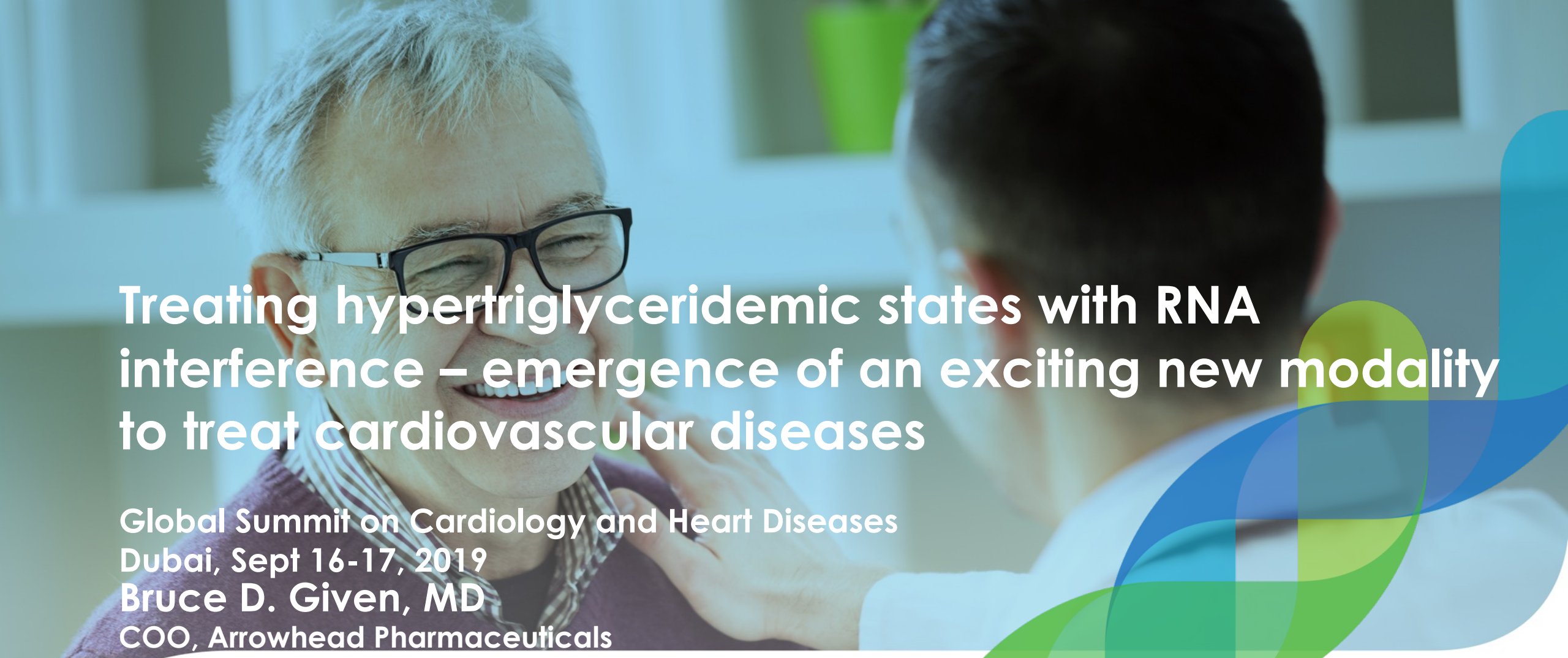

Treating hypertriglyceridemic states with RNA interference – emergence of an exciting new modality to treat cardiovascular diseases

Global Summit on Cardiology and Heart Diseases
Dubai, Sept 16-17, 2019

Bruce D. Given, MD
COO, Arrowhead Pharmaceuticals

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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.

Disclosures

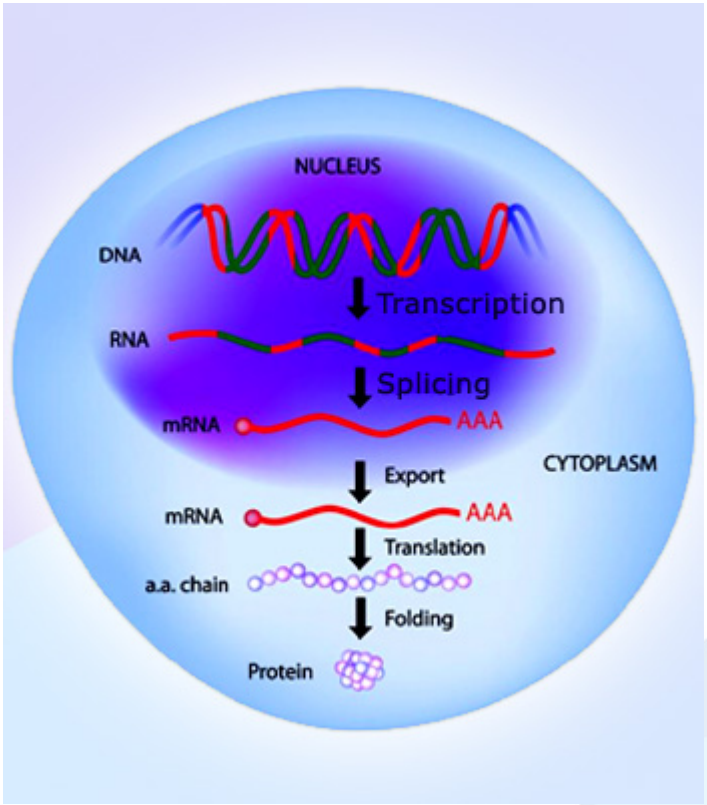
- Dr. Given is an employee and shareholder of Arrowhead Pharmaceuticals, Inc.
- All products and indications discussed in this presentation are investigational

Outline

- **Some Background on RNA Interference (RNAi)**
- The CV Pipeline in RNAi
- Hypertriglyceridemia as an independent risk factor
- ApoC3 and AngPTL3 knockdown in animals and first data in humans
- Conclusions

Small Molecule Pharmaceuticals Generally Target Proteins

- The central dogma of molecular biology
  - Transcription and translation
    - the information in genes flows into proteins
- Small molecule pharmaceuticals generally target proteins
  - Enzymes
  - Receptors
- However
  - Not all proteins are targetable
  - Very difficult to address proteins in a tissue-specific manner



DNA → mRNA → protein

Small molecule therapeutics

The Discovery of siRNA

- In 1998, RNAi was discovered by Andrew Fire and Craig Mello.
- In 2001, siRNA was first used as a tool to silence genes in mammalian cells
- Awarded the Nobel Prize in Physiology or Medicine 2006

