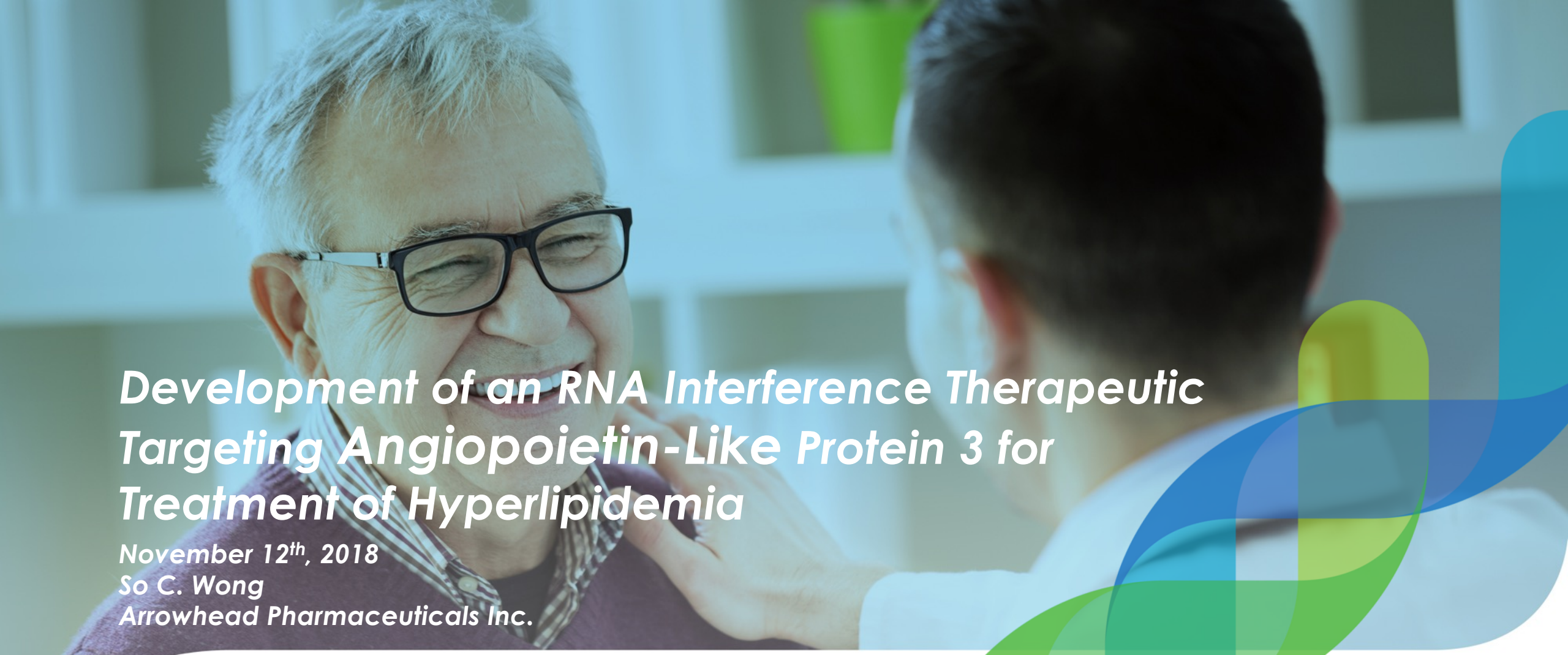


Development of an RNA Interference Therapeutic Targeting Angiopoietin-Like Protein 3 for Treatment of Hyperlipidemia

November 12th, 2018

So C. Wong
Arrowhead Pharmaceuticals Inc.

