National University Health System

Yong Loo Lin School of Medicine • National University Hospital • Faculty of Dentistry

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Achieving Functional Cure in HBV

SHC-HK ASLD Webinar series

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Singapore

Disclosures

- Advisory Board
  - Gilead
  - Roche
  - Abbvie
  - Abbott
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  - Kaleido Bioscience
- Speaker’s Bureau
  - MSD
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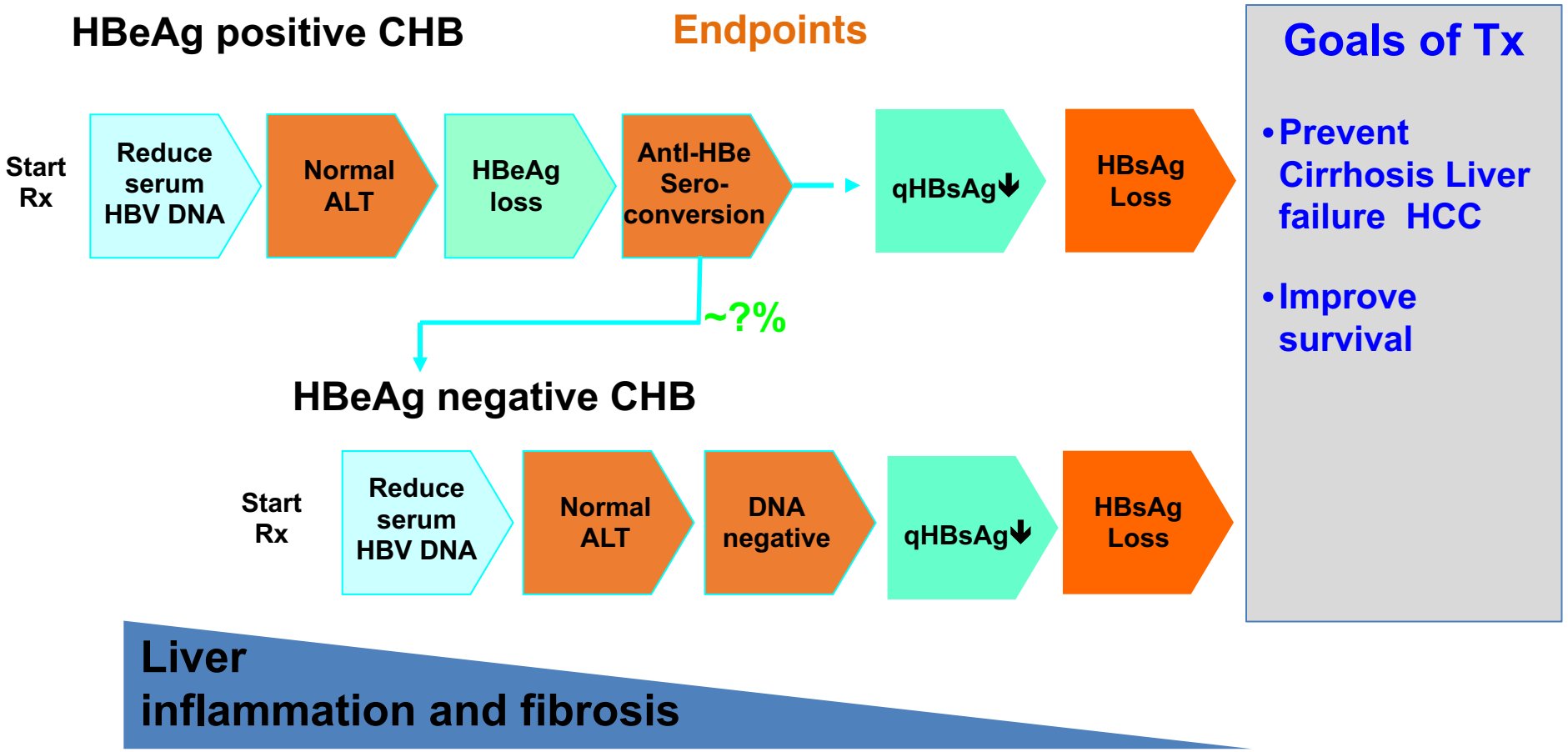
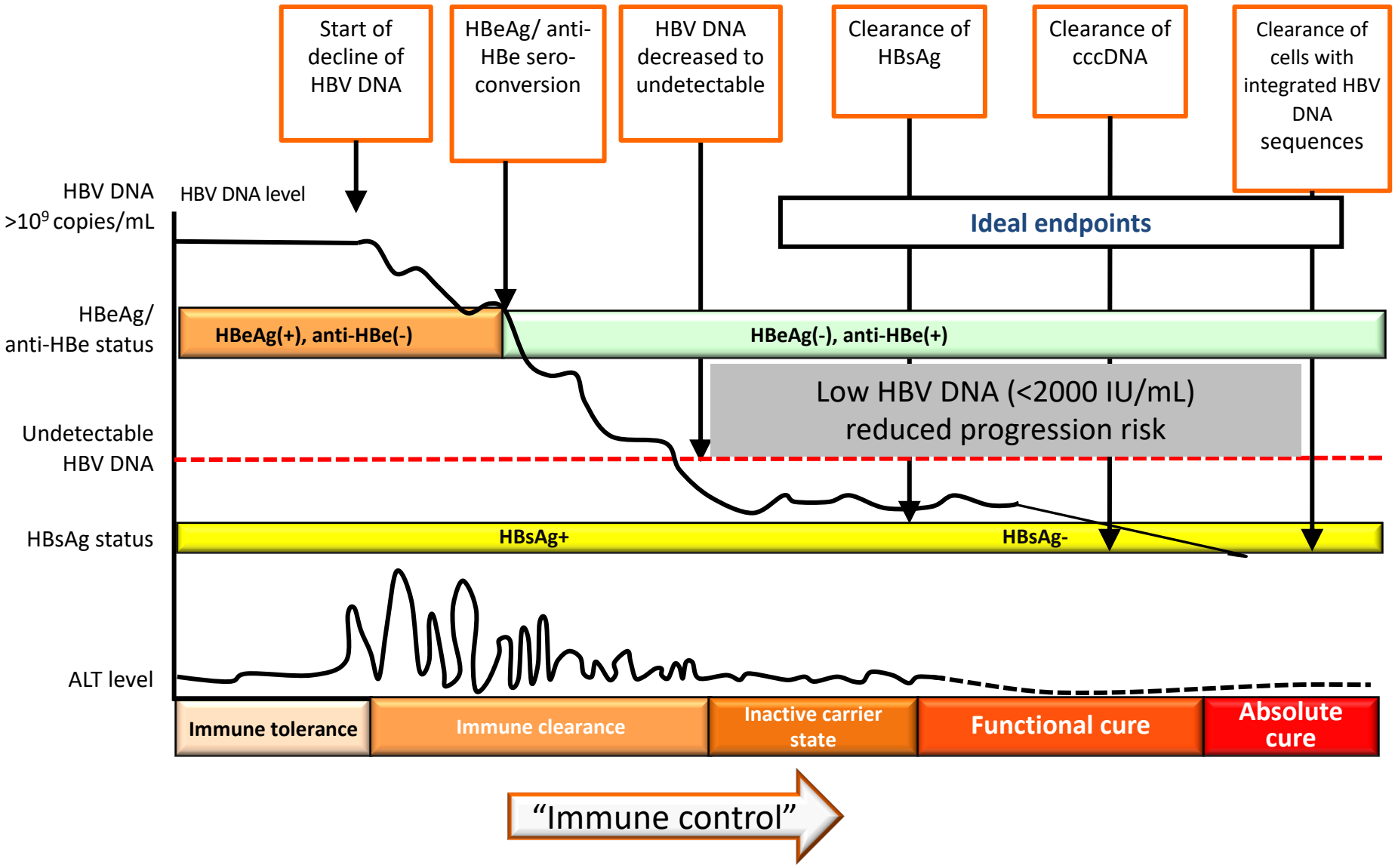
Endpoints versus Goals



EASL Clinical Practice Guidelines 2017

Endpoints in HBV Treatment



What is HBV Functional Cure?

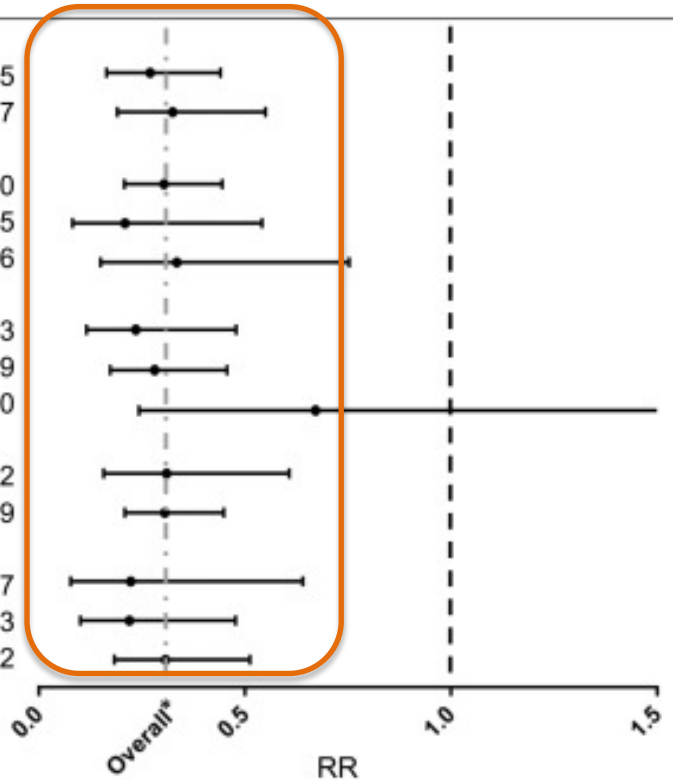
Term	Definition	Achievability
Functional Cure	• Sustained HBsAg loss/seroconversion 24 weeks off therapy • Undetectable HBV DNA	• Can be achieved with existing therapy • Ideally ~30% in phase III studies
Absolute or complete Cure	• Absence of cccDNA • Absence of integrated HBV	• Unlikely to be achieved in foreseeable future

Cornberg, J Hepatology 2020;72(3):539–557

HBsAg loss is associated with improved survival & complications: meta analysis

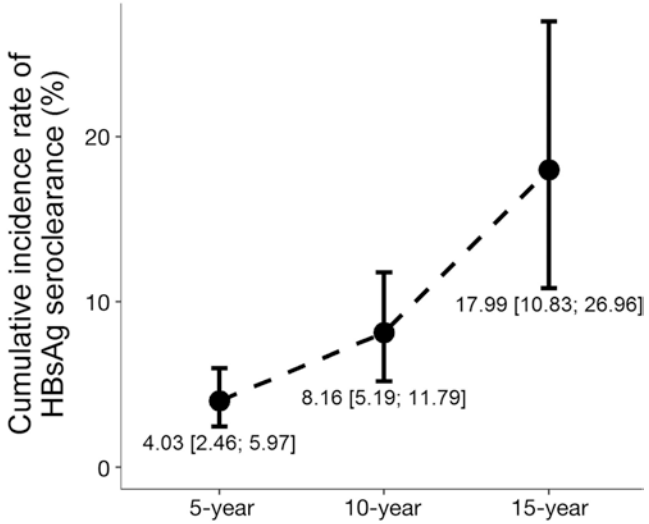
Endpoint	n^{srclr}	P-Y^{srclr}	n^{prstnt}	P-Y^{prstnt}	RR and 95% CI (0.0 – 0.5 – 1.0)	Reduction	RR	Lower limit	Upper limit	*P*-value
Liver Decompensation	4382.7	21426	105126.3			72%	0.28	0.13	0.59	.001
HCC	273264.3	154519	1211810.9			70%	0.30	0.20	0.44	<.001
LTx/death	7663.9	9131	69053.6			78%	0.22	0.13	0.39	<.001
First Clinical Event	273095.2	155030	1212985.9			69%	0.31	0.23	0.43	<.001

Variable	Subgroup	K	N	P-Y	RR	Lower limit	Upper limit	*P*-value
Study Design								
	Retrospective	18	182465	1416301.5	0.27	0.17	0.44	<.001
	Prospective	10	5851	69779.7	0.33	0.19	0.55	<.001
Cohort type								
	Untreated	12	155534	1312287.0	0.30	0.21	0.44	<.001
	Treated	13	31086	151408.5	0.21	0.08	0.54	.001
	Both	3	1696	22385.6	0.33	0.15	0.75	.008
Race								
	Caucasian	9	2698	18861.3	0.24	0.12	0.48	<.001
	Asian	18	185180	1461423.9	0.28	0.18	0.46	<.001
	Other	1	438	10849.0	0.67	0.25	1.85	.444
Co-infected subpopulation								
	Yes	3	148485	1217211.2	0.31	0.16	0.61	.001
	No	25	39831	268869.9	0.31	0.21	0.45	<.001
HBeAg Status at Baseline								
	(+)	7	1717	10496.7	0.22	0.08	0.64	.005
	(-)	6	3787	45751.3	0.22	0.10	0.48	<.001
	Both	15	182812	1429833.2	0.31	0.18	0.51	<.001

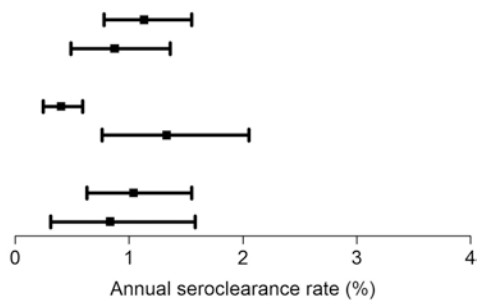


Anderson, Clin Gastro Hep 2020 (online ahead of print)

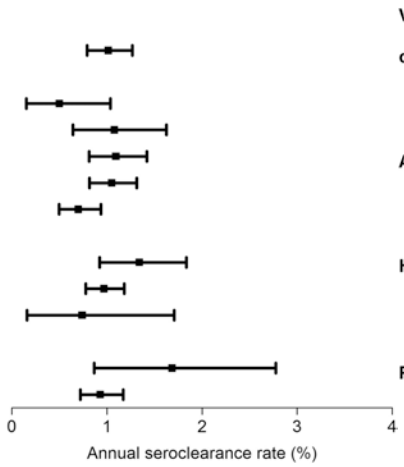
Factors leading to HBsAg loss



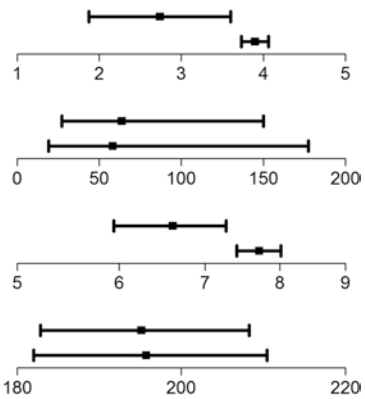
Feature	Subgroup	K	N	ASR (95% CI)
Sex				
	Male	16	11142	1.13 [0.78; 1.55]
	Female	14	6080	0.87 [0.49; 1.36]
Baseline HBeAg				
	HBeAg+	9	3922	0.40 [0.25; 0.59]
	HBeAg-	9	15205	1.33 [0.76; 2.05]
Baseline cirrhosis				
	No	12	13398	1.04 [0.63; 1.55]
	Yes	8	970	0.84 [0.31; 1.58]



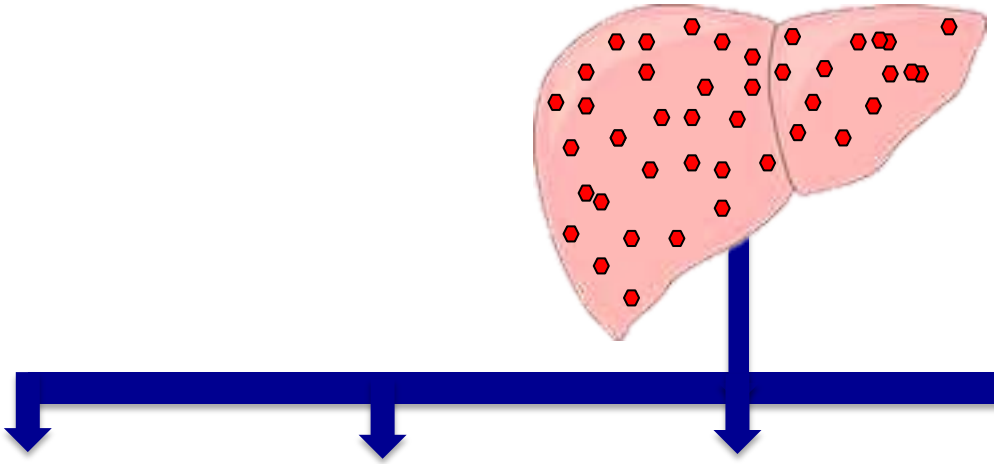
Feature	Subgroup	K	N	ASR (95% CI)
Overall		34	42588	1.02 [0.79; 1.27]
Study region				
	North America	3	4984	0.50 [0.15; 1.04]
	Europe	5	2364	1.08 [0.64; 1.63]
	Asia Pacific	23	32866	1.09 [0.81; 1.42]
	Middle East	2	1826	1.05 [0.82; 1.31]
	South America	1	548	0.70 [0.50; 0.94]
Practice setting				
	Community	8	9435	1.34 [0.92; 1.83]
	University	16	9521	0.97 [0.78; 1.18]
	Mixed	6	12101	0.74 [0.16; 1.71]
Scale of study				
	Population-based	4	5779	1.68 [0.86; 2.78]
	Healthcare service-based	30	36809	0.93 [0.72; 1.17]



Variable	HBsAg seroclearance	K	N	Mean (95% CI)
qHBsAg (log_{10} IU/mL)				
	Yes	5	1173	2.74 [1.87; 3.60]
	No	5	6246	3.90 [3.73; 4.06]
ALT (U/L)				
	Yes	16	1663	63.75 [27.09; 149.99]
	No	16	14974	58.18 [19.08; 177.46]
HBV DNA (log_{10} IU/mL)				
	Yes	10	1431	6.61 [5.94; 7.27]
	No	10	16590	7.71 [7.41; 8.02]
Platelet count (10^9/L)				
	Yes	10	822	195.14 [182.82; 208.29]
	No	10	9536	195.71 [182.02; 210.43]



What approaches can we use with current therapies?



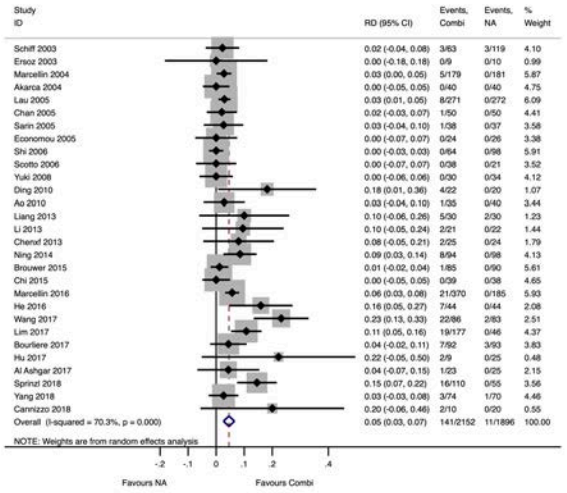
Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
Continue Nucs	Peg-interferon	Combination pegIFN +Nucs	Nucs switch to Peg-interferon	Stop Nucs

Which is the best strategy?

