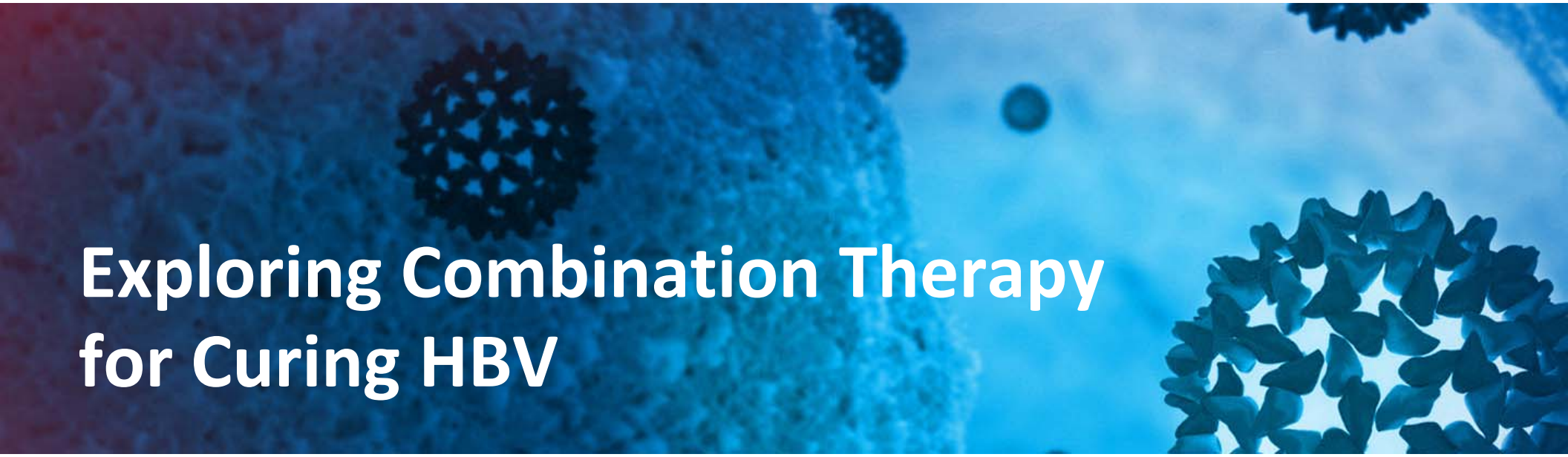
Arbutus BIOPHARMA



Exploring Combination Therapy for Curing HBV

Preclinical Combo Studies with Capsid Inhibitor AB-423 and siRNA Agent ARB-1740

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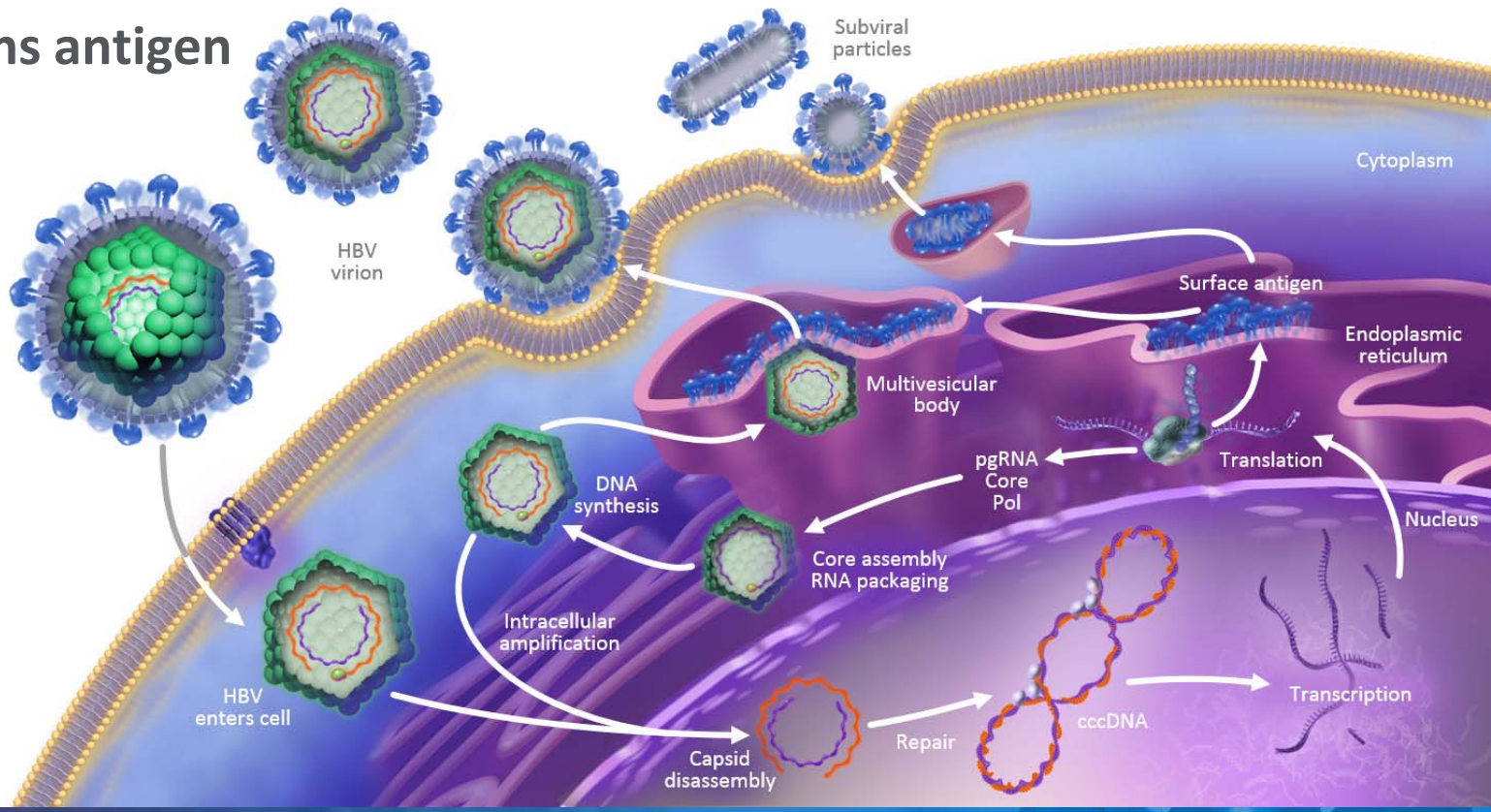
HBV Lifecycle

Complex biology requires combinatorial solution

- **Multiple points of intervention with direct anti-viral mechanisms**
  - Replication, capsid assembly/core protein function, cccDNA
- **cccDNA clearance is the cornerstone of HBV cure**
  - cccDNA maintains antigen production
- **Host immune response is attenuated by viral antigens**

