Hepatitis B virus & current and investigational therapies

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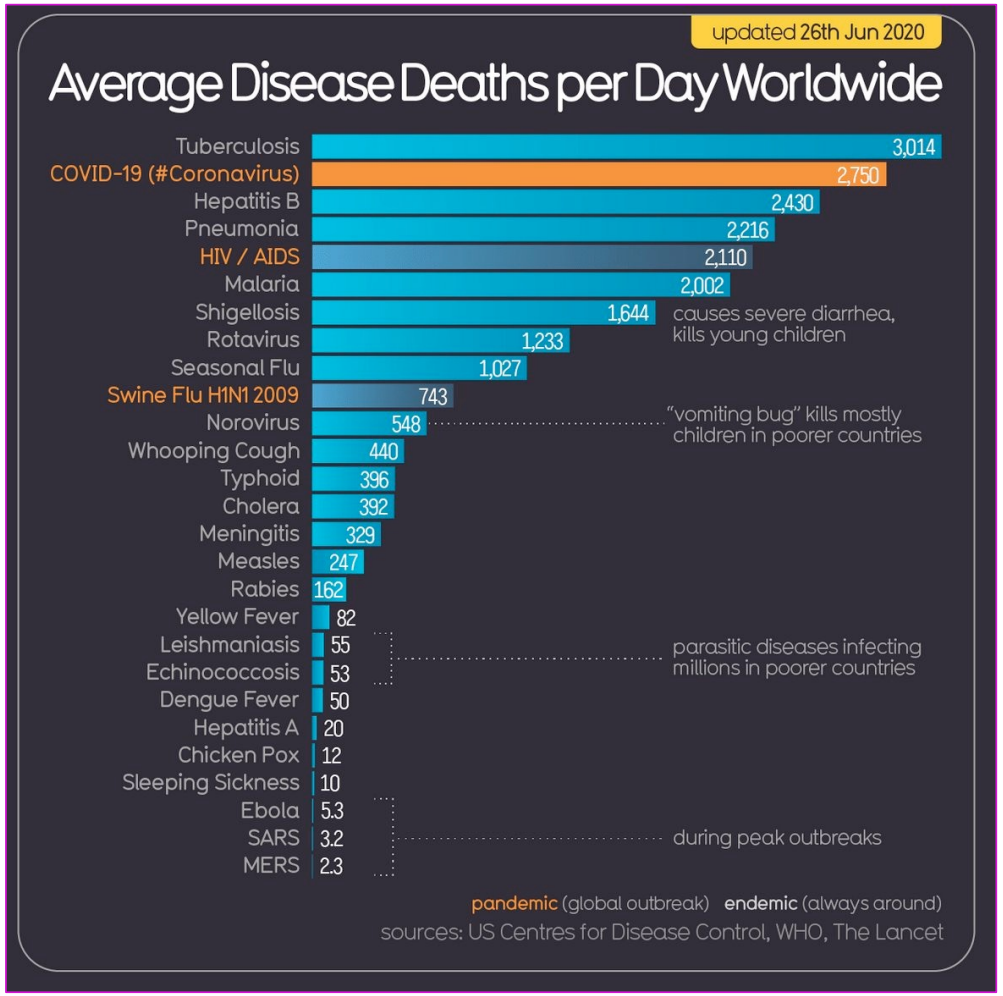
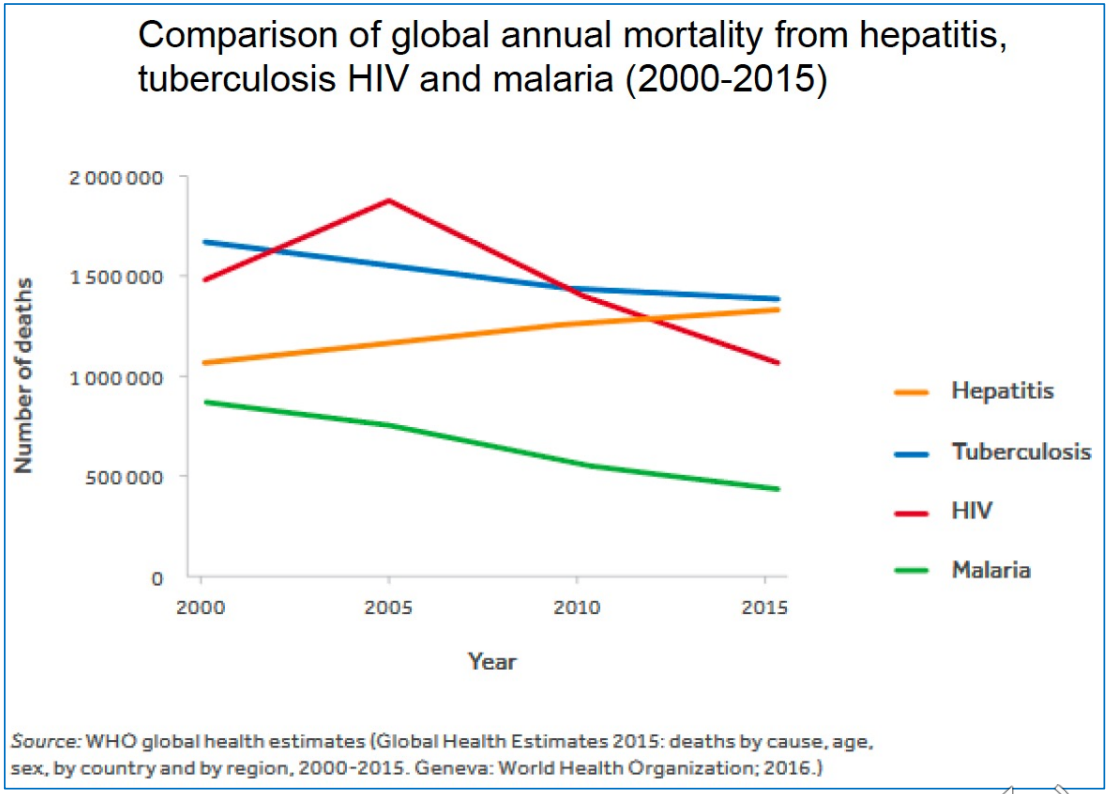
Background/Introduction

Viral hepatitis burden, mainly that caused by HBV, is yet increasing over other health threatening conditions

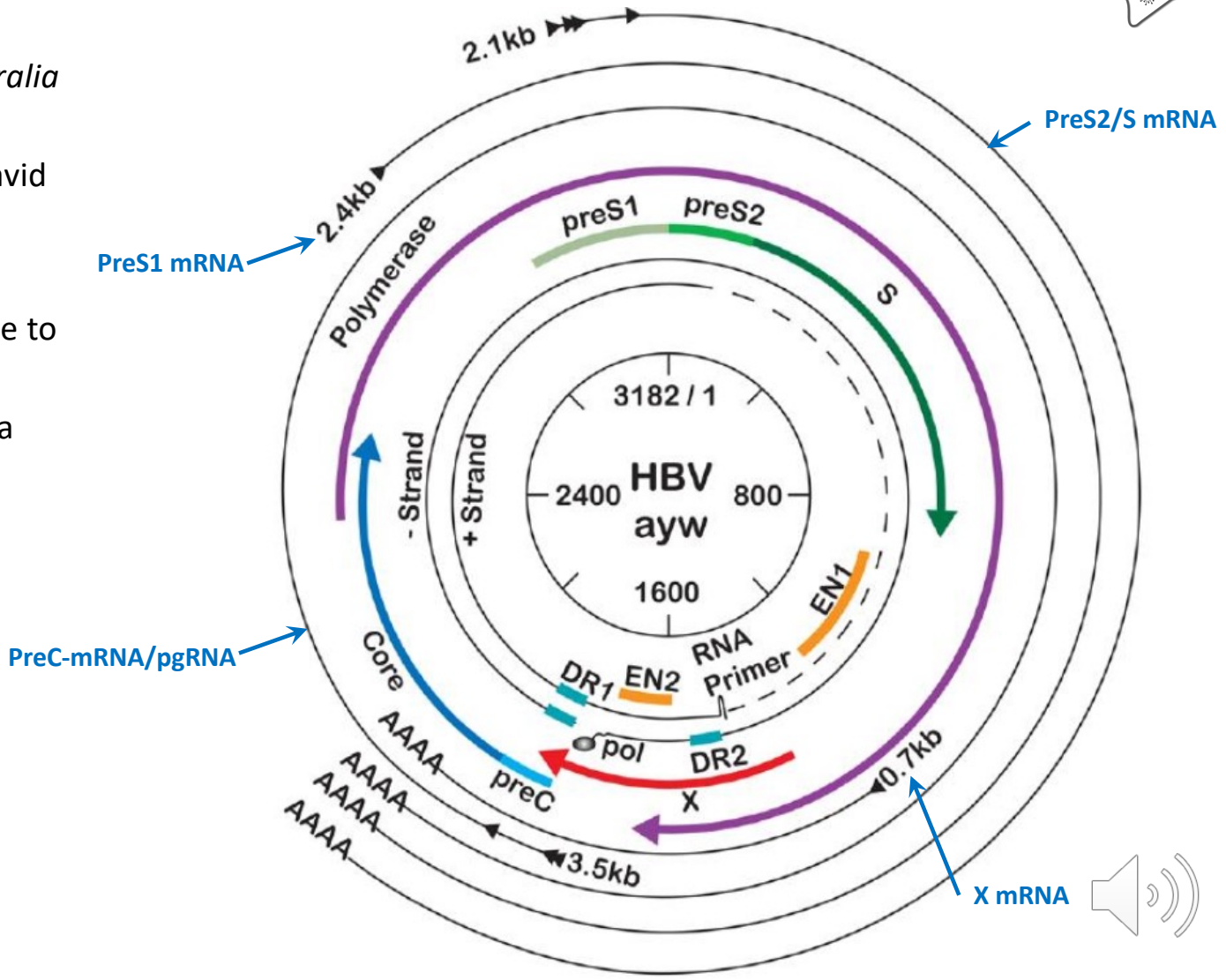




Sources: WHO

Generalities on HBV & genome organization

- ✓ Discovered by Dr Baruch Blumberg (*Australia antigen*; Nobel prize 1976)
- ✓ First seen under the microscope by Dr David Dane in 1970
- ✓ Belongs to *Hepadnaviridae* family
- ✓ Class VII of Baltimore's classification; close to retroviruses (see life cycle)…
- ✓ 3.2 kb double-stranded DNA genome, in a relaxed-circular conformation (rcDNA)
- ✓ Four open reading frames (ORFs)
- ✓ Viral transcripts
  - ➢ Pregenomic RNA (pgRNA)
  - ➢ Precore mRNA
  - ➢ PreS1 mRNA
  - ➢ PreS2/S mRNA
  - ➢ X mRNA
  - ➢ Spliced RNA

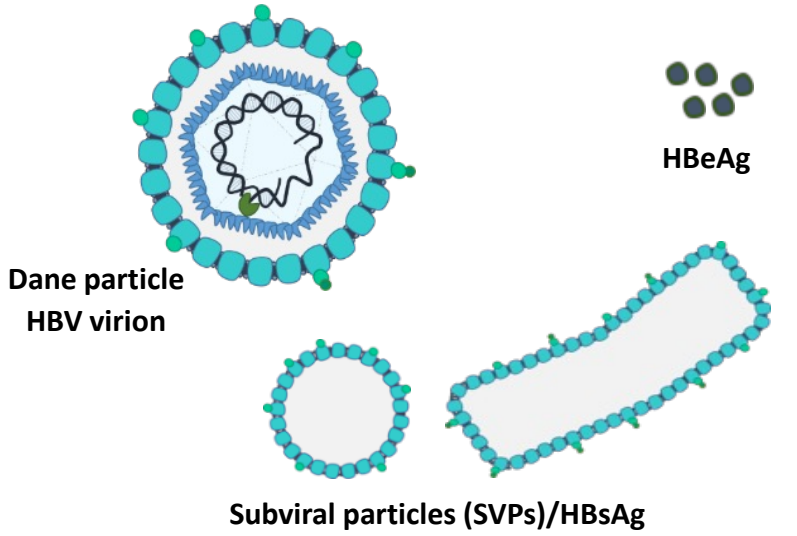


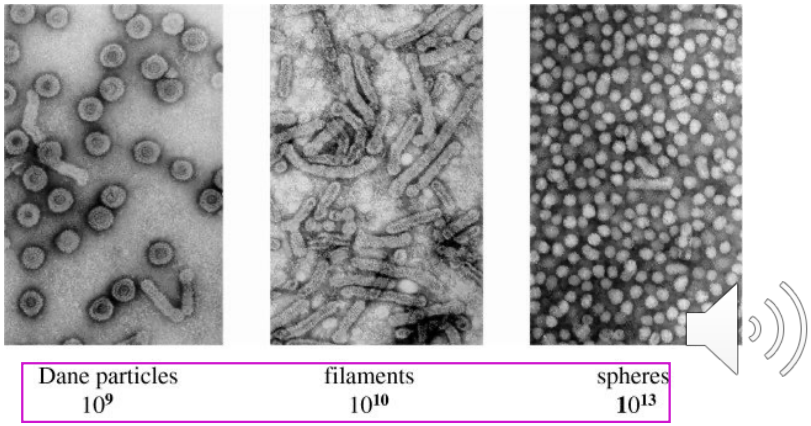
Adapted from Seeger et al., Field's Virology 2015

HBV coding capacities (1)

Viral transcripts	Viral proteins
Pregenomic RNA (pgRNA)	HBV Pol, HBcAg
Precore mRNA	HBeAg
PreS1 mRNA	L-HBsAg
PreS2/S mRNA	S-HBsAg, M-HBsAg
X mRNA	HBx
Spliced RNA	HBSP

Viral component in blood



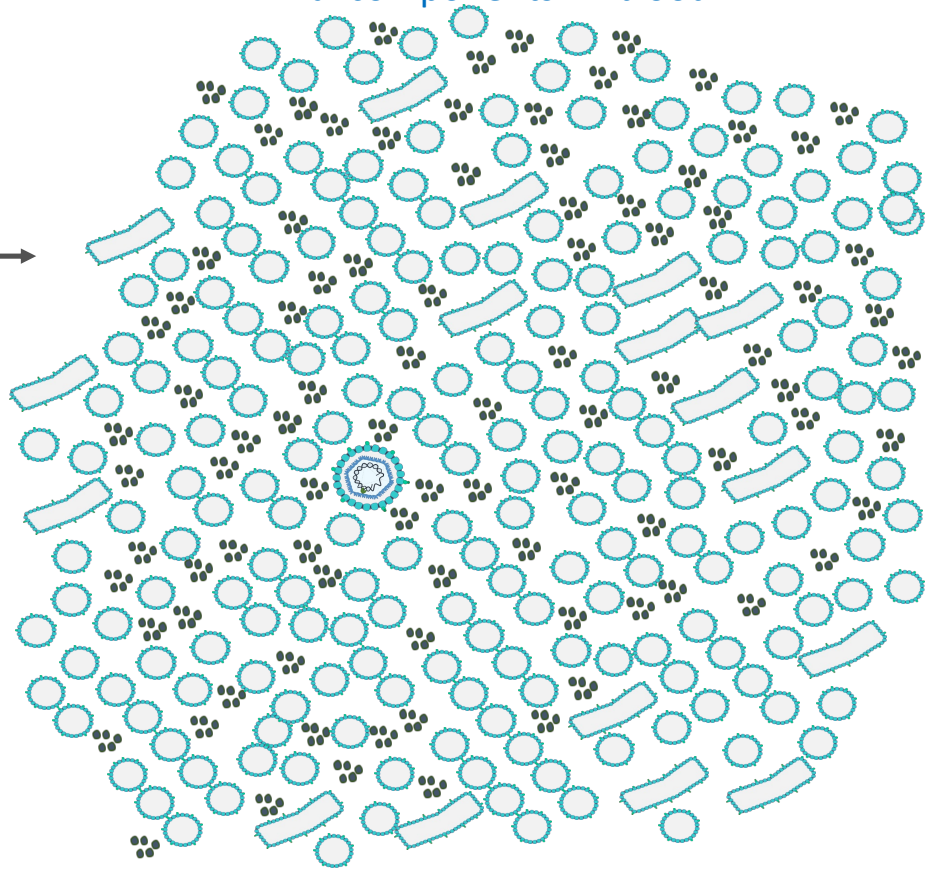


Modified from: Lucifora & Delphin, Antiviral Res., 2020
Tsukuda & Watashi, Antiviral Res., 2020

HBV coding capacities (2)

Viral transcripts	Viral proteins
Pregenomic RNA (pgRNA)	HBV Pol, HBcAg
Precore mRNA	HBeAg
PreS1 mRNA	L-HBsAg
PreS2/S mRNA	S-HBsAg, M-HBsAg
X mRNA	HBx
Spliced RNA	HBSP

Viral components in blood



SVPs/HBsAg > HBeAg >>> virions

1,000 to 100,000 fold excess of SVPs over virions

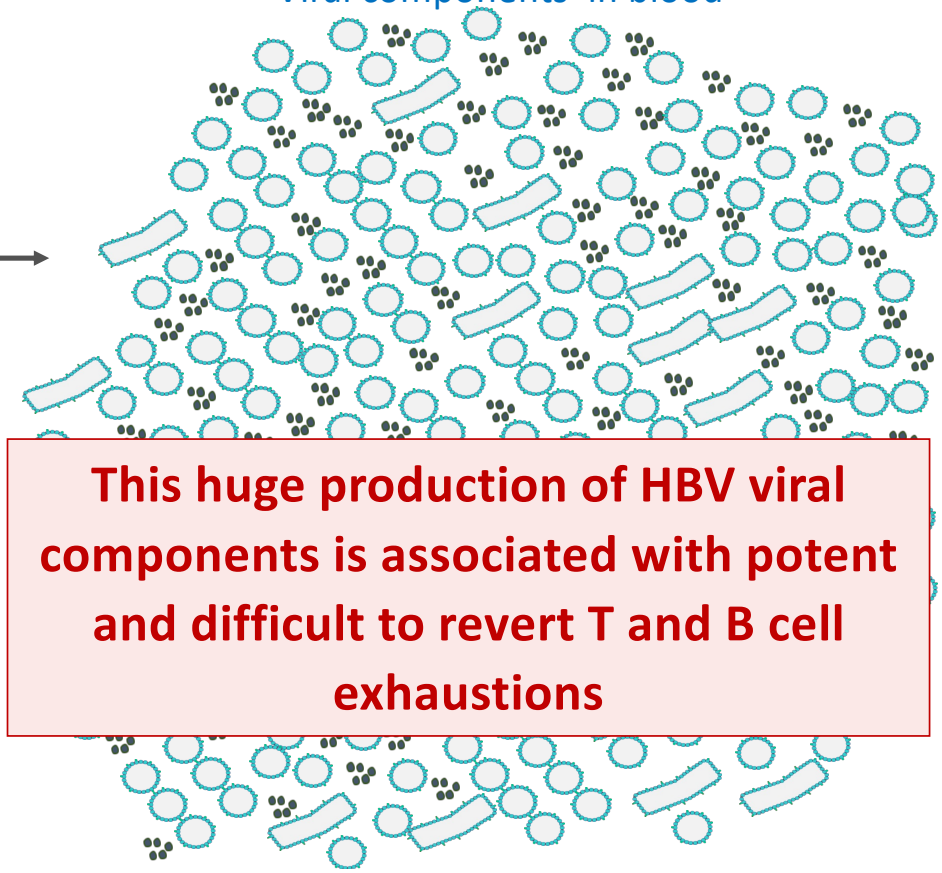
HBsAg up to 1mg/mL in blood !

Modified from: Lucifora & Delphin, Antiviral Res., 2020
Tsukuda & Watashi, Antiviral Res., 2020

HBV coding capacities (3)

Viral transcripts	Viral proteins
Pregenomic RNA (pgRNA)	HBV Pol, HBcAg
Precore mRNA	HBeAg
PreS1 mRNA	L-HBsAg
PreS2/S mRNA	S-HBsAg, M-HBsAg
X mRNA	HBx
Spliced RNA	HBSP

Viral components in blood



This huge production of HBV viral components is associated with potent and difficult to revert T and B cell exhaustions

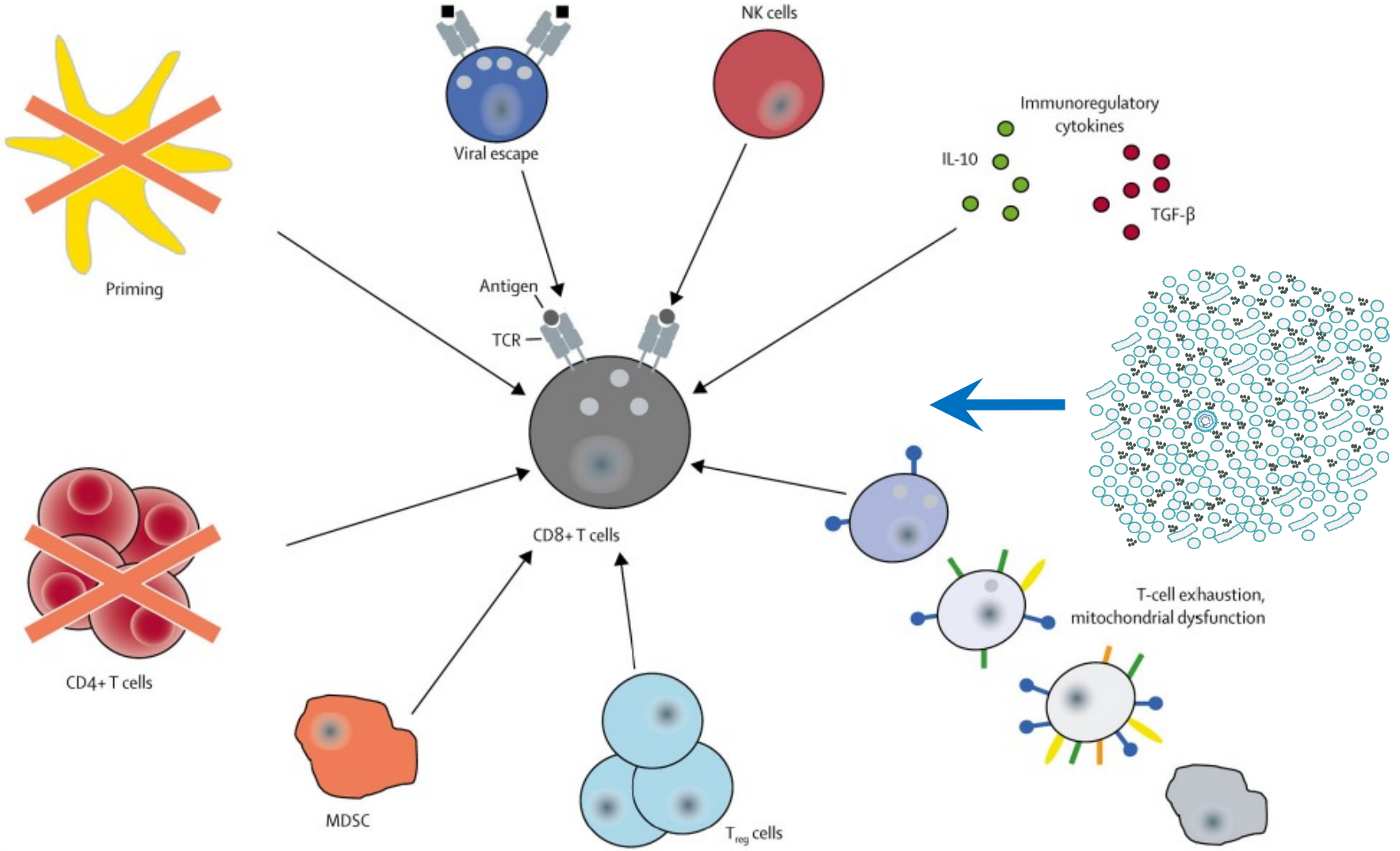
SVPs/HBsAg > HBeAg >>> virions

1,000 to 100,000 fold excess of SVPs over virions

HBsAg up to 1mg/mL in blood !