arrowhead pharmaceuticals

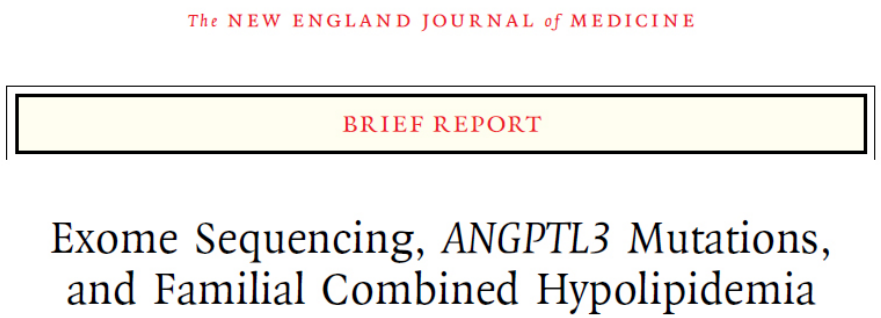
SCIENTIFIC SESSIONS 2018

Disclosures

All authors are employees and shareholders of Arrowhead Pharmaceuticals Inc.

Angiopoietin-like 3 (ANGPTL3) Background

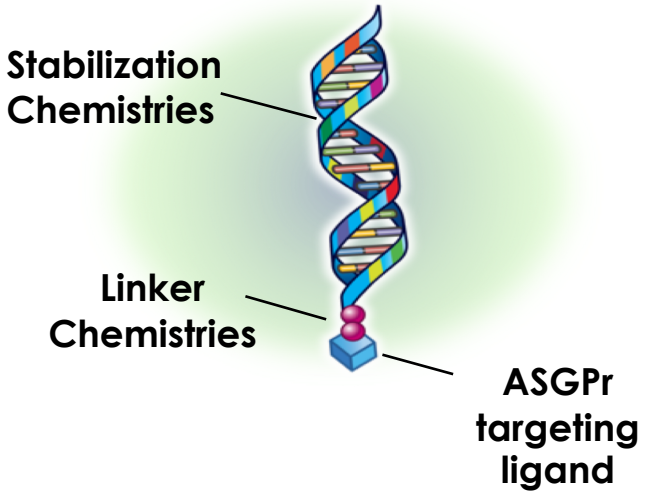
- A key regulator of LDL-C, HDL-C and triglyceride metabolism
- Homozygous and heterozygous loss-of-function mutations in *ANGPTL3* lead to low plasma levels of LDL-C, HDL-C and triglycerides
  - Reduced risk of cardiovascular disease based on GWAS



- ANGPTL3 is primarily synthesized in hepatocytes
- Well suited target gene as an RNAi therapeutic using Arrowhead's hepatocyte-targeting TRiM™ platform

