The promise of RNA interference as a therapeutic approach for treatment of cardiovascular diseases

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Disclosures

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

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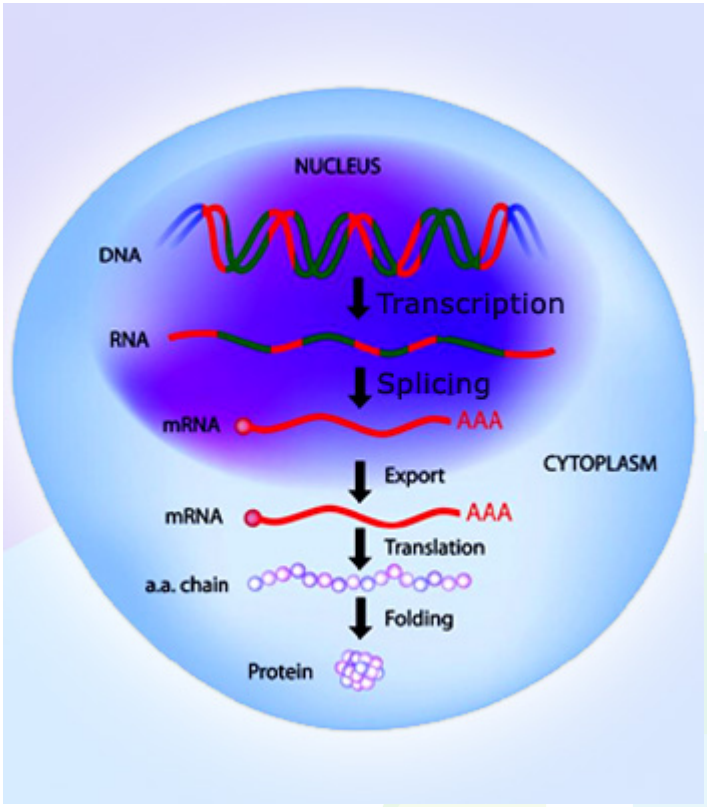
Outline

- **Some Background on RNA Interference (RNAi)**
- The CV Pipeline in RNAi
- Some Examples
- Conclusion

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



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
  - "for their discovery of RNA interference-gene silencing by double-stranded RNA"

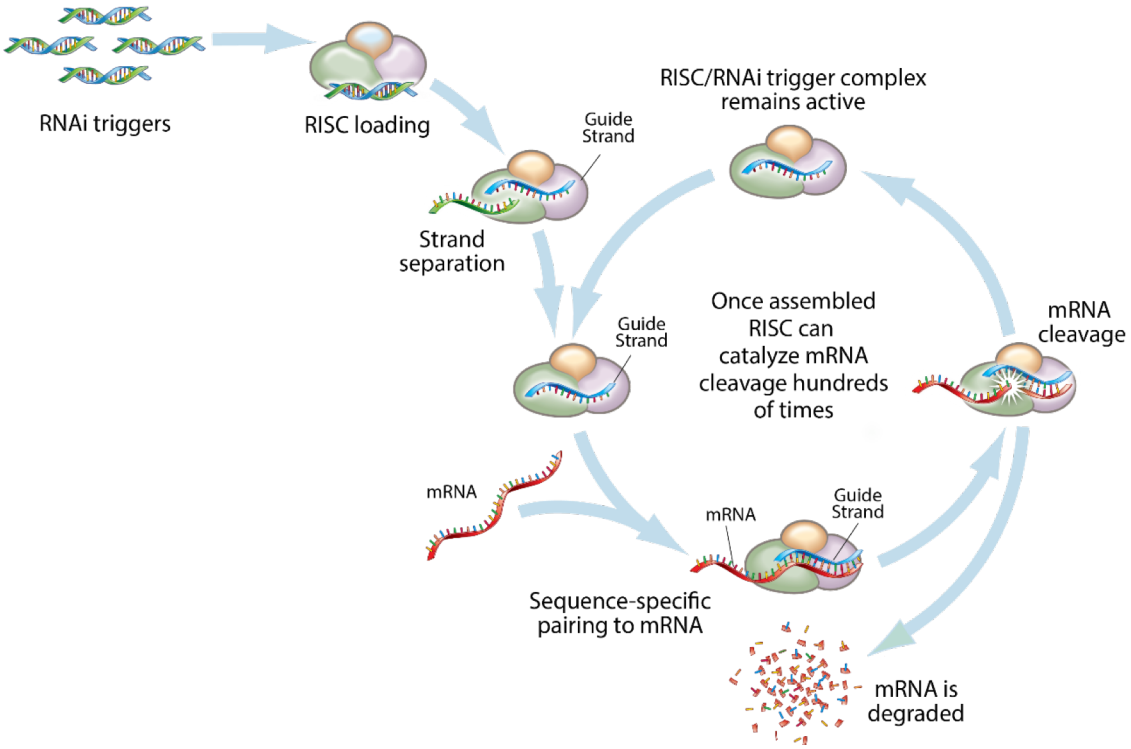
Andrew Z. Fire

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 knockdown 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