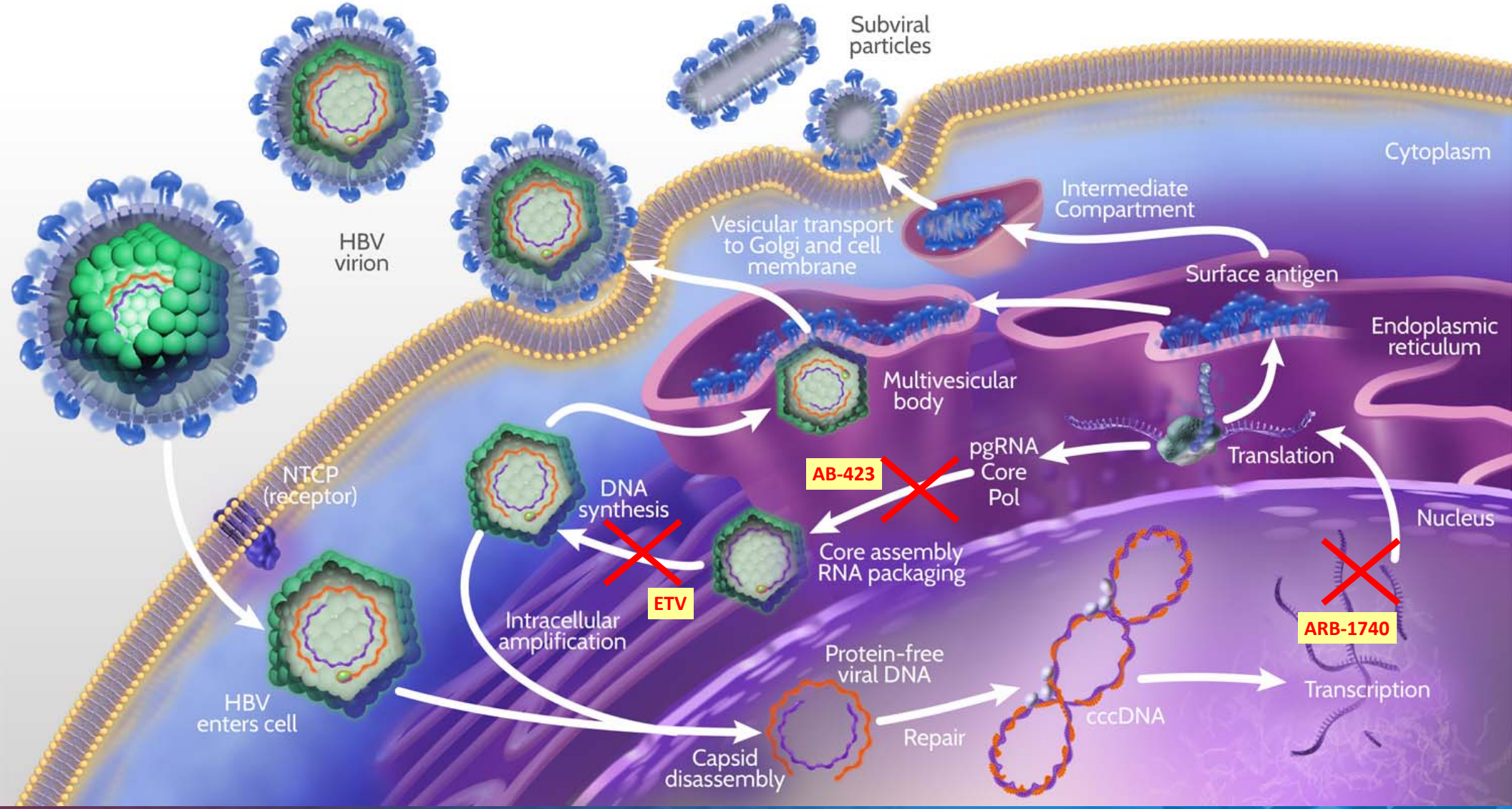


Arbutus' Preclinical Combination Studies

Combination	Marker(s)	Activity		
		Antagonism	Additivity	Synergy
AB-423 + Entecavir *Core Protein/Capsid Assembly Inhibitor + NUC*	cccDNA synthesis and expression, HBV rcDNA synthesis, and Serum HBV DNA	X	✓	✓
AB-423 + ARB-1467 *Core Protein/Capsid Assembly Inhibitor + RNAi*	cccDNA synthesis and expression, HBV rcDNA synthesis, and Serum HBV DNA	X	✓	✓
AB-423 + Interferon *Core Protein/Capsid Assembly Inhibitor + IFN*	HBV DNA	X	✓	
ARB-1467 + Entecavir *RNAi + NUC*	HBV rcDNA synthesis	X	✓	
ARB-199 + Entecavir *cccDNA Formation Inhibitor + NUC*	cccDNA synthesis and expression; HBV rcDNA synthesis	X		✓
ARB-199 + Lamivudine *cccDNA Formation Inhibitor + NUC*	cccDNA synthesis and expression; HBV rcDNA synthesis	X		✓

RNAi & Core Protein/Capsid Inhibitor

Two Novel Agents studied in combination with SoC



RNAi & Core Protein/Capsid Inhibitor

Two Novel Agents studied in combination with SoC

AB-423 (Core/Capsid Inhibitor)

- Orally administered small molecule
- Sub-micromolar potency
- Misdirects capsid assembly and inhibits pgRNA encapsidation

ARB-1740 (RNAi)

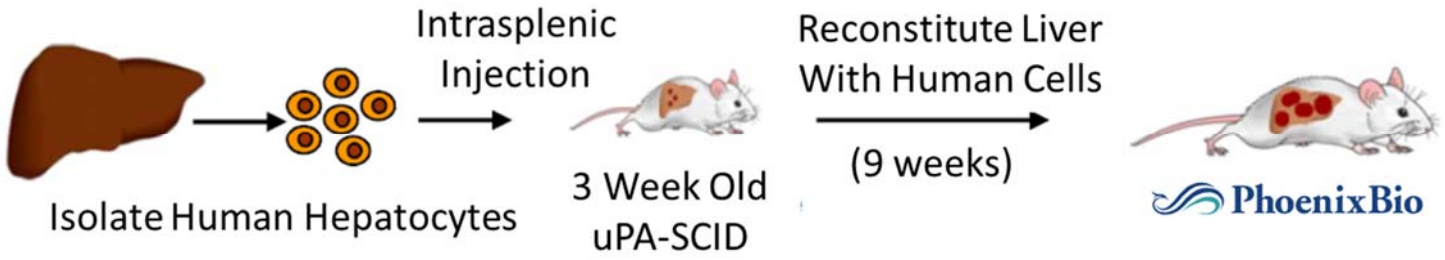
- Second generation RNA interference agent
- Three siRNAs encapsulated in a lipid nanoparticle delivery system
- Primarily, targets surface antigen produced by cccDNA & integrated DNA

