# Targeting HBV Core Protein to Achieve Higher Cure Rates

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Targeting HBV
New Drug Development for HBV & Other Infectious Diseases
September 25, 2017
Boston, MA

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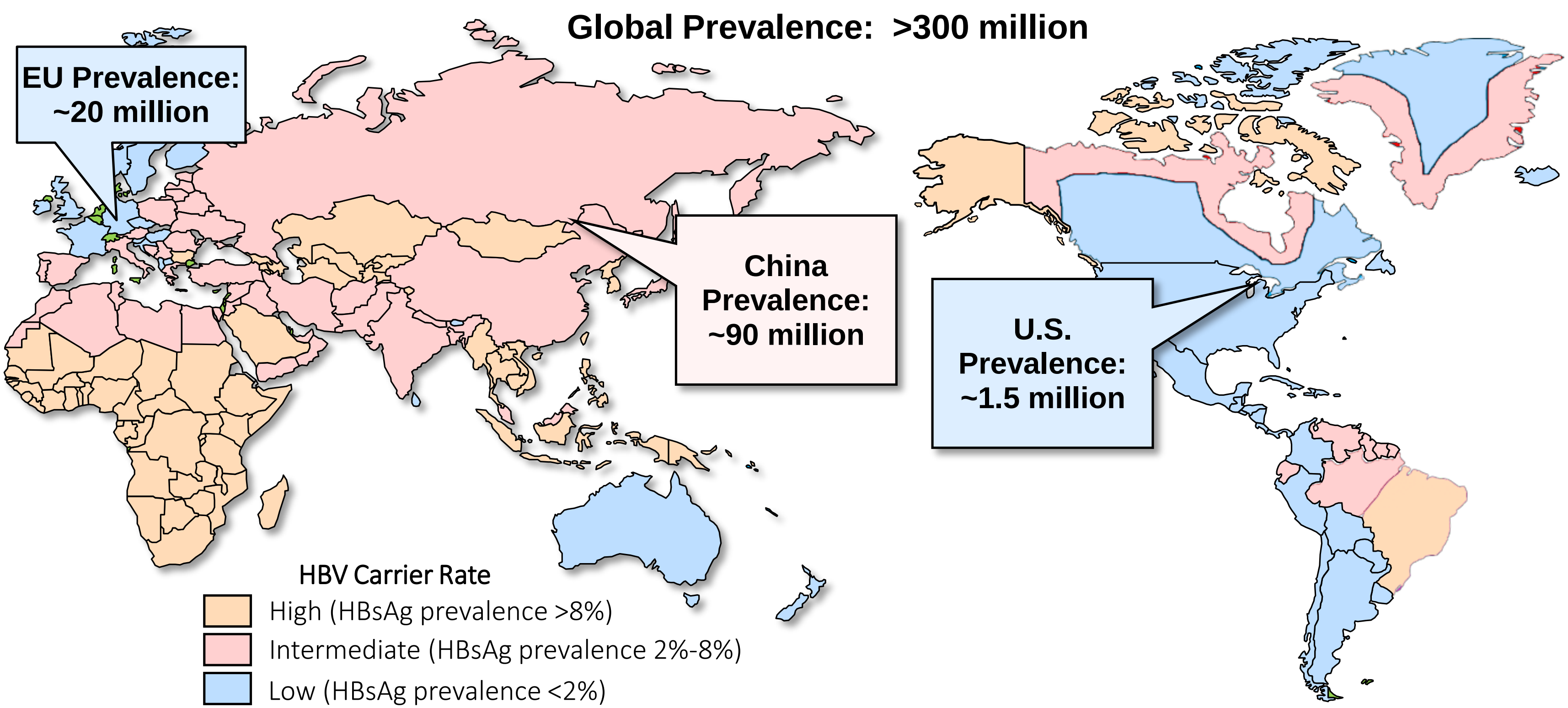
biosciences

# Cautionary Note Regarding Forward-looking Statements

Some of the information in this presentation contains forward-looking statements regarding future events, including statements about the clinical and therapeutic potential of Assembly's development programs and drug candidates. Certain forward-looking statements may be identified by reference to a future period or periods or by use of forward-looking terminology such as "may," "expected," "should" or "predictive." Assembly intends such forward-looking statements to be covered by the safe harbor provisions contained in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. More information about the risks and uncertainties faced by Assembly are more fully detailed under the heading "Risk Factors" in Assembly's Annual Report on Form 10-K for the year ended December 31, 2016, and Quarterly Report on Form 10-Q for the quarter ending June 30, 2017 filed with the Securities and Exchange Commission. Except as required by law, Assembly assumes no obligation to update publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

# Significant Need Remains for Curative Therapies

- Number of chronically-infected HBV patients exceeds the number of patients infected with HCV (~170M) plus HIV (~37M) combined
- The majority are undiagnosed – often asymptomatic for years
- Chronic HBV infection results in chronic inflammation and progressive liver damage, potentially leading to liver cirrhosis, HCC and death (~1M deaths/year)




*Jidong Jia. HBV HCV epidem & therapy 2013*
http://www.who.int/hepatitis/en/

# Current HBV Therapies

- Currently Approved
  - 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, inhibiting reverse transcription of negative-strand DNA from pgRNA and positive-strand HBV DNA synthesis to generate rcDNA
  - Highly effective reduction and maintenance of HBV DNA at undetectable levels in virtually all treatment-naïve patients
  - HBV DNA undetectability maintained for prolonged periods (years)
  - One pill, once-a-day dosing
  - Very well tolerated, with no meaningful resistance emergence over prolonged treatment periods
  - Unfortunately, cure rates are very low despite prolonged therapy

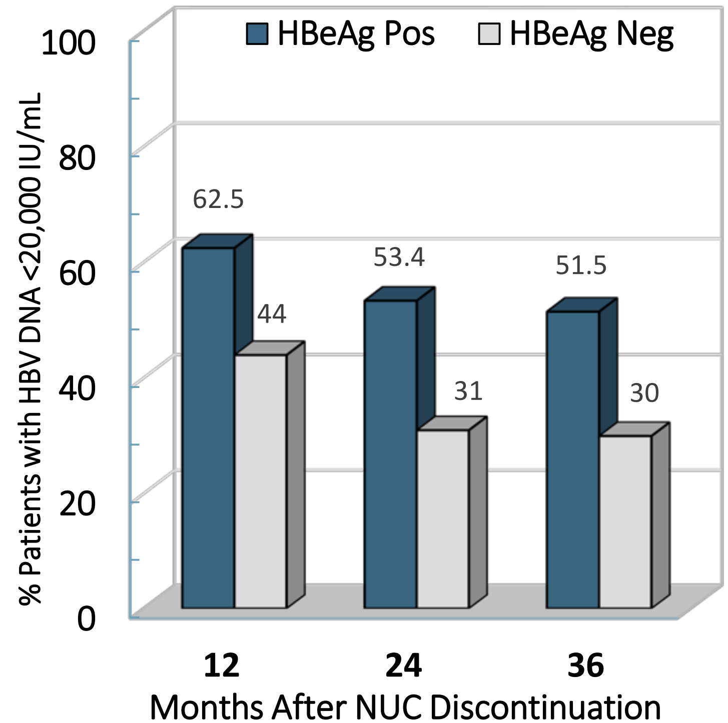
# Deficiencies of Current Approved Therapies

Results at 48 Weeks

| HBV Patients | 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]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
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 2004:351:1206-1*

