Hitting HBV everywhere; why RNAi holds so much potential as a platform therapy in CHB

Bruce D. Given, M.D.
COO, Arrowhead Pharmaceuticals
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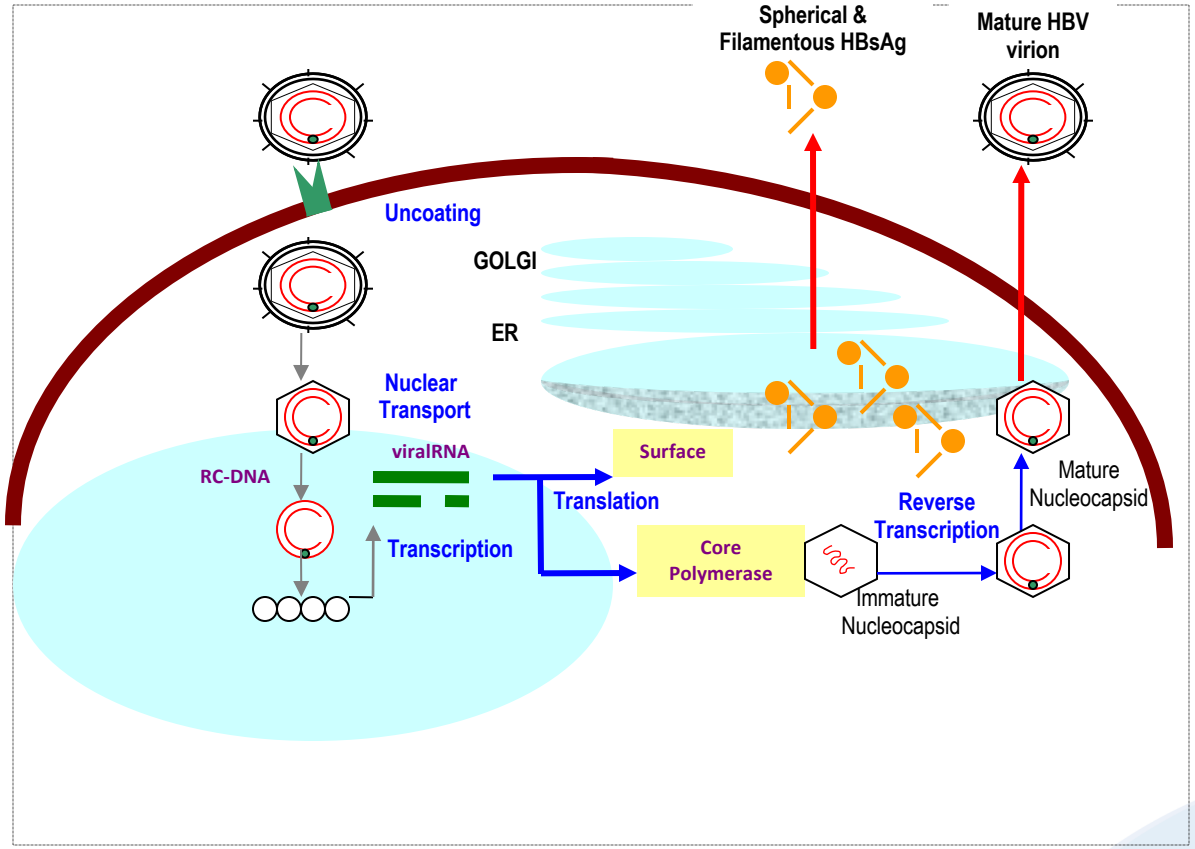
HBV Replication: HBsAg (Episomal [cccDNA]) Pathway



