Reduction in Angiopoietin-Like Protein 3 via RNA Interference Improves Dyslipidemias and Hepatic Steatosis

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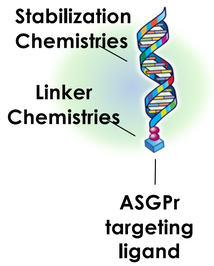
BACKGROUND

- Hypertriglyceridemia and hyperlipidemia represent causative risks for atherosclerosis, and elevated triglycerides (TG) also manifest as part of the metabolic syndrome and hepatic steatosis
- Human genetic analysis has identified that individuals with loss-of-function mutations in angiopoietin-like protein 3 (ANGPTL3) have very low plasma levels of triglycerides (TGs) and low-density lipoprotein (LDL-C), and a reduced risk of cardiovascular disease
- An RNA interference (RNAi) based therapy using Arrowhead Pharmaceuticals' TRiM™ platform to reduce liver ANGPTL3 production by gene silencing may be an effective approach to treat dyslipidemias and metabolic diseases (AHA 2018)

TRiM™ Platform



ARO-ANG3

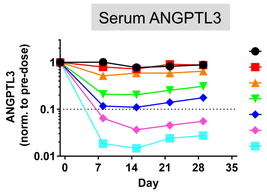
- Short dsRNA targeting *ANGPTL3* mRNA
- Hepatocyte ASGPr targeting ligand
- Subcutaneous (SQ) dosing
- Designed to reduce production of ANGPTL3 to potentially treat dyslipidemias
- Specific, catalytic and highly efficient

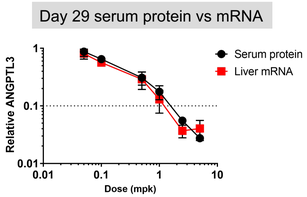
METHODS

- Highly potent and specific RNAi conjugates cross-reactive to human, rodent and non-human primate-(NHP) *ANGPTL3* transcripts were identified and studied for reductions in serum ANGPTL3 protein and liver *ANGPLT3* mRNA levels
- Lead optimization studies in wild type mice and chow-fed NHPs identified development candidate ARO-ANG3
- Dyslipidemic mouse models and a dyslipidemic fructose-fed NHP model were treated with ARO-ANG3 to examine lipid lowering and metabolic effects

RESULTS

Dose response in C57BL/6J wild-type mice, N = 4/group, single SQ injection of ARO-ANG3 (Day 1)



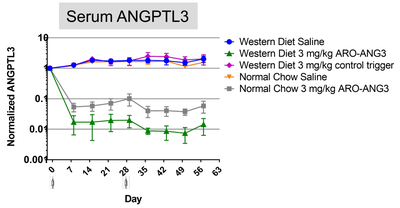


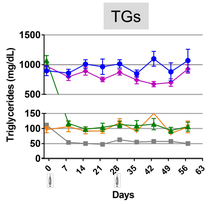
- Dose-dependent reductions in serum ANGPTL3 levels
- Day 29 hepatic *ANGPTL3* mRNA correlated with serum ANGPTL3 reductions

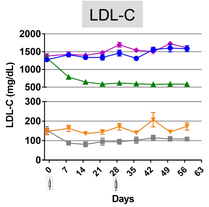
Reduction of serum lipids in *LDLr* KO mice

Mice on Western diet (n=12) or Standard chow (n=4)
ARO-ANG3 injected on Day 1 and 29

- Maximum serum ANGPTL3 reductions of 98-99% (Western diet) and 95-96% (chow)
- TGs reductions of 90% (Western diet) and 48% (chow)
- LDL-C reductions of 48% (Western diet) and 43% (chow) through LDLr independent pathways

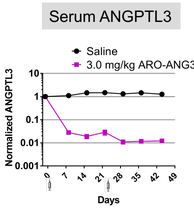


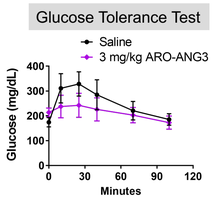




Improvements in glucose tolerance and reduction in hepatic steatosis in DIO mice

8 weeks old DIO mice on high fat diet, N=7/group
3 mg/kg ARO-ANG3 on Days 1 and 24
Glucose Tolerance Test on Day 41

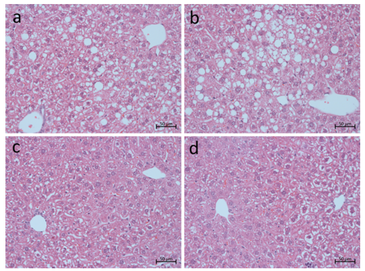




- Maximum serum ANGPTL3 reductions of 99% (after second dose)
- Maximum TGs reductions of 54% (from 70 mg/dL to 31 mg/dL)
- Maximum LDL-C reductions of 65% (from 20 mg/dL to 7 mg/dL)

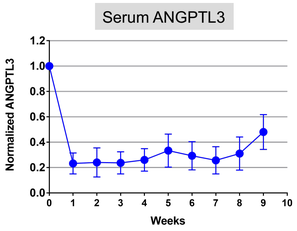
Liver Histology (H&E)

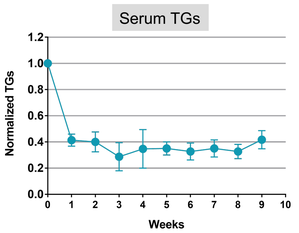
Saline (a, b)
ARO-ANG3 (c, d)



Single dose duration in chow-fed cynomolgus monkeys

Single 2 mg/kg ARO-ANG3 injected on Day 1, N=3



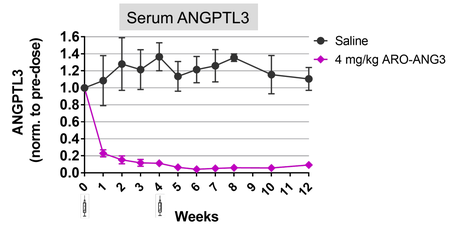


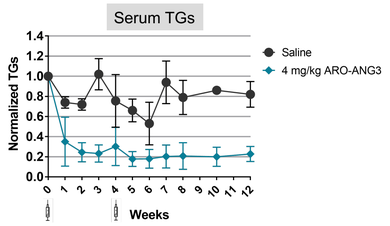
- Maximum mean serum ANGPTL3 reductions of ~80% sustained for at least 4 weeks after a single 2 mg/kg dose
- Significant reductions in TGs were observed

Efficacy in a fructose-fed dyslipidemic rhesus monkey model (Bremer et al Clin. Trans. Sci., 2019)

Animals on fructose diet for 6 weeks before dosing
4 mg/kg ARO-ANG3 (N=4), Saline (N=2), SQ injected on Days 1 and 29

- Over 95% maximum reductions in serum ANGPTL3
- 80% maximum mean reductions in TGs
- 20-60% max reductions in LDL-C (not shown)





CONCLUSIONS

- Our results support an ANGPTL3-targeted RNAi therapeutic as a treatment for dyslipidemia, with potential metabolic benefits
- Results in NHPs suggest human dosing intervals of once every 3 months or longer in ongoing human studies

ACKNOWLEDGEMENTS

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