# Thought We Had A Chance for Cure 12 Years Ago

**Woodchuck Hepatitis B Virus Model**

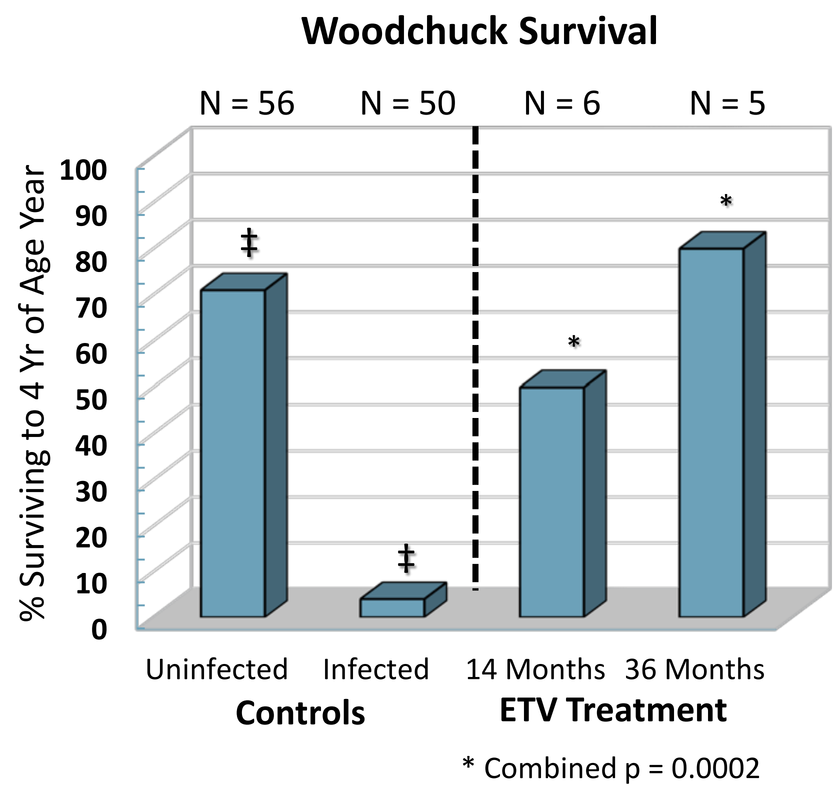
- WHBV infection at 3 days of age results in a carrier state with life-long viremia
- Chronically-infected animals mimic the HBV carrier state in man (viral pathogenesis & development of HCC)
- Infected woodchucks have a >90% chance of dying of HCC within 4 years
- Predictive model for toxicity and effectiveness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

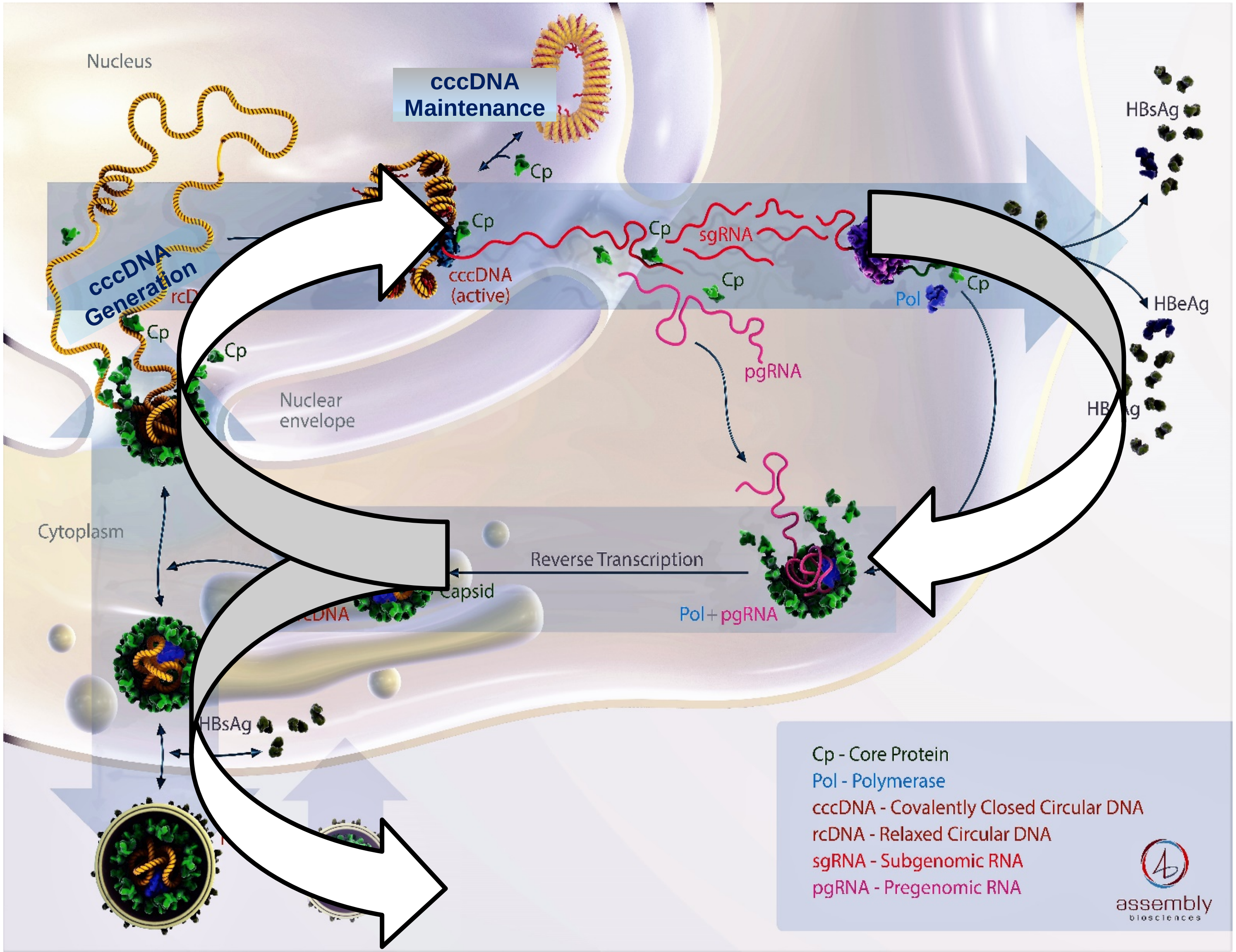
- ETV Treatment (0.5 mg/kg)
  - 2 months of daily treatment
  - 12 or 34 months of weekly treatment
- Sustained suppression (≥ 8 logs) of viral DNA levels for 1-3 years – no rebounds or evidence of resistance
- cccDNA levels reduced >4 logs
- WHBsAg levels reduced 91% at Week 96
- Survival in ETV-treated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



