



Looking Back to Move Forward - Designing Next Gen RNAi for HBV

HepDart
December 5, 2017



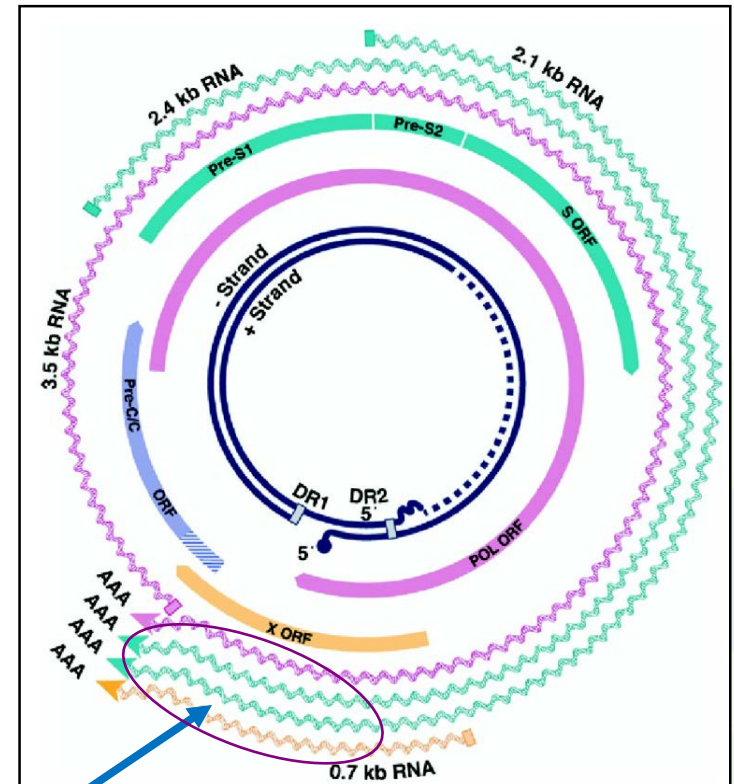
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All HBV RNA Derived from cccDNA Can Be Targeted with One siRNA—An All Targets DAA?

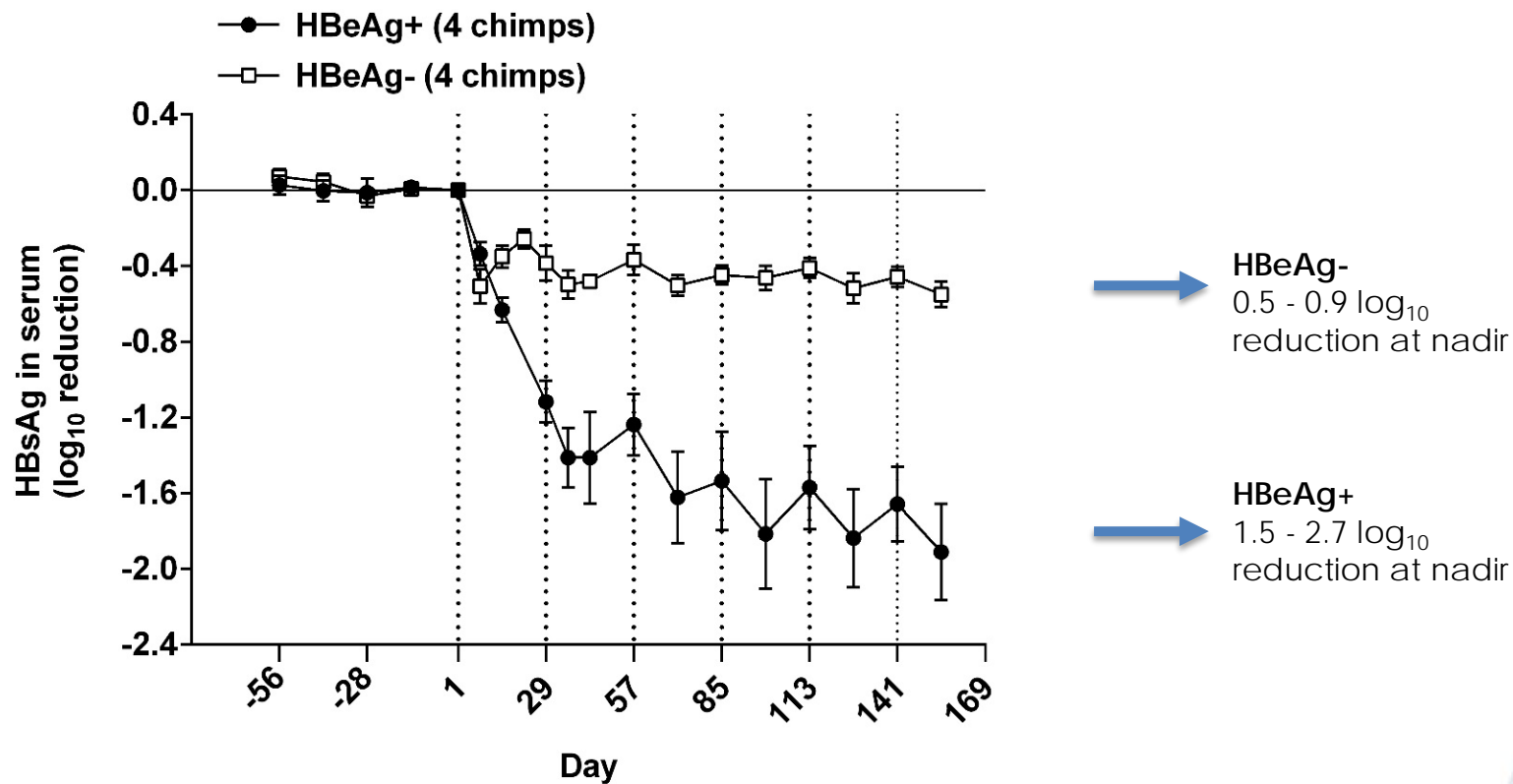
- All HBV transcripts, including pregenomic RNA, have common sequence and terminate with the same polyadenylation signal.

