

What Causes Aspirin-Exacerbated Respiratory Disease (AERD)?

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Jeff and Penny Vinik
CENTER FOR TRANSLATIONAL IMMUNOLOGY RESEARCH
DISEASERY | INNOVATION | CURE



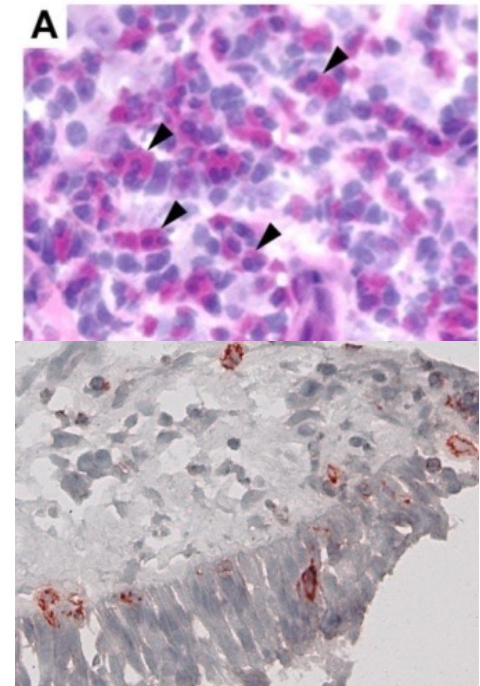
HARVARD
MEDICAL SCHOOL

Conflict of Interest Disclosure

- Relevant financial relationships with commercial interests in the preceding 12 months:
Sanofi/Aventis

Aspirin-Exacerbated Respiratory Disease (AERD) Characteristic Features

- Adult-onset asthma (5-10% of all asthma; ~15-30% of severe asthma)
- Severe eosinophilic rhinosinusitis with nasal polyposis
- Pathognomonic respiratory reactions to aspirin and other drugs that inhibit COX-1 (not COX-2) (pharmacological rather than immunological)
- Many are non-atopic despite type 2 immunopathology
- Aberrant cysteinyl leukotriene production, eosinophilia, mast cell activation, impaired COX-2/PGE₂ system

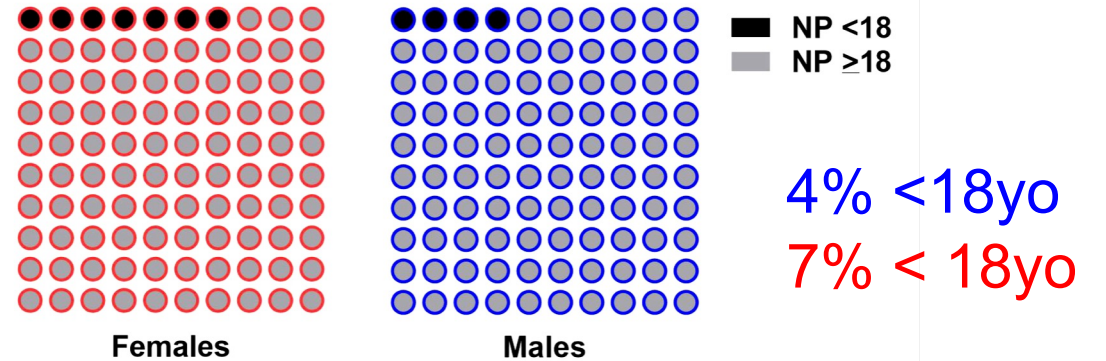
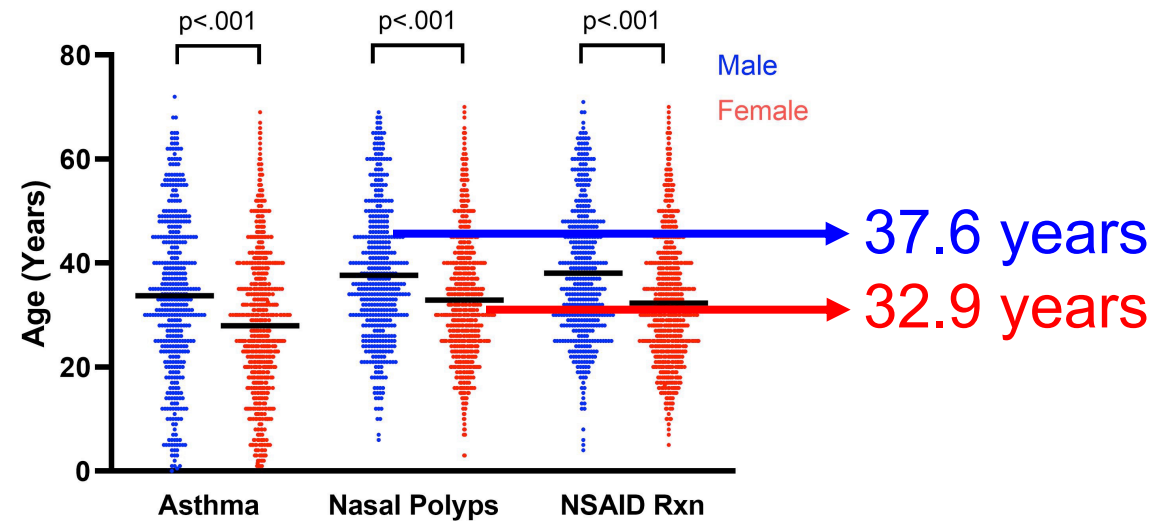
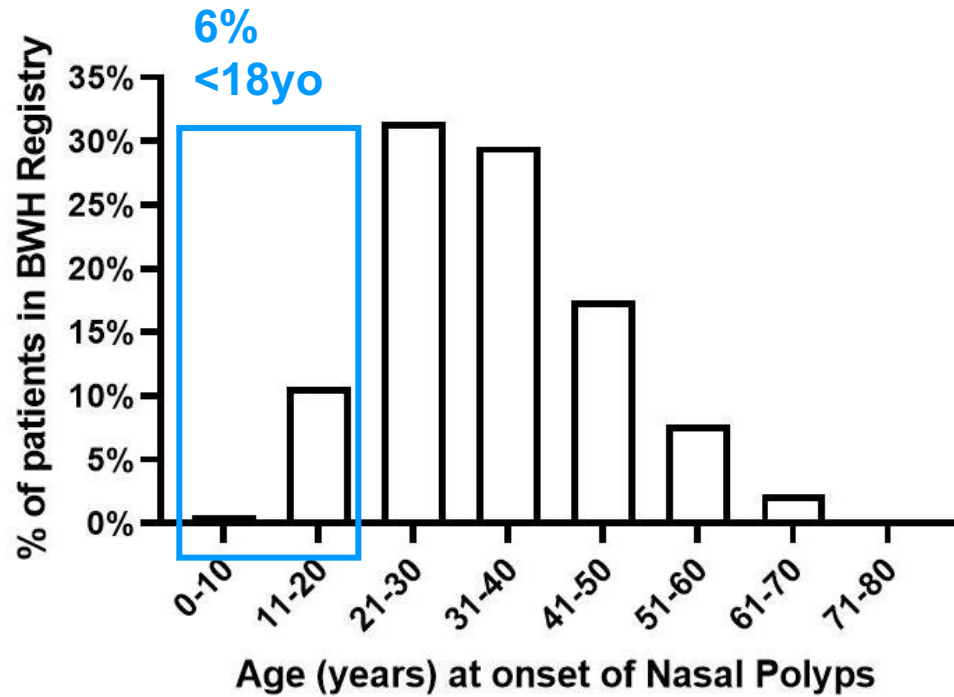


H & E

Tryptase

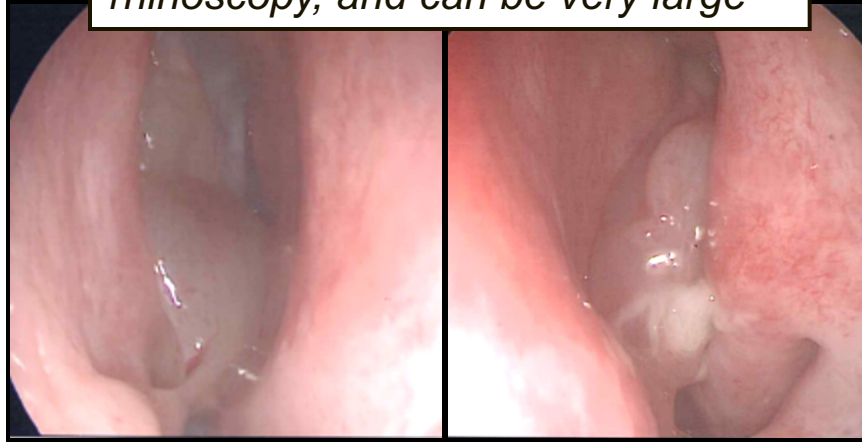
Age and gender: >2000 patients at BWH AERD Center

Largely adult-onset disease...

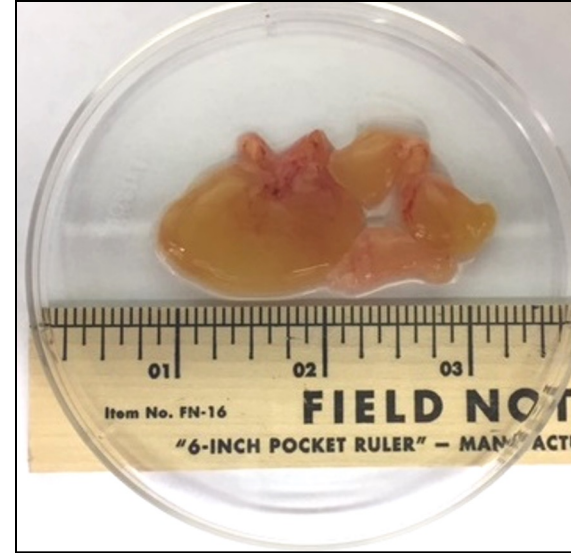


Recurrent nasal polyps is a cardinal feature of AERD

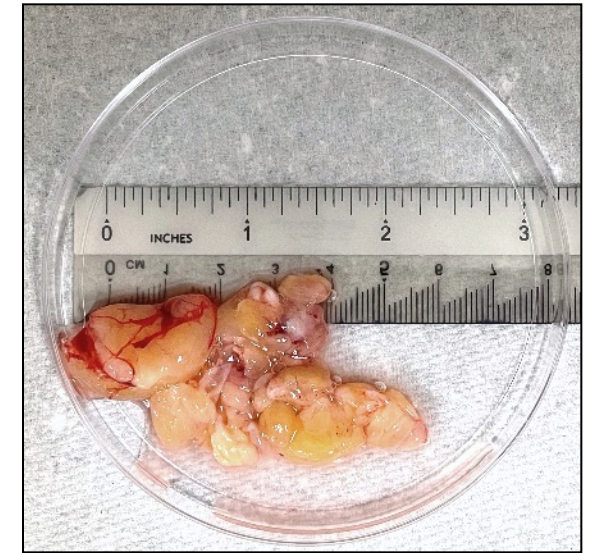
Typical appearance of polyps on rhinoscopy, and can be very large



Nasal polyps on rhinoscopy. 2015. – Selig, YK.



Nasal polyps excised.
2016 – Bhattacharyya, N.



Nasal polyps excised.
2022 – Lee, S.

Surgical histories from patients at the BWH AERD Center

History of polyp surgery:

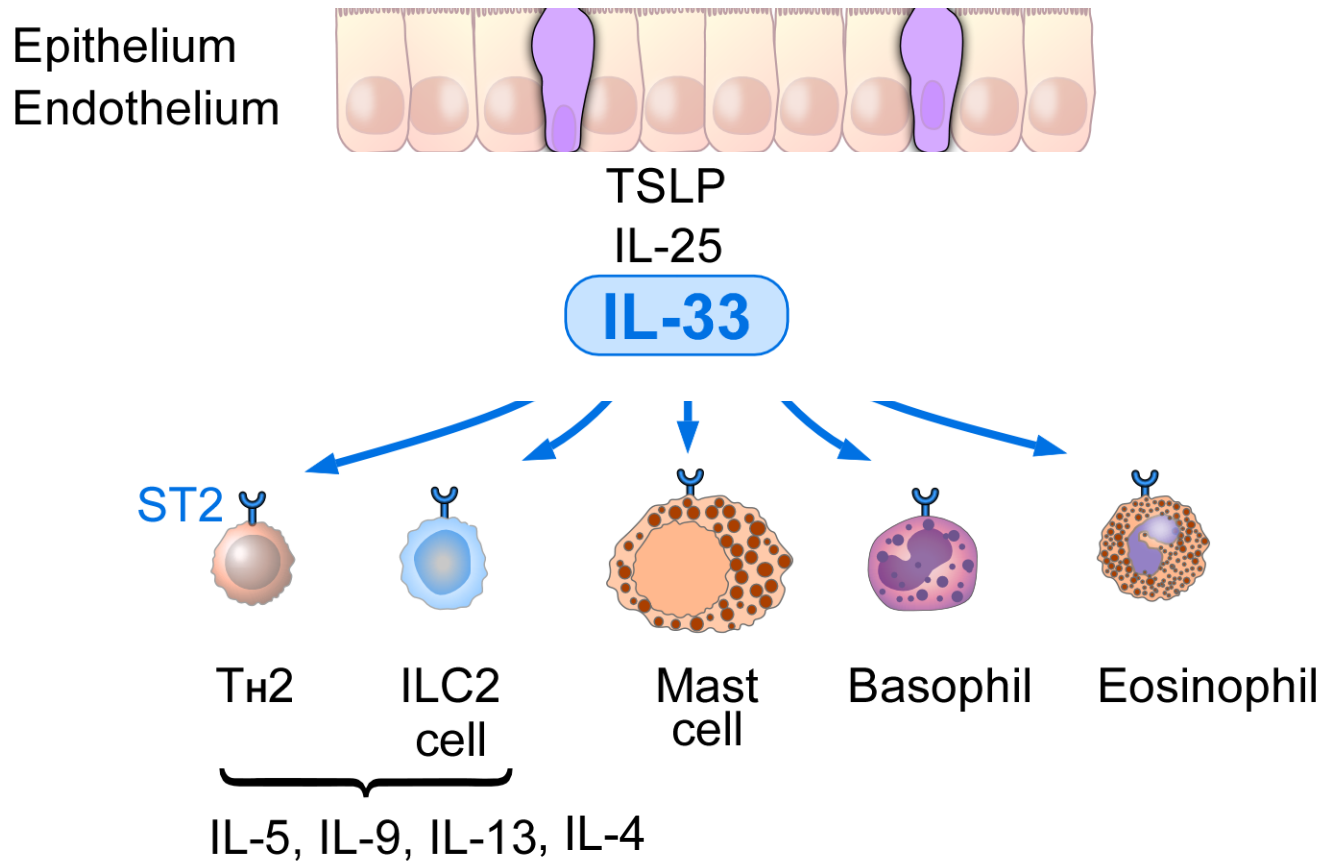
- 60% have had ≥ 2 surgeries
- 10% have had ≥ 5 surgeries