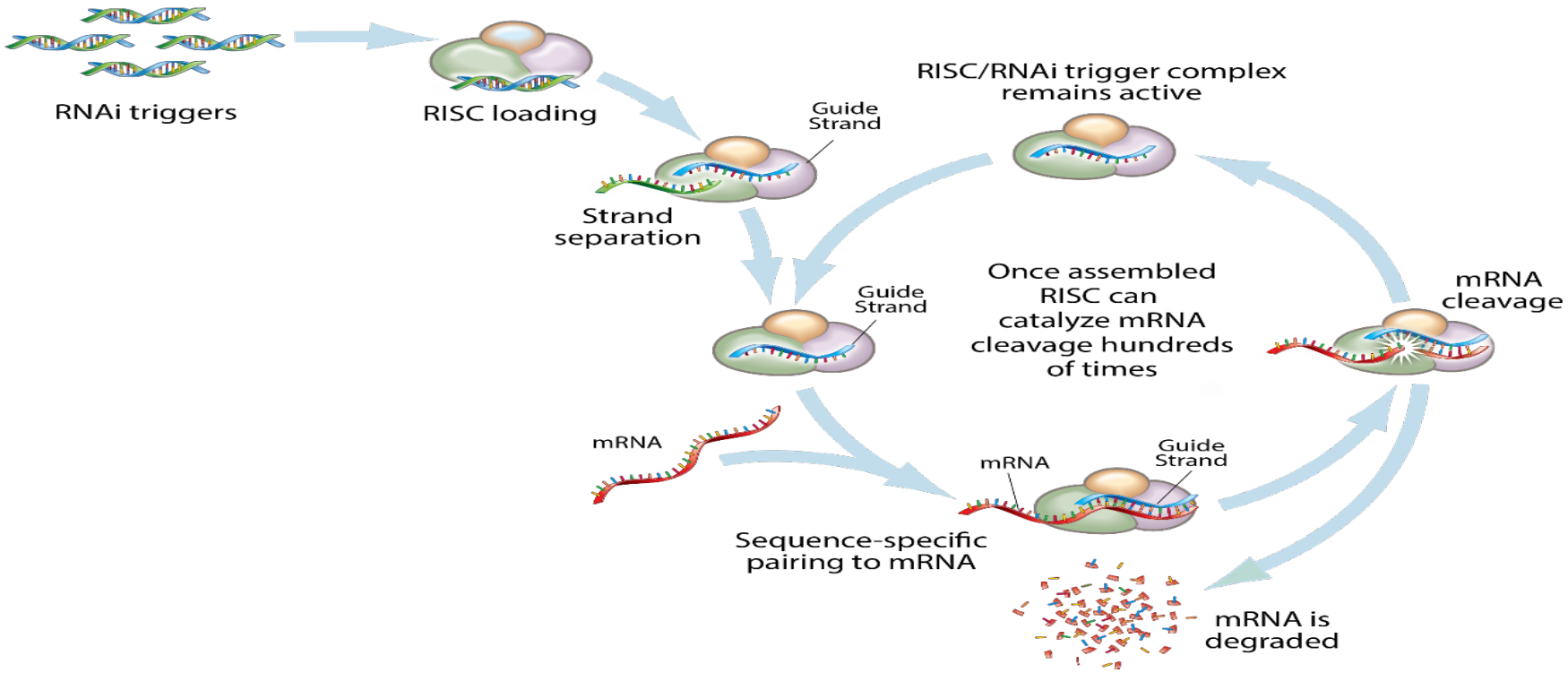
Andrew Z. Fire

Craig C. Mello

Basics of RNA interference (RNAi)

- Uses an endogenous host mechanism that modulates host gene expression post-transcription
- Designed for *high specificity* – generally one RNAi molecule will knock down only one gene
- The field has learned how to avoid unwanted stimulation of innate immunity
- In early years, the field was held back by poor delivery, currently leading companies all use ligand mediated delivery

Target the Gene, Silence the Disease

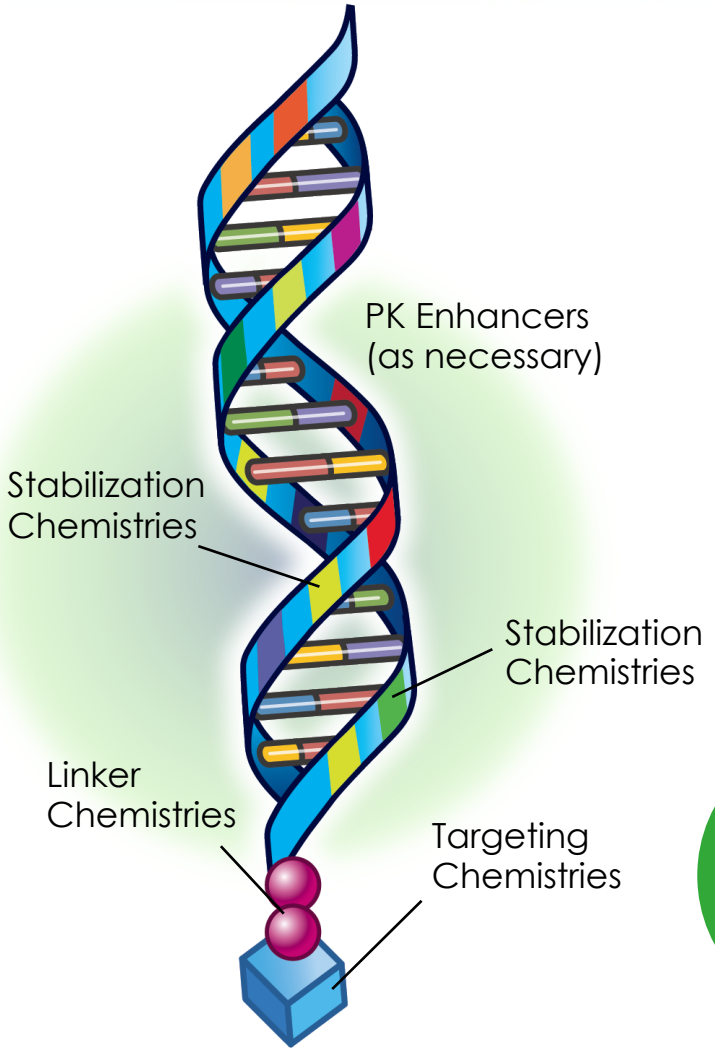


Therapeutic gene silencing with **RNA interference** is highly precise and efficient

When is RNAi the Right Choice?

- When ligand-mediated or local delivery can provide beneficial/needed organ specificity:
  - Addressing the target outside of the organ of interest creates unacceptable toxicity (e.g. amiloride analogs for blocking pulmonary ENaC or other similar targets, several NASH targets, etc)
- When antibodies don't fit the need
  - Target not accessible (various intracellular proteins)
  - The volume of protein produced is too high (Lp(a), hepcidin)
  - Target is both intracellular and extra-cellular (AngPTL3)
- When a longer (monthly or more) gap between doses delivers patient-centered benefits
  - The proposed advantage of PCSK9 RNAi drug

TRiM™: Simplicity, Specificity, and Activity



Components:

- Stabilization chemistries
- PK enhancers as necessary
- Linker chemistries
- Targeting ligands

Now capable of achieving deep KD in diverse tissues using subQ, iv, and inhaled administration routes

arrowhead pharmaceuticals

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- **The CV Pipeline in RNAi**
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Public CV RNAi Programs

CV RNAi Programs

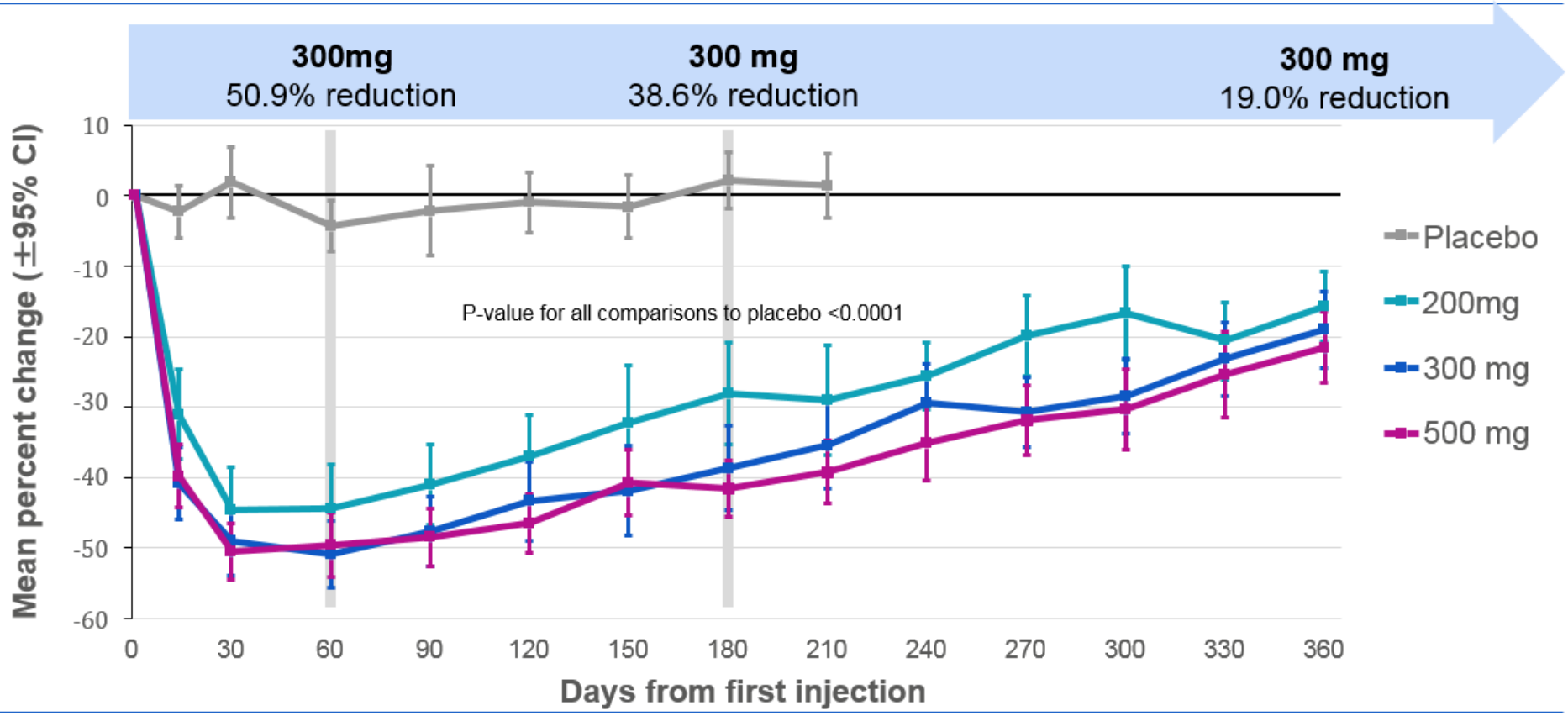
AngPTL3	Arrowhead
APOC3	Arrowhead
Cardiac amyloidosis	Alnylam
Factor 12	Arrowhead
Lp(a)	Amgen *
PCSK9	Medicines Company ^