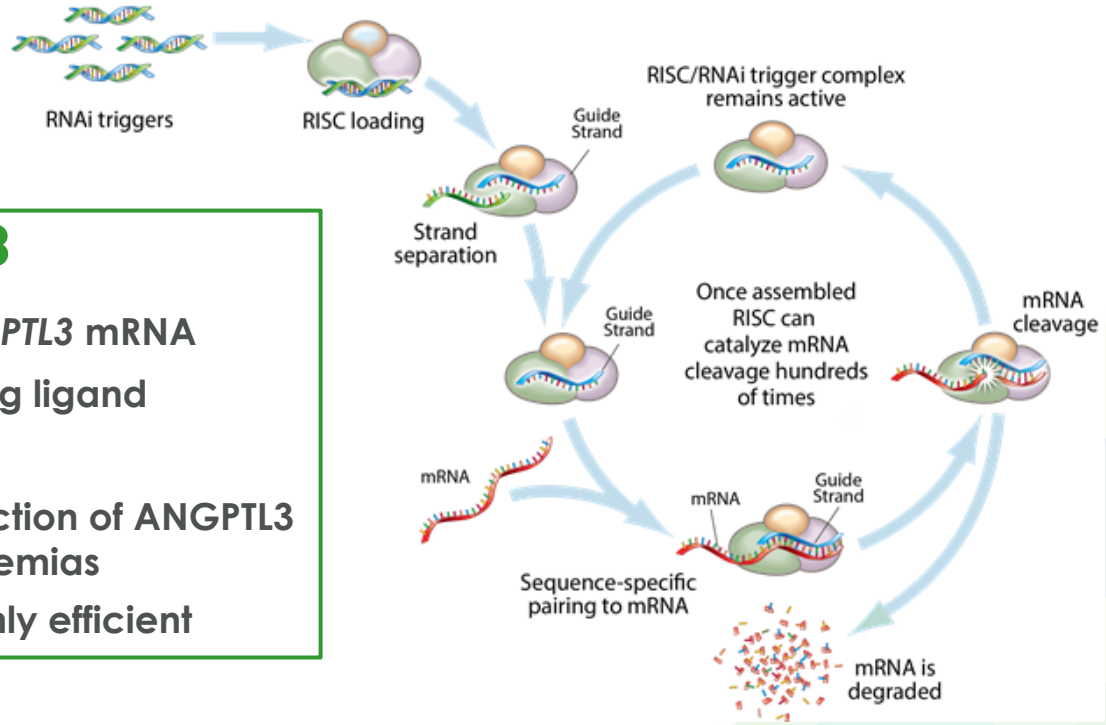
Silencing ANGPTL3 with RNA Interference

Targeted RNAi Molecule
TRiM™ platform



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:

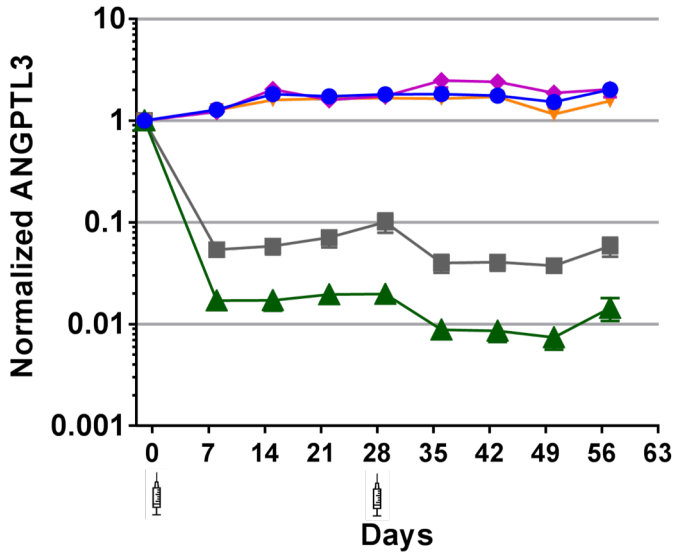
- Diet induced obese (DIO) mice
- Obese db/db mice
- *LDLr* KO mice

- 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

Group averages ± SEM

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



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

	After 1st dose	After 2nd dose
Standard chow	95%	96%
Western diet	98%	99%

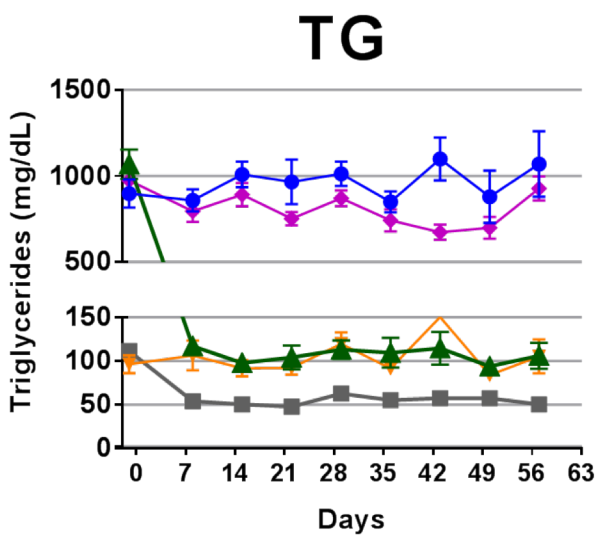
- **Liver mRNA knockdown was 96-97% at all time points tested (relative to saline group)**
- **No effects on serum ANGPTL3 in Saline or Control trigger treated groups**

