



Combination Therapy for Curing HBV

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NASDAQ: ABUS

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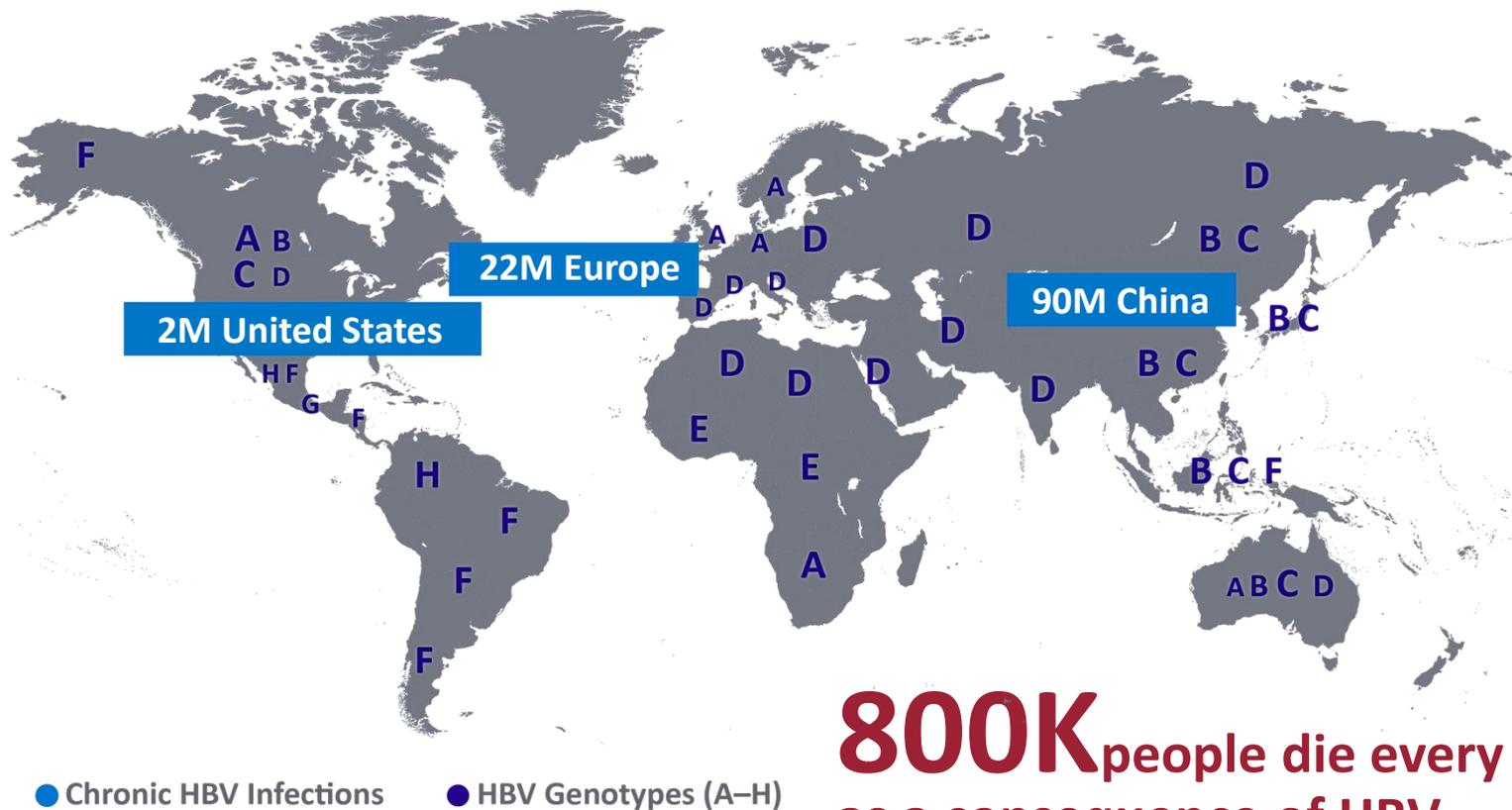
Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, and forward looking information within the meaning of Canadian securities laws (collectively, “forward-looking statements”). Forward-looking statements in this presentation include statements about, among others: meeting a significant unmet medical need and market opportunity; developing a curative regimen for HBV; accomplishing the objectives of ARB-1467; HBsAg reduction data from the Phase II trial expected in 2H16; IND (or equivalent) filing for the Core Protein/Capsid Formation Inhibitor Program in 2H16; IND (or equivalent) filing for cccDNA Formation Inhibitor Program in 2H16; the development of HBV products in 2016, with projected milestones; proprietary clinical combination studies in 2017; current cash funding the company into late 2018; and non-dilutive financing potential from non-HBV assets and LNP licensing.

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Chronic HBV –Global Unmet Medical Need

350M people chronically infected with HBV

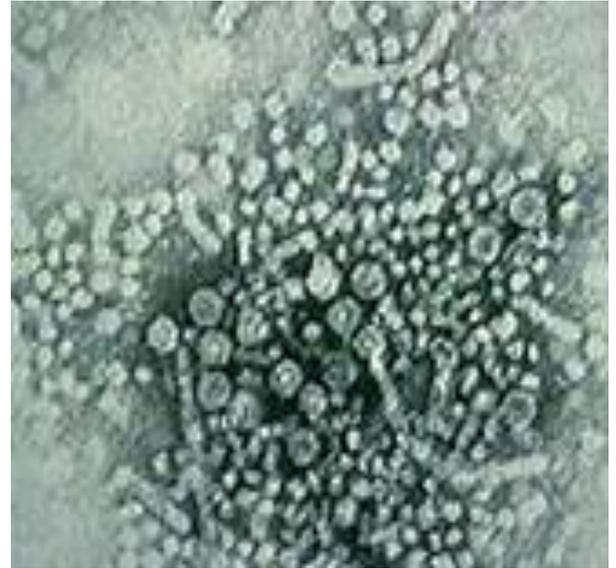


800K people die every year as a consequence of HBV

- Lozano R, Naghavi M, Foreman K et al. The Lancet 2012; 380: 2095-128
- World Health Organization: Fact Sheet No. 204. Hepatitis B, revised, August 2008. Geneva: WHO. www.who.int/mediacentre/factsheets/fs204/en/index.html

Hepatitis B Virus (HBV)

- *Hepadnaviridae* member that primarily infects liver cells
- DNA virus
- 10^{11} virions produced per day
- 100 times more infective than HIV
- Found in blood and body fluids
- Viral reservoir: cccDNA in nucleus of hepatocytes
- Small segments of viral DNA do integrate
- Infection is not cytopathic
- Outcome of infection and severity of associated liver disease are determined by nature and magnitude of host immune response



Ott et al. J Pediatr Health Care. 1999;13(5):211-216.
Ribeiro, et al. Microbes and Infection. 2002;4:829-835.
MMWR. 2003;52:1-33.

Relative Efficacy of Approved HBV Therapies

	Entecavir ^{1,2}	Tenofovir ³	PEG-IFN α-2a ^{4,5}
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25% ^a
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9%^b
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63% ^a
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6%^b

