV cure is a priority
2. What are the objectives (endpoints) ?
3. **HBV virology, viral cycle and targets**
4. Direct-acting antivirals
5. Host antivirals
6. Conclusion

HBV

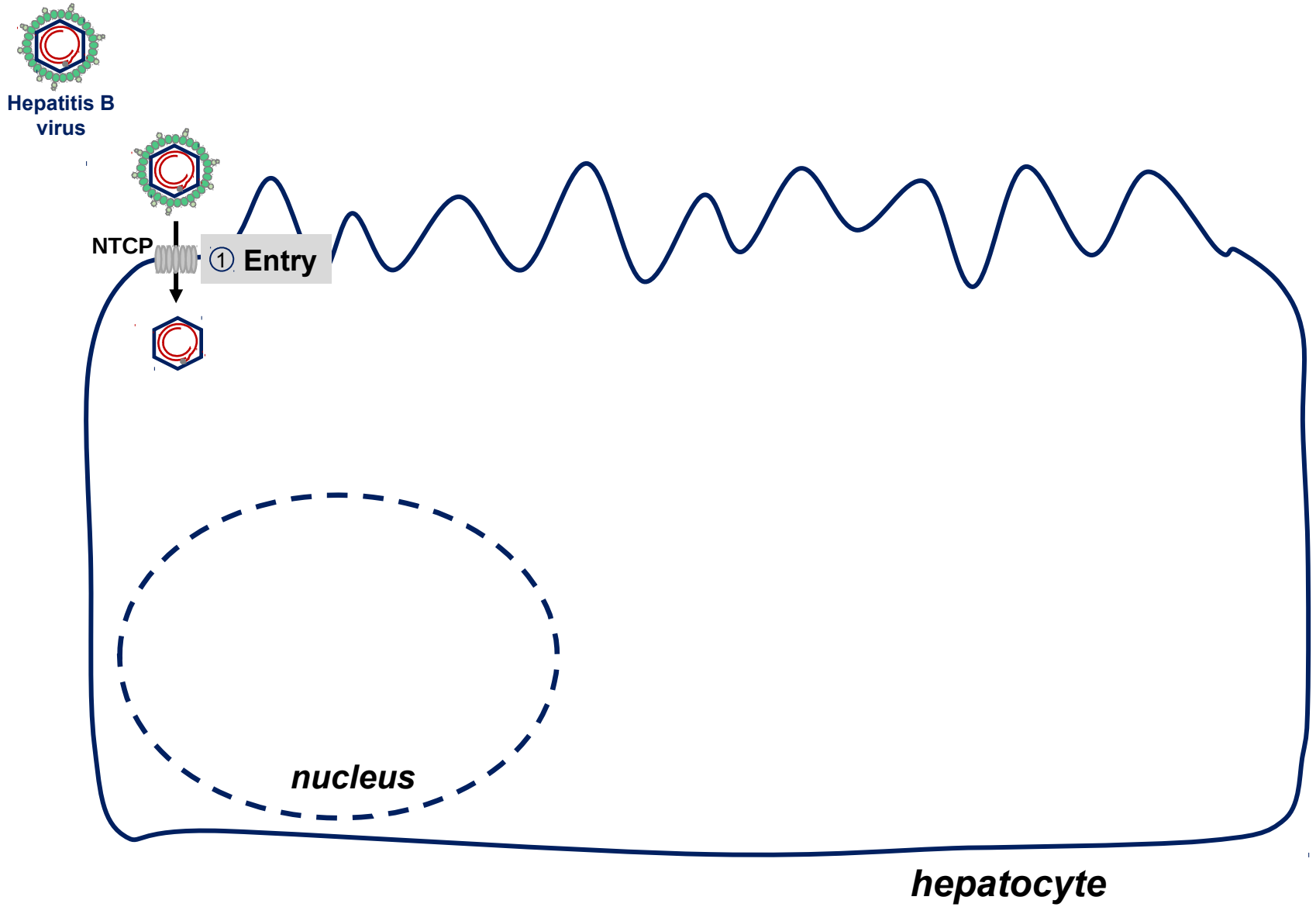

HBV virion
Filamentous
Spherical
Nucleocapsid
Viral envelope proteins
S
M
L
relaxed circular DNA (rcDNA)
Polymerase
42-47nm
22nm
22nm

HBV: Genome



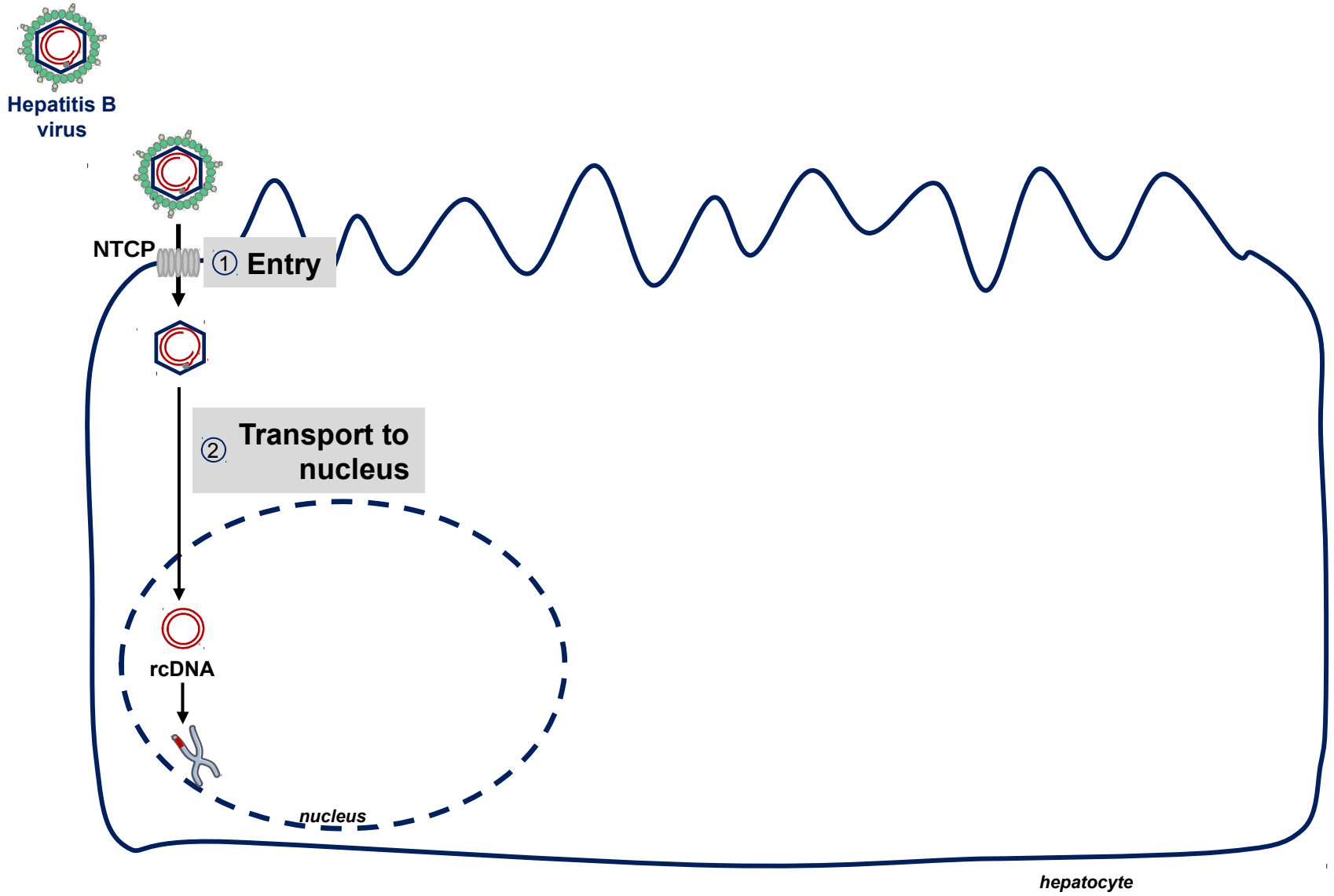
- Compact genomic structure (~ 3.2 kb).
- 4 overlapping open reading frames
- Reverse transcriptase/DNA polymerase domain overlaps with surface gene
- Encodes 4 sets of viral proteins – HBsAg, HB core Ag, viral polymerase and HBx protein.

