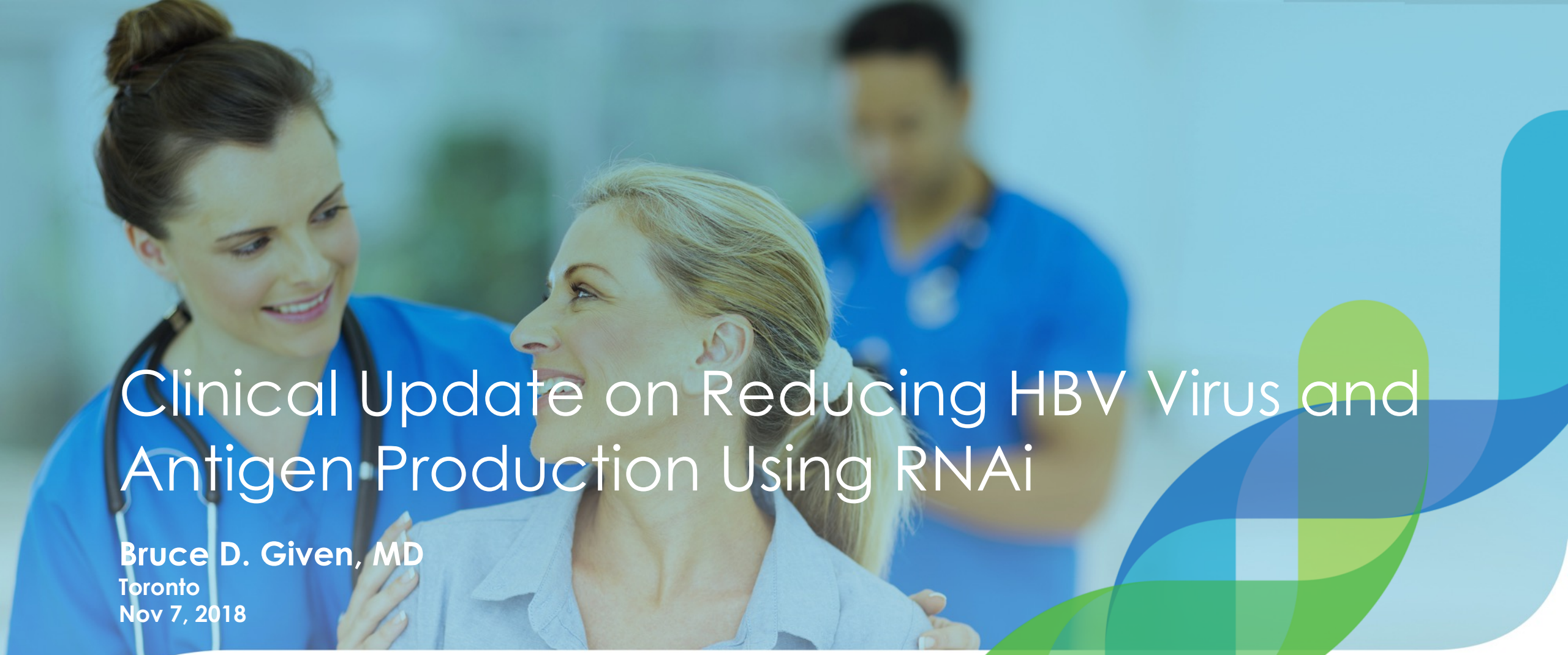


Clinical Update on Reducing HBV Virus and Antigen Production Using RNAi

Bruce D. Given, MD

Toronto
Nov 7, 2018

arrowhead pharmaceuticals

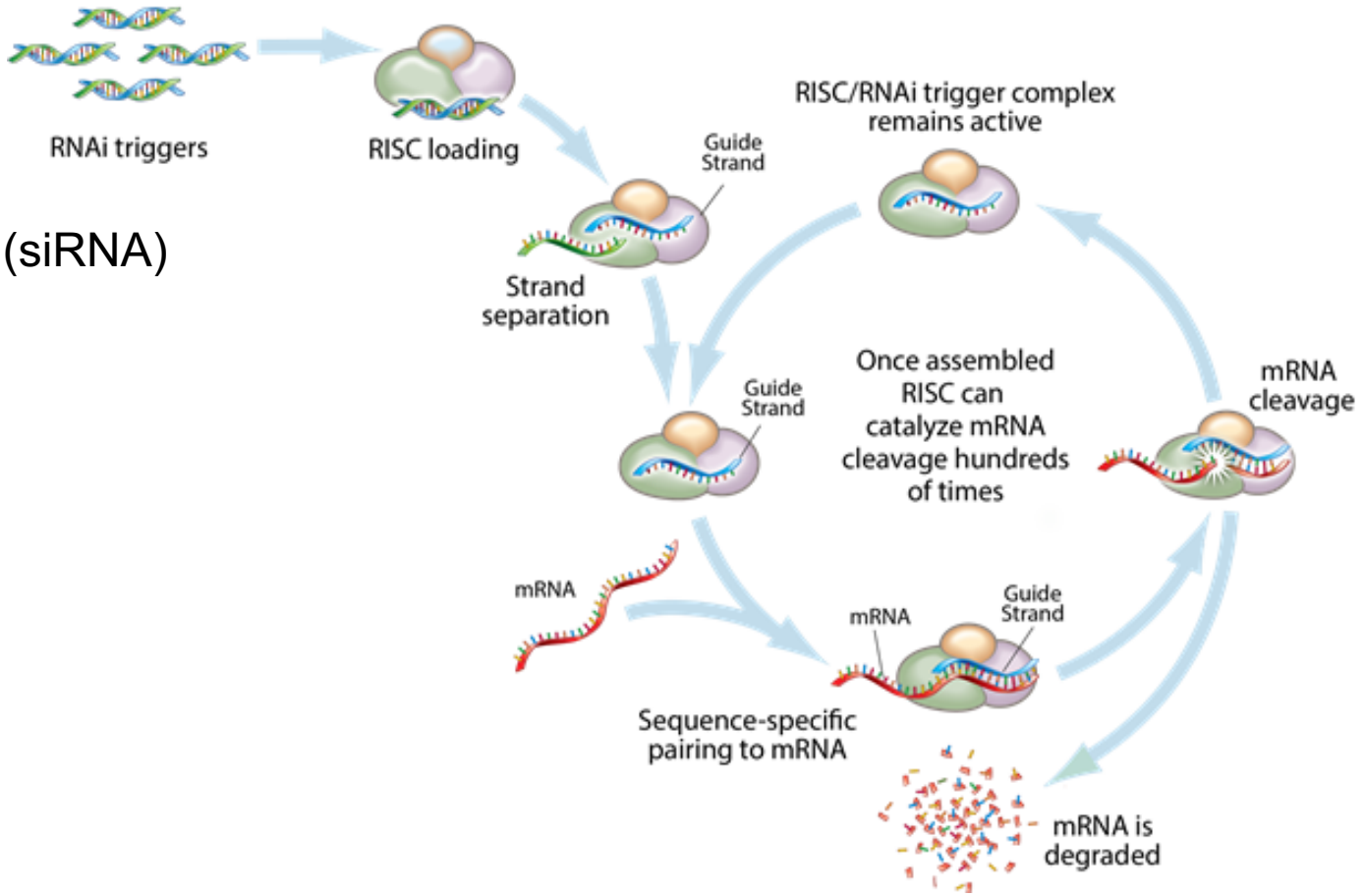
