The Evolution of siRNA Therapeutics Targeting HBV at Arrowhead Pharmaceuticals

Sept 25, 2018

arrowhead pharmaceuticals

Disclosures

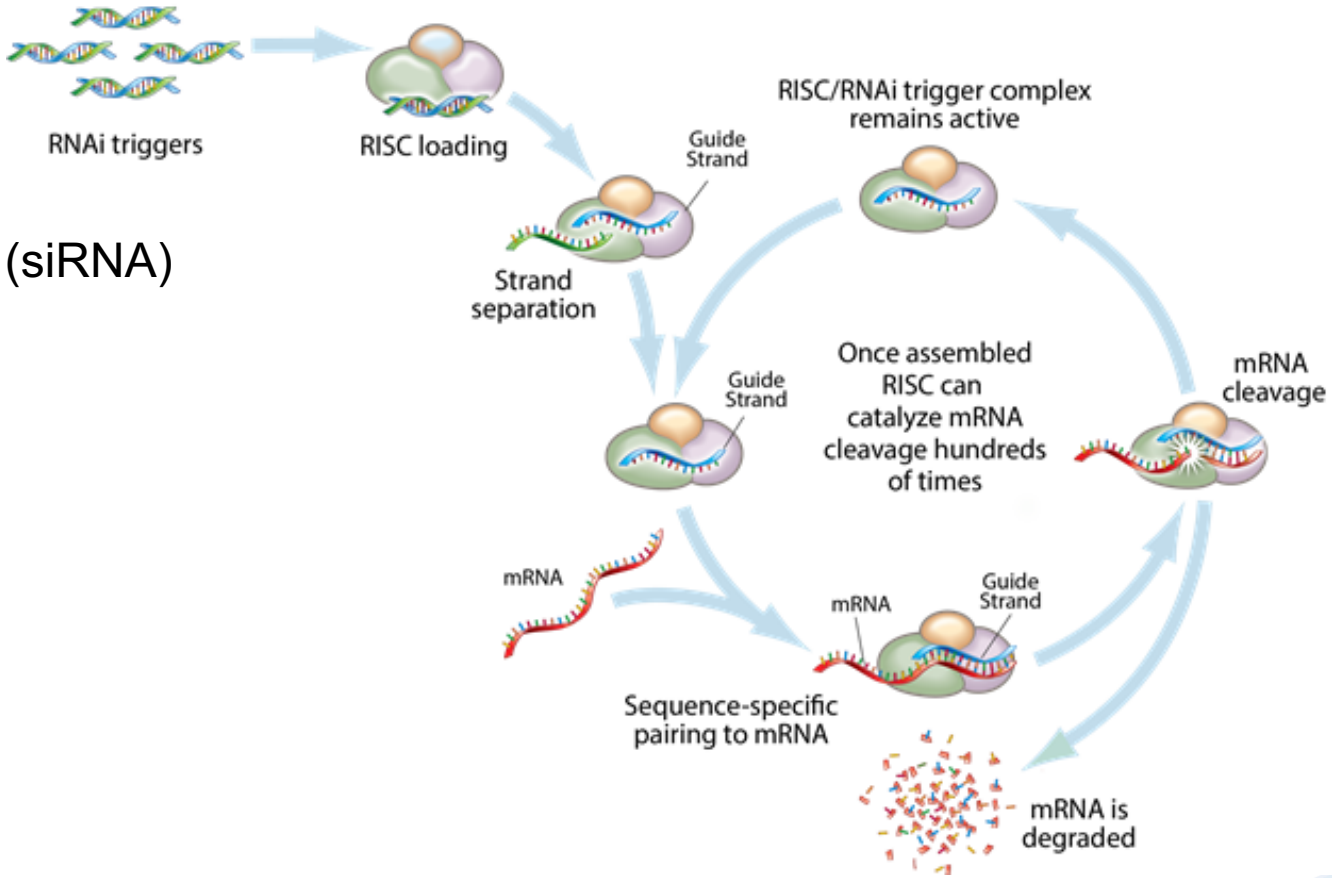
- I am an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

arrowhead pharmaceuticals

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

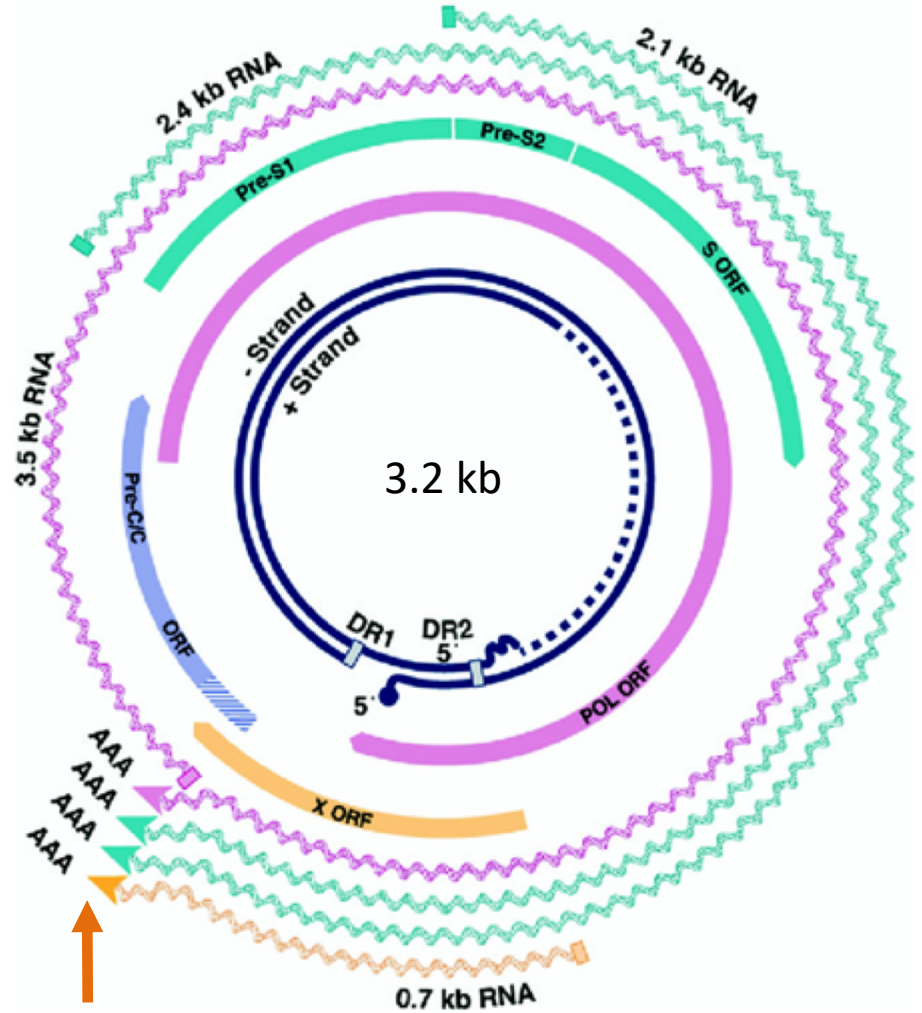
RNAi: Target the Gene Silence the Disease



