RNAi in HBV, the next backbone therapy for use in combinations?

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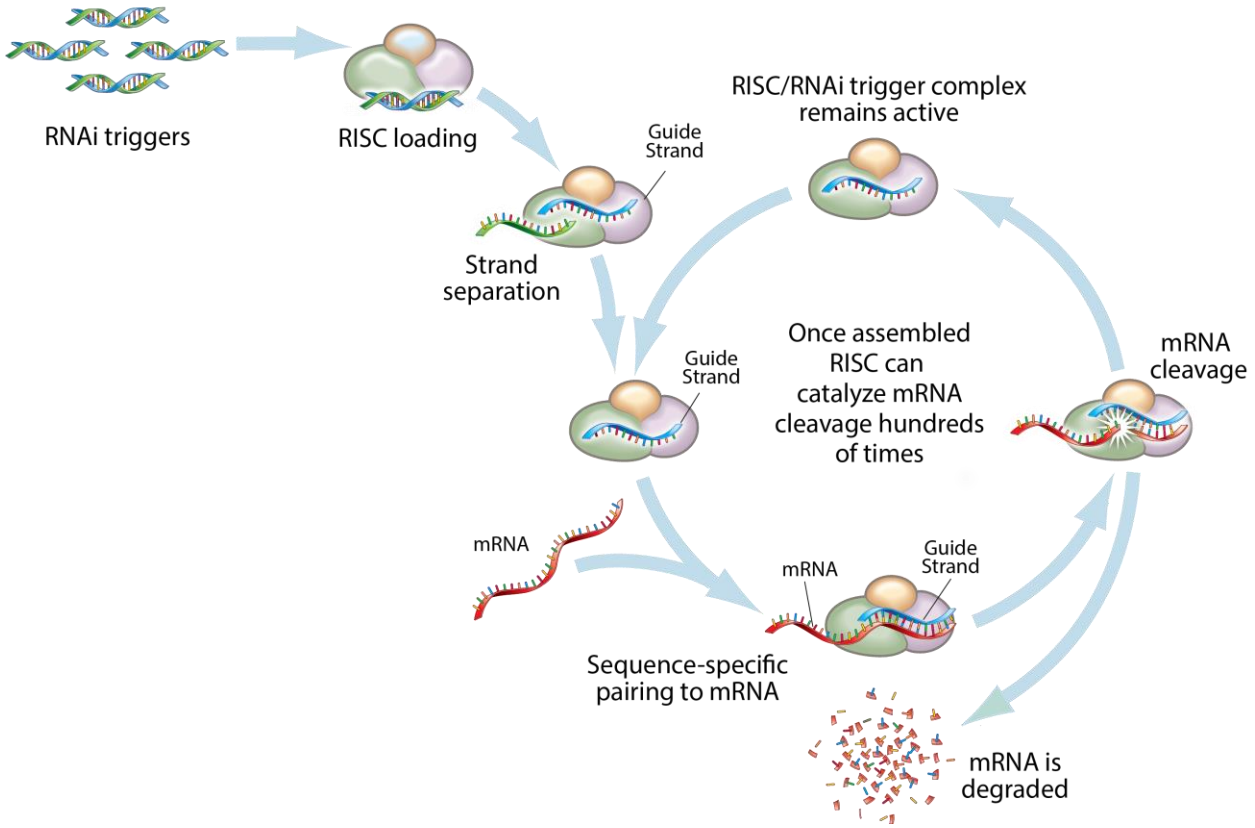
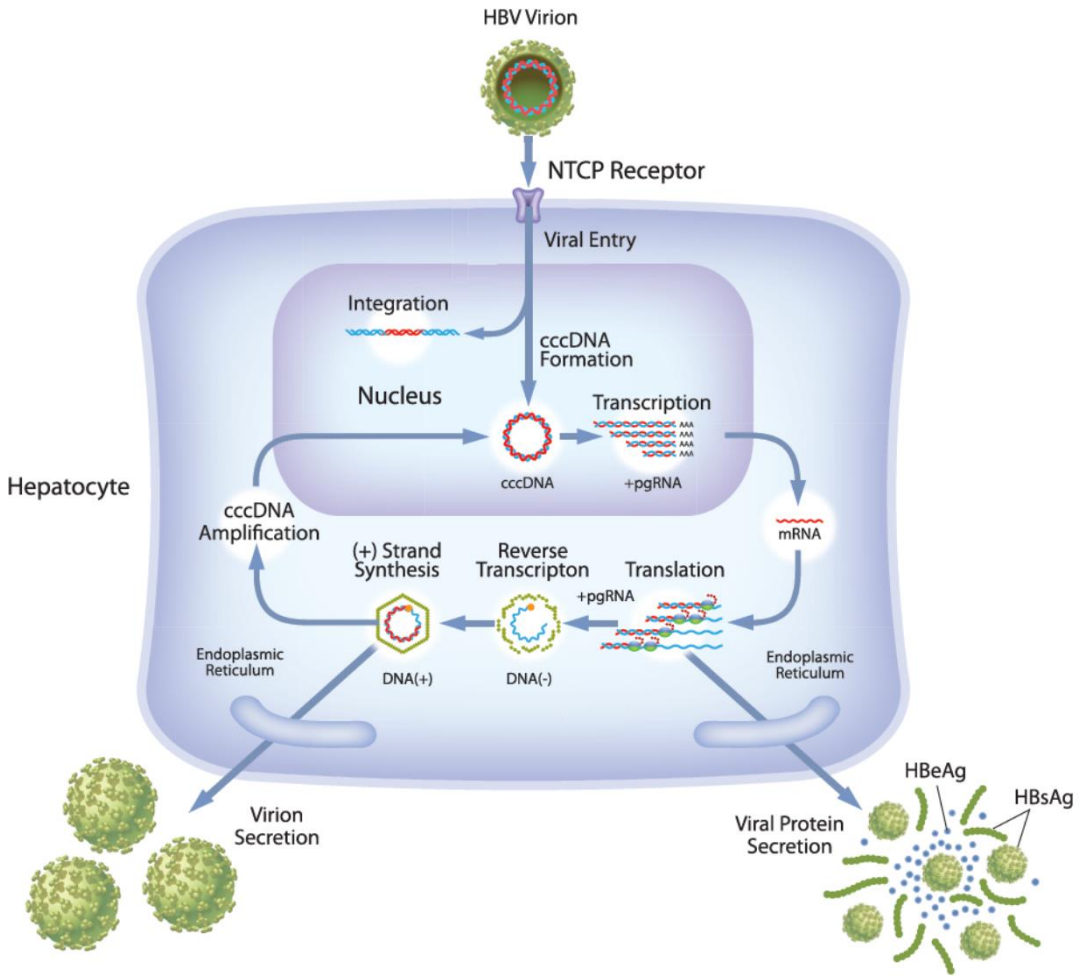
Target the Gene, Silence the Disease



