Finding the path forward to sterilizing cure of HBV: Lessons learned from the clinic

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Chief Scientific Officer
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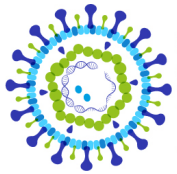
Workshop B 11.30AM-2.30PM

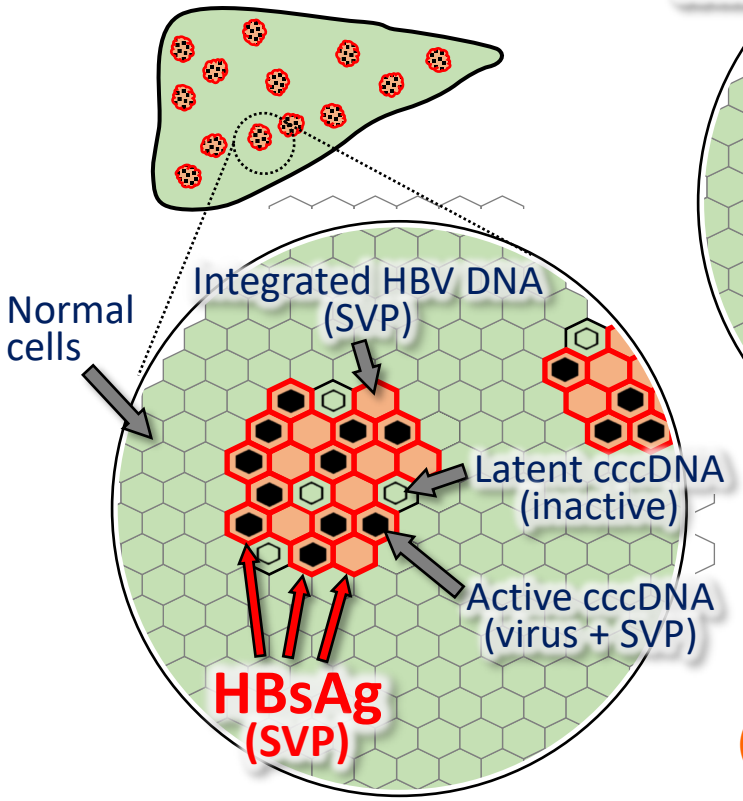
Mechanisms, Regulation & Therapeutic Potential: Targeting cccDNA to Attain HBV Cure



2nd Annual
Chronic HBV Drug Development
From Late Translational to Phase II Clinical Progress
April 25 - 27, 2022, Boston | MA

