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Second Wave of HBV Antivirals

Advantages of Direct Acting Antivirals

- Targets the virus and not the host
  - Inhibitors are highly selective for target
  - No cellular homologs of target, avoid off target side effects
- Target highly defined with better understanding of inhibitory mechanism
- Can apply maximum suppression on the target
- Easier pathway to oral administration
- Combination of DAAs possessing different mechanisms potentiates potency and establishes a high genetic barrier to resistance

Thought We Had A Change of Cure 12 Years Ago

- Currently approved therapy
  - Nucleoside Analogs: Entecavir, Lamivudine, Telbivudine
  - Nucleotide Analogs: Tenofovir, Adefovir, Tenofovir Alafenamide
  - Interferons (IFN and peg-IFN)
- Entecavir and Tenofovir
  - Safe, highly effective therapies and the current drugs of choice
  - Target the viral polymerase, functional mechanisms include
    - Inhibition of the reverse transcription of negative strand DNA from pgRNA
    - Inhibition of positive strand HBV DNA synthesis
  - Highly effective suppression of HBV DNA levels in virtually all treatment-naïve patients
  - HBV DNA undetectability maintained for prolonged periods (years)
  - One pill, once-a-day dosing
  - Very well tolerated
  - No meaningful resistance emergence

Woodchuck Hepatitis B Virus Model

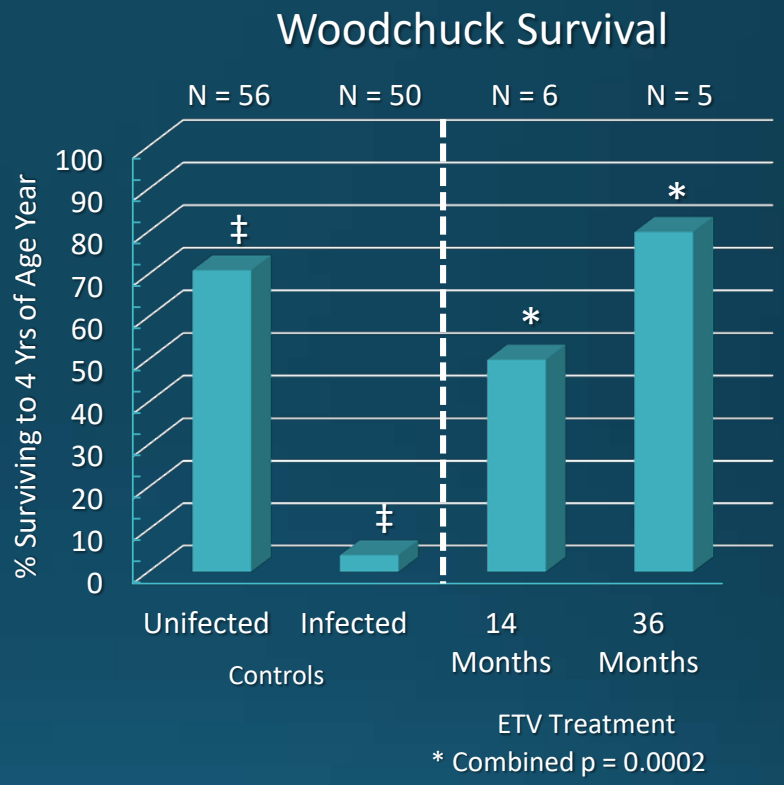
- Infection at 3 days of age with WHBV results in a carrier state with life-long viremia
- Chronically-infected animals mimic the HBV carrier state in man (viral pathogenesis & development of HCC)
- Infected woodchucks have a >90% chance of dying of HCC within 4 years
- Predictive model for toxicity and effectiveness of antivirals in man
- ETV potency against WHBV equivalent to HBV

Long-term treatment study conducted to determine if prolonged ETV therapy could cure woodchucks?

Colonno, et al. JID 2001;184:1236-45

Long-Term Woodchuck Study: Cure and Survival

- ETV Treatment (0.5 mg/kg)
  - 2 Months of daily administration
  - 12 or 34 months of weekly treatment
- Sustained suppression (≥ 8 logs) of viral DNA levels for 1-3 years – no rebounds or evidence of resistance
- cccDNA levels reduced >4 logs
- WHBsAg levels reduced 91% at Week 96
- Survival in ETV-treated animals significantly improved over historical controls
- Clear evidence that ETV can cure woodchucks based on multiple parameters



Unfortunately, this is not what happens in HBV patients with prolonged therapy

‡Historical control. Tennant, et al. Viral Hepatitis and Liver Disease 1988: 462-464
Colonno, et al. JID 2001;184:1236-45

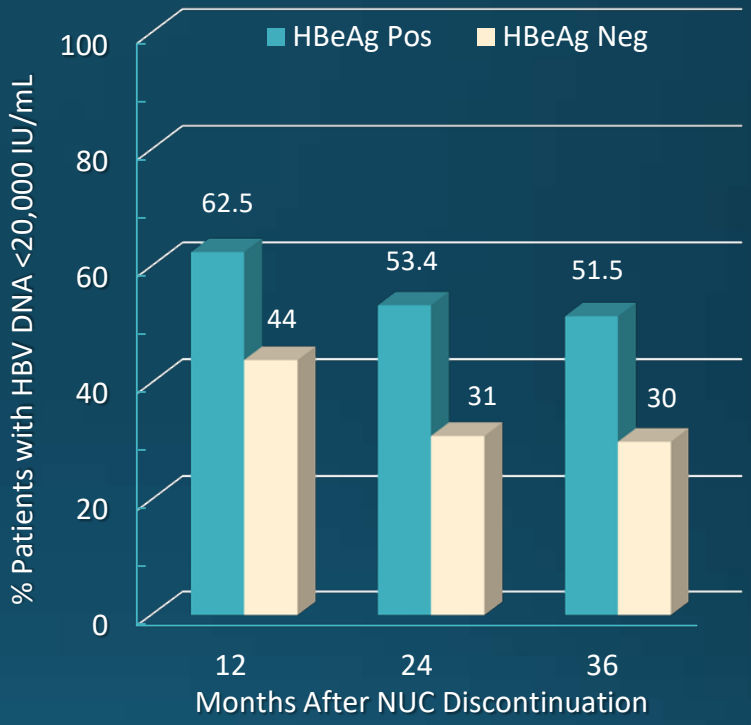
Relative Efficacy of Approved HBV Therapies