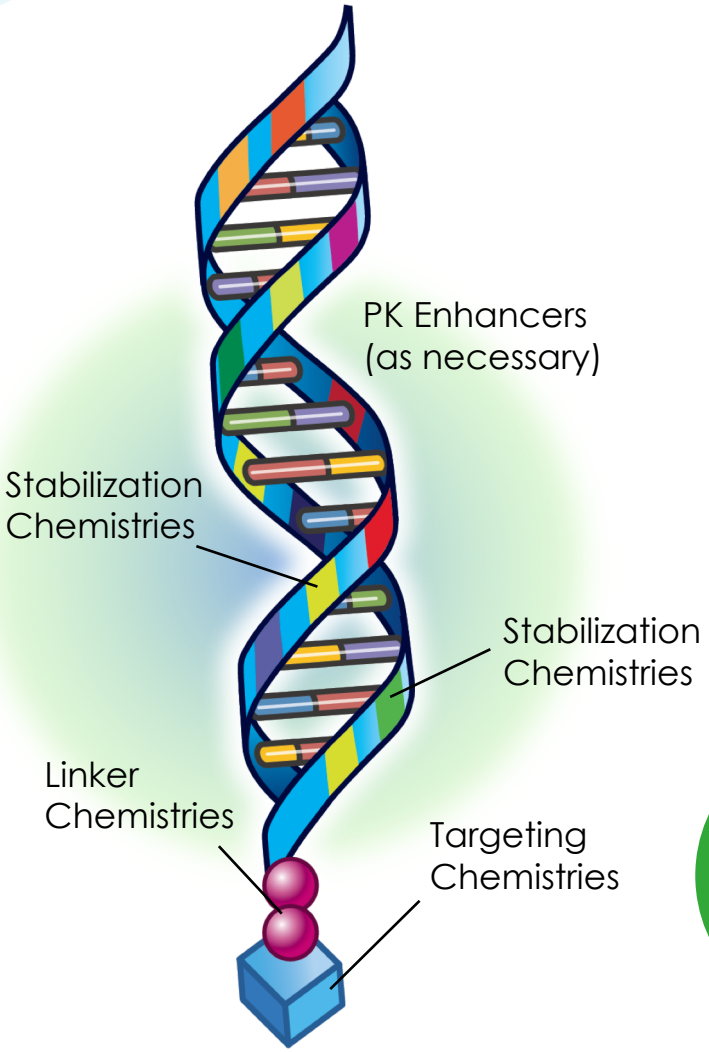


Therapeutic gene silencing with **RNA interference** is highly precise and efficient

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 in PCSK9

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

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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 ^
Undisclosed	Amgen *

* Licensed from Arrowhead

^ Licensed from Alnylam

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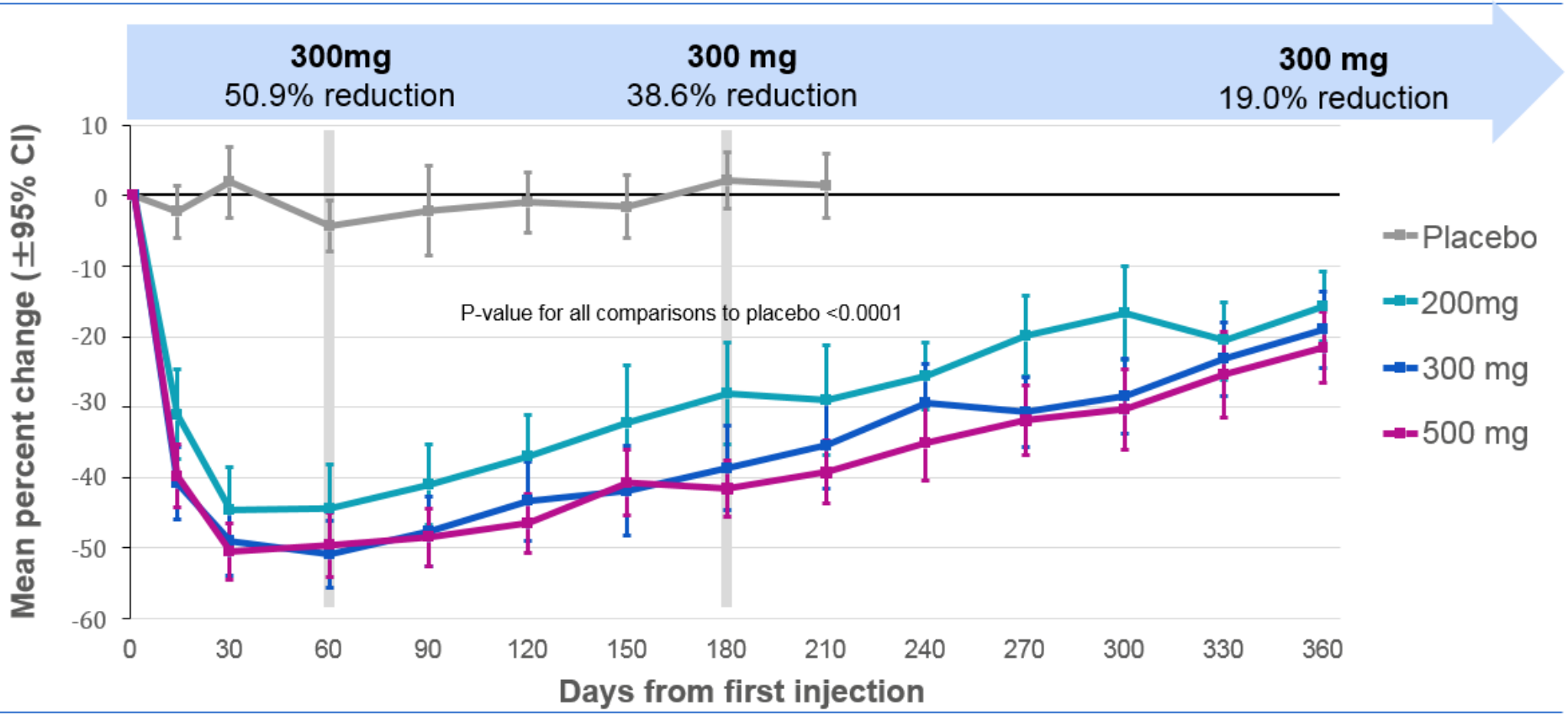
Robust and Sustained LDL-C Reductions with Inclisiran*

