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Curing Chronic Hepatitis B

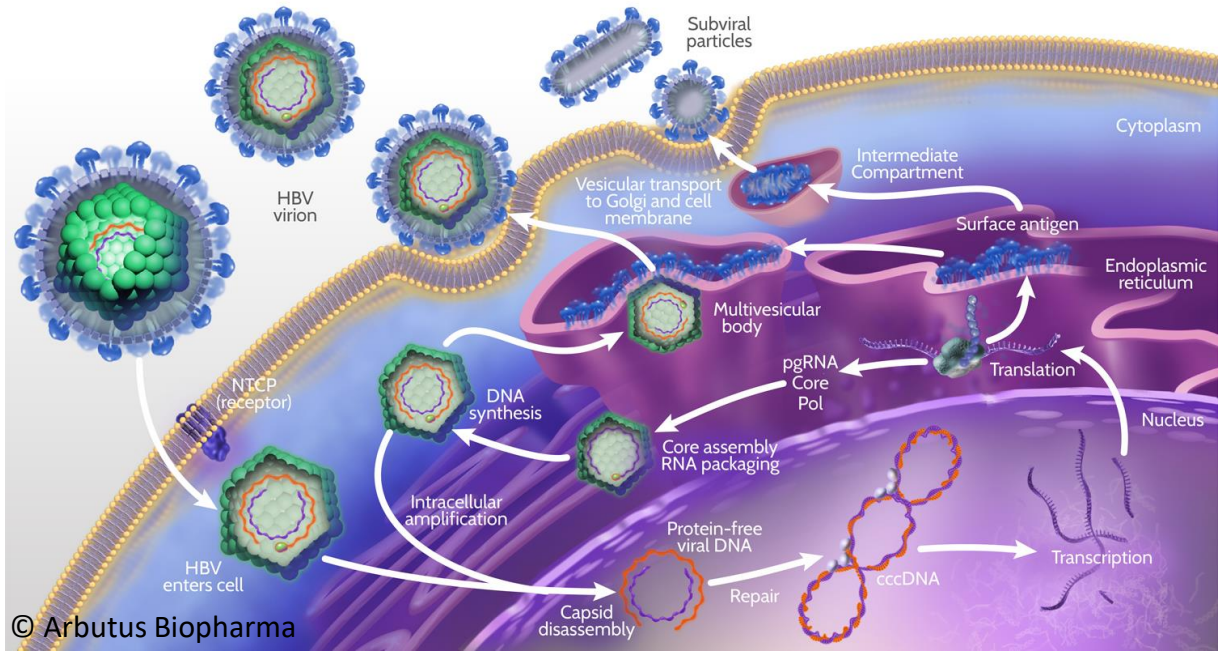
Progress Toward an HBV Cure Combination Therapy

Michael J. Sofia

December 2021, HepDart

Key Characteristics Associated with Chronic HBV Infection

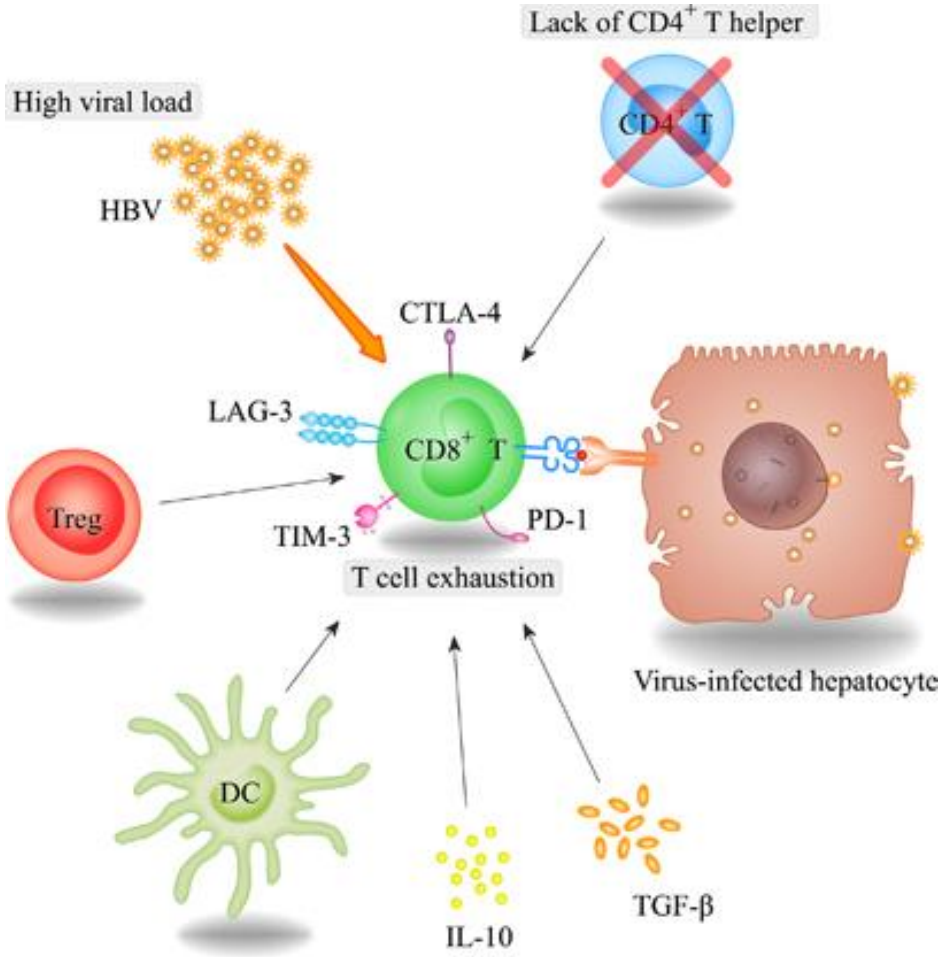
Virus Life Cycle



- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune tolerizing HBsAg
- HBV specific T-cell and B-cell immune silencing

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.