- **Dominant in <u>naïve</u> HBeAg-pos CHB**

Courtesy of S. Locarnini

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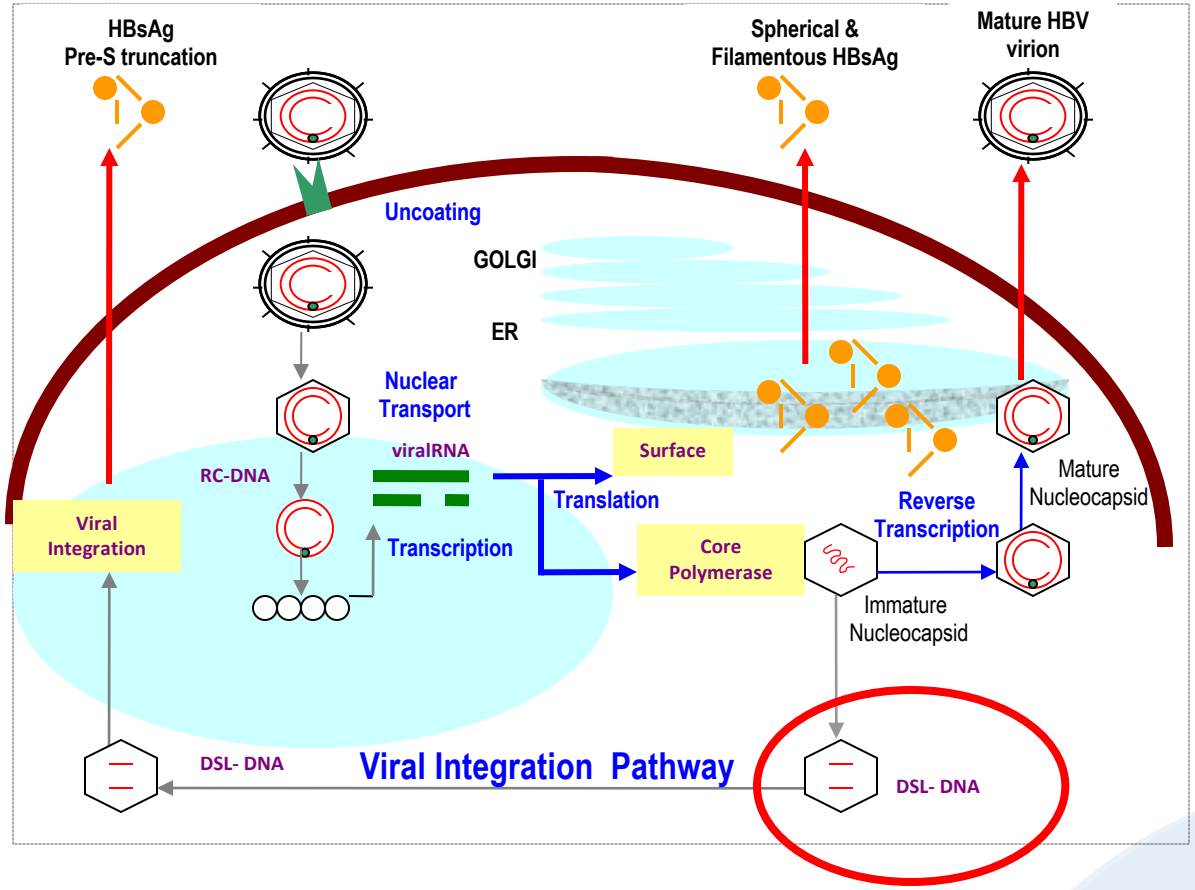
HBV Replication: HBsAg (Integrated) Pathway



