# Pulmonary R&D Day

May 26, 2022

arrowhead pharmaceuticals

Pulmonary R&D Day, May 26, 2022

# Welcome and Introductions

## Vince Anzalone, CFA

arrowhead pharmaceuticals

# Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

# Panelists

## University of Kansas Medical Center

**Mario Castro, MD, MPH**
L. E. Phillips and Lenora Carr Phillips Professor of Medicine
Vice Chair for Clinical and Translational Research
Chief, Division of Pulmonary, Critical Care and Sleep Medicine

**Matthias Salathe, MD**
Interim Vice Chancellor of Research
Professor and Chair of Internal Medicine

## Arrowhead Pharmaceuticals

**Vince Anzalone, CFA**
Vice President, Finance & Investor Relations

**Chris Anzalone, PhD**
President and CEO

**Erik Bush, PhD**
Group Vice President, Biology

**James Hamilton, MD, MBA**
Senior Vice President, Discovery & Translational Medicine

**Javier San Martin, MD**
Chief Medical Officer

**Anjli Warner, MBA**
Senior Director, Commercial

# Agenda

| | |
|---|---|
| 10:00-10:05 | Welcome and Introductions – Vince Anzalone |
| 10:05-10:15 | Overview of Arrowhead – Chris Anzalone |
| 10:15-10:35 | Non-clinical Pharmacology – Erik Bush |
| 10:35-10:50 | Non-clinical Toxicology – James Hamilton |
| 10:50-11:20 | Mucins in Obstructive Lung Disease – Mario Castro |
| 11:20-11:40 | RAGE: Pulmonary Inflammatory Disease – Matthias Salathe |
| 11:40-11:55 | Break to Serve Lunch |
| 11:55-12:15 | Clinical Development – Javier San Martin |
| 12:15-12:25 | Market Research and Opportunity – Anjli Warner |
| 12:25-12:35 | Concluding Remarks – Chris Anzalone |
| 12:35-1:00 | Q & A – Panel |

Pulmonary R&D Day, May 26, 2022

# Overview of Arrowhead

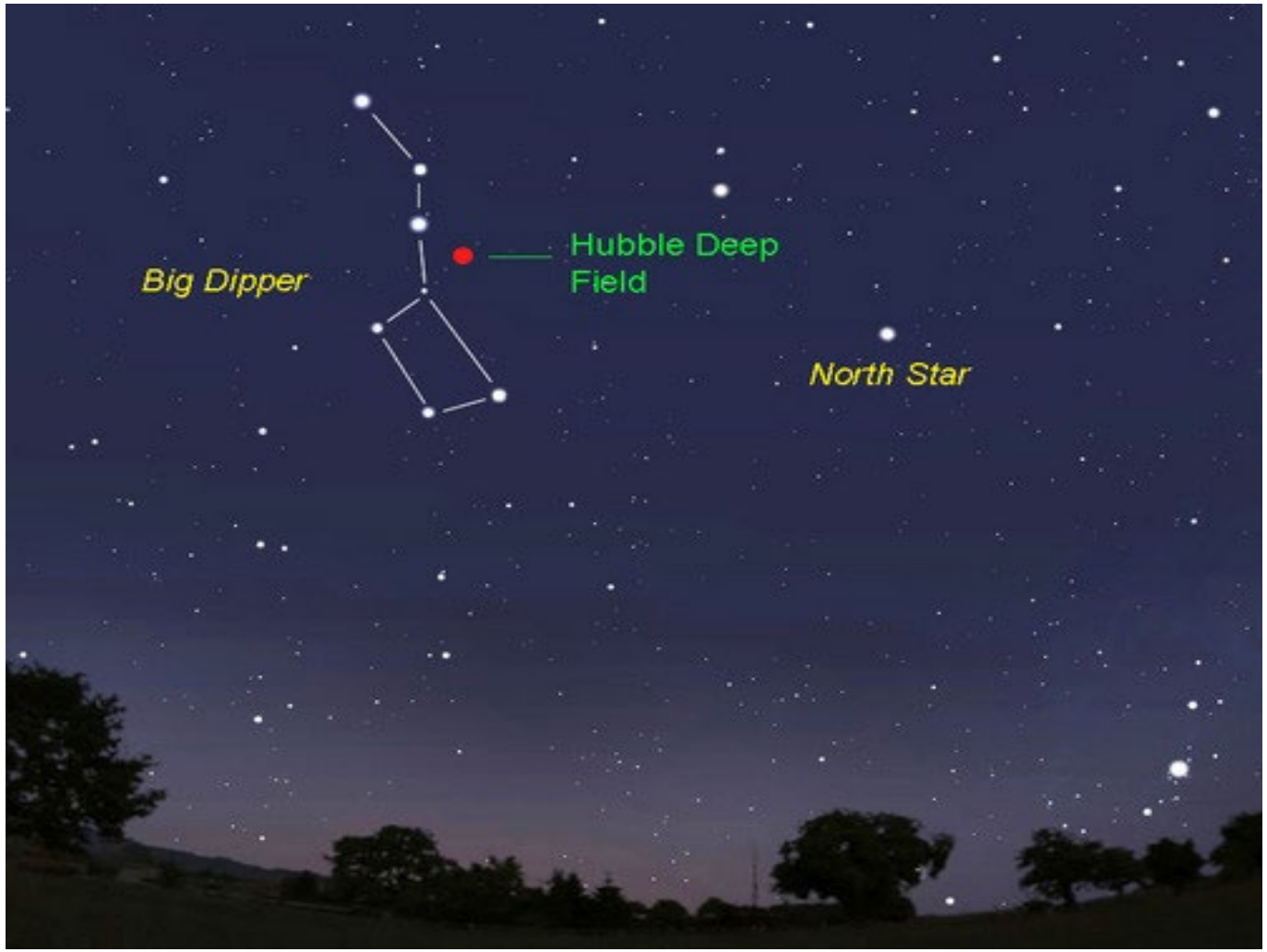
Chris Anzalone, PhD

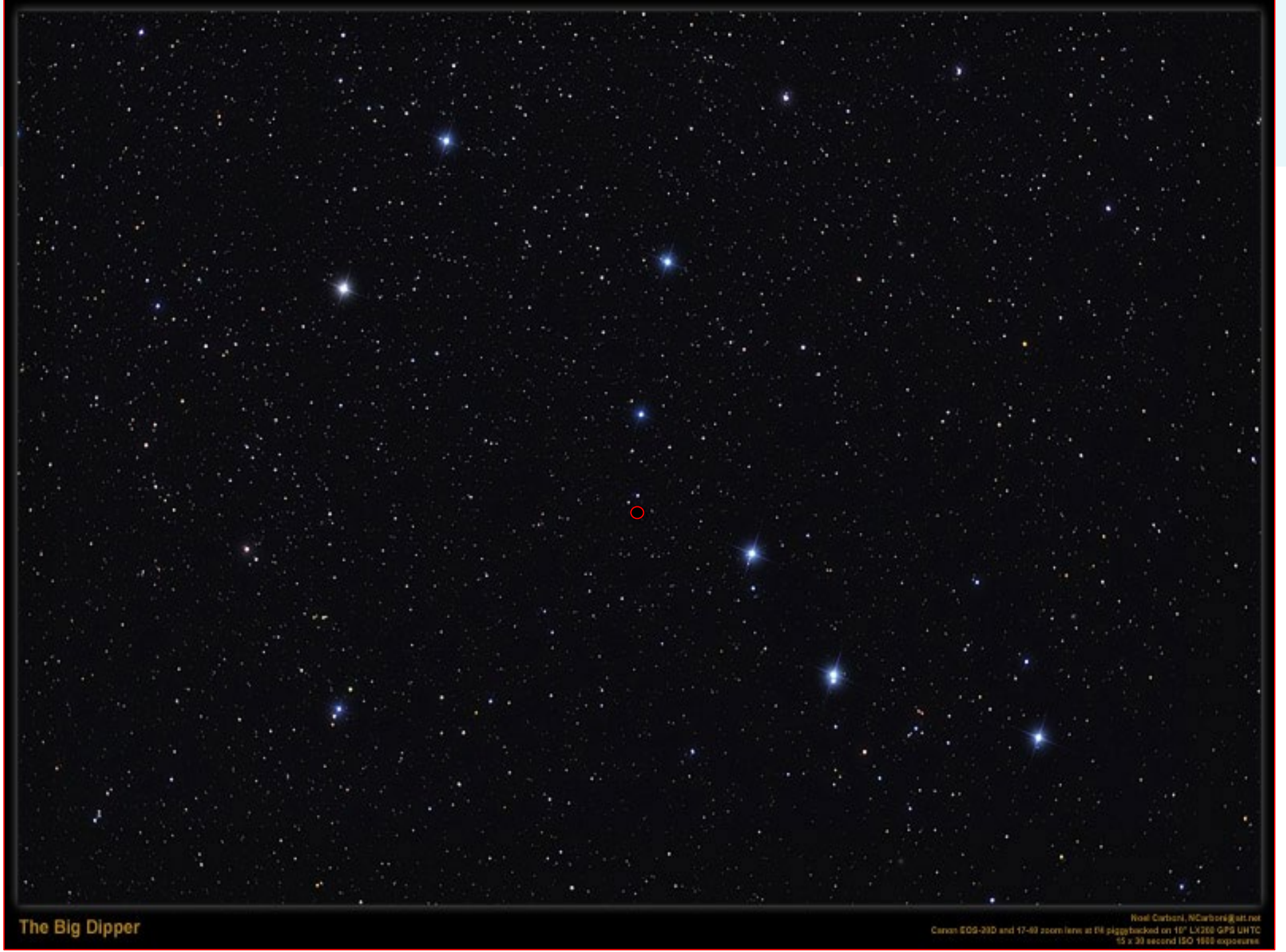
arrowhead pharmaceuticals

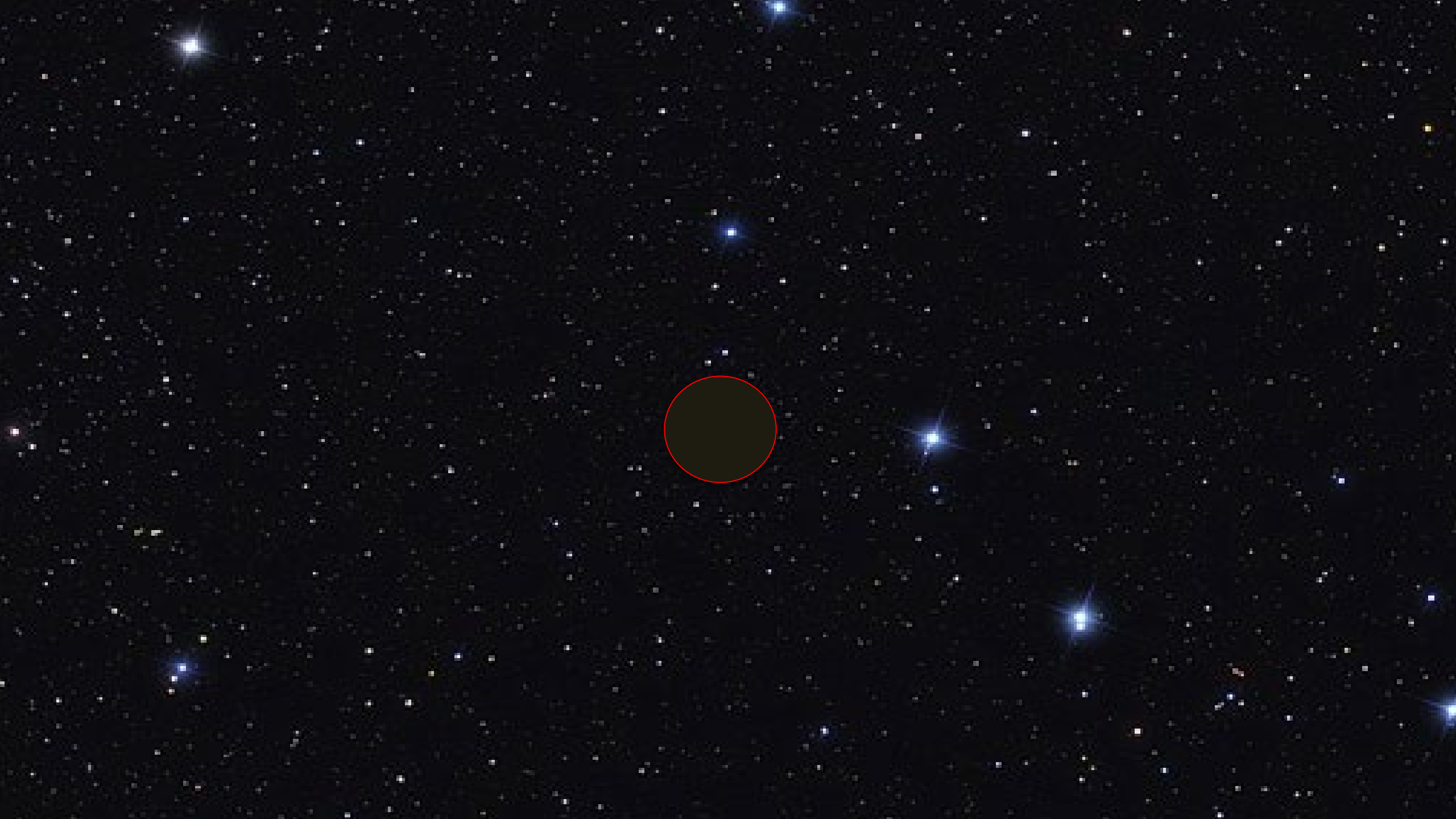
# ~4 ½ years ago we had an R&D Day to introduce TRiM™

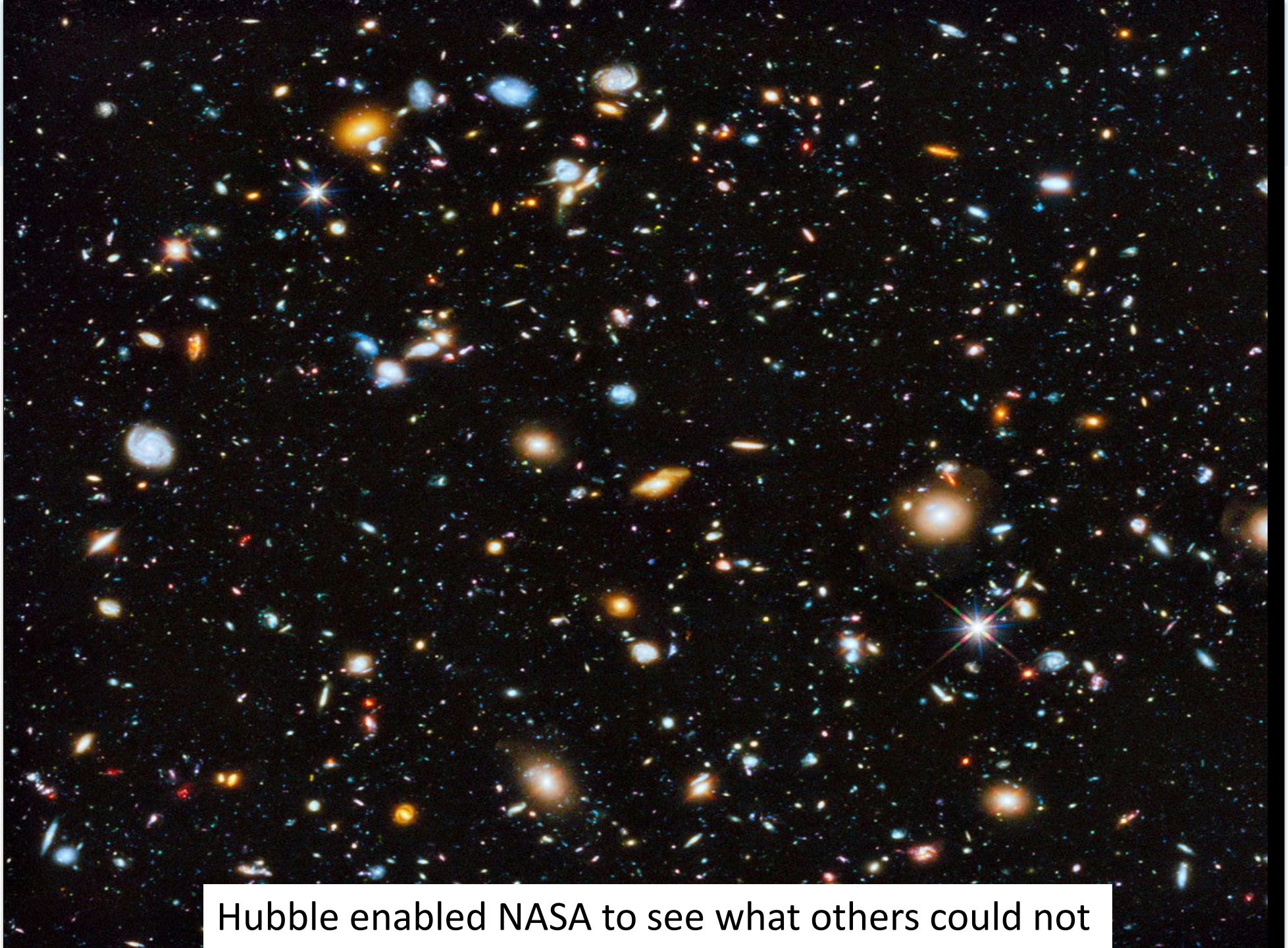
- The prior year we discontinued the DPC Platform
- Our stock was trading ~$3.00
- I showed the following slides about the Hubble telescope

# Hubble Telescope




The Big Dipper
Noel Carboni, NCarboni@att.net
Canon EOS-20D and 17-40 zoom lens at f/4 piggybacked on 10" LX200 GPS UHTC
15 x 30 second ISO 1600 exposures





Hubble enabled NASA to see what others could not

# We developed tools to enable us to see what others could not

- We used them to develop the TRiM™ platform
  - Highly potent RNAi triggers
  - Important new hepatocyte-directed drug candidates
  - The possibility of getting outside the liver
- Today's presentations are an outgrowth of that
  - Expanding RNAi: taking it to where unmet medical needs are
  - Also an expression of our commitment to continuous innovation
    - We learned from our first clinical pulmonary program
    - In less than 1 year after we stopped treating patients with ARO-ENaC, we expect to start dosing human subjects in our 2 new programs

# Today, I hope you walk away with the following messages

- The targets we are addressing are important and potentially powerful
- Substantial unmet medical need persists
- Our non-clinical data suggest that we have a good shot at success
- Our clinical plan is appropriate and achievable
- We're just getting started: with the pulmonary platform, potential for **many** important medicines

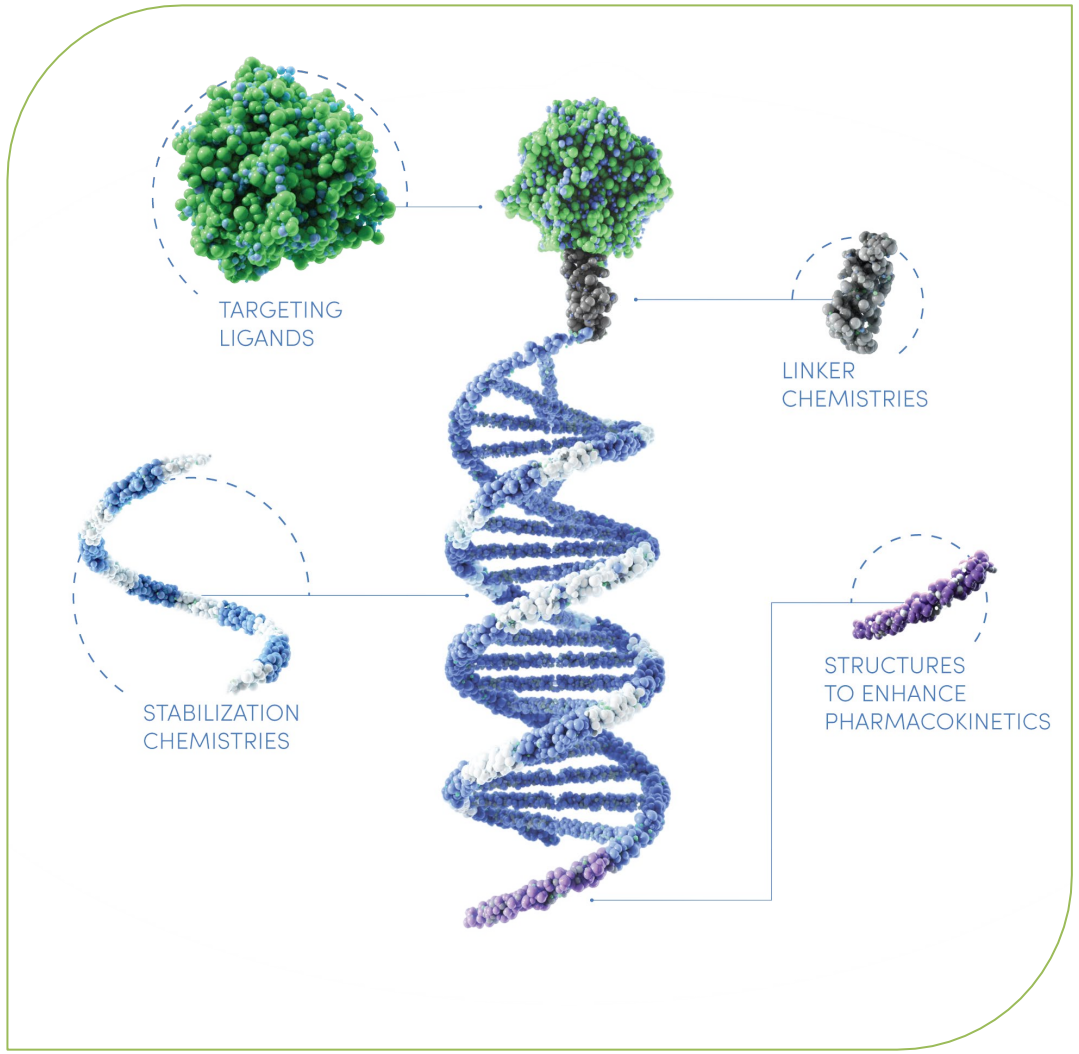
Pulmonary R&D Day, May 26, 2022

# Non-clinical Pharmacology

Erik Bush, PhD

arrowhead pharmaceuticals

# TRiM™ Platform for Pulmonary Delivery




## Algorithmic approach to sequence design and selection is unchanged

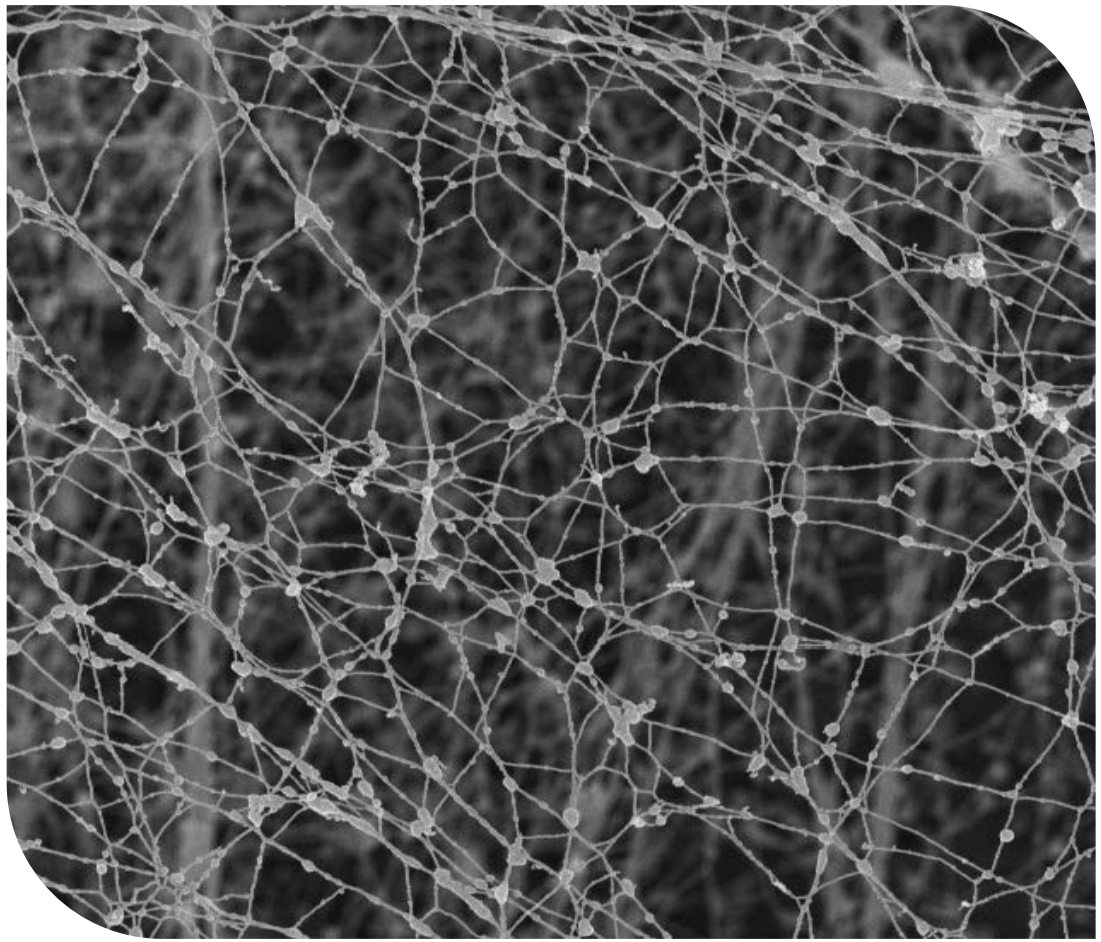
- Avoid microRNA and off-target knockdown while maximizing on-target activity
- Enhanced focus on early compound screening in non-GLP inhaled tox studies

## Enhanced modification chemistry (ARO-RAGE)

- Maximize duration of knockdown, minimize dose frequency

## avβ6 small molecule targeting ligand drives epithelial cell uptake

# TRiM™ Platform for Pulmonary Delivery



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<br>Respiratory viruses, mRNA-LNP ~100 nm |
| **Net negative charge** | Anionic compounds minimize electrostatic interactions with mucus |
| **Soluble** | |

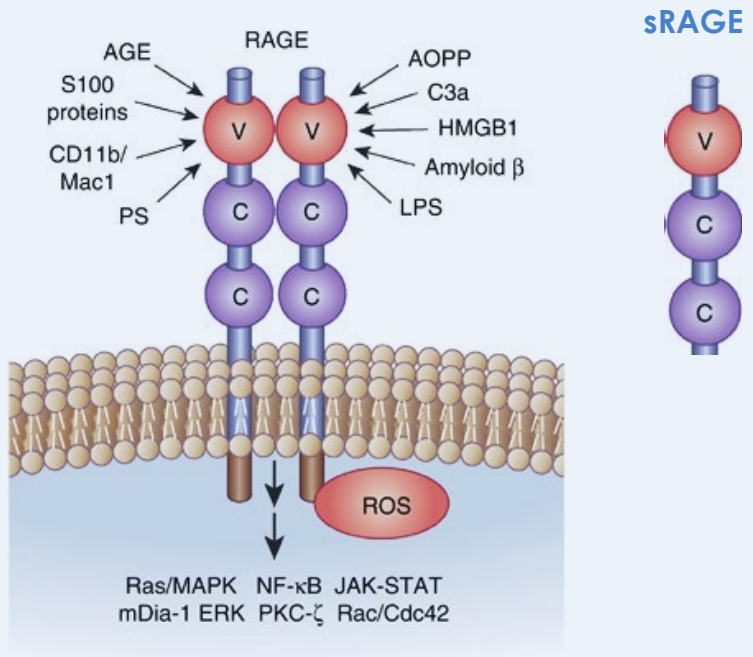
## Evidence for efficient delivery through airway mucus

- *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 Rationale

- **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 ALI/ARDS & viral inflammation
- **Difficult to drug with small molecules**
- **Full-length receptor cleaved to release soluble sRAGE (circulating biomarker of target engagement)**

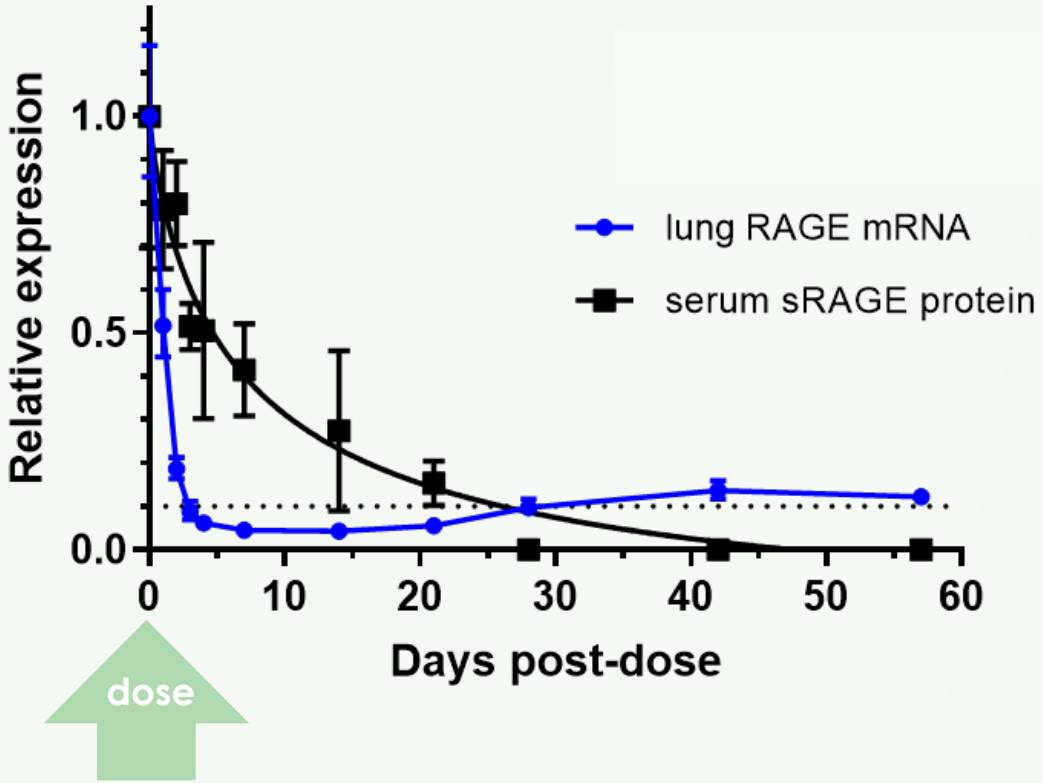
**Receptor for advanced glycation end-products**



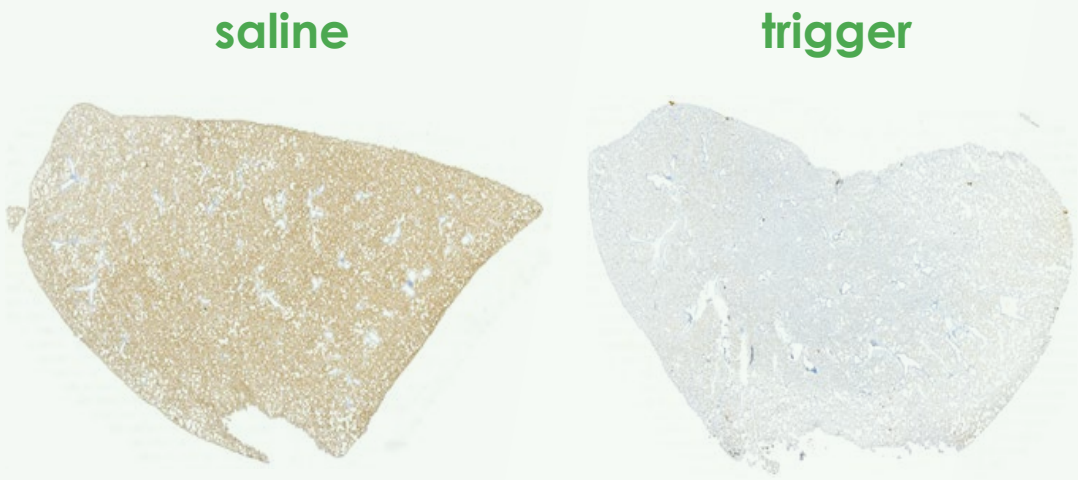

*Kidney International (2012), 82, 733-734*

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

**Rat RAGE expression**
**0.5 mg/kg inhaled deposited dose**
**RNAi trigger conjugate**

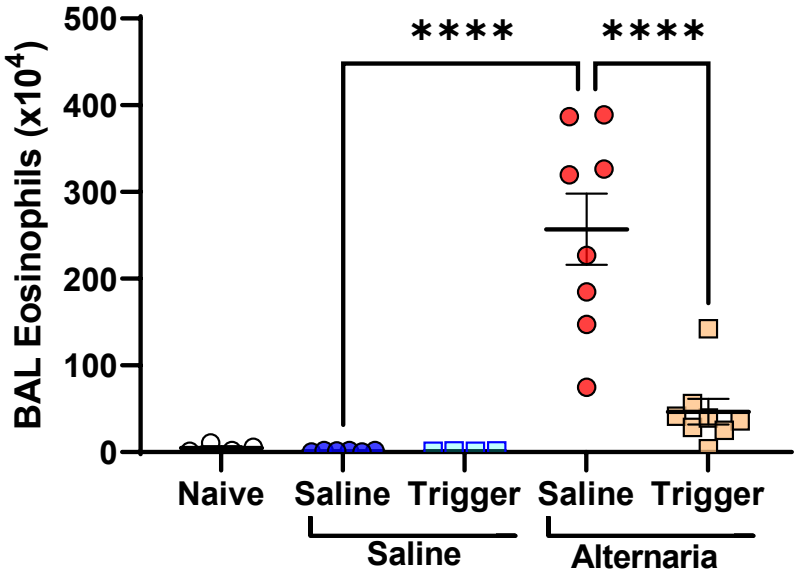


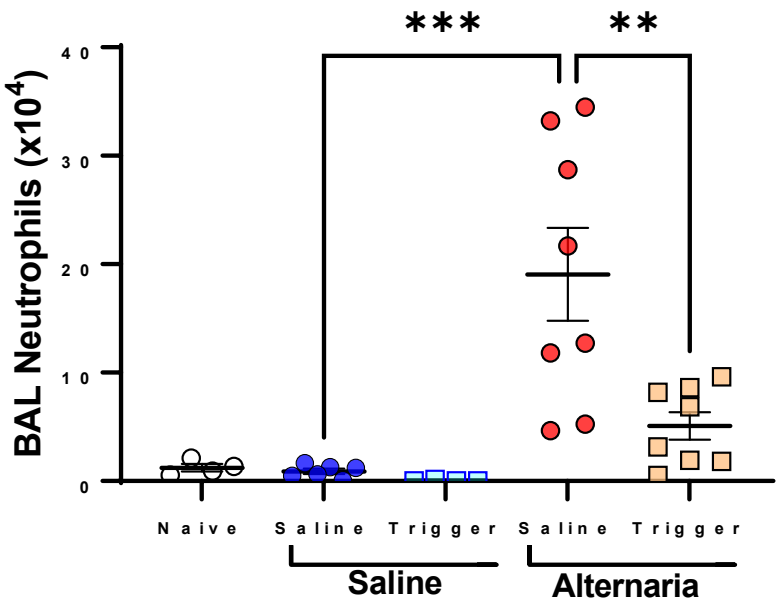

**Day 36 lung**
**RAGE protein IHC**

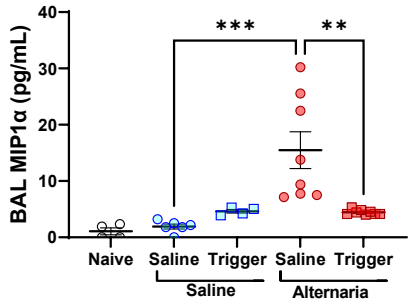


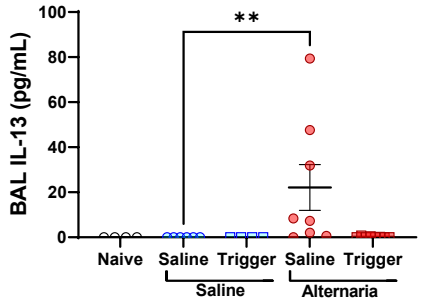

Kasaharas, et al,, A5013, ATS 2022

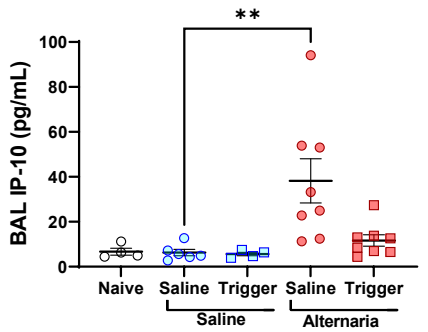
# Silencing RAGE Limits Inflammation in a Rat Model of Allergic Asthma