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

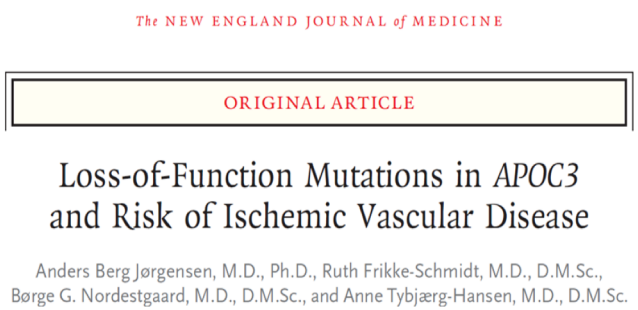
The Medicines Company

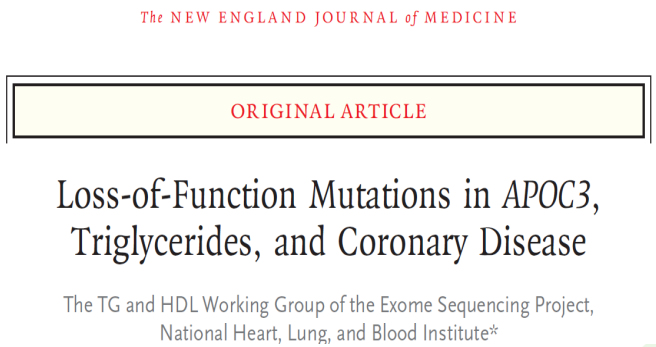
Alnylam PHARMACEUTICALS

Triglycerides Targets: APOC3, ANGPTL3

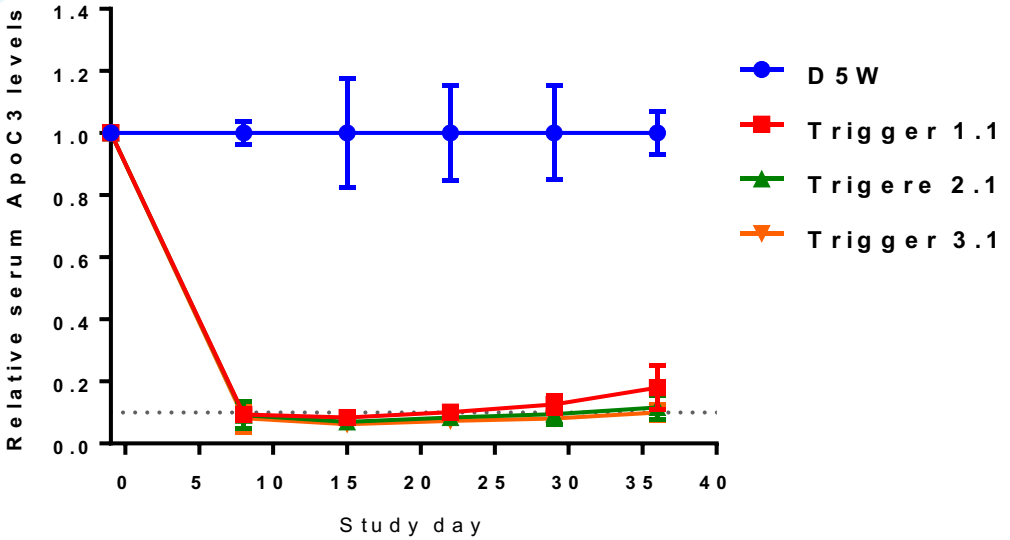
Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