Therapeutic gene silencing with **RNA interference** is highly precise and efficient

arrowhead pharmaceuticals

Organization of the HBV genome makes it ideal for RNAi



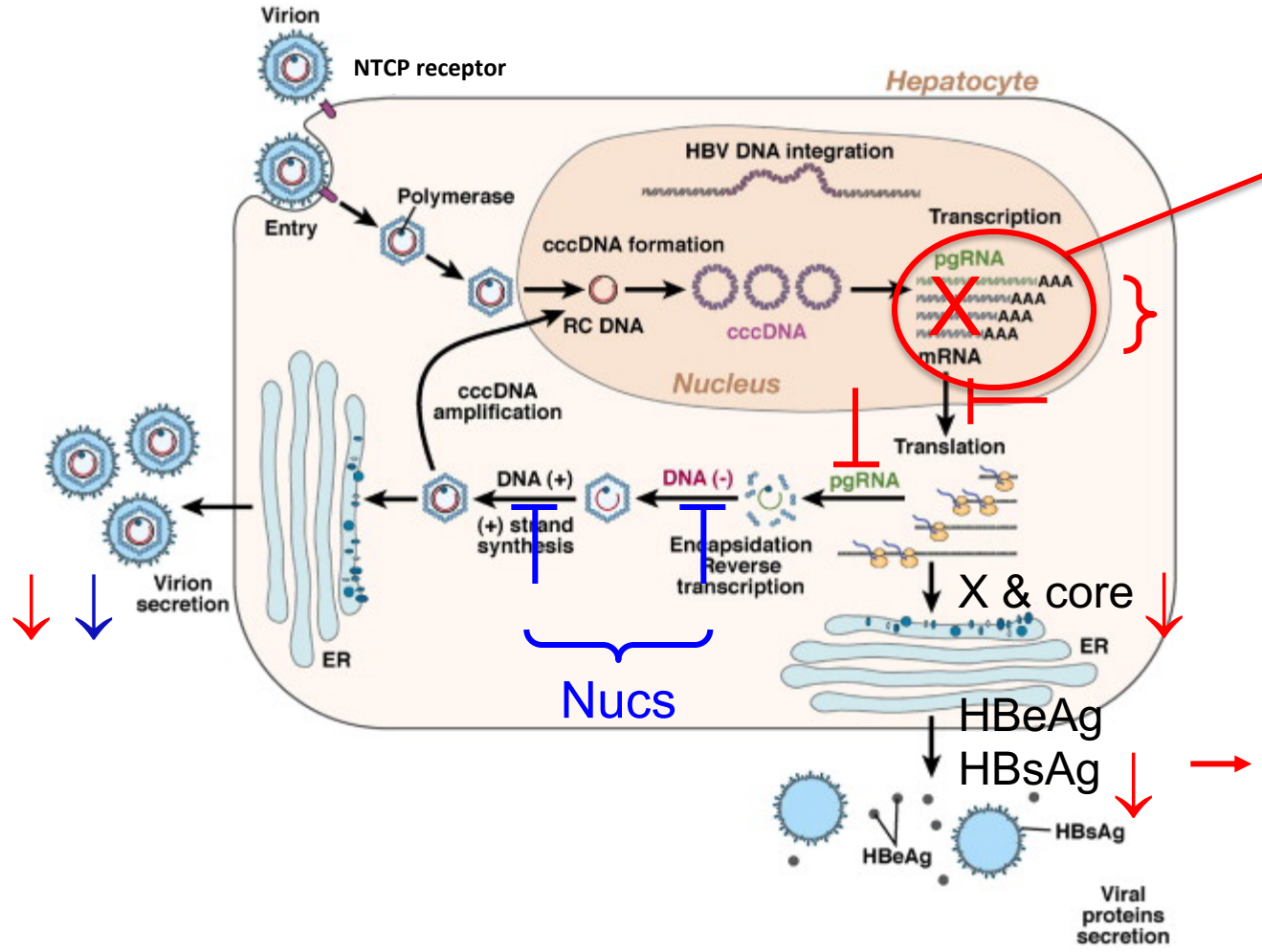
Same polyadenylation signal for all mRNAs

- **5 viral mRNAs**
  - 3.5 kb pre-genomic RNA
  - 3.5 kb pre-core mRNA
  - 2.4 kb pre-S1 mRNA
  - 2.1 kb pre-S2/S mRNA
  - 0.7 kb X mRNA
- **7 major proteins**
  - Polymerase (with reverse transcriptase function)
  - Core (HBcAg), forms capsid
  - e antigen (HBeAg), also called pre-core, a secreted protein
  - Large, medium and small surface proteins (HBsAg), form envelope
  - X protein (Transactivator)

arrowhead pharmaceuticals

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

RNAi Silence All HBV viral mRNA

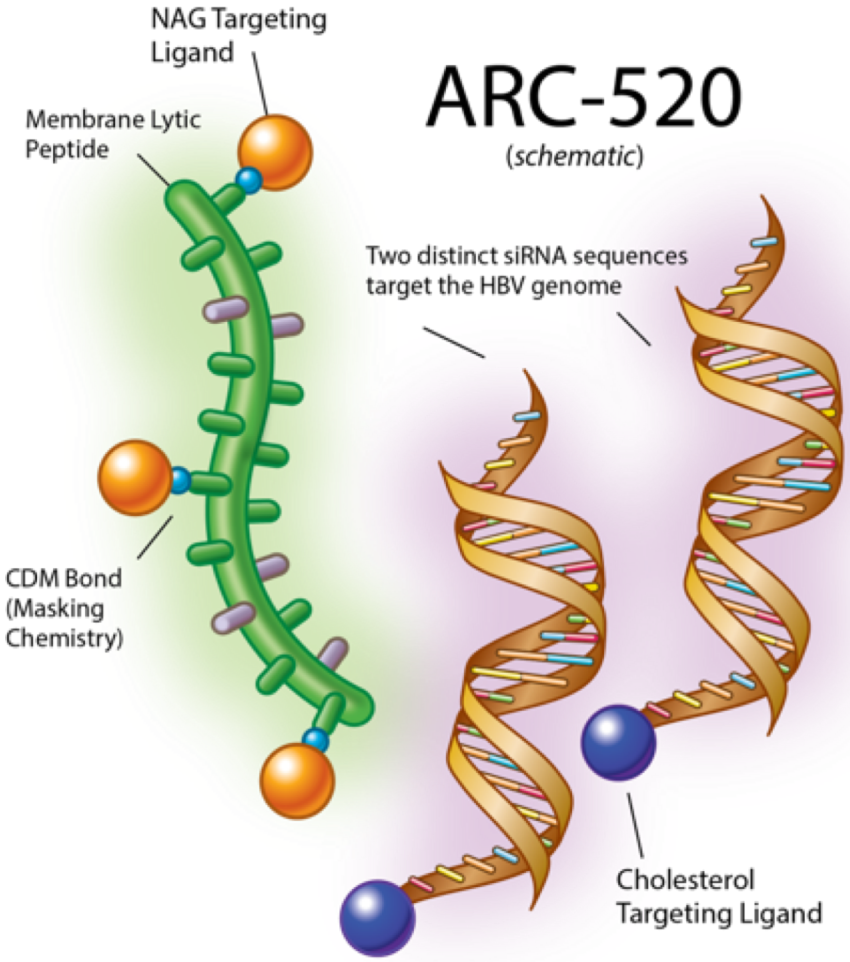


1. Large titers of HBsAg exhaust immune response
2. siRNA silences all viral mRNA transcripts.
3. Attack the viral life cycle on multiple levels and reduce HBsAg
4. Hypothesis: revive host immune response

arrowhead pharmaceuticals

1st Gen: RNAi therapeutic ARC-520 for chronic HBV infection

Designed to reduce all transcripts from HBV cccDNA



- **ARC-520 Excipient**
  - Hepatocyte-targeted DynamicPolyConjugate™ peptide (NAG-MLP) to enhance siRNA delivery
  - Lyophilized powder, stable
- **ARC-520 API**
  - Mixture of 2 cholesterol-conjugated siRNAs in solution
  - Inclusion of two siRNAs gives broader genotype coverage (>99%)

