RNAi in HBV – Learnings from the Arrowhead program

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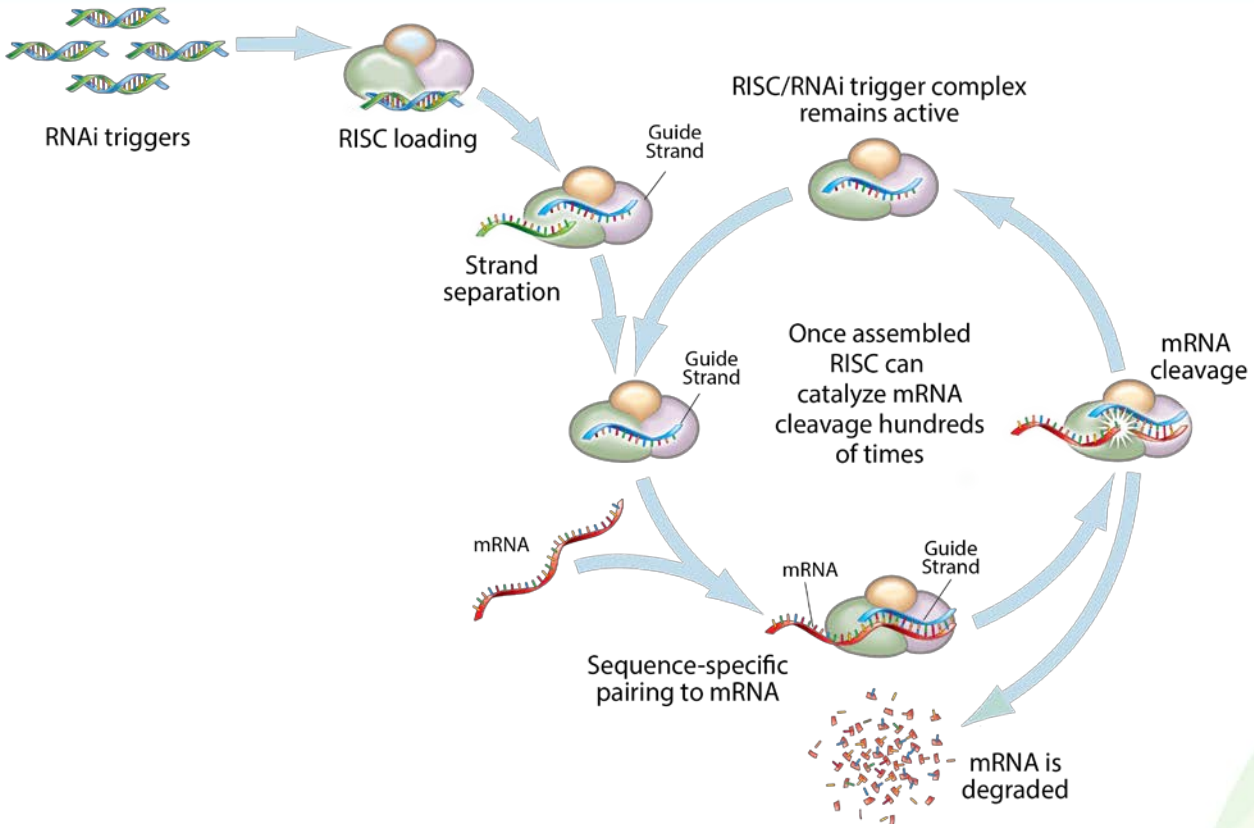
Target the Gene, Silence the Disease



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

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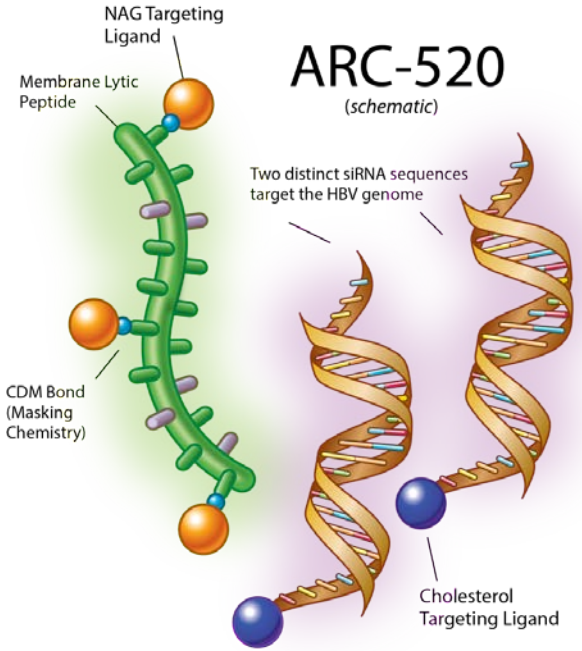
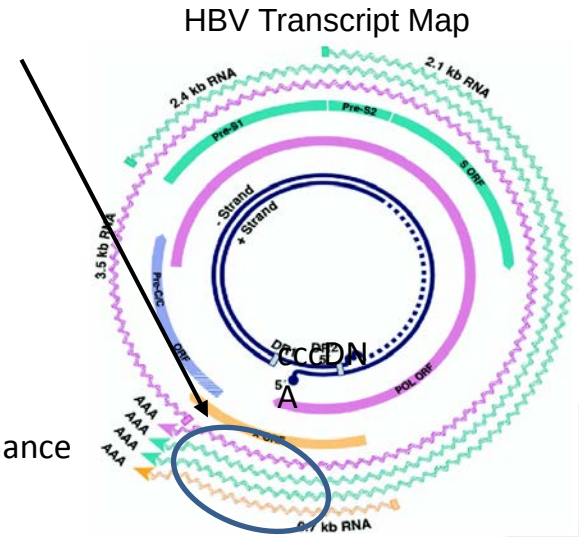
RNA interference therapeutic ARC-520 for chronic HBV infection

