Investor and Analyst R&D Day 2018

October 16, 2018

arrowhead pharmaceuticals

Welcome and Introductions

Vince Anzalone, CFA
Vice President, Investor Relations

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 obtain projected milestone payments and licensing fees, our ability to fund our operations, 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.

Panelists

New York University Langone School of Medicine

Ira Goldberg, M.D.
Bronfman Professor of Medicine
Chief of the Division of Endocrinology, Diabetes and Metabolism

Arrowhead Pharmaceuticals

Vince Anzalone, CFA
Vice President, Investor Relations

Chris Anzalone, Ph.D.
President and CEO

Bruce Given, M.D.
COO and Head of R&D

Zhen Li, Ph.D.,
Senior Vice President, Chemistry and Non-Clinical Development

Erik Bush, Ph.D.,
Senior Director, Extra-Hepatic Targeting

So Wong, Ph.D.,
Director, Oncology

Agenda

- Welcome and Intros – Vince Anzalone
- Pipeline and Platform Strategy – Chris Anzalone
- Apolipoprotein C-III – Ira Goldberg
- ARO-APOC3 – Bruce Given
- Angiopoietin-like protein 3 – Ira Goldberg
- ARO-ANG3 – Bruce Given
- TRiM™ Platform – Zhen Li
- ARO-ENaC Gen1 – Erik Bush
- ARO-HIF2 – So Wong
- Concluding Remarks – Chris Anzalone
- Q & A – Panel

Pipeline and Platform Strategy

Chris Anzalone, Ph.D.
President and CEO

We do science.

Janssen Partnership

Development and Commercialization Partnership for HBV and 3 New Targets

- **Deal value up to $3.7bn**
  - $250m up front
    - $175m cash + $75m equity at $23/share
  - $1.6bn in potential milestone payments for HBV, including $50m after P2 initiation
  - $1.9bn in potential milestone payments for the 3 new targets
    - Targets will be novel: not from our pipeline
    - Hepatocytes and non-hepatocytes possible
  - Tiered royalties to mid teens

Validation

The right partner

Capital: transformational opportunities

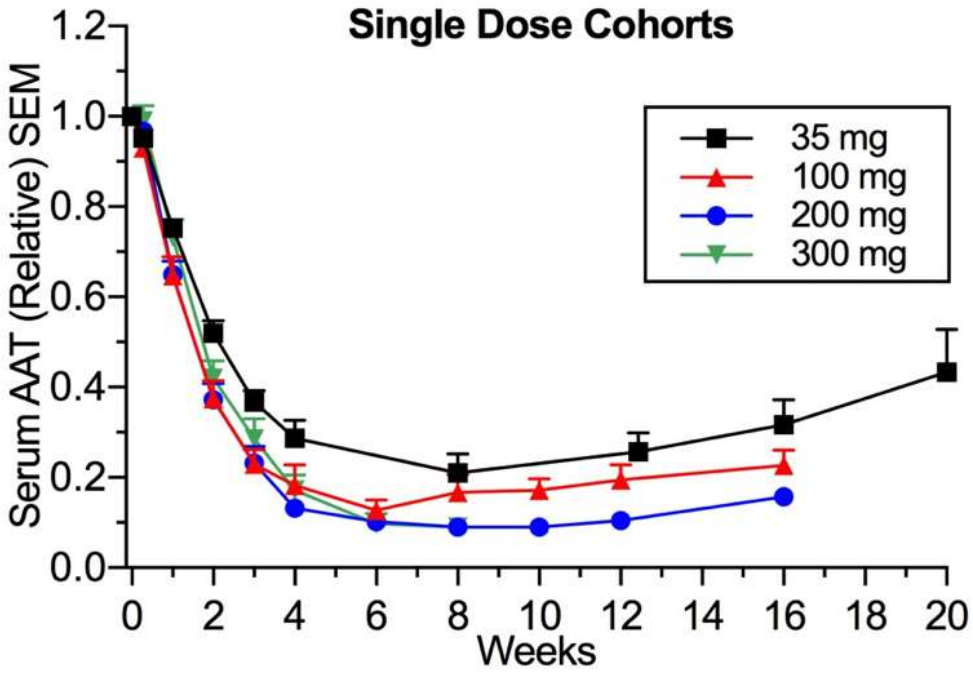
TRiM™ Validation

- Amgen deal 2 years ago for Lp(a) and an undisclosed CV target
  - Progressing well: P1 milestone payment triggered for AMG 890
- Best in class speed
  - We will go from 0 to 5 clinical programs in 1 year
- Good and consistent activity with ARO-HBV and ARO-AAT in the clinic
- Good tolerability with ARO-HBV and ARO-AAT; more than 100 human subjects treated

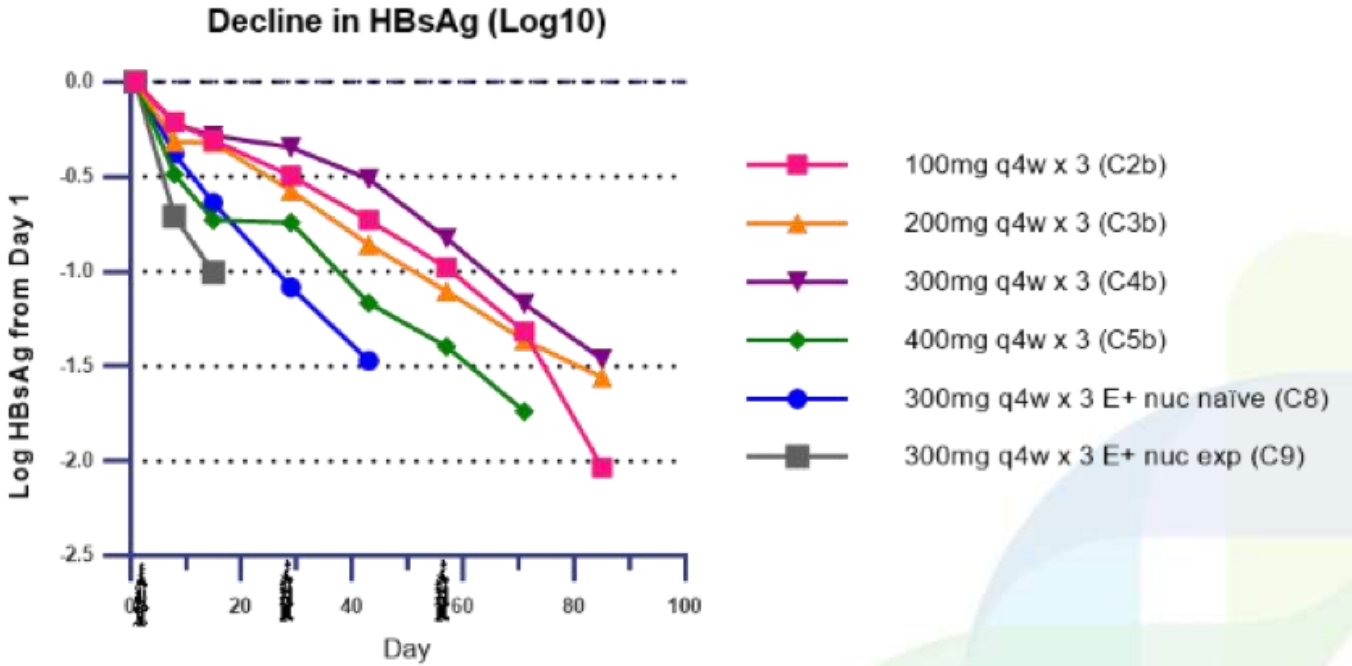
Janssen provides additional validation with a 4 target deal: one of the largest non-acquisition potential deal values in biotech history

TRiM™ Clinical Data from AASLD 2018 Abstracts

ARO-AAT



ARO-HBV



Janssen as a Partner

We view Janssen as an ideal partner for HBV

- Demonstrated clear commitment to HBV: most committed in pharma?
- Substantial resources with global reach
- Well positioned to take on the biology risk associated with addressing chronic HBV
  - Large, well-funded virology group
  - Multiple agents/mechanisms in-house
- Experience in complex global trials
  - Many cohorts will be required: HBV genotypes, different therapy combinations, different dosing schedules
- Well positioned for global launch

Capital Infusion: Transformational

Balance sheet and access to additional capital transforms our business

- Cash at last 10Q + Amgen payment: ~$90m
- $250m at close + $50m after ARO-HBV Phase 2 initiated = $300m of near-term capital
- **Together $390m: represents 6-8 years of operations at current burn**

- Will our burn increase over time? Yes, but:
  - **~$4bn of additional potential milestone payments between Janssen and Amgen**

Enables us to create value as *Pharmaceutical* company rather than small biotech company

Arrowhead as a Commercial Enterprise

Arrowhead can now create value by retaining most of its pipeline and commercializing its drugs

Effectively traded clinical and commercial control of HBV and 3 novel targets (while retaining substantial upside exposure) for the ability to commercialize our own drugs

- Plans for ARO-AAT to initiate a Phase 2/3 study in Q1 2019
  - Pre-IND meeting with the FDA this month
  - Expectations for biopsies pre- and post-treatment
    - Decrease in monomer, polymer, and globules
    - Possible decrease in fibrosis
- 4 additional programs (now) targeting 3 different cell types

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

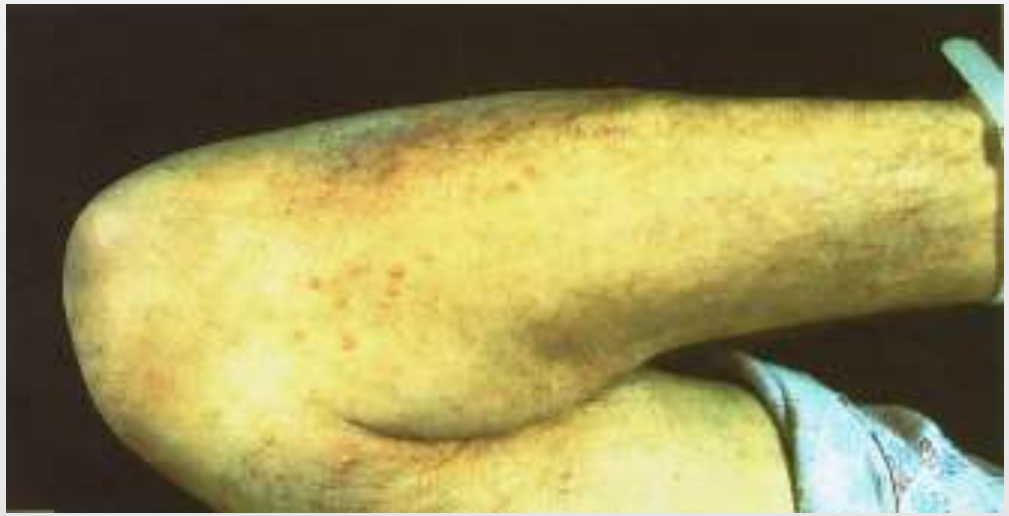
Apolipoprotein C-III

Ira Goldberg, M.D.
Bronfman Professor of Medicine
Chief of the Division of Endocrinology, Diabetes and Metabolism
New York University Langone School of Medicine

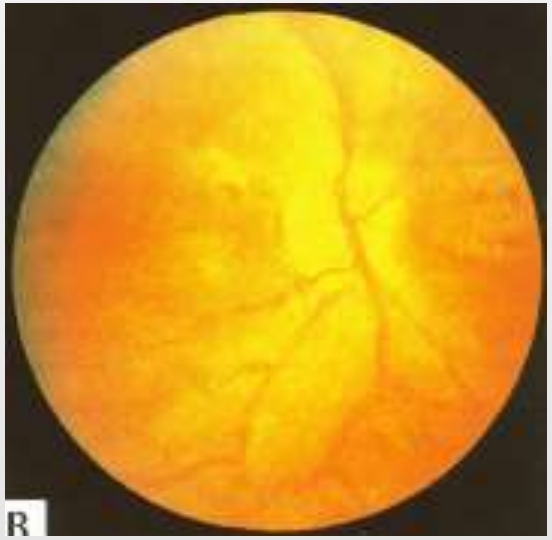
Describe the causes of severe hypertriglyceridemia

Explain the evidence linking hypertriglyceridemia with acute and chronic disease

Clinical Signs of Severe Hypertriglyceridemia



Eruptive Xanthomas



Lipemia Retinalis

How common and what are the risk factors for hyperTG pancreatitis

- Review of Kaiser Permanente, S. California
- Triglyceride over 1000 mg/dL (11 mMol)
- 5,550 patients/$2.3x10^6$ total. ~0.2%
- 301 (5.4%) with pancreatitis during the 12 month follow up
- 42.1% with diagnosis of unspecified hyperlipidemia (so most not with hyperTG)
- Pancreatitis group average TG 2,148 mg/dL
- Co-morbidities included younger age, alcohol, prior history, hypertension, renal disease.

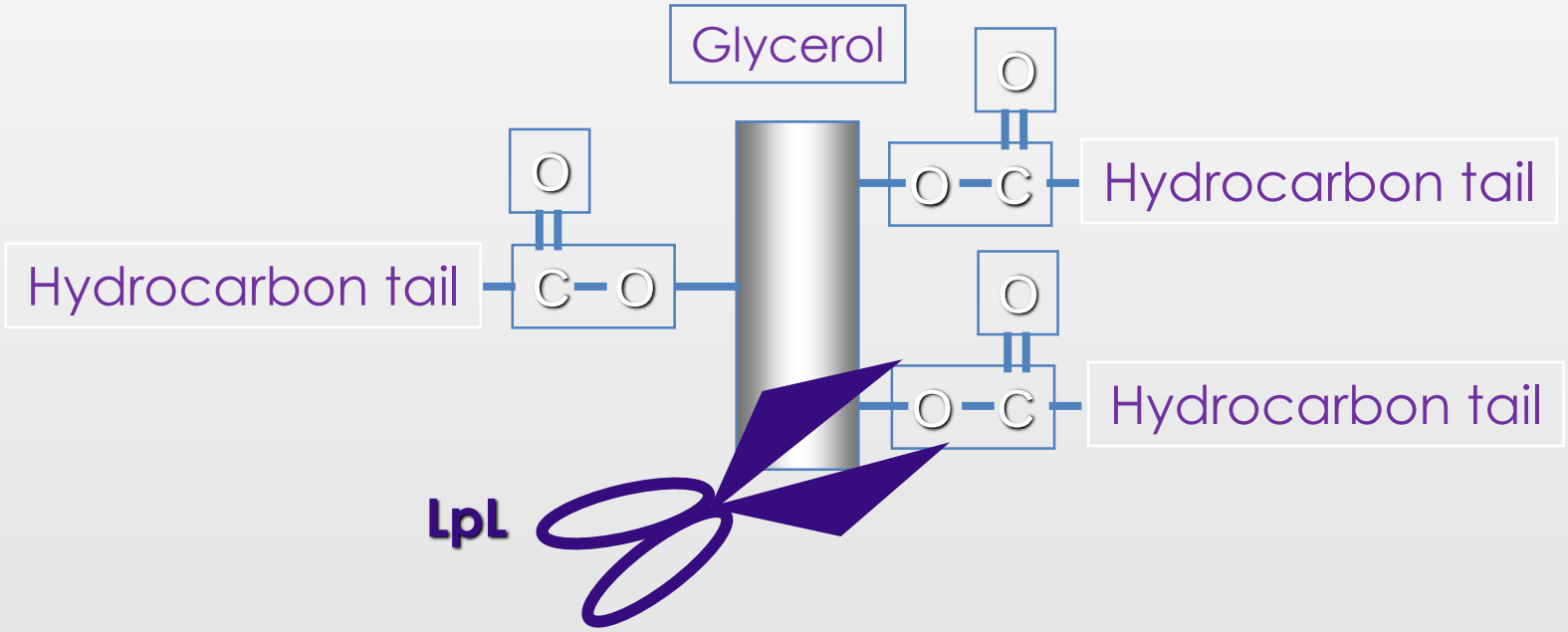
- *Rashid et al. 2016. al. J Clin Lipidol 10, 880*

NYU

Why does hyperchylomicronemia cause pancreatitis?

I don’t know!

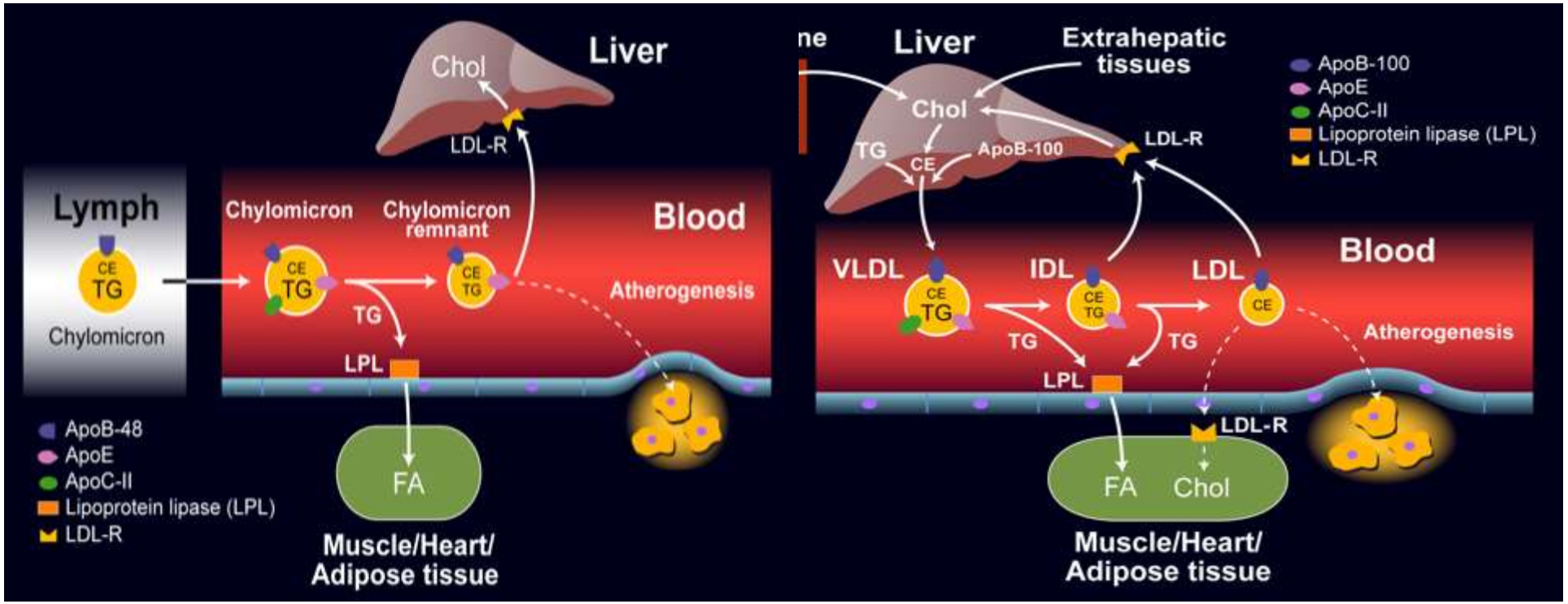
Triglyceride (TG) and Lipoprotein Lipase (LpL)



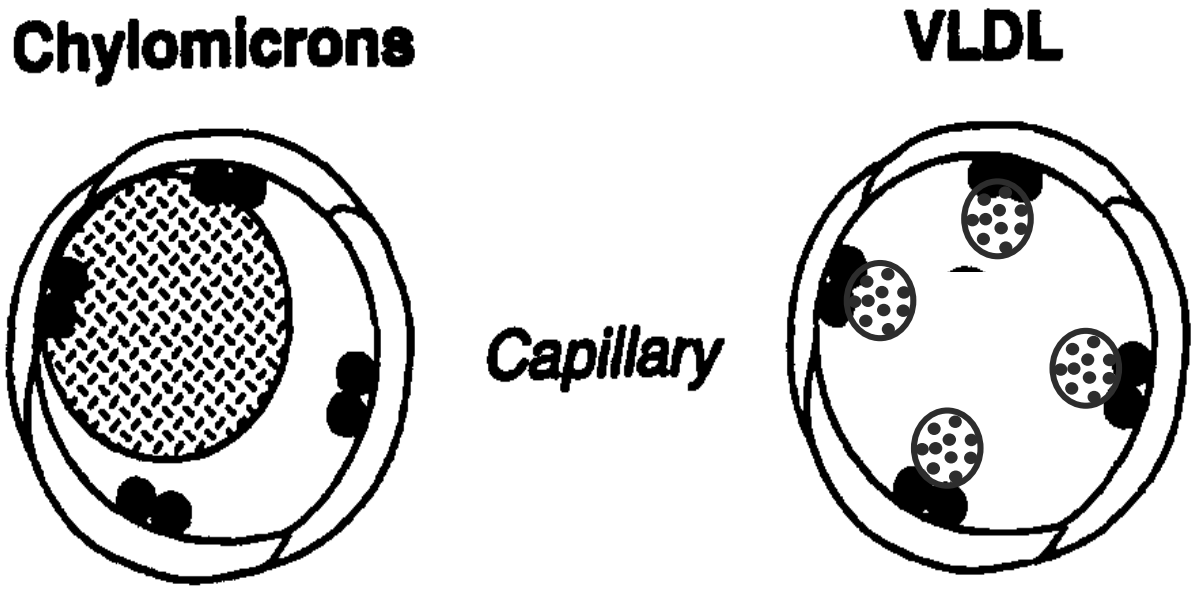
TG from liver and gut use LpL

Chylomicron Transport

Endogenous Pathway

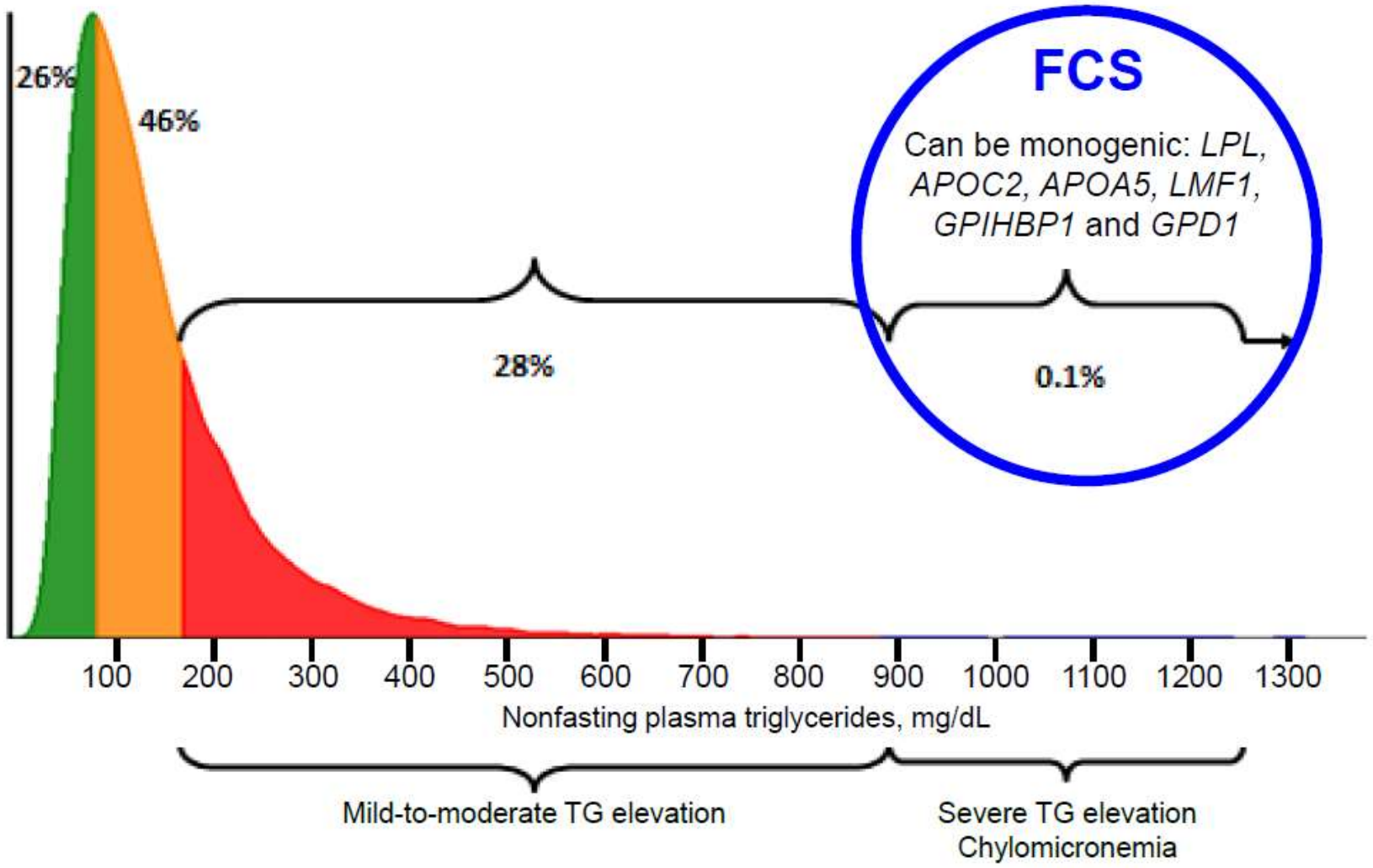


High Concentrations Of VLDL Block Chylomicron Lipolysis



Goldberg, J Lipid Res. 1996. Apr;37(4):693-707.

Increased TG as a function of genetics



Hegele et al. Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66.

What regulates lipolysis?

