HBV - NEW AGENTS

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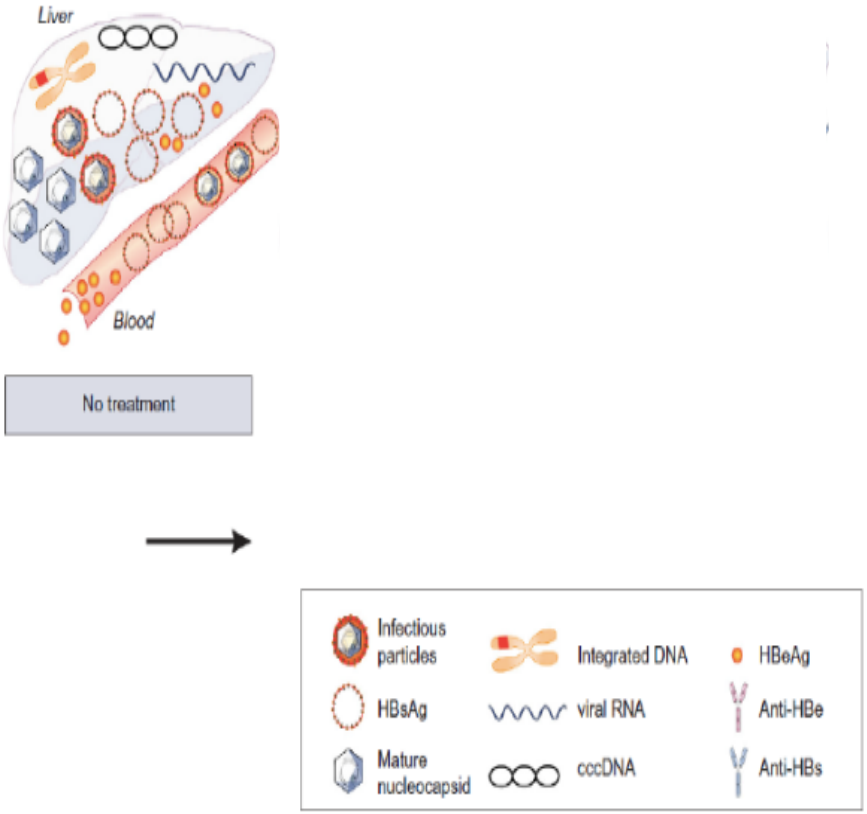
Outline

- What are we aiming for?
- Can we do better with what we have got already?
  - Nucleos(t)ides
  - Interferon
- What about new ‘directly acting’ antivirals?
- What about new ‘host directed’ agents?
- What other issues are there?

What are we aiming for?



Durantel D *et al. J Hepatol.* 2016 Apr;64(1 Suppl):S117-31

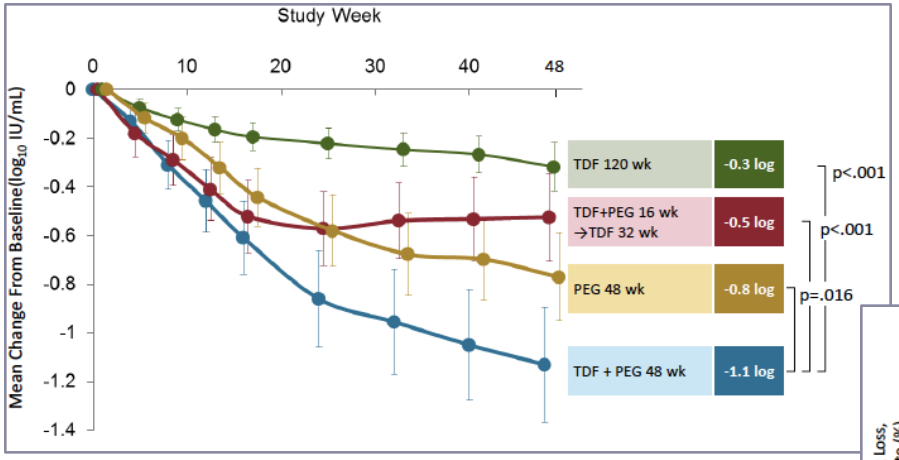
Can we do better with what we have already got?

- Nucleos(t)ides:
  - Entecavir
  - Tenofovir

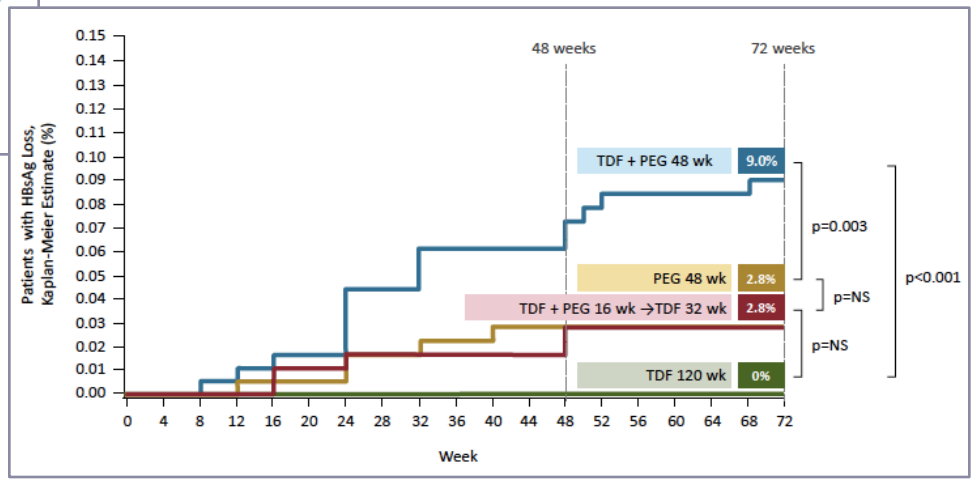
- Interferons:
  - Peg-interferon alpha

- So what about using them together or one after the other?

Sequential or Concurrent Nucs and Interferon…



Some promising data…

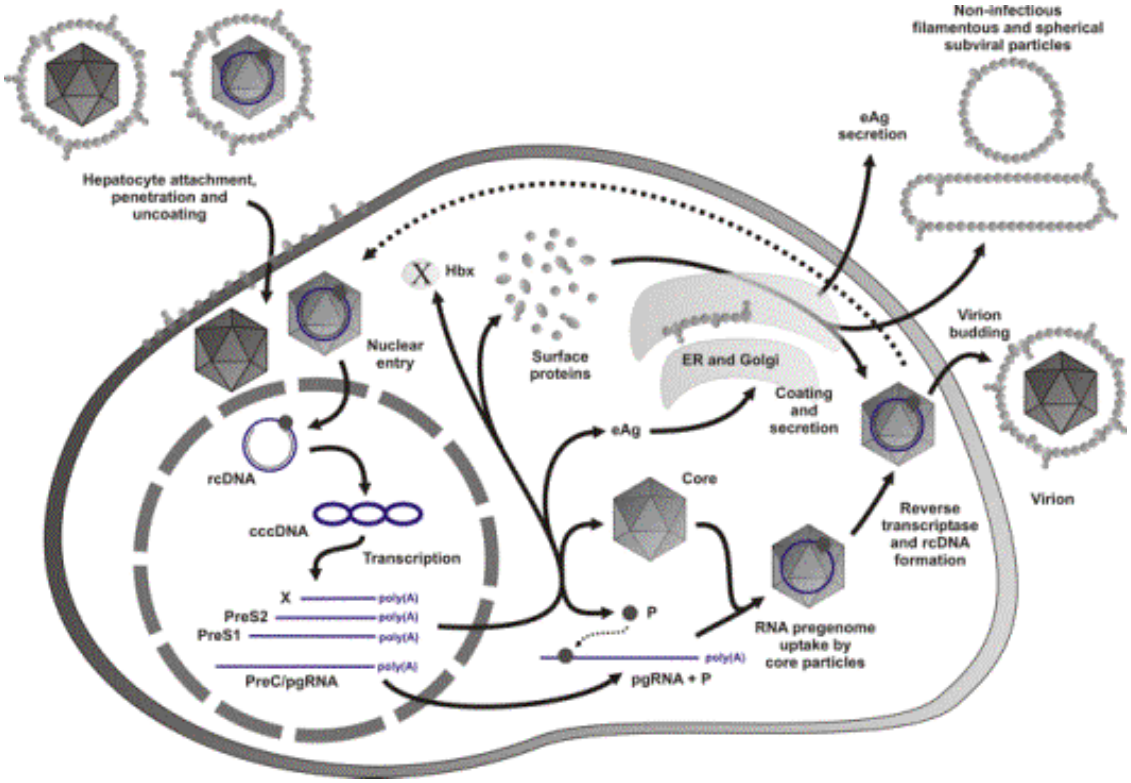


- But not all strategies have shown a benefit…
- And those that have are small studies
- And is it enough anyway?

