HIV Management
Hepatitis Management

THE NEW YORK COURSE

HBV Treatment Pipeline: Prospects for a Cure

Marion Peters, MD
UCSF
San Francisco, CA

HBV Control

- Inflammatory: normalize serum ALT, biopsy
- Virologic: decrease HBV DNA
- Immune: seroconversion
  - HBeAg to anti-HBe
  - HBsAg to anti-HBs
- HBV as of 2017 not "cured" but controlled

Types of HBV Cure

Functional cure—clinical resolution

Sustained, off drug:

- No inflammation: ALT and liver biopsy
- HBsAg loss
- HBsAb gain

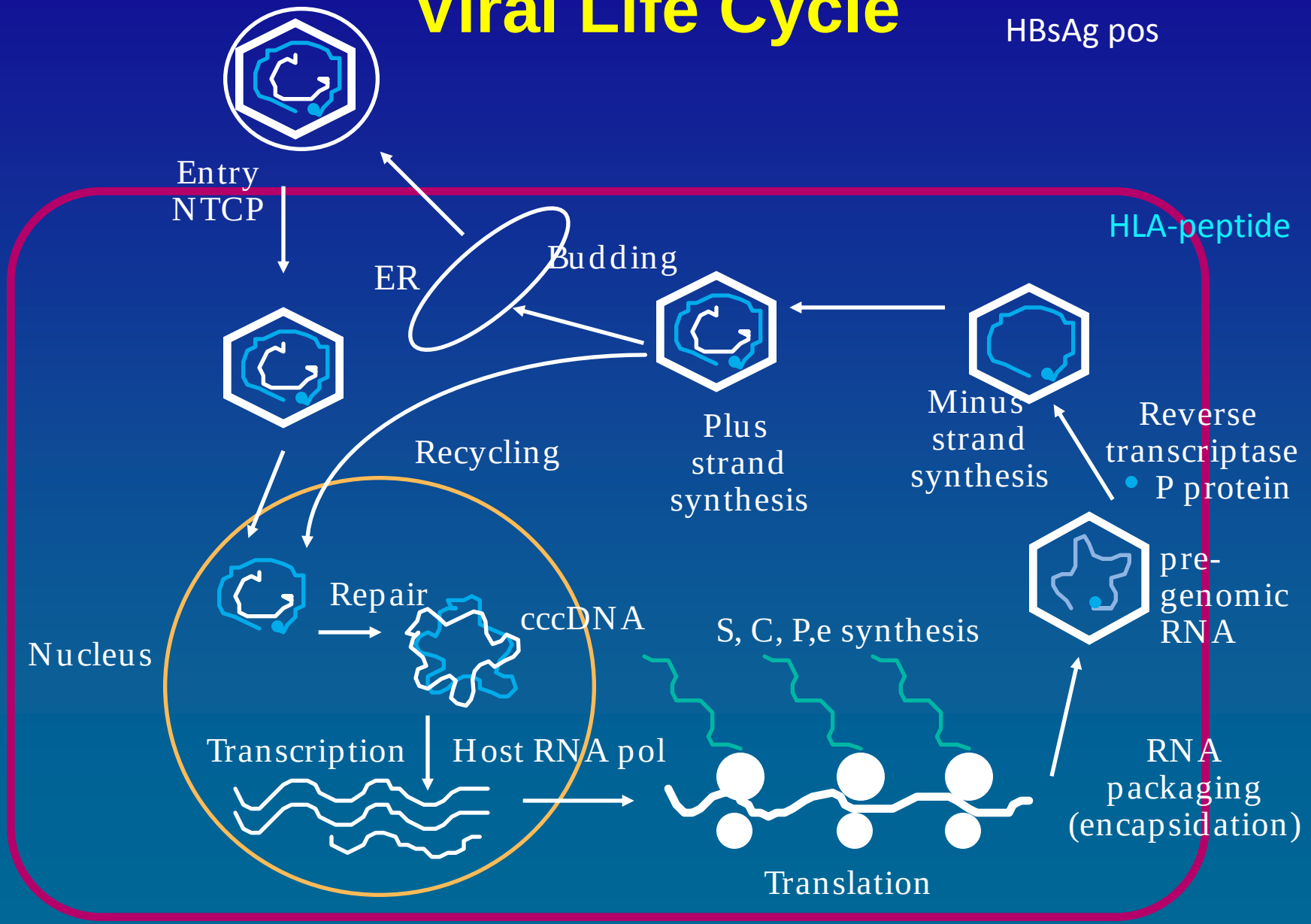
Complete cure—virological cure

- All of above plus
- Loss of cccDNA in liver

Inactive state—an interim goal?

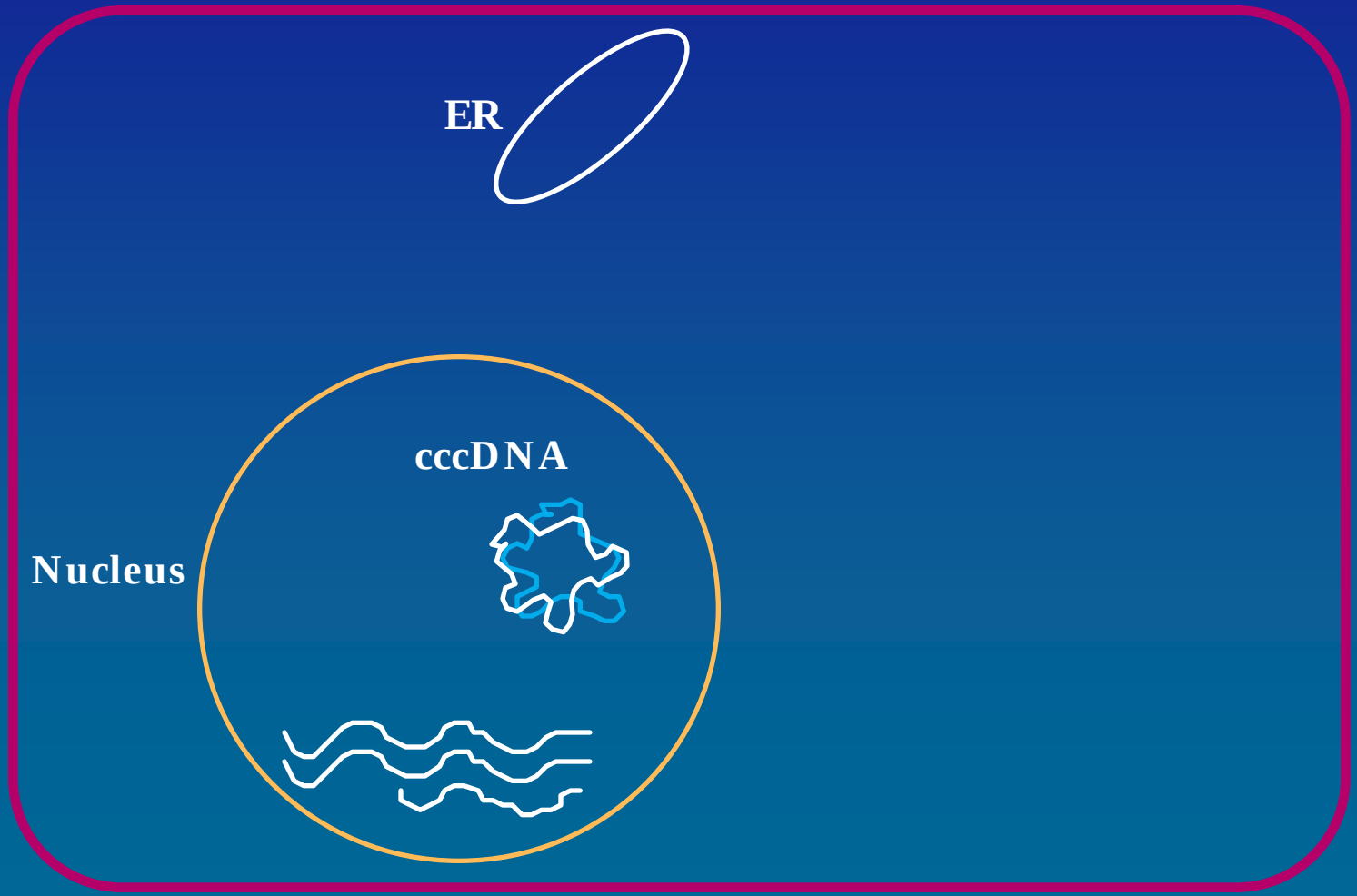
- No inflammation: ALT and liver biopsy
- HBV DNA low or u/d
- HBsAg positive