arrowhead pharmaceuticals

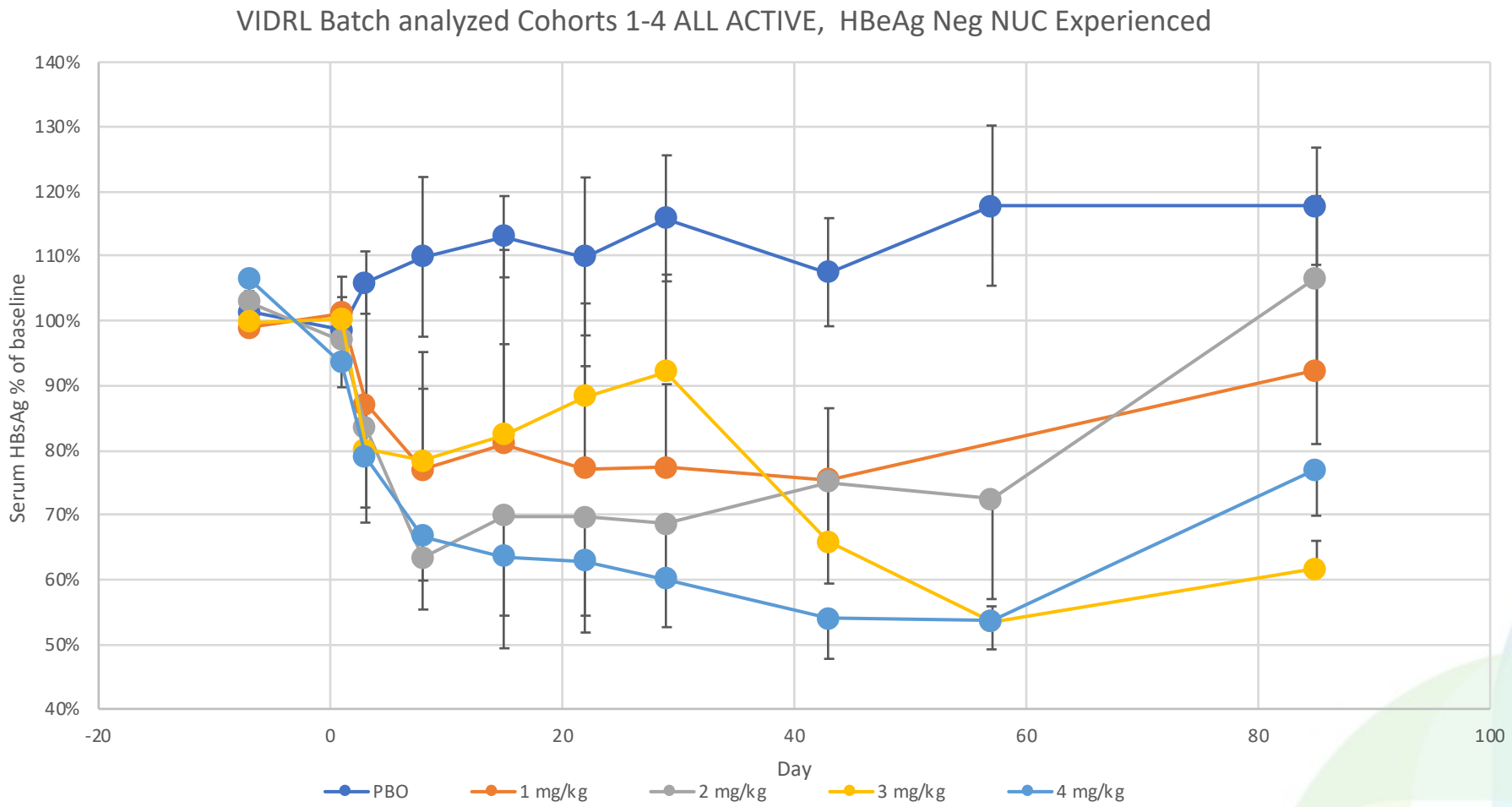
ARC-520 History

- 1st Gen: ARC-520 evaluated in multiple CHB studies
  - Heparc-2001: SAD with multi-dose extension in CHB patients
  - Heparc-2002: 4, Q28 day doses in HBeAg neg NUC experienced CHB patients
  - Heparc-2003: 4, Q28 day doses in HBeAg pos NUC experienced CHB patients
  - Heparc-2007: extension study of 2002/2003
  - Heparc-2008: up to 12, Q28 day doses as monotherapy or in combination with NUCs alone or NUC+PEG IFN-alpha

ARC-520 Review

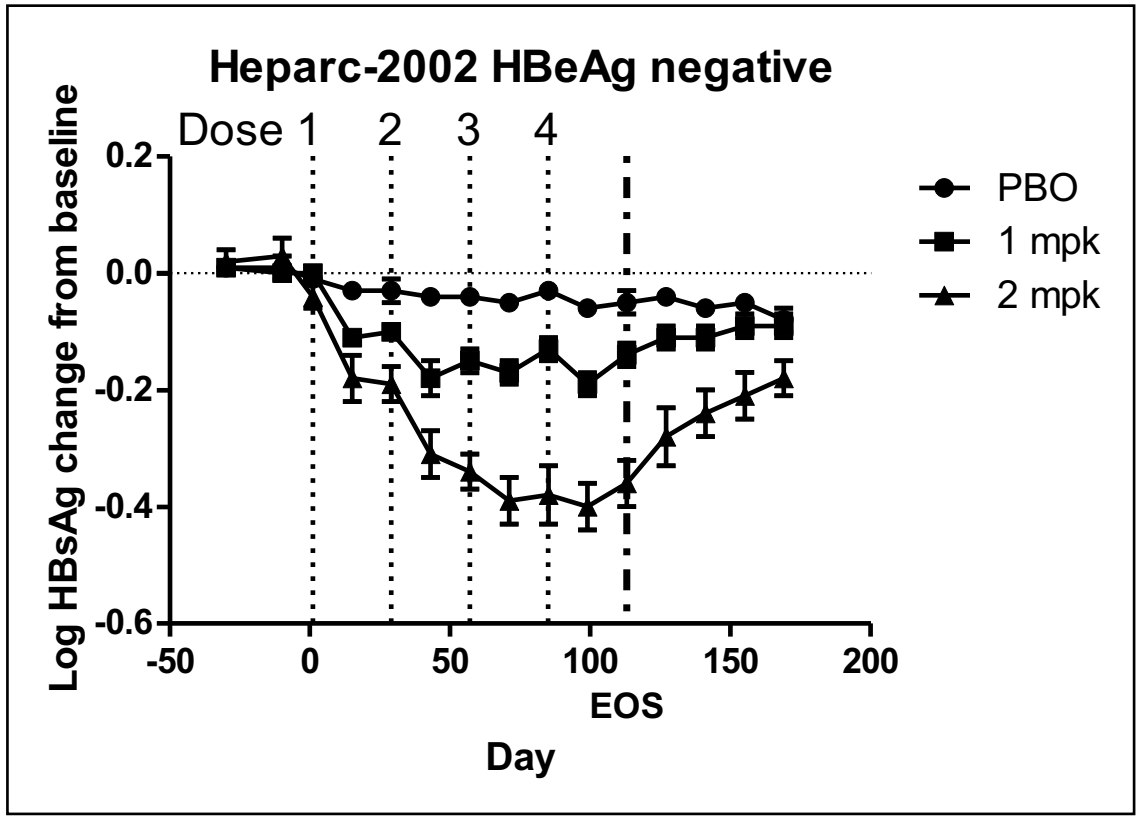
- ~260 HVs and CHB patients received ARC-520
  - Up to doses of 6 mg/kg
- Required intravenous administration, oral antihistamine pre-treatment
  - In general well tolerated
  - Approximately 6% of doses with signs or symptoms consistent with infusion reaction
  - 2 SAEs of fever (possibly related), 1 SAE of cholangiocarcinoma (not related)
- All ARC-EX1 (ARC-520, 521, AAT) programs terminated due to deaths in a non-human primate multi-dose toxicity study (only EX1 arms)

Heparc-2001: Cohorts 1- 4 show less than expected activity



arrowhead pharmaceuticals

Similar findings in multi-dose studies with ARC-520 Heparc-2002: HBeAg neg, NUC experienced

