Arrowhead Analyst R&D Day

October 18, 2019

New York

arrowhead pharmaceuticals

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.

Welcome and Introductions

Vince Anzalone, CFA
Vice President, Investor Relations

Panelists

New York University Langone School of Medicine

Ira Goldberg, M.D.
Clarissa and Edgar Bronfman Professor of Medicine, and Director 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

James Hamilton, M.D.
Vice President, Clinical Development

So Wong, Ph.D.
Director, Oncology

Erik Bush, Ph.D.
Vice President, Extra-Hepatic Targeting

Tao Pei, Ph.D.
Vice President, Chemistry

Agenda

8:30-8:35	Welcome and Introductions – Vince Anzalone
8:35-8:55	Overview of Arrowhead – Chris Anzalone
8:55-9:05	Guiding Principles for R&D Organization – Bruce Given
9:05-9:45	Cardiometabolic, ARO-APOC3, and ARO-ANG3 – Ira Goldberg & Bruce Given
9:45-10:00	ARO-AAT – James Hamilton
10:00-10:15	Coffee Break
10:15-10:25	ARO-HSD – Bruce Given
10:25-10:35	ARO-HIF2 – So Wong and James Hamilton
10:35-10:45	ARO-ENaC – Erik Bush and Bruce Given
10:45-10:55	TRiM™ Advances – Tao Pei
10:55-11:05	Concluding Remarks – Chris Anzalone
11:05-11:30	Q & A – Panel

Overview

Chris Anzalone, Ph.D.
President and CEO

From Standing Start in 2016

In October 2016, we abandoned our old platform

Over the following 3 years, we accomplished a tremendous amount, all based on the TRiM™ platform:

- ARO-HBV enters the clinic: Q1 2018
- ARO-AAT enters the clinic: Q1 2018
- AMG-890 (formerly ARO-LPA) enters the clinic: Q3 2018
- ARO-HBV + 3 novel targets partnered with JnJ: Q4 2018
  - $3.7bn of potential payments
  - Royalties on sales to mid teens
- ARO-ANG3 enters the clinic: Q1 2019
- ARO-APOC3 enters the clinic: Q1 2019
- ARO-AAT initiates potentially pivotal P2/3 study: Q3 2019
- Established ability to target pulmonary epithelial cells
- Established ability to target skeletal muscle cells

Expectations Through end of Next Year

- ARO-HSD CTA expected by EOY 2019
- ARO-HIf2 CTA expected by EOY 2019
- ARO-ENaC CTA expected 1H 2020
- 1st P3 pivotal study with ARO-APOC3 expected to launch 2020
- 1st P3 pivotal study with ARO-ANG3 expected to launch 2020
- First muscle-targeting CTA by EOY 2020

So…in a little over 1 year from now, we expect to have:

- **At least 7 wholly-owned candidates in clinical studies**
- **2 partnered programs in P2 or later**
- **3 wholly-owned P3 pivotal studies**
- **Drug candidates in 4 different cell types**

Culture and technology enable this progress

Culture

- Fiercely innovative and collaborative
- Speed is imperative
- Do a lot in parallel
  - Willing to take financial risk to maximize speed
- Have always punched above our weight

Technology is increasingly validated

- We have treated **214 people with 432 doses** of TRiM™-enabled candidates
  - No drug related SAEs; any local injection site reactions have been mild
- >1500 patients were treated in MedCo's P3 study of Inclisiran
  - Appears active and generally well-tolerated
    - Supports our hepatocyte targeted candidates
- Components of extra-hepatic well understood
- **Decreased risk profile and continued high success rate**

Pipeline

Competitive Position	Drug	Disease
First RNAi	ARO-AAT	Alpha-1 Liver Disease
First RNAi	ARO-APOC3	Hypertriglyceridemia
First RNAi	ARO-ANG3	Dyslipidemia
First RNAi	ARO-HSD	Liver Disease
First RNAi	ARO-ENaC	Cystic Fibrosis
First RNAi	ARO-HIF2	Renal Cell Carcinoma
Leading RNAi	JNJ-3989	Hepatitis B
First RNAi	AMG 890	Cardiovascular Disease
Undisclosed Target	ARO-JNJ1	Undisclosed

Pipeline selection: seeking to minimize biology risk

The TRiM™ platform is so broad that it enables us to address a wide variety of diseases across multiple organ systems

Good for medicine, but a challenge for the company: how can you be an expert in many, unrelated areas?

Focus on well-validated targets

We are not in the target validation business

LP(a):	Genetic validation
APOC3:	Genetic + clinical validation
ANG3:	Genetic + clinical validation
AAT:	Clear biology
HSD:	Genetic validation
Hif-2a:	Experimental + Pharma validation
ENaC:	Genetic + experimental validation

High likelihood of clinical benefit with KD

HBV:	Good data; evidence that functional cures attainable; but complicated biology

Strategic rationale for partnering

Diminished "unknowns" in the clinic

Building a pipeline on:

Validated targets

↓

Confidence in clinical benefit of KD

Increasingly Validated technology

↓

Confidence in ability to KD target and safety profile

Approach the clinic de-risked relative to traditional small molecule drugs

And

Increases our expected success rate once in the clinic

Competitive landscape

Target	Indications	Possible competition	Expected ARWR advantages
AAT	AAT liver disease	RNAi; protein corrector	Years ahead of RNA competition; Corrector addresses a fraction of the protein ARO-AAT turns off
ANG3	Rare and large indications	ASOs; mAB	Better safety and less frequent dosing expected compared to ASOs; Monthly iv vs less frequent sc dosing, mAB unlikely treat liver fat & insulin sensitivity
APOC3	Rare and large	ASOs	Better safety and less frequent dosing expected compared to ASOs
HSD	NASH/ASH	Only HSD in clinic	
Hif-2a	RCC	Small molecule	Merck acquired only other Hif-2a inhibitor in clinical development
ENaC	CF	Only ENaC in clinic	
LP(a)	CVD	ASOs	Better safety and less frequent dosing expected compared to ASOs
HBV	Chronic HBV	RNAi; ASOs	Years ahead of RNAi competition; Better safety and durability expected compared to ASOs

Pipeline expansion

Hepatocytes		Solid tumors	Lung	Muscle	New cells
HBV	ANG3	Hif2-a	ENaC	Undisclosed	Undisclosed
LP(a)	APOC3				
AAT	HSD				

Expansion into new targets	Expansion into new targets	Expansion into new targets	Expansion into new targets	Expansion into new targets

Rapidly scalable pipeline:

10 TRiM™-enabled clinical candidates expected next year

Potentially **20** just 3 years later

Pipeline designed to continue to minimize risk

We expect to be first RNAi in the new cell types:

Focus on low-hanging fruit of well-validated targets

**By the time another company catches up,
we would expect them to either focus on riskier targets
or be years behind our competing programs**

Model and value proposition

We are building a long-term pharmaceutical company that will commercialize important medicines

We view this as best path for patients *and* investors

- Fastest way to get medicines to patients
- Maximizes shareholder value by capturing full value of our medicines

This is an ambitious goal: is it realistic to think of Arrowhead in these terms?

- Yes, but need to plan for commercial build-out and have financing plan
  - Actively assembling the core commercial team now
  - Substantial financing opportunities via existing and future partnerships

Financing plan

Building a commercial enterprise is expensive

Current partnerships with Amgen and Janssen

- Eligible for up to ~$4bn of potential milestone payments

Future partnerships

- TRiM™ platform is so broad that *no company* could extract all value from it
- We will create new TRiM™-enabled drugs for partners: "found" value
- Substantial inbound interest
  - Open to partnerships on new targets, but not currently focused on partnering pipeline

Any equity financing would be opportunistic

- We do not want to be dependent on the capital markets for operations

In the strong position to source "cheapest" capital

- Strategic costs, opportunity costs, dilutive costs

Today you will see…

This is a special company and a unique time

- We have demonstrated best in class speed and execution
- We have an expectation of a high success rate in the clinic
  - Increasingly validated technology
  - Validated targets
- We are working on important medical conditions
- We have a pipeline that is rapidly scalable into diverse tissues

Over the next few years we expect to have products at or approaching market *and* a deep pipeline that increasingly looks like that of big pharma

Arrowhead R&D Guiding Principles

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

A Frequently Asked Question

How are you guys so fast?

How are we so fast?

- It is by design
  - Program Management is a muscular function
  - We do as much in parallel as possible
    - If we think of a question, we go answer it
  - We relentlessly address internal bottlenecks and minimize the need to go outside
  - No slack is allowed between activities on the critical path

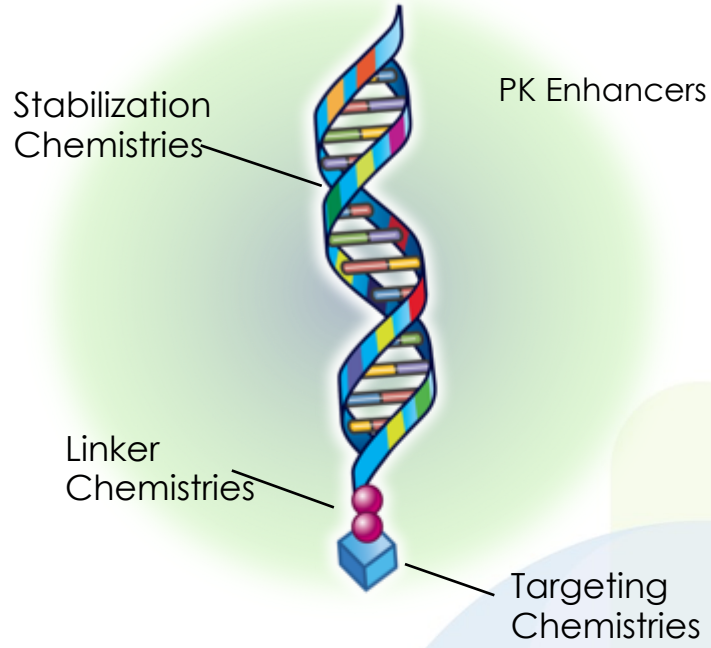
Really good program management is not enough

How are we so fast?

- Precedent bores us
  - We always ask "Can we do it better, faster"

TRiM™ - Potency, Efficacy, 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
  - Identify RNA triggers based on intrinsic characteristics
- We don't trust in vitro screening
  - Allows us to identify novel trigger families and improve activity
- Enables us to expect a wide therapeutic index on our compounds
  - Can afford to be ***very stringent*** in sequence selection
  - Minimize, through bioinformatic analysis, potential off-target effects due to sequence homology and microRNA
  - Huge advantage for RNAi compared with small molecule therapeutics, but not everyone can take advantage



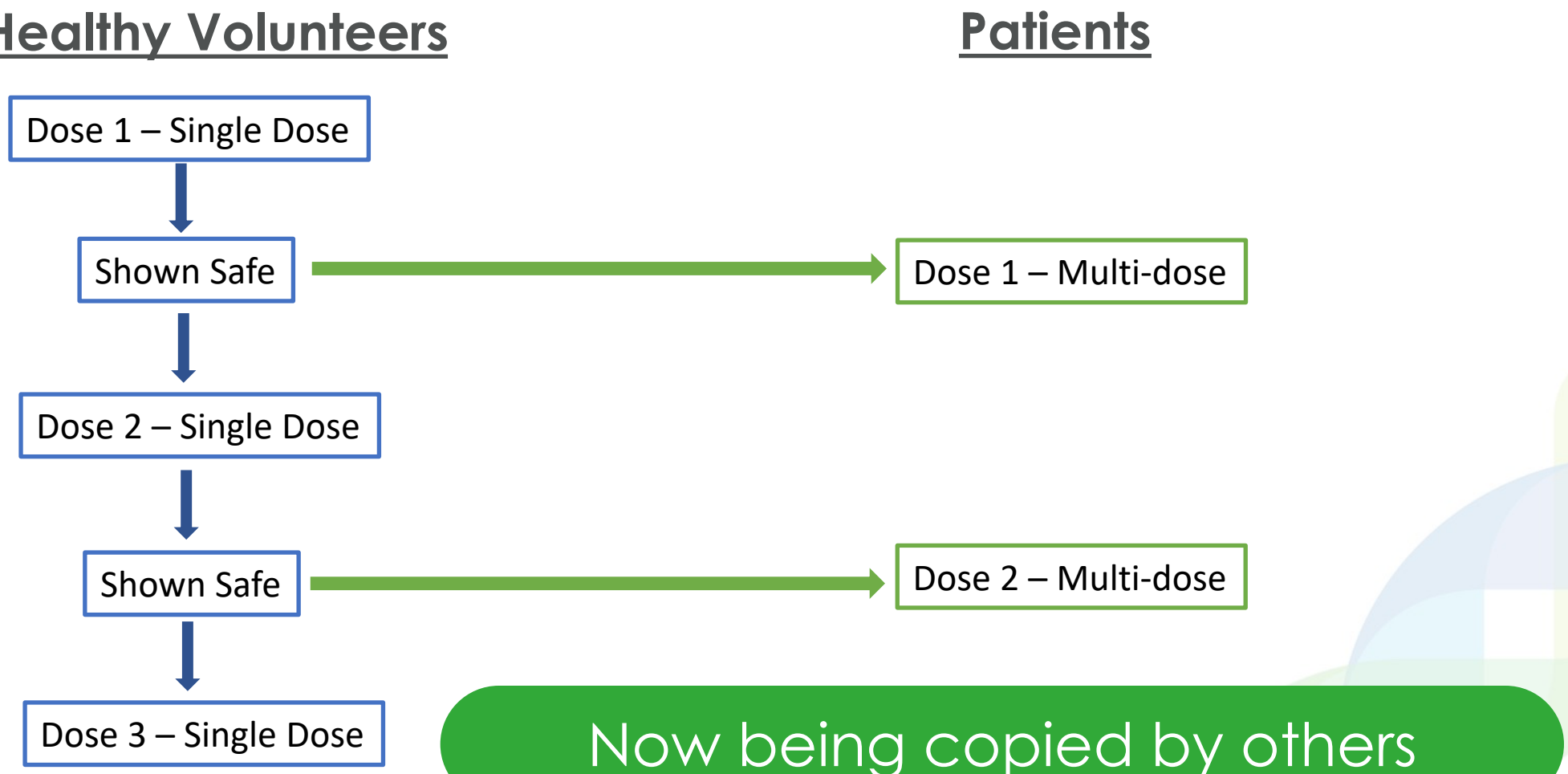
Targeted RNAi Molecule

TRiM™ platform

How are we so fast?

- Precedent bores us
  - We always ask "Can we do it better, faster"
  - First in human work usually in ANZ allowing predictability in review processes
  - We re-engineered the clinical trial process to collect key data in our first trial in volunteers and patients
    - Satisfies traditional criteria for Phase 1a and 1b data
    - Generally provides Phase 2a level data in patients
    - Due to the unique durability of RNAi, we often wind up with multi-month activity data usually only achieved in Phase 2b for most drugs

Base First-in-Human Clinical Design



Now being copied by others

How are we so fast?

- Our R&D culture embraces innovation
  - Open collaboration is celebrated and rewarded
  - Our R&D mantra is ‘everyone grows, everyone leads’
  - We celebrate success but never punish honest failures or risks that don’t work out
    - The only way to truly get folks to do things in parallel and not build slack into pipelines
  - Hierarchy is hard to find
    - No review and approval committees, stage gates, etc
    - Teams make decisions but leaders participate actively in teams while often not leading them

Cardiometabolic

Ira Goldberg, M.D.
New York University Langone School of Medicine

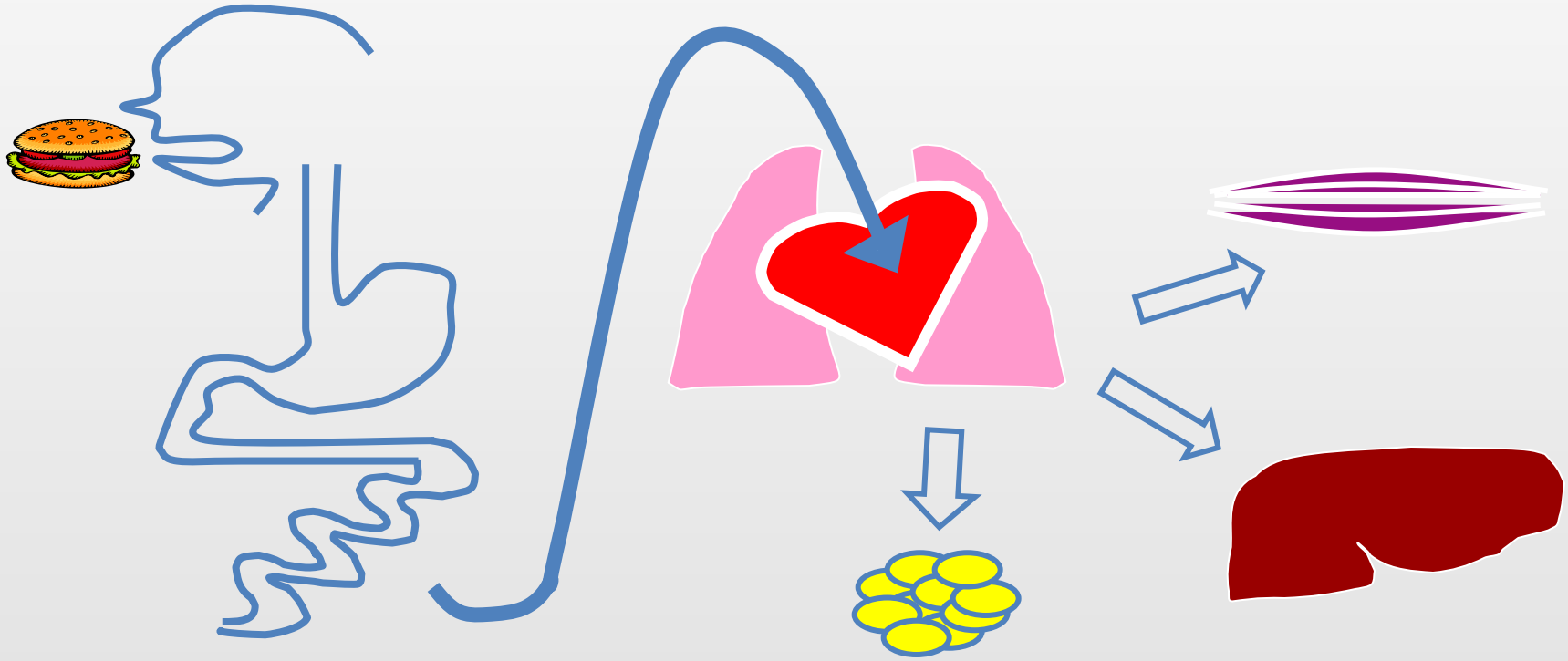
Lipids and disease
A Future for Hepatic Genetic Modification

Ira J. Goldberg
Clarissa and Edgar Bronfman Professor
Director, Division of Endocrinology, Diabetes and Metabolism
New York University School of Medicine

Hypertriglyceridemia and disease

LDL cholesterol and why statins are not enough

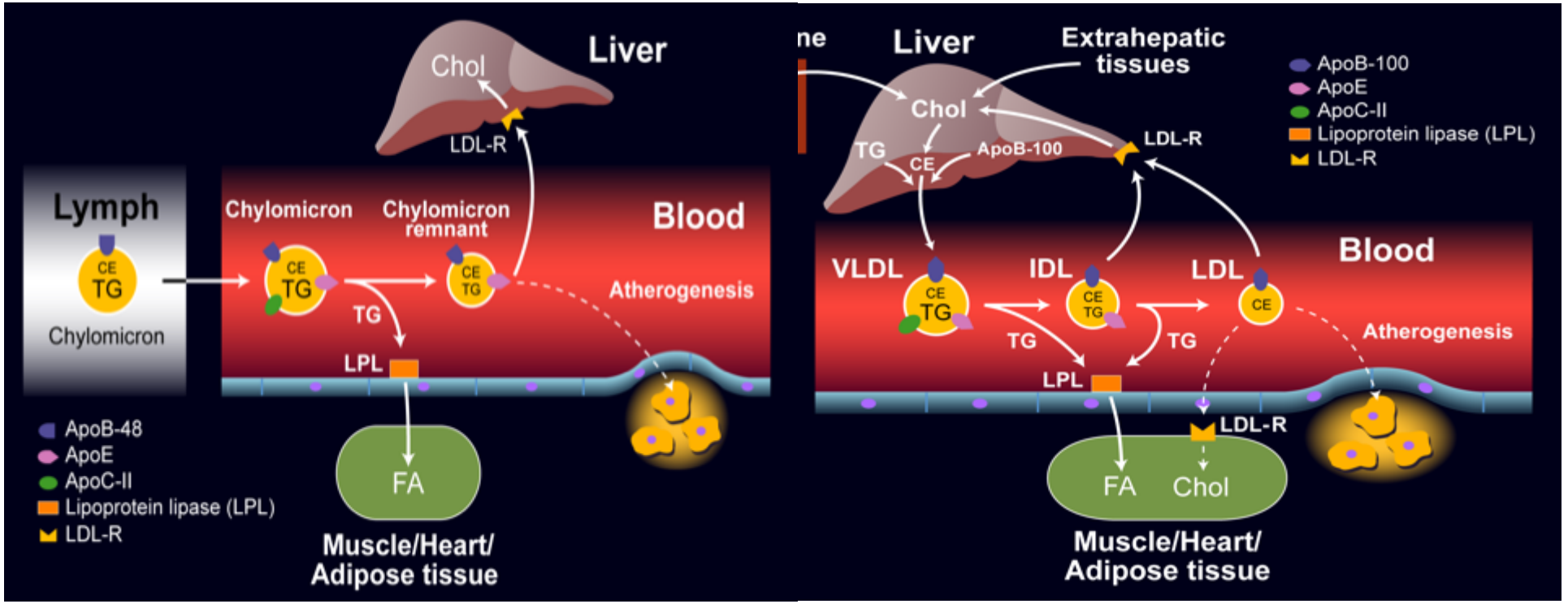
The Way to the Heart is Through the Stomach



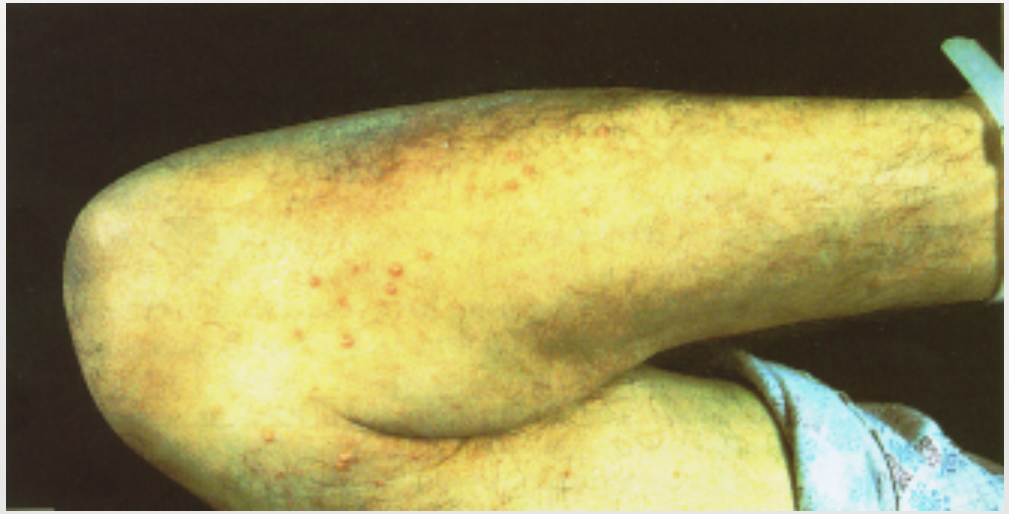
TG from liver and gut use LpL

Chylomicron Transport

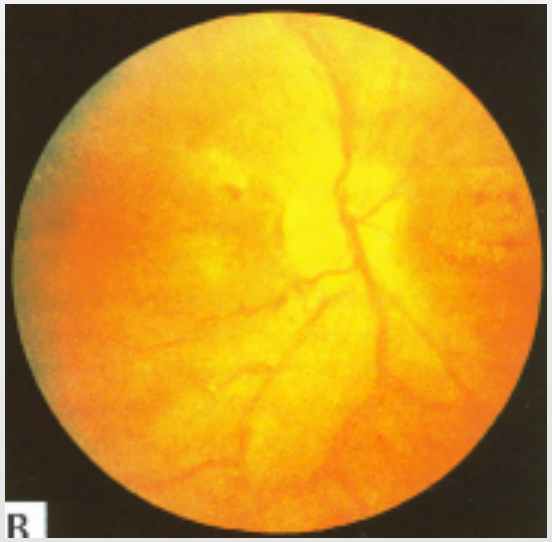
Endogenous Pathway



Clinical signs of severe hypertriglyceridemia

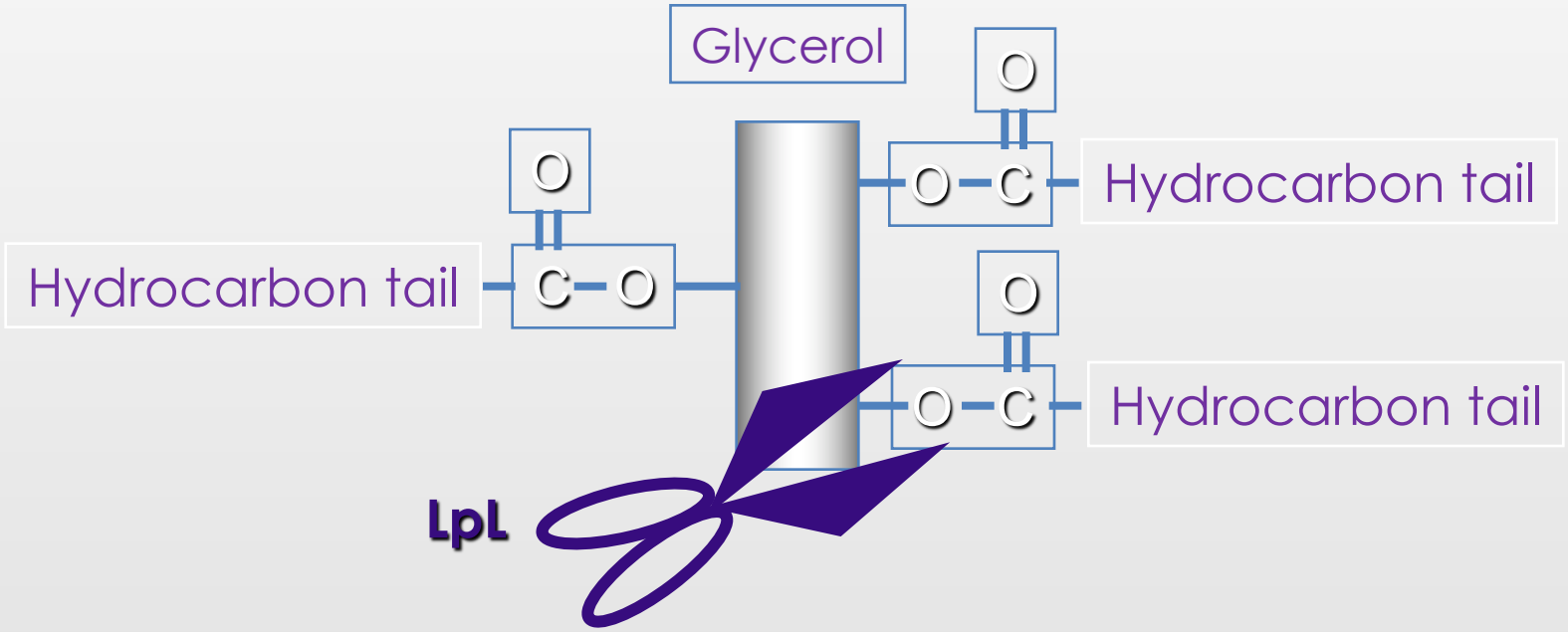


Eruptive xanthomas

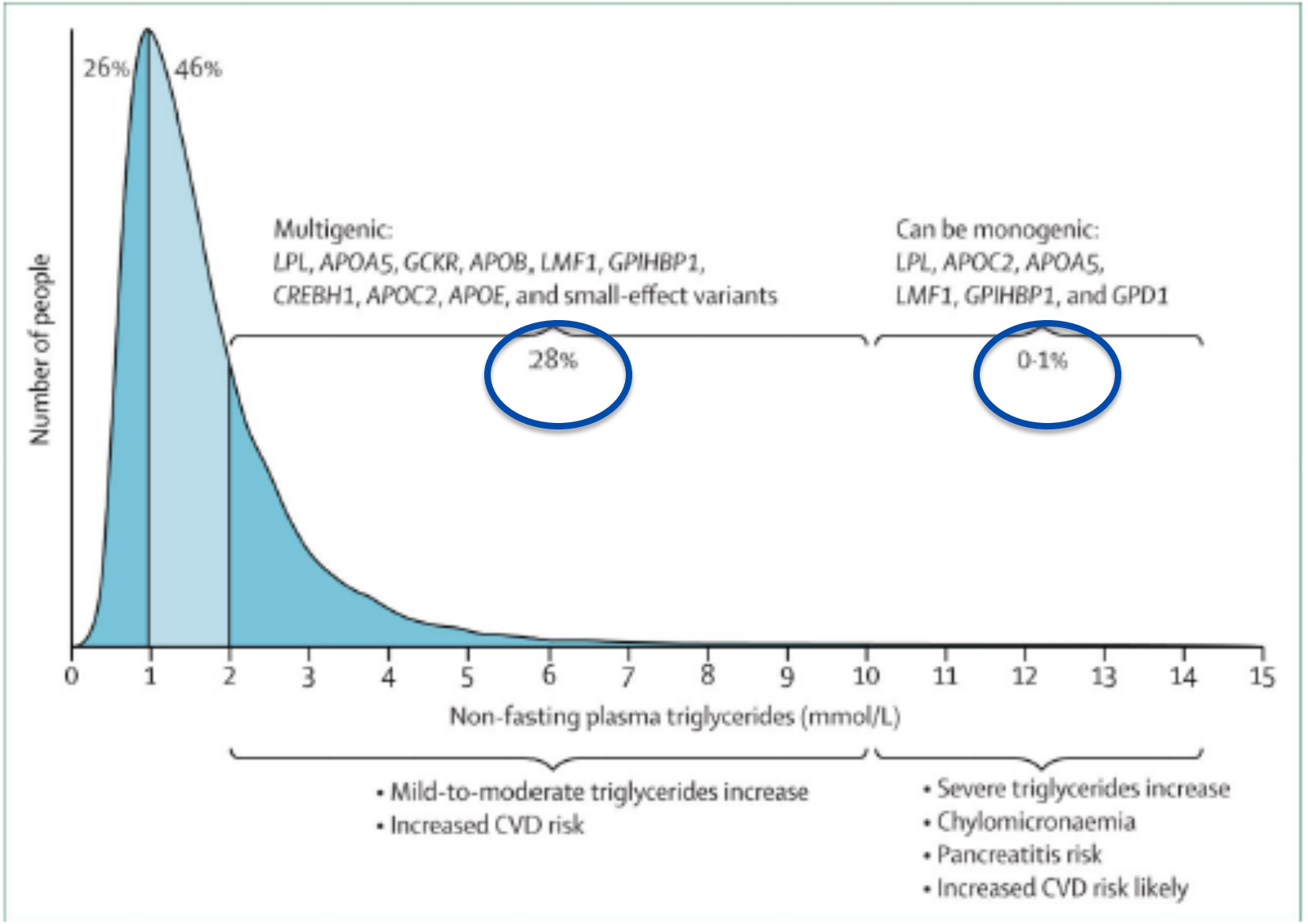


Lipemia Retinalis

Triglyceride (TG) and Lipoprotein Lipase (LpL)



Increased TG as a function of genetics



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

What regulates lipolysis?