Viral Life Cycle



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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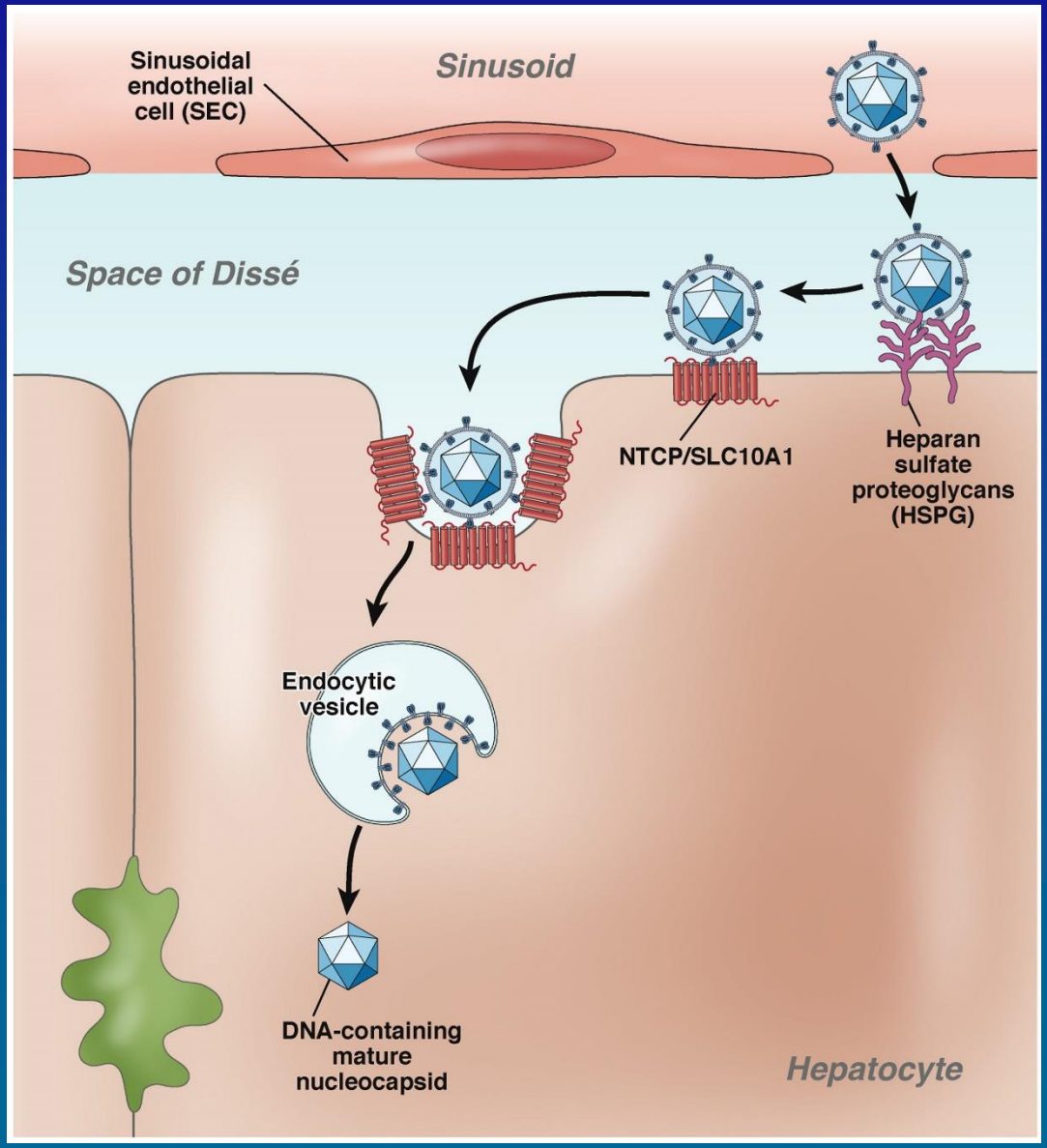
HBV Entry through NTCP Receptor



Gastroenterology 2014 147, 48-64DOI: (10.1053/j.gastro.2014.04.030)

