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New Insights on HBV Biology from the ARC-520 Development Program

HepDART 2015
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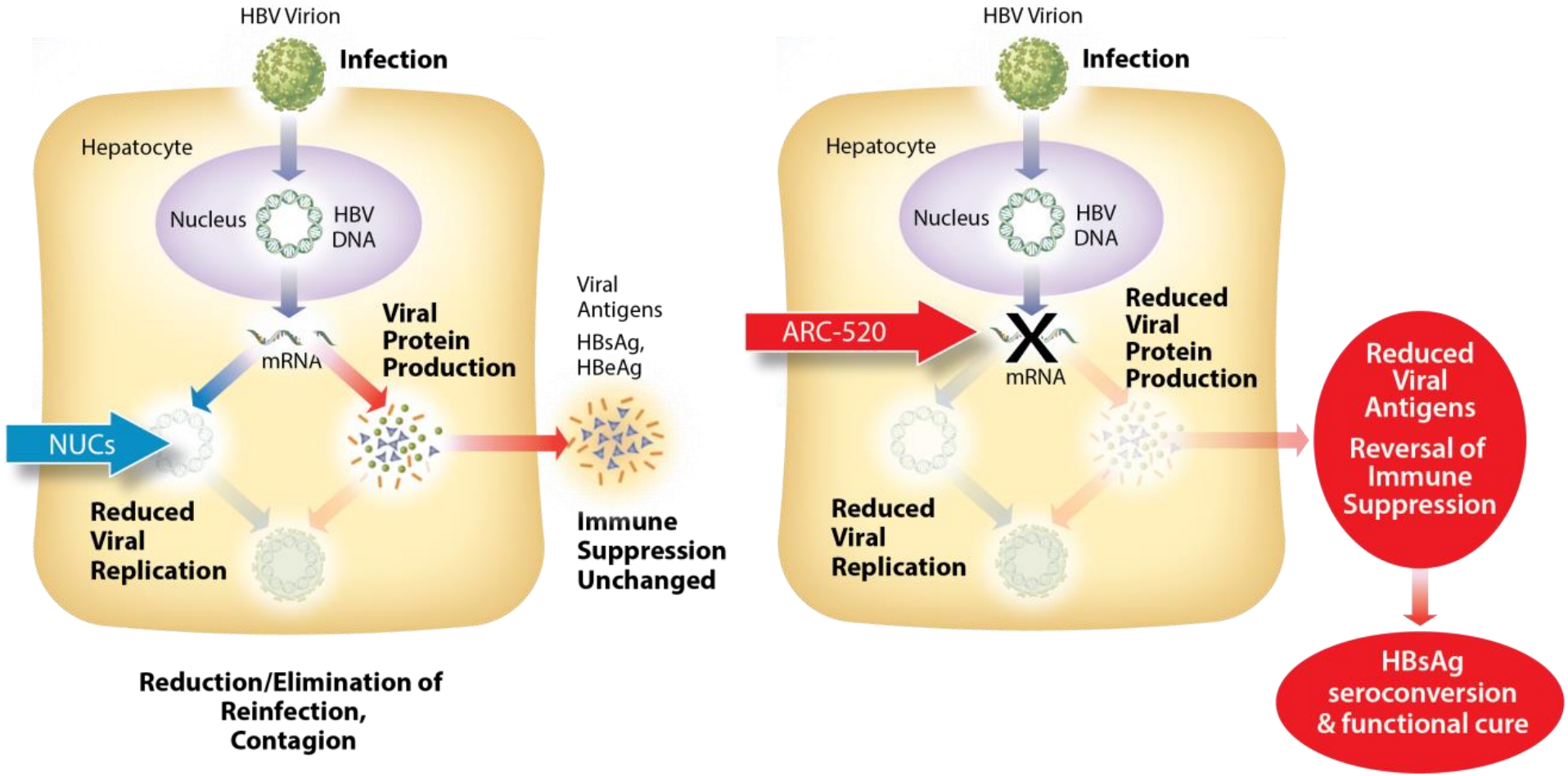
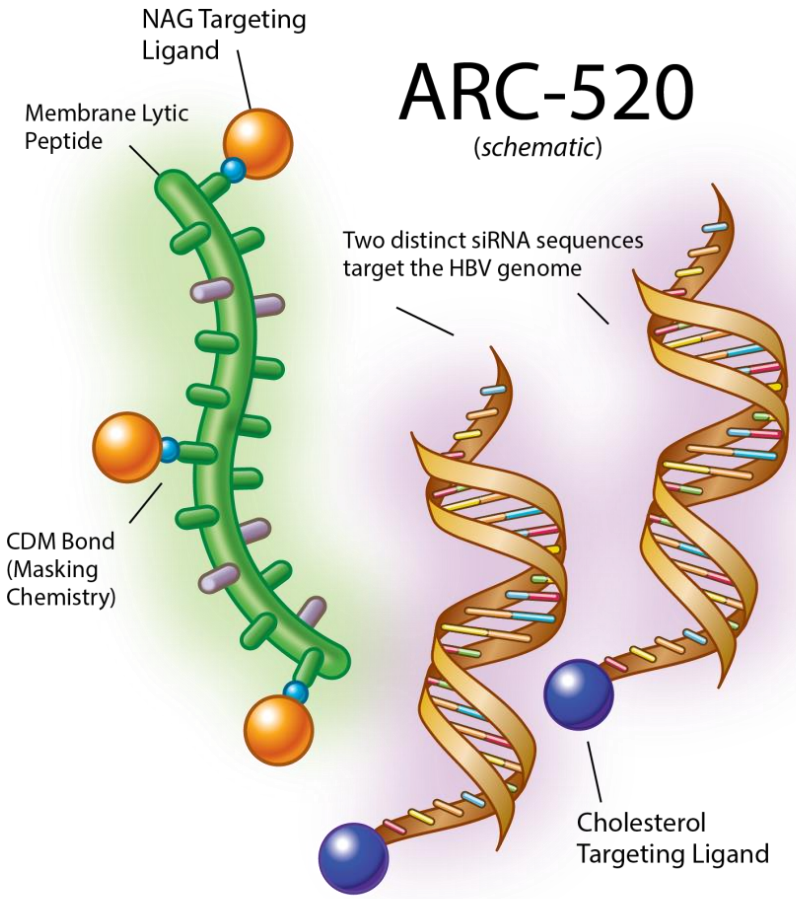
Mechanistic comparison of RNAi therapeutics vs. reverse transcriptase inhibitors (NUCs)



