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Curing Chronic Hepatitis B

Preclinical antiviral drug combination studies utilizing novel orally bioavailable agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, an HBV RNA destabilizer

Rene Rijnbrand

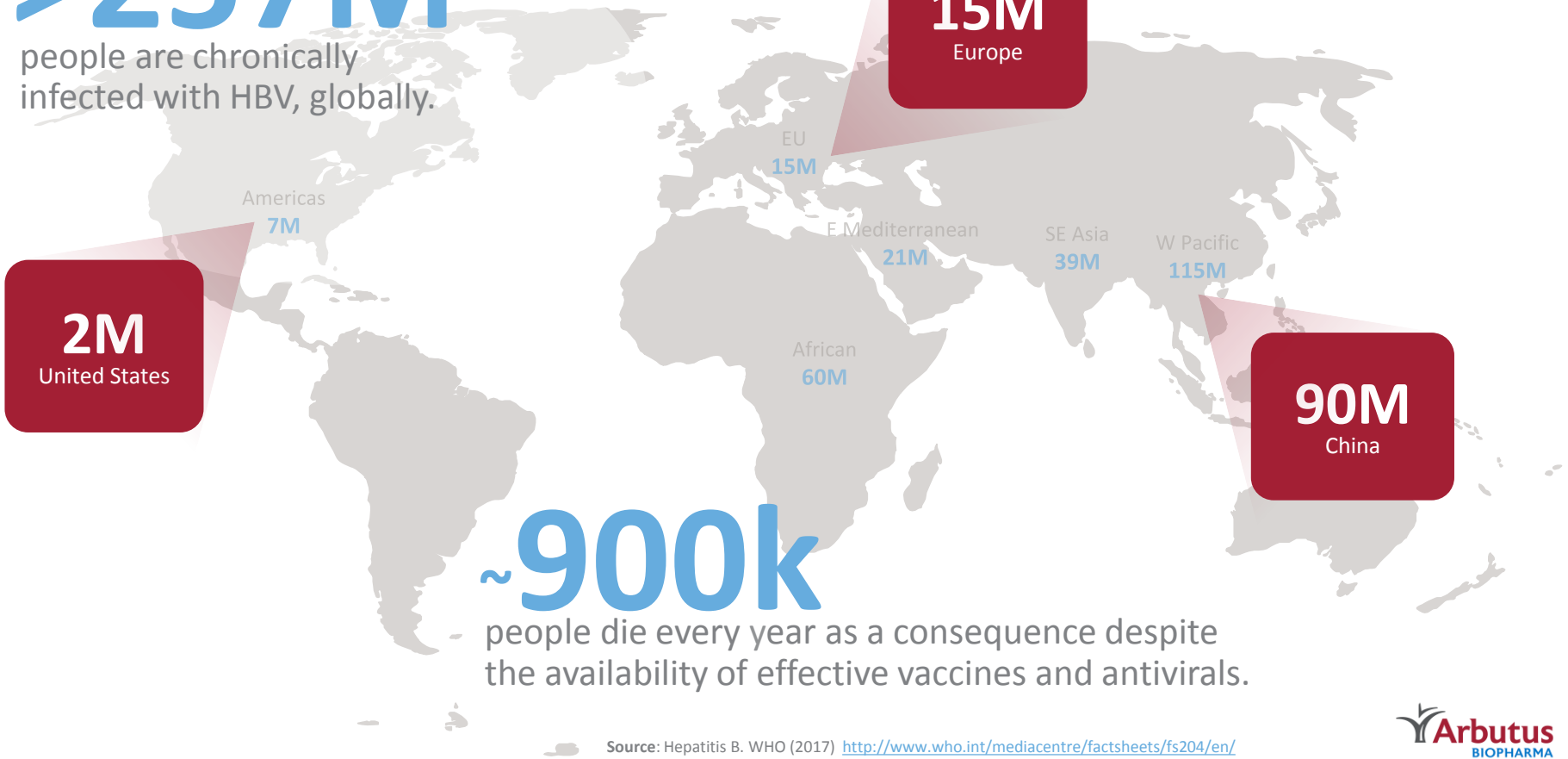
Arbutus Biopharma Inc.

Antivirals: Targeting HBV and Beyond

September 25, 2018, Boston, MA

>257M

people are chronically infected with HBV, globally.



~900k

people die every year as a consequence despite the availability of effective vaccines and antivirals.

Source: Hepatitis B. WHO (2017) http://www.who.int/mediacentre/factsheets/fs204/en/

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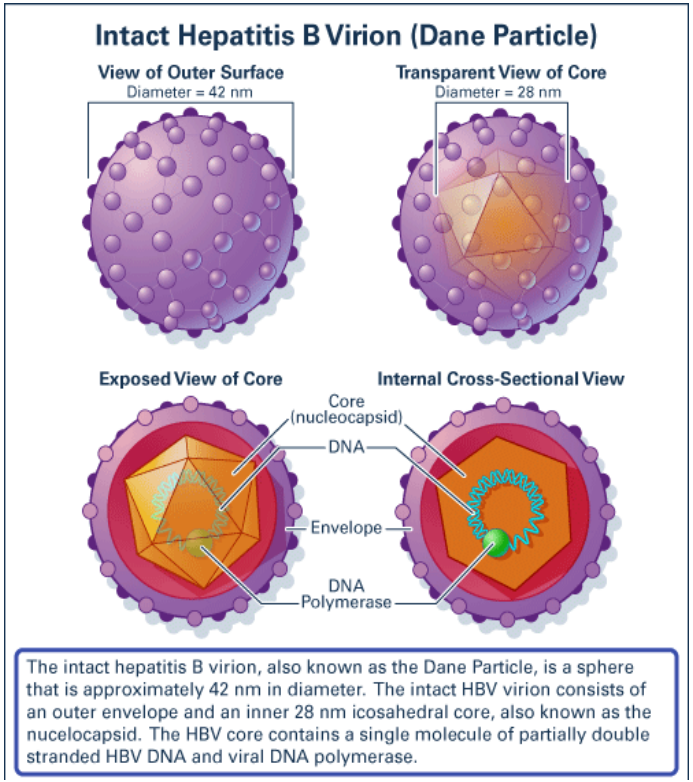
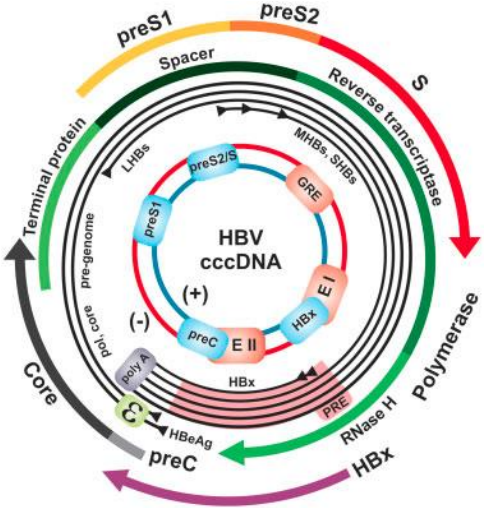
The Hepatitis B Virus