*Both these investigational agents possess **pan-genotypic activity***

HBV-Infected Chimeric Mouse

Humanized Liver supports complete HBV life cycle

- Stabilized chronic HBV infection
- Viral replication driven from accumulated cccDNA

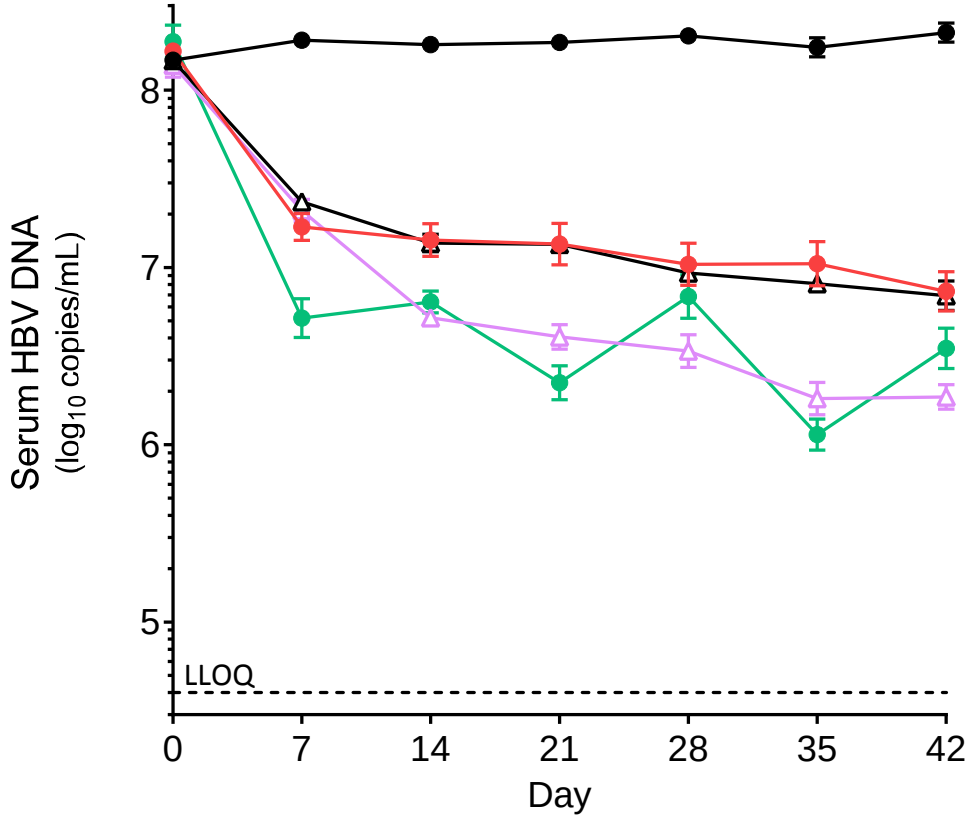


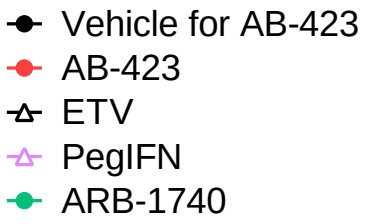
	Type	HBsAg (log_{10} IU/mL)	HBV DNA (log_{10} copies/mL)
PXB Mouse (Gt C)	Hemizygous uPA	3.5 (2.8-3.8)	8.3 (7.7-8.5)
CHB Patient	HBeAg positive	4.0 (1.8-5.0)[1] 4.4 (±0.7)[2]	9.2 (±0.8)[2]
	HBeAg negative	3.2 (0.8-5.0)[1] 3.9 (±0.5)[2]	6.8 (±1.2)[2]

Reference 1: Seto et al. HEPATOLOGY 2013; 58: 923-931, Reference 2: P. Arends et al. Journal of Viral Hepatitis 2014