Modified from: Lucifora & Delphin, Antiviral Res., 2020
Tsukuda & Watashi, Antiviral Res., 2020

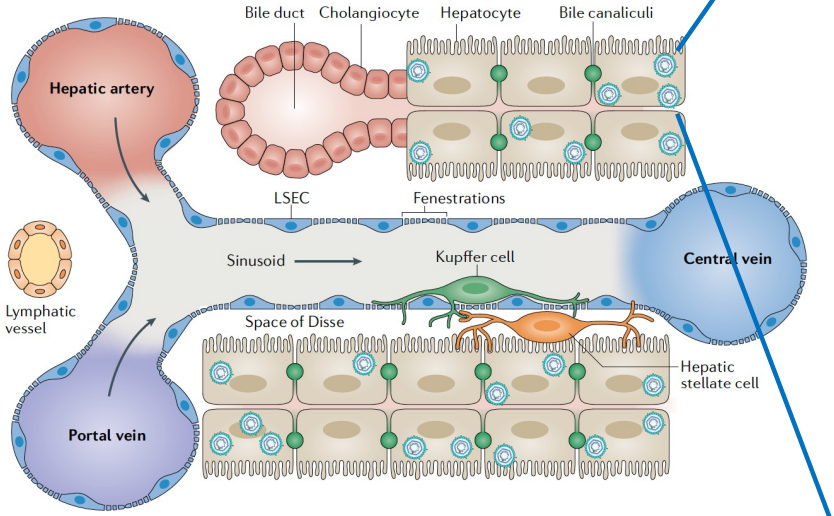
Exhaustion of immune system in CHB patients

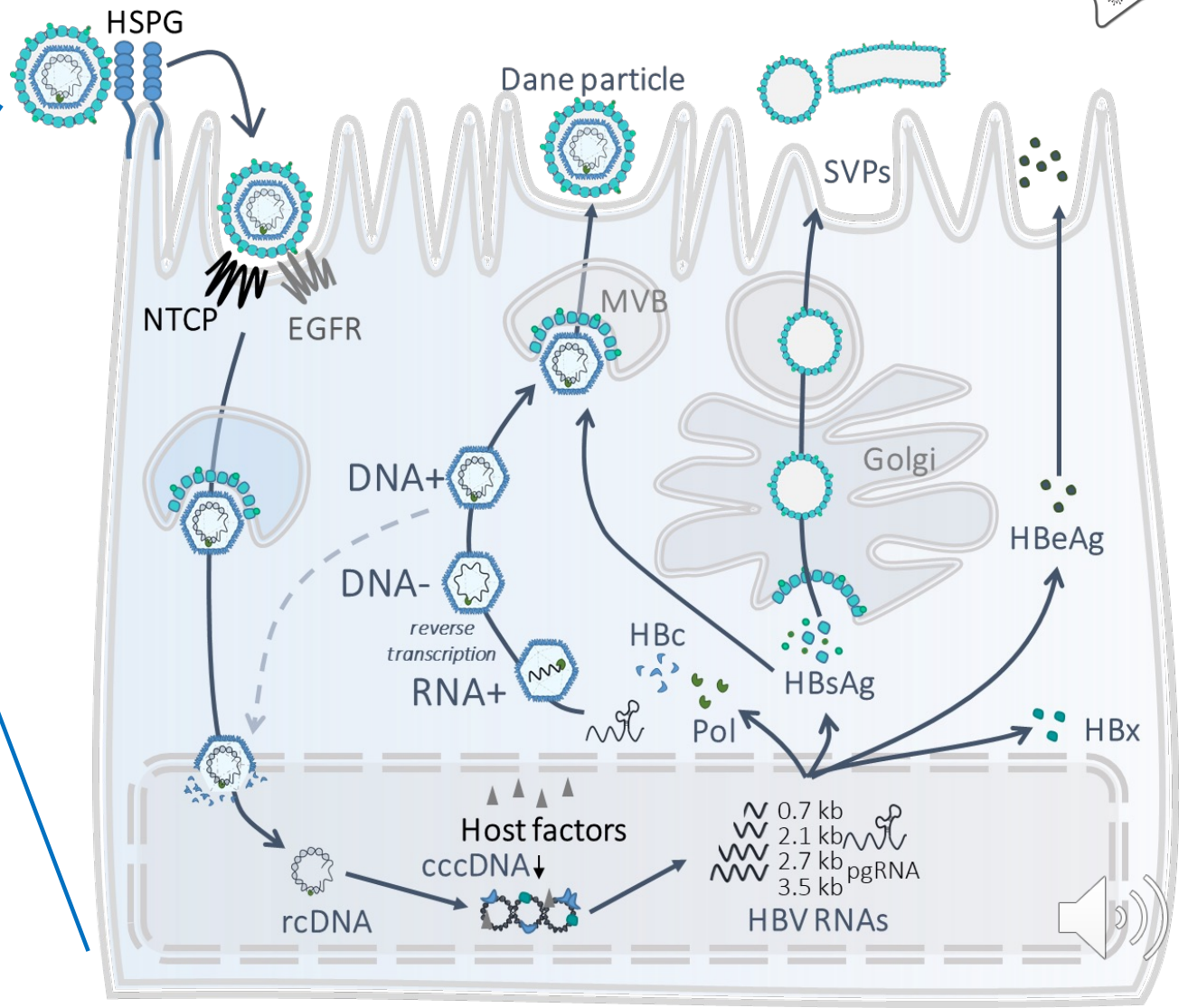


Very high antigens and virion load

Revill et al., Lancet Gastroenterol. Hepatol., 2019

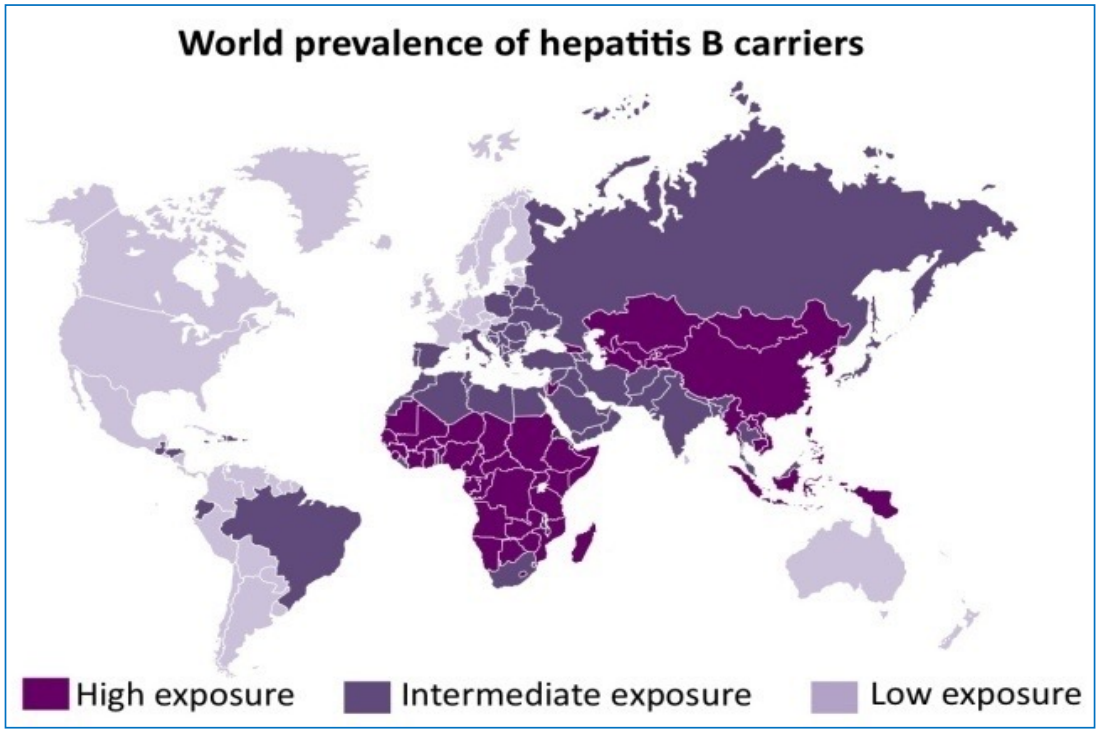
HBV life cycle in hepatocytes

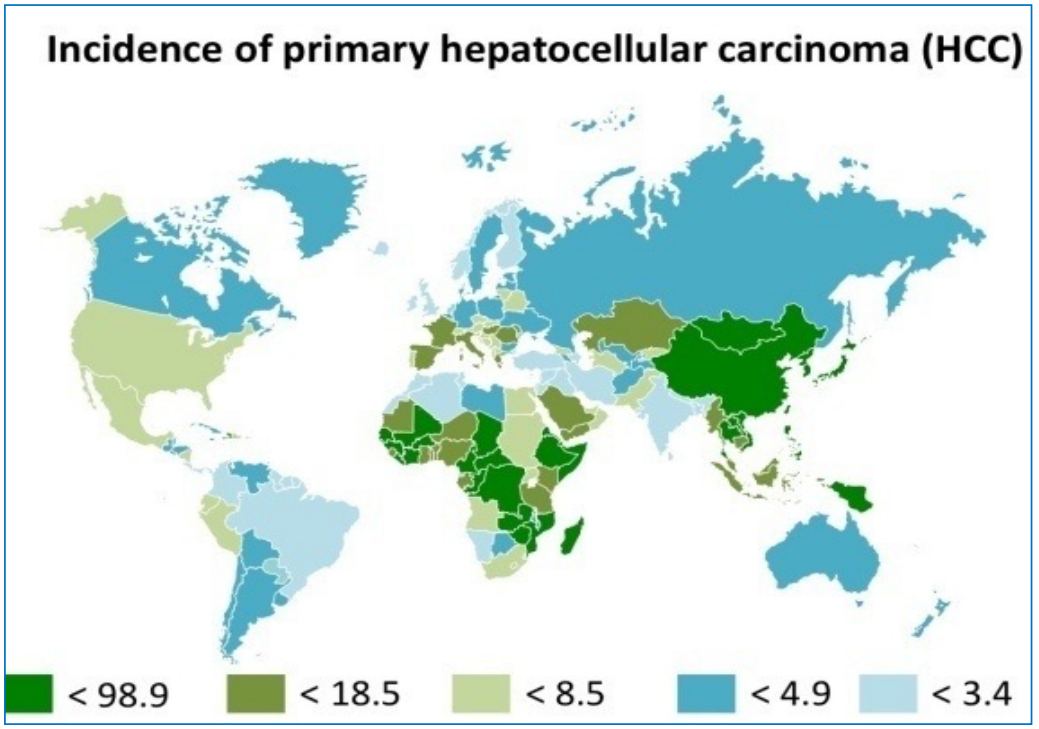




Modified from: Tsukuda & Watashi, Antiviral Res., 2020

World prevalence of HBV chronic carriers and incidence of primary hepatocellular carcinoma (HCC)





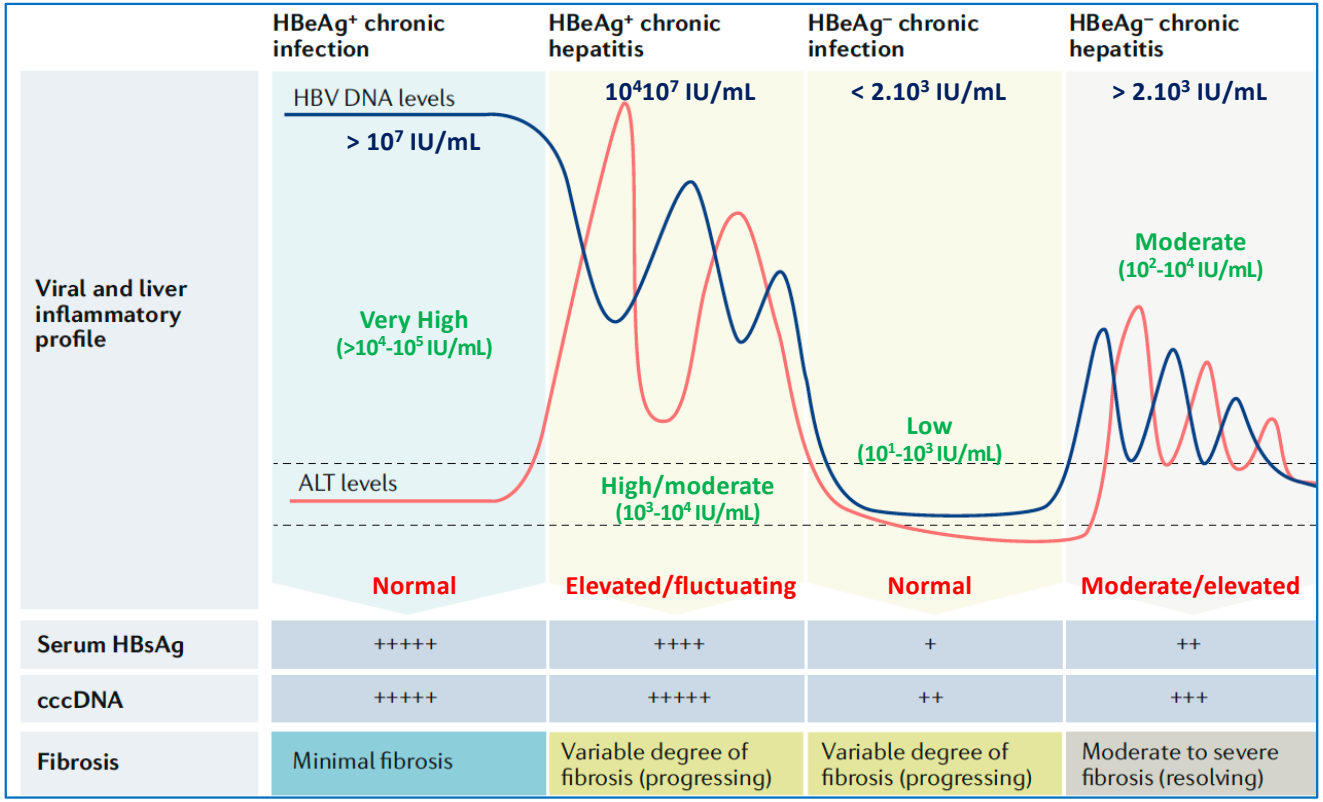
50% of HCC are a consequence of chronic HBV infections

Around 850,000 individuals die from HCC each year

Gouas et al., Cancer Lett. 2009; El Serag, Gastroentrerology 2018;
Globocan, IARC-WHO, 2018; De Martel et al. The Lancet Global Health 2020

HBV natural history of HBV chronic infections (CHB): a very complex pattern

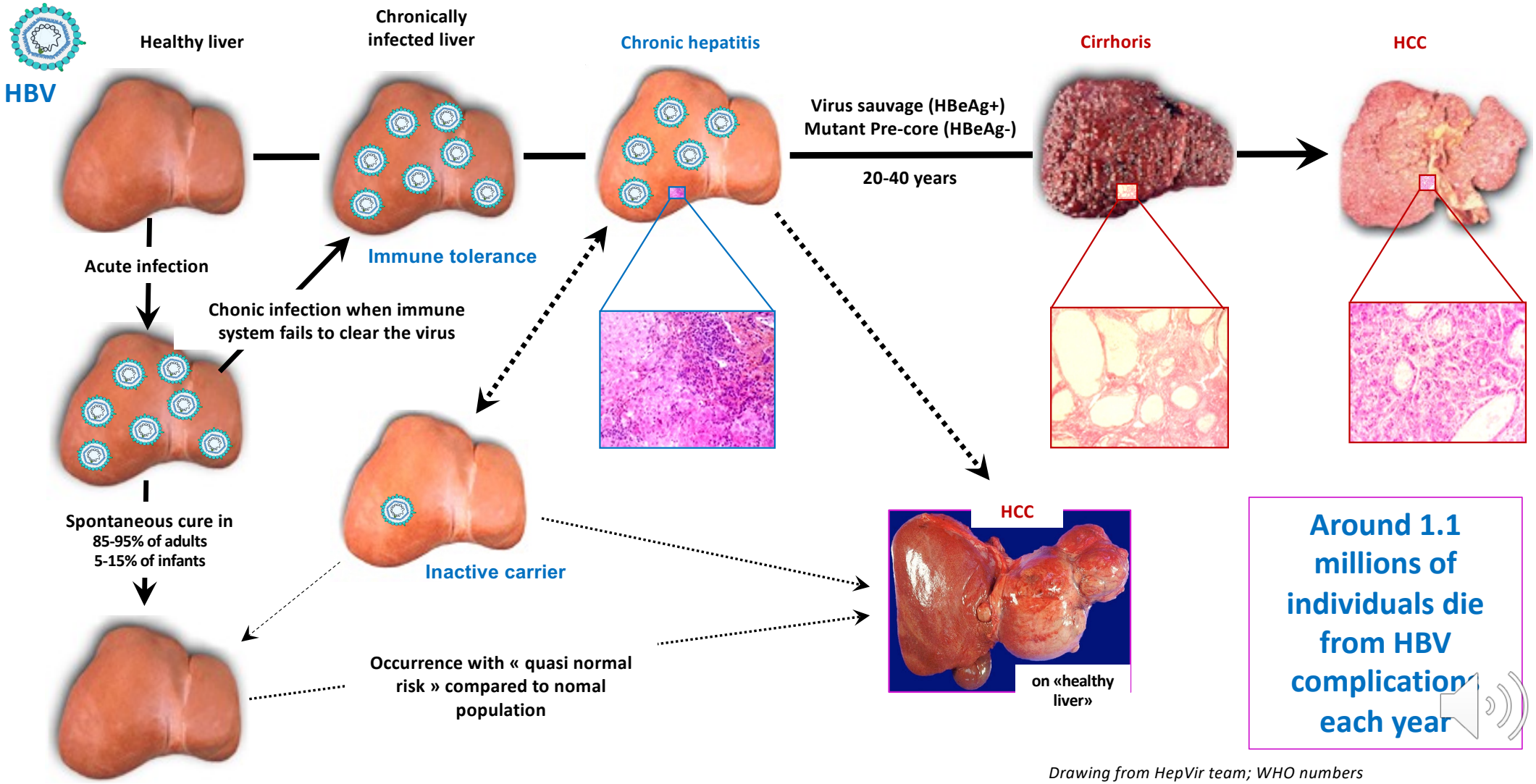
HBV DNA levels
ALT levels
HBsAg levels



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

EASL recommandations, J. Hepatol., 2017; Modified from Fanning et al., Nature review Drug Disco., 2019

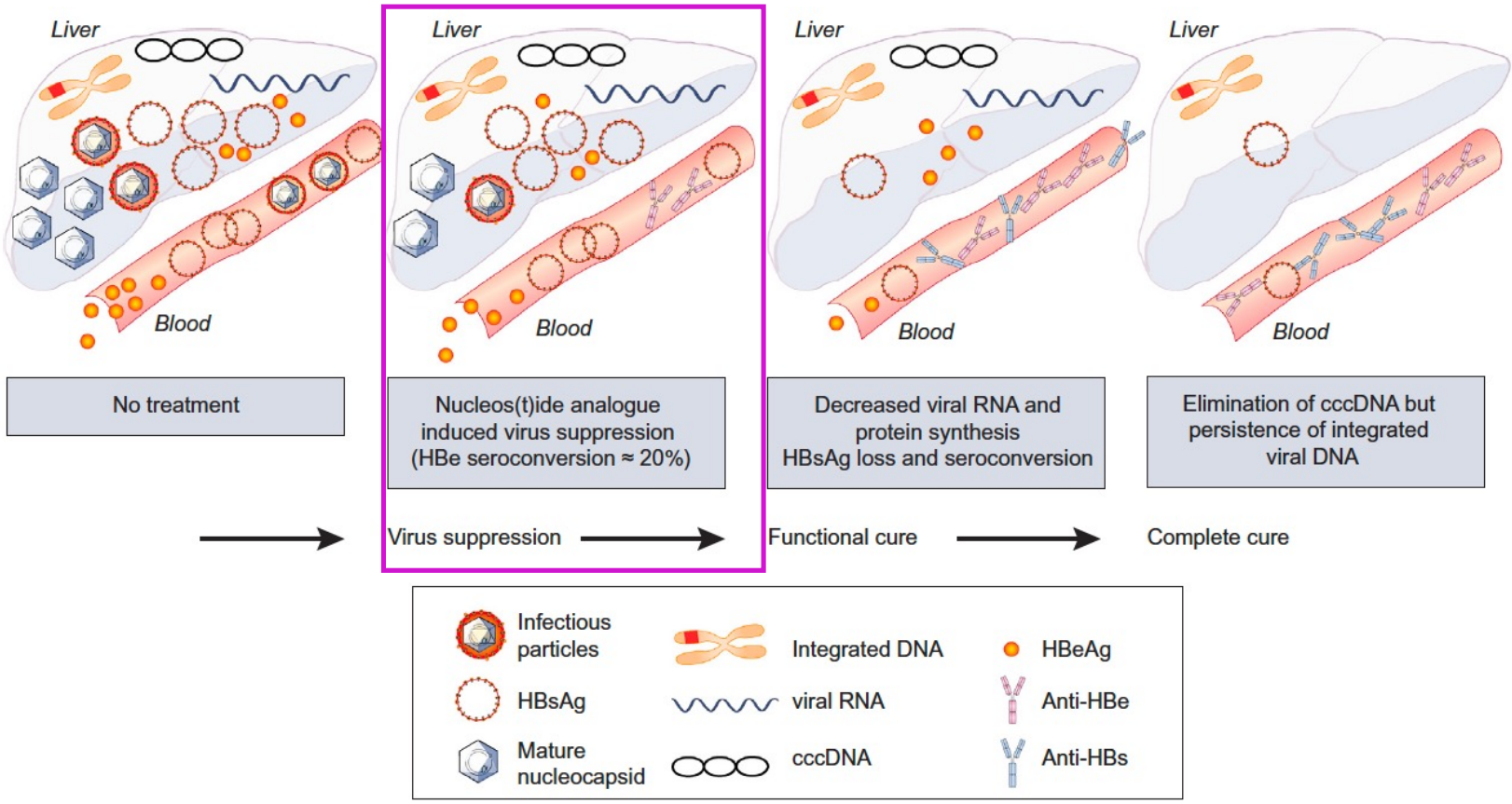
HBV natural history: overall view



Drawing from HepVir team; WHO numbers

Current therapies

Goal of therapies: “Virosuppression” versus “Functional Cure” versus “Complete Cure”



