Discovery and Development of Arrowhead Clinical Candidates ARO-AAT and ARO-HBV

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Outline

• RNA Interference

• Arrowhead’s Targeted RNAi Molecule (TRiM™) platform for targeting hepatocytes

• Discovery and development of Arrowhead clinical Candidates
  • ARO-AAT
  • ARO-HBV
RNAi Therapeutics – the Promise and Advantages

• Small molecule pharmaceuticals target proteins
  • Enzymes
  • Receptors

• RNAi
  • Cleave mRNA
    • Stop the translation process
    • Block the production of disease causing proteins

• The promise:
  • Treat and cure currently undruggable diseases
    • Genetic disorders, cancer, infectious diseases, cardiovascular diseases, pulmonary diseases

• The advantages over small molecule therapeutics
  • Platform technology
  • Target specific cell type
  • Target specific mRNA
  • Precision medicine
    • Only knockdown the target gene in the target cell type
Target the Gene, Silence the Disease

Therapeutic gene silencing with **RNA interference** is highly precise and efficient
A Long Journey for RNAi: Focused on the Vehicles Not Payloads

• Treated distinctly as two separate components: vehicles and payload
• The focus was on delivery vehicles for years in academia and industry
• The vehicles
  • Provided shielding for siRNA as in polymers and LNPs
  • Enabled rapid endosome escape as in polymers, LNP and DPC
• Lessons learned
  • Limited delivery
    • Mainly to the liver and some local deliveries
  • Observed toxicity from some delivery vehicles
Arrowhead RNAi Platform: TRiM™

Simplicity, Specificity, and Activity

TRiM™ has rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
- Rational use and placement of modifying chemistries
- RNAi chemistry insights and expertise have allowed us to see what others have not

Targeted RNAi Molecule

TRiM™ platform
Direct Conjugation for Hepatocyte Delivery

- Asialoglycoprotein receptor (ASGP-R)
  - Tridentate receptor, overly expressed on the surface of hepatic cells, but minimally on extra-hepatic cells
  - Recycled every 15 mins

- Natural ligand to ASGP-R
  - N-Acetyl-Galactosamine (NAG)

- Binding of NAG to ASGP-R initiates endocytosis

Huang etc.  
*Bioconjugation*, 2016
Chemical Modifications

- Chemical modifications to increase stability
  - Potentially fully modified at 2’ positions (e.g., -F and –OMe)
  - Use of multiple phosphorothioates, instead of phosphates, including at terminal positions to increase nuclease resistance
Hepatic siRNA Discovery/Development

- **Key Design Elements in Hepatic Platform**
  - Subcutaneous dosing, monthly or less dosing frequency
  - Stable and potent sequences
    - No need for the use of endosome escape moieties
  - Expectation of wide therapeutic index

- Uncover new triggers

- Rational design of chemical modifications to improve
  - Stability in endosome and cytoplasm
  - Potency

- Targeting moiety investigation:
  - NAG cluster
  - Linker chemistry
  - Overall ligand design
  - Topology

**Two challenges: RNAi CHEMISTRY and DELIVERY**

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ARO-AAT
Alpha-1 Antitrypsin Deficiency (AATD)

- AAT is an abundant serum protein
  - Primarily synthesized in the liver, about 10% made extrahepatically
- Physiological function includes:
  - Inhibition of neutrophil proteases to protect host tissues during inflammation
  - Especially important in the lung
- Mutation in AAT gene (Z-AAT) leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver
Alpha-1 Antitrypsin Deficiency

Normal AAT

- Normal blood levels of normal protein protect lungs
- Normal secretion into the blood

Abnormal AAT (Z-AAT)

- Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection
- High accumulation of misfolded Alpha-1 Antitrypsin protein leads to liver injury

No current treatment

Treated with AAT protein replacement therapy today
ARO-AAT: Mechanism of Action

- ARO-AAT designed to stop Z-AAT production by silencing AAT gene via cleavage of mRNA to
  - Prevent production and accumulation of disease-causing protein in liver
  - Prevent repeated cycles of cellular damage
  - Allow clearance of accumulated protein
  - Reverse fibrosis associated with prior damage

