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Curing Chronic Hepatitis B

Abstract #8

A Next Generation HBV Capsid Inhibitor, AB-506: *In Vitro* and *In Vivo* Antiviral Characterization

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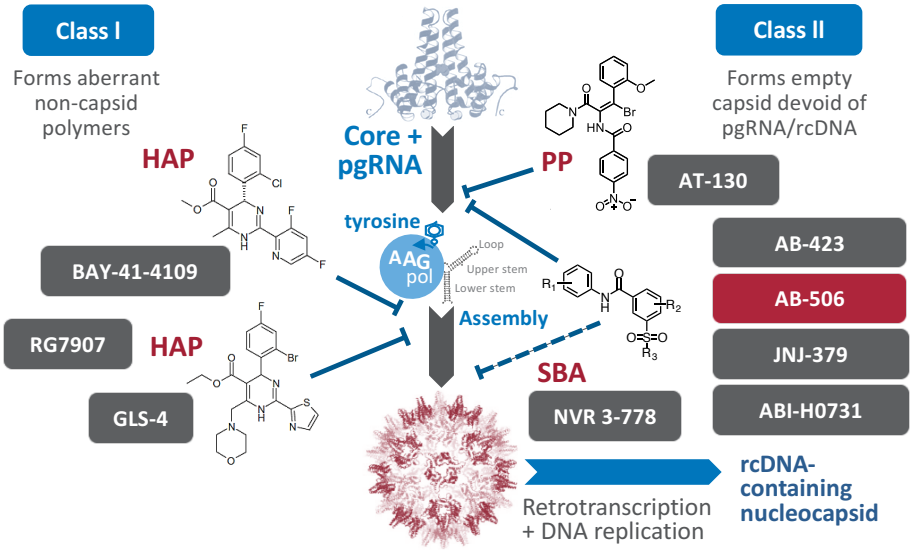
Disclosure Statement: This work includes co-authors who are employees of Arbutus Biopharma

HBV Capsid Assembly

An attractive target for drug development

HBV capsid assembly pathway and examples of capsid inhibitors



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

- Hepatitis B virus replication is strictly dependent upon capsid assembly around pgRNA
- Proper assembly of HBV nucleocapsid is essential for viral genome (rcDNA) synthesis, infectious virion production and maintenance of a nuclear cccDNA pool
- Interfering with HBV capsid assembly with small molecule inhibitors has been shown to translate into antiviral activity *in vitro* and *in vivo*
- The capsid assembly process thus represents a *bona fide* antiviral target
- Constitutes a novel mechanism that is distinct from the nucleos(t)ide analogs currently available for clinical use

cccDNA = covalently closed circular DNA; rcDNA = relaxed circular DNA; pgRNA = pregenomic RNA

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AB-506 Is A Next Generation HBV Capsid Inhibitor

- AB-506 is our 2nd generation HBV capsid inhibitor from a novel chemical series
- Demonstrates potent inhibition of viral replication in different HBV cell culture models

Compound	HepDE19 (rcDNA_bDNA) (µM)			HepBHAe82 (HBeAg AlphaLISA) (µM)			HepG 2.2.15 (HBV DNA qPCR) (µM)	
	EC_{50}	EC_{90}	CC_{50}	EC_{50}	EC_{90}	CC_{50}	EC_{50}	CC_{50}
AB-506	0.07 ±0.02	0.28 ±0.10	>25	0.04 ±0.02	0.20 ±0.06	>25	0.04 ± 0.01	>10

- In an HBV infected primary human hepatocyte assay, AB-506 inhibits HBV replication with an EC_{50} of 0.03 µM
- Maintains activity in the presence human serum with a modest ~6 fold increase in EC_{50} in 40% human serum
- No cross-resistance with Nuc^R variants, consistent with its distinct mechanism of action
- Active against the most prevalent HBV genotypes (A-D) globally
- Demonstrates high degree of antiviral selectivity for HBV; no inhibition of HCV, WNV, RSV, IFA, HSV, HCMV, DENV, HRV

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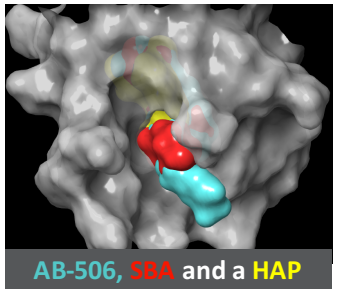
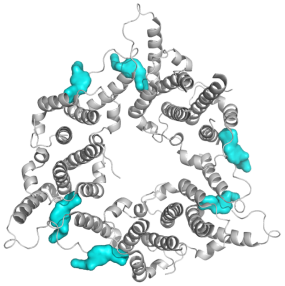
AB-506 Binds To Core Protein At The Dimer:Dimer Interface