Designed to reduce all transcripts from HBV cccDNA



- **ARC-520 Excipient**
  - Hepatocyte-targeted DynamicPolyConjugate™ peptide (NAG-MLP) to enhance siRNA delivery
- **ARC-520 API**
  - Mixture of 2 cholesterol-conjugated siRNAs in solution
  - Inclusion of two siRNAs gives broader genotype coverage (>99%)



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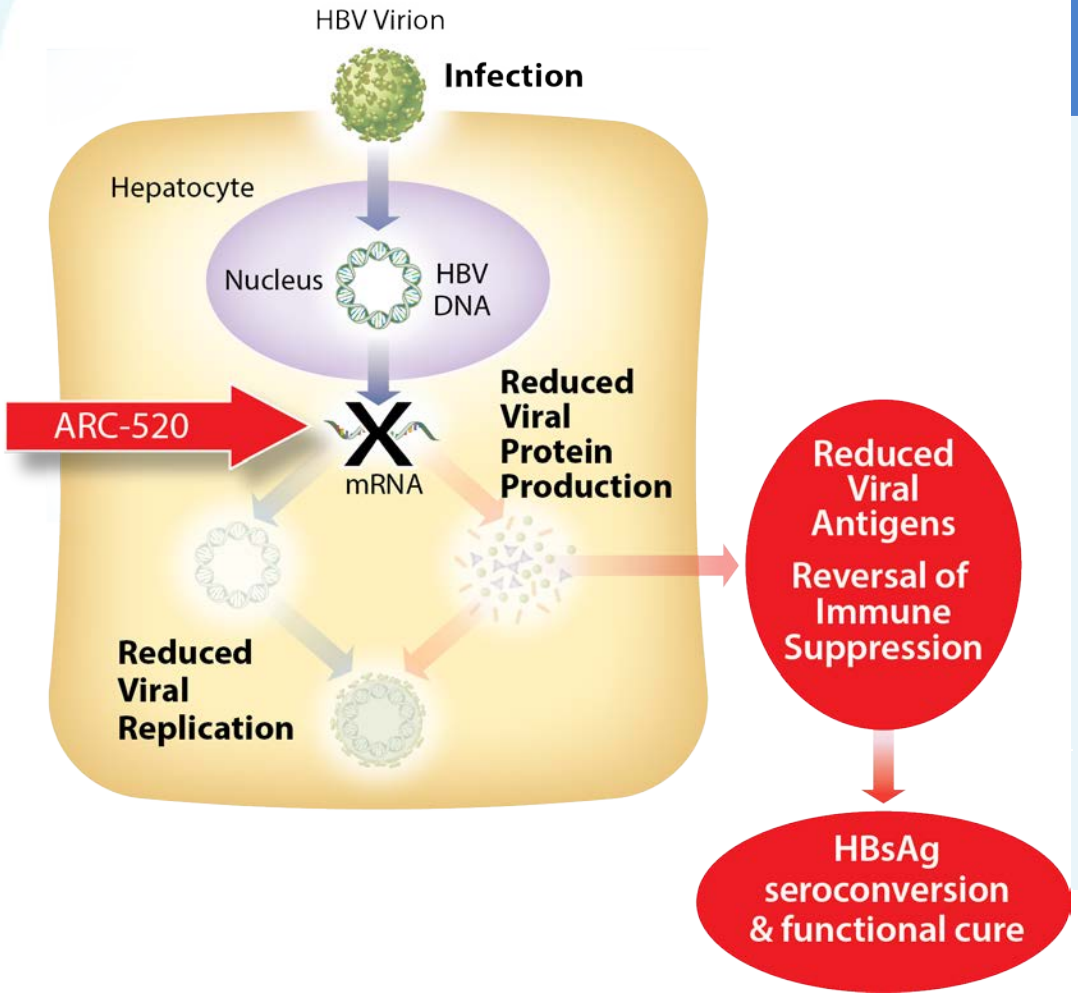
Theory of HBV RNAi Therapeutic