Source: Gerlich, W. 2013. Virology Journal, 10:239

Genome Structure of HBV



Glebe, D., etal, Sem. Liver Dis, 33, 2013, 103

- 4 Promoter elements
- 2 enhancer elements
- 10 transcription start sites

5 mRNAs:

- Pregenomic/core/pol (3.5 kb)
- Precore (3.5 kb)
- PreS1 (2.4 kb)
- PreS2/S (2.1 kb)
- X (0.7 kb)

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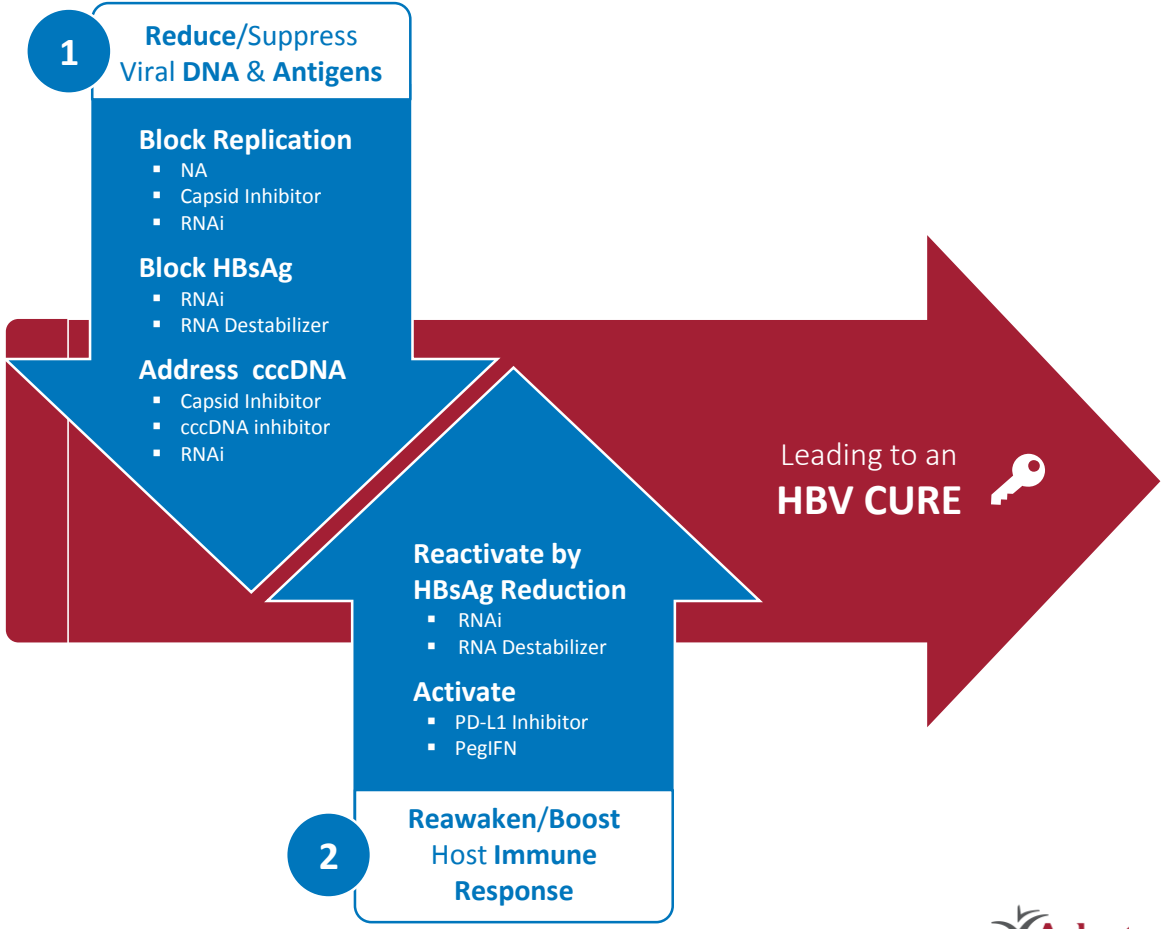
Keys to **Therapeutic Success**

Therapeutic success will *combine* drugs with *complementary MOAs.*



MOA: Mechanism Of Action | **NA:** Nucleot(s)ide Analog | **PegIFN:** Pegylated Interferon | **HBsAg**: HBV Surface Antigen