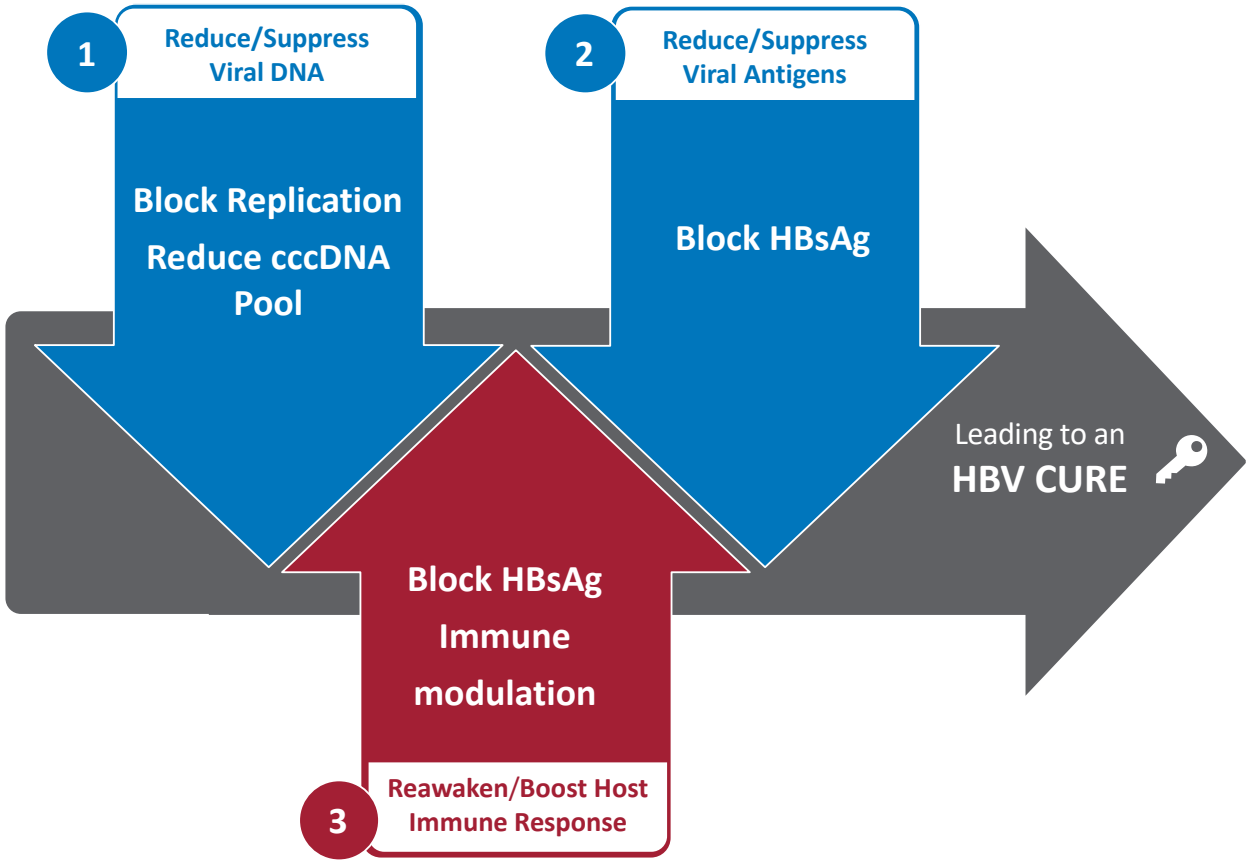
Immune Exhaustion

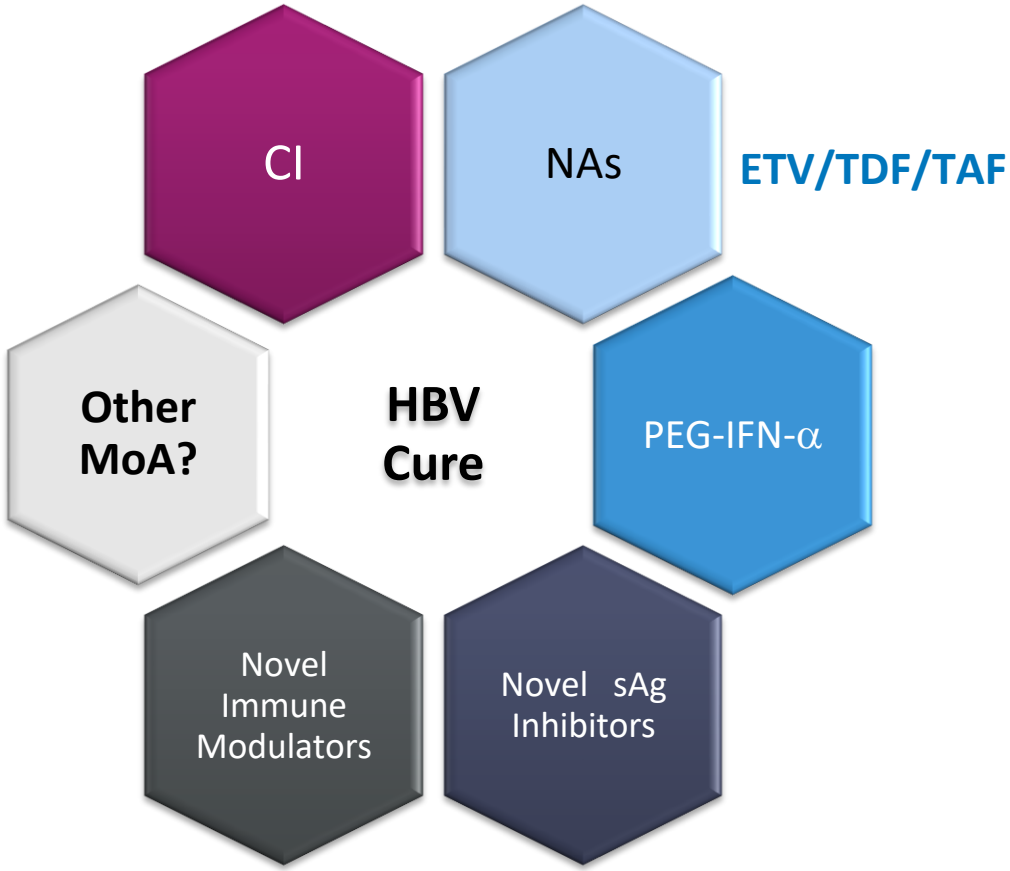


Ye et al 2015 Cell Death and Disease **6:** e1694

Therapeutic Success in CHB: Combination is Key

Reduce viral DNA and antigens + activate/reactivate immune response





- Goal: Identify combinations that lead to improved functional cure in CHB patients

CI = capsid inhibitors; NAs = nucleos(t)ide analogs; IFN-α = interferon-α; HBsAg = HBV surface antigen

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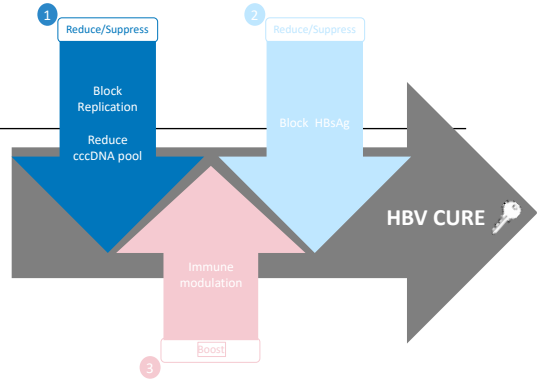
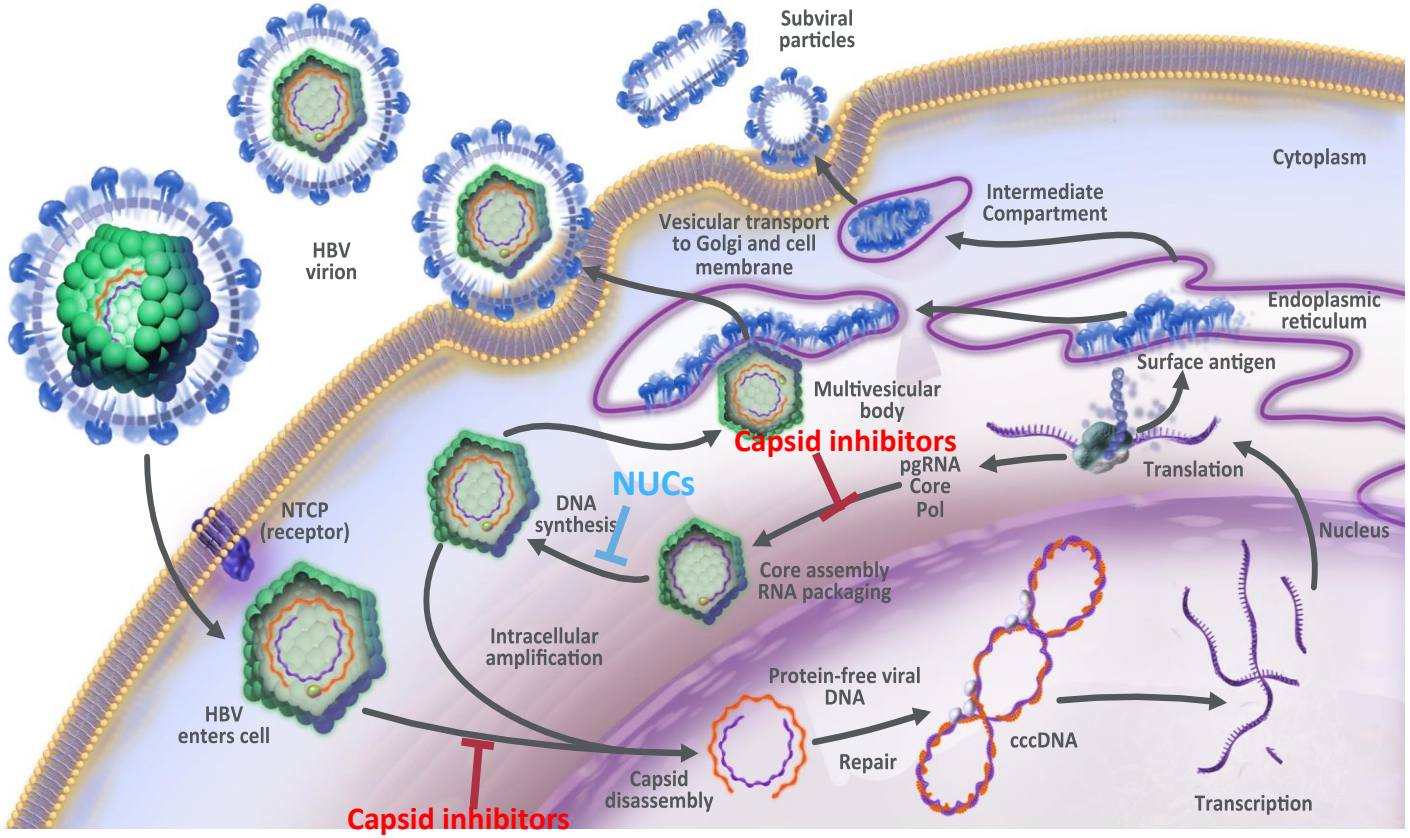
Hepatitis B Virus

Targeting Viral Replication and cccDNA Replenishment





- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune tolerizing HBsAg
- HBV specific T-cell and B-cell immune silencing