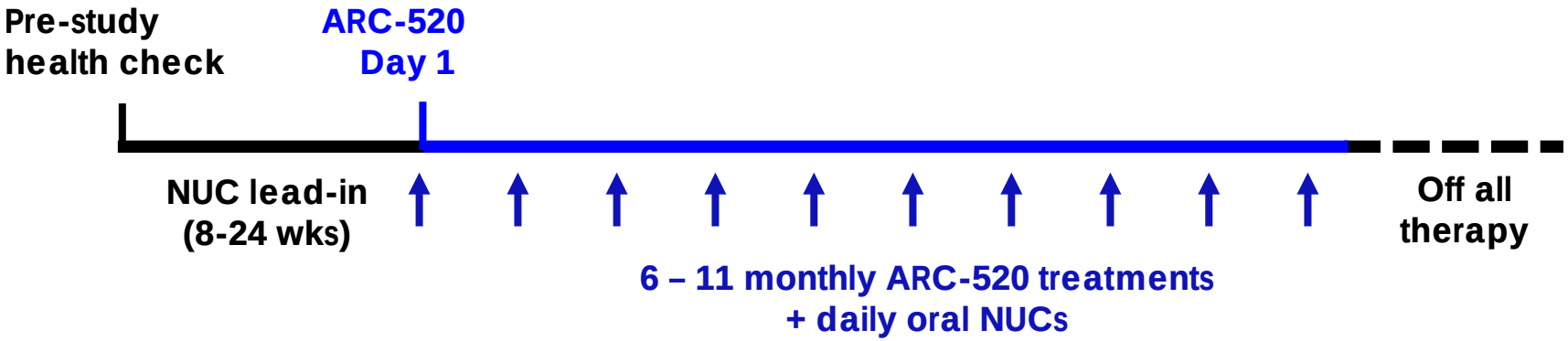


Silence Entire HBV Genome

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

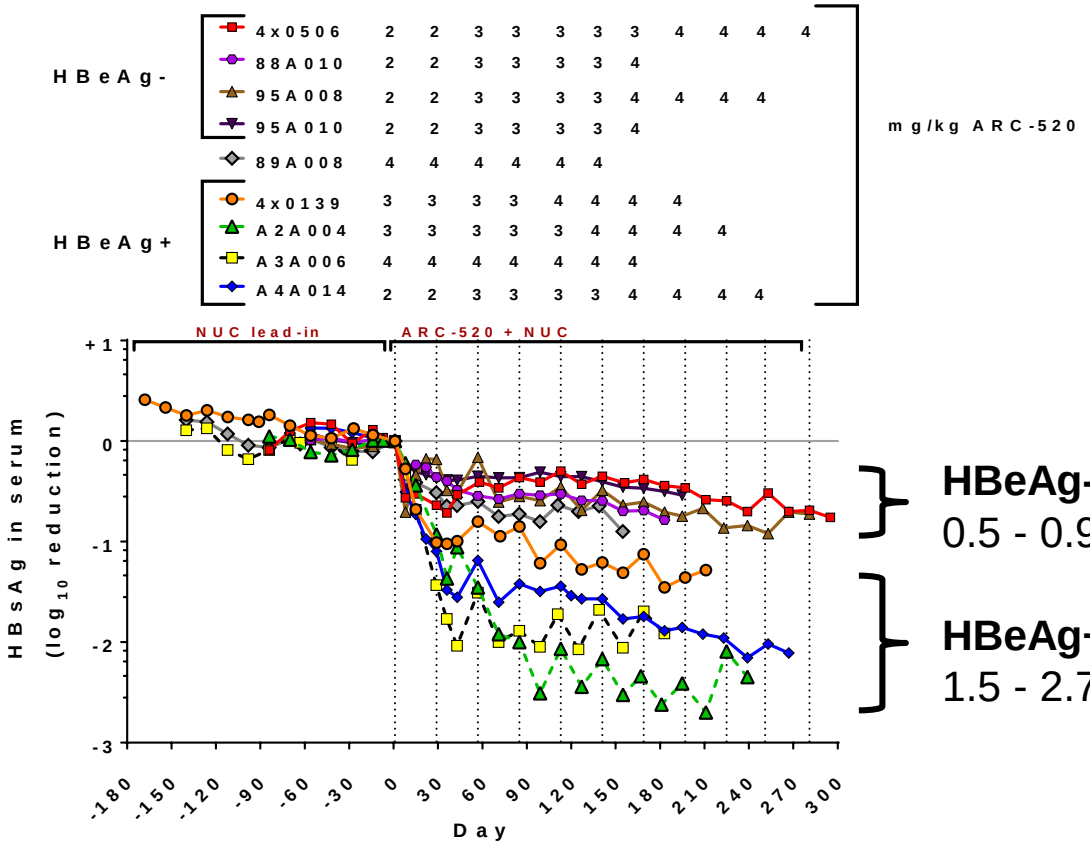
ENABLE A FUNCTIONAL CURE

Treatment of chimps with RNAi therapeutic ARC-520



- **Chimps**
  - 5 males, 4 females
  - 9-37 years old, HBV infected mostly since birth
  - 5 HBeAg+, 4 HBeAg- (1 became HBeAg- during NUC lead-in)
- **Treatment**
  - Daily oral NUCs
  - Up to 4 mg/kg ARC-520 dosed monthly
- **Monitor safety and efficacy**
  - Regular blood collection and periodic liver needle biopsies

