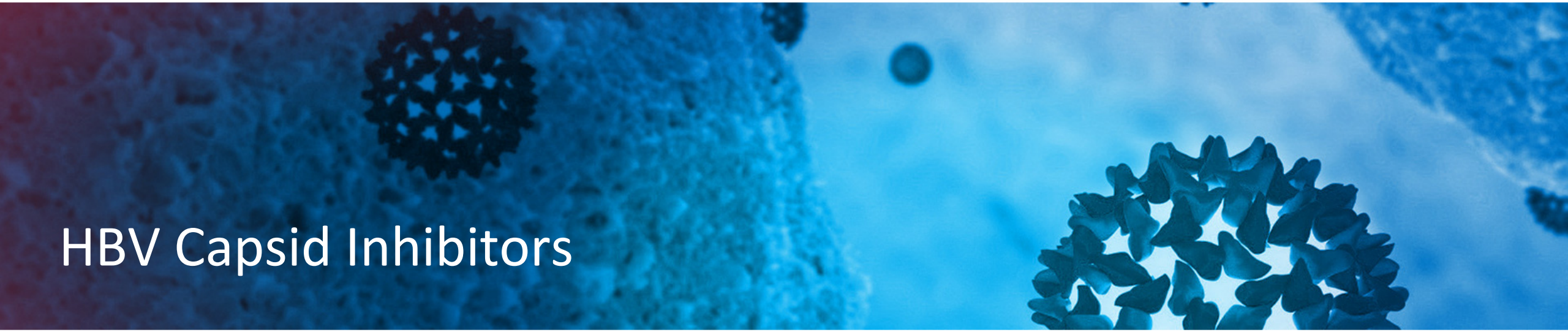
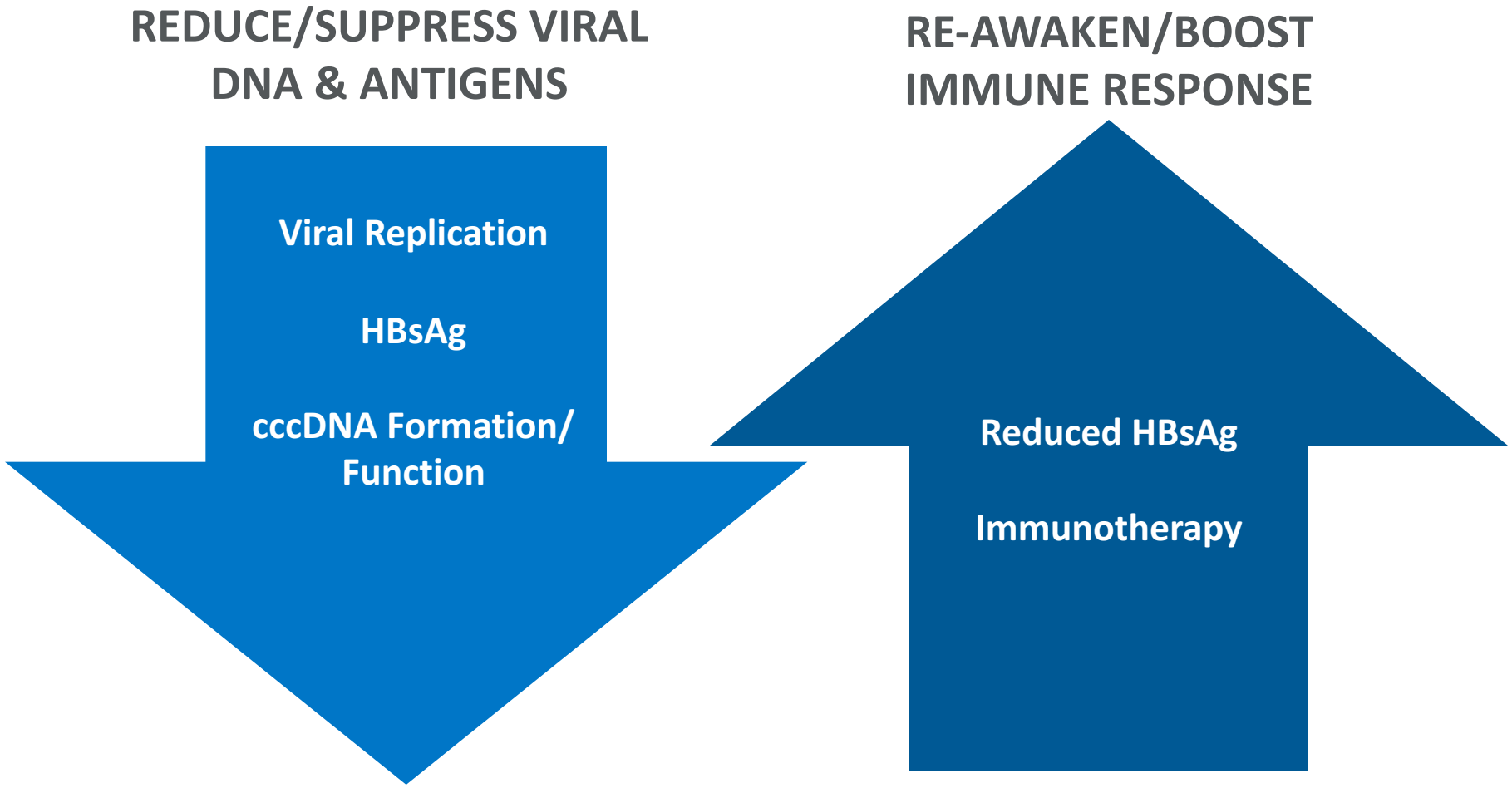
Arbutus BIOPHARMA



HBV Capsid Inhibitors

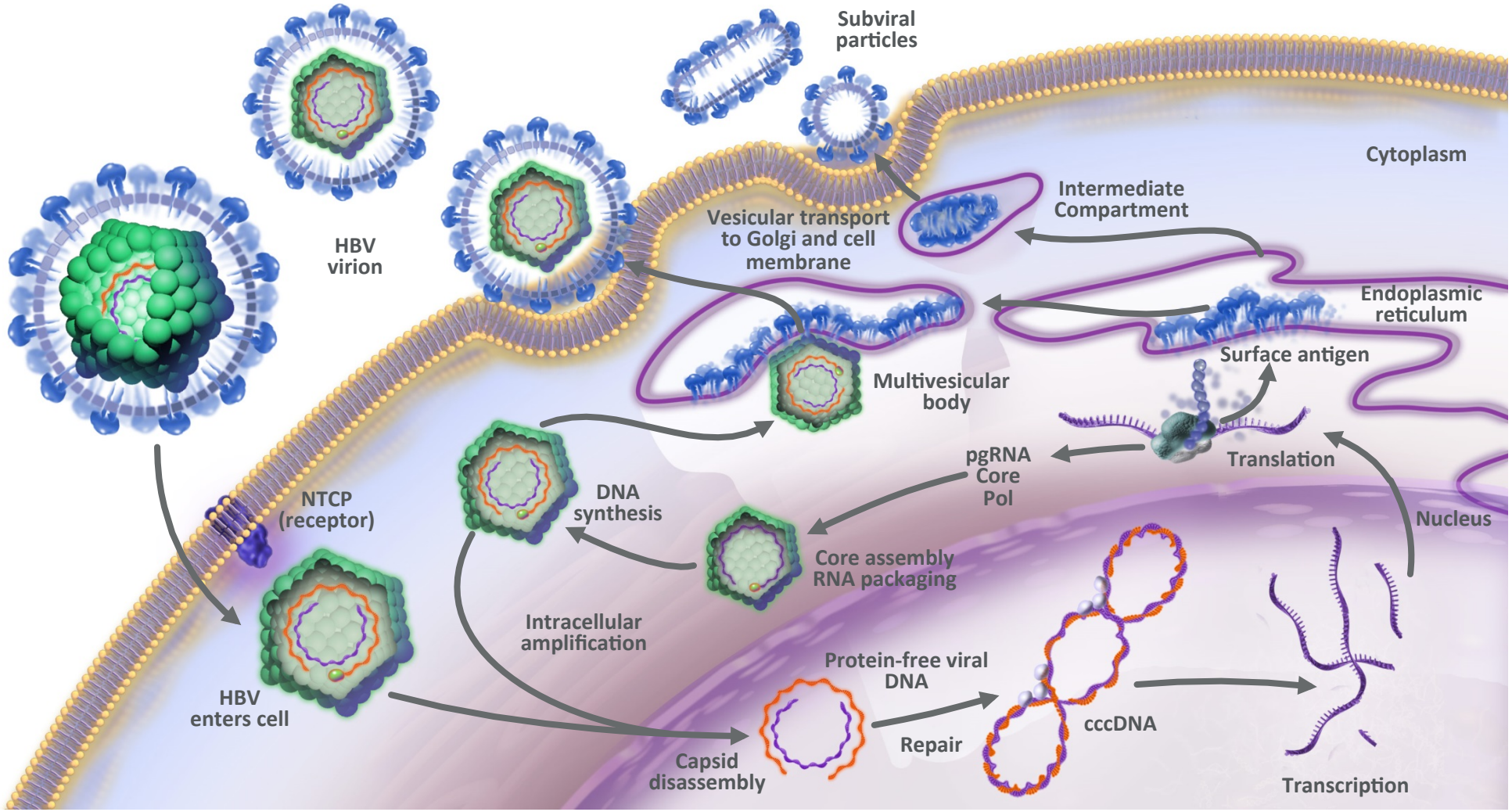
Michael J. Sofia, PhD
Chief Scientific Officer