Marcellin P et al, AASLD 2014

So what about new drugs?

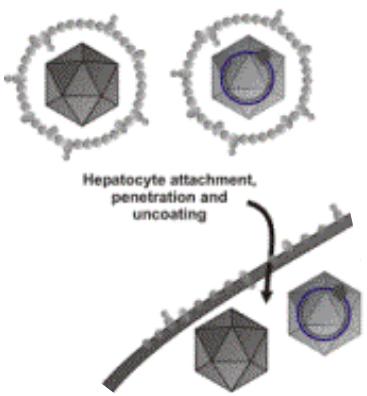
Lifecycle of HBV



Main Points

- Not as easy as the HIV lifecycle…
- But vital to understand...

Viral entry into hepatocyte



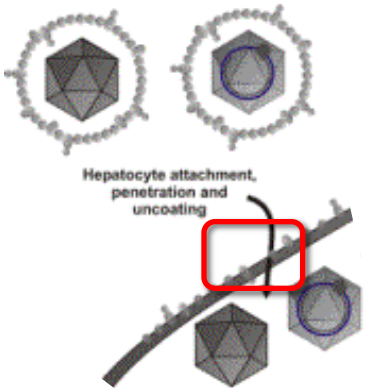
Binding:

- HBV grabs hold of heparan sulfate proteogycans
- Then binds to Sodium-Taurocholate Co-Transporting Polypeptide (NTCP) receptor

Entry:

- Via endocytosis or fusion
- Nucleocapsid released into cytoplasm

Viral entry into hepatocyte

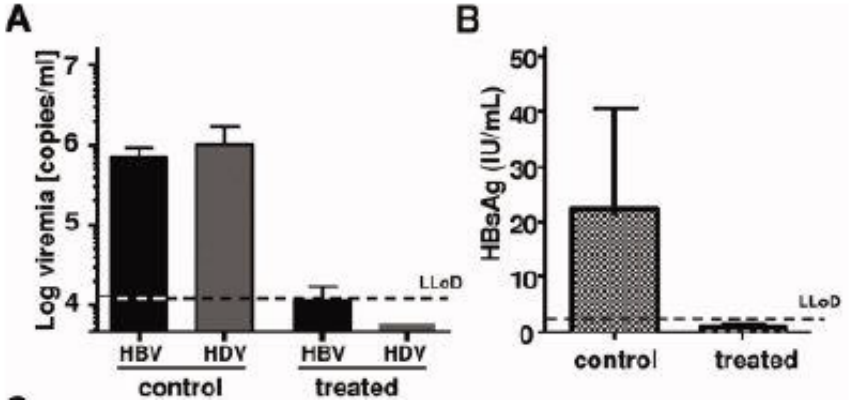


Myrcludex B

- Synthetic lipopeptide that blocks NTCP

Main Points

- Small studies
- Well tolerated but ?concern at high doses:
  - Hyperbilirubinaemia, interactions etc
- Unlikely effective on its own
  - But may have vital role in combination
  - Perhaps important in liver transplantation



Phase 2a:

- 10mg daily:
  - >1$\log_{10}$ drop in VL at wk12 in 6/8 HBeAg-ve patients

Lutgehetmann et al., Hepatology 2012; Urban et al., AASLD 2014

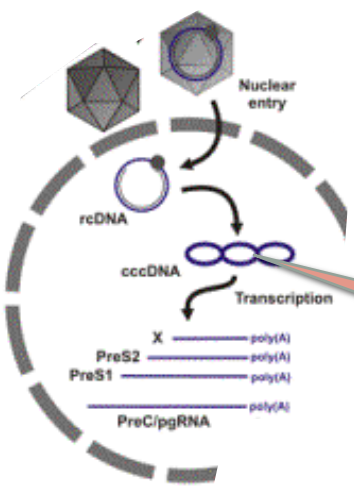
Entry into nucleus, conversion to cccDNA and then transcription

DNA enters nucleus ➔ converted to the highly stable cccDNA

- ‘covalently closed circular’ DNA
  - like a HBV mini-chromosome

cccDNA is template for transcription of viral mRNAs:

- Surface proteins
- HBV X protein
- Pregenomic RNA



cccDNA is the key to HBV ‘cure’….

Directly attacking cccDNA…

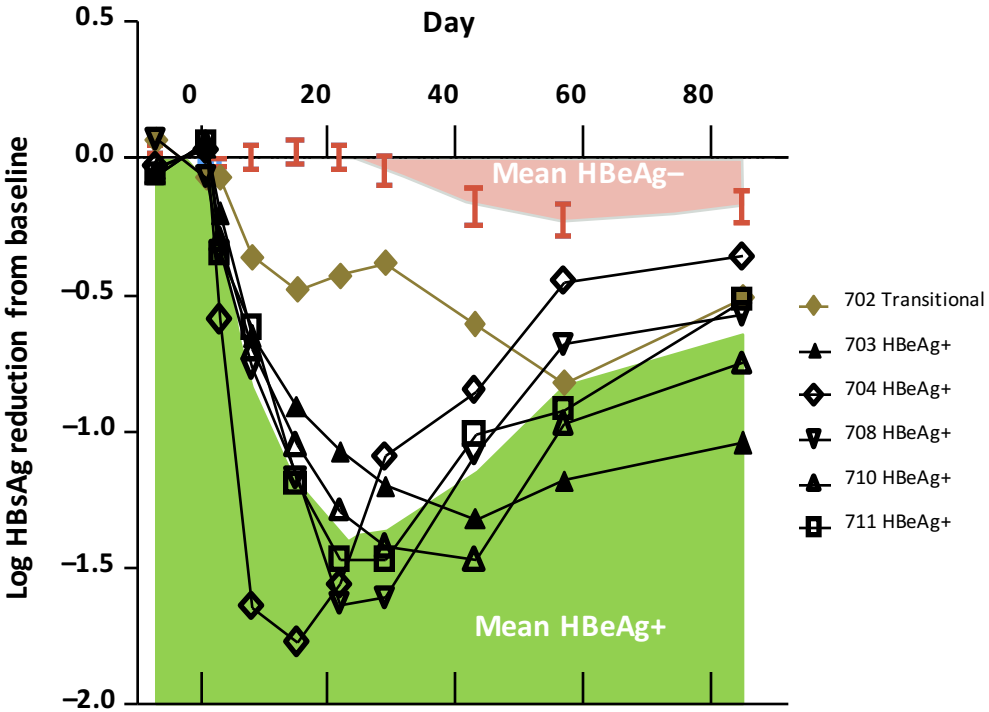
- In development:
  - Zinc-finger nucleases
  - Disubstituted sulfonamide compounds
    - Degrade cccDNA, inhibit rcDNA to cccDNA conversion, target epigenetic control of cccDNA
  - APOBEC proteins
    - Degrade cccDNA
  - CRISPR/Cas9
  - RNA-interference etc.