Combining Novel Agents with Standard of Care

Each Monotherapy lowers HBV DNA in blood



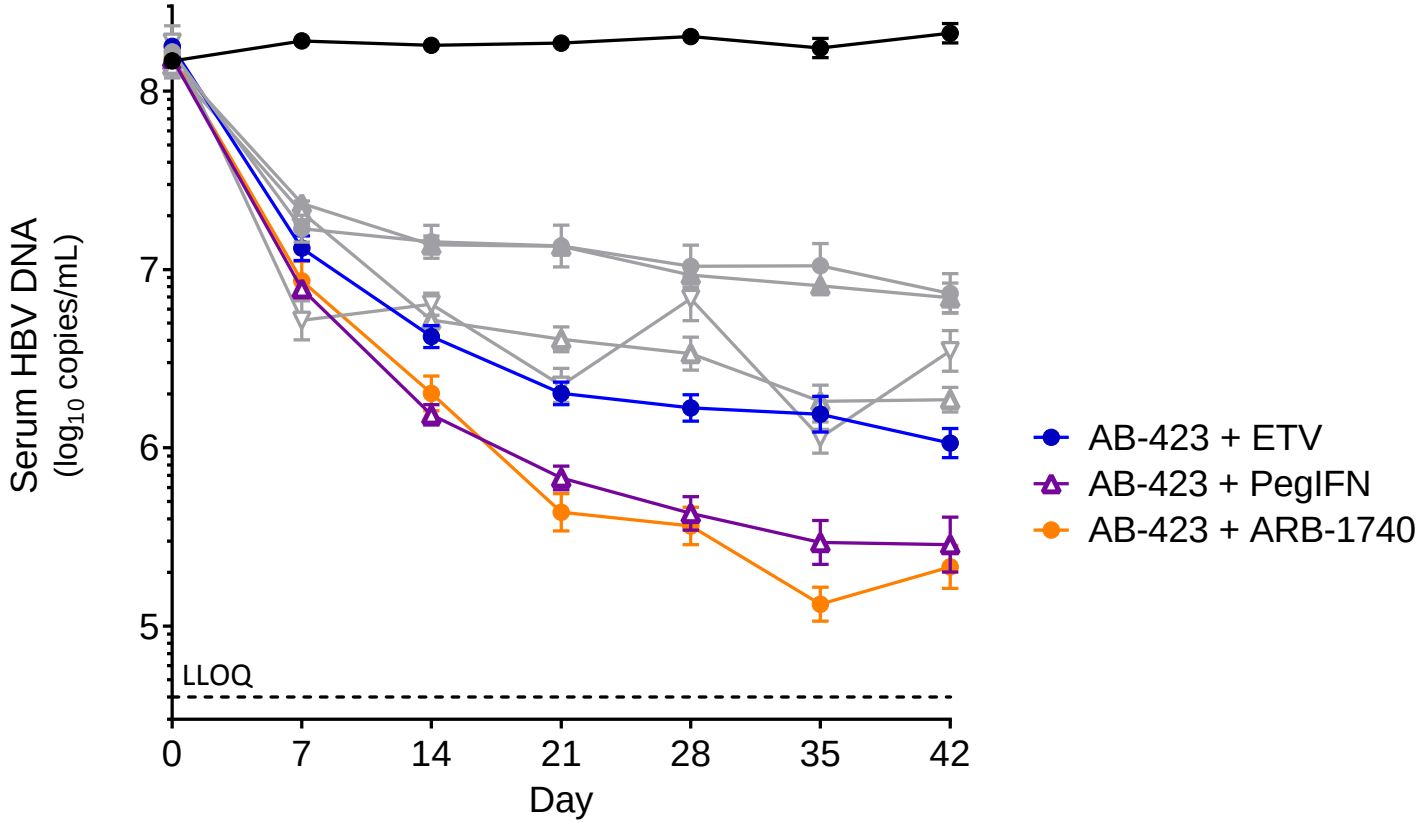


	Treatment for 6 weeks		
	Dosage	**Route**	**Frequency**
AB-423	100 mg/kg	PO	BID
ETV	1.2 µg/kg	PO	QD
PegIFN	30 µg/kg	SQ	2×/wk
ARB-1740	3 mg/kg	IV	biweekly

- All individual agents have stand-alone activity against HBV virus
- Both AB-423 and ARB-1740 have rapid rate of onset

Combining Novel Agents with Standard of Care

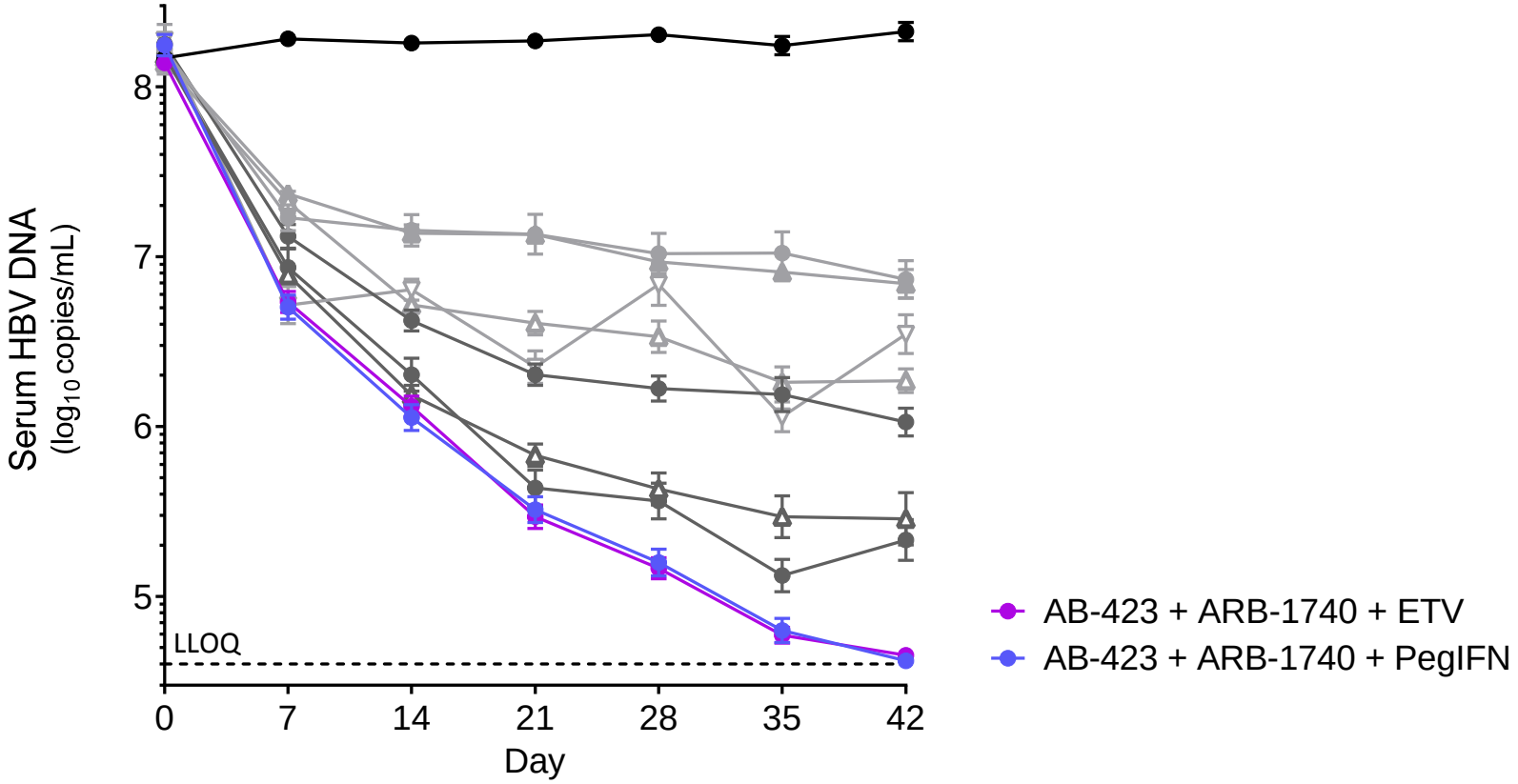
Additive Benefit for all capsid inhibitor AB-423 dual-combos



- AB-423 capsid inhibitor plus SoC or RNAi = greater control of viral replication

