Cardiovascular and Lipid Disorders: A Next Frontier for TRiM RNAi

RNA and Oligonucleotide Therapeutics
Cold Springs Harbor Laboratory
March 28, 2019
This presentation contains forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.
RNAi: Target the Gene Silence the Disease

Therapeutic gene silencing with RNA interference is highly precise and efficient
Arrowhead RNAi Platform: TRiM™: Simplicity, Specificity, and Activity

TRiM™ platform

Targeted RNAi Molecule

Simplicity, Specificity, and Activity

TRiM™ uses rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
### Pipeline

<table>
<thead>
<tr>
<th>Competitive Position</th>
<th>Drug</th>
<th>Disease</th>
<th>Pre-clinical</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>First RNAi</td>
<td>ARO-AAT</td>
<td>Alpha-1 Liver Disease</td>
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<td>First RNAi</td>
<td>ARO-APOC3</td>
<td>Hypertriglyceridemia</td>
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<td>First RNAi</td>
<td>ARO-ANG3</td>
<td>Dyslipidemia</td>
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<td>First RNAi</td>
<td>ARO-ENaC</td>
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<td>Renal Cell Carcinoma</td>
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<td>Leading RNAi</td>
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<td>Hepatitis B</td>
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<td>Partnered with Janssen</td>
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<td>First RNAi</td>
<td>AMG 890</td>
<td>Cardiovascular Disease</td>
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<td>Partnered with Amgen</td>
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<td>Undisclosed Target</td>
<td>ARO-AMG1</td>
<td>Cardiovascular Disease</td>
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<td>Partnered with Amgen</td>
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**Note:**
- ARO-AAT: Partnered with Amgen
- ARO-APOC3: Partnered with Janssen
- ARO-HBV: Partnered with Janssen
- AMG 890: Partnered with Amgen
- ARO-AMG1: Partnered with Amgen
Duration of TRIM™ in Humans - ARO-AAT Phase 1, NHV SAD/MAD study

Single dose ARO-AAT

Multiple dose ARO-AAT

Supports quarterly or less frequent dosing

U.S. IND filed for Phase 2/3 ARO-AAT study
ARO-AAT Summary Safety

• 45 NHV subjects received at least 1 dose

• No SAEs

• No Severe AEs

• 12% of injections resulted in AE at injection site (e.g. bruising, pain, erythema). All mild.
  • No dropouts due to injection site AEs

• No statistically significant difference in adverse FEV1 changes (active v placebo)
Cardiovascular RNAi

• We go where the technology takes us and where RNAi may have an advantage

• CV/Dyslipidemia targets optimal for siRNA
  • Still large unmet medical need related to residual CVD risk (after maximal lowering of LDL-C)
  • Niche orphan populations with inadequate treatment (FPL, FCS, HoFH)
  • Lipoproteins primarily synthesized in the hepatocyte yield serum biomarkers
  • Many targets supported by GWAS (LOF mutations seen with APOC3, ANGPTL3, LP(a), others)
Human Genetic Validation of Hypertriglyceridemia/Hyperlipidemia Targets

**The New England Journal of Medicine**

**ORIGINAL ARTICLE**

Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease


**ORIGINAL ARTICLE**

Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute®

**BRIEF REPORT**

Exome Sequencing, ANGPTL3 Mutations, and Familial Combined Hypolipidemia

**ORIGINAL ARTICLE**

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

arrowhead pharmaceuticals
APOCH3, ANGPTL3 Supporting Genetic Data

Mean or Median changes in lipid parameters in heterozygotes and homozygotes for APOCH3 and ANGPTL3 LOF mutations versus non-carriers

<table>
<thead>
<tr>
<th>Metric (serum level)</th>
<th>APOCH3 deficient heterozygote¹</th>
<th>APOCH3 deficient homozygote²</th>
<th>ANGPTL3 deficient heterozygote³</th>
<th>ANGPTL3 deficient homozygote⁴</th>
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<tbody>
<tr>
<td>ApoC-III</td>
<td>-46%</td>
<td>-88.9%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ANGPTL3</td>
<td>NA</td>
<td>NA</td>
<td>-40% to -87%</td>
<td>undetectable</td>
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<tr>
<td>Triglycerides</td>
<td>-39%</td>
<td>-59.6%</td>
<td>-21.1%</td>
<td>-71.2%</td>
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<tr>
<td>LDL-C</td>
<td>-16%</td>
<td>Similar to non-carrier</td>
<td>-8.6%</td>
<td>-67.2%</td>
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<tr>
<td>HDL-C</td>
<td>+22%</td>
<td>+26.9%</td>
<td>-16.8%</td>
<td>-39.0%</td>
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<td>CAD risk</td>
<td>-40%</td>
<td>Not reported</td>
<td>-41%⁴</td>
<td>NA</td>
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<td>Adverse Phenotype/AEs</td>
<td>None described</td>
<td>None described</td>
<td>None described</td>
<td>None described</td>
</tr>
</tbody>
</table>

1. Triglyceride working group, NEJM 2014
3. Minicocci et al., J of Lipid Research 2013
4. Dewey et al, NEJM 2017
**Target Mechanism**

**APOC3 inhibition**
- Enhances peripheral LPL activity leading to enhanced VLDL clearance
- Enhanced VLDL/CM remnant particle clearance at hepatocyte

