Cardiovascular and Lipid Disorders: A Next Frontier for TRiM RNAi

RNA and Oligonucleotide Therapeutics
Cold Springs Harbor Laboratory
March 28, 2019

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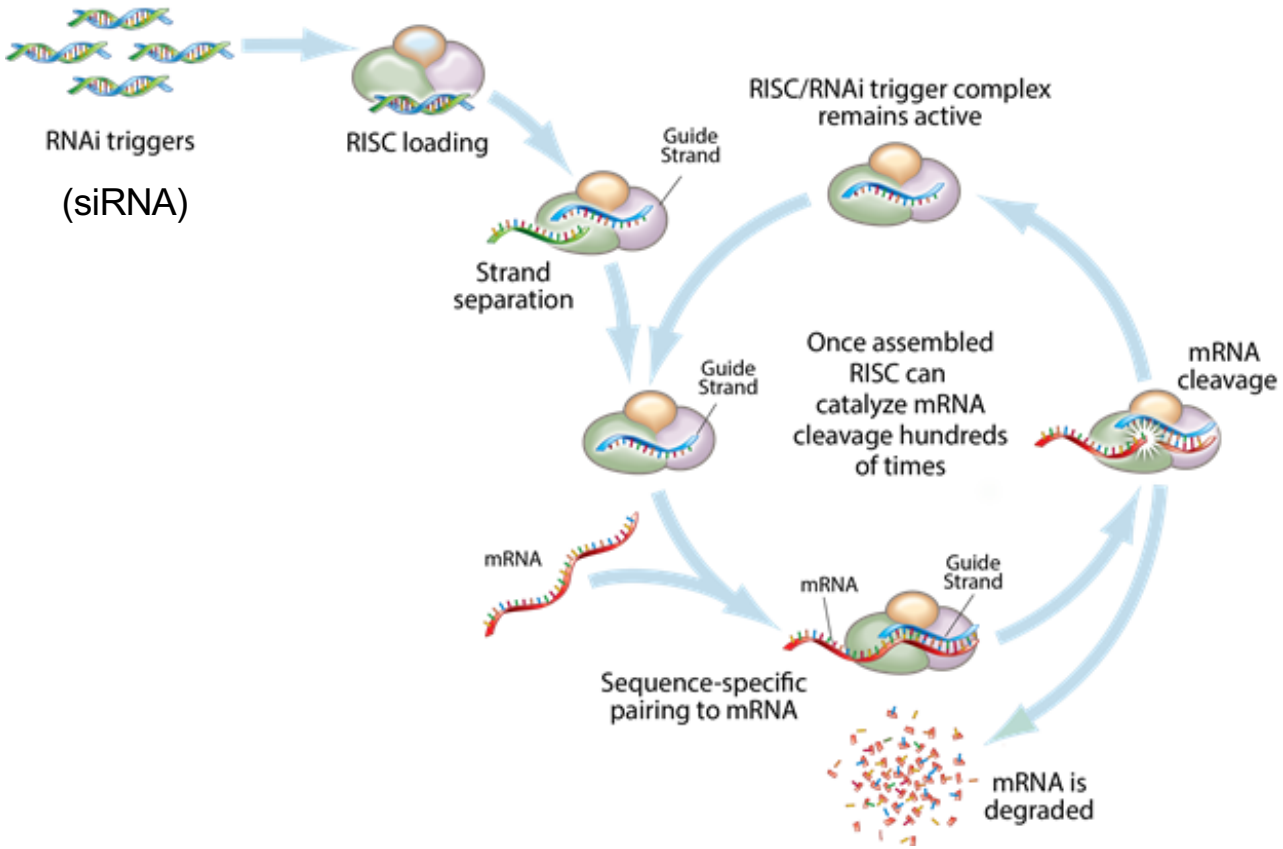
Safe Harbor Statement

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

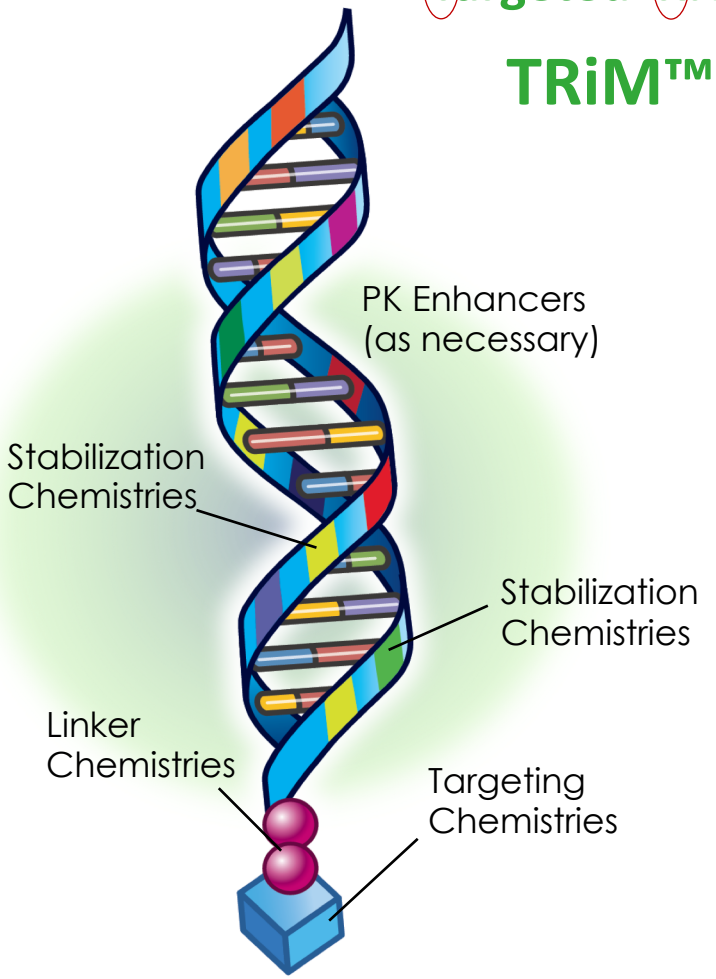


Therapeutic gene silencing with **RNA interference** is highly precise and efficient