Disclosures

- Dr. Given is an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

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.

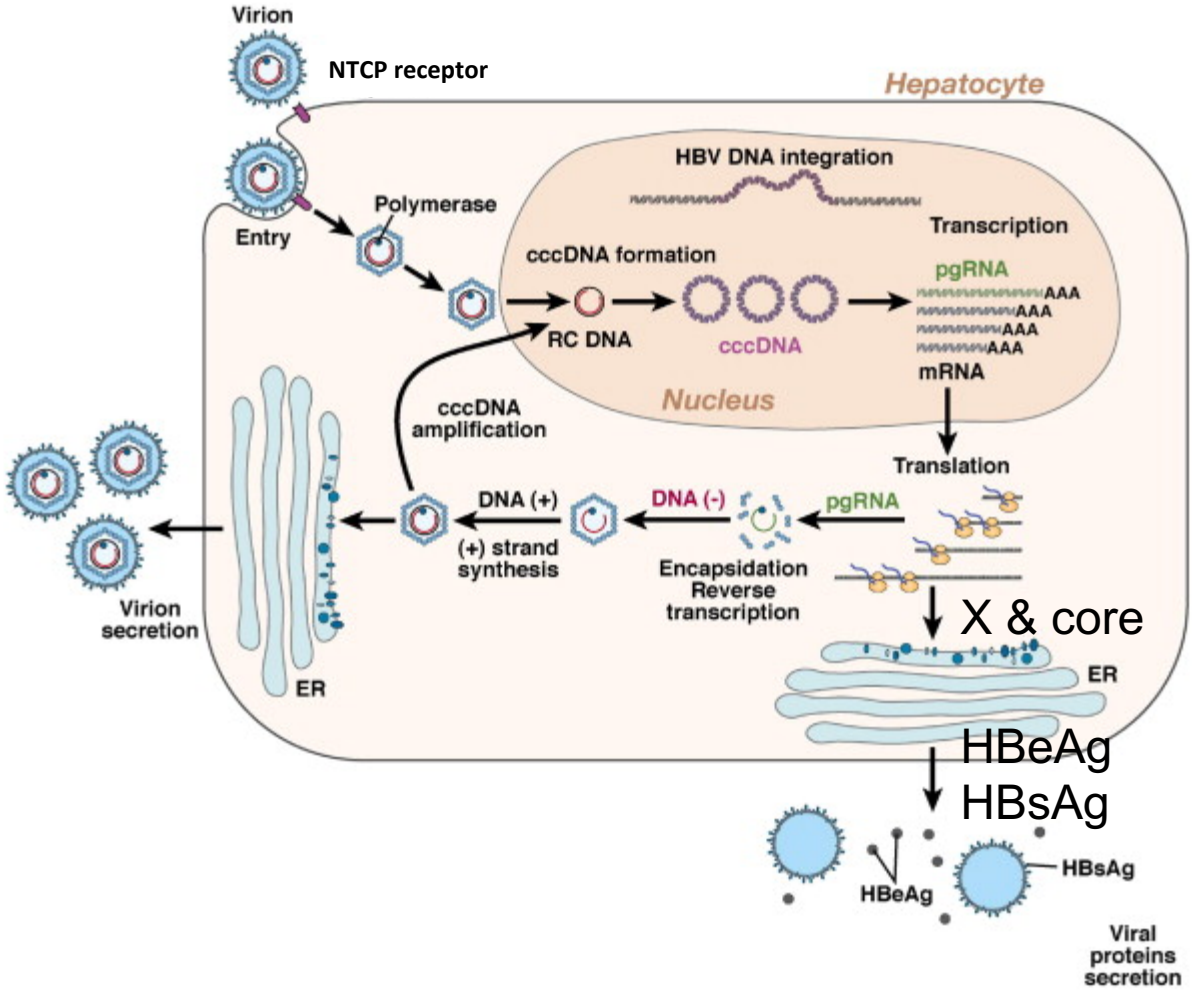
RNAi: Target the Gene Silence the Disease