HBV cycle

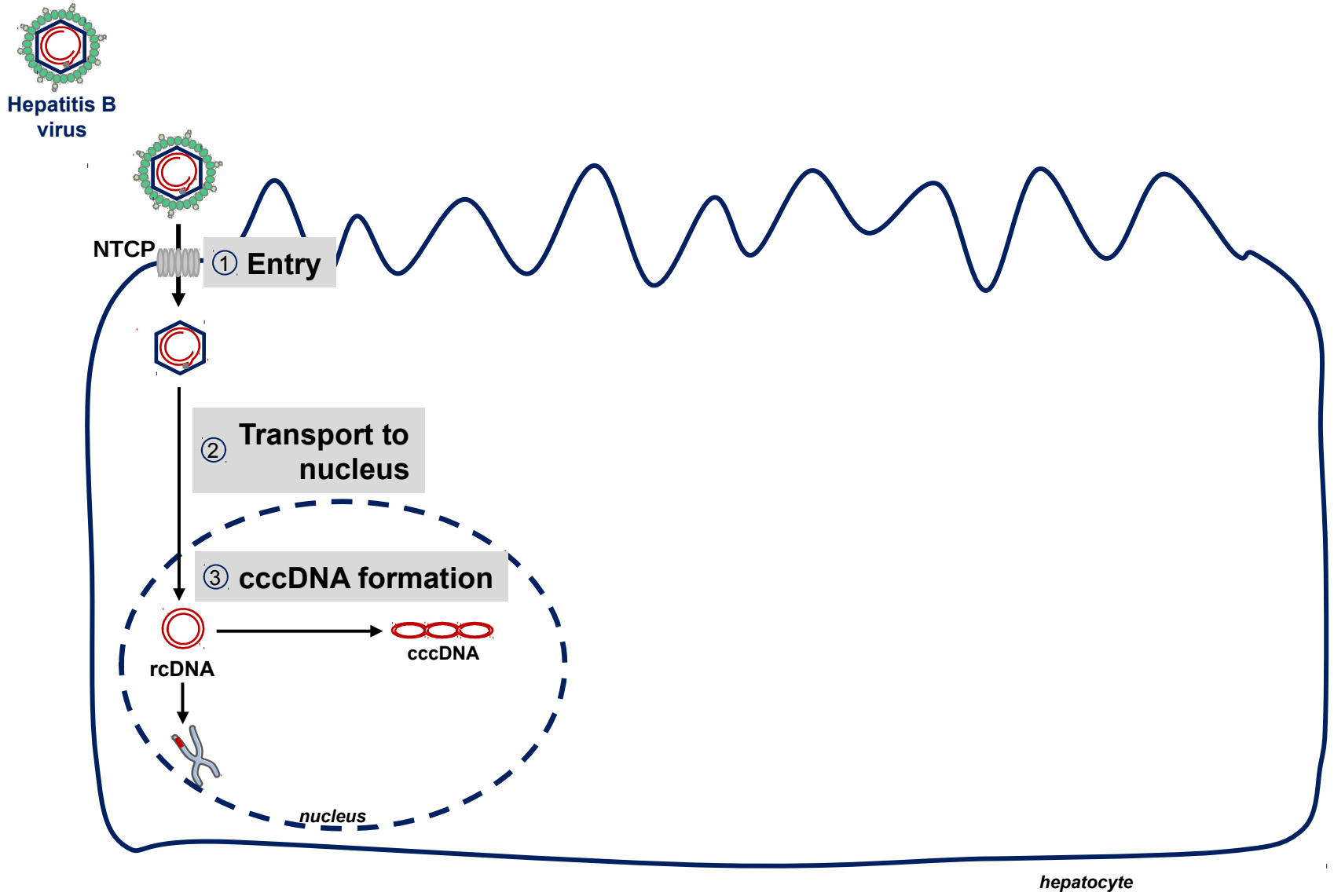


Yan H. et al, Elife. 2012 Nov 13;1:e00049

HBV cycle

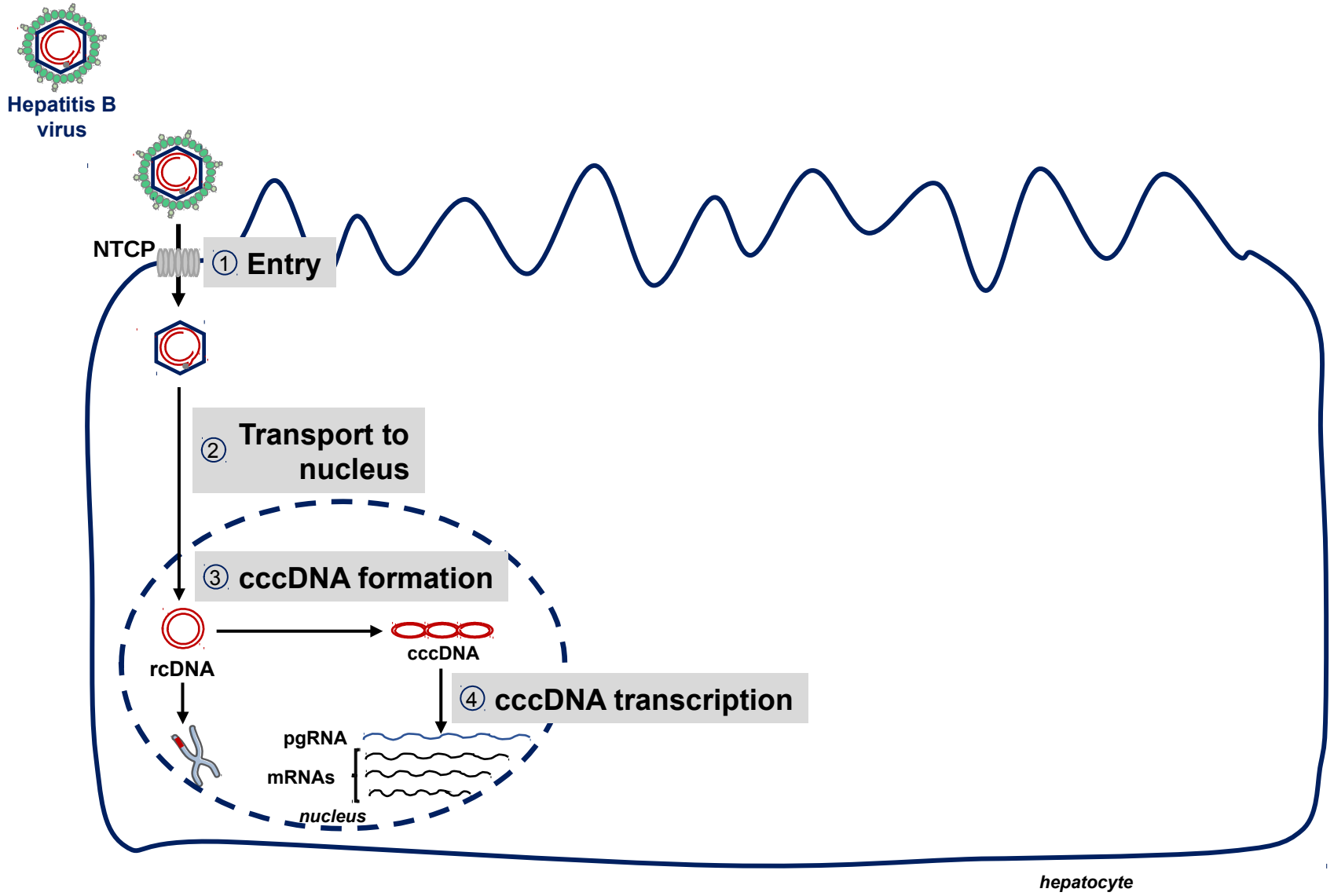

Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
rcDNA
nucleus
hepatocyte

HBV cycle

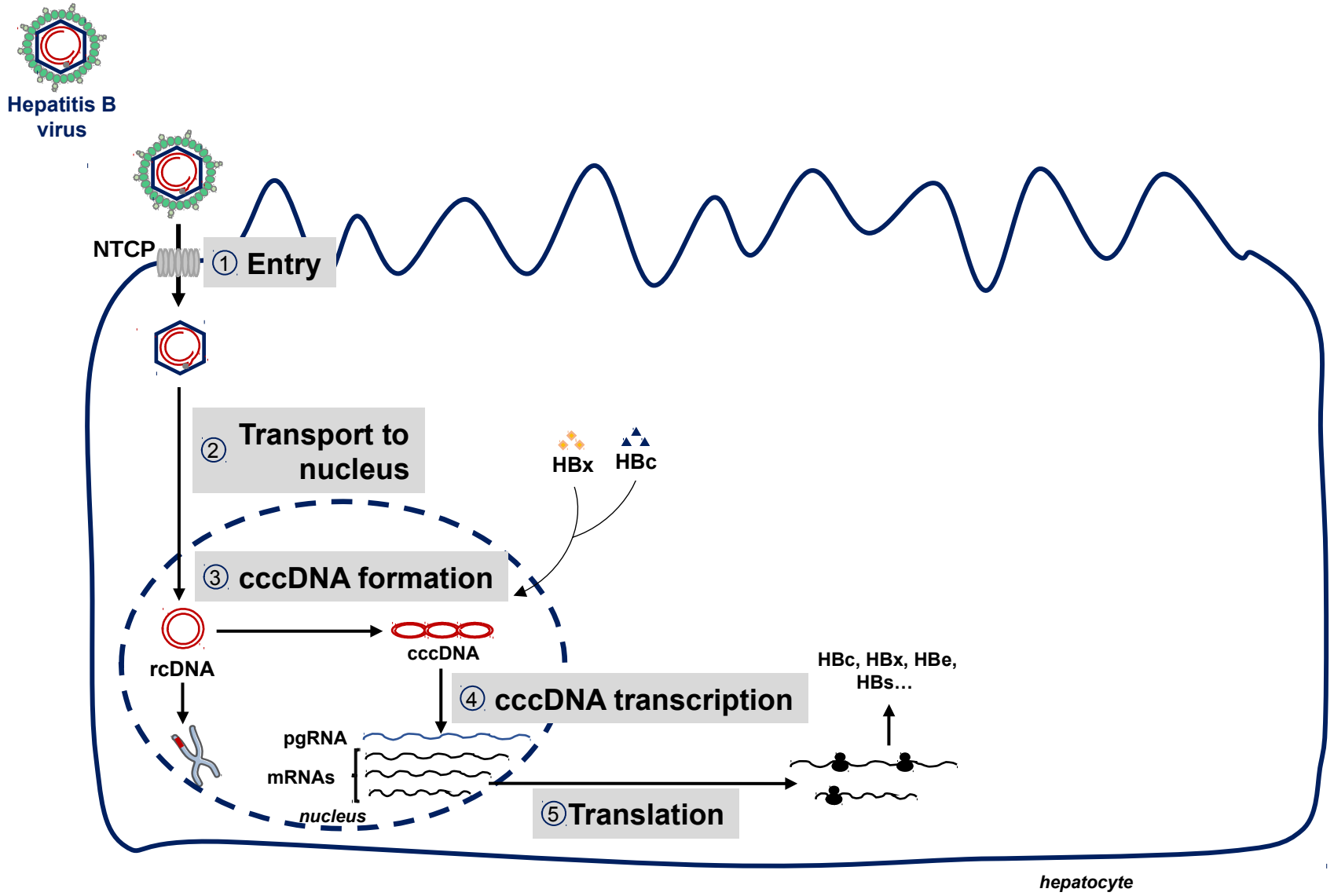


cccDNA : covalently closed circular DNA

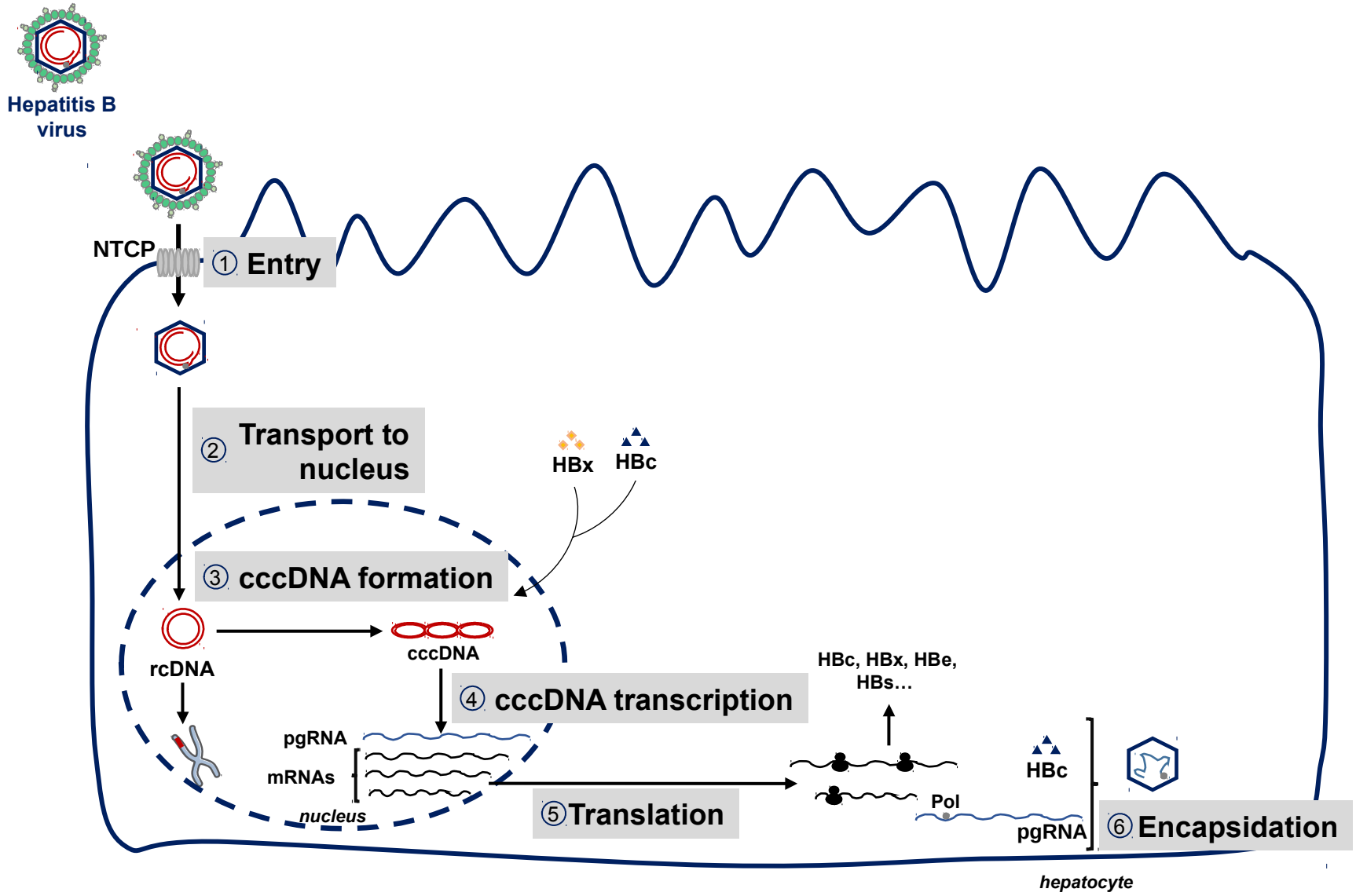
HBV cycle


Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
③ cccDNA formation
rcDNA
cccDNA
④ cccDNA transcription
pgRNA
mRNAs
nucleus
hepatocyte

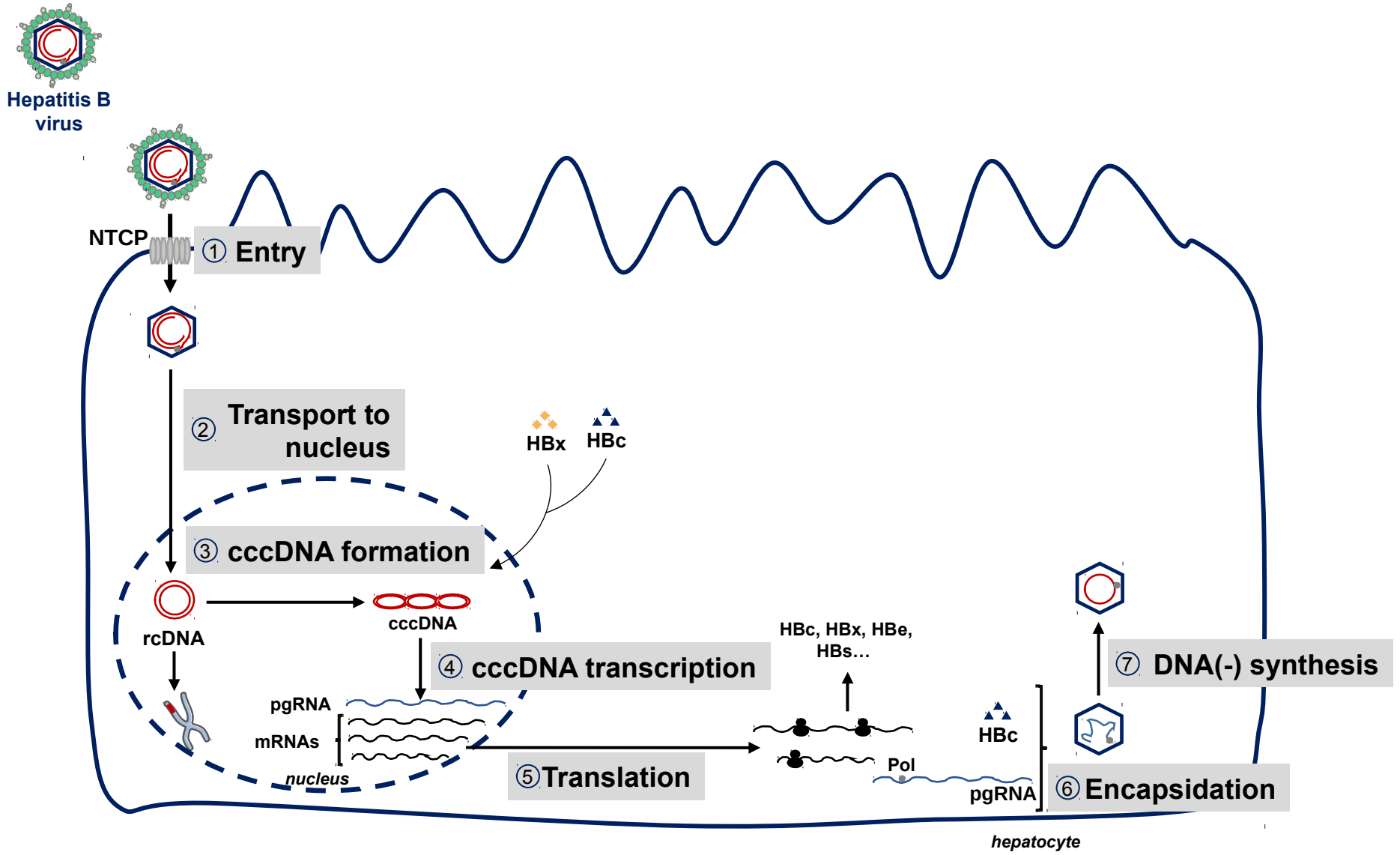
HBV cycle


Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
HBx
HBc
③ cccDNA formation
rcDNA
cccDNA
④ cccDNA transcription
HBc, HBx, HBe, HBs…
pgRNA
mRNAs
nucleus
⑤Translation
hepatocyte