HBV Transcript Map



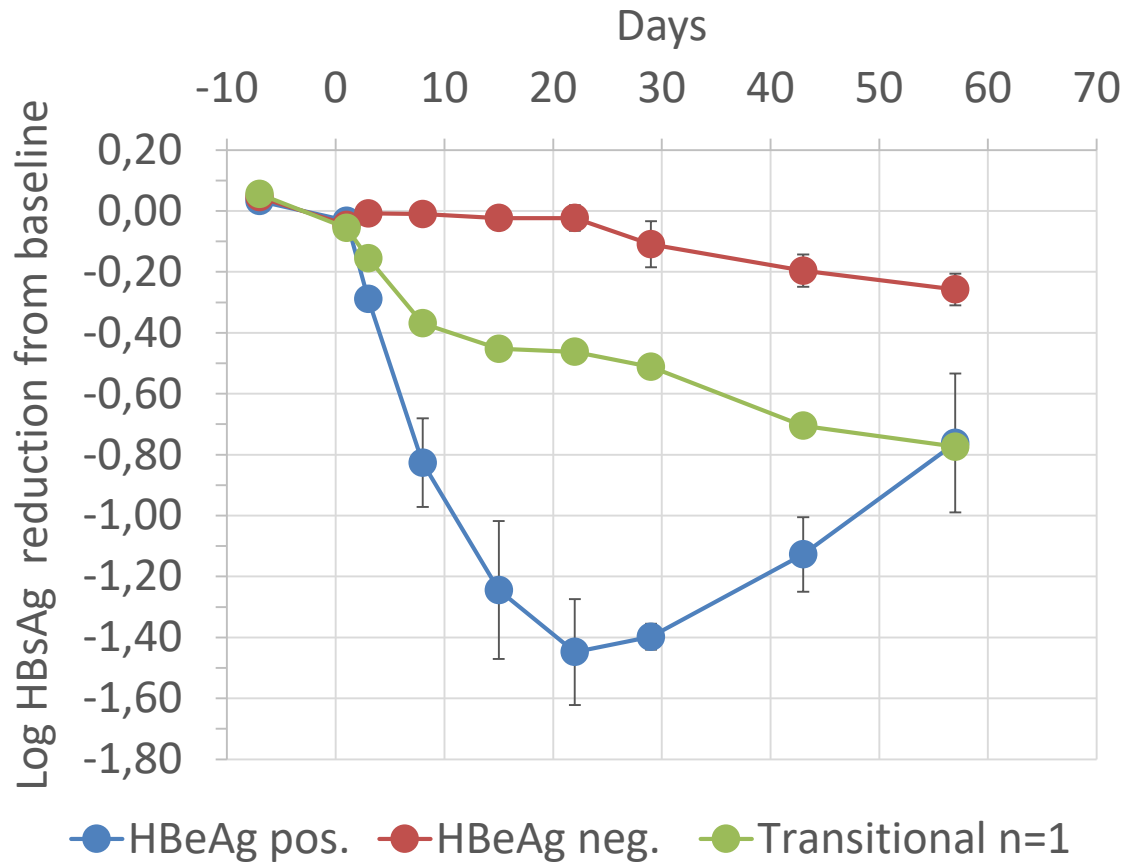
Single siRNA can reduce all HBV proteins

Differential HBsAg Reduction Observed in Chimpanzees with ARC-520



HBeAg positive responded better than HBeAg negative chimps

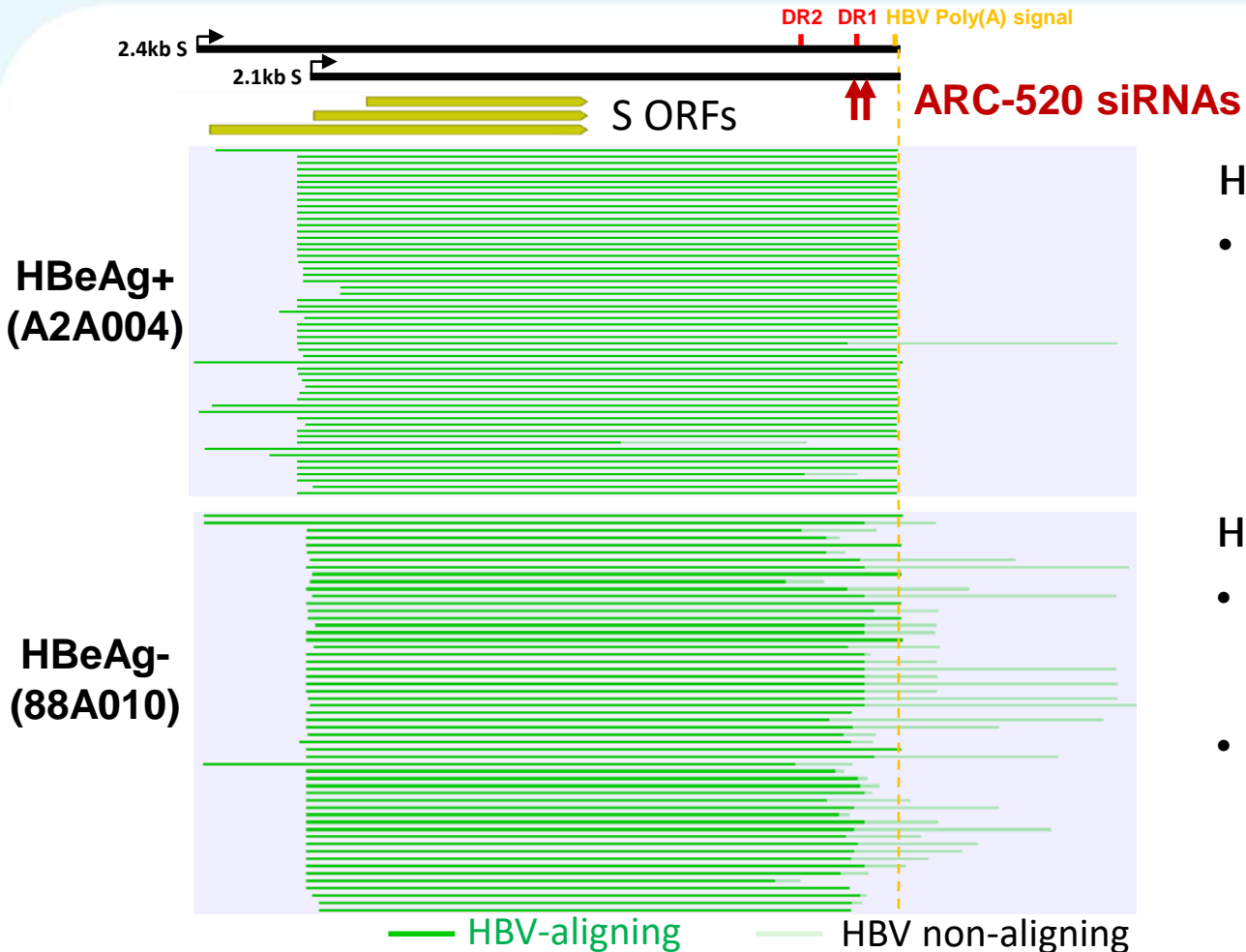
Differential Response Also Seen in Treatment Naïve Chronic HBV Patients