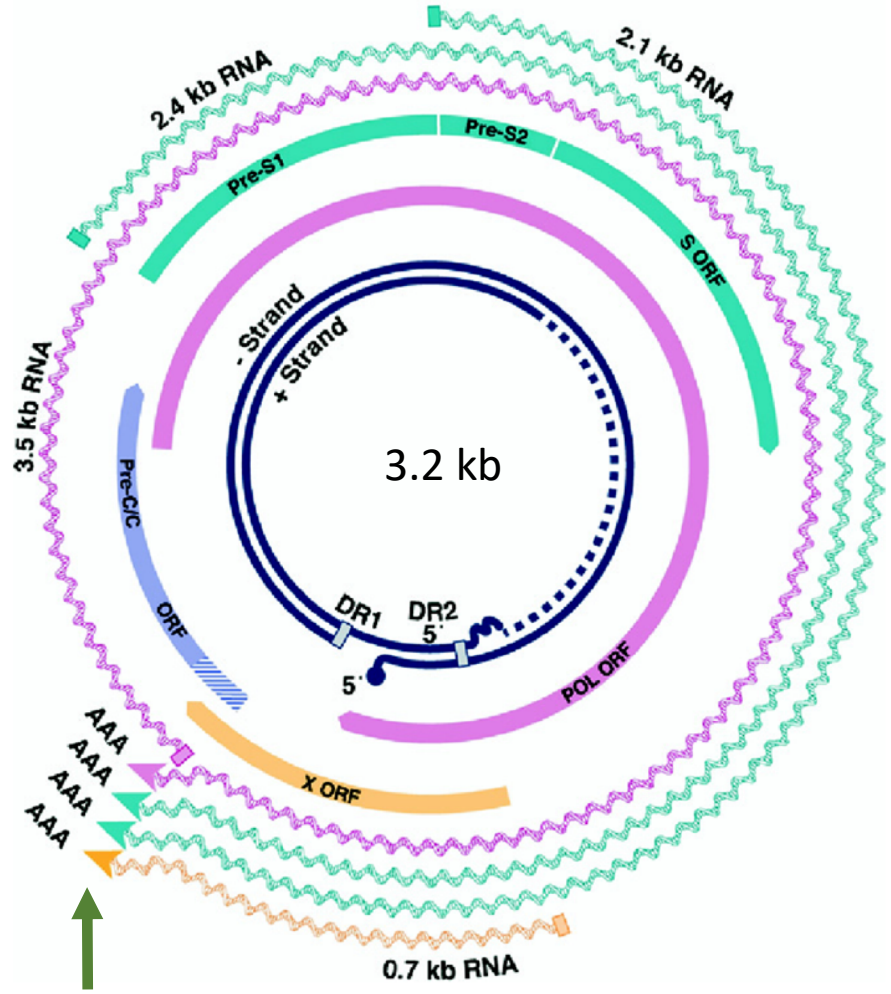
Therapeutic gene silencing with **RNA interference** is highly precise and efficient