HBsAg reduction correlated with HBeAg status

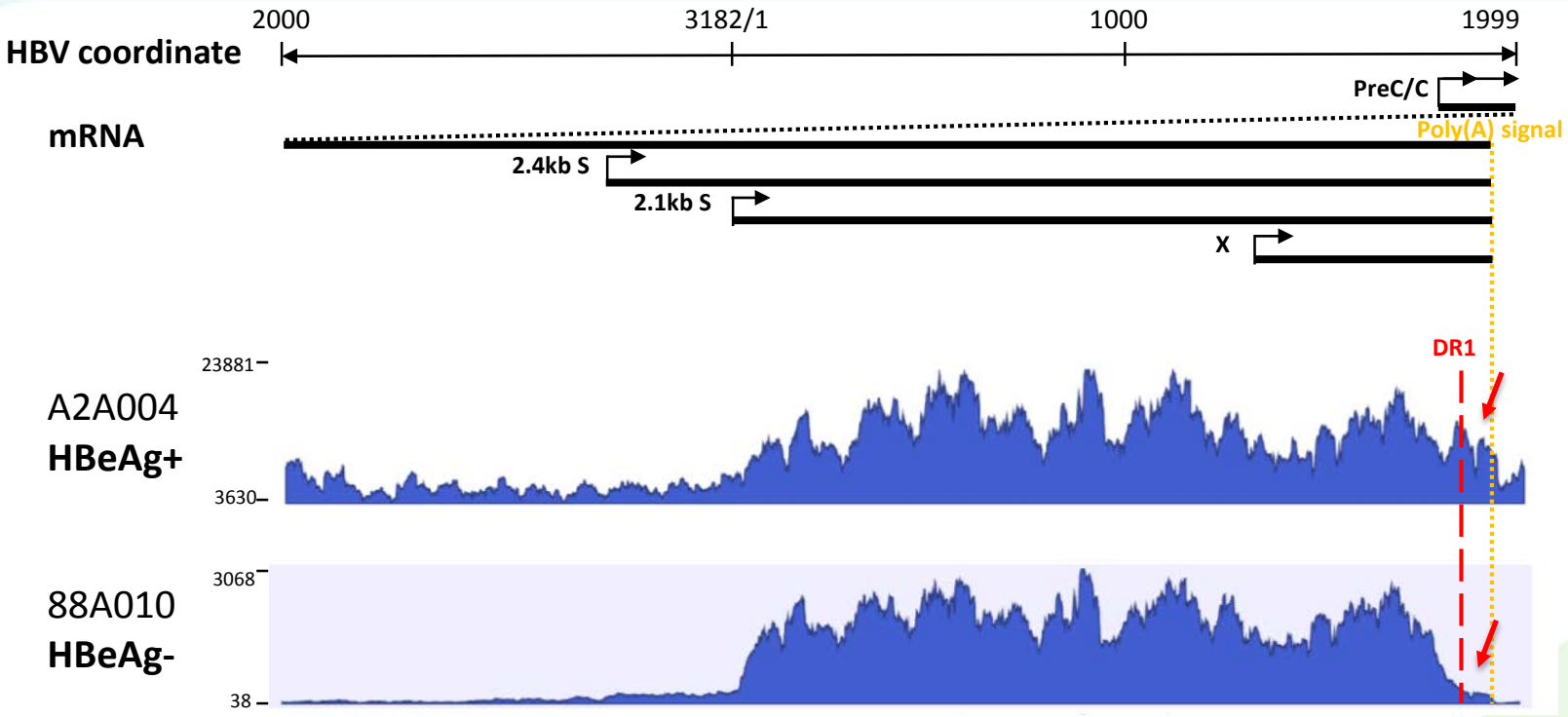


HBeAg-
0.5 - 0.9 $\log_{10}$ reduction at nadir

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

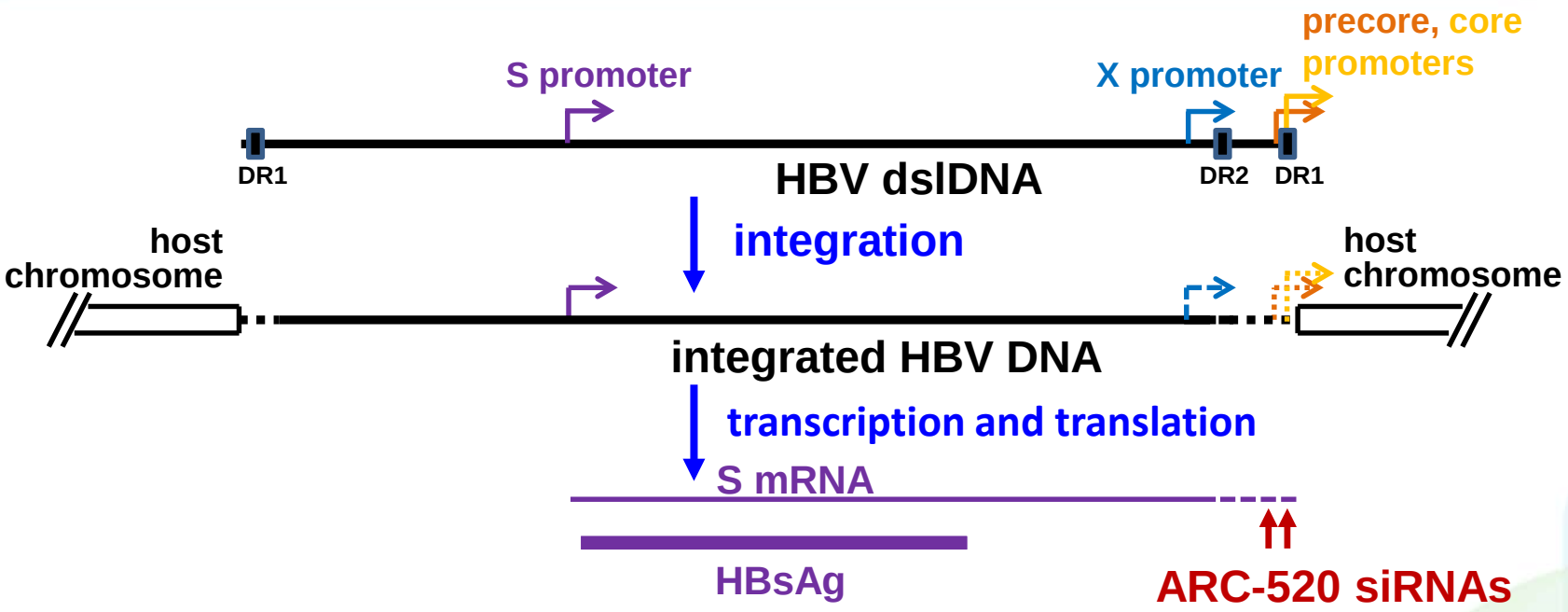
- *What accounts for the difference in response between HBeAg positives vs. negatives?*

