Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

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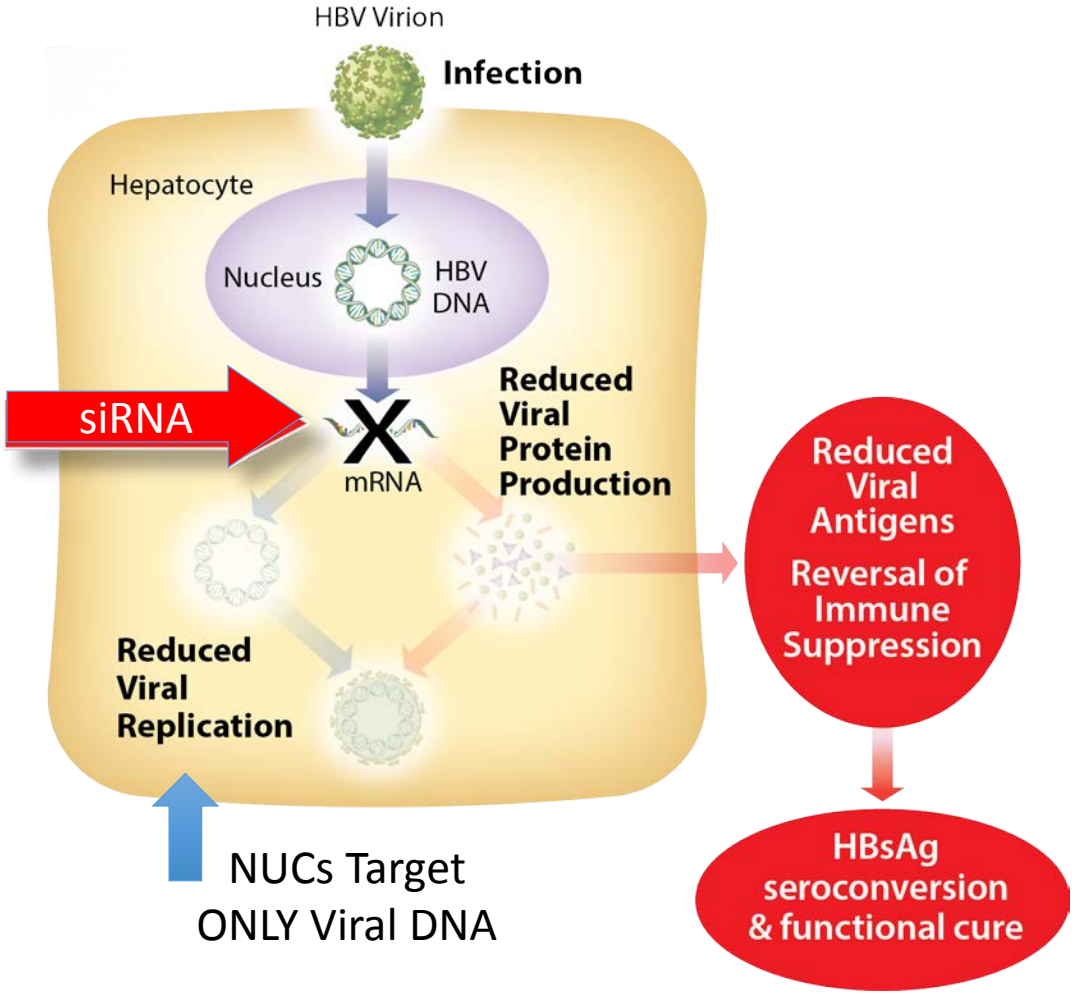
Simplified theory of an HBV RNAi therapeutic



Silence Entire HBV Genome

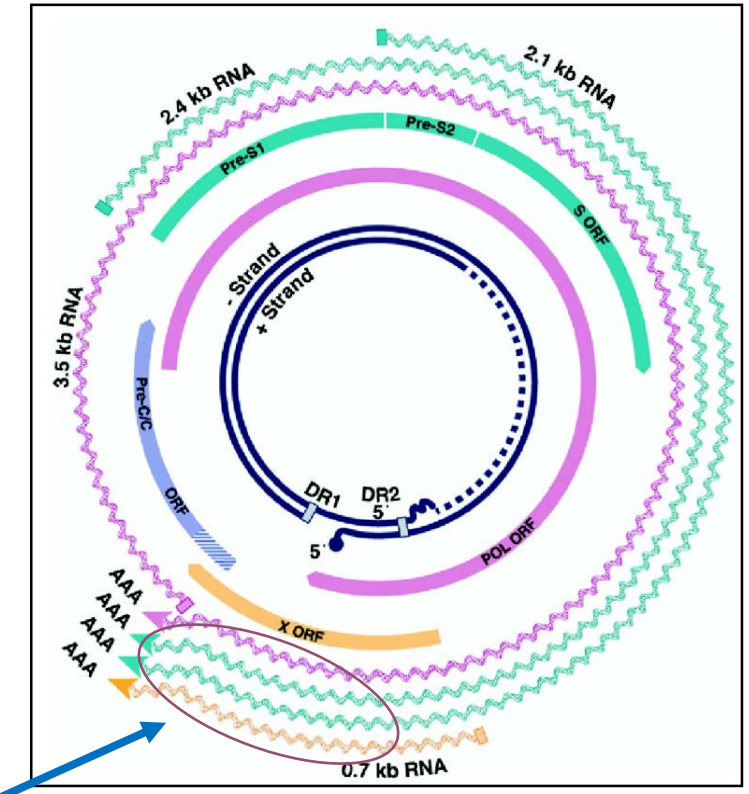
1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - Silencing all antigens and pgRNA could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

