RNA Interference Mediated Apolipoprotein C3 Gene Silencing as a Therapeutic for Hypertriglyceridemia

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SCIENTIFIC 2018 SESSIONS

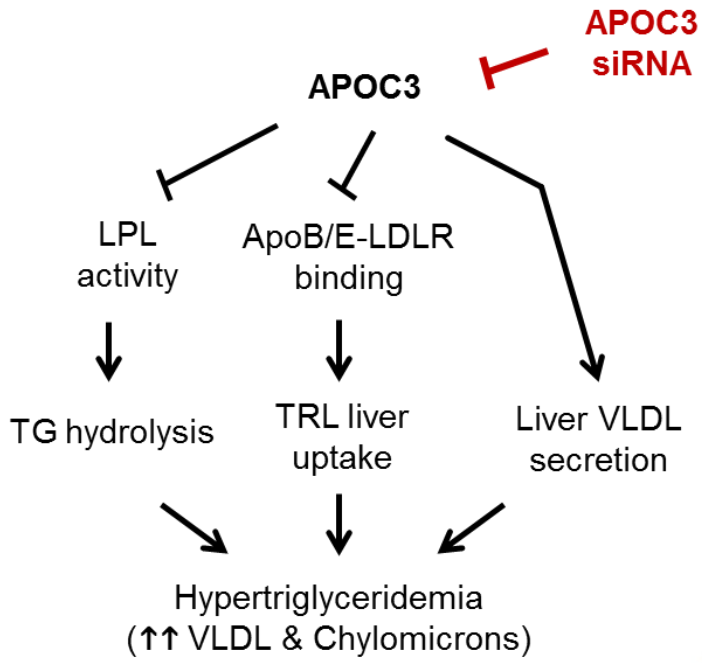
Disclosures

All authors are employee and shareholders of Arrowhead Pharmaceuticals.

Clinical Indications Related to High Triglycerides

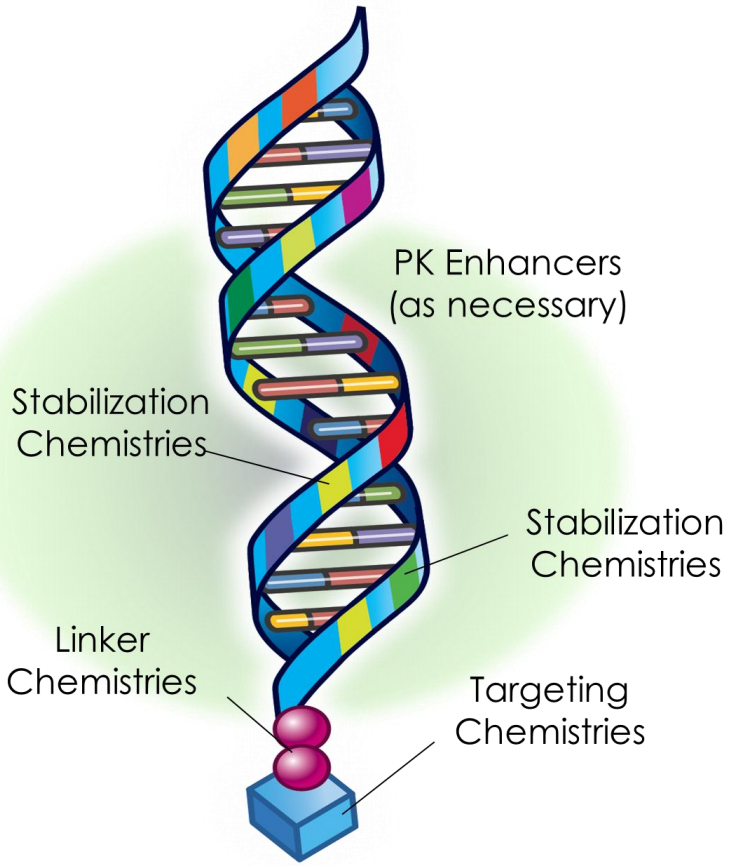
Two primary indications to lower TGs with pharmacotherapy

1. Reduce pancreatitis risk (TGs > ~900 mg/dL)
   - Goal is to get well below 500 mg/dL to prevent pancreatitis associated with 2-3X rise post ETOH/fatty meal
2. Reduce residual CVD risk following maximized LDL lowering



Triglyceride rich lipoproteins = VLDL, chylomicrons
LDLR= low density lipoprotein receptor
LPL= Lipoprotein lipase
VLDL= very low density lipoprotein