Arrowhead RNAi Platform: TRiM™: Simplicity, Specificity, and Activity

Targeted RNAi Molecule

TRiM™ platform



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

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Pipeline

Competitive Position	Drug	Disease	Pre-clinical	Pre-IND	Phase 1	Phase 2	Phase 3
First RNAi	ARO-AAT	Alpha-1 Liver Disease					
First RNAi	ARO-APOC3	Hypertriglyceridemia					
First RNAi	ARO-ANG3	Dyslipidemia					
First RNAi	ARO-ENaC	Cystic Fibrosis					
First RNAi	ARO-HIF2	Renal Cell Carcinoma					
Leading RNAi	ARO-HBV	Hepatitis B					Partnered with Janssen
First RNAi	AMG 890	Cardiovascular Disease					Partnered with Amgen
Undisclosed Target	ARO-AMG1	Cardiovascular Disease					Partnered with Amgen

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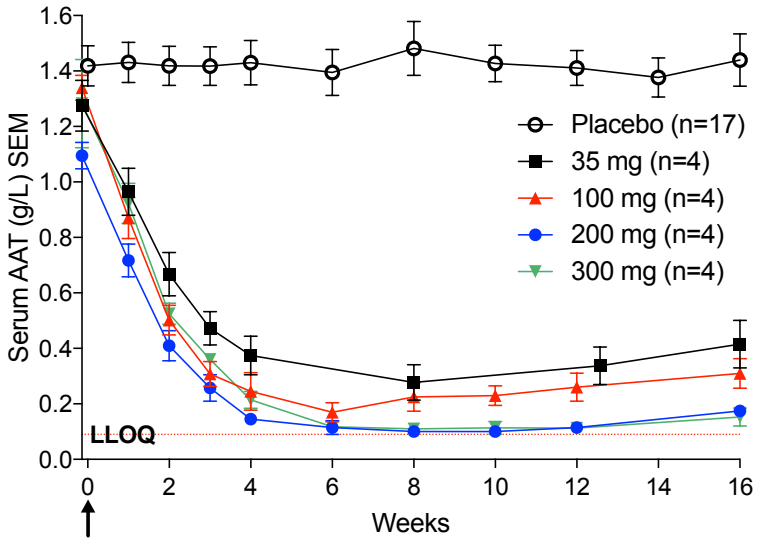
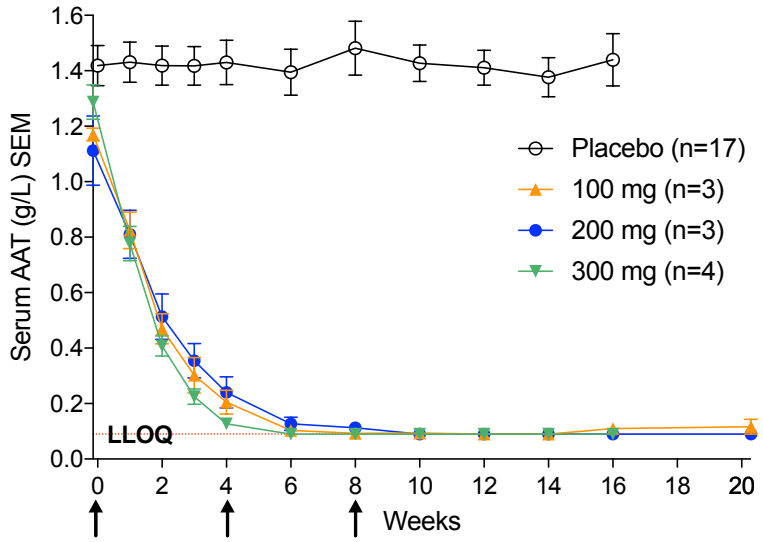
Duration of TRIM™ in Humans - ARO-AAT Phase 1, NHV SAD/MAD study

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

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

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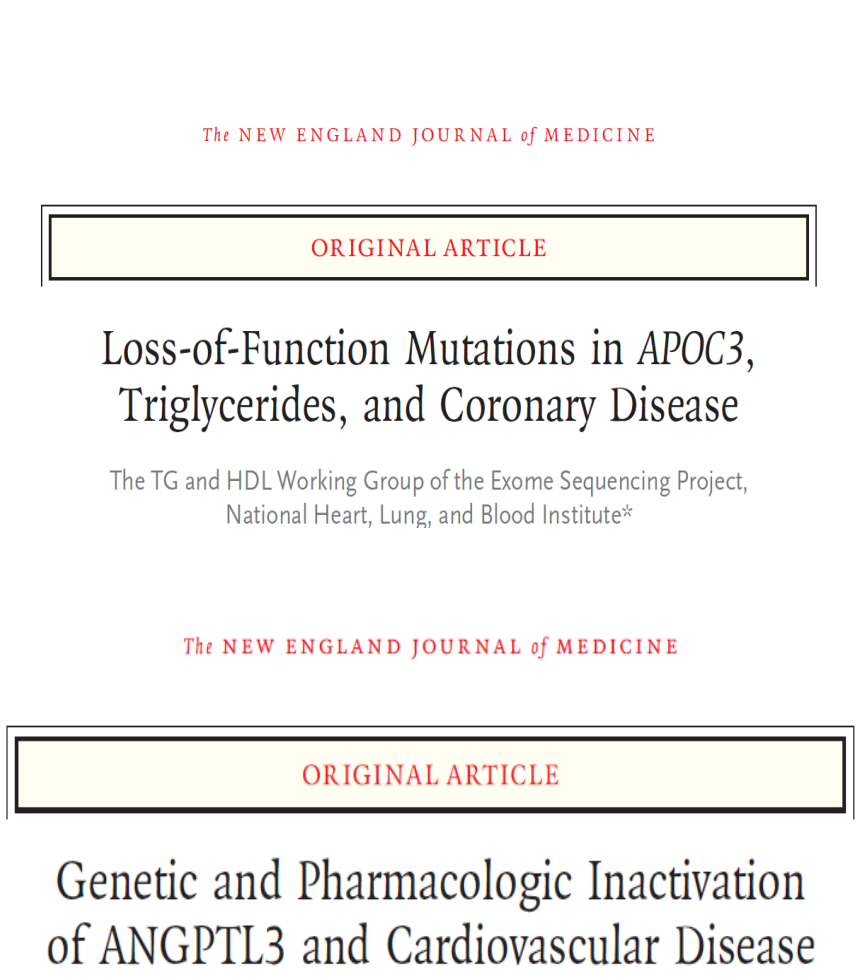
BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia



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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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

APOC3, ANGPTL3 Supporting Genetic Data

Mean or Median changes in lipid parameters in heterozygotes and homozygotes for *APOC3 and ANGPTL3* LOF mutations versus non-carriers

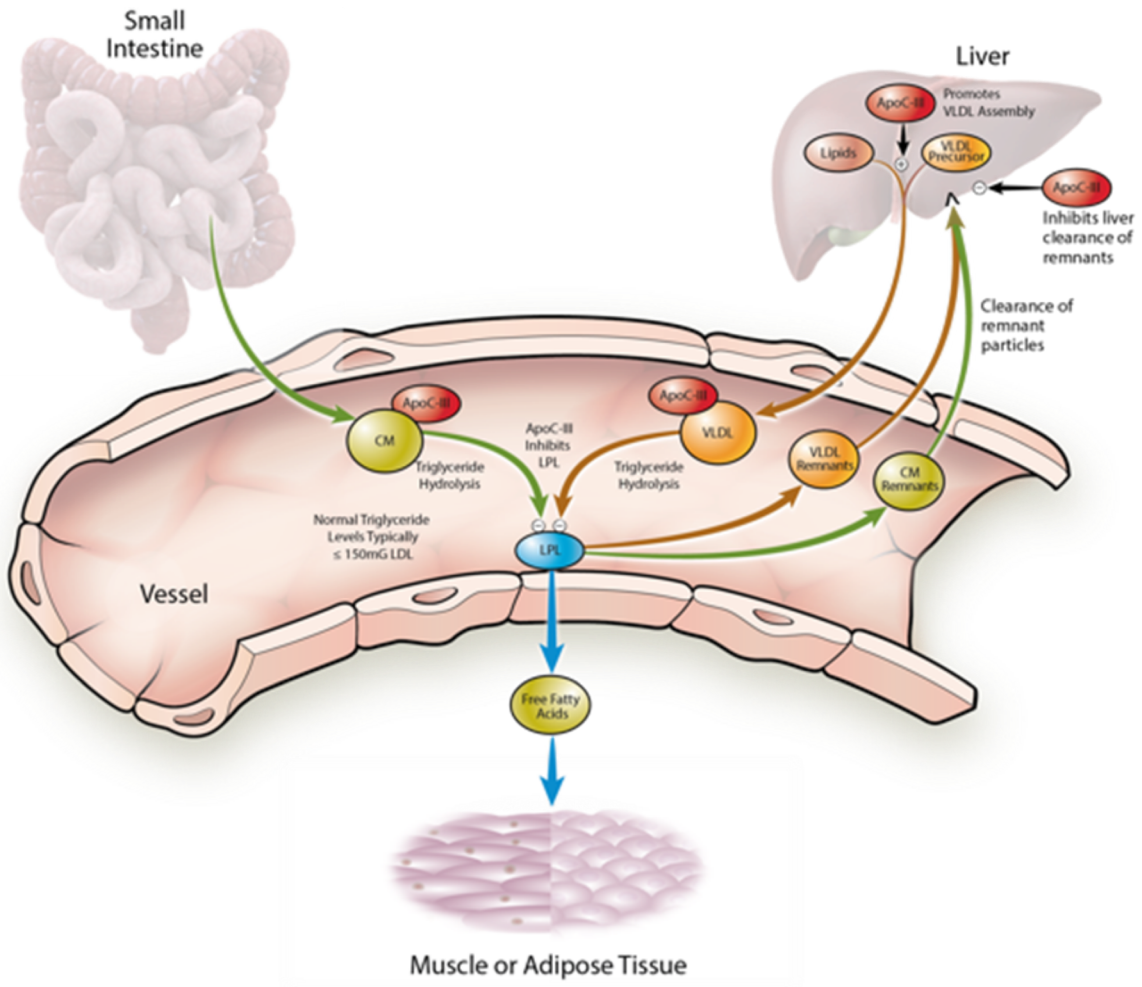
Metric (serum level)	*APOC3* deficient heterozygote[1]	*APOC3* deficient homozygote[2]	*ANGPTL3* deficient heterozygote[3]	*ANGPTL3* deficient homozygote[4]
ApoC-III	-46%	-88.9%	NA	NA
ANGPTL3	NA	NA	-40% to -87%	undetectable
Triglycerides	-39%	-59.6%	-21.1%	-71.2%
LDL-C	-16%	Similar to non-carrier	-8.6%	-67.2%
HDL-C	+22%	+26.9%	-16.8%	-39.0%
CAD risk	-40%	Not reported	-41%[4]	NA
Adverse Phenotype/AEs	None described	None described	None described	None described

1. Triglyceride working group, NEJM 2014
2. Saleheen et al., Nature 2016
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