- **Dominant in HBeAg-neg CHB**

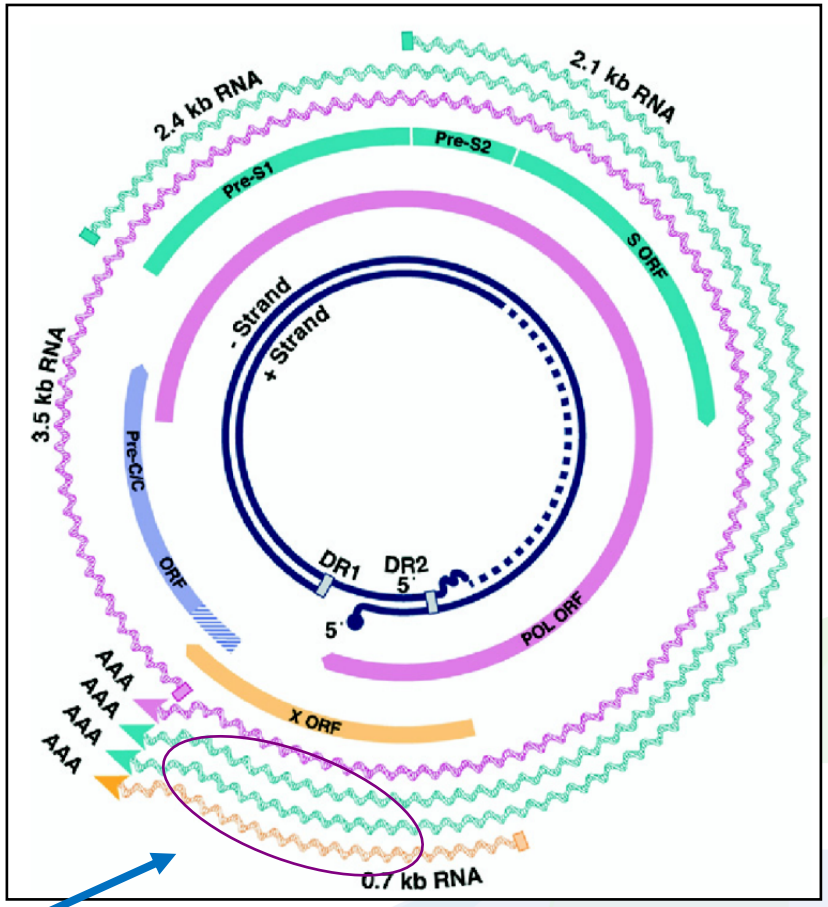
Courtesy of S. Locarnini

HBV Has Evolved to Defeat Challenges

- HBeAg has been proposed as important for tolerance development early
  - Later mutations or therapies that lead to elimination of circulating HBeAg are not curative
- Mutation is a key defense
  - Early Nucs were easily defeated with selection of resistant strains
  - Core antagonist (CPAMs) are predicted to have similar issues
- cccDNA can remain dormant for decades even in the setting of HBsAg seroclearance

All HBV RNA from cccDNA can be targeted with one siRNA

- All HBV transcripts, including pregenomic RNA, terminate with the same polyadenylation signal.
- A single siRNA targeting this common region can reduce all HBV transcripts.



