TRiM™ Platform Based RNAi Therapeutics for AATD and Cardiometabolic Diseases

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arrowhead pharmaceuticals

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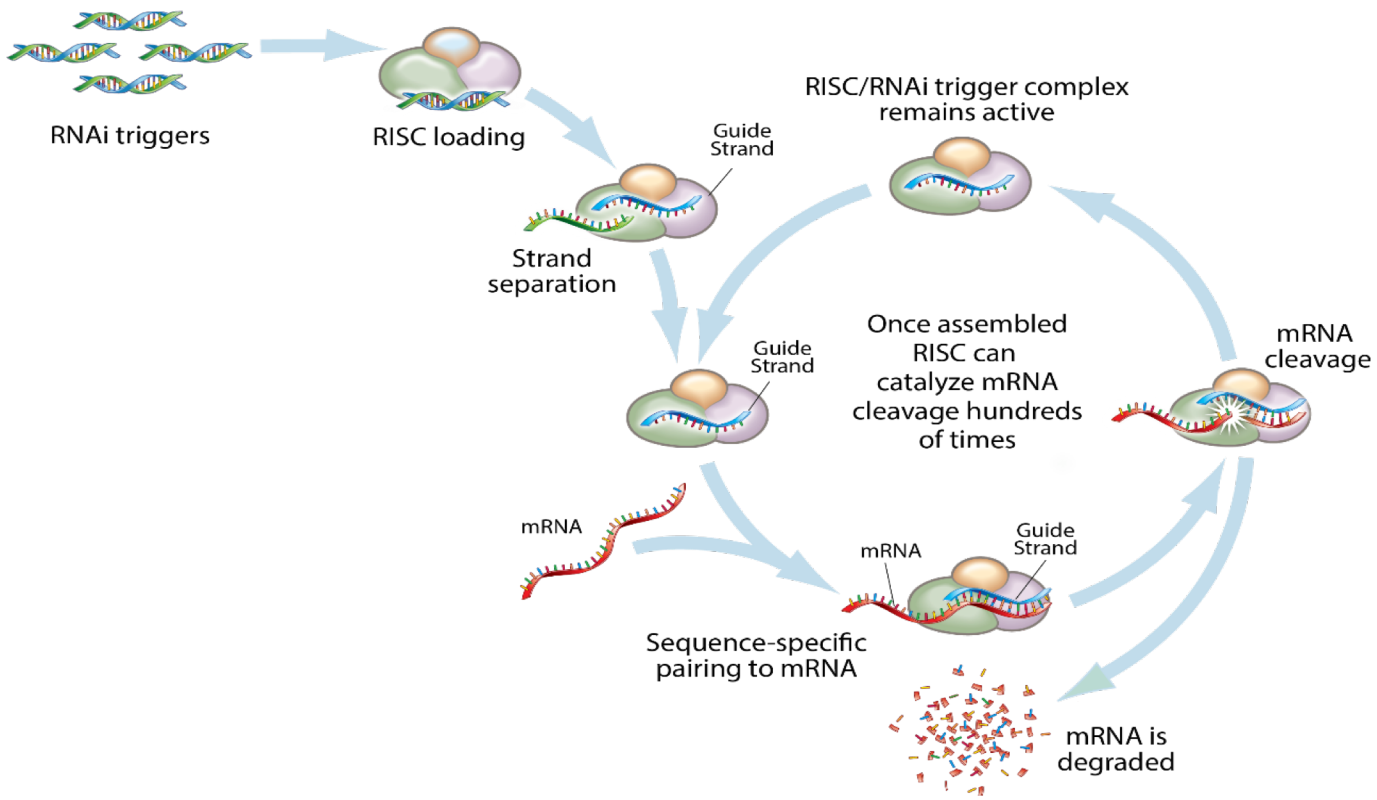
- I am an employee and shareholder of Arrowhead Pharmaceuticals, Inc.

Outline

- Arrowhead's Targeted RNAi Molecule (TRiM™) platform for targeting hepatocytes
- Discovery and development of Arrowhead clinical candidate
  - ARO-AAT
- Discovery and development of ARO-ANG3 for treatment of hyperlipidemia

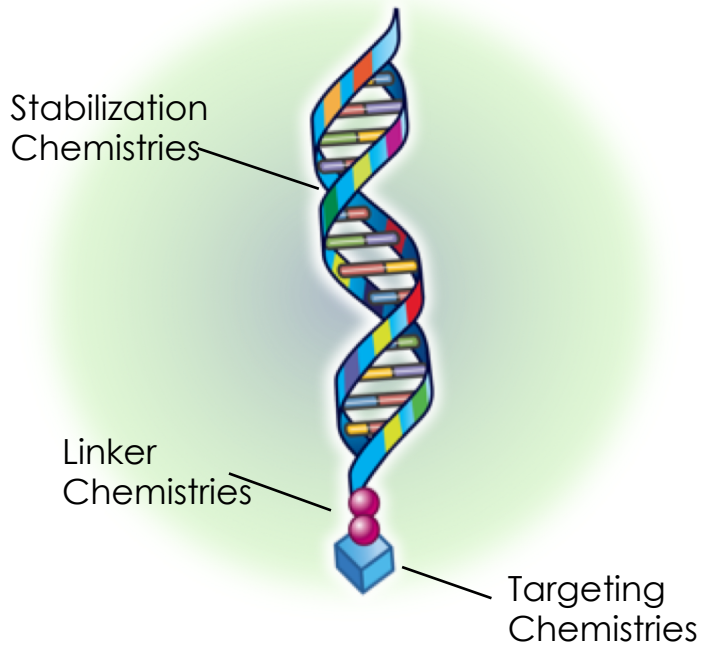
Target the Gene, Silence the Disease



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

Arrowhead RNAi Platform: TRiM™

Simplicity, Specificity, and Activity



Targeted RNAi Molecule

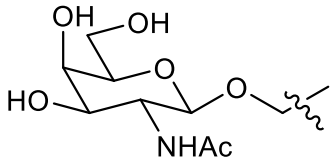
TRiM™ platform

TRiM™ has rules and algorithms to optimize trigger sequence

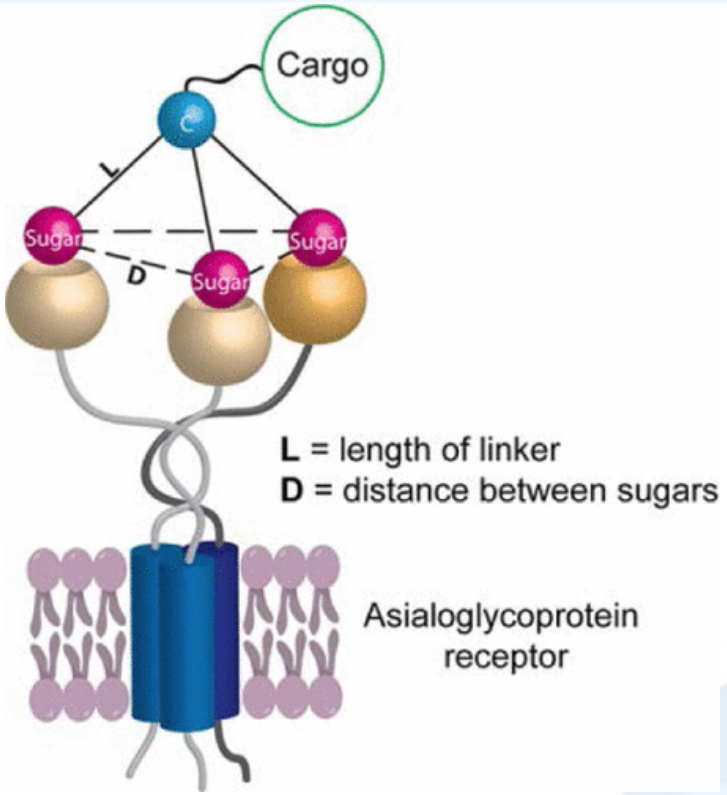
- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
- Rational use and placement of modifying chemistries
- RNAi chemistry insights and expertise have allowed us to see what others have not