Combining Novel Agents with Standard of Care

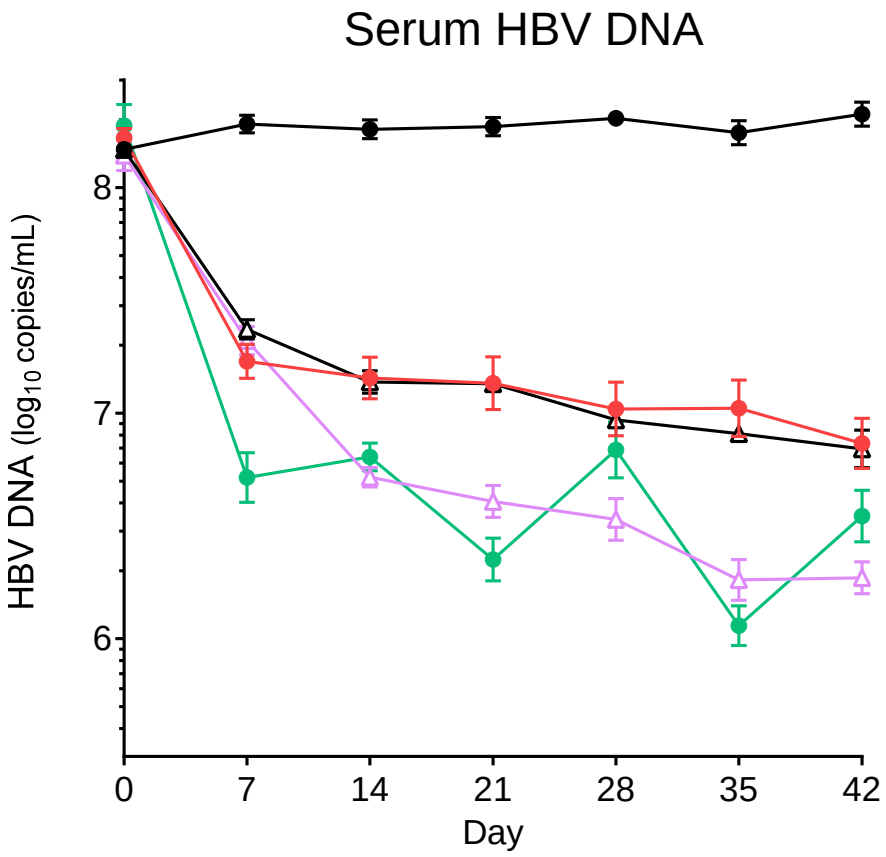
Triple therapy provides greatest reduction of HBV DNA

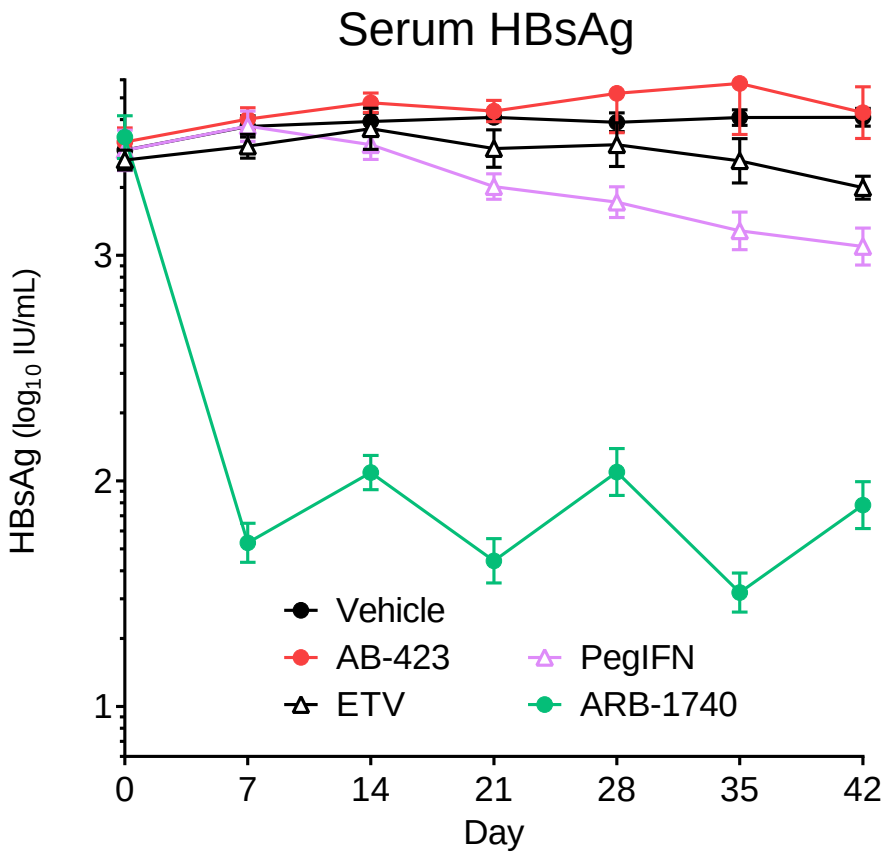


- Triple drug combinations provided even more reduction of virus in serum

Characterizing Antiviral Efficacy:

Moving beyond serum HBV DNA

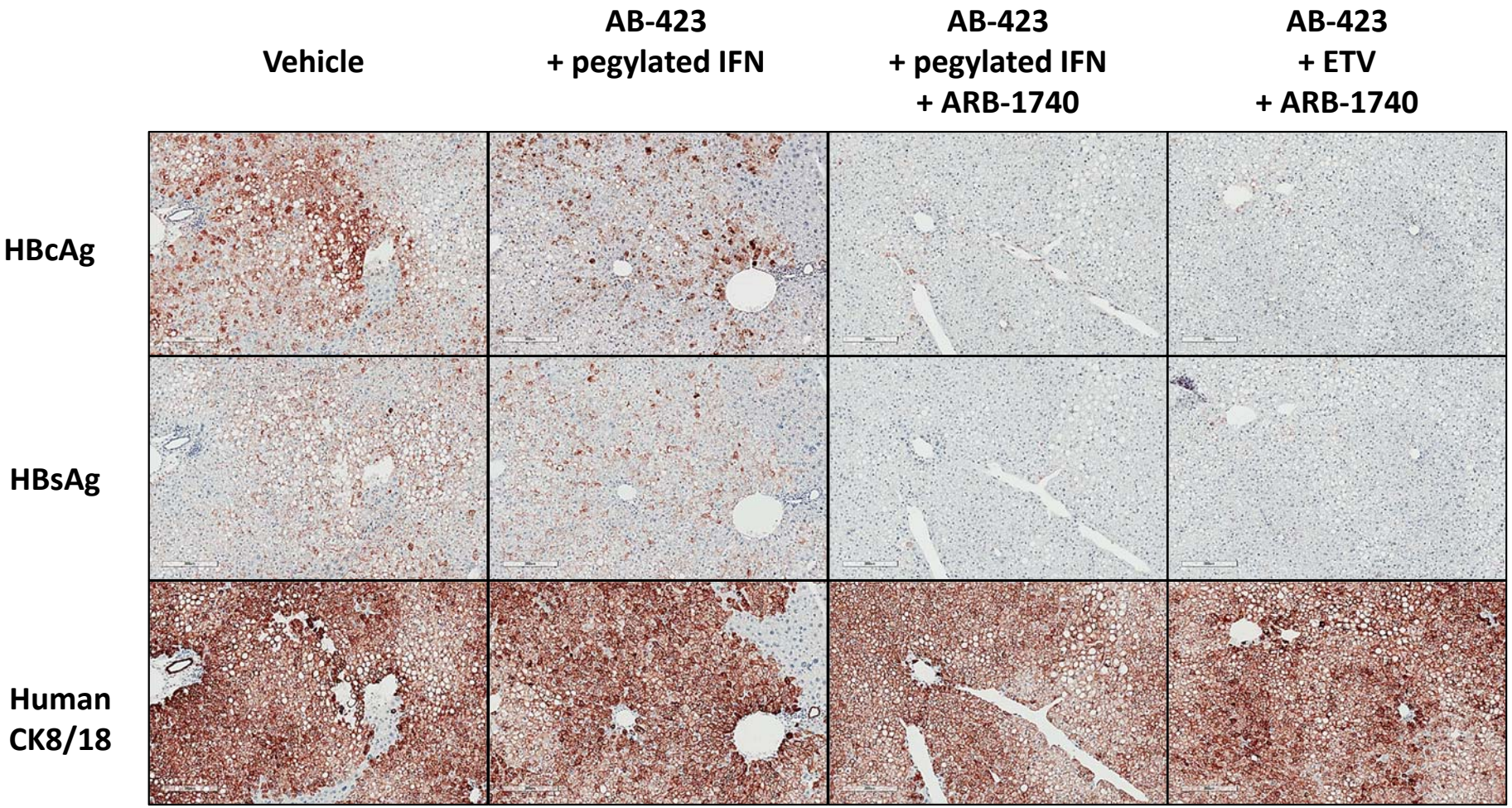




- Unlike the other agents,
  ARB-1740 causes similar reductions in serum HBsAg, HBeAg and HBV DNA
- HBV antigens are produced at high levels and have **immune suppressive effect**

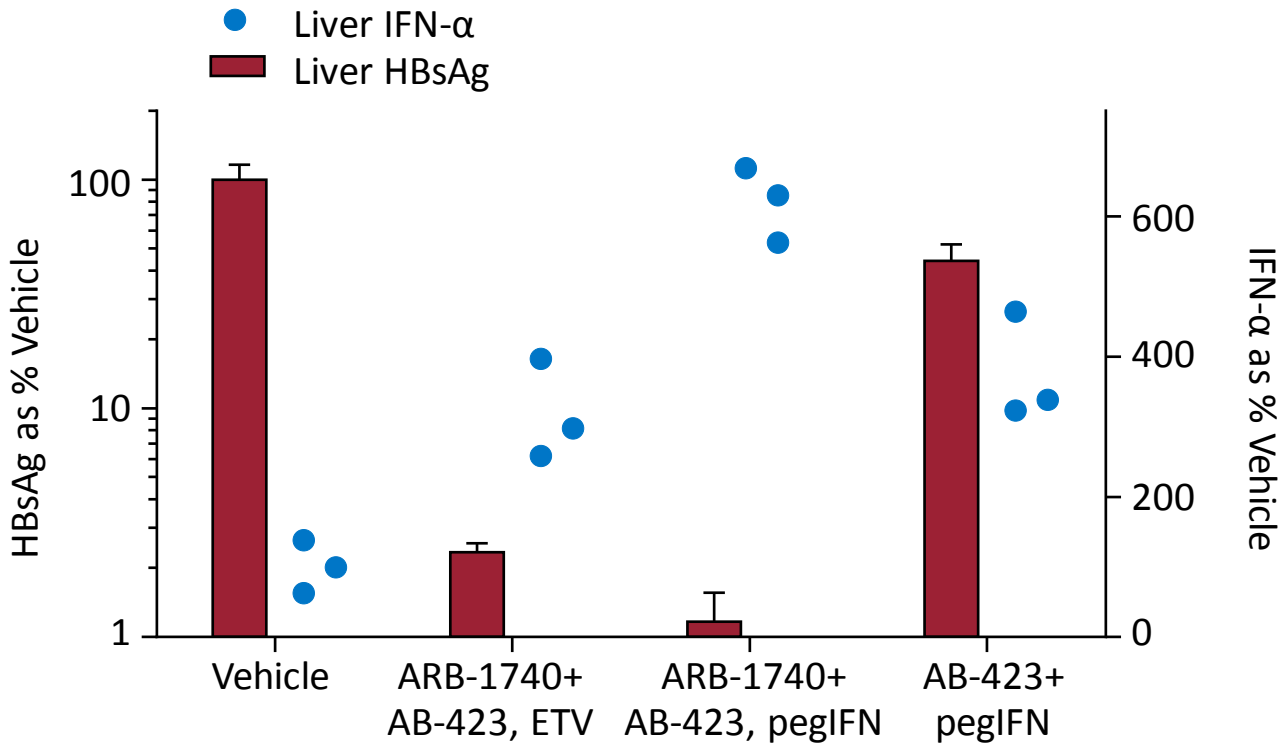
ARB-1740 Inhibits Production of All HBV Proteins

Removal from liver, a key immunosuppressive environment



- Liver HBV antigens at end of 6-week treatment

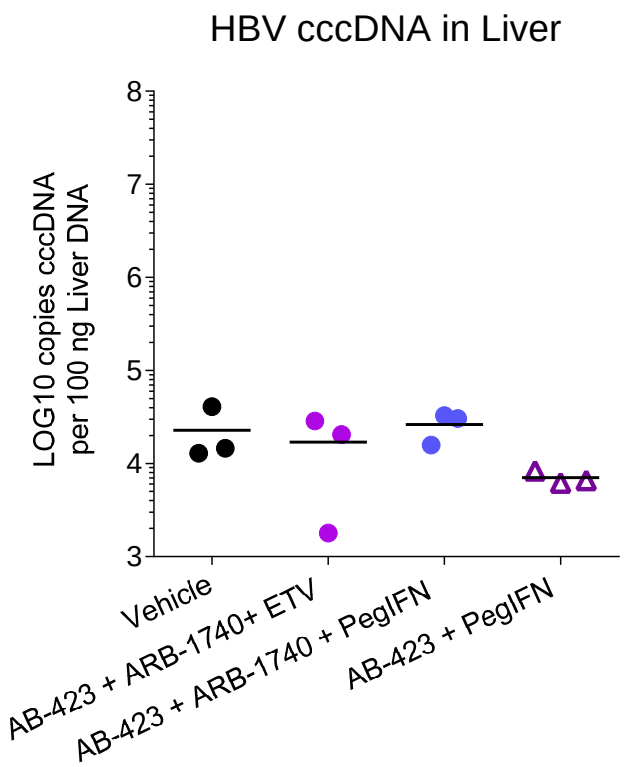
HBsAg Removal Correlates with ↑Host Response