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

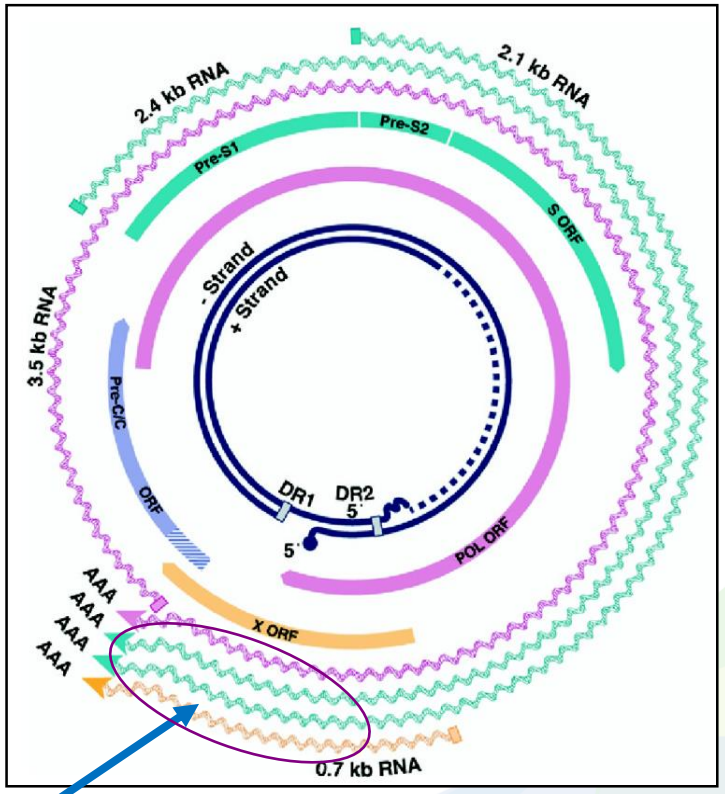
Hepatitis B Virus Life Cycle



All HBV RNA derived from cccDNA can be targeted with one siRNA

- 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

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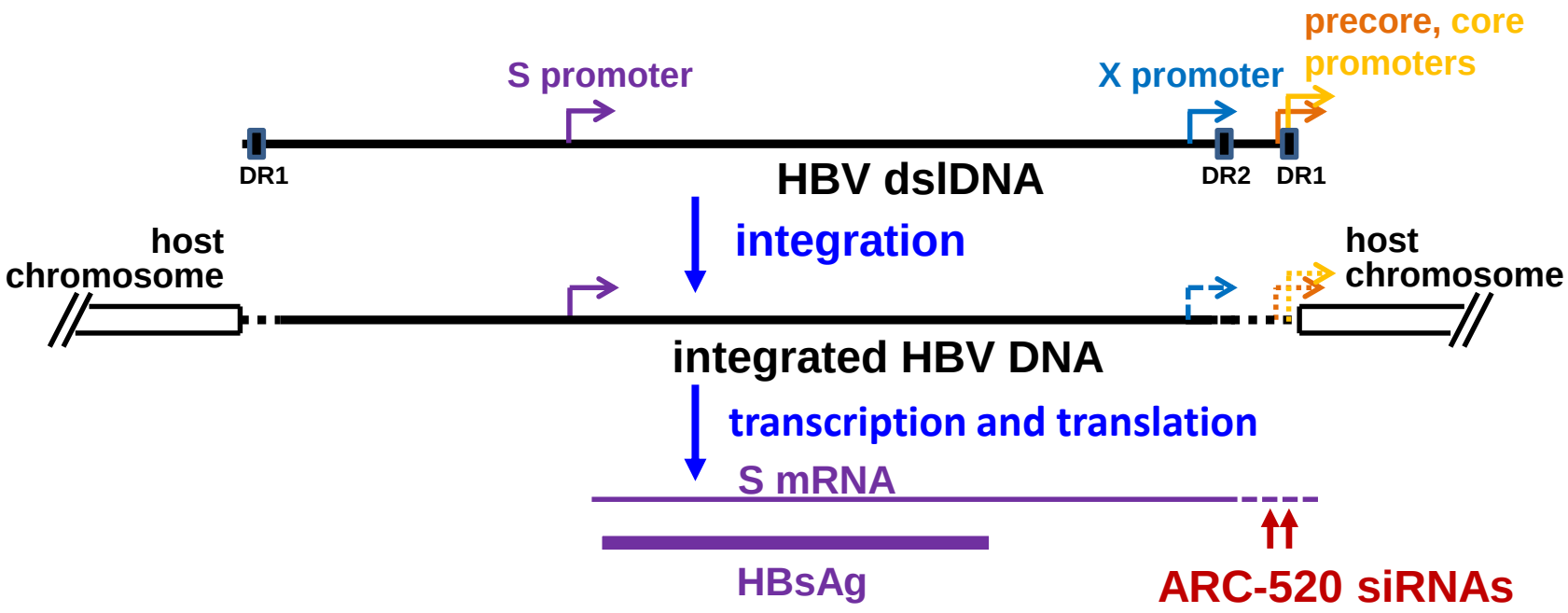
Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