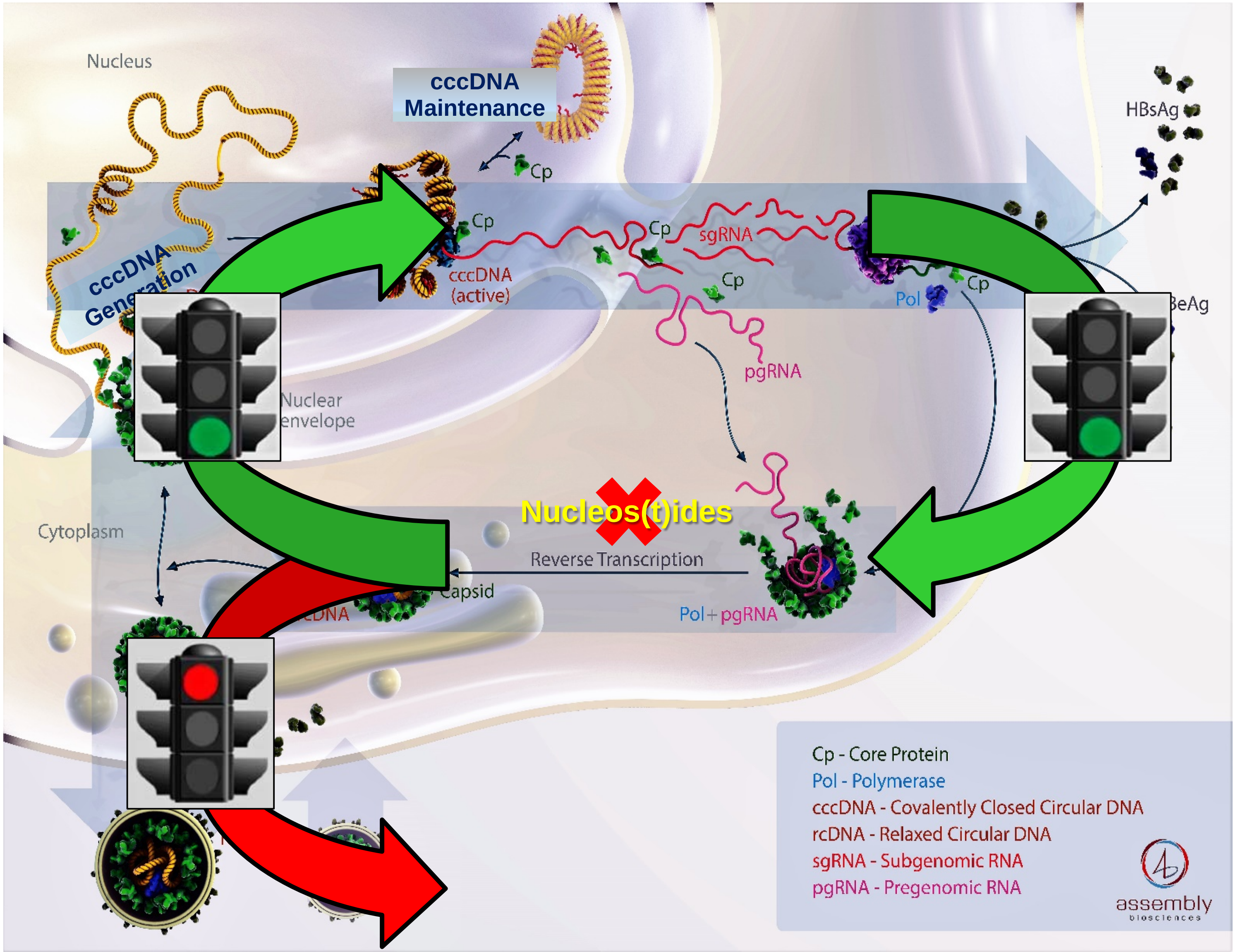

**Unfortunately, this is not what happens in HBV patients with prolonged therapy**

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

# HBV Life Cycle: Complex and Poorly Understood



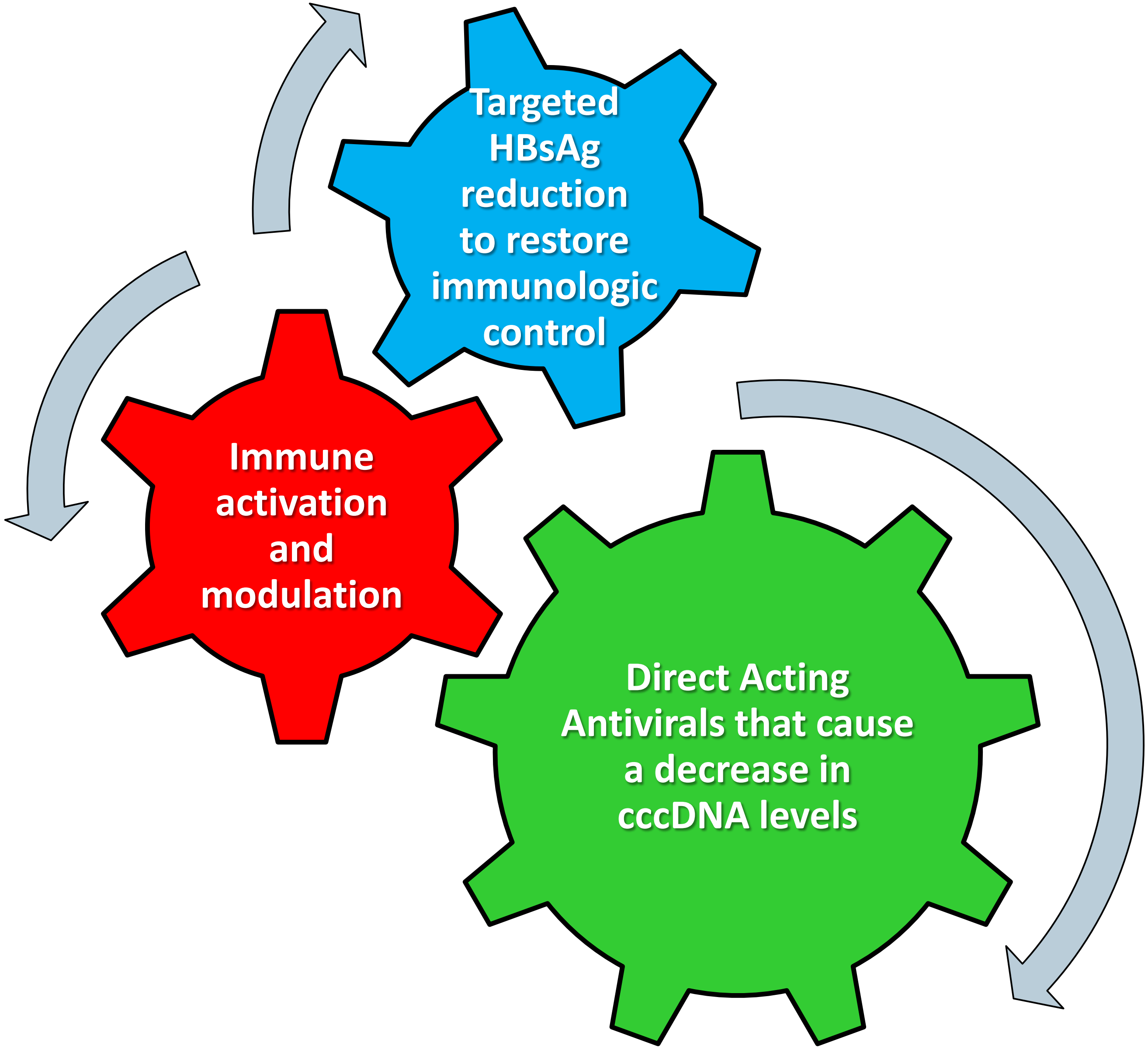
# HBV Life Cycle: Failure of Nucs to Inhibit cccDNA



# Aspirational Objectives for Clinical Cure in Humans

- We want what we achieved in woodchucks!
- Must cause depletion of cccDNA pools
  - Inhibit generation of new cccDNA
  - Direct silencing or elimination of existing cccDNA (more challenging)
- Decrease HBsAg levels to restore/enhance immune response
- Treatment of less than 2 years
  - Convenient dosing (QD?) 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 ideally, seroconversion
  - Reversal of liver damage, lack of hepatic inflammation
  - Significant reduction in the risk of future HCC development

# Strategic Approaches Being Pursued for Cure



# Assembly Biosciences Focused on Targeting Core Protein to Decrease cccDNA Levels

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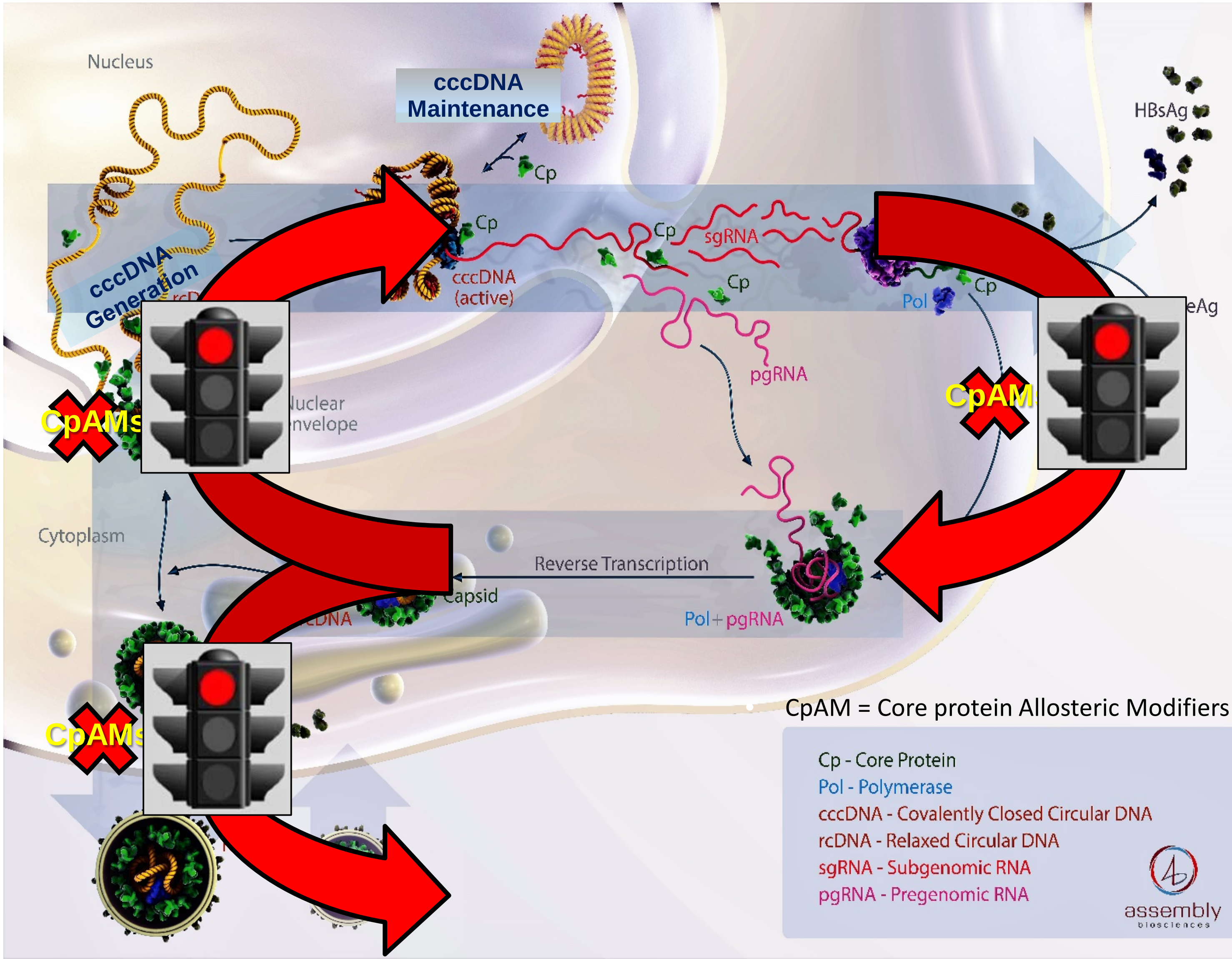
# ASMB Focused on Inhibitors of Core Protein