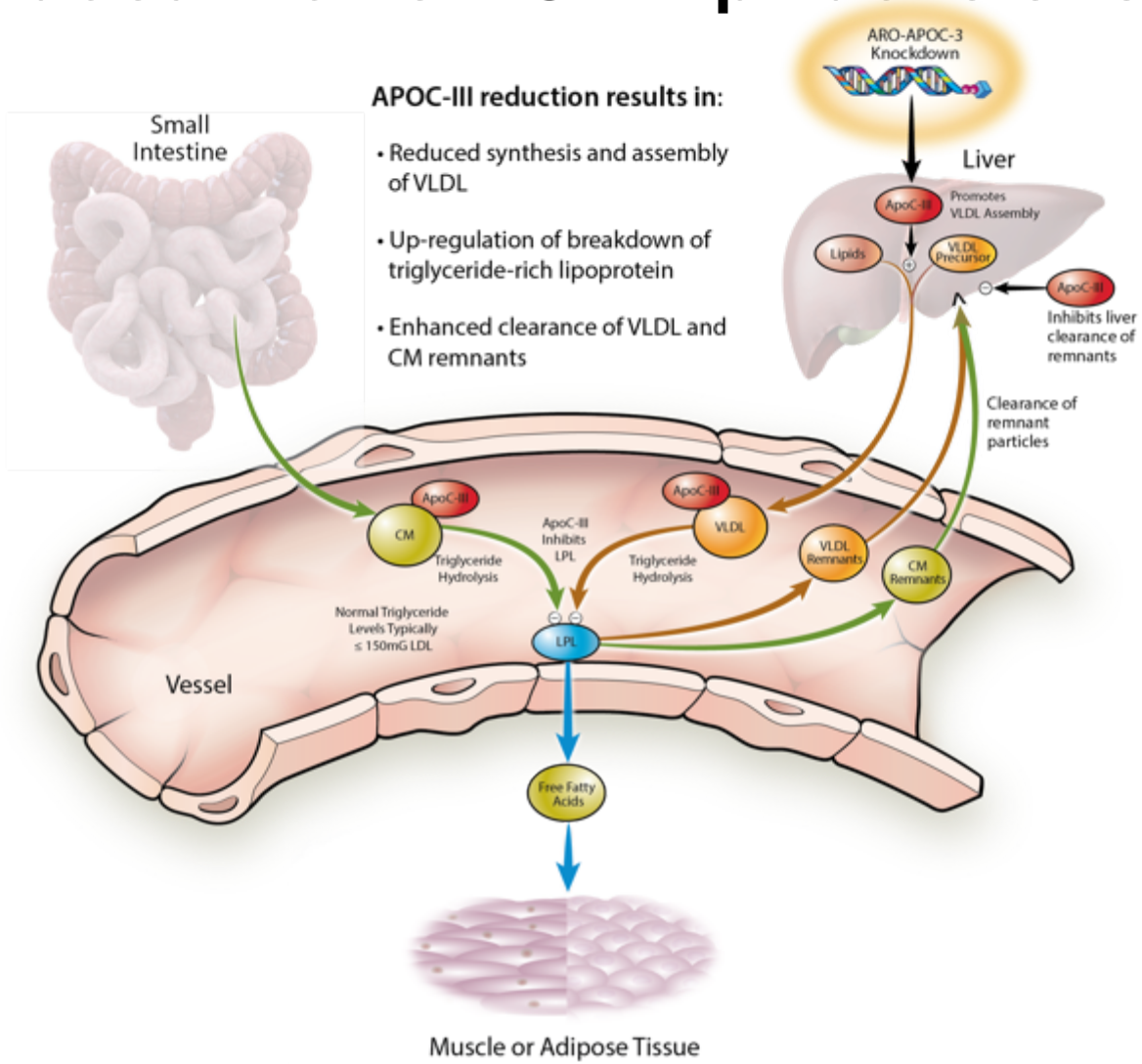
Activators

- 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

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



Most hypertriglyceridemia is not a pancreatitis risk

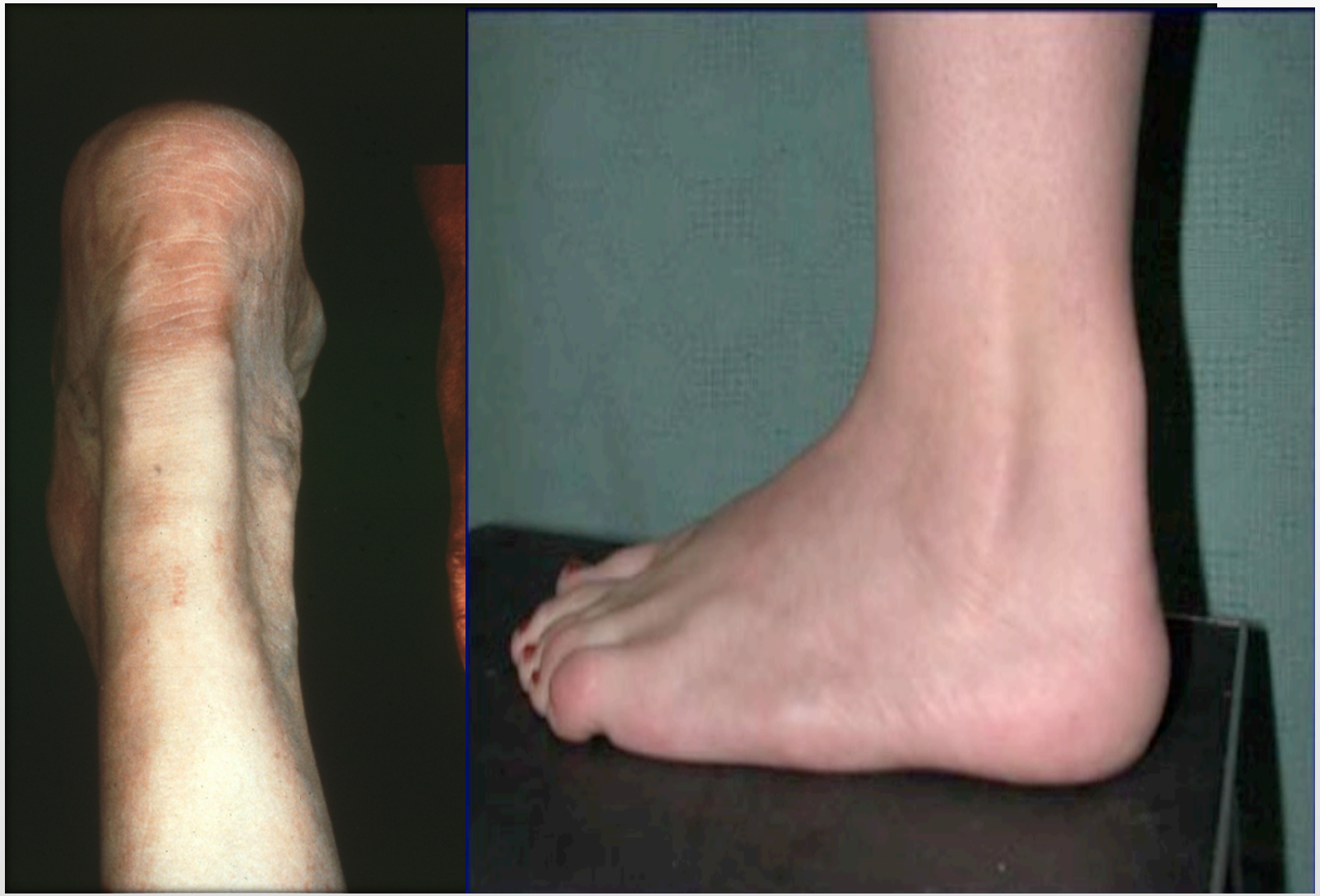
Does it cause heart disease?

NYU Langone Health

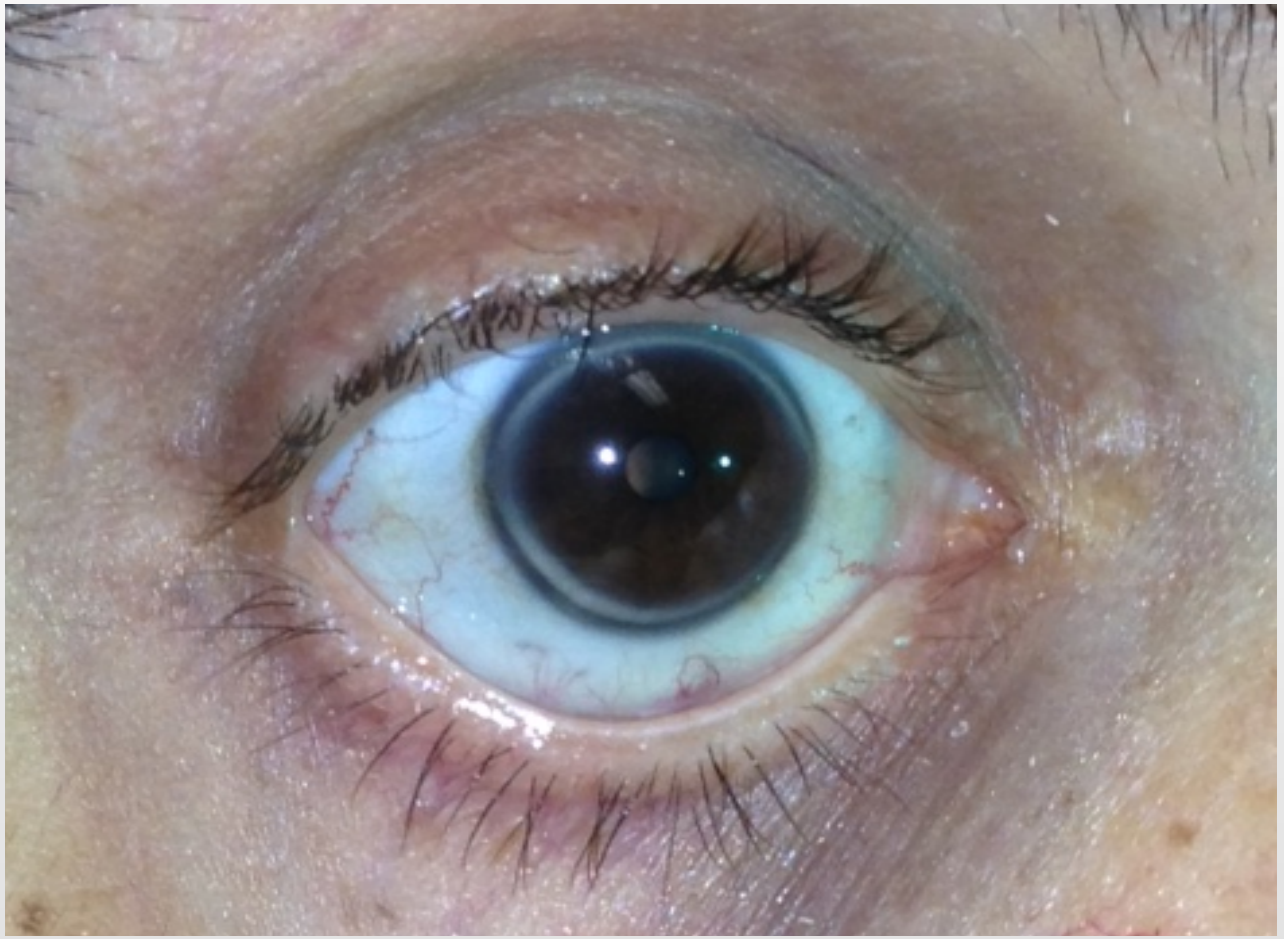
2019 – REDUCE-IT

- Icosapent ethyl (Vascepa) omega 3 fatty acid vs mineral oil
- Four grams, >8,179 subjects
- Statin treatment on top of statin, LDL average 75.
- Triglyceride >150 mg/dL, 150-499 mg/dL (average 216).
- Trilgyceride Reduced 18.3% (placebo increased 2.2%)
- ~23% reduction in MACE

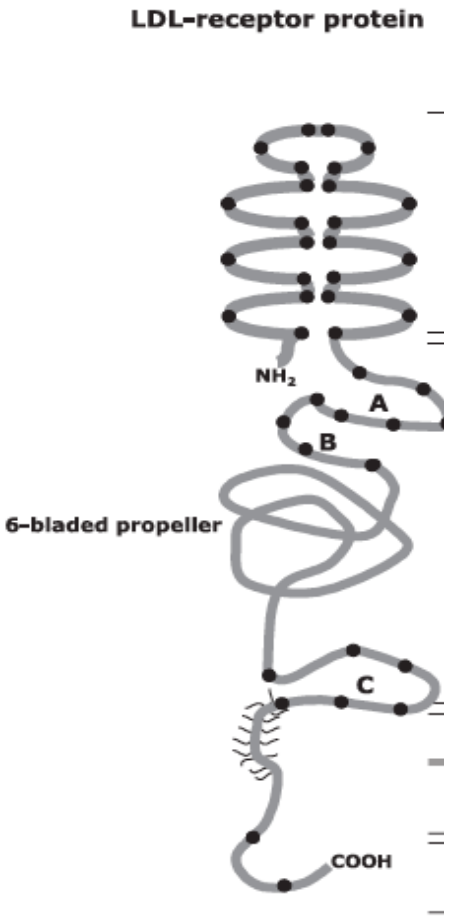
N Engl J Med. 20190 Bhatt et al PMID 30415628.

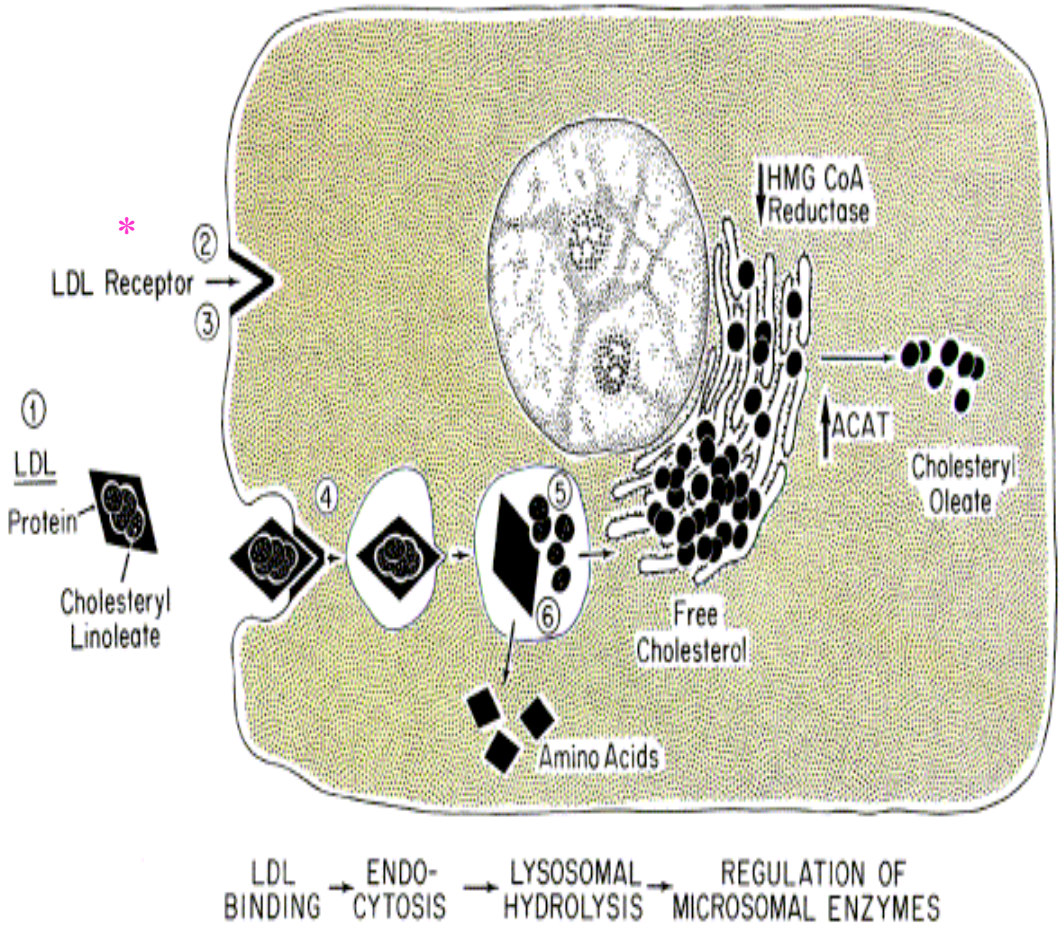


Premature Arcus



Low Density Lipoprotein (LDL) Receptor Regulates Circulating LDL levels





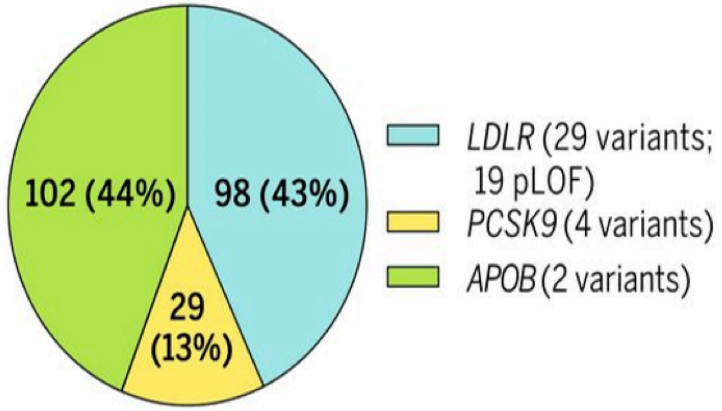
Science 191 (1976), 150-154

Genetic Causes of FH are Common

BUT NOT All are Due to LDL Receptor Mutations on

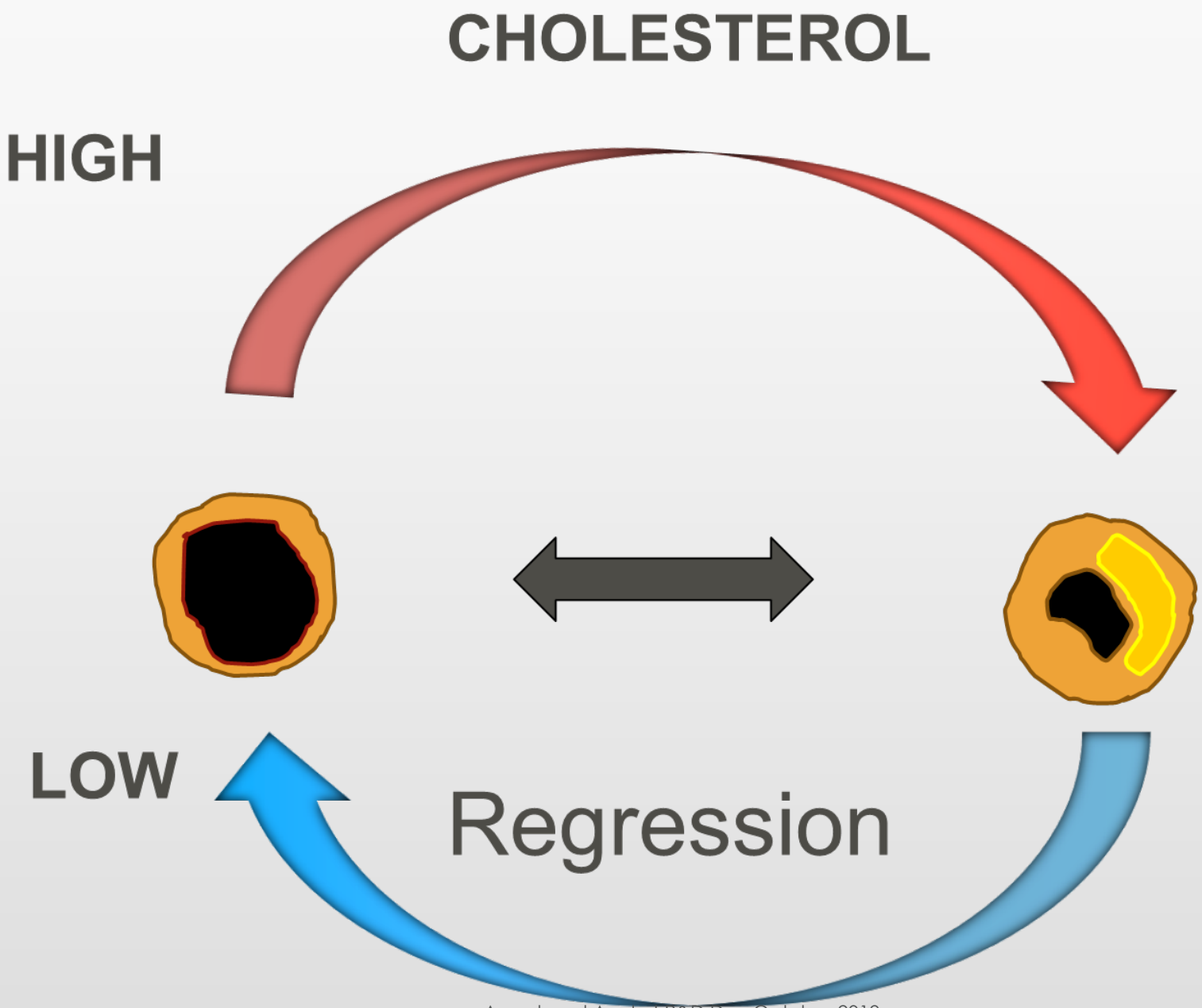
A

Distribution of 229 heterozygous carriers by FH gene

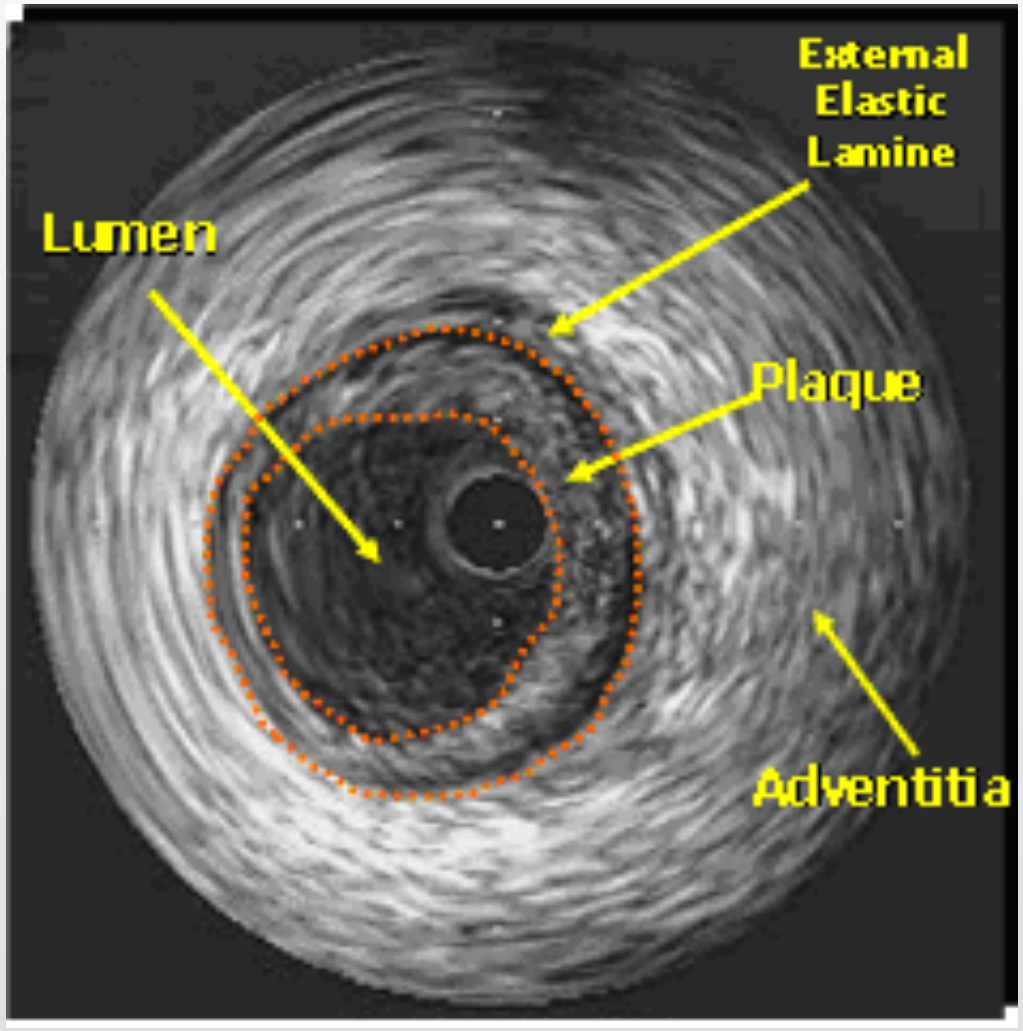


B

Population characteristics	FH variant positive/total	Estimated prevalence
All DiscovEHR participants	229/50,726	1:222
Participants recruited from cardiac catheterization lab	57/6,747	1:118
Participants recruited from other sites	172/43,979	1:256


CHOLESTEROL
HIGH
LOW
Regression

Intravascular Ultrasound to Detect Plaques not Lumen Diameter



From: **Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated PatientsThe GLAGOV Randomized Clinical Trial**

JAMA. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951

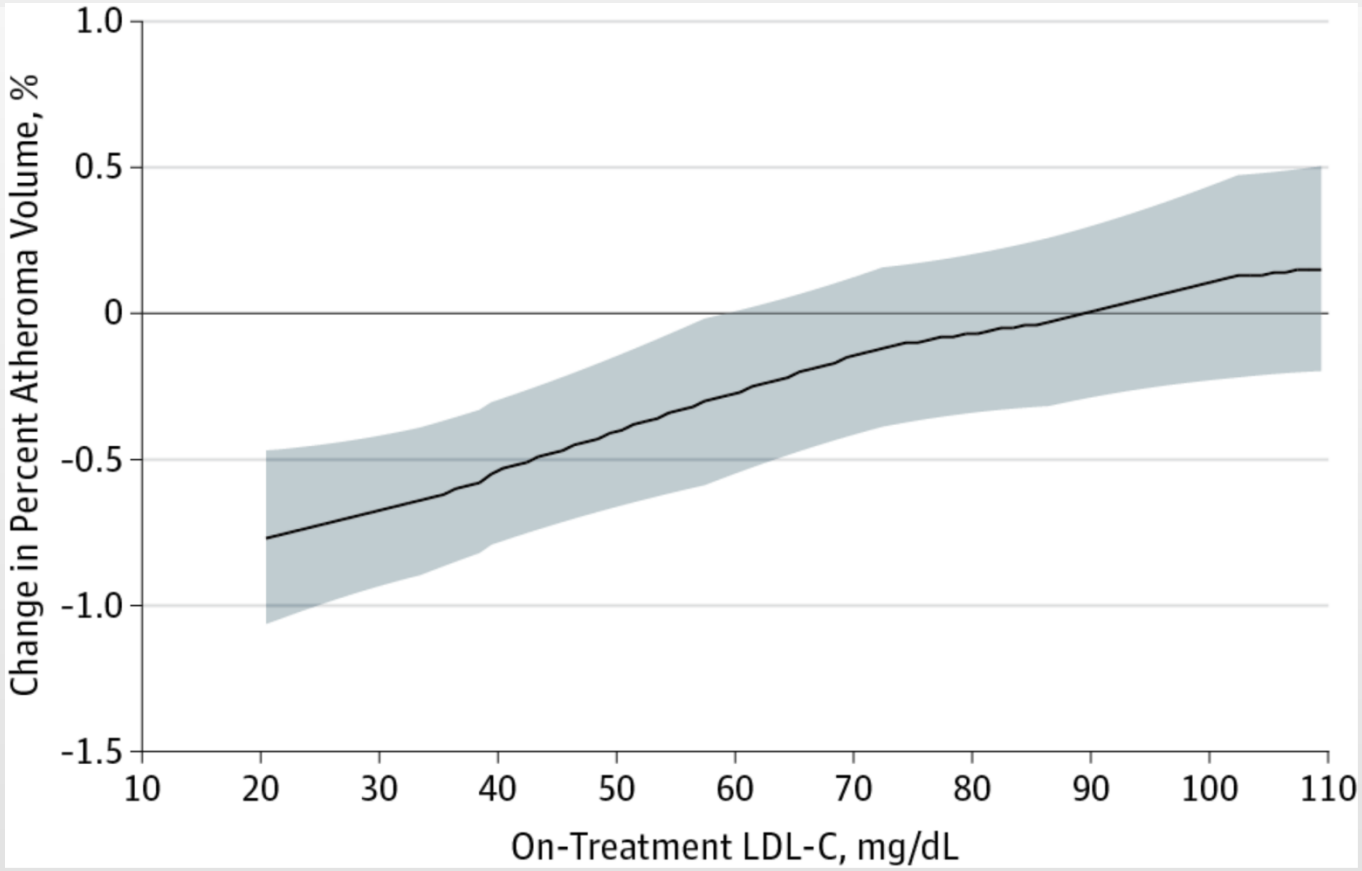


Figure Legend:

Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma VolumeLocal regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

EDITORIAL

Heart Attacks: Gone with the Century?

This issue of *Science* highlights the progress and promise of research in cardiovascular disease, the most frequent cause of death in men over age 35 and women over age 65 in the United States. Heart attacks were recognized as a public health problem only in this century. They are likely to lose this notoriety early in the next. The reason? Four decades of progress in understanding cholesterol and the lipoproteins that carry it in blood plasma.

Nobel Prize Alert: 1985

A Receptor-Mediated Pathway for Cholesterol Homeostasis

Michael S. Brown

Joseph Goldstein

Science. 1996 May 3;272(5262):629

Maybe with CVD, you can never have LDL too low!

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.

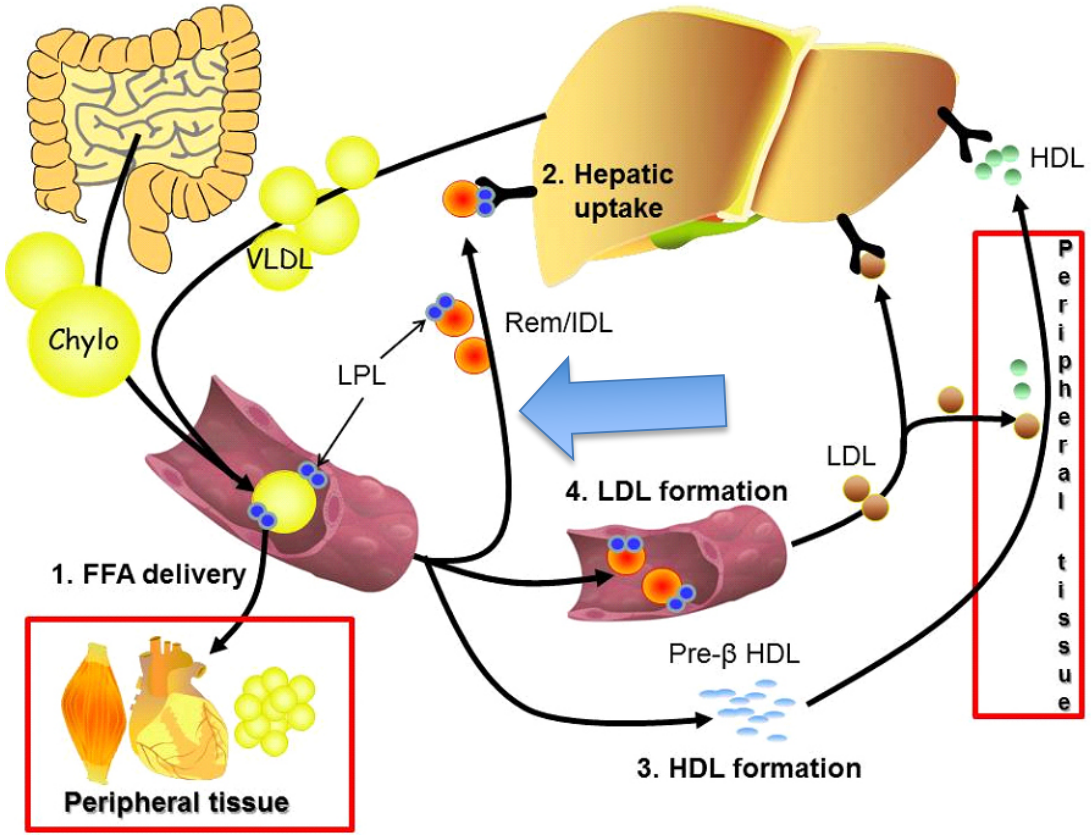
Table 1. Low-Density Lipoprotein (LDL) Receptor Function and Responses to Evinacumab at 4 Weeks.*

Patient	LDL Receptor Genotype†	Baseline LDL Cholesterol Level‡	Decrease from Baseline in LDL Cholesterol Levels at Wk 4	Absolute Decrease from Baseline in LDL Cholesterol Level at Wk 4	LDL Cholesterol Level at Wk 4
		mg/dl	%	*mg/dl*	
A	Homozygous (non-null/non-null)	516	25	128	388
B	Compound heterozygous (non-null/null)	297	27	81	216
C	Homozygous (non-null/non-null)	153	90	138	15
D	Compound heterozygous (non-null/null)	357	77	275	82
E	Homozygous (null/null)	746	26	193	553
F	Homozygous (null/null)	312	42	132	180
G	Compound heterozygous (null/null)	736	44	323	413
H	Compound heterozygous (non-null/non-null)	152	51	77	75
I	Compound heterozygous (non-null/non-null)	117	61	71	46
Overall mean ±SD	—	376±241	49±23	157±90	219±191
Overall median (IQR)	—	312 (153 to 516)	44 (27 to 61)	132 (81 to 193)	180 (75 to 388)

* IQR denotes interquartile range.
† All reported mutations cause familial hypercholesterolemia. Details are provided in Table S1 in the Supplementary Appendix.
‡ Levels were measured while patients were taking baseline lipid-lowering therapy. Details are provided in Table S1 in the Supplementary Appendix.