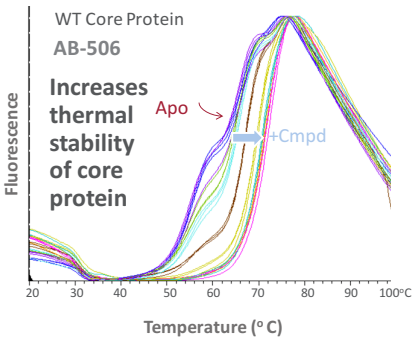
Increases thermal stability of core protein; accelerates capsid assembly

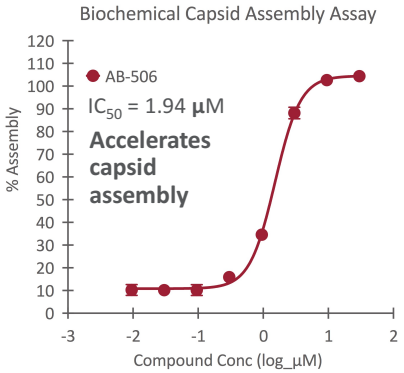
Binding site overlaps with other Capsid Inhibitors



Binds to dimer:dimer interface of core protein







- X-ray crystal structure of AB-506 with Cp-Y132A mutant solved (2.5Å)
- AB-506 binds at the dimer:dimer interface similar to other known Class I (HAP) and Class II (SBA) capsid inhibitors
- AB-506 binding increases thermal stability of WT core protein by 6 °C.
- In a biochemical capsid assembly assay, AB-506 accelerated capsid assembly

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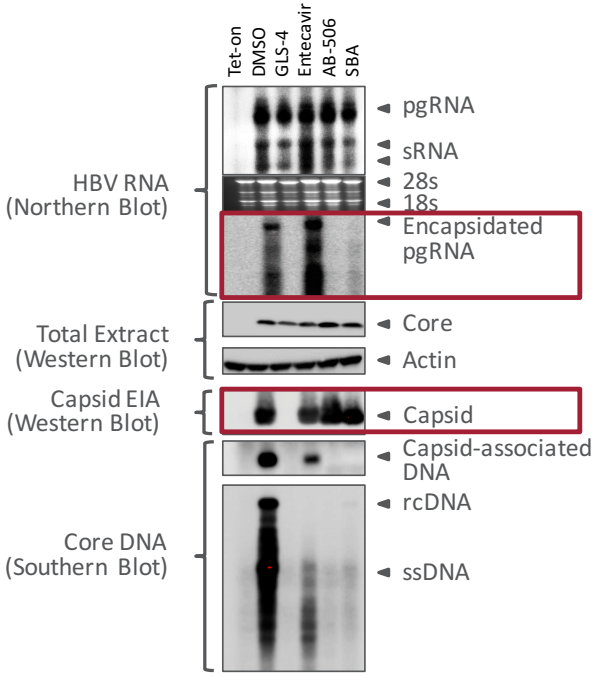
AB-506 Forms Empty Capsids Devoid of pgRNA or rcDNA

Mechanistic differentiation from nucleos/tide analogs (NA) and class I capsid inhibitors



GLS4 = 3 µM; Entecavir = 1 µM , AB-506 = 1 µM; SBA = 3 µM

- Mode of action studies conducted in AD38 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 inhibitor and NA's

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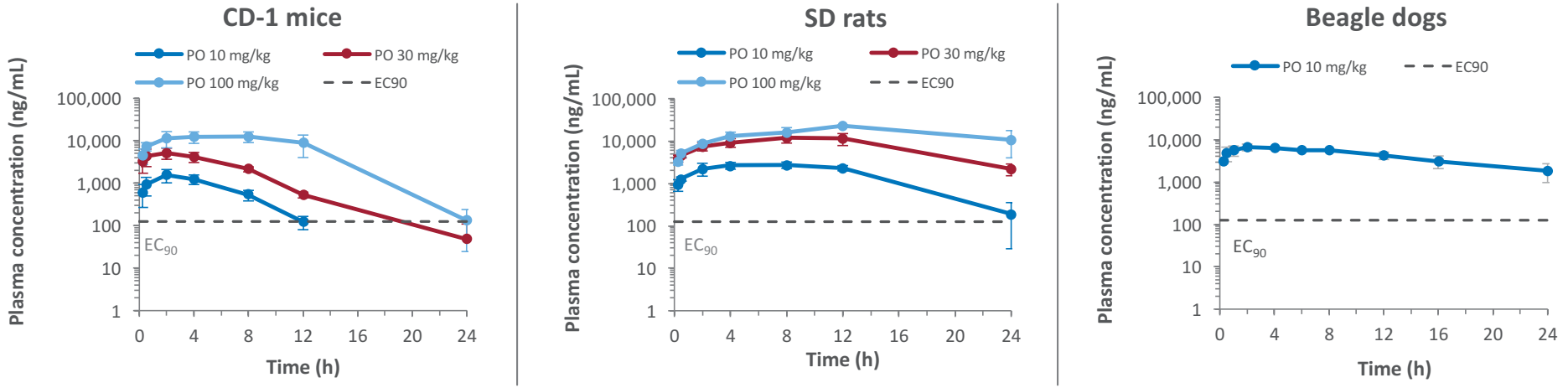
AB-506 Shows Potential For QD Dosing In Humans