Functional vs sterilizing cure of chronic HBV infection

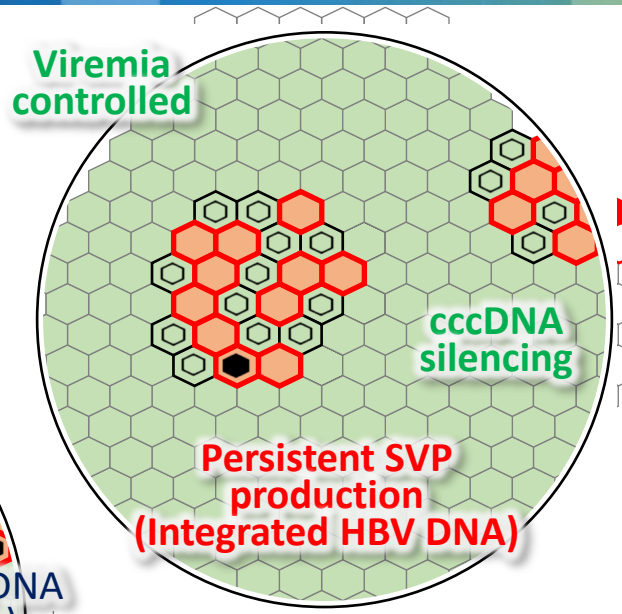
Chronic HBV



HBsAg blocks immune control

Progression of liver disease

Risk of HCC



Current Therapy

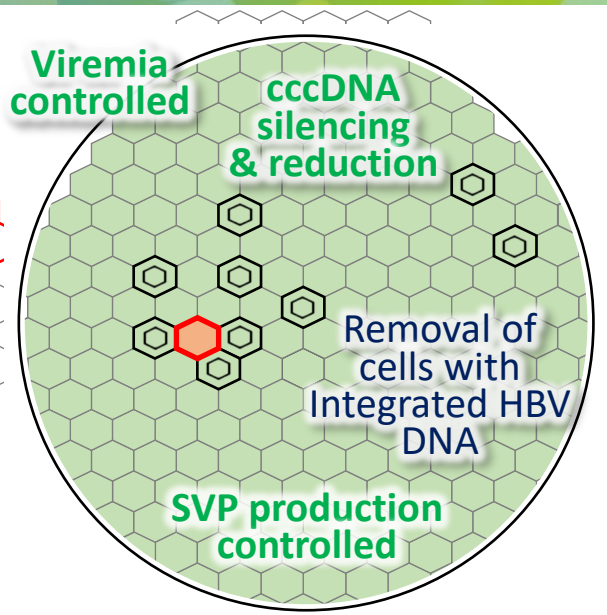
(NUCs)

No immune control

Life long therapy (viral rebound if removed)

Controlled progression of liver disease

Risk of HCC (late initiation of therapy)



Functional Cure

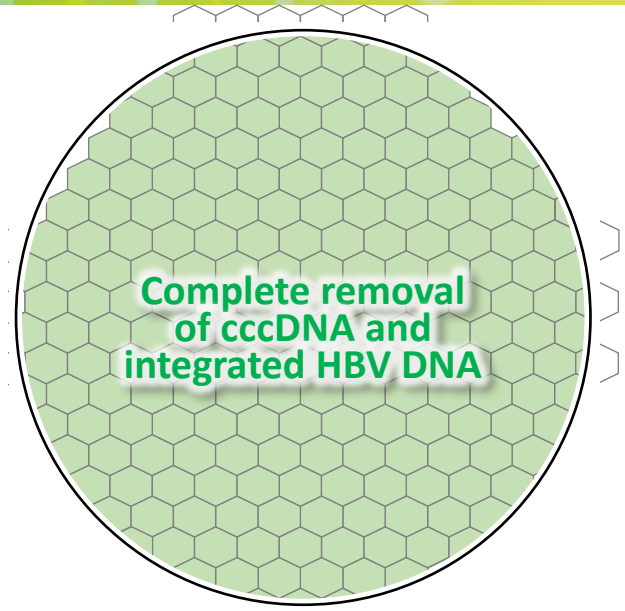
Restoration of immune control

Finite therapy

Reversal of liver disease

Reduced risk of HCC

48 weeks NUCs + pegIFN:
9% functional cure (GT A)
0% functional cure (GT D)