Activators

- ApoC-II (activator)
- GPIHBP1 (endothelial cell binding site)
- Lipase maturation factor (LMF, intracellular production)
- ApoA-V (increases binding to endothelial cells)

Inhibitors

- ApoC-III
- Angiopoietin-like proteins 3,4,8

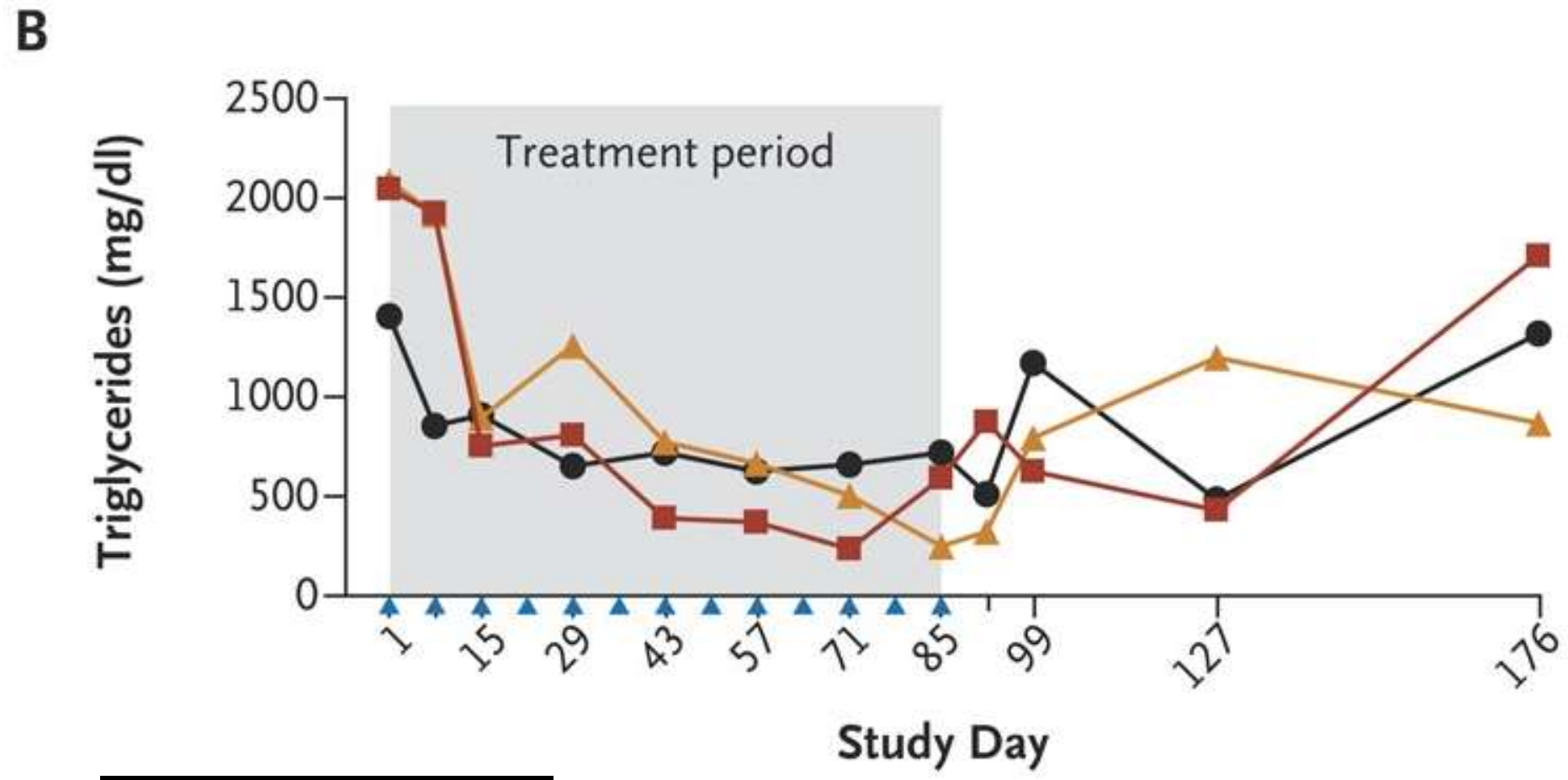
NYU

A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

Apolipoprotein C-III (apoC-III) inhibits triglyceride hydrolysis and has been implicated in coronary artery disease. Through a genome-wide association study, we have found that about 5% of the Lancaster Amish are heterozygous carriers of a null mutation (R19X) in the gene encoding apoC-III (*APOC3*) and, as a result, express half the amount of apoC-III present in noncarriers. Mutation carriers compared with noncarriers had lower fasting and postprandial serum triglycerides, higher levels of HDL-cholesterol and lower levels of LDL-cholesterol. Subclinical atherosclerosis, as measured by coronary artery calcification, was less common in carriers than noncarriers, which suggests that lifelong deficiency of apoC-III has a cardioprotective effect.

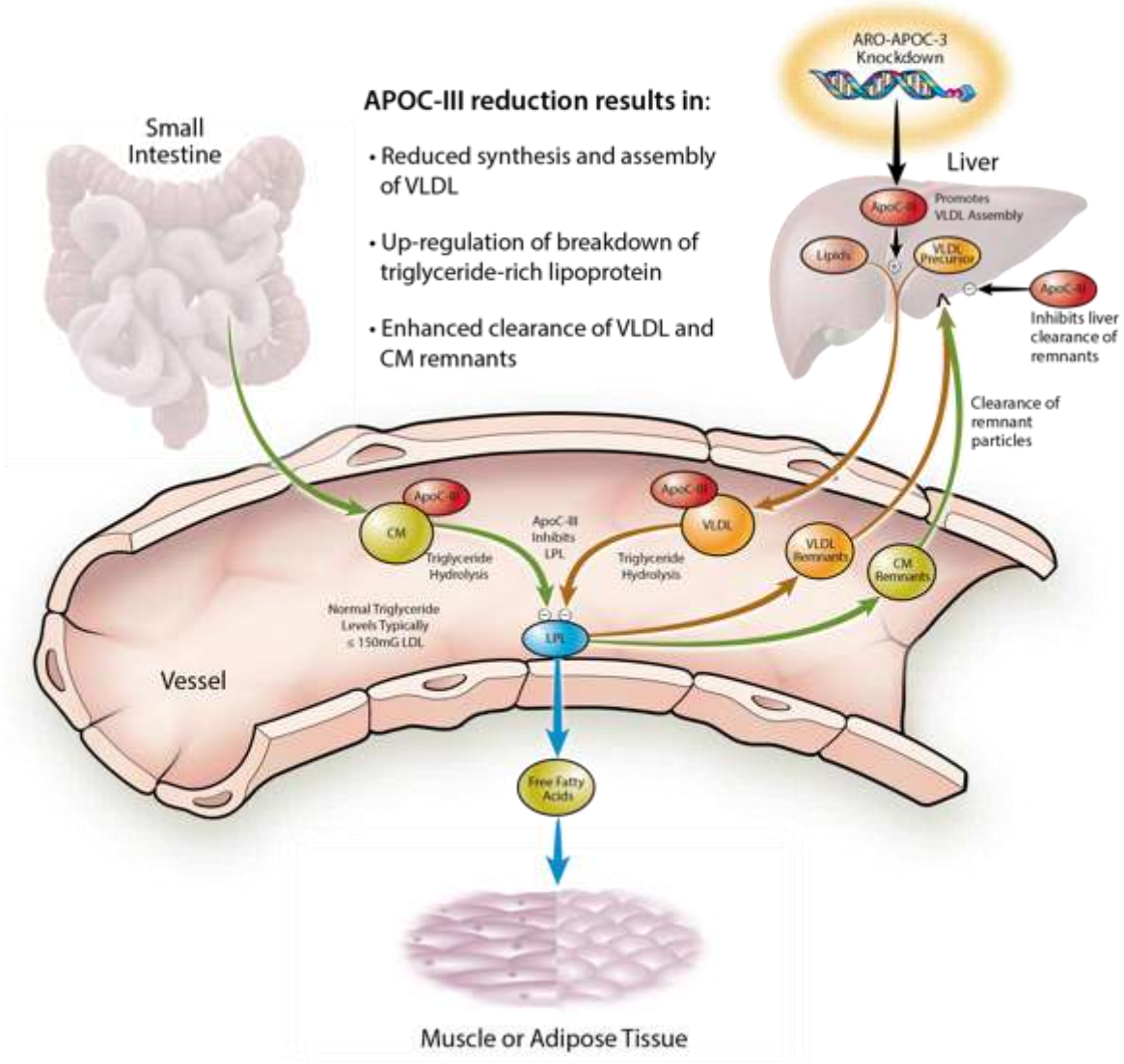
ApoC-3 ASO Reduced Triglycerides In LPL Deficiency



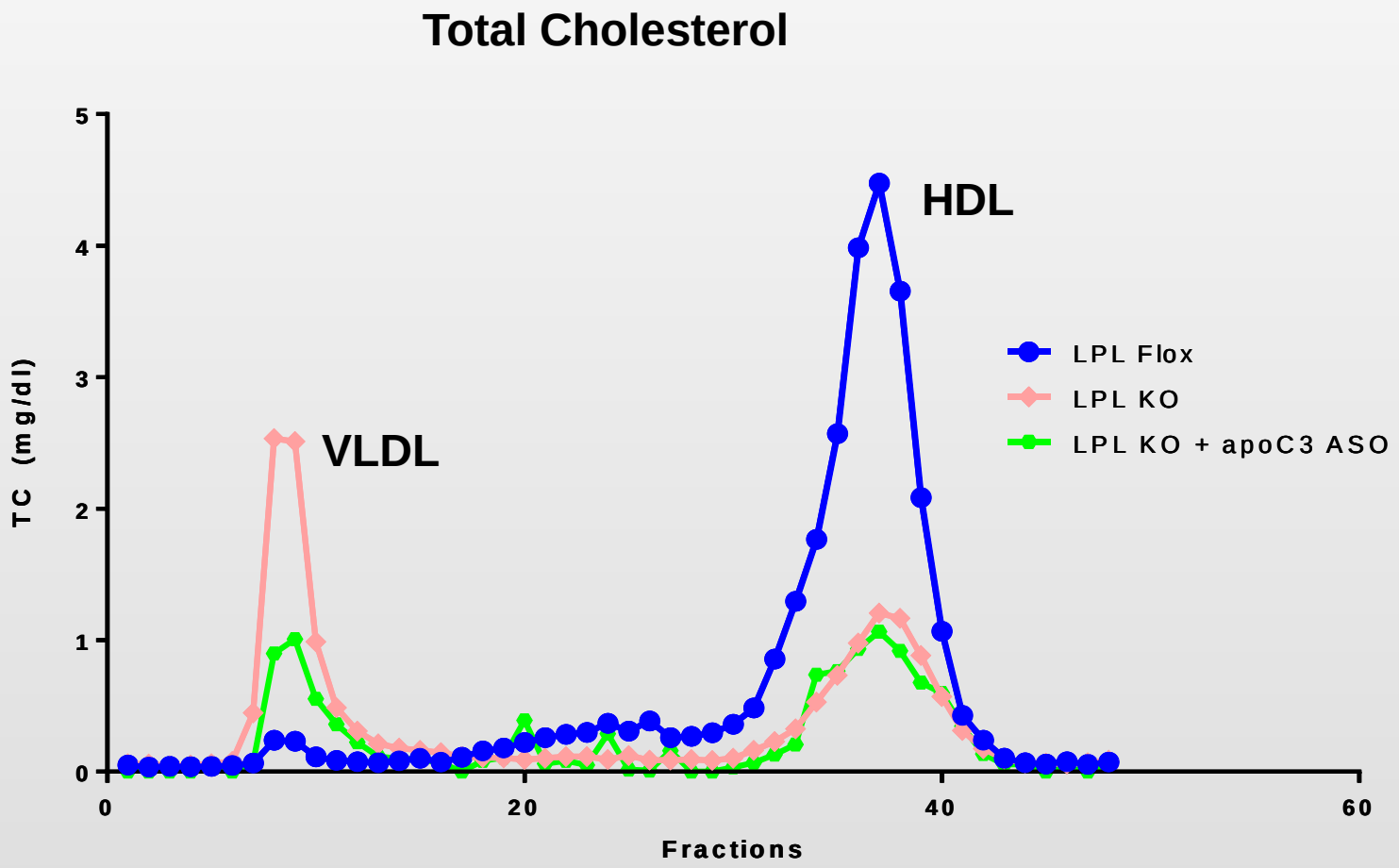
The NEW ENGLAND JOURNAL of MEDICINE

Gaudet D et al. N Engl J Med 2014;371:2200-2206

If apoC-III is an inhibitor of lipoprotein lipase, how does it lower TG in LpL deficiency??



Antisense Oligonucleotide (ASO) Reduced TG but Did Not Increase HDL



Basu in Gordts, et al. J Clin Invest. 2016 126: 2855-2866

Most hypertriglyceridemia is not a pancreatitis risk

Does it cause heart disease?

Trials on-going

Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

NYU Langone Health

2018 – REDUCE-IT

- Icosapent ethyl (Vascepa) omega 3 fatty acid
- Four grams, >8,179 subjects at high risk
- Statin treatment on top of statin, LDL average 75
- Triglyceride >150 mg/dL, 150-499 mg/dL (average 216)
- PRESS RELEASE September 12, 2018, full data at AHA in November
- ~23% reduction in MACE

Why did this work?

- In higher risk subjects, higher dose, all subjects with increased triglycerides
- Reduced circulating triglyceride levels
- Altered the composition of lipolysis products, which may be anti-inflammatory
- Affected platelet function
- Altered intracellular signaling pathways – omega 3 changes in intracellular lipids
- Something special about this formulation
- WE DO NOT KNOW! AND REDUCED TG LEVELS OR REDUCED APOC-III COULD HAVE SIMILAR BENEFITS

Take Home Message

- Rare recessive genetic diseases lead to severe hypertriglyceridemia and pancreatitis.
- But this can occur in patients with a single mutations and a second insult: estrogen, alcohol, diabetes.
- Triglyceride and HDL levels are usually inversely correlated.
- Data on treatment of triglyceride to reduce CVD is inconclusive.
- Newer drugs (inhibitors of ApoC-III and Angplt3) will hopefully prevent hypertriglyceridemic pancreatitis and might also reduce CVD

ARO-APOC3

Bruce Given, M.D.
COO and Head of R&D

Some introductory thoughts

Public CV RNAi Programs Shows Growing Interest

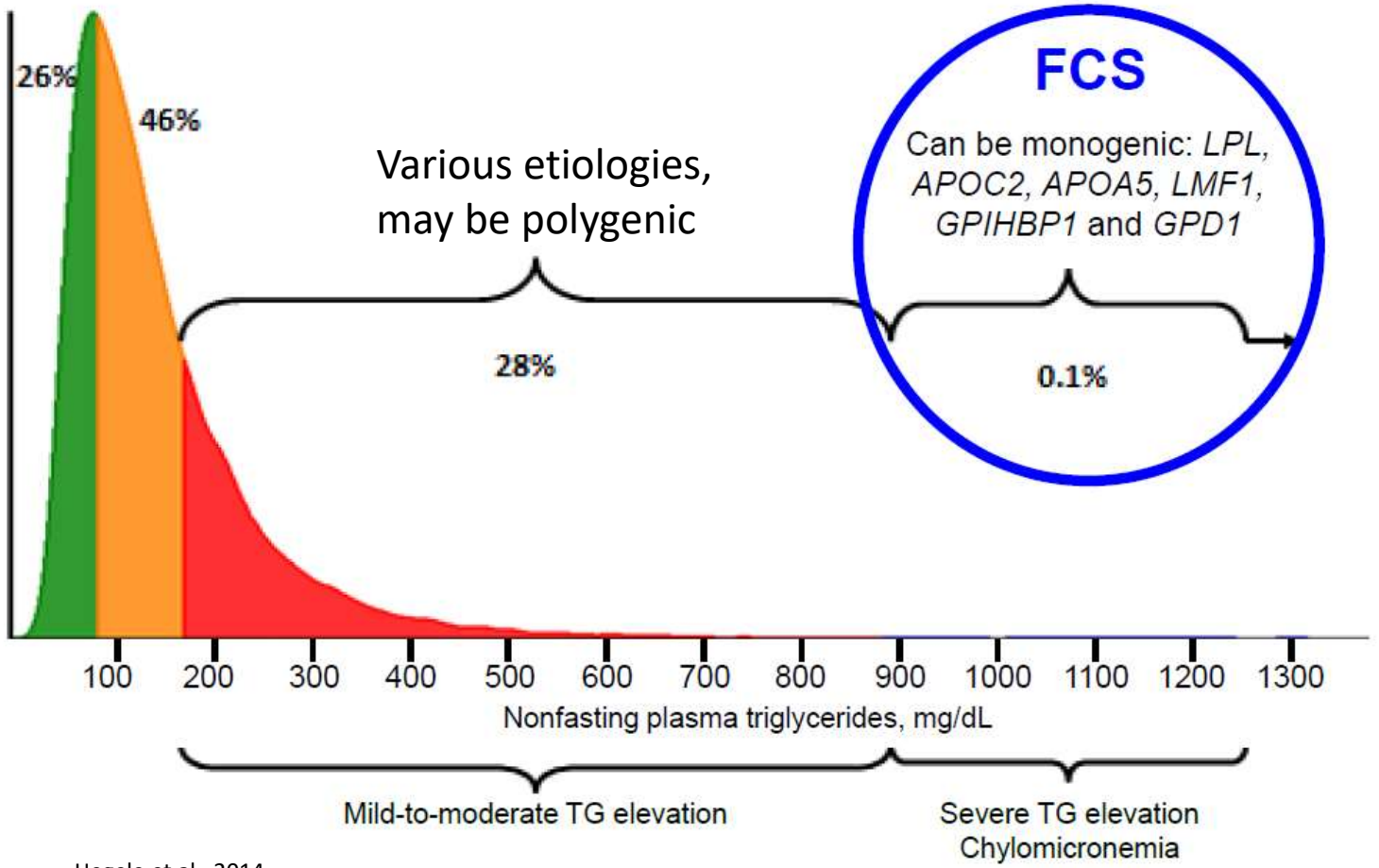
CV RNAi Programs

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

* Licensed from Arrowhead

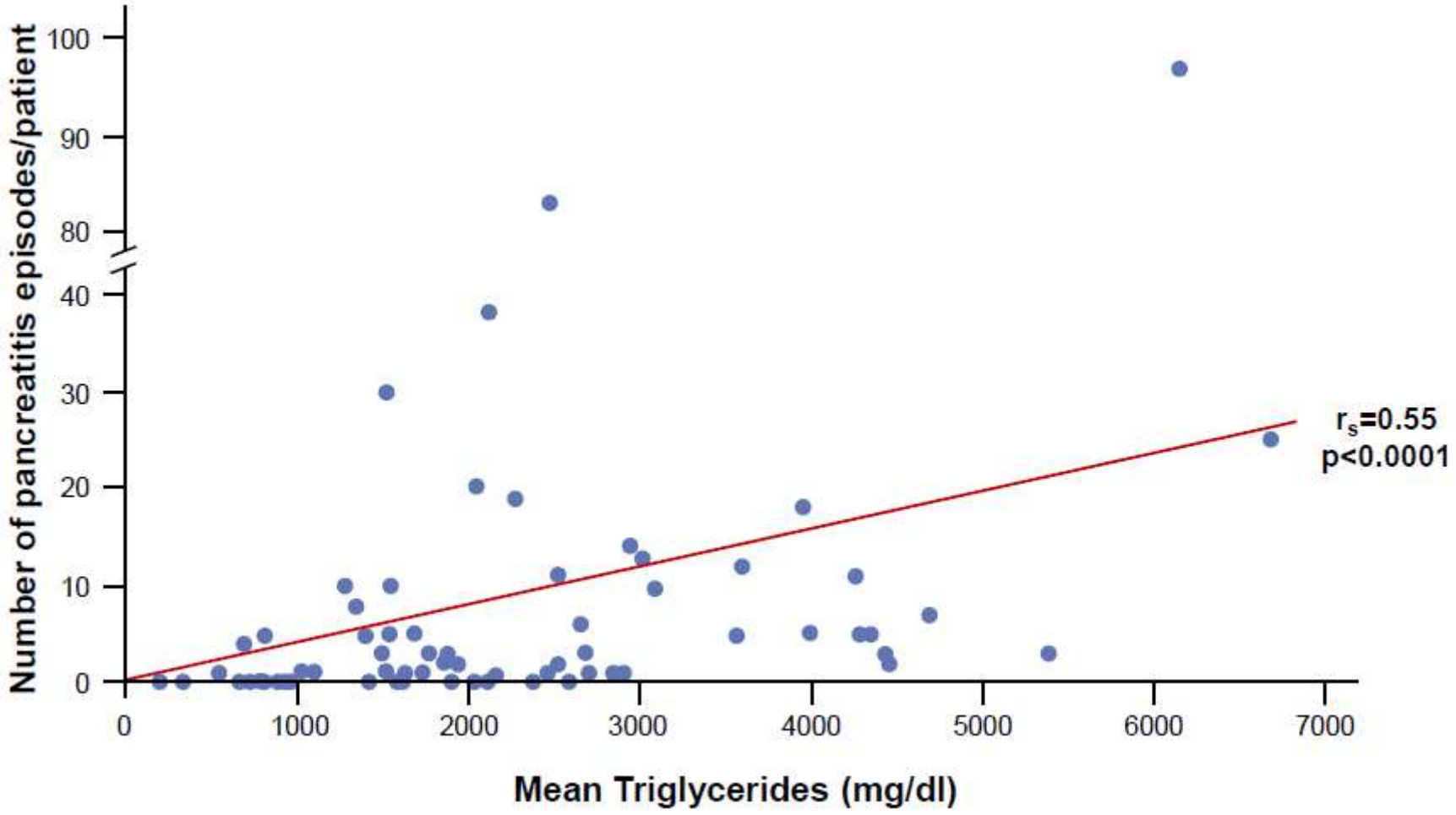
^ Licensed from Alnylam

Clinical Indications: Moderate to Severe Hypertriglyceridemia



Hegele et al., 2014

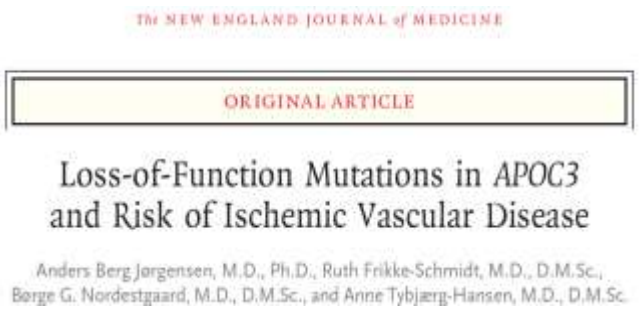
Triglyceride Levels Correlate with Frequency of Pancreatitis Attacks



Triglycerides Targets: Nothing Like When Nature De-risks for You!

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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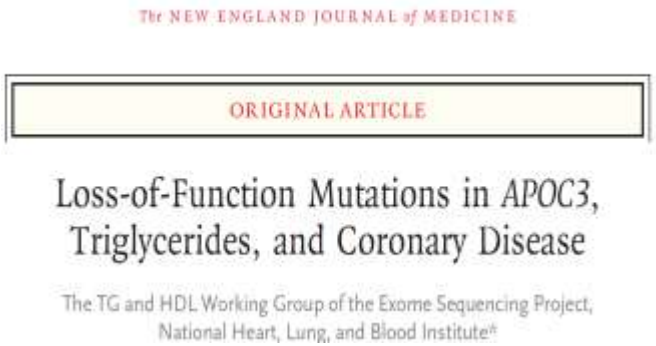
ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

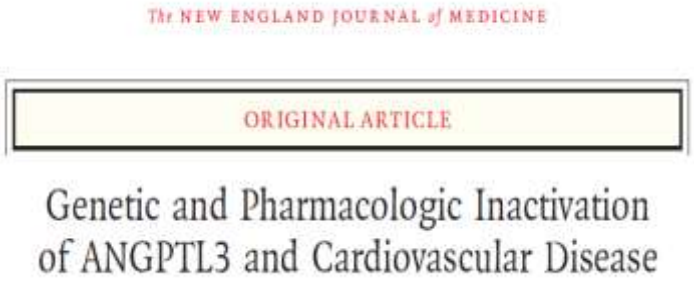
Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.


The NEW ENGLAND JOURNAL of MEDICINE

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 Genetic Validation and Clinical Data

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]

ARO-APOC3

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
   - Drugs used in conjunction with exercise, strict diet (< 20 grams of fat per day)
2. Reduce residual CVD risk following maximized LDL lowering

ApoC-III: What is it and Why is it Important?