Promising but only in-vitro and animal work to date

Zimmerman KA et al., J Virol 2008; Cai D et al., Antimicrob Agents Chemother 2012; Lucifora J et al., Science 2014; Dong C et al., Antiviral Res 2015; Liu X et al., J Gen Virol 2015; Kenedy EM et al., Virology 2015

SiRNA: RNA interference therapy

Reduction of HBsAg in treatment-naïve CHB patients after a single dose of 4 mg/kg ARC-520

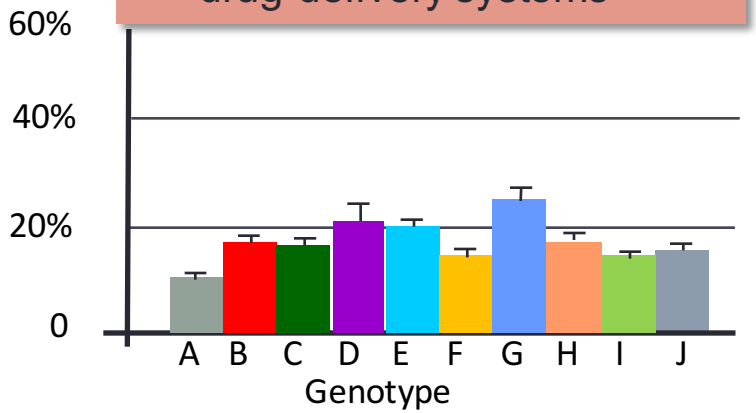


Hepatocyte Targeting - ALN-HBV

- N-acetyl galactosamine (GalNAc) ligand binds to asialoglycoprotein receptor (ASGPR)

Main Points

- Early promising results
- However need further improvements in stable drug delivery systems



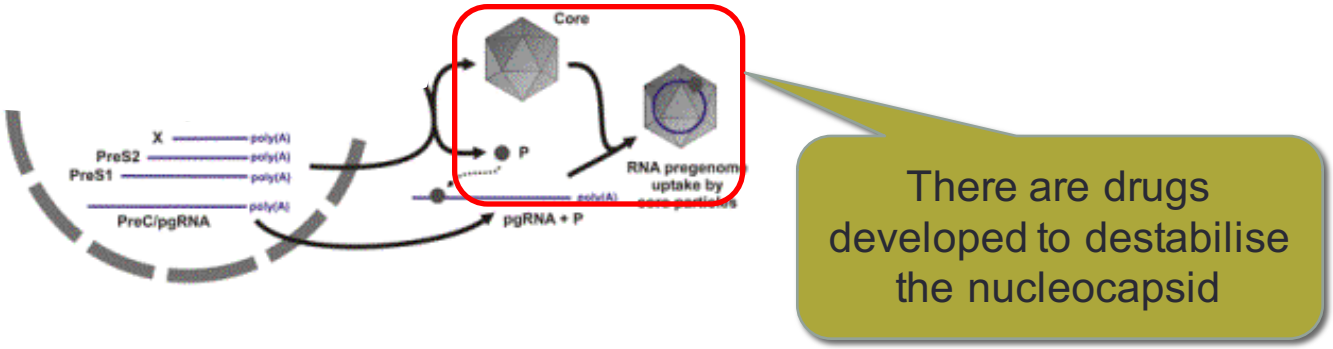
Yuen M-F *et al. EASL* 2016, Barcelona. THU-193

Sepp-Lorenzino L, et al. AASLD 2015, San Francisco. #36

Translation of mRNA and formation of capsids

mRNAs translated:

- ➔ Surface proteins
- ➔ X protein
- Pregenomic RNA
  - ➔ Core and polymerase proteins
  - ➔ RNA template for conversion to genomic DNA

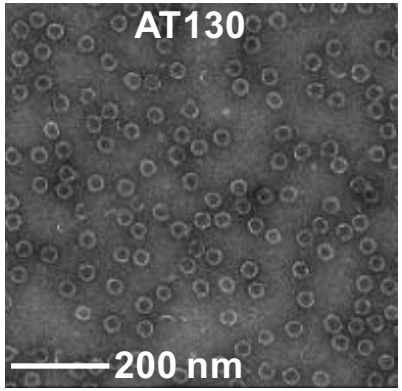


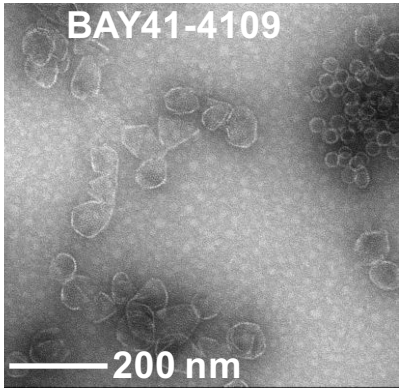
Capsid assembly modulators

- CAMs induce the formation of two types of capsids *in vitro*
  - Empty capsids with normal geometry and size
    - Phenylpropenamides (e.g. AT130) and sulfamoylbenzamide derivatives
  - Empty capsids with abnormal geometry and size
    - Heteroaryldihydropyrimidines (e.g. BAY41-4109)

Electron microscopy

Recombinant HBV core dimers + 150mM NaCl +/- 30µM CAM (24h)





Berke *et al. AASLD* 2016

HBV core inhibitors

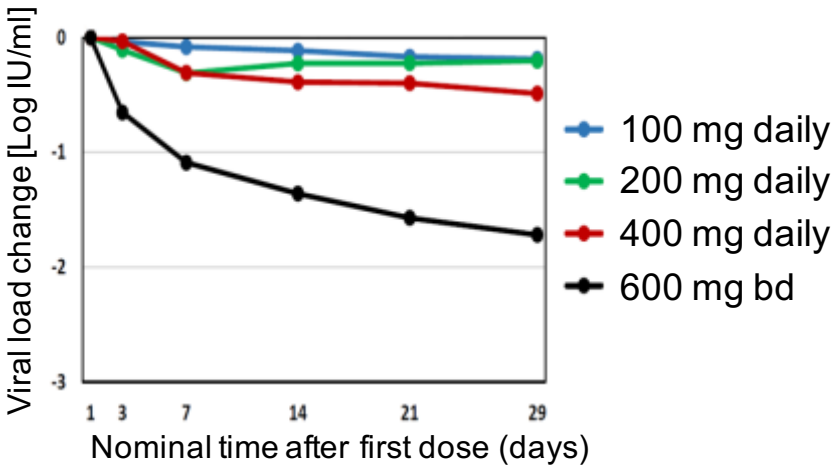
Main Points

- Still only very early and small studies for capsid and core inhibitors

HBeAg-positive CHB patients

- Serum HBV DNA >20,000 IU/mL
- ALT levels 1-7 times upper limit of normal
- Randomized to NVR 3-778 capsules at 4 doses (*vs* placebo) x 28 days

Mean viral load change (HBV DNA)



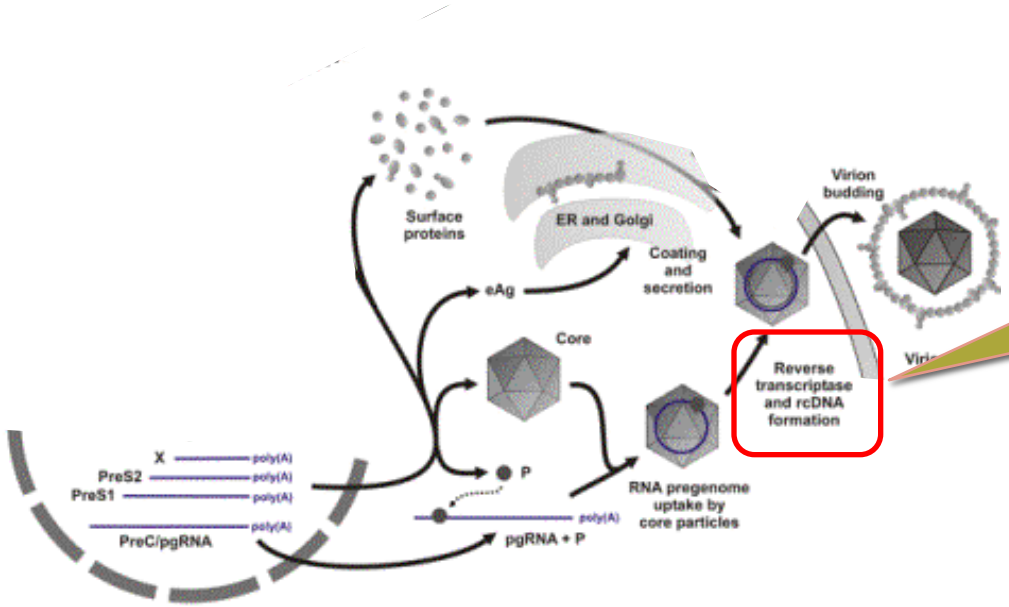
NVR 3-778 600 mg bd associated with mean 1.72 $\log_{10}$ IU/mL HBV DNA reduction in 28 days

Yuen M-F *et al. AASLD* 2015, San Francisco. #LB-10

Coated with surface proteins, RNA in capsid converted to relaxed circular DNA, and released….