Arrowhead's 1st generation RNAi therapeutic ARC-520

- All HBV transcripts from cccDNA overlap at the 3' end and terminate with the same polyadenylation signal
- A single siRNA targeting this common X region can reduce all cccDNA-derived transcripts
- ARC-520 contained 2 RNAi triggers in the X region (greater genotype coverage, reduce possibility of resistance) plus an endosome escape agent EX1
- ARC-520 well tolerated in humans, but EX1 caused findings in toxicology study: ARC-520 withdrawn
- Learnings from 1st in human HBV RNAi therapy: Some patients did respond with sustained host control of HBV

See Poster FRI-362 for patient update

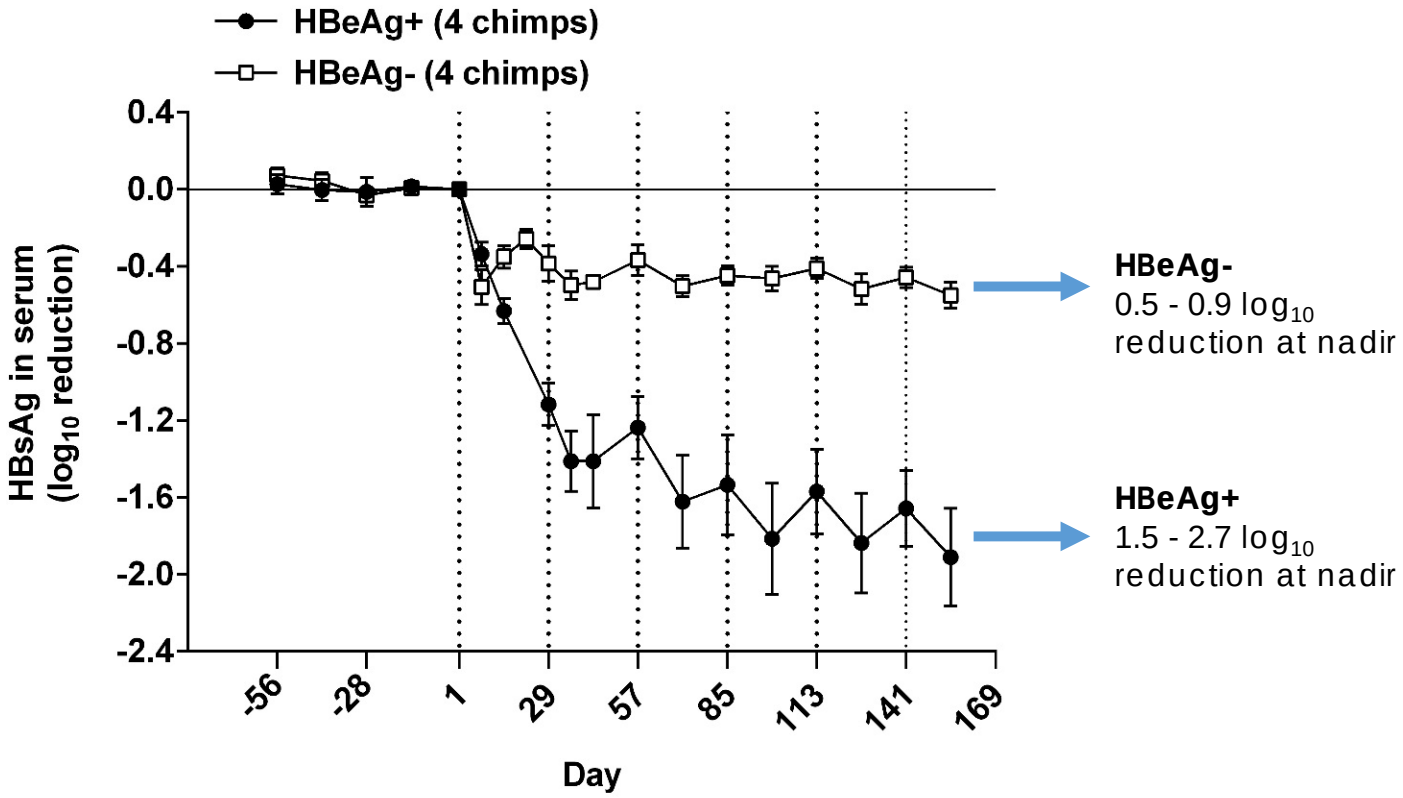
HBV Transcript Map



X region

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

Differential HBsAg reduction observed in chimpanzees with ARC-520

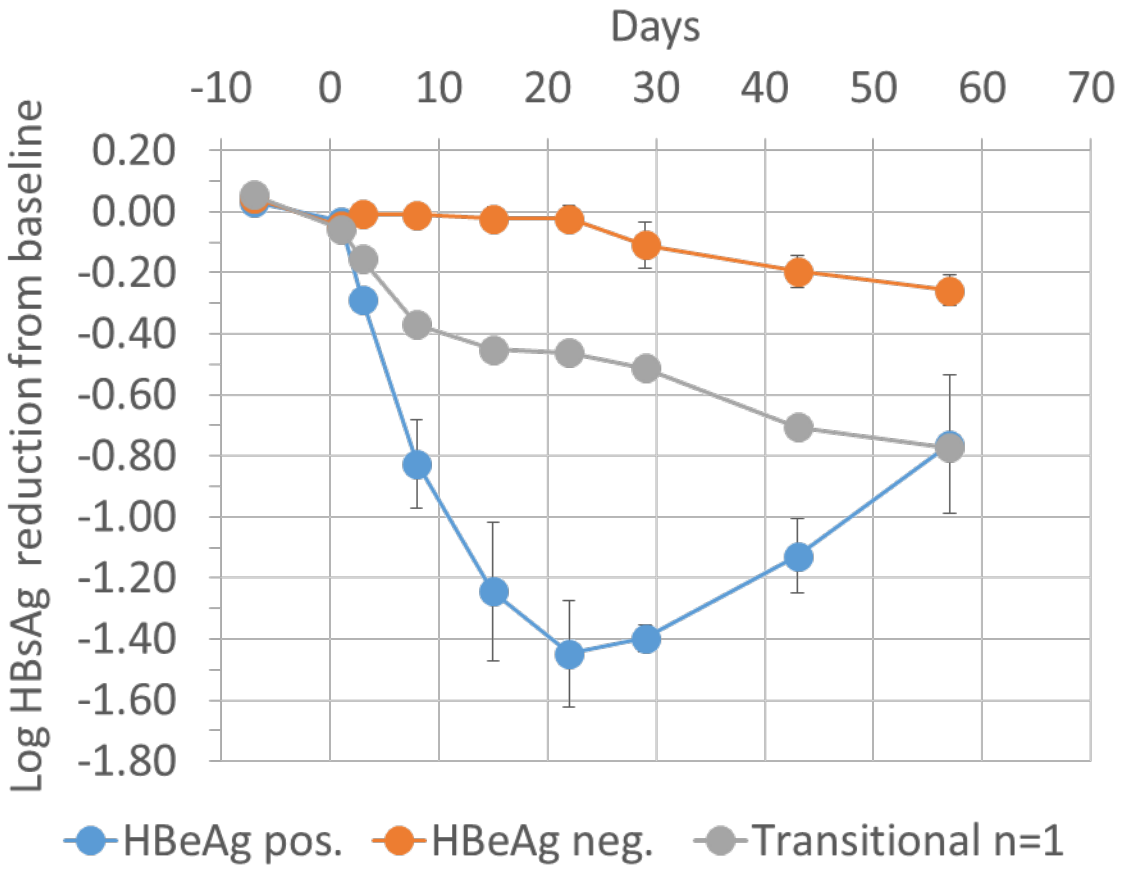


C. I. Wooddell*, M.-F. Yuen*, H. L-Y. Chan, R. G. Gish, S. A. Locarnini, D. Chavez, C. Ferrari, B. D. Given, J. Hamilton, S. B. Kanner, C.-L. Lai, J. YN Lau, T. Schluep, Z. Xu, R. E. Lanford, and D. L. Lewis (2017) Science Translational Medicine (27 Sept)

