2024 Summer Series of R&D Webinars
Part 3 – Pulmonary Programs

July 16, 2024

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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.

Pulmonary Webinar – July 16, 2024

Introductions and Overview

Vince Anzalone, CFA
Vice President, Finance and IR

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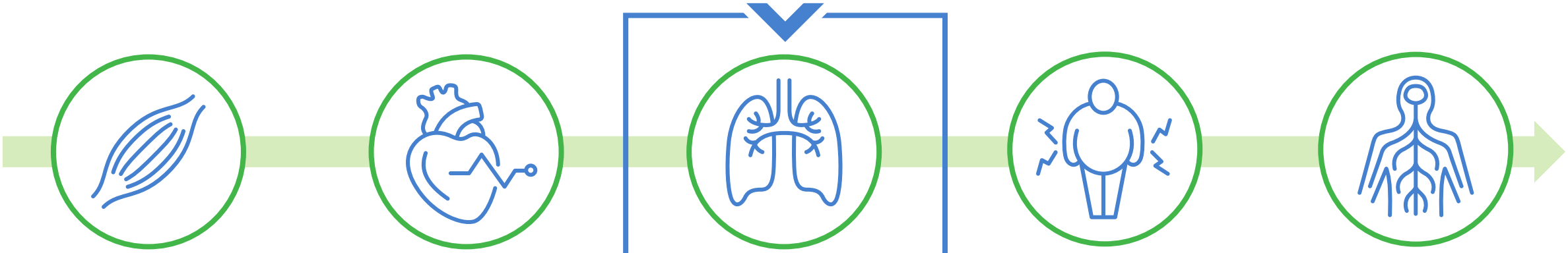
2024 Summer Series of R&D Webinars



Muscle

ARO-DM1 and ARO-DUX4

May 23, 2024

Cardiometabolic

Plozasiran and Zodasiran

June 25, 2024

Pulmonary

ARO-RAGE, ARO-MUC5AC, ARO-MMP7

July 16, 2024

Obesity / Metabolic

ARO-INHBE and New Adipose Target

August 15, 2024

Central Nervous System

Platform and Pipeline Updates

Sept. 25, 2024

2024 Summer Series Goals

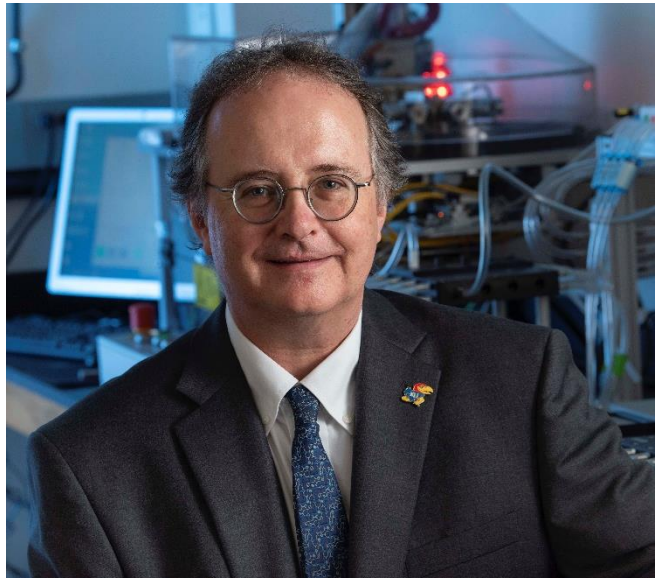
- Provide focused time to cover underappreciated parts of our pipeline
- Detail advances in the TRiM™ platform
- Hear directly from the Arrowhead team that worked on the programs
- Get external physician perspective on each disease area

Pulmonary Webinar Agenda

Time	Topic	Presenter
11:00–11:10	Introductions, Arrowhead Overview and Pipeline	Vince Anzalone, CFA
11:10–11:30	Pulmonary Platform Overview	James Hamilton, MD, MBA
11:30–11:45	RAGE Pathway in the Context of Current Asthma Therapies	Matthias Salathe, MD
11:45–11:55	Pulmonary Clinical Update	John Huetsch, MD
11:55–12:00	Concluding Remarks	Vince Anzalone, CFA
12:00–12:20	Q&A	Panel

Pulmonary Opinion Leader

Matthias Salathe, MD



Professor and Chair, Department of Internal Medicine
Vice Chancellor of Research and Interim Executive Vice Chancellor,
University of Kansas Medical Center

Dr. Salathe received his MD from the University of Basel, Switzerland, and trained clinically in anesthesiology, internal medicine, pulmonary and critical care, and basic sciences. He was Division Chief of Pulmonary, Critical Care and Sleep Medicine at the University of Miami and is now Chair of Internal Medicine and Vice Chancellor for Research at the University of Kansas. He has been funded continuously since 1999 by the NIH, the State of Florida, the Cystic Fibrosis (CF) Foundation and several other foundations, and he has held leadership roles in national societies and foundations.

As a translational researcher, Dr. Salathe repurposes approved medications for use in airway inflammation caused by CF, smoking, and vaping, and actively advocates against teen vaping. As an educator, he developed the respiratory system module in Miami, receiving multiple student awards for excellence in teaching. He also mentored graduate students, postdoctoral fellows, and junior faculty. As a clinician, he built the adult CF Center in Miami and continues to see CF patients and patients in the medical intensive care unit at KUMC. As Chair, he supports the growth of the clinical, educational, and research enterprises of the Department of Internal Medicine, and he continues to strengthen the infrastructure to expand basic and clinical research as Vice Chancellor of Research.

Who We Are

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

Broad Pipeline

- **14 clinical stage programs** (10 wholly-owned; 4 partnered)
- Mix of **early, mid, and late-stage** candidates targeting **rare and high-prevalence diseases**
- Growing pipeline with **2–3 new clinical programs planned per year**

Proprietary Platform

- **Targeted RNAi Molecule (TRiM™)** platform achieves **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**

Financial Resources

- **Non-dilutive capital** from Amgen, Takeda, GSK, and Royalty Pharma as milestones are achieved and royalties are earned
- Potential for **additional** product, platform, and structured finance **deals**

20 in '25: We Expect to Have 20 Individual Drugs in Clinical Trials or At Market in 2025

Arrowhead Pipeline

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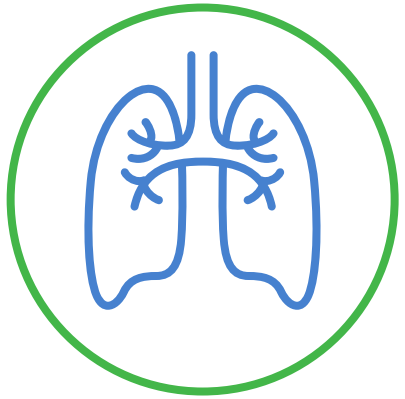
Pulmonary Webinar – July 16, 2024



Arrowhead's Pulmonary Platform

James Hamilton, MD, MBA
Chief of Discovery and Translational Medicine

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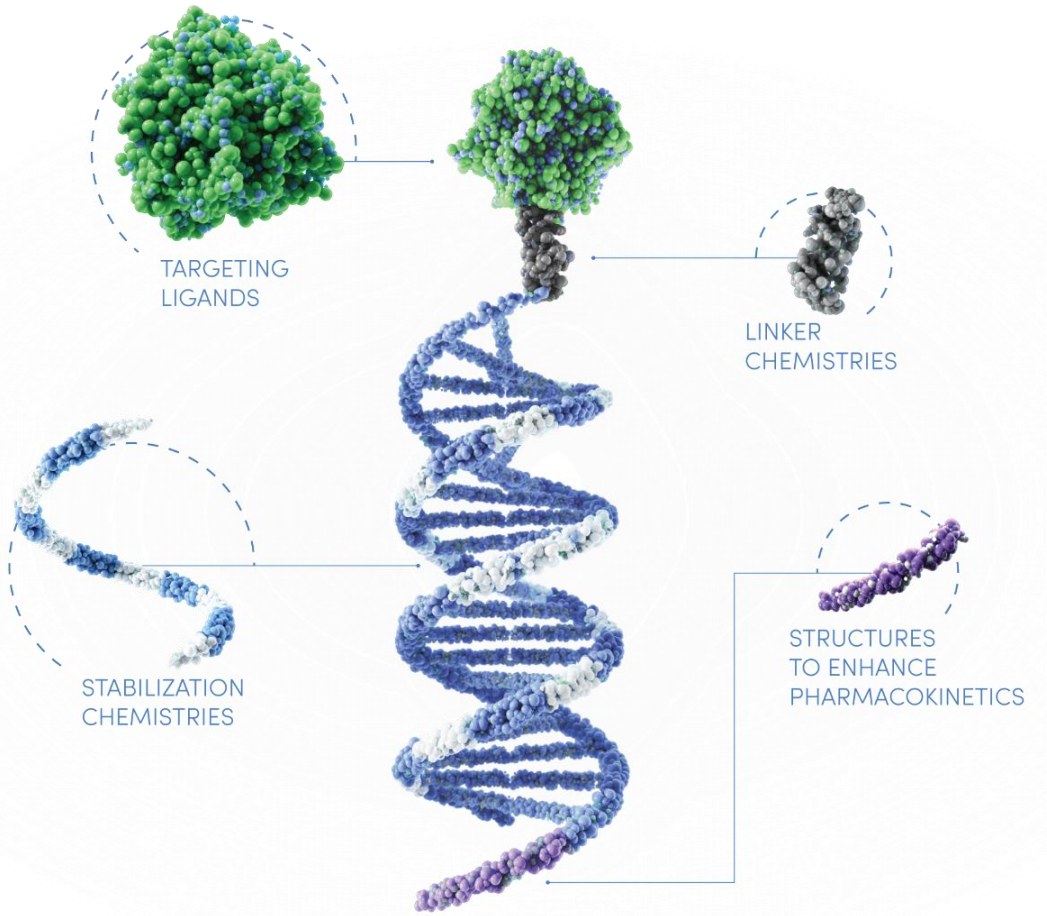
TRiM™ Platform for Pulmonary Delivery



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

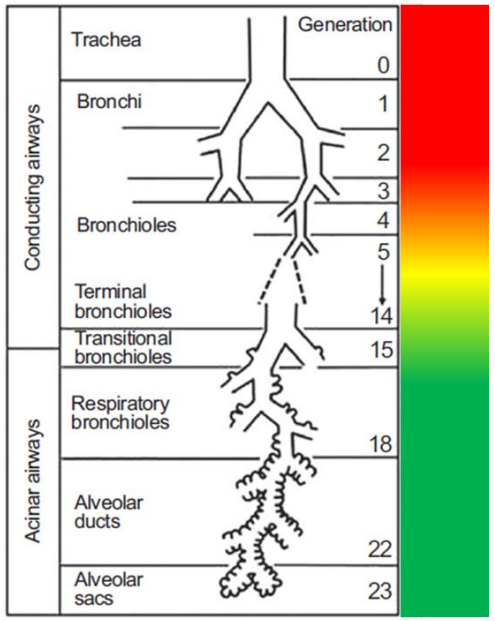
- Maximize depth and duration of knockdown, minimize dose frequency

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

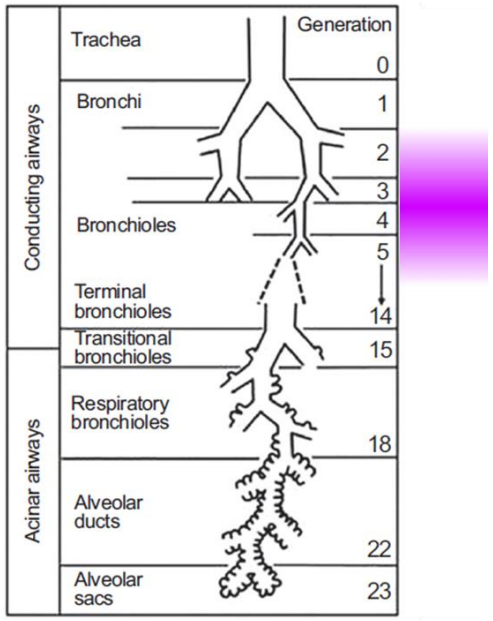
TRiM™ Pulmonary Platform Effectively Silences Deep Lung Targets

Platform Activity



Measurements

Biopsy



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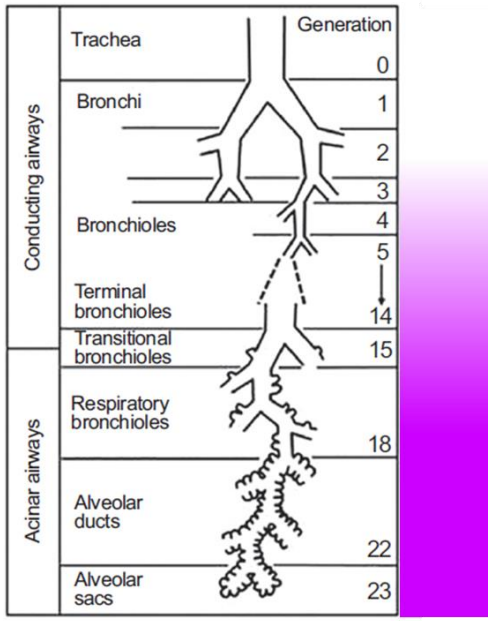
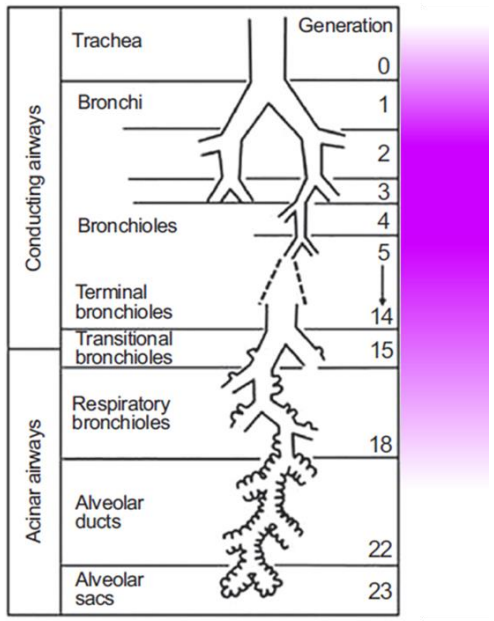


Sputum



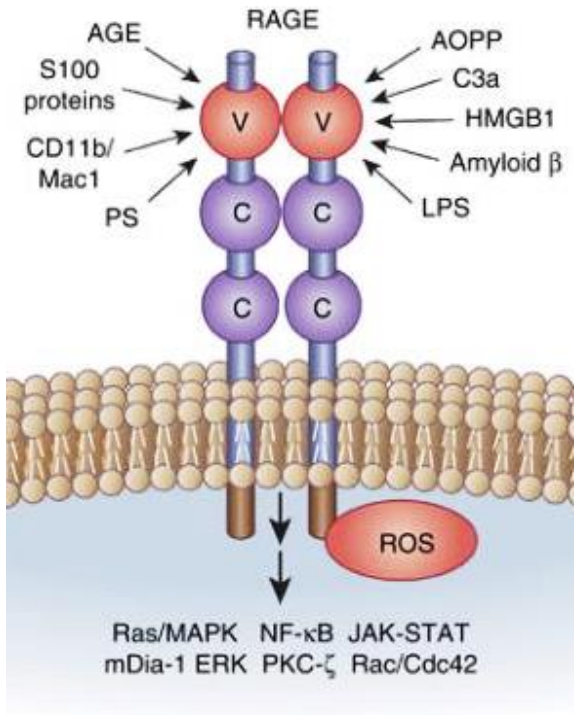
Proximal Activity Potentially Limited By

- Mucociliary clearance
- Aerosol deposition
- Small surface area of proximal airway vs deep lung

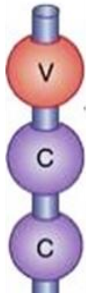
Targeting RAGE for Inflammatory Lung Disease

- Pro-inflammatory pattern recognition receptor and member of immunoglobulin superfamily
  - Abundant in alveolar epithelium
  - Amplifies and sustains chronic inflammation
- Activated by multiple pro-inflammatory ligands: sugar-modified proteins & lipids, immune cell "alarmins" (HMGB1, S100 proteins, oxidized IL33), LPS
- Drives type 2 and type 1 cytokine induction, reactive oxygen species production, mucin synthesis
- Knockout mouse phenotype
  - Robust protection from type 1 and type 2 inflammation (allergens, LPS, viral infection, etc.)
- Full-length receptor cleaved to release soluble sRAGE (circulating biomarker of target engagement)

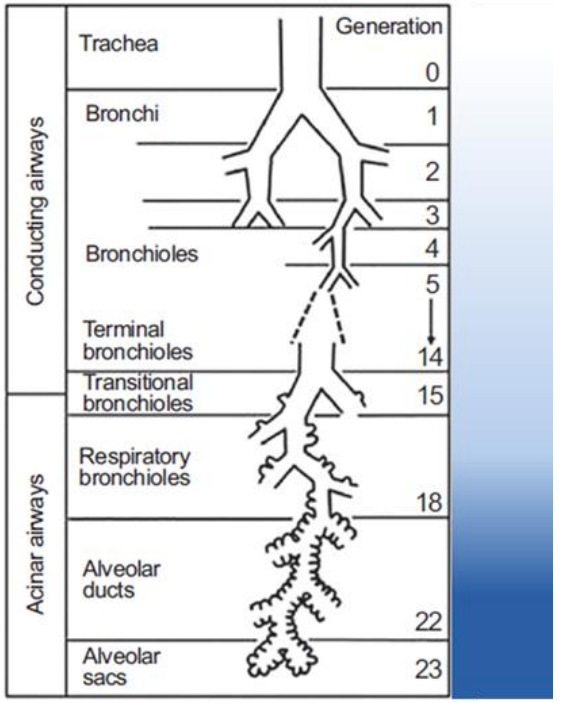
Receptor for Advanced Glycation End-products



sRAGE

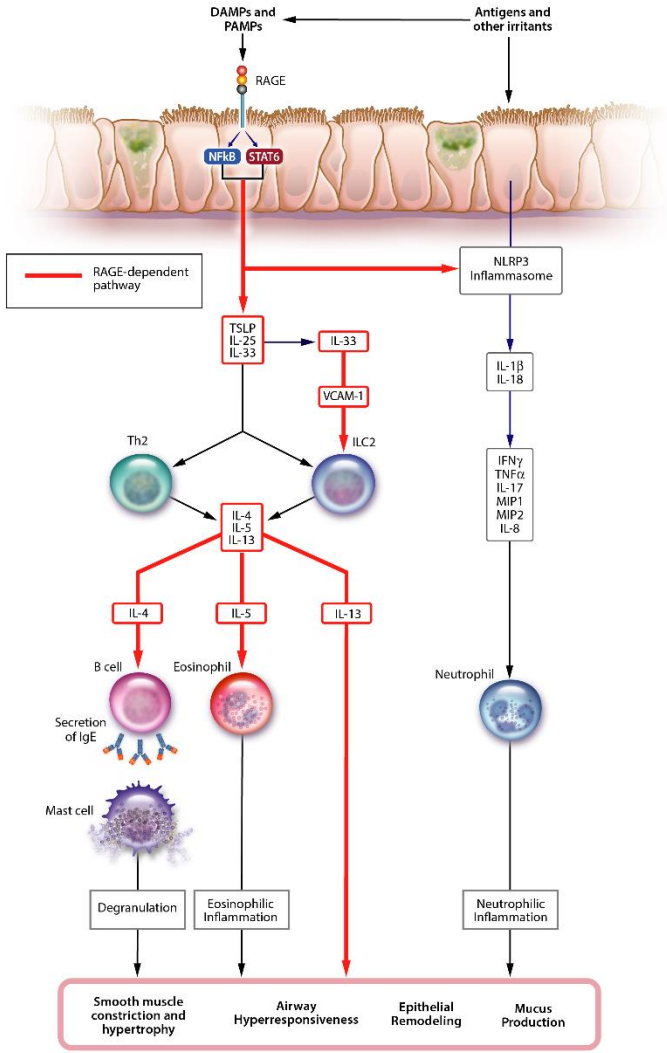


RAGE Expression



Perkins TN et al. *Allergy* 2020. Oczypok EA et al. *J Allergy Clin Immunol* 2015. Killian KN et al. *Front Immunol* 2023. Image: Yamamoto Y et al. *Kidney Int* 2012.