- Capsid inhibitors can shut down the ”leakiness” of NUCs in a combination regimen
- Capsid inhibitors have the potential to reduce the pool of cccDNA

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AB-836: A Differentiated Chemotype

Designed and optimized using structure-based drug design, medicinal chemistry, and SAR

Capsid Inhibitors
Evolving Clinical Landscape

Attributes

2015

Proof of Concept
- Suboptimal Efficacy
- BID; High Pill Burden

- Improved Efficacy
- QD/ Lower Pill Burden
- Combinations
- Suboptimal Resistance
- Lower potency vs 2nd MoA

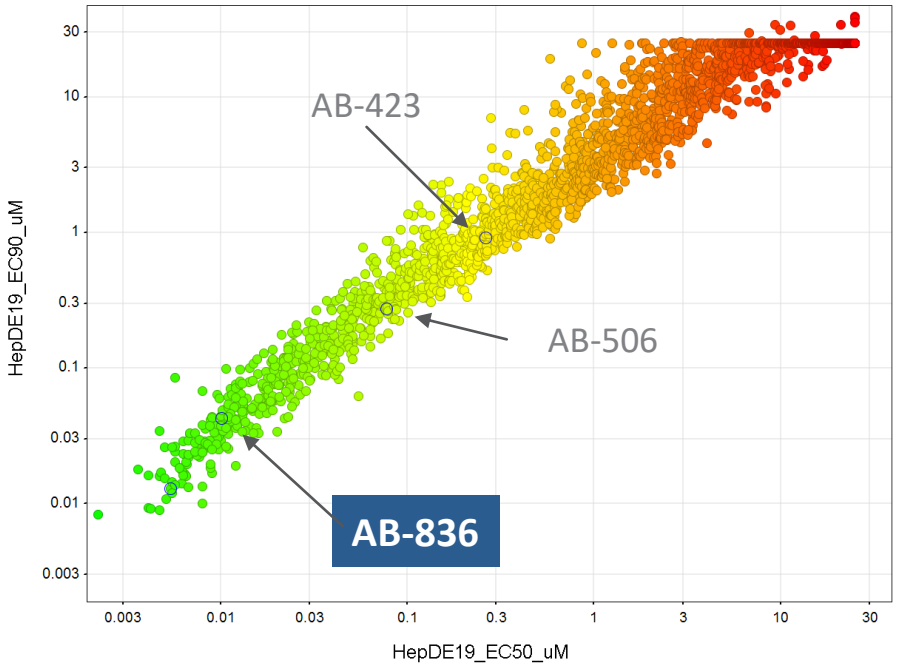
2021

Improved Potency
- QD; Lower Pill Burden
- Improved resistance coverage
- Improved potency vs 2nd MoA
- New Combinations

Target Profile

- **Distinct Chemotype**
- **Improved Potency** (WT, Resistant Variants, Capsid Uncoating)
- **QD Dosing**
- ***In vivo* Efficacy**

Discovery of AB-836



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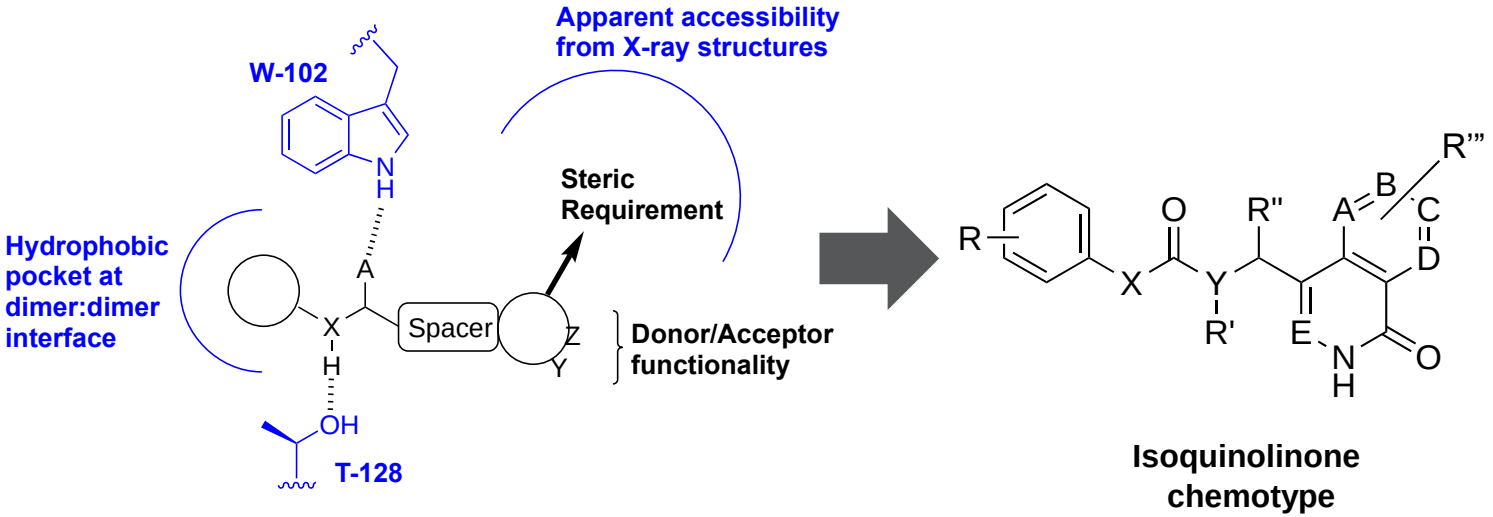
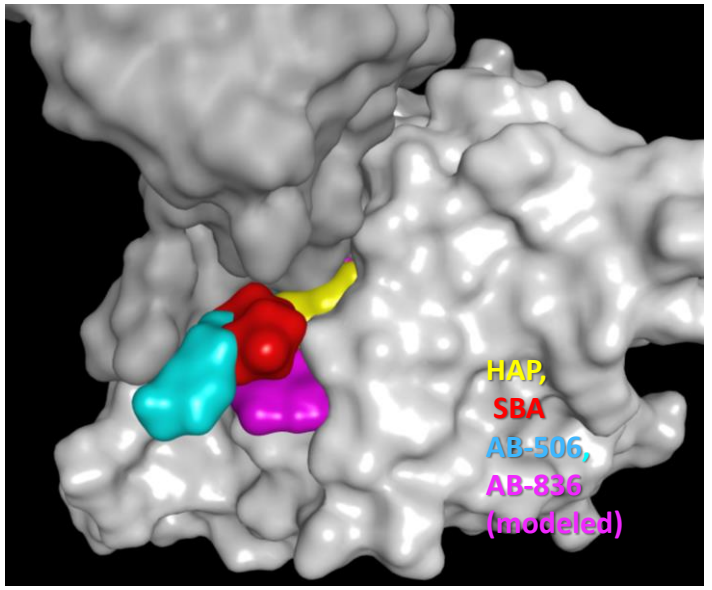
AB-836: A Differentiated Chemotype

Design Concepts



Utilizing the Y132A crystal structure and following criteria

- Binding to hydrophobic pocket at dimer:dimer junction
- H-bond acceptor to interact with W-102
- H-bond donor to interact with T-128
- Spacer connected to a ring system incorporating H-bonding capability
- Steric bulk projecting in NE direction



- X-ray crystallography data from closely-related compounds confirms that AB-836 binds to the same site as HAPs and SBAs; at the dimer:dimer interface

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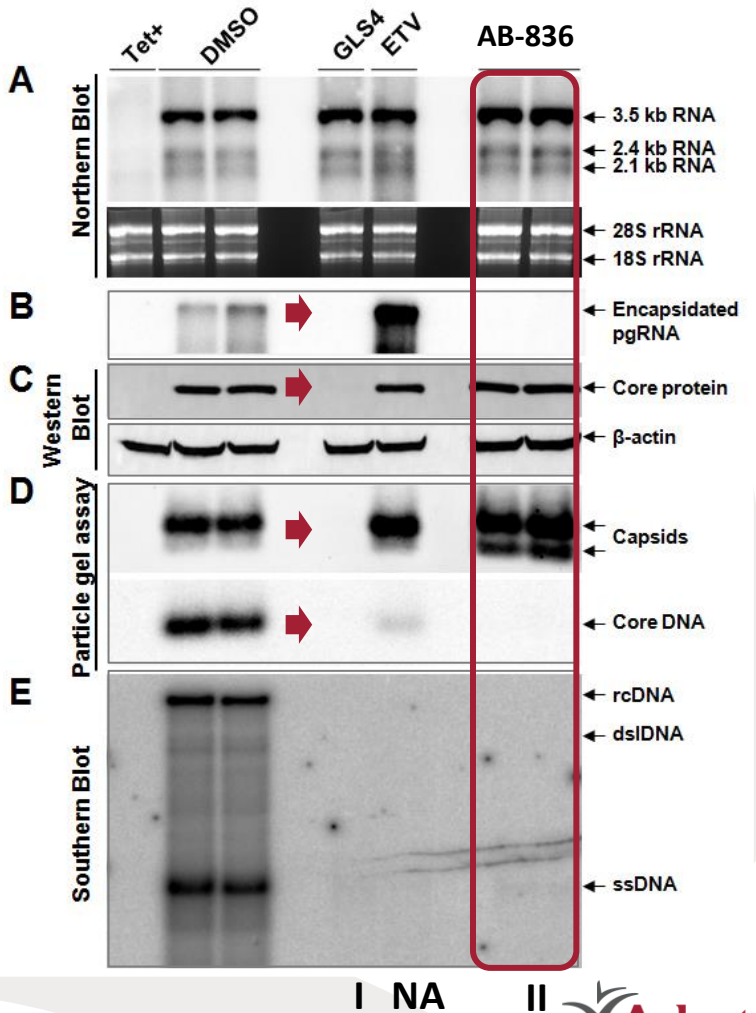
AB-836: A Potent Class II HBV Capsid Inhibitor