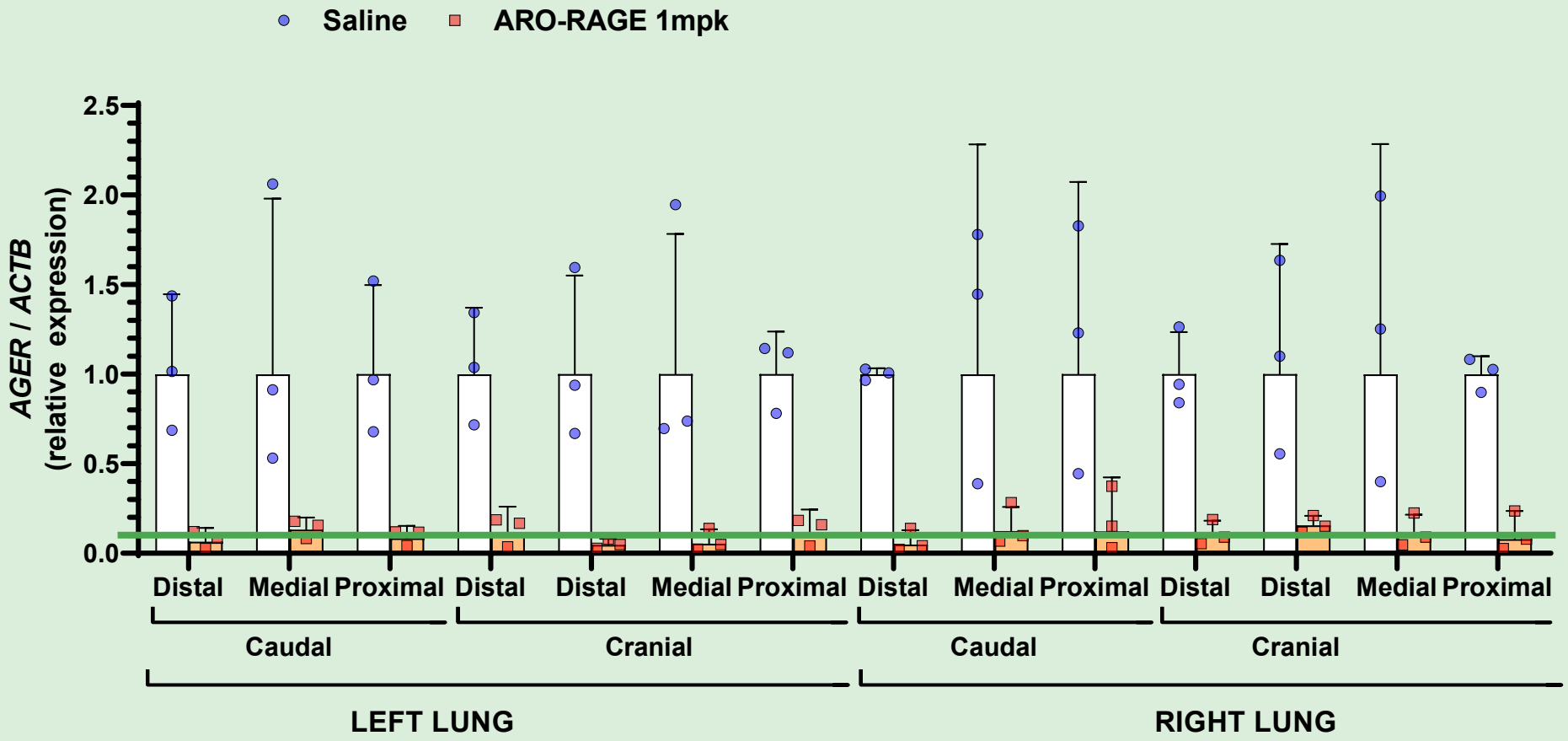




RAGE silencing reduces inflammatory cell recruitment and cytokines

Kasaharas, et al,, A5013, ATS 2022

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




90% silencing

Kasaharas, et al,, A5013, ATS 2022

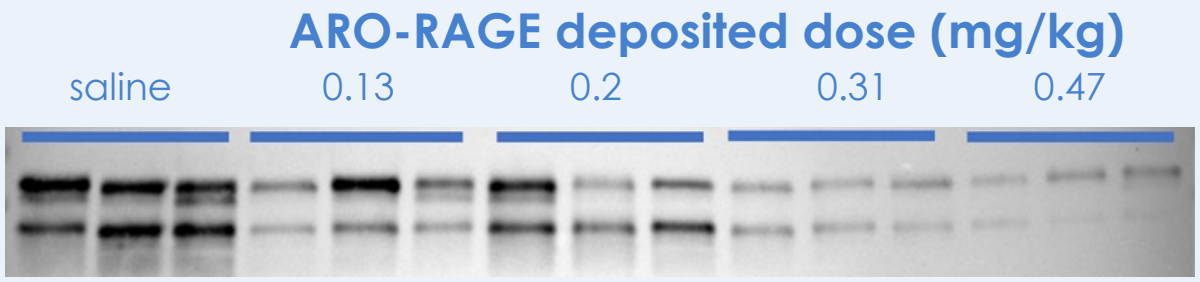


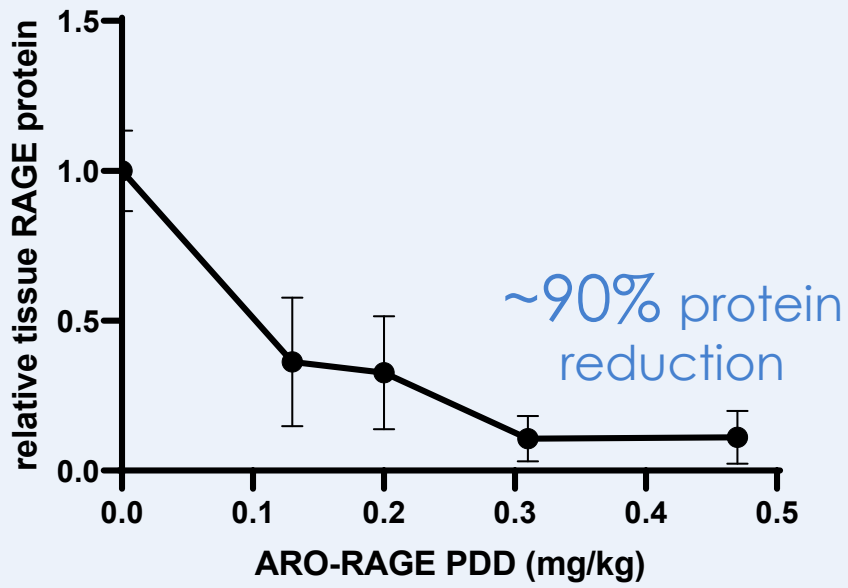
Pulmonary R&D Day May 26, 2022

# ARO-RAGE Dose-Response in Cynomolgus Monkeys

## Cyno lung RAGE protein expression

4 weeks post-inhalation (single dose)

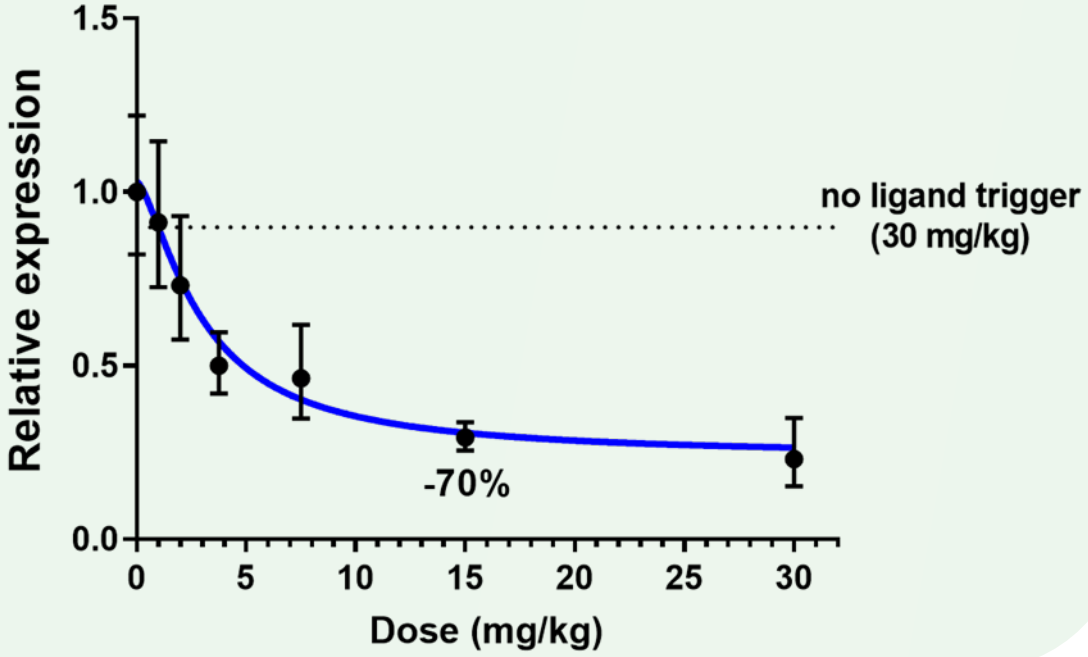


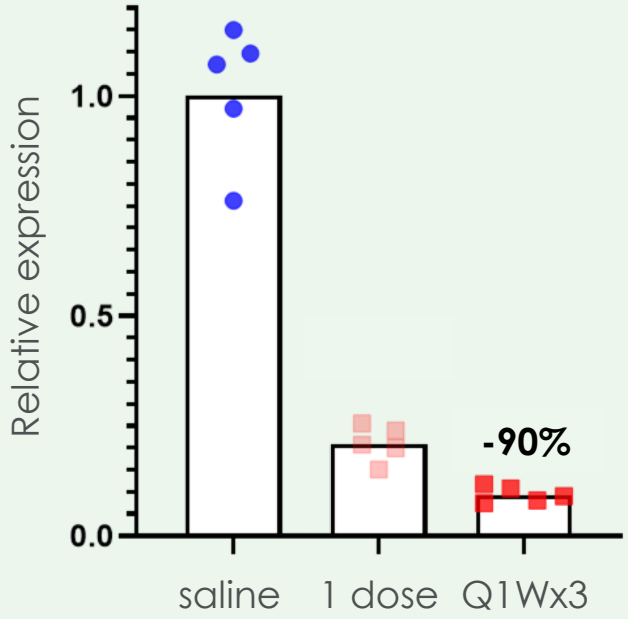
# Silencing Pulmonary RAGE with Subcutaneous RNAi Trigger Conjugate Administration

**Subcutaneous ARO-RAGE may potentially provide another route of administration option for patients and physicians**

## Rat whole lung RAGE mRNA expression
1 week after single subcutaneous injection

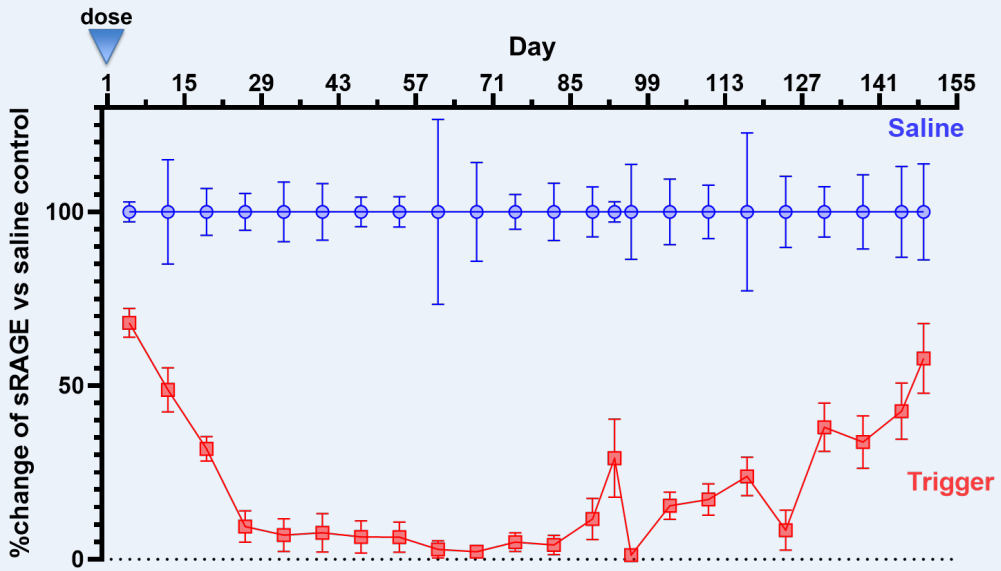



## Rat whole lung RAGE mRNA expression
15 mg/kg subcutaneous injection

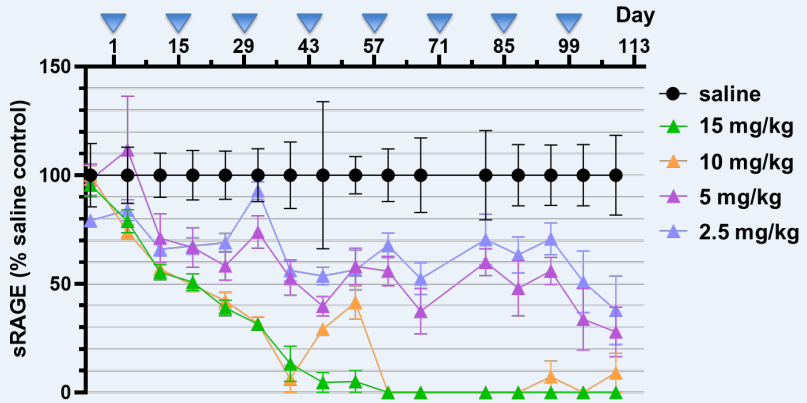


# Subcutaneous Administration Achieves Deep and Sustained Reduction in RAGE Expression

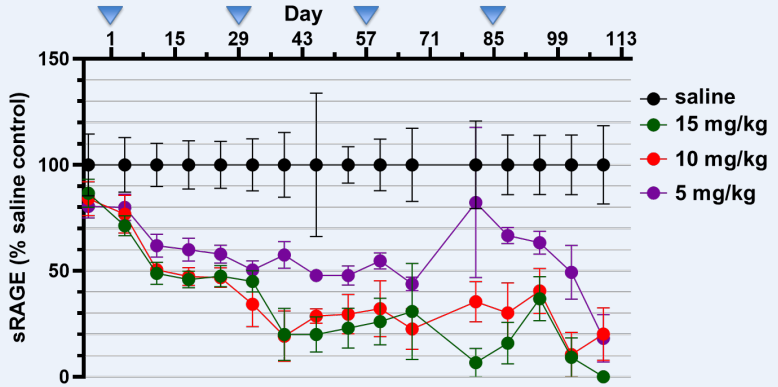
## Single inhaled aerosol dose (0.5 mg/kg)




## Q2W subcutaneous



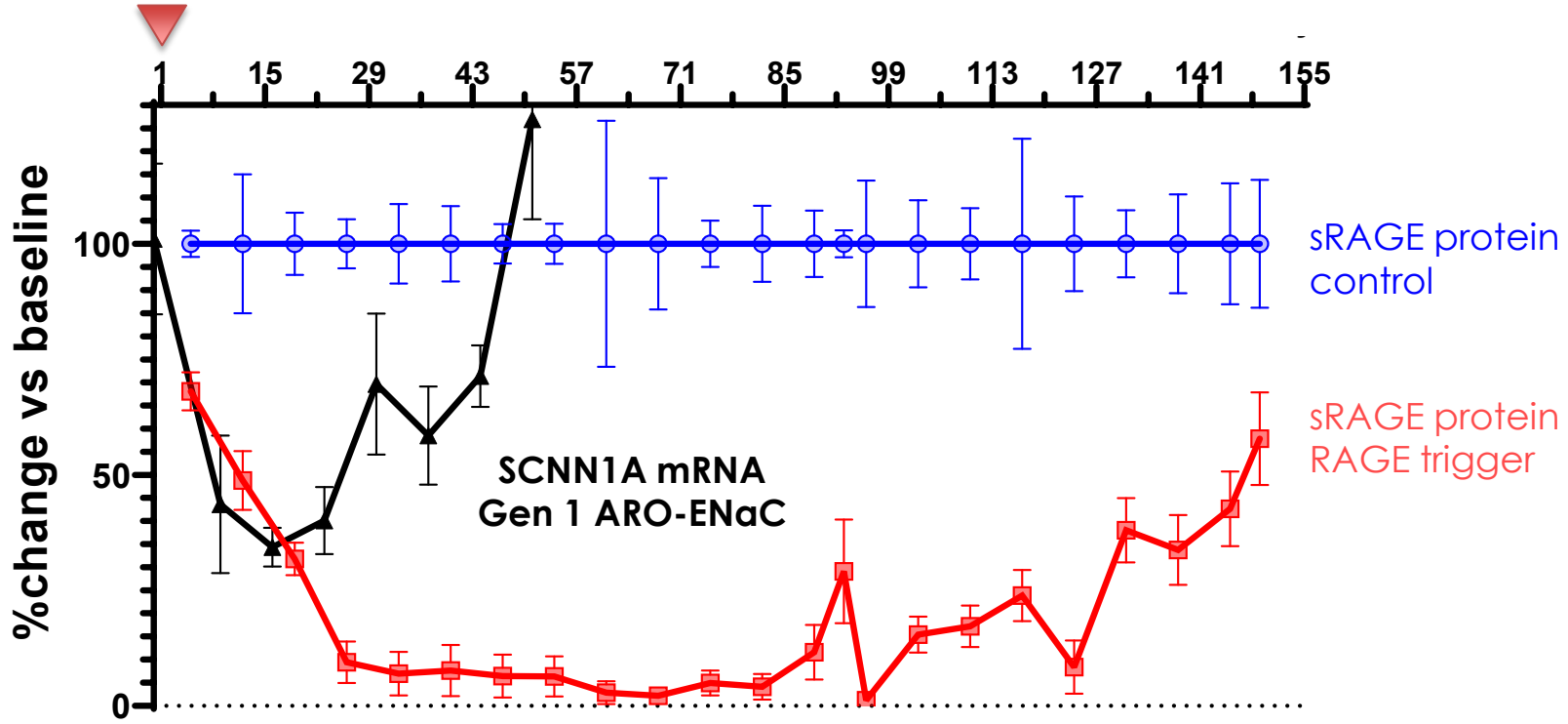

## Q4W subcutaneous



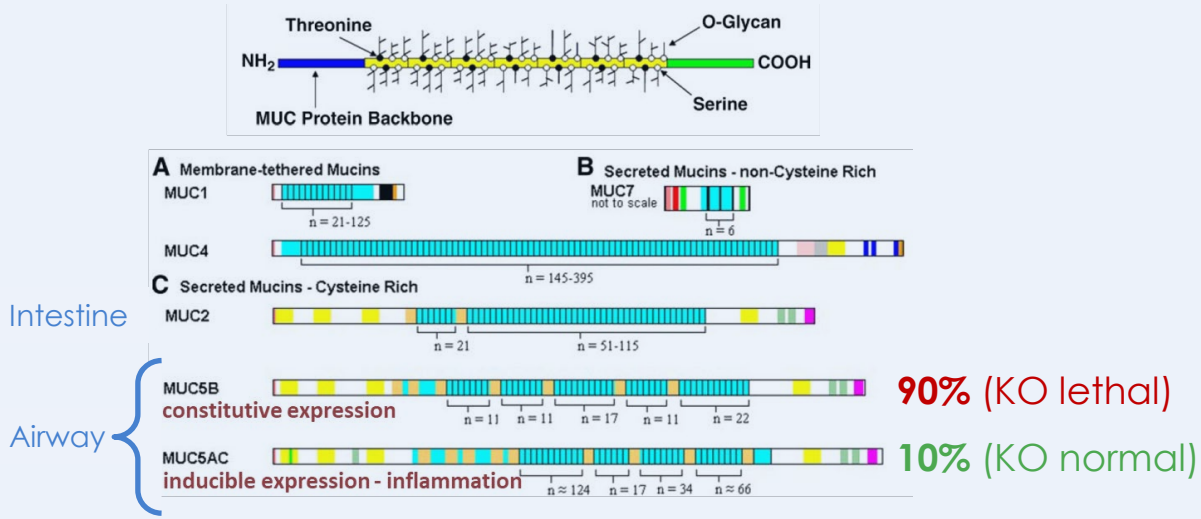
# Improved Pharmacodynamic Response with Next Generation Pulmonary Drugs: RAGE trigger vs ARO-ENaC

ARO-ENaC: 2 x 0.7 mg/kg (Day 1 and 2)

RAGE trigger: 0.5 mg/kg (Day 1)

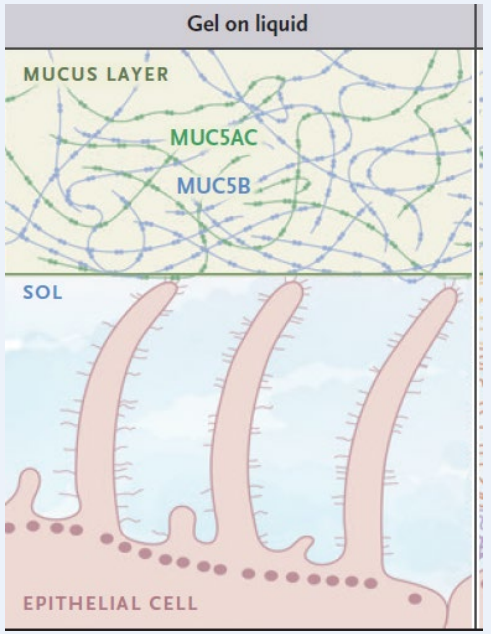


# Targeting MUC5AC for Severe Asthma Rationale

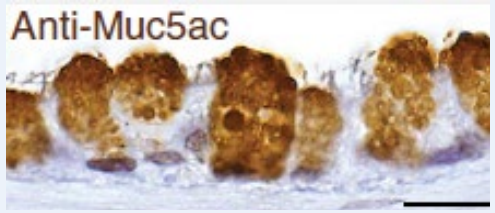



**90%** (KO lethal)

**10%** (KO normal)




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


- **High MUC5AC mucus plugs associated with fatal asthma**

Am J Respir Crit Care Med 2016,194. 1296-1299
Lancet Respir Med 2019, 7. 20-34

# Targeting MUC5AC for Severe Asthma Rationale

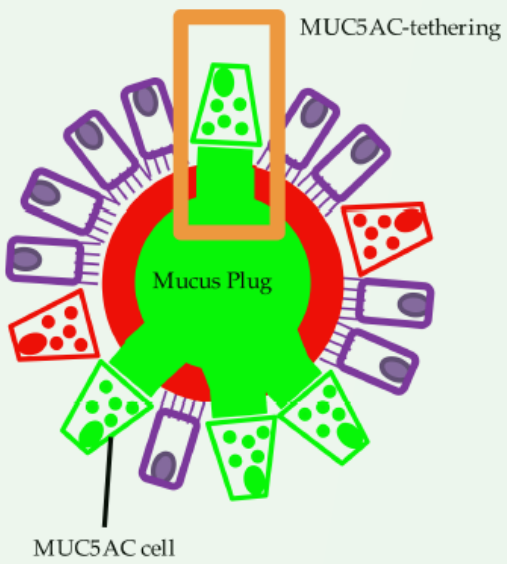
The Journal of Clinical Investigation BRIEF REPORT

## 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**

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,

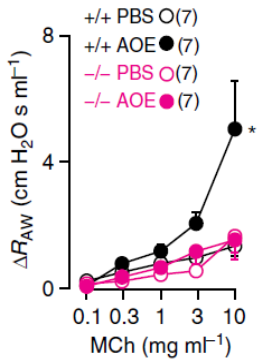
# Targeting MUC5AC for Severe Asthma Rationale

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

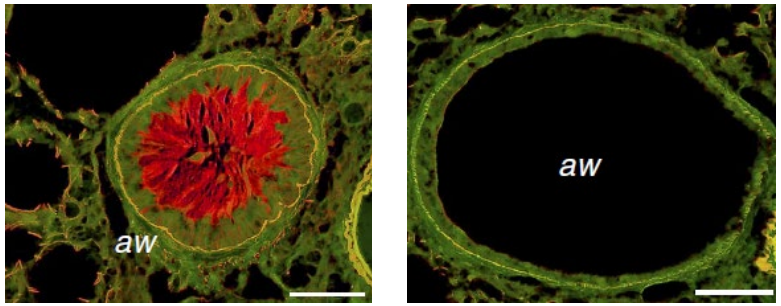
**The polymeric mucin Muc5ac is required for allergic airway hyperreactivity**

**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$^{-/-}$**



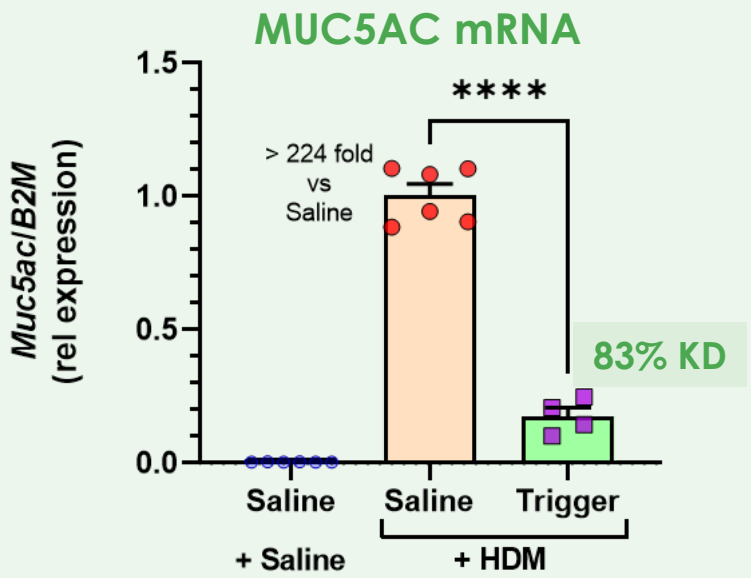

Nat. Commun. 2015, 6:6281

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

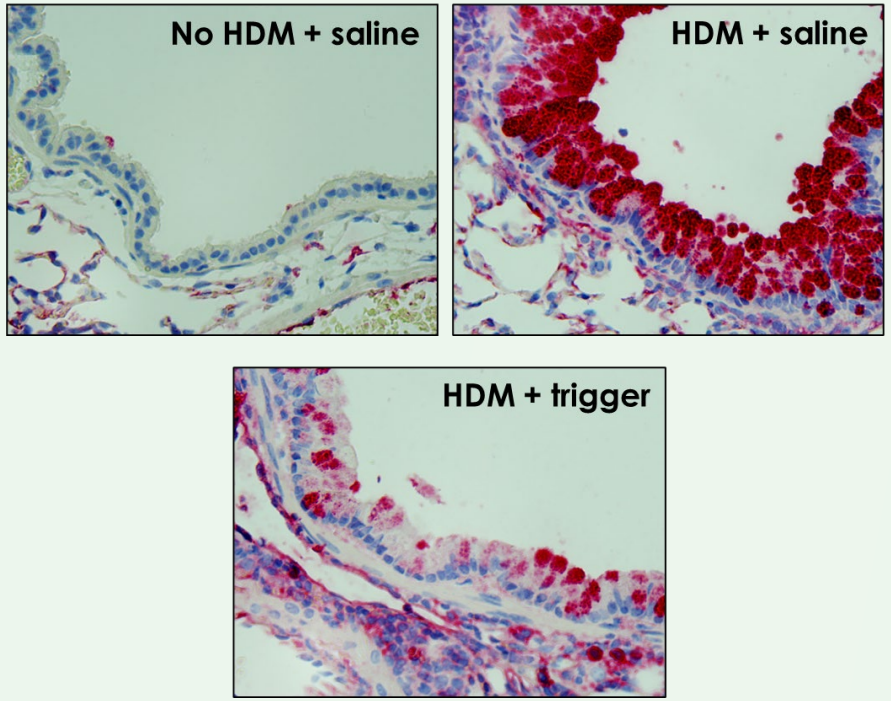
- Inflammatory mediators promote MUC5AC expression and secretion
- Reflects clinically important prolonged effects of allergen exposure experienced by asthma patients

# Silencing MUC5AC Expression in a Mouse Model of Allergic Asthma

## Mouse allergic asthma models: HDM, IL-13




## MUC5AC protein (IHC)

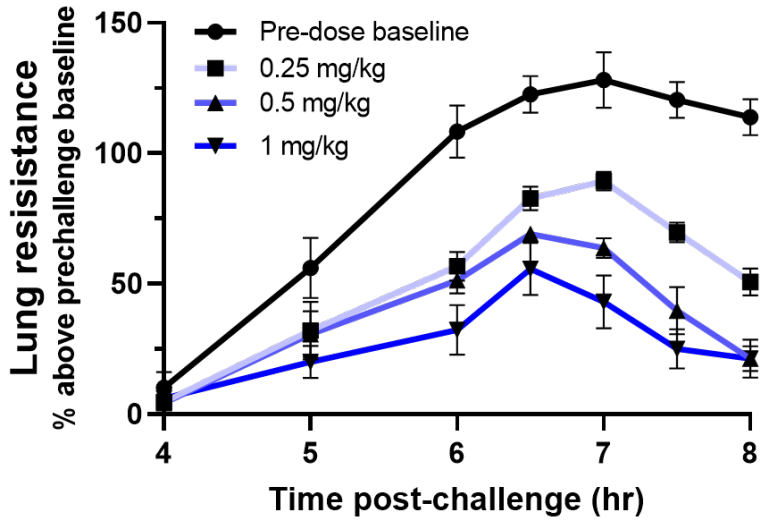



70-90% silencing of induced MUC5AC expression (similar result in cynos)

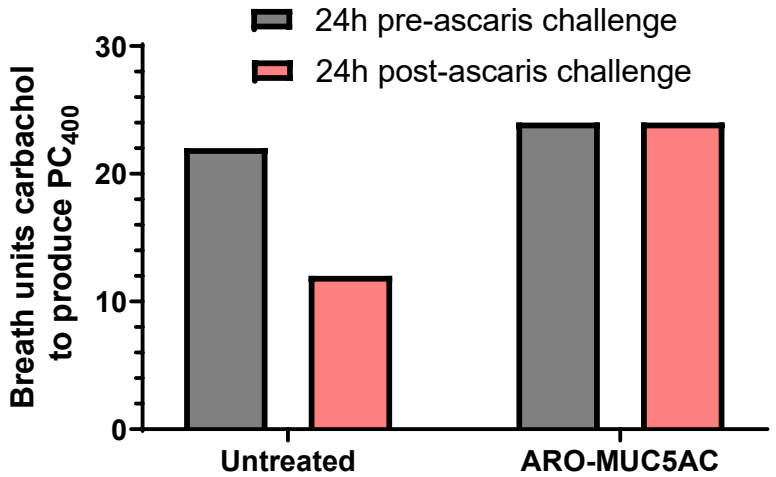
Nicholas, et al,, A5491, ATS 2022

# 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)



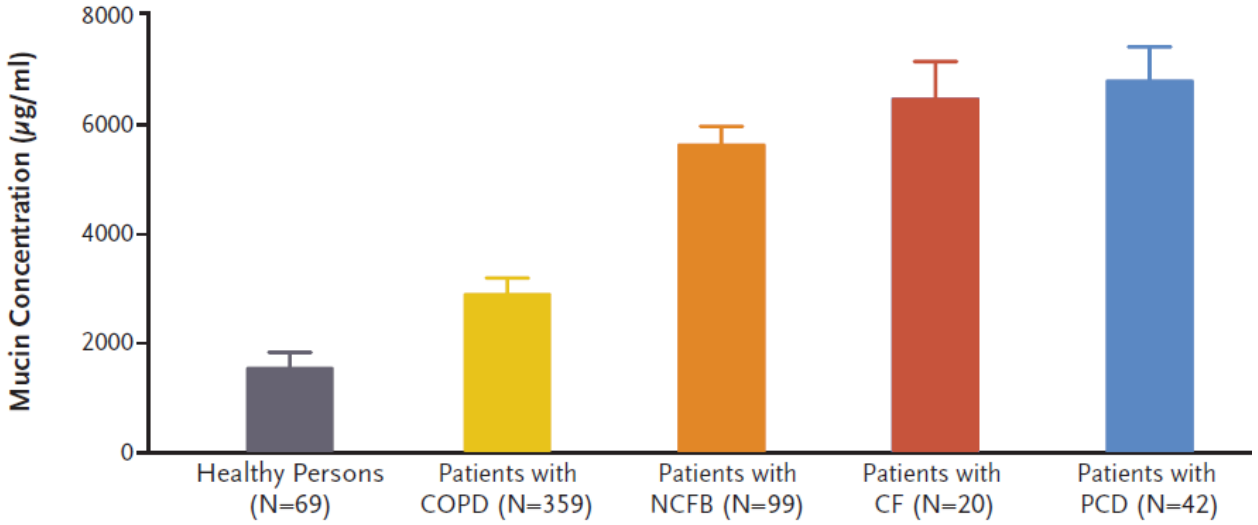

RISC-loading blocked version of ARO-MUC5AC is inactive

**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

# Targeting MUC5AC for Mucoobstructive Lung Disease Rationale




**COPD (induced sputum MS assay)**
- MUC5B increases 3x
- **MUC5AC increases >10x**

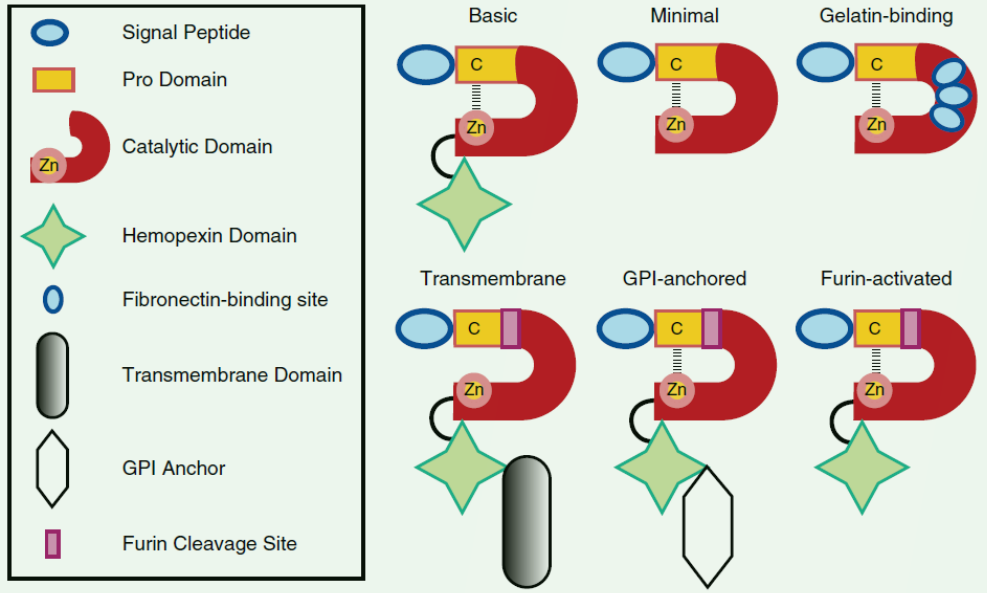
**NCFB (induced sputum MS assay)**
- MUC5B increases 6x
- **MUC5AC increases 17x**

**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 Apr 29. doi: 10.1165/rcmb.2021-0359OC

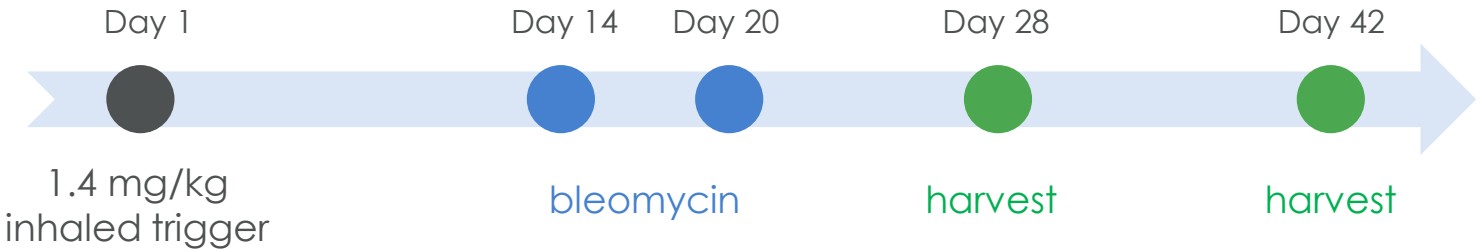
# Targeting Matrix Metalloproteinase 7 (MMP7) for IPF Rationale

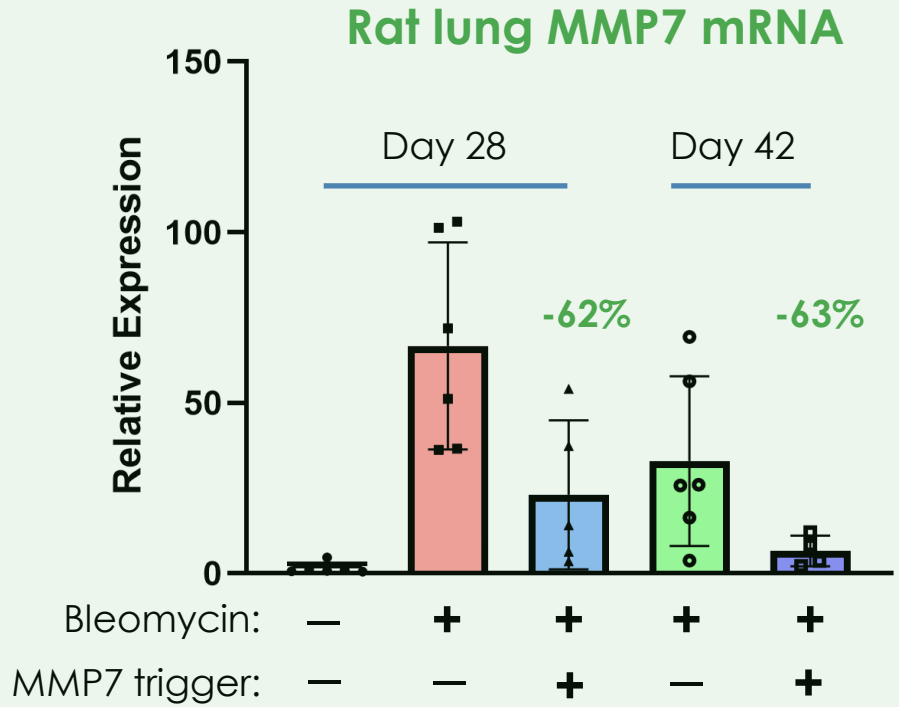
- Secreted endopeptidase expressed by injured epithelia
- One of 24 MMPs in gene family with diverse functions
- Highly overexpressed in IPF patients
- **Validated IPF biomarker:** Serum and BALF MMP7 correlate with disease severity and progression
- **Multiple roles in IPF pathogenesis:** Promotes inflammation,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