Key to Therapeutic Success



A combination approach to these key factors will drive cures

HBV Life Cycle

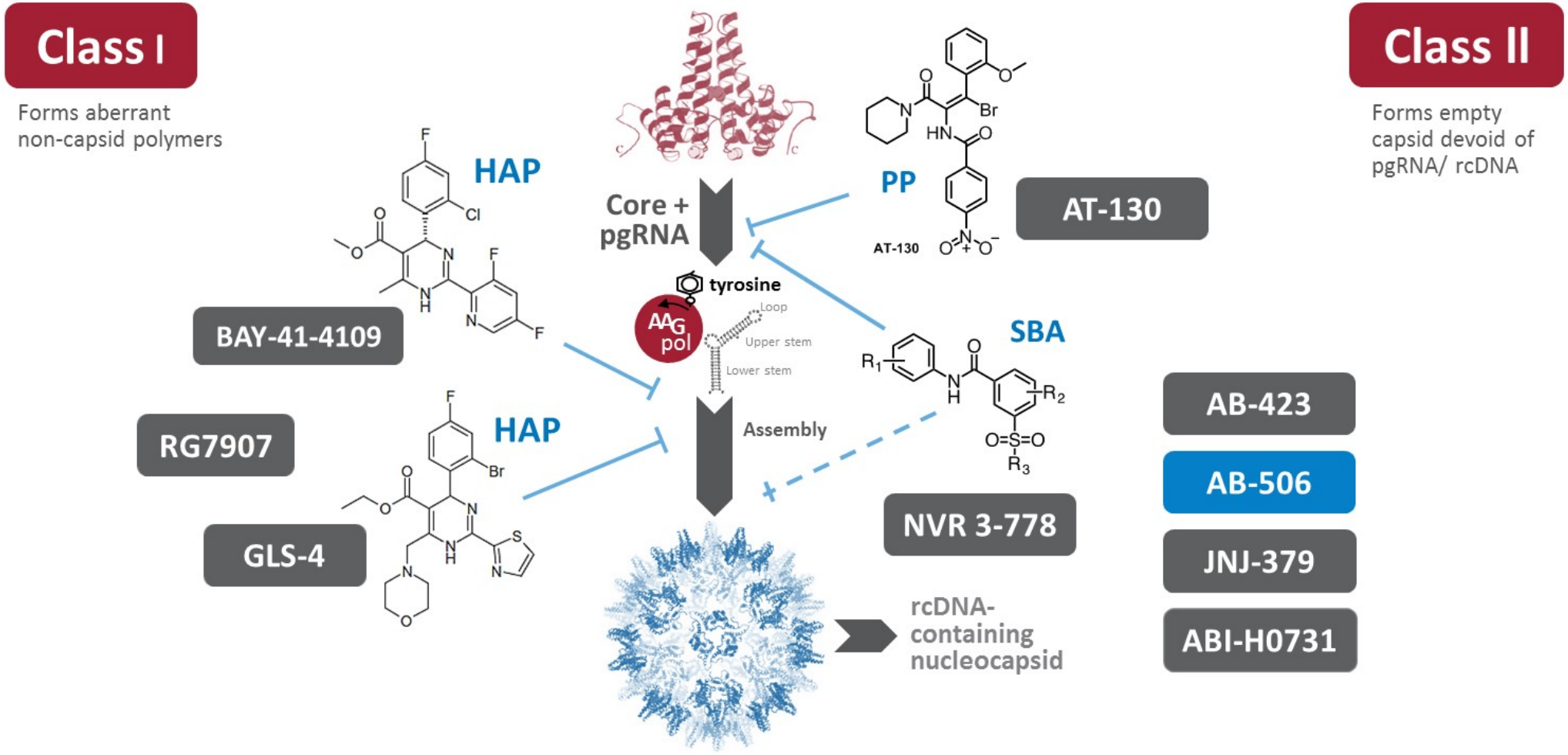


Capsid Inhibitor Overview

- Hepatitis B virus replication is strictly dependent upon capsid assembly around pregenomic RNA (pgRNA) prior to rcDNA and subsequent cccDNA synthesis
- Interfering with HBV capsid assembly has translated into antiviral activity *in vitro* and *in vivo* and constitutes a novel MOA over approved therapies
- Capsid assembly inhibitors show significant distinctions in mechanism of antiviral activity vs currently approved NUCs
- Two classes of capsid assembly inhibitors exist:
  - Class I forms abberant linear polymers
  - Class II forms empty capsids
- All capsid assembly inhibitors bind to the same core protein pocket
- Multiple capsid assembly inhibitor compounds in clinical development (Capsid Inhibitors, Capsid Assembly Inhibitors and Core Protein Allosteric Modulators (CpAMs) are the same)

HBV capsid assembly pathway

Class I and Class II Capsid Inhibitors



HAP: heteroaryldihydropyrimidines; | **SBA:** sulfamoylbenzamides; | **PP:** = phenylpropenamides

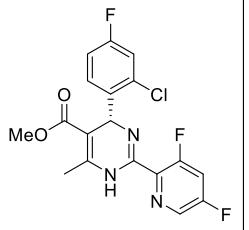
Two Known Classes of Capsid Assembly Inhibitors

Most Companies Focused on Class II

- Class I (Heteroaryldihydropyrimidines (HAP) – Forms abberant linear polymers of core protein
- Class II (Propenamides/Sulfonylbenzamides) – Form empty capsids