**ANGPTL3 inhibition**
- Enhances peripheral LPL activity leading to enhanced VLDL clearance
- Enhanced VLDL/CM remnant particle clearance at hepatocyte
- Reduced VLDL synthesis/assembly by hepatocyte
- Enhanced LDL-C clearance through non-LDLr mechanism
ARO-ANG3: Translational and Early Clinical Development
ARO-ANG3 Dose Response in WT Mice

- 80% knockdown (KD) of ANGPTL3 with good duration at 0.5 mpk dose in WT mice
- 90%, 96% and 98% KD at 1 mpk, 2.5 mpk and 5 mpk, respectively
ANGPTL3 protein knockdown in LDLr^-/- Mice

**Study design**
- Mice on Western diet (n=12) or Standard chow (n=4) for 3 weeks before dosing
- ARO-ANG3 injected on Day 1 and 29 subcutaneously
- Weekly blood collection for lipid parameters and ANGPTL3 levels
- Liver Angptl3 mRNA on Day 15, 29 and 57 (Western diet) by qRT-PCR

**Maximum ANGPTL3 protein reductions in ARO-ANG3 after each dose**

<table>
<thead>
<tr>
<th></th>
<th>After 1st dose</th>
<th>After 2nd dose</th>
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<tbody>
<tr>
<td>Standard chow</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Western diet</td>
<td>98%</td>
<td>99%</td>
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</table>

- Liver mRNA knockdown was 96-97% at all time points tested (relative to saline group)
- No effects on serum ANGPTL3 in Saline or Control trigger treated groups
ARO-ANG3 Reduces LDL-C and Triglycerides in LDLr⁻/⁻ Mice

All graphs showing group averages ± SEM

- Western Diet, Saline
- Western Diet, 3 mg/kg ARO-ANG3
- Western Diet, 3 mg/kg Control trigger
- Standard Chow, Saline
- Standard Chow, 3 mg/kg ARO-ANG3

- Mice on both Western diet and Standard chow had elevated serum lipids compared to wild-type normal mice (TGs: 35-45 mg/dL, LDL-C: 10-15 mg/dL)

Reductions in LDL-C via a non-LDLr mechanism
ARO-ANG3 in chow-fed cynomolgus monkeys: single 2 mg/kg dose

- Single 2 mg/kg ARO-ANG3 SC dose on study Day 1
- Reductions normalized to pre-dose values
- 70-90% maximum reduction in serum ANGPTL3 protein levels

- Normal cynos have vegan like serum lipids
- Significant reductions in TGs were observed
ARO-ANG3 in HFCS-induced dyslipidemic rhesus monkeys

- SC doses on Day 1 and 29
- Over 95% maximum reductions in serum ANGPTL3 protein levels
- Normalized to pre-dose values

- Animals on fructose diet for 6 weeks
- Variable diet-induced dyslipidemia
- 80% maximum mean reductions in TGs
- 30-40% reductions in LDL
AROANG31001 Clinical Study

• First NHV subject dosed January 2019

• Single dose safety, PD, PK in NHVs

• Multiple dose ranging in patients with:
  • NAFLD
  • Elevated LDL-C on statins
  • HoFH/HeFH
  • Elevated triglycerides (> 500mg/dL)
ARO-APOC3
Clinical Indications: Moderate to Severe Hypertriglyceridemia

Various etiologies, may be polygenic

FCS
Can be monogenic: LPL, APOC2, APOA5, LMF1, GPIHBP1 and GPD1

Nonfasting plasma triglycerides, mg/dL

Mild-to-moderate TG elevation
Severe TG elevation
Chylomicronemia

Hegele et al., 2014
Familial Chylomicronemia Syndrome (FCS)

- FCS: Severely elevated triglycerides (often over 2,000 mg/dL)
  - Loss-of-function in gene(s) responsible for LPL dependent triglyceride clearance (LPL, APOC2, APOA5, LMF1)
  - Multiple systemic manifestations
    - Recurrent abdominal pain
    - Acute pancreatitis (admission, narcotics, 10% mortality)
    - Neurocognitive problems
    - Type 2 diabetes mellitus
    - Eruptive xanthomas
- Estimated 3,000-5,000 patients worldwide
- No effective available therapy
  - Available drugs (fibrates, fish oils, niacin) ineffective as they work through LPL dependent pathway
  - Currently managed by severe dietary restrictions (< 20 grams of daily fat)
    - Adherence difficult, doesn't normalize triglycerides, only reduces pancreatitis risk
ARO-APOC3 Dose-response in Human-APOC3 Transgenic Mice

Method
APoC3 transgenic mice were given various SQ doses of ARO-APOC3 ranging from 0.01 to 3 mg/kg on study Day 1

Results
Dose-dependent effects on depth and duration of serum ApoC3 knockdown (KD)
ARO-APOC3 Dose-response in Human-APOC3 Transgenic Mice

- Dose-dependent reductions in Triglycerides, Total Cholesterol and LDL-C, and increase in HDL-C
ARO-APOC3 in Dyslipidemic Rhesus Monkeys

- 4 mg/kg ARO-APOC3 on Day 1 and 29

Efficacy correlates to serum APOC3 levels and severity of dyslipidemia

Serum APOC3

- Control (n=2)
- 4 mg/kg ARO-APOC3 (n=4)

![Graphs showing changes in APOC3, TG, TC, LDL-C, and HDL-C over time.](image-url)
AROAPOC31001 Clinical Study

- First subject dosed March 2019
- Single dose safety, PD and PK in NHVs
- Multiple dose ranging in patients with elevated triglycerides
- Multi-dose cohort enrolling limited number of FCS patients