Representative HBV transcript profiles in HBeAg+ and HBeAg- chimps (Illumina RNA-seq analysis)



- Fewer transcripts with HBV poly(A) signal in HBeAg- vs HBeAg+ chimps
- In HBeAg- chimps, frequency of reads is reduced in region near DR1 : known for high frequency integration
- *Are these transcripts coming from integrated HBV DNA?*

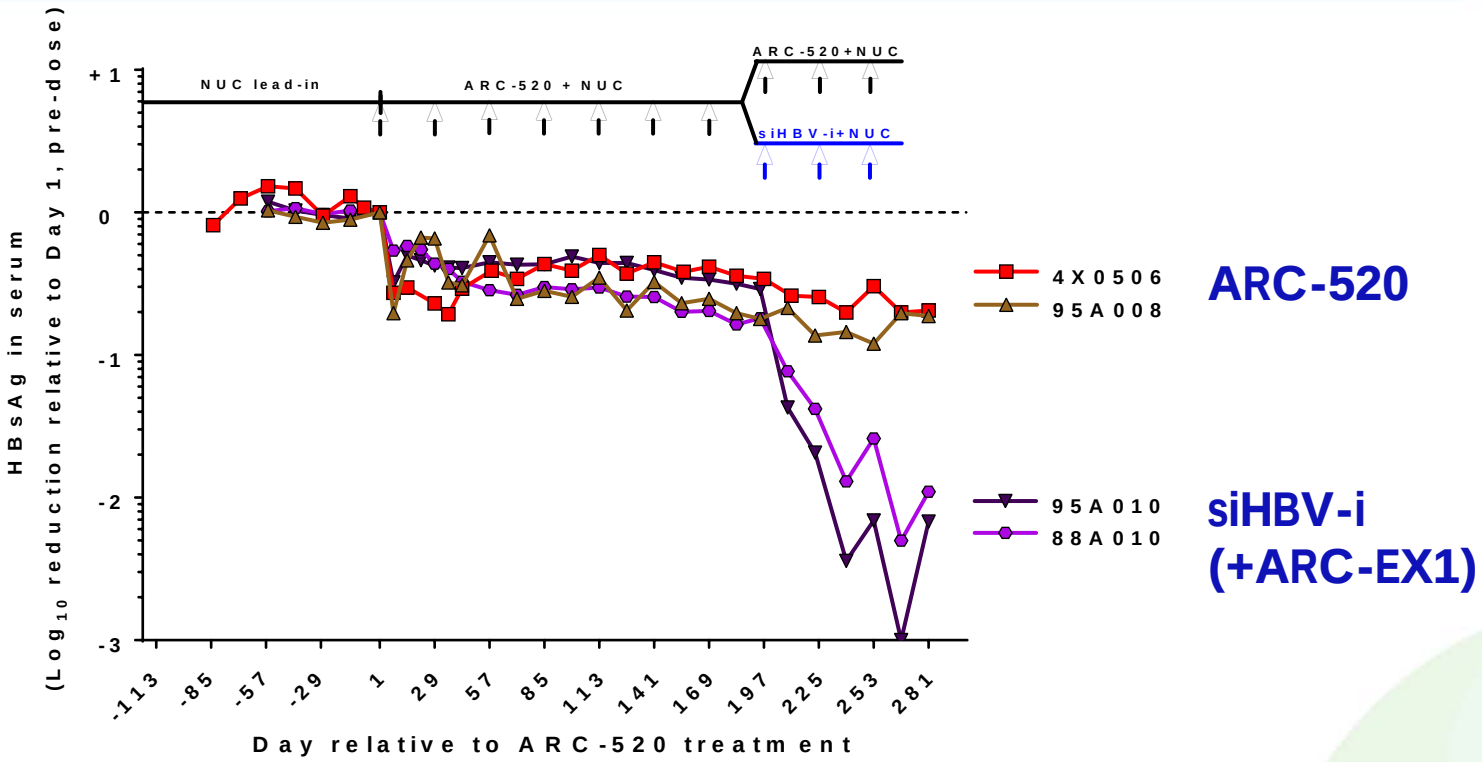
HBV integration into the host genome



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

siRNA designed to target RNA derived from HBV integration products in HBeAg- chimps