HBeAg positive responded better than HBeAg negative chimps

Differential response in HBeAg-positive vs. HBeAg-negative patients

Treatment naïve chronic HBV

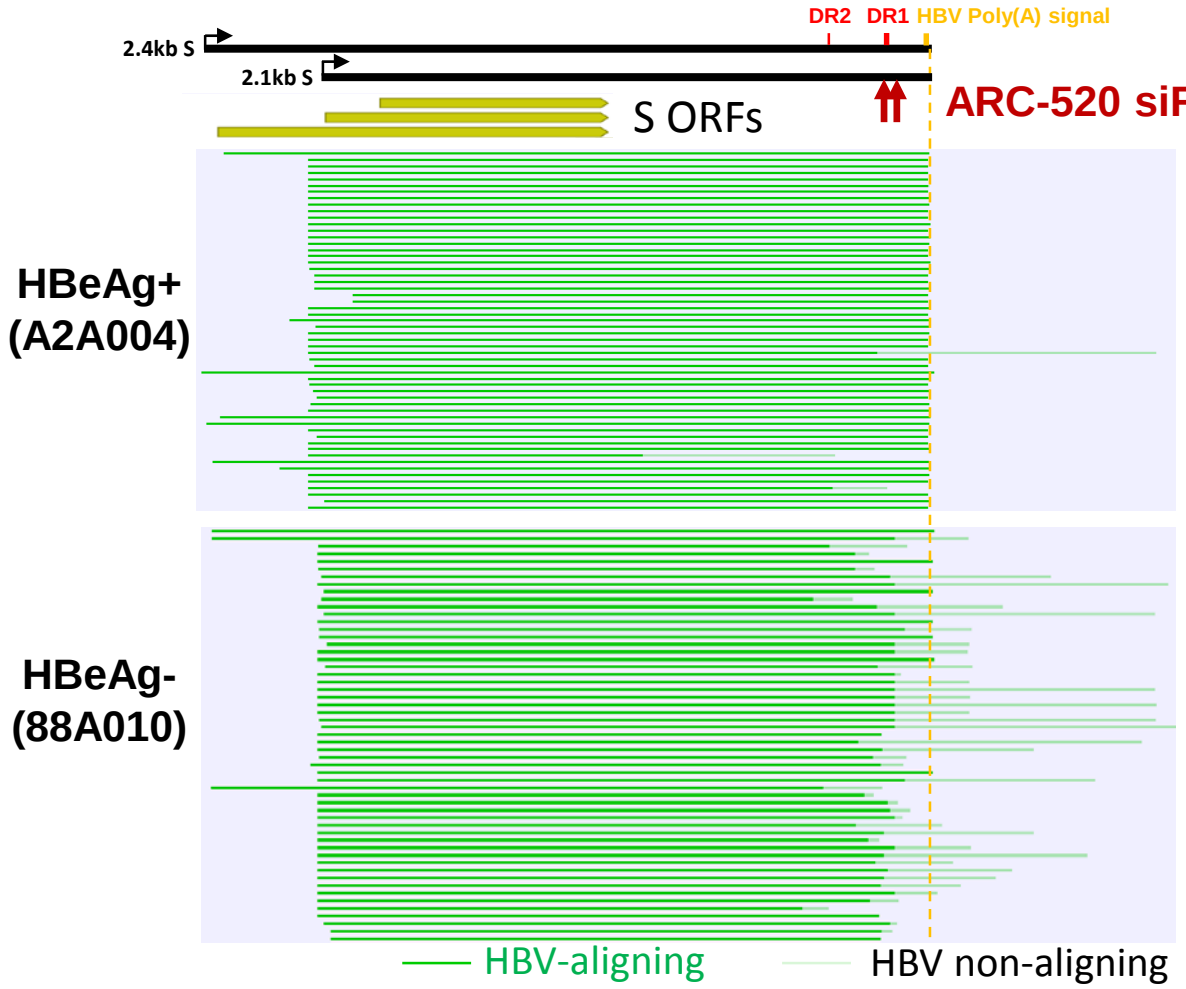


- Deep knockdown of HBsAg in HBeAg-positive patients after a single dose
- HBeAg-negative patients had much less response

Wooddell, Yuen et al, Sci Trans Med 2017

Most HBsAg in HBeAg-negative chimps produced from integrated HBV

PacBio Single Molecule Real-Time (SMRT) Sequencing



HBeAg+

- **Most S transcripts terminate near HBV poly(A) signal as expected**

HBeAg-

- **Majority of S transcripts are fused at the 3' end to chimp sequence**
- **Fusion points typically between DR2 and DR1. Expected if transcripts arose from integrated HBV dslDNA**

Many S transcripts in HBeAg-neg. chimps lacked target sites for ARC-520

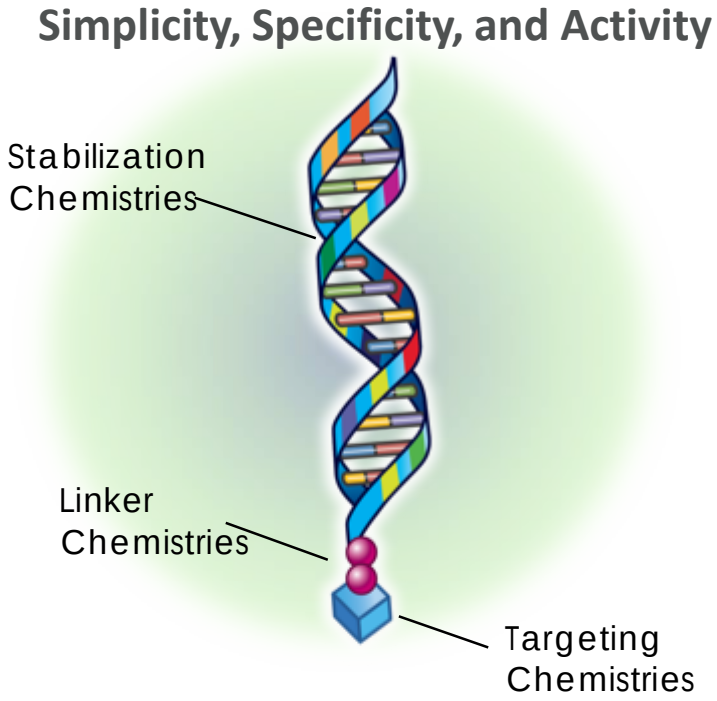
Wooddell*, Yuen* et al. (2017) Sci Transl Med

ARO-HBV: Key Design Elements for the Next Generation

The Wish List:

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

Arrowhead RNAi Platform: TRiM™



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

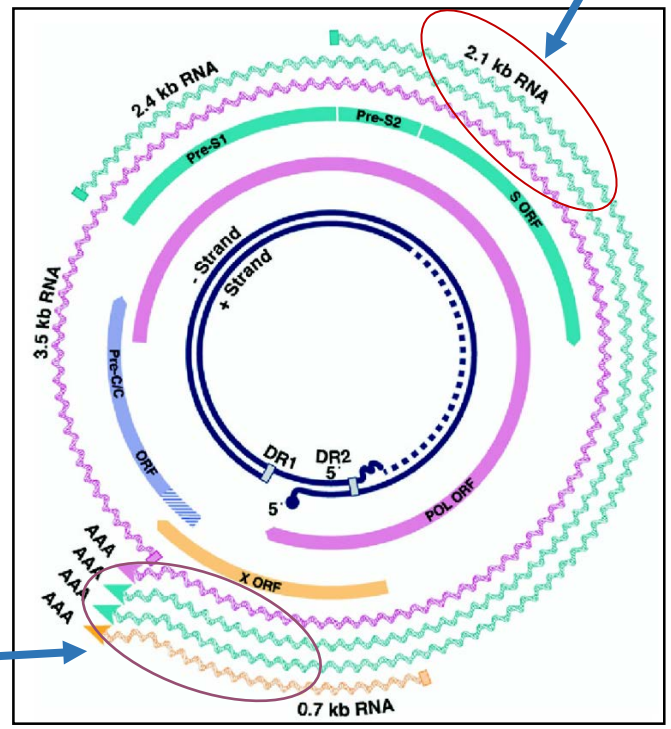
TRiM™ platform

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

New S Trigger

HBV Transcript Map

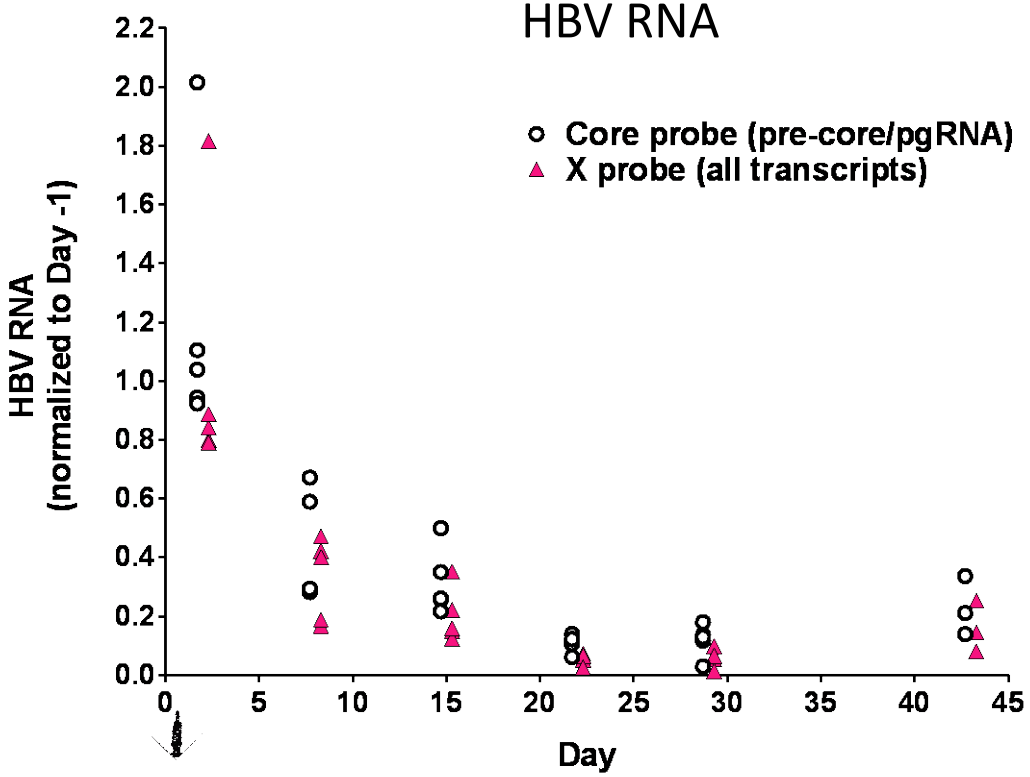


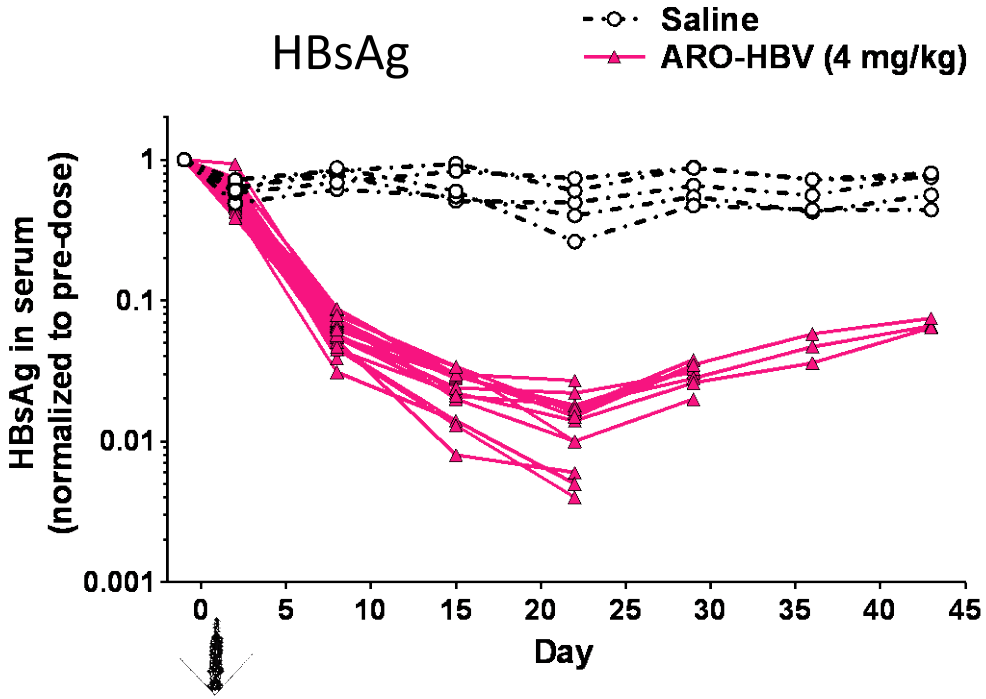
Validated X Trigger

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