Inhibits rcDNA synthesis and cccDNA establishment in infection systems

Cell Culture System	HBV Marker	EC_{50} ± SD / CC_{50} (µM)
HepDE19	rcDNA	0.010 ± 0.003 / >25*
HBV infected PHH	rcDNA	0.002 ± 0.0004 / >10**
	HBsAg	0.050 ± 0.013
HBV infected HepG2-NTCP-C4	rcDNA	0.012 ± 0.005 / >10**
	HBsAg	0.197 ± 0.015
	cccDNA	0.175 ± 0.040

* Cell Titer Glo assay for cell viability **GAPDH RNA inhibition

- Class II HBV Capsid Inhibitor: forms empty capsids devoid of pgRNA and rcDNA
- Pan genotypic activity (Genotypes A – H EC_{50} = 4-66 nM)
- Demonstrates potent antiviral activity against primary and secondary mechanism
- Modest 2.3x decrease in potency in presence of 40% human serum *in vitro*
- Selective inhibitor of HBV. EC_{50} /CC_{50} of >30 µM against panel of RNA and DNA viruses



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AB-836 Shows Potent Inhibition of HBV Core Variants *In Vitro*

All core variants tested showed sub-micromolar EC_{50} values for replication inhibition

HBV Core Variant	AB-836 Avg. EC_{50} ± SD (µM)
WT (GT-D)*	0.012 ± 0.003
L30F	0.056 ± 0.006
T33N	0.777 ± 0.091
T33Q	0.509 ± 0.094
L37Q	0.250 ± 0.119
Y38F	0.013 ± 0.004
I105T	0.099 ± 0.044
I105V	0.015 ± 0.006
T109M	0.024 ± 0.012

*HBV genotype D background for all variants; HBV DNA measured with bDNA assay

HBV Core Variant	AB-836 Avg. EC_{50} ± SD (µM)
WT (GT-D)*	0.019 ± 0.002
D29G	0.047 ± 0.009
T33S	0.028 ± 0.007
Y38H	0.009 ± 0.002
T109I	0.007 ± 0.003
T109S	0.027 ± 0.006
T114I	0.023 ± 0.002
Y118F	0.009 ± 0.001
Y132F	0.004 ± 0.002
Y38F + T109S	0.020 ± 0.006

n ≥ 3 independent determinations

- AB-836 shows comparable activity against a panel of NA-resistant variants

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AB-836 Shows a Favorable Preclinical PK and Robust Multi-log HBV Inhibition In Vivo

QD dosing potential in humans: high multiples over the EC_{90} in the liver (24 h post dose)

In Vivo PK

Mouse

Test Cmpd	PO AUC_{inf} (ng/mL*h)	IV CL (mL/min/kg)	IV $T_{1/2}$ (h)	[24 h liver] (ng/mL)	[24 h] liver fold over EC_{90}
AB-836	13,040	**13**	3.1	395	25x

Rat

Test Cmpd	PO AUC_{inf} (ng/mL*h)	IV CL (mL/min/kg)	IV $T_{1/2}$ (h)	[24 h liver] (ng/mL)	[24h] liver fold over EC_{90}
AB-836	5,740	**11**	4.4	334	20x

Monkey

Test Cmpd	PO AUC_{inf} (ng/mL*h)	IV CL (mL/min/kg)	IV $T_{1/2}$ (h)	[24 h liver] (ng/mL)	[24 h] liver fold over EC_{90}
AB-836	6,740	**9**	5.2	ND	ND

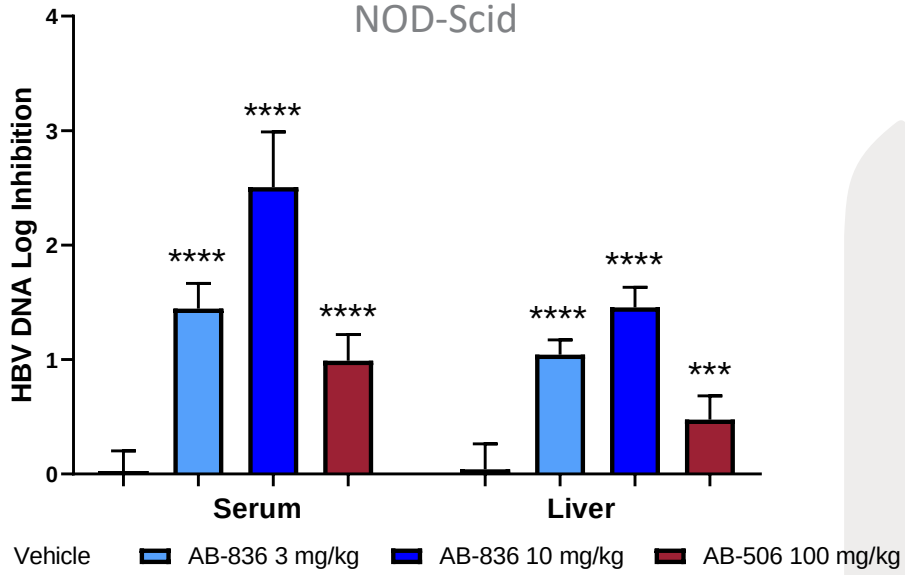
ND – Not determined

IV PK was done at 2 mg/kg and PO PK data was done at 10 mg/kg`

- Oral bioavailability ranged from 30 – 100% with high liver:plasma ratio in rodents

HBV HDI Mouse Efficacy

NOD-Scid



- Up to 2.5 log_{10} reduction in serum HBV DNA observed when dosed orally at 10 mg/kg once daily for 7 days

  -AB-836 greater than 33× more active *vs.* our prior generation capsid inhibitor

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AB-836 Phase 1a/1b Clinical Trial Preliminary Data

Parts 1 & 2: Single and multi-doses of AB-836 in healthy subjects

- **Safety:**
  - No deaths or SAEs
  - 1 subject (50mg once daily) discontinued on day 13 due to AE of agitation
  - All but 3 AEs were mild (Grade 2 headache, agitation and bronchitis), one assessed as drug related (Grade 1 rash)
  - No clinically significant abnormalities in clinical laboratory tests, ECGs, vital signs or physical exams noted.

Part 3: 50mg and 100mg of AB-836 once daily for 28 days in patients with HBV

- **Safety:**
  - No deaths or AEs
  - 1 patient had transient increase in ALT from baseline Grade 1 to Grade 3 that resolved with continued dosing
  - No clinical abnormalities in ECGs, vital signs or physical exams
- **Efficacy (Cohort G - 100 mg QD):**
  - Provides robust antiviral activity - mean (SE) log10 change from baseline of **-3.1** (0.5) at Day 28 (n=4)