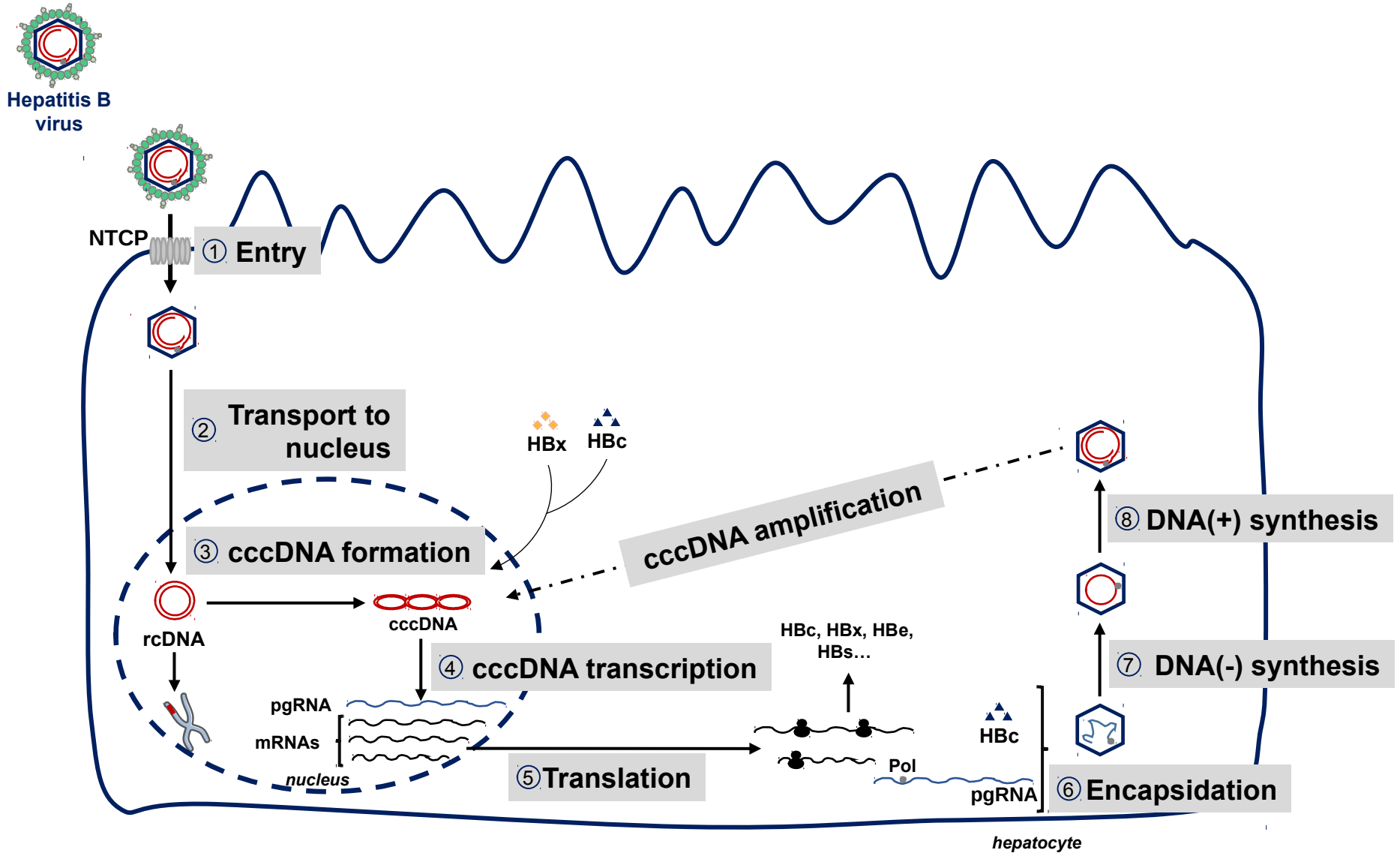
HBV cycle


Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
HBx
HBc
③ cccDNA formation
rcDNA
cccDNA
④ cccDNA transcription
pgRNA
mRNAs
nucleus
⑤Translation
HBc, HBx, HBe, HBs…
Pol
pgRNA
HBc
⑥ Encapsidation
hepatocyte

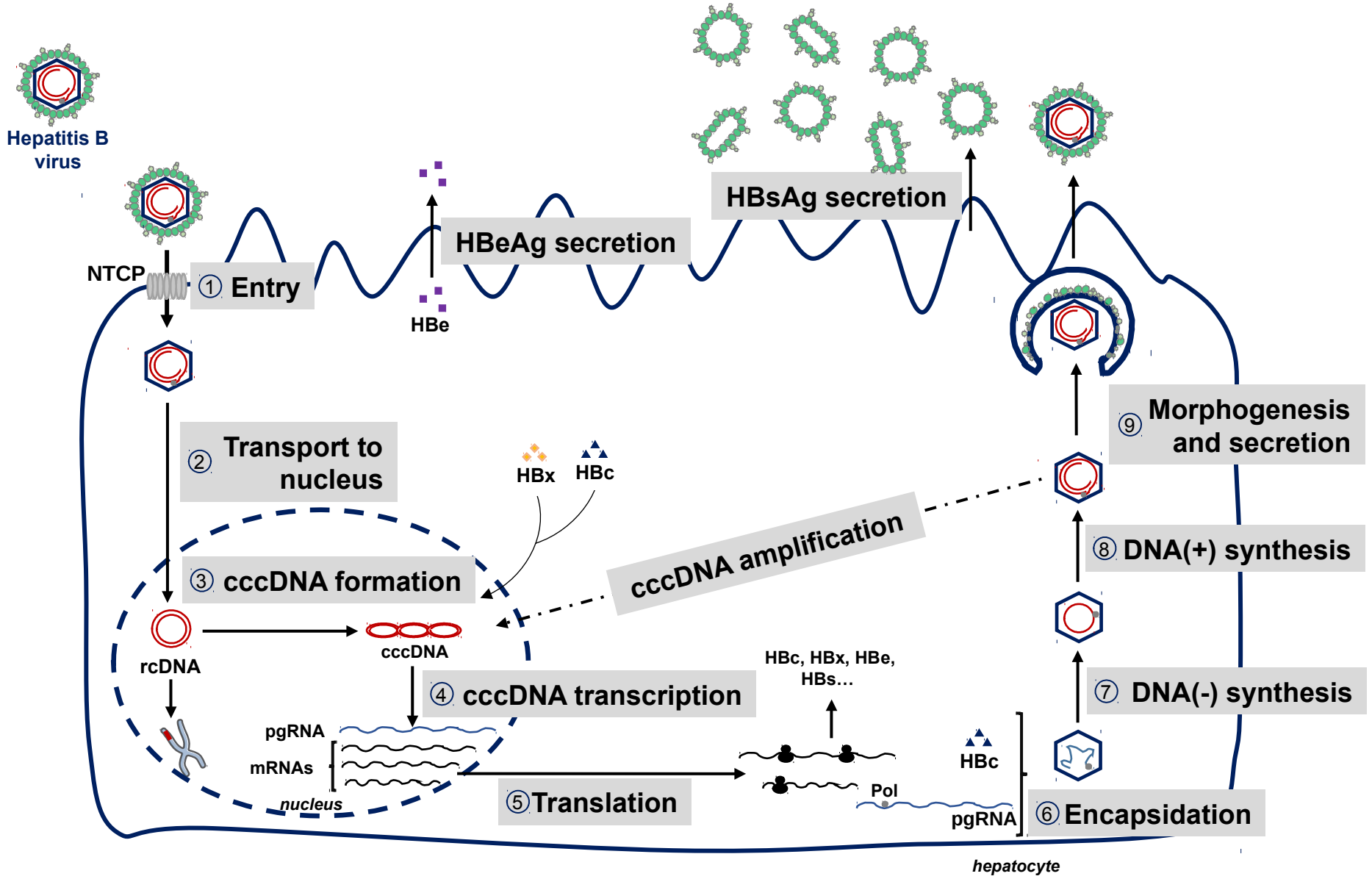
HBV cycle


Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
HBx
HBc
③ cccDNA formation
rcDNA
cccDNA
④ cccDNA transcription
pgRNA
mRNAs
nucleus
⑤Translation
HBc, HBx, HBe, HBs…
Pol
pgRNA
HBc
⑥ Encapsidation
⑦ DNA(-) synthesis
hepatocyte

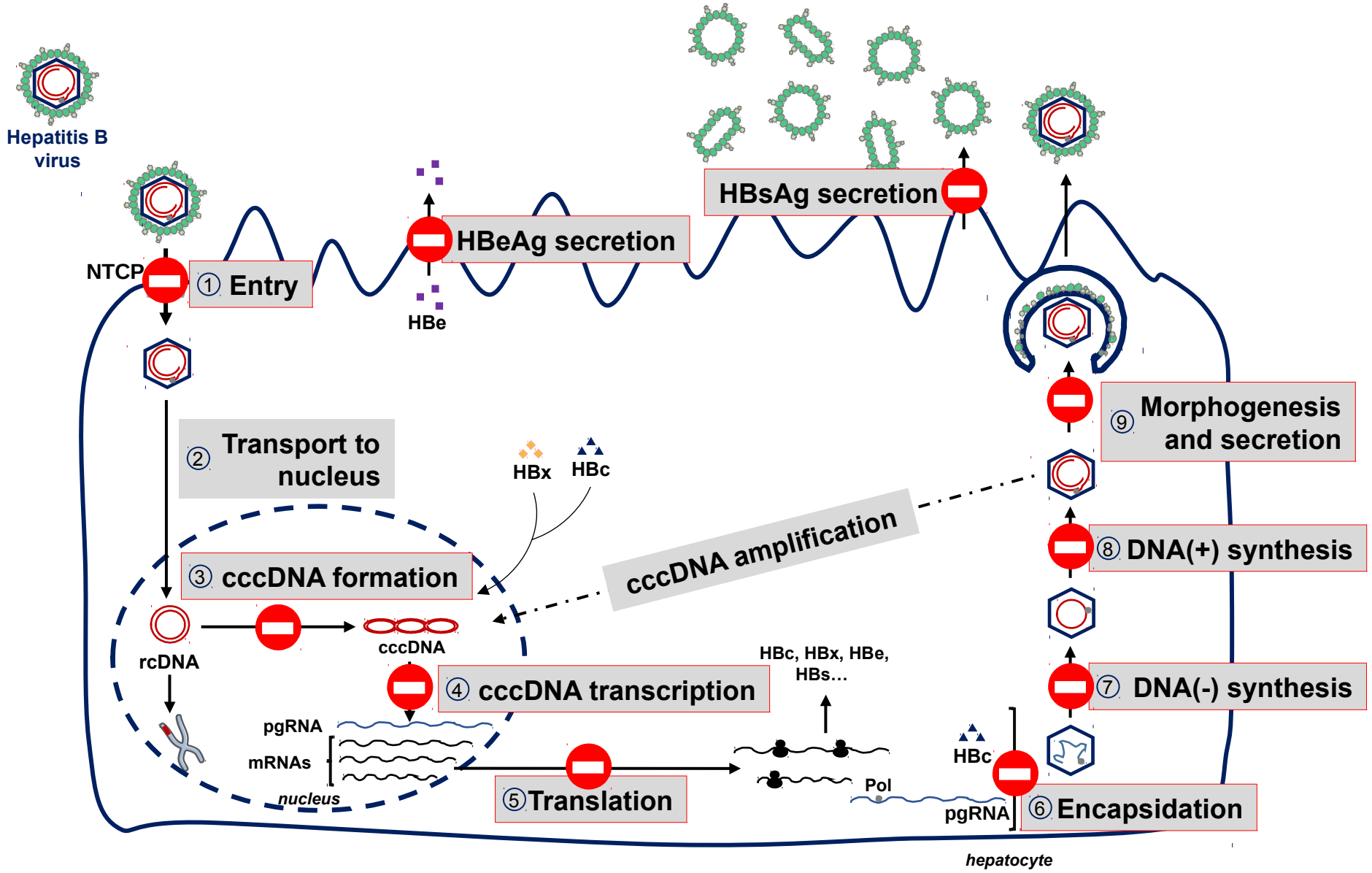
HBV cycle


Hepatitis B virus
NTCP
① Entry
② Transport to nucleus
HBx
HBc
③ cccDNA formation
cccDNA amplification
rcDNA
cccDNA
④ cccDNA transcription
HBc, HBx, HBe, HBs…
pgRNA
mRNAs
nucleus
⑤Translation
HBc
Pol
pgRNA
⑥ Encapsidation
⑦ DNA(-) synthesis
⑧ DNA(+) synthesis
hepatocyte