ARO-HBV reduces all HBV transcripts

Hydrodynamically injected (HDI) minicircle HBV1.3 in NOD-SCID mice





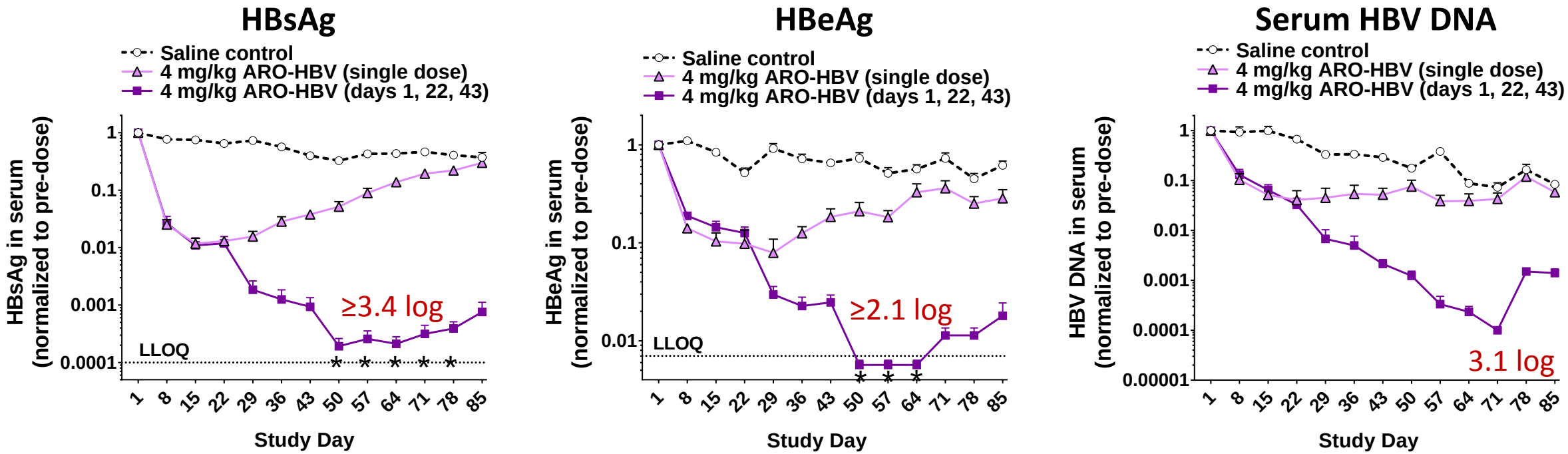
HBV RNA Knockdown from 4 mg/kg ARO-HBV on Day 22 Nadir	
Core probe (pre-core/pgRNA)	90%
X probe (all HBV transcripts)	95%

- **All HBV transcripts deeply reduced (≥90%) at Day 22 nadir**
- **S transcripts more deeply reduced than pre-core/pgRNA**