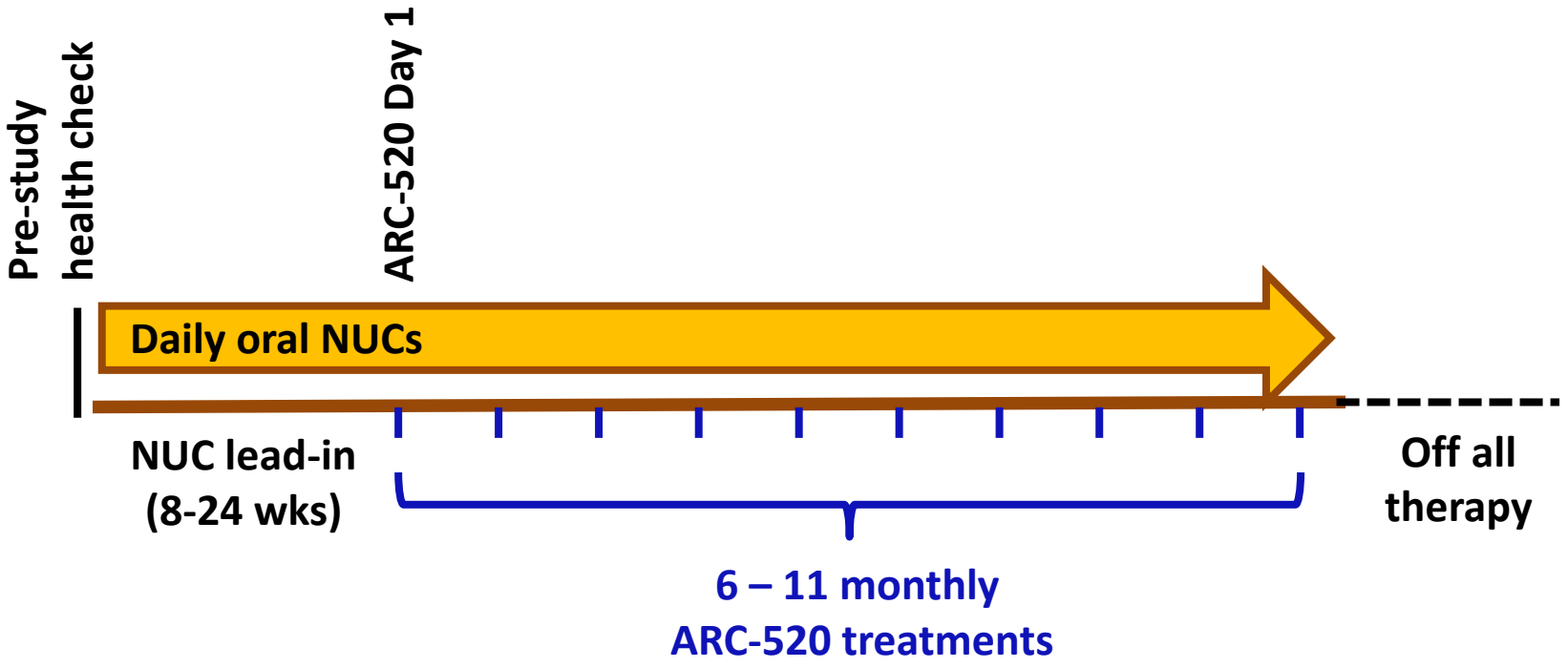
RNA interference therapeutic ARC-520 for chronic HBV infection