HBsAg loss with current therapy: meta analysis

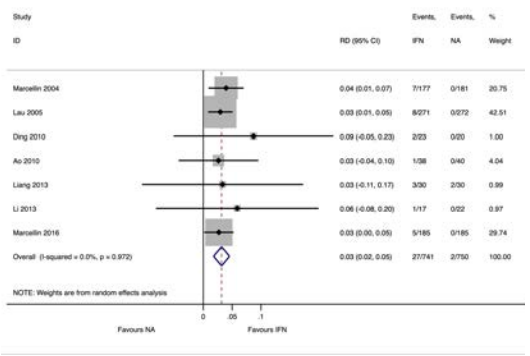
43 high quality RCTs with low risk of bias

Combination(IFN+NA) vs NA



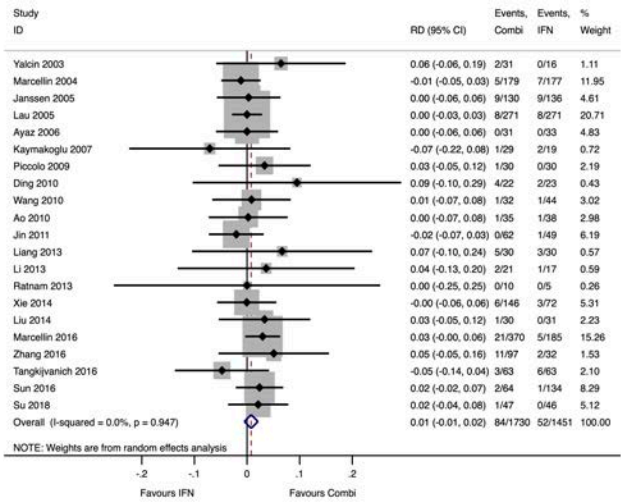
Combination	NA
6.55%	0.58%

IFN vs NA



IFN	NA
3.64%	0.27%

Combination(IFN+NA) vs IFN



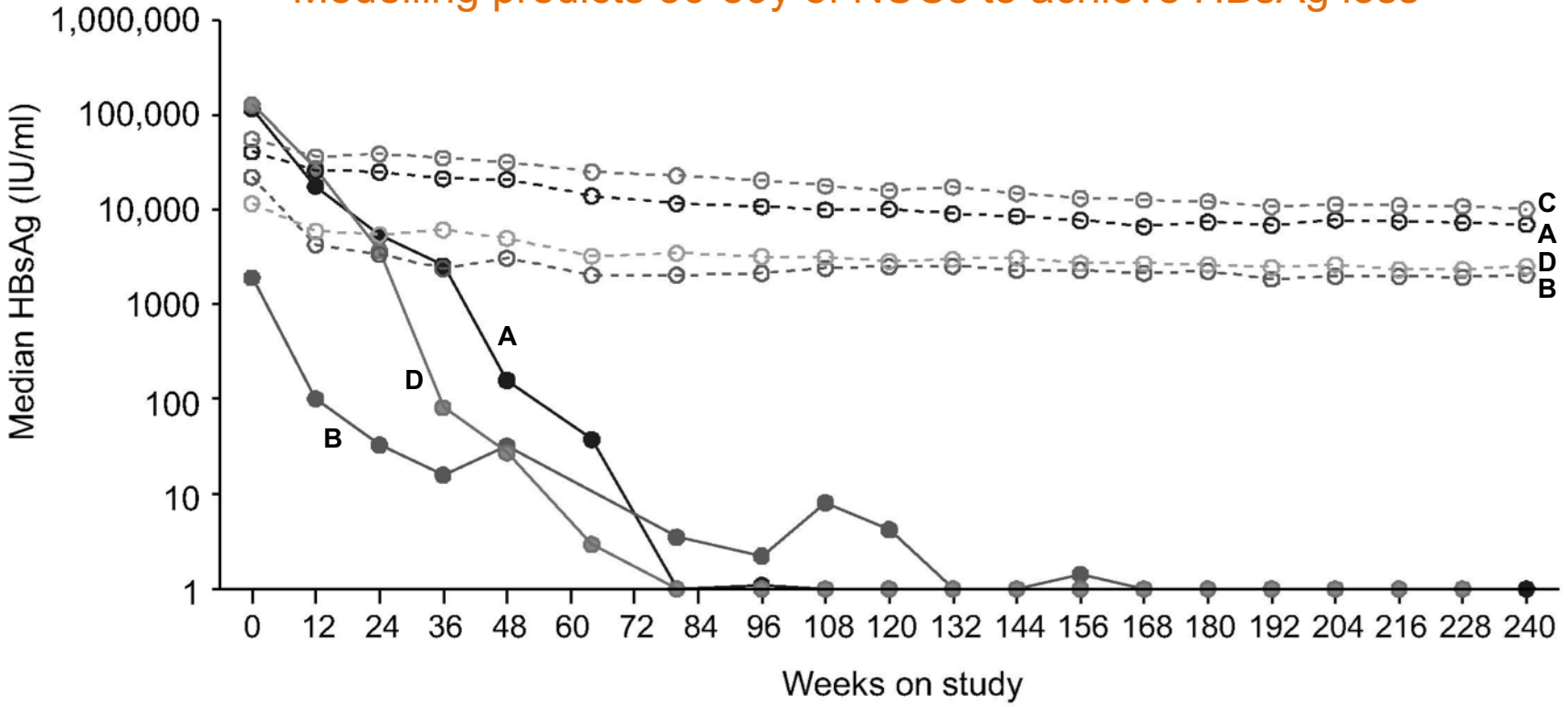
Combination	IFN
4.8%	3.6%

- IFN or combination is superior to NA but no difference to each other
- Current therapies achieve HBsAg loss<10%

Fonseca M , Lim SG, J Viral Hepat. 2020 Jul;27(7):650-662.

Patterns of qHBsAg decline during 5y TDF therapy

Modelling predicts 36-39y of NUCs to achieve HBsAg loss

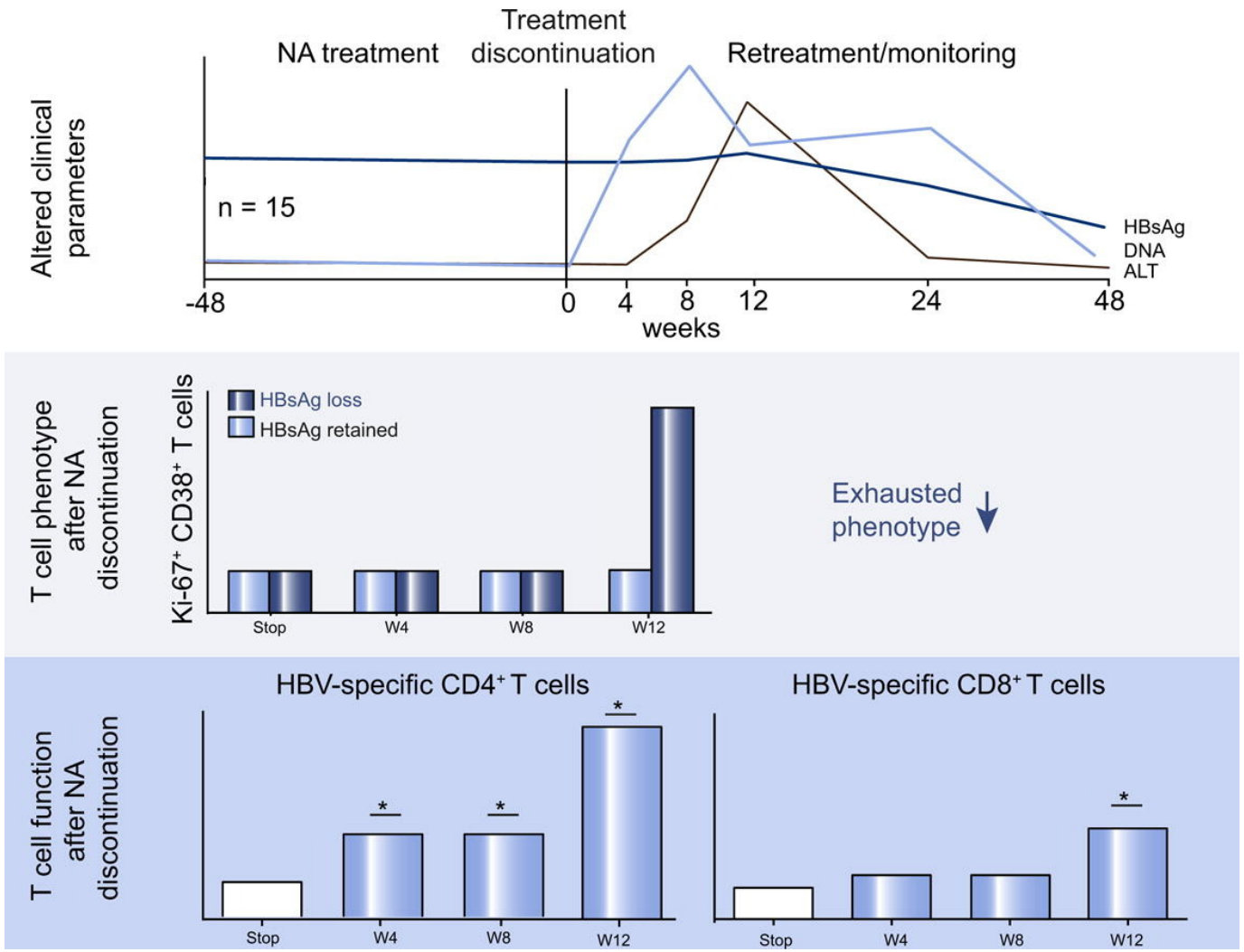


HBsAg loss - Genotype A	N = 14	14	14	13	13	13	13	12	12	11	10	11	10	10	9	8	8	8	7	7
HBsAg loss - Genotype B	N = 1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1		
HBsAg loss - Genotype D	N = 7	7	7	7	7	6	6	6	6	6	4	4	3	2	2	3	2	2	2	
No HBsAg loss - Genotype A	N = 45	44	43	43	42	40	40	40	40	39	39	35	38	37	36	37	35	32	32	33
No HBsAg loss - Genotype B	N = 34	33	33	31	30	26	24	24	22	23	22	22	22	22	22	21	22	22	21	21
No HBsAg loss - Genotype C	N = 68	68	66	65	65	60	59	57	57	58	58	57	56	53	53	52	51	47	49	46
No HBsAg loss - Genotype D	N = 77	76	77	73	73	72	68	67	66	65	62	62	59	58	58	57	55	58	57	53

Marcellin, J Hepatol 2014;61(6):1228–1237; Zoutendijk R, et al. J Infect Dis 2012;206:974–80

Stopping NA therapy

What can we learn from stopping NA therapy?



Increased T cell activation and reduced exhausted T cell phenotype in those who stop therapy

Rinker, J Hep 2018;69(3):584-593

Stopping Long-Term Nuc Therapy

	Stay off treatment	HBsAg loss	Predictors of HBsAg loss	PPV	NPV
Sonneveld (48 wk F/U)	**53%**	**4%**	**BL HBsAg <10**	**27%** (7/26)	**98%** (428/43)
van Bömmel (48 wk F/U)	**86%**	**10%**	**BL HBsAg<1000**	**27%** (7/25)	**98%** (53/54)
Hall (48 wk F/U)	**89%**	**5%**	**BL HBsAg <10**	**63%** (5/8)	**100%** (95/95)

- NUC discontinuation may be safe in noncirrhotic patients
- 30-60% will remain off-treatment and 5-10% will lose HBsAg
- Best predictor is low HBsAg level at discontinuation

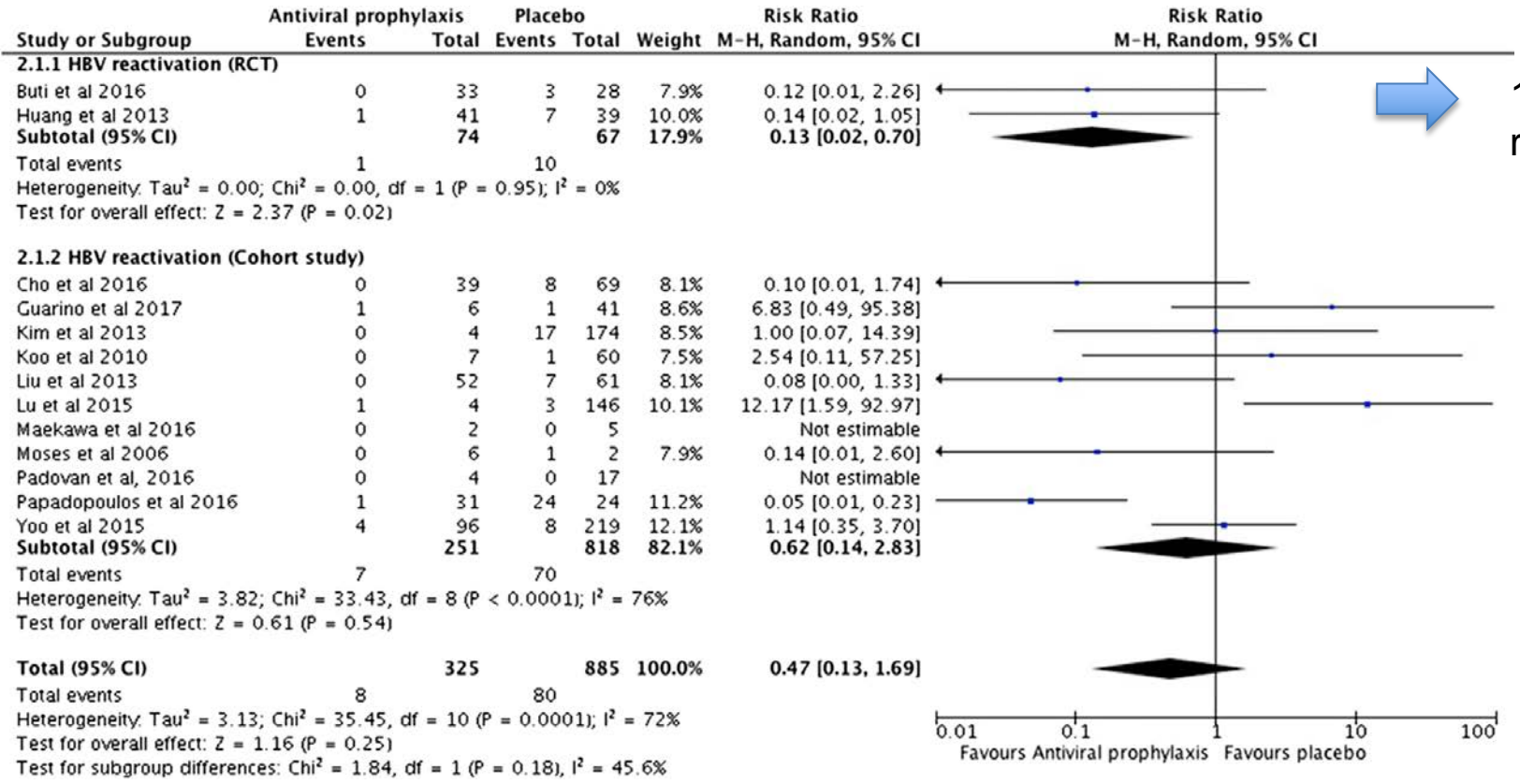
Likelihood of HBsAg loss after stopping NA therapy based on qHBsAg levels: Systematic Review

EOT qHBsAg level	HBsAg loss
<100 IU/mL	21.1%-58.8%
100-200 IU/mL	25.5%
100-500 IU/mL	4.4%
>500 IU/mL	2.3%
>1,000 IU/mL	0.0%

Liu, Hepatology 2019;70(3):1045-1055

After HBsAg loss, can HBV return?

HBV reactivation in HBsAg negative, anti-HBc Ab positive patients with Rituximab Therapy



14.9% reactivation

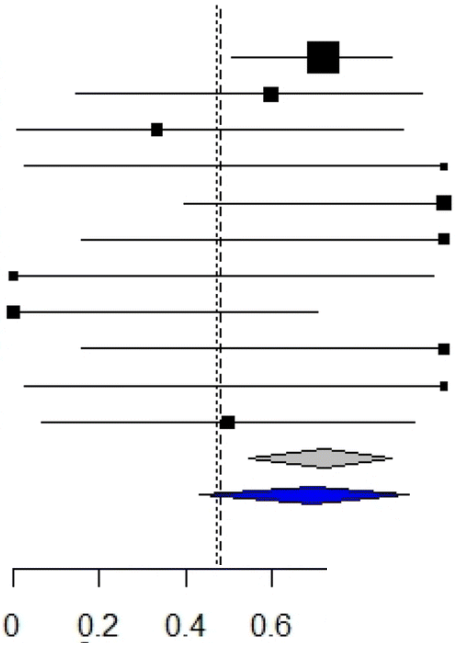
- Blocking B cell function leads to HBV reactivation in ~15% of HBsAg negative patients

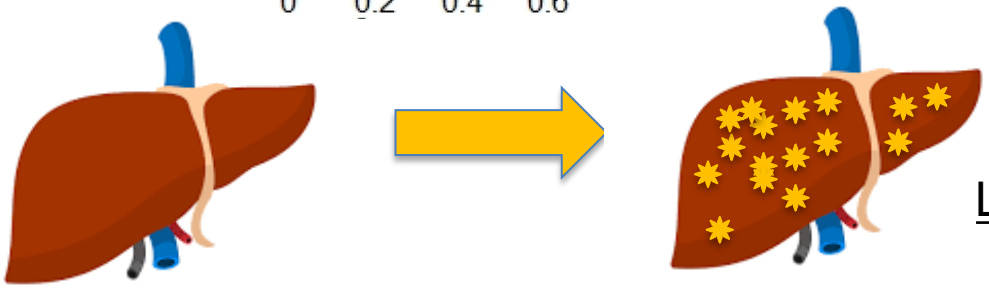
Su, Eur J Clin Pharmacol. 2018 Sep;74(9):1111-1119.

De novo HBV post Liver Transplant

Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
HBcAb negative						
Dodson 1997 [2]	18	25	0.72	[0.51; 0.88]	29.5%	10.3%
Douglas 1997 [3]	3	5	0.60	[0.15; 0.95]	6.4%	7.4%
Rokuharo 2000 [6]	1	3	0.33	[0.01; 0.91]	4.0%	6.1%
Manzabeita 2002 [9]	1	1	1.00	[0.03; 1.00]	1.7%	3.7%
Roque 2002 [11]	4	4	1.00	[0.40; 1.00]	5.2%	6.8%
Chen 2002 [12]	2	2	1.00	[0.16; 1.00]	2.9%	5.1%
Barcena 2006 [19]	0	1	0.00	[0.00; 0.98]	1.7%	3.7%
Prakoso 2006 [21]	0	3	0.00	[0.00; 0.71]	4.0%	6.1%
Kim 2011 [26]	2	2	1.00	[0.16; 1.00]	2.9%	5.1%
Pan 2011 [28]	1	1	1.00	[0.03; 1.00]	1.7%	3.7%
Han 2015 [33]	2	4	0.50	[0.07; 0.93]	5.2%	6.8%
Fixed effect model		**51**	**0.72**	**[0.55; 0.88]**	**65.3%**	--
Random effects model			**0.70**	**[0.43; 0.92]**	--	**64.9%**

Heterogeneity: I^2 = 37%, p = 0.10





Liver Transplant Donor

HBsAg neg
Anti-HBc pos

Liver Transplant Recipient

Up to 72% De Novo HBV In anti-HBc neg recipients

Yang, Hepatol Int 2020 Mar;14(2):202-211.

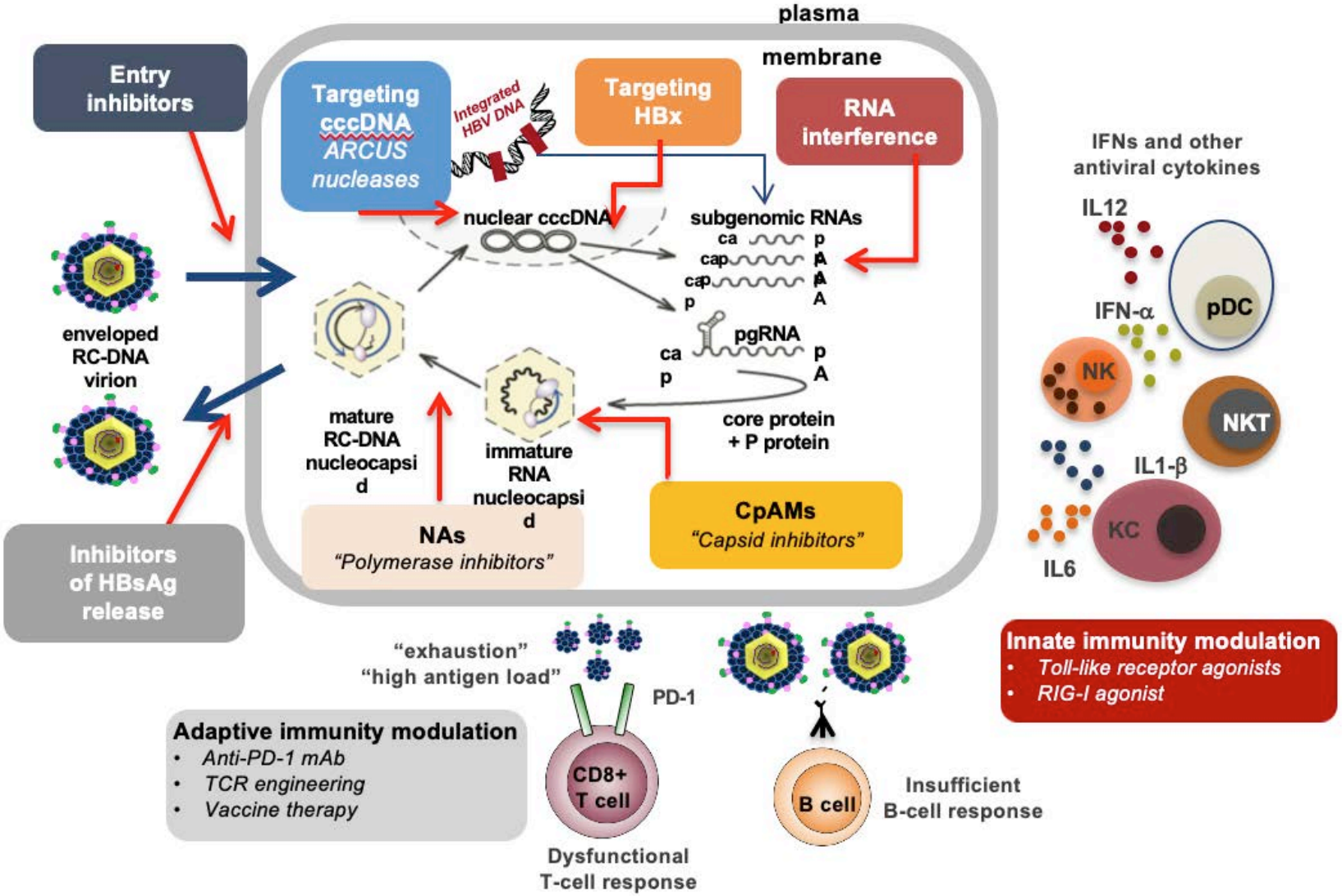
Summary

- Immune suppression leads to reactivation of HBV in those who are HBsAg neg, anti-HBc positive
- In the most extreme case of liver transplant this is as high as 72%