- Apolipoprotein C3 (apoC-III) is a component of triglyceride rich lipoproteins (TRLs) including VLDL and chylomicrons and is a key regulator of triglyceride metabolism
- apoC-III is primarily synthesized in hepatocytes (80%)
- apoC-III regulates triglyceride (TG) levels through several mechanisms:
  1. Inhibits hydrolysis of TGs by lipoprotein lipase (LPL)
  2. Attenuates hepatic uptake of triglyceride containing remnant lipoproteins
  3. Promotes VLDL assembly and secretion by hepatocytes

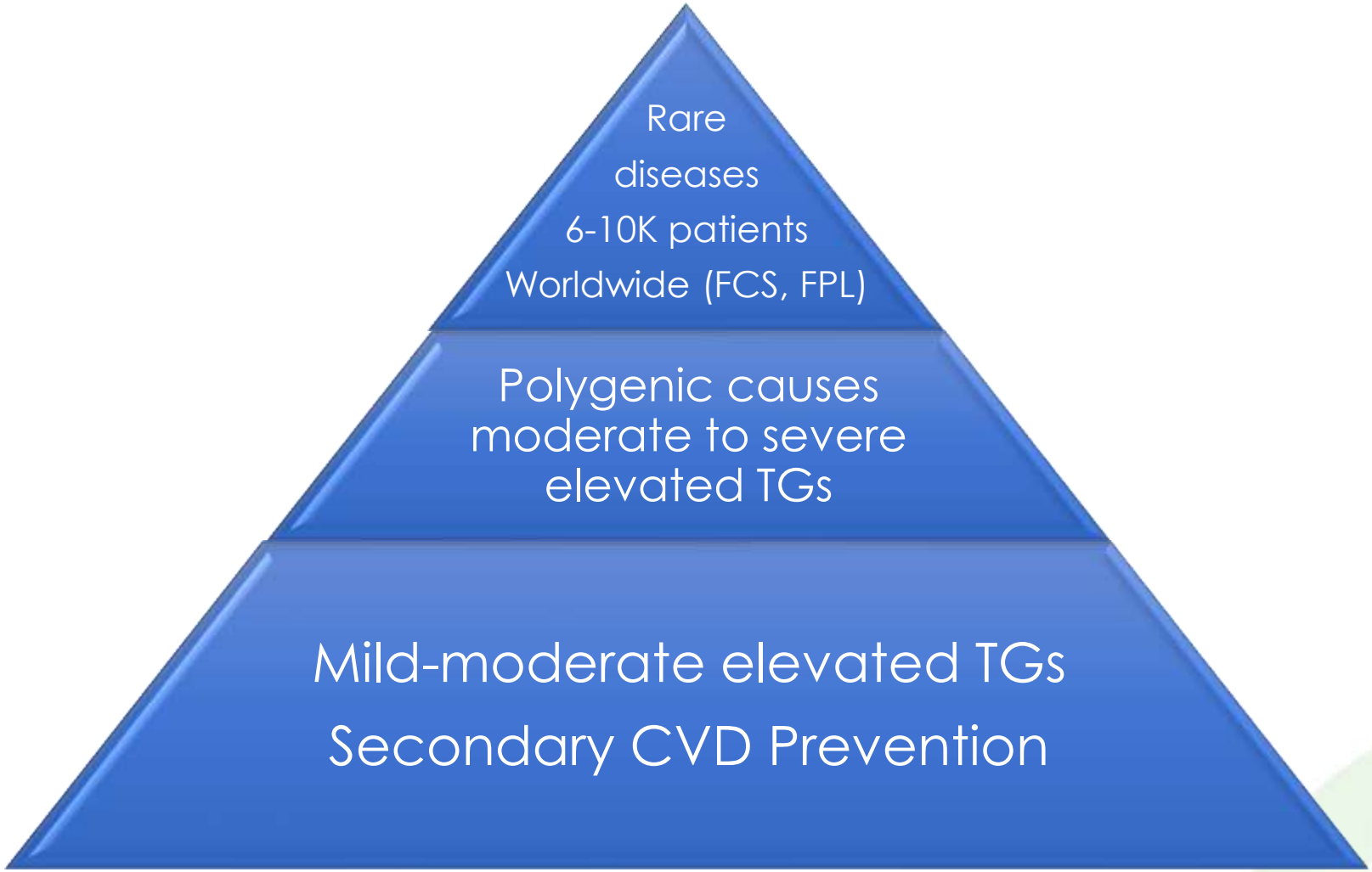
Familial Chylomicronemia Syndrome (FCS)

- 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

Familial Partial Lipodystrophy (FPL)

- FPL: mutations in genes responsible for efficient lipid storage in adipose tissue (e.g. *LNMA* gene, responsible for normal adipocyte development)
  - Multiple systemic manifestations
    - Very high triglycerides (>1000 mg/dL)
    - Pancreatitis
    - Insulin resistance
    - Hepatic steatosis
    - CVD
- Estimated 3,000-5,000 patients worldwide
- Very limited effective available therapy
  - Manage with low fat, high carbohydrate diet

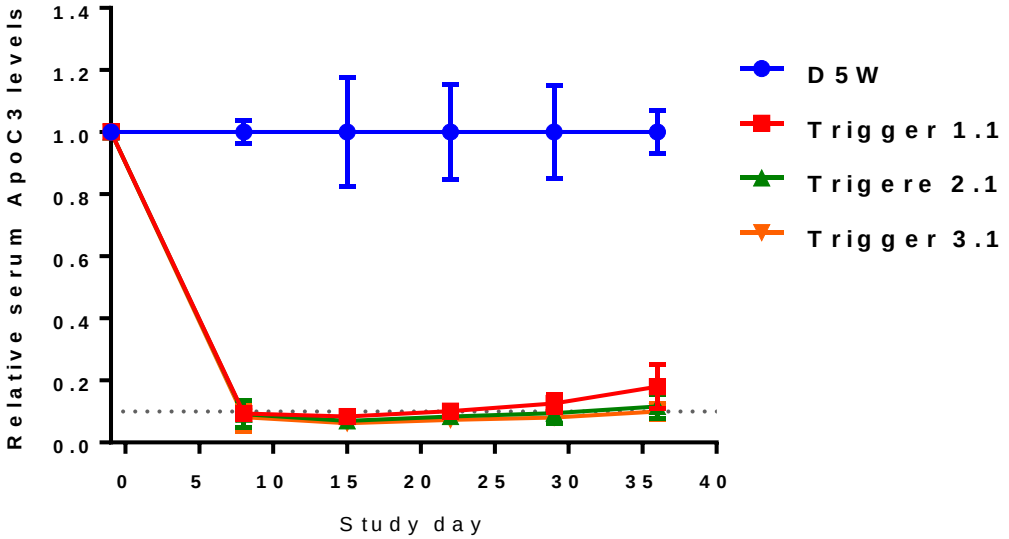
Clinical Indications for APOC3: Tiered by Size and Regulatory Complexity



RNAi for ApoC-III Brings Special Challenges

- Gene is small and has limited homology from rodents to humans/NHPs
  - ✓Solution – Human ApoC-III transgenic mouse for screening
- Lipid profiles in cynos are more like vegans than humans on a western diet
  - ✓Solution – High fructose fed rhesus study
- Proportion of ApoC-III coming from intestines appears much higher in NHPs than humans yielding confusing results from plasma ApoC-III measurements in cynos
  - ✓Solution – liver biopsy measurements in cynos (AHA abstract)

Single-dose Study in ApoC-III Transgenic Mice

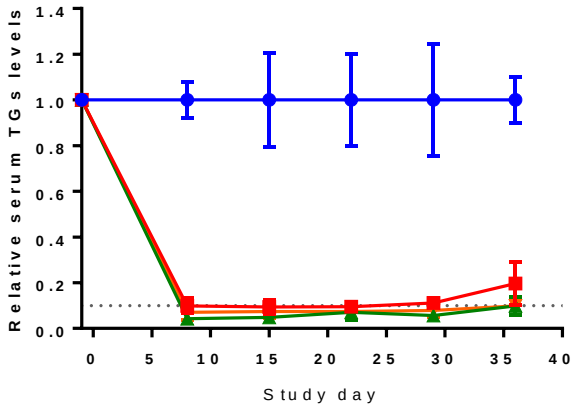


- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile

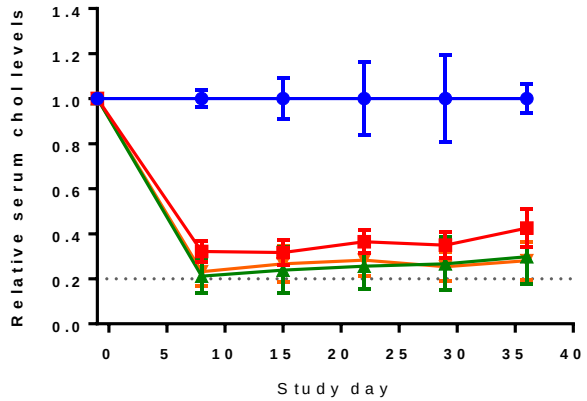
All dosed on study day 1 at 2 mpk

Data normalized to pre-dose and D5W control

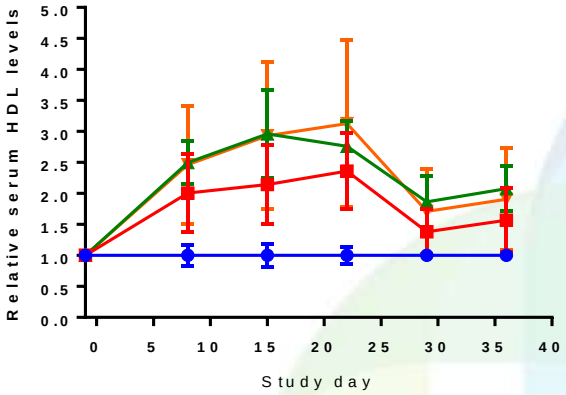
Trig



Chol



HDL

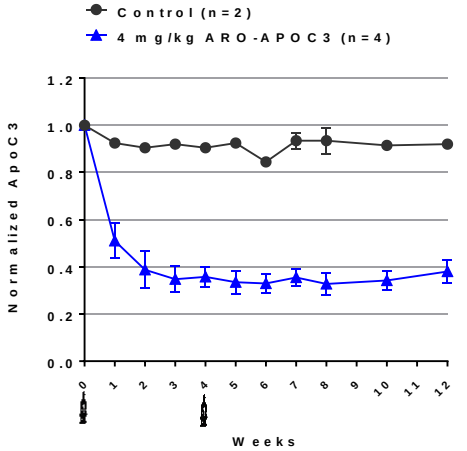


ARO-APOC3 in Dyslipidemic Rhesus Monkeys

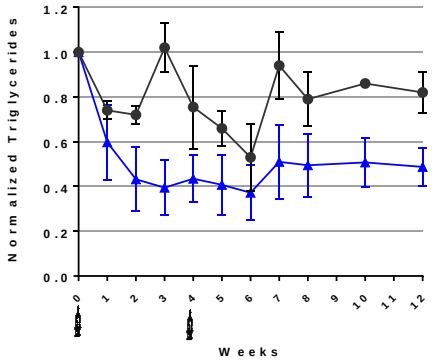
4 mg/kg ARO-APOC3 on Day 1 and 29

- Efficacy correlates to serum ApoC-III levels and severity of dyslipidemia

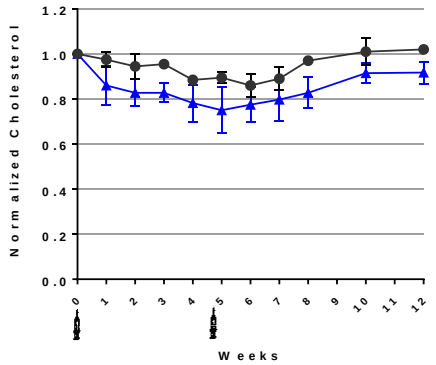
Serum APOC3



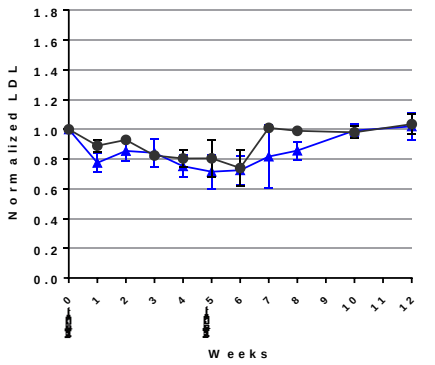
TG



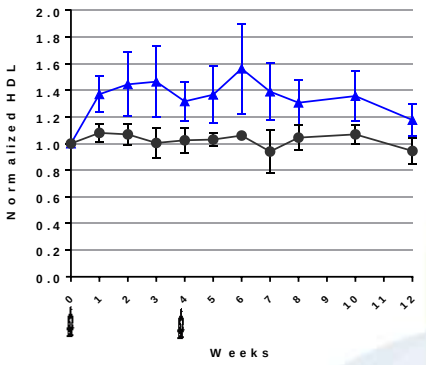
TC

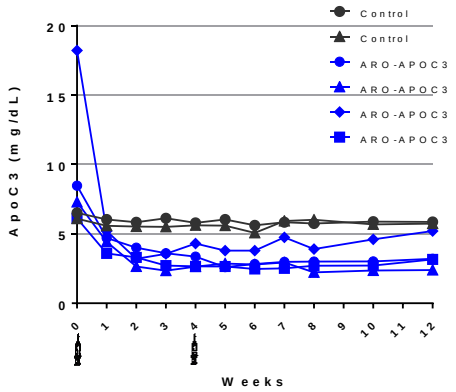


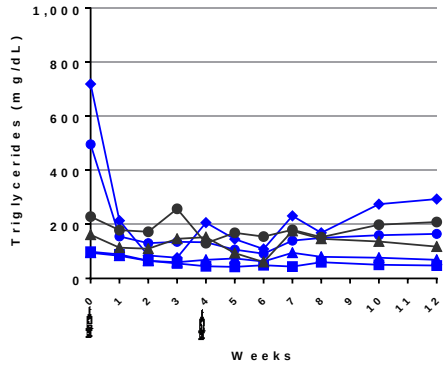
LDL-C

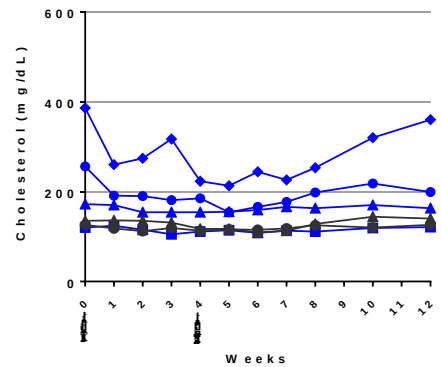


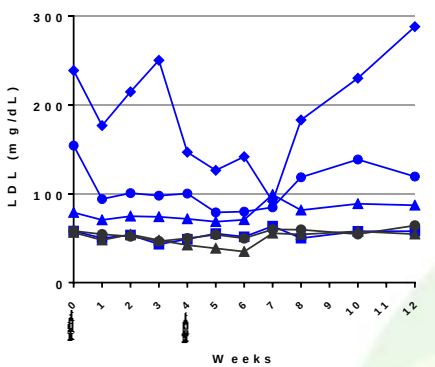
HDL-C

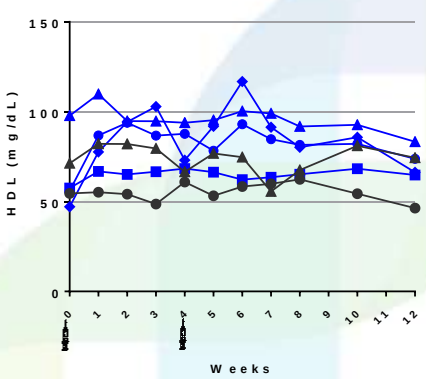












Plan for ApoC3

- AHA abstract Nov 12, 2018
- CTA planned for late in the year
- Plan for the protocol is to do single dose safety and PK in NHVs
- Multiple dose ranging in patients with elevated triglycerides
- Orphan indications would be FCS, FPL and polygenic elevated TGs with pancreatitis

Angiopoietin Like Protein 3

Ira Goldberg, M.D.
Bronfman Professor of Medicine
Chief of the Division of Endocrinology, Diabetes and Metabolism
New York University Langone School of Medicine

Two discoveries lead to the identification of novel regulators of plasma lipids

Angplt3 deficient mice

Hypobetalipoproteinemic patients

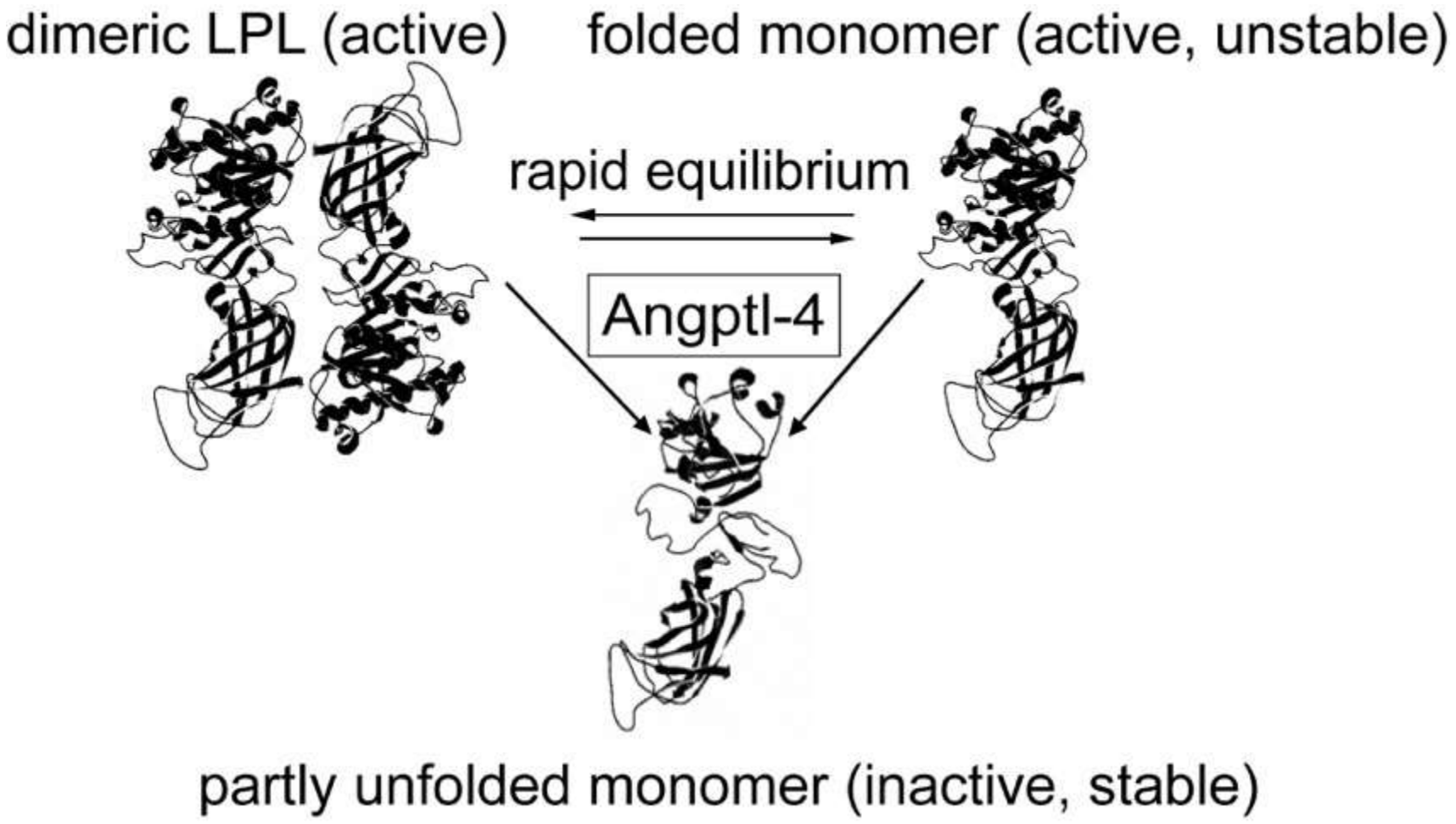
A new piece in the diabetes puzzle

Luciano Rossetti & Ira J. Goldberg

Nature Medicine, **volume 8**,112–114 (2002)

“Positional cloning has led to the identification of a liver-derived protein, angiopoietin-like protein 3, that is largely responsible for diabetic dyslipidemia in an animal model of type 2 diabetes”

Novel Regulators of Lipoprotein Lipase Activity



Angiopoietin-like proteins 3, 4, 8

Genetics affecting Triglyceride Levels Correlate with CVD Risk

- Coding Variation in **ANGPTL4, LPL**, and SVEP1 and the Risk of Coronary Disease Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. N Engl J Med. 2016 374(12):1134-44..
- Inactivating Variants in **ANGPTL4** and Risk of Coronary Artery Disease. Dewey FE, Gusarova V,…….....Shuldiner AR. N Engl J Med. 2016 Mar 24;374(:1123-33.

Angplt4 is highly regulated by PPAR transcription factors

Changes in its expression lead to altered LpL activity in adipose (not associated with changes in LpL mRNA or protein)

Angplt4 deficiency or inhibition leads to gut inflammation

Abetalipoproteinemia - Low cholesterol

65 year old woman

As a child was found to have difficulty eating foods with high fat and noted to have cholesterol levels below 50, most of which was HDL

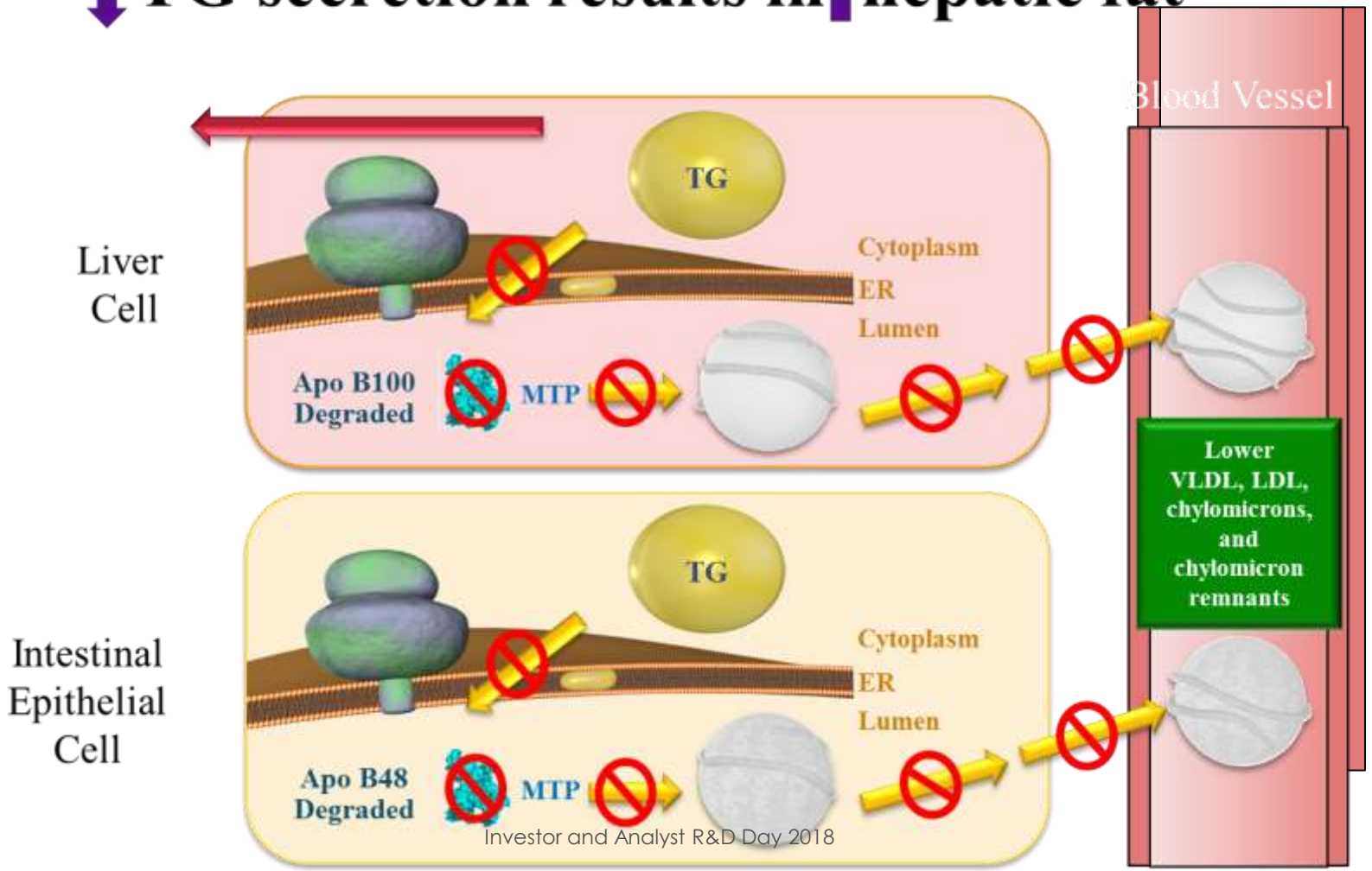
Very low levels of fat soluble vitamins (A, D, E, K) and begun on supplements

Increased LFTs and NAFLD

Now with bilateral lower extremity numbness and unable to detect pin prick below the ankles.

