HBV: *Is It a Curable Disease*

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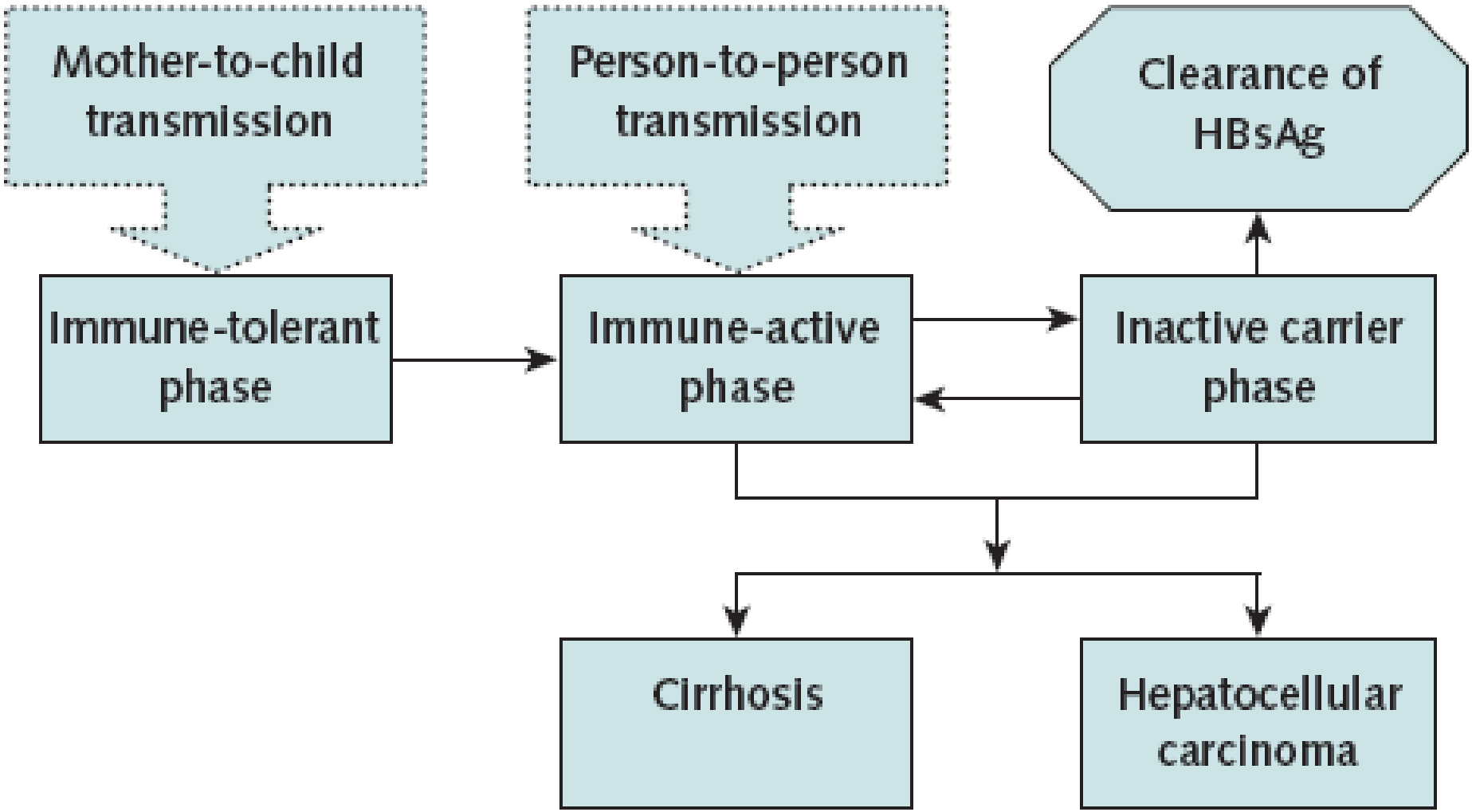
12-2016

Potential conflicts of interest

- Honararia from Gilead, J&J, Merck, Genetech, Abbott
- Spouse works for Hoffmann La Roche

Natural history of HBV

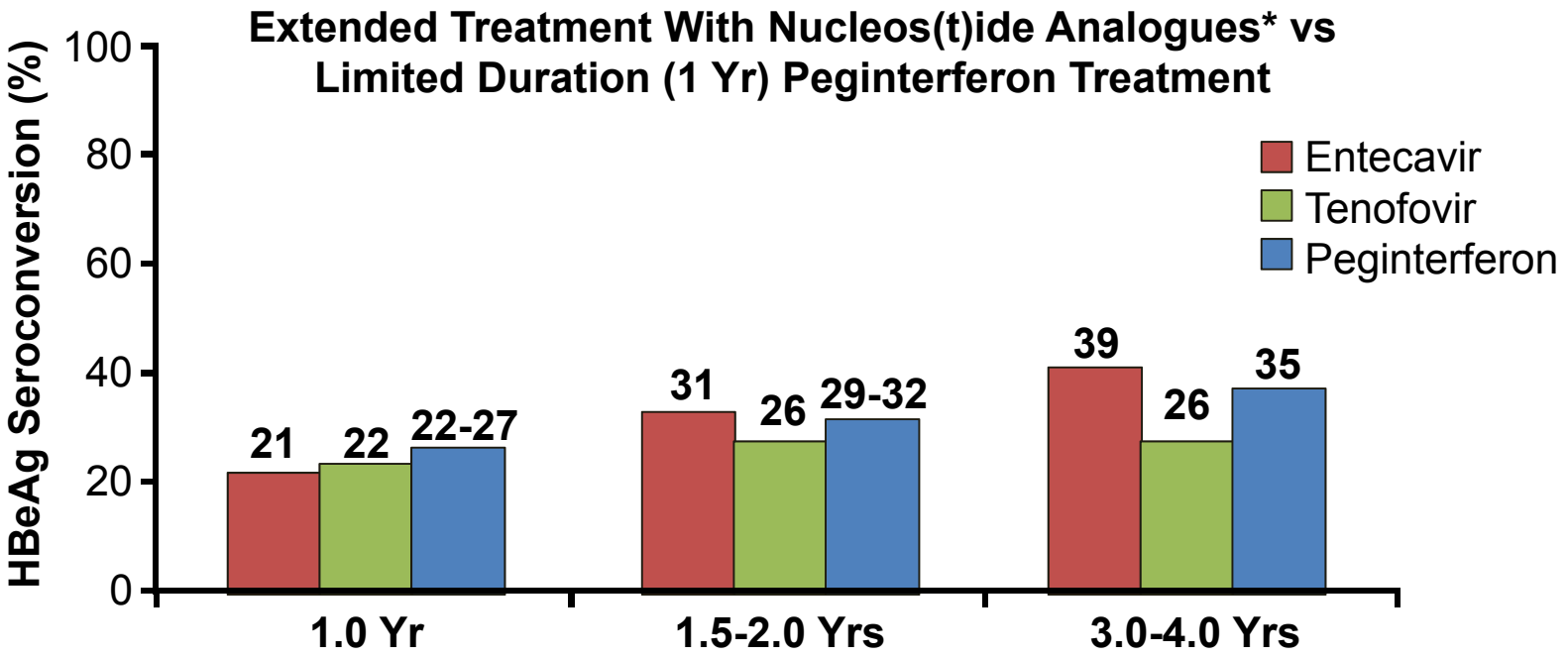


HBV Control

- Inflammatory: normalize serum ALT, biopsy
- Virologic: decrease HBV DNA
- Immune: seroconversion
  - HBeAg to anti-HBe
  - HBsAg to anti-HBs
- HBV as of 2016 not “cured” but controlled

HBeAg Seroconversion Rates Over Time in HBeAg Positive Patients

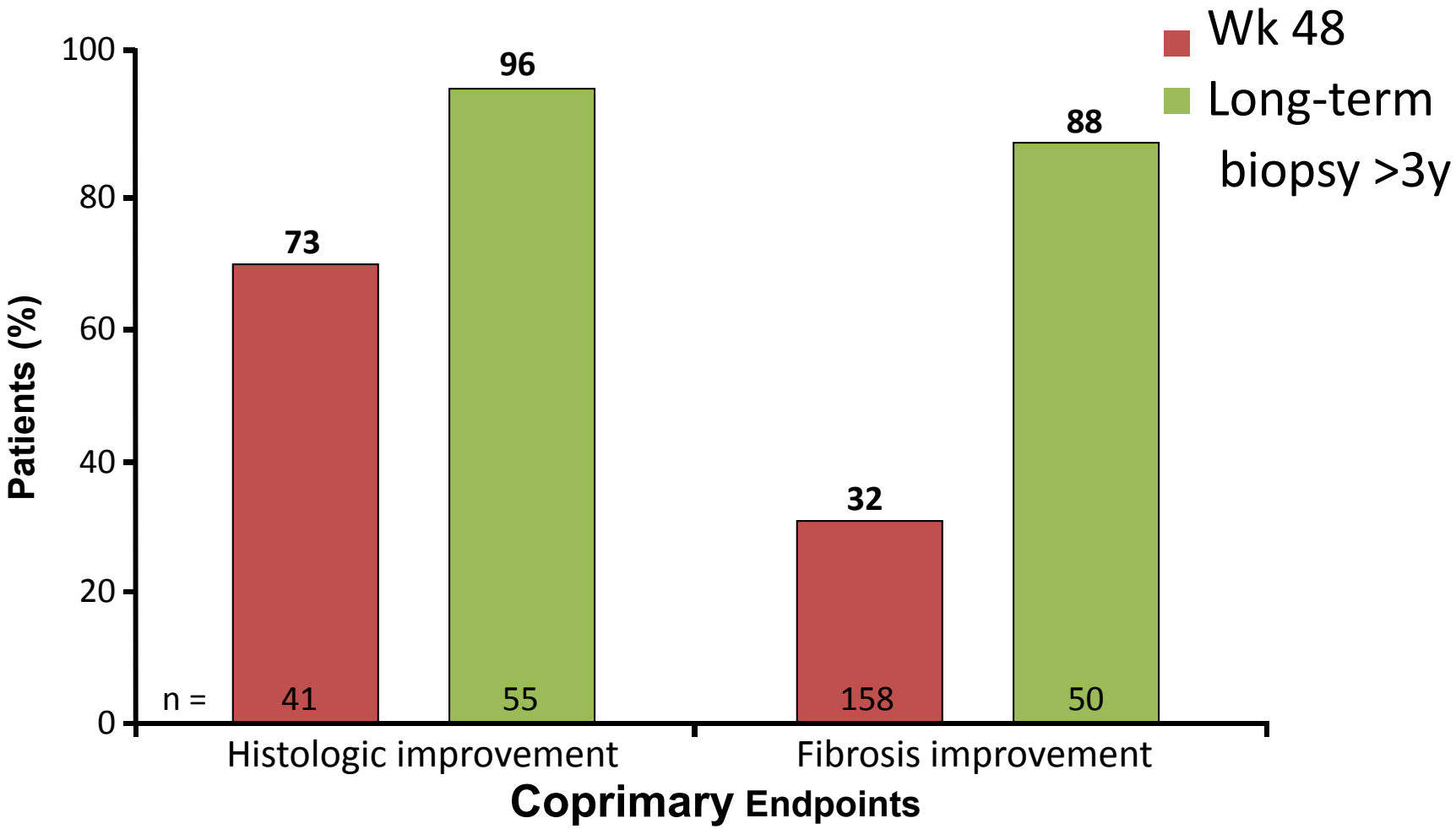
Not head-to-head trials; different patient populations and trial designs



*With sustained undetectable HBV DNA.

Chang TT, et al. J Viral Hepat. 2009;16:784-789. Chang TT, et al. AASLD 2006. Abstract 109. Lau GK, et al. N Engl J Med. 2005;352:2682-2695. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135;459-467. Heathcote J, et al. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483.
Janssen HL, et al. Lancet. 2005;365;123-129.