RAGE: Upstream Regulator of Type II and Neutrophilic Inflammatory Mediators



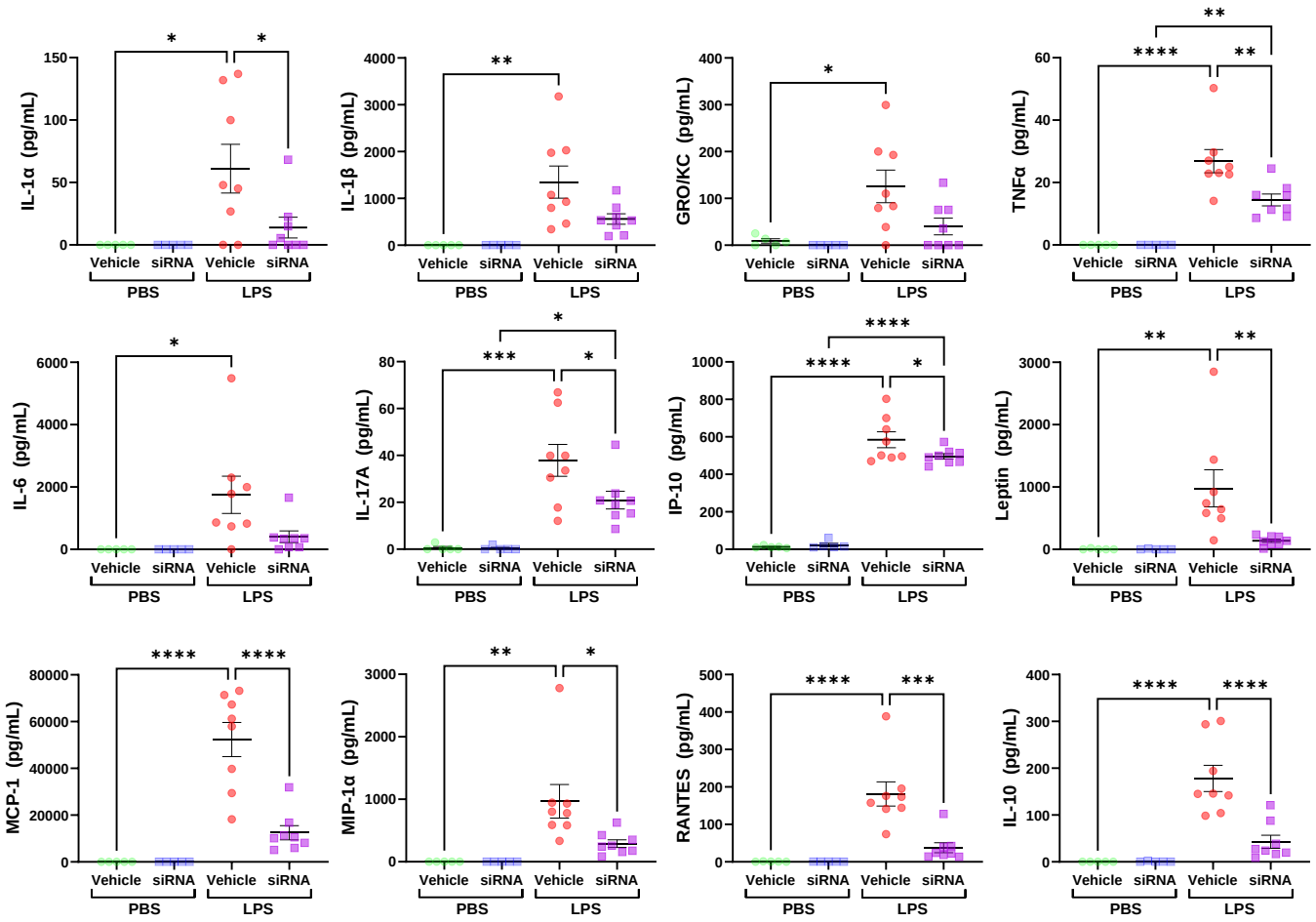
BAL Cytokine	KO Mice (published)	RAGE Inhibitor Mice (published)	RAGE Silenced Rat (in house)	Roles
IL-33	Y	Not reported	Antibody unavailable	Upregulation of type-2 cytokines and type-2 immune cells
TSLP	Y (moderate effect)	Not reported	Antibody unavailable	Upregulation of type-2 cytokines and type-2 immune cells
IL-25	Y	Not reported	Not tested	Upregulation of type-2 cytokines and type-2 immune cells
IL-5	Y	Y	Y	Recruitment and activation of eosinophils
IL-4	N	Y	Not detectable	Stimulation of mucus secretion, IgE production, recruitment of eosinophils
IL-13	Y	In vitro	Y	Nitric oxide production (FeNO), stimulation of mucus secretion, smooth muscle remodeling
IL-6	Y	Y	N (non-significant trend to reduction)	Recruitment of neutrophils
IL-17	Y	Y	Y	Recruitment of neutrophils
IL-1b	Y	Y	N (non-significant trend to reduction)	Multiple pro-inflammatory effects
IL-18	Not reported	Not reported	Y	Multiple pro-inflammatory effects
CXCL1	Y	Not reported	Y	Recruitment of neutrophils
CXCL10 (IP-10)	Not Reported	Not reported	Y	Recruitment of macrophages and monocytes
MIP-1a	Y	Not reported	Y	Multiple pro-inflammatory effects
RANTES (CCL5)	Not Reported	Y	Y	Recruitment of T-cells, eosinophils, and basophils

RAGE Silencing Inhibits Varied Inflammatory Pathways in Preclinical Models of Allergic Asthma, Acute Lung Injury, COPD

1. **Allergic asthma (previously shown)**
2. **Neutrophilic inflammation in acute lung injury (new data)**
3. **COPD / emphysema (new data)**

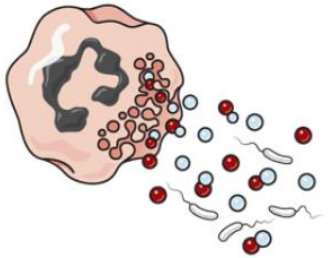
RAGE Silencing Attenuates Neutrophilic Inflammatory Mediators in Rat LPS Model of Acute Lung Injury (ALI)

Multiple BAL Cytokines and Chemokines Attenuated by RAGE Silencing

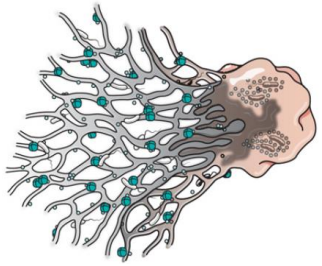


Rat lipopolysaccharide (LPS) Model

RAGE Silencing Limits Neutrophil Response in Rat LPS Model of ALI

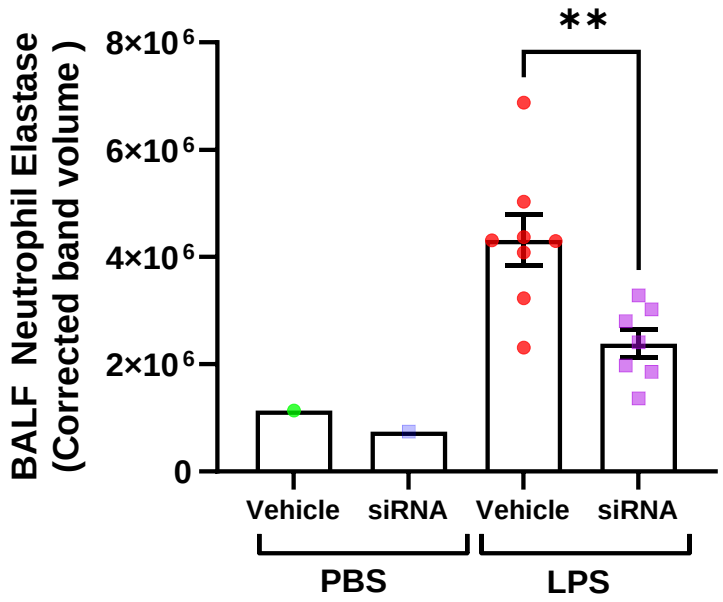


Neutrophil Elastase Release

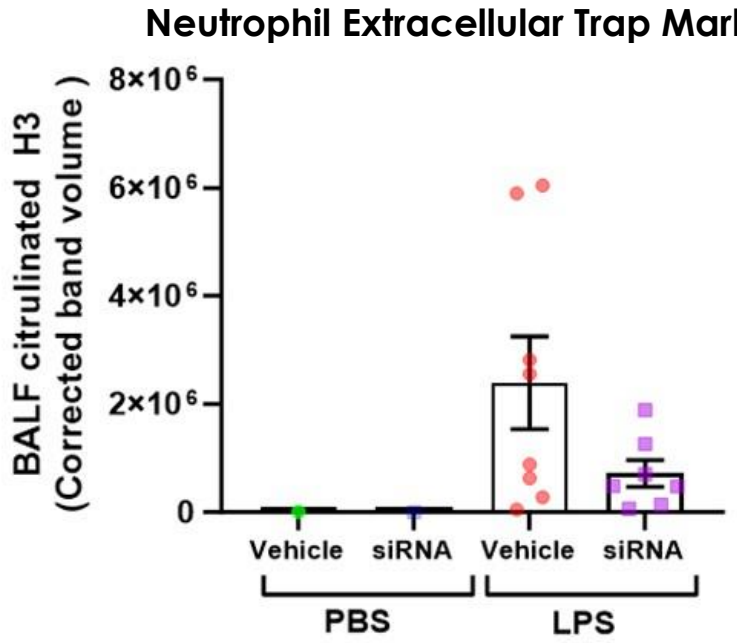


Neutrophil Extracellular Trap Formation (NETosis)

BALF Neutrophil Elastase



BALF citH3



Images: Ley et al. *Sci. Immunol*. 2018.

RAGE Linked to COPD / Emphysema

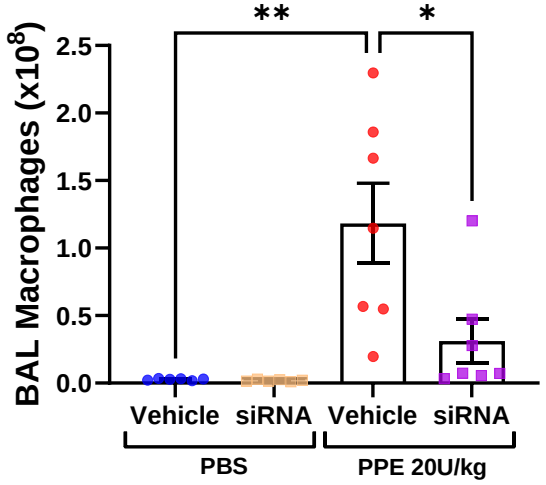
- RAGE expression is increased in COPD lungs
- Exogenous RAGE overexpression causes inflammation and emphysema in mice
- RAGE knockout protects mice against elastase-induced lung inflammation and emphysema
- Lung RAGE silencing with siRNA or small molecule RAGE antagonist protects mice lungs against cigarette smoke-induced inflammation and emphysema

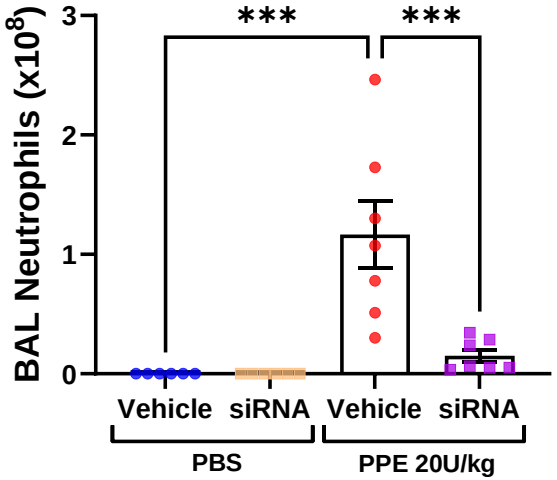
Objective

Evaluate anti-inflammatory effect of RAGE silencing in rat model of elastase-induced inflammation and emphysema

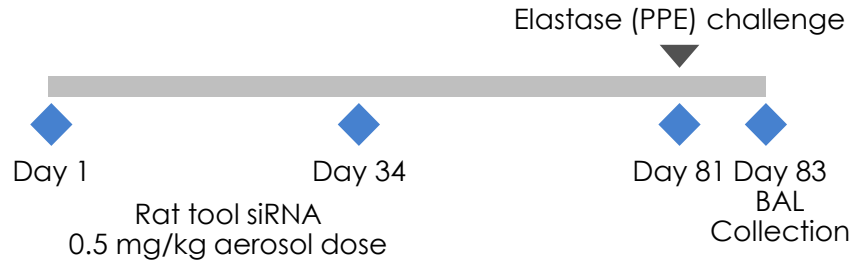
Lee et al, *FASEB J.* 2017. Stogsdill et al, *AJRCMB* 2013. Waseda et al, *AJRCMB* 2015. Pouwels et al, *AJP Lung* 2021. Chang et al, *Resp Research* 2024.

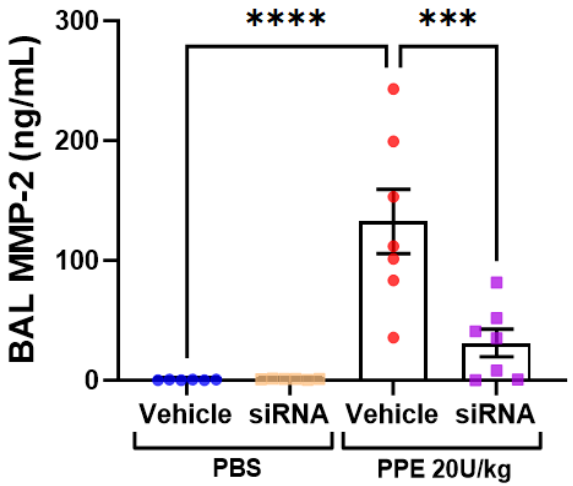
RAGE Silencing Limits Pulmonary Inflammation and Injury in Rat Model of COPD / Emphysema

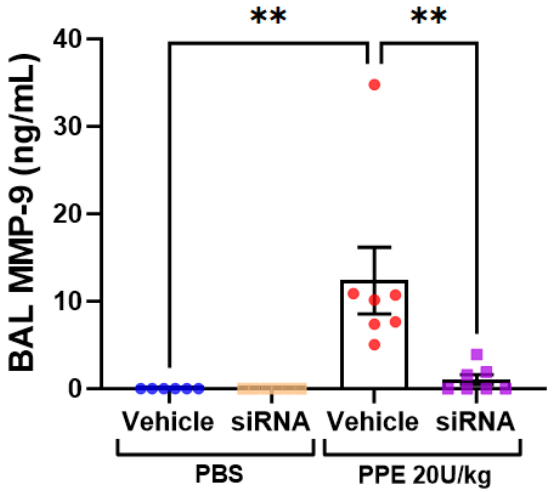


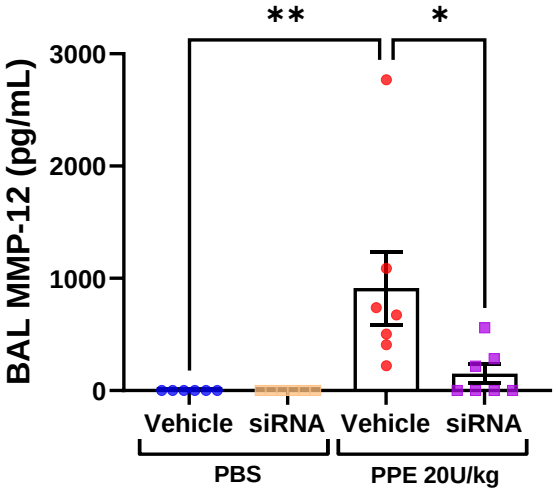


Rat COPD / Emphysema Model (Porcine Elastase Injury)









PPE: Pancreatic Porcine Elastase

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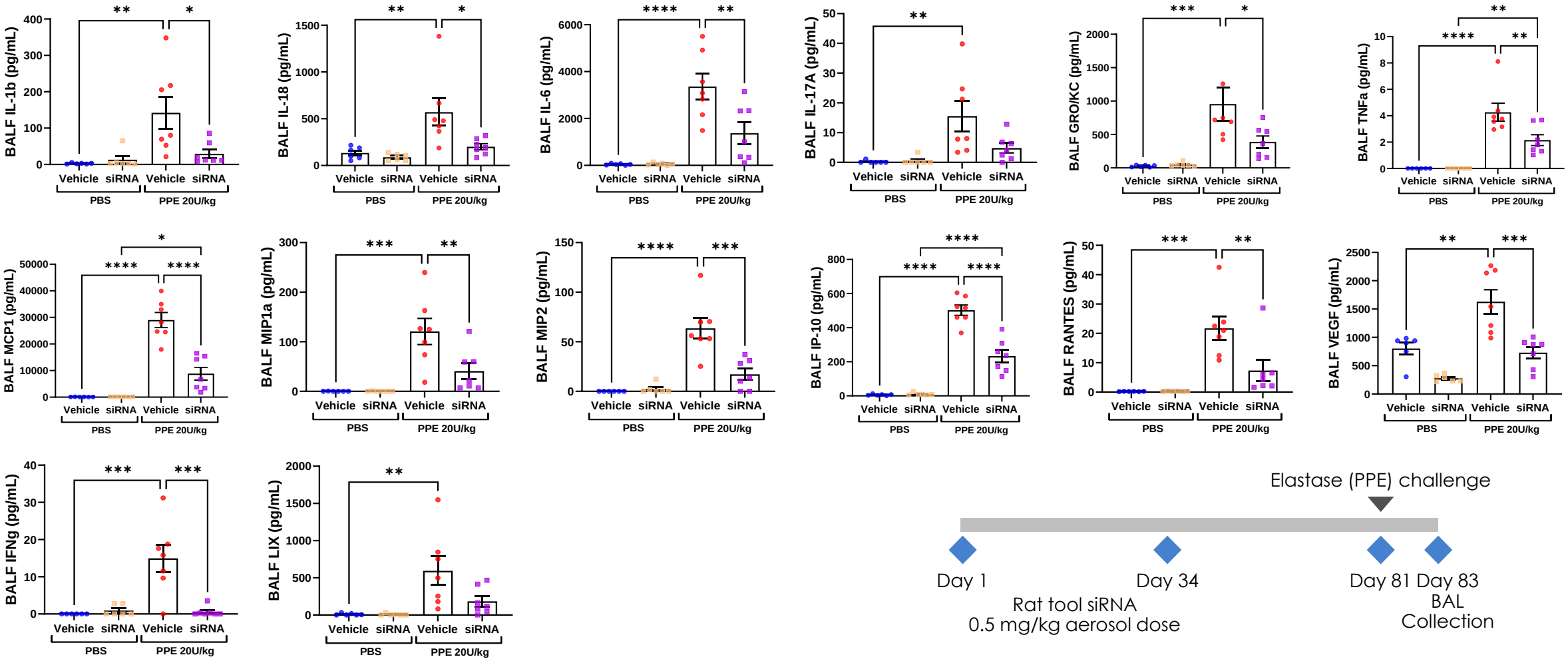
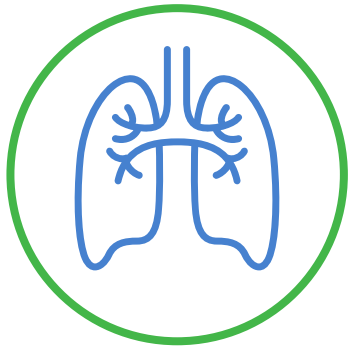
RAGE Silencing Limits Pulmonary Inflammation and Injury in Rat Model of COPD / Emphysema