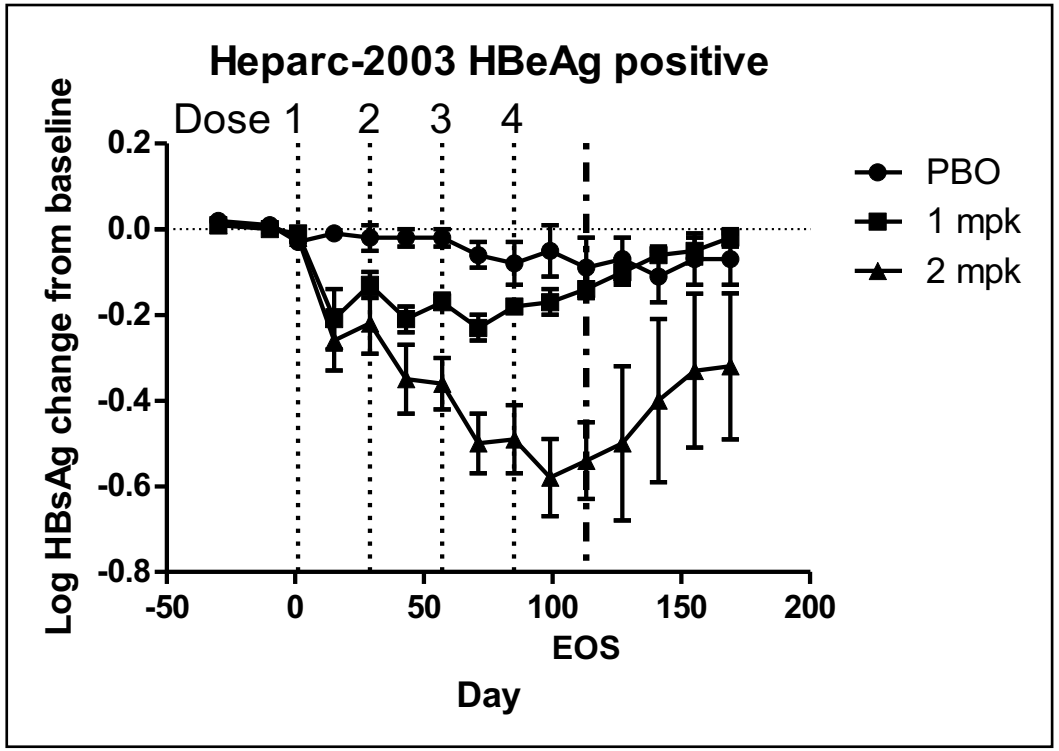


- Mean max KD = -0.40 log on day 99 at 2 mpk
- 6/21 patients had > 0.5 log KD at 2 mpk

Patients on NUCS throughout the study

arrowhead pharmaceuticals

Similar findings in multi-dose studies with ARC-520 Heparc-2003: HBeAg pos, NUC experienced

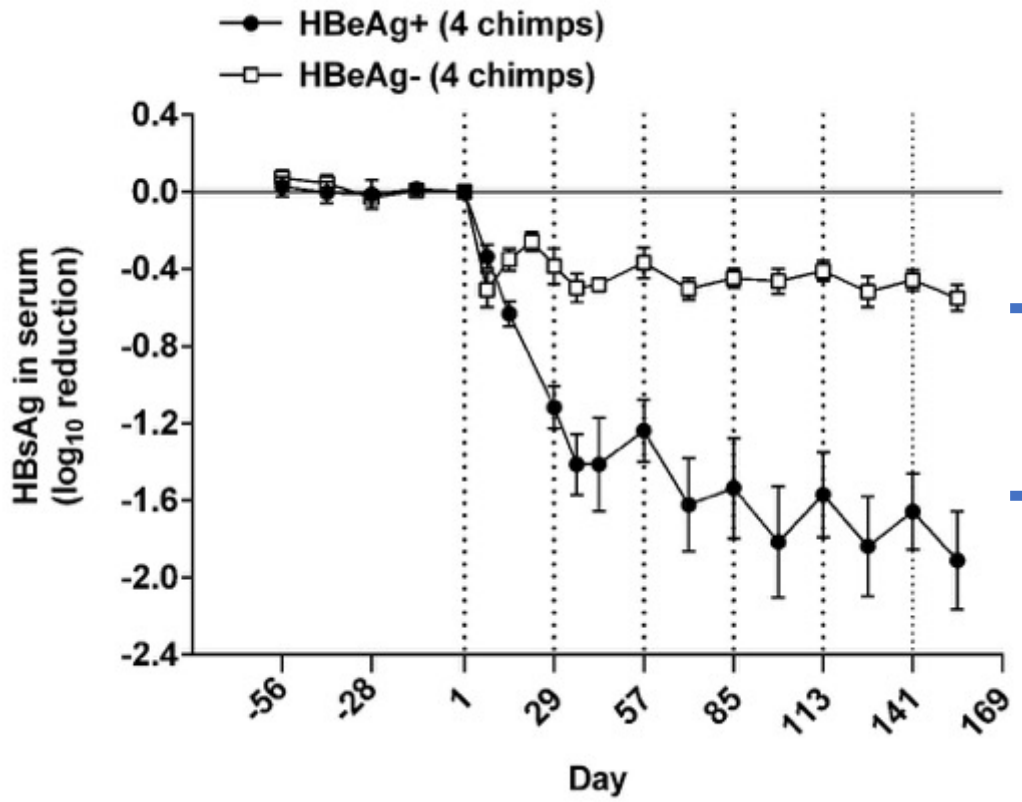


Patients on NUCS throughout the study

- Mean max KD = -0.58 log on day 99 at 2 mpk
- 2/11 patients had > 1 log KD at 2 mpk
- 7/11 patients had > 0.5 log KD at 2 mpk

arrowhead pharmaceuticals

Differential HBsAg Reduction Observed in Chimpanzees (and Humans) with ARC-520



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

INFECTIOUS DISEASE

RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg

Christine I. Wooddell,[1*†] Man-Fung Yuen,[2*] Henry Lik-Yuen Chan,[3] Robert G. Gish,[4] Stephen A. Locarnini,[5,6] Deborah Chavez,[7] Carlo Ferrari,[8,9] Bruce D. Given,[1] James Hamilton,[10] Steven B. Kanner,[1] Ching-Lung Lai,[2] Johnson Y. N. Lau,[11] Thomas Schluep,[10] Zhao Xu,[1] Robert E. Lanford,[7] David L. Lewis[1]