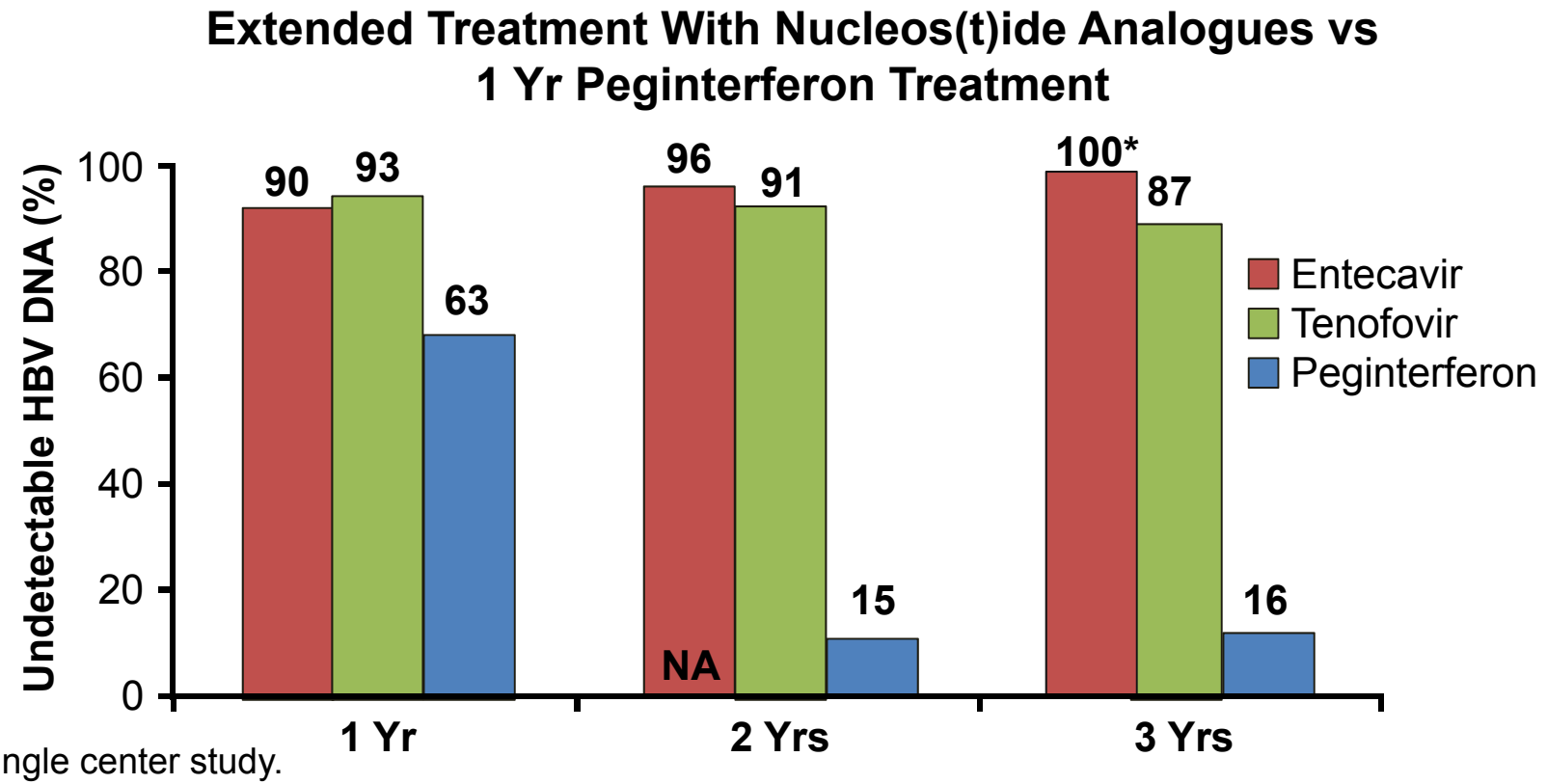
Long-term Entecavir Treatment Improves Liver Histology and Fibrosis



Chang TT, et al. Hepatology. 2010;52:886-893 CCO Hepatitis.

Undetectable HBV DNA Over Time in HBeAg Negative Patients

Not head-to-head trials; different patient populations and trial designs

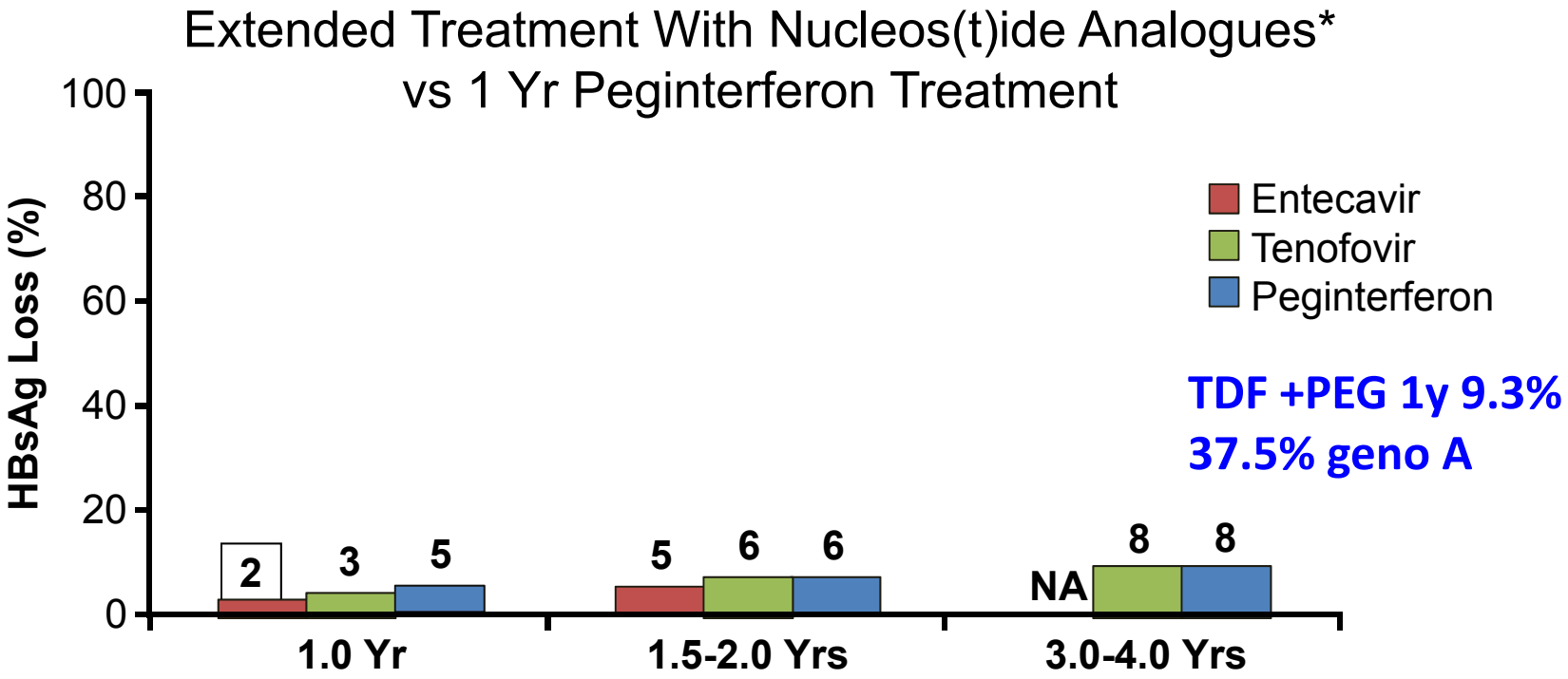


*Single center study.

Lok AS, et al. Hepatology. 2009;50:661-662. Marcellin P, et al. AASLD 2008. Abstract 146. Marcellin P, et al. AASLD 2009. Abstract 481. Marcellin P, et al. Gastroenterology. 2009;136:2169-2179. Baqai S, et al. AASLD 2009. Abstract 476. Lai CL, et al. Hong Kong International Liver Congress 2006.

HBsAg Loss Over Time in HBeAg Positive Patients

Not head-to-head trials; different patient populations and trial designs



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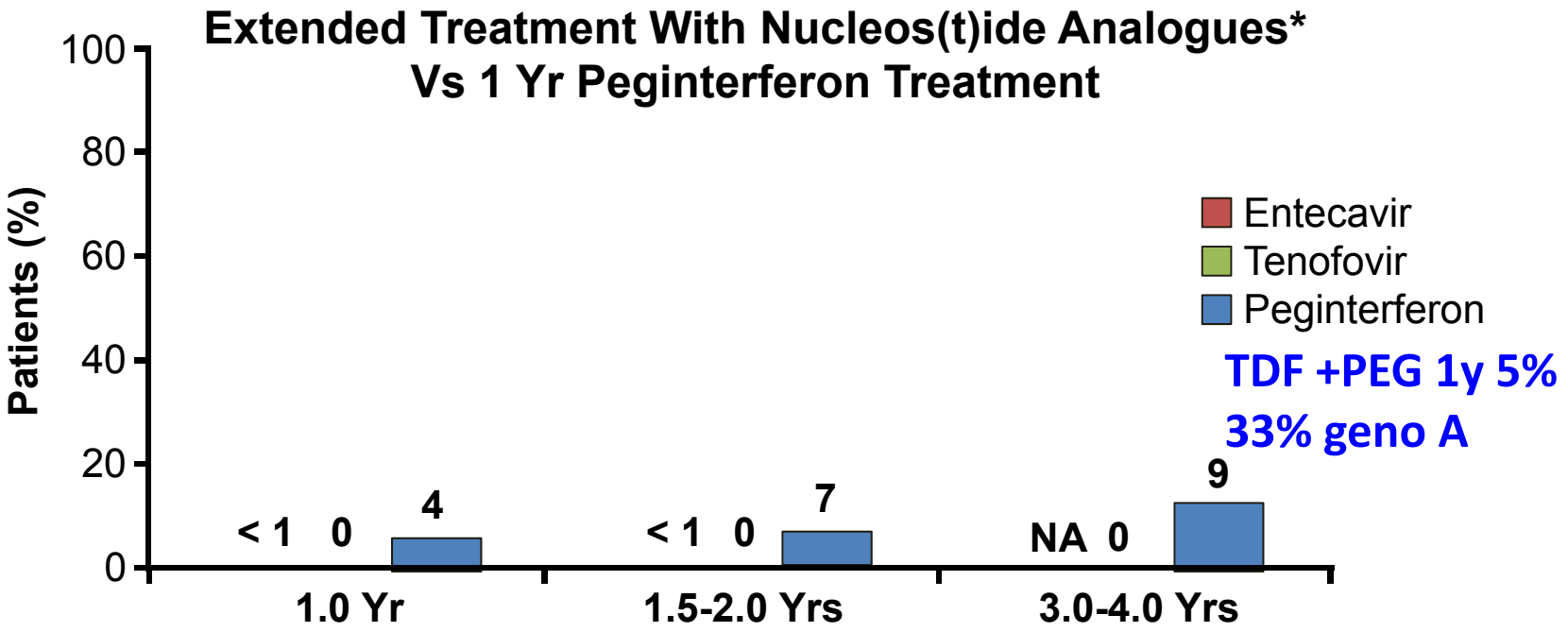
Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129; Marcellin Gastro 2016

