Arrowhead Pharmaceuticals Analyst R&D Day

June 1, 2023

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Analyst R&D Day June 1, 2023

Welcome and Introductions

Vince Anzalone, CFA

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Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, entering into new collaborations and achieving existing projected milestones, rapid technological changes 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.

Key Opinion Leader Panelists

Michael Benatar, MD, PhD

University of Miami, Miller School of Medicine

- Professor of Neurology and Public Health Sciences
- Chief, Neuromuscular Division
- Executive Director, The ALS Center
- Vice Chair, Clinical and Translational Research, Department of Neurology

Matthias Salathe, MD

University of Kansas Medical Center

- Professor, Pulmonary, Critical Care and Sleep Medicine
- Department Chair, Internal Medicine
- Vice Chancellor for Research

Ira Goldberg, MD

NYU Langone Medical Center

- Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology, Department of Medicine at NYU Grossman School of Medicine
- Director, Division of Endocrinology, Diabetes and Metabolism

Agenda

Time	Topic	Presenter
09:00–09:05	Welcome and Intros	Vince Anzalone, CFA
09:05–09:15	Overview of Arrowhead	Chris Anzalone, PhD
09:15–09:25	Therapy Development for SOD1 ALS	Michael Benatar, MD, PhD
09:25–09:40	CNS: Novel Platform and Pre-clinical Overview	Christine Esau, PhD
09:40–09:50	TRiM™ Platform Expansion	James Hamilton, MD, MBA
09:50-10:00	Q&A	
10:00–10:10	Pulmonary Platform Pre-clinical Review	Erik Bush, PhD
10:10–10:25	Pulmonary Clinical Update	James Hamilton, MD, MBA
10:25–10:40	Pulmonary Clinical Results: Significance and Context	Matthias Salathe, MD
10:40–10:55	Pulmonary Clinical Development Path	Javier San Martin, MD
10:55-11:15	Q&A and Break	
11:15-11:25	Early Programs: ARO-C3 and ARO-PNPLA3	James Hamilton, MD, MBA
11:25-11:40	Treatment of Lipid Disorders Landscape: Unmet Need and Residual Risk	Ira Goldberg, MD
11:40–11:55	Cardiometabolic Programs Update: ARO-APOC3 and ARO-ANG3	Javier San Martin, MD
11:55–12:05	Cardiometabolic Commercial Overview	Tracie Oliver
12:05-12:15	Concluding Remarks	Chris Anzalone, PhD
12:15-12:30	Q & A	Panel
12:30	Lunch	

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Overview of Arrowhead

Chris Anzalone, PhD

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Every. Day. Matters.

Who We Are

Arrowhead is an **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates

Broad Pipeline

- **12 clinical stage programs** (7 wholly-owned; 5 partnered)
- Mix of **early, mid, and later-stage** candidates targeting **rare and high prevalence diseases**
- Growing pipeline with **2–3 new clinical programs planned per year**

Proprietary Platform

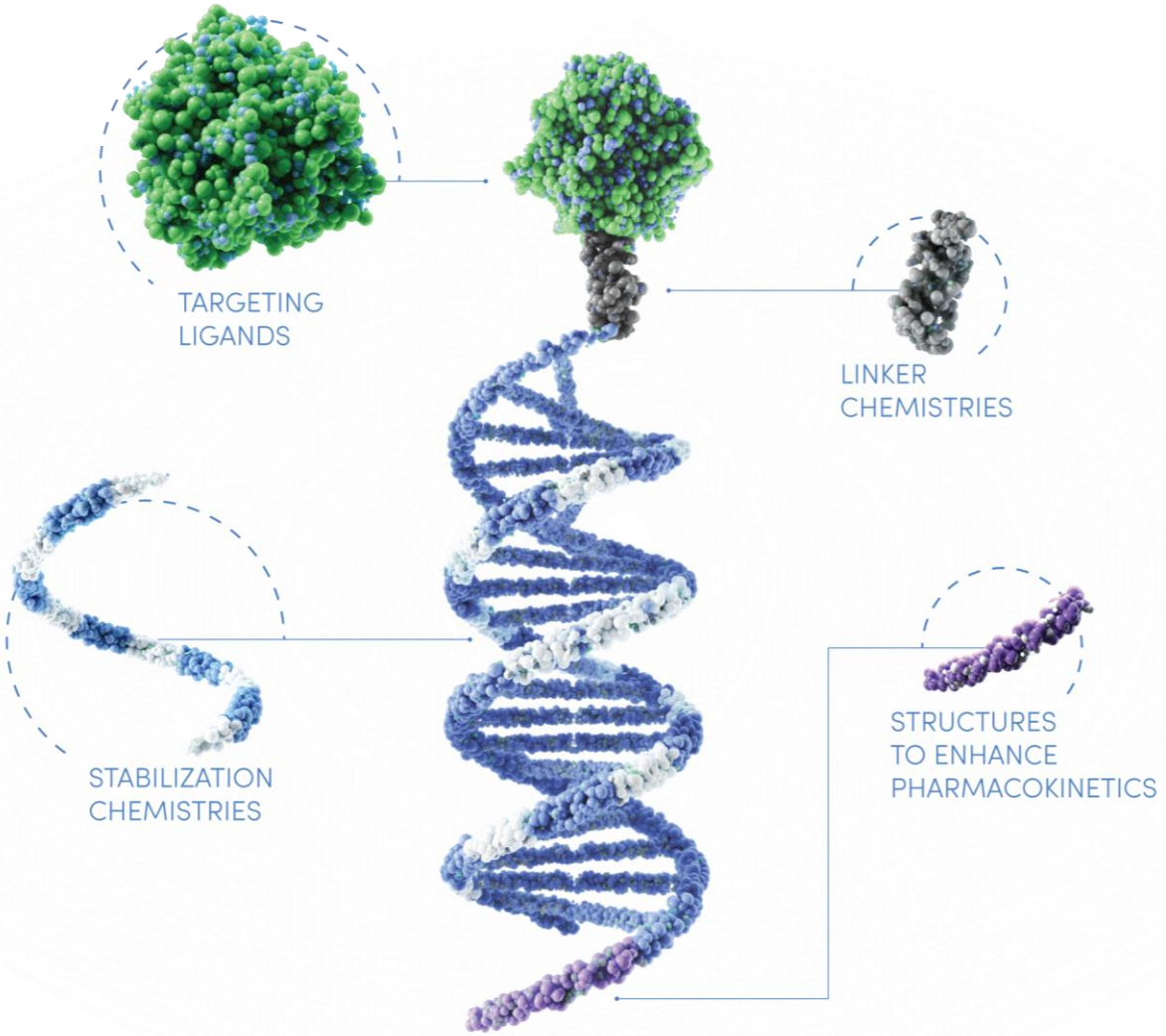
- **Targeted RNAi Molecules** platform **(TRiM™)** designed for **deep and durable gene silencing**
- Potential to be **best in class**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**

Financial Resources

- Strong balance sheet to **push candidates towards commercialization**
- **Non-dilutive capital** from Amgen, Takeda, Horizon, GSK, and Royalty Pharma as milestones are achieved and royalties are earned
- Potential for **additional** product and/or platform **deals**

20 in '25: We expect to have 20 individual drugs in clinical trials or at market in 2025

A Different Kind of Biotech Company



We created a modular, structurally simple system to:

1. Address multiple cell types
   - Go where disease is
2. Provide platform continuity/confidence
   - Enhanced expectation of success for new candidates
   - Lessons from prior candidates inform future candidates
   - **Potential for more candidates becoming approved drugs than industry average**
3. Move rapidly from idea to the clinic

Has it worked?

Yes

In 2017, we had the TRiM™ platform
but **0 drug candidates in clinical studies**

By the end of 2023, just 6 years later, we expect to have brought
18 drug candidates into clinical studies

1. Addressing multiple cell types
   - Liver, solid tumor, pulmonary, CNS, skeletal muscle
2. Providing platform continuity/confidence
   - Only 2 of the potential 18 candidates have been discontinued
3. Treating many people
   - >3,500 people in clinical studies, and counting
4. Moving rapidly
   - Expect to be in 4 P3 studies by end of 2023

Imagine what we can accomplish in the next 6 years

Today's Focus

Updates on some of our clinical programs

- Cardiometabolic
- Pulmonary
- C3
- PNPLA3

Discussion about what's next

- CNS
- Future CNS systemic delivery
- Delivery to Adipose tissue

Arrowhead Pipeline

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Therapy Development for SOD1 ALS

Michael Benatar, MD, PhD

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Therapy Development for SOD1 ALS

Michael Benatar, MD, PhD

Walter Bradley Chair in ALS Research

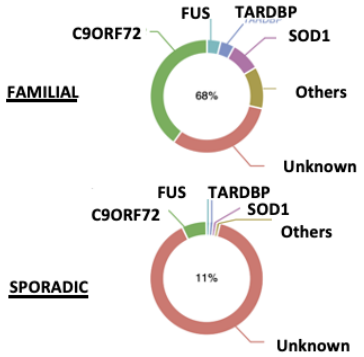
University of Miami

Disclosures

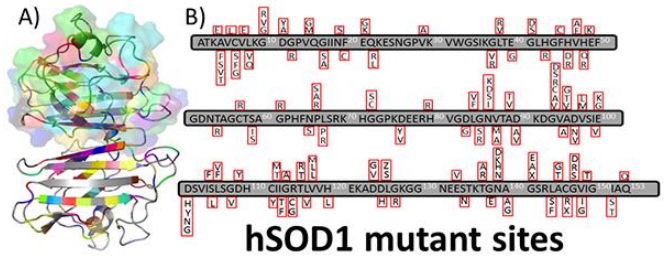
- Industry trials
  - Biogen, Orphazyme
- Consulting
  - Alector, Alexion, Annexon, Arrowhead, Biogen, Cartesian, Denali, Eli Lilly, Horizon, Immunovant, Janssen, Novartis, Roche, Sanofi, Takeda, UCB, UniQure
- Research Funding
  - Federal: NIH
  - Foundation: ALSA, MDA

SOD1 ALS

- Account for ~2% of all ALS

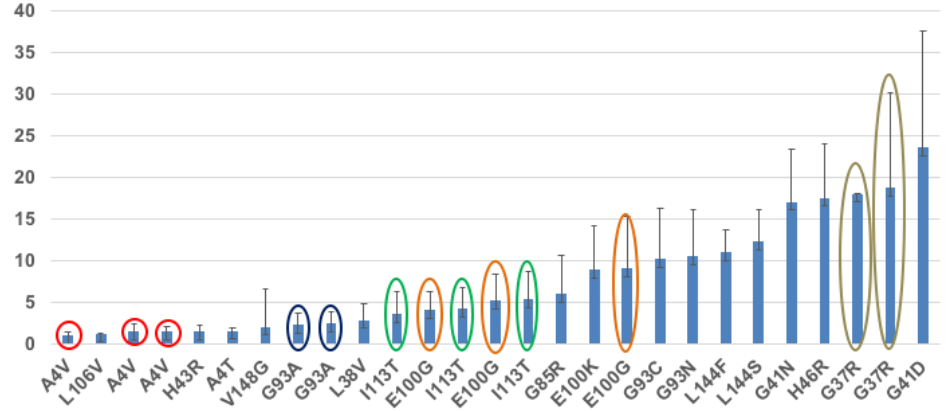


- 200+ different *SOD1* mutations



Zwiegers and Shaw, *Journal of Controversies in Biomedical Research 2015*

- Marked phenotypic heterogeneity

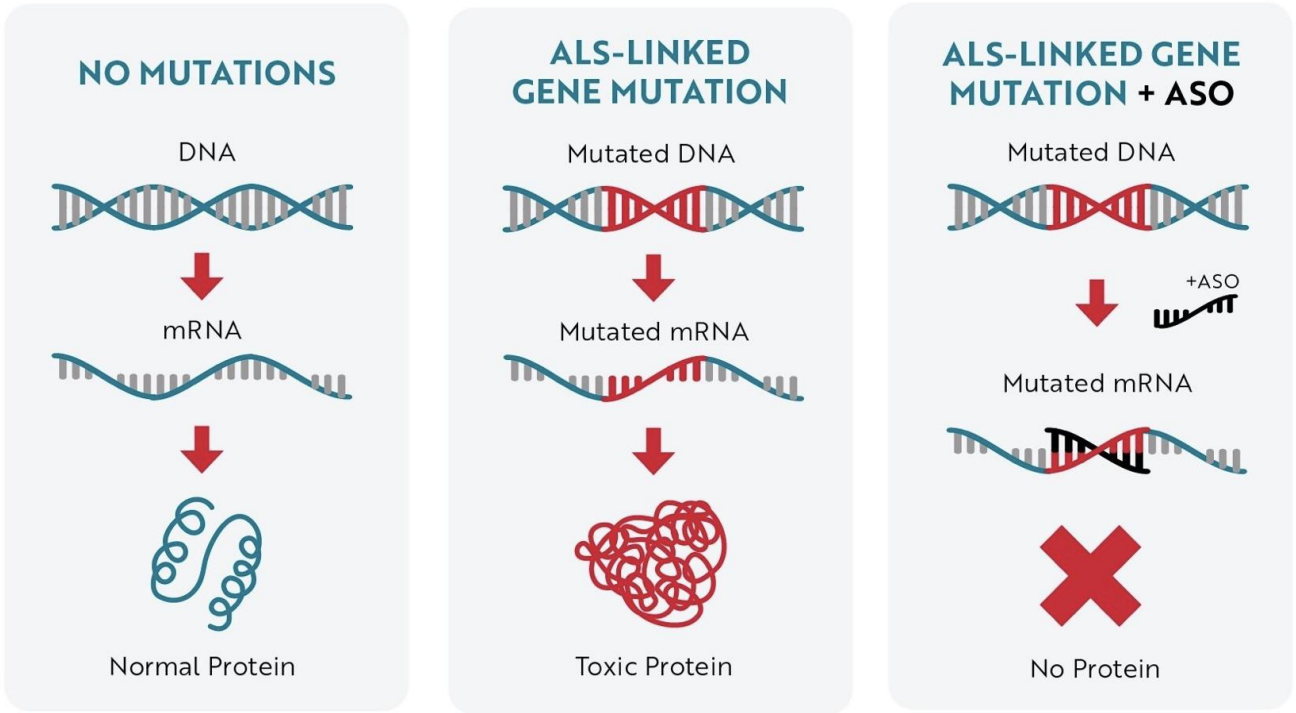


Juneja et al 1997. Cudkowicz et al 1997. Bali et al 2016. Benatar et al 2017.

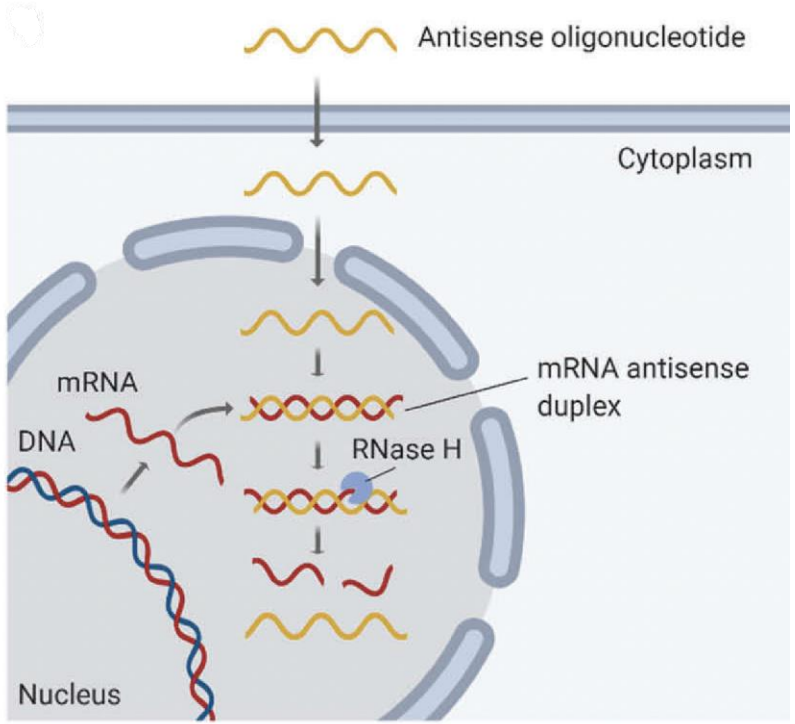
- Toxic gain-of-function

Shvil et al. Cell Death & Disease, 2018

SOD1 Antisense Oligonucleotide (Tofersen)



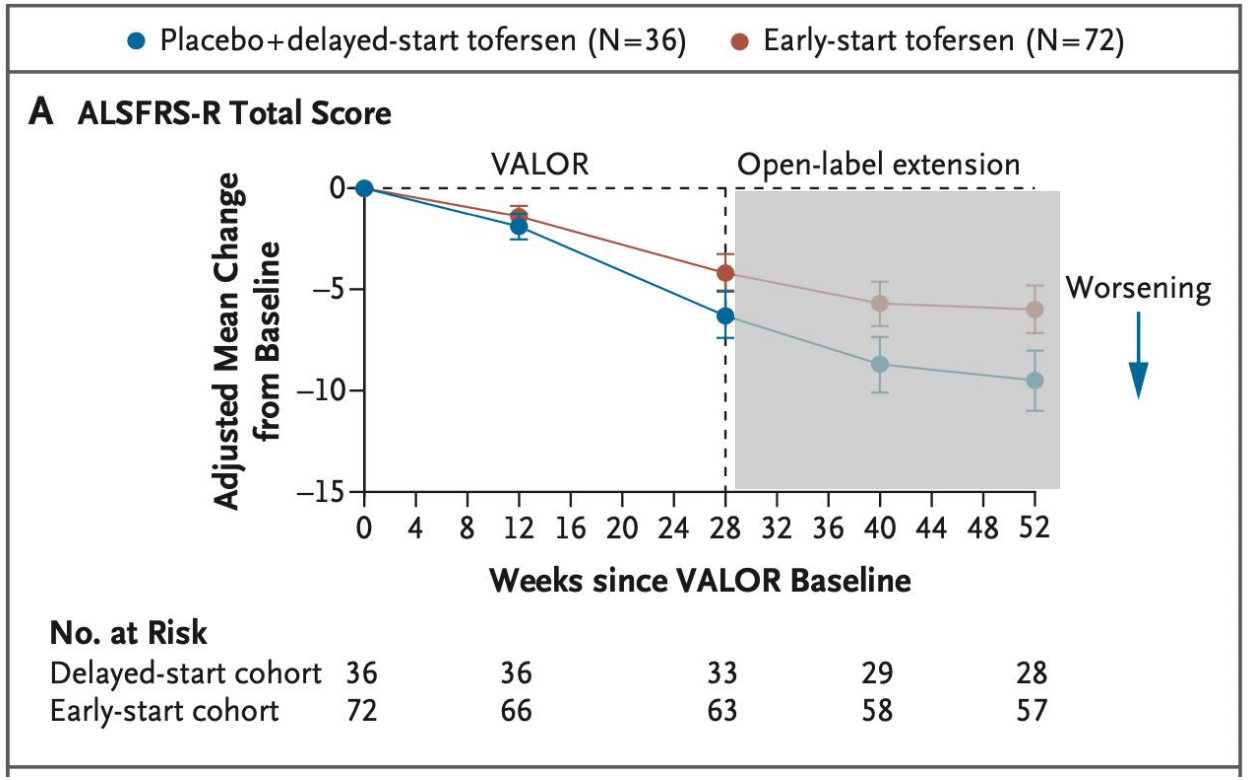
https://www.als.org/navigating-als/living-with-als/fda-approved-drugs/tofersen



Tromp et al, Exp. Opin. Invest. Drugs, 2020

Tofersen Phase 3 Results (VALOR Study)

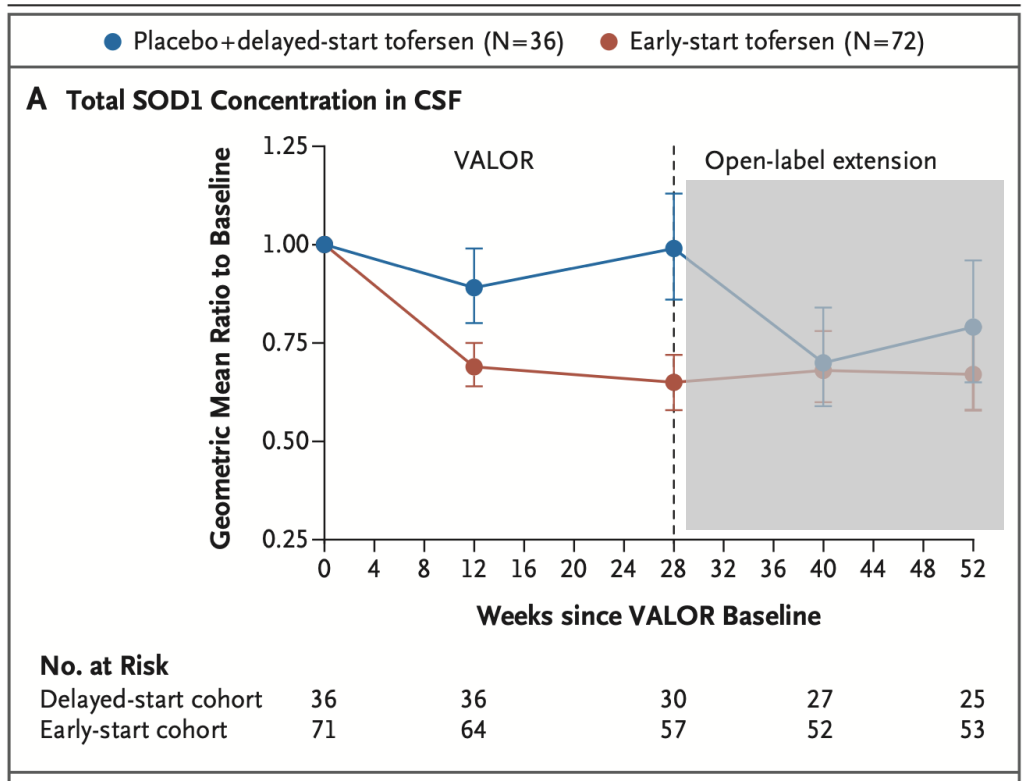
Impact of *SOD1 ASO* on Clinical Function



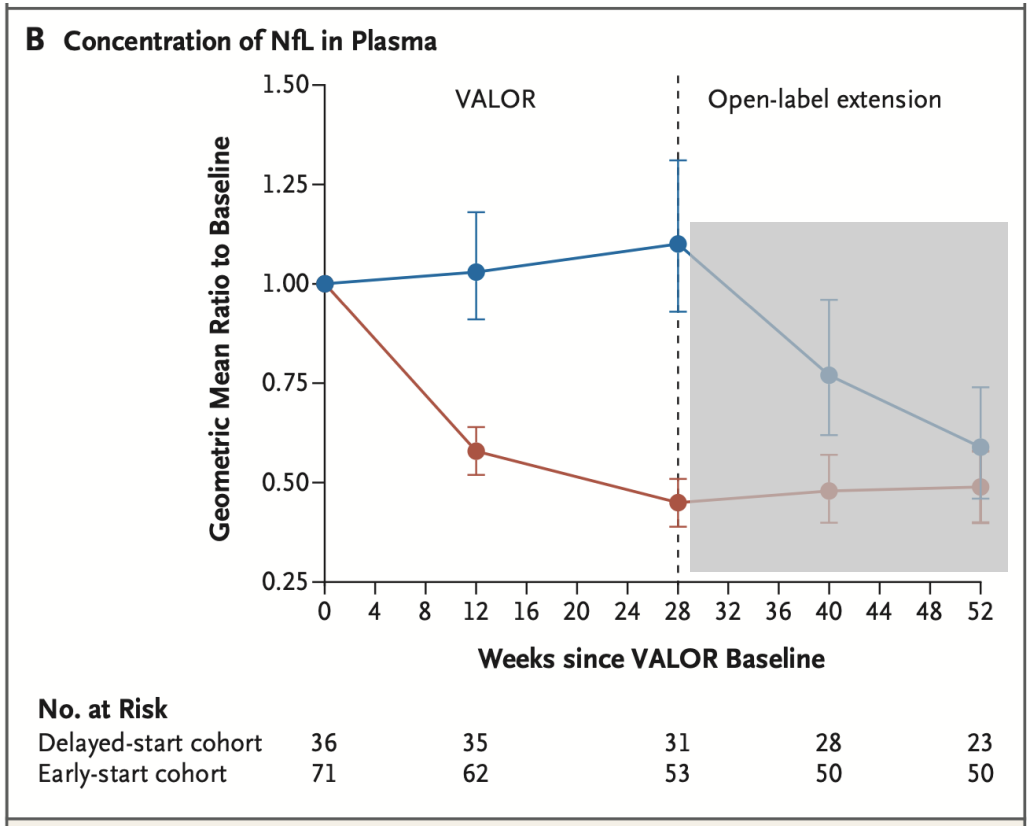
Miller T, et al. NEJM 2022 387(12):1099-1110

Tofersen Phase 3 Results (VALOR Study)

Impact of *SOD1 ASO* on CSF SOD1



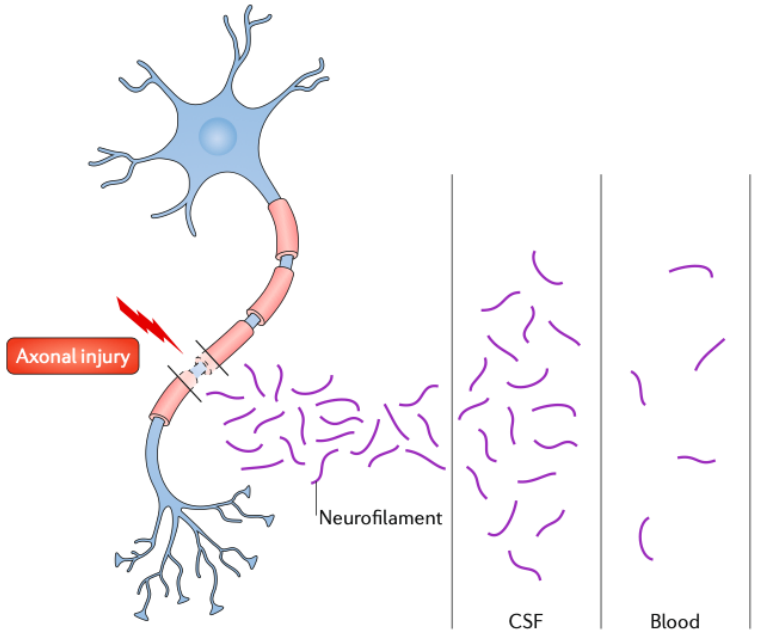
Impact of *SOD1 ASO* on Neurofilament light



Miller T, et al. NEJM 2022 387(12):1099-1110

Supported accelerated approval by the FDA

Neurofilaments



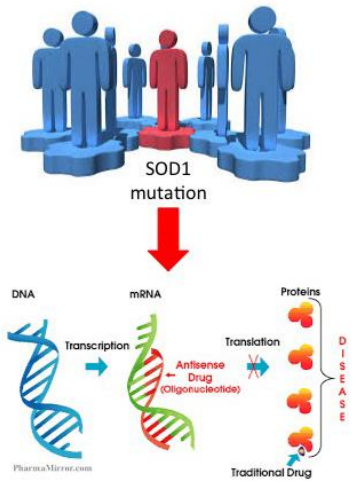
Khalil et al (Nature Reviews Neurology, 2018)

- Major structural components of nerve cells
- Released into:
  - Cerebrospinal fluid (CSF) following nerve injury (or neurodegeneration)
  - Blood
- Light and heavy chains
- Reliably measured

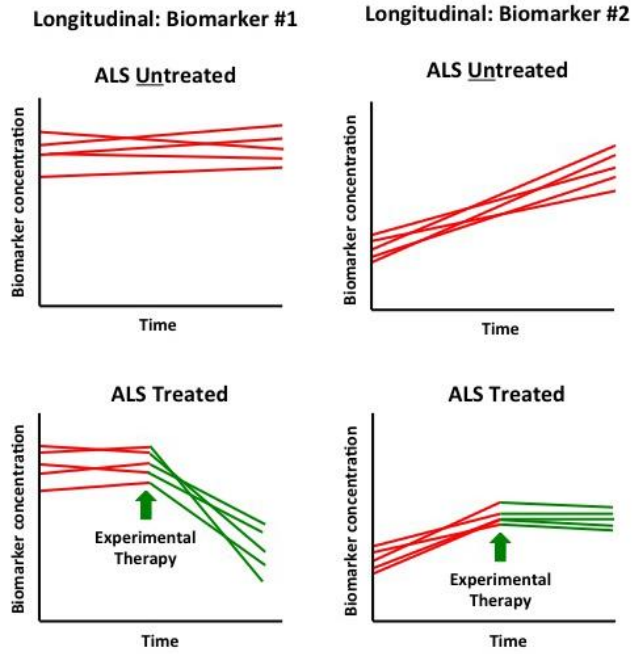
Benatar et al. NfL in drug development for ALS. Brain, 2022

Biomarkers

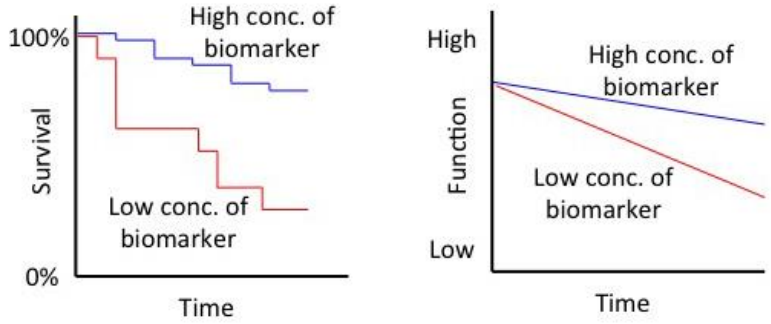
- Predictive



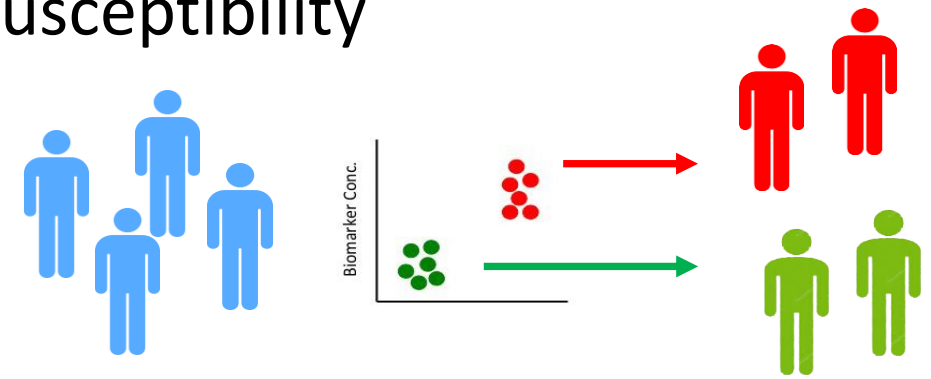
- Response



- Prognostic

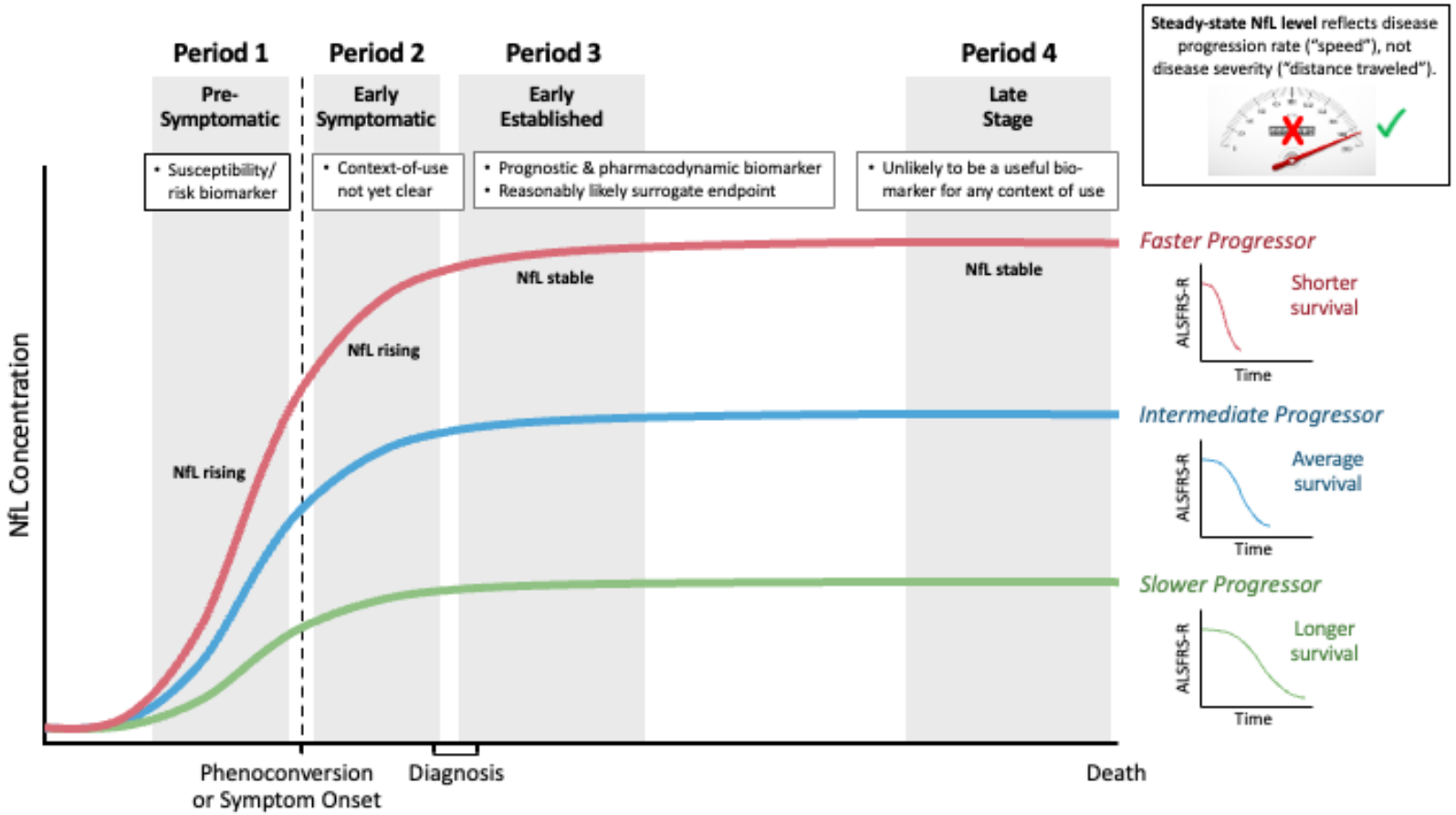


- Risk/Susceptibility



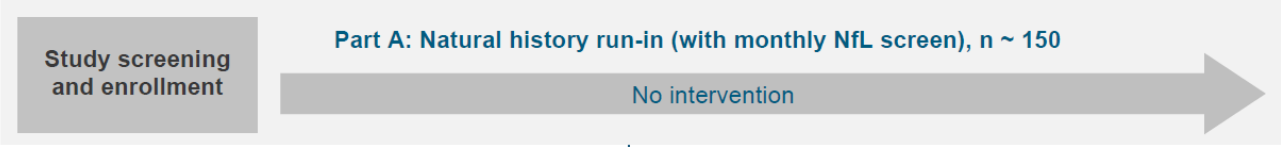
Benatar et al. ALS biomarkers for therapy development. Muscle & Nerve, 2016

NfL as a Biomarker for Therapy Development



Benatar et al. NfL in drug development for ALS. Brain, 2022

Preventing SOD1 ALS: The ATLAS Trial



[a] Measured using Siemens Healthineers NfL assay.
[b] Assuming other eligibility criteria are met.

Modified from: Benatar M, et al. Design of a Randomized, Placebo-Controlled, Phase 3 Trial of Tofersen Initiated in Clinically Presymptomatic SOD1 Variant Carriers: the ATLAS Study. *Neurotherapeutics 2022* 19(4):1248-1258

- This trial will (hopefully) provide FDA with confirmatory evidence of efficacy

Unmet Therapeutic Needs for SOD1 ALS

- Disease progression despite tofersen
- Potential for greater therapeutic effect with more marked lowering of CSF SOD1
- Value in developing a therapeutic paradigm that entails less frequent intrathecal dosing
  - Especially for therapies that may be lifelong (including in the pre-symptomatic population)

Lessons from tofersen for future trials

- Value of NfL as a response biomarker that is acceptable to the FDA
- Trial eligibility
  - Mutational spectrum
  - Use (or not) of ALSFRS-R pre-slope
  - Disease duration
- Incorporation of NfL as a prognostic marker
  - Stratification vs. dynamic randomization
- Trial duration
  - 6 months may be insufficient to measure clinical outcome

Potential Paths for Future Phase 3 Trial

- Geographies in which tofersen is not available
- Head-to-head comparison
  - Non-inferiority re efficacy
  - Superiority re safety and patient acceptability re frequency of dosing
- Full array of options is critically dependent on
  - Results of initial study
  - Longer term efficacy and safety data with tofersen

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CNS: Novel Platform and Pre-Clinical Overview

Christine Esau, PhD

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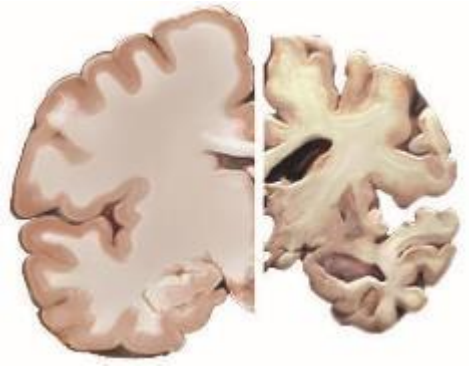
Neurodegenerative Diseases are an Enormous Burden Uniquely Addressable by RNA Therapeutics

Over **50 million** neurodegeneration patients worldwide[1] and few disease modifying therapies

Healthy Brain



Diseased Brain

- Common feature is abnormal protein aggregation and neurotoxic gain of function: difficult mechanism to drug but RNAi approach knocks out disease-causing protein
- Recent progress in genetics and biomarker development are enabling clinical development in a broad range of neurodegenerative diseases, increasing probability of success

1. *Lancet Neurology* 2019, 18:459

TDP-43 proteinopathies
- Amyotrophic Lateral Sclerosis (ALS)
- Fronto-temporal dementia (FTD)

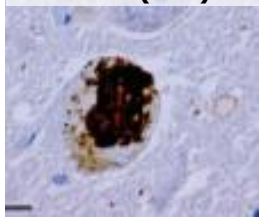
Tauopathies
- Alzheimer's disease (AD)
- Fronto-temporal dementia (FTD)
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

Amyloidoses
- Alzheimer's disease (AD)
- Prion diseases

Synucleinopathies
- Parkinson's disease (PD)
- Lewy body dementia
- Multiple system atrophy

Expansion Repeat Disorders
- Huntington's disease (HD)
- Spinocerebellar ataxias (SCA)

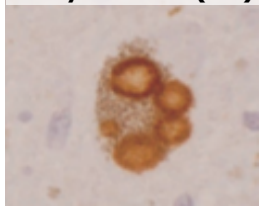
SOD1 (ALS)



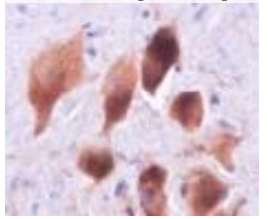
Tau tangles

Amyloid plaques

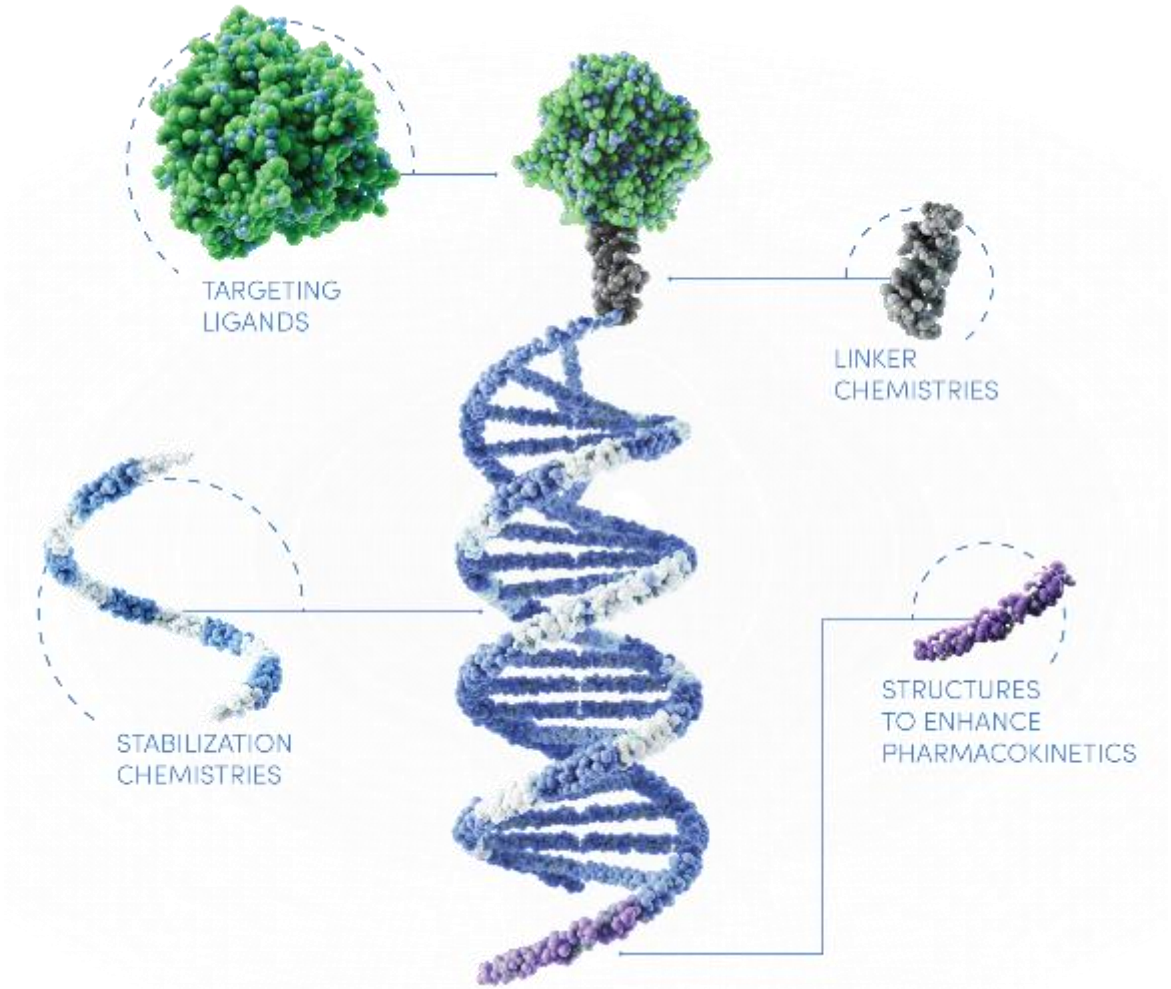
Lewy bodies (PD)



ATXN2 (SCA2)



CNS-Targeting TRiM™ Platform



We have developed an optimized intrathecal delivery platform for CNS:

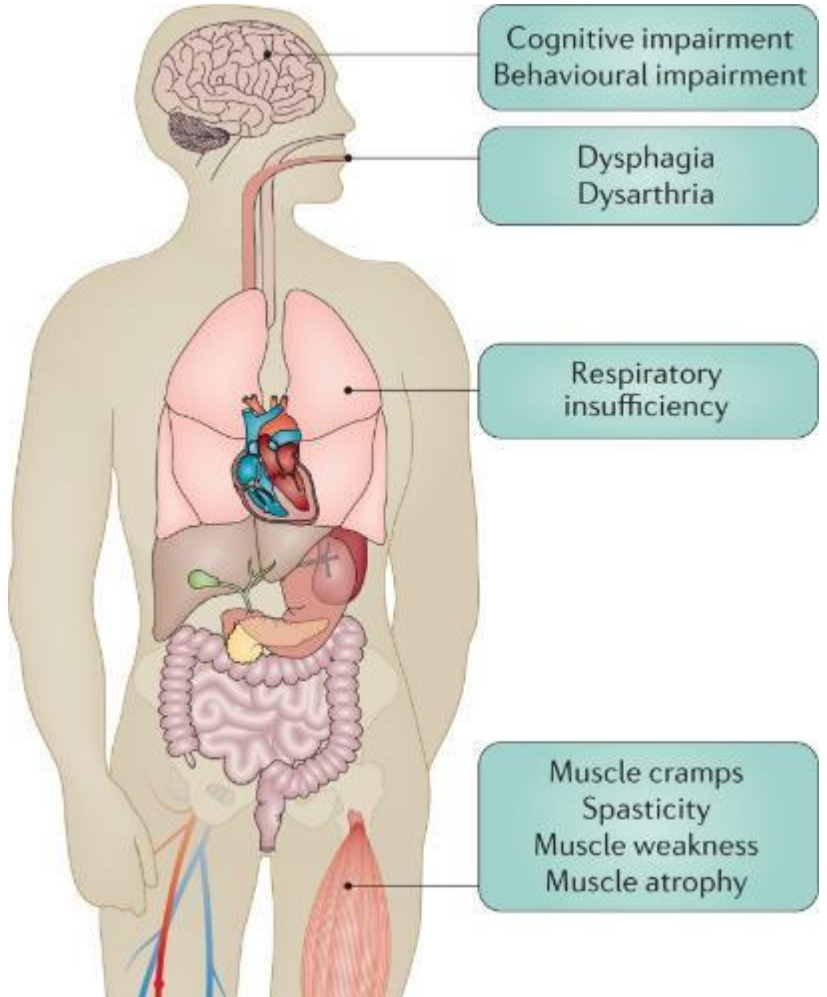
- **Simplified** lipid-conjugate design
- **Potent** target mRNA reduction
- **Broad distribution** throughout the brain and to all relevant cell types in rodent and monkey
- **Long duration of action** with potential for infrequent (quarterly or half-yearly) dosing
- **Safety** Initial GLP tox complete and NOAEL highest dose tested in rat and NHP

SOD1-ALS
First Arrowhead Intrathecal CNS Program

- ALS is a progressive motor neuron disease, often fatal within 2-5 years of diagnosis
- SOD1 mutations that promote toxic protein aggregation are one of the most common genetic causes of ALS
- Biomarkers are available to monitor target engagement (SOD1 in CSF) and response to treatment (serum NfL), facilitating clinical development
- Tofersen represents a major advance for patients, but fell short of demonstrating functional benefit and requires a burdensome monthly lumbar puncture
- We think ARO-SOD1 has potential to achieve better efficacy with less frequent dosing

Hardiman et. al., 2017 *Nat Rev Dis Primers*

Amyotrophic Lateral Sclerosis Symptoms



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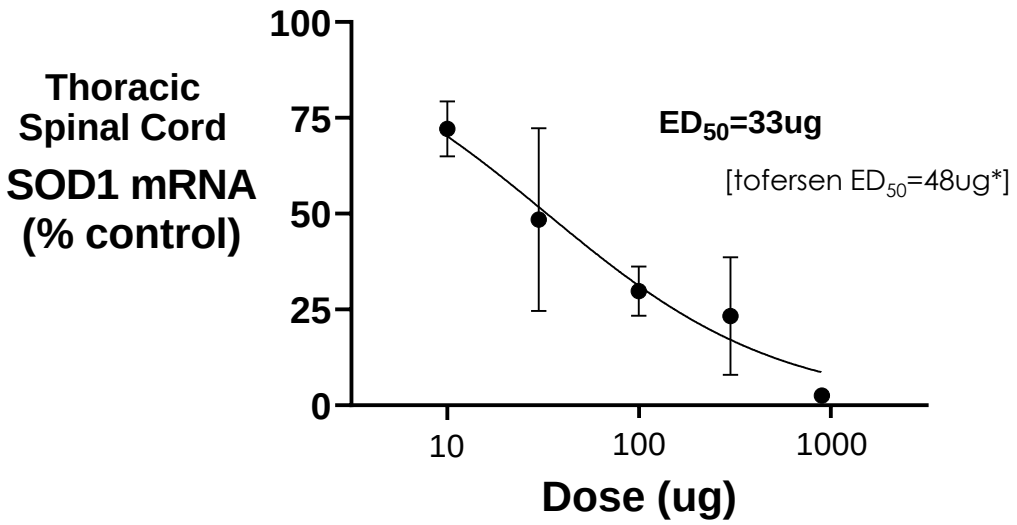
ARO-SOD1
Potency in Human SOD1 G93A Transgenic Rodent Models

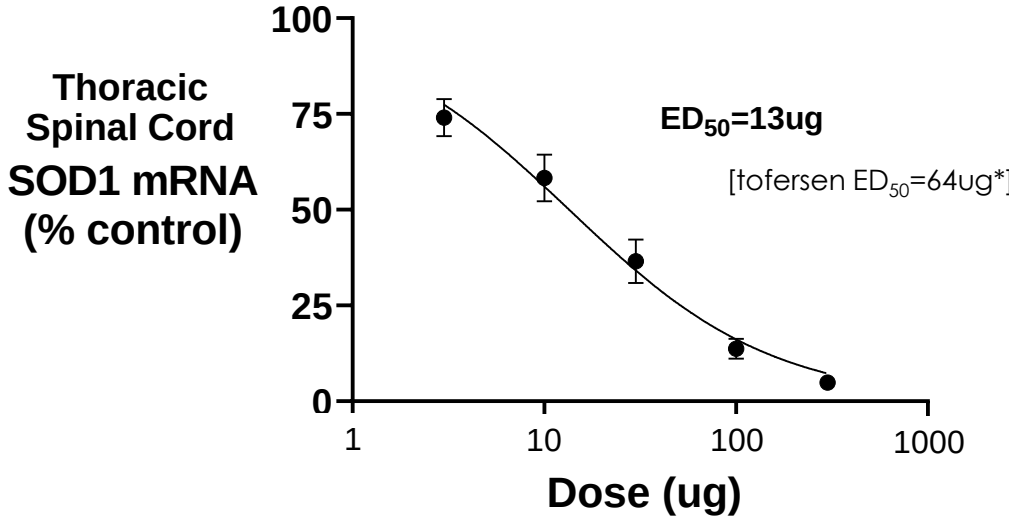
Transgenic Rat

Single dose IT – 4 weeks post dose



Transgenic Mouse

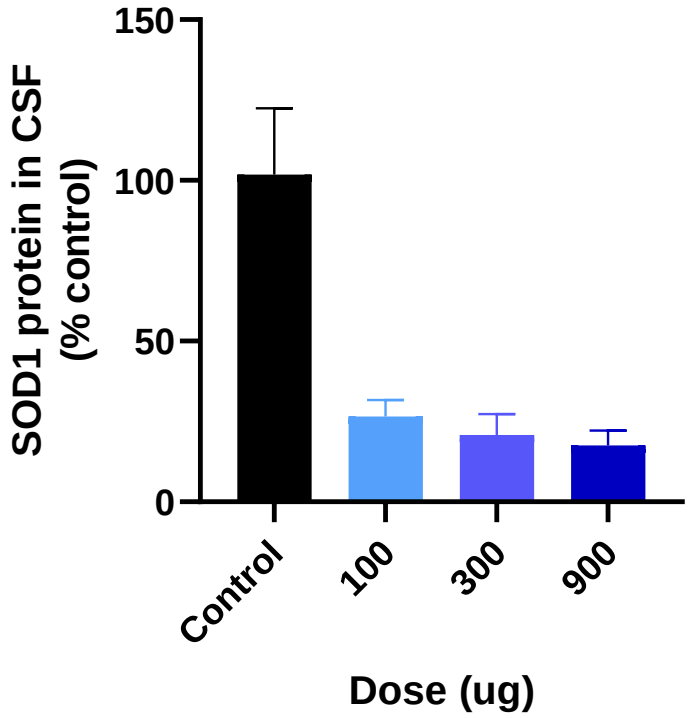
Single dose ICV – 2 weeks post dose



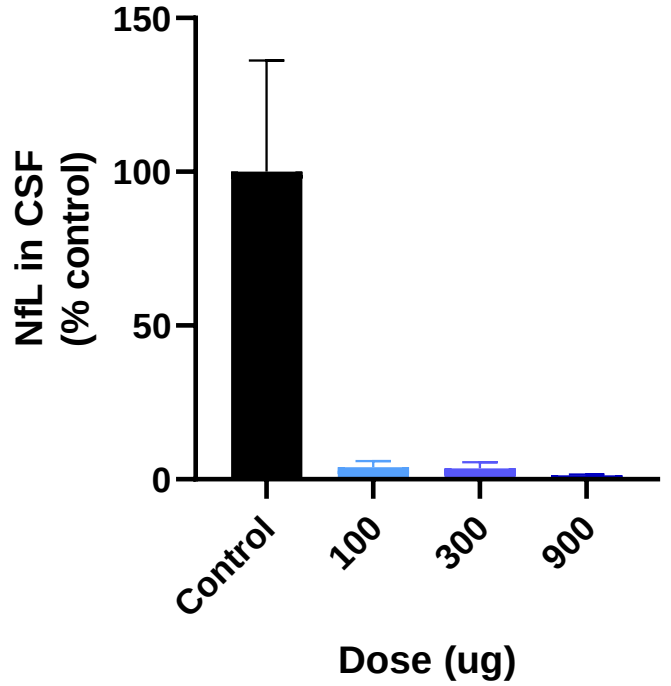
*McCampbell et. al. 2018

ARO-SOD1 Potently Reduces SOD1 Protein and NfL in SOD1 Transgenic Rat CSF

SOD1 Protein in CSF



Neurofilament (NfL) in CSF

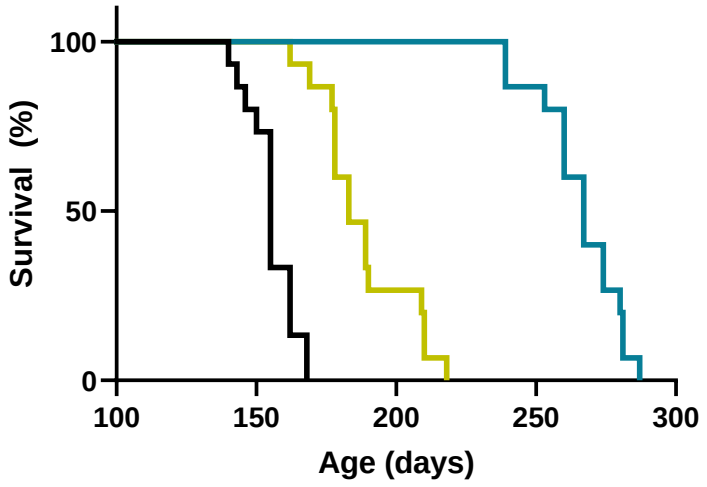


Three months after single intrathecal dose. n=4, mean ±SEM

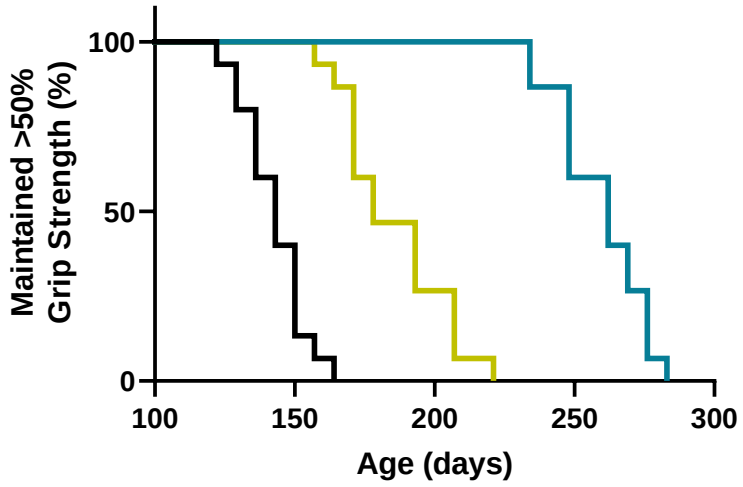
SOD1 G93A Transgenic Rat Model

ARO-SOD1 Treatment Extends Survival and Motor Function of SOD1 G93A Transgenic Mice Better than ASO

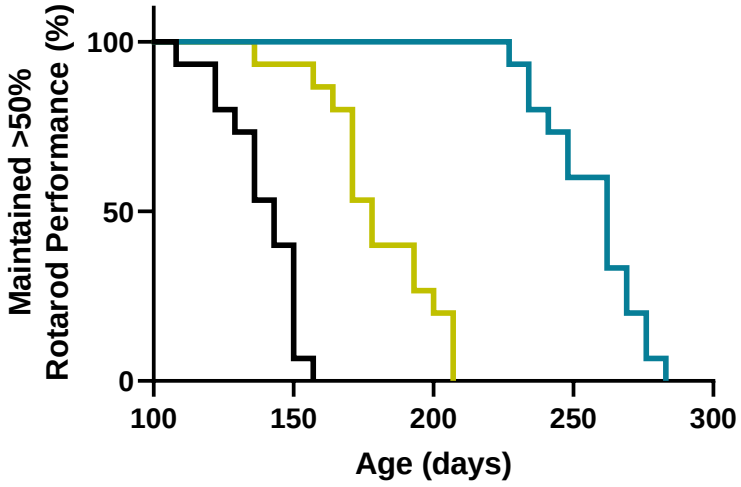
Survival



Grip Strength



Rotarod Performance



Age at Group Median (Days):	Treatment	Survival	Grip Strength	Rotarod
	Control	155	143	143
	ASO*	183	178	178
	ARO-SOD1	267	262	262