HBV integration into the host genome



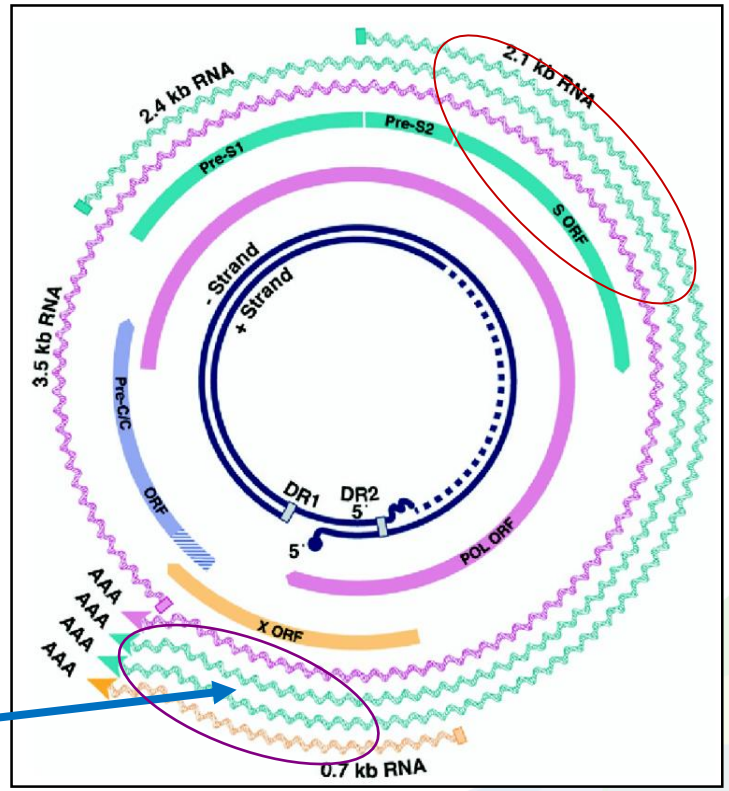
1. HBV DNA integrates into host chromosome, during which regions between DR2 and DR1 can be randomly deleted (not new!)
2. Significant HBsAg mRNA can be produced from integrated HBV DNA
   - These S transcripts contain complete HBsAg CDS
   - Expected loss of ARC-520 target sites in many

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

HBV Transcript Map



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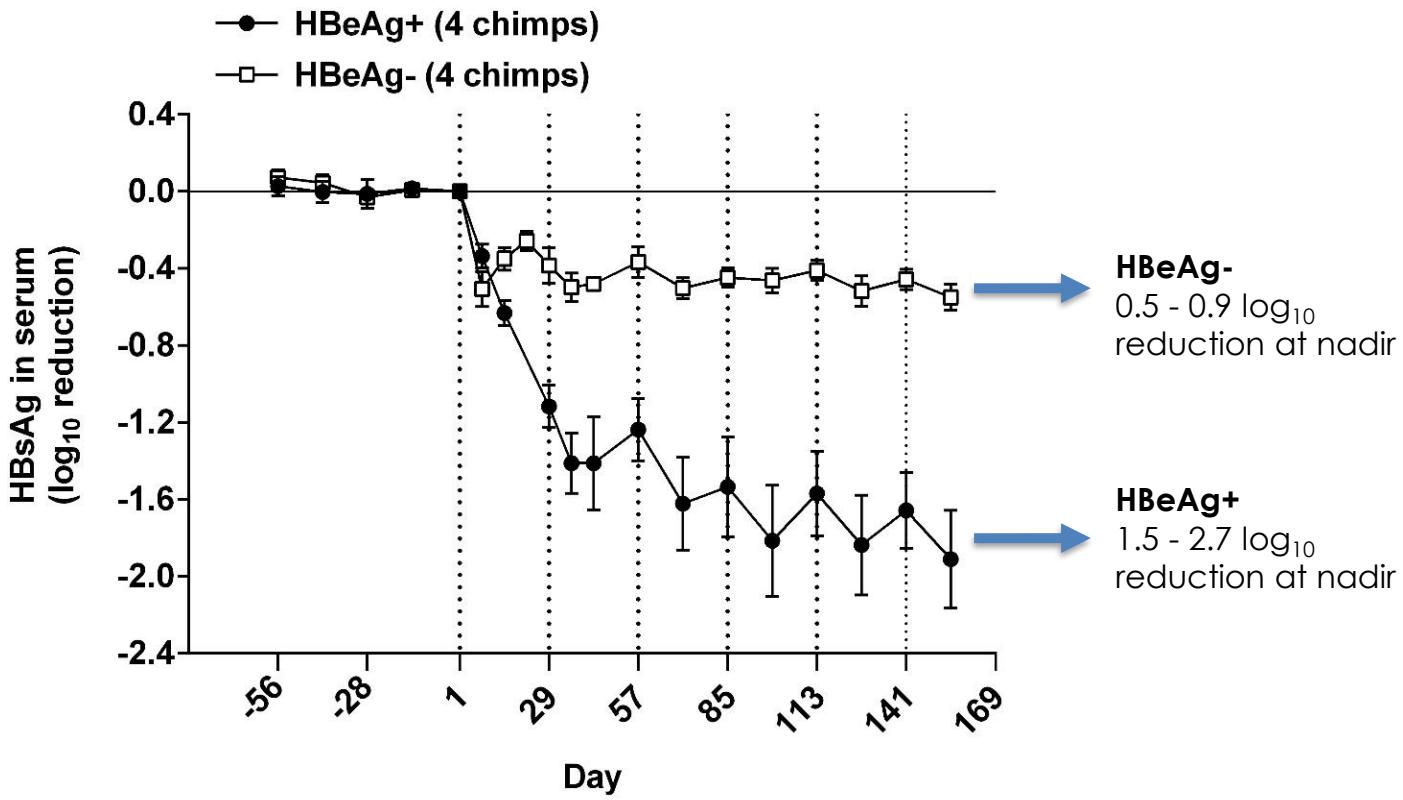
Differential HBsAg Reduction Observed in Chimpanzees (and Humans) with ARC-520