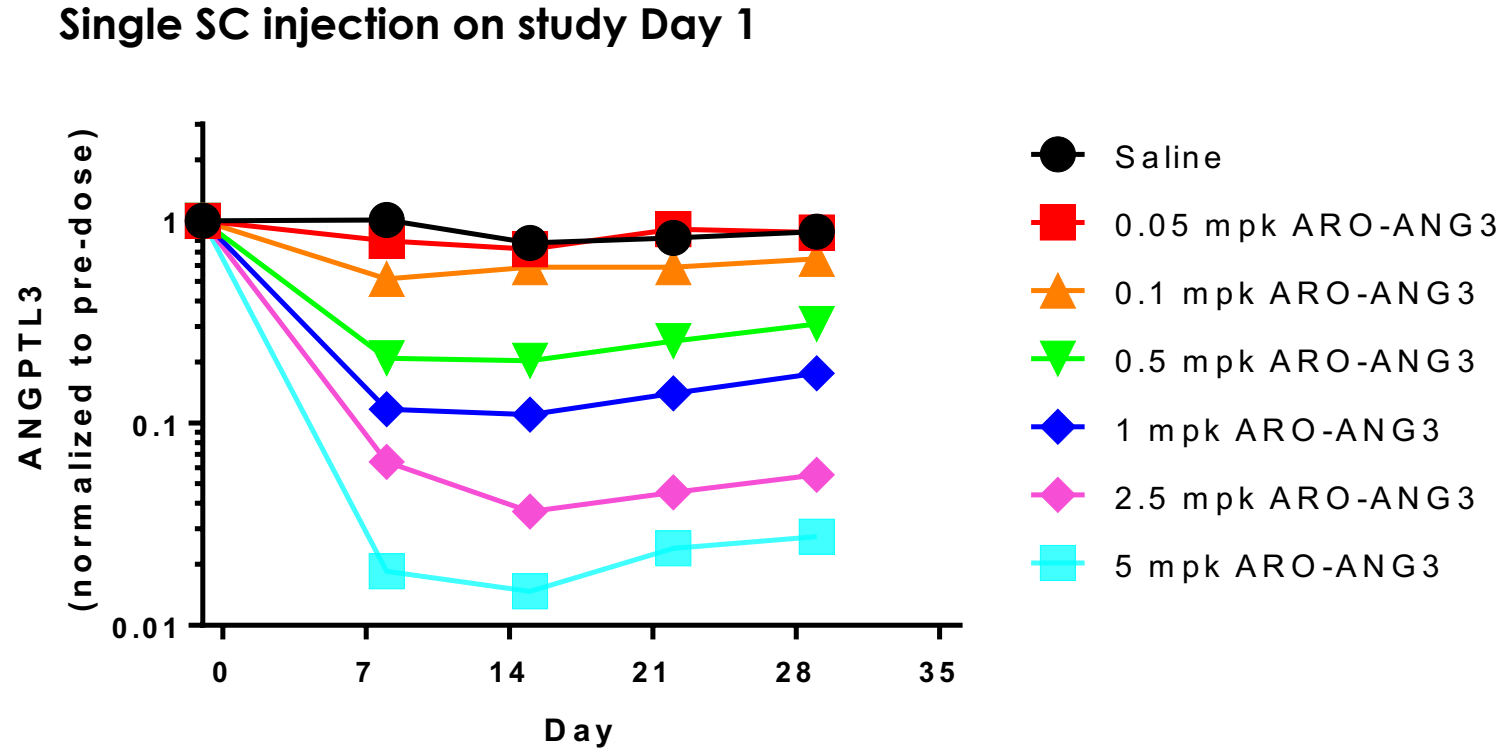


ANGPTL3 inhibition

- 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

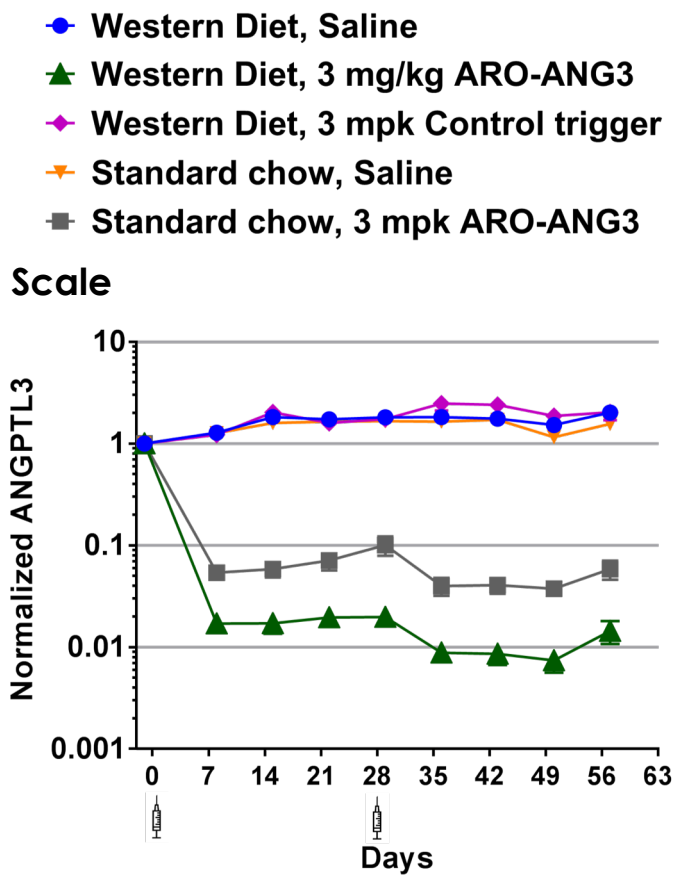
ARO-ANG3 Dose Response in WT Mice



- 80% knockdown (KD) of ANGPLT3 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

Group averages ± SEM



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

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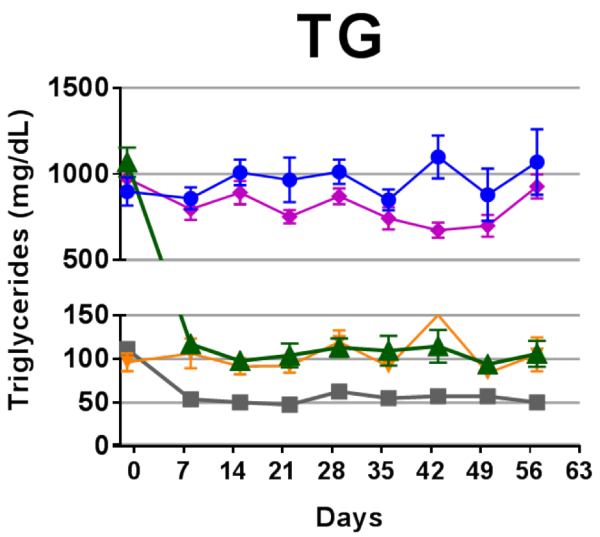
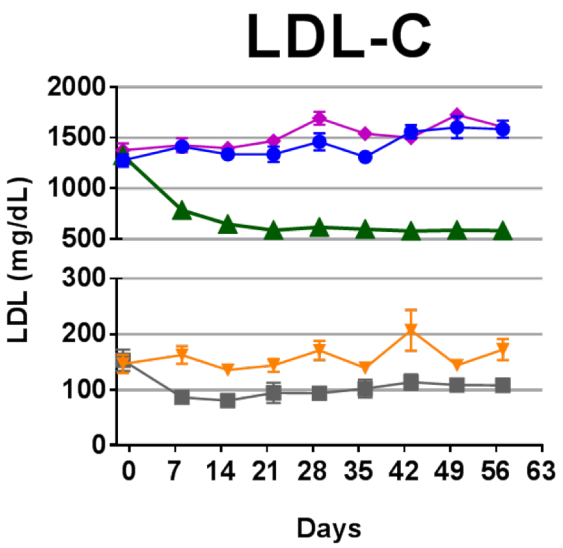
ARO-ANG3 Reduces LDL-C and Triglycerides in *LDLr* $^{-/-}$ Mice