- Deep knockdown of HBsAg in HBeAg positive patients after a single dose

HBV Transcripts in HBeAg+ vs. HBeAg- Chimps

PacBio Single Molecule Real-Time (SMRT) Sequencing



HBeAg+

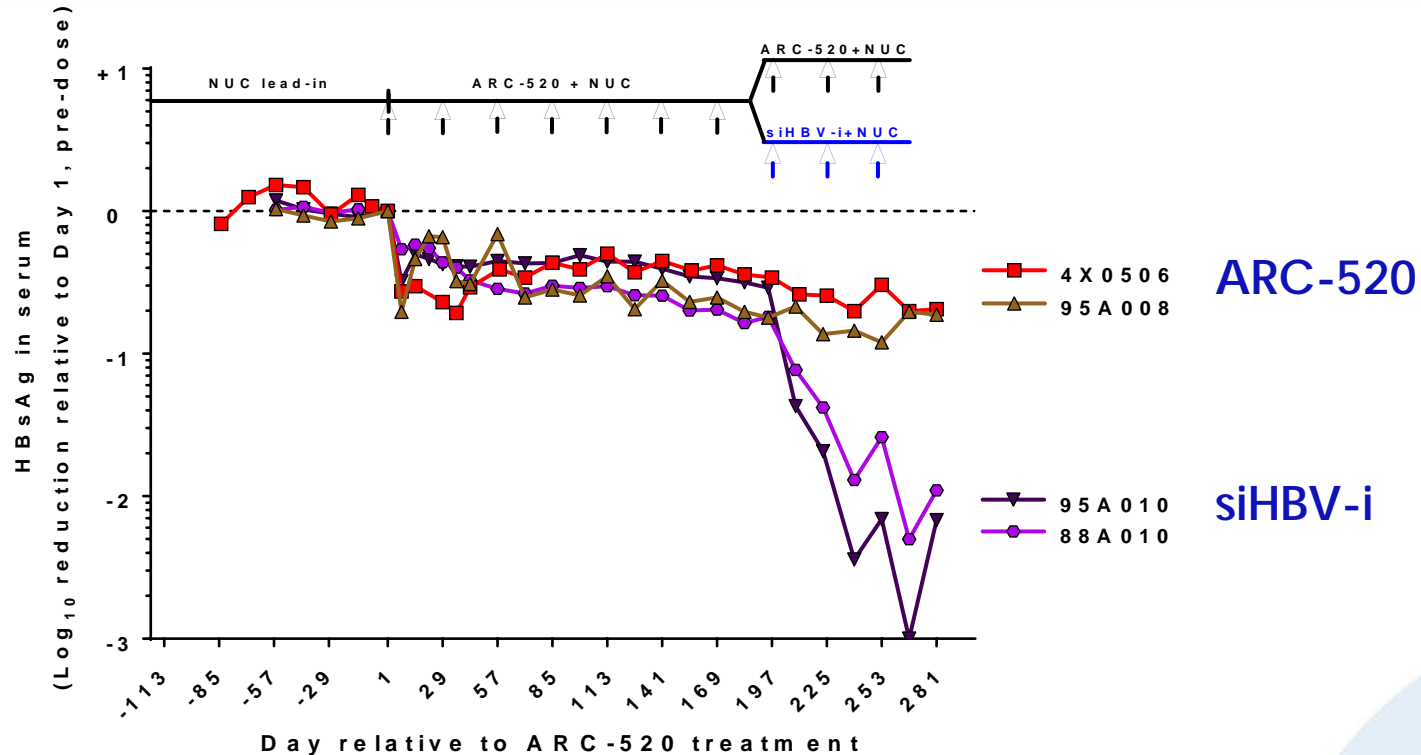
- Most S transcripts terminate near HBV poly(A) signal as expected

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 dsDNA

S transcripts in HBeAg- chimps often lack target sites for ARC-520

siRNA Designed to Target RNA Derived From HBV Integration Products in HBeAg- Chimps