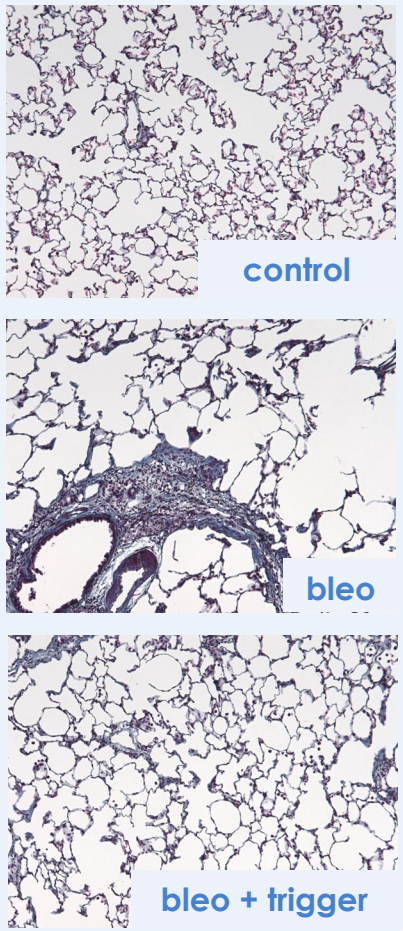

Matrix metalloproteinase (MMP) protein domain structure

# Silencing MMP7 Expression in Rat Bleomycin Injury Model of IPF

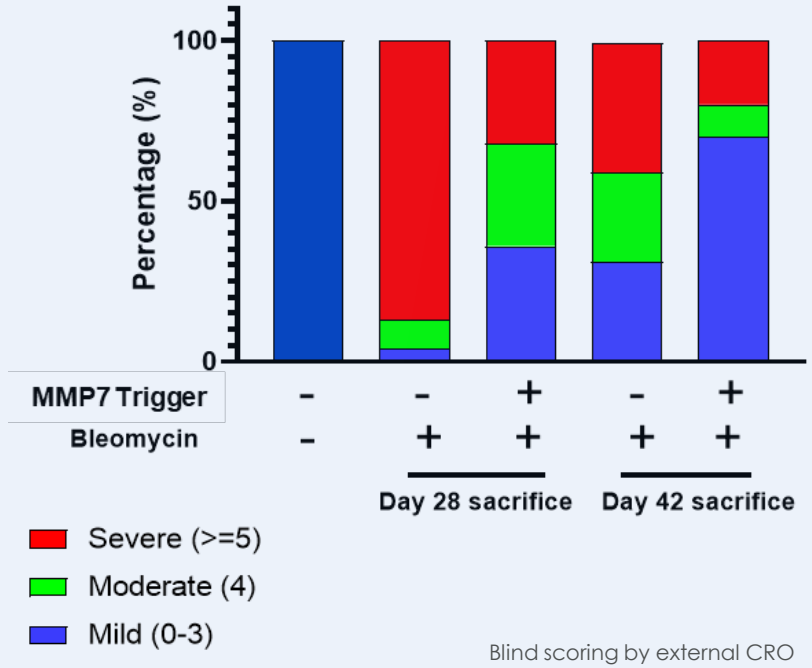


# Silencing MMP7 Limits Lung Fibrosis in Rat IPF Model



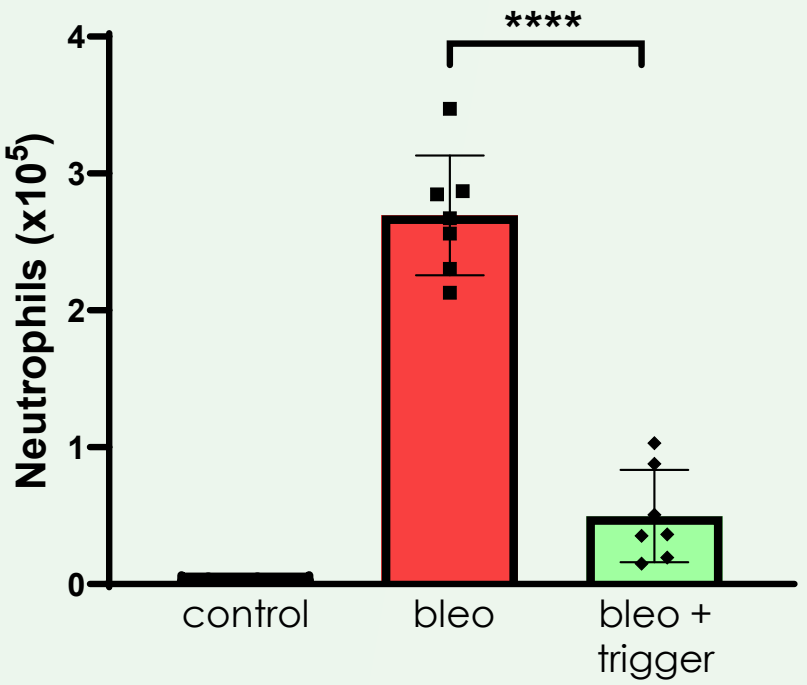

## Ashcroft pulmonary fibrosis score



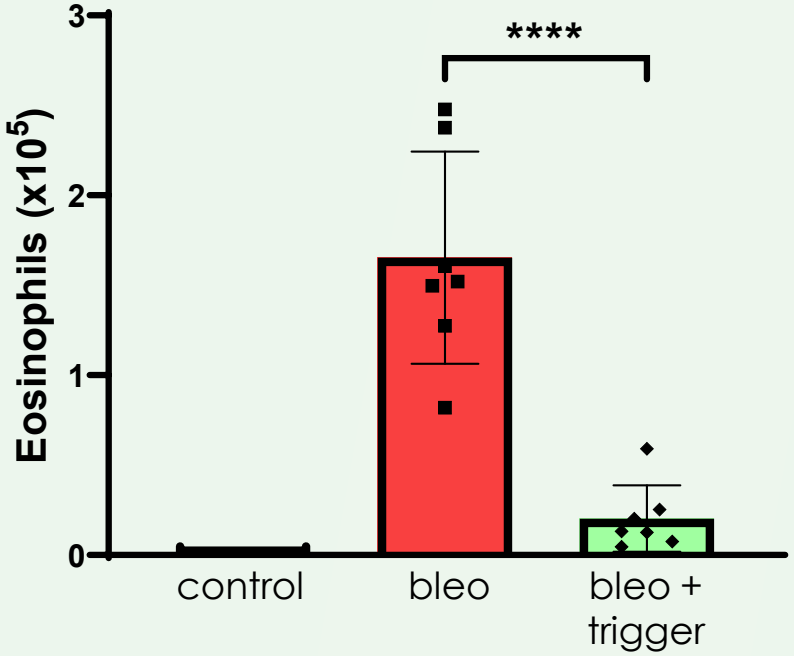

Blind scoring by external CRO

# Silencing MMP7 Reduces Inflammatory Cell Infiltration in Rat IPF Model

## BAL neutrophils



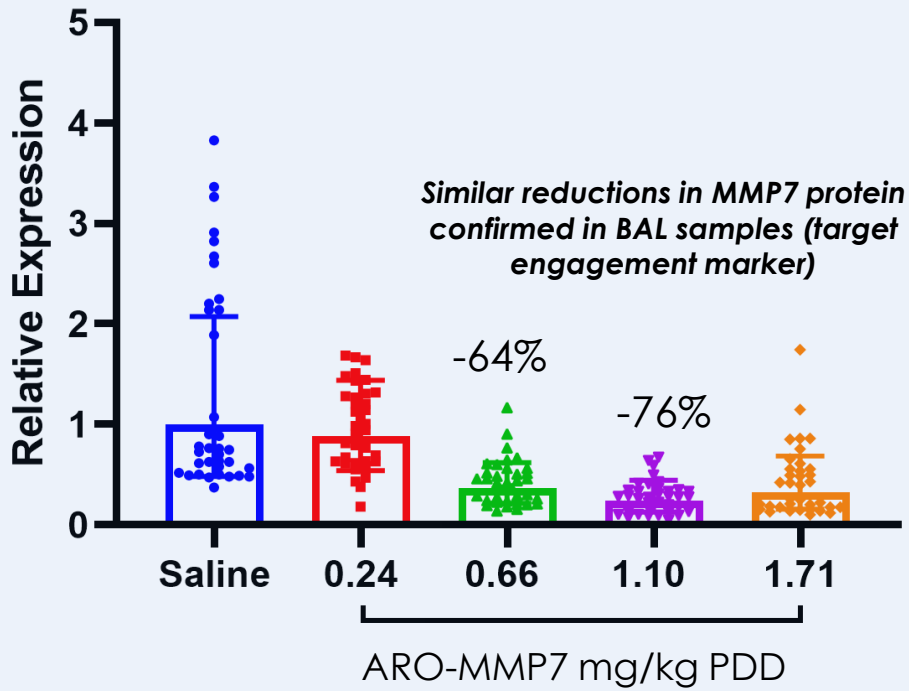

## BAL eosinophils



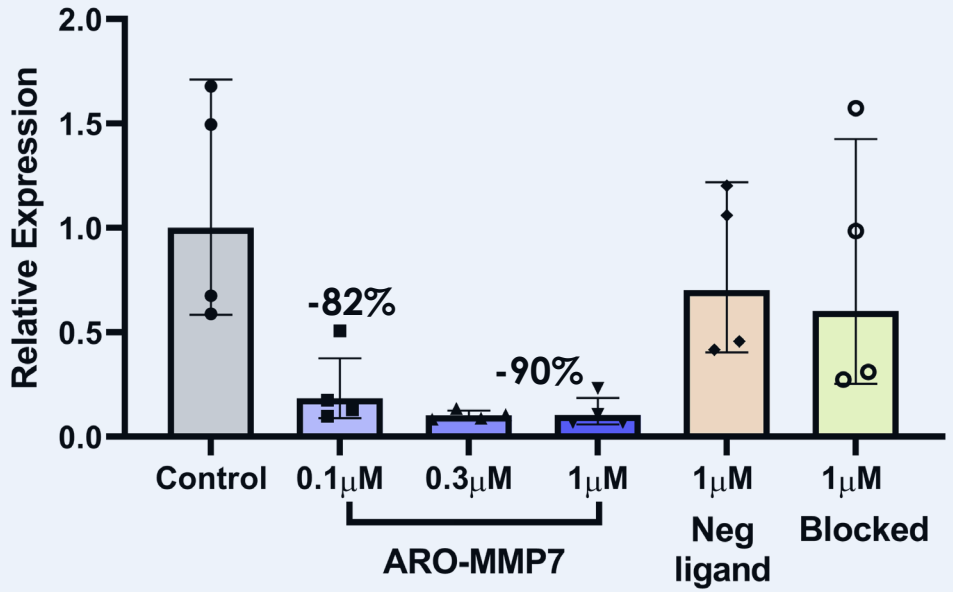

Gill et al., AJRCMB, Vol. 55, 243-251, 2016
Li et al., Cell, Vol. 111, 635–646, 2002

# ARO-MMP7 Silences MMP7 Expression in Cynomolgus Monkeys and Human Lung Tissue

## Cyno lung MMP7 mRNA expression
## N=3 cynos/group; multiple lung regions




## Human lung slice MMP7 mRNA expression
## 1 week treatment ARO-MMP7




*Additional nonclinical data will be presented at ERS meeting (September 2022)*

# Respiratory Virus Discovery

- Platform allows direct silencing of viral gene expression
- Programmable antiviral therapeutics for existing and emergent diseases
- ARO-COV candidate vs. SARS-CoV-2; lead optimization in progress
- Pipeline of additional respiratory virus candidates in discovery

# Preclinical Pharmacology Summary

- ARO-MUC5AC and ARO-RAGE are candidates for muco-obstructive and inflammatory lung diseases
- New platform designs offer improved potency, duration, and potential for subcutaneous as well as inhaled delivery
- Expanding therapeutic area opportunities into pulmonary fibrosis (ARO-MMP7) and respiratory virus (ARO-COV)

Pulmonary R&D Day, May 26, 2022

# Non-clinical Toxicology

James Hamilton, MD

arrowhead pharmaceuticals

# ARO-ENaC Voluntary Hold Based on Preclinical Findings Despite Clean Safety Profile in Clinic

- **No safety signals identified** in the AROENaC1001 Phase 1/2a clinical study
  - 24 healthy volunteers, each received doses D1, 2, 3
  - 4 CF patients, each received doses D1, 2, 3 then D22, 23, 24

- ARO-ENaC showed **no evidence of adverse effect on:**
  - Lung function ($FEV_1$)
  - Oxygen saturation
  - Chest x-rays
  - Respiratory AEs/SAEs

- Adverse local lung effects seen in chronic (6-month) rat and NHP (9-month) GLP toxicology studies
  - NHP groups received Day 1, 2, 3 dose administration every two weeks
  - Rats
    - Most groups received Day 1, 2, 3 dosing every two weeks
    - One rat group received **single dose every two weeks. This exposure level was the rat NOAEL.**

- Due to histopathologic changes noted in chronic rat study, the ARO-ENaC clinical study placed on voluntary hold

# Mechanism Underlying ARO-ENaC Chronic Toxicology Findings: Lung Macrophage Overload

## Particulate Lung Macrophage Overload — Studied for Over 40 Years (Morrow, 1988)

- **"A condition of impaired macrophage mediated clearance of particles in the lung following prolonged high-dose exposure to poorly soluble particles** (PSPs) of low inherent toxicity" (Bevan et al, 2018)
- **With increasing amounts of inhaled material, excessive macrophage stimulation leads to recruitment of other inflammatory cells and can eventually produce secondary tissue damage** (ECETOC, 2013 and 2016; ILSI, 2000)
- **Inflammatory effects are due to a generic particle response for which thresholds can be established** (ECETOC, 2013 and 2016; ILSI, 2000)
- Histologic findings from chronic rat/NHP tox studies are consistent with literature description of macrophage overload
  - **Consulting Pathologist (KOL) - interpretation consistent with macrophage overload**

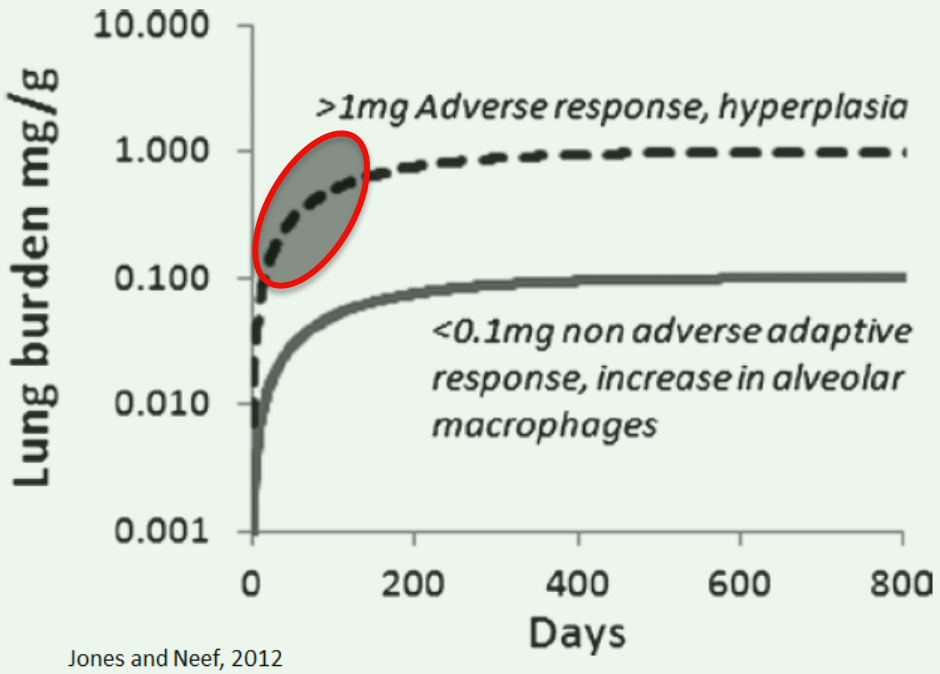
Morrow, Fundemental and Applied Toxicology, Vol. 10, 369-384, 1988

# ARO-ENaC Chronic Tox Findings are Consistent with Macrophage Overload

| Literature Description of Classic Lung Overload Observation* | ARO-ENaC Chronic Rat Study | ARO-ENaC Chronic NHP Study |
|---|---|---|
| Enhanced transfer of particles to lymph nodes | ✓ | ✓ |
| Increases in lung weight | ✓ | ✓ |
| Pulmonary Inflammation<br>• Alveolar macrophage accumulation<br>• Neutrophilic infiltrate | ✓<br>✗ | ✓<br>✗ |
| Alveolar epithelial<br>• Hyperplasia (increased number of cells)<br>• Metaplasia (cellular transformation) | ✓<br>✗ | ✓<br>✗ |
| Fibrosis | ✓ (Both Low incidence and severity in high dose; non-adverse) | ✗ |
| Carcinogenesis | No preneoplastic lesions | |

*European Center for Ecotoxicology and Toxicology of Chemicals. Poorly Soluble Particles/Lung Overload. Technical Report No., 122.

# Higher Drug Tissue Concentrations Increase Risk of Macrophage Overload



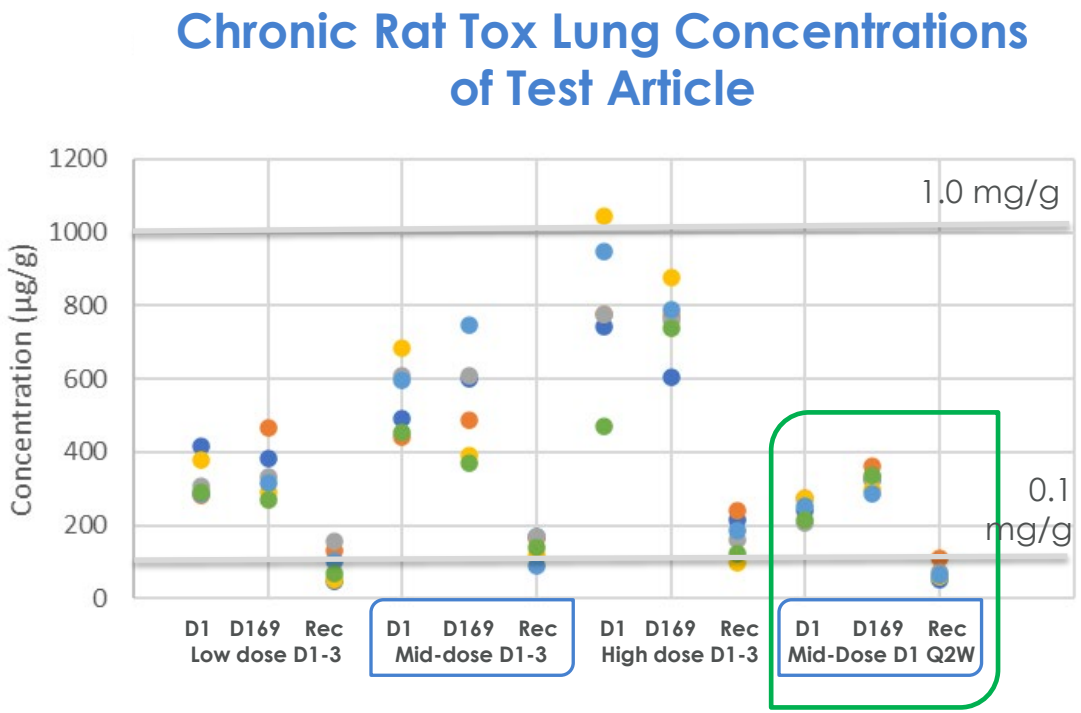

Jones and Neef, 2012

Based on literature, > 1.0 mg/g lung concentration threshold is associated with adverse histological findings

< 0.1 mg/g lung concentration associated with non-adverse adaptive response (increased alveolar macrophages)

Between 0.1 to 1.0 mg/g considered region of variable findings

# Less Frequent Dose Administration Decreased Rate of Adverse Findings




Four ARO-ENaC treatment groups: low, mid, high D1, 2, 3 Q2 wk and mid dose D1, Q2 week.

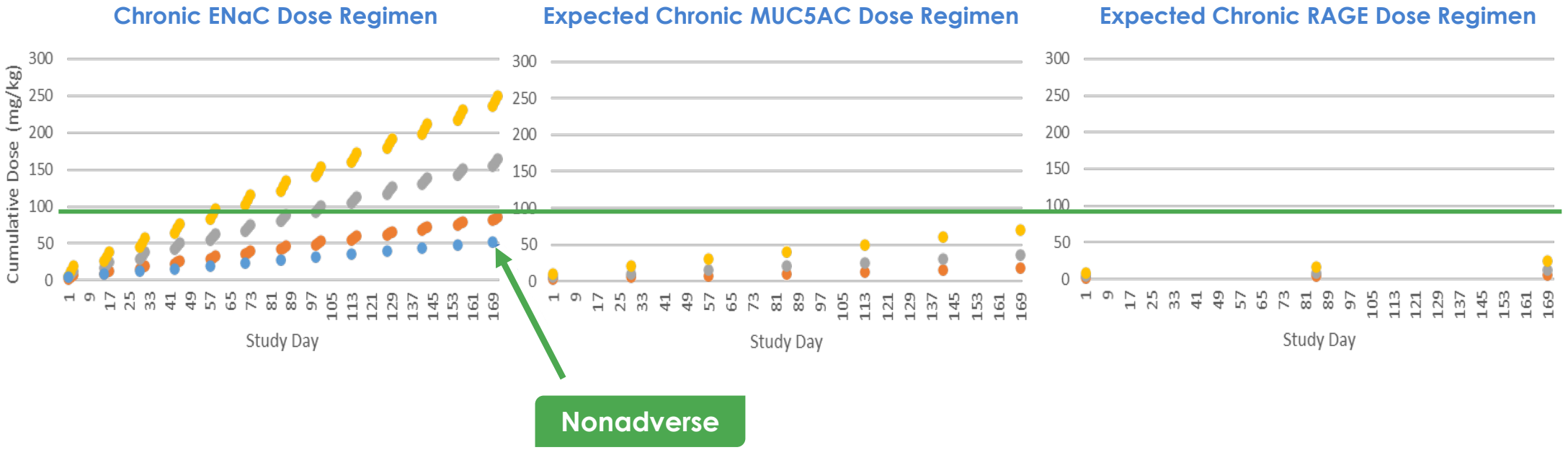
No NOAEL in any D1, 2, 3 Q2 wk dosing group.

Lung concentrations of 0.2 to 0.4 mg/g **achieved a NOAEL (mid-dose D1, Q2wk)**

Achieved by **decreasing dose frequency from Day 1, 2, 3 Q2wk to Day 1 Q2wk**

**Dosing Q28 days or Q90 days** even less likely to induce macrophage overload

# Lower Cumulative Dose in Chronic Tox Studies Decreases Risk of Adverse Findings




In ARO-ENaC rat 6-month chronic GLP tox study:

- Adverse findings ≥ **100 mg/kg cumulative dose**
- NOAEL achieved at the lowest cumulative exposure

Planned 6-mo rat ARO-MUC5AC and ARO-RAGE dose levels and intervals yield a **cumulative dose well** below 100 mg/kg where adverse findings appeared in ENaC study

# ARO-RAGE, ARO-MUC5AC Phase 1-enabling GLP Toxicology Results: No Adverse Findings at Any Dose

## ARO-MUC5AC

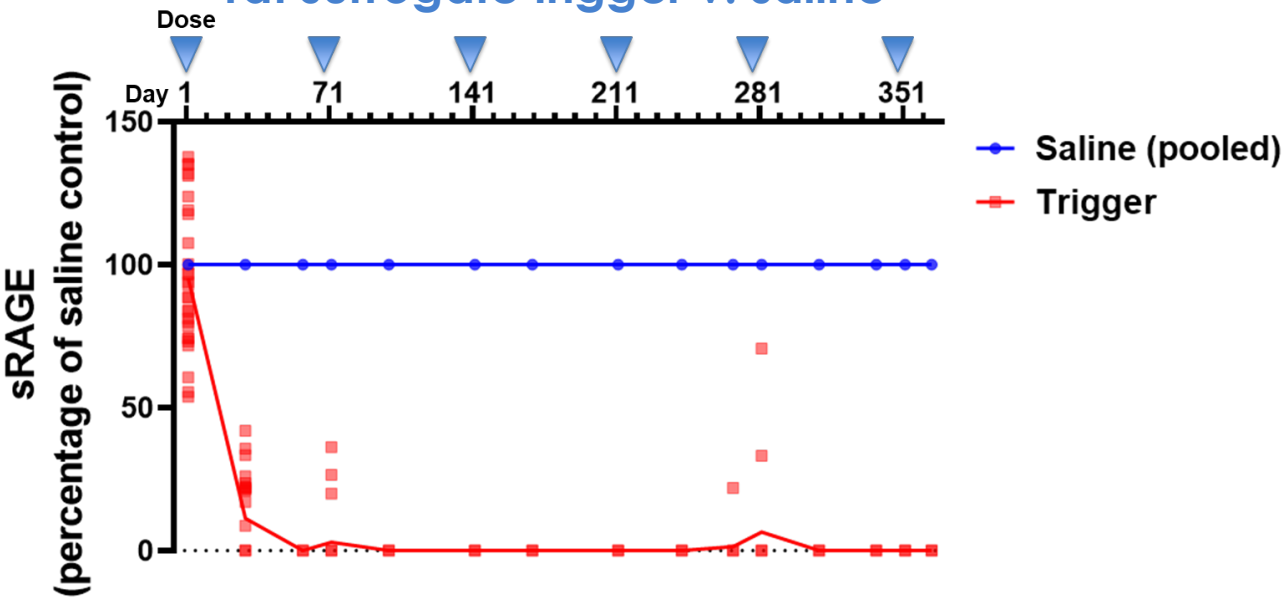
- Both rat and monkey received doses D1, 15, 29
- **No adverse clinical or histologic findings at any dose level**, top dose was NOAEL
- Ample safety margin between top planned Phase 1 clinical dose and animal NOAEL

## ARO-RAGE

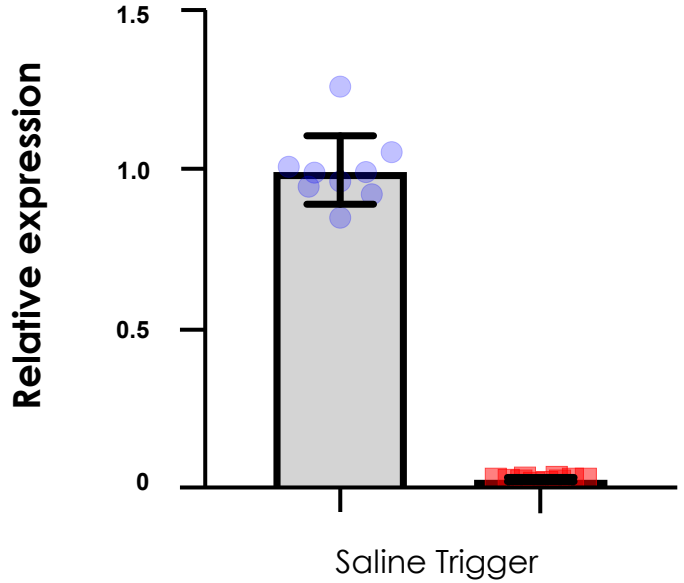
- Both rat and monkey received doses on D1, D29 (Based on data showing longer duration)
- **No adverse clinical or histologic findings at any dose level**, top dose was NOAEL
- Ample safety margin between top planned Phase 1 clinical dose and animal NOAEL

# No Adverse Findings in Rats with 12-month Exposure at Pharmacologic Dose Achieving > 90% RAGE Reduction

**Q70d inhaled 0.5 mg/kg rat surrogate trigger v. saline**




**Lung RAGE mRNA Day 170**




- Well tolerated
- No significant treatment-related adverse changes in labs (chemistry, hematology)
- No significant treatment-related adverse histopathological changes at Day 170 (no evidence of macrophage overload)

# ARO-ENaC Experience Helps De-risk Future Chronic Toxicology Studies

## New clarity regarding:

- Mechanism of toxicity (pulmonary macrophage overload)

- Understanding correlation between exposure level (dose level and intervals) and adverse effects
  - Learnings from ARO-ENaC chronic GLP toxicology study inform on need for less frequent doses to avoid macrophage overload

- Improved siRNA triggers:
  - ARO-RAGE, ARO-MUC5AC acute tox findings compare favorably to GLP/non-GLP inhaled acute tox studies with other triggers
  - Longer pharmacodynamic duration allows less frequent dose administration and a lower cumulative exposure in planned tox studies, thus less likely to overload lung clearance mechanisms

- Available biomarkers allow better understanding of dose response and inform clinical and chronic tox dose/dose interval selection. This was not available with ARO-ENaC.

Pulmonary R&D Day, May 26, 2022

# Mucins in Obstructive Lung Disease

Mario Castro, MD, MPH

arrowhead pharmaceuticals

# Mucins in Obstructive Lung Disease


Mario Castro MD, MPH

Asthma & Airway Translational Research Unit

University of Kansas School of Medicine

Kansas City, Kansas, USA

# Disclosures

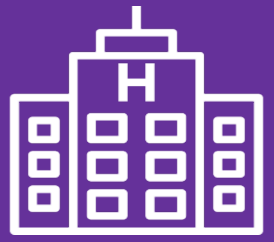
Dr. Mario Castro, MD, MPH reports the following relationships: royalties paid by Elsevier, serves on the Speakers Bureau for AstraZeneca, Genentech, GlaxoSmithKline, Regeneron, Sanofi, and Teva. Dr Castro has also works as a consultant for Genentech, Teva, Sanofi-Aventis and Novartis, and receives Pharmaceutical Grant Funding from AstraZeneca, GlaxoSmithKline, Pulmatrix, Sanofi-Aventis, Shinogi and Arrowhead

# Burden of Asthma in the United States

## ≈25 million Americans have asthma

**In 2016:**

More than 11 million people reported having ≥1 **asthma exacerbation** in previous year



Almost 1.8 million **emergency room visits**

≈189,000 **hospitalizations**

More than 3400 **deaths**



Centers for Disease Control and Prevention (CDC). 2021 (www.cdc.gov/asthma/asthmadata.htm).

# Multiple Unmet Medical Needs in Asthma

**Despite national and international guidelines, asthma control is not optimal with current standard-of-care treatment[1,2]**

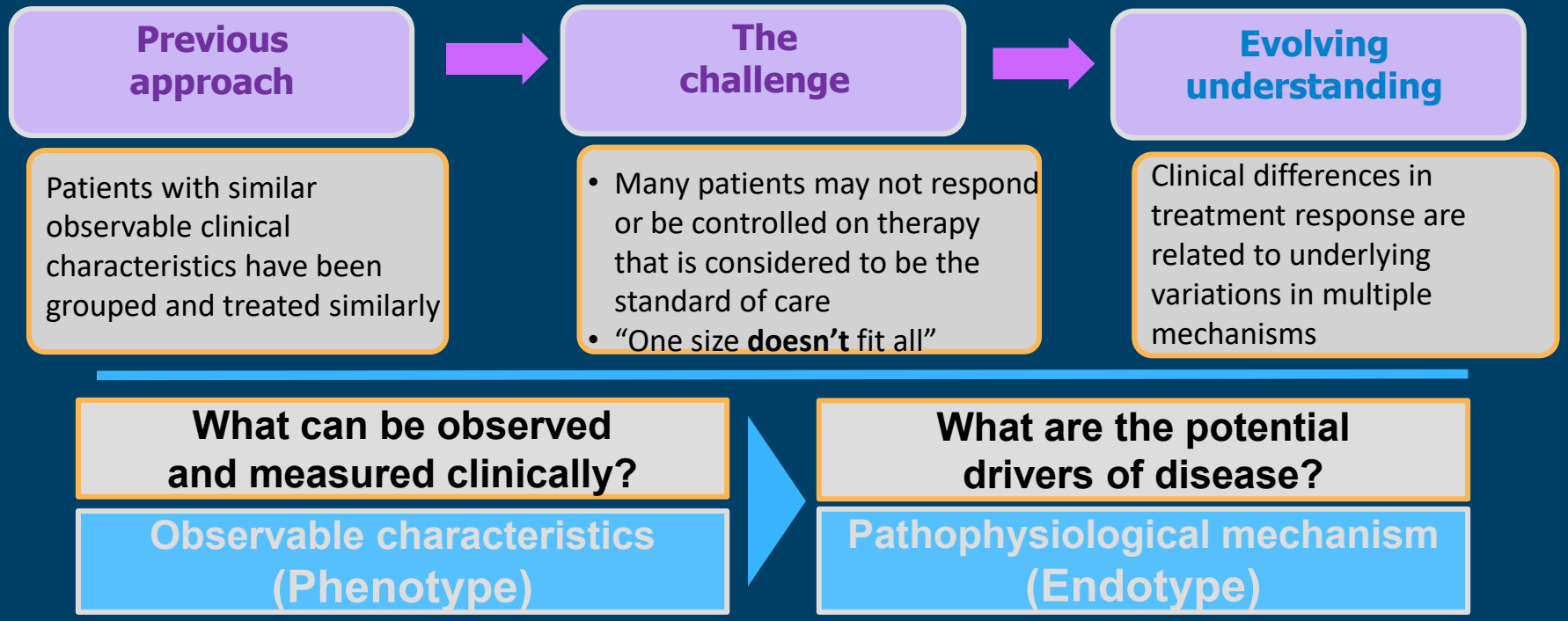
**Large number of hospitalizations for people with severe asthma every year**

**Uncontrolled asthma is associated with significant morbidity and mortality and a high economic burden[3]**

**5%-10% of patients have severe asthma[4,5] that often fails to respond to conventional therapy[5,6]**

1. Bateman ED, et al. *Am J Respir Crit Care Med*. 2004;170:836-844. 2. Bateman ED, et al. *Eur Respir J*. 2007;29:56-62. 3. Chipps BE, et al. *J Allergy Clin Immunol*. 2012;130:332-342.e10. 4. Chung KF, et al. *Eur Respir J*. 2014;43:343-373. 5. Holgate ST, Polosa R. *Lancet*. 2006;368:780-793. 6. Partridge MR. *Eur Respir Rev*. 2007;16:67-72.

# Our Understanding of Asthma Is Changing
## Focus Shifting Toward Disease Mechanisms

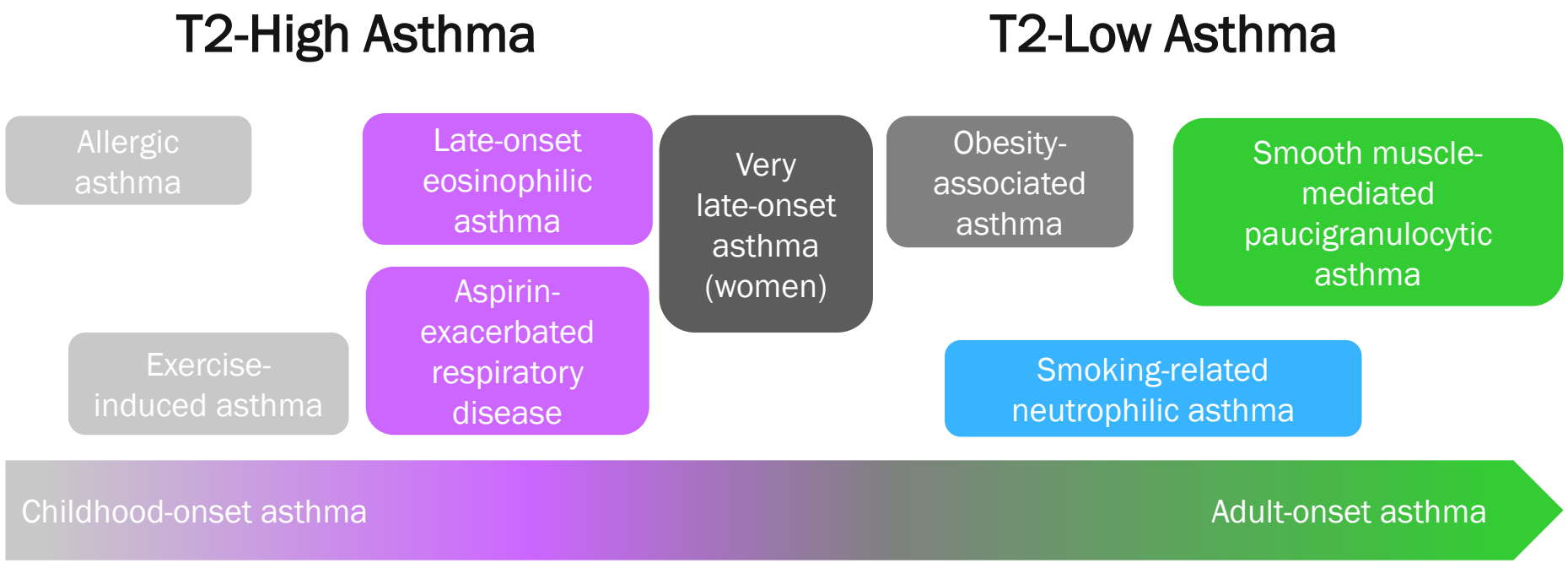



**The heterogeneity in treatment response has inspired discussion of a precision approach to care that tailors treatment to the patient**



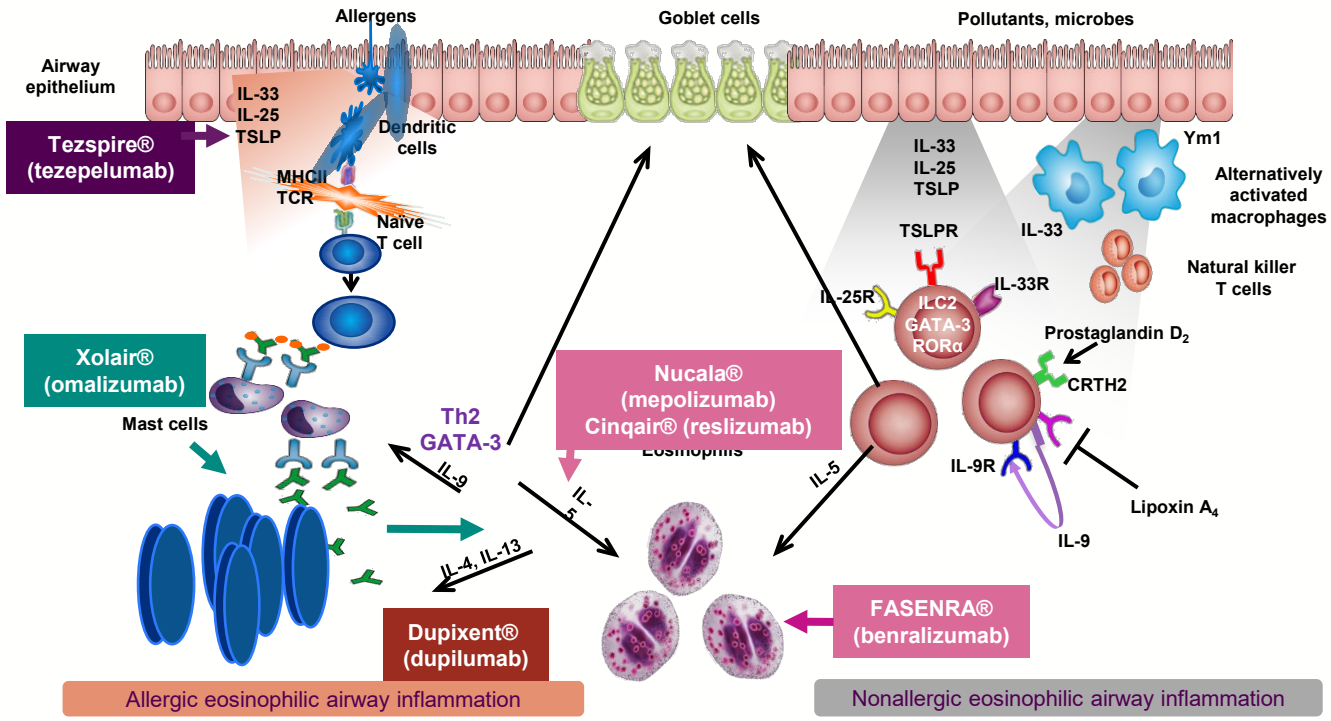
Muraro A, et al. *J Allergy Clin Immunol*. 2016;137:1347-1358. Lötvall J, et al. *J Allergy Clin Immunol*. 2011;127:355-360.