* Licensed from Arrowhead

^ Licensed from Alnylam

Robust and Sustained LDL-C Reductions with Inclisiran*

Results to Day 360 Following One Dose



*Phase 2 study results; Ray *et al., ESC*, Aug 2017

Inclisiran also known as "ALN-PCSsc" and "PCSK9si"

The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful

The Medicines Company

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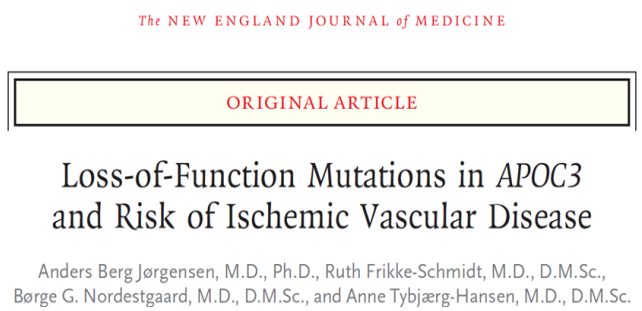
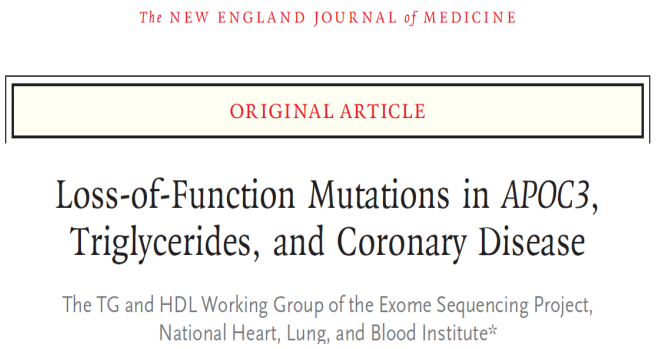
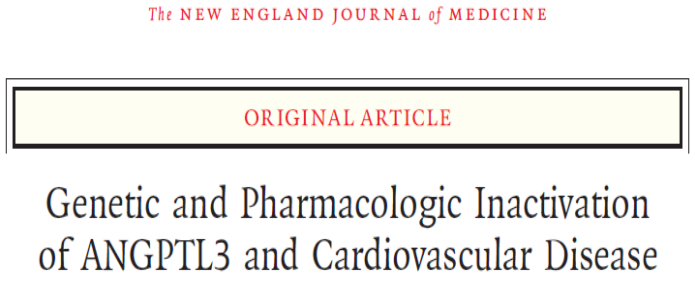
Triglyceride Targets Emerge: APOC3, ANGPTL3

Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

- Genetic studies support causal relationship
- Independent of LDL-C or HDL-C







Genetic Validation, Clinical Data for APOC3 & ANGPTL3

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

Metric (serum level)	*APOC3* deficient heterozygote[1]	*APOC3* deficient homozygote[2]	*APOC3* ASO inhibition[3]	*ANGPTL3* deficient heterozygote[4]	*ANGPTL3* deficient homozygote[4]	*ANGPTL3* ASO inhibition[6]	ANGPTL3 Mab Inhibition[7] 25 mg/kg IV
ApoC-III	-46%	-88.9%	-77.5%	NA	NA	-58.8%	NA
ANGPTL3	NA	NA	NA	-40% to -87%	undetectable	-84.5%	NA
Triglycerides	-39%	-59.6%	-43.8%	-21.1%	-71.2%	-50.4%	-76% i.v. (median)
LDL-C	-16%	Similar to non-carrier	-3.9%	-8.6%	-67.2%	-32.9%	-25%
HDL-C	+22%	+26.9%	+8.0%	-16.8%	-39.0%	-26.9%	-25%
CAD risk	-40%	Not reported	NA	-41%[5]	NA	NA	NA
Adverse Phenotype/AEs	None described	None described	**Thrombocytopenia, ISRs, renal**	None described	None described	None described	**Elevated ALT (11% in active v 0% PBO)**

1. Triglyceride working group, NEJM 2014
2. Saleheen et al., Nature 2016
3. Graham et al., Circulation Research 2013. [Phase 1 MAD study, 400 mg dosed D1, D3, D5, D8, D15 and D22 with non-GalNac targeted ASO. Median % change 1-week after last dose in NHV population compared to baseline]
4. Minicocci et al., J of Lipid Research 2013
5. Dewey et al, NEJM 2017
6. Graham et al., NEJM 2017 [Six weekly 60 mg doses using GalNac conjugate ASO in NHV population, mean values 1 week after last dose versus baseline]
7. Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Engl J Med 2017;377:211-21. [approximate mean nadir reduction at highest IV dose]

Outline

- Some Background on RNA Interference (RNAi)
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- **ApoC3 and AngPTL3 knockdown in animals and first data in humans**
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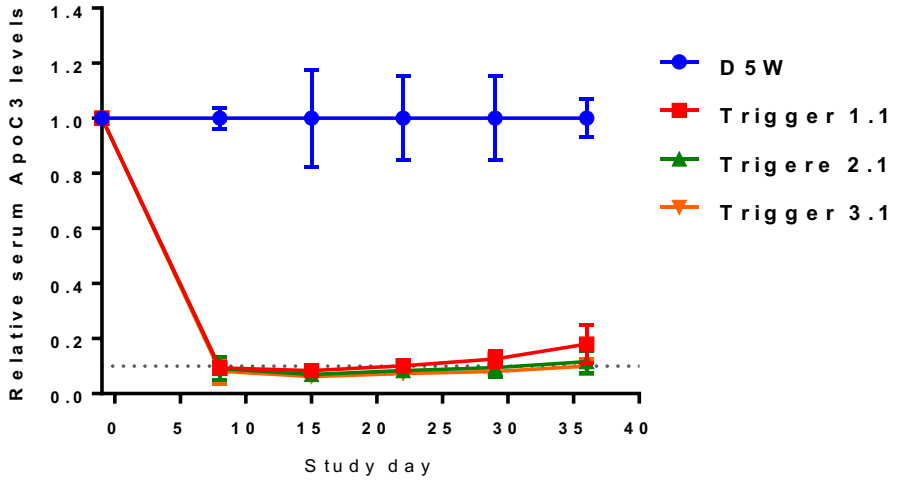
ARO-APOC3