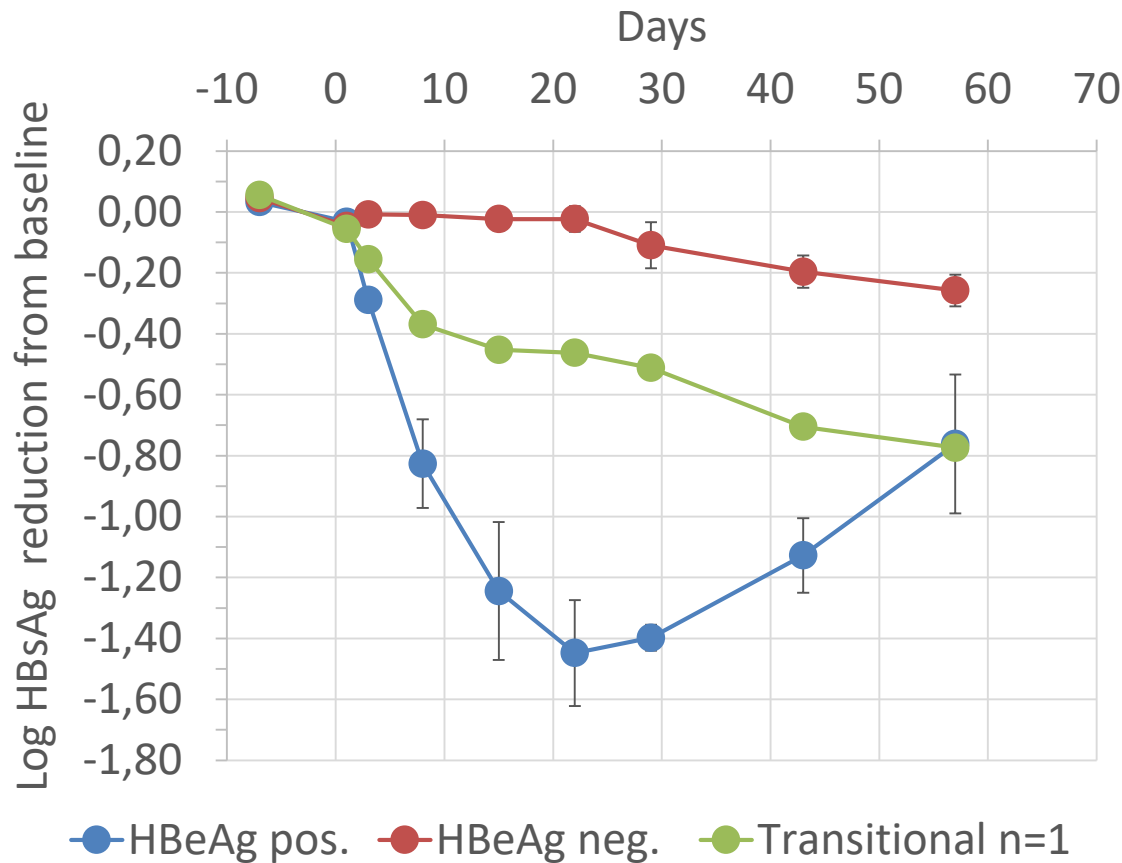


- siHBV-i targets HBsAg RNA even if expressed from integrated HBV DNA
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps

Learnings – Part 1

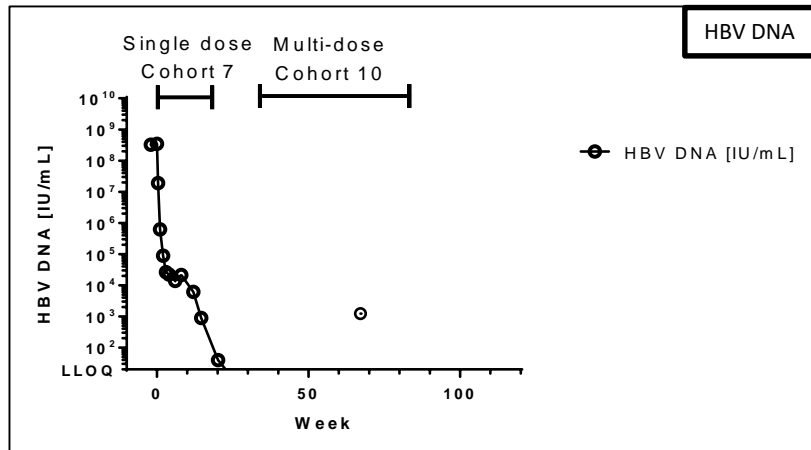
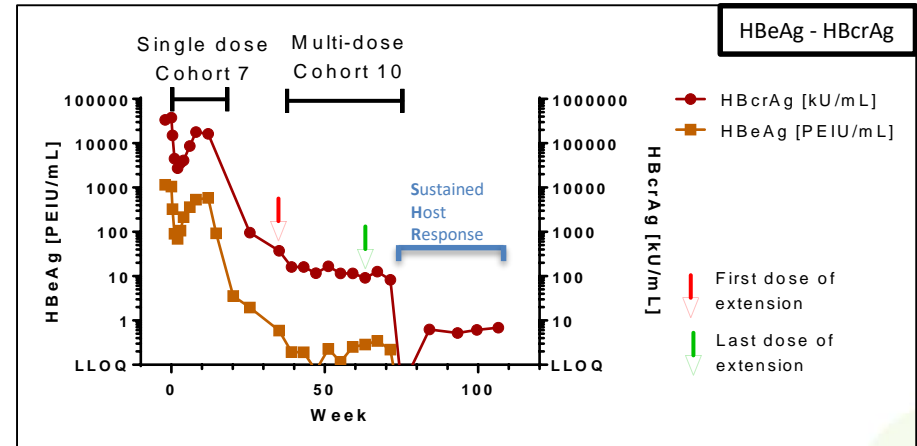
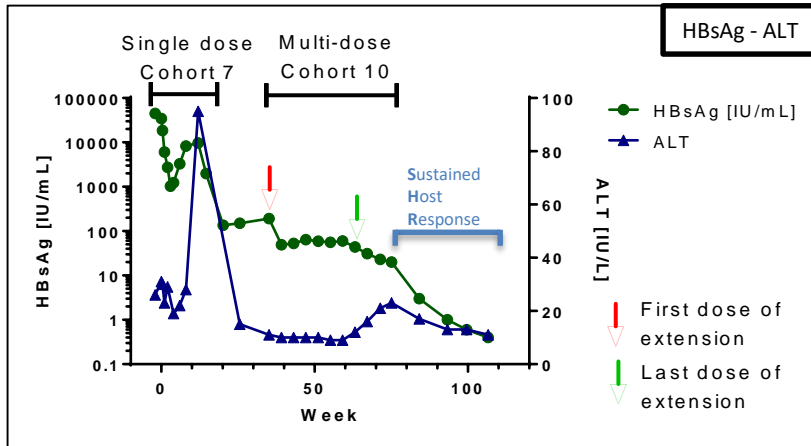
- If HBsAg is a key target – we need to account for both cccDNA and integrated-derived sources