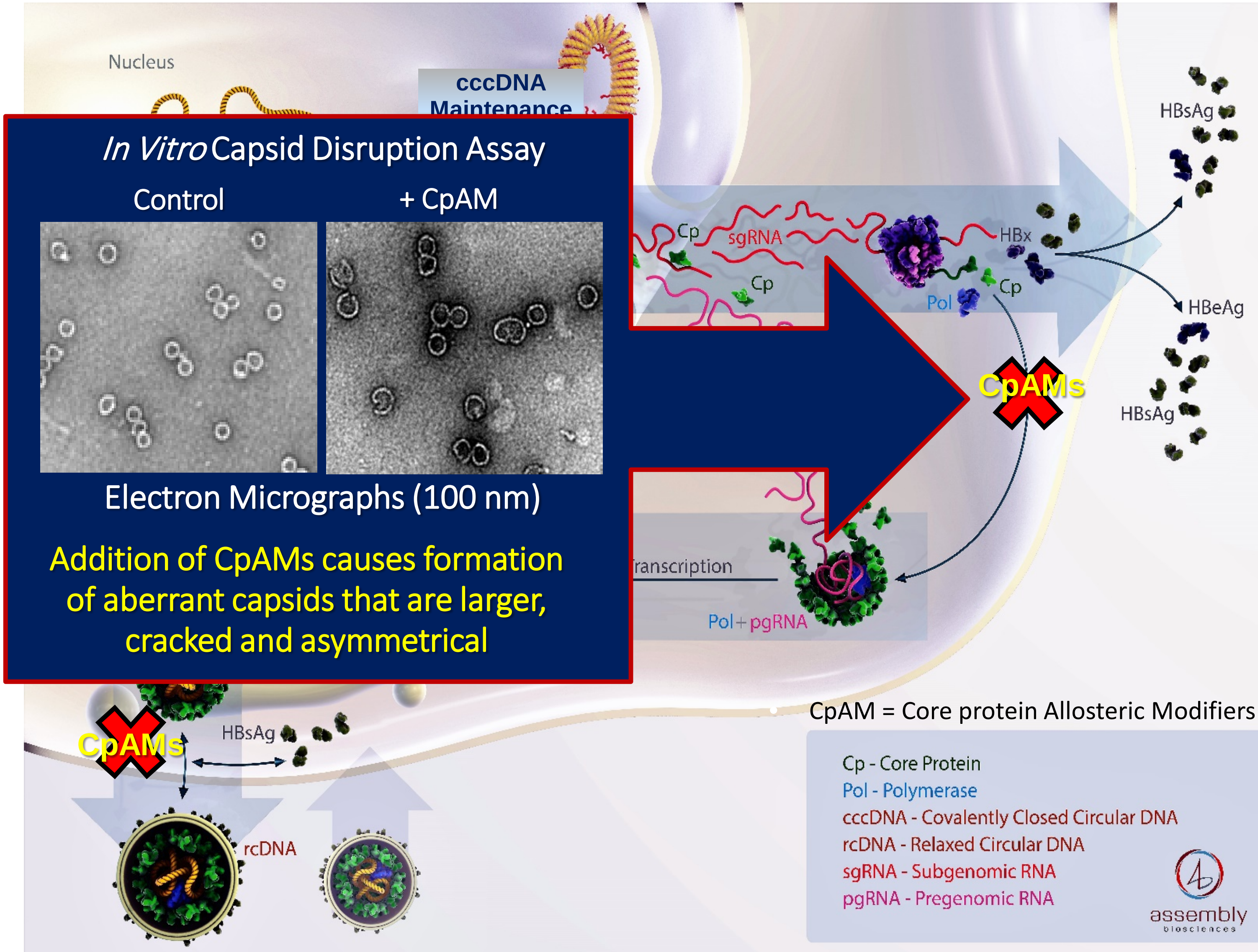


# CpAMs Inhibit HBV Life Cycle at Several Steps

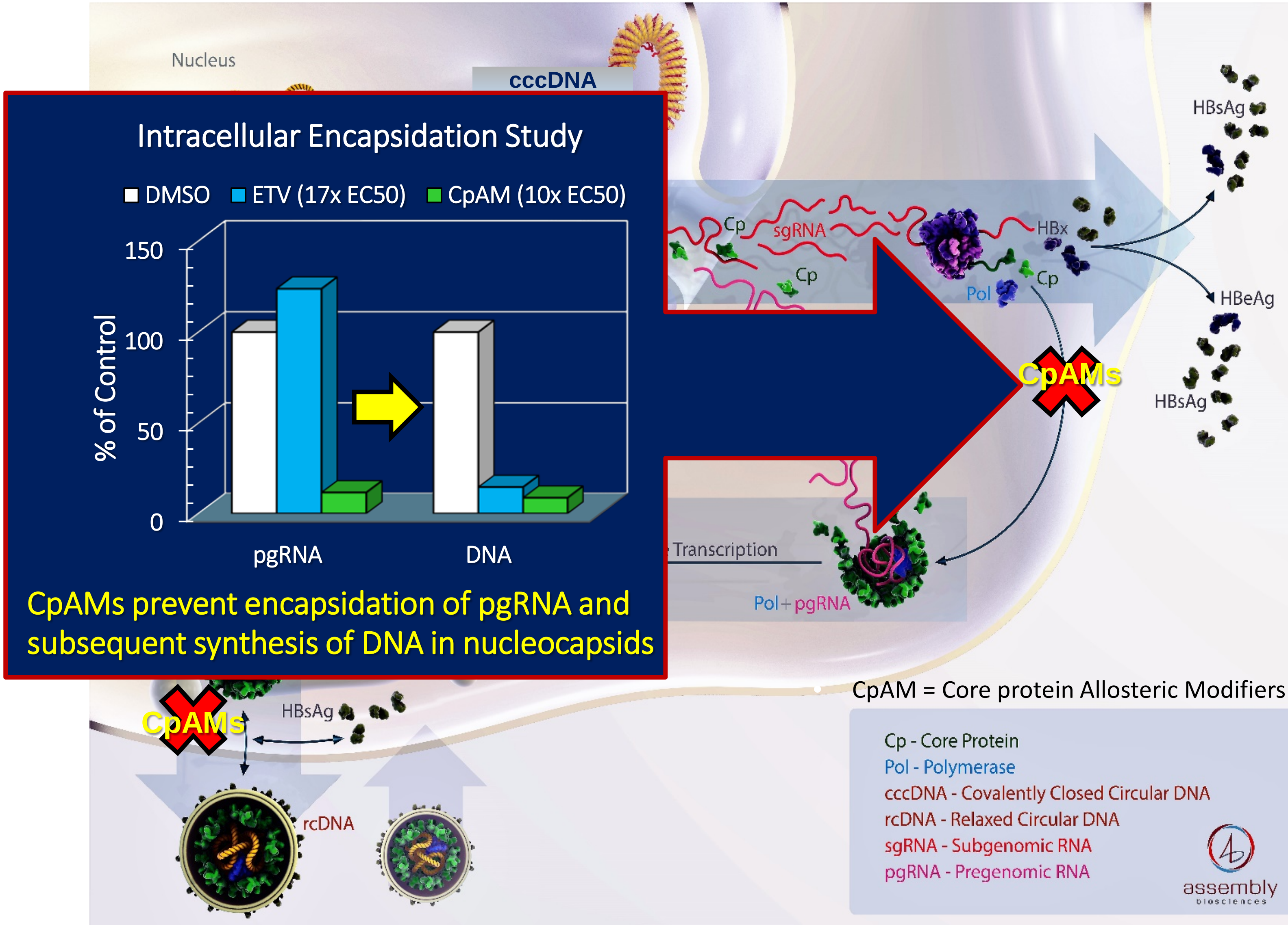
- CpAMs (Core protein Allosteric Modifiers) target Core protein and inhibit key functional steps required for to cccDNA generation
- Bind at dimer-dimer interface and disrupt the orderly folding of Core protein dimers into functional nucleocapsids, generating empty aberrant capsids
- Prevent encapsidation of Pol and pgRNA, a pre-requisite for RT activity and generation of rcDNA
- Prevent maturation of infectious viral particles
- Prevent trafficking of encapsidated rcDNA to nucleus for conversion to cccDNA
- Alter phosphorylation levels of Core protein, and may also lead to Core protein elimination in infected cells
- Ability to disrupt existing nucleocapsids