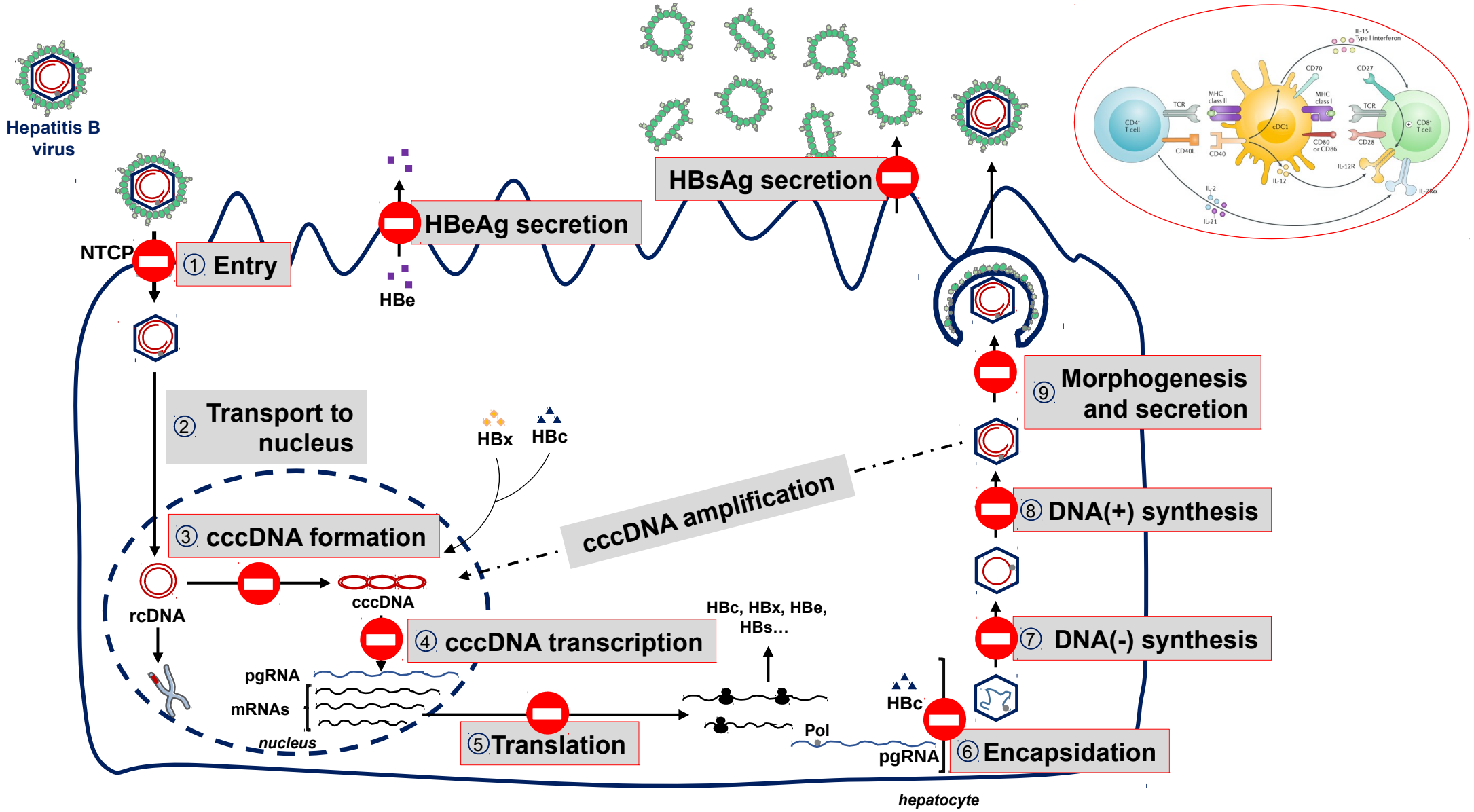
HBV cycle


Hepatitis B virus
NTCP
① Entry
HBeAg secretion
HBe
HBsAg secretion
② Transport to nucleus
HBx
HBc
③ cccDNA formation
cccDNA amplification
rcDNA
cccDNA
④ cccDNA transcription
HBc, HBx, HBe, HBs…
pgRNA
mRNAs
nucleus
⑤Translation
HBc
Pol
pgRNA
⑥ Encapsidation
⑦ DNA(-) synthesis
⑧ DNA(+) synthesis
⑨ Morphogenesis and secretion
hepatocyte

Therapeutic targets : points of inhibition



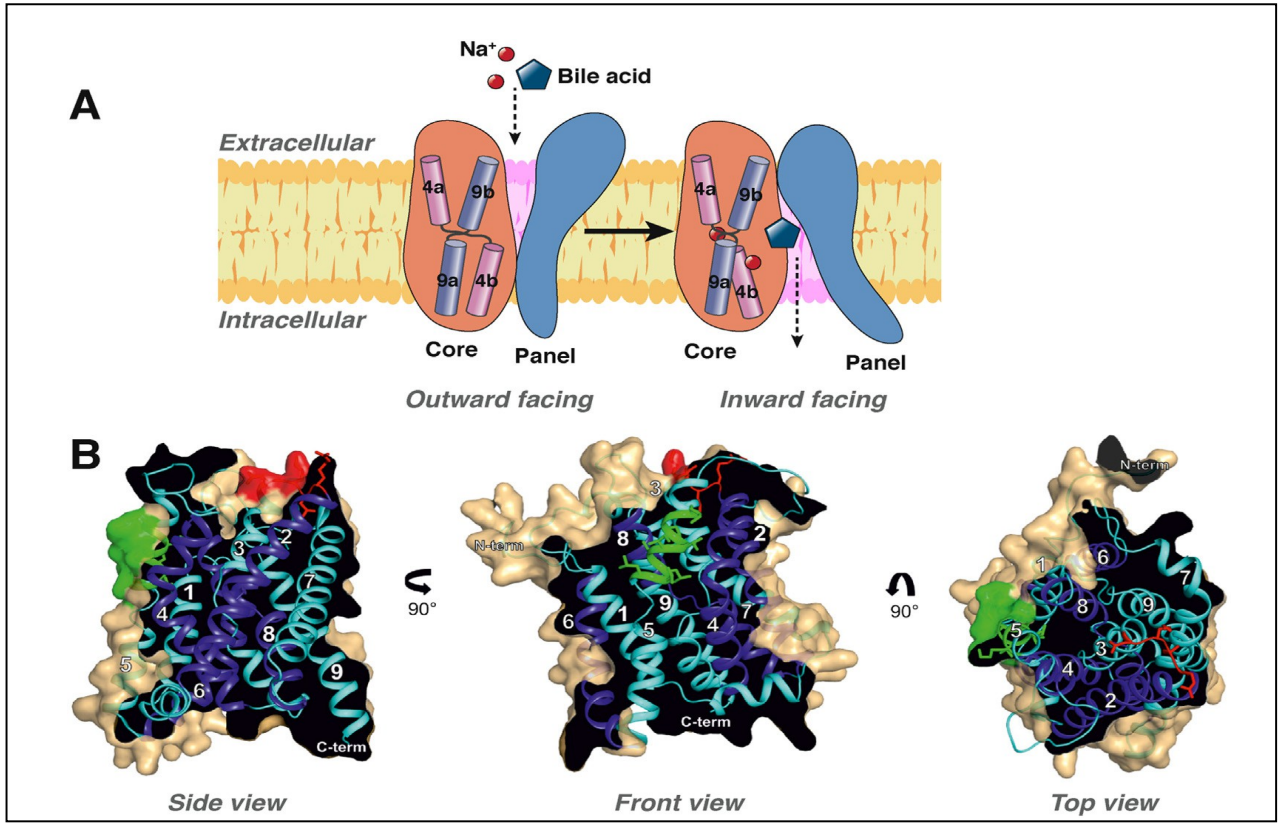
Therapeutic targets : points of inhibition

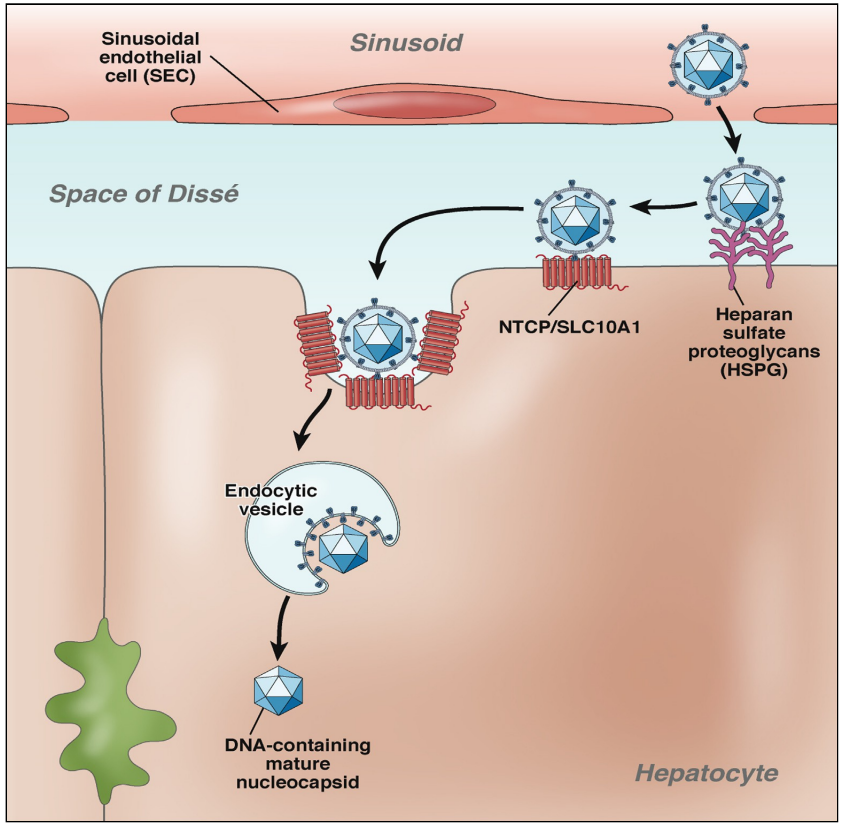


Targets and new drugs for HBV

1. HBV cure is a priority
2. What are the objectives (endpoints) ?
3. HBV virology, viral cycle and targets
4. **Direct-acting antivirals**
5. Host antivirals
6. Conclusion

HBV receptor:
Sodium taurocholate cotransporting polypeptide (NTCP)



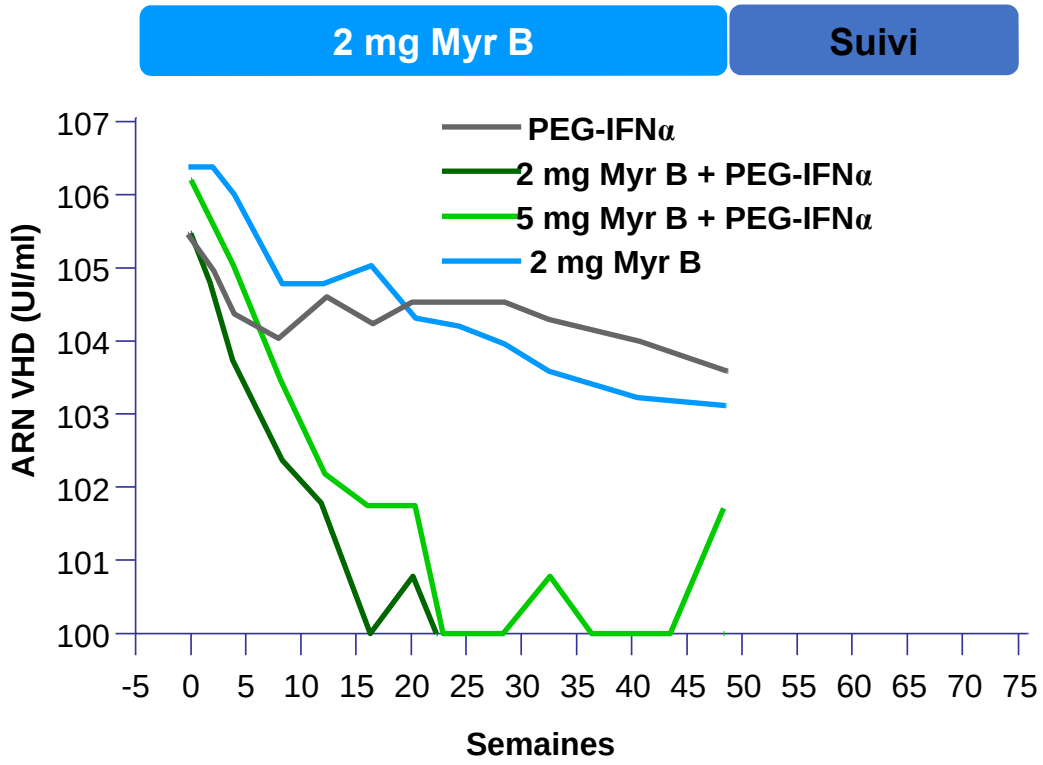


Yan H. et al, Elife. 2012 Nov 13;1:e00049
Urban et al. Gastroenterology. 2014;147(1):48-64.