Results at 48 Weeks

	ETV[1,2]	TFV[3]	Peg-IFN[4,5]
HBeAg Positive	N = 354	N = 176	N = 271
HBV DNA Undetectable	67%	76%	25%[a]
HBeAg Seroconversion	21%	21%	27%
ALT Normalization	68%	68%	39%
HBsAg Loss	2.0%	3.2%	2.9%
HBeAg Negative	N = 325	N = 250	N = 177
HBV DNA Undetectable	90%	93%	63%[a]
ALT Normalization	78%	76%	38%
HBsAg Loss	0.3%	0%	0.6%[b]

[a] HBV DNA <400 copies/mL; [b]At 72 weeks

Virologic Relapse After Nuc Discontinuation



HBeAg Positive Patients
14 studies, 733 initially HBeAg positive
Pooled HBsAg loss: 1%

HBeAg Negative Patients
17 studies, 967 HBeAg negative patients
Pooled HBsAg loss: 1.7%

Papatheodoridis G. et al, Hepatology 2016

Table courtesy of Geoff Dusheiko

[1] Chang T-T, et al. N Engl J Med 2006:354:1001-10
[2] Lai C-L, et al. N Engl J Med 2006:354:1011-20
[3] Marcellin P, et al. N Engl J Med 2008:359:2442-55
[4] Lau GKK, et al. N Engl J Med 2005:352:2682-95
[5] Marcellin P, et al. N Engl J Med 2004:351:1206-17

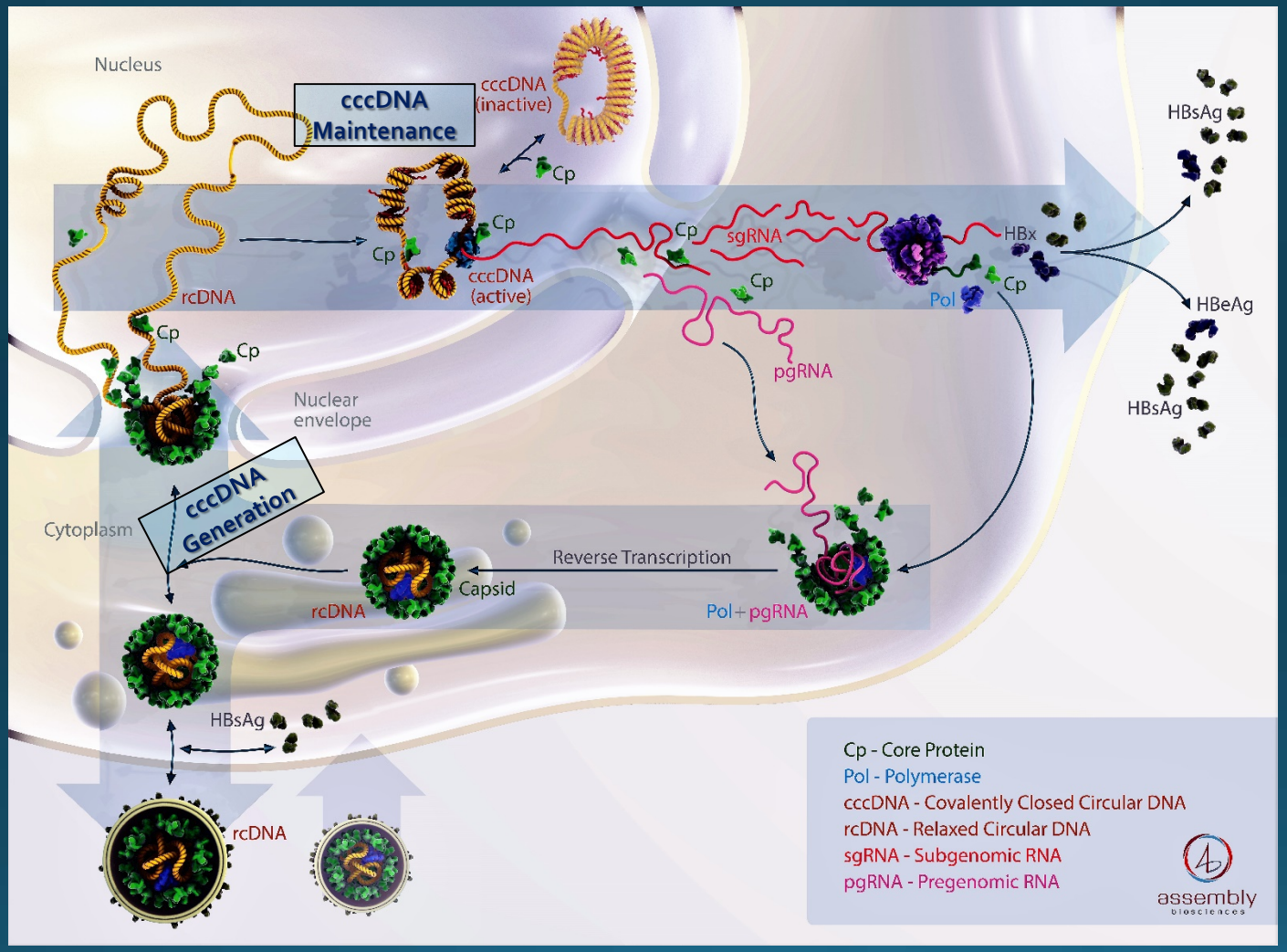
Aspirational Objectives for Clinical Cure in Humans

We want what we achieved in woodchucks!