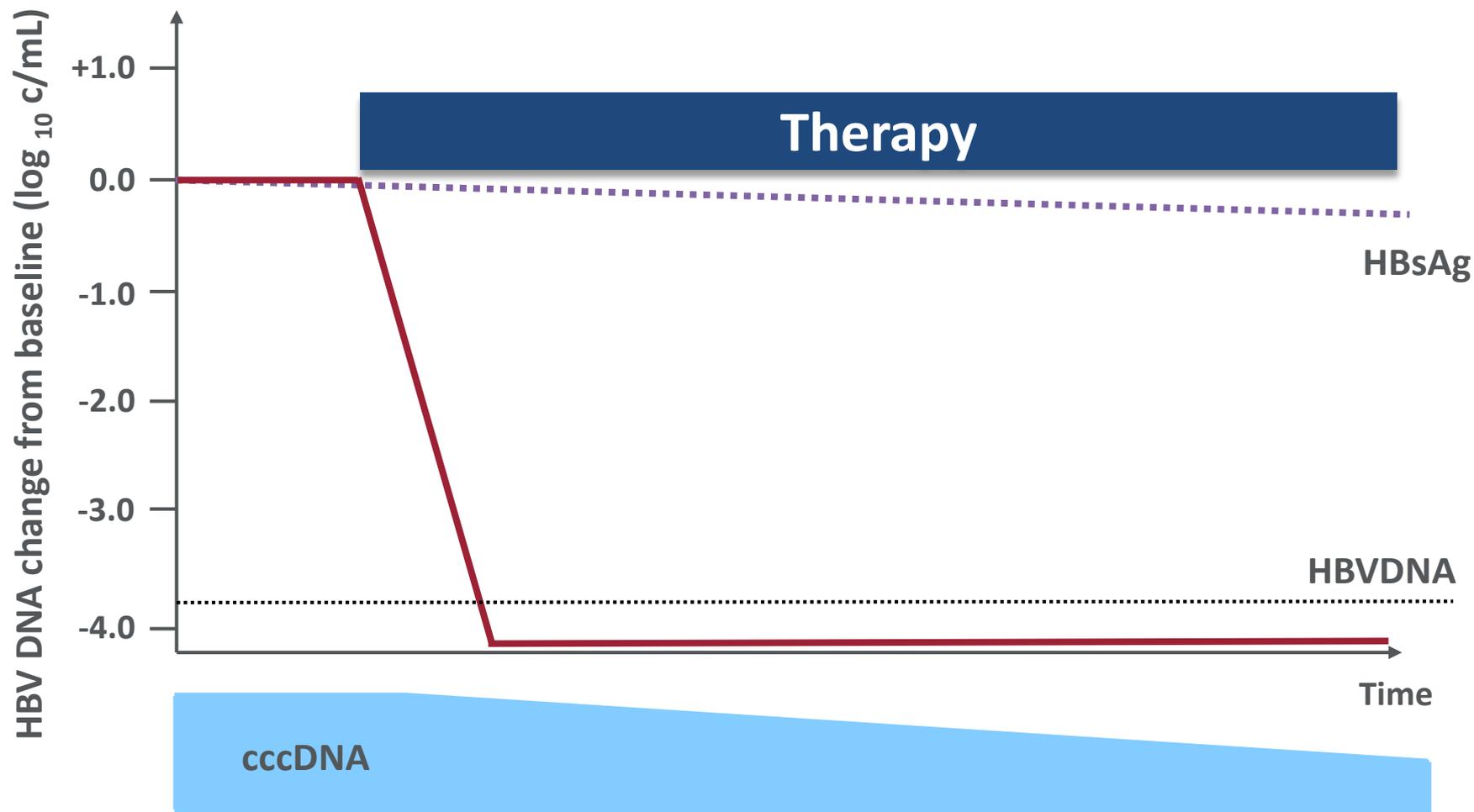
Results at 48 weeks

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

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.

Viral Suppression Requires Long-term Therapy



Werle et al, Gastroenterology 2004

Combination Therapy

Path to a Cure with a Finite Duration of Treatment

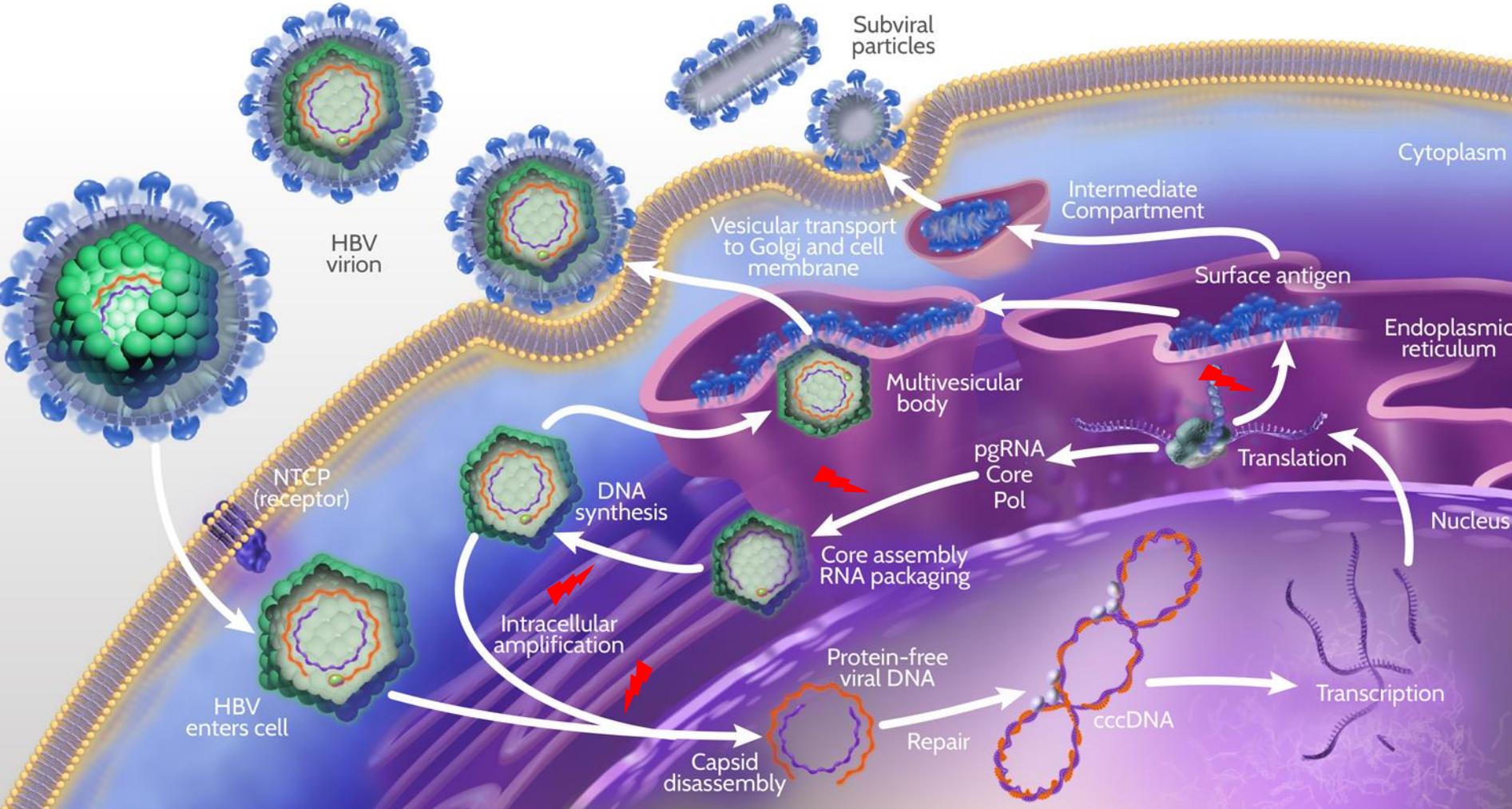
- Generally accepted that blocking a single target will not be sufficient to deliver a cure
- As in HCV and HIV combinations of drugs with different MOA will be the solution
- Which combination will deliver the ultimate “cure” is yet to be determined?
- Can a significant reduction in treatment duration be achieved using drug combinations?

A Strategy for Delivering an HBV Cure

3 Characteristics of a Curative Regimen:

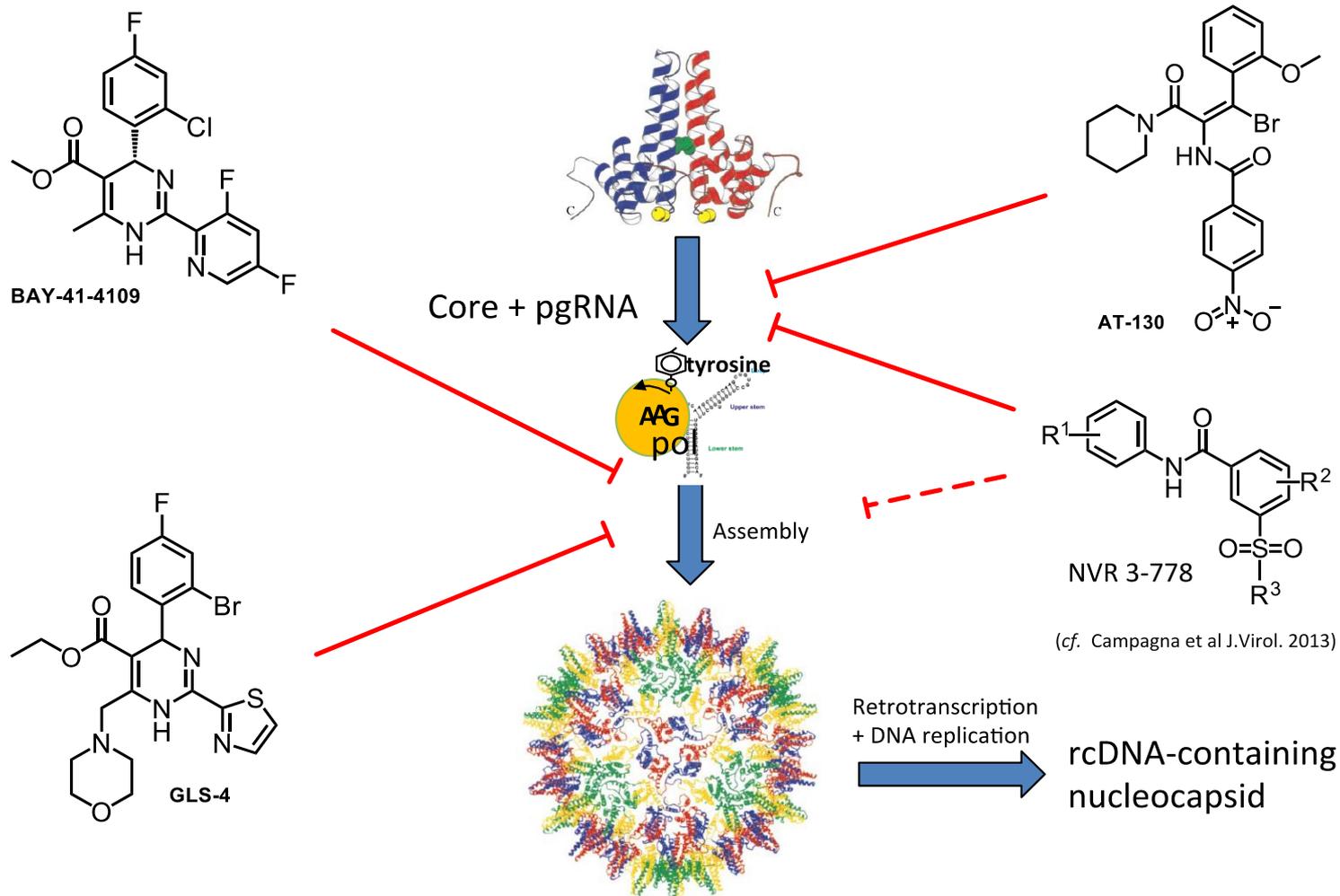
- 1. Rapidly and sustainably drive viral load down to undetectable levels**
 - Cripple the virus
 - Reduce viral DNA pools
 - Reduce impact on immune suppression
- 2. Reactivate the host immune response**
 - Release immune tolerance
- 3. Shrink and eventually clear cccDNA pools**
 - Stop replenishment of nuclear cccDNA pools
 - Dramatically reduce or stop production of new immune inhibitory viral proteins and genomic materials