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





Single-dose Study in ApoC3 Transgenic Mice

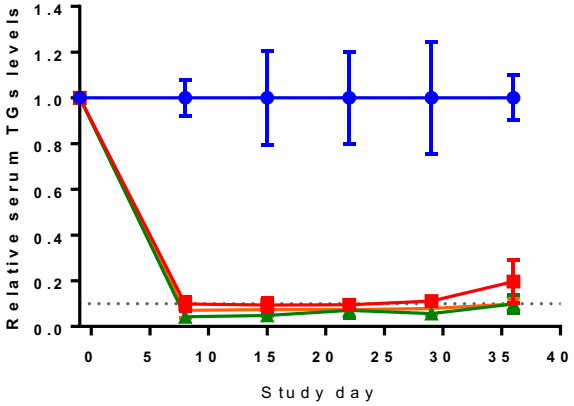


- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile

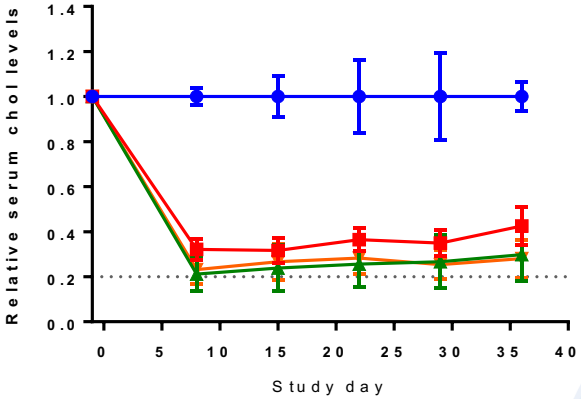
All dosed on study day 1 at 2 mpk

Data normalized to pre-dose and D5W control

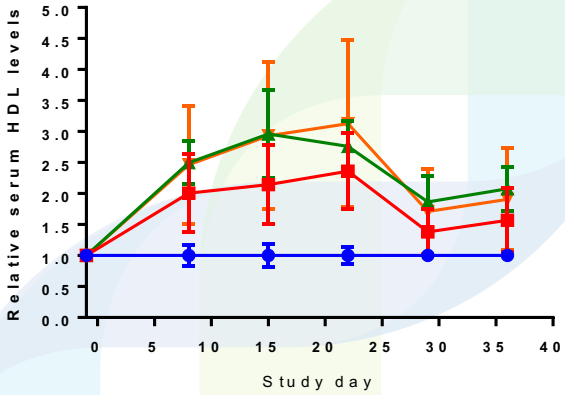
Trig



Chol



HDL