Part 3 of the trial continues to enroll patients

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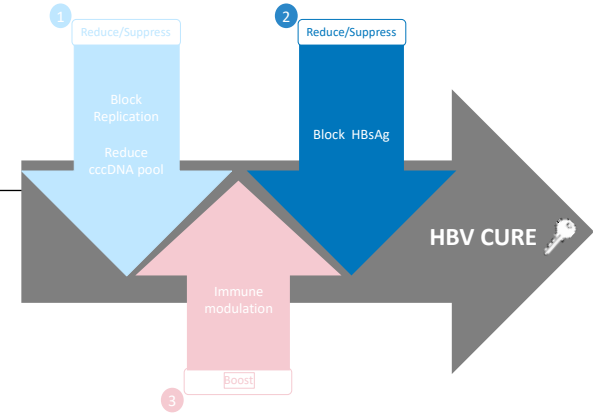
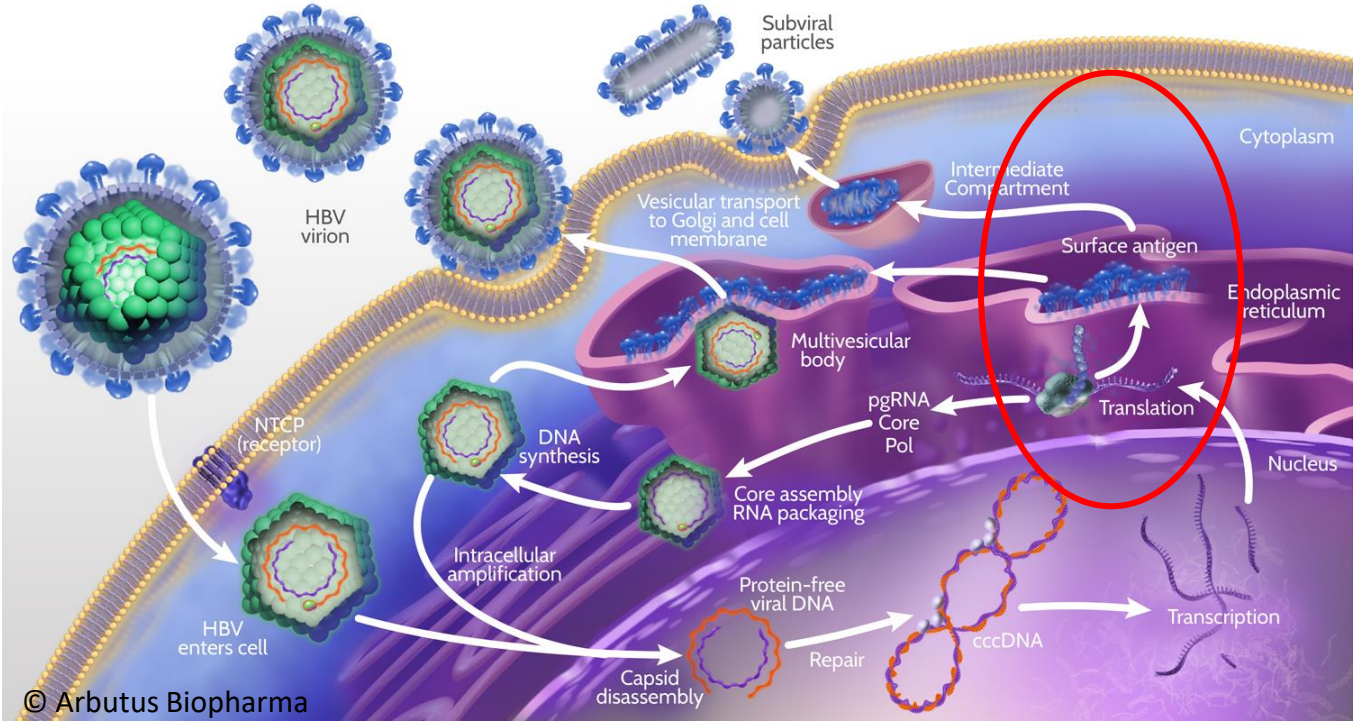
Hepatitis B Virus

Targeting Surface Antigen (HBsAg)





- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune tolerizing HBsAg
- HBV specific T-cell and B-cell immune silencing

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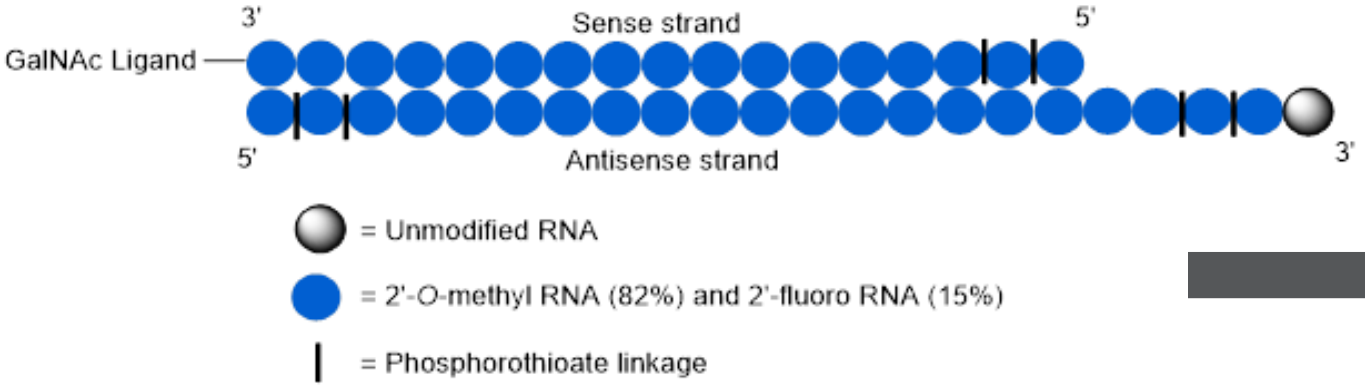
AB-729: A Liver Targeted GalNAc Conjugated RNAi Agent



Molecular Weight 15,313 g/mol

- Single trigger RNA interference agent
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Proprietary liver targeting technology based on GalNAc ligand interaction with ASPGr
- Long duration of activity from single SC dose

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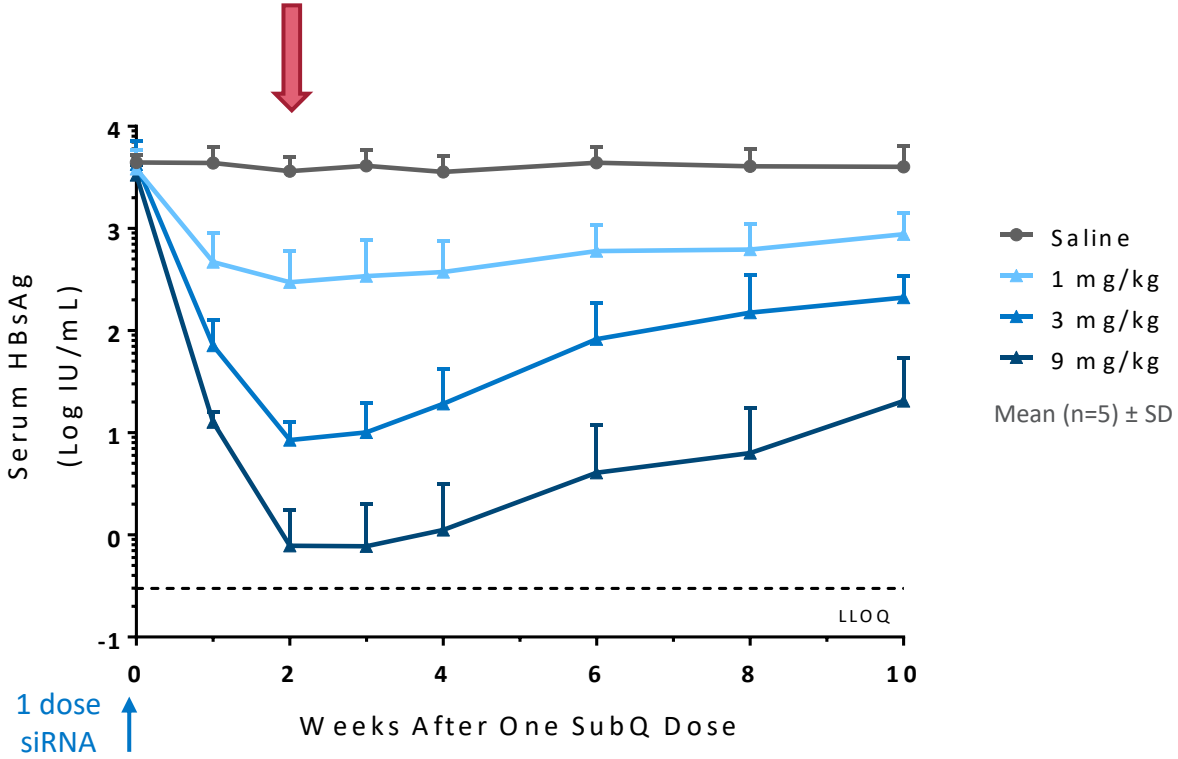
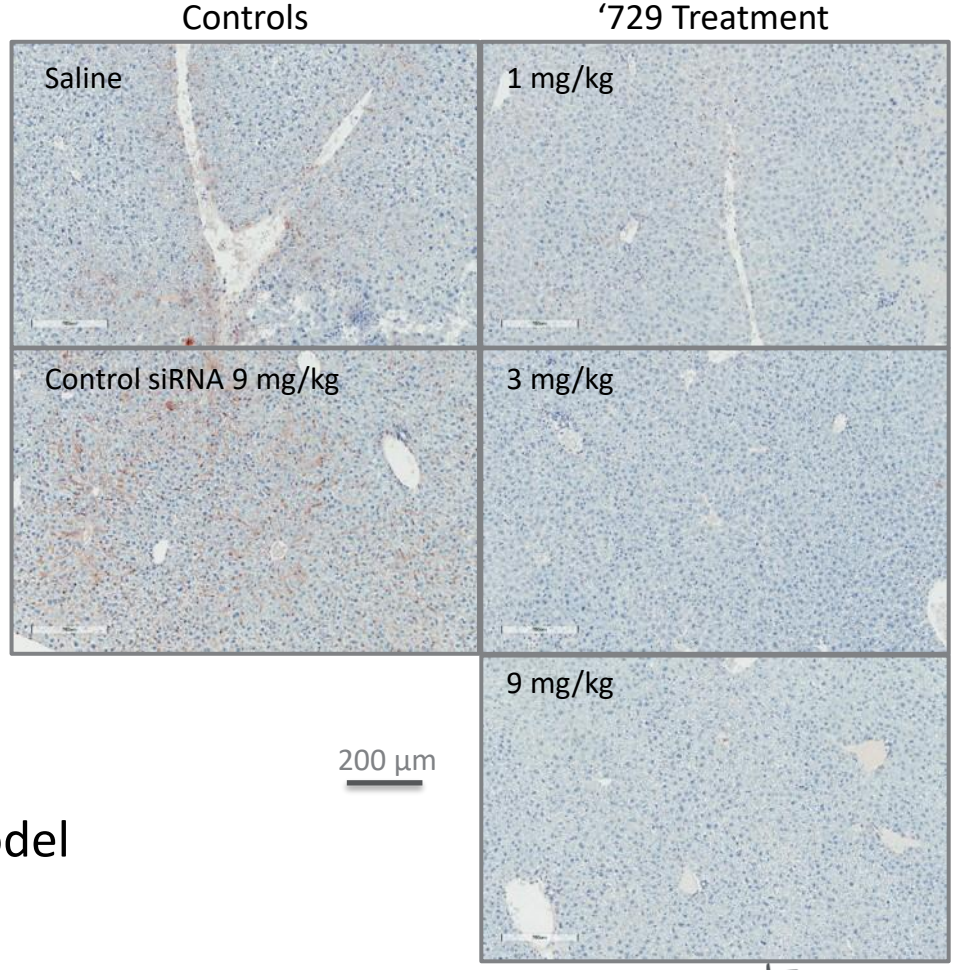
AB-729 *In Vivo* Single Dose Response & Duration