- Treatment of less than 2 years
  - Convenient dosing (once daily?) and low pill burden
  - Excellent safety profile, with minimal side effects
- Sustained remission off therapy
  - Viral DNA replication remains undetectable
  - Elimination of cccDNA reservoirs
- Clinical efficacy
  - HBsAg loss and seroconversion
  - Reversal of liver damage, lack of hepatic inflammation
  - Significant reduction in the risk of future HCC development

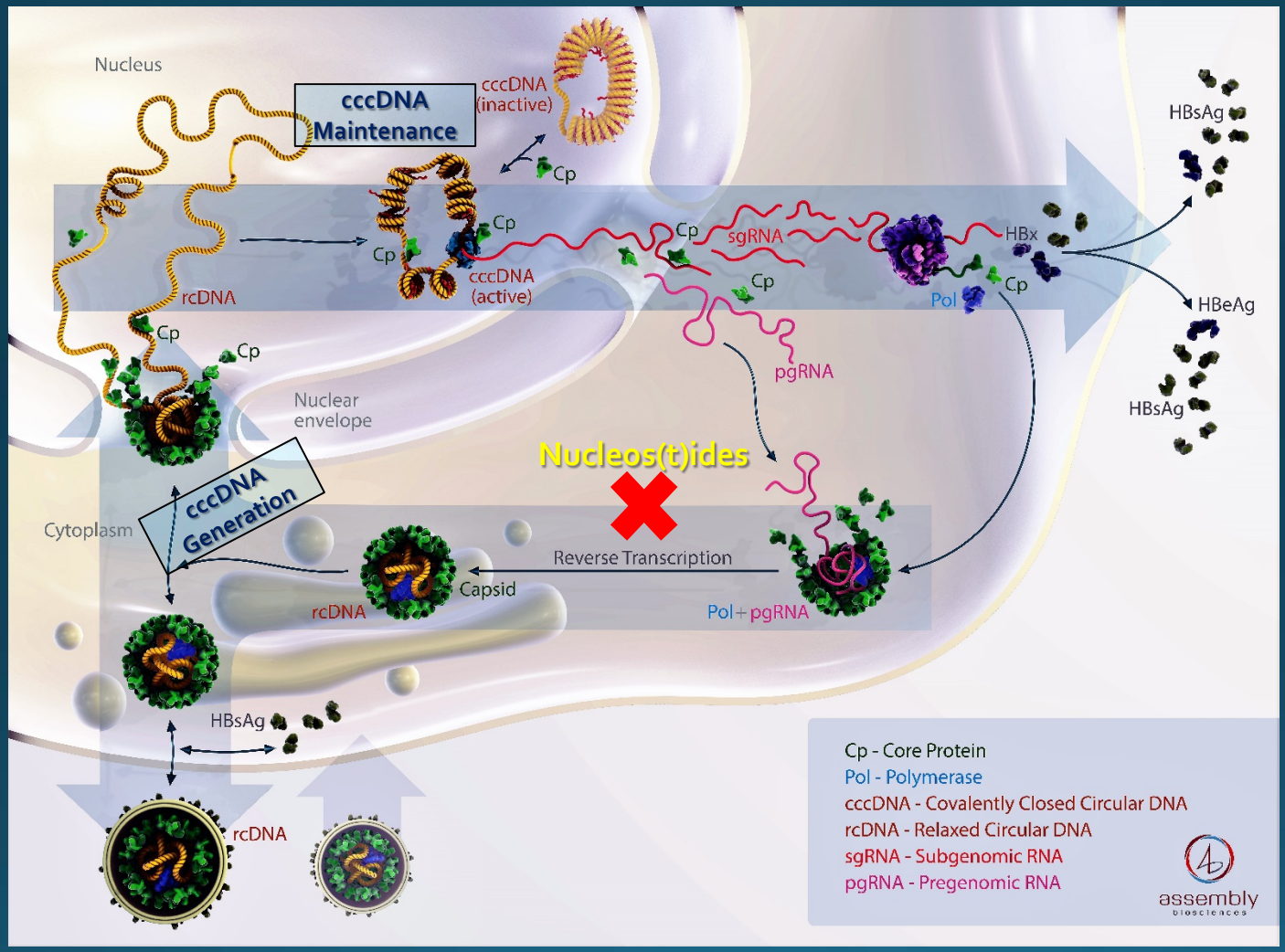
To achieve clinical cure, new therapies will likely needs to Inhibit the generation of new cccDNA and/or Eliminate (or Silence) existing cccDNA reservoirs