HBsAg Loss Over Time in HBeAg Negative Patients

Not head-to-head trials; different patient populations and trial designs



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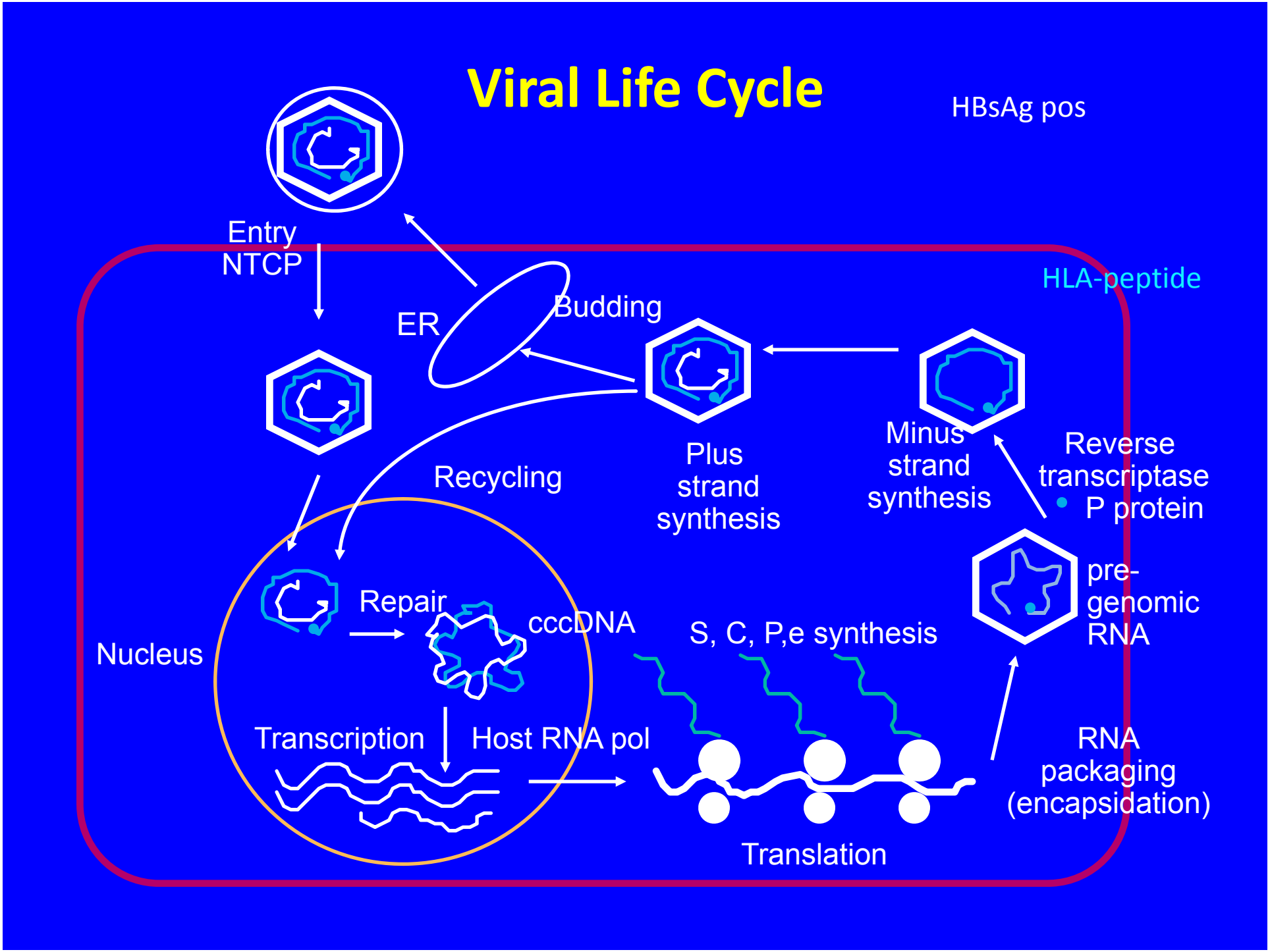
Lai CL, et al. N Engl J Med. 2006;354:1011-1020. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Marcellin P, et al. AASLD 2008. Abstract 146. Shouval D, et al. J Hepatol. 2009;50:289-295.
Marcellin P, et al. AASLD 2009. Abstract 481. Brunetto M, et al. EASL 2008. Abstract 683.Marcellin Gastro 2016

Types of HBV cure

Functional Cure- clinical resolution
Sustained, off drug:
- No inflammation: ALT and liver biopsy
- HBsAg loss
- HBsAb gain

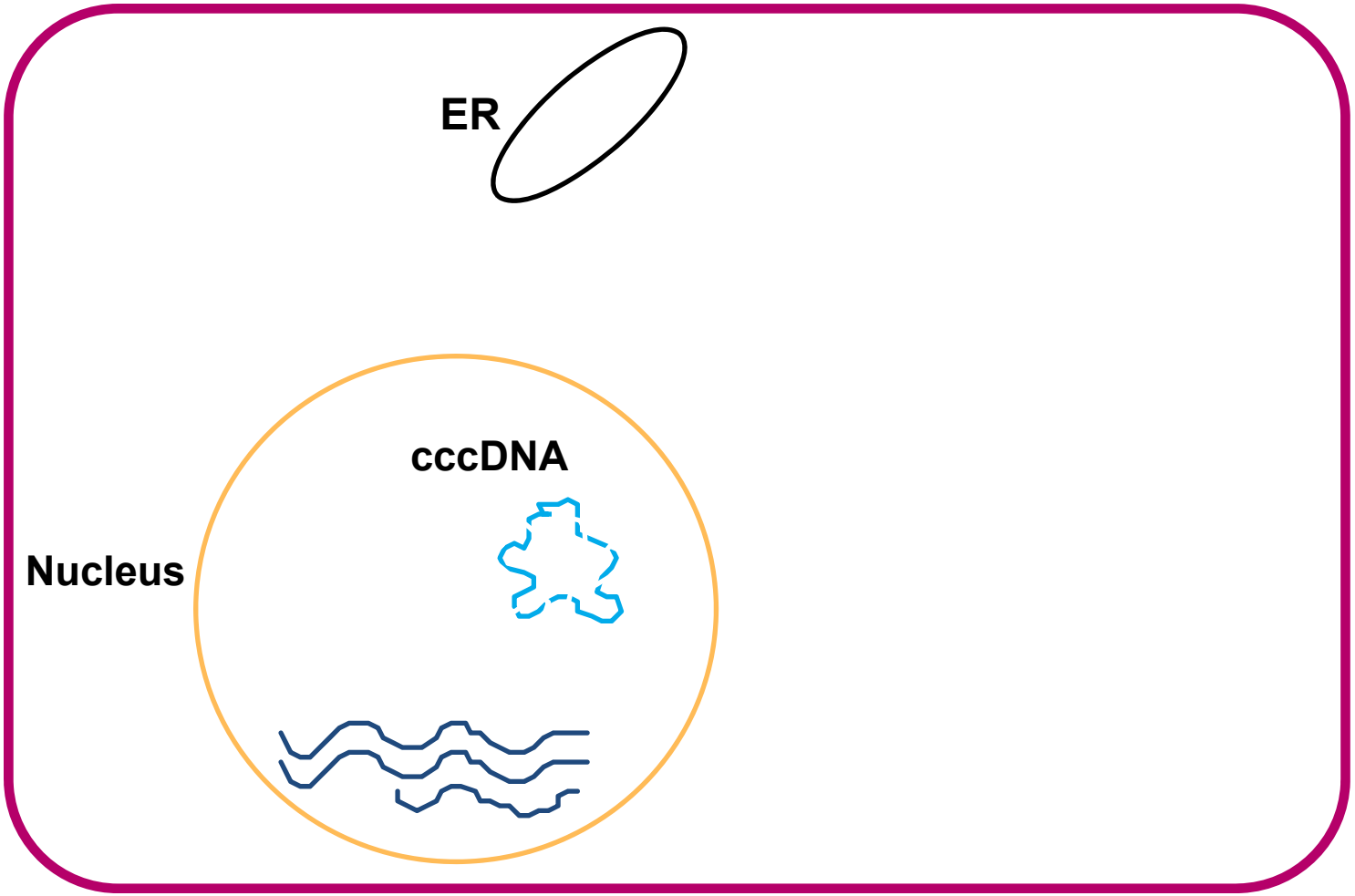
Complete cure- virological cure
- All of above plus
- Loss of cccDNA in liver

Inactive state -an interim goal?
- No inflammation: ALT and liver biopsy
- HBV DNA low or u/d
- HBsAg positive


Viral Life Cycle
HBsAg pos
Entry
NTCP
ER
Budding
HLA-peptide
Plus
strand
synthesis
Minus
strand
synthesis
Reverse
transcriptase
P protein
Recycling
pre-
genomic
RNA
Repair
cccDNA
Nucleus
S, C, P,e synthesis
Transcription
Host RNA pol
RNA
packaging
(encapsidation)
Translation

Viral Life Cycle- “latent or recovered” HBV: functional cure

Immune system considers this “recovered”
BUT cccDNA remains: template for viral replication



HBsAg neg
Anti-HBs
Anti-HBc

Strategies to Eradicate HBV

Virologic approaches

- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- polymerase inhibitors
- Secretion inhibitors

Host immune approaches

- Interferons
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
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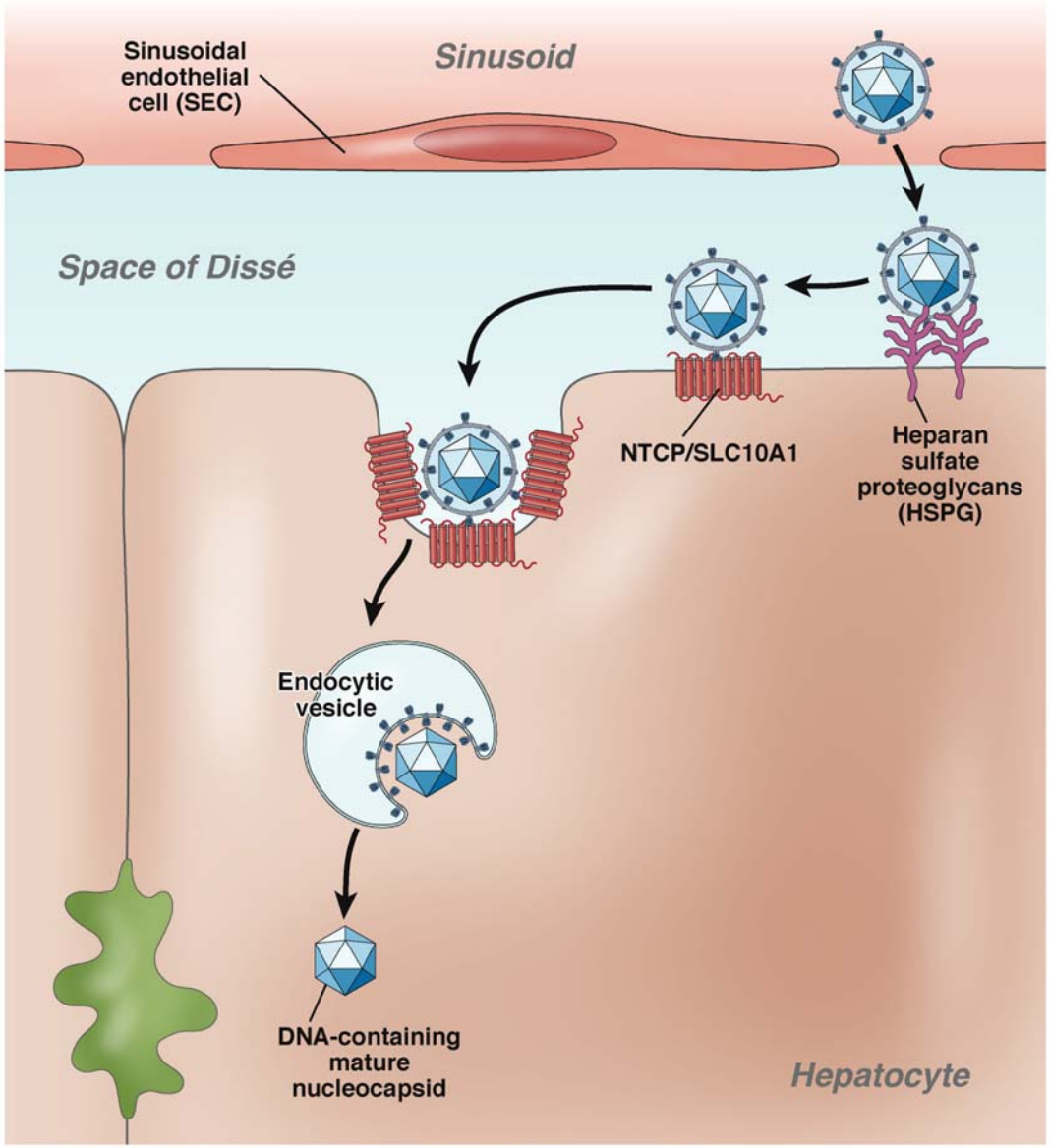
HBV entry through NTCP receptor