arrowhead pharmaceuticals

A Very Simplified View of the HBV Lifecycle



Organization of the HBV Genome Makes it Ideal for RNAi



Same polyadenylation signal for all mRNAs

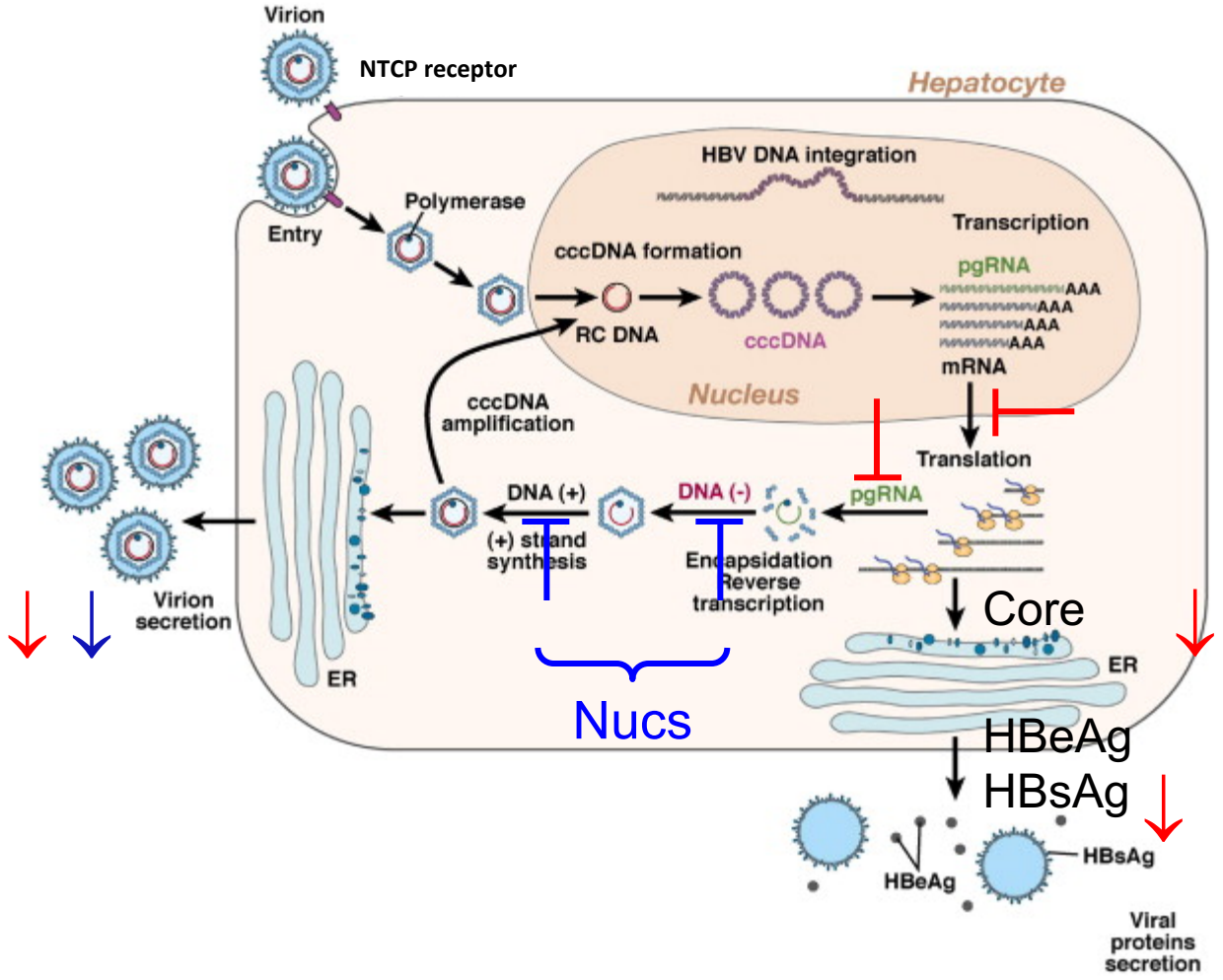
- **5 viral mRNAs**
  - 3.5 kb pre-genomic RNA
  - 3.5 kb pre-core mRNA
  - 2.4 kb pre-S1 mRNA
  - 2.1 kb pre-S2/S mRNA
  - 0.7 kb X mRNA
- **7 major proteins**
  - Polymerase (with reverse transcriptase function)
  - Core (HBcAg), forms capsid
  - e antigen (HBeAg), also called pre-core, a secreted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

arrowhead pharmaceuticals

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

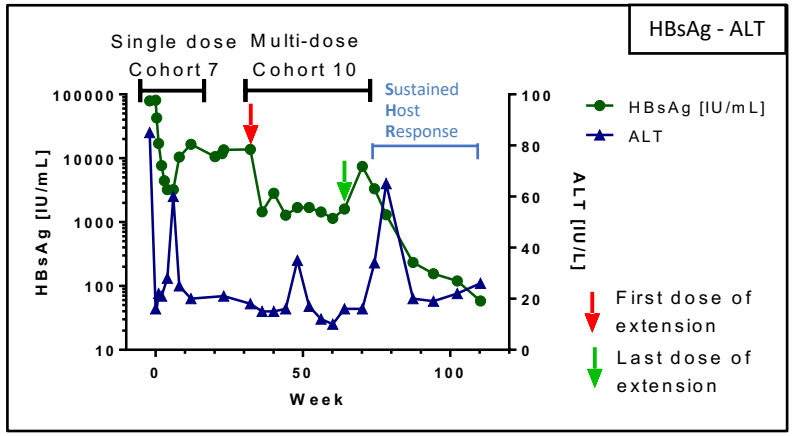
RNAi Therapeutics to Reduce HBV Viral RNAs

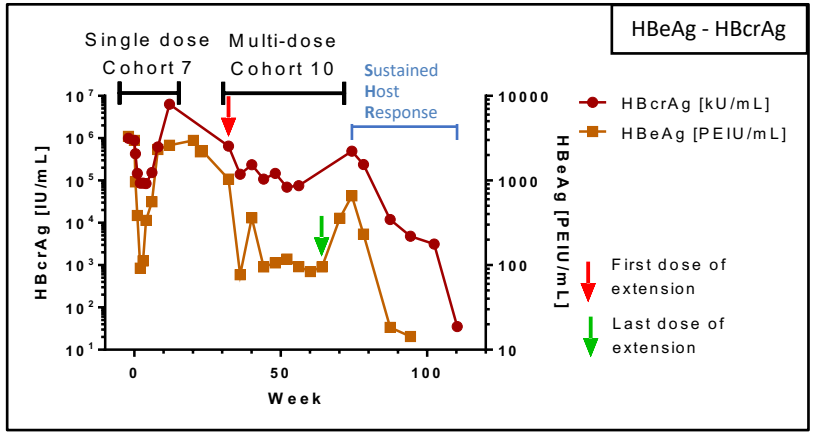
Differentiation from nucleos(t)ide reverse transcriptase inhibitors