N ENGL J MED 377;3 NEJM.ORG JULY 20, 2017

Lipoprotein Lipase (LpL) and Lipid Metabolism



Reference: Lipigon Pharmaceuticals AB
Tvistevägen 48 C, SE-90736 Umeå, Sweden

Hypertriglyceridemia and disease

LDL cholesterol and why statins are not enough

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

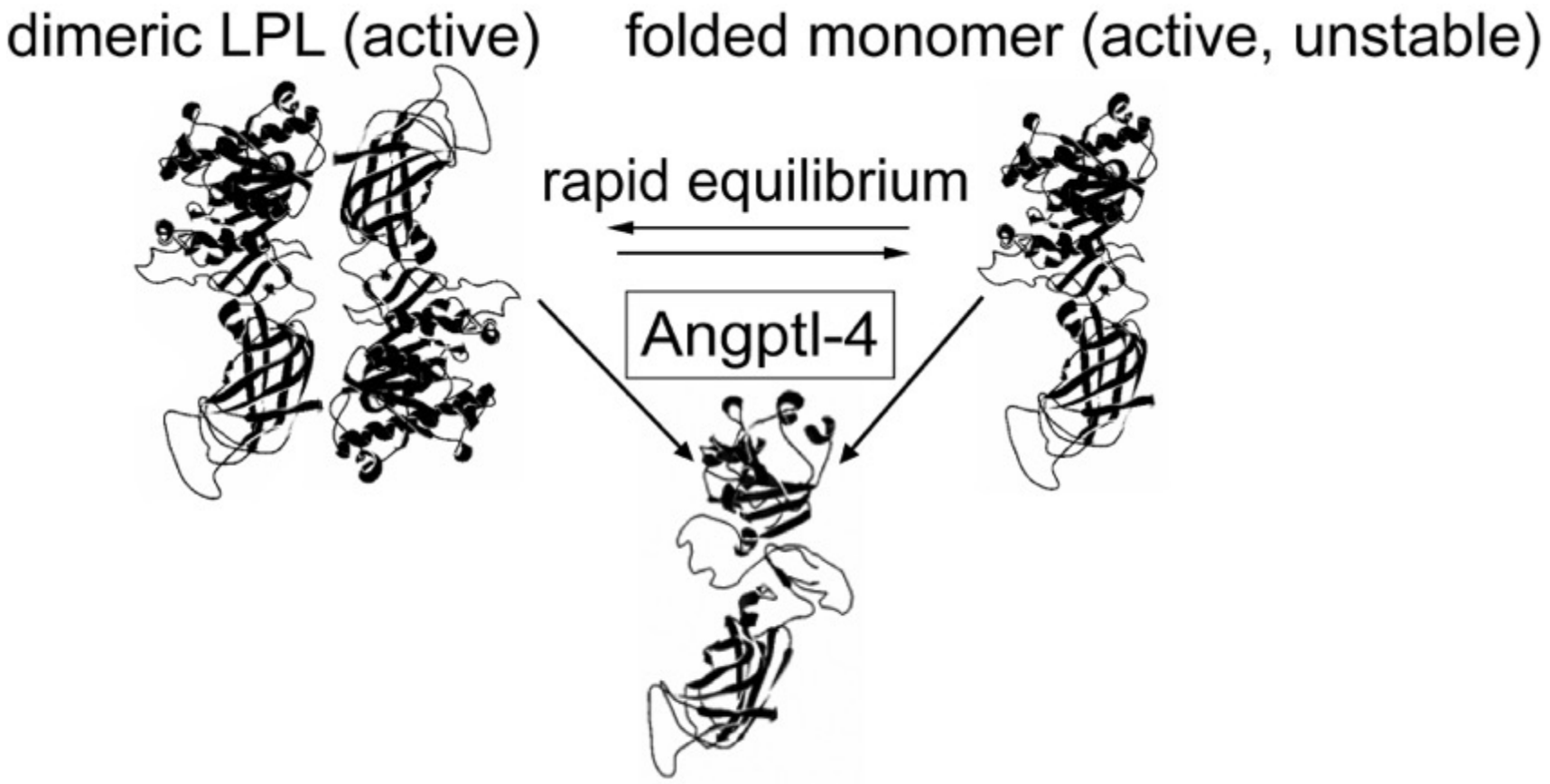
42.1% with diagnosis of unspecified hyperlipidemia (so most not with hyperTG)

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

Novel Regulators of Lipoprotein Lipase Activity



Angiopoietin-like proteins 3, 4, 8

ARO-APOC3 and ARO-ANG3

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

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 inhibition3	*ANGPTL3* deficient heterozygote[4]	*ANGPTL3* deficient homozygote[4]	ANGPTL3 ASO inhibition6	ANGPTL3 Mab Inhibition7 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)**

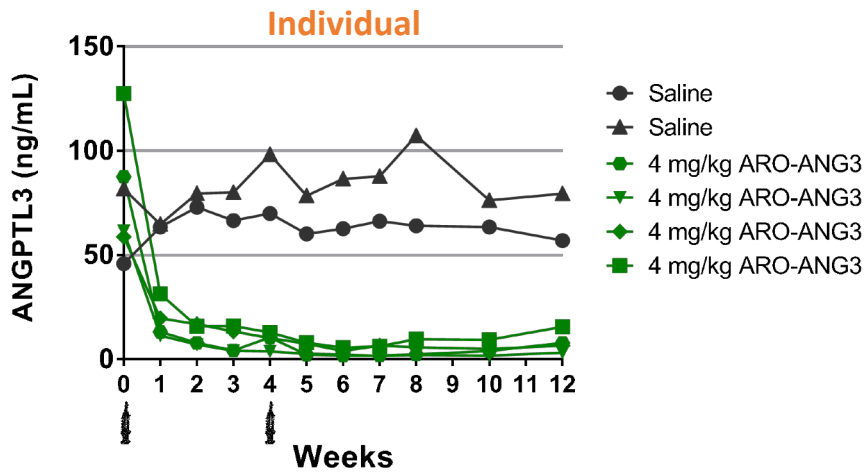
1. Triglyceride working group, NEJM 2014
2. Saleheen et al., Nature 2016
3. Graham et al., Circulation Research 2013. [Phase 1 MAD study, 400 mg dosed D1, D3, D5, D8, D15 and D22 with non-GalNac targeted ASO. Median % change 1-week after last dose in NHV population compared to baseline]
4. Minicocci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

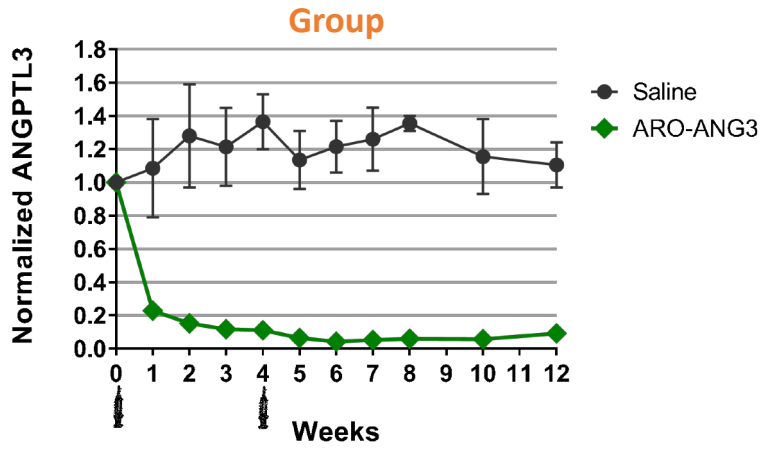
ARO-ANG3 and ARO-APOC3 in High-fructose Corn Syrup (HFCS) Diet-fed Rhesus

- Study was conducted at the University of California, Davis, CA, under the direction of Dr. Peter Havel
- Rhesus monkeys were put on HGCS diet 43 days (Day -43) before dosing. These animals were known to develop increased plasma triglycerides on a HFCS diet protocol
- Key study parameters:
  - ARO-ANG3 and ARO-APOC3 (N=4 each) dosed at 4 mg/kg on day 1 and 29, two animals received normal saline control

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

Reductions in serum ANGPTL3 protein levels

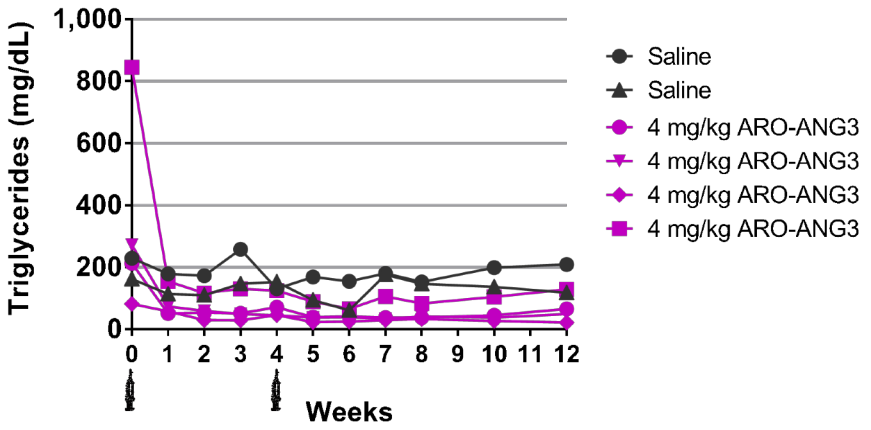


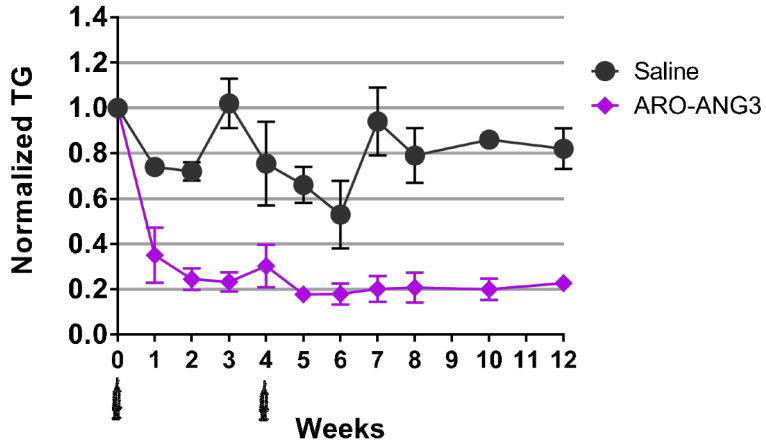


- SQ doses on Day 1 and 29
- Over 95% maximum reductions in serum ANGPTL3 protein levels
- Normalized to pre-dose values

Reductions in serum TGs

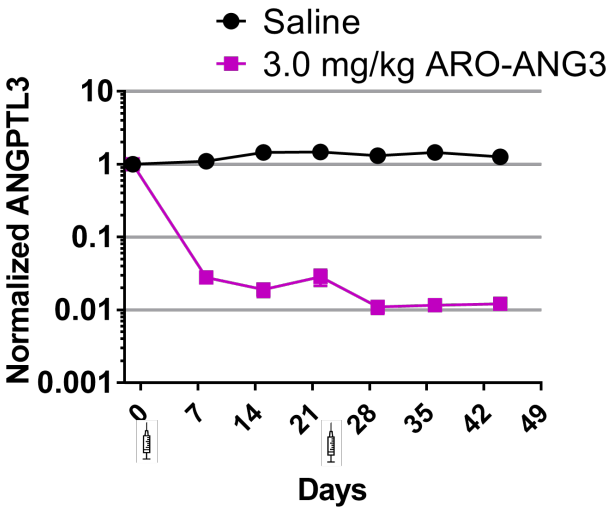
Group averages ± SEM

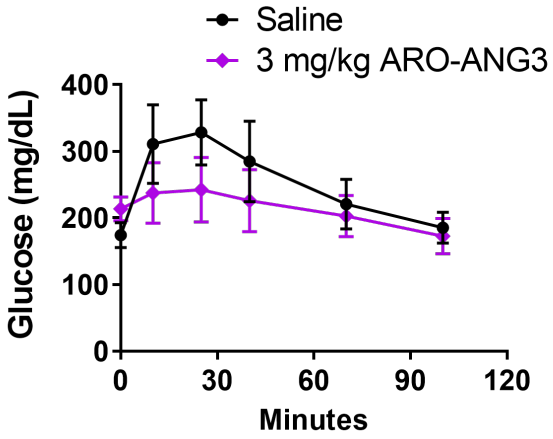




- Animals on fructose diet for 6 weeks
- Variable diet-induced dyslipidemia
- 80% maximum mean reductions in TGs
- **30-40% reductions in LDL**

Improvements in Glucose Tolerance and Reduction in Hepatic Steatosis in 8 Week Old DIO Mice

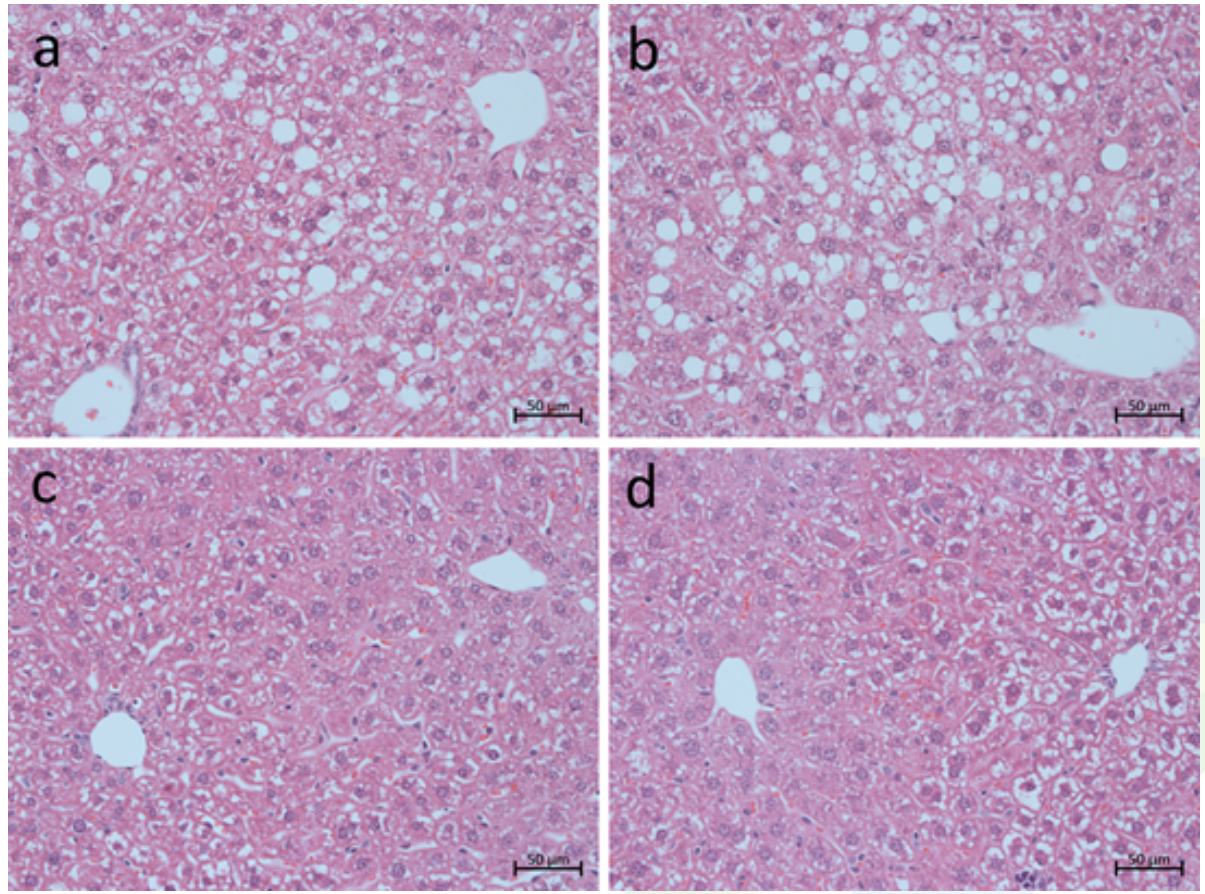




- **Maximum serum ANGPTL3 reductions of 99% (after second dose)**
- **Maximum TGs reductions of 54% (from 70 mg/dL to 31 mg/dL)**
- **Maximum LDL-C reductions of 65% (from 20 mg/dL to 7 mg/dL)**

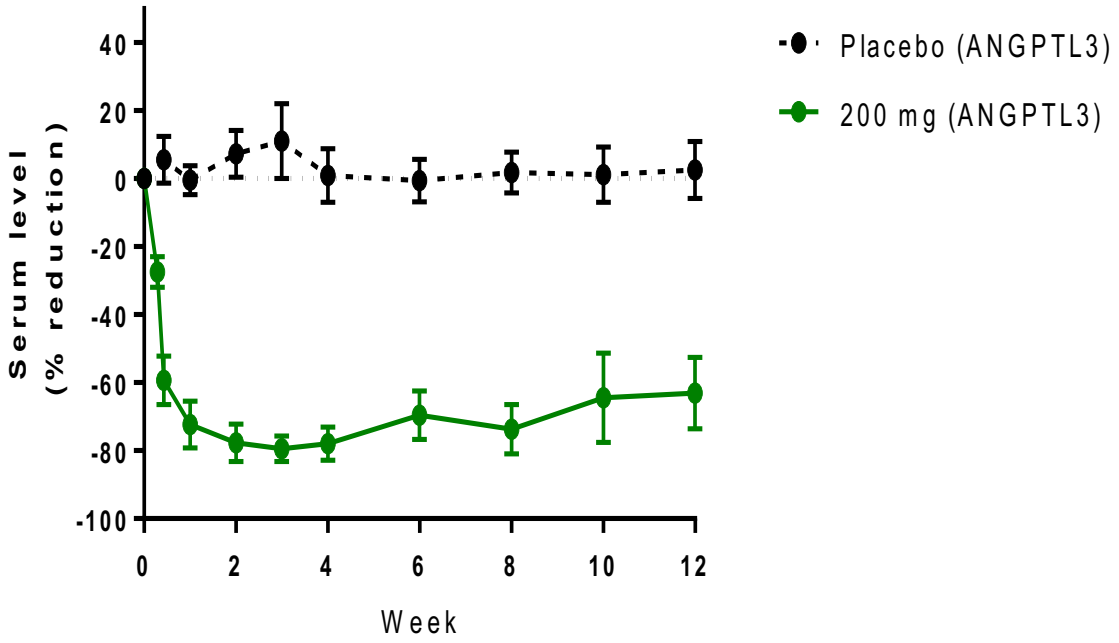
Liver Histology (H&E)

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

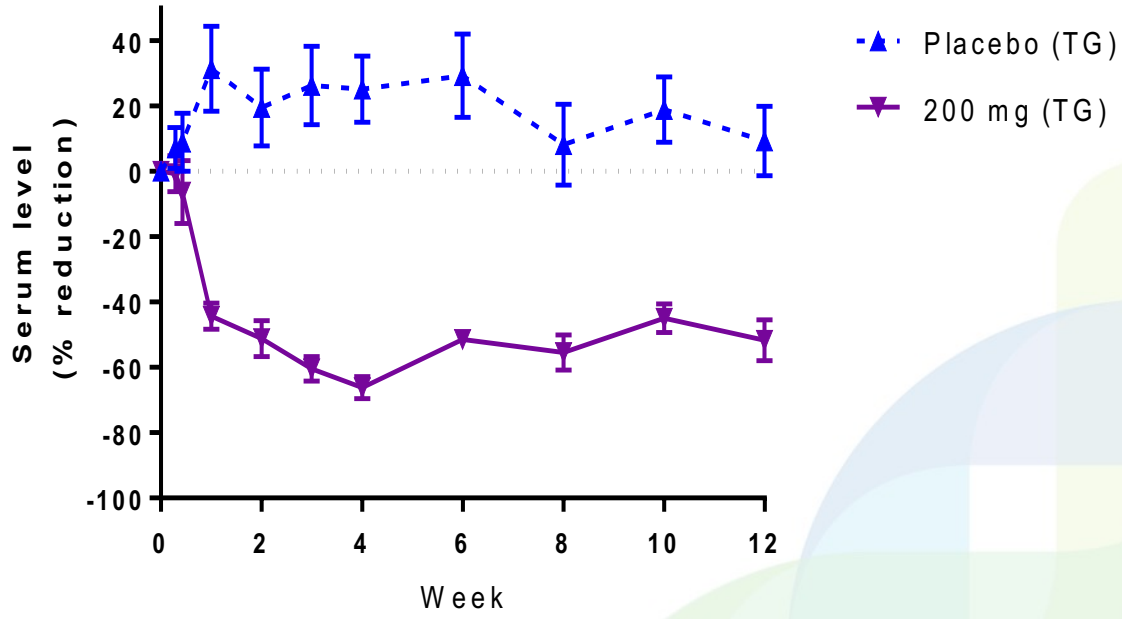


First Look at ARO-ANG3 in Healthy Volunteers – Single 200 mg dose through week 12

ANGPTL3



TGs



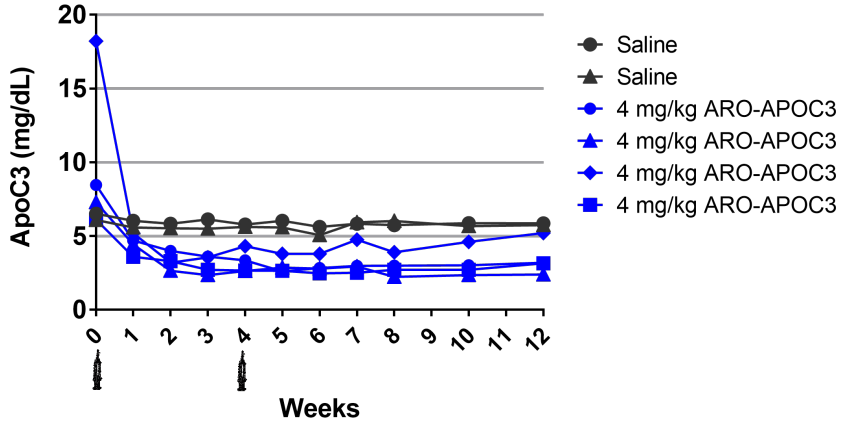
Top Line Safety Observations with ARO-ANG3

- 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

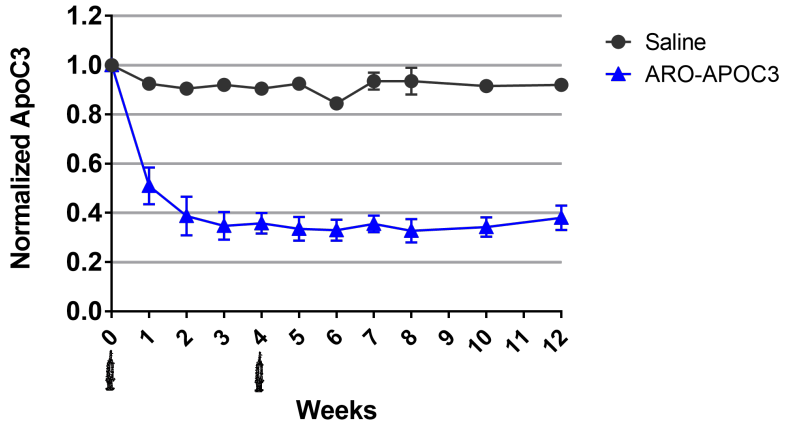
ARO-APOC3 in HFCS-induced Dyslipidemic Rhesus Monkeys

Reductions in serum APOC3 protein levels

Individual



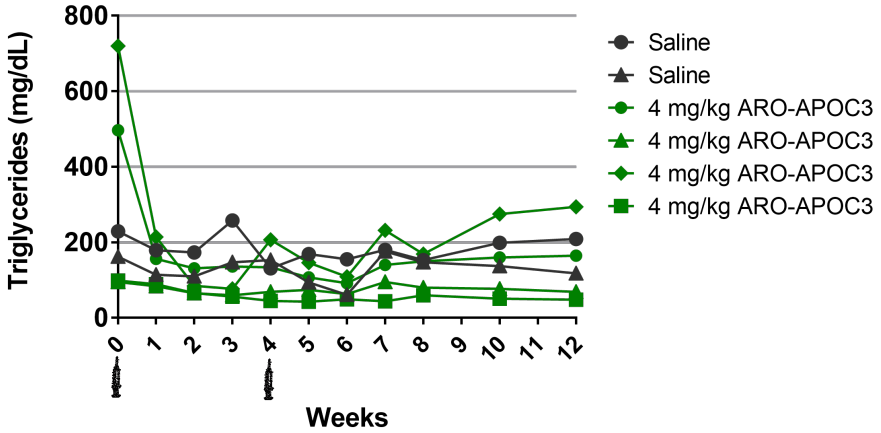
Group

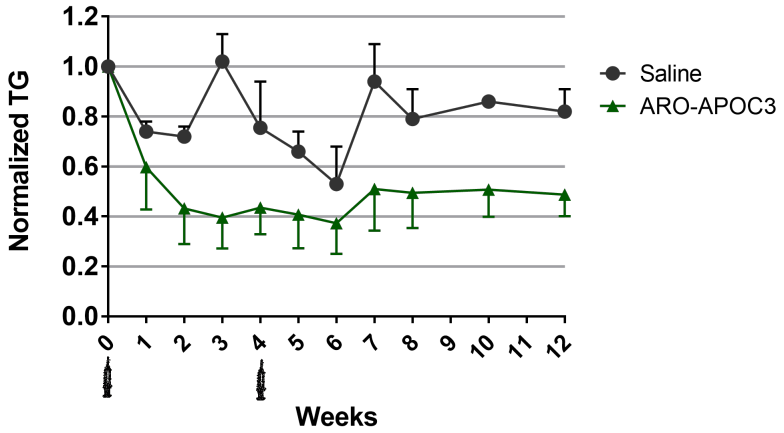


- SC doses on Day 1 and 29
- **Over 67% maximum reductions in serum APOC3 protein levels**
- Normalized to pre-dose values

Reductions in serum TGs

Group averages ± SEM

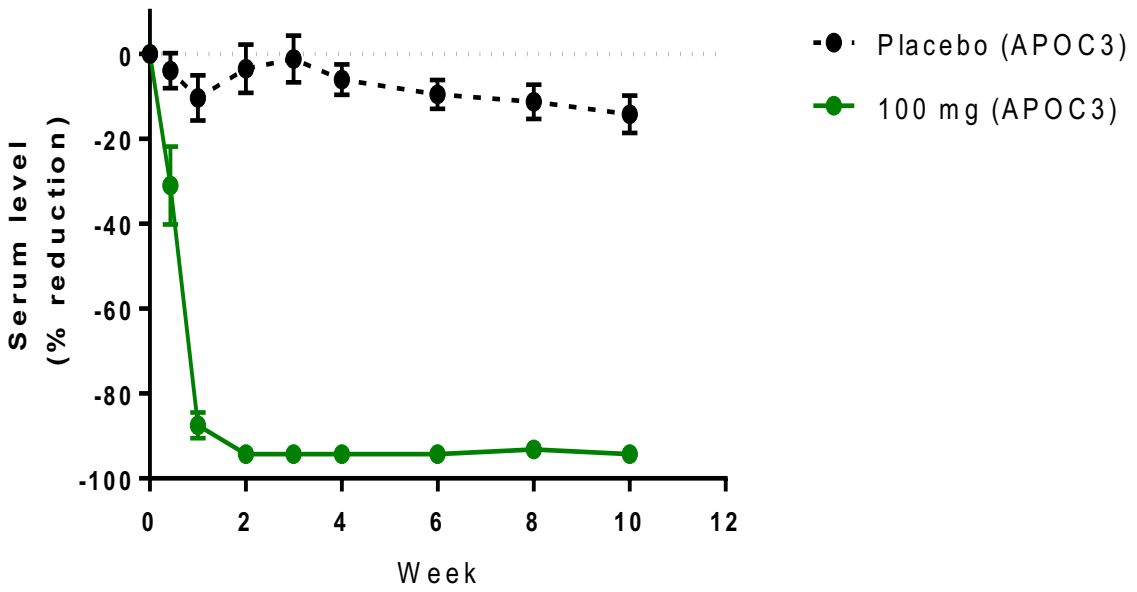




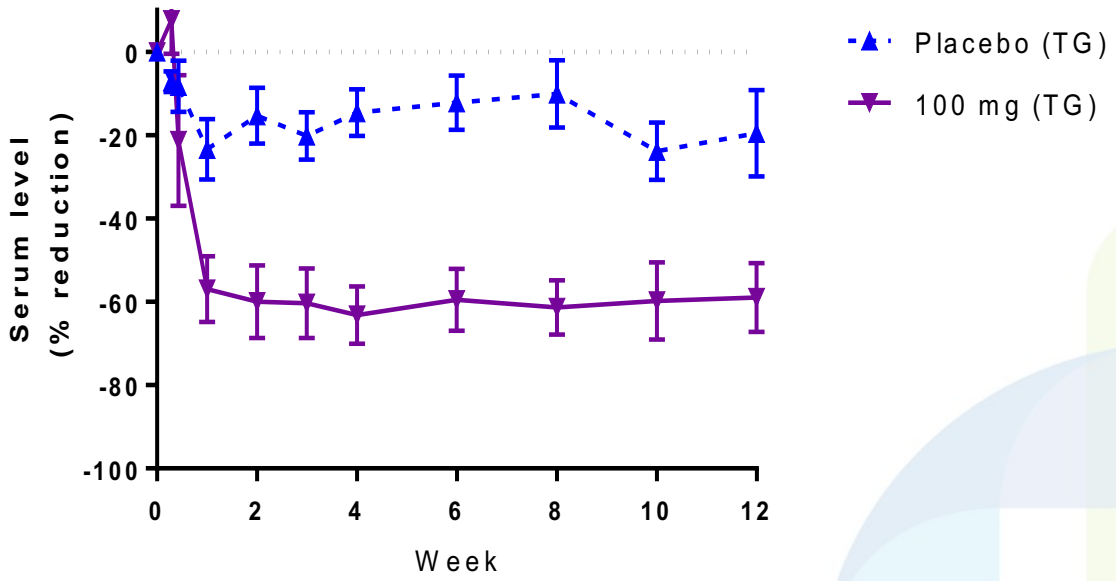
- Animals on fructose diet for 6 weeks
- Variable diet-induced dyslipidemia
- **63% max mean reductions in TGs**
- **30% max mean reductions in LDL**

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)

Potential points of differentiation

- **APOC3**
  - We don't expect Waylivra® to make it to market in US or be competitive if it does
  - If the LICA version is developed in orphan indications we would expect:
    - Similar performance to ARO-APOC3 regarding observed lipid changes in like patient populations
    - Shorter duration of activity necessitating more frequent dosing
    - Uncertain safety profile regarding class effects on platelets, skin lesions, etc

- **ANGPTL3**
  - If the LICA version is developed in orphan indications we would expect:
    - Similar performance to ARO-ANG3 regarding observed lipid changes in like patient populations
    - Shorter duration of activity necessitating more frequent dosing
    - Uncertain safety profile regarding class effects on platelets, skin lesions, etc
  - For the Regeneron monoclonal antibody (evinacumab) we would expect:
    - Similar performance to ARO-ANG3 regarding observed lipid changes in like patient populations
    - Much shorter duration of activity requiring monthly IV doses or more frequent subcutaneous doses
    - Limited/no effects on steatosis and insulin sensitivity

Preliminary Development Plan for ARO-ANG3

- ***Note that this could change after review of full multi-dose dataset in various patient populations from current study and after discussions with FDA/EMA***

- Current thinking is that HoFH would be studied in a single core pivotal study (n=50-60) with 24 week duration. Reduction in LDL-C as endpoint
- Safety data would be supplemented with a study in HeFH not achieving goal despite maximum statins ± PCSK9 inhibitors
  - Possibility of this patient population for labeling will require discussions with regulatory agencies.
- Other potential indications such as secondary prevention, NASH to be considered in the future

Preliminary Development Plan for ARO-APOC3

- ***Note that this could change after review of full multi-dose dataset in various patient populations from current study and after discussions with FDA/EMA***

- Current thinking is that FCS would be studied in a single core pivotal study (n=50-60) with 24 week duration. Reduction in plasma triglycerides as endpoint
- Safety data would be supplemented with a study in polygenic patients with severely elevated triglycerides and a history of pancreatitis
    - Possibility of this patient population for labeling will require discussions with regulatory agencies.
- Other potential indications such as FPL and secondary prevention to be considered in the future

What to expect at upcoming meetings

- AHA
  - Late breakers for both ARO-APOC3 and ARO-ANG3 will be presented on Nov 18 in the Late Breaking Science VI: New Frontiers in Lipid Therapy session
  - Presentations will cover full dose response for single doses in normal volunteers and will include results for a wide selection of lipids and apo-lipoproteins

- Meetings in first half 2020
  - Expect to submit late breakers for ACC and NLA meetings
  - If accepted, these should include multiple dose data from volunteers and various patient groups

Conclusions

- There is strong genetic validation that loss of function mutations in ANGPTL3 or APOC3 result in improved cardiovascular outcomes relative to the population at large associated with clear lipid phenotypes
- These loss of function mutations have not been associated with demonstrated adverse phenotypes
- The ability to re-capitulate the lipid phenotypes seen in these genetic studies has been demonstrated for anti-sense, monoclonal antibodies (ANGPTL3 only) and now RNAi
- There are both orphan and non-orphan potential indications for these drugs
- Competitor compounds have vulnerabilities making RNAi an important potential option