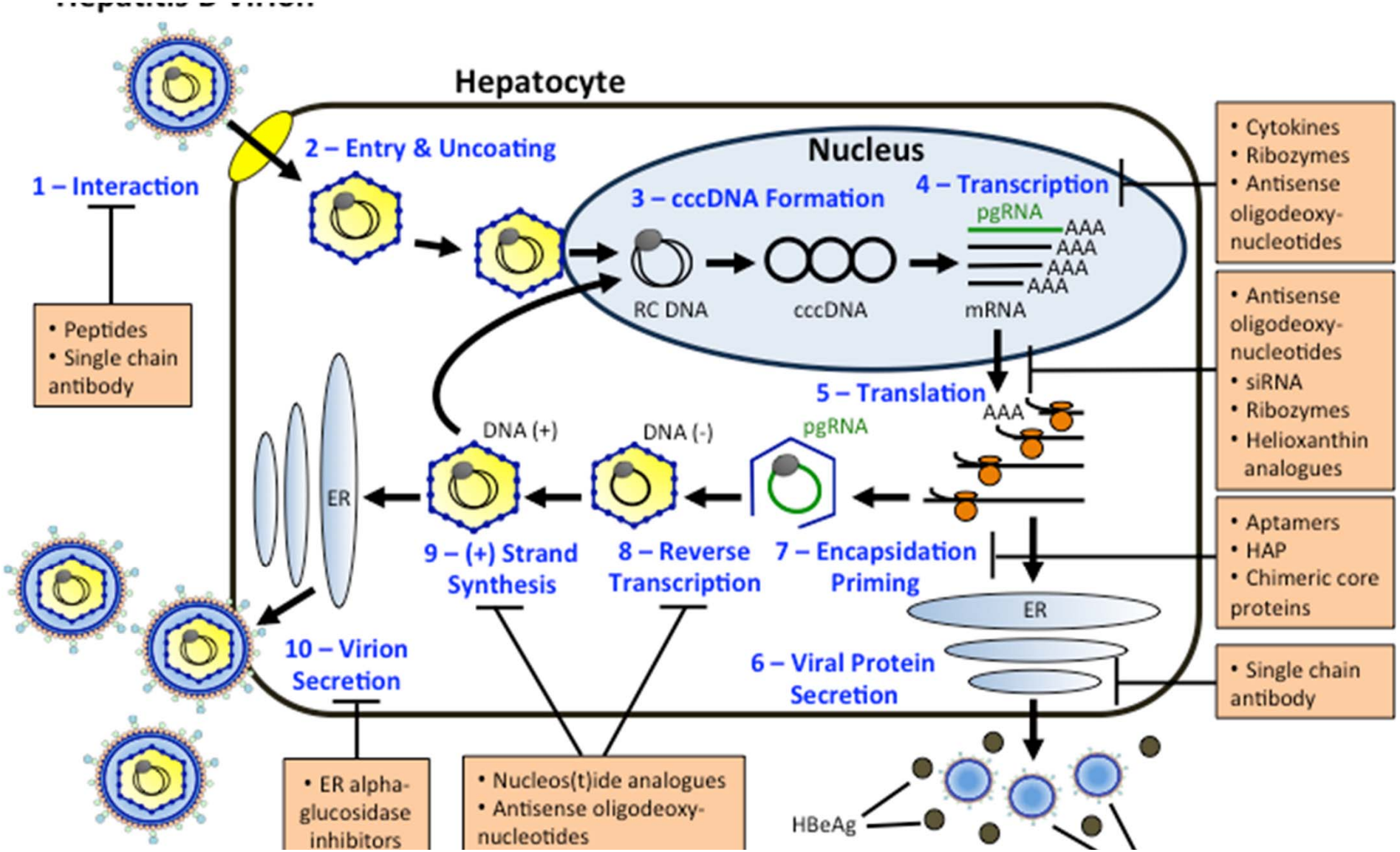


HBV Targeting cell entry

Small molecule compounds binding to Sodium taurocholate cotransporting polypeptide (NTCP)

- HBV pre-S1-derived lipopeptide Myrcludex-B competes with HBV/HDV for binding to NTCP
  - prevents HBV/HDV entry
- Phase II in Russia (HBeAg -, naïve, ↑ALT, DNA >2k
  - →nl ALT 5/8, ↓qHBsAg 5/8, myr preSAbs 3/8, HBV DNA dec 5/8; reactivation in 2 post Rx.
  - Blocks entry at pM concentrations increased serum bile acids
  - Decrease new cccDNA production

Urban AASLD 2016; Gastro 2014



Gonzalez 2015 Antimicrobe

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cccDNA

- Cannot replicate itself but is replenished from cytoplasmic nucleocapsid rcDNA
- Complexes with HBc, histones to form a minichromosome
  - Not static has inactive and active forms
  - Long half life
  - Stable in quiescent cells
  - Turnover with cell death
  - Diluted by cell proliferation but survives cell division

Potential Mechanisms to Target cccDNA

- preventing cccDNA formation
- eliminating cccDNA
- silencing cccDNA transcription
- Control of cccDNA
  - capsid disassembly
  - inhibition of rcDNA (relaxed circ cccDNA precursor) entry into the nucleus
  - inhibition of conversion of rcDNA to cccDNA
  - physical elimination of cccDNA
  - inhibition of cccDNA transcription (epigenetic control)
  - inhibition of viral or cellular factors contributing to cccDNA stability/formation.
  - HBx regulates cccDNA (Levrero AASLD 2015)

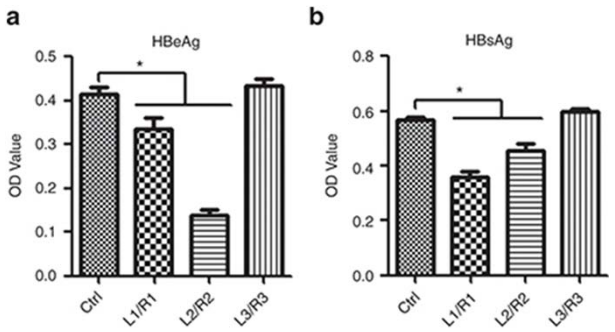
HBV targeting cccDNA formation/ decay

disubstituted sulfonamide (DSS) compounds

- inhibitors of cccDNA in cell-based assays.
- inhibit de novo cccDNA formation by interfering with rcDNA conversion into cccDNA

DNA cleavage enzymes, specifically targeting the cccDNA are currently being engineered

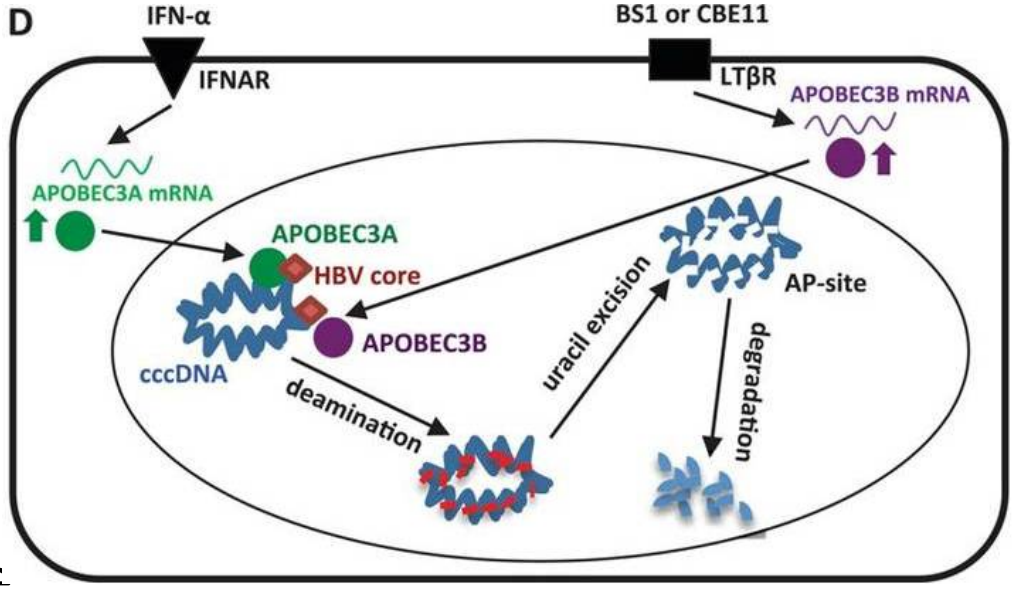
- homing endonucleases or meganucleases
- zinc-finger nucleases introduce ds breaks and cleave HBV DNA targets
- *TALEN* effector nucleases HBeAg/sAg (right)
- CRISPR(clustered regularly interspaced short palindromic repeats)/Cas9 as platform to mutate or inactivate viral genomes (Cullen)



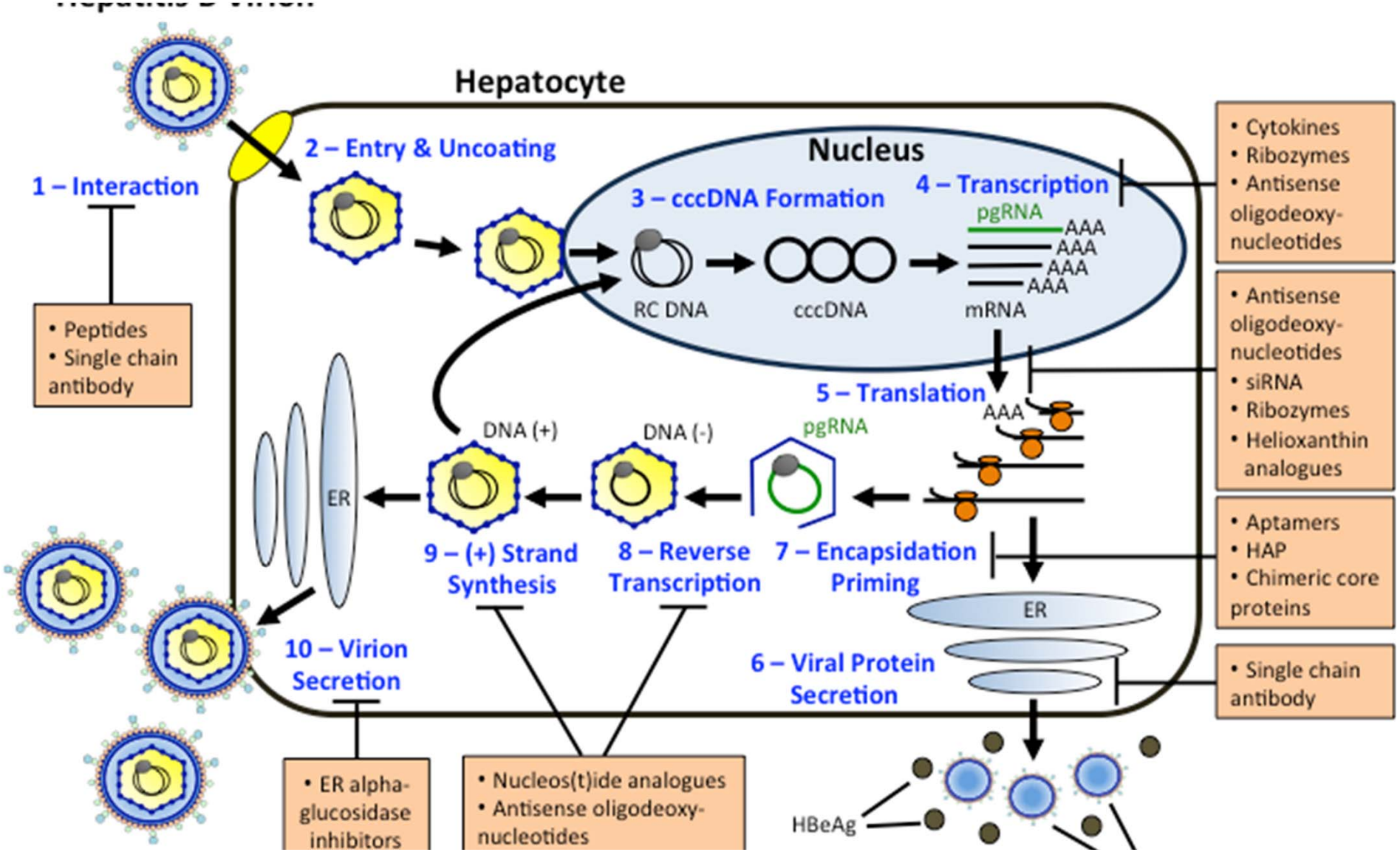
Chen et al, *Molecular Therapy* 2014; Weber 2014; Zimmerman 2008 Ren 2014

APOBEC3A/3B and cccDNA modification by IFN-α/LTβR

- IFN-a, LTBR activation up-regulated APOBEC3A/B cytidine deaminases
- Binds to HBV core protein
- interaction with nuclear cccDNA- resulting in cytidine deamination, apurinic/apyrimidinic site formation, and finally cccDNA degradation that prevents HBV reactivation
- No effect on inactive cccDNA
- New therapeutic target