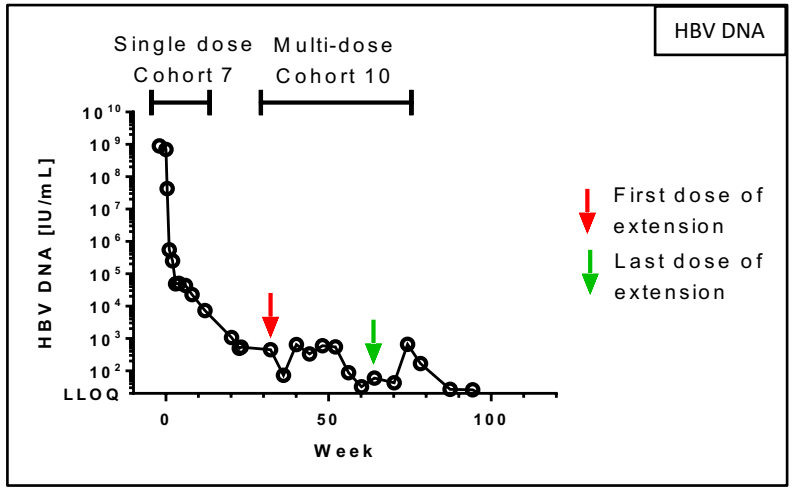


siRNA

RNAi Can Reduce all cccDNA-derived Viral Antigens



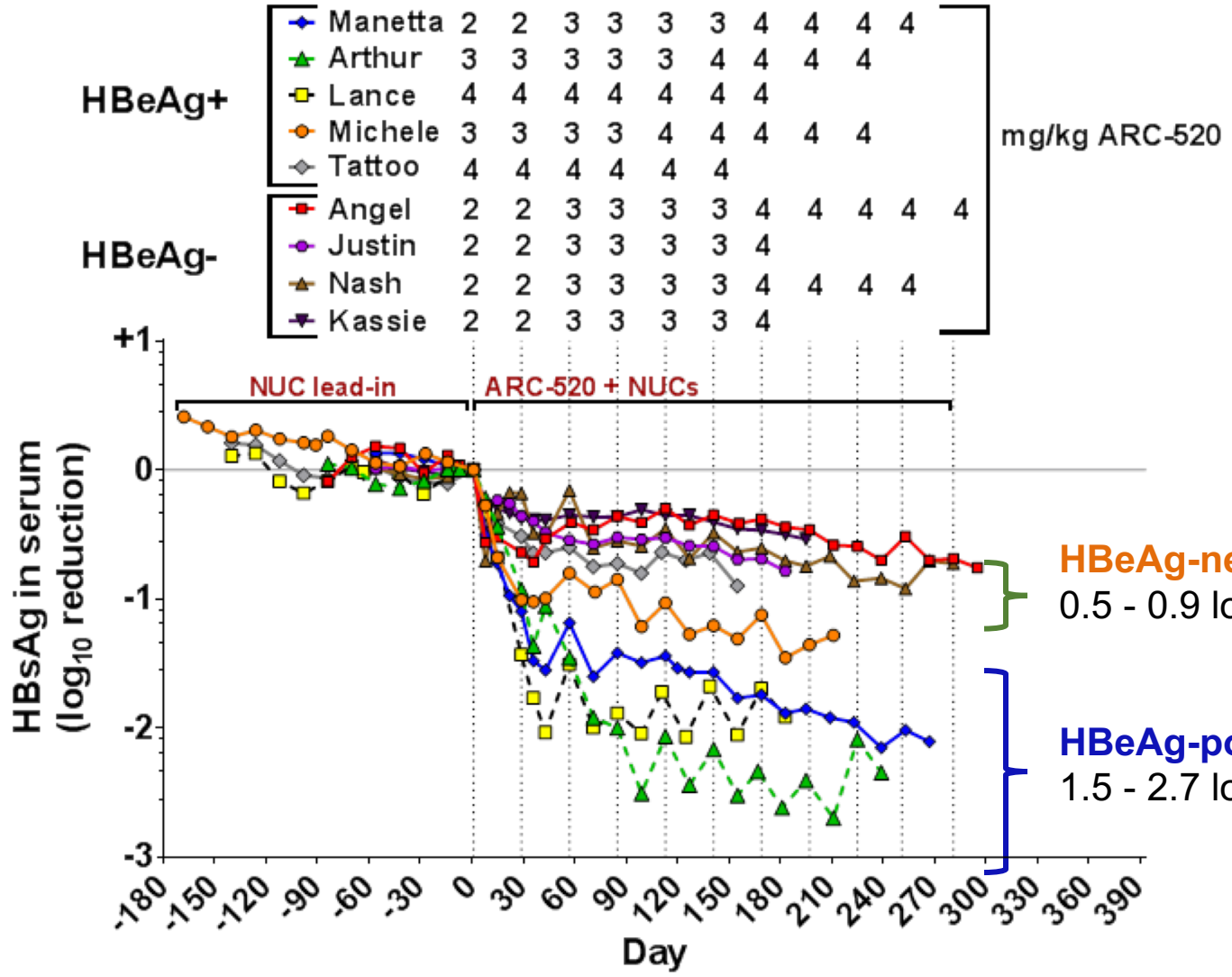




Patient 01-7982

- **Synergistic effect with NUCs on DNA**
- **Contemporaneous reductions in HBeAg, HBcrAg, HBV RNA (not shown here)**