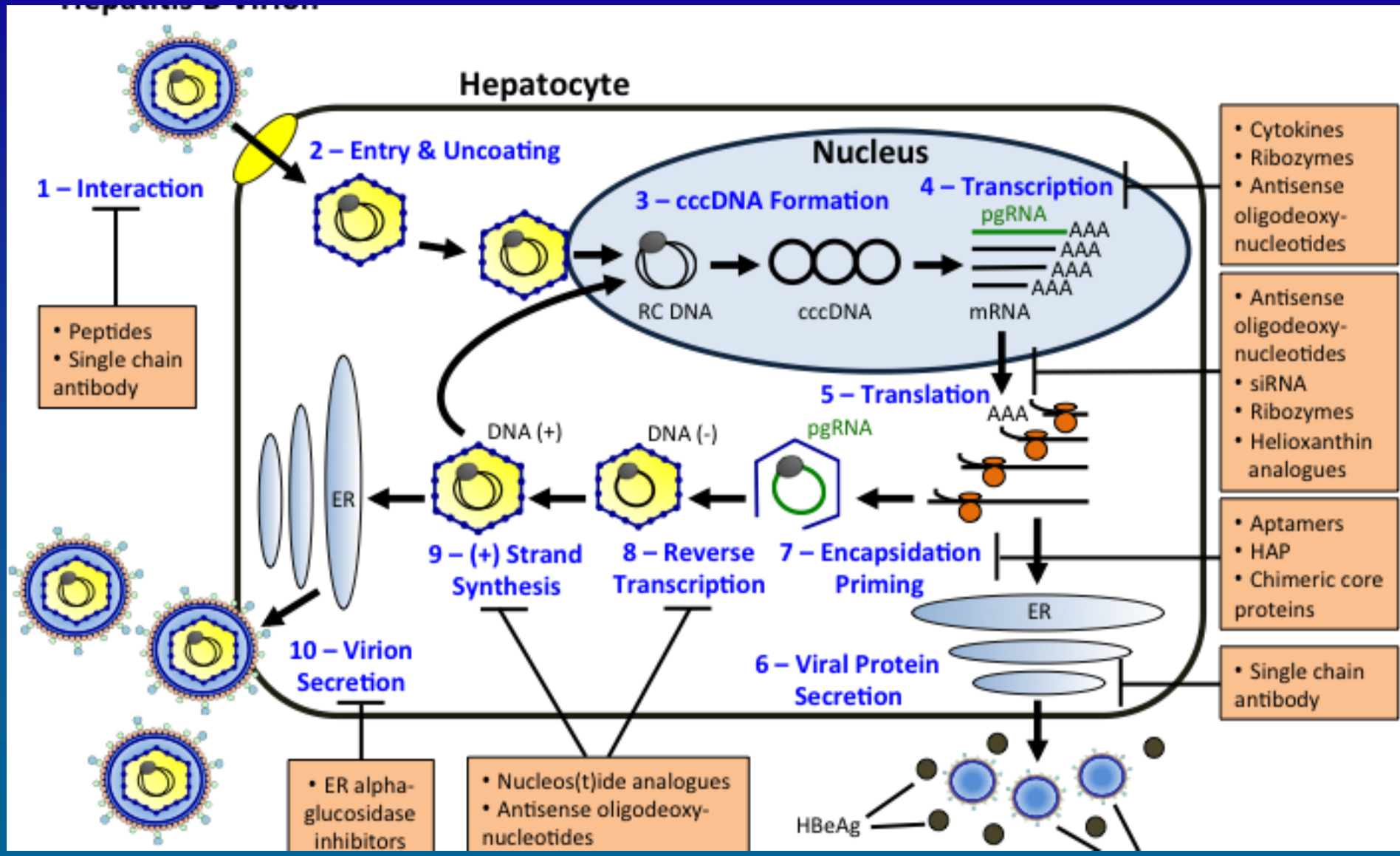
HBV Targeting Cell Entry

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 (24 HBeAg-, naïve, ↑ALT, DNA >2k
  - →nl ALT 6/8; HDV RNA dec 5/7; myr preSAbs 9/14, no change in qHBsAg; reactivation in 2 post-Rx.
  - Blocks entry at pM concentrations increased serum bile acids
  - Stops new infection of hepatocytes

Zeisel Gut 2015

Urban AASLD 2016; Gastro 2014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HBsAg

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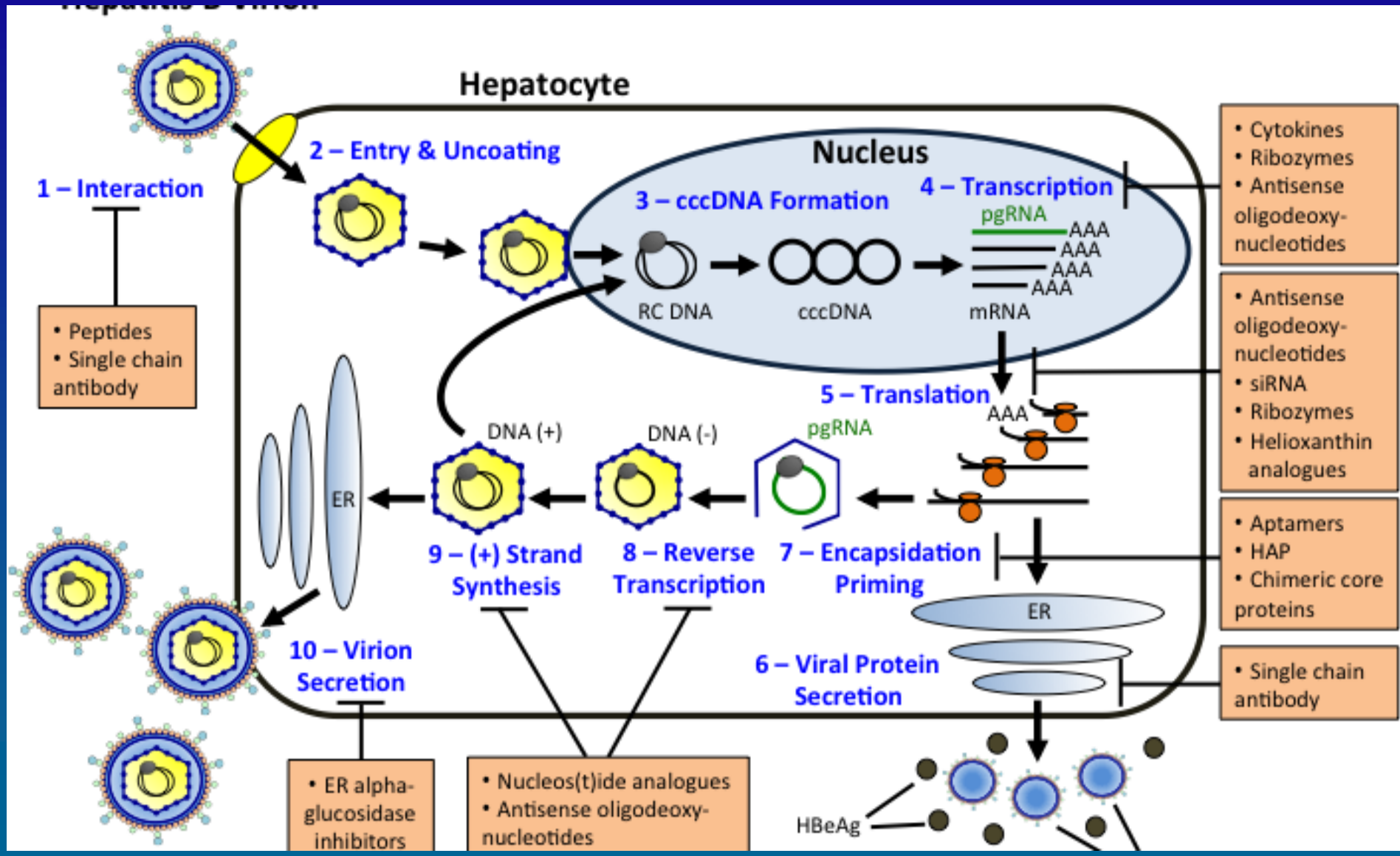
cccDNA

- 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)