Lucifora, Protzer; Science 2014



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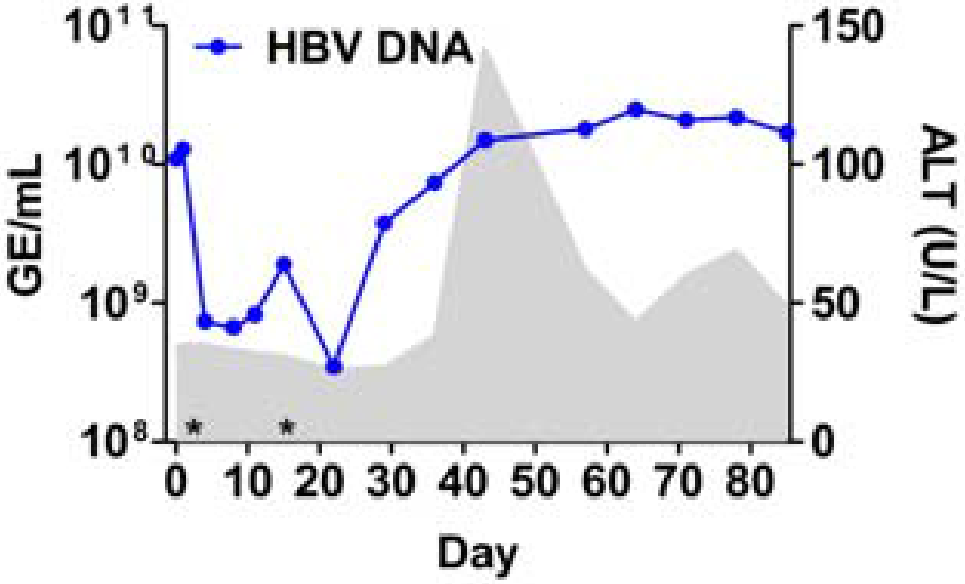
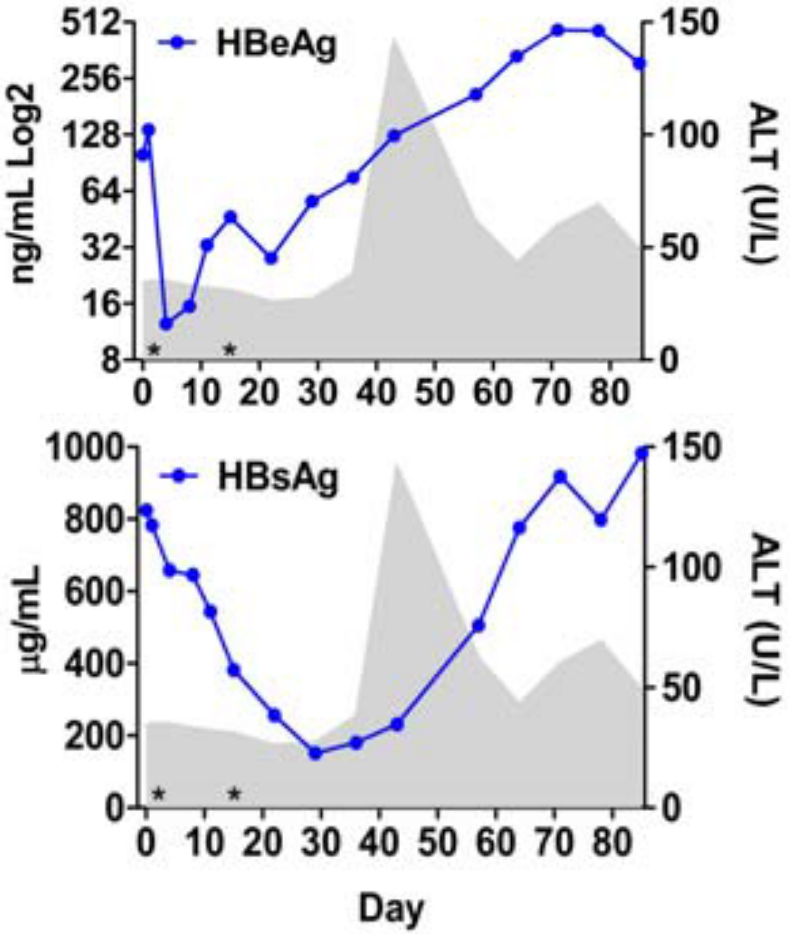
Silencing HBV gene expression using RNAi-based therapy

- ARC-520 is a combination of siRNAs directed against conserved HBV RNA sequences and efficiently knocks down HBV RNA, proteins and DNA levels.
  - phase II clinical trial NCT02065336
- 2 siRNAs (cover 99.6% of known HBV sequences) conjugated to cholesterol and hepatocyte-targeted ligands
- Taken up by endosomes in hepatocyte then released into cytoplasm after lysis of endosomal membrane
  - Given (Arrowhead Hepdart 2015)
  - Arbutus ARB-1740 decreases HBsAg, HBeAg, HDV RNA (AASLD 2016)

siRNA: ARC520

- suppressing both viral load and HBsAg: Data from chimp model





Phase IIb iv q mo in
HBV suppressed (Given-2015)
On clinical hold 11-16 for animal tox

Lanford et al, AASLD 2013

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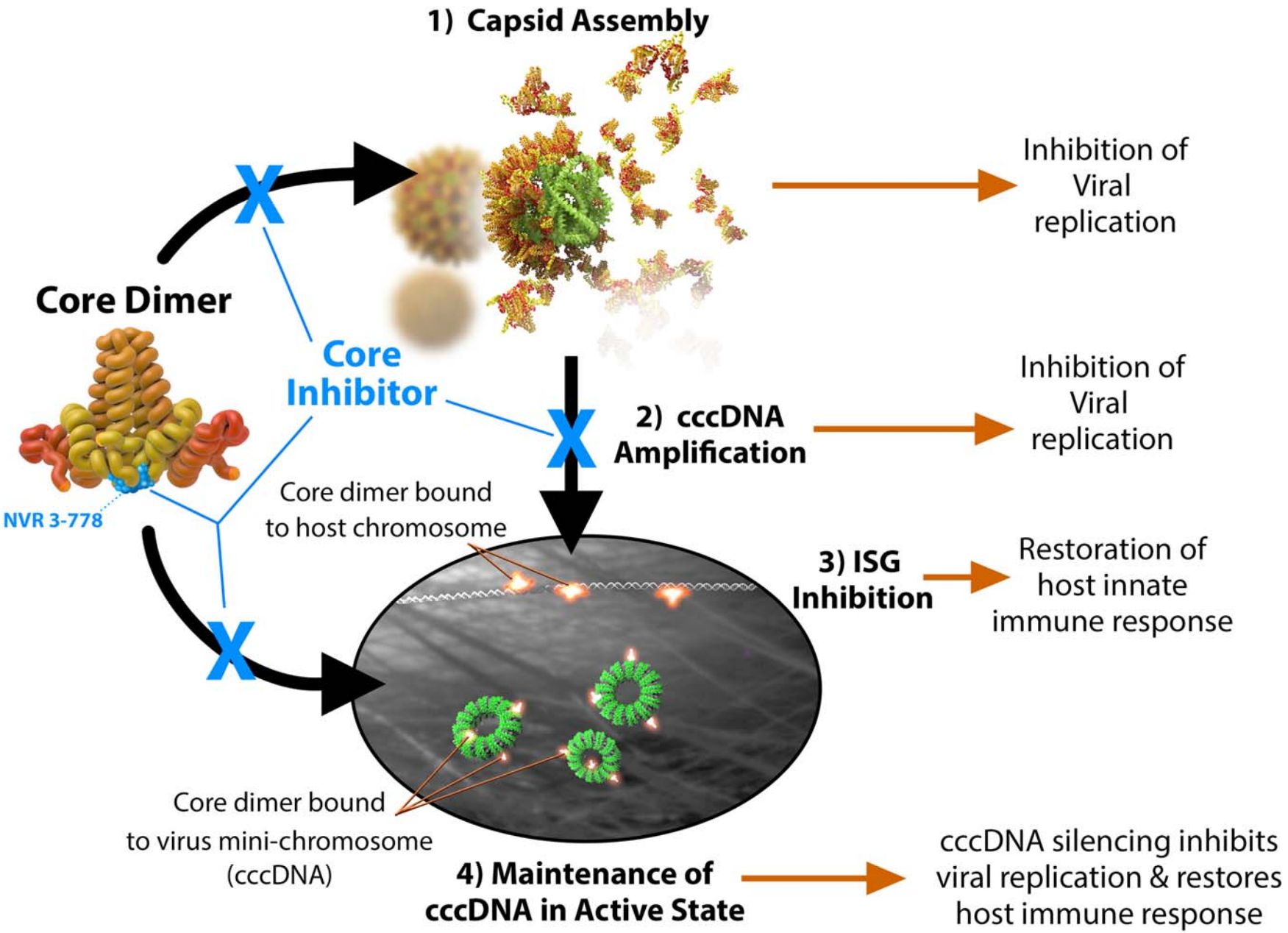
HBV capsid

- It is essential for
  - HBV genome packaging
  - reverse transcription
  - intracellular trafficking
  - maintenance of chronic infection as encapsidated HBV genomes are imported into the nucleus.
- NVR- 3-778- capsid inhibitor
  - Small molecule and direct acting antiviral through aberrant core protein assembly that inhibits capsid assembly and viral replication
  - Phase IIa Novira -HBsAg pos, ↑ALT
  - Endpoints normal ALT then HBsAg decrease/loss



Novira website 2015

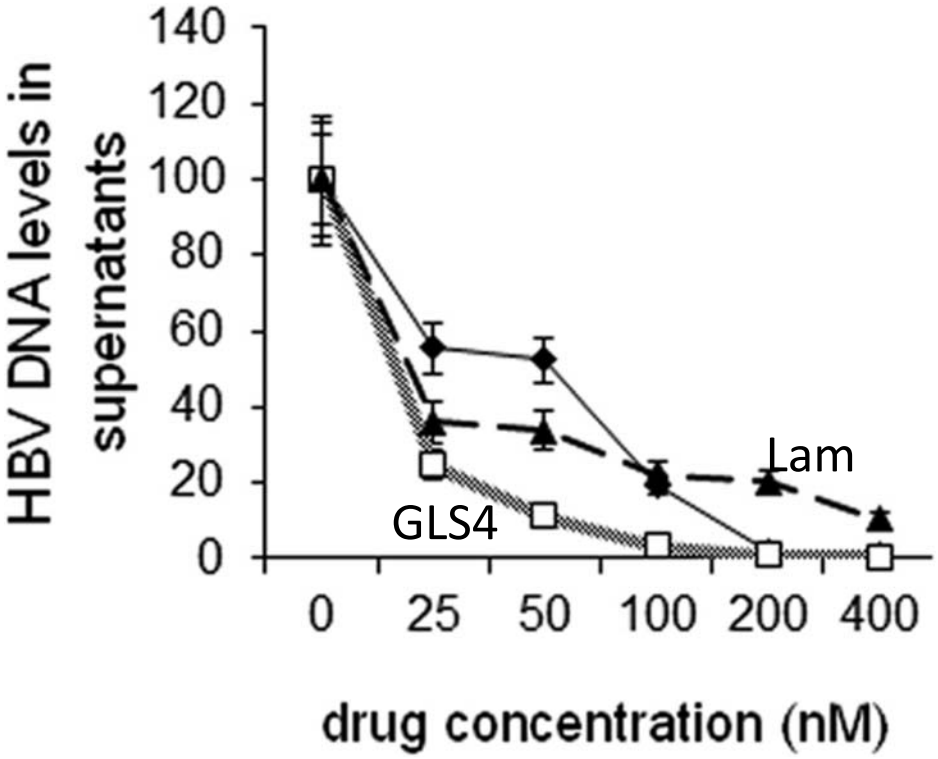
HBV Nucleocapsid Inhibitors

Heteroaryldihydropyrimidines (HAPs)

- bind to core particles to reduce both HBV DNA and HBcAg levels, the latter via degradation by the proteasome pathway.
- enhance viral assembly
  - favour assembly of aberrant particles, indicating that HAPs interfere with capsid formation/stability in a complex manner.
- Similar to phenylpropenamide derivatives, HAPs are able to efficiently inhibit “nuc” resistant viral variants