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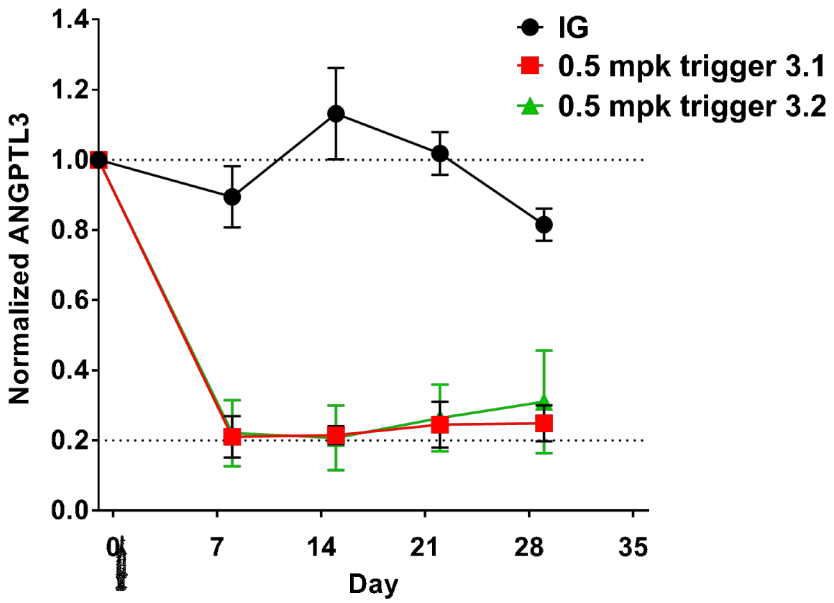
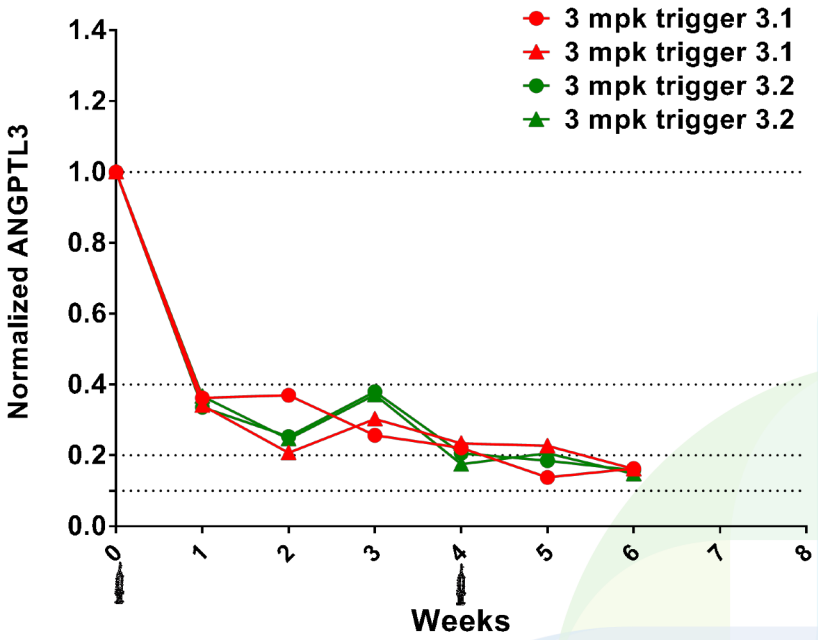
ANGPTL3 Triggers – WT Mice and Cynos

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

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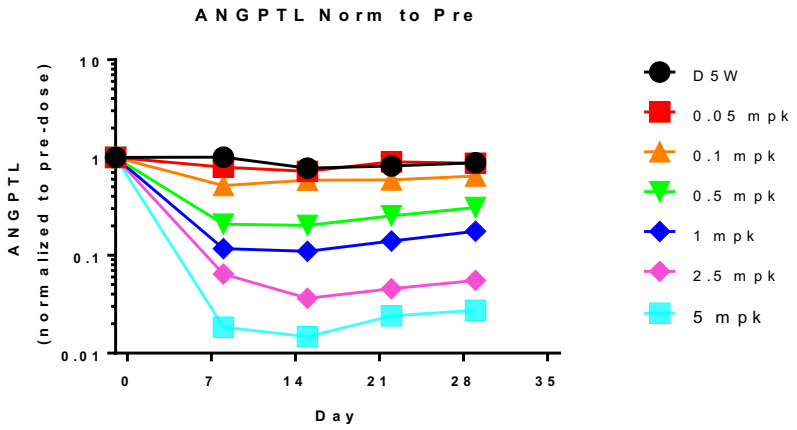
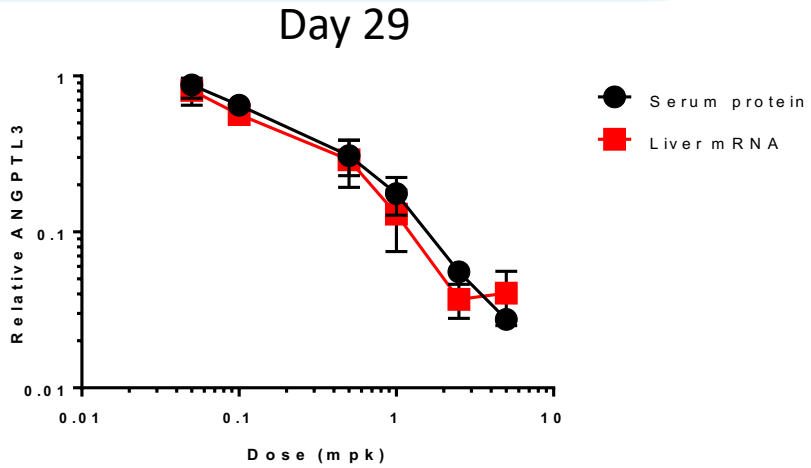
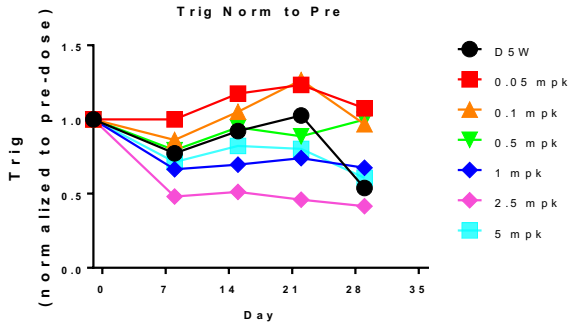
ANGPTL3 Dose Response in WT mice