Direct Conjugation for Hepatocyte Delivery

- Asialoglycoprotein receptor (ASGP-R)
  - Tridentate receptor, overly expressed on the surface of hepatic cells, but minimally on extra-hepatic cells
  - Recycled every 15 mins
- Natural ligand to ASGP-R
  - N-Acetyl-Galactosamine (NAG)

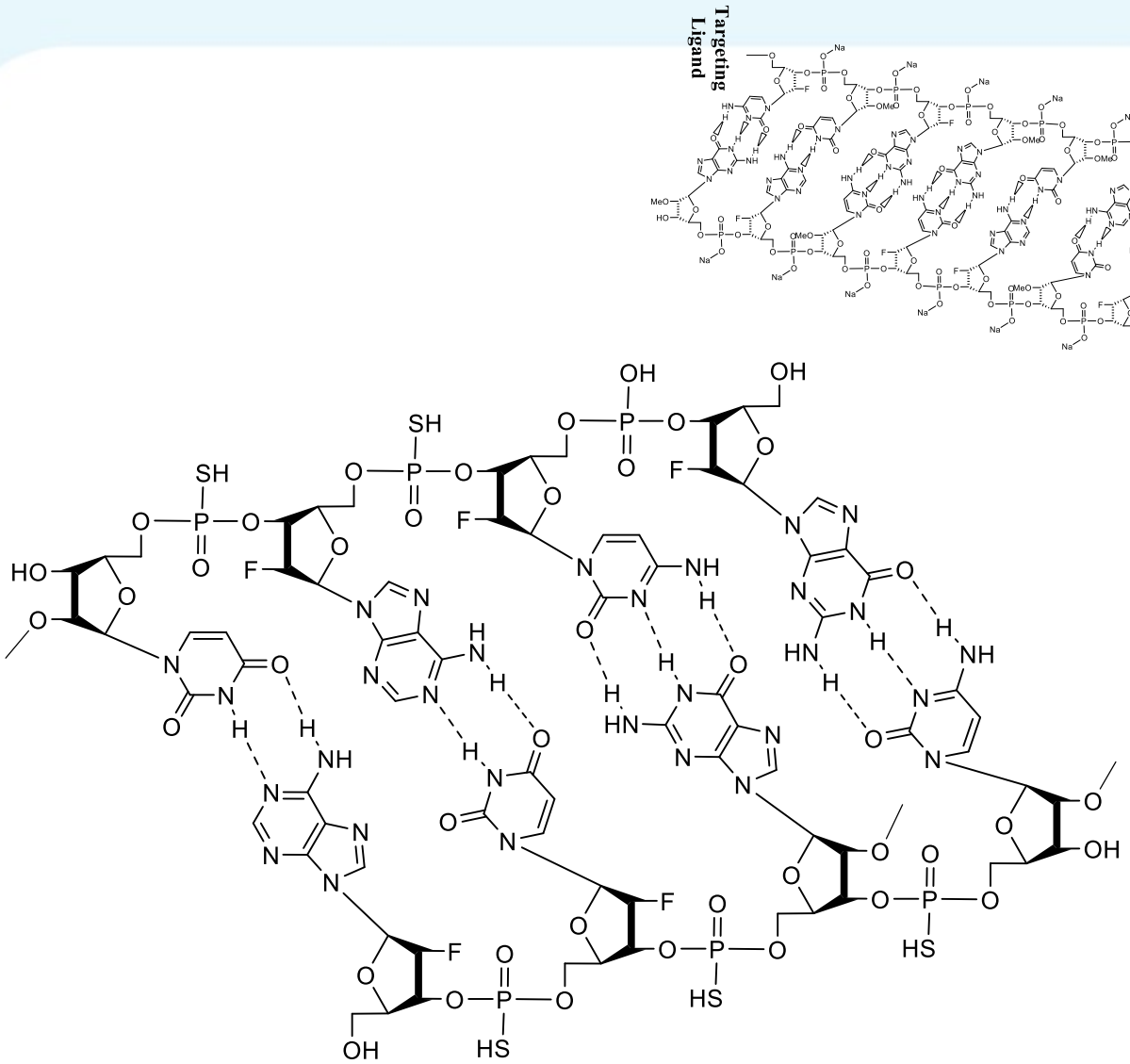


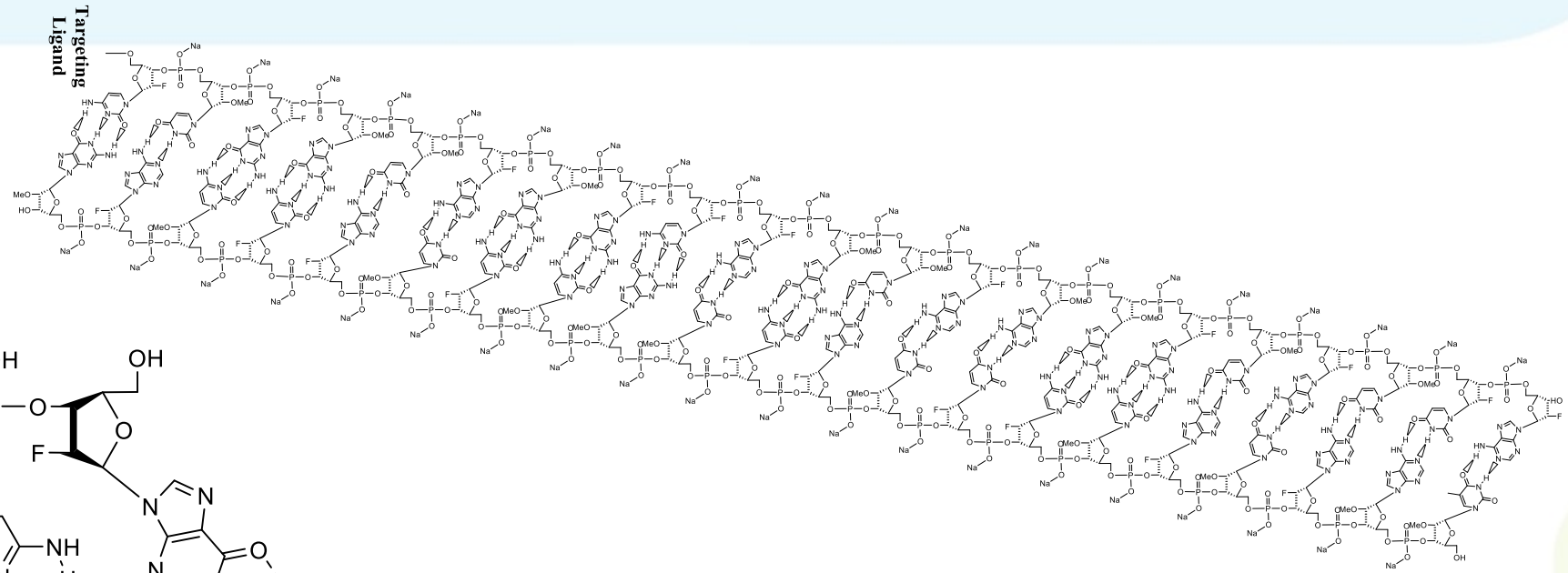
- Binding of NAG to ASGP-R initiates endocytosis



Huang etc. *Bioconjugation, 2016*

Chemical Modifications





- Chemical modifications to increase stability
  - Potentially fully modified at 2' positions (e.g., -F and –OMe)
  - Use of multiple phosphorothioates, instead of phosphates, including at terminal positions to increase nuclease resistance