arrowhead pharmaceuticals

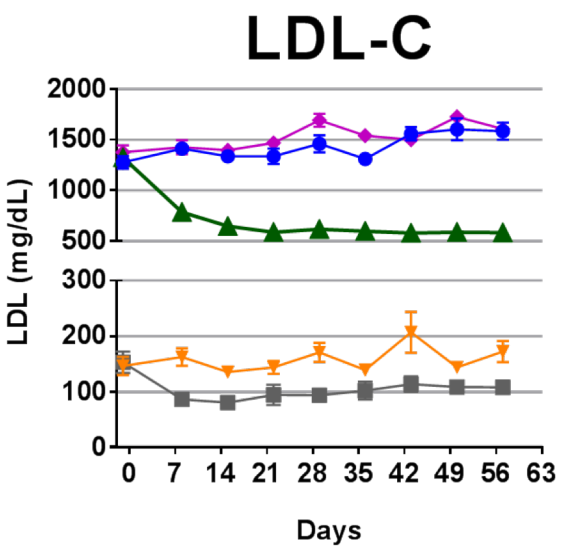
ARO-ANG3 Reduces LDL-C and Triglycerides in *LDLr* KO Mice

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



Western diet: 90% Max
Standard chow: 49% Max



Western diet: 48% Max
Standard chow: 43% Max

- 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)

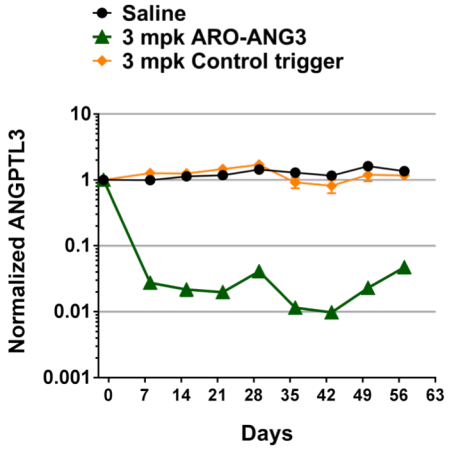
Reductions in LDL-C via a non-LDLr mechanism

arrowhead pharmaceuticals

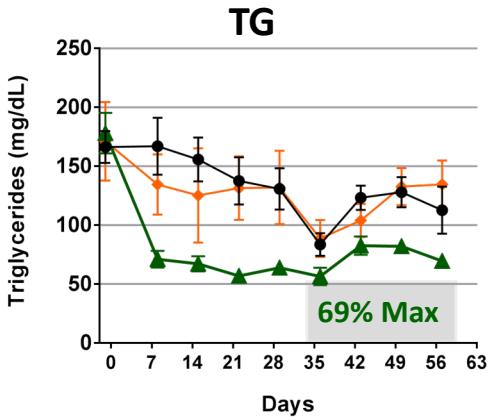
Similar Responses in Obese (db/db) or DIO Mouse Models