# Approach to Asthma Phenotyping




Wenzel SE. *Nat Med*. 2012;18:716-725.

# 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.

# Treatment of T2-Low Asthma

~40%-50% of patients with asthma **do not** have type 2 inflammation, but the proportion may be lower in severe asthma

- Asthma without evidence for type 2 inflammation referred to as “type 2 (T2)-low asthma”
- Treatment options for T2-low asthma:
  - Tezepelumab
  - Macrolide antibiotics
  - Bronchial thermoplasty
  - ??

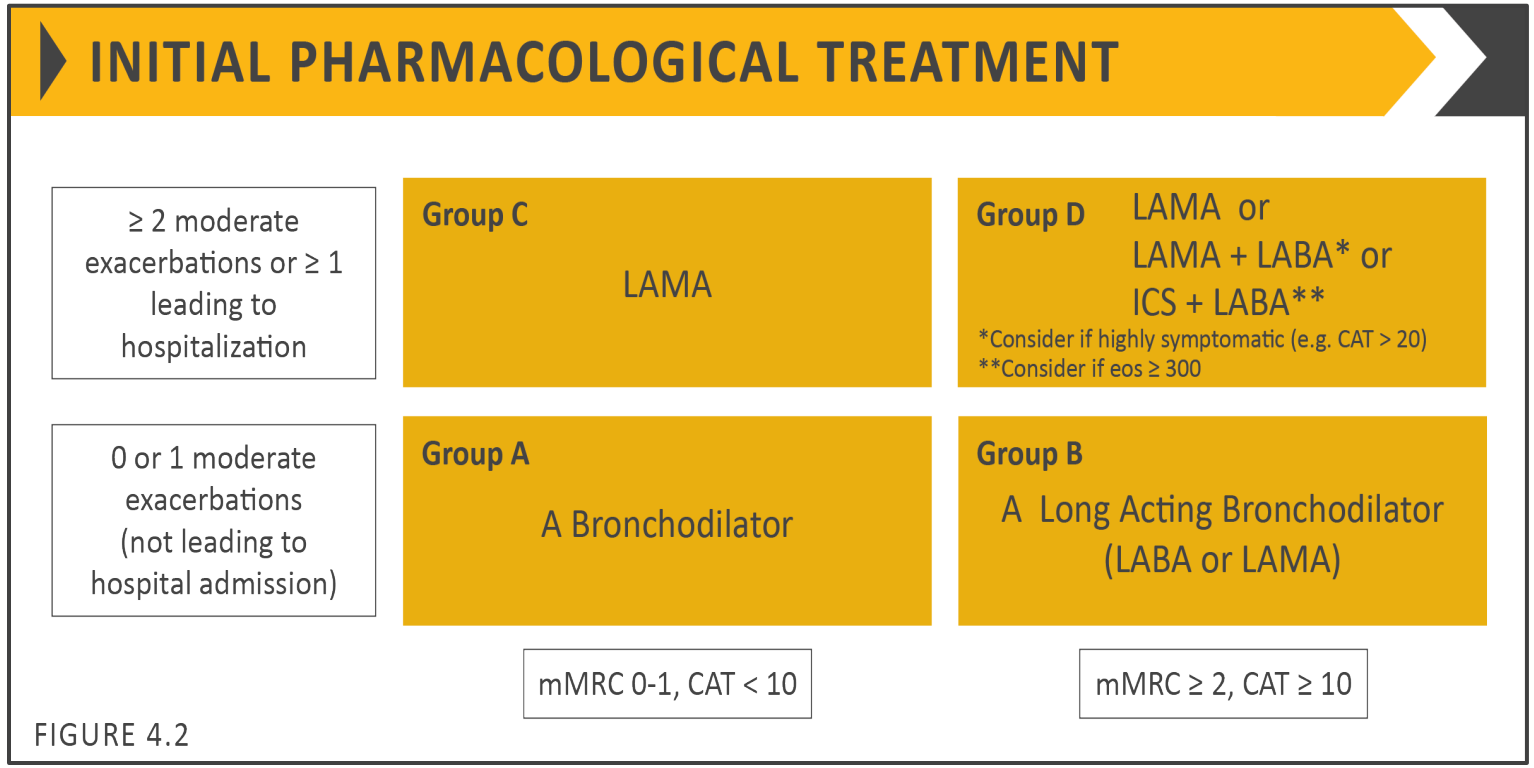


Fajt ML, Wenzel SE. *Allergy Asthma Immunol Res*. 2017;9:3-14.

# COPD Is a Major Public Health Problem and Leading Cause of Disability

- More than 20 million Americans have COPD[1]
- COPD prevalence is 6% (females > males)
  - 12.7 million diagnosed and 12 million undiagnosed
  - Asthma prevalence is 8% (28 million) - NHANES
- Chronic lower respiratory disease (COPD) is now the third leading cause of death (surpassing stroke)
- Second leading cause of disability (first is heart disease)
- Third leading cause of death worldwide
- 70% of patients are <65 years old

# Initial Pharmacological Management of COPD Recommended by GOLD 2022



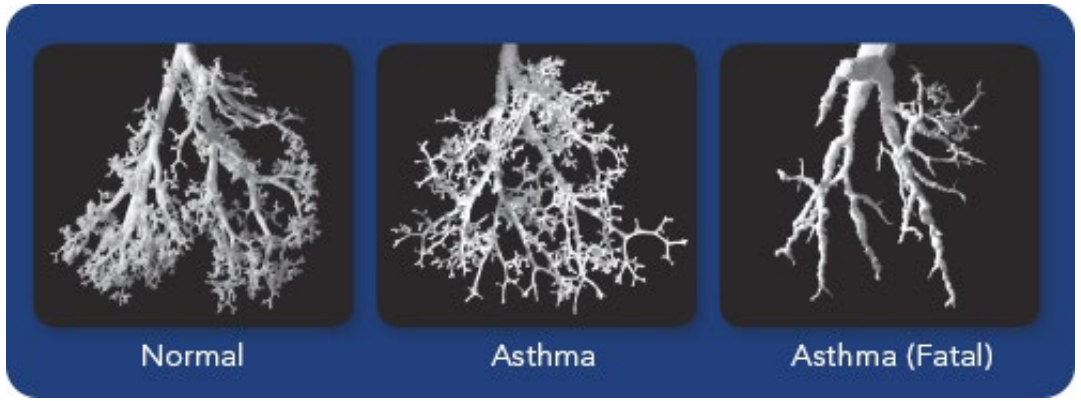
# Unmet Need in Muco-Obstructive Lung Diseases

- Key Message:
  - Mucus-directed therapy remains a significant gap in current therapies for obstructive lung diseases
  - There remains a need for disease modifying therapies:
    - Biologics improve but do not resolve disease in T2-high asthma patient and are significantly less efficacious in T2-low asthma
    - Effective anti-inflammatory approaches to COPD are lacking

# Mucus Hypersecretion Is Central to the Pathophysiology of Asthma

At Autopsy:

*"Pathologically the outstanding feature of the asthmatic lung lies in the failure of clearance of bronchial secretions" Huber 1922*



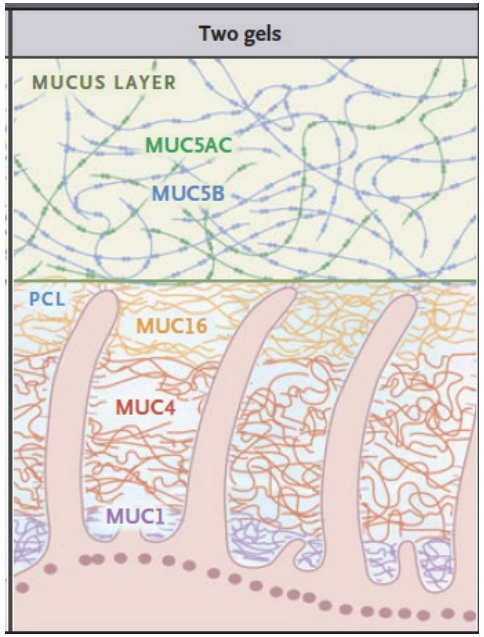

Bronchial casts of the airway from Healthy, Non-fatal Asthma and Fatal Asthma showing truncation of airways secondary to mucus

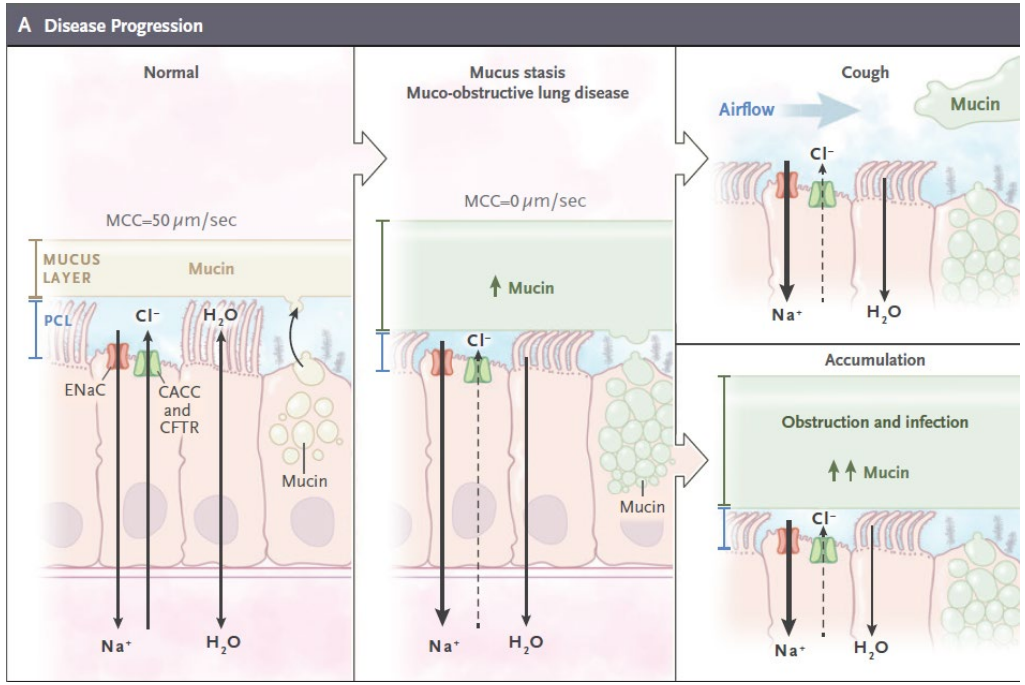




Dunican EM, et al. *AnnalsATS* 2018;15(Suppl 3):S184-S191.
Unpublished figures

# Mucin Concentration Regulates Mucociliary Clearance



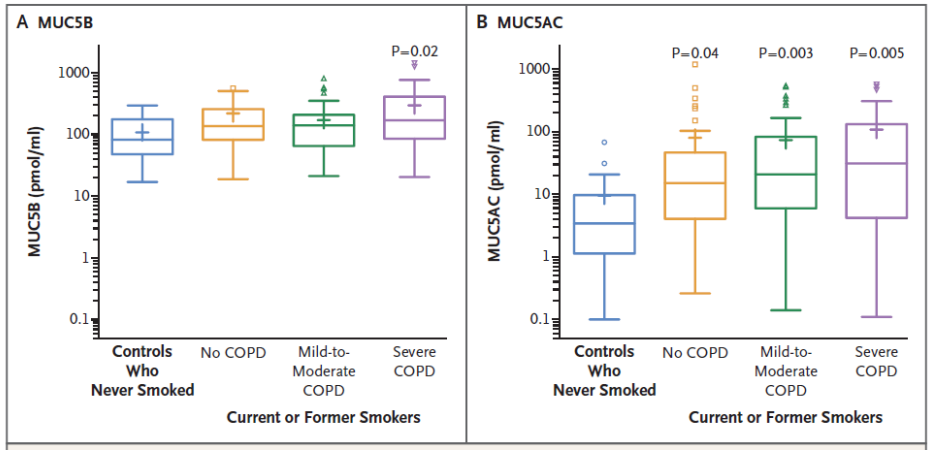




Mucus layer is composed of MUC5AC and MUC5B. Thickened mucus layer slows mucociliary clearance and causes muco-obstruction.

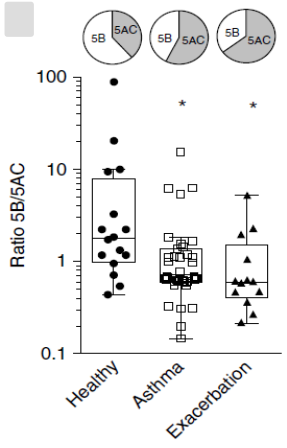
Boucher, NEJM, 2019.

# Muco-Obstructive Disease is Driven by MUC5AC Upregulation

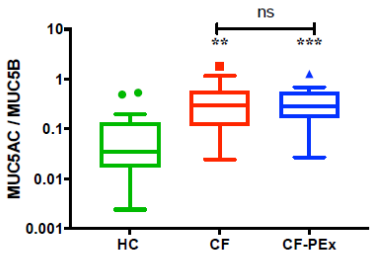
**COPD**



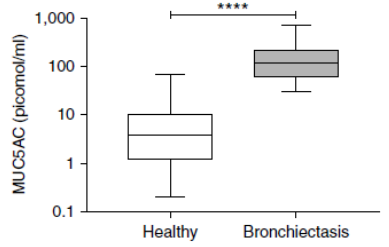

**Asthma**




**Cystic Fibrosis**



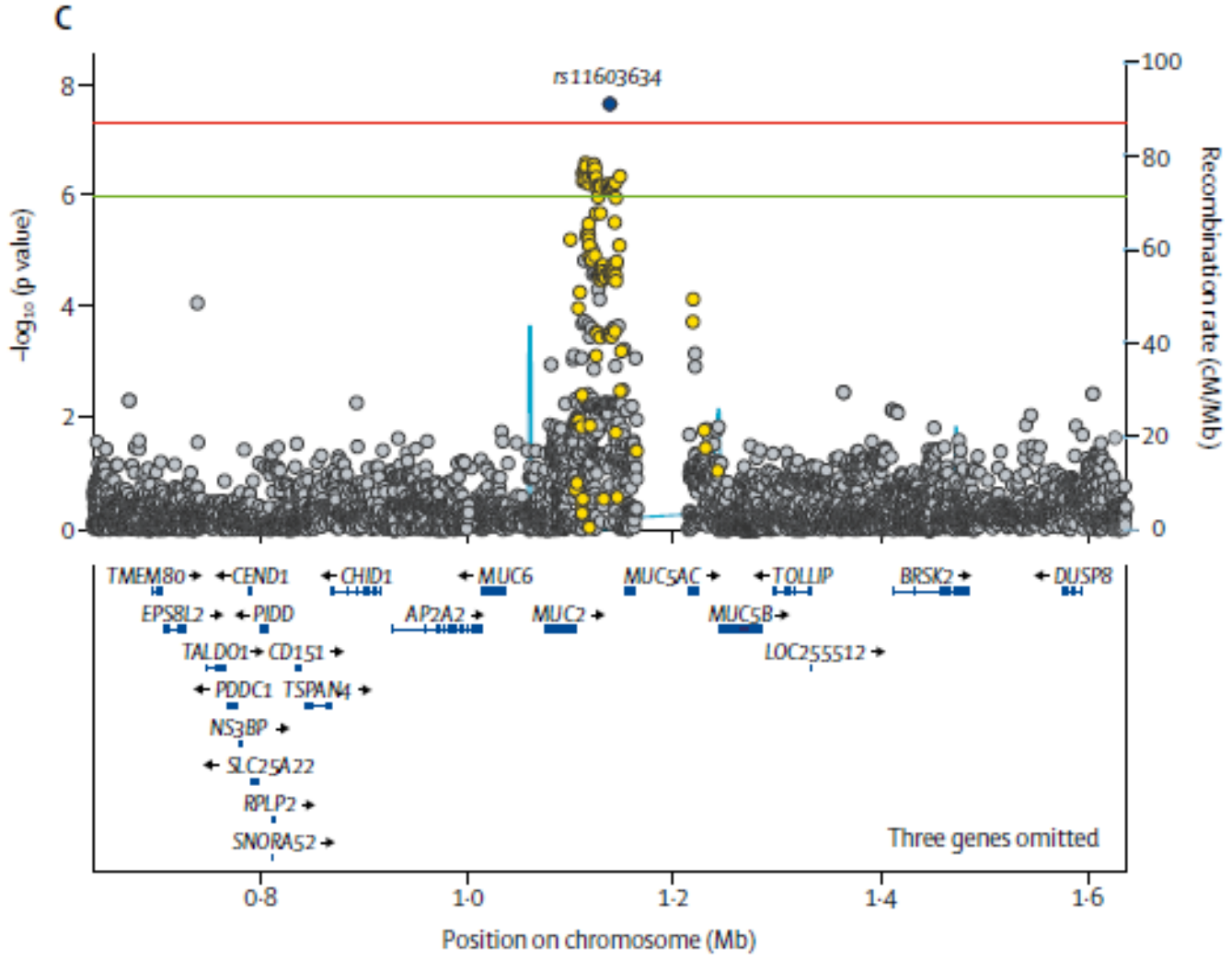

**Non-CF Bronchiectasis**




Muco-obstructive diseases are characterized by increased production of MUC5AC relative to MUC5B

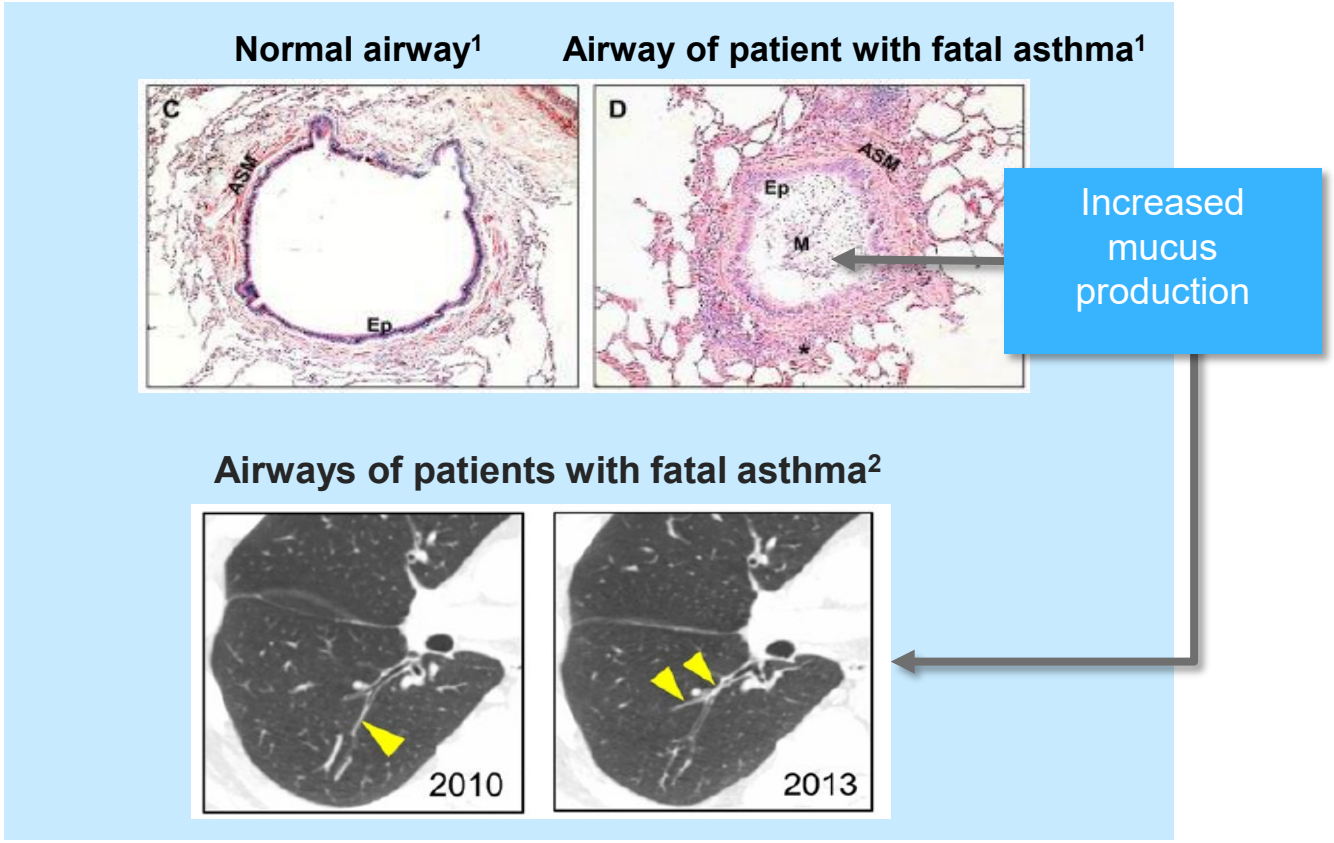
Kesimer, NEJM, 2017; Lachowicz-Scroggins, AJRCCM, 2016; Batson, AJRCMB, 2022; Ramsey, AJRCCM, 2020.

# Multiple GWAS Studies Suggest Causal Role for MUC5AC in Asthma




Shrine, Lancet Respir Med, 2019; Pividori, Lancet Respir Med, 2019.

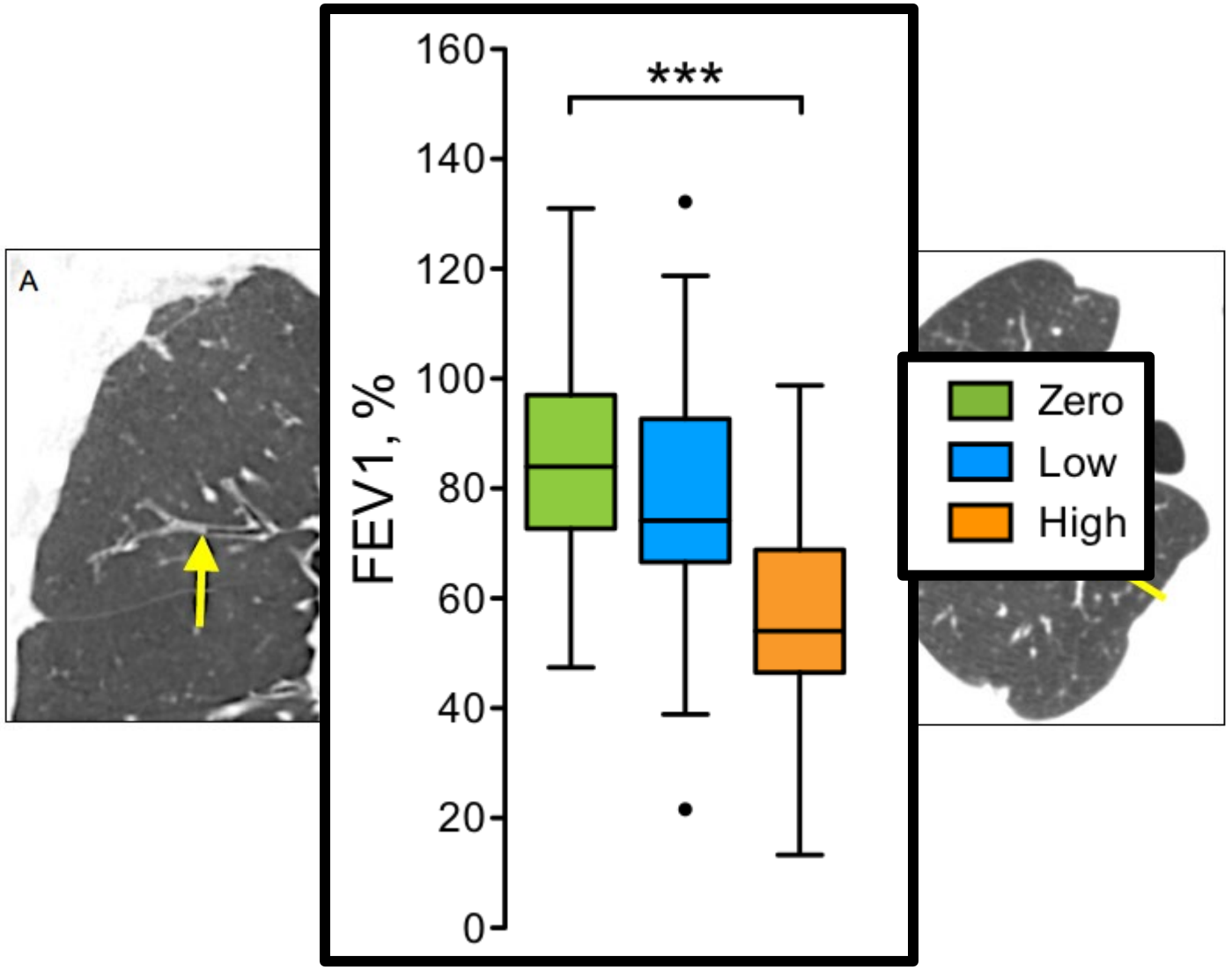
# Goblet Cell Hyperplasia, Excess Mucus Production and Mucociliary Dysfunction Are Common Features in Asthma





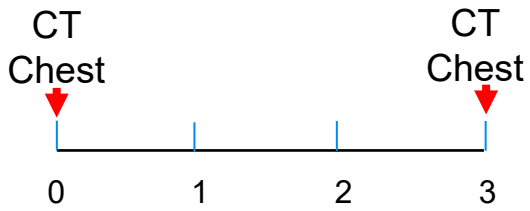
1. Mauad T, et al. *J Allergy Clin Immunol*. 2007
2. Dunican EM, et al. *J Clin Invest*. 2018

# Radiographically Detectable Mucus Plugs in Asthma

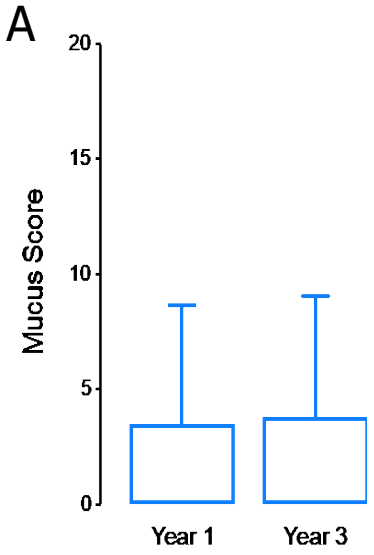


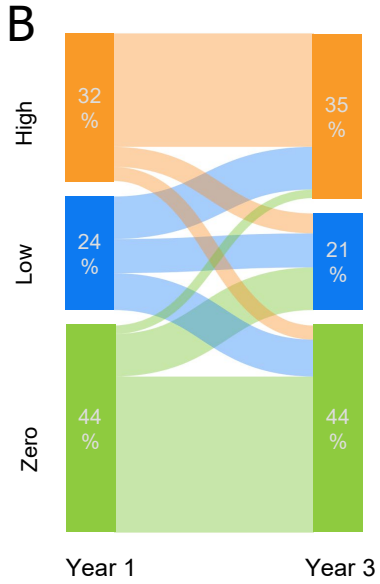

*Dunican E & SARP. J Clin Invest 2018*

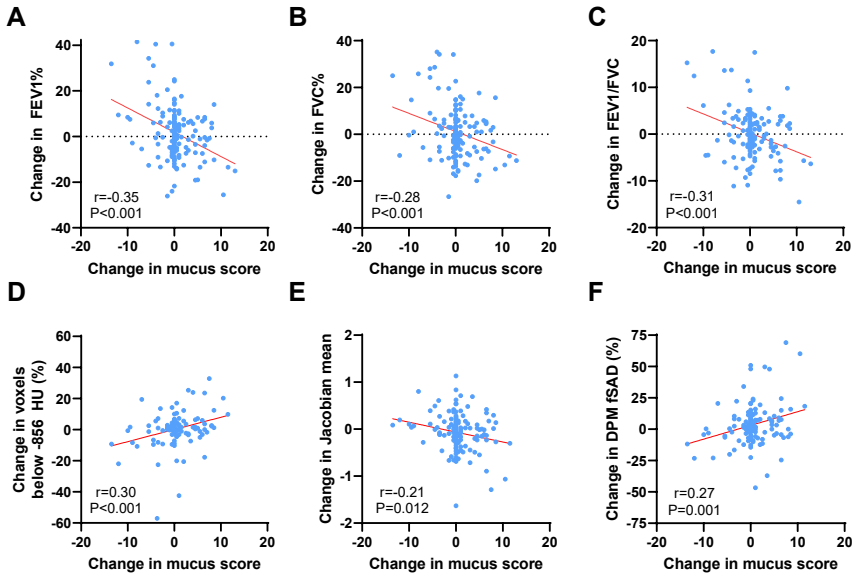
# Persistent Airway Mucus Plugs in Severe Asthma




168 subjects with Year 1
and Year 3 CT scans

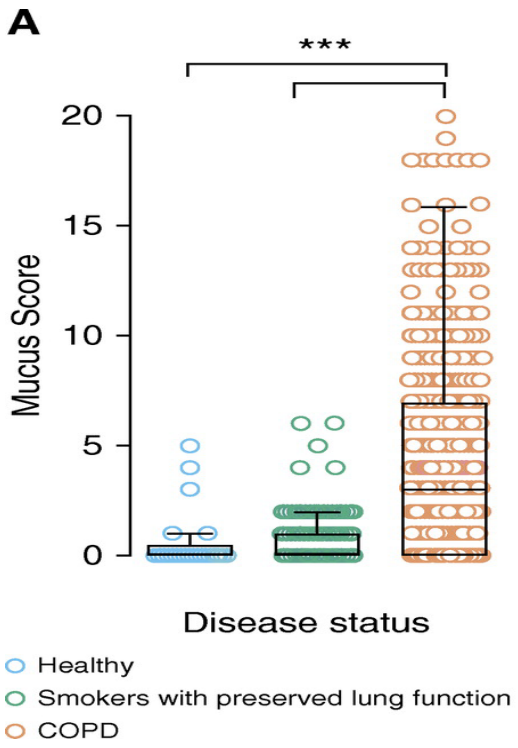


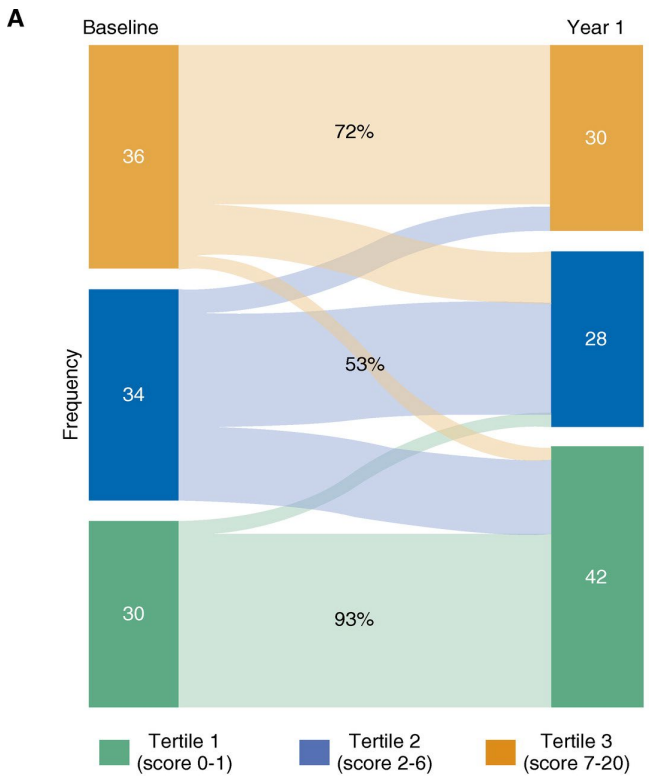



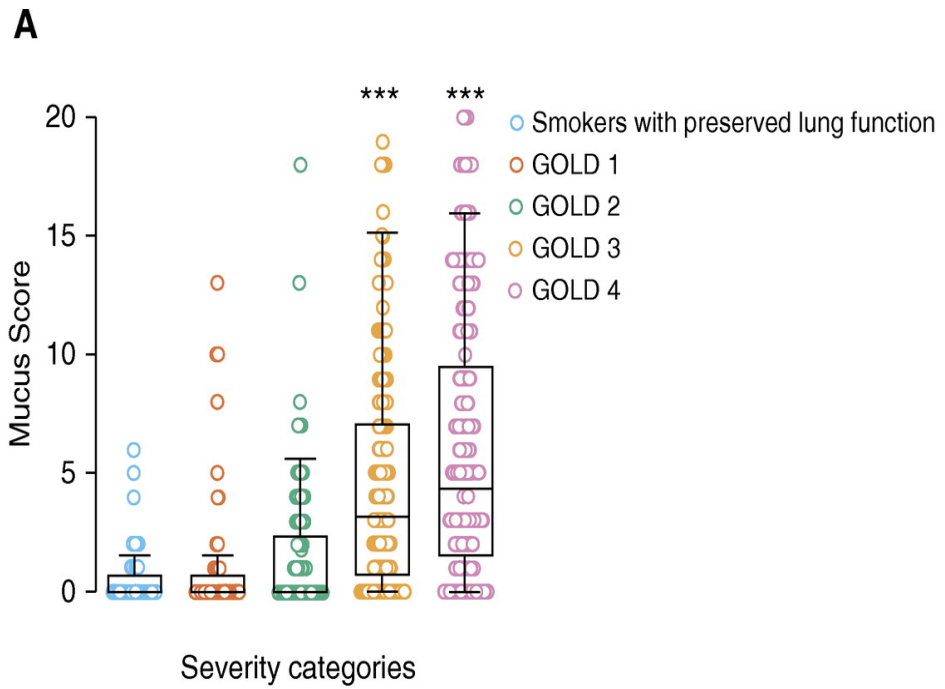




*Tang M & SARP. AJRCCM* 205, Iss 9, pp 1036–1045

# Mucus Plugs: Role in COPD



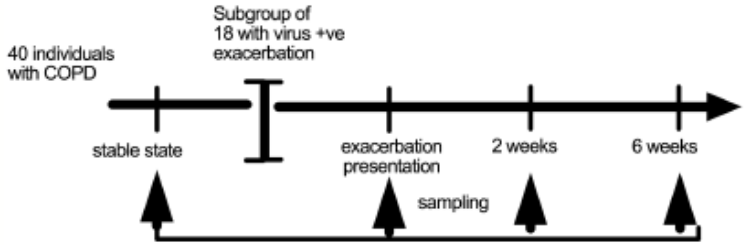

Dunican E et al Am J Respir Crit Care Med, 2021

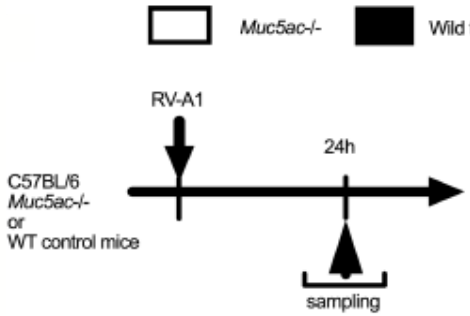
# MUC5AC Upregulation Contributes to Disease Exacerbations

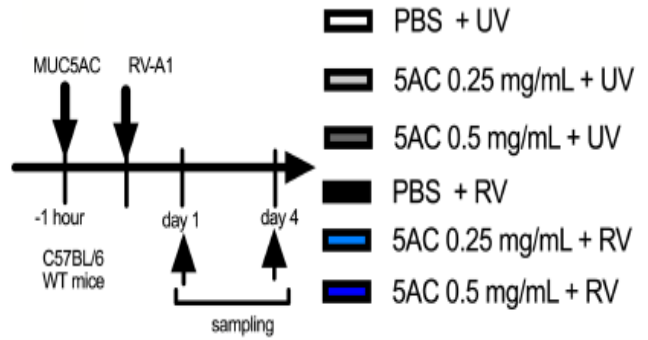
COPD patients with viral exacerbation experience transient spike in MUC5AC