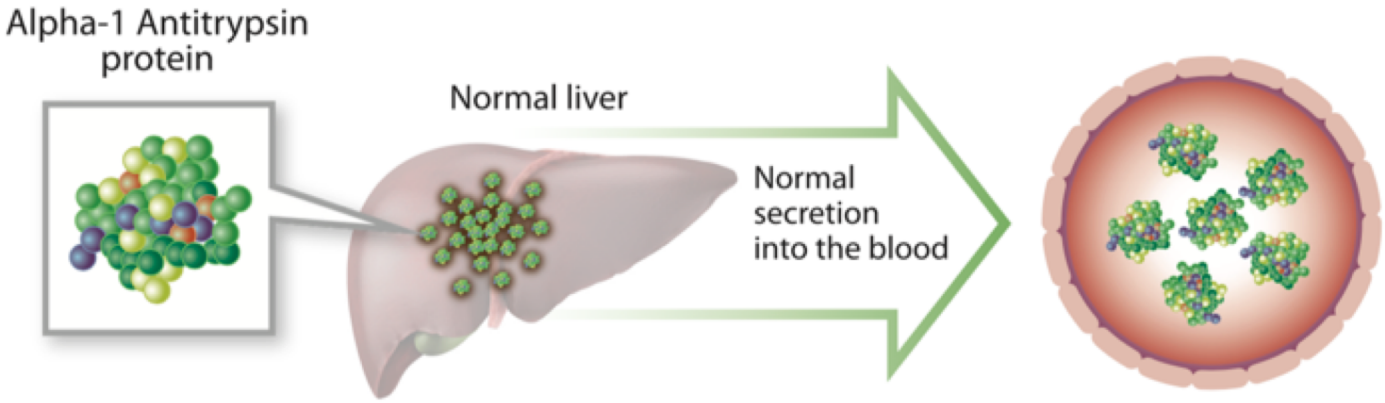
ARO-AAT

Alpha-1 Antitrypsin Deficiency (AATD)

- AAT is an abundant serum protein
  - Primarily synthesized in the liver, about 10% made extrahepatically
- Physiological function includes:
  - Inhibition of neutrophil proteases to protect host tissues during inflammation
  - Especially important in the lung
- Mutation in AAT gene (Z-AAT) leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver

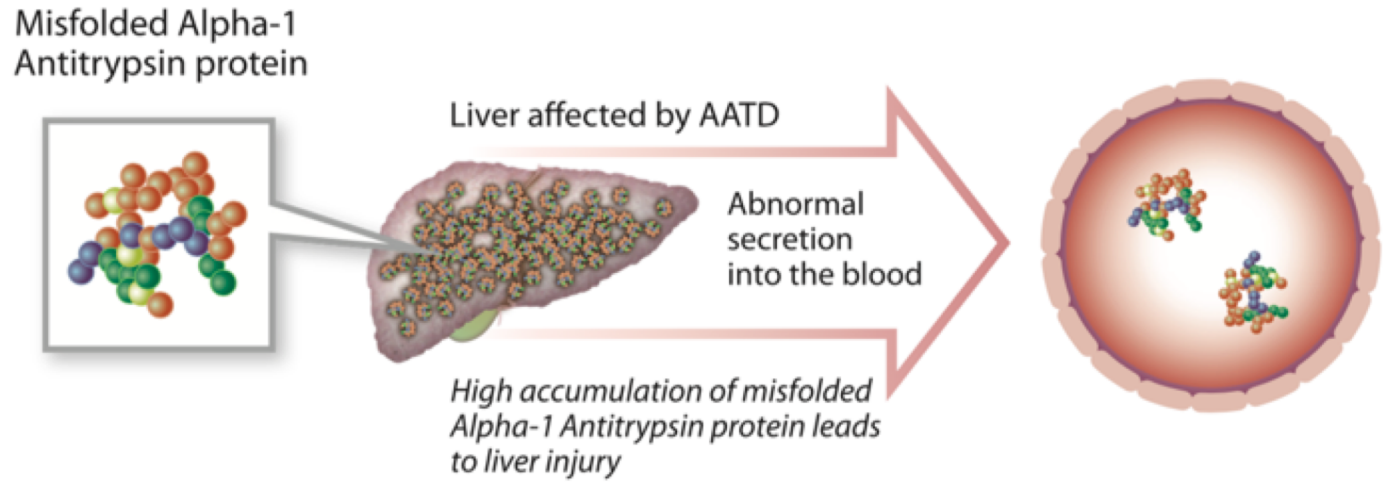
Alpha-1 Antitrypsin Deficiency

Normal AAT



Normal blood levels of normal protein protect lungs

Abnormal AAT (Z-AAT)



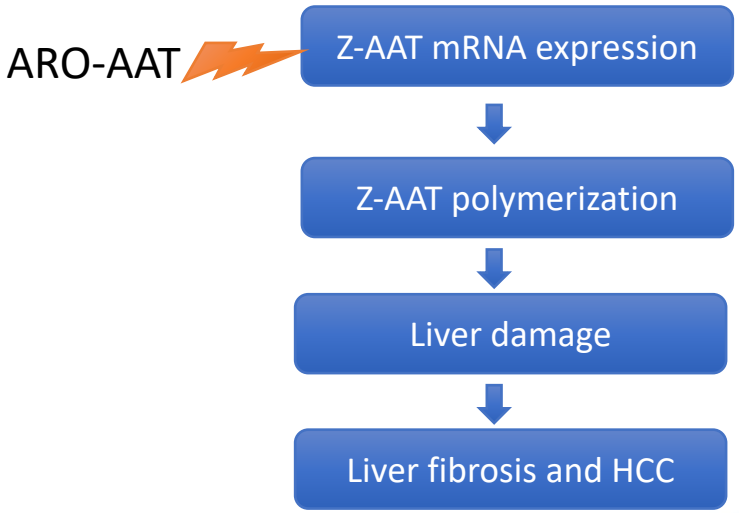
Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection

No current treatment

Treated with AAT protein replacement therapy today

ARO-AAT: Mechanism of Action

- ARO-AAT designed to stop Z-AAT production by silencing AAT gene via cleavage of mRNA to
  - Prevent production and accumulation of disease-causing protein in liver
  - Prevent repeated cycles of cellular damage
  - Allow clearance of accumulated protein
  - Reverse fibrosis associated with prior damage