Main Points

- What benefit will they have over existing nucs?
  - Already have good control of virus & very low resistance
  - No extra impact on cccDNA expected

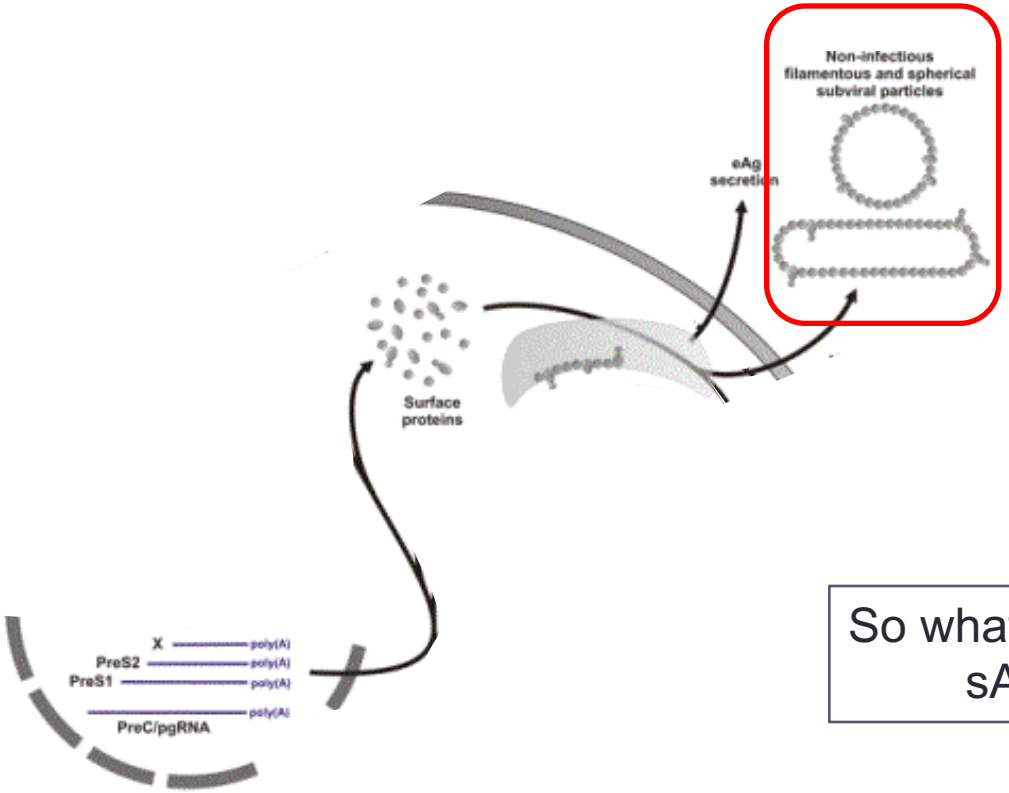


This is where nucleos(t)ides work

And there are potentially more on the way:

- Besifovir, CMX 157, AGX-1009, MIV-210

But lets think for a moment about sAg

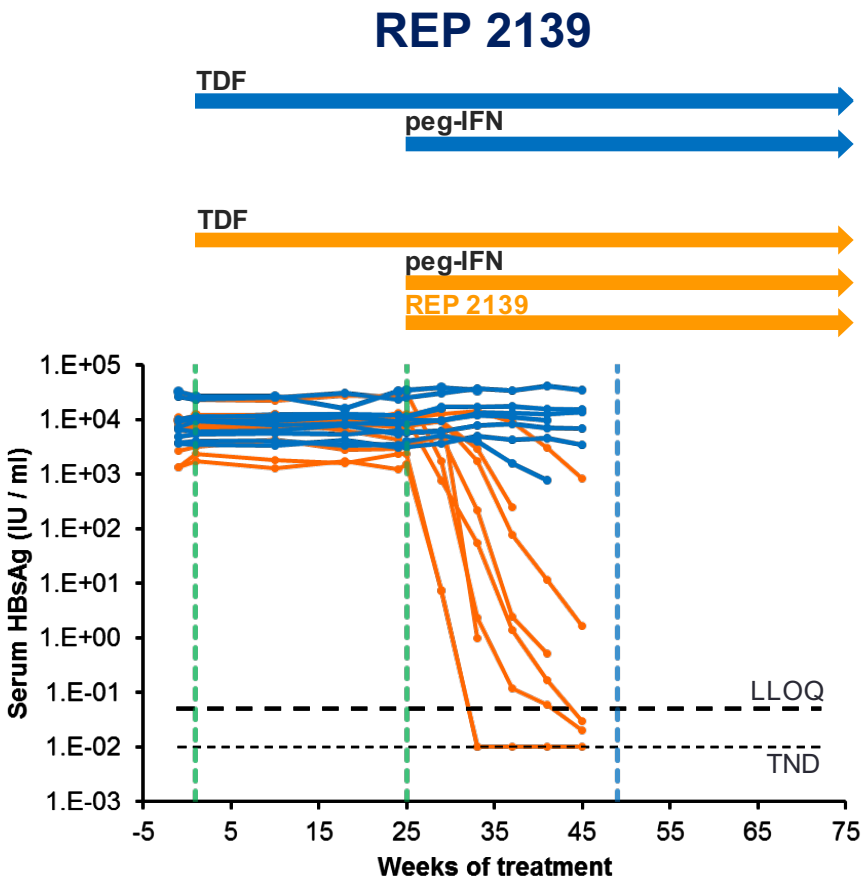


Why?

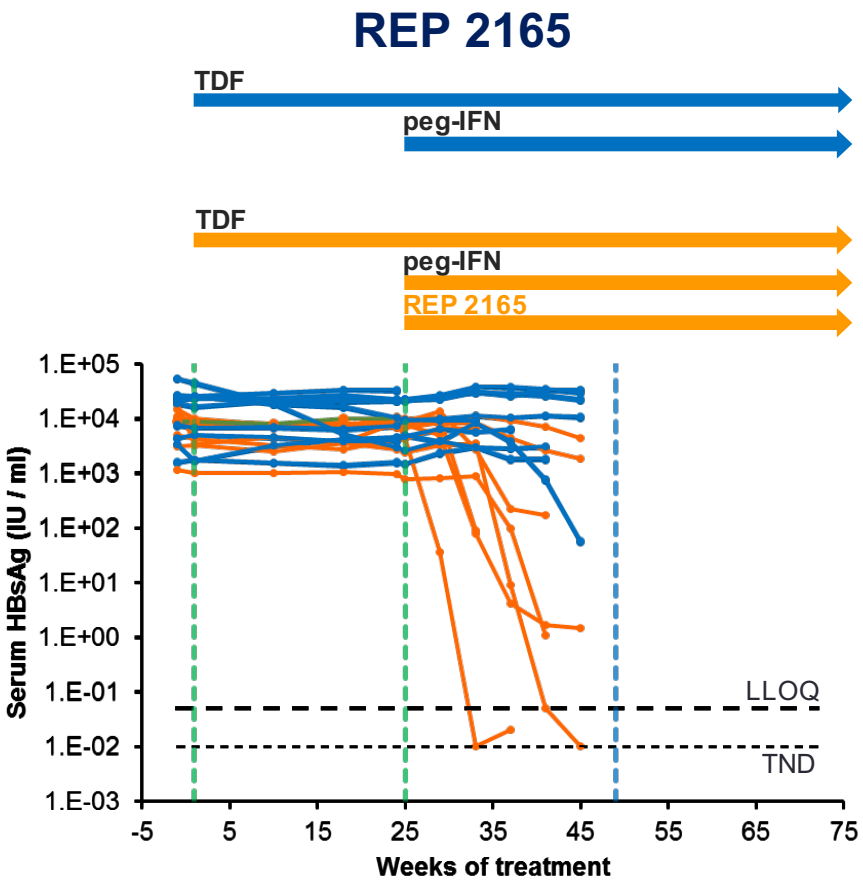
- Absorb neutralising antibodies
- Induce T cell tolerance & immune exhaustion