Combination Studies



Validated Targets

Inhibition of HBV Capsid Assembly and pgRNA Encapsidation



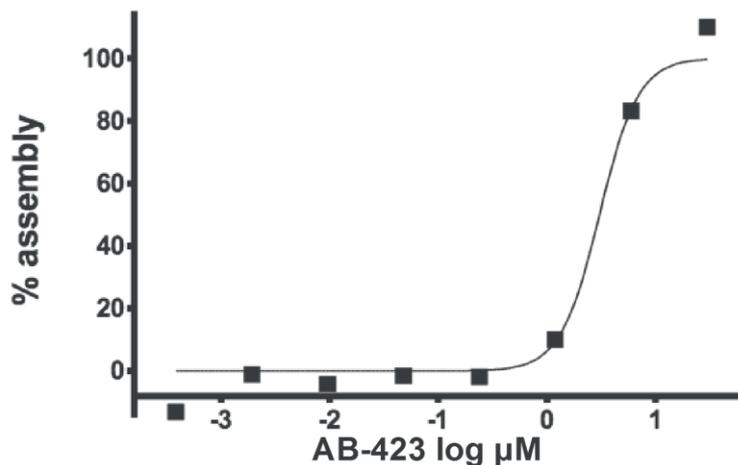
Hu et al., Ann. Rep. in Med. Chem. 2013

Winne et al, Mol.Cell 1999

In Vitro Studies

AB-423 is a Potent Inhibitor of HBV Replication

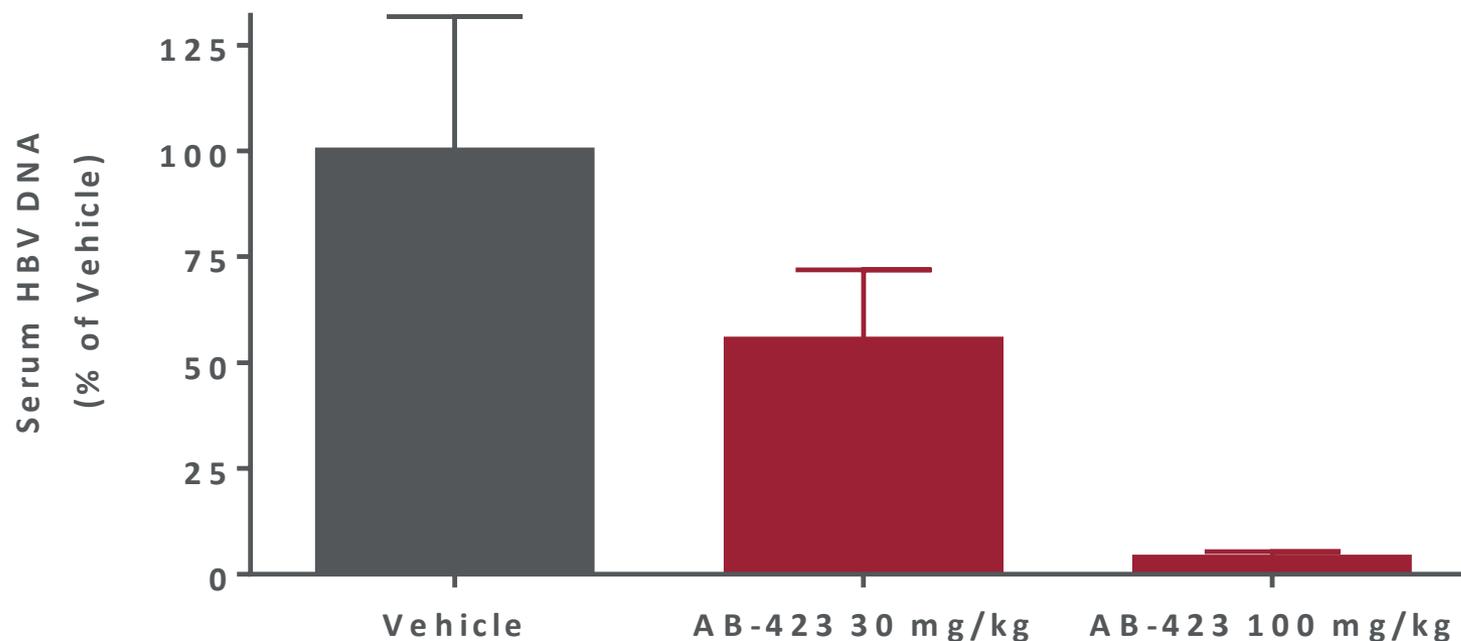
Potency	EC ₅₀	EC ₉₀	CC ₅₀	Endpoint
DESHAe82 (μM)	0.25	1.17	>10	eAg/ELISA
AML12-HBV10 (μM)	0.15	ND	>10	rcDNA/Dot Blot
AML12-HBV10 (μM)	0.28	1.96	>10	rcDNA/bDNA
HepDE19 (μM)	0.34	0.63	>10	rcDNA/bDNA



AB-423 misdirects capsid assembly in a biochemical assay. In a biochemical capsid assembly assay, AB-423 misdirects capsid assembly with an IC₅₀ value of 3 μM.

In Vivo Antiviral Activity

AB-423 Shows Potent Activity in a Mouse Model of HBV Infection

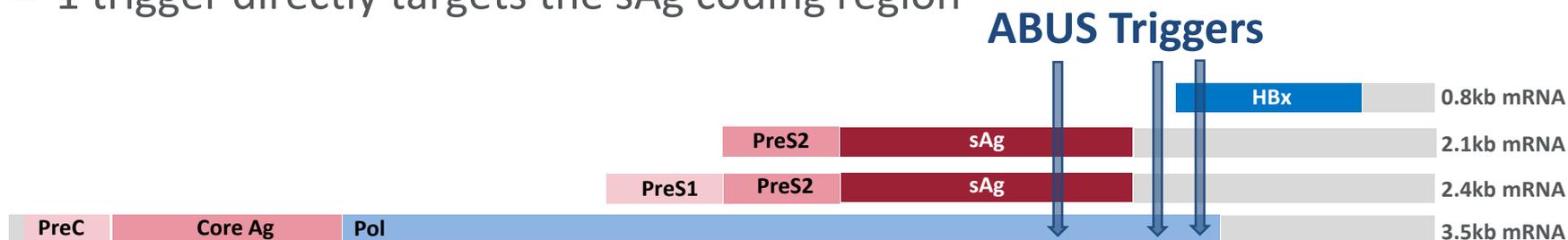
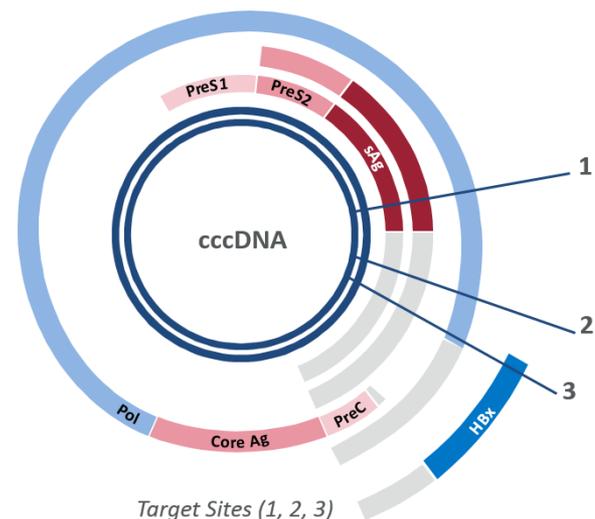


NOD.CB17-*Prkdc*^{scid/J} mice express HBV from a 1.3-fold overlength copy of a genotype D genome that had been administered to the liver *via* hydrodynamic injection (HDI) of plasmid pHBV1.3 (Guidotti 1995). Subsequently, the animals were given oral doses of vehicle or AB-423 twice a day for 7 days. On Day 7, serum HBV DNA was measured by QPCR and individual animal changes calculated against pre-dose values on Day 0. Data shown as mean \pm SEM (n=5-6).

