Immunology and Pathophysiology of Asthma and COPD

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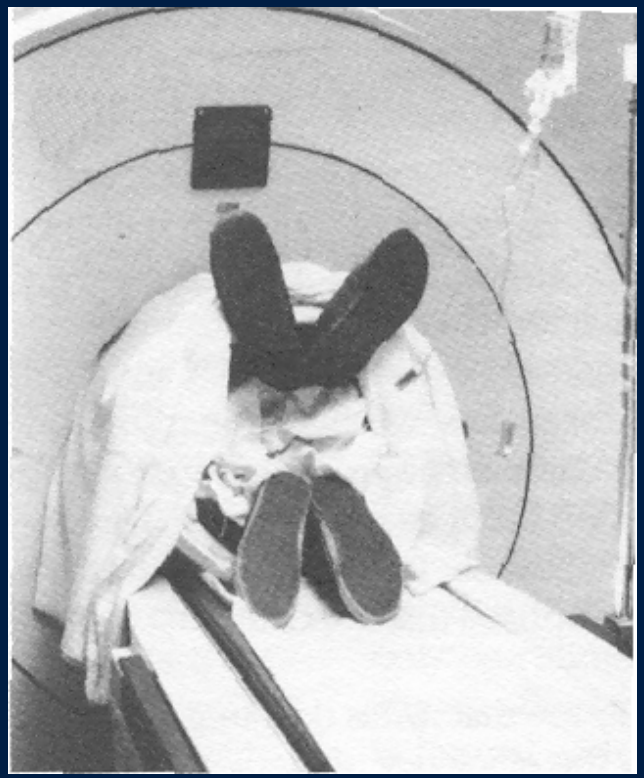
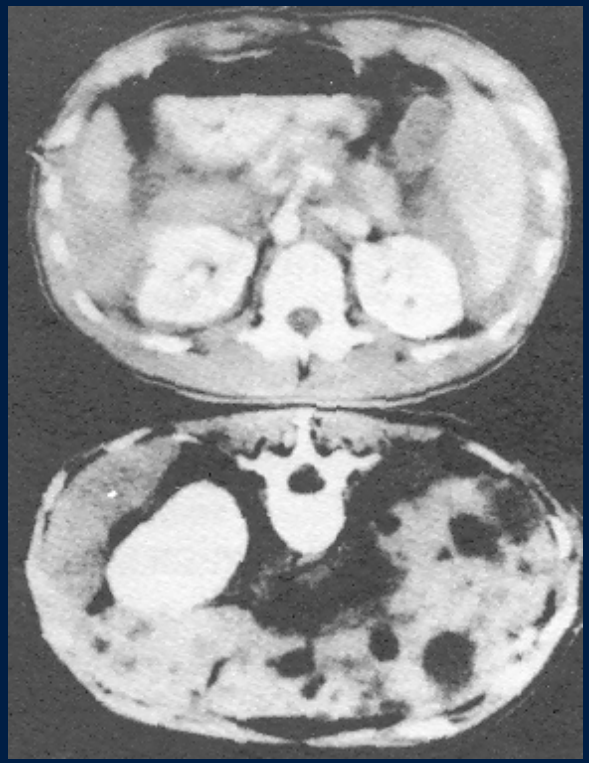
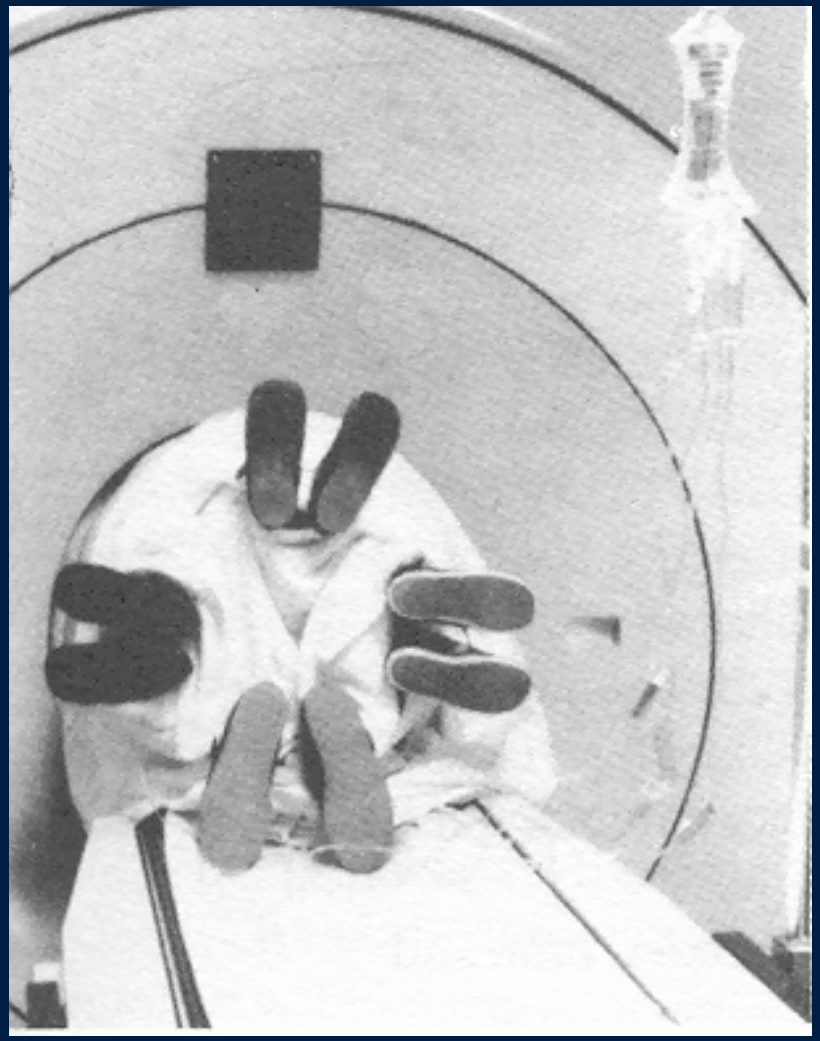
Disclosures