PPE: Pancreatic Porcine Elastase

Note: CRO/KC= CXCL1, MCP1= CCL2, MIP1a= CCL3, MIP2= CXCL2, IP-10=CXCL10, RANTES= CCL5; LIX = CXCL5

ARO-RAGE: Broad Potential Pulmonary Anti-inflammatory Applications



Type-2 Inflammation

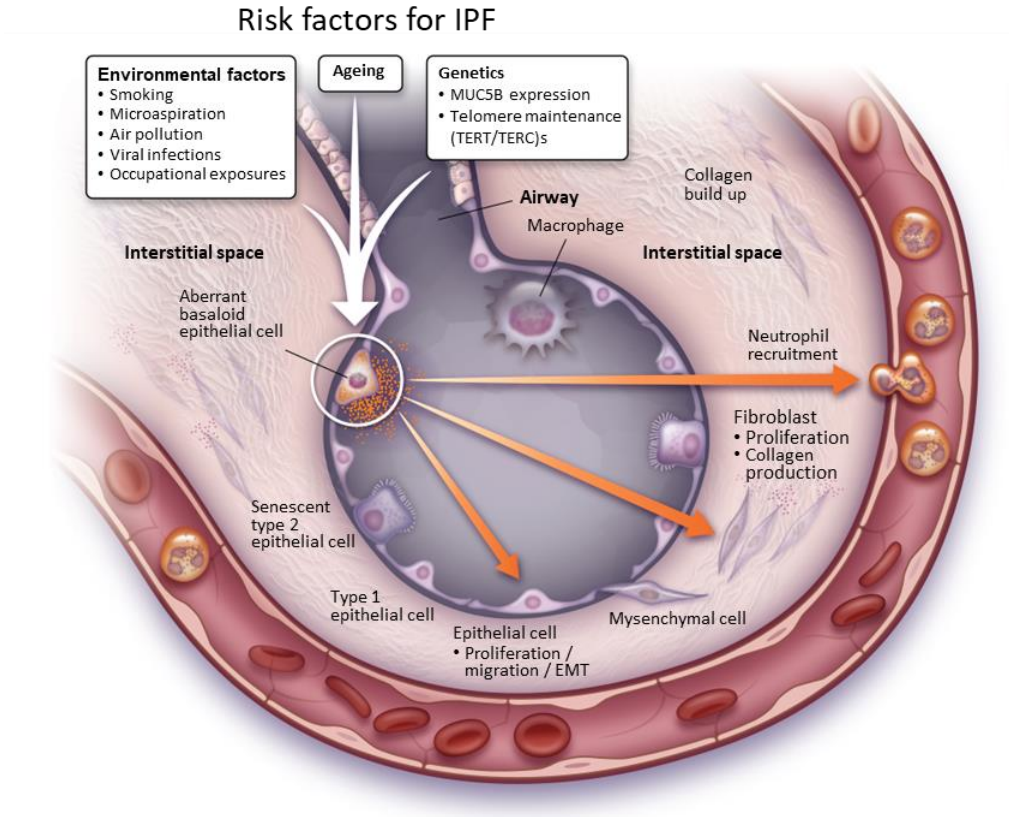
- Type-2 high asthma
- Type-2 high COPD

Neutrophilic Inflammation

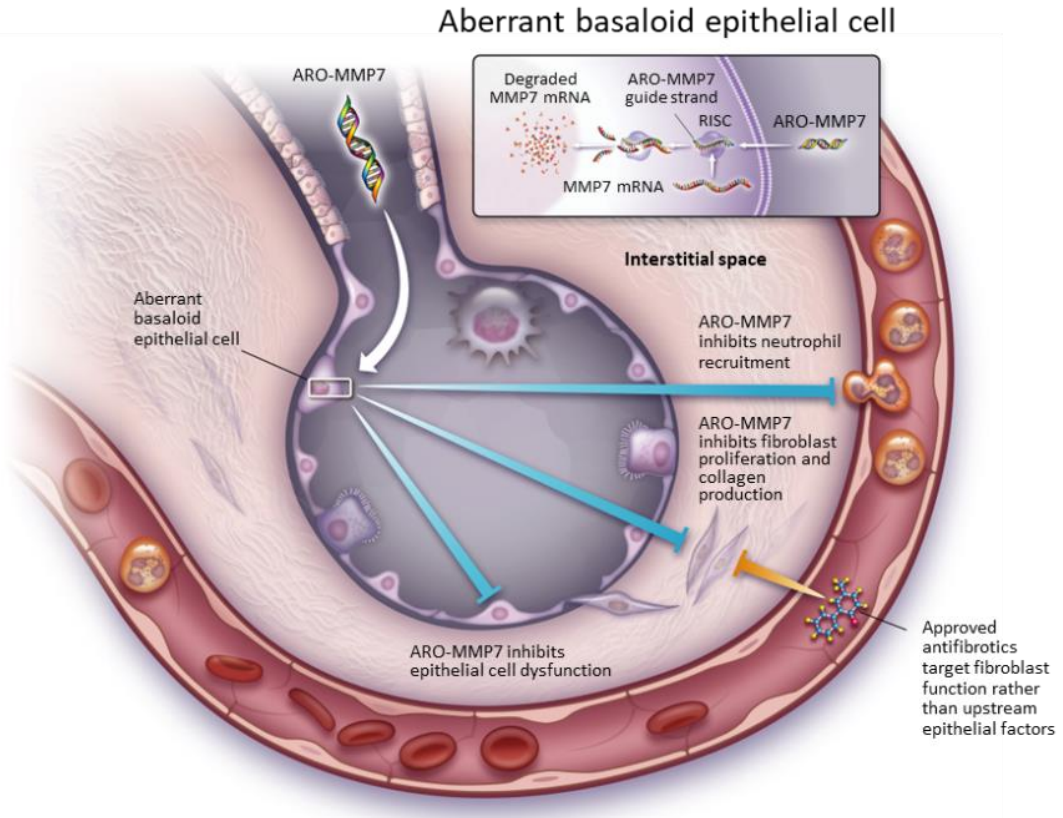
- Type-2 low asthma
- COPD / Emphysema
- COPD / Chronic bronchitis
- Cystic fibrosis

ARO-MMP7: Addressing Pulmonary Fibrosis at its Source

MMP7 Promotes Fibrosis Development



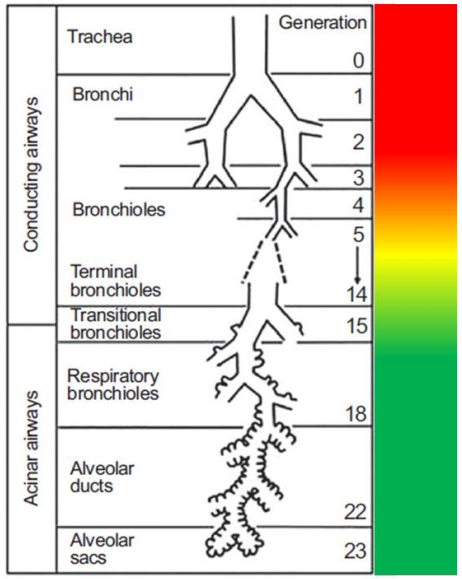
ARO-MMP7 Inhibits Fibrosis Development by Silencing MMP7



Select References: Zuo et al. *PNAS* 2002. Li et al. *Cell* 2002. Craig et al. *AJRCMB* 2015.

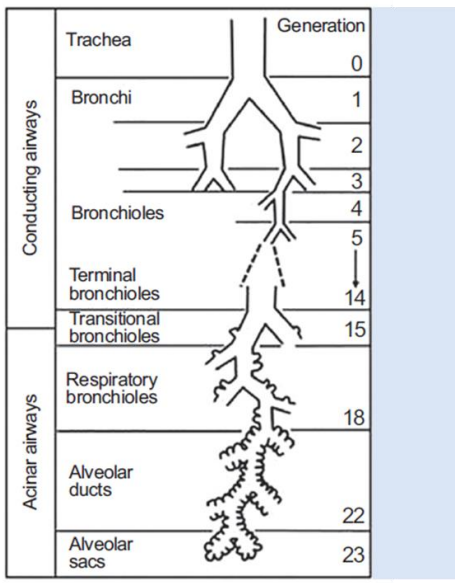
ARO-MMP7: Silencing a Fibrotic Mediator in Small Airways & Alveoli

Platform Activity

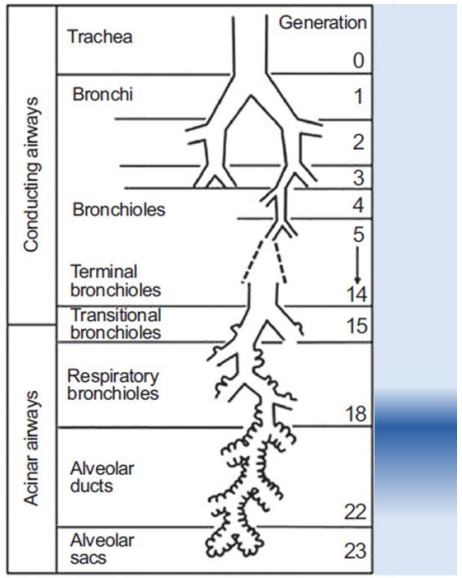


MMP7 Expression

Normal



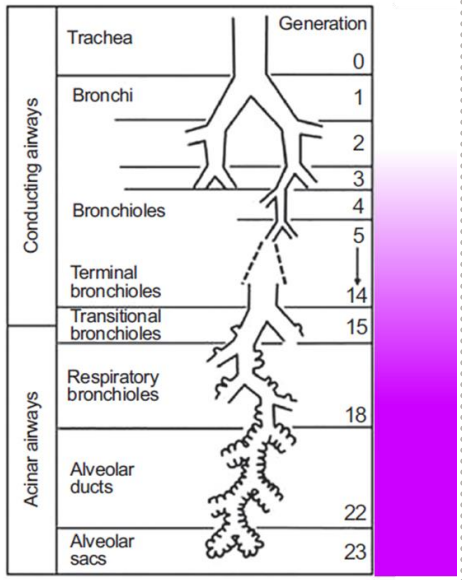
IPF



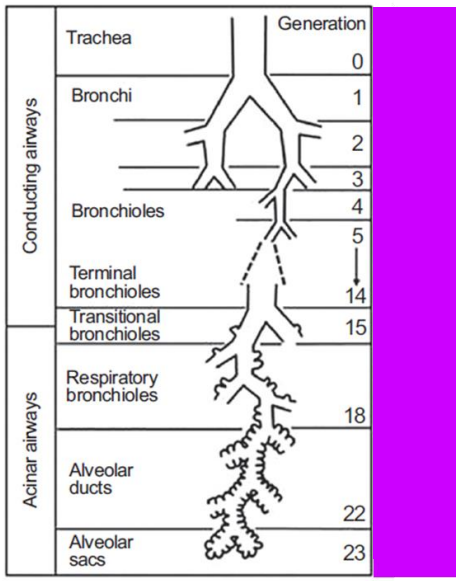
Aberrant basaloid expression in distal lung

Measurements

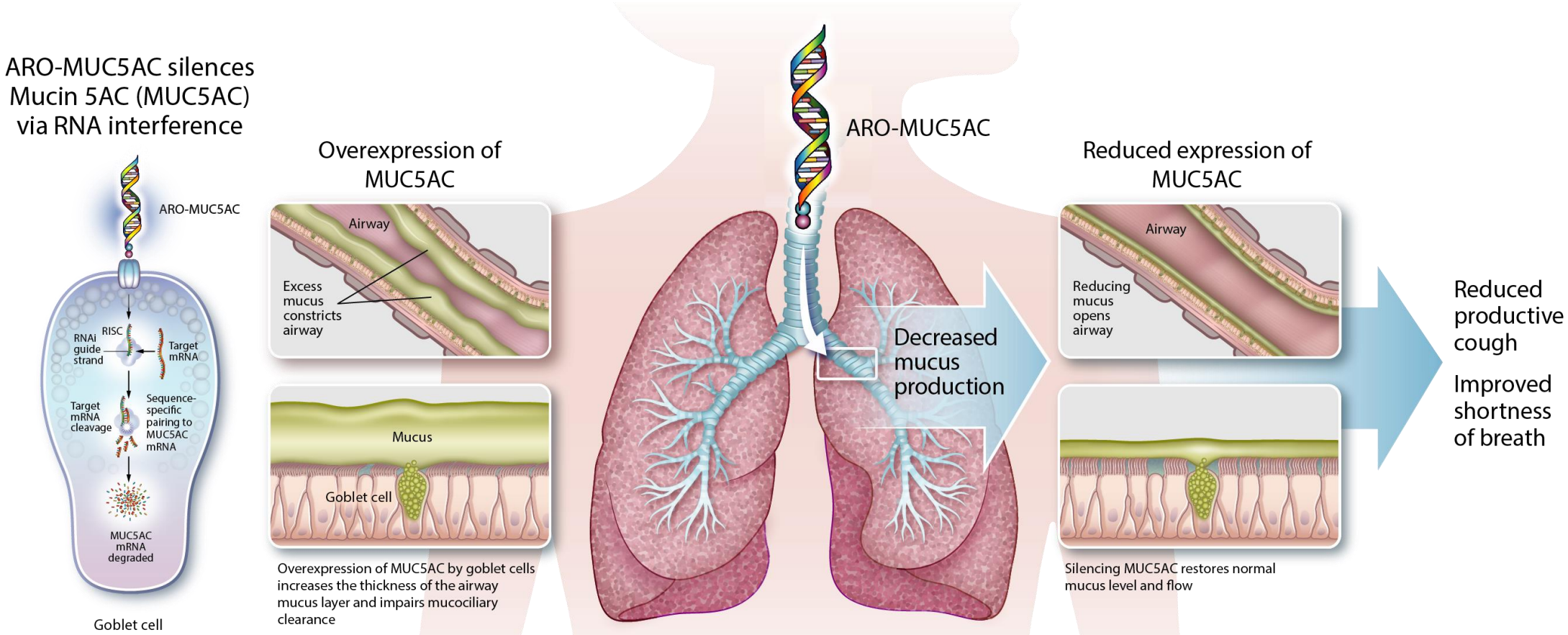
BAL



Serum



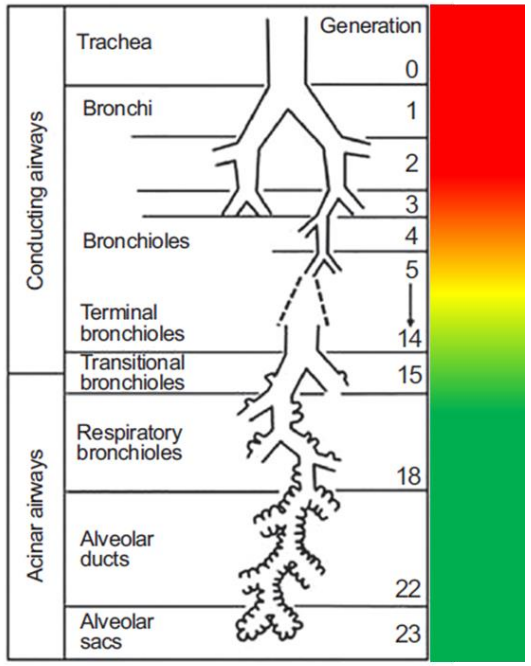
ARO-MUC5AC Silences Airway Mucus Production to Relieve Muco-obstruction



Select References: Boucher. *NEJM* 2019. Lachowicz-Scroggins et al. *AJRCCM* 2016. Dunican et al. *JCI* 2018. Radicioni et al. *Lancet Respir Med* 2021.

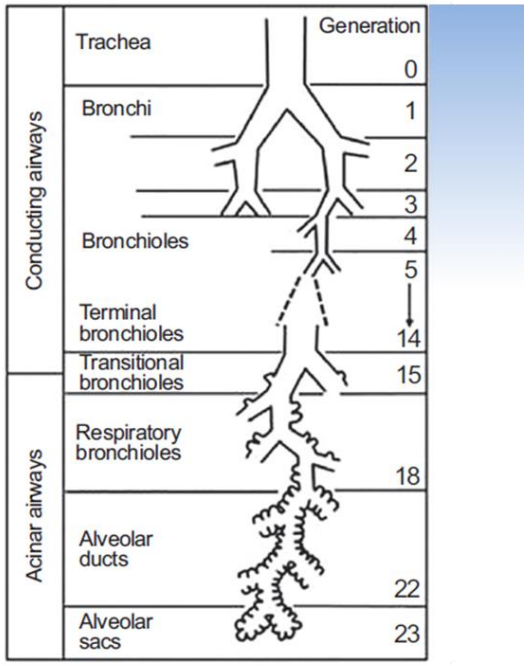
ARO-MUC5AC: Targeting Small Airway Muco-obstruction

Platform Activity

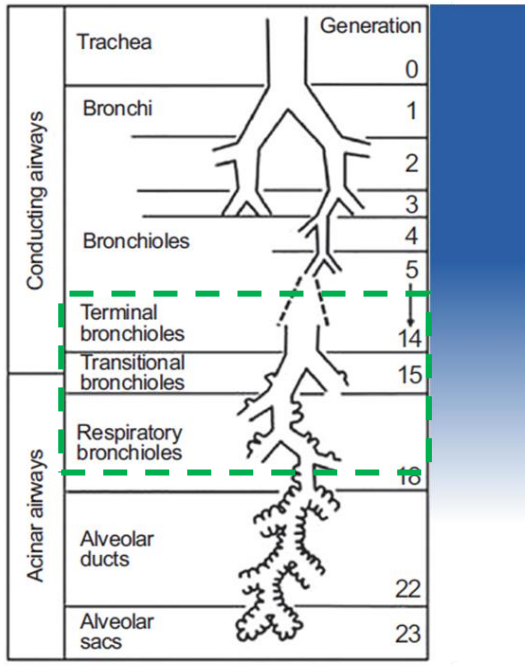


Muc5AC Expression

Normal



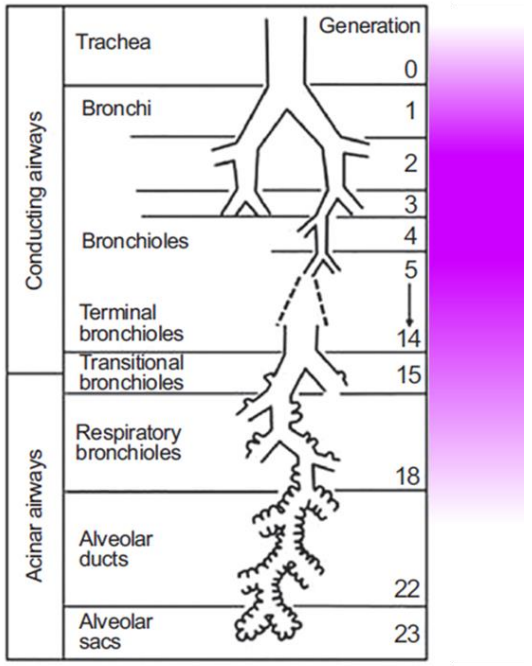
Muco-obstructive Disease



Small airway muco-obstruction

Measurements

Sputum



Pulmonary Webinar – July 16, 2024

RAGE Pathway in the Context of Current Asthma Therapies

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

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RAGE Pathway in the Context of Current Asthma Therapies

Matthias Salathe, MD

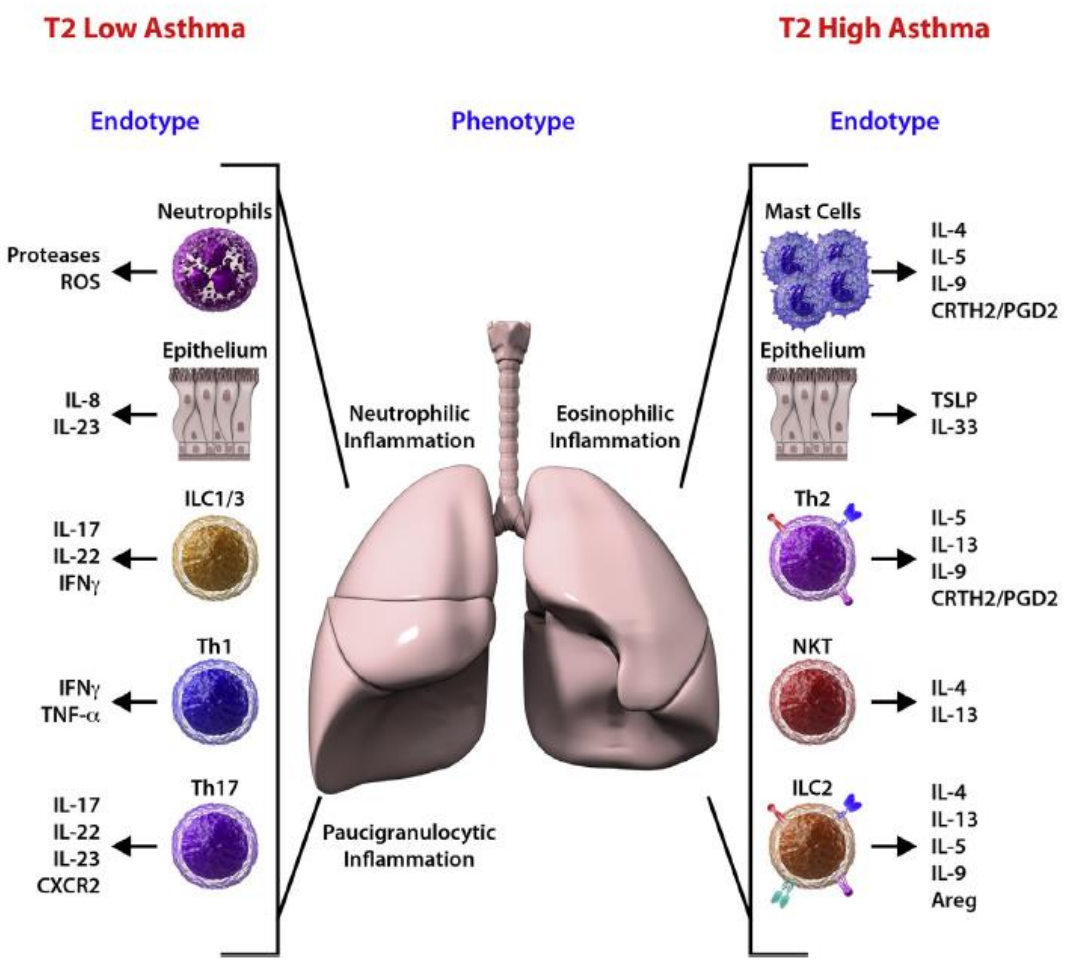
Vice Chancellor, Research

Professor and Chair, Department of Internal Medicine

KU SCHOOL OF MEDICINE
The University of Kansas

Main Types of Asthma and Biologics

Absence of Targeted Therapies



Inflammatory Mediators Targeted by:

Tezepelumab

Dupilumab

IL-5-directed therapies

Viswanathan, AAAI 2020.