Differences in Degree of HBsAg Reduction Correlated with HBeAg Status in Chimpanzees



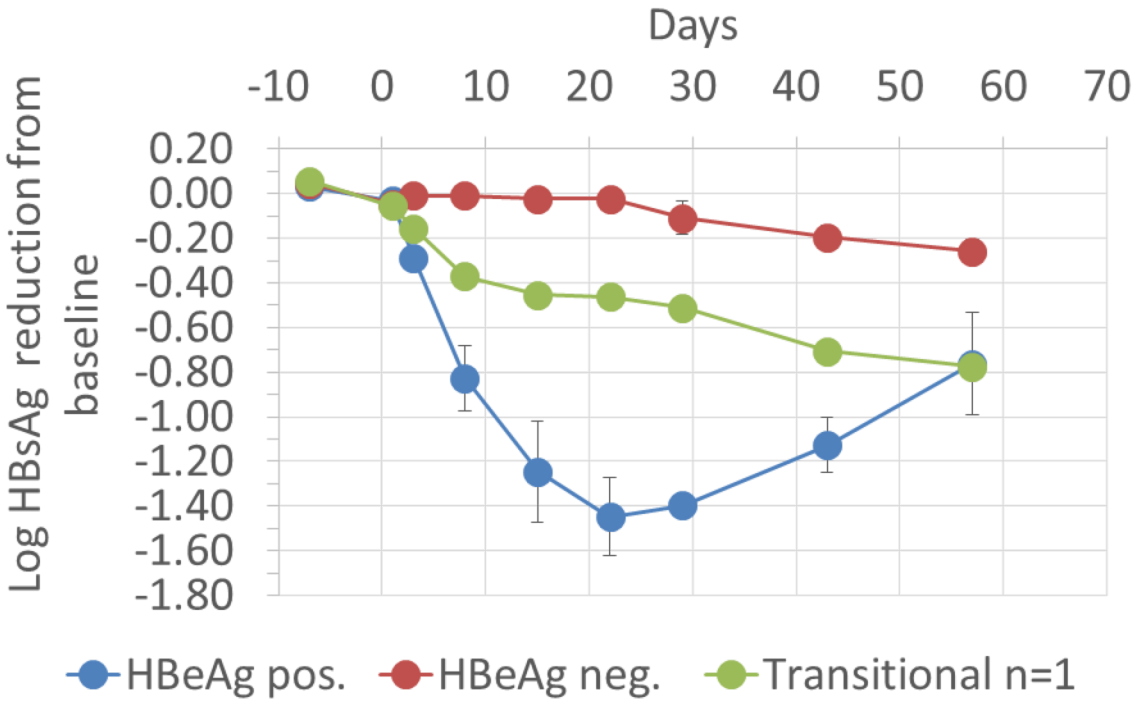
HBeAg-negative
0.5 - 0.9 log_{10} reduction at nadir

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

arrowhead pharmaceuticals

ARC-520 in Treatment-naïve Chronic HBV Patients:

Human HBsAg data reflects chimp data



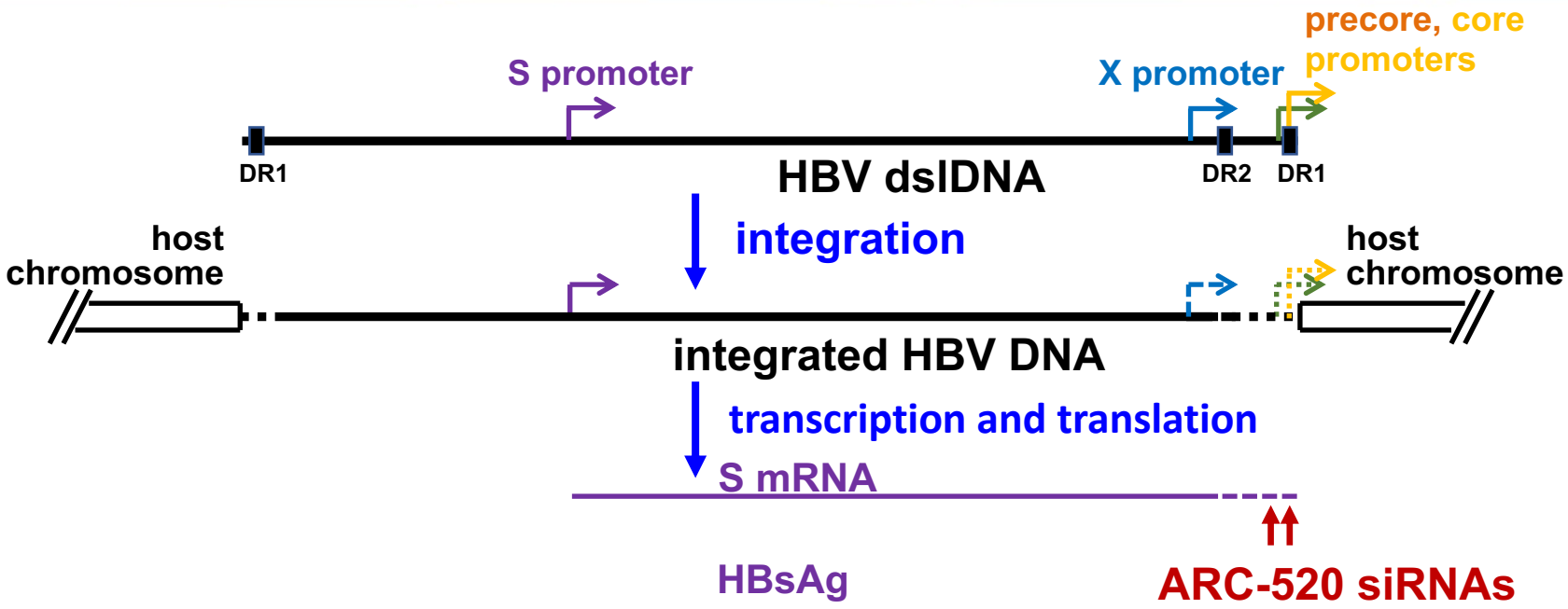
4 mg/kg ARC-520: NUC-naïve chronic HBV patients