Rate of polyp regrowth post-op:

- 50% report regrowth ≤ 6 months
- Only 15% report no regrowth > 2 years

Type 2 Inflammation (T2I)

Viruses, injury, parasites, allergens



Epithelial metaplasia and gene induction (*INOS*, *CLCA3*, *MUC5AC*, *ALOX15*)

Tissue eosinophilia

IgE production

Mast cell hyperplasia and activation

Moffat MF, et al. NEJM 2010

Allakverdi Z, JEM 2007

Guo Z, et al. J. Asthma 2014

Reh D, et al Am J. Rhinol 2014

SRS-A: K. Frank Austen

Reprint Series
9 April 1982, Volume 216, pp. 196-198

SCIENCE

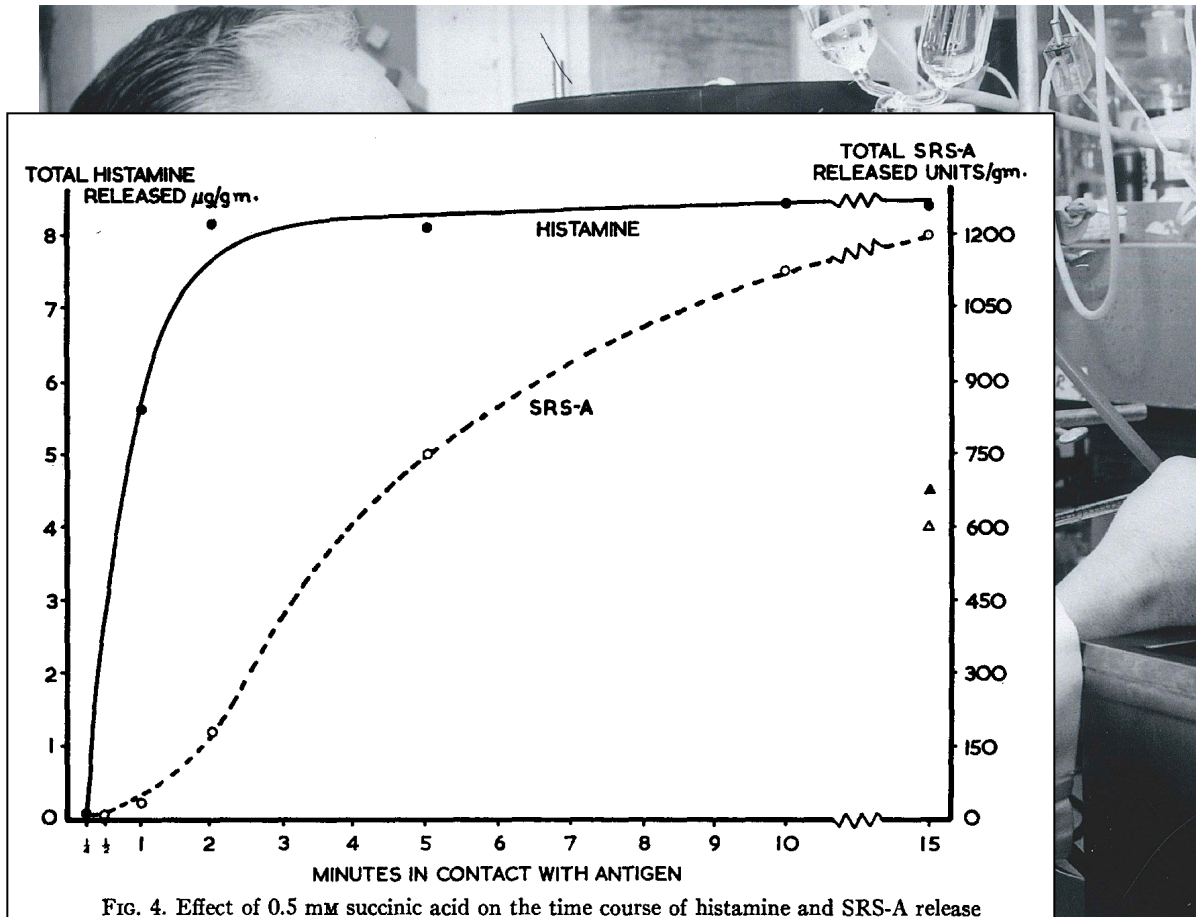
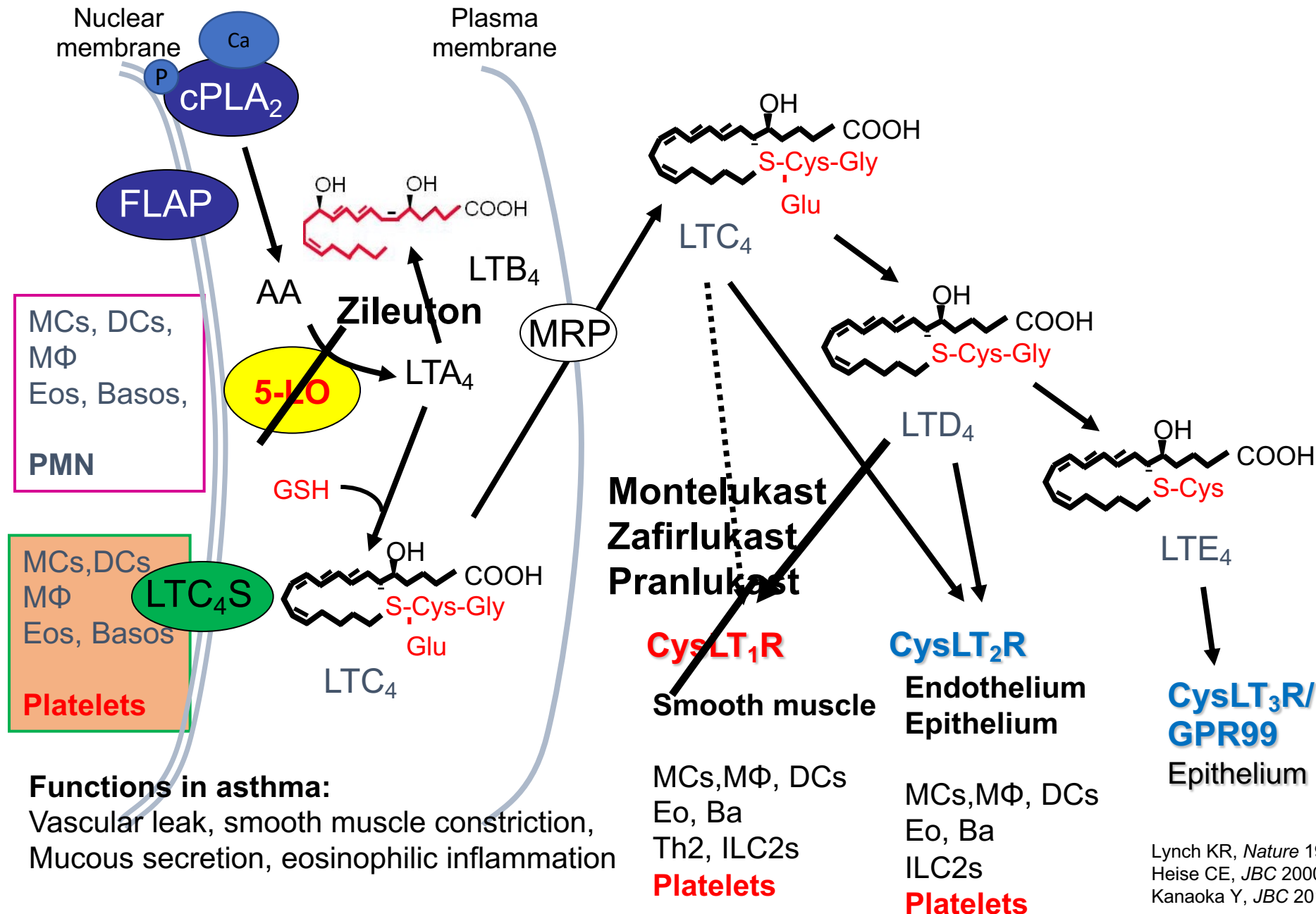


FIG. 4. Effect of 0.5 mM succinic acid on the time course of histamine and SRS-A release after addition of antigen. The solid and open triangles respectively indicate the anaphylactic release of histamine and SRS-A from control tissue incubated in normal Tyrode's solution.

Bronchoconstrictor Effects of Leukotriene C in Humans

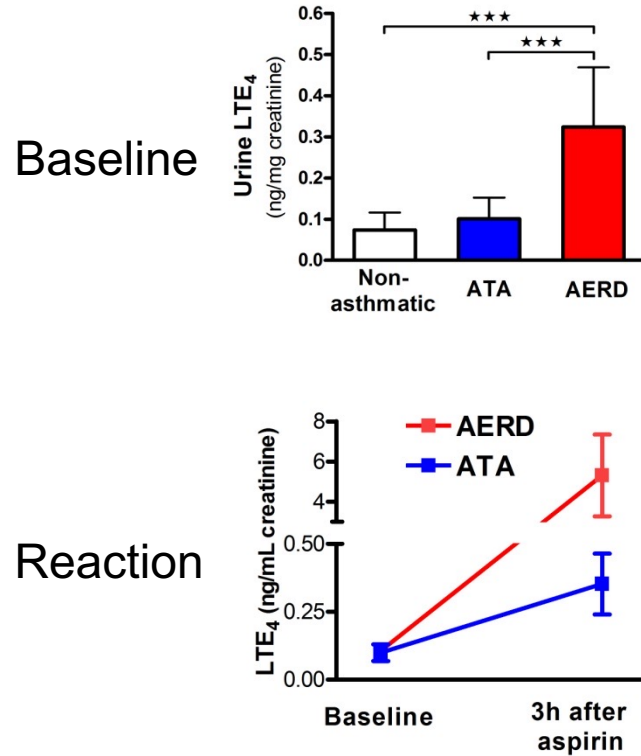
J. Woodrow Weiss, Jeffrey M. Drazen, Nancy Coles, E. Regis McFadden, Jr., Peter F. Weller, E. J. Corey, Robert A. Lewis, and K. F. Austen