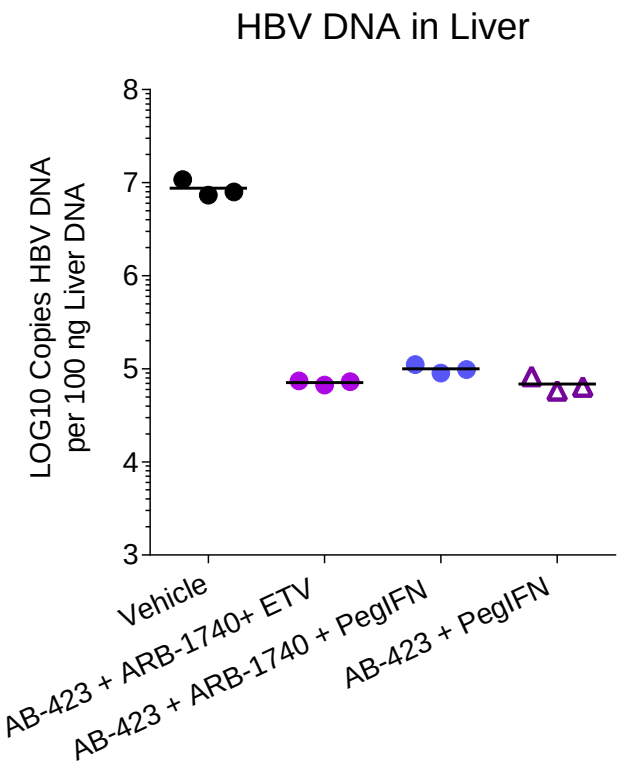


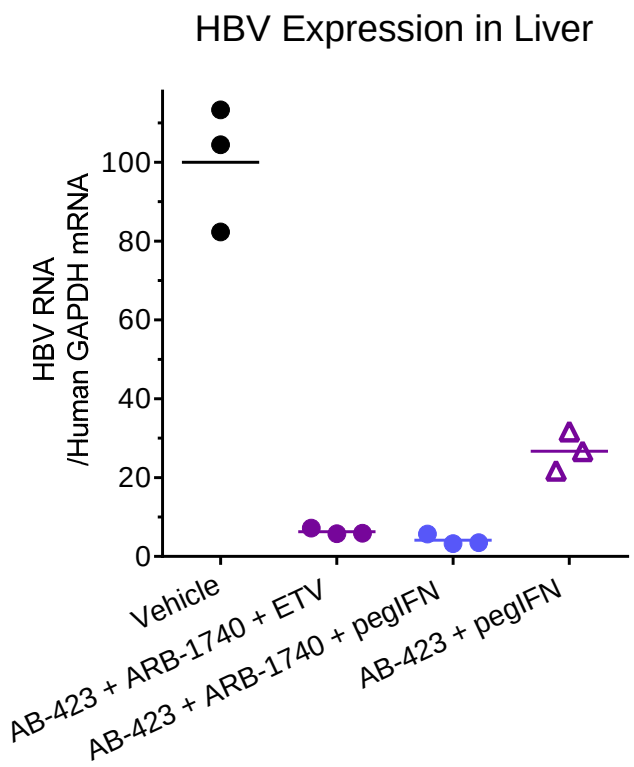
- HBsAg removal by ARB-1740 correlated with gain in human IFN-α expression
- In vivo human hepatocyte innate immune response was further potentiated by combining ARB-1740 with pegylated interferon

Liver Reservoir of cccDNA

Not just "*how many copies*" but also "*is it transcriptionally active?*"



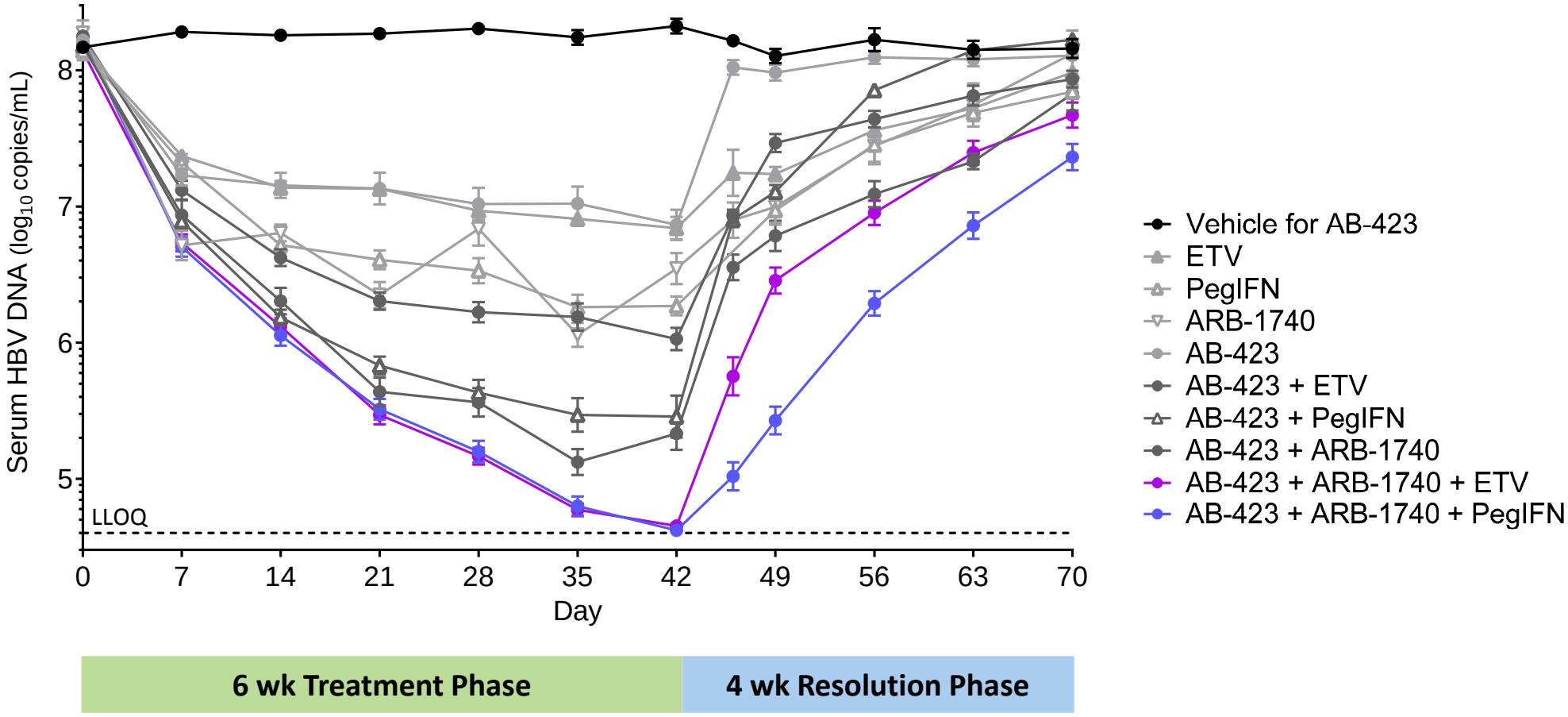




- **Pre-established cccDNA was unchanged after 6 wk treatments;**
- **HBV rcDNA suppression may have reached a maximum with chosen combos;**
- **However, differential control of cccDNA transcriptional activity was observed**