- Indicates that cccDNA has not been eliminated
- More likely cccDNA has been silenced
- Measurement of cccDNA in liver tissue as an endpoint of therapy may be problematic
  - Sensitivity not high
  - Assays not standardized

New Therapies are needed to achieve functional cure

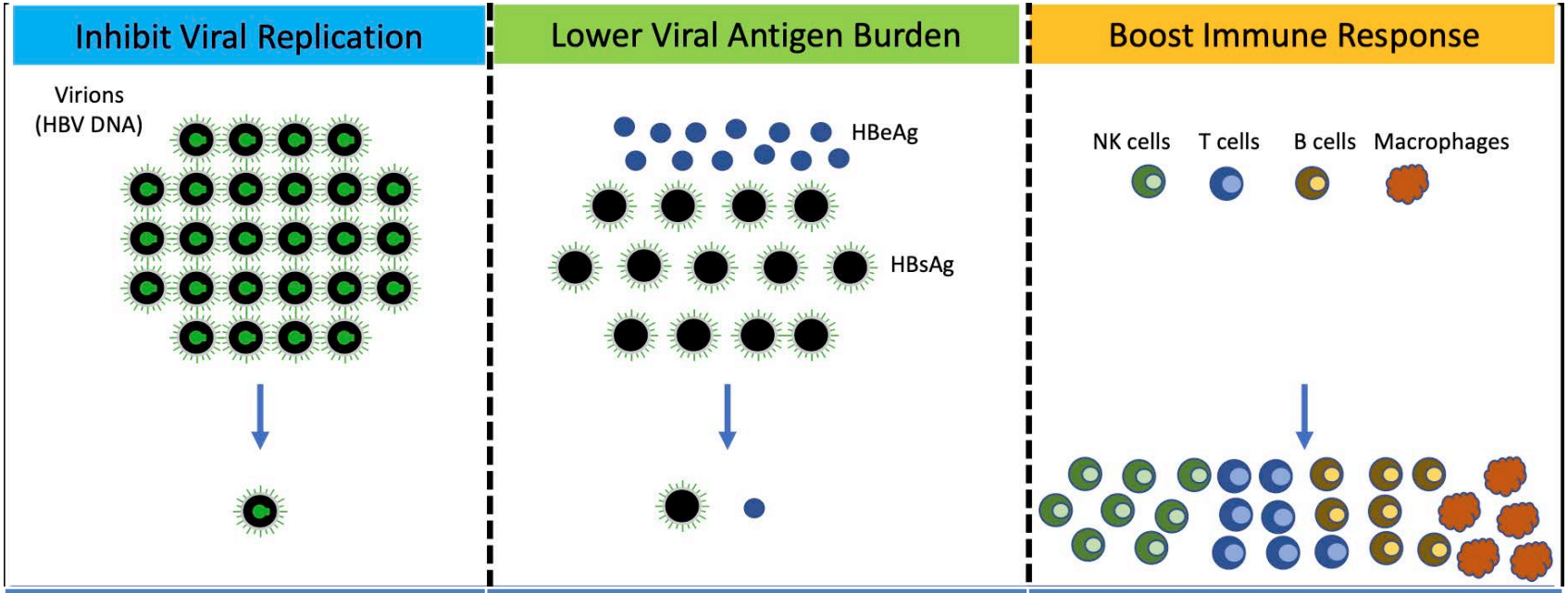
Novel therapeutic targets for HBV



CpAM: core protein allosteric modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK (T): natural killer (T cell); DC: plasmocytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor

Adapted from: Levrero M, et al. Curr Opin Virol 2016;18:135–43;
)

Three Strategies

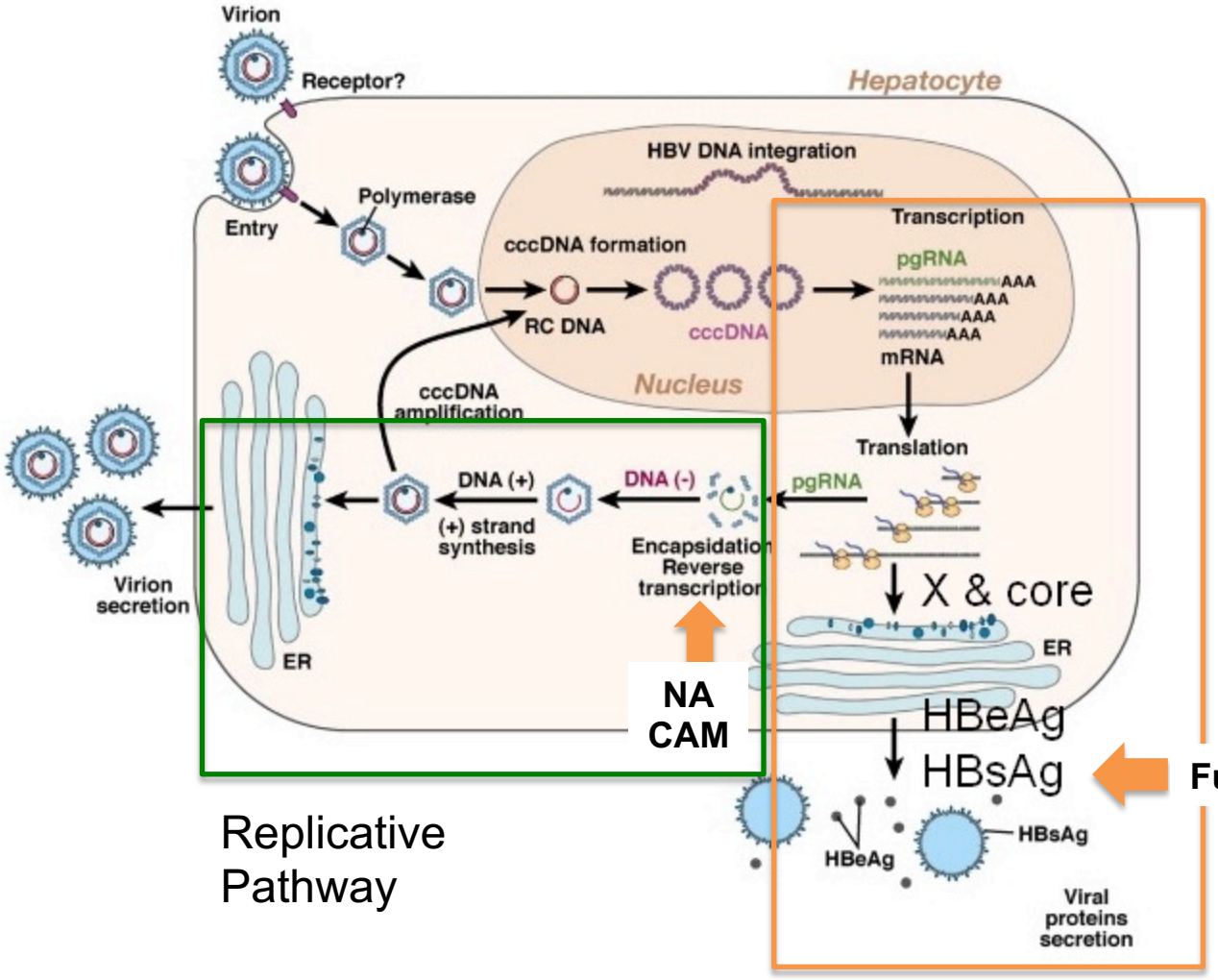


- Nucleoside Analogues
- Capsid Assembly Modulators
- Entry Inhibitors

- RNA interference
- Nucleic Acid Polymers

- Innate immunity Modulators (TLR)
- Immune enhancers (checkpoint inhibitors)
- Therapeutic Vaccines

Overlapping pathways in HBV lifecycle



Replicative Pathway

Functional Cure

Translational Pathway

Two main controllers of viral transcription

- **Core promoter & enhancers control pregenomic RNA**
- **"S" promoter controls "S" transcripts**
- **S Ag production is affected by amount of cccDNA and its activity, as well as by epigenetic factors controlling "S" promoter (eg methylation)**

How do we know which agents are effective?

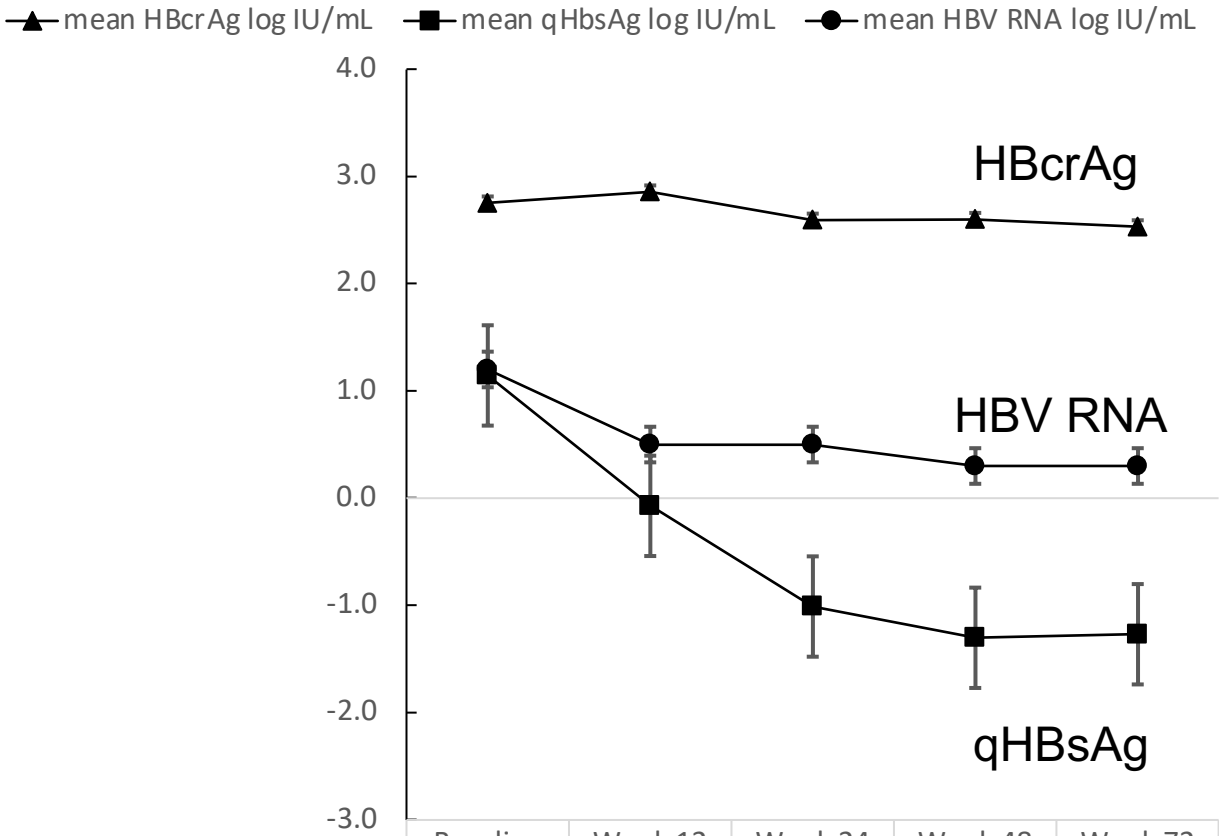
HBsAg

- HBsAg loss ideal but difficult to achieve in Phase I-II RCT
- qHBsAg<100
- Reduction in qHBsAg (>1 log, >2 log?), the bigger the better

Other markers

- HBeAg loss/seroconversion
- HBV DNA reduction
- HBV RNA reduction
- HBcrAg reduction
- Measurement of cccDNA

Biomarkers for HBsAg loss in CHB treated with pegIFN+NA



	Baseline	Week 12	Week 24	Week 48	Week 72
mean HBcrAg log IU/mL	2.75	2.86	2.59	2.60	2.53
mean qHbsAg log IU/mL	1.14	-0.07	-1.01	-1.30	-1.27
mean HBV RNA log IU/mL	1.20	0.50	0.50	0.30	0.30

Baseline AUROC for HBsAg loss

- qHBsAg (0.916)
- HBcrAg (0.649)
- HBV RNA (0.542)

On treatment qHBsAg week 8 was best predictor

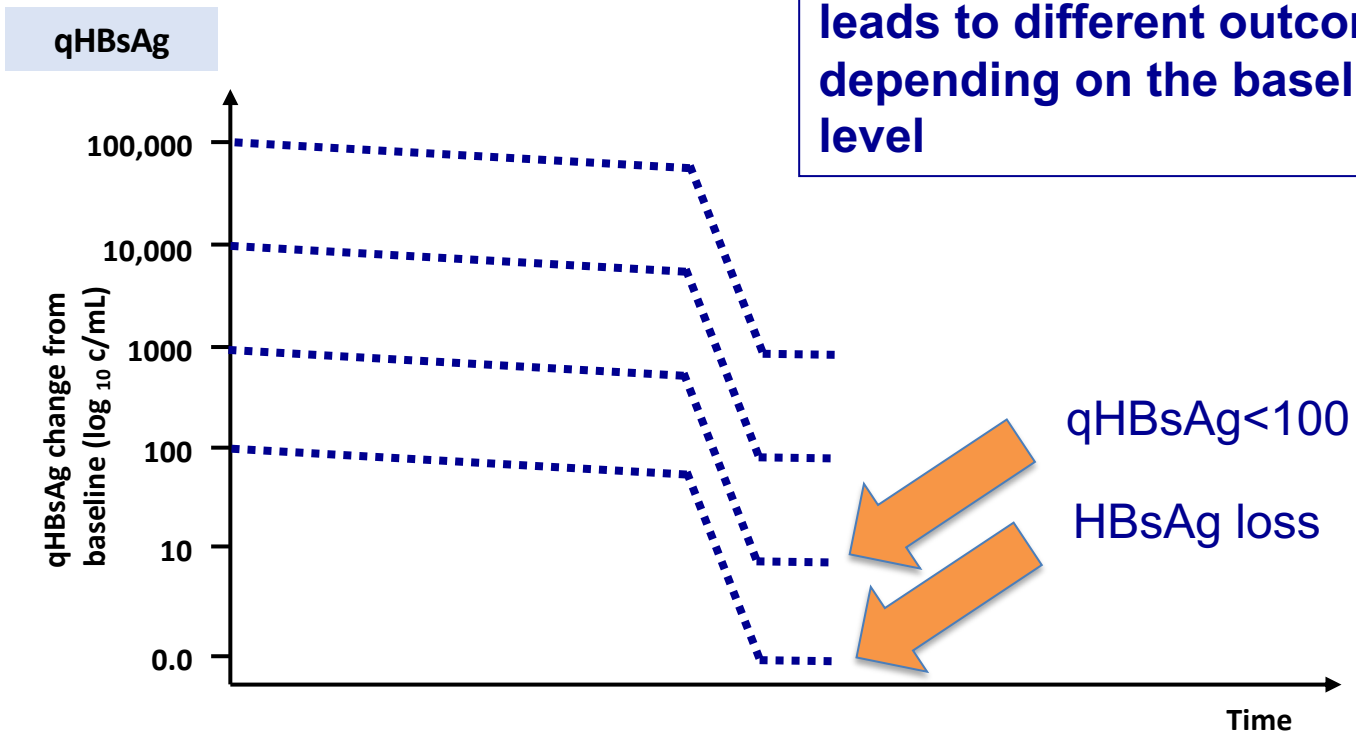
- Threshold 69 IU/ml
- AUROC=0.963

qHBsAg was superior to HBV RNA and HBcrAg in predicting HBsAg loss

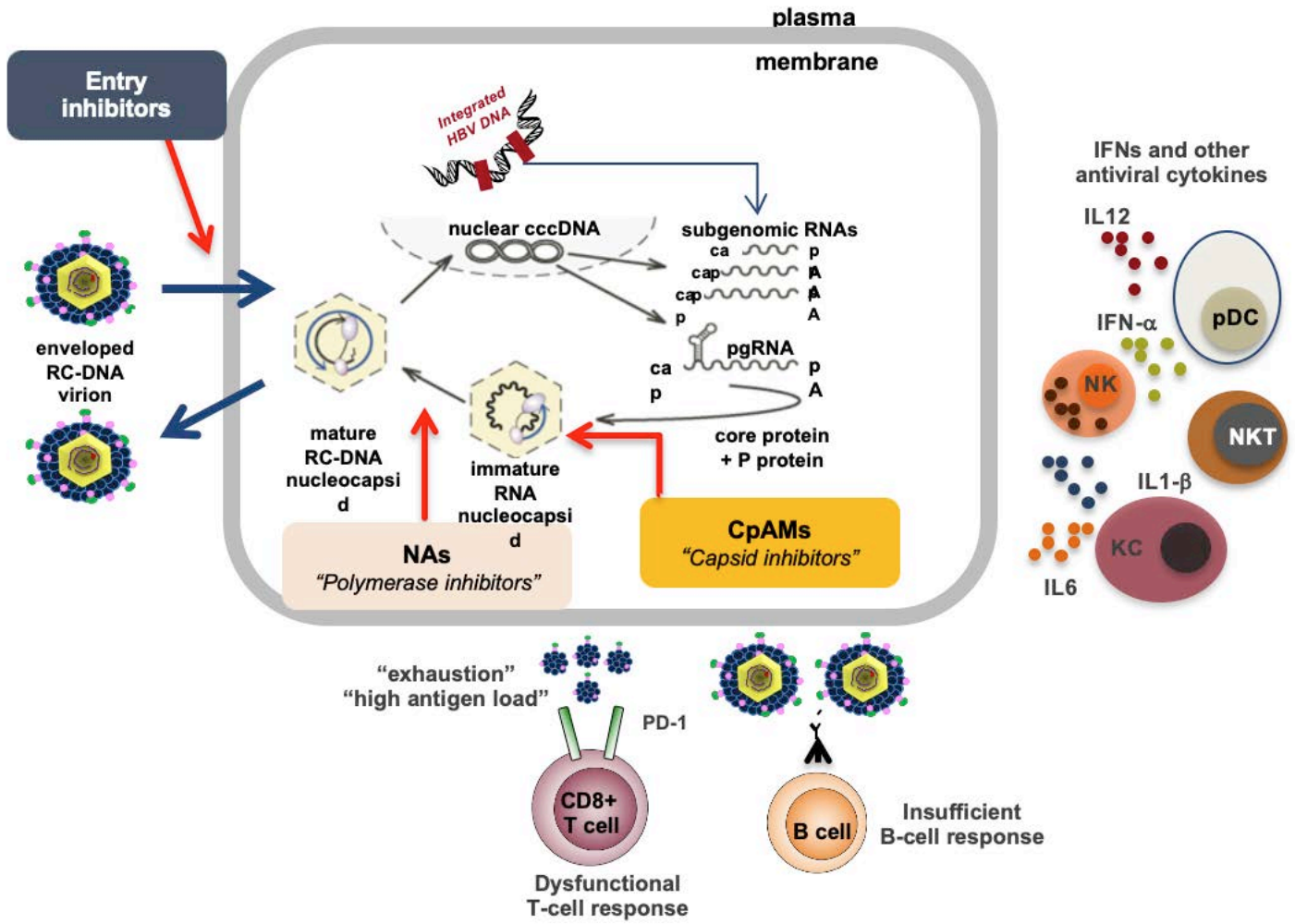
Lim SG et al, J Viral Hepatitis 2020 (in press)

Definitions of response

qHBsAg 2 log reduction leads to different outcomes depending on the baseline level



Pathways that inhibit/reduce intracellular HBV & replication



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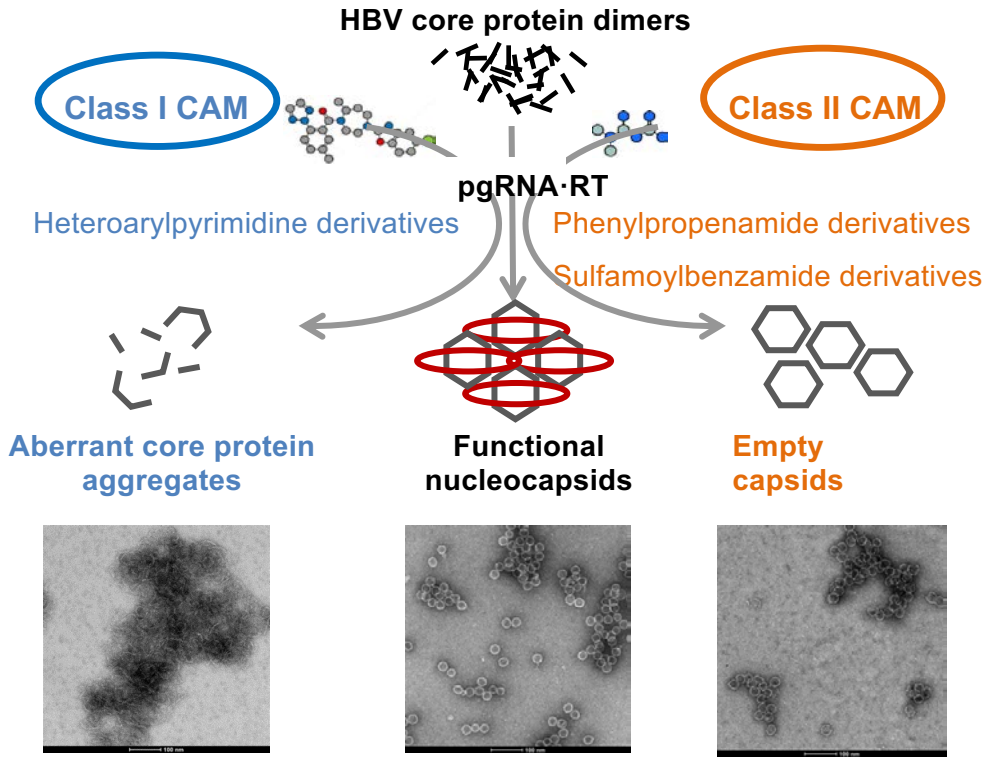
Capsid Assembly Modulators (CAMs)