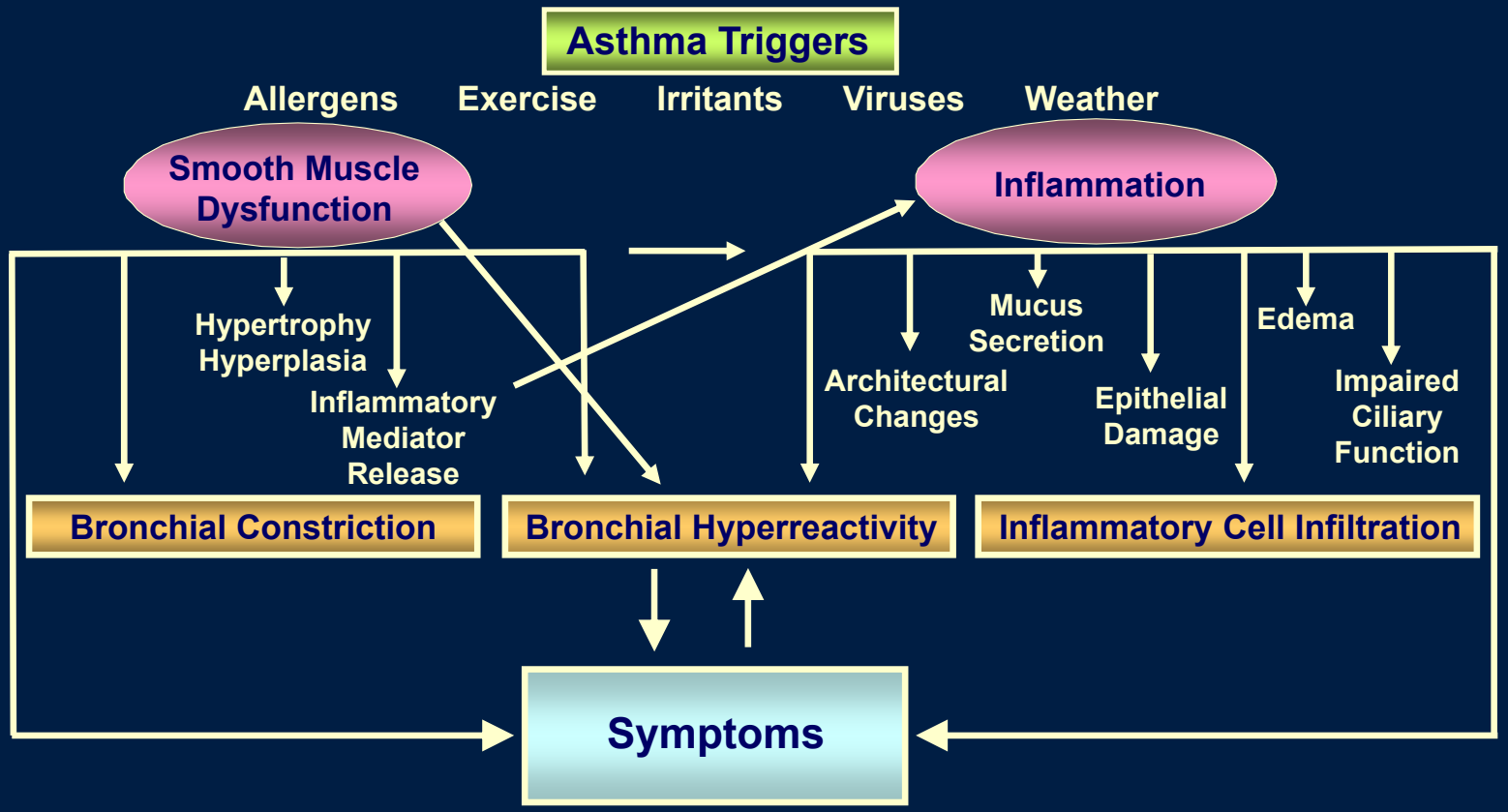
- Professor of Medicine; National Jewish Health; University of Colorado, Denver
- Appeals Committee, Accreditation Council of Graduate Medical Education
- “Opinions and assertions herein are not representative of any of the named entities but are of my own opinion”
- AstraZeneca: Employment ended 8/2022, honoraria