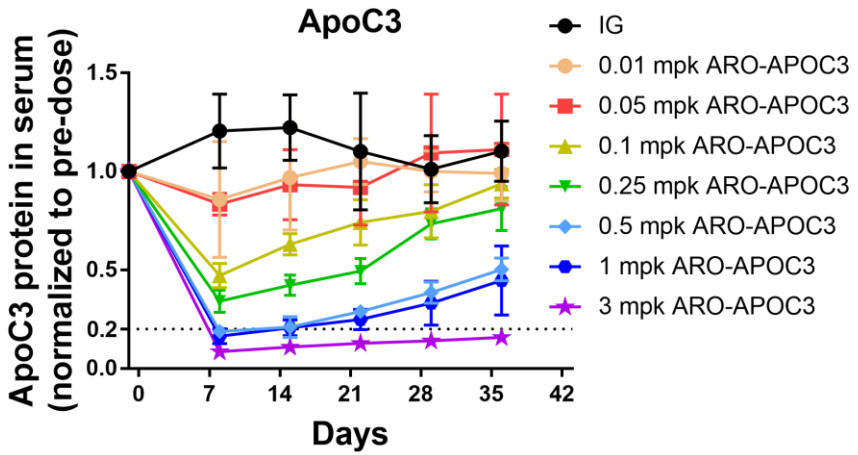
Targeted RNAi Molecules - TRiM™ Platform



- Rules and algorithms allow selection of optimized RNAi trigger sequences
- Limit cross-reactivity with off-target genes
- Maximize innate stability
- Rational use and placement of modifying chemistries
- Active endosomal escape chemistries not required
- Targeting ligands and linker chemistries improve delivery to target tissues

TRiM™ platform for hepatic targets has shown good activity in clinical programs

ARO-APOC3 Dose-response in Human-APOC3 Transgenic Mice

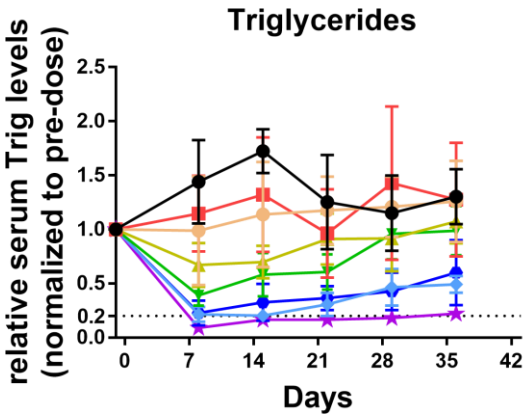


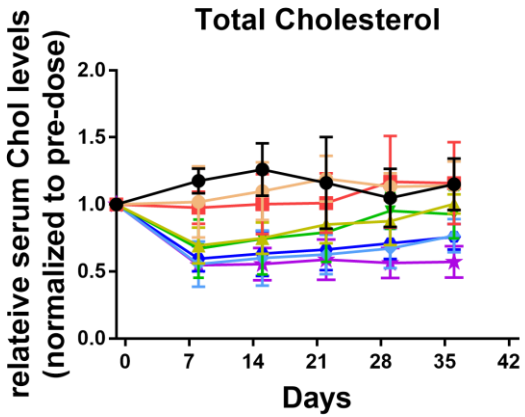
Method

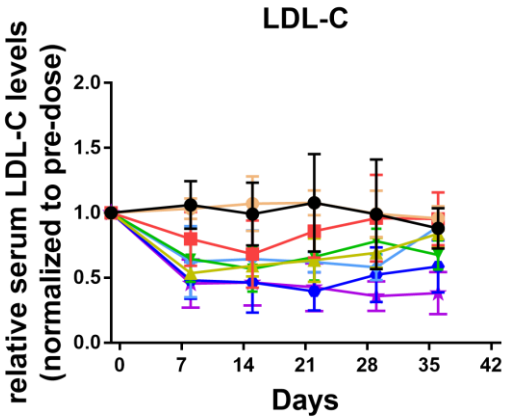
- APOC3 transgenic mice were given various SQ doses of ARO-APOC3 ranging from 0.01 to 3 mg/kg on study Day 1

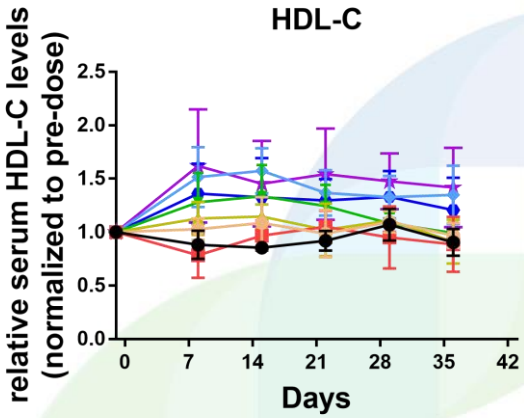
Results

- Dose-dependent effects on depth and duration of serum ApoC3 knockdown (KD)
- Dose-dependent reductions in Trig, Total Chol and LDL-C, and increase in HDL-C









RNAi for APOC3 Brings a Special Challenge

- Proportion of APOC3 coming from intestines appears much higher in non-human primates than humans yielding confusing results from plasma APOC3 measurements