CAM-I or A Class

- RO7049389
- BAY41-4109[1]
- HAP-12
- GLS4JHS
- HAP_R01
- SBA_R01
- RG-7907



Capsid assembly *in vitro* (electron microscopy)

CAM-II or N Class

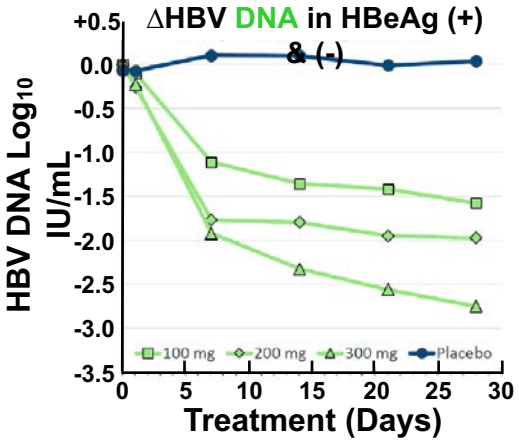
- NVR 3-778
- JNJ-379[2]
- JNJ-440[3]
- AT130
- AB-506[4]
- GLP-26
- ABI-H0731[5]
- ABI-H2158[6]
- ABI-H3733
- ALG-001024[7]
- ALG-001075[8]
- TBA #701[9]

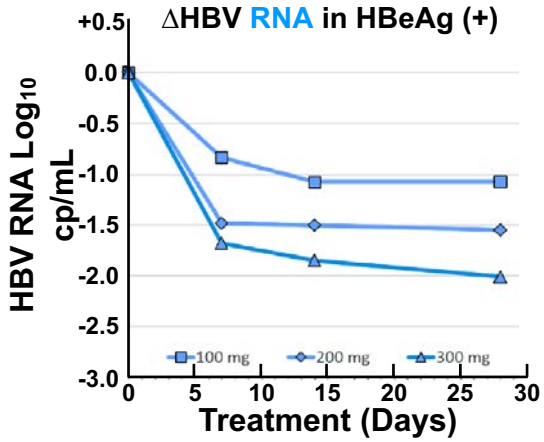
Antiviral Activity, Safety, and PK of ABI-H0731 in CHB (Study101B) without NA

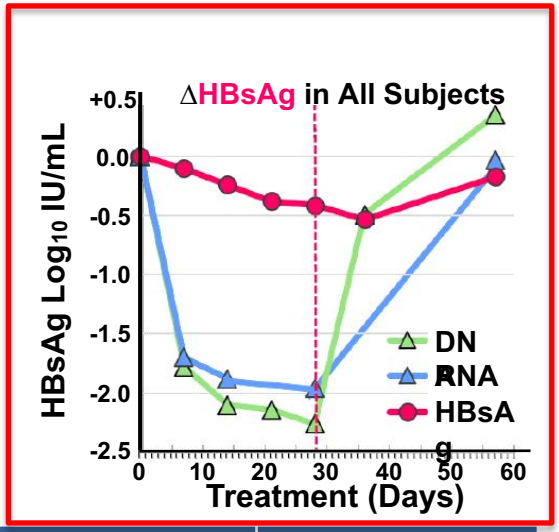
Study Design:

- Once Daily Dosing
- HBeAg (+), (-): 7:5
- Follow up for 28 days

Efficacy







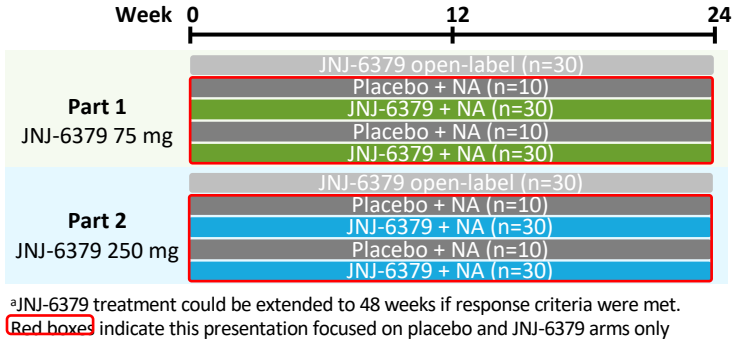
Safety

Adverse Event	100mg (N=10)	200mg (N=10)	300mg (N=10)	400mg (N=2)	Placebo (N=6)
Grade 1	9 (90%)	4 (40%)	6 (60%)	2 (100%)	4
Grade 2	0	0	0	0	0
Grade 3	0	0	0	1 (Rash)	0
ALT Flare	No ALT flare was observed during or post treatment				

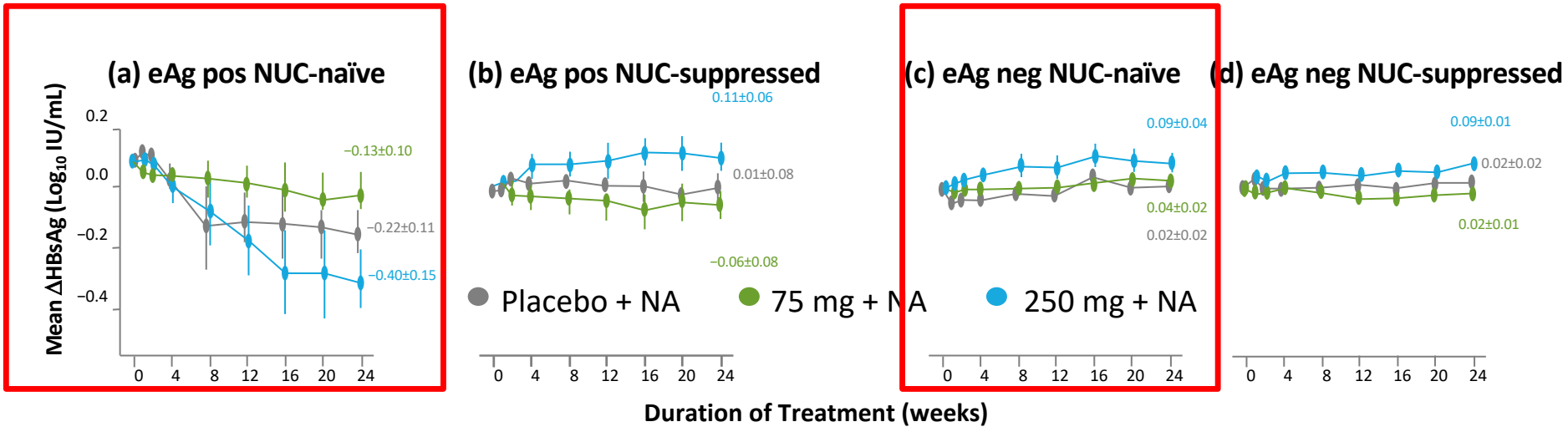
MF Yuen, 2018 AASLD-2018, Abstract 73

Treatment with 24 weeks CAM +NA

- Phase II JADE study of JNJ-6379 (CAM-N, class II)
  - 2 doses (75mg and 150mg) plus NUC
  - Monotherapy arms d/c due to breakthrough
  - Read out at 24 weeks
  - Primary endpoint is change in HBsAg level



[a]JNJ-6379 treatment could be extended to 48 weeks if response criteria were met.
Red boxes indicate this presentation focused on placebo and JNJ-6379 arms only

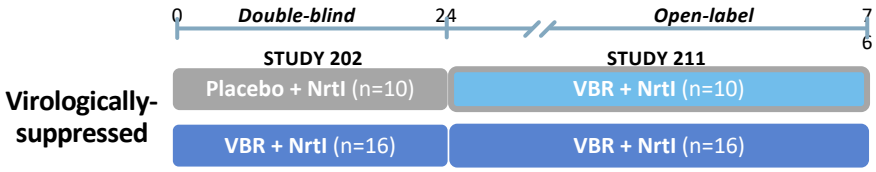


Janssen H, et al. EASL dILC2020. #LBP12

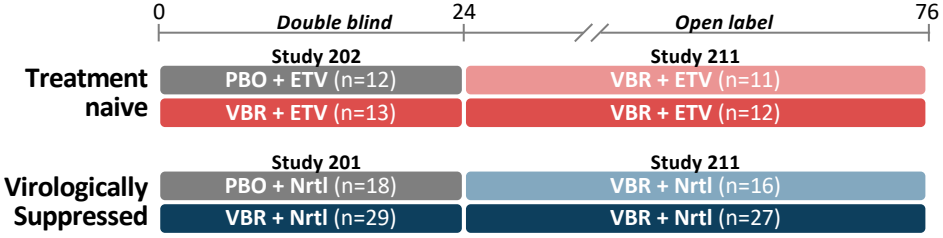
Treatment with 72 weeks CAM +NA

- Phase 2 open label extension study of Vebicorvir (ABI-H0713)
- Class II CAM

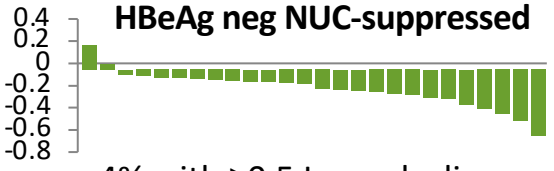
1. HBeAg negative CHB[1]



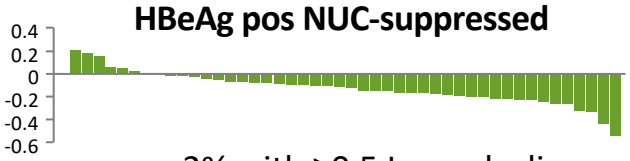
2. HBeAg positive CHB[2]



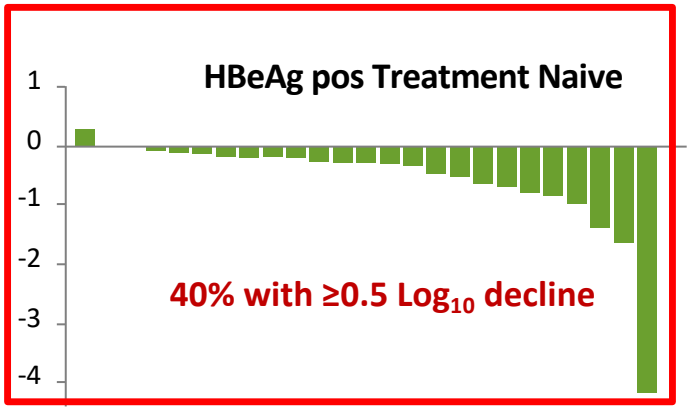
- Efficacy: HBsAg decline at end of 72 weeks VBR



4% with ≥0.5 Log_{10} decline



2% with ≥0.5 Log_{10} decline



[1] Fung S, et al. EASL dILC2020. #AS070
[2] Yuen M-F, et al. EASL dILC2020. #LBP30

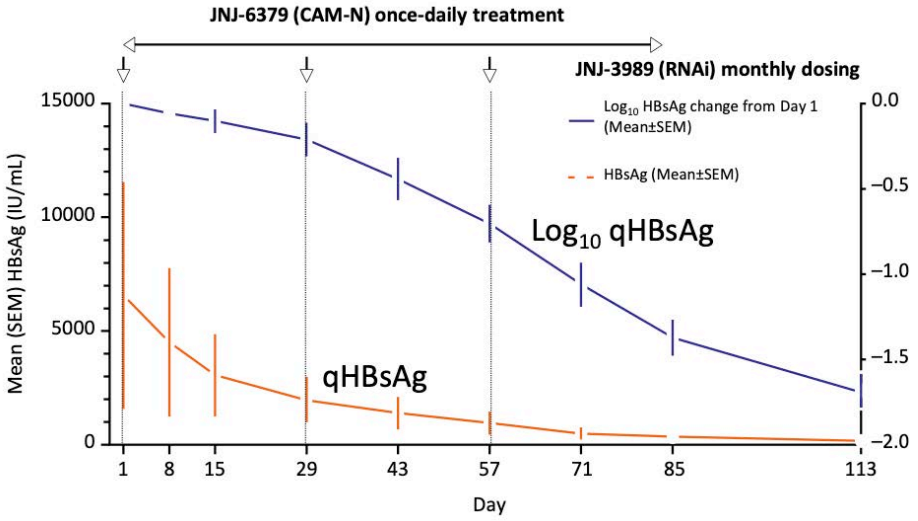
Efficacy of CAMs

Compound	Pharma	class	CHB	Duration & therapy	HBV DNA	HBV RNA	HBsAg
JNJ-56136379	Janssen	II	Not treated	24w +NA	↓4-5.89 log	↓3.13 log	↓0.4 log in HBeAg(+)
JNJ-56136379		II	Treated	24w +NA	NA	↓1.07 log	No change
ABI-H0731	Assembly	II	Not treated	75w +NA	50% LLOQ	NA	40%≥0.5 log↓
ABI-H0731		II	Treated	77w +NA	NA	NA	2%≥0.5 log↓
AB-506	Arbutus	II	Not treated	28d	↓2.8 log	↓2.4 log	No change

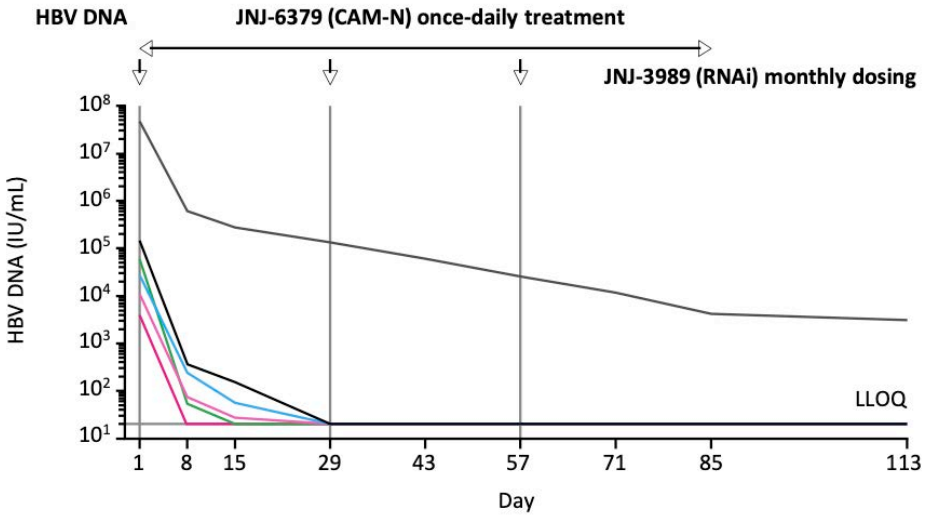
Janssen, LBP-012, EASL 2020
Sims, HepDART 2019
Yuen, EASL 2020

Triple therapy: NA+CAM+RNAi

HBsAg



HBV DNA



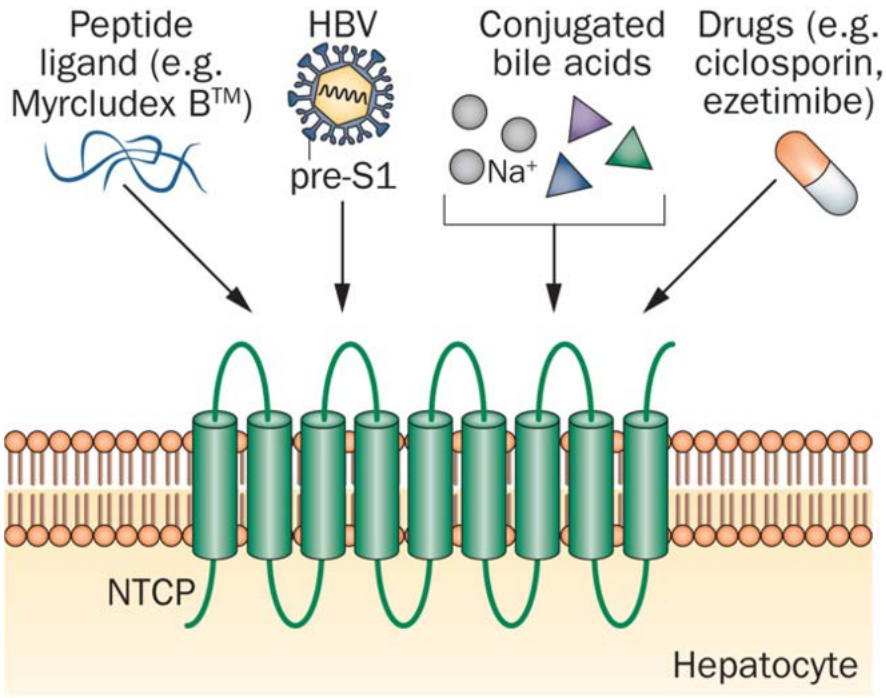
- HBeAg+ n=4 / HBeAg- n=8, NA-naïve n=5 / experienced n= 7, All 12 Asian
- Three 200 mg JNJ-3989 subcutaneous doses on Days 1, 29 and 57
- Oral JNJ-6379 250 mg once daily for 12 weeks (until Day 85)
- Started or already on ETV or TDF treatment on Day 1 to beyond the end of JNJ-6379 dosing
- Response rates similar between HBeAg+ and HBeAg-

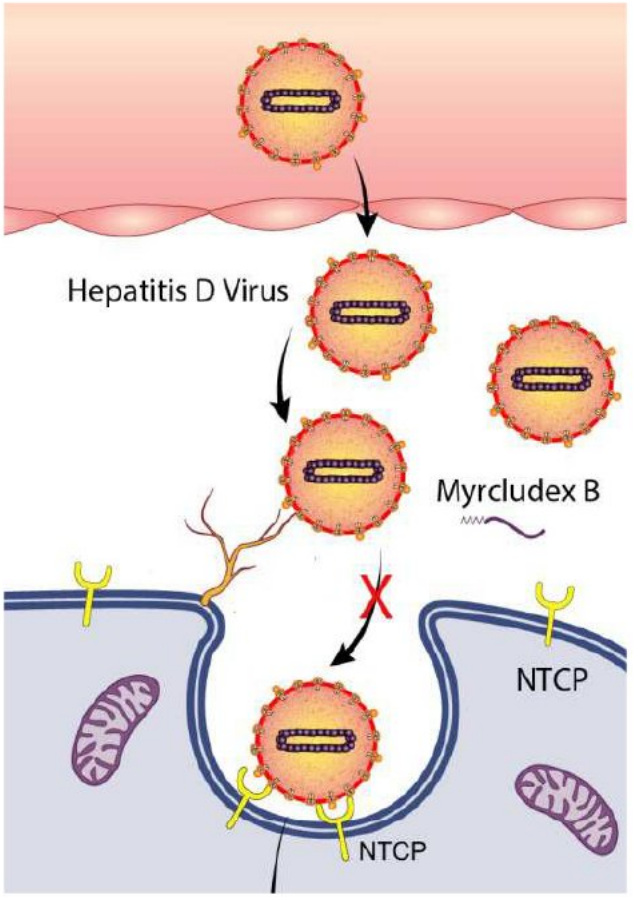
Yuen et al Abstract LP4, AASLD 2019

Summary

- CAMs are a new class of antiviral agents that disrupt capsid formation
- Early phase studies show reduction in HBV DNA and pgRNA but little change in qHBsAg levels
- Extended duration studies show that some patients may have reduction in qHBsAg
- Unlikely it can be used alone, more likely in combination