**ARO-AAT**

- **Z-AAT mRNA expression**
- **Z-AAT polymerization**
- **Liver damage**
- **Liver fibrosis and HCC**

AATD is a large scale orphan disease

- Alpha-1 Foundation estimates 100,000+ in the US
- Approximately 100,000+ in Europe
Lead Optimization Leads to ARO-AAT

- 91% serum AAT knockdown achieved with one 2 mpk dose
- Knockdown sustained for 3 weeks with one 2 mpk dose

**RNAi triggers in mouse study**
- 2 mpk AAT_trigger_3.1
- 2 mpk AAT_trigger_3.2
- 2 mpk AAT_trigger_3.3
- 2 mpk AAT_trigger_3.4

**Chemical modifications led to deep reduction of AAT protein and long duration at dose of 2mg/kg**

91.2% KD
ARO-AAT Provides Durable AAT knockdown in NHP
Multi-dose in NHP, dosed subcutaneously

- 92% maximum serum AAT knockdown achieved in cynomolgus monkeys
- Knockdown sustained for 7+ weeks following second dose

- Completed GLP toxicology study
- No dose limiting toxicities were identified

Durable knockdown supports once monthly or less frequent dosing
**ARO-AAT Biodistribution 3mpk SubQ Administration**

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<th>Kidney</th>
<th>Lung</th>
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<th>Heart</th>
<th>Spleen</th>
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*Only one rat showed quantifiable concentration other two were below limit of quantitation (BLQ).*
ARO-AAT Clinical Data Shows Platform Profile

- Open Label AAT Plasma Data: Single Dose, Healthy Volunteers

- **Potency, efficacy, durability**
  - 93%: Maximum Serum AAT reduction achieved 6-weeks following a single dose
  - 87%: Mean maximum serum AAT reduction achieved 6-weeks following a single dose

- **Safety**
  - No Severe AEs
  - Most AEs reported as mild (one moderate gastroenteritis)
  - Mild injection site AEs occasionally reported
  - No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin or pattern of adverse laboratory changes seen
Chronic hepatitis B (CHB): Disease pathogenesis

2 billion infected with HBV  ➔  250 million living with chronic HBV infection

1. Direct antiviral agents = Nucleos(t)ide Analogues (NA’s: TDF, ETV, ADV, LAM)
2. Immune modulators (Pegylated IFNa)

Therapeutic Virus suppression

Liver Cancer
Develops in 15-25% CHB cases

30-50 years

Neither preventative vaccination nor viral suppression influence CHB cure

Primary prevention

1. Vaccination (EngerixB)
Small Molecule Drugs vs RNAi Therapeutics

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

Silence Entire HBV Genome

Potencial to enable a functional cure
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
- A single siRNA targeting this common region can reduce all HBV transcripts derived from cccDNA

Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA
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

Study Day

HBsAg in serum (normalized to pre-dose)

Saline

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

Multiple animals with HBsAg BLOQ

>3 log₁₀ reduction after 3 doses

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With Deep Knockdown also Observed for HBeAg and HBV DNA

**HBeAg in serum (normalized to pre-dose)**

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

3.44 \( \log_{10} \) = >99.9% reduction

**HBV DNA in serum (normalized to pre-dose)**

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

2.2 \( \log_{10} \) = 99.4% reduction to LLOQ
ARO-HBV Safety Evaluation

- GLP toxicology studies completed
  - ARO-HBV is well tolerated
- Significant therapeutic index achieved
Summary

• Arrowhead TRiM™ platform demonstrates consistent activity
• Subcutaneous dosing, monthly or less frequent
• No need for active endosomal escape agent
• Powerful HBsAg reduction for ARO-HBV
• Powerful AAT reduction for ARO-AAT
• Wide therapeutic index
• Good early signs of activity and safety in human subjects

Evolution from biologic complexity to small molecule precision and execution
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