Arrowhead’s TRiM™ delivery system – potent, modular and versatile for RNAi

Bruce D. Given, M.D.
COO, Arrowhead Pharmaceuticals
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Arrowhead Pharmaceuticals

- Company focused on developing siRNA therapeutics
- Working in RNAi for over 15 years
- Exclusively focused in RNAi since 2011
- Worked with multiple delivery systems
  - Polymer nanoparticles
  - Liposomes
  - Dynamic Polyconjugates (DPCs)™
  - NAG targeted conjugates
  - Conjugates targeting extra-hepatic tissues
Dynamic Polyconjugates

DPC™ system consists of:
• Vial 1: DPC Polymer
• Vial 2: liver targeted siRNA
• Mixed in pharmacy and co-administered via IV infusion
Mechanism of DPC™-mediated siRNA delivery to cells

1. **DPC™ peptide and RNAi trigger attach to their respective cell surface targets**

2. **DPC™ peptide and RNAi trigger are internalized**

3. **DPC™ peptide and RNAi trigger are enclosed in endosomes. Low pH results in peptide unmasking**

4. **DPC™ peptide promotes endosomal escape of RNAi trigger into cell cytoplasm**

5. **RNAi trigger engages the cell’s interference machinery, resulting in knockdown of target gene expression**

![Diagram showing the mechanism of DPC™-mediated siRNA delivery](image-url)
ARC-AAT: Phase 1 Healthy Volunteer AAT Levels

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>PBO (n=18)</th>
<th>0.38 (n=4)</th>
<th>1 (n=4)</th>
<th>2 (n=4)</th>
<th>3 (n=4)</th>
<th>4 (n=4)</th>
<th>5 (n=4)</th>
<th>6 (n=4)</th>
<th>7 (n=3)</th>
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<tbody>
<tr>
<td>Max KD</td>
<td></td>
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<tr>
<td>24.8%</td>
<td>9.3%</td>
<td>31.9%</td>
<td>36.3%</td>
<td>61.0%</td>
<td>76.1%</td>
<td>86.7%</td>
<td>87.1%</td>
<td>85.1%</td>
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<tr>
<td>Mean Max</td>
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<td>8.4%</td>
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<td>P value</td>
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</table>
DPCs Found to Produce Toxicity in NHPs

Arrowhead Pharma sinks after shelving three drug programs

Reuters Staff

(Reuters) - Shares of Arrowhead Pharmaceuticals Inc sank more than 60 percent in premarket trading on Wednesday, a day after the company said it would stop developing all drugs being tested on humans due to a setback in its drug-delivery technology.
The Painful Learnings

- RNAi happens in the cytoplasm and triggers require extensive modification to get there unaided
  - Early emphasis on delivery platforms
  - Several promising programs lost to delivery-related toxicities
  - Polymer, nanoparticle, LNP etc. . . delivery systems all have toxicity issues

- Delivery vehicle toxicity eliminated with conjugates
  - Assumes chemistries around ligands, linkers and RNA stabilization don’t create new issues

- Does not eliminate typical small molecule drug concerns
  - Off-target toxicity, target/biology risk, idiosyncratic reactions (e.g. DILI), etc.
  - Specific tissue targeting may reduce risk
TRiM™ Platform Enables Amgen Partnership

Three weekly 3 mg/kg SQ RNAi trigger doses (3xqw), n=2/group

Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)

Amgen strikes $674M cardiovascular RNAi pact with Arrowhead
Components:

- Stabilization chemistries
- pk enhancers as necessary
- Linker chemistries
- Targeting ligands

Now capable of achieving deep KD in diverse tissues using subQ, iv, and inhaled administration routes

*Without active endosomal escape*
ARO-AAT/ARO-HBV: Key Design Elements Expected for the Next Generation

Check List:
Subcutaneous dosing, monthly or less frequent
No need for endosomal escape agent
Full suppression of liver AAT production (ARO-AAT)
Coverage of full HBV transcriptome (ARO-HBV)
Expectation of wide therapeutic index
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ARO-AAT Provides Durable AAT knockdown: Multi-dose in NHP, dosed subcutaneously

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

Durable knockdown supports once monthly or less frequent dosing
Integration Modeled in a New, Mutated pHBV Transfected Mouse

HBsAg knockdown is deep and prolonged despite loss of HBx-trigger site
Based on clinical observations, clinical pathology and histopathology evaluations, ARO-HBV and ARO-AAT were well tolerated in repeated dose studies in rats and monkeys administered 3 weekly subcutaneous doses at dose levels of 30, 60, 120, and 300 mg/kg.

Expect wide safety margin
ARO-HBV and ARO-AAT poised to enter the clinic

Dec 22, 2017
Arrowhead Pharmaceuticals Files for Regulatory Clearance to Begin Phase 1/2 Study of ARO-HBV

Dec 20, 2017
Arrowhead Pharmaceuticals Files for Regulatory Clearance to Begin Phase 1 Study of ARO-AAT
Building Out CV Portfolio Using TRiM™ platform

Already building candidates for Lp(a) and Gene X with Amgen, Now adding as wholly-owned assets:

ARO-APOC3
- For treatment of hypertriglyceridemia
- Up to 90% KD in TG rodent models (intestines also a source of production)
- SubQ administration
- NHP work and non-GLP tox studies to follow

CTA planned in Q4 2018

ARO-ANG3 (against ANGPTL3)
- For treatment of hypertriglyceridemia/dyslipidemia
- >90% KD in rodent models with several good triggers
- SubQ administration
- Still optimizing chemistries
- NHP work and non-GLP tox studies to follow

CTA planned in Q4 2018
The Next Frontier - Extra-hepatic Delivery

• Why the hepatocyte space is crowded
  – ASGPR receptor is very high density
  – It is a clearance receptor with low stringency and rapid cycling
  – In a organ designed for high clearance

• Reciprocal challenges outside of the liver
  – Receptor density generally lower
  – Receptor stringency often higher
  – Internalization and recycling times differ
  – Cell availability to circulating molecules often less

• Implications - Every aspect has to be optimized
  – Need internalizing receptors of sufficient density
  – Highly optimized targeting ligands
  – Highly optimized RNAi triggers
Delivery and Efficacy in Renal Cell Carcinoma Mouse Model using TRiM™

ARO-Hif2
- Up to 85% KD
- iv or sq administration
- Tumor targeting

![Graph showing SEAP by group over time](image-url)
Targeting Lung Using TRiM™ Platform

ARO-Lung1
• Almost 90% KD in rodent models
• 30 day duration after single dose
• Inhaled administration
• Large animal studies and disease models underway
• Non-GLP tox studies underway

CTA planned in Q4 2018

Red: lung target protein expression by IHC

vehicle

ARO-Lung1

airway
### Arrowhead Pipeline

<table>
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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Pre-clinical</th>
<th>Pre-IND</th>
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Conclusions

• Complex delivery systems often bring difficult safety issues in clinical use

• Direct conjugation has shown good performance for achieving RNAi activity in hepatocytes and can be expected to offer safety/tolerability

• With thoughtful target selection and appropriate SAR chemistry work, it is now feasible to move out of the liver and still achieve strong RNAi activity
Thank you!