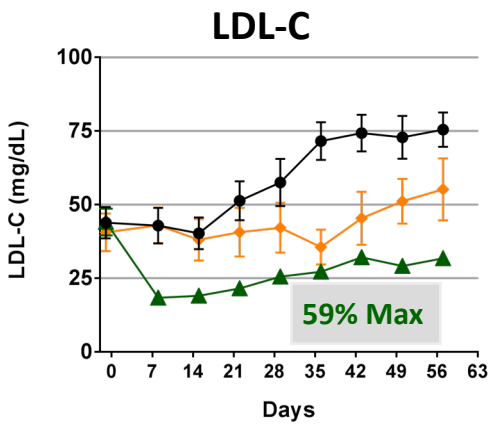
Leptin deficient db/db mice

All graphs showing group averages ± SEM

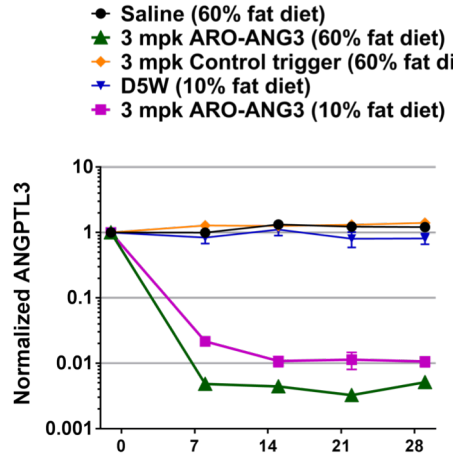


- SQ doses on Day 1 and 29
- Deep serum ANGPTL3 reductions
- 98% (1st dose) and 99% (2nd dose) reduced

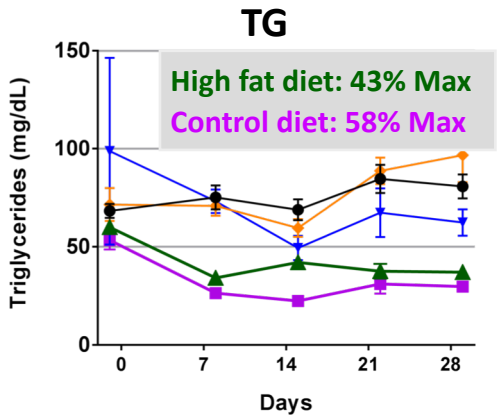


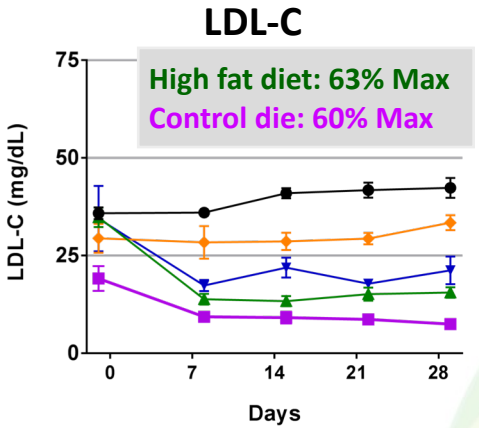


DIO (diet-induced obese) mice



- Single SQ dose on Day 1
- Deep serum ANGPTL3 reductions
  - High fat diet 97% reduced
  - Control diet 90% reduced





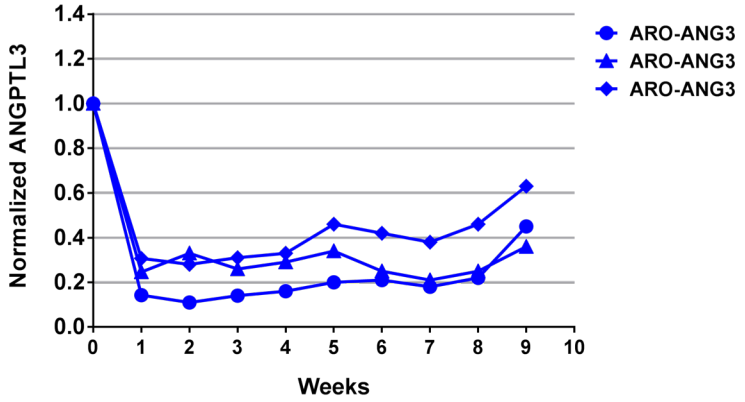
- **Models with moderate increases in lipid parameters**
- **ARO-ANG3 significantly reduces serum lipid levels**
- **ARO-ANG3 may be efficacious in a wide spectrum of hyperlipidemia**