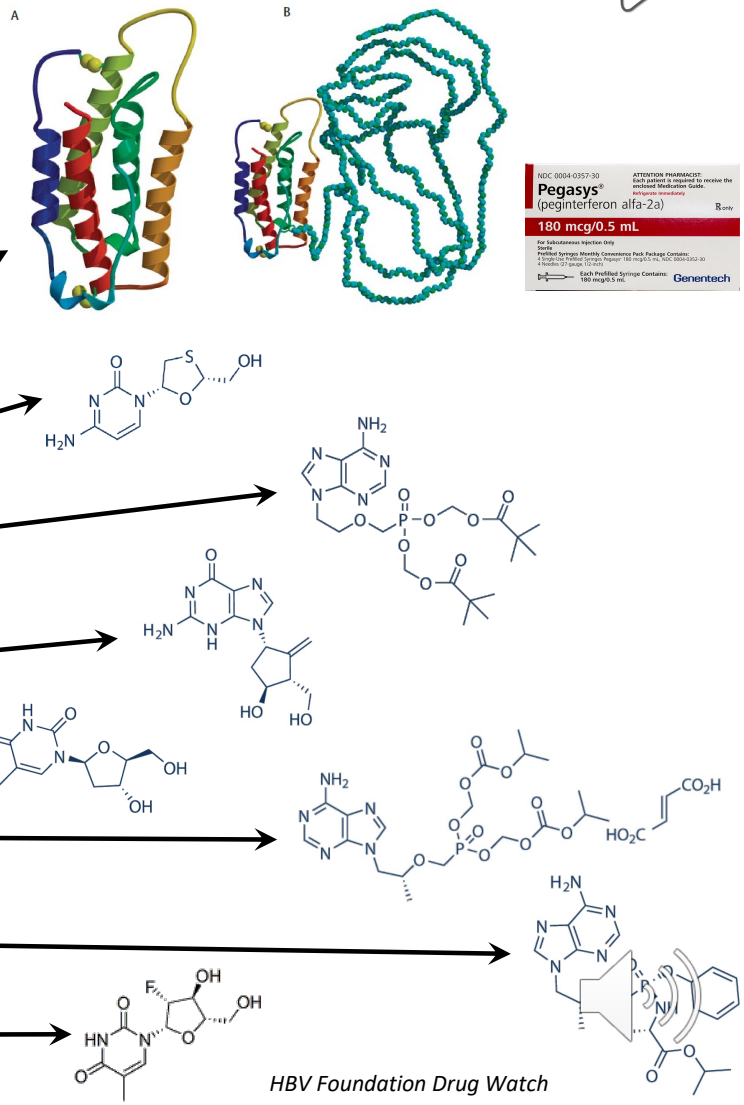
Viro-suppression **= on-treatment suppression of viral load in blood of CHB patients**

Functional cure **= long-term HBV virosuppression + HBsAg loss (+ anti-HBs seroconversion) after cessation of treatment (finite duration of treatment)**

Durantel & Zoulim, J. Hepatol., 2016

FDA approved drugs used in clinic against HBV (1)

	FAMILY/DRUG NAME	MECHANISM	COMPANY	WEBSITE	USA STATUS
IFNs	**Interferons: Mimic infection-fighting immune substances naturally produced in the body**				
	Intron A (Interferon alfa 2b)	Immunomodulator	Merck, USA	merck.com	Approved 1991
	Pegasys (Peginterferon alfa 2a)	Immunomodulator	Genentech, USA	gene.com	Approved 2005
NUCs	**Nucleos(t)ide Analogues: Interfere with viral DNA polymerase used for HBV replication**				
	Epivir (Lamivudine) **Generics available*	Inhibits viral DNA polymerase	GlaxoSmithKline (GSK)	gsk.com	Approved 1998
	Hepsera (Adefovir dipivoxil) **Generics available*	Inhibits viral DNA polymerase	Gilead Sciences, USA	gilead.com	Approved 2002
	Baraclude (Entecavir) **Generics available*	Inhibits viral DNA polymerase	Bristol-Myers Squibb, USA	bms.com	Approved 2005
	Tyzeka (Telbivudine) **Generics available*	Inhibits viral DNA polymerase	Novartis, USA	novartis.com	Approved 2006
	Viread (Tenofovir) **Generics available*	Inhibits viral DNA polymerase	Gilead Sciences	gilead.com	Approved 2008
	Vemlidy (TAF or tenofovir alfenamide)	Prodrug of Tenofovir	Gilead Sciences	gilead.com	Approved 2016
	Levovir (Cledvudine)	Inhibits viral DNA polymerase	Bukwang, S. Korea	bukwang.co.kr	Approved 2006 in S. Korea



HBV Foundation Drug Watch

FDA approved drugs used in clinic against HBV (2)

Table 2. Main concepts and features of current treatment strategies of chronic hepatitis B.

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)[1]
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	Many (*i.e.*, decompensated disease, co-morbidities etc.)	None (dose adjustment according to eGFR[2])
Strategy	Induction of a long-term immune control by finite treatment	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Moderate (variable response pattern)	Universally high
Effect on HBeAg loss	Moderate, depending on baseline characteristics	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Variable, depending on baseline characteristics (overall higher as compared to NA)	Low: slowly increases with treatment time in HBeAg-positive patients[3]; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance development	No	Minimal to none[4]

PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; NA, nucleoside/nucleotide analogues; eGFR, estimated glomerular filtration rate.

[1] See section on 'Treatment strategies'.

[2] Dose adjustments in patients with eGFR <50 ml/min are required for all NA, except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis).

[3] A plateau in serologic responses has been observed beyond treatment year 4.

[4] So far no TDF or TAF resistance development has been detected.

EASL recommandations, J. Hepatol., 2017

FDA approved drugs used in clinic against HBV (3)

	Pegylated interferon alfa 48–52 weeks (post therapy)		Entecavir (on therapy)		Tenofovir disoproxil fumarate (on therapy)		Tenofovir alafenamide (on therapy)	
	6 months	3 years	1 year	7–10 years*	1 year	10 years†	1 year	5 years‡
HBeAg positive								
ALT normalisation	32–41%	57%	68%	78–79%	68%	78%	72%	76%
HBeAg seroconversion	29–32%	35%	21%	38%	21%	27%	10%	27%
HBV DNA undetectable§	7–14%	25%	67%	80–97%	76%	98%	64%	93%
HBsAg clearance	3–7%	11%	2%	4%	3%	5%	1%	1%
HBeAg negative								
ALT normalisation	59%	31%	78%	78–79%	76%	83%	83%	76%
HBV DNA undetectable§	19%	23–26%	90%	80–97%	93%	100%	94%	93%
HBsAg clearance	4%	8–14%	0	4%	0	3%	0	1%

HBV definition: HBeAG=hepatitis B e-antigen. HBsAG=hepatitis B virus surface antigen. Results from randomised controlled trials or follow-up studies of these trials. Not direct comparison. Response rates reported during long-term follow-up are imprecise because not all patients in the original cohorts were followed up and some studies reported combined results for HBeAg-positive and HBeAg-negative patients. ALT=alanine aminotransferase. HBV=hepatitis B virus. *Entecavir year 7–10 response rates were mainly based on one study in Japan and included both HBeAg-positive and HBeAg-negative patients; HBeAg clearance, but not HBeAg seroconversion rates, were reported.[99] Another study from China provided combined virological response rates at year-10 in HBeAg-positive and HBeAg-negative patients.[100] †Tenofovir disoproxil fumarate year 10 response rates were based on follow-up of phase 3 trial cohort, but only 32% completed year-10 follow-up.[101] ‡Tenofovir alafenamide year-5 response rates were based on follow-up of phase 3 trial cohorts and included both HBeAg-positive and HBeAg-negative patients.[102] §Lower limit of detection of HBV DNA assays varied from 10 IU/mL to 80 IU/mL for studies on entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide. HBV DNA less than 2000 IU/mL was used as definition of virological response in pegylated interferon alfa trials.

Table: **Efficacy of approved hepatitis B therapies in patients with HBeAg-positive or HBeAg-negative chronic hepatitis B[99-102]**

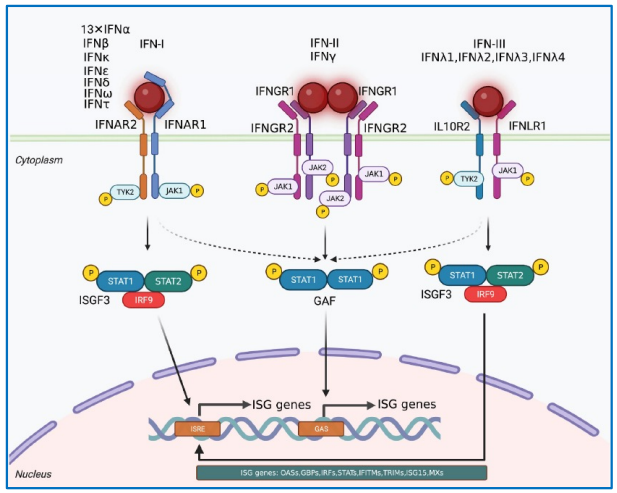
Virosupression

Functional cure

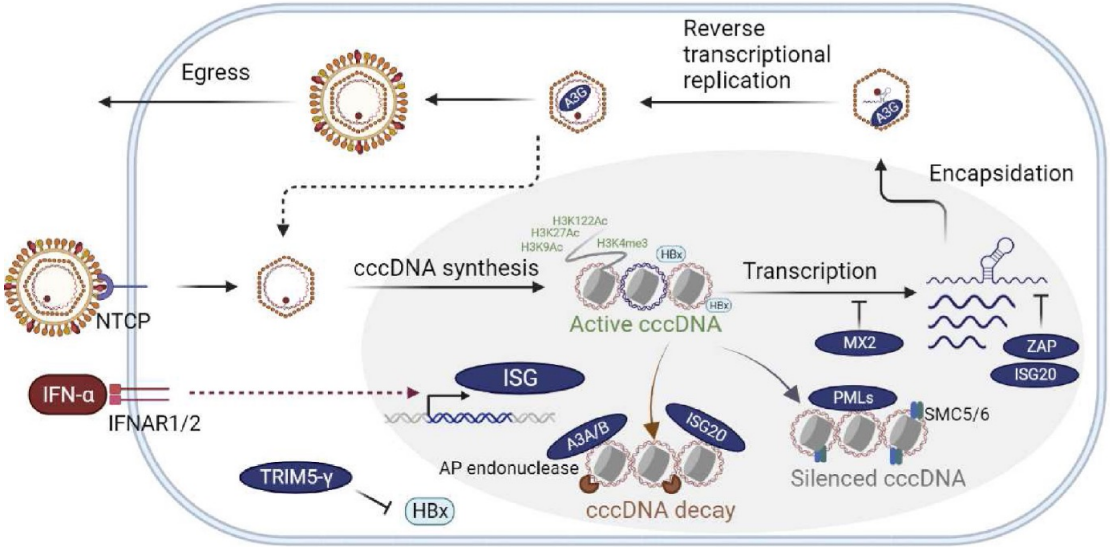
Disease control

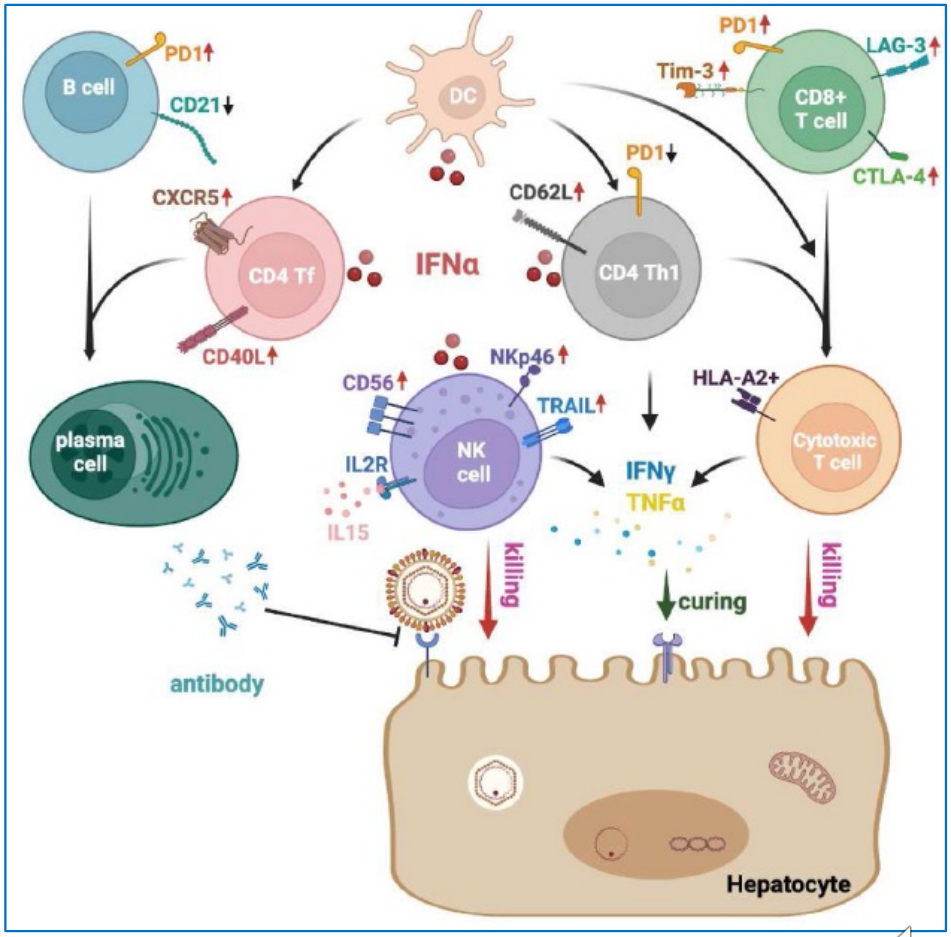
Jeng et al., The Lancet, 2023

Mode of action of Interferon-alpha: Direct versus indirect MoA



Direct effect in hepatocytes

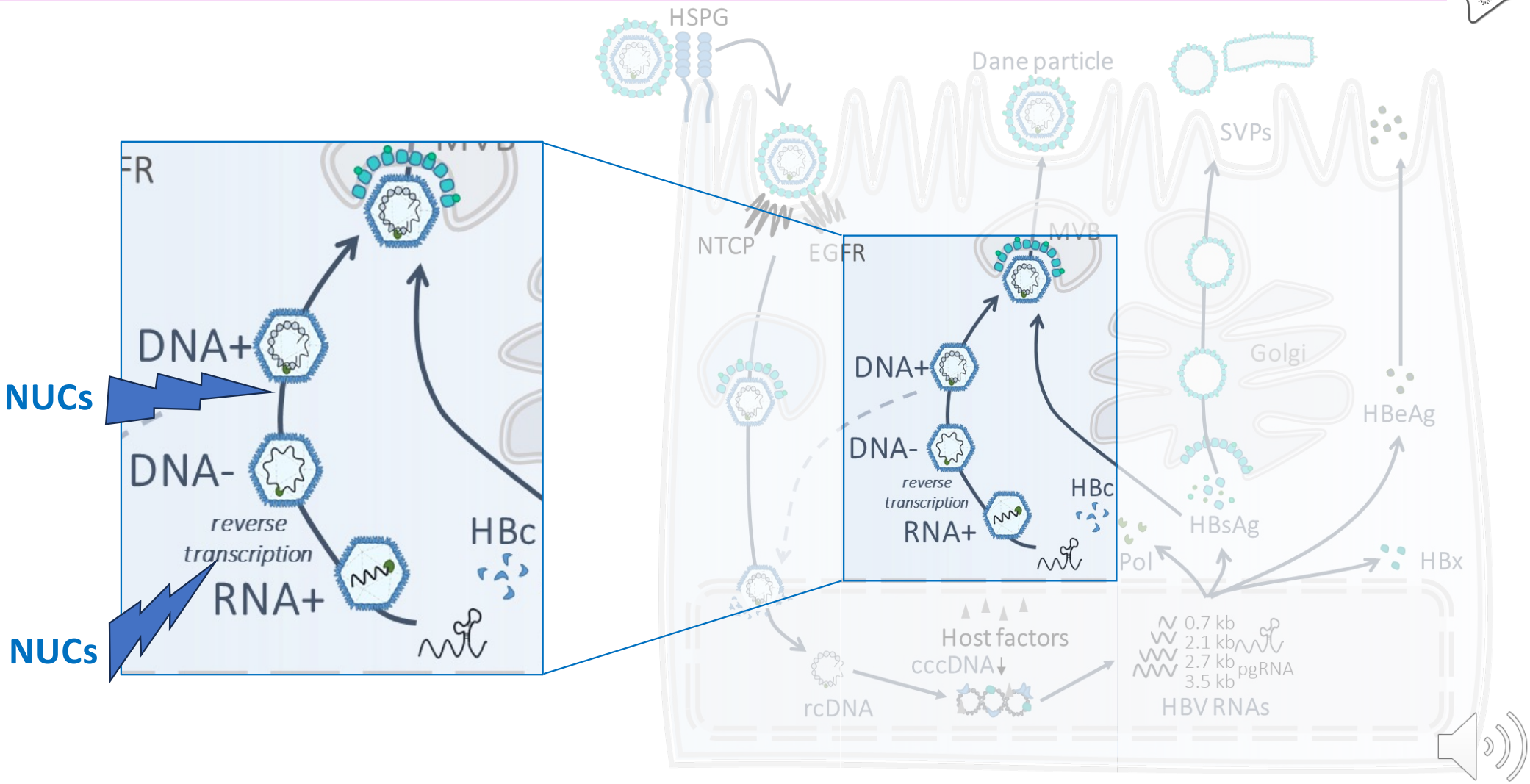




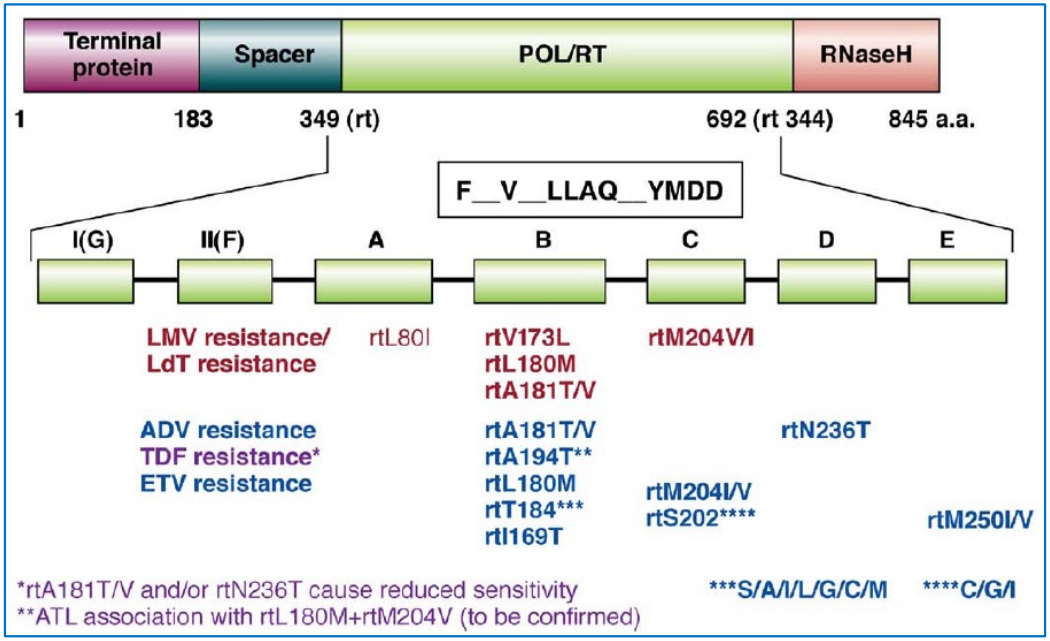
Indirect effect through activation of immune syst

Zhao et al., Antiviral Res., 2024

Mode of action of NUC (1)



Resistance to NUCs: in clinics → Not a problem anymore!