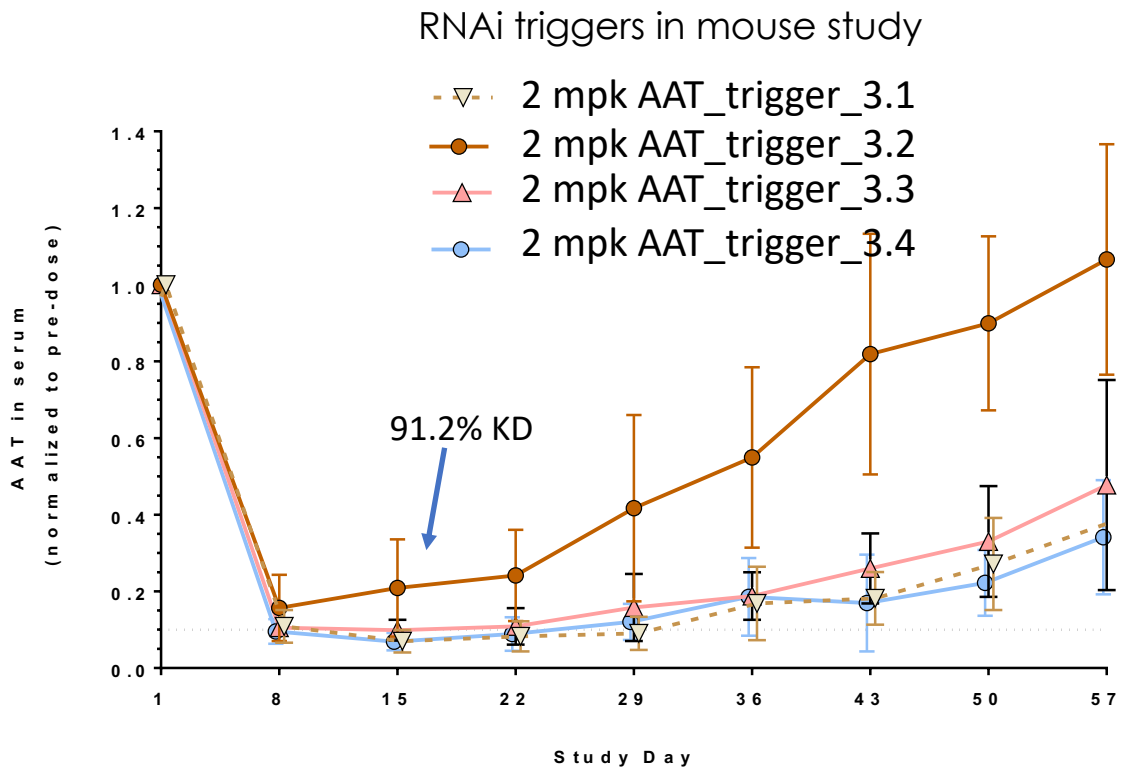


AATD is a large scale orphan disease

- Alpha-1 Foundation estimates 100,000+ in the US
- Approximately 100,000+ in Europe

Lead Optimization Leads to ARO-AAT

- 91% serum AAT knockdown achieved with one 2 mpk dose
- Knockdown sustained for 3 weeks with one 2 mpk dose

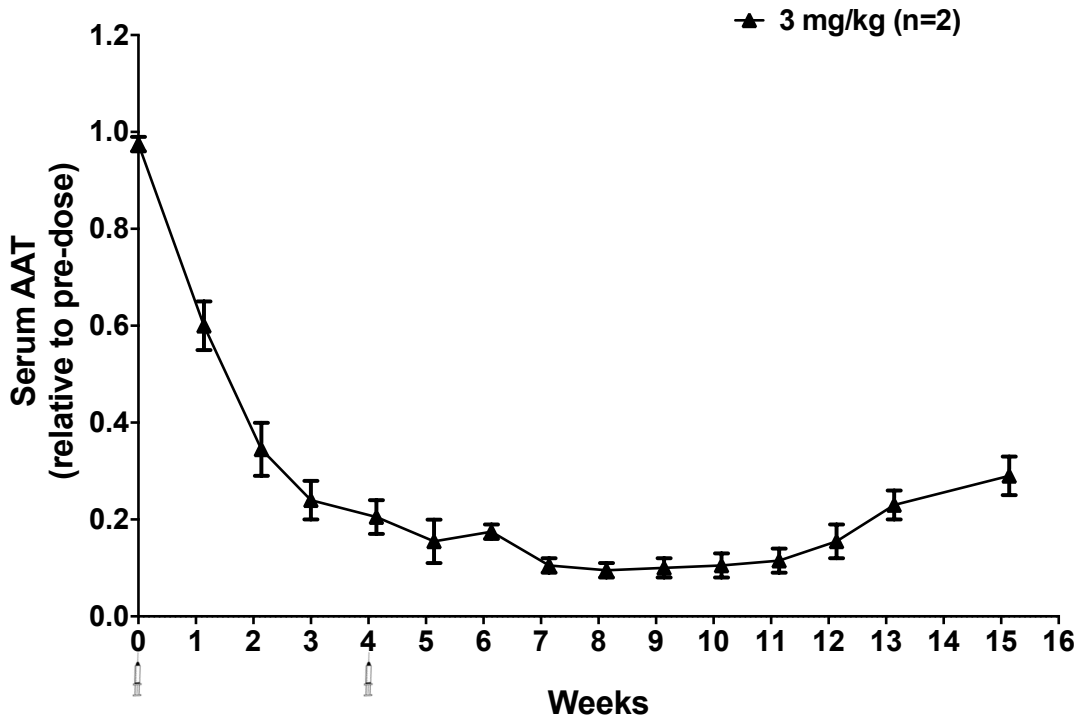


- **Chemical modifications led to deep reduction of AAT protein and long duration at dose of 2mg/kg**

ARO-AAT Provides Durable AAT knockdown in NHP

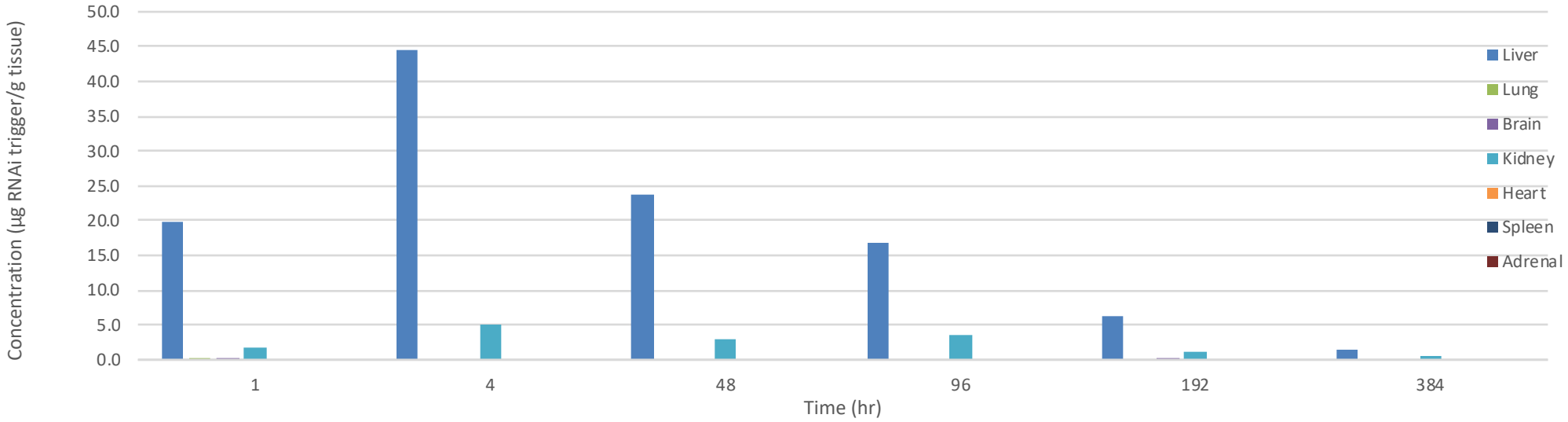
Multi-dose in NHP, dosed subcutaneously

- 92% maximum serum AAT knockdown achieved in cynomolgus monkeys
- Knockdown sustained for 7+ weeks following second dose