**Because their distinct inhibitory mechanism(s), CpAMs and Nucs together should exhibit enhanced antiviral potency and have the potential to reduce levels of both cccDNA and HBsAg**

# Antiviral Effects of CpAMs



# Antiviral Effects of CpAMs



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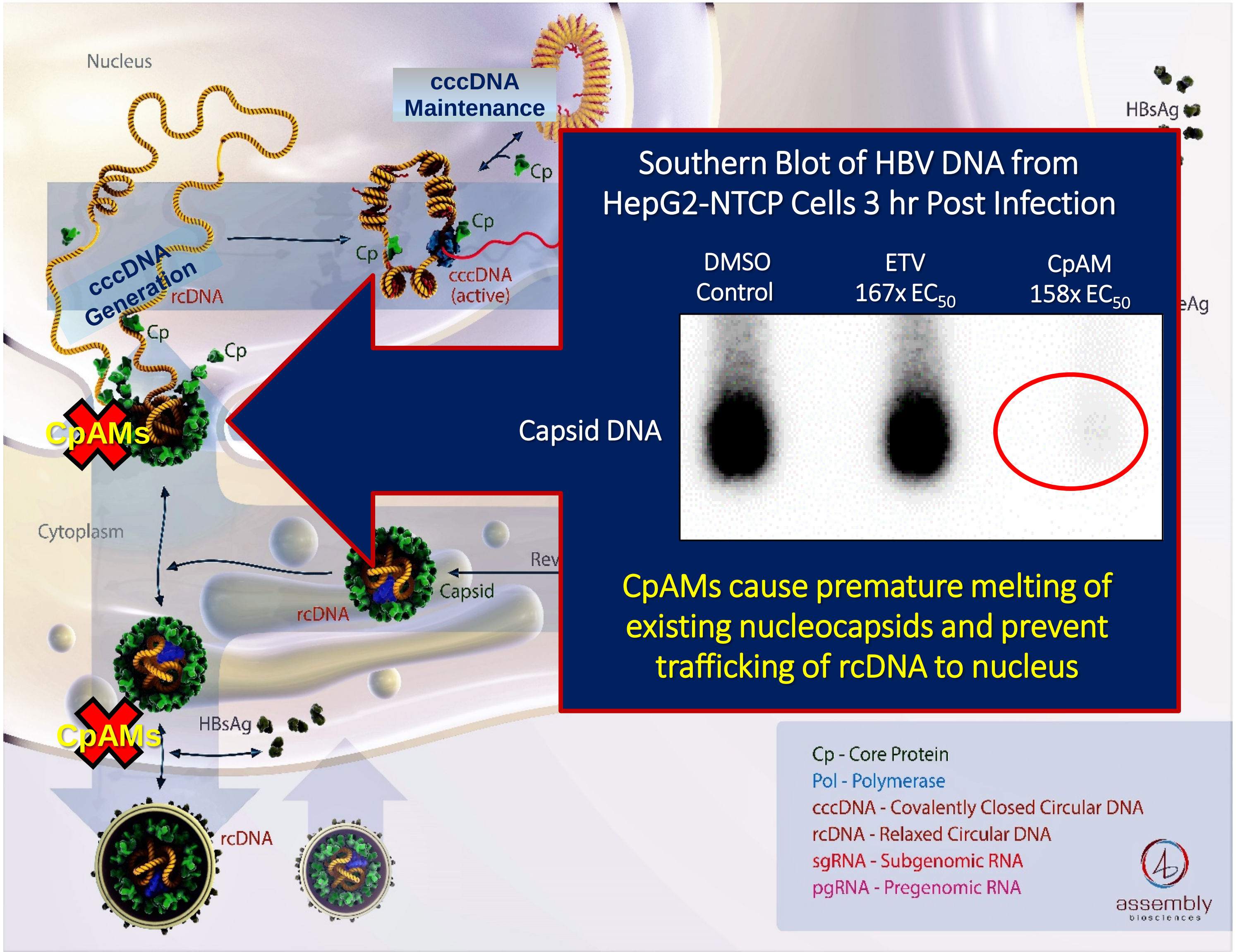
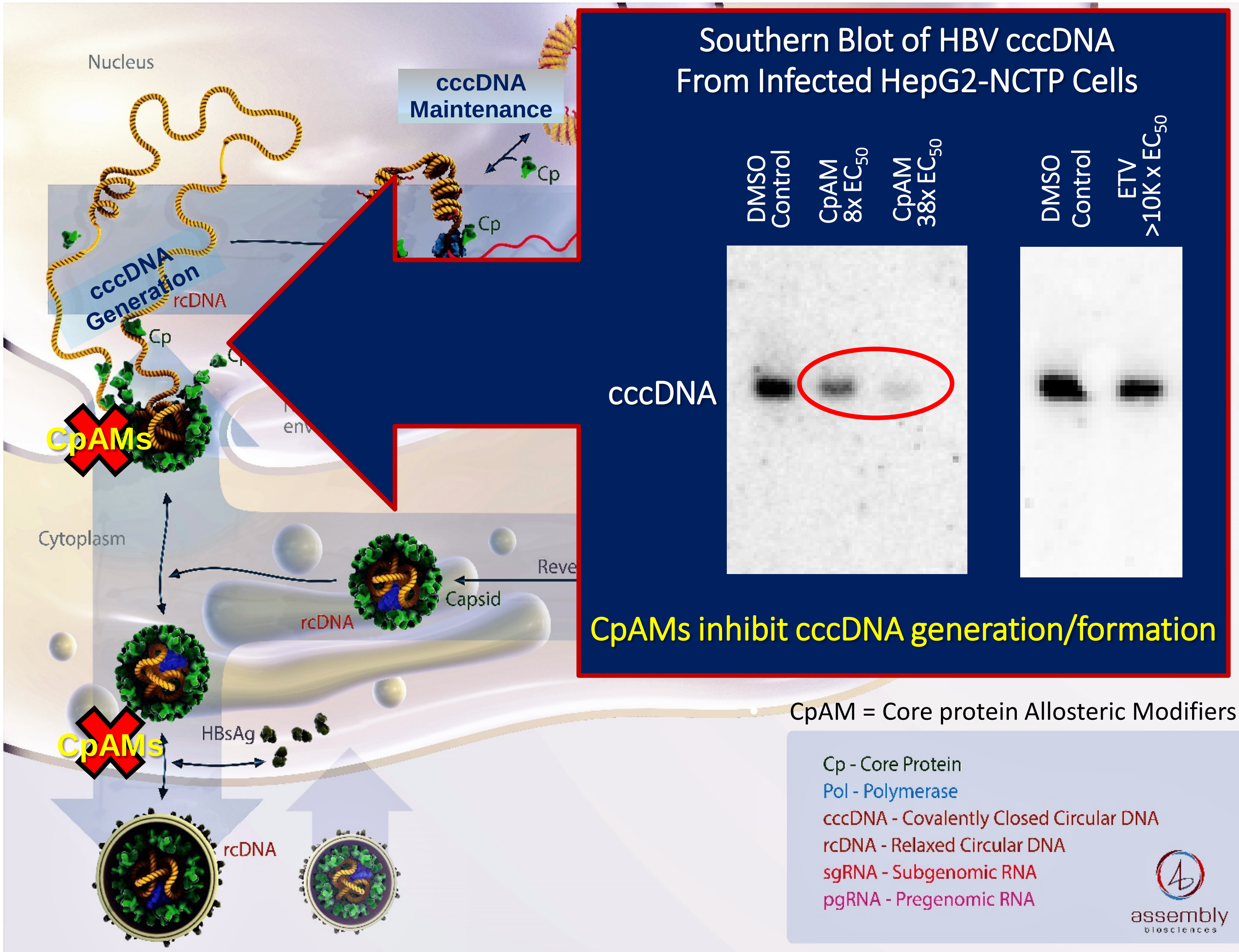
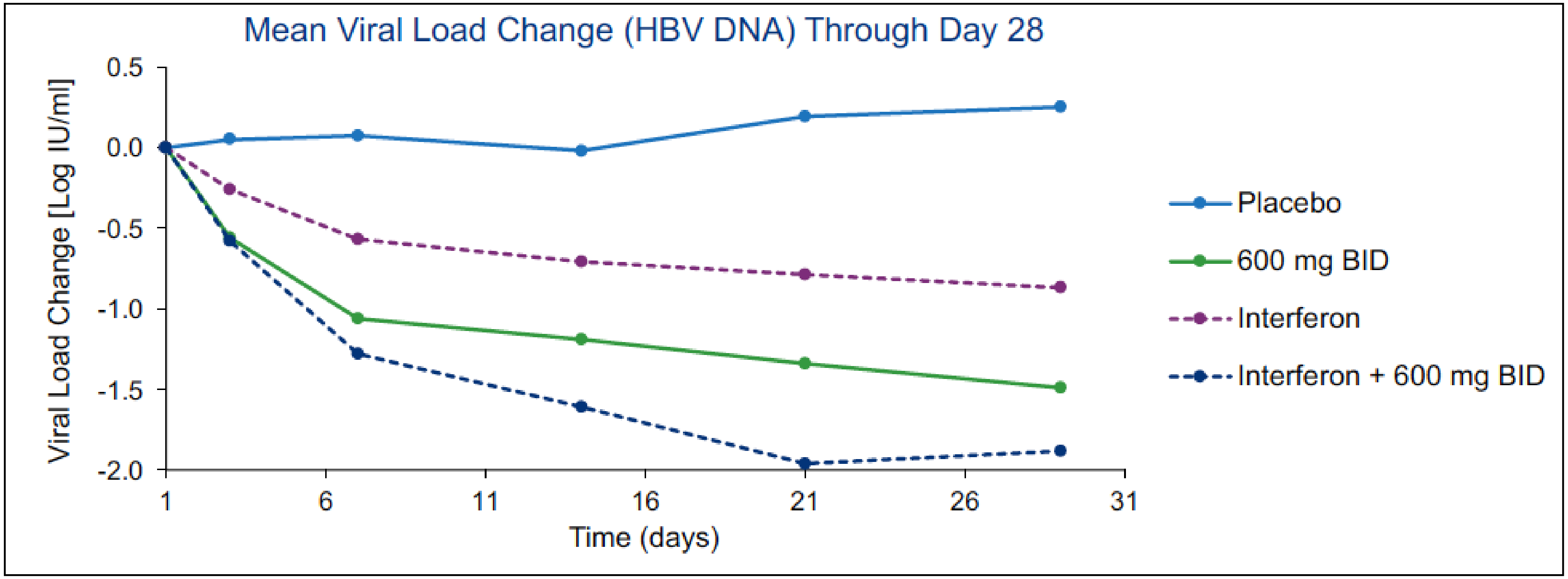