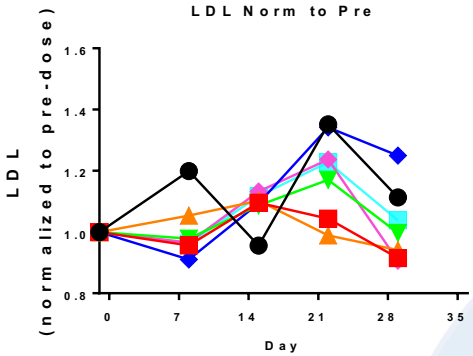


- Max KD on day 15
- 5 mpk close to assay detection limits



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





- Minimal effects on LDL
- Baseline LDL levels 10-15 mg/dL

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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

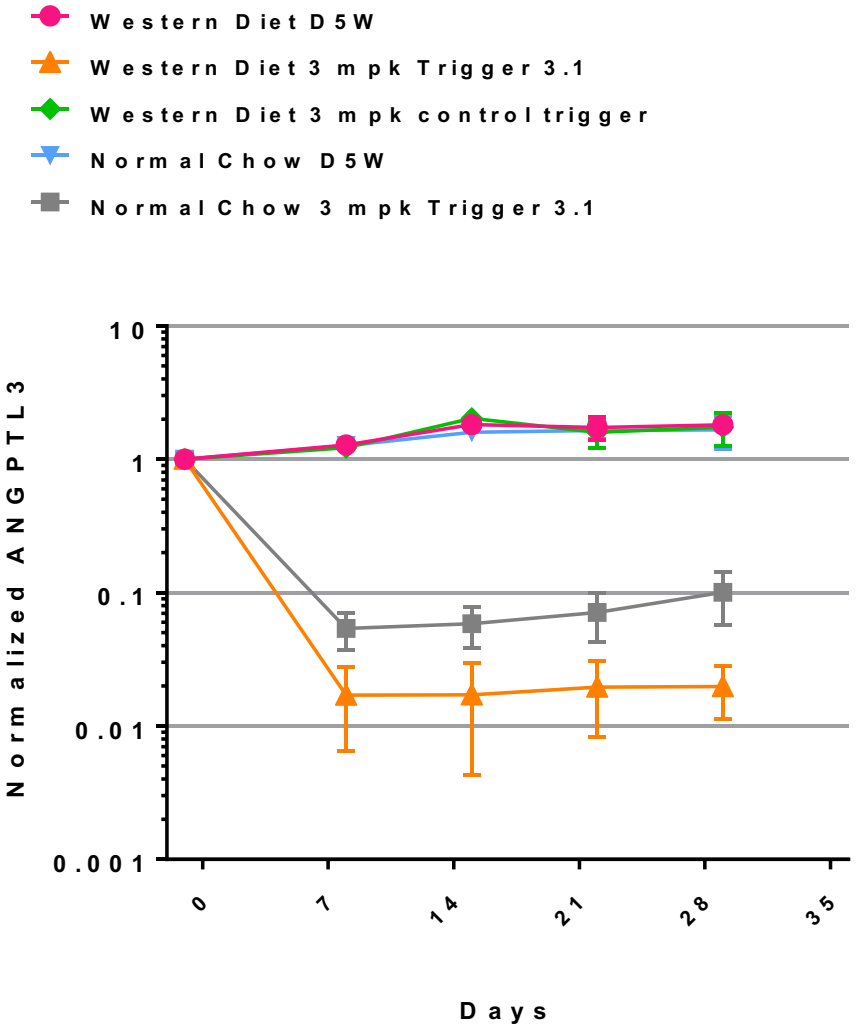
- All studies dosed at 3 mg/kg

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

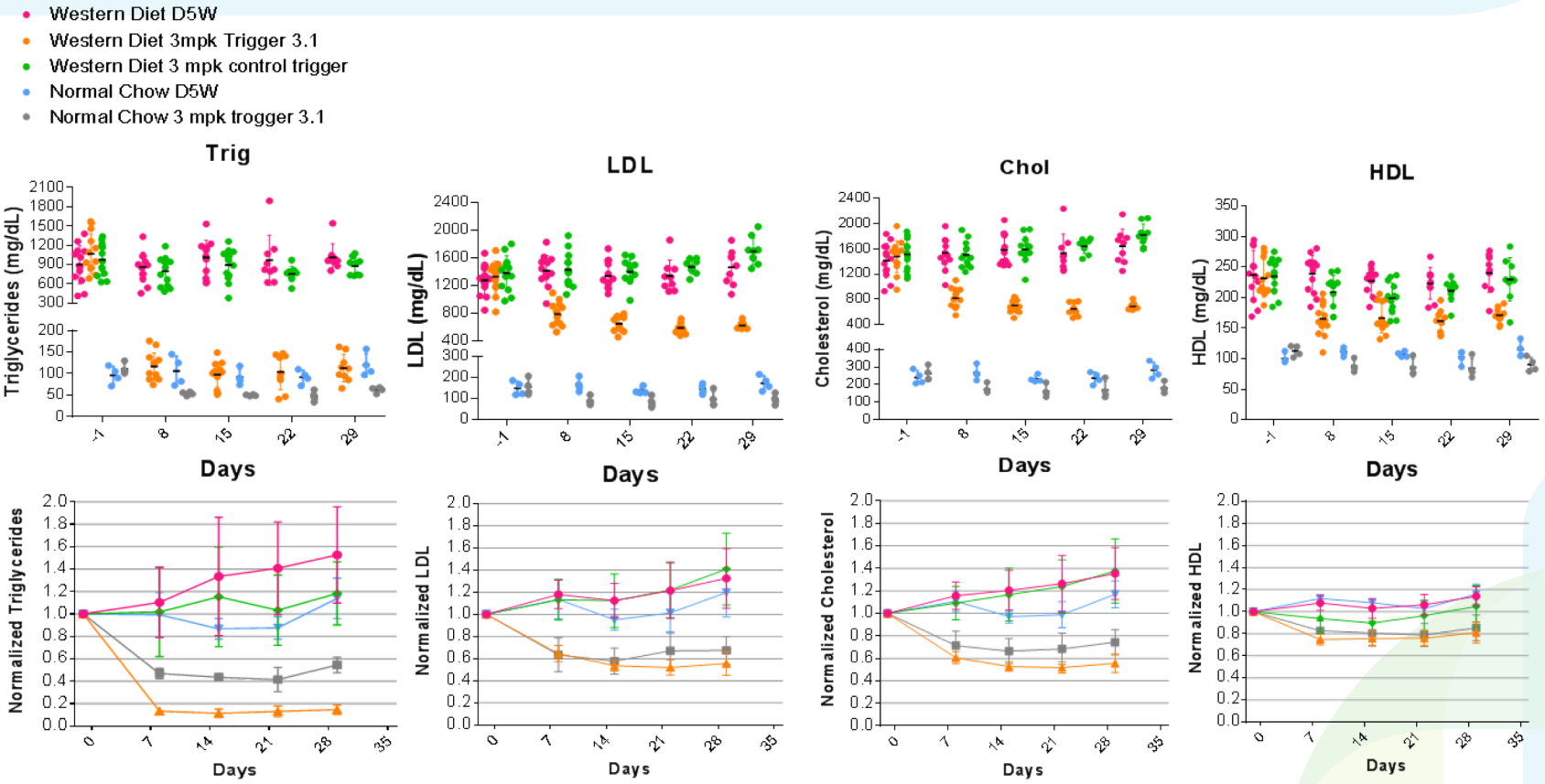
ANGPTL3 Protein KD in LDLr $^{-/-}$ Mice