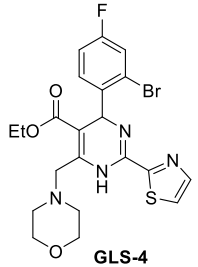
Class I

Bayer



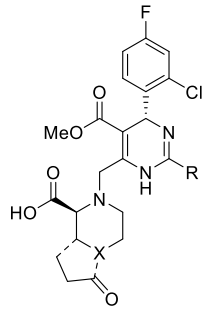
BAY-41-4109

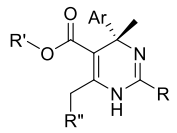
Sunshine Lake Pharm



GLS-4

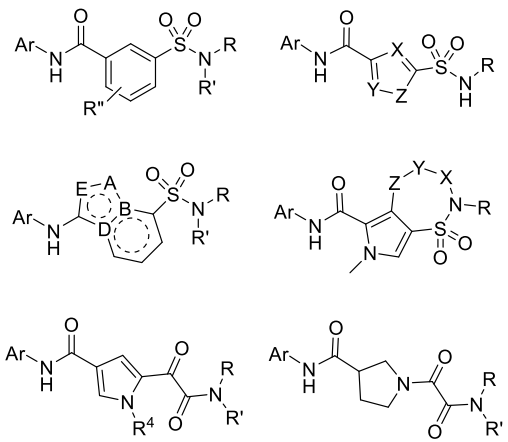
Roche



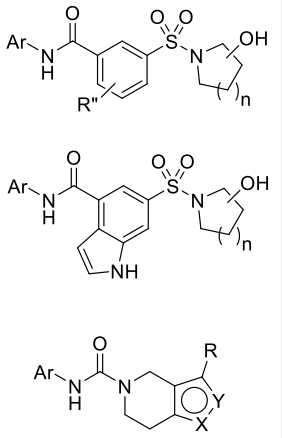


Class II

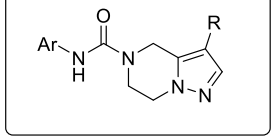
Janssen



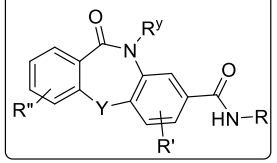
Novira



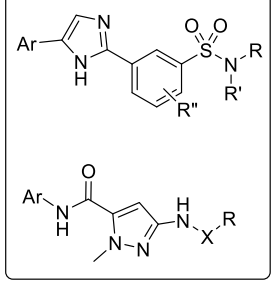
Roche



Assembly

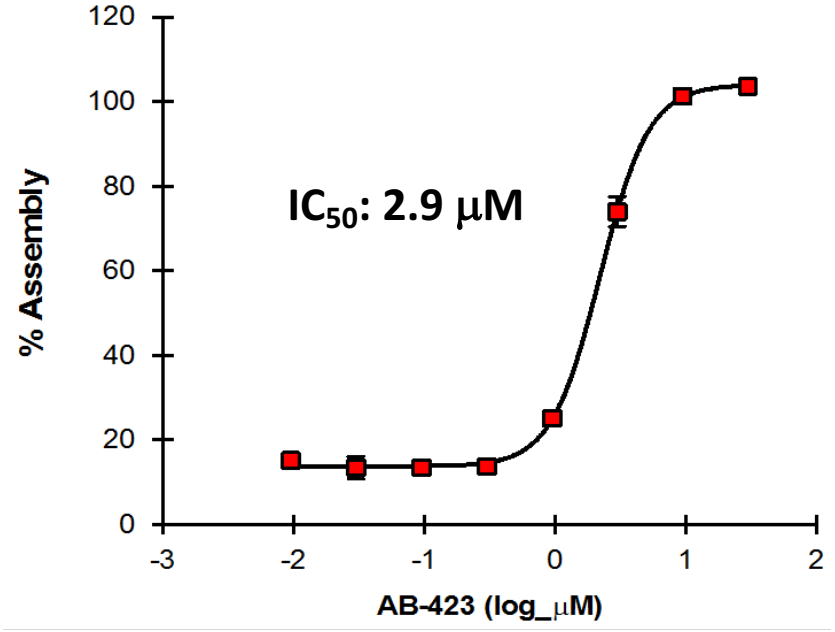


Enanta

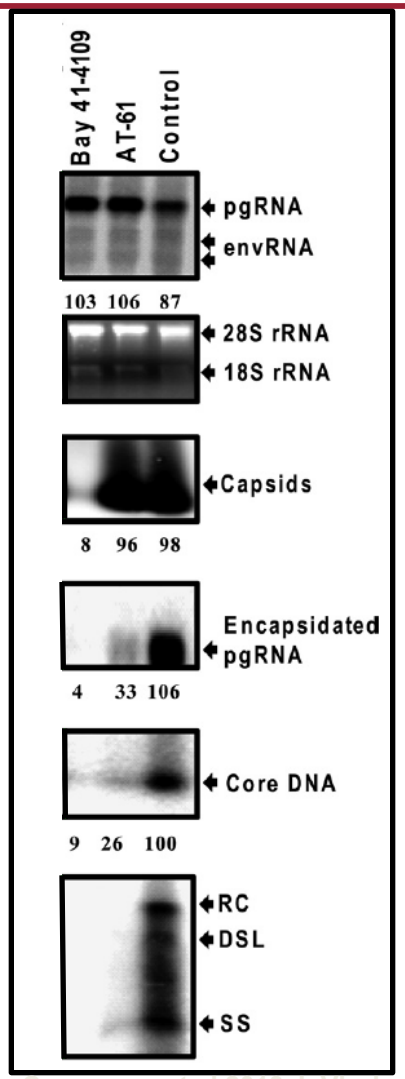


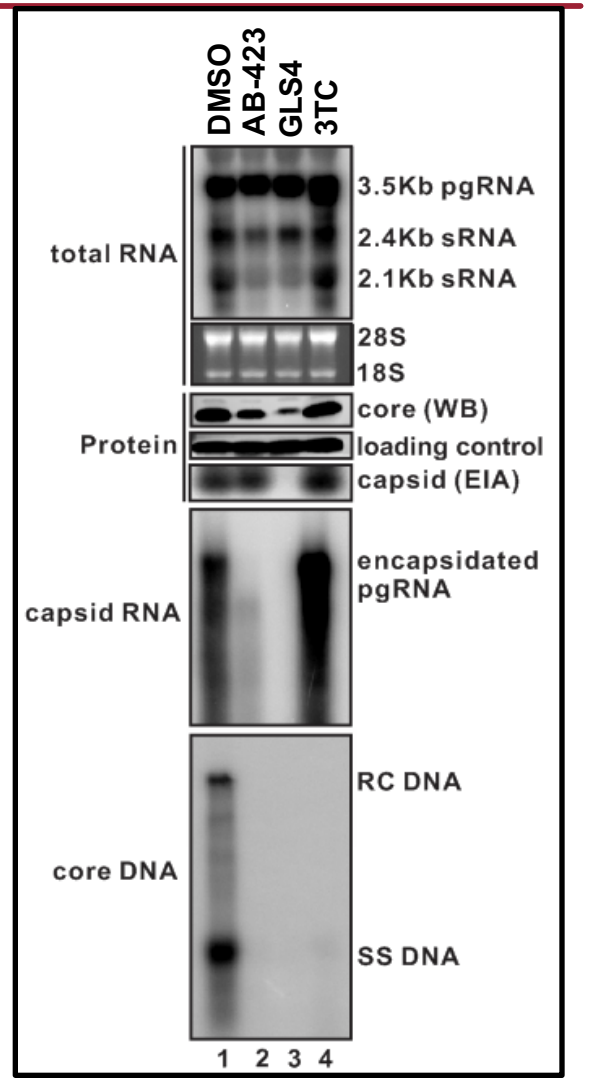
AB-423 Inhibits HBV pgRNA Encapsidation and Misdirects Capsid Assembly *In Vitro* and in Tissue Culture

- In a biochemical capsid assembly assay, AB-423 misdirects capsid assembly



- AB-423 inhibits pgRNA encapsidation in an HBV cell culture model system

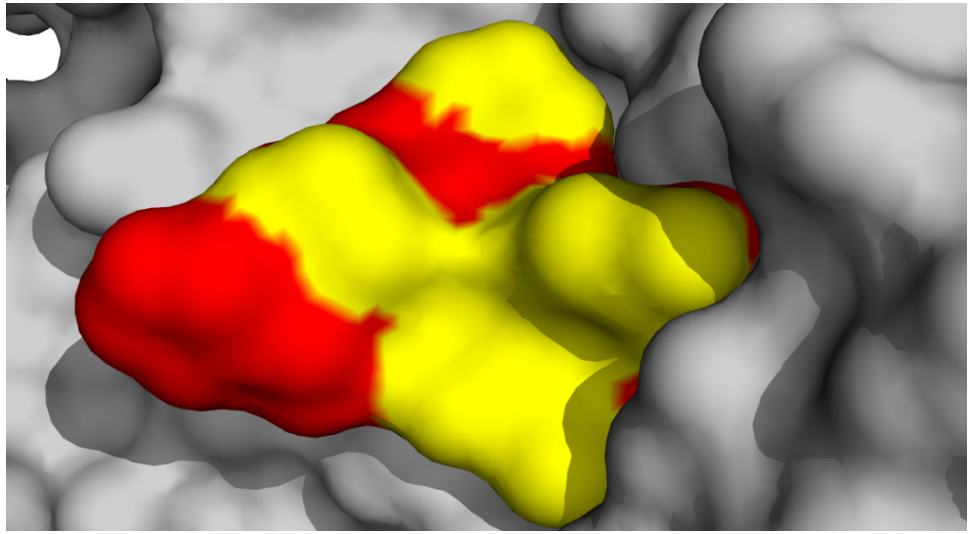




Campagna et al 2013 J. Virol

Structural Insights into Binding of Core Protein Allosteric Modulators (CpAM)

- Two classes of CpAMs have been defined
  - Class I CpAMs induce non-capsid polymers
  - Class II CpAMs allows capsid formation devoid of pgRNA
- High resolution X-ray structures of capsid inhibitors bound to capsid protein have been published
- Class I and II core protein assembly modulators bind to the same site, the dimer:dimer interface, yet have different effects on HBV biology
- Molecule related to AB-423 binds in the same site

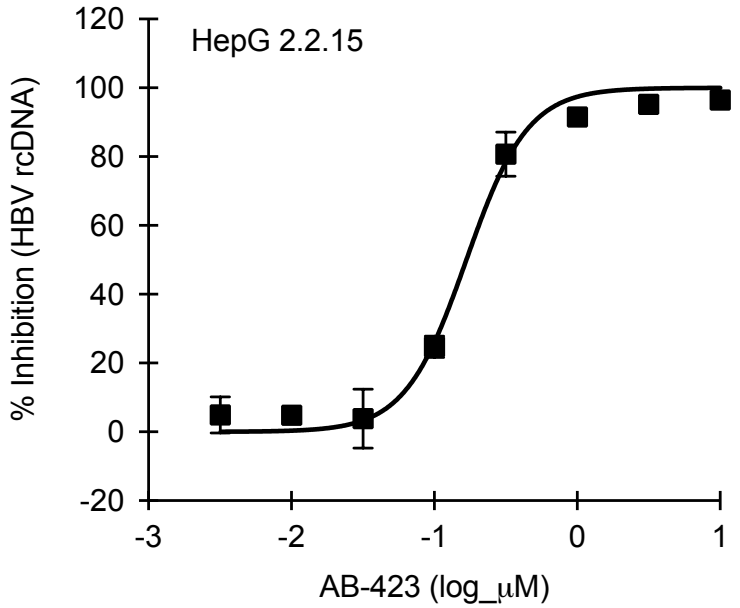


Overlay of a NVR-010–001-E2, a class I CpAM, (HAP, Yellow) and a novel Class II CpAM (Red) bound to CpY132A core protein. Bourne *et al* 2006; Katen *et al* 2013; Klumpp *et al* 2015; Qiu *et al* 2016; Cole, 2016; Arbutus Biopharma unpublished data