Zeizel Gut 2015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siRNA

HBsAg

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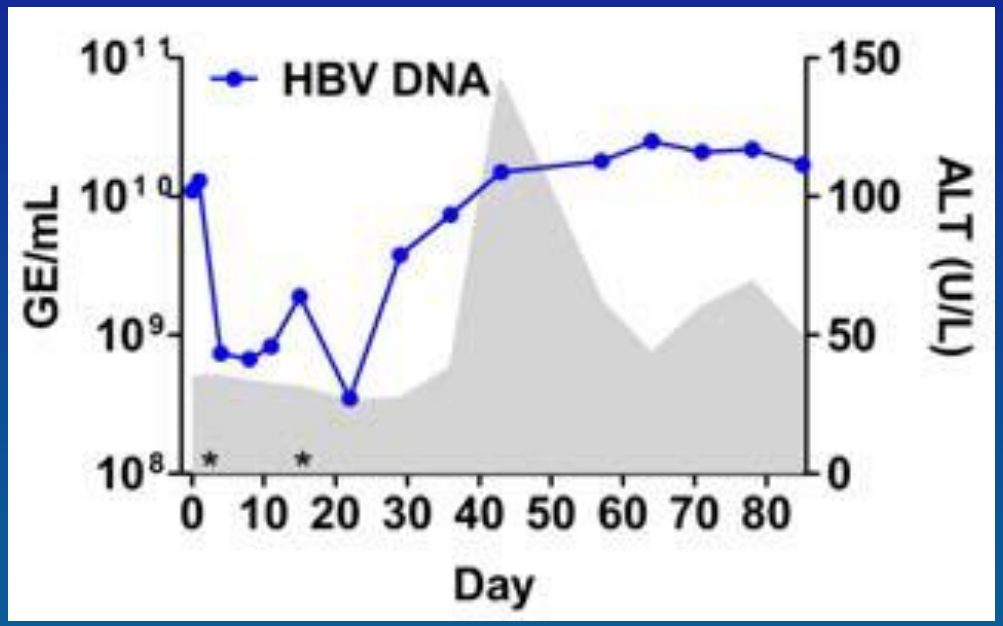
Silencing HBV Gene Expression Using RNAi-based Therapy

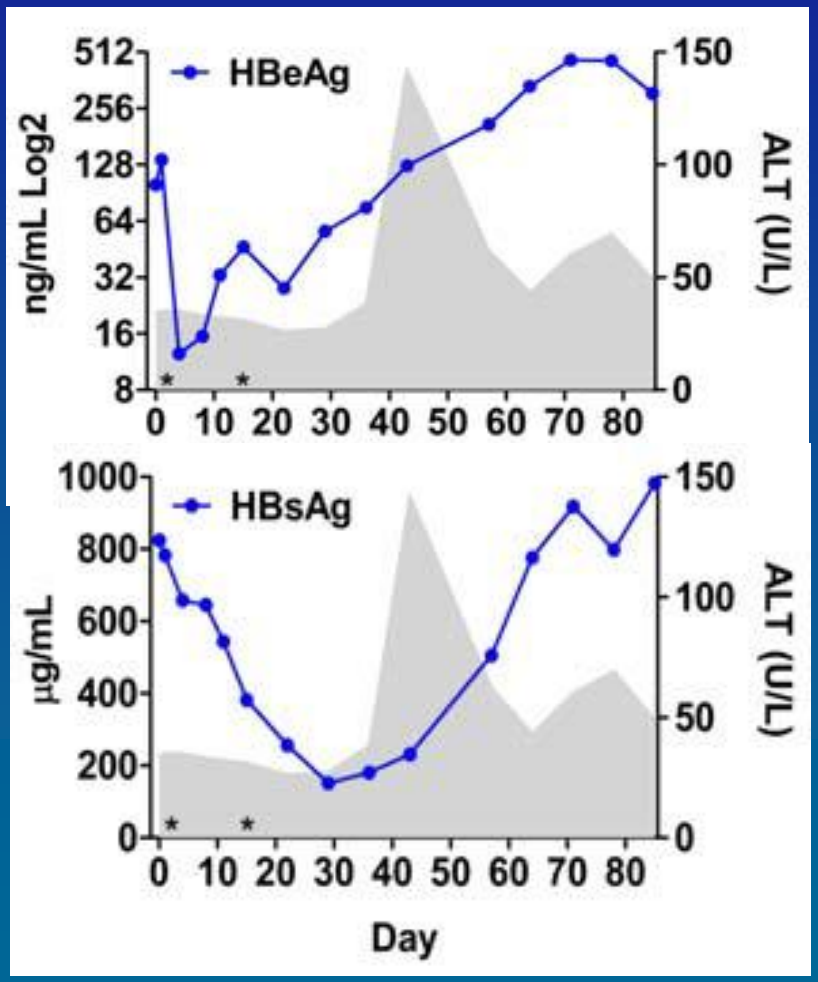
- ARC-520 is a combination of siRNAs directed against conserved HBV RNA sequences and efficiently knocks down HBV RNA, proteins, and DNA levels.
  - Phase II clinical trial NCT02065336 stopped 11-2016
- 2 siRNAs (cover 99.6% of known HBV sequences) conjugated to cholesterol and hepatocyte-targeted ligands
- 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)

Zeisel Gut 2015

siRNA: ARC520

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





Phase IIb IV q mo in
HBV suppressed (Given-2015)
Program stopped 11-16 for animal tox

Lanford et al, AASLD 2013

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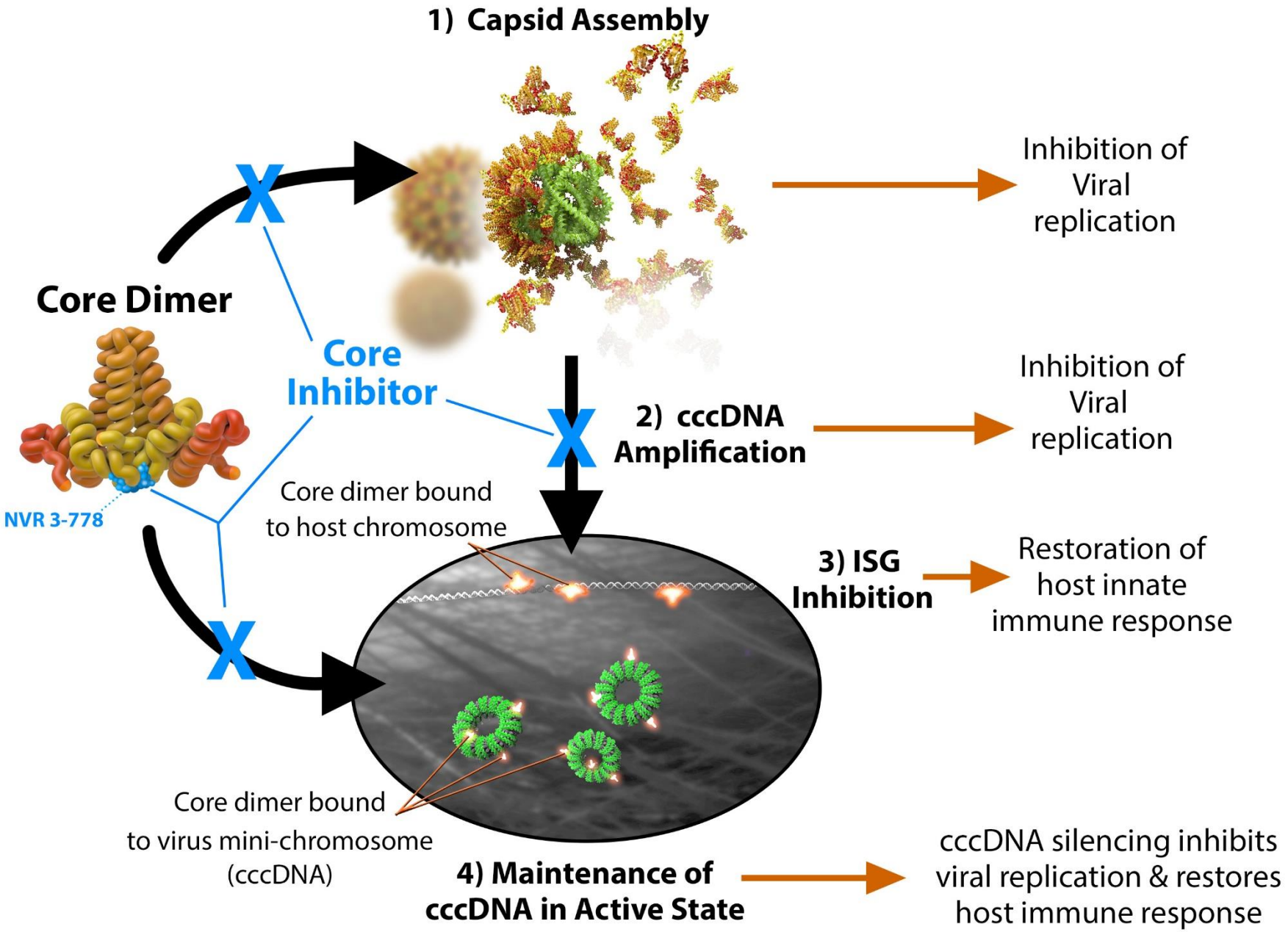
HBV Capsid