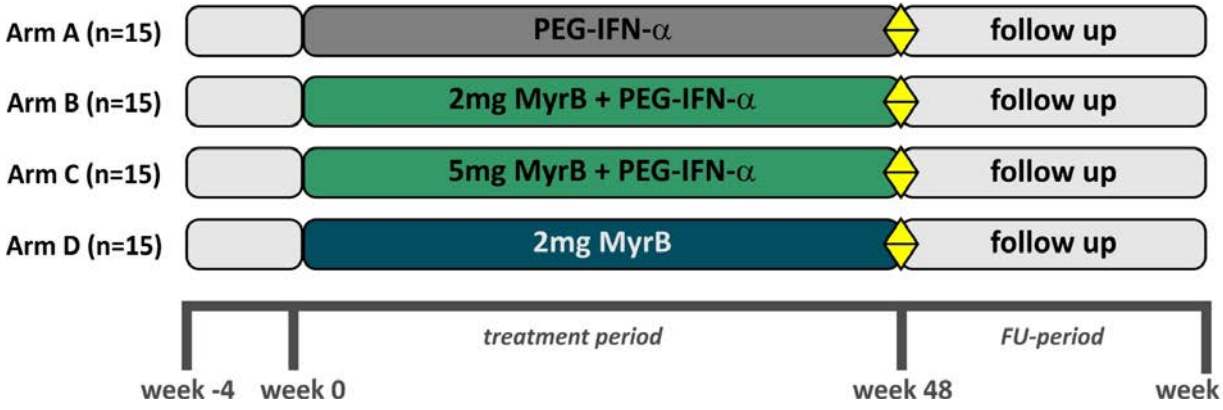
Entry inhibitors: Myrcludex



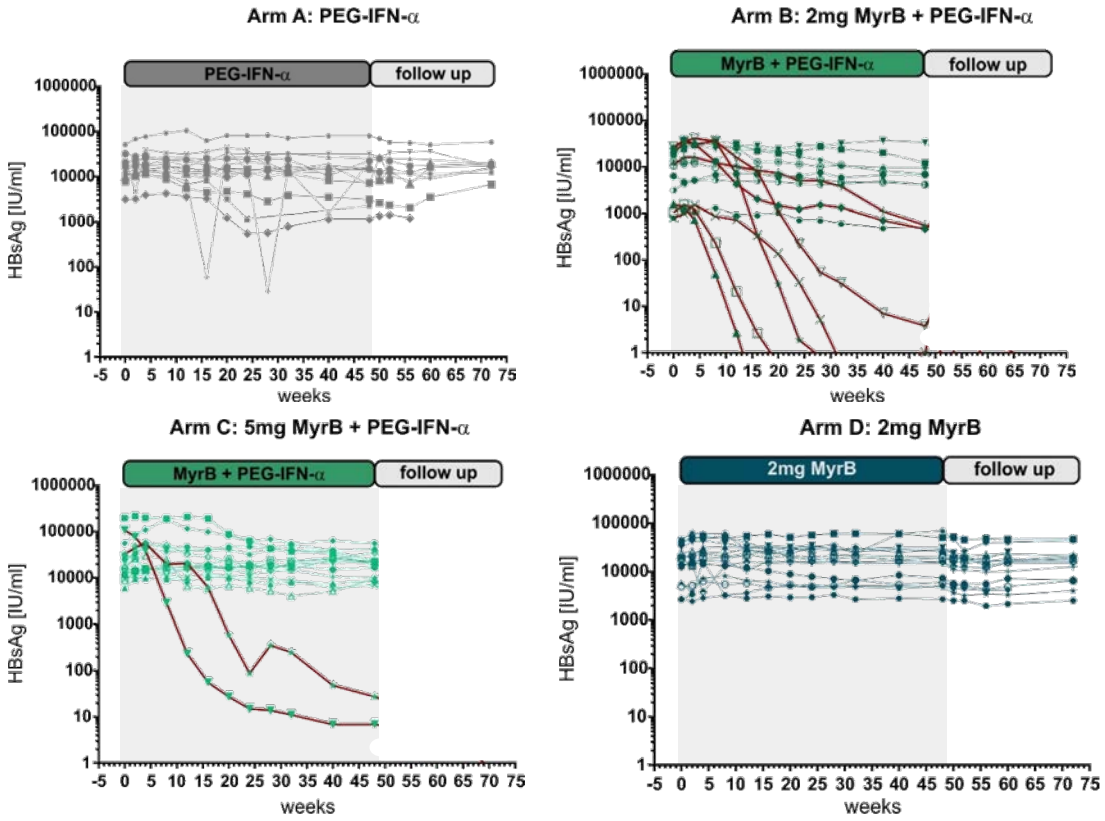


Myrcludex B is a synthetic lipopolypeptide consisting of a myristolylated pre-S1 domain of the large HBsAg with binding to the HBV entry receptor

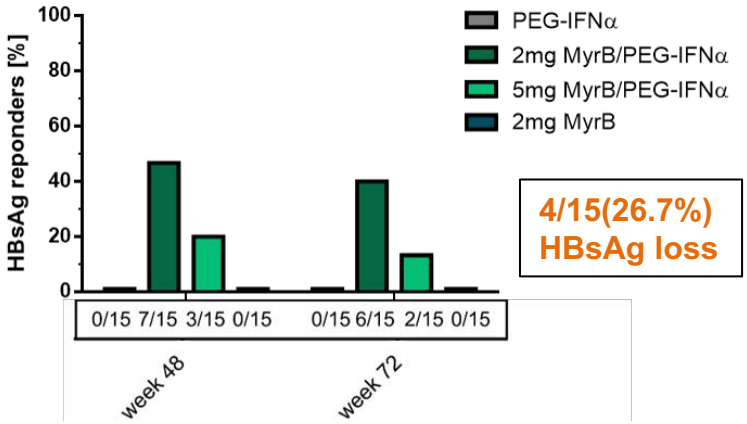
MYR203 Study for HBV-HDV co-infection



- 60 patients with chronic HBV/HDV co-infection were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 15 patients per arm
- MyrB was self administered by patients once daily s.c.



Definition of HBsAg Response (≥1log$_{10}$ decline or undetectable)

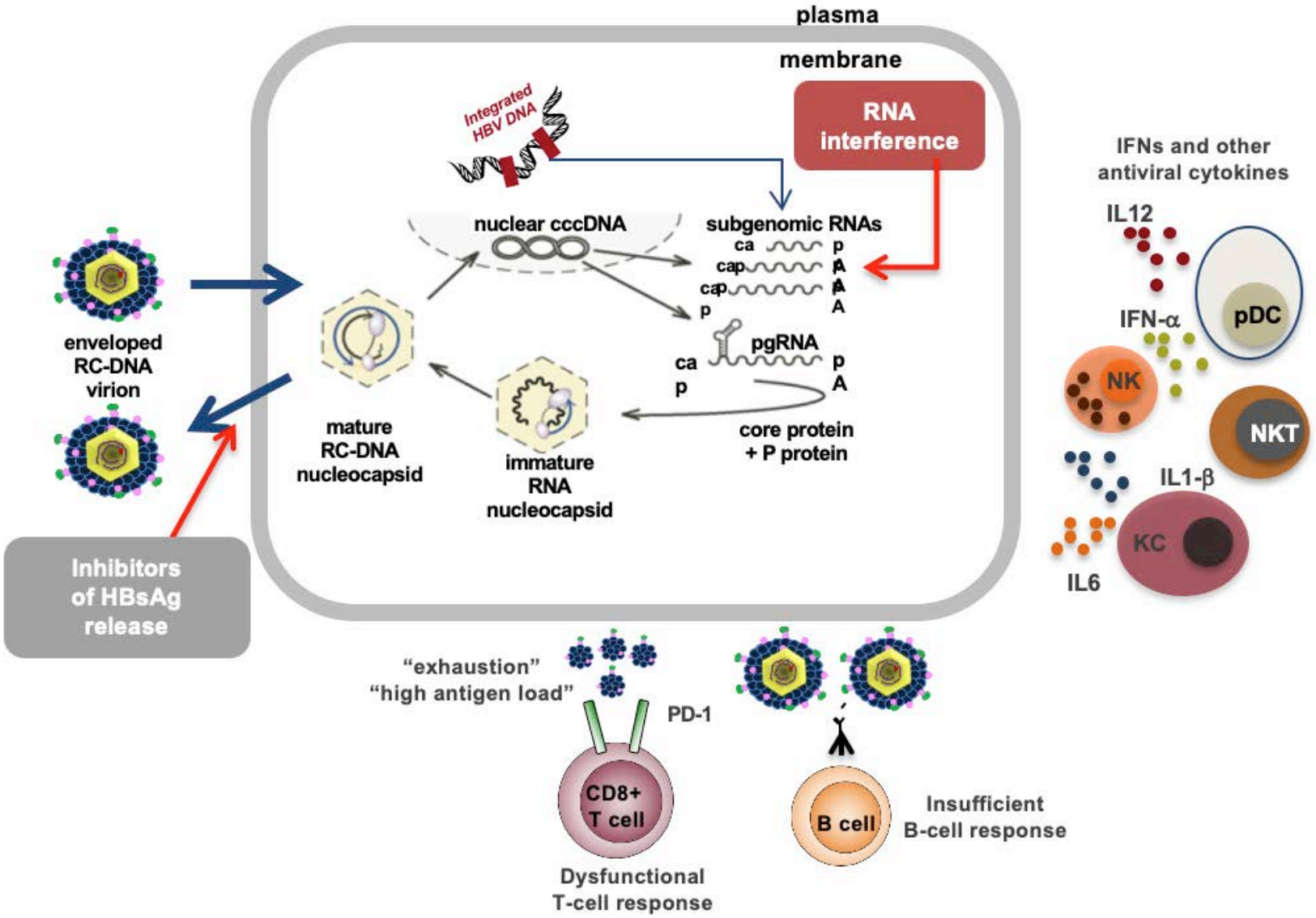


Wedemeyer, EASL 2019, OL-011

Summary

- Myrcludex B monotherapy (2mg sc/qd):
  - continuous linear HDV RNA decline and ALT reduction over 48 weeks
  - relapse in most patients (73.3%) after the end of therapy
  - However no significant reduction in qHBsAg
- Myrcludex B/PEG-IFNα combination therapy:
  - HDV RNA undetectable in 53.3% (2mg/PEG-IFNα) and 26.7% (5mg/PEG-IFNα) at week 72, and 0% (PEG-IFNα)
  - HBsAg response in 40% (2mg/PEG-IFNα; incl. 26.7% HBsAg loss) and 13.3% (5mg/PEG-IFNα) at week 72

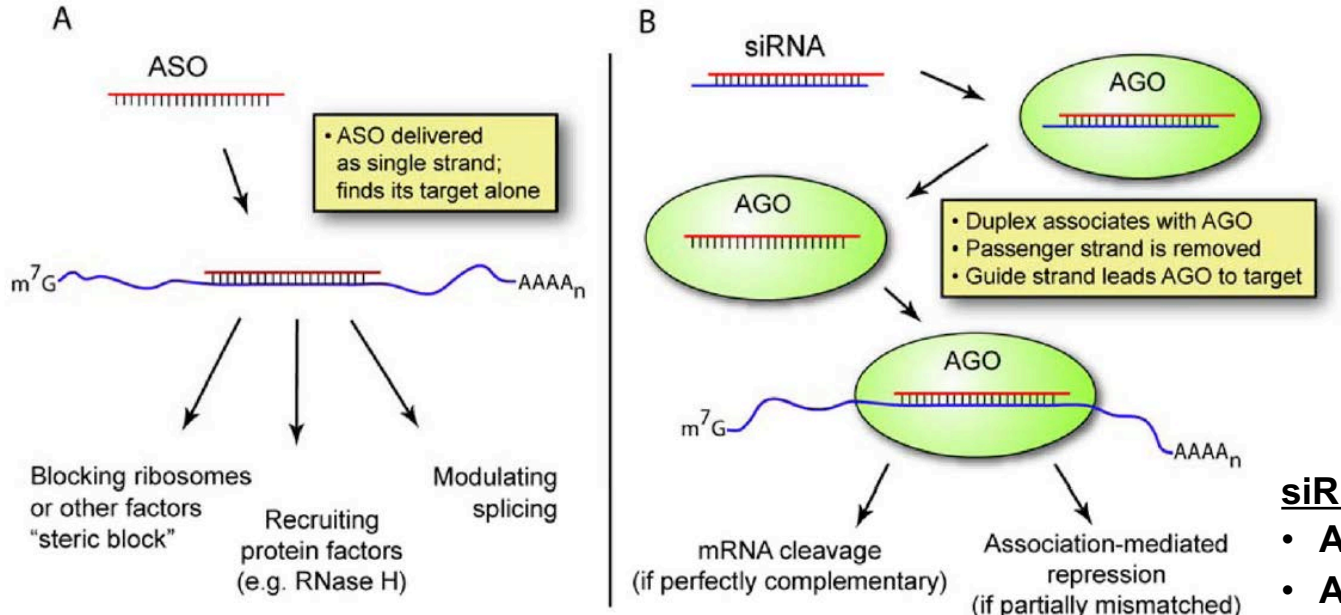
Pathway to reduce viral antigen production



CpAM: core protein allosteric modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK (T): natural killer (T cell); DC: plasmocytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor

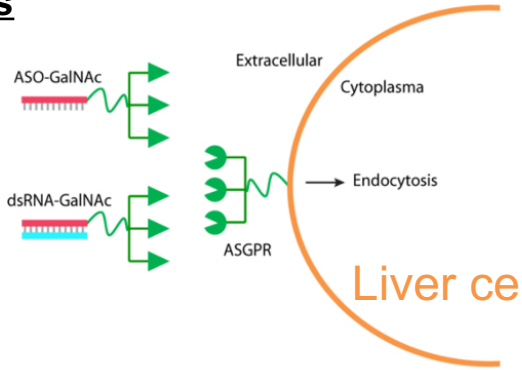
Adapted from: Levrero M, et al. Curr Opin Virol 2016;18:135–43;
)

RNA interference: ASO vs siRNA



Anti-Sense Oligo/LNAs

- **RO7062931**
- **GSK3228836**
- **GSK3389404**
- **ISIS 505358**



siRNAs

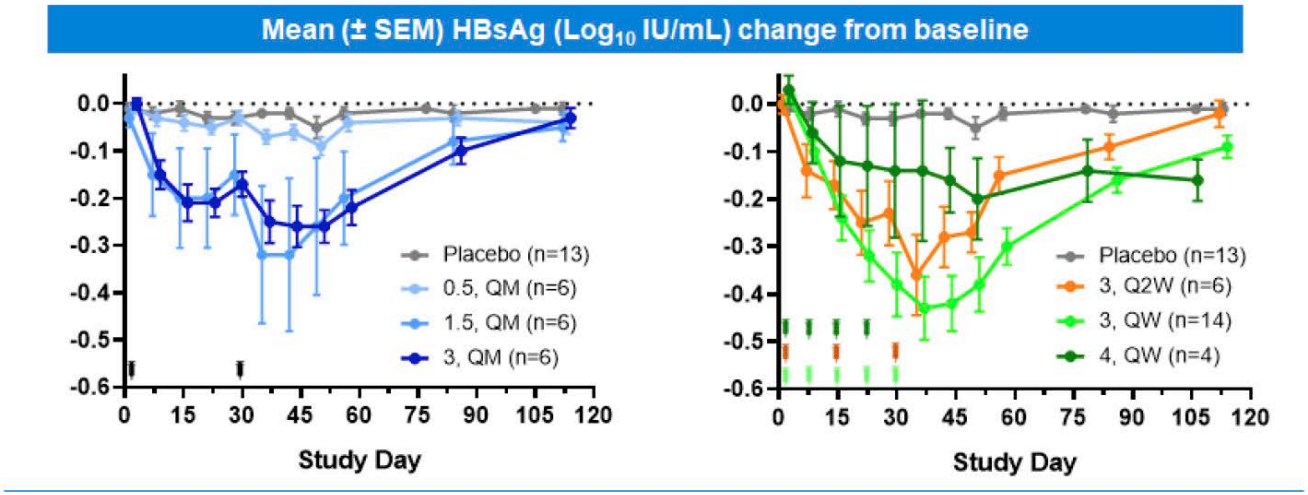
- **ARC-520**
- **ARC-521**
- **ALN-HBV**
- **ARB-1467**
- **ARB-1740**
- **AB-729**
- **ARO-B/JNJ-3989**
- **GalXC-HBVS/DCR-HBVS**
- **ALN HBV02/VIR-2218**

Mechanism of RNA interference: block production of viral proteins in a sustained manner esp HBsAg, hence reduce viral antigen burden, and HOPEFULLY allow recovery of immune cell exhaustion (not yet been demonstrated)

Watts, J Pathol. 2012 January ; 226(2): 365–379
Shen, Nucleic Acids Research, 2018;46(4):1584–1600

RO7062931: a liver-targeted, single-stranded oligonucleotide (SSO) with locked nucleic acid (LNA)

- RO7062931 is an SSO LNA targeting a highly conserved sequence in the HBV genome
- N-acetylgalactosamine(GalNAc) conjugation achieves liver-targeting through interaction



- RO7062931 treatment resulted in statistically significant* time-dependent HBsAg reductions compared to placebo for the 1.5 mg/kg and 3.0 mg/kg dose groups
- Maximum HBsAg decline typically occurred ~2wks post-treatment, with rebound to baseline levels by ~12wks post-treatment
- HBV RNA levels showed similar, although less profound and more variable, kinetics (data not shown)
- No significant changes were observed for HBcrAg levels (data not shown)

*90% Confidence Intervals for adjusted treatment differences from the statistical analysis (data not shown) did not include 0.

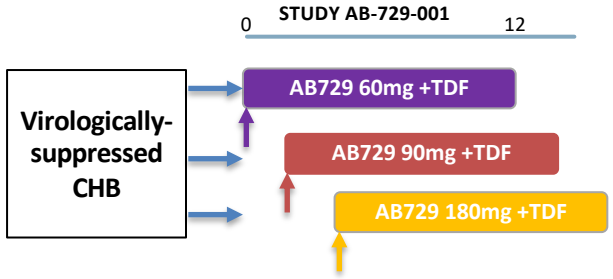
HBcrAg, hepatitis B core-related antigen

Short term therapy leads to reduction in qHBsAg<0.5 log followed by rebound

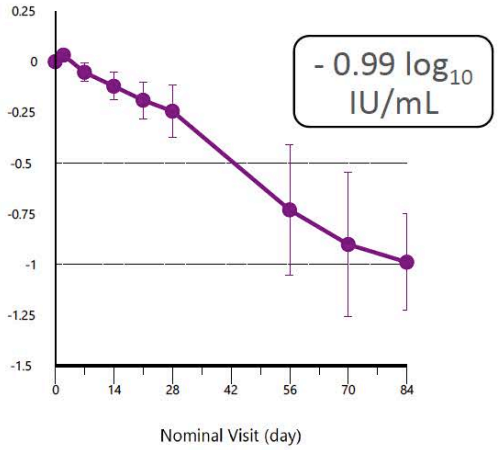
Yuen et al, EASL 2020

AB-729 RNAi Therapeutic

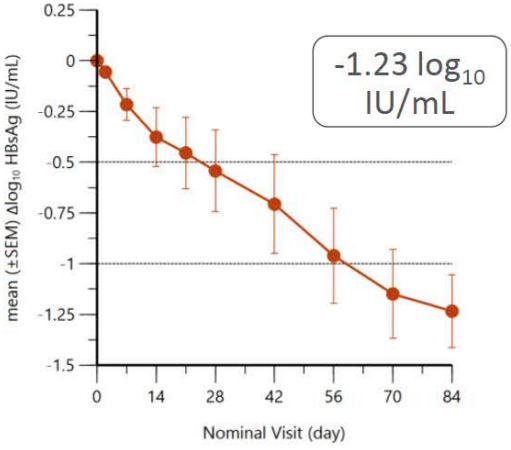
- Single trigger RNAi agent targeting all HBV transcripts
- Inhibits HBV replication and lowers all HBV antigens
- Pan-genotypic activity across HBV genotypes
- Demonstrated complementarity with capsid inhibitors
- GalNAc-conjugate actively targets the liver
- Active against cccDNA derived and integrated HBsAg transcripts



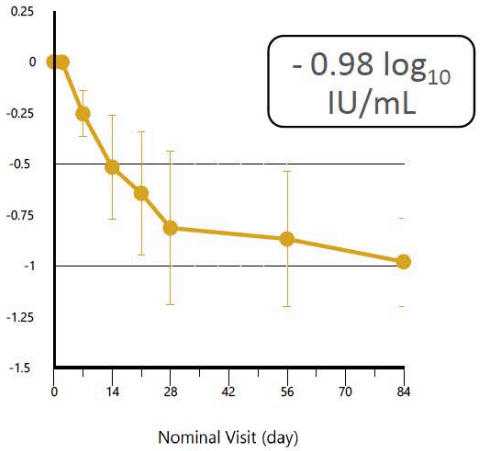
AB-729 60 mg (N=6)



AB-729 90 mg (N=6)



AB-729 180 mg (N=4)



60 mg week 6 data (N=2) excluded for consistency as Week 6 not collected in 180 mg cohort