Single intracerebroventricular administration of 300ug at 66 days old, n=15

**ASO as described in Miller TM et. al., NEJM 2022*

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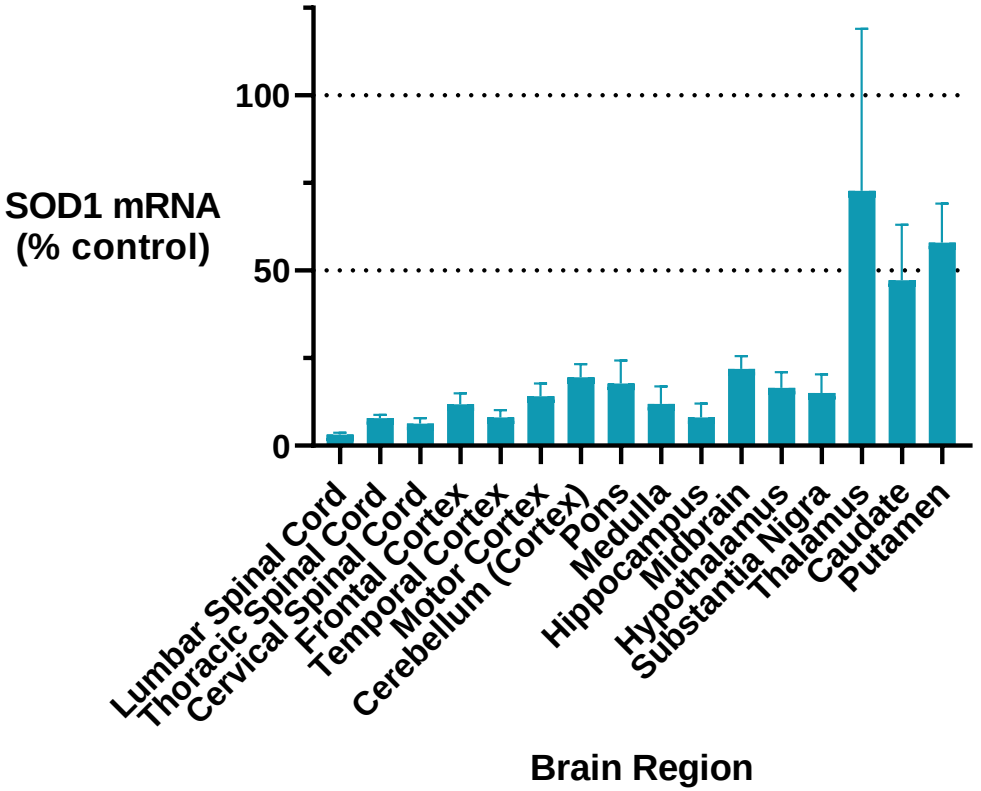
Target Knockdown Throughout the Brain and Distribution to All Relevant Cell Types in Non-Human Primate

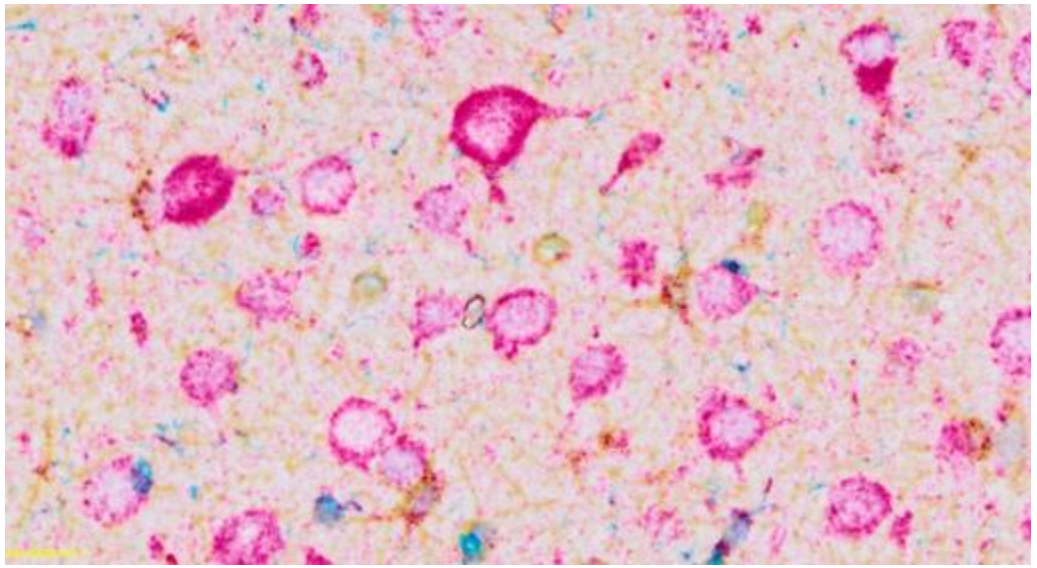
SOD1 mRNA Reduction in NHP

Single intrathecal dose of ARO-SOD1, 45mg, Day 29, n=3



siRNA Delivery to Relevant Cell Types in NHP Cortex

Neurons, astrocytes, microglia



miRNAscope™ detection of siRNA by in situ hybridization

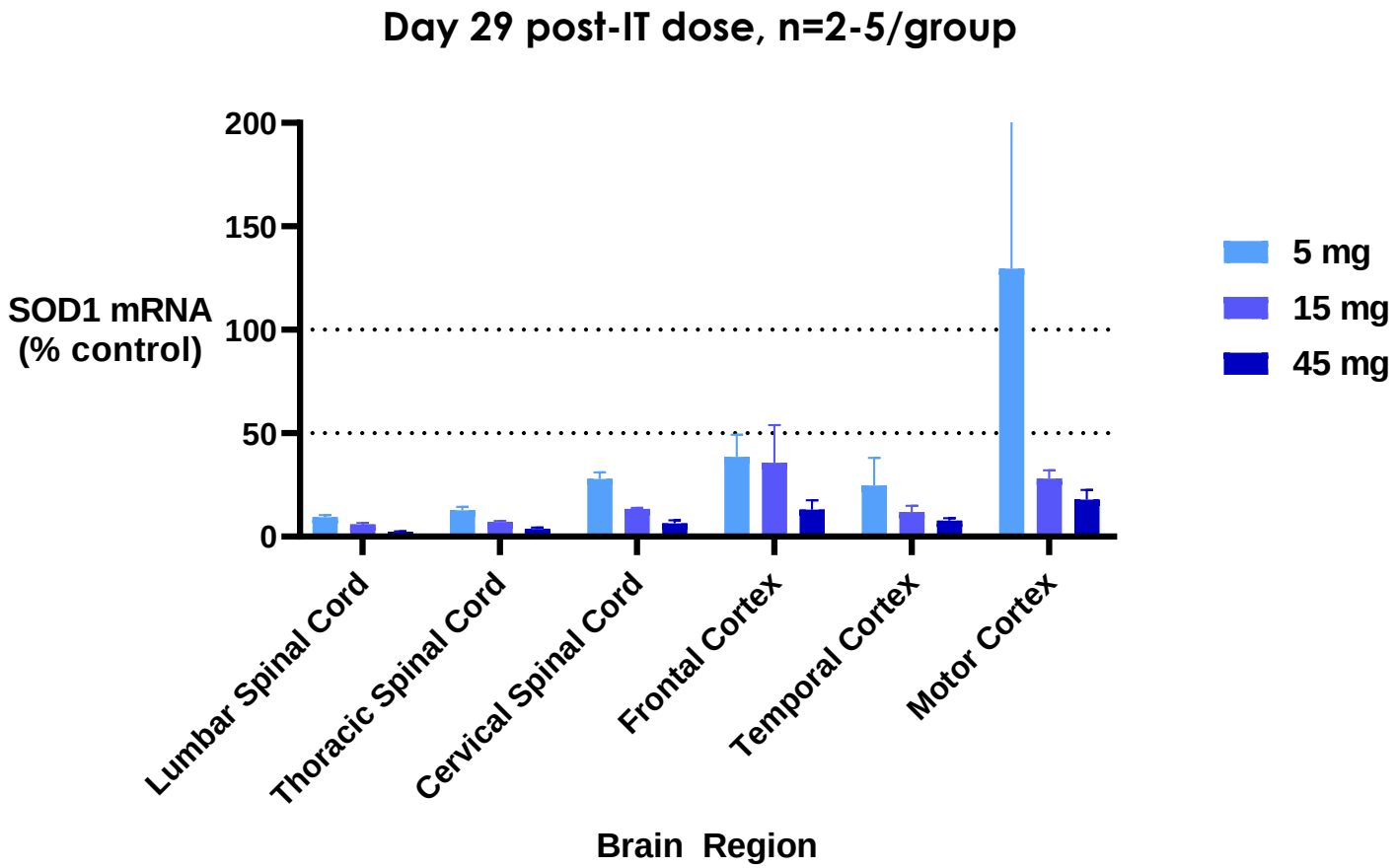
Red = siRNA

Yellow = astrocytes (GFAP)

Blue = microglia (IBA1)

ARO-SOD1 Shows Dose-Dependent SOD1 Reduction in Relevant NHP Brain Regions

Non-Human Primate



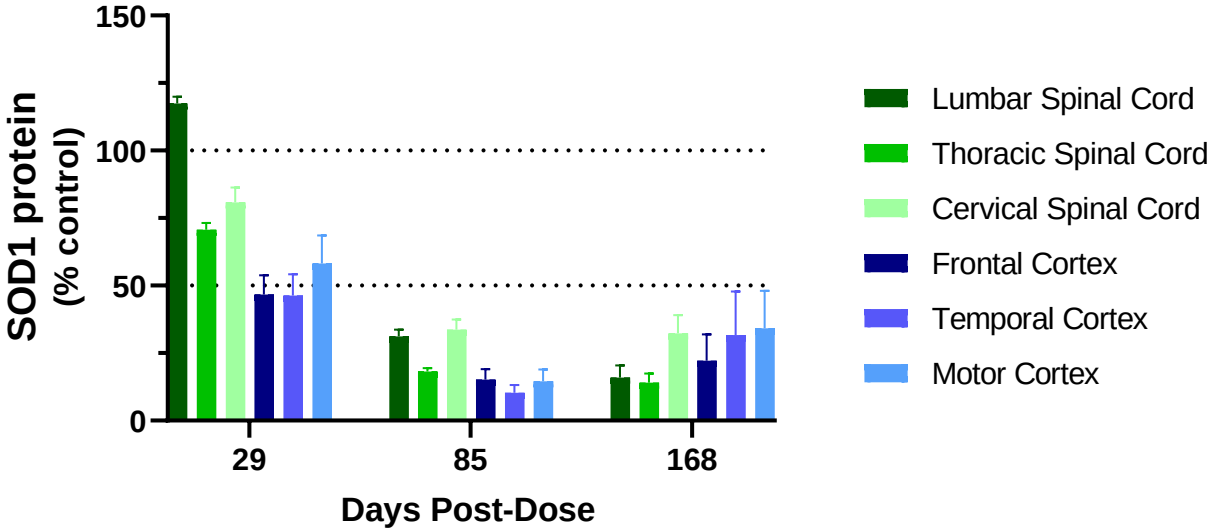
90–95%

SOD1 mRNA knockdown in disease-relevant spinal cord and cortex brain regions

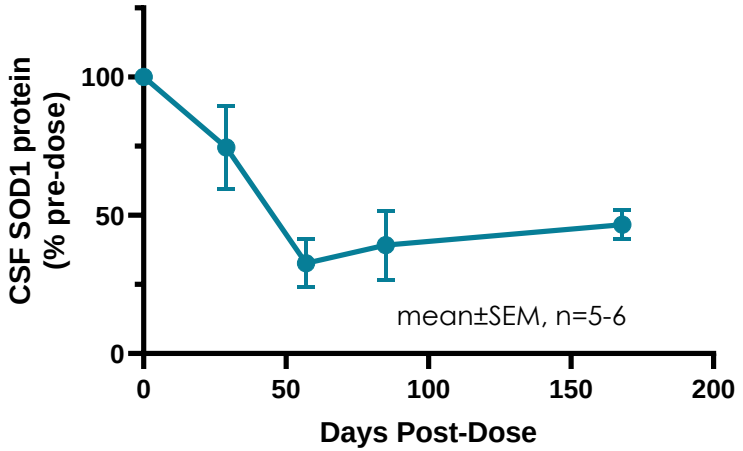
ARO-SOD1 Long Duration of Action in NHP Supports Up to Half-Yearly Dosing

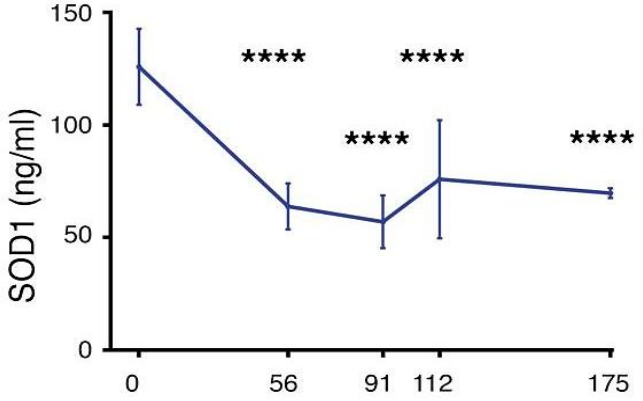
SOD1 Protein Reduction

Single 45mg IT dose, n=3-5/group, mean±SEM



SOD1 Protein in CSF





McCampbell et. al. 2018

Up to 70% reduction after single 45mg dose

Tofersen ~50% reduction in CSF SOD1 in NHP 5 x 35mg doses

ARO-SOD1 Phase 1: Placebo-Controlled, Single-Ascending Dose in Symptomatic SOD1-ALS Patients

Primary endpoint:

- Safety

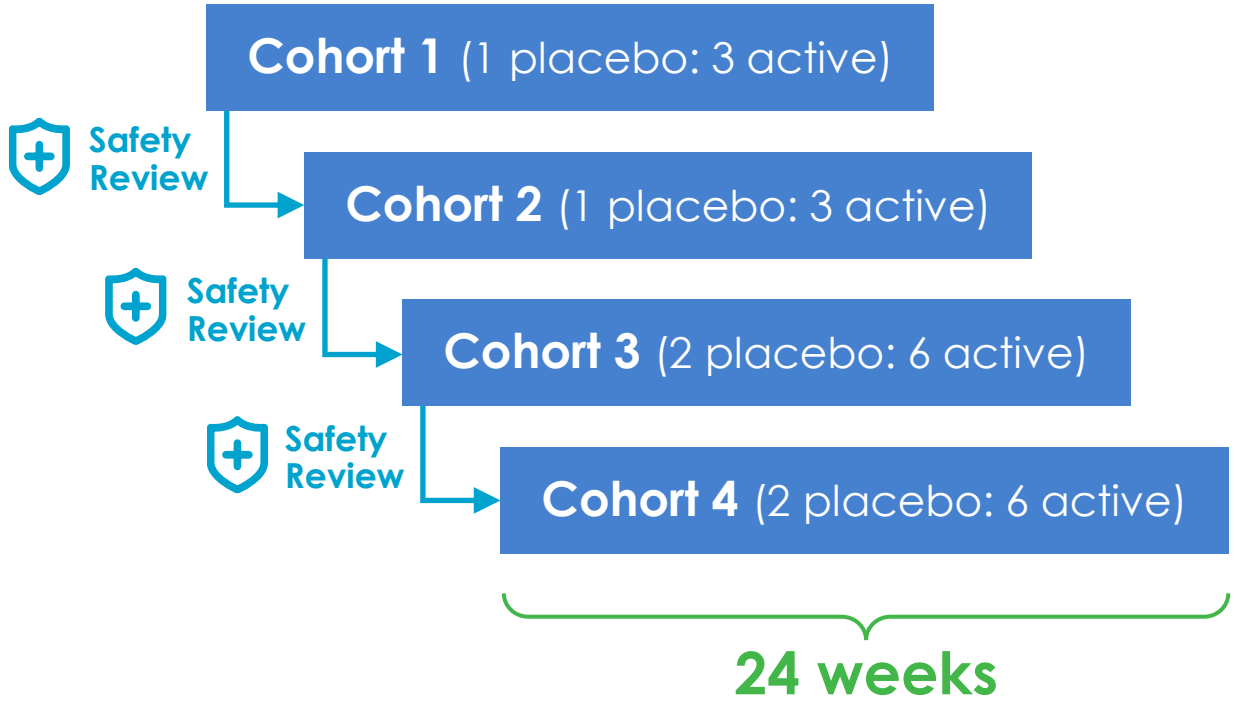
Secondary endpoints:

- Pharmacokinetics in plasma, urine and CSF
- Change from baseline in CSF SOD1 protein
- Change from baseline in plasma and CSF NfL protein

Exploratory endpoints:

- Change from baseline in ALSFRS-R
- Change from baseline in handheld dynamometry
- Change from baseline in predicted slow vital capacity

Study Overview:



CNS-targeting TRiM™ Platform Enables a Portfolio of Programs

- We have developed an optimized CNS-targeting TRiM™ platform

- ARO-SOD1 could be best-in-class treatment for SOD1-ALS
  - Potential for better efficacy with less burdensome dosing regimen compared to tofersen
  - GLP toxicology package is completed and NOAEL is highest dose tested in rat and NHP
  - CTA submission expected in Q3 2023

- A portfolio of CNS programs are moving forward, building on the foundation established with ARO-SOD1
  - Broad brain distribution of intrathecal platform enables application to many neurodegenerative diseases

Analyst R&D Day June 1, 2023

TRiM™ Platform Expansion

James Hamilton MD, MBA

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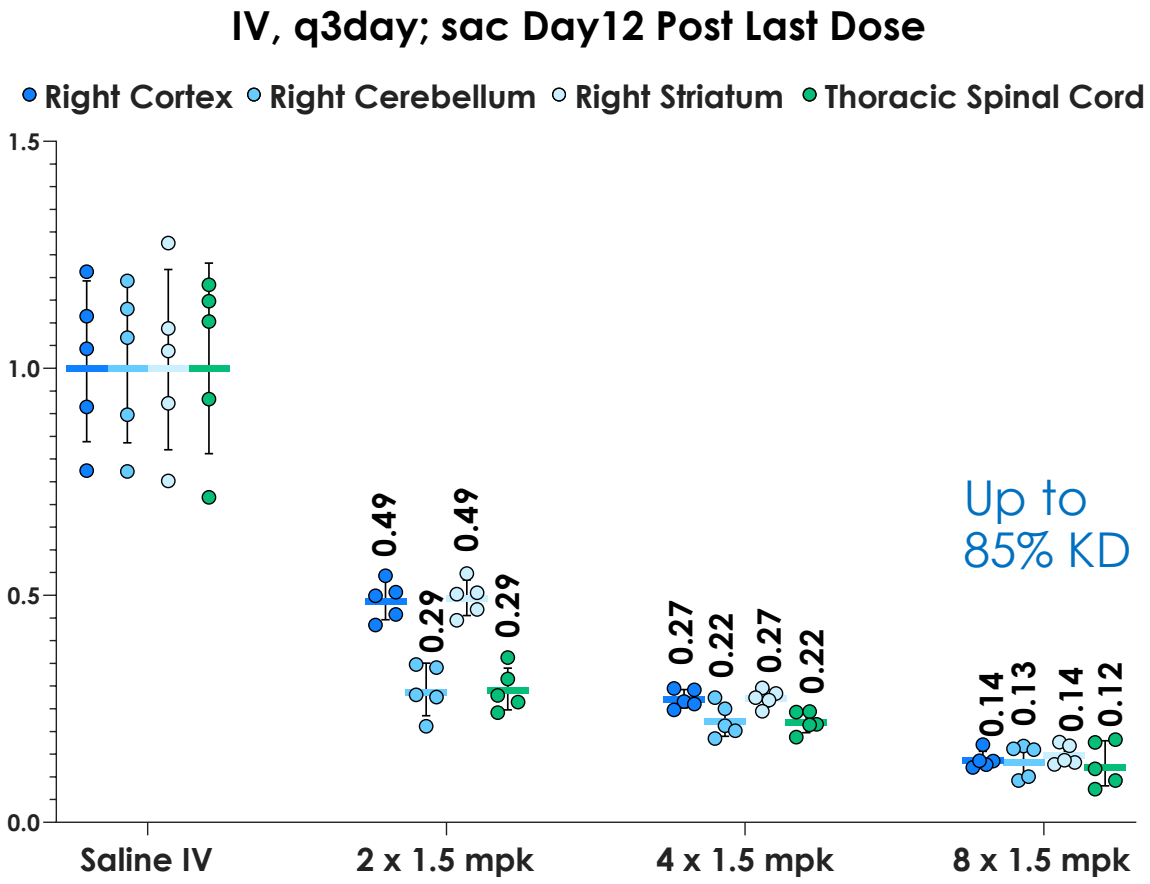
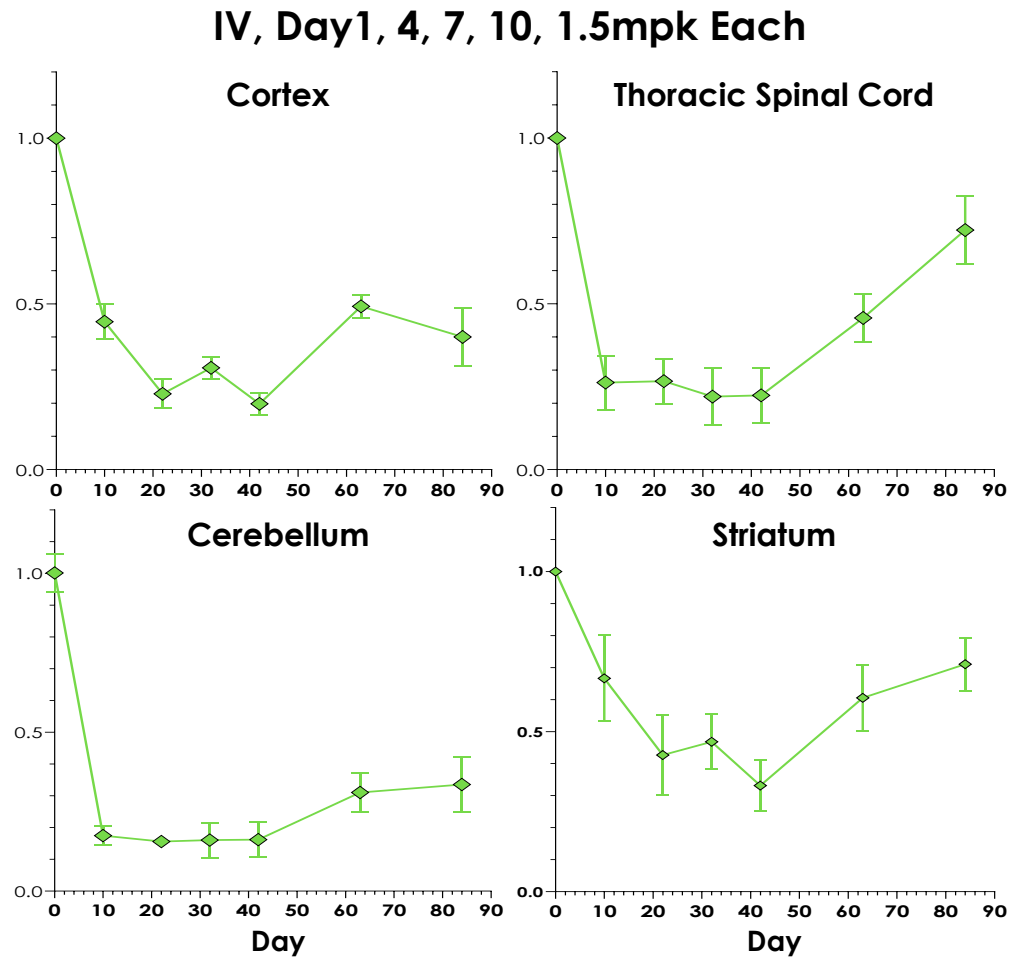
Deep and Durable Knockdown in Mouse Brain with Platform Designed to Deliver siRNA Across the Blood Brain Barrier

Gene1 mRNA Relative Expression

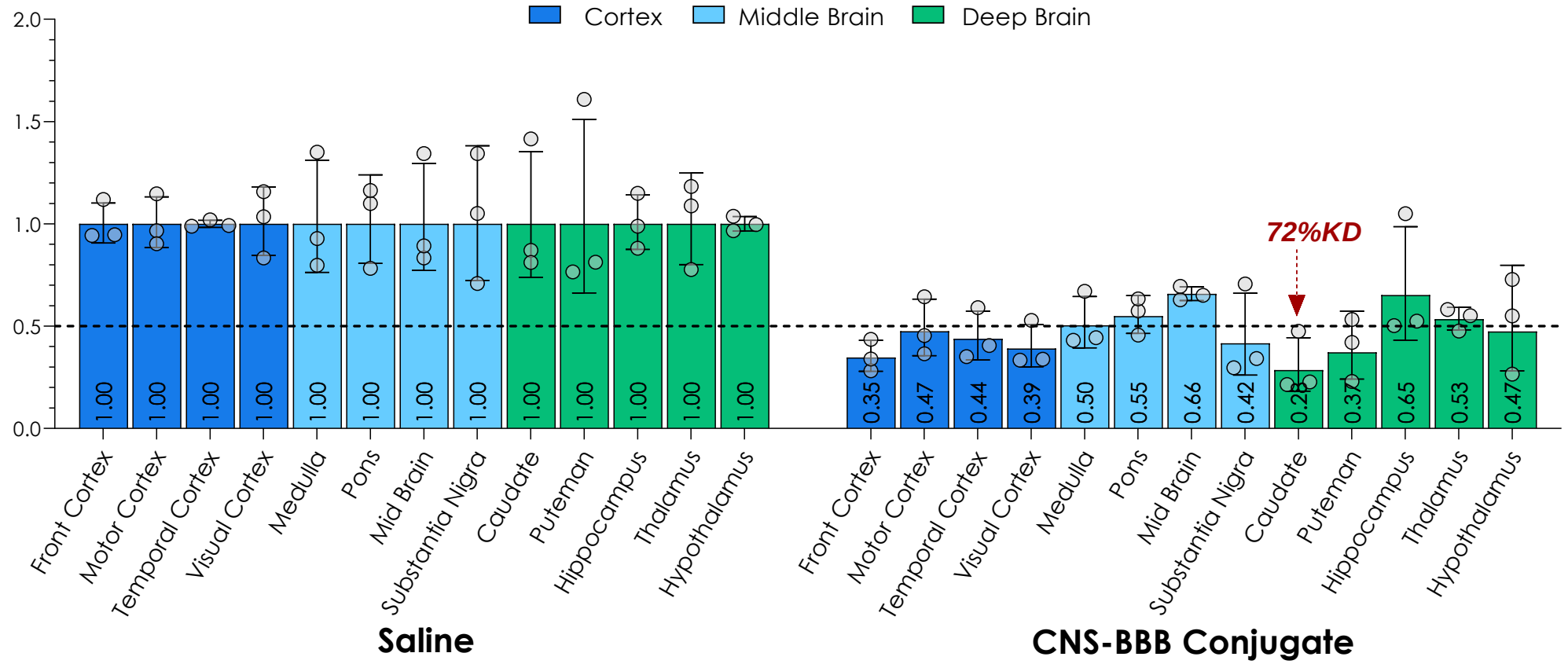




Knockdown in NHP Achieved in All Brain Regions Including Deep Brain Using Platform Delivering siRNA Across Blood Brain Barrier

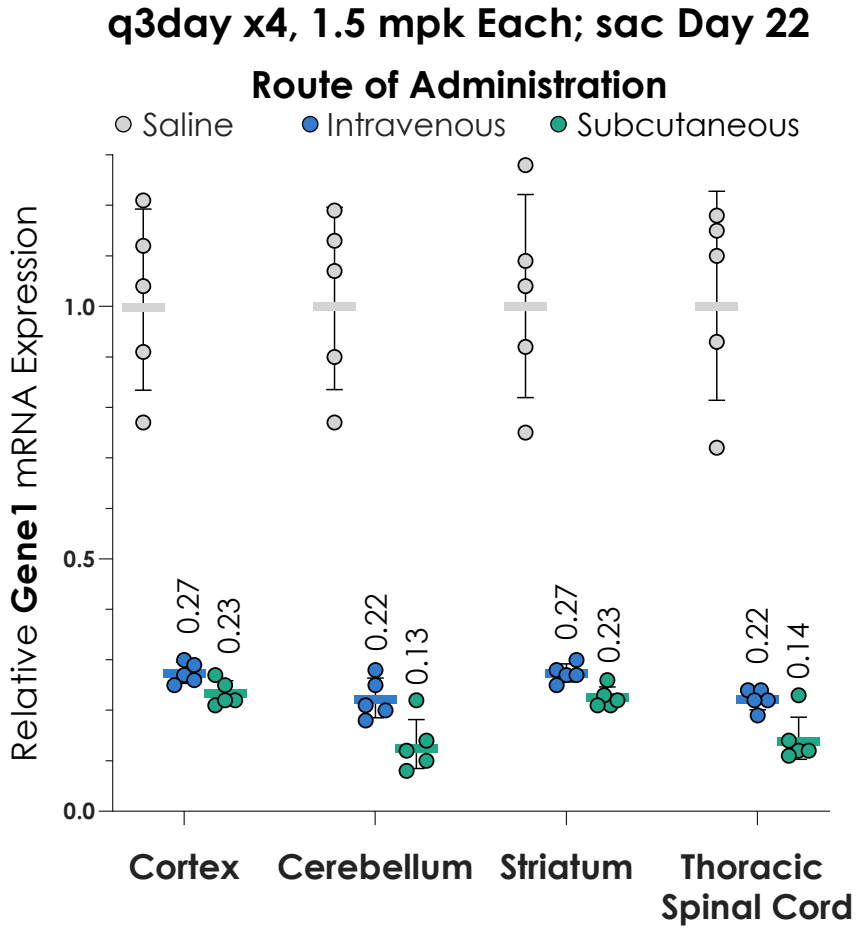
NHP Gene2 Relative Expression

IV, q3day x6, 1 mpk Each; sac Day31



CNS-BBB Platform May Be Compatible with Subcutaneous Administration

Mouse IV vs. SQ



SC route of administration achieves ~80-90% knockdown in various brain regions

Blood Brain Barrier Platform Expansion

- Ligand targeted platform in early development designed to deliver siRNA across BBB
- Potential for IV or SC administration with clear advantages over intrathecal route
- Potential ability to target deep brain regions (e.g. striatum) which may be important for certain neurodegenerative diseases such as Huntington's.

New Platform Designed to Delivery to Adipose Tissue

- Largest endocrine organ in the body
- Produces/secretes numerous adipokines (messengers) which regulate numerous physiological functions
- Adipose dysfunction has been associated with:
  - Obesity
  - Type 2 diabetes (T2D)
  - Dyslipidemia
  - Inflammatory disease
  - Cardiovascular disease
  - Cancers

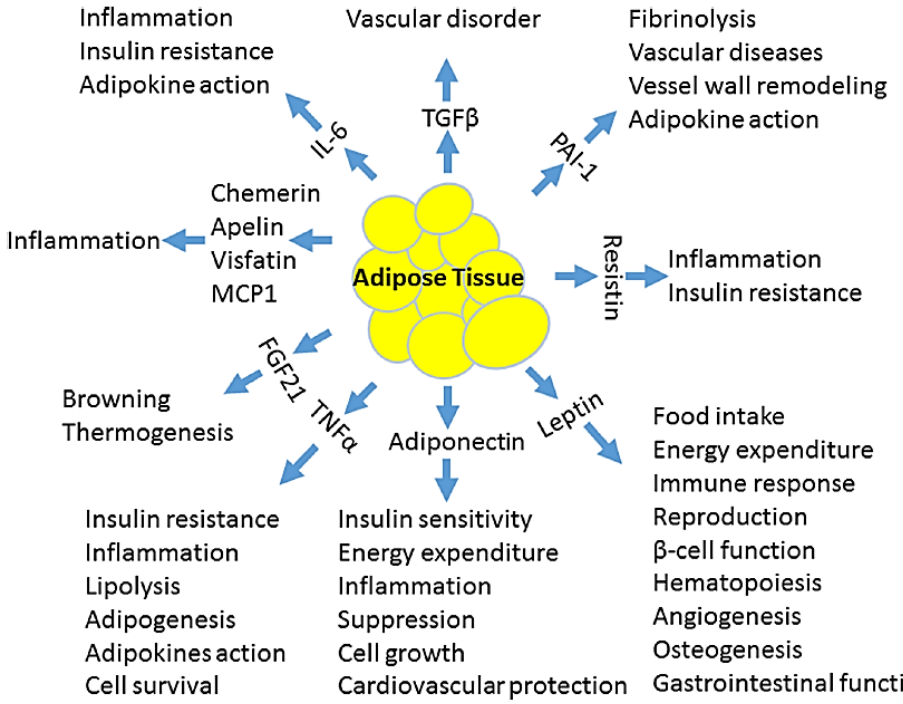
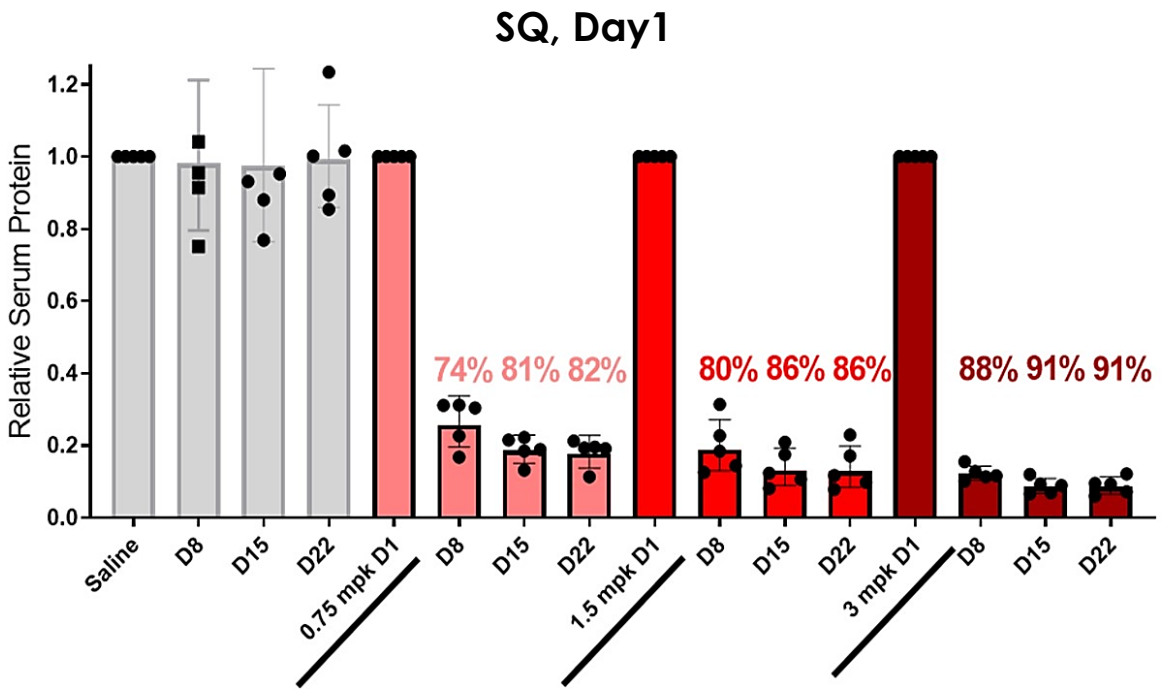


Figure 2. The physiological functions of adipokines, Adipokines, the cytokines derived from adipose tissue, act to regulate insulin sensitivity, inflammation, cardiovascular function, behaviour and cell growth, resulting in the development of obesity-induced metabolic diseases. ASP, acylating simulation protein; FGF21, fibroblast growth factor 21; IL6, interleukin 6; MCP1, monocyte chemoattractant protein 1; PAI1, plasminogen activator inhibitor 1; TNFa, tumour necrosis factor alpha.

Luo, L.; Liu, M. Adipose Tissue in Control of Metabolism. *J. Endocrinology,* 2016, 213, R77-R99.

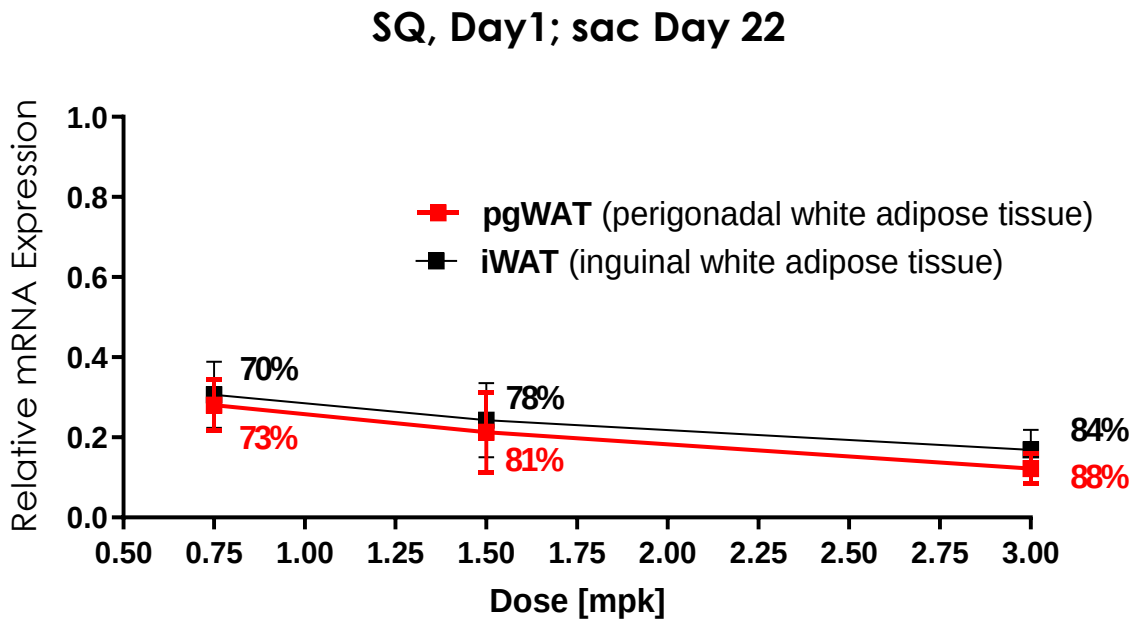
Deep Protein and mRNA Knockdown in Mouse Adipocytes with a Single Subcutaneous (SQ) Dose

Gene3 Serum Protein KD



- Deep KD of serum protein achieved in dose-response manner

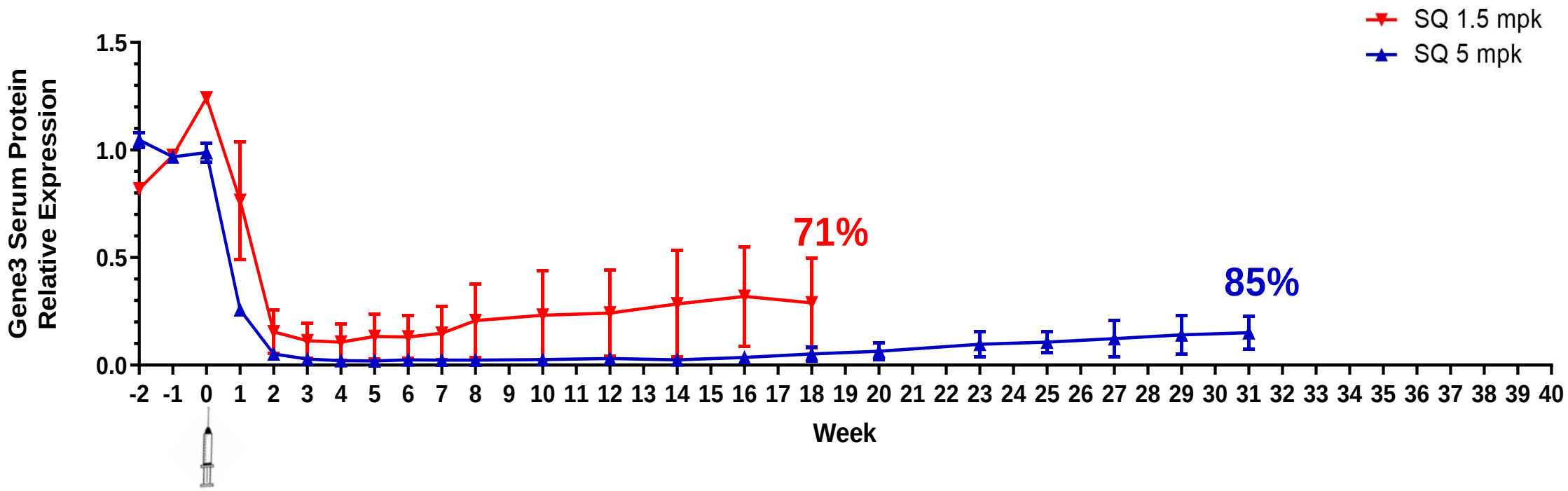
Gene3 Tissue mRNA KD



- Deep KD of tissue mRNA achieved in 2 types of white adipose tissue (WAT)
- Depth of mRNA KD comparable to serum protein KD

Deep and Durable Knockdown Achieved in NHP Adipocyte Specific Gene with a Single Subcutaneous (SQ) Dose

Gene3 Serum Protein KD – Combined Data



- Single SQ 5 mg/kg dose achieved up to 98% knockdown and maintained ≥85% knockdown over 31 weeks

Adipose Platform Development Supported by Toxicologic Profile

- Non GLP exploratory tox study in rat
  - Day1, Day15 SQ dose up to 120 mg/kg
  - Necropsy at Day16 and Day29
- No mortality
- No noteworthy clinical observations or body weight changes
- Minimal findings in clinical chemistry, hematology and coagulation
- No adverse drug related findings on histopathology

Hepatic Dimer Platform Delivers Equivalent or Better Efficacy and Duration in NHP Comparing to Monomer Mixture

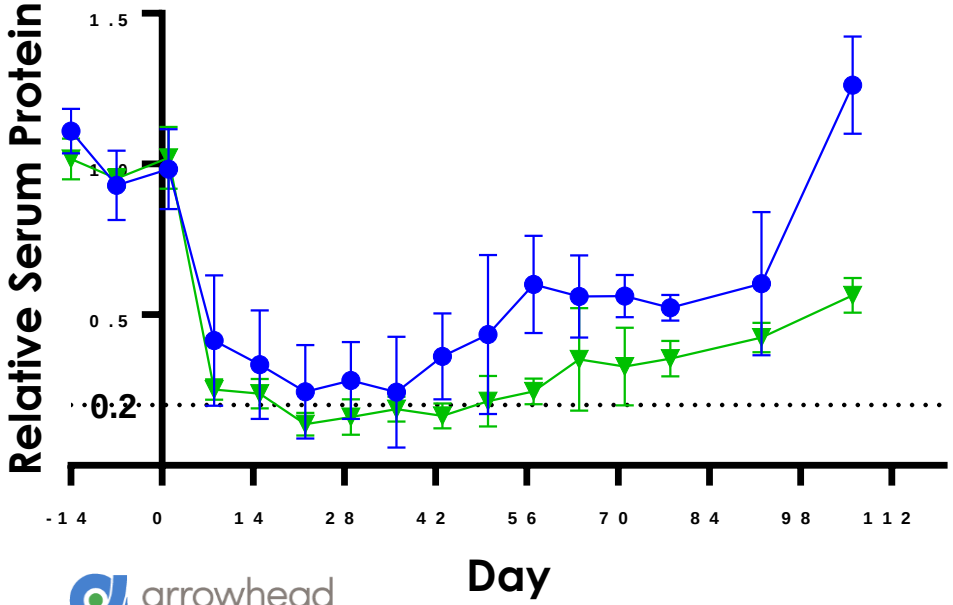
NHP Dimer vs. Monomer

Single SQ, Day1

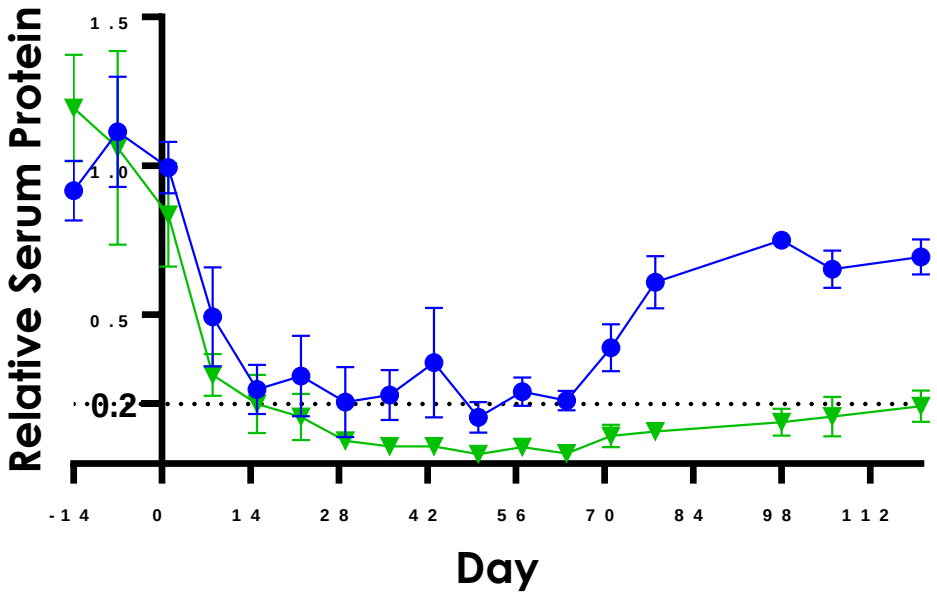
- **Monomer mixture, 3mpk + 3mpk**
- **Dimer, 6mpk**

Hepatic Dimer

Target 4



Target 5



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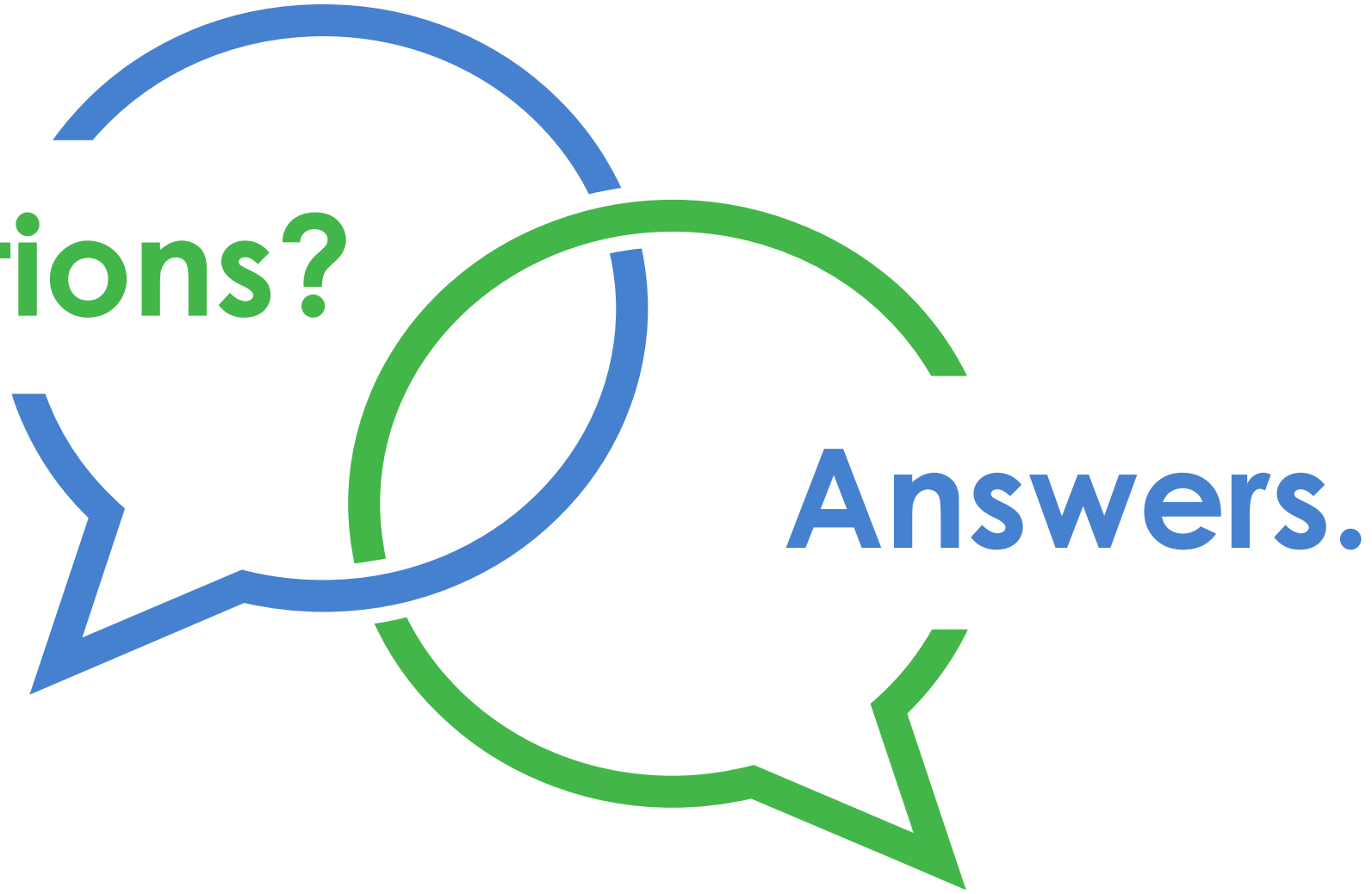
Questions?



Answers.