Single siRNA can reduce all HBV proteins

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

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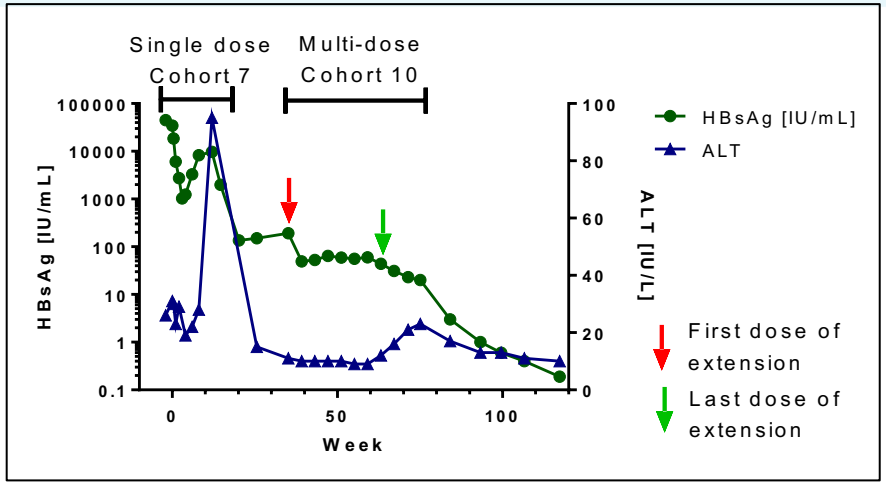
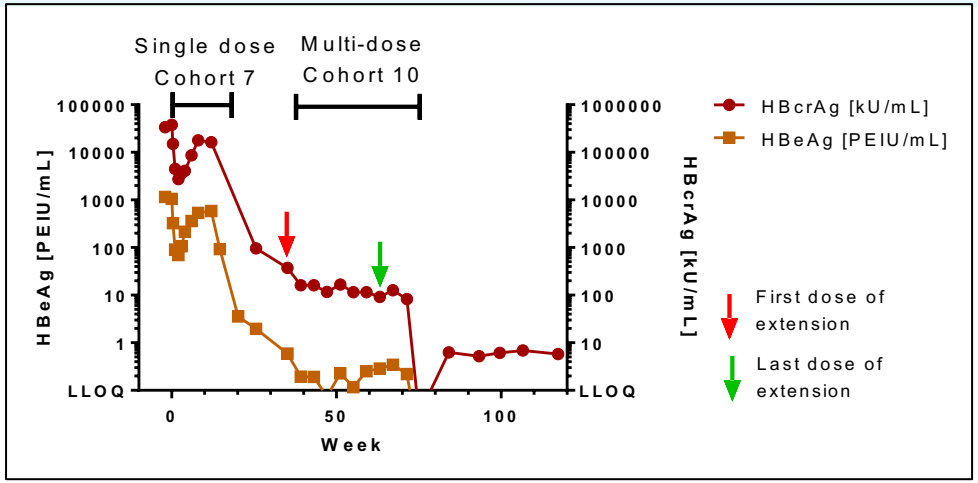
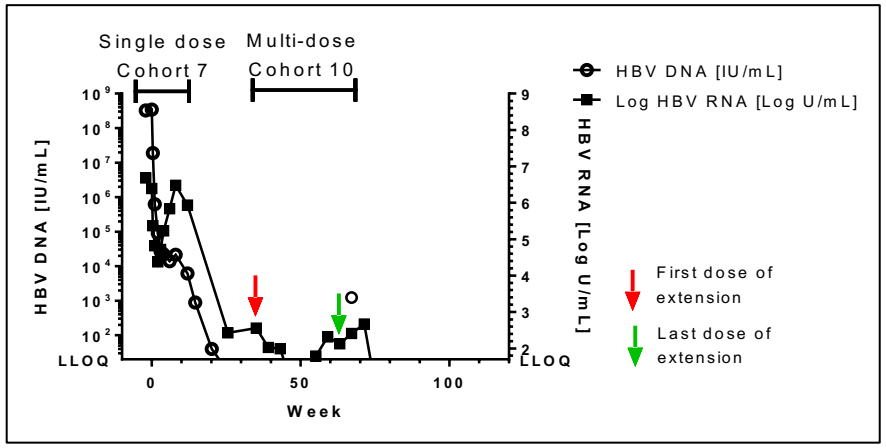
Patient 01-7985: Naïve HBeAg Positive Patient







- HBsAg, RNA, HBeAg, HBcrAg all respond similarly to a single dose of ARC-520
- HBV DNA shows synergistic reduction in response to ARC-520 plus entecavir