- CpAMs: core protein allosteric modifiers Assembly Biosciences

Nucleocapsid inhibitors: GLS4 first member of HAP nucleocapsid compounds

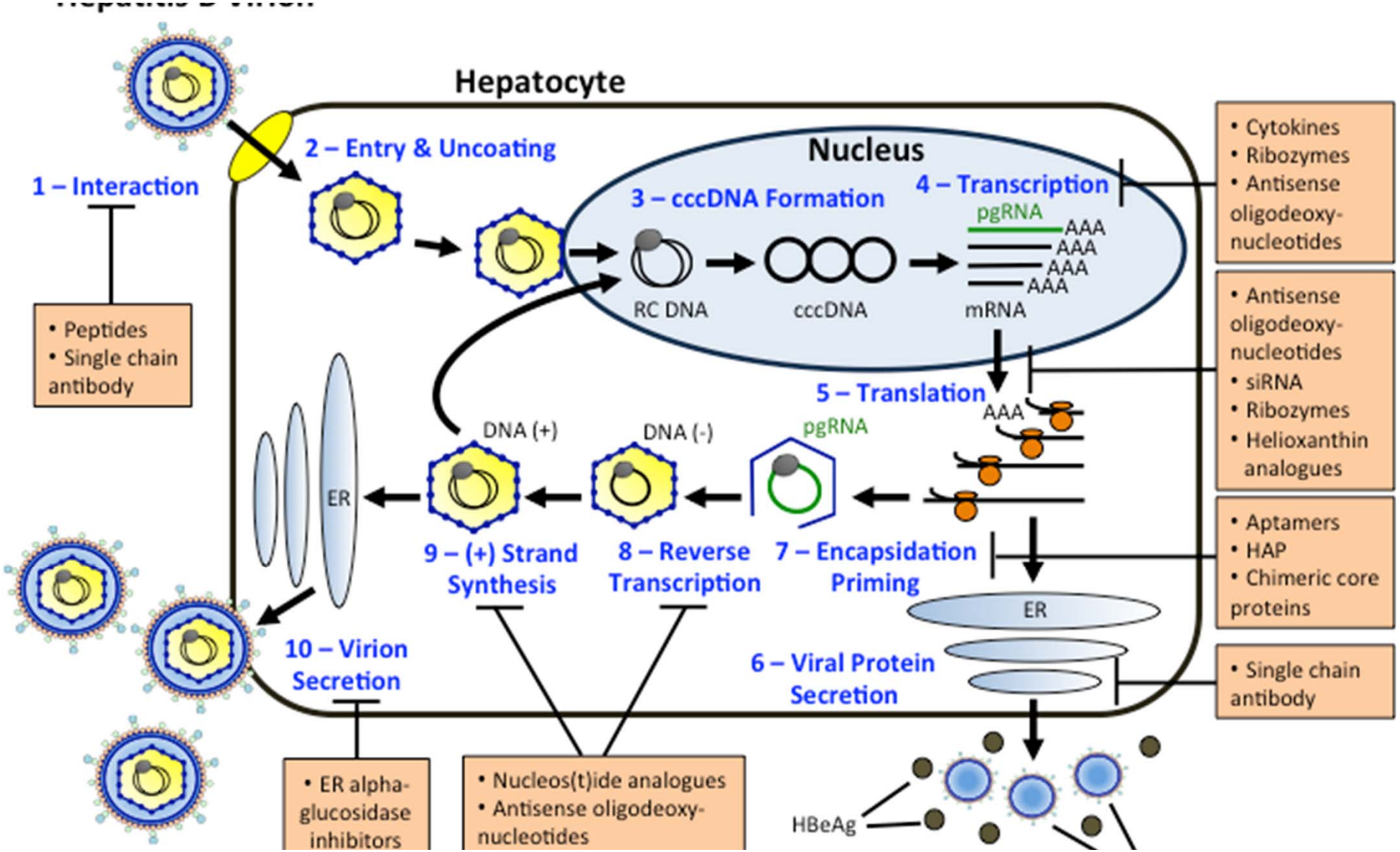


Morphothiadine mesilate (GLS4)

- Triggers aberrant core particle assembly
- Hep AD38 cells

Phase I/ II trials in China

Wu G et al. Antimicrob. Agents Chemother. 2013



Gonzalez 2015 Antimicrobe

GS-108/110: Changes in BMD With TAF vs TDF in HBV Pts

- Randomized, double-blind, active-controlled phase III studies in which pts with chronic HBV infection* treated with TAF 25 mg QD (n = 866) or TDF 300 mg QD (n = 432)[1]
  - Noninferior efficacy between groups previously shown[2,3]

Mean Change in BMD at Wk 72, %	TAF	TDF	*P* Value
Hip	-0.29	-2.43	< .001
Spine	-0.60	-2.52	< .001

- TDF also associated with significantly decreased hip and spine BMD at Wks 24 and 48 vs TAF (*P* < .001 for all comparisons)

*HBV DNA ≥ 20,000 IU/mL, ALT > 60/38 U/L (male/female).

1. Seto WK, et al. AASLD 2016. Abstract 67.
2. Buti M, et al. Lancet Gastroenterol Hepatol. 2016;1:196-206.
3. Chan HLY, et al. Lancet Gastroenterol Hepatol. 2016;1:185-195.

When to use TAF or TDF

- Tenofovir (disoproxil fumarate or alafenamide) can be used in all HBV patients
- TAF (25mg) should be used if
  - renal disease
  - bone disease
  - older
  - No data about Fanconi's: recurrence or resolution

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HBsAg Release Inhibitor-
Nucleic Acid Polymer (NAP) REP 2139

- Taken up by hepatocytes, targets apolipoprotein, block entry and formation of subviral particles (not virion production)
- Phase Ib: iv q w x15 lead in then, 15w plus peg IFN, then PEGIFN for 48w in 12 HBV HDV pts
  - ⬇HBsAg and HDV RNA.
  - Many patients had u/d serum HBsAg or HDV RNA at 15w
  - 24w f/u HBsAg lo 7/12; ud 5/12; HDVAg <LLQ 7/12; 4 anti-HBs
  - Does not decrease HBV DNA by itself ?need NA or IFN
- Phase II +/- PEG-IFN
  - Combination of REP 2139 and immune stimulant and oral nucleos(t)ide being tested

Vaillant AASLD 2016 Plos one 2016

HBV Inhibit Secretory Pathway

- Benzimidazole BM601
  - selectively inhibit intracellular relocalisation of the HBV surface protein to the Golgi apparatus
  - Thus decreases HBsAg and HBV release
  - without affecting HBeAg secretion
- iminosugar derivatives of butyldeoxynojirimycin and related glycolipids
- α-glucosidase inhibitors
- triazol-o-pyrimidine derivatives

- Will suppression of HBsAg in serum restore T cell responsiveness?

Xu 2014; Block 1994; Simseck 2006; Yu 2011

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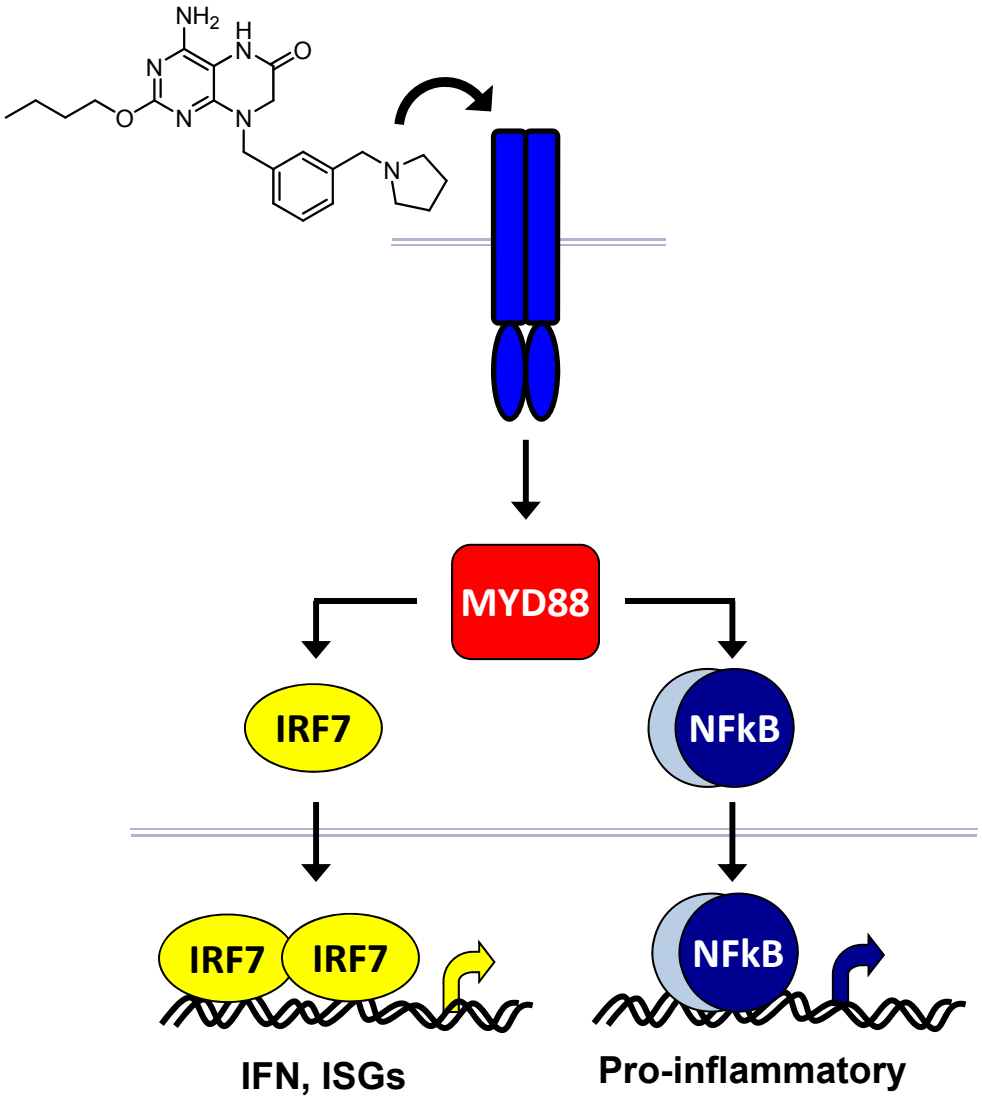
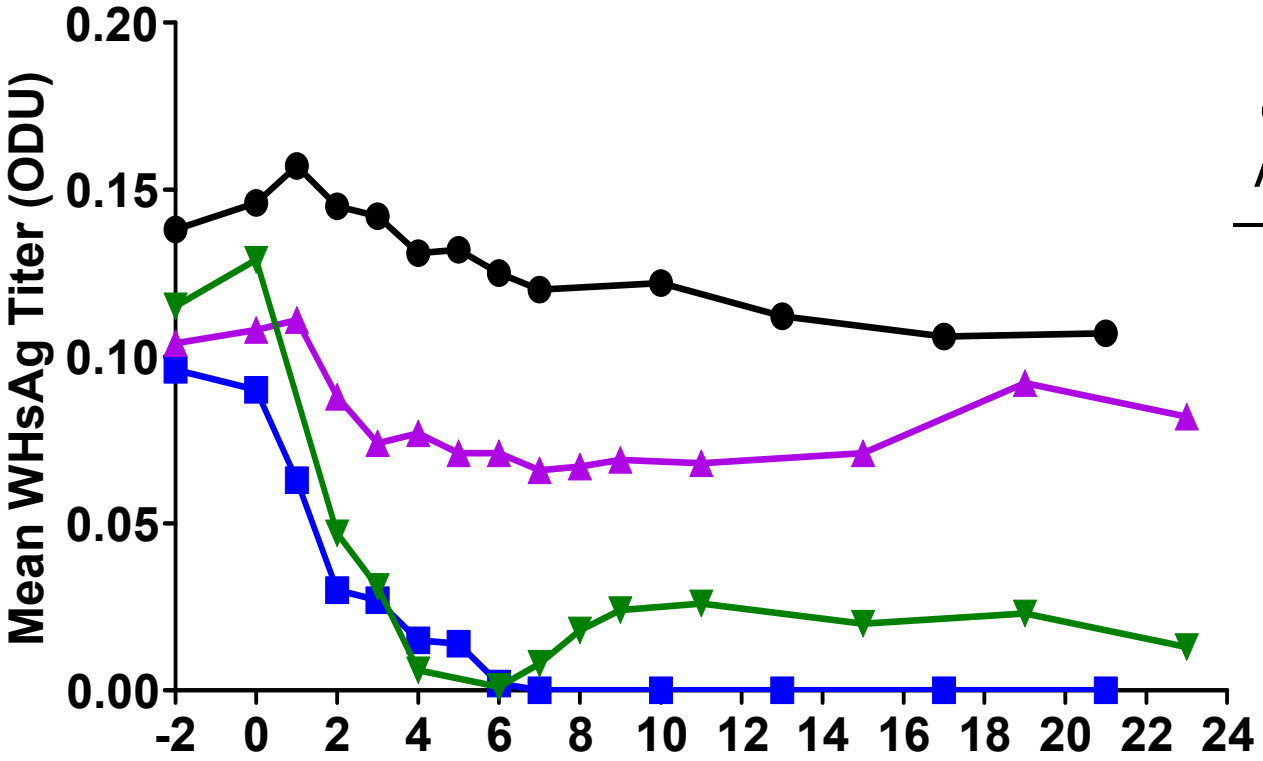
TLR-7 Agonist for HBV