Max 94% KD

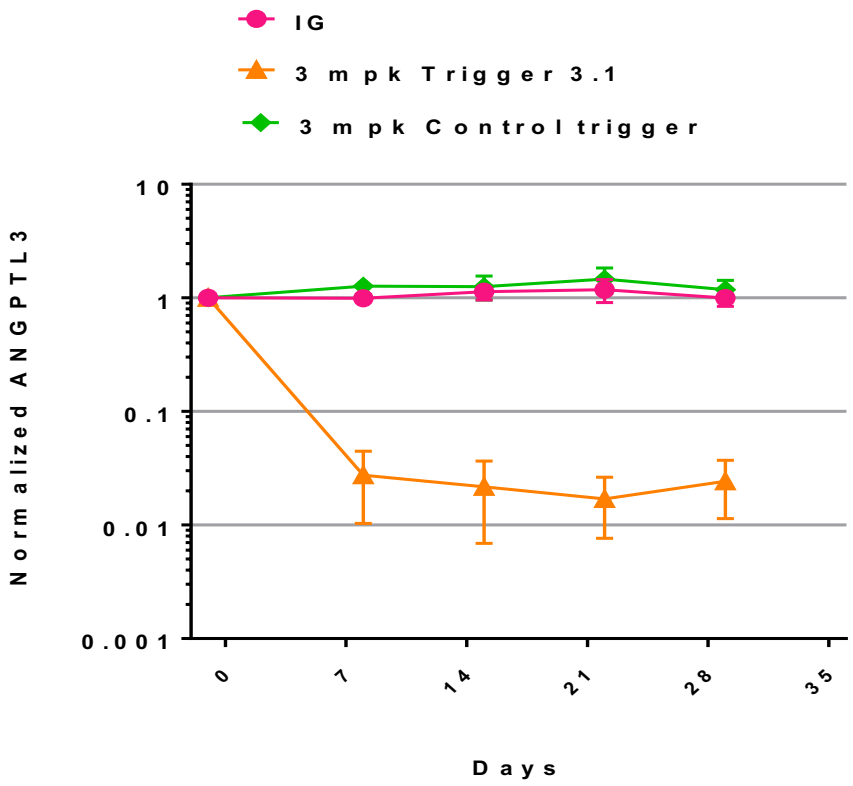
Max 98% KD

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



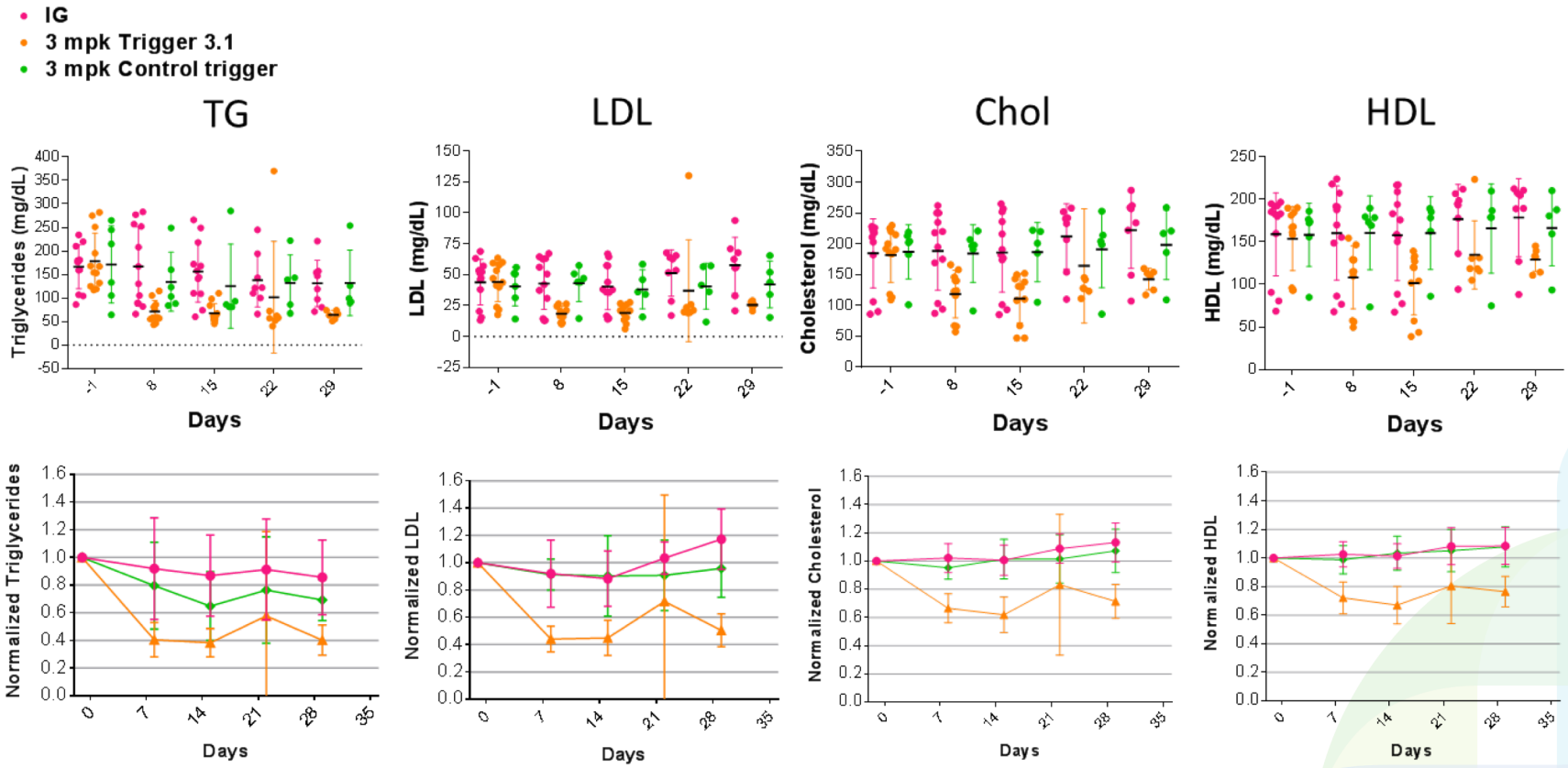
- Deep ANGPTL3 KD in both Western diet or chow-fed mice
- Significant decreases in lipid parameters
- Western diet-fed mice had similar or better % decrease in lipid parameters but absolute values still higher than chow-fed mice