Differential Response Also Seen in Treatment Naïve Chronic HBV Patients



- Deep knockdown of HBsAg in HBeAg positive patients after a single dose

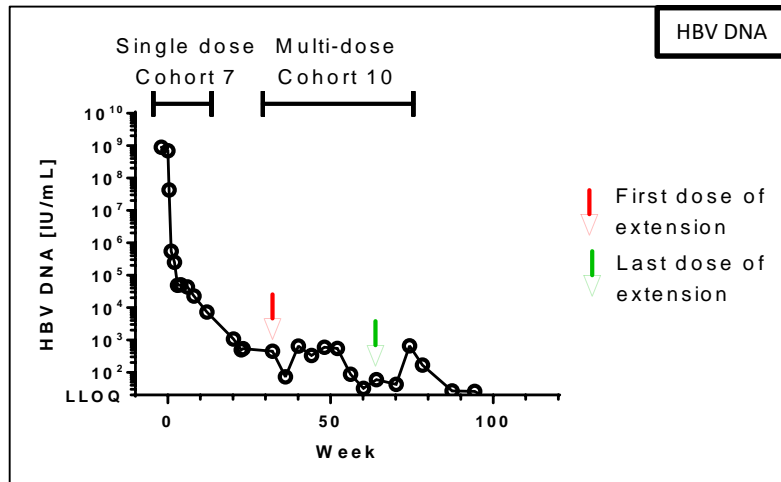
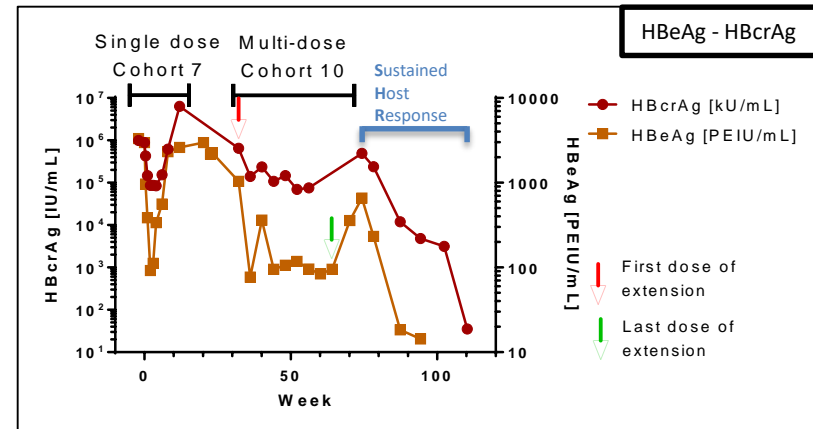
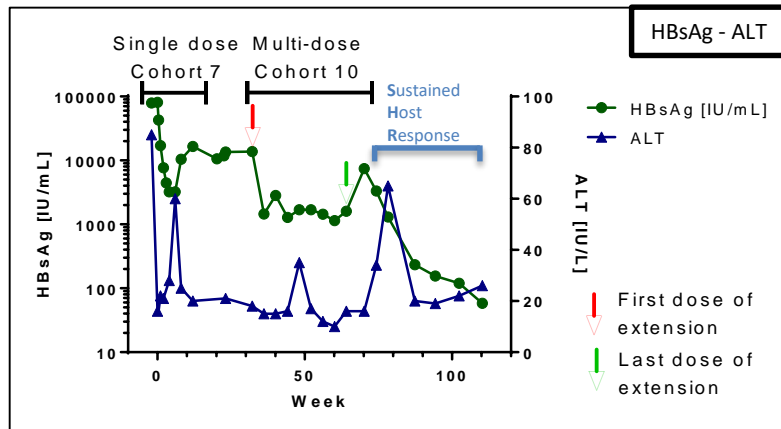
Case Study 1: HBeAg Positive Patient at 0.36 IU/ml



- 5.0 Log₁₀ HBsAg reduction from baseline
- 4.8 Log₁₀ HBcrAg and >4.2 Log₁₀ HBeAg reduction
- Rapid reduction of HBV DNA to BLOQ
- ALT elevation after initial antigen and DNA reductions and then after ARC-520 stopped
- Antigen decrease during ARC-520 treatment holiday consistent with increased host control of HBV virus