HBV Life Cycle: Complicated with Limited Targets

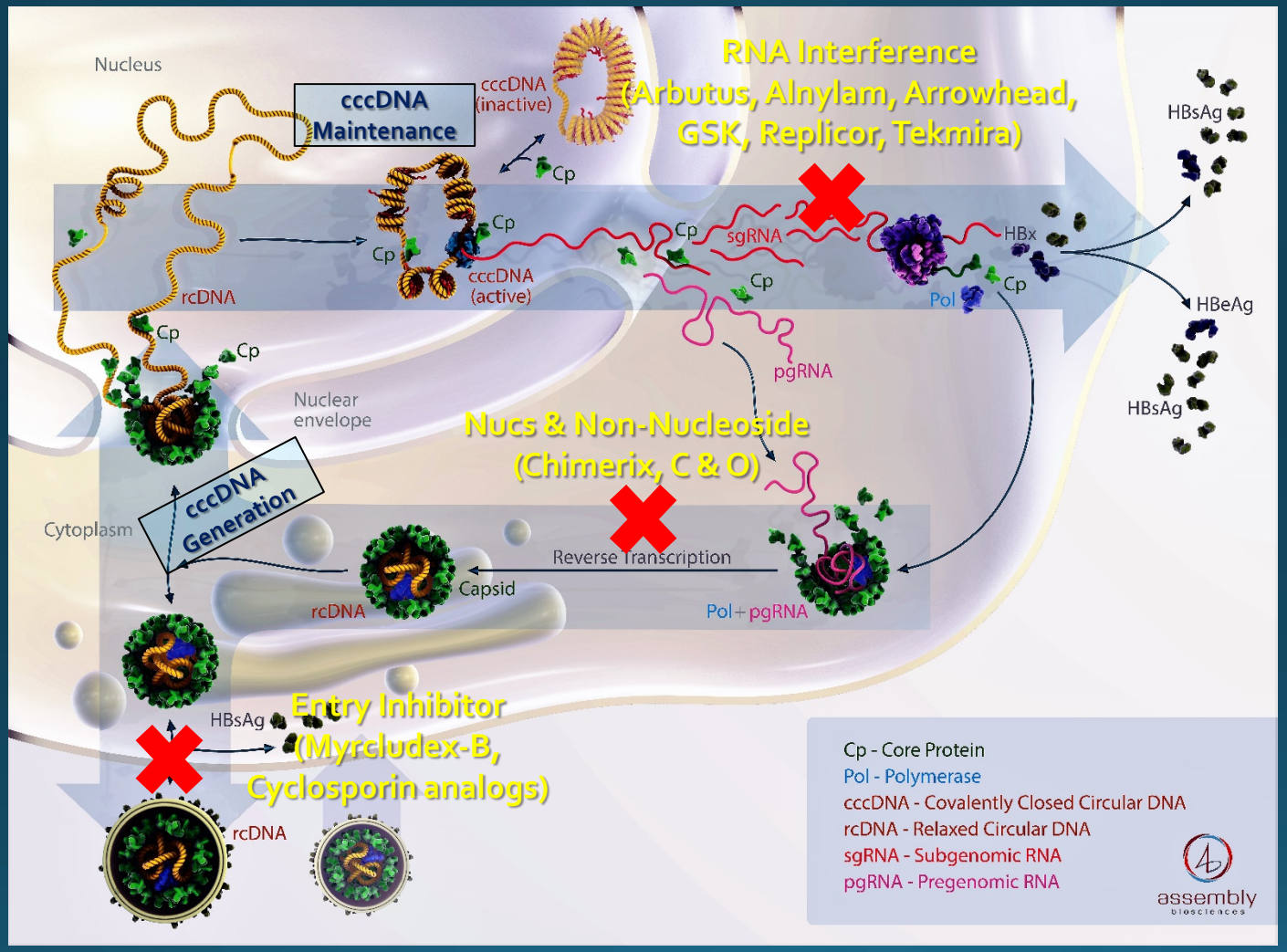


HBV genome only encodes four known genes: Core, X, Polymerase and S (HBsAg)

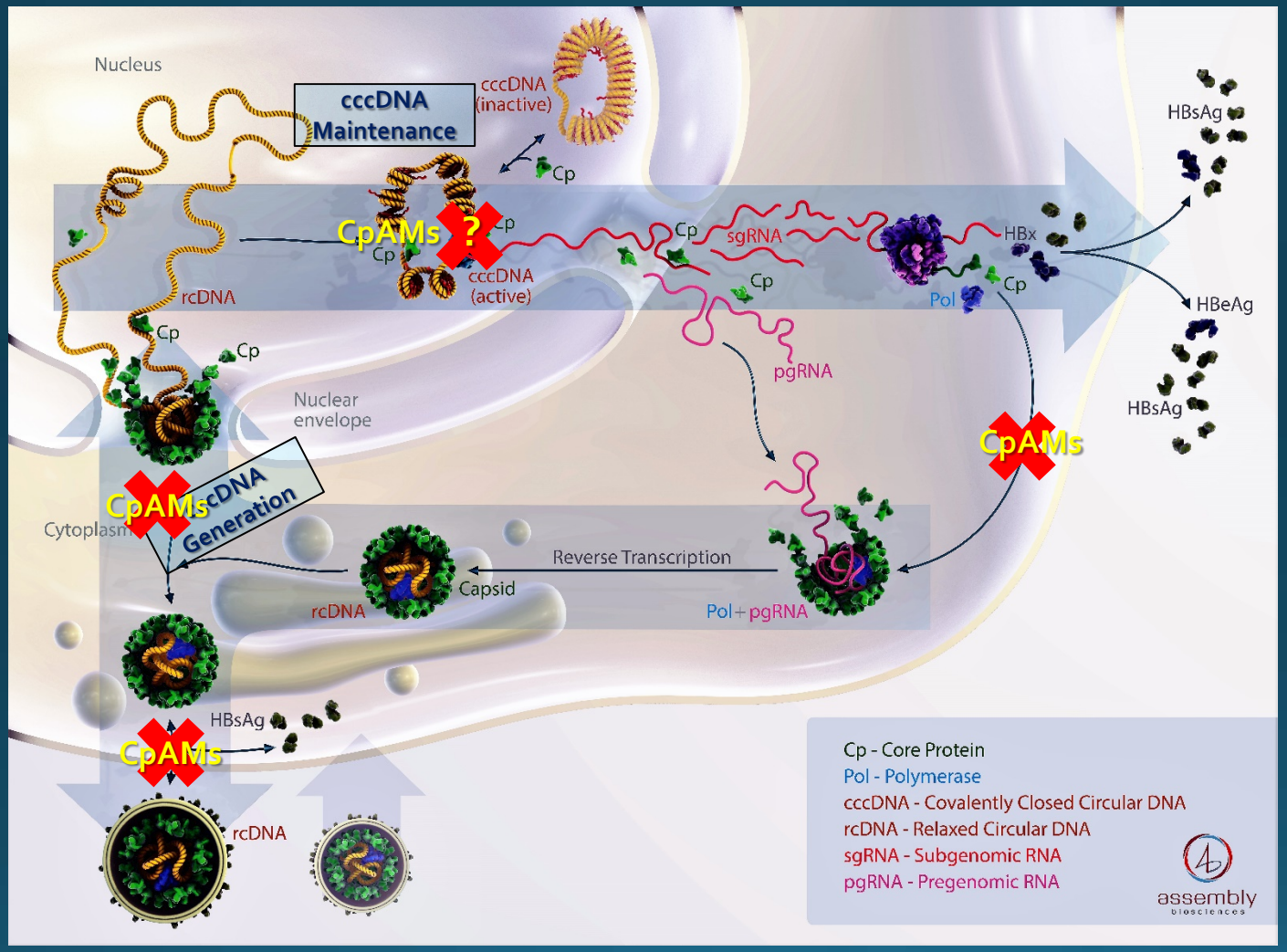
HBV Life Cycle: Failure of Nucs to Inhibit cccDNA