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

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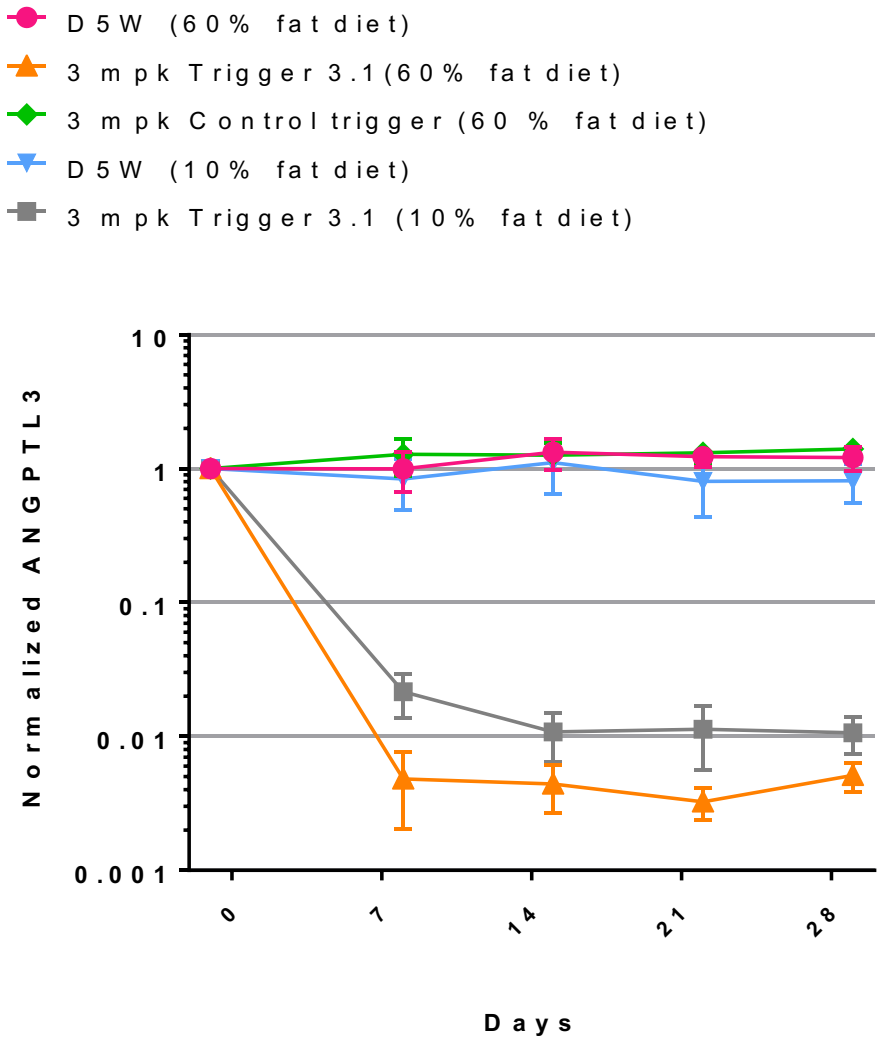
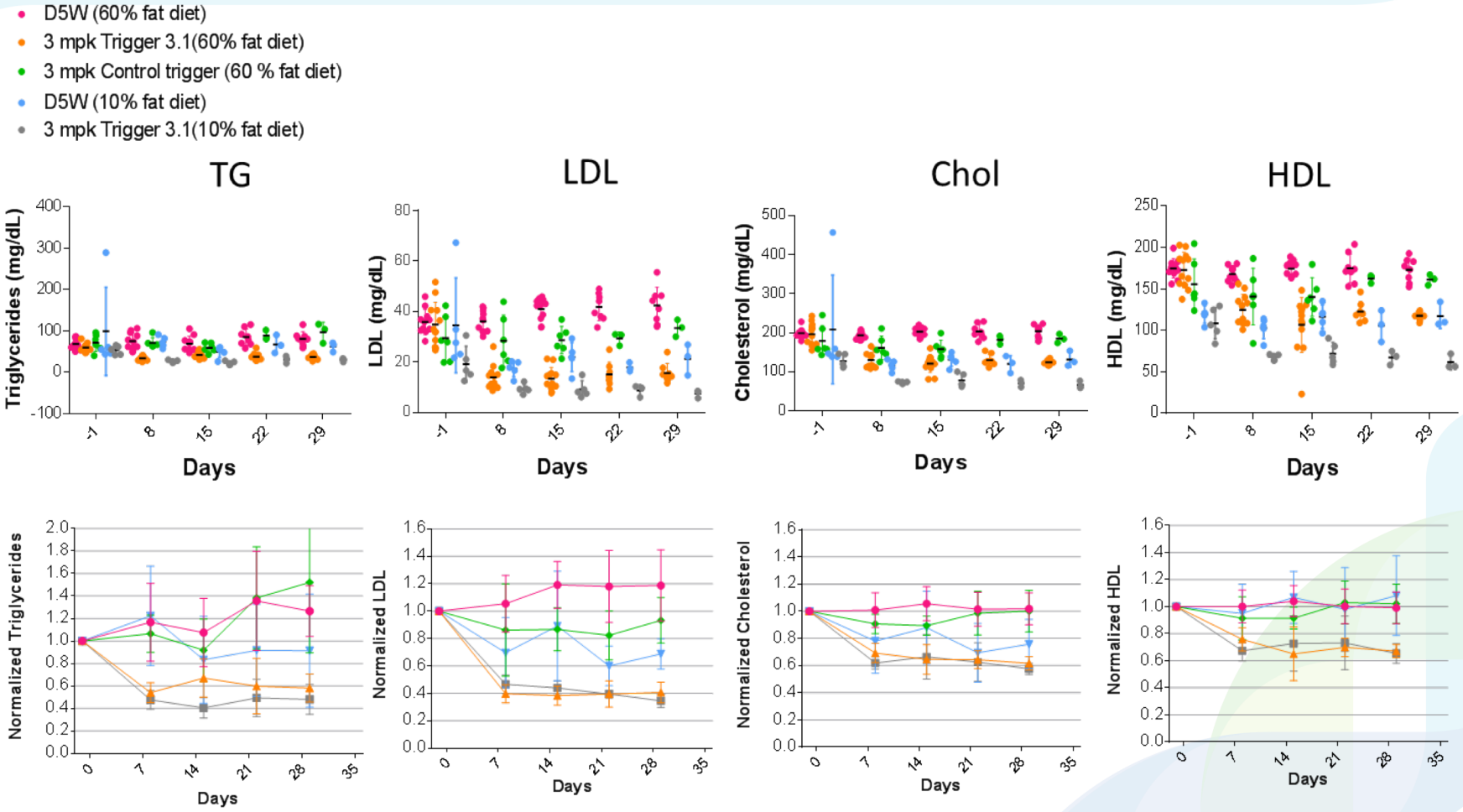
ANGPTL3 Protein KD in Diet-Induced Obese (DIO) Mice



Max KD ~ 99%

Max KD ~99.7%

Effects of ANGPTL3 KD in DIO Mice



- Lipid parameters 2-3 fold higher than WT mice
- ~ 50-60% reduction in TG and LDL levels

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Conclusions Regarding RNAi in CV Diseases

- Certain CV targets very well suited to RNAi
- Current advanced programs limited to hepatocyte targets
  - Once the platform is established, simple to address 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 1-6 months will be the norm

Arrowhead Team