Cysteinyl Leukotrienes (cysLTs) and their Receptors

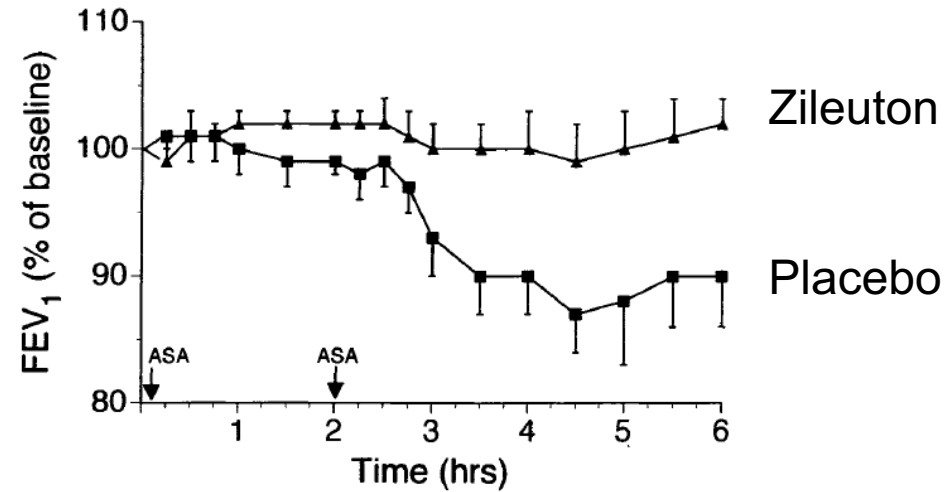


Importance of cysLTs in AERD and Reactions to ASA

Urinary LTE₄



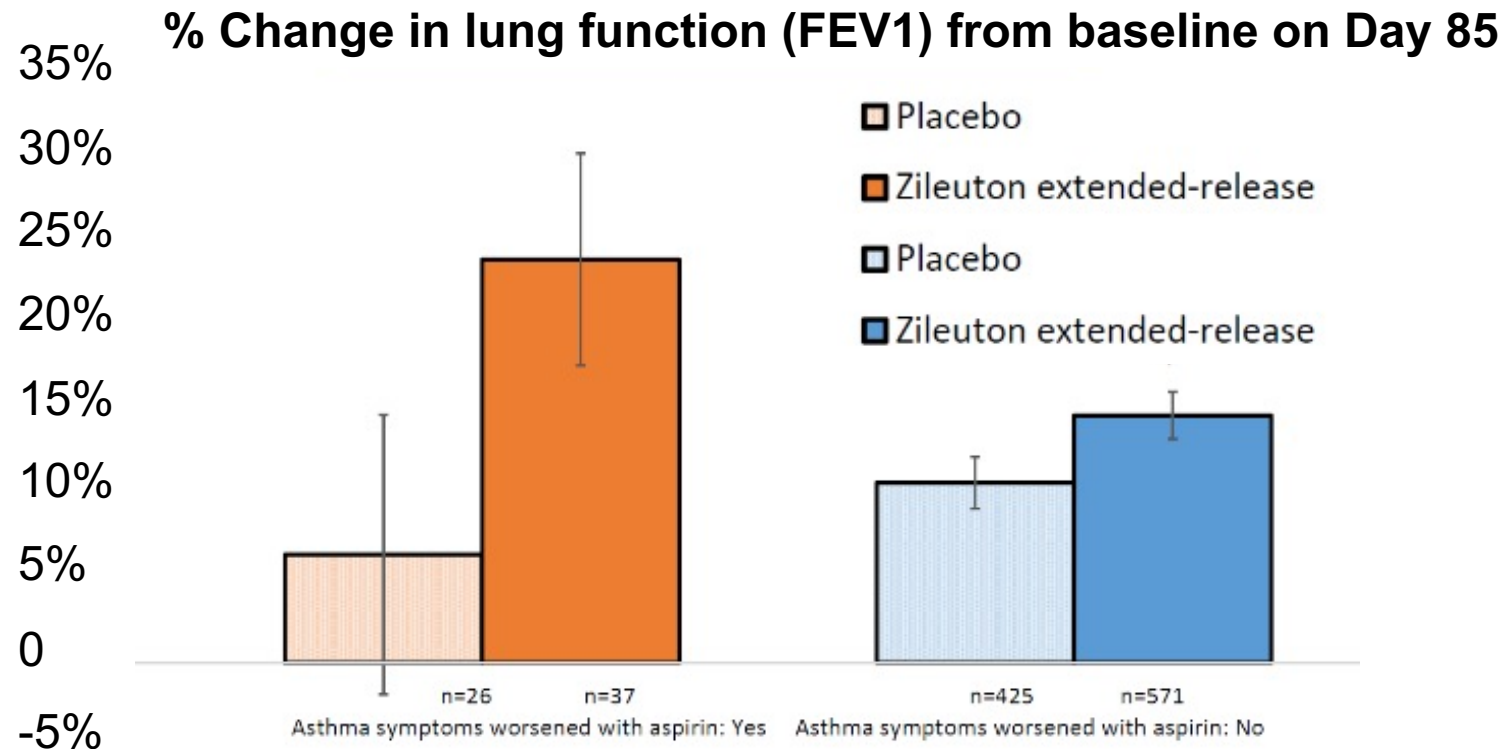
Effect of 5-LO blockade on lung function



*CysLT₁R antagonists also attenuate bronchoconstriction but not extrapulmonary features of reactions

Zileuton is more effective in patients with AERD than in aspirin-tolerant asthma

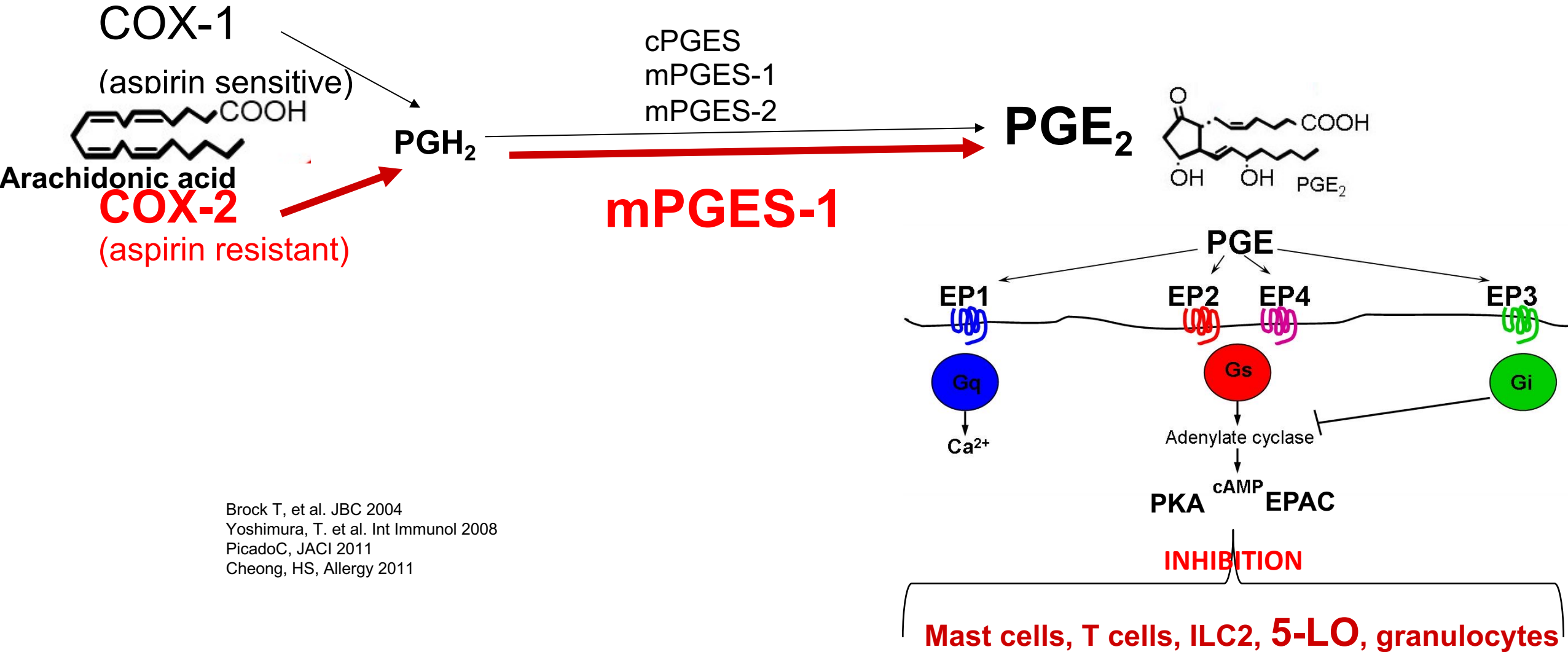
“Efficacy of Zileuton in Patients with Asthma and History of Aspirin Sensitivity: A Retrospective Analysis of Data from Two Phase 3 Studies”



AERD patients

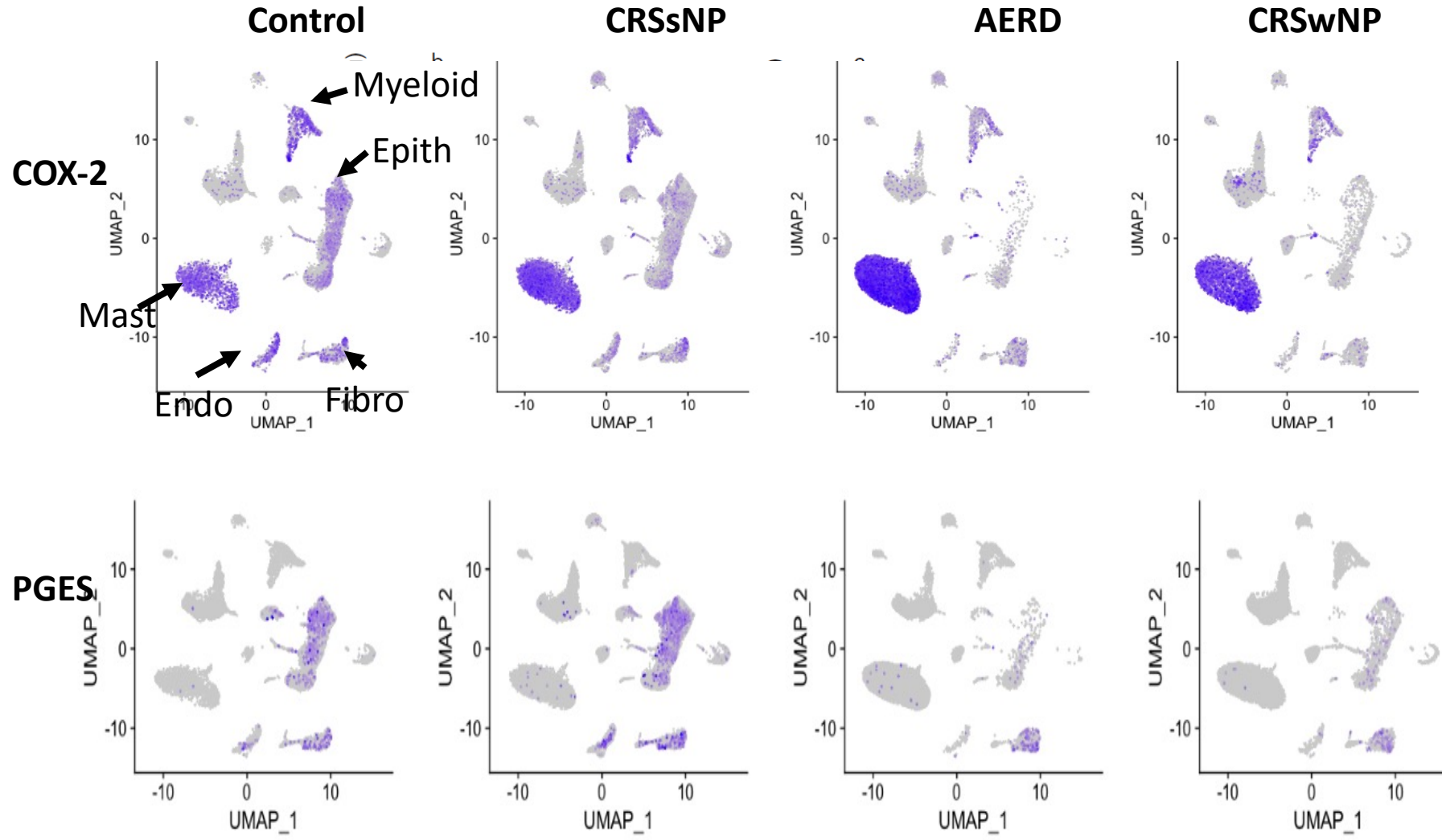
Prostaglandin E₂ (PGE₂)

Macrophages, epithelium, fibroblasts



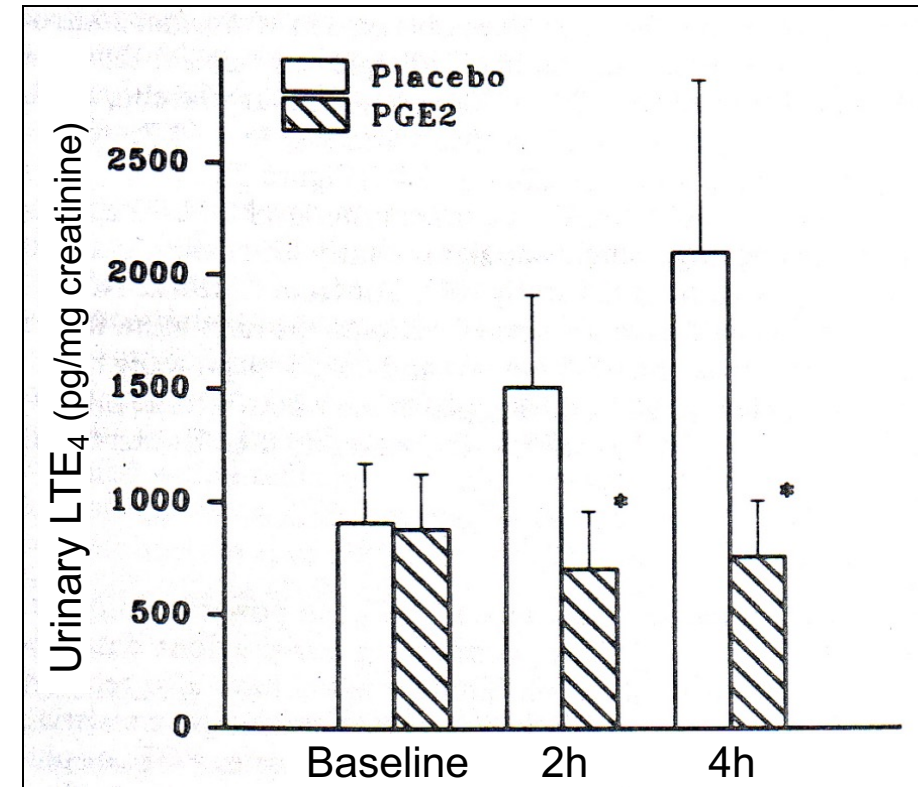
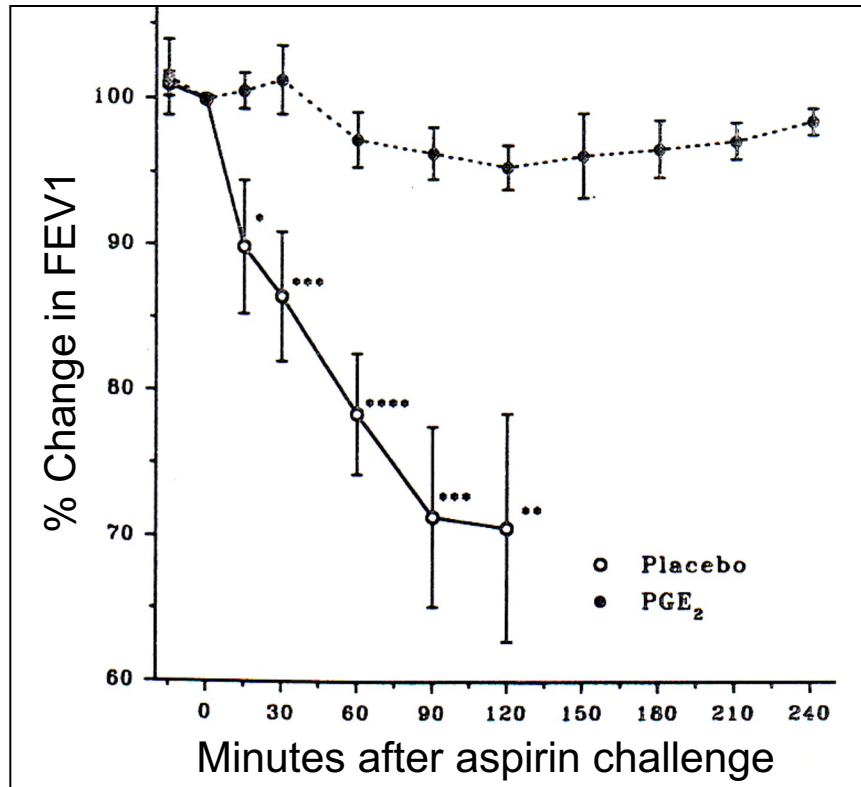
Brock T, et al. JBC 2004
Yoshimura, T. et al. Int Immunol 2008
PicadoC, JACI 2011
Cheong, HS, Allergy 2011

