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

HepDart
December 5, 2017

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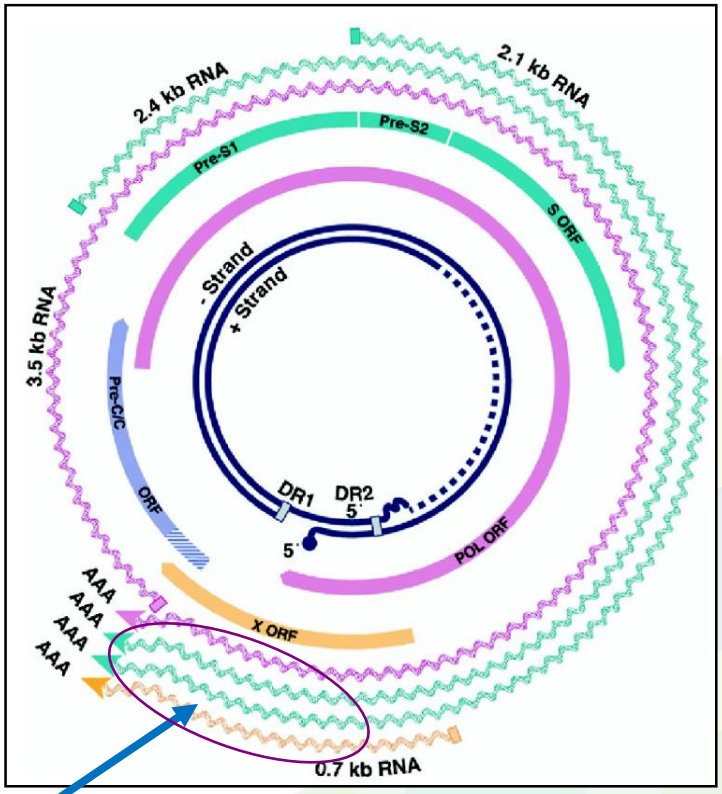
All HBV RNA Derived from cccDNA Can Be Targeted with One siRNA–An All Targets DAA?

