Development of an RNA Interference Therapeutic Targeting Angiopoietin-Like Protein 3 for Treatment of Hyperlipidemia

November 12th, 2018
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All authors are employees and shareholders of Arrowhead Pharmaceuticals Inc.
Angiopoietin-like 3 (ANGPTL3) Background

• A key regulator of LDL-C, HDL-C and triglyceride metabolism
• Homozygous and heterozygous loss-of-function mutations in ANGPTL3 lead to low plasma levels of LDL-C, HDL-C and triglycerides
  • Reduced risk of cardiovascular disease based on GWAS

ANGPTL3 is primarily synthesized in hepatocytes
• Well suited target gene as an RNAi therapeutic using Arrowhead’s hepatocyte-targeting TRiM™ platform
Silencing ANGPTL3 with RNA Interference

**Targeted RNAi Molecule**

**TRiM™ platform**

- **Stabilization Chemistries**
- **Linker Chemistries**
- **ASGPr targeting ligand**

**ARO-ANG3**

- Short dsRNA targeting ANGPTL3 mRNA
- Hepatocyte ASGPr targeting ligand
- Subcutaneous (SQ) dosing
- Designed to reduce production of ANGPTL3 to potentially treat dyslipidemias
- Specific, catalytic and highly efficient
Potential Clinical Indications for ARO-ANG3

• Rare diseases:
  • Familial hypercholesterolemia – non LDL receptor mechanism
  • Familial partial lipodystrophy

• Polygenic causes of elevated triglycerides:
  • Moderate to severely elevated TGs with history of pancreatitis
  • Secondary prevention for residual CVD risk despite maximized LDL lowering
ARO-ANG3 Pre-clinical Studies
ARO-ANG3 in Dyslipidemic Mouse Models

Mouse models:
- Diet induced obese (DIO) mice
- Obese db/db mice
- LDLr KO mice
- Deep and persistent reductions in serum ANGPTL3 and liver mRNA
- Reductions in triglycerides and LDL-C
- No negative effects on body weight
ARO-ANG3 in LDLr KO 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

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<tr>
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<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>
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<tr>
<td>Western diet</td>
<td>98%</td>
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• 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 KO 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
Similar Responses in Obese (db/db) or DIO Mouse Models

**Leptin deficient db/db mice**
- SQ doses on Day 1 and 29
- Deep serum ANGPTL3 reductions
- 98% (1\textsuperscript{st} dose) and 99% (2\textsuperscript{nd} dose) reduced

**DIO (diet-induced obese) mice**
- Single SQ dose on Day 1
- Deep serum ANGPTL3 reductions
  - High fat diet 97% reduced
  - Control diet 90% reduced

All graphs showing group averages ± SEM

- Models with moderate increases in lipid parameters
- ARO-ANG3 significantly reduces serum lipid levels
- ARO-ANG3 may be efficacious in a wide spectrum of hyperlipidemia
ARO-ANG3 in Chow-fed Cynomolgus Monkeys: Single Dose

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

**Reductions in serum ANGPTL3 protein levels**

- Normal cynos have vegan like serum lipids
- Significant reductions in TGs were observed
Reductions in serum ANGPTL3 protein levels

- SQ doses on Day 1 and 29
- Over 95% maximum reductions in serum ANGPTL3 protein levels

Reductions in serum TGs

- Animals on fructose diet for 6 weeks
- Variable diet-induced dyslipidemia
- 80% maximum mean reductions in TGs
- 20-60% max reductions in LDL-C
Summary and Clinical Plans for ARO-ANG3

- ARO-ANG3 reduces ANGPTL3 expression in liver and reduces serum TGs and LDL in multiple pre-clinical dyslipidemic animal models
- Documents requesting permission to commence human studies submitted October 2018
- Single ascending dose in NHVs
- Multiple doses in special populations
  - Familial hypercholesterolemia (HoFH orphan indication)
  - Treated hypercholesterolemics to assess ability to achieve further reductions
  - Polygenic hypertriglyceridemia (>500 mg/dL)
  - Subjects with elevated liver fat by MRI
Acknowledgements

**Arrowhead Co-authors:**
Rui Zhu  
Julia Hegge  
Casi Schienebeck  
Gary Christensen  
Lucas Trilling  
Holly Hamilton  
Jeremy Briggs  
Meredith Hinkes  
Stephanie Bertin  
Aaron Andersen  
Mark Seefeld  
Zhen Li

**UC Davis:**
Peter Havel  
James Graham
Thank you