AB-423 is an Inhibitor of HBV Replication

	EC_{50} (µM)*	EC_{90} (µM)*	CC_{50} (µM) #	Assay
HepG 2.2.15	0.146± 0.024	0.993 ± 0.855	>10	(rcDNA/qPCR) human hepatoma cell line
HepDE19	0.262 ± 0.127	0.905 ± 0.332	>10	(rcDNA/bDNA) human hepatoma cell line
AML12-HBV10	0.263 ± 0.177	1.319 ± 1.076	>10	(rcDNA/bDNA) mouse hepatoma cell line
HepBHAe82	0.267 ± 0.135	1.246 ± 0.466	>10	(eAg/ELISA) human hepatoma cell line
PHH	0.078±0.031	0.333±0235	>10	(virion DNA/qPCR) Primary human hepatocytes

* EC_{50}/EC_{90} ± SD
# Highest concentration tested



AB-423 has Pan Genotypic Activity

- Most tissue culture systems represent gt D

Genotype	AB-423 EC_{50} (µM)
A-1	0.057
A-2	0.089
B-1	0.039
B-2	0.091
C-1	0.052
C-2	0.055
D	0.195

- Activity maintained across gt A-D maintained within a 4-fold range, with gt A-C being more sensitive than gt D

AB-423 Shows Potent Activity Against Nuc^{R} Variants

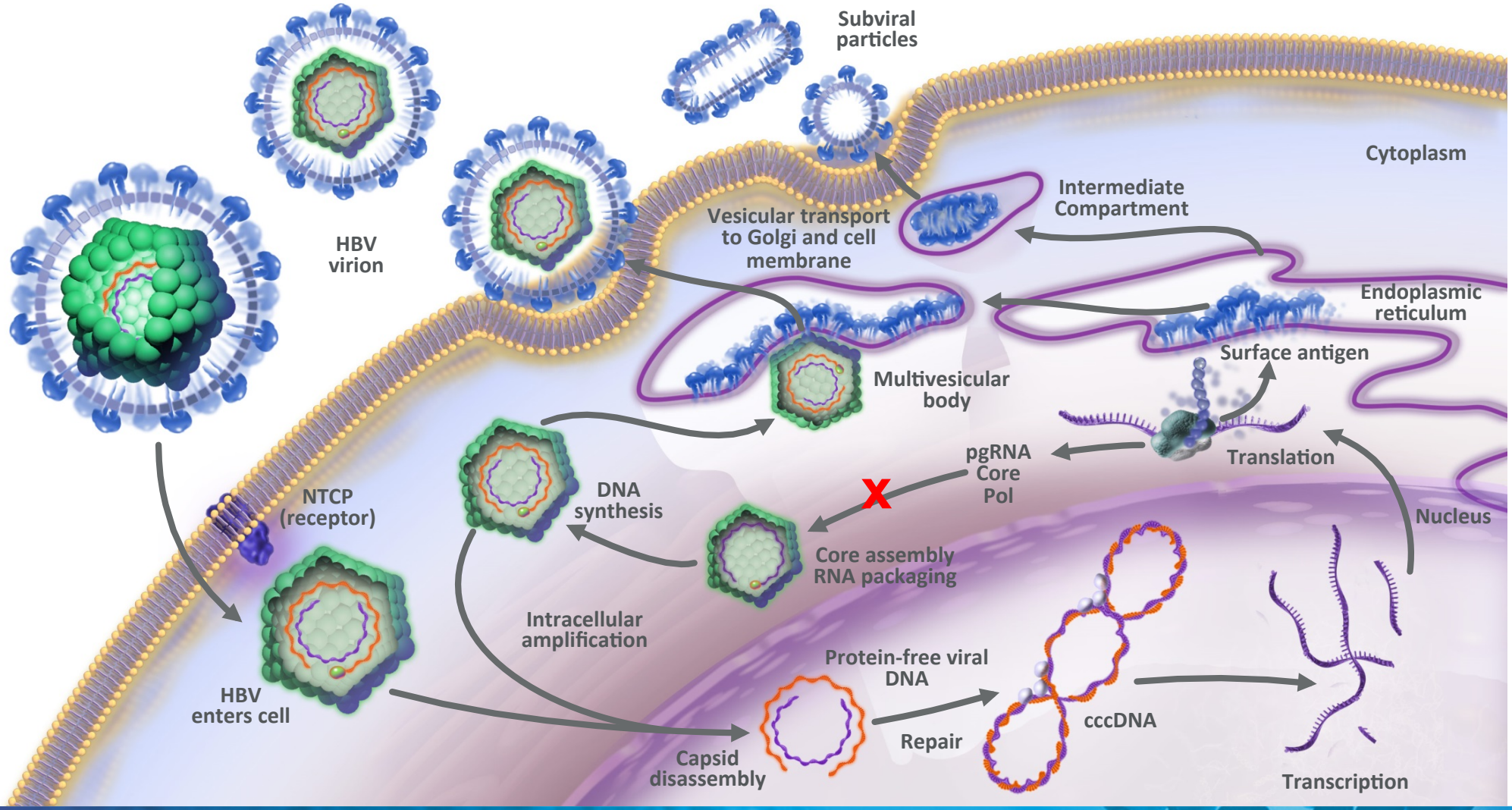
HBV Variant	AB-423 EC_{50} (µM)	ETV EC_{50} (µM)	LAM EC_{50} (µM)
rtM204I	0.192	ND	>100
rtM204I+V173L	0.151	ND	>100
rtM204I+S202G	0.190	10.7	ND
rtM204V+L180M	0.175	ND	>100
rtM204I+S202G+M250V	0.235	9.042	ND
U95551 (WT, GtD)	0.105	0.002	0.03
rtM204I	0.192	ND	>100
rtM204I+V173L	0.151	ND	>100
rtM204I+S202G	0.190	10.7	ND

- **No cross-resistance with Nuc^{R} variants. Consistent with their distinct mechanisms of action.**

AB-423 is a Selective Inhibitor of HBV

Virus	Family	Genome	EC_{50} (µM)	CC_{50} (µM)	Host Cell Line
Hepatitis C	Flaviviridae	(+) ssRNA	11.2	>30	Huh7
WNV	Flaviviridae	(+) ssRNA	>30	19	VERO
Dengue Virus	Flaviviridae	(+) ssRNA	>30	>30	Huh7
Rhinovirus (HRV 1A)	Picornaviridae	(+) ssRNA	7.18	>30	H1/HeLa
Influenza A Virus	Orthomyxoviridae	segmented (-) ssRNA	>30	>30	MDCK
RSV	Paramyxoviridae	non-segmented (-)ssRNA	19.2	>30	HEp2
Human Cytomegalovirus	Herpesviridae	dsDNA	>30	>30	MRC5
Herpes Simplex Virus	Herpesviridae	dsDNA	>30	>30	VERO
HIV	Retroviridae	ssRNA to DNA	>30	16.2	CEMSS