In AAV Mouse Model of HBV Infection



Liver sections stained for HBsAg (day 14 post dose)



- Clear dose response, achieved max effect detectable in this model
- Supports clinical dosing frequency of 1 month (or more)

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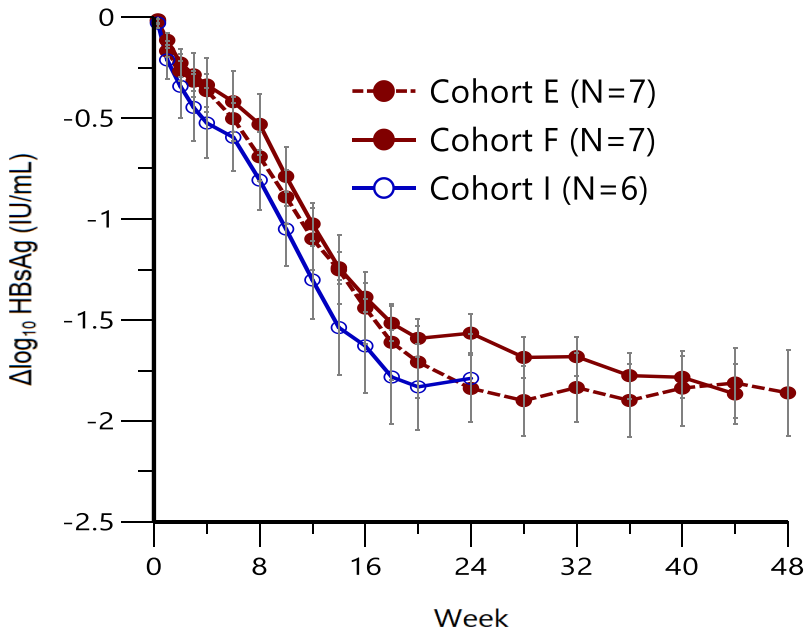
AB-729: Phase 1b Clinical Proof of Concept

Reduction of HBsAg in virally suppressed and treatment naïve chronic hepatitis B subjects



- **Long-term dosing with AB-729 resulted in 74% of patients reaching <100 IU/mL of HBsAg**
  - HBsAg suppression at levels of <100 IU/mL maintained up to 28 weeks off AB-729 treatment
- **Preliminary data suggest that long-term suppression of HBsAg with AB-729 results in increased HBV-specific immune response**
- **AB-729 monotherapy (90 mg single-dose) resulted in robust HBsAg and HBV DNA declines in HBV DNA + patients**
- **AB-729 was safe and well-tolerated through 40-48 weeks of dosing**

Mean (SE) ΔHBsAg with repeat dosing of AB-729

	HBV DNA-				HBV DNA+
Visit	Cohort E 60mg Q4W (n=7)	Cohort F 60mg Q8W (n=7)	Cohort I 90mg Q8W (n=6)	Cohort J 90mg Q12W (n=7)	Cohort G 90mg Q8W (n=7)
Baseline	3.51 (0.20)	3.53 (0.17)	3.36 (0.23)	3.37 (0.28)	3.14 (0.14)
Week 12	-1.10 (0.15)	-1.02 (0.11)	-1.30 (0.19)	-1.06 (0.31)	-1.56 (0.32)
Week 24	-1.84 (0.16)	-1.57 (0.09)	-1.79 (0.22)	-1.56 (0.25)	-1.82 (0.29)
Week 40	-1.84 (0.19)	-1.78 (0.10)	-1.93 (0.25)	-1.89 (0.35)	-2.03+ (0.33)
Week 44	-1.81 (0.17)	-1.88 (0.13)	-2.16 (0.31)	-1.86 (0.38)	---
Week 48	-1.89 (0.18)	-1.90 (0.14)	---	---	---
Off Treatment (# weeks post last dose)					
Week 16	-1.74 (0.20)	-1.76 (0.19)	---	---	---
Week 20	-1.61 (0.20)	-1.55 (0.28)	---	---	---
Week 24	-1.54 (0.19)	---	---	---	---

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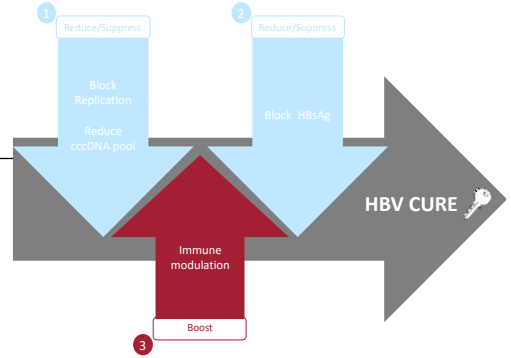
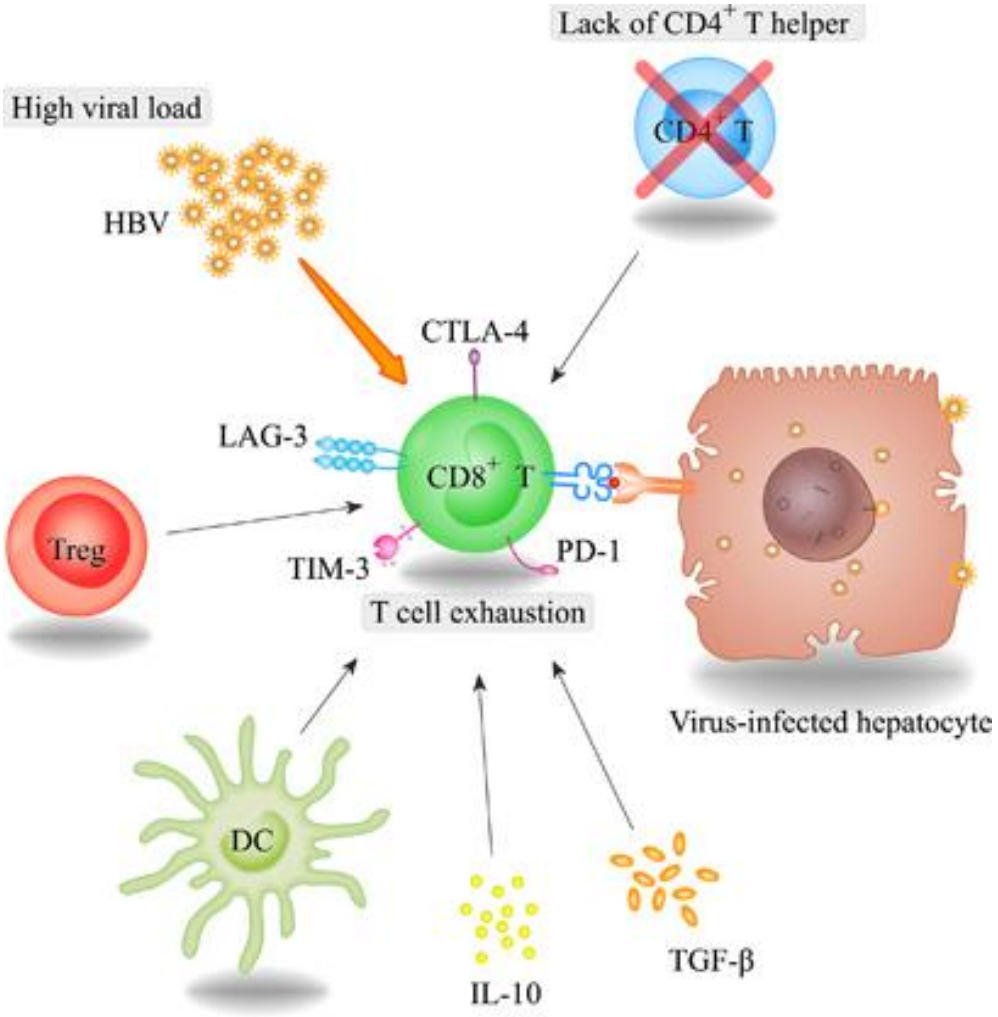
Hepatitis B Virus