Durable knockdown supports once monthly or less frequent dosing

ARO-AAT Biodistribution 3mpk SubQ Administration

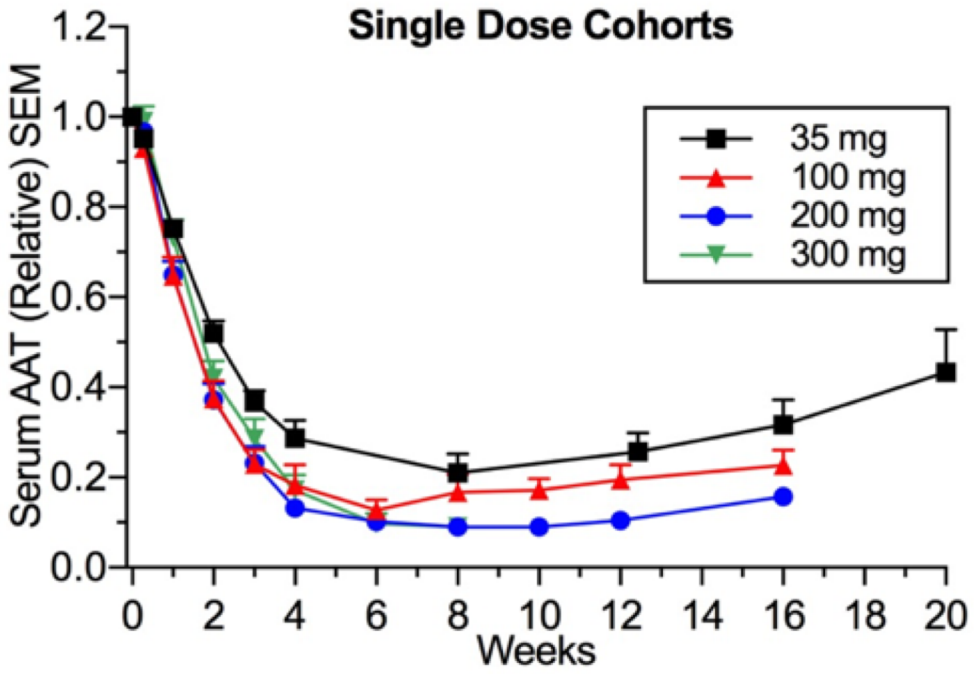


	Average Concentration of ARO-AAT (µg/g tissue)						
Time (h)	Liver	Kidney	Lung	Brain	Heart	Spleen	Adrenal
1	19.9	1.8	0.3	0.1*	BLQ	BLQ	BLQ
4	44.4	5.1	BLQ	BLQ	BLQ	BLQ	BLQ
48 (Day 2)	23.7	2.9	BLQ	BLQ	BLQ	BLQ	BLQ
96 (Day 4)	16.8	3.5	BLQ	BLQ	BLQ	BLQ	BLQ
192 (Day 8)	6.4	1.2	BLQ	BLQ	BLQ	BLQ	BLQ
384 (Day 16)	1.4	0.5	BLQ	BLQ	BLQ	BLQ	BLQ

*Only one rat showed quantifiable concentration other two were below limit of quantitation (BLQ).

ARO-AAT Clinical Data Shows Platform Profile

- Open Label AAT Plasma Data:
  Single Dose, Healthy Volunteers



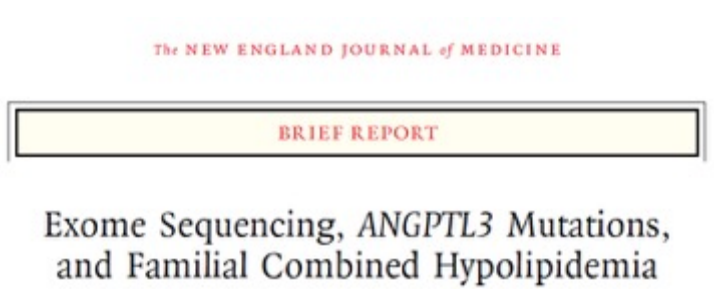
- **Potency, efficacy, durability**
  - 93%: Maximum Serum AAT reduction achieved 6-weeks following a single dose
  - 87%: Mean maximum serum AAT reduction achieved 6-weeks following a single dose
- **Safety**
  - No Severe AEs
  - Most AEs reported as mild (one moderate gastroenteritis)
  - Mild injection site AEs occasionally reported
  - No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin or pattern of adverse laboratory changes seen

ARO-ANG3

Angiopoietin-like 3 (ANGPTL3)

- A key regulator of LDL-C, HDL-C and triglycerides metabolism
  - Inhibitor of lipoprotein lipase and endothelial lipase
- Homozygous and heterozygous loss-of-function in *ANGPTL3* lead to low plasma levels of LDL-C, HDL-C and triglycerides
  - Reduced risks of cardiovascular disease

- ANGPTL3 is primarily synthesized in hepatocytes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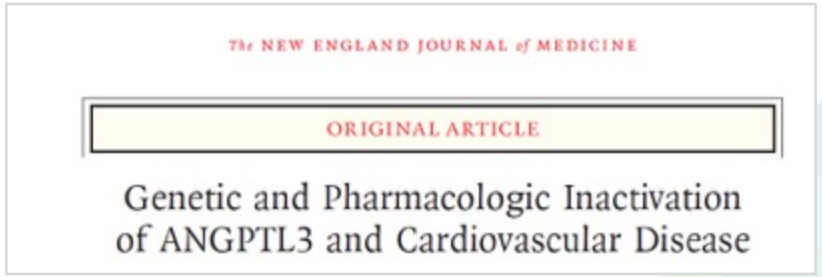
BRIEF REPORT

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

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

Potential Clinical Indications for ARO-ANG3

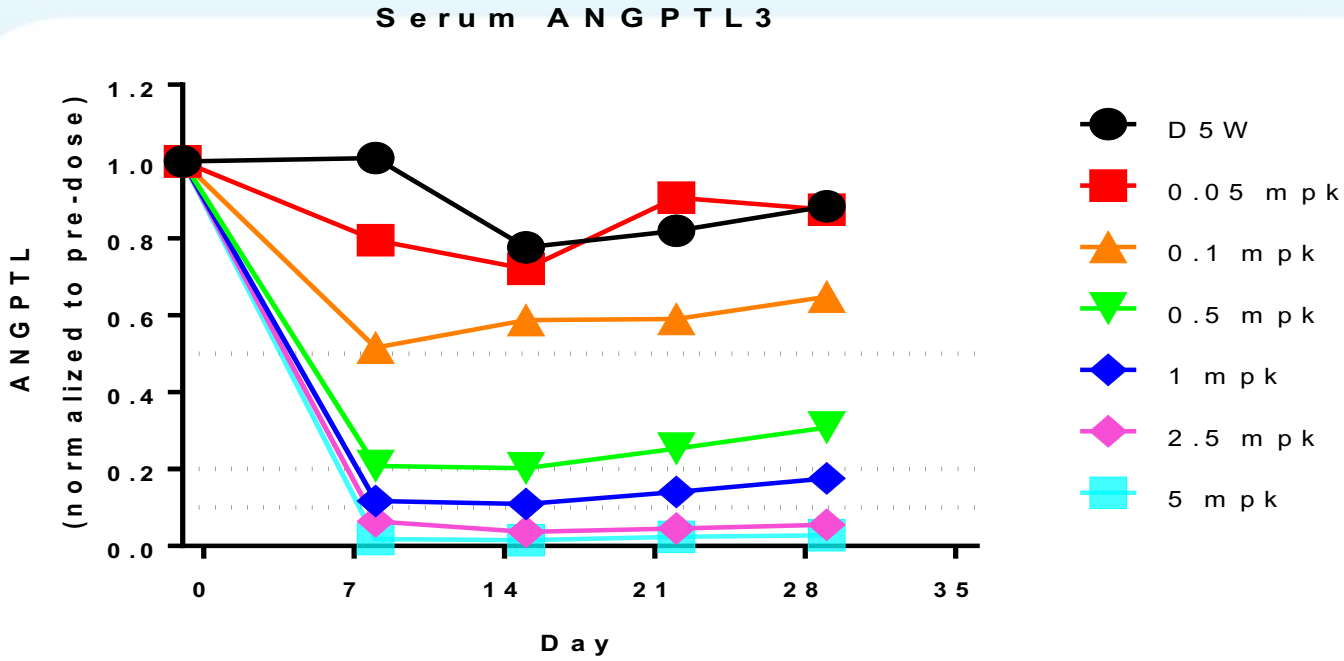
Rare diseases:

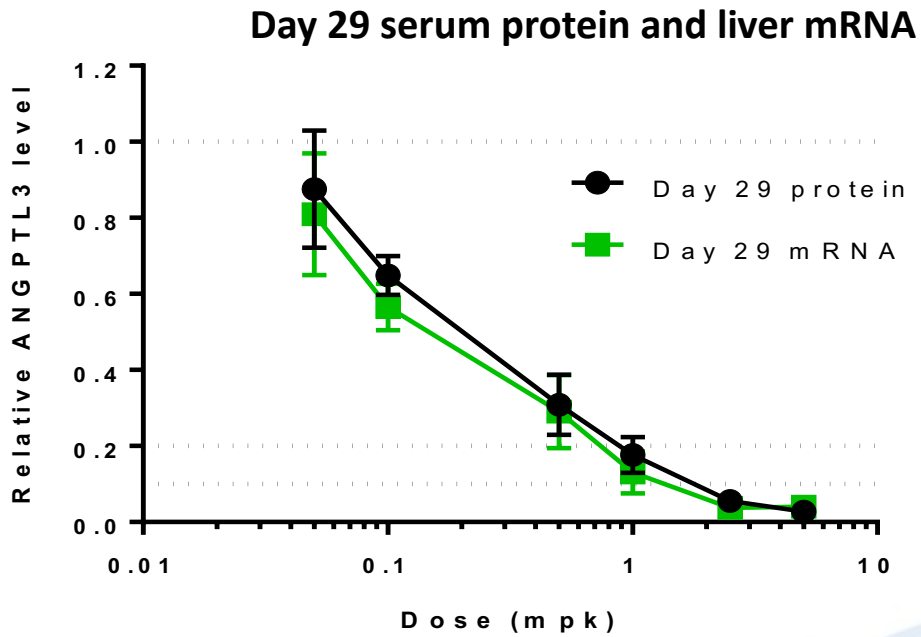
- Familial hypercholesterolemia – non LDL receptor mechanism
- Familial partial lipodystrophy

Polygenic causes of elevated triglycerides:

- Moderate to severely elevated TGs with history of pancreatitis
- Secondary prevention for residual CVD risk following maximized LDL lowering

ARO-ANG3 Dose Response in WT mice

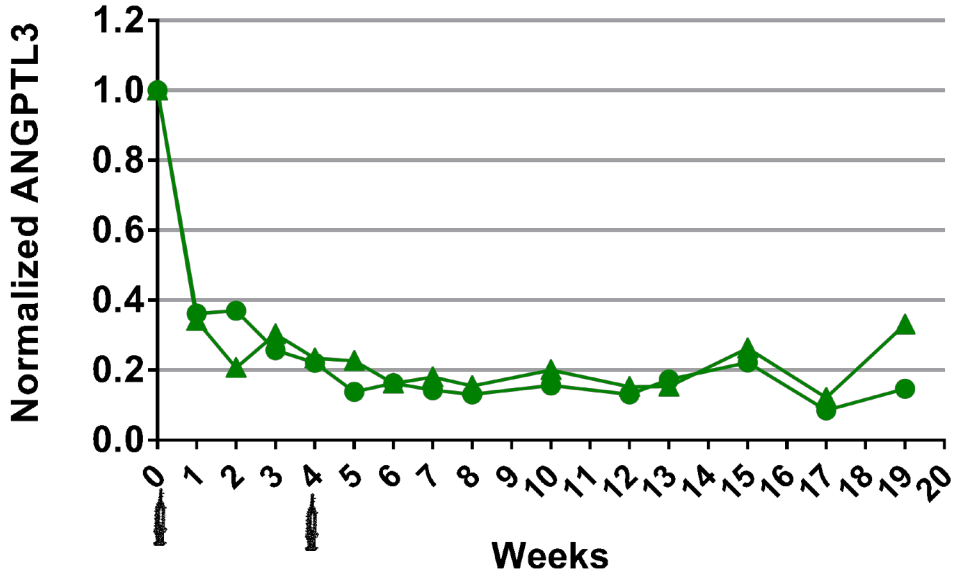




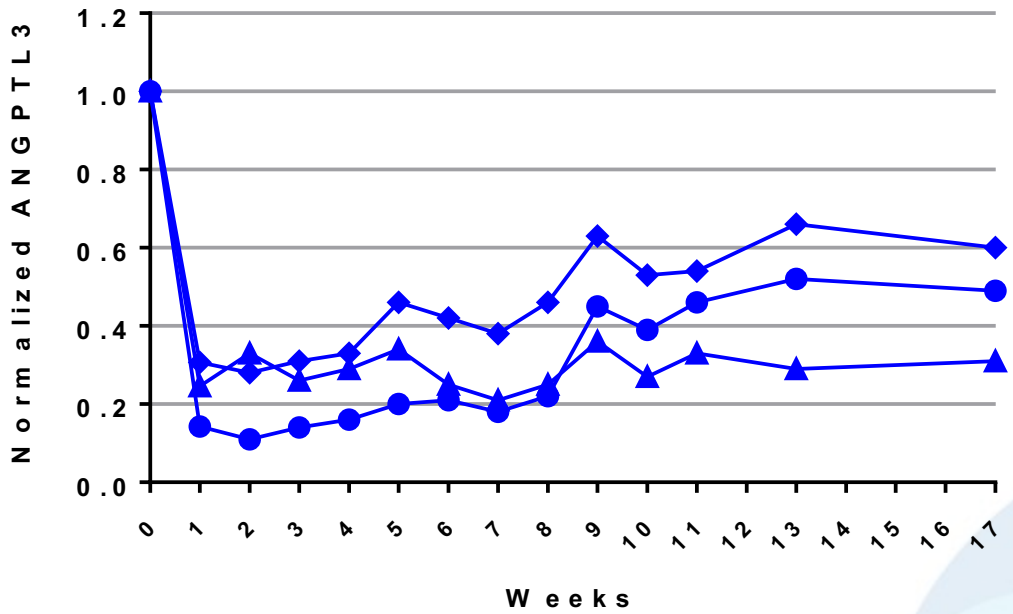
- Protein reduction of ~80% at 0.5 mpk, ~90% at 1 mpk on day 15
- Over 95% KD at 2.5 and 5 mpk
- Long duration
- Excellent correlation between serum ANGPTL3 and liver mRNA levels

ARO-ANG3 in Lean Cynos

4 mpk 2x q4w



3 mpk single dose



- Multi-dose: 2 doses of 4 mpk maintained ~80% reduction for 13 weeks
- Single dose: single dose of 3 mpk gave average 75% reduction for 4 weeks