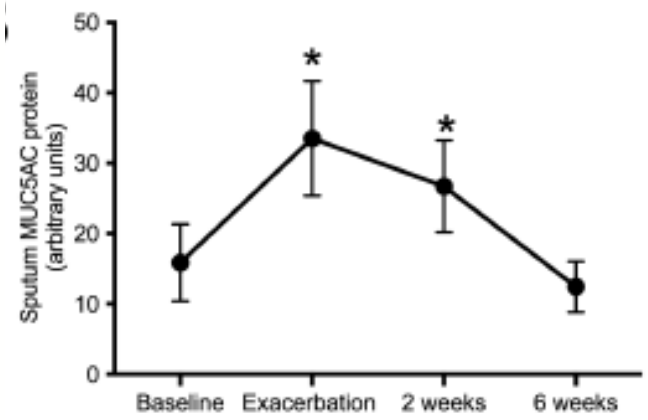
MUC5AC knockout mice have attenuated airway inflammation following rhinovirus infection

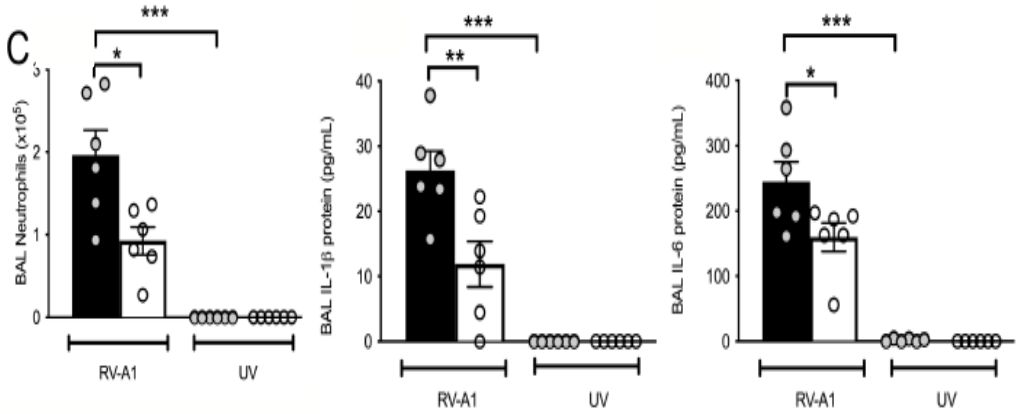
MUC5AC augmentation increases viral-induced inflammation in mice

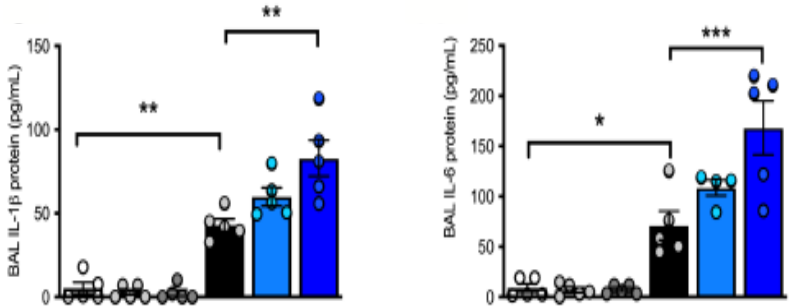


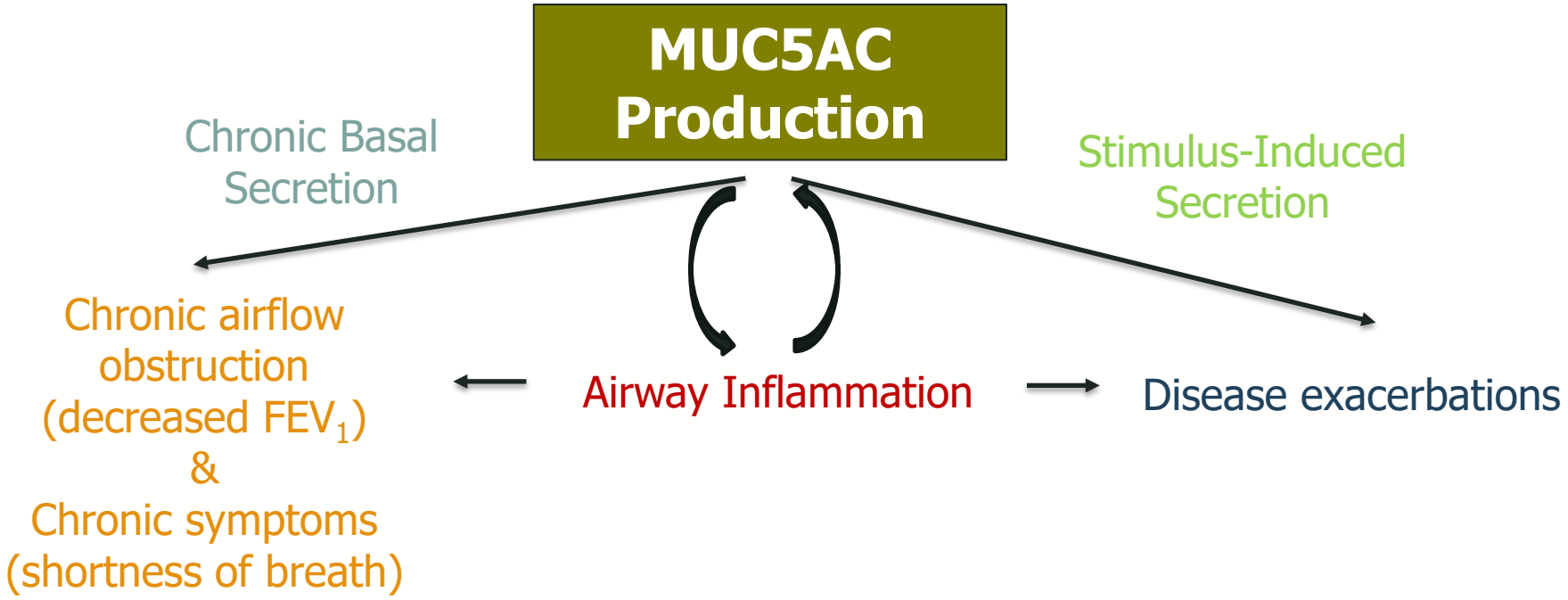



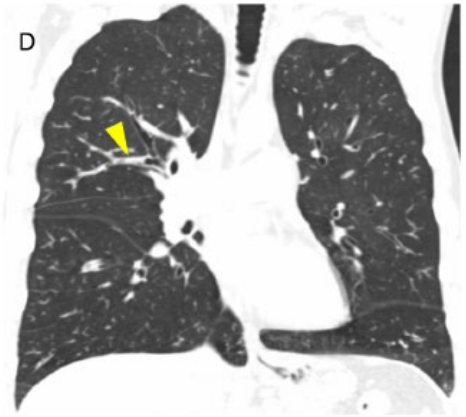



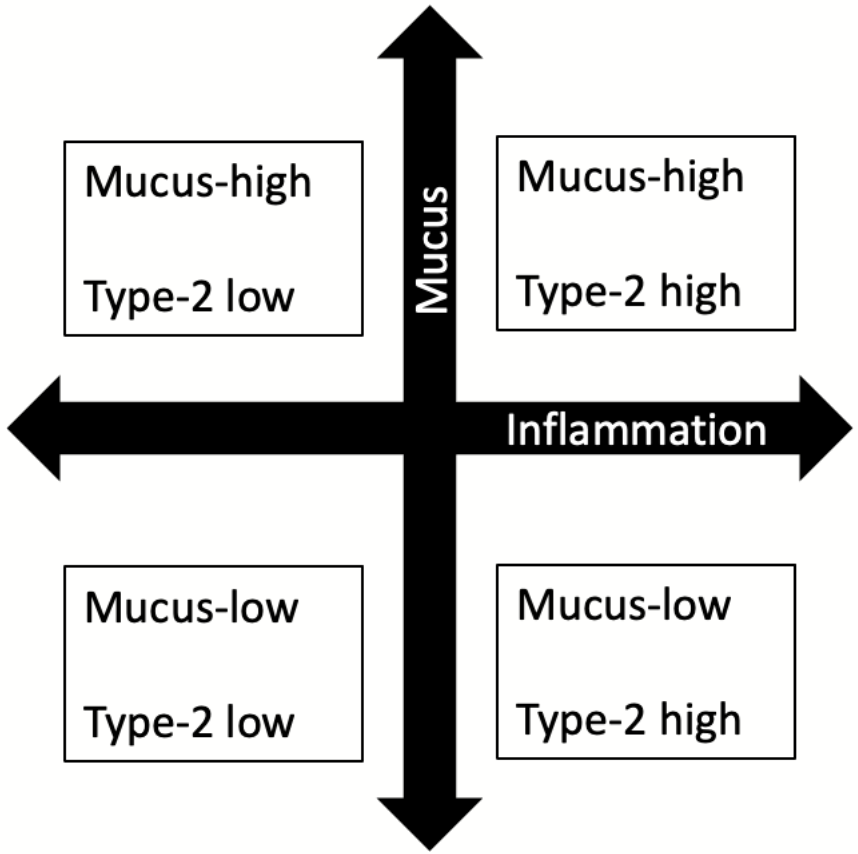

Singanayagam, JCI, 2022.

# MUC5AC Underlies Key Components of Disease Morbidity



# 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.

# MUC5AC is a Target of High Interest for Obstructive Lung Disease

- Mechanistically implicated in pathogenesis:
  - MUC5AC KO mice protected from allergen-induced airway hyperreactivity
  - GWAS data suggest a causal role in asthma
  - Mucus plugs made of MUC5AC contribute to airflow obstruction and progressive loss of lung function
  - Role in augmenting viral-induced inflammation leading to disease exacerbations
- Novel approach to a component of disease pathophysiology that is distinct from current therapeutics
- Potential for benefit in multiple muco-obstructive lung diseases: Asthma, COPD, CF, NCFB, PCD

Pulmonary R&D Day, May 26, 2022

# RAGE: Pulmonary Inflammatory Disease

Matthias Salathe, MD

arrowhead pharmaceuticals

# RAGE
# Pulmonary Inflammatory Disease

**Matthias Salathe**


KU SCHOOL OF MEDICINE
The University of Kansas

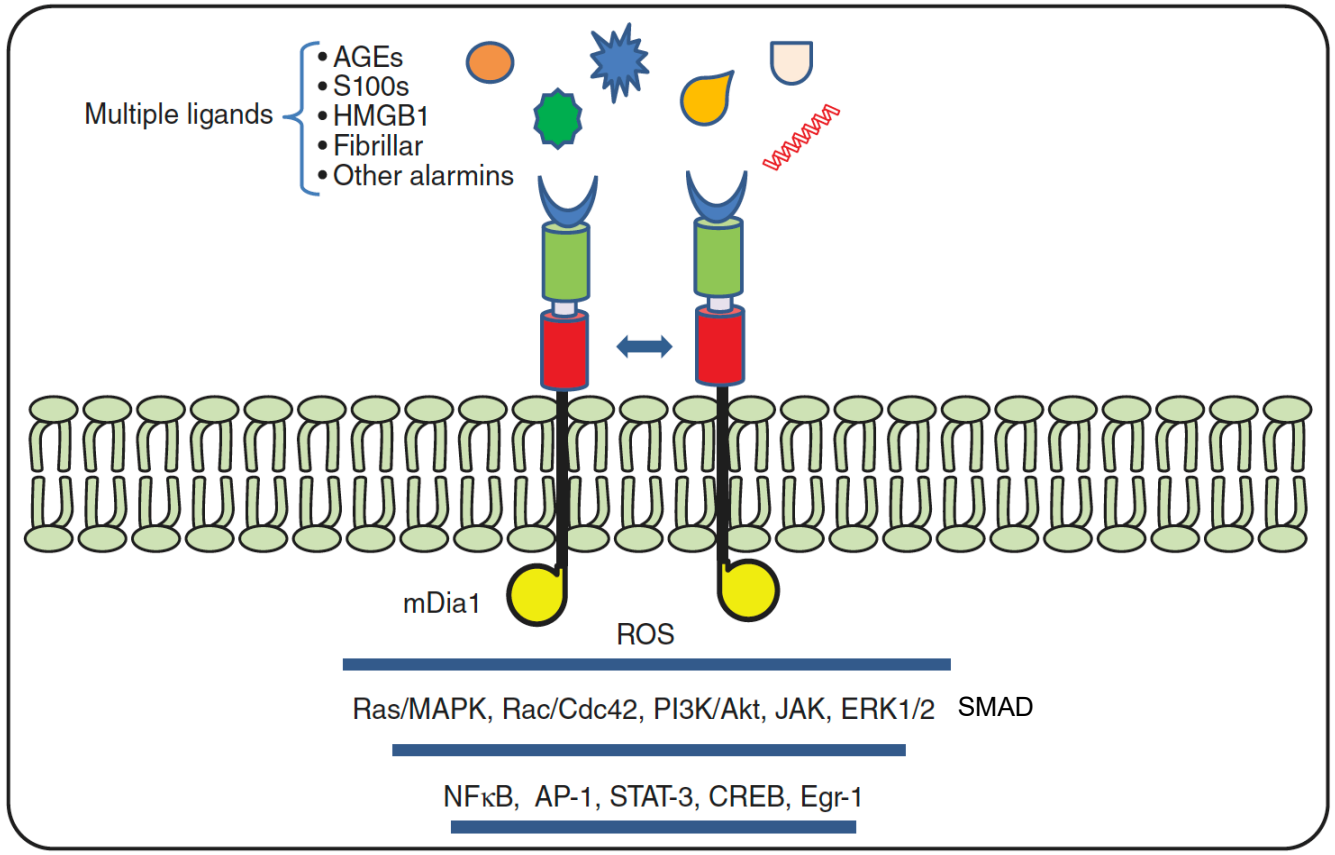
# Disclosures

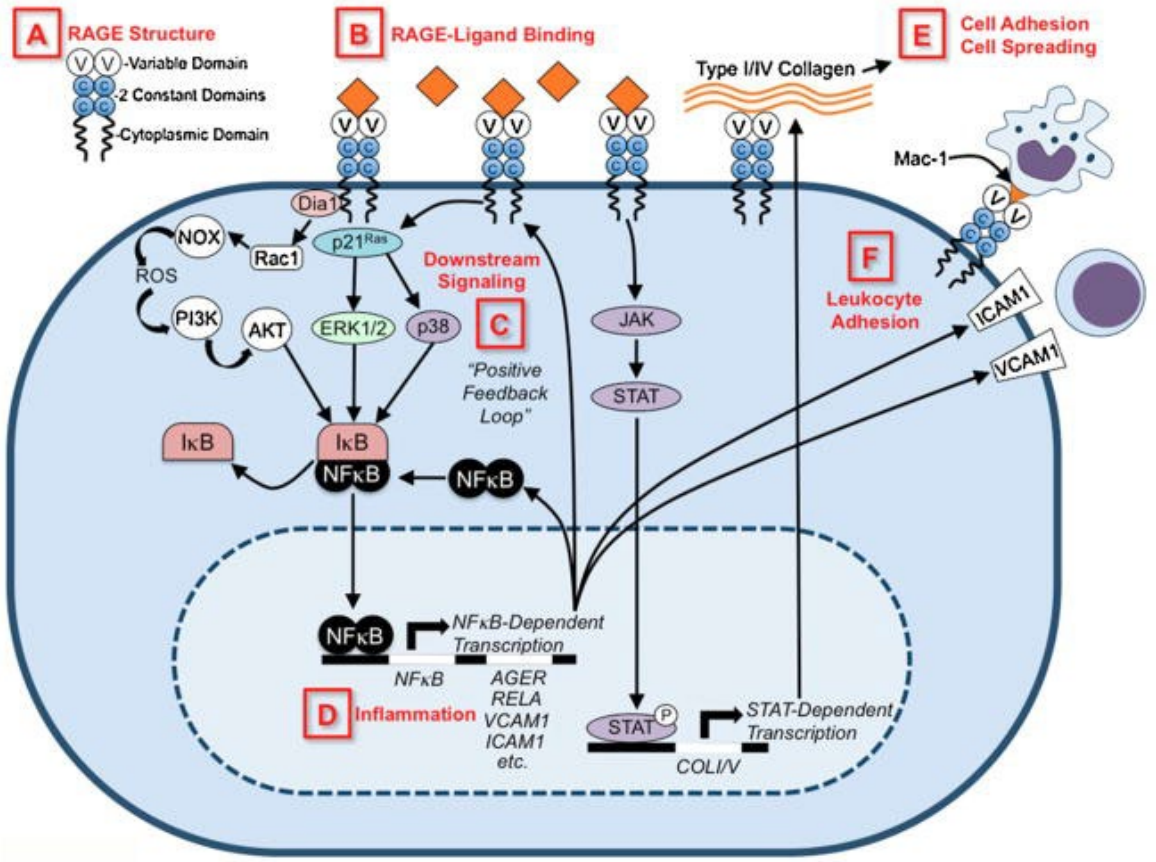
**Grants**
- NIH
- FAMRI
- J&E King State of Florida
- CF Foundation

**Consulting**
- Arrowhead Pharmaceuticals

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

# RAGE:
# Receptor For Advanced Glycation End-Products




Rojas et al. eLS. John Wiley & Sons, Ltd: Chichester. 2017. Oczypok et al. Paediatr Respir Rev. 2017; 23: 40–49.

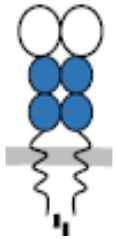
KU SCHOOL OF MEDICINE
The University of Kansas

# RAGE → Pulmonary Inflammation Response to a Range of Stimuli





RAGE

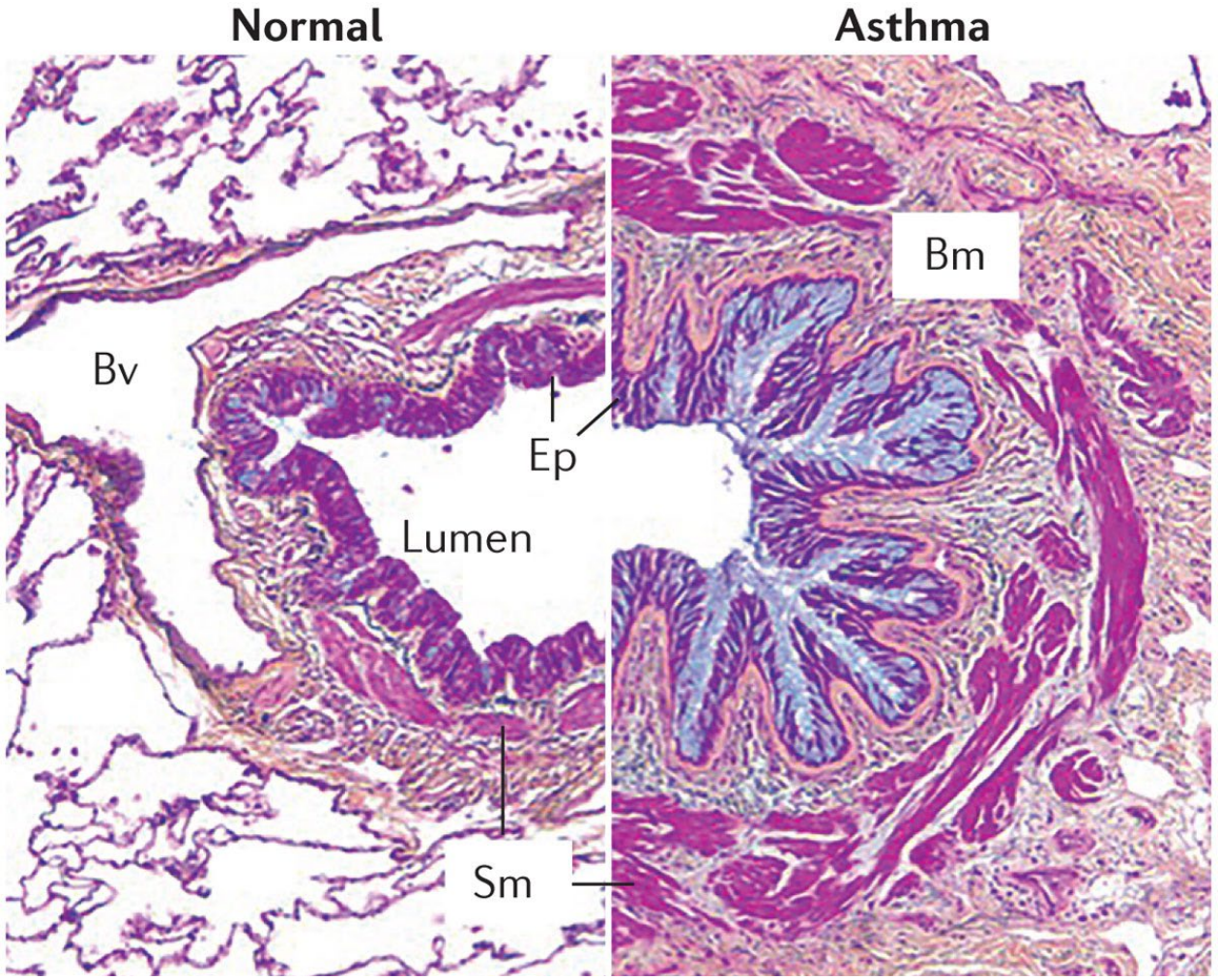


| CF | COPD | Asthma |
|---|---|---|
| • IL-1β<br>• IL-6<br>• IL-8<br>• TGF-β | • IL-1β<br>• MIP-2<br>• MCP-1<br>• Neutrophils | • IL-5<br>• IL-13<br>• IL-33<br>• Eosinophils |



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.

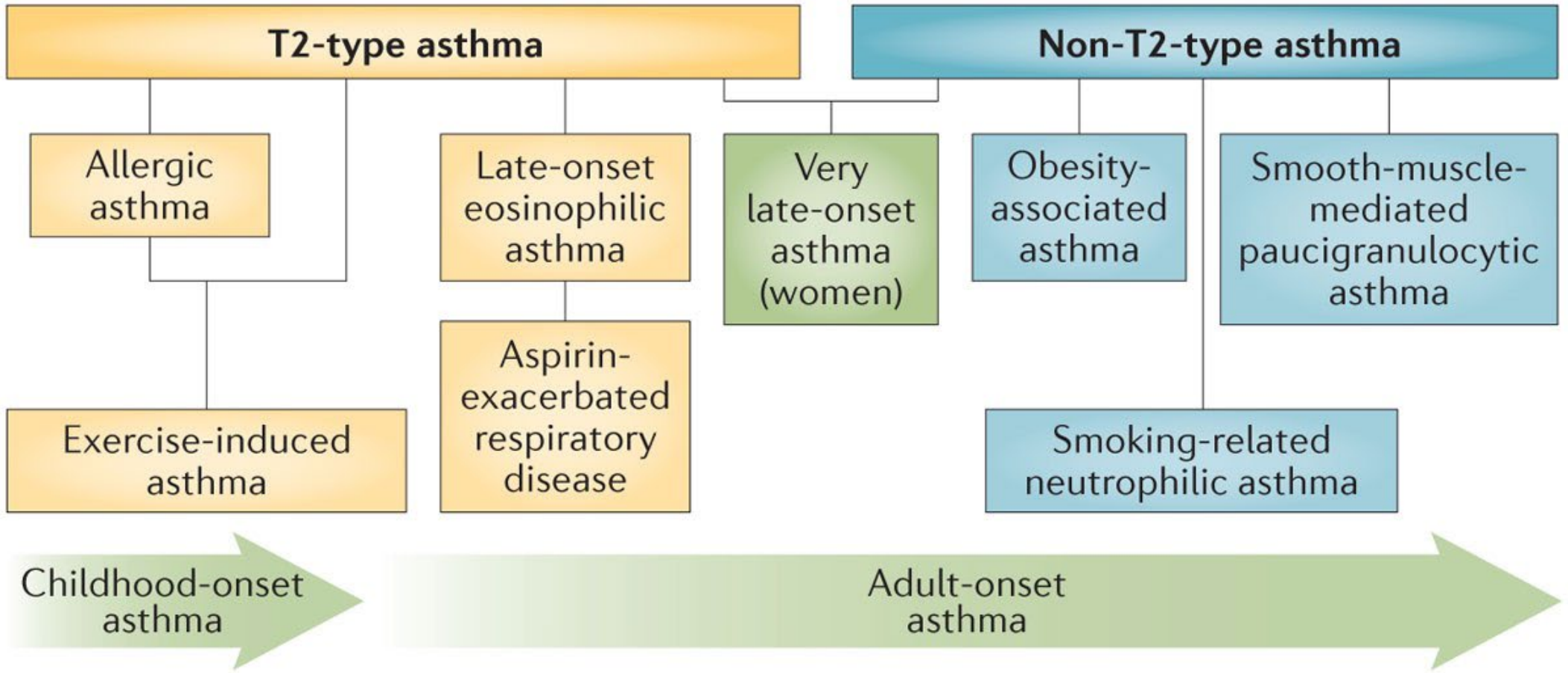
# Asthma





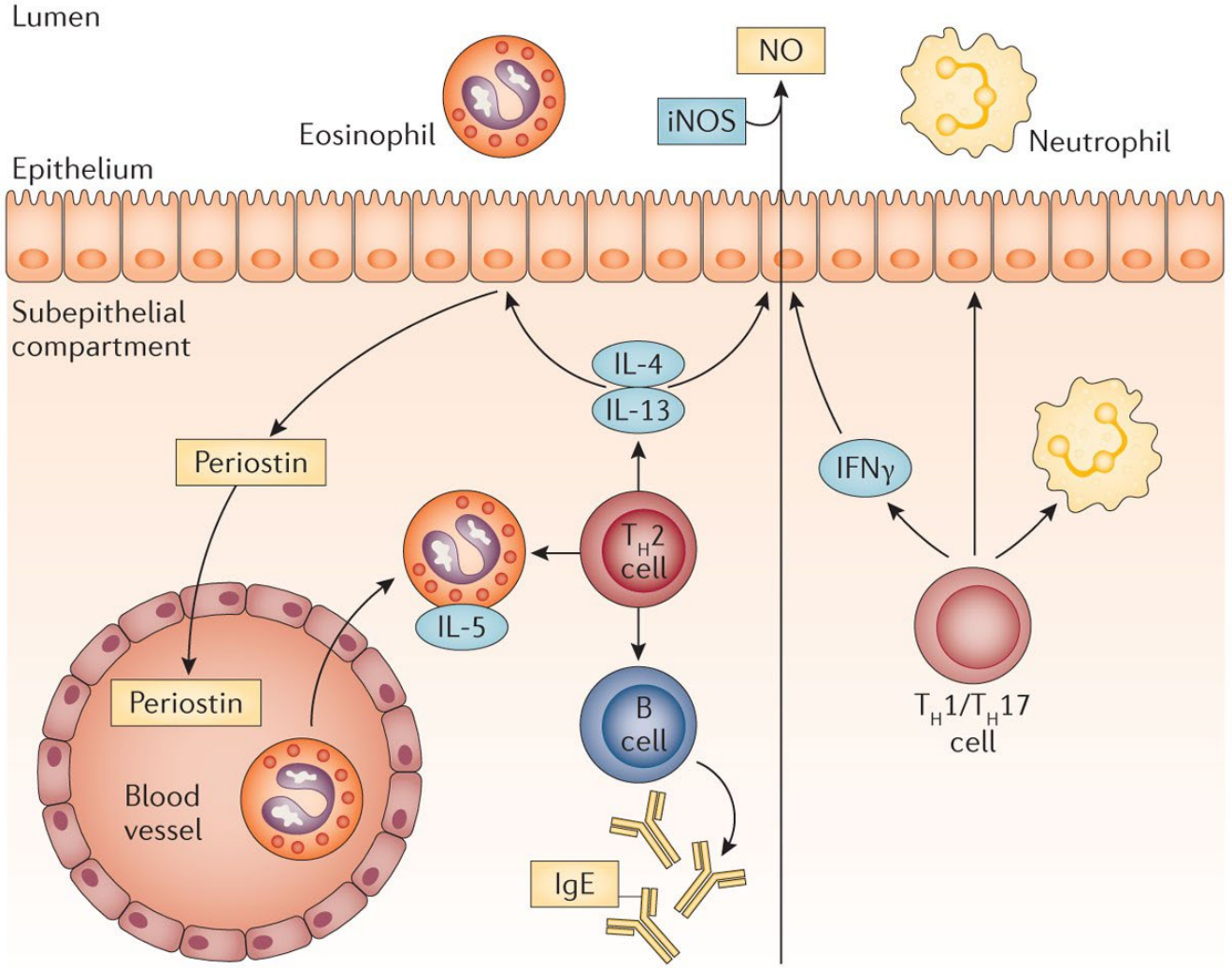

Wadsworth, S. e al. J Asthma Allergy. 2011; 4: 77–86.

# Asthma



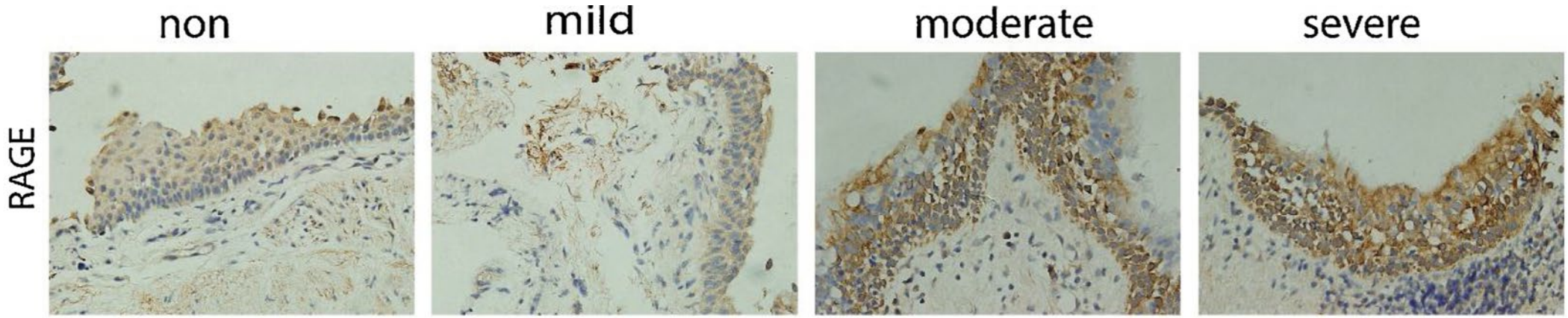

Holgate, S. T. et al. Asthma. Nat. Rev. Dis. Primers 2015 doi:10.1038/nrdp.2015.25

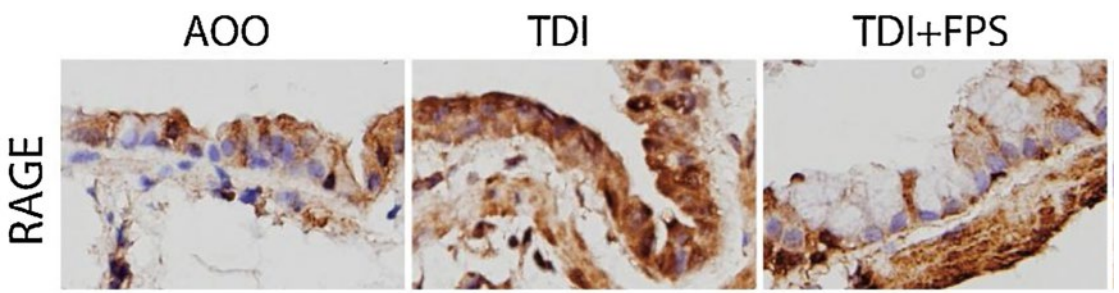
# Asthma

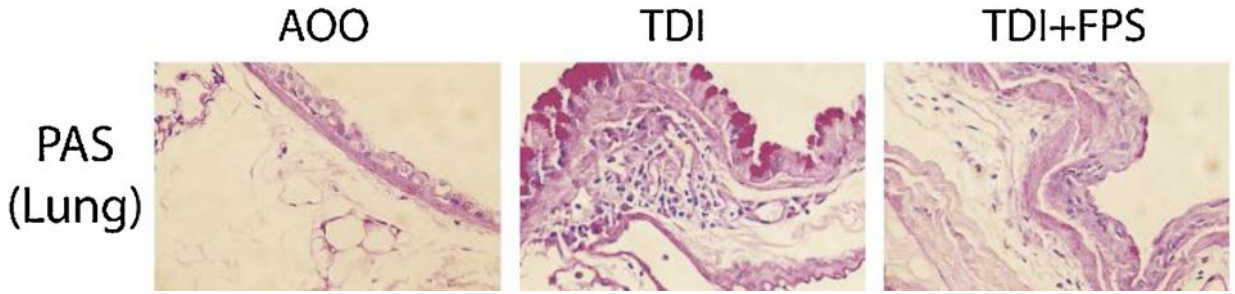



Holgate, S. T. et al. Asthma. Nat. Rev. Dis. Primers 2015 doi:10.1038/nrdp.2015.25

# RAGE Upregulated in Allergic Airway Diseases



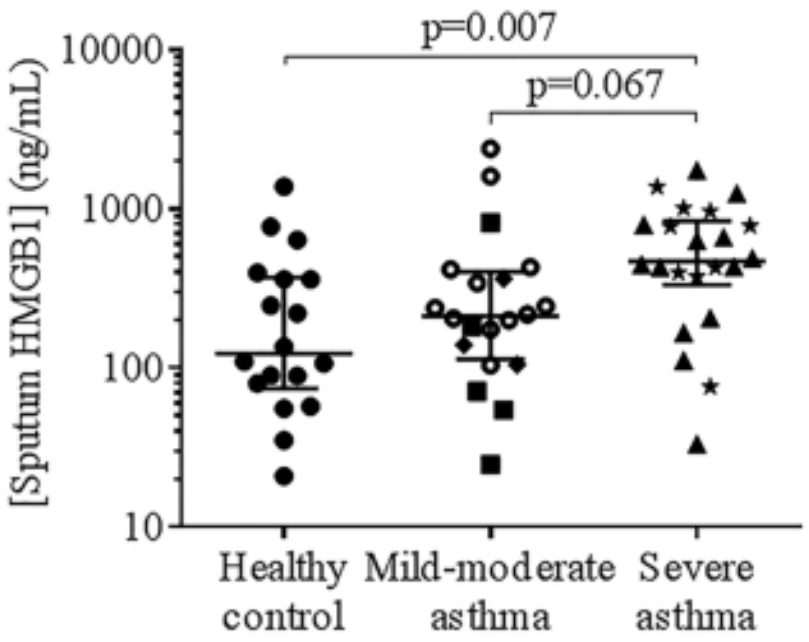



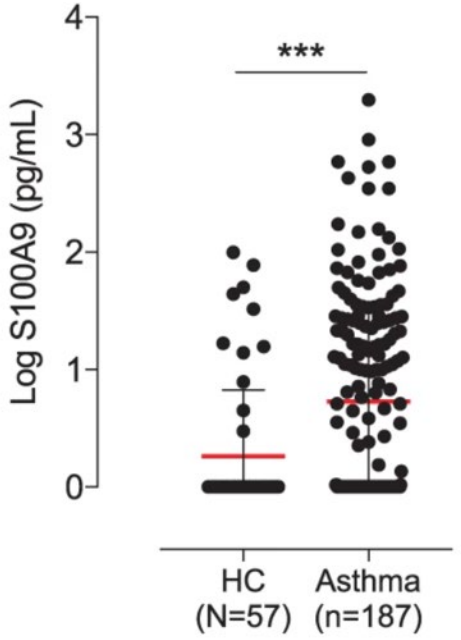



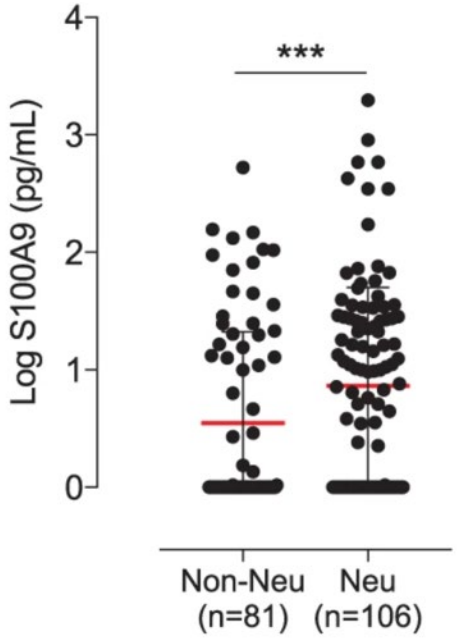

Huang et al. Toxicol Lett. 2021;336:57-67. Ferhani et al. Am J Respir Crit Care Med. 2010;181:917-927.