Pharmacokinetic studies in mouse, rat and dog



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

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

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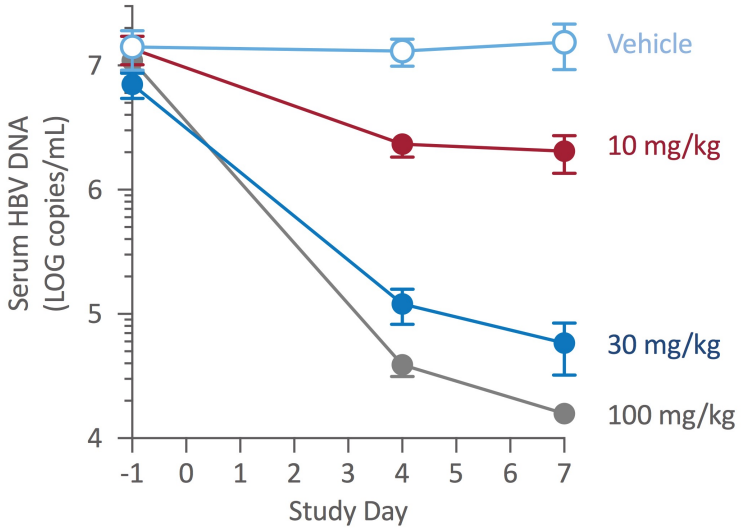
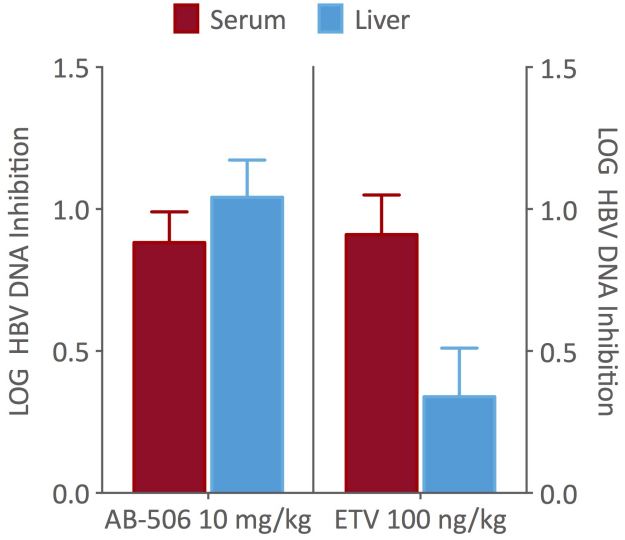
AB-506 shows dose-responsive antiviral activity *in vivo*

Antiviral activity in a mouse HDI model of HBV



Reduction in serum HBV DNA is dose-dependent following AB-506 administration



AB-506 surpassed ETV at inhibiting liver HBV DNA, at dosages where the serum HBV DNA inhibition was equivalent

The *in vivo* antiviral activity was assessed in a hydrodynamic injection (HDI) HBV mouse model utilizing pHBV1.3 (Guidotti 1995). Test article was administered orally for 7 days starting on Day 0, AB-506 and vehicle twice daily and ETV once daily. HBV DNA was measured using qPCR. Reported liver HBV DNA values are vector-subtracted

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Summary

- AB-506 is a next generation highly selective HBV capsid inhibitor
- *In vitro* AB-506:
  - showed potent inhibition of HBV replication in cell culture models including HBV infected PHH
  - demonstrated pan-genotypic activity (A-D) and potency against Nuc^R variants; did not inhibit a panel of other viruses
  - bound at the dimer:dimer interface of core protein in X-ray crystallography studies
  - inhibited pgRNA encapsidation in HepAD38 cells
  - accelerated rate of capsid assembly in a biochemical assay
  - conferred increased thermal stability to core protein indicating improved target engagement compared to first gen. capsid inhibitors
- Dosing performed in multiple species suggest QD potential and significant liver concentrations achieved
- AB-506 showed potent *in vivo* anti-viral activity in a HDI mouse model of HBV
  - *Even low-dose AB-506 substantially reduced liver HBV DNA*
- AB-506 is being evaluated for advancement into clinical development

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Acknowledgments

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