Deficient respiratory PGE₂ production is a feature of AERD/CRSwNP



Yoshimura et al, Allergology Int. 2008
Dwyer, D, unpublished

Inhaled PGE₂ prevents aspirin-induced bronchoconstriction and urinary LTE₄ excretion



AERD-like PGI₂A

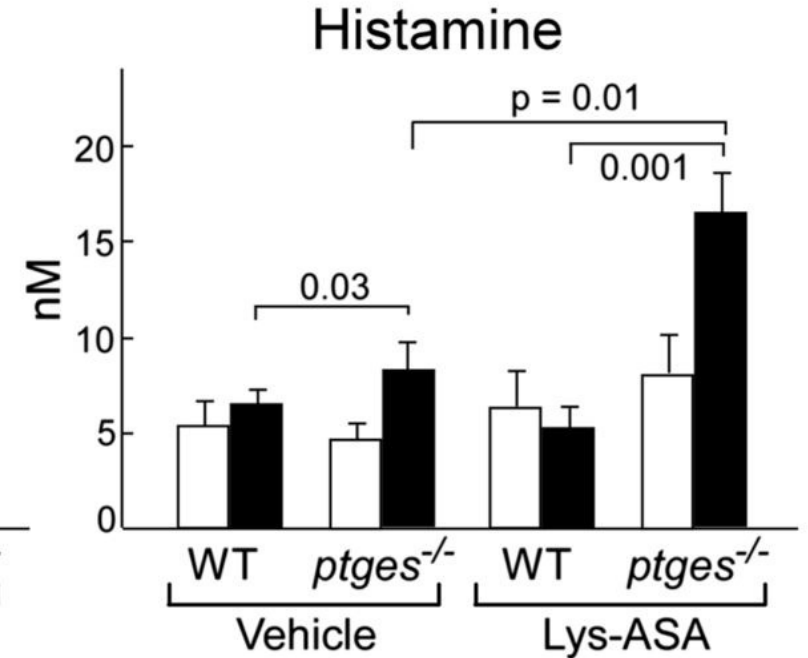
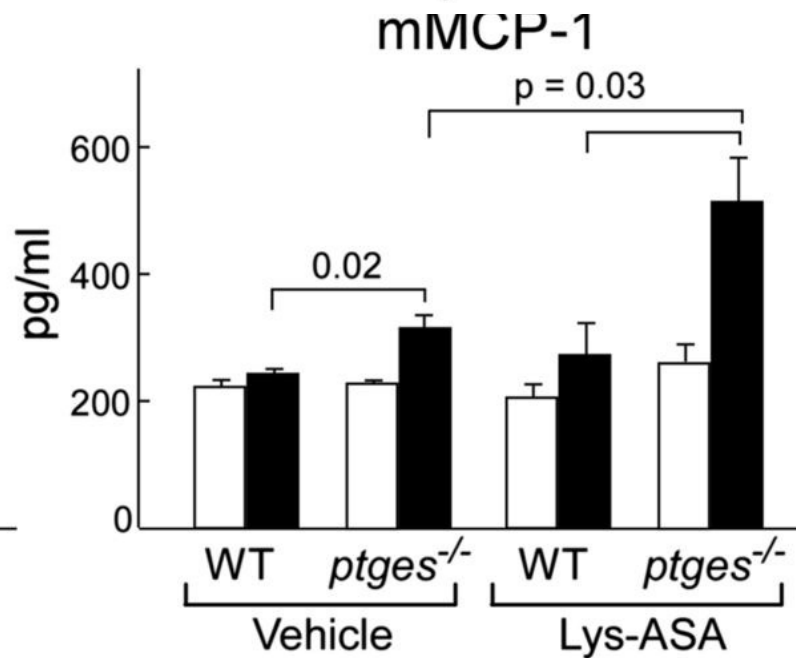
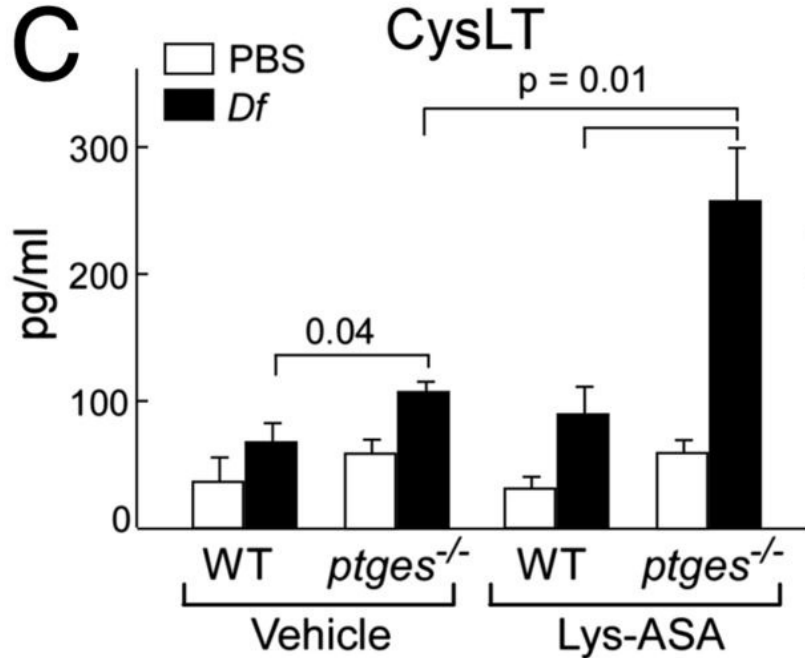
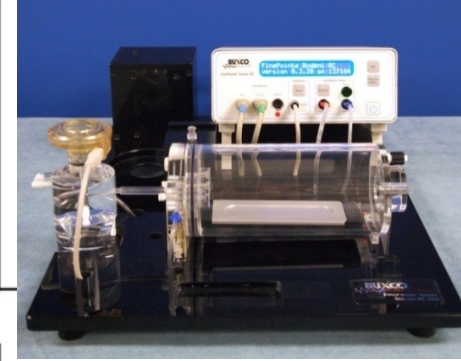
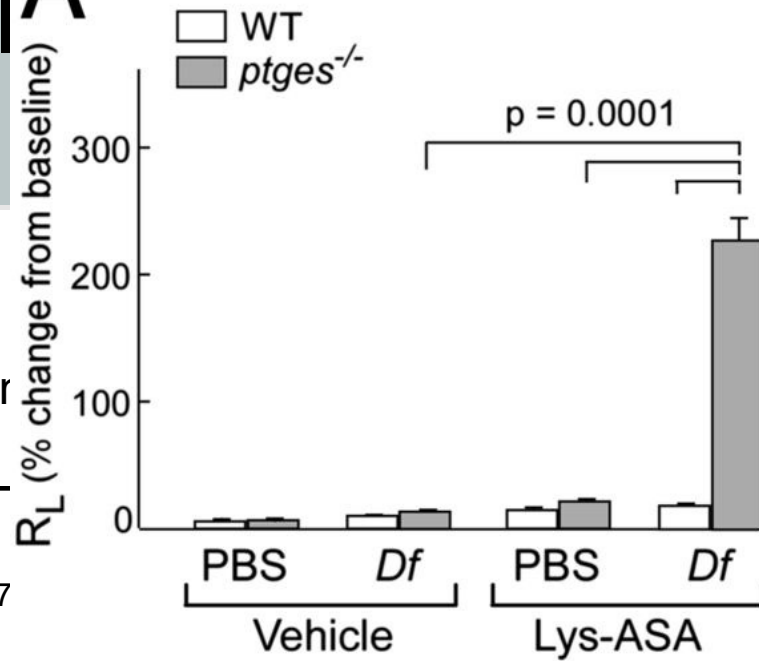
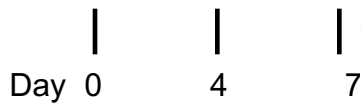
display an IL-33/ST2-type



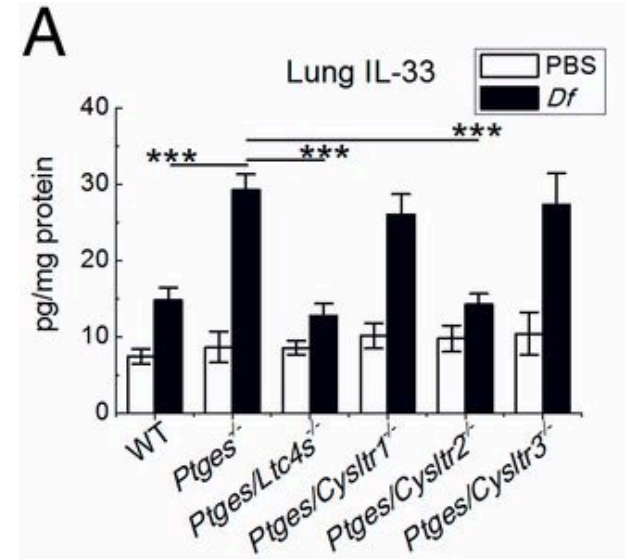
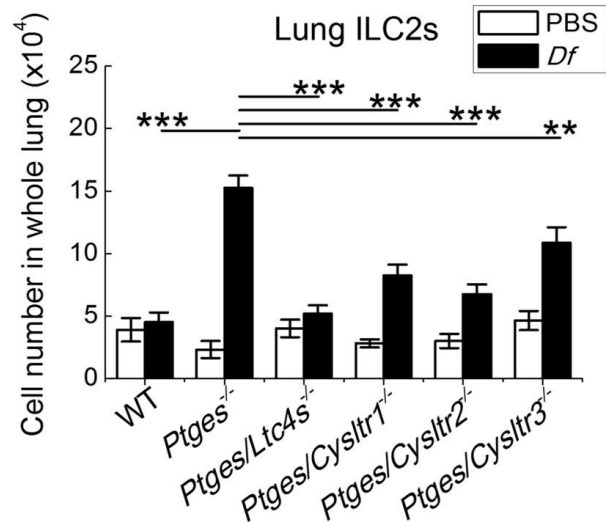
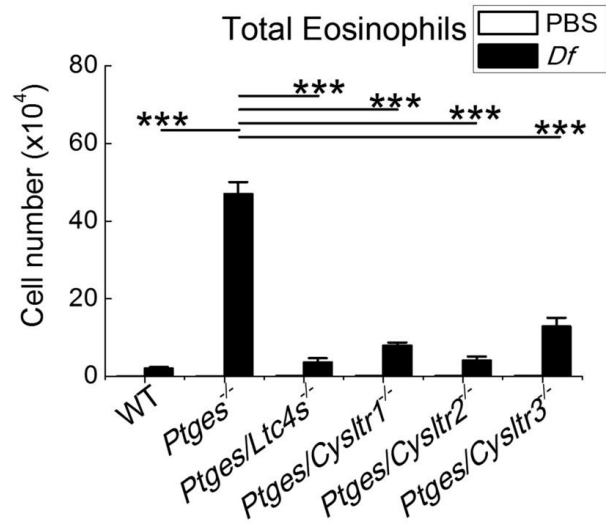
Tao Liu

Model

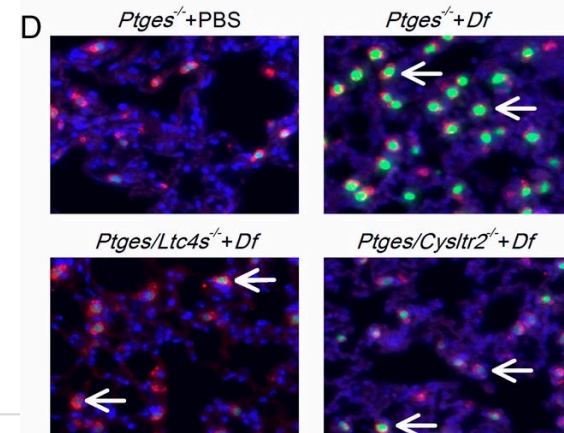
- WT C57BL/6 are



Cysteinyl leukotrienes drive type 2 inflammation in PGE₂-insufficient “AERD-like” mice

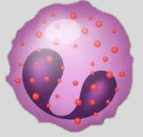


IL-33 immunofluorescence

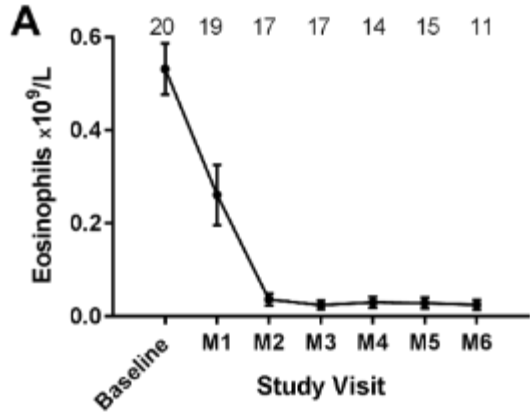


IL-33
SPC

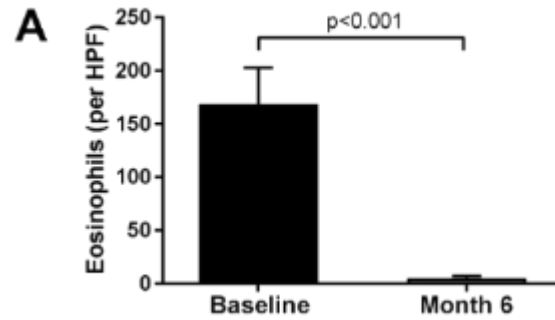
Dexramipexole in CRSwNP – how important are eosinophils?