ARO-ANG3 in Dyslipidemic Preclinical Models

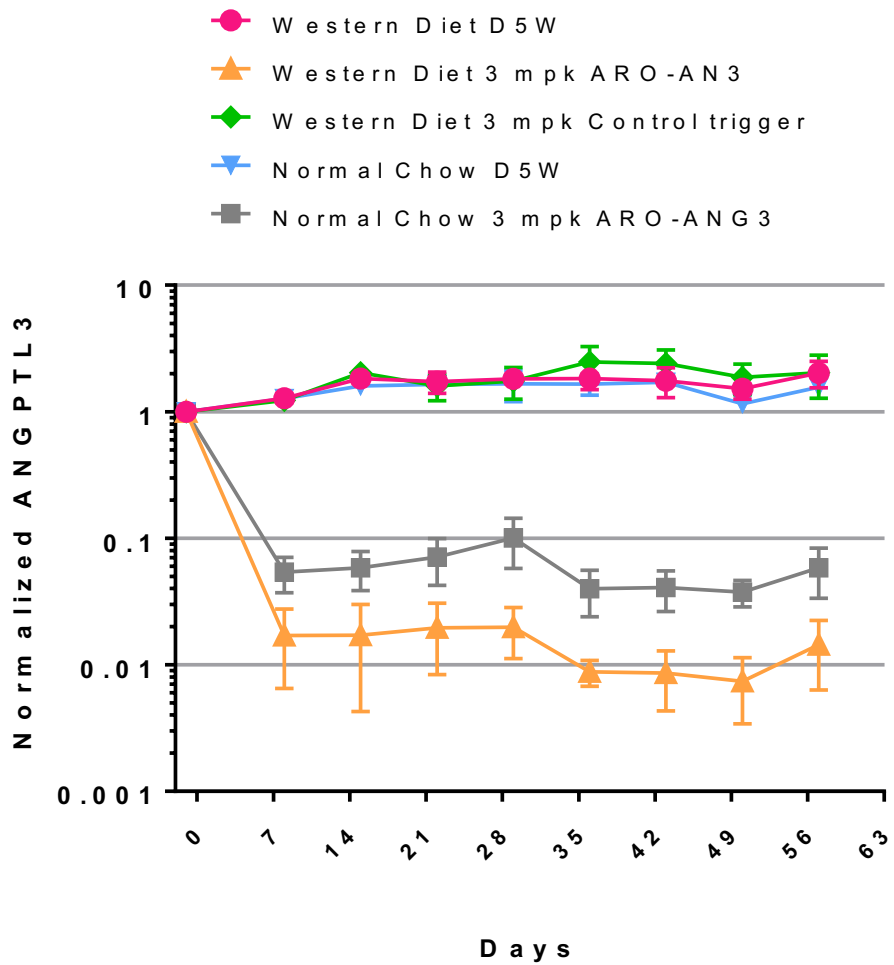
Mouse models:

- *LDLr* KO mice
- Diet induced obese mice
- Obese db/db mice

NHP model:

- High fructose diet-induced dyslipidemic rhesus monkeys

ANGPTL3 Protein Reduction in LDLr$^{-/-}$ Mice with Treatment of ARO-ANG3



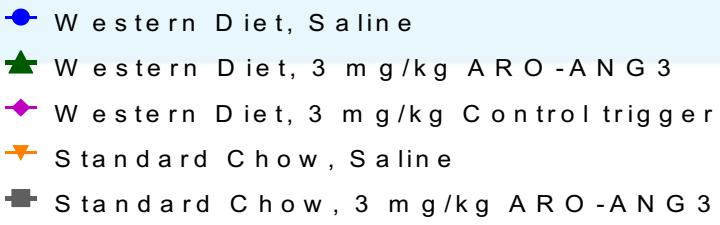
- SQ 3 mpk dose on day 1 and 29

Nadir after each dosing

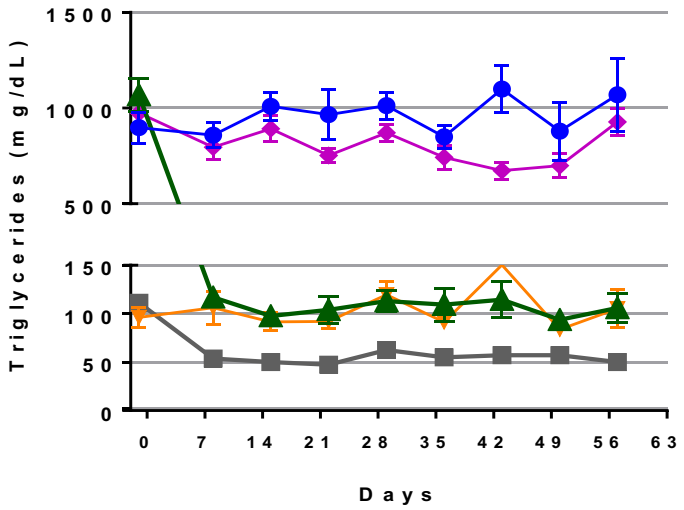
Diet with Treatment	Reduction 1st dose	Reduction 2nd dose
Normal Chow with ARO-ANG3	94.6%	96.2%
Western diet with ARO-ANG3	98.3%	99.3%

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

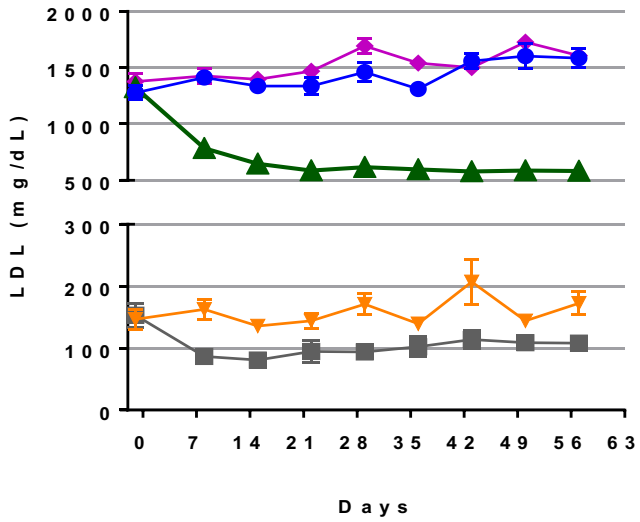
ARO-ANG3 on Serum Lipids in Dyslipidemic LDLr KO mice



TG All graphs showing group averages ± SEM



LDL-C



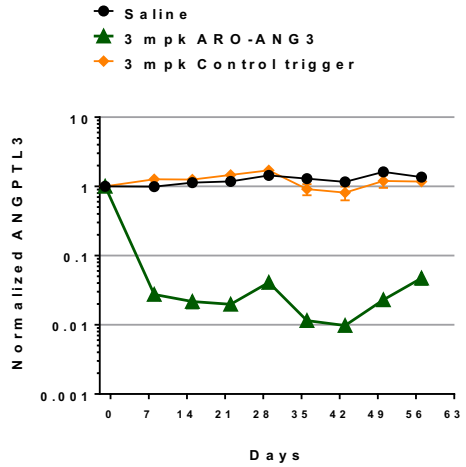
- Reductions in LDL-C via a non-LDLr mechanism
- Mice on both Western diet and Standard chow had elevated serum lipids compared to wild-type normal mice (TGs: 35-45 mg/dL, LDL-C: 10-15 mg/dL)

Western diet with ARO-ANG: maximum TG reduction 90%
Standard chow with ARO-ANG3 : maximum TG reduction 49%

Western diet with ARO-ANG3: maximum LDL-C reduction 48%
Standard chow with ARO-ANG3: maximum LDL-C reduction 43%