Effects Of MTP And ApoB Inhibition

↓ TG secretion results in ↑ hepatic fat



NYU

ONE CAUSE OF HYPOBETALIPOPROTEINEMIA IS NOT ASSOCIATED WITH NAFLD AND MIGHT LEAD TO NEW TREATMENTS OF HYPERLIPIDEMIA

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

SUMMARY

We sequenced all protein-coding regions of the genome (the "exome") in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for

N Engl J Med 2010;363:2220-7

Monoclonal antibodies and ASO to Angplt3 reduce circulating LDL

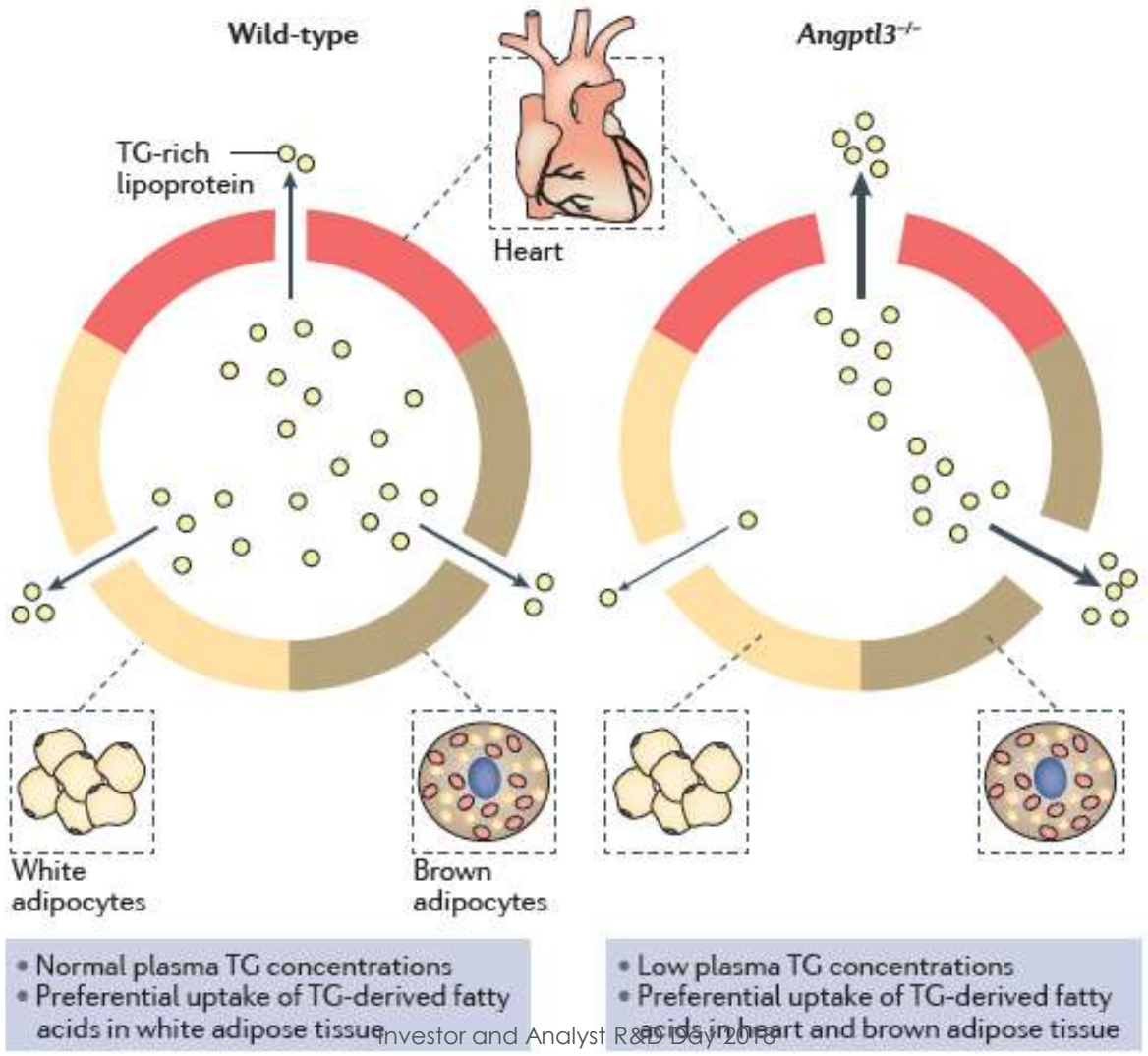
Genetic and Pharmacologic Inactivation of **ANGPTL3** and Cardiovascular Disease.
Dewey et al. **N Engl J Med**. 2017 377(3):211-221.
PMID:28538136

Cardiovascular and Metabolic Effects of **ANGPTL3** Antisense Oligonucleotides.
Graham et al. **N Engl J Med**. 2017 377(3):222-232.
PMID:28538111

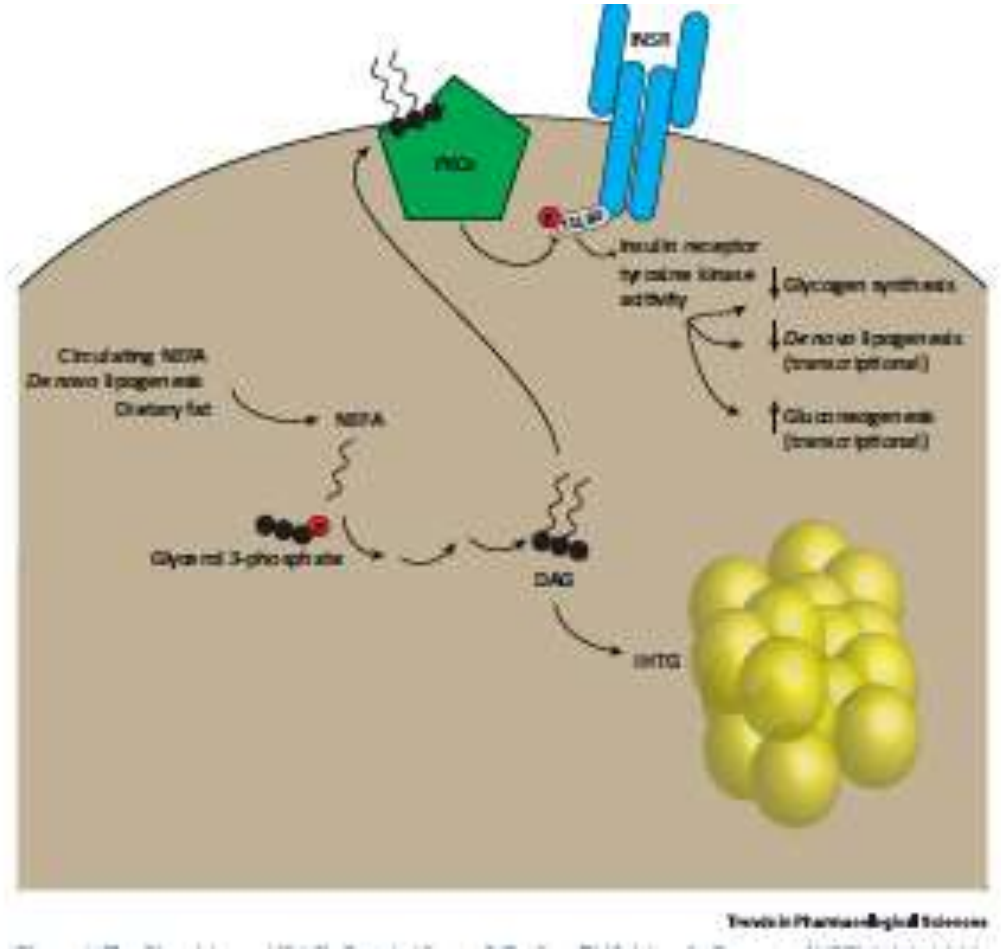
In Mice – Angplt3 Modulate Fat Distribution

Kersten, Nat Rev. 13: 731, 2017

Fed – Angptl3 Reduces TG uptake in heart and BAT



Will Angplt3 Inhibition Decrease NAFLD and Improve Diabetes by Increasing Peripheral FA Oxidation?



[Roles of Diacylglycerols and Ceramides in Hepatic Insulin Resistance](#)
Trends in Pharmacological Sciences, Volume 38, Issue 7, 2017, pp. 649-665
Max C. Petersen, Gerald I. Shulman

How does Angplt3 work?

Will it reduce TG levels in LpL deficiency?

Does it block liver production of lipoproteins (VLDL and LDL)?
Why?

How does it regulate cholesterol and LDL production?

ARO-ANG3

Bruce Given, M.D.
COO and Head of R&D

Clinical Indications for ARO-ANG3 Related to Dyslipidemias

Two primary indications to lower TGs with pharmacotherapy

- Polygenic patients with history of pancreatitis
- Secondary prevention for residual CVD risk following maximized LDL lowering

Familial hypercholesterolemia (FH) – non LDL receptor mechanism

One wild card indication

- *NASH*

APOC3, ANGPTL3 Genetic Validation and Clinical Data

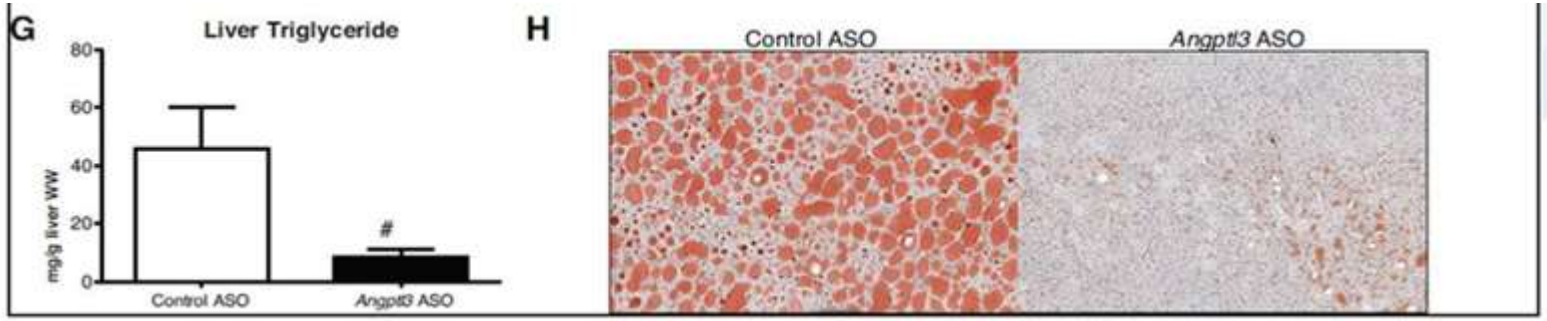
Mean or Median changes in lipid parameters after therapy and in heterozygotes and homozygotes for *APOC3 and ANGPTL3* LOF mutations versus non-carriers

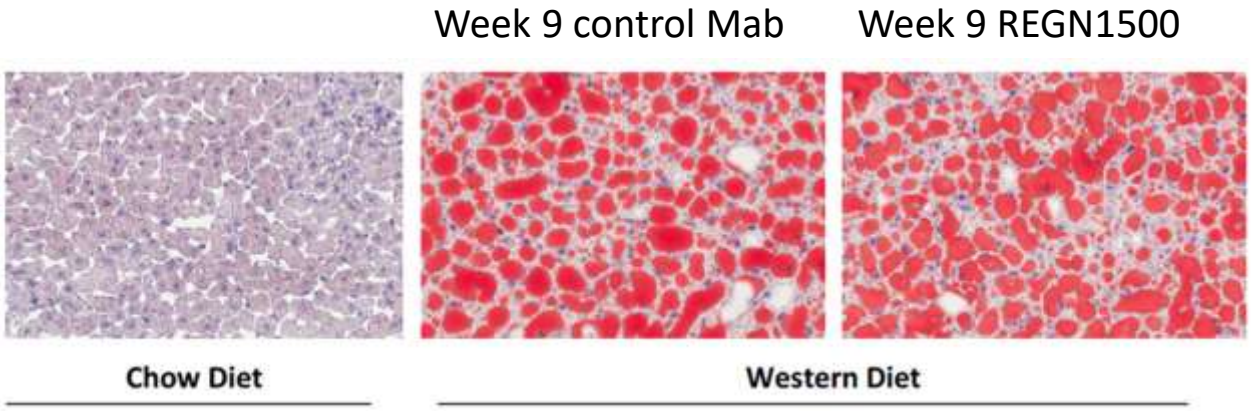
Metric (serum level)	*APOC3* deficient heterozygote[1]	*APOC3* deficient homozygote[2]	*APOC3* ASO inhibition[3]	*ANGPTL3* deficient heterozygote[4]	*ANGPTL3* deficient homozygote[4]	*ANGPTL3* ASO inhibition[6]	ANGPTL3 Mab Inhibition[7] 25 mg/kg IV
ApoC-III	-46%	-88.9%	-77.5%	NA	NA	-58.8%	NA
ANGPTL3	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)**

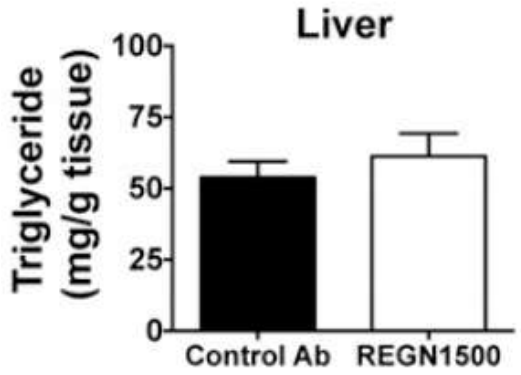
1. Triglyceride working group, NEJM 2014
2. Saleheen et al., Nature 2016
3. Graham et al., Circulation Research 2013. [Phase 1 MAD study, 400 mg dosed D1, D3, D5, D8, D15 and D22 with non-GalNac targeted ASO. Median % change 1-week after last dose in NHV population compared to baseline]
4. Minicocci 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]

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

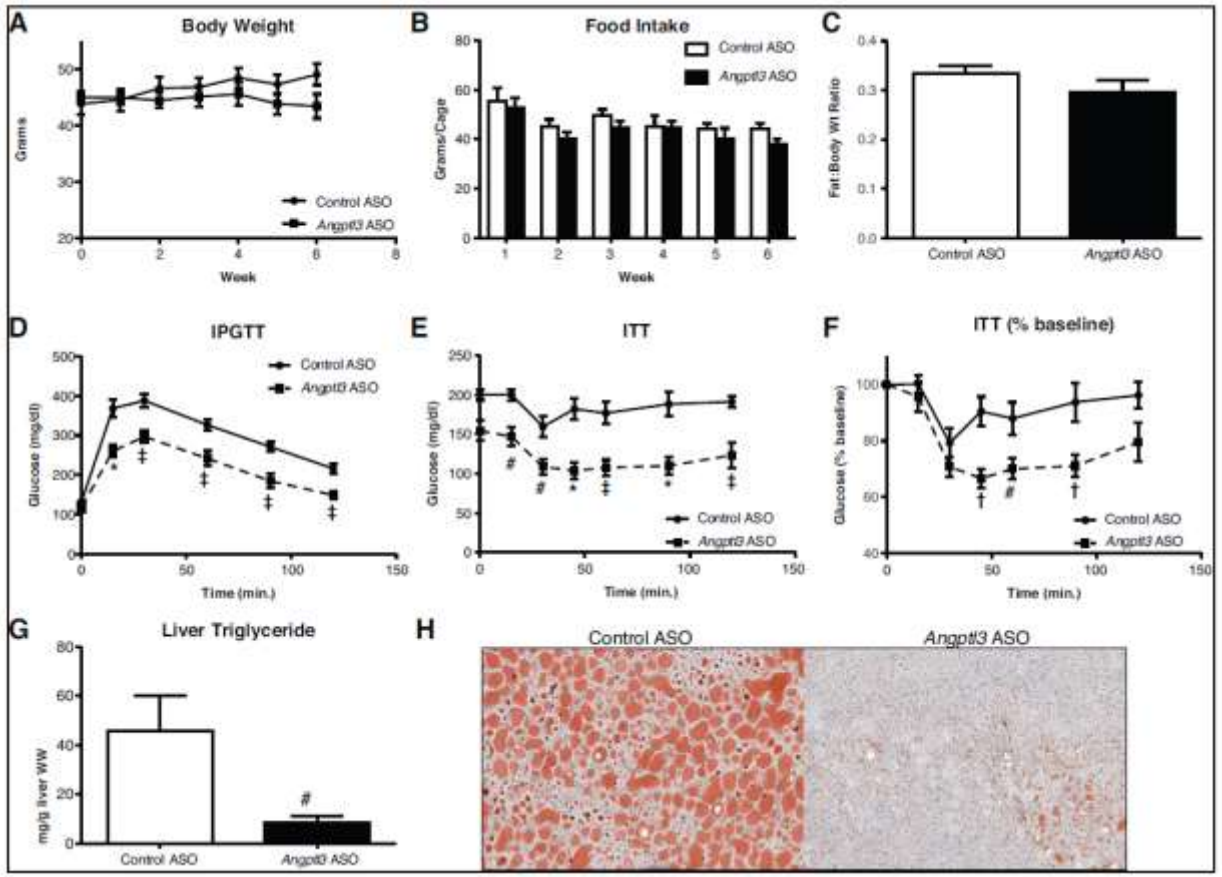






ANGPTL3 KD with ASOs Improve Insulin Resistance

WT mice with diet induced obesity treated with weekly 50 mg/kg (non-GalNac) anti-ANGPTL3 ASO x 6 week



No adverse changes in liver mass, transaminases or liver histopathology

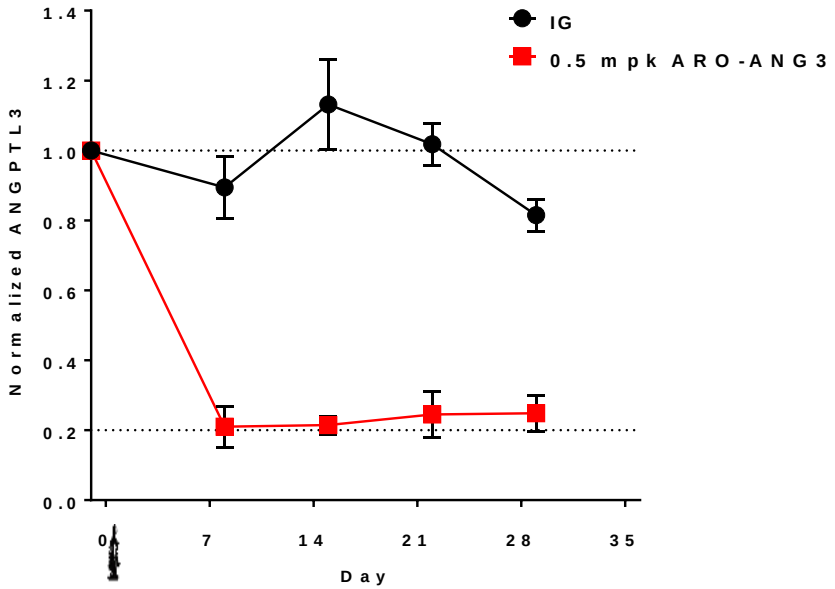
Graham et al., NEJM 2017

Developing ARO-ANG3 Brings Less Challenges

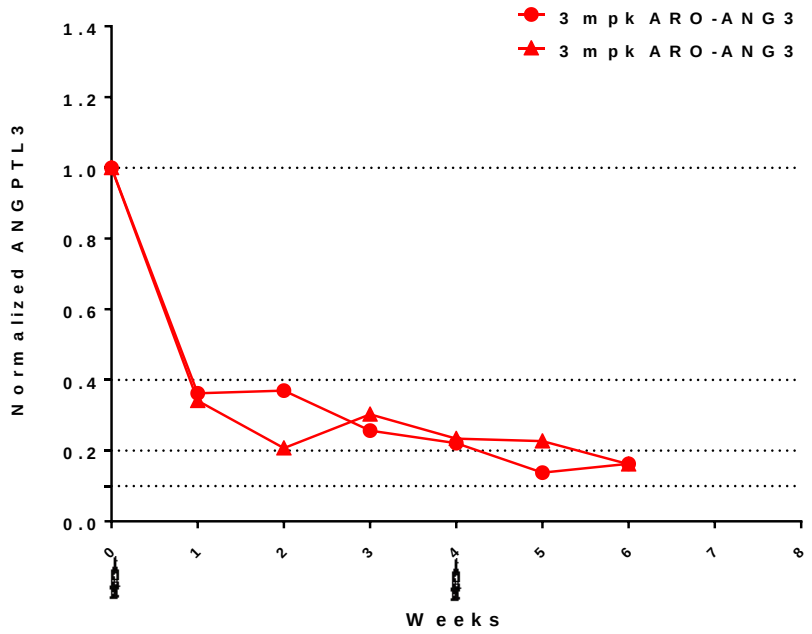
- Good homology between mouse, cyno and human genes
- Can use standard mouse models of dyslipidemias
- Very little, if any, production outside of the liver

ANGPTL3 Triggers – Wild Type Mice and Cynos

0.5 mpk single subQ injection in wild type mice



3 mpk subQ injection on days 1 and 29 in NHP



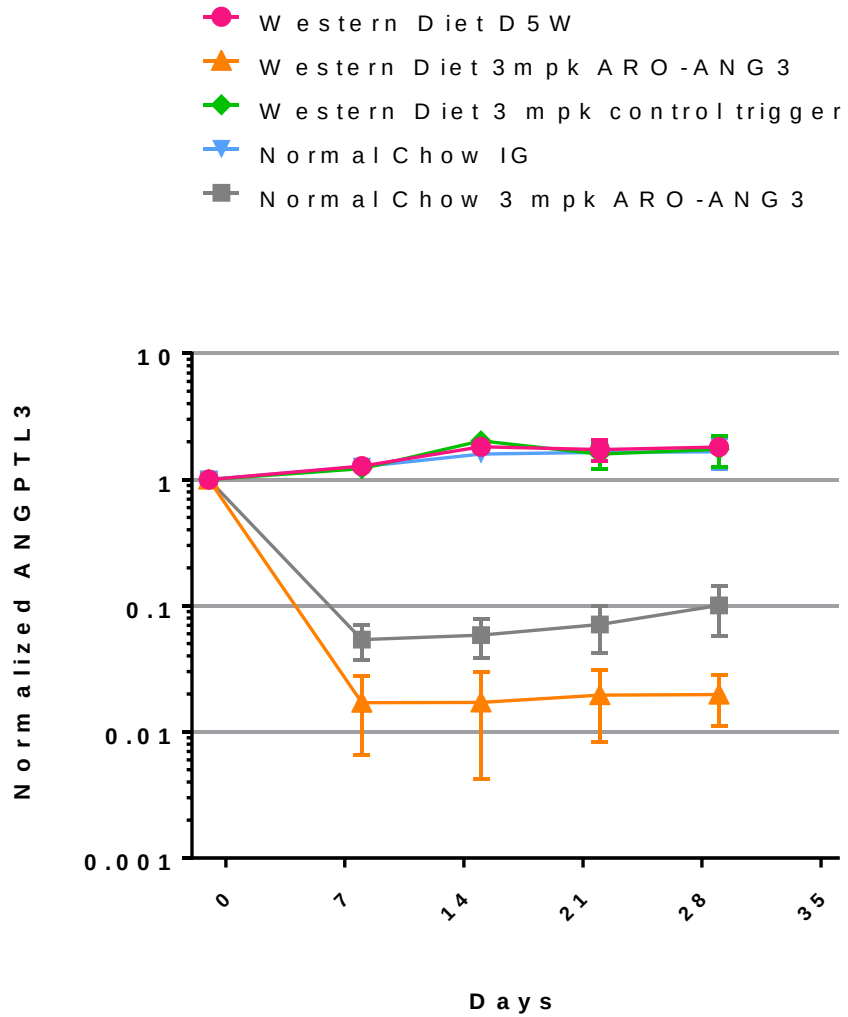
- 80% KD with good duration at 0.5 mpk dose in mouse study
- Single dose at 3mpk provided 80% KD in NHP

Mouse Disease Models

Mouse disease models for ANGPTL3

- LDLr $^{-/-}$ mice, western diet (example shown today)
- Diet-induced obese (DIO) mice, 60% fat diet
- Leptin receptor defective db/db mice

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

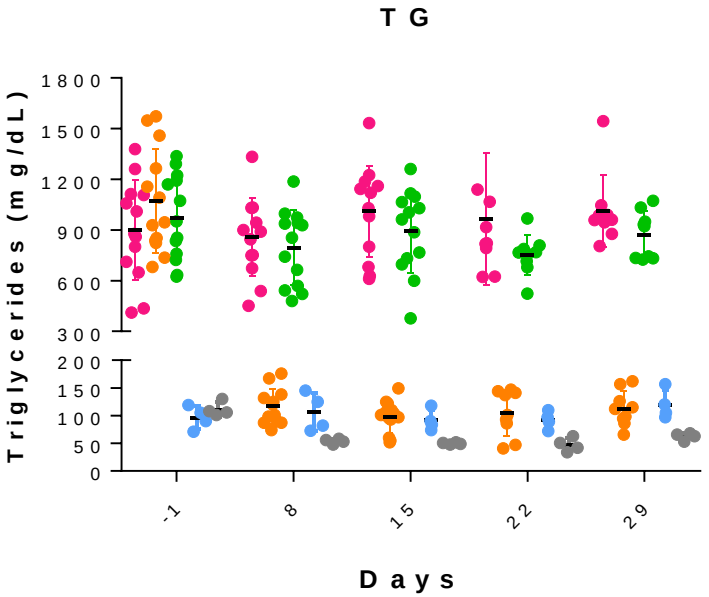


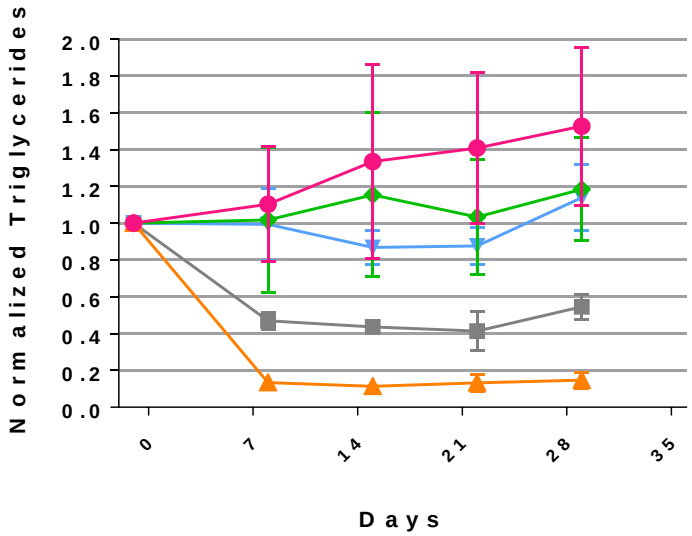
Max 94% KD

Max 98% KD

ARO-ANG3 Reduces Triglycerides in LDLr$^{-/-}$ mice

- Western Diet D5W
- Western Diet 3mpk ARO-ANG3
- Western Diet 3 mpk control trigger
- Normal Chow D5W
- Normal Chow 3 mpk ARO-ANG3