RNAi TRiM™ Candidate Targeting APOC3

Single-dose Study in ApoC3 Transgenic Mice

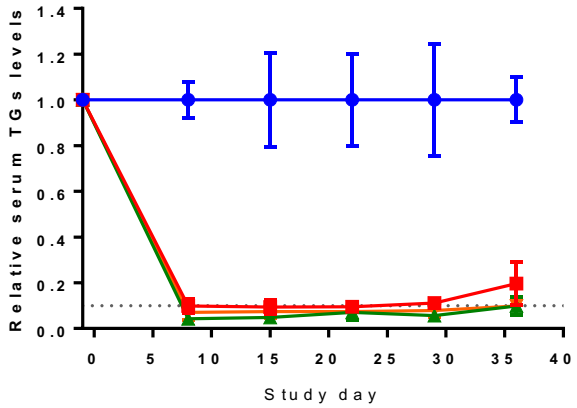


- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile

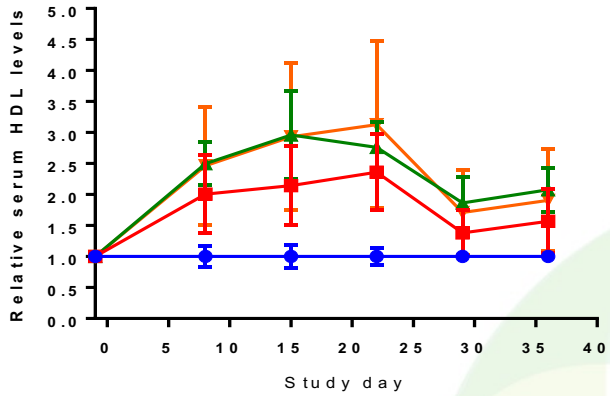
All dosed on study day 1 at 2 mpk

Data normalized to pre-dose and D5W control

Trig

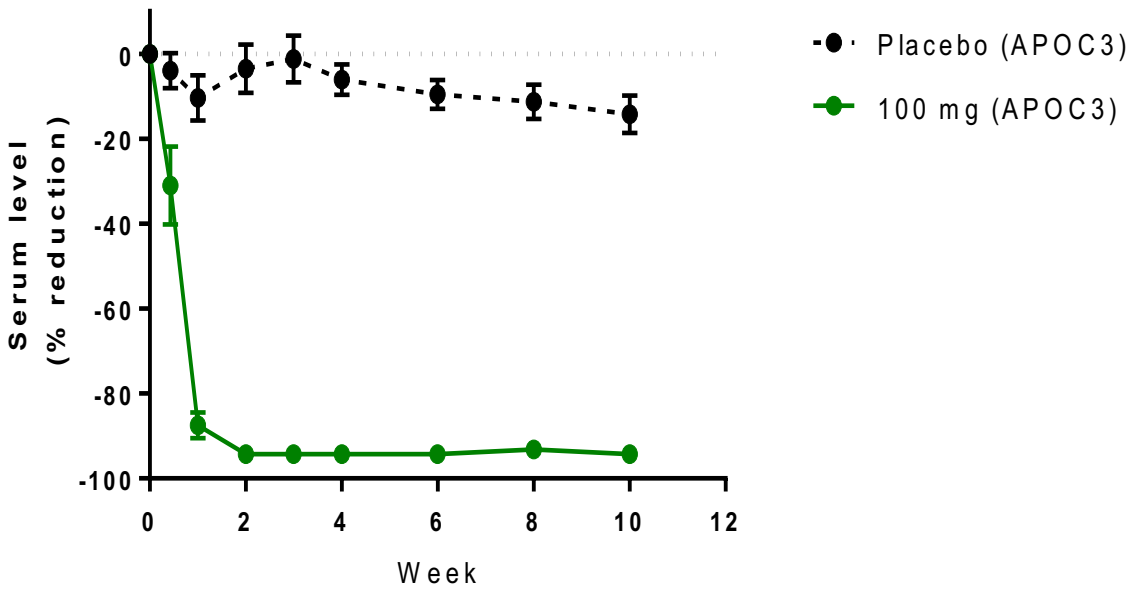


HDL

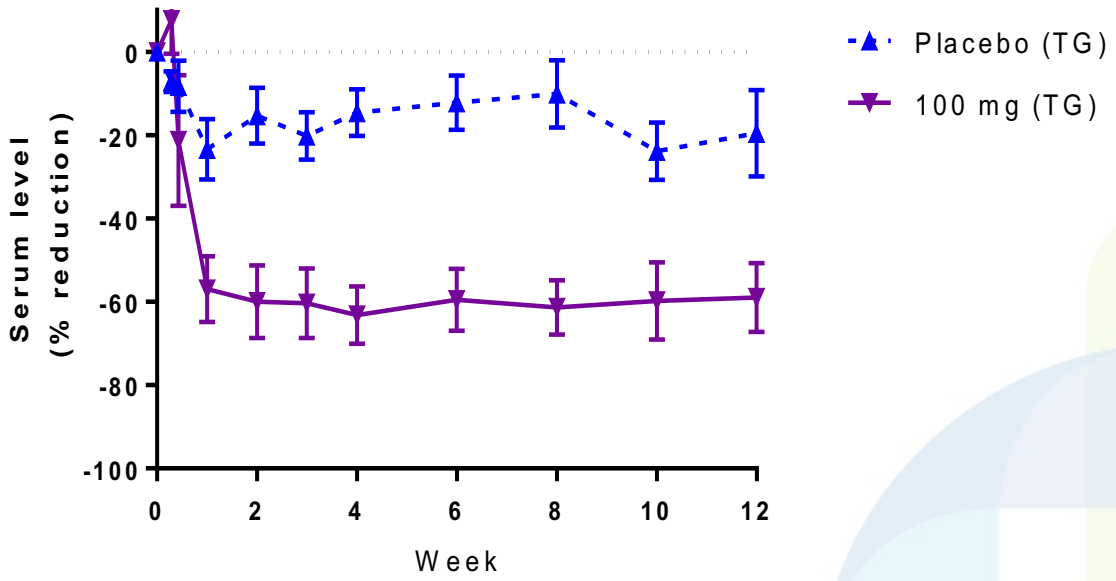


First Look at ARO-APOC3 in Healthy Volunteers - Single 100 mg dose through week 12

APOC3



TGs



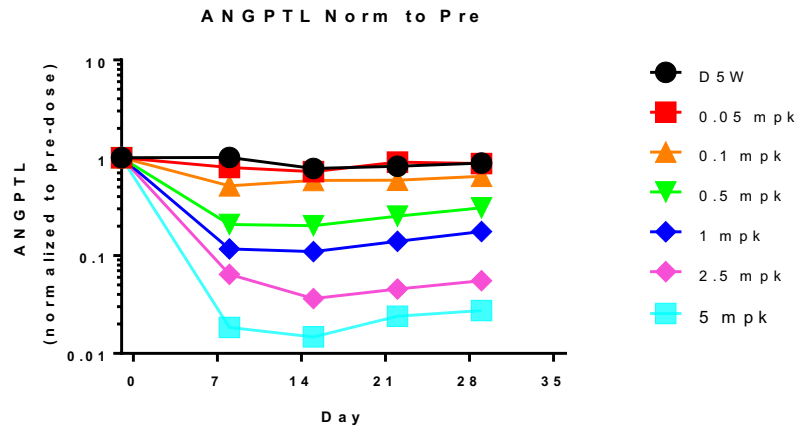
Top Line Safety Observations with ARO-APOC3

- No premature discontinuations in 24 healthy volunteers treated with ARO-APOC3
- No serious adverse events (such as deaths, hospitalizations, etc)
- No adverse events rated as severe
- Most common reported AEs: headache, upper respiratory infections and (all mild) injection site findings (flushing, bruising, etc)

ARO-ANG3

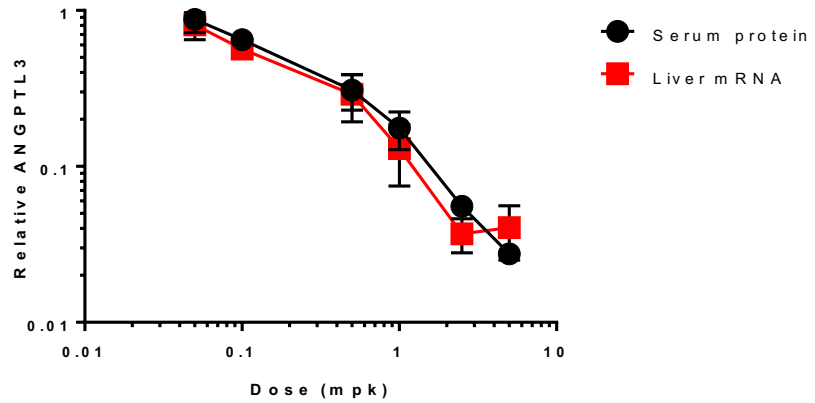
RNAi TRiM™ Candidate Targeting AngPTL3

ANGPTL3 Dose Response in WT mice



- Max KD on day 15
- 5 mpk close to assay detection limits

Day 29



- Similar relative mRNA and protein KD on day 29
- If any, ANGPLT3 from other tissues is minimal

Mouse Disease Models Interrogated with KD of ANGPTL3

- Mouse models
  - LDL receptor knock-out (LDLr $^{-/-}$) mice, western diet
  - Diet-induced obese (DIO) mice, 60% fat diet
  - Leptin receptor defective db/db mice, 60% fat diet
- All studies dosed at 3 mg/kg