- GS-9620, an orally available agonist
- Selective for antiviral vs proinflammatory response
- Preclinical studies: Reduces sAg, viral DNA in woodchucks & chimpanzees
- Phase 1a (SAD) complete: Safety shown in healthy volunteers



Lopatin U et al. *Antivir Ther* 2013; 18:409-418

TLR-7 agonist Induces sAg Seroconversion in Chronically Infected Woodchucks

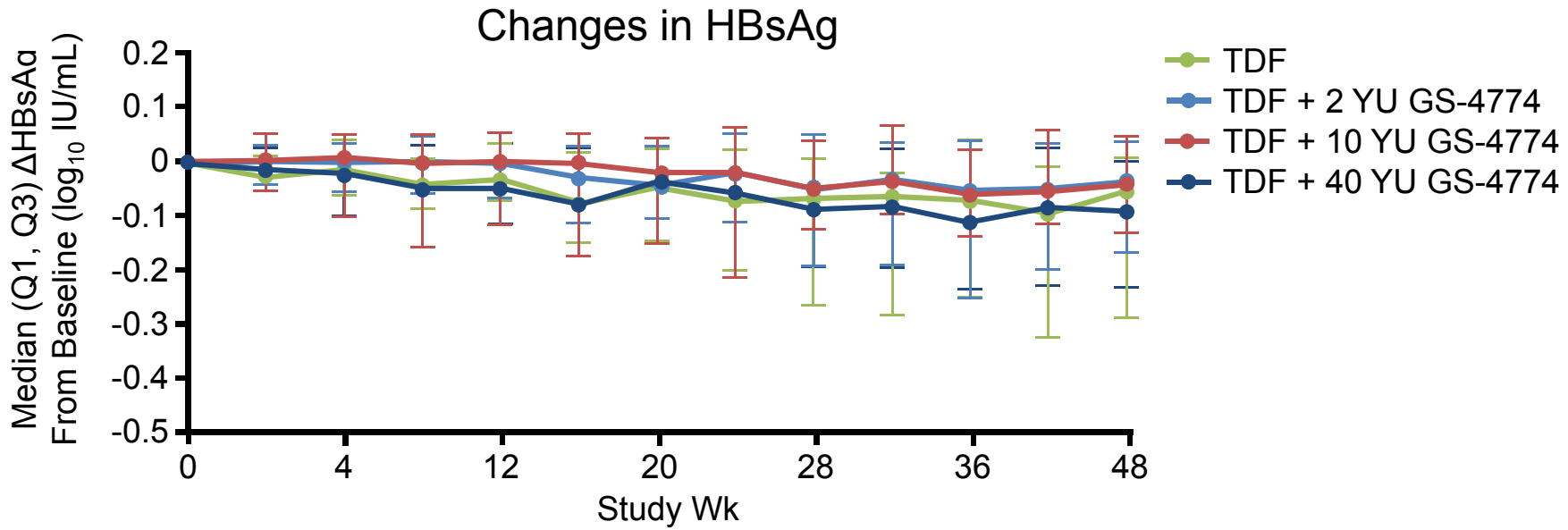


	α-sAg Ab+ (#)	Max Δ DNA (log_{10})
5 mg/kg	0/7	- 0.6
5/2.5 mg/kg	1/7	- 1.0
5/2.5 mg/kg	3/7	- 3.9
Placebo	2/7	- 4.7

GS-9620 Phase II in suppressed HBV patients

GS-4774, a Heat-Inactivated, Yeast-Based T-Cell Vaccine for Pts With Chronic HBV

- Randomized phase II study assessing the GS-4774 vaccine* + TDF in pts with chronic HBV who were not on antivirals (HBV DNA ≥ 2000 IU/mL) (N = 195)
- Through Wk 48, HBsAg changes similar between GS-4774 + TDF and TDF alone groups; no pts lost HBsAg



- At Wks 24 and 48, similar rates of pts in GS-4774 + TDF and TDF alone groups with HBV DNA < 20 IU/mL

*Includes HBV core, surface, and X proteins.

Janssen HL, et al. AASLD 2016. Abstract 231. Reproduced with permission.

Slide credit: clinicaloptions.com

GS-1059: TLR-7 Agonist GS-9620 for Pts With Suppressed Chronic HBV Infection

- Randomized, double-blind, placebo-controlled phase II trial analyzing the immunomodulatory effects of GS-9620
  - Pts with chronic HBeAg-negative GTD HBV infection suppressed with nucleos(t)ide analogue for ≥ 3 yrs were randomized to 12 wks GS-9620 1, 2, or 4 mg PO QW (N = 26) or placebo; all pts continued nucleos(t)ide analogue
- Key results:
  - At Wk 24, no pts treated with GS-9620 had HBsAg change > 0.5 log10; no pts lost HBsAg
  - Improvements in specific T-cell responses observed with GS-9620 (eg, IFN-γ and IL-2 production)

Boni C, et al. AASLD 2016. Abstract 13.
ClinicalTrials.gov. NCT02166047.

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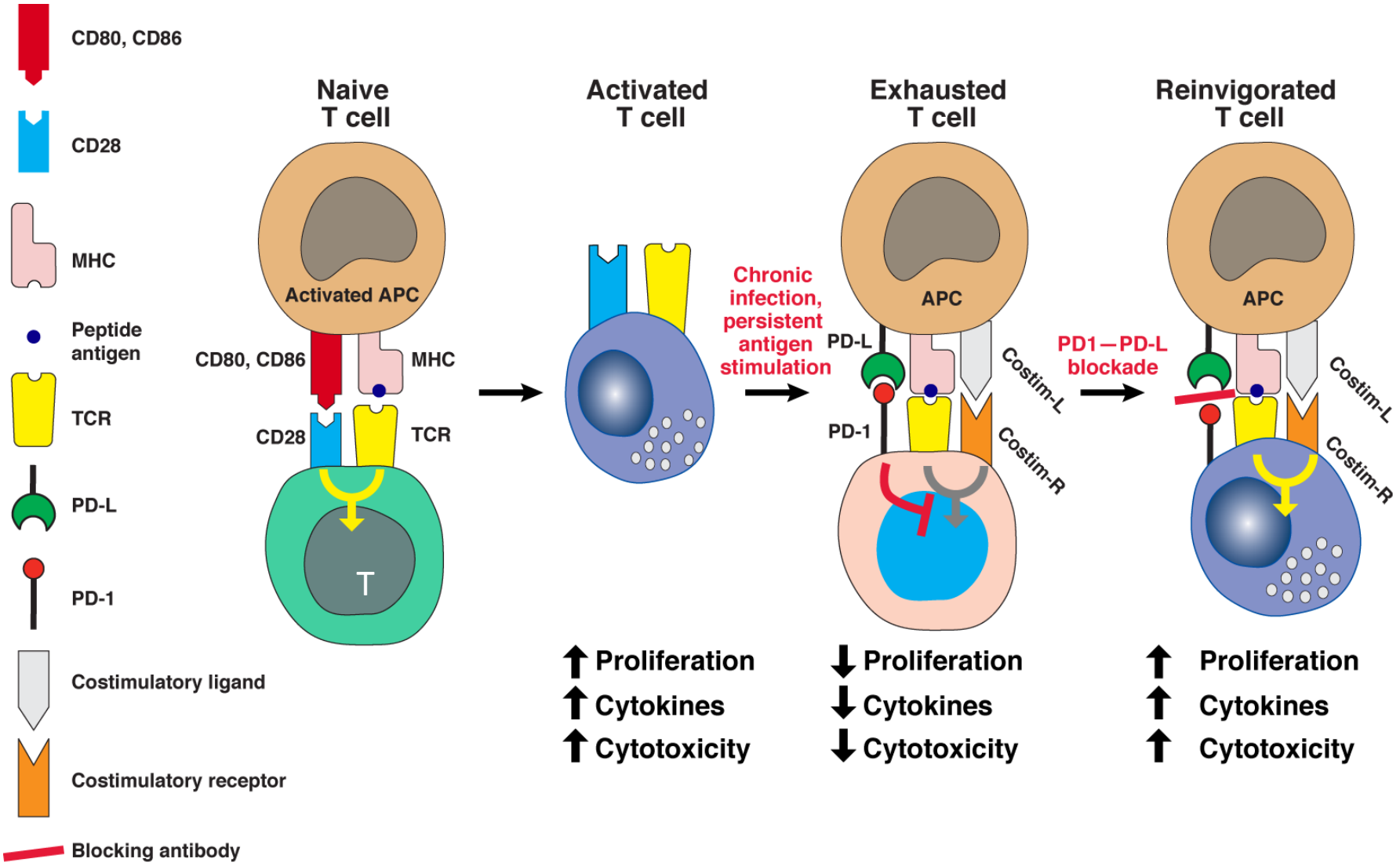
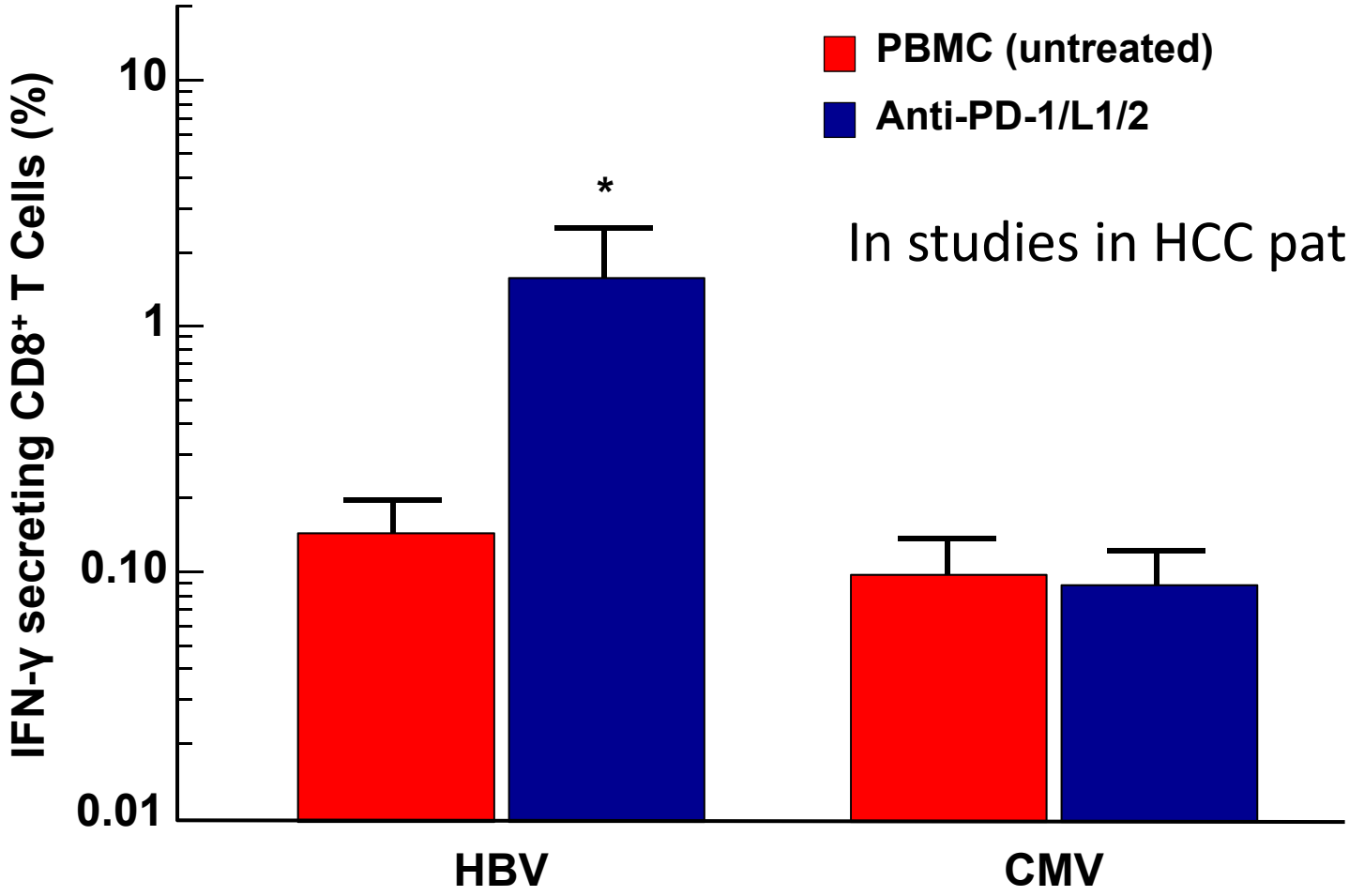
  - Yeast based vaccines