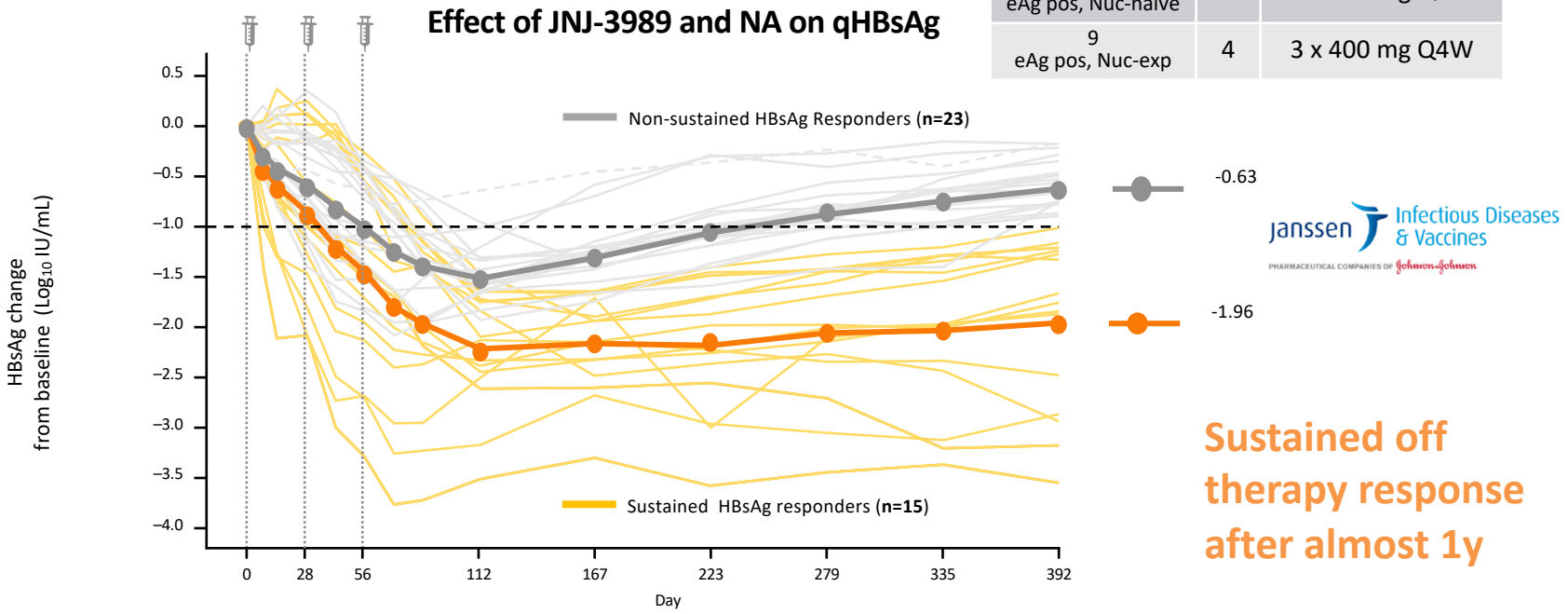
Comparable Mean HBsAg Declines with a Single 60 mg, 90 mg or 180 mg Dose of AB-729 at Week 12

Arbutus press release 2020

siRNA JNJ-3969 (ARO-HBV)

- 3 X Q4W doses of JNJ-3989 + NUC in CHB patients
- Extended follow-up to 1 year post-siRNA to assess long-term safety of siRNAs and also sustained responses in HBsAg, HBV RNA, HBeAg and HBcrAg

Cohort	N	Dose
2b	8	3 x 100 mg Q4W
3b	8	3 x 200 mg Q4W
4b	8	3 x 300 mg Q4W
5b	8	3 x 400 mg Q4W
8 eAg pos, Nuc-naive	4	3 x 300 mg Q4W
9 eAg pos, Nuc-exp	4	3 x 400 mg Q4W

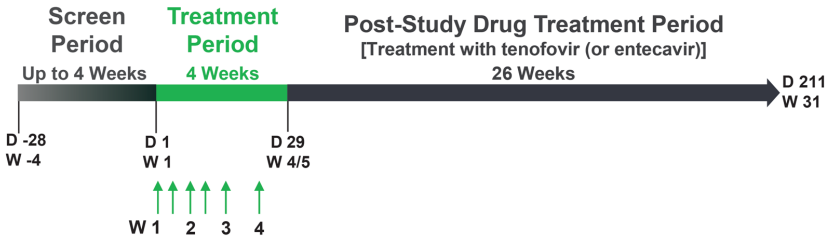


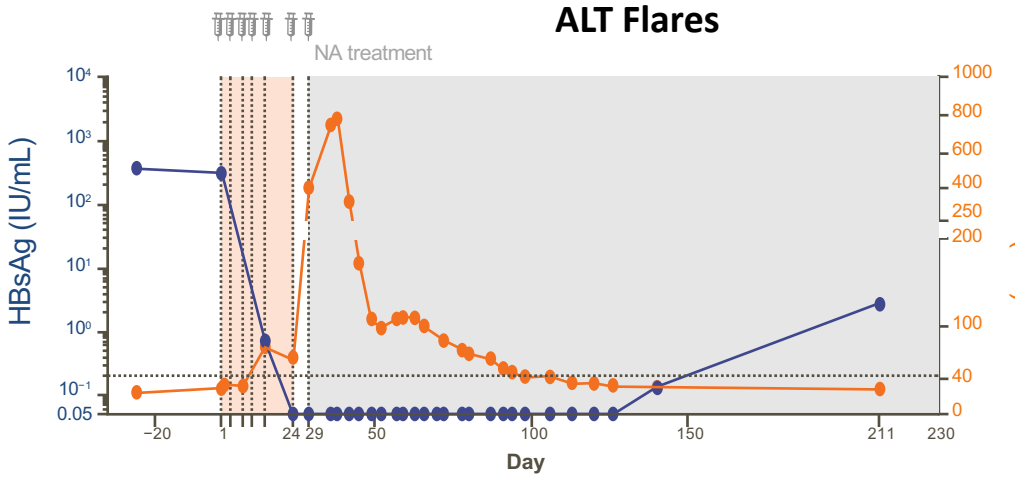
- **Efficacy: HBsAg Response (n=40)**
- 85% had ≥ 1 log reduction during treatment.
- 39% had ≥1 log reduction at 48 weeks post-dose; i.e. were sustained HBsAg responders
- **Off-Treatment Sustained HBsAg Responder**
- ≥1 Log_{10} IU/mL reduction in HBsAg from at Day 392

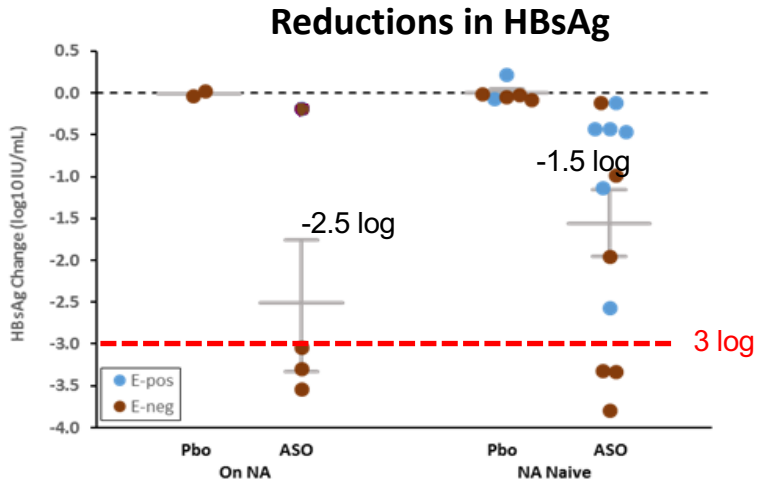
Gane E, et al. EASL dILC2020. #GS10

ASO ISIS 505358 (GSK)

- Naked (non-Gal-NAC) conjugated ASO
  - 300mg Loading and frequent dosing over 28 days
  - NUC-naïve (12) and suppressed (4); HBeAg pos and neg







- 4 patients had levels falling below the limit of quantification (qHBsAg<0.05 IU/ml).
- **Prolonged HBsAg loss was observed in 2 patients:**
  - **one-NA treated patient (from Day 36 to Day 113)**
  - **one NA-naïve patient (from Day 23 to Day 126).**

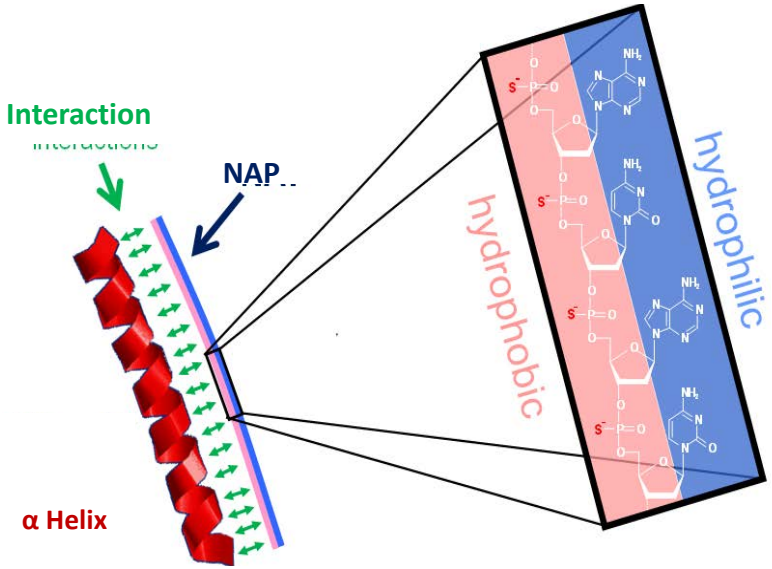
Yuen M-F, et al. EASL dILC2020. #AS067

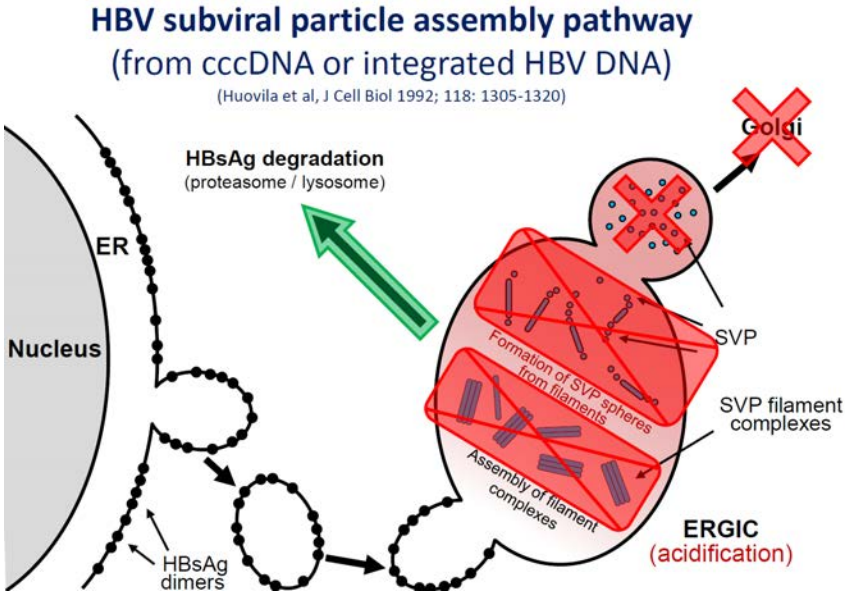
Summary

- RNA interference is directed to reduce production of viral proteins, esp HBsAg
- Needs to be given by injection
- Studies of extended followup after limited treatment show sustained suppression of HBsAg for over one year
- Proof of sustained HBsAg loss demonstrated
- There have been associated ALT flares with reduction in qHBsAg
- Most likely it will be best used in combination therapy

Nucleic Acid Polymers (NAPs)
S-antigen traffic-inhibiting oligonucleotide polymers (STOPs)

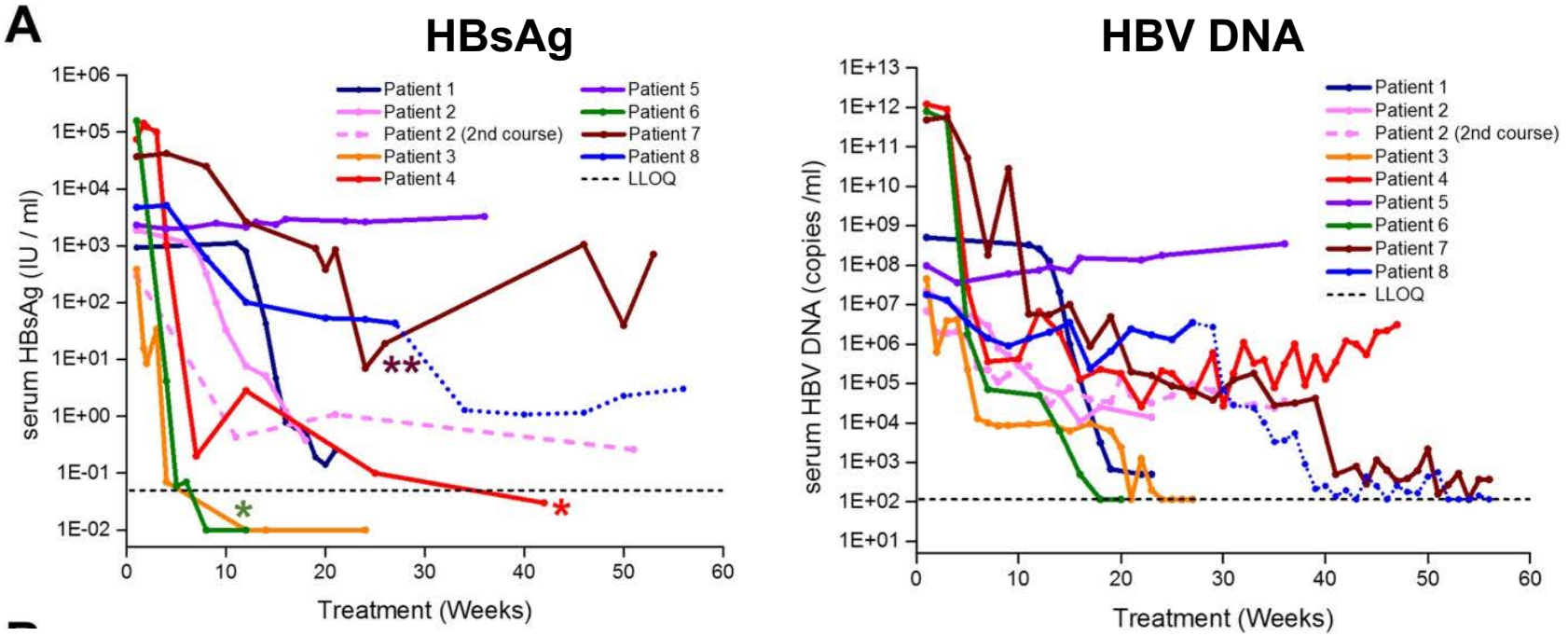
Company	Investigational New Drug	Clinical Trial
Replicor Inc.	REP-2139	Phase 2
Replicor Inc.	REP-2165	Phase 2
Replicor Inc.	REP-2055	Phase 1





Bazinet M, EASL-2017, #LBP-507

Efficacy results with REP 9AC monotherapy



REP 2055 was given by IV infusion 400mg weekly for 40w

Number of patients	Number with sustained off therapy responses	No with viral relapse req rescue or re-treatment
8 HBeAg negative CHB	2 (25%)	5*

* One patient lost to followup

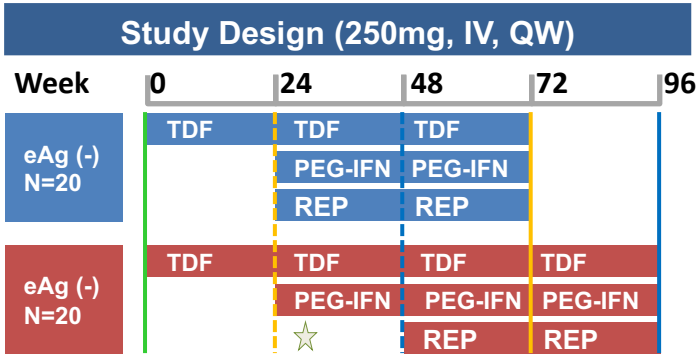
Al-Mahtab, PLoS One. 2016; 11(6): e0156667.

Nucleic Acid Polymers (REP-2139, 2165): Study 401

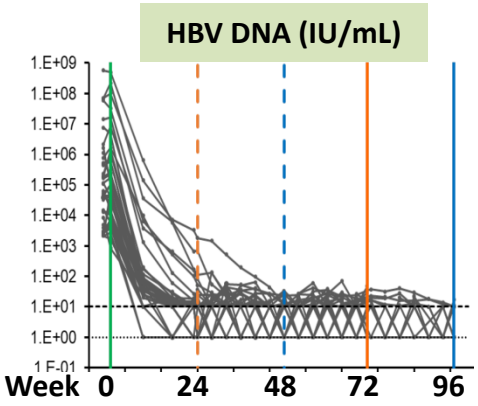
REP 401 is a randomized, controlled trial assessing safety and efficacy of REP+TDF+PEGIFN in HBeAg (-) CHB.

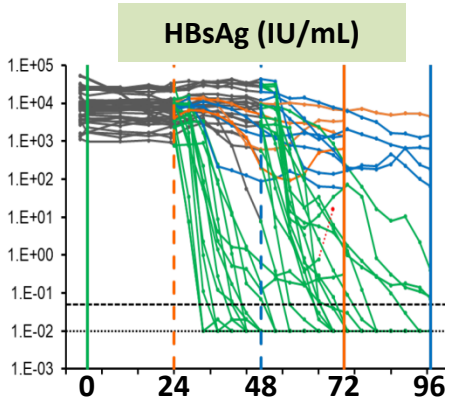
IND	NAP Sequence Design	Stable
REP-2139	ACACACACACACAC ACACACACACACAC ACACACACACAC	93%
REP-2165	ACACACACACA*CAC ACACACACACACAC ACACACACACAC	89%

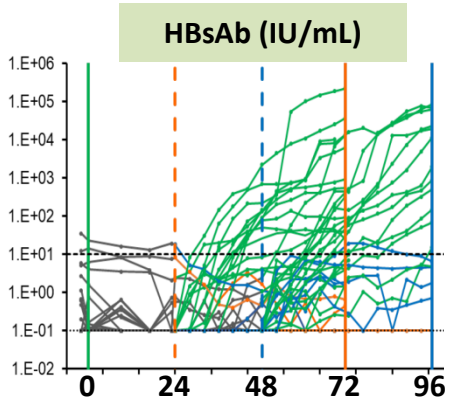
*Replacement of 2'Ome with 2'OH at 11, 21 and 31

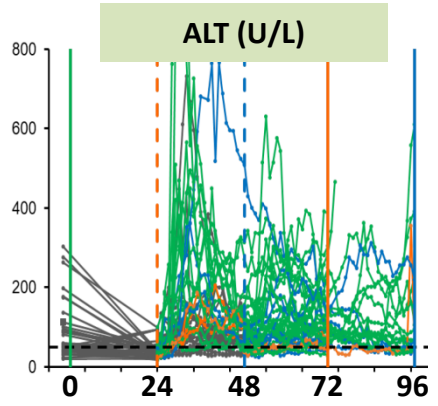


BL Factor	Study Arm	Ctrl Arm
Age (m/m)	36.9/36.0	38.6/39.5
Sex (M/F)	17/3	16/4
GT (A/D)	1/19	2/18
F (1/2/3/4)	12/4/0/4	10/7/2/1
HBsAg/Ab (IU/mL)	9300/0.1	8700/0.1
HBV DNA (IU/mL)	$3.6x10^7$	$4.8x10^6$









Bazinet M, Gastroenterology 2020;158(8):2180-2194

Final REP 401 outcome summary

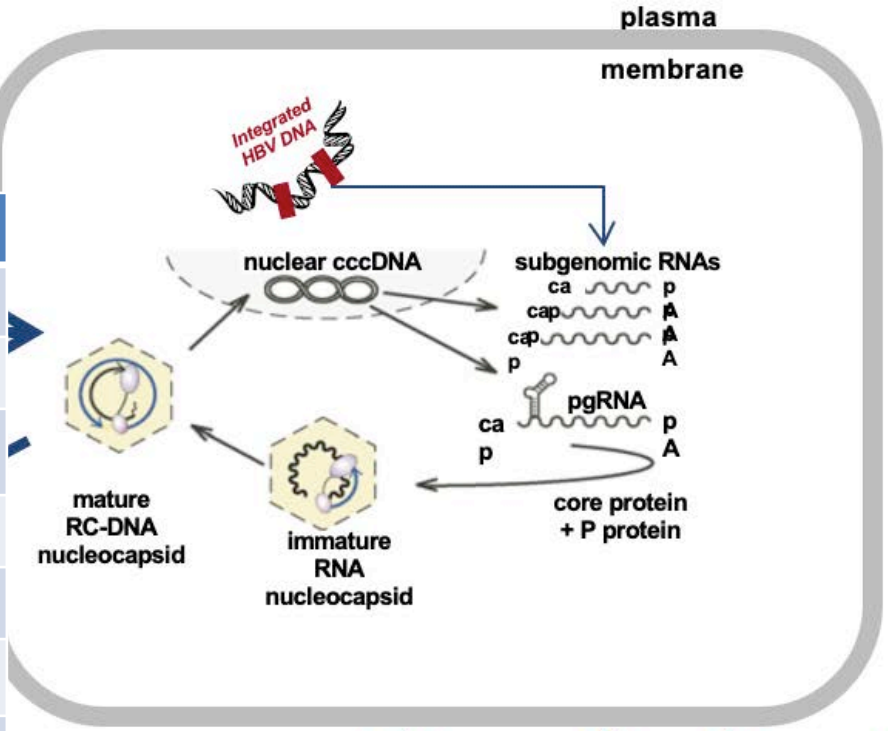
Completed treatment and ≥ 24 weeks of follow-up		35 (32 completed 48 weeks of follow-up)
Clinical response	Normal ALT	91%
	Normal median hepatic stiffness	57%
HBsAg response	< 1000 IU/mL	74%
	< 1 IU/ml	51%
	≤ LLOQ (0.05 IU/mL)	43%
	Seroconversion	54%
HBV DNA response	≤ 2000 IU/mL	83%
	< 100 IU/mL	63%
	Target not detected (TND)	49%
Virologic response	**Functional control** **(HBV DNA ≤ 2000 IU/mL, normal ALT)**	**43%**
	Functional cure **(HBsAg < LLOQ, HBV DNA TND, normal ALT)**	**40%**
	Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	**83%**