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

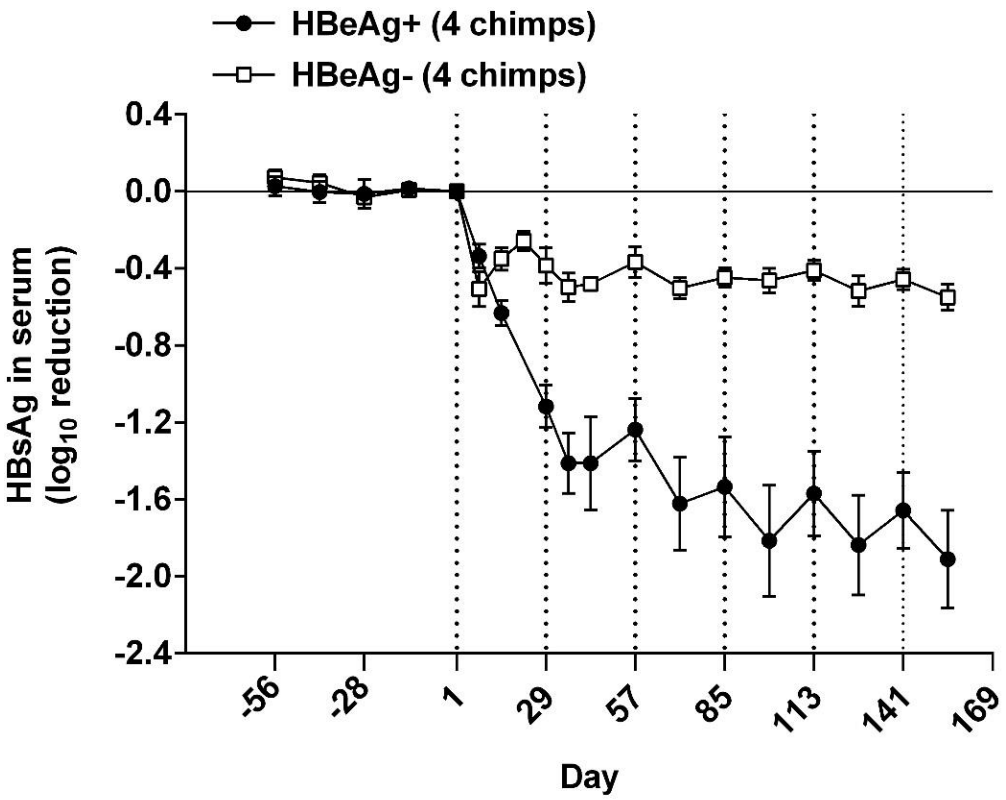
HBV Transcript Map



Single siRNA can reduce all HBV proteins

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

Differential HBsAg Reduction Observed in Chimpanzees with ARC-520



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

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

HBeAg positive responded better than HBeAg negative chimps

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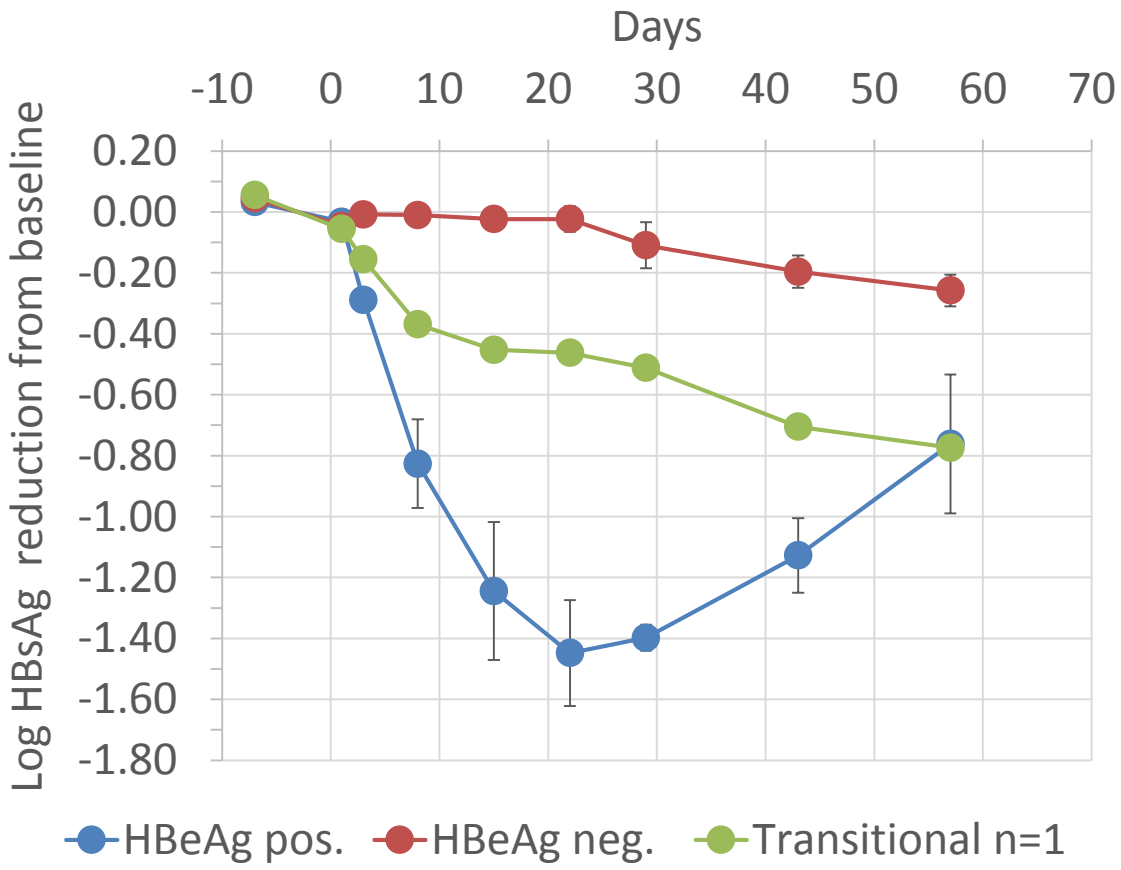
Wooddell, Yuen et al, Sci Trans Med 2017