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Analyst R&D Day June 1, 2023

Pulmonary Platform Pre-clinical Review

Erik Bush, PhD

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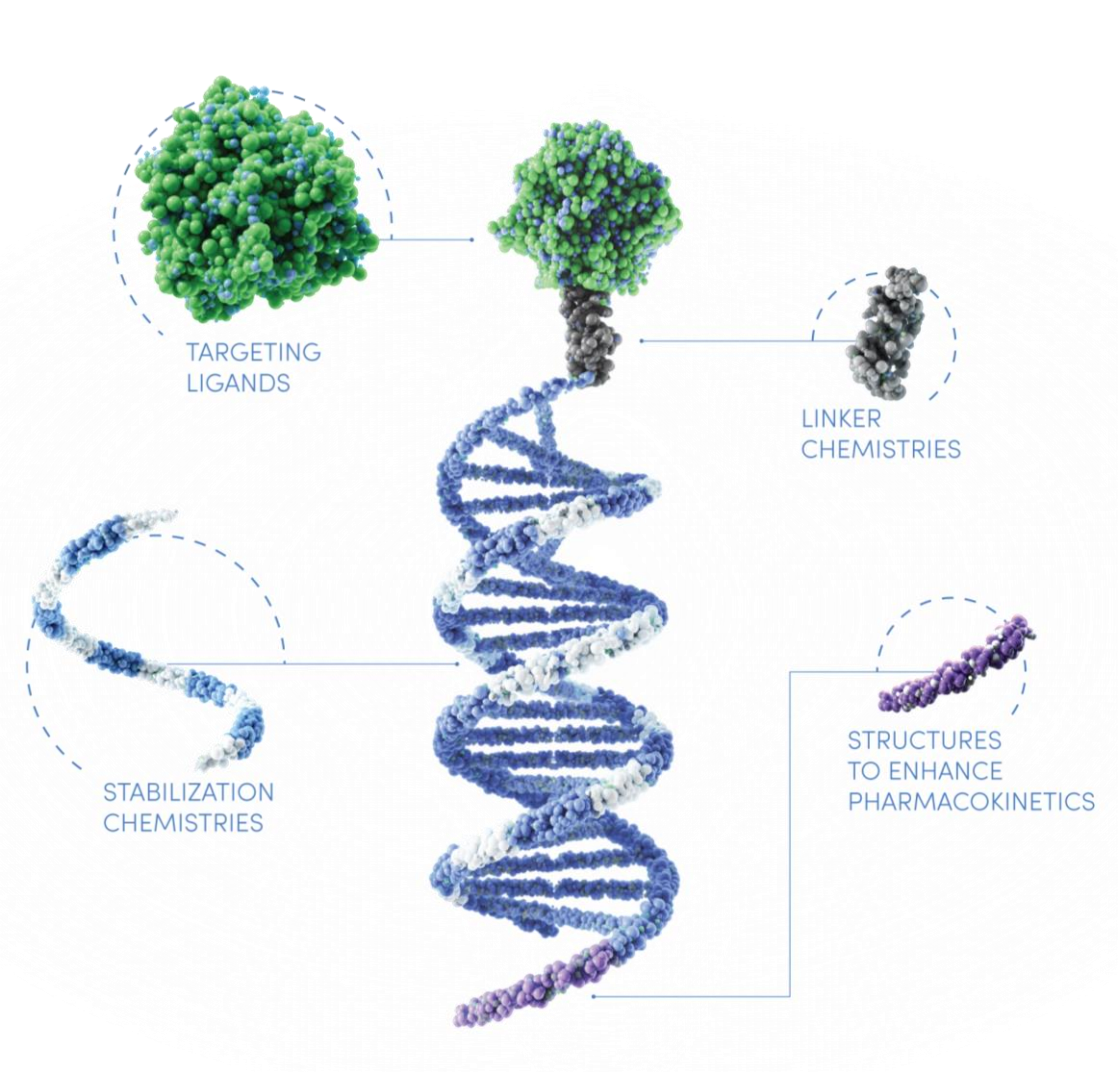
TRiM™ Platform for Pulmonary Delivery



Algorithmic Approach to Sequence Design and Selection is Unchanged

- Avoid microRNA and off-target knockdown while maximizing on-target activity
- Enhanced focus on early compound screening in non-GLP inhaled tox studies

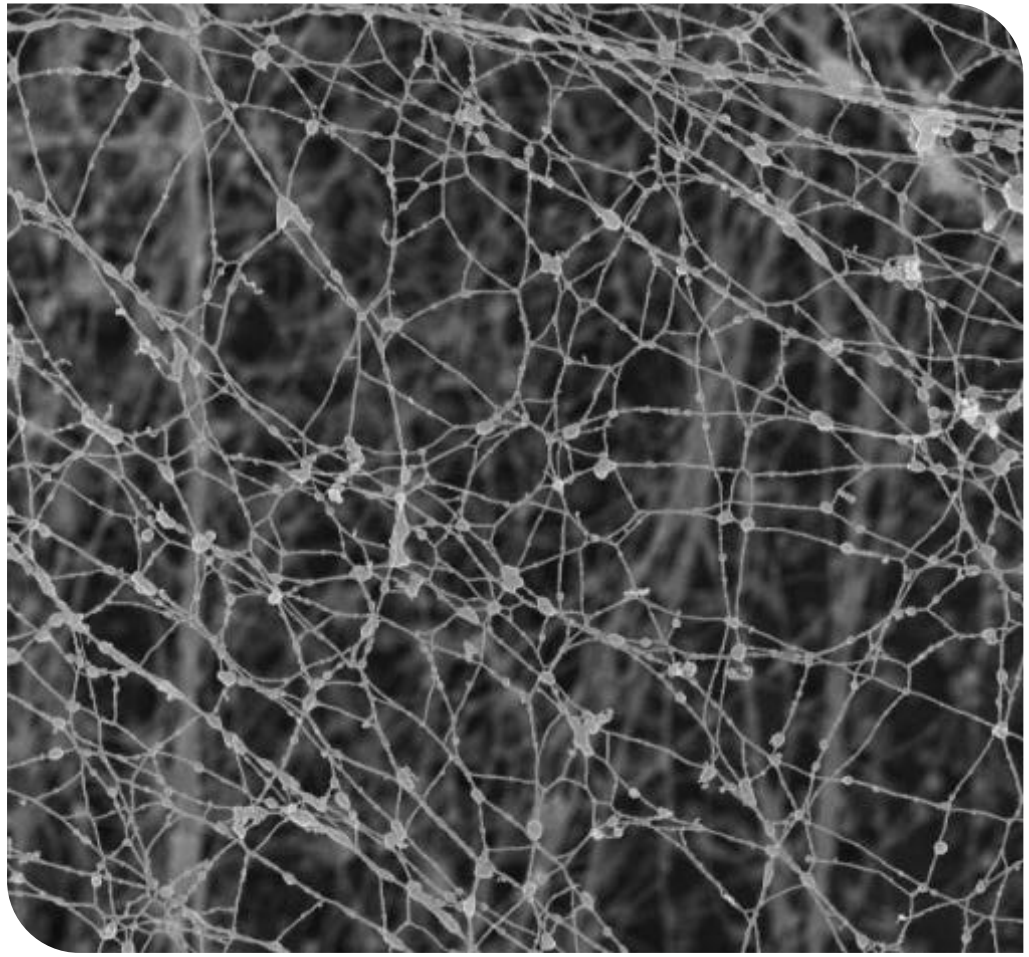
Enhanced Modification Chemistry (ARO-RAGE)

- Maximize depth and duration of knockdown, minimize dose frequency

avβ6 Integrin Small Molecule Targeting Ligand Drives Epithelial Cell Uptake

- Increases potency of inhaled RNAi triggers; required for systemic delivery to lung
- Preferential delivery to epithelium over macrophage
- Transient receptor internalization
- No evidence of integrin receptor pharmacology

TRiM™ Platform for Pulmonary Delivery Expected to Penetrate Airway Mucus



Murgia et al. Advanced Drug Delivery Reviews 124 (2018) 82-87

Physicochemical Properties Compatible with Mucus Transit

Small Size (3–10 nm)	Mesh pore size 100–200 nm Respiratory viruses ~100 nm
Net Negative Charge	Anionic compounds minimize electrostatic interactions with mucus
Soluble	

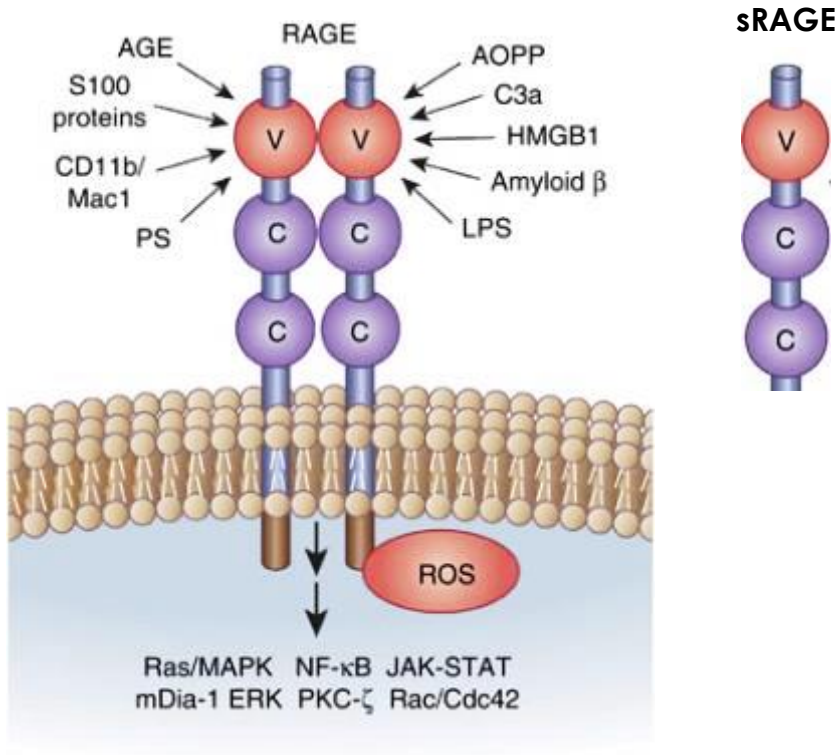
Evidence for Efficient Delivery Through Airway Mucus

- *In vitro* uptake through mucus layer in cultured human airway cells
- Efficient *in vivo* delivery and activity in models of airway mucus hypersecretion

Targeting RAGE for Inflammatory Lung Disease

- Pro-inflammatory pattern recognition receptor
  - Abundant in alveolar epithelium
  - Low extrapulmonary RAGE; induced by inflammation
- Many pro-inflammatory ligands: Sugar-modified proteins & lipids (AGEs), immune cell "alarmins" (HMGB1, S100 proteins)
- Signaling culminates in cytokines, mucin, ROS, RAGE
- Amplifies/perpetuates chronic inflammation
- KO phenotype
  - Complete physiological and histological protection from allergic asthma
  - Protection from ALI/ARDS & viral inflammation
- Difficult to drug with small molecules
- Full-length receptor cleaved to release soluble sRAGE (circulating biomarker of target engagement)

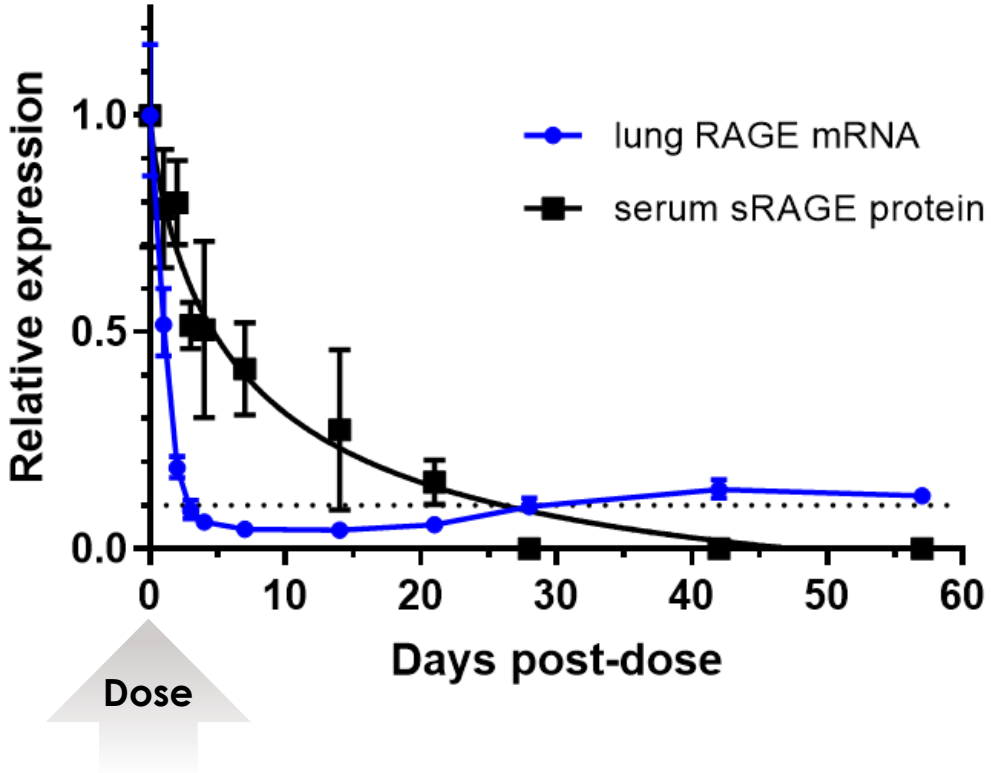
Receptor for Advanced Glycation End-products



Kidney International (2012), 82, 733-734

Deep and Sustained Lung RAGE Silencing After Single Inhaled 0.5 mg/kg Dose of RNAi Trigger Conjugate

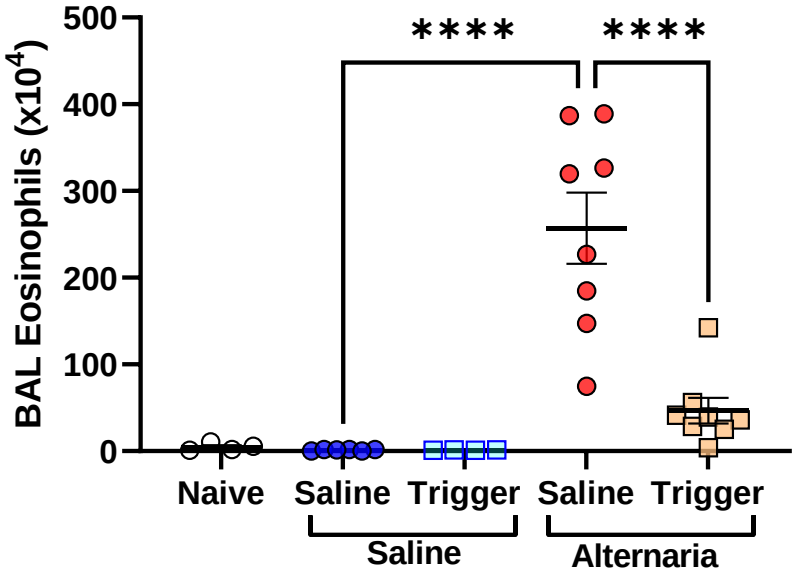
Rat RAGE Expression 0.5 mg/kg Inhaled Deposited Dose – RNAi Trigger Conjugate

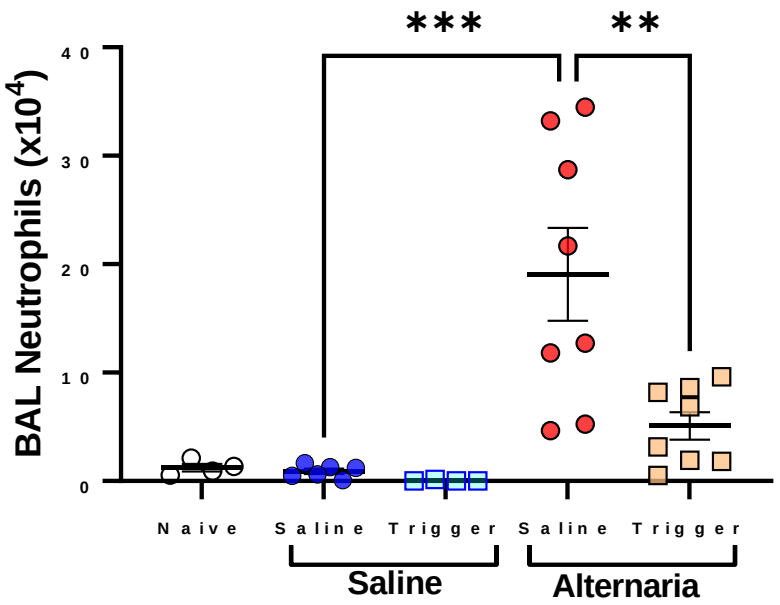


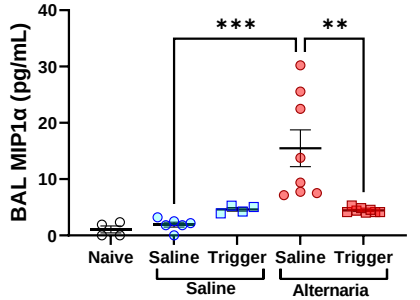
Day 36 Lung RAGE Protein IHC

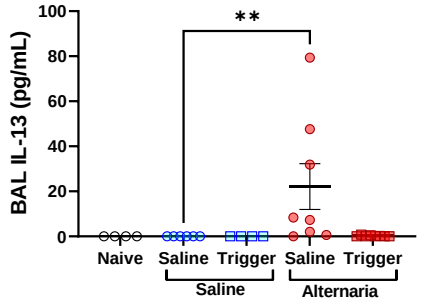
Kasahara, et al, A5013, *ATS* 2022

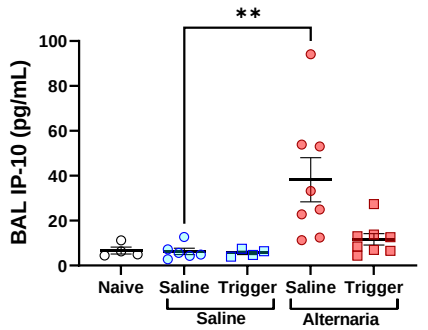
Silencing RAGE Limits Inflammation in a Rat Model of Allergic Asthma











RAGE Silencing Reduces Inflammatory Cell Recruitment and Cytokines

Kasahara, et al, A5013, *ATS* 2022

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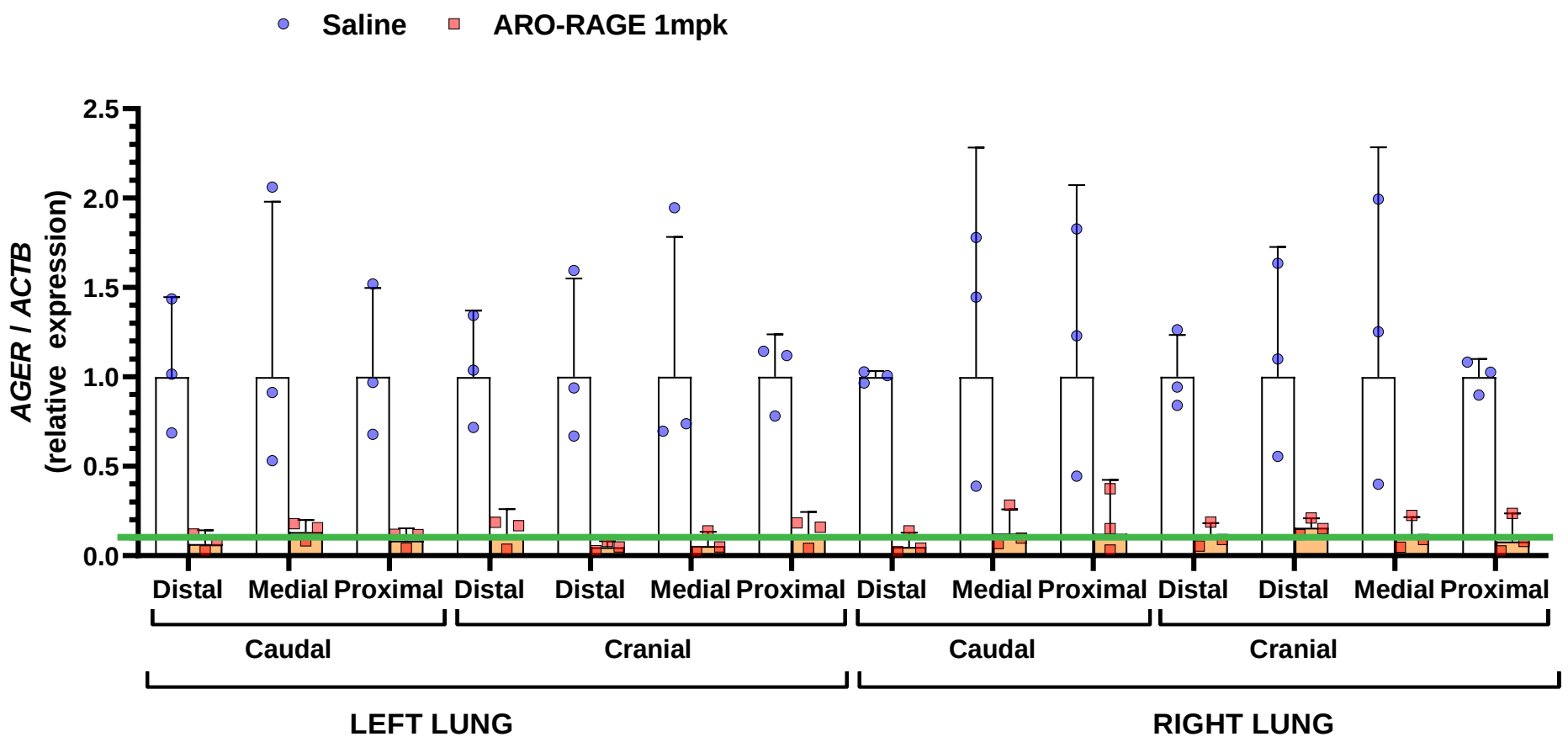
A Single Inhaled Dose of ARO-RAGE Silences >90% of Lung RAGE mRNA in Cynomolgus Monkeys

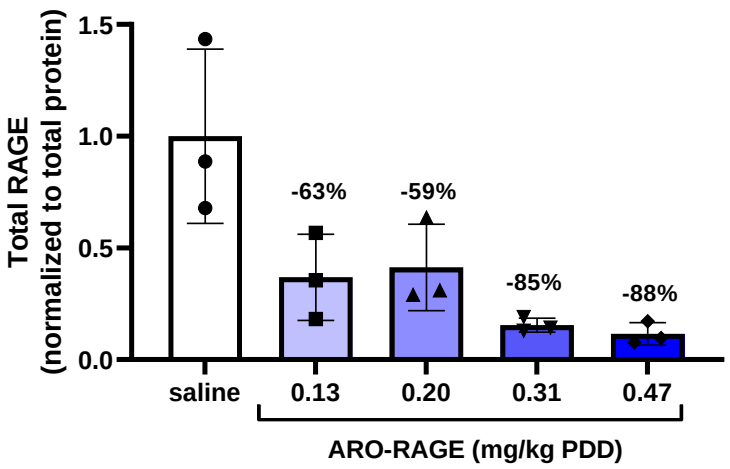


90%
Silencing

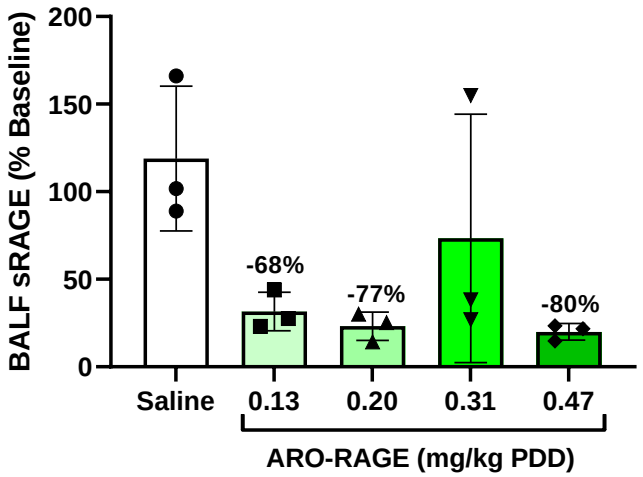
Kasahara, et al, A5013, *ATS* 2022

Serum sRAGE Underrepresents Depth of Lung RAGE Protein Silencing in Cynomolgus Monkeys

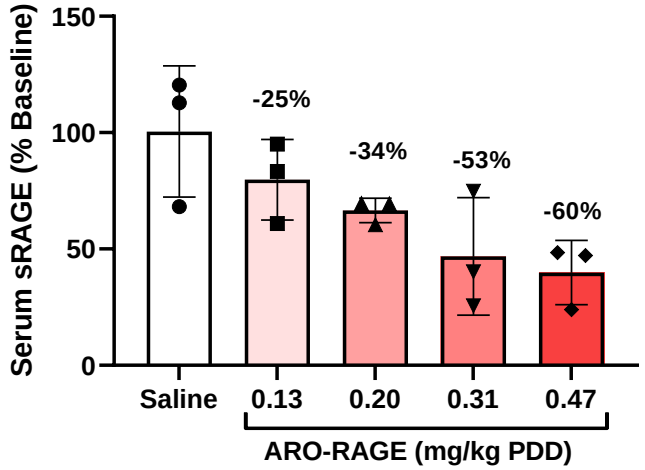
Lung Tissue RAGE Protein Day 29



BAL sRAGE Day 29



Serum sRAGE Day 29



- In NHP, deeper lung RAGE protein KD than serum sRAGE
- Extrapulmonary sRAGE sources may include vasculature, muscle and immune cells

Targeting MUC5AC for Muco-obstructive Lung Disease

90% (KO Lethal) MUC5B constitutive expression

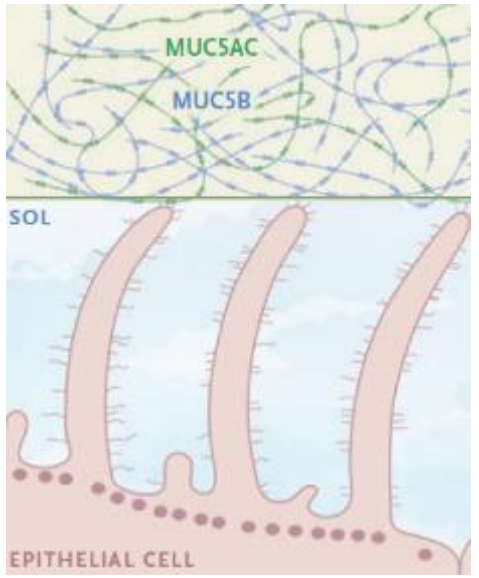
n = 11 n = 11 n = 17 n = 11 n = 22

10% (KO Normal) MUC5AC inducible expression - inflammation

n ≈ 124 n = 17 n = 34 n ≈ 66

Am J Respir Crit Care Med 2016,194. 1296-1299
Lancet Respir Med 2019, 7. 20-34
Evans, et al, *Nat. Commun.* 2015, 6:6281

Gel on Liquid



- Mucin hypersecretion underlies asthma & other muco-obstructive lung diseases (MUC5B ↑, MUC5AC ↑↑↑)
- **First therapeutic approach to directly silence pathologic MUC5AC expression**

Baseline

+ Allergen

Targeting MUC5AC for Severe Asthma

The Journal of Clinical Investigation BRIEF REPORT

Epithelial Tethering of MUC5AC-rich Mucus Impairs Mucociliary Transport in Asthma

Luke R. Bonser,[1] Lorna Zlock,[2] Walter Finkbeiner,[2] and David J. Erle[1]

[1]Lung Biology Center and [2]Department of Pathology, UCSF, San Francisco, California, USA.

The development of pathologic mucus, which is not readily cleared from the airways, is an important contributor to the morbidity and mortality associated with asthma. It is not clear how the major airway mucins MUC5AC and MUC5B are organized within the mucus gel or how this gel contributes to airway obstruction in asthma. Here, we demonstrated that mucus plugs from individuals with fatal asthma are heterogeneous gels with distinct MUC5AC- and MUC5B-containing domains. Stimulation of cultured human bronchial epithelial cells with IL-13, a key mediator in asthma, induced the formation of heterogeneous mucus gels and dramatically impaired mucociliary transport. Impaired transport was not associated with defects in ciliary function but instead was related to tethering of MUC5AC-containing mucus gel domains to mucus-producing cells in the epithelium. Replacement of tethered mucus with untethered mucus restored mucociliary transport. Together, our results indicate that tethering of MUC5AC-containing domains to the epithelium causes mucostasis and likely represents a major cause of mucus plugging in asthma.

Healthy

Asthma

High MUC5AC Mucus Plugs Associated with Fatal Asthma

J. Clin. Invest. 2016;126(6):2367–2371
J. Clin. Med. 2017, 6, 112
J. Clin. Med. 2019, 8, 1955
Am J Respir Crit Care Med 2009,180. 388–395

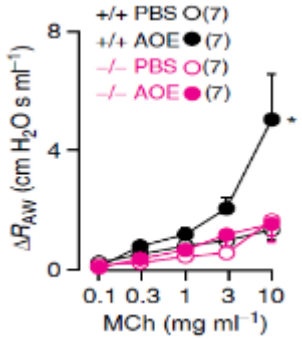
Targeting MUC5AC for Severe Asthma

Nat Commun. ; 6: 6281. doi:10.1038/ncomms7281.

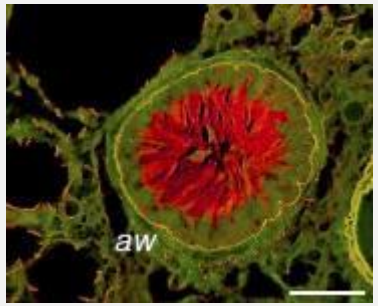
The polymeric mucin Muc5ac is required for allergic airway hyperreactivity

Christopher M. Evans[1,*], Dorota S. Raclawska[1], Fani Ttofali[1], Deborah R. Liptzin[2], Ashley A. Fletcher[1], Daniel N. Harper[1], Maggie A. McGing[1], Melissa M. McElwee[3], Olatunji W. Williams[4], Elizabeth Sanchez[3], Michelle G. Roy[3], Kristen N. Kindrachuk[5], Thomas A. Wynn[5], Holger K. Eltzschig[6], Michael R. Blackburn[7], Michael J. Tuvim[3], William J. Janssen[1,8], David A. Schwartz[1], and Burton F. Dickey[3]

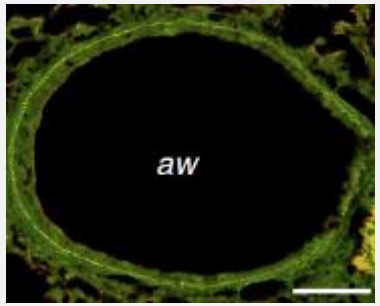
Airway Resistance Aspergillus (AOE) Allergic Mice 48h Post-challenge (Late Phase)



Muc5ac$^{+/+}$



Muc5ac$^{-/-}$



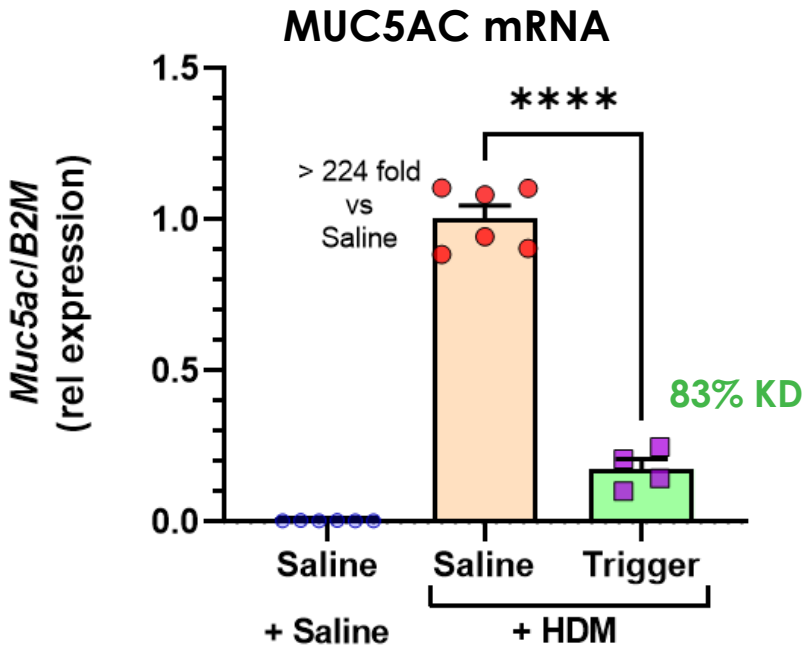
MUC5AC KO mice protected from airway hyperresponsiveness during late-phase allergic airway response (hours / days post-challenge)

- Inflammatory mediators promote MUC5AC expression and secretion
- Reflects clinically important prolonged effects of allergen exposure experienced by asthma patients

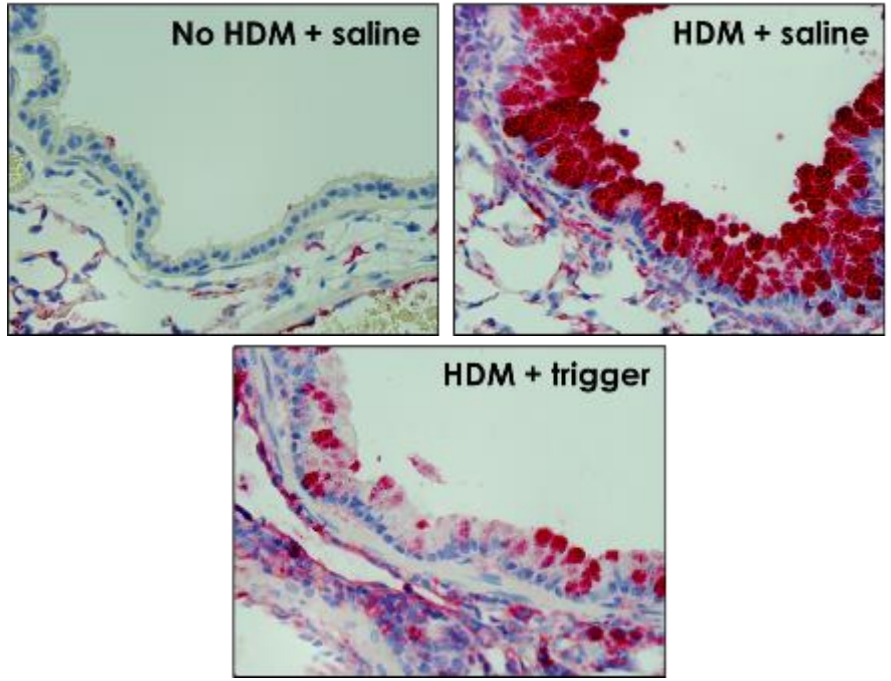
Evans, et al, *Nat. Commun.* 2015, 6:6281

Silencing MUC5AC Expression in a Mouse Model of Allergic Asthma

Mouse Allergic Asthma Models: HDM, IL-13



MUC5AC Protein (IHC)

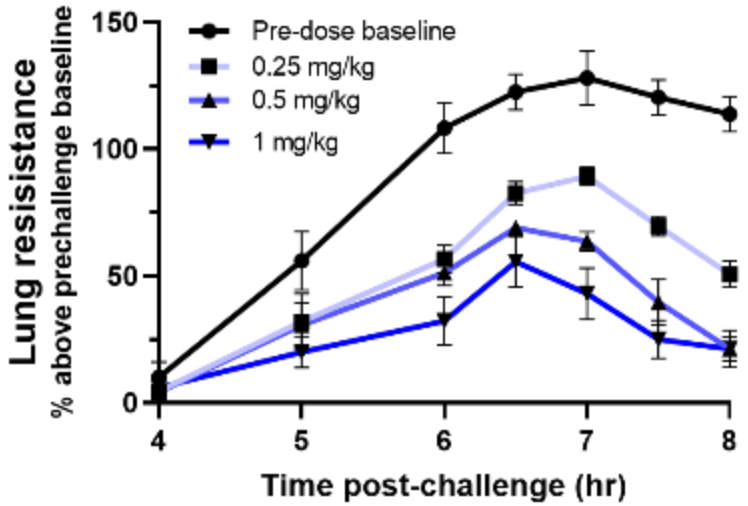


70–90% silencing of induced MUC5AC expression (similar result in cynos)

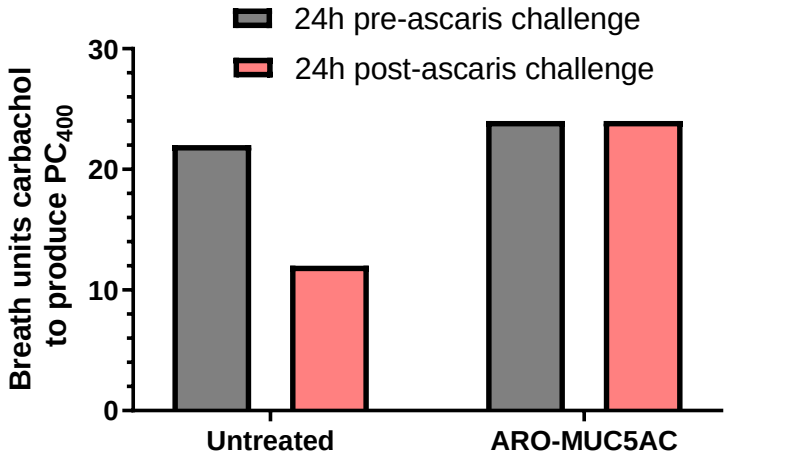
Nicholas, et al, A5491, *ATS* 2022

ARO-MUC5AC Preserves Airway Function in a Sheep Model of Allergic Asthma

Late Phase Response (4–8 hr Post-ascaris Challenge) ARO-MUC5AC Dose-response



Airway Hyperresponsiveness (24h Post-challenge)



RISC-loading blocked version of ARO-MUC5AC is inactive

Sensitized sheep challenged with inhaled nematode antigen provokes allergic asthma airway response → **Bronchoconstriction** → **Immune cell recruitment** → **Mucus hypersecretion (airway occlusion)** → **Responds to standard-of-care therapies**

Nicholas, et al, A5491, *ATS* 2022

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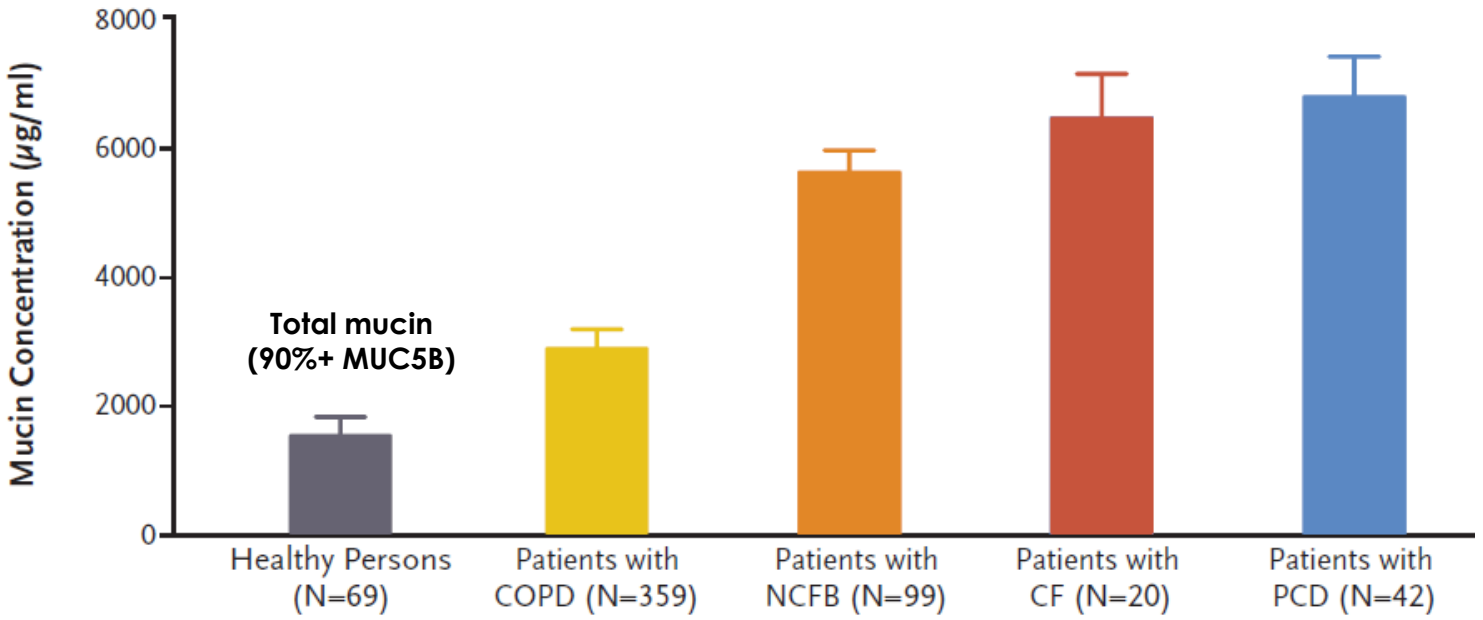
MUC5AC Overexpression in Muco-obstructive Lung Diseases

Induced Sputum Total Mucin Concentration



COPD (induced sputum MS assay)

- MUC5B increases 3x
- **MUC5AC increases >10x**

NCFB (induced sputum MS assay)

- MUC5B increases 6x
- **MUC5AC increases 17x**

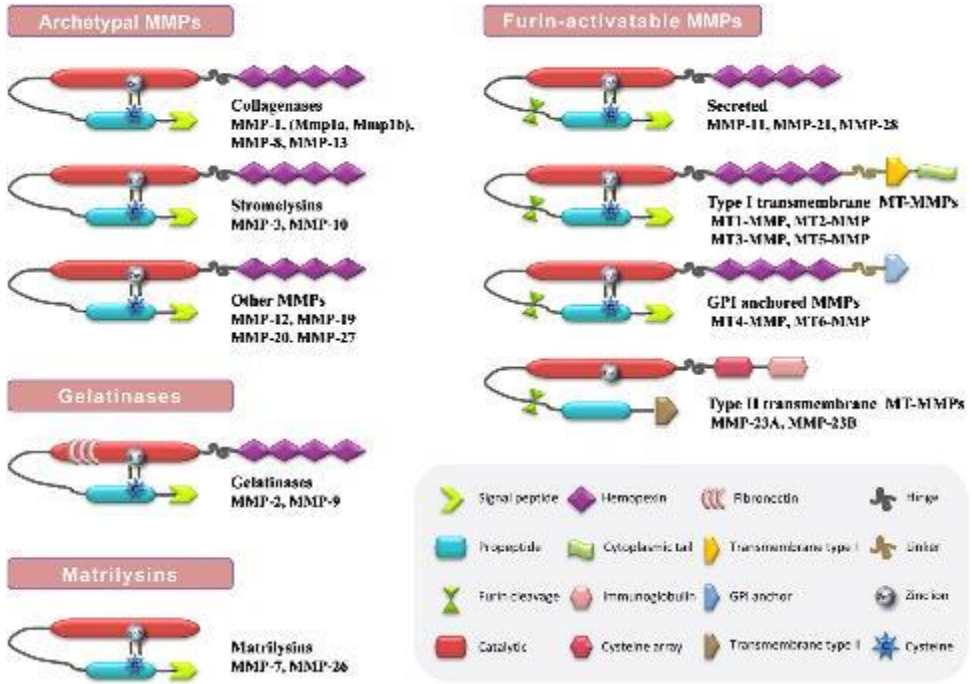
CF (induced sputum MS assay)

- MUC5B increases 8x
- **MUC5AC increases 30x**

N Engl J Med 2019;380:1941-53
Am J Respir Crit Care Med 2020; 201: 661–670
N Engl J Med. 2017; 377(10): 911–922
Am J Respir Cell Mol Biol. 2022; 67(2):253-265

Targeting Matrix Metalloproteinase 7 (MMP7) for Idiopathic Pulmonary Fibrosis (IPF)

- Protease secreted by injured epithelia
- One of 24 MMPs in gene family with diverse functions
- Highly overexpressed in IPF patients
- **Validated IPF biomarker:** Serum and BALF MMP7 correlate with disease severity and progression
- **Multiple roles in IPF pathogenesis:** Promotes inflammation, aberrant epithelial repair and fibrosis
- **MMP7 knockout** well-tolerated & mice protected from bleomycin injury IPF model
- **Hard to drug:** Catalytic domain homology a barrier to isoform-specific small molecule inhibitors



- **In rat bleo injury model, MMP7 silencing phenocopies protection seen with knockout mice**
- **ARO-MMP7 inhalation durably silences lung MMP7 expression in cynos (tissue and BAL)**

Biochim Biophys Acta Mol Cell Res 2010, 1. 3-19

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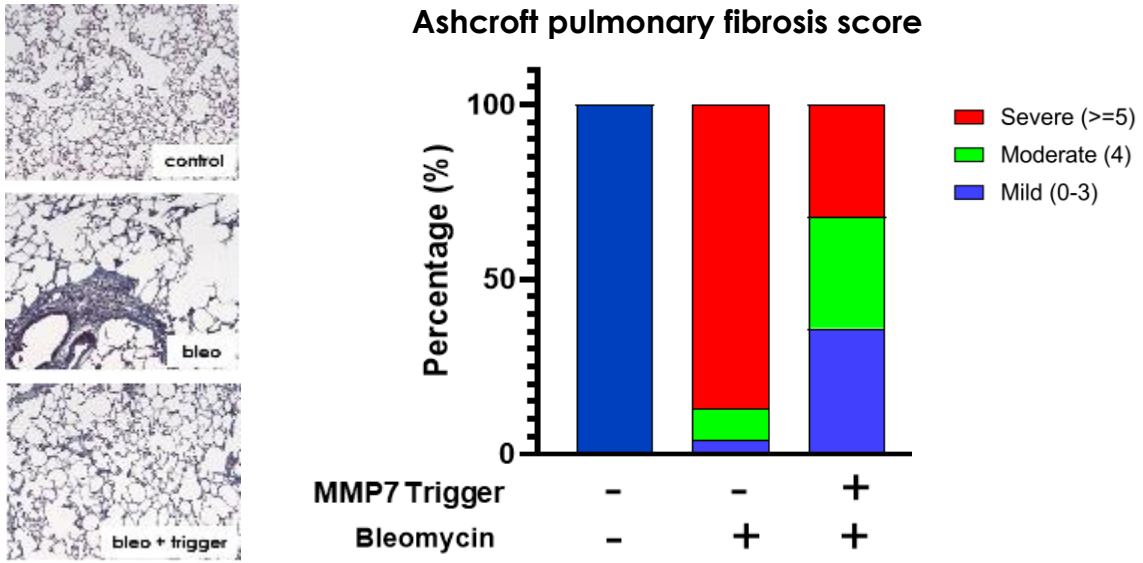
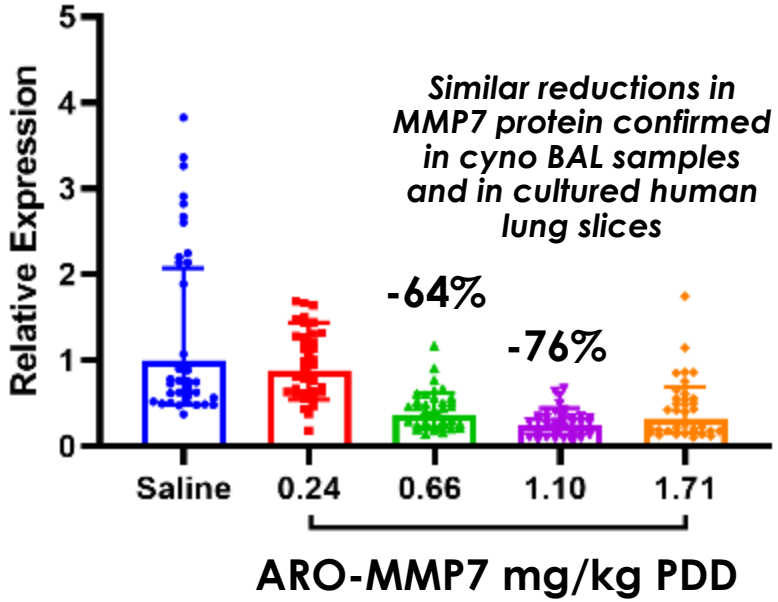
MMP7 TRiMs Protect Rats from Bleomycin Injury and Mediate Silencing in Nonhuman Primate Lung

Rat Bleomycin Injury IPF Model



Cyno Lung MMP7 mRNA Expression
N=3 cynos/group; multiple lung regions



- Reduced inflammation (BAL neutrophils & eosinophils)
- Improved pulmonary function (compliance and O2sat)
- Reduced mortality

Yuan et al, *Eur Resp J* 2022, 60: 864

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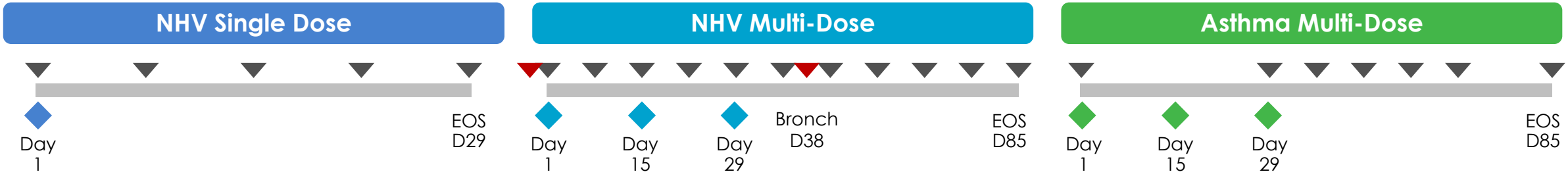
Analyst R&D Day June 1, 2023

Pulmonary Clinical Update

James Hamilton MD, MBA

arrowhead pharmaceuticals

ARO-MUC5AC First-in-Human Study (AROMUC5AC-1001): Safety, Target Engagement & Dose-Response and Duration



Population

Healthy Volunteers	Healthy Volunteers	Asthma
		• Moderate to severe disease (GINA 4-5) • Airflow obstruction (FEV_1 40-80%) • May be on any concomitant therapies

Cohorts

24 mg Cohort 1a		
D15 Safety Eval →	**24 mg Cohort 1b**	
56 mg Cohort 2a		
D15 Safety Eval →	**56 mg Cohort 2b**	**56 mg Cohort 2c**
108 mg Cohort 3a		
D15 Safety Eval →	**108 mg Cohort 3b**	**108 mg Cohort 3c**
6 subjects each (4:2)	**8 subjects each (6:2)**	**8 subjects each (6:2)**

AROMUC5AC-1001 Key Endpoints

Safety (Pulmonary)

- Respiratory Adverse Events
- Lung function
- Inflammatory Cells: BALF Cell Count and Differential
- Chest X-rays

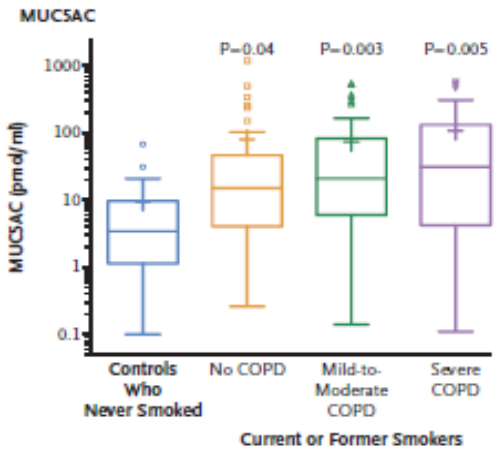
Target Engagement

MUC5AC Protein

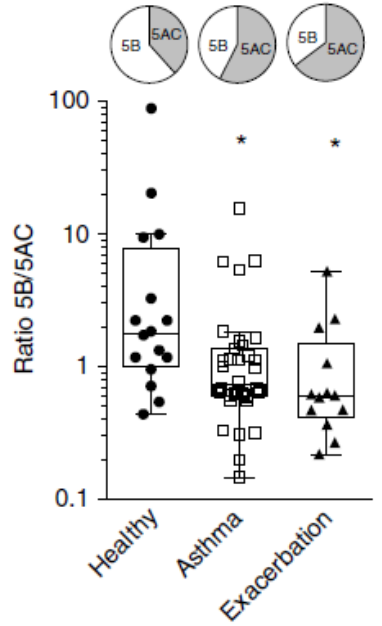
- Sputum
- Airway swab (bronchoscopy)

Fold Increase in Mucin Compared to NHV	MUC5AC Protein	MUC5B Protein
Asthma	>4X	2X
COPD	>10X	3X
NCFB	17X	6X
CF	30X	8X

COPD



Asthma



Kesimer M, *N Engl J Med.* 2017;377:911-922;
Lachowicz-Scroggins ME, *Am J Respir Crit Care Med.* 2016;194:1296-1299;
Batson B, *AJRCMB* 2022;67:253-265; Ramsey KA, *AJRCCM* 2020;201:661-670; Tajiri T, *Allergol Int* 2022;71:193-199.

ARO-MUC5AC Has Shown a Favorable Safety Profile To Date

Adverse Events:

- No serious adverse events
- No severe adverse events
- No study withdrawals or drug discontinuations due to adverse events
- No adverse events due to change in lung function

BALF Cell Count & Differential:

- No change in pattern of airway immune cells

Chest X-rays:

- All read as normal

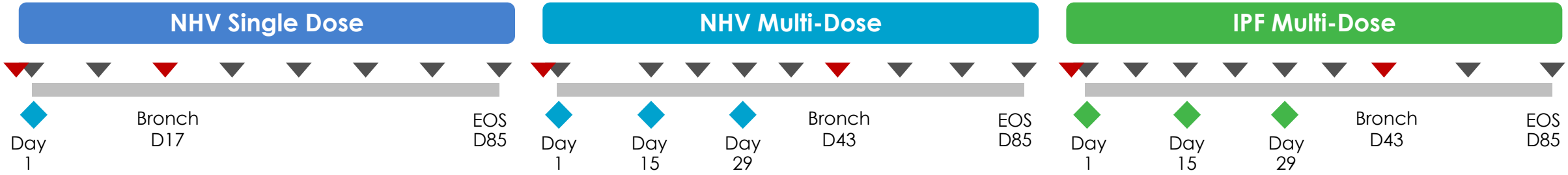
Safety Labs:

- No patterns of adverse changes

AROMUC5AC-1001 Summary & Next Steps

- The AROMUC5AC-1001 study is ongoing
  - Favorable safety profile to date
  - Evaluation of MUC5AC knockdown is ongoing using samples from NHVs and muco-obstructed patients (COPD/Asthma)
- Continued enrollment of asthma cohorts
- Addition of COPD cohorts
  - Plan 2 COPD cohorts in parallel with 2 asthma cohorts
    - Large patient population with highly upregulated MUC5AC expression and limited therapeutic options
  - Exploring possibility of additional studies with new biomarker options (e.g. changes in airflow using MRI) for use in asthma/COPD patient populations

ARO-MMP7 First-in-Human Study (AROMMP7-1001): Safety, Target Engagement & Dose-Response and Duration



Population

Healthy Volunteers	Healthy Volunteers	IPF
		• Disease that is not end-stage

Cohorts

First 2 cohorts have dosed

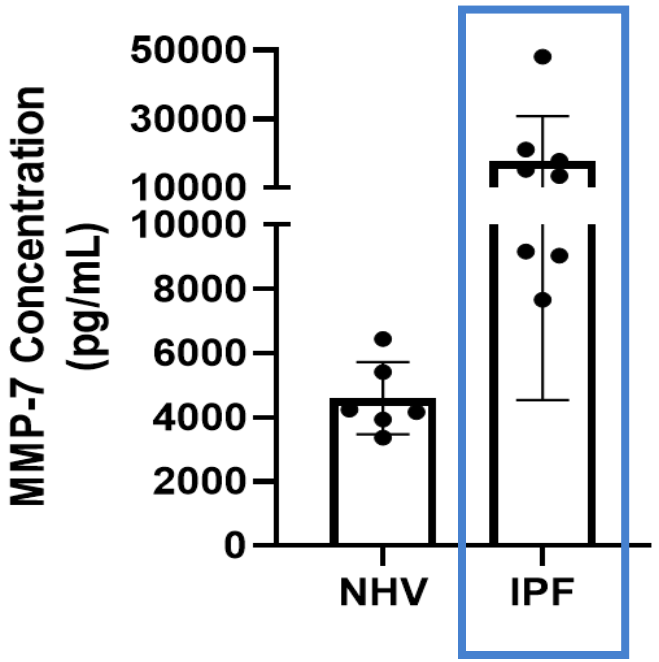
15 mg Cohort A1	≤ 60 mg Cohort B1	Cohort C1: Dose TBD
D15 Safety Eval		
32 mg Cohort A2	≤ 60 mg Cohort B2	Cohort C2: Dose TBD
D15 Safety Eval		
60 mg Cohort A3	≤ 60 mg Cohort B3	Cohort C3: Dose TBD
D15 Safety Eval		
116 mg Cohort A4	≤ 116 mg Cohort B4	
D15 Safety Eval		
8 subjects each (6:2)	6 subjects each (4:2)	7 subjects each (5:2)

Elevated MMP7 Expression in IPF BALF and Serum Provides Key Insights For Pharmacodynamic Endpoints

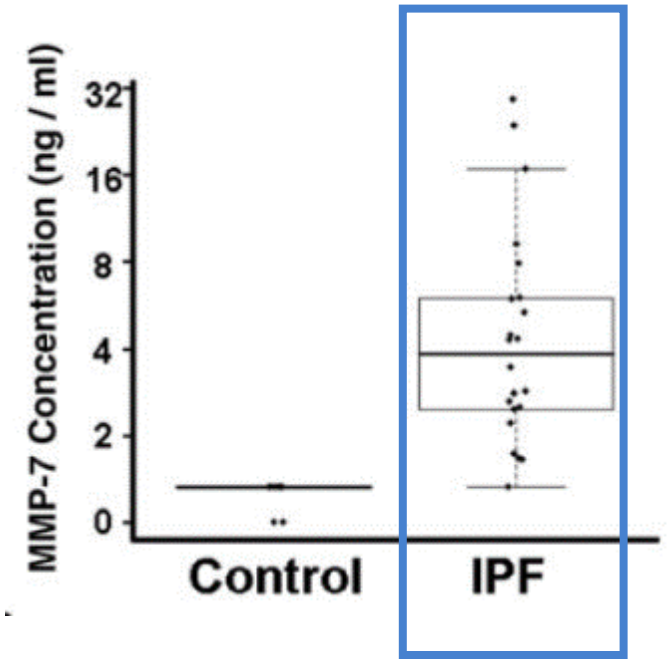
Target Engagement Biomarkers in Healthy Volunteers & IPF Patients

- Serum MMP7 protein
- BALF MMP7 protein
- Bronchosorption MMP7 protein
- Serum and BALF MMP7 levels are increased in IPF relative to NHVs
- IPF Patient samples are most relevant for measuring pharmacodynamic effect

MMP7 in Serum

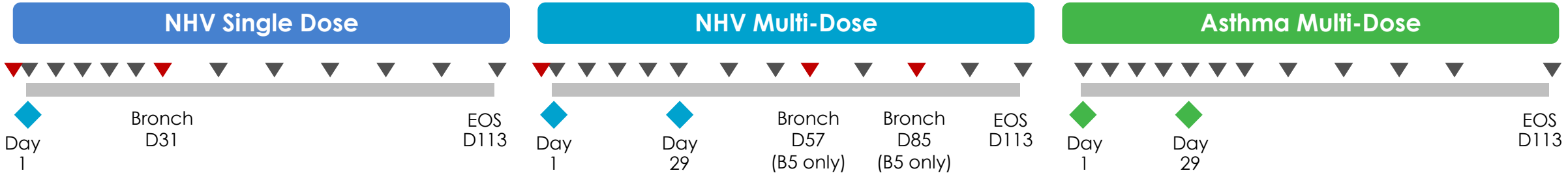


MMP7 in BALF



Rosas IO, *PLoS Med*. 2008;5(4):e93.