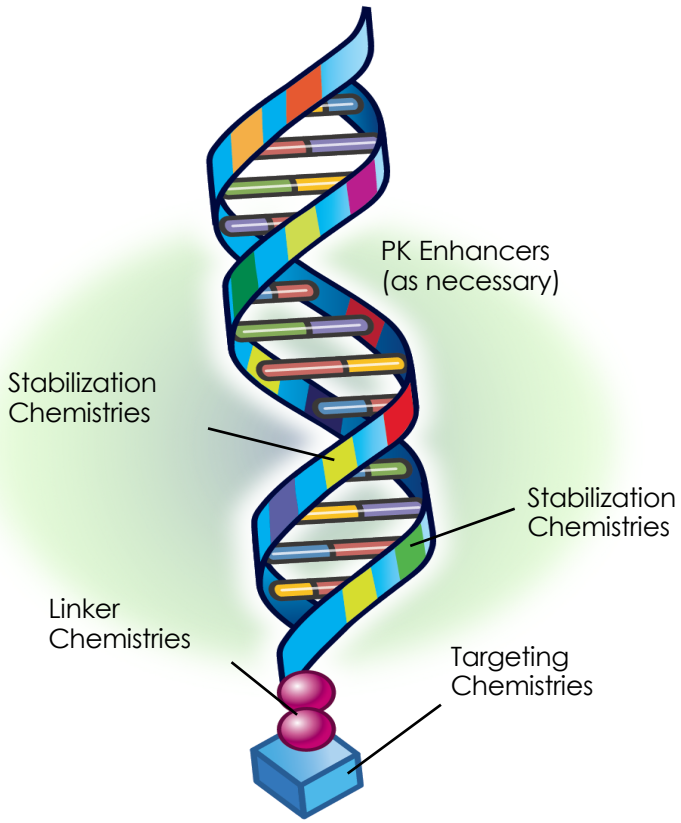
ARO-AAT

James Hamilton, M.D.
Vice President, Clinical Development

ARO-AAT

Targeted RNAi Molecule

TRiM™ platform



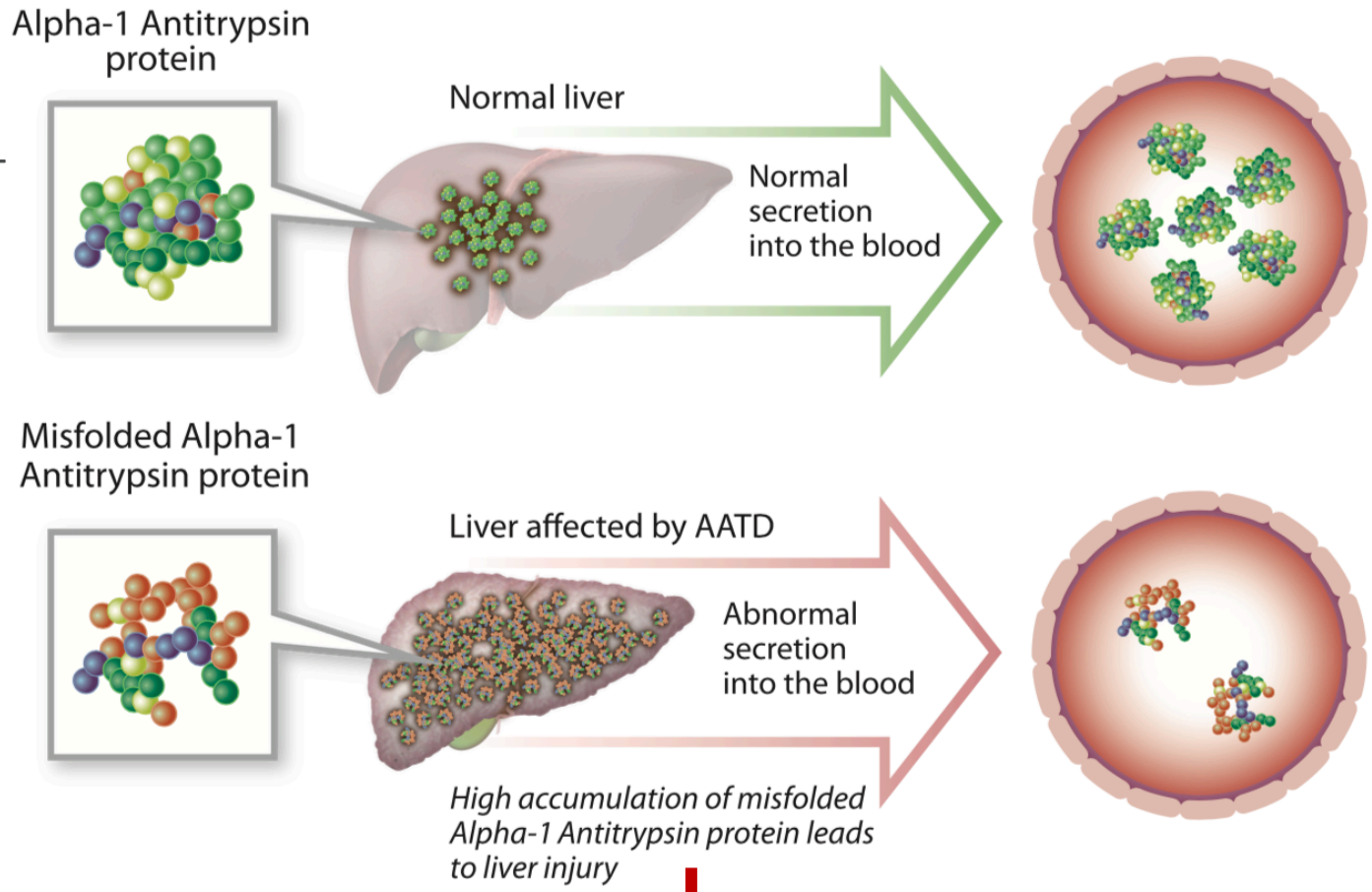
ARO-AAT: Investigational product in development to address liver disease in AATD

Hepatocyte targeted RNAi molecule

Specifically targets AAT mRNA

- Silencing is hepatocyte specific
- Designed to minimize off-target gene silencing

Liver Disease in Alpha-1 Antitrypsin Deficiency



Normal blood levels of normal protein protect lungs, no liver accumulation

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

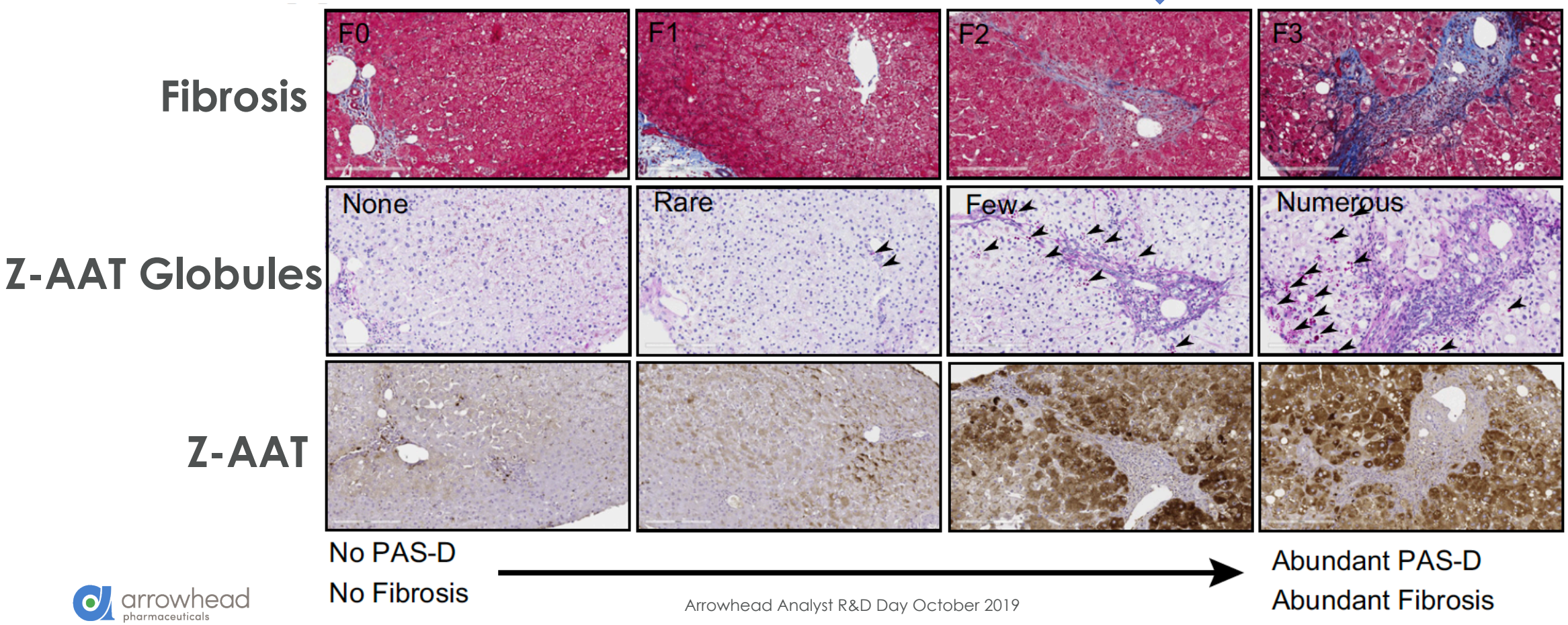
No current treatment

Lung Disease Treated with AAT protein replacement therapy today

Underlying Fibrosis Found in Natural History Study

- 94 ZZ Patients underwent a Biopsy
- **33 (35%)** had what was considered significant (≥ F2)fibrosis
- Similar findings in EU PiZZ natural hx study *(Hamesch et al., Gastro, 2019)*

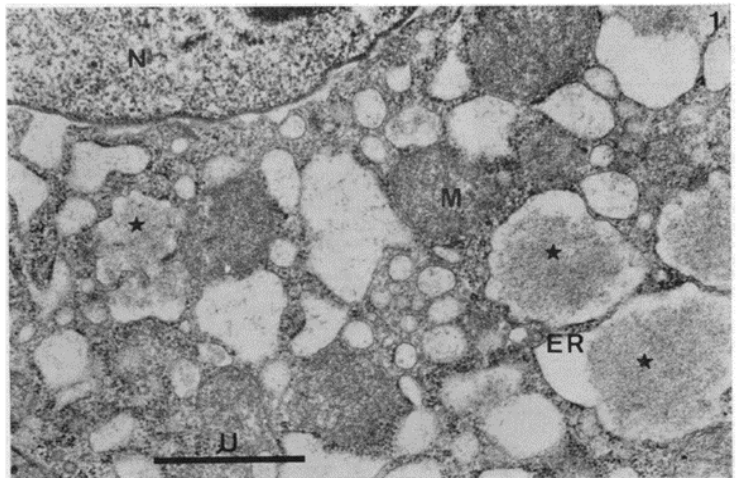
Clark et., *J. Hep.* 2018



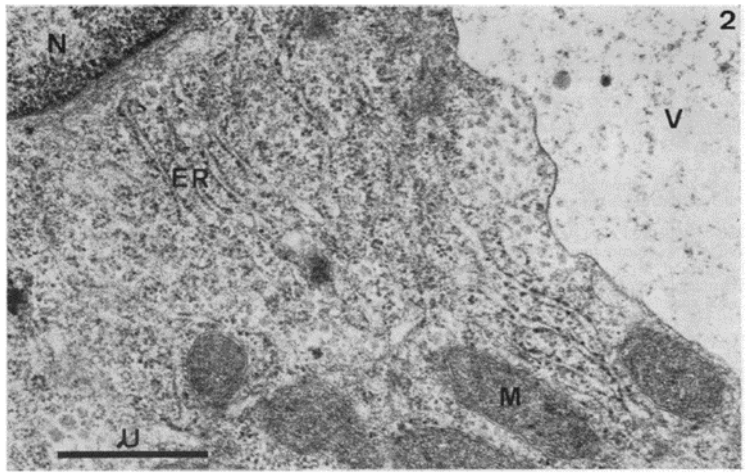
ARO-AAT Therapeutic Rationale

- RNAi trigger designed to stop Z-AAT production by silencing AAT gene to:
  - Prevent accumulation of Z-AAT in liver
  - Allow clearance of accumulated Z-AAT protein
  - Prevent repeated cycles of cellular damage
  - Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)

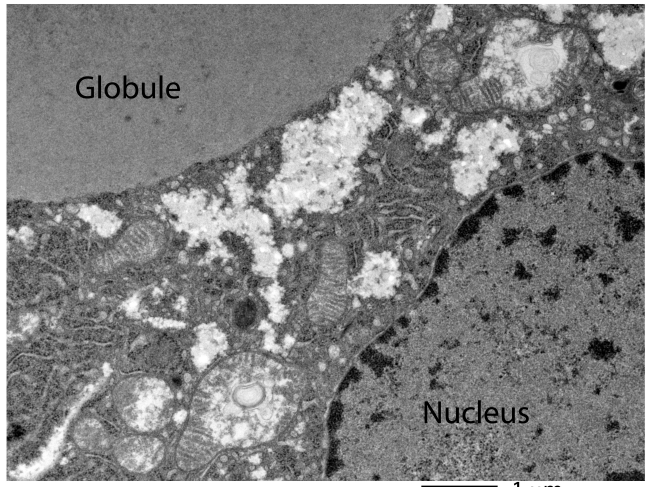


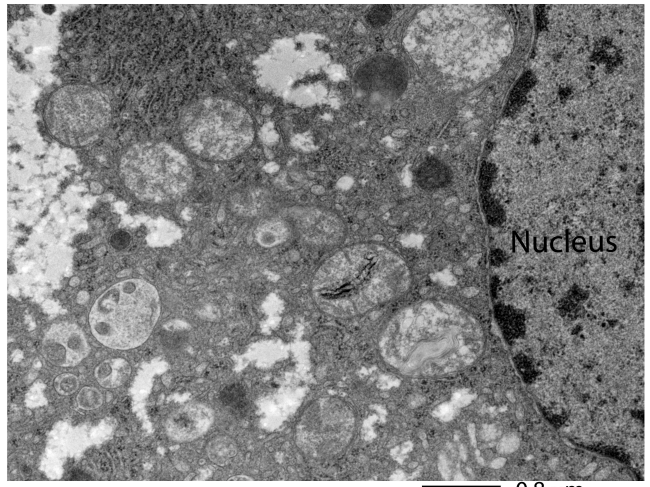
Pi null phenotype (normal)



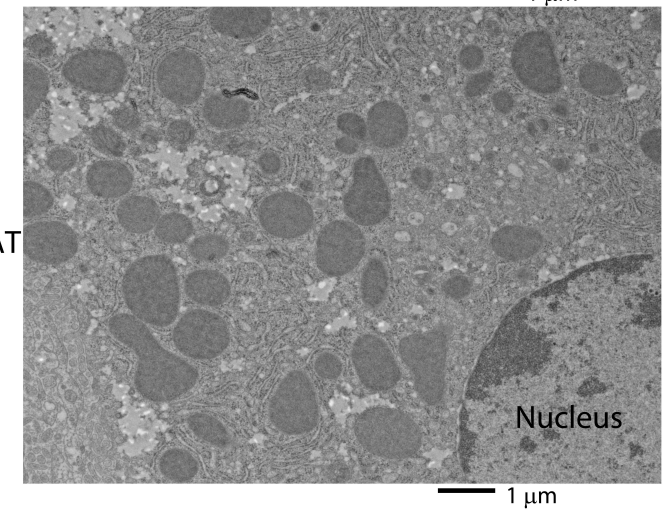
RNAi treatment of PiZ mice restored hepatocyte ultrastructure

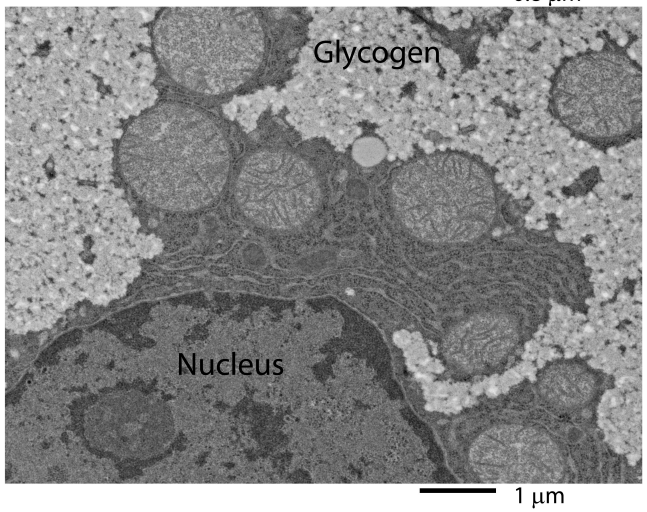
PiZ saline





PiZ ARC-AAT

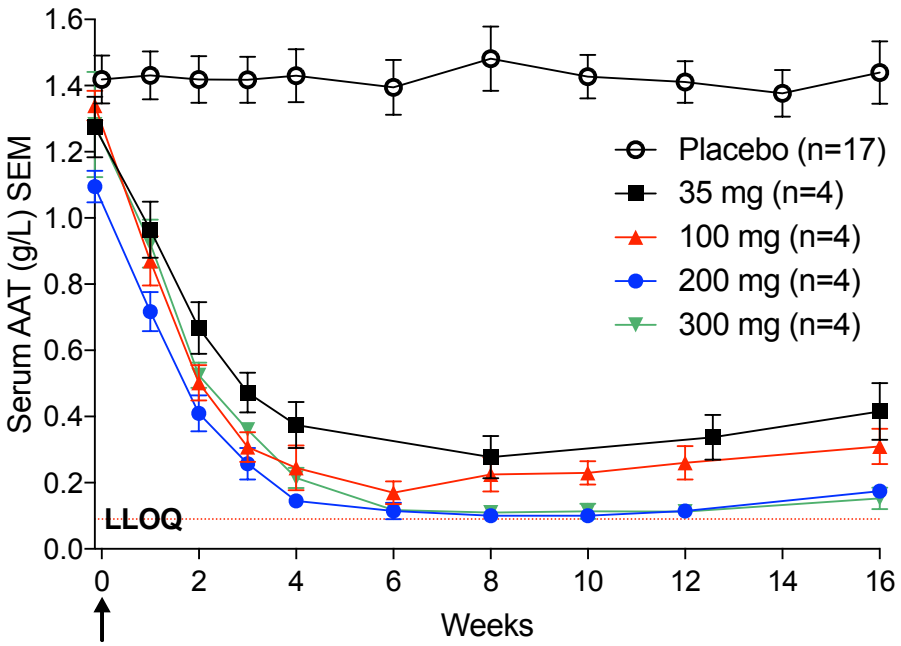




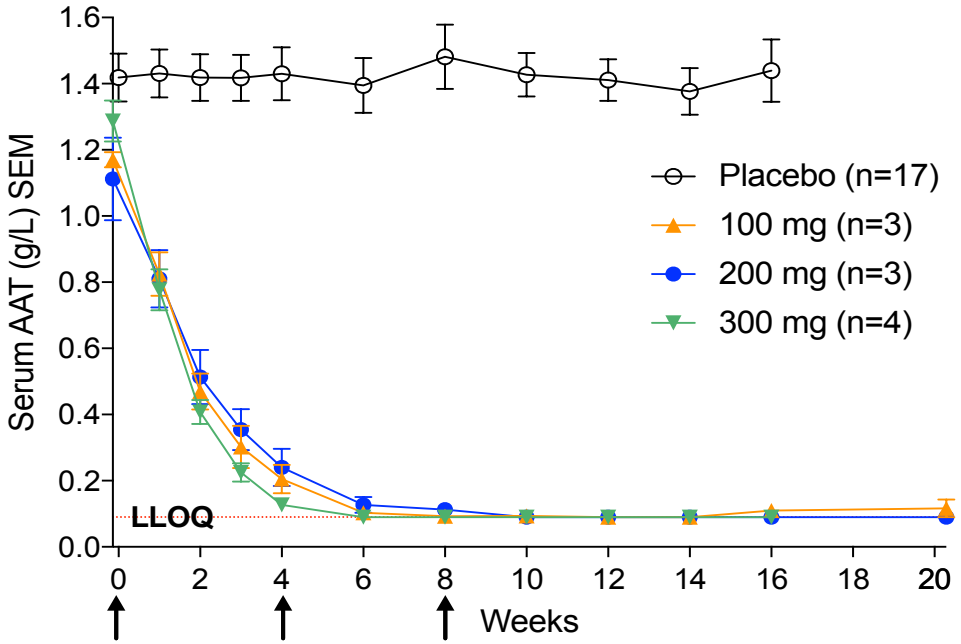
- Age-matched saline-injected control PiZ mice
  - Very large globules
  - Few and mostly damaged mitochondria
  - Dilated ER
  - Reduced glycogen and metabolic space
- RNAi-treated PiZ mice
  - No Globules
  - Abundant mitochondria that have a normal (healthy) appearance
  - Normalized ER more similar to wild-type mouse
  - Abundant glycogen storage

ARO-AAT Phase 1, NHV SAD/MAD Study

Single dose ARO-AAT



Multiple dose ARO-AAT



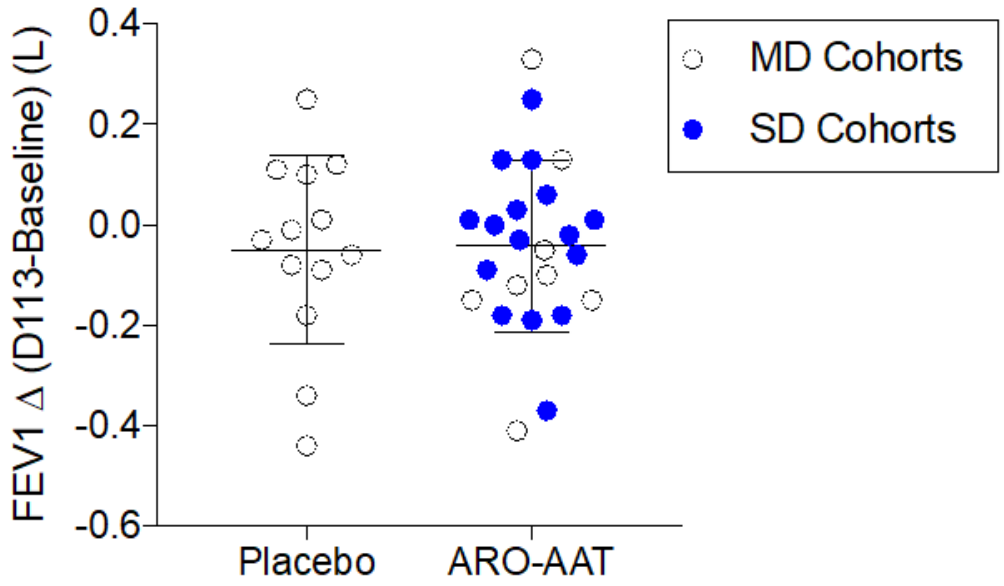
Supports quarterly or less frequent dosing

ARO-AAT Phase 1: Summary Safety

ARO-AAT Phase 1, NHV SAD/MAD study Safety Summary

- 45 NHVs received at least 1 dose (28 active, 17 placebo)
- No deaths, severe AEs or serious AEs reported
- Mild Local Injection Site Reaction (LISR) in 4% of ARO-AAT injections
  - LISR defined based on MedDRA preferred term for injection site AEs with duration of at least 48 hours
- No AEs secondary to platelet count declines, changes in renal function parameters or changes in markers of liver injury/function
  - 3 treatment emergent grade 1 ALT elevations, all returned to baseline by end of study, with max elevation < 2X ULN

FEV1 Summary Through Day 113/EOS

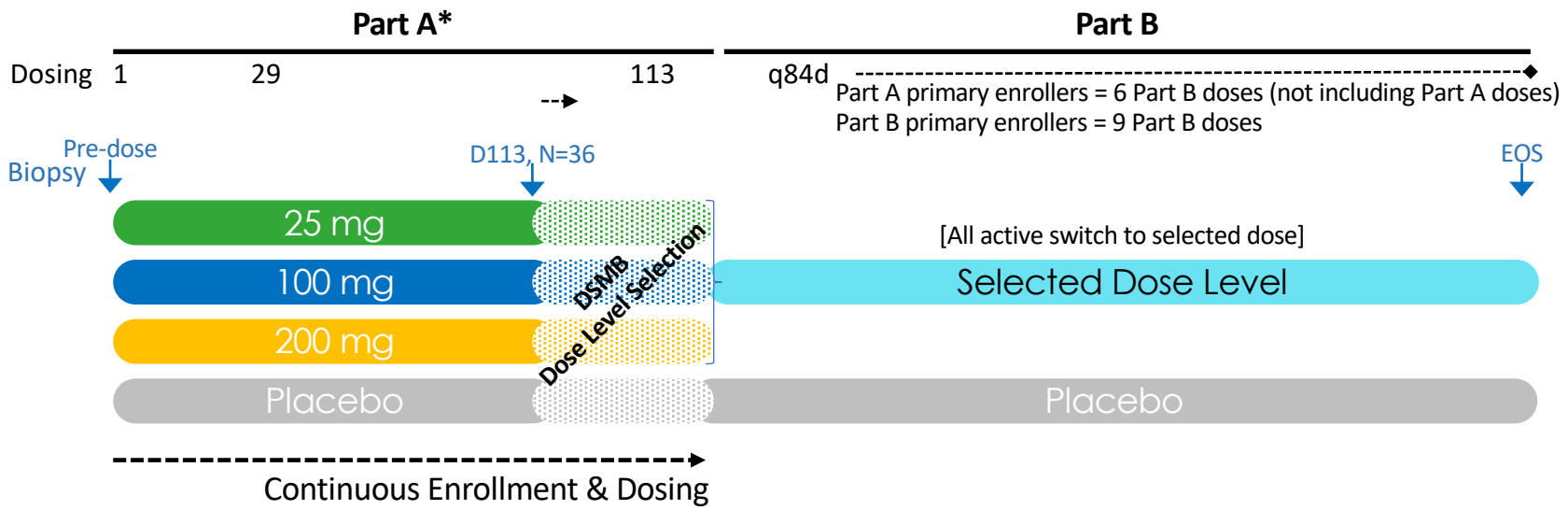


AASLD 2018

- No AEs of dyspnea or other symptoms consistent with lung parenchymal damage
- No statistically significant difference (ANCOVA) between active versus placebo FEV1 changes (% predicted or mL) at any study visit.

SEQUOIA (AROAAT2001) Study Design

N=120 total, Randomization = 2:1 (active:placebo)



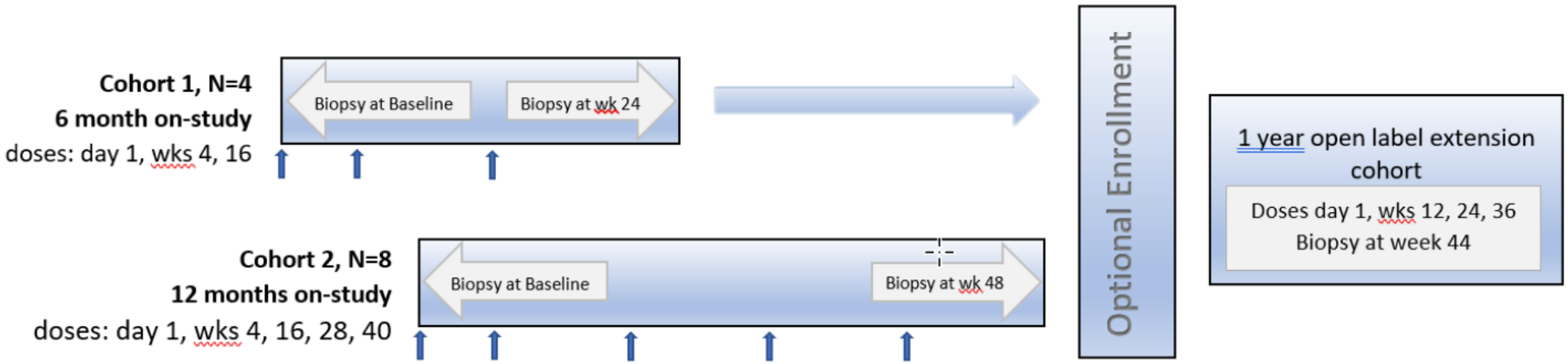
* All patients enrolled prior to Part B dose selection will be randomized to Part A cohorts and receive at least 3 doses at the Part A dose level before switching to Part B dose level. Only 1st 36 will require D113 biopsy.

Placebo patients will be rolled over to ARO-AAT at end of study

Key Questions to Answer in SEQUOIA

- Phase 2 (Part A)
  - Dose response for hepatocyte Z-AAT knockdown in PiZZ AATD patients
  - Safety/tolerability (including pulmonary) of multi-dose treatment in PiZZ AATD patients
  - Best dose for maximizing AAT knockdown in context of safety/tolerability
    - Best dose selection by DSMB in consultation with FDA (sponsor remains blinded)
- Phase 3 (Part B)
  - Improvement in an AATD specific histological scale without worsening of fibrosis
  - Safety with special attention to pulmonary effects

AROAAT2002 Study Design



Study Rationale: Understand changes in liver histology with varied treatment durations

Primary Objective: To evaluate effect of ARO-AAT on a histological liver disease activity scale in patients with AAT-associated liver disease over time

Clinical Development: Future Directions

- Pediatrics:
  - Timing of liver disease presentation bimodal with peaks in first few years of age and 5th decade.
  - Pediatric disease may progress rapidly, thus opportunity to intervene early with clear treatment effect.
  - Opportunity to use biomarkers or historical controls in trial design?
- AATD Cirrhosis:
  - Very common for patients to present with cirrhosis
  - Preliminary safety and PK key prior to launching study in cirrhotic alpha-1 patients

The goal is to eventually address all patient populations that need treatment

Conclusions

- Significant fibrotic AATD is present in 1/3 of asymptomatic PiZZ adults even with normal ALT
- In the absence of smoking history, 28% of AATD patients die from cirrhosis (HA Tanash et al., Thorax, 2008)
- Other than AATD-specific globules, histological features in AATD are similar to those occurring in other fibrotic diseases such as viral hepatitis
- Ultra-structural changes thought to drive hepatocyte death in AATD (mitochondrial and ER disruption) improve with effective RNAi in transgenic PiZ mice
- SEQUOIA (AROAAT2001) is the first study designed to be a potentially pivotal study in PiZZ AATD liver disease

ARO-HSD

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

LOF mutations of HSD17B13 protect against cirrhosis

LOF variant rs72613567

- Associated with a reduced risk of nonalcoholic steatohepatitis and fibrosis
  - Dose dependent decreased odds of developing alcoholic and non-alcoholic liver disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease

N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, U.L. Mirshahi, D.J. Carey, C.D. Still, M.D. Feldman, A. Small, S.M. Damrauer, D.J. Rader, B. Zambrowicz, W. Olson, A.J. Murphy, I.B. Borecki, A.R. Shuldiner, J.G. Reid, J.D. Overton, G.D. Yancopoulos, H.H. Hobbs, J.C. Cohen, O. Gottesman, T.M. Teslovich, A. Baras, T. Mirshahi, J. Gromada, and F.E. Dewey

Ref: *N Engl J Med.* **2018**, 1096-1106

B Genotypic and Allelic Odds Ratios

Description	Genotype	Case Patients	Controls	Genotypic Odds Ratio (95% CI)	Allelic Odds Ratio (95% CI)	P Value
Simple steatosis (N=787) vs. normal (N=541)					1.11 (0.94–1.32)	0.21
	T/T	405	286	1		
	T/TA	300	214	1.00 (0.80–1.27)		
	TA/TA	82	41	1.43 (0.95–2.16)		
NASH (N=948) vs. normal (N=541)					0.86 (0.72–1.02)	0.09
	T/T	545	286	1		
	T/TA	350	214	0.87 (0.69–1.09)		
	TA/TA	53	41	0.71 (0.45–1.11)		
NASH (N=948) vs. simple steatosis (N=787)					0.77 (0.66–0.90)	6.5×10^{-4}
	T/T	545	405	1		
	T/TA	350	300	0.87 (0.71–1.06)		
	TA/TA	53	82	0.48 (0.33–0.70)		
NASH with fibrosis (N=648) vs. simple steatosis (N=787)					0.74 (0.62–0.88)	4.2×10^{-4}
	T/T	376	405	1		
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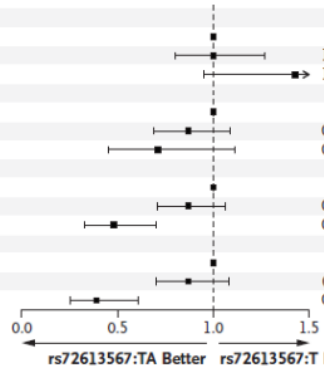

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	T/TA	54	11,754	0.58 (0.42–0.80)		
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	TA/TA	3	2,090	0.27 (0.09–0.85)		
Nonalcoholic liver disease (N=1857) vs. normal (N=29,928)					0.84 (0.78–0.91)	1.3×10^{-5}
	T/T	1090	16,084	1		
	T/TA	665	11,754	0.83 (0.75–0.92)		
	TA/TA	102	2,090	0.70 (0.57–0.87)		
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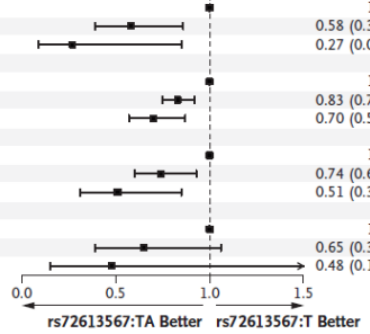

LOF mutations of HSD17B13 protect against cirrhosis

LOF variant rs72613567

- Associated with a reduced risk of nonalcoholic steatohepatitis and fibrosis
  - Dose dependent decreased odds of developing alcoholic and non-alcoholic liver disease

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	TA/TA	82	41	1.43 (0.95–2.16)		
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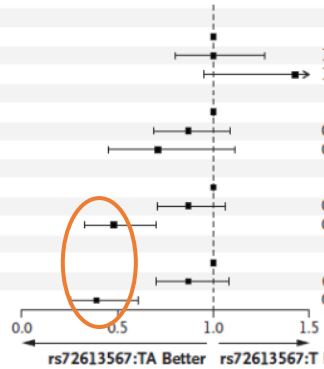

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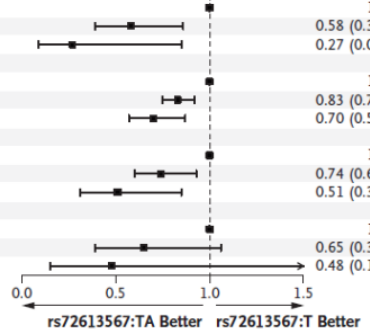