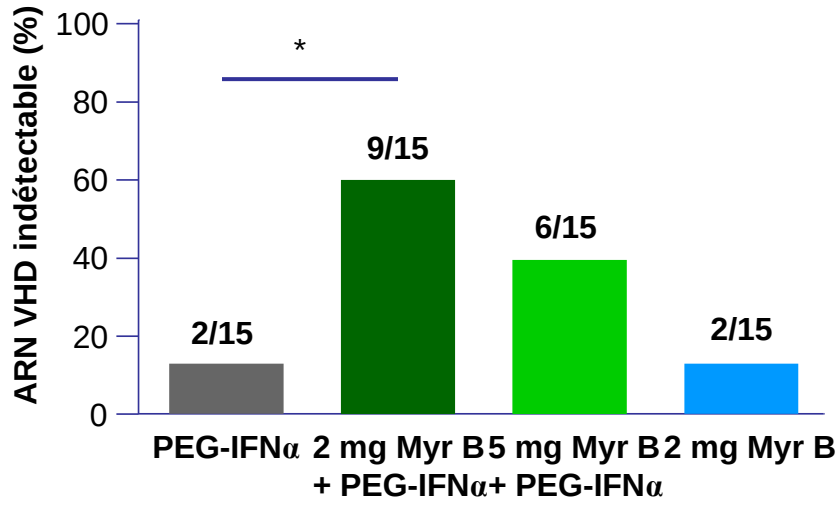
Entry inhibitor : Myrcludex B (Bulevirtide) ± PEG-IFN : HDV chronic infection (MyrPharma)

Phase II , Myrcludex B (NTCP inhibitor) ± PEG-IFN for 48 weeks

HDV RNA



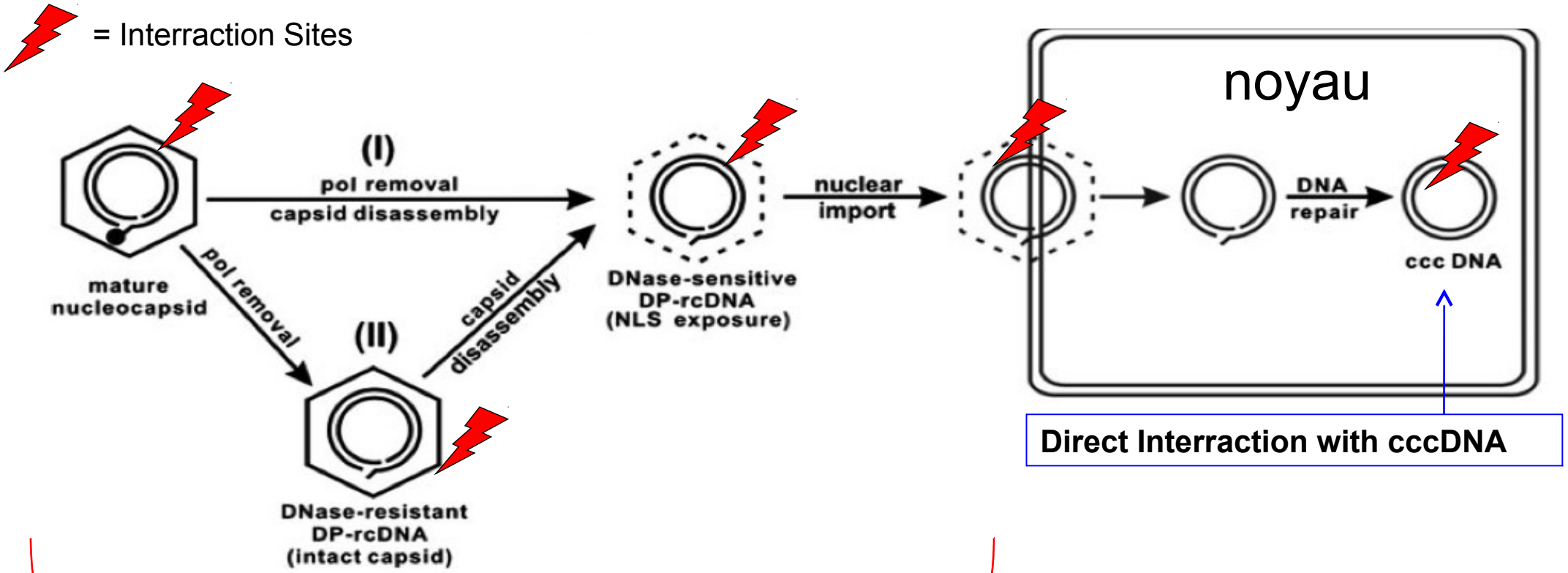
Undetectable HDV RNA at W48



* p < 0,01

Wedemeyer et al. A16; AASLD 2018,

Capsid as an attractive target (interraction with cccDNA synthesis)



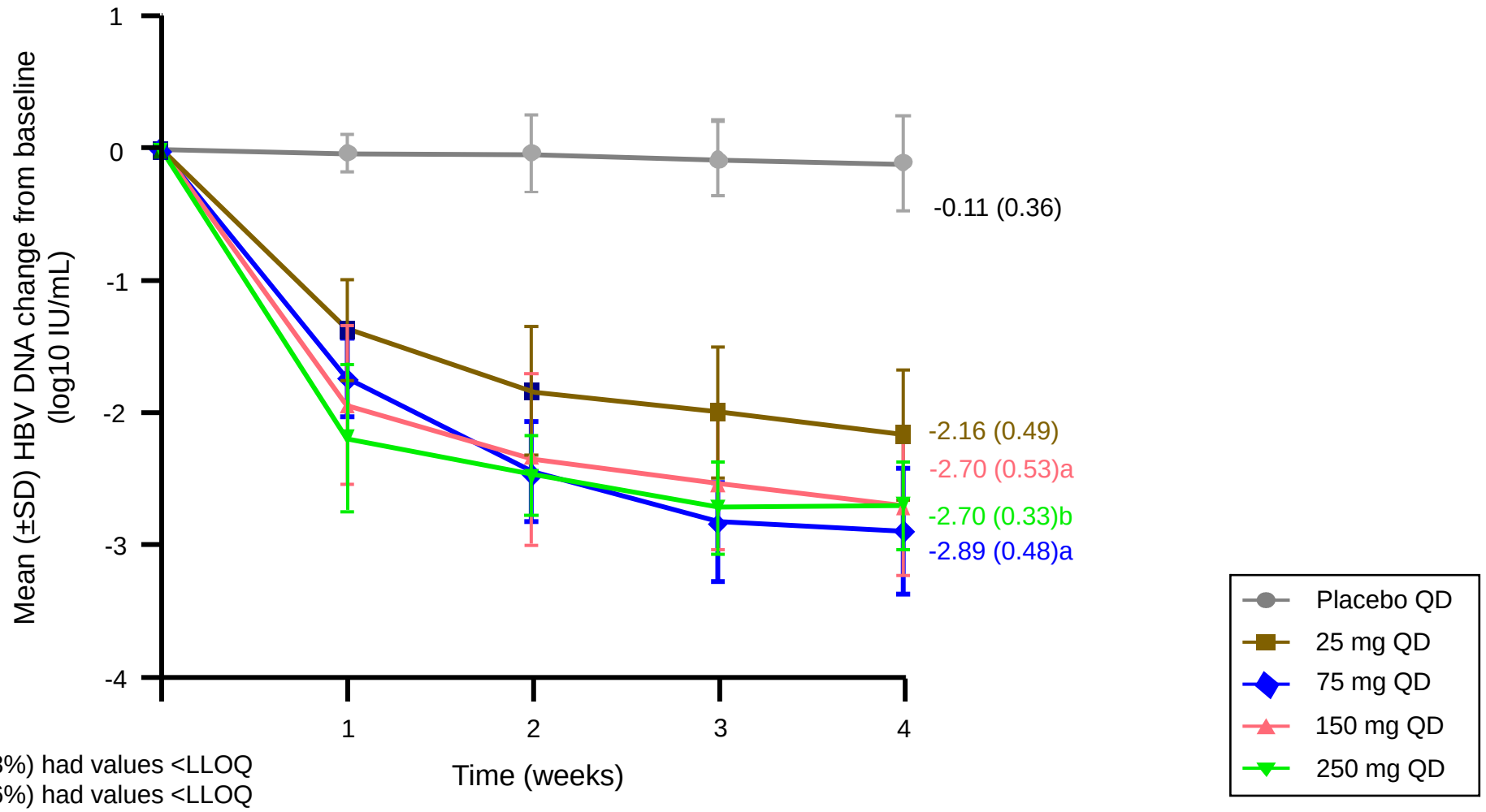
Guo et al. 2007

Y-H Guo et al. 2011

Capsid assembly modulator (CAM) : JNJ-6379

HBV DNA decrease after 4 weeks on treatment (Janssen)

Phase II , JNJ-6379 (Capsid inhibitor) for 4 weeks, Janssen



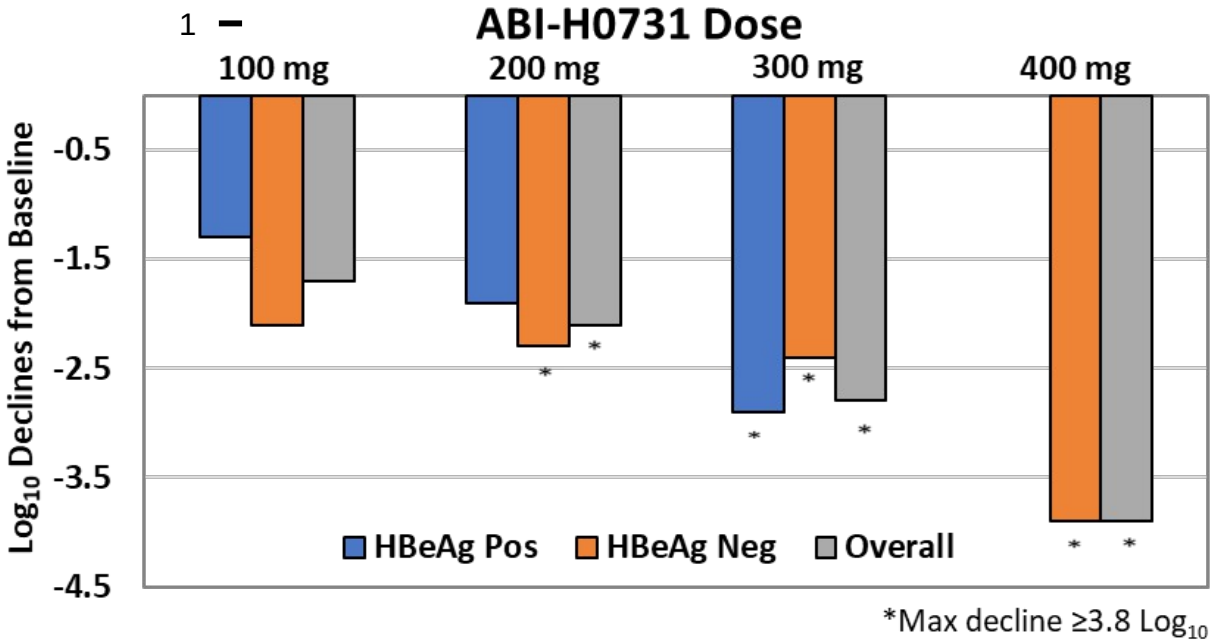
a 3 of 8 patients (38%) had values <LLOQ
b 5 of 9 patients (56%) had values <LLOQ

LLOQ = Lower limit of quantification (20 IU/mL) of the HBV DNA assay

Zoulim et al, AASLD 2018, A74

Core protein allosteric modifier (CpAM) : ABI-HO731 : HBV DNA decrease after 28 days on treatment (Assembly Biosciences)

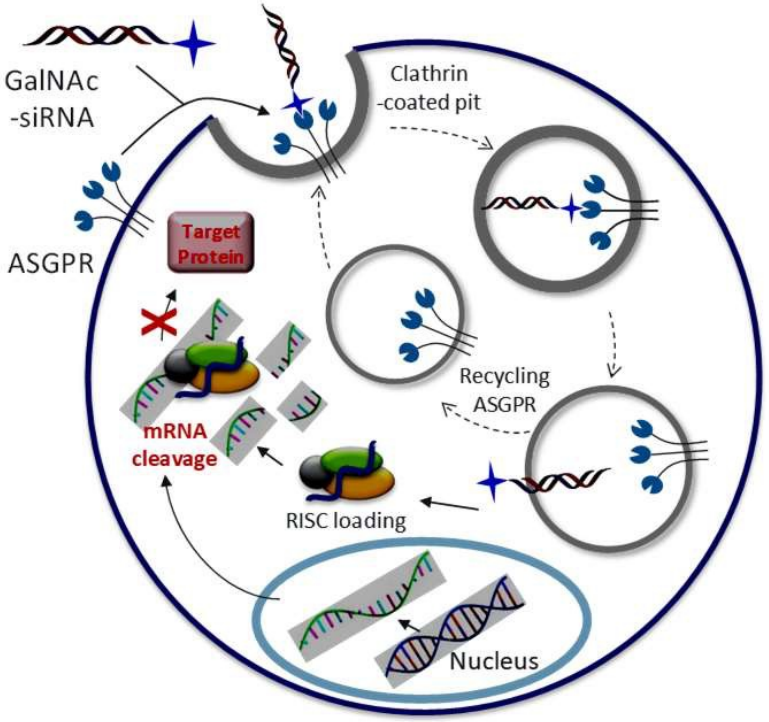
Phase Ib , ABI-HO731 , 12 patients for 28 days, Assembly Biosciences