- It is essential for
  - HBV genome packaging
  - Reverse transcription
  - Intracellular trafficking
  - Maintenance of chronic infection as encapsidated HBV genomes are imported into the nucleus.
- AL- 3778- capsid inhibitor
  - Small molecule, direct-acting antiviral through aberrant core protein assembly that inhibits capsid assembly and viral replication
  - Phase IIa AL- 3778 po + PEGIFN -73 HBsAg pos, ↑ALT
  - Found decrease in HBV DNA, HBV RNA, no change in qHBsAg (APASL 2017)

Zeisel Gut 2015



Novira/Alios website 2015

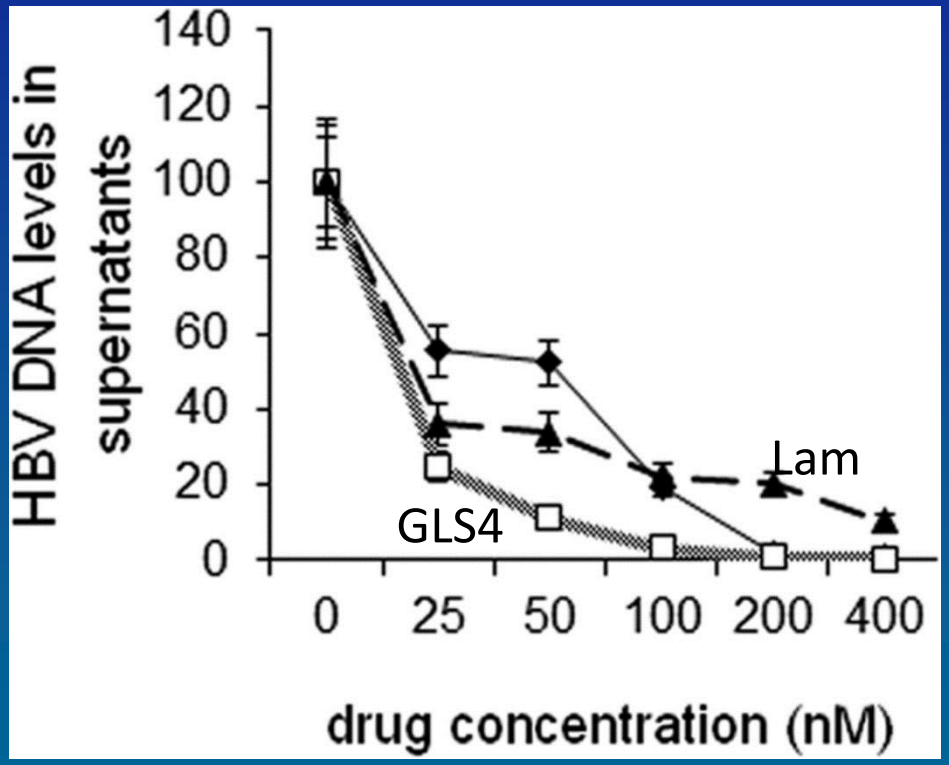
HBV Nucleocapsid Inhibitors

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
  - Favor 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