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rs72613567:TA Better rs72613567:T Better

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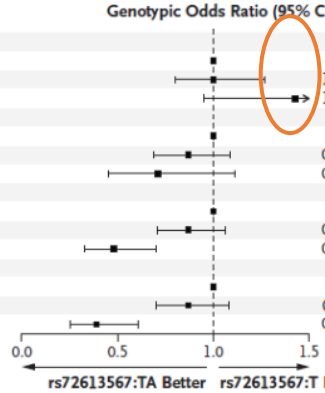

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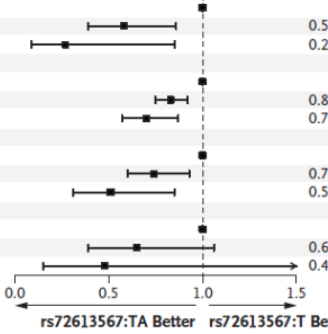

arrowhead pharmaceuticals

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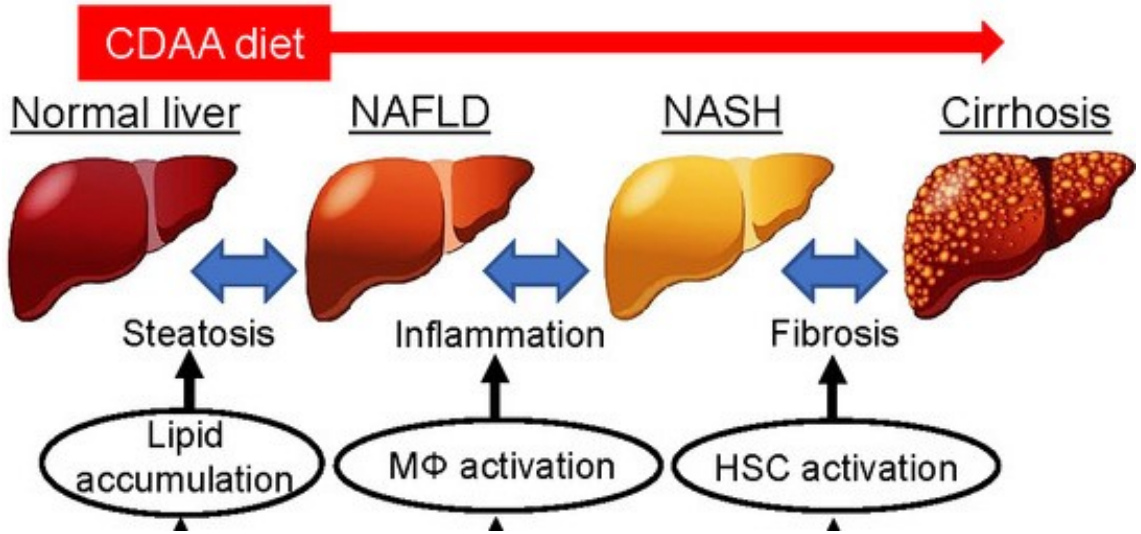
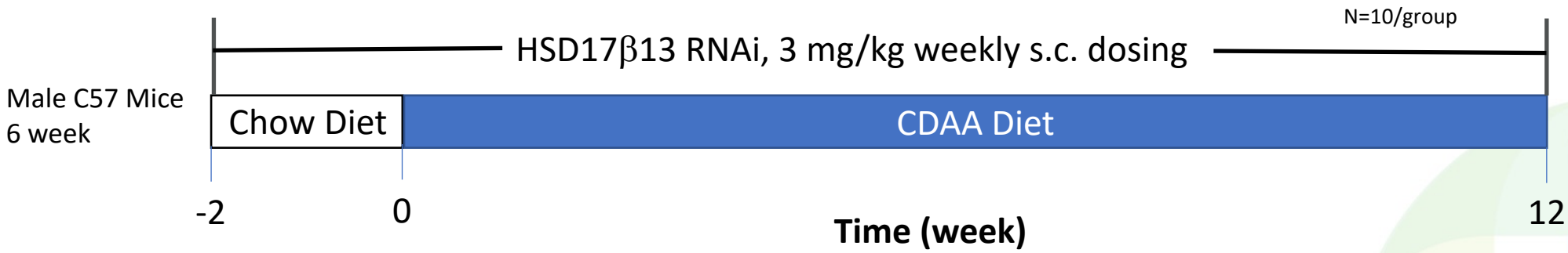
Study of HSD17β13 RNAi Conjugate in Mouse Model of NASH Induced by CDAA Diet



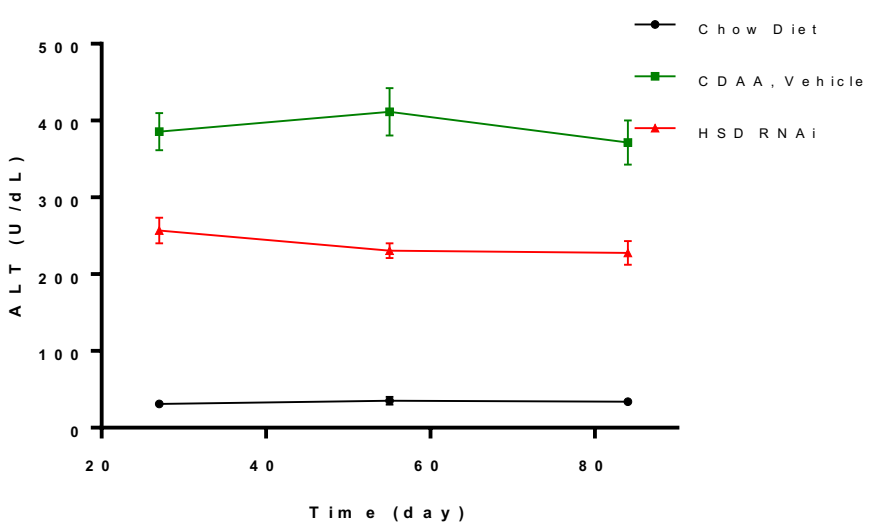
- CDAA diet: choline-deficient, methionine-reduced, 60% fat
- Phase 3 Investigational Drugs Ocaliva, Cenicriviror and Galectin-3 have demonstrated efficacy in CDAA diet-induced NASH model

Study Protocol:

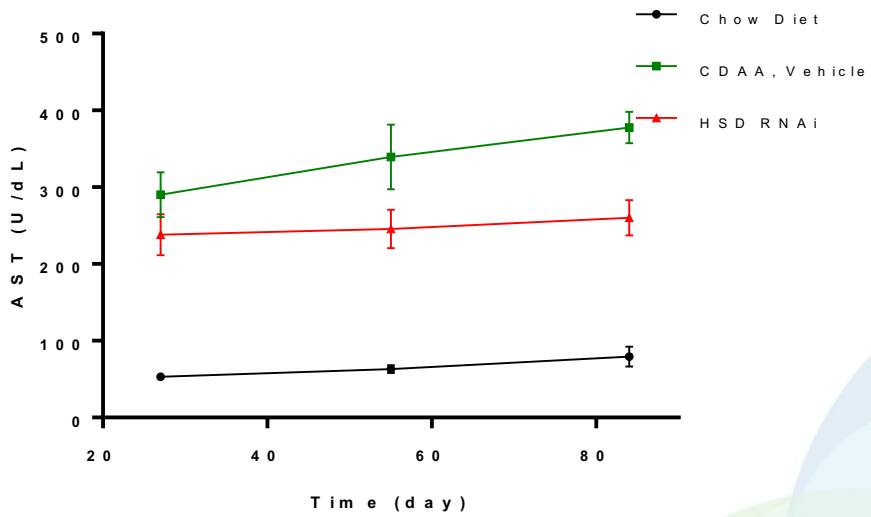


Inhibition of HSD17β13 by RNAi Decreases Liver Enzymes

Alanine Aminotransferase

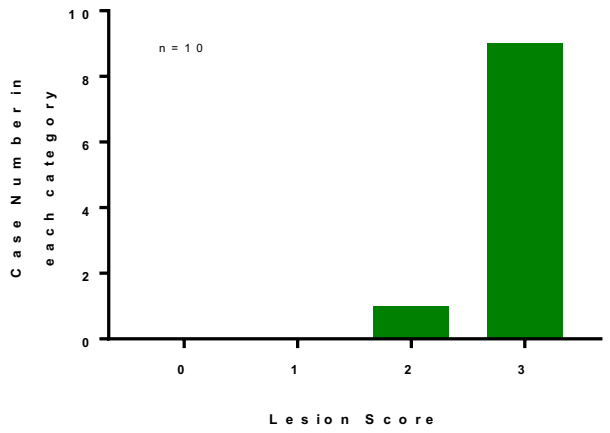


Aspartate Aminotransferase

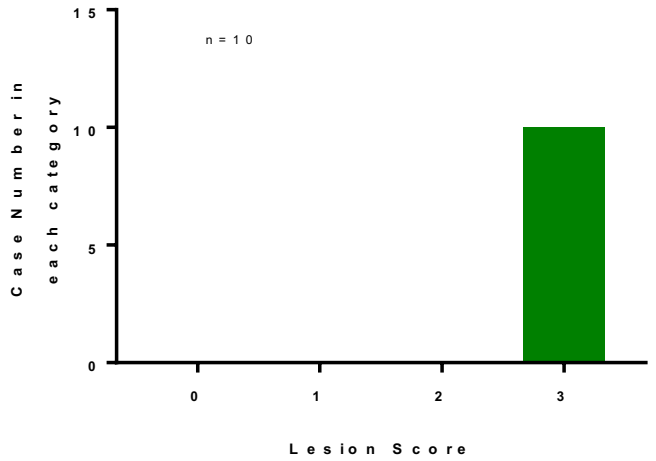


Animals Fed CDAA Diet Develop NASH Hepatic Lesions

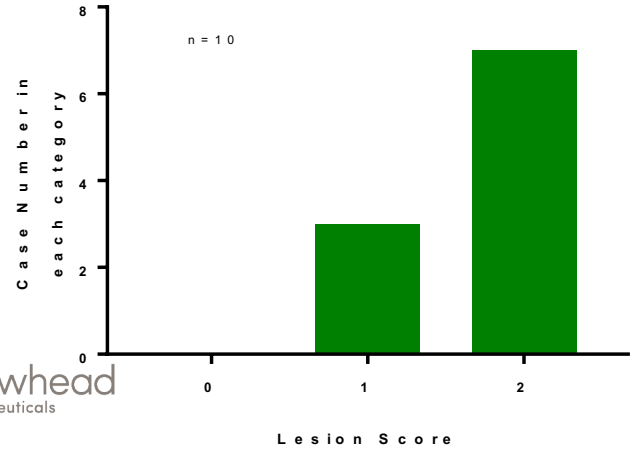
Macrovesicular Steatosis



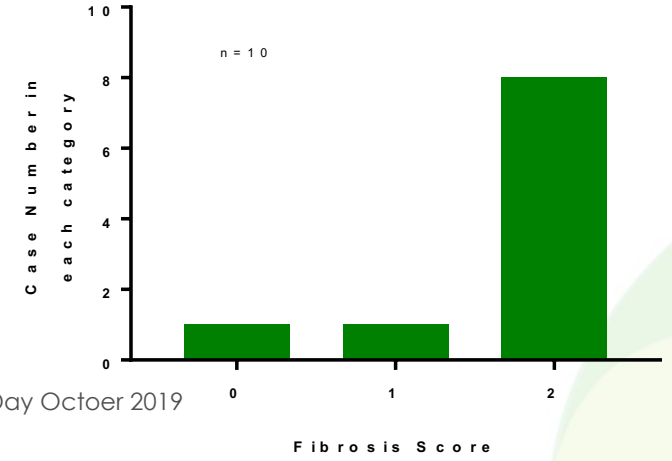
Inflammation



Hepatocyte Degeneration (including Ballooning)



Bridging Fibrosis



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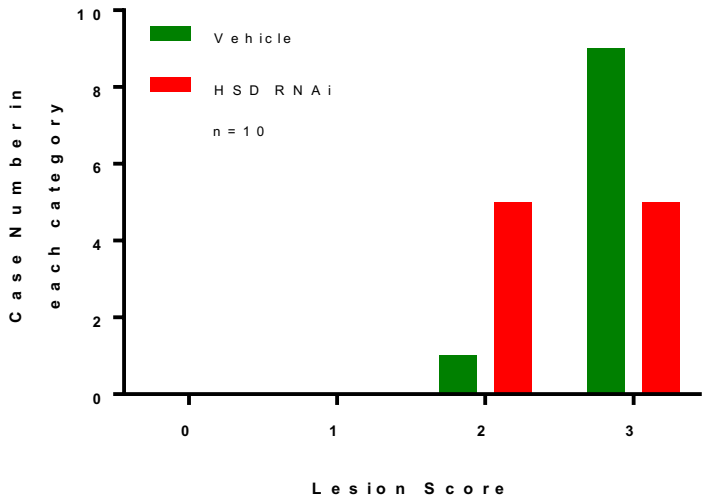
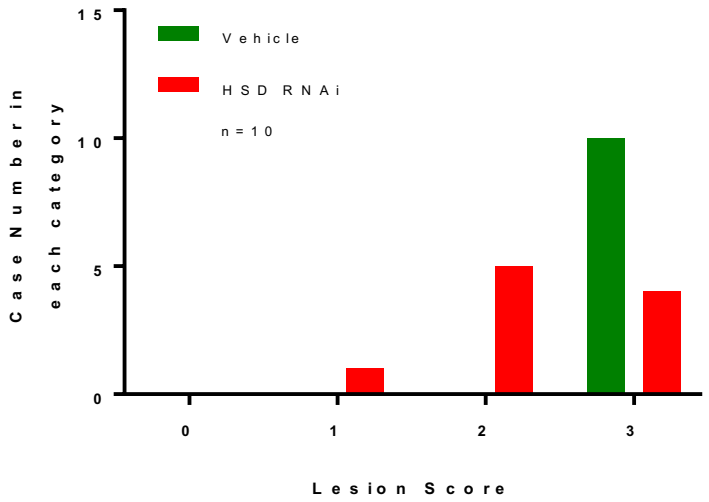
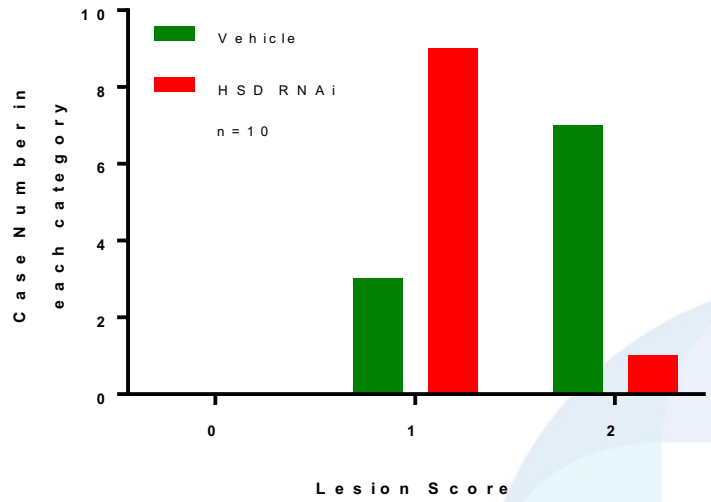


Inflammation

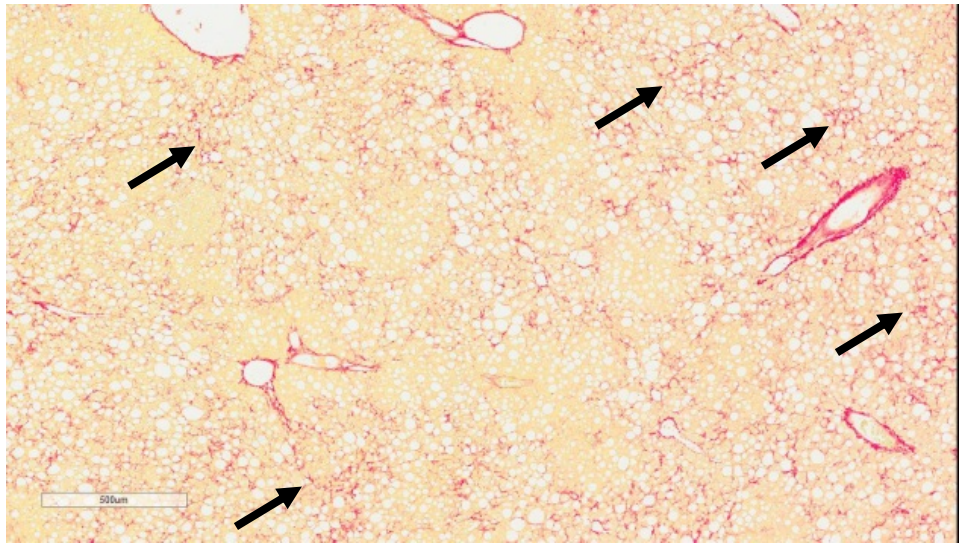


Hepatocyte Degeneration (including Ballooning)

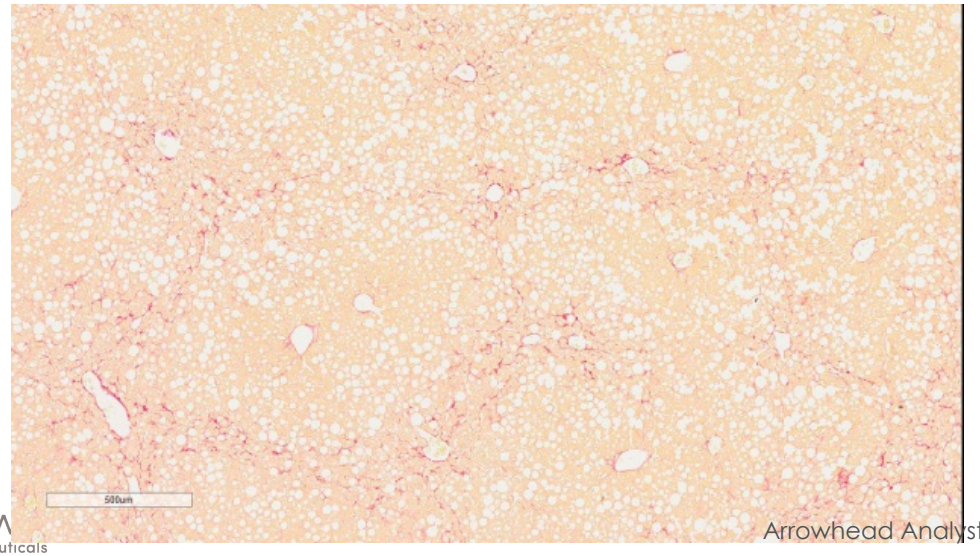


Inhibition of HSD17β13 by RNAi Decreases Liver Fibrosis

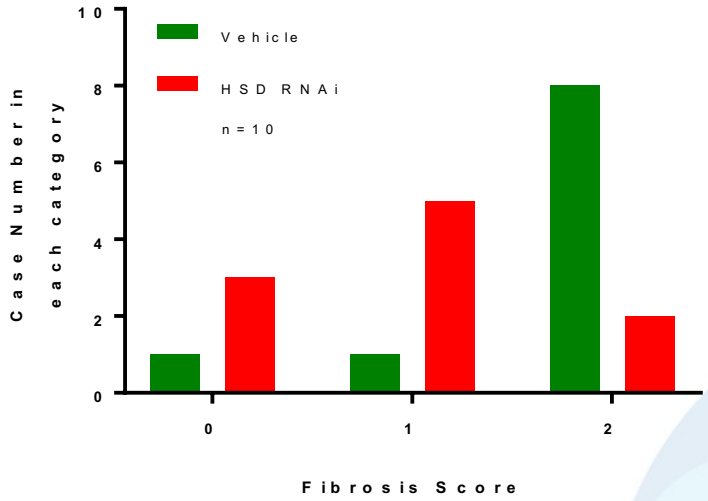
Vehicle



HSD17β13 RNAi



Bridging Fibrosis



Clinical Plans

- Arrowhead translational development mantra: obtain meaningful dose range finding pharmacodynamic data as soon as possible
- Anticipate filing with regulators by YE 2019
  - Planning to open multiple sites in Asia-PAC
- Design likely to resemble other Arrowhead Phase 1/2 studies with enrollment of NHVs, NASH patients
  - Key challenge with this target is lack of serum biomarker
  - 1st study likely to include liver biopsies to assess depth/duration of HSD knockdown
  - MRI-PDFF assessment of liver fat of uncertain utility based on genetic data

Conclusions

- Genetic data indicates that loss of function mutation in HSD17b13 provides strong protection against NASH cirrhosis and alcoholic hepatitis and cirrhosis
- Interestingly, there are indications that steatosis may be more prevalent in these patients
- The mechanism for these effects is not yet known
- Improvements in NASH and fibrosis were seen with HSD17b13 knockdown in a commonly used NASH model (CDAA diet model)
- In life phase for GLP toxicology studies is complete and we expect to file a CTA before year end
- With no known plasma readout for activity, we expect to determine depth and duration of knockdown and dose response using biopsies in our first in human trial, expected to start in the first half of next year

ARO-HIF2

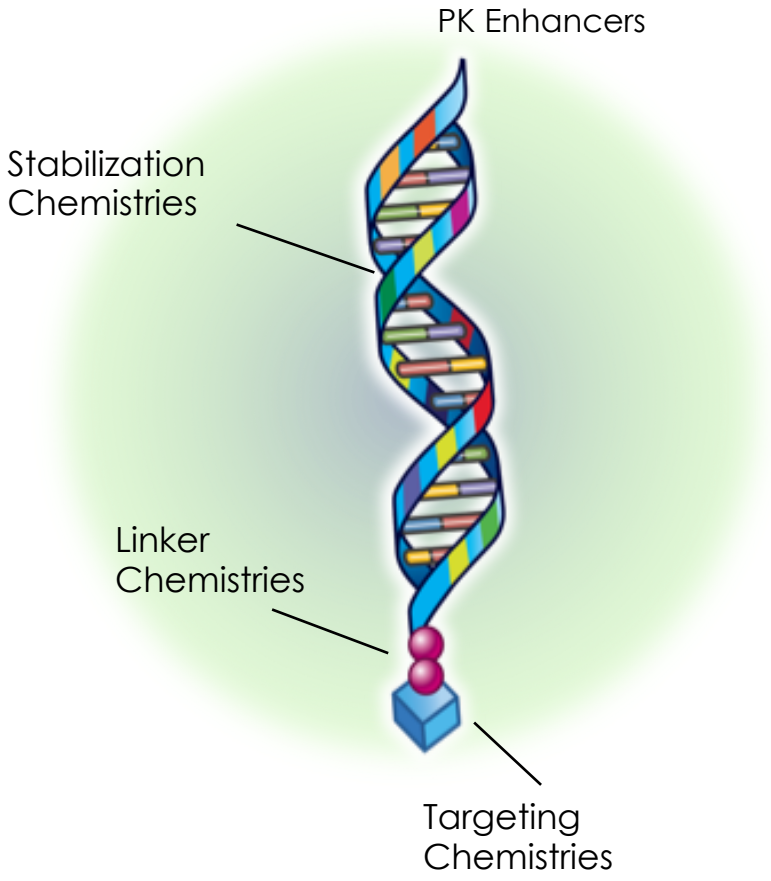
So Wong, Ph.D.
Director, Oncology

James Hamilton, M.D.
Vice President, Clinical Development

Clear Cell Renal Cell Carcinoma (ccRCC)

- Kidney cancer is one of the 10 most common cancers
  - 73,820 new cases for 2019 (ACS estimates)
- 70-80% of kidney cancer are ccRCC
- 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
- Various studies link HIF2α overexpression as a tumorigenic driver of ccRCC
- HIFs transcriptionally activates numerous genes involved in cellular processes including glycolysis, angiogenesis, and metastasis of cancer cells
- Suppression of HIF2α may provide greater efficacy than VEGF receptor kinase inhibitors as many VEGF-independent tumor promoting pathways will be inhibited

ARO-HIF2



- ARO-HIF2 is our first systemic extrahepatic program
- TRiM™ molecule that uses a receptor (avβ3) that is over-expressed in many cancers
  - Tumor tissue microarrays confirmed receptor expression in ccRCC at high frequency
- RNAi trigger specifically targets HIF2α mRNA
  - Limited restrictive expression in normal tissues
  - Over-expression in ccRCC especially with VHL mutations
    - HIF2α is regarded as a key tumorigenic driver of ccRCC
  - Minimal off-target risks
  - Chemically modified to enhance potency and prevent immune activation

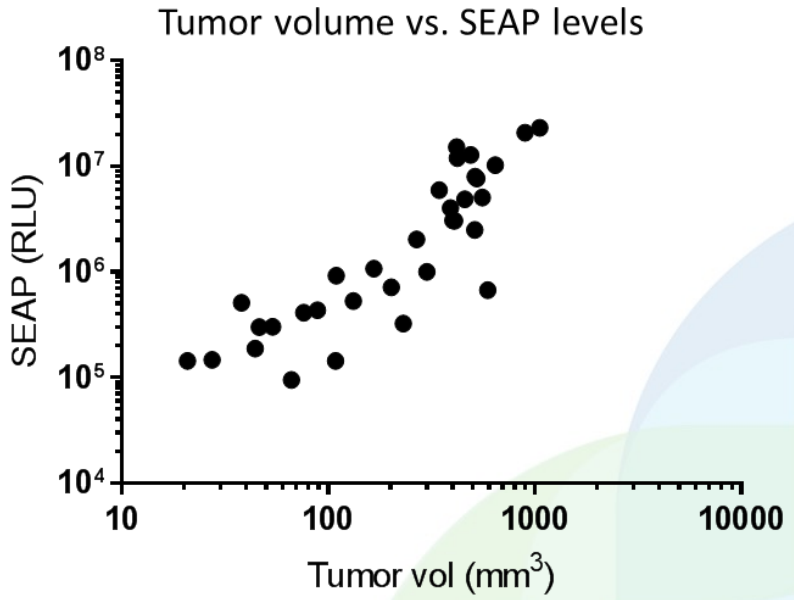
ARO-HIF2 in Xenograft Mouse Model

A498 orthotopic kidney xenograft mouse model

- A498 is an established ccRCC cancer cell line
  - VHL mutated, HIF2a over-expressed
  - Integrin avβ3 positive

- SEAP-A498 model
  - Stably expresses SEAP (secreted embryonic alkaline phosphatase)
  - Good correlation between SEAP levels and tumor volumes

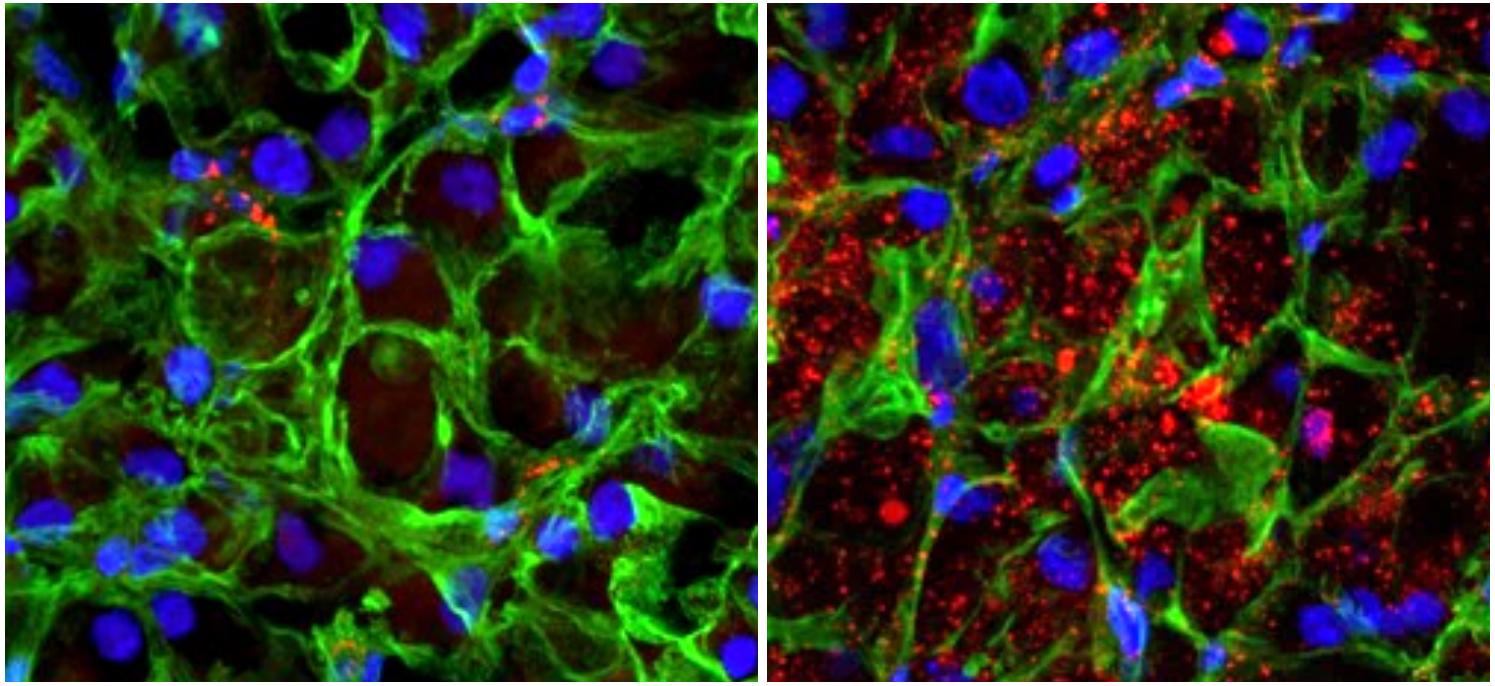
- Sensitive serum biomarker to monitor tumor growth



Tumor Delivery is Ligand Dependent

No ligand

With Ligand



A498 ccRCC orthotopic tumor mouse model

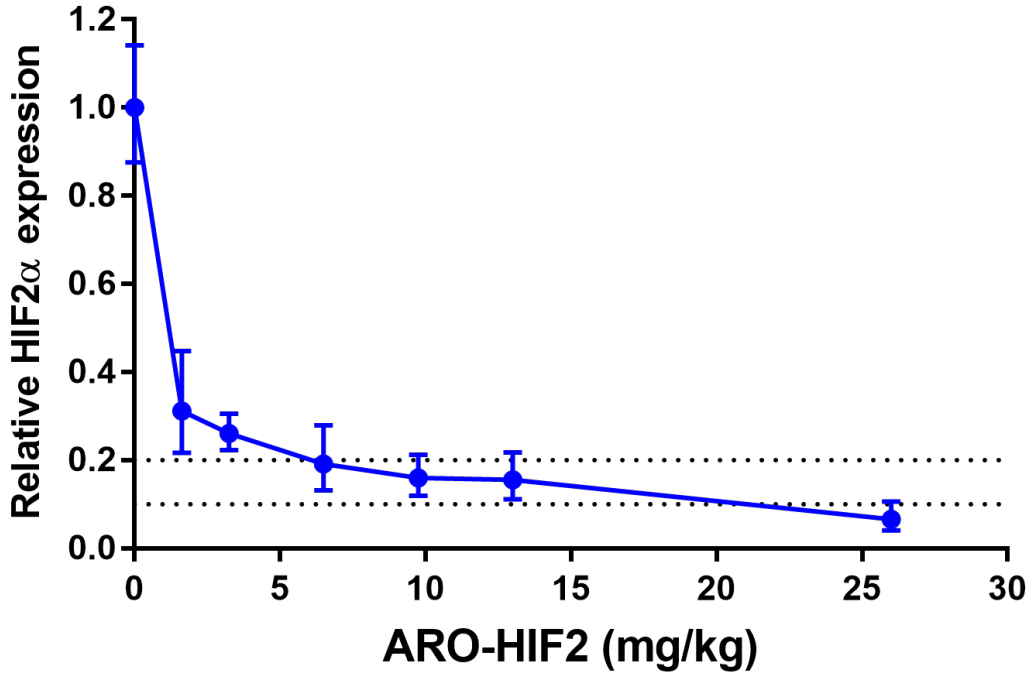
- **Efficient delivery to all tumor cells**
- **No delivery without ligand**

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

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

ARO-HIF2 Dose Response in A498 mouse model

ARO-HIF2 Dose Response (single injection)

