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

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

Single siRNA can reduce all HBV proteins

Ghany & Liang (2007), Gastroenterology **132**: 1574-1585
Differential HBsAg Reduction Observed in Chimpanzees with ARC-520

HBeAg+ (4 chimps)
HBeAg- (4 chimps)

HBsAg in serum (log10 reduction)

0.0
-0.4
-0.8
-1.2
-1.6
-2.0
-2.4

56 28 1 29 57 85 113 141 169

Day

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

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

2.1kb S

HBeAg-
(88A010)

HBeAg-
(A2A004)

2.4kb S

DR2

DR1

HBV Poly(A) signal

S ORFs

ARC-520 siRNAs

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 dsDNA

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

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

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

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

- **2.4 Log10 HBsAg reduction from baseline to 0.051 IU/mL**
- Delayed HBsAg response
- HBcAg 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

Patient 01-7983
Case Study 4: HBeAg Negative Patient Trending Toward HBsAg Seroclearance

- **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
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
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 WTpHBV Mice Reduces HBV DNA by 3.44 log10, HBsAg and HBeAg to LOQ

**HBsAg**
- Saline
- 4 mg/kg ARO-HBV (Days 1, 22 and 43)

>3 log₁₀ reduction after 3 doses

**HBeAg**
- Saline
- 4 mg/kg ARO-HBV (Days 1, 22 and 43)

2.2 log₁₀ = 99.4% reduction to LLOQ

**HBV DNA**
- Saline
- 4 mg/kg ARO-HBV (Days 1, 22 and 43)

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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