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



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



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

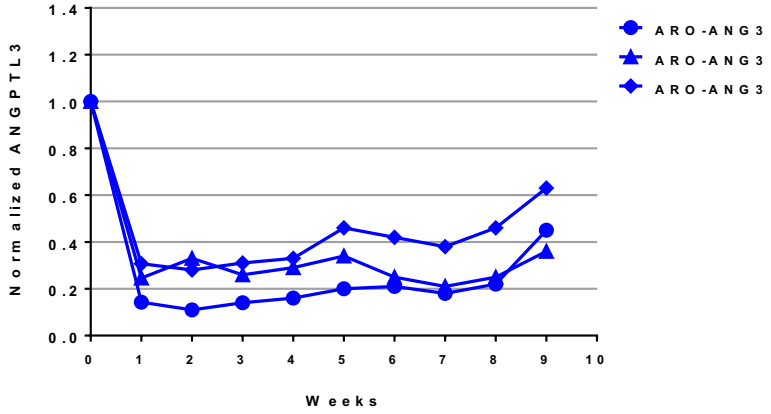
- Mice on both Western diet and Standard chow had elevated serum lipids compared to wild-type normal mice (TGs: 35-45 mg/dL, LDL-C: 10-15 mg/dL)

Reductions in LDL-C via a non-LDLr mechanism

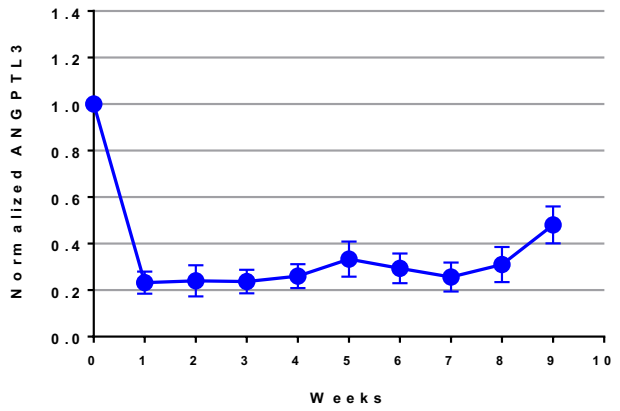
ARO-ANG3 in chow-fed cynomolgus monkeys: single 2 mg/kg dose

Reductions in serum ANGPTL3 protein levels

Individual



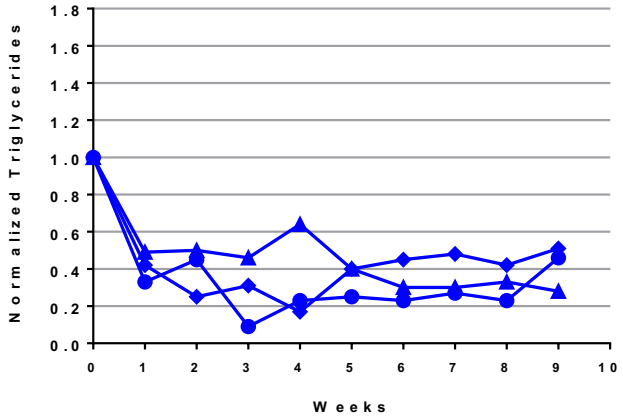
Group

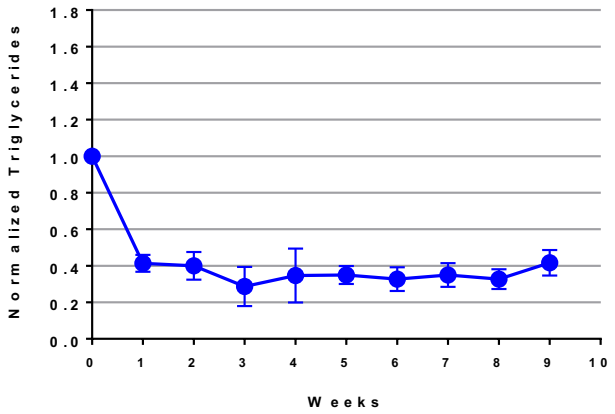


- Single 2 mg/kg ARO-ANG3 SC dose on study Day 1
- Reductions normalized to pre-dose values
- **70-90% maximum reduction in serum ANGPTL3 protein levels**