Designed to reduce all transcripts from HBV cccDNA



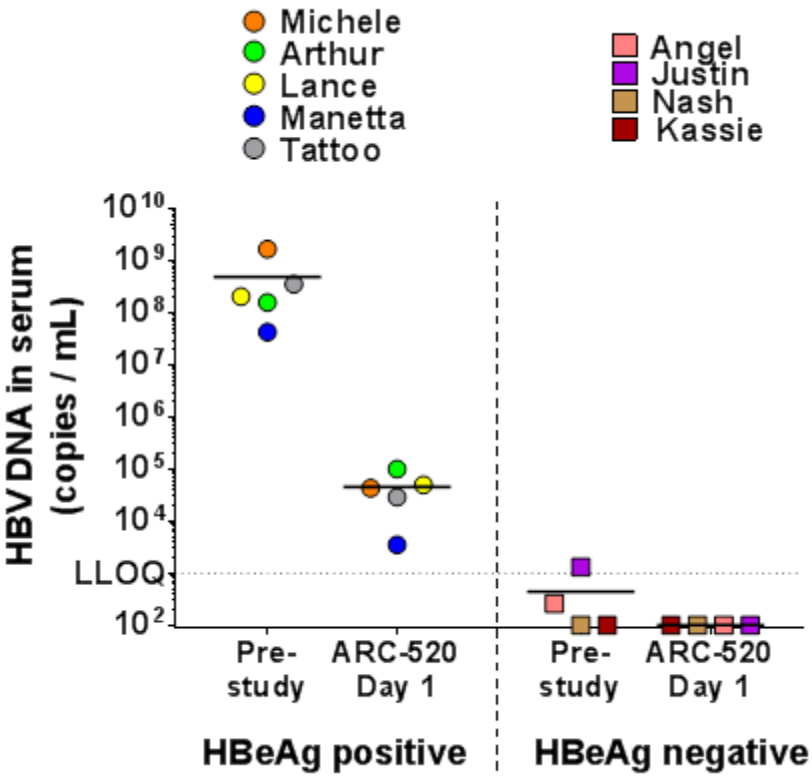
- **ARC-520 Excipient**
  - Hepatocyte-targeted DynamicPolyConjugate™ peptide (NAG-MLP) to enhance siRNA delivery
- **ARC-520 API**
  - Mixture of 2 cholesterol-conjugated siRNAs in solution
  - Inclusion of two siRNAs gives broader genotype coverage (>99%)

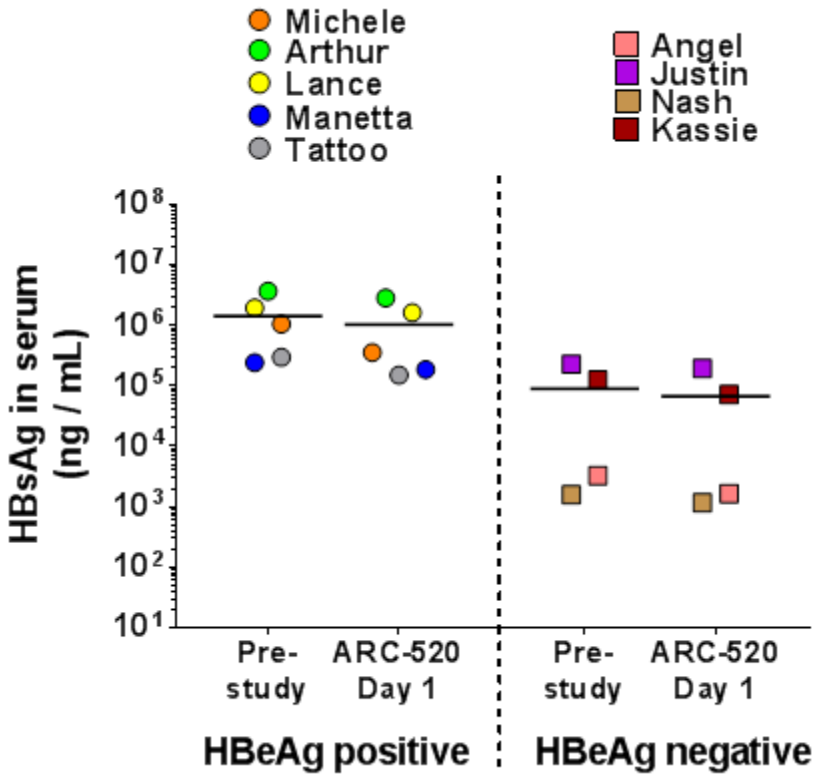
Chimp dosing and sampling timeline



- Daily oral NUCs:
  - 0.5 or 1.0 mg entecavir (ETV)
  - 300 mg tenofovir added at week 15 for chimp Michele
- Monitor safety and efficacy
  - Blood collection performed throughout study
  - Periodic liver needle biopsies