HBeAg positive responded better than HBeAg negative chimps

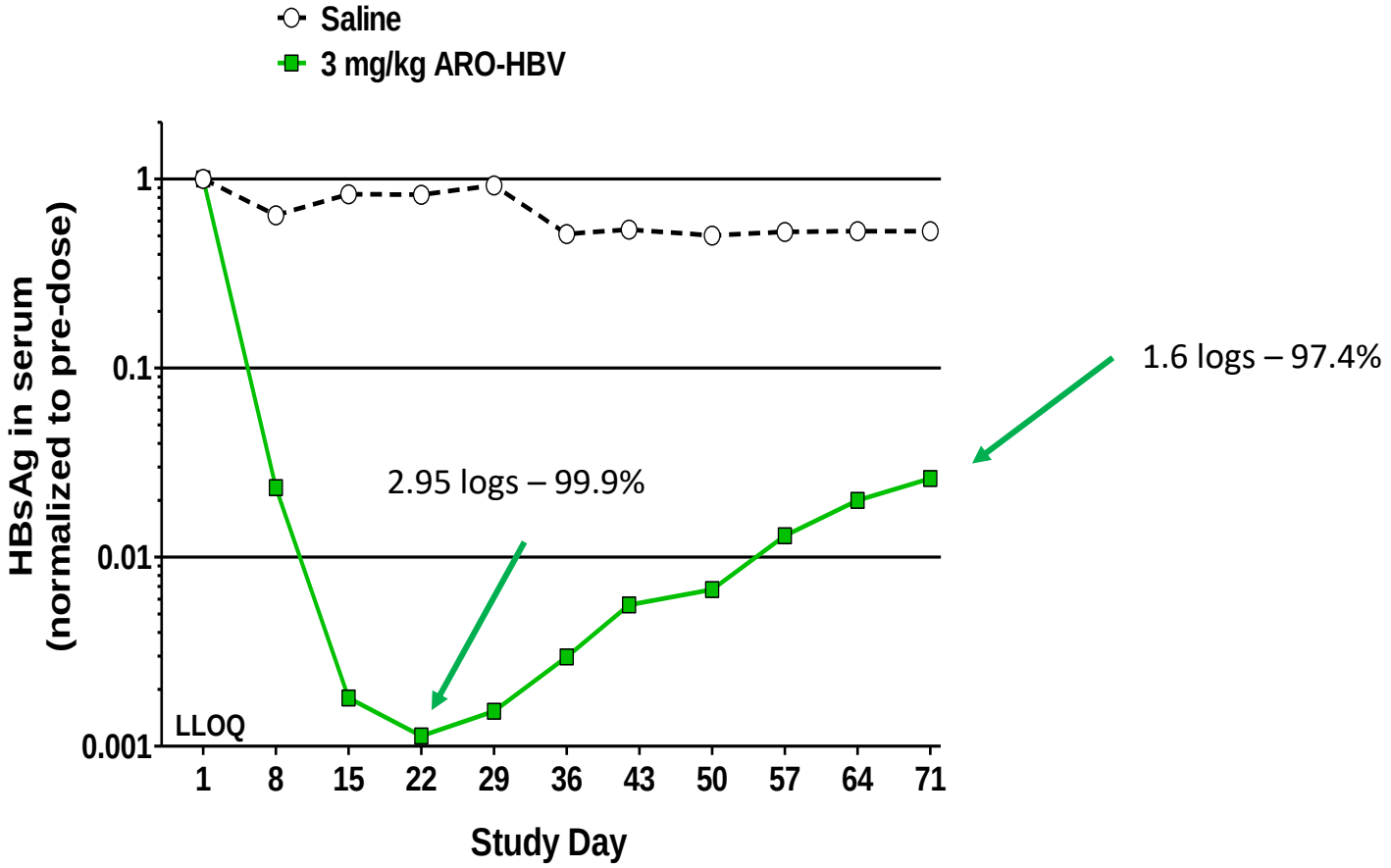
The same observation was made for treatment-naïve humans