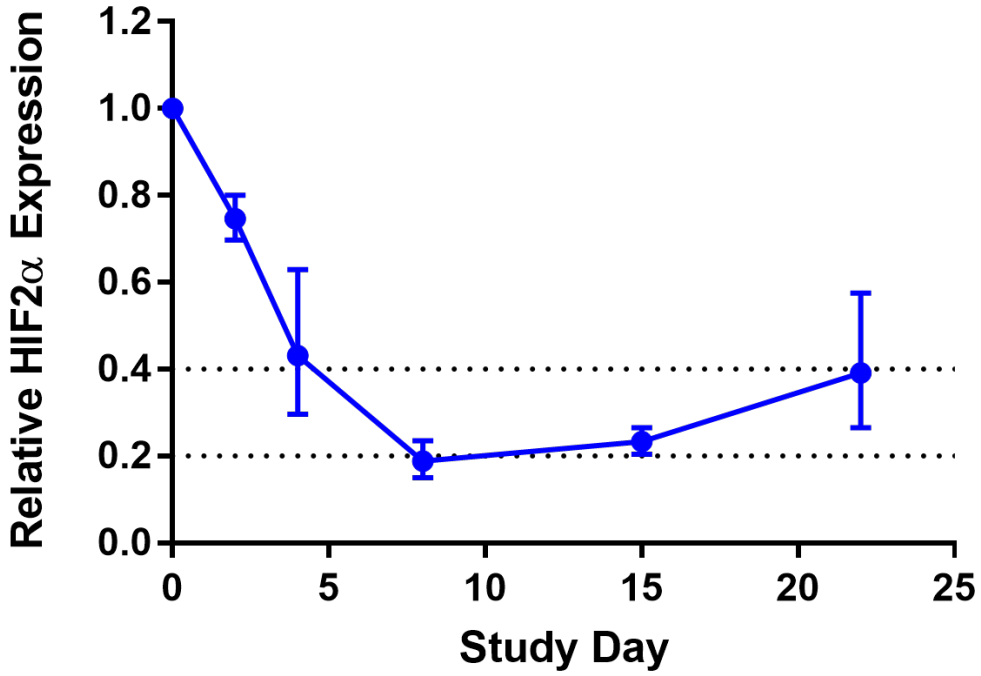


- Single dose on study Day 1
- Gene expression (KD) on Day 8

- Shallow dose response above 6 mg/kg

ARO-HIF2 response duration in A498 mouse model

HIF2a KD duration after a single 13 mg/kg injection

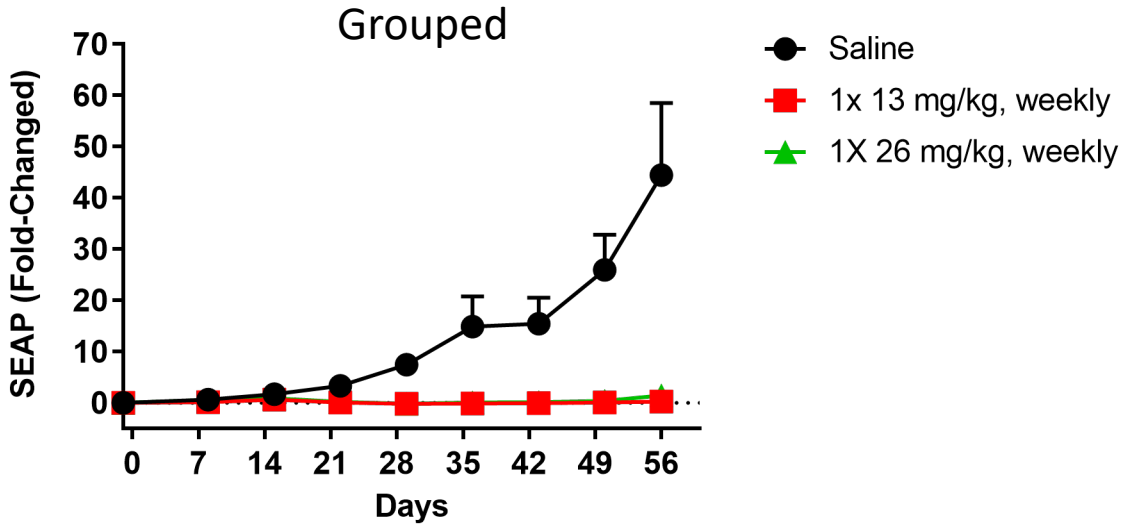


- Single dose on study Day 1
- Nadir Day 8, HIF2α 82.2 % KD
- Max KD last for about 1 week

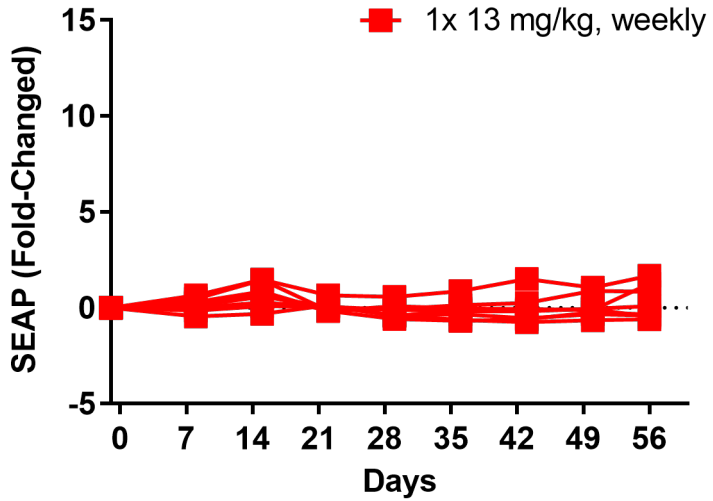
Tumor Growth Inhibition (TGI) Study

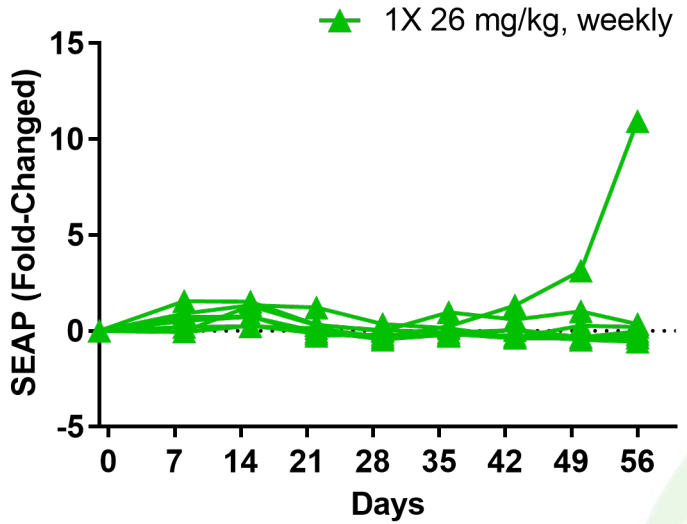
- Eight weekly doses of 13 mg/kg or 26 mg/kg of ARO-HIF2
- Weekly SEAP monitoring for TGI
- End of study tumor HIF2a gene silencing, sizes and histology

ARO-HIF2 TGI Study: Response by SEAP



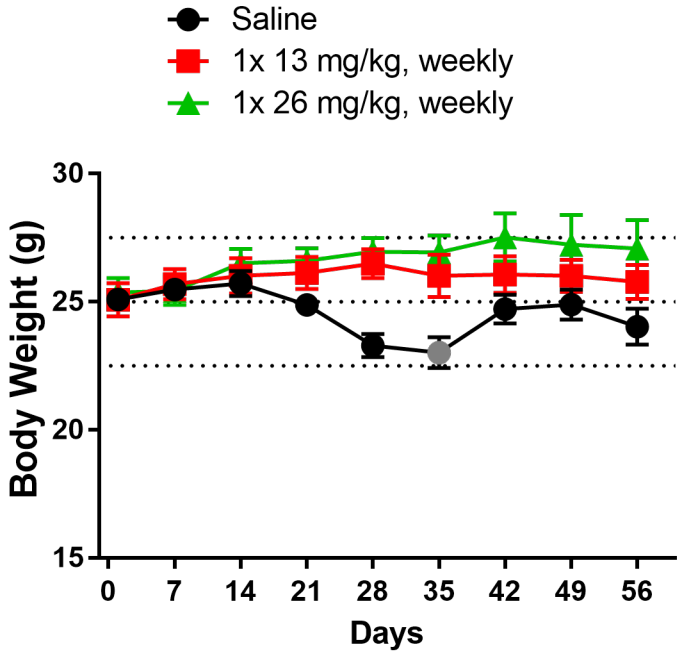
- A498 orthotopic SEAP mouse model
- Similar TGI response based on SEAP readout
- Both treatment groups had mice showed regression by SEAP
- One mouse in 26 mg/kg treatment group showed sign of treatment escape by SEAP readout



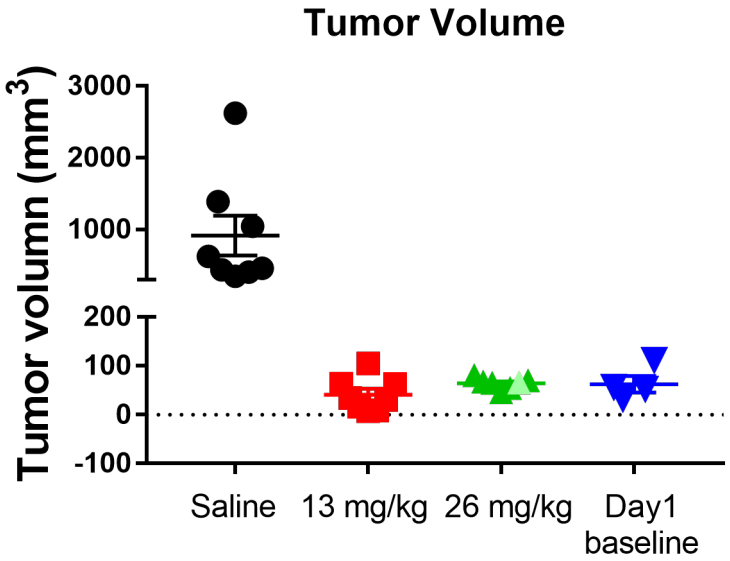


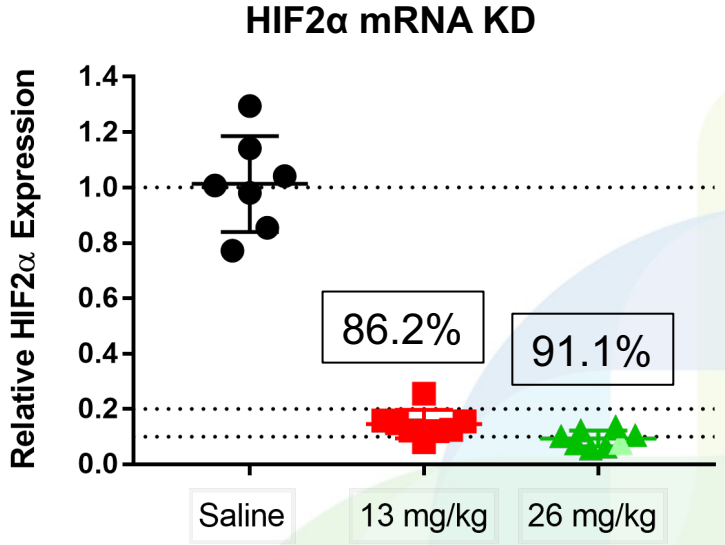
A498 TGI study: response by tumor volume and gene silencing

- Treatment groups shows better BW maintenance
- Both dose levels showed strong tumor growth inhibition (TGI) and deep HIF2a mRNA KD
- Escapee (by SEAP) had good HIF2a KD



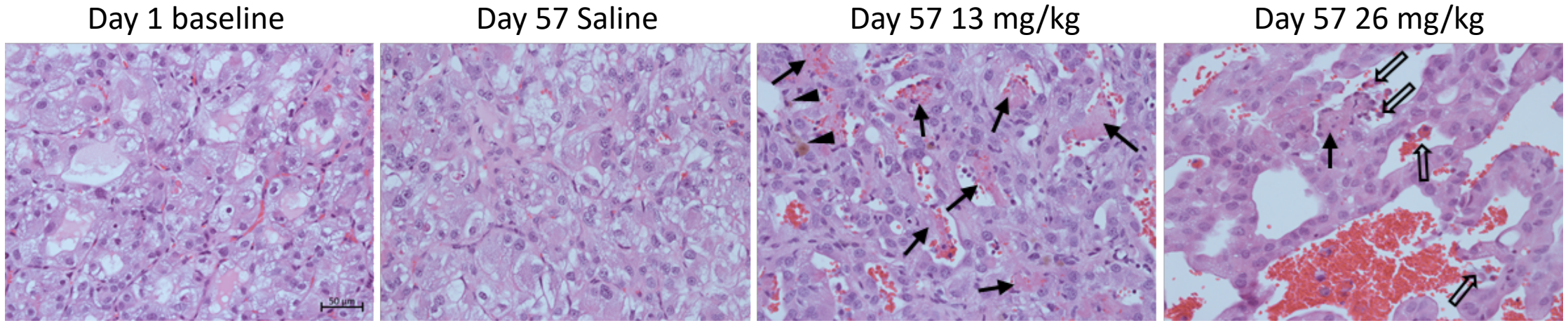
D37 euthanized 1 mouse





- Symbols with lighter tone: escapee by SEAP
- All graphs shows mean (SEM)

Tumor Histology



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

→ Necrosis
► Macrophage infiltration
⇨ Apoptosis

Summary and Plan for ARO-HIF2

Summary

- Efficient ligand dependent tumor delivery of ARO-HIF2 demonstrated
- Deep HIF2α mRNA knockdown in tumor
- Strong tumor growth inhibition with signs of regression in some mice
- IND-enabling GLP toxicology studies complete

Plan

- IND filing planned for end of 2019

ccRCC Treatment Landscape

- Metastatic or locally advanced (Stage IV) ccRCC treatment approach
  - Systemic first line therapy includes I/O w/ or w/o VEGFr TKIs (e.g. nivolumab + ipilimumab or pembrolizumab + axitinib)
  - Patients with progression on I/O first line often receive anti-VEGF (e.g. cabozantinib)
- anti-HIF2 therapy is a new approach likely for use in combination with I/O or anti-VEGF
- Oral Hif2-alpha inhibitor PT2977, Peloton Therapeutics/Merck
  - 120 mg QD monotherapy, 55 previously treated ccRCC patients
  - Confirmed response rate of 22%
  - Durable disease control (median PFS not yet reached as of Jan, 2019)
  - Systemic non-targeted oral therapy: dose dependent reductions in erythropoietin with associated 75% (20% grade 3) anemia **(not expected with tumor targeted siRNA)**
  - Acquired by Merck for $1 billion upfront, $1 billion in milestones

ARO-HIF2 Clinical Plans

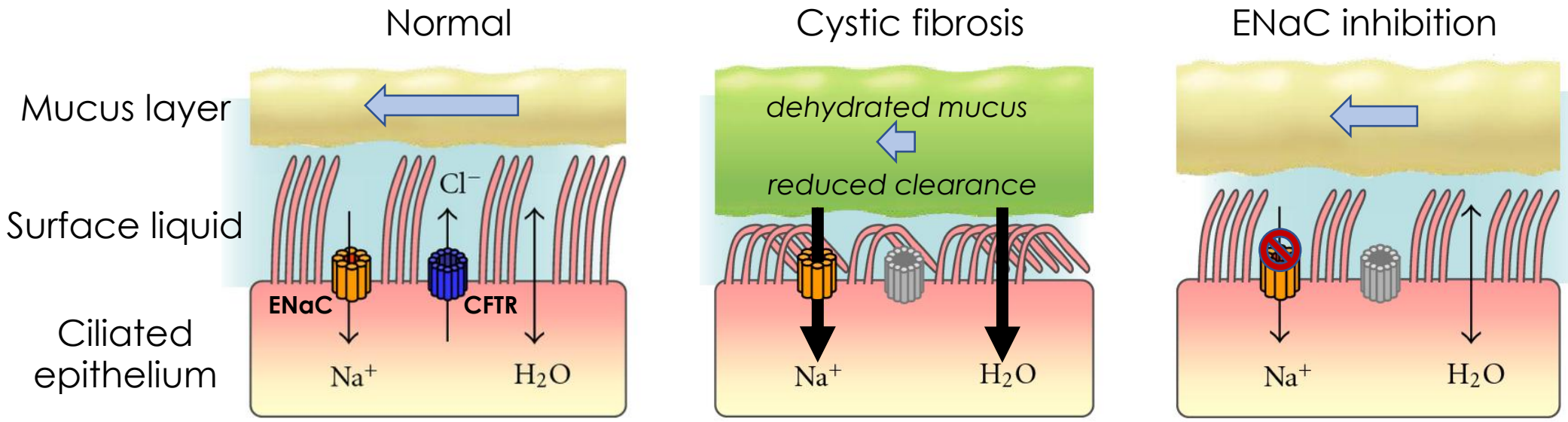
- Regulatory filing planned this quarter
- Phase 1 dose range finding study done under U.S. IND
  - To be conducted in I/O and/or anti-VEGF refractory ccRCC patients
- Primary Objectives:
  - Incidence of AEs & determination of phase 2 dose
- Secondary Objectives
  - PK, efficacy based on RECIST
- Key Exploratory Objective
  - Tissue HIF2 alpha expression based on tumor biopsy

ARO-ENaC

Erik Bush, Ph.D.
Vice President, Extra-Hepatic Targeting

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

Increased epithelial sodium channel (ENaC) activity promotes mucus dehydration in all cystic fibrosis genotypes



Common mechanism in other muco-obstructive lung diseases
COPD, bronchiectasis & asthma

Human genetics validate ENaC as CF target

Excess ENaC activity worsens CF phenotype

J Physiol 2010; 588.8: 1211-1225

***CFTR* (- / -) = cystic fibrosis**

***CFTR* (- / +) = normal**

↓

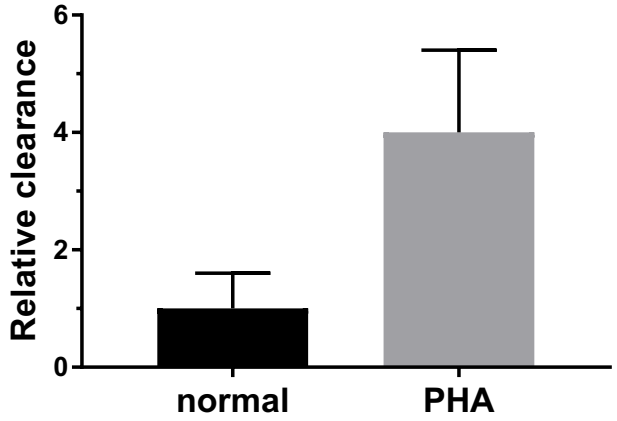
***ENaC* activating mutation** **= 'atypical' CF**

Loss of ENaC activity increases lung hydration and clearance

N Engl J Med 1999;341: 156-62

***ENaC* (- / -) = PHA**

Mucociliary clearance



Partial ENaC activity improves CF phenotype

Am J Respir Cell Mol Biol 2017; 57: 711-720

***CFTR* (- / -) = cystic fibrosis**

↓

***ENaC* (- /+) = 'nonprogressive' CF**

50% reduction in expression may be disease-modifying?

Development of inhaled small molecule ENaCi has been limited by on-target renal toxicity and short duration of action in lung

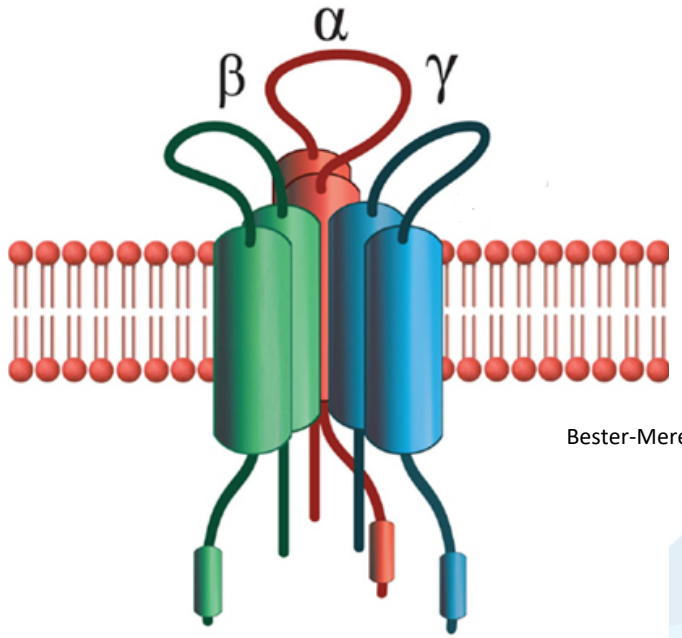
Parion, Gilead, Vertex, Amgen, AZ, Novartis, BI

- 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]

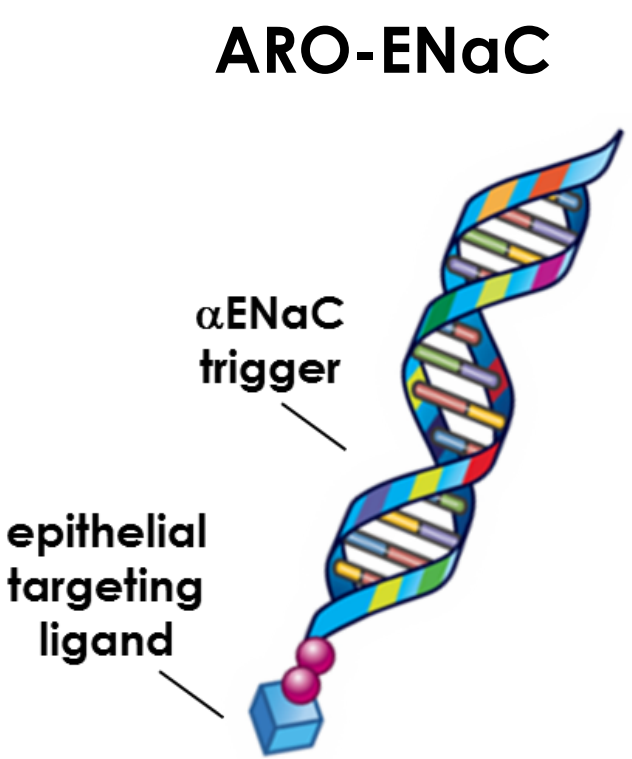
"The rational design of new ENaC blockers must include not only the provision of a sustained increase in mucociliary clearance, but also the avoidance of clinically significant renal exposure…"

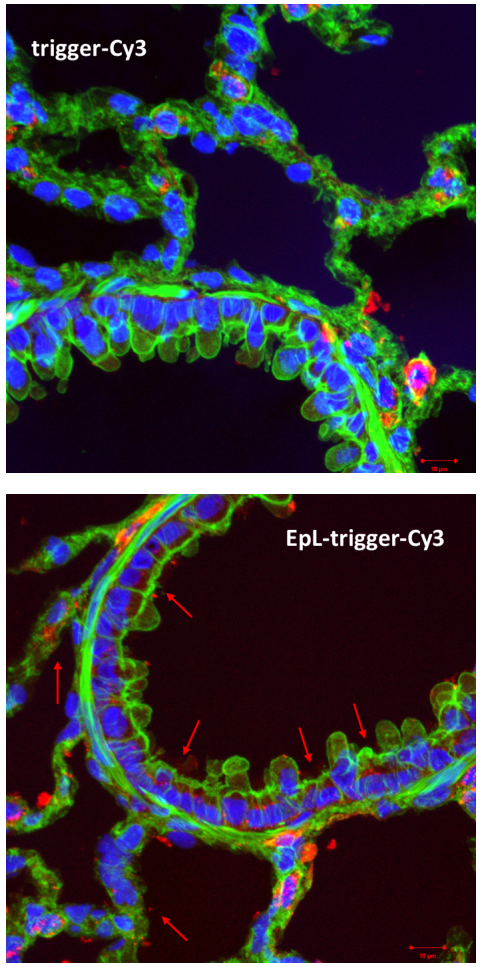


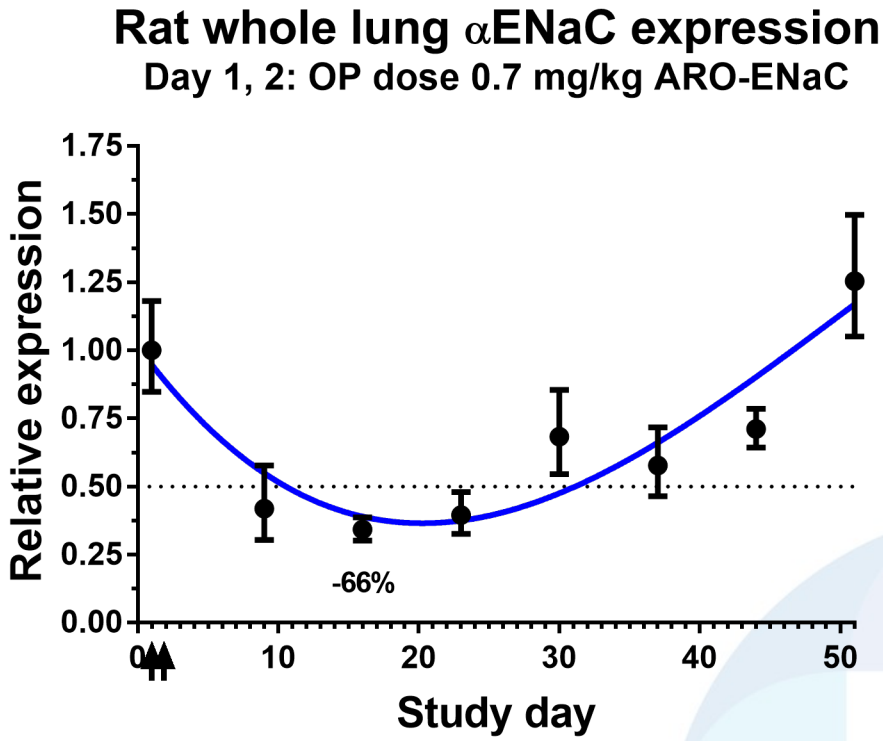
Bester-Meredith 2015

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

ARO-ENaC utilizes the TRiM™ platform for pulmonary delivery

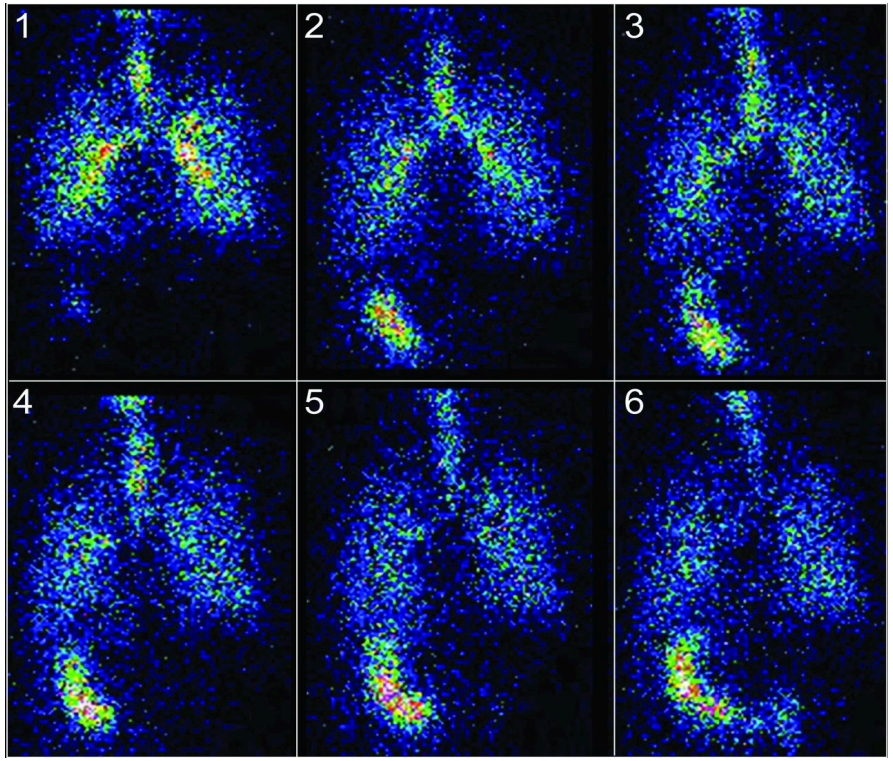






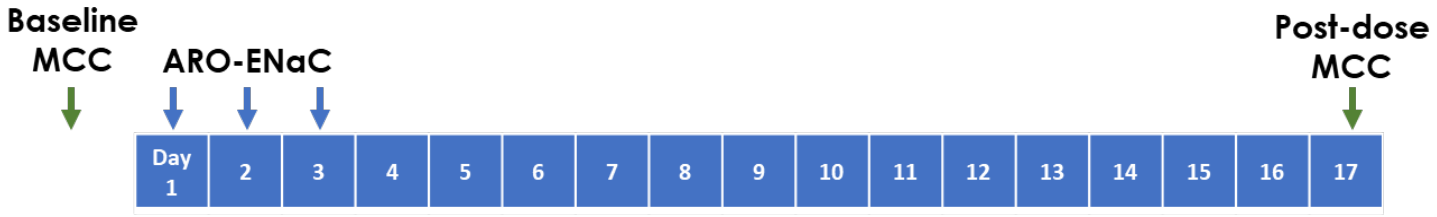
Durable mRNA silencing supports every other week (or less frequent) dose regimens

Mucociliary clearance (MCC) in normal sheep
A large animal model of airway physiology



Respiratory Care 2015, 60 (6) 850-857

- Inhaled aerosolized ^{99m}Tc-radiolabeled sulfur colloid
- Gamma imaging over 1-2 hours



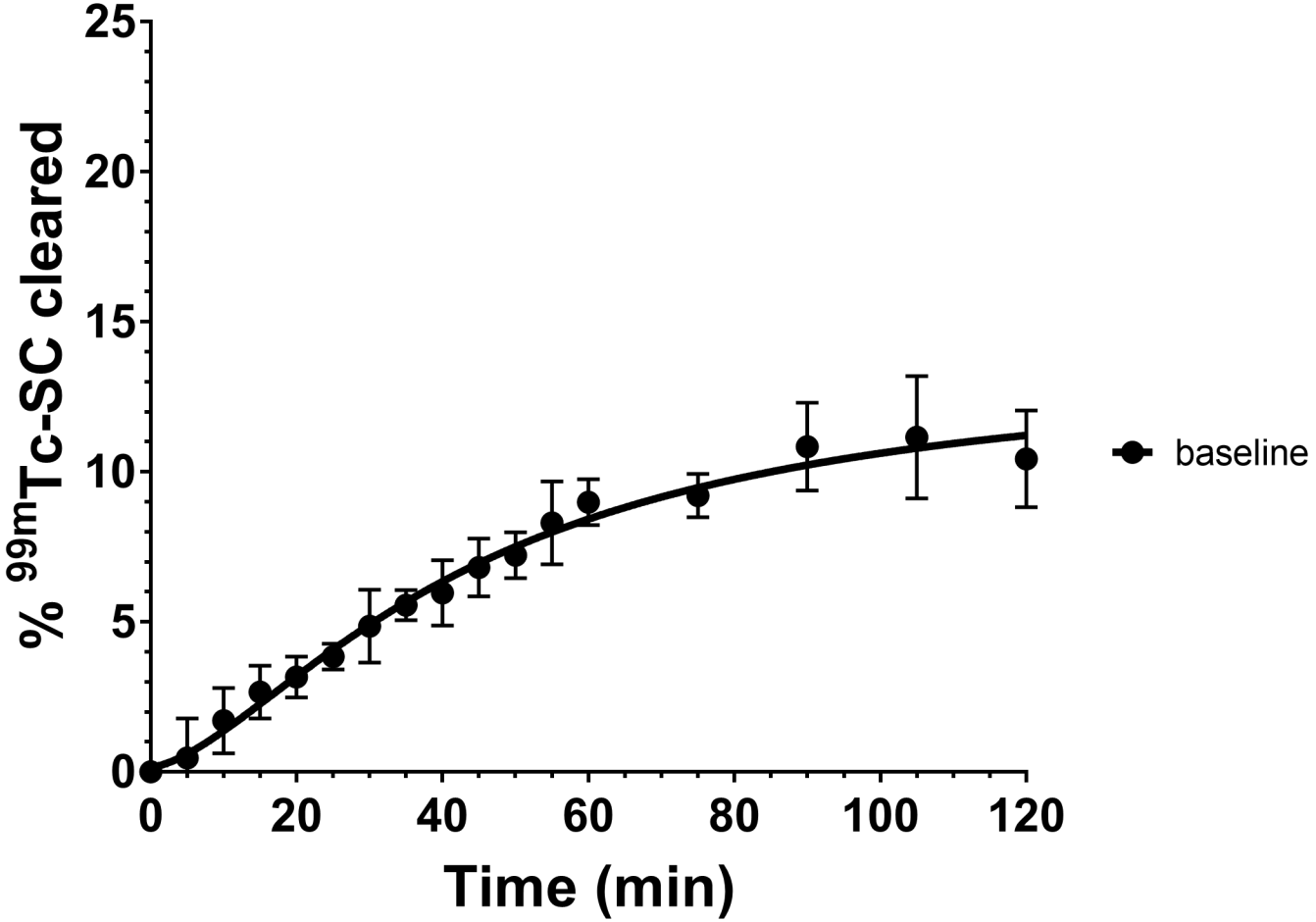
Day -3: Pre-dose baseline MCC scan

Days 1-3: Aerosolized ARO-ENaC inhalation

Day 17: Post-dose MCC scan

arrowhead pharmaceuticals

ARO-ENaC accelerates mucociliary clearance in sheep two weeks after inhaled dosing