HBeAg-
0.5 - 0.9 log_{10} reduction at nadir

More HBsAg from integrants

HBeAg+
1.5 - 2.7 log_{10} reduction at nadir

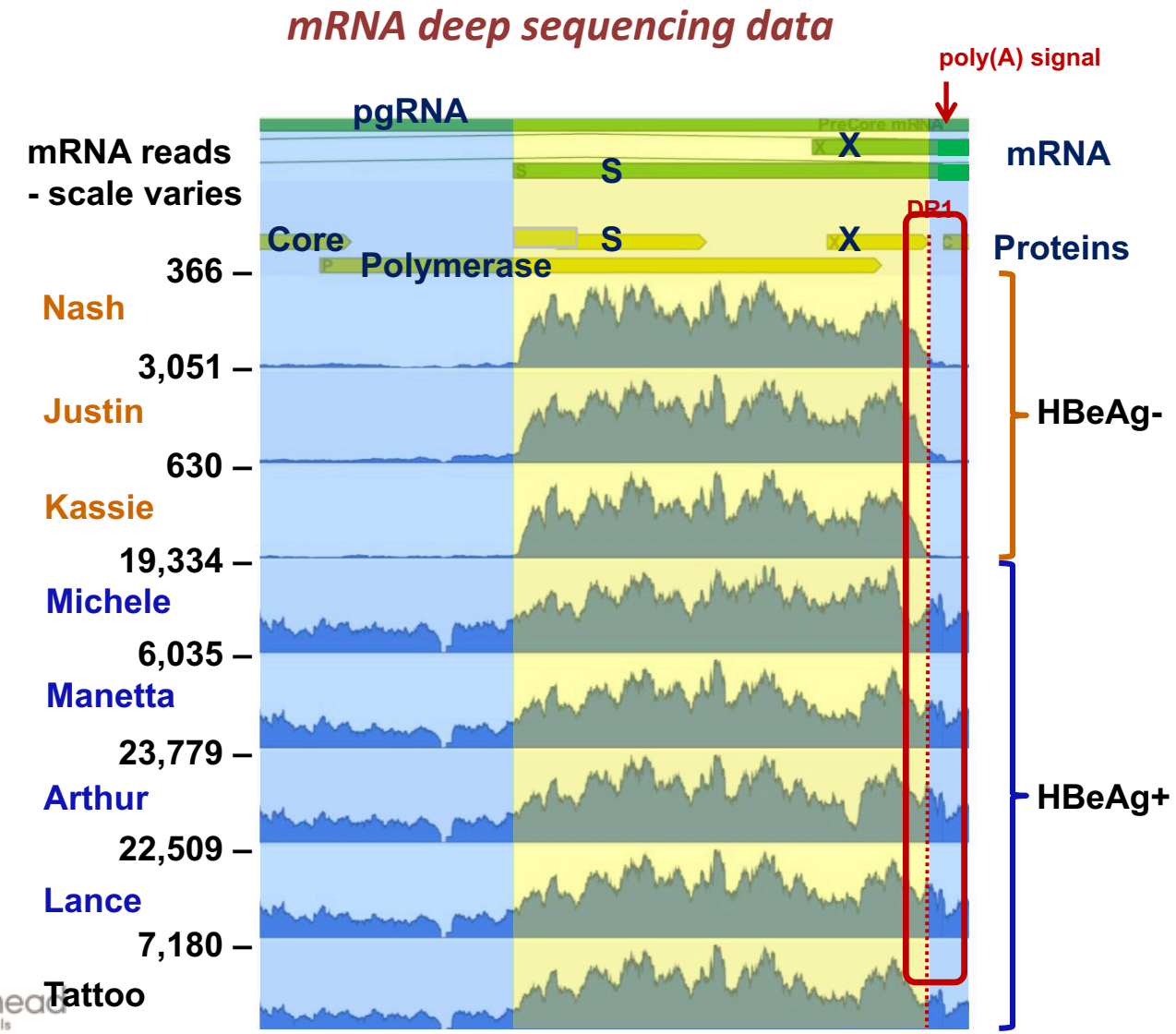
More HBsAg from cccDNA

HBeAg positive responded better than HBeAg negative chimps

The same observation was made for treatment-naïve humans

arrowhead pharmaceuticals

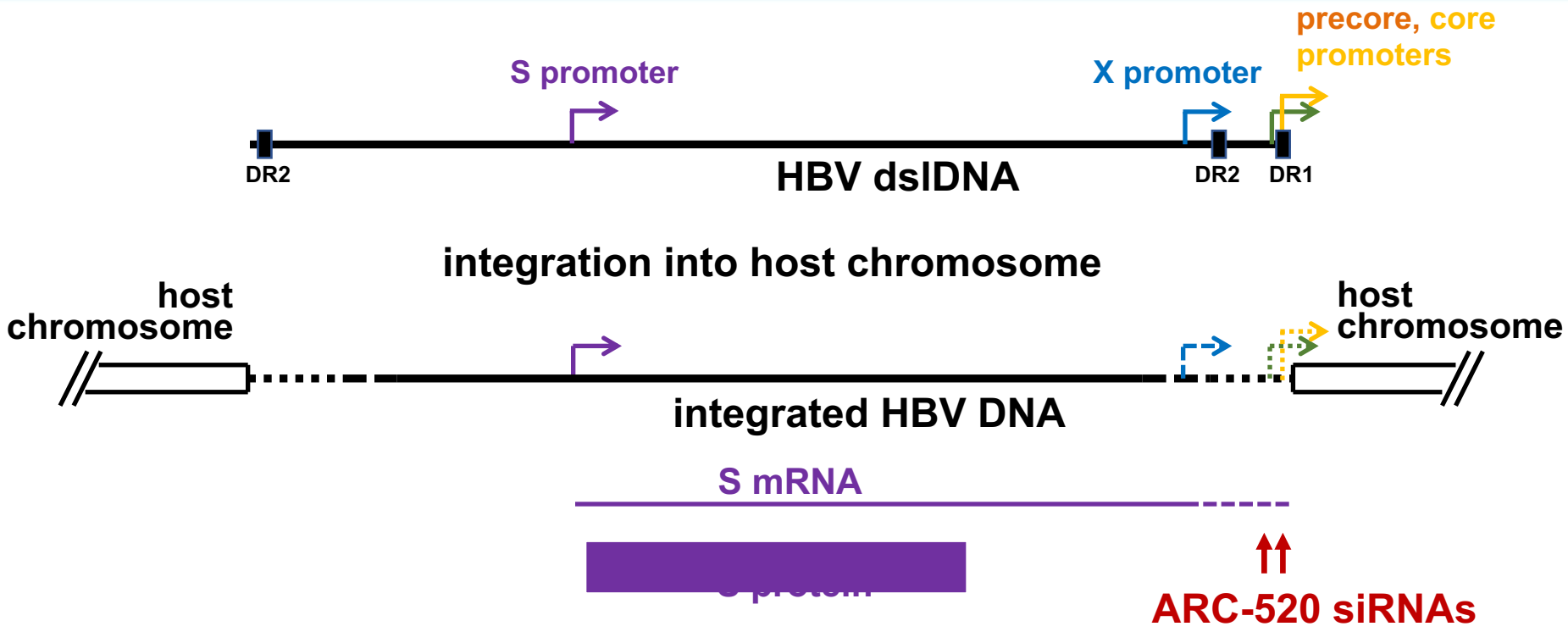
HBV transcript profiles differ between HBeAg- and HBeAg+ chimps



- ***HBeAg positive chimps***
  - Relatively balanced transcription of S and other cccDNA-dependent transcripts
- ***HBeAg negative chimps***
  - S transcripts make up a higher proportion of total HBV transcripts
  - Frequency of S gene transcript reads is reduced in region upstream of the DR1 site.
  - **These results are Indicative of expression from integrated HBV DNA**

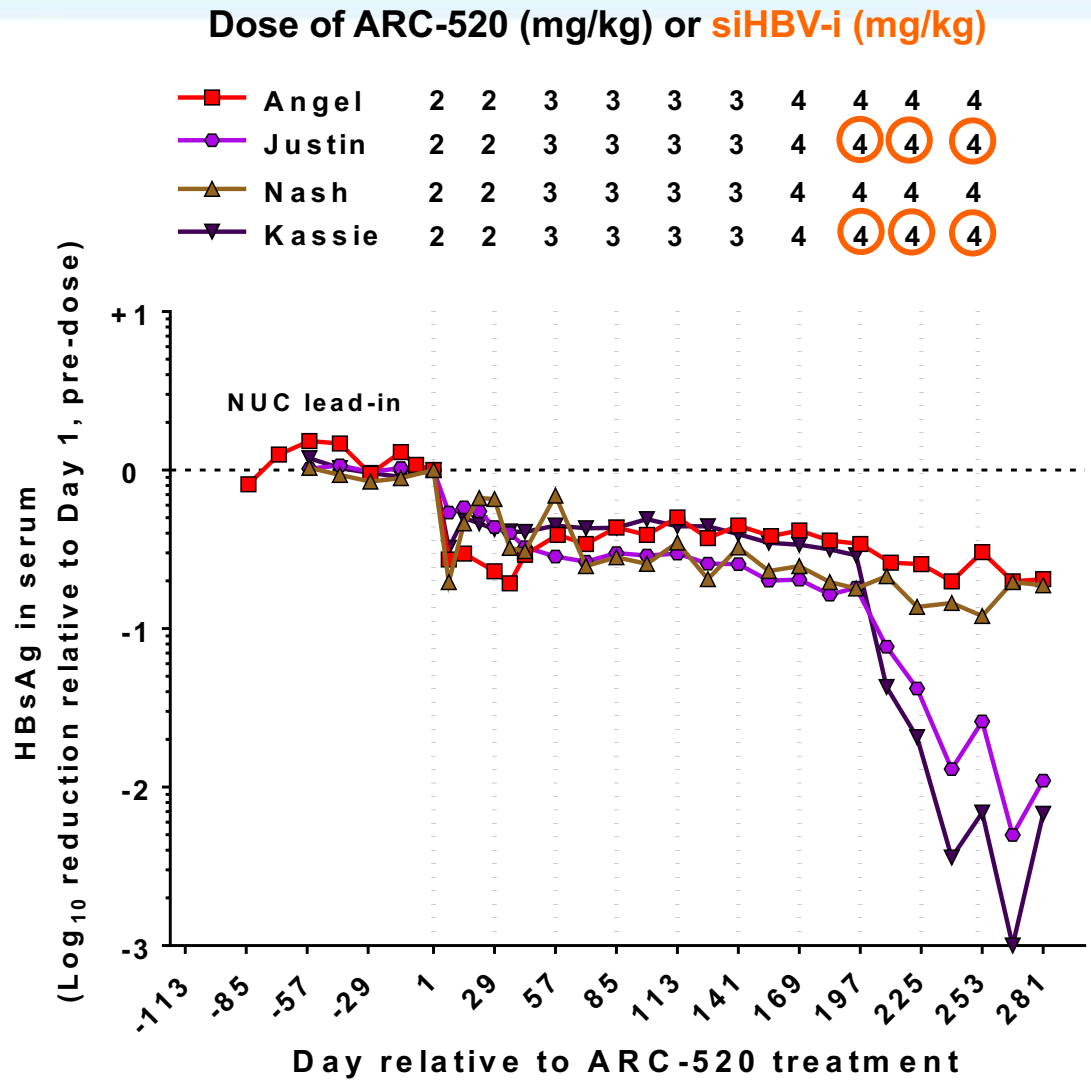
arrowhead pharmaceuticals

Target sites for ARC-520 siRNAs can be deleted in integrated HBV DNA



Loss of ARC-520 target sites in integrated HBV DNA explains lower KD of HBsAg in HBeAg negative chimps

siRNA designed to target RNA derived from HBV integration products in HBeAg- chimps