Biologics & Asthma Control

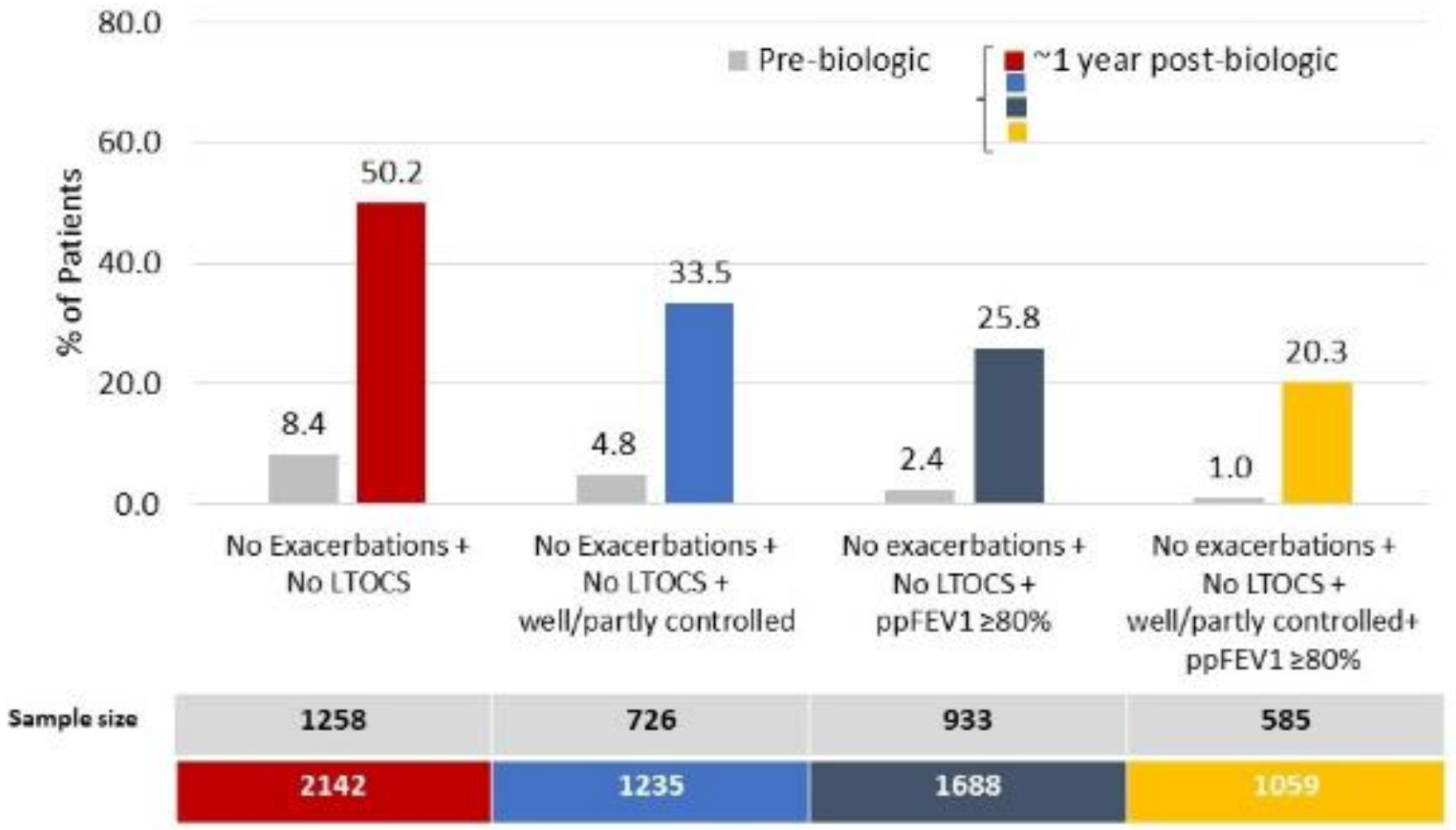
Criteria for Remission	Dupilumab		Benralizumab			Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/ CALIMA Phase 3	2022[4] ANDHI Phase 3b	2023[5] XALOC-1	2022[6,7] NAVIGATOR Phase 3	2022[8] REDES	2022[9] CHRONICLE	2022[10] Danish Registry
Absence of symptoms[a,b] **and**	ACQ-5 < 1.5	ACQ-5 < 1.5	ACQ-6 < 1.5" or ≤ 0.75	ACQ-6 < 1.5" or ≤ 0.75	ACQ-5 < 1.5 or ACT ≥ 16	ACQ-6 ≤ 1.5[a,b]	ACT ≥ 20	Majority ≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function **and**	Post-BD FEV_1pp ≥ 80%	Post-BD FEV_1 ≥ 80% *OR* pre-BD FEV_1 ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Not included	Pre-BD FEV_1pp > 80% *OR* Pre-BD FEV_1 > 20% from baseline; FEV1 > 95% of baseline**	Not included	Not included	Post-BD FEV_1pp ≥ 80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	26.3%"	28.7%	43%	14%ˆ- 28.5%**	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated
ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted. ˆ Includes agreement between physicians and patient assessments of control (clinical global impression of change CGI-C; Patient Global Impression of Severity)

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Jackson DJ Poster presented at AAAAI 2023 San Antonio TX USA 6. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 7. Wechsler, M ERS 2023 Milan, Italy (Unpublished) 8. Ribas DC et al. Drugs 2021;81(15):1763-1774.
9. Chipps, B et al. JACI 2022;149:Suppl AB147 10. Hansen S et al ERJ 2022;60:3553

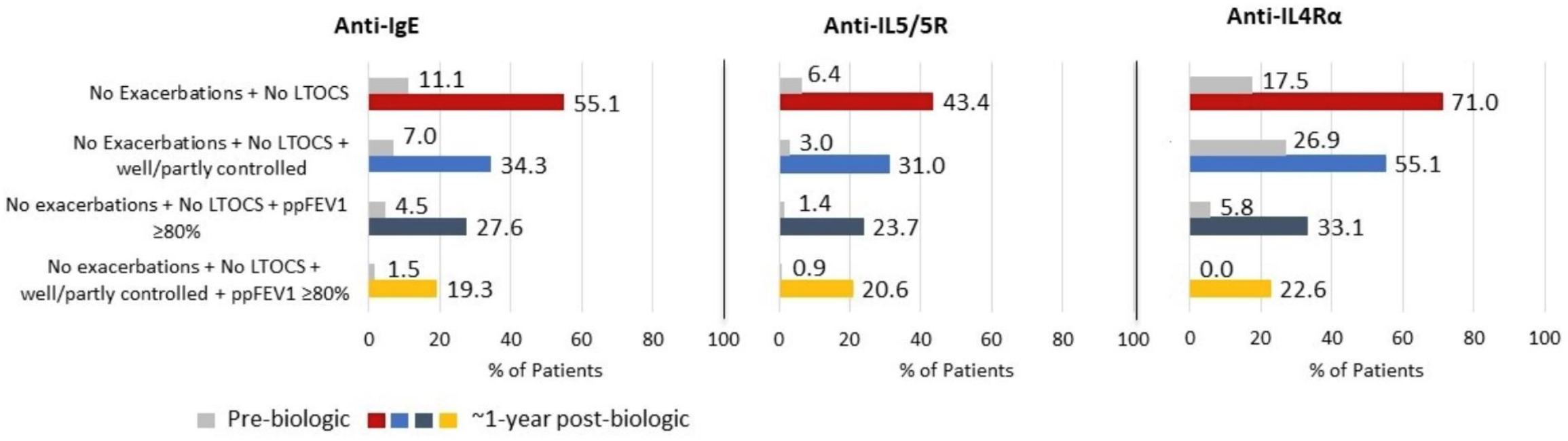
Lugogo, Chest 2023.

Biologics & Asthma Control



Perez-De-Llano, AJRCCM 2024.

Biologics & Asthma Control



Sample size	316	172	223	131	845	528	658	440	97	26	52	14
	732	379	584	322	1189	778	971	675	221	78	133	62

Perez-De-Llano, AJRCCM 2024.

Need for Broader Anti-inflammatories

Tezepelumab: Efficacy mostly in T2-high

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
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Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
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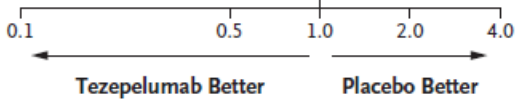
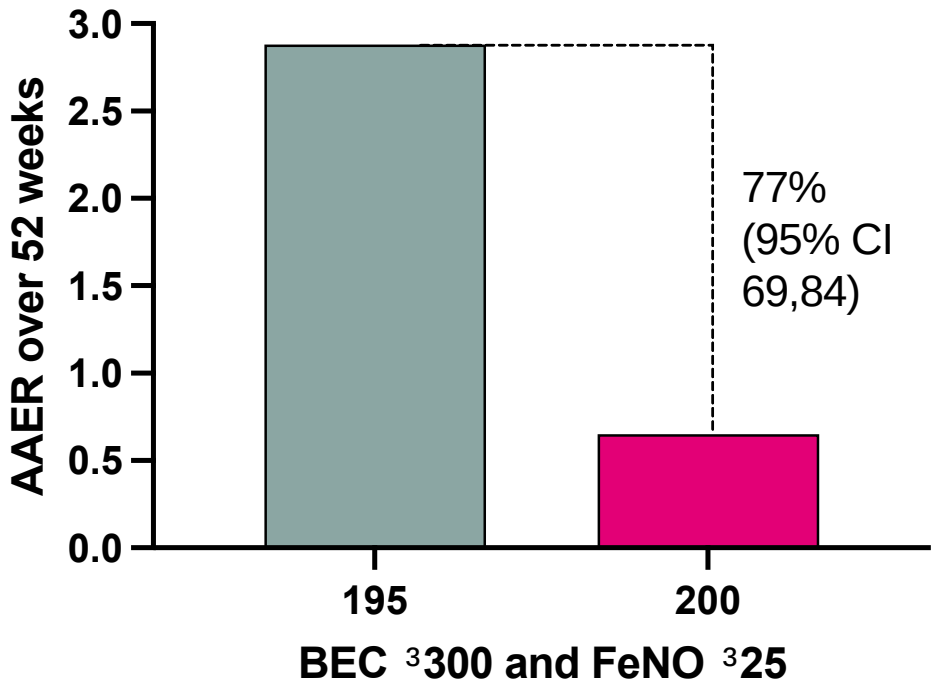


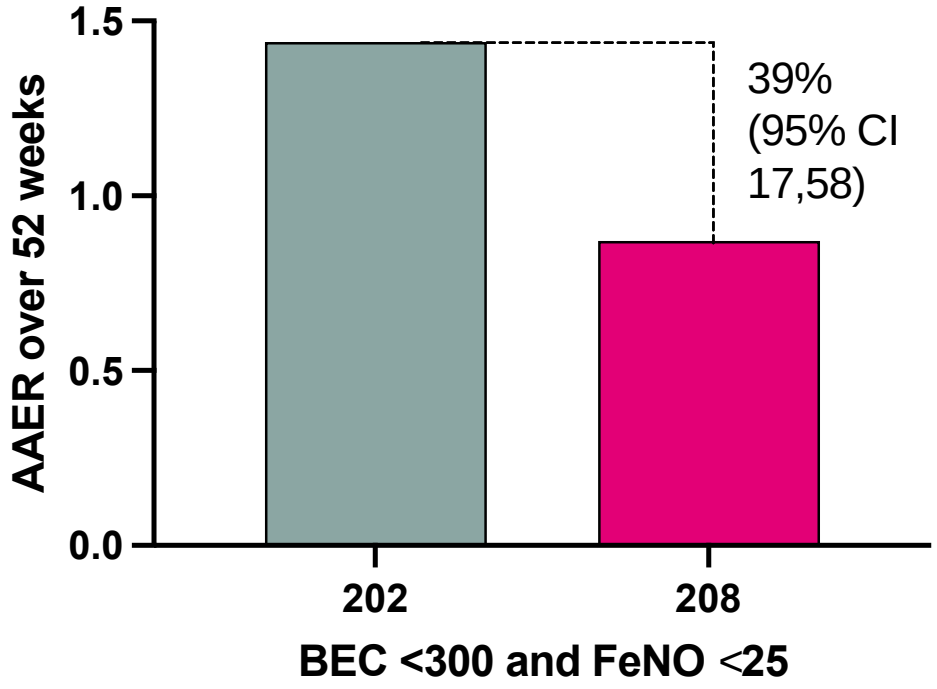
Figure 1. Annualized Rate of Asthma Exacerbations over a Period of 52 Weeks in the Overall Population and According to Baseline Biomarker Category or Allergic Status.

Allergic status was determined according to fluorescence enzyme immunoassay for specific IgE against various perennial allergens (for details, see the Supplementary Appendix). FENO denotes fraction of exhaled nitric oxide, and ppb parts per billion.

Menzies-Gow, NEJM 2021

Need for Broader Anti-inflammatories





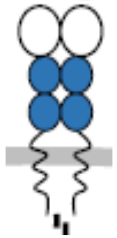
Corren et al. AJRCCM 2023.

RAGE → Pulmonary Inflammation
Response to a Range of Stimuli





RAGE

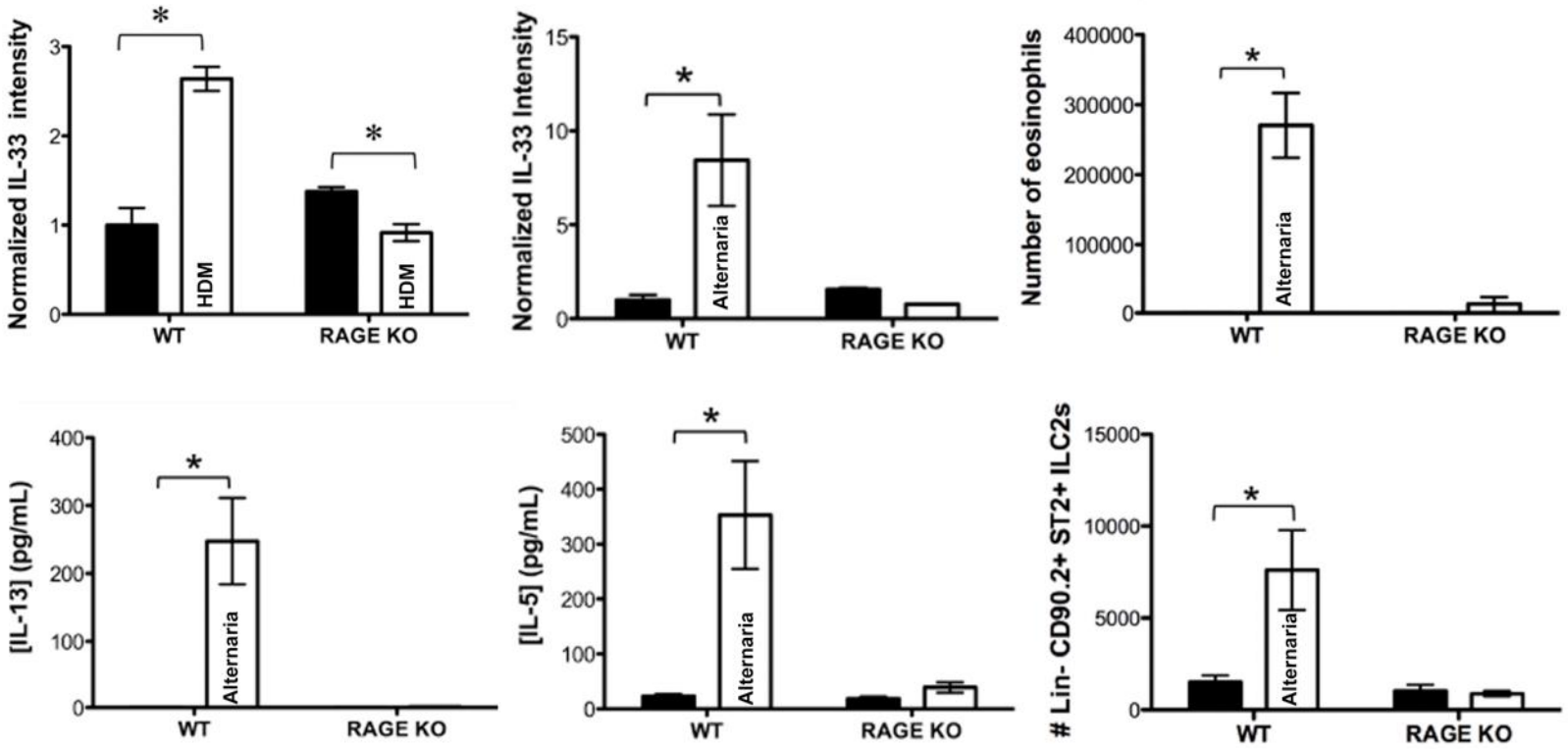


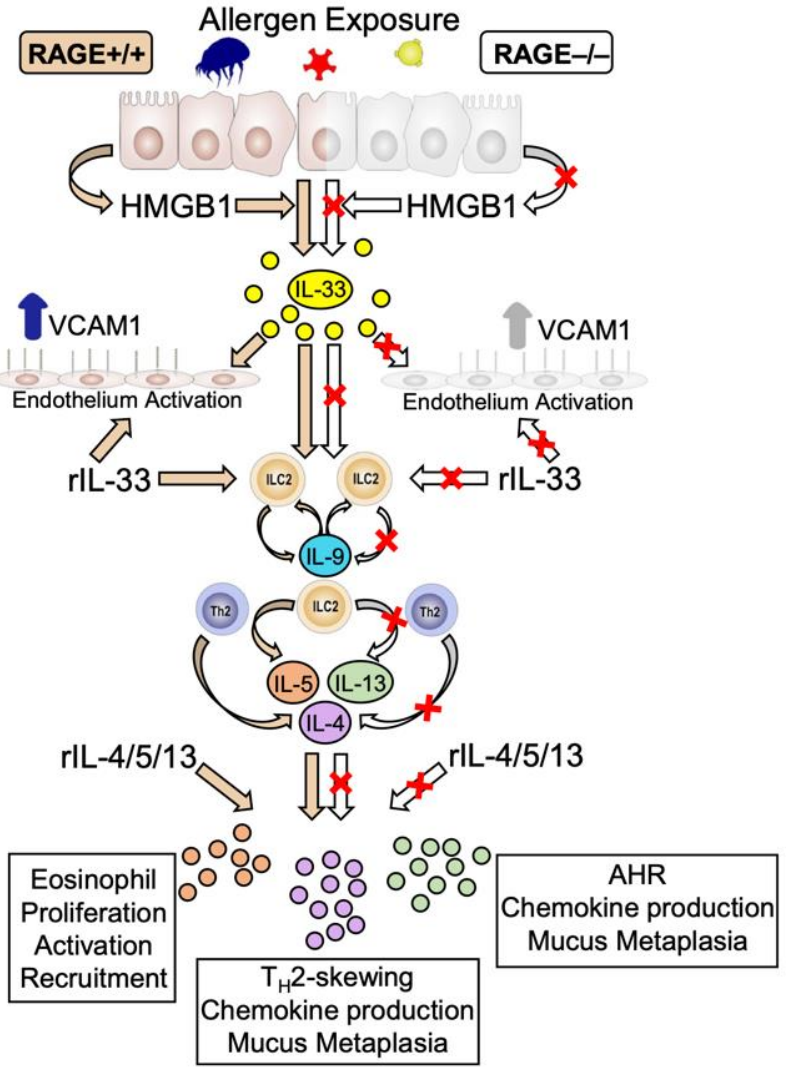
CF	COPD	Asthma
• IL-1β • IL-6 • IL-8 • TGF-β	• IL-1β • MIP-2 • MCP-1 • Neutrophils	• IL-5 • IL-13 • IL-33 • Eosinophils

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.