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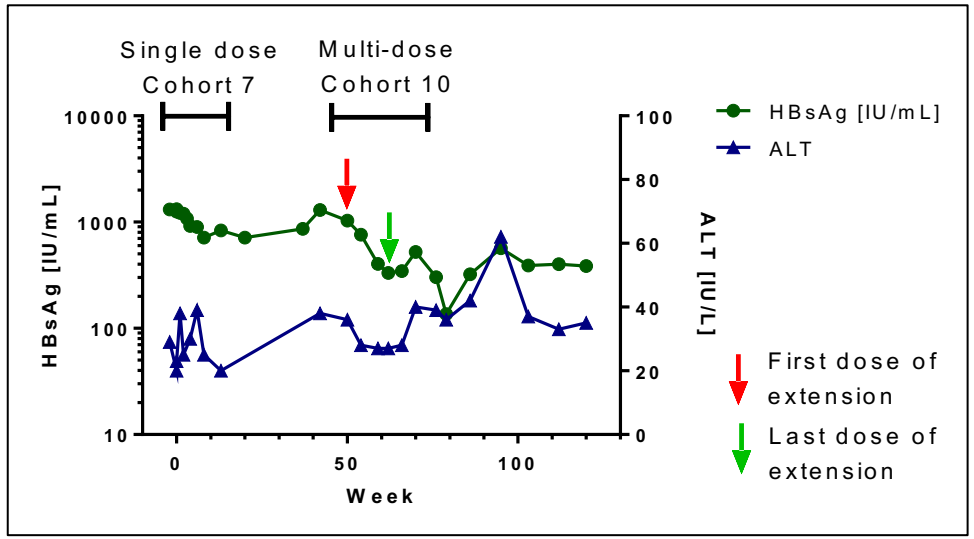
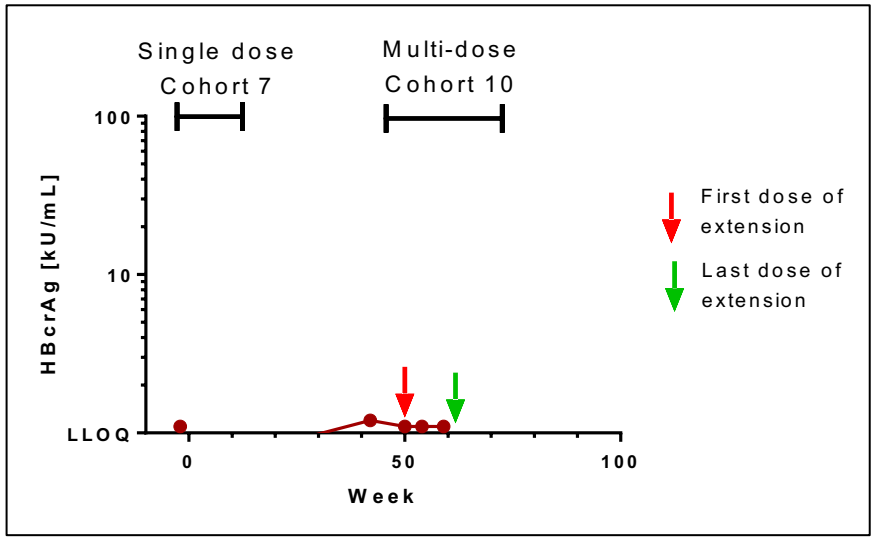
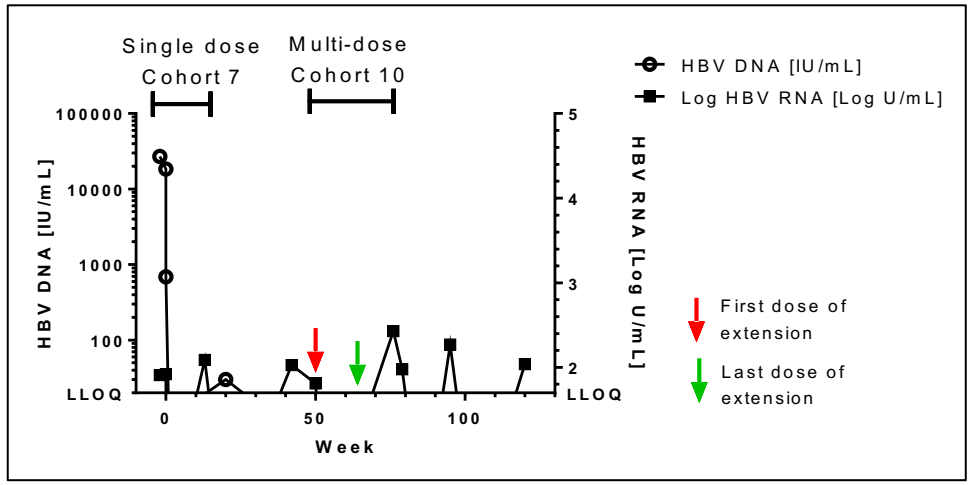
HBV Has Evolved to Defeat Challenges