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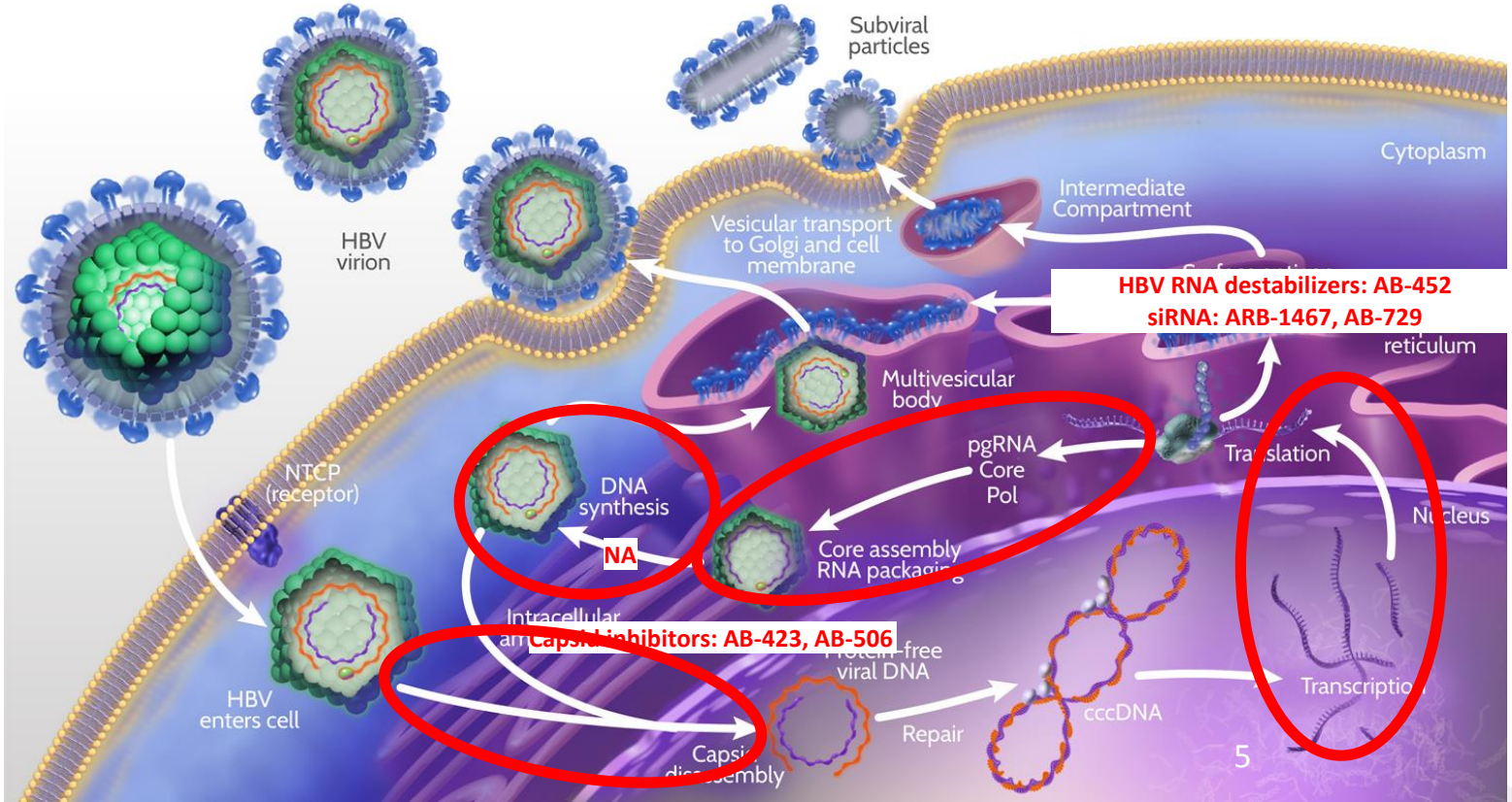
Key to Therapeutic Success:

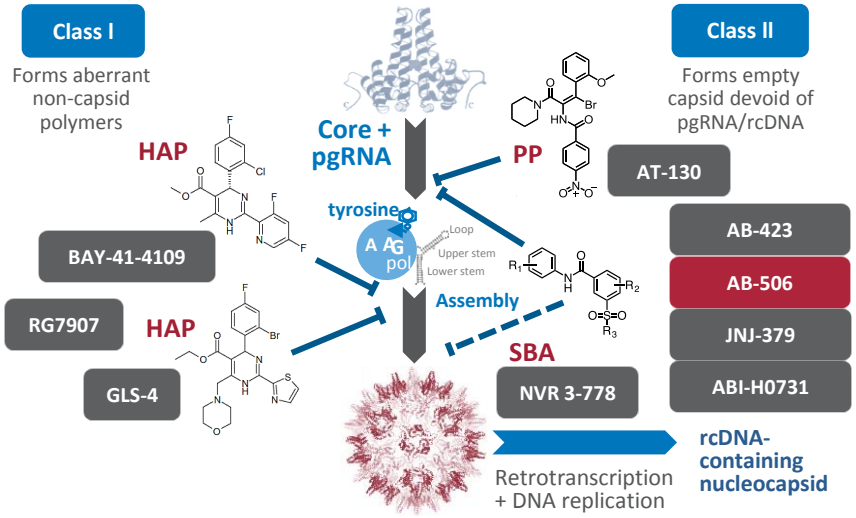
Combining Agents with Different MOA



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 32 nM
- 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 HBV genotypes A-H
- Demonstrates high degree of antiviral selectivity for HBV; no inhibition of HCV, WNV, RSV, IFA, HSV, HCMV, DENV, HRV

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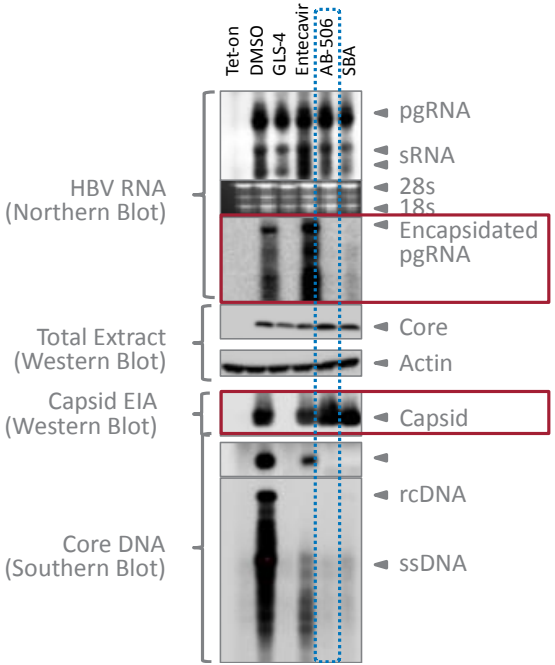
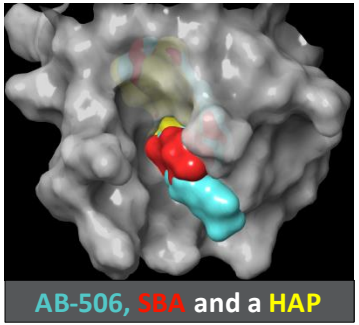
AB-506: A Next Gen HBV Capsid Inhibitor