	Log$_{10}$ Mean Maximal Declines (SD)			
Dose (mg)	**100**	**200**	**300**	**400**
HBeAg Pos	-1.3 (0.3)	-1.9 (0.7)	-2.9 (0.8)	N/A
HBeAg Neg	-2.2 (1.3)	-2.4 (0.9)	-2.5 (1.7)	-3.9 (0.1)
Overall	-1.7 (0.9)	-2.1 (0.8)	-2.8 (1.1)	-3.9 (0.1)

Yuen et al. AASLD 2018, Abstract 73

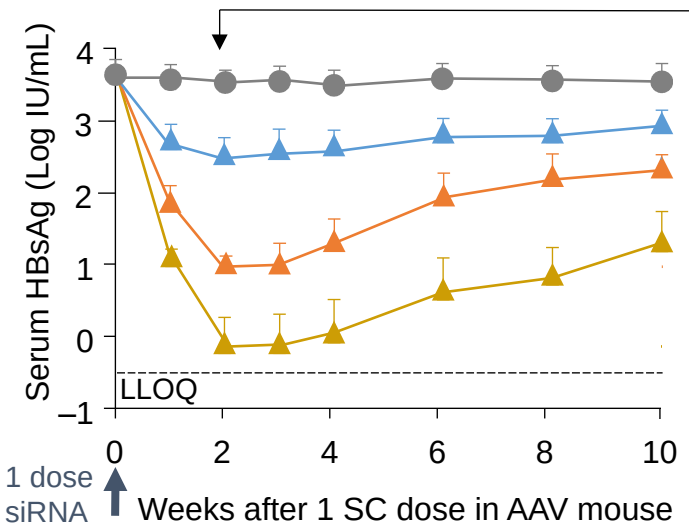
GalNAc-conjugated siRNA

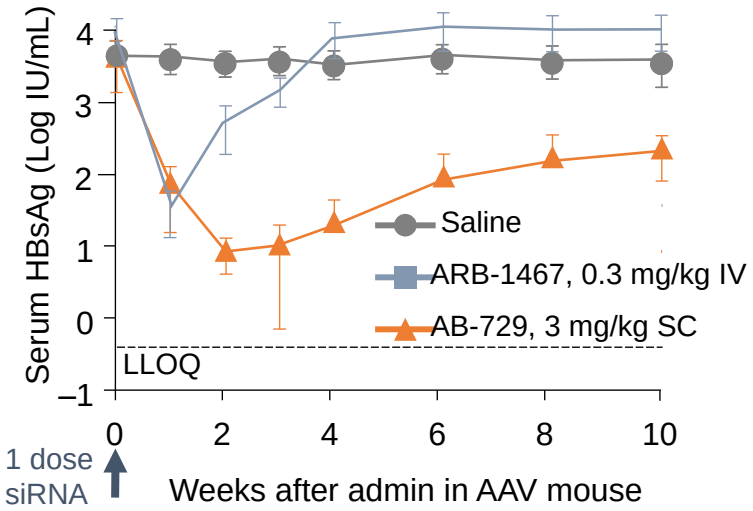


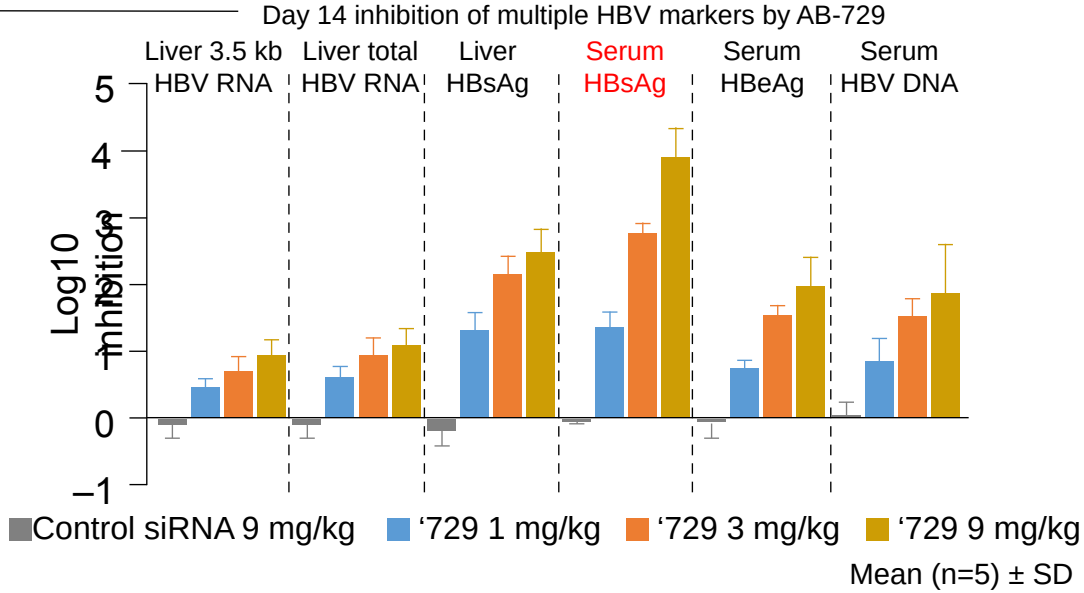
- siRNA delivery is mediated by a conjugated targeting ligand; GalNAc
  - **Cell uptake via GalNAc interaction with ASGPR**
  - Asialoglycoprotein Receptor
    - Highly expressed in/on hepatocytes
    - High rate of uptake
    - 15 min recycling time
    - Conserved across species

Lee A, et al. EASL 2018, Paris. #PS-029

SC GalNAc-conjugated siRNA agent AB-729 in preclinical models: HBV DNA and HBs decline (Arbutus)

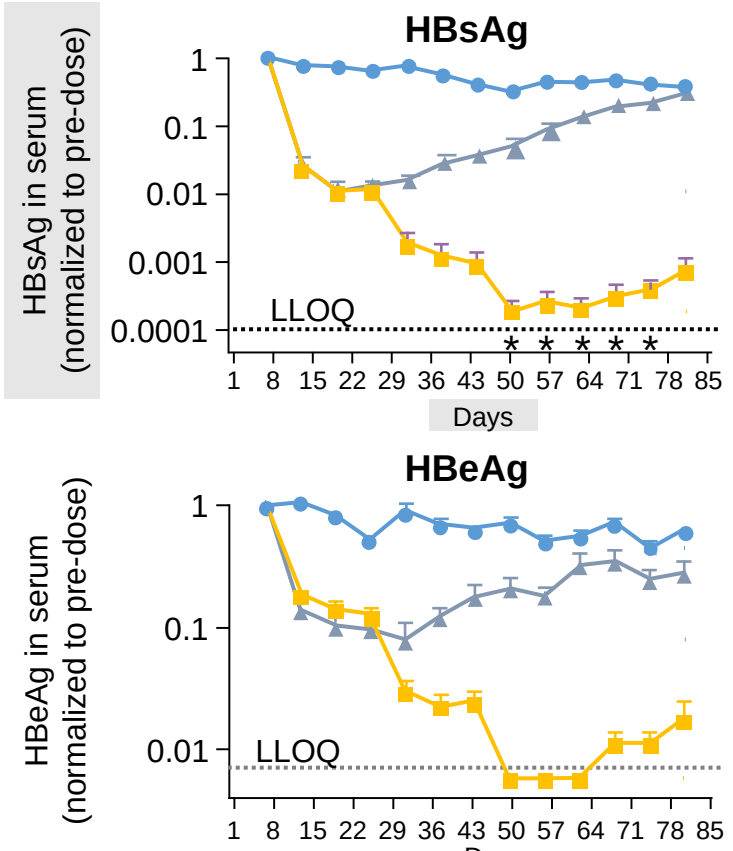






Lee ACH, et al. ILC 2018, #PS-029

RNA interference (RNAi) therapeutic ARO-HBV :
HBs decline (Arrowhead)



*Includes samples <LLOQ. Combination index study in the pHBV mouse model demonstrated synergy between ARO-HBV and entecavir. ARO-HBV is a promising new candidate for progression to clinical trials of chronic HBV and is expected to synergize with other antiviral compounds

Wooddell C, et al. ILC 2018, #PS-030

cccDNA as an important target HBV Persistence

cccDNA persistence is thought to be the cause of **chronic** HBV disease

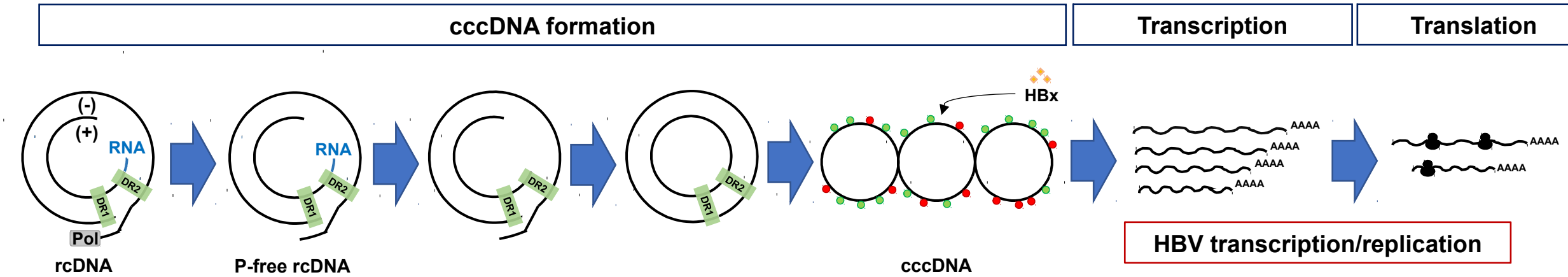
- cccDNA exists as a minichromosome in the nucleus
- cccDNA persists in the absence of active viral replication
- cccDNA levels reduced, but not eliminated with treatment/ liver regeneration

HBV Cure:

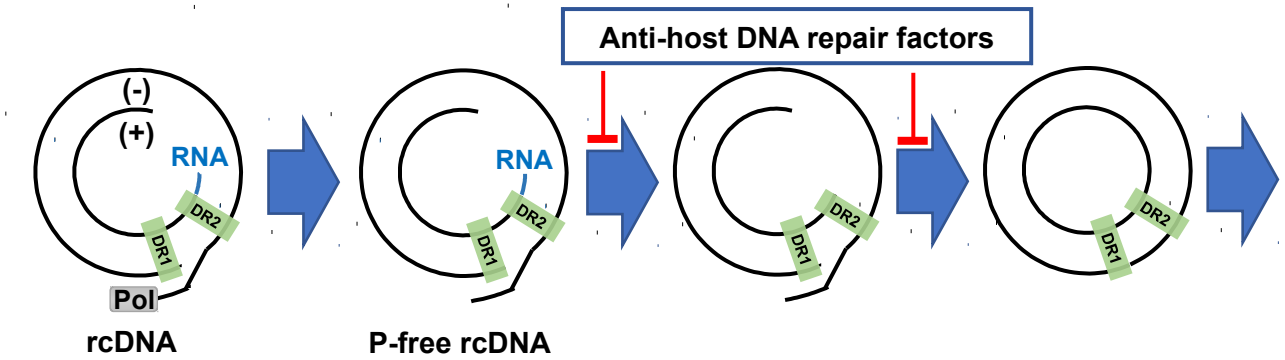
Elimination, suppression or control of cccDNA