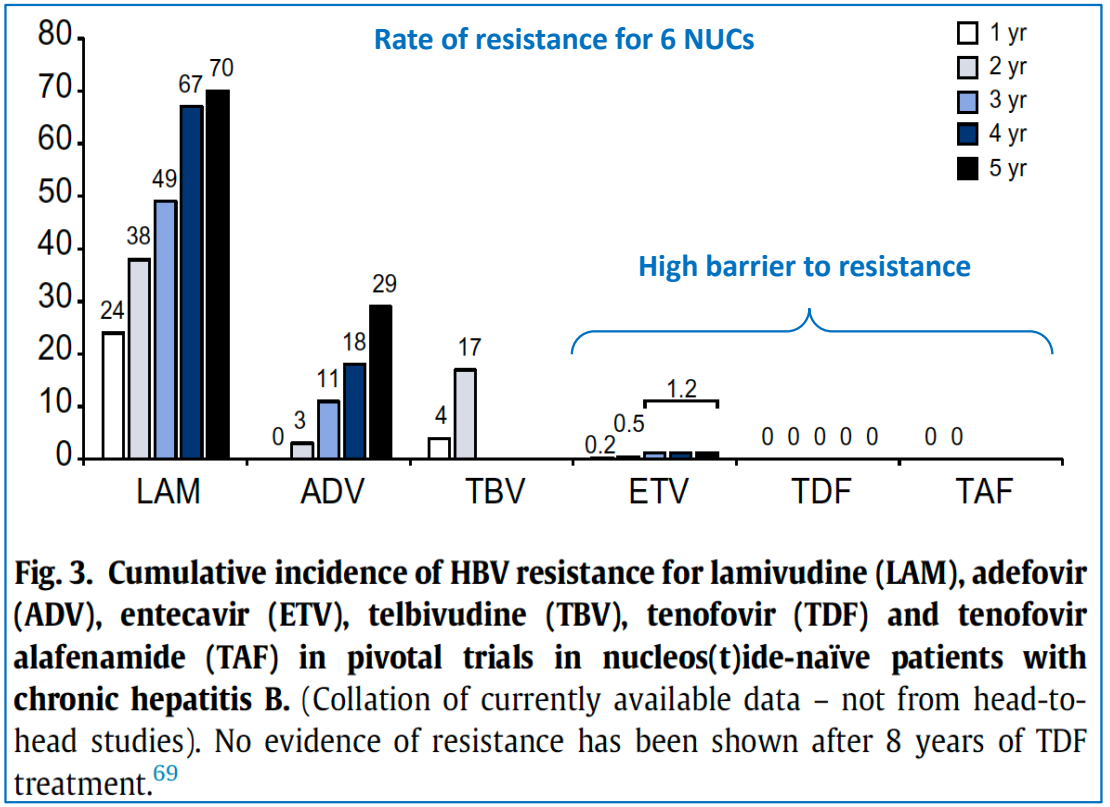
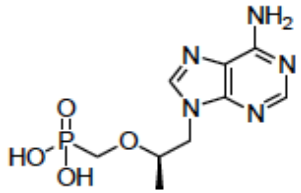


Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

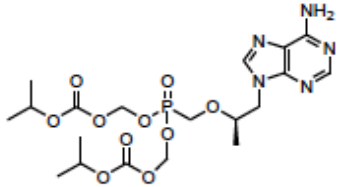
Zoulim & Locarnini, Gastroenterology, 2009;
EASL recommandations, J. Hepatol., 2017

Latest FDA-approved NUC developed



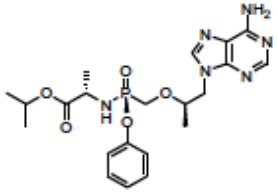
TFV

Tenofovir



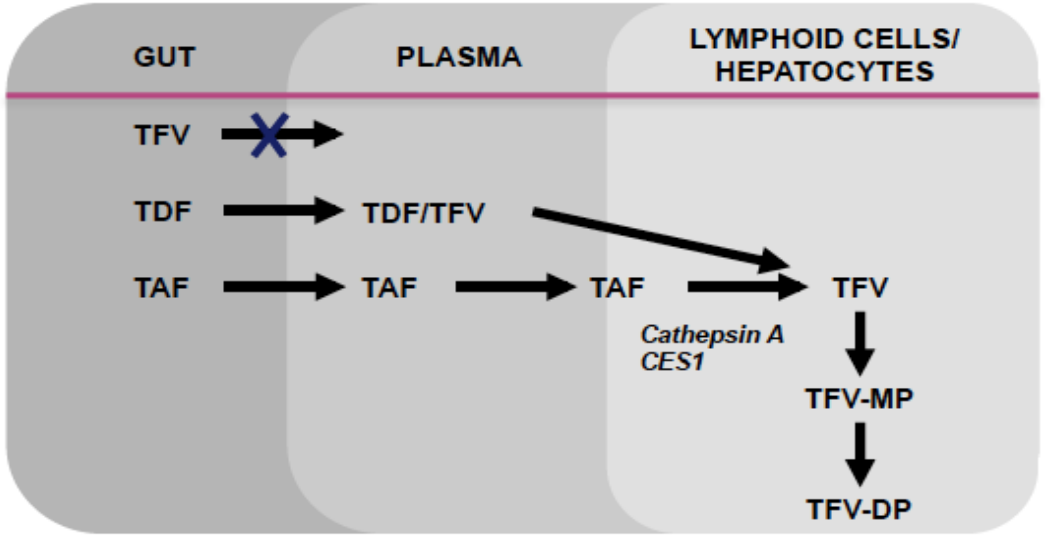
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide



- Improved stability in plasma:
  - Enhanced delivery of active form (TFV-DP) to hepatocytes
  - Lower doses are used; systemic exposures of TFV reduced

✓ **Similar efficacy between TDF and TAF**

✓ **But, weaker dosing for TAF (25 mg) versus TDF (300 mg)**

✓ **Lower long-term toxicity (renal and bones) of TAF**

Agarwal et al., AASLD 2013, poster#973

Peg-IFNa and NUC/NA effects in patients: take home messages

- ✓ Peg-IFNa (48 weeks of treatment) leads to HBV functional cure in 8 to 14% of cases
  - When functional cure is obtained in patient, fibrosis is reverted and HCC risk return to that of normal population
  - In functionally cured patients, if there is a strong immune-suppression (e.g. rituximab) later in life, reactivation of HBV infection is possible → **patients with a *functional cure* are not *totally cured* from HBV**
  - If functional cure is not obtained, HBV infection comes back → this why NUC/NA are preferred in occidental countries

- ✓ When NUC/NA are taken long-life, it leads to HBV functional cure in 1 to 3 % of cases
  - Functional cure rate is negligible
  - Yet viral suppression in blood allow fibrosis regression and HCC risk returning to only 2x higher than normal risk population

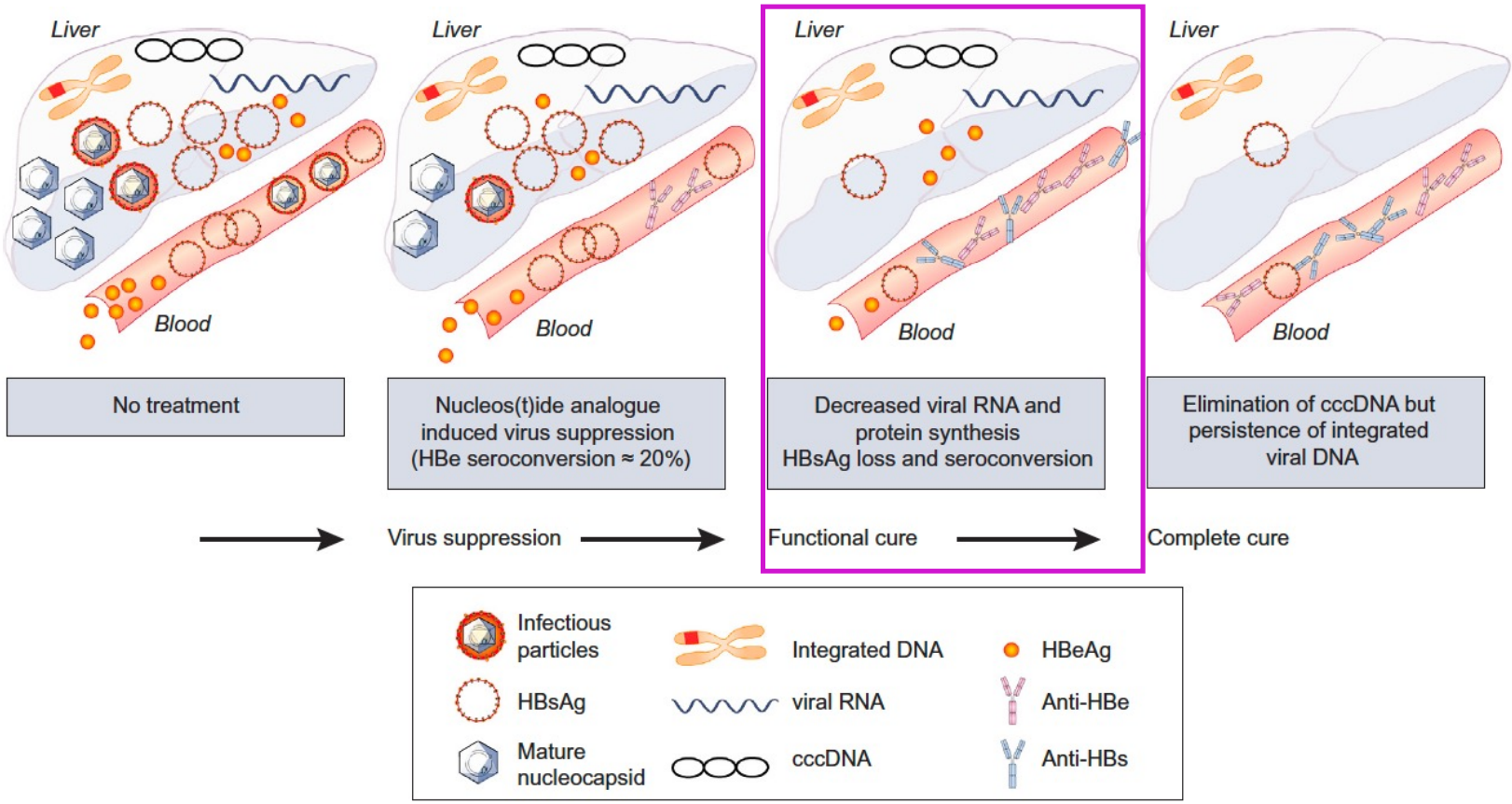
But patients want/deserve finite treatments, increased *functional cure* rate (30-50%) and more than *functional cure* (*i.e.* full cure)

Investigational anti-HBV drugs and strategies

Aim is to increase the rate of *functional cure*!

Functional cure **= long-term HBV virosuppression + HBsAg loss (+ anti-HBs seroconversion) after cessation of treatment** **(finite duration of treatment)**

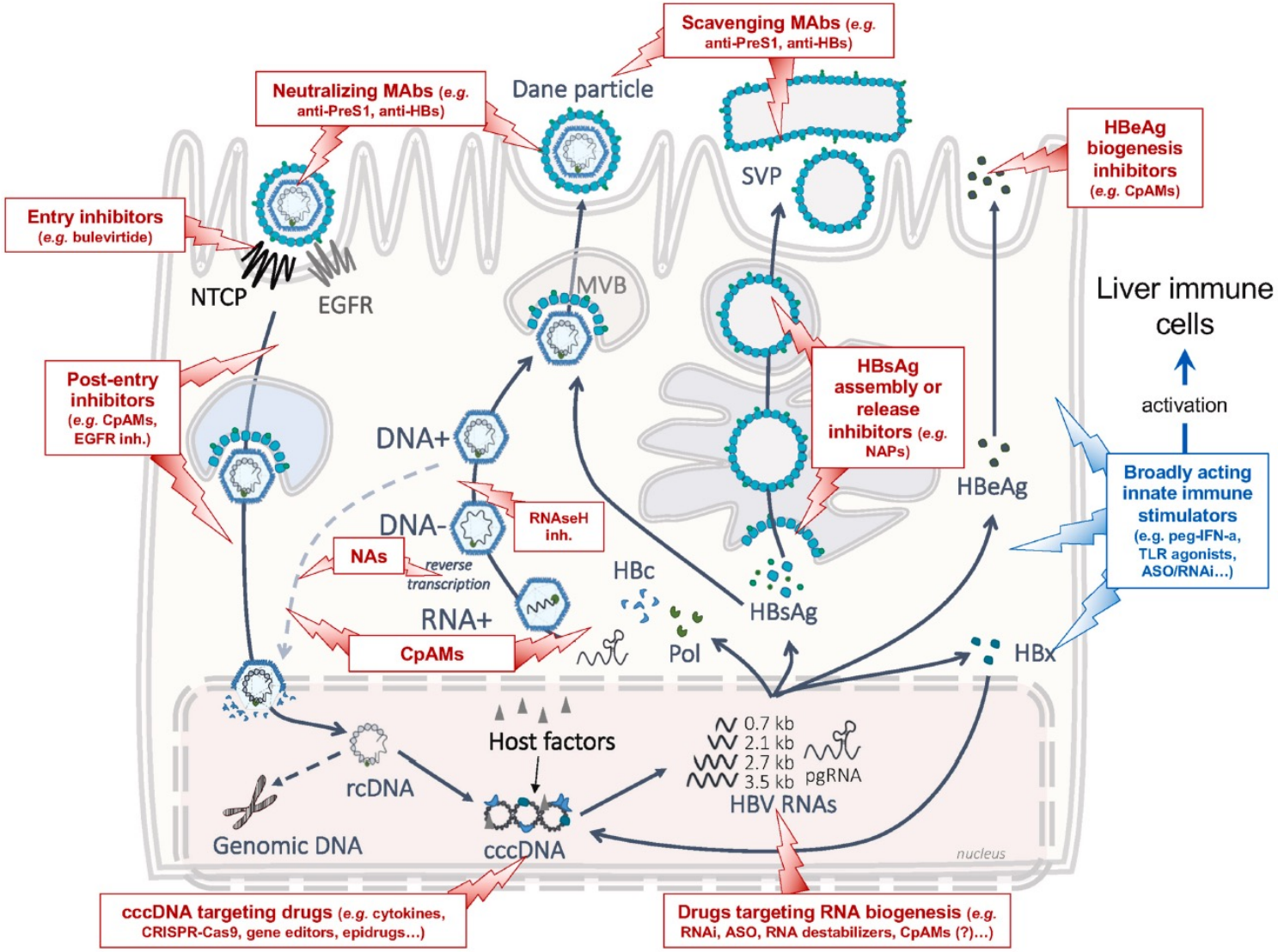
Goal of therapies: “Virosuppression” versus “Functional Cure” versus “Complete Cure”



Functional cure **= long-term HBV virosuppression + HBsAg loss (+ anti-HBs seroconversion) after cessation of treatment (finite duration of treatment)**

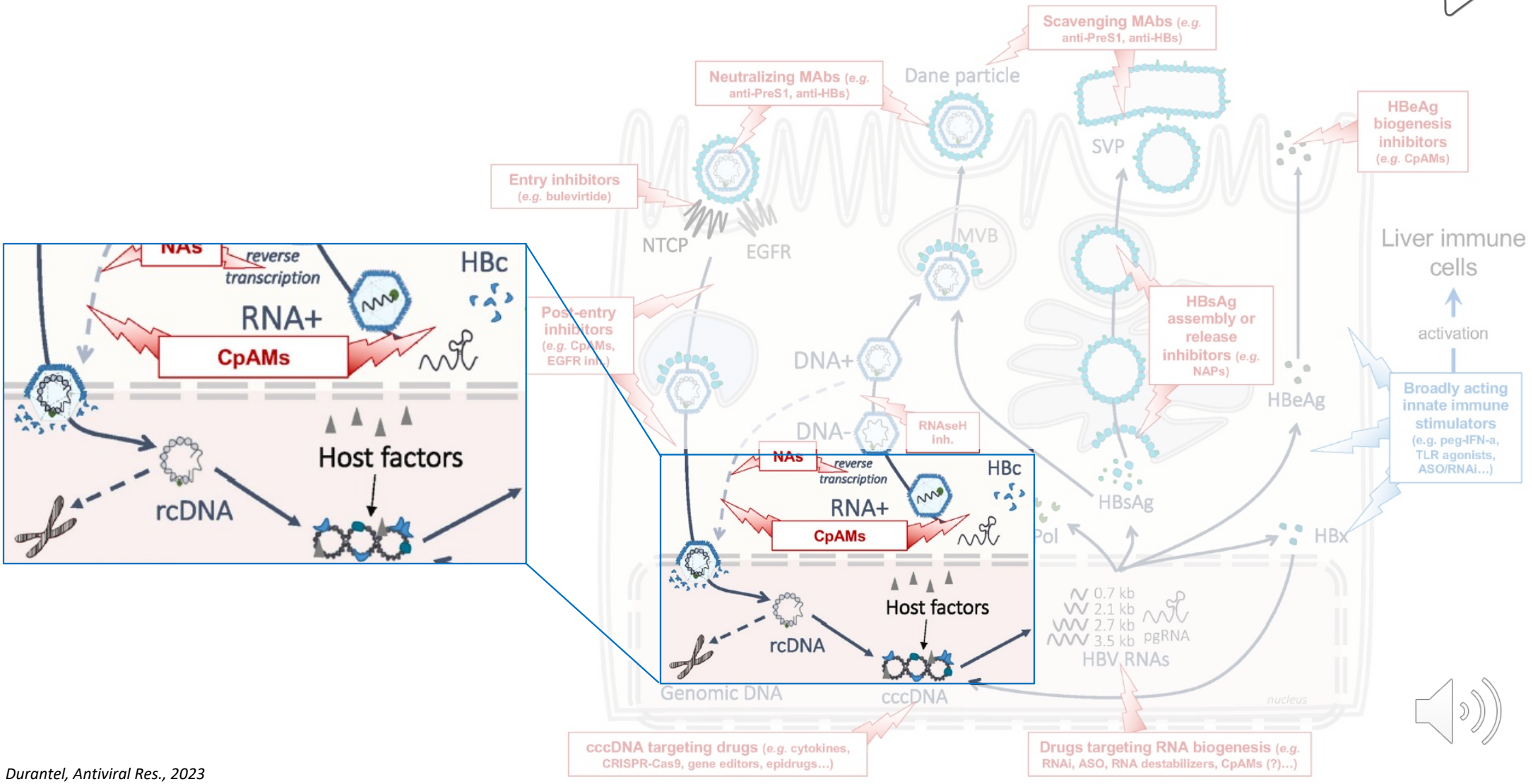
Durantel & Zoulim, J. Hepatol., 2016

Overview of the pipeline of novel anti-HBV



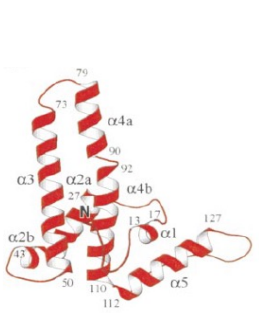
Durantel, Antiviral Res., 2023

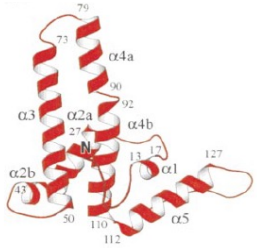
Core assembly modulators (CAMs or CpAMs)

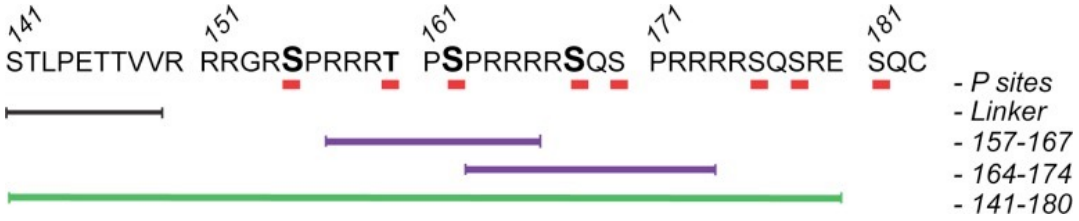


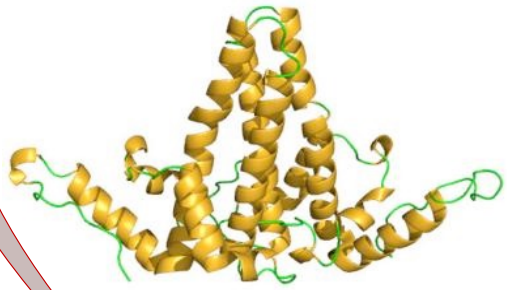
Durantel, Antiviral Res., 2023

Assembly of HBV capsid is an excellent target

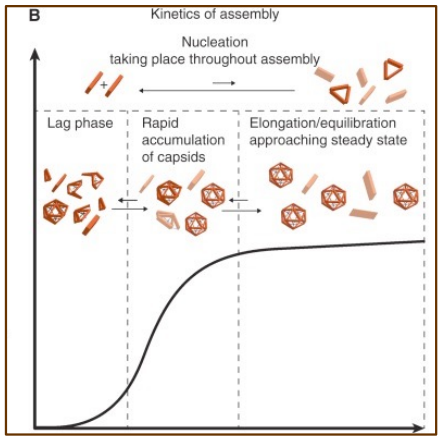




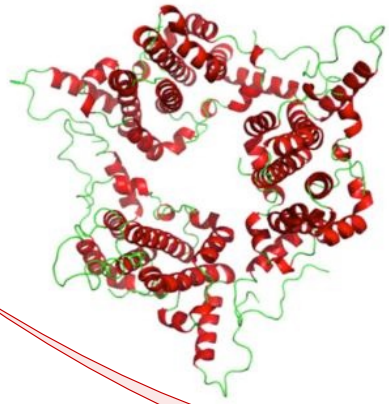


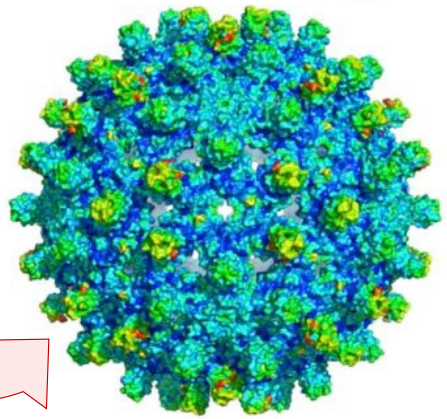


- ✓ 240 capsomers/HBc
- ✓ 120 dimers of HBc with S-S bonds
- ✓ T4 symetry (also T3 symetry)