ARO-HBV: Key Design Elements for the Next Generation

The Wish List:

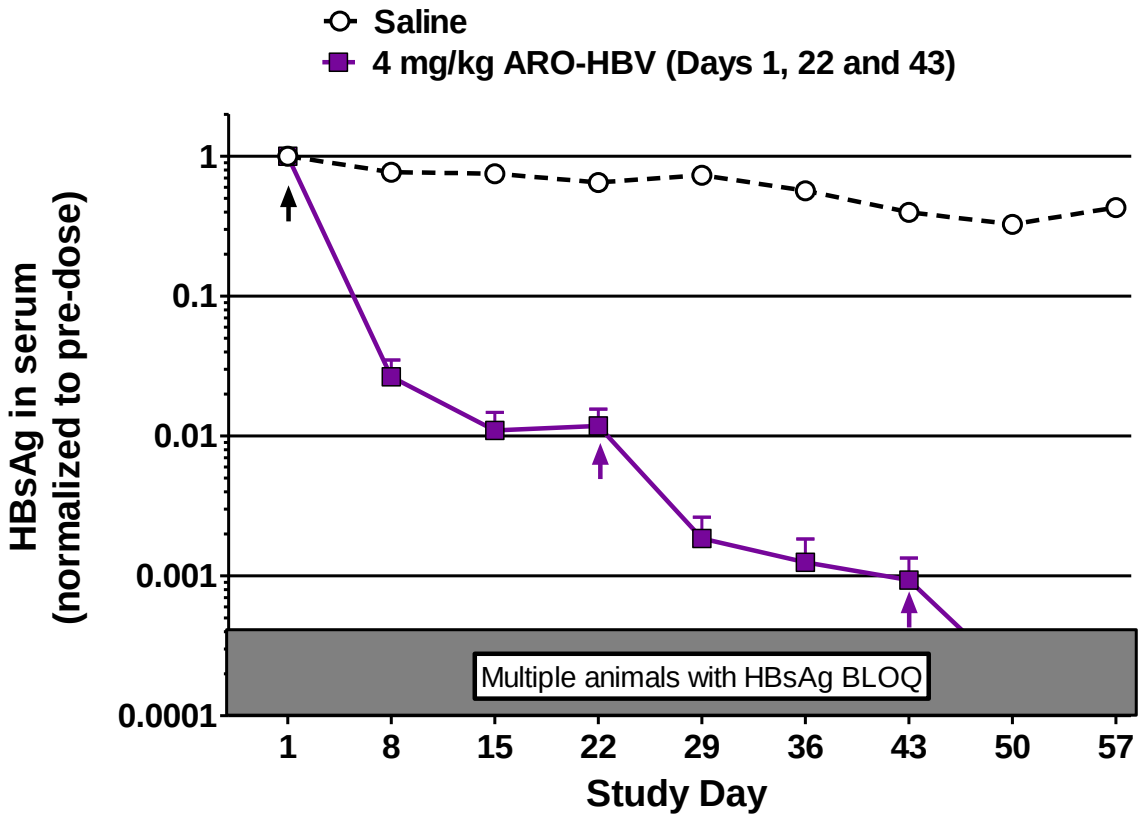
- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- Addresses full HBV transcriptome
  - Works for cccDNA *and* integrated-derived transcripts
- Multiple triggers to avoid resistance development
- Powerful HBsAg reduction
- Expectation of wide therapeutic index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