ARO-RAGE First-in-Human Study (ARORAGE-1001): Safety, Target Engagement & Dose-Response and Duration



Population

Healthy Volunteers	Healthy Volunteers	Asthma
		• Broad range of disease severity (GINA 1-4) • Type-2 High (Blood eos ≥ 200)

Cohorts

10 mg Cohort A1	10 mg Cohort B1	
D22 Safety Eval		
20 mg Cohort A2	20 mg Cohort B2	
D22 Safety Eval		
44 mg Cohort A3	44 mg Cohort B3	44 mg Cohort C1
D22 Safety Eval		
92 mg Cohort A4	92 mg Cohort B4	92 mg Cohort C2
D22 Safety Eval		
184 mg Cohort A5	184 mg Cohort B5	184 mg Cohort C3
D22 Safety Eval		
8 subjects each (6:2)	6 subjects each (4:2)	8 subjects each (6:2)

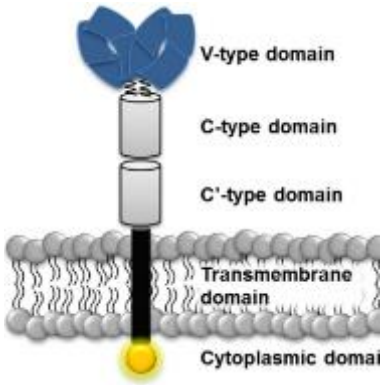
AORAGE-1001 Key Endpoints

Safety (Pulmonary):

- Respiratory Adverse Events
- Lung function
- Inflammatory Cells: BALF Cell Count and Differential
- Chest X-rays

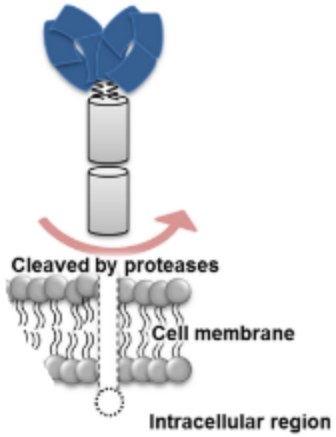
Full-length Membrane-associated RAGE (mRAGE)

Therapeutic target



Soluble RAGE (sRAGE)

Target engagement marker



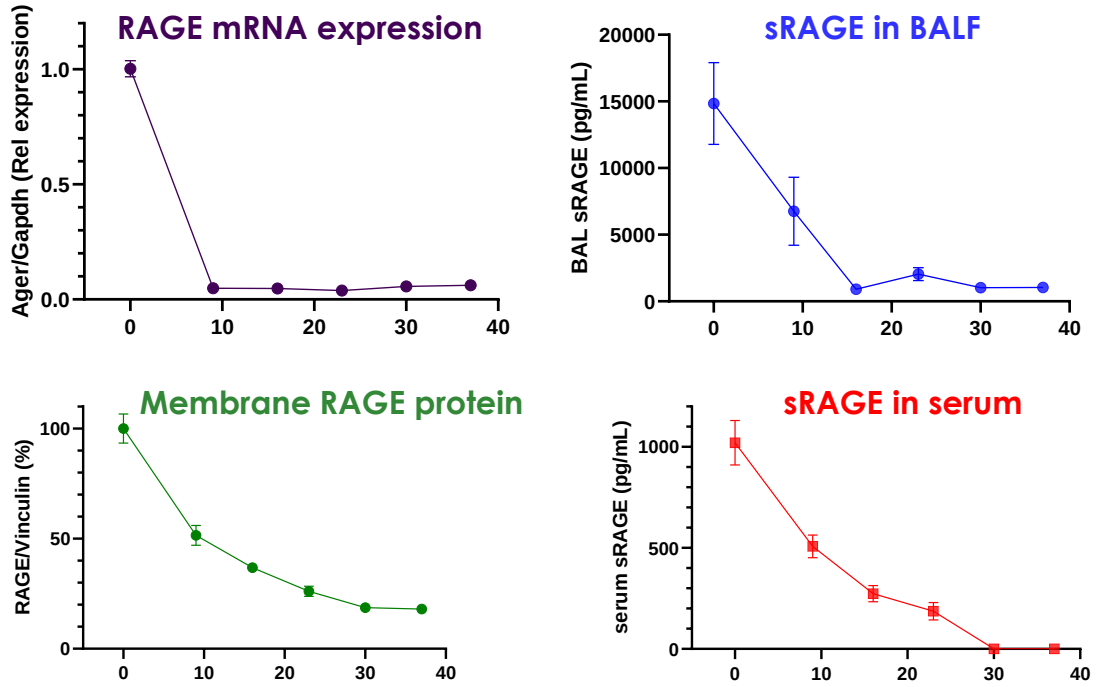
Fishman, et al, *J. Mol. Med*. 2018, 24:59

Target Engagement:

Soluble RAGE protein (sRAGE)

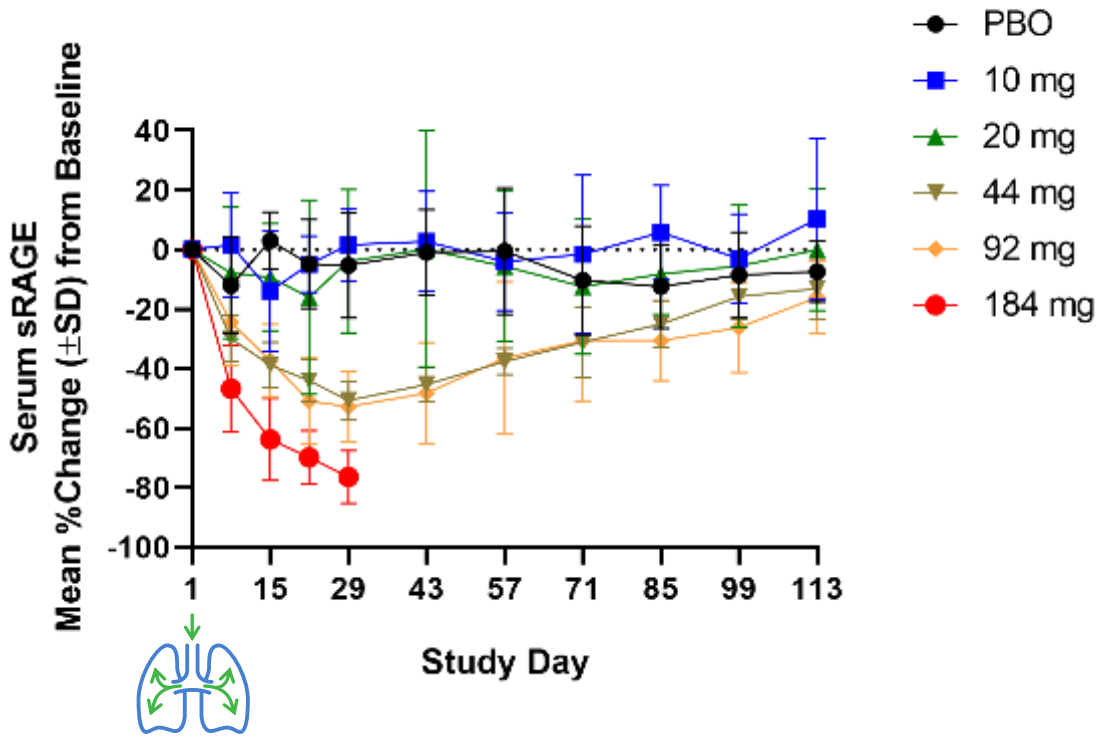
- Serum
- BALF

Time-course of Effect
Days Post Single Dose in Rats

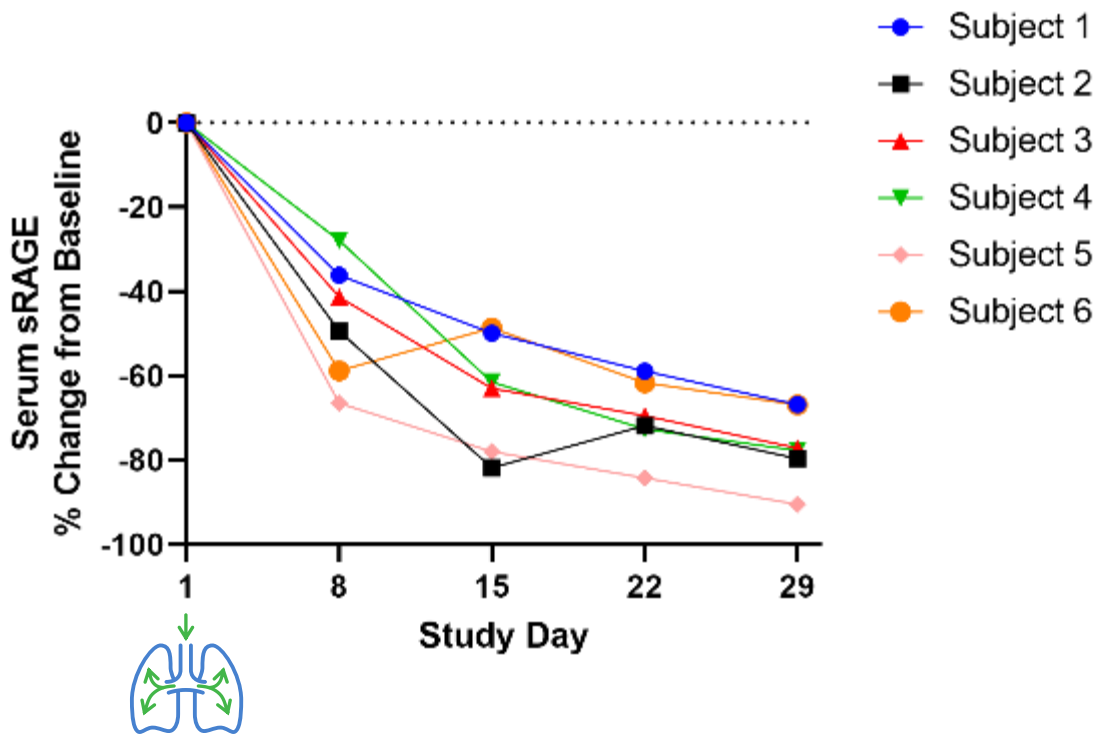


New Single Dose Data: Mean Serum sRAGE Protein Reduction of Up to **76%** with Maximal Reduction of **91%** at Top Dose Level

Single Dose Cohorts



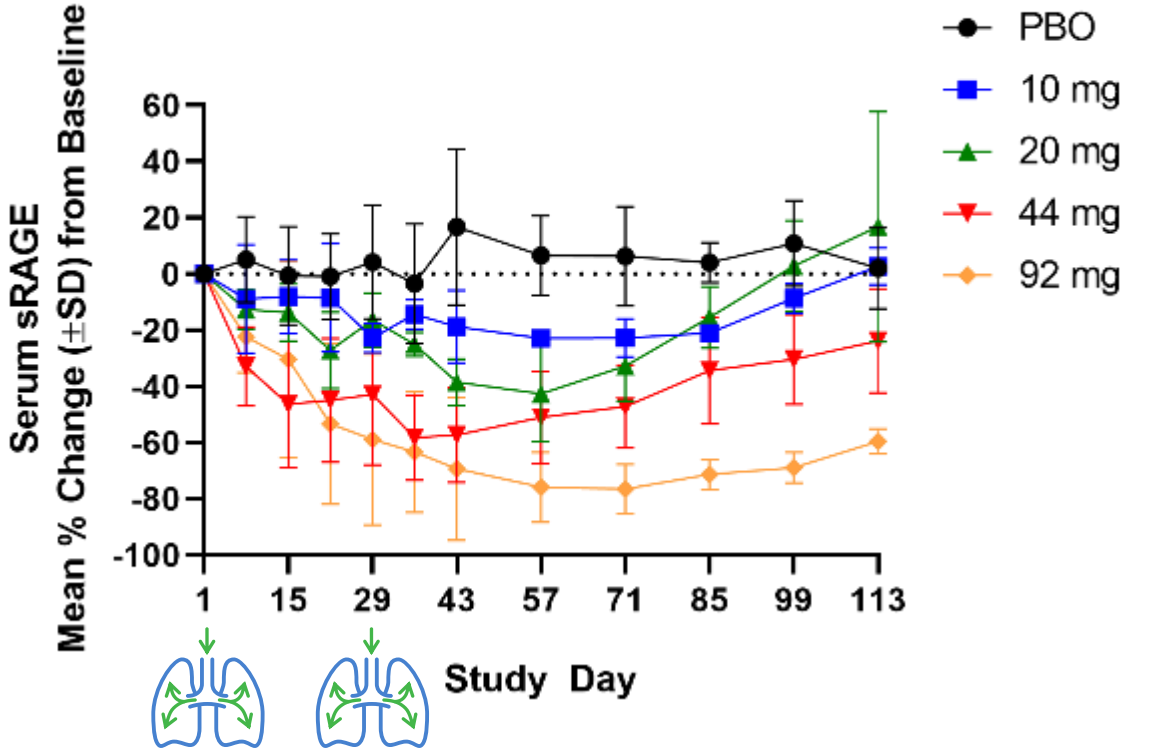
184 mg Single Dose Cohort



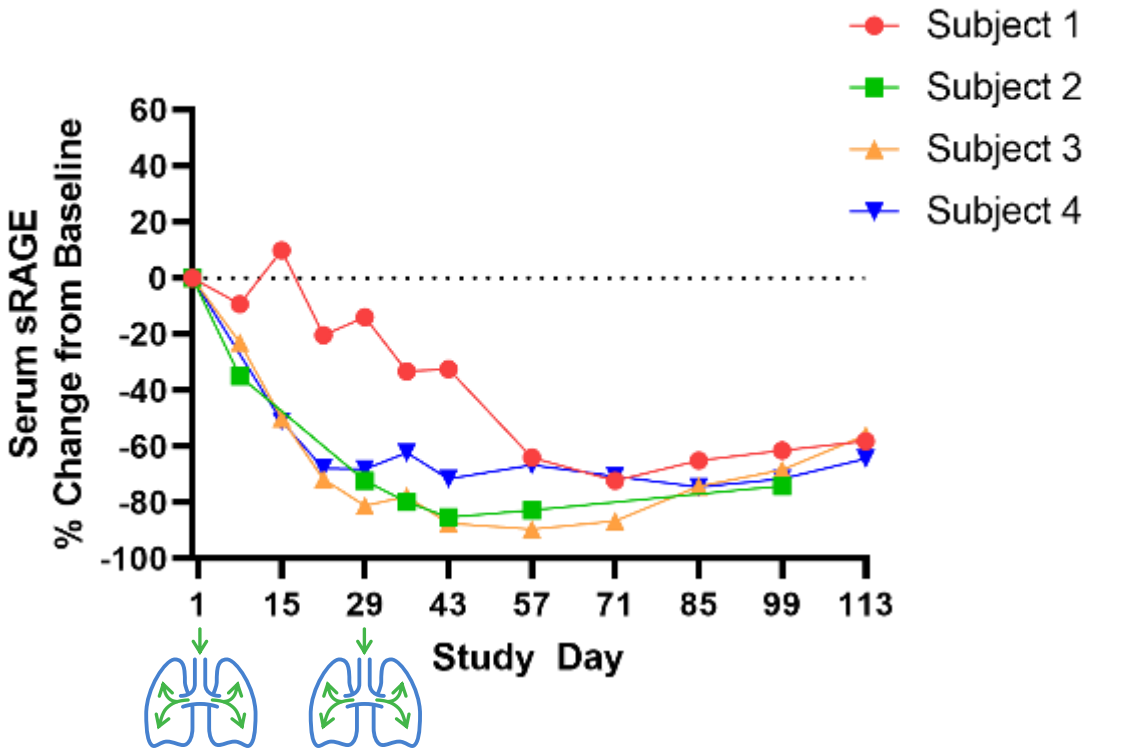
Data cut May 2023

Multiple Doses of ARO-RAGE Result in Mean Maximum Serum sRAGE Reduction of **80%**, Maximal Reduction Up to **90%**

Multiple Dose Cohorts



92 mg Multiple Dose Cohort



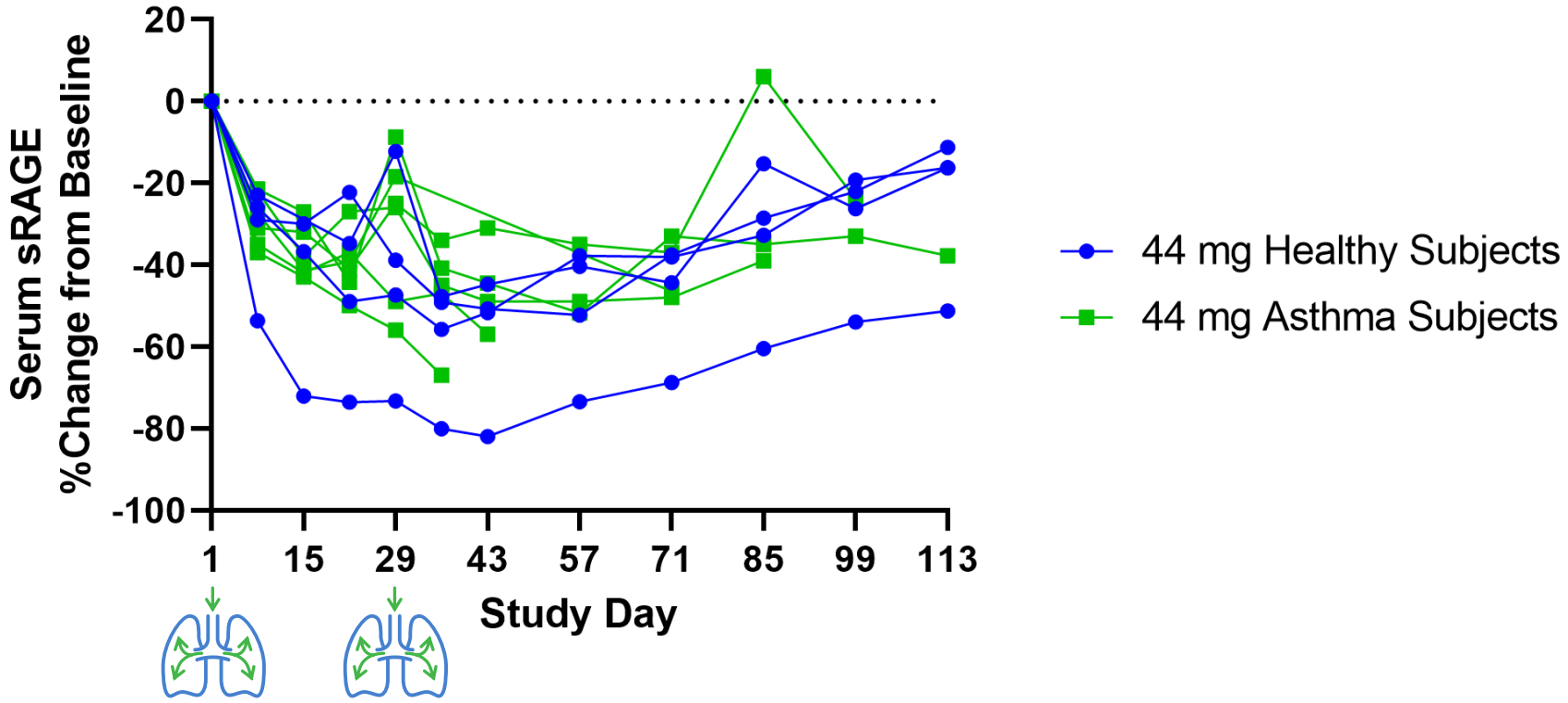
Duration Supports Q2 Month Dosing

Data cut May 2023

184 mg Dose Data Still Pending

ARO-RAGE Achieves Serum sRAGE Reductions in Asthma Patients Consistent with Effects Seen in NHVs

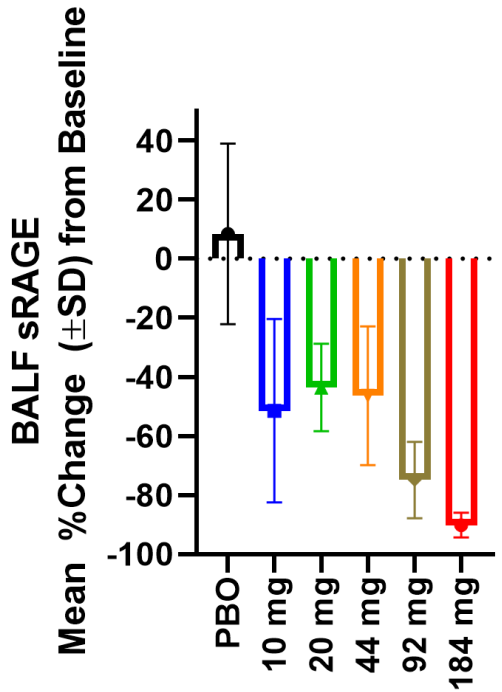
44 mg Multiple Dose Cohorts: Healthy vs. Asthma



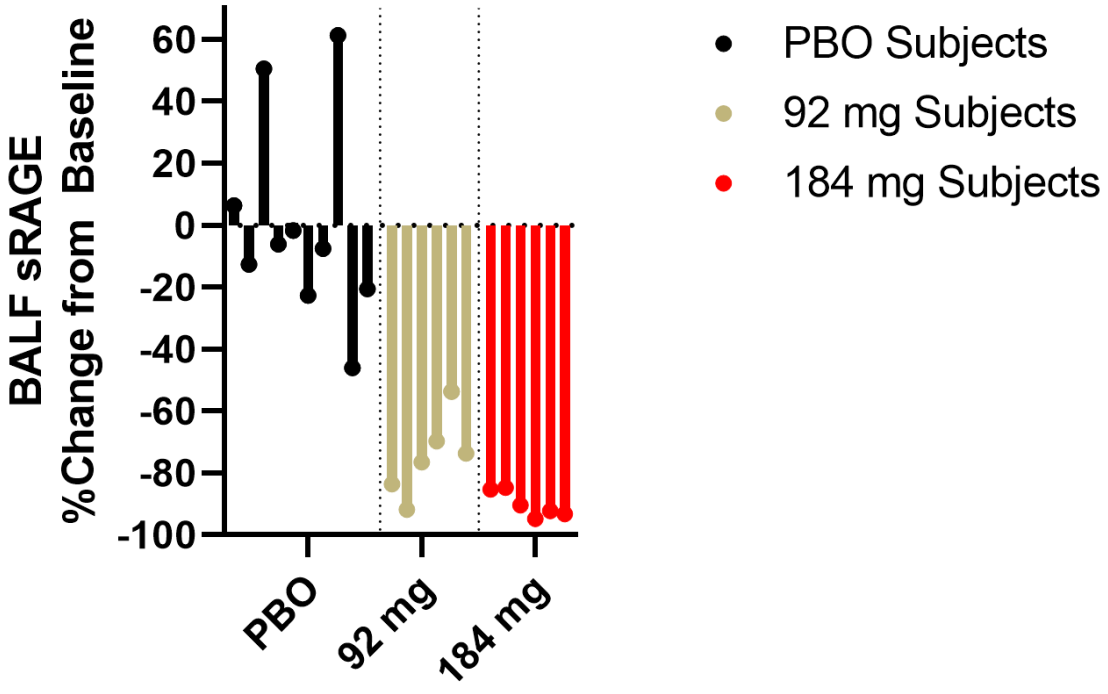
Data cut May 2023

New Single Dose BALF Data: Mean BALF sRAGE Protein Reduction of **90%** at Top Dose, Max Reduction of **95%**

Single Dose Cohorts Change from Baseline at Day 31



92 mg and 184 mg Single Dose Cohorts Change from Baseline at Day 31



Data cut May 2023

ARO-RAGE Has Shown a Favorable Safety Profile To Date

Adverse Events:

- No serious adverse events
- No severe adverse events
- No study withdrawals or drug discontinuations due to adverse events
- No adverse events due to change in lung function

BALF Cell Count & Differential:

- No change in pattern of airway immune cells

Chest X-rays:

- All read as normal

Safety Labs:

- No patterns of adverse changes

Data cut April 2023

ARORAGE-1001 Summary & Next Steps

- ARO-RAGE achieves deep and durable reductions in serum and BALF sRAGE in an NHV population, with similar silencing effects seen in asthma patients
  - Serum sRAGE reductions generally consistent with BALF sRAGE reductions
- We believe this is the first compelling clinical evidence of gene target silencing in the lung using siRNA
- The safety profile to date in NHVs and asthma patients has been supportive of later stage clinical development
- The full NHV data will be presented at an upcoming medical meeting
- Addition of "High FeNO" asthma cohorts
  - Evaluation of anti-inflammatory in asthma patients with baseline high FeNO

Analyst R&D Day June 1, 2023

Pulmonary Clinical Results: Significance and Context

Matthias Salathe, MD

arrowhead pharmaceuticals

RAGE in Asthma and Pulmonary Inflammatory Diseases
MUC5AC in Muco-Obstructive Diseases

Matthias Salathe

KU SCHOOL OF MEDICINE
The University of Kansas

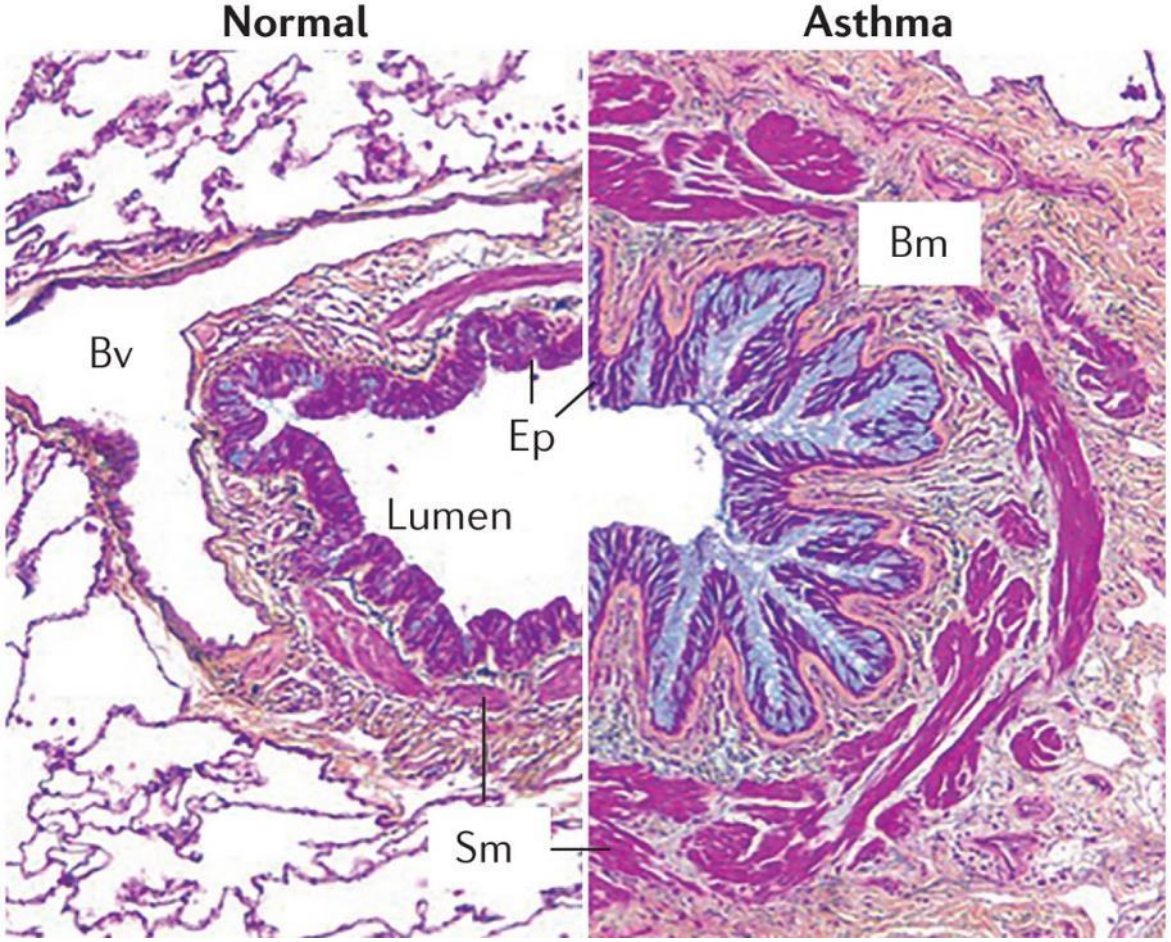
Disclosures

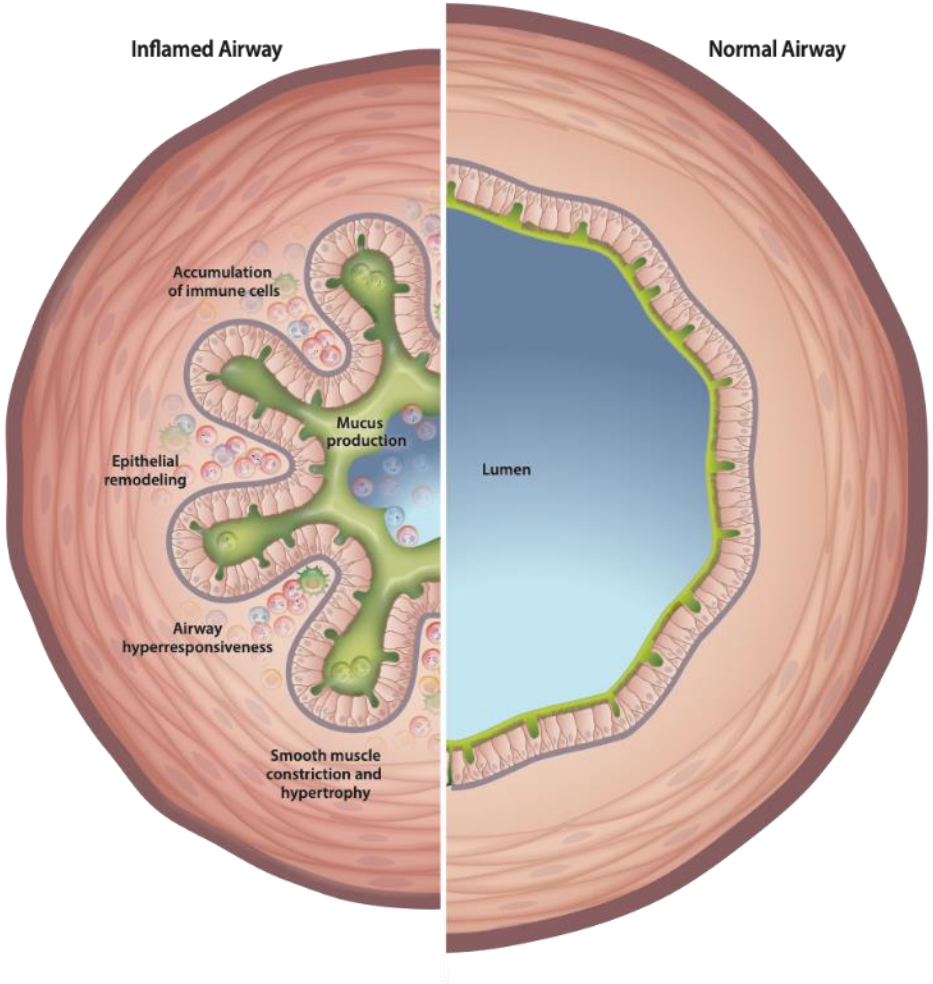
Grants
- NIH
- FAMRI
- J&E King State of Florida
- CF Foundation

Consulting
- Arrowhead Pharmaceuticals

Previous Clinical Trials
- ACTIV-1 (NIH)
- Aradigm
- Bayer
- CSL Behring
- Gilead
- Hologix
- Insmed
- JHP
- Kalobios
- MPEX
- Novartis
- Pharmaxis
- PTC
- Vertex
- Savara

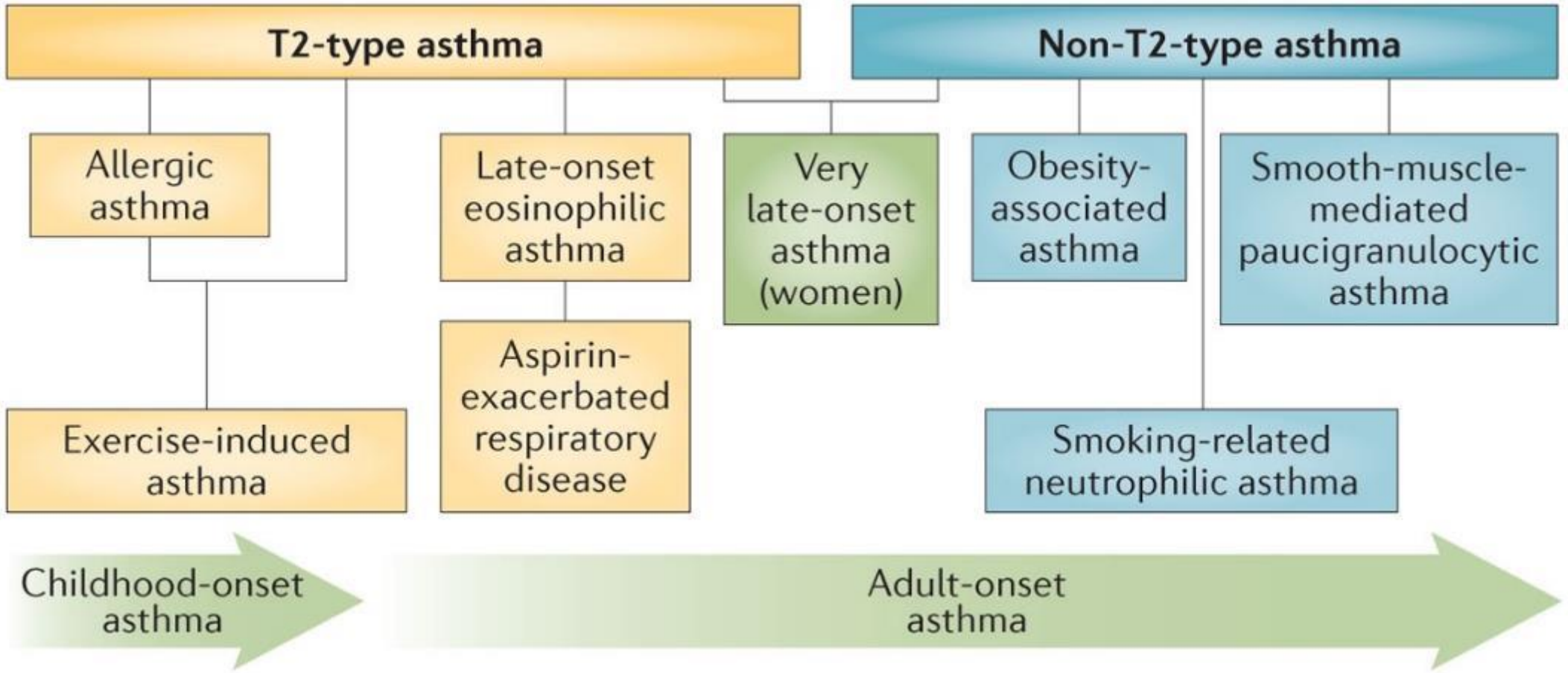
Asthma





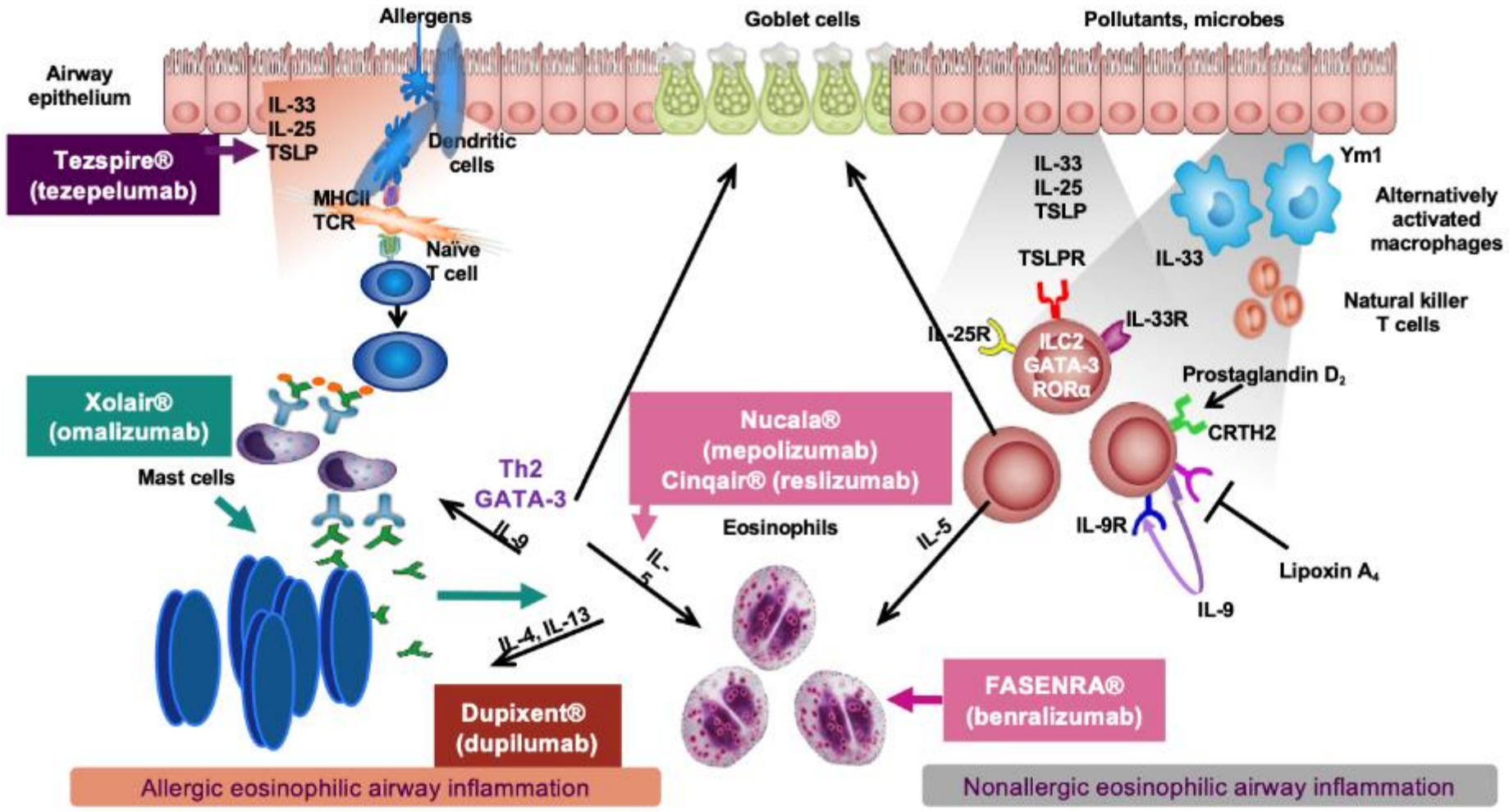
Wadsworth, S. e al. J Asthma Allergy. 2011; 4: 77–86.

Asthma



Holgate, S. T. et al. Asthma. Nat. Rev. Dis. Primers 2015 doi:10.1038/nrdp.2015.25

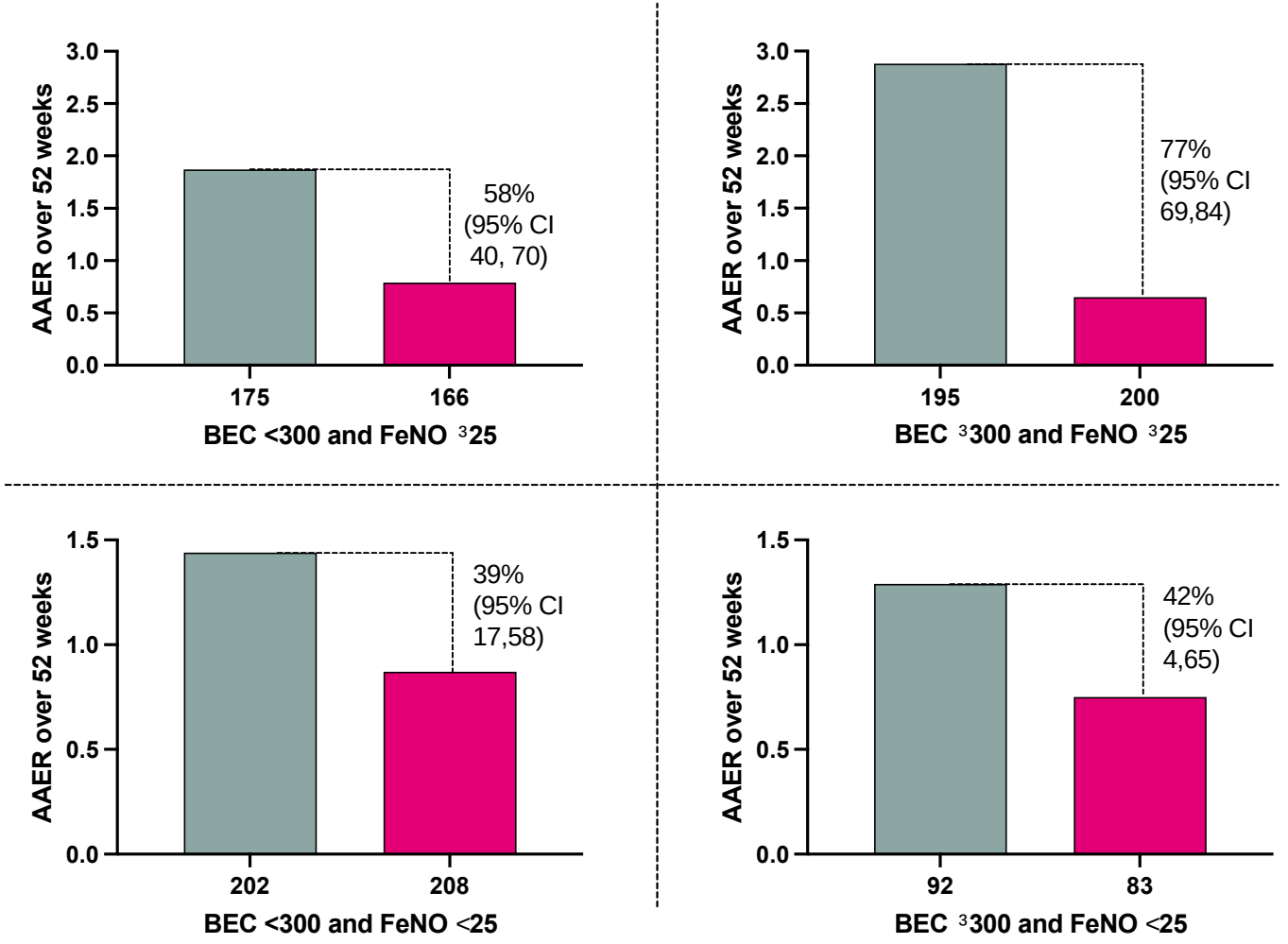
Targeting Allergic and Nonallergic Asthma



IL=interleukin; ILC=innate lymphoid cell; MHC=major histocompatibility complex; TCR=T cell antigen receptor; TSLP(R)=thymic stromal lymphopoietin (receptor).

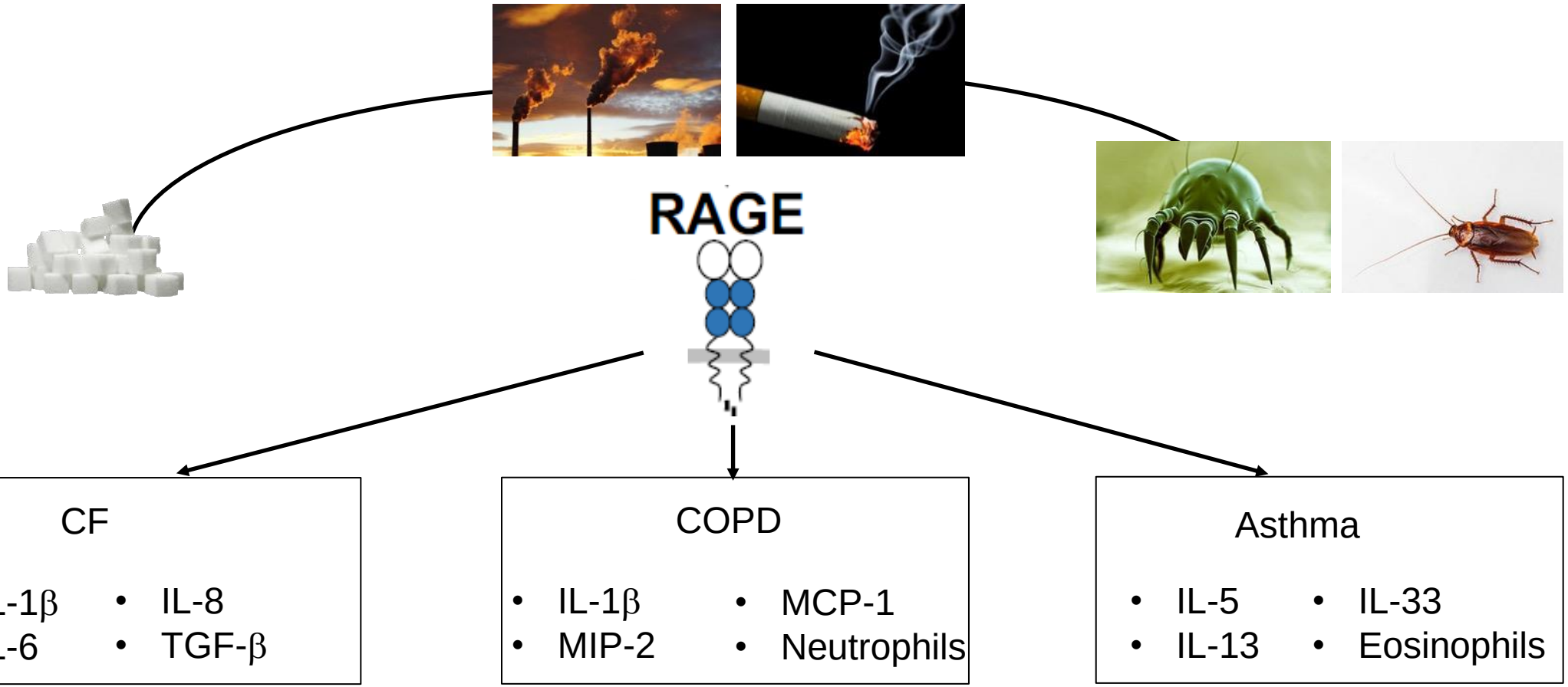
Adapted from Lambrecht BN and Hammad H. *Nat Immunol.* 2015;16:45–56.
GG Brusselle, GH Koppelman. N Engl J Med 2022;386:157-171.

Targeting Low and High T2 Asthma



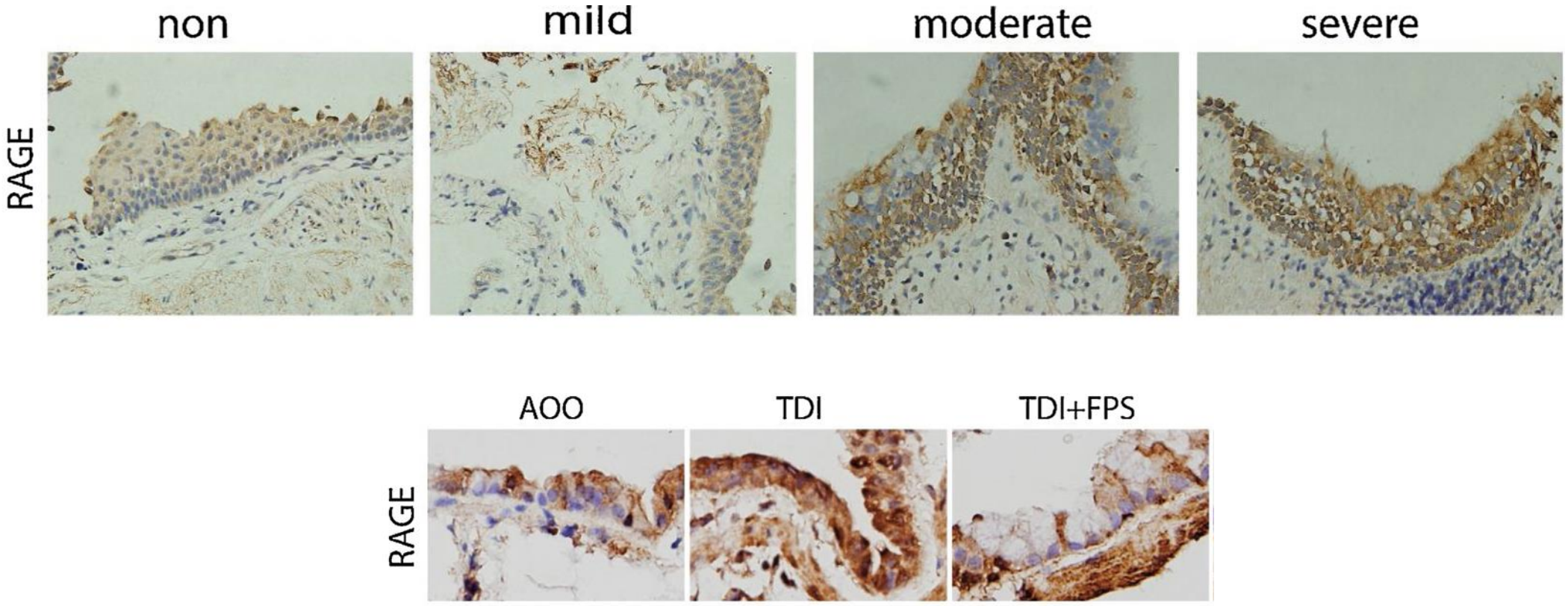
Corren et al. AJRCCM 2023
https://doi.org/10.1164/rccm.202210-2005OC

RAGE → Pulmonary Inflammation
Response to a Range of Stimuli



Perkins et al. Allergy. 2021;76:1350-1366; Waseda et al. Am J Respir Cell Mol Biol. 2015;52:482-491. Bengtson et al. Eur Respir J. 2021;57:2000509.

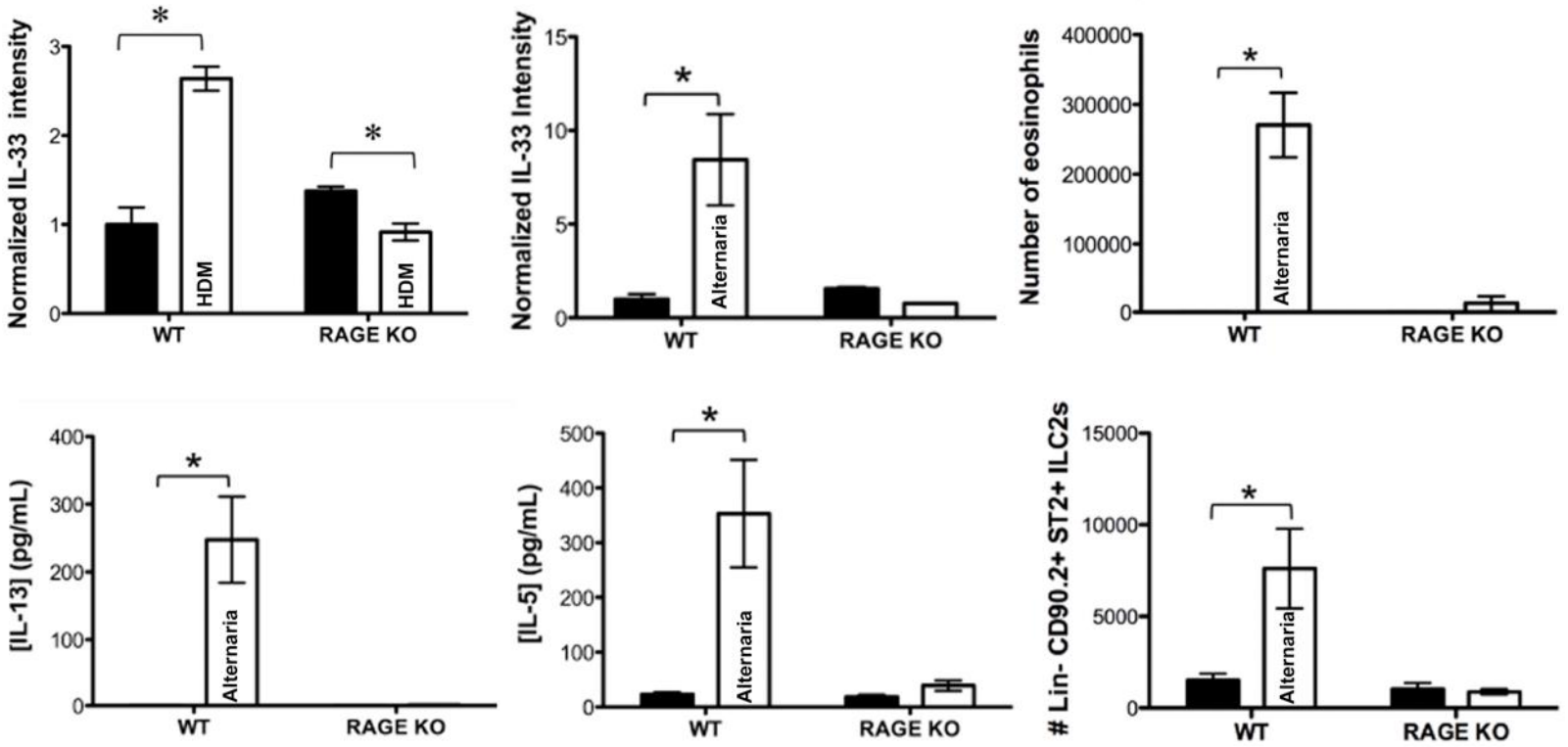
RAGE Upregulated in Allergic Airway Diseases

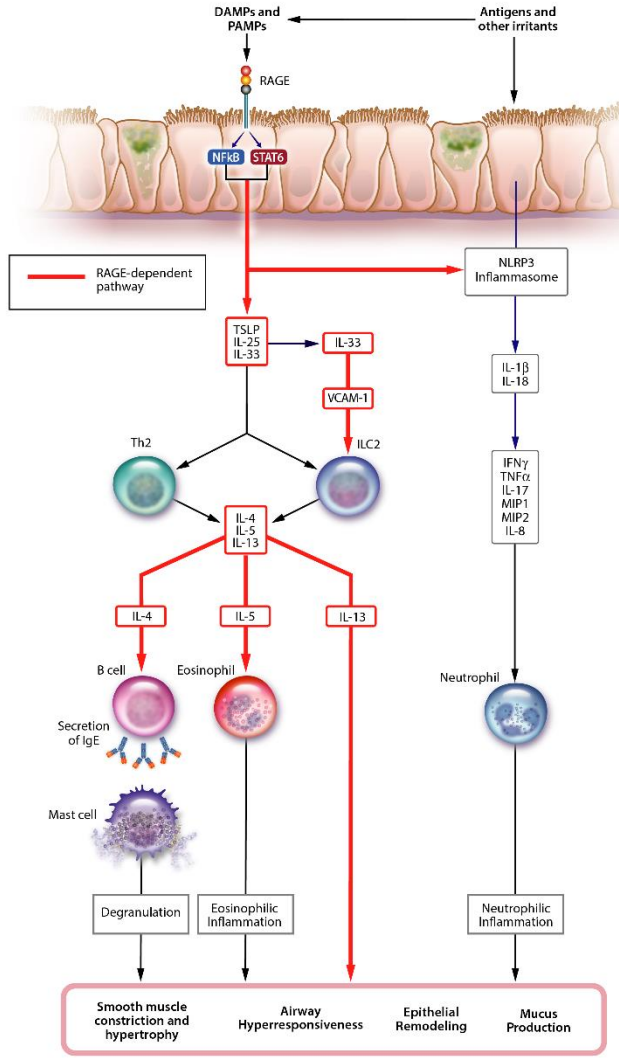


Huang et al. Toxicol Lett. 2021;336:57-67.

RAGE: Necessary for Type-2 Inflammation

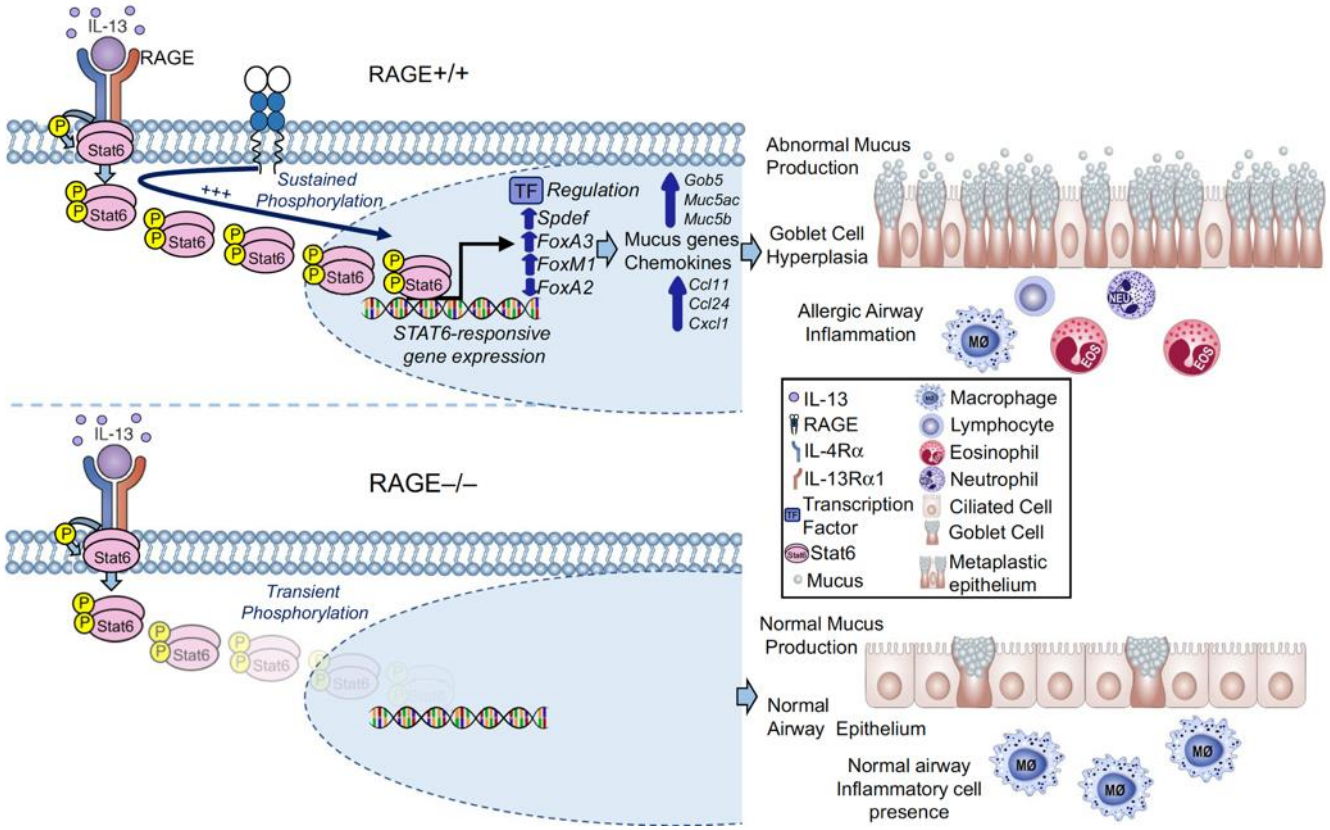
RAGE KO Erases Key Elements of the Type-2 Response to Allergens

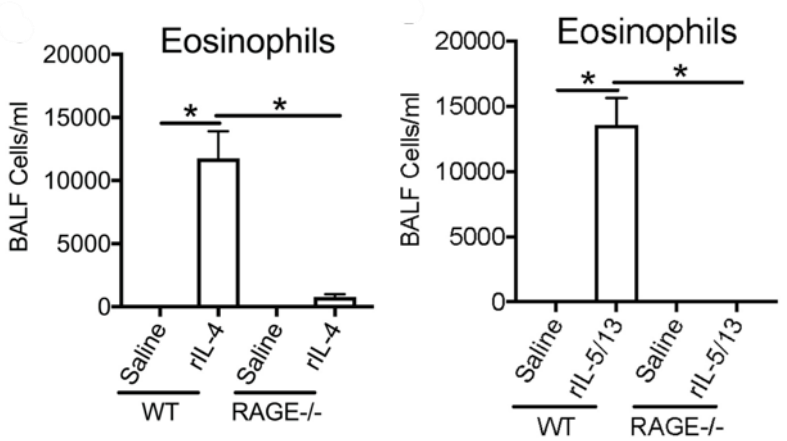


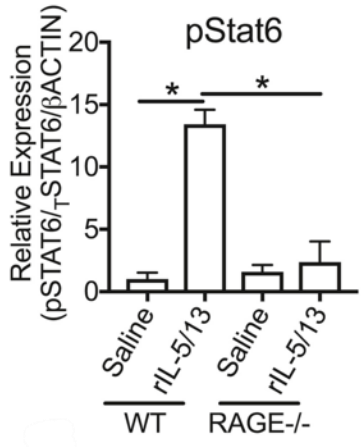


Perkins et al. Allergy. 2021;76:1350-1366; Oczypok et al. J Allergy Clin Immunol. 2015;136:747-756.