- HBeAg has been proposed as important for tolerance development early
  - Later mutations or therapies that lead to elimination of circulating HBeAg are not curative
- Mutation is a key defense
  - Early Nucs were easily defeated with selection of resistant strains
  - CPAMs are predicted to have similar issues
- cccDNA can remain dormant for decades even in the setting of HBsAg seroclearance
- *Perhaps most ingenious of all is the use of DNA integration to continue HBsAg production in the absence of measurable evidence of ongoing cccDNA activity*

Patient 01-7986: Naive HBeAg Negative Patient







- HBsAg can remain elevated despite undetectable HBV DNA and borderline detectable cccDNA driven activity (in this case, HBV RNA and HBcrAg)
- *If cccDNA could be totally ablated, would this patient seroclear ?*

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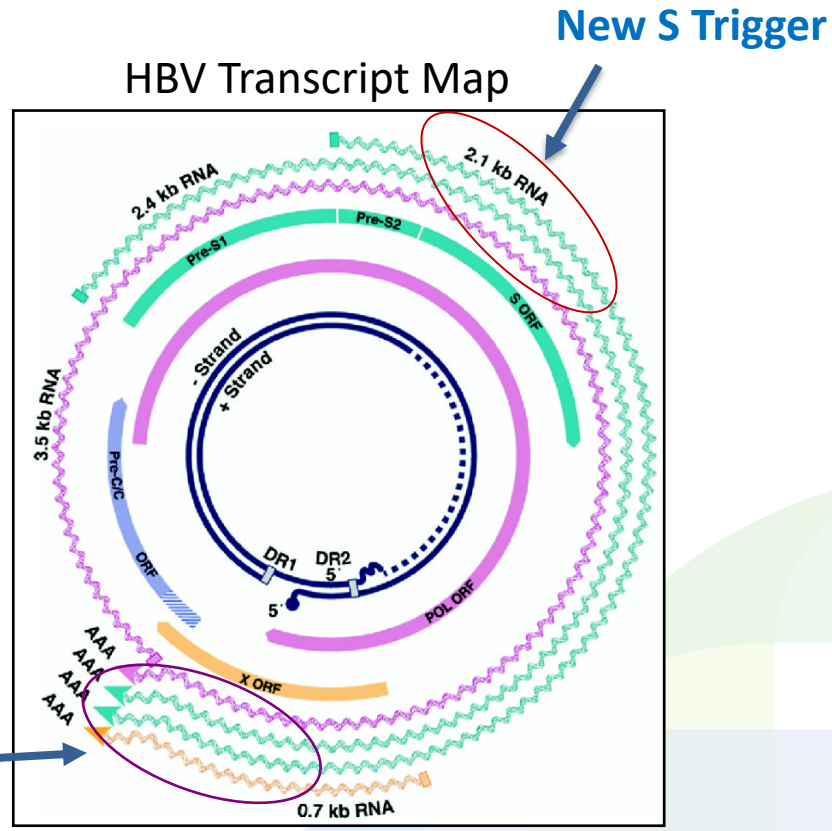
Importance of integrated HBV DNA as S mRNA source has changed RNAi strategy

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match of 17mer in ~7000 HBV genomes)
  - Reduce chance of resistance



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Summary

- Effective RNAi with careful trigger selection should be able to suppress all cccDNA transcription products
  - Synergy has been demonstrated with NUCs
  - We expect synergy with other DAAs such as capsid inhibitors
- RNAi can also address HBsAg produced from integrated DNA
  - Not clear what if any of the other classes will be effective here
  - Functional cure might not be achievable in many/?most patients without addressing this HBsAg source
- RNAi likely to be a necessary component of finite treatment regimens, at least for the time being

Thank you !

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