KU SCHOOL OF MEDICINE
The University of Kansas

# RAGE Ligands are Increased in Allergic and Neutrophilic Asthma



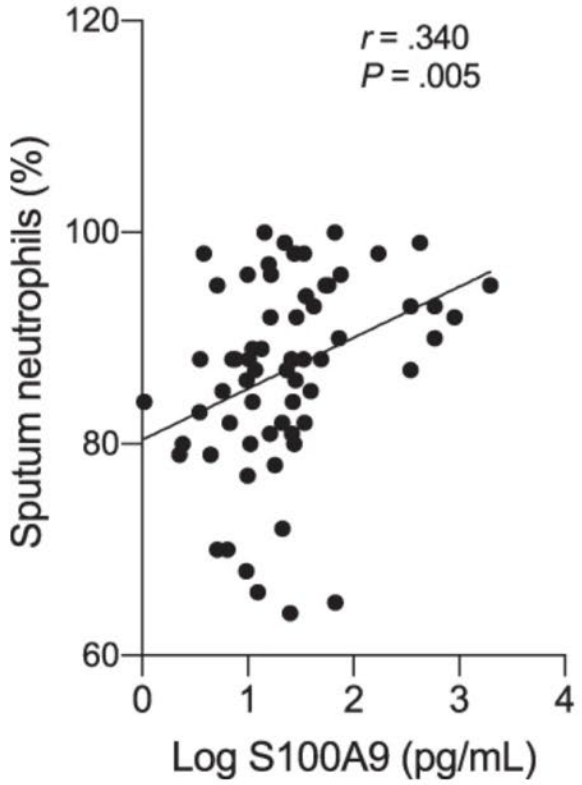



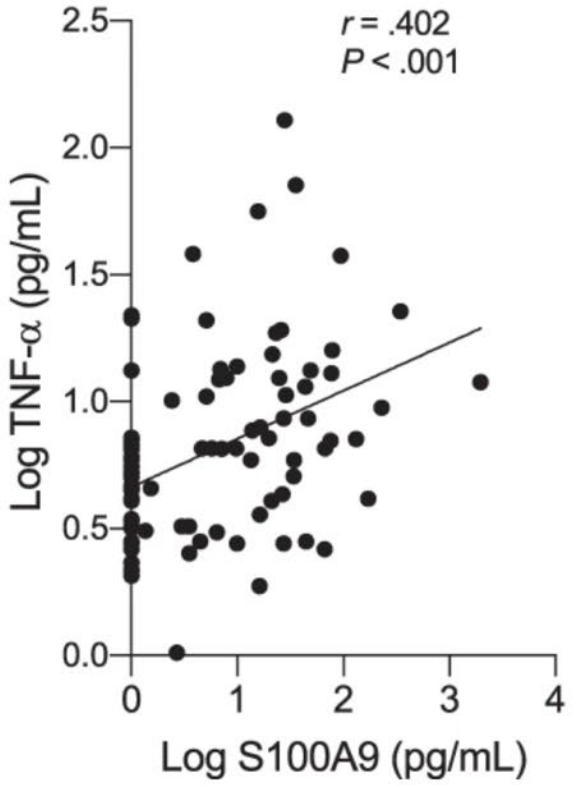



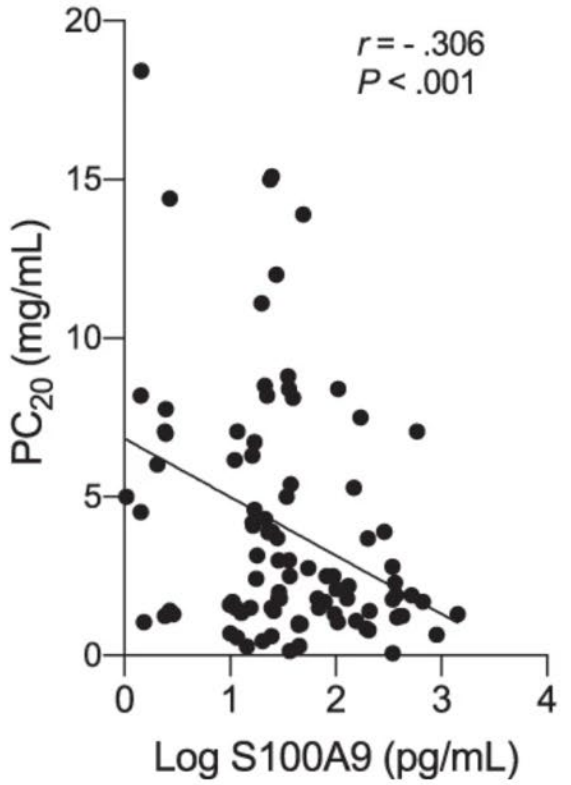

Di Candia et al. J Allergy Clin Immunol. 2017;140:584-587. Quoc et al. EMM 2021; 53: 1170-1179.

KU SCHOOL OF MEDICINE The University of Kansas

# RAGE Ligands are Increased in Neutrophilic Asthma

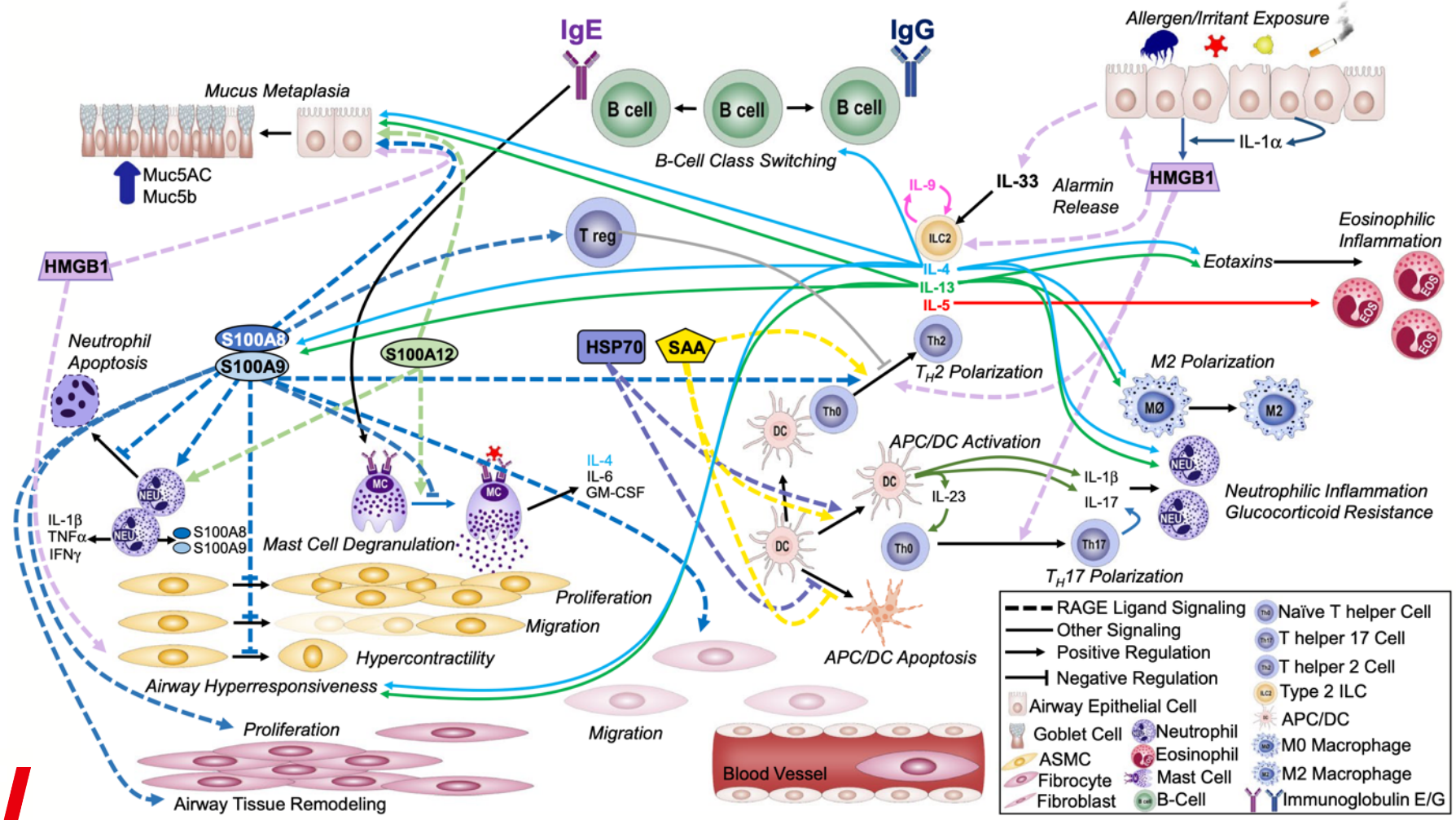



Quoc et al. EMM 2021; 53: 1170-1179.

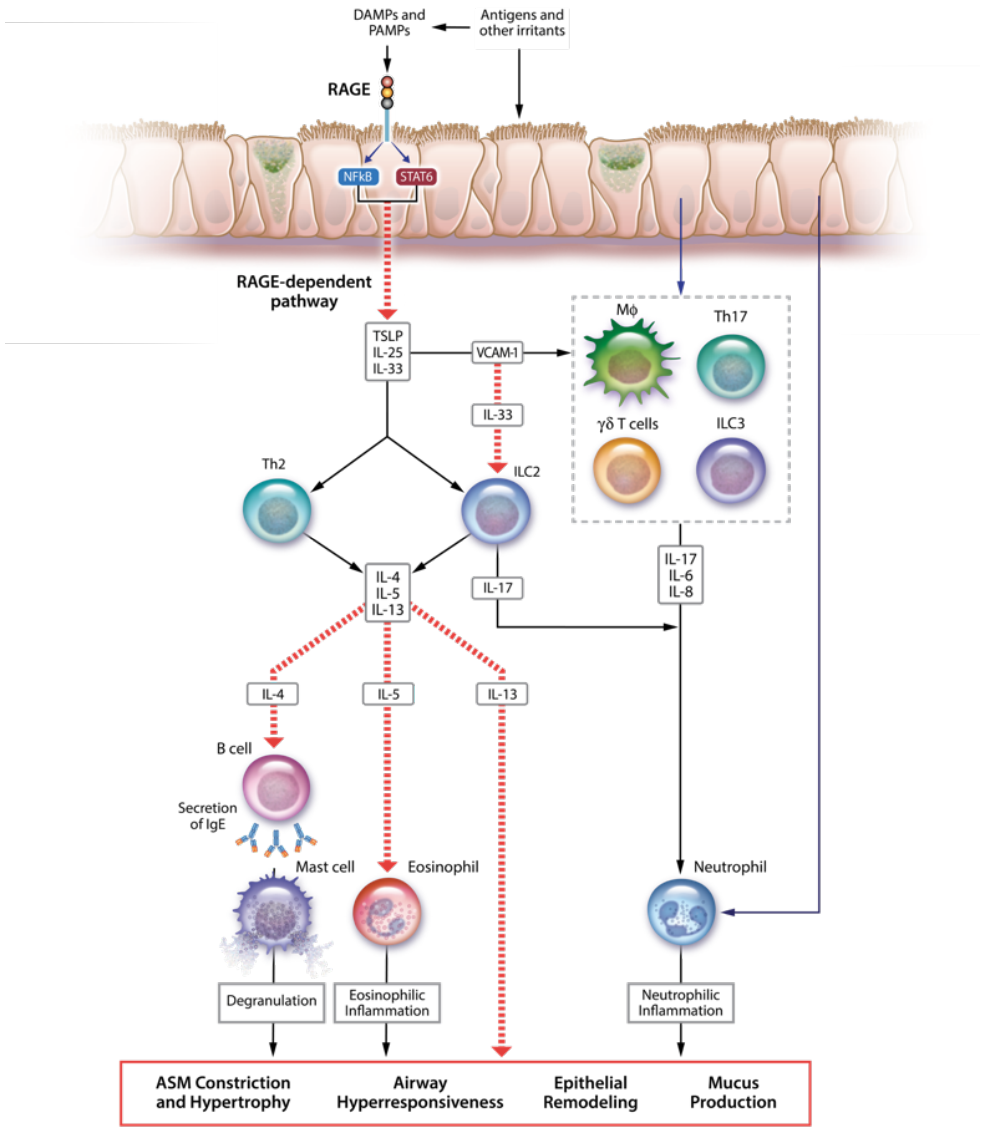
# RAGE Ligands: Overview in Allergic Airway Disease





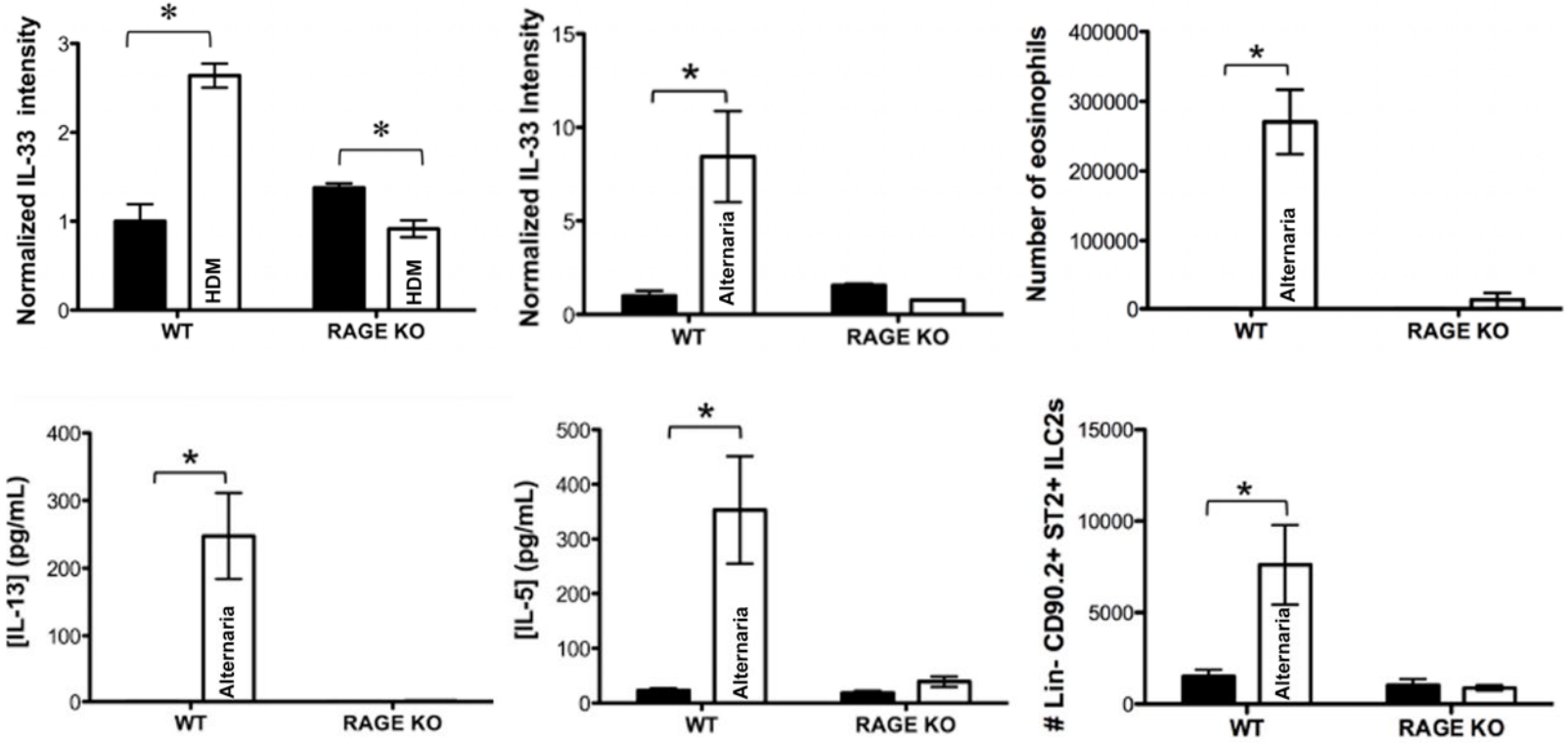

Perkins et al. Allergy. 2021;76:1350-1366

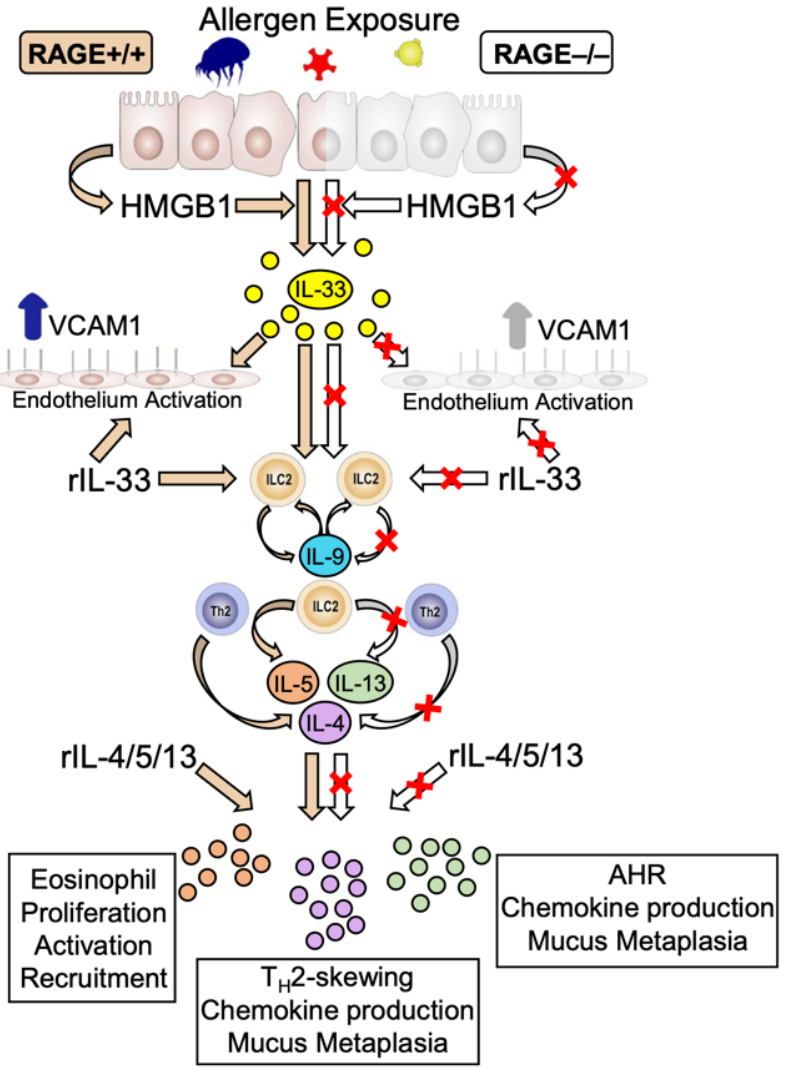
# RAGE: Proximal Inflammation Mediator in Asthma



# RAGE: Necessary for Type-2 Inflammation

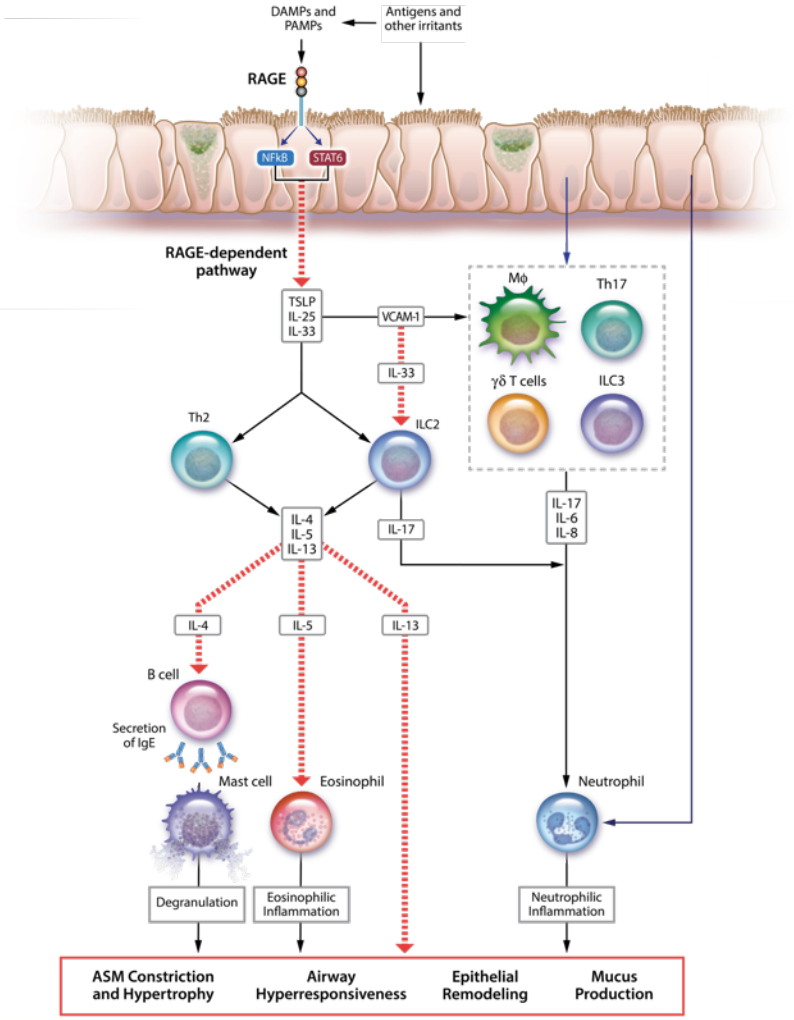
RAGE KO Erases Key Elements of the Type-2 Response to Allergens



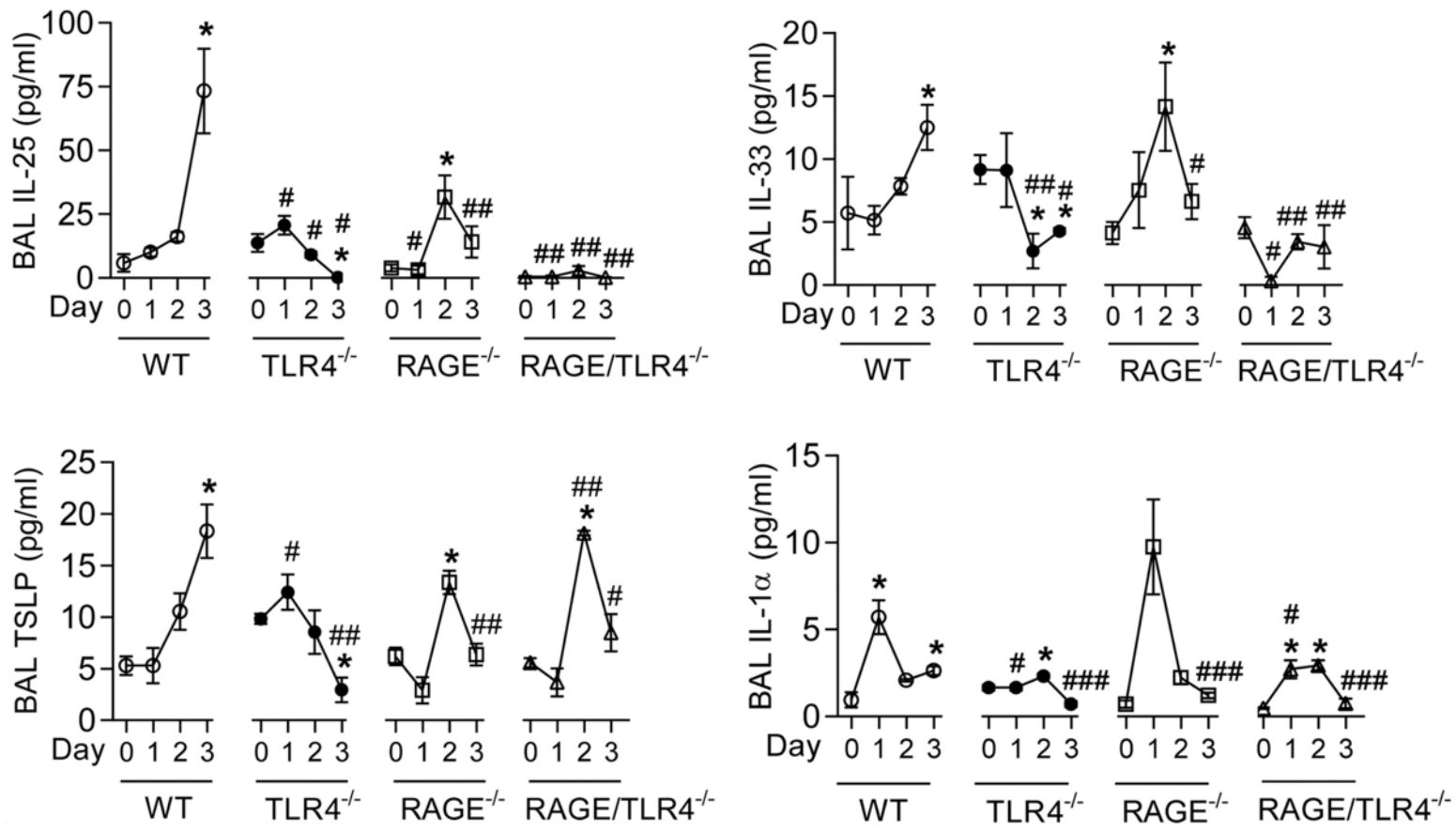




Perkins et al. Allergy. 2021;76:1350-1366; Oczypok et al. J Allergy Clin Immunol. 2015;136:747-756.

# RAGE Regulates Key Upstream Alarmins

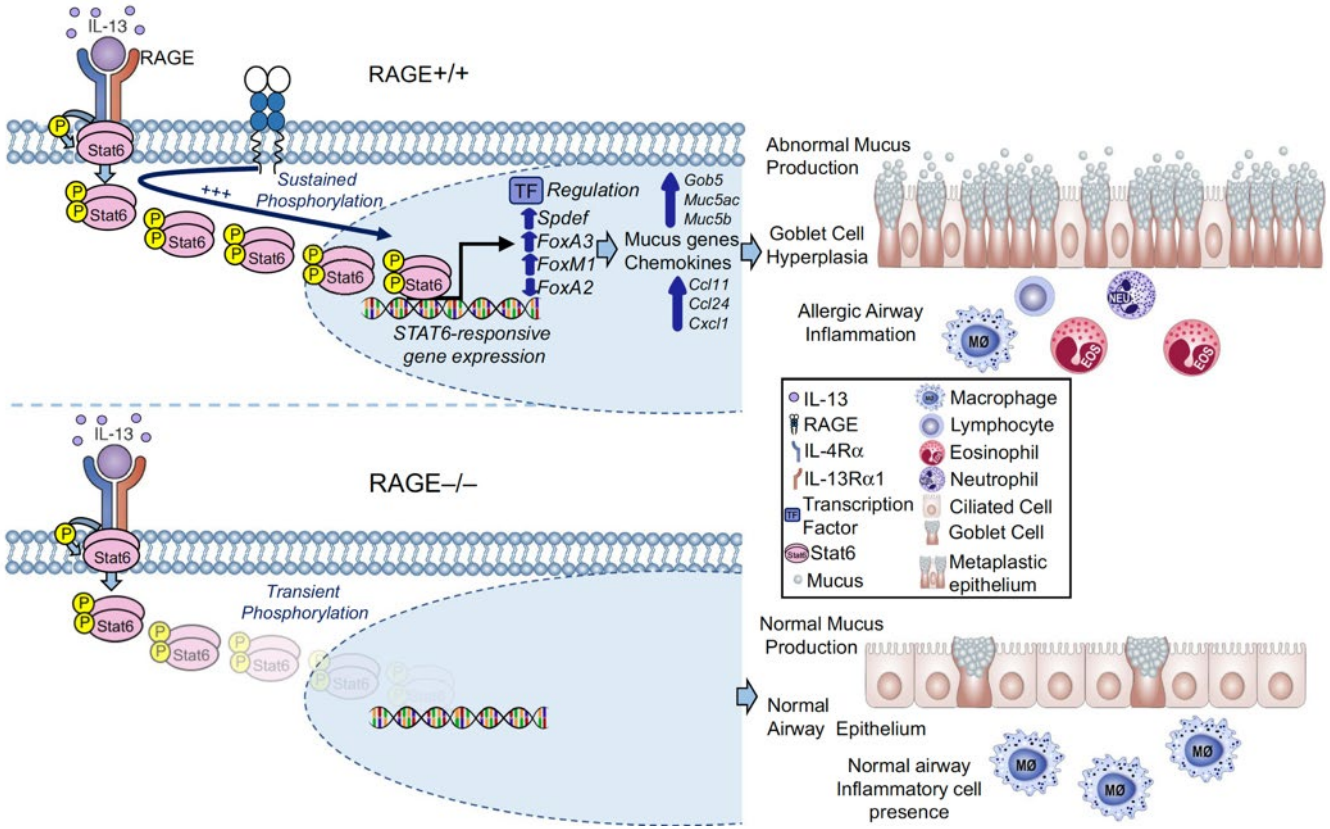


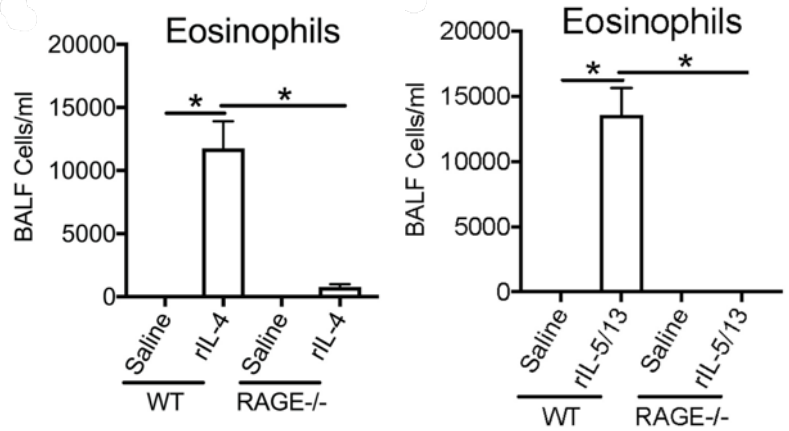

RAGE KO Blunts IL-25, TSLP, and IL-33 Response Following HDM Allergen Sensitization

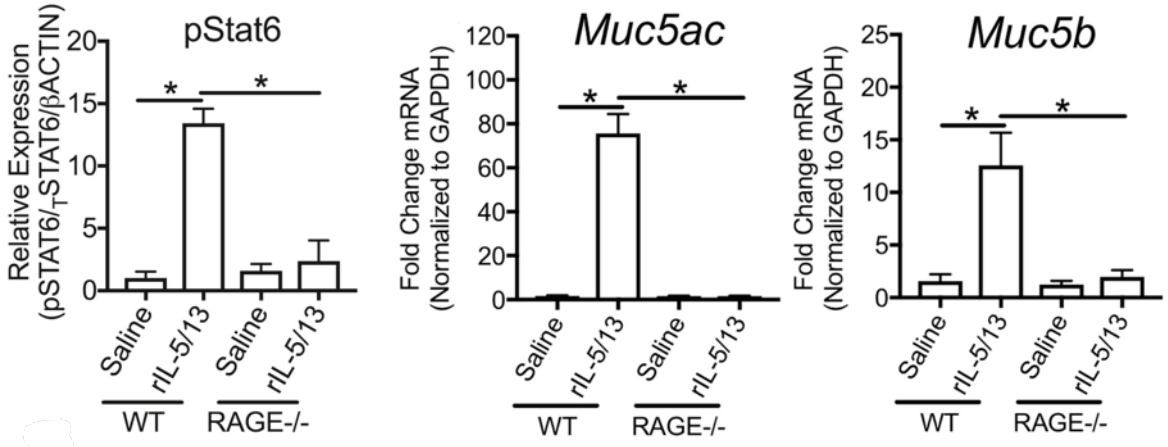



Ullah et al. J Allergy Clin Immunol. 2014;134:4[illegible]

# RAGE is Necessary for Sustained Signaling by Multiple Effector Cytokines

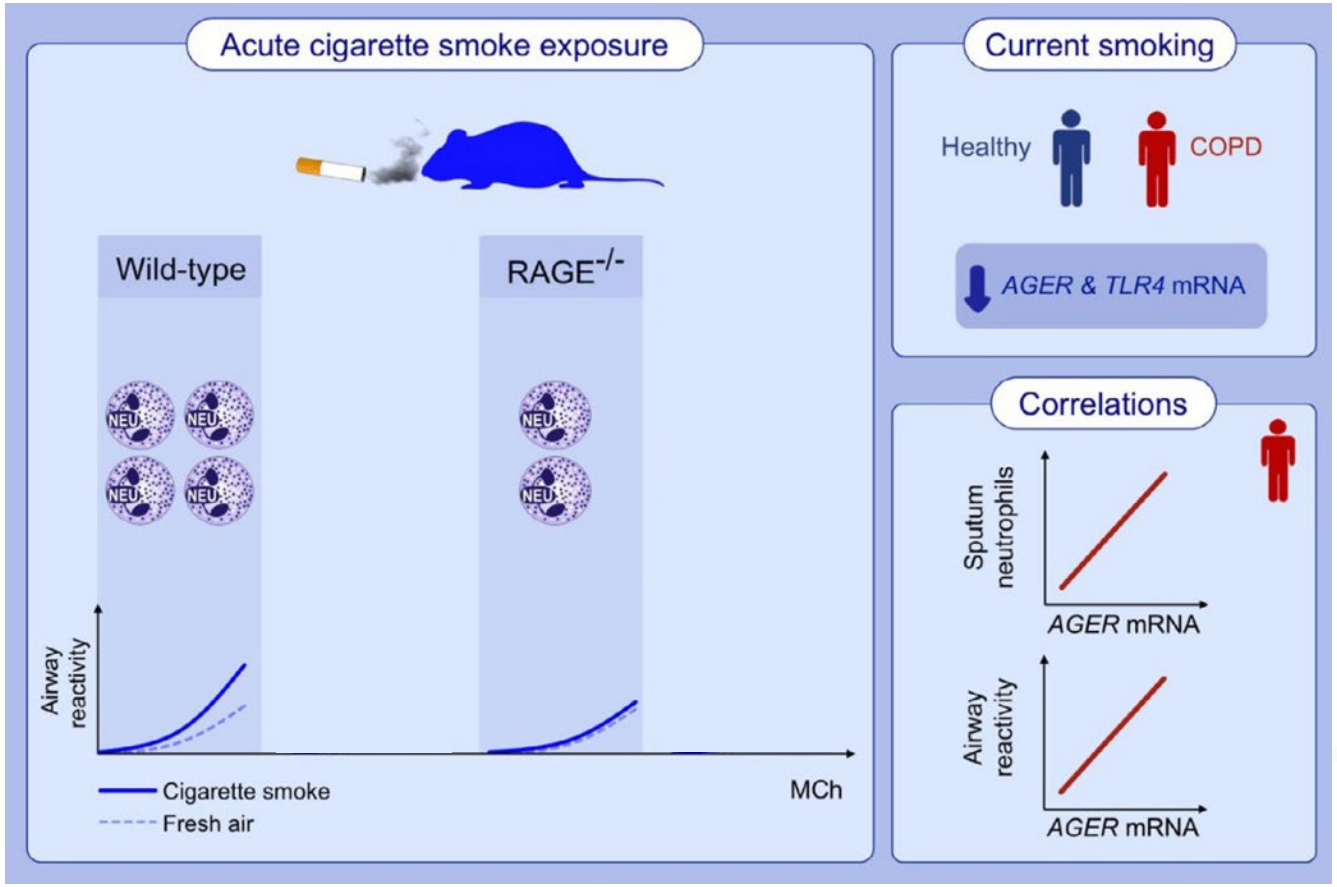


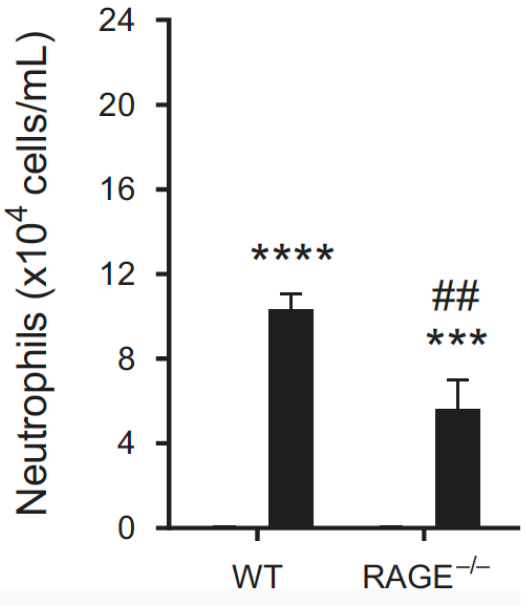



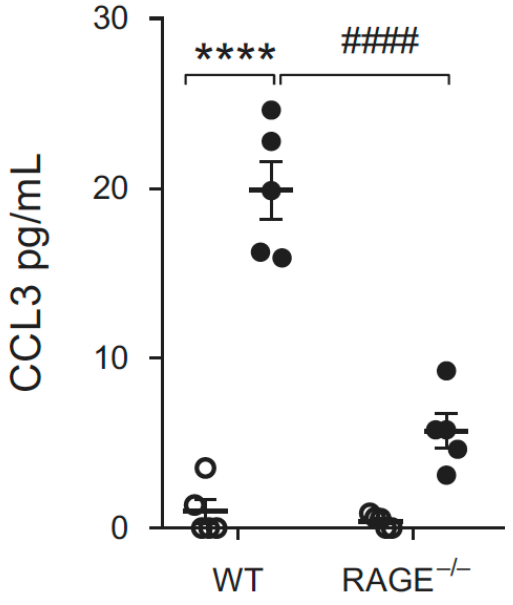




Perkins et al. JACI. 2019; 144:796-808. Perkins et al. Allergy. 2021;76:1350-1366

# RAGE is Implicated in T2-Low Inflammation




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

# Current Treatment Recommendations Asthma

**AGES 12+ YEARS:** STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

| | Intermittent Asthma | Management of Persistent Asthma in Individuals Ages 12+ Years | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **STEP 1** | **STEP 2** | **STEP 3** | **STEP 4** | **STEP 5** | **STEP 6** ■ |
| **Preferred** | PRN SABA | Daily low-dose ICS and PRN SABA<br>or<br>PRN concomitant ICS and SABA▲ | Daily and PRN combination low-dose ICS-formoterol▲ | Daily and PRN combination medium-dose ICS-formoterol▲ | Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲ | Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA |
| **Alternative** | | Daily LTRA* and PRN SABA<br>or<br>Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA | Daily medium-dose ICS and PRN SABA<br>or<br>Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA<br>or<br>Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA | Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲<br>or<br>Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA | Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA | |
| | | Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲ | | | Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)** | |

Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**

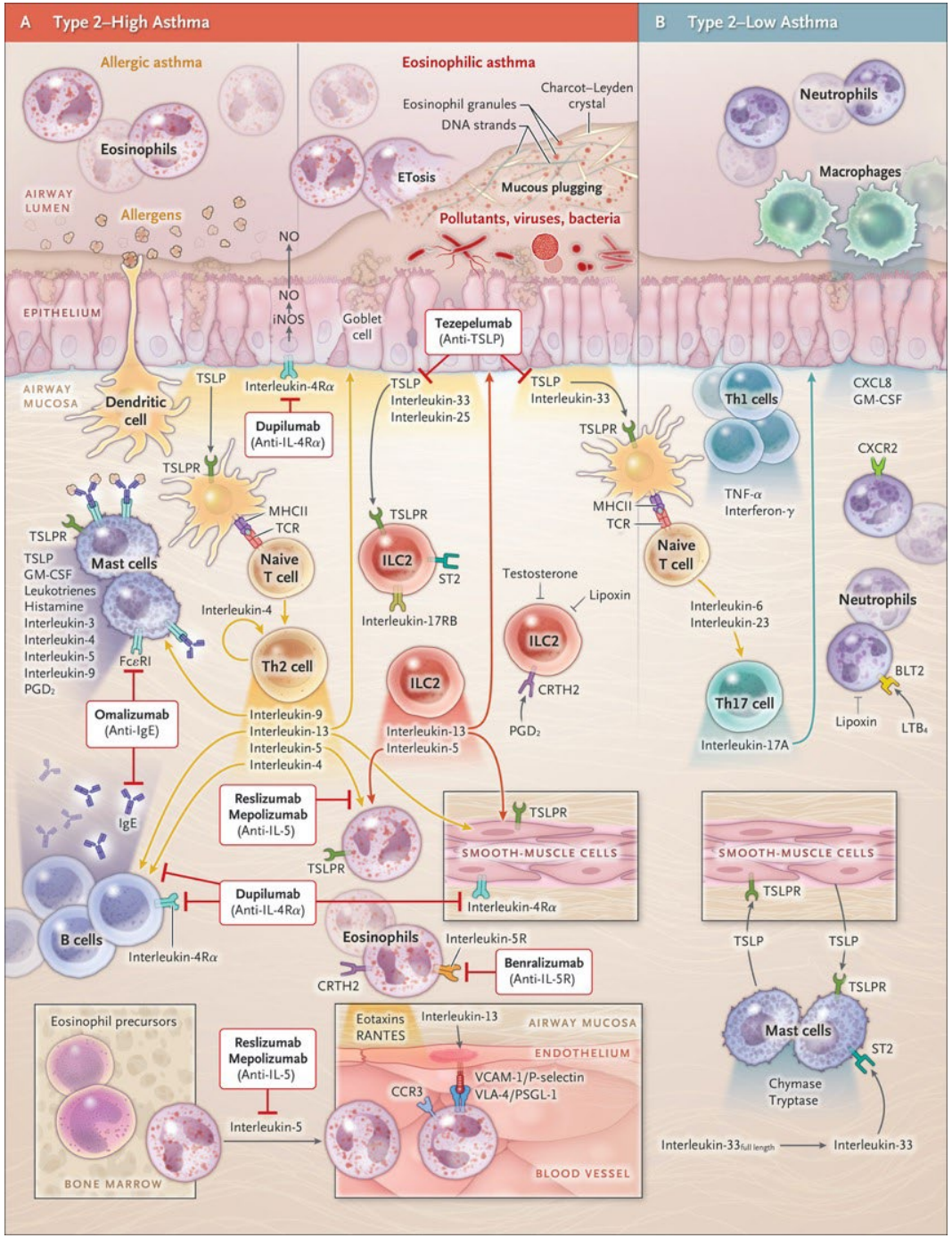
KU SCHOOL OF MEDICINE
The University of Kansas



 https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates

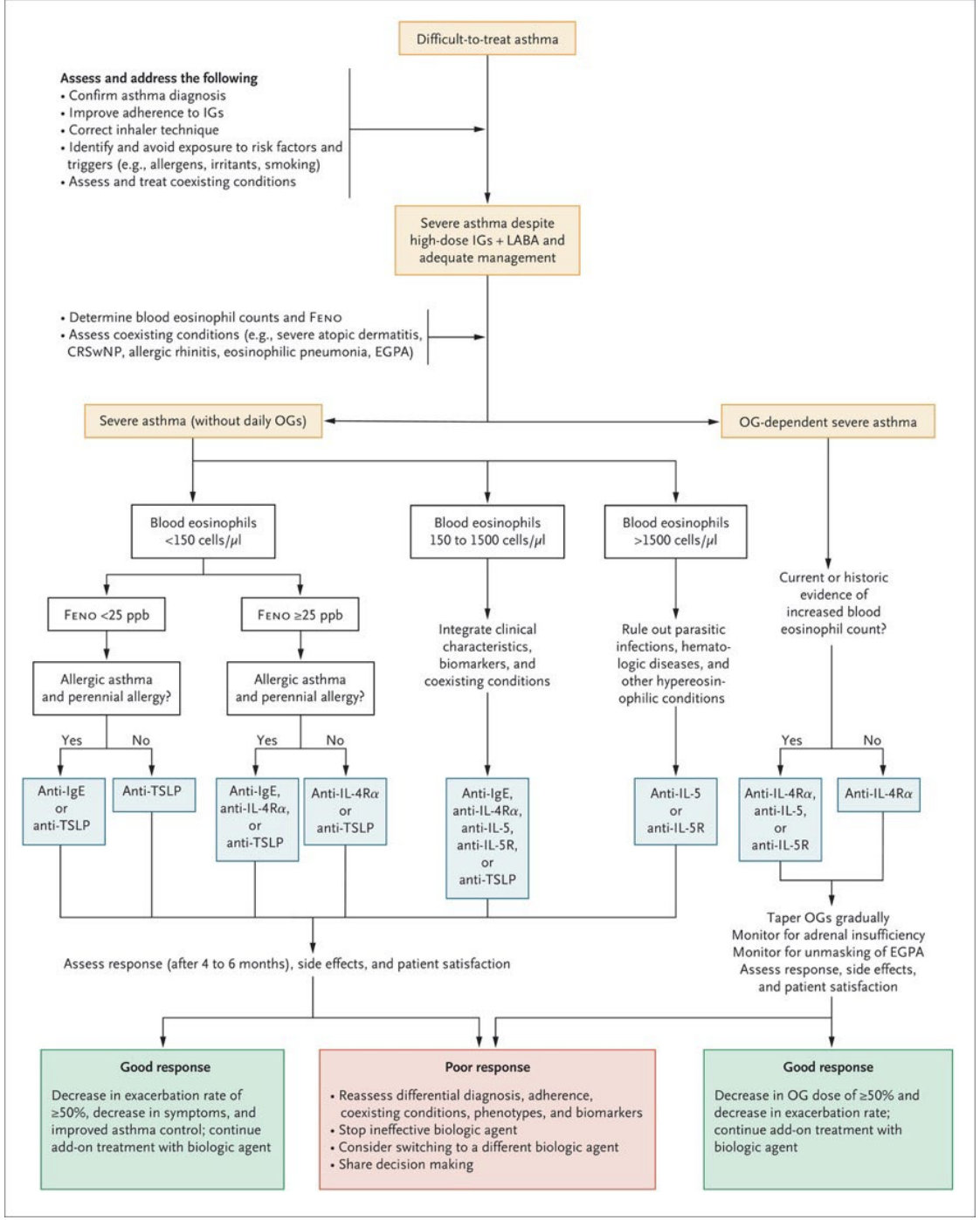
# Current Biologics – Severe Asthma

GG Brusselle, GH Koppelman. N Engl J Med 2022;386:157-171.



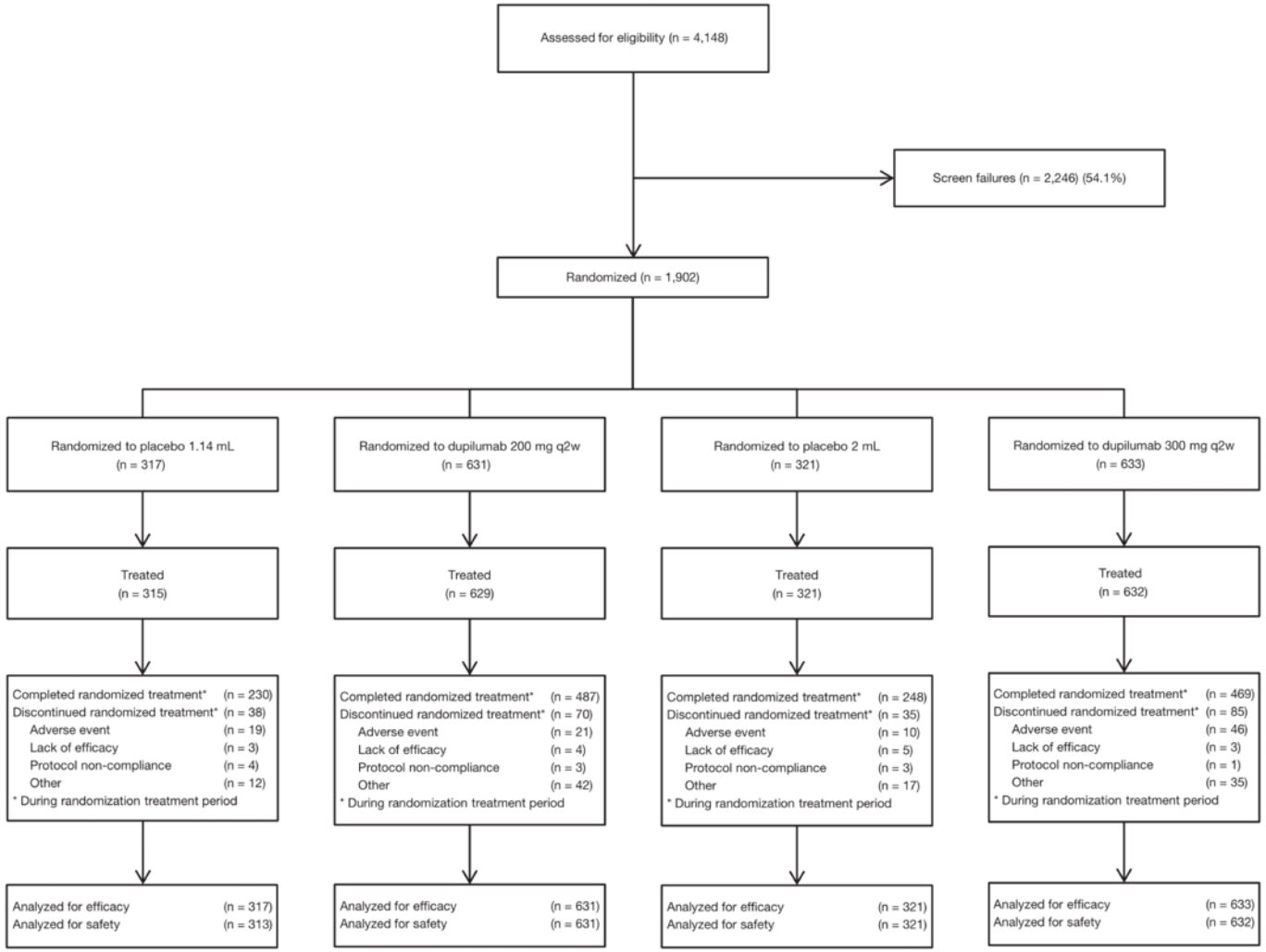
# Current Biologics – Severe Asthma

GG Brusselle, GH Koppelman. N Engl J Med 2022;386:157-171.




KU SCHOOL OF MEDICINE
The University of Kansas

# Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma



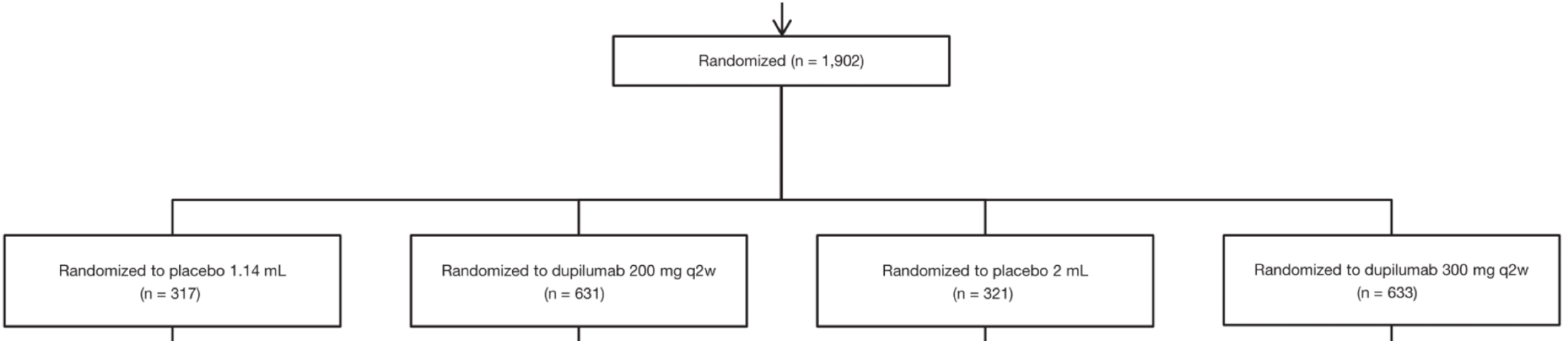

KU SCHOOL OF MEDICINE The University of Kansas





M Castro et al. N Engl J Med 2018;378:2486-2496

# Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

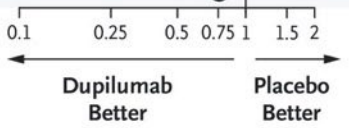



M Castro et al. N Engl J Med 2018;378:2486-2496

# Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

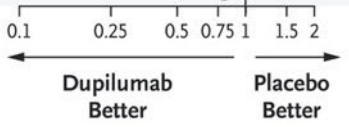
**A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo**

| Subgroup | No. of Patients | | Relative Risk vs. Placebo (95% CI) |
|---|---|---|---|
| | Placebo | Dupilumab | |
| Overall | 317 | 631 | 0.52 (0.41–0.66) |
| Eosinophil count | | | |
| ≥300 cells/mm³ | 148 | 264 | 0.34 (0.24–0.48) |
| ≥150 to <300 cells/mm³ | 84 | 173 | 0.64 (0.41–1.02) |
| <150 cells/mm³ | 85 | 193 | 0.93 (0.58–1.47) |
| $FE_{NO}$ | | | |
| ≥50 ppb | 71 | 119 | 0.31 (0.18–0.52) |
| ≥25 to <50 ppb | 91 | 180 | 0.39 (0.24–0.62) |
| <25 ppb | 149 | 325 | 0.75 (0.54–1.05) |




**B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo**

| Subgroup | No. of Patients | | Relative Risk vs. Placebo (95% CI) |
|---|---|---|---|
| | Placebo | Dupilumab | |
| Overall | 321 | 633 | 0.54 (0.43–0.68) |
| Eosinophil count | | | |
| ≥300 cells/mm³ | 142 | 277 | 0.33 (0.23–0.45) |
| ≥150 to <300 cells/mm³ | 95 | 175 | 0.56 (0.35–0.89) |
| <150 cells/mm³ | 83 | 181 | 1.15 (0.75–1.77) |
| $FE_{NO}$ | | | |
| ≥50 ppb | 75 | 124 | 0.31 (0.19–0.49) |
| ≥25 to <50 ppb | 97 | 186 | 0.44 (0.28–0.69) |
| <25 ppb | 144 | 317 | 0.79 (0.57–1.10) |



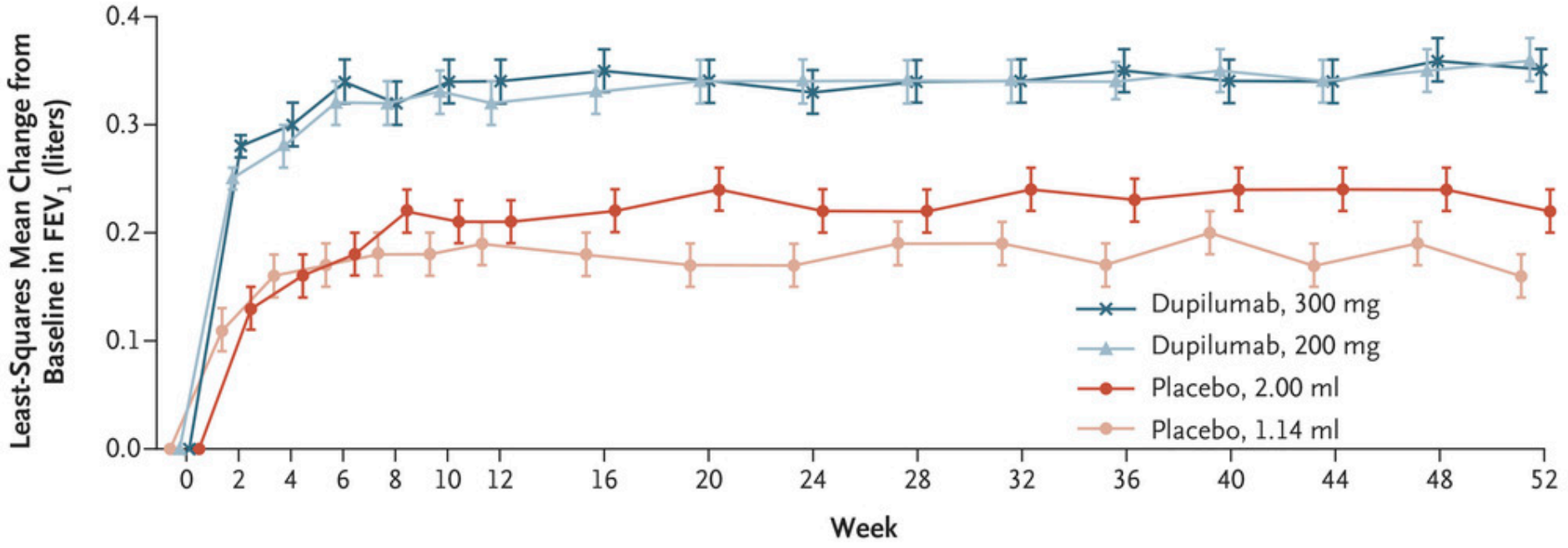

KU SCHOOL OF MEDICINE
The University of Kansas





M Castro et al. N Engl J Med 2018;378:2486-2496

# Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma




| No. at Risk | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dupilumab, 300 mg | 633 | 625 | 614 | 612 | 609 | 598 | 610 | 611 | 593 | 596 | 586 | 579 | 584 | 584 | 570 | 562 | 488 |
| Dupilumab, 200 mg | 631 | 610 | 613 | 615 | 604 | 607 | 611 | 605 | 601 | 599 | 589 | 585 | 590 | 577 | 581 | 570 | 477 |
| Placebo, 2.00 ml | 321 | 313 | 311 | 313 | 311 | 309 | 313 | 310 | 304 | 296 | 304 | 301 | 301 | 297 | 292 | 290 | 250 |
| Placebo, 1.14 ml | 317 | 315 | 307 | 301 | 305 | 301 | 307 | 300 | 303 | 300 | 290 | 286 | 289 | 287 | 288 | 281 | 240 |

M Castro et al. N Engl J Med 2018;378:2486-2496

# ARO-RAGE: Patient Profile

## 35 yo F with asthma

- Adult onset
- Negative allergen testing

Therapies

- Advair 500/50mcg BID
- Spiriva 18mcg daily
- Prednisone 20mg daily

- Blood eosinophils 200/ml
- 3 exacerbations in past year
  - 2 requiring increase in OG at home
  - 1 requiring hospitalization
- $FEV_1$ 65% predicted

dupilumab Trial →

- Decreased prednisone to 10 mg daily
- Suffered another exacerbation
- $FEV_1$ up to 75%; less short of breath

Somewhat improved, but still quite symptomatic

stop dupilumab →

mepolizumab Trial

- Still on prednisone 10mg daily
- 1 exacerbation per year
- $FEV_1$ back to 68%; short of breath with moderate activity

Continued significant morbidity due to asthma

? →

KU SCHOOL OF MEDICINE The University of Kansas

# Why RAGE as a Treatment Target for Asthma?

***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 biologic therapies: TSLP, IL-5, etc.
- RAGE regulates inflammatory pathways relevant to both T2-high and T2-low asthma

***COPD***

- RAGE regulates smoking-induced neutrophilia and airway inflammation

***Cystic Fibrosis***

- RAGE regulates (hyperglycemia-induced) airway inflammation and mucociliary dysfunction

Pulmonary R&D Day, May 26, 2022

# Clinical Development

Javier San Martin, MD

arrowhead pharmaceuticals

# Mechanisms of Airway Disease & Available Therapeutics

## Airway Muscle Constriction

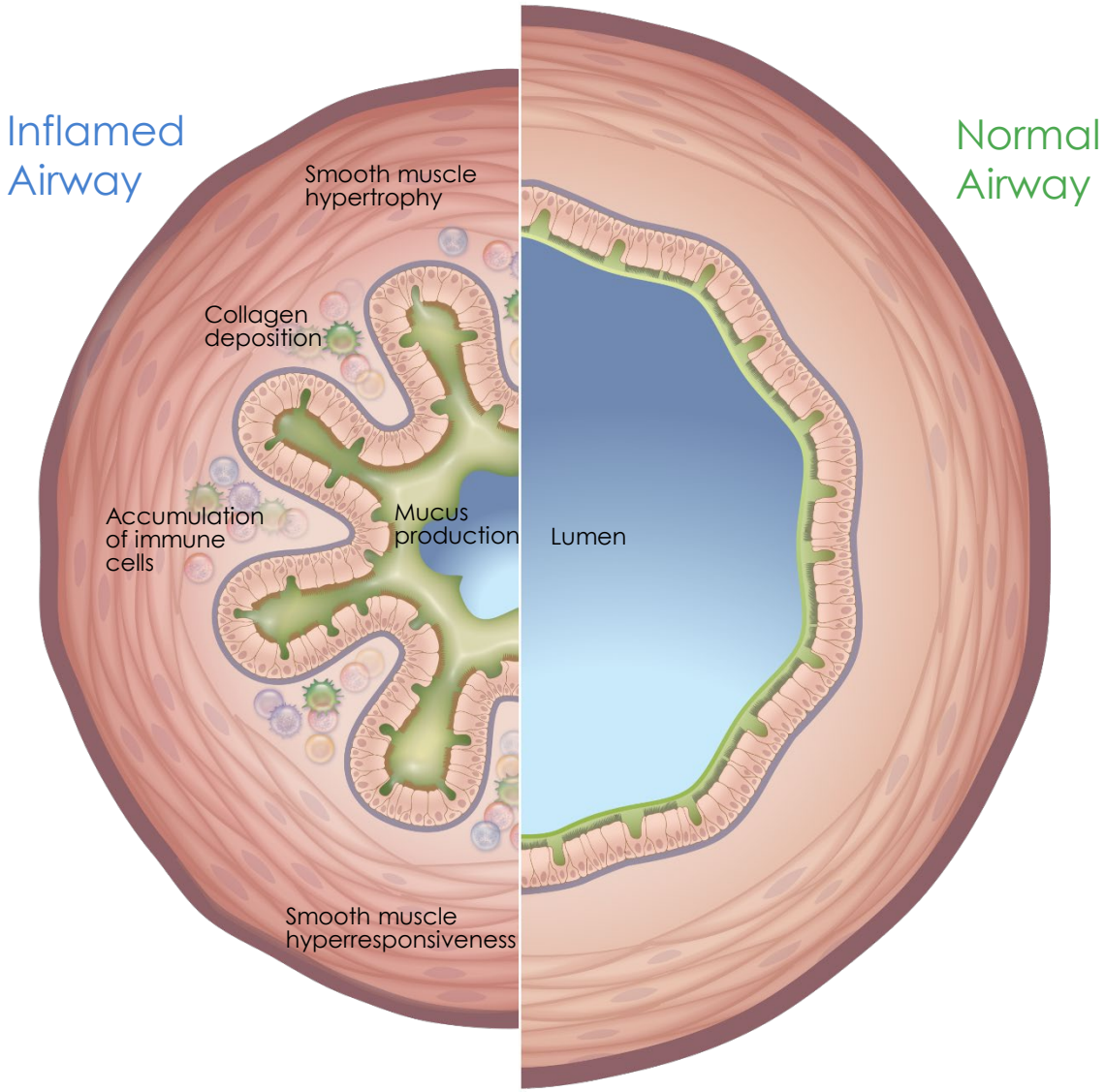
- Beta-agonists and LAMAs

## Airway Inflammation

- Corticosteroids
- Biologics

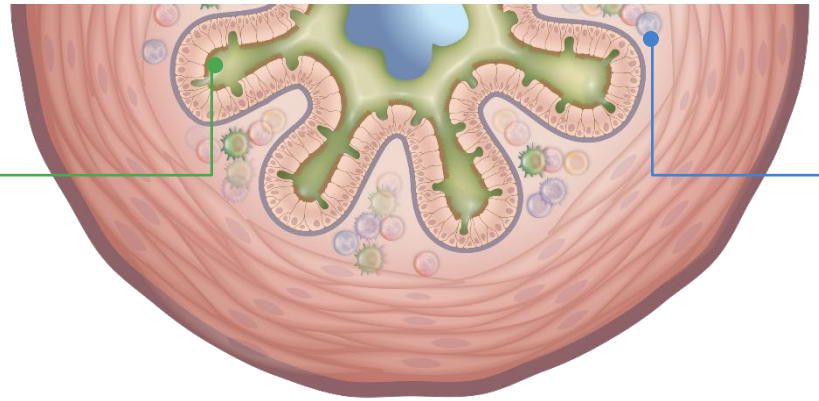
## Mucus Secretion

- None available



# ARO-MUC5AC & ARO-RAGE:
# Unique Approaches to Distinct Components of Airway Pathophysiology

Mucus secretion



Airway inflammation

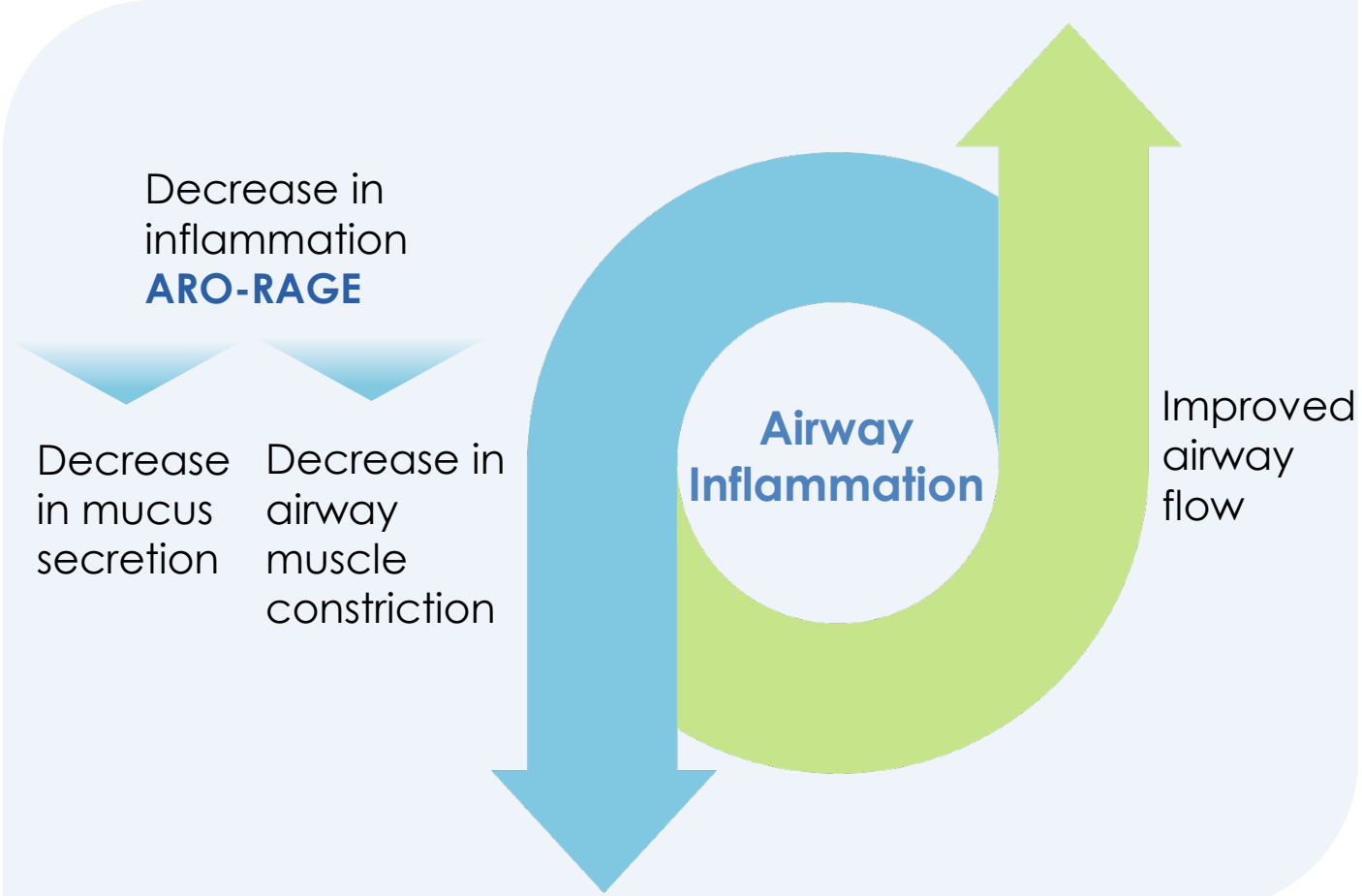
## ARO-MUC5AC

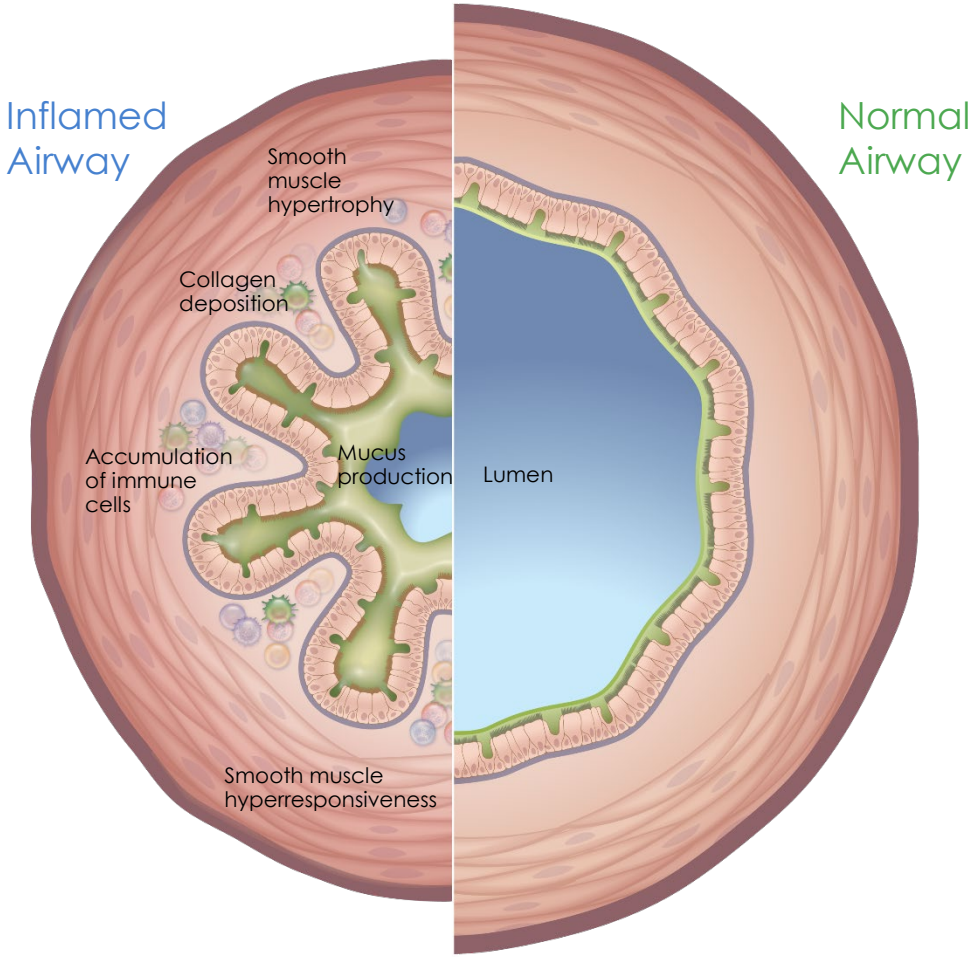
- New class of drug: Blocks overproduction of mucus
- Unique patient population: Chronic mucus hypersecretion, independent of underlying inflammatory phenotype
- Aim to benefit patients with persistent muco-obstruction irrespective of background muco-obstructive mechanism

## ARO-RAGE

- A better anti-inflammatory therapy
  - Broader anti-inflammatory effects than current biologics
  - Local delivery, convenient administration mode
- Broad effects = broad patient population: prevent switching therapies
- Aim to be best in class approach to anti-inflammatory therapies

# ARO-RAGE:
# Addressing Inflammation by Blocking RAGE and Downstream Cytokines



# RAGE Is a Promising Target for Addressing Asthmatic Inflammation

- Upregulation of RAGE expression in airway epithelium is correlated with asthma severity
- Airway concentration of RAGE ligands is associated with asthma severity
- RAGE KO mice are protected from allergen-induced upregulation of key asthma inflammatory mediators:
  - Alarmins: IL-33, IL-25, and TSLP
  - Type-2 cytokines: IL-5 and IL-13
  - Type-2 effector cells: ILC2s and eosinophils
- RAGE KO mice show attenuated neutrophilia following stimuli relevant to Type-2 low asthma
- RAGE-directed RNAi recapitulates protection from allergen-induced inflammation in a rat model of asthma

# There is Need for a Better Anti-Inflammatory Therapy

- **Biologics improve but do not resolve asthma symptoms**
  - Mild effects on airflow
    - Mepolizumab: ~100 mL $FEV_1$ improvement
  - Continued exacerbations
    - Tezepelumab: Still ~1 exacerbation per year on therapy
  - Persistent need for oral corticosteroids
    - Tezepelumab: 40% OCS-dependent patients unable to decrease steroid dose by at least half

- **Less (or no) efficacy in patients with Type-2-low asthma**

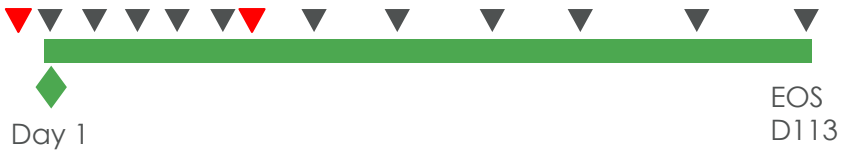
- **Systemic subcutaneous administration required for biologics**

Due to shortcomings and incomplete response, switching between biologics remains common

Ortega et al. NEJM 2014.
Menzies-Gow et al. NEJM 2021.
Wechsler et al. Lancet Respir Med 2022.
Eger et al. J Allergy Clin Immunol Pract 2020.