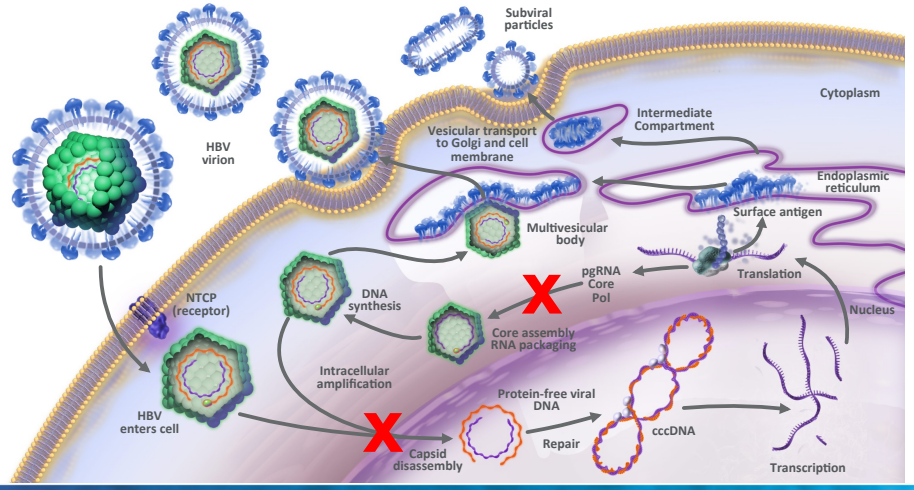
AB-423 Inhibits Viral Replication

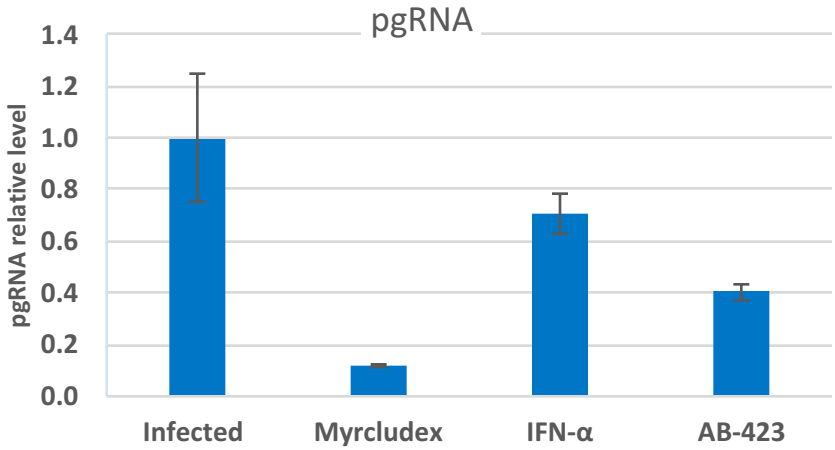


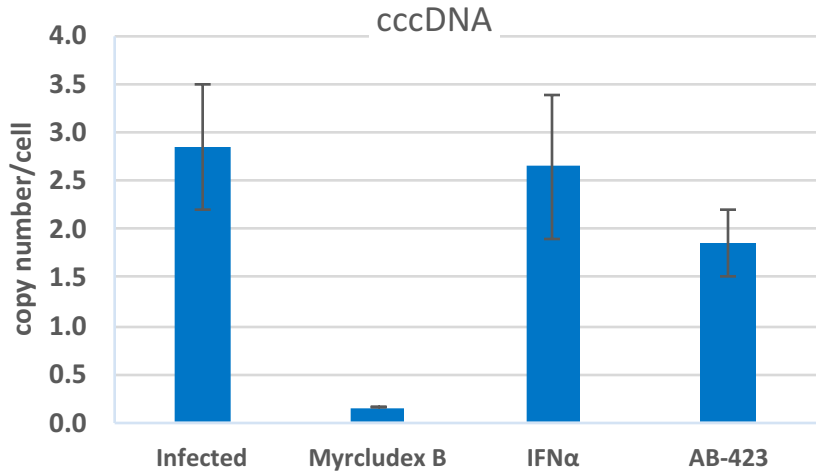
Capsid Inhibitors Have Multiple Modes of Action

- AB-423 inhibited cccDNA synthesis during *de novo* HBV infection of C3A^{hNTCP} cells

- Data suggests AB-423 has multiple modes of inhibition:
  - Inhibits encapsidation of pgRNA during ongoing infection
  - Inhibits cccDNA synthesis presumably *via* inhibition of the capsid uncoating step:
    - Likely relevant for cccDNA recycling during ongoing infection and de novo infection of new hepatocytes

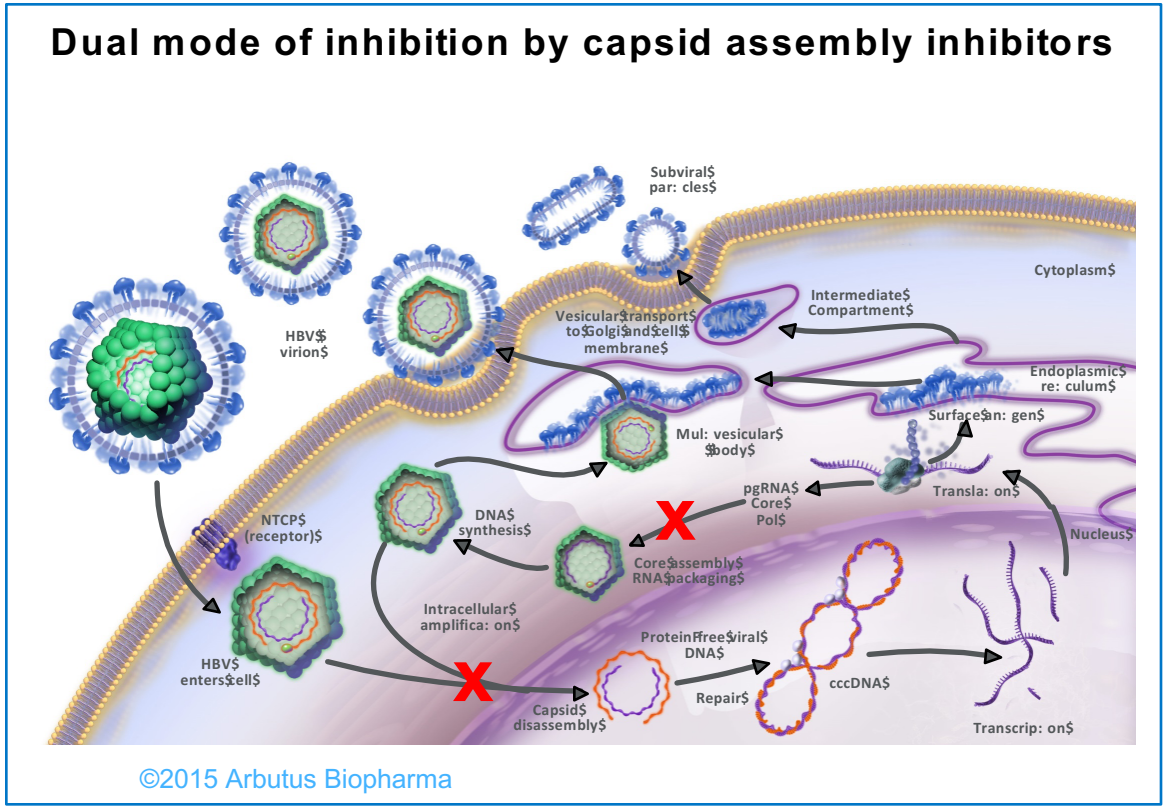






AB-423 Inhibits Conversion of Encapsidated rcDNA to cccDNA in an Infectious Virus System

- Data suggests AB-423 has a dual mode of inhibition:
  - Inhibits encapsidation of pgRNA during ongoing infection
  - Inhibits cccDNA synthesis presumably *via* inhibition of the capsid uncoating step



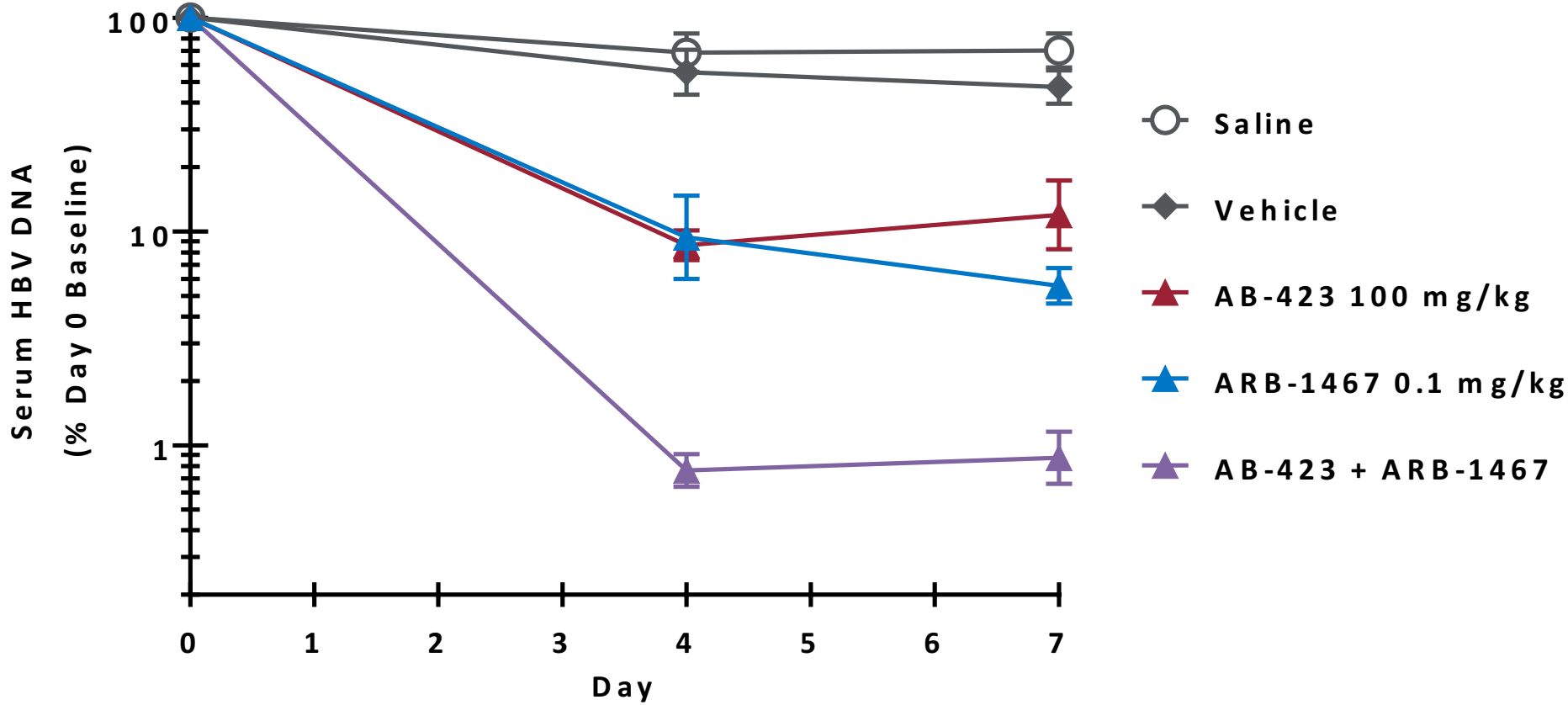
In vitro Data Indicates Potential for Combining AB-423 with Nucs, IFN, and RNAi agents