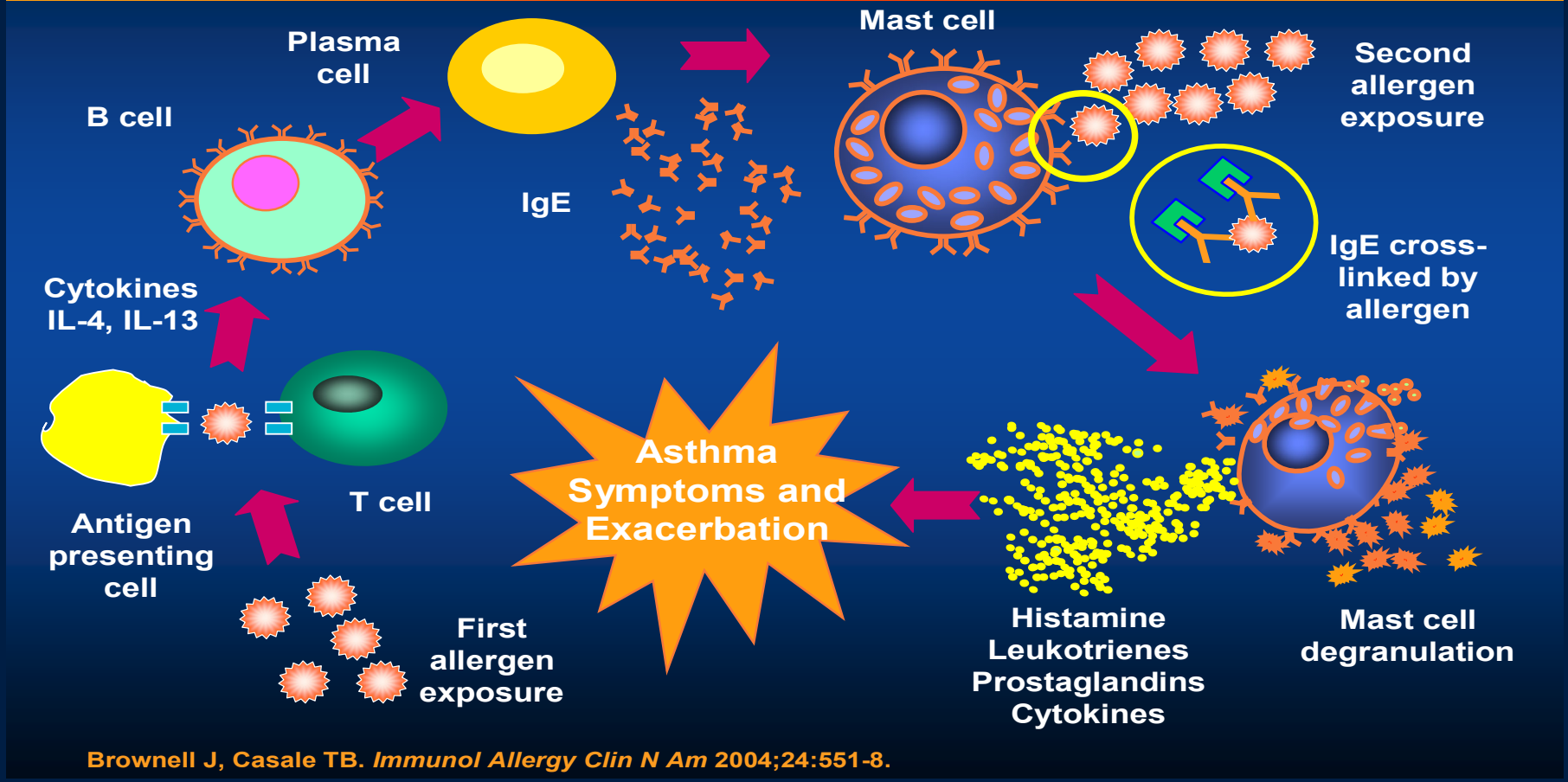


Mechanisms of Asthma Leading to Symptoms



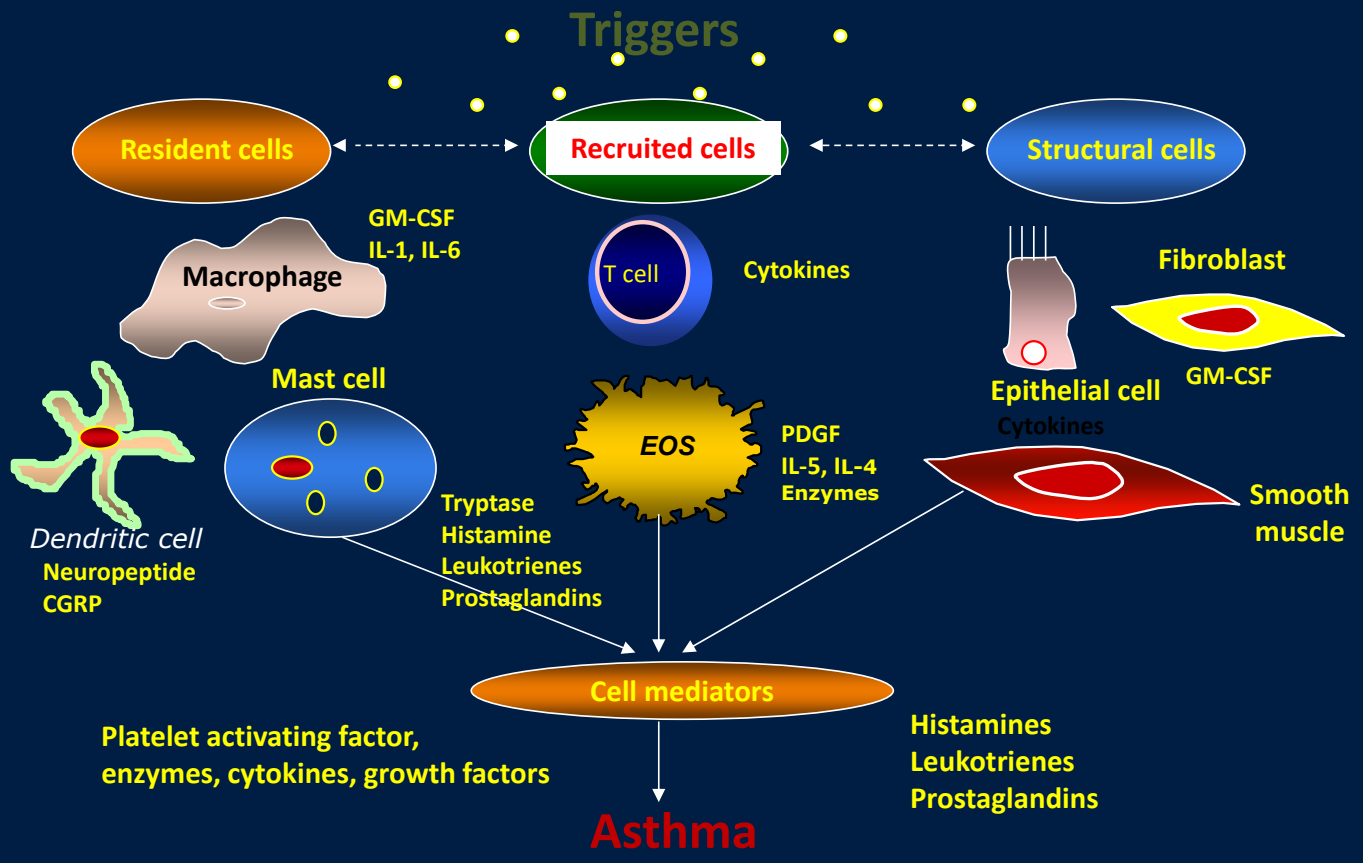
Adapted from Creticos. *Adv Stud Med*. 2002;2:499-503.

Overview of the Inflammatory Cascade



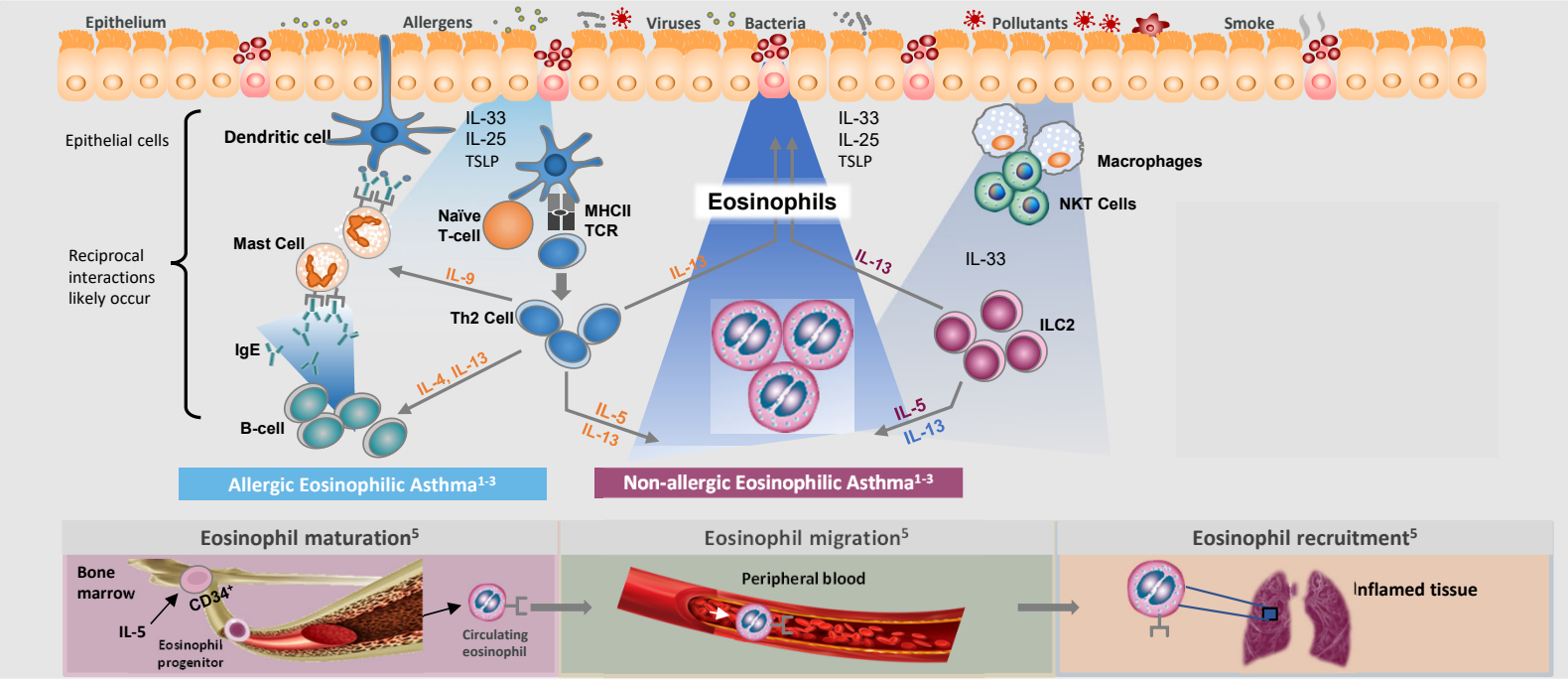
Brownell J, Casale TB. *Immunol Allergy Clin N Am* 2004;24:551-8.