So what if we could inhibit sAg secretion?

sAg release inhibitors



9/9 HBsAg response > 1 log

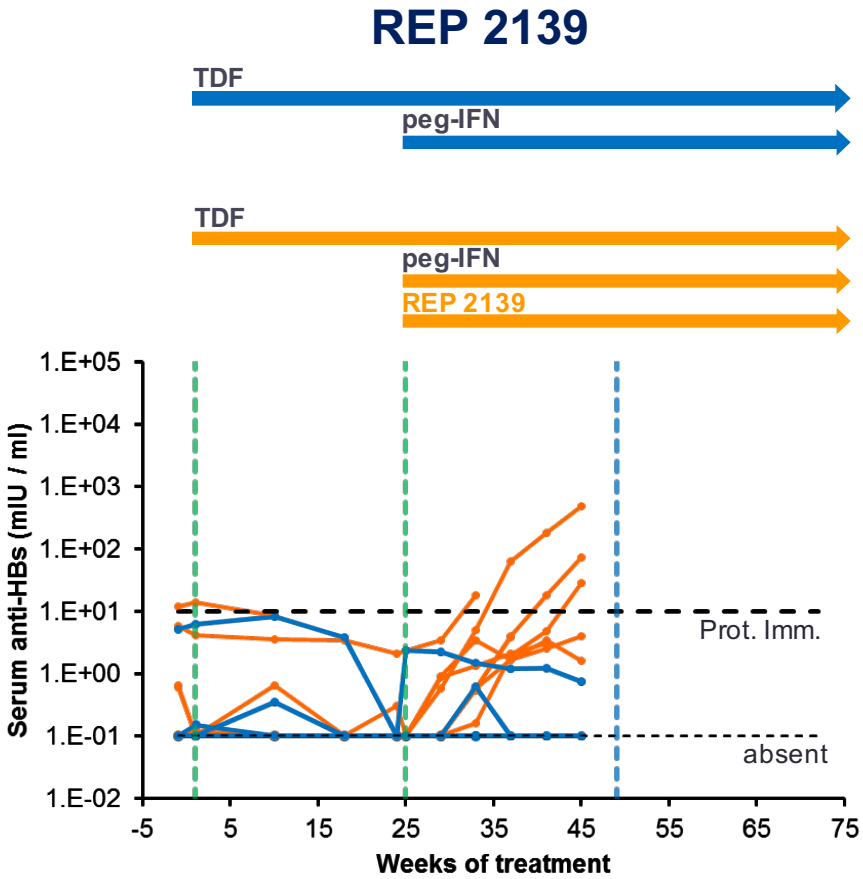


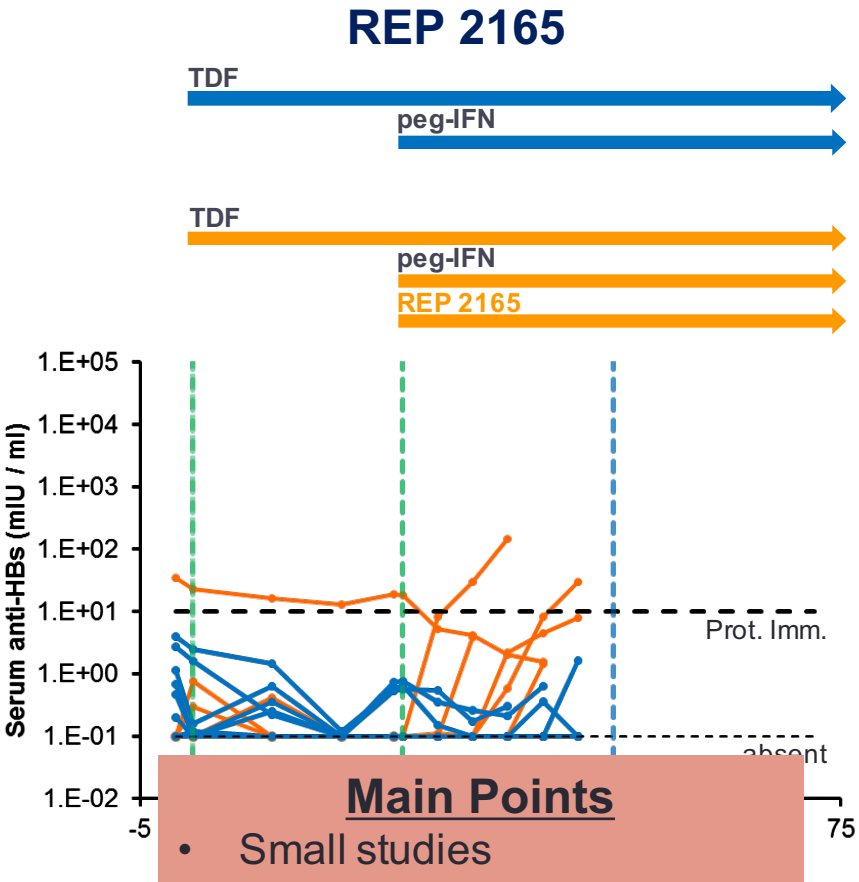
6/9 HBsAg response > 1 log

LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU / mL)

Bazinet *et al. AASLD* 2016

sAg release inhibitors





Elevation in serum anti-HBs correlated with

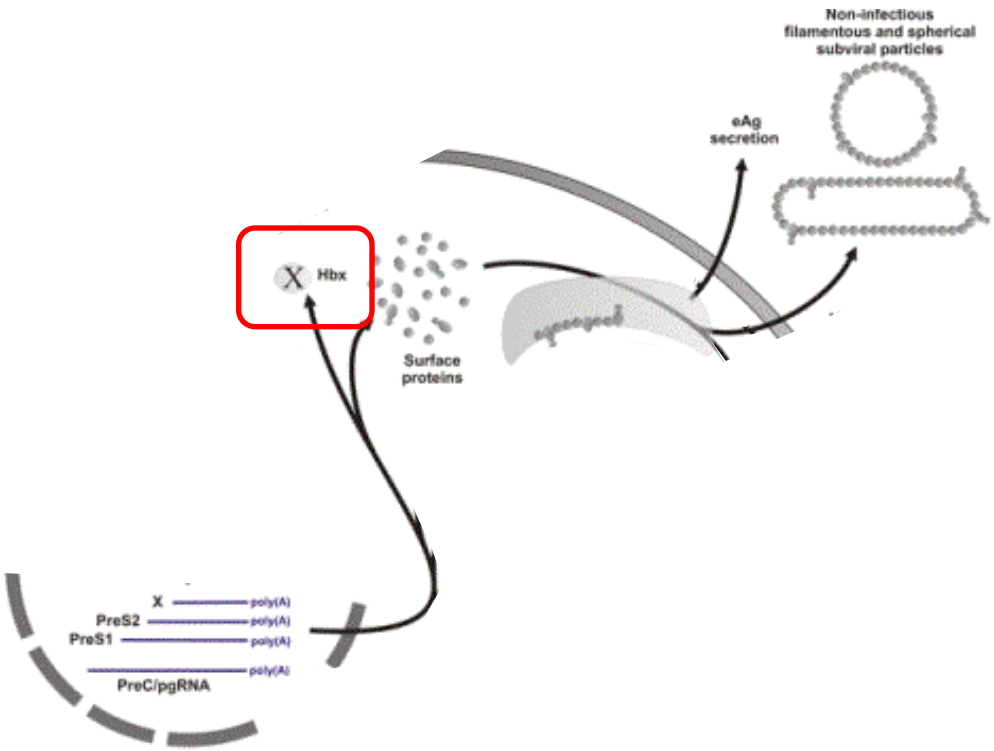
Main Points

- Small studies
- Is there a potential toxicity concern?
  - Akin to a storage disease?