Importance to develop "surrogate markers" of cccDNA

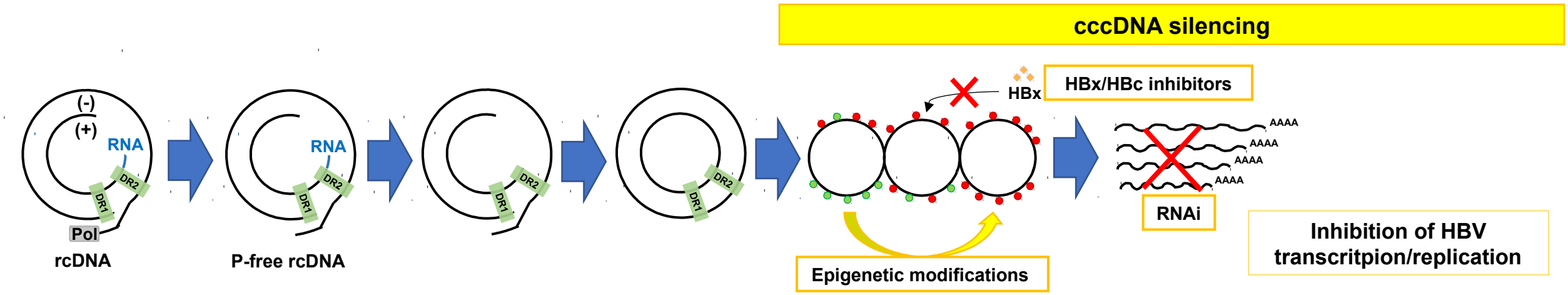
cccDNA : Targuet



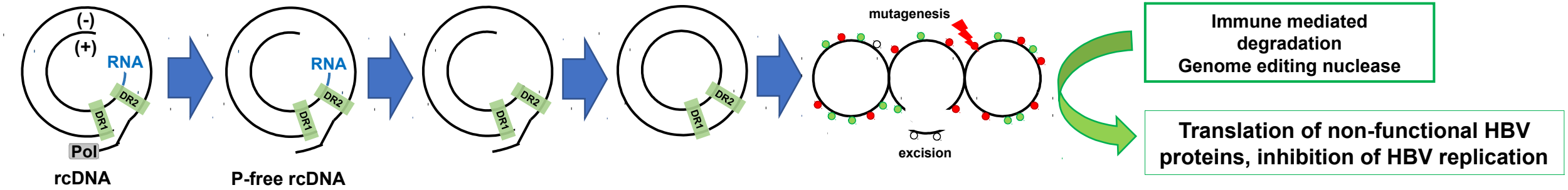
Inhibition of cccDNA formation

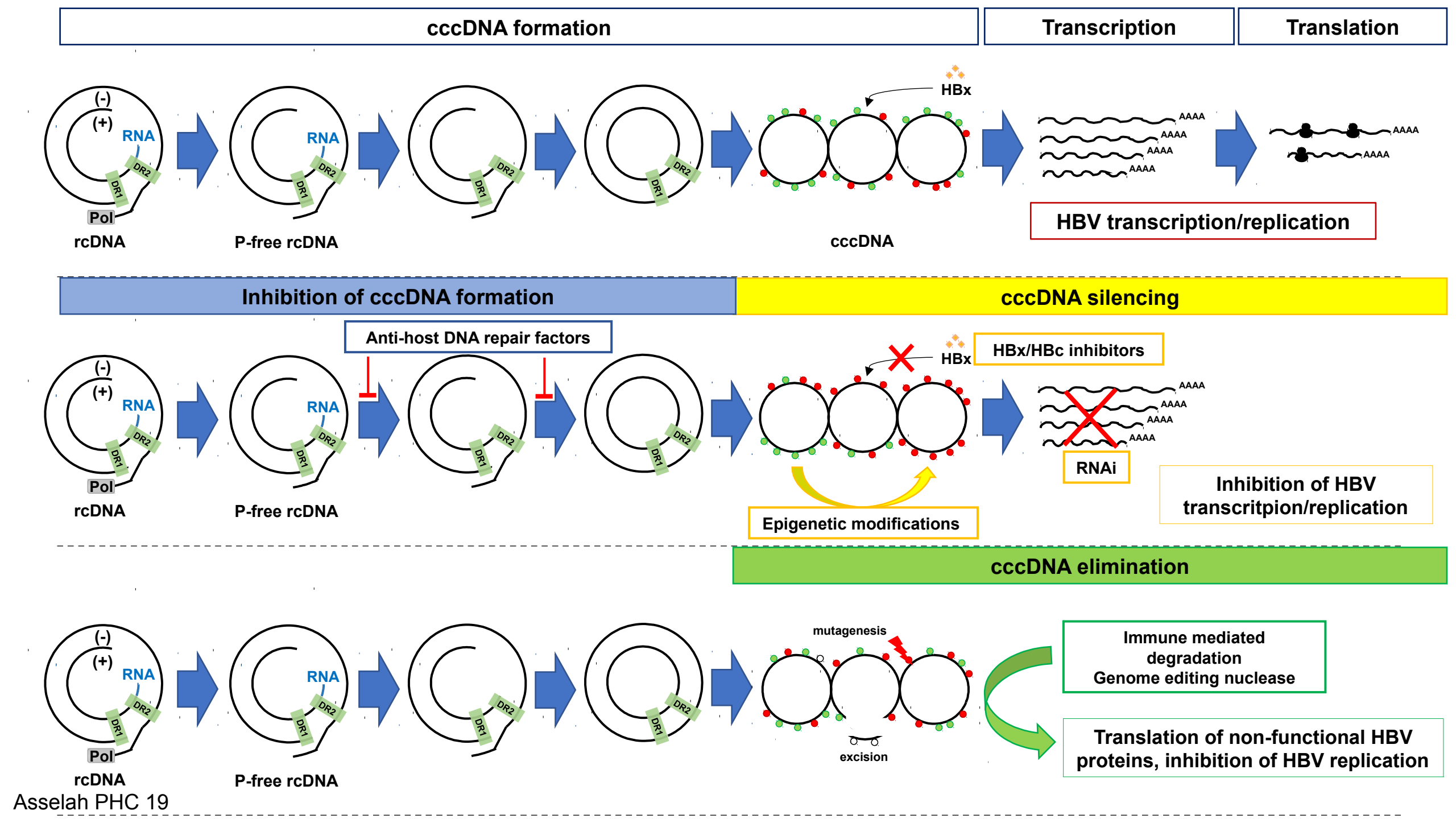


No cccDNA formation, inhibition of HBV transcription/replication


cccDNA silencing
(-)
(+)
RNA
DR2
DR1
Pol
rcDNA
RNA
DR2
DR1
P-free rcDNA
DR2
DR1
DR2
DR1
HBx
HBx/HBc inhibitors
AAAA
AAAA
AAAA
AAAA
RNAi
Epigenetic modifications
Inhibition of HBV transcritpion/replication

cccDNA elimination

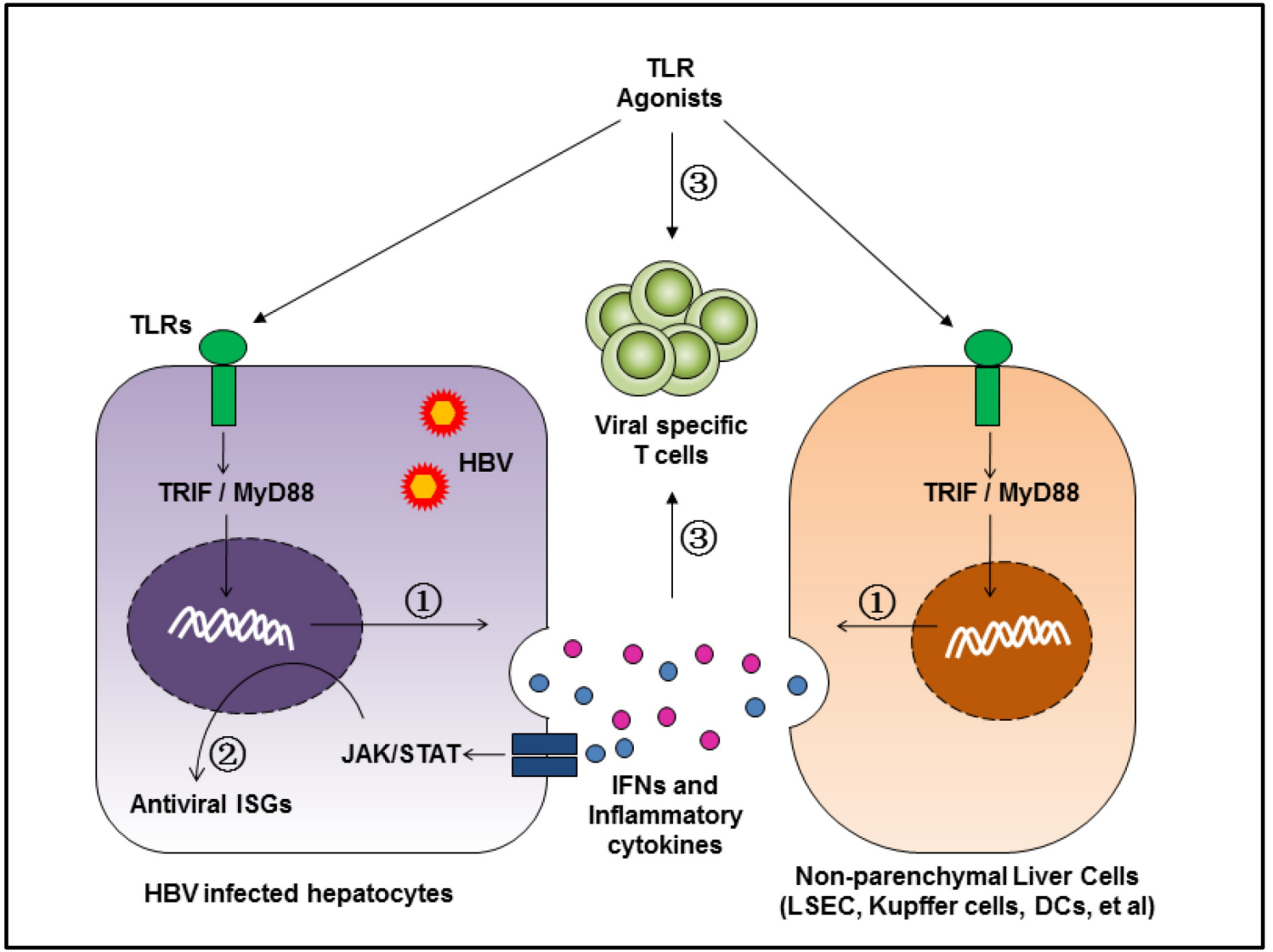



cccDNA formation
Transcription
Translation
(-)
(+)
RNA
DR2
DR1
Pol
rcDNA
P-free rcDNA
cccDNA
HBx
AAAA
HBV transcription/replication
Inhibition of cccDNA formation
cccDNA silencing
Anti-host DNA repair factors
HBx/HBc inhibitors
RNAi
Epigenetic modifications
Inhibition of HBV transcritpion/replication
cccDNA elimination
mutagenesis
excision
Immune mediated degradation
Genome editing nuclease
Translation of non-functional HBV proteins, inhibition of HBV replication

Targets and new drugs for HBV

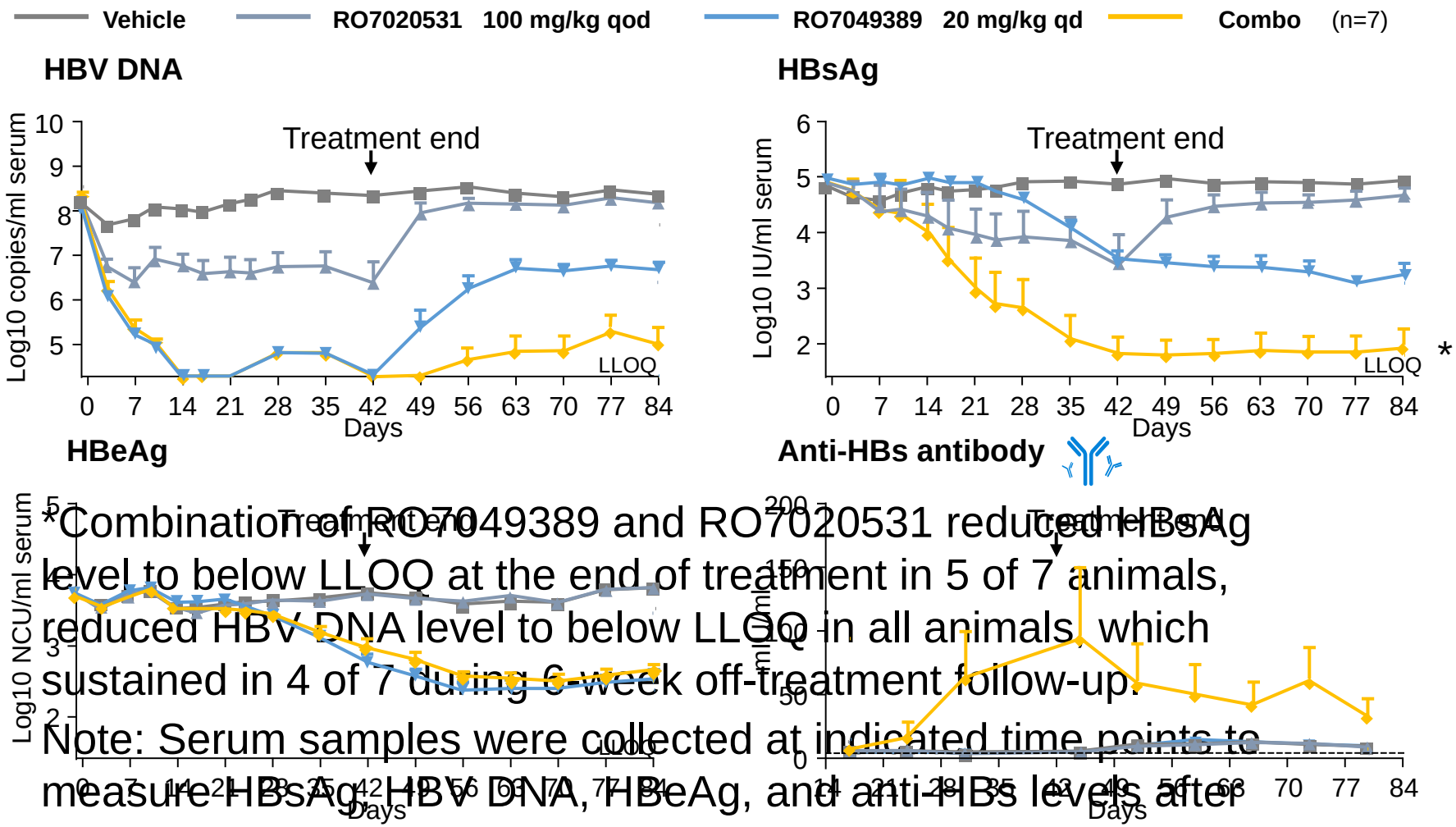
1. HBV cure is a priority
2. What are the objectives (endpoints) ?
3. HBV virology, viral cycle and targets
4. Direct-acting antivirals
5. **Host antivirals**
6. Conclusion