We Modeled Integration in a New, Mutated pHBV Transfected Mouse



HBsAg knockdown is deep and prolonged despite loss of x trigger site

Multiple dosing in intact pHBV mice reduces HBsAg below level of quantitation



>3 $\log_{10}$ reduction after 3 doses

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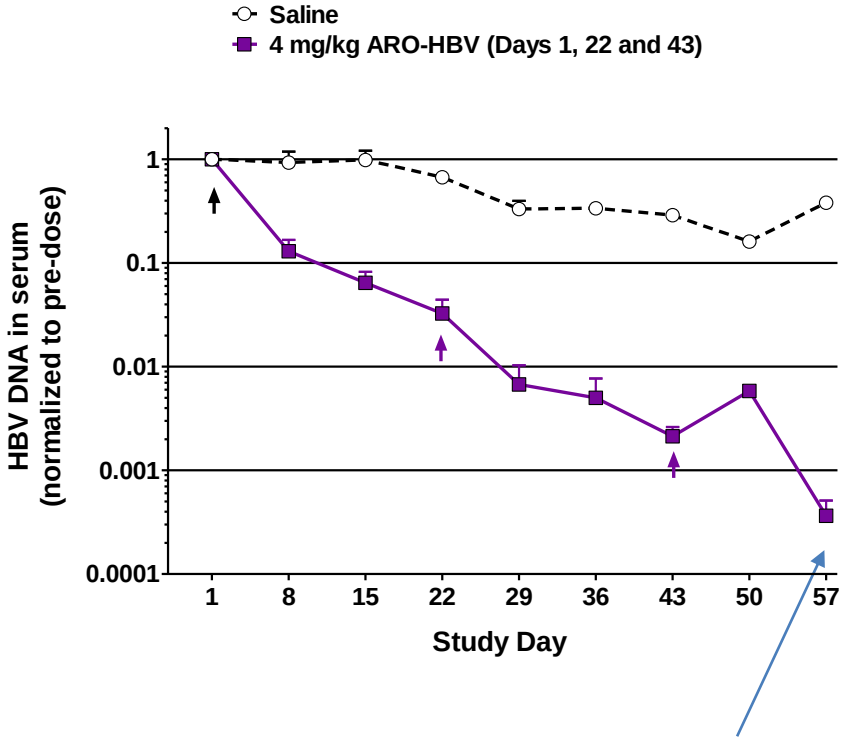
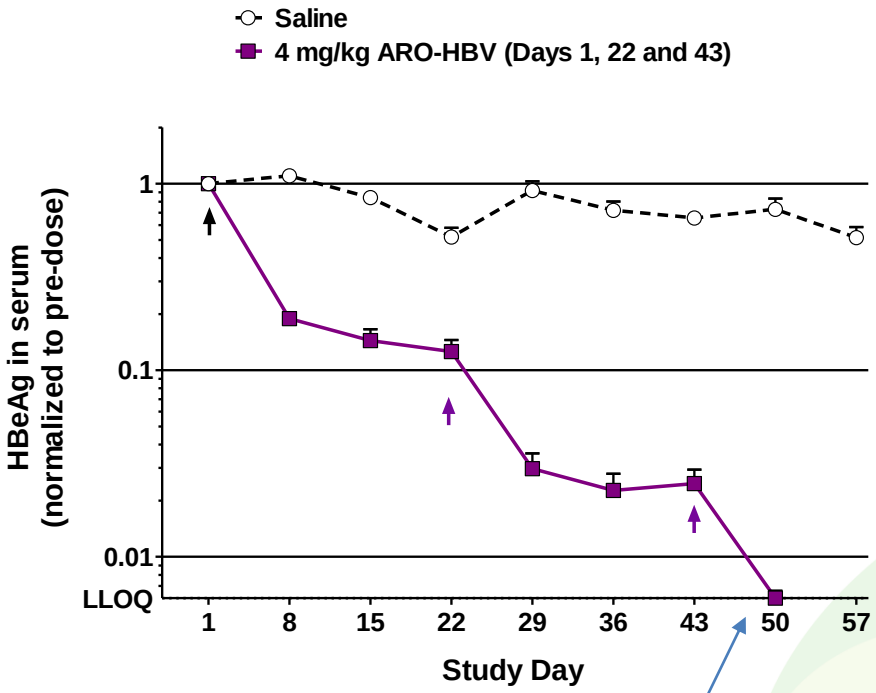
…..With deep knockdown also observed for HBeAg and HBV DNA





3.44 log10 =
>99.9% reduction

2.2 log10 =
99.4% reduction
to LLOQ

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Efficacy and safety in HBV patients (pending)

Why We see a Central Role for RNAi in HBV

- Attacks the entire transcriptome
  - Should synergize with **most/all** hepatocyte-active compounds (e.g. NUCs, NAPs, capsid inhibitors, x protein drugs, Rig-I inhibitors, etc) by reducing their viral inputs
  - Can reduce HBsAg from integrated DNA, which they likely can't
- Monthly (or less frequent) SQ dosing with unusually good tolerability should fit well with oral regimens
- ARC-520 data shows examples of immune recovery and control in humans and chimps
  - Creates real excitement that future combination work can build on this