arrowhead pharmaceuticals

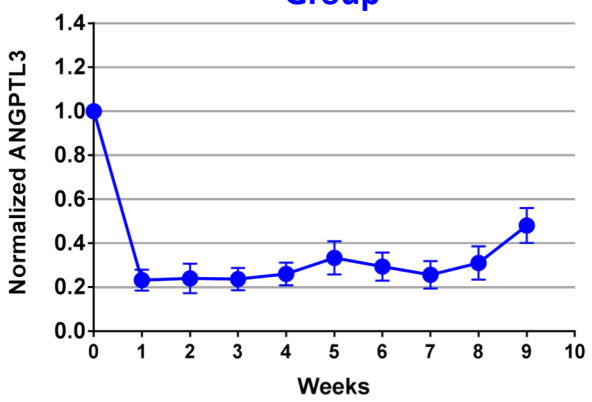
ARO-ANG3 in Chow-fed Cynomolgus Monkeys: Single Dose

Reductions in serum ANGPTL3 protein levels

Individual



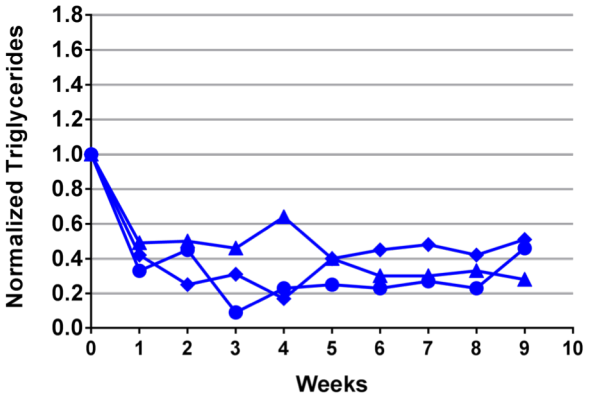
Group

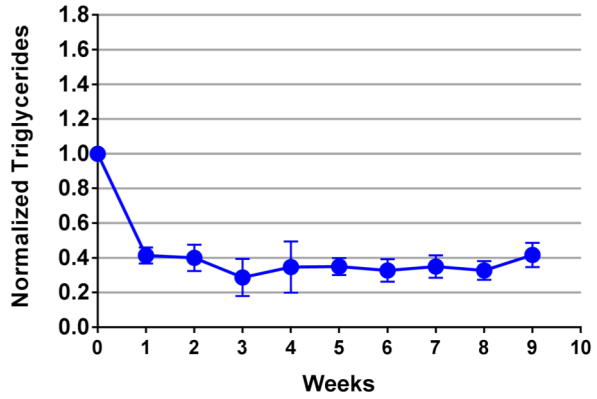


- **Single 2 mg/kg ARO-ANG3 SQ dose on study Day 1**
- **Reductions normalized to pre-dose values**
- **70-90% maximum reduction in serum ANGPTL3 protein levels**

Reductions in serum TGs

Group averages ± SEM





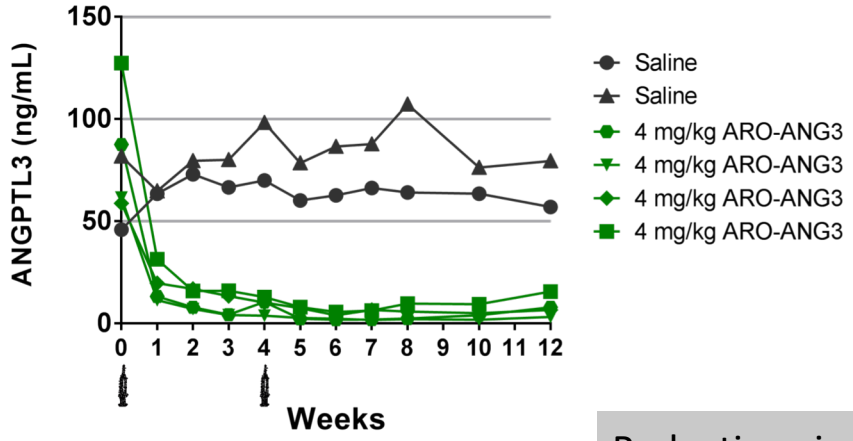
- **Normal cynos have vegan like serum lipids Significant reductions in TGs were observed**