# Antiviral Effects of CpAMs



# Clinical POC of CpAMs as Effective HBV Antivirals

## NVR 3-778 Phase 1b 28-Day Monotherapy Results in HBV-Infected Patients




- Satisfactory safety at all dose levels, no pattern of treatment-related clinical AEs or lab abnormalities
- Oral doses of 600 mg BD in chronic HBV patients resulted in a potent antiviral response in 28 days
  - Mean 1.72 $\log_{10}$ IU/mL HBV DNA reduction
  - Mean 0.86 $\log_{10}$ copies/ml reduction in serum HBV RNA levels

*Lawrence Blatt, J&J R&D Day Presentation 6-17*

# Assembly Biosciences
# Establishing A Pipeline of CpAMs

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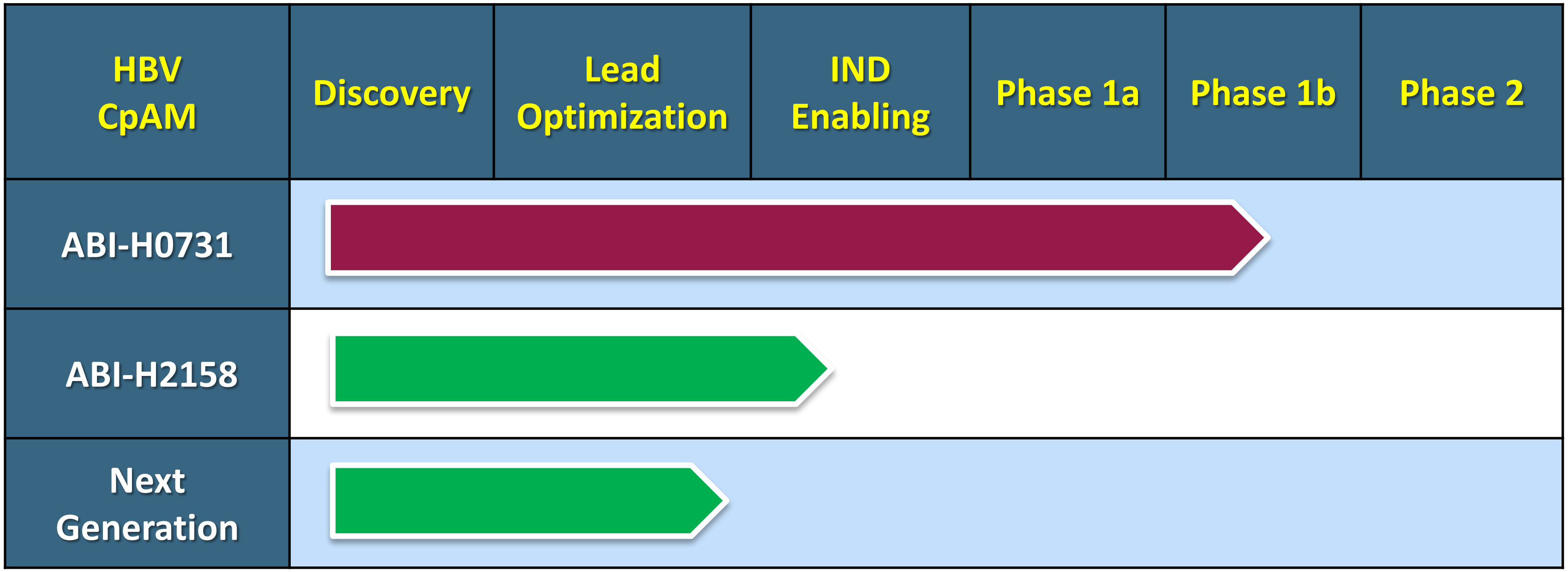
# Drugable Properties Will Play an Important Role

- Higher concentrations of CpAMs will be required to decrease cccDNA levels relative to inhibiting viral DNA levels
- Premium will be placed on CpAMs with favorable DMPK properties that are able to achieve and maintain higher effective concentrations in infected hepatocytes
- Convenient oral dosing (frequency and pill burden)
- Metabolic stability in hepatocytes to enable maximal sustained inhibition
- Good PK profile
  - Oral bioavailability, half-life, $C_{max}$ and $C_{min}$
  - Rapid achievement of steady state
- Controlled and predictable liver:plasma concentrations, minimal accumulation in liver
- Limited drug-drug interactions
- Well tolerated – good safety profile with prolonged dosing

# Assembly Pipeline of CpAMs




- ABI-H0731 has completed Phase 1a evaluation, and is currently being studied in HBV patients in a 28-day, double-blind, placebo-controlled Phase 1b study
- ABI-H2158 selected as our next generation CpAM clinical candidate and is currently undergoing IND-enabling studies for initiation of Phase 1a studies
- Plan to identify and select a third CpAM clinical candidate by year end
- All ASMB CpAMs derived from distinct proprietary chemical scaffolds unrelated to previous HAP and Novira-like molecules