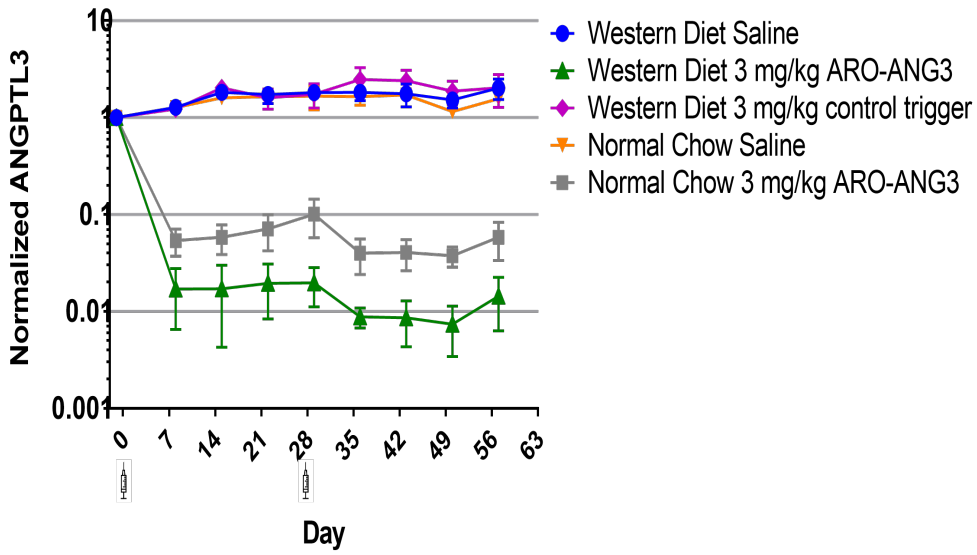
Mouse Disease Models: Pre-Dose Baseline Lipid Profiles

Mouse Model	WT Normal Chow	DIO 10% Fat Diet	DIO 60% Fat Diet	LDLr-/- Normal Chow	LDLr-/- Western Diet	db/db 6% Fat Diet
# of animals	N= 39	N=9	N=29	N= 16	N=39	N=30
Trig (mg/dL)	41 ± 6	52 ± 9	65 ± 14	98 ± 11	980 ± 288	172 ± 58
Chol (mg/dL)	69 ± 6	136 ± 17	195 ± 27	211 ± 30	1467 ± 253	184 ± 48
HDL (mg/dL)	61 ± 5	115 ± 16	170 ± 21	99 ± 7	234 ± 33	157 ± 41
LDL (mg/dL)	12 ± 2	22 ± 7	34 ± 8	114 ± 27	1327 ± 232	43 ± 16