	Inhibitor B	Cell Culture Model	Conclusion*
pgRNA → rcDNA → cccDNA			
AB-423	ARB-1740 (*RNAi 2.0*)	HepBHAe82 (precore RNA/qRT-PCR)	Synergy
AB-423	ETV	HepBHAe82 (precore RNA/qRT-PCR)	Synergy
pgRNA → rcDNA			
AB-423	ARB-1467 (*RNAi 1.0)*	AML12-HBV10 (bDNA/rcDNA)	Additive
AB-423	ARB-1740 (*RNAi 2.0*)	AML12-HBV10 (bDNA/rcDNA)	Additive
AB-423	ETV	AML12-HBV10 (bDNA/rcDNA)	Additive
AB-423	TDF	HepDE19 (bDNA/rcDNA)	Additive
rcDNA and eAg			
AB-423	TAF	HBV infected PHH (HBV DNA/HBeAg)	Additive
AB-423	IFN	HBV infected PHH (HBV DNA/HBeAg)	Synergy

*MacSynergy II Analysis; Bliss Independence Model; Prichard and Shipman 1990. Antiviral Research, 14(4-5):181-205

- Combination of AB-423 with RNAi agents, Nucs, or IFN is supported by additive to synergistic antiviral activity in *in vitro* studies

Enhanced Activity for AB-423 in Combination with siRNA ARB-1467



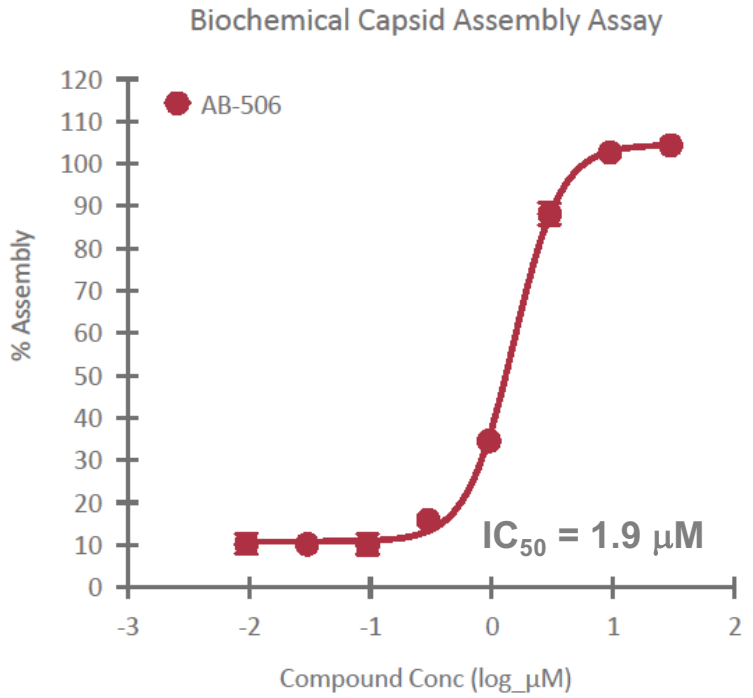
- *In vivo* combination of AB-423 with RNAi agent 1467 in a HDI mouse is supportive with *in vitro* observed additive effects

AB-506

A Second Generation Capsid Inhibitor

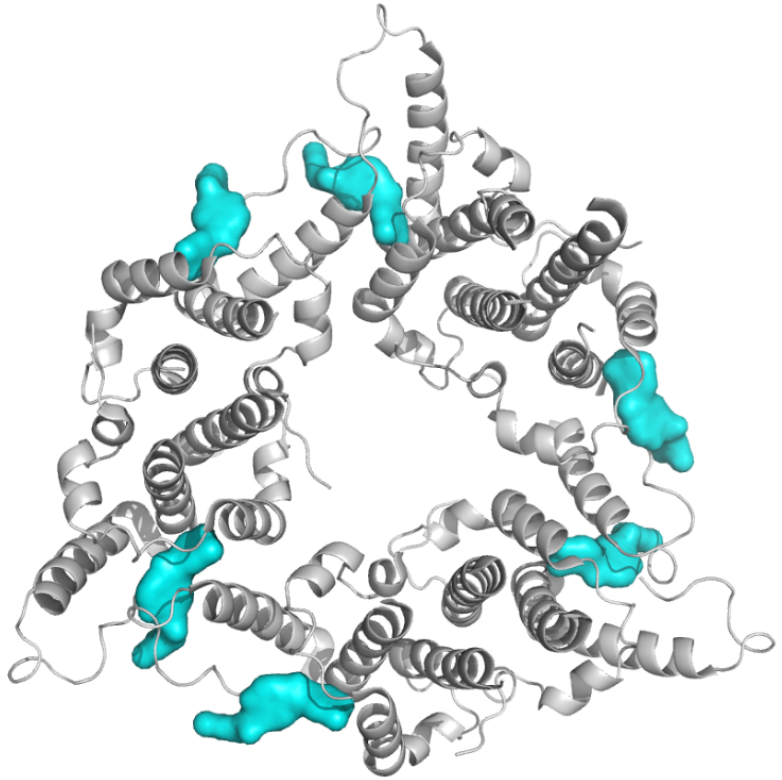
Compound	HepDE19 (rcDNA_bDNA)			HepBHAe82 (HBeAg AlphaLISA)			HepG 2.2.15 (HBV DNA qPCR)	
	EC_{50}	EC_{90}	CC_{50}	EC_{50}	EC_{90}	CC_{50}	EC_{50}	CC_{50}
AB-506 **(µM)**	0.07	0.27	>25	0.04	0.20	>25	0.04	>10

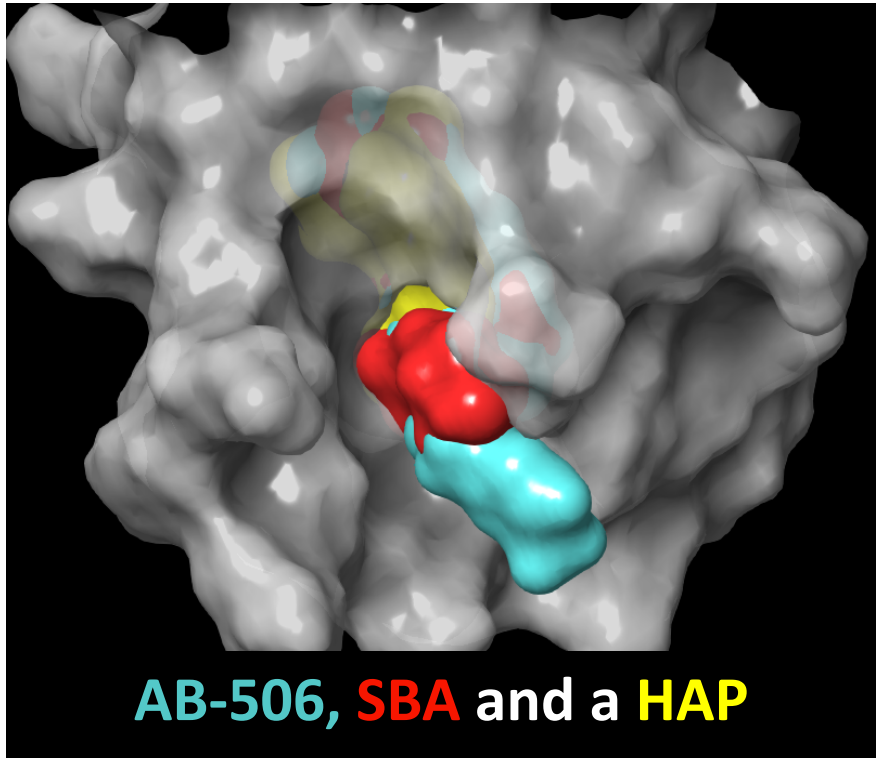
- **AB-506 is a novel Capsid Inhibitor demonstrating potent cellular activity in multiple cell culture models of HBV**
- **In a biochemical assay, AB-506 demonstrates acceleration of capsid assembly**