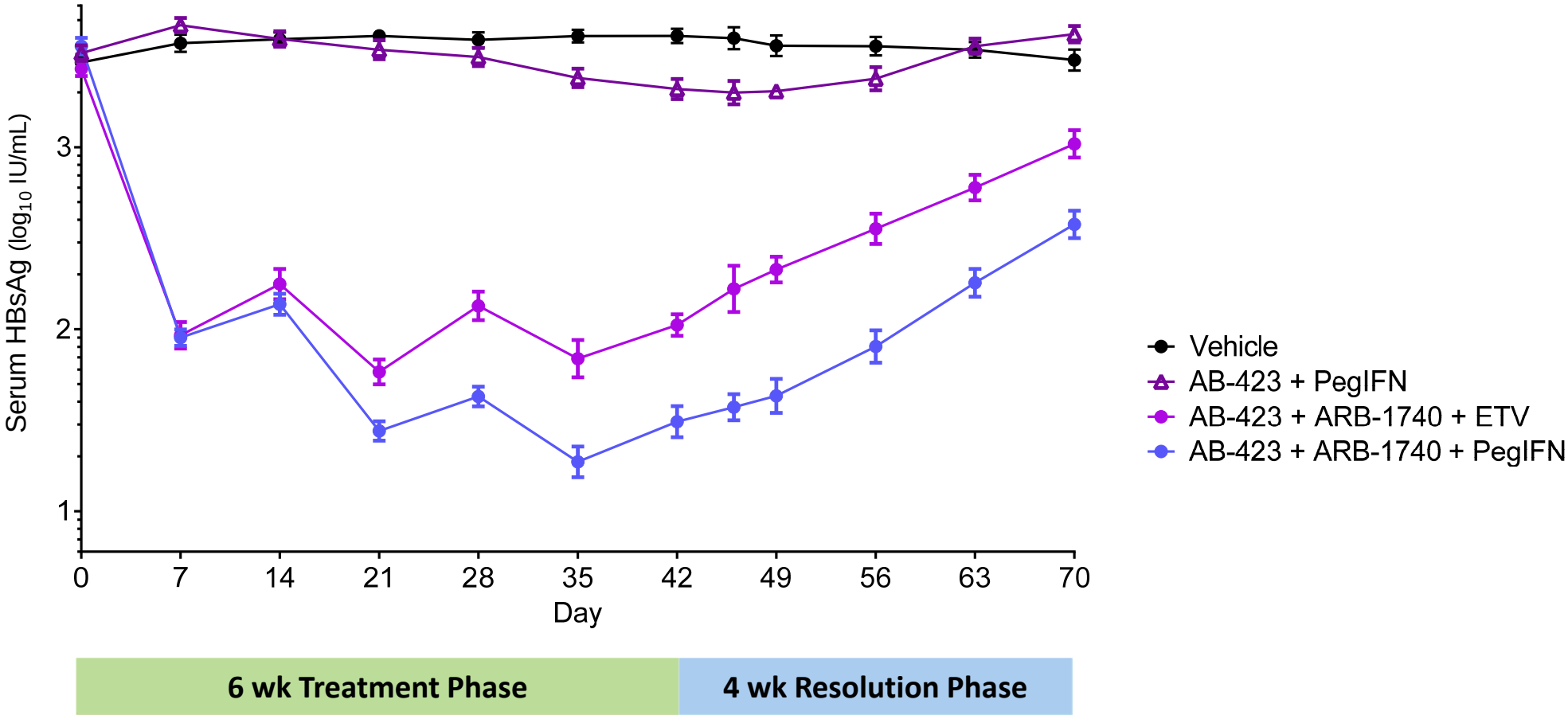
Viral Recovery Impeded Most

By the triple drug combo containing pegIFN (vs ETV)



Viral Antigen Load Control Greatest

By the triple drug combo containing pegIFN (vs ETV)

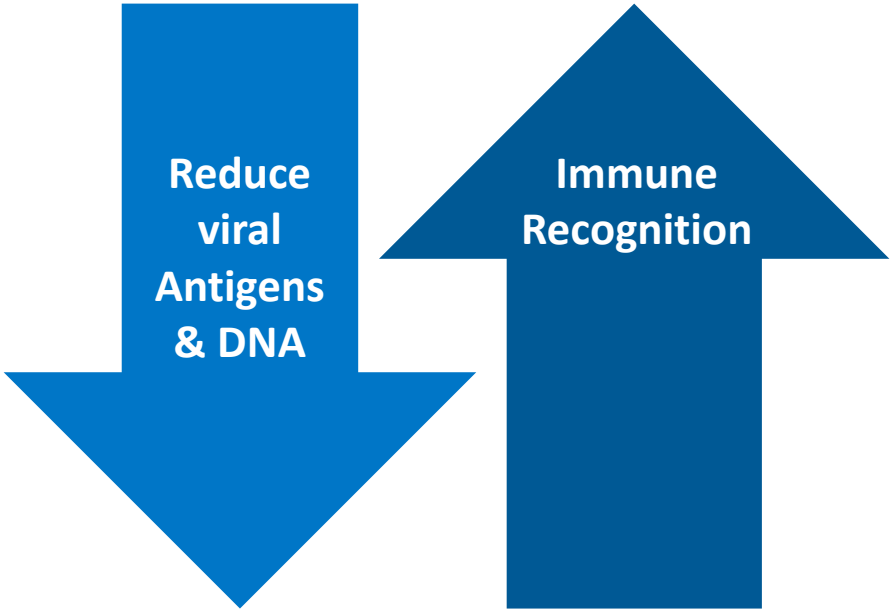


Summary

- Preclinical investigations of drug combinations can provide supportive data to help inform the design of investigative human trials

- Combination of novel MOA agents AB-423 (capsid inhibitor) and ARB-1740 (RNAi) can enhance control of HBV by current standard drugs

- These data support the hypothesis that HBV antigen removal will promote immune recognition and viral control



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