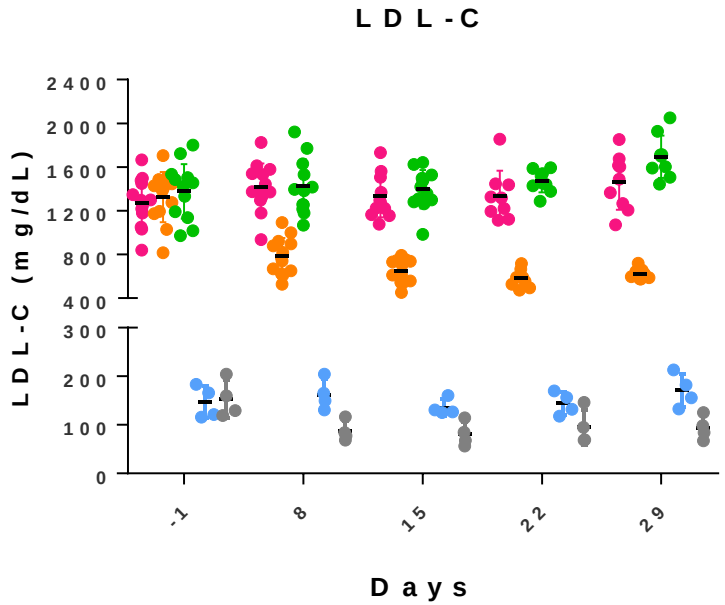


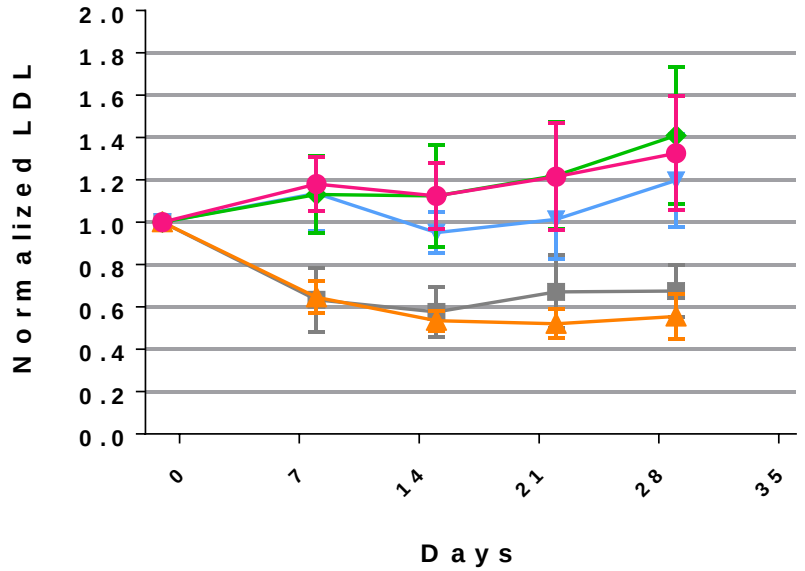


ARO-ANG3 Reduces LDL-C in LDLr$^{-/-}$ mice

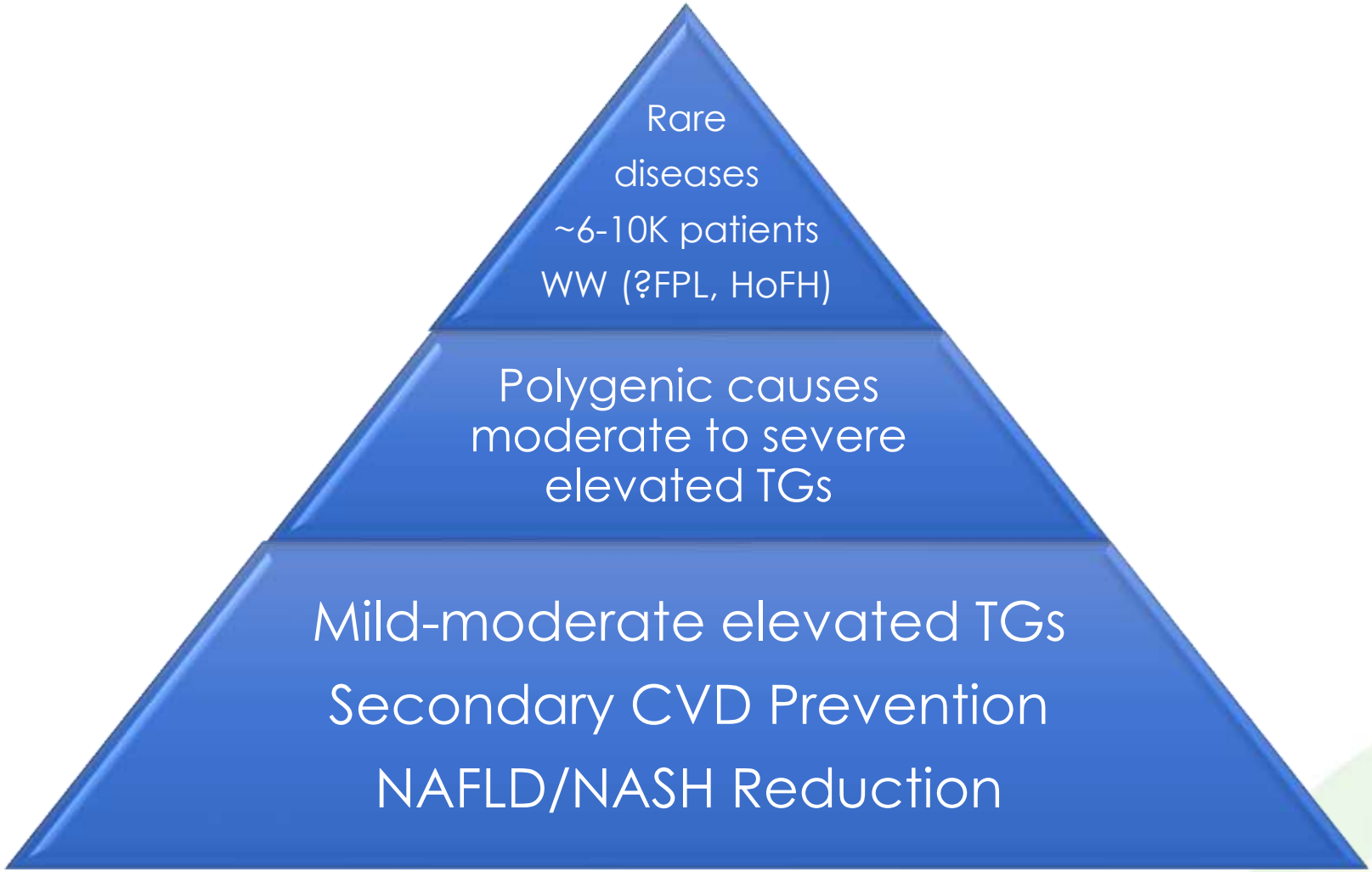
- Western Diet D5W
- Western Diet 3mpk ARO-ANG3
- Western Diet 3 mpk control trigger
- Normal Chow D5W
- Normal Chow 3 mpk ARO-ANG3

- 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





Clinical Indications: Tiered by Size and Regulatory Complexity



Plan for ARO-ANG3

- AHA oral presentation November 12, 2018
- CTA submitted on October 12, 2018
  - Single and multiple doses in NHVs with high enough TGs for dynamic range
- Multiple doses in special populations
  - NAFLD to assess effect on liver fat
  - Treated hypercholesterolemics to assess ability to knock down further
  - Familial hypercholesterolemia
  - Polygenic hypertriglyceridemia (>500 mg/dl)
- **Orphan indication would be familial hypercholesterolemia**
- Mass populations would be secondary prevention (independent of LDL but with added LDL benefit) and/or NASH

Investor and Analyst R&D Day 2018

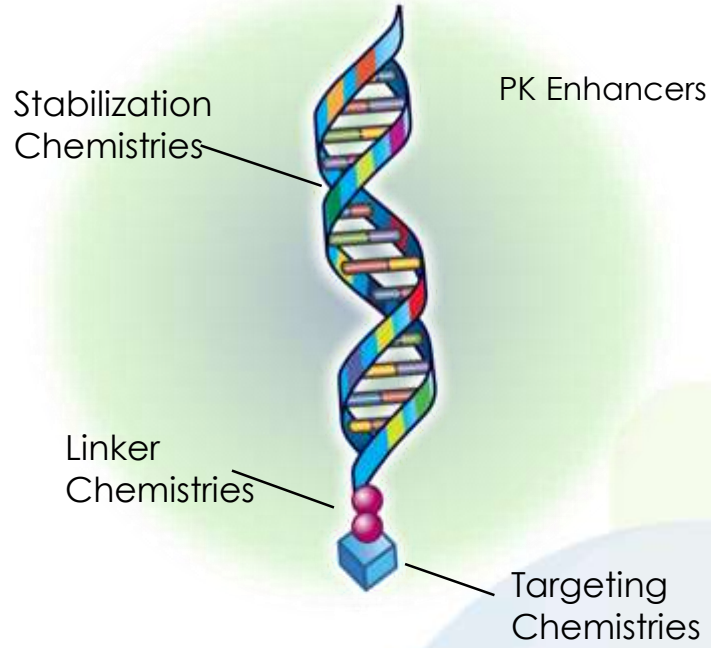
Targeted RNAi Molecule (TRiM™) Platform

Zhen Li, Ph.D.
Senior Vice President, Chemistry and Non-Clinical Development

arrowhead pharmaceuticals

TRiM™ - Potency, Activity, Durability and Safety

- Based on insights at molecular level of critical factors in each step of RNAi:
  - RISC loading, mRNA cleavage, trigger metabolism, off target interactions
- Enables us to uncover potent and efficacious sequences
  - Identify RNA triggers based on intrinsic characteristics
    - See what others have not
- Allows us to stabilize/improve sequences when needed
  - Achieve long duration and increase activity
- Enables us to have a wide therapeutic index on our compounds
  - Can afford to be *very stringent* in sequence selection
    - Through bioinformatic analysis, exclude sequences with potential off-target effects due to sequence homology and microRNA
    - Significant advantage for RNAi compared with small molecule therapeutics



Targeted RNAi Molecule

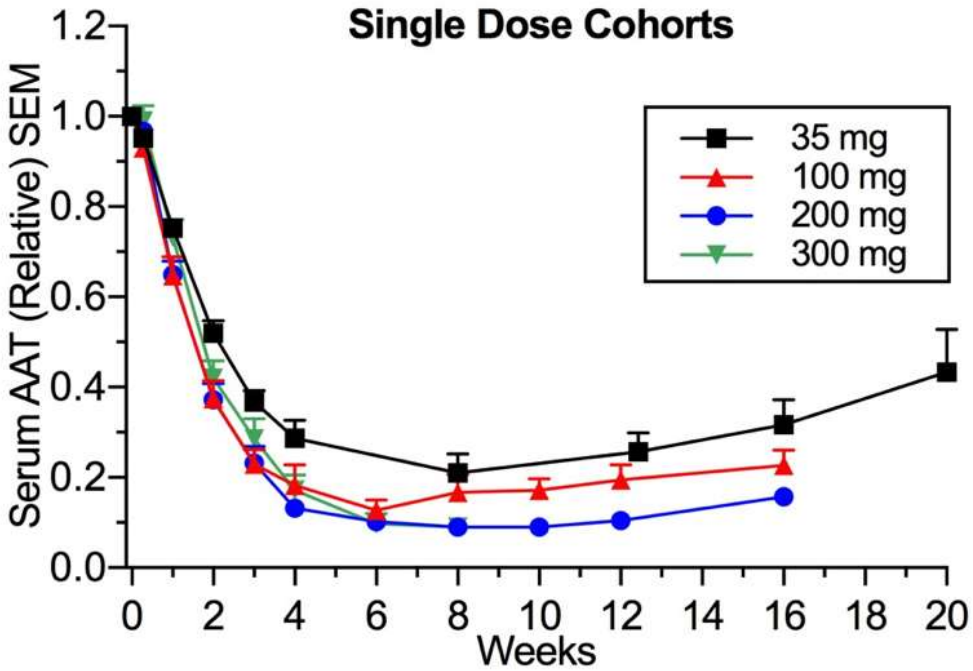
TRiM™ platform

Our Story Since Unveiling TRiM™ Platform in 2017

- Three candidates entered the clinic, and currently in phase 1/2 clinical studies
  - ARO-AAT (entering phase 2)
  - ARO-HBV (phase1/2)
  - AMG 890 (phase1, partnered with Amgen)
- Two candidates at clinical submission stage
  - ARO-ANG3
    - Completed GLP toxicology study, **filed CTA**
  - ARO-APOC3
    - Completed exploratory toxicology studies, in GLP toxicology study now
- Our insight enables speed and high success rates in our development programs
  - All candidates (clinical and pre-clinical) are potent, efficacious and have been well tolerated
  - No candidates failed at GLP toxicology studies stage or exploratory tox stage (100% success rate to date)

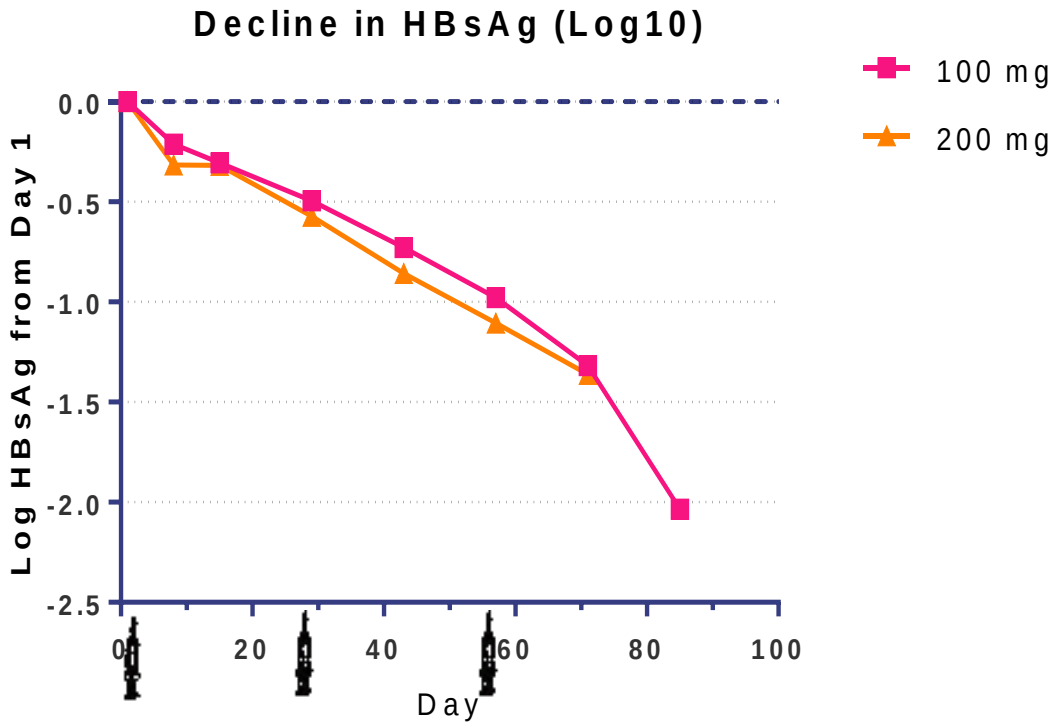
ARO-AAT Clinical Data Shows Platform Promise

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



- **Safety**
  - No SAEs
  - 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-HBV Carries the Same Message



HBsAg Reduction with ARO-HBV After 3 monthly Doses

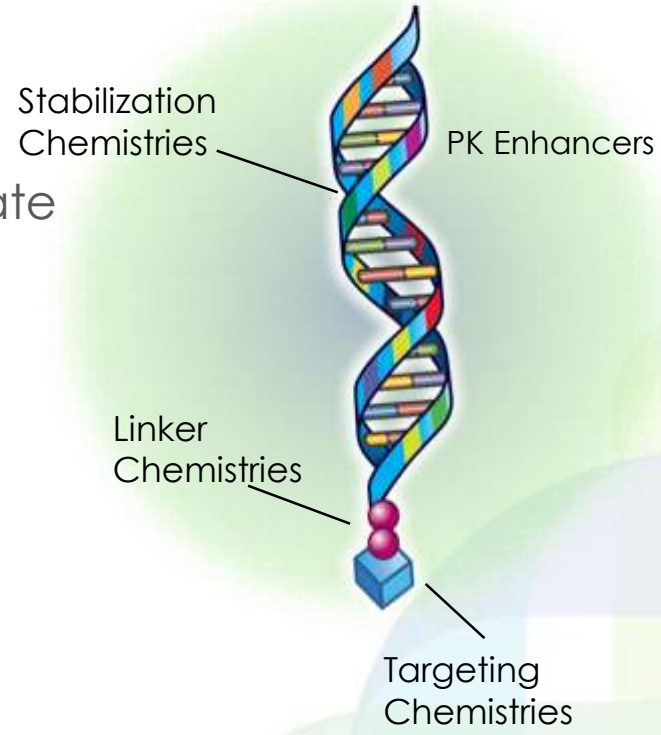
- Safety
  - No SAEs reported
  - No subject dropouts
  - Mild injection site AEs occasionally reported (~11% of injections)
  - No pattern of adverse laboratory changes reported

TRiM™ for Extrahepatic Targets

TRiM™ Platform for Extrahepatic Delivery

Requires all components of TRiM™ working synergistically

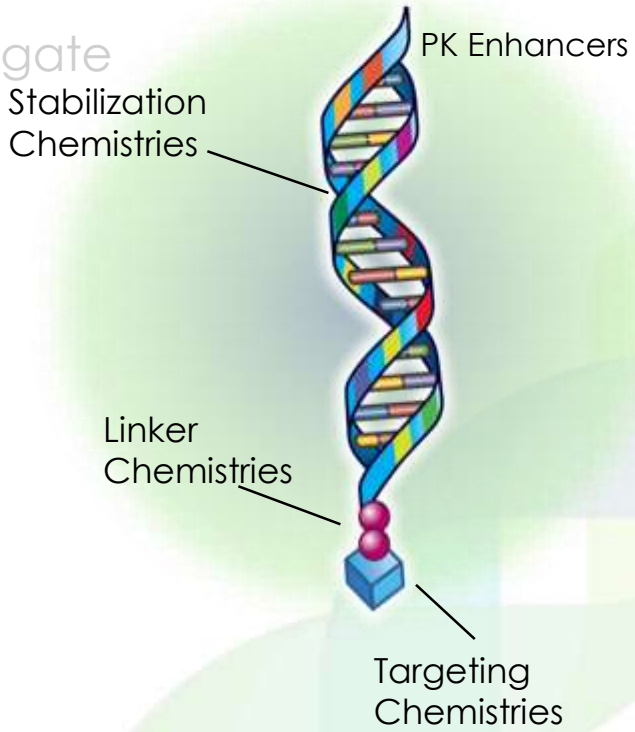
- RNAi sequence selection and optimization
  - Paramount importance
  - Determines potency, specificity (off-target)and stability of the conjugate



TRiM™ Platform for Extrahepatic Delivery

Requires all components of TRiM™ working synergistically

- RNAi sequence selection and optimization
  - Paramount importance
  - Determines potency, specificity (off-target)and stability of the conjugate
- Ligand/receptor pairs discovery and development
  - Critical for RNAi delivery
    - Enable tissue specific, cell specific delivery and maximum potency
    - Require deep expertise in medicinal chemistry and biology for ligand discovery and SAR
- PK enhancers
  - To maximize circulation time for ligand/receptor interaction
- Linker optimization - SAR here also can improve activity

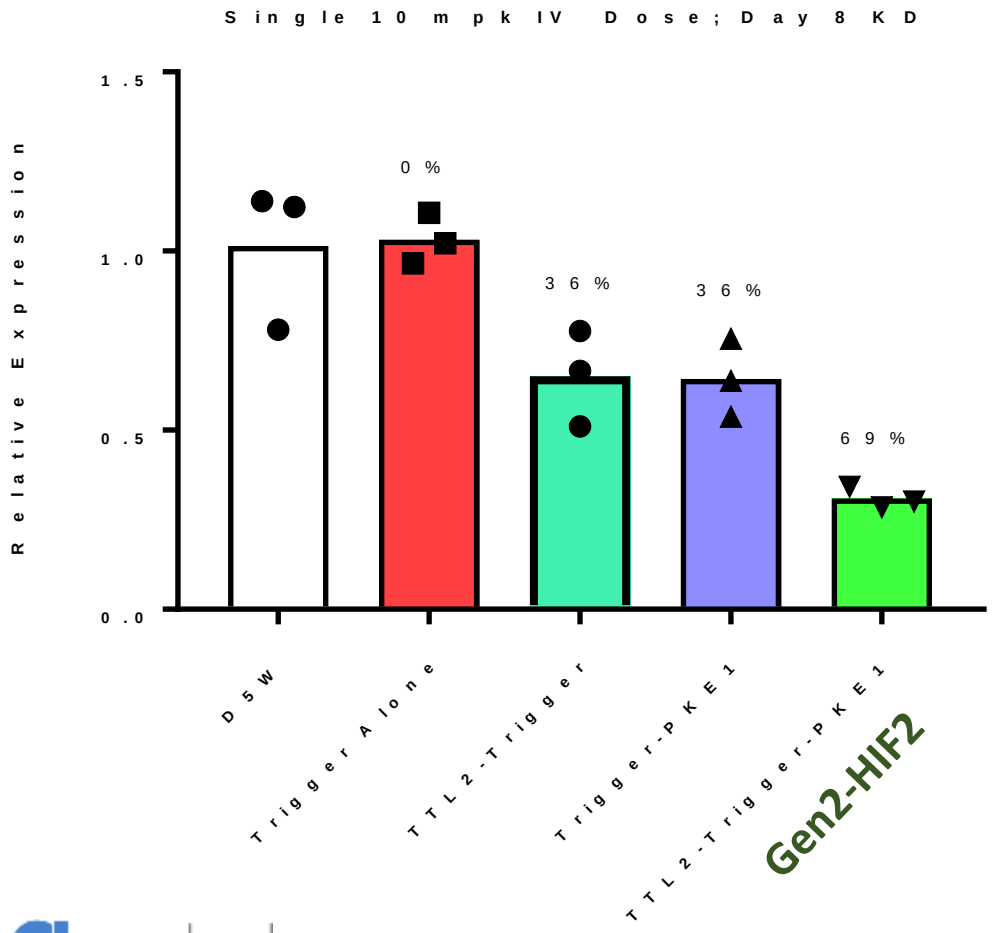


Potency, Activity, Durability and Safety

ARO-HIF2
For the treatment of ccRCC (clear cell renal cell carcinoma)

Ligand/Receptor and PK Enhancers

A498 Tumor Model: Hif2a Expression

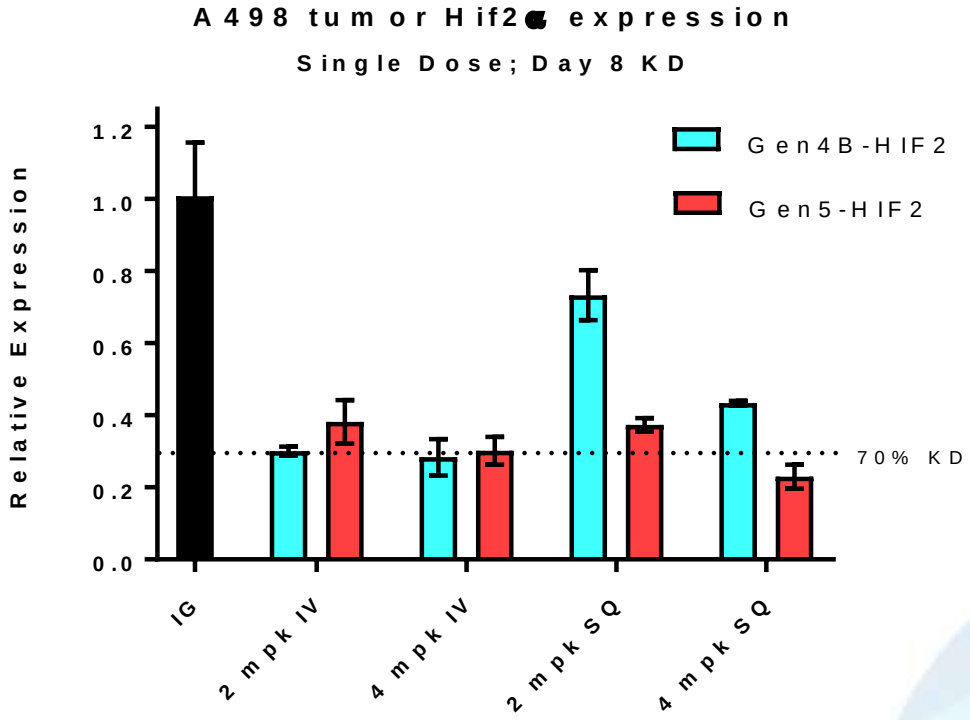


- Trigger alone – no delivery
- Clear ligand effect observed
- PK enhancer plays critical role

Demonstrated Synergistic Effects of Ligand and PK Enhancer

Increasing Potency and Enabling Subcutaneous Administration

- Subcutaneous vs IV ROA
- ARO-HIF2 demonstrates equal or better potency via subcutaneous administration compared with IV
- Demonstrates the power of TRiM™ platform