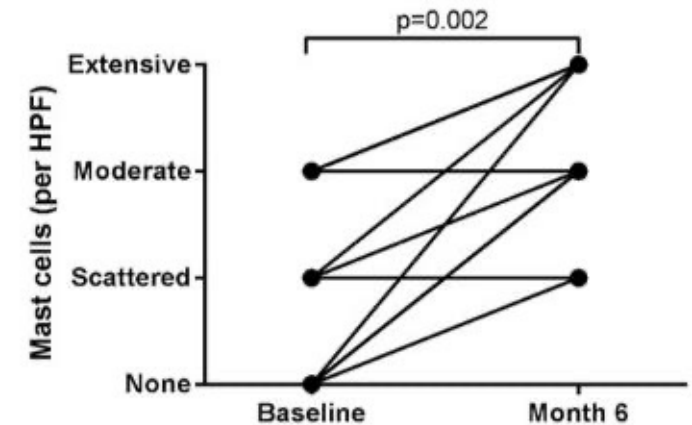
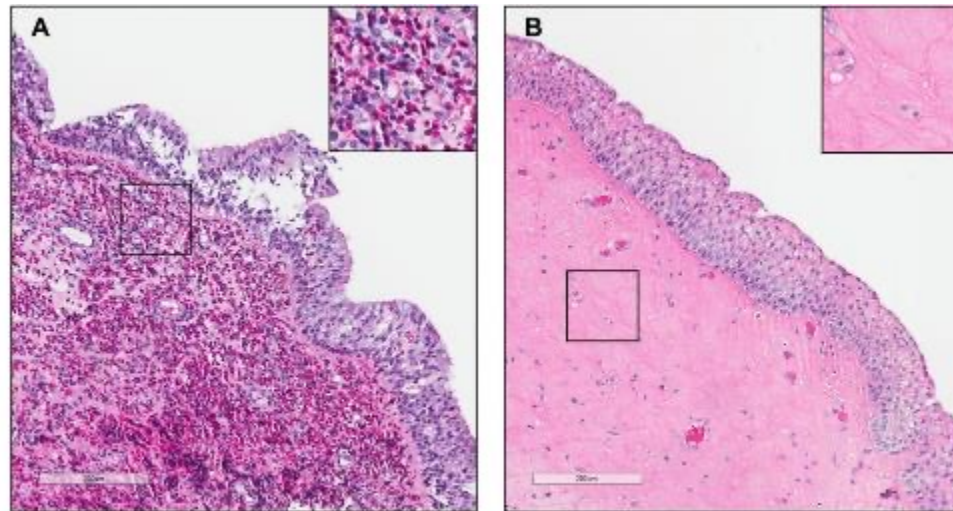
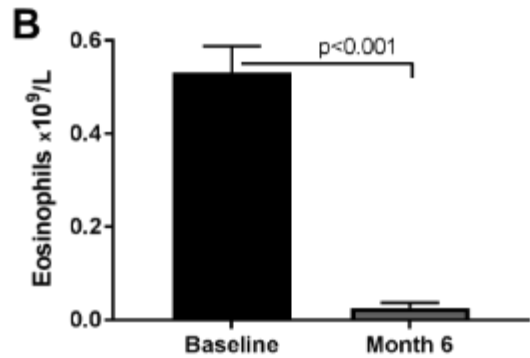
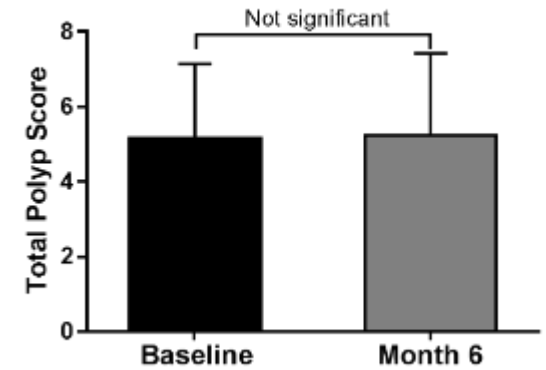
Blood eosinophils decrease



Polyp eosinophils decrease

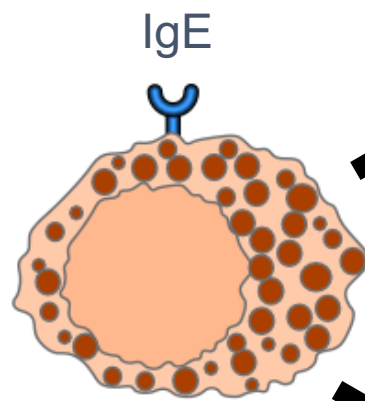


No improvement in polyp size



Mast cell activators and products

ADAPTIVE IMMUNITY (allergy)



Preformed Mediators (Minutes)

Histamine
Proteases
TNF- α

Newly Formed Eicosanoids (Minutes)

LTC₄
PGD₂,
TXA₂, LTB₄

Induced Cytokines/Chemokines (Hours)

IL-3
IL-4 MIP-1 α
IL-5 MIP-1 β
IL-6 MCP-1
IL-8 TNF- α
IL-9 IL-25
IL-11 IL-33
IL-13

Early
(Edema,
Broncho-Constriction,
Vasopermeability)

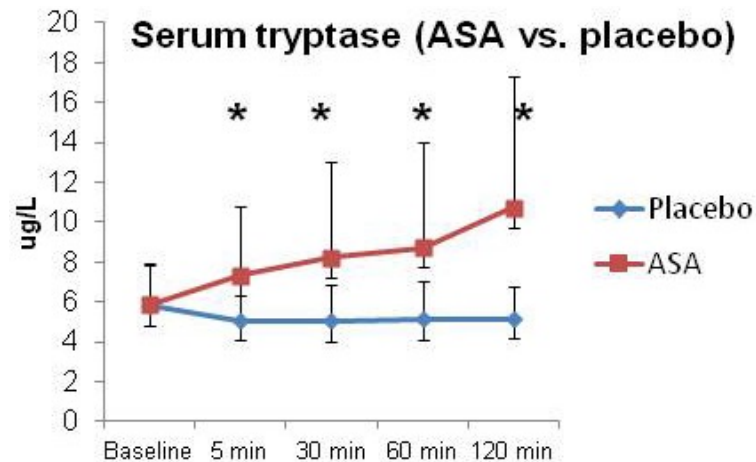
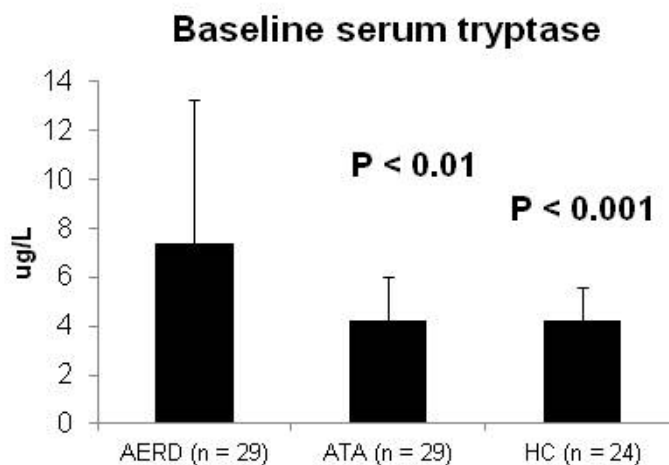
Late
(Inflammation,
Cell Recruitment, AHR)

INNATE IMMUNITY

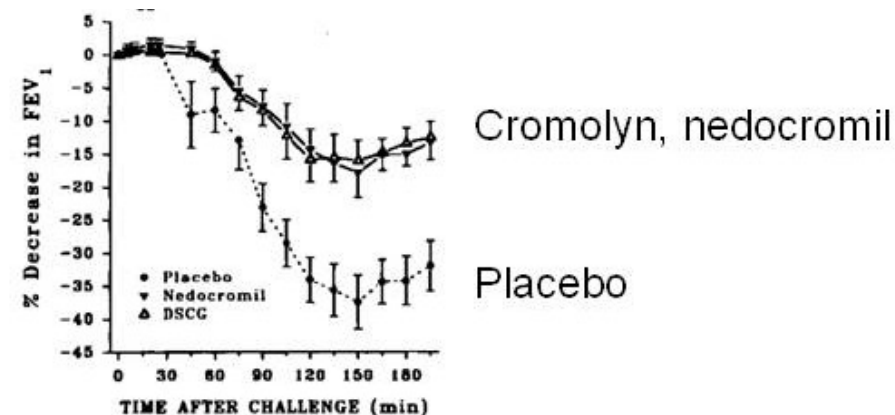
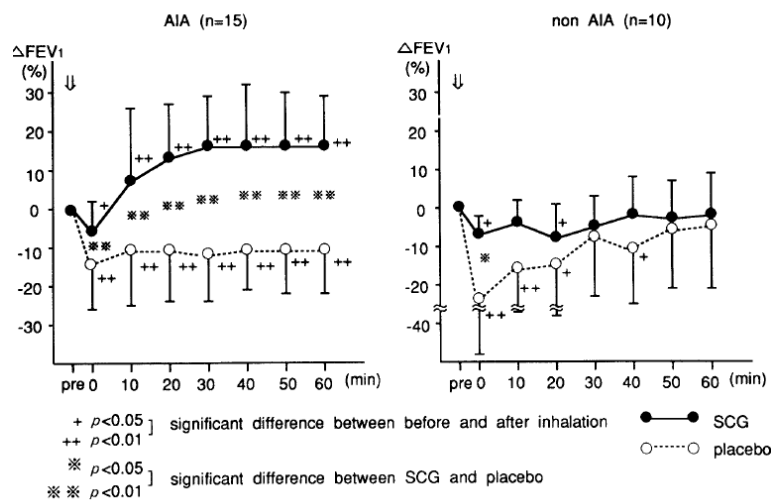
- Microbial products
- Complement components
- Antimicrobial peptides (MRGPRX2)
- **Innate cytokines (IL-33)**



Mast cell activation contributes to airway caliber in AERD (baseline and reaction)

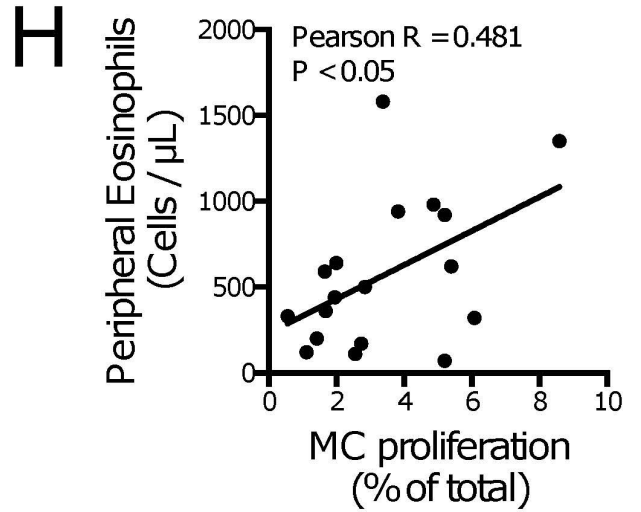
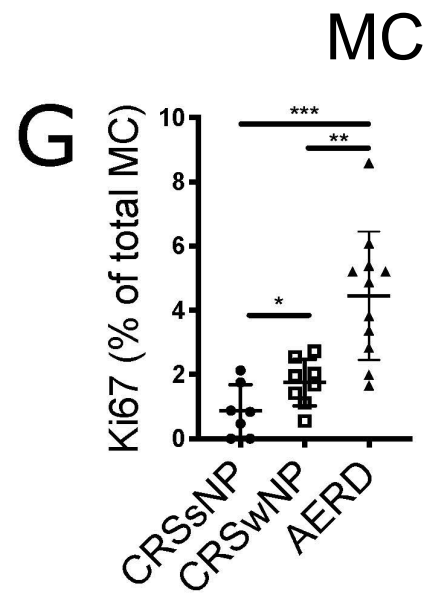
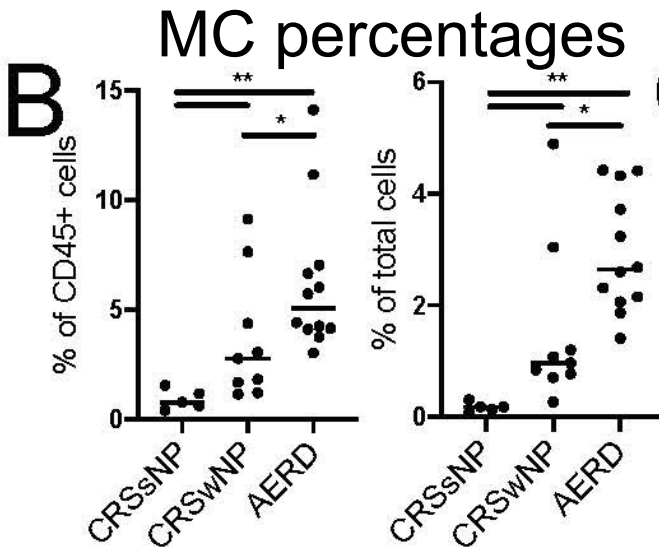
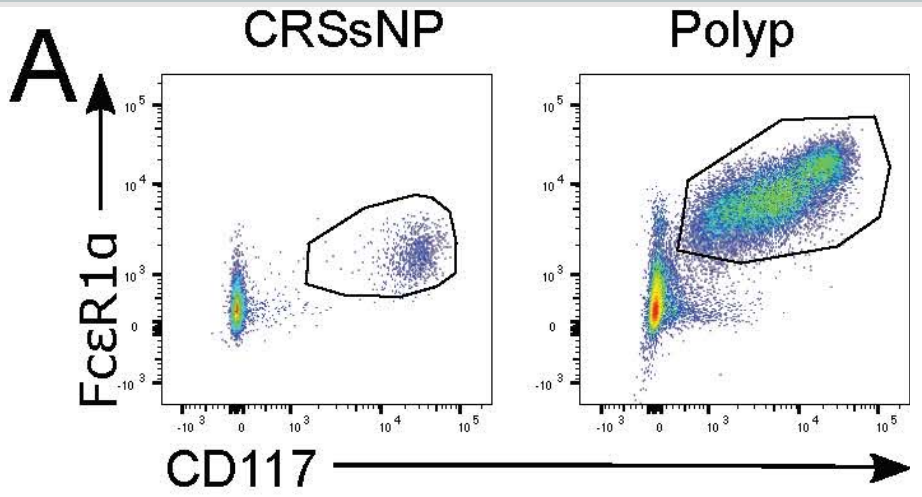