Targeting Immune Reawakening





Ye et al 2015 Cell Death and Disease **6:** e1694

- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune tolerizing HBsAg
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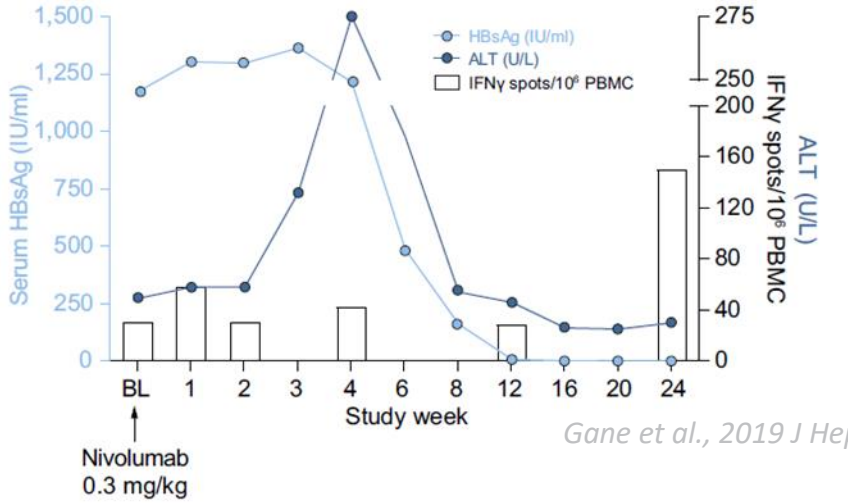
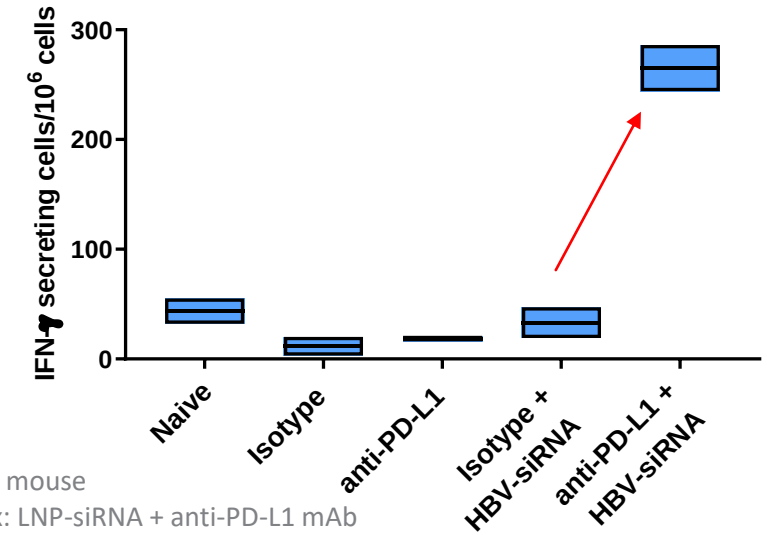
PD-L1: Target for HBV Immune Reawakening

- HBV immune tolerance is a critical driver of CHB infection
- PD-1:PD-L1 checkpoint axis plays a key role in immune tolerization in CHB
  - ➢ PD-L1 expression upregulated during HBV infection
  - ➢ PD-1 upregulated on HBV-specific T- and B-cells
  - ➢ Inhibition associated with HBsAg loss in some CHB patients



Gane et al., 2019 J Hep.

Preclinical combination of PD-L1 inhibitor with HBsAg reduction results in HBV immune response activation



PD-L1 mAb + RNAi
Liver HBV T Cell Response

AAV-HBV mouse
6 week tx: LNP-siRNA + anti-PD-L1 mAb

Liu, et al., 2014 Plos Pathogens;
Fisicaro, et al., 2012 Gastroenterology;
Fisicaro, et al., 2010 Gastroenterology
Wang, et al., 2021 AASLD presentation Nov 15

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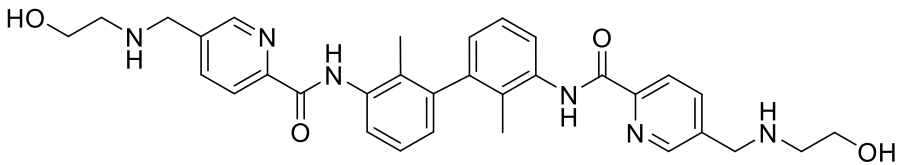
PD-L1 Inhibitors: Arbutus' Small Molecule Approach

- Advantages of a small molecule approach:
  - Enables oral dosing
  - Minimizes systemic safety issues seen with antibodies
  - Tuneable control of checkpoint inhibition
  - Better tissue penetrance, potential for increased efficacy

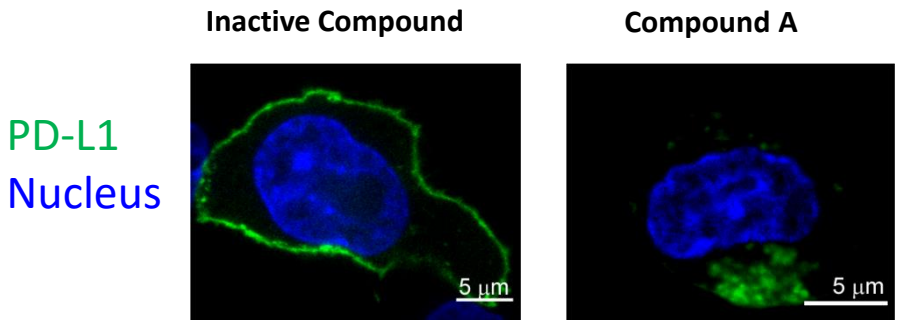
- Novel mechanism of action differentiated from Abs



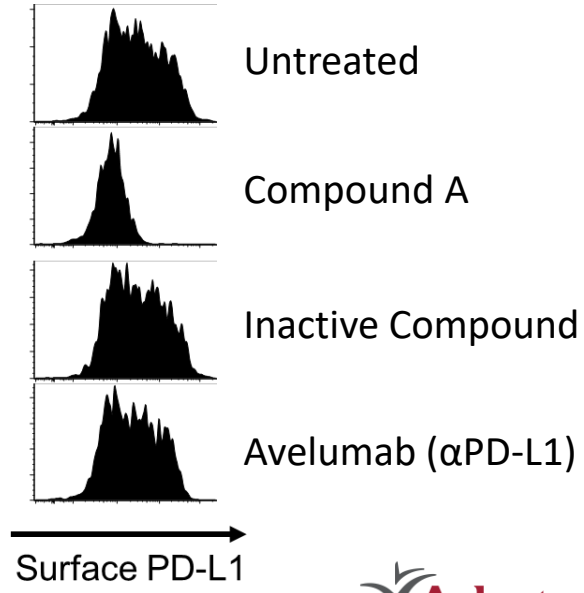
Compound A

HTRF IC_{50} = 0.8 nM
Bioassay EC_{50} = 15.8 nM

Internalization mechanism of action



CHO-K1 hPD-L1



Park et al., 2021 Nat Comm.