Nucleocapsid Inhibitors: GLS4 First Member of HAP Nucleocapsid Compounds

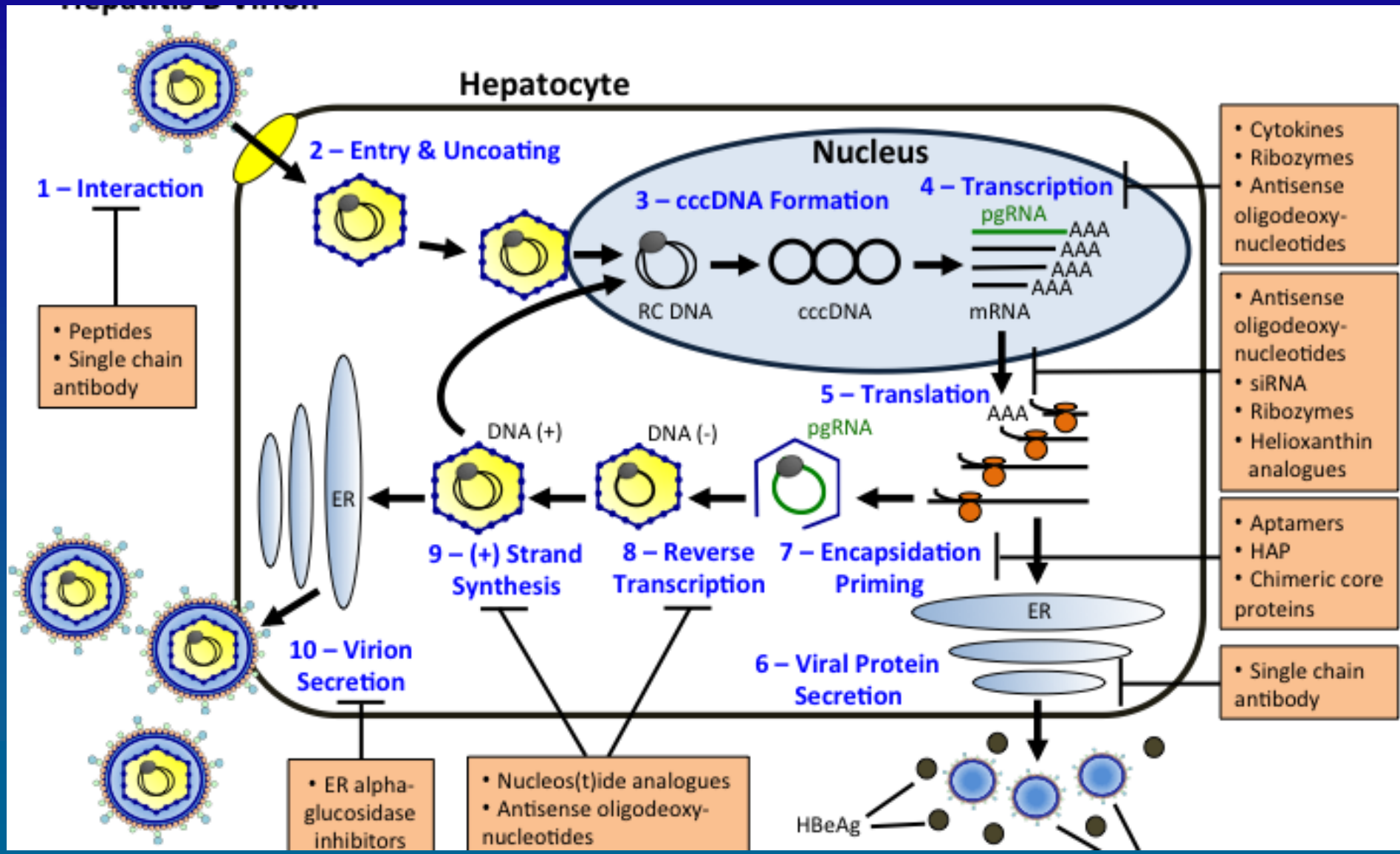


Morphothiadine mesilate (GLS4)

- Triggers aberrant core particle assembly
- Hep AD38 cells

Phase I/II trials in China

Wu G et al. Antimicrob. Agents Chemother. 2013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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

HBV Inhibit Secretory Pathway

- Benzimidazole BM601
  - Selectively inhibit intracellular relocalization 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
Zeisel Gut 2015

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- **TLR-7**
- PD-1/ PDL-1
- IL-7
- Birinapant selectively induces TNF-mediated apoptosis (Pelligrini WEHI)
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GS-1059: TLR-7 Agonist GS-9620 for Pts With Suppressed Chronic HBV Infection

- Antiviral and proinflammatory- in chimps
- 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: no antiviral effect
  - At Wk 24, no pts treated with GS-9620 had HBsAg change >0.5 $\log_{10}$; no pts lost HBsAg
  - Improvements in specific T-cell responses observed with GS-9620 (eg, IFN-γ and IL-2 production)

Slide credit: clinicaloptions.com

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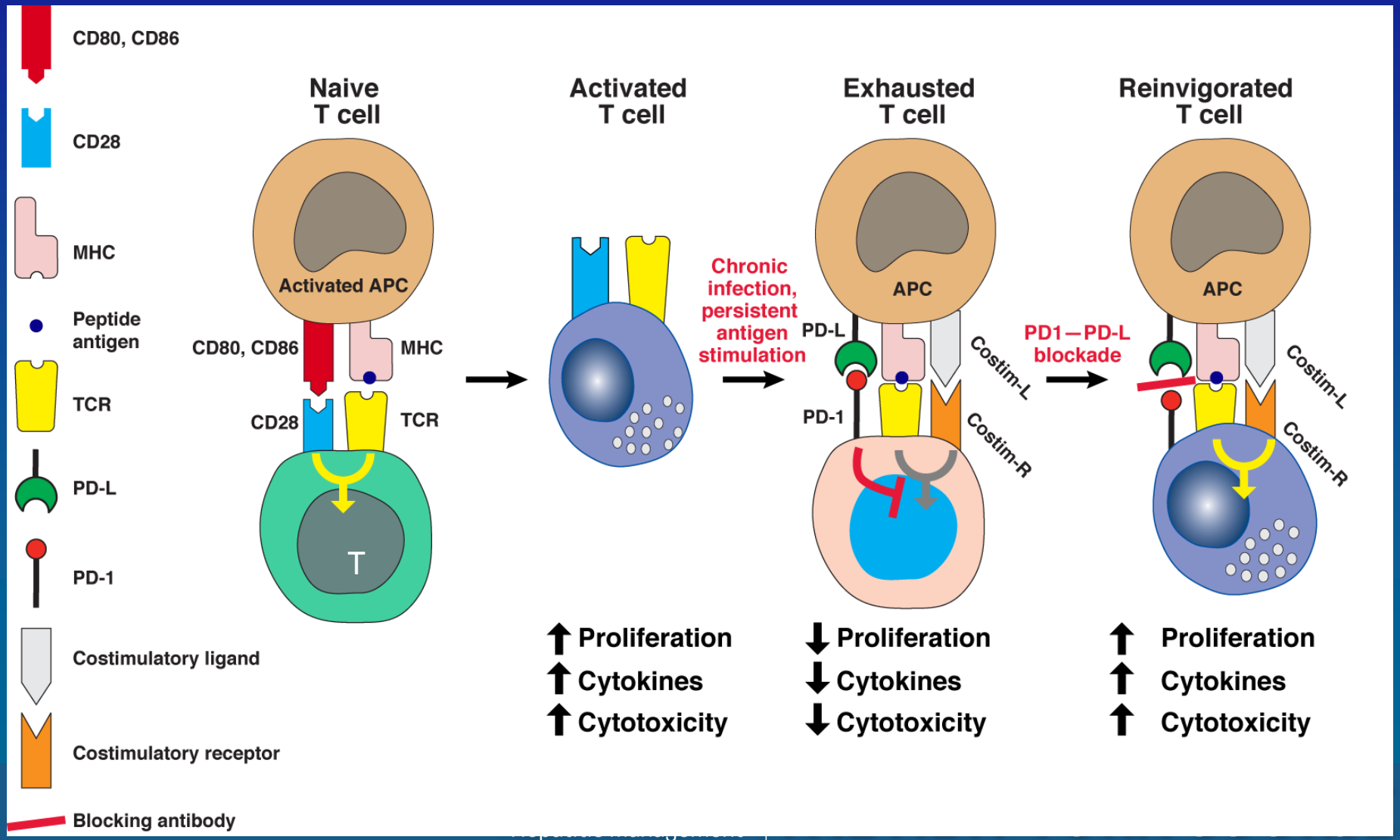
Effect of PD-1/L1 on Antiviral Immunity