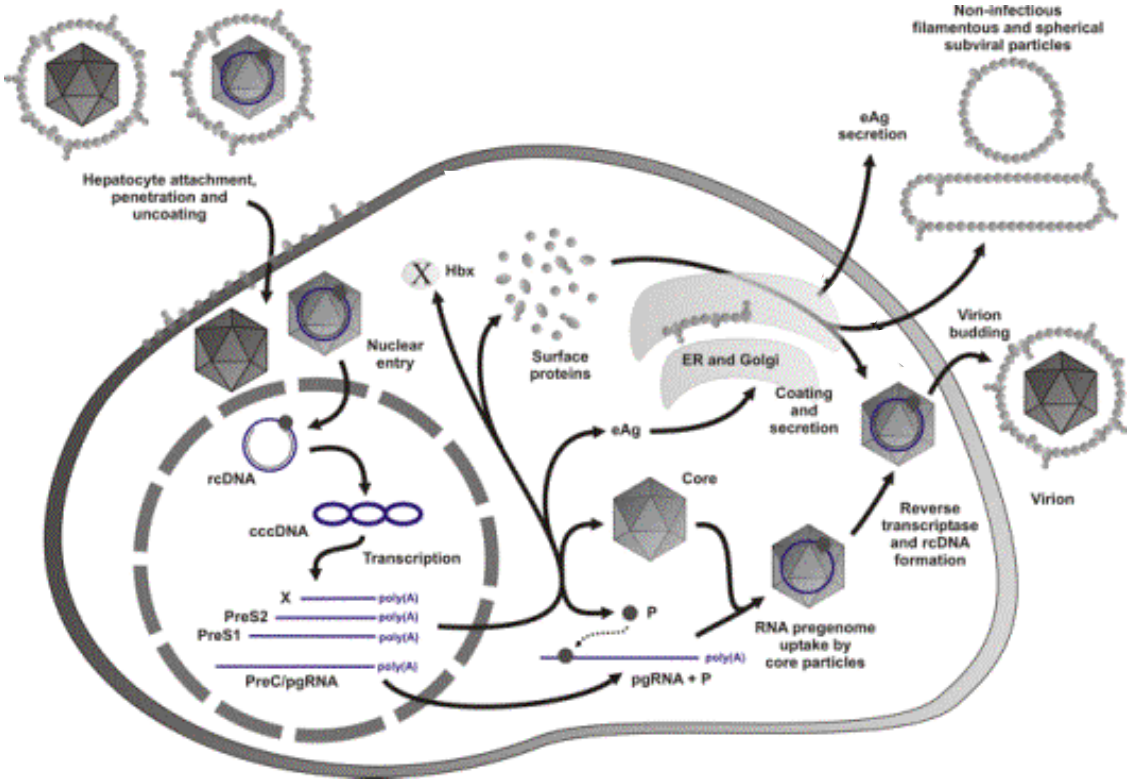
Prot. Imm. = Architect defined threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

Bazinet *et al. AASLD* 2016

There is also the X-protein



There is also replenishment of the cccDNA *within* the cell



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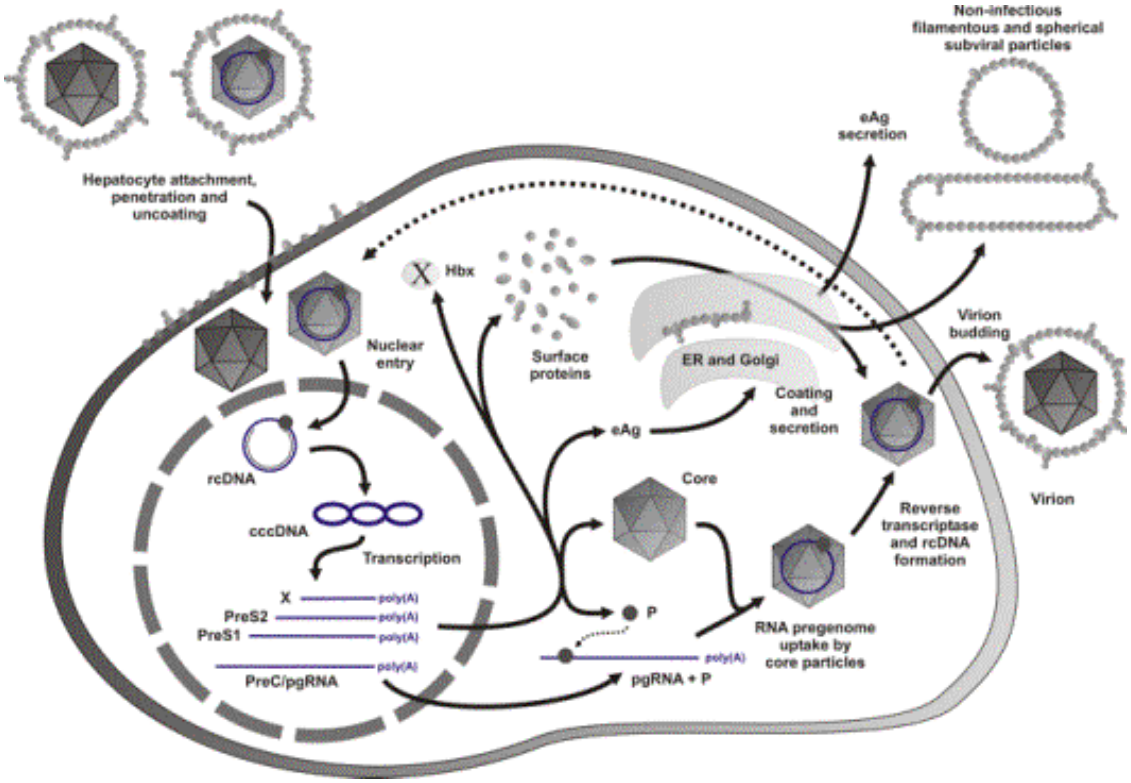
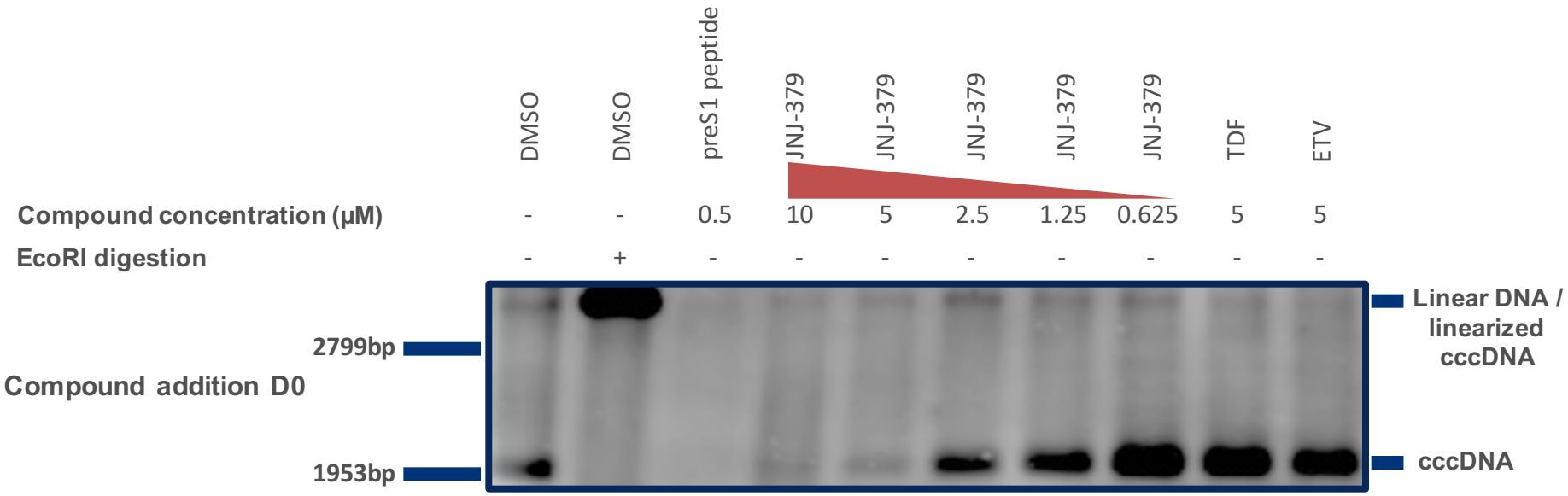