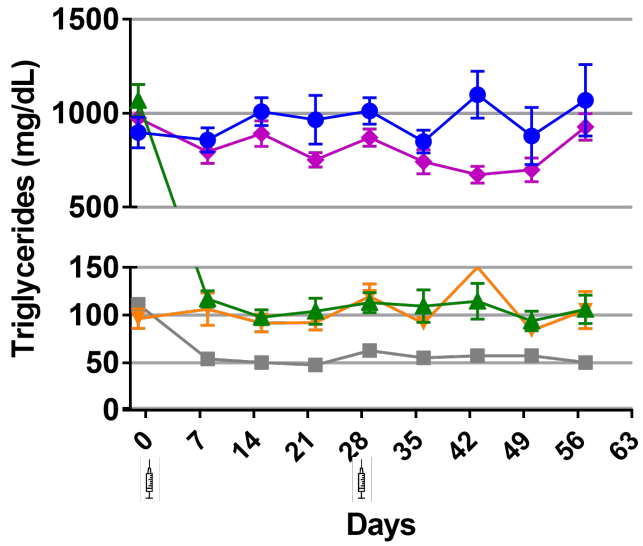
All from day -1 pre-dose bleed

Effects of ANGPTL3 KD in LDLr $^{-/-}$ Mice

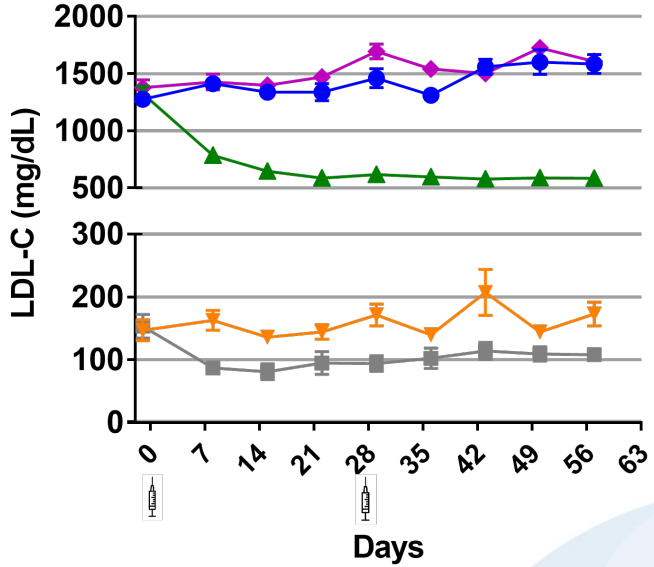
Serum ANGPTL3



TGs

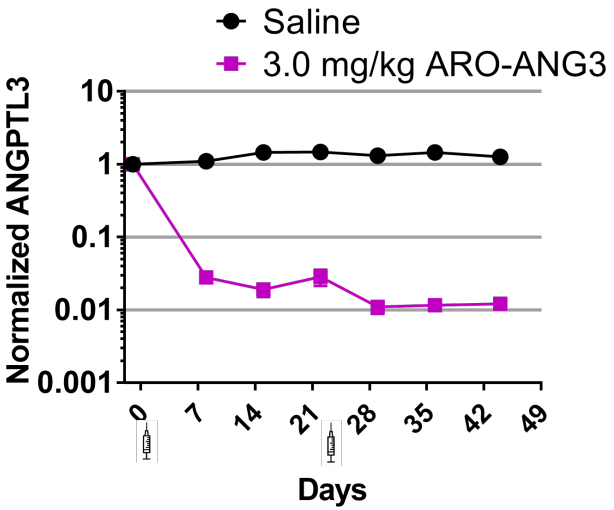


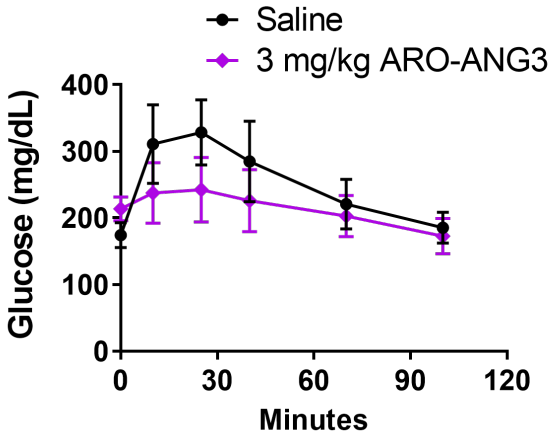
LDL-C



- **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 8 week old DIO mice

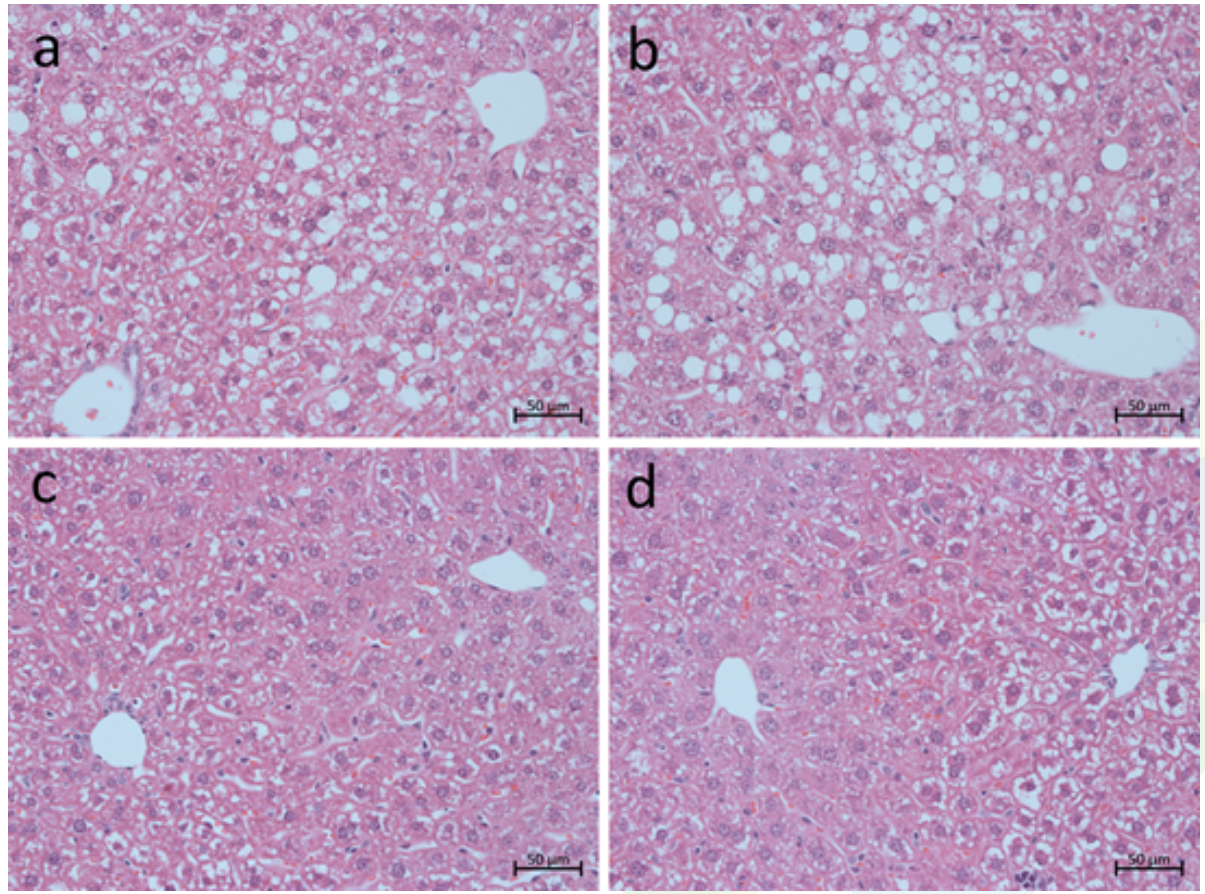




- **Maximum serum ANGPTL3 reductions of 99% (after second dose)**
- **Maximum TGs reductions of 54% (from 70 mg/dL to 31 mg/dL)**
- **Maximum LDL-C reductions of 65% (from 20 mg/dL to 7 mg/dL)**

Liver Histology (H&E)

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



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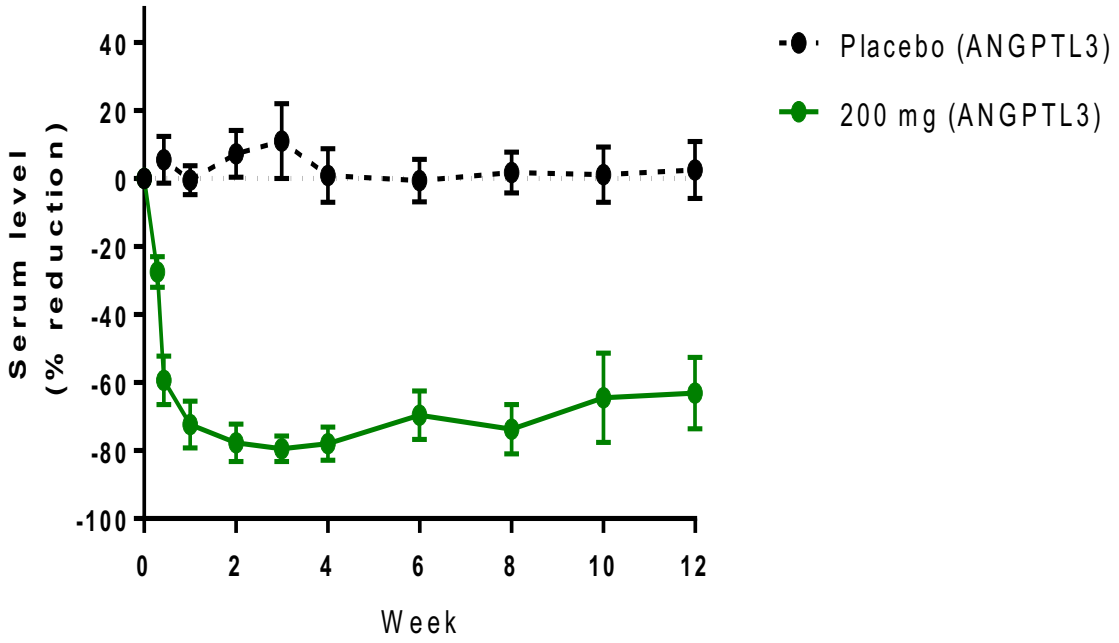
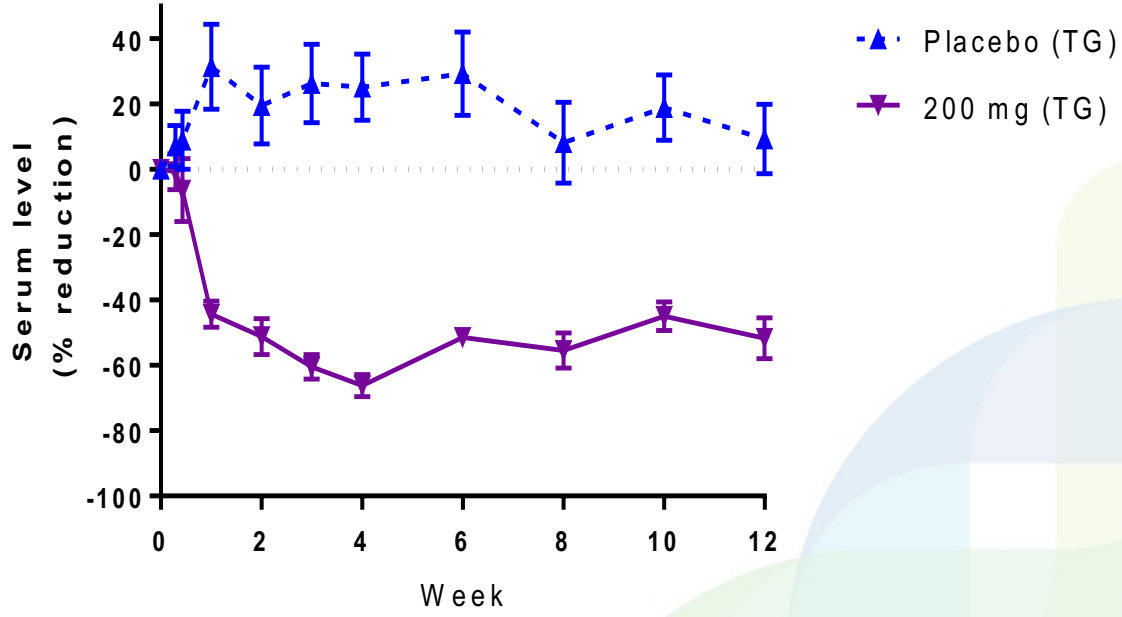
First Look at ARO-ANG3 in Healthy Volunteers – Single 200 mg dose through week 12

AngPTL3



TGs



Top Line Safety Observations with ARO-ANG3

- No premature discontinuations in ~36 volunteers/patients treated with ARO-ANG3
- No drug-related serious adverse events (such as deaths, hospitalizations, etc)
- No drug-related adverse events rated as severe
- Most common reported AEs: headache and upper respiratory infection

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- Some Background on RNA Interference (RNAi)
- The CV Pipeline in RNAi
- Hypertriglyceridemia as an independent risk factor
- ApoC3 and AngPTL3 knockdown in animals and first data in humans
- **Conclusions**

Conclusions Regarding RNAi in CV Diseases

- Certain CV targets very well suited for RNAi
- Current advanced programs limited to hepatocyte targets
  - Once the platform is established in a cell type, simple to address most new targets
  - Rapid advances point to future programs outside the liver
- Ligand-directed RNAi offers the advantage of specificity
  - Tissue
  - Gene
  - This specificity offers potential for safety advantages
- Dosing intervals of 3-6 months expected to be the norm