Effects of mast cell stabilizers



Adapted from Bochenek G., et al., *JACI* 2003
 Robuschi *AJRCCM* 1997
 Imokawa S, *Aerugi* 2002

Mast cell hyperplasia and proliferation in AERD



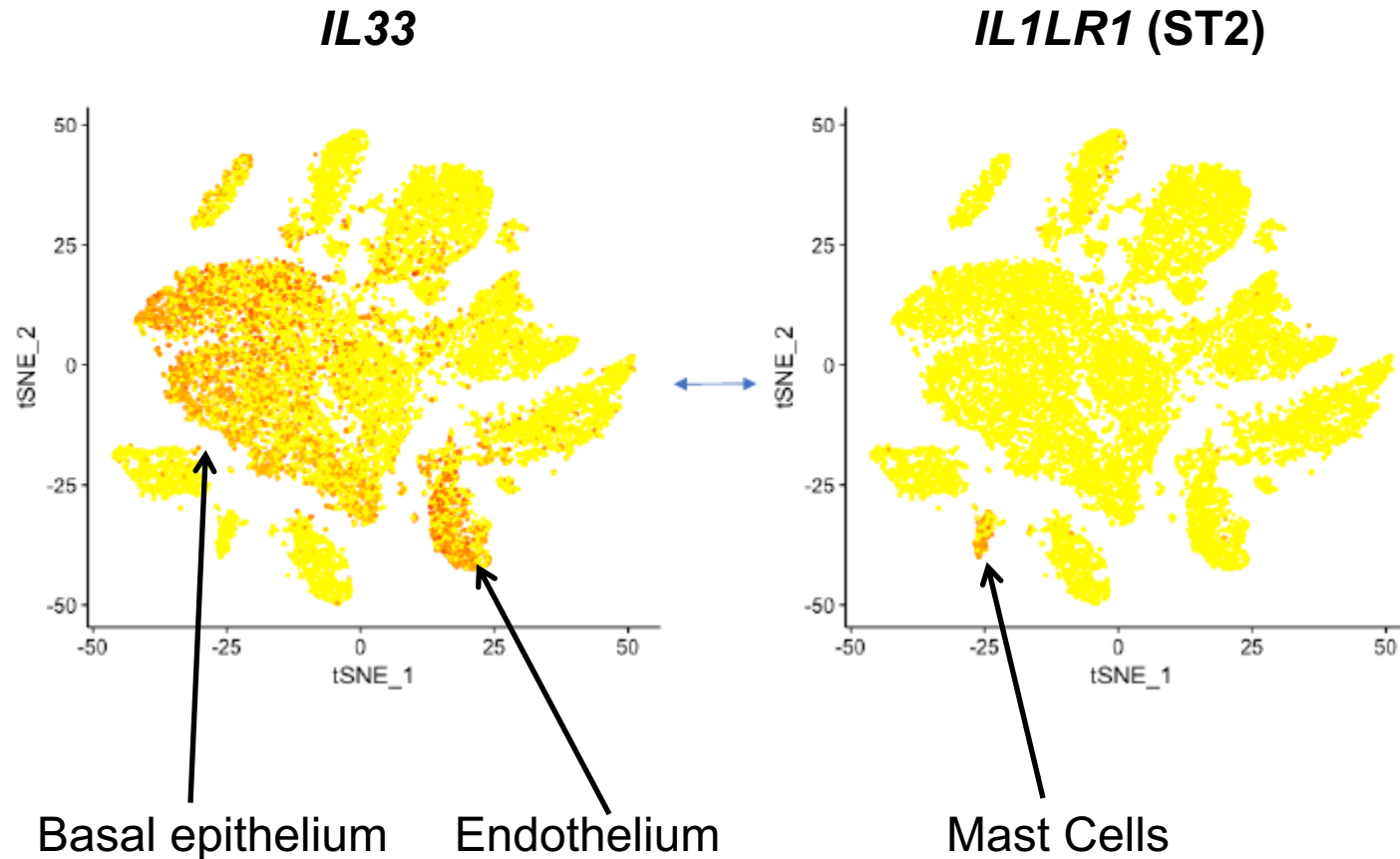
Single cell RNAseq analysis suggests an IL-33/MC axis in CRSwNP/AERD



Jose Ordovas-Montanez



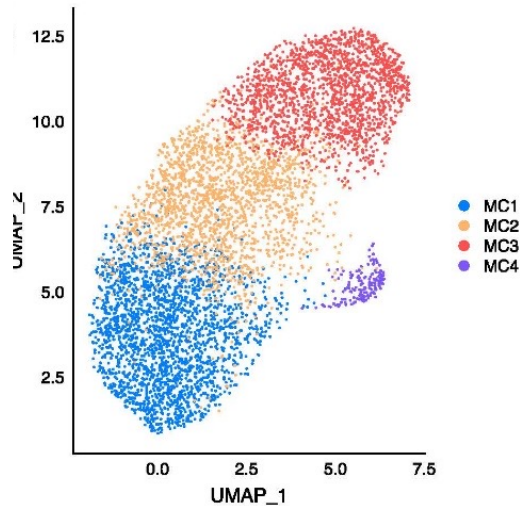
Dan Dwyer



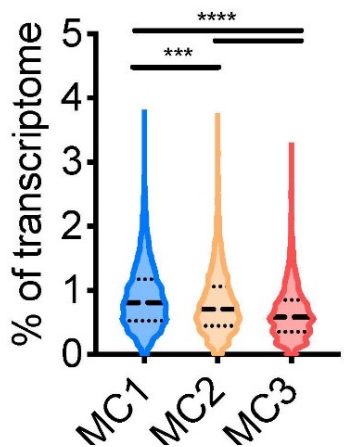
Ordovas Montanez J, et al, Nature 2018
Dwyer D, et al, Science Immunol 2021

Evidence for both IgE- and IL-33-driven mast cell activation in AERD/CRSwNP

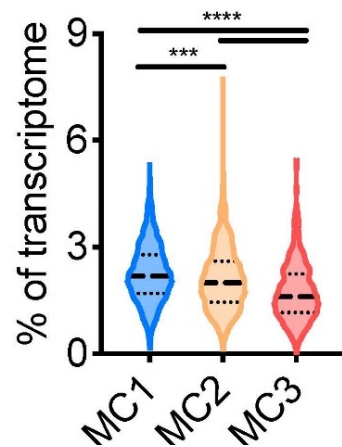
Nasal polyp
Mast cell clusters



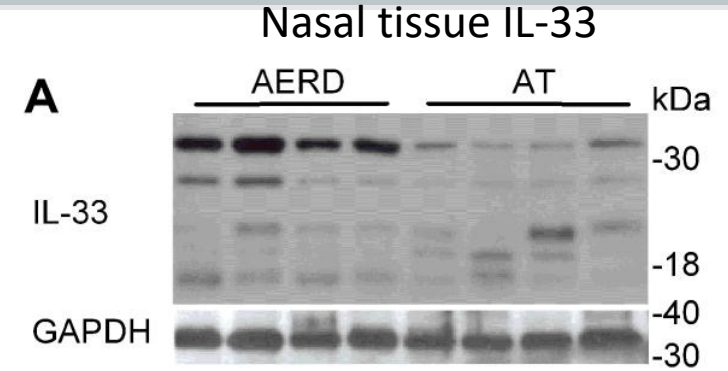
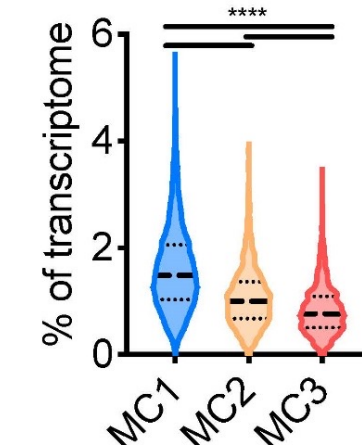
IgE activation signature



IL33 activation signature

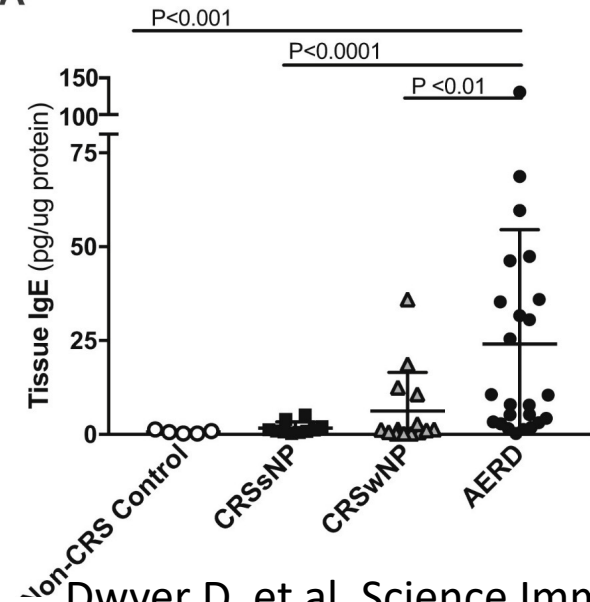


Shared activation signature



Nasal tissue IgE levels

A

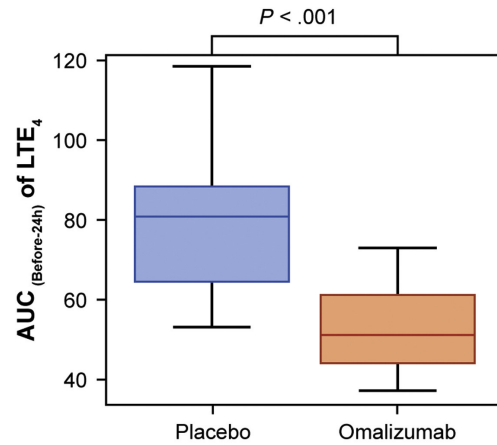


Dwyer D, et al. Science Immunol 2021

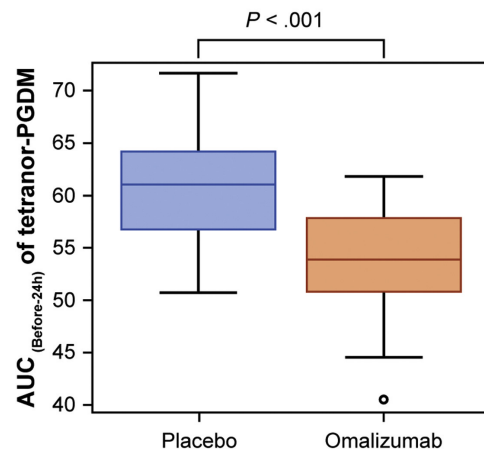
Buchheit K, et al, JACI 2020

Liu T, et al, J Immunol 2015

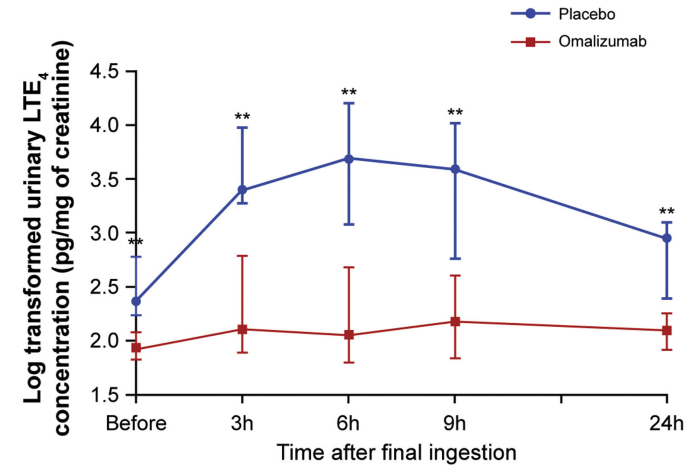
Anti-IgE (omalizumab) decreases reaction severity and mast cell-derived lipid mediators in AERD