ARO-HBV multi-dosing deeply reduced HBsAg, HBeAg and HBV DNA

1 or 3 subcutaneous injections

HDI minicircle HBV1.3, n=6

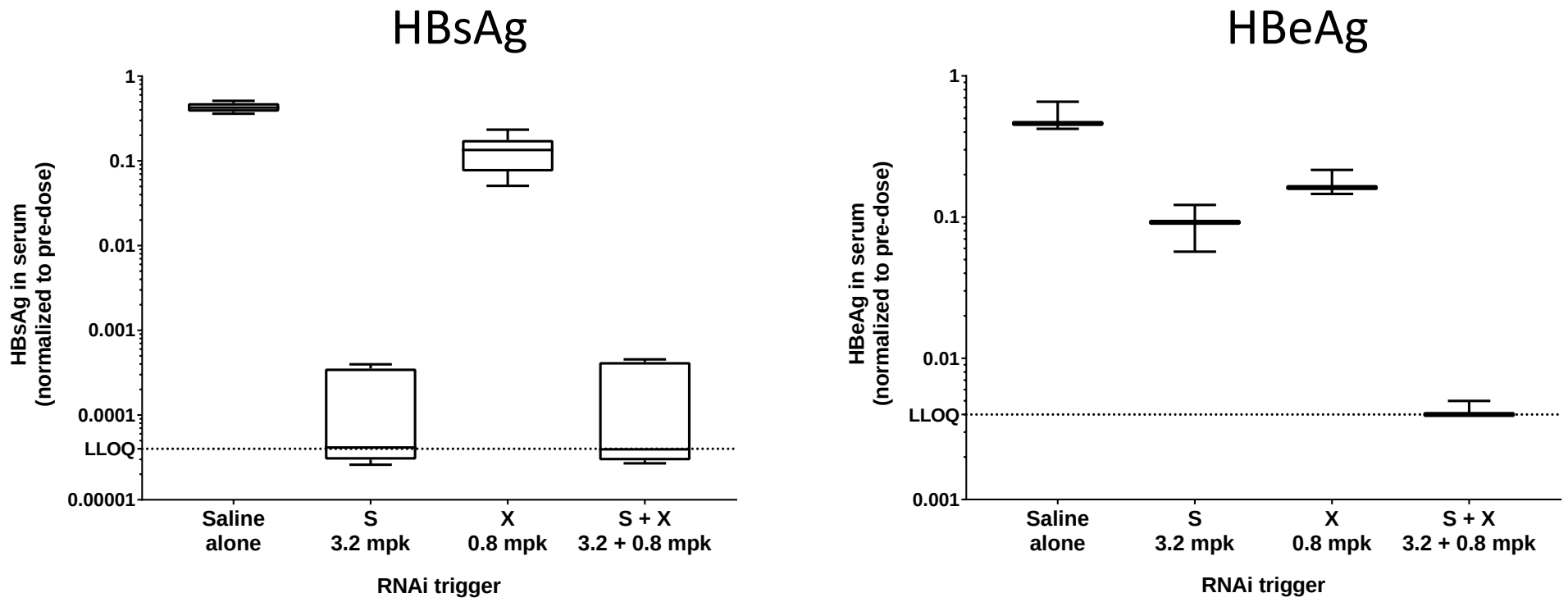


* One or more samples <LLOQ

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

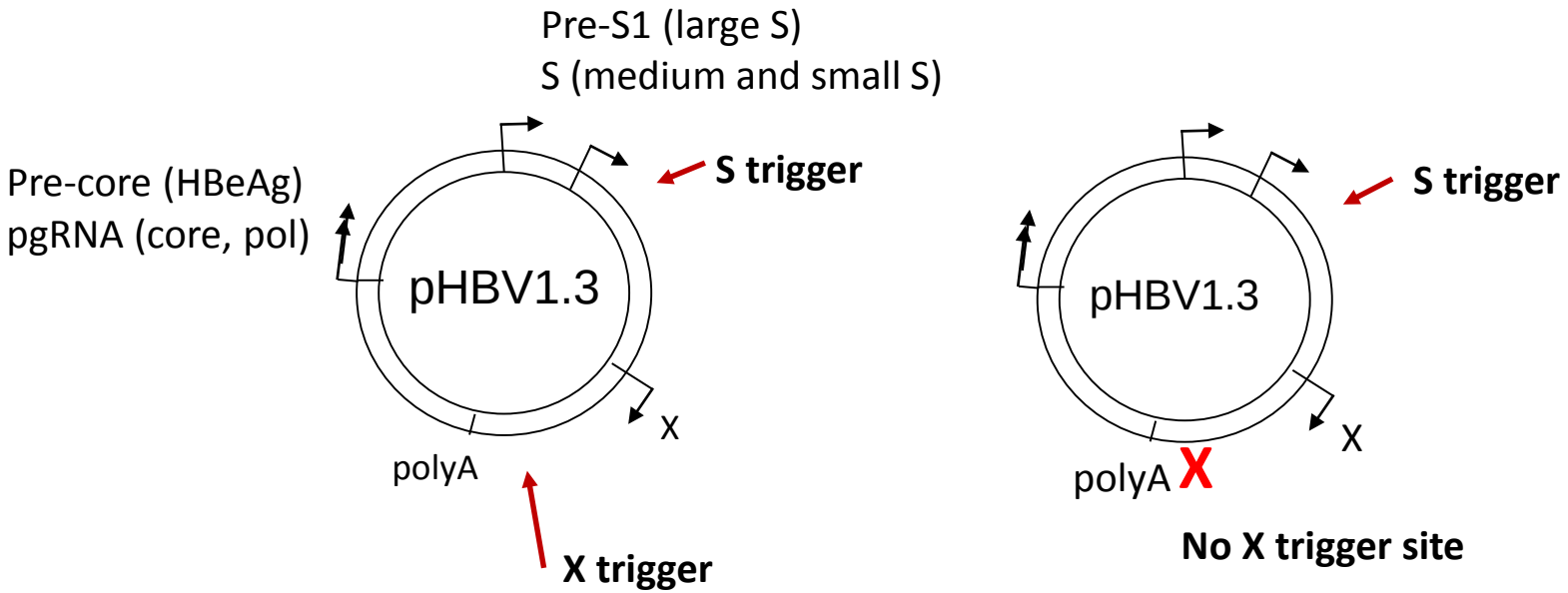
Addition of X trigger has differential effect on HBsAg vs HBeAg

HDI minicircle HBV1.3 (n=6), 3 x Q3W doses, Day 57 evaluation



- **S trigger alone effectively reduces HBsAg but not as effective for HBeAg**
- **Addition of small amount X trigger resulted in significantly greater HBeAg reduction**