Initial Conclusions Regarding ARO-ANG3 and ARO-APOC3

- Genetic studies indicate that plasma triglycerides are an independent risk factor for CV disease
- Loss of function mutations of APOC3 or AngPTL3 are associated with markedly reduced triglycerides and other lipid parameters without reported adverse phenotype
- Knockdown of APOC3 in familial chylomicronemia patients with anti-sense (data not shown) was associated with marked reductions in plasma triglycerides
- Topline data with ARO-APOC3 in healthy volunteers indicate that it reduces plasma APOC3 and triglycerides without serious or severe adverse events
- In animal studies AngPTL3 has endocrine effects on triglyceride and LDL-C metabolism and apparent autocrine effects on hepatic steatosis and insulin sensitivity
    - ARO-ANG3 reduces triglycerides and LDL-C in LDL receptor knockout mice
    - ARO-ANG3 also ameliorates steatosis and improves insulin sensitivity in diet-induced obese mice
- Topline data with ARO-ANG3 in healthy volunteers indicate that it reduces plasma AngPTL3 and triglycerides without drug-related serious or severe adverse events
- If accepted, more complete data will be available at AHA 2019 in November

Arrowhead Team

Backup Slides

Comparison of Single Dose Results (APOC3)

Mean Maximal % reduction from baseline (SD)	Serum ApoC3	Triglycerides
ARO-APOC3 (100 mg)	94.2% (1.3)	63.2% (16.9)
AKCEA-APOCIII-L_{Rx} (60 mg)*[1]	64.7% (21.7)	43% (19.7)
AKCEA-APOCIII-L_{Rx} (120 mg)**[1]	91.2% (2.5)	79.6% (3.7)

ARO-APOC3 inclusion criteria of TG > 80 mg/dL
*60 mg dose was the highest dose given to subjects with fasting TG ≥ 90 mg/dL
** 120 mg dose was the highest dose given to subjects with inclusion criteria of TG >200 mg/dL
[1]Alexander et al, Eur Heart J, 2019 40:2785-2796.

Single Dose comparison (ANGPTL3)

Mean Maximal % reduction from baseline (SD) [unless noted]	Serum ANGPTL3	Triglycerides
ARO-ANG3 (200 mg)	79.4% (8.4)	66.2% (7.6)
AKCEA-ANGPTL3-L_{Rx} (80 mg)*[1]	61.7% (1.1)	56.1% (1.1)
Evinacumab (250 mg, SC)[2]	NR**	51.1%[&]
Evinacumab (250 mg, SC)[3]	NR**	55.5%[&]

* Inclusion criteria of TG = 90-150 mg/dL

** Dose-depended increases in ANGPTL3 indicating target binding of evinacumab were observed

[&] Median % change

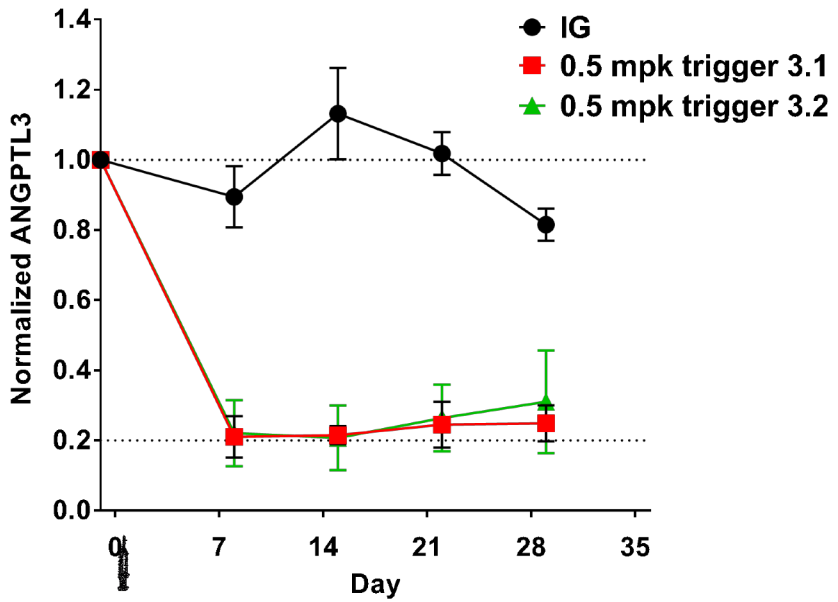
[1] Graham et al, NEJM 2017 377:222-232

[2] Dewey et al, NEJM 2017 377:211-221

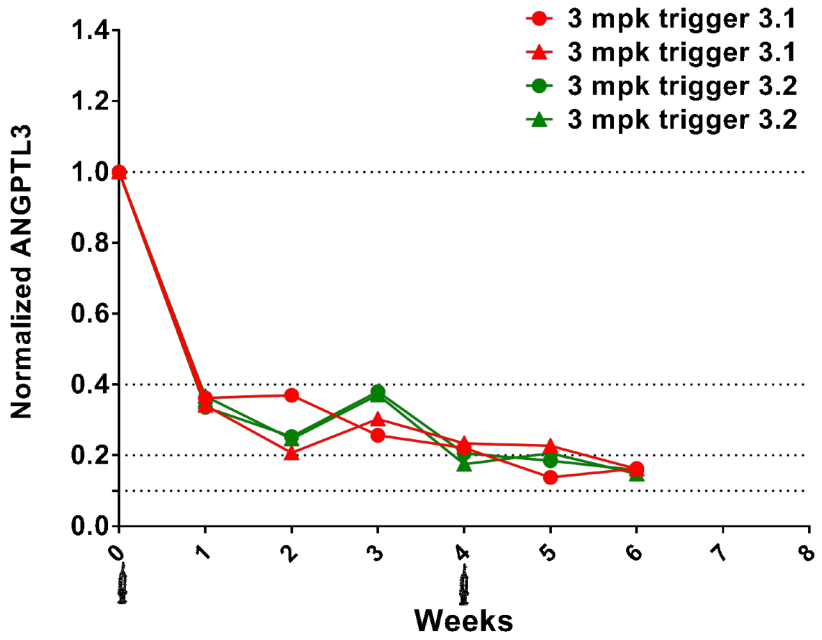
[3] Ahmad et al, Circulation 2019 140: 470-486