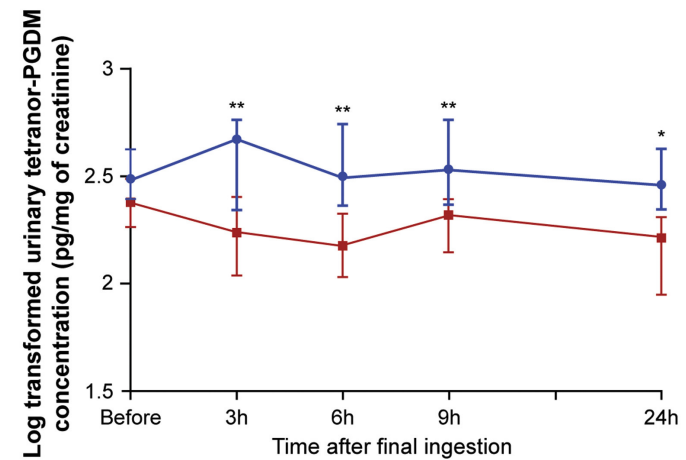
A



B



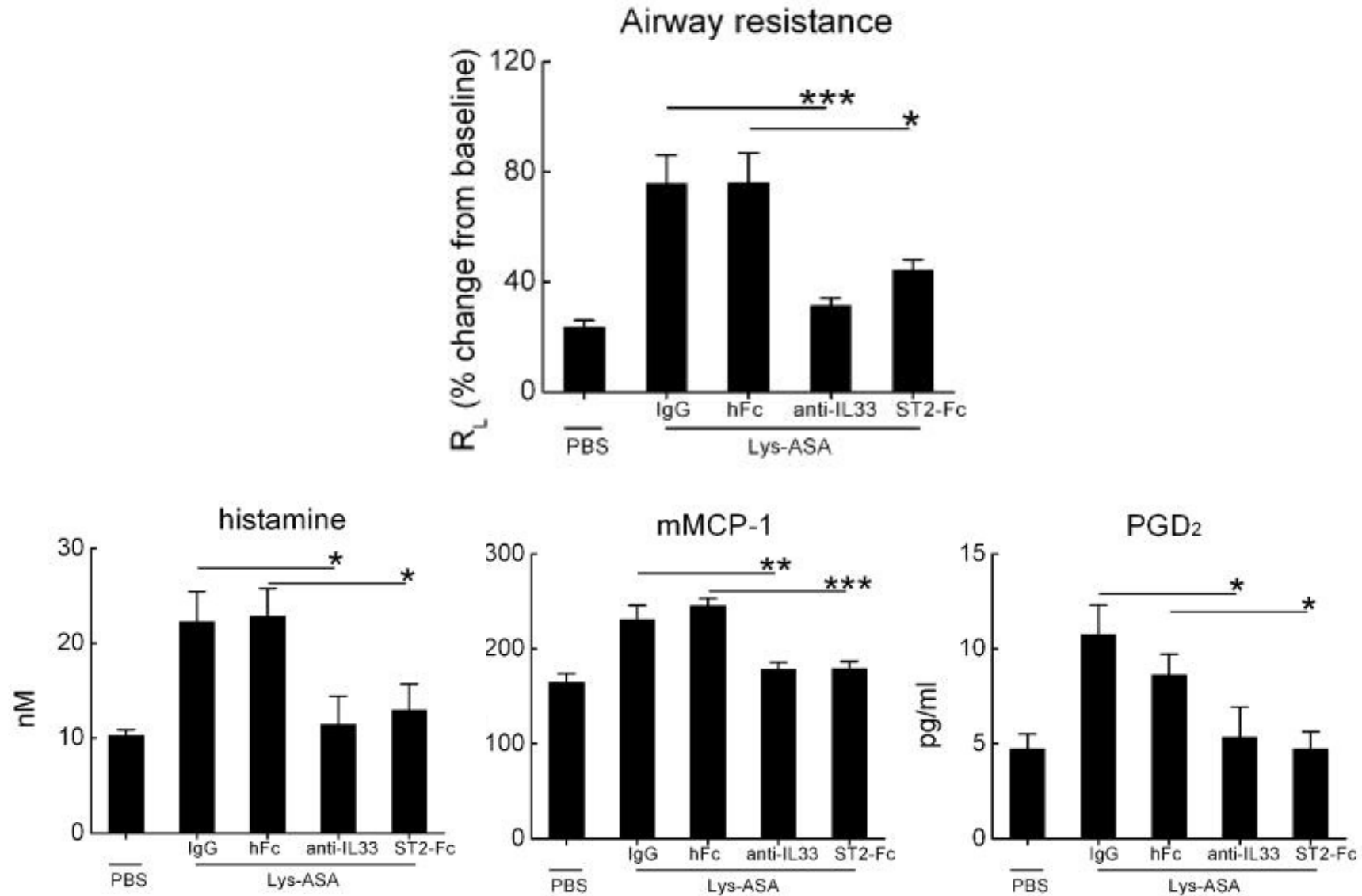
C



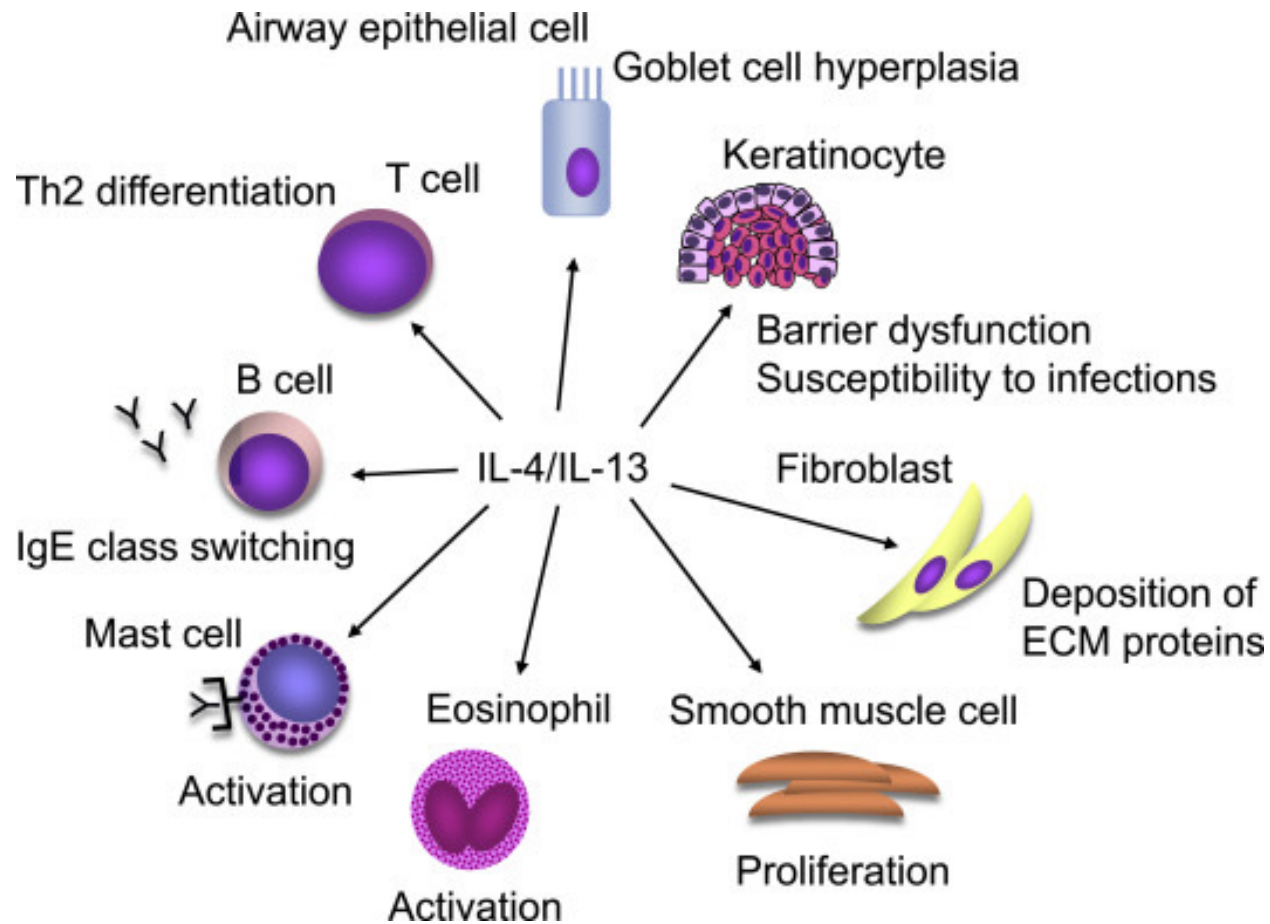
D



AERD-like PGE₂-deficient mice display an IL-33/ST2-dependent phenotype



IL-4 reactive cytokines in type 2 inflammation



IL-4/13 ⇒ key cytokines that drive inflammation relevant to CRSwNP:

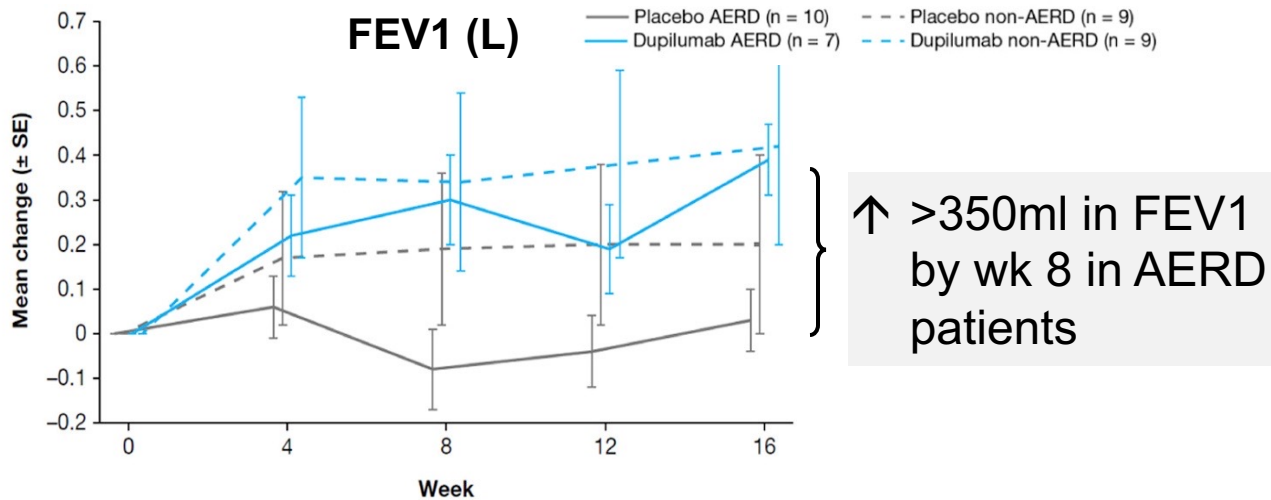
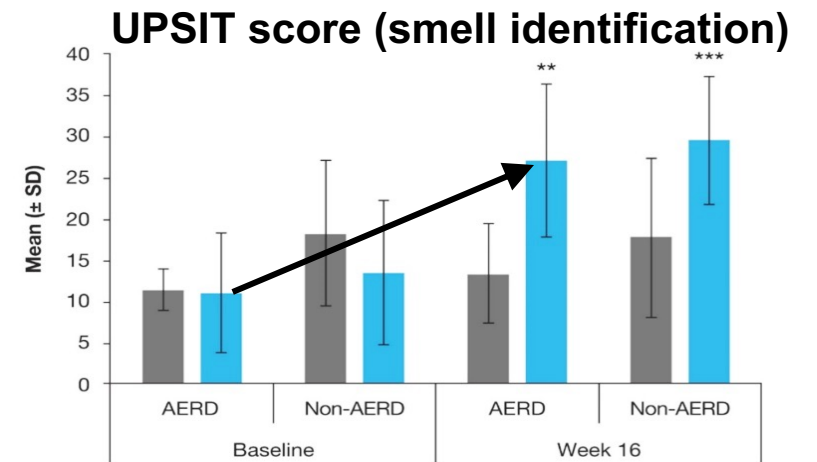
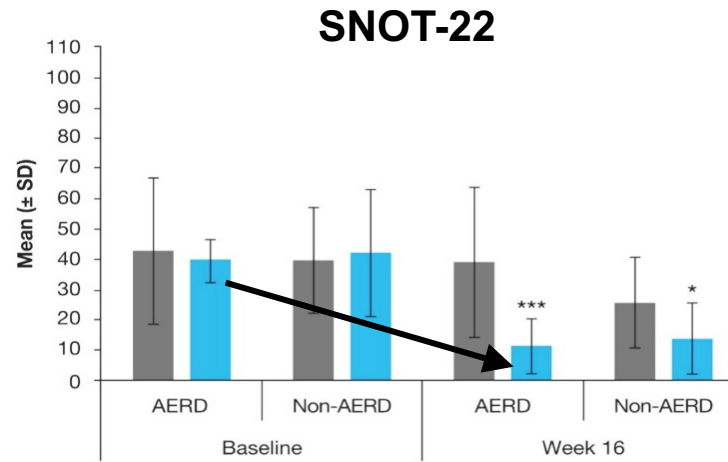
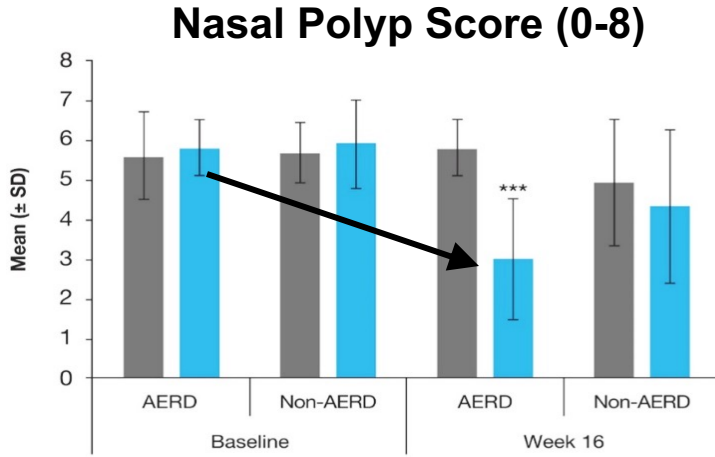
- **Epithelial basal cell reprogramming**
- **Basement membrane thickening**
- **Epithelial barrier disruption**
- **Eosinophil activation** in bone marrow
- **Mast cell priming for activation**, ↑IgE receptor expression
- **Inflammatory cell trafficking to tissues**
- **B cell class switching & ↑IgE production**