HBV Life Cycle: New Antiviral Targets Being Pursued

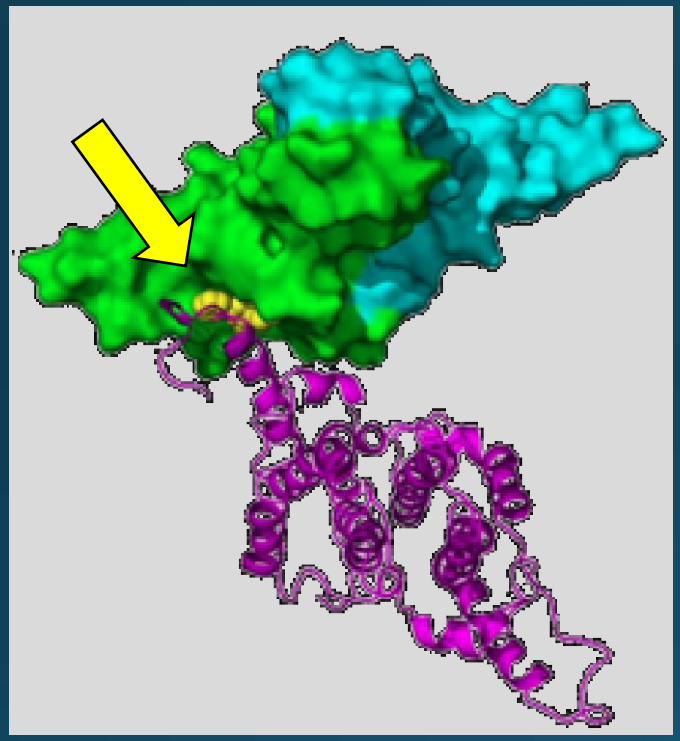


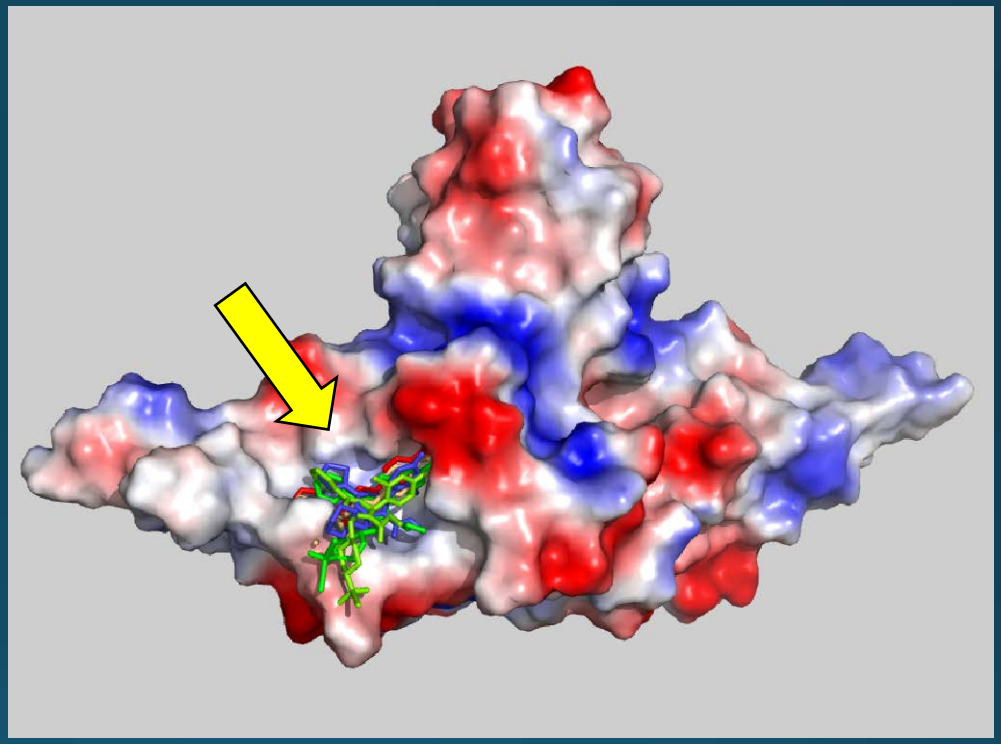
HBV Core Protein Is Required Throughout Lifecycle



CpAMs (Core Protein Allosteric Modulators) are being pursued at Assembly Biosciences, Arbutus, Enanta, Gilead, HEC, J&J and Roche

CpAMs Bind Core Protein and Interfere with Multiple Steps of Viral Replicative Cycle