True Cure

No immune control required

Finite therapy

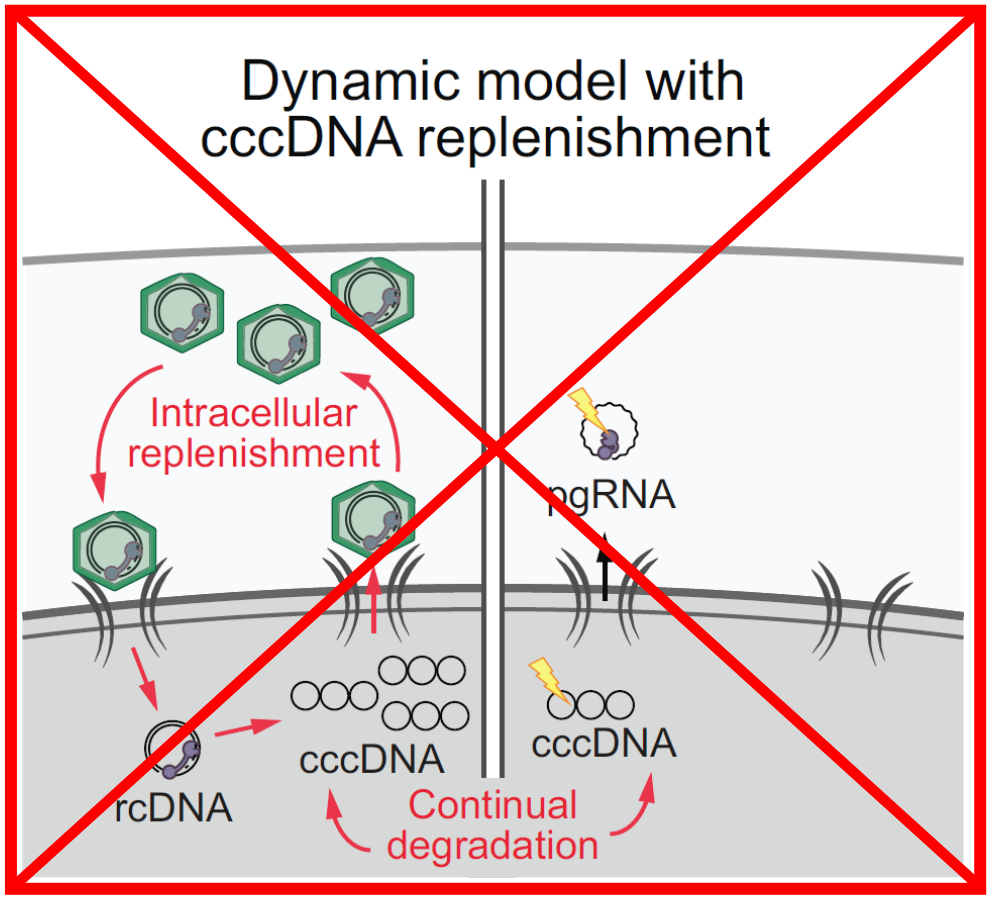
Reversal of liver disease

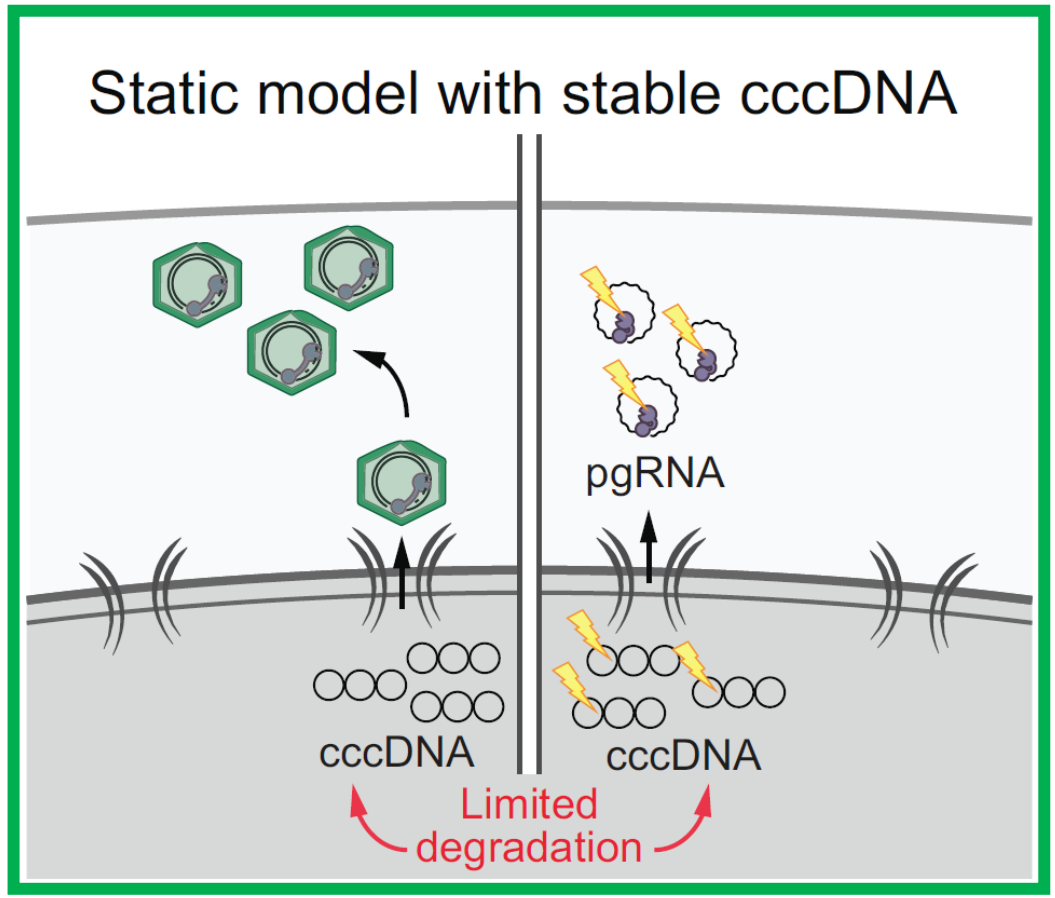
Reduced risk of HCC

Persistence of latent cccDNA is a high barrier

Vaillant, ACS Viruses 2021; 13: 745

Intracellular cccDNA maintenance

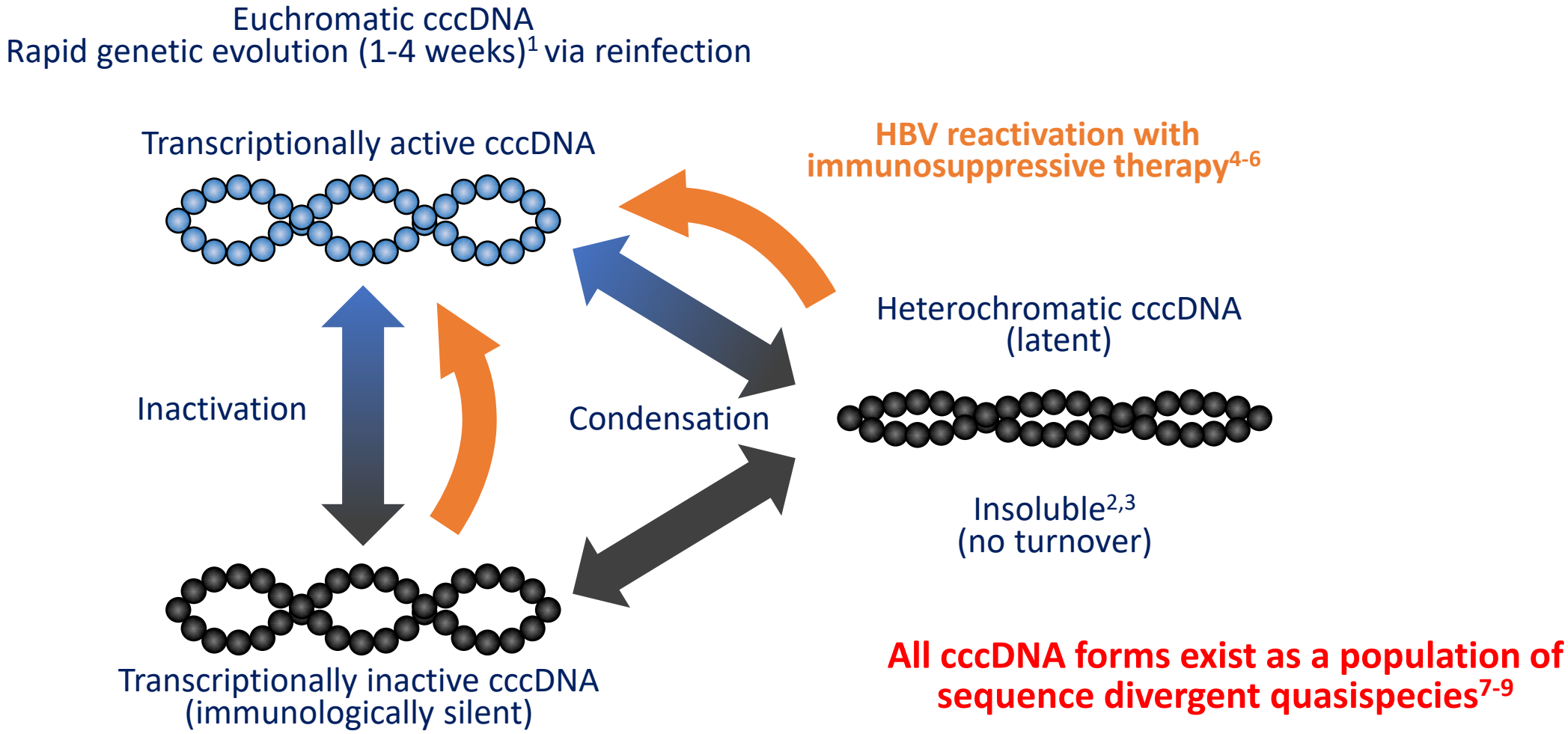




cccDNA is established and is maintained in the absence of core antigen

Tu et al., JHEP reports 2021; 3: 100195

The core challenge for sterilizing cure: cccDNA transitional forms

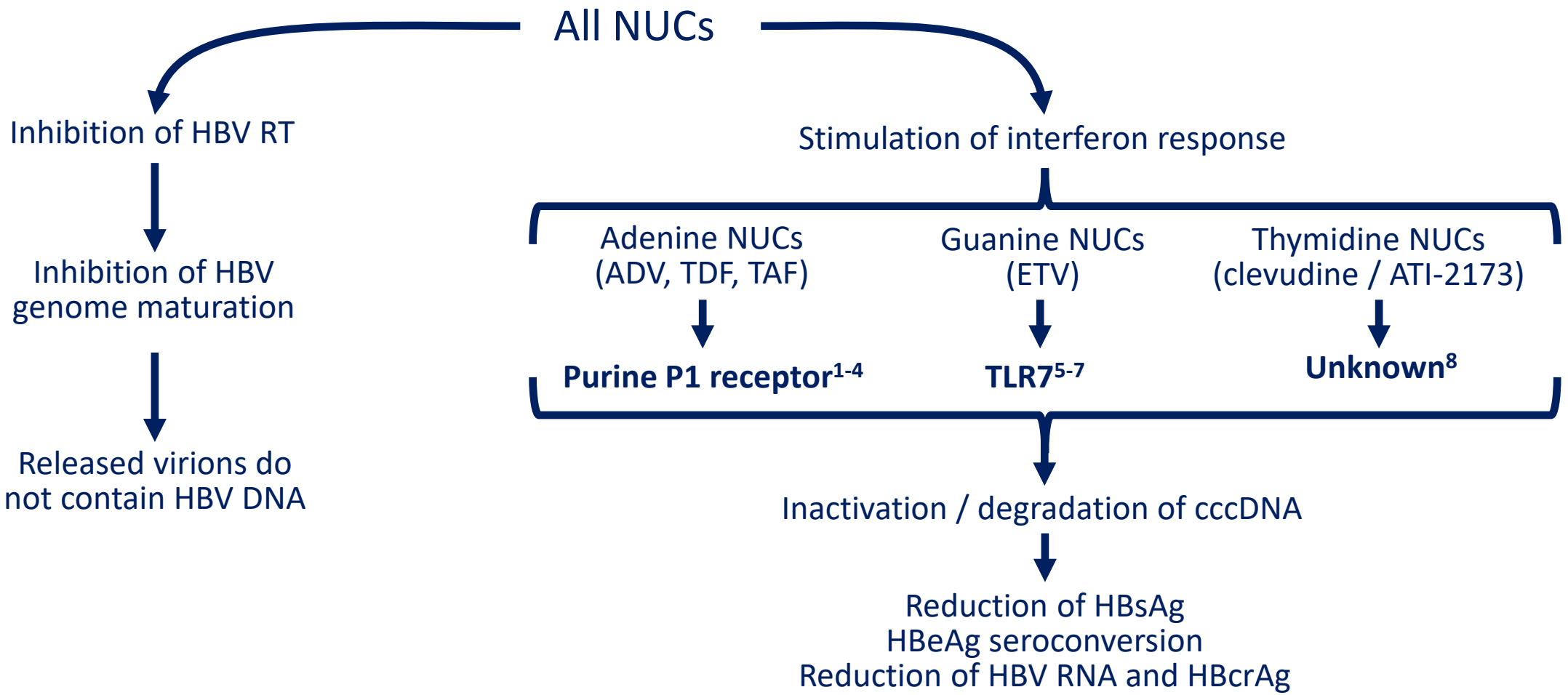


1. Huang et al., Hepatol 2021; 73: 41-52
2. Cam et al., Cell 2009; 136: 610-614
3. Chen et al., Nuc Acids Res 2016; 44: 6482-6492
4. Loomba and Jiang, Gastroenterol. 2017; 152: 1297-1309