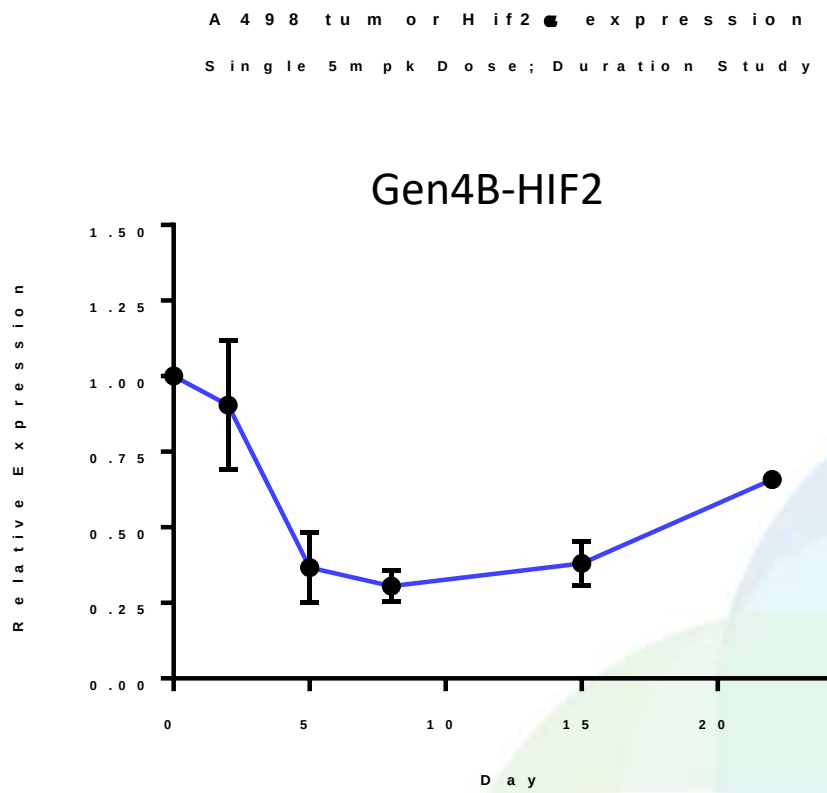


Achieved Efficient silencing of an Extrahepatic Target gene via Subcutaneous Administration

Wide Therapeutic Index and Good Durability

- **Safety**
- Exploratory toxicity study in rats (non-GLP) with Gen4B-HIF2
  - 3 daily doses of *30 mpk each* given over 5 weeks (total of 15 doses) by IV injection
    - Compared with dosing in TGI study – 5 mpk, twice a week for 2 weeks, followed by weekly doing of 5 mpk for 3 weeks (total of 7 doses of 5 mpk each)

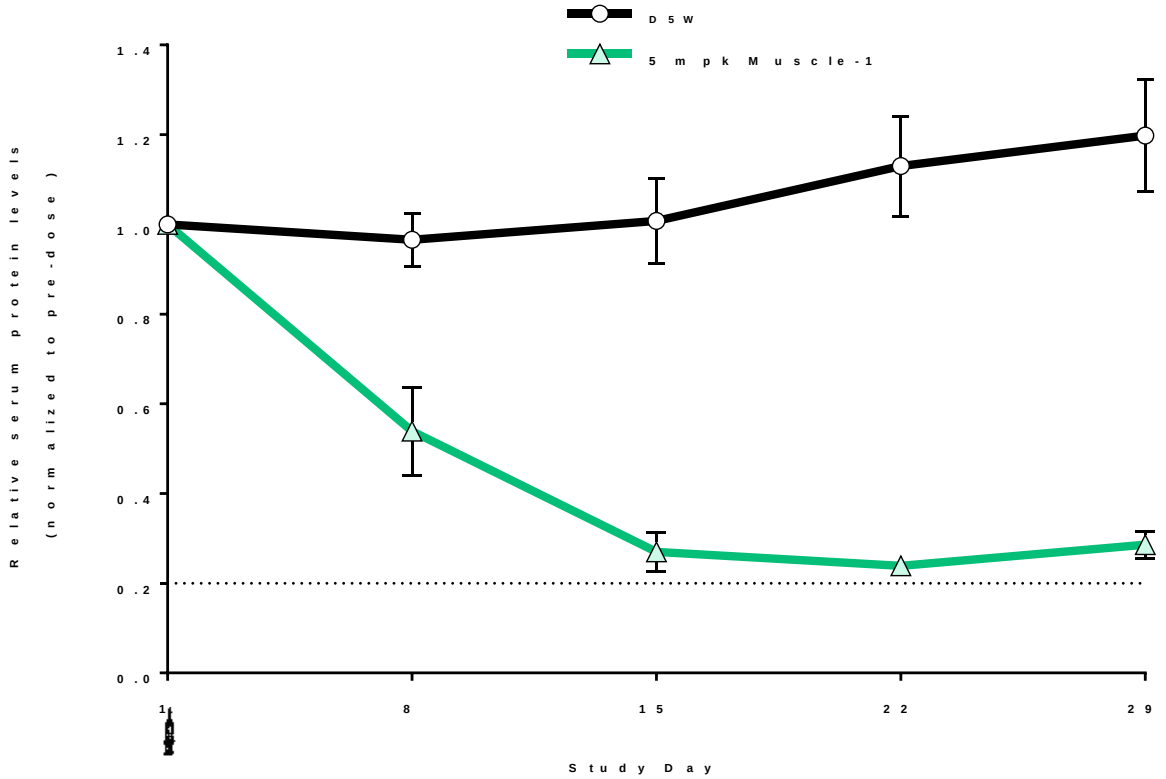
- **Durability**
  - About 10-day duration



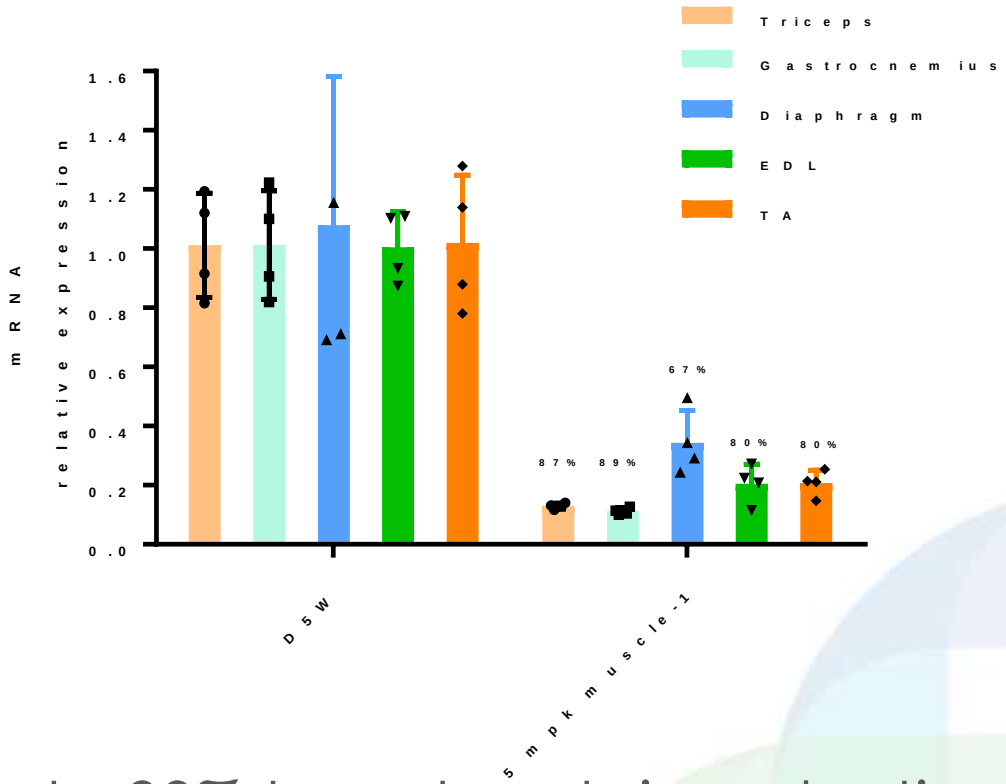
No significant findings or indications of toxicity observed

New Extrahepatic Tissue - Muscle

Deep Knockdown across Multiple Muscle Types



mRNA expression in muscle tissues harvested on day 29



- Single dose of 5 mpk produced close to 80% target protein reduction and efficient mRNA knockdown

Summary and Next Steps

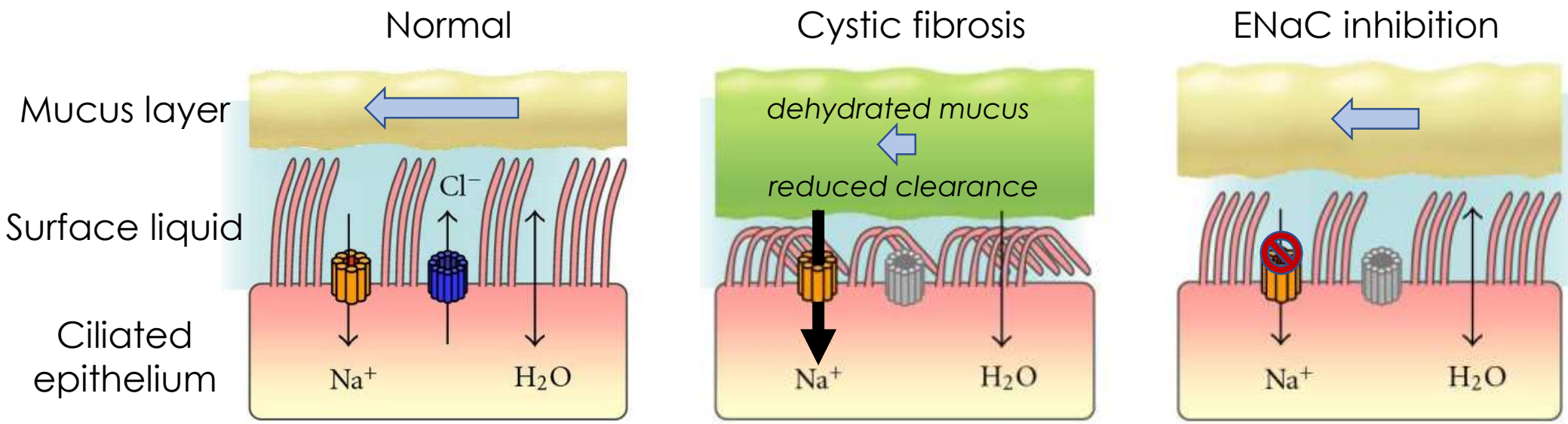
- TRiM™ platform demonstrates versatility for both hepatic and extrahepatic targets
  - Potency, efficacy, durability and safety
  - Speed and high success rate
- Hepatocyte targets
  - Expertise in RNAi chemistry and biology
  - We have yet to encounter a hepatocyte gene that we could not knock down effectively and with wide therapeutic index
- Extrahepatic targets
  - Requires all TRiM™ platform modules to be fully optimized
  - Expertise in uncovering ligand/receptor pairs
  - Expertise in ligand designs to enable maximal uptake through endocytosis
- Successful extrahepatic, systemic delivery of RNAi triggers via IV and subcutaneous administrations in ccRCC

Every tissue is a new frontier in RNAi – we can potentially target any gene in any tissue using the power of RNA interference

ARO-ENaC Gen 1

Erik Bush, Ph.D.
Senior Director, Extra-Hepatic Targeting

Increased Epithelial Sodium Channel (ENaC) Activity Promotes Mucus Dehydration in Cystic Fibrosis Lung Disease



- Increased ENaC channel activity is seen with all cystic fibrosis genotypes
- Loss-of-function alleles of ENaC subunits increase mucociliary clearance, resulting in milder CF phenotypes
- Gain-of-function alleles of ENaC subunits worsen CF phenotypes
- ENaC inhibitors promise genotype-agnostic therapeutic approach for all CF patients, including those with Class I mutations that produce no CFTR protein
- Common mechanism in other muco-obstructive lung diseases like COPD, bronchiectasis & asthma

Inhaled Small Molecule ENaC Inhibitors Limited by On-Target Renal Toxicity and Short Duration of Action in Lung

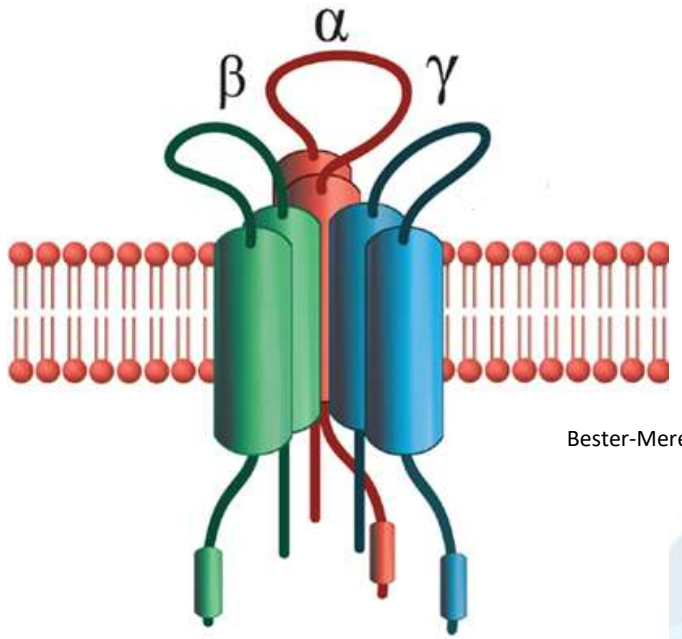
Parion, Gilead, Vertex, Amgen, AZ, Novartis, BI

- Inhaled small molecule inhibitors transiently improve lung clearance, but are rapidly absorbed
- Systemic exposure results in renal ENaC inhibition and hyperkalemia

Acute Hyperkalemia Associated with Inhalation of a Potent ENaC Antagonist: Phase 1 Trial of GS-9411

Thomas G. O'Riordan, MD,[1] Karl H. Donn, PhD,[2] Peter Hodsman, MD,[3] John H. Ansede, PhD,[2] Terry Newcomb, PhD,[1] Sandra A. Lewis, MS,[1] William D. Flitter, PhD,[1] Vicki Shigekane White, BS,[1] M. Ross Johnson, PhD,[2] A. Bruce Montgomery, MD,[4] David G. Warnock, MD,[5] and Richard C. Boucher, MD[6]

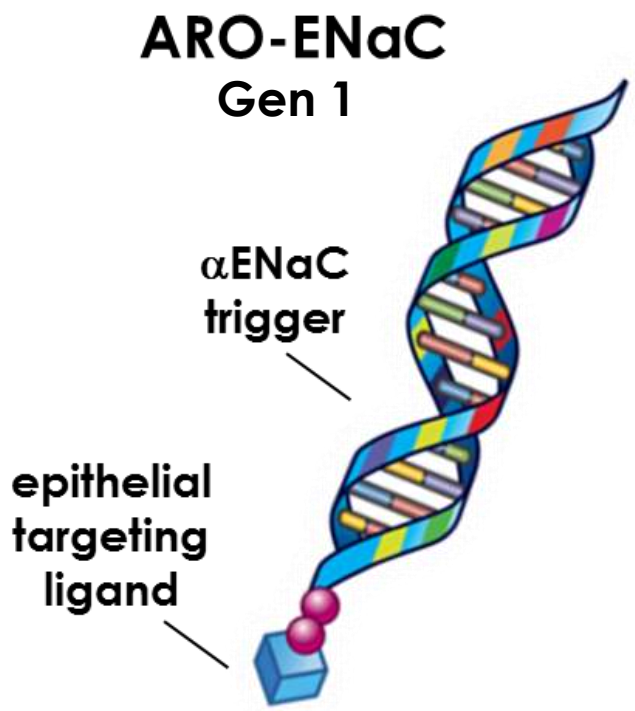
"The rational design of new ENaC blockers must include not only the provision of a sustained increase in mucociliary clearance, but also the avoidance of clinically significant renal exposure…"



Bester-Meredith 2015

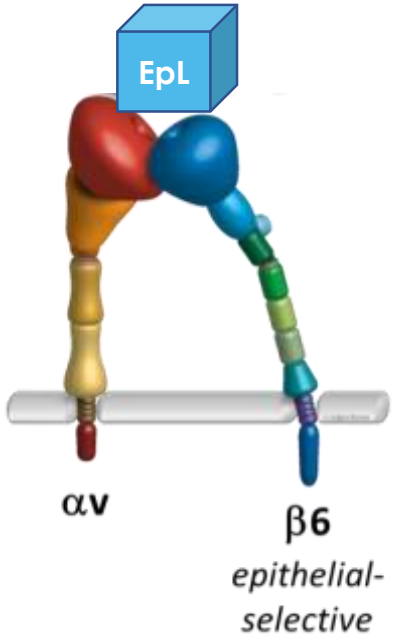
Targeted RNAi trigger delivery will allow durable, renal-sparing ENaC inhibition in the lung

TRiM™ Platform for Pulmonary Delivery



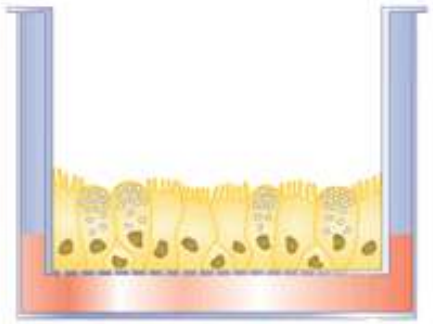
EpL = integrin αvβ6 ligand

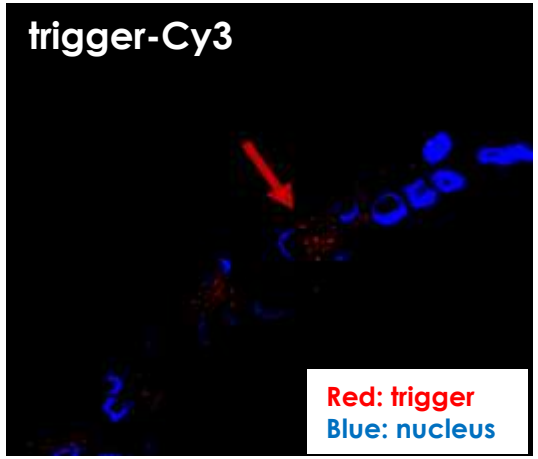
- Optimized RNAi trigger sequence vs. αENaC mRNA
- Integrin αvβ6 ligands facilitate uptake and endocytosis of triggers by pulmonary epithelium

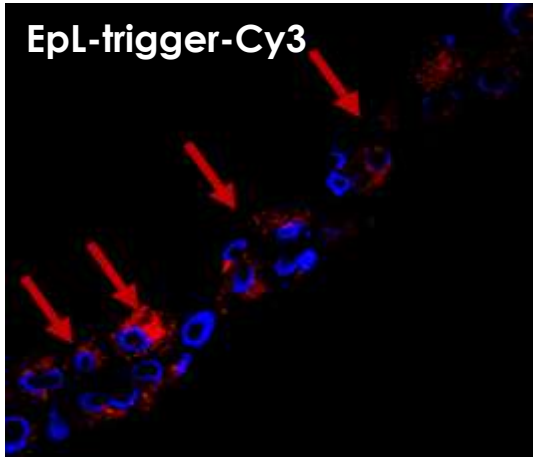


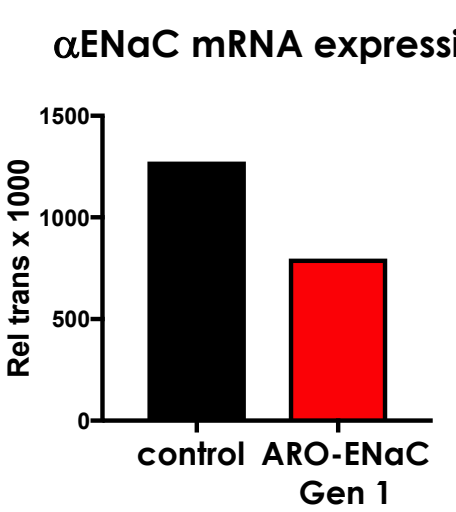
EpL-trigger Conjugates Internalized by Human Bronchial Epithelial Cells and Reduce αENaC Expression and Activity

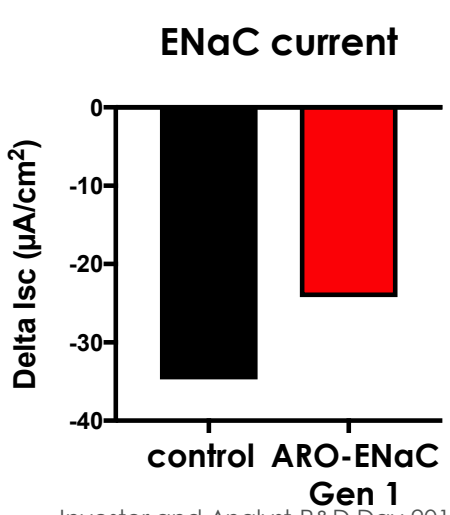
Fully differentiated HBE cells in air-liquid interface culture

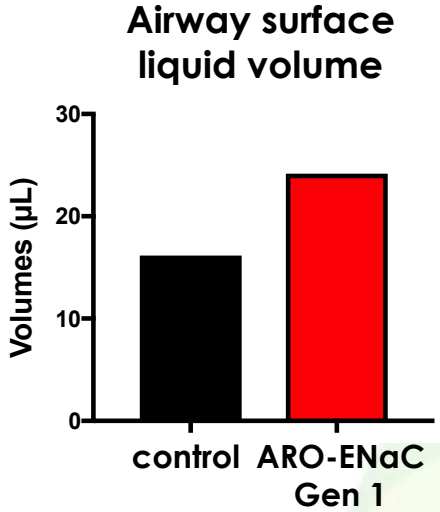






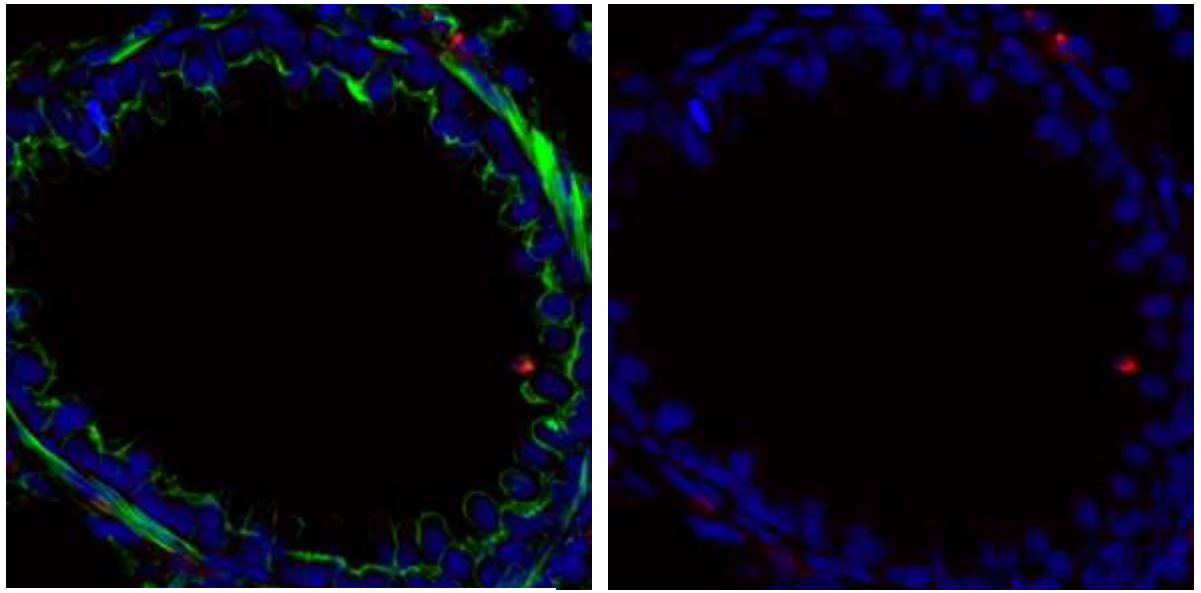




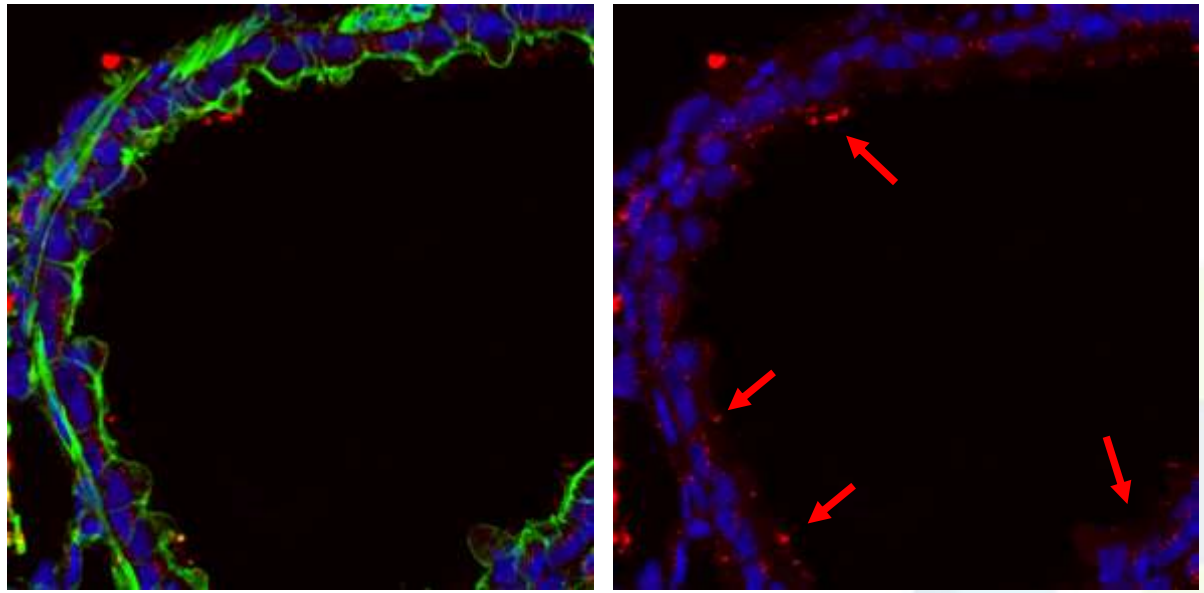


EpL-trigger Conjugates Internalized by Rat Bronchiolar Epithelial Cells in vivo Following Oropharyngeal Delivery