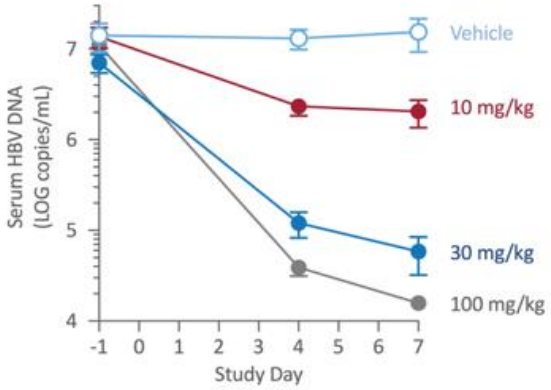
Potent inhibitor of HBV replication *in vitro*



- **AB-506 forms capsids devoid of pgRNA**
- **Inhibits formation of rcDNA**



Capsid inhibitors bind at the dimer:dimer interface of the core protein and induce the formation of empty capsid particles



Dose Dependent Reduction in serum HBV DNA in an HDI mouse model of HBV

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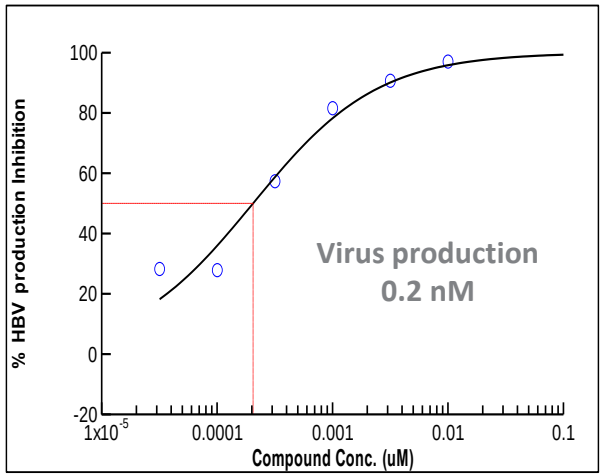
AB-452: A Potent HBV RNA Destabilizer

Novel small molecule HBV RNA Destabilizer

AB-452 *In vitro* Potency

In HepG2.2.15 cells



		EC_{50}, nM
PHH	sAg	8.7
	eAg	8.8
HepG2/NTCP	sAg	9.7
	eAg	3.6
Genotype*	A	1.3
	B	1.8
	C	2.0
	D	0.8
Human serum effect		2x

- **AB-452 is a potent, highly selective small molecule inhibitor of HBV replication through destabilization of HBV RNA**
- ***In vitro* AB-452 showed: drops in viral RNA, s/e/c Ag, and virion production**
  - **Pan-genotypic activity**
  - **No cross-resistance with Nuc^R variants**
  - **Highly degree of antiviral selectivity for HBV**

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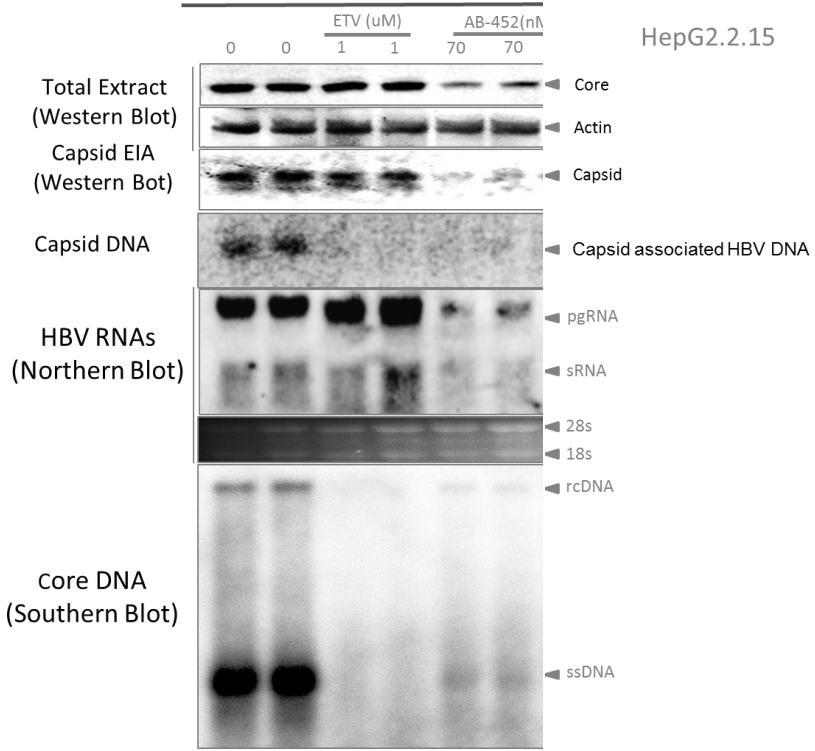
Multiple Stages of HBV Life Cycle Affected by AB-452



- **HBV RNAs destabilized by AB-452:**
  - **viral gene expressions**
  - **DNA replication**
  - **virion assembly**

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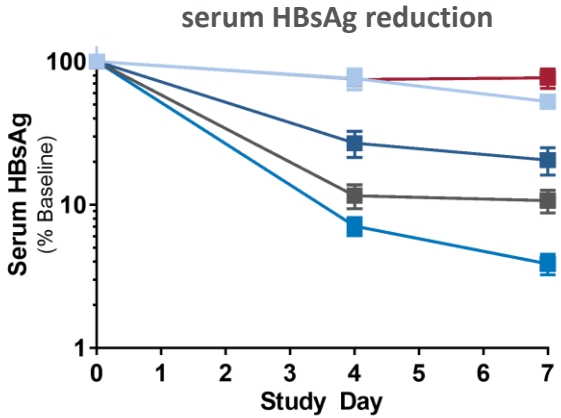
AB-452: A Potent HBV RNA Destabilizer

Novel small molecule HBV RNA Destabilizer



- BID PO dosing resulted in up to 1.4 log10 serum HBsAg reduction. Correlated with liver HBV RNA levels.