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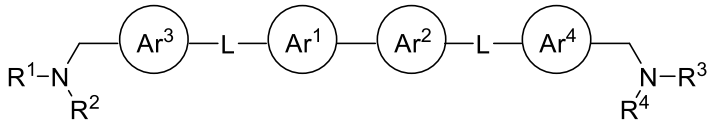
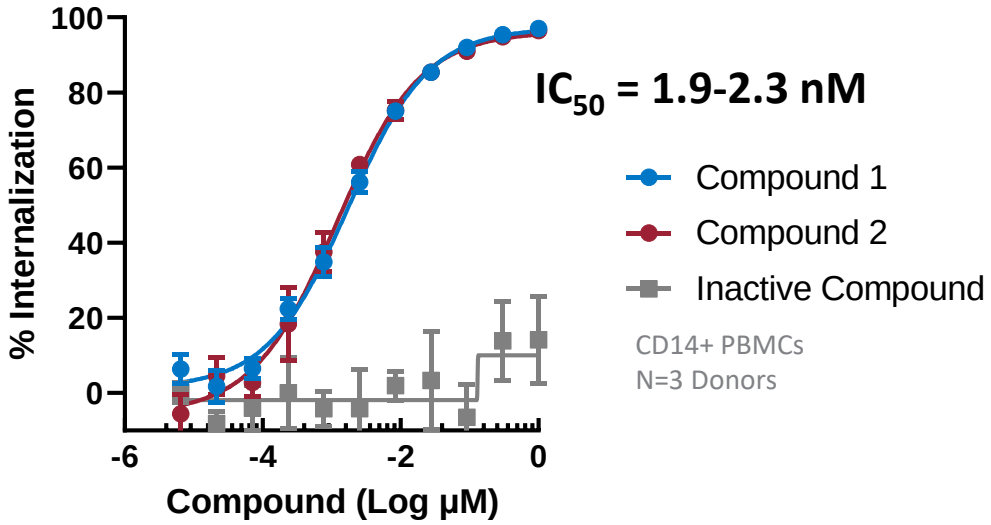
PD-L1 Inhibitors: Arbutus' Small Molecule Approach

- Compounds are highly potent with demonstrated activity against cells from CHB patients

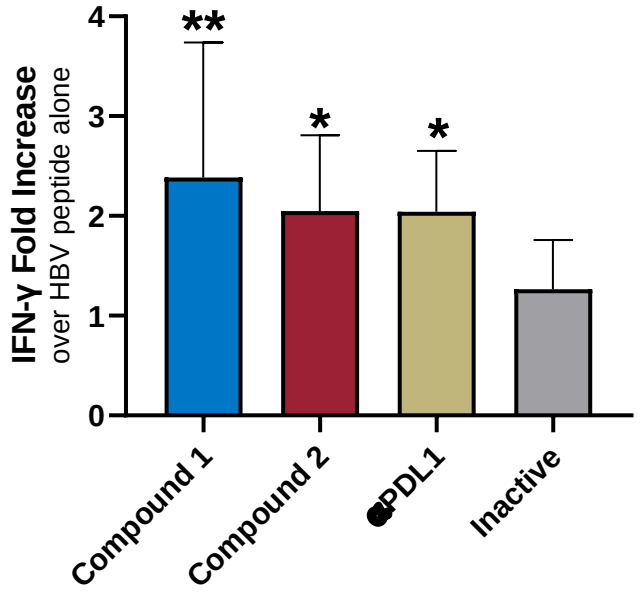


Able to reinvigorate HBV-specific T cells from CHB patients

Human Primary Myeloid Cells



CD14+ PBMCs
N=3 Donors



PBMCs
N=9 CHB patient
*p<-0.05 or **p<0.01 by One-way ANOVA

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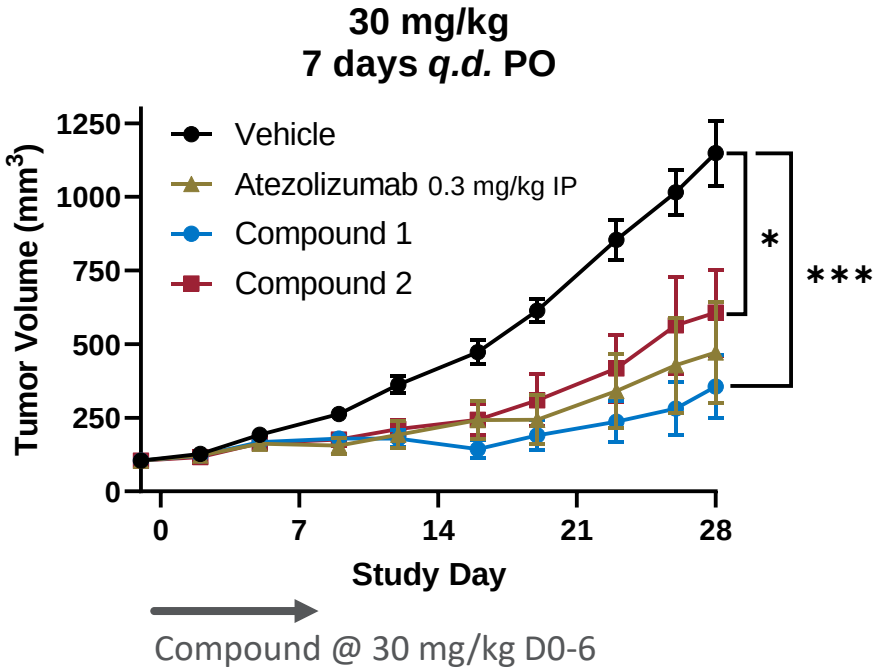
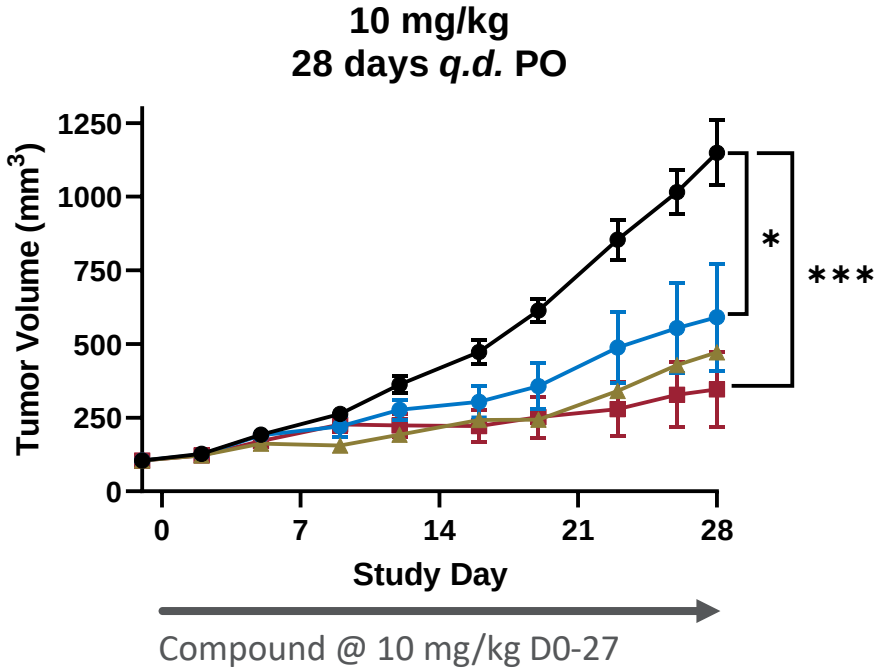
PD-L1 Inhibitors Mediate Anti-Tumor Responses *In Vivo*

- Preclinical *in vivo* demonstration of checkpoint inhibitor activity typically done in immuno-oncology models
- Robust tumor inhibition observed with oral daily dosing for 7 days or 28 days





MC38 hPD-1/hPD-L1 mouse
*p<0.05 or ***p<0.001 by Welch's t test

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Summary

- Shutting down viral replication, reducing the S-antigen load and reactivating the host immune response to HBV are key to achieving a broad-based functional cure
- AB-836, AB-729 and small-molecule PD-L1 inhibitors address the key characteristics that define CHB infection.
- In combination with SOC, AB-836, AB-729 and small molecule PD-L1 inhibitors have the potential to deliver a therapeutic advance for chronic hepatitis B patients
- Each of these agents are currently in development with the expectation of exploring a combination regimen

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Kim Stever
Lucy Wang
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Thank You

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