AB-506

Binds at the HBV Core Protein Dimer:Dimer Interface

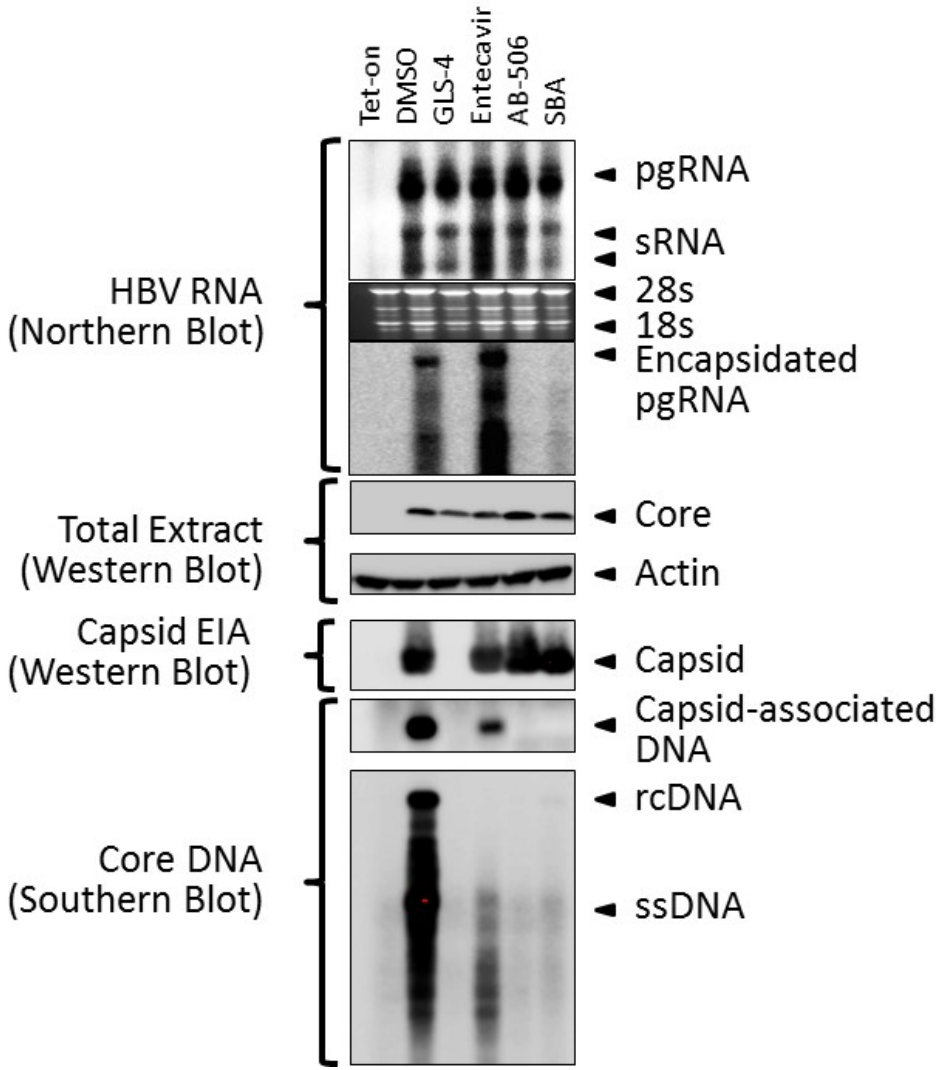




- **X-ray crystal structure of AB-506 with CpY132A mutant solved at 2.25 Å**
- **Compound binds at the dimer:dimer interface similar to other known Class I (HAP) and Class II (SBA) Capsid Inhibitors**

AB-506

Mechanism of Action Studies

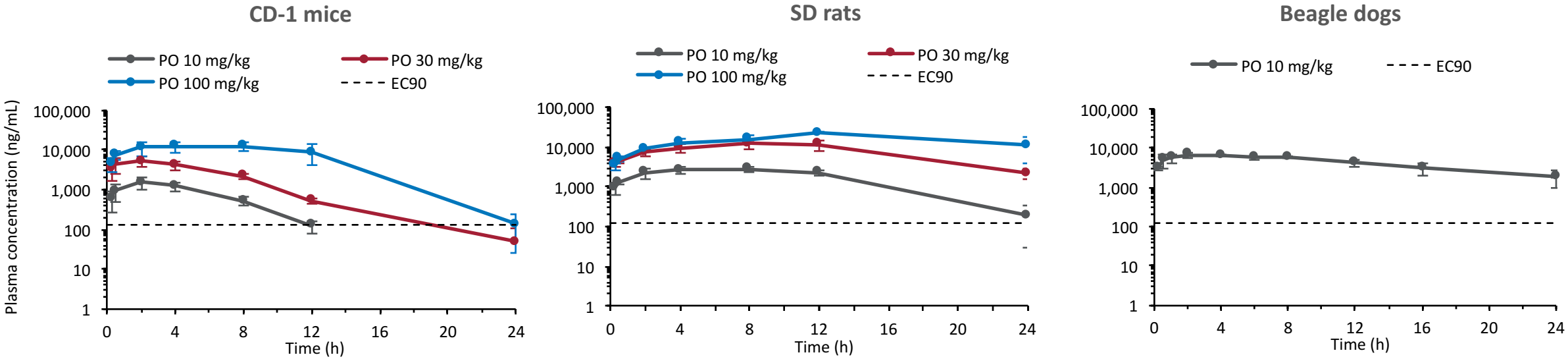


- **Mode of action studies conducted in HepAD38 cells**
- **Capsid formation maintained with AB-506 treatment**
- **AB-506 forms empty capsids devoid of pgRNA or rcDNA**
- **AB-506 MoA is consistent with a Class II inhibitor**
  - ***Distinct from GLS4, a Class I (HAP) inhibitor***

AB-506

Potential Best in Class Profile, Superior Potency and PK Relative to AB-423

- **PK evaluation in multiple species shows favorable exposure and significant liver accumulation, supportive of QD dosing**



Oral PK parameters	Mice	Rats	Dogs
$T_{1/2}$ (h)	2.6	4.3	11.4
F (%)	~100	~100	~100
24 hr liver/plasma	3.0	3.5	NA

AB-506

Potential Best in Class Profile, Superior Potency and PK Relative to AB-423

- **Significantly more potent than AB-423 *in vitro*. Improved PK supports predicted QD dosing in humans with a reduced pill burden**

Cmpd	*In Vitro* Potency (EC_{50} / EC_{90} / CC_{50})								
	HepDE19 rcDNA_bDNA (μM)			HepBHAe82 HBeAg ELISA (μM)			HepG 2.2.15 HBV DNA qPCR (μM)		
	EC_{50}	EC_{90}	CC_{50}	EC_{50}	EC_{90}	CC_{50}	EC_{50}	EC_{90}	CC_{50}
AB-423	0.26	0.91	>10	0.27	1.25	>10	0.15	1.0	>10
AB-506	**0.07**	**0.27**	**>25**	**0.04**	**0.20**	**>25**	**0.04**	**ND**	**>10**

In Vivo PK (@10/2 mpk *p.o./i.v.*) (Mouse / rat / dog)								
Plasma Exposure, AUC_{inf} (h*ng/mL)			12 h Plasma Concentrations (ng/mL)			Clearance (CL) (mL/min/kg)		
2,238	532	21,100	40	n/d	612	31	18	8
9,867	**39,580**	**134,195**	**123**	**2,318**	**4,250**	**19**	**5**	**1.3**