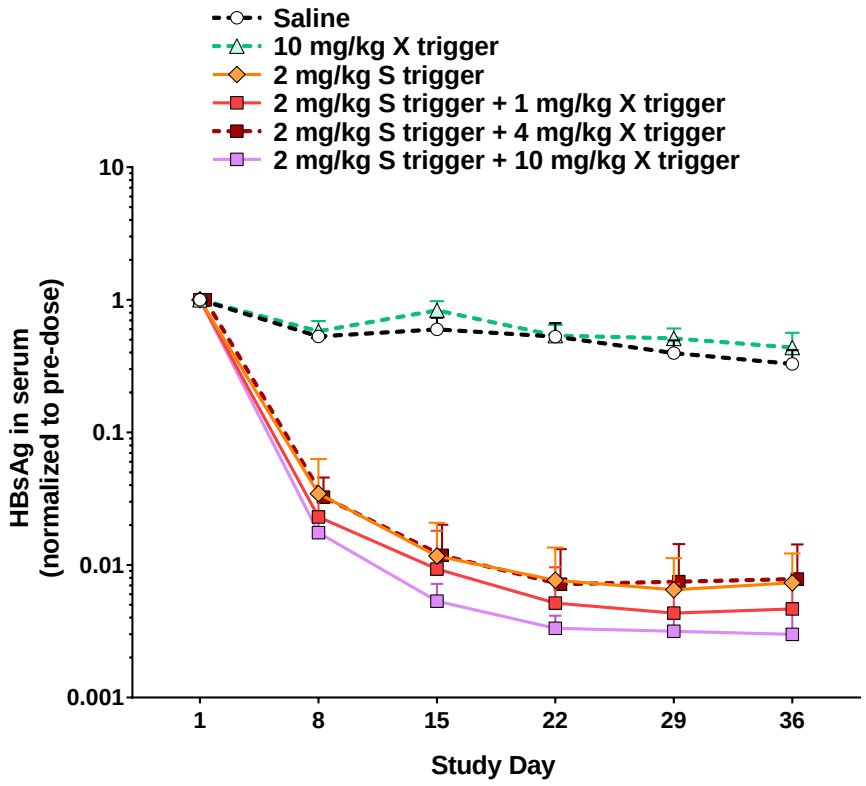
Model to simulate integrated HBV



These plasmids allow us to address potential competition between X trigger and others in combination

Full activity of S trigger in presence of X trigger

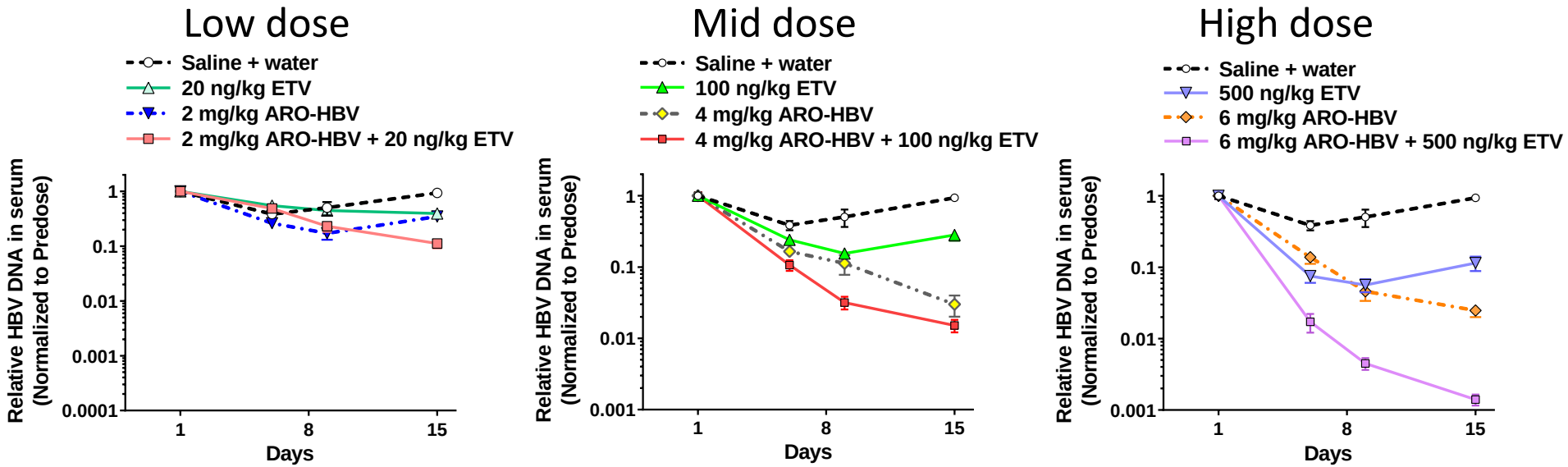
HDI of X mutant pHBV1.3 in NOD-SCID mice



- **As expected, X trigger alone does not knock down HBsAg in the mutant HBV model**
- **The X trigger does not interfere with activity of S trigger**

ARO-HBV and Entecavir synergistically inhibit HBV replication

HDI minicircle HBV1.3



Single injection	Daily ETV (ng/kg)	Fold reduction HBV DNA relative to control	Fraction affected	Combination Index (Day 15)
Saline	20	3 ± 2	0.579	N/A
Saline	100	4 ± 1	0.699	N/A
Saline	500	11 ± 7	0.878	N/A
2 mg/kg ARO-HBV	0	3 ± 1	0.630	N/A
4 mg/kg ARO-HBV	0	64 ± 59	0.968	N/A
6 mg/kg ARO-HBV	0	50 ± 32	0.974	N/A
2 mg/kg ARO-HBV	20	10 ± 5	0.880	0.690
4 mg/kg ARO-HBV	100	88 ± 70	0.984	0.644
6 mg/kg ARO-HBV	500	803 ± 364	0.998	0.474

In Conclusion…

ARO-HBV is a subcutaneously administered RNAi therapeutic targeting all HBV transcripts produced by both cccDNA and integrated HBV

- One RNAi trigger in the S region and another in the X region
- S and X triggers each contribute to knockdown of HBeAg, the combined effect being greater than that of either trigger alone
- Full activity of S trigger expected on HBV integration-derived HBsAg lacking X trigger site
- Durable reduction of HBV RNA, HBsAg, HBeAg and serum HBV DNA from single dose
- Repeat dosing produces deep reduction of HBsAg, HBeAg and serum HBV DNA
- ARO-HBV is synergistic with entecavir and expected to be synergistic with other direct acting HBV therapeutics
- Doses up to 300 mg/kg given weekly x 3 well tolerated in rats and cynomologus monkeys

- **Clinical trial began dosing March 2018**

Thank you !