NUC lead-in: HBV serum DNA but not HBsAg decreased

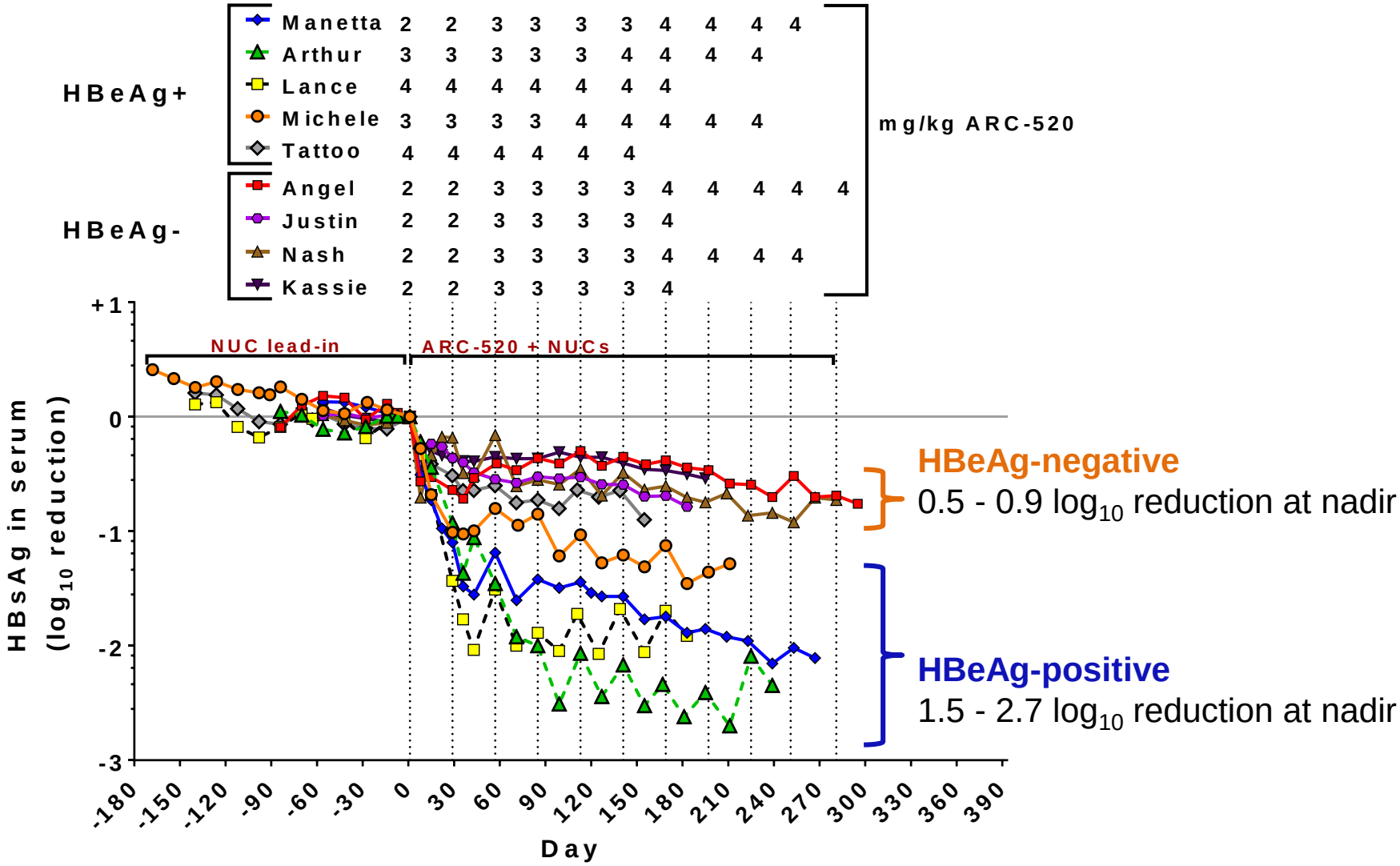




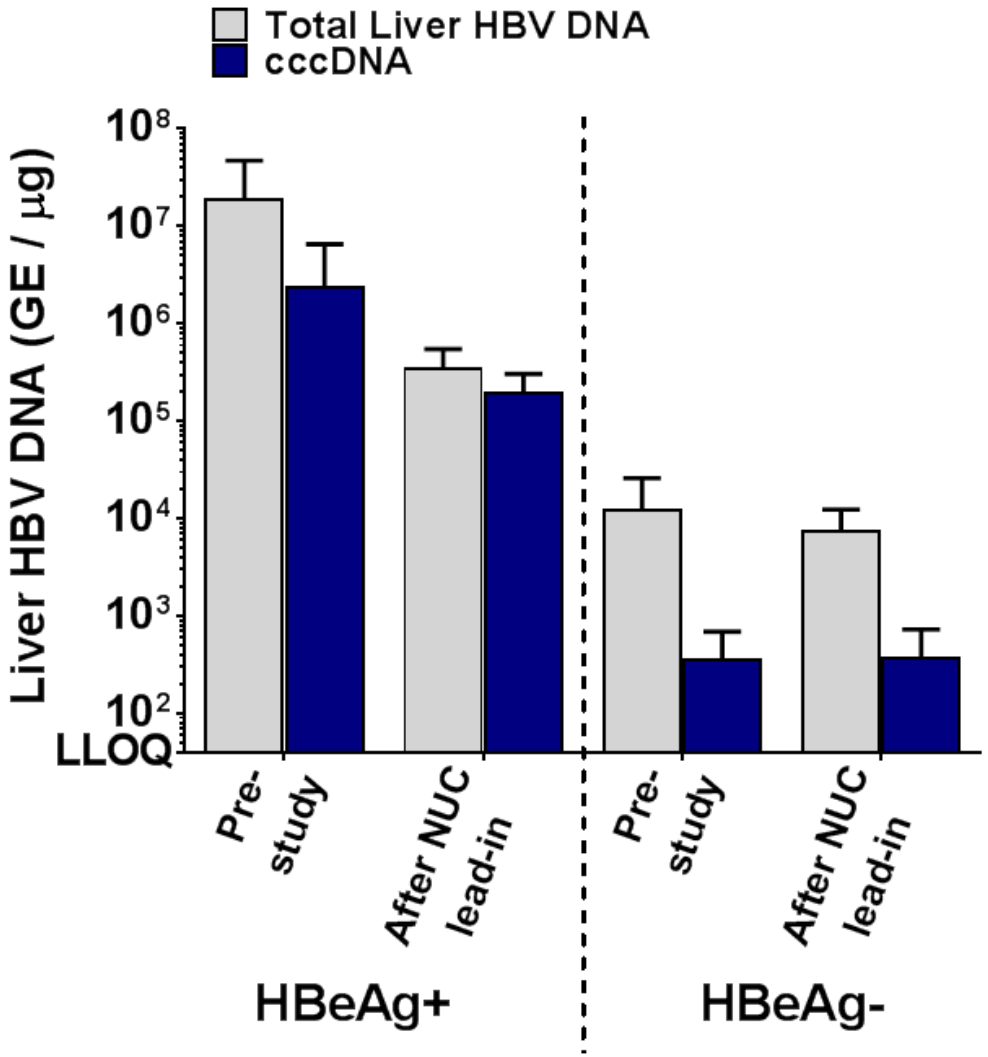
Chimp response to NUC therapy similar to humans:

- Deep decrease in serum HBV DNA in HBeAg+ chimps
- Serum HBV DNA in HBeAg- chimps dropped below the LLOQ
- NUC treatment had minimal effect on HBsAg levels

Chimp Study: Differences in degree of HBsAg reduction are correlated with HBeAg status