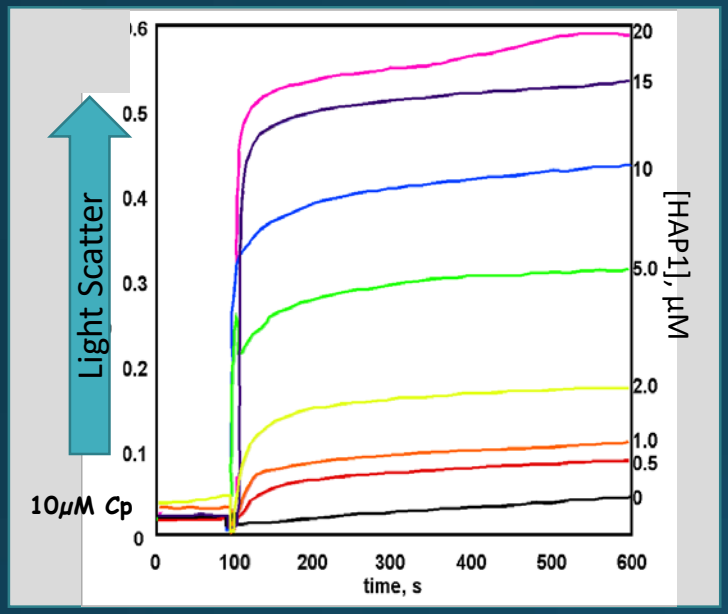


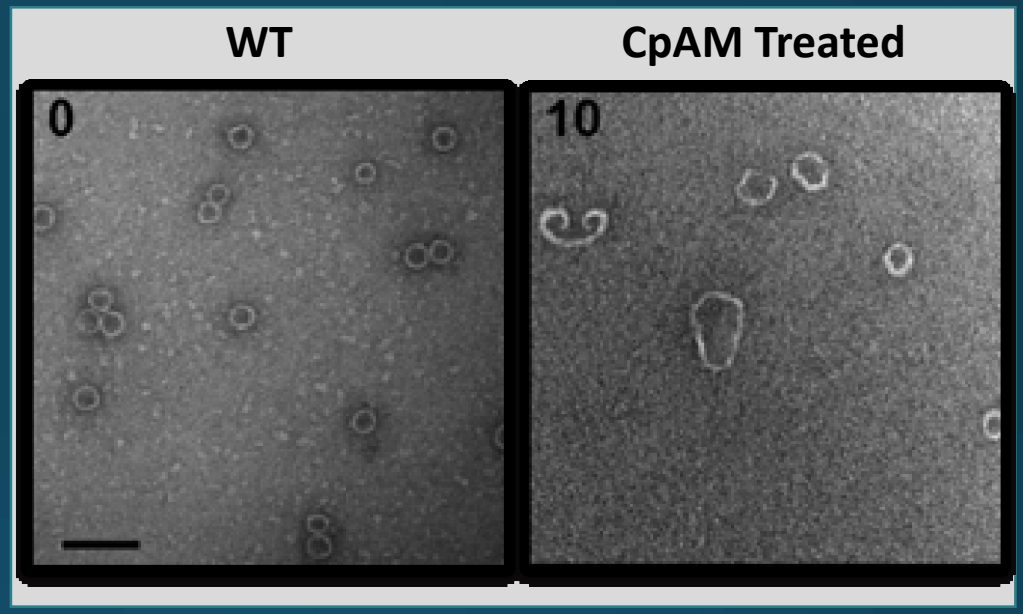


Katen, et al. Structure, 2013. 21:1406; Klumpp, et al., Proc Natl Acad Sci U S A, 2015. 112:15196; Venkatakrishnan, et al., J Virol, 2016. 90:3994

- CpAMs bind to a pocket in Core protein located at the dimer-dimer interface
- As a class, CpAM antiviral activity is HBV specific and pangenotypic