5. Wang et al., Hematologica 2019; 104: 435-443
6. Zhang et al., J Immunother Canc. 2019; 7: 322
7. Li et al., Clin Microbiol Infect 2015; 21: 280-287
8. Yang et al., J Clin Microbiol 2015; 53: 2203-2214
9. Gencay et al., PLoS One 2017; 12: e0172101

Targeting cccDNA with conventional approaches

Mechanism	Active cccDNA	Inactive cccDNA immunologically silent	Latent cccDNA insoluble
Entry inhibition (myrcludex B)	NO Volz et al., J Hepatol 2013; 58: 861-867	NO	NO
HBV RT inhibition (NUCs)	YES Stimulation of innate immunity	YES (?) Lucifora et al., Science 2014; 343: 1221-1228	NO
Capsid assembly modulation (CAMs)	NO (?) Tu et al., JHEP reports 2021; 3: 100195	NO (?)	NO
Targeting SVP (NAPs)	YES SVP clearance allows reactivation of innate immunity	YES (?) Lucifora et al., Science 2014; 343: 1221-1228	NO (even with high rates of functional cure)
RNAi / antisense	YES TLR3 / TLR9 stimulation of innate immunity	YES (?) Lucifora et al., Science 2014; 343: 1221-1228	NO
CRISPR Cas9	?? mutational escape	?? mutational escape	NO Heterochromatin refractive to DNA-protein interactions Chen et al., Nuc Acids Res 2016; 44: 6482-6492
I-Cre I (ARCUS™)	?? mutational escape	?? mutational escape	NO Heterochromatin refractive to DNA-protein interactions Chen et al., Nuc Acids Res 2016; 44: 6482-6492
Stimulating innate immunity	YES	YES (?) Lucifora et al., Science 2014; 343: 1221-1228	NO
Stimulating T-cell mediated clearance	YES	NO	NO

NUCs are bifunctional agents



1. Zidek et al., Eur J Pharmacol 2003; 475: 149-159
2. Potměšil et al., Eur J Pharmacol 2006; 540: 191-199
3. Murata et al., Gut 2018; 67: 362-371
4. Murata et al., Hepatol 2020; 71: 1533-1545
5. Lee et al., PNAS 2003; 100: 6646-6651
6. Davenne et al., Eur J Immunol 2019; 50: 56-62
7. Kurihara et al., Antiviral Ther 2018; 23: 239-248
8. Vollmer et al., Antisense Nuc Acid Drug Dev 2002; 12: 165-175

NUC effects

NUC	Response expected based on MOA	Effect on cccDNA (inactivation)				Sustained HBV DNA response after removal
	HBV DNA reduction	HBV RNA reduction	HBsAg reduction	HBeAg reduction	HBcrAg reduction	
ETV	YES	YES	YES	YES	YES	NO (except with HBsAg loss)
TDF	YES	YES	YES	YES	YES	NO (except with HBsAg loss) or HBeAg+ GTA
Clevudine	YES	NR	NO	NR	NR	NO
ATI-2173 (clevudine prodrug)	YES	YES	NR	NR	NR	??
TDF + ATI-2173	YES	YES	NR	NR	NR	??