ANGPTL3 Triggers – WT Mice and Cynos

0.5 mpk single subQ injection in wild type mice – Trigger 3.1 and 3.2

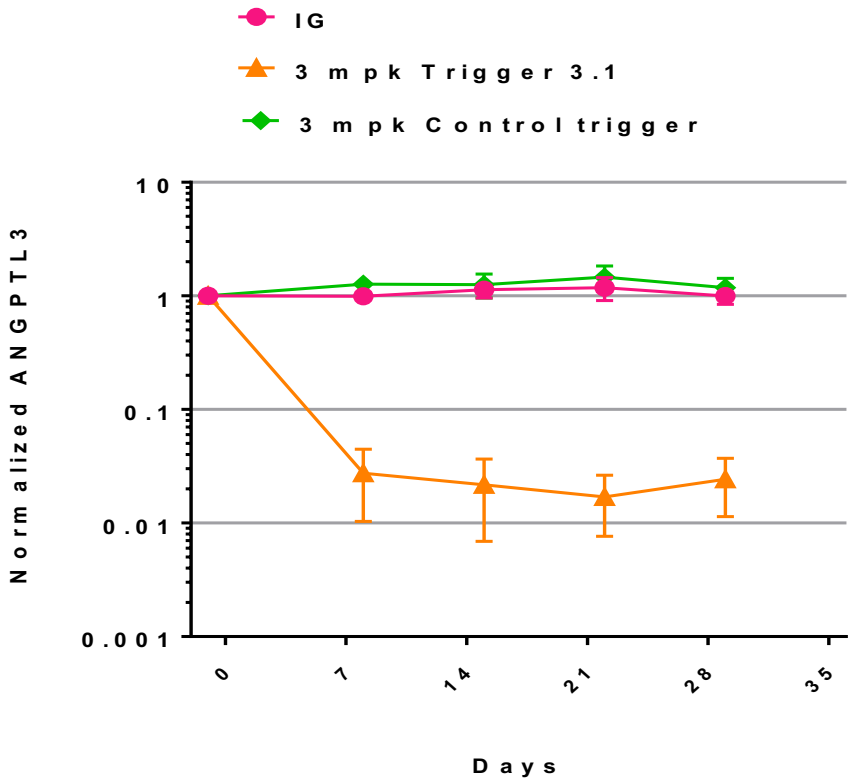


3 mpk subQ injection on days 1 and 29 in NHP – Trigger 3.1 and 3.2



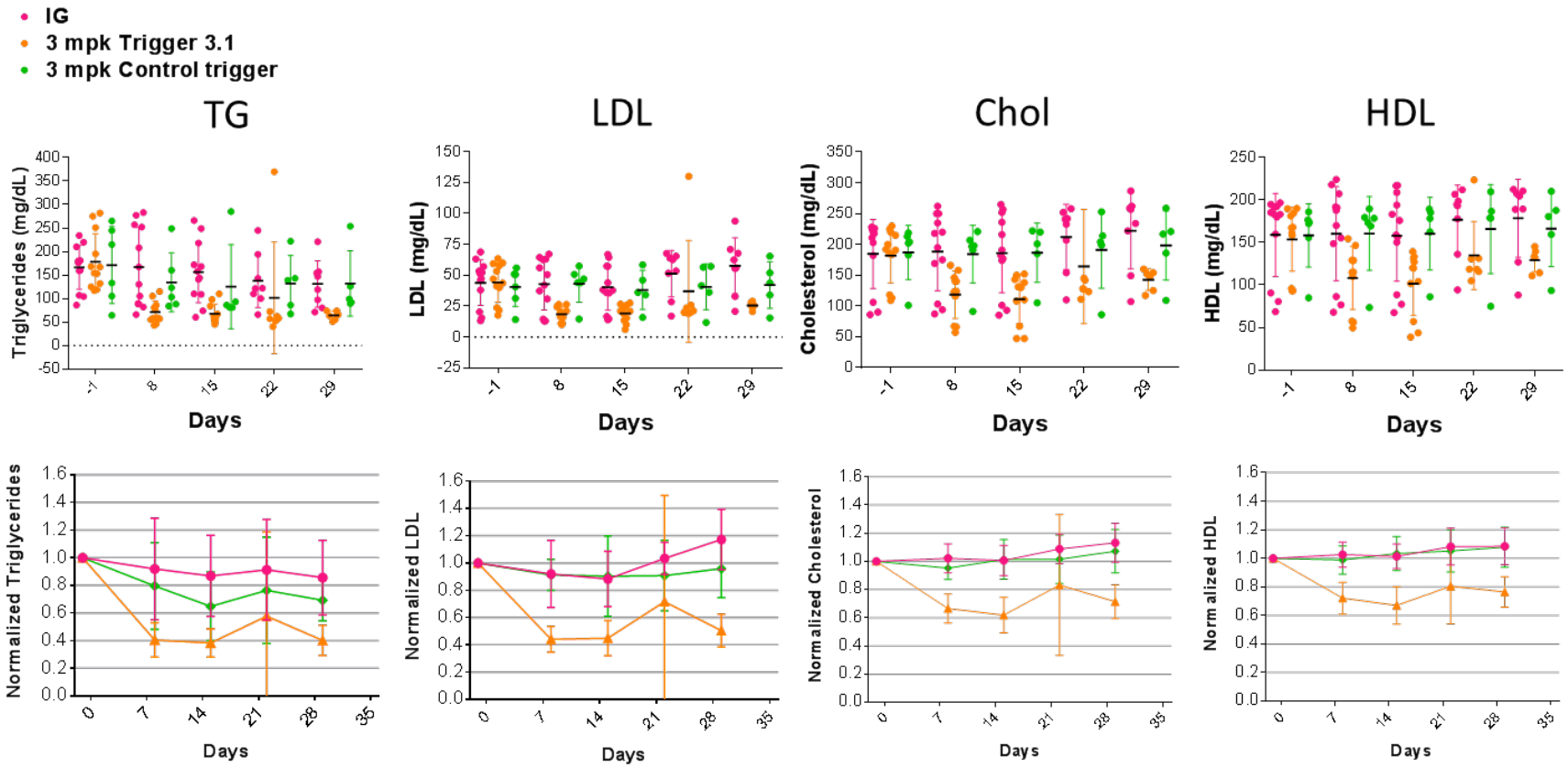
- 80% KD with good duration at 0.5 mpk dose in mouse study
- Single dose at 3mpk provided 80% KD in NHP

ANGPTL3 Protein KD in db/db mice



Max KD 98%

Effects of ANGPTL3 KD on Lipid Parameters: db/db Mice



- Lipid parameters not as high as the Western diet-fed LDLr$^{-/-}$ mice but 3-4 fold higher than WT mice
- ~ 60% reduction in TG and LDL levels

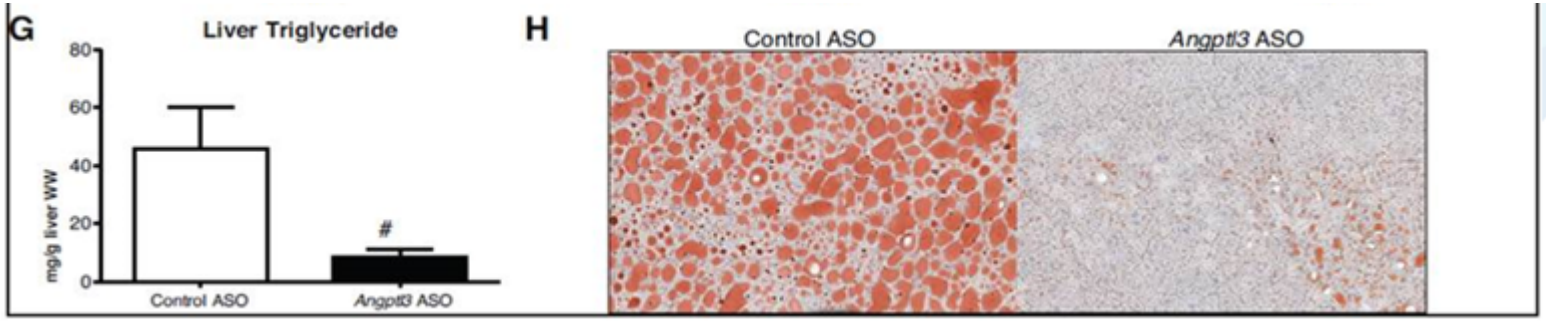
Mouse Disease Models: Pre-Dose Baseline Lipid Profiles

Mouse Model	WT Normal Chow	DIO 10% Fat Diet	DIO 60% Fat Diet	LDLr-/- Normal Chow	LDLr-/- Western Diet	db/db 6% Fat Diet
# of animals	N= 39	N=9	N=29	N= 16	N=39	N=30
Trig (mg/dL)	41 ± 6	52 ± 9	65 ± 14	98 ± 11	980 ± 288	172 ± 58
Chol (mg/dL)	69 ± 6	136 ± 17	195 ± 27	211 ± 30	1467 ± 253	184 ± 48
HDL (mg/dL)	61 ± 5	115 ± 16	170 ± 21	99 ± 7	234 ± 33	157 ± 41
LDL (mg/dL)	12 ± 2	22 ± 7	34 ± 8	114 ± 27	1327 ± 232	43 ± 16

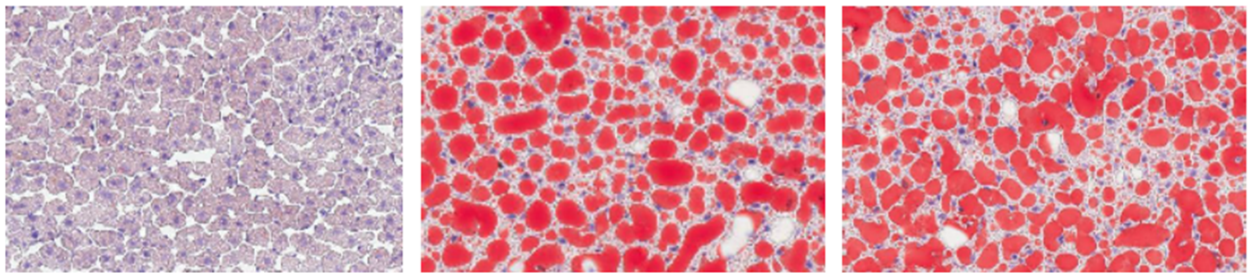
All from day -1 pre-dose bleed

ASOs appear to aid steatosis while Mabs do not

- Monoclonal antibodies cannot target intrahepatocyte ANGPTL3, will not improve NAFLD which is typical in metabolic syndrome in contrast to KD approach



Week 9 control Mab Week 9 REGN1500



Chow Diet Western Diet