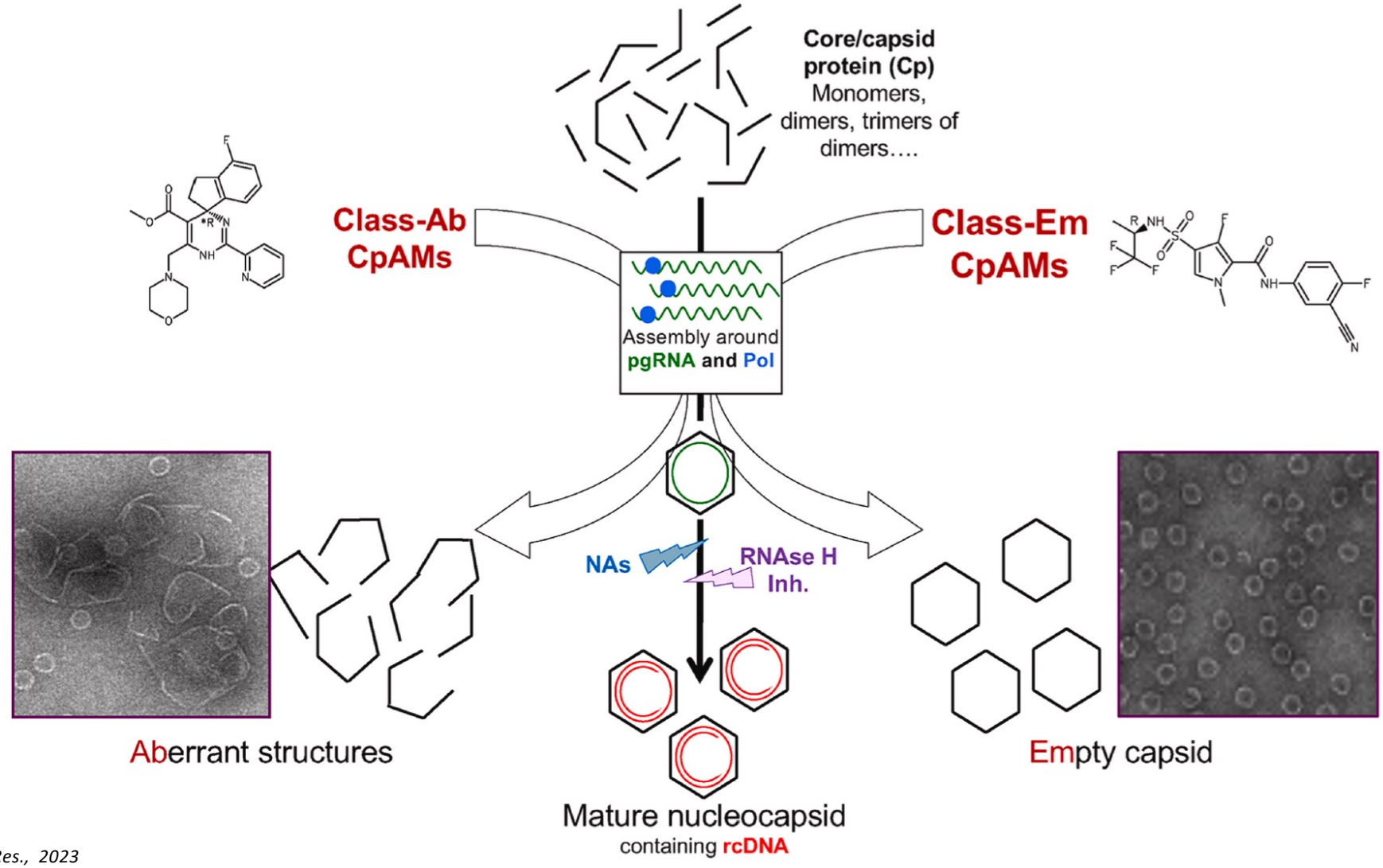
Assembly process





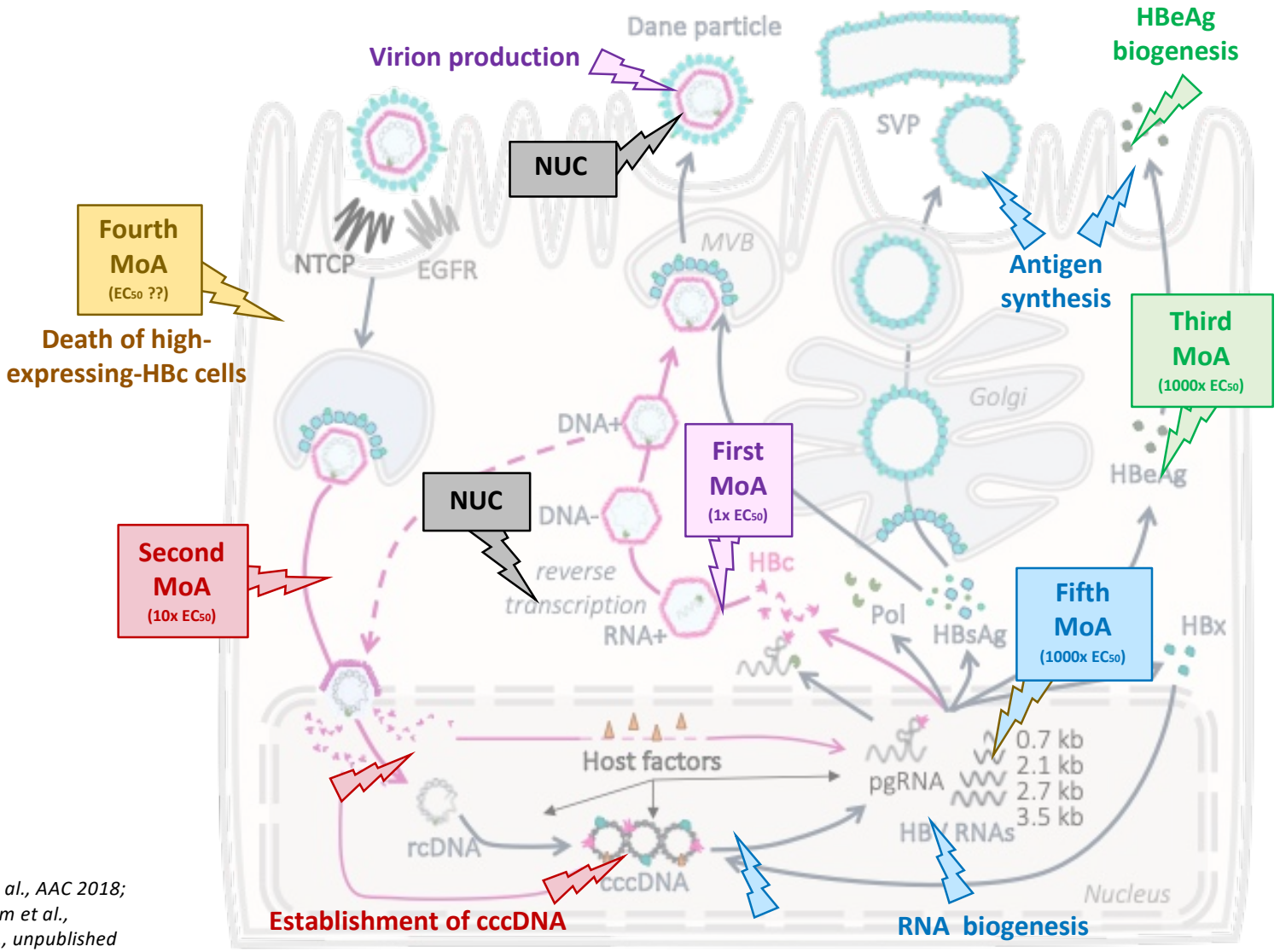
Chen et al., PlosPath 2016; Katen et al., Structure 2013; Alexander et al., PNAS 2013; Kratz et al., PNAS 1999; Zlotnick et al., Antiviral Res 2015

Caspsid/Core assembly modulators (CpAMs or CAMs) – Primary mode of action



Durantel, Antiviral Res., 2023

Other modes of action of CAMs



Berke et al., AAC 2017; Lahlali et al., AAC 2018; Durantel Antiviral Res., 2024; Kum et al., Hepatology, 2023; Pronost et al., unpublished

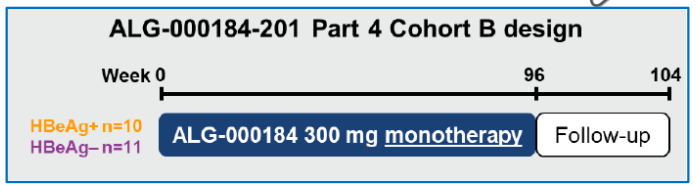
Past and current CAMs in clinical trials

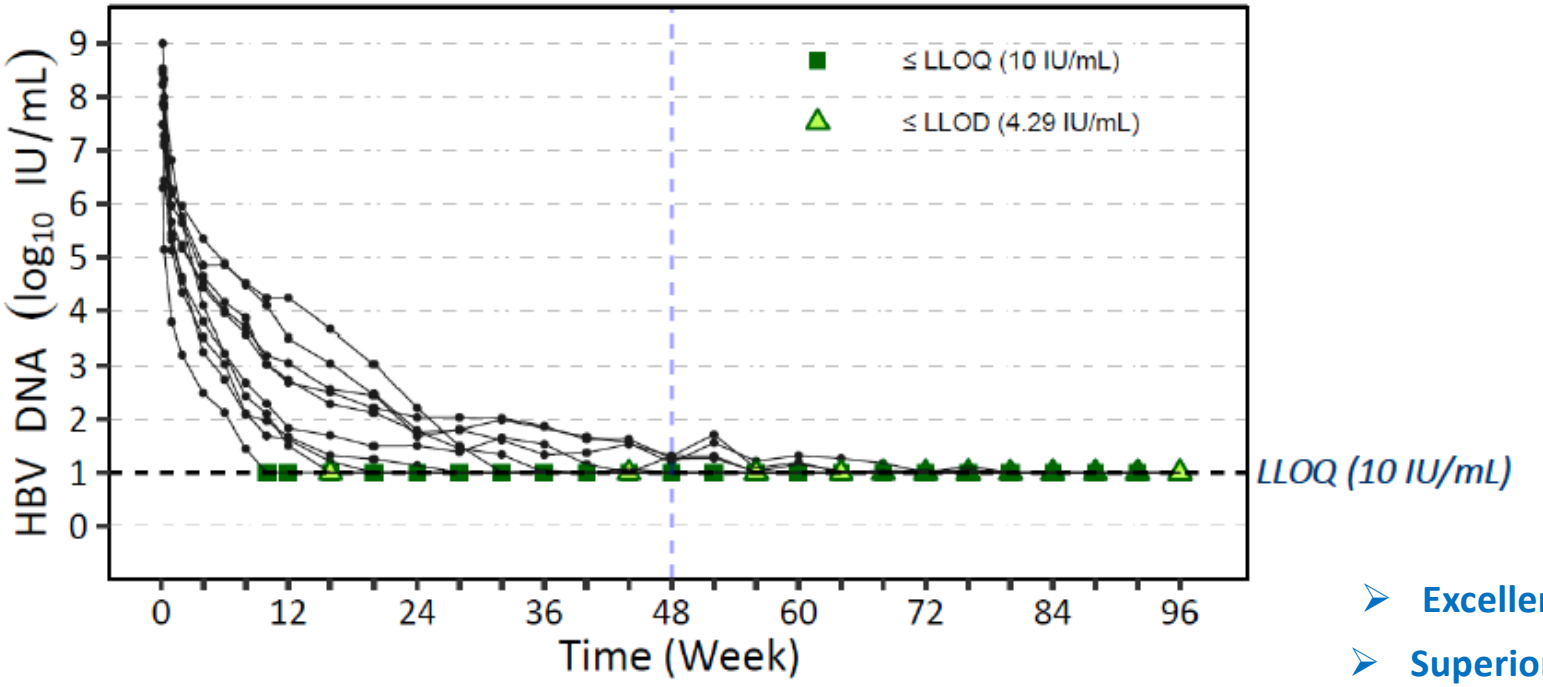
Capsid or Core Inhibitors: Interferes with the viral DNA protein shield				
ZM-H1505R	Capsid inhibitor	Zhimeng Biopharma, PR China	core-biopharma.com	Phase II
ALG-000184	Capsid inhibitor	Aligos Therapeutics, USA	aligos.com	Phase II
EDP-514	Capsid inhibitor	Enanta Pharma, USA	enanta.com	Phase I
ABI-4334	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase I

- **Previous generation of CAMs includes : NVR 3-778, GLS4, RO7049389, JnJ-6379,ABI-H0731, AB-423, EDP-367, AB-506, ABI-H2158…**
- **So far CAMs failed to move to Ph-3 trials because of lack of superiority over NUCs/NAs**
- **But 3rd generation of CAMs are more potent and hopefully safer…**

ALG-184: the most promosing CAM currently in clinical trial (1)

Individual HBV DNA Levels
300 mg ALG-000184 monotherapy for ≤ 96 weeks





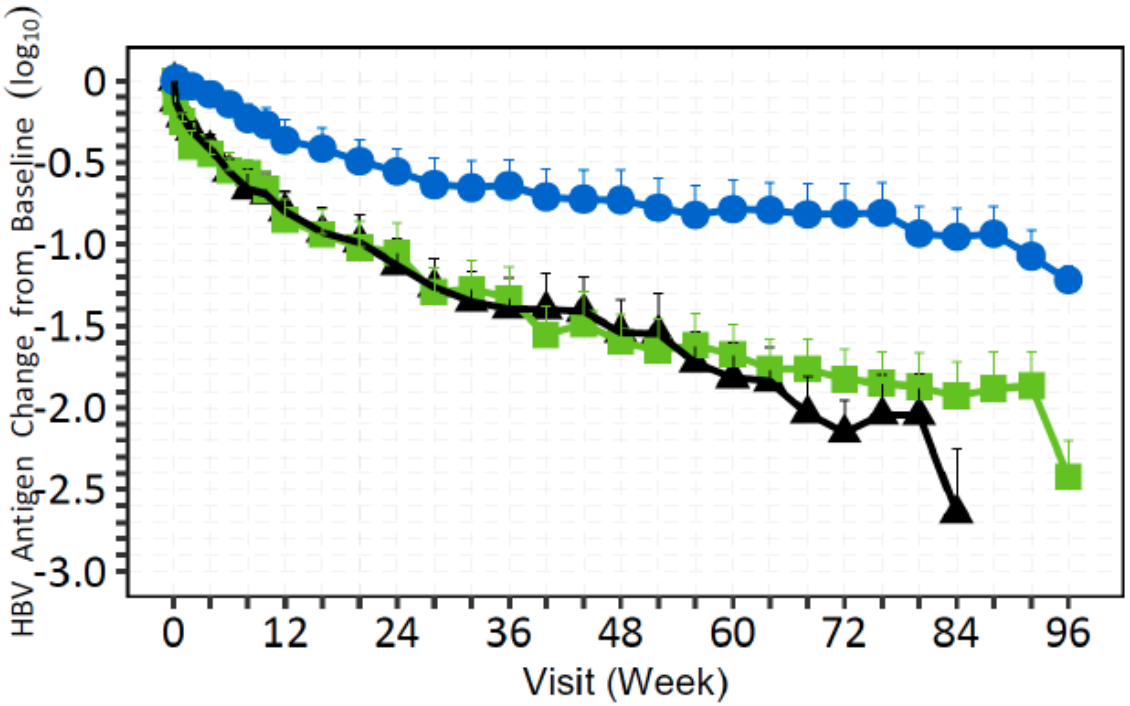
Number of subjects	10	10	10	9	10	10	10	9	3
n ≤ LLOQ (10 IU/mL)	0	1	2	5	6	7	9	9	3
n ≤ LLOD (4.29 IU/mL)	0	0	0	0	0	0	2	3	3

Yuen MF et al., APASL 2025

- **Excellent virosupression**
- **Superior to that obtained with NUC ? Current phase 2 studies will tell us!**
- **Safety profile = OK**

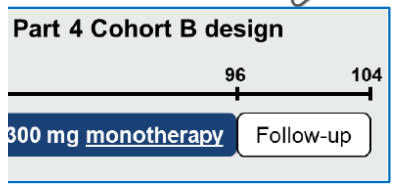
ALG-184: the most promosing CAM currently in clinical trial (2)

Mean Antigen Reductions
300 mg ALG-000184 monotherapy for ≤ 96 weeks



HBsAg	10	10	10	10	10	10	10	9	3
HBeAg	10	10	10	10	10	10	10	9	3
HBcrAg	10	10	10	10	10	10	9	3	

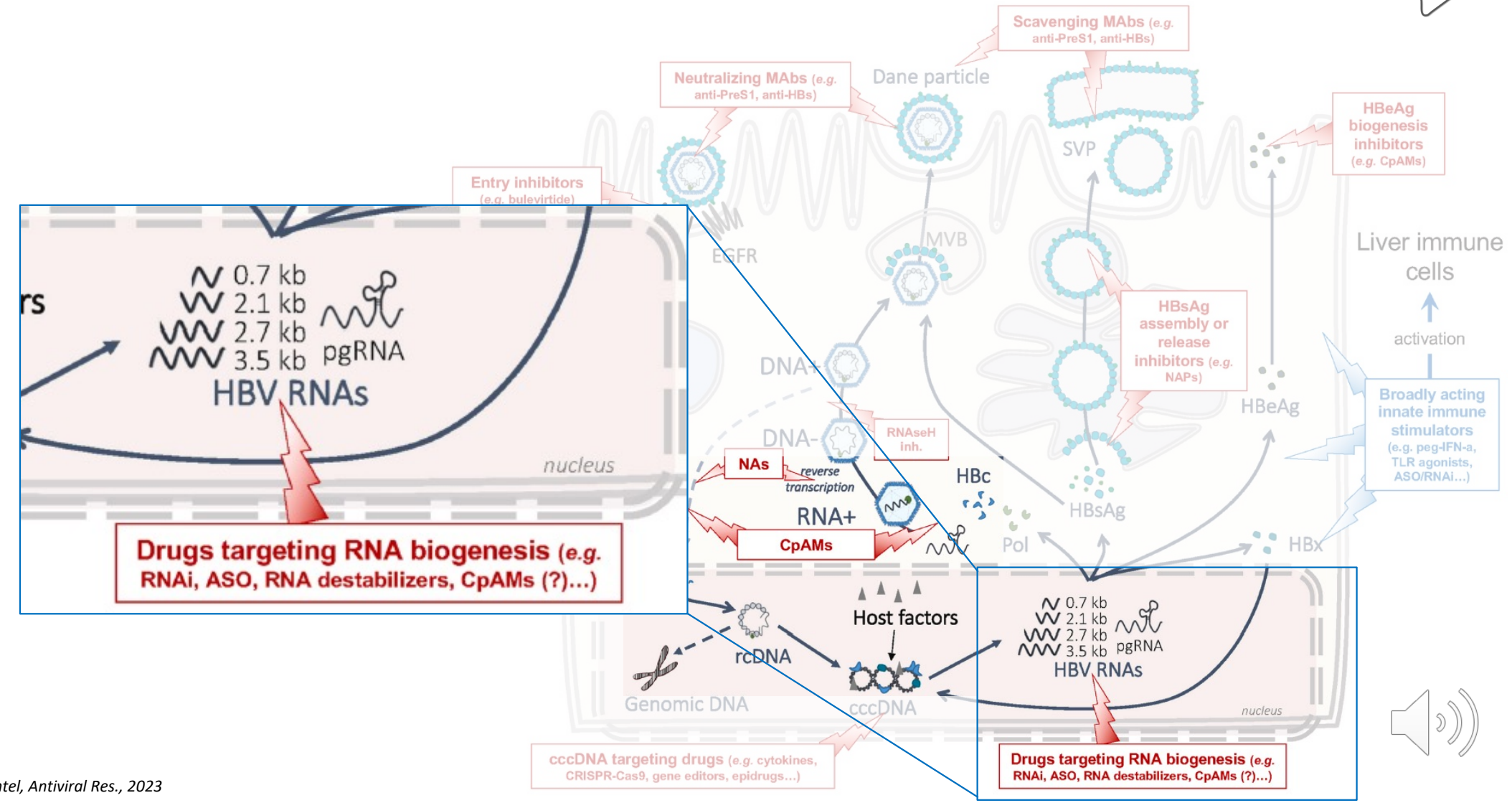
Units for HBsAg, HBeAg and HBcrAg are log_{10}IU/mL, log_{10}PEI U/mL and log_{10}U/mL, respectively



- **Strong effect of CAM ALG-184 on HBeAg reduction**
- **CAM ALG-184 leads to 1log10 HBsAg reduction after 2 years of treatment**
- **CAM >>> NUC on these viral parameters**
- **Should lead to higher rate of FC !**

Yuen MF et al., APASL 2025

Drugs targeting HBV RNAs

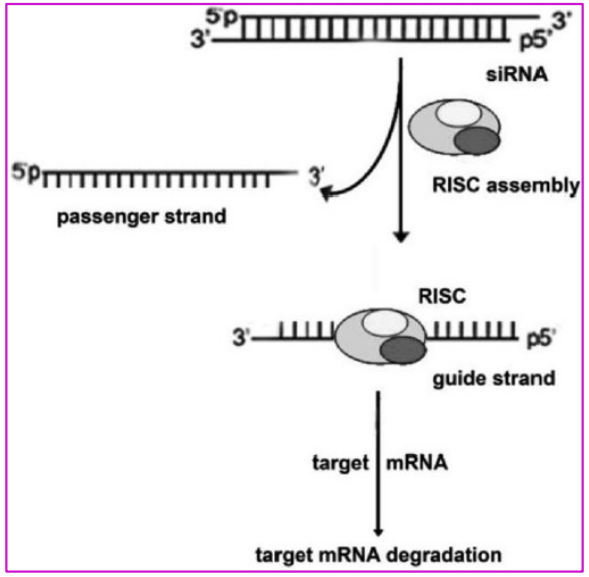


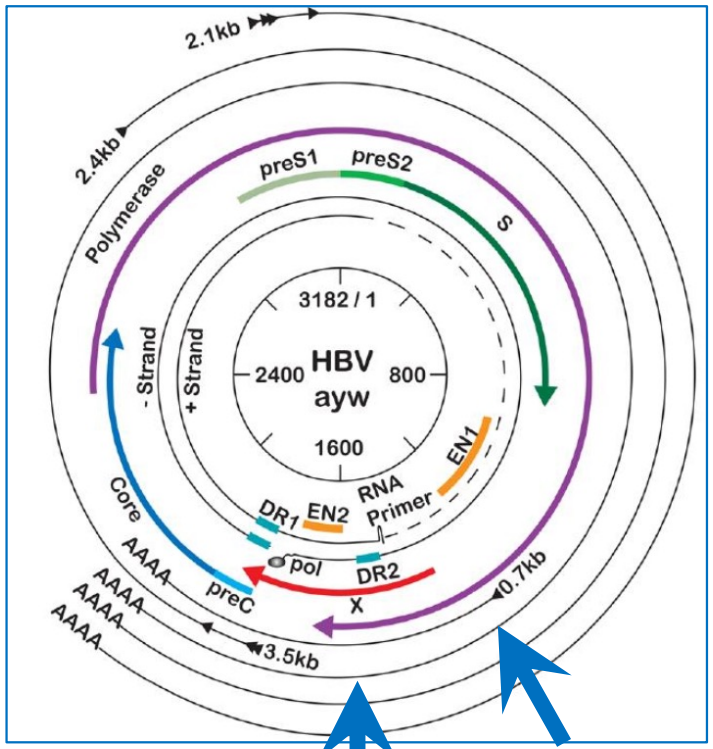
Durantel, Antiviral Res., 2023

Si-RNAs and AntiSense Oligonucleotides (ASOs): nature and modes of action

siRNAs

- ✓ Easy to design and produce
- ✓ Strong background in the field
- ✓ Easy to deliver to liver and to hepatocytes (GalNAc moiety or LNPs)
- ✓ Safety profile/off target effect ?

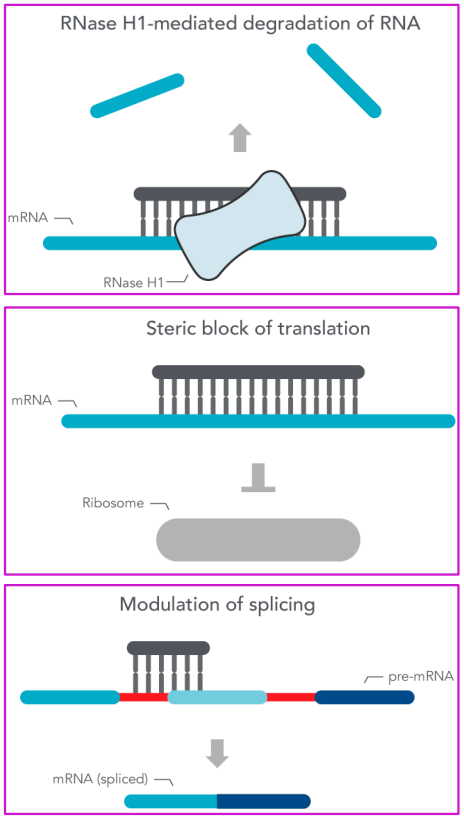




All RNAs are targeted Including RNA synthesized from host-chromosome integrated HBV

ASOs

- ✓ Easy to design and produce
- ✓ Easy to deliver to liver and to hepatocytes (GalNAc moiety or LNPs)
- ✓ Safety profile/off target effect ?