ARB-1467 (RNAi 1.0)

Targets Multiple HBV Genomic Sites

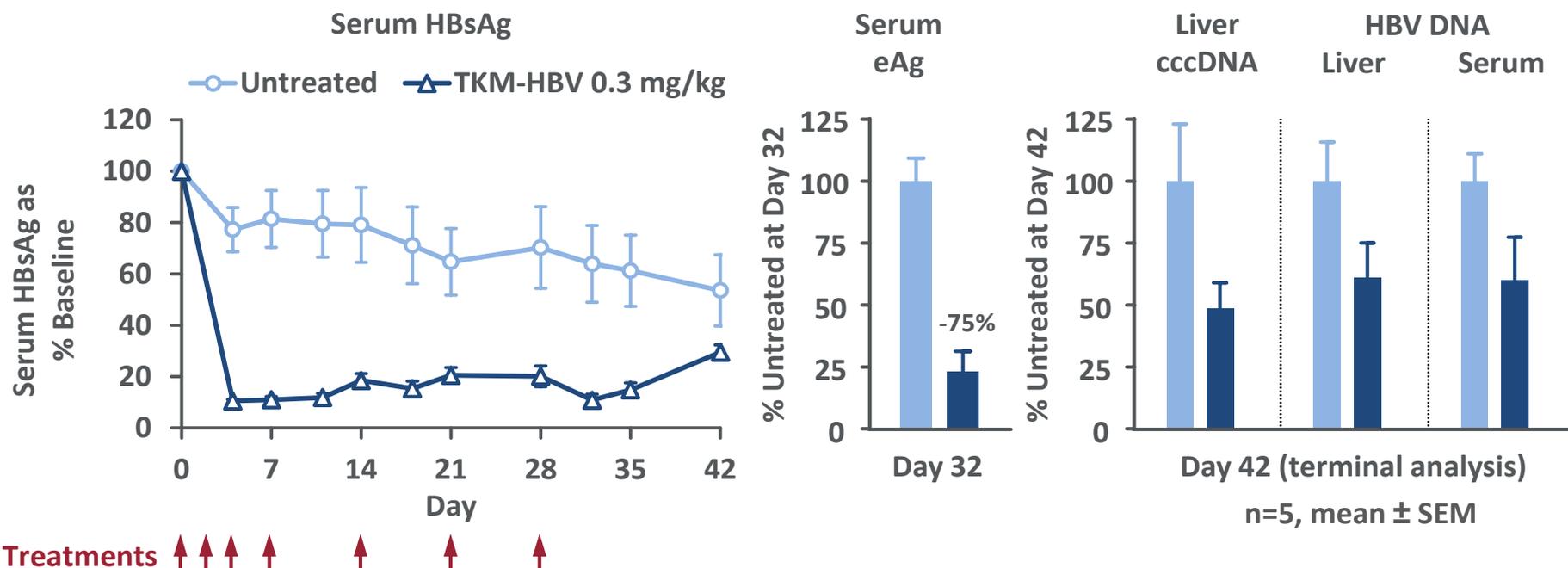
- Primary viral target is HBsAg
- Target sites are regions of high conservation in HBV viral genomes
- Advantages of the **3-trigger combo**:
 - Increased potency
 - Coverage extension to 99.8% of HBV genotypes
 - Targets all HBV transcripts and prevents production of all antigens
 - 1 trigger directly targets the sAg coding region



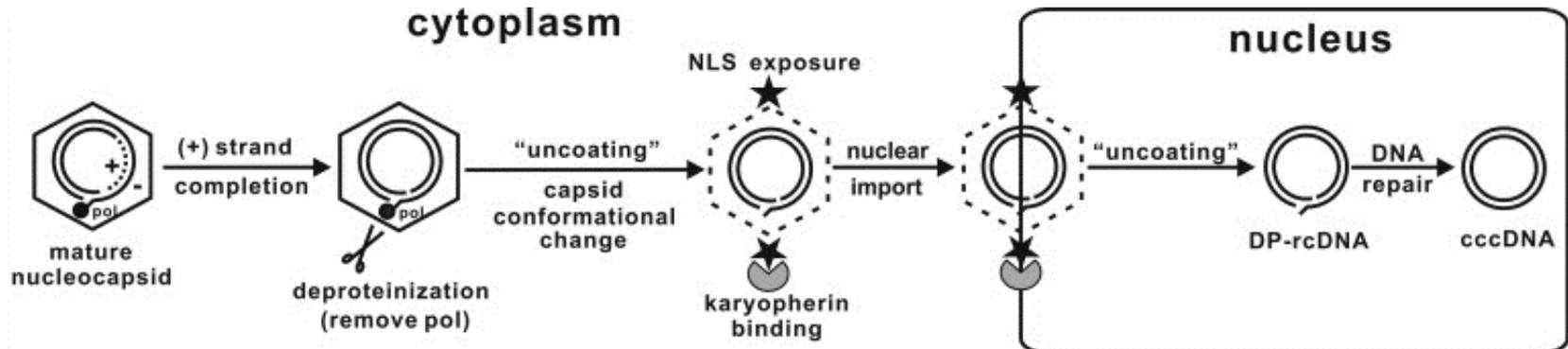
ARB-1467 Reduction in Multiple HBV Markers

Chimeric Mouse Model

- Strong inhibition of HBsAg and HBeAg
- Viral DNA and cccDNA are reduced by ARB-1467



cccDNA Formation Inhibition: ARB-199



Reproduced from (2): Ju-Tao Guo, Haitao Guo, Metabolism and function of hepatitis B virus cccDNA: Implications for the development of cccDNA-targeting antiviral therapeutics. Antiviral Research, Volume 122, 2015, 91–100

- The process of cccDNA formation, establishment and expression offers several points of potential interdiction
- These steps are crucial to the replenishment and maintenance of the cccDNA pool in the infected liver.

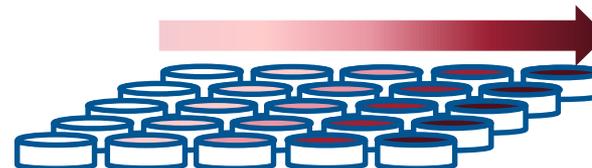
Compound	Targeted stage of the HBV life cycle	Potency (EC ₅₀ , μM)	Cytotoxicity (CC ₅₀ , μM)
ARB-199	cccDNA formation	0.843	>50

In Vitro Studies

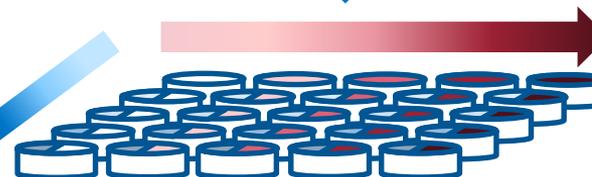
Evaluation of the Effect of 2 compounds on HBV



96-well plate containing cells infected by HBV or expressing HBV reporter



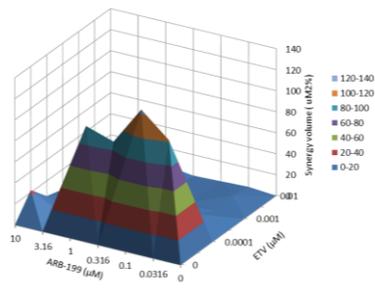
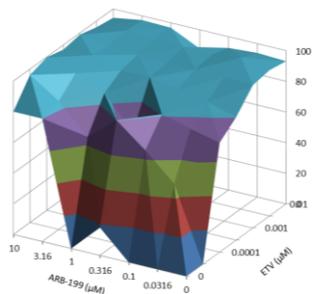
Add concentration range for 1st compound