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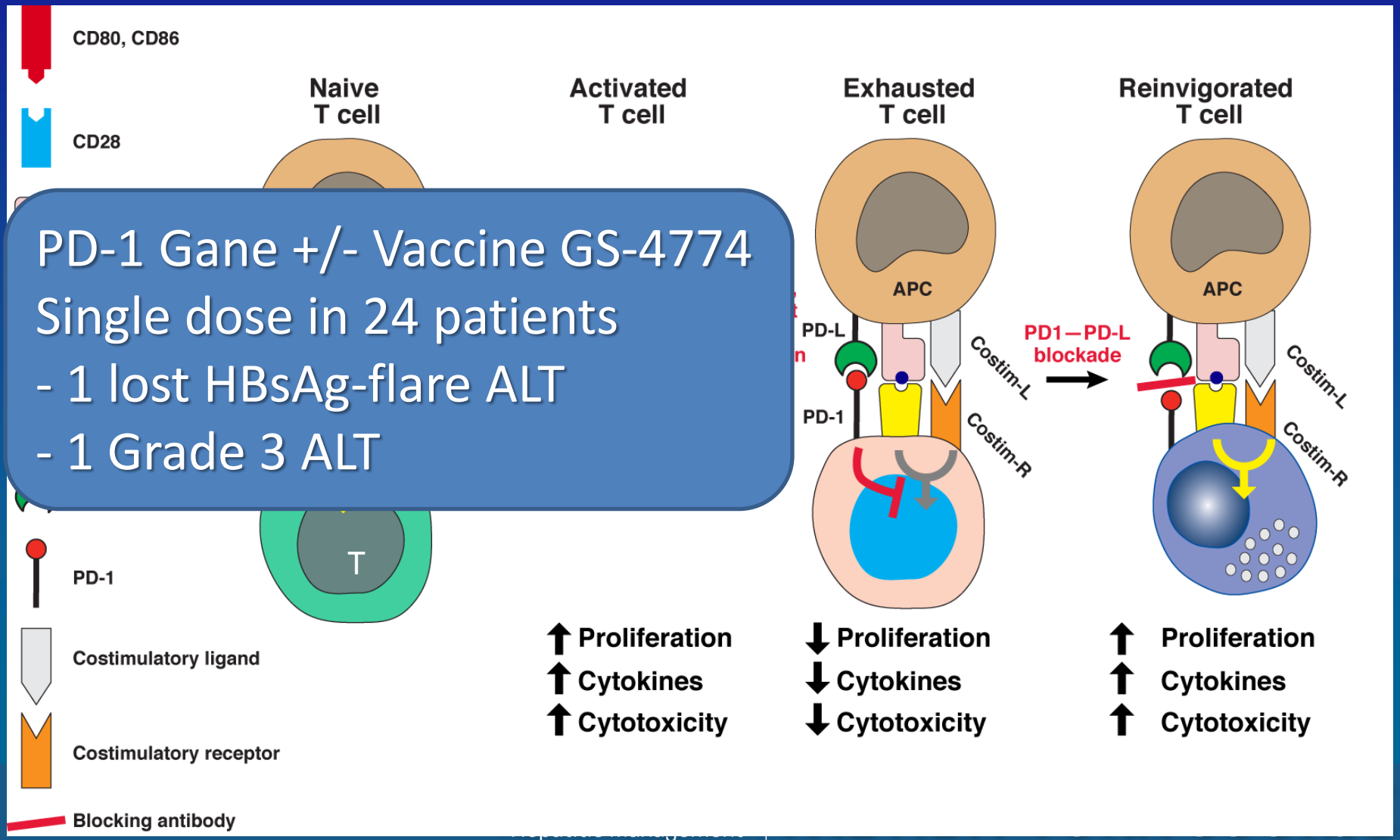

PD-1 Gane +/- Vaccine GS-4774
Single dose in 24 patients
- 1 lost HBsAg-flare ALT
- 1 Grade 3 ALT

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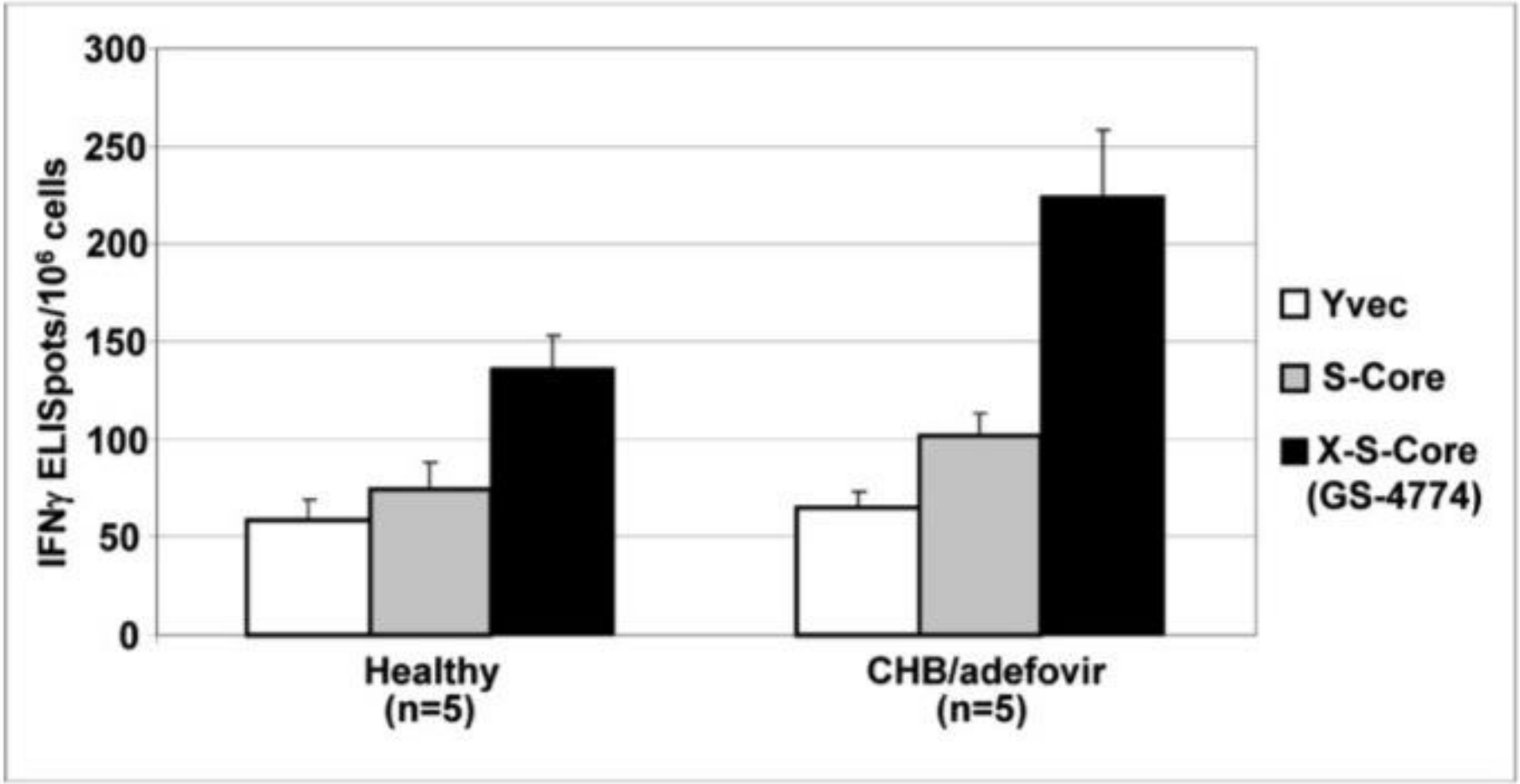
Tarmogens can induce HBV-specific T cell response in vitro