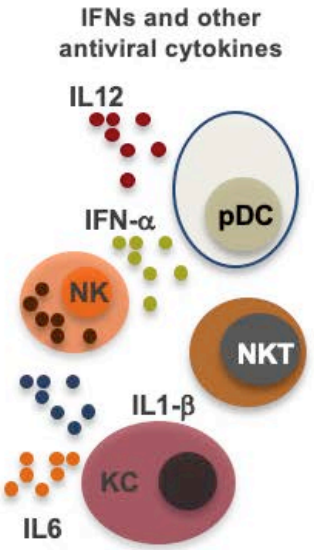
Summary

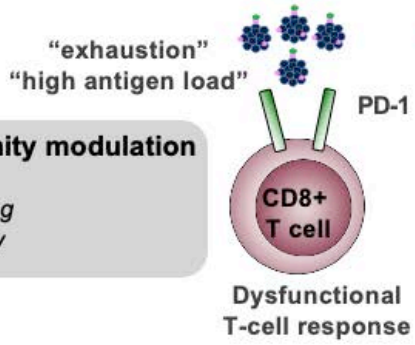
- This novel treatment shows promise even as monotherapy
- Impact of TDF+pegIFN has limited impact on HBsAg reduction until addition of NAP
- Combination therapy with NA and pegIFN has demonstrated functional cure in 40%

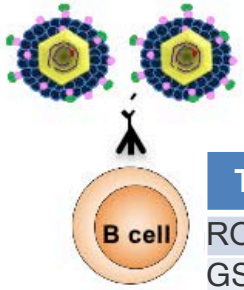
Immune Modulation

Therapeutic Vaccines	
AIC 649	AiCuris, Germany
INO-1800	Inovio, USA
HB-110	Ichor Med Systems with Janssen, USA
TG1050	Transgene, France
HepTcell	Altimmune, USA
HB-110	Ichor Medical Genexine, USA
VTP-300	Vaccitech, USA









Adaptive immunity modulation
- *Anti-PD-1 mAb*
- *TCR engineering*
- *Vaccine therapy*

Innate immunity modulation
- *Toll-like receptor agonists*
- *Interferon*

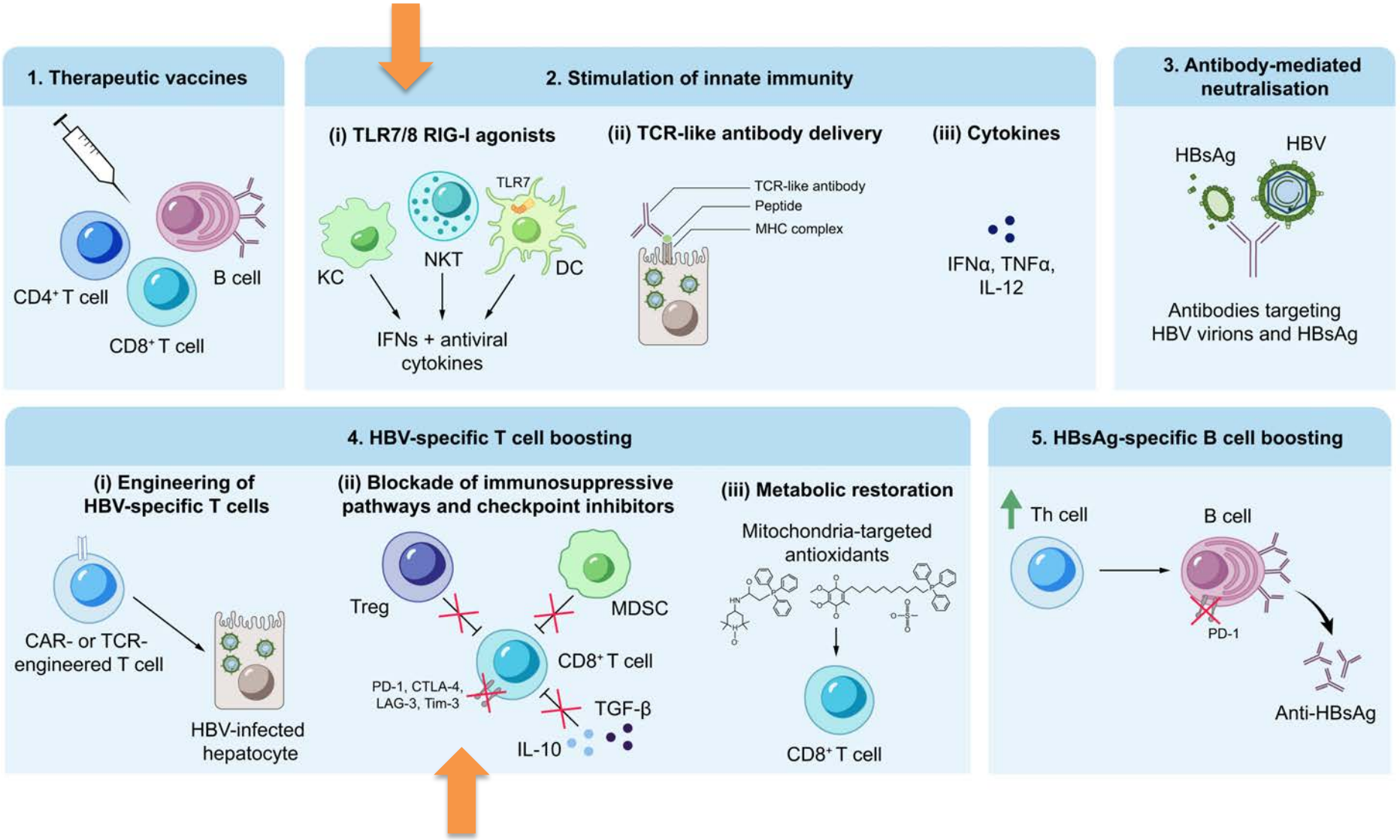
TLR agonists		
RO6864018	TLR-7 agonist	Roche
GS 9688	TLR-8 agonist	Gilead Sciences

Checkpoint inhibitor		
nivolumab	PD-1inhibitor	BMS

Adapted from: Levrero M, et al. Curr Opin Virol 2016;18:135–43

CpAM: core protein allosteric modulators; HBx: hepatitis B X protein; IFN: interferon; IL: interleukin; KC: Kupffer cells; mAb: monoclonal antibody; NA: nucleos(t)ide analogue; NK (T): natural killer (T cell); DC: plasmocytoid dendritic cell; PD-1: programmed cell death-1; TCR: T cell receptor

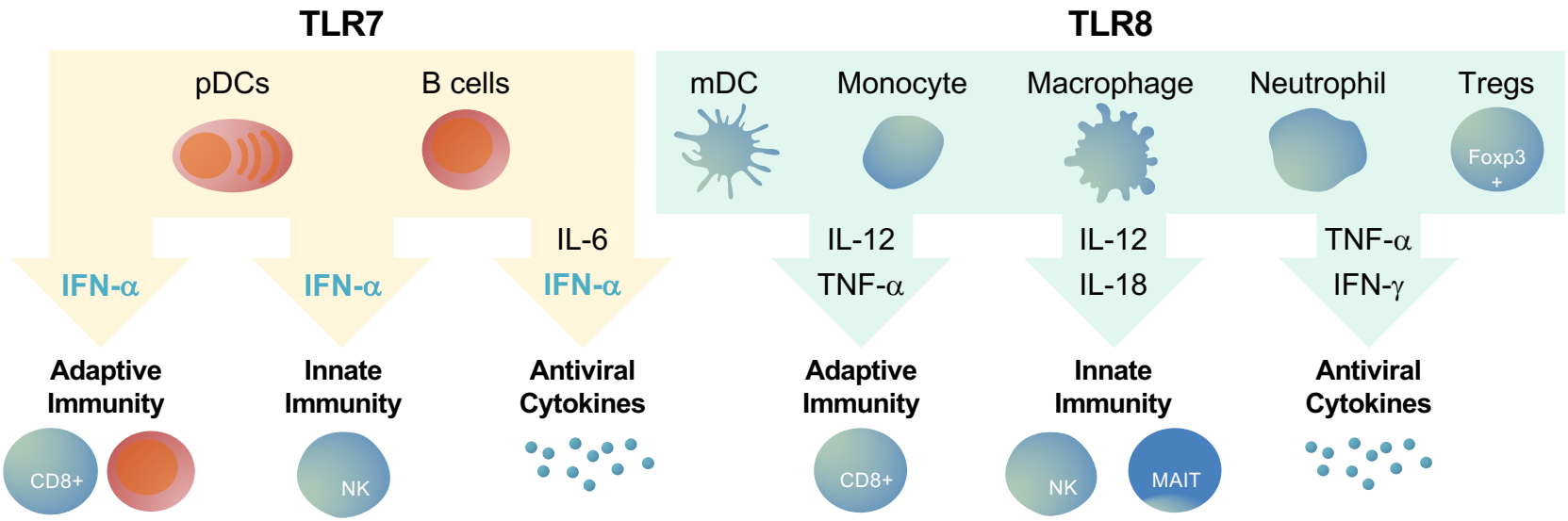
Overview of immune modulation therapies for HBV



Tout, J Hepatology 2020 73(2): 409-422

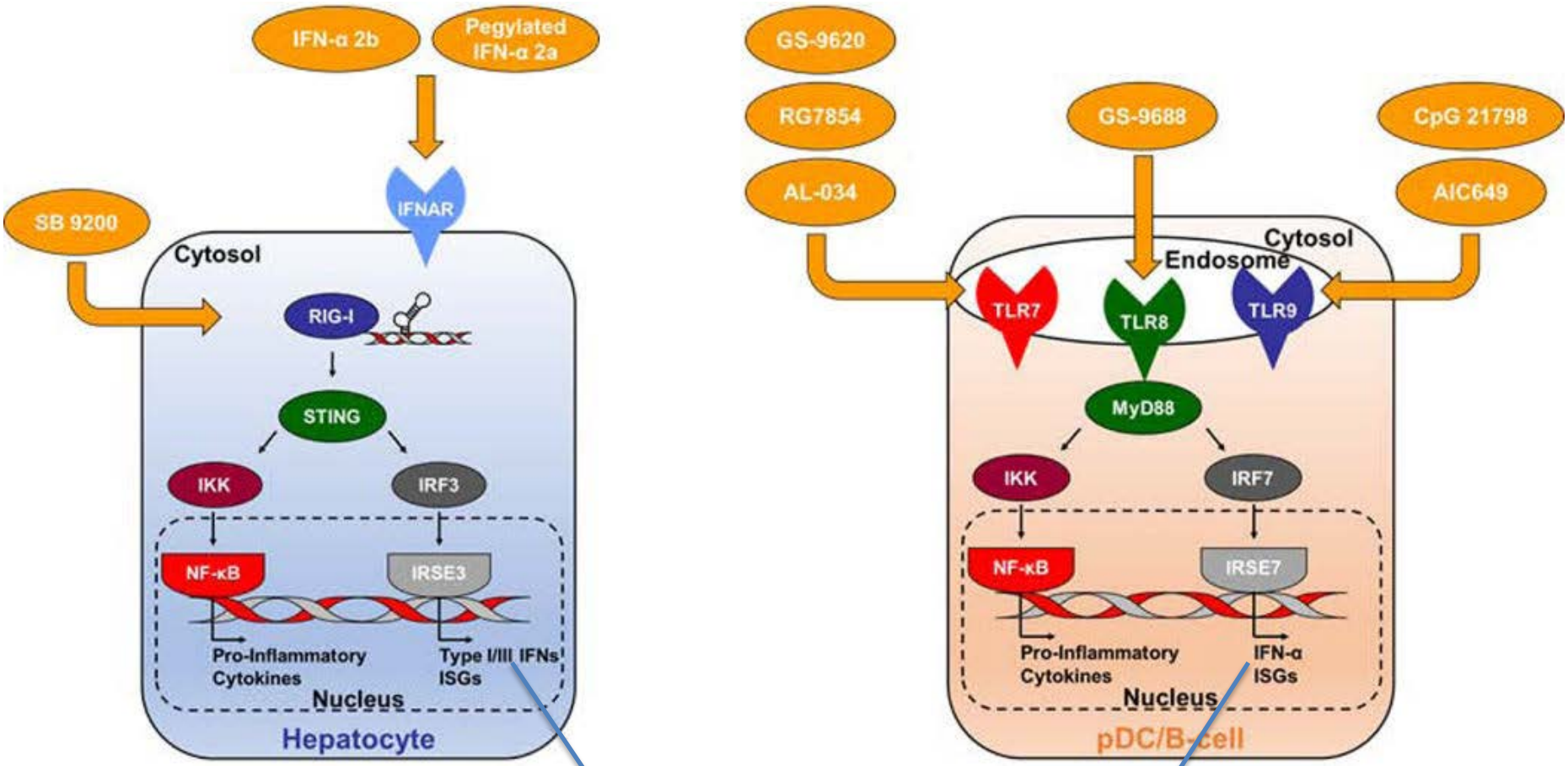
Toll-like Receptor Agonist Mechanism of Action

- TLRs are PRRs that recognise pathogen-associated molecular patterns
- Crucial for early host response and linking innate with adaptive responses



IFN, interferon; IL, interleukin; MAIT, mucosal-associated invariant T cells; mDC, myeloid dendritic cells; NK, natural killer cells; pDCs, plasmacytoid dendritic cells; PRR, pattern recognition receptor; TNF, tumor necrosis factor; Tregs, regulatory T cells. 1. Schurich A, et al. PLoS Pathog 2013;9(3):e1003208;
2. Du H, et al. Vaccine 2013;28;31:4209-15; 3. Jo J, et al PLoS Pathog 2014;10:e1004210; 4. Isorce N, et al. Antiviral Res 2016;130:36-45.

Activation of Innate Immunity in HBV

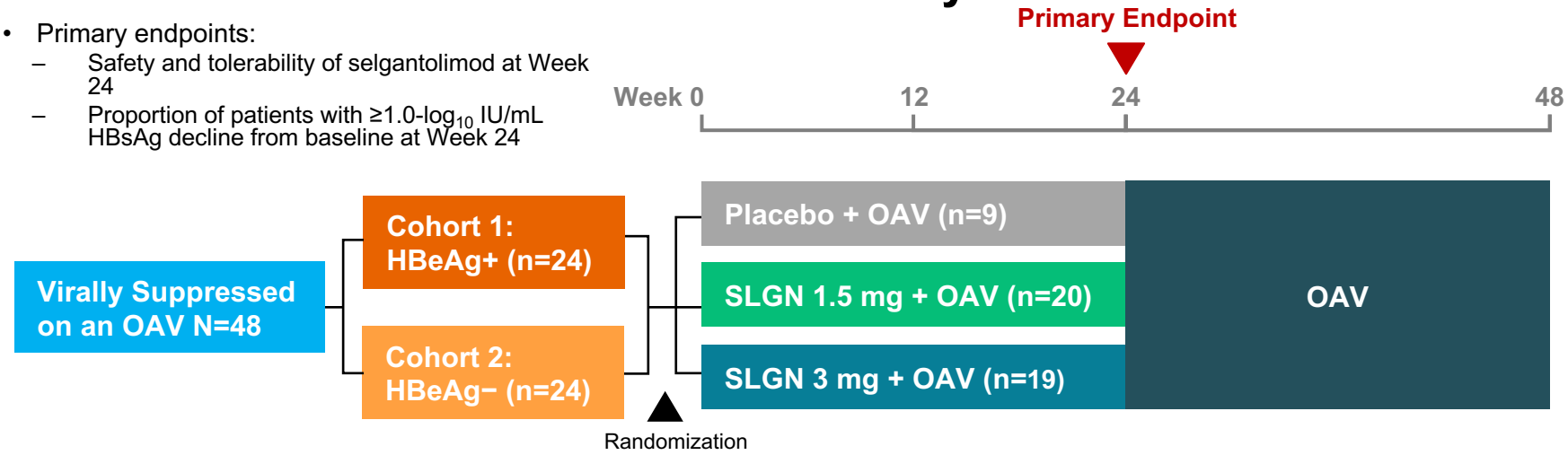


Common requirement to act via IFN pathway

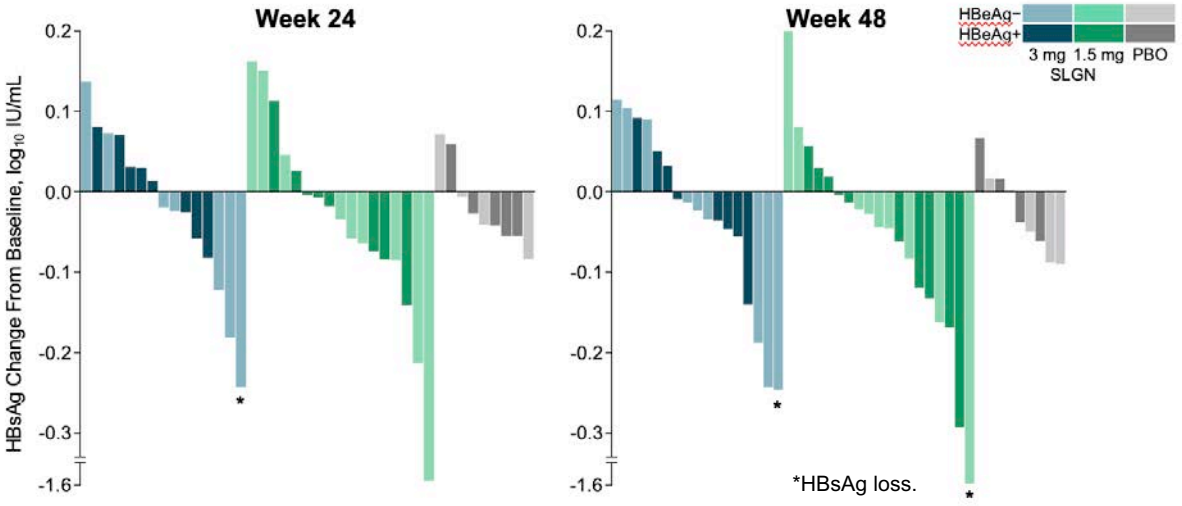
Suslov, Curr Opin Virol. 2018 June ; 30: 9–17

Efficacy and Safety of Oral TLR8 Agonist Selgantolimod (GS-9688, SLGN) in Virally Suppressed Adult Patients with CHB: Phase 2 study

- Primary endpoints:
  - Safety and tolerability of selgantolimod at Week 24
  - Proportion of patients with ≥1.0-$\log_{10}$ IU/mL HBsAg decline from baseline at Week 24



Individual HBsAg Change From Baseline At Week 24 and 48



In SLGN-treated patients, HBsAg was sustained or continued to decline during the 24 weeks of post-treatment follow up HBsAg decline ≥0.1-$\log_{10}$ IU/mL was observed only in SLGN-treated patients

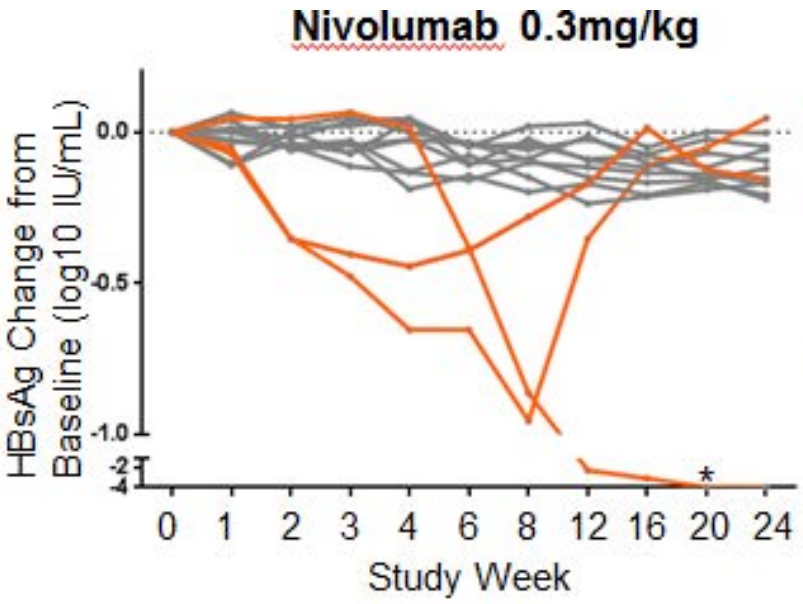
- 2/39(5%) patients had HBsAg loss
- However the reduction in qHBsAg overall was<1 log
- One patient with HBsAg loss had only ~0.25 log reduction