Si-RNA and ASOs in current R&D

Silencing RNA's (siRNAs): Interferes and destroys viral RNA

VIR-2218 (Elebsiran) BRII-835	RNAi gene silencer	Vir Biotech with Brii Biosciences, USA	vir.bio and briibio.com	Phase II
Xalnesiran (RG6346, DCR HBVS)	RNAi gene silencer	Dicerna, USA with Roche	dicerna.com	Phase II
Imdurisan (AB-729)	RNAi gene silencer	Arbutus Biopharma, USA	arbutusbio.com	Phase II
BW-20507	RNAi gene silencer	Argo Biopharma Australia	private company	Phase II
ALG-125755	RNAi gene silencer	Aligos Therapeutics, USA	aligos.com	Holding for partner
BB-103	RNAi gene silencer	Benitec, Australia	benitec.com	Preclinical
JNJ-3989 (ARO-HBV)	RNAi gene silencer	GSK, USA	gsk.com	Phase II
HT-101	RNAi gene silencer	Hepa Thera, PR China	www.hepathera.com/eng	Phase I (out USA)

Antisense Molecules: Binds to the viral mRNA to prevent it from turning into viral protein

Bepirovirsen	HBV Antisense	GSK, USA	gsk.com	Phase III
AHB-137	HBV Antisense	AusperBio	ausperbio.com	Phase III, PR China

Si-RNA and ASOs in current R&D

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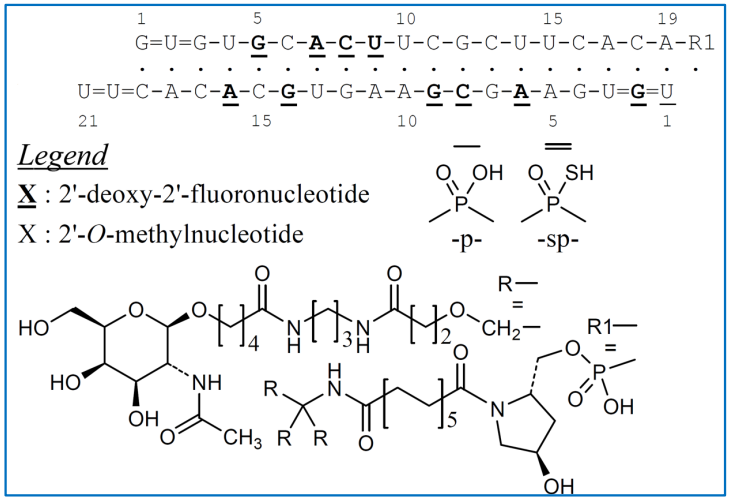
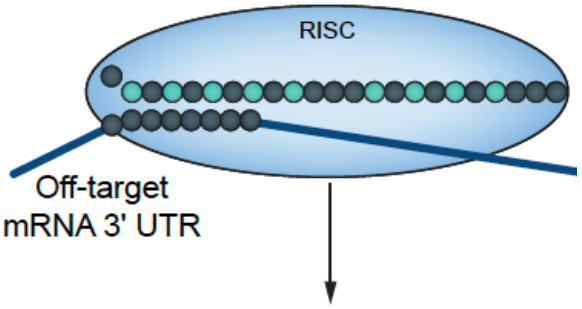
From ALN-HBV to VIR-2218 (Elebsiran): improvement of safety profile



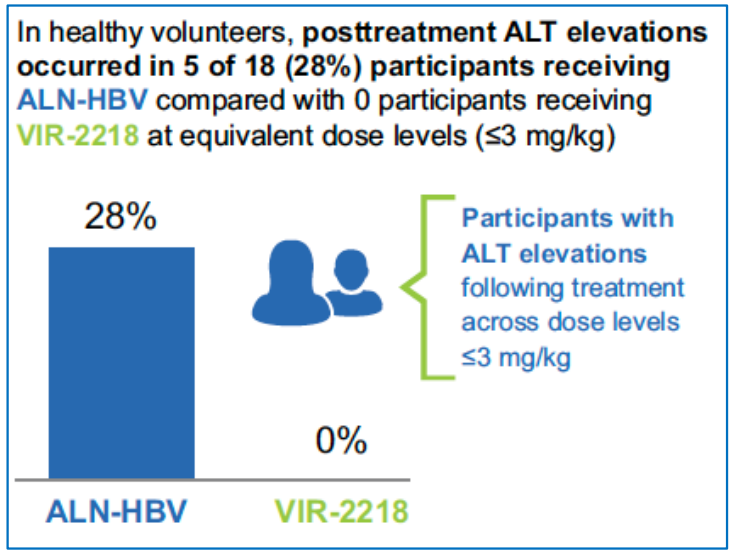
No ESC+ conjugate

miRNA-like seed-mediated binding to off-targets



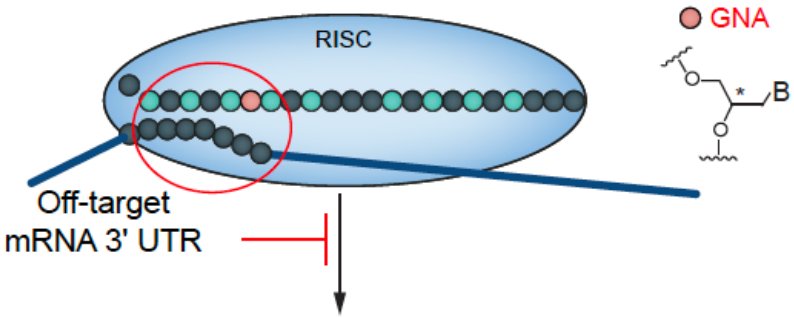
Translation repression, mRNA destabilization

Off-target effects



ESC+ conjugate

Destabilize seed-mediated binding to off-targets; retain on-target activity

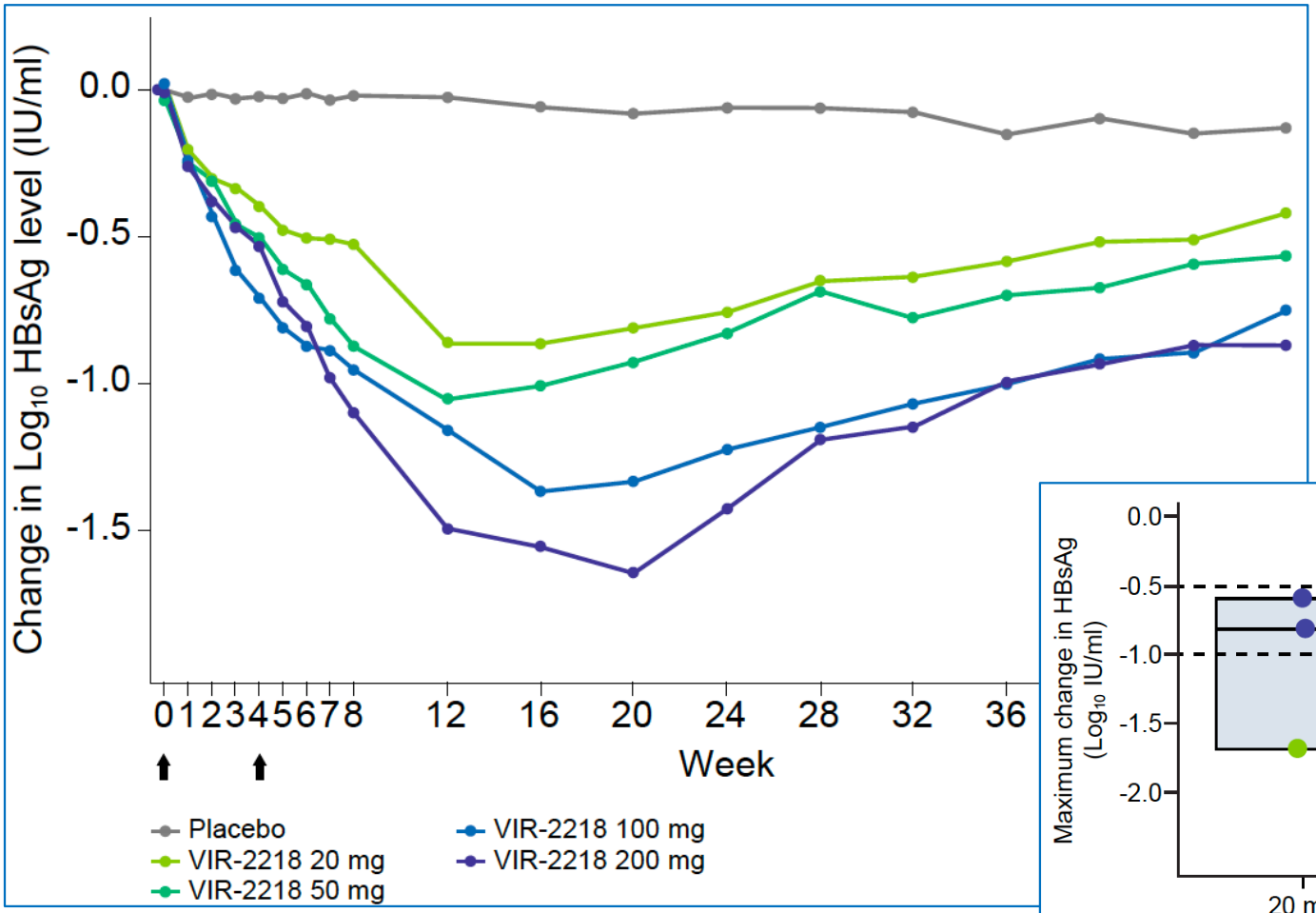


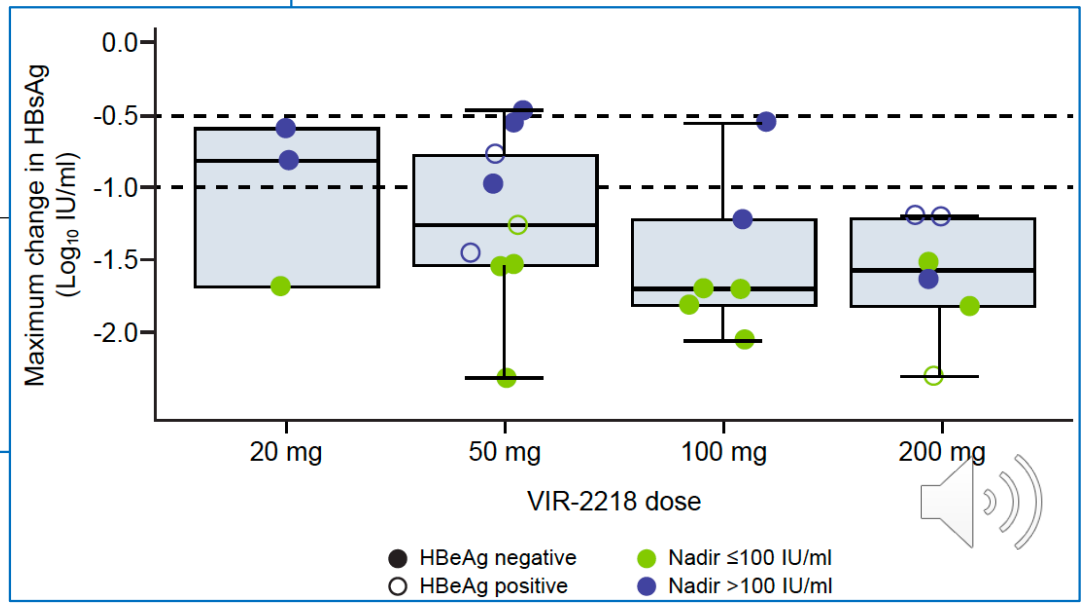
Translation repression, mRNA destabilization

Off-target effects minimized

Gane et al., J. Hepatol., 2023

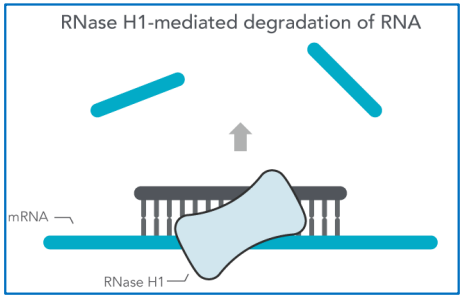
Clinical trial results for VIR-2218 (Elebsiran)

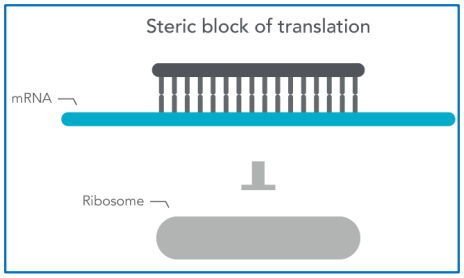


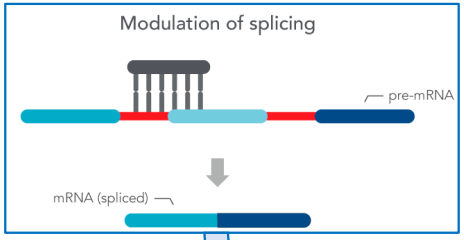


Gane et al., J. Hepatol., 2023

Bepirovirsen: an ASO with various modes of action (= combination with a single drug!)







RNA (modified) — DNA — RNA (modified)

X: 2'-O-(2-methoxyethyl)nucleotide

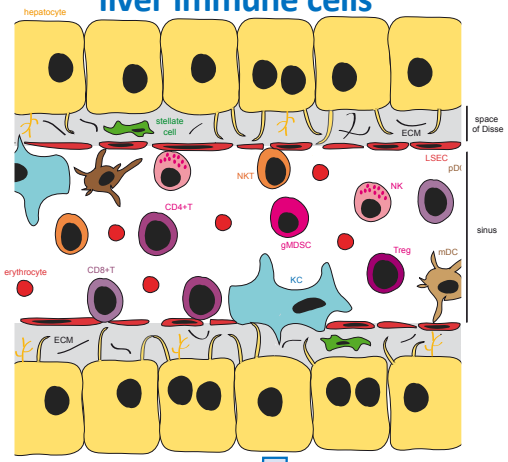
mX: 2'-O-(2-methoxyethyl)-5-methylnucleotide

d(X): 2'-deoxynucleotide

d(mX): 2'-deoxy-5-methylnucleotide

mC: 2'-O-(2-methoxyethyl)-5-methylcytidine

Stimulation of TLR8 in liver immune cells



Production of proinflammatory cytokines (IL-6, TNFa, IL1b) in liver microenvironment

Direct and via restoration of immune responses

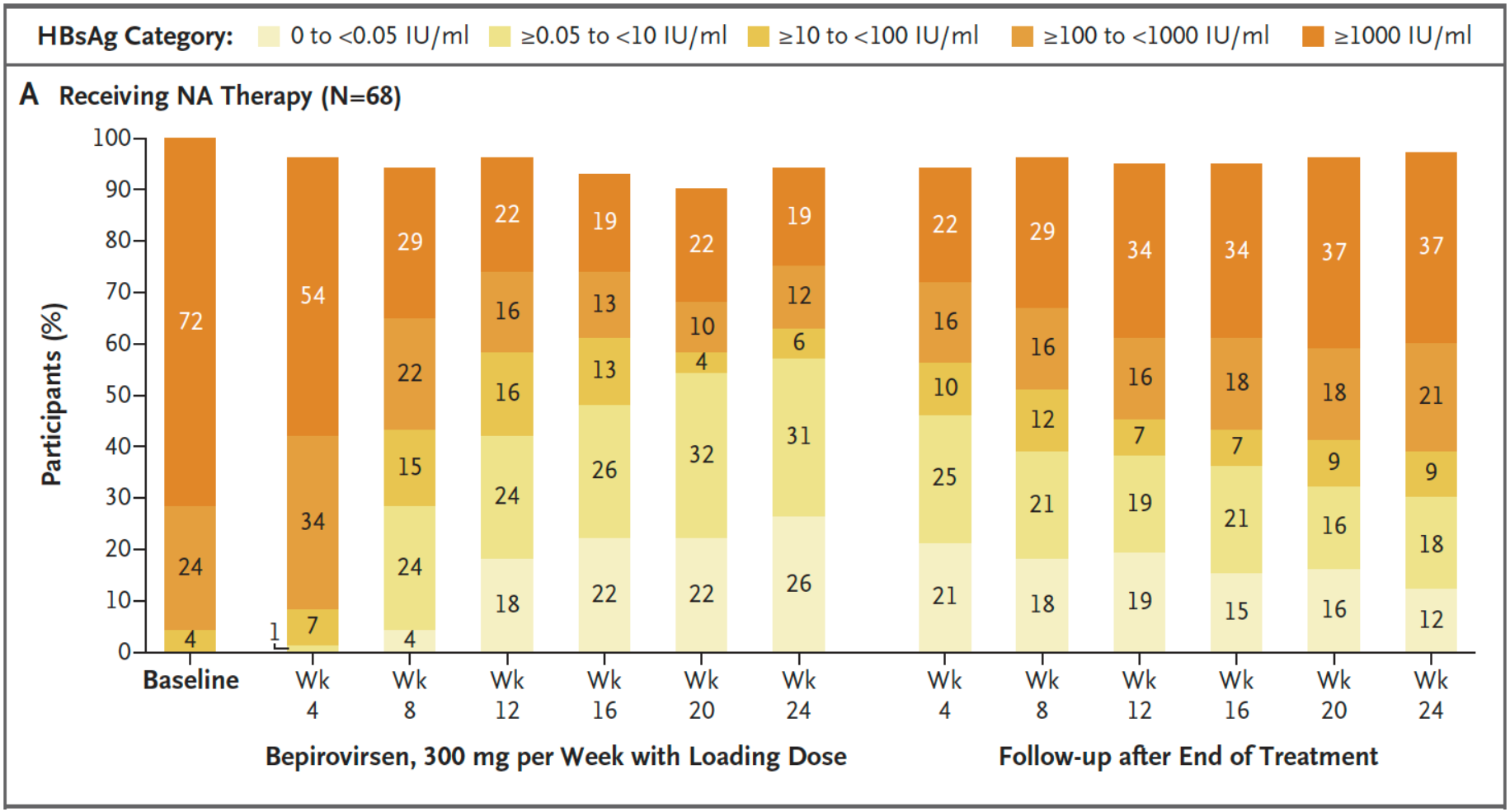
Overall antiviral effect

HBV RNAs (pgRNA and mRNA) decline, leading to less rcDNA/virion production and proteins/antigens syntheses

HBsAg decline, leading to immune restoration?

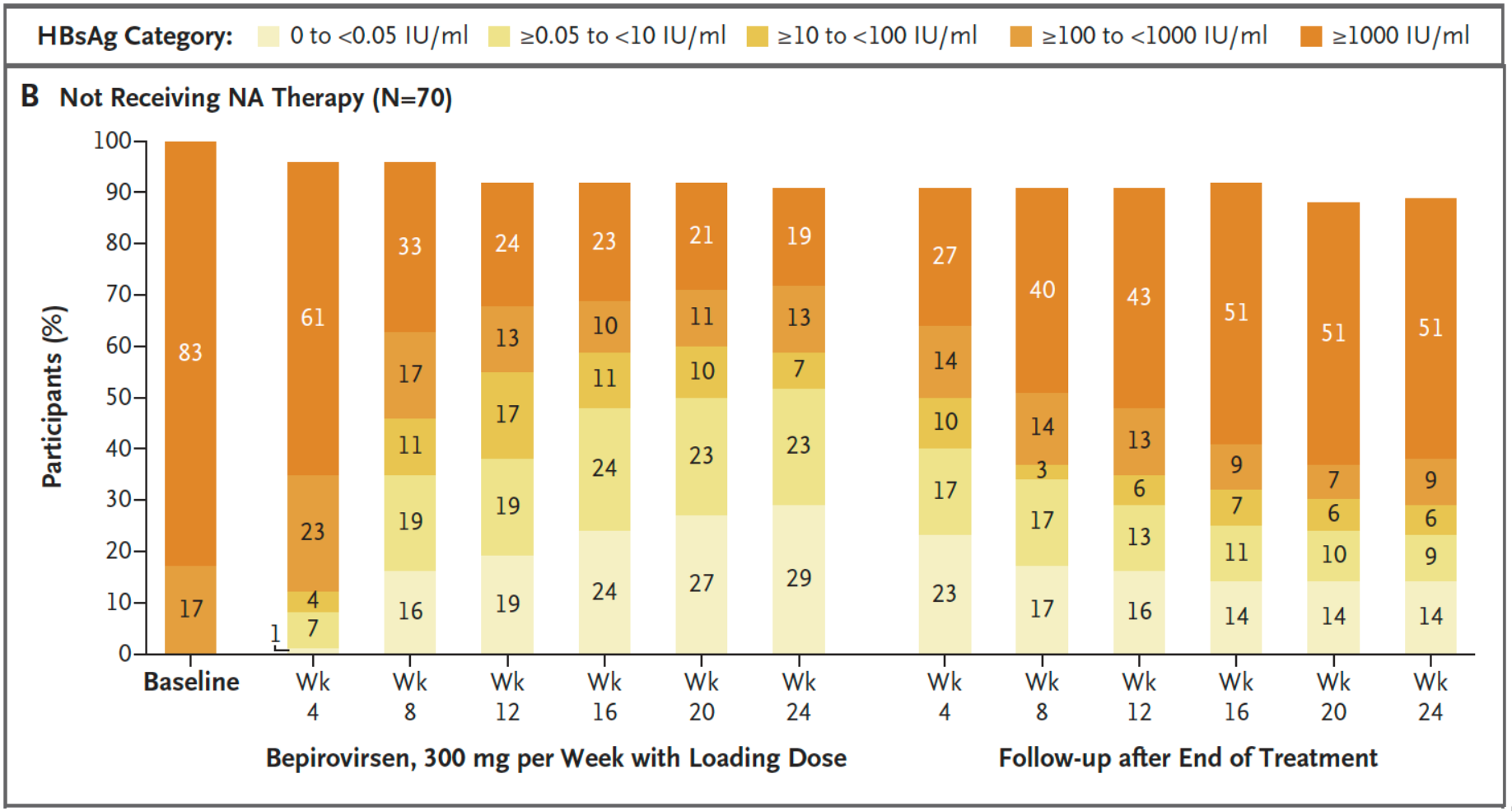
Drawing from HepVir team

B-Clear clinical trial results for Bepirovirsen: results of combination with NUC/NA



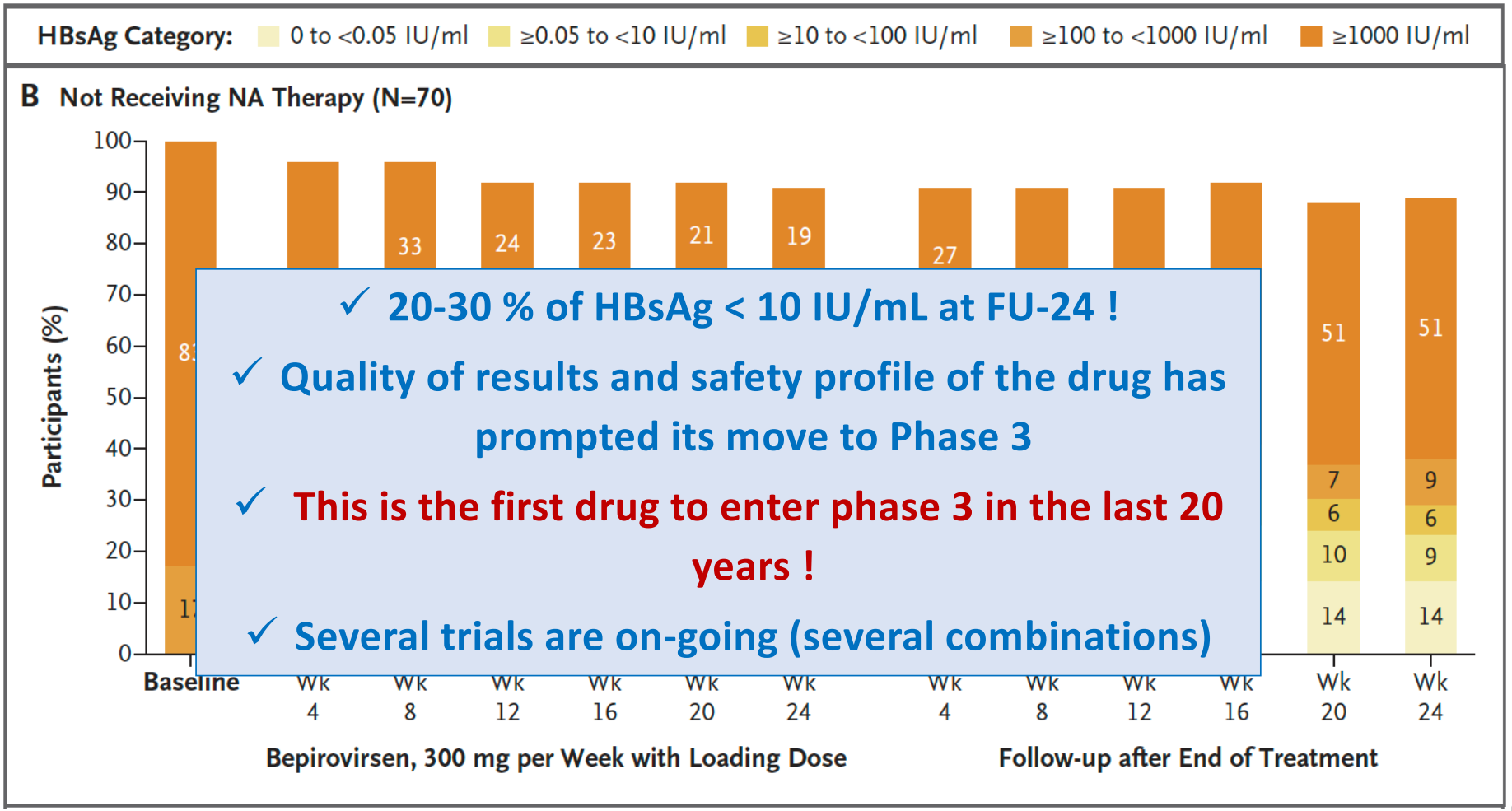
Yuen et al., N. Engl J. Med., 2022

B-Clear clinical trial results for Bepirovirsen: results of in monotherapy



Yuen et al., N. Engl J. Med., 2022

B-Clear clinical trial results for Bepirovirsen: results of in monotherapy



✓ 20-30 % of HBsAg < 10 IU/mL at FU-24 !