Greater Potency

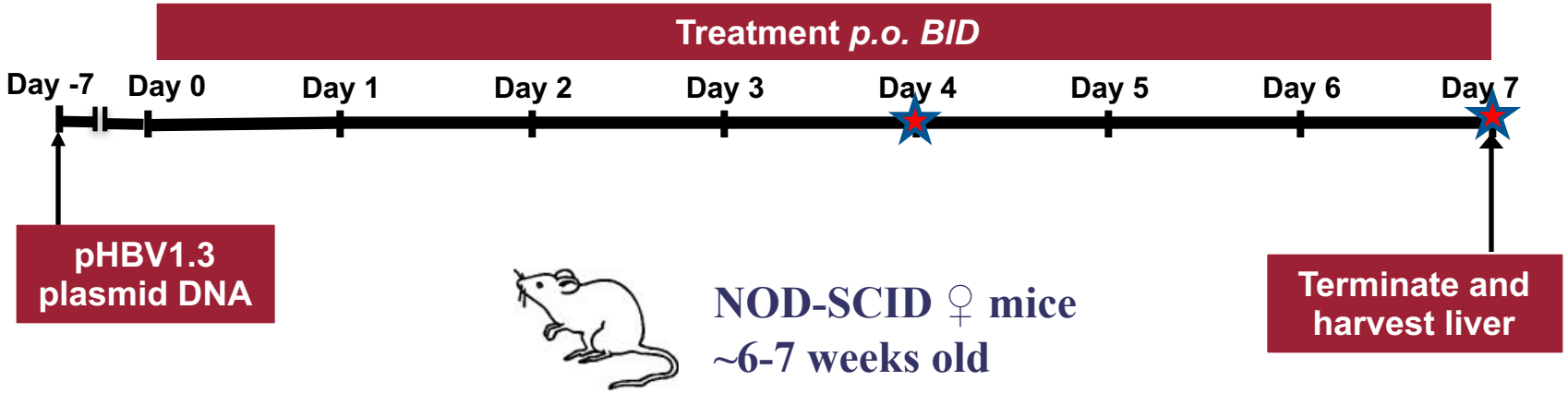
Greater Plasma Exposure

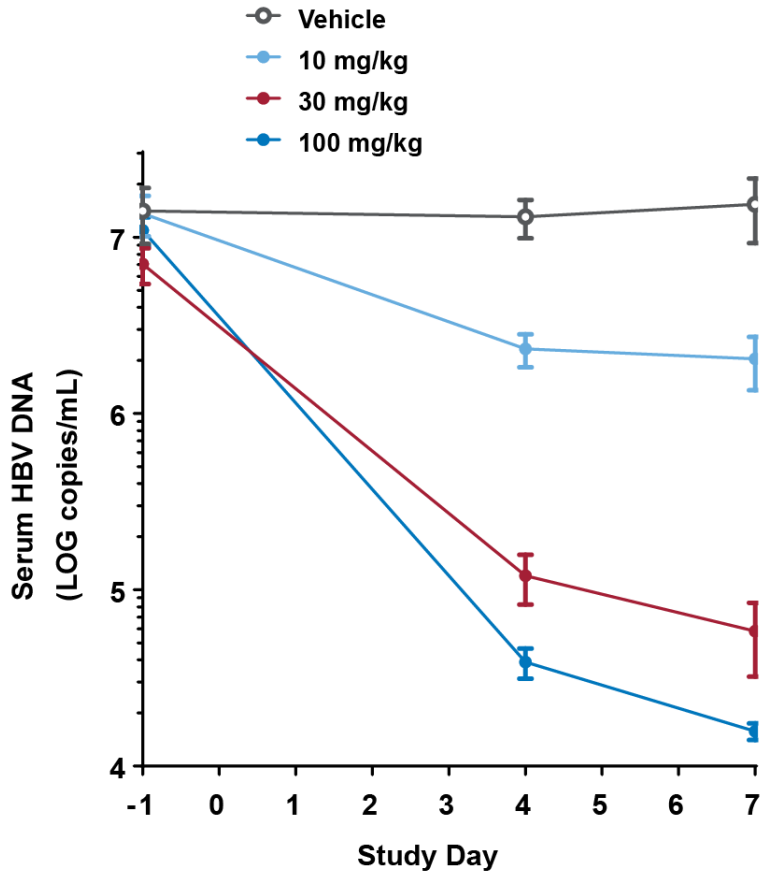
Higher Plasma Concentration

Reduced Clearance

AB-506

In vivo antiviral activity in a mouse HDI model of HBV





- AB-506 Demonstrates a dose dependent (up to 3 log) reduction in HBV DNA in a mouse HDI model of HBV

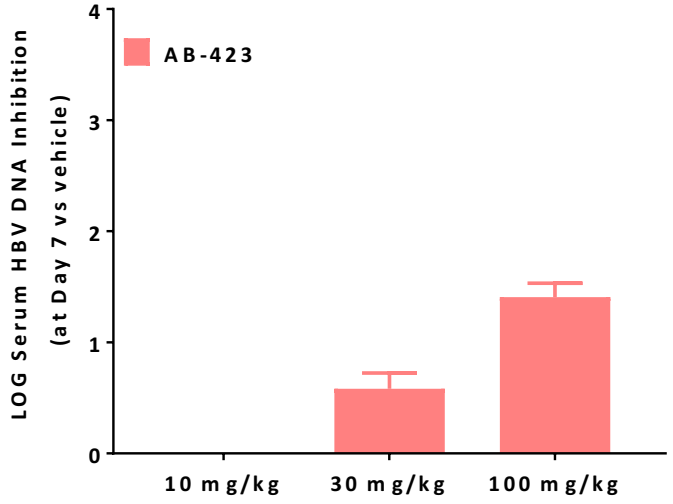
AB-506

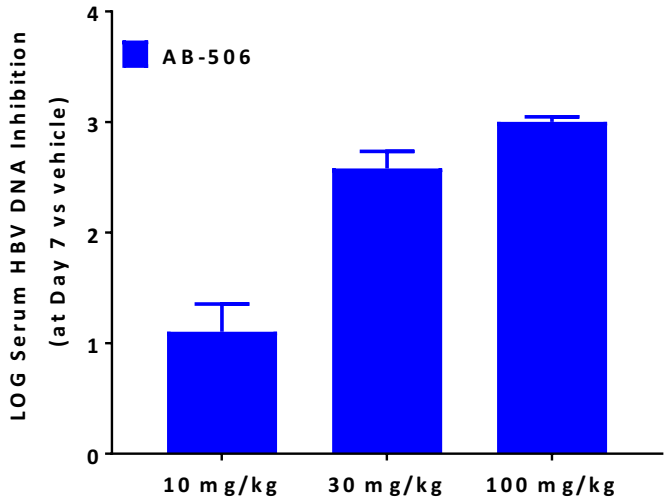
Potential Best in Class Profile, Superior Potency and PK Relative to AB-423

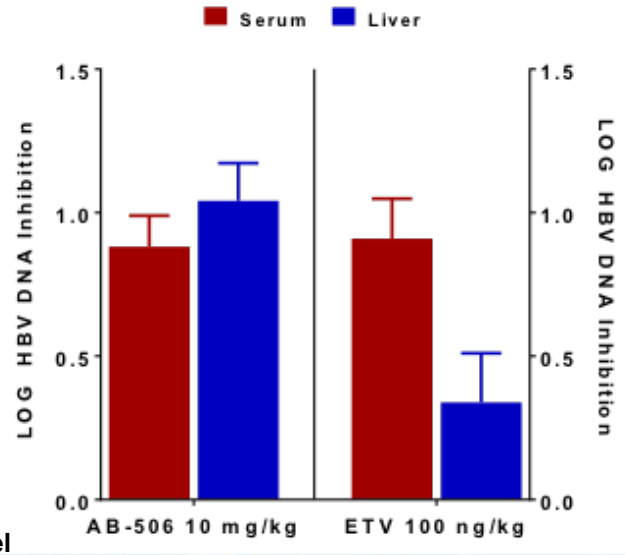
- **AB-506 is significantly more potent than AB-423 *in vitro***

Compound	Potency	HepDE19 (rcDNA_bDNA)(µM)	HepBHAe82 (HBeAg ELISA)(µM)	HepG 2.2.15 (HBV DNA qPCR)(µM)
AB-423	$EC_{50}/EC_{90}/CC_{50}$	0.26/0.91/>10	0.27/1.25/>10	0.15/1.0/>10
AB-506	$EC_{50}/EC_{90}/CC_{50}$	0.07/0.27/>25	0.04/0.20/>25	0.04/ND/>10

- **AB-506 is significantly more potent than AB-423 *in vivo*, with better liver HBV DNA reductions than ETV**







HDI Mouse Model

Summary

- AB-423 is a potent, highly selective inhibitor of HBV replication.
- AB-423 showed dual mode of inhibition:
  - *inhibited encapsidation of pgRNA during ongoing infection*

    inhibited cccDNA synthesis presumably via inhibition of the capsid uncoating step
- In vitro AB-423 showed:
  - *pan-genotypic activity*
  - *potent activity against HBV Nuc^R variants*
  - *additive/synergistic activity in combination with Nucs, IFN, and RNAi agents*
  - *no significant activity against unrelated viruses*
- AB-506 has greater potency and improved PK properties vs. AB-423
- Results indicate that HBV encapsidation inhibitors show significant distinctions in mechanism of antiviral activity from the Nucs