RAGE: Necessary for Type-2 Inflammation

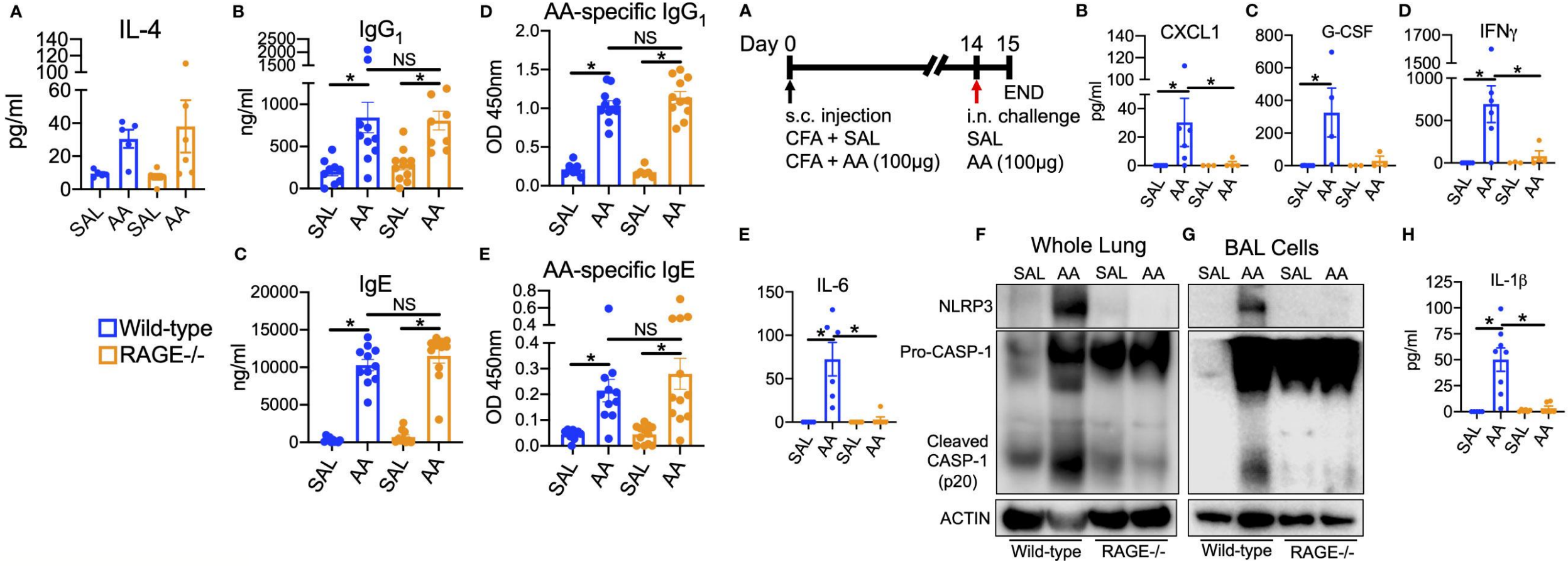
RAGE KO Erases Key Elements of the Type-2 Response to Allergens





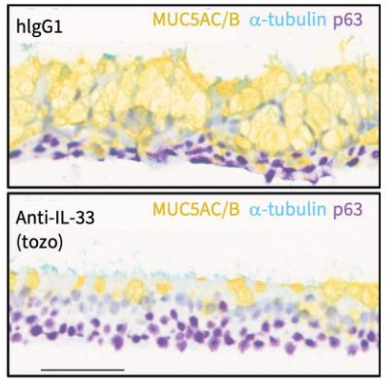
Perkins, Allergy 2021.
Oczypok, J Allergy Clin Immunol. 2015.

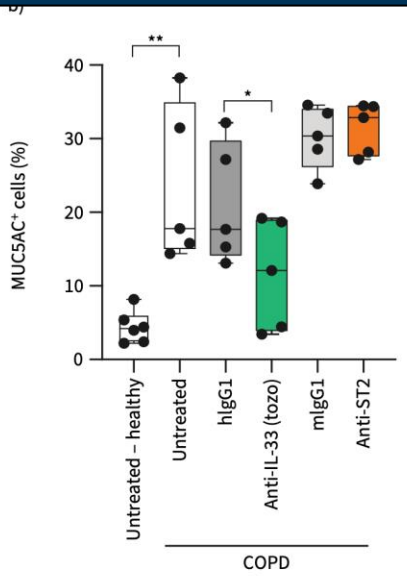
RAGE is Implicated in T2-Low Inflammation

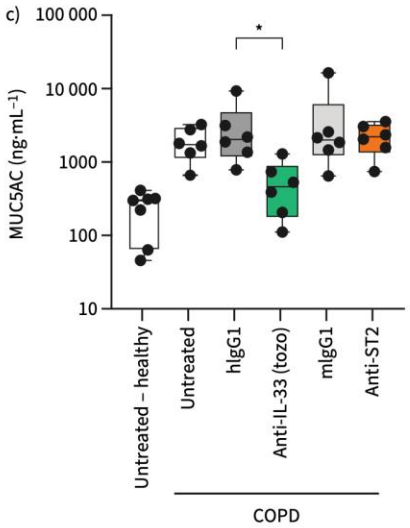


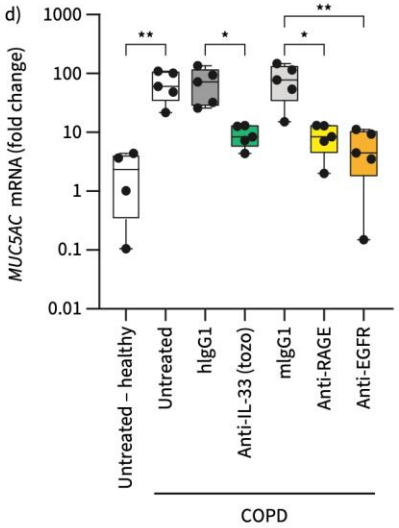
Killian, Front. Immunol. 2023.

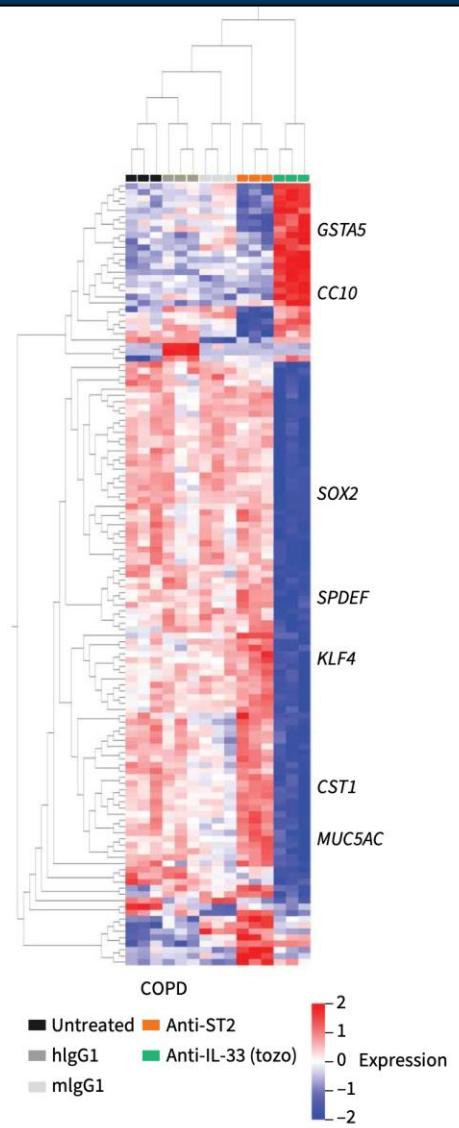
RAGE Facilitates Mucus Production in COPD

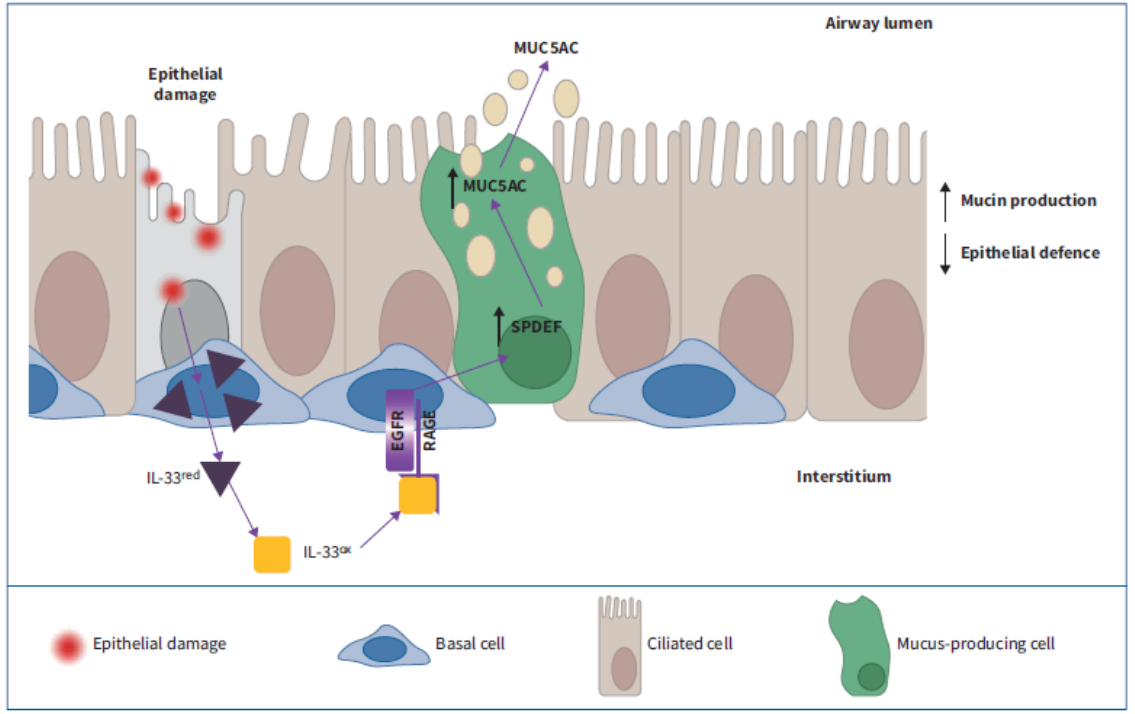








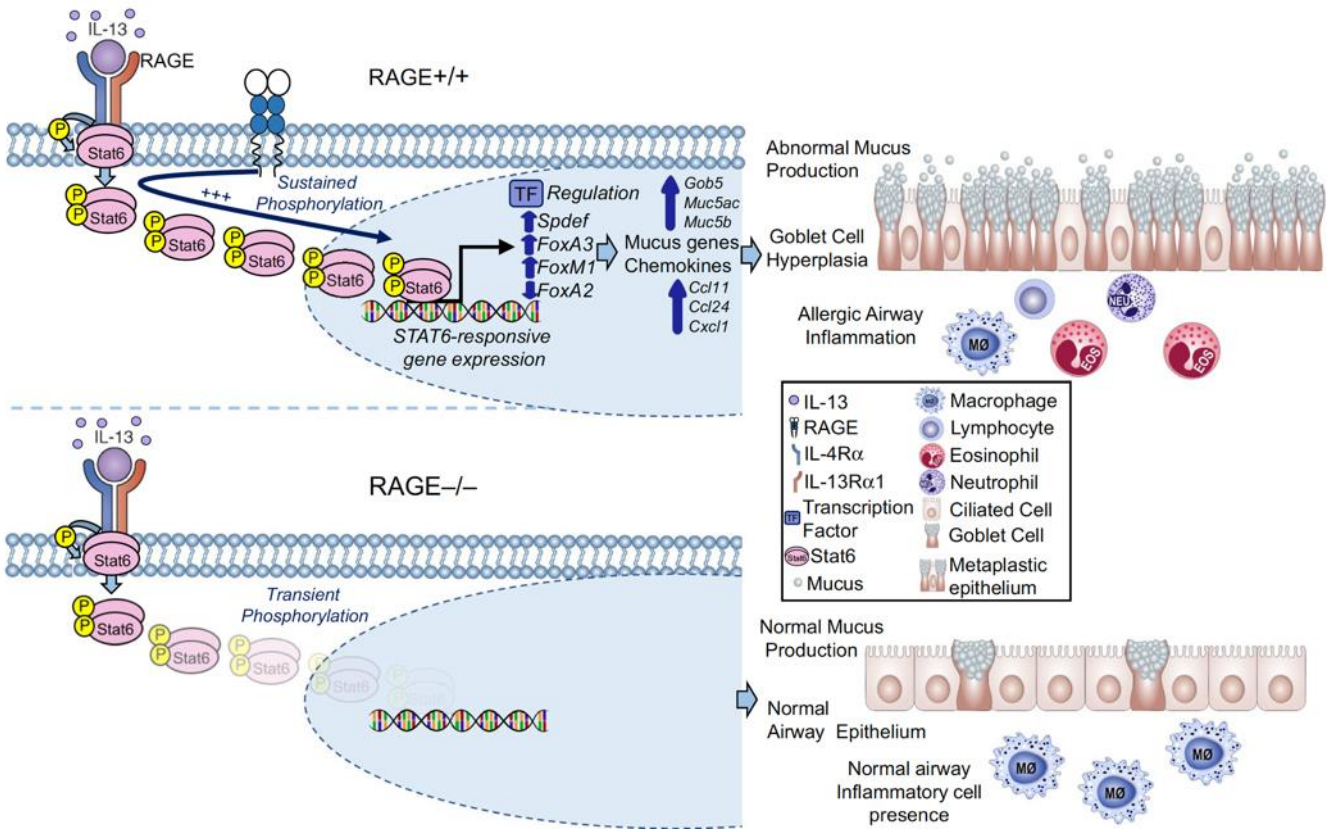


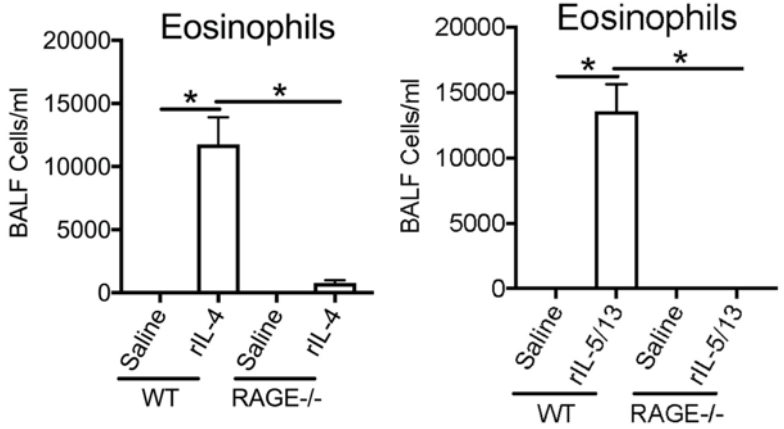


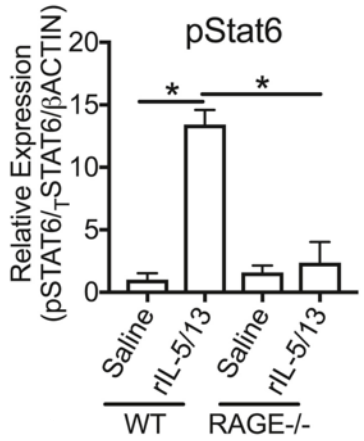
GRAPHICAL ABSTRACT IL-33^{ox} binds to receptor for advanced glycation end products (RAGE) to signal via epidermal growth factor receptor (EGFR). Activation of the IL-33^{ox}–RAGE/EGFR pathway redirects epithelial cell fate, promoting a mucin hypersecretion phenotype at the expense of epithelial defence functions.

Strickson, Eur Respir J. 2023.

RAGE is Necessary for Sustained Signaling by Multiple Effector Cytokines

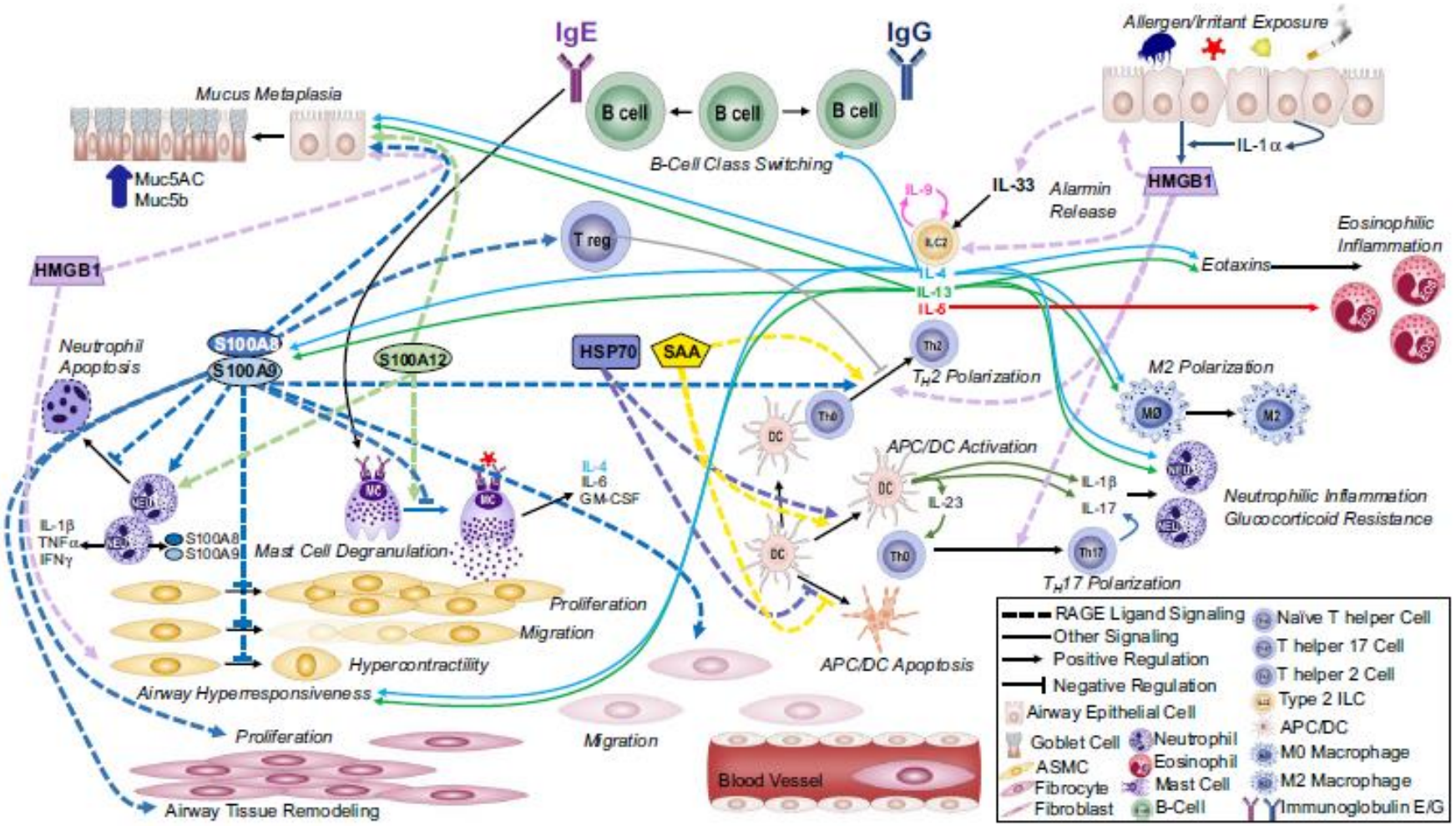






Perkins, JACI 2019
Perkins, Allergy 2021

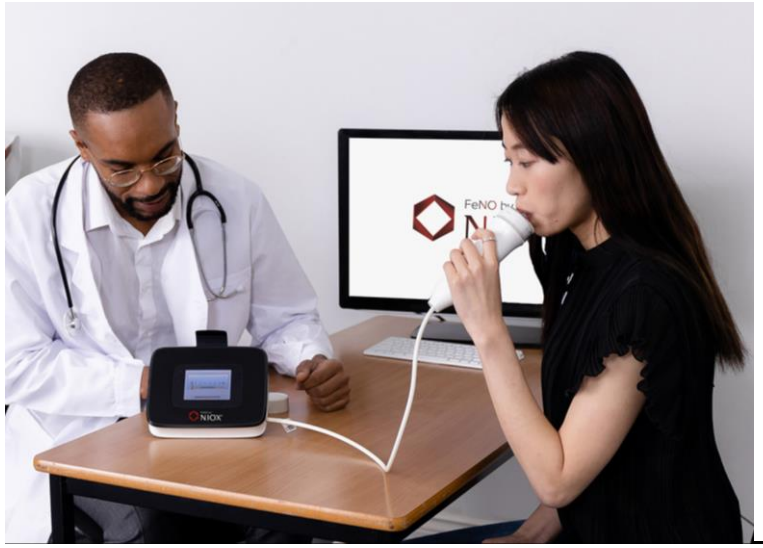
RAGE Ligand Signaling is Broad



Perkins, Allergy 2020.