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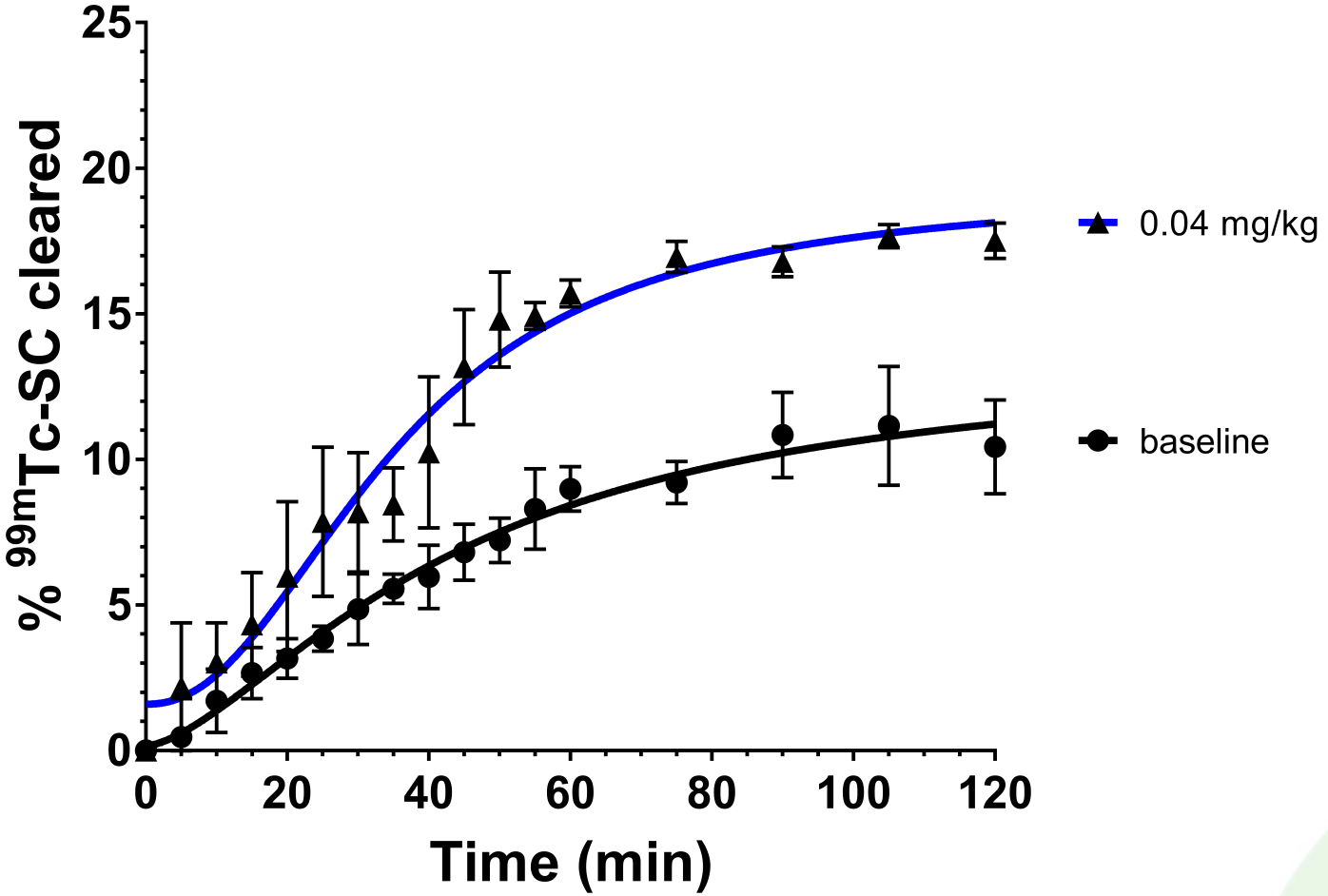

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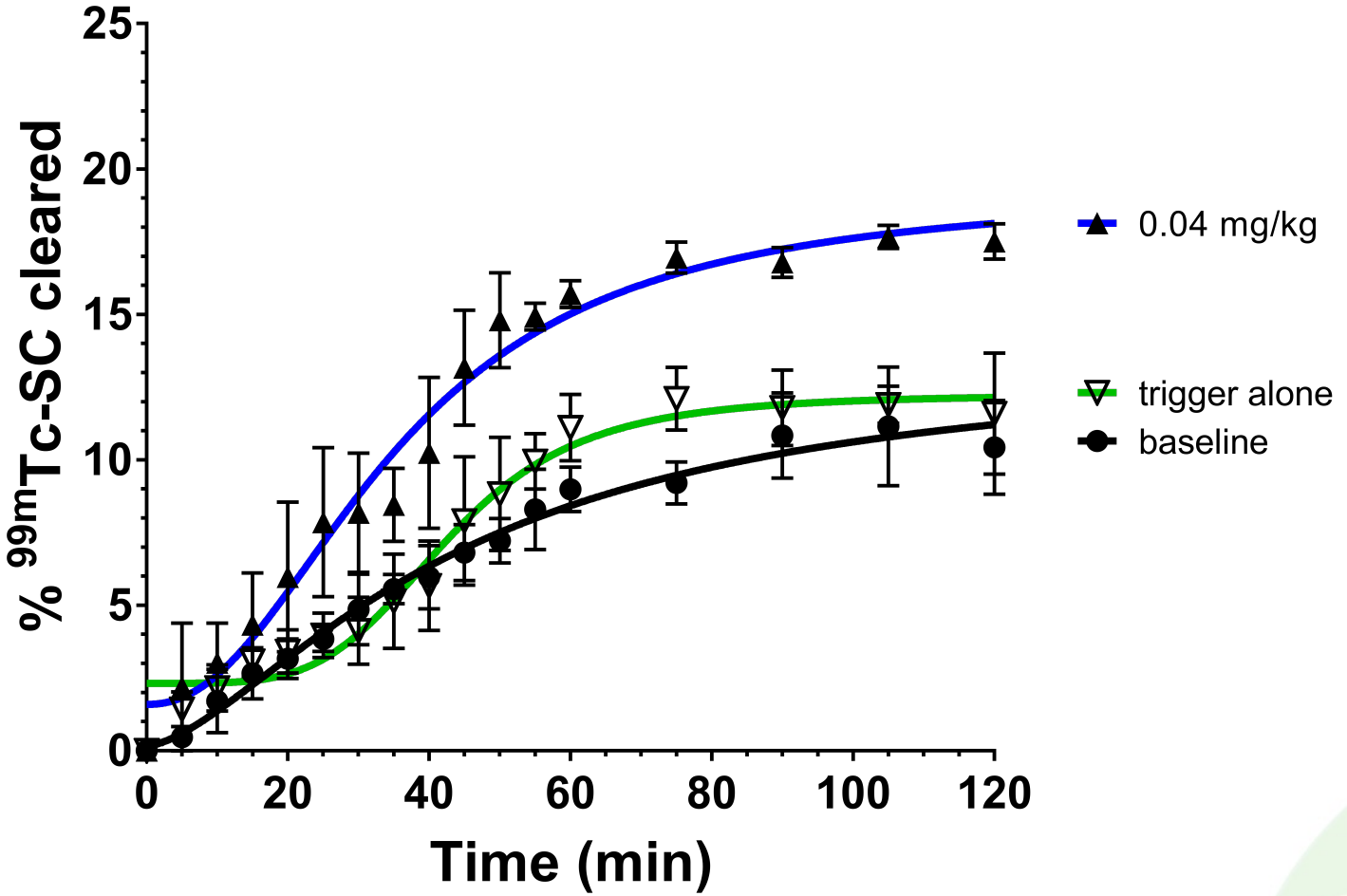

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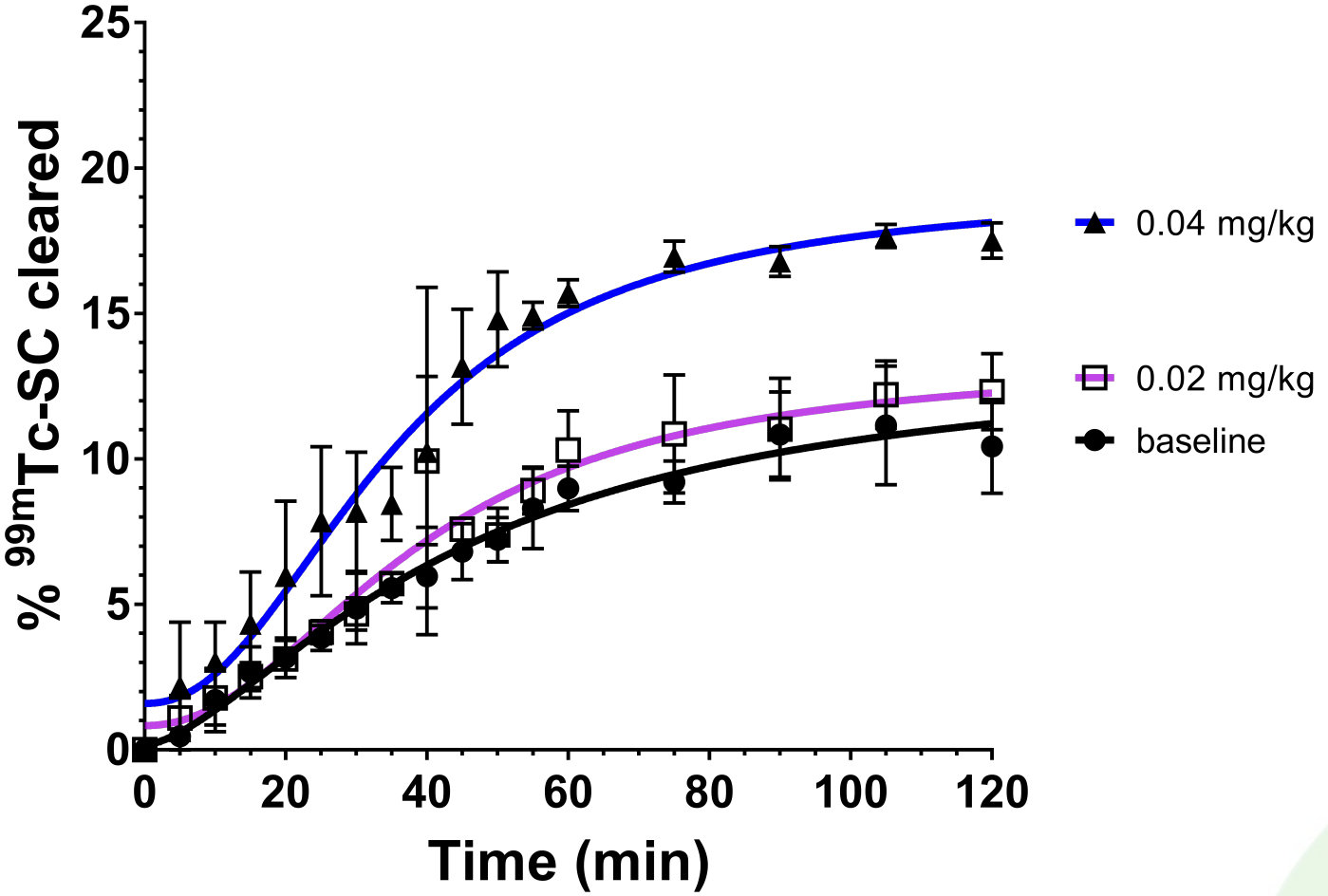
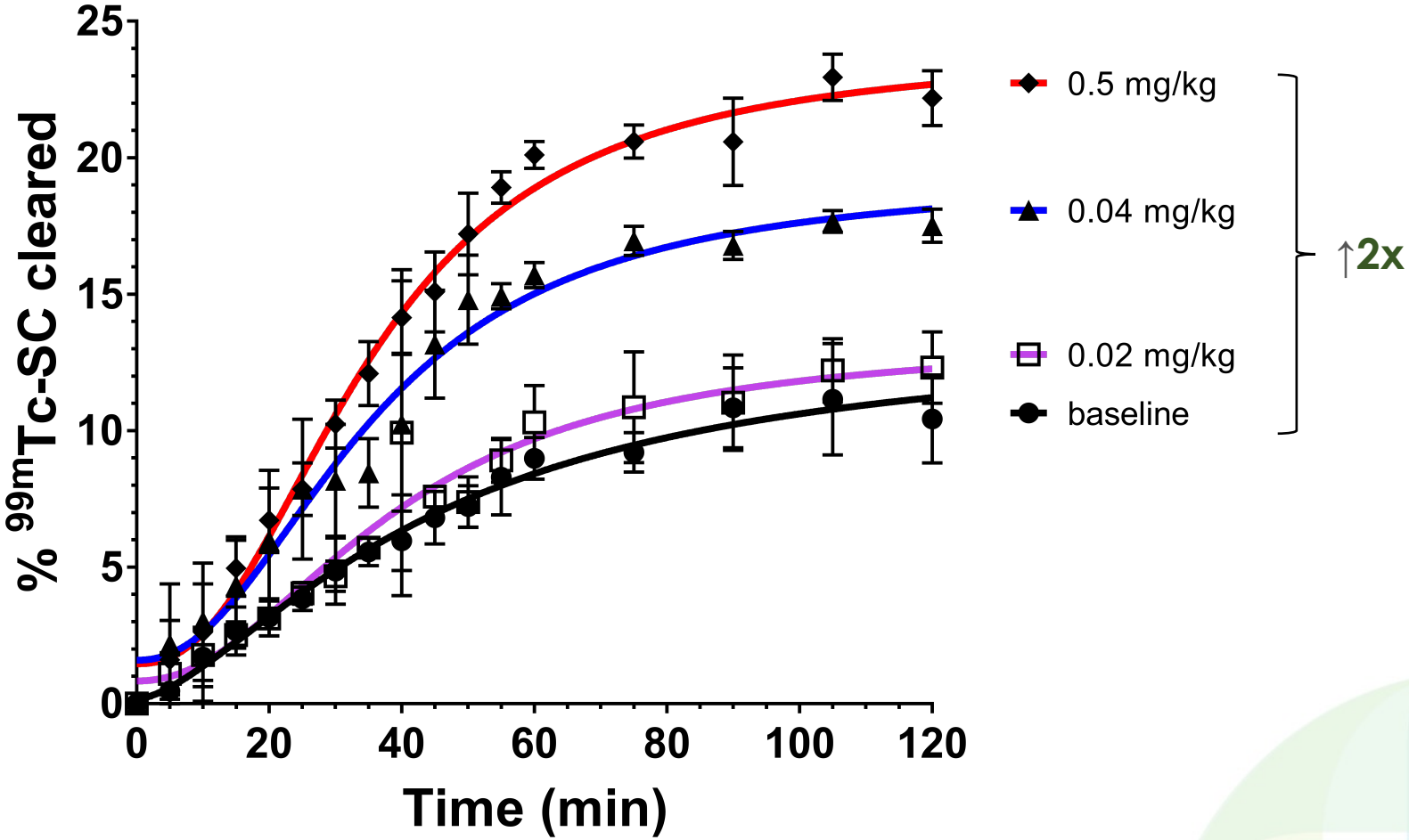
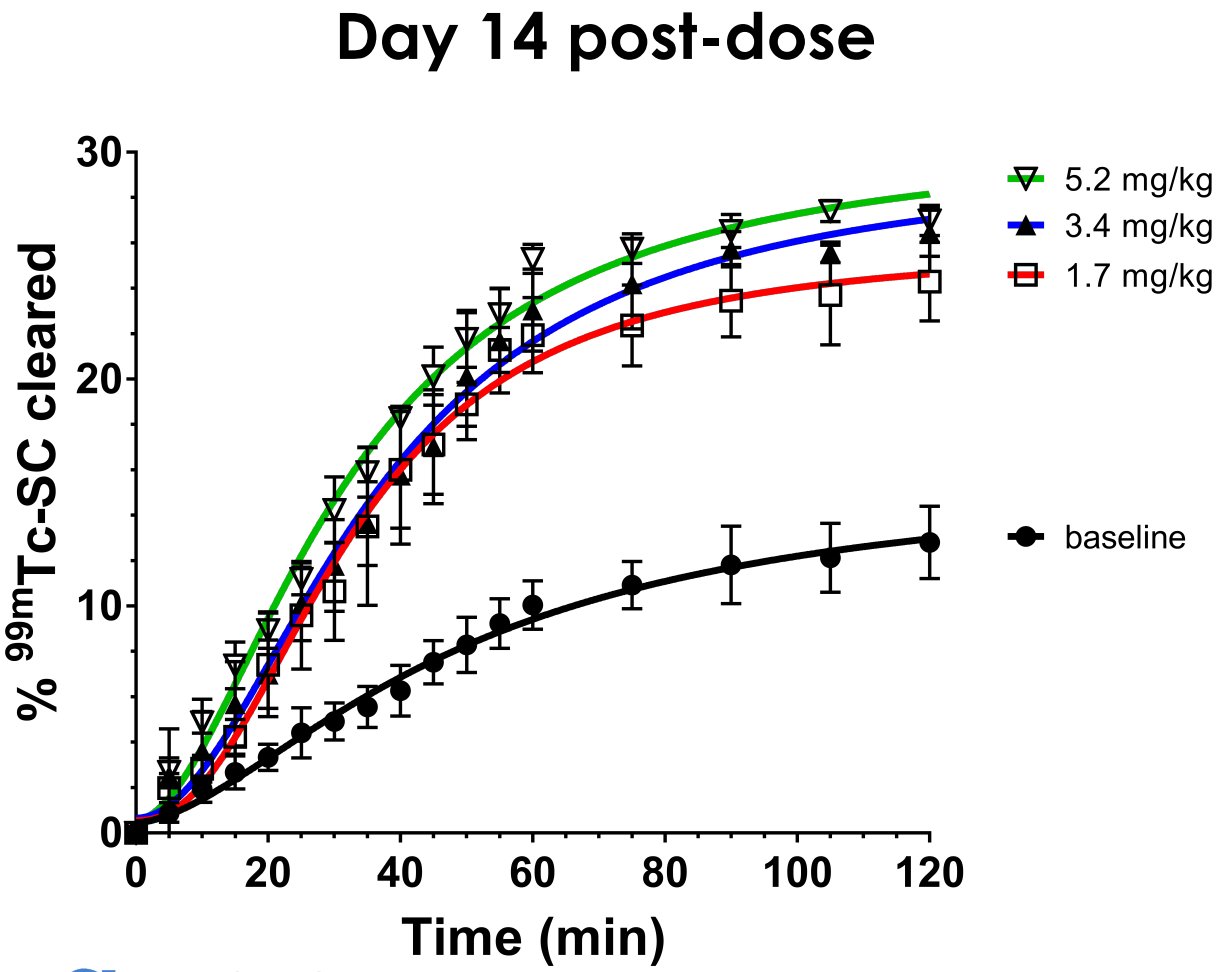
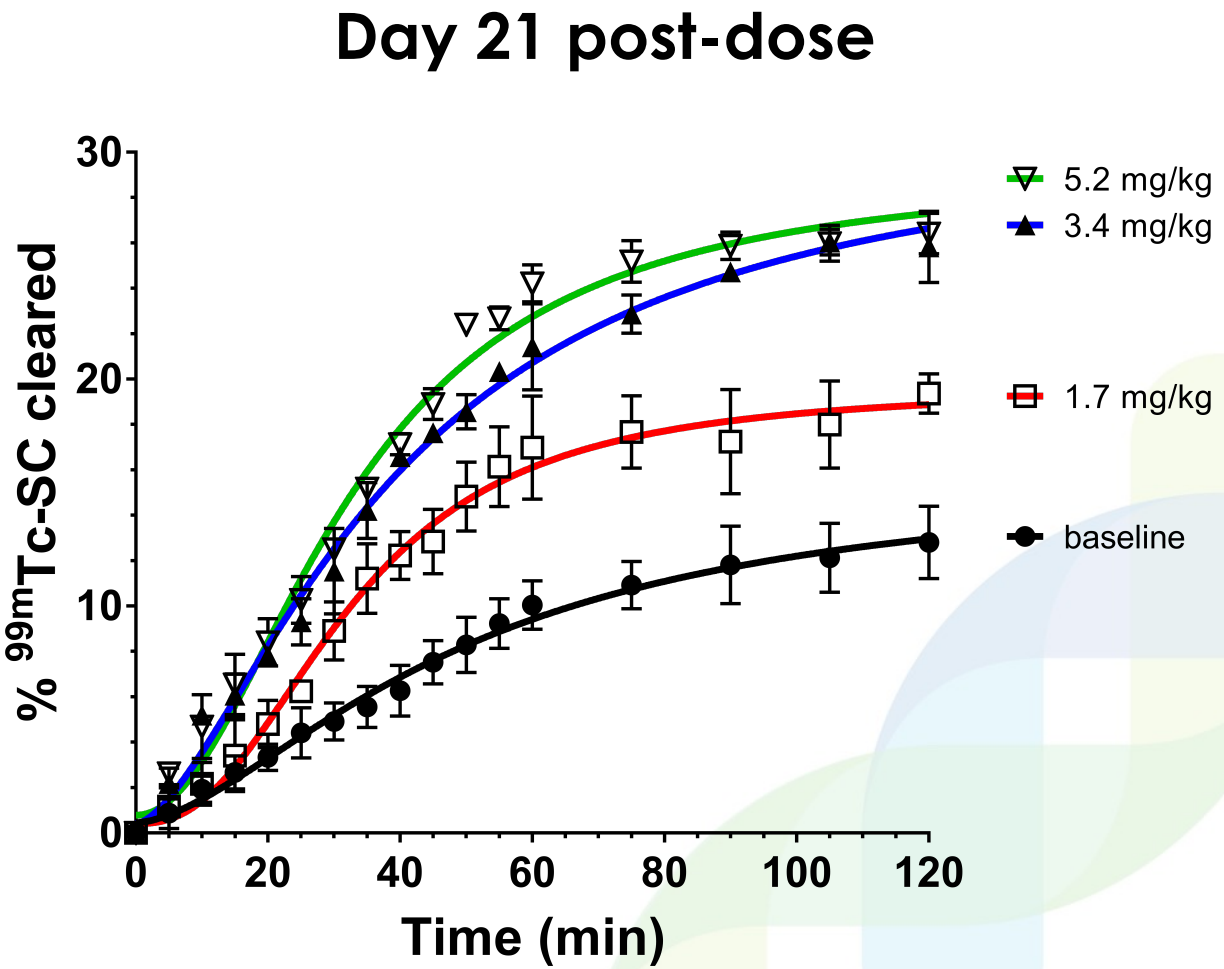


ARO-ENaC accelerates mucociliary clearance in sheep two weeks after inhaled dosing



A single inhaled dose of ARO-ENaC accelerates MCC in normal sheep up to three weeks





ARO-ENaC preserves function in a sheep disease model of impaired mucocilary clearance

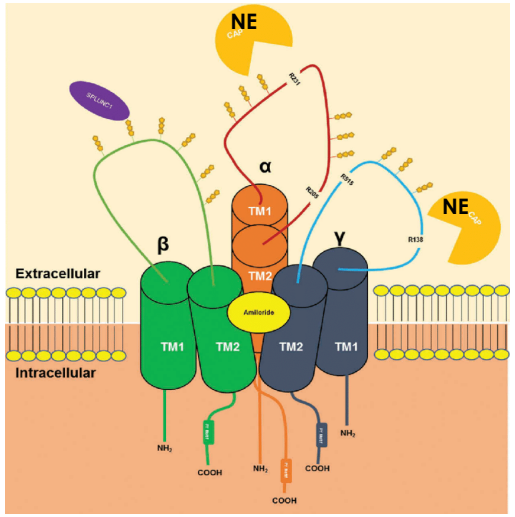
Am J Physiol Lung Cell Mol Physiol 288: L813–L819, 2005.
First published January 7, 2005; doi:10.1152/ajplung.00435.2004.

TRANSLATIONAL PHYSIOLOGY

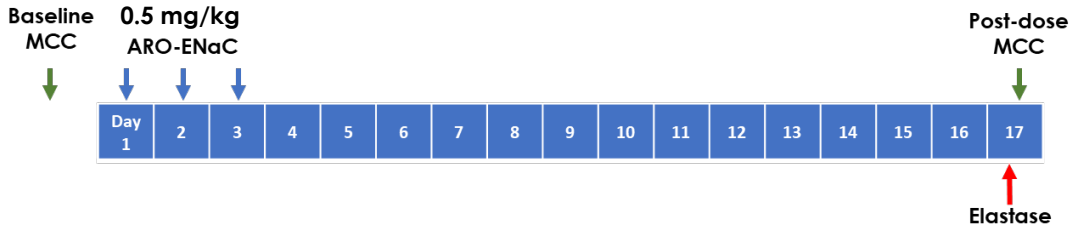
Neutrophil elastase activates near-silent epithelial Na^+ channels and increases airway epithelial Na^+ transport

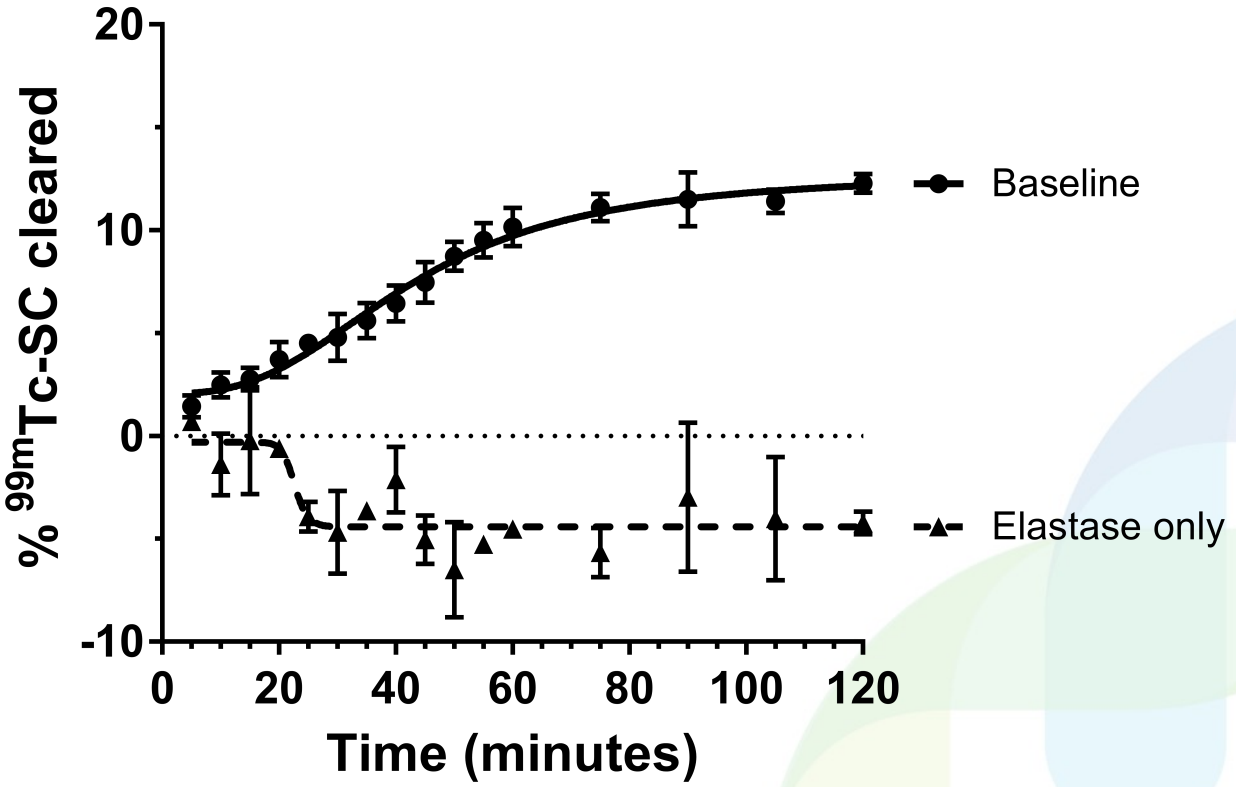
Ray A. Caldwell, Richard C. Boucher, and M. Jackson Stutts
The Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina, Chapel Hill, North Carolina

Submitted 19 November 2004; accepted in final form 5 January 2005



Expert Opin Ther Tar 2018; 22: 687-701





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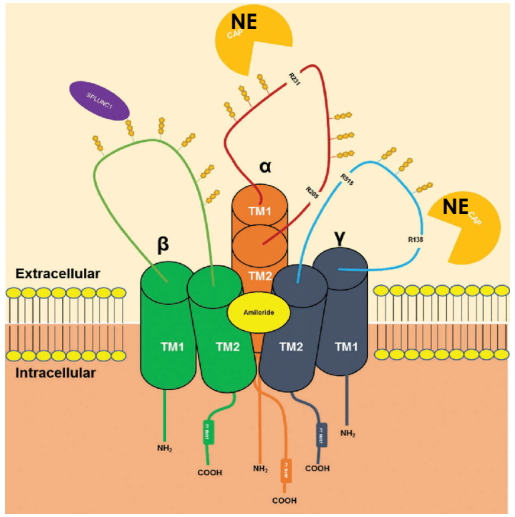
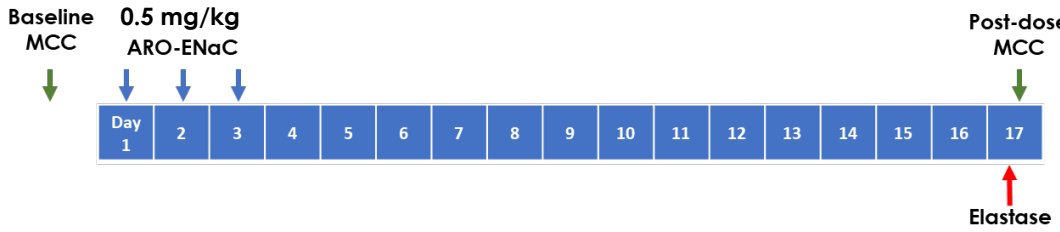
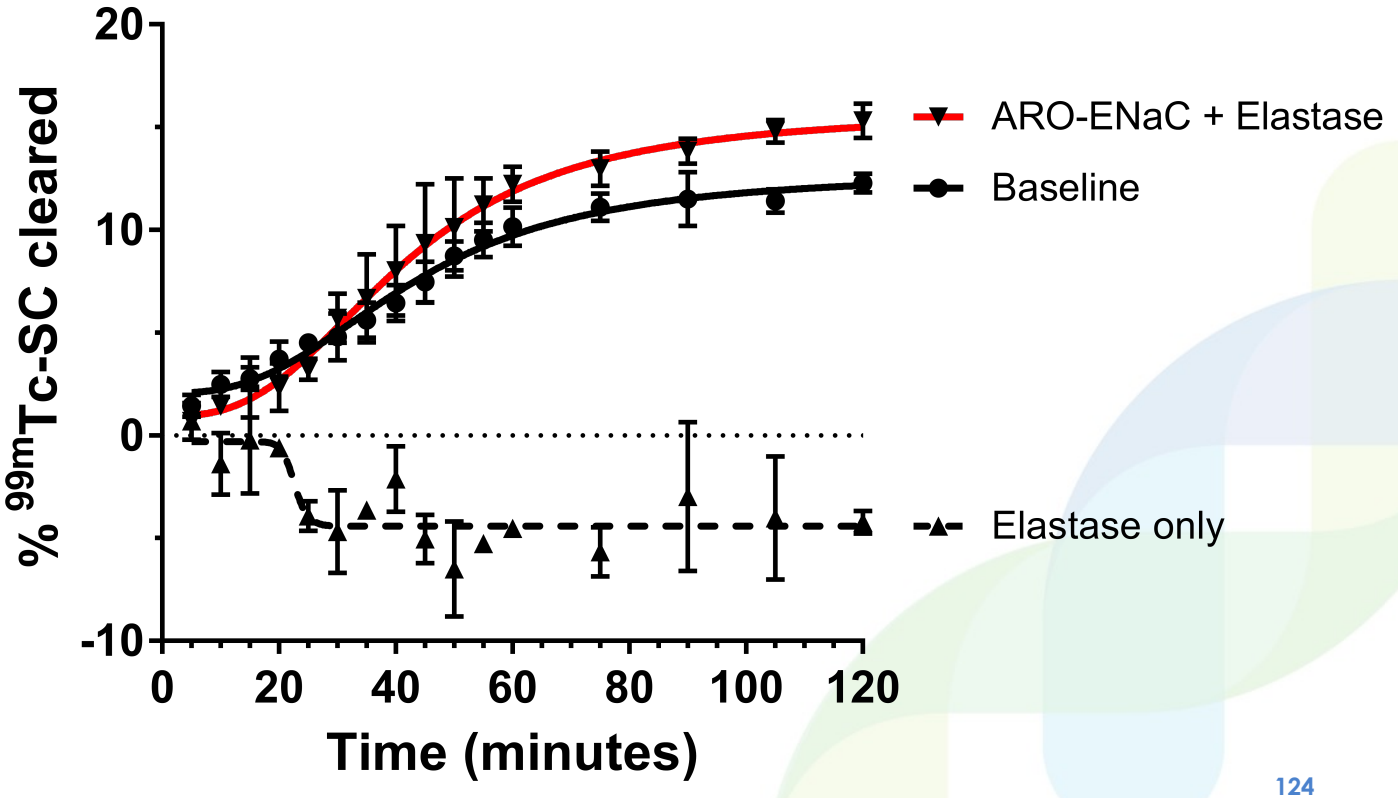


Expert Opin Ther Tar 2018; 22: 687-701





How much ENaC silencing is required to produce a disease-modifying improvement in MCC?

JCI insight

Effect of ivacaftor on mucociliary clearance and clinical outcomes in cystic fibrosis patients with G551D-CFTR

Scott H. Donaldson, … , Steven M. Rowe, William D. Bennett

JCI Insight. 2018;3(24):e122695. https://doi.org/10.1172/jci.insight.122695.

Clinical Medicine | Pulmonology

BACKGROUND. The ability to restore cystic fibrosis transmembrane regulator (CFTR) function with effective small molecule modulators in patients with cystic fibrosis provides an opportunity to study relationships between CFTR ion channel function, organ level physiology, and clinical outcomes.