GS-4774 ± TDF Phase 2: ↓ qHBsAg

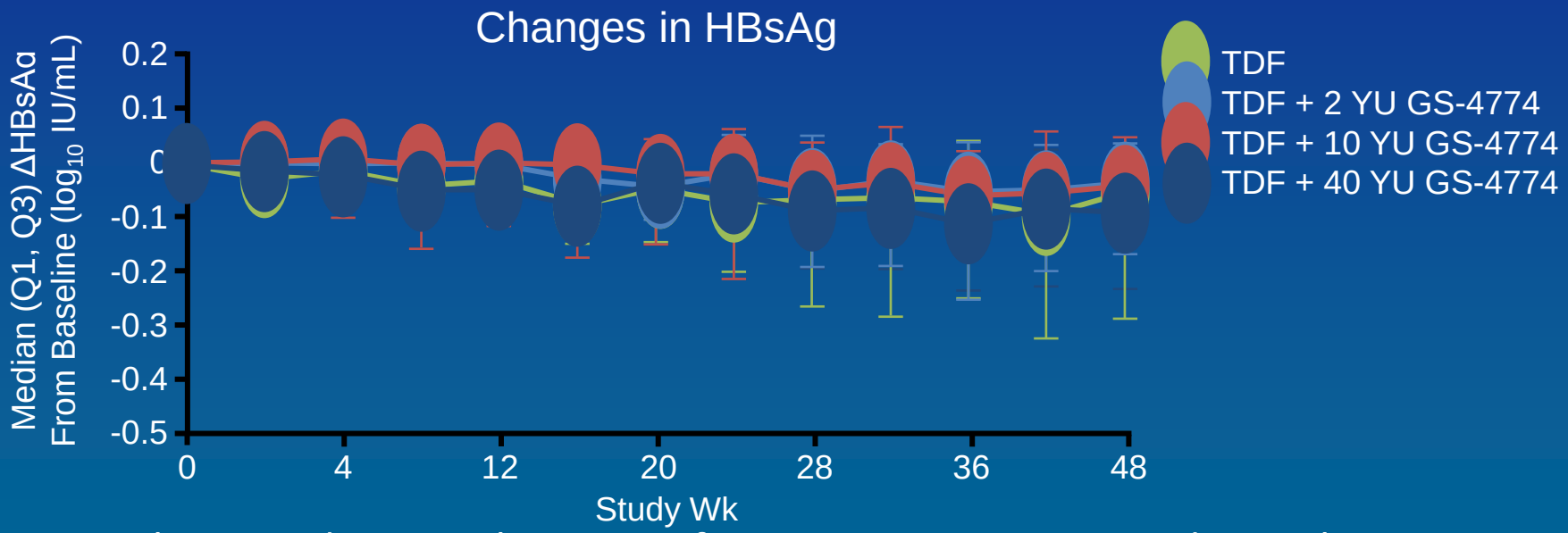


King T et al. PLOS ONE (2014), 9 (7): e101904

Yeast based vaccine immunotherapy

GS-4774, a Heat-Inactivated, Yeast-Based T-Cell Vaccine for CHB

- 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.

Slide credit: clinicaloptions.com

Janssen HL, et al. AASLD 2016. Abstract 231.

Emerging DAAs against HBV

Many currently in the pipeline

- 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
- PEG-IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1

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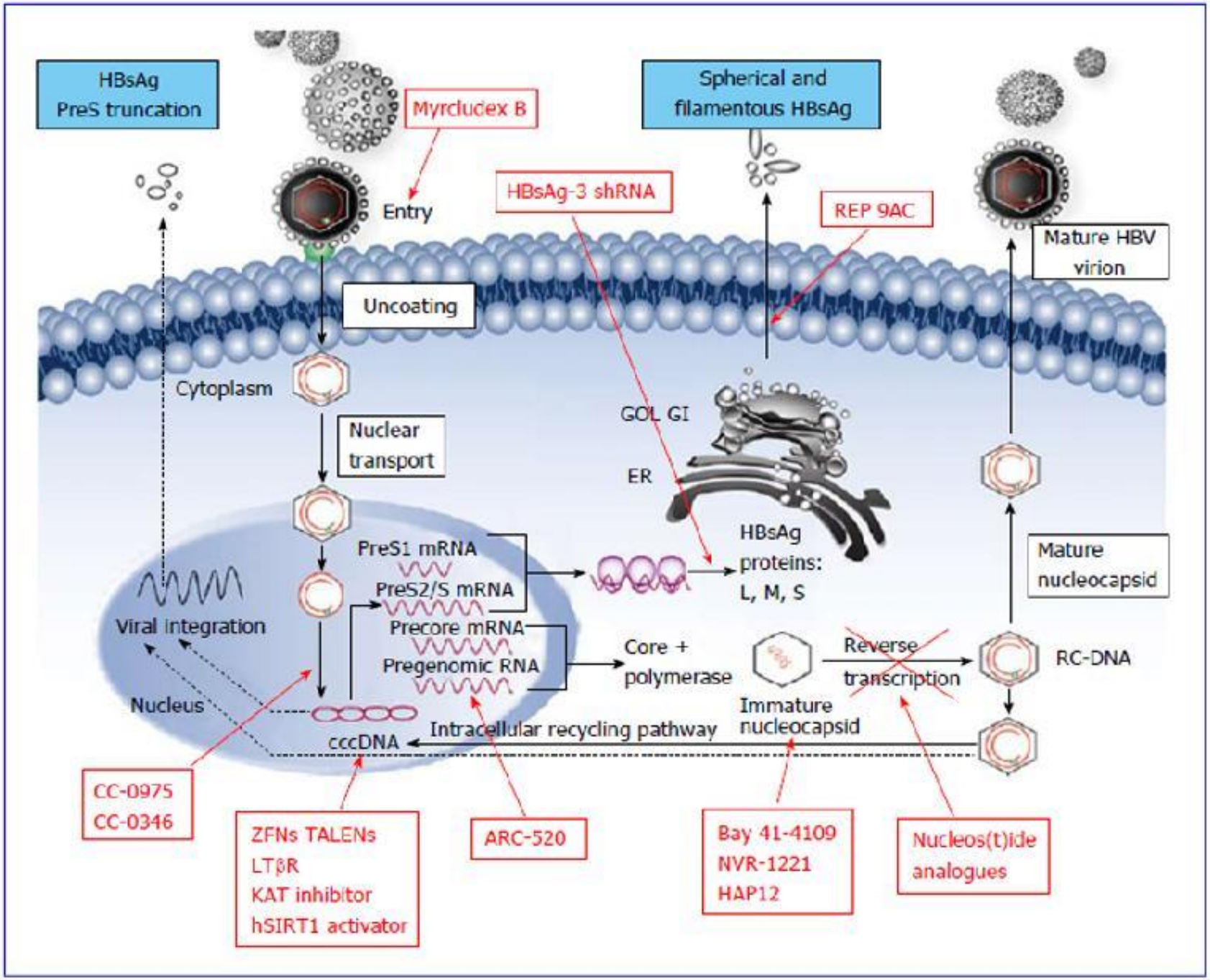
BUT Selection of HBV patient will be critical

Optimization of HBV endpoints needed

Zeizel Gut 2015


HBsAg
PreS truncation
Myrcludex B
Entry
Spherical and
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HBsAg-3 shRNA
REP 9AC
Mature HBV
virion
Uncoating
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transcription
RC-DNA
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nucleocapsid
Viral integration
Nucleus
cccDNA
Intracellular recycling pathway
Immature
nucleocapsid
CC-0975
CC-0346
ZFNs TALENs
LTβR
KAT inhibitor
hSIRT1 activator
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Bay 41-4109
NVR-1221
HAP12
Nucleos(t)ide
analogues

HIV Management
Hepatitis Management

THE NEW YORK COURSE