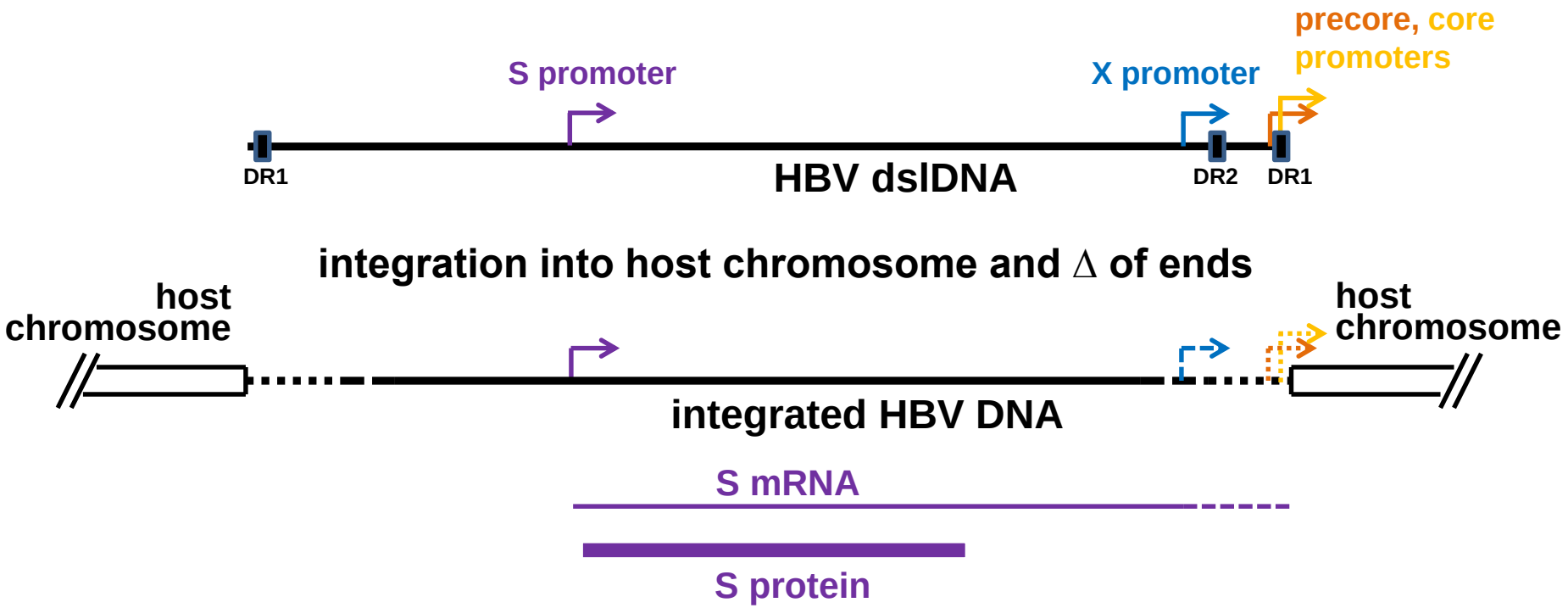


Predominant form of liver HBV DNA differs in HBeAg- vs. HBeAg+: NUC lead-in data



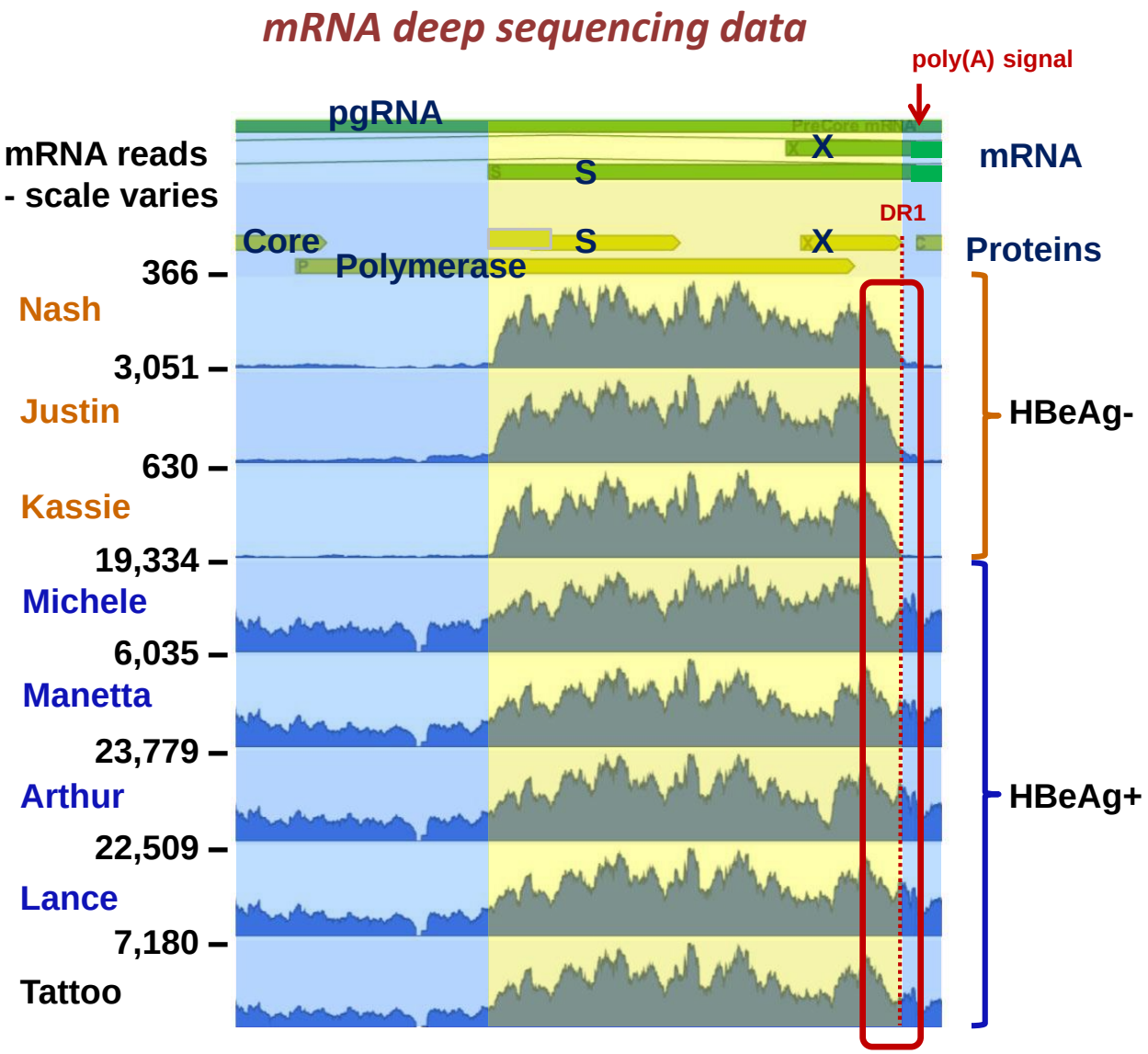
- ***HBeAg positive chimps***
  - Total HBV and cccDNA is decreased on NUCs
  - Reflective of high level of productive HBV replication
- ***HBeAg negative chimps***
  - Marginal decrease of total HBV DNA with NUCs
  - Low levels of cccDNA
  - **Data suggests most HBV DNA is integrated (not dependent on HBV replication)**