Group averages ± SEM

Reductions in serum TGs





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

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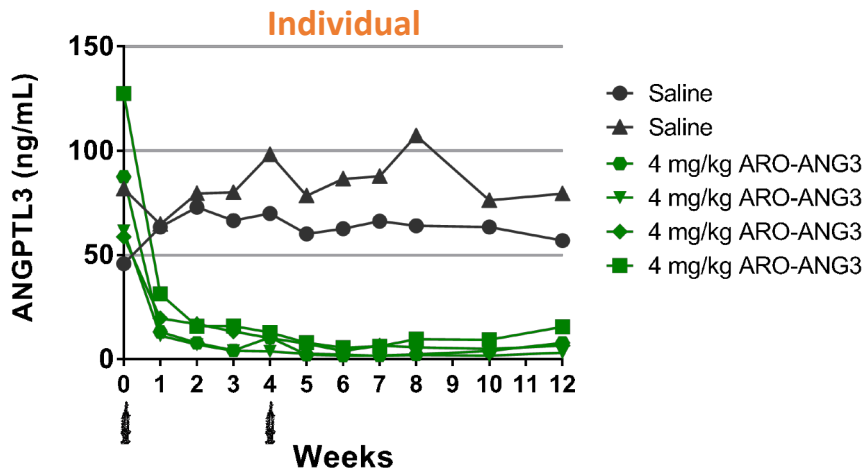
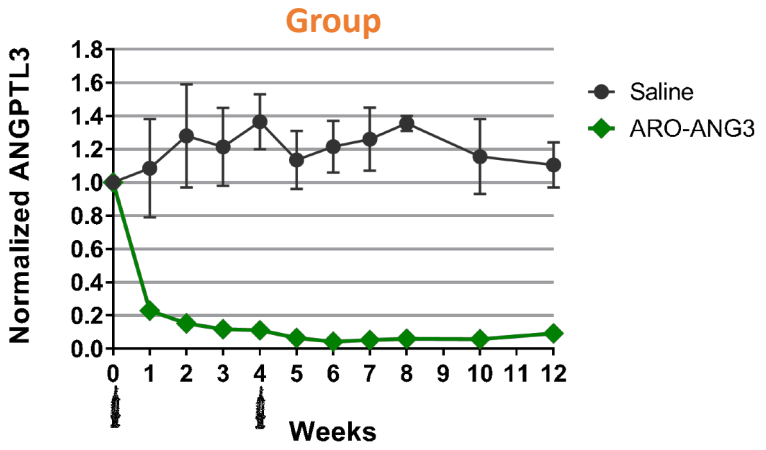
ARO-ANG3 in HFCS-induced dyslipidemic rhesus monkeys

Reductions in serum ANGPTL3 protein levels

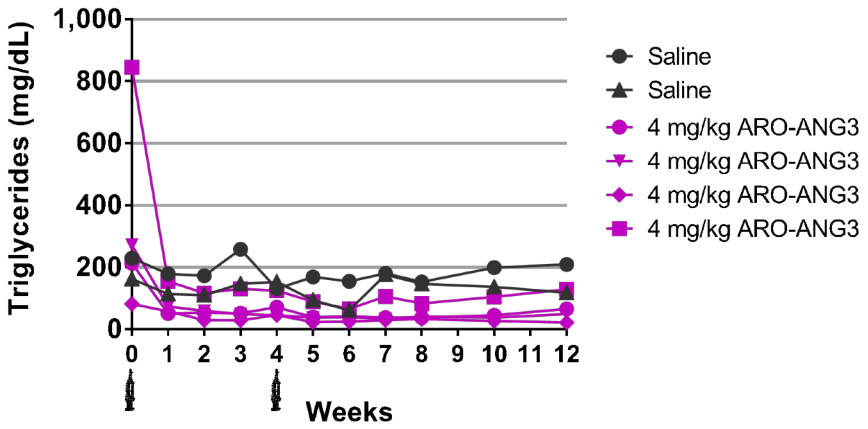


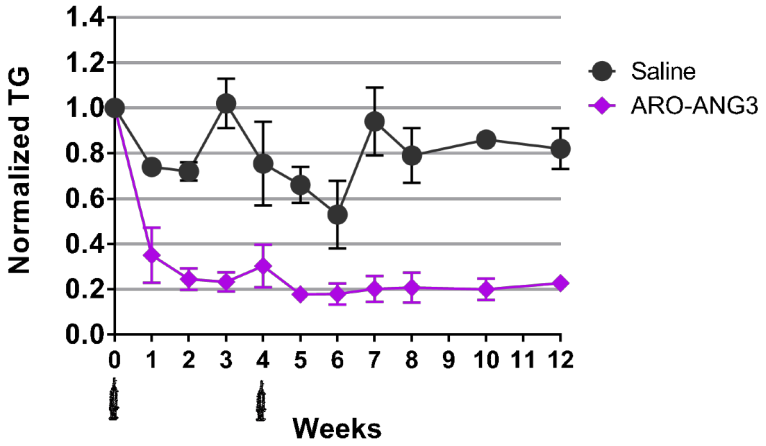


- SC doses on Day 1 and 29
- **Over 95% maximum reductions in serum ANGPTL3 protein levels**
- Normalized to pre-dose values