Add concentration range for 2nd compound



Test activity of the 2 compounds together



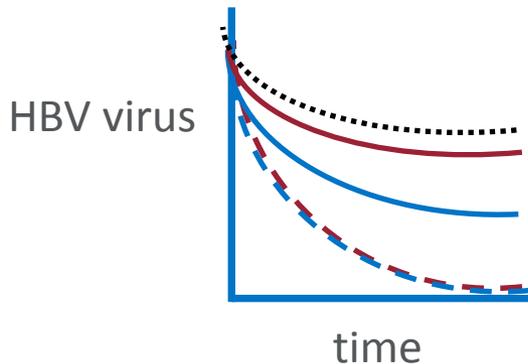
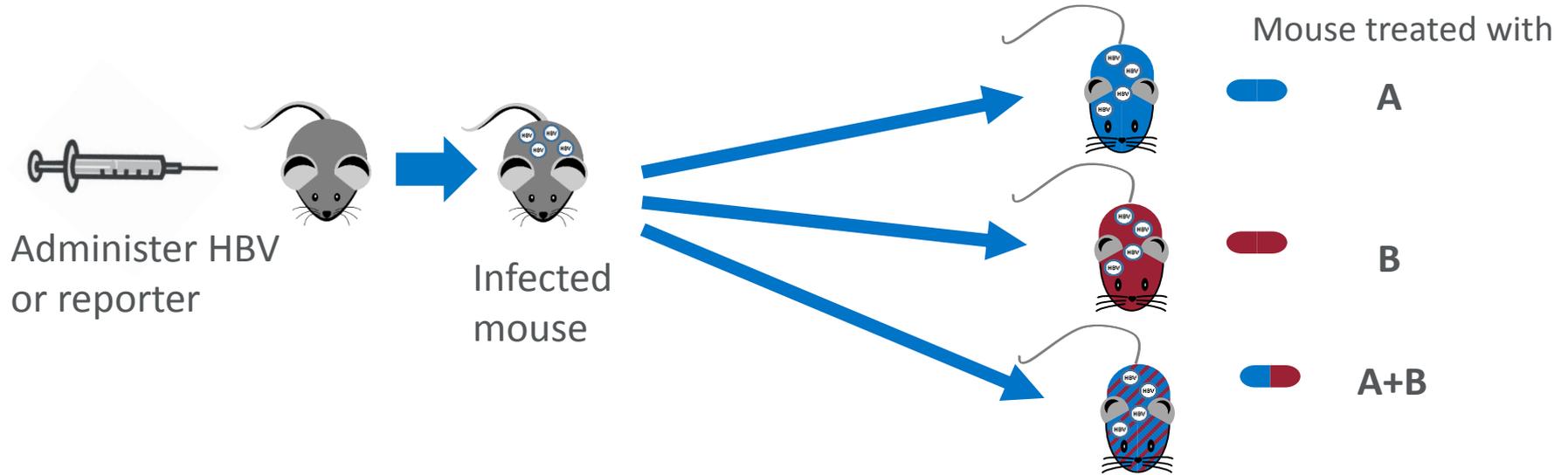
- Greater than additive effects seen at lowest ETV + ARB-199
- Total Synergy volume at 99.99 % CI = 554.53 (log 138.63)
- Total Antagonism volume = -31.19

Outcomes:

- Compounds work against each other: **Antagonism**
- Compounds don't interfere with each other: **Additive**
- Compounds enhance each other: **Synergy**

In Vivo Studies

Evaluation of the Effect of 2 compounds on HBV



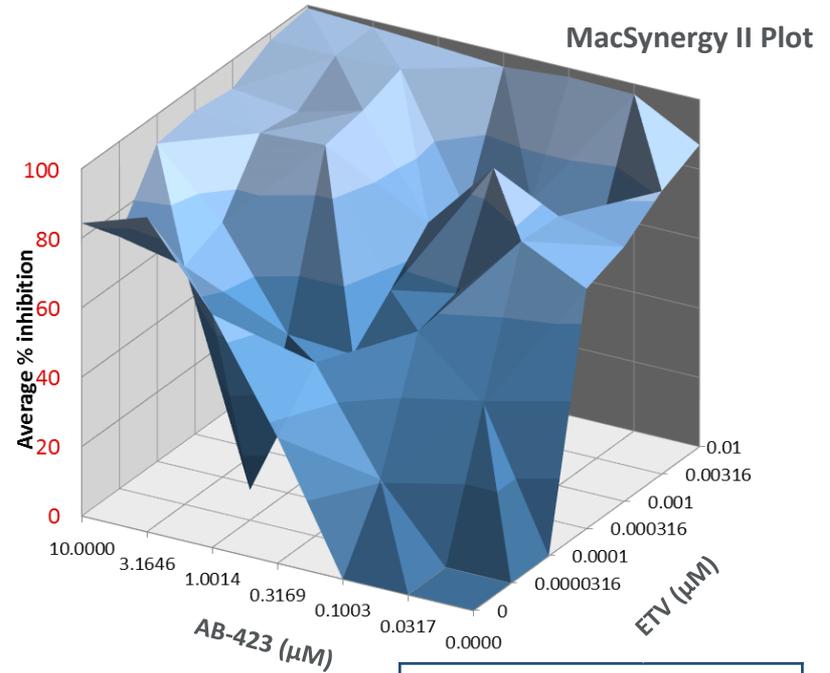
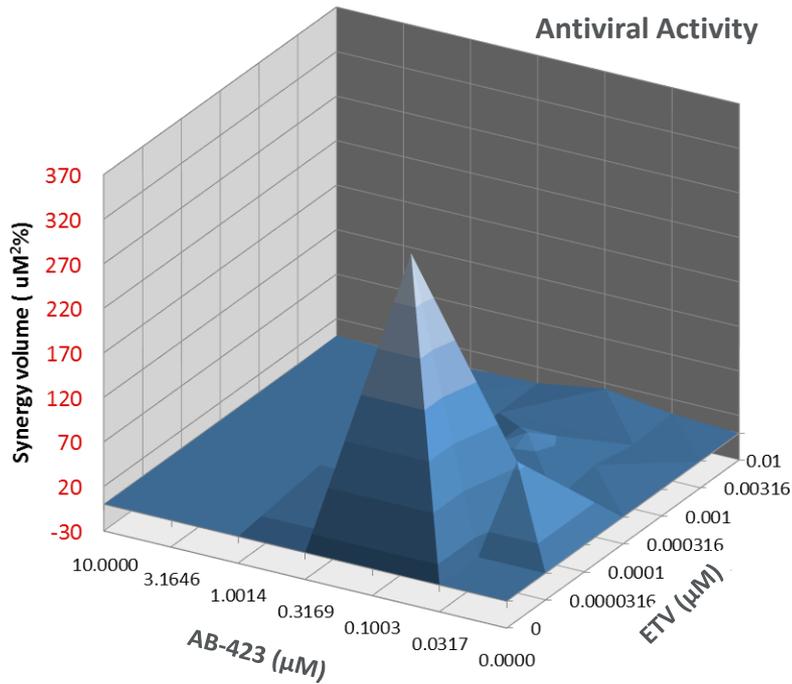
Outcomes:

- Compounds work against each other: **antagonism**
- Compounds don't interfere with each other: **additive** or **synergy**

Note: Fewer test conditions can be examined in animals than in cell culture

In Vitro Combination Studies

Capsid Assembly Inhibitor AB-423 with Entecavir (ETV)



**cccDNA Synthesis and Expression by
qRT-PCR assay**

- Synergistic Interaction
- No Antagonism
- MacSynergyII Analysis
- EC50 values comparable to historical values

SYNERGY PLOT (99.9%)