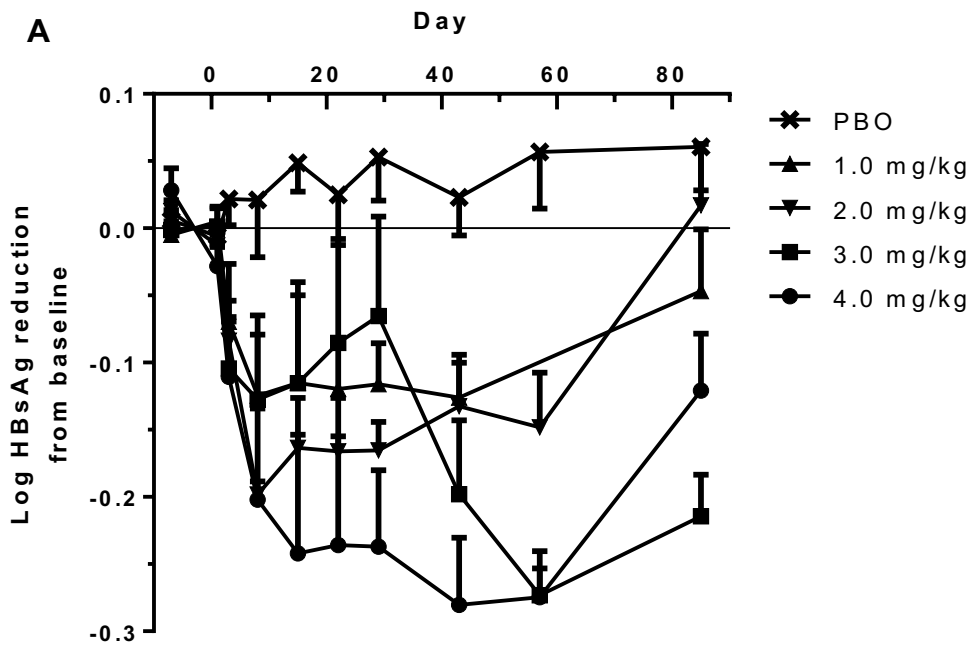
- siRNA with target sequence outside of DR1-DR2 (siHBV-i) was designed to target HBV RNA expressed from integrated HBV DNA.
- siHBV-i was administered to two HBeAg- chimps once a month for 3 months following ARC-520 therapy.
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps.

arrowhead pharmaceuticals

Heparc-2001: ARC-520 single dose virology data

- Cohorts 1-4: HBeAg negative, NUC experienced patients
  - Patients continued their NUC and received a single dose of ARC-520 on day 1

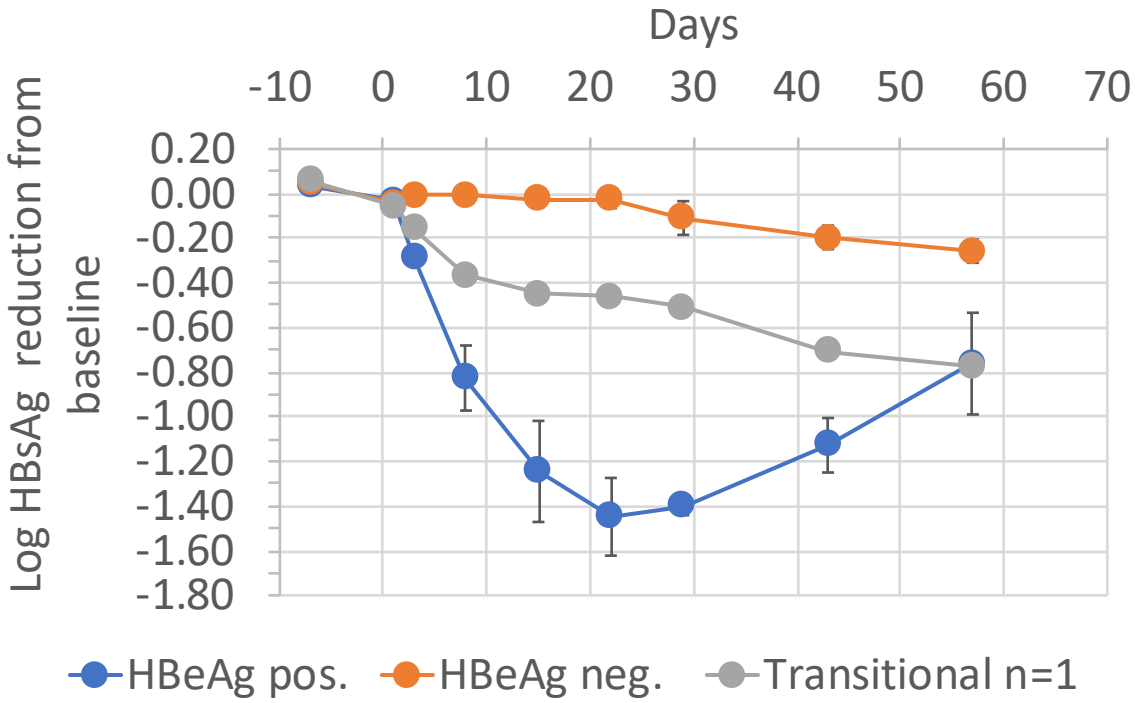
- Best response primarily limited to HBeAg+ NUC naïve patients (cohort 7)



				Log reduction from baseline Mean (max)		
Cohort	Dose [mg/kg]	HBeAg status	Prior ETV	HBsAg	HBcrAg	HBeAg
1	1	Neg	Y	-0.2 (-0.3)*	-0.2 (-0.2)	N/A
2	2	Neg	Y	-0.2 (-0.3)*	-0.5 (-0.5)	N/A
3	3	Neg	Y	-0.3 (-0.4)*	-0.4 (-0.7)	N/A
4	4	Neg	Y	-0.4 (-0.5)*	-0.9 (-1.1)	N/A
5	4	Pos	Y	-0.3 (-0.7)*	-0.9 (-1.1)	-1.2 (-1.7)
6‡	2x2	Pos	Y	-0.5 (-0.8)+	-0.7 (-1.2)	-0.7 (-1.1)
7‡,†	4	Pos	N	-1.5 (-1.9)+	-1.4 (-1.8)	-1.6 (-2.0)
7‡	4	Neg	N	-0.3 (-0.4)+	-0.7 (-0.7)	N/A

arrowhead pharmaceuticals

ARC-520 in chronic HBV patients:
Human HBsAg data reflects chimp data



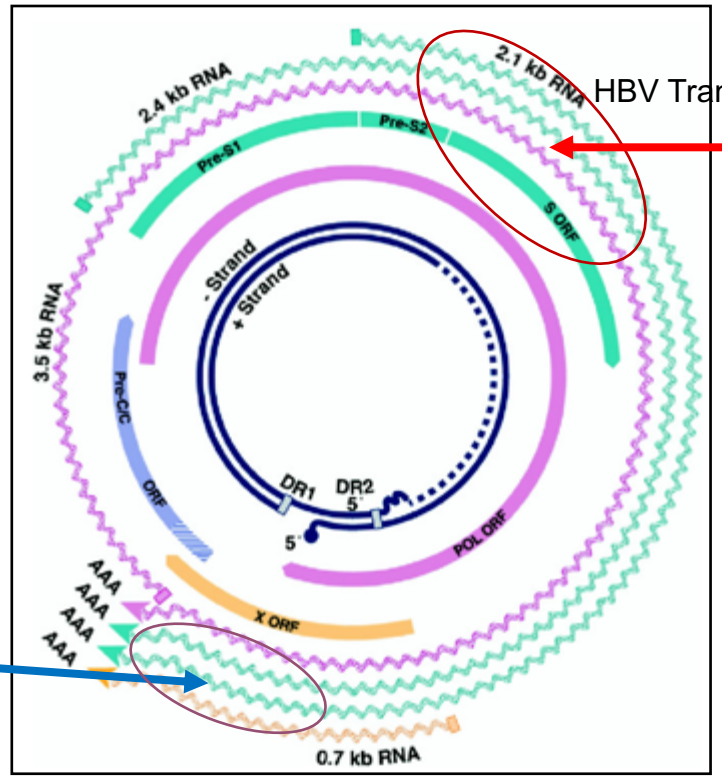
- High level knockdown of HBsAg in HBeAg positive patients
- HBeAg negative patients respond less well
- HBeAg transitional patient is intermediate