Differential Response Also Seen in Treatment Naïve Chronic HBV Patients

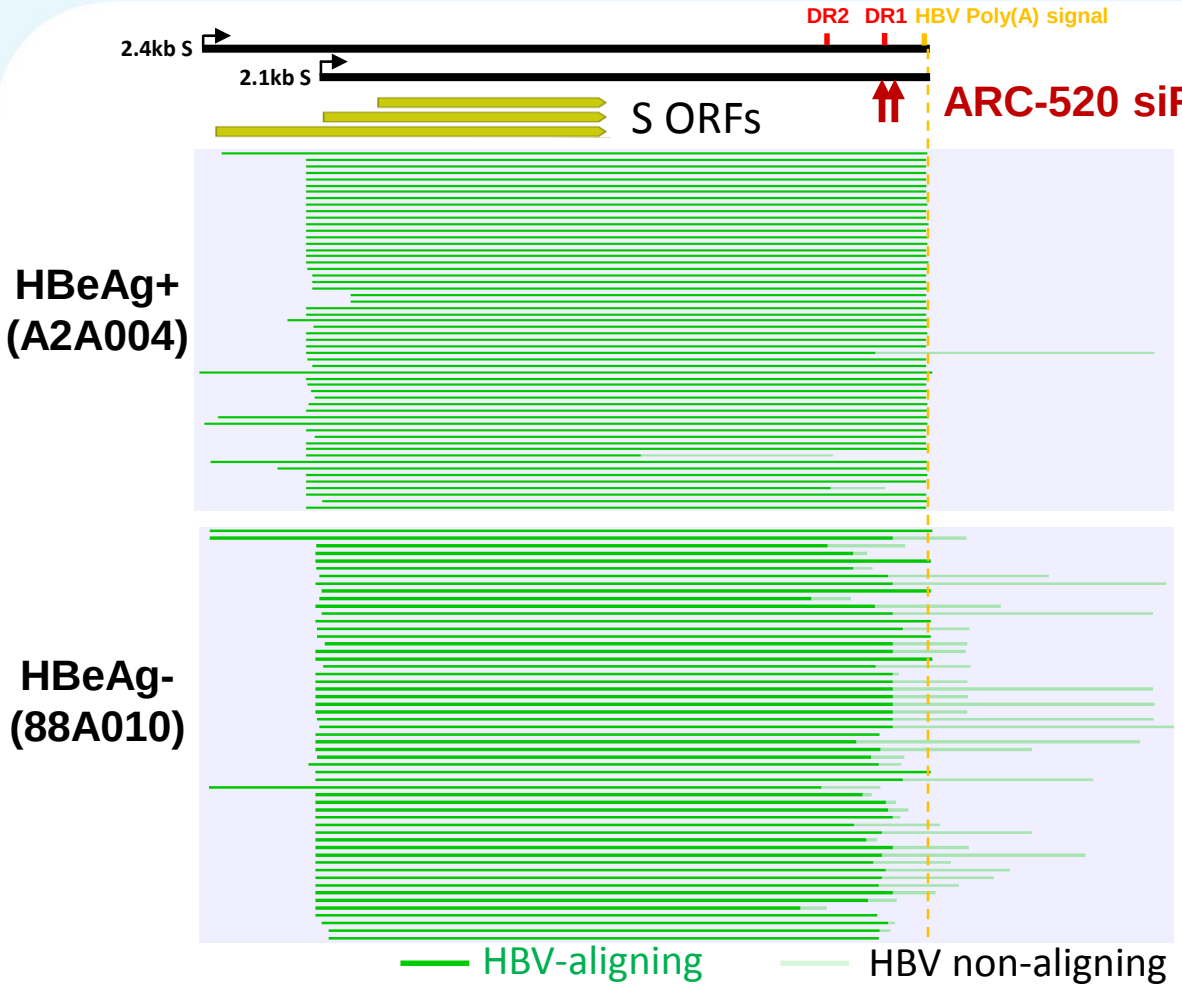


- Deep knockdown of HBsAg in HBeAg positive patients after a single dose

Wooddell, Yuen et al, Sci Trans Med 2017

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 dslDNA**

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

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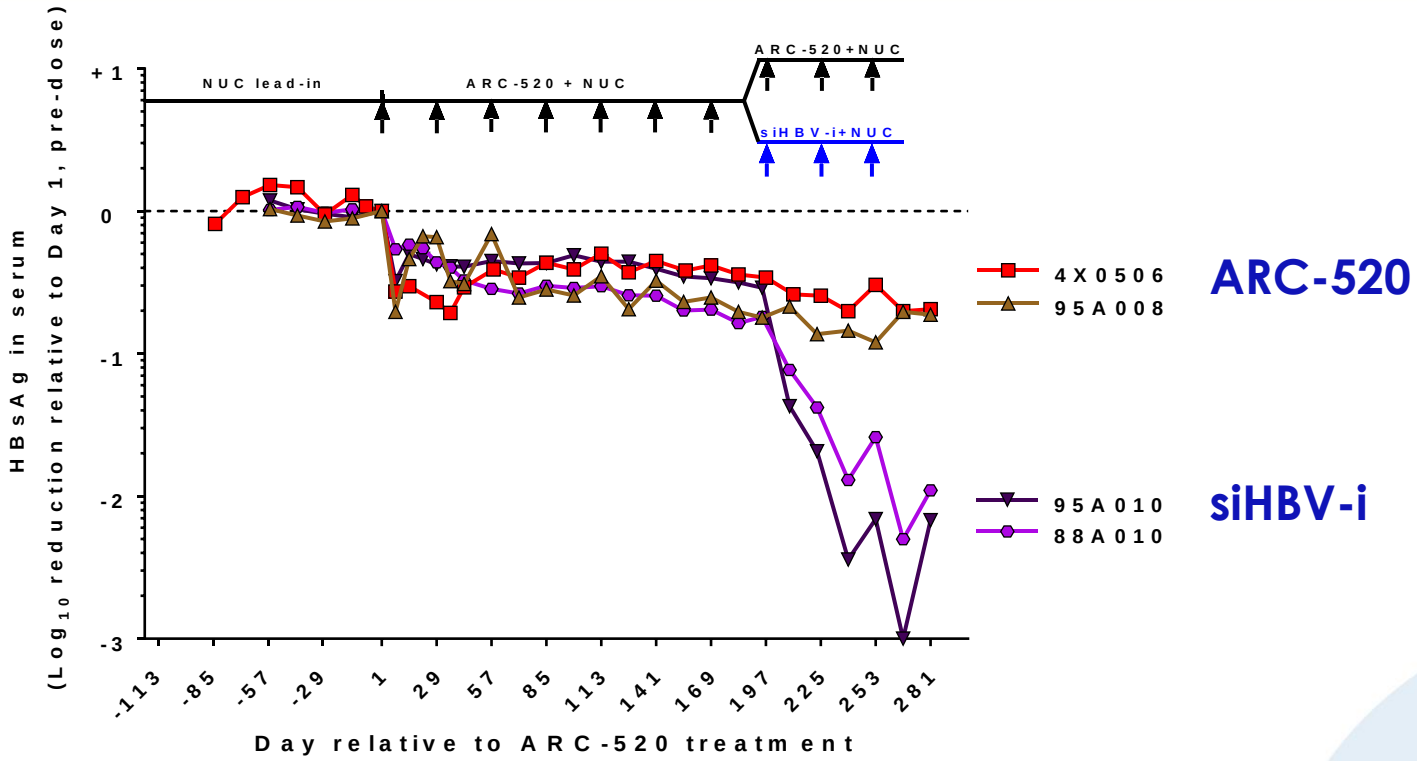
Wooddell, Yuen et al, Sci Trans Med 2017