Bonferroni Adj. 96%

SYNERGY 679.15

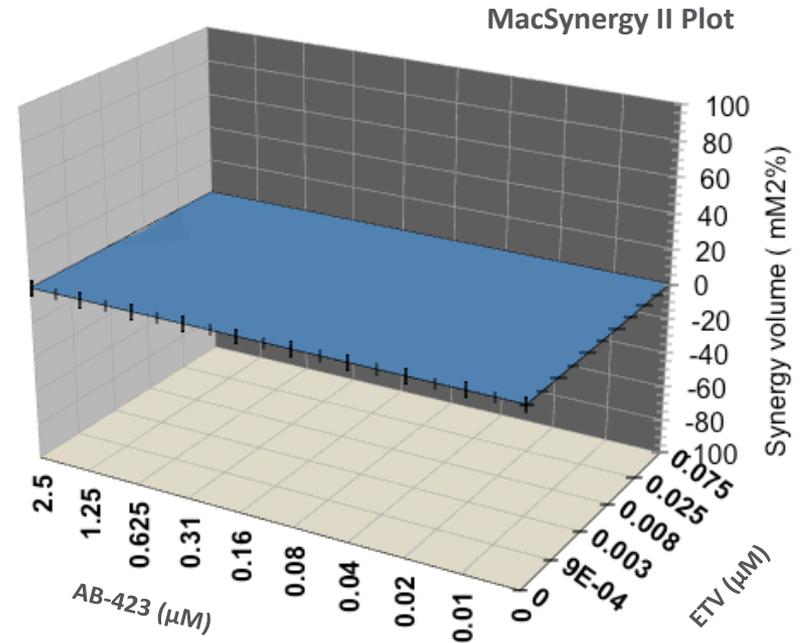
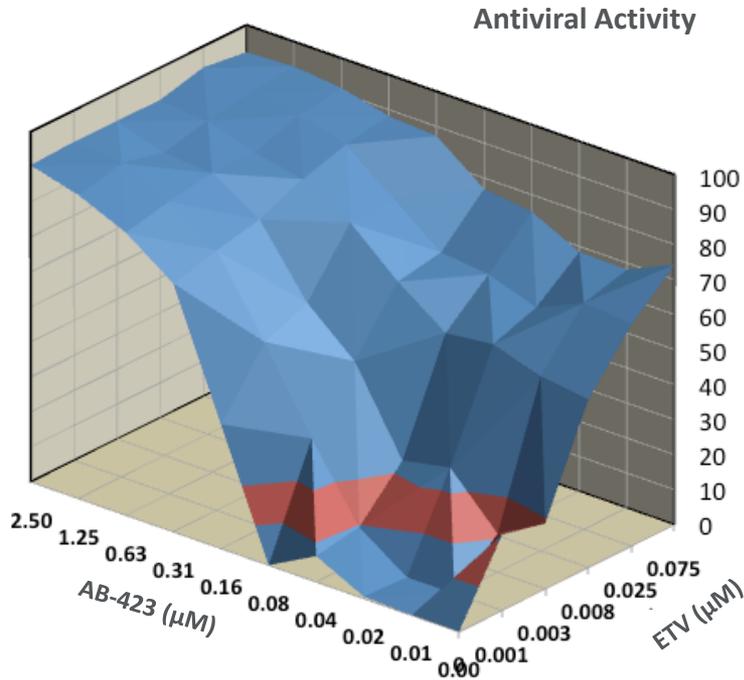
log volume 169.58

ANTAGONISM 0

log volume 0

In Vitro Combination Studies

Capsid Assembly Inhibitor AB-423 with Entecavir (ETV)



HBV rcDNA Synthesis by bDNA assay

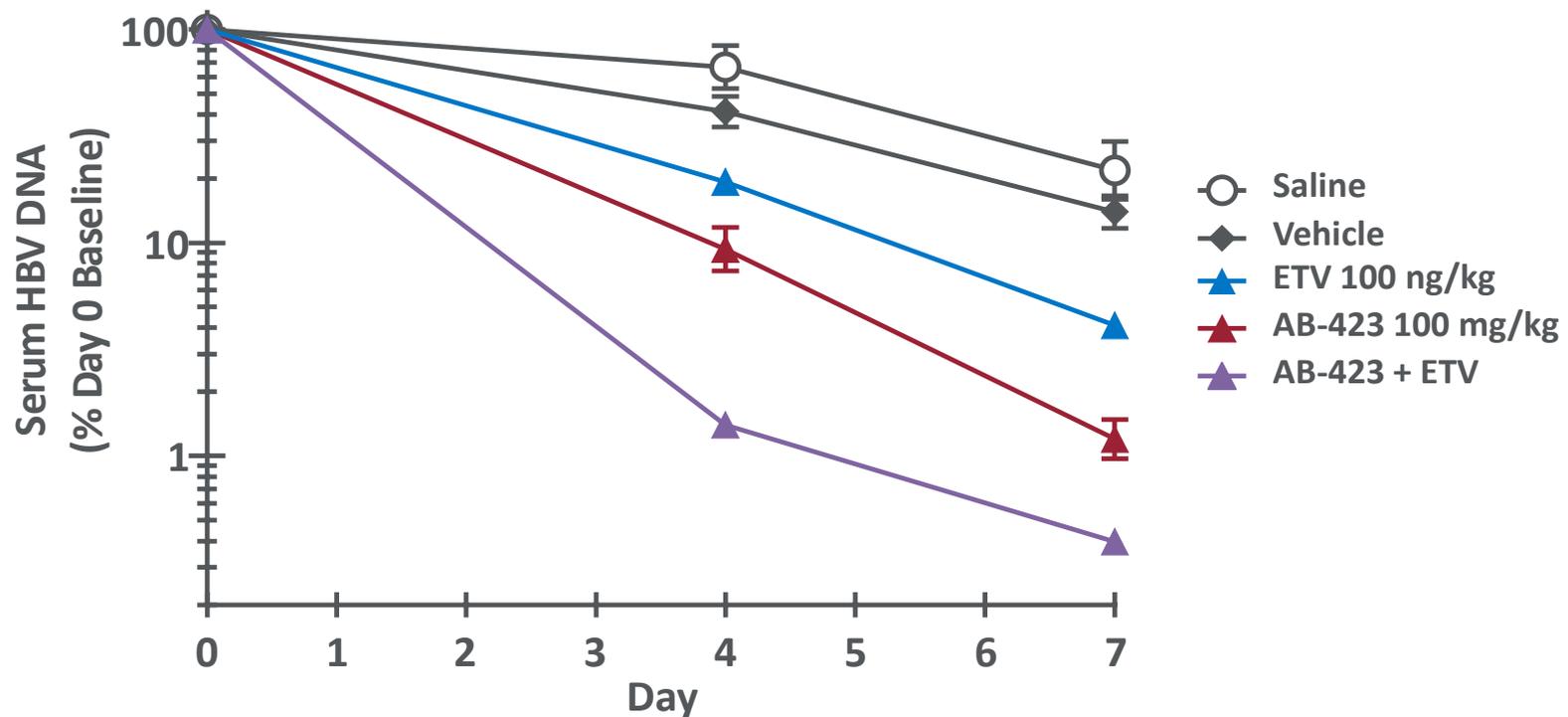
- Additive Interaction
- No Antagonism
- MacSynergyII Analysis
- EC50 values comparable to historical values
- No cytotoxicity detected by Cell TiterGlo assay in combination

SYNERGY PLOT (99.9%)	
<i>Bonferroni Adj.</i>	96%
SYNERGY	0
<i>log volume</i>	0
ANTAGONISM	-1.29
<i>log volume</i>	-0.19

In Vivo Combination Studies

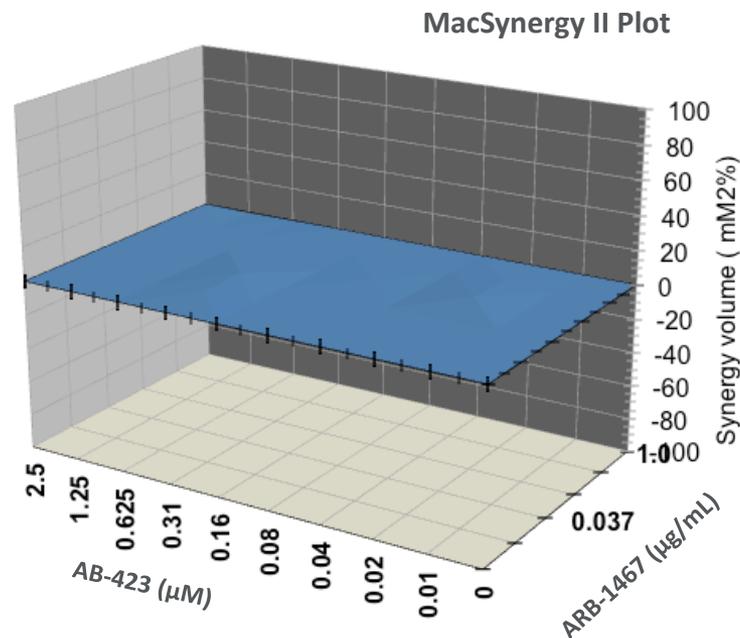
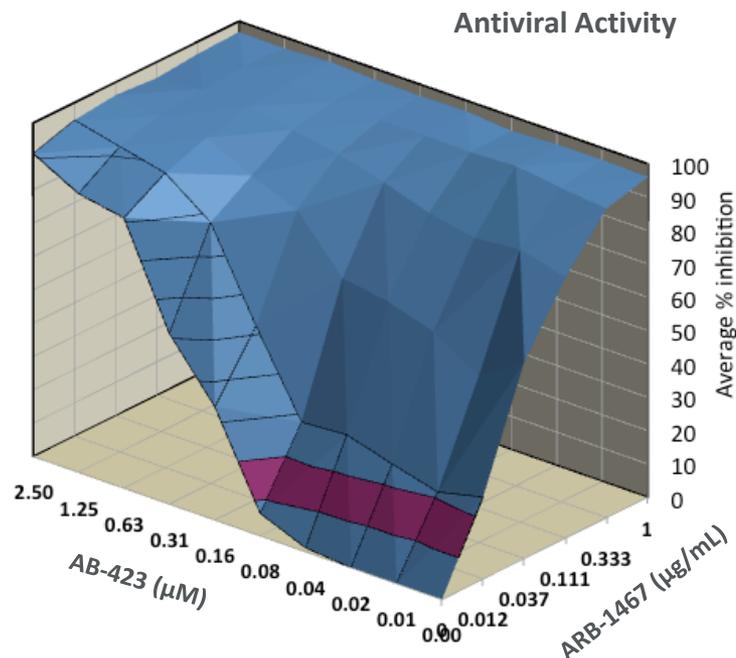
Capsid Assembly Inhibitor AB-423 with Entecavir (ETV)