arrowhead pharmaceuticals

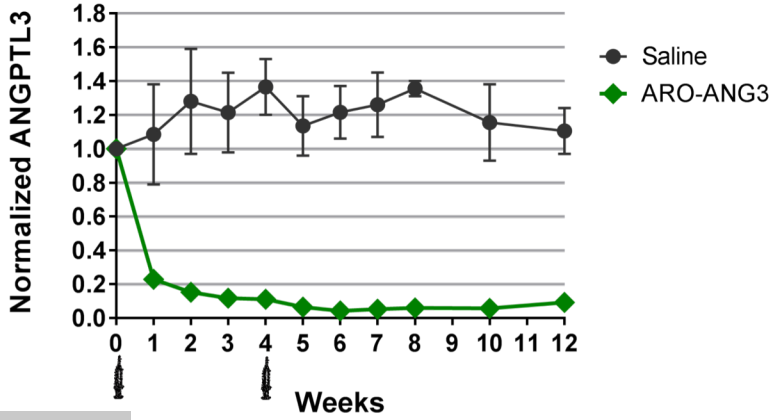
ARO-ANG3 in High Fructose Diet Dyslipidemic Rhesus Monkeys

Reductions in serum ANGPTL3 protein levels

Individual



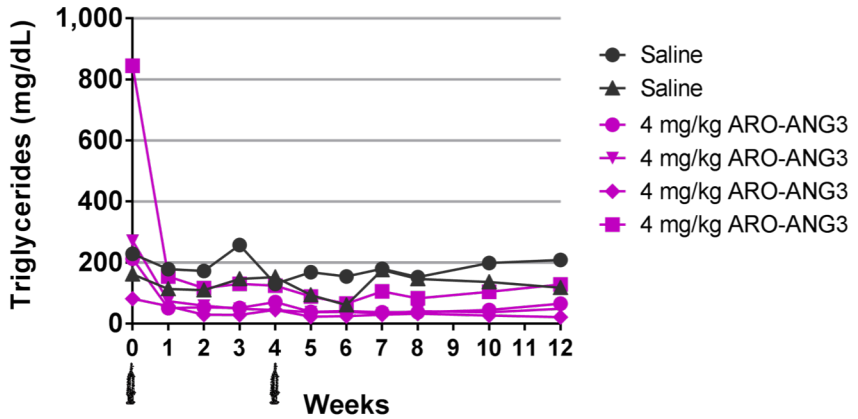
Group

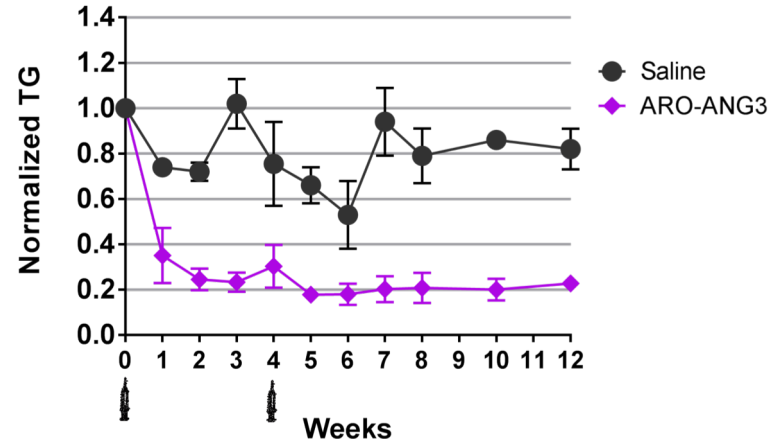


Group averages ± SEM

- 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

arrowhead pharmaceuticals

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