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

Leptin deficient db/db mice



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

All graphs showing group averages ± SEM

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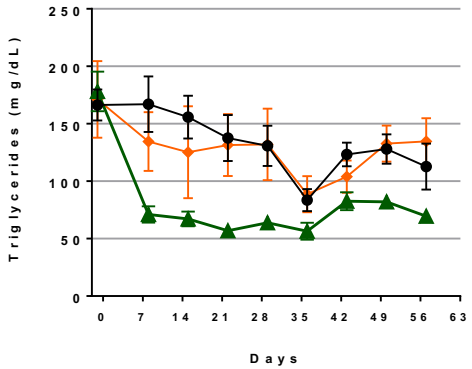
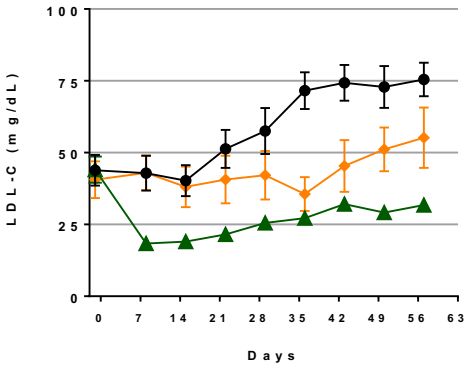
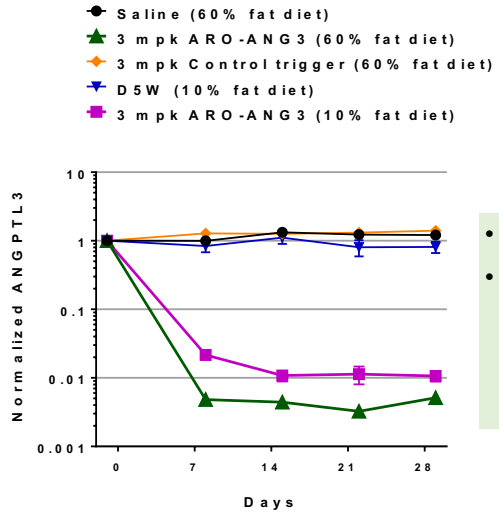


LDL-C



DIO (diet-induced obese) mice



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

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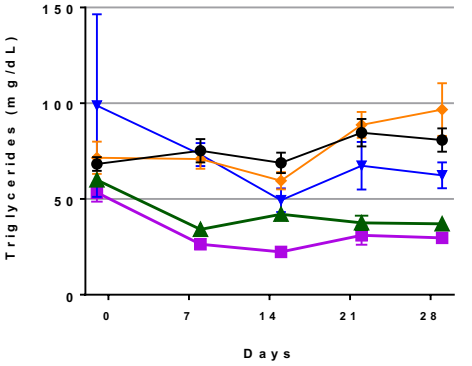
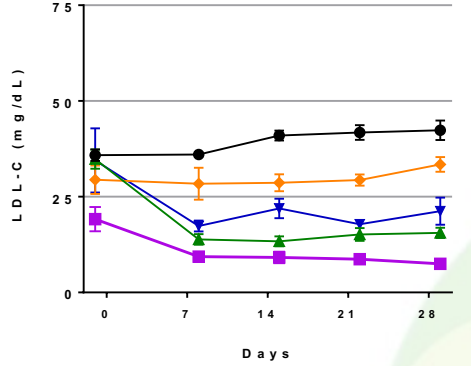


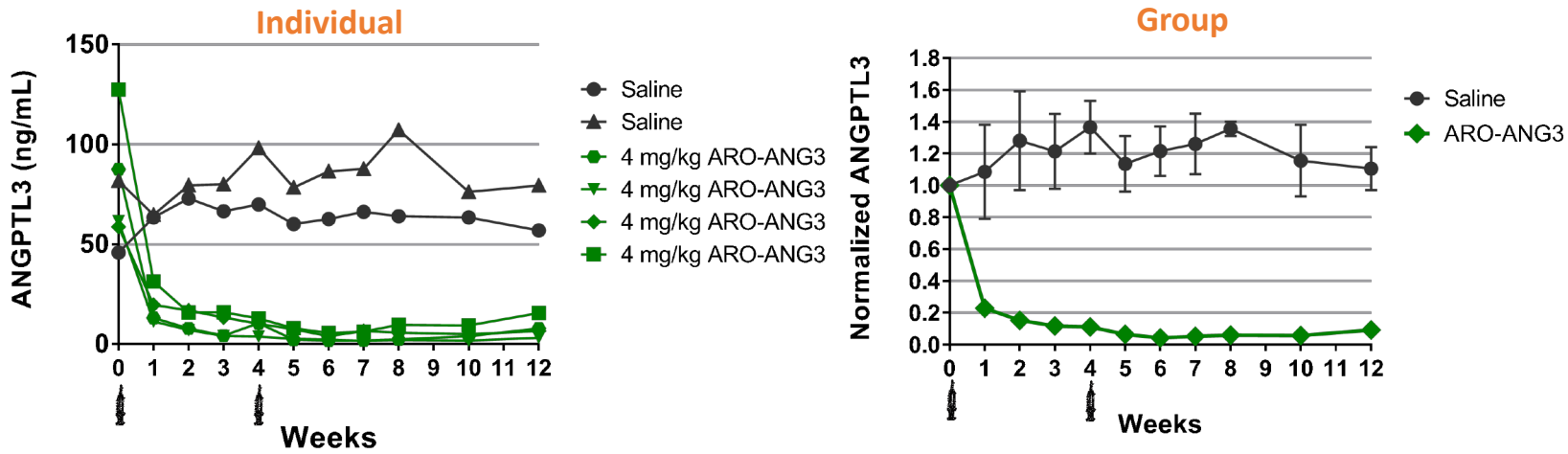
LDL-C



- ARO-ANG3 significantly reduces serum lipid levels
- ARO-ANG3 may be efficacious in a wide spectrum of hyperlipidemia

ARO-ANG3 in High Fructose Diet-induced Dyslipidemic Rhesus Monkeys

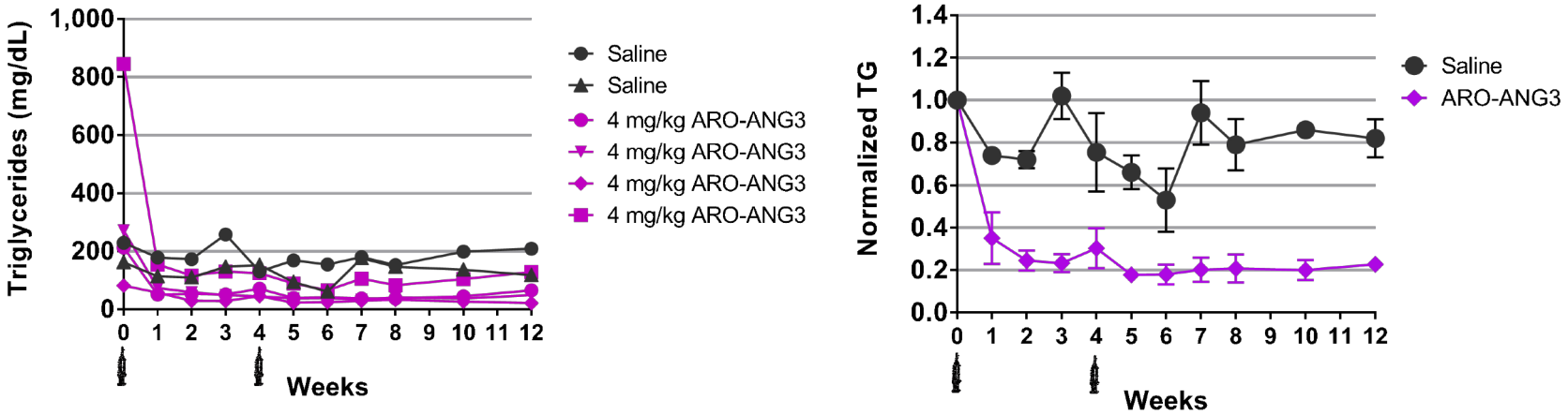
Reductions in serum ANGPTL3 protein levels



Group averages ± SEM

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

Reductions in serum TGs



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

Summary

- Arrowhead TRiM™ platform demonstrates consistent activity towards target mRNA
- Subcutaneous dosing, monthly or less frequent
- Wide therapeutic index
- ARO-AAT: Powerful AAT reduction in preclinical species and in phase 1 clinical studies with no SAEs
- ARO-ANG3:
  - Deep and persistent reductions in serum ANGPTL3 and liver mRNA
  - Reductions in serum triglycerides, LDL in multiple pre-clinical dyslipidemic animal models
  - GLP toxicology completed in rodent and NHP
  - CTA filed Oct. 2018

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