What Does FeNO Tell Us?

- Point-of-care test to identify Type-2 airway inflammation, but only moderately accurate
- IL-13 drives increased FeNO, not necessarily eosinophils



Source: https://www.niox.com

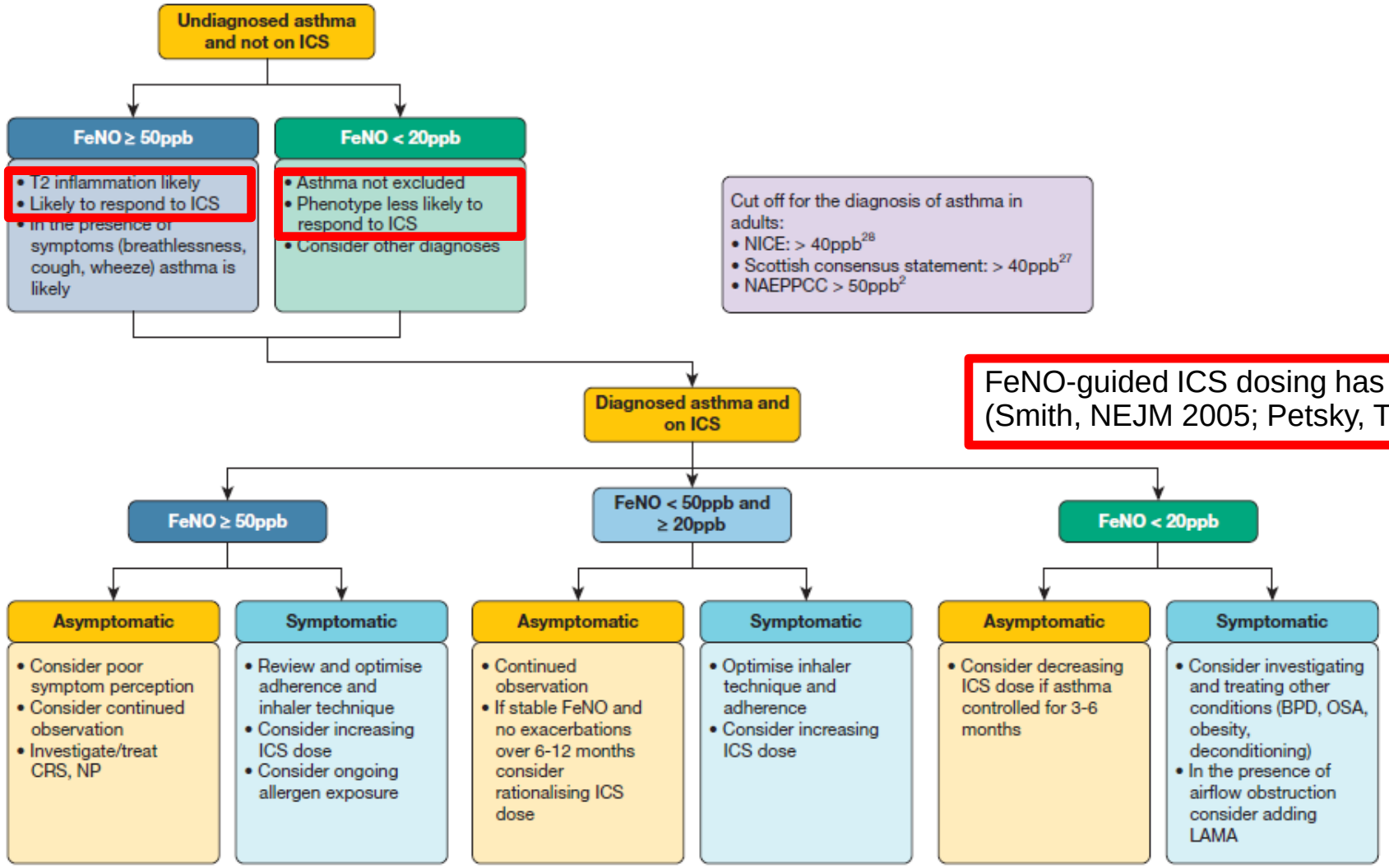
	Sputum eosinophils ≥3%				Sputum eosinophils ≥2%			
	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)
FeNO (ppb)	12	1720	0·66 (0·57–0·75)	0·76 (0·65–0·85)	9	1667	0·65 (0·55–0·74)	0·75 (0·62–0·84)
Blood eosinophils (per µL)	12	1967	0·71 (0·65–0·76)	0·77 (0·70–0·83)	6	1180	0·66 (0·56–0·75)	0·83 (0·62–0·94)
Blood eosinophils (%)	5	920	0·76 (0·52–0·90)	0·74 (0·67–0·80)	2	171	..	..
Serum IgE (IU/mL)	6	699	0·64 (0·42–0·81)	0·71 (0·42–0·89)	4	754	0·63 (0·36–0·84)	0·59 (0·37–0·79)

FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

Table 2: **Summary estimates of sensitivity and specificity for detecting sputum eosinophilia in adults**

Korevaar, Lancet Respir Med 2015

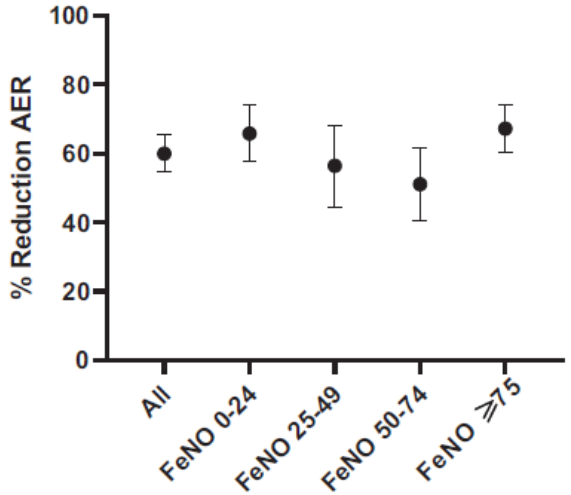
Clinical Use of FeNO

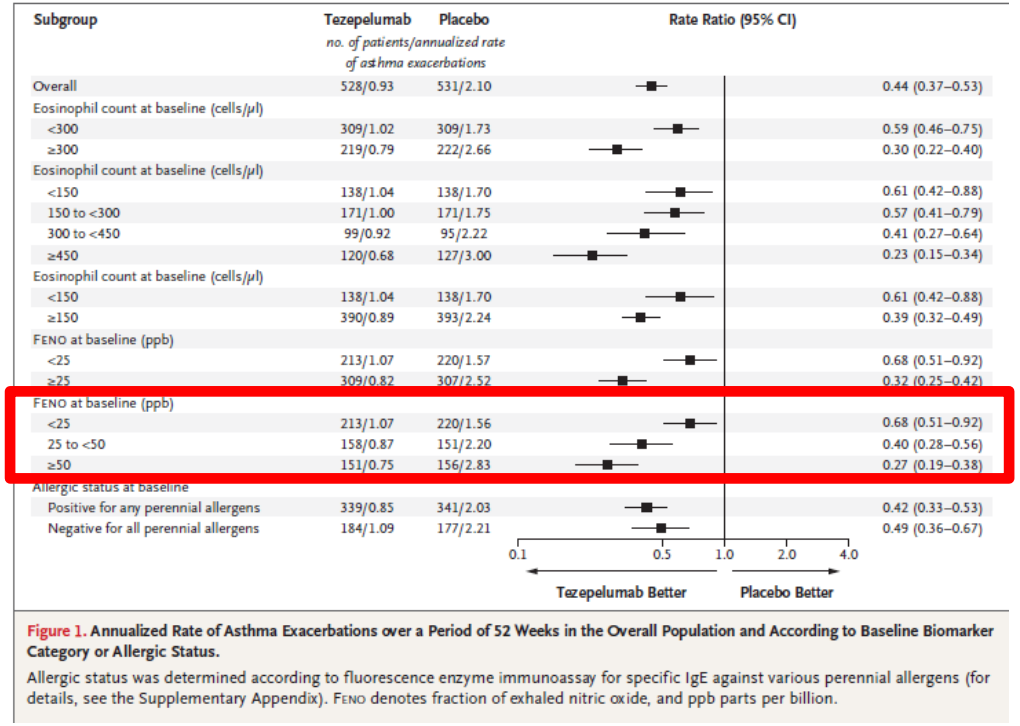


FeNO-guided ICS dosing has mixed results (Smith, NEJM 2005; Petsky, Thorax 2018)

Rupani, Chest 2022

Predictive Use of Baseline FeNO





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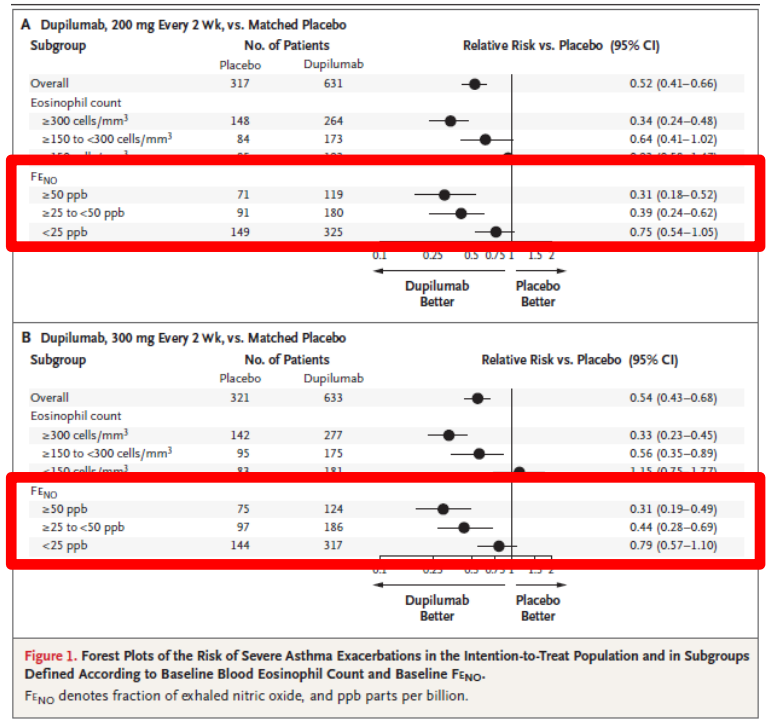


A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

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)
F_{ENO}			
≥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)
F_{ENO}			
≥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)

Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline F_{ENO}.

F_{ENO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

Baseline FeNO does not predict exacerbation rate response to anti-IL-5/5R therapy

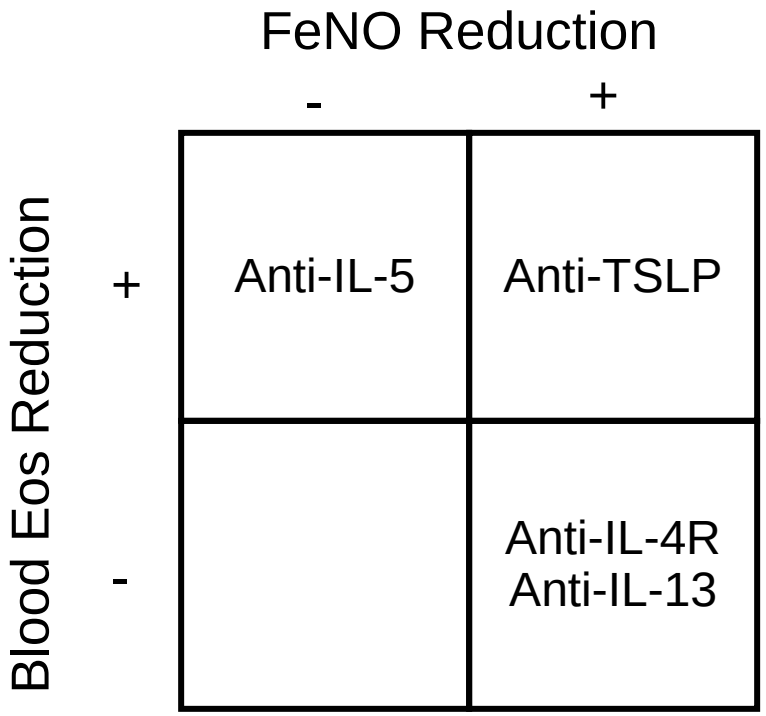
Baseline FeNO predicts response to tezepelumab and dupilumab

Hearn, JACI Pract 2021.
Castro, NEJM 2018.
Menzies-Gow, NEJM 2021.

KU SCHOOL OF MEDICINE
The University of Kansas

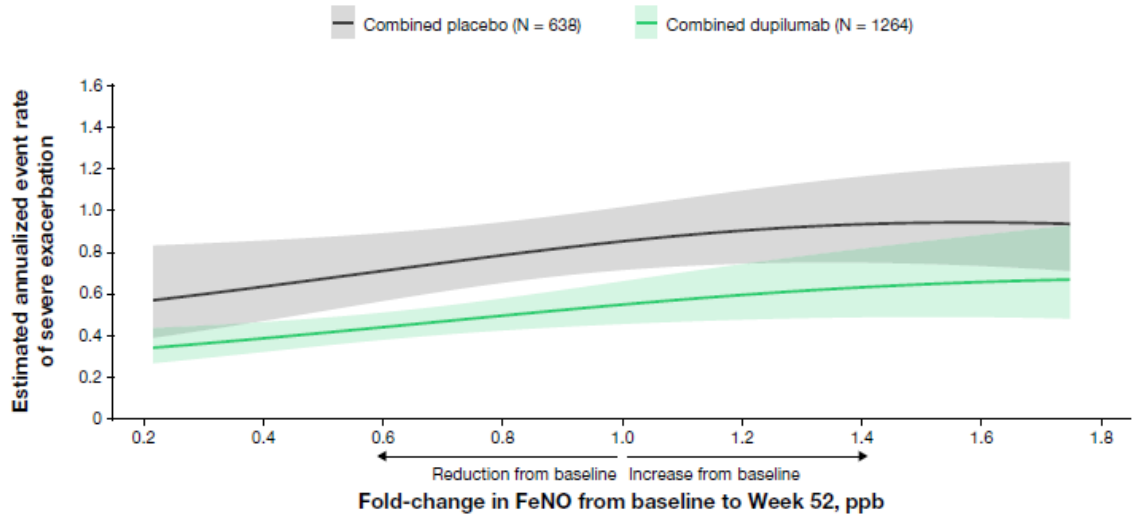
Change in FeNO with Biologics

- FeNO and eosinophils reflect different aspects of T2 inflammation

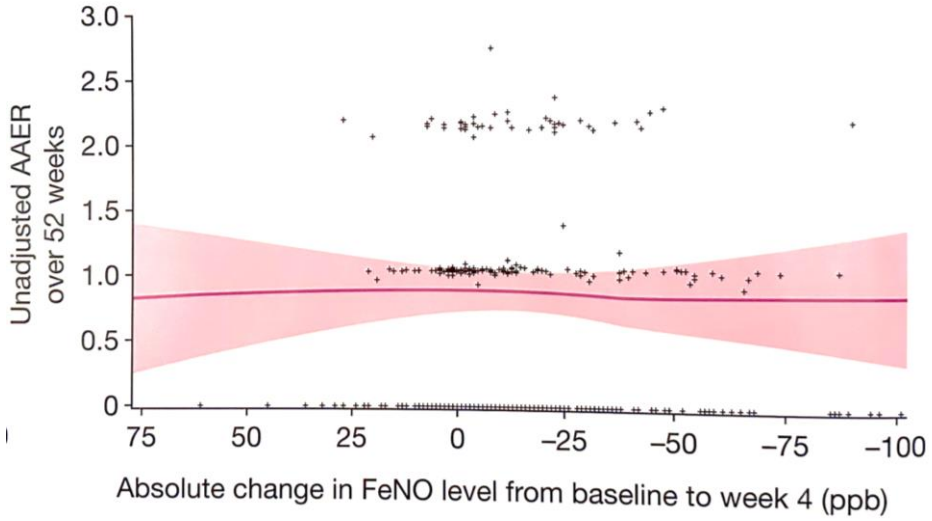


Change in FeNO does not predict Exacerbation Reduction in Response to Biologics

Dupilumab



Tezepelumab



Pavord, JACI Pract 2024
Israel, ATS Poster 2024

Summary

- Asthma Therapy: there is still an unmet need
  - T2 low especially
  - T2 high not fully resolved with biologics either
- RAGE
  - Opportunity to target inflammatory pathways upstream of current biologics
  - Plays an important role in airway diseases beyond asthma
- Assessing therapies with biomarkers
  - All have limited value
  - FeNO can be used to possibly predict response to therapy in T2 high
  - FeNO changes are not correlating with changes in exacerbation.
- Efficacy is best evaluated via asthma control in phase 2 and later clinical trials

Pulmonary Webinar – July 16, 2024

Pulmonary Clinical Update

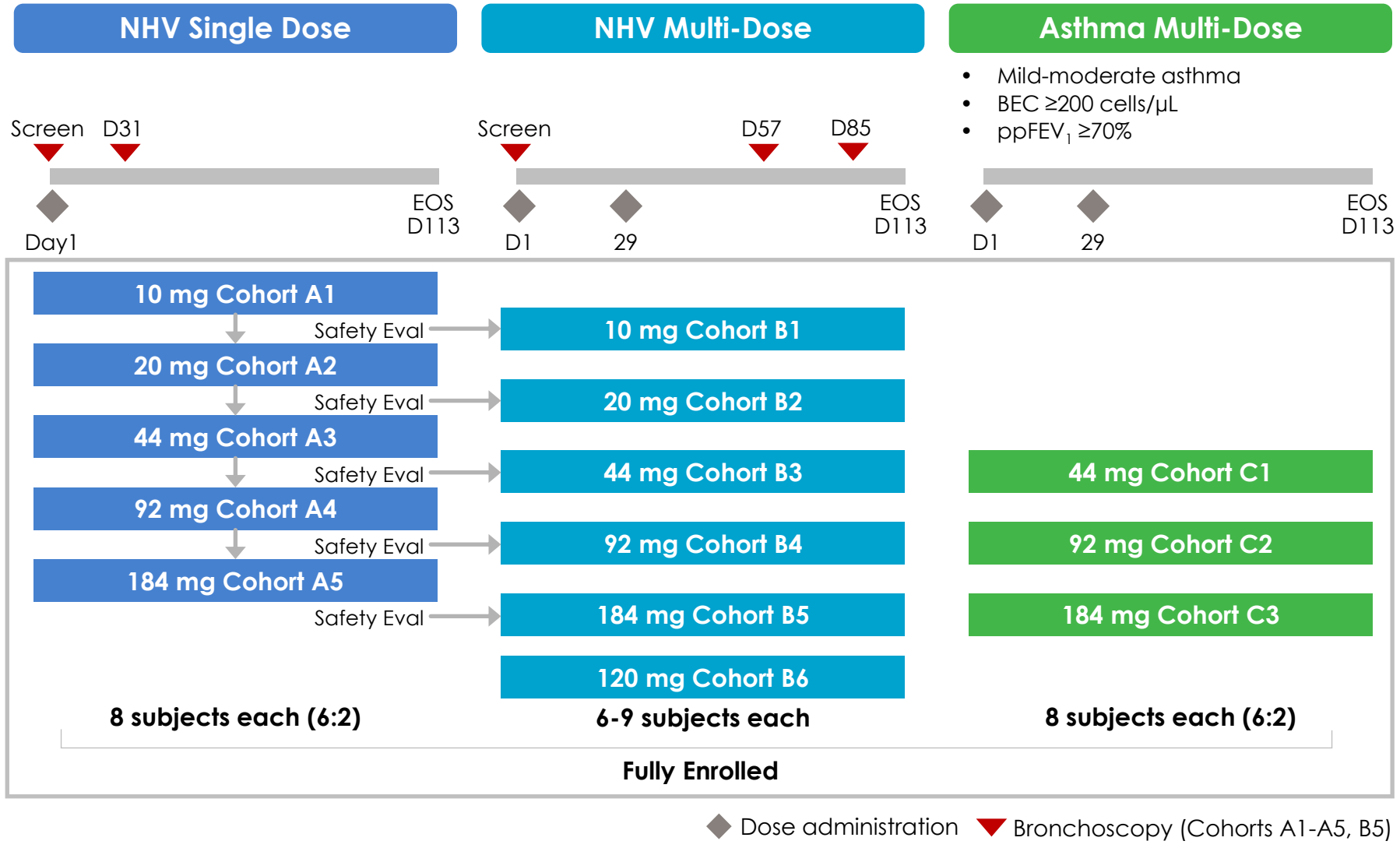
John Huetsch, MD
Senior Medical Director
Pulmonary Lead Physician

arrowhead pharmaceuticals

ARO-RAGE

arrowhead
pharmaceuticals

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



Key Objectives

- Safety
- Target Engagement (sRAGE)