- AB-452 significantly inhibited HBV replication and reduced viral RNA and antigens in an immunocompetent AAV mouse model

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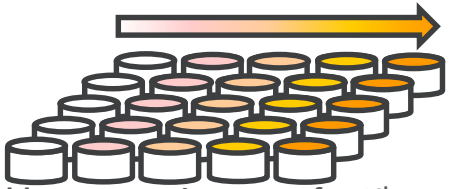
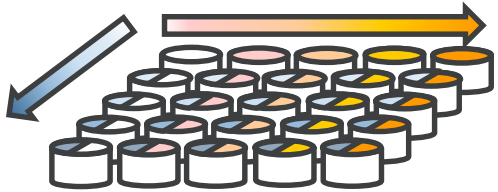
Evaluation of the Effect of Multiple Compounds on HBV:

In Vitro Synergy Studies

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

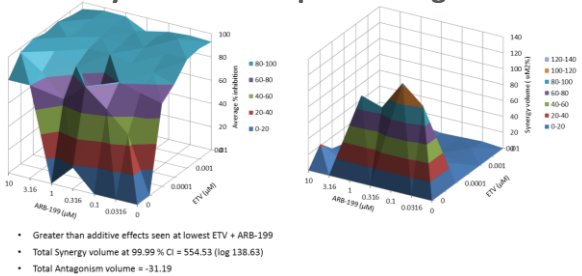


Add concentration range for 1st compound



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**

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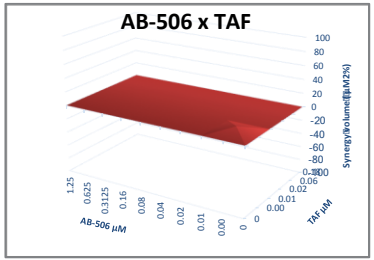
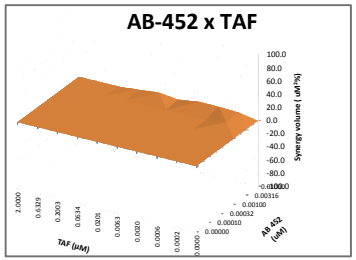
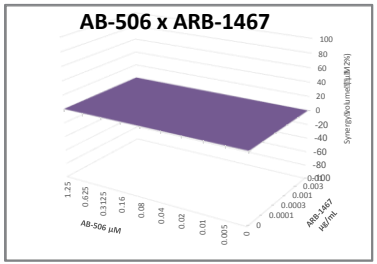
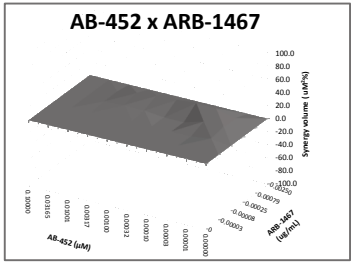
Combination of AB-506 and AB-452 With NAs and siRNA

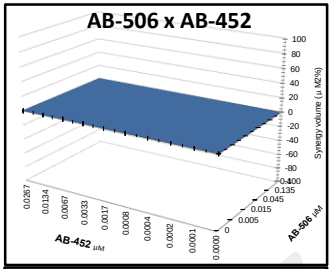
Molecules are mechanistically compatible

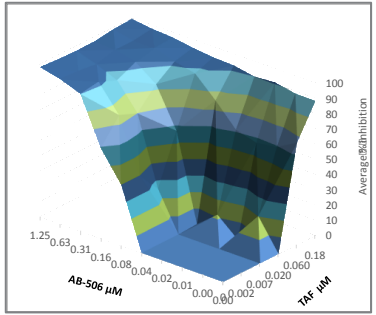


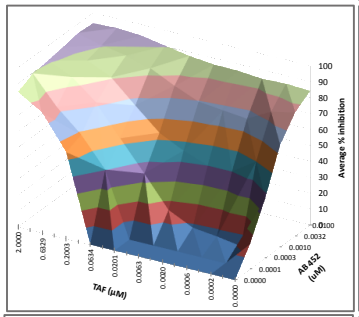


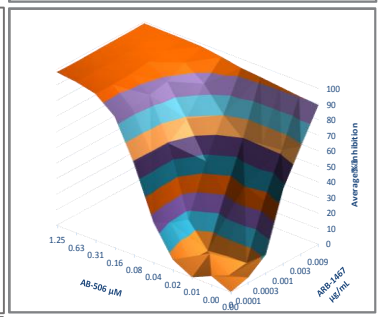


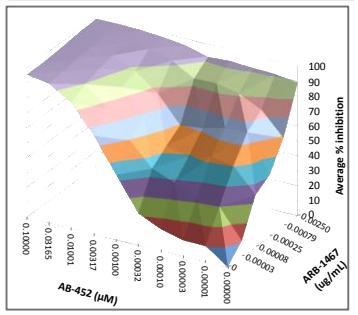


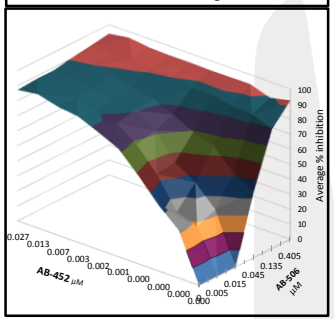


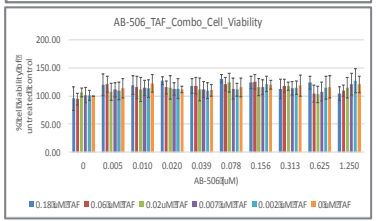


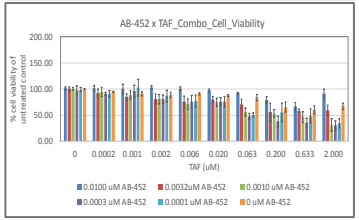


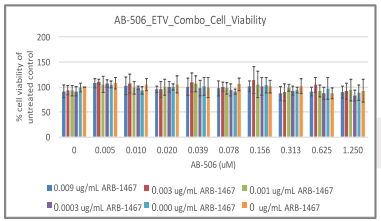


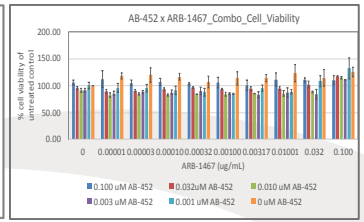


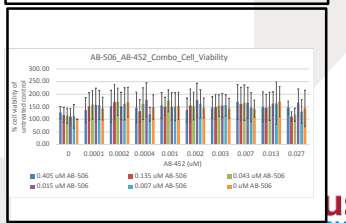












HepDE19 (rcDNA/bDNA) | HepG 2.2.15 (rcDNA/bDNA) | HepDE19 (rcDNA/bDNA) | HepG 2.2.15 (sAg) | HepG 2.2.15 (rcDNA/bDNA)