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

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

arrowhead pharmaceuticals

HBV Integration Into the Host Genome Becomes Crucial



1. HBV DNA integrates into host chromosome, during which regions between DR2 and DR1 can be randomly deleted (not new!)

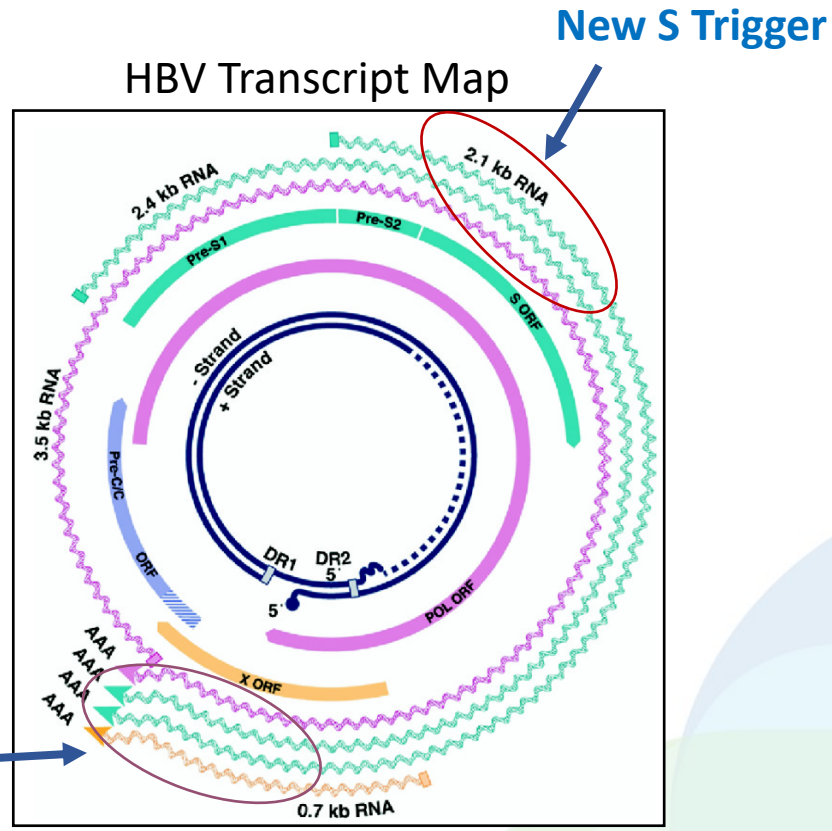
2. Significant HBsAg mRNA can be produced from integrated HBV DNA
   - These S transcripts contain complete HBsAg CDS
   - Expected loss of ARC-520 target sites in many

ARO-HBV: Key Design Elements

- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- **Addresses full HBV transcriptome**
  - **Works for cccDNA *and* integrated-derived transcripts**
- Multiple triggers to avoid resistance development
- Powerful HBsAg reduction
- Wide therapeutic index
- Efficacy and safety in HBV patients