RAGE is Necessary for Sustained Signaling by Multiple Effector Cytokines

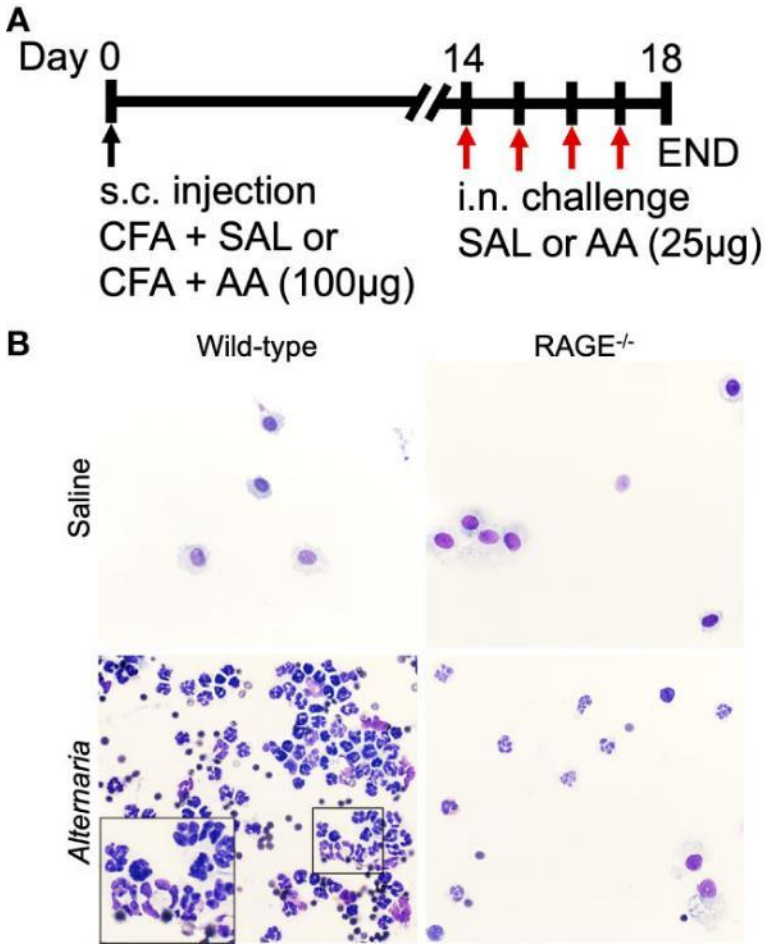


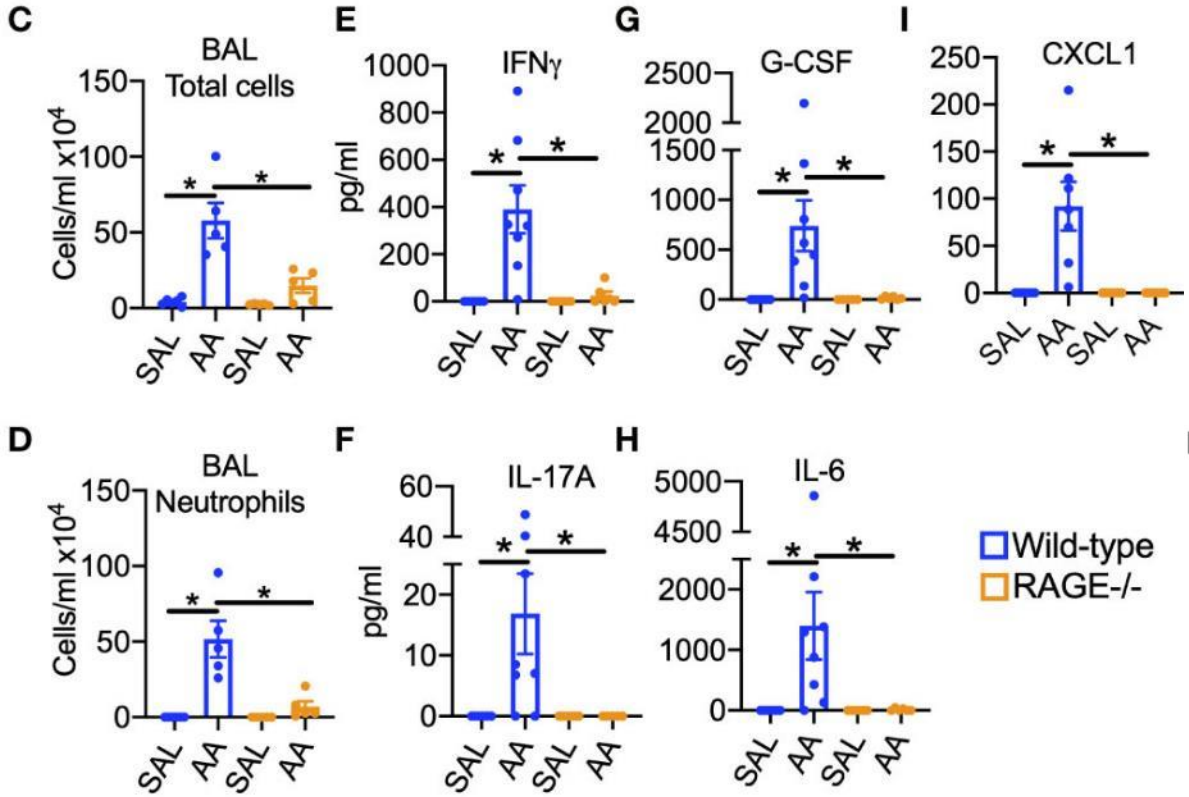


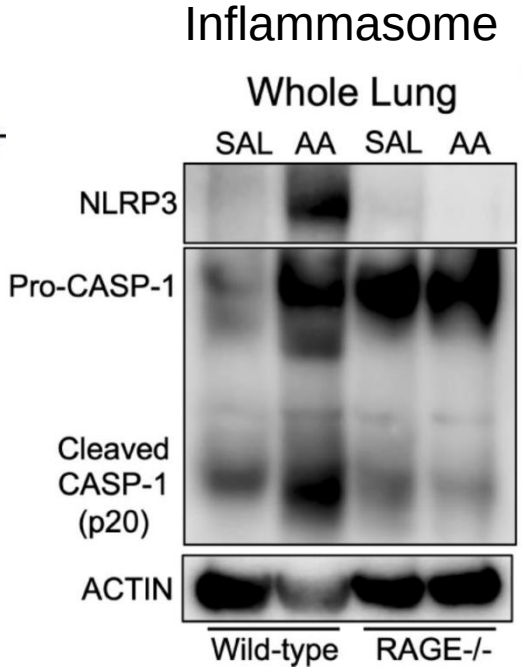


Perkins et al. JACI. 2019; 144:796-808. Perkins et al. Allergy. 2021;76:1350-1366

RAGE is Implicated in T2-Low Inflammation







Killian et al. Front. Immunol. 2023; 14:1039997.

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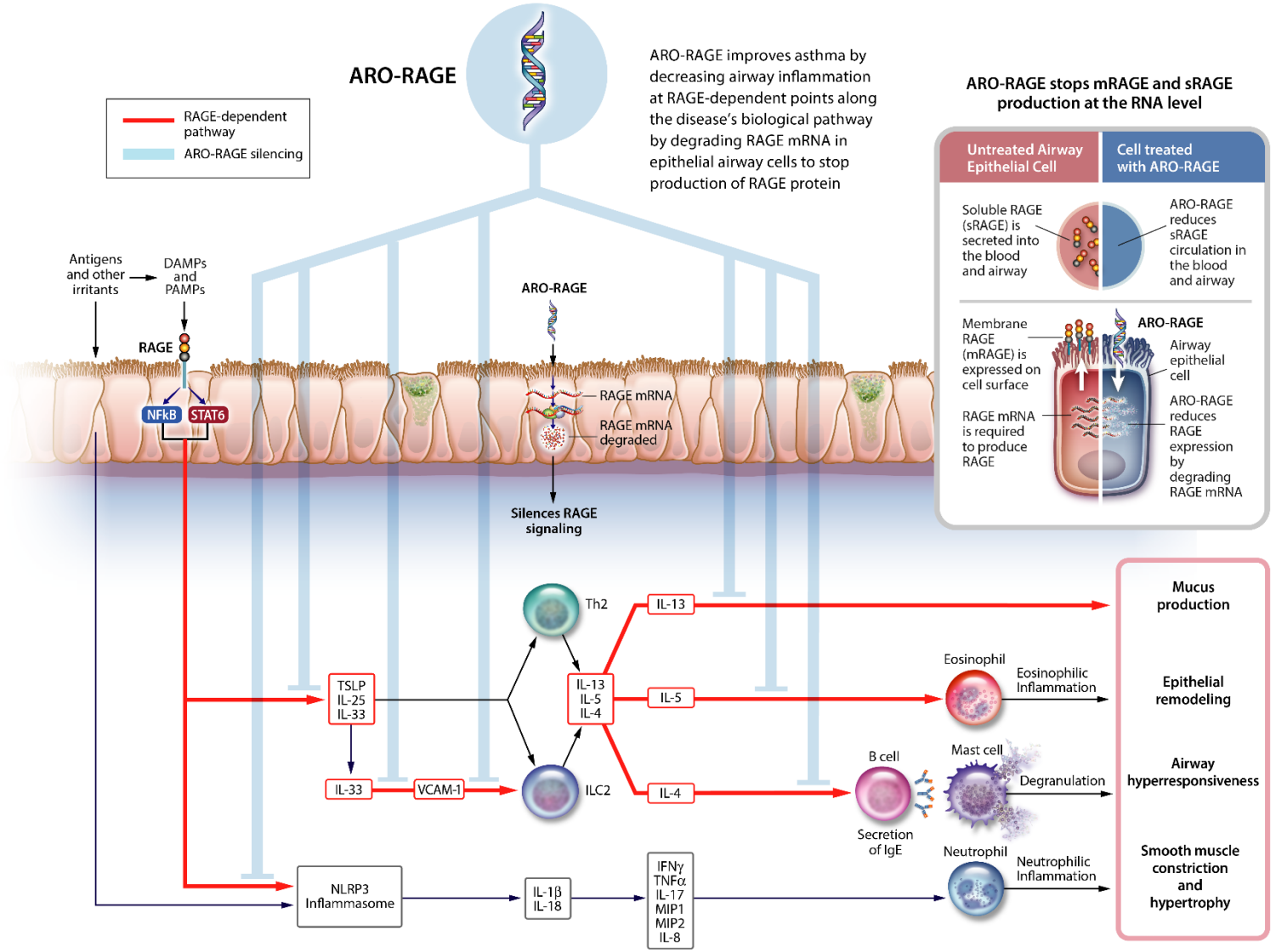
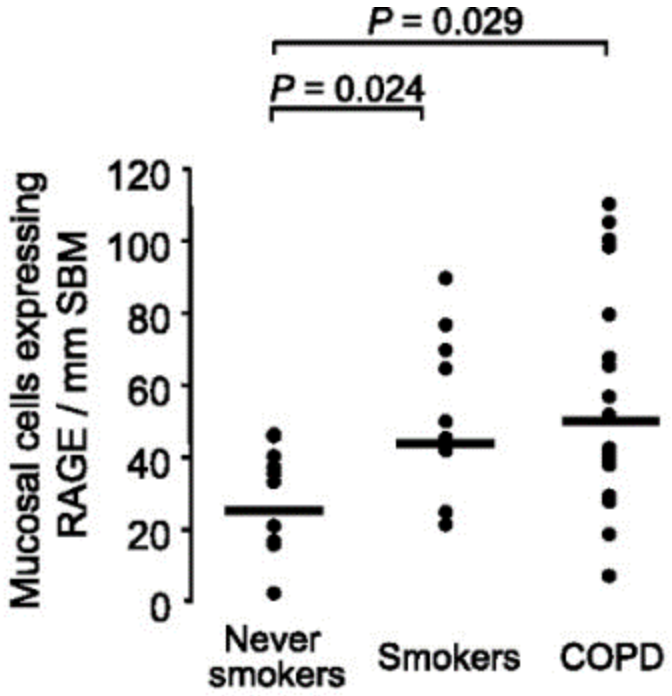
RAGE as a Target for Asthma

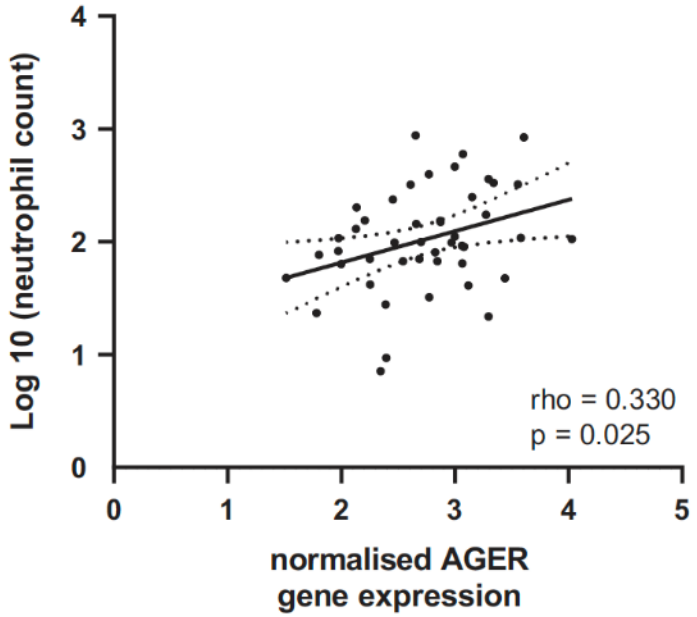


RAGE - COPD

Human

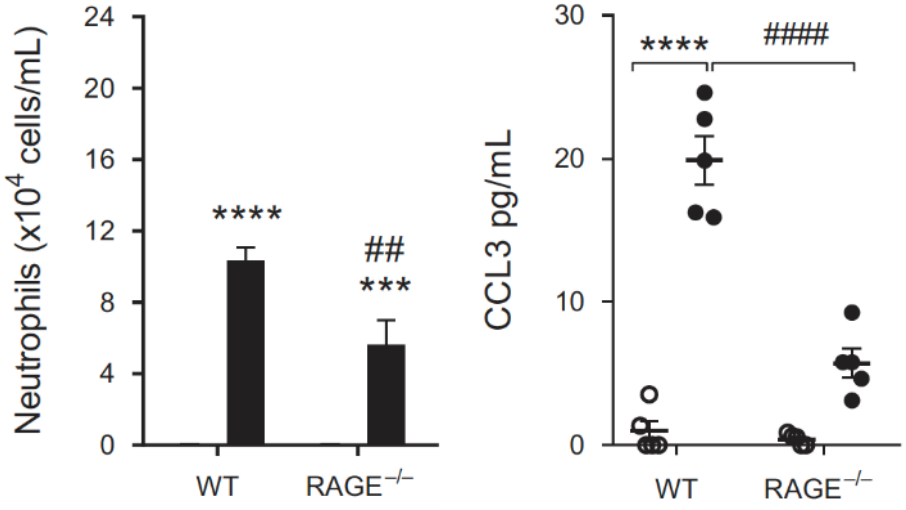


Ferhani et al. AJRCCM. 2010;181:917-927



Allam et al. Allergy. 2021;76:1123-1135

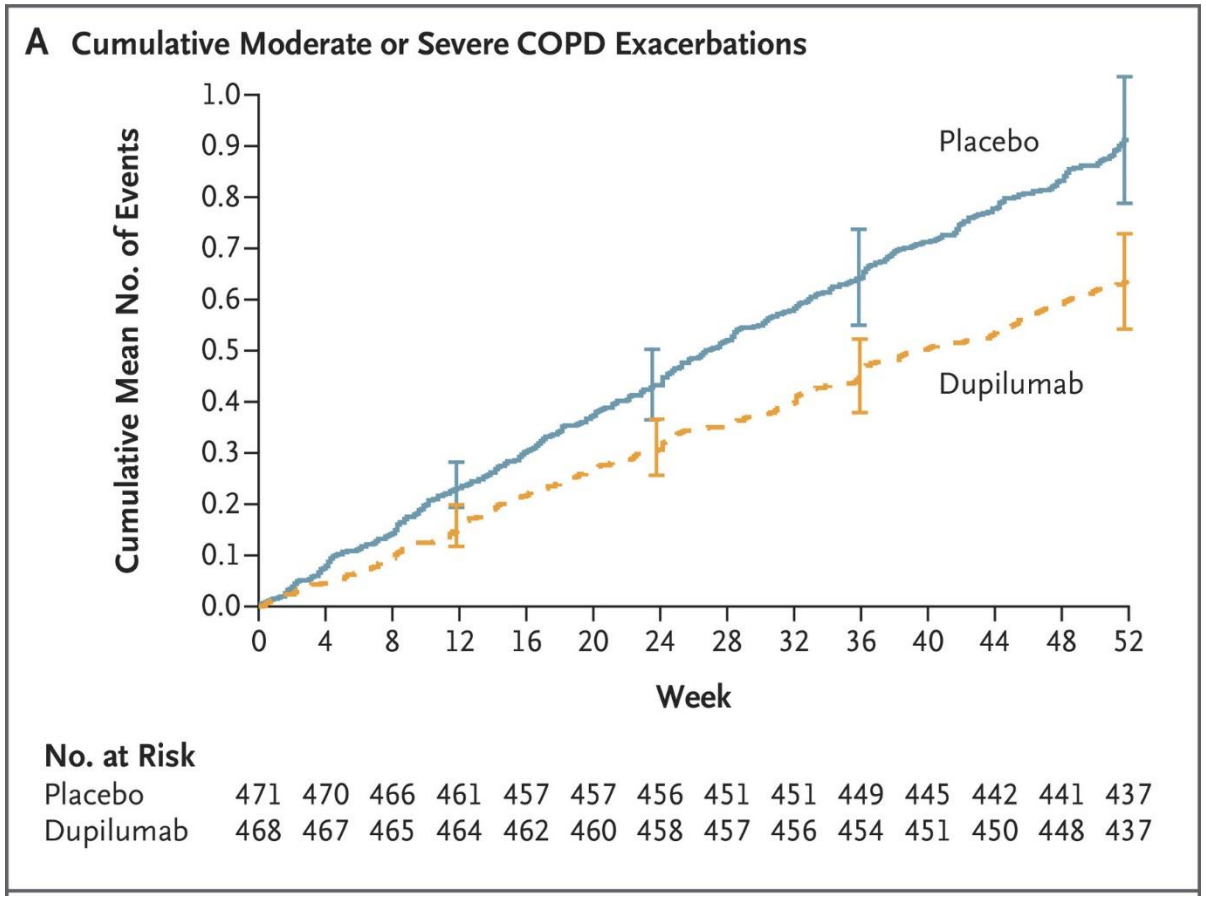
Mice

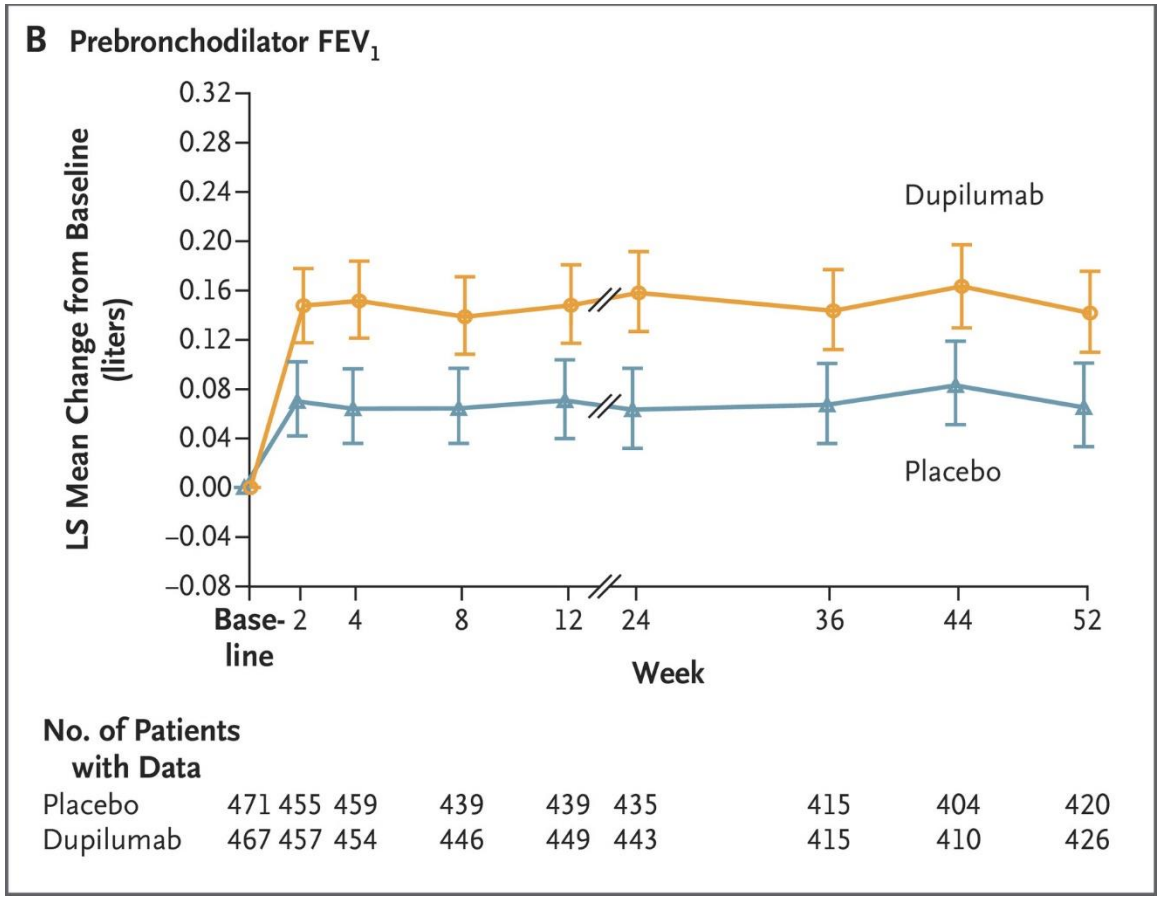


Allam et al. Allergy. 2021;76:1123-1135

KU SCHOOL OF MEDICINE The University of Kansas

RAGE – COPD with Type 2 Inflammation



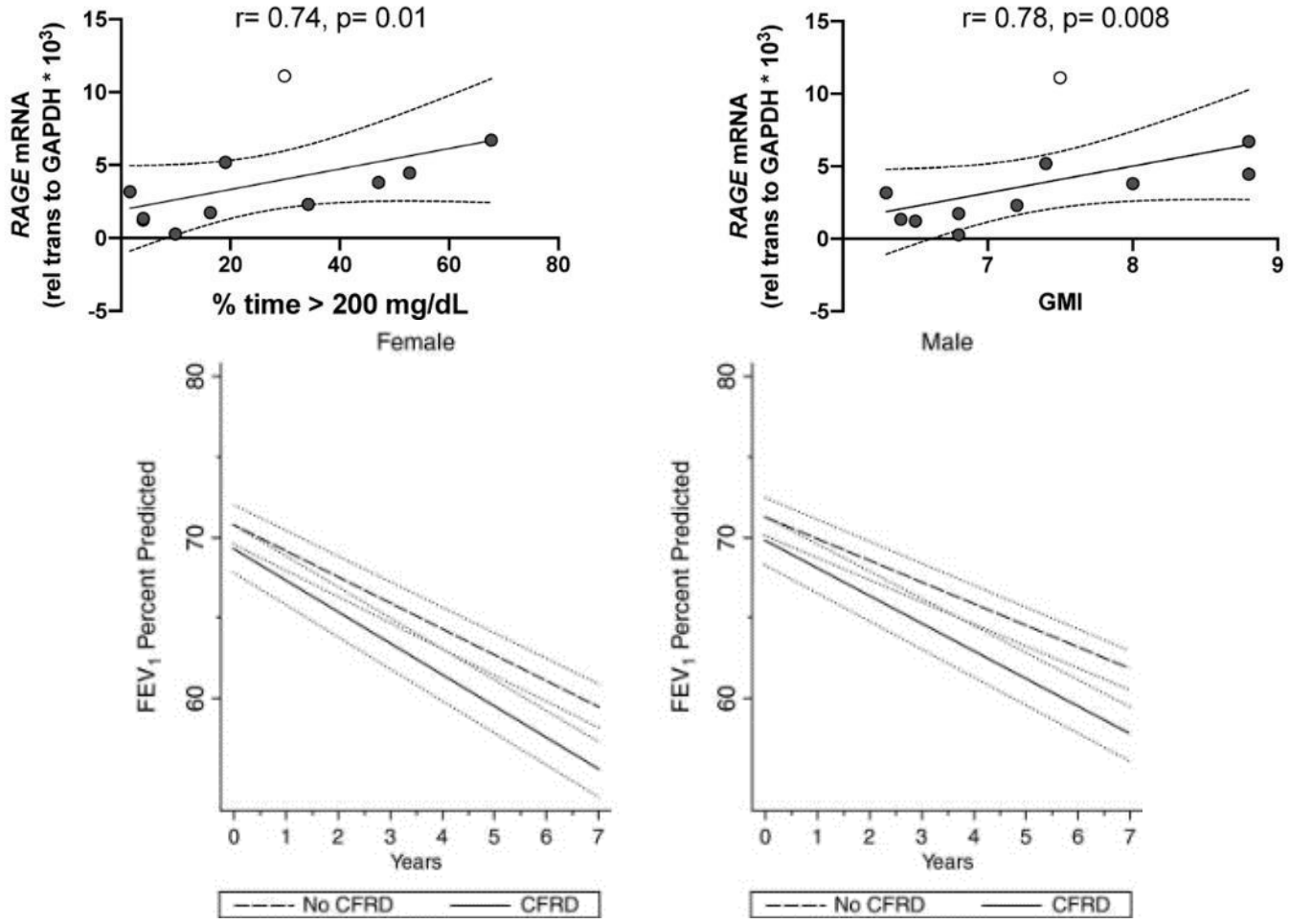


Dupilumab BOREAS trial (NCT03930732): Randomized, double-blind, placebo-controlled trial

- 939 adults, 40 to 80 y, **COPD**, **eosinophils >300,** on maximal triple inhaled therapy
- 1:1 to receive **dupilumab** or placebo s/c every 2 weeks for 52 weeks

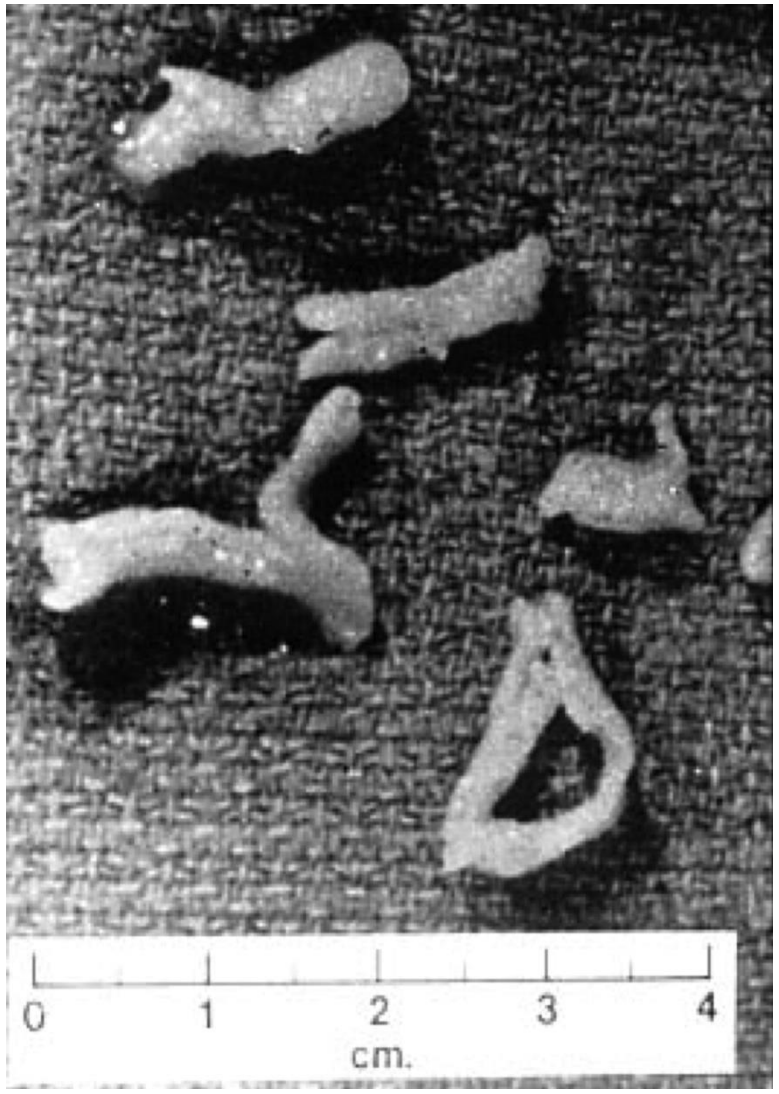
Bhatt et al. NEJM 2023: DOI: 10.1056/NEJMoa2303951

RAGE - CF



Bengtson. Eur Respir J. 2021 Jan 14;57(1):2000509. doi: 10.1183/13993003.00509-2020.
Bengtson. AJRCCM. 2021 Dec 1;204(11):1343-1345. doi: 10.1164/rccm.202104-1060LE.

Muco-obstructive Disease - Asthma

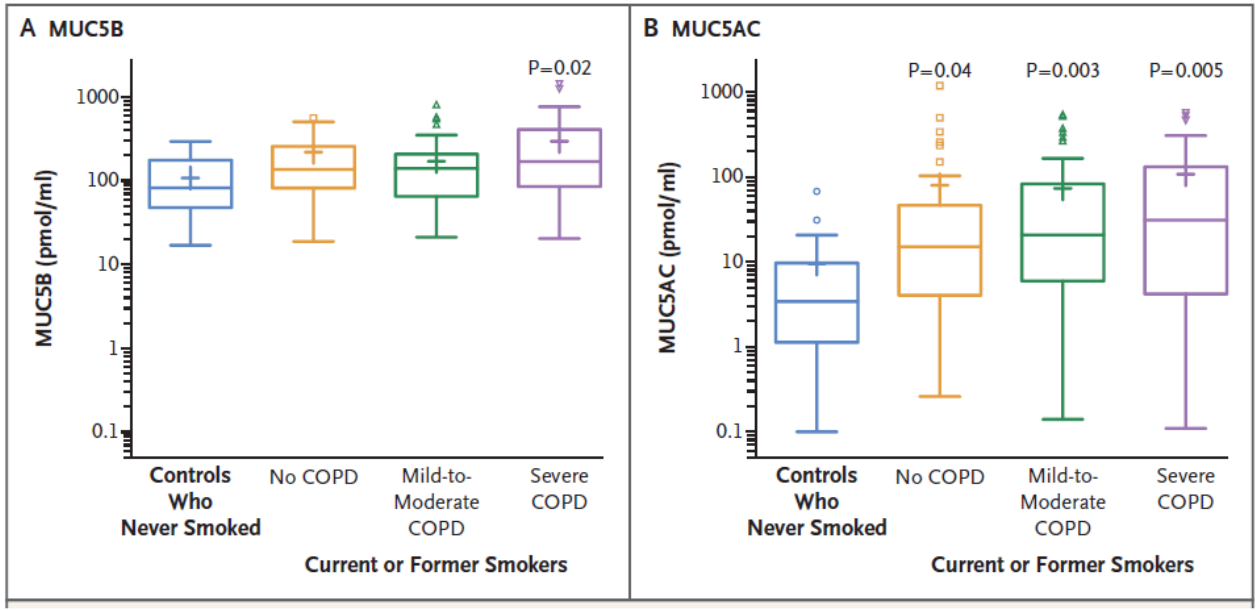


- MUC5AC
- At Autopsy:
  "Pathologically the outstanding feature of the asthmatic lung lies in the failure of clearance of bronchial secretions"
  Huber 1922

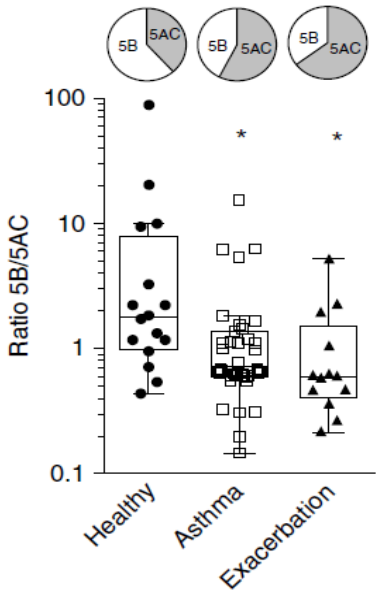
Image from Lang DM. Ann Allergy. 1991 Sep;67(3):324-30

Muco-obstructive Disease is Driven by MUC5AC Upregulation

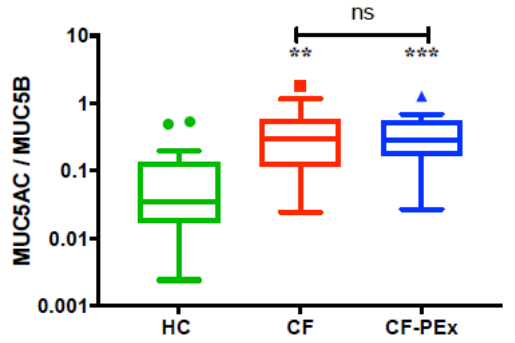
COPD



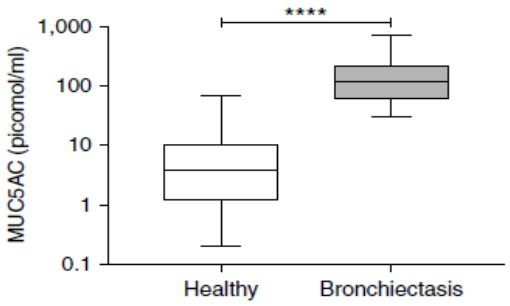
Asthma



Cystic Fibrosis

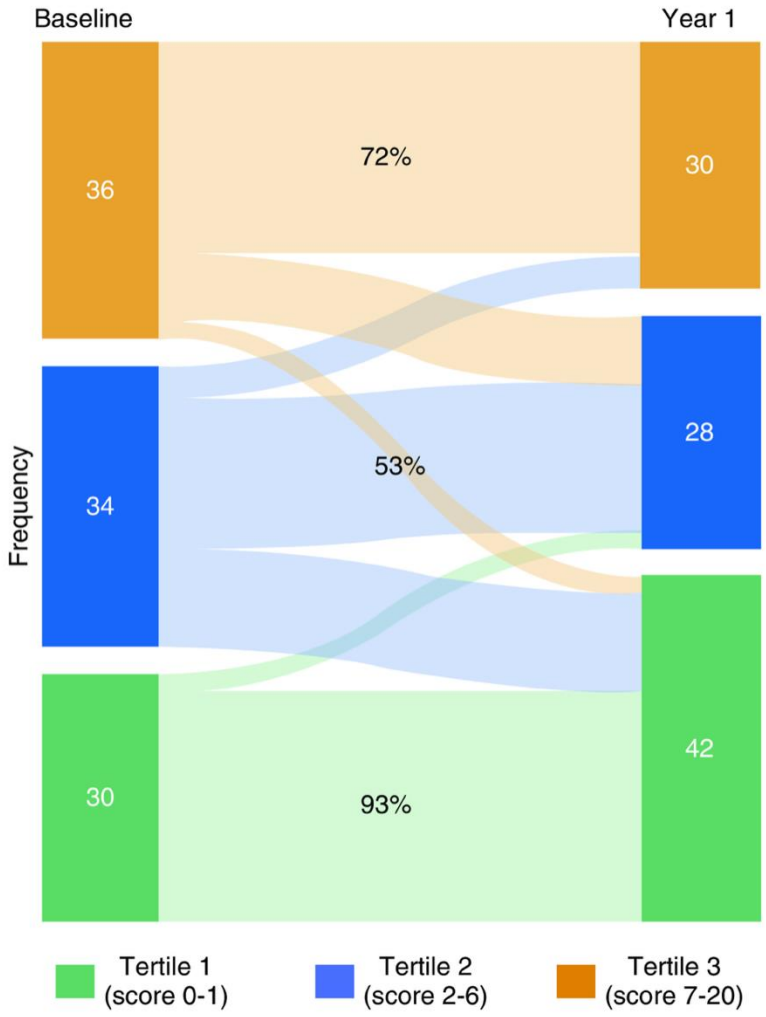


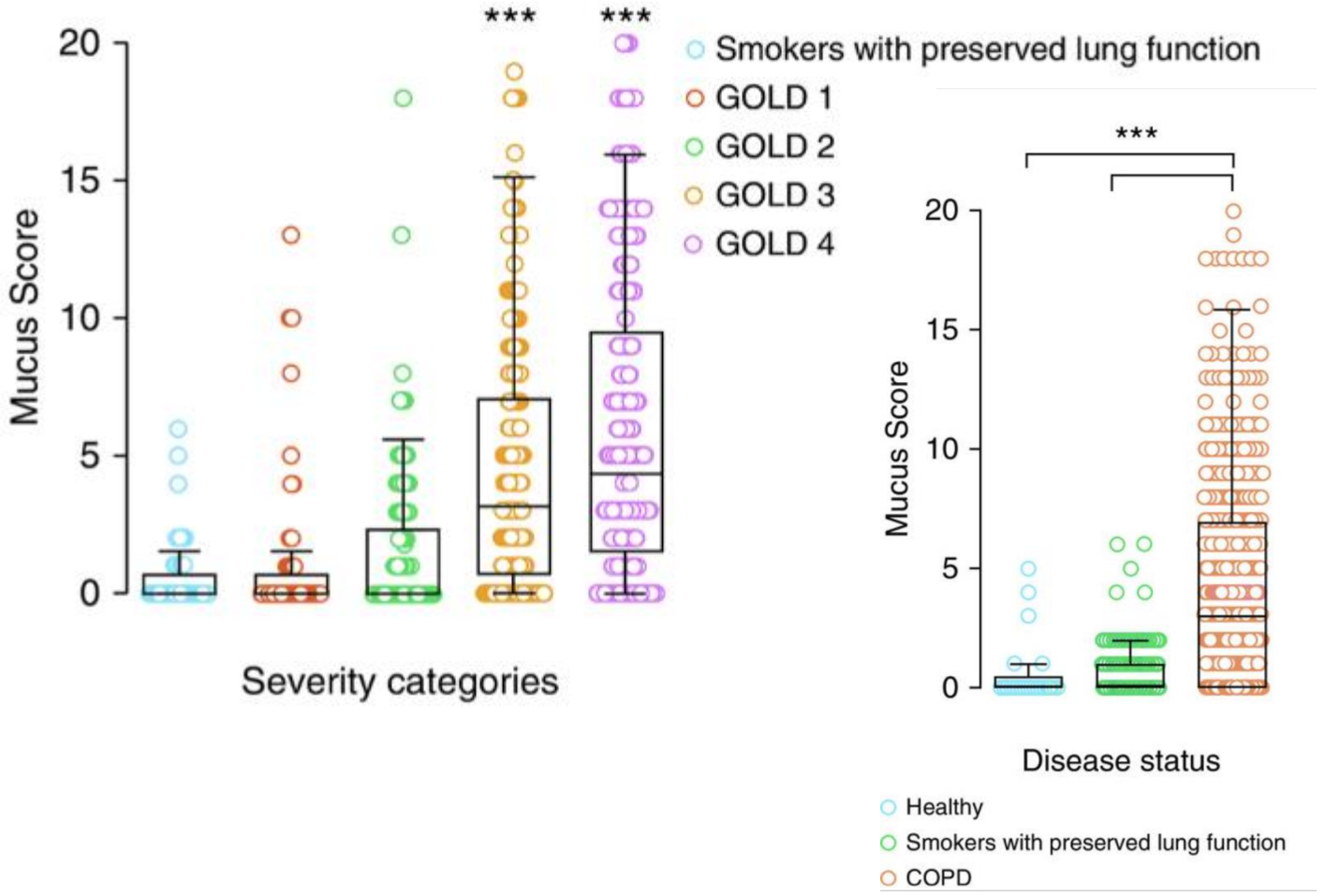
Non-CF Bronchiectasis



Kesimer, NEJM, 2017; Lachowicz-Scroggins, AJRCCM, 2016; Batson, AJRCMB, 2022; Ramsey, AJRCCM, 2020.

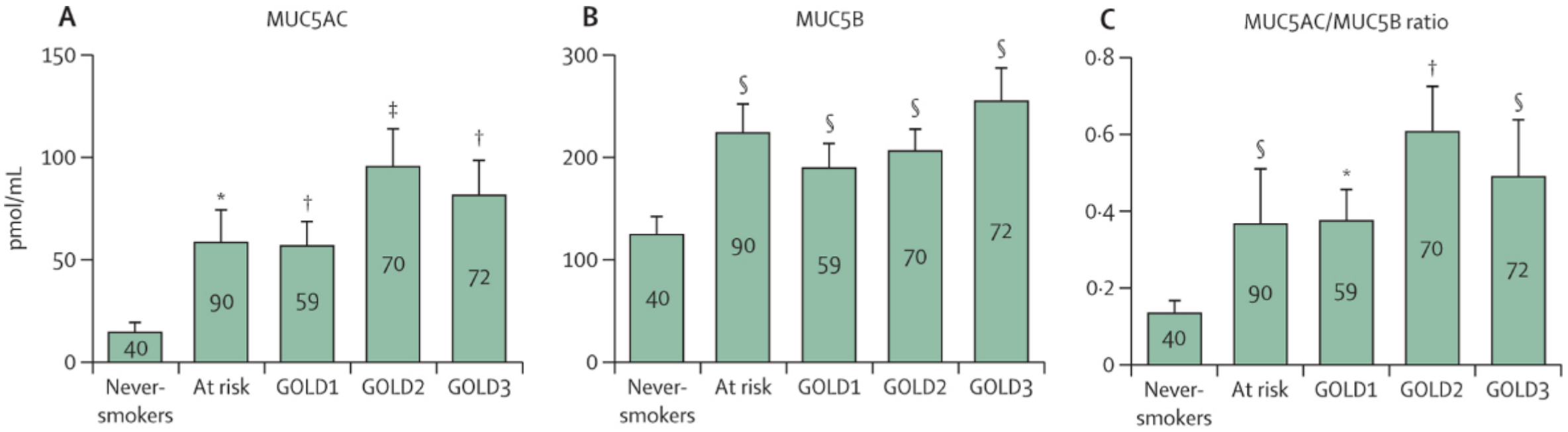
Muco-obstructive Disease - COPD





Dunican. AJRCCM. 2021 Apr 15;203(8):957-968. doi: 10.1164/rccm.202006-2248OC.

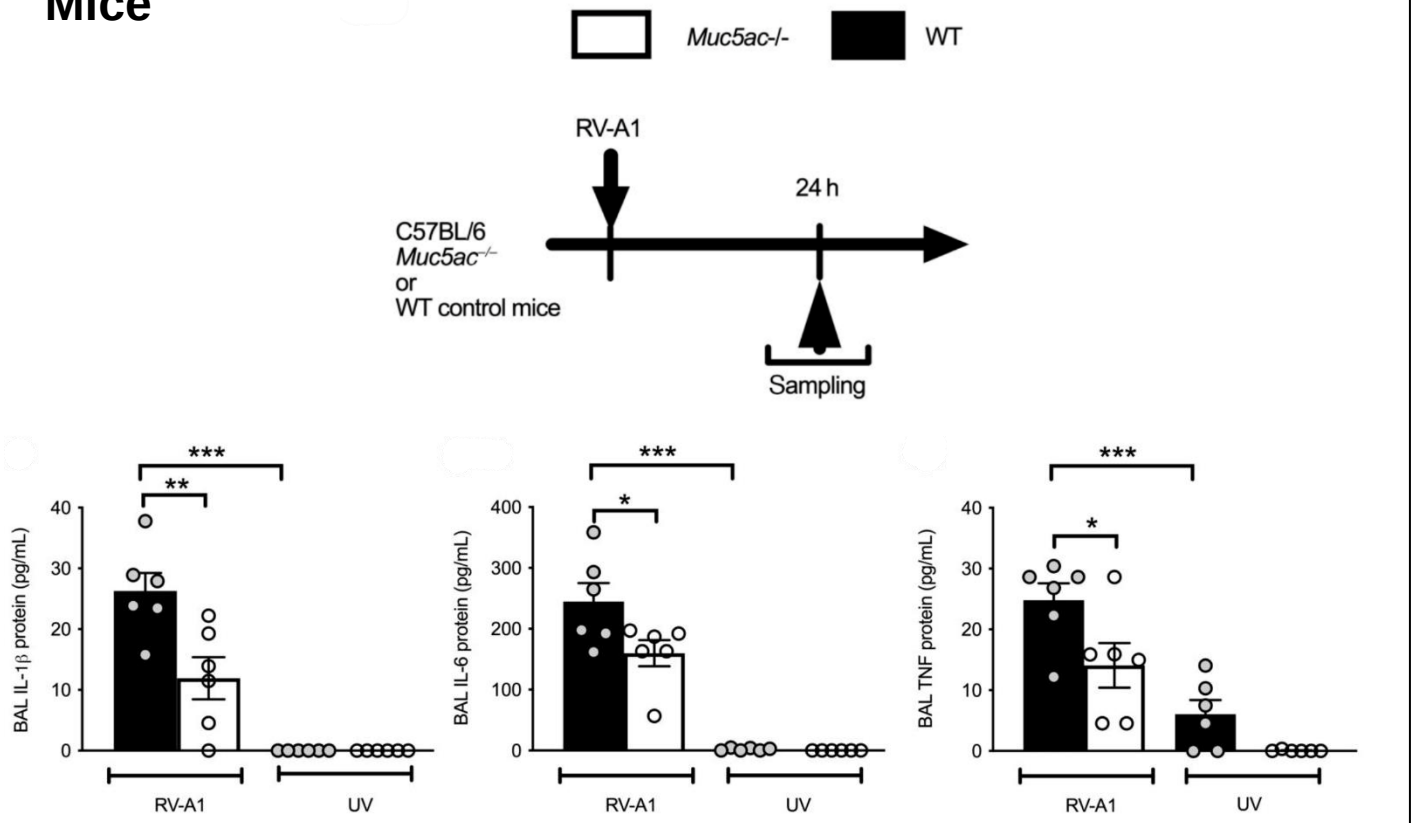
Muco-obstructive Disease - COPD



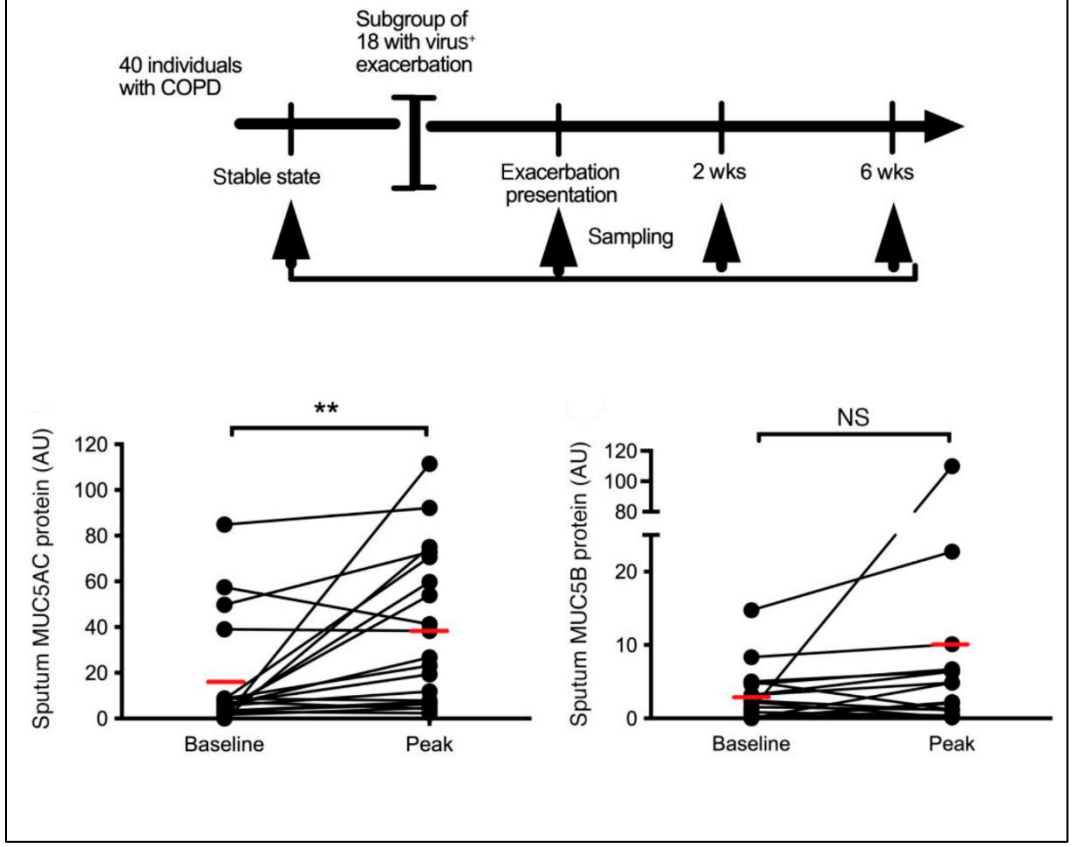
Radicioni Lancet Respir Med. 2021 Nov;9(11):1241-1254. doi: 10.1016/S2213-2600(21)00079-5.

MUC5AC Contributes to Viral Exacerbations of COPD

Mice

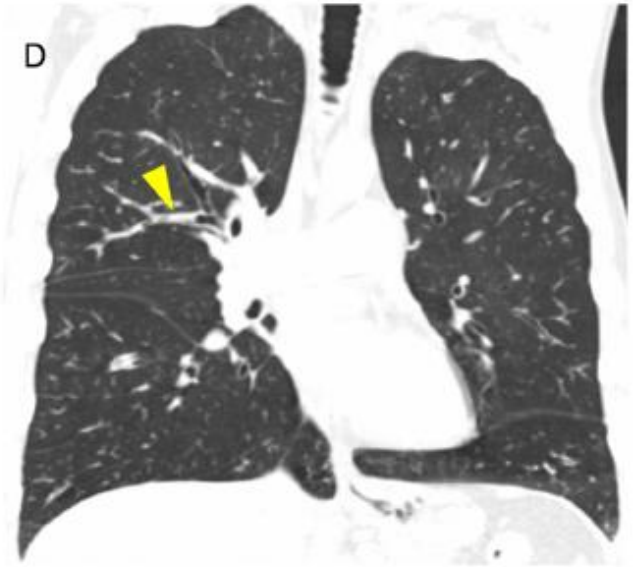


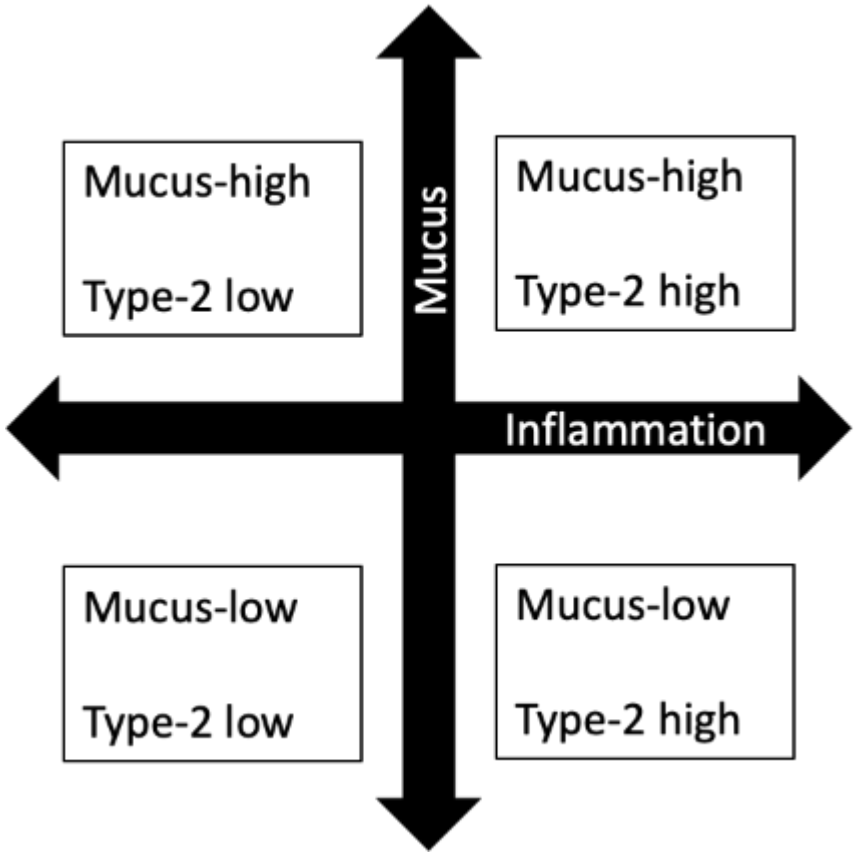
Humans



Singanayagam. J Clin Invest. 2022 Apr 15;132(8):e120901. doi: 10.1172/JCI120901.

Mucus-Directed Therapy Represents a Novel Approach to Obstructive Lung Diseases





Chest CT mucus scores represent a potential mechanism of identifying patients with a high mucus burden:
a "mucus-high" phenotype

Dunican, AJRCCM, 2021.