Capsid Assembly Inhibitor - JNJ-379: Effect on cccDNA in HBV-infected PHHs



Dose-dependent inhibition of cccDNA formation in presence of JNJ-379

Berke *et al. AASLD* 2016

Host-Directed Therapies

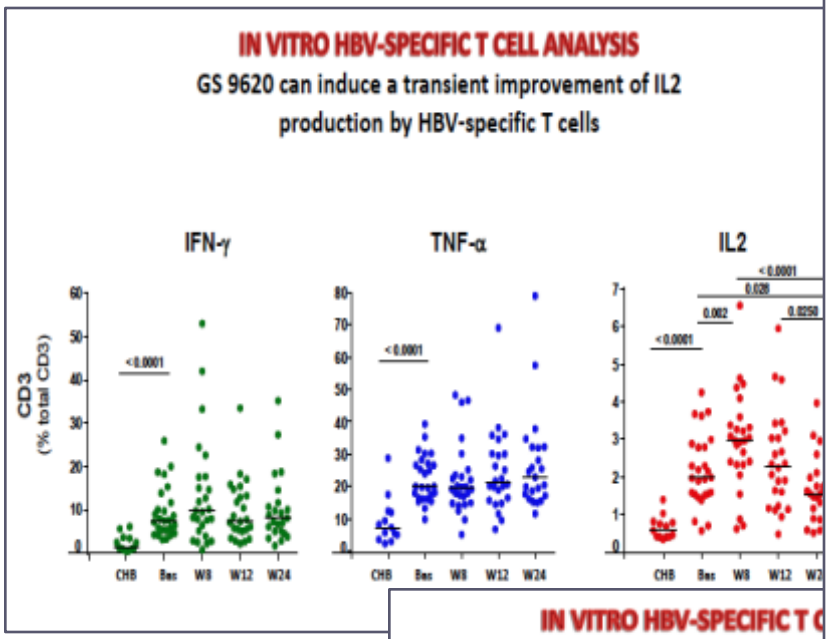
OK – what about optimising the immune response?

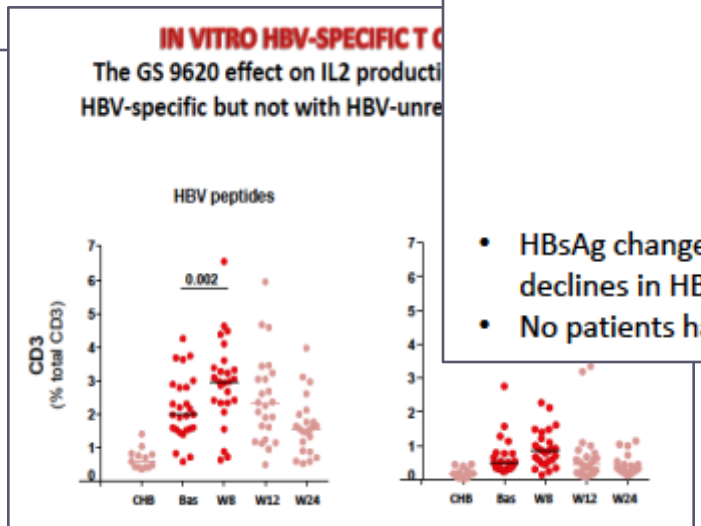
Immune Stimulators?

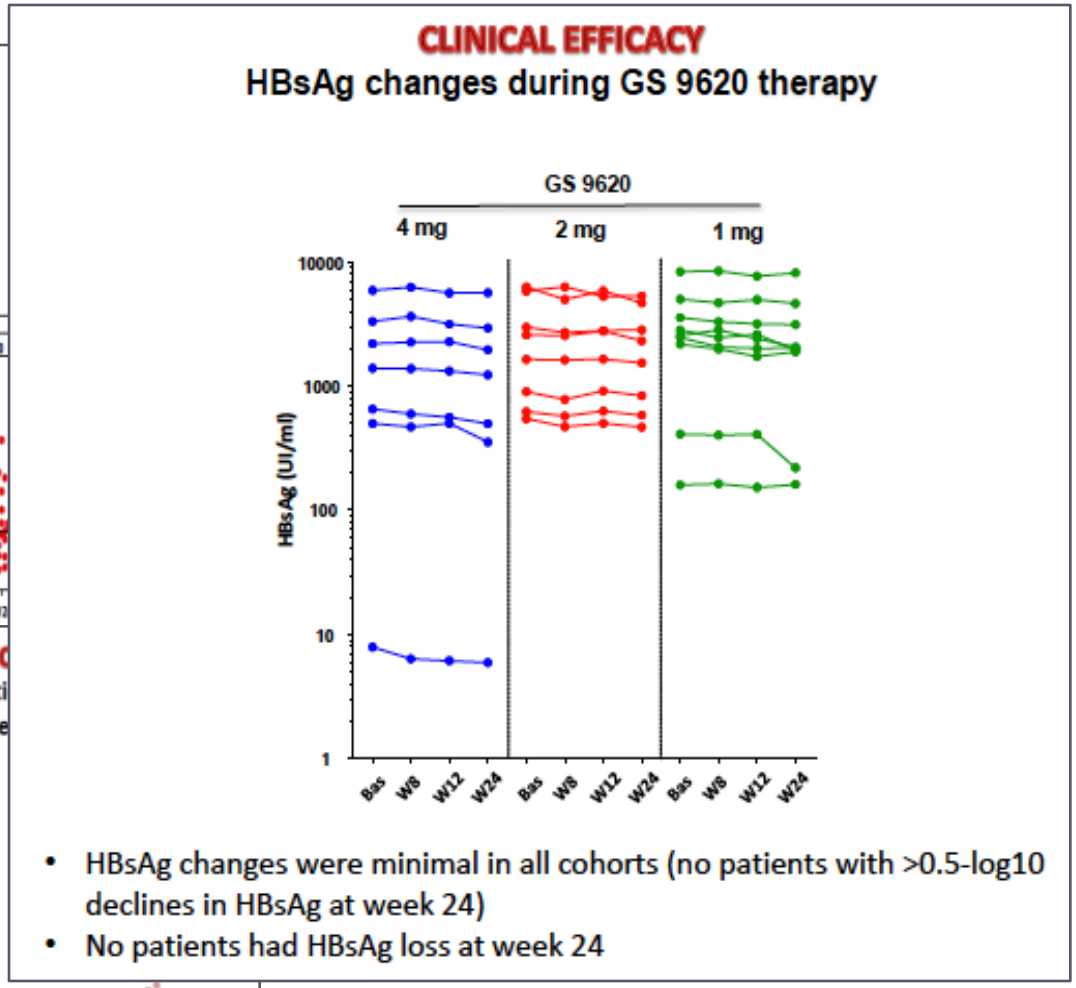
- New Interferons
  - Interferon lambda
    - Better VL and ALT drop and better tolerated
    - However poorer off-treatment/longer-term responses than IFN-alpha
- Toll-like receptor agonists
  - TLR 7
  - TLR 9
- Lymphotoxin-B receptor
  - Possibly acting via APOBEC family
- Others…
  - IL-7, IL-12, IL-18, IL-1, STING agonists etc

Lanford RE *et al. Gastroenterology.* 2013; Menne S *et al. J Hepatol.* 2015; Goldstein and Goldstein, 2009; Lucifora J *et al. Med Sci* (Paris). 2014