CpAMs Accelerate/Promote Capsid Assembly

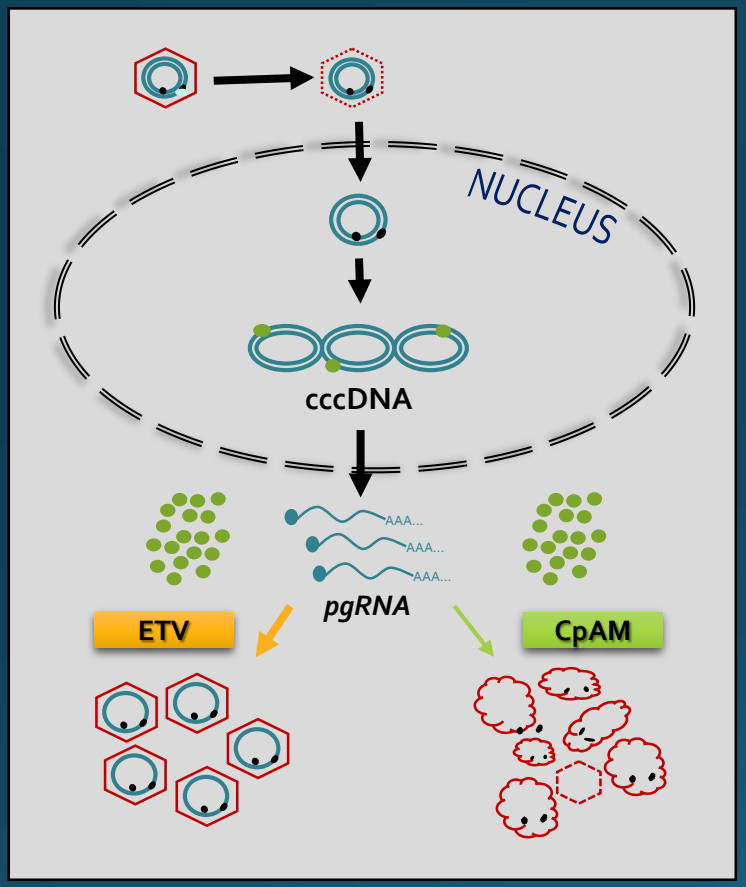


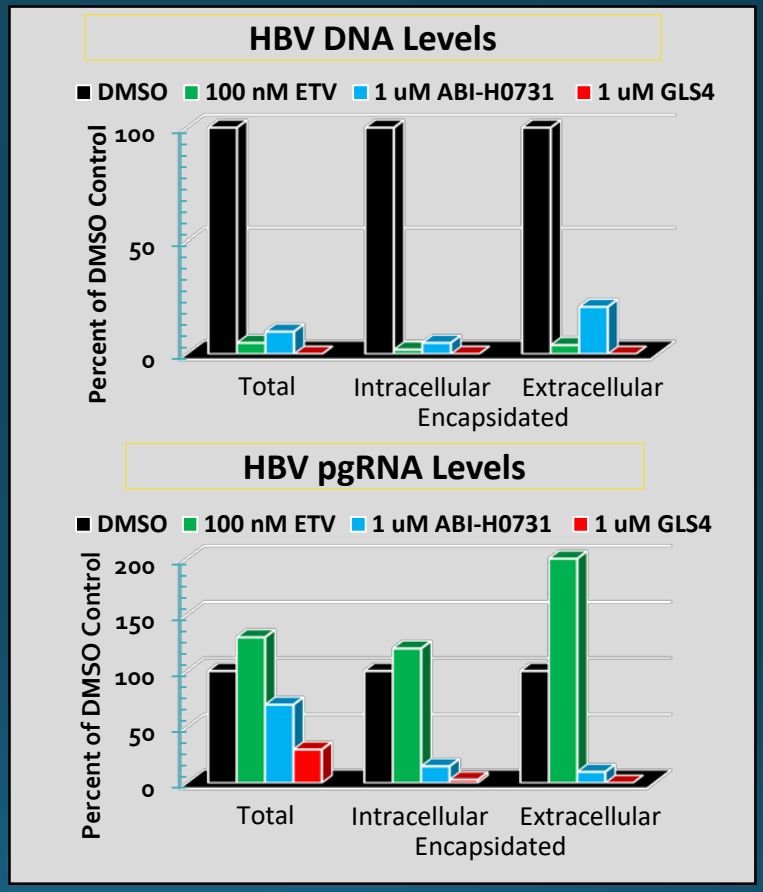


Stray et al 2005. PNAS102, 8138-43

- Treatment results in aberrant empty capsid structures that are not infectious
- Some CpAMs can also cause premature capsid disassembly

CpAMs and ETV Inhibit HBV Replication by Distinct Mechanisms

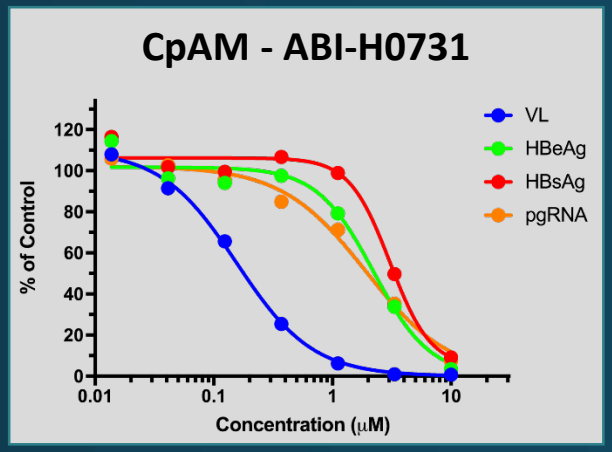


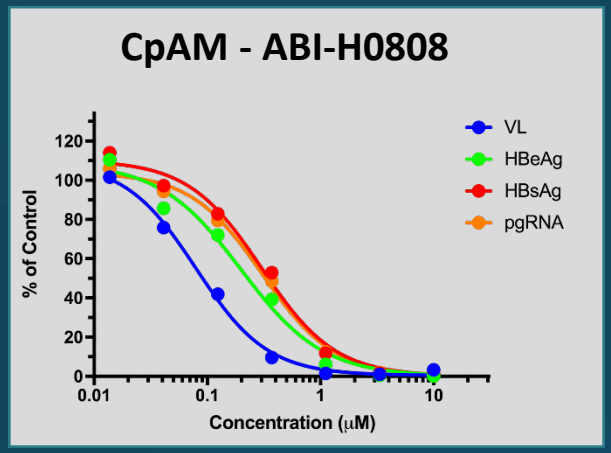


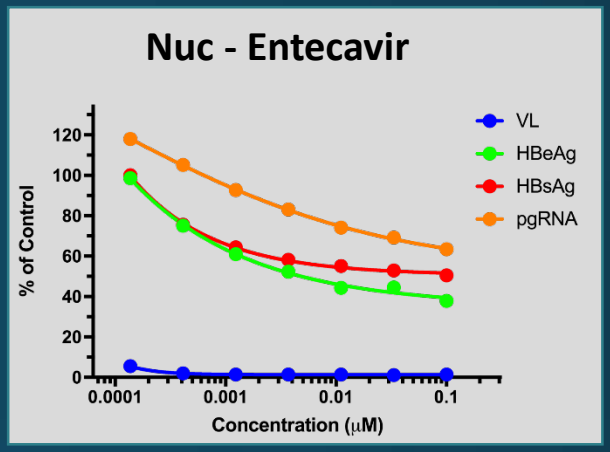
- CpAMs ABI-H0731 & GLS4 inhibit encapsidation of both viral DNA and pgRNA
- ETV inhibited HBV DNA synthesis, but increased levels of pgRNA in intracellular capsids by failing to create the RNA:DNA duplex digested by RNaseH