- siHBV-i targets HBV 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

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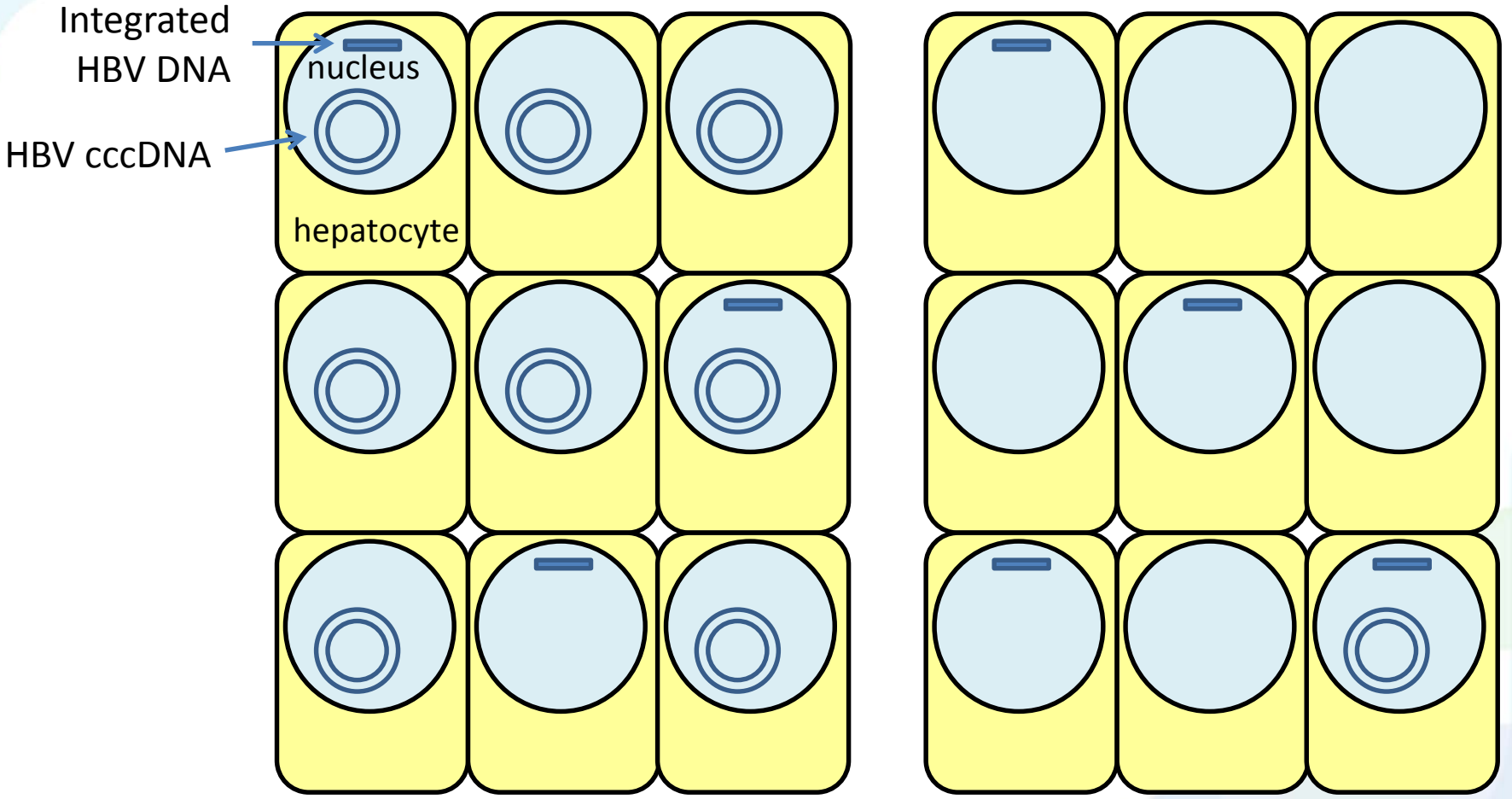
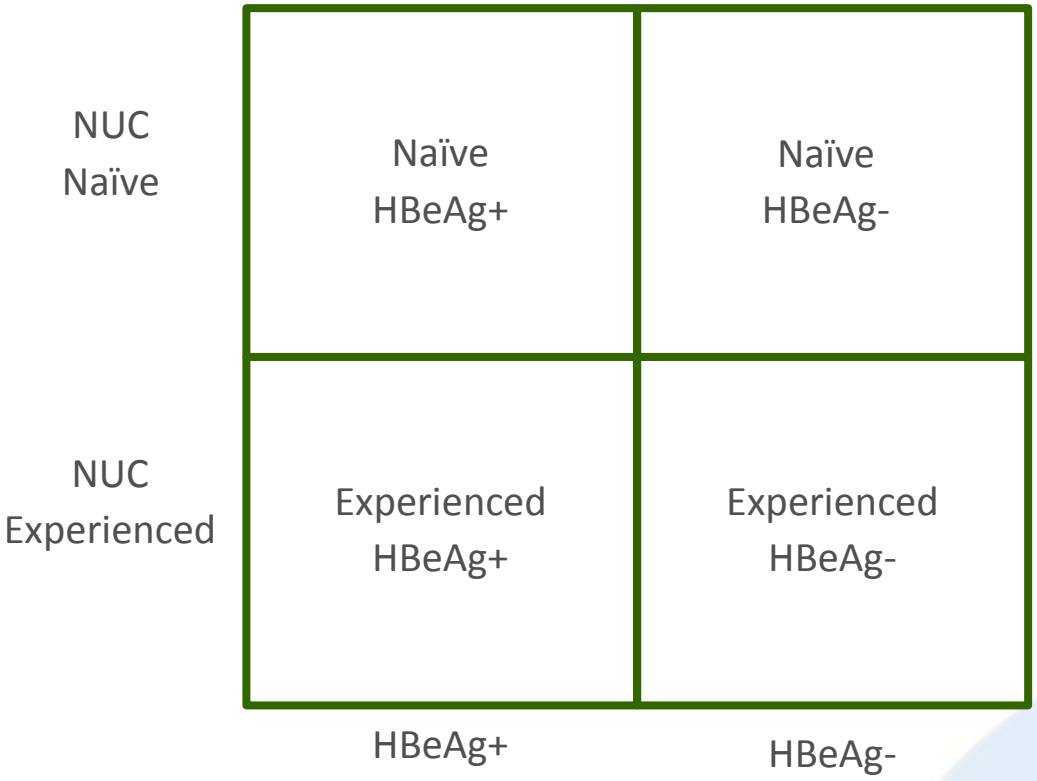
Conceptual representation of HBV DNA in liver lobules of HBeAg pos and HBeAg neg chimps