# ABI-H0731 Preclinical Overview

- Selective targeting of dimer-dimer interface of HBV Core protein, leading to inhibition of cccDNA generation in infected cell assays
- Pangenotypic coverage of HBV genotypes (A – D)
- No significant activity noted against a panel of other viruses or in cytotoxicity assays utilizing a panel of cell types
- Additive to synergistic in combination with Nuc
- Highly favorable DMPK properties
  - High (62-95%) oral bioavailability observed in all animal species tested
  - T½ predictive of human QD dosing
  - Limited accumulation with repeat dosing
  - Enhanced liver concentrations relative to plasma levels, parallel half-lives
  - Highly stable, excretion predominantly as intact compound
- Clean safety profile in a panel of GLP toxicology studies, no organ toxicities identified

# ABI-H0731 Clinical Overview

## Phase 1a Completed

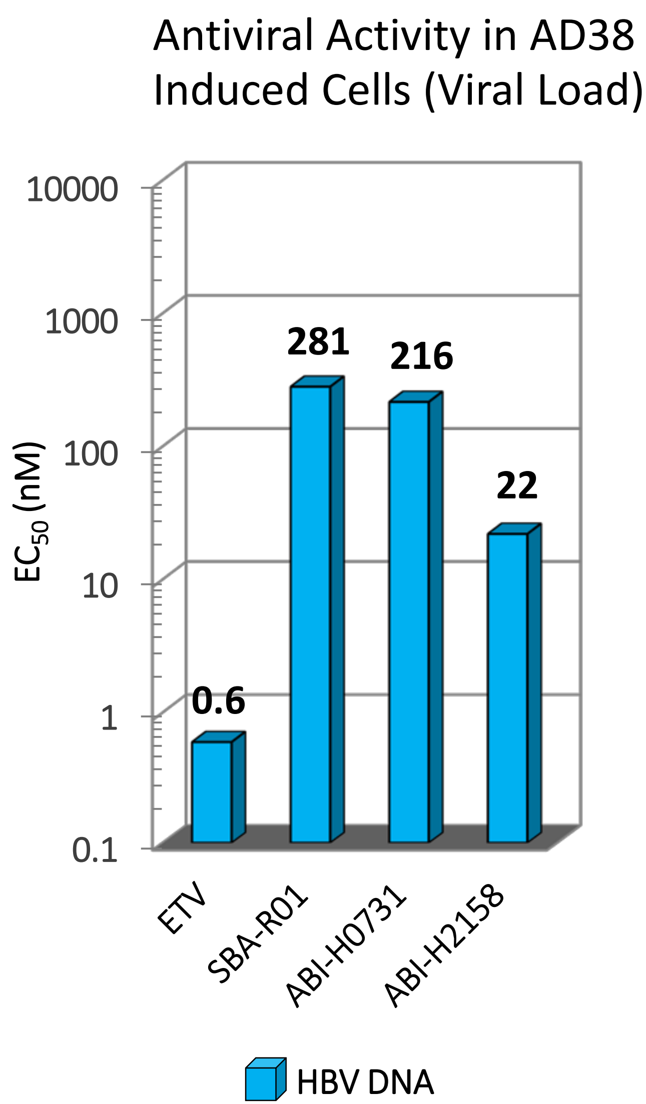
- Single oral doses from 100 to 1,000 mg, multiple doses of 800 mg QD and 800 mg BID x 7 days evaluated
- Favorable PK profile with a half-life consistent with QD dosing
- Well absorbed, with achievement of concentrations believed to be sufficient to suppress viral replication and cccDNA generation
- No SAEs, no clinically significant AEs and no withdrawals due to AEs
- Treatment emergent AEs deemed "possibly related," such as headache and rash, were mild and transient, and only observed at the highest doses
- No clinically significant treatment emergent laboratory abnormalities, vital sign changes or ECG findings

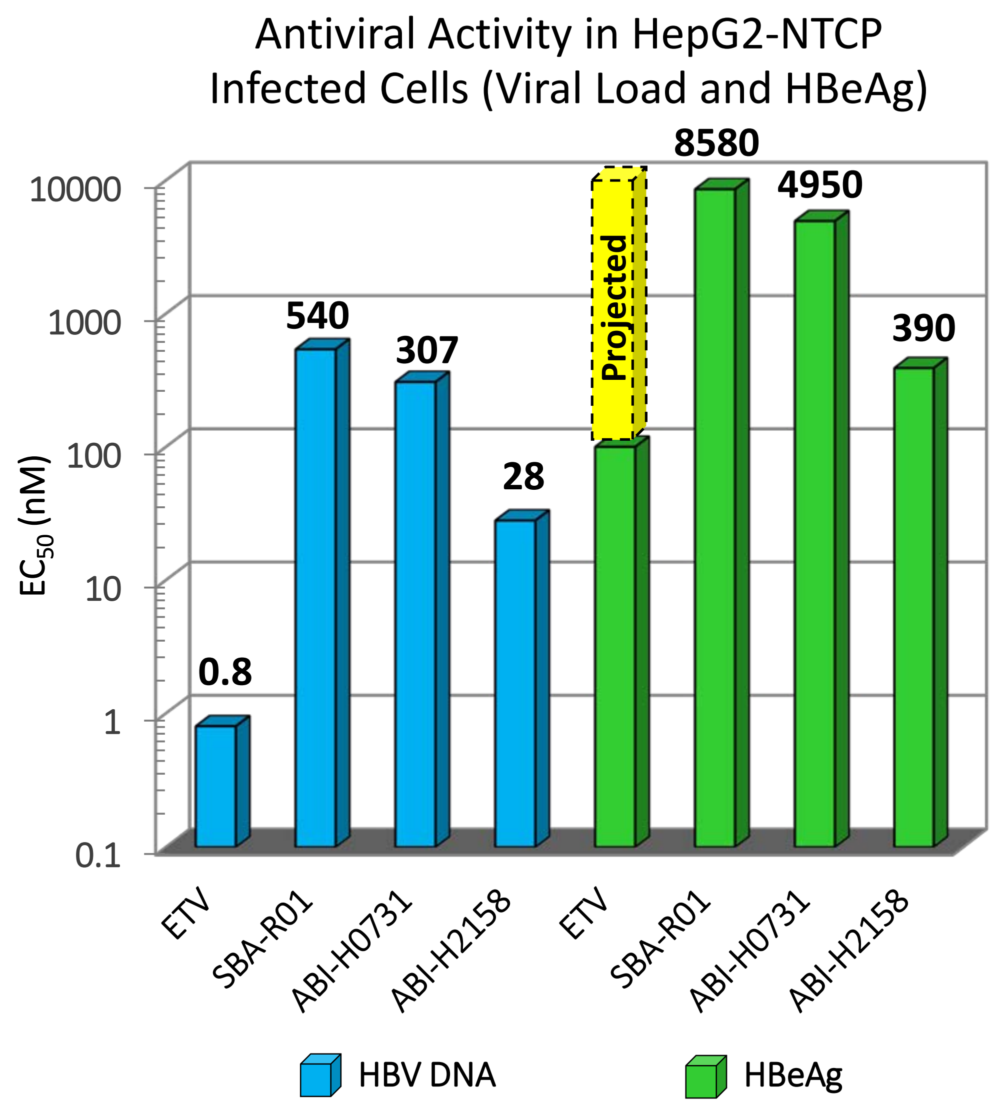
***Data to be presented at AASLD, October 2017 in Washington, DC***