trigger-Cy3

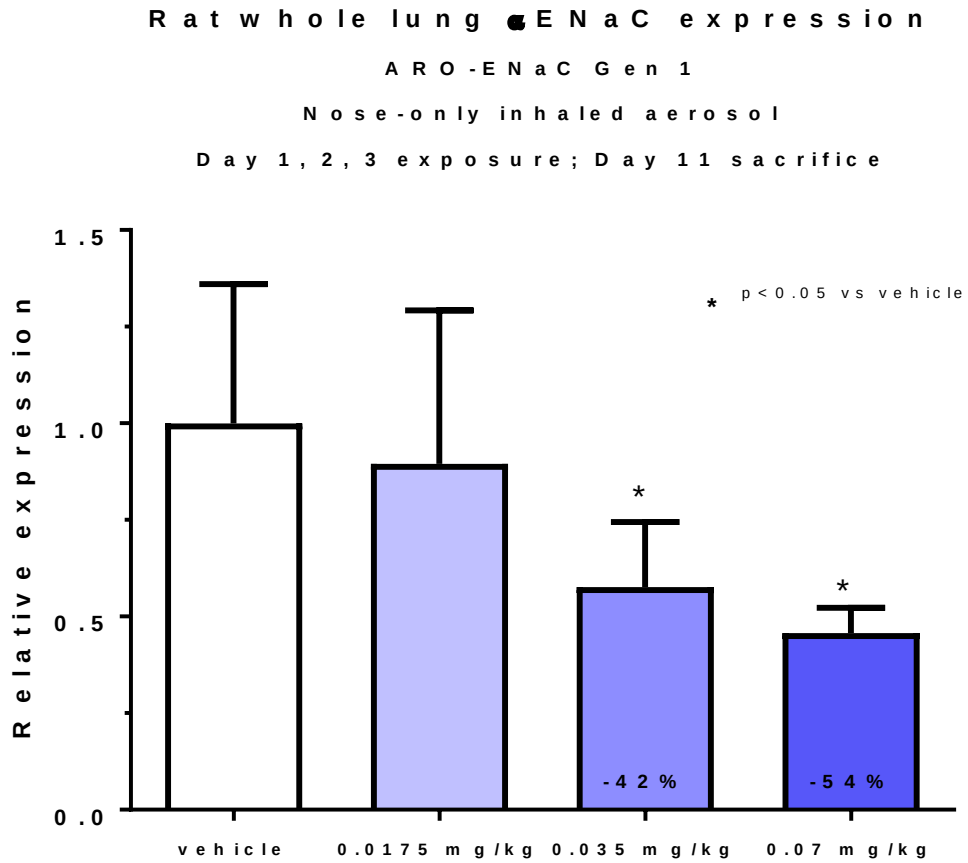


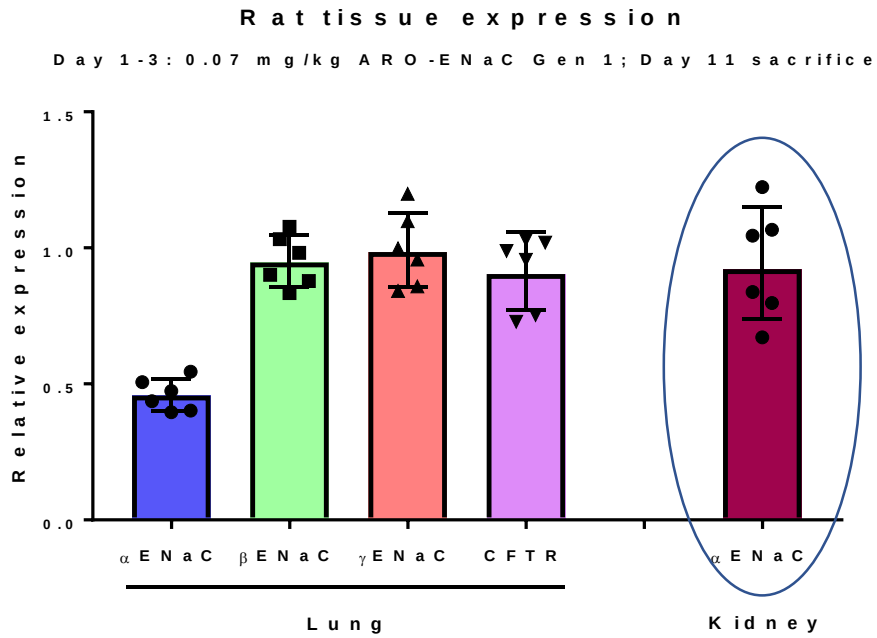
EpL-trigger-Cy3



Red: trigger
Green: actin
Blue: nucleus

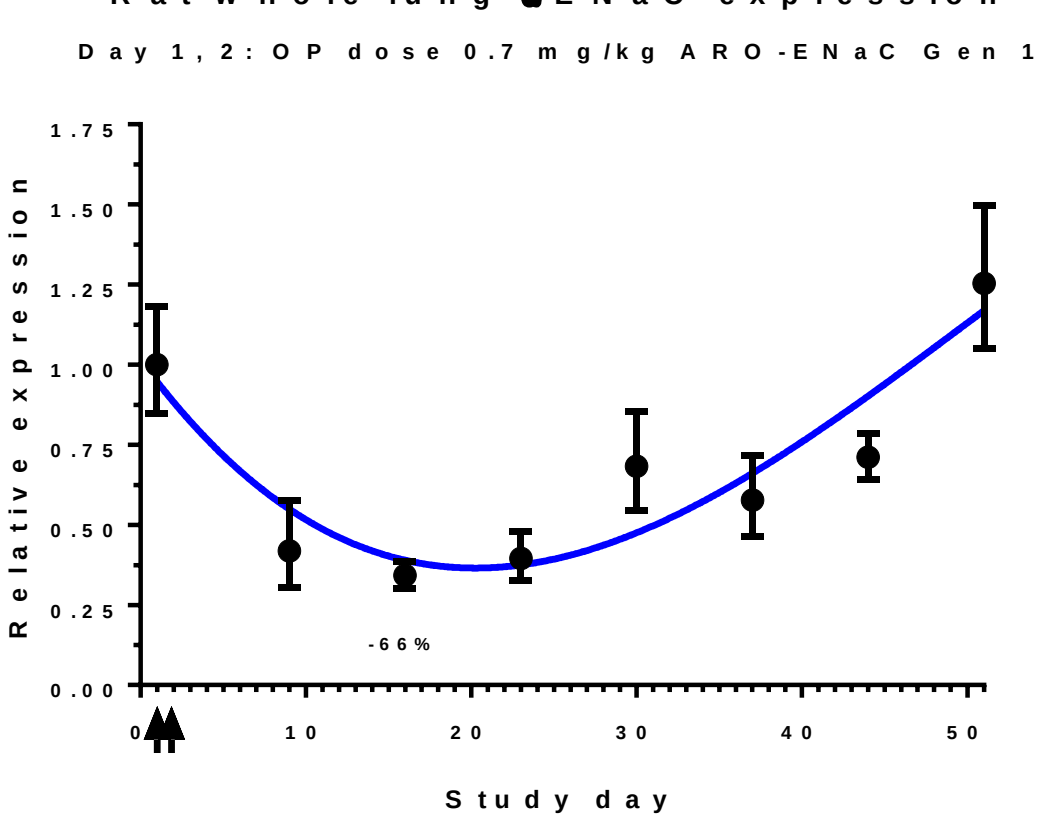
Inhalation of Aerosolized ARO-ENaC Gen 1 Selectively Silences αENaC mRNA Expression in the Rat Lung





- No changes in renal αENaC mRNA expression or serum potassium levels
- Well-tolerated, with no significant findings in clinical chemistry, hematology or histopathology

ARO-ENaC Gen 1 Durably Silences Lung αENaC mRNA Expression



Durable mRNA silencing supports every other week (or less frequent) dose regimens

Sheep Airway Mucociliary Clearance Study

Mucocilary clearance (MCC) measurements: pre-dose baseline and Day 17

- Inhalation of aerosolized ^{99m}Tc-labeled sulfur colloid
- Clearance measured via gamma imaging (5 min intervals over two hours)

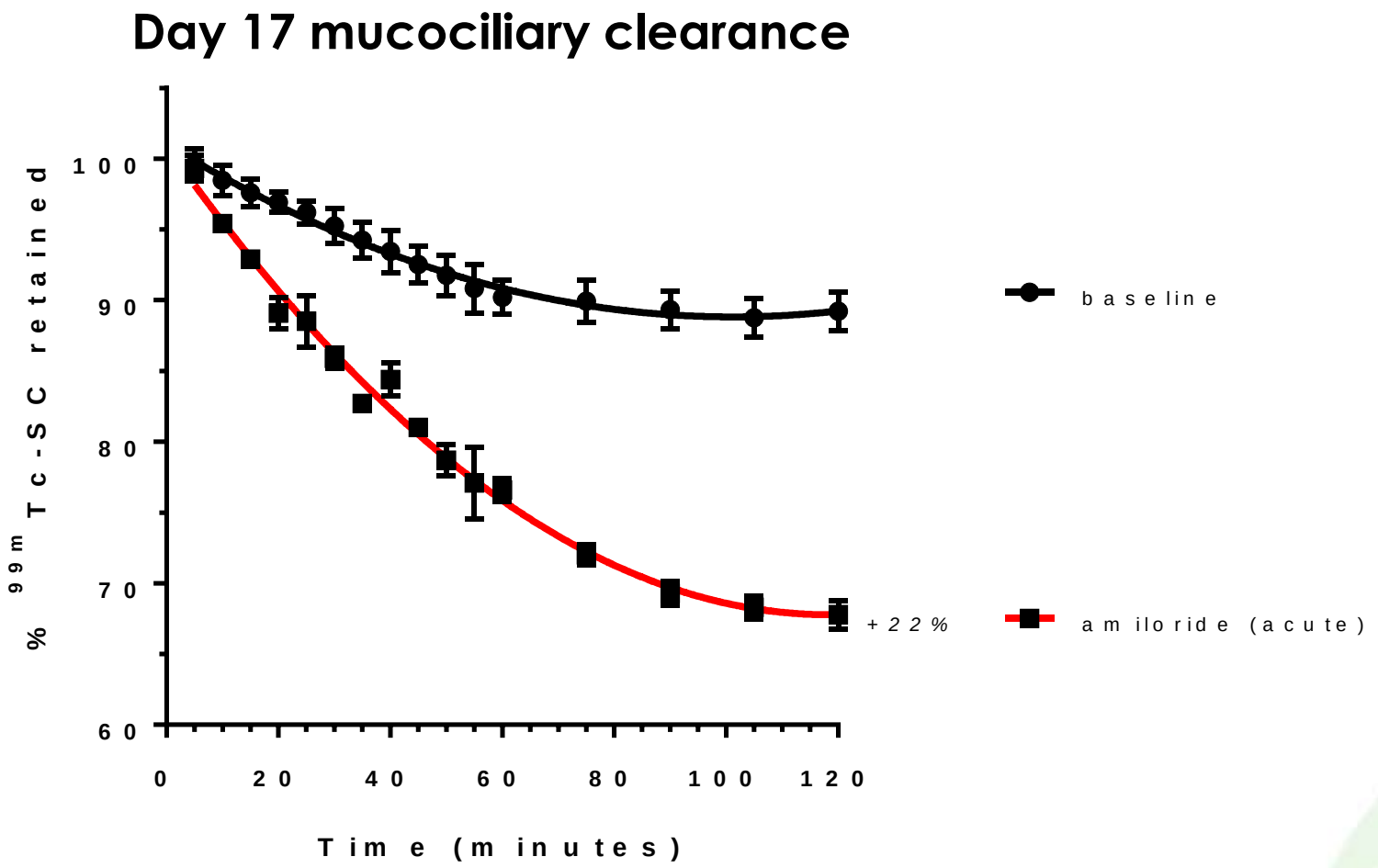
Groups 1-3 (n=3 each): aerosolized ARO-ENaC Gen 1 on Days 1-3

- 0.07, 0.35 or 0.7 mg/kg deposited dose

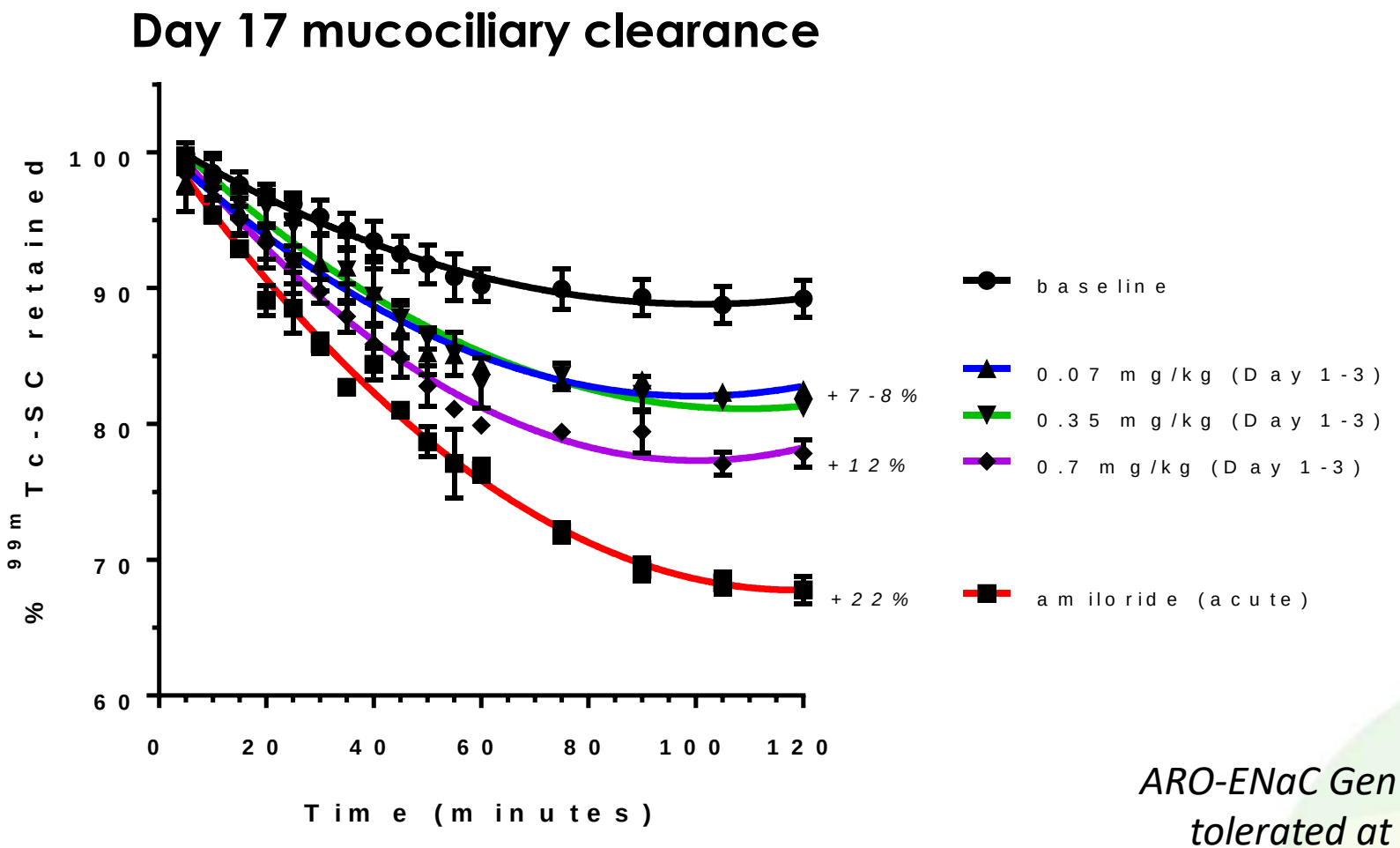
Group 4 (n=2): aerosolized amiloride (3 mL 3 mM) on Day 17

- Administered immediately prior to MCC scan (1-2 hour effect in lung)

ARO-ENaC Gen 1 Increases Mucociliary Clearance in Sheep Two Weeks after Inhaled Dosing



ARO-ENaC Gen 1 Increases Mucociliary Clearance in Sheep two Weeks after Inhaled Dosing



ARO-ENaC Gen 1 was well-tolerated at all doses

Conclusions and Next Steps

- NACFC poster presentation October 18, 2018
- Inhaled ARO-ENaC Gen 1 conjugates produce selective, durable, renal-sparing silencing of pulmonary αENaC expression
- Improved mucociliary clearance is observed in sheep two weeks after inhalation of aerosolized Gen 1 conjugate
- Work on next-generation ARO-ENaC is focused on further increasing potency to produce in vivo clearance increases similar to short-acting small molecule ENaC inhibitors
- The platform may be adapted to additional therapeutic targets in the pulmonary epithelium, particularly those that are currently inaccessible to traditional small molecule or antibody approaches

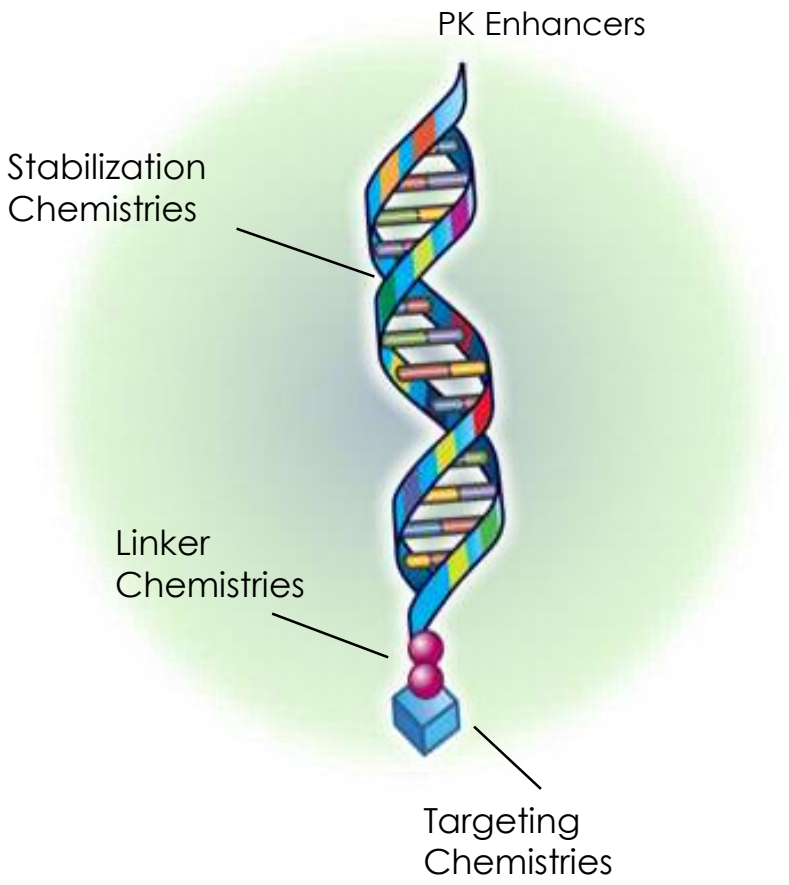
ARO-HIF2

So Wong, Ph.D.
Director, Oncology

Clear Cell Renal Cell Carcinoma (ccRCC)

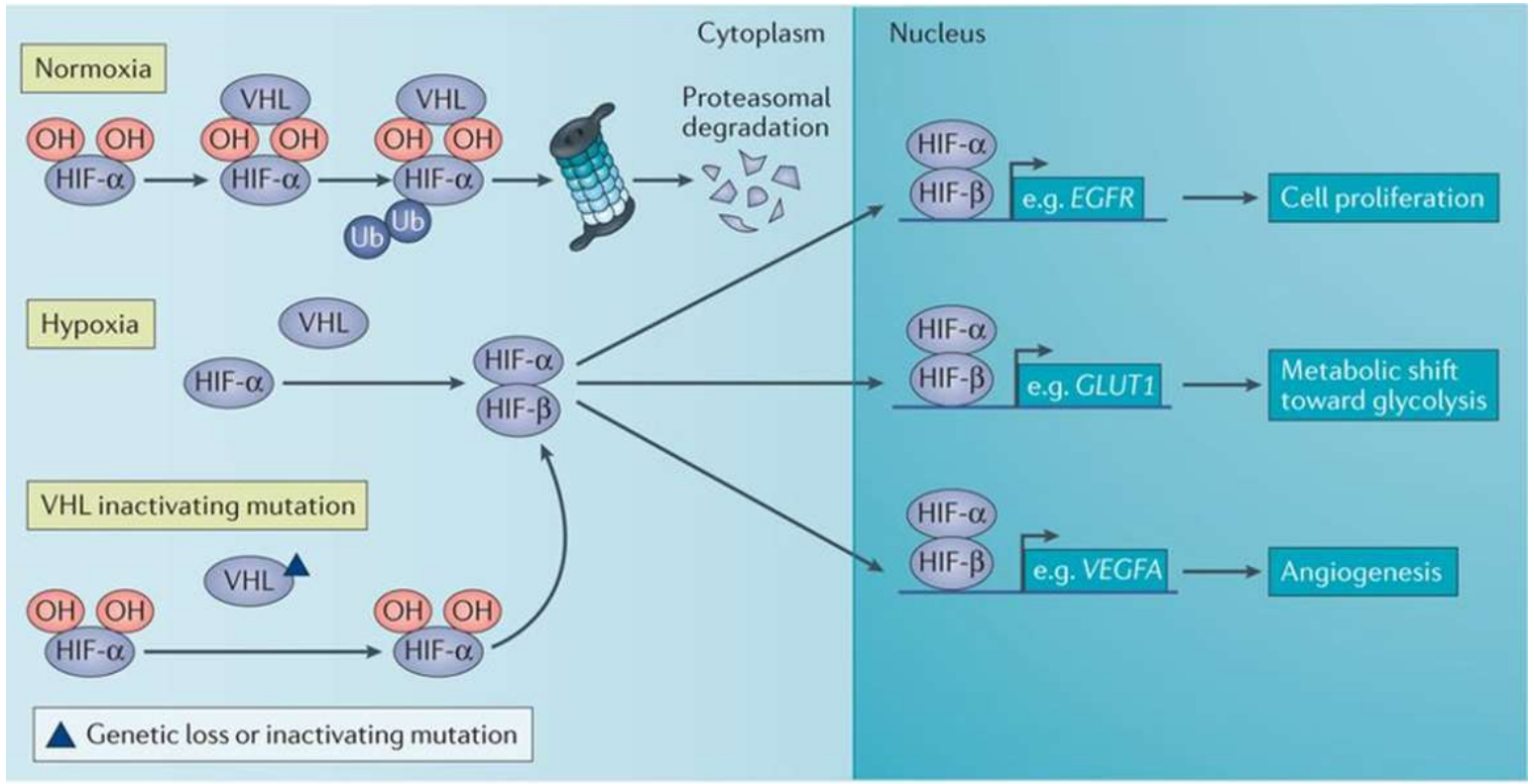
- Kidney cancer is one of the 10 most common cancers
  - 64,000 new cases in 2017
- 70-80% of kidney cancer are ccRCC
  - Characteristic clear cytoplasm due to lipid and glycogen accumulation
- In most ccRCC, the Von Hippel-Lindau (VHL) tumor suppressor gene is inactivated
  - pVHL regulates the degradation of hypoxia inducible factors (HIFs)
  - VHL inactivation leads to accumulation of HIFs
- HIFs transcriptionally activates numerous genes involved in cellular processes including glycolysis, angiogenesis, and metastasis of cancer cells
- Various studies link HiF2α overexpression as a tumorigenic driver of ccRCC

ARO-HIF2



- ARO-HIF2 is our first systemic extrahepatic program
- TRiM™ molecule that uses a receptor that is over-expressed in many cancers
  - Tumor tissue microarrays confirmed receptor expression in ccRCC
- RNAi trigger specifically targets HIF2α mRNA
  - Limited restrictive expression in normal tissues
  - Over-expression in ccRCC
  - Minimal off-target risks
  - Chemically modified to enhance potency and prevent immune activation
- Exploratory safety studies predict a wide therapeutic margin

MOA: ARO-HIF2 vs Small Molecule HIF2α Inhibitor



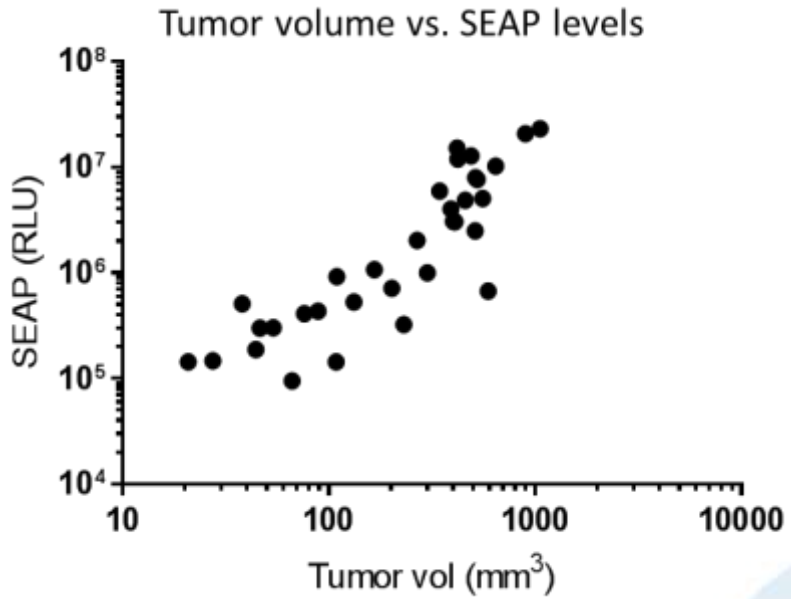
Riazalhosseini and Lathrop, Nature Reviews Nephrology, 2016