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

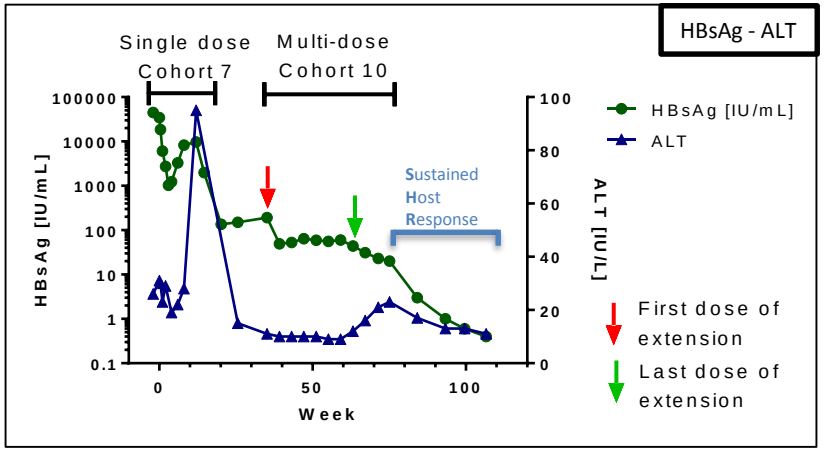


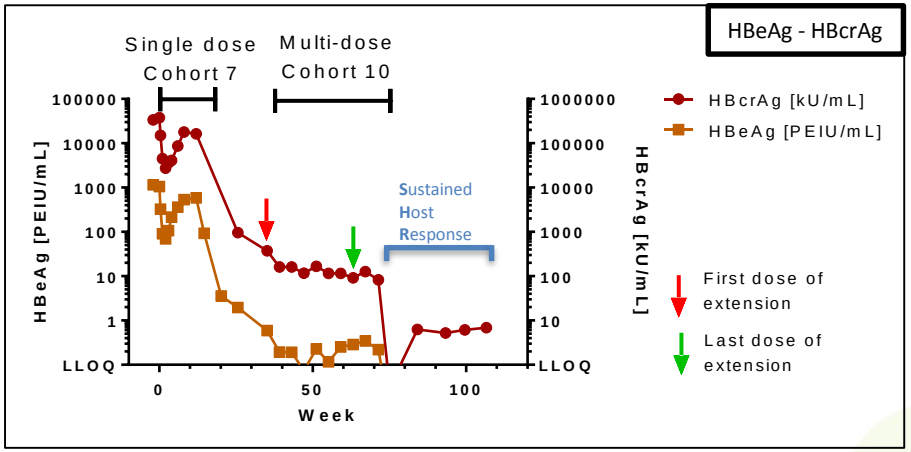
- siHBV-i targets HBsAg RNA even if expressed from integrated HBV DNA
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps

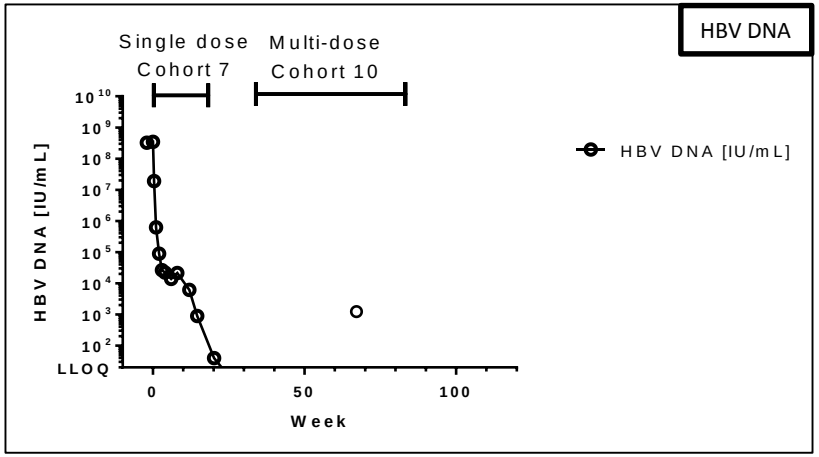
Learnings – Part 1

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

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







Patient 01-7985

- **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

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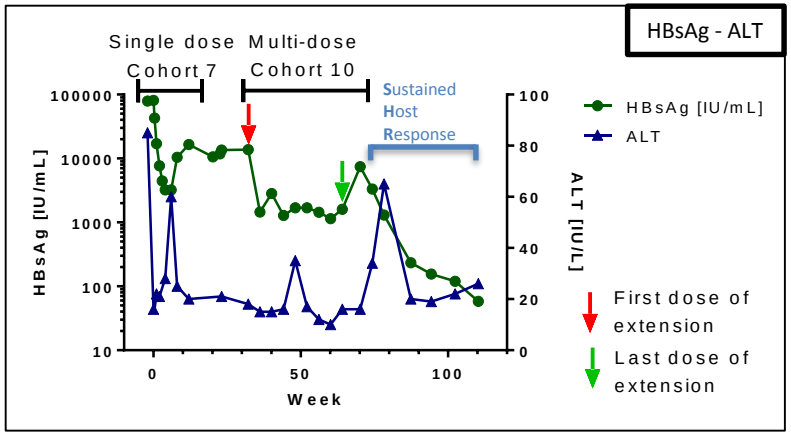
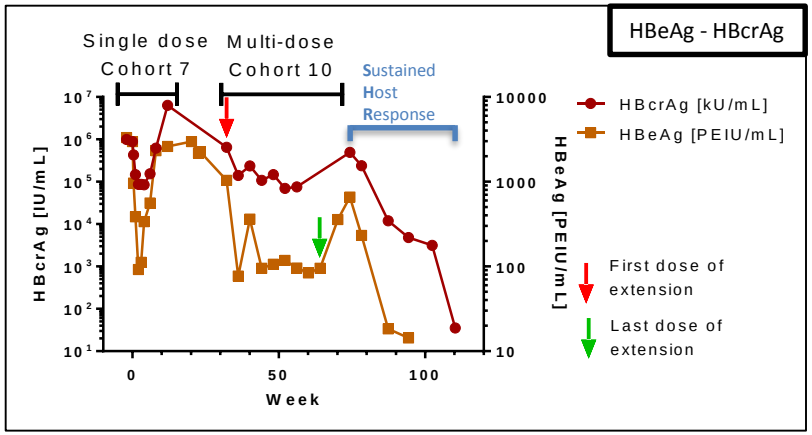
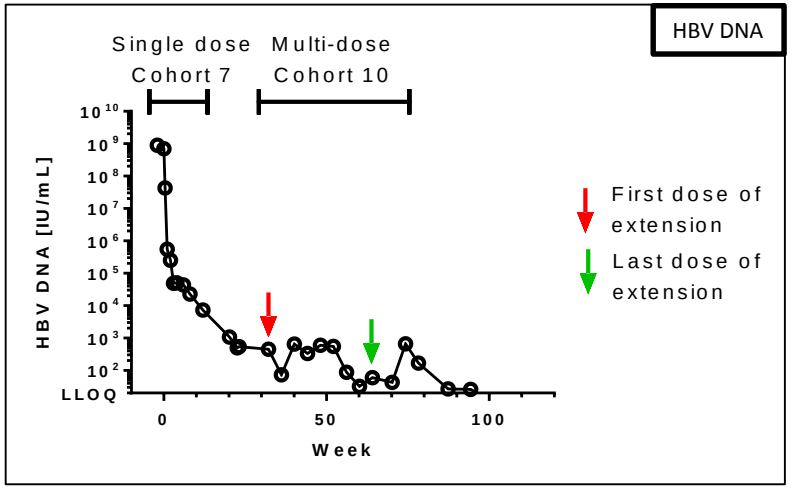
Case Study 2: HBeAg Positive Patient Flared when ARC-520 Stopped