Cells and Cell Mediators Involved in the Asthmatic Inflammatory Response



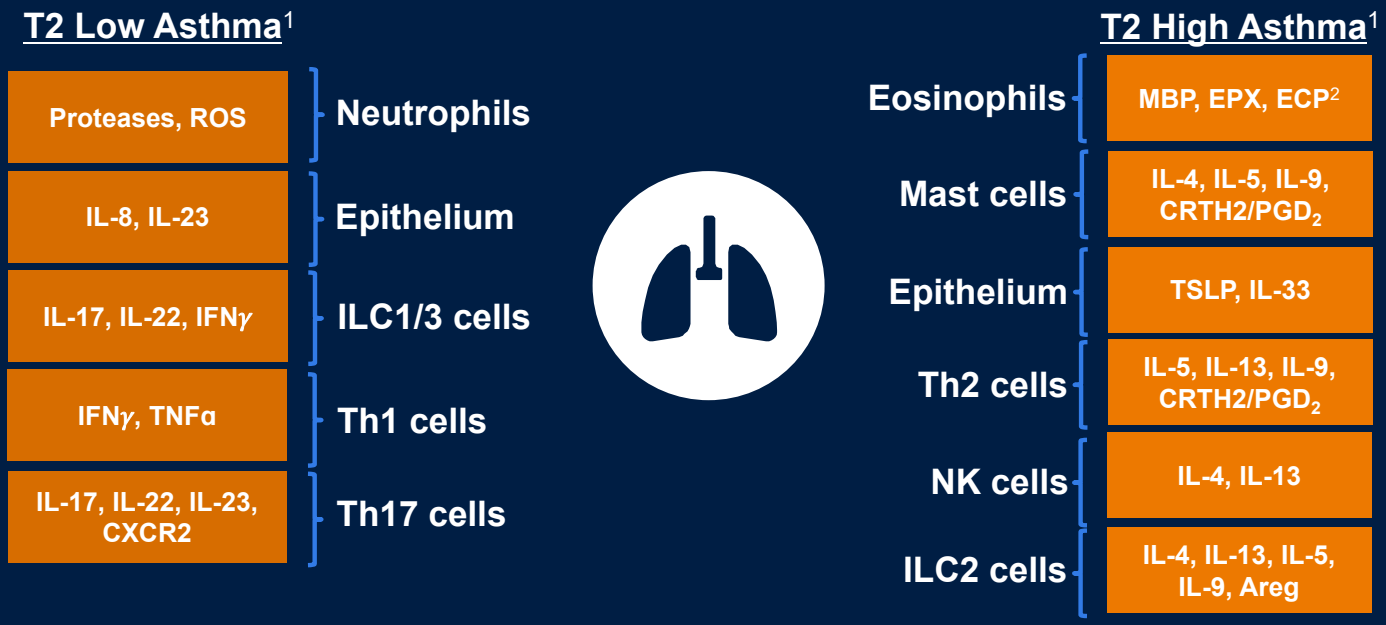
Barnes PJ, et al. *Am J Respir Crit Care Med*. 1998;157:S1-S53; Spina D. *J Pharm Pharmacol*. 2000;52:125-145.

Eosinophils Can Have Reciprocal Interactions With Other Immune Cells to Perpetuate Chronic Inflammation[1]



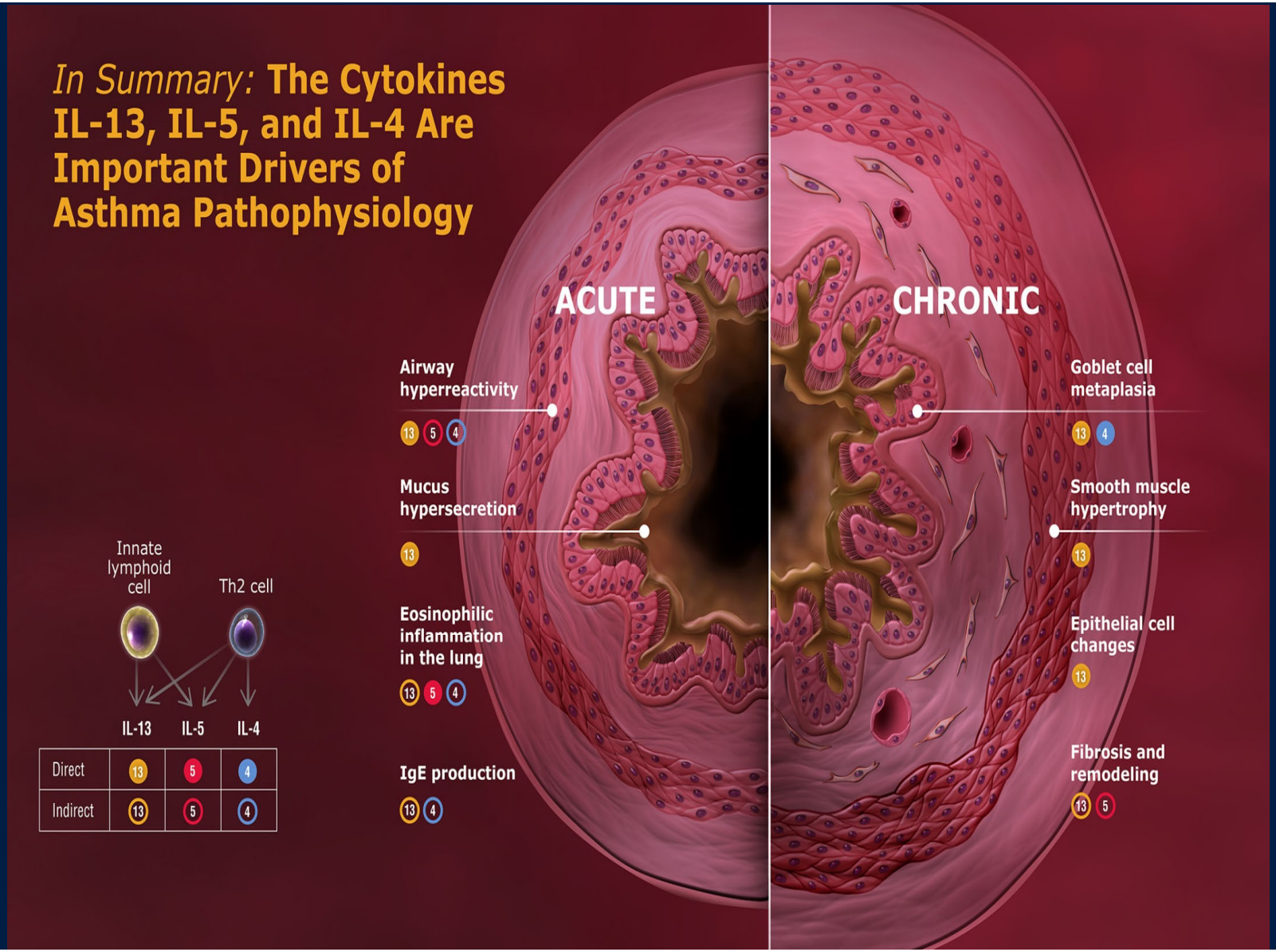
1. Jacobsen EA et al. *Annu. Rev. Immunol.* 2021. 39:719-757; 2. Brusselle GG et al. *Nat Med.* 2013;19:977-979; 3. Lambrecht BN et al. *Nat Immunol.* 2015;16:45-56; 4. Peters MC et al. *Lancet.* 2020;1;395:371-383; 5. Pelaia C et al. *Front. Physiol.* 2019.