Reductions in serum TGs

Group averages ± SEM





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

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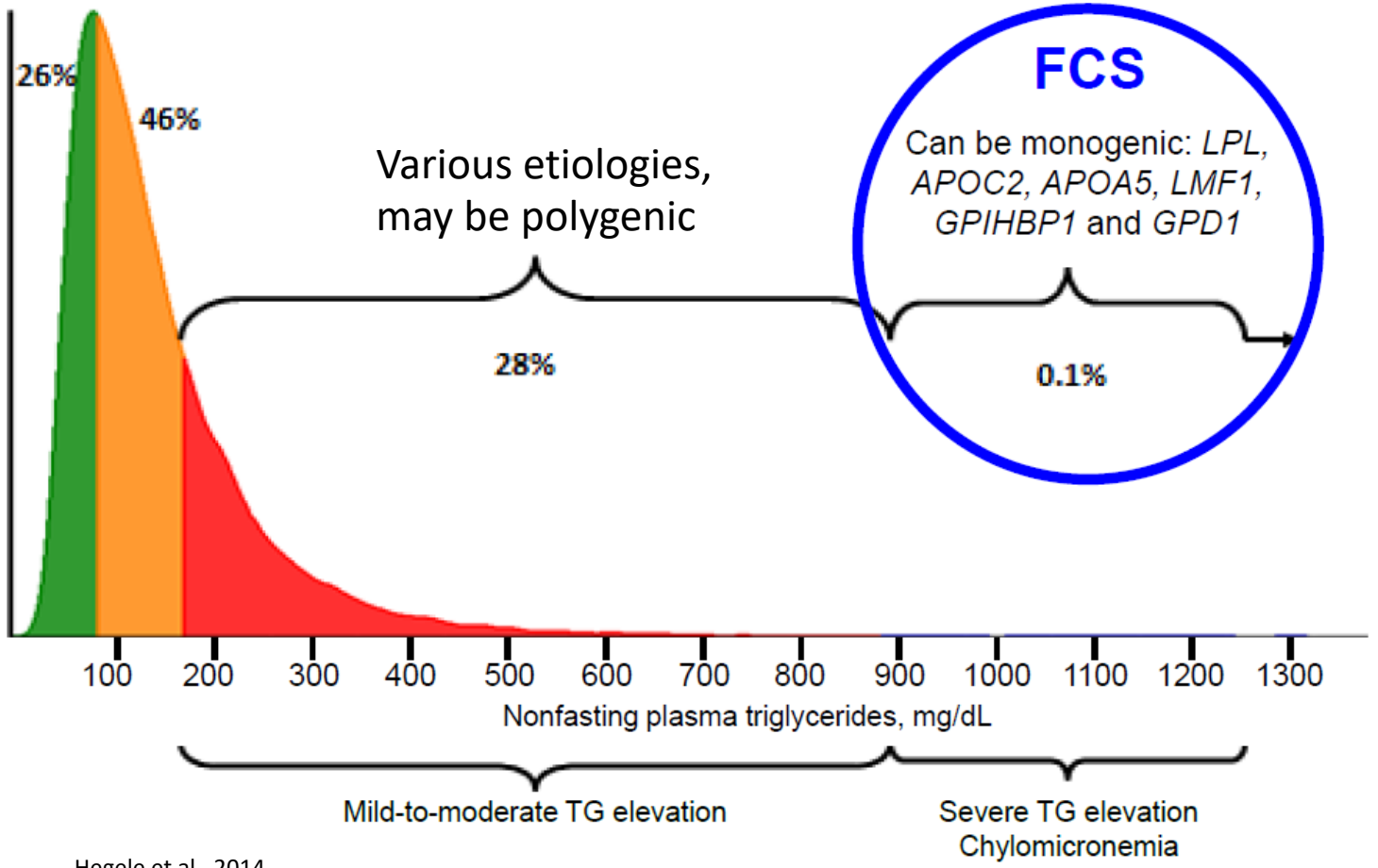
AROANG31001 Clinical Study

- 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

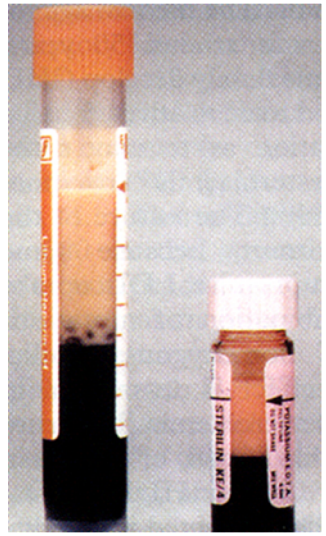
Clinical Indications: Moderate to Severe Hypertriglyceridemia



Hegele et al., 2014

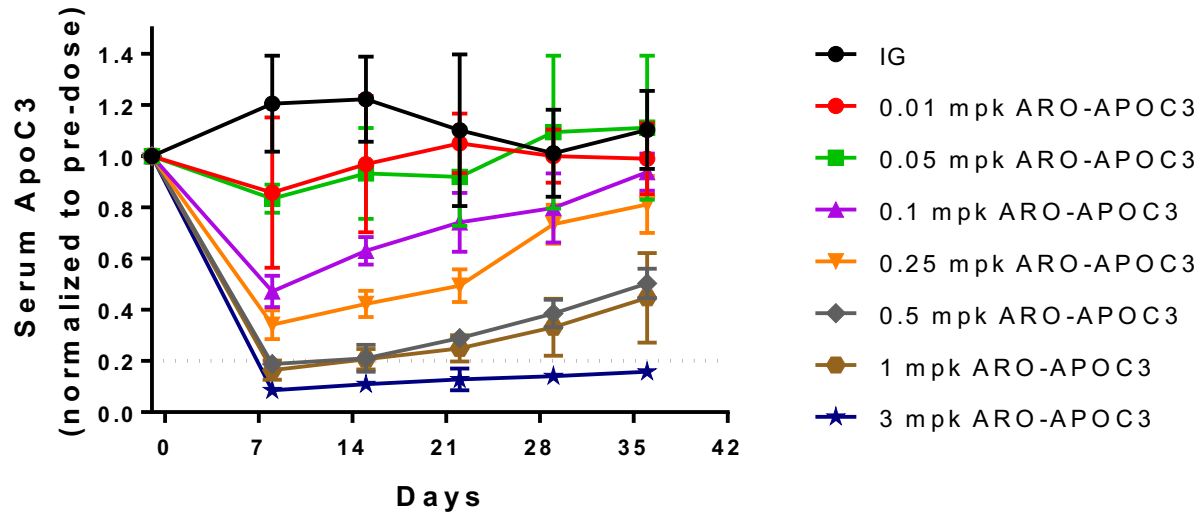
Familial Chylomicronemia Syndrome (FCS)