Patient 01-7985

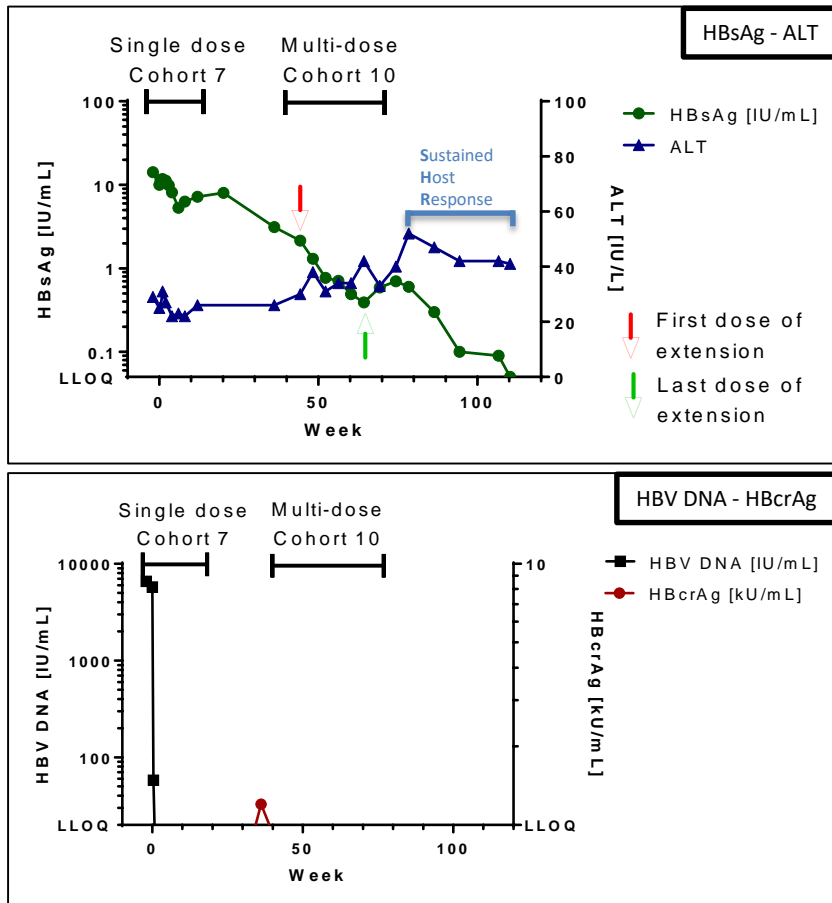
Case Study 2: HBeAg Positive Patient Flared when ARC-520 Stopped



Patient 01-7982

- **3.1 Log₁₀ HBsAg reduction from baseline**
- **4.4 Log₁₀ HBcrAg and 2.3 Log₁₀ HBeAg reduction**
- **Biphasic reduction of HBV DNA by >7.5 Log₁₀ to BLOQ**
- **Initial ALT elevations coinciding with antigen and DNA reductions**
- **HBsAg and HBeAg did not return to baseline after single dose ARC-520**

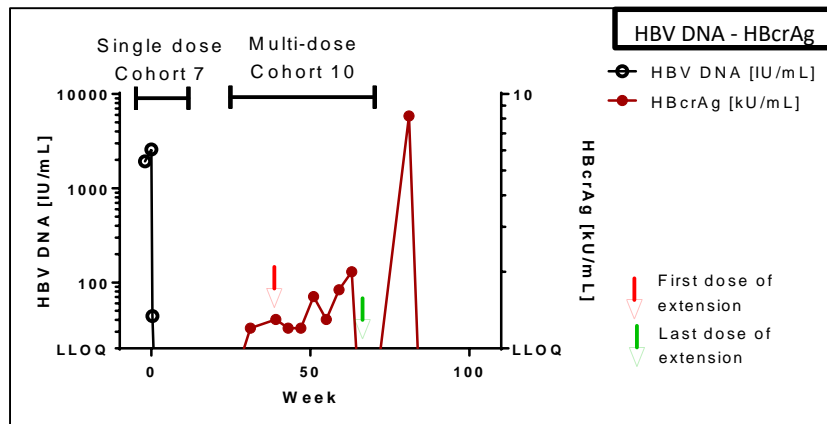
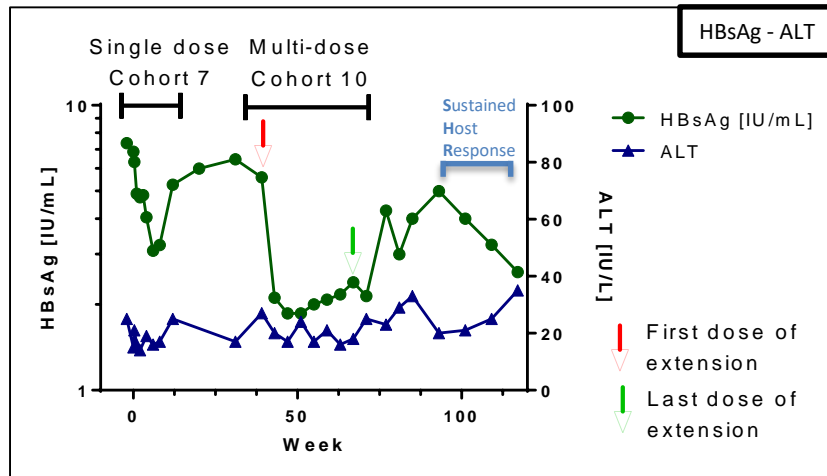
Case Study 3: HBeAg Negative Patient Now at 0.051 IU/ml



- 2.4 Log₁₀ HBsAg reduction from baseline to 0.051 IU/mL
- Delayed HBsAg response
- HBcrAg BLOQ throughout the study
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir
- Antigen decrease during treatment holiday consistent with increased host response to virus

Patient 01-7983

Case Study 4: HBeAg Negative Patient Trending Toward HBsAg Seroclearance



Patient 01-7973

- **0.6** Log₁₀ HBsAg reduction from baseline to NADIR, with rebound followed by additional reduction off-therapy
- Current HBsAg is 2.6 IU/ml
- HBcrAg floating around LLOQ throughout study, except one spike post ARC-520.
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir

Learnings – Part 2

- If HBsAg is a key target – we need to account for both cccDNA and integrated-derived sources
- At least in naïve patients, the host can respond productively as early as following the first dose of RNAi trigger and a Nuc
- Productive host responses can be subtle – for instance an increase in ALT from 10 to 20 IU/ml heralded HBeAg seroclearance and trend toward clearance of HBsAg in patient 1
- HBeAg negative patients with BLOQ DNA, HBcrAg and HBV RNA can still have quite significant circulating HBsAg (as high as ~1000 IU/ml in our patients)

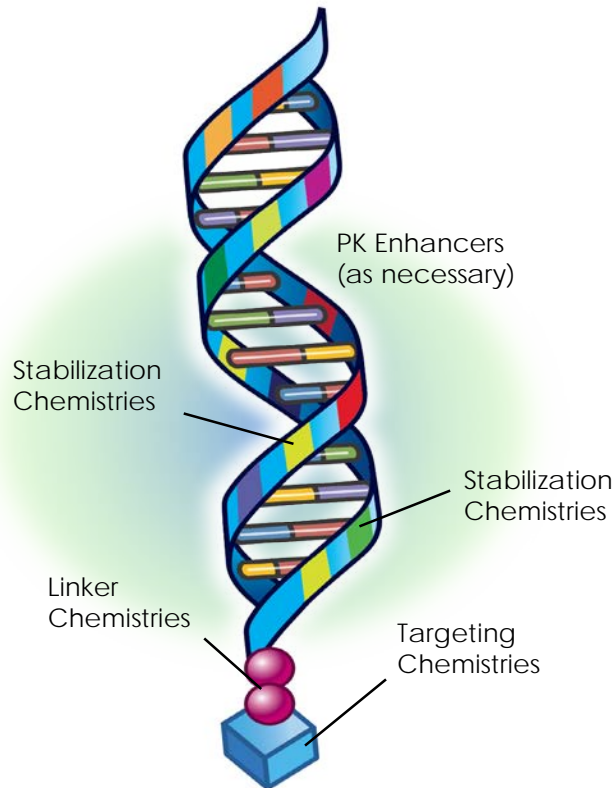
2 of 3 HBeAg+ and 2 of 5 HBeAg- patients achieved Sustained Host Response, even though ARC-520 was imperfect because it only silenced cccDNA expression

ARO-HBV: Key Design Elements for the Next Generation

The Wish List:

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

Targeted RNAi Molecules - TRiM™ Platform

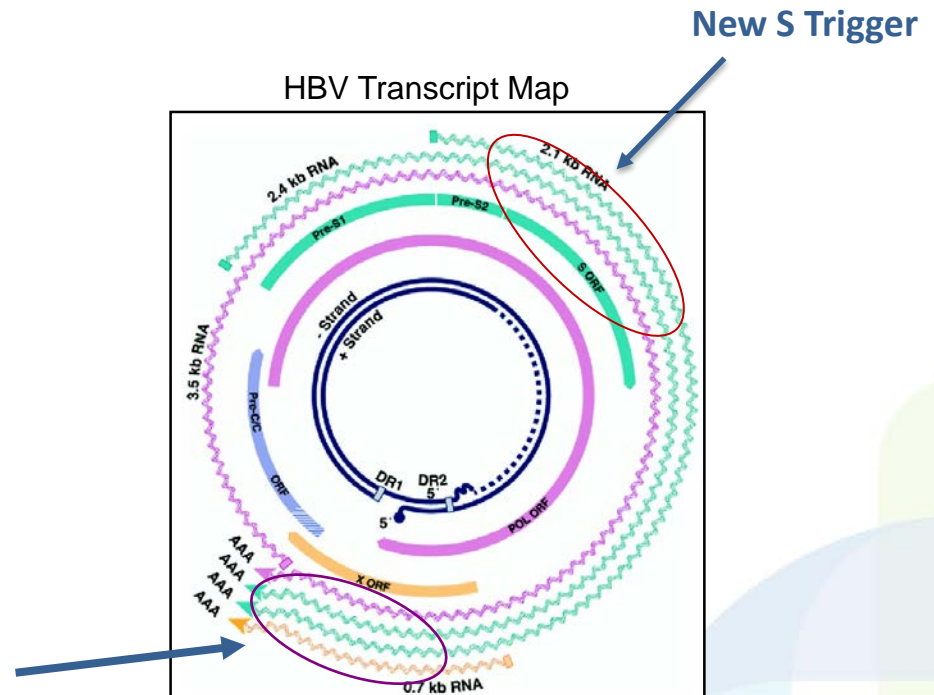


- Growing libraries of targeting agents, linkers, stabilization chemistries, and PK enhancers enable modular approach... in a simple structure:
 - Faster time to clinical candidates
 - Multiple routes of administration
 - Simplified manufacturing at reduced cost
 - Wide safety margins
 - Taking RNAi to the liver, lung, and other tissues

Importance of Integrated DNA as mRNA Source has Changed RNAi Strategy

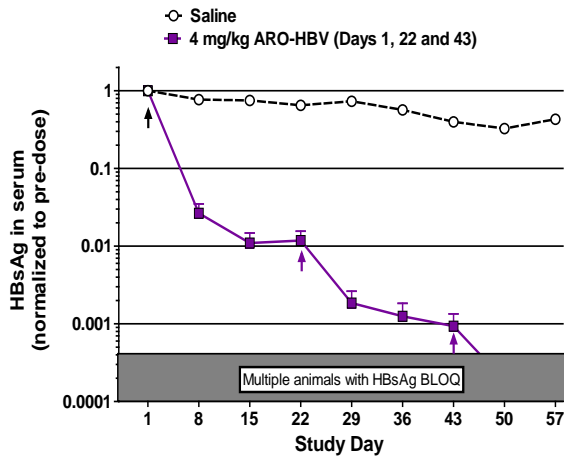
- All HBV transcripts, including pregenomic RNA, overlap and terminate with the same polyadenylation signal

Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA



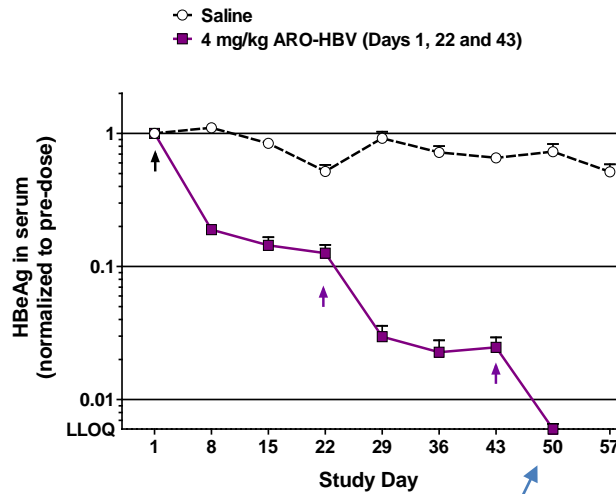
Multiple Dosing in WT pHBV Mice Reduces HBV DNA by 3.44 log₁₀, HBsAg and HBeAg to LOQ

HBsAg



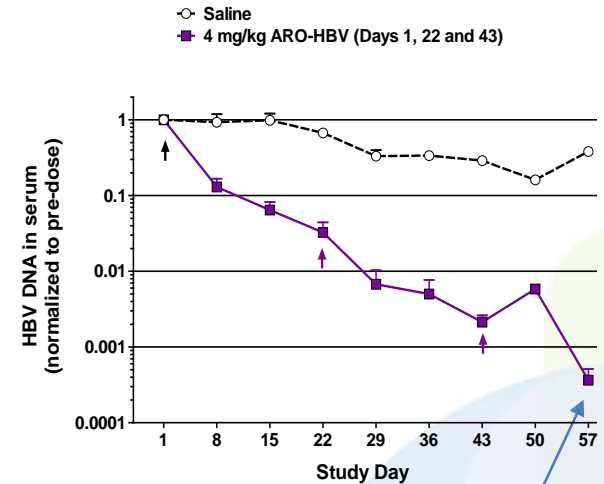
>3 log₁₀ reduction after 3 doses

HBeAg



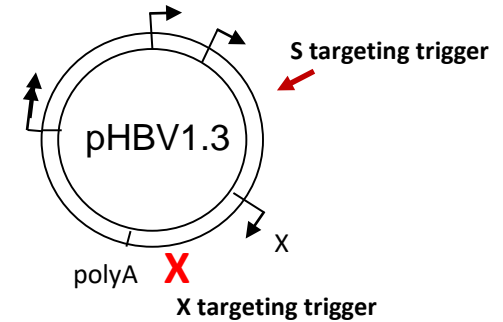
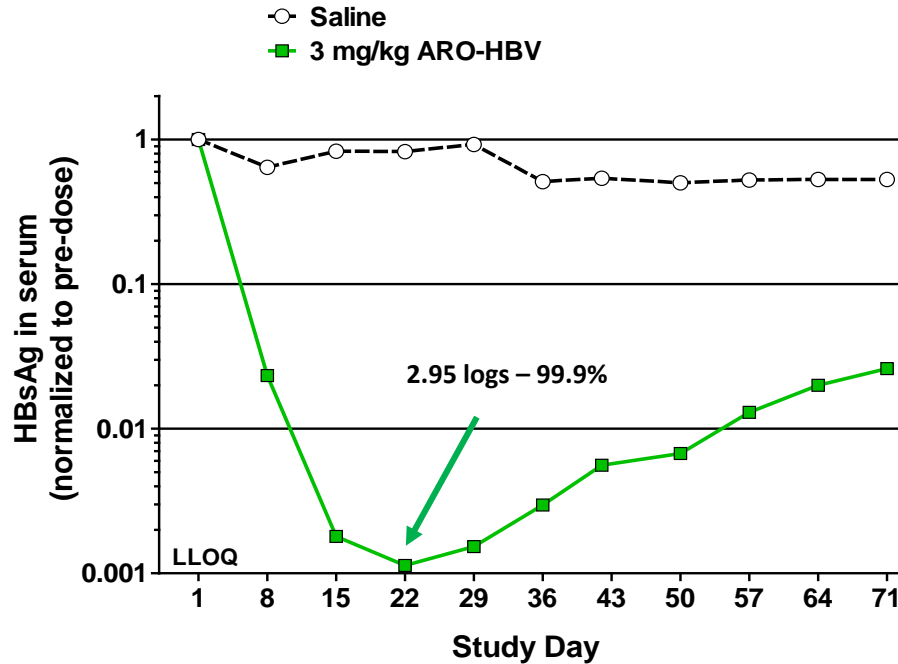
2.2 log₁₀ = 99.4% reduction to LLOQ

HBV DNA



3.44 log₁₀ = >99.9% reduction

Integration Modeled in a New, Mutated pHBV Transfected Mouse



HBsAg knockdown is deep and prolonged despite loss of HBx-trigger site

Conclusions

- RNAi has a strong basis for staking a claim as a cornerstone therapy for the foreseeable future
- Effective RNAi for HBV should take into account both cccDNA and integrated-derived RNA transcripts
- Chronic dosing with ARC-520 and ETV in naïve patients showed promise of RNAi-induced host control despite design flaw
- ARO-HBV has been designed based on learnings from ARC-520 and ARC-521 programs
- Monthly subcutaneous dosing appears to be feasible based on pHBV mouse data
- Clinical Studies are planned to begin 1H 2018

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