Rebound of HBV DNA after cessation of nucleos/tide analogues in chronic hepatitis B patients with undetectable covalently closed circular DNA

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JHEP Reports **2020.** https://doi.org/10.1016/j.jhepr.2020.100112

Long term therapy with ETV (n=8) / TDF (n=2) / LdT (n=3)

Undetectable cccDNA in liver biopsy (n=13)

Undetectable HBV DNA and HBV RNA (n=13)

HBeAg negative (n=12)

Undetectable HBcrAg (n=4)

All HBsAg positive (from integrated HBV DNA)

↓

Remove NUC therapy

↓

Rebound of infection in all patients

Retreatment required with original NUC (n=12)

Can CAM effects alter cccDNA pools?

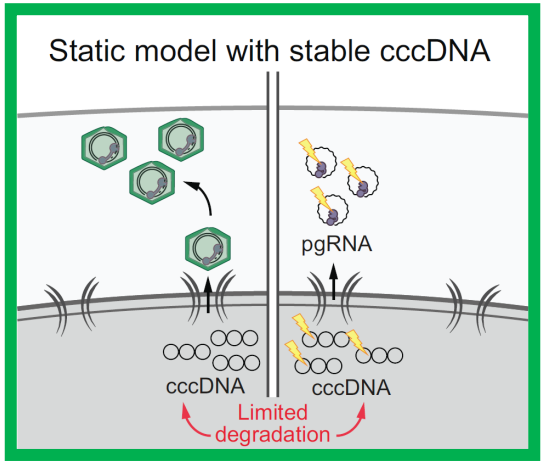
All CAMs

Aggregation of core protein (Class I)

Formation of aberrant capsids (Class II)

Inhibition of nuclear capsid import

Erosion of existing cccDNA pool ??



Tu et al., JHEP reports 2021; 3: 100195

CAM monotherapy in phase II trials

Class	CAM	Response expected based on mechanism of action		Effect on cccDNA (active cccDNA can turn over in ~7 days)			Sustained response with 48 weeks therapy
		HBV DNA reduction	HBV RNA reduction	HBsAg reduction	HBeAg reduction	HBcrAg reduction	
Class I Core protein aggregation	GLS4JHS (morphothiadin)	YES	YES	NO	NO	NO	NO
	RG7907 (RO7049389)	YES	YES	NO	NR	NR	
Class II Empty capsids	JNJ-56136379	YES	YES	NO	NO	NR	NO (+ NUCs) (+ NUCs + RNAi)
	JNJ-64530440	YES	YES	NO	NO	NO	
	ABI-H0731 (vebicorvir)	YES	YES	NO	NO	NO	NO (+ NUCs)
	NVR3-778	YES	YES	NO	NO	NO	
	ALG-000184 (GLP-26 prodrug)	YES	YES	NO	NR	NR	
	EDP-514	YES	YES	NO	NO	NO	

Summary

Static model for cccDNA regulation appears correct in human infection
no continual replenishment from re-infection / capsid import required

Current direct acting antiviral approaches appear unlikely to achieve sterilizing cure
even in combination

Novel cccDNA targeting agents are required for sterilizing cure!

Capable of targeting inactive and latent cccDNA
novel host factors?
novel cccDNA morphology in latent state?

Sequence dependent mechanisms should be avoided

How to tell if sterilizing cure has been achieved?
Outcomes are the same as functional cure!
Current cccDNA detection techniques are inadequate.