ARO-RAGE Shows a Favorable Safety Profile to Date

Adverse Events

- No treatment-related serious adverse events
- No severe adverse events
- No study withdrawals or drug discontinuations due to adverse events

Lung Function

- No patterns of adverse changes

BALF Cell Count & Differential

- No change in pattern of airway immune cells

Chest X-rays

- All post-dose x-rays read as normal

Safety Labs

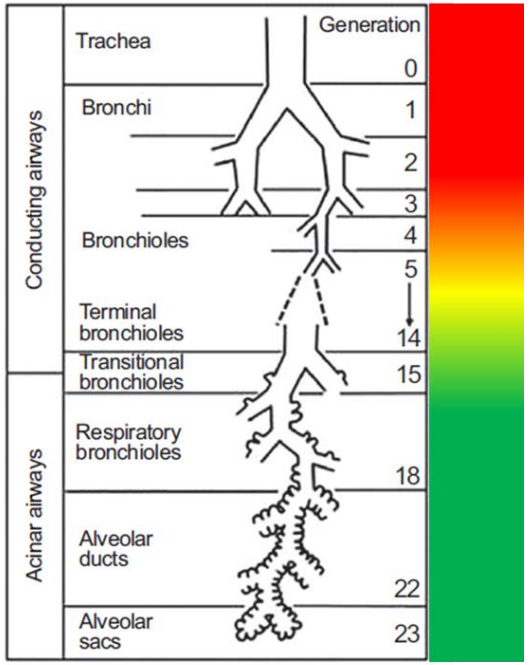
- No patterns of adverse changes

Data cut April 2024

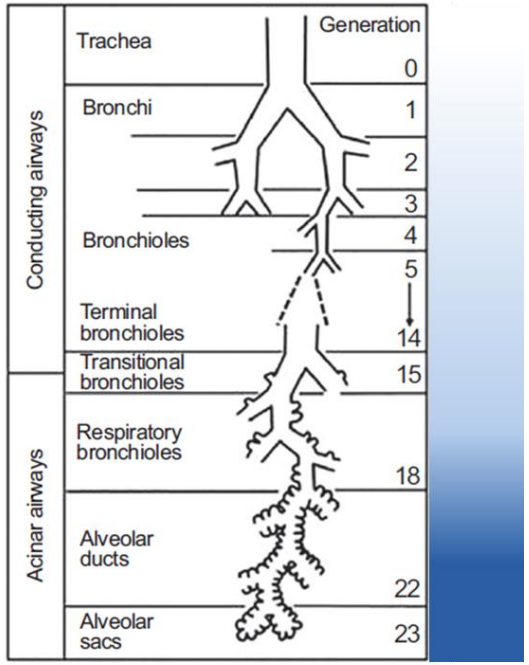
arrowhead pharmaceuticals

ARO-RAGE: Targeting Inflammatory Mediators Generated in Small Airways

Platform Activity

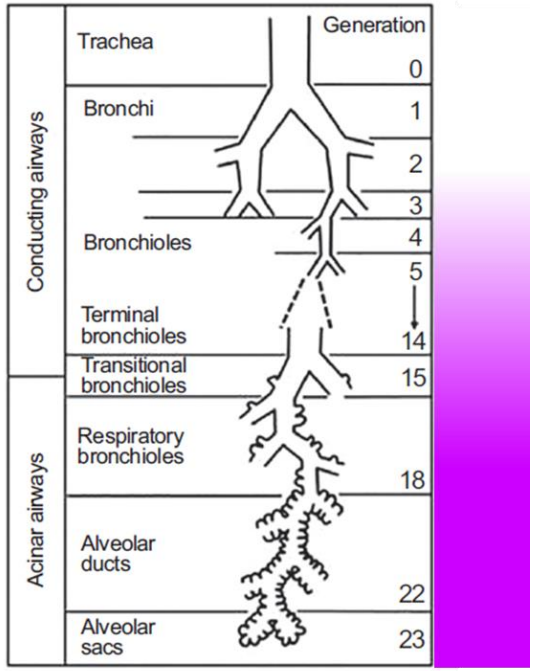


RAGE Expression

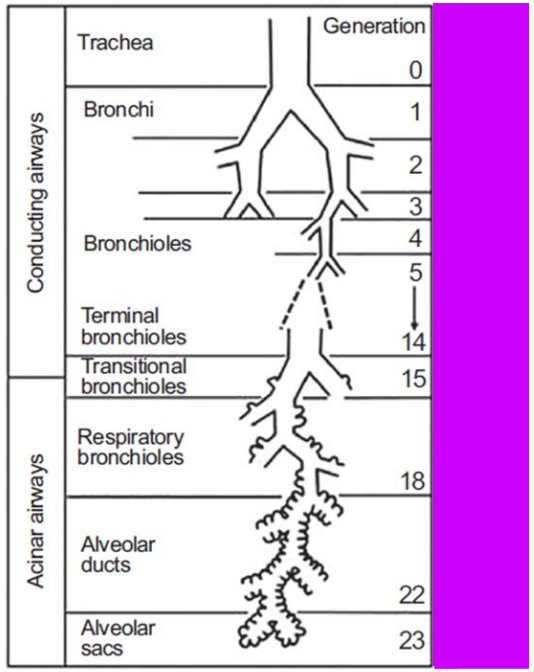


Biomarker Measures

BAL



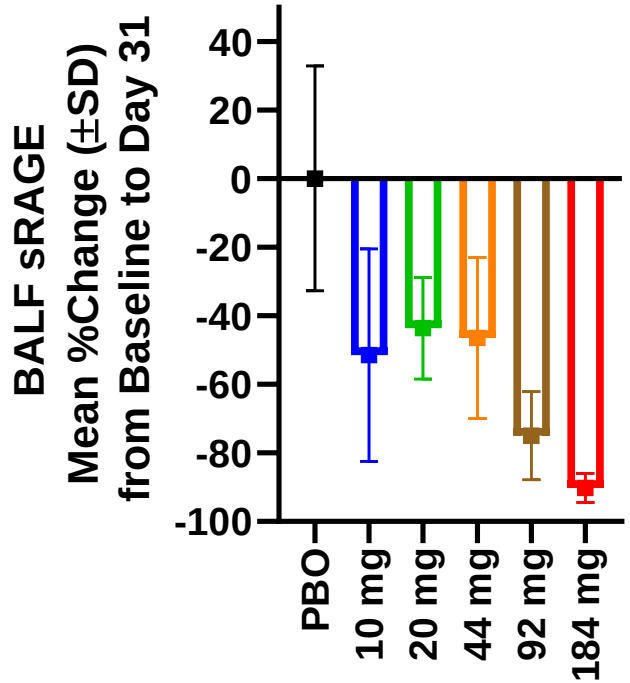
Serum



ARO-RAGE Results in Deep & Durable Silencing of RAGE in the Airway

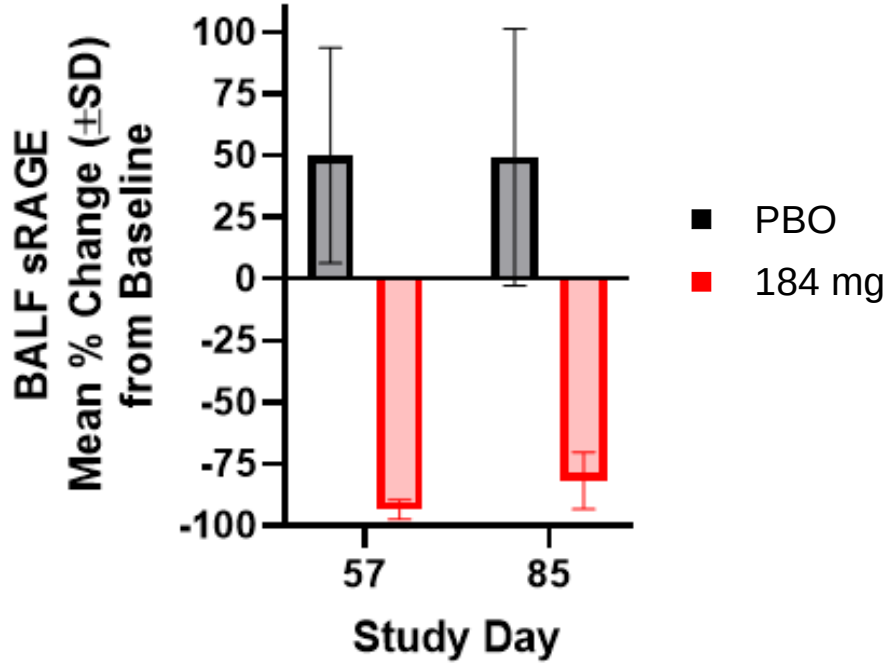
Single Dose Healthy Cohorts

Change from Baseline at Day 31



Multiple Dose 184mg Healthy Cohort Dosing Days 1 & 29

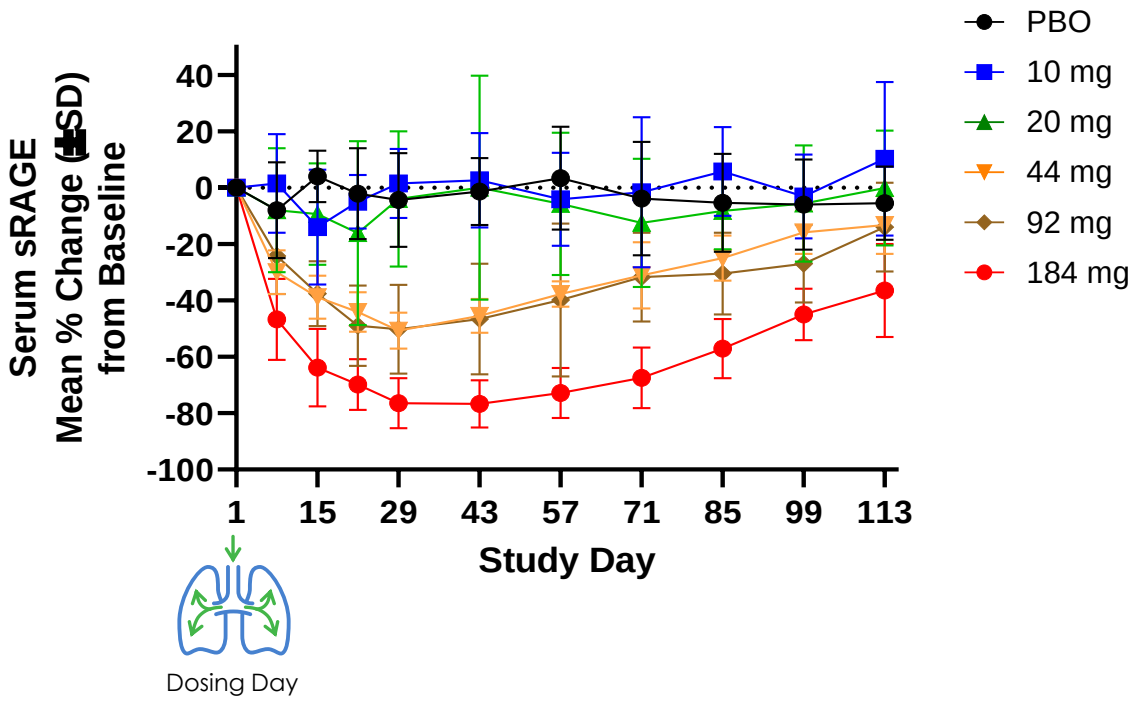
Change from Baseline at Days 57 & 85



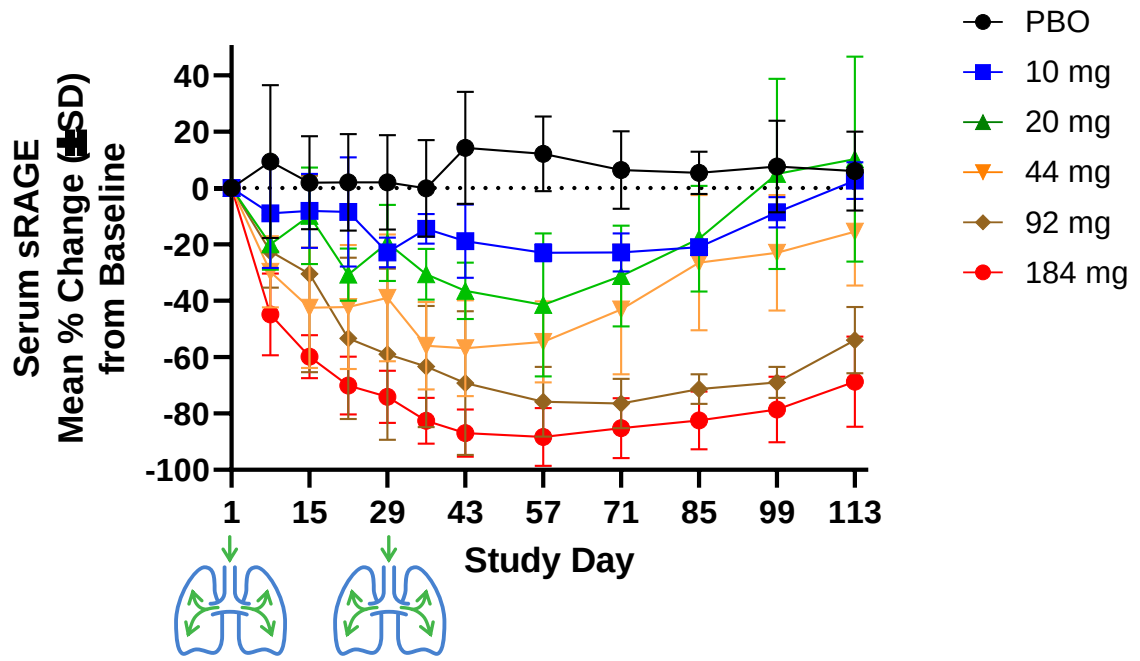
O'Carroll et al. *ATS* 2024.
Data cut April 2024

Pulmonary RAGE Silencing is Measurable with the Serum sRAGE Biomarker, with up to 88% Mean Reduction at 184 mg Dose

Single Dose Healthy Cohorts



Multiple Dose Healthy Cohorts



O'Carroll et al. *ATS* 2024.
Data cut April 2024

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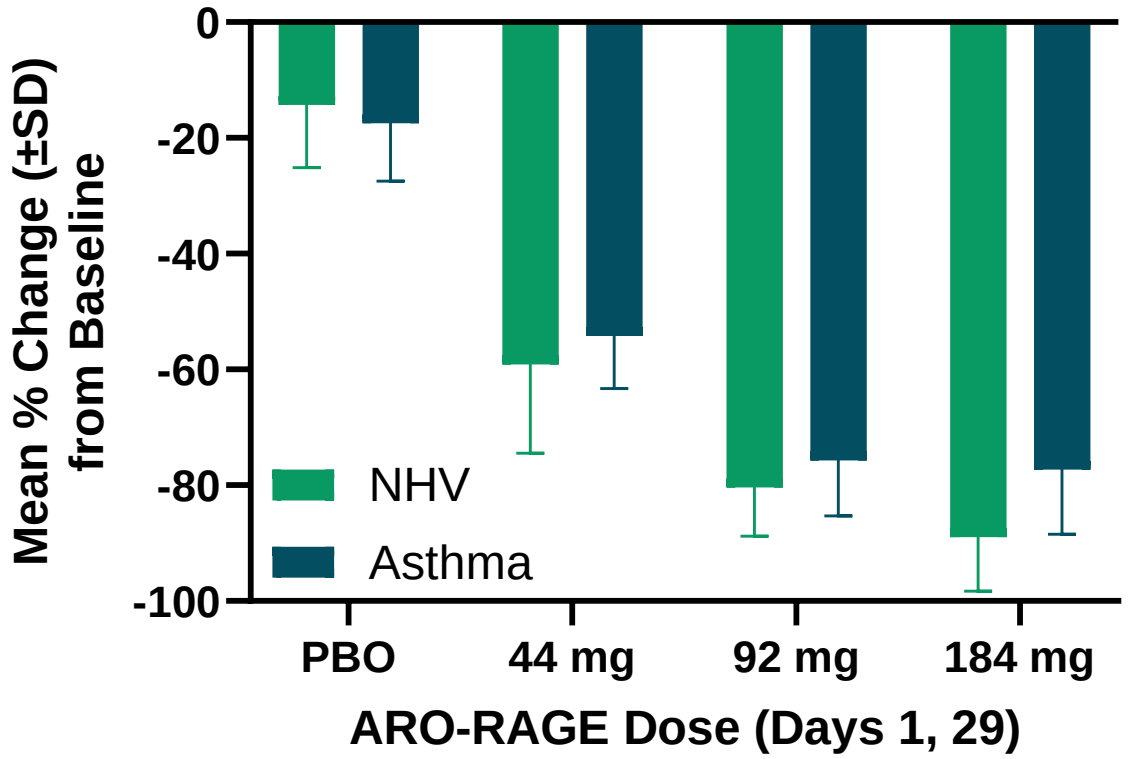
ARO-RAGE Results in Deep RAGE Silencing in Asthma Patients

Mean Maximum Serum sRAGE Reduction Following 2 Doses of ARO-RAGE



Serum sRAGE Modeling Supports Q2 Month Dosing in Subsequent Studies

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O'Carroll et al. *ATS* 2024.
Data cut April 2024

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

Asthma High-FeNO Multi-Dose

- Stable maintenance ICS regimen
- High FeNO (≥35 ppb)
- $ppFEV_1$ ≥40%

184 mg Cohort (12:6)

120 mg Cohort (12:6)

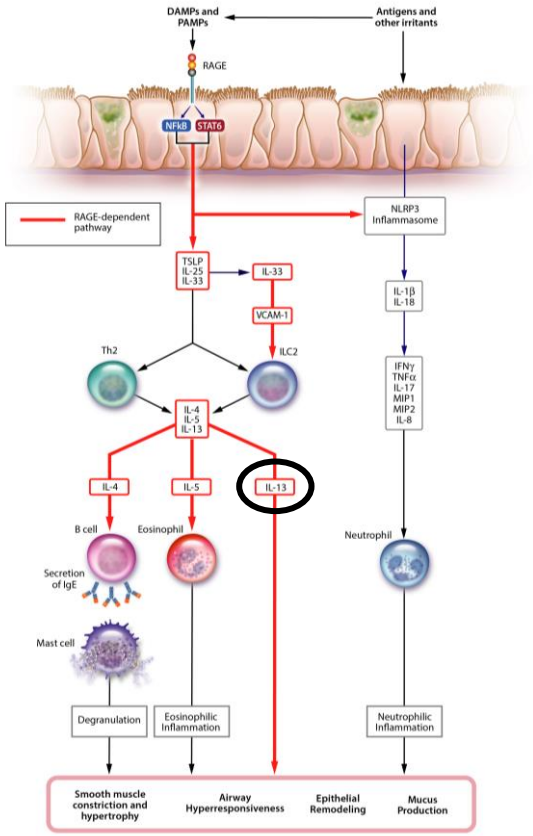
92 mg Cohort (6:2)

Actively Enrolling

Key Objective

Effect on FeNO

FeNO Primarily Reflects Activity of IL-13, One of Many Inflammatory Mediators Regulated by RAGE in Animal Models



FeNO Effect Does Not Predict Clinical Efficacy of Asthma Therapies and Does Not Represent Gating Point for Further Development of ARO-RAGE