Integration of HBV DNA into the host chromosome



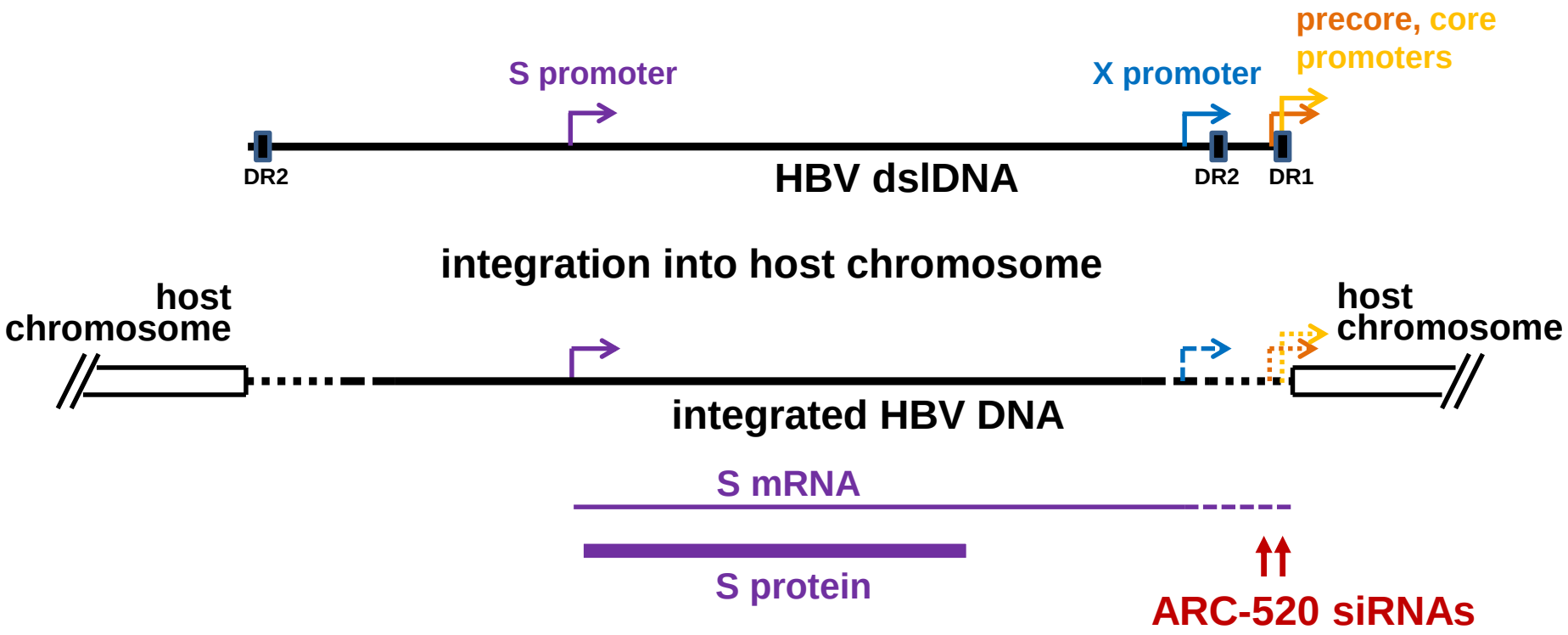
- HBV DNA integration occurs throughout infection largely via dslDNA and introduces deletions near the DR sites
- S protein ORF and trx control elements remain intact and would allow expression of HBsAg
- **A significant proportion of total HBV DNA in HBeAg negative chimps may be integrated DNA**