Q. Huang, et al. Intl HBV Meeting, Seoul, Korea, September 2016

CpAMs inhibit cccDNA Generation in Primary Human Hepatocytes







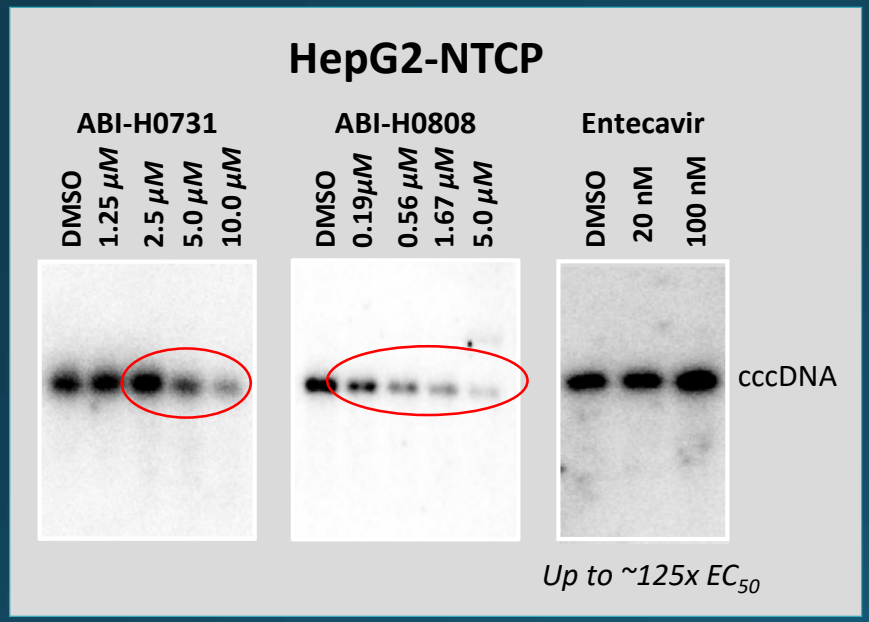
	EC_{50} (nM)			
Compound	**Viral DNA**	**HBeAg**	**HBsAg**	**pgRNA**
ABI-H0731	**154**	**2,210**	**3,000**	**1,840**
ABI-H0808	**80**	**196**	**310**	**305**
ETV	**<0.1**	**Incomplete**	**Incomplete**	**Incomplete**

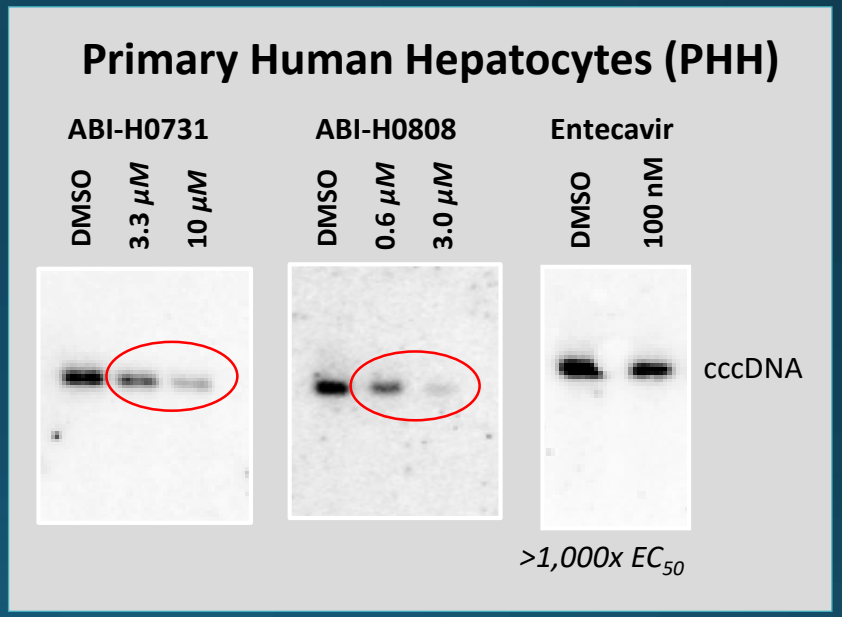
- CpAMs reduced viral HBV DNA levels and known surrogate markers for cccDNA (HBeAg, HBsAg and pgRNA)
- ETV was highly effective at inhibiting HBV DNA levels, but exhibited limited effect on cccDNA surrogate markers

Q. Huang, et al. Intl HBV Meeting, Seoul, Korea, September 2016

CpAMs Block cccDNA Formation in HBV Infected Cells

Southern blot of extracted extrachromosomal DNA from HBV infected cells following sequential T5 exonuclease and EcoRI endonuclease digestion





- Only CpAMs reduced cccDNA formation in HepG2-NTCP and PHH
- ETV (125-1,000x EC_{50}) had minimal effect on cccDNA levels

Q. Huang, et al. AASLD Meeting, Boston, MA, November 2016

Summary

- People unfortunately, are not woodchucks!
- Strong imperative to identify treatments/strategies that result is significantly higher cure rates
- HBV cccDNA appears to be obvious target, as this moiety is believed to be responsible for sustaining a chronic infection and is not significantly impacted by “standard of care” therapy
- HBV Core protein plays multiple roles throughout the HBV lifecycle and represents an excellent target by which to impact cccDNA levels
- CpAMs represent a new class of direct acting antivirals that target Core protein, are selective for HBV and inhibit *de novo* cccDNA formation
- The combination of a Nuc with a CpAM should show strong antiviral activity, have a high resistance barrier and most importantly, decrease cccDNA levels
- The addition of other classes of antiviral or immunologic agents may help to accelerate this process