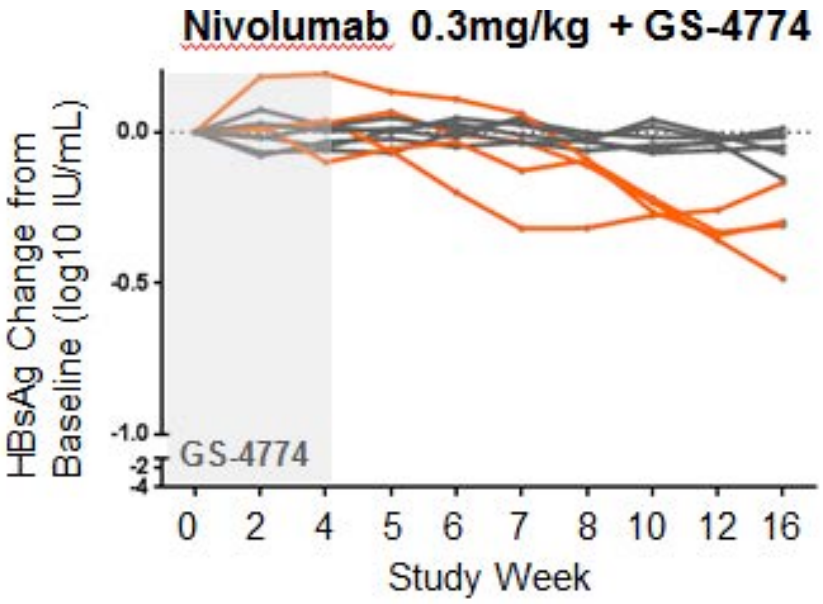
OAV, oral antiviral; TLR, toll-like receptor.
Gane E, et al. EASL 2020. 71

Adaptive immunity: restoration of exhausted T cells: PD-1 inhibition

Nivolumab: Monoclonal antibody against PD-1 Approved for solid organ tumors and lymphomas

GS-4774: Heat-inactivated yeast-based therapeutic T-cell vaccine developed for CHB



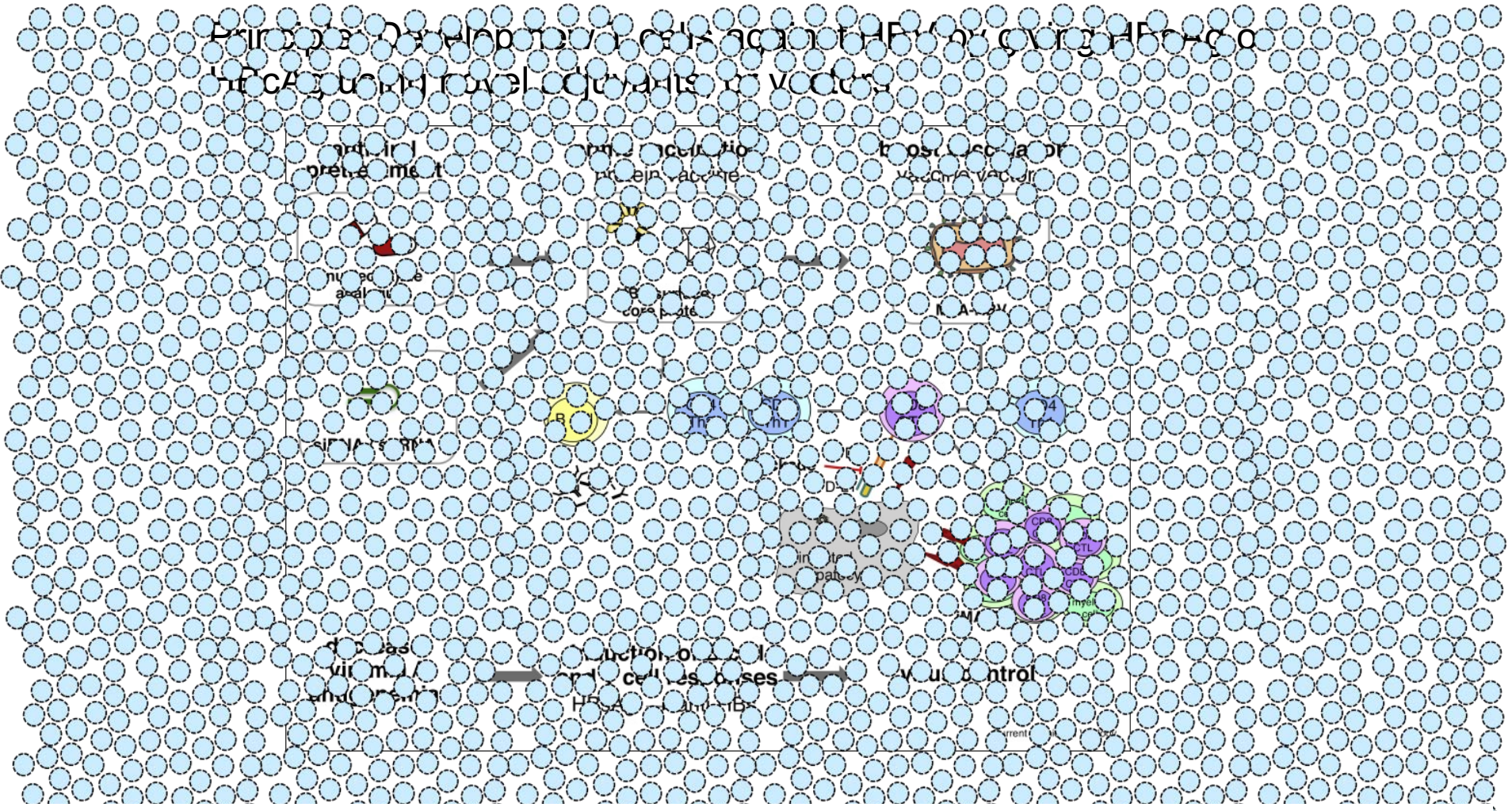


1/10 patients had HBsAg seroclearance

0/12 patients had HBsAg seroclearance

Gane, EASL 2017

Therapeutic Vaccines: can they work?



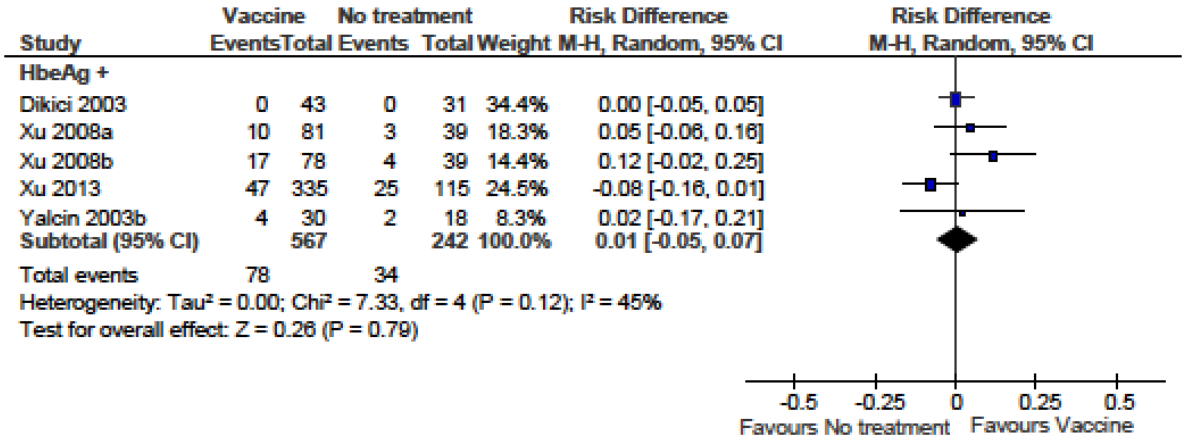
Problem: overcoming immune tolerance to HBV due to huge HBsAg antigen load

Kosinska, Protzer et al, Current Op Virology, 2017;23:75-81

Meta-analysis of RCTs: Therapeutic Vaccine vs No Therapy/Placebo

HBeAg seroconversion

[End of followup (off therapy)]

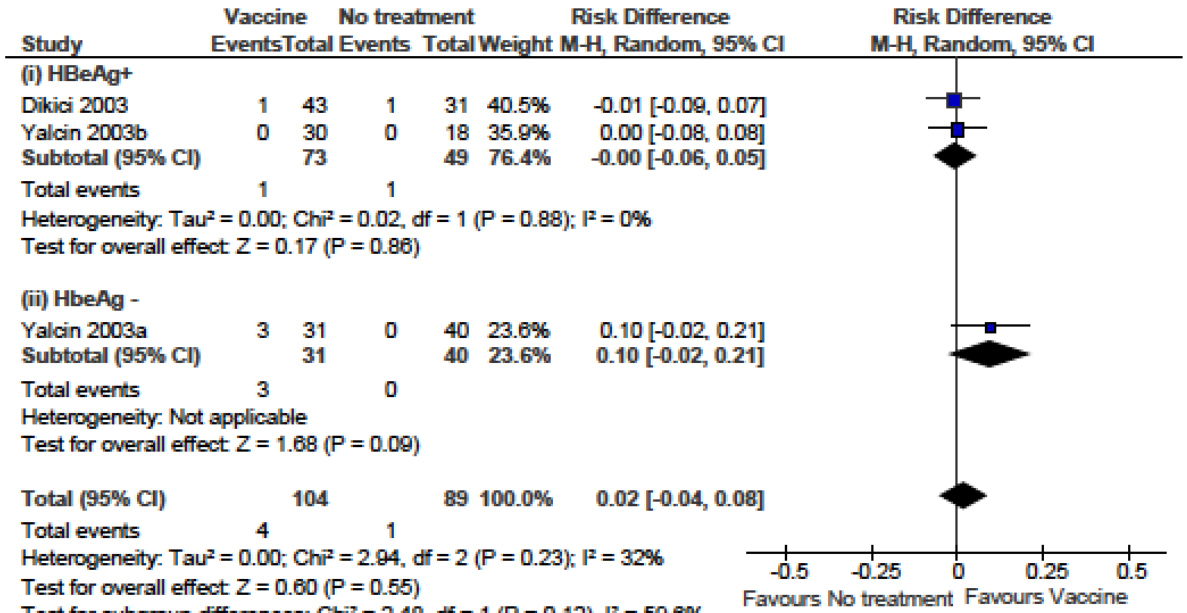


Total 16 RCTs

- **Therapeutic Vaccine=1090 pt**
- **PLB/no therapy=591 pt**

HBsAg loss

[End of followup (off therapy)]



Therapeutic Vaccine vs no therapy/placebo = No efficacy for:

- **HBeAg SC**
- **HBsAg loss**

Lim SG et al, Viral Hepat 2019;26(7):803-817.

Meta-analysis: Therapeutic Vaccine + SOC* vs SOC*

HBeAg seroconversion

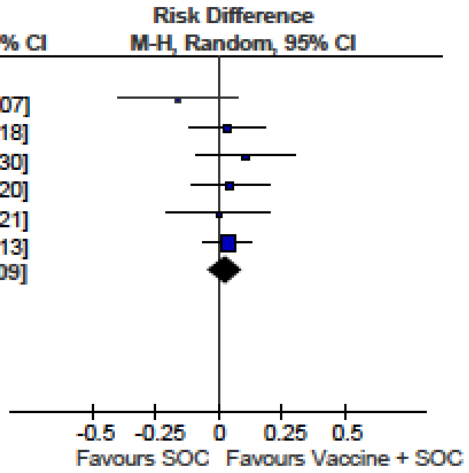
[End of followup (off therapy)]

*SOC = Standard of Care

Study	Vaccine + SOC Events	Total	SOC Events	Total	Weight	Risk Difference M-H, Random, 95% CI
HbeAg +						
Helvaci 2004	4	25	8	25	6.9%	-0.16 [-0.39, 0.07]
Hoa 2009b	15	60	13	60	16.4%	0.03 [-0.12, 0.18]
Lok 2016	4	37	0	7	9.7%	0.11 [-0.09, 0.30]
Schneider 2006b	1	21	0	11	15.7%	0.05 [-0.11, 0.20]
Yang 2012	2	22	1	11	8.7%	0.00 [-0.21, 0.21]
Yang 2017	18	107	15	115	42.6%	0.04 [-0.06, 0.13]
Subtotal (95% CI)		272		229	100.0%	0.03 [-0.03, 0.09]
Total events	44		37			

Heterogeneity: Tau² = 0.00; Chi² = 3.45, df = 5 (P = 0.63); I² = 0%

Test for overall effect: Z = 0.91 (P = 0.36)



HBsAg loss

[End of followup (off therapy)]

Study	Vaccine + SOC Events	Total	SOC Events	Total	Weight	Risk Difference M-H, Random, 95% CI
(i) HbeAg +						
Helvaci 2004	1	25	1	25	13.4%	0.00 [-0.11, 0.11]
Hoa 2009b	2	60	1	60	39.6%	0.02 [-0.04, 0.07]
Subtotal (95% CI)		85		85	53.0%	0.01 [-0.04, 0.06]
Total events	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.52 (P = 0.60)

(ii) HBeAg -						
Brillanti 2013	2	5	0	5	0.9%	0.40 [-0.05, 0.85]
Lok 2016	0	151	0	27	46.1%	0.00 [-0.05, 0.05]
Subtotal (95% CI)		156		32	47.0%	0.16 [-0.33, 0.65]
Total events	2		0			

Heterogeneity: Tau² = 0.10; Chi² = 4.83, df = 1 (P = 0.03); I² = 79%

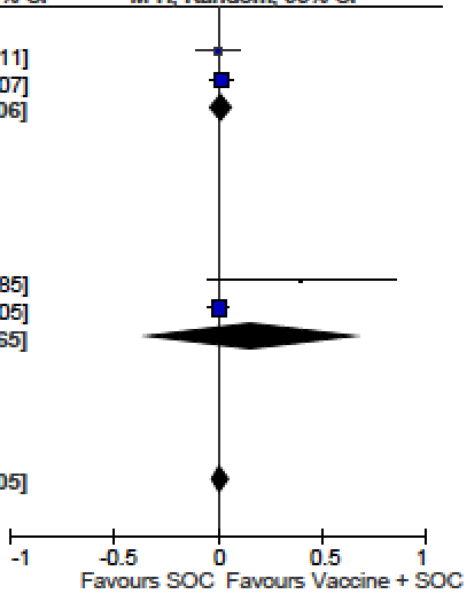
Test for overall effect: Z = 0.64 (P = 0.52)

Total (95% CI)		241		117	100.0%	0.01 [-0.03, 0.05]
Total events	5		2			

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 3 (P = 0.30); I² = 17%

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%



Therapeutic Vaccine + SOC vs SOC
= No efficacy for:

- **HBeAg SC**
- **HBsAg loss**

Lim SG et al, Viral Hepat 2019;26(7):803-817.

What type of studies have led to significant functional cure?

Interferon based studies

- PegIFN mono or Nuc/PegIFN therapy 8 - 10% (End of FU)
- Myrcludex B 2mg/pegIFN 48w in HBV/HDV co-infection 26.7% (End of FU)
- TDF + pegIFN + NAP Triple Therapy 40% (End of FU)

Stopping Nucs studies

- 19-46% HBsAg loss from different studies
- Rates for HBsAg loss rely on low qHBsAg at EoT

Hadziyannis SJ, et al. *Gastroenterology.* 2012;143:629-636
Papatheodoridis, Antiviral Ther 2018;23(8):677-685
Chen, Clin Microbiol Infect. 2018 Sep;24(9):997-1003
Yao, Sci Rep. 2017 May 12;7(1):1839

More than one path to functional cure

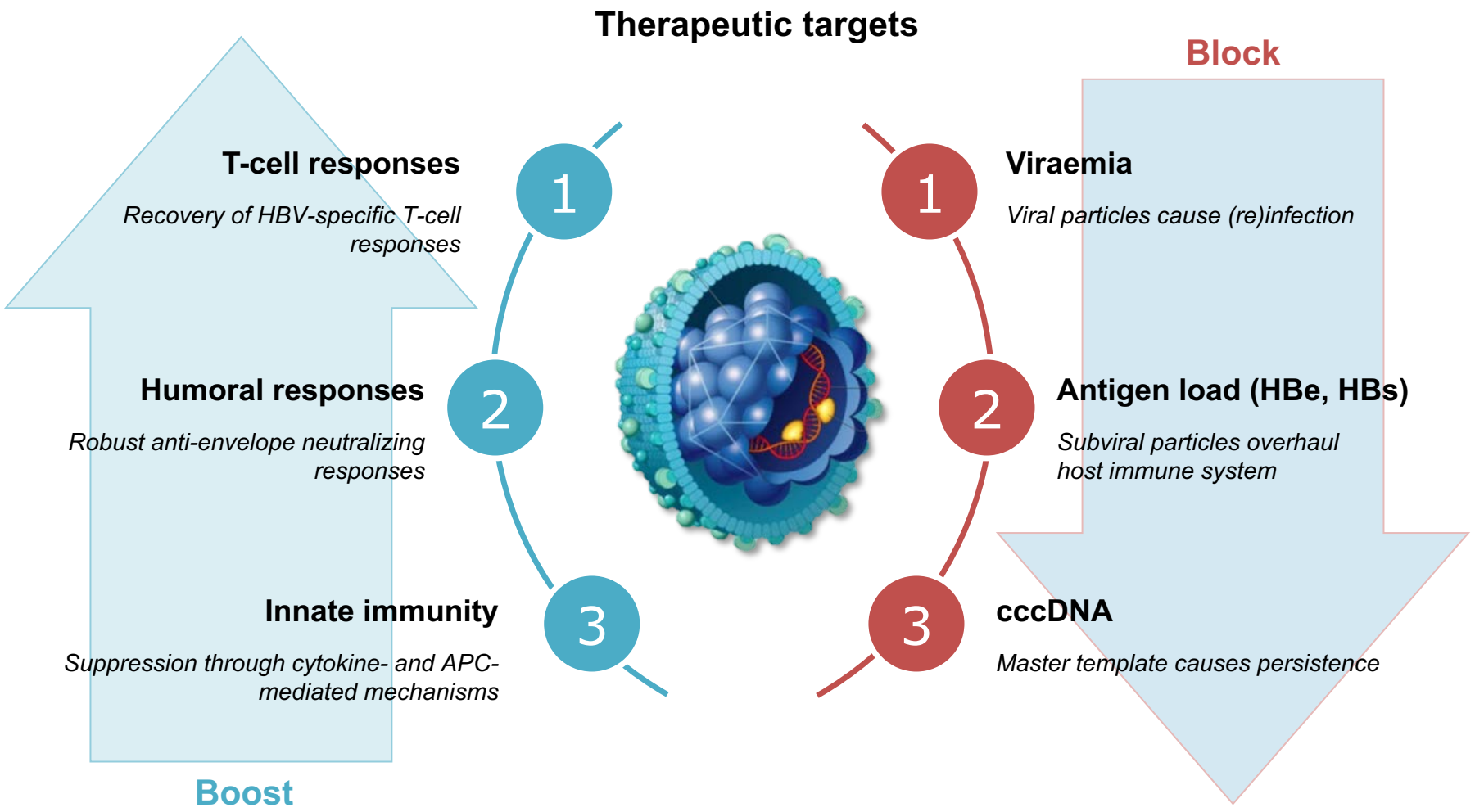
Potent combination therapy

- Combine agents from different classes
- Most of these combinations rely on immune modulators (48w therapy)
  - JNJ triple combination
  - Mycludex, TDF + pegIFN (26.7% HBsAg loss)
  - NAPs, TDF +pegIFN (40% HBsAg loss)

HBsAg reduction followed by immune therapy?

- Stopping NA successfully leads to functional cure in qHBsAg<100 IU/ml associated with HBV flares and improved T cell function, but HBsAg loss takes as long as 3-5years
- Potential therapeutic strategy

HBV Treatment Strategies



Conclusions

- Functional cure is an achievable endpoint associated with improved clinical outcomes
- Functional cure is most likely associated with cccDNA silencing than eradication
- Agents that have little effect on qHBsAg in early studies cannot be completely discounted (eg Myrcludex), and may still have efficacy in combination
- Combination therapy is the most promising but sequential therapy may be another therapeutic strategy.
  - This may be useful when agents can reduce qHBsAg<100 IU/ml, and given immunomodulators
- Quite likely there are multiple pathways to achieve functional cure, but therapies currently that have been successful in achieving functional cure in >20% have relied on pegIFN

Acknowledgements

Special thanks to the following for allowing their slides to be shared

- Gilead
- Janssen
- Roche
- Assembly
- Arbutus
- Replicor
- Ed Gane

Singapore Hepatology Conference

Sharp focused updates in Hepatology

UPDATES

3 ADDITIONAL LIVE WEBINARS		
Topic: Speaker: Date And Time:	**New Biomarkers For Chronic Hepatitis B: Ready For Clinical Use?** **PROF. M.F. YUEN** Monday, 12 October 2020 8.00pm – 9.00pm HKT/SGT	
Topic: Speaker: Date And Time:	**Unmet Needs In CHB Guideline** **PROF. MARC GHANY** Monday, 19 October 2020 8.00pm – 9.00pm HKT/SGT	
Topic: Speaker: Date And Time:	**Should We Stop Long Term Nucleoside Analogue Therapy?** **PROF. TEERHA PIRATVISUTH** Monday, 26 October 2020 8.00pm – 9.00pm HKT/SGT 7.00pm - 8.00pm Bangkok Time	

Singapore Hepatology Conference

Sharp focused updates in Hepatology

PLEASE REMEMBER TO FILL IN THE SURVEY FORM!