Different Patterns of Inflammation Can Drive Asthma

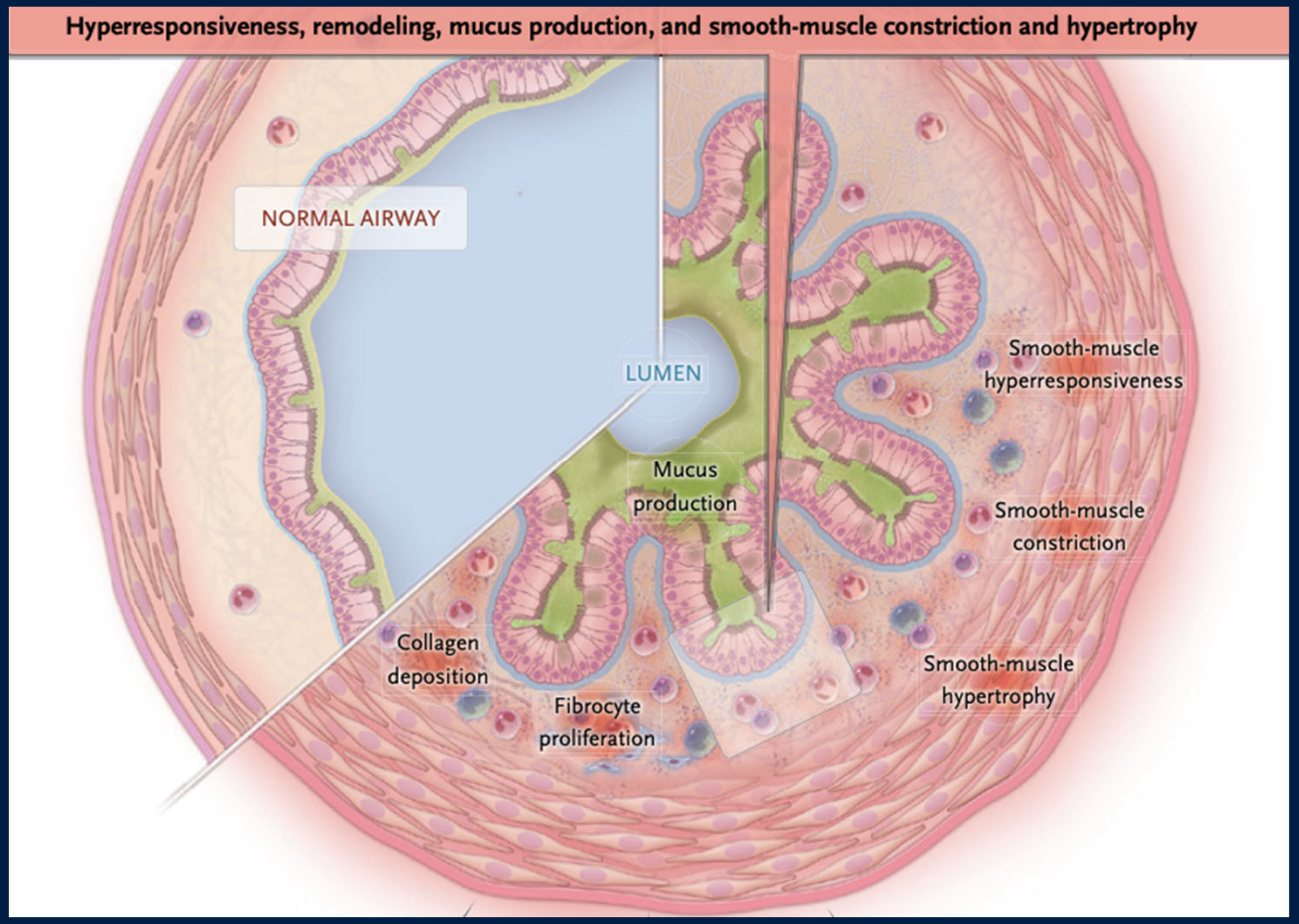


Areg=amphiregulin; CRTH2=chemoattractant receptor homologous molecule on T2 cells; CXCR2=C-X-C motif chemokine receptor 2; ECP=eosinophil cationic protein; EPX=eosinophil peroxidase; IFN=interferon; ILC1=type 1 innate lymphoid cells; ILC2=type 2 innate lymphoid cells; ILC3=type 3 innate lymphoid cells; MBP=major basic protein; NK=natural killer; PGD_2=prostaglandin D_2; ROS=reactive oxygen species; Th=T helper cells; TNF=tumor necrosis factor; TSLP=thymic stromal lymphopoietin.

1. Adapted from Tabatabaian F, et al. *Immunol Allergy Clin North Am.* 2017;37:329-343. 2. Carr TF, et al. *World Allergy Organ J.* 2016;9:21.