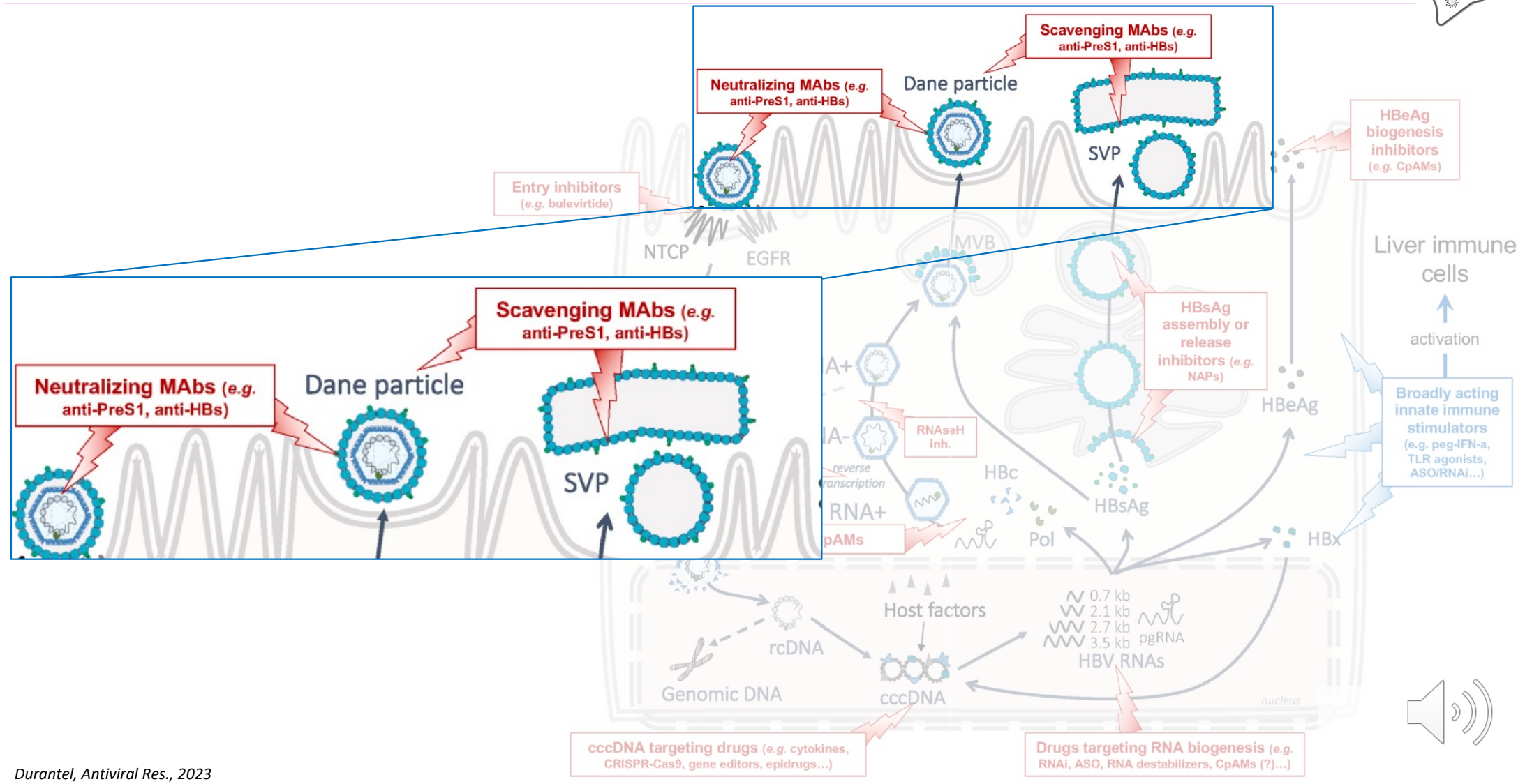
✓ Quality of results and safety profile of the drug has prompted its move to Phase 3

✓ This is the first drug to enter phase 3 in the last 20 years !

✓ Several trials are on-going (several combinations)

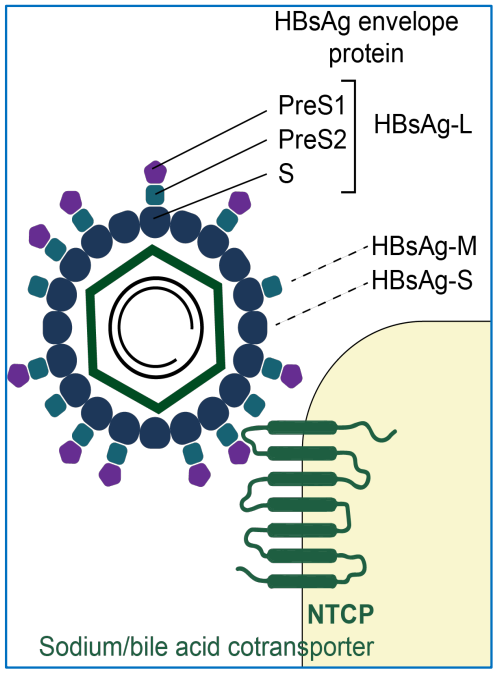
Yuen et al., N. Engl J. Med., 2022

Monoclonal antibodies against HBV



Durantel, Antiviral Res., 2023

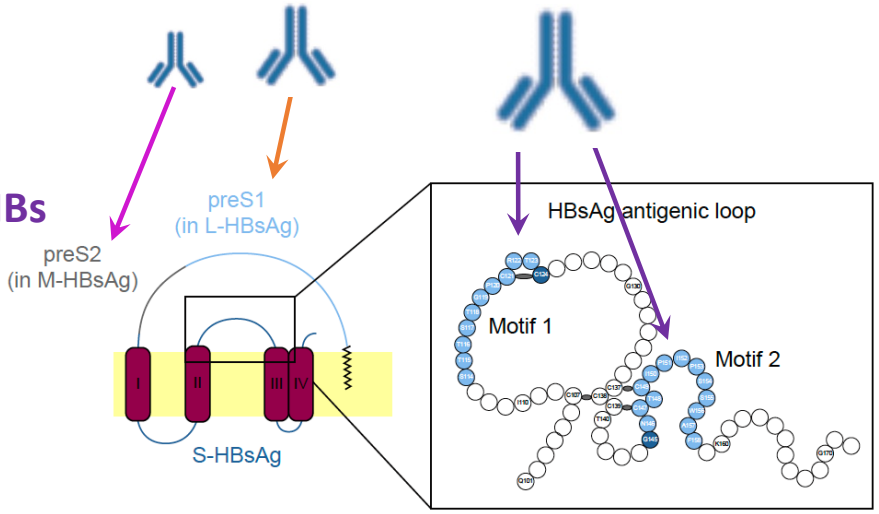
Monoclonal antibodies targeting HBV envelope proteins: nature and MoA (1)

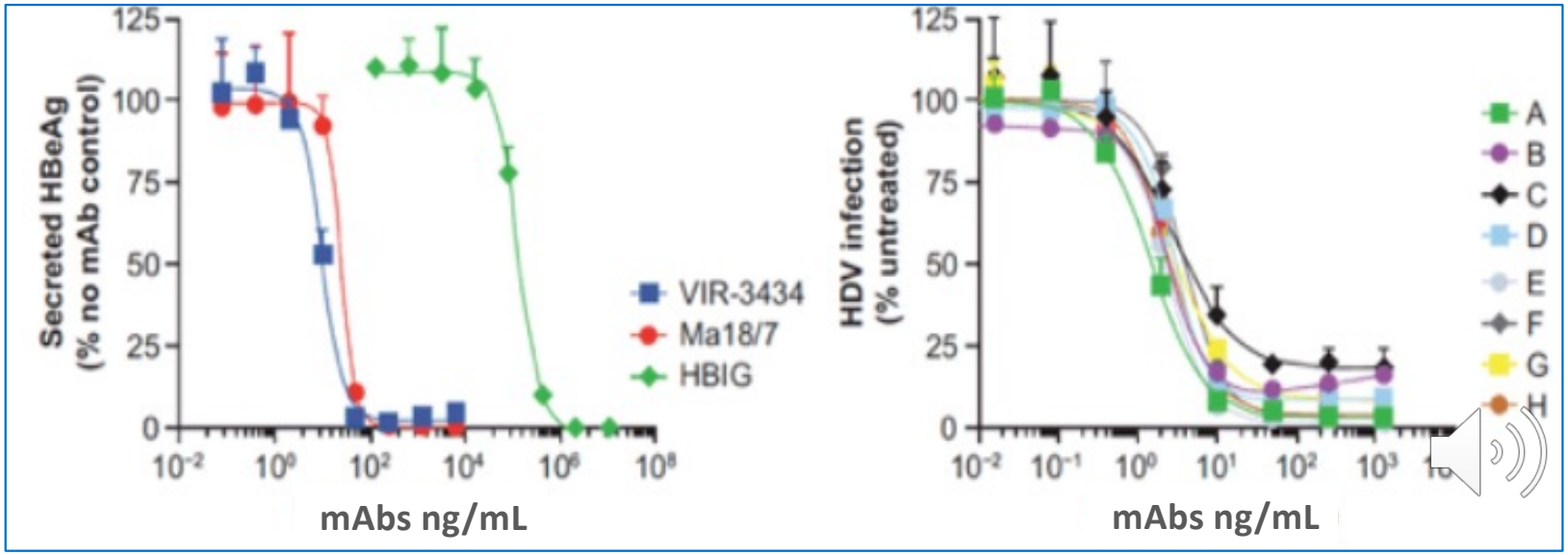


Anti-PreS1

Anti-PreS2

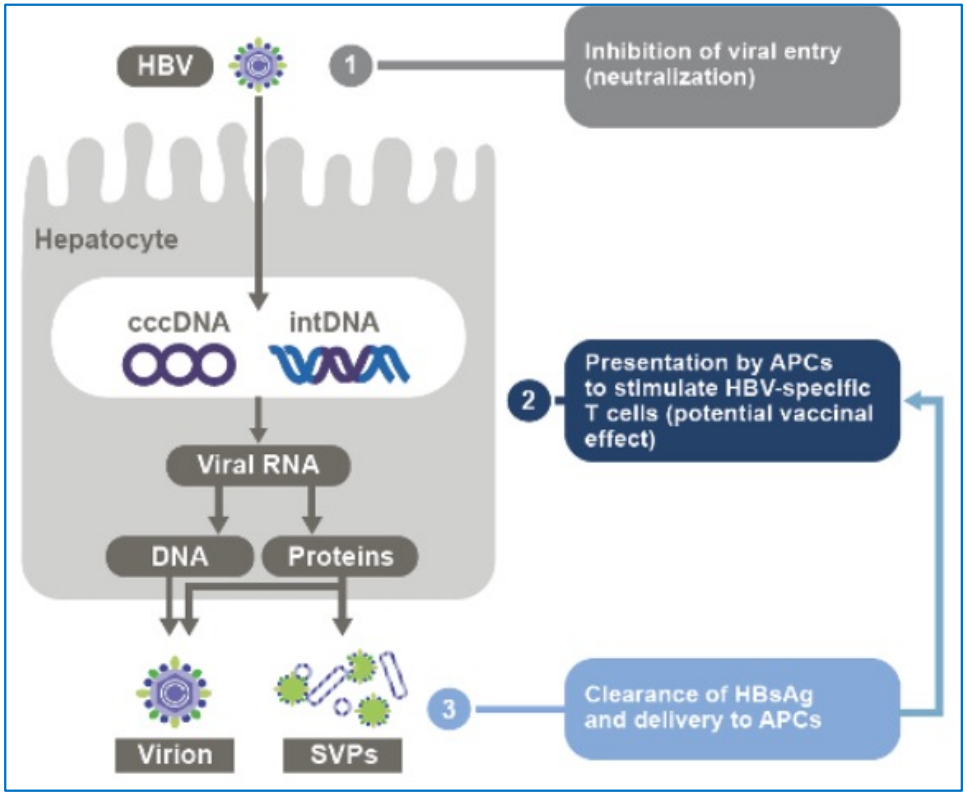
Anti-S/anti-HBs

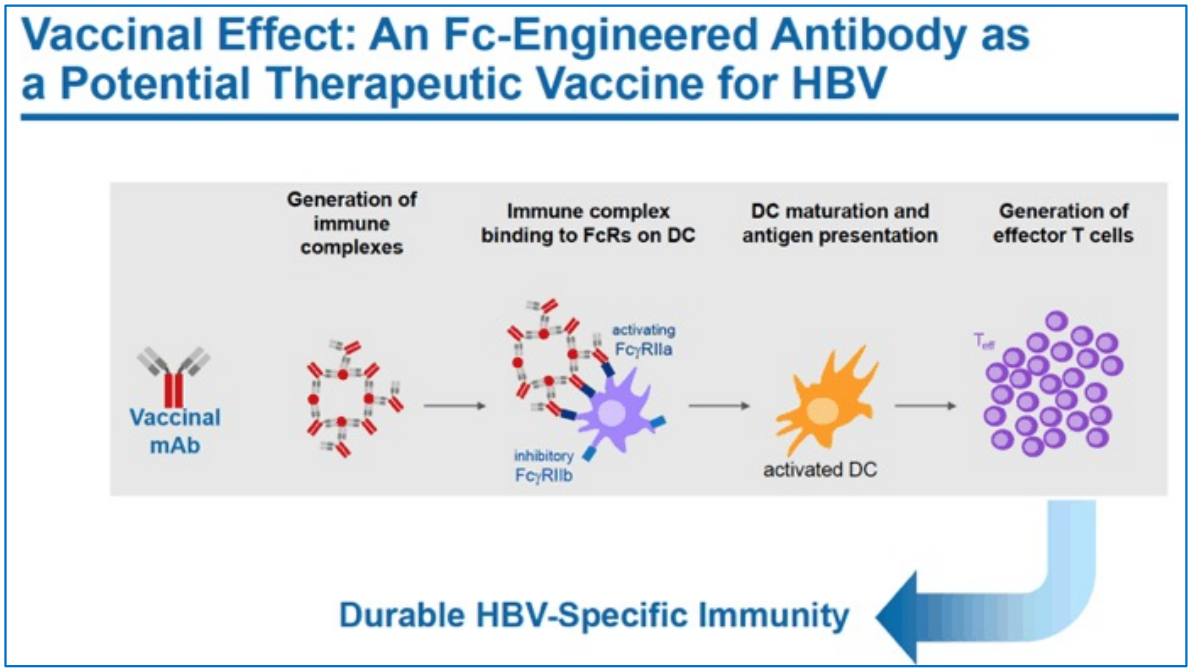




Lempp et al., J. Hepatol.,2023
Drawing from HepVir team

Monoclonal antibodies targeting HBV envelope proteins: nature and MoA (2)



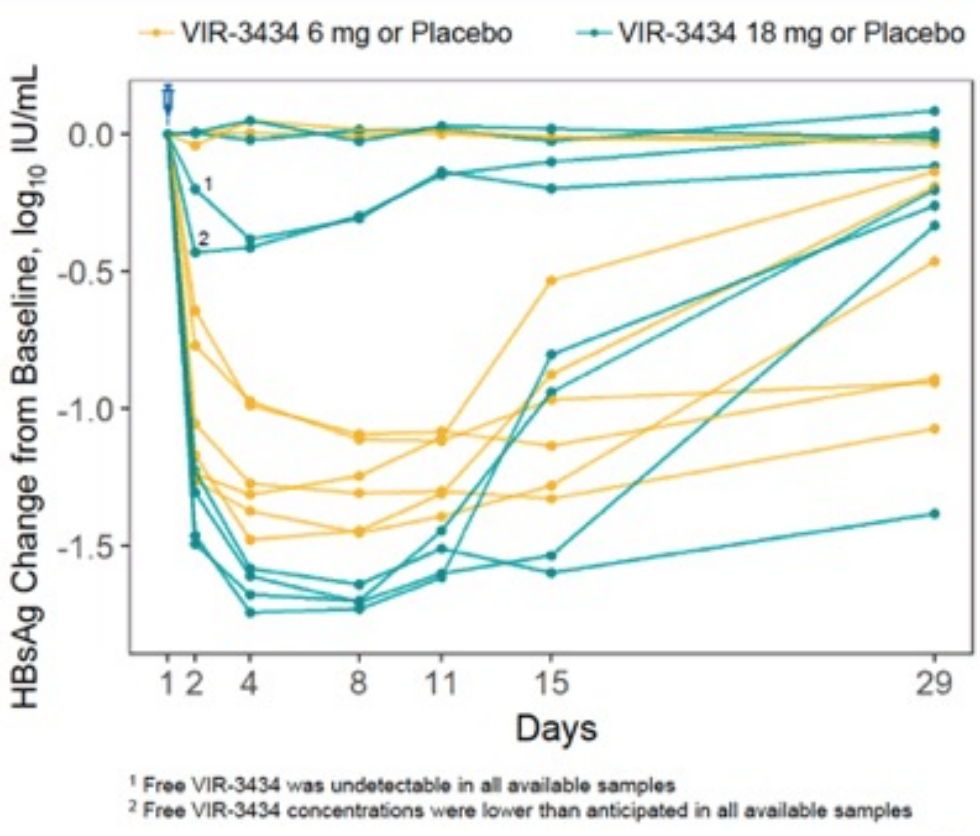


Bournazos et al., Nature Rev. Immunol., 2020; drawing from VIR pharma

Monoclonal Antibodies in current R&D

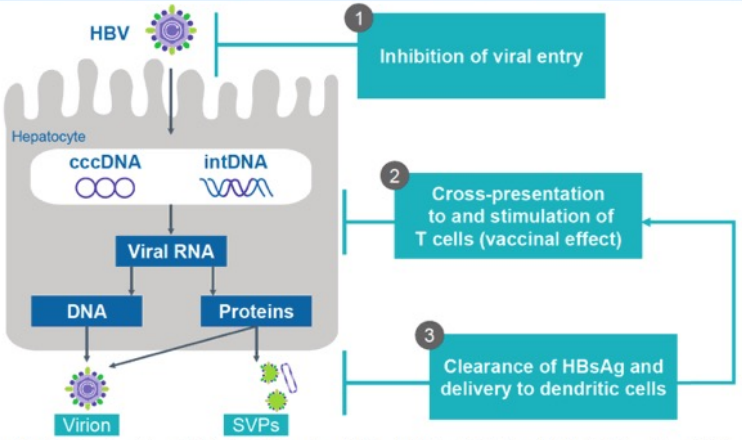
Monoclonal Antibodies: Neutralize or bind the HBV proteins to reduce infection				
VIR-3434 (Tobevibart) BRII-837	Monoclonal antibody	Vir Biotech with Brii Biosciences, USA	vir.bio and briibio.com	Phase II
Burfiralimab (IgG4)	Monoclonal antibody	ImmuneMed, South Korea	immunemed.co.kr/eng	Phase II
BJT-778	Monoclonal antibody	Blue Jay Therapeutics, USA	bluejaytx.com	Phase I
RG6449	Monoclonal antibody	Roche	roche.com	Phase I
GIGA-2339	Polyclonal antibody	GigaGen, USA	gigagen.com	Phase I
HT-102	Monoclonal antibody	Hepa Thera, PR China	www.hepathera.com/eng	Preclinical