RAGE and MUC5AC as Treatment Targets

RAGE: Inflammation

Asthma

- RAGE is an upstream component of the asthma inflammatory cascade
- RAGE inhibition results in broad anti-inflammatory effects
- RAGE silencing results in downregulation of targets of current biologic therapies: TSLP, IL-5, etc.
- RAGE regulates inflammatory pathways relevant to both T2-high and T2-low asthma

COPD

- RAGE regulates neutrophilia and airway inflammation

Cystic Fibrosis

- RAGE regulates (hyperglycemia-induced) airway inflammation

MUC5AC: Muco-obstruction

Asthma and COPD

- MUC5AC significantly contributes to muco-obstructive disease
- Mucus plays an important role in airflow obstruction, symptoms, and disease exacerbations
- Mucus-directed therapy represents a significant unmet need and a distinct therapeutic approach compared to anti-inflammatory biologics

Analyst R&D Day June 1, 2023

Pulmonary Clinical Development Path

Javier San Martin, MD

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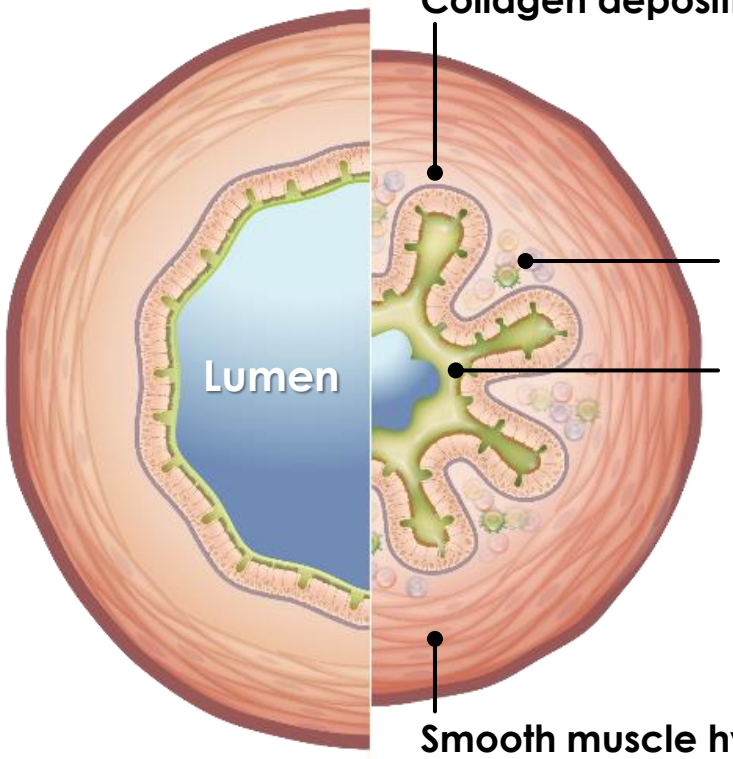
Arrowhead's Pulmonary Therapeutic Platform Addresses Distinct Cell Types Targeting Specific Mechanisms of Lung Disease

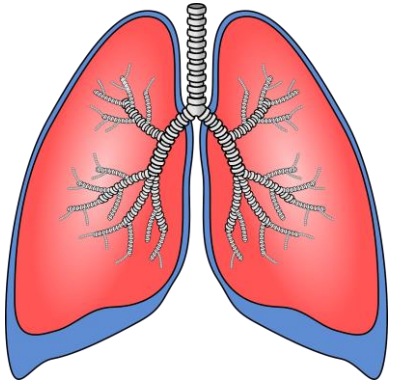
Normal Airway | **Inflamed Airway**

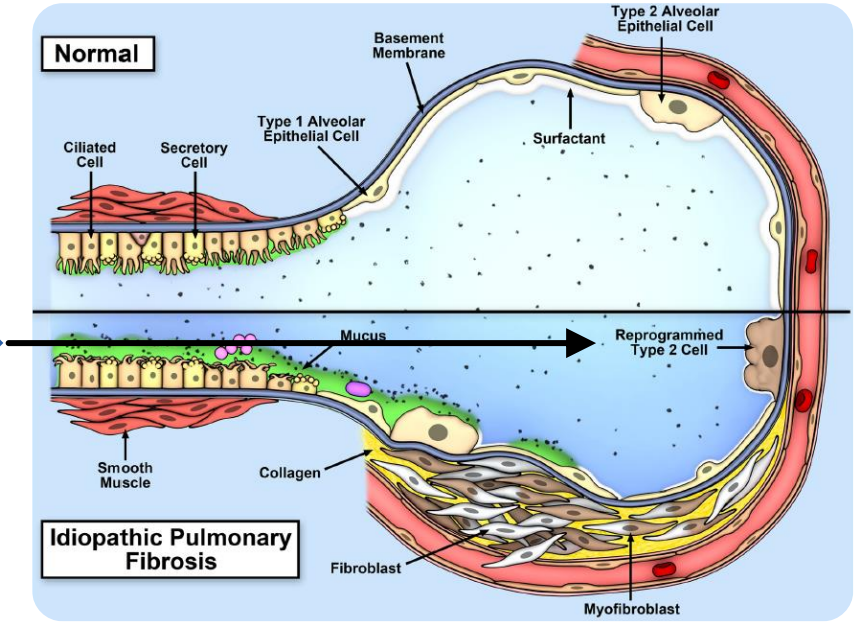


Accumulation of immune cells ← **ARO-RAGE**

Mucus production ← **ARO-MUC5AC**

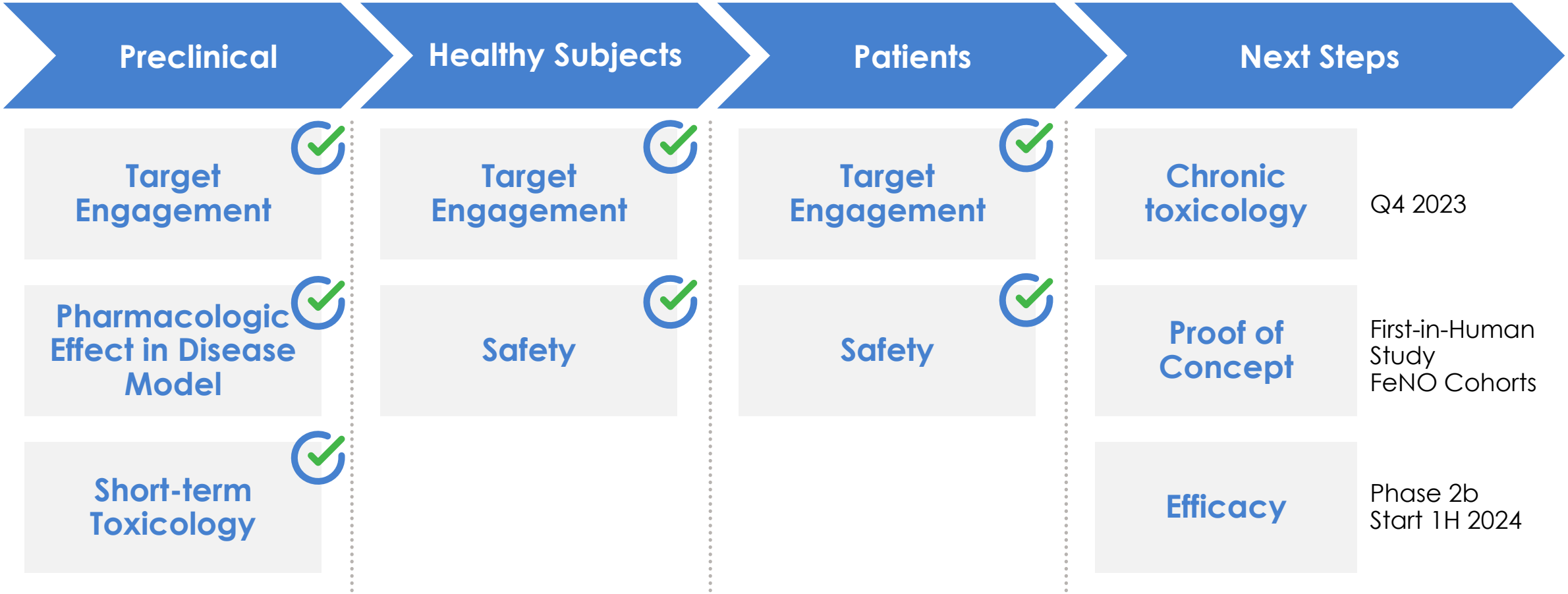
ARO-MMP7 →





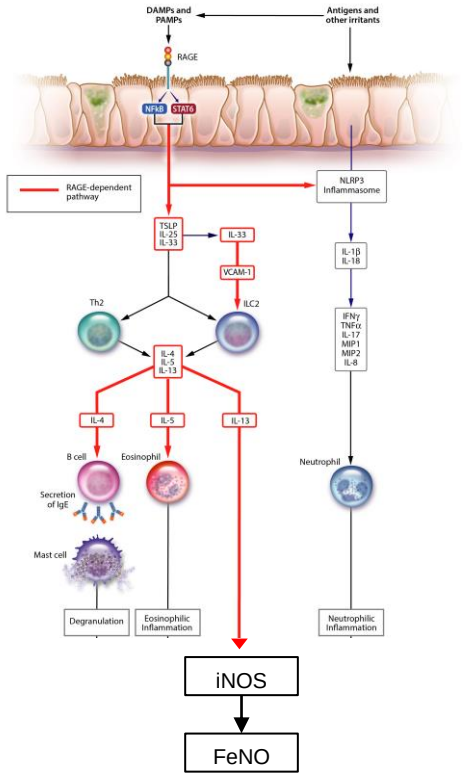
Evans CM, *Physiol Rev*. 2016;96:1567-1591.

ARO-RAGE Has Passed Key Early Development Milestones

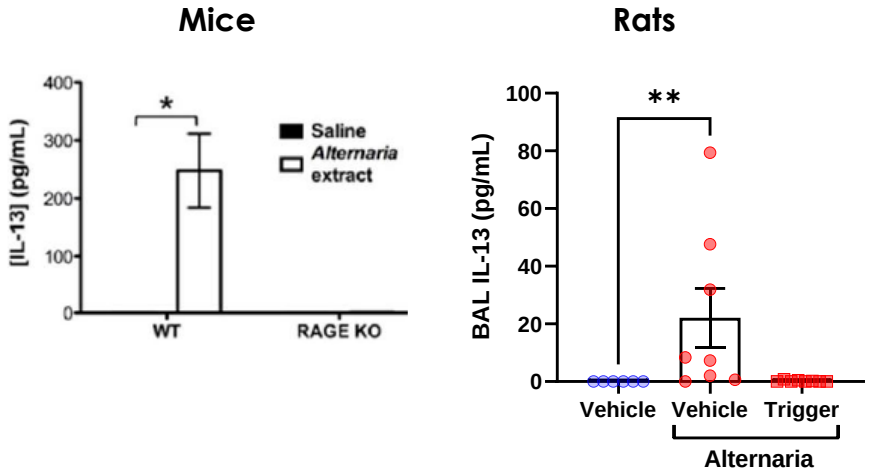


Anti-inflammatory Proof-of-Concept Using FeNO

RAGE Regulates IL-13 Which Drives FeNO



RAGE Silencing Reduces IL-13 in RAGE KO Mice and in Rats Treated with RAGE-Directed RNAi Trigger



FeNO Reduction is a Feature of Anti-inflammatory Biologic Therapies for Asthma

Tezepelumab

42% reduction

Dupilumab

47% reduction

Effect of ARO-RAGE on FeNO can be assessed in first-in-human study

- Enrich for population with high baseline FeNO
- Small sample size (~25 subjects) is adequate to assess for effect similar to that of biologics

1. Oczypok EA, *J Allergy Clin Immunol*. 2015;136:747-756. 2. Menzies-Gow A, *N Engl J Med*. 2021;384:1800-1809. 3. Castro M, *N Engl J Med*. 2018;378:2486-2496.-

Biologic Therapies Provide a Well-Defined Path for Phase 2b in Severe Asthma

Patient Population

- Severe asthma
- Any blood eosinophil level, stratified into high and low groups

Key Outcomes

- Asthma exacerbation rate
- FEV_1
- Quality of life

Trial Size

- Approx. 500 subjects

What We Will Learn

- Effect on asthma exacerbations
- Effect on lung function (FEV_1)
- Effect on symptoms
- Effect on markers of airway inflammation
- Dose selection for Phase 3

Complete First-in-Human Study

Asthma Cohorts

Key Outcomes:

- Anti-inflammatory Proof-of-Concept
- Safety

Phase 2b

Severe Asthma

Key Outcome:

- Efficacy

Phase 3

Severe Asthma

Key Outcome:

- NDA: Initial indication

Additional Indications

COPD

Cystic Fibrosis

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ARO-MUC5AC Has the Potential to Address the Muco-Obstructive Component of COPD

Disease Burden	• 16M COPD Patients • 9M COPD Patients with Chronic Bronchitis • Decreased life expectancy of up to 6 years
Current Therapies	• Bronchodilators: LABA, LAMA • Anti-inflammatory: ICS, azithromycin • Roflumilast

Significant Morbidities	Frequent Exacerbations	Airflow Obstruction	Decreased QoL
Clinical Trial Endpoints	Exacerbation Rate	FEV_1	PRO Measures

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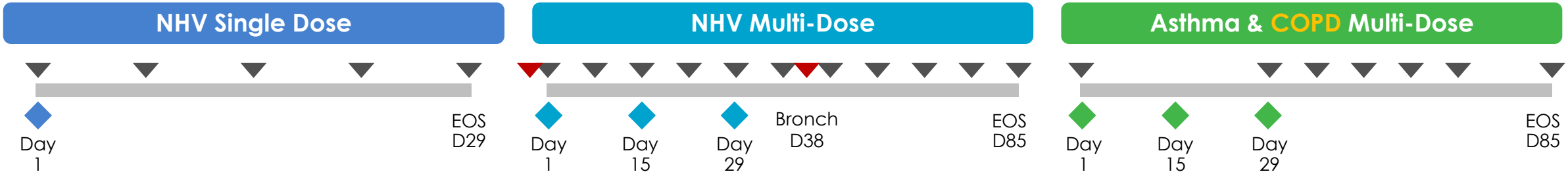
Shavelle RM et al. *Int J COPD* 2009.

Addition of COPD Cohorts to MUC5AC First-in-Human Study (AROMUC5AC-1001)



Population	Healthy Volunteers	Healthy Volunteers	Asthma	COPD
Cohorts	24 mg Cohort 1a → D15 Safety Eval	24 mg Cohort 1b		
	56 mg Cohort 2a → D15 Safety Eval	56 mg Cohort 2b	56 mg Cohort 2c	56 mg Cohort 2d
	108 mg Cohort 3a → D15 Safety Eval	108 mg Cohort 3b	108 mg Cohort 3c	108 mg Cohort 3d
	6 subjects each (4:2)	8 subjects each (6:2)	8 subjects each (6:2)	8 subjects each (6:2)

Mucus Drives Chronic Symptoms in Patients with COPD

COPD is Characterized by Chronic Symptoms That Have the Potential to Respond to ARO-MUC5AC

Breathlessness, Cough, & Sputum Scale (BCSS)

- How much difficulty did you have breathing today?
- How was your cough today?
- How much trouble did you have due to sputum today?

COPD Assessment Test (CAT)

- I never cough vs. I cough all the time
- I have no phlegm in my chest at all vs. My chest is completely full of phlegm
- When I walk up a hill or one flight of stairs I am not breathless vs. When I walk up a hill or one flight of stairs I am very breathless

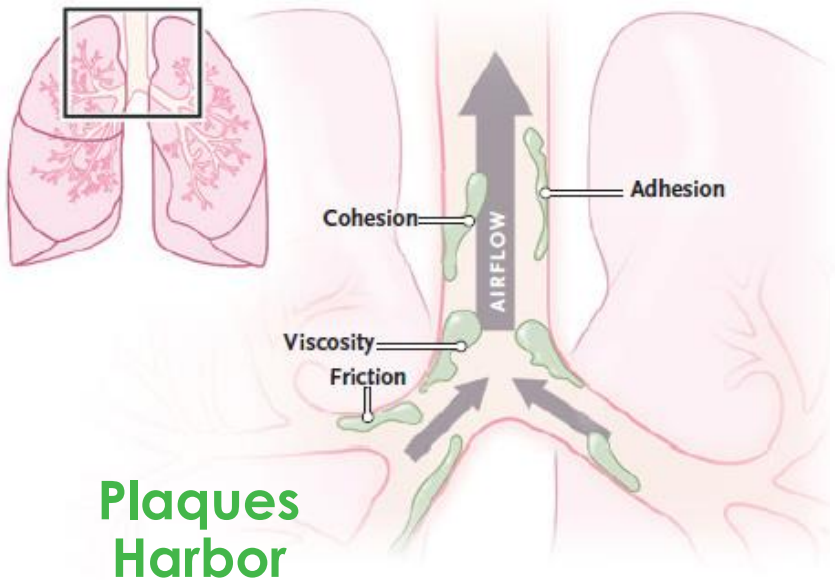
St. George's Respiratory Questionnaire (SGRQ)

- How often do you cough?
- How often do you bring up phlegm?
- How often do you feel shortness of breath?
- My cough makes me tired (True/False)
- My cough or breathing disturbs my sleep (True/False)

Mucus Hypersecretion: A Key Component of the Pathophysiology of COPD & Other Muco-obstructive Lung Diseases

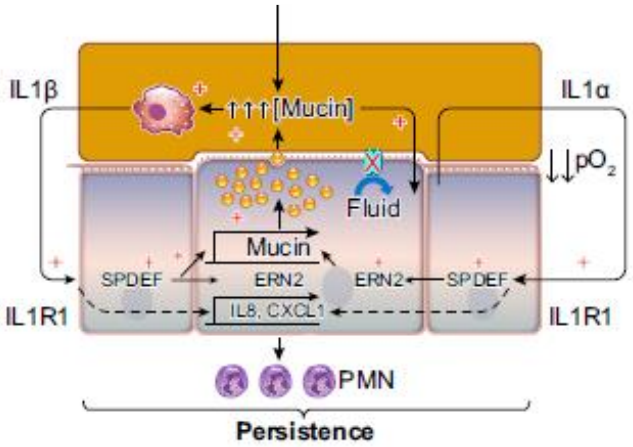
Patients with Excessive Mucus Experience Airway Dysfunction & Are Identifiable with CT Imaging

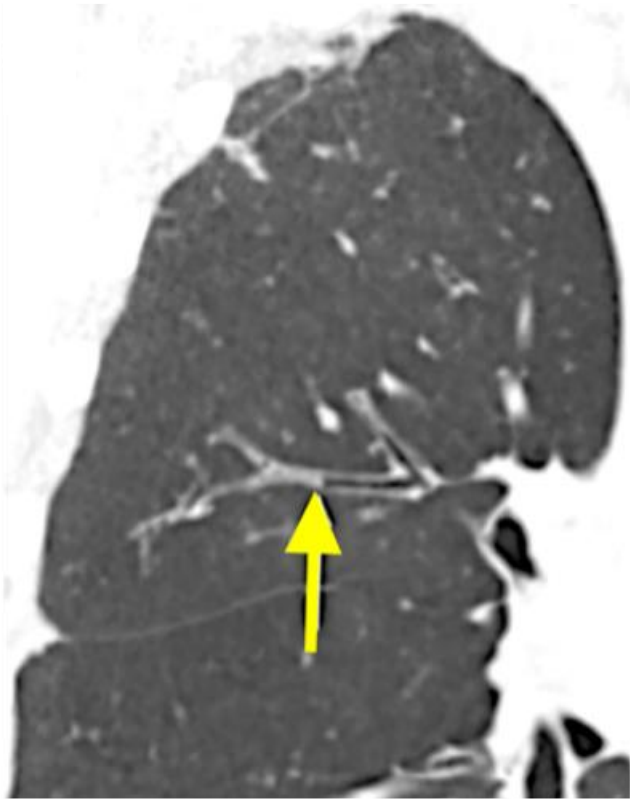
Airflow Blockage



Plaques Harbor Bacteria

Inflammation





1. Hill DB. *Physiol Rev* 2022;102:1757-1836. 2. Boucher RC. *N Engl J Med.* 2019;380:1941-1953. 3. Dunican EM, *J Clin Invest*. 2018;128(3):997-1009.

Phase 2b Will Evaluate Efficacy in COPD, a Muco-Obstructive Disease with Significant Unmet Need

Patient Population

- COPD, with mucus hypersecretion

Key Outcomes

- FEV_1
- Exacerbation rate
- Mucus score
- Quality of life

Trial Size

- Approx. 500 subjects

What We Will Learn

- Effect on airflow (FEV_1)
- Effect on exacerbations
- Effect on symptoms: cough, sputum and shortness of breath
- Effect on mucus plugs
- Patient population for Phase 3: "Mucus-high"
- Dose selection for Phase 3

ARO-MUC5AC Development: Path to Registration in COPD and Other Muco-Obstructive Diseases

Complete First-in-Human Study

Asthma & COPD Cohorts

Key Outcomes:

- Target engagement
- Safety

Phase 2b

COPD, with mucus hypersecretion

Key Outcome:

- Efficacy

Phase 3

COPD, with mucus hypersecretion

Key Outcome:

- NDA: Initial indication

Late Phase

Primary Ciliary Dyskinesia

Key Outcome:

- Efficacy

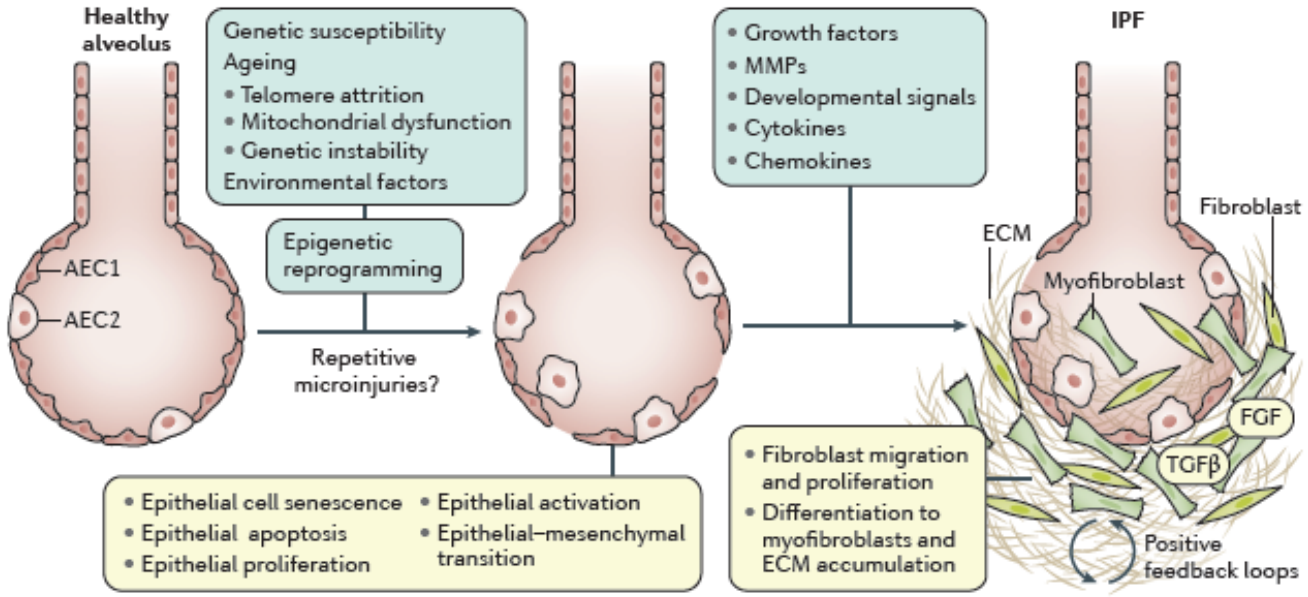
Additional Indications

Non-CF Bronchiectasis

Asthma

Cystic Fibrosis

ARO-MMP7: Addressing Pulmonary Fibrosis at its Source



ARO-MMP7 acts on injured & activated epithelial cells

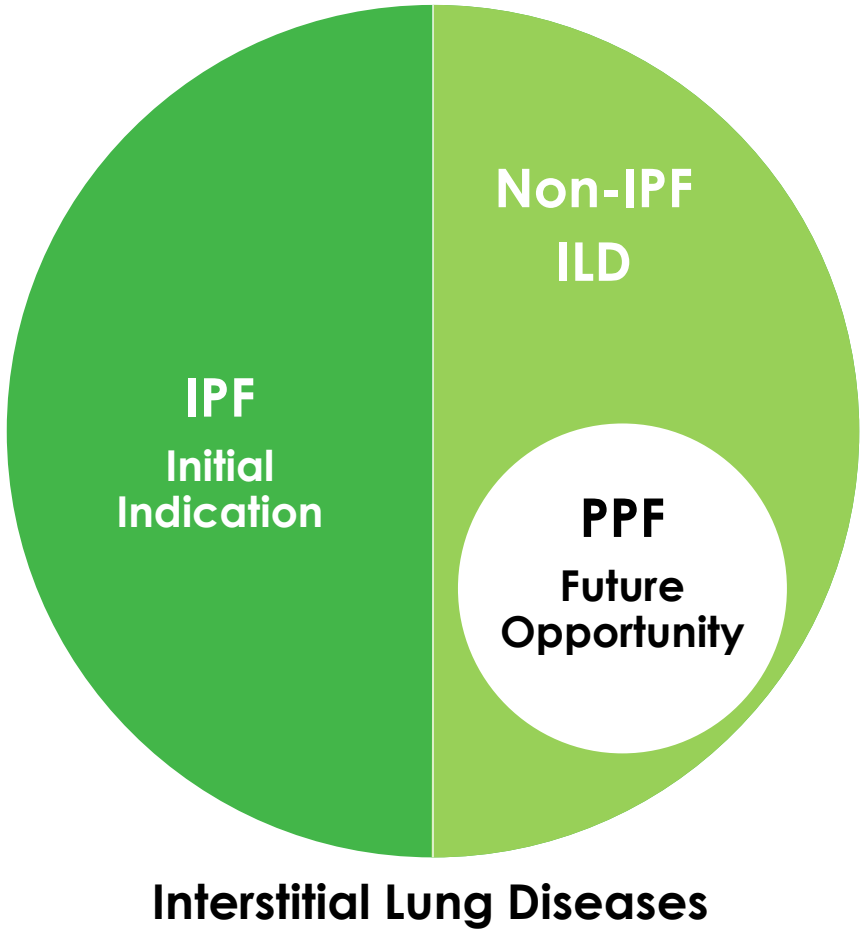
Current therapies act on fibroblasts

Martinez FJ, *Nat Rev Dis Primers*. 2017;3:17074.

Potential for ARO-MMP7:

- Inhibits key mediator released by dysfunctional epithelium
- Use in combination with current therapies
- Avoidance of systemic toxicities seen with current therapies or systemic therapeutic approaches

ARO-MMP7 Development: Path to Registration in IPF and Other Fibrotic Lung Diseases



Progressive Pulmonary Fibrosis (PPF)

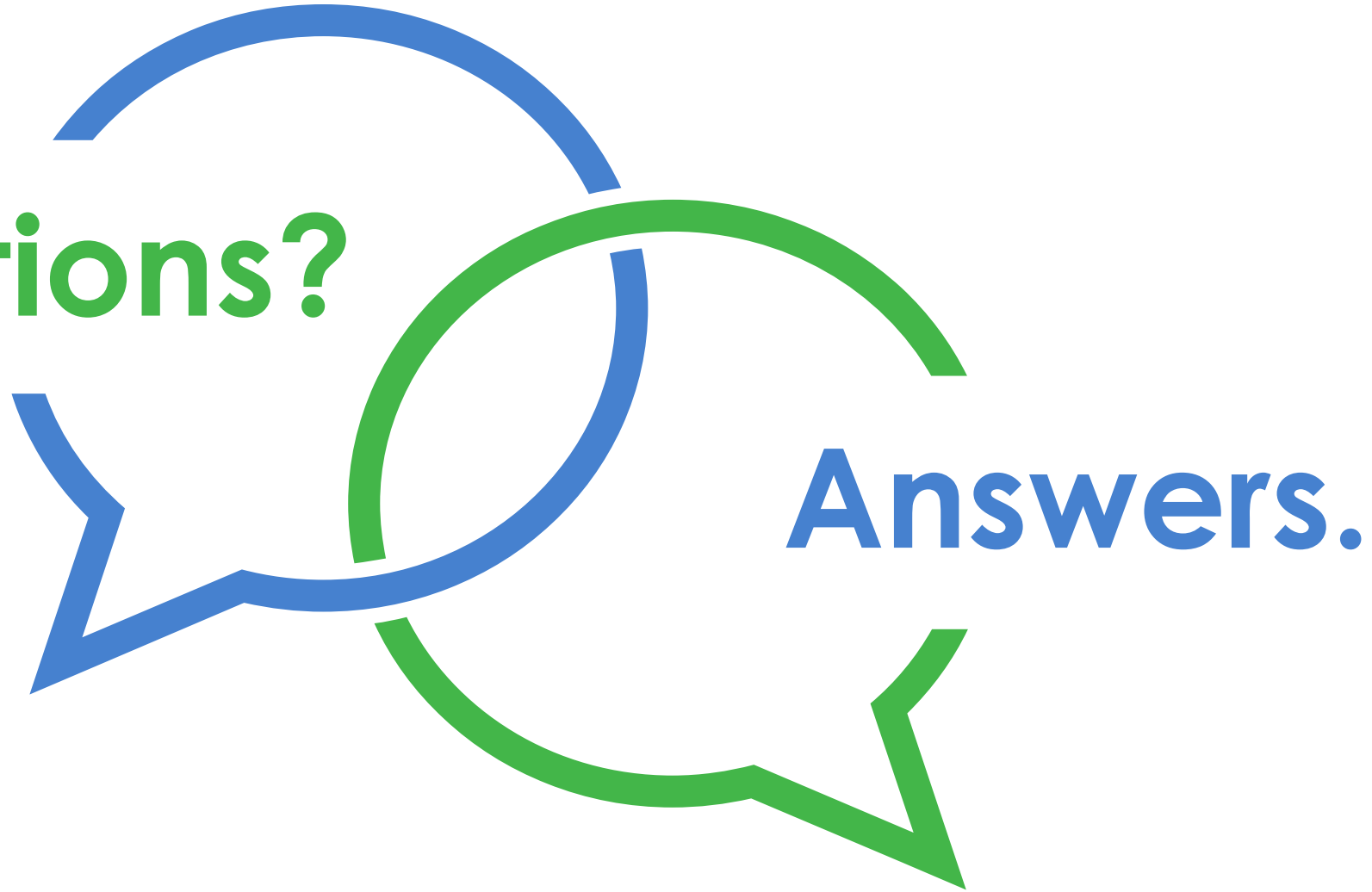
- Pattern of fibrotic disease progression common to many ILDs, such as:
  - Hypersensitivity pneumonitis
  - Connective tissue disease ILD
  - Idiopathic interstitial pneumonias
- IPF-like phenotype, with progressive lung function decline and early mortality
- Track record of anti-fibrotic efficacy across IPF and PPF

Oldham JM, *Eur Respir J*. 2022;59(6):2101396.
Flaherty KR, *N Engl J Med*. 2019;381:1718-1727.

Arrowhead's Pulmonary Portfolio Has the Potential to Address the Underlying Components of Many Lung Diseases

MOA/ ARO-Target	Anti-Inflammation ARO-RAGE	Mucus Depletion ARO-MUC5AC	Anti-Fibrosis ARO-MMP7
Asthma	✓	✓	
COPD	✓	✓	
Cystic Fibrosis	✓	✓	
Non-CF Bronchiectasis		✓	
Primary Ciliary Dyskinesia		✓	
Idiopathic Pulmonary Fibrosis			✓
Interstitial Lung Diseases			✓

Questions?



Answers.

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Analyst R&D Day June 1, 2023

Early Programs: ARO-C3 and ARO-PNPLA3

James Hamilton MD, MBA

arrowhead pharmaceuticals

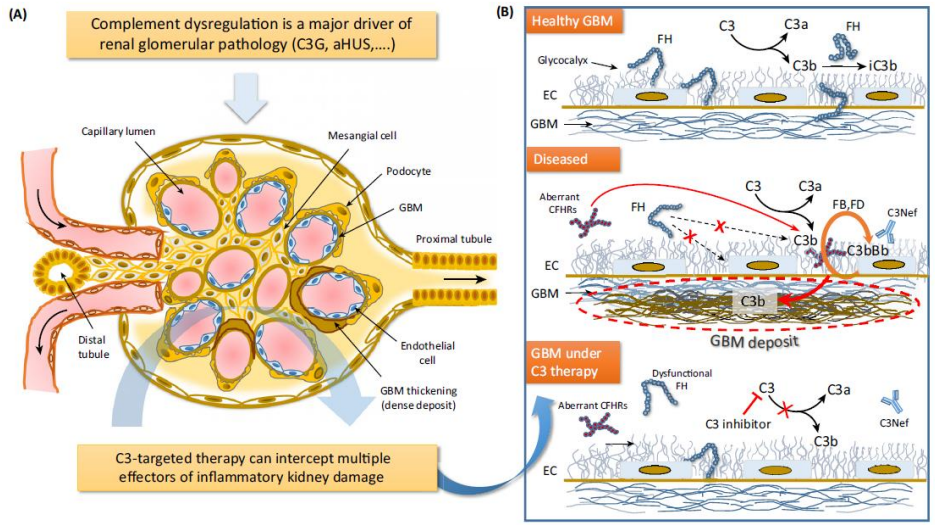
ARO-C3 Development Focus On Complement-mediated Renal Diseases with Remaining High Unmet Need

C3 Glomerulopathy (C3G)

- ~6,000 patients in US **(~50,000 globally)**
- **Half** of patients progress to **end-stage renal** disease in 10 years
- Post-transplant **recurrence in >50%** of patients
- No approved therapies

C3 is a promising target for C3G

- Disease entirely driven by excess C3 glomerular deposition



IgA Nephropathy (IgAN)

> 1million patients globally

- Accounts for ~40% of all cases of glomerulonephritis
- Up to 60% of patients reach end-stage renal disease in 10 years, averaging about 1.5% to 2% per year

Alternative pathway (AP) activation is implicated in glomerular injury in IgAN

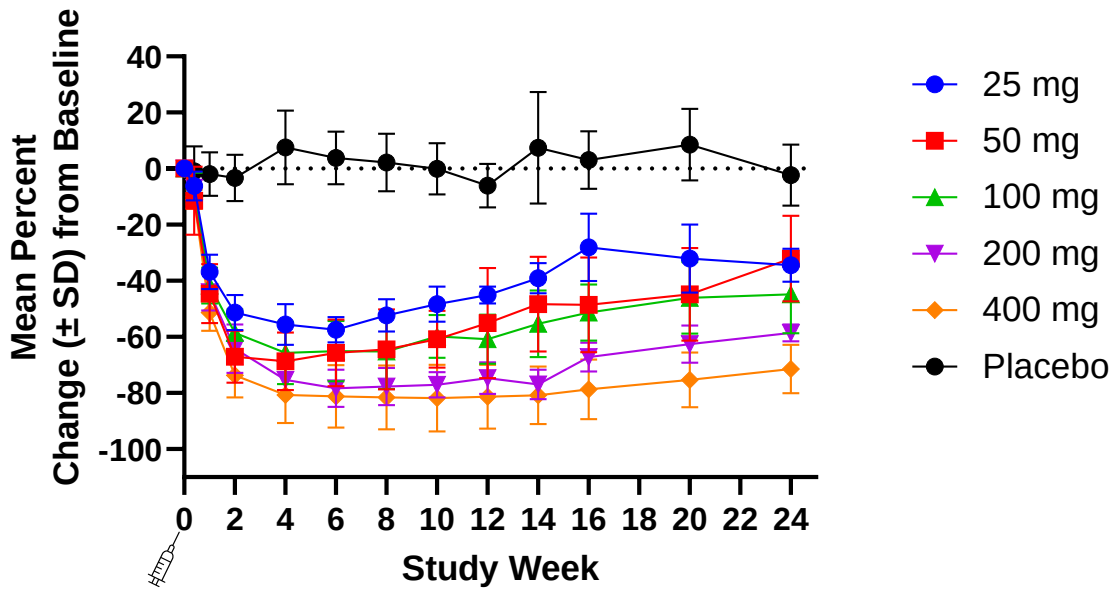
- > 90% of IgAN biopsies have evidence of AP activation
- Increased C3 breakdown products in serum of IgAN patients
- Genetic studies support AP overactivity in disease pathogenesis (Rizk, 2019)

Urine protein reduction could be a pathway for accelerated regulatory approval

Mastellos DC et al., *Trends Immunol*. 2017 Jun;38(6):383-394.
Rizk et al., *Front Immunol*. 2019;10:504.

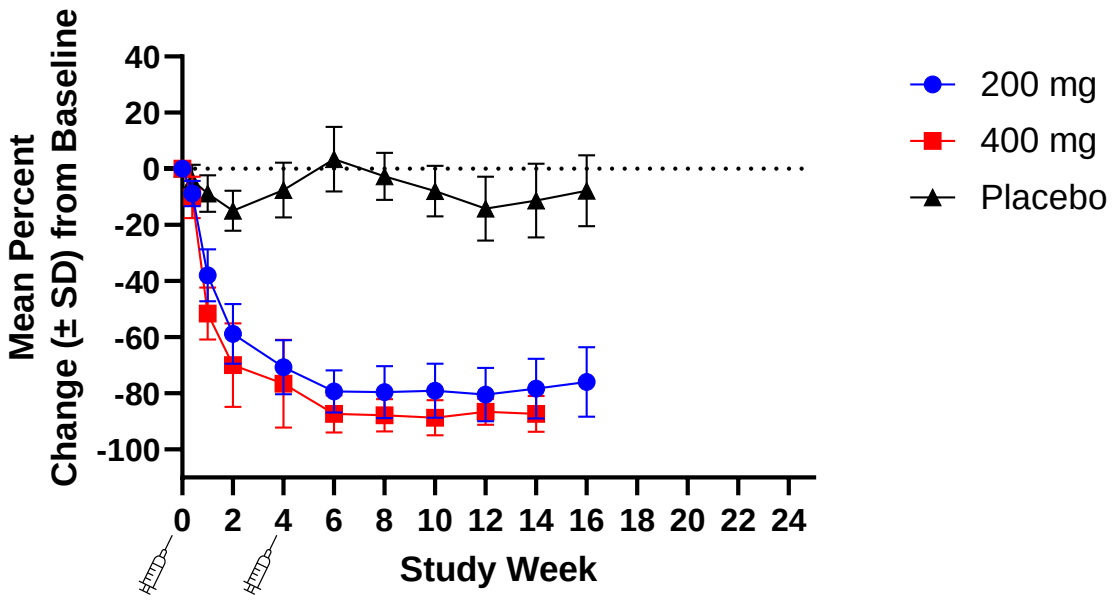
ARO-C3 Reduces C3 in Healthy Volunteers Up to 88% After Two Doses

Single Dose Cohorts



Up to **82%** mean reduction was sustained through week 16 at 400mg

Multiple Dose Cohorts



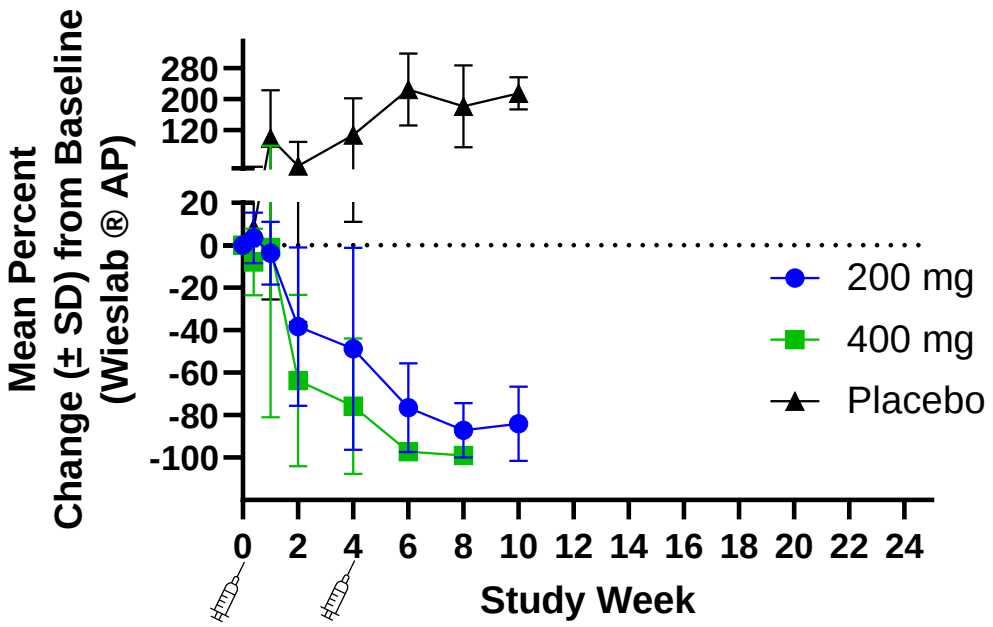
Up to **80%** and **88%** mean reductions in C3 sustained through week 12–16 at 200 mg and 400 mg, respectively

Data cut: 13 Apr 2023

ARO-C3 Achieves >90% Reduction in Functional Alternative Pathway Activity

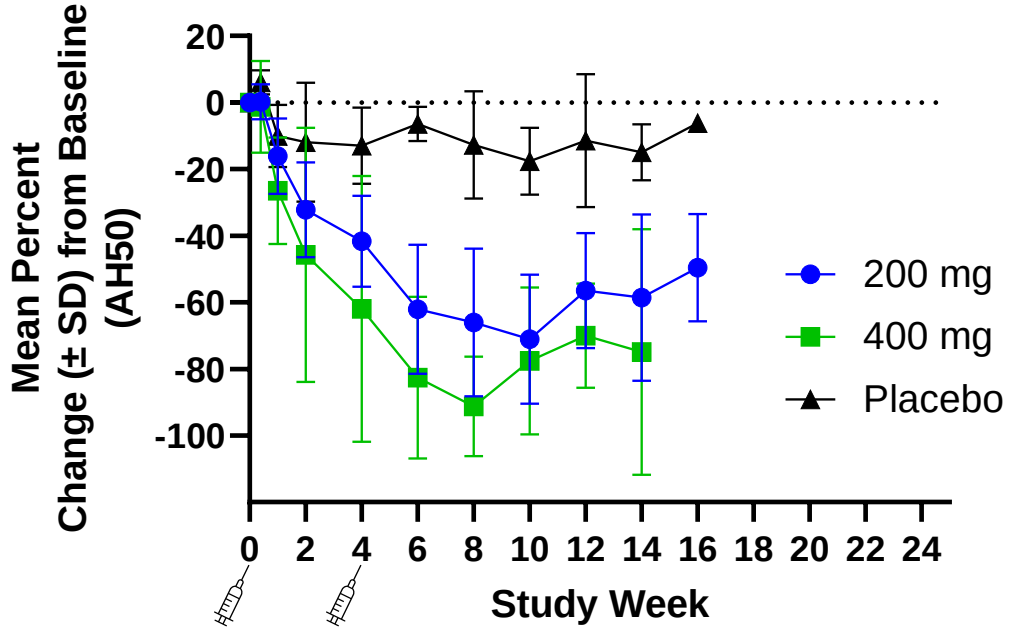
Measured by Wieslab® AP and AH50

Multiple Dose Cohorts



87% and **99%** mean reduction in Wieslab® AP at week 8 at 200 and 400mg, respectively

Multiple Dose Cohorts



66% and **91%** mean reduction in AH50 by week 8 at 200 mg and 400 mg, respectively

Wieslab results were calculated per the assay manufacturer's recommended NC/PC (Negative Control/Positive Control) Ratio
Data cut: 13 Apr 2023

ARO-C3 Healthy Volunteer Safety Profile Supports Further Development

Preferred Term # (%)	Pooled Placebo (n=14)	Pooled Active (n=28)
Headache	5 (36%)	13 (46%)
Upper Resp Infection	4 (29%)	5 (18%)
Injection Site AEs	0	5 (18%)
Seasonal Allergy	0	4 (14%)

- No SAEs or dropouts due to AEs.
- No dose limiting toxicity
- No infections with encapsulated organisms
- Most common AEs include headache > upper respiratory infection > injection site AEs > seasonal allergy

Data cut 15 Jan 2023

AROC3-1001 Study Summary and ARO-C3 Next Steps

- ARO-C3 achieved mean C3 knockdown of 88% with duration to justify quarterly or less frequent dosing
- Favorable safety profile
- Corresponding reductions in hemolytic and functional activity of alternative pathway should be competitive with other AP-targeted therapeutics
- Small volume, infrequent injections with long duration of effect can provide advantages over therapies requiring large dose SQ infusions or oral BiD dosing
- C3G and IgAN cohorts are open for enrollment in the AROC3-1001 study

Analyst R&D Day June 1, 2023

ARO-PNPLA3 Clinical Summary and Development Plan

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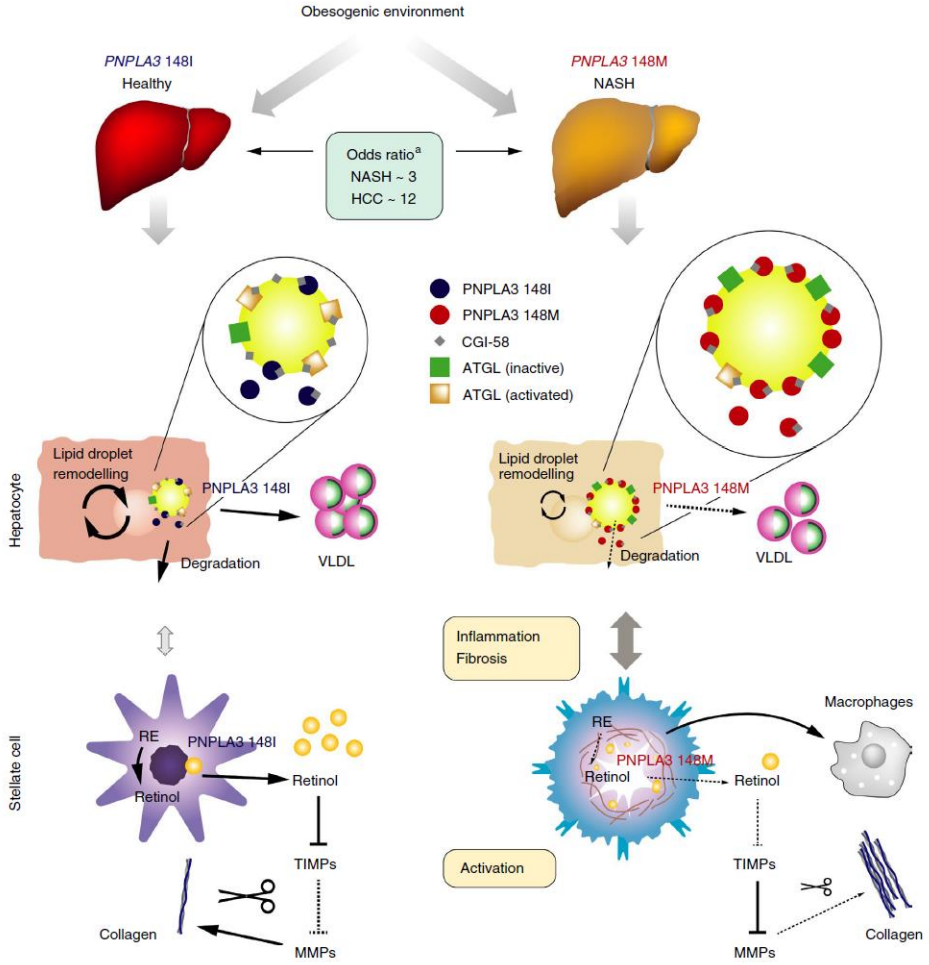
PNPLA3 is a Well-suited Target for RNAi Therapeutic Approach

- Normally, patatin like phospholipase domain containing protein 3 (PNPLA3) sits on lipid droplets and acts as a lipase in hepatocyte
- I148M variant gene codes for a non-functional protein, resistant to proteasomal degradation
- Accumulates on lipid droplets and blocks other lipases from metabolizing TG stored in lipid droplets
  - Leads to hepatic steatosis, inflammation, NASH, and ultimately liver cirrhosis
- Difficult to target with other treatment modalities:
  - Intracellular, difficult to target with Mab
  - Non-functional protein without active catalytic site, difficult to modulate with small molecule

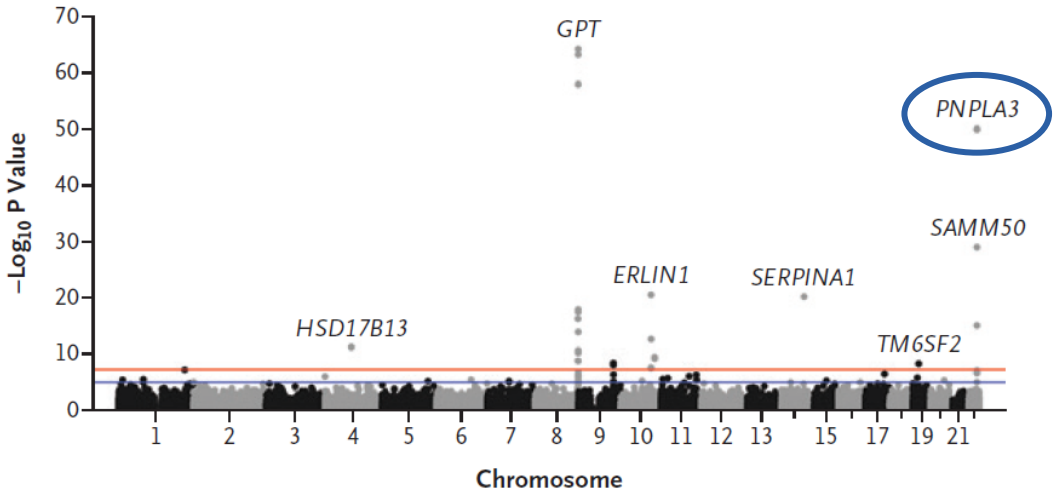


Carlsson et al., *Aliment Pharmacol Ther.* 2020 Jun;51(12):1305-1320.

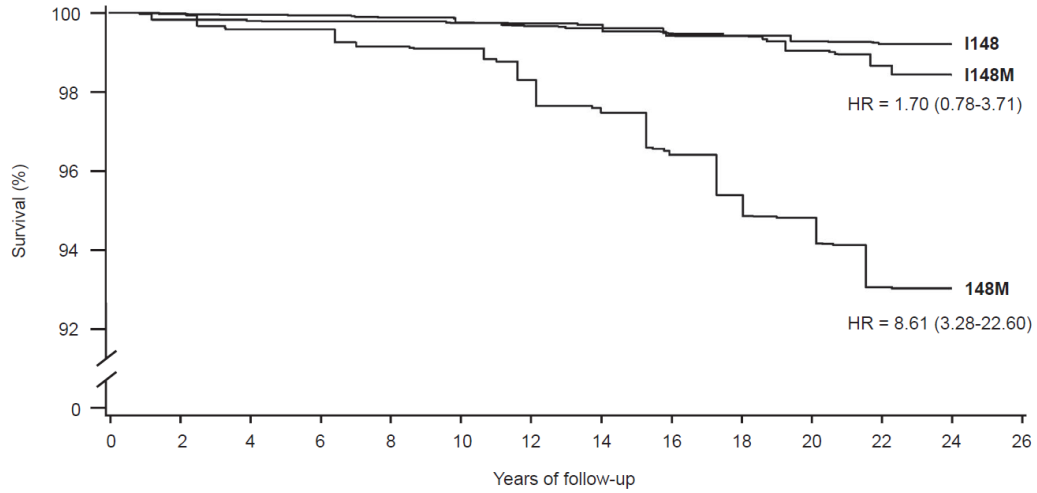
PNPLA3 I148M Variant is an Independent Risk Factor for NASH and Liver Disease Mortality

- I148M is associated with liver steatosis[1]
- I148M is associated with increased ALT[2]
- I148M is associated with progression of NAFLD, NASH and NAFLD-related hepatocellular carcinoma [3]
- I148M **homozygosity** is associated with a large increase in liver disease mortality in the US population [4]

Alanine Aminotransferase



Cumulative Liver Disease Mortality by PNPLA3 I148M Genotype



[1]Romeo et al., *Nat Genet.* 2008 Dec;40(12):1461-5.
[2]Abul-Husn et al., *N Engl J Med.* 2018 Mar 22;378(12):1096-1106.
[3]Salameh et al., *J Clin Transl Hepatol.* 2016 Sep 28;4(3):175-191.
[4]Unalp-Arida, *Hepatology.* 2020 Mar;71(3):820-834.

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NASH Patients with PNPLA3 Polymorphism Constitute a High Risk, Genetically Defined Sub-Population

NAFLD global prevalence is 25%

- **1.6B World Wide / 85M US[1]**

NASH global prevalence is 7% to 30% of NAFLD

- **312M World Wide / 15M US[1]**

NASH patients with PNPLA3 polymorphism

- Allelic frequency is 45%
  - **140M World Wide / 6.6M US**
- Homozygous PNPLA3 I148M
  - **12.5M in China, Japan, Germany, Italy, UK and US[2]**
  - **4.5M in US alone[2]**

NASH Patients With PNPLA3 I148M Polymorphism Present a Sizeable Genetically Defined Population Amenable to a Precision Medicine Approach with RNAi Therapy

[1]Younossi et al., *Diabetes Care*. 2020 Feb;43(2):283-289.
[2]Carlsson et al., *Aliment Pharmacol Ther.* 2020 Jun;51(12):1305-1320.