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

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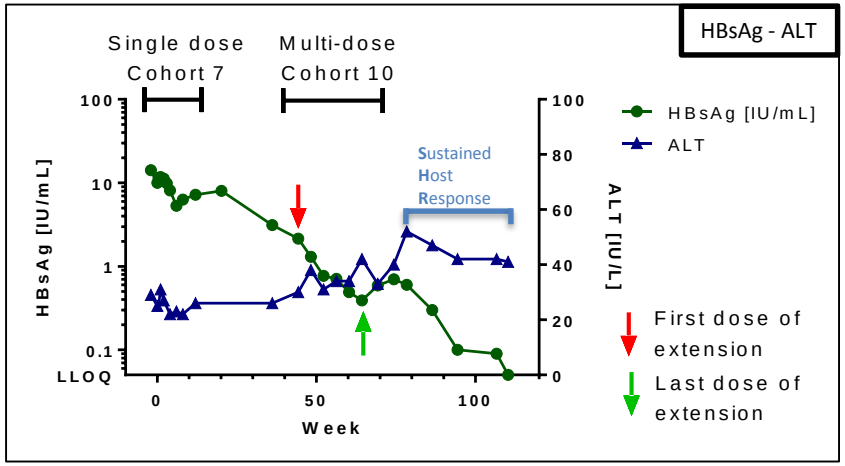
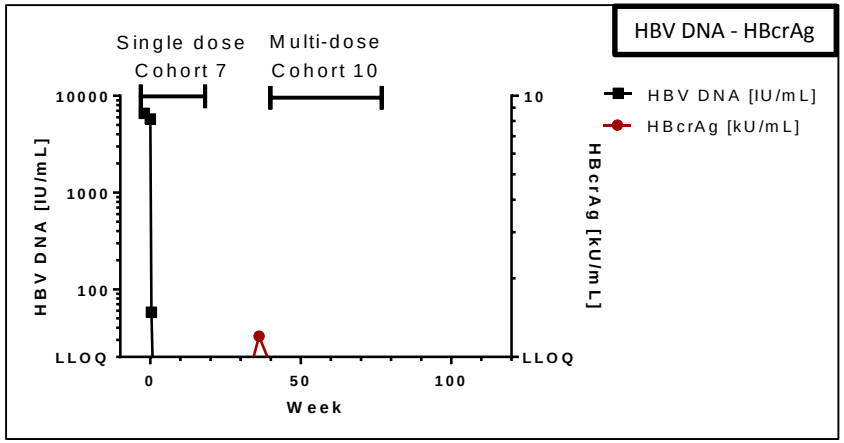
Case Study 3: HBeAg Negative Patient Now at 0.051 IU/ml





Patient 01-7983

- **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

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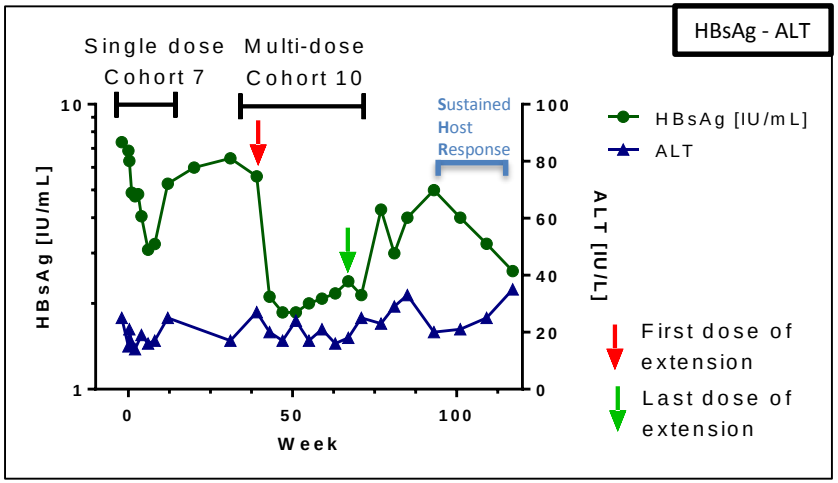
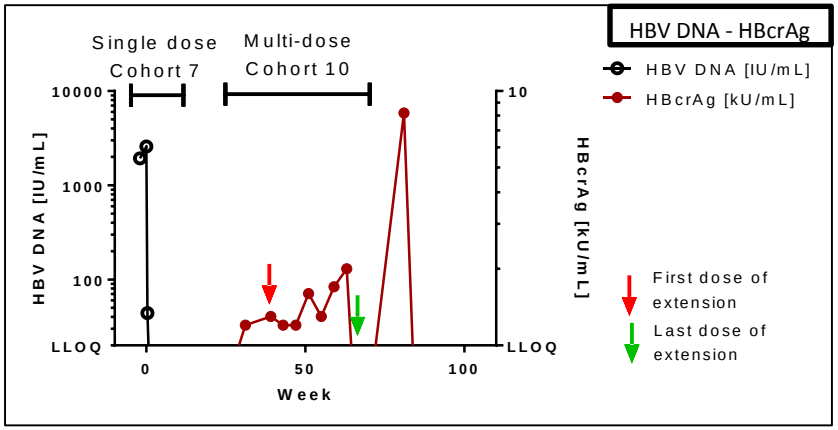
Case Study 4: HBeAg Negative Patient Trending Toward HBsAg Seroclearance