HBV transcript profiles differ between HBeAg- and HBeAg+ chimps



- ***HBeAg positive chimps***
  - Relatively balanced transcription of S and other cccDNA-dependent transcripts
- ***HBeAg negative chimps***
  - S transcripts make up a higher proportion of total HBV transcripts
  - Frequency of S gene transcript reads is reduced in region surrounding the DR1 site.
  - **These results are Indicative of expression from integrated HBV DNA**

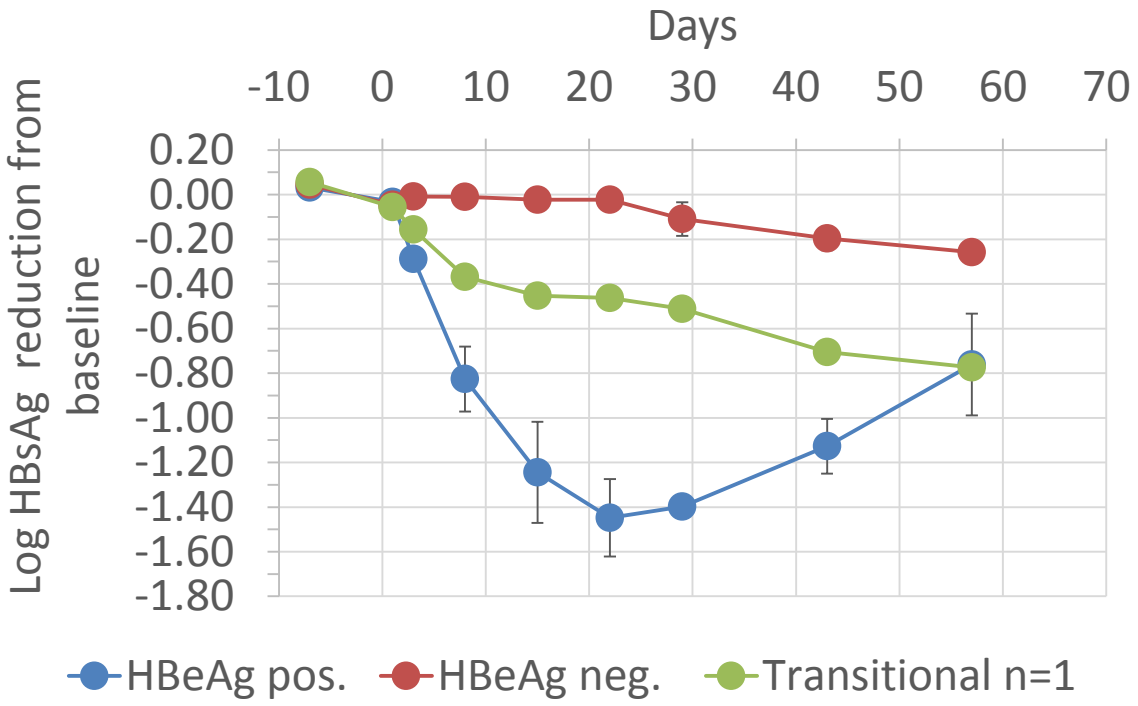
Target sites for ARC-520 siRNAs can be deleted in integrated HBV DNA



Loss of ARC-520 target sites in integrated HBV DNA explains lower KD of HBsAg in HBeAg negative chimps

ARC-520 in chronic HBV patients:

Human HBsAg data reflects chimp data



4 mg/kg ARC-520: NUC-naïve chronic HBV patients

- High level knockdown of HBsAg in HBeAg positive patients
- HBeAg negative patients respond less well
- HBeAg transitional patient is intermediate

As in chimps, HBeAg negative patients likely produce significant amounts of HBsAg from integrated DNA not targeted by ARC-520

Conclusions

- ARC-520 provides effective knock-down of cccDNA derived viral mRNA transcripts with resultant reductions in viral proteins and DNA
- In HBeAg negative chimps, *we believe* that significant HBsAg production is derived from integrated DNA, which is untargeted by ARC-520
- Human data from the Heparc-2001 study in chronic HBV is consistent with these chimp findings in naïve patients and also suggest that integrated DNA supports HBsAg in chronic NUC-treated patients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