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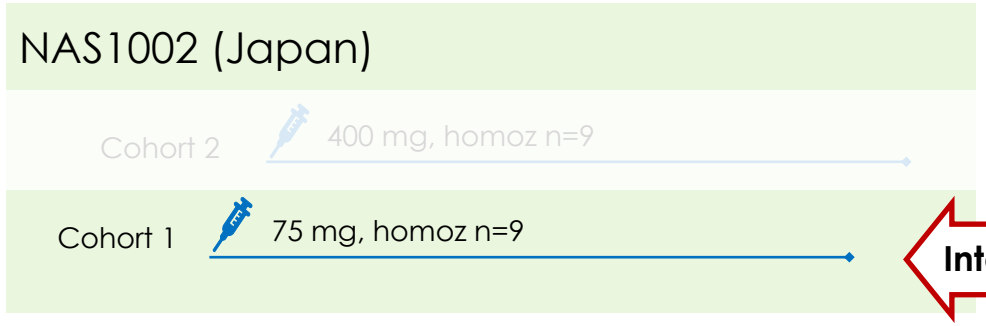
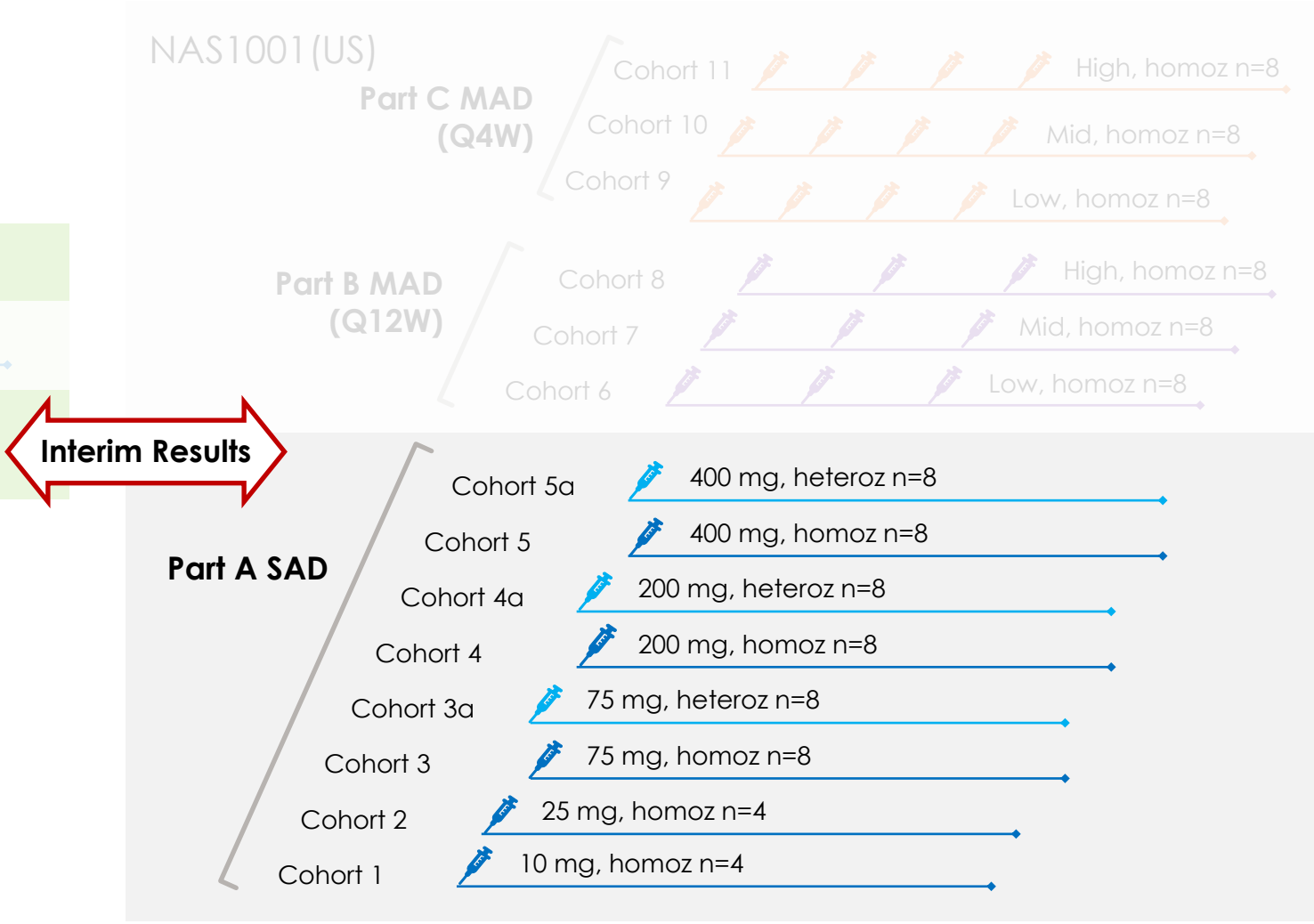
ARO-PNPLA3 Phase 1 Study Design

- Single and multiple ascending dose phase 1 study in US (NAS1001)
- Single dose study in Japanese subjects (NAS1002)





- Patient population
  - NAFLD ≥8% liver fat by MRI-PDFF (except cohorts 1, 2, and sentinels in cohorts 3–5a)
  - Confirmed homozygous and heterozygous I148M mutation
  - ALT or AST ≤ 1.5 X ULN
  - No significant hepatic fibrosis by FibroScan (LSM ≥ 7.6 kPa excluded)

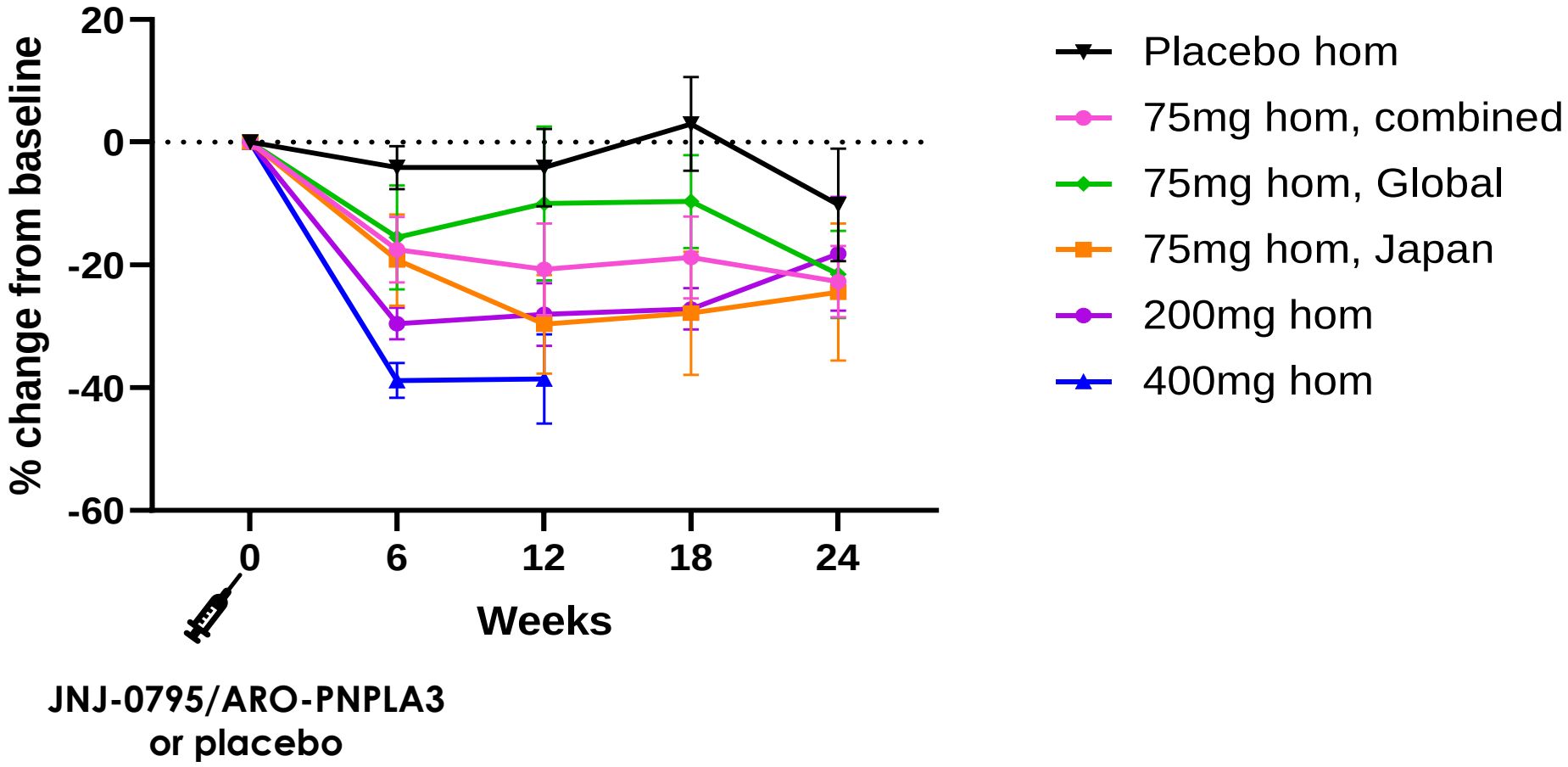
ARO-PNPLA3 Interim Ph.1 Study Demographics (NAS1001, US and NAS1002, JP)

	US Homozygous n = 31	US Heterozygous n = 24	Japan Homozygous N=9
Gender			
• Males, n (%)	13 (41.9)	11 (45.8)	8(88.9)
• Females, n (%)	18 (58.1)	13 (54.2)	1(11.1)
Age (years)			
• Mean	48.7	51.1	48.9
• Min, Max	24, 61	32, 65	38, 61
Ethnicity			
• Hispanic, n (%)	29 (93.5)	24 (100)	0(0)
BMI (kg/m^2)			
• Mean	30.4	32.5	28.96
• Min, Max	19.4, 39.1	19.4, 38.8	25.6, 36.8
Liver Fat Content (%)			
• Mean	15.1	10.9	18.1
• Min, Max	1.4, 36.7	2.1, 25.9	8.7, 30.3
• n<8%/n>8%	6/25*	6/18	0/9

* 4 subjects with liver fat <8% were in Cohorts 1 and 2, 1 in Cohort 3 and 1 in Cohort 5

ARO-PNPLA3 Produced Dose-dependent Reductions in Liver Fat in Homozygous Subjects in Phase 1 Study

Mean Percent Change in Liver Fat from Baseline (+/- SEM)



ARO-PNPLA3 Shows Favorable Overall Safety Profile To Date

- No apparent treatment emergent increases in triglycerides or LDL-cholesterol
- No Severe or Serious AEs
- No AEs leading to treatment or study discontinuation
- No clinically meaningful trends observed in any of the following:
  - Vital signs
  - Physical Examination
  - ECGs
  - Safety Labs
- Mostly mild AEs observed, No evidence of increased gastrointestinal AEs

ARO-PNLPA3 Clinical Development Plan

- Continue development of ARO-PNPLA3 in subjects with homozygous PNPLA3 I148M mutation
- **Phase 2a study:** Evaluate multiple doses (D1, 85) in patients with NAFLD and liver inflammation / elevated baseline ALT
  - Evaluate the effect of ARO-PNPLA3 on liver fat reduction, ALT, other non-invasive biomarkers (e.g. FibroScan, ELF, Pro-C3)
- **Phase 2b study:** Patients with NASH, homozygous for PNPLA3 I148M
  - Evaluate effect on histological endpoints (inflammation, ballooning, steatosis, fibrosis)

Analyst R&D Day June 1, 2023

Treatment of Lipid Disorders Landscape: Unmet Need and Residual Risk

Ira Goldberg, MD

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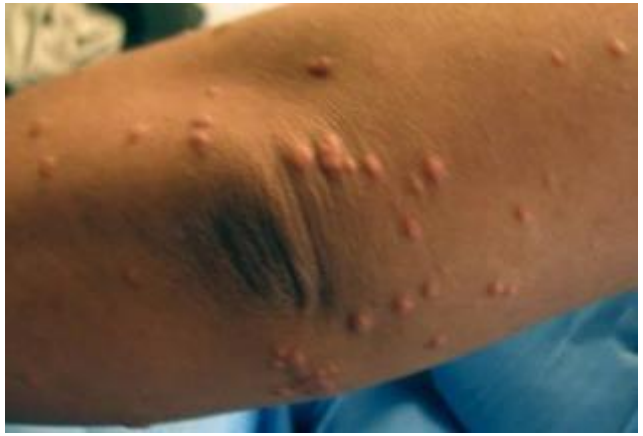
NYU Langone Health

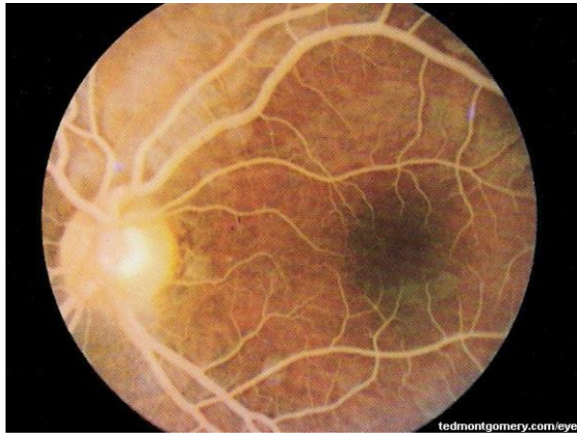
TREATMENT OF LIPID DISORDERS LANDSCAPE: UNMET NEED AND RESIDUAL RISK

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

Physical Findings of Severe Hypertriglyceridemia Associated with Recurrent Pancreatitis

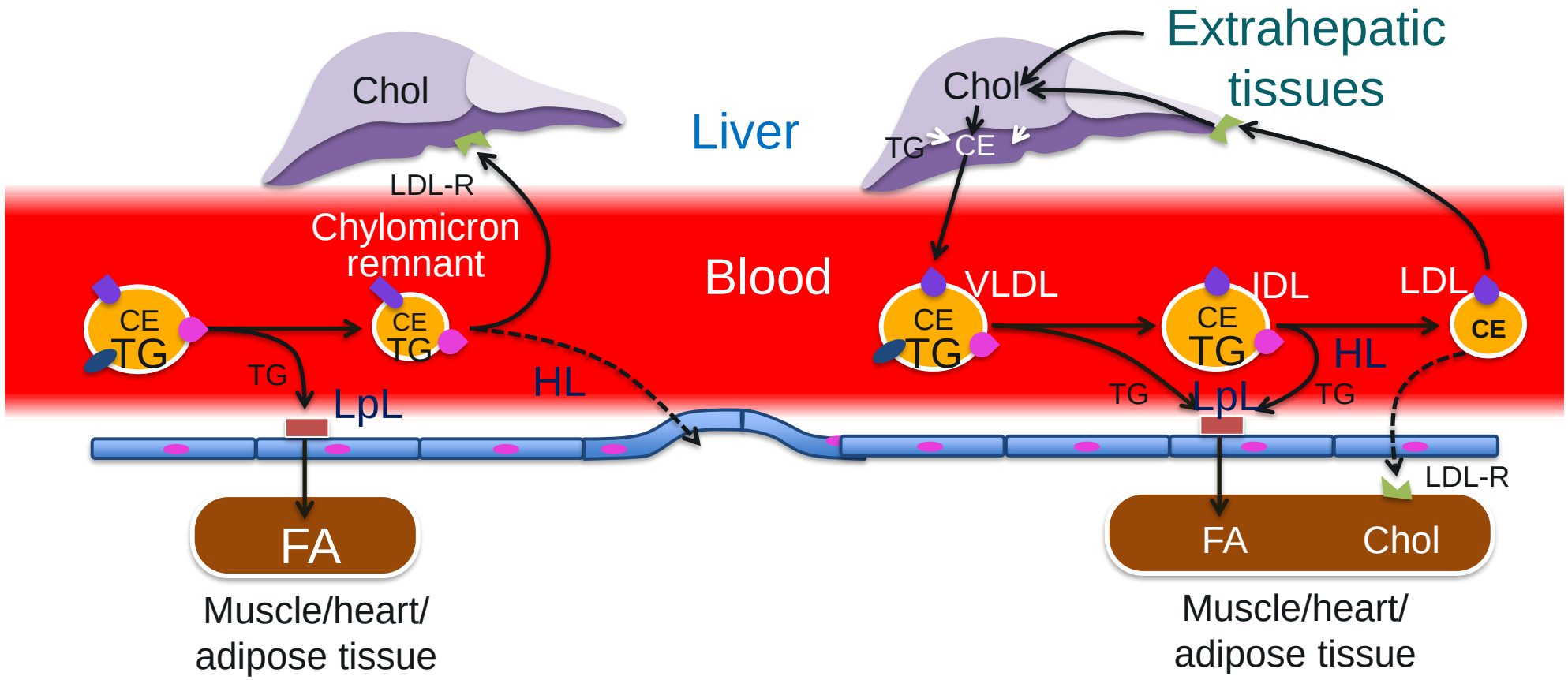


Merola et al., *Dermathology Online Journal* **2008**

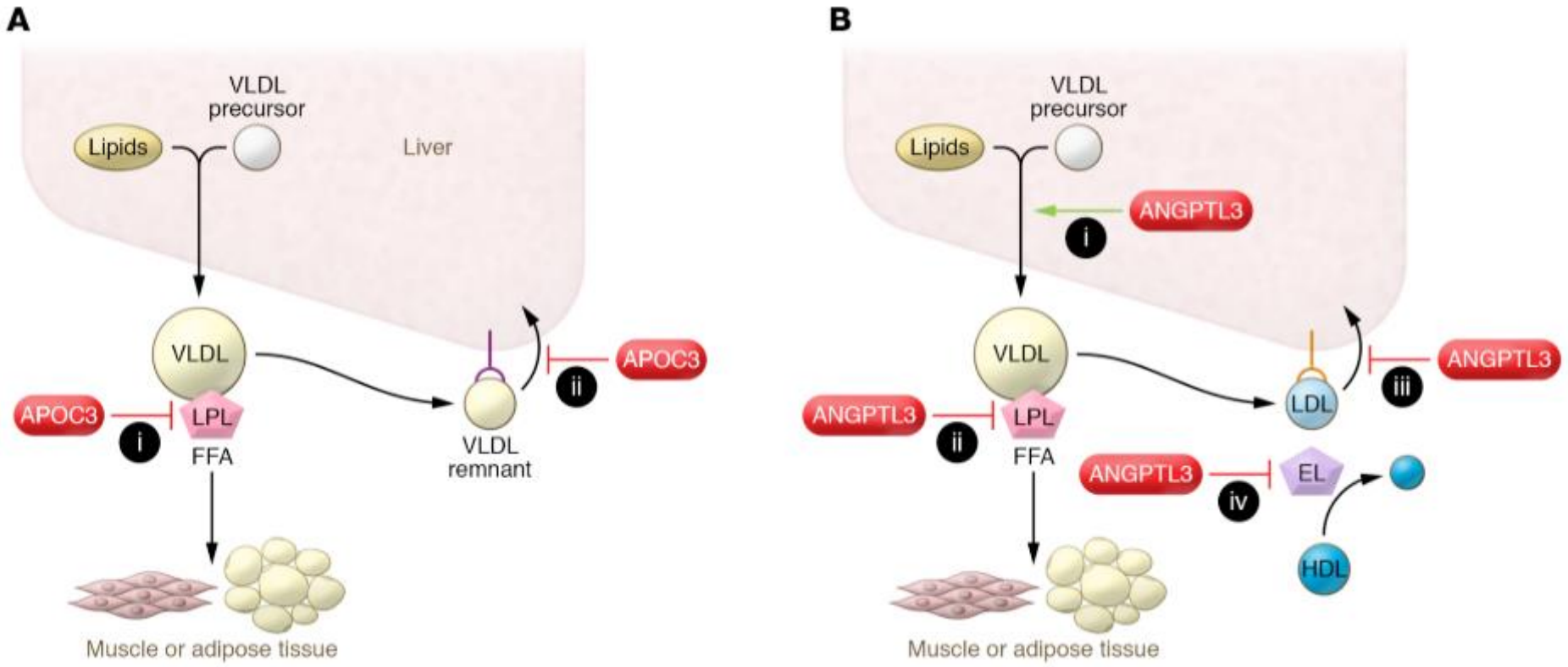


Lipemia Retinalis

Chylomicrons and VLDL Compete for LpL



ApoC3 and ANGPTL3 inhibition reduces triglyceride



Addressing dyslipidemic risk beyond LDL-cholesterol

Alan R. Tall,[1] David G. Thomas,[1] Ainara G. Gonzalez-Cabodevilla,[2] and Ira J. Goldberg[2] J Clin Invest 132:2022, PMID 34981790

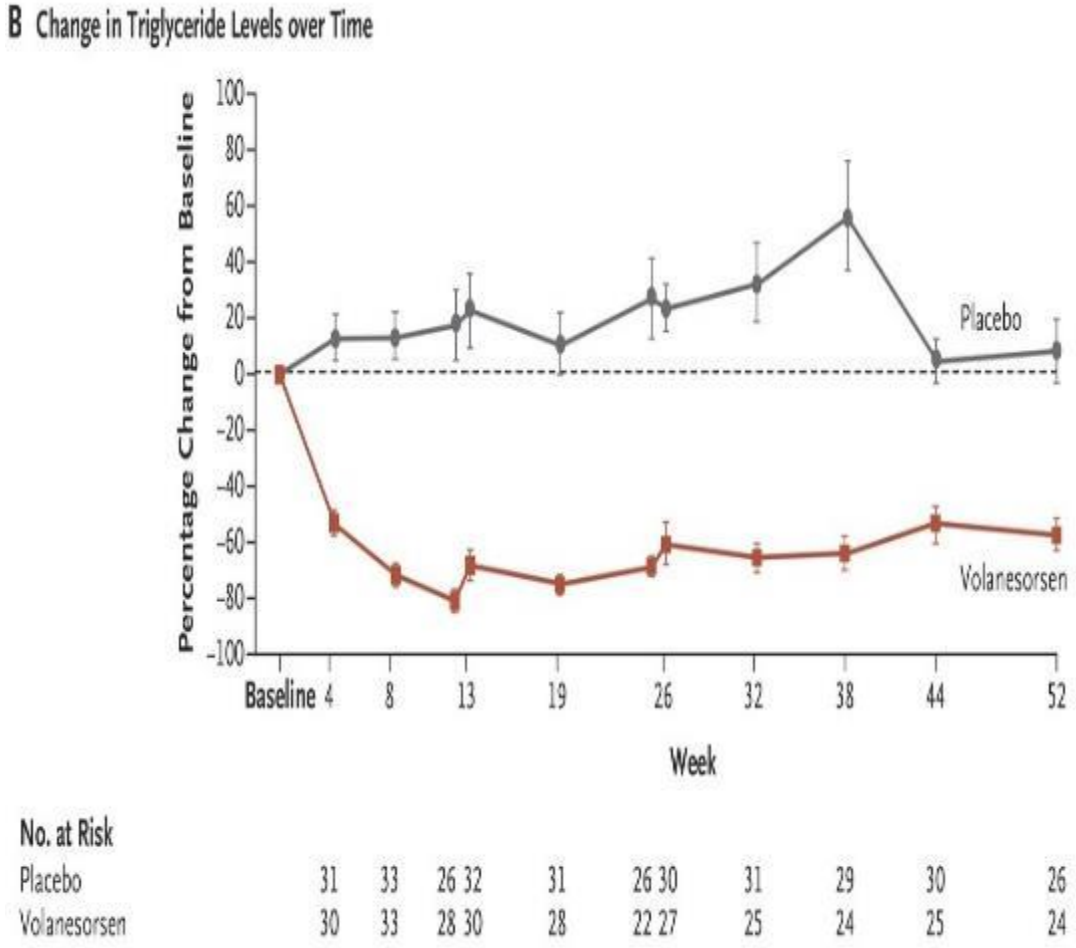
ApoC3

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]

1702 12 DECEMBER 2008 VOL 322 SCIENCE www.sciencemag.org

ApoC3 ASO reduced TG >60% in LpL Deficiency



Subjects with genetic hyperlipidemia

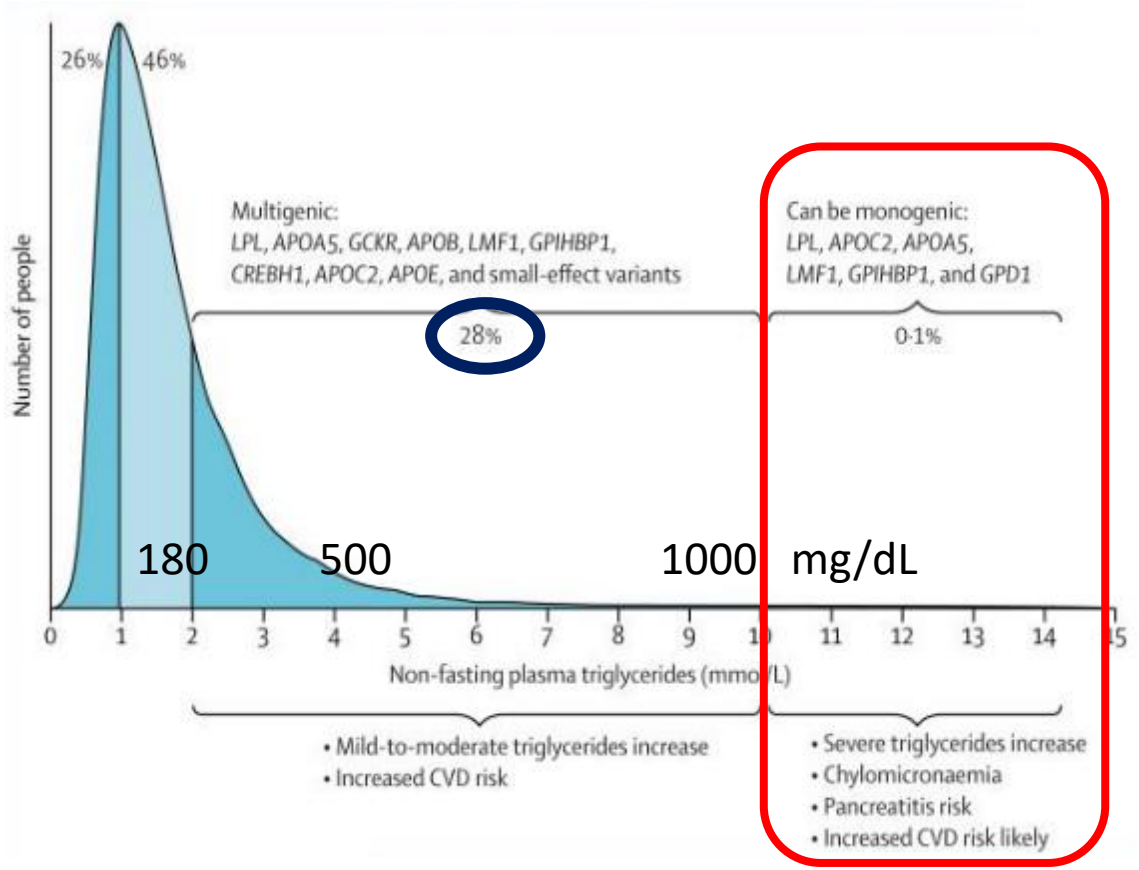
Baseline TG 2152 mg/dL

Pancreatitis 12 episodes (3 patients) versus 1

Side effect: reduced platelet counts

* NEJM 381:531-542; 2019

Hypertriglyceridemia and genetics



Hegele et al, Lancet Diabetes Endocrinology, 2014; 2: 655-66

Hyperlipidemia in Coronary Heart Disease

I. LIPID LEVELS IN 500 SURVIVORS OF MYOCARDIAL INFARCTION

JOSEPH L. GOLDSTEIN, WILLIAM R. HAZZARD, HELMUT G. SCHROTT, EDWIN L. BIERMAN, and ARNO G. MOTULSKY with the assistance of MARY JO LEVINSKI and ELLEN D. CAMPBELL

From the Departments of Medicine (Division of Medical Genetics, University Hospital, and Division of Metabolism and Gerontology, Veterans Administration Hospital) and Genetics, University of Washington, Seattle, Washington 98195

"These results raise the possibility that hypertriglyceridemia may be as an important a risk factor for coronary atherosclerosis as hypercholesterolemia."

J Clin Invest. 1973 Jul;52(7):1533-43

Original Article

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris,

New England J. Medicine, Nov 5 2022

10,497 patients (66.9% with CVD)

TG 271, LDL 78, HDL 33

3.4 years

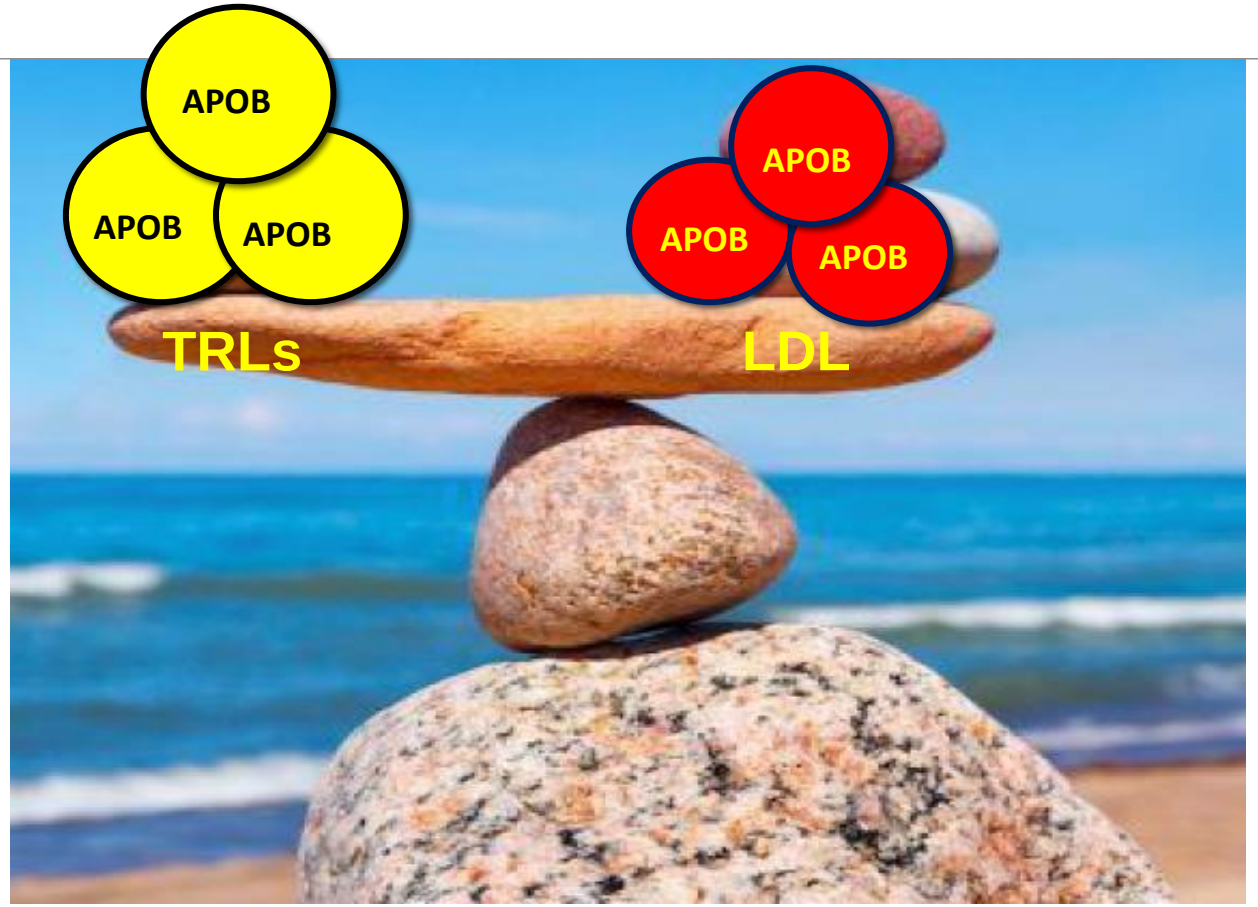
TG reduction 26.2%, +4.8% for apoB (LDL increased 91 versus 80)

No change in overall cholesterol, no significant change in apoB

MACE 3.6 versus 3.51%

Side effect – venous thrombosis (71 versus 35), more renal changes as creatinine levels increase with fibrates

TG-rich apoB lipoproteins are as atherogenic as LDL.

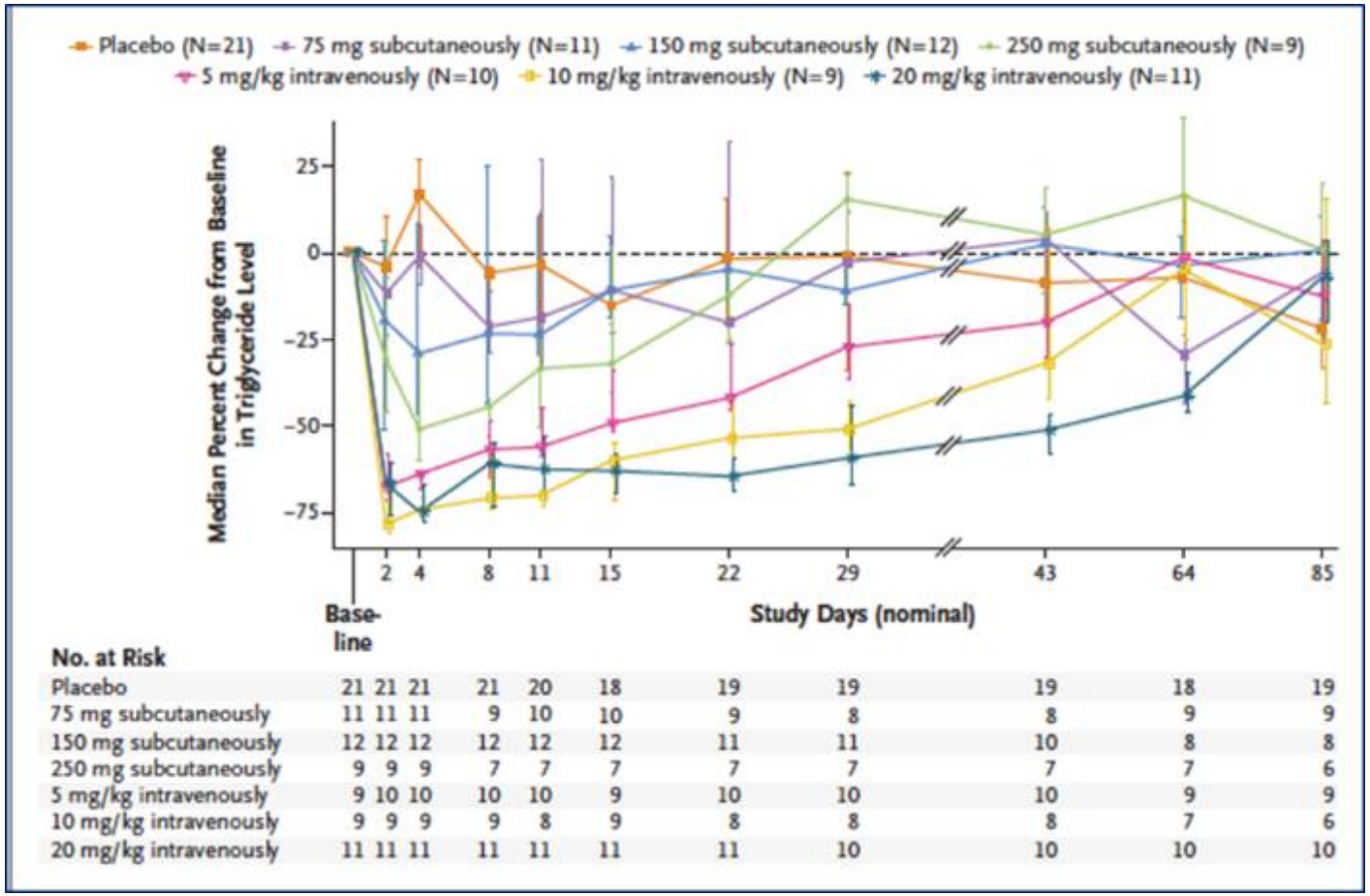


Changes in Lipid Parameters of ARO-APOC3
TG reduction without an increase in LDL

Average Lipid Profiles in MUIR (ARO-APOC3 50 mg) at Week 16

	APOC3	TG	Non-HDL-C	LDL-C	ApoB	Remnant Cholesterol	HDL-C
Pre-treatment	15	220	150	110	95	46	42
Post-treatment	**2**	**59**	**107**	**98**	**75**	**17**	**69**
% change	-90%	-73%	-29%	-11%	-21%	-62%	+65%

Inhibition of ANGPTL3 with a monoclonal antibody (or ASO) Lowers TG. ASO - NAFLD

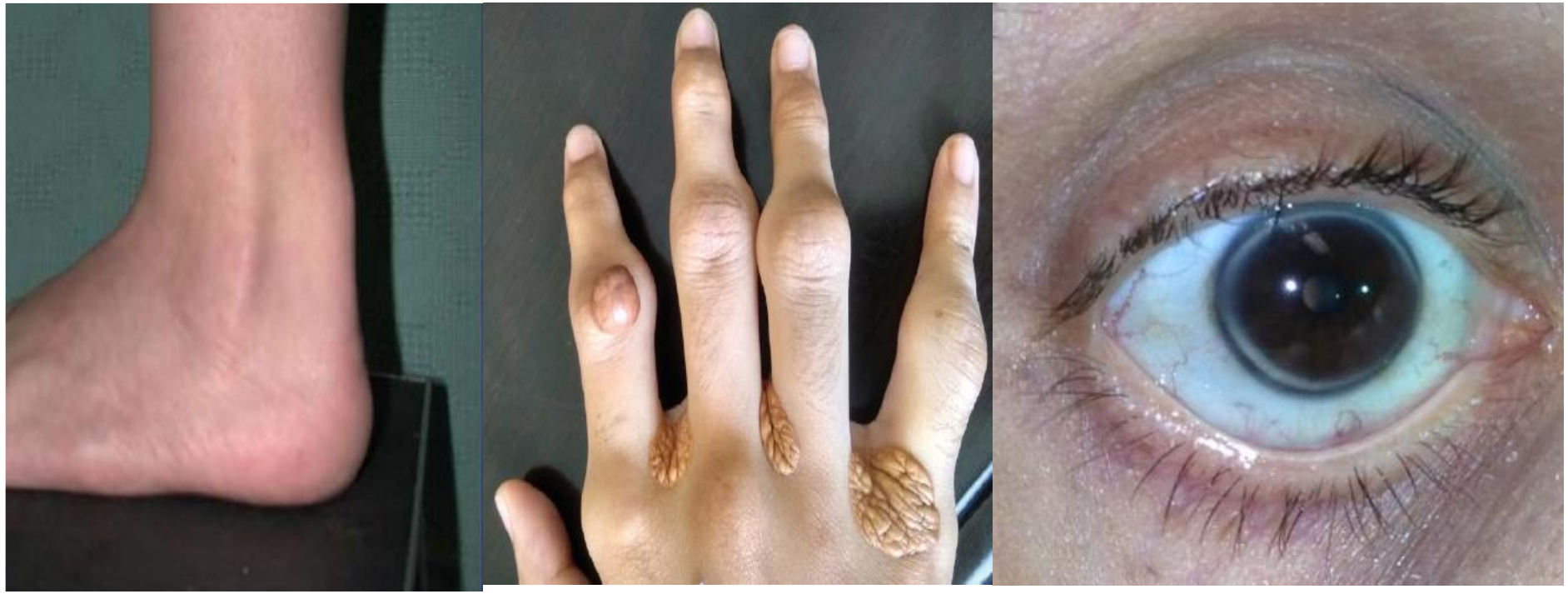


No. at Risk											
Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg subcutaneously	11	11	11	9	10	10	9	8	8	9	9
150 mg subcutaneously	12	12	12	12	12	12	11	11	10	8	8
250 mg subcutaneously	9	9	9	7	7	7	7	7	7	7	6
5 mg/kg intravenously	9	10	10	10	10	9	10	10	10	9	9
10 mg/kg intravenously	9	9	9	9	8	9	8	8	8	7	6
20 mg/kg intravenously	11	11	11	11	11	11	11	10	10	10	10

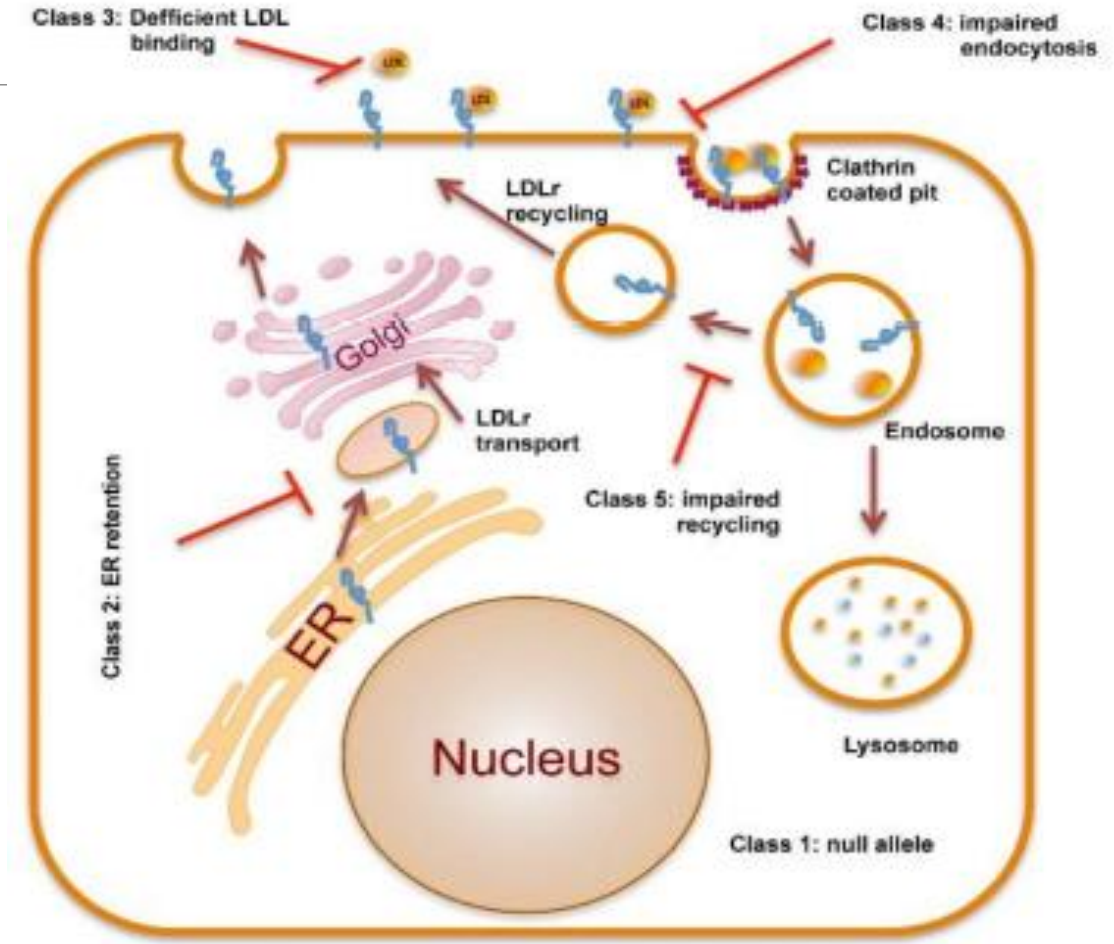
* Graham NEJM 2017, 222-232; Dewey NEJM 2017 377:211

** NEJM 2020; 383:711-720; **NEJM 2020, Nov 15.**

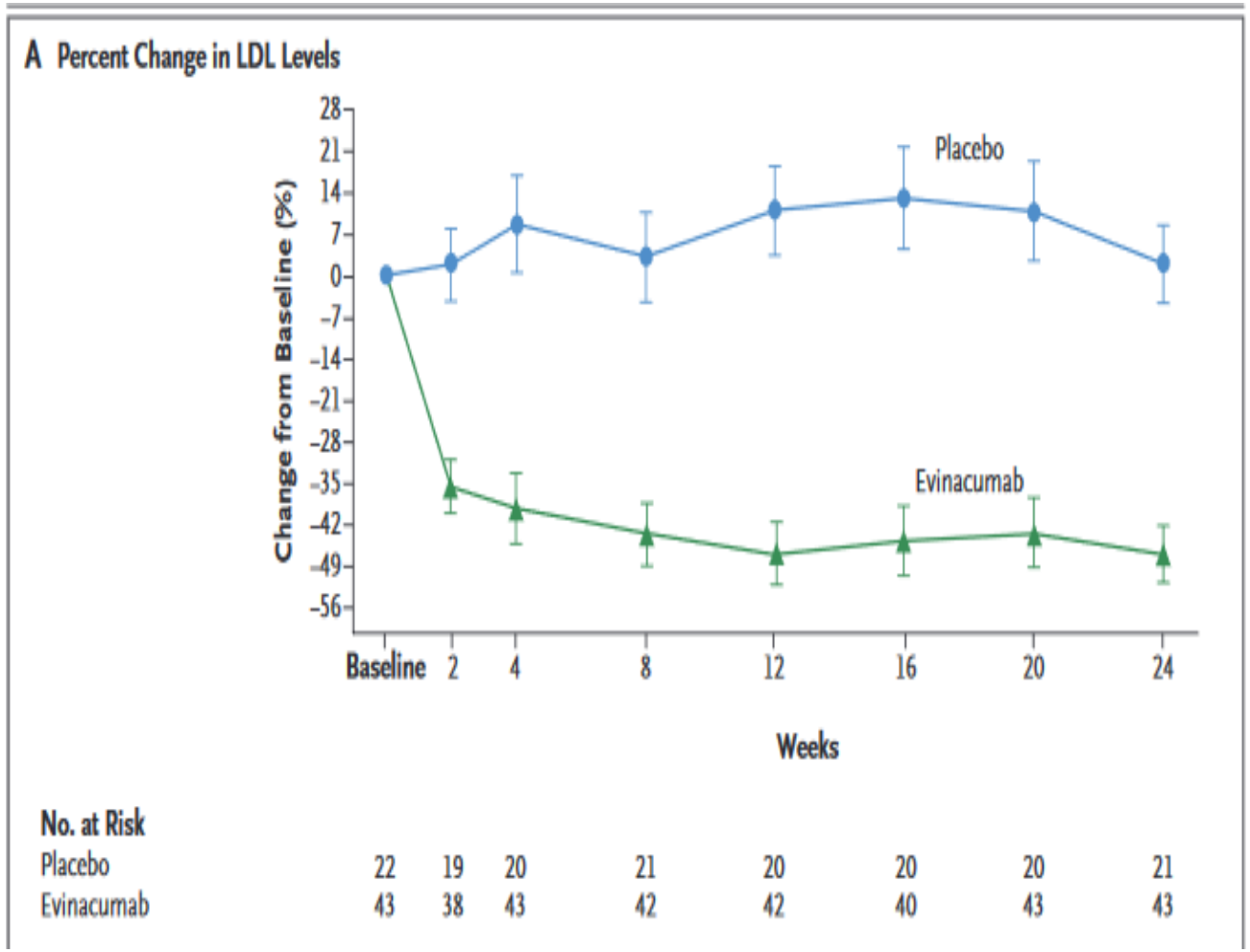
Signs of Genetic Hypercholesterolemia



LDL receptor pathway

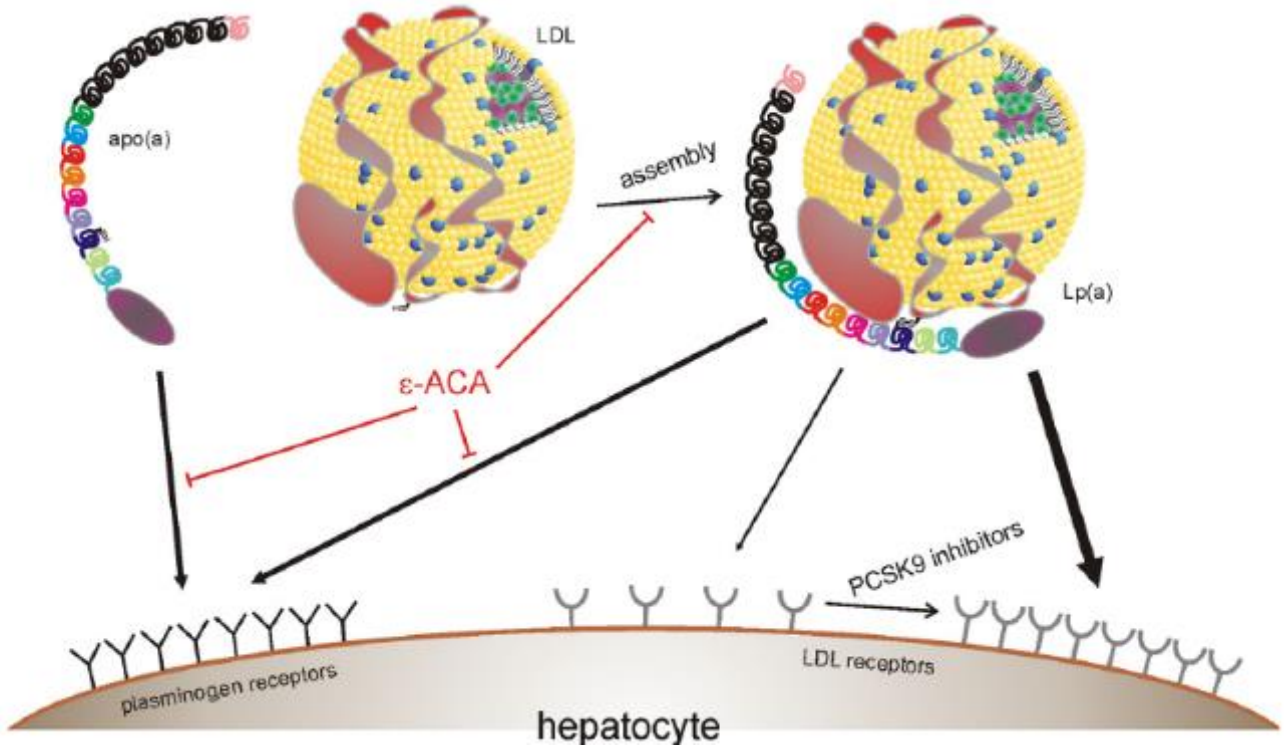


Inhibition of ANGPTL3 with a monoclonal antibody reduces LDL >50% in LDL receptor deficient patients



** NEJM 2020; 383:711-720; **NEJM 2020, Nov 15.**

Lipoprotein (a) is a Genetic Risk Factor



Koschinsky ML, JOURNAL OF BIOLOGICAL CHEMISTRY VOLUME 290•NUMBER 18•MAY 1, 2015

Conclusions

ApoC3 inhibition treats familial chylomicronemia syndrome.

Unlike fibrates, ApoC3 inhibition lowers triglyceride without increasing LDL.

ANGPTL3 inhibition lowers triglyceride and LDL.

Lp(a) inhibition is in clinical trials.

Analyst R&D Day June 1, 2023

Cardiometabolic Programs Update: ARO-APOC3 and ARO-ANG3

Javier San Martin, MD

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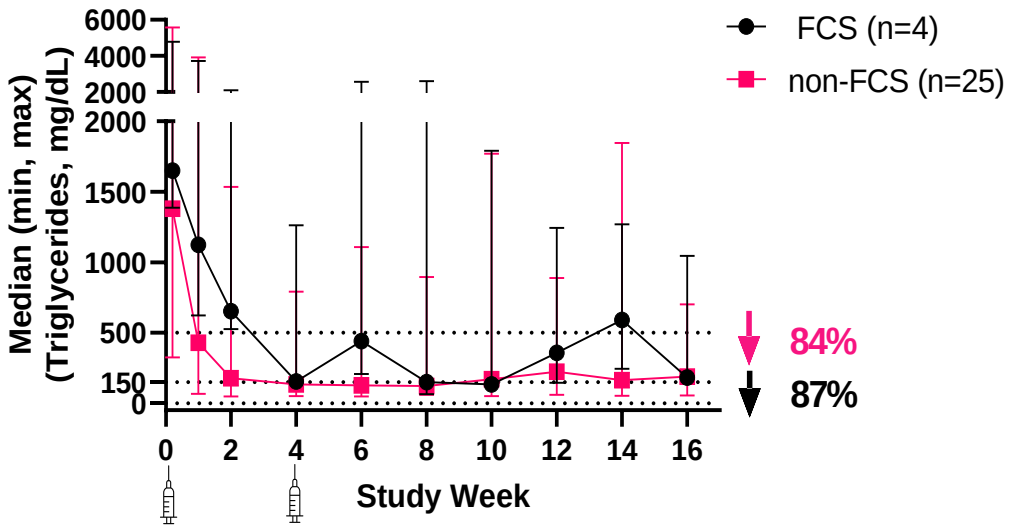
Ongoing Cardiometabolic Studies Support Multiple Indications

Program	Study	Indication	Study Title	Status
SUMMIT PROGRAM	PALISADE	FCS	A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome	Fully Enrolled
	SHASTA-2	sHTG	A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia	Fully Enrolled
	MUIR	Mixed Dyslipidemia	A Double-Blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia and open-label extension	Fully Enrolled
Vista Program	Gateway	HoFH	Phase 2 Study to Evaluate the Safety and Efficacy of ARO-ANG3 in Subjects with Homozygous Familial Hypercholesterolemia (HoFH) and open-label extension	Fully Enrolled
	Arches-2	Mixed Dyslipidemia	A Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults with Mixed Dyslipidemia and open-label extension	Fully Enrolled

ARO-APOC3 for the Treatment of FCS: AROAPOC3-1001 and PALISADE Baseline Characteristics

- Phase 1/2a (AROAPOC3-1001) study – ARO-APOC3 decreased TG levels in FCS patients to below 500 mg/dL, a threshold at which pancreatitis is unlikely

Triglycerides

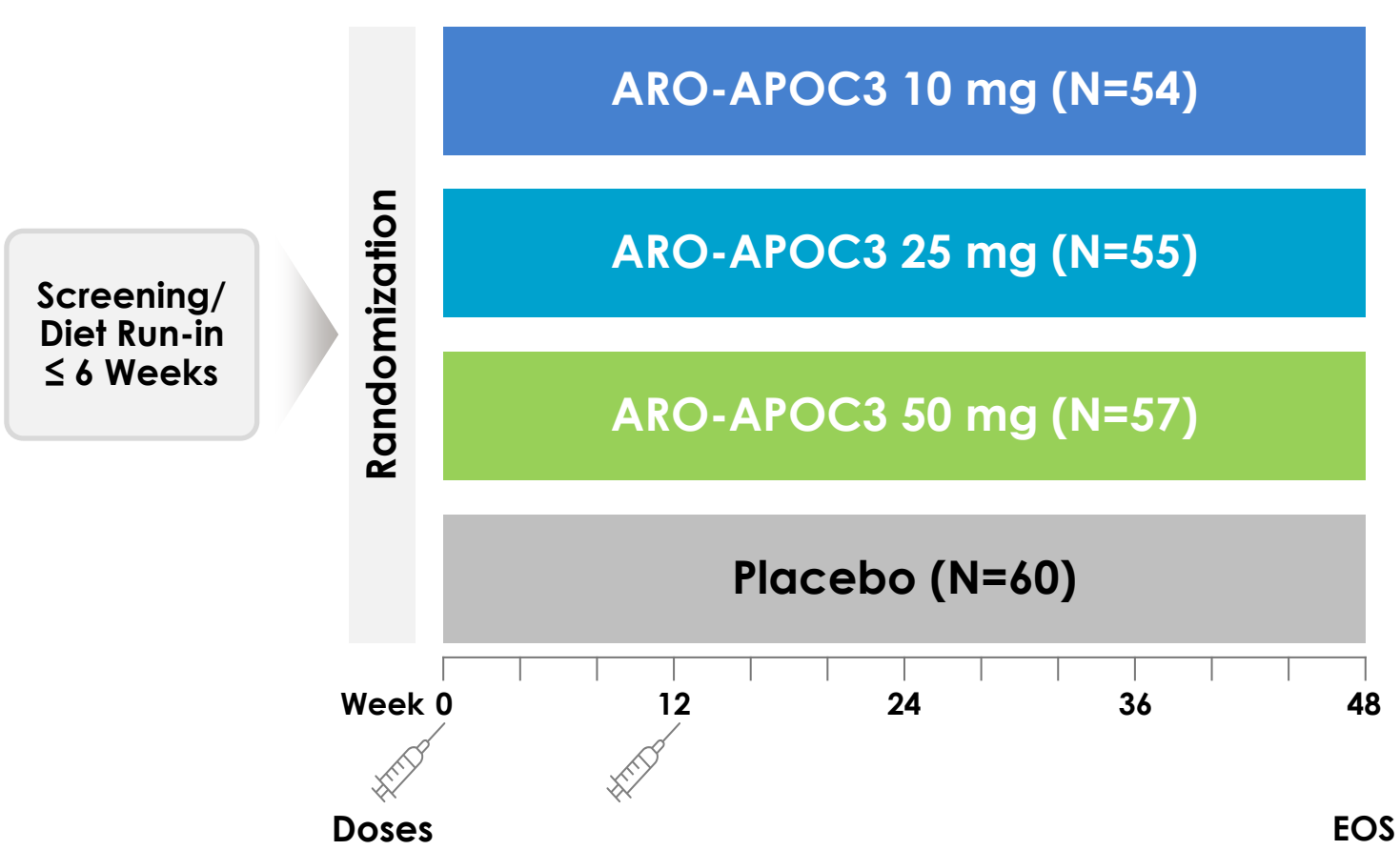


- Phase 3, placebo-controlled (AROAPOC3-3001) fully enrolled as of May 10, 2023

Baseline Characteristics	Enrolled (N=75) *
Mean (SD) Age, Years	46.04 (13.27)
Men, n (%)	37 (49.3%)
Median (Q1, Q3) TG, mg/dL	2158 (663, 3317)
Genetically or Clinically Confirmed FCS, n (%)	75 (100%)
Genetically Confirmed FCS	44*
History of Pancreatitis, n (%)	66 (88%)^

- Defined regulatory pathway and strategy

ARO-APOC3 for the Treatment for SHTG : SHASTA 2 Study Design



Study Population:

- SHTG history of TG > 500 mg/dL
- Fasting TG of 500 mg/dL – 4,000 mg/dL during screening

Key Endpoints*:

- % change from baseline in:
  - TG
  - APOC3
  - non-HDL-C
  - LDL-C
  - HDL-C

Data Analysis:

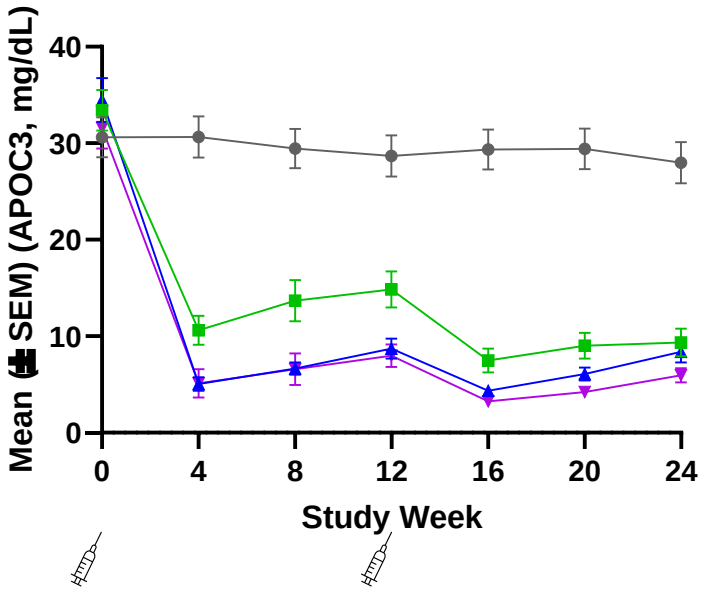
- Ongoing Phase 2 study data evaluated when all subjects had reached Week 24 (Data cutoff date of 14 Apr 2023)

SHASTA-2 Baseline Characteristics

	Pooled Placebo (N=60)	ARO-APOC3		
		10 mg (N=54)	25 mg (N=55)	50 mg (N=57)
Mean (SD) age, years	56.2 (10.97)	53.0 (9.57)	56.0 (10.64)	54.3 (11.00)
Female, n (%)	14 (23.3%)	8 (14.8%)	12 (21.8%)	16 (28.1%)
White, n (%)	55 (91.7%)	47 (87.0%)	48 (87.3%)	53 (93.0%)
Mean (SD) BMI, kg/m^2	30.55 (3.779)	32.46 (4.943)	31.81 (5.057)	31.52 (5.294)
Mean (SD) APOC3, mg/dL	30.626 (15.8708)	33.419 (15.3795)	34.470 (16.7953)	31.571 (16.1109)
Median (Q1, Q3) triglyceride, mg/dL	678.62 (539.61, 929.06)	696.02 (558.75, 1087.62)	597.69 (517.34, 982.05)	663.06 (530.76, 1028.32)
Median (Q1, Q3) LDL-C (UC), mg/dL	62.0 (42.0, 92.0)	65.0 (46.0, 96.0)	71.0 (44.0, 97.0)	65.0 (41.0, 96.0)
Mean (SD) non-HDL-C, mg/dL	184.8 (78.73)	208.8 (73.60)	206.3 (91.30)	195.7 (87.60)
Mean (SD) ApoB, mg/dL	94.91 (28.607)	103.10 (44.383)	103.44 (31.806)	109.80 (54.499)
Mean (SD) remnant cholesterol,[a] mg/dL	115.4 (82.15)	134.1 (87.94)	132.1 (98.30)	123.8 (91.45)
Mean (SD) HDL-C, mg/dL	29.7 (11.58)	28.3 (8.75)	29.5 (11.15)	30.5 (12.62)

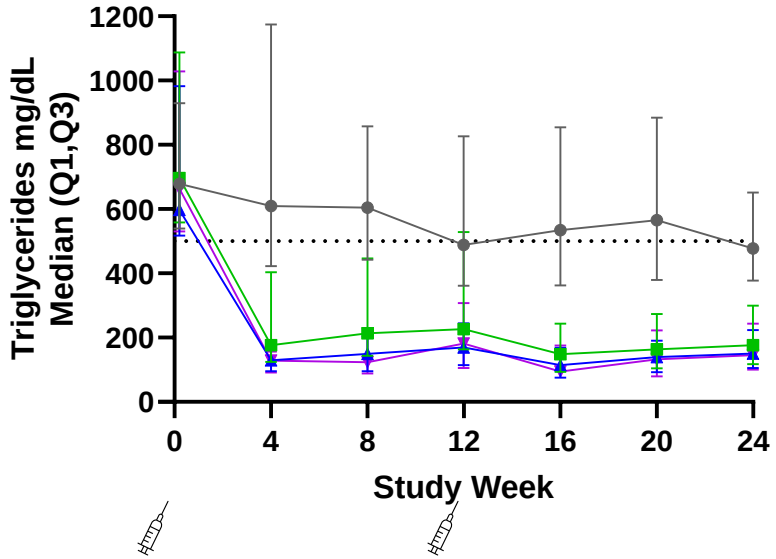
ARO-APOC3 Decreases APOC3 and Triglycerides in sHTG