Dupilumab in AERD (Phase 2)

Re-analysis of Phase 2 study;
19/60 subjects had aspirin sensitivity



■ Dupilumab ■ Placebo



↑ >350ml in FEV1 by wk 8 in AERD patients

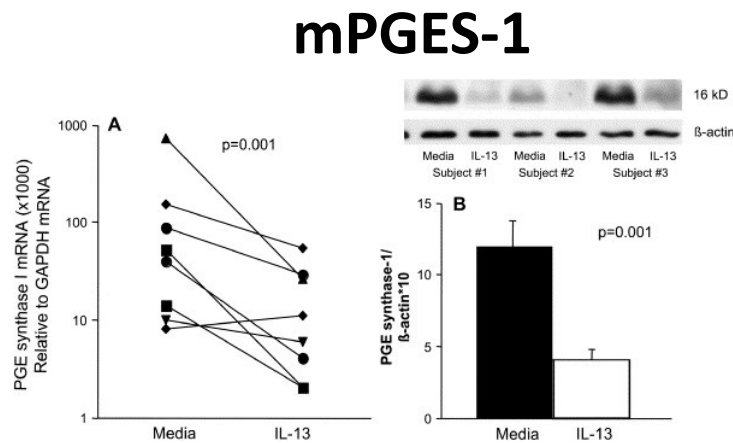
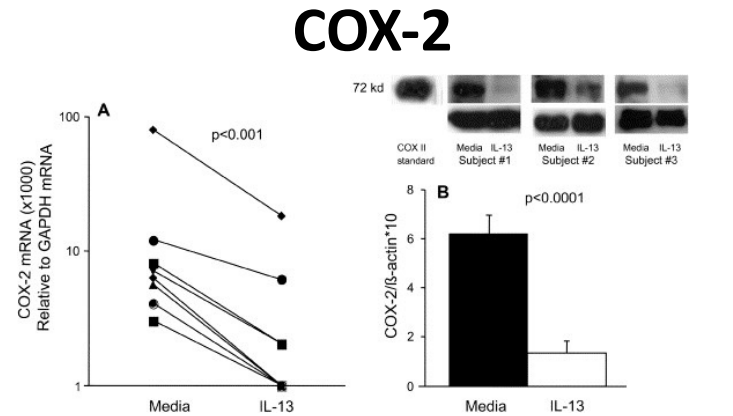
SINUS-52; Phase 3 nasal polyps

- 448 patients total
 - ↓ NP score of 2.06 at 24wks
 - Smell improvement (UPSIT) of 11 pts.
- 79 AERD patients
 - ↓ NP score of 2.54 at 24wks

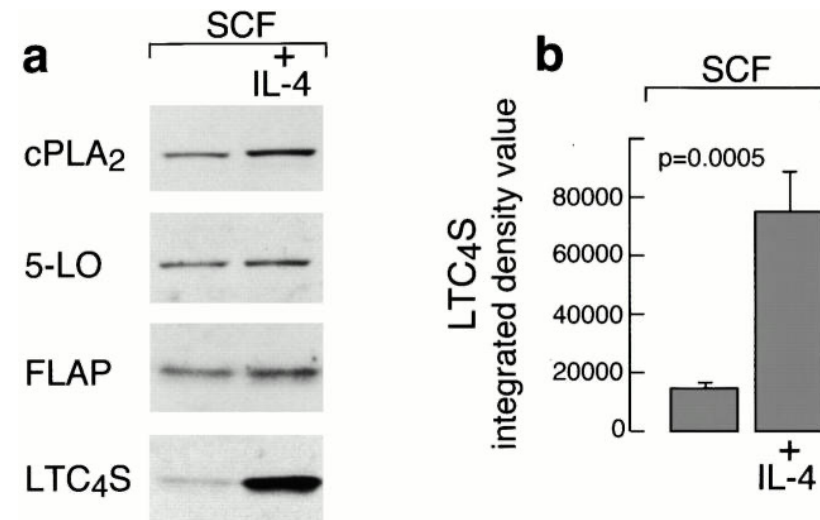
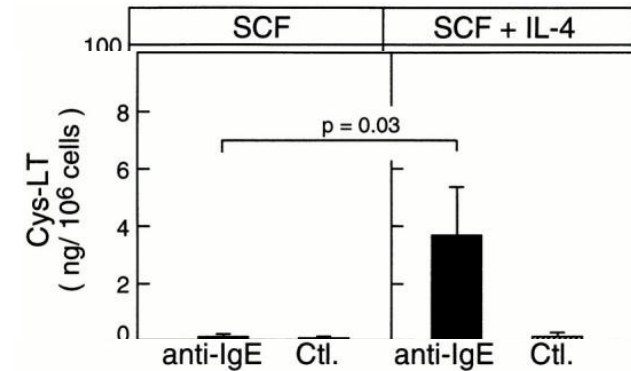
IL-4R-active cytokines suppress COX-2/mPGES-1 system and upregulate LTC₄ production

IL-13-stimulated bronchial epithelial cells

IL-4-stimulated mast cells



Trudeau J, et al, JACI 2006

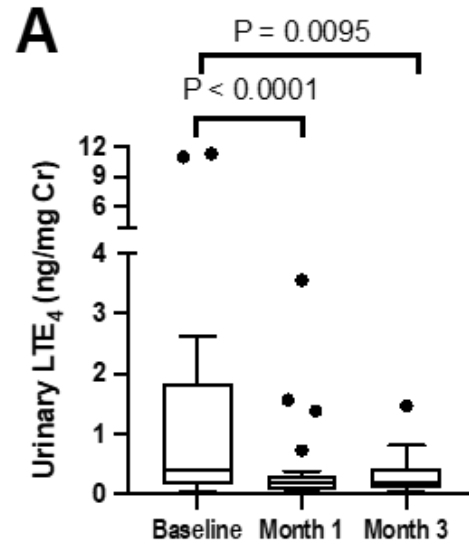


Hsieh F, et al, JEM 2001

Mechanisms of dupilumab-induced improvement in AERD – pilot trial

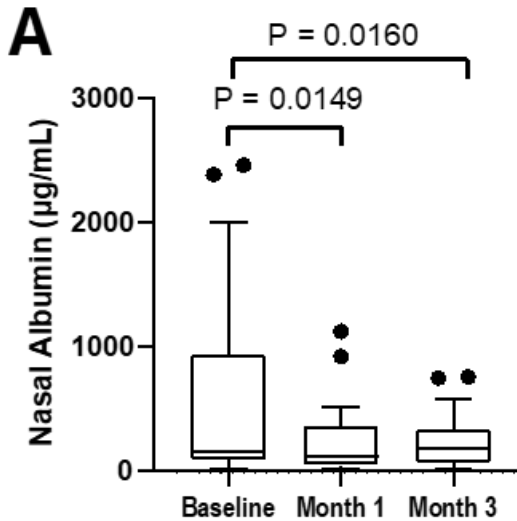
LTE₄

Urine

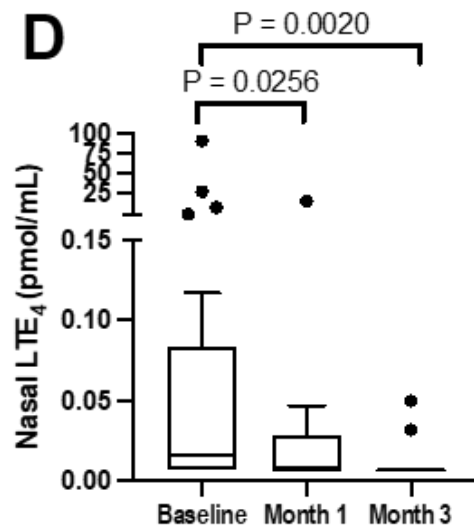


A

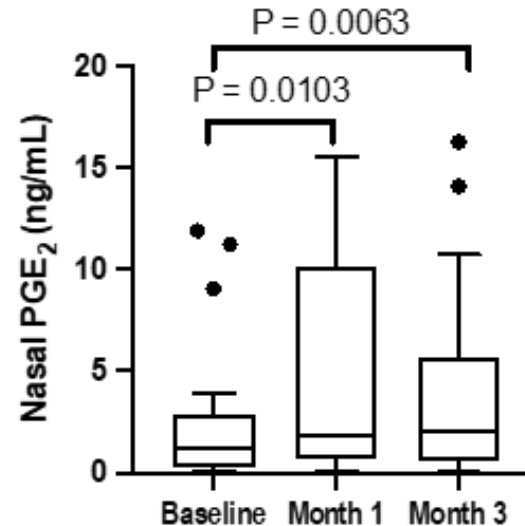
Nasal surface fluid albumin



Nasal surface fluid



Nasal surface fluid PGE₂



Summary

- AERD is prevalent and severe
- Type 2 respiratory inflammation is driven/amplified by high cysLTs, low PGE₂
- Deficient COX-2-PGE₂ likely responsible for reactions to COX-1-active drugs
- IL-4 receptor signaling contributes to characteristic disturbances in lipid mediators
- Eosinophils are prominent but role is not known
- Mast cell involvement very likely
- Biologics provide both therapeutic benefit and mechanistic insights

Acknowledgements

Funding

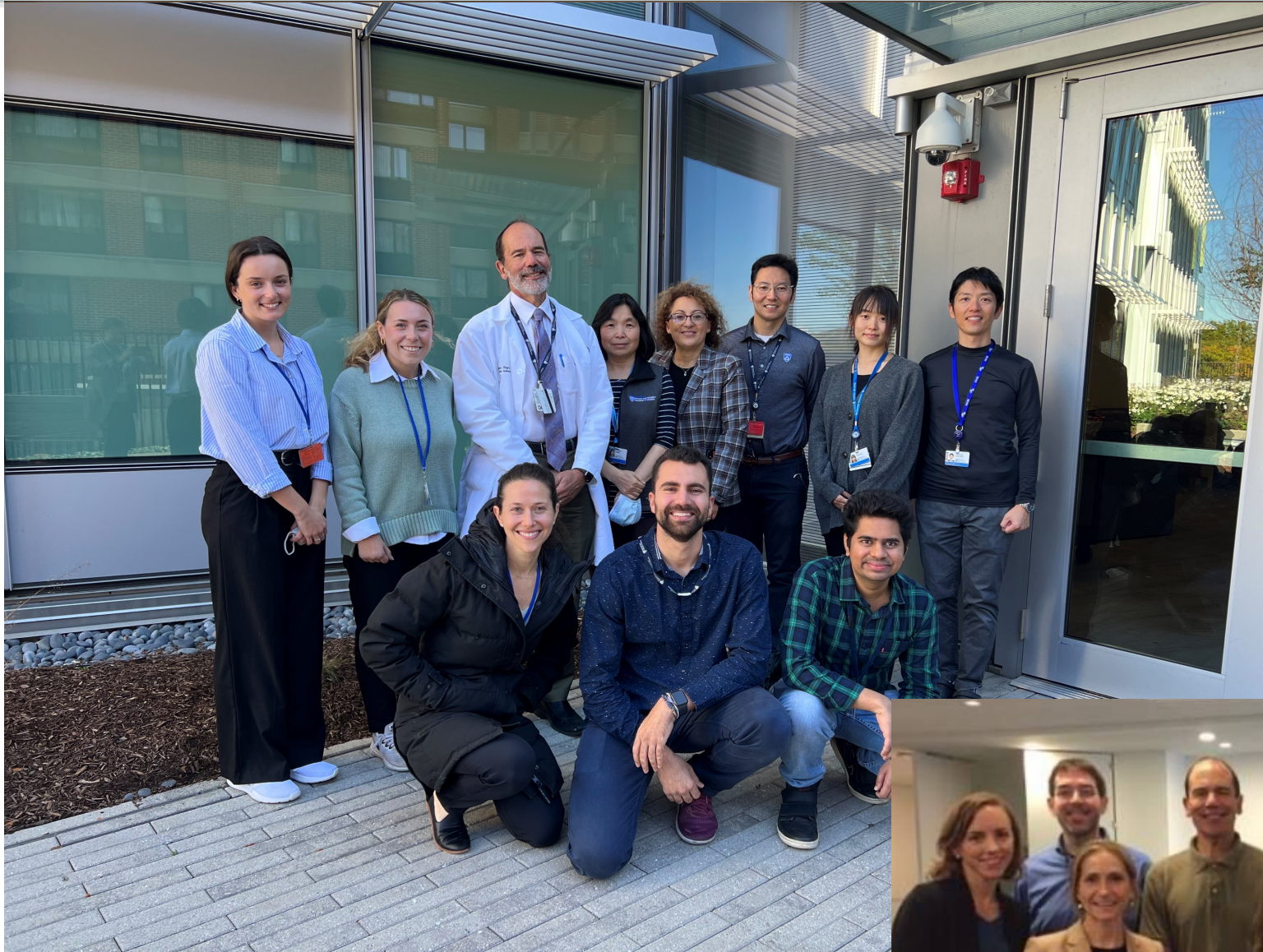


National Heart, Lung,
and Blood Institute



National Institute
of Allergy and
Infectious Diseases

Vinik, Kaye, and
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