- 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



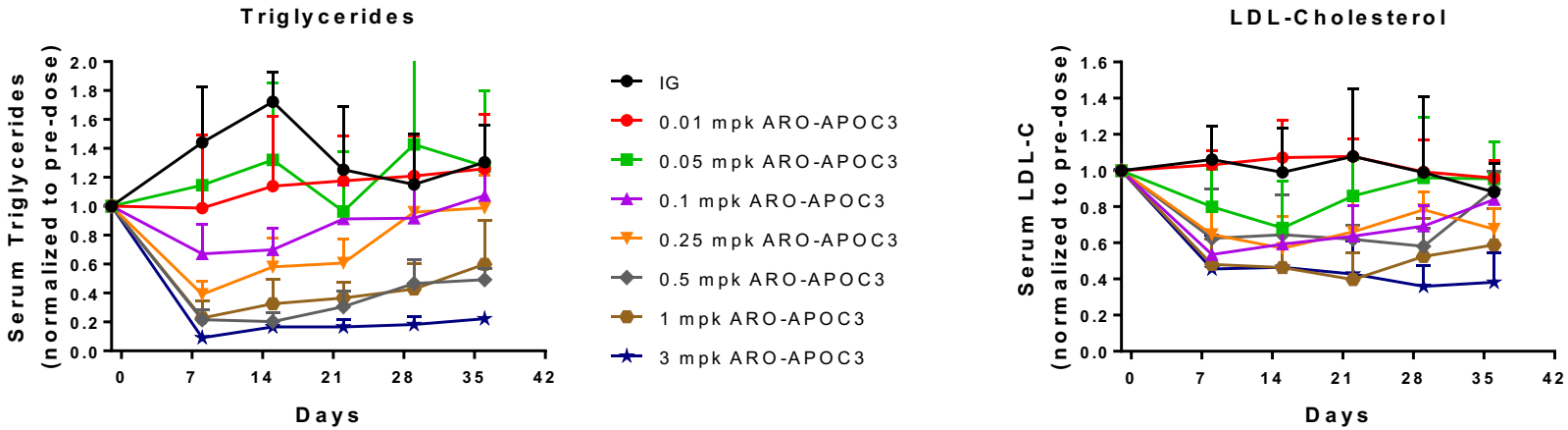
Method

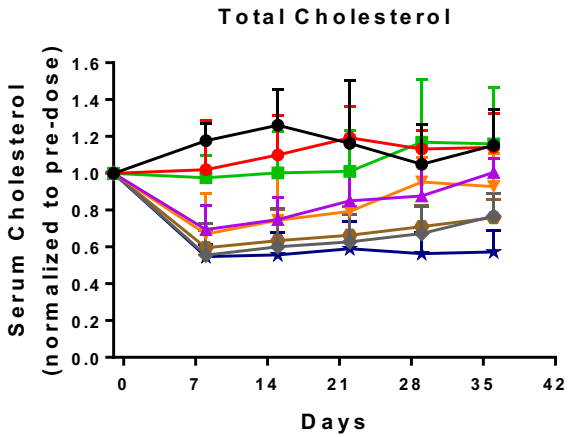
APOC3 transgenic mice were given various SQ doses of ARO-APOC3 ranging from 0.01 to 3 mg/kg on study Day 1

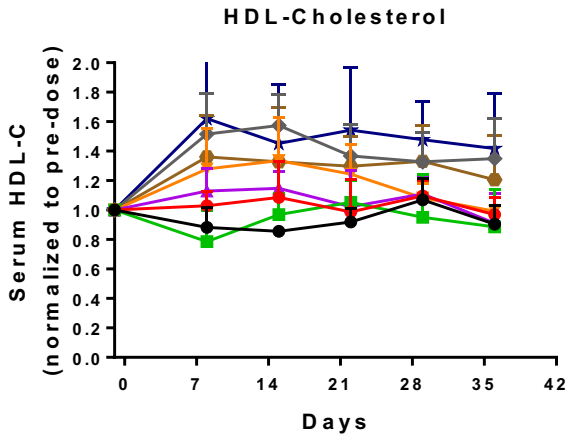
Results

Dose-dependent effects on depth and duration of serum ApoC3 knockdown (KD)

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





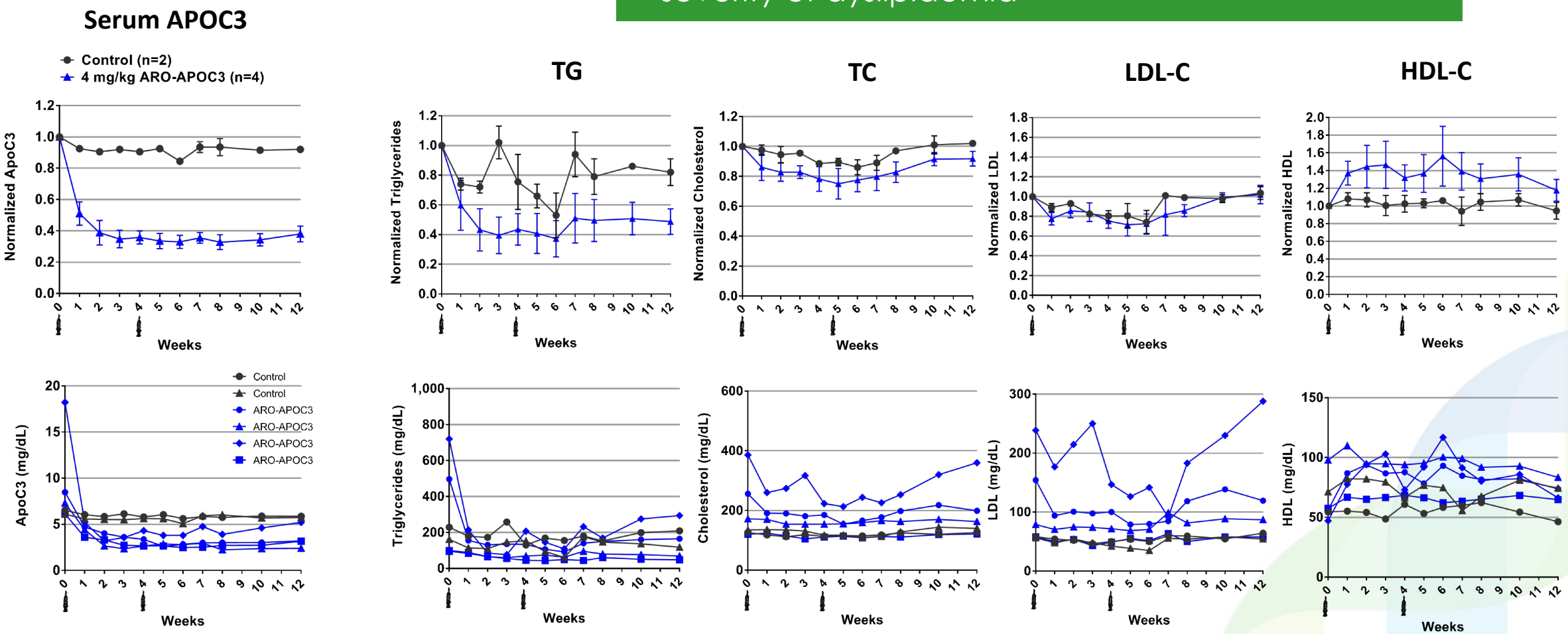


- Dose-dependent reductions in Triglycerides, Total Cholesterol and LDL-C, and increase in HDL-C

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



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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

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