- HDI mouse model
- AB-423 at 100 mg/kg BID on Days 0-7, ETV given QD D0-7



In Vitro Combination Studies

Capsid Assembly Inhibitor AB-423 with ARB-1467 (RNAi 1.0)



HBV rcDNA synthesis by bDNA assay

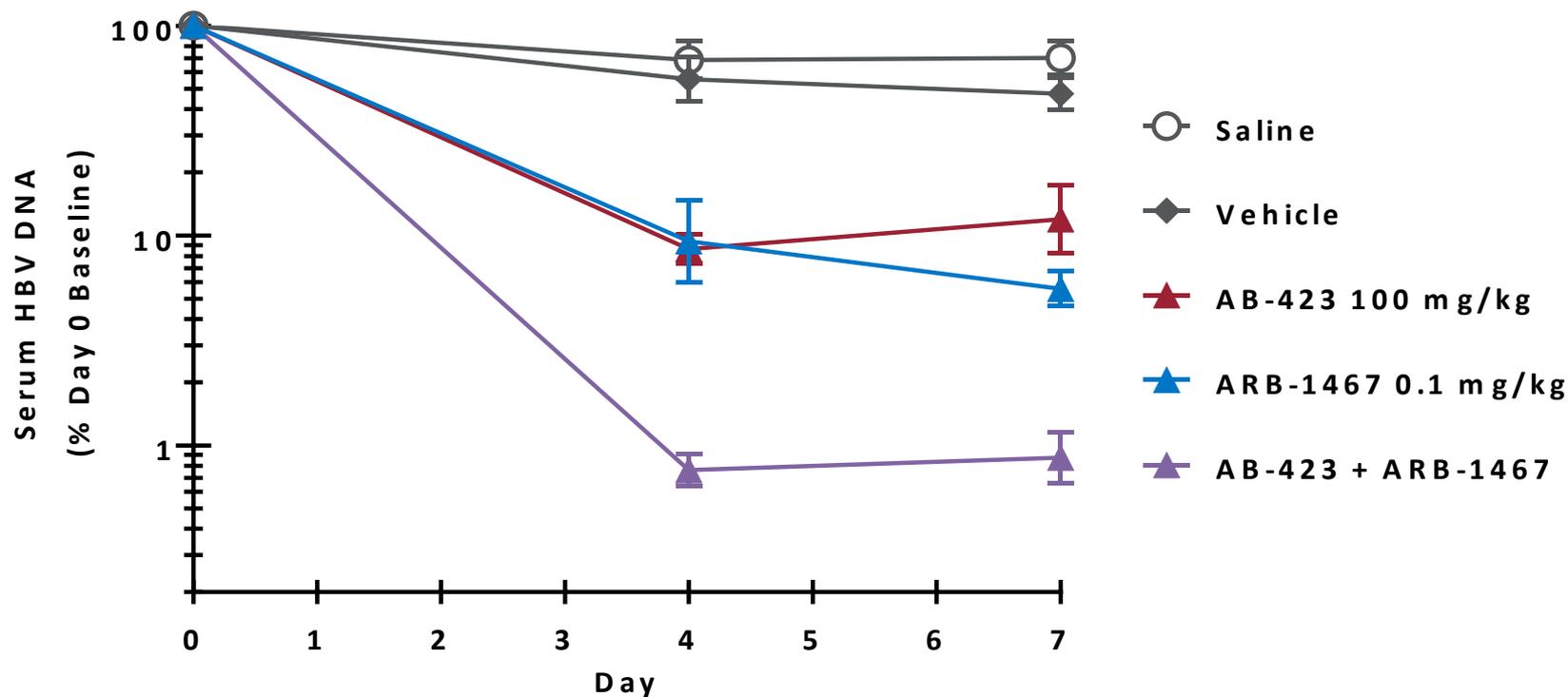
- Additive Interaction
- No Antagonism
- MacSynergyII Analysis
- EC50 values comparable to historical values
- No cytotoxicity detected by Cell TiterGlo assay in combination

SYNERGY PLOT (99.9%)	
<i>Bonferroni Adj.</i>	96%
SYNERGY	6.96
<i>log volume</i>	1
ANTAGONISM	-0.81
<i>log volume</i>	-0.12

In Vivo Combination Studies

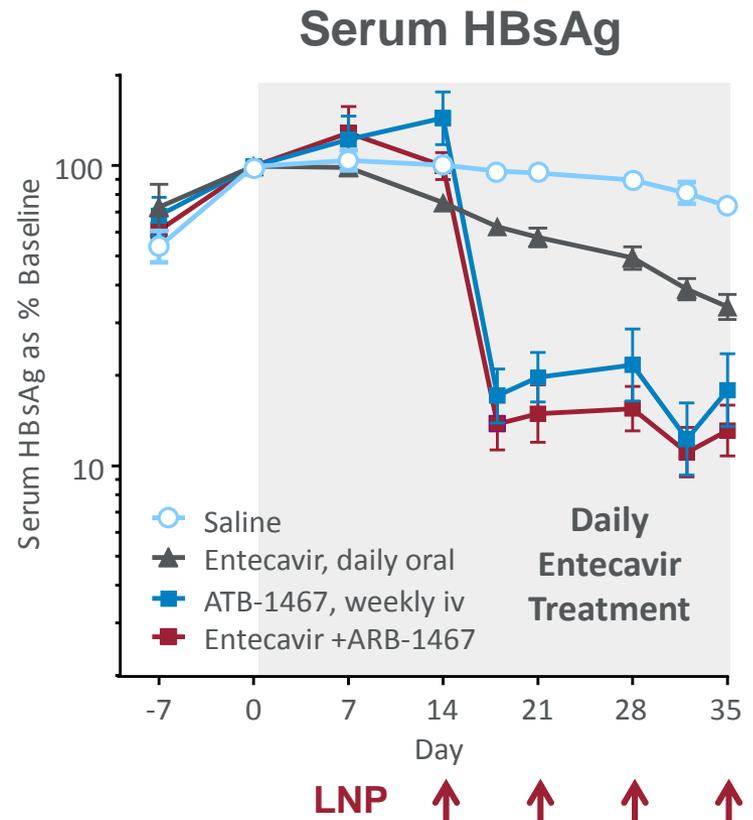
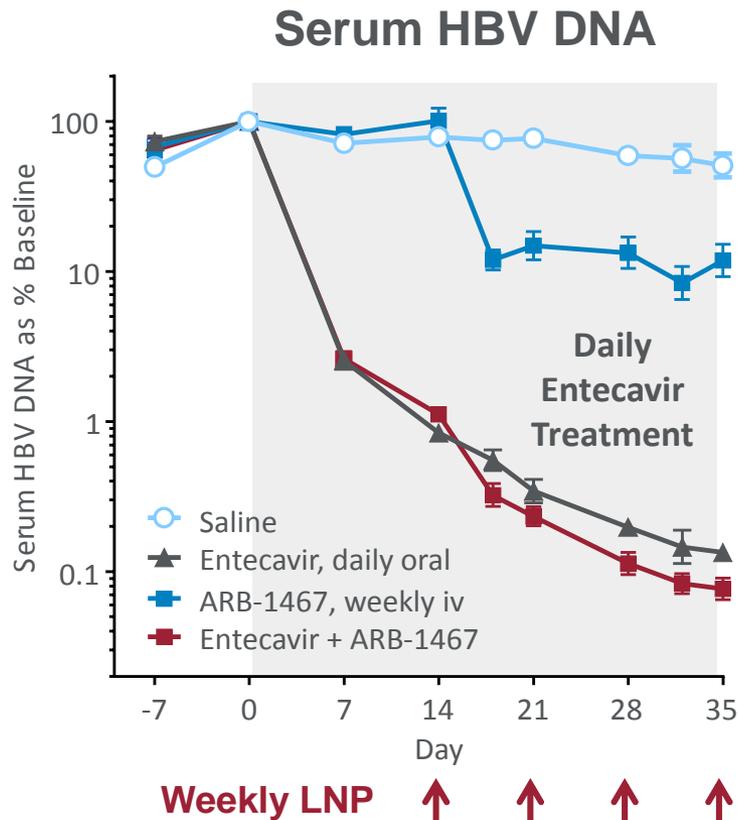
Capsid Assembly Inhibitor AB-423 with ARB-1467 (RNAi 1.0)