HBV and Toll Like Receptors (TLR)



Ma et al. Vaccines 2018

TLR7 agonist RO7020531 + CpAM RO7049389 :
HBV DNA decrease and HBsAg loss in an AAV-HBV mouse model (Roche)



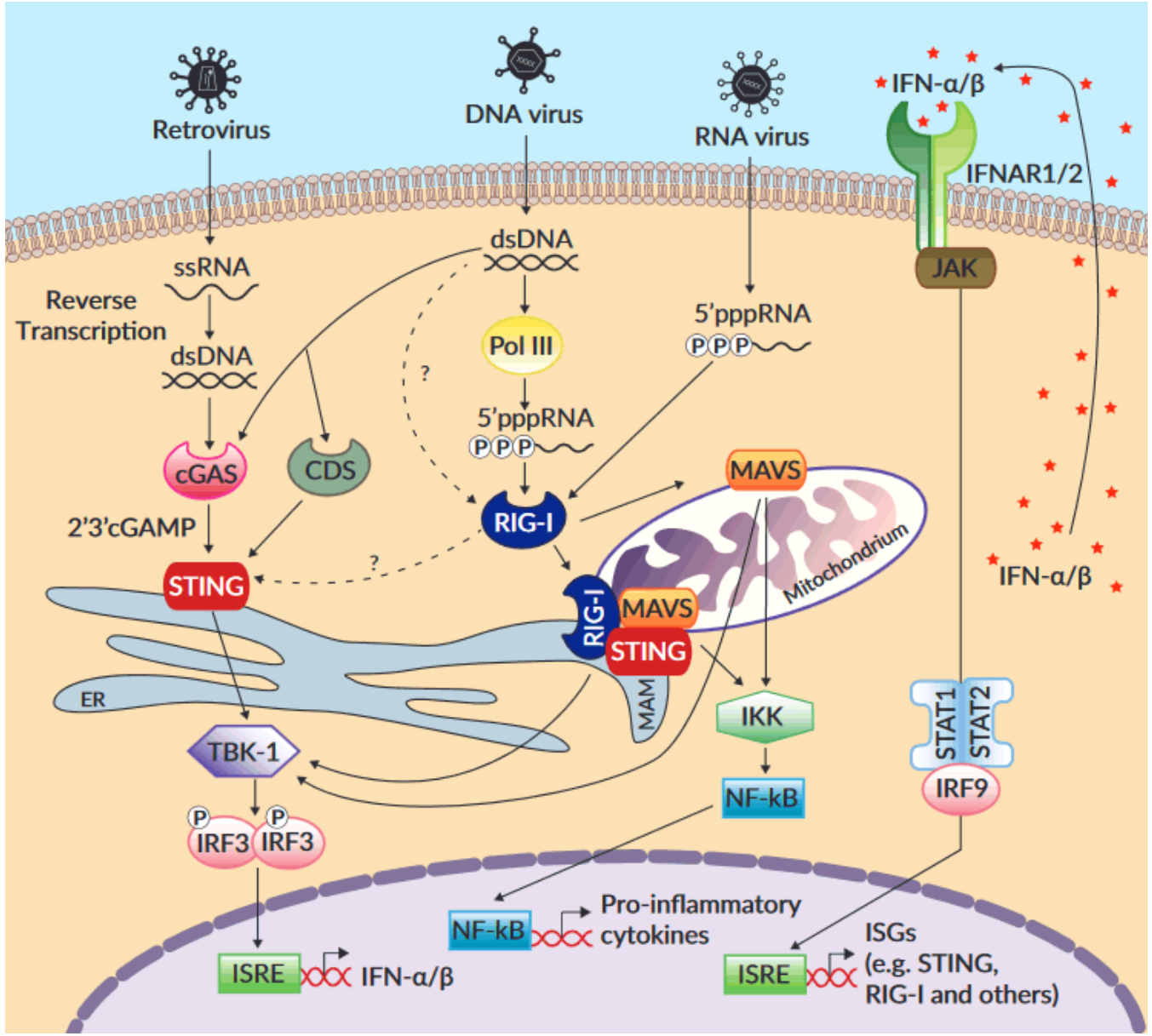
*Combination of RO7049389 and RO7020531 reduced HBsAg level to below LLOQ at the end of treatment in 5 of 7 animals, reduced HBV DNA level to below LLOQ in all animals, which sustained in 4 of 7 during 6-week off-treatment follow-up.

Note: Serum samples were collected at indicated time points to measure HBsAg, HBV DNA, HBeAg, and anti-HBs levels after compound treatment and during the off-treatment period.

Results are presented as mean ± SEM (n=7)

Dai L, et al. ILC 2018, #PS-028

HBV and RIG-I pathway

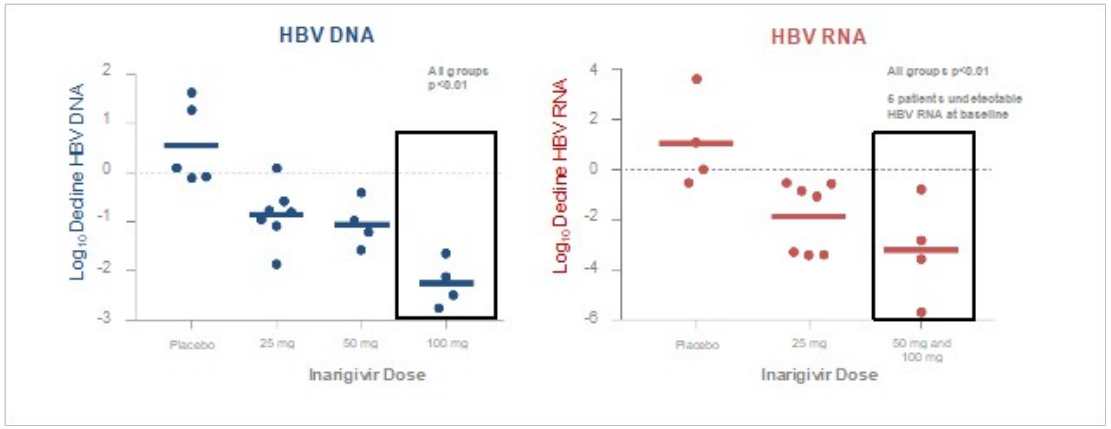


RIG-I agonist : Inarigivir

HBV DNA decrease after 28 days on treatment (Spring Bank)

Inarigivir (oral RIG-1 agonist), for 12 weeks

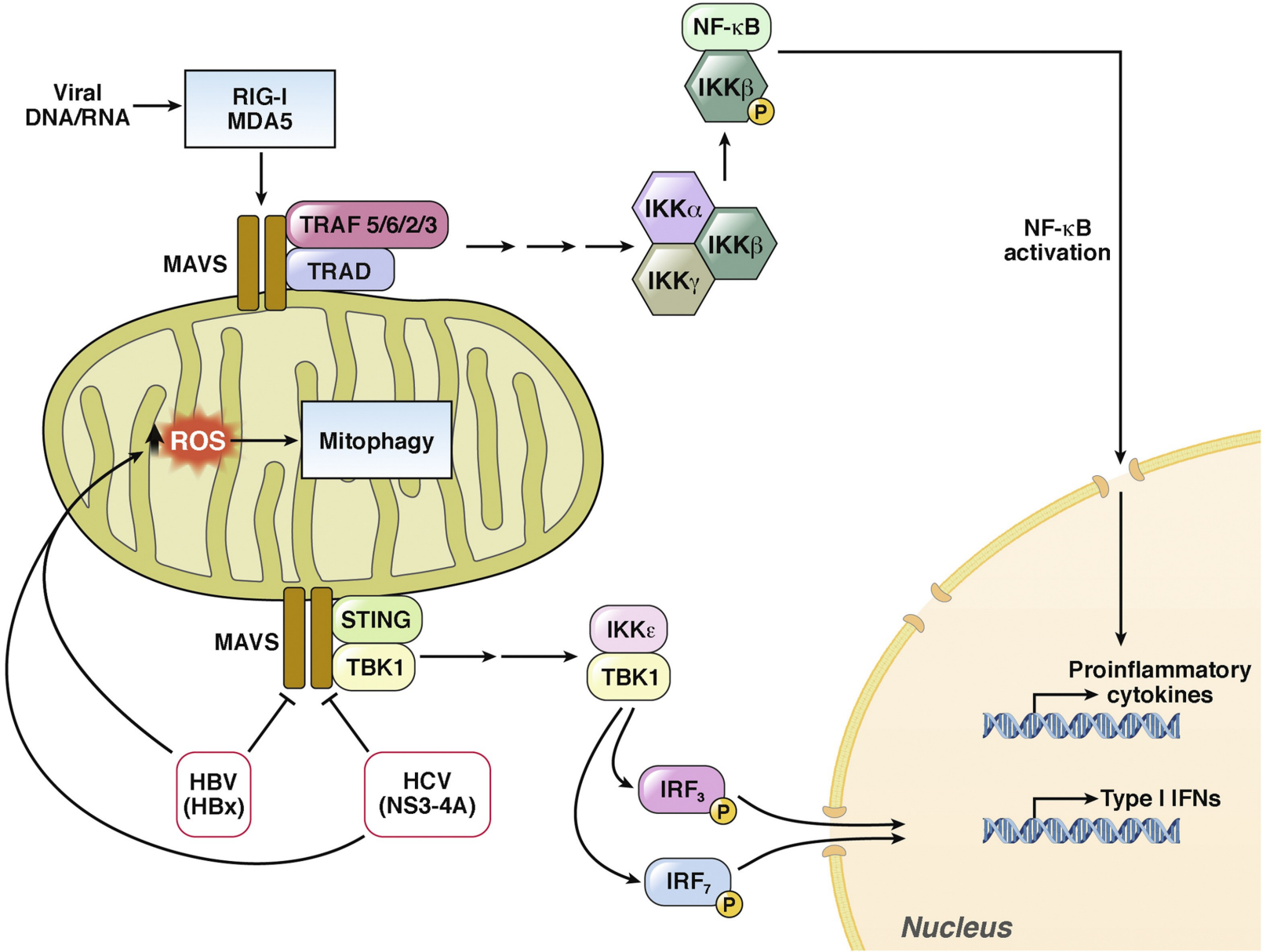
Inarigivir demonstrates a continuing positive dose response in HBeAg -ve patients at week 12



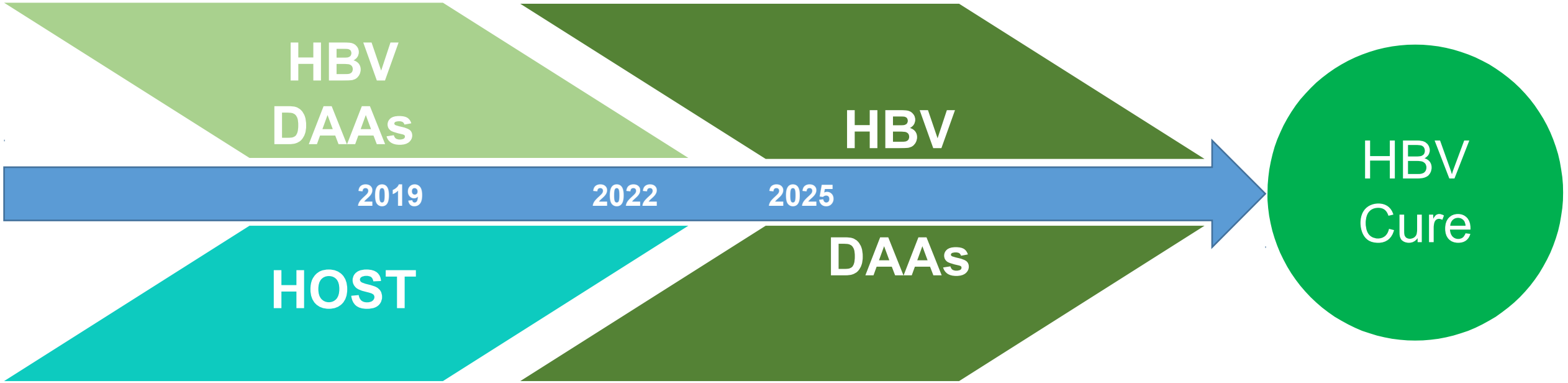
Inarigivir demonstrates a continuing positive dose response in HBeAg +ve patients at week 12

Yuen et al. AASLD 2018, Abstract 75

HBV interactions with Mitochondrial Immune Response



Mansouri, Gattolliat and Asselah. Gastroenterology 2018


HBV
DAAs
HBV
2019
2022
2025
HOST
DAAs
HBV
Cure

« Failure is the foundation of success »

Lao Tseu, 6th-century BC

« A pessimist sees the difficulty in every opportunity,

An optimist sees the oportunity in each difficulty »

Winston Churchill