Phase-1b results for VIR-34-34



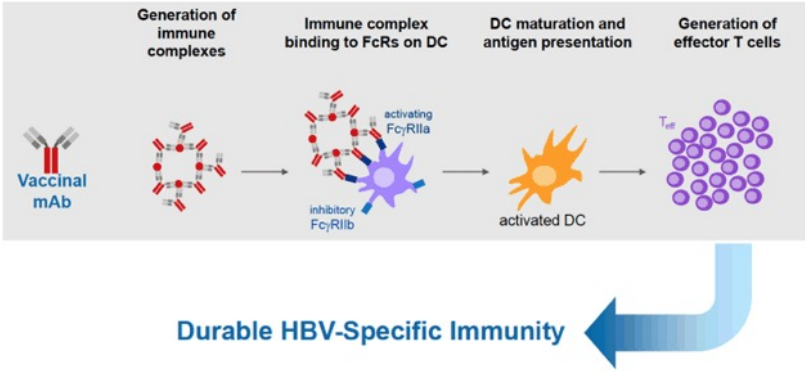
Bournazos et al., Nature Rev. Immunol., 2020; data from VIR pharma

VIR-3434: An Engineered Human Antibody Against HBsAg with Multiple Potential Mechanisms of Action

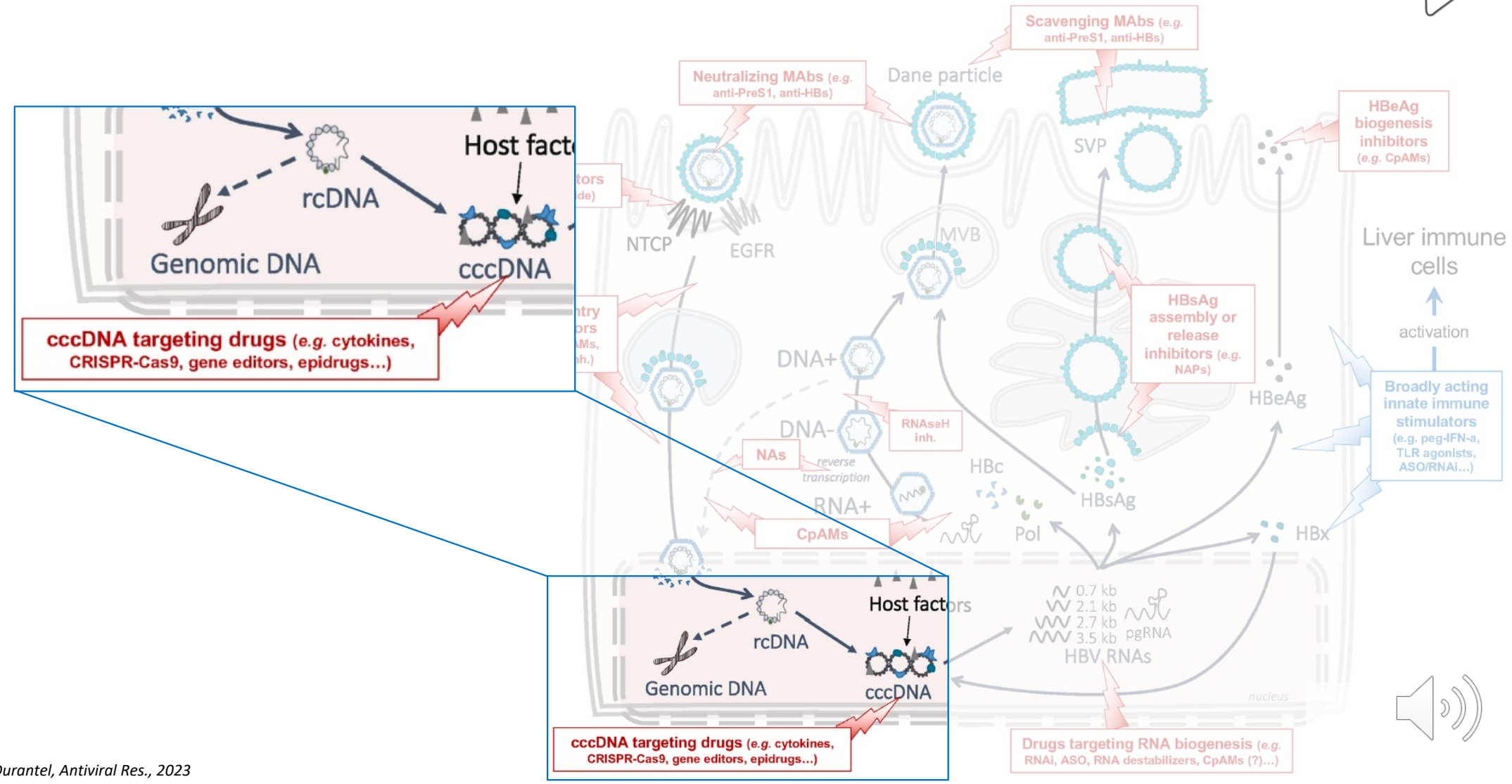


cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; intDNA, integrated DNA; RNA, ribonucleic acid; SVPs, subviral particles

Vaccinal Effect: An Fc-Engineered Antibody as a Potential Therapeutic Vaccine for HBV

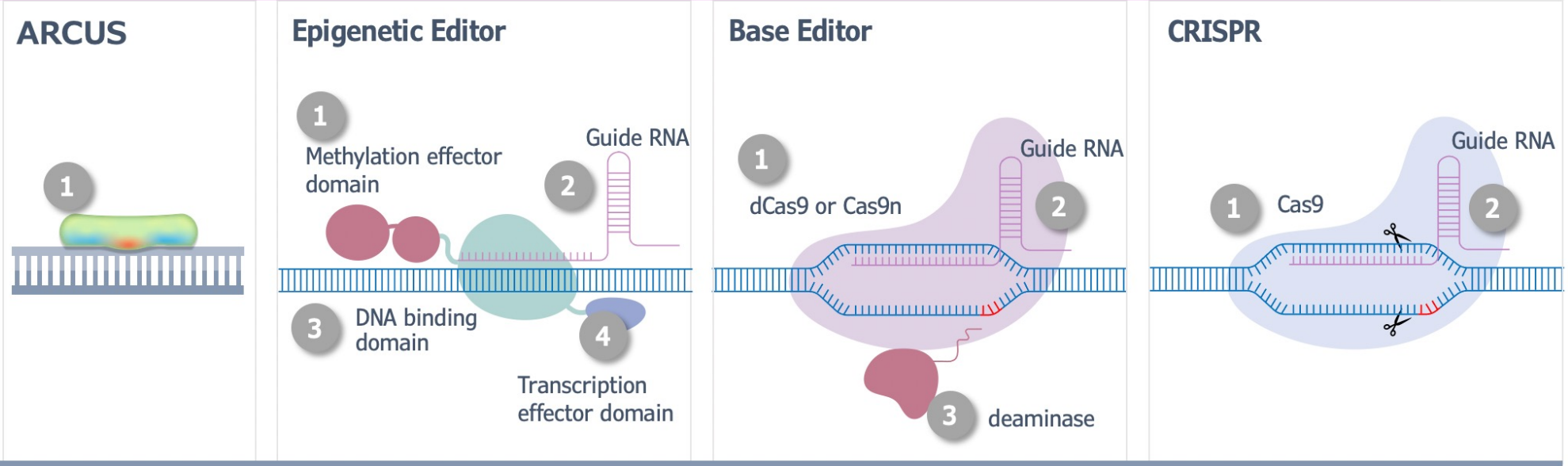


Drugs targeting cccDNA



Durantel, Antiviral Res., 2023

Gene Editors Include Components to Identify the Target Site and Make a Cut
Epigenome Editors Include a Methylation Effector

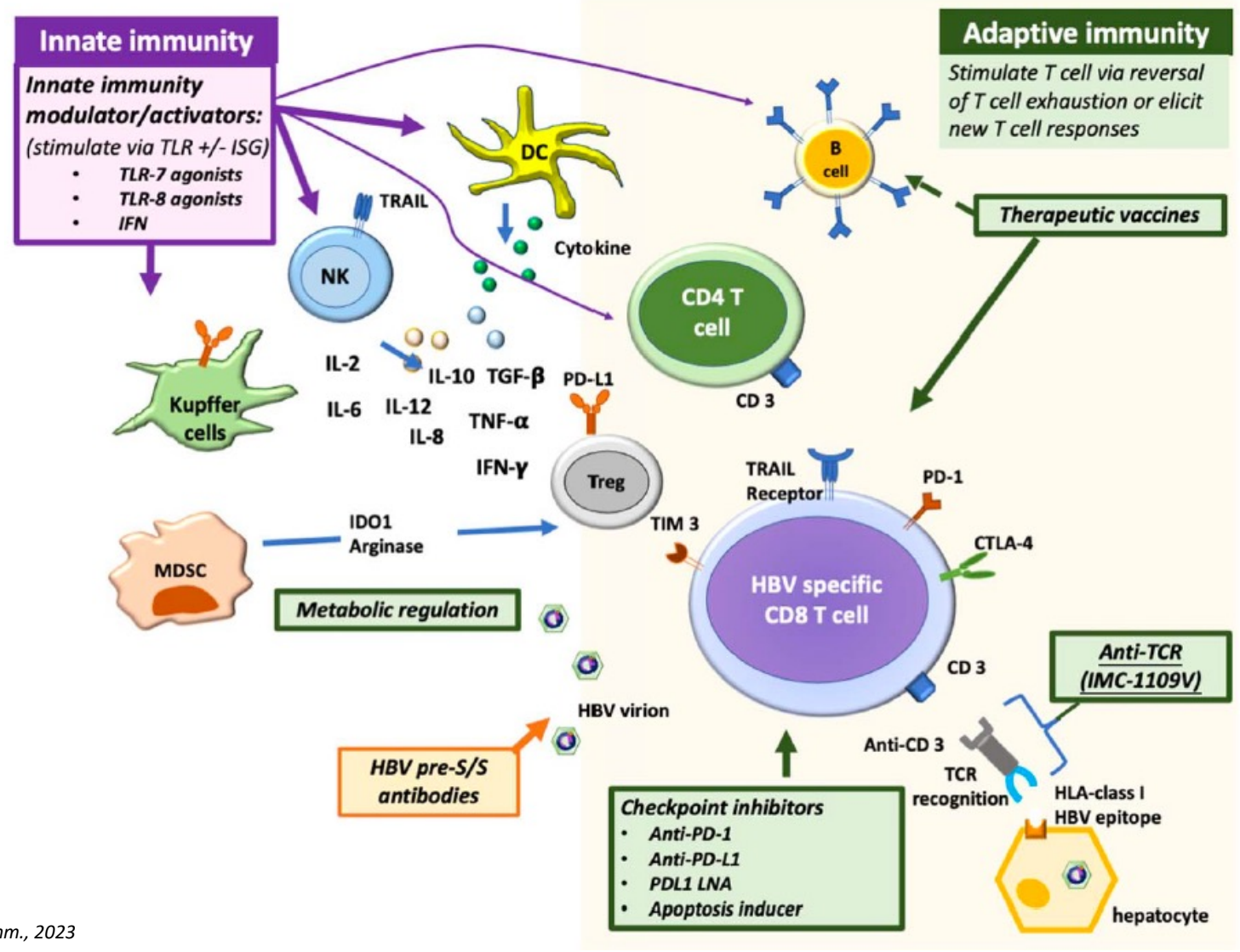


	ARCUS	Epigenetic Editor[1]	Base Editor[2]	CRISPR Editor[3]
Intended Edit Result	Eliminate cccDNA, inactivate integrated DNA	Silences cccDNA and integrated DNA via methylation	Mutates and inactivates cccDNA and integrated DNA	Creates cccDNA indels or excises portion of DNA with multiple guides
Cut type	Cut resulting in double stranded break with 3′ overhangs	Methylation (No Cut)	Single Stranded Nick	Cut resulting in double stranded break with blunt ends
Kilobases (kb)	~1 kilobase	~7 kilobases	4.8-5.4 kilobases	3.2-4.1 kilobases
# of Components	1 component	≥3 components (based on number of gRNAs)	≥3 components (based on number of gRNAs)	≥2 components (based on number of gRNA)

No head-to-head studies of these approaches have been conducted and therefore no conclusions concerning safety or efficacy can be drawn

[1] Epigenetic Editor data to date presented by Chroma Medicine [2] Base editor data to date presented by Beam Therapeutics [3] Seeger, et al. 2014, 2016; https://pubmed.ncbi.nlm.nih.gov/25514649/; https://pubmed.ncbi.nlm.nih.gov/27203444/

Immunotherapeutic components (1)



Jeng & Lok, Hepatology Comm., 2023

Toward a triple combination ?

Combination therapies for increasing the rate of *Functional Cure ?*

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

hNTCP
Entry inhibitors: bulevirtide, other small molecules & MAb
HBV polymerase
NUC: ETV, TDF, TAF, novel NUCs & RNAseH inhibitors
Nucleocapsids
CAM: ALG 000184, ZM-H1505R, ABI-H4334, EDP-514, JNJ-56136379

Transcription
FXR agonist: EYP001
Viral RNAs
siRNA: JNJ-3989, VIR-2218 (Elebsiran), AB-729 (Imdurisan), ALG-125755
ASO: Bepirovirsen, AHB-137
LNA: RO7062931
RNA destabilizers: GSK 3965193, BJT-628
HBsAg release
NAPs: REP 2139

Invigorate immune responses
Innate immunity
TLR7: GS9620, RG7854 (Ruzotolimod)
TLR8: Selgantolimod, CB06, GSK 5251738
Immune check points
Anti-PD1: nivolumab
Anti-PDL1: envafolimab (ASC22)
PDL1 LNA: RG6084
Oral PDL1 sm: AB-101

Stimulate HBV specific B/T cells
Therapeutic Vaccines
HepTcell
VTP-300
GSK3528869A
VVX001
HB-400 (GS2829/GS6779)
TherVacB
AVX70371
BRII-179

Exogenous HBs Mab
VIR-3434
BJT-778
RG6449

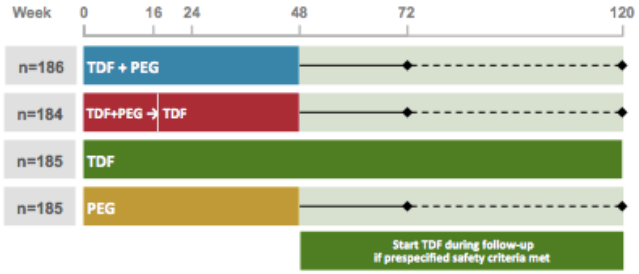
T Cell Engineering

Gene and epigenome editing

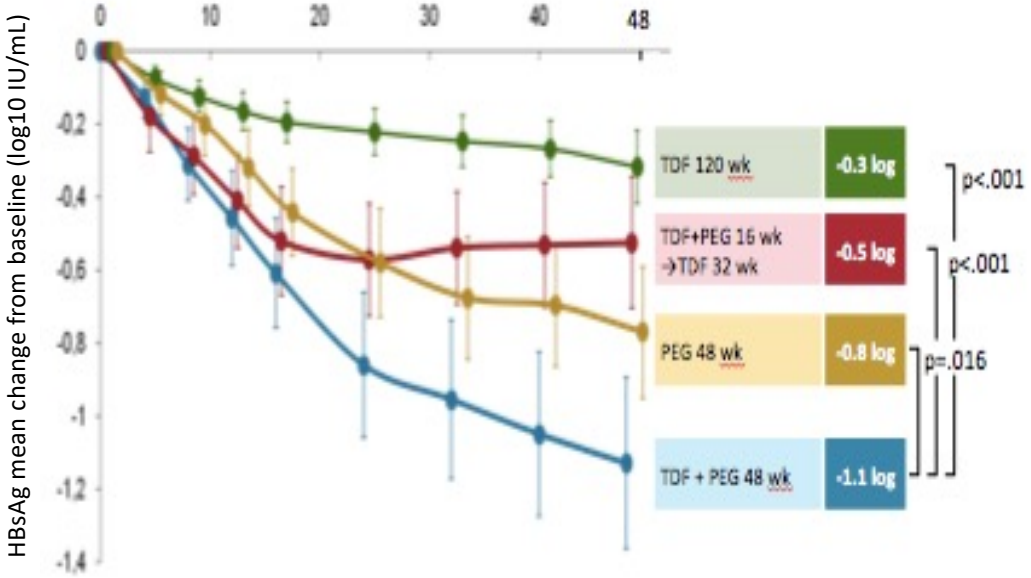
Revill et al, Lancet Gastroenterol Hepatol 2019; Lim et al Nat Rev Gastroenterol Hepatol. 2023; Feld et al, Clin Gastroenterol Hepatol 2023; https://www.hepb.org/treatment-and-management/drug-watch;

Generous gift by Pr M. Levrero

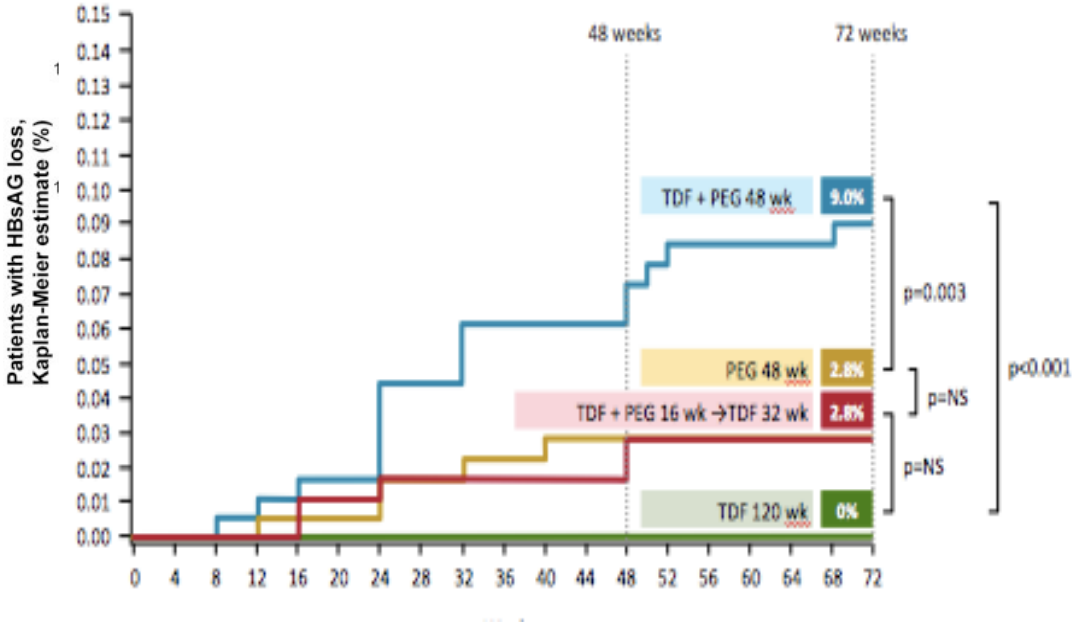
Best approved current option for combination = NUC/NA + PegIFNa



- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype



On-Treatment Changes in HBsAg Levels (wk 48)



HBsAg Loss Over Time (wk 72)

- ✓ **Around 10% of functional cure!**
- ✓ **This rate can be higher or lower in fct of HBV genotype in real life**

Marcellin et al., Gastroenterology 2016

Summary of road map to “HBV cure” (1)

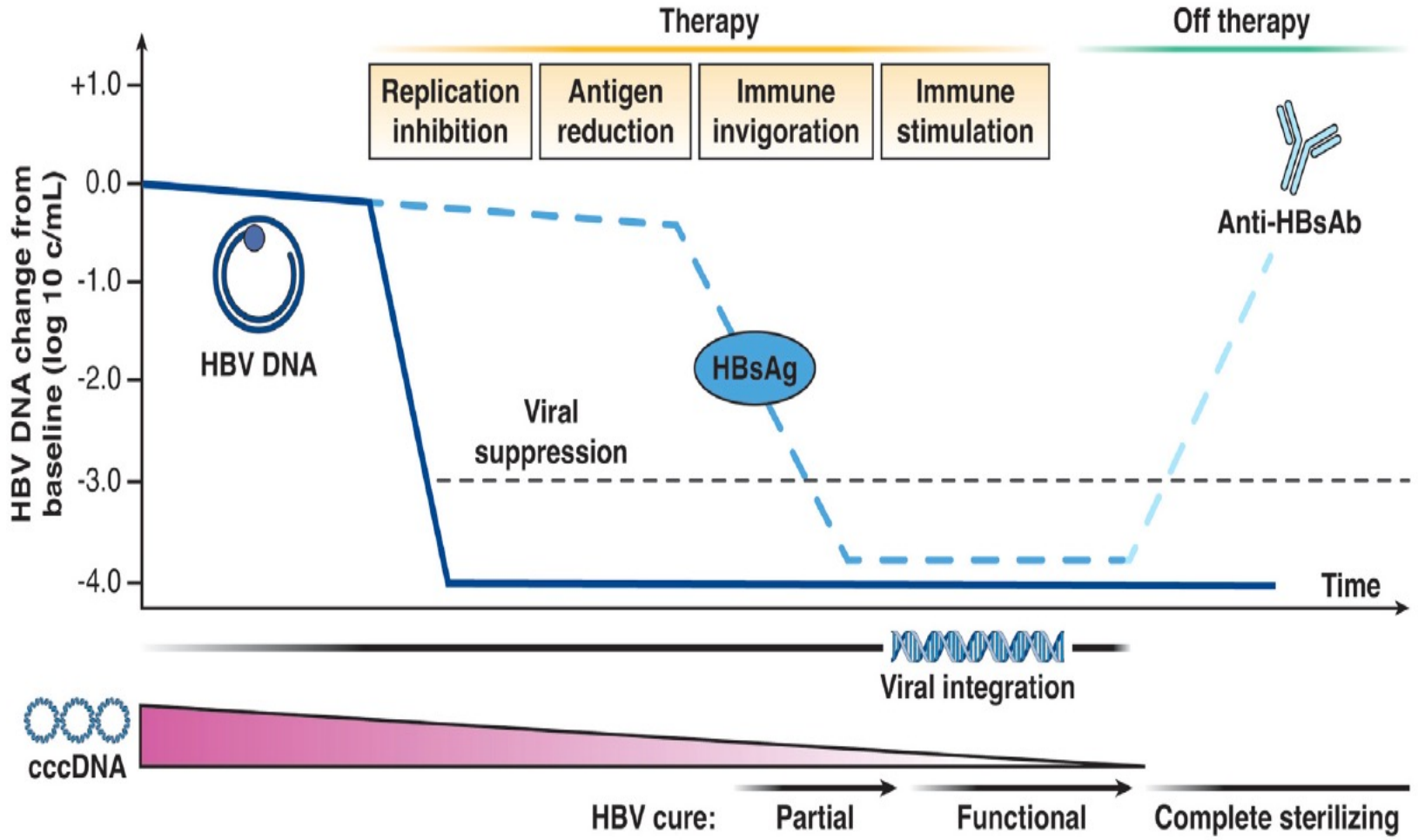


Figure 1. The different classes of direct acting antivirals and immune modulators. Potential for combination therapy based on complementary mode of action on the HBV life cycle and host immune responses. HBsAb, hepatitis B surface antibody.

Feld et al., Clinical Gastro. & Hepatol., 2023

Important TAKE HOME message = Access to treatment needs to change!