- Drugs that decrease FeNO do not necessarily control asthma (example: IL-13 mAbs)
- Drugs can control asthma by impacting other pathways that do not inhibit IL-13 or reduce FeNO (example: IL-5 mAbs)
- For drugs that reduce FeNO, a patient's FeNO response is not associated with their asthma exacerbation response (examples: dupilumab, tezepelumab)

Panettieri, *Lancet Respir Med* 2018. Haldar, *NEJM* 2009. Pavord, *JACI Pract* 2024. Israel, *ATS* 2024

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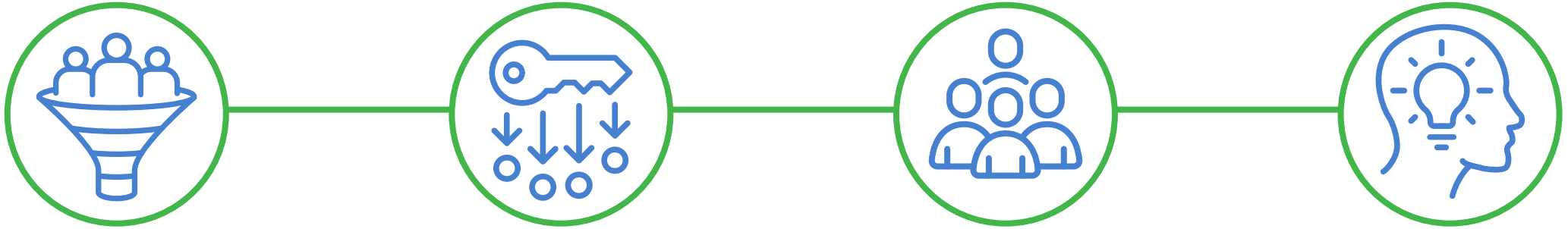
ARORAGE-2001 Phase 2a Overview



Patient Population

- Severe asthma (patients uncontrolled on background ICS/LABA)
- Any blood eosinophil level: approx. 50% type-2 high and 50% type-2 low

Key Outcomes

- Asthma worsening events (composite of severe exacerbations and milder loss-of-control events)
- FEV_1
- Patient-reported outcomes capturing asthma symptoms, control, and quality-of-life

Trial Size and Length

- Approx. 250 subjects
- Treatment period of approx. 6 months

What We Will Learn

Proof-of-concept in target patient population to evaluate ARO-RAGE effects on:

- Asthma control
- Asthma exacerbations
- Lung function
- Symptoms

ARORAGE-1001 Summary

- ARO-RAGE has been safe and well-tolerated at all dose levels, in healthy subjects and asthma patients
- ARO-RAGE has shown evidence of deep and durable target engagement, enabling every-2-month dosing in future studies
- Enrollment into High-FeNO asthma cohorts remains ongoing. FeNO effects are of interest but may provide limited insight into the ARO-RAGE anti-inflammatory effects beyond IL-13. FeNO results are not expected to predict clinical efficacy.
- A Phase 2 study is planned to evaluate the effects of ARO-RAGE on asthma control, which will start-up in parallel with the completion of the High-FeNO cohorts

ARO-MMP7

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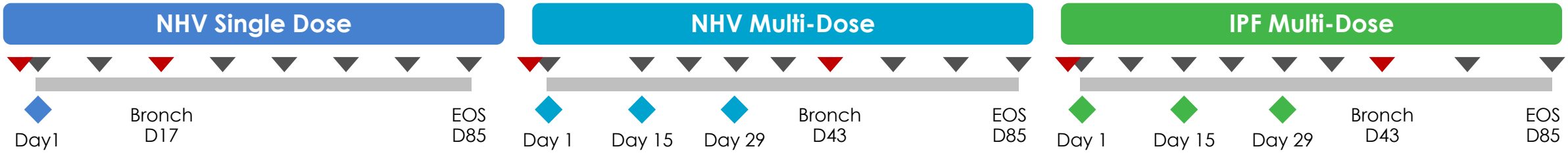
ARO-MMP7 First-in-Human Study (AROMMP7-1001): Safety, Target Engagement & Dose-Response and Duration



Population

Healthy Volunteers

Healthy Volunteers

IPF

- Excludes end-stage disease
- Concomitant IPF therapies allowed

Cohorts

Cohorts Complete

15 mg Cohort A1 → Safety Eval

32 mg Cohort A2 → Safety Eval

60 mg Cohort A3 → Safety Eval

116 mg Cohort A4 → Safety Eval

224 mg Cohort A5 → Safety Eval

8 subjects each (6:2)

15 mg Cohort B1

32 mg Cohort B2

60 mg Cohort B3

116 mg Cohort B4

224 mg Cohort B5

6-9 subjects each (4:2 or 6:3)

Cohort C1: 116 mg*

Cohort C2: ≤224 mg

Cohort C3: ≤224 mg

7 subjects each (5:2)

*Currently enrolling

◆ Dose administration ▼ MMP7 protein serum measurement ▼ MMP7 protein bronchoscopy measurement

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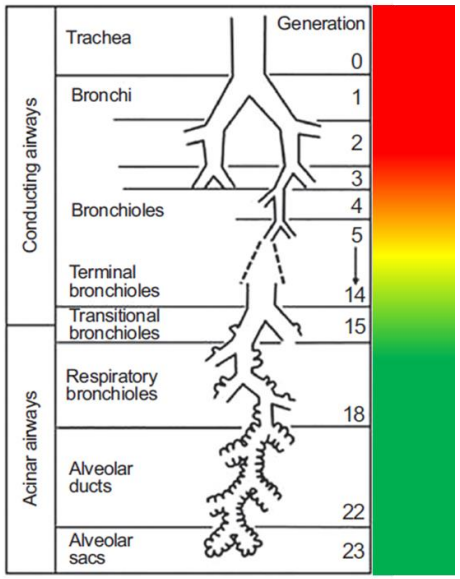
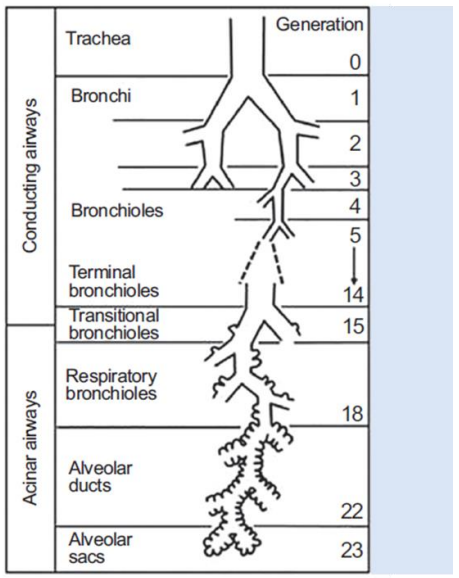
ARO-MMP7: Silencing a Fibrotic Mediator in Small Airways & Alveoli

Platform Activity

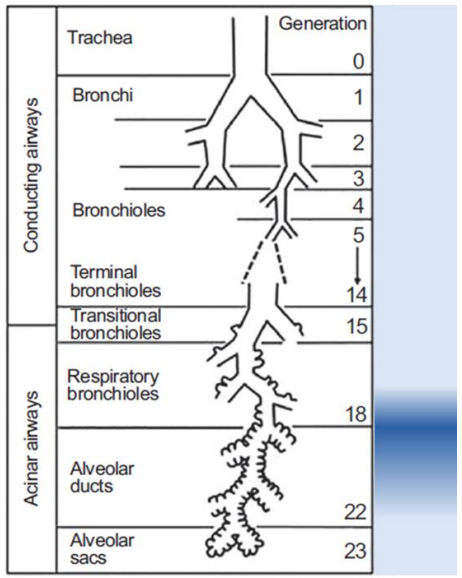


MMP7 Expression

Normal



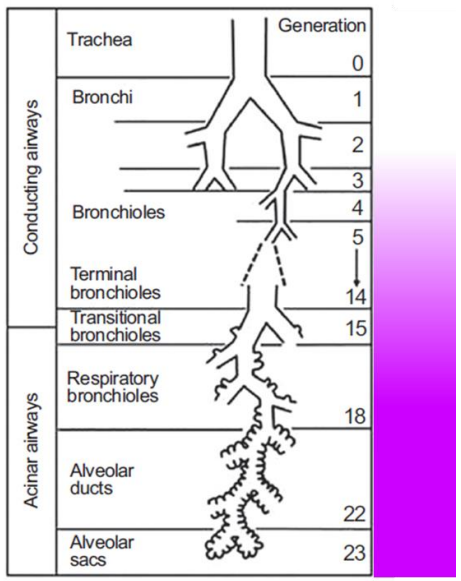
IPF



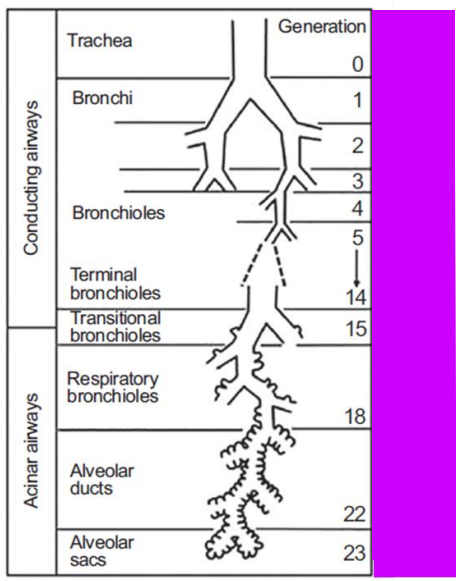
Aberrant basaloid expression in distal lung

Biomarker Measures

BAL



Serum



ARO-MUC5AC

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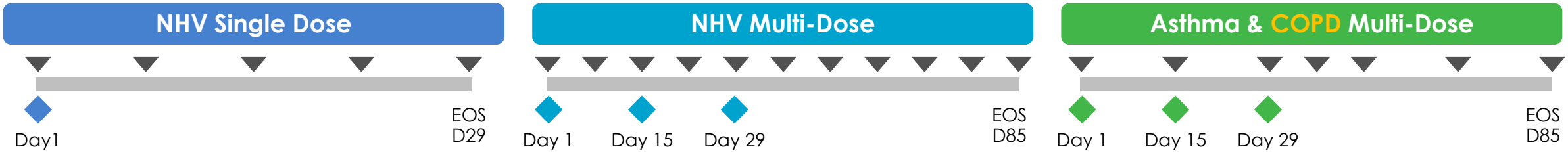
ARO-MUC5AC First-in-Human Study (AROMUC5AC-1001): Safety, Target Engagement & Dose-Response and Duration



Population

Healthy Volunteers	Healthy Volunteers	Asthma	COPD

Cohorts

Cohorts Complete

24 mg Cohort 1a → Safety Eval	24 mg Cohort 1b		
56 mg Cohort 2a → Safety Eval	56 mg Cohort 2b	56 mg Cohort 2c	56 mg Cohort 2d*
108 mg Cohort 3a → Safety Eval	108 mg Cohort 3b	108 mg Cohort 3c*	108 mg Cohort 3d
232 mg Cohort 4a → Safety Eval	232 mg Cohort 4b	232 mg Cohort 4c	232 mg Cohort 4d
6 subjects each (4:2)	**8 subjects each (6:2)**	**8 subjects each (6:2)**	**8 subjects each (6:2)**

*Currently enrolling

◆ Dose administration ▼ MUC5AC measurement by induced sputum

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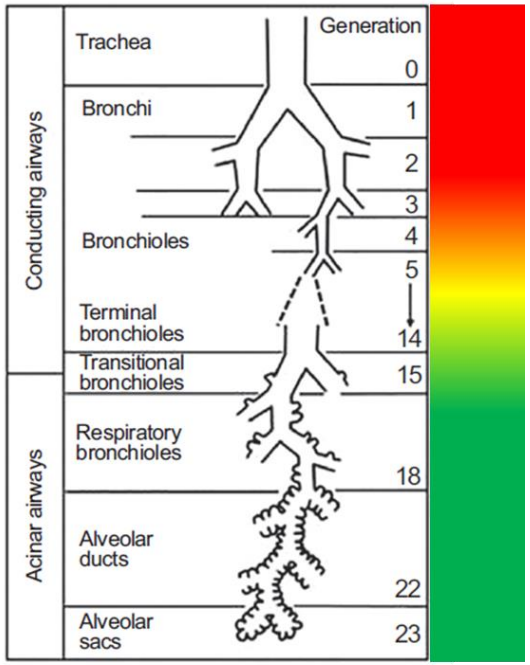
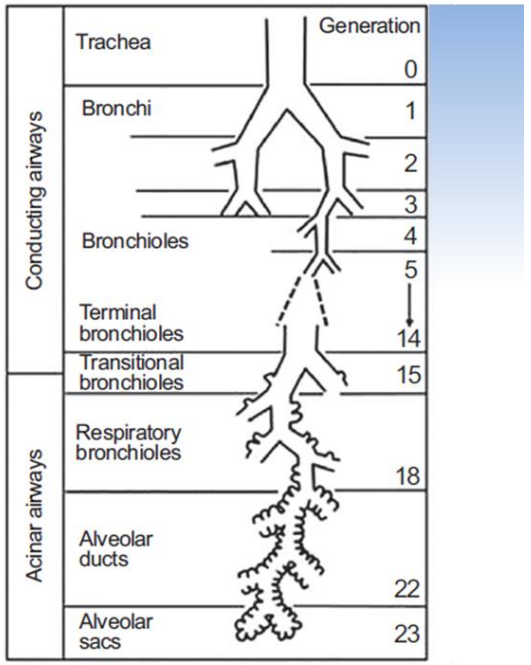
ARO-MUC5AC: Targeting Small Airway Muco-obstruction

Platform Activity

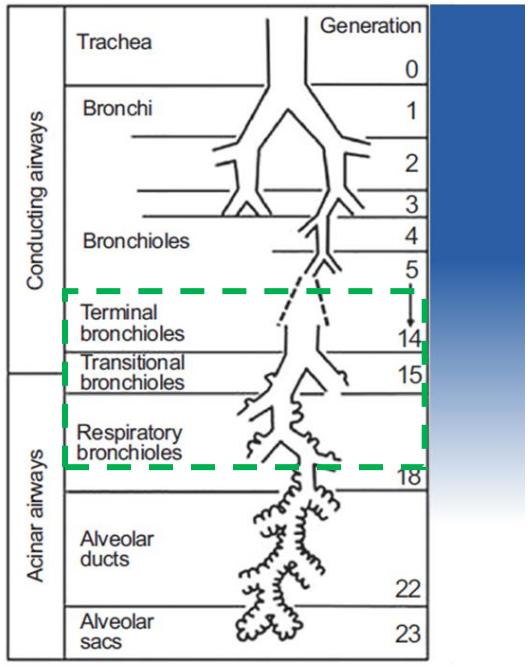


Muc5AC Expression

Healthy



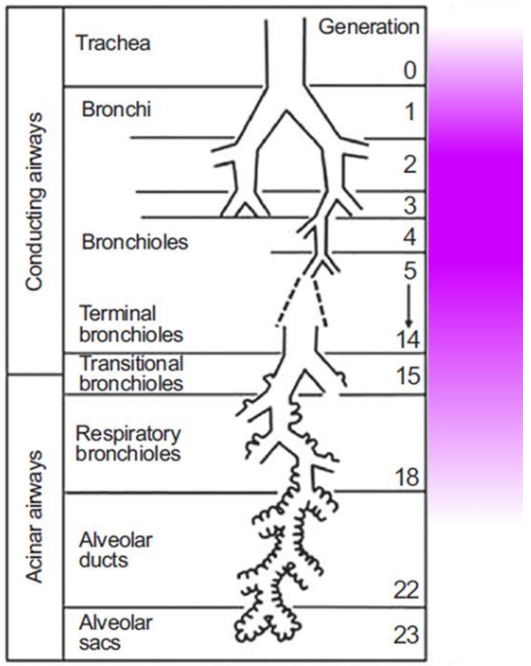
Muco-obstructive Disease



Small airway muco-obstruction

Biomarker Measures

Sputum



Pulmonary Webinar July 16, 2024

Concluding Remarks

Vince Anzalone, CFA
Vice President, Finance and IR

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Clinical Pulmonary Portfolio May Address Multiple Lung Diseases

	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			✓

Key Anticipated Timelines

1 ARO-RAGE

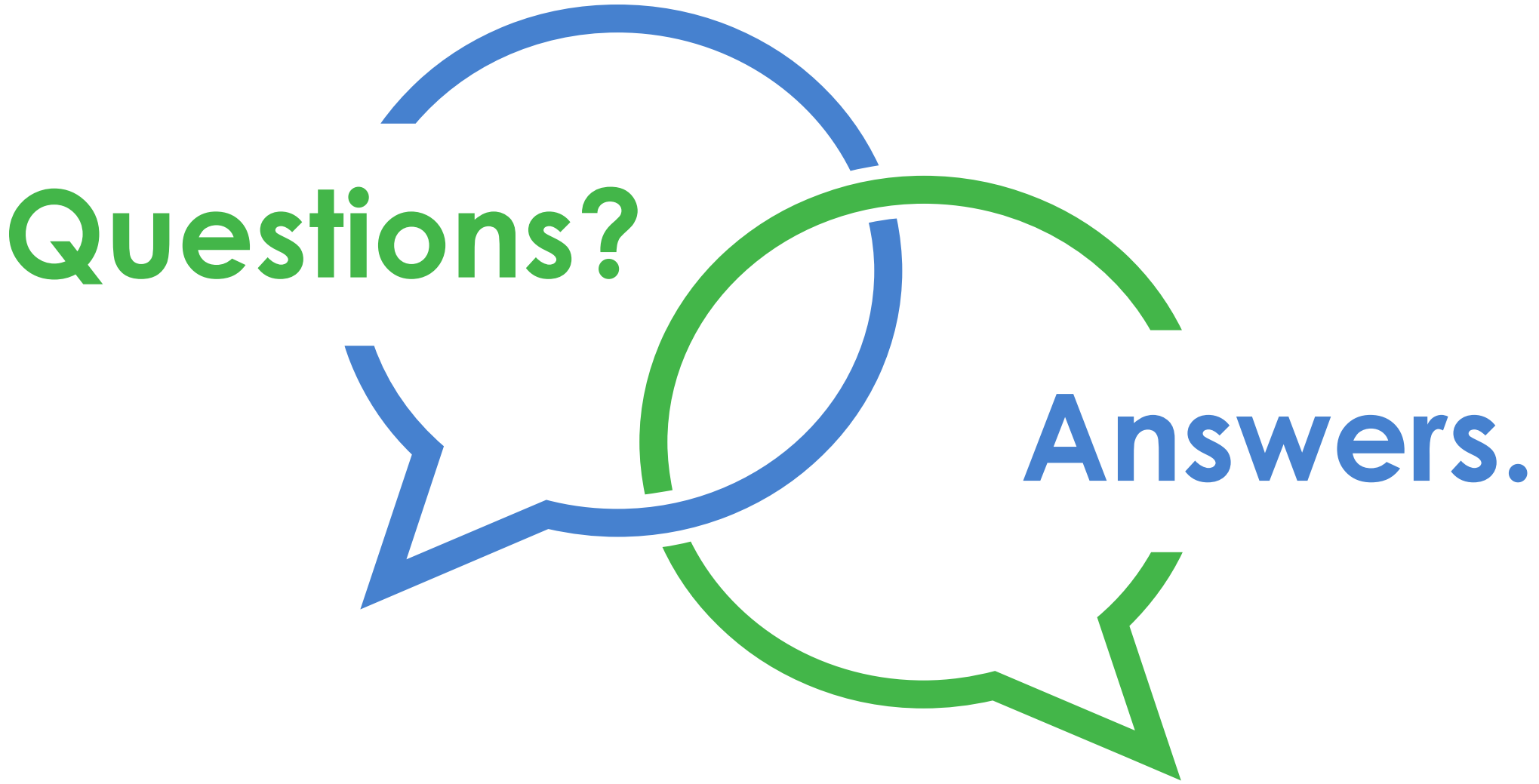
- Regulatory interactions on Phase 2
  - 2nd half 2024
- Phase 2 start
  - 1st half 2025
- High FeNO cohort completion
  - 1st half 2025

2 ARO-MUC5AC

- Topline Phase 1/2 readout on safety/tolerability, target engagement
  - 1st half 2025
- Phase 2 design/planning
  - 1st half 2025

3 ARO-MMP7

- Topline Phase 1/2 readout on safety/tolerability, target engagement
  - 1st half 2025
- Phase 2 design/planning
  - 1st half 2025


Questions?
Answers.