Structural Changes in Asthma



Airway Remodeling: Sub-epithelial Fibrosis

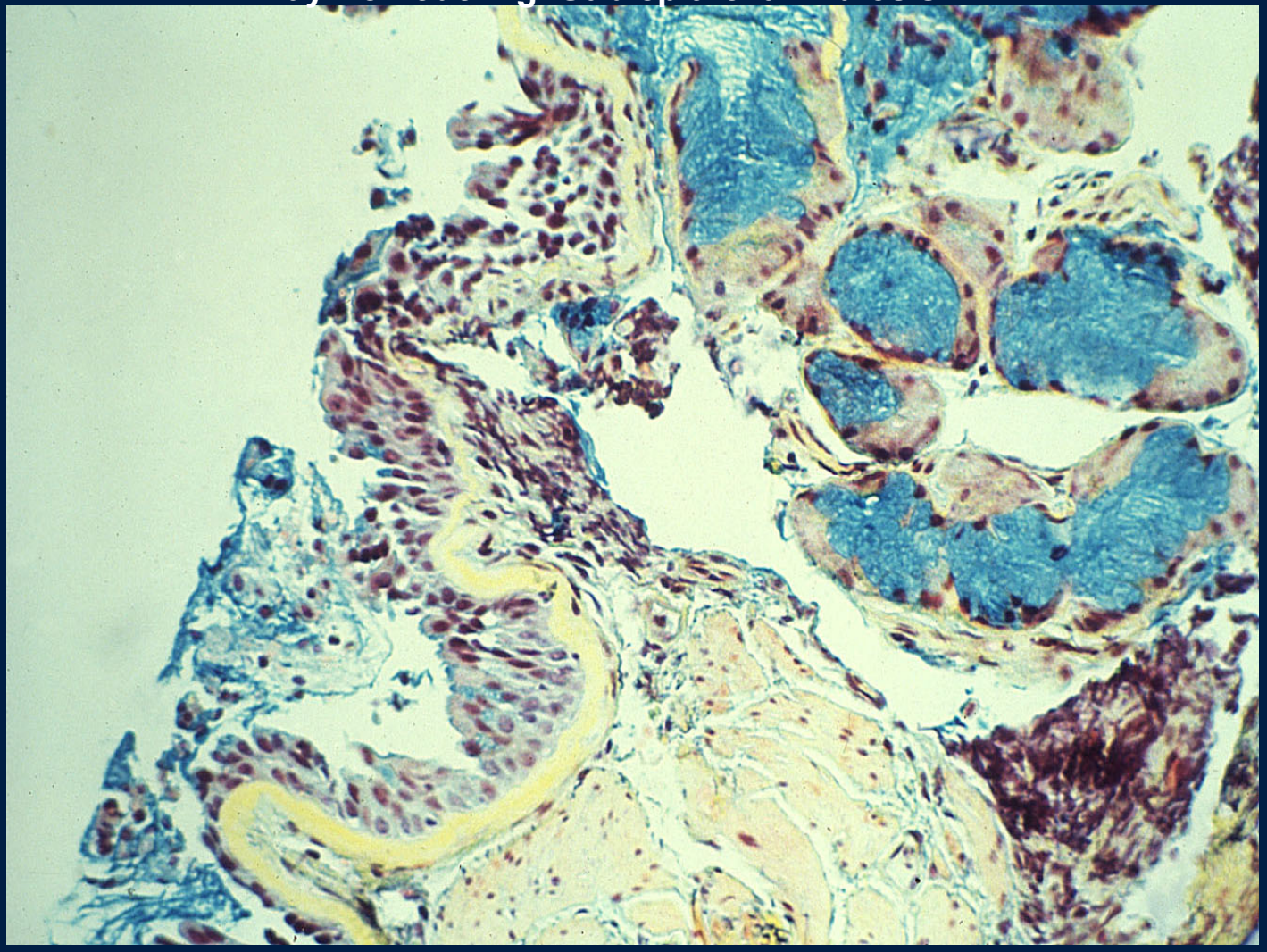
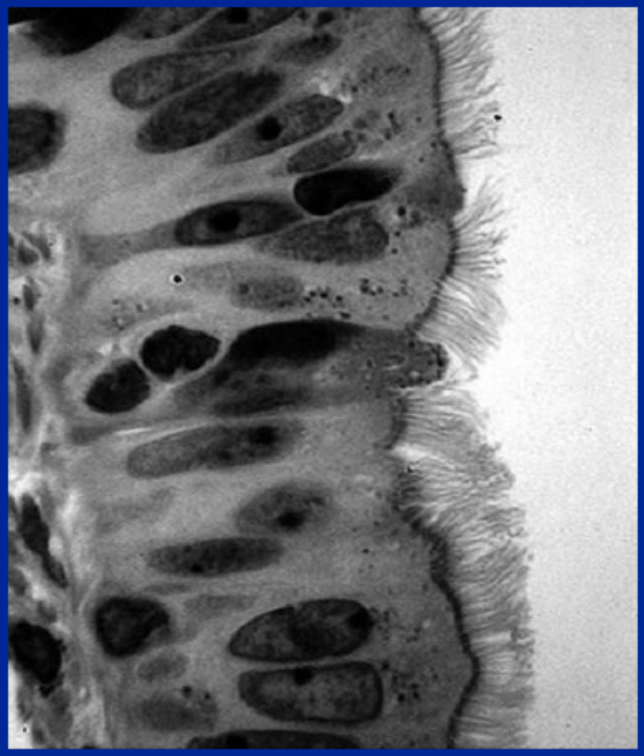
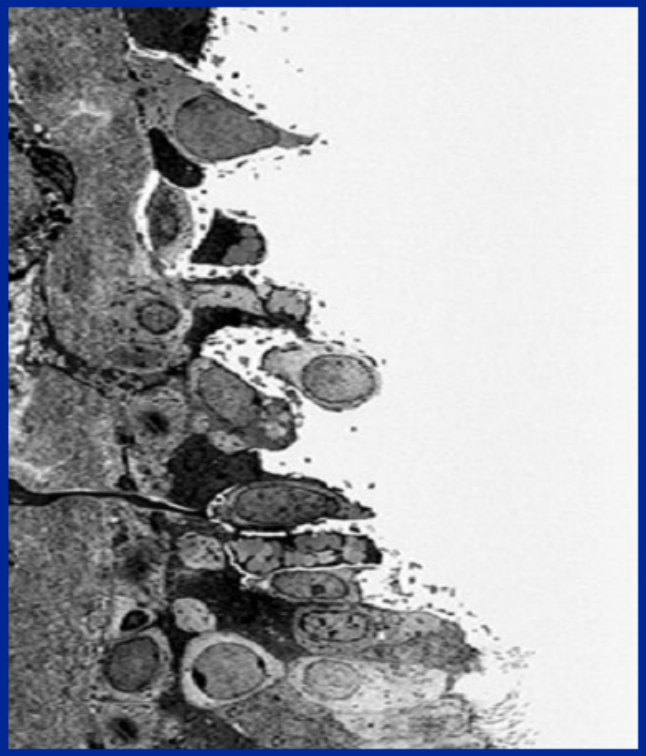


Image courtesy of Rohit Katial, MD.