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

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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

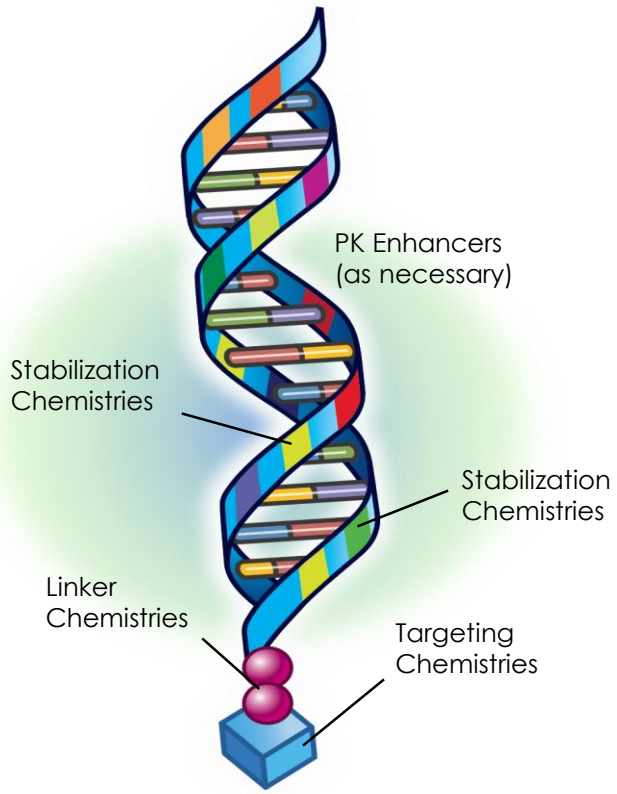
2 of 3 HBeAg+ and 2 of 5 HBeAg- patients achieved Sustained Host Response, even though ARC-520 was imperfect because it only silenced cccDNA expression

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

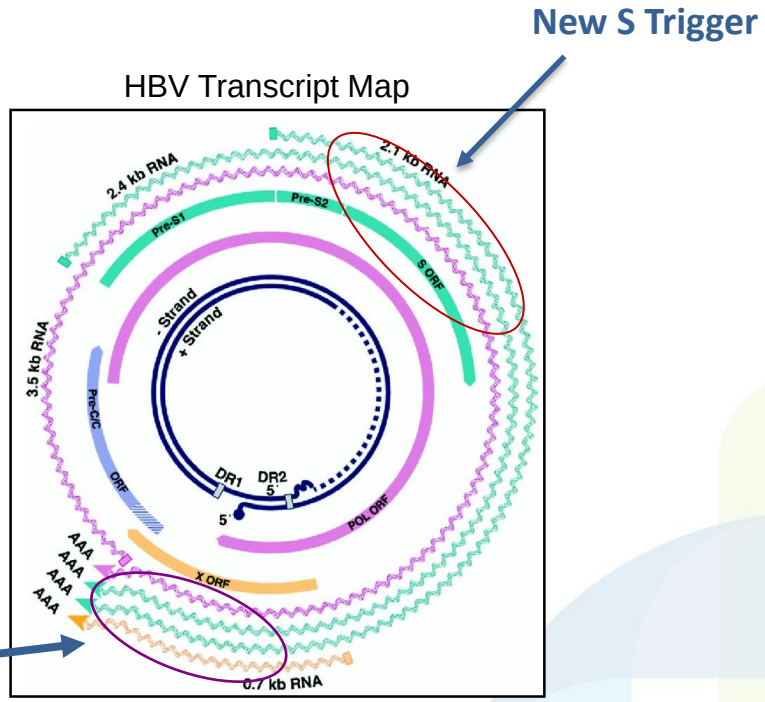


- Growing libraries of targeting agents, linkers, stabilization chemistries, and PK enhancers enable modular approach… in a simple structure:
  - Faster time to clinical candidates
  - Multiple routes of administration
  - Simplified manufacturing at reduced cost
  - Wide safety margins
  - Taking RNAi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

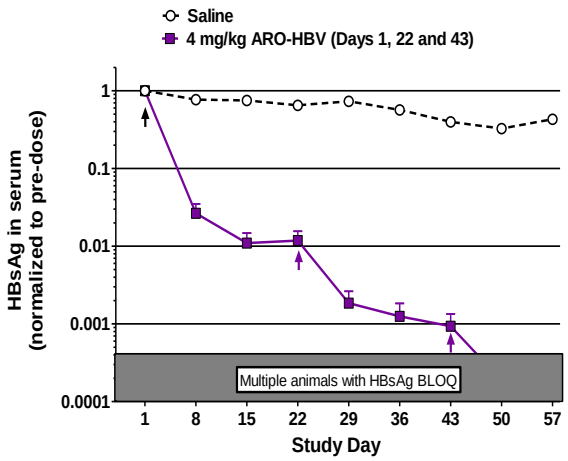
Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA



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

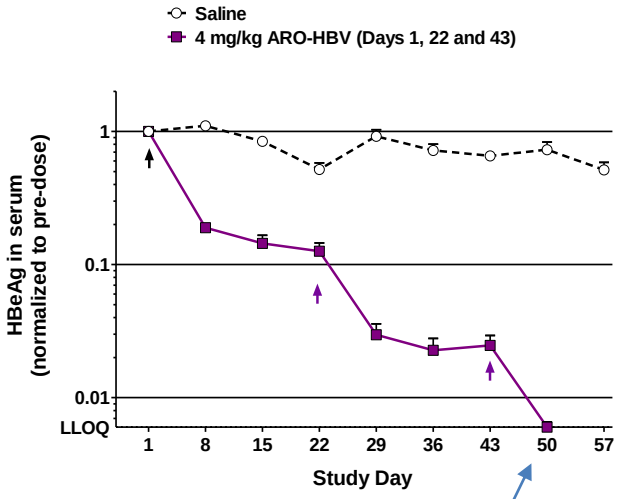
Multiple Dosing in WT pHBV Mice Reduces HBV DNA by 3.44 log10, HBsAg and HBeAg to LOQ

HBsAg



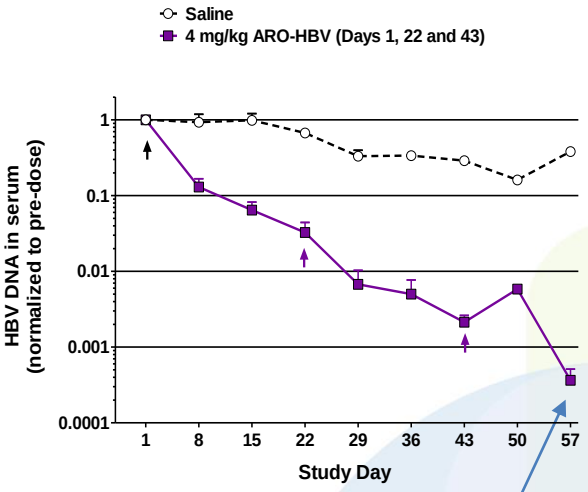
>3 log_{10} reduction after 3 doses

HBeAg



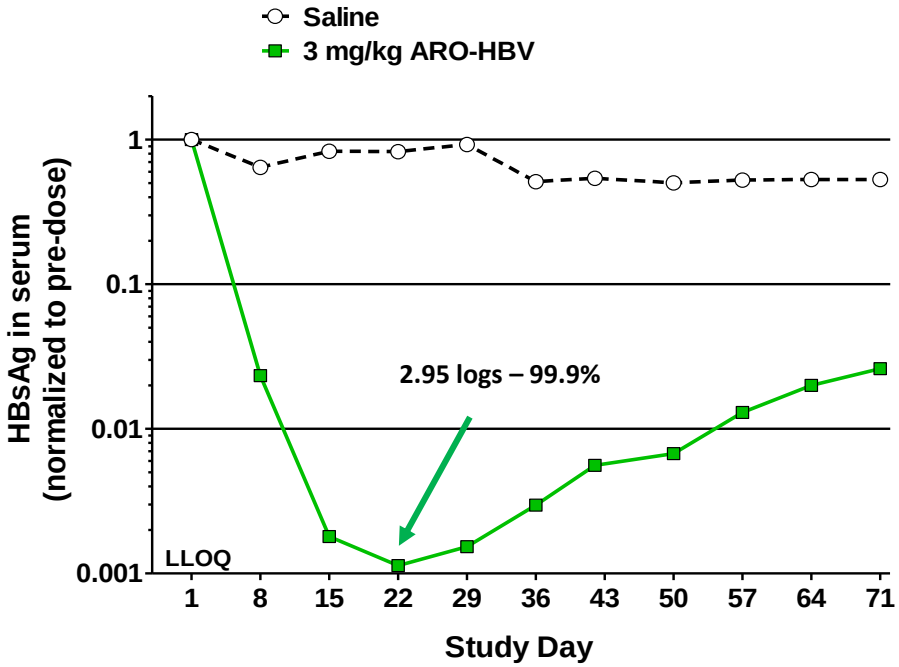
2.2 log10 = 99.4% reduction to LLOQ

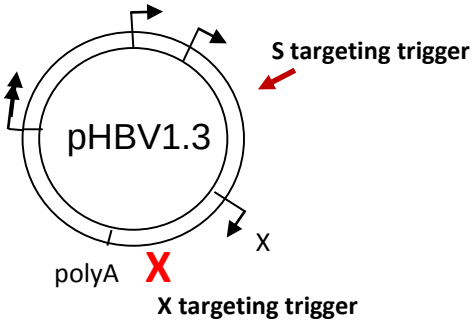
HBV DNA



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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