TLR agonists







Boni et *al. AASLD* 2016

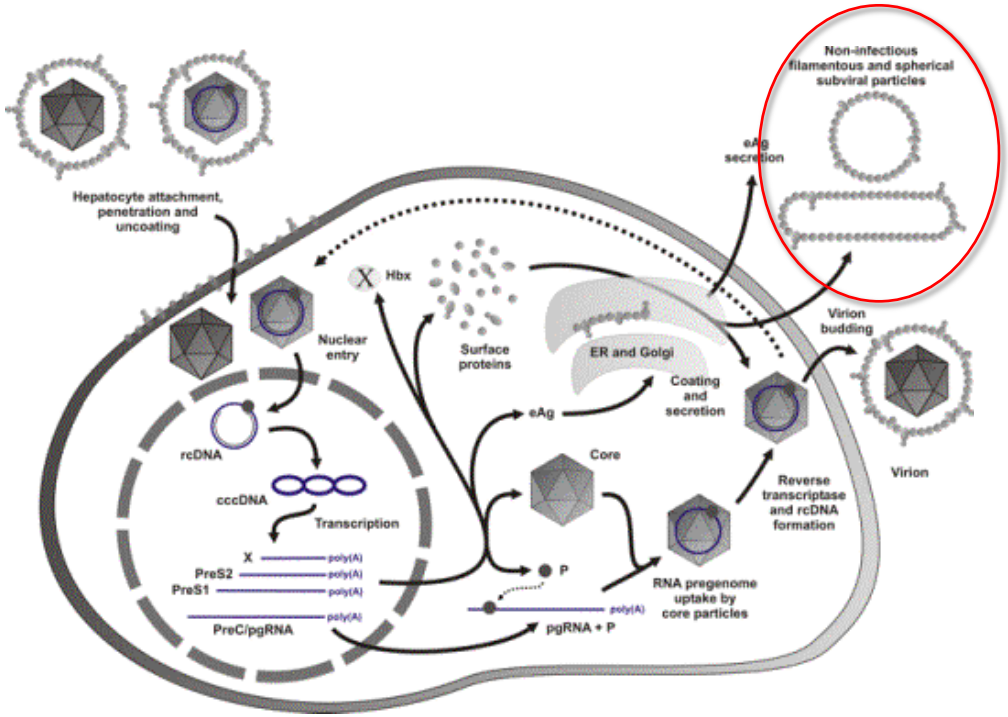
Correction of immune exhaustion?

Checkpoint inhibitors

- PD-1, PD-L1, CTL-4 inhibitors etc.

Main Points

- Small studies
- Toxicity profile of current generation therapies



Vaccination?

Therapeutic vaccines

- S and Pre-S antigen vaccines
- DNA vaccines (especially of S)
- T cell vaccines
- Adenoviral vectors
- And many more…

Main Points

- But probably need to break immune tolerance and exhaustion first…
- May be issues with genotype specificity

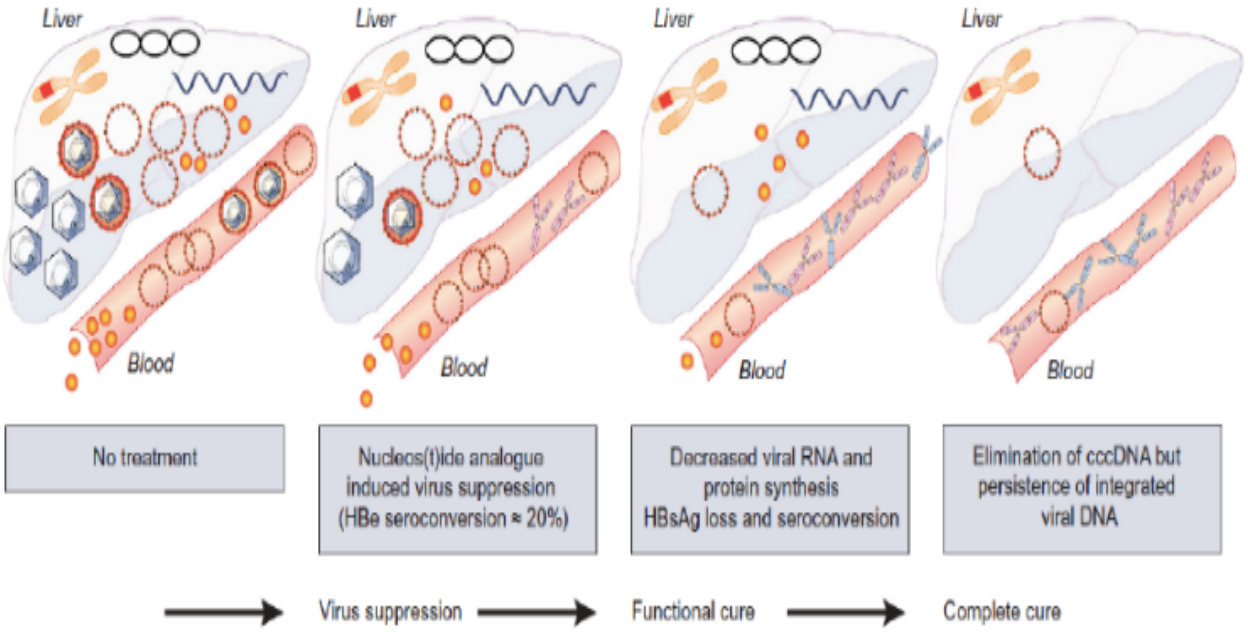
But there are major issues…

It is quite likely that a single drug or target will not be sufficient
Therefore some kind of combination….

- But how do we decide what to combine with what?

How do we assess response?

What are we aiming for and how do we know we have got there?



What are we aiming to achieve?

What is our endpoint for studies?

Regardless – the future is bright and exciting…

Table 1. A summary of clinical trials and their strategies for HBV treatment.

	Targets	Compounds	Developer	Stage of development	ClinicalTrials.gov identifier
DAA	HBpol	GS-7340; Tenofovir Alafenamide (prodrug of tenofovir)	Gilead	Phase 3	NCT01940471 and NCT01940341
	HBpol	AGX-1009 (prodrug)	Agenix	Phase 3 (?)	No identifier found
	HBpol	Besifovir	IlDong Pharmaceutical	Phase 3	NCT01937806
	HBpol	CMX-157 (lipid acyclic nucleoside phosphonate)	Contravir	Phase 1	NCT02585440
	HBc	GLS-4 (Morphothiadine mesilate)	HEC Pharm/SUnshine	Phase 2	China-CFDA
	HBc	NVR 3-778	Novira Pharmaceuticals	Phase 1	NCT02112799 & NCT02401737
	HBs	REP-2139 (nucleic acid polymers)	Replicor	Phase 2 for both HBV and HDV	NCT02565719 and NCT02233075
	Viral RNAs	siRNA: ARC-520/ARC-521	Arrowhead	Phase 2	NCT02604212 and NCT02604199
	Viral RNAs	siRNA: ISIS-HBVRx	Ionis pharmaceuticals	Phase 1 or 2 (?)	No identifier found
HTA	NTCP	Myrcludex	Hepatera and MYR GmbH	Phase 2 for both HBV and HDV	Development in Russian Federation
	Promotion of apoptosis in infected cells	Birinapant	Tetralogic	Phase 1	NCT02288208
	Prenylation/farnesylation	Lonafarnib	Eiger BioPharmaceuticals	Phase 2 for HDV	NCT02430181, NCT02430194, NCT02511431
	Immune stimulation	Thymosin alpha	Seoul National University Hospital	Phase 4	NCT00291616
	pDC stimulation	GS-9620 (TLR7 agonist)	Gilead	Phase 2	NCT02166047 & NCT02579382
	Immune stimulation	INO-1800	Inovio Pharmaceuticals	Phase 1	NCT02431312
	Immune stimulation	Cyt-107 (IL-7)	Cythesis	Phase 1/2 (discontinued)	NCT01027065
	Immune stimulation	IFN-lambda	BMS	Phase 2 (discontinued)	NCT01204762
	Adaptive responses	ABX-203	Abivax	Phase 2/3	NCT02249988
	Adaptive responses	GS-4774 (therapeutic vaccine)	Gilead	Phase 2	NCT01943799 & NCT02174276
	Adaptive responses	TG-1050 (therapeutic vaccine)	Transgene	Phase 1	NCT02428400
	Adaptive responses	DV-601 (therapeutic vaccine)	Dynavax	Phase 1	NCT01023230
	Adaptive response	HB-110	Genexine	Phase 1	NCT01641536
	Adaptive responses	Nivolumab (Anti-PD1 mAb)	Ono Pharmaceuticals/ BMS	Phase 1/2 for HCC	NCT01658878

There is a full pipeline for HBV drugs in development

Durantel D *et al. J Hepatol.* 2016 Apr;64(1 Suppl):S117-31

Not yet clear what will work, in which combination, in which patient, at what time etc…..