## Phase 1b In Progress

- 28-Day monotherapy dosing in HBV patients

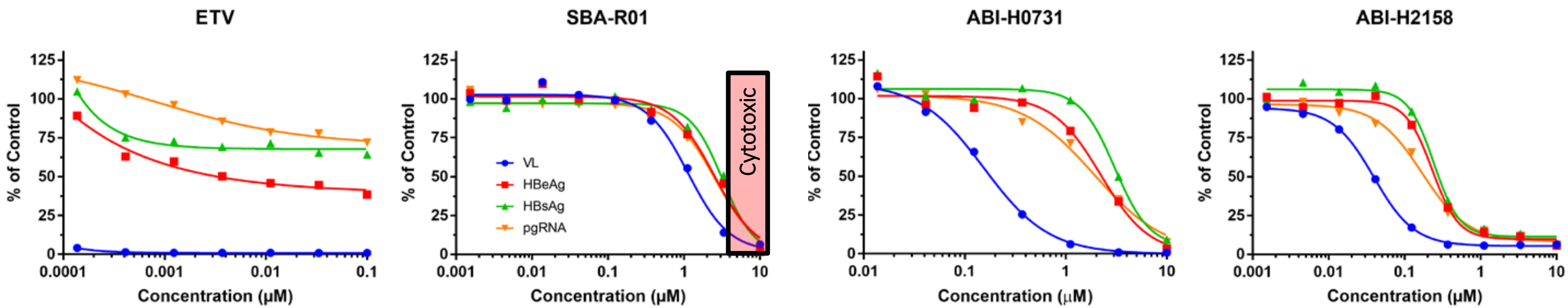
# ABI-H2158 - Next Generation CpAM




*SBA-R01 is believed to be NVR 3-778 or a very close analog (Pei Y. et al. , J. Med. Chem. 2017; 60, 6461−6479)*

# CpAMs Profiling in Primary Human Hepatocytes




| CpAM | HBV DNA $EC_{50}$ (nM) | HBeAg $EC_{50}$ (nM) | HBsAg $EC_{50}$ (nM) | pgRNA $EC_{50}$ (nM) |
|---|---|---|---|---|
| ETV | <0.1 | Est >100 | Est >100 | Est >100 |
| SBA-R01 | 1,130 | 2,502 | 3,192 | 2,554 |
| ABI-H0731 | 154 | 2,210 | 3,000 | 1,840 |
| ABI-H2158 | 39 | 230 | 242 | 169 |

- 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

***Data to be presented at AASLD, October 2017 in Washington, DC***

# Profile of ASMB Clinical Candidates

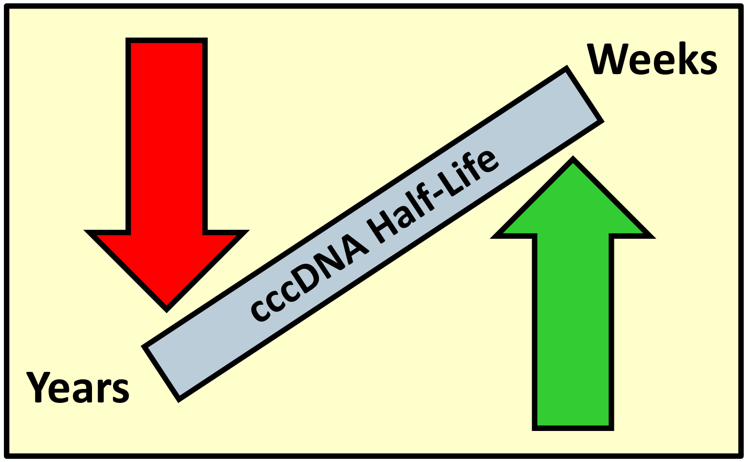
| Virology Parameters | SBA-R01 | ABI-H0731 | ABI-H2158 |
|---|---|---|---|
| AD38 VL $EC_{50}$ (nM) | 281 | 170 | 14 |
| HC9AT HBeAg $EC_{50}$ (nM) | 8,580 | 4,950 | 390 |
| PHH VL $EC_{50}$ (nM) | 1,130 | 150 | 23 |
| PHH HBeAg $EC_{50}$ (nM) | 2,502 | 2,210 | 230 |
| DMPK Parameters | | | |
| Human Liver Microsomes (% remaining at 45 min) | 100 | 87 | 91 |
| CYP Profile ($IC_{50}$) | All > 10 µM | All >10 µM | All ≥10 µM |
| Protein Binding (%) | 98 | 97 | 97 |
| Rat PK (1 mg/kg) %F<br>$T_{1/2}$ (hr)<br>$C_{max}$ (ng/mL)<br>Oral $AUC_{last}$ (hr*ng/mL) | | 95<br>6.1<br>162<br>1,470 | 50<br>2.9<br>536<br>3,671 |

- Unclear what potency/exposure levels are required to suppress cccDNA generation
- Liver concentrations of ABI-H0731 projected to be ~25x plasma concentrations
- If needed, ABI-H2158 has superior antiviral potency to ABI-H0731, while maintaining favorable DMPK properties

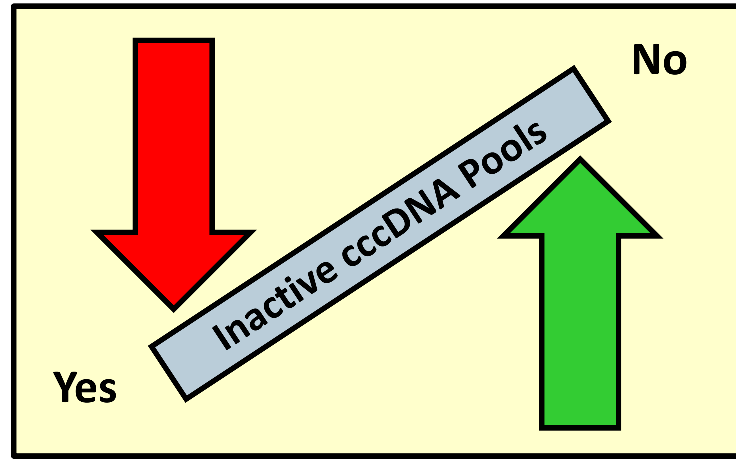
# Will CpAM Treatment Result in Higher Cure Rates?

## Potential Challenges

**Long Intracellular cccDNA Half-life**




**Significant Pools of Inactive cccDNA**




**Studies underway using patient samples to gain insight into both topics**

- Lamivudine (LVD) and Telbivudine (LdT) treatment results in rapid emergence of resistant variants due to their low barrier to resistance
- LVD/LdT resistance maps to L180M and M204I substitutions in the Pol gene
- Used these genetic markers to monitor the turnover of cccDNA, pgRNA and viral DNA in patient samples

# cccDNA Studies – Initial Results

- All biological molecules have a half-life, including cccDNA
- Longitudinal study conducted on samples (serum and biopsies) from patients with emerging resistance to LVD and TBV
- Appearance and enrichment of resistant mutations used as a genetic marker in monitoring populations of viral DNA, pgRNA and cccDNA
- Results demonstrated rapid establishment of newly formed cccDNA pools harboring Nuc-resistant mutations
- Significant turnover of wt pgRNA molecules within months suggests that existing cccDNA may decay faster than previously predicted in the absence of any gross inflammation
- Little evidence for the existence and maintenance of substantial pools of inactive wt cccDNA in patient samples

***Data to be presented at AASLD, October 2017 in Washington, DC***

# CpAM Summary

- Mechanism-based studies demonstrated that CpAMs bind to Core protein and disrupt viral replication at multiple steps
- Importantly, and distinct from Nucs, CpAMs appear to block the generation of new cccDNA molecules!
- ASMB's CpAM pipeline consists of candidate compounds selected and optimized from distinct and proprietary chemical series
- While the precise level of intrinsic potency needed for cccDNA inhibition in patients is yet to be established, emphasis has been placed on increasing potency while maintaining favorable DMPK properties
- Lead candidate ABI-H0731 has completed Phase 1a with favorable safety and PK properties predictive of QD dosing in patients, and is currently undergoing evaluation in chronically-infected patients (Phase 1b)
- Second generation candidate ABI-H2158 exhibits enhanced potency while retaining the favorable DMPK properties of ABI-H0731
- Future combinations of CpAMs and Nucs should result in enhanced antiviral activity, have a high resistance barrier and most importantly, decrease cccDNA levels

# Acknowledgements

## Assembly Biosciences HBV Team


| Virology | Chemistry/DMPK | Clinical/Regulatory |
|---|---|---|
| Qi Huang | Leping Li | Uri Lopatin |
| Dawei Cai | Bill Turner | Sandy Laiw |
| Ran Yan | Simon Haydar | Eric Ruby |
| Yi Zhou | Lynn Bannen | |
| Yuhua Zong | Mark Bures | |
| Alex Mercier | Roopa Rai | |
| Pao-Chen Li | Kelvin Chan | |
| Emily Connelly | Samson Francis | |
| Lida Guo | | |
| Lichun Li | Ray Kauffman | |
| Esteban Carabajal | Lee Arnold | |
| Xuman Tang | | |