In Vitro Combination Studies: Summary

Molecules are mechanistically compatible

HBV Inhibitor		ETV	TDF	TAF	ARB-1467	AB-506
AB-506 Next Gen Capsid Inhibitor*		Additive	Additive	Moderate Synergy	Additive	NA
AB-452 HBV RNA Destabilizer**	sAg	ND	ND	ND	Minor Synergy	ND
	HBV DNA	Moderate Synergy	Additive	Additive	ND	Additive

- *HepDE19 HBV cell culture model with rcDNA quantitation
- **HepG2.2.15 HBV cell culture model with HBV DNA and HBsAg quantitation

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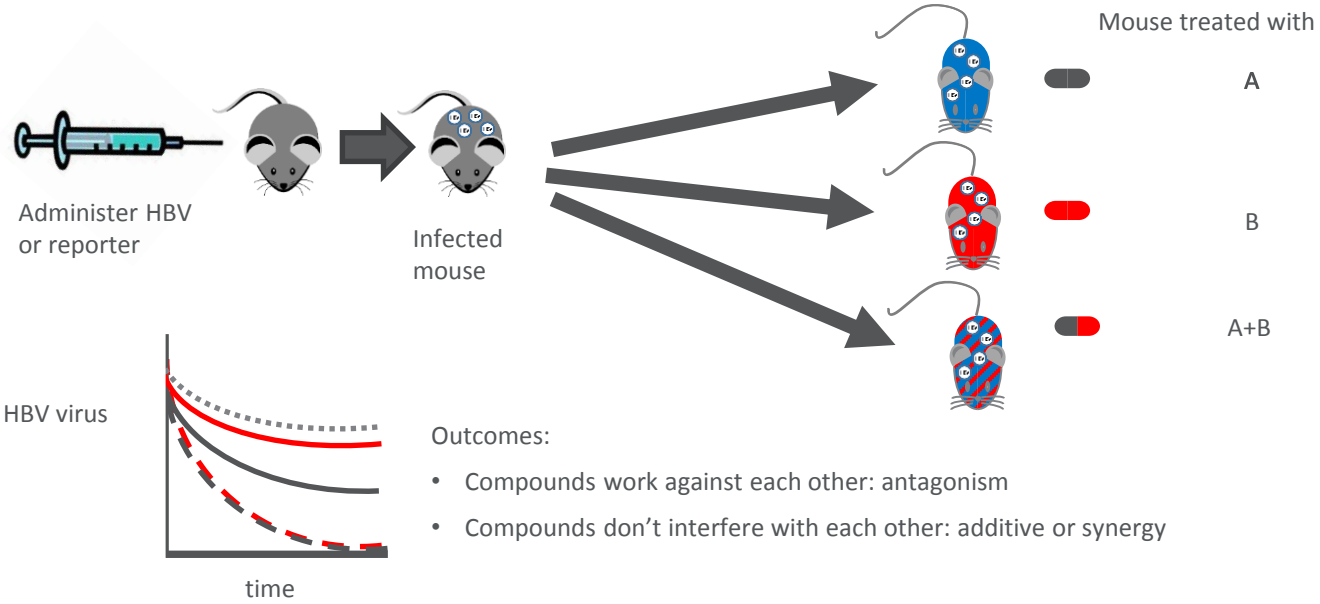
Evaluation of the Effect of Multiple Compounds on HBV:

In Vivo Evaluation



Outcomes:

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

- **Fewer test conditions can be examined in animals than in cell culture**
- **Prior dose selection is critical; mono-therapy arms are run at sub-optimal dose levels so that potential additive effect of combination therapy can be detected**

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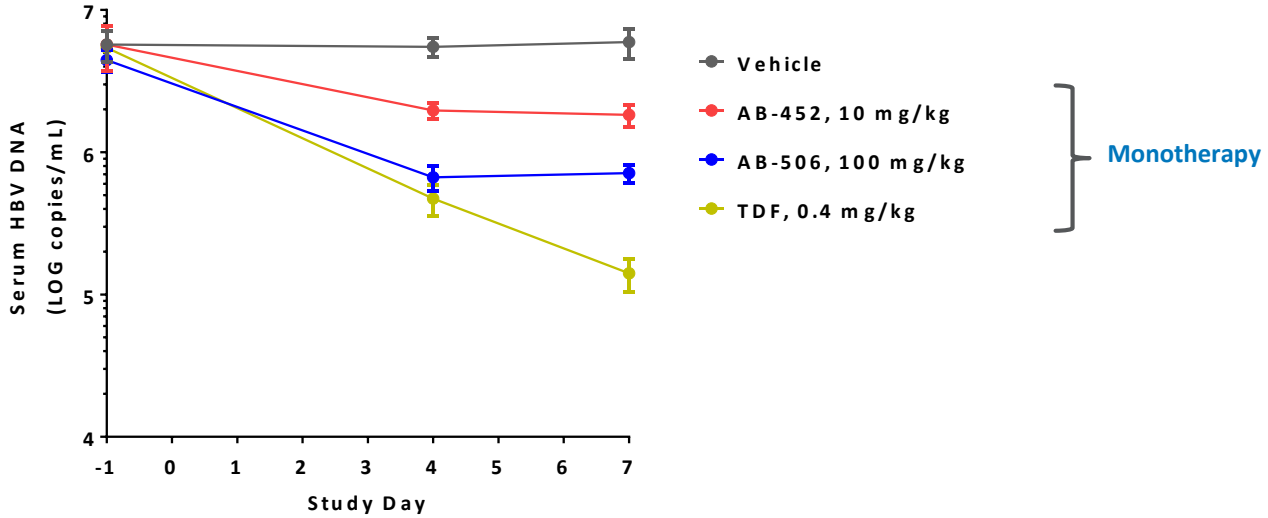
In Vivo Dual and Triple Combination of AB-506, AB-452 and TDF