Epithelial Remodeling in Asthma

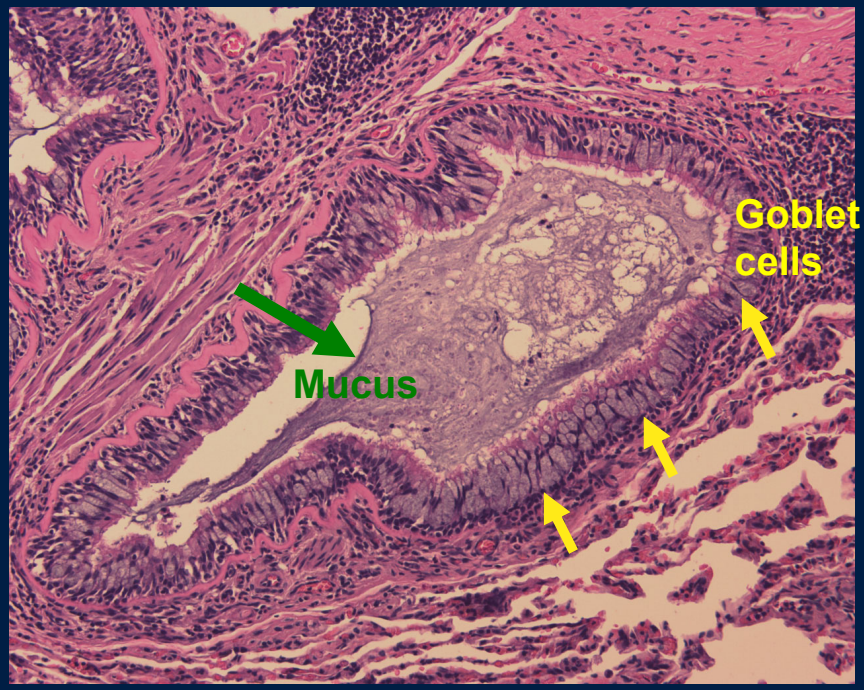


Normal



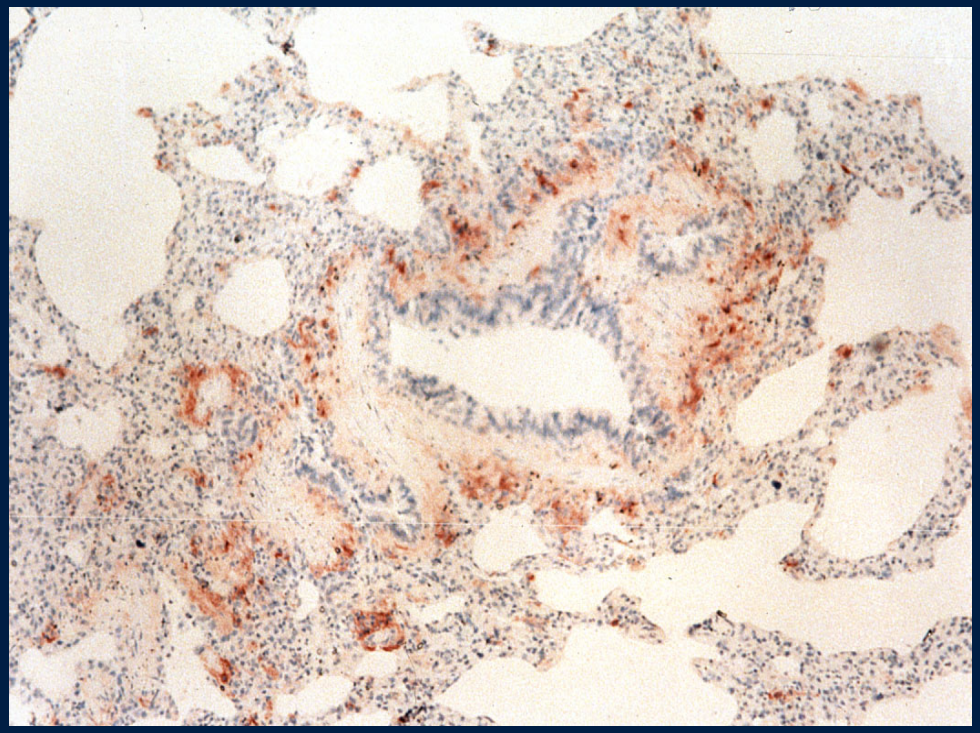
Asthmatic

Epithelial cells: goblet cell increases

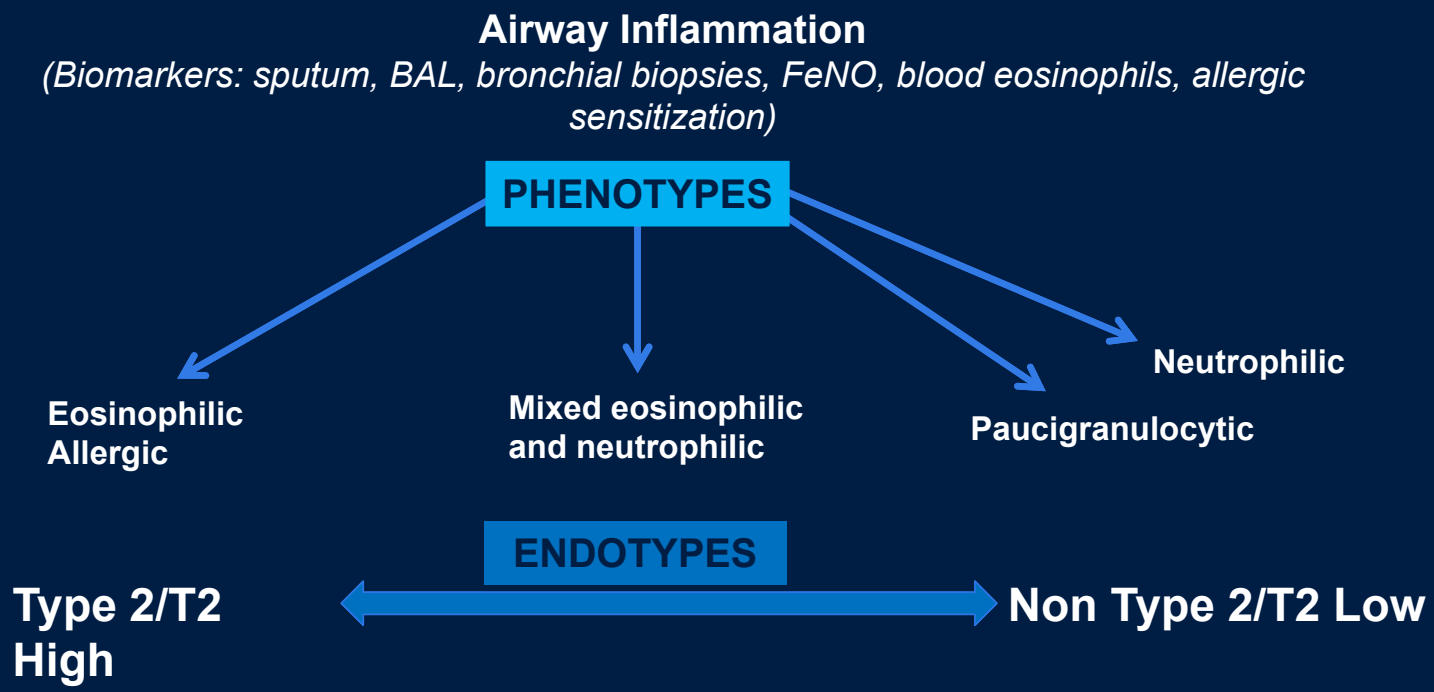


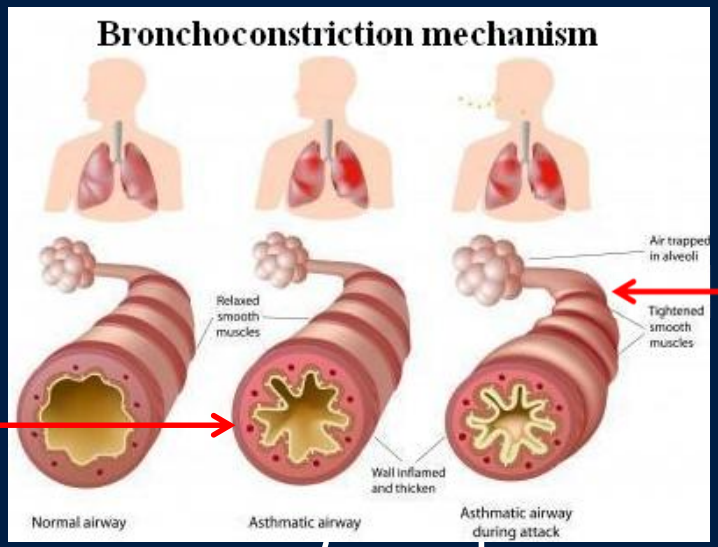
Courtesy of Hong Wei Chu

Different distribution of inflammatory cells: Mast cells



Inflammatory Subtypes of Asthma





Distinct Molecular Mechanisms

Distinct Molecular Mechanisms

Cellular/pathological/physiologic features underlying phenotype A