  - ✓ Solution – liver biopsy to evaluate *APOC3* mRNA knockdown in cynomolgus monkeys

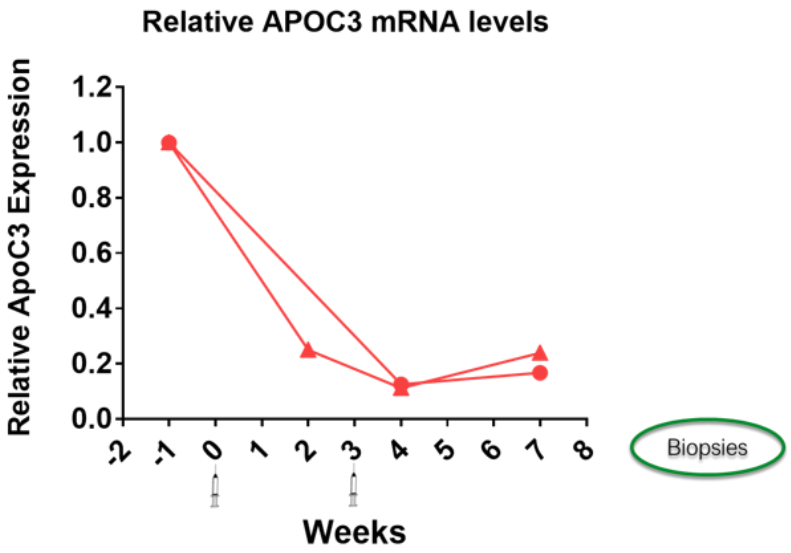
ARO-APOC3 KD in Cynomolgus Monkeys

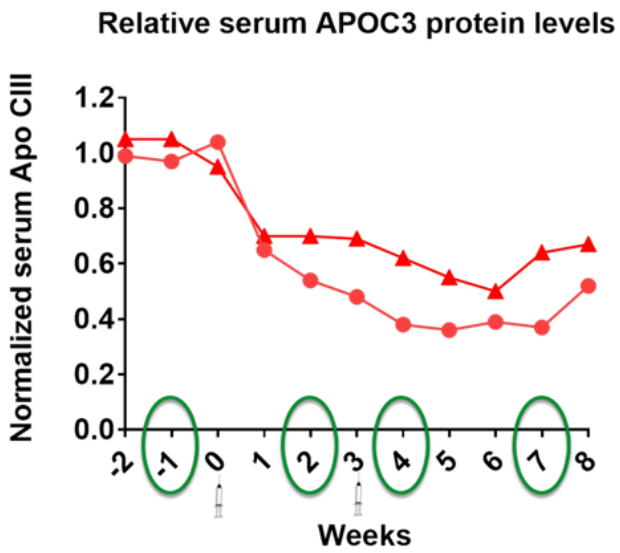
Methods

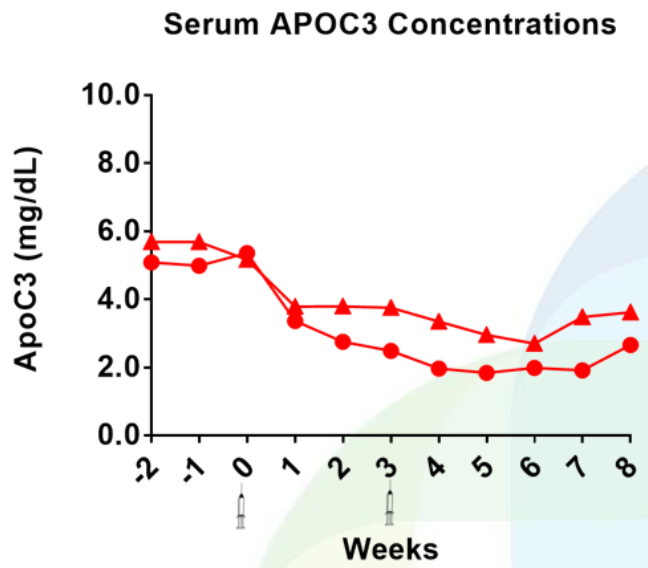
- Cynomolgus monkeys (n=2) were administered a subcutaneous injection of 4 mg/kg ARO-APOC3 on study day 1 and again on day 22. Liver biopsies were performed on days -7, 15, 29 and 50 for mRNA analysis.

Results

- ~90% KD of liver *APOC3* mRNA level was observed
- 50-60% reduction in serum APOC3 levels
- Remaining serum APOC3 likely from small intestine







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Summary and Plans for ARO-APOC3

- Preclinical studies in animal models demonstrated potent target gene knockdown and expected effects on serum lipids
- ARO-APOC3 holds promise for treatment of patients with hypertriglyceridemia
- Filing for First-in-human studies planned for the end of 2018

Acknowledgements

Arrowhead ApoC3 Discovery Team

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