HDI Mouse Model of HBV: Serum HBV DNA and HBsAg Reductions



- **Dual combinations of AB-506 + AB-452, AB-506 + TDF, and AB-452 + TDF showed strong antiviral activity with mean 1.4, 1.9 and 2.2 $\log_{10}$ reductions in serum HBV DNA *vs* the vehicle control, respectively**
- **Triple combination effected larger serum HBV DNA reduction of 2.8 $\log_{10}$ *vs* the vehicle control**
- **As expected, serum HBsAg reductions observed only in AB-452 groups**

Once-Daily Oral Dose × 7 Days
Mean (n=7-8) ± SEM
Open symbol indicates close to LLOQ

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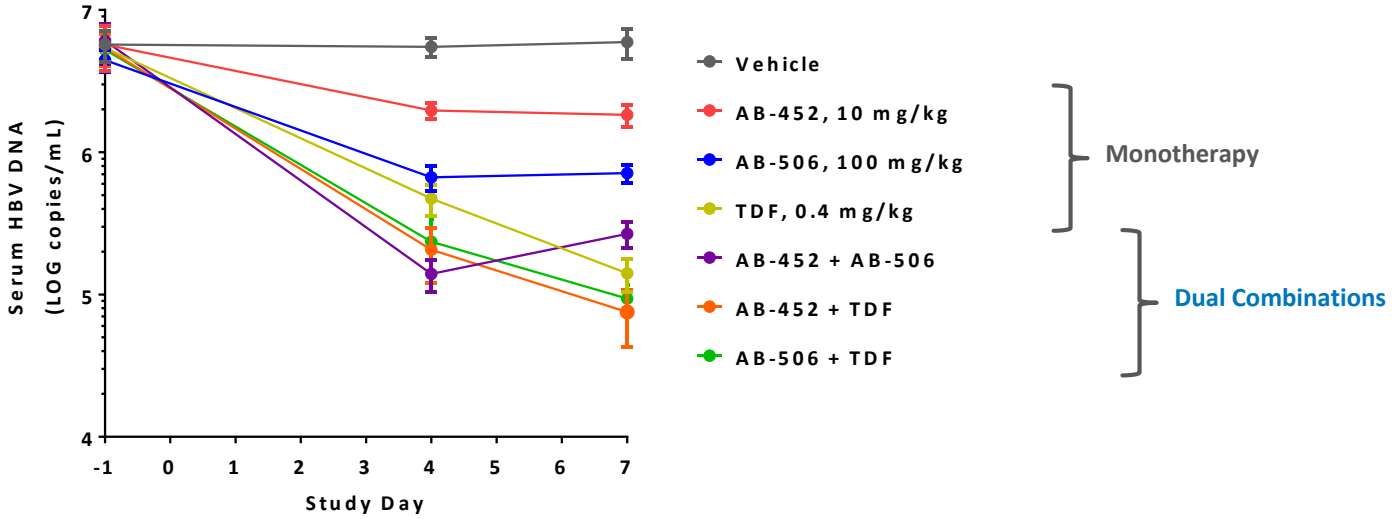

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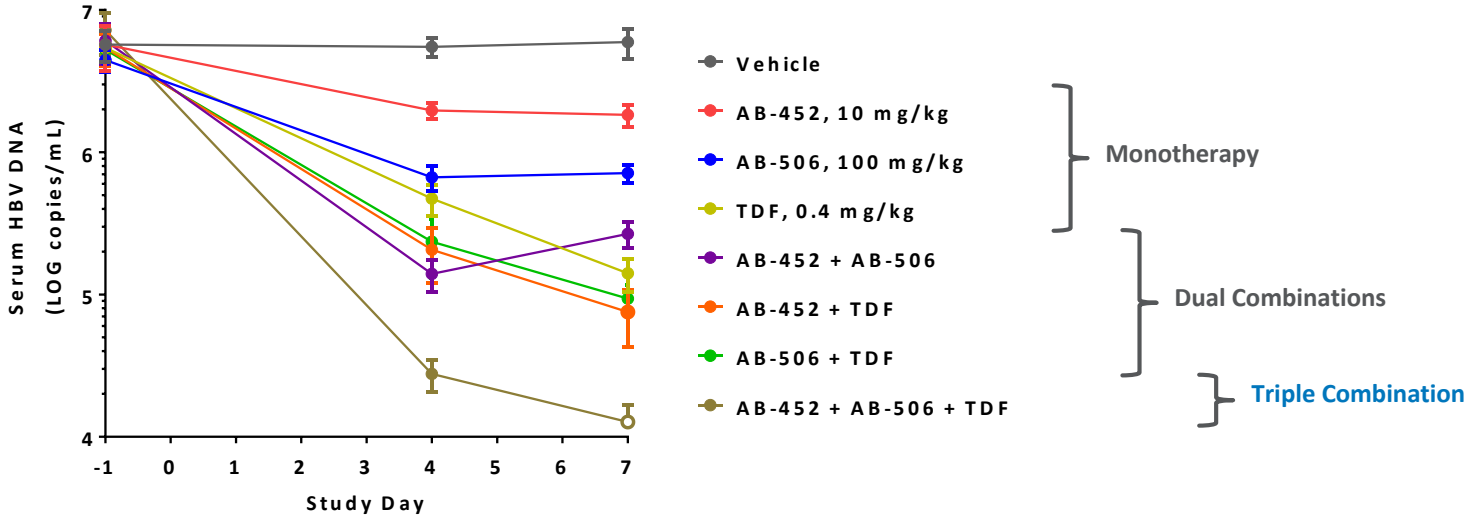