# ARO-RAGE First-in-Human Study:
## Safety, Target Engagement & Dose-Response and Duration

### NHV Single Dose




### Asthma Multi-Dose


◆ Dose administration ▼ sRAGE measurement by serum and/or induced sputum ▼ Bronchoscopy for BAL sRAGE

| | Healthy Volunteers | Asthma |
|---|---|---|
| **Population** | | • Broad range of disease severity (GINA 1-4)<br>• Type-2 High (Blood eos ≥ 200) |

**Cohorts**

**10 mg Cohort A1**
↓ D22 Safety Eval
**20 mg Cohort A2**
↓ D22 Safety Eval
**40 mg Cohort A3**
↓
**80 mg Cohort A4**

8 subjects each (6:2)

D22 Safety Eval → **≤ 40 mg Cohort B1**

D22 Safety Eval → **≤ 80 mg Cohort B2**

8 subjects each (6:2)

**All doses represent dose loaded into nebulizer**

# Soluble RAGE Protein Assay:
## A Non-invasive Pharmacodynamic Biomarker

**Pharmacodynamic Biomarkers for First-in-Human Study in Multiple Matrices**

**Soluble RAGE (sRAGE) Protein Concentration**

Serum

Sputum

Bronchoalveolar lavage fluid

**RAGE mRNA expression from bronchial brushings**

Defining correlation between effects on airway and blood biomarkers will enable use of serum sRAGE as PD biomarker through later development

# Biologic Precedents Provide a Well-Defined Pathway for Drug Development in Asthma

## Overview of Development of Dupilumab for Asthma

| | | Patients | Sample Size (Treatment Duration) | Endpoints |
|---|---|---|---|---|
| Phase 2a | | Moderate-severe asthma with blood eos ≥300 | 104 (12 weeks) | Asthma exacerbation following ICS/LABA taper |
| Phase 2b | | Moderate-severe asthma, any blood eos | 769 (24 weeks) | 1°: $FEV_1$<br>2°: AAER & ACQ/AQLQ |
| Phase 3 | Trial 1: | Moderate-severe asthma, any blood eos | 1902 (52 weeks) | 1°: AAER<br>2°: $FEV_1$ & ACQ/AQLQ |
| | Trial 2: | Severe OCS-dependent asthma | 210 (24 weeks) | Reduction in OCS dose |

AAER: Annualized asthma exacerbation rate
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
OCS: Oral corticosteroids
ICS: Inhaled corticosteroids
LABA: Long-acting beta-agonist

# ARO-RAGE Development:
## Path to Registration in Moderate-to-Severe Asthma

### Phase 2: Type-2 High and Type-2 Low Asthma

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

### Phase 3: Type-2 High and Type-2 Low Asthma

Expected Outcomes
- Decreased exacerbation frequency
- Improved airflow ($FEV_1$)
- Improved symptoms and Quality of Life

### Additional Opportunities

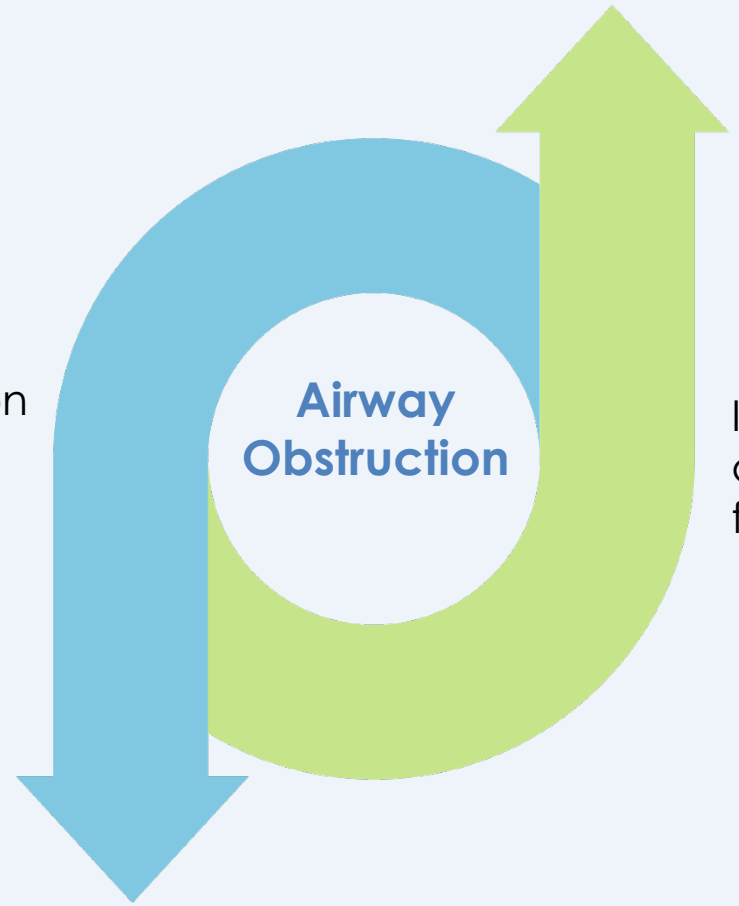
COPD
Cystic Fibrosis

Non-invasive PD biomarker (serum sRAGE) will inform on dose response

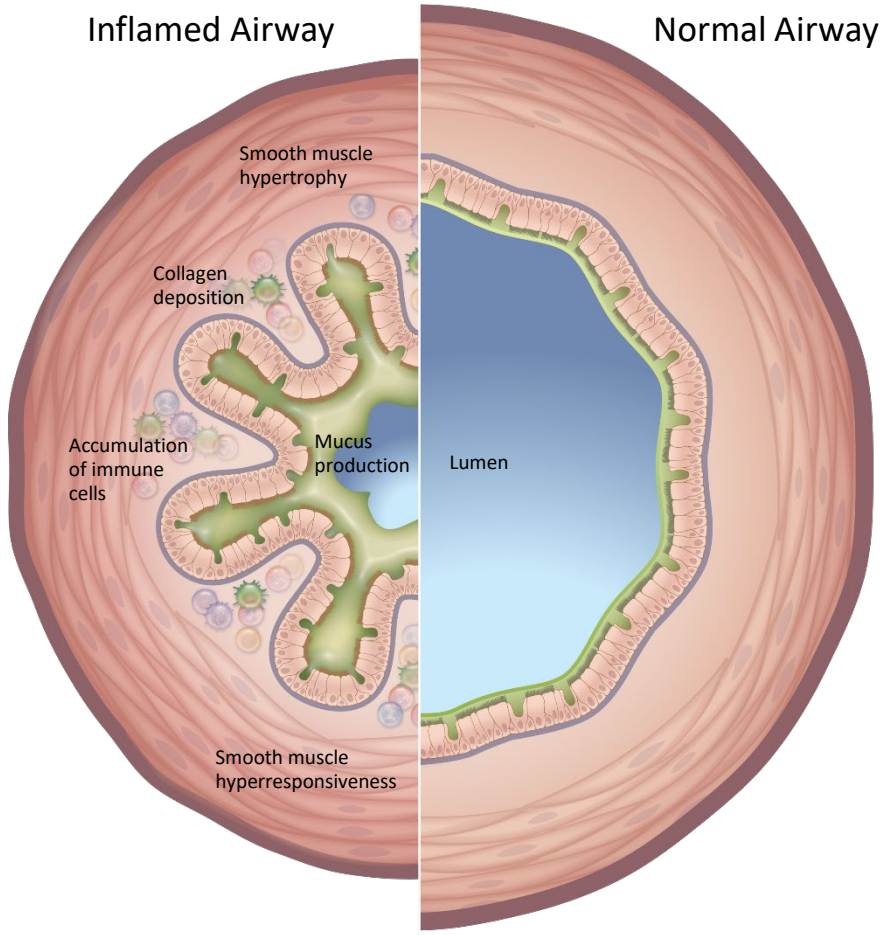
# ARO-MUC5AC: Addressing Muco-obstructive Lung Diseases

Decrease in muco-obstruction **ARO-MUC5AC**

Decrease in inflammation




Improved airway flow

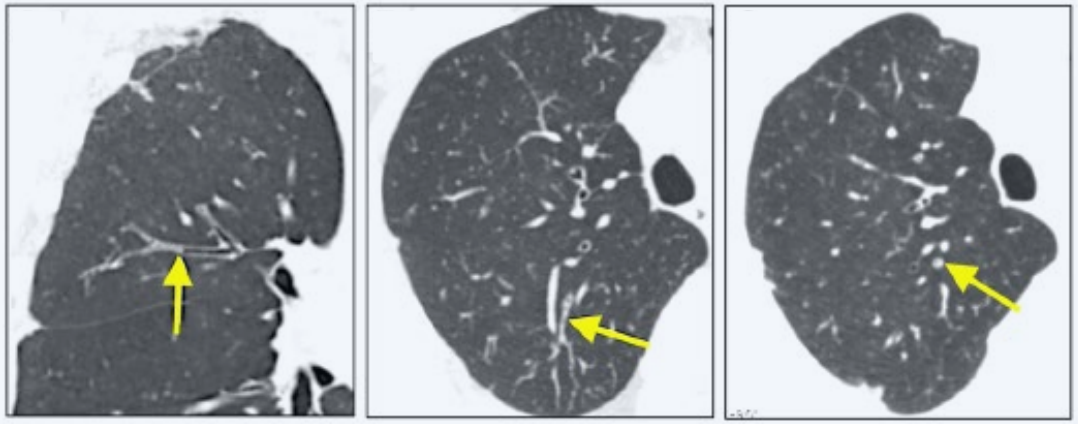


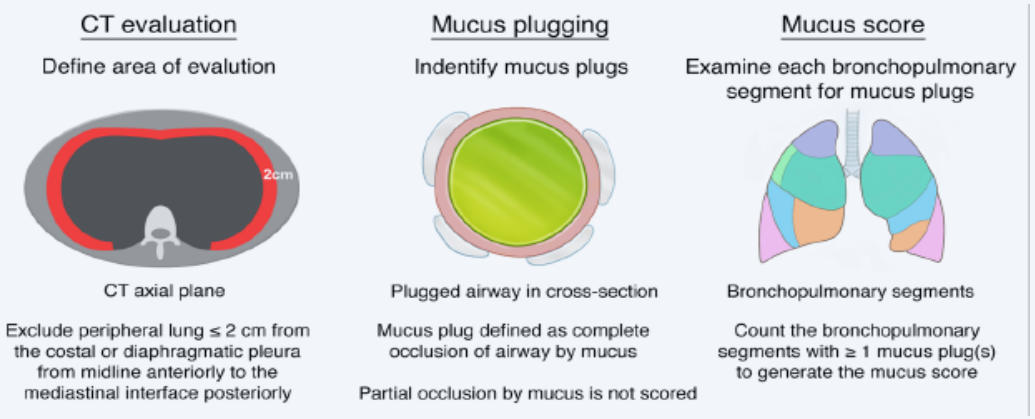
# MUC5AC is a Promising Target for Addressing Muco-Obstructive Lung Disease

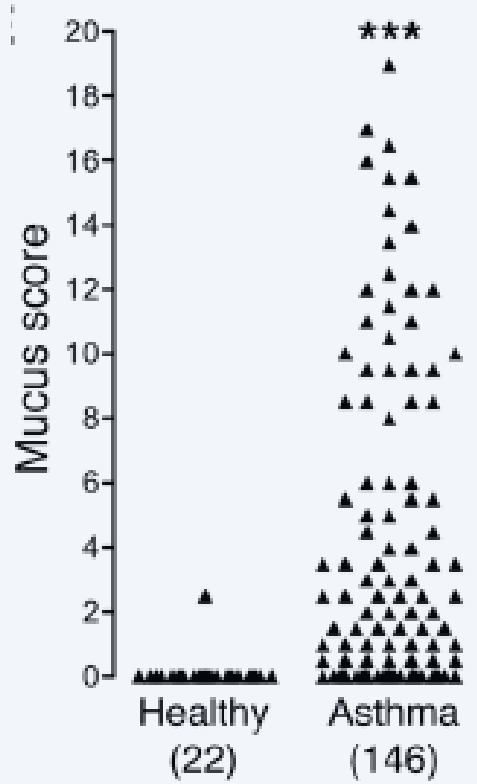
- Increased concentration of sputum MUC5AC is associated with more severe airflow obstruction (lower $FEV_1$)
- Increased MUC5AC expression is correlated with higher numbers of mucus plugs on chest CT
- MUC5AC expression increases during disease exacerbations and augments viral-induced airway inflammation
- Multiple GWAS suggest a causal role for MUC5AC in asthma
- MUC5AC KO mice are protected from allergen-induced airway hyperreactivity
- ARO-MUC5AC protects sheep from allergen-induced increases in airway resistance and hyperreactivity

# Chest CT is a Novel Approach to Identify Asthma Patients with a High Mucus Burden

## "Mucus-High" as a Distinct Phenotype of Airways Disease

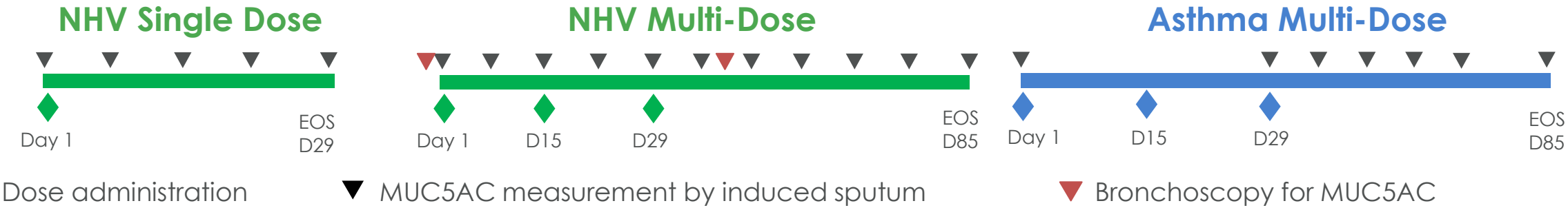





Dunican et al. J Clin Invest 2018.

# ARO-MUC5AC First-in-Human Study:
## Safety, Target Engagement & Dose-Response and Duration




**Population**

**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) | | |

**All doses represent dose loaded into nebulizer**

# ARO-MUC5AC Clinical Development: Path to Registration

## Phase 2: Moderate-Severe Asthma

What Will We Learn

- Effect on airflow: spirometry and MRI
- Effect on exacerbations
- Effect on symptoms: cough, sputum and shortness of breath
- Effect on mucus plugs: CT scan
- Identify the "mucus-high" population

## Phase 3: Moderate-Severe Asthma

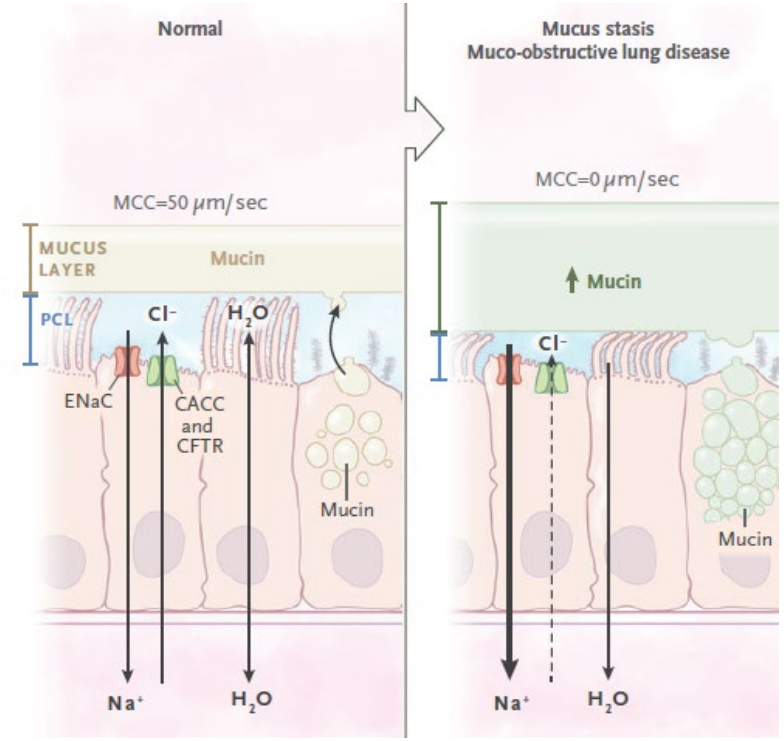
Expected Outcomes

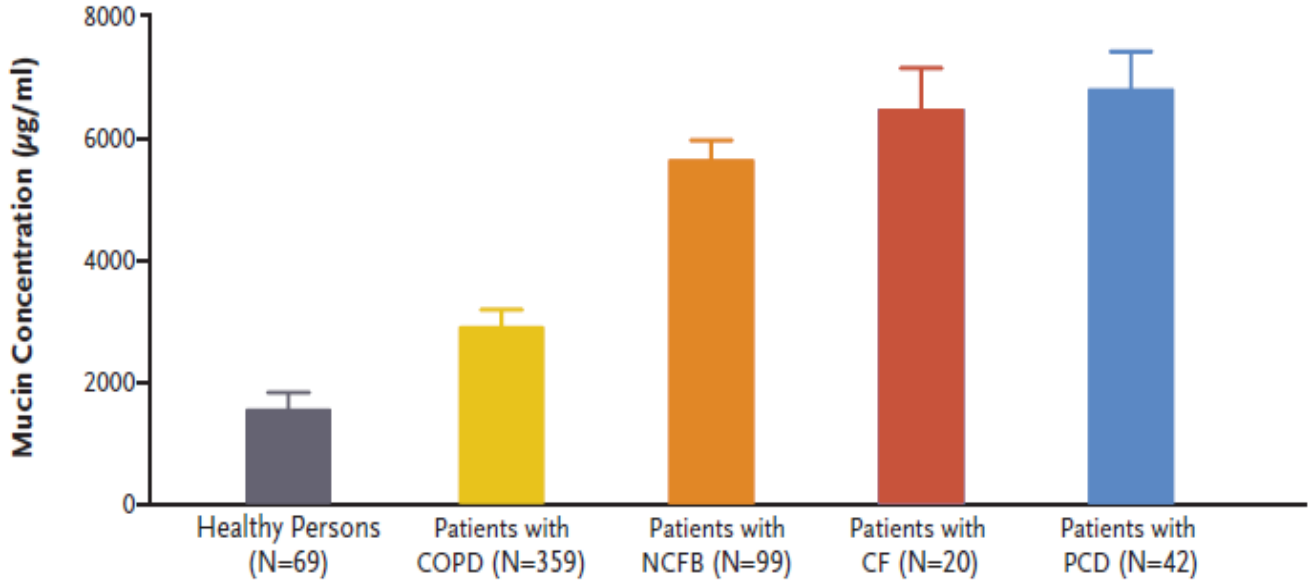
- Decreased exacerbation frequency
- Improved airflow ($FEV_1$)
- Improved symptoms and Quality of Life

## Other Muco-obstructive Diseases

- COPD
- Cystic Fibrosis
- Non-CF Bronchiectasis
- Primary Ciliary Dyskinesia

# Mucin Upregulation is the Common Foundation of Muco-obstructive Lung Diseases and Asthma




Increased mucin expression causes airway diseases by disrupting mucociliary clearance

Boucher. NEJM 2019.

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

| | |
|---|---|
| **Disease Burden:** | • 16M COPD Patients<br>• 9M COPD Patients with Chronic Bronchitis |
| **Current Therapies:** | • Bronchodilators: LABA, LAMA<br>• Anti-inflammatory: ICS, azithromycin<br>• Roflumilast |

| | | | |
|---|---|---|---|
| **Significant Morbidities:** | **Frequent Exacerbations** | **Airflow Obstruction** | **Decreased QoL** |
| **Clinical Trial Endpoints:** | **Exacerbation Rate** | **$FEV_1$** | **PRO Measures** |

# Mucus Drives Chronic Symptoms in 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)

# ARO-MUC5AC Clinical Development Program in COPD

## 2 Phase 2: Moderate-Very Severe COPD

**What Will We Learn**

- Effect on exacerbations
- Effect on airway obstruction ($FEV_1$)
- Effect on symptoms: cough, sputum, & shortness of breath
- Effect on mucus plugs: CT scan

## 3 Phase 3: Moderate-Very Severe COPD

**Expected Outcomes**

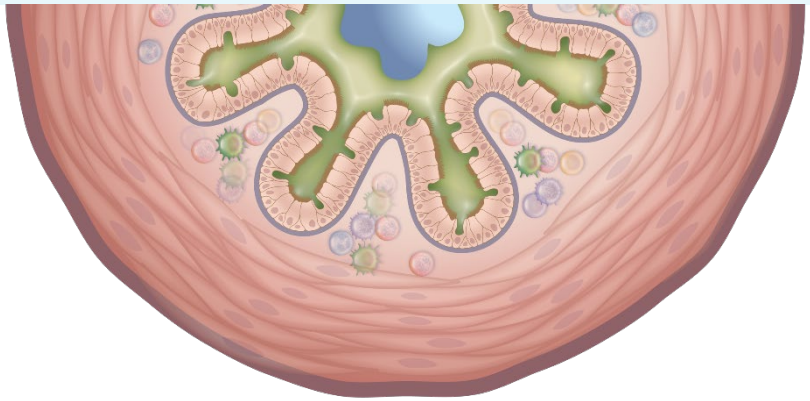
- Decreased exacerbation frequency
- Improved airflow ($FEV_1$)
- Improved symptoms and Quality of Life

# Large Unmet Medical Need in Rarer Muco-obstructive Diseases. MUC5AC has the Potential to Address the Underlying Pathophysiology

| | Patients Numbers in US | Available Therapies |
|---|---|---|
| Primary Ciliary Dyskinesia | ~3,000 | Antibiotics<br>Airway hydration<br>Bronchodilators |
| Non-CF Bronchiectasis | ~350,000 | Antibiotics<br>Airway hydration<br>Bronchodilators |
| Cystic Fibrosis | 31,000 | CFTR Modulators<br>Antibiotics<br>Inhaled mucolytics<br>Airway hydration<br>Bronchodilators |

# Novel & Differentiated Approaches to the Unmet Need in Airway Disease

**First-in-class anti-mucus therapy**



**A better anti-inflammatory therapy**

## ARO-MUC5AC

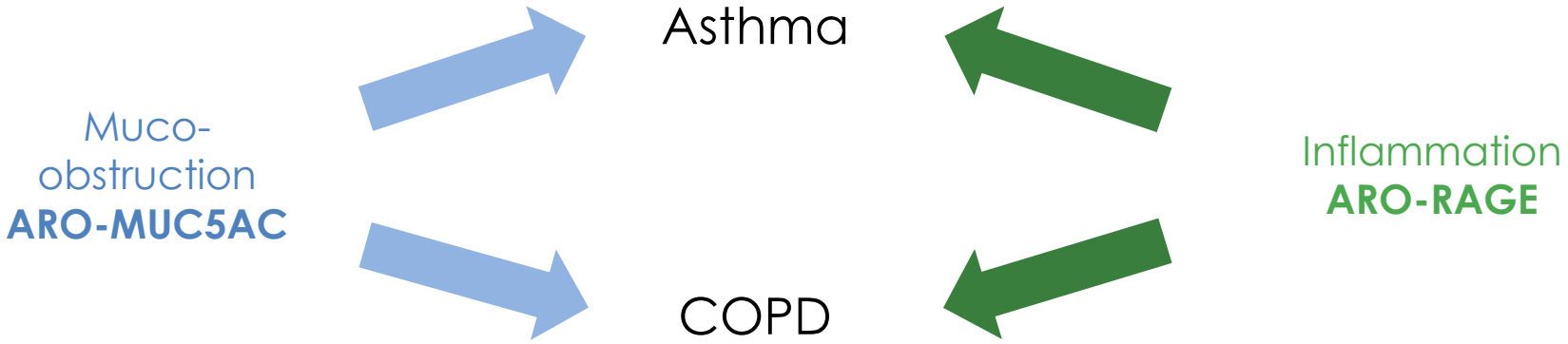
- Mechanism differentiated from biologics: combination not competition
- Chest CT as innovative tool to identify the "mucus-high" phenotype
- Broad pipeline potential in muco-obstructive diseases beyond asthma

## ARO-RAGE

- Pan-cytokine depletion
- Local administration, not systemic
- Broad pipeline potential in airway inflammatory diseases beyond asthma

# Multiple Development Paths to Address a Broad Spectrum of Airway Diseases

Distinct Pathways & Subpopulations within Airway Diseases




Development Approach Tailored to the Disease State

Rare Diseases:

PCD | CF | NCFB

Potential for Accelerated Development Pathway

High Prevalence Diseases:

Well-Defined Regulatory Pathway

Asthma | COPD

Pulmonary R&D Day, May 26, 2022

# Market Research and Opportunity

Anjli Warner, MBA

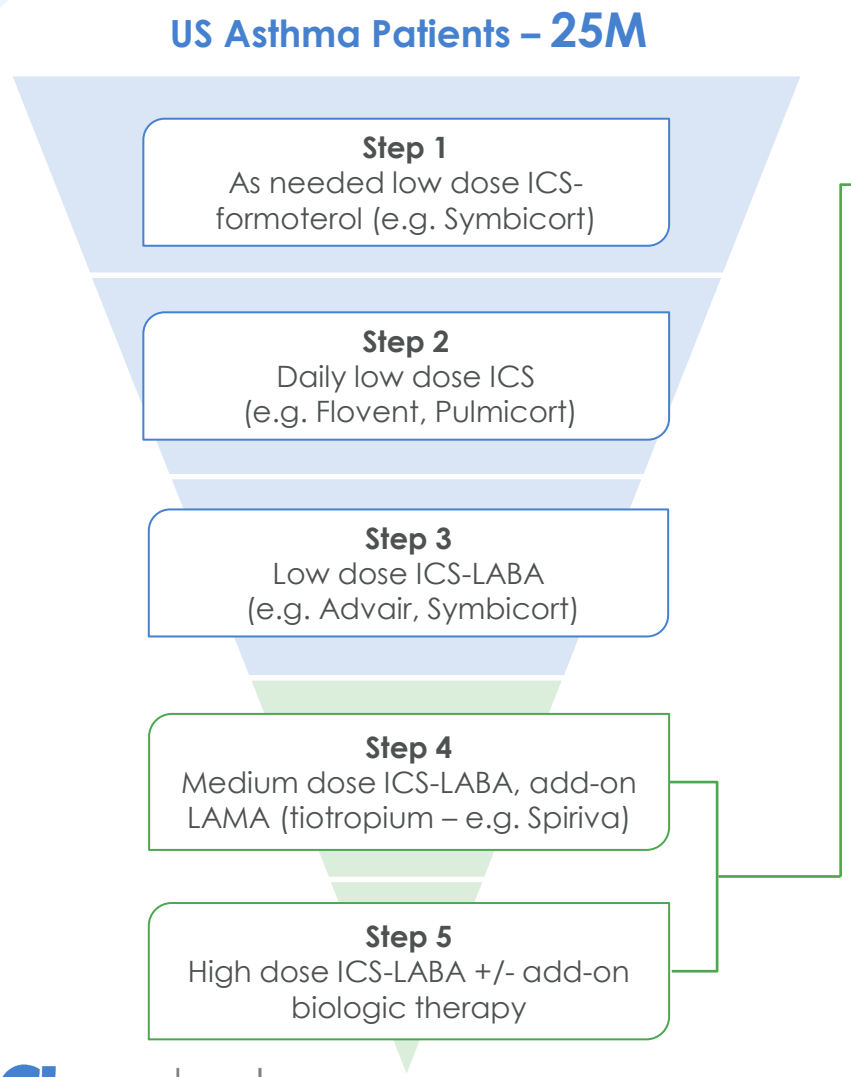
arrowhead pharmaceuticals

# ARO-RAGE & ARO-MUC5AC:
## Separate Mechanisms of Action with Distinct Opportunity

| | U.S. Diagnosed Patients | Target Inflammation ARO-RAGE | Target Mucus Obstruction ARO-MUC5AC |
|---|---|---|---|
| Asthma | 25M[1] | ✓ | ✓ |
| COPD | 16M[2] | ✓ | ✓ |
| Non-CF Bronchiectasis | 350K[3] | | ✓ |
| Cystic Fibrosis | 31K[4] | ✓ | ✓ |
| Primary Ciliary Dyskinesia | 3K[5] | | ✓ |

1. CDC National Center for Health Statistics, National Health Interview Survey (NHIS). National Surveillance of Asthma: United States, 2001-2017.
2. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease — United States, 2013. MMWR Morb Mortal Wkly Rep. 2015:64 (11):290–295.
3. Weycker et al. *Chron Respir Dis*. 2017;14(4):377-384; McShane et al. *Am J Respir Crit Care Med*. 2013;188(6):647-656; Maselli et al. *Int J Clin Practe*. 2017 Feb;71(2); Chalmers. *Chest* 2017; 151(6): 1204–1206
4. Cystic Fibrosis Foundation Patient Registry Annual Data Report 2020
5. PCD Foundation website

# Severe Asthma: Large Unmet Need




## Addressable Patients

Mod-severe asthma
(Step 4/5)
6M[1] pts

**50[2]-70[1]%**

Uncontrolled asthma
3-4M

**25%[1]**

Severe asthma
1M

- Largely uncontrolled due to compliance
  - 80% of patients do not use daily inhalers correctly
  - 50% of patients do not take medication

- Low penetration of biologics
- Underserved T2-low patient population comprise roughly 50% of severe asthma patients

[1]GINA 2018, Dutch population study
[2]Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43(2):343-73.
Fang J et al. Demographic, clinical characteristics and control status of pediatric, adolescent, and adult asthma patients by GINA Step in a US longitudinal cohort. Am J Resp Crit Care Med 2018;197:A1903

# Severe Asthma: Unmet Need in Disease Control & Compliance


### Disease Control

Ensure treatment compliance to control asthma progression through active management

"I'll try to focus on a **more longer acting product** that can treat asthma with **improved compliance** without the need for a twice per day therapy alone."
– Community Pulmonologist

### Non-Th2 Asthma Medication

Develop effective therapies to treat severe asthma patients without signature biomarkers

"We don't really have an answer for those who **don't have eosinophilic inflammation**, or elevated IGE levels. Those patients end up getting frequent steroids and are less responsive to the inhaled steroids. We don't have a good biologic agent at this time. "
– Community Allergist

### Address Underlying Cause of Disease

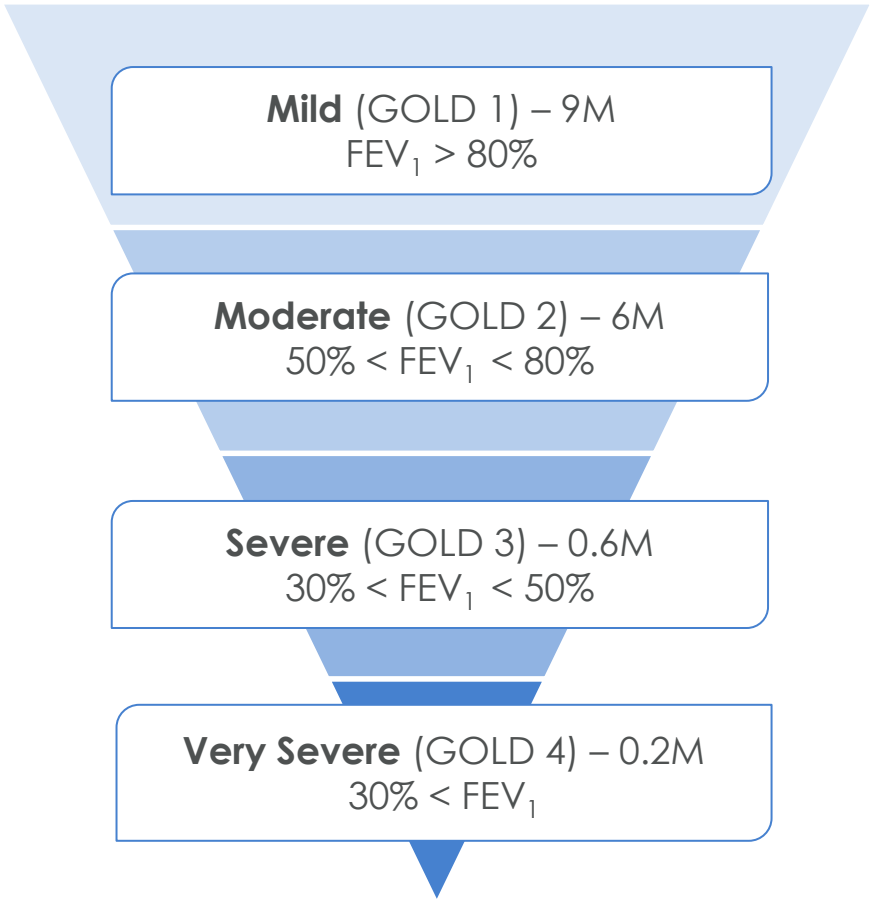
Design a treatment that addresses and restores lung epithelial function

"Drugs **focused on the epithelial component of the lung** will be huge. The pathophysiology is going not just through eosinophils but through the epithelial component" – Community Allergist

Sources: 2021 Arrowhead Pulmonary Market Research

# COPD: Large Unmet Need

## US Diagnosed COPD Patients 16M[1]




## US COPD Burden

**~3.4M**
patients with multiple annual exacerbations[2]

**1.5M**
Annual Emergency Room Visits[1]

**~$50B**
direct + indirect costs[3]

1. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease — United States, 2013. MMWR Morb Mortal Wkly Rep. 2015:64 (11):290–295.
2. Hurst et al NEJM
3. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon outcomes Res 2013; 5: 235-45

# COPD: Unmet Need in Disease and Symptom Control

## COPD Unmet Needs and Treatment Challenges[1]

### Ranked by Perceived Importance to Solve (1-10)

| | |
|---|---|
| Prevent COPD progression | 7.8 |
| Manage exacerbations | 6.6 |
| Suppress inflammation | 6.1 |
| Easy to use inhalers | 4.9 |
| Biomarkers for use of biologics | 4.3 |
| Improve patient compliance | 4.0 |

"Unmet need is for an agent **that can address the causal pathway in COPD, not just symptoms**" – Community Pulmonologist

"COPD **has a major inflammatory component of disease** that is being ignored."
– Community Pulmonologist

"COPD patients with cognitive, dexterity issues, severe disease, or low inspiratory rates are unable to use existing inhalers effectively"
– Academic Pulmonologist

"We need products where we don't have to drag elderly COPD patients into the office every two weeks."
– Academic Pulmonologist

Sources:
1. DRG COPD Landscape and Forecast - February 2020
2. 2021 Arrowhead Pulmonary Market Research

# ARO-RAGE & ARO-MUC5AC: Potential for Disease Control and Compliance

| | ARO-RAGE | ARO-MUC5AC |
|---|---|---|
| Novel Targeted Approach | Better anti-inflammatory | First-in-class therapy targeting mucus obstruction |
| Efficacy | Reduce exacerbations<br>Improve airflow<br>Improve patient quality of life<br>Address underlying disease progression | |
| Convenience | Inhaled therapy with biologic-like targeting and less frequent dosing leading to patient acceptance and compliance | |

# Arrowhead's pulmonary portfolio has the potential to address the underlying components of a broad range of lung diseases

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

Pulmonary R&D Day, May 26, 2022

# Concluding Remarks

Chris Anzalone, PhD

arrowhead pharmaceuticals

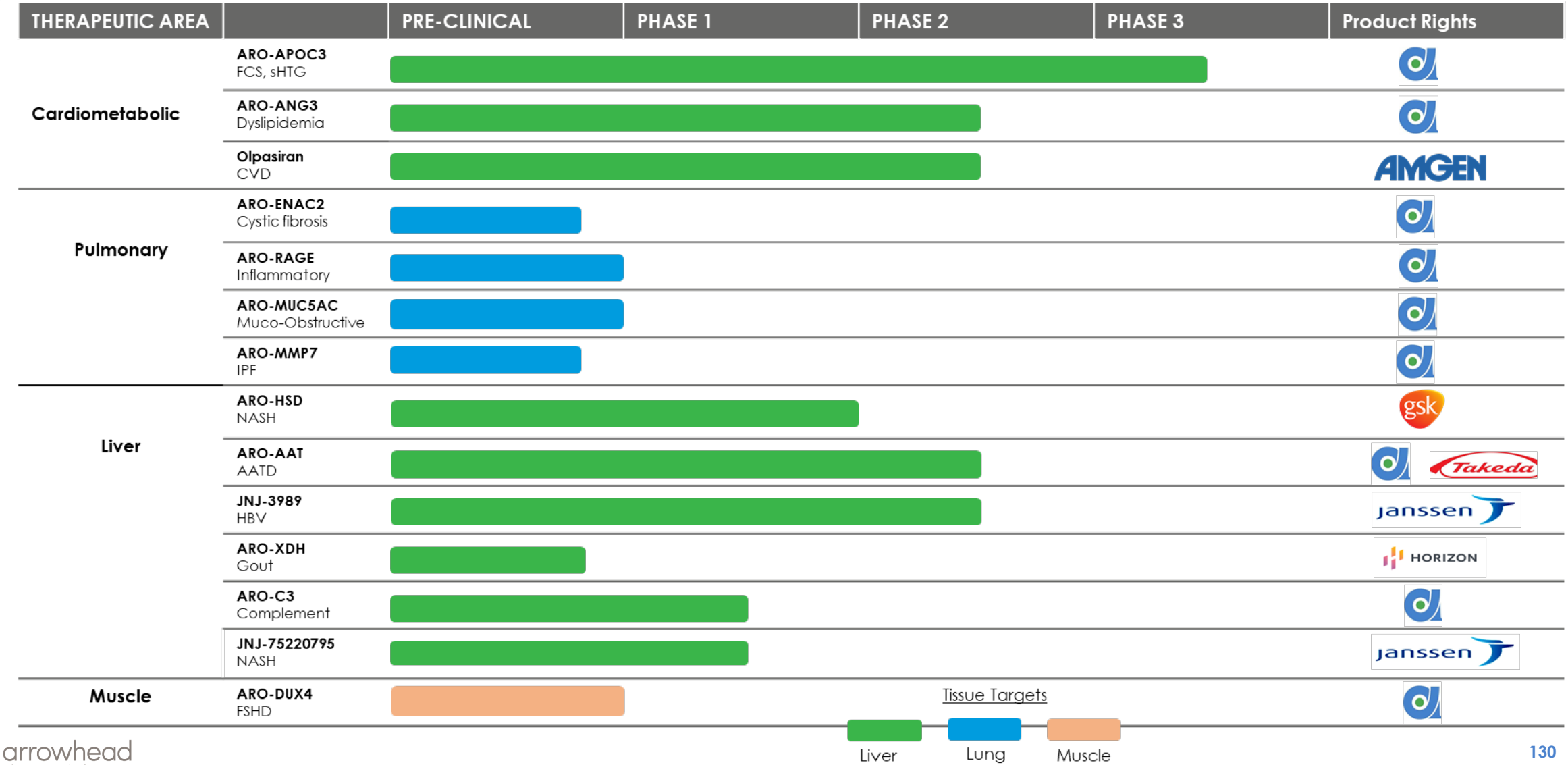
# 4 ½ years ago at our R&D Day, we had **zero** clinical programs

By the end of this year, I expect to have **13** drug candidates in clinical studies

- 7 wholly-owned
- 6 partnered

Consider that track record when assessing our chances of success

# Pipeline


THERAPEUTIC AREA
PRE-CLINICAL
PHASE 1
PHASE 2
PHASE 3
Product Rights
Cardiometabolic
ARO-APOC3
FCS, sHTG
ARO-ANG3
Dyslipidemia
Olpasiran
CVD
Pulmonary
ARO-ENAC2
Cystic fibrosis
ARO-RAGE
Inflammatory
ARO-MUC5AC
Muco-Obstructive
ARO-MMP7
IPF
Liver
ARO-HSD
NASH
ARO-AAT
AATD
JNJ-3989
HBV
ARO-XDH
Gout
ARO-C3
Complement
JNJ-75220795
NASH
Muscle
ARO-DUX4
FSHD
Tissue Targets
Liver
Lung
Muscle

# Over the past 4 ½ years since introducing TRiM™:

We built what we see as a robust, scalable, and substantially de-risked pipeline of hepatocyte-directed drug candidates

- Providing hope for huge number of patients
- Creating substantial value

We believe we are on the cusp of doing this in the lung

Pulmonary R&D Day, May 26, 2022

# Q&A Session

## Panel

arrowhead pharmaceuticals