HBV patients as a 2 x 2 matrix

Think of the groups as quadrants
Defined by HBeAg status and NUC experience



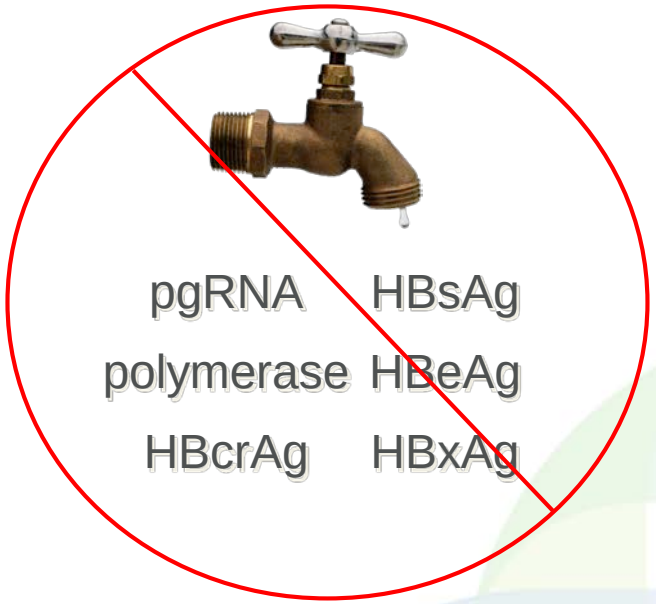
Basis of Difference in HBsAg Responses

Two Sources of Gene Expression

HBV DNA
Integrated into host DNA

HBsAg

HBV cccDNA



ARC-520 Silences cccDNA expression;
cccDNA decreases with transition from HBeAg+ to HBeAg-

Clinical Data from ARC-520 Phase 2a SAD

				Log reduction from baseline Mean (max)		
Cohort	Dose [mg/kg]	HBeAg status	Prior ETV	HBsAg	HBcrAg	HBeAg
4	4	Neg	Y	-0.4 (-0.5)	-0.9 (-1.1)	N/A
5	4	Pos	Y	-0.3 (-0.7)	-0.9 (-1.1)	-1.2 (-1.7)
7	4	Pos	N	-1.5 (-1.8) †	-1.4 (-1.8)	-1.6 (-2.0) †
7	4	Neg	N	-0.3 (-0.5)	N/A (-0.7)	N/A

† Excluding transitional patient

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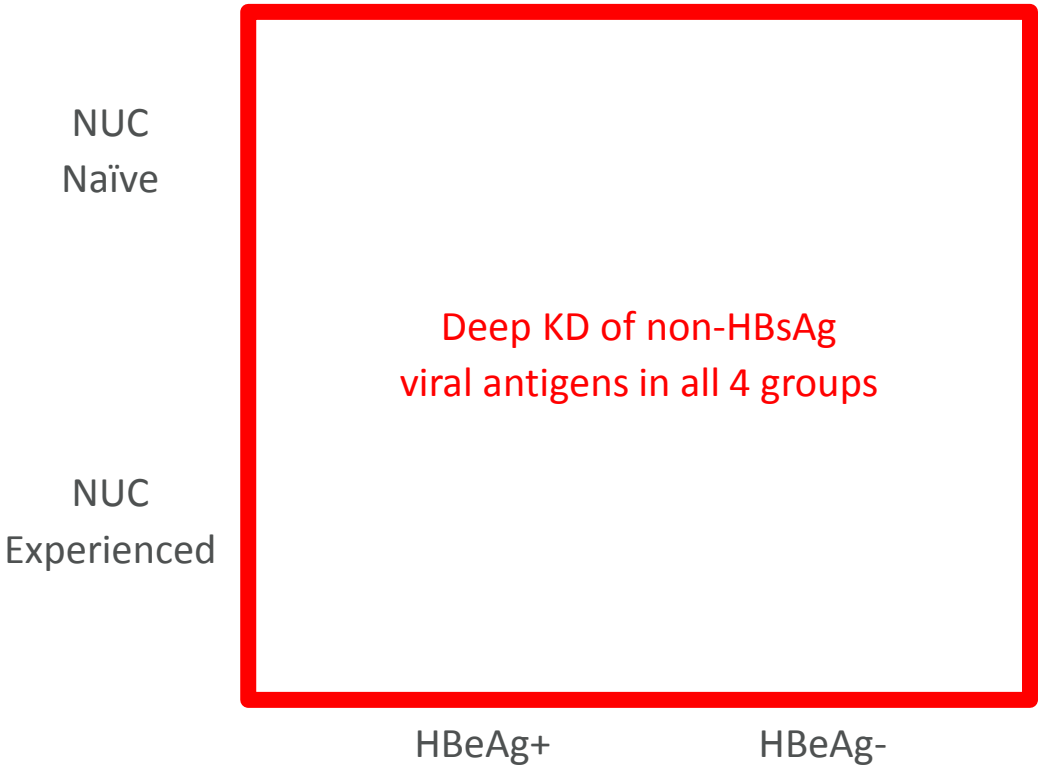
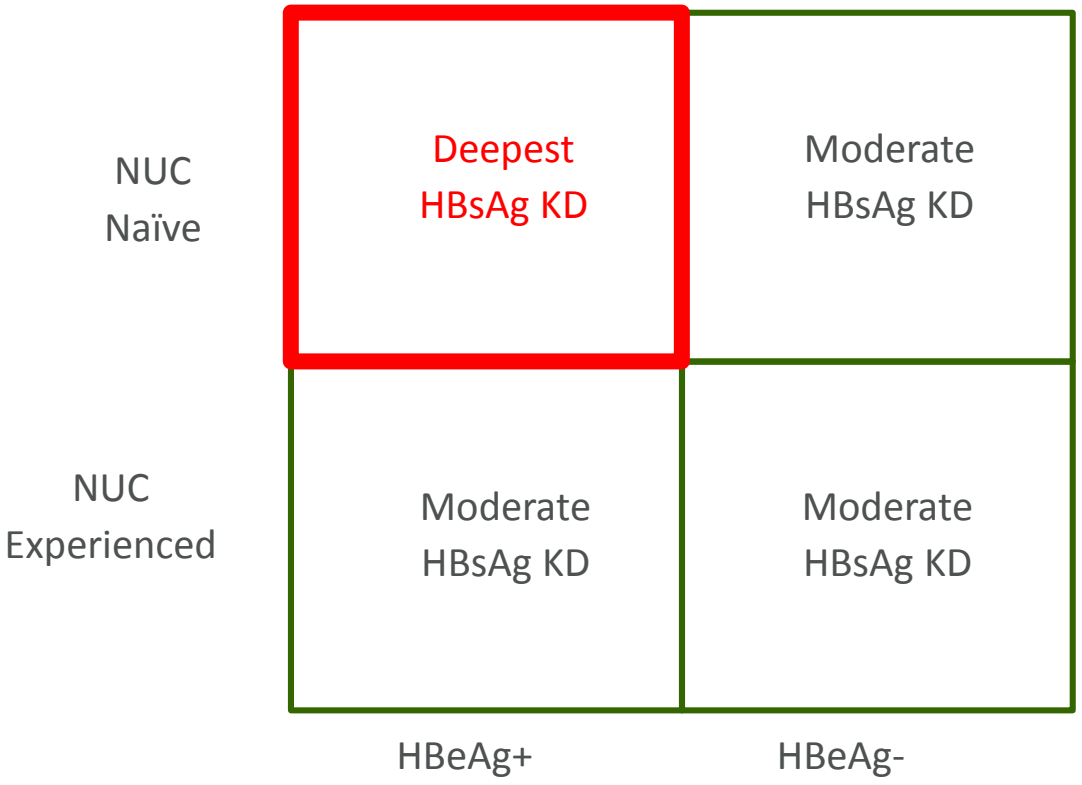
ARC-520 cccDNA-derived KD Profiles in the Four HBV Groups