- HIF2a/HIF1B dimer regulates transcription pathways that promote tumor growth and metastasis
- Small molecule HIF2a inhibitor (Peloton) prevents binding of HIF2a to HIF-1B
- ARO-HIF2 employs RNAi to degrade HIF2α mRNA and prevent production of HIF2α protein and down-regulate target genes

ARO-HIF2 in Tumor Growth Inhibition Study

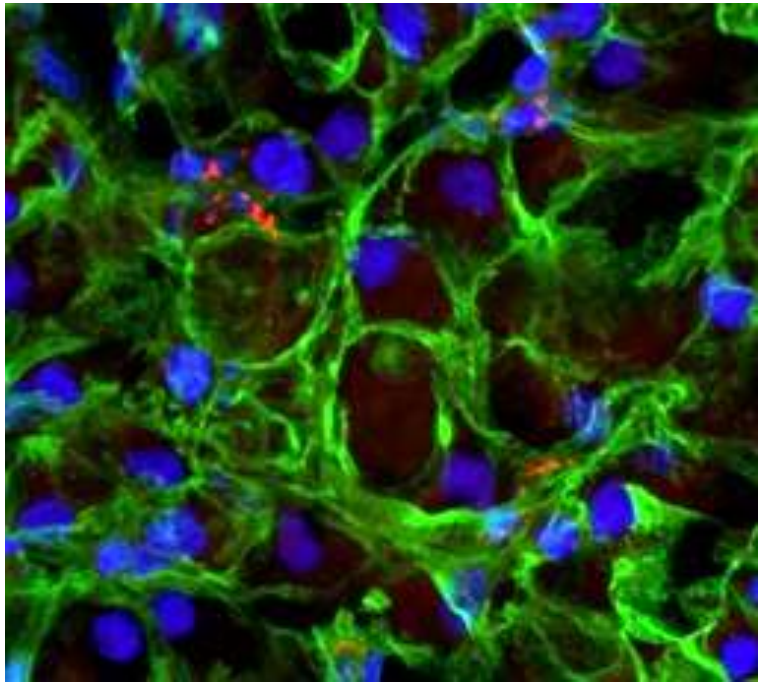
A498 orthotopic kidney xenograft mouse model

- A498 is an established ccRCC cancer cell line
- Tumor growth by SEAP expression
  - Stably expresses SEAP (secreted embryonic alkaline phosphatase)
  - Good correlation between SEAP levels and tumor volumes
- Sensitive serum biomarker to monitor tumor growth

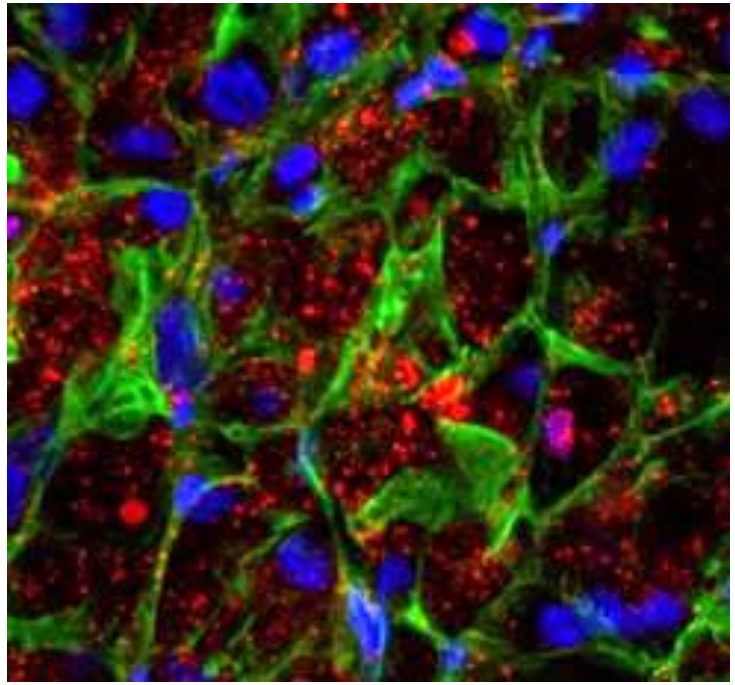


Tumor delivery is ligand dependent

No ligand



With Ligand



A498 ccRCC orthotopic tumor mouse model

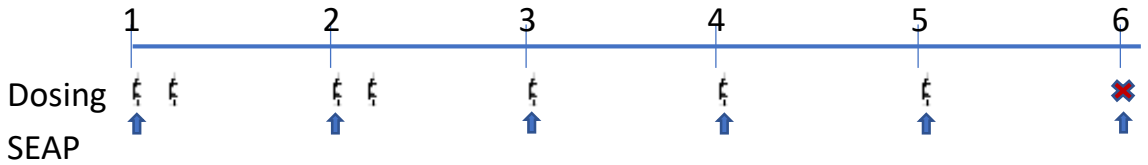
- Efficient delivery to all tumor cells
- No delivery without ligand

2 mg/kg Cy3-labled ARO-HIF
4 h after injection

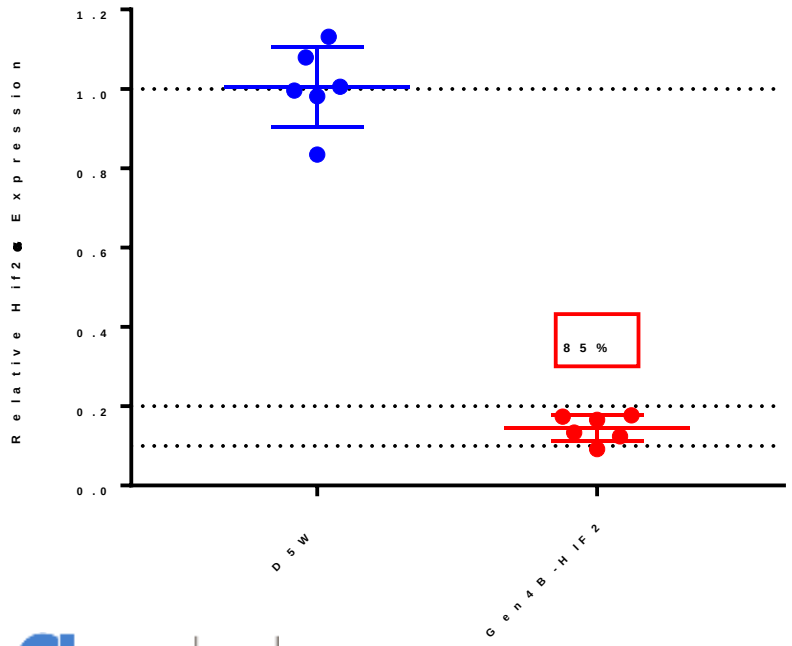
Red = ARO-HIF2
Blue = nuclei
Green = actin fiber (cell membrane)

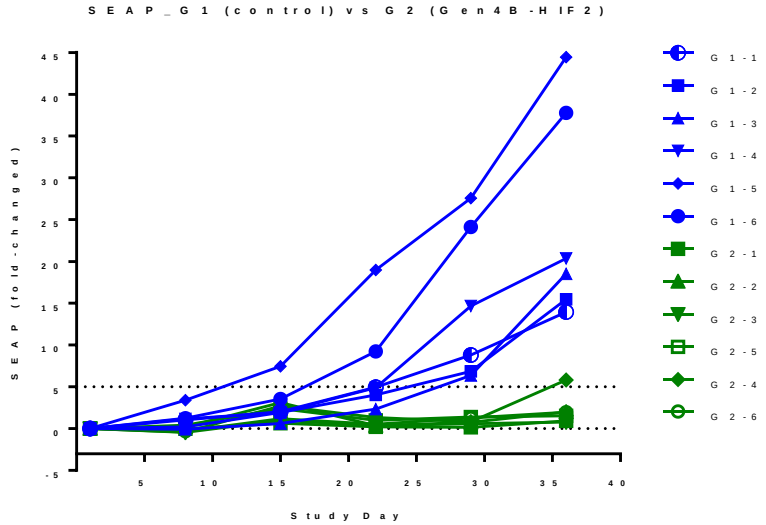
ARO-HIF2 Inhibits Tumor Growth

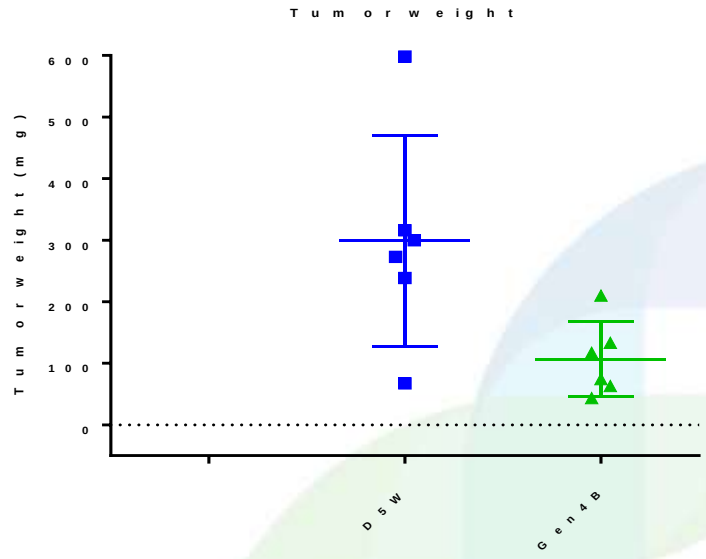
A498-SEAP orthotopic xenograft mouse model



- Deep HIF2a mRNA knockdown with lower dose levels and frequency compared to earlier generations
- Inhibition of tumor growth by SEAP expression and tumor mass

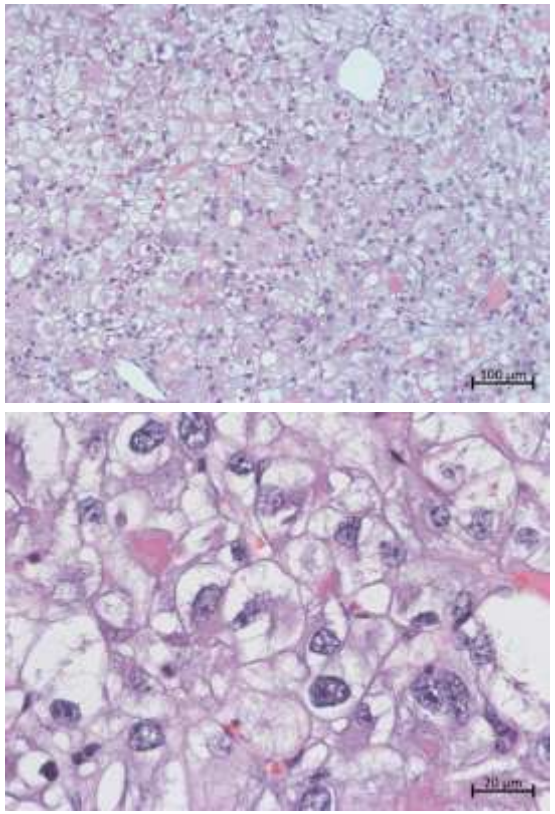




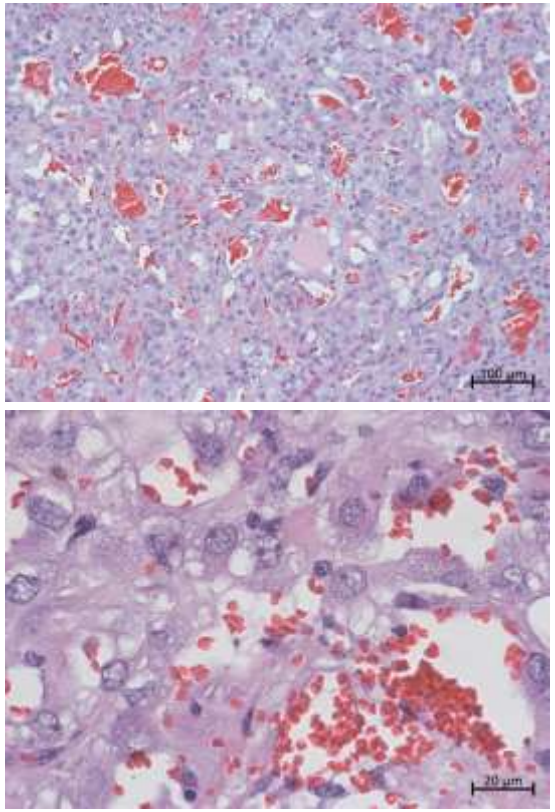


ARO-HIF2 Induces Tumor Degeneration

Control tumor (Day 36)



ARO-HIF2 (Day 36)

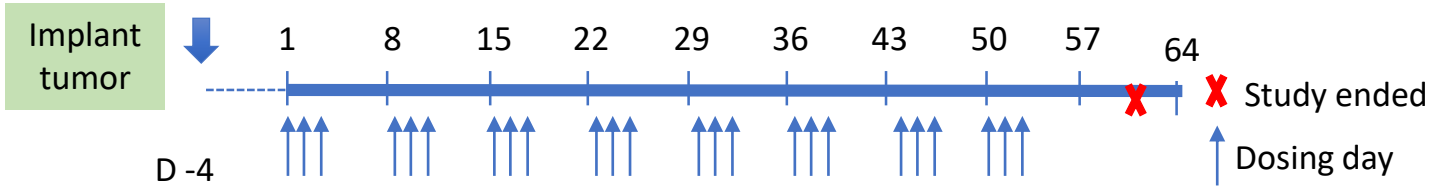


- ARO-HIF2 treated group showed wide-spread tumor damage
- Areas of apoptosis and necrosis
- Loss of clear cell characteristic

Evaluation in Patient Derived Xenograft Models

- Fragments or cells from a patient's tumor implanted into immunodeficient mice
- Advantages over established cancer cell lines
  - Maintains the genetic abnormality found in the patient
  - Reduced transformation of tumor cells
  - May be more predictive of patient response

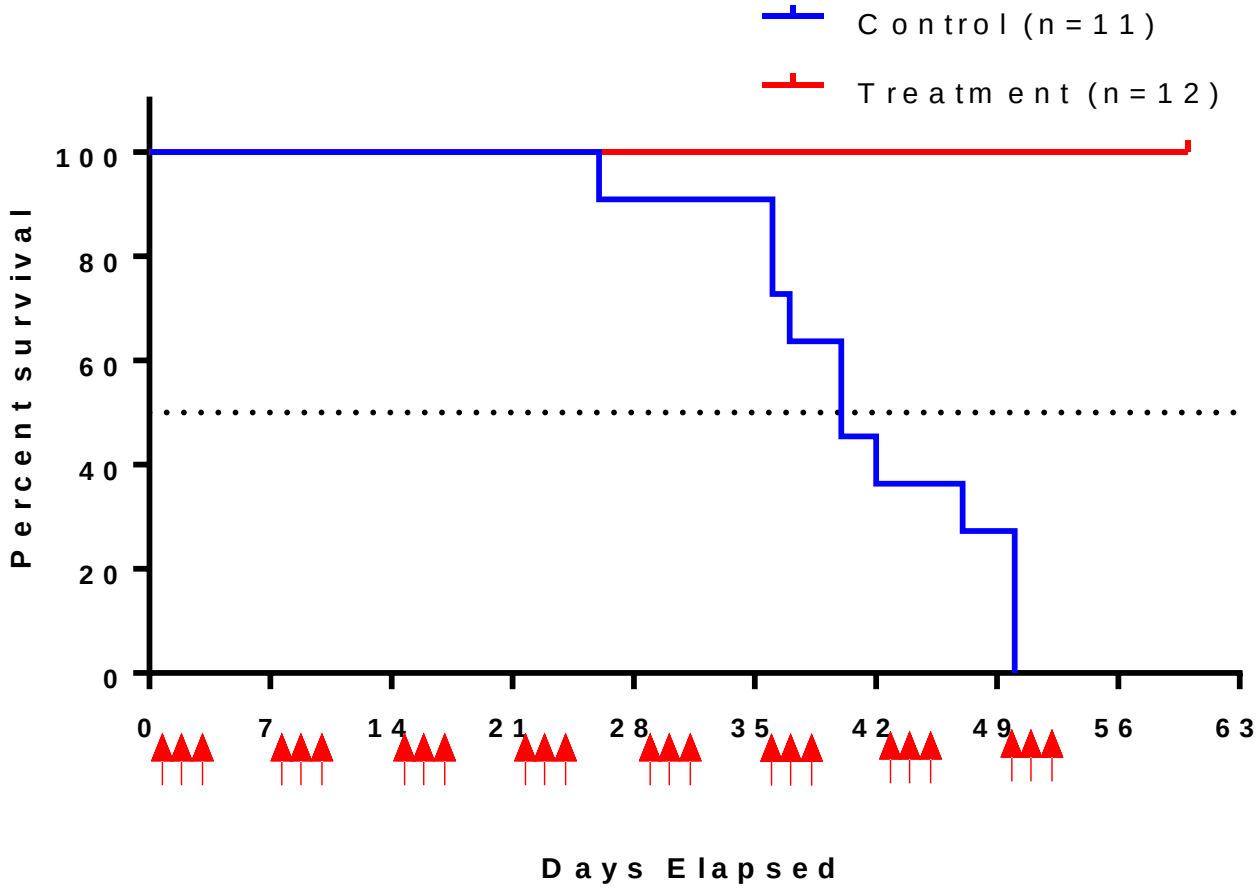
Survival Study: Patient Derived Xenograft (PDX) Mouse Model with Prior Generation Compound



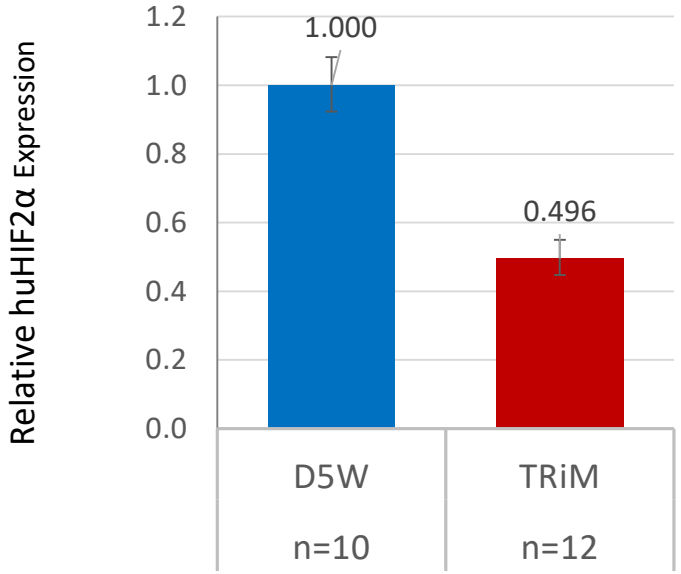
- Dosing began 4 days after tumor implant, 3 daily doses/week (15 mpk/dose)
- Monitor body weight weekly and health check daily
- Palpate tumor weekly to estimate growth rate
- End-point is overall survival

Improved Overall Survival in PDX Mouse Model

Kaplan-Meier survival analysis



HiF2α mRNA KD

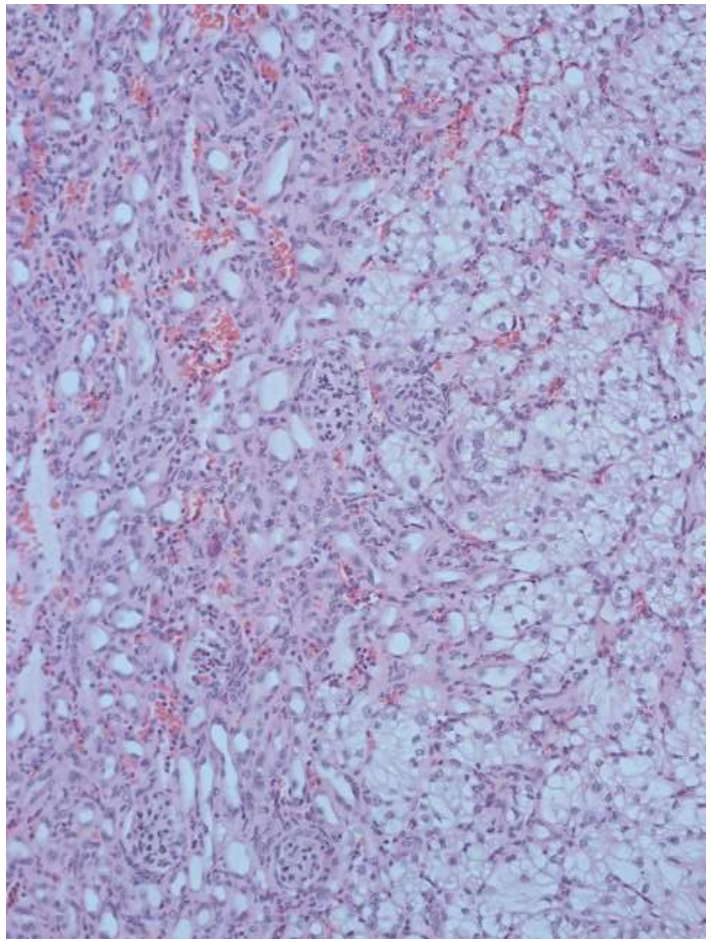


Tumor Histopathology with Gen2

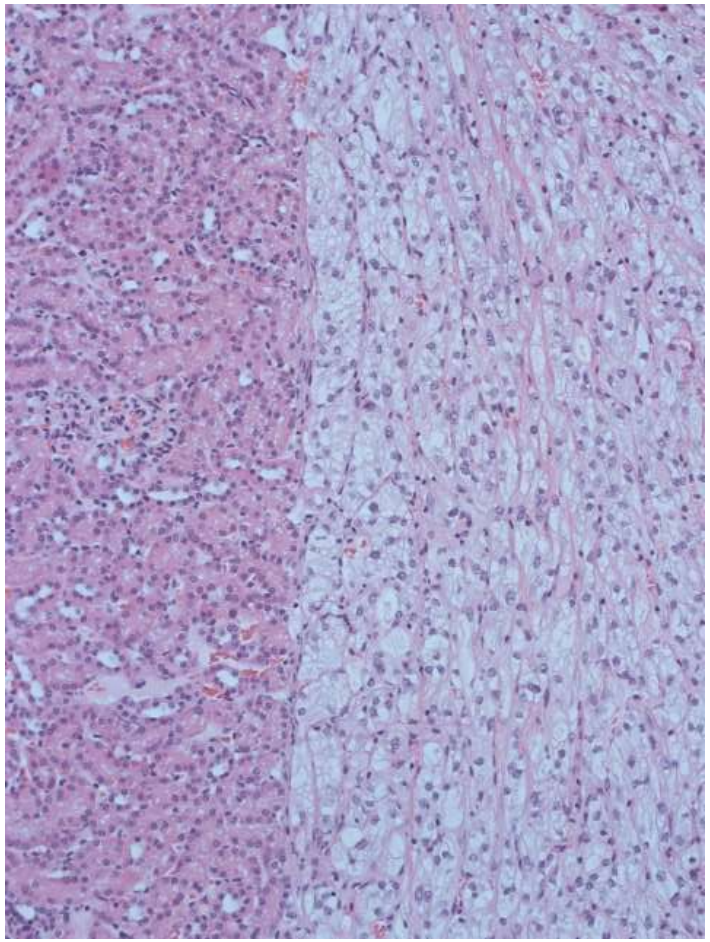
- Frequent tumor necrosis/degeneration
- Less invasiveness at tumor/kidney interface

ARO-HIF2 Reduced PDX Tumor Invasiveness

Control



ARO-HIF2



- Less invasiveness at tumor/kidney interface with clear demarcation line between tumor and kidney
- Silencing HIF2a may prevent metastasis development

A new survival study using the current lead candidate is on-going

Summary and Plan for ARO-HIF2

Summary

- Efficient ligand dependent tumor delivery of ARO-HIF2 demonstrated
- Deep HIF2α mRNA knockdown in tumor
- Inhibition of tumor growth and improved overall survival in tumor models
- Rat exploratory toxicity studies predict a wide safety margin

Plan

- Late breaking poster at the EORTC/AACR/NCI symposium, Nov 13 - 16
- Development candidate nomination in coming months
- CTA planned for 2019

Investor and Analyst R&D Day 2018

Concluding Remarks

Chris Anzalone, Ph.D.
President and CEO

arrowhead pharmaceuticals

Looking to 2019

2019 will be productive

- **Expect 2 new CTAs**
  - ARO-HIF2
  - ARO-ENaC
- **Expect to be in Phase 2 or later with 3 wholly-owned candidates**
  - ARO-AAT, ARO-ANG3, ARO-APOC3
- **Expect progress with partnered clinical candidates**
  - ARO-HBV, AMG 890
- **Wildcards**
  - New Janssen targets
  - Amgen undisclosed CV target
  - Muscle targeting
  - ARWR breakthroughs

Looking Beyond 2019

Innovation and speed will continue to define us

- We expect 2 - 3 new CTAs ***every*** year
- We expect to be able to target a new cell type every ~18 months
- We expect 10 TRiM™ enabled clinical programs by the end of 2020
- Just need to execute: look to the past year for our ability to execute

Investor and Analyst R&D Day 2018

Q&A Session
Panelists

arrowhead pharmaceuticals