4 mg/kg ARC-520: NUC-naïve chronic HBV patients

As in chimps, HBeAg neg patients likely produce significant amounts of HBsAg from integrated DNA not targeted by ARC-520

arrowhead pharmaceuticals

2nd generation trigger combination: ARC-521



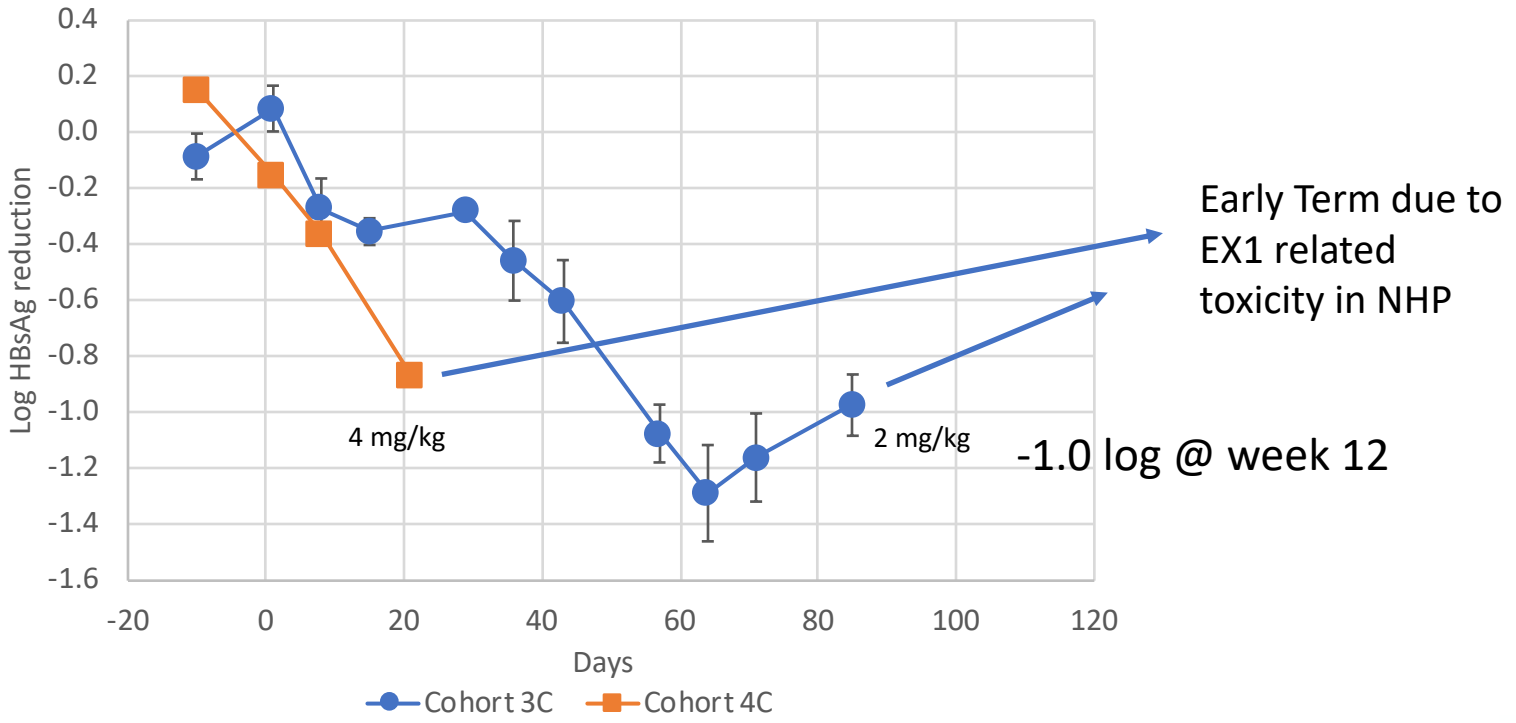
S-trigger: designed to target HBsAg from integrated source as well as other transcripts (misses HBxAg)

X-trigger: targets all cccDNA derived transcripts, Binding site near DR1

arrowhead pharmaceuticals

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

2nd Gen: ARC-521 HBsAg Reduction in HBeAg Negative, NUC Experienced Patients (Q28 day dosing X3)



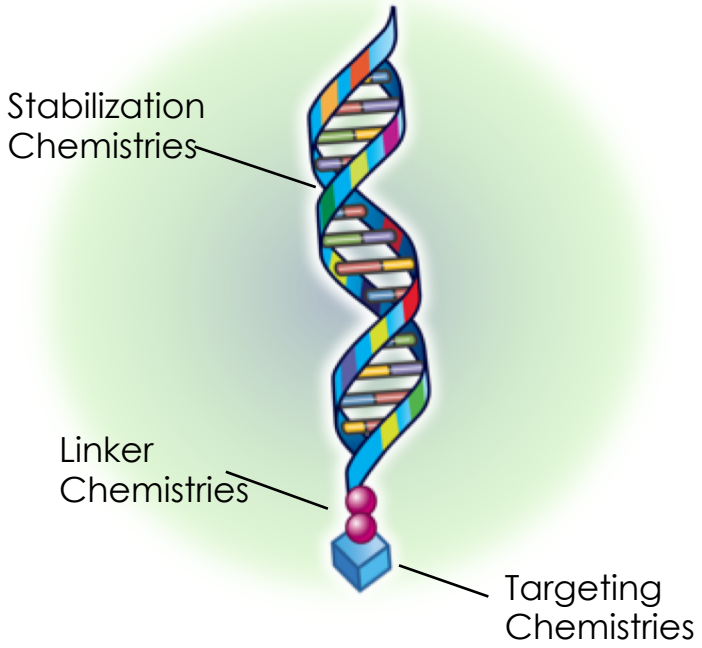
Heparc-2002: E neg NUC exp @ 2 mpk nadir HBsAg decline: -0.40 log

As anticipated, ARC-521 worked better than ARC-520 in patients with high levels of HBsAg expression from integrated HBV DNA

arrowhead pharmaceuticals

Arrowhead RNAi Platform: TRiM™

Simplicity, Specificity, and Activity



TRiM™ has rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
- Rational use and placement of modifying chemistries

Targeted RNAi Molecule

TRiM™ platform

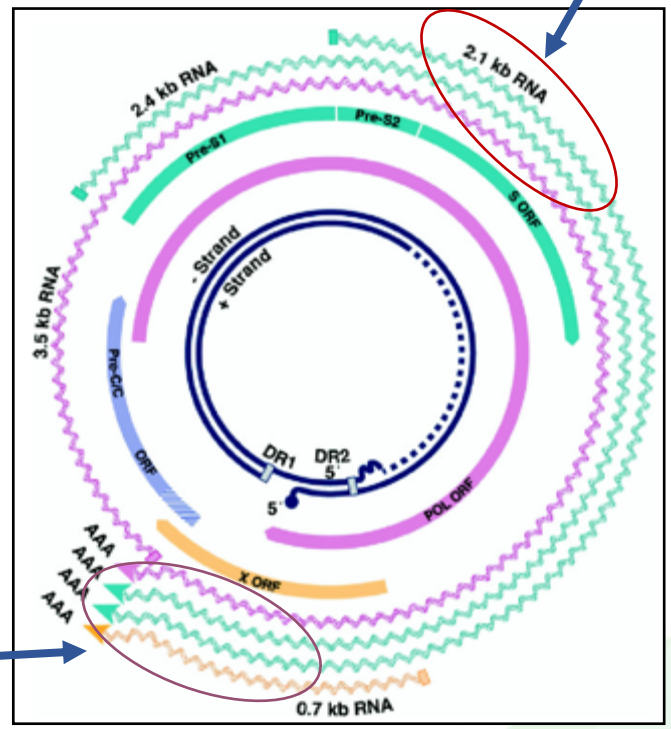
arrowhead pharmaceuticals

ARO-HBV

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- S trigger designed to bind safely in integrated region should hit all mRNA except the 0.7 kb X mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match in ~7000 HBV genomes)
  - Reduced chance of resistance
  - X antigen coverage