Cellular/pathological/physiologic features underlying phenotype B

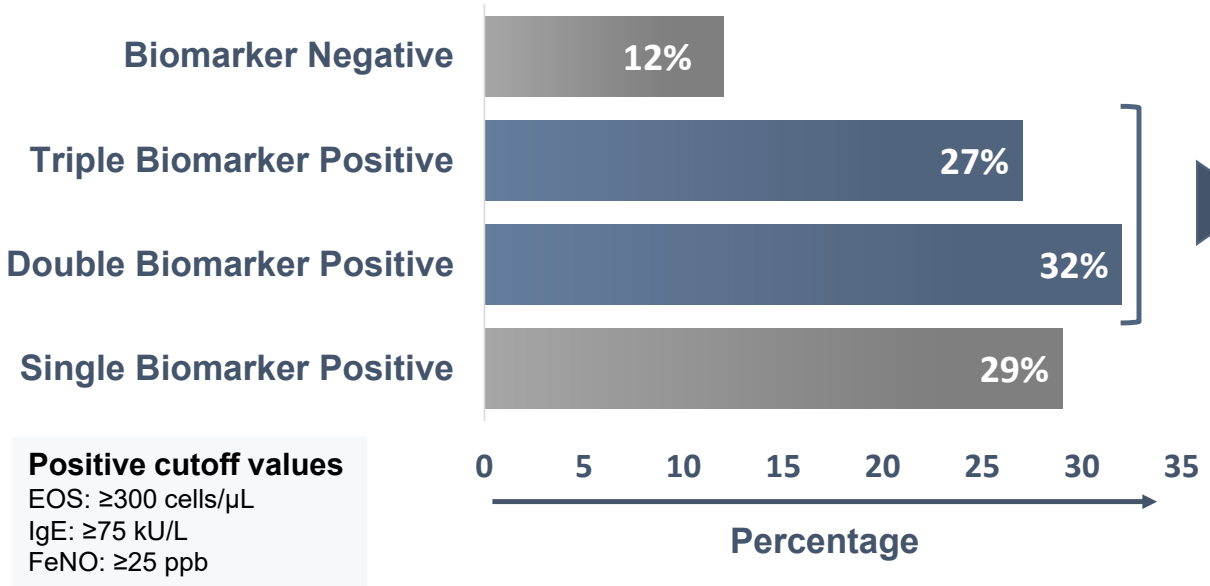
Clinical Phenotype A

Clinical Phenotype B

Recognizable Disease Syndrome

We Now Appreciate That Patients With Severe Asthma Have Overlapping Biomarker Profiles Indicating Multiple Activated Pathways

International Severe Asthma Registry (n=1175): Asthma Clusters Related to Biomarker Level*



Positive cutoff values
EOS: ≥300 cells/µL
IgE: ≥75 kU/L
FeNO: ≥25 ppb

Nearly 2/3 of patients with ≥2 or more biomarkers elevated

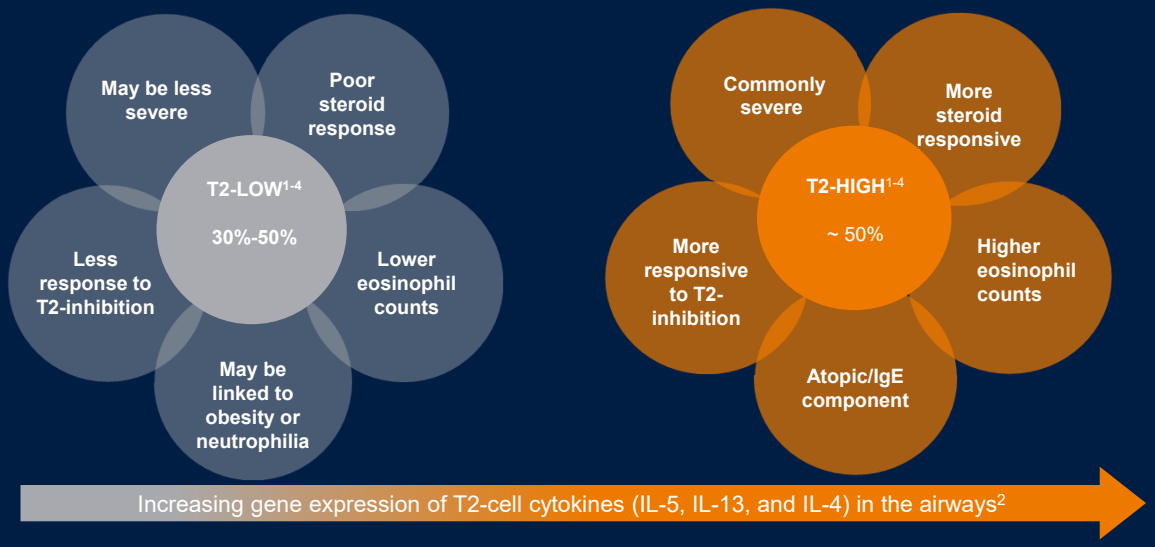
EOS