METHODS. We performed a multisite, prospective, observational study of ivacaftor, prescribed in patients with the G551D-CFTR mutation. Measurements of lung mucociliary clearance (MCC) were performed before and after treatment initiation (1 and 3 months), in parallel with clinical outcome measures.

RESULTS. Marked acceleration in whole lung, central lung, and peripheral lung MCC was observed 1 month after beginning ivacaftor and was sustained at 3 months. Improvements in MCC correlated with improvements in forced expiratory volume in the first second (FEV_1) but not sweat chloride or symptom scores.

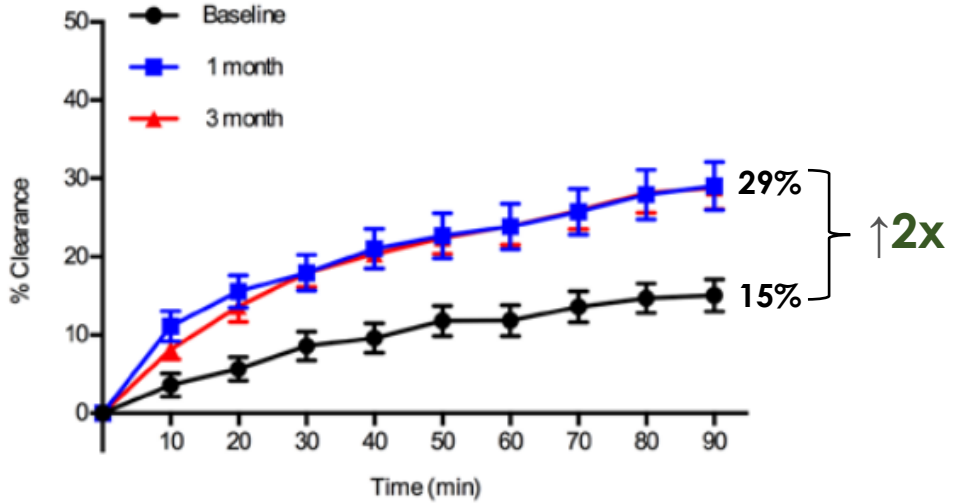
CONCLUSIONS. Restoration of CFTR activity with ivacaftor led to significant improvements in MCC. This physiologic assessment provides a means to characterize future CFTR modulator therapies and may help to predict improvements in lung function.

TRIAL REGISTRATION. ClinicialTrials.gov, NCT01521338.

ivacaftor
150 mg BID

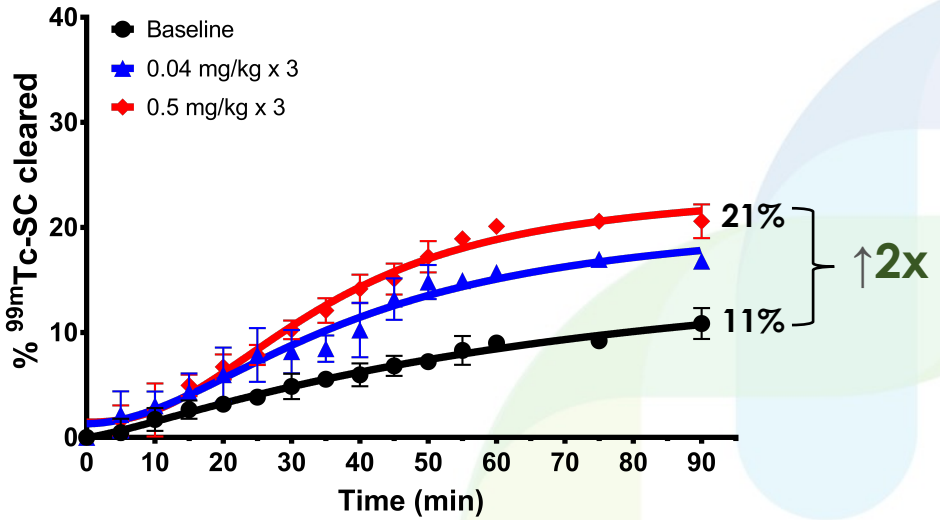
Accelerated MCC correlated with improved FEV_1

CF patient MCC

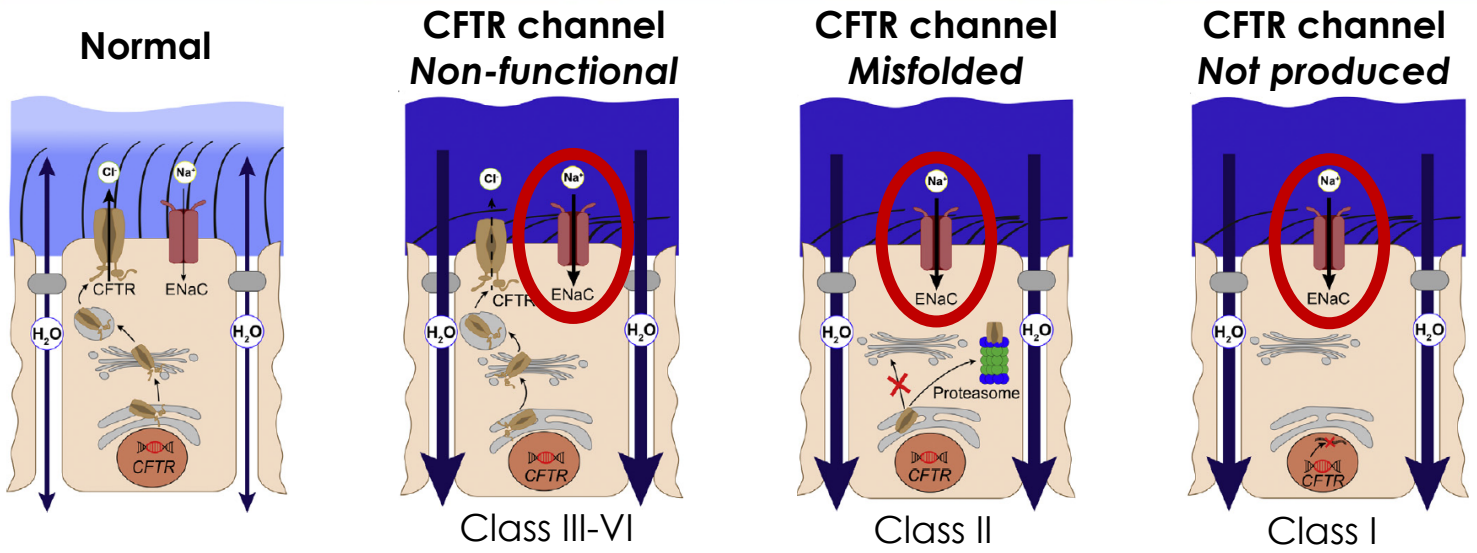


ARO-ENaC

Sheep MCC two weeks post-dose



ARO-ENaC and ion channel modulators in CF



Enhanced ENaC activity associated with all genotypes

CFTR potentiator monotherapy for patients with at least one Class III-VI mutation

- Ivacaftor potentiator produces **~10% increase in FEV_1**
- Restores **~50% normal CFTR function**
- Initially approved for G551D gating mutations
- Expanded to other mutations: ~15% of CF population

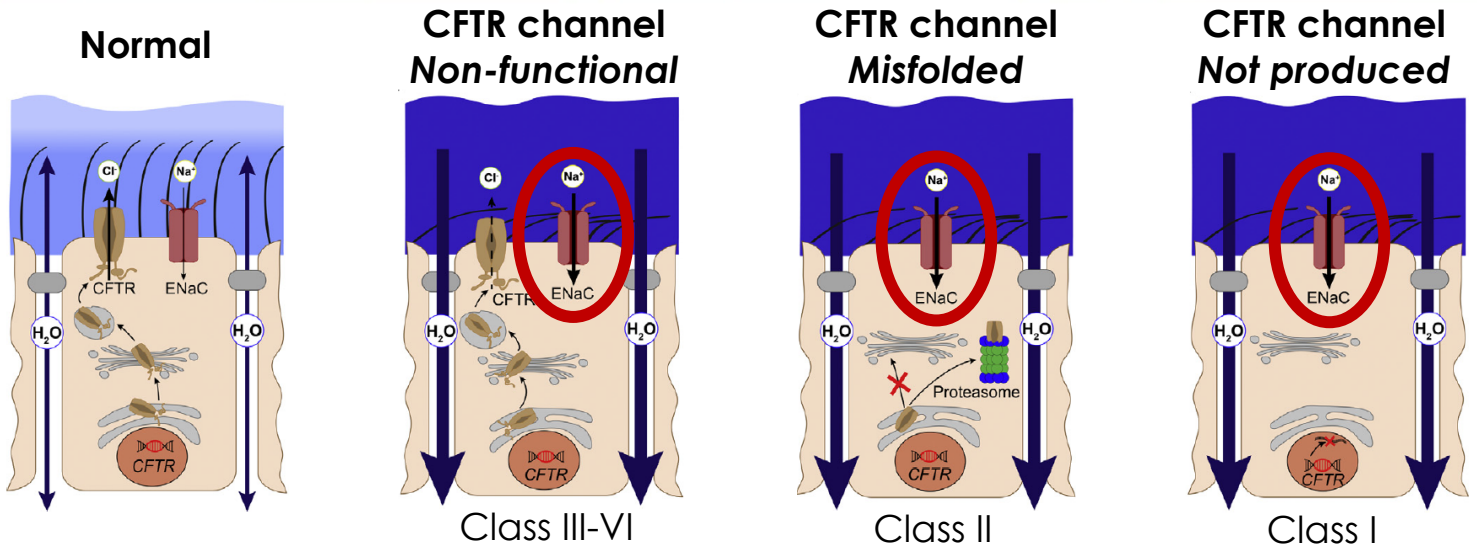
CFTR corrector / potentiator combinations for patients with Class II mutations (F508del)

- 90% CF patients have at least one copy F508del
  - 50% homozygous, 40% heterozygous
- Lumacaftor corrector increases amount of CFTR reaching cell membrane, but potentiator also needed to restore activity
- Combo produces **3-4% increase in FEV_1** in F508del homozygous
- Restores **~10-20% normal CFTR function**
- No clinical benefit for F508del heterozygous patients
- New triple-combinations adding next-generation modulators may extend treatment to F508del heterozygous patients

CHEST 2018; 154(2): 383-393

arrowhead pharmaceuticals

ARO-ENaC and ion channel modulators in CF



Enhanced ENaC activity associated with all genotypes

RNAi-mediated ENaC inhibition could provide clinical benefit to all CF patients, regardless of genotype, and in combination with existing or new CFTR-targeted therapies

ARO-ENaC Phase 1/2a Plan

- First in human, first in CF patients Phase1/2a study
  - Conducted at a single site in NZ (NHVs) or multiple sites in ANZ (CF patients)
  - Enroll CF patients, regardless of underlying mutation or other concomitant therapies
  - Few patients in NZ on CFTR modulators
- NHV SAD study design
  - Planned 6 cohorts (ea 4 active:4 placebo)
- CF cohorts in parallel to NHV cohorts
  - 4 MAD cohorts (2 Q2wk doses)
  - 3 CF patients (open label) per cohort

ARO-ENaC Phase 1 Concept

- Primary Objectives: safety in NHV and CF patients
  - AEs, physical exam, vitals, CXR change, standard labs (fasting), spirometry as safety, fasting K+, ECG, urine electrolytes
- Secondary Objectives:
  - Improvements in FVC, FEV1 in CF patients after 2 Q2 week doses
  - Evaluate PK in NHVs only

Conclusions and next steps

- NACFC poster presentation October 31, 2019
- ARO-ENaC inhalation results in durable and dose-dependent silencing of pulmonary αENaC expression in rats, accelerating mucociliary clearance for weeks post-dose in sheep
- ARO-ENaC preserves lung clearance in a sheep mucostatic model of cystic fibrosis lung disease
- IND/CTA-enabling studies are in process to support regulatory filings for first-in-human studies
- Arrowhead is expanding the platform to address additional pulmonary targets, particularly those that are currently inaccessible to traditional small molecule or antibody approaches

Arrowhead Analyst R&D Day October 2019

TRiM™ Advances

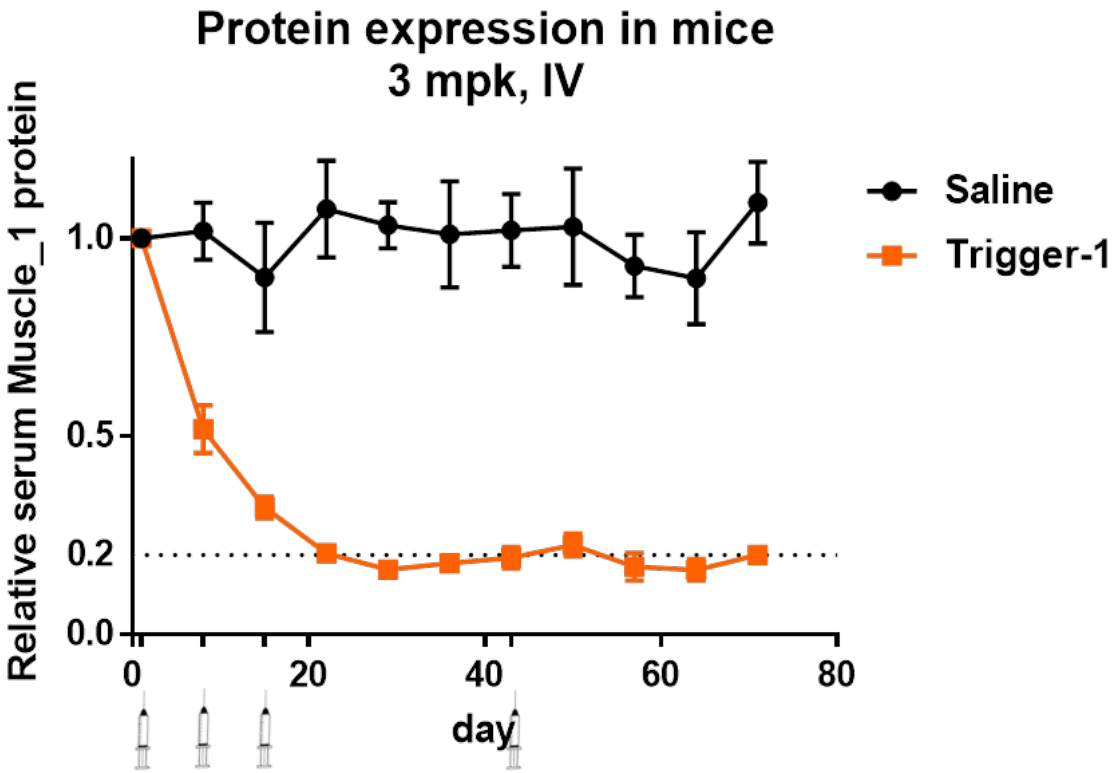
Tao Pei, Ph.D.
Vice President, Chemistry

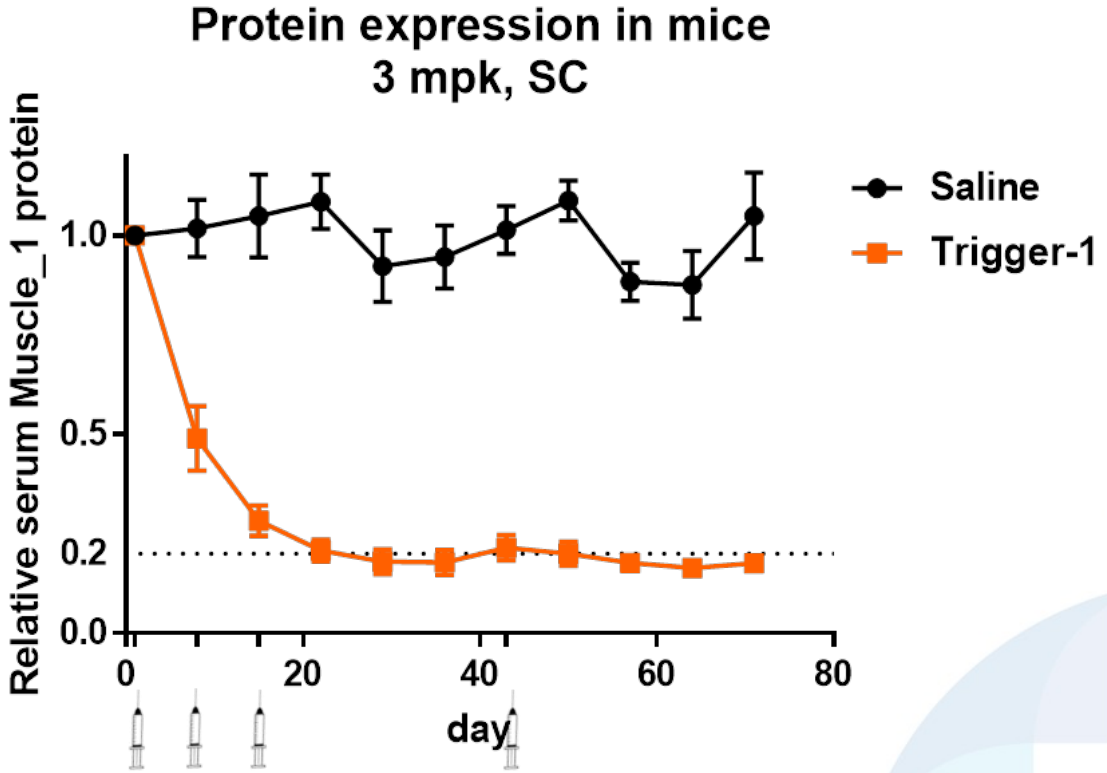
2nd Generation Skeletal Muscle Delivery Platform

Status

- Good efficacy and duration in mice
- Subcutaneous administration compatible
- Simplified construct, manufacture friendly

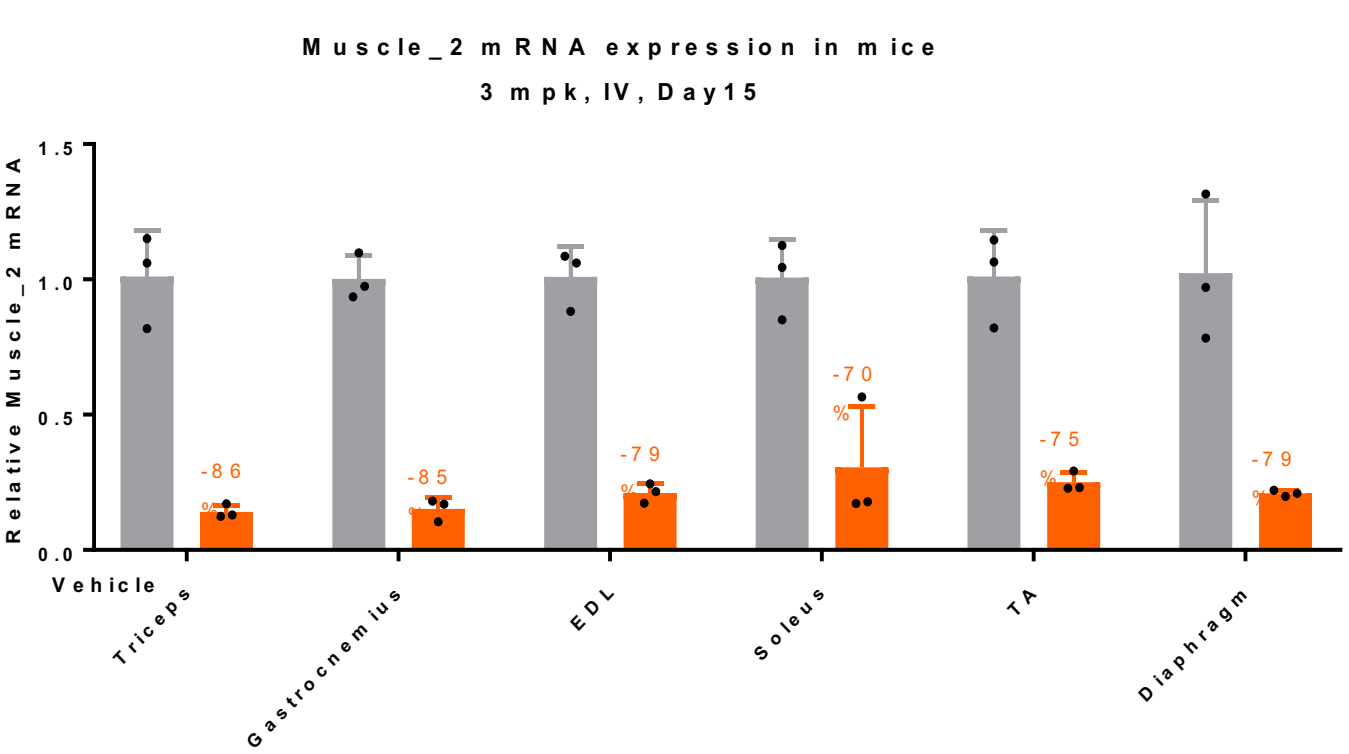
Deep and Durable Serum Protein Reduction via IV or SC

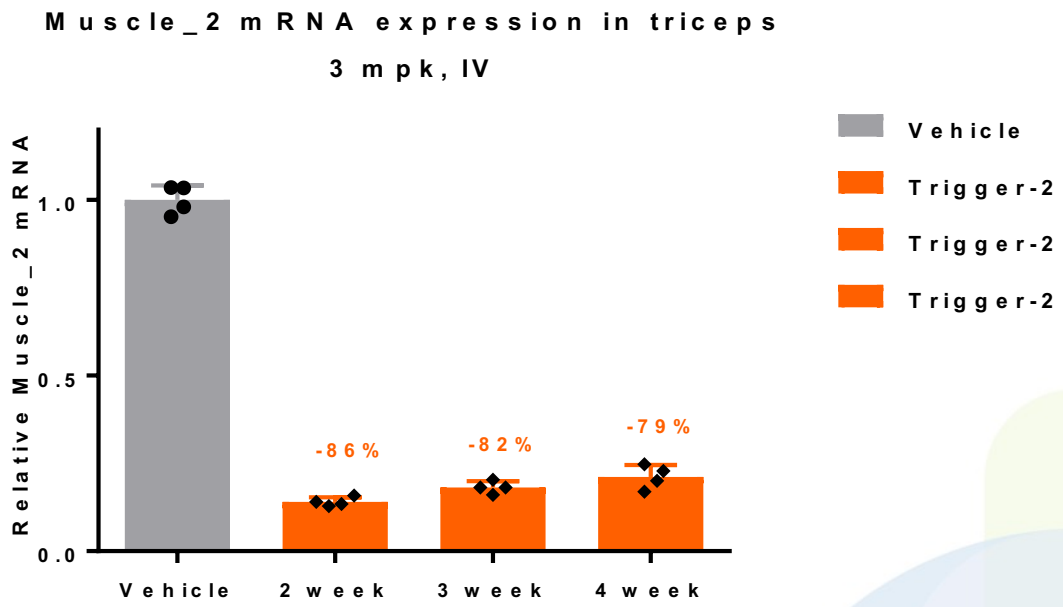




- >80% reduction of serum Muscle_1 protein with 3 weekly doses in mice
- A single 3 mpk maintenance dose maintained ~80% KD
- Comparable target protein reduction via IV or SC dosing

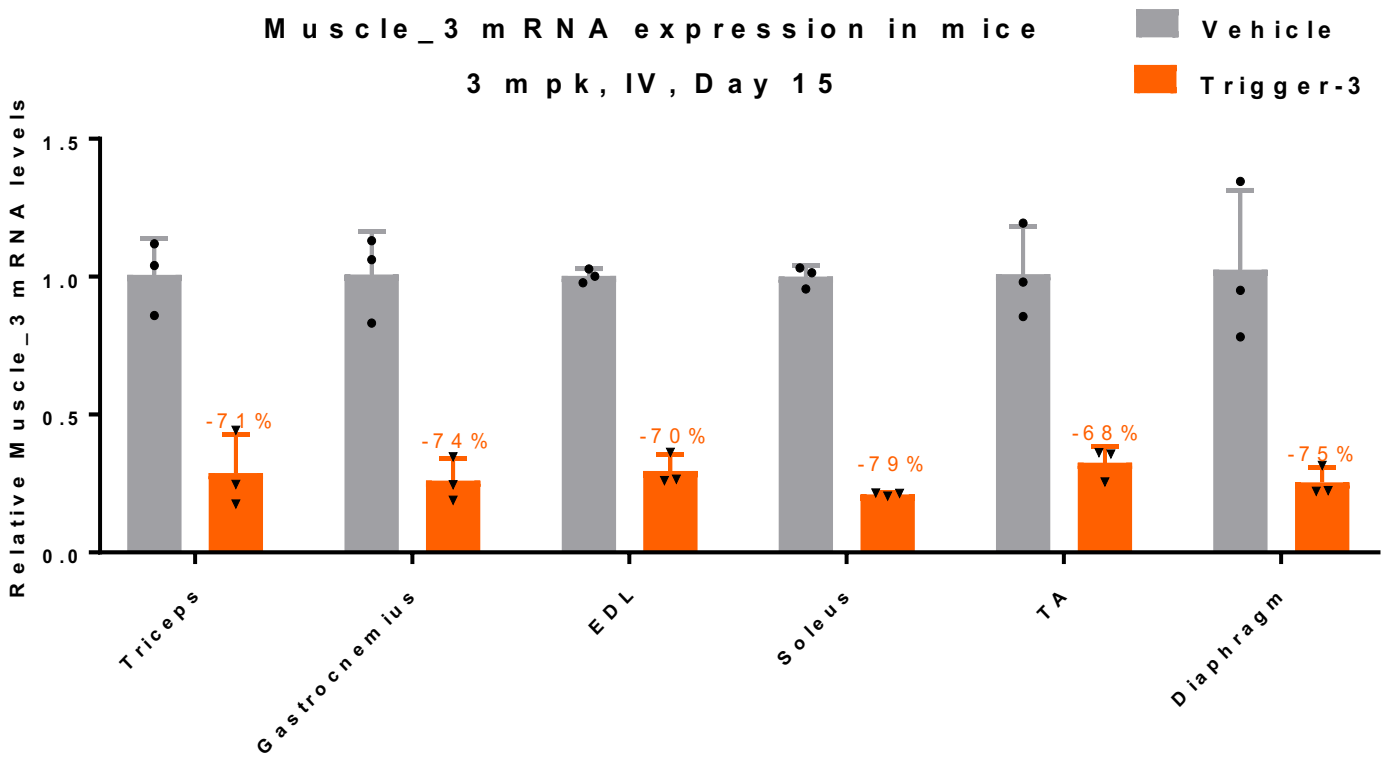
Reduction of a 2nd Muscle Target Gene in Mice After a Single Dose

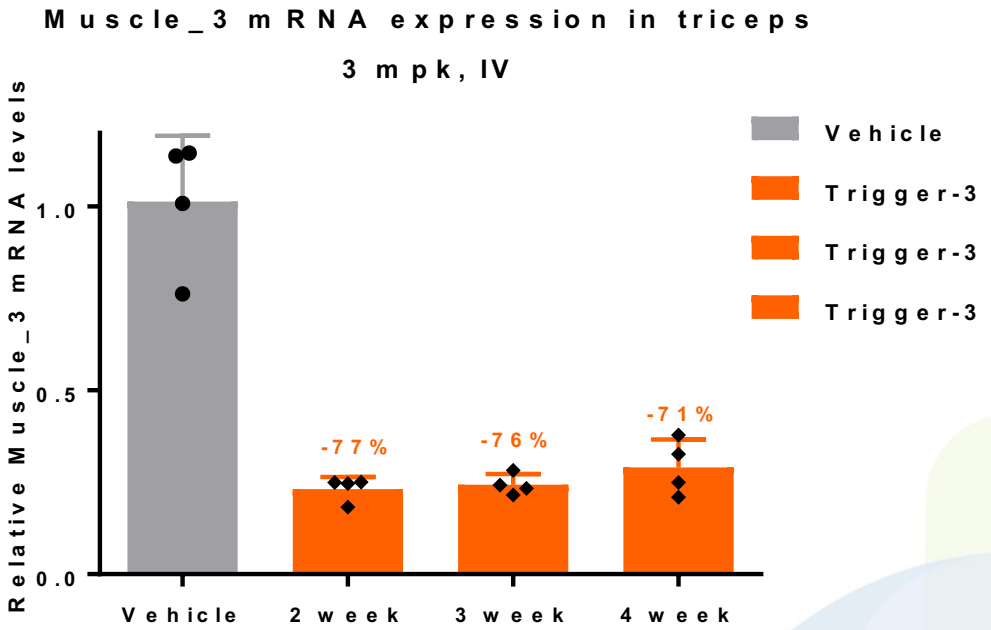




- 70-86% Muscle_2 mRNA KD in multiple muscle tissues on day15 post a single 3 mpk IV dose
- Durable Muscle_2 mRNA KD (close to 80% KD in triceps at 4 weeks post dosing)

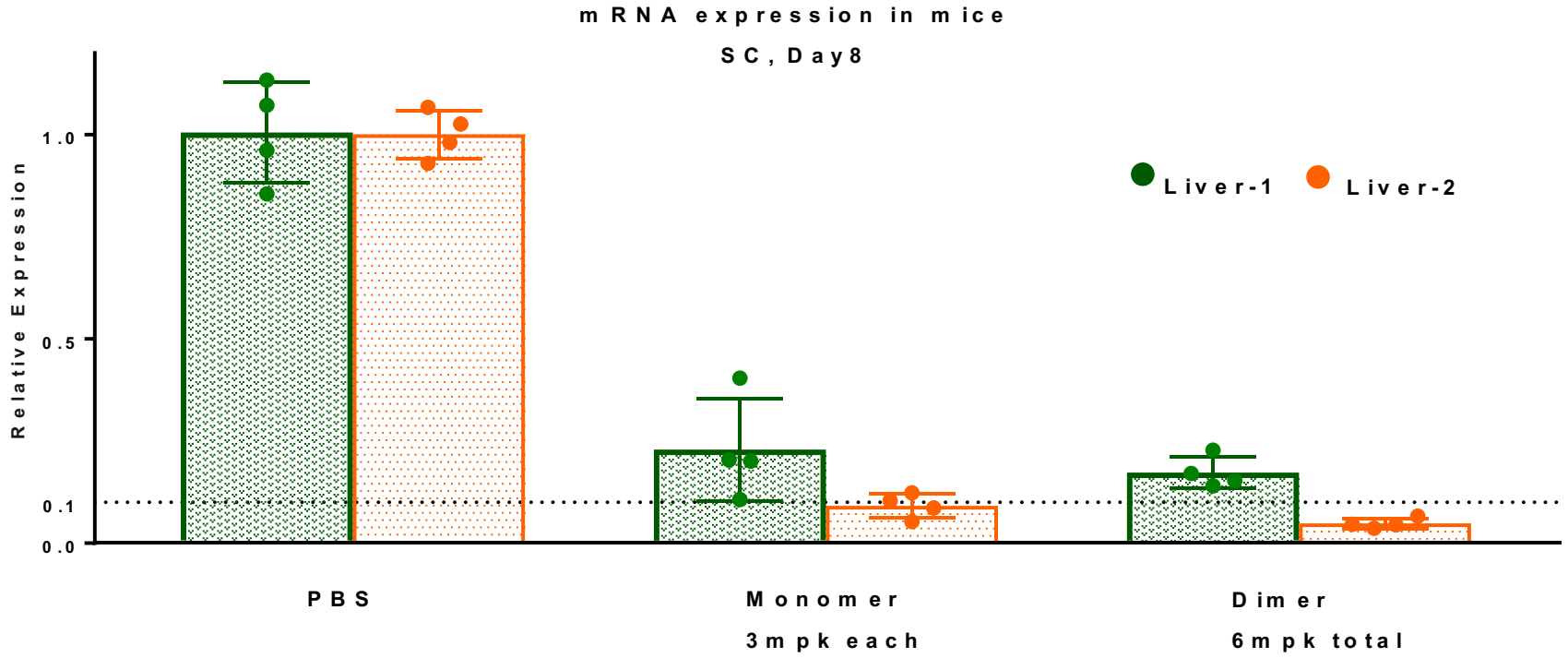
Reduction of a 3rd Muscle Target Gene in Mice After a Single Dose





- 68-79% Muscle_3 mRNA KD in multiple muscle tissues on day15 post a single 3 mpk IV dose
- Durable Muscle_3 mRNA KD (>70% KD in triceps for at least 4 weeks post dosing)

Efficient Knockdown of Dual mRNA Targets in Liver with a Single NAG-siRNA Dimer



- Covalently linked two different siRNAs using a single NAG moiety
- Comparable mRNA reduction achieved, monomer vs. dimer

Summary

We have developed

- An efficient muscle delivery platform
- A dimer approach
- A potential pathway to achieve maximum therapeutic benefit, *including if we wish to simultaneously knock down 2 genes*

Concluding Remarks

Chris Anzalone, Ph.D.
President and CEO

Important times for Arrowhead

We have always been focused on driving the field forward, and we are on the cusp of a series of firsts. Over the next 12 months, we expect:

- The first clinically relevant oncology RNAi drug candidate in the clinic
- The first lung-targeted RNAi drug candidate in the clinic
- The first muscle-targeted RNAi drug candidate in the clinic
- The first RNAi drug candidate that silences 2 genes

…and we have no intention to slow down

We are just getting started…

By the end of next year we expect:

- At least 7 wholly-owned clinical candidates
- 2 partnered programs at P2 or later
- 3 wholly-owned P3 pivotal studies
- Drug candidates across 4 different cell types

Over the near- to mid-term
we expect our pipeline to increasingly have the depth and breadth associated with big Pharma

Q&A Session
Panel