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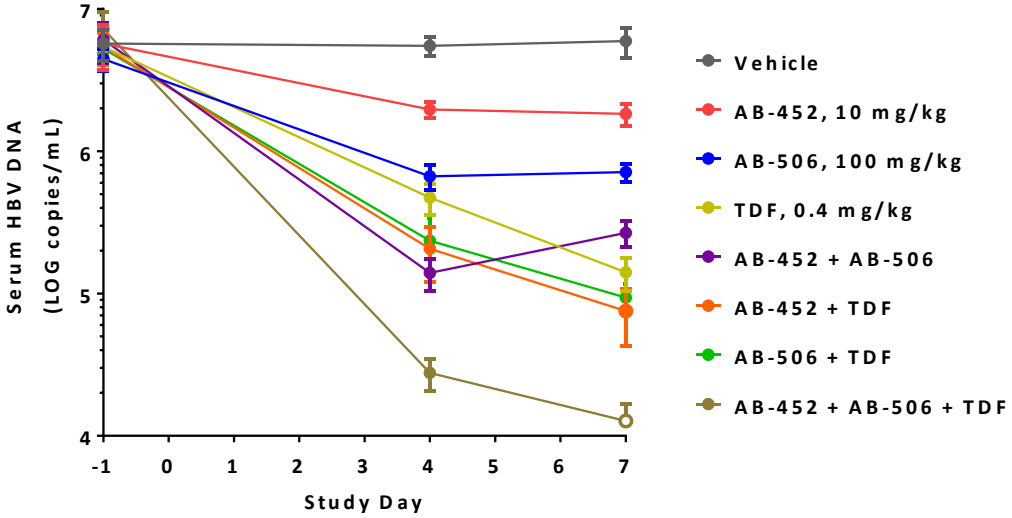

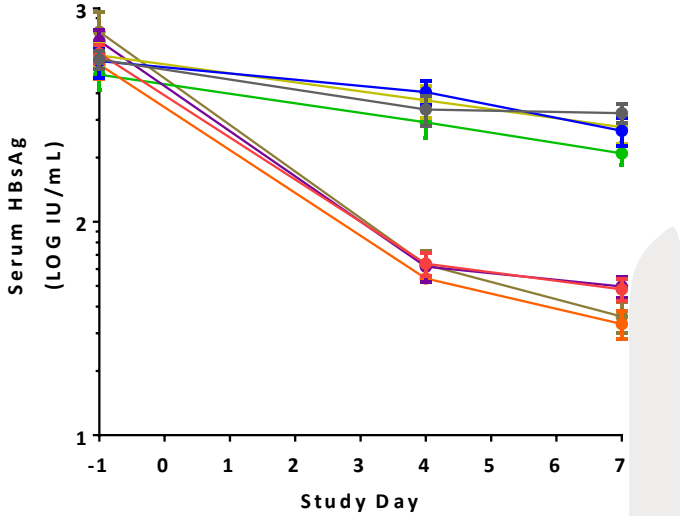

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Once-Daily Oral Dose × 7 Days
Mean (n=7-8) ± SEM
Open symbol indicates close to LLOQ

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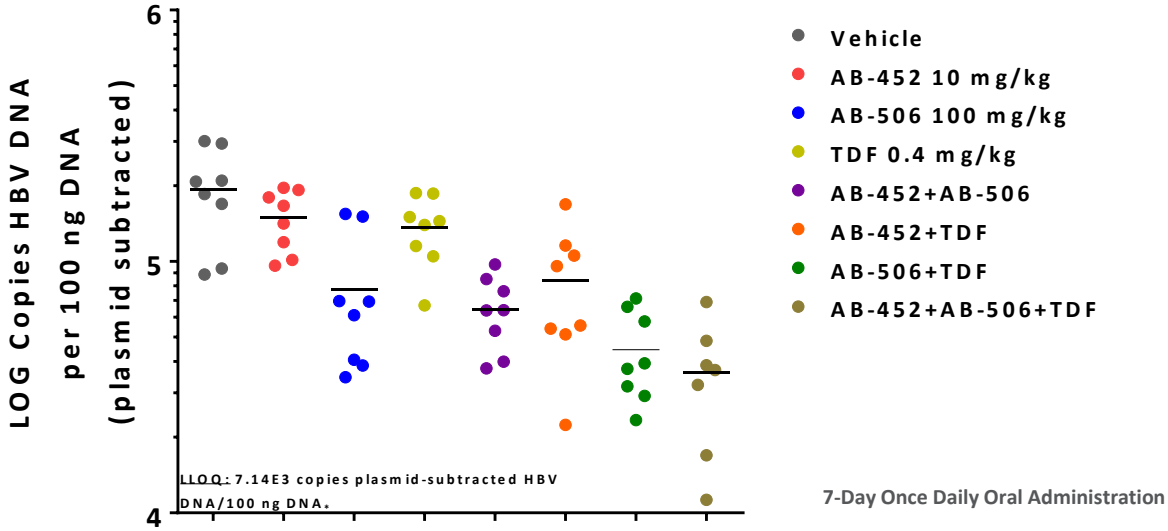
In vivo Dual and Triple Combination of AB-506, AB-452 and TDF

HDI Mouse Model of HBV: Liver HBV DNA and HBsAg Reductions



- Liver HBV DNA reductions reflect serum HBV DNA reductions
- AB-506 showed greater effect on liver HBV DNA reduction than TDF
- Only AB-452 containing groups showed liver HBsAg reductions

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Summary

- Key to therapeutic success will involve combination of different MoA agents
  - Reduce/Suppress Viral DNA and Antigens
  - Reawaken/Boost host immune responses
- Agents with novel MoA undergoing clinical evaluation; more in preclinical stages
- eg: Capsid Inhibitors, HBV RNA Destabilizers, RNAi Agents, NA, others
- *In vitro* and *in vivo* antiviral evaluations of Capsid Inhibitor AB-506, RNA Destabilizer AB-452, siRNA, and NA agents show favorable additive to synergistic effects in combination

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Acknowledgments

Arbutus Team

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Robbin Burns
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Dimitar Gotchev
Troy O. Harasym
Agnes Jarosz
Salam Kadhim
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Steven G. Kultgen
Kaylyn Kwak
Amy C.H. Lee
Sara Majeski
Kevin McClintock
Joanna Pan
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