Effect of PD-1/L1 on Antiviral Immunity



Expansion of HBV-specific CD8 T Cell Response by Blocking PD-1/L1/2 Interaction *In Vitro* (mice)



In studies in HCC patients

Sherman AC et al. *AIDS Res Hum Retr* 2012

Published Efficacy Data in HCC: Nivolumab, ASCO 2015 (BMS)

	Uninfected (n = 21)	HBV+ (n = 10)	HCV+ (n = 11)	Total (N = 42)
Duration of response (months, range)	7.2 – 12.5	11.9	1.4 – 8.3	1.4 – 12.5
Duration of stable disease (months, range)	1.1 – 17.3	2.9 – 14.0	2.7 – 6.9	1.1 – 17.3
Overall survival at 9 months (%, 95% CI)				70 (52 – 82)
Overall survival at 12 months (%, 95% CI)				62 (42 – 76)
Objective response*	3 (14%) (10 stable, 8 progressive)	1 (10%) (5 stable, 4 progressive)	4 (36%) (5 stable, 2 progressive)	8 (19%) (20 stable, 8 progressive)
Complete responses*	2 (10%)			2 (5%)

*Investigator-determined best overall response assessed by RECIST

El-Khoueiry A, J Clin Oncol 33, 2015 BMS PD-1Ab

Published Safety Data in HCC: Nivolumab (anti-PD-1)

- 32/47 (68%) reporting one or more drug-related AE's
  - Most frequent (>10%): transaminase ↑, lipase ↑, amylase ↑, rash
- 9/47 (19%) experienced related Grade ≥3 AE
  - ALT: 4 patients (9%)
  - AST: 5 patients (11%)
  - Increased lipase: 4 patients (8%)
- 2 discontinuations due to AE's
  - 1 unrelated increased total bilirubin
  - 1 related increased ALT/AST

El-Khoueiry A, J Clin Oncol 33, 2015 ASCO

- Failed naïve lung (non small cell) cancer trial 8-2016
- Pembrolizumab (Merck PD-1) approved 10-2015
- Tecentriq PDL-1 approved for bladder ca 5-2016 (GNE)

Strategies to Eradicate HBV

Virologic approaches

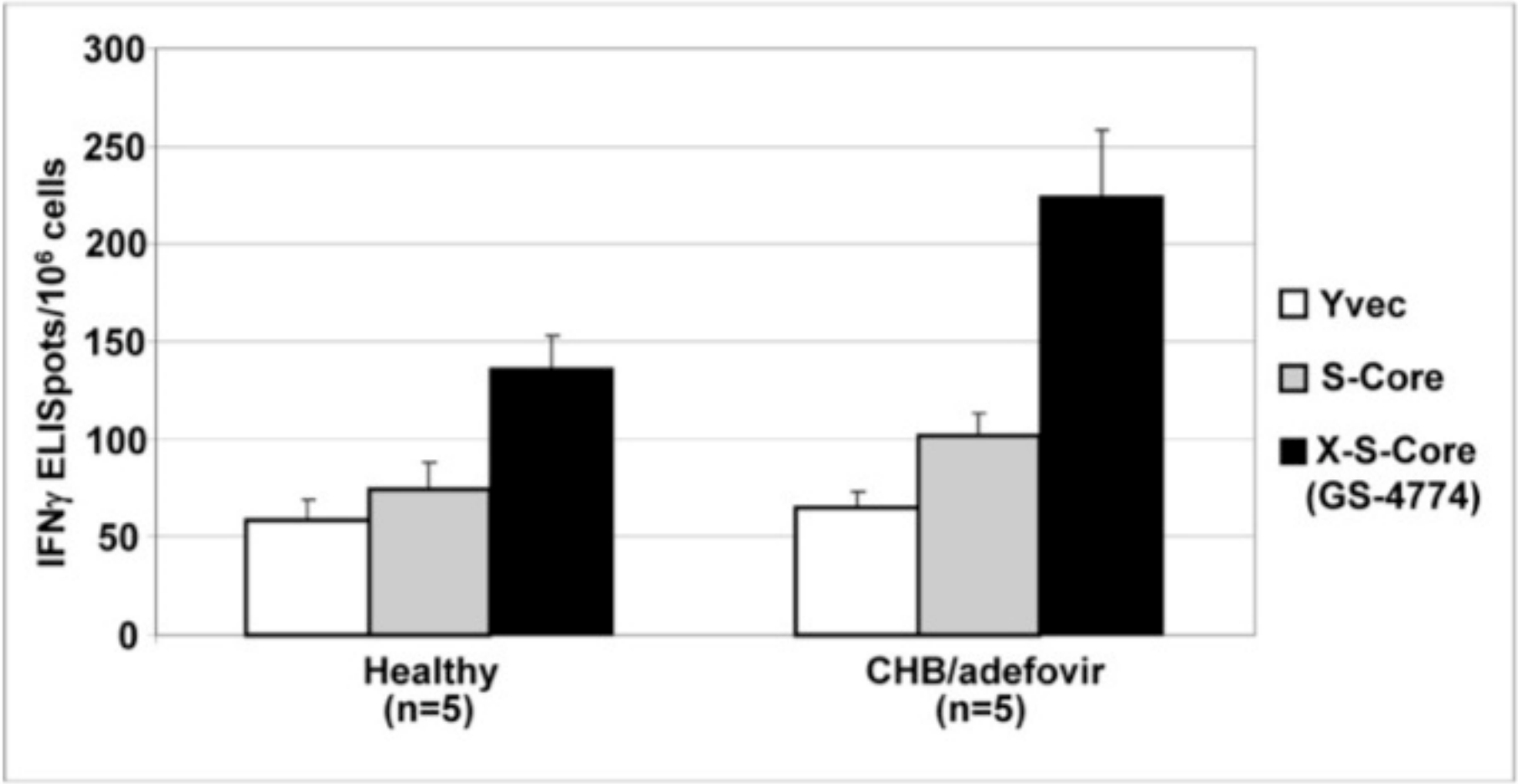
- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- polymerase inhibitors
- Secretion inhibitors

Host immune approaches

- Interferons
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
  - Nasal HBV (NASVAC) vaccines
  - DNA vaccines
  - T cell vaccines
  - Adenovirus based vaccines (TG1050)
  - Yeast based vaccines

Tarmogens can induce HBV-specific T cell response in vitro

GS-4774 ± TDF Phase 2: ↓ qHBsAg



King T et al. PLOS ONE (2014), 9 (7): e101904

Yeast based vaccine immunotherapy

Emerging DAAs against HBV

Many currently in the pipe-line

- novel polymerase inhibitors
- capsid inhibitors
- cccDNA inhibition or eradication
- Packaging inhibitors- not very potent alone
- small interfering RNA (siRNA)-based strategies
- Immune activators

Combination therapy will likely be required for cure

- inhibitors of polymerase, entry, core, cccDNA etc
- IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1

BUT

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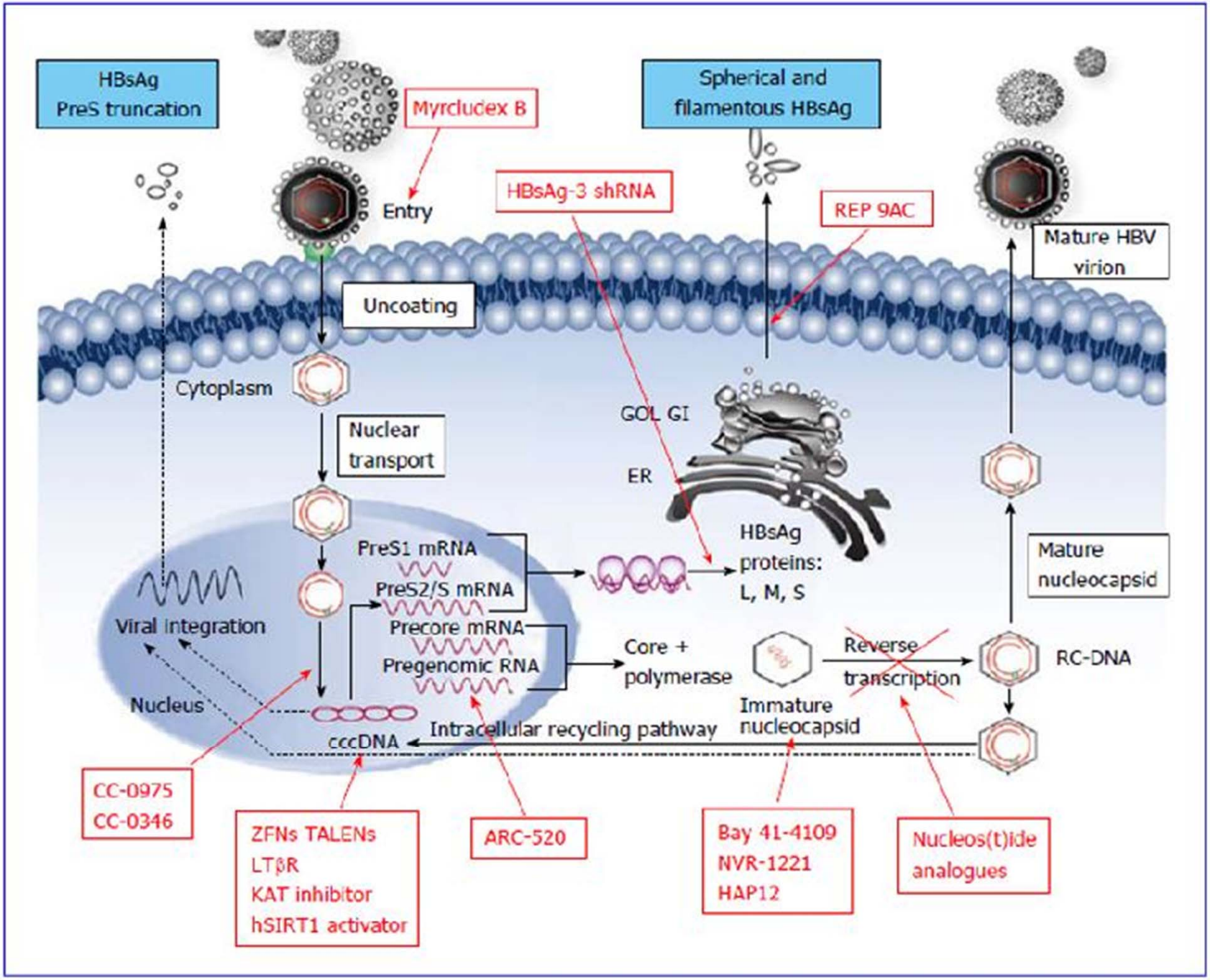
BUT Selection of HBV patient will be critical

Optimization of HBV endpoints needed

For HBV Cure studies

- What surrogate markers of efficacy are needed to monitor success?
  - Immunologic
  - Virologic
  - Pathologic

- Which patients should and can we treat with new drugs?
  - Should patients be already suppressed on nucs?
  - Is risk/ benefit different depending on therapy, age of patient or phase of disease?
  - Do different phases need different therapies?


HBsAg
PreS truncation
Myrcludex B
Entry
Spherical and
filamentous HBsAg
HBsAg-3 shRNA
REP 9AC
Mature HBV
virion
Uncoating
Cytoplasm
Nuclear
transport
GOL GI
ER
HBsAg
proteins:
L, M, S
PreS1 mRNA
PreS2/S mRNA
Precore mRNA
Pregenomic RNA
Core +
polymerase
Reverse
transcription
RC-DNA
Mature
nucleocapsid
Viral integration
Nucleus
cccDNA
Intracellular recycling pathway
Immature
nucleocapsid
CC-0975
CC-0346
ZFNs TALENs
LTβR
KAT inhibitor
hSIRT1 activator
ARC-520
Bay 41-4109
NVR-1221
HAP12
Nucleos(t)ide
analogues