New S Trigger

HBV Transcript Map



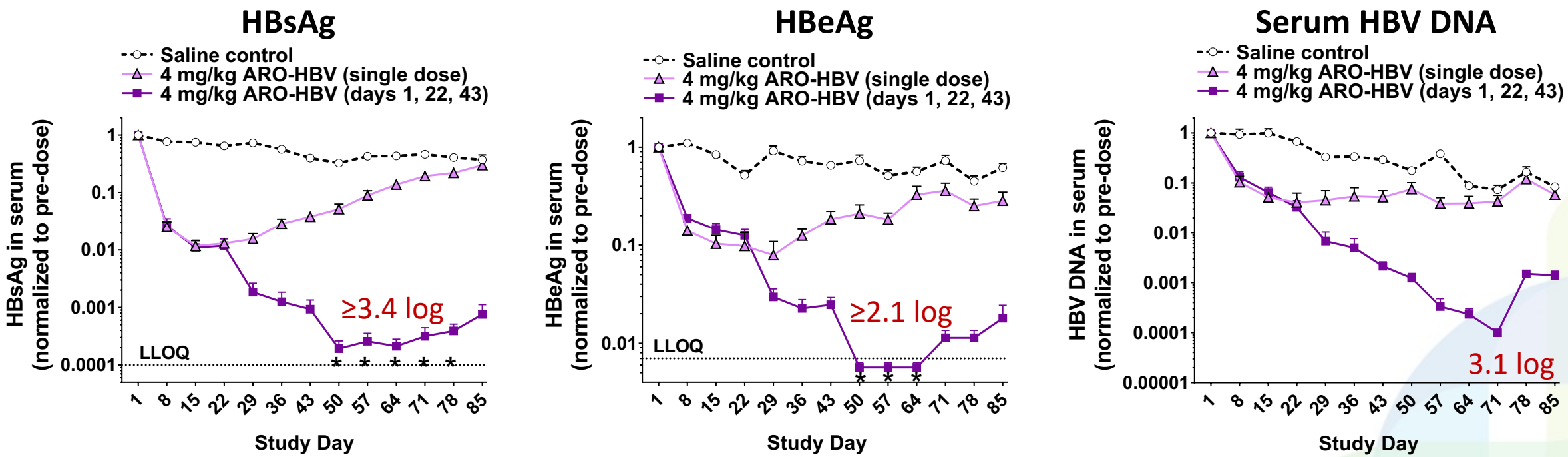
Validated X Trigger

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

arrowhead pharmaceuticals

ARO-HBV multi-dosing deeply reduced HBsAg, HBeAg and HBV DNA: 1 or 3 subcutaneous injections

HDI minicircle HBV1.3, n=6



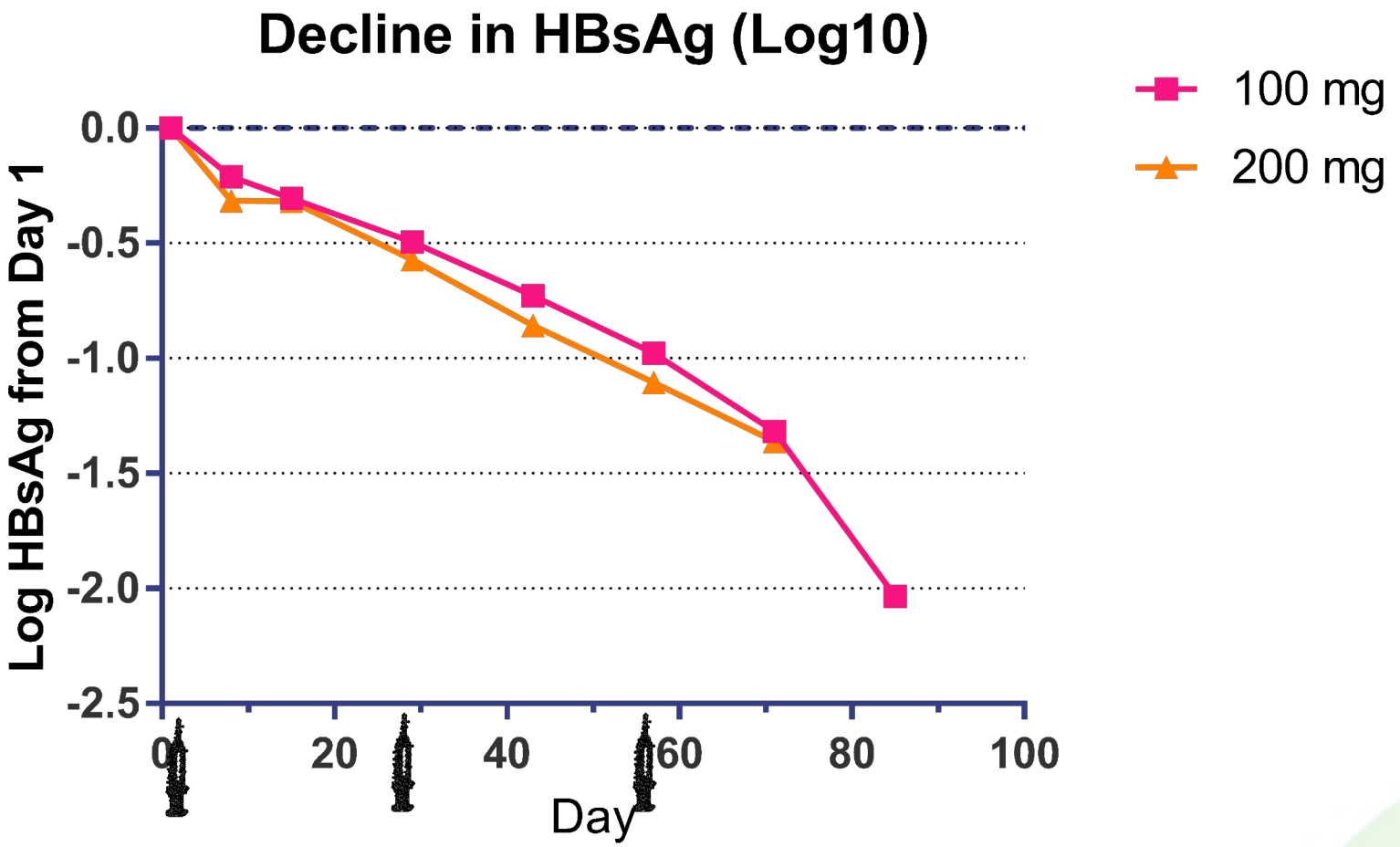
* One or more samples <LLOQ

- **Durable reduction of HBsAg, HBeAg and serum HBV DNA**
- **Increasingly reduced with each injection**

arrowhead pharmaceuticals

HBsAg Reduction with ARO-HBV After 3 monthly Doses

Includes cohorts with complete data through 14 days after 3rd dose



arrowhead pharmaceuticals

Conclusions

- siRNA targeting HBV can be administered safely
- ARC-520 demonstrated proof-of-concept for targeting HBV with siRNA and aided in optimizing siRNA as a therapeutic modality for HBV
- HBsAg from integrated DNA sources contributes meaningfully to circulating HBsAg
- ARC-521 clinical results supported our hypothesis regarding need to cover transcripts from integrated DNA
- ARO-HBV demonstrates superior potency compared to 1st and 2nd gen compounds in all HBV sub-populations (e.g. HBeAg neg/pos, NUC naïve/experienced)

Thank You