- HDI mouse model
- AB-423 at 100 mg/kg BID on Days 0-7, RNAi 1.0 given on Day 0



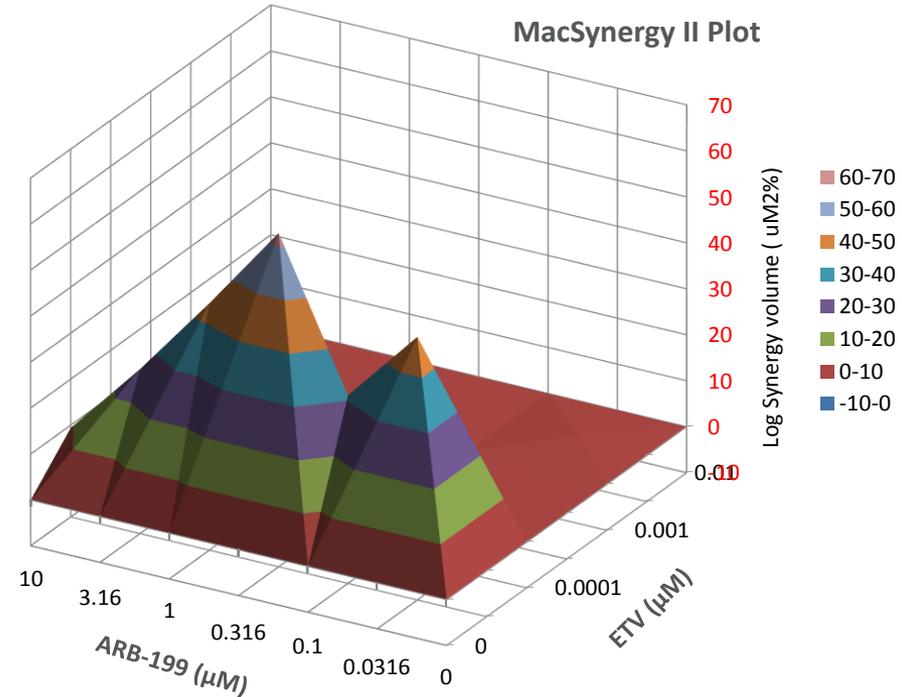
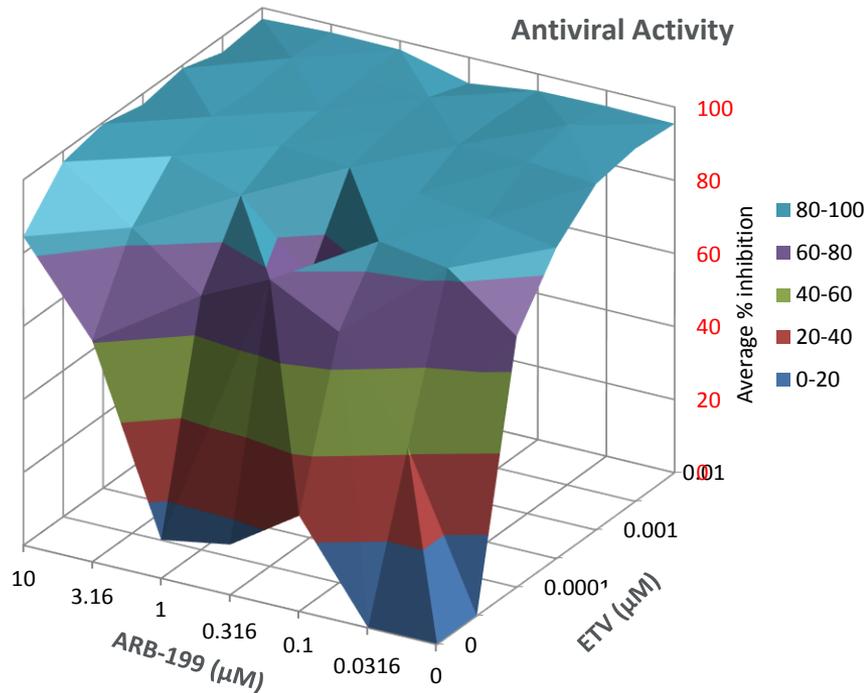
In Vivo Combination Studies

ARB-1467 (RNAi 1.0) Complements NUC Standard of Care



In Vitro Combination Studies

cccDNA Formation Inhibitor ARB-199 with Entecavir (EVT)



cccDNA Synthesis and Expression by qRT-PCR assay

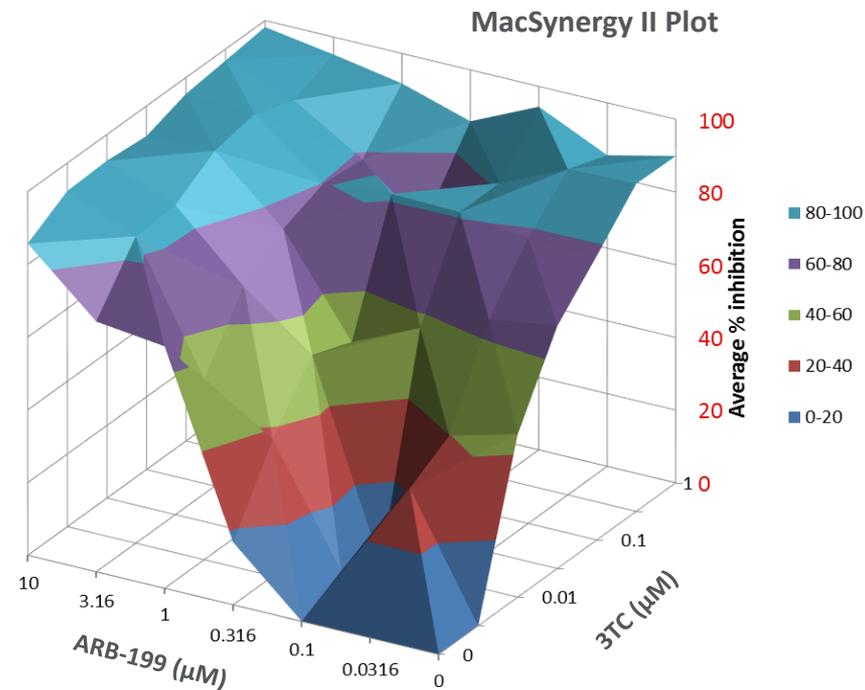
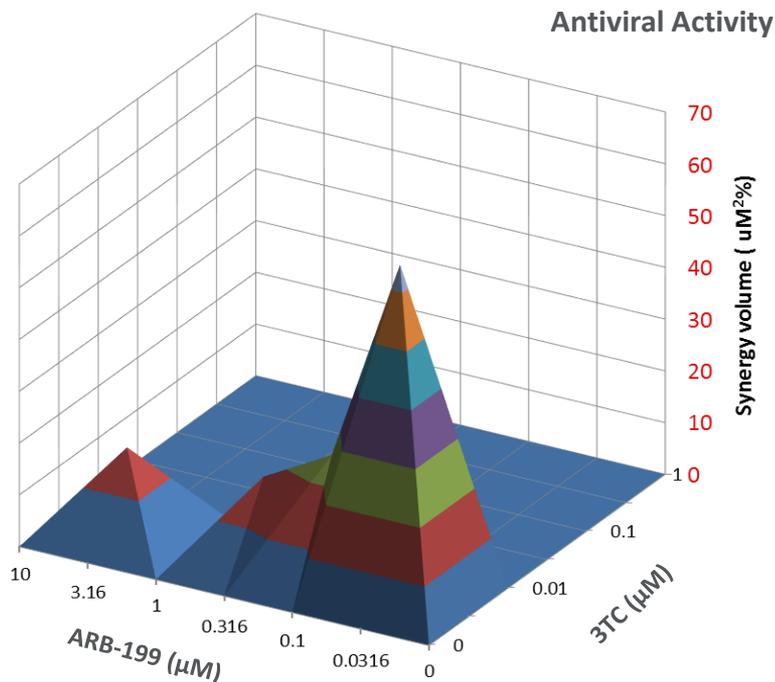
- Synergistic Interaction
- No Antagonism
- MacSynergyII Analysis
- EC50 values comparable to historical values
- No cytotoxicity detected by Cell TiterGlo assay in combination

SYNERGY PLOT (99% CI)

SYNERGY	554.53
<i>log volume</i>	138.63
ANTAGONISM	-31.19
<i>log volume</i>	-7.8

In Vitro Combination Studies

cccDNA Formation Inhibitor ARB-199 with Lamivudine (3TC)



cccDNA Synthesis and Expression by qRT-PCR assay

- Synergistic Interaction
- No Antagonism
- MacSynergyII Analysis
- EC50 values comparable to historical values

SYNERGY PLOT (99% CI)	
SYNERGY	125.65
<i>log volume</i>	31.41
ANTAGONISM	0
<i>log volume</i>	0

Summary

- Drug combinations have the potential to deliver a HBV cure with a finite treatment duration
- Drug combinations that address the three key aspects of HBV persistence have the highest probability of delivering on a curative regimen
- In vitro and in vivo preclinical studies have shown that 2 drug combinations of capsid/core assembly inhibitors, cccDNA formation inhibitors, RNAi and nucleosides provide additive to synergistic anti-HBV effects.

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