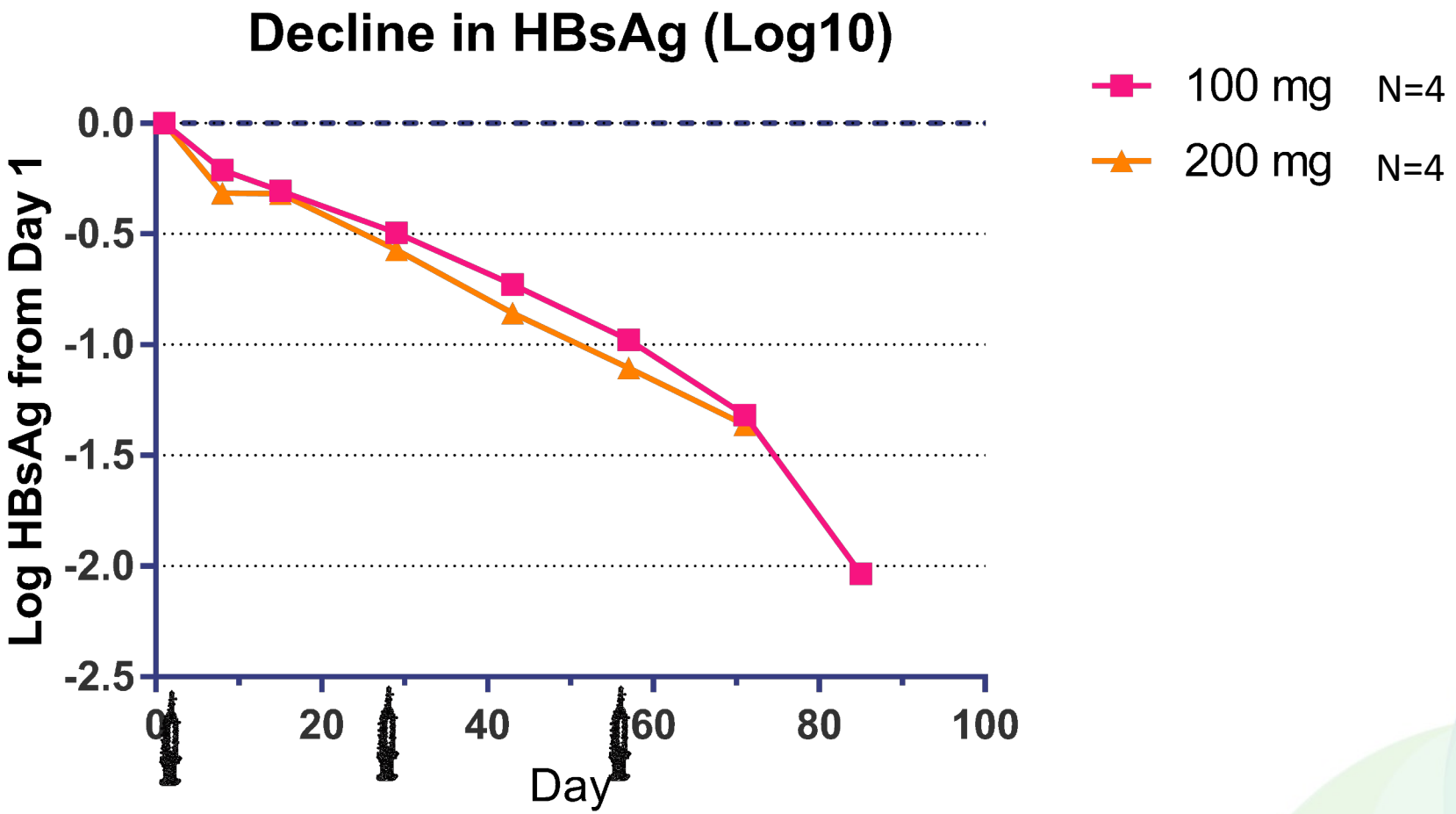
Importance of Integrated HBV DNA as S mRNA Source has Changed RNAi Strategy

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match of 17mer in ~7000 HBV genomes)
  - Reduce chance of resistance



HBsAg Reduction with ARO-HBV After 3 monthly Doses

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



See AASLD late-breaker poster Nov 12, 2018 for expanded and updated data

CHB patient AE Table

AEs in >1 subject (data cut 8/24/2018)

AROHBV1001 HBV Patients	**Cohort 2b, 100mg X3 Q28 days**	**Cohort 3b, 200mg X3 Q28 days**	**Cohort 4b, 300mg X3 Q28 days**	**Cohort 5b, 400mg X3 Q28 days**	**Cohort 6, 100mg X3, Q2 wk**	**Cohort 7, 100mg X3 weekly**	**Cohort 8, e+ 300mg X3 Q28 day**	**Cohort 9, e+ 300mg X3 Q28 day**	**Cohort 10, 200mg X3 weekly**	**Cohort 11, 300mg X3 weekly**	**Total AEs**
AE Reported Terms	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	
Insect bites ankles, Flea bites on neck	1		1								2
Upper respiratory tract infection, Sore throat, Laryngitis, Dry cough	1		1		3	1			1		7
Erythema around injection sites, Injection site redness, Haematoma at injection site, Injection Site Bruise			1	2		2	1			1	7
Facial acne, acne							2				2
Headache, headache – intermittent			1			2					3
Raised Creatine kinase			1				1				2
TOTALS	**2**	**0**	**5**	**2**	**3**	**5**	**4**	**0**	**1**	**1**	**23**

Interim AROHBV1001 Findings as Reported Sept 2018

Update with Late Breaker AASLD Poster Nov 12, 2018

- Activity demonstrated in all patient types (HBeAg pos/neg, NUC naïve/treated)
- Response appeared to be independent of starting HBsAg levels
- ARO-HBV appeared to be generally well-tolerated as of the data cutoff (August 24, 2018)
  - Injection site reactions were observed in approximately 10% of injections

Acknowledgements

Patients and Heathy Volunteers

Investigators:
- Ed Gane
- MF Yuen
- William Sievert
- Alexander Thompson
- Wendy Cheng
- TH Lim
- Simone Strasser
- Christian Schwabe

Clinical Advisory Board:
- Robert Gish
- Stephen Locarnini
- Carlo Ferrari
- CL Lai

Assay Assistance
- Gavin Cloherty
- Danny Wong
- Kathy Jackson
- Icon Labs

CRO:
- Novotech