APOC3



Mean % Change	
Wk 16	Wk 24
+4%	+0%
-76%	-71%
-86%	-73%
-87%	-79%

Triglycerides



Median % Change	
Wk 16	Wk 24
-19%	-29%
-81%	-75%
-85%	-76%
-85%	-80%

Placebo — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

Median	Placebo	10 mg	25 mg	50 mg
Baseline	678.62	696.02	597.69	663.06
Wk 16	534.00	148.50	114.00	94.00
Wk 24	477.82	176.16	150.34	145.34

SHASTA-2 Study:Clinical Data Cutoff 14 Apr 2023

ARO-APOC3 Reduces TGs Below the Level Associated with Risk of Pancreatitis

Participants with Baseline TG > 880 mg/dL

n/N (%)	Placebo (Pooled) (N=16)	ARO-APOC3 (10 mg) (N=16)	ARO-APOC3 (25 mg) (N=16)	ARO-APOC3 (50 mg) (N=18)
TG < 500 mg/dL at Wk 4	3/16 (**18.8%**)	10/16 (**62.5%**)	14/16 (**87.5%**)	16/18 (**88.9%**)
TG < 500 mg/dL at Wk 16	2/16 (**12.5%**)	10/14 (**71.4%**)	16/16 (**100.0%**)	17/18 (**94.4%**)
TG < 500 mg/dL at Wk 24	5/15 (**33.3%**)	9/14 (**64.3%**)	13/16 (**81.3%**)	14/17 (**82.4%**)

TEAEs Reflect the Underlying Co-morbidities in the sHTG Population

	Pooled Placebo (N=60)	ARO-APOC3		
		10 mg (N=54)	25 mg (N=55)	50 mg (N=57)
TEAEs	42 (70.0)	41 (75.9)	35 (63.6)	48 (84.2)
TEAEs Occurring in ≥ 5 Subjects				
Diarrhoea	5 (8.3)	3 (5.6)	1 (1.8)	1 (1.8)
COVID-19	10 (16.7)	10 (18.5)	8 (14.5)	8 (14.0)
Urinary Tract Infection	5 (8.3)	3 (5.6)	1 (1.8)	2 (3.5)
Type 2 Diabetes Mellitus	3 (5.0)	1 (1.9)	4 (7.3)	7 (12.3)
Headache	3 (5.0)	8 (14.8)	5 (9.1)	2 (3.5)
TRAEs	8 (13.3)	14 (25.9)	8 (14.5)	10 (17.5)
Serious TEAEs	7 (11.7)	4 (7.4)	2 (3.6)	5 (8.8)
TEAEs Leading to Drug Discontinuation, Dose Interruptions, or Study Withdrawal	0	1 (1.9)	0	0
Pancreatitis	3 (5.0)	1 (1.9)	2 (3.6)	1 (1.8)

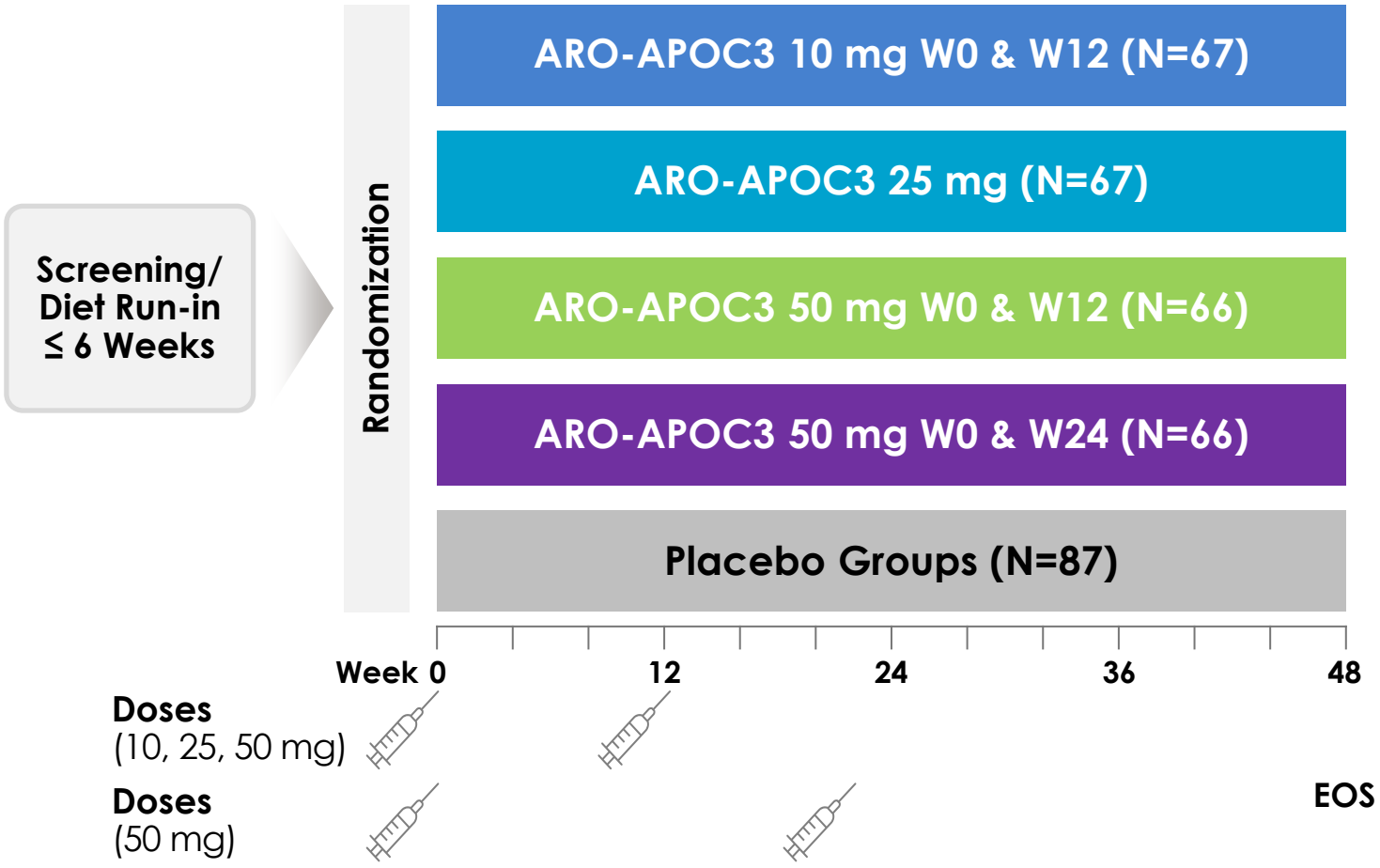
- All SAEs were not related to ARO-APOC3
- Increases in HbA1c were noted in the 50 mg group among patients with poorly controlled diabetes
- HbA1c improves upon DBT treatment adjustments

ARO-APOC3 Regulatory Path to Accelerate Registration While Delivering Best Clinical Profile

Phase 3	Study Design and Specifics	N
Registrational Study #1: SHASTA-3 Randomized, Double blind Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia	• **Participants with sHTG (TG >500 mg/dL)** • **Primary endpoint – % change in TG at 6 months** • **Secondary endpoints acute pancreatitis events** • Randomized (3:1), double-blind, placebo-controlled	600 total, 450 receiving active drug
Registrational Study #2: SHASTA-4 Randomized, Double blind Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia at high risk of pancreatitis	• **Participants with sHTG at high risk for pancreatitis (TG >880 mg/dL and recent history of pancreatitis)** • **Primary endpoint - % change in TG at 6 months** • **Secondary endpoints including hospitalizations for acute pancreatitis and abdominal pain and PROs** • Randomized (1:1) , double-blind, placebo-controlled • **Month 6 planned analysis** to support registration – **continued 18-month blinded period to support potential pancreatitis endpoint**	200 total, 100 receiving active drug

- Optimize commercial attractiveness and value proposition with novel endpoints to differentiate against competitor compounds and comparative data to support payer coverage

ARO-APOC3 for the Treatment for Mixed Dyslipidemia: MUIR Study Design



Study Population:

- Fasting TG 150–499 mg/dL and either
  - LDL-C ≥ 70 mg/dL or
  - Non-HDL-C ≥ 100 mg/dL
- Stable optimal statin therapy

Key Endpoints*:

- % change from baseline in:
  - TG
  - APOC3
  - non-HDL-C, ApoB, LDL-C, HDL-C
  - Remnant Cholesterol

Data Analysis:

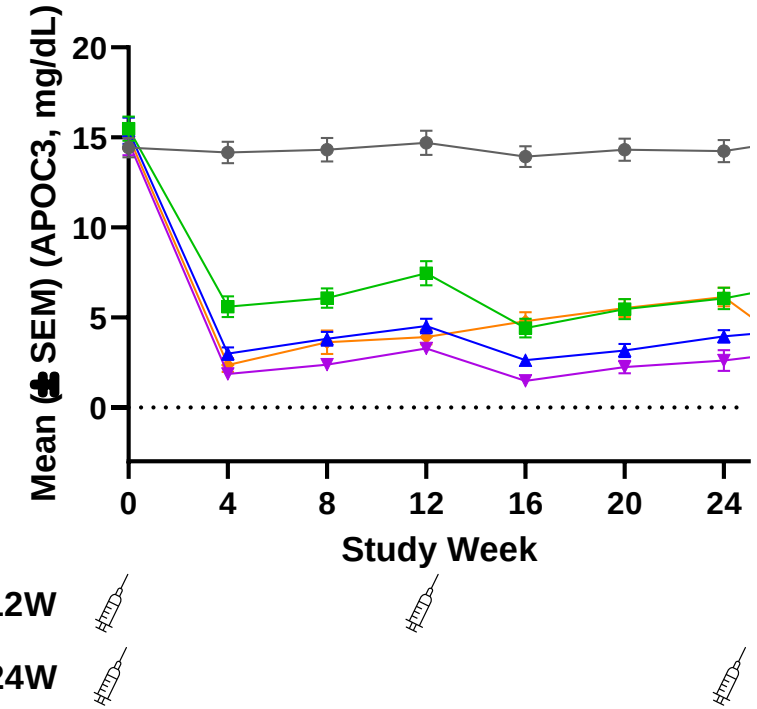
- Ongoing Phase 2 study data evaluated when all subjects reached Week 24

MUIR: Baseline Characteristics

	Pooled Placebo (N=87)	ARO-APOC3 (W0 and W12) 10 mg (N=67)	ARO-APOC3 (W0 and W12) 25 mg (N=67)	ARO-APOC3 (W0 and W12) 50 mg (N=66)	ARO-APOC3 (W0 and W24) 50 mg (N=66)
Mean (SD) Age, Years	58.9 (9.7)	60.2 (11.7)	61.3 (11.3)	62.6 (10.5)	61.3 (11.8)
Female, n (%)	41 (47.1%)	31 (46.3%)	30 (44.8%)	29 (43.9%)	23 (34.8%)
White, n (%)	79 (90.8%)	62 (92.5%)	60 (89.6%)	63 (95.5%)	62 (93.9%)
Mean (SD) BMI, kg/m²	31.19 (5.436)	30.48 (5.660)	32.36 (6.698)	32.56 (6.528)	32.03 (5.638)
Mean (SD) APOC3, mg/L	14.4 (4.9)	15.5 (5.5)	15.4 (5.8)	14.7 (6.0)	15.0 (5.5)
Median (Q1,Q3) Triglyceride, mg/dL	217.18 (132.4, 438.8)	222.94 (133.2, 413.0)	213.86 (132.4, 445.7)	228.93 (117.7, 446.5)	232.69 (136.5, 457.5)
Mean (SD) LDL-C (UC), mg/dL	101.6 (38.68)	105.1 (37.03)	101.6 (43.38)	103.0 (39.74)	105.6 (31.83)
Mean (SD) non-HDL-C, mg/dL	148.3 (43.4)	153.5 (42.0)	147.7 (48.4)	151.8 (49.3)	153.0 (42.7)
Mean (SD) ApoB, mg/dL	102.7 (29.5)	102.8 (23.3)	101.4 (23.3)	99.5 (26.1)	104.0 (24.2)
Mean (SD) Remnant Cholesterol,[a] mg/dL	45.0 (18.88)	48.3 (20.49)	46.1 (20.27)	48.8 (27.24)	47.4 (23.08)
Mean (SD) HDL-C, mg/dL	42.1 (11.1)	42.2 (11.1)	44.7 (13.6)	42.7 (11.7)	40.8 (12.6)

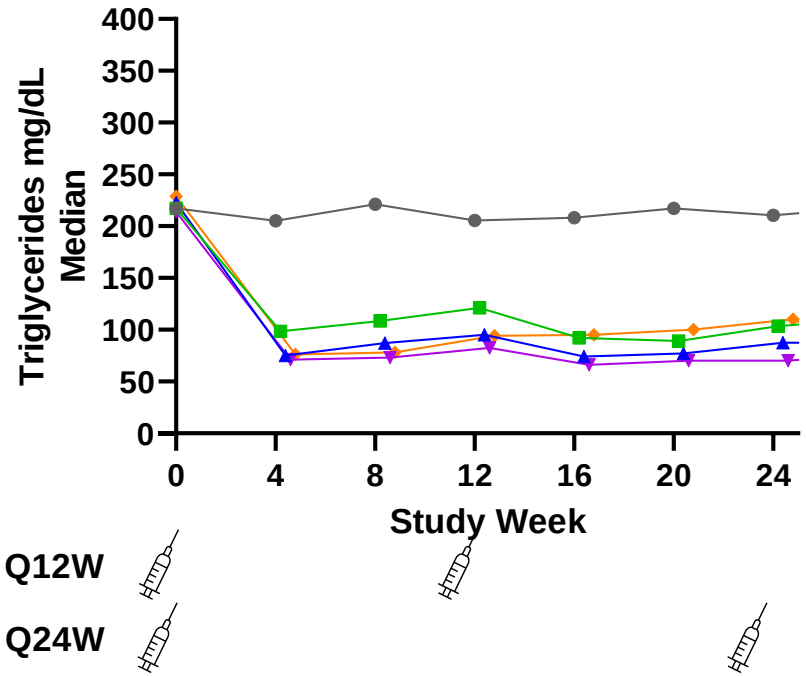
MUIR: ARO-APOC3 Results in Durable Decreases in Serum APOC3 and Triglycerides at All Doses Studied

APOC3[a]



Mean % Change	
Wk 16	Wk 24
-3%	-0%
-68%	-60%
-69%	-60%
-82%	-74%
-90%	-80%

Triglycerides

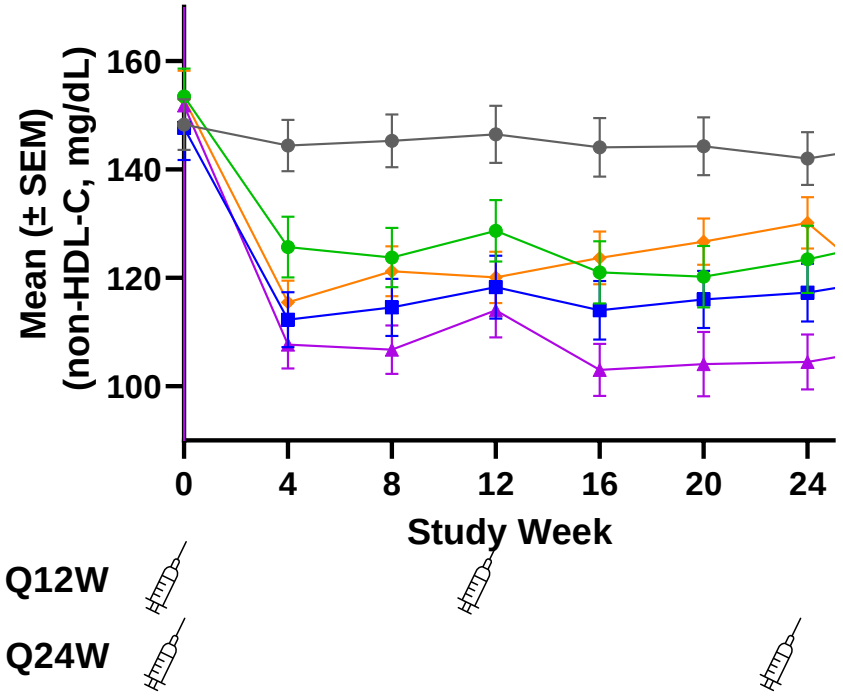


Mean % Change	
Wk 16	Wk 24
-5%	-9%
-57%	-49%
-62%	-55%
-67%	-59%
-73%	-67%

Placebo — 50 mg ARO-APOC3 (Q24W) — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

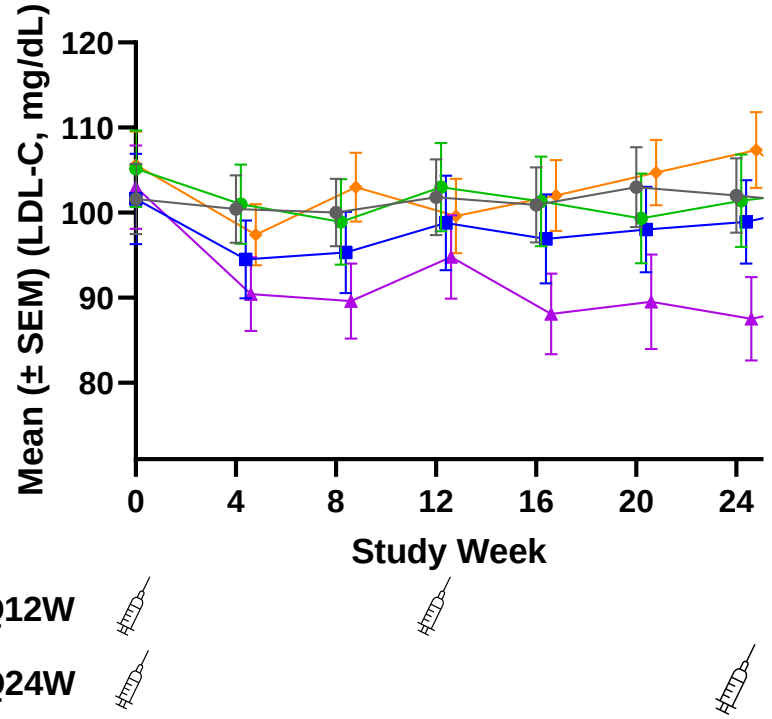
MUIR: ARO-APOC3 Decreases Non-HDL-C and LDL-C

Non-HDL-C



Mean % Change	
Wk 16	Wk 24
-1%	-2%
-16%	-11%
-20%	-19%
-24%	-20%
-29%	-28%

LDL-C [a]

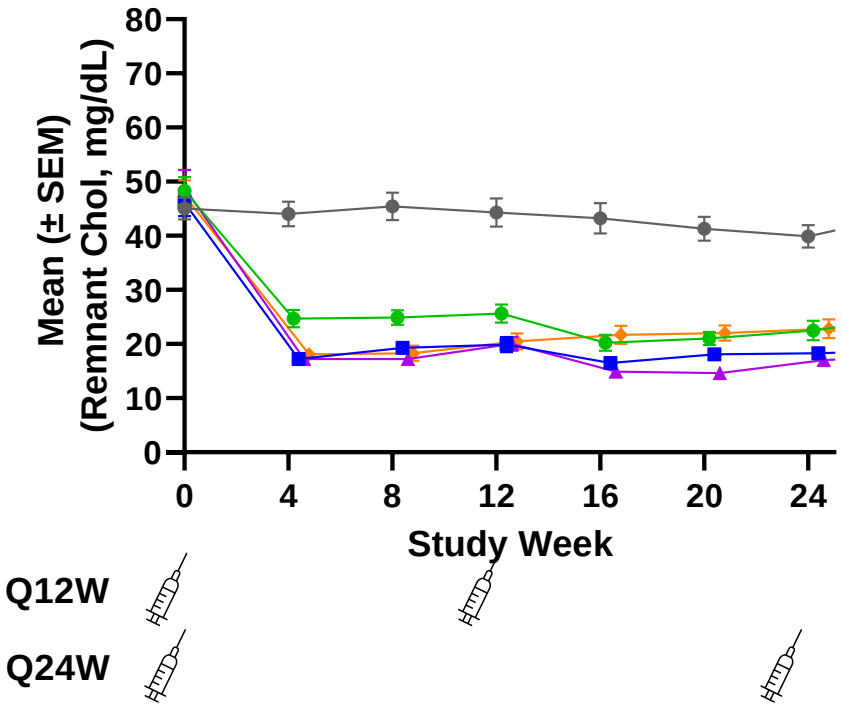


Mean % Change	
Wk 16	Wk 24
+ 2%	+ 3%
- 1%	+ 5%
- 1%	- 0%
- 1%	+ 2%
-10%	-11%

Placebo | 50 mg ARO-APOC3 (Q24W) | 10 mg ARO-APOC3 | 25 mg ARO-APOC3 | 50 mg ARO-APOC3

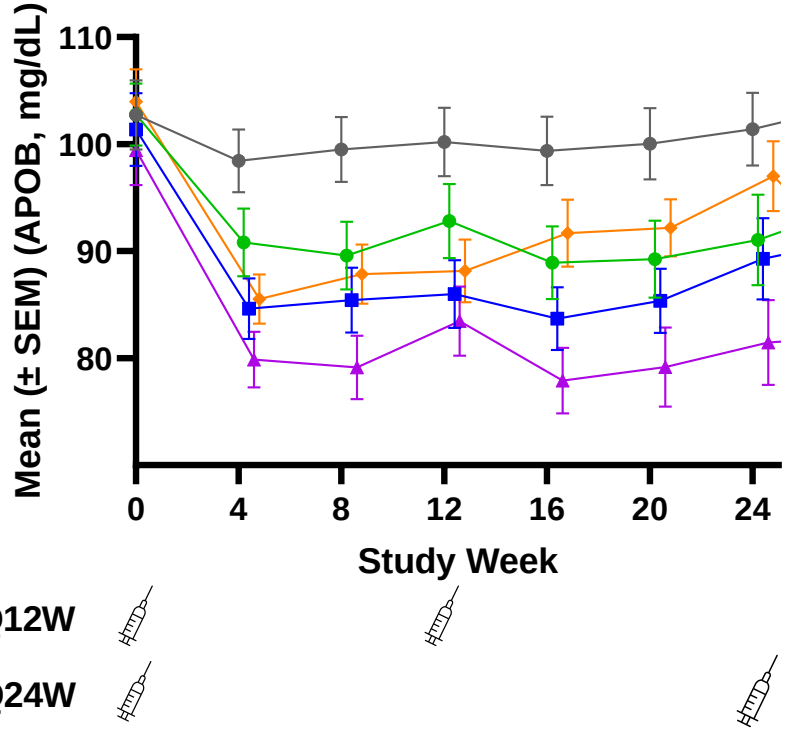
MUIR: ARO-APOC3 Decreases Serum Remnant Cholesterol and APOB

Remnant Cholesterol[a]



Mean % Change	
Wk 16	Wk 24
+1%	-3%
-44%	-43%
-53%	-50%
-57%	-54%
-62%	-54%

APOB



Mean % Change	
Wk 16	Wk 24
- 1%	- 2%
-10%	- 4%
-12%	-10%
-17%	-12%
-21%	-18%

Placebo — 50 mg ARO-APOC3 (Q24W) — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

[a] Based on calculation: Total cholesterol – HDL-C – LDL-C (ultracentrifugation)
MUIR Study: Clinical Data Cutoff 24 MAR 2023

TEAEs Reflect the Underlying Co-morbidities in the Mixed Dyslipidemia Population

	Pooled Placebo (N=87)	ARO-APOC3 (W0 and W12)			ARO-APOC3 (W0 and W24)
		10 mg (N=67)	25 mg (N=67)	50 mg (N=66)	50 mg (N=66)
Treatment-Emergent Adverse Events (TEAEs)	52 (59.8)	42 (62.7)	45 (67.2)	47 (71.2)	48 (72.7)
TEAEs Occurring in ≥5 Subjects					
Covid 19	10 (11.5)	6 (9.0)	8 (11.9)	7 (10.6)	5 (7.6)
Type 2 Diabetes Mellitus	4 (4.6)	4 (6.0)	4 (6.0)	7 (10.6)	11 (16.7)
Upper Respiratory Tract Infection	7 (8.0)	3 (4.5)	5 (7.5)	1 (1.5)	8 (12.1)
Headache	3 (3.4)	1 (1.5)	2 (3.0)	4 (6.1)	5 (7.6)
Urinary Tract Infection	5 (5.7)	2 (3.0)	4 (6.0)	4 (6.1)	0
Bronchitis	0	4 (6.0)	1 (1.5)	2 (3.0)	5 (7.6)
TRAEs	8 (9.2)	7 (10.4)	8 (11.9)	11 (16.7)	8 (12.1)
Serious TEAEs	3 (3.4)	1 (1.5)	5 (7.5)	7 (10.6)	4 (6.1)
TEAEs Leading to Drug Discontinuation, Dose Interruptions, or Study Withdrawal	2 (2.3)	0	0	1 (1.5)	0
Deaths	0	0	1 (1.5)	2 (3.0)	1 (1.5)

- No reported SAEs attributed to ARO-APOC3. Most SAEs recovered with no sequelae
- Increases in HbA1c were noted in the 50 mg group among patients with poorly controlled diabetes
- HbA1c improves upon DBT treatment adjustments

ARO-APOC3 Improves Lipid Parameters has the Potential to Benefit Cardio-metabolic Health Outcomes

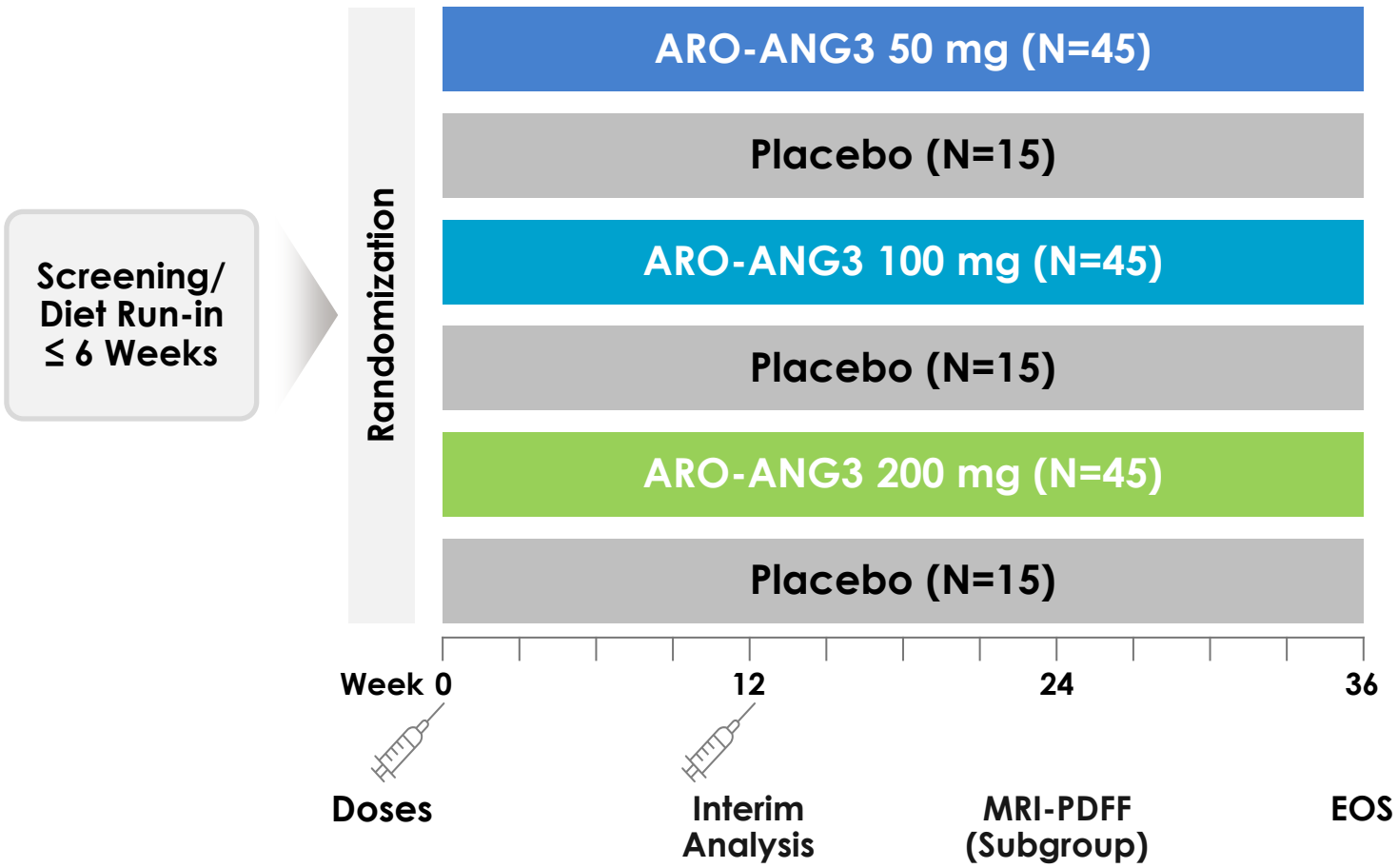
Average Lipid Profiles in MUIR (ARO-APOC3 50 mg) at Week 16

	APOC3	TG	Non-HDL-C	LDL-C	ApoB	Remnant Cholesterol	HDL-C
Pre-treatment	15	220	150	110	95	46	42
Post-treatment	**2**	**59**	**107**	**98**	**75**	**17**	**69**
% change	-90%	-73%	-29%	-11%	-21%	-62%	+65%

- These results justify a cardiovascular outcomes trial
- Clinical Research Organization and Academic Research Organization selection ongoing

ARO-ANG3 for the Treatment of Mixed Dyslipidemia

Arches-2



Study Population:

- Fasting TG between 150–499 mg/dL and either
  - LDL-C ≥ 70 mg/dL or
  - Non-HDL-C ≥ 100 mg/dL
- Stable optimal statin therapy

Key Endpoints*:

- Serum TG
- ANGPTL3
- Non-HDL-C
- ApoB
- LDL-C
- Remnant cholesterol
- HDL-C
- Liver fat fraction by MRI-PDFF (subgroup)
  - 61 subjects with liver fat fraction ≥ 8% at baseline were evaluated again at Week 24

Interim Analysis:

- Conducted when all subjects reached Week 36 (Data cutoff 09 Dec 2022)

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ARO-ANG3 Shows Favorable Changes in Lipoproteins in Mixed Dyslipidemia Patients

Arches-2

	ANGPTL3	TG	LDL-C (UC)	Remnant Cholesterol	Non-HDL-C	ApoB
ARO-ANG3*	-76%	-60%	-18%	-61%	-36%	-22%

- ARO-ANG3 is not associated with an increase in liver fat fraction at Week 24, with no AEs related to LFT changes reported to date
- TEAEs reported to date are consistent with those expected in this patient population and with associated underlying comorbidities
- Increase in HbA1c in subset of patients with poorly controlled diabetes
- The favorable changes in serum lipids and lipoproteins support the potential value of ARO-ANG3 for the treatment of mixed dyslipidemia in patients at risk of atherosclerotic cardiovascular disease

*Week 16 data 200mg 09 Dec 2022 data cut

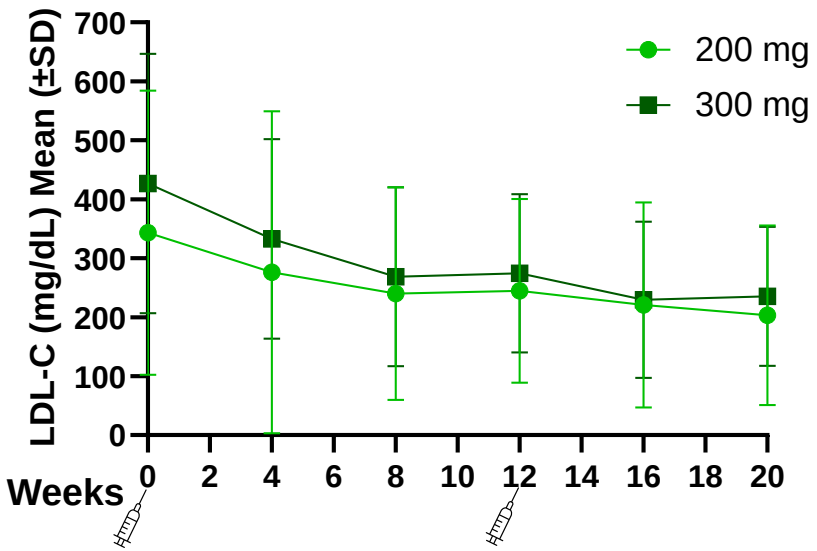
ARO-ANG3 Addresses Unmet Need in Homozygous Familial Hypercholesterolemia (HoFH)

- HoFH: Severely elevated LDL-C
  (Untreated LDL-C > 500 mg/dL; Treated LDL-C >300 mg/dL)
  - Two mutant alleles in LDLR (95%), APOB (5%), PCSK9 (<1%), or LDLRAP1 (<1%)
- Clinical Manifestations
  - First major CV events in childhood/adolescence
    (MI, angina pectoris, death in early childhood)
- Prevalence – (estimated 500–2,000 patients in US)
- Current Standard of Care
  - Lifestyle, statins, ezetimibe, PCSK9 inhibitors, EVKEEZA™, apheresis
    (LDL- or general)
  - Fewer convenient treatment options in pediatric population

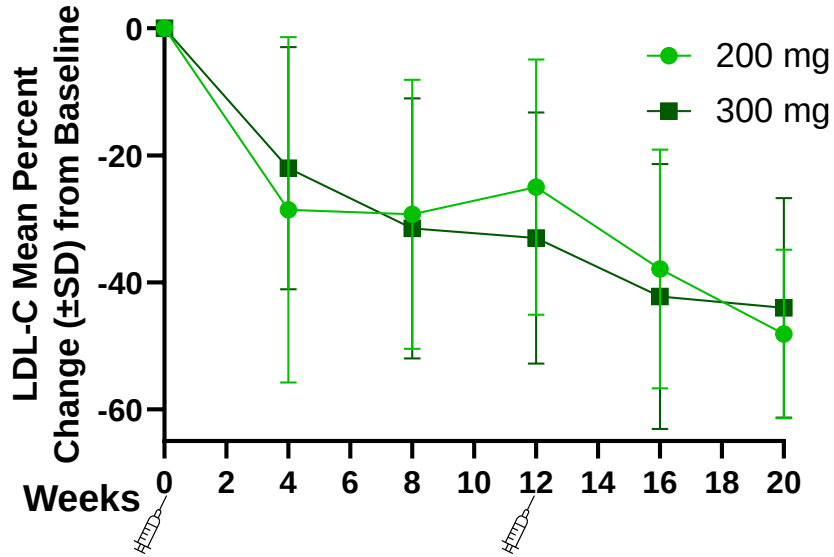
ARO-ANG3 Reduces LDL-C in HoFH Patients
Open Label 16 Patients Study Randomized to 200mg or 300mg

Gateway

Absolute LDL-C Change



Percent LDL-C Change from Baseline



- Week 16 LDL-C (Martin-Hopkins) reductions of 122.6 mg/dL to 171.5 mg/DL and **37.9%** to **42.2%** at 200 mg, 300 mg dose, respectively
- Week 20 LDL-C (Martin-Hopkins) reductions of 169.6 to 191.2 mg/dL and **48.1% to 44.0%** at 200 mg, 300 mg dose, respectively

EAS 2023 Abstract #1495
Data cut 17 Apr 2023

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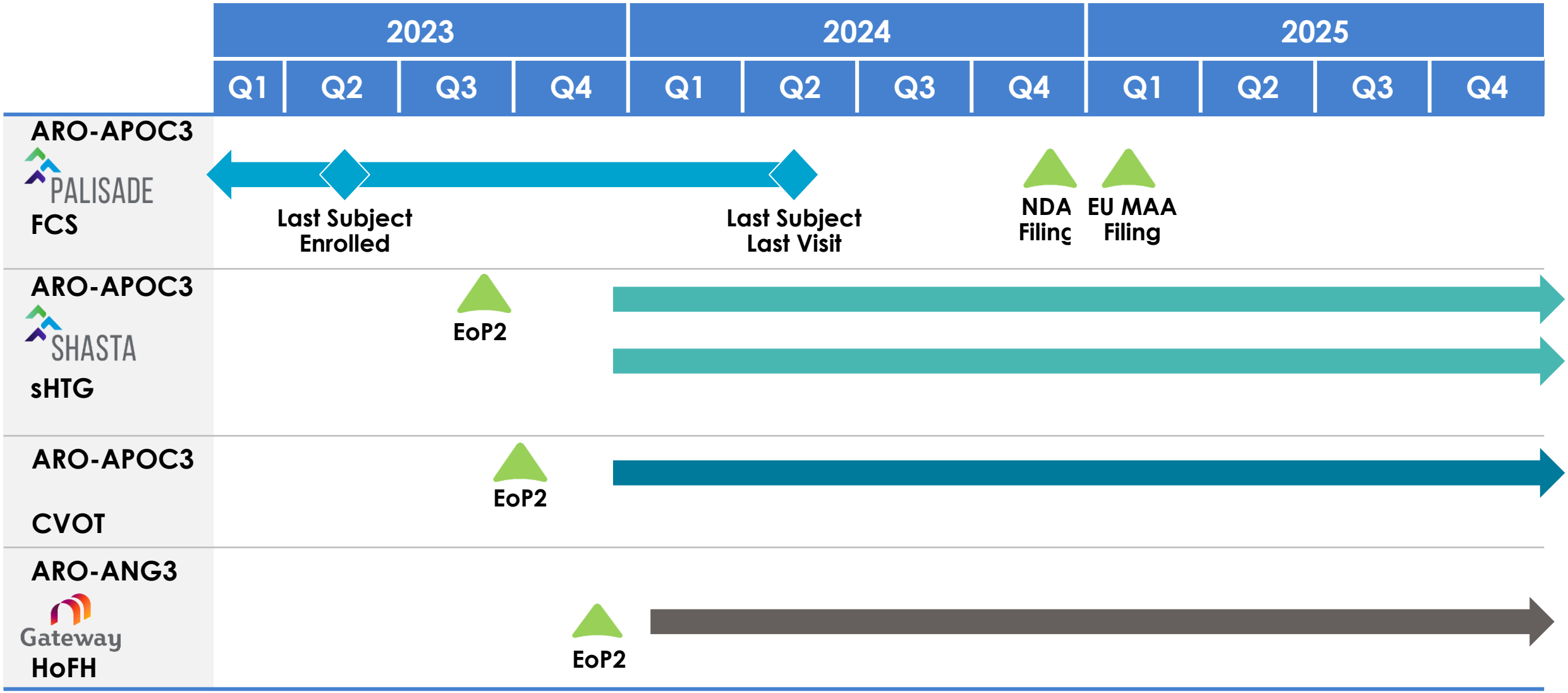
ARO-APOC3 and ARO-ANG3 Moving to Registration Phase



Analyst R&D Day June 1, 2023

Cardiometabolic Commercial Overview

Tracie Oliver

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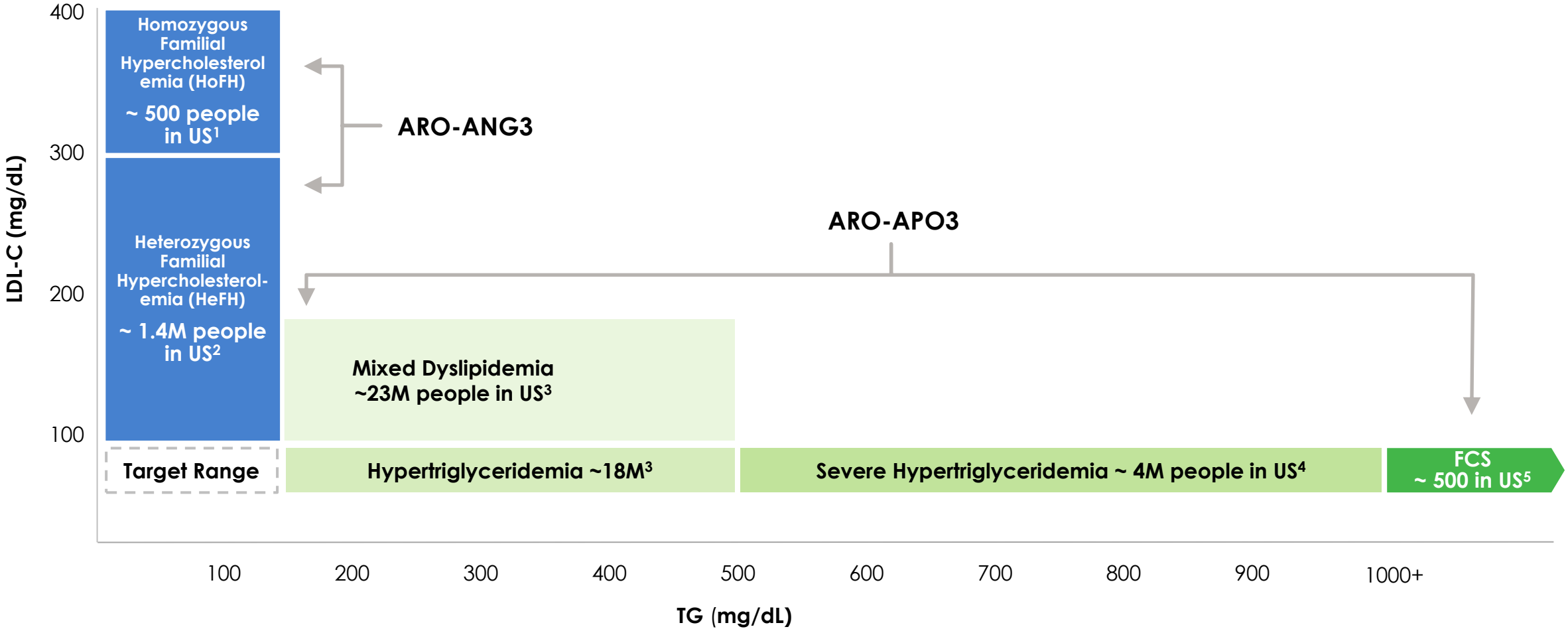
Key Takeaways

- ANGPTL3 and APOC3 are validated targets in the treatment of dyslipidemia
- Initial indications have orphan drug designation, but robust clinical development program will allow expansion to indications with blockbuster potential
- ARO-APOC3 is well differentiated leading to strong value proposition for patients, physicians and payers
- Arrowhead is confident in commercializing our first drug

ARO-APOC3 and ARO-ANG3 Poised to Address Significant Unmet Across Spectrum of Dyslipidemia



1. Goldstein JL, *Clin Invest*. 1973;52:1544-1568.; 2. Akioyamen LE et al. *BMJ Open*. 2017;7:1-13.; 3. Tóth PP et al. *Journal of Clinical Lipidology*. 2012; 6: 325-330.; 4.Christian JB. *Am J Cardiol*. 2011;107 (6);891-7.; 5. www.livingwithfcs.org

ARO-ANG3 Focus on HoFH

1 HoFH

Ultra-orphan disease associated with significant morbidity

Efficacy of ANGPTL3 inhibition in HoFH established by Evinacumab

Differentiation:
- MoA does not rely on LDL activity – predictable response
- Generally well tolerated:
  - No elevated liver enzymes
  - No hepatotoxicity
- Administration:
  - Small injection volume
  - SC injection vs Evinacumab IV
  - Convenient quarterly dosing vs Q2W or monthly dosing (Repatha, Praluent)

2 Refractory Hypercholesterolemia

Estimated 55% people in US not at goal despite treatment with maximally tolerated statins and PCSK9i's[1]

Differentiation:
- POC established with evinacumab[2]
- Convenience of SC RoA and quarterly dose frequency

Market potential >$1B

3 Mixed Dyslipidemia

Estimated 6-10 million people in US not at LDL-C and TG goals with existing therapies[3]

Differentiation:
- Potential to have significant impact on multiple atherogenic lipids and lipoproteins
  - LDL-C
  - ApoB
  - TG
- Convenience of SC RoA and quarterly dose frequency

Market potential >$1B

1. Rallidis LS et al. Very high-risk familial hypercholesterolemia patients in real life: the remaining gap in achieving the current LDL-C targets despite the use of PCSK9 inhibitors. *Atherosclerosis.* 2020; 309:67-9.
2. Rosenson RS et al. Evinacumab in patients with refractory hypercholesterolemia. *NEJM.* 2020; 383 (24): 2307-2319
3. Shen M et al. Contemporary national patterns of eligibility and use of novel lipid-lowering therapies in the United States. J Am Heart Assoc. 2022;11:e026075

ARO-APOC3 Indication Expansion to Blockbuster Potential

1 FCS

Ultra-orphan disease associated with significant morbidity

PALISADE study not limited to genetically confirmed FCS

Limited revenue potential due to size of market

Important in establishing Arrowhead as commercial-stage organization and sets up follow-on indication in related SHTG indication

2 SHTG

Estimated 4 million people in US[1]

Larger market with some similarities to FCS and ability to leverage insights and initial commercial efforts

Market potential >$1B

3 Mixed Dyslipidemia

Estimated 6-10 million people in US not at LDL-C and TG goals with existing therapies[2]

Unique opportunity to improve CVD outcomes by reducing residual risk posed by atherogenic lipoproteins

CVOT study planned

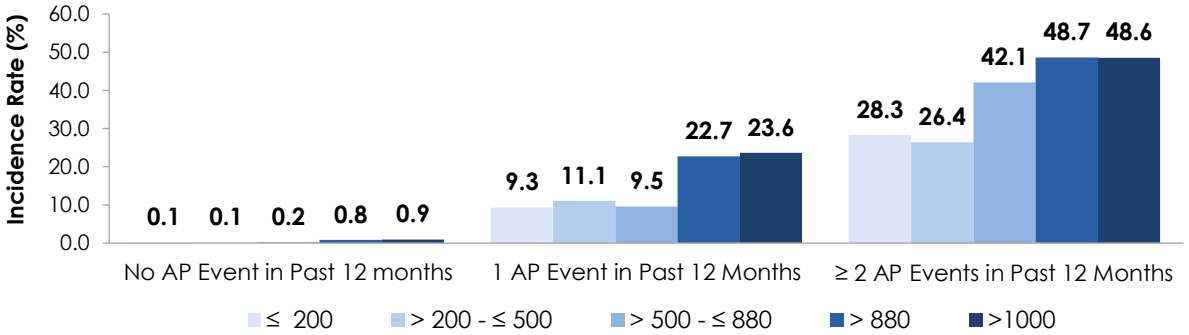
Market Potential >$1B

1. Christian JB. *Am J Cardiol.* 2011;107 (6);891-7.
2. Shen M et al. Contemporary national patterns of eligibility and use of novel lipid-lowering therapies in the United States. J Am Heart Assoc. 2022;11:e026075

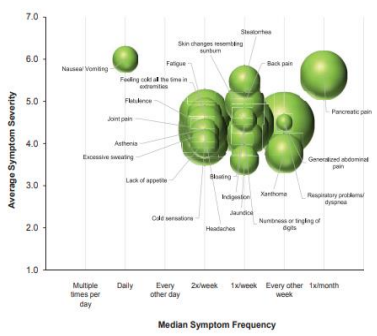
Evidence Generation Directed at Unmet Needs will Further Differentiate ARO-APOC3 and Support Reimbursement

- Genetically confirmed or clinical diagnosis of FCS
- Hypertriglyceride-associated pancreatitis
  - Major risk in FCS & SHTG and increases with increasing TG levels and history of pancreatitis
  - 12% of patients with TG levels >500 mg/dL report an episode of pancreatitis in the past 12 months[1]
- Quality of Life and Burden of Illness
  - Severely elevated triglycerides have significant impact on quality of life and pain, cognition, anxiety and other symptoms contribute to burden of illness
- Residual risk posed by atherogenic lipids and lipoproteins

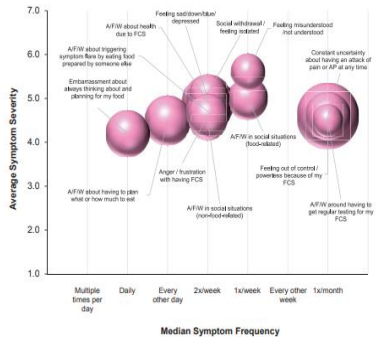
Incidence Rate of Acute Pancreatitis(AP) by Triglyceride Concentration and History of Hospitalization for AP[3]



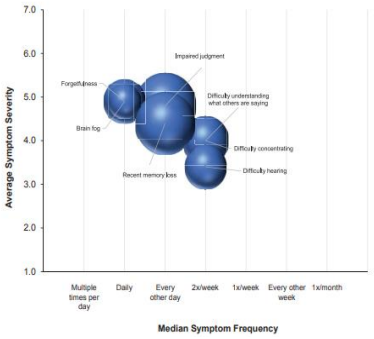
Physical Symptoms[2]



Emotional Symptoms[2]



Cognitive Symptoms[2]



1. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med*. 2014 Oct;25(8):689-94.; 2. Davidson et al Burden of disease in patients with FCS. *Journal of Clinical Lipidology*, Vol 12, No 4, August 2018.; 3. Adapted from: Sanchez RJ et al. Association of triglyceride levels with the incidence of initial and recurrent pancreatitis. *Lipids in Health and Disease*. 2021; 20:72.; 4. Burbridge C et al. Symptoms and dietary impact in hypertriglyceridemia-associated pancreatitis: Development and content validity of two new measures. Pharmacoeconomics – Open. 2020; 4: 1919-201

Key Areas of Focus

Prepare the Product

- Differentiate ARO-APOC3
  - Optimize label with novel endpoints beyond TG and LDL-C lowering
  - Broaden patient populations through new indications
  - Accelerate launch timelines

Prepare the Market

- Create Urgency for Accurate Diagnosis and Optimal Treatment
  - Patients are seen by an average of 5 physicians before a diagnosis of FCS and almost half receive a misdiagnosis before correct diagnosis
- Educate physicians on hypertriglyceridemia as risk factor for pancreatitis, CVD and poor quality of life
  - Educate patients that hypertriglyceridemia is risk factor for pancreatitis, CVD
  - Encourage referral to specialists where appropriate
- Optimize Reimbursement and Access
  - Build compelling value proposition across all indications
  - Pricing structure that is cost effective
  - Optimize convenience for patients for site-of-care

Prepare the Company

- Prepare Company for Launch
  - Hire local and global expertise
  - Build internal capabilities across key functions
  - Finalize go-to-market strategy for Tier 1 markets: US, Canada, UK+EU4, Japan by Q4

Analyst R&D Day June 1, 2023

Concluding Remarks

Chris Anzalone, PhD

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Update today represents substantial potential value

Late-stage clinical programs moving rapidly toward commercial

- ARO-APOC3, ARO-ANG3, Fazirsiran, Olpasiran

Earlier clinical programs show promise and clear path

- ARO-C3, ARO-PNPLA3

Pulmonary appears to work

- ARO-RAGE up to 95% KD
- ARO-MMP7 and ARO-MUC5AC to follow
- Many additional targets

Platform expansion continues

- Skeletal muscle
  - Will partner or initiate P1 for ARO-DUX4 over next month
  - CTA for next muscle target expected in Q4
- CNS
- CNS systemic delivery
- Adipose

Many areas we address have been historically neglected, but are now better appreciated

Cardiovascular Disease

Treating CV was under investigated because of length and cost of CVOTs. CV is now major focus due to continued risk and genetic data: **ARO-APOC3 and ARO-ANG3**

NASH

NASH treatment has seen many failures, but...Recent NASH treatment data have been promising and PNPLA3 is arguably the best genetically-validated target in NASH. **ARO-PNPLA3**

Pulmonary

Few inhaled drugs have been approved. Persistent need in COPD, asthma, and IPF, and recent advances have increased interest in the field. **ARO-RAGE, ARO-MUC5AC, ARO-MMP7, more...**

CNS

Recent CNS advances have increased interest in new treatments. **ARO-SOD1, more...**

Adipose

Interest in obesity has increased and persistent metabolic treatment need. **Many targets**

We mentioned the last 6 years, what about the next 6?

During the 6 years between 2017 and 2023, we will have brought **18 drug candidates into clinical studies**

During the 6 years between 2023 and 2029, we expect to bring **~20 additional drug candidates into clinical studies**

Given that RNAi and the TRiM™ platform are increasingly validated, **we expect the majority of these ~40 drug candidates to make it to approval**

We don't look for benchmarks: we want to *be* the benchmark

Expectations over the next 6 years

- **Multiple product launches**
  - Spanning small and broad markets
  - Different therapeutic areas
  - Wholly-owned and partnered
- ***Dozens* of drug candidates in clinical studies**
  - Spanning early- to late-stage development
  - Across different therapeutic areas
  - Wholly-owned and partnered

We are truly a different kind of biotech company

But how do we pay for it?

Multiple Capital Sources to Reduce Long Term Cost of Capital

Equity

- Common stock
- **Last raise was 3.5 years ago**

Business Development

- Milestones from current deals and new deals
  - **$956m brought in from BD to date**
  - **Expect ~1 new deal/year**

Debt

- Convertible bonds
- Bonds
- Secured debt/ Term loans

Creative Sources

- Product financing
- Royalty monetization

Commercial Sales

- Expect several launches over next 5 years
- Royalties from partner launches

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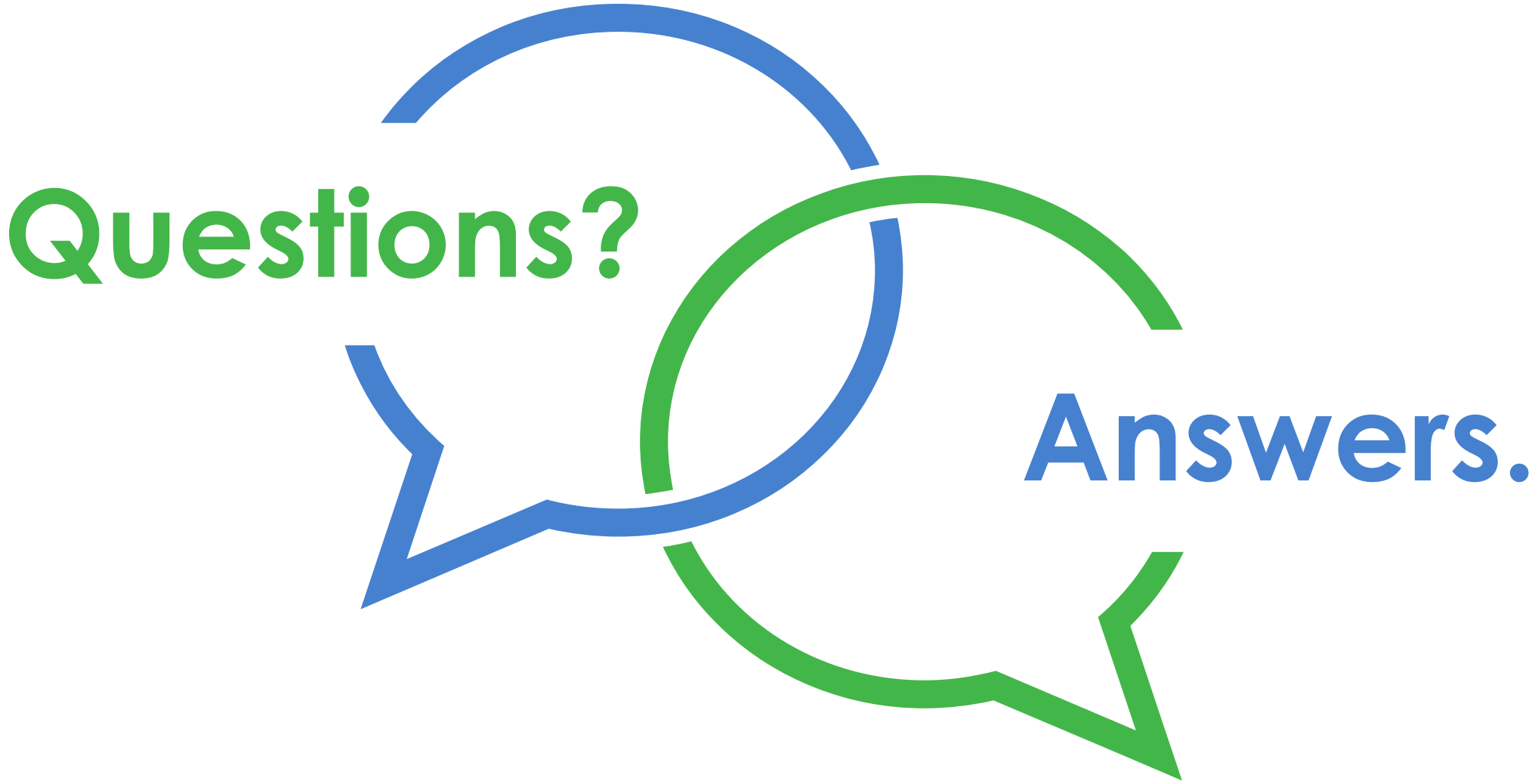

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