ARC-520 targets cccDNA; all non-HBsAg antigens are only expressed by cccDNA

ARC-520 HBsAg reduction in All Subgroups; Most Potent in One



~50% of US market in this subgroup
~40% of Asian market in this subgroup
~33% of European market in this subgroup

ARC-520 Key Points

- Well tolerated, infusion reactions in 6% of infusions
- Deep HBsAg KD in treatment-naïve HBeAg+ patients
  - Max 99% HBsAg KD (1.9 log); mean nadir 97% (1.5 logs)
  - Speaks to "HBsAg theory" of achieving functional cure
- Clearly disrupts virus in NUC-experienced and HBeAg- patients
  - >1 log KD of HBeAg, HBcrAg, and presumably others
  - ARC-520 intended for multi-dose therapy: sustained measurable HBsAg KD and very deep KD of **all** other antigens could be important to reaching functional cure
  - Could be important beyond "HBsAg theory"

ARC-520 is very potent at silencing cccDNA: could be key component in achieving functional cure

What About the Rest of The Market

ARC-521

- Safety expected = ARC-520
- Optimized to silence integrated- and cccDNA
- Validated in chimps
  - >99% KD
- Complement to ARC-520
- Accelerated design Phase 1/2 ongoing
  - SAD in healthy volunteers started June 2016
  - MAD in HBV patients started September 2016

De-risked program with safety/activity of ARC-520
Multiple data readouts starting in early 2017

Ongoing HBV Clinical Studies

- ARC-520 multiple dose P2b studies underway
  - 2002: ARC-520 + NUCS in e- NUC-experienced patients (Europe/Asia)
    - Expected to complete enrollment in 2016
  - 2003: ARC-520 + NUCS in e+ NUC-experienced patients (Europe/Asia)
    - Expected to complete enrollment in 2016
  - 2004: ARC-520 + NUCS in e+ NUC-experienced patients (US only)
    - On clinical hold
  - 2001 extension: ARC-520 + NUCS in e-/e+ NUC-experienced/naïve patients (open label)
    - Expected to complete enrollment in 2016
  - 2007: Long term open label extension study for 2002 & 2003
  - Monarch (2008) combination studies: : ARC-520 alone; ARC-520 + NUCS + other agents in NUC-naïve patients (open label)
    - Monotherapy and triple combination with NUCs and interferon actively enrolling now
    - Expect additional arms with new combinations this year and beyond
- ARC-521 in Phase 1/2 underway
  - SAD in healthy volunteers dosing
  - MAD in HBV patients dosing
  - Readouts expected to start in 2017

Selected lessons that we've learned

- RNAi works as expected in HBV
  - We'll learn a lot about combinations over next year +
- Integrated DNA is an important source of HBsAg
  - Forces the field to re-think development programs
  - Complete cccDNA suppression won't clear HBsAg on its own
  - HBsAg clearance vs inactive carrier status as best endpoint?
- In naïve patients ARC-520 accelerates the response to NUCs and drives DNA suppression faster
- For ARC-520, HBSAg response is maximal in naïve, HBeAg positive patients as predicted from chimps
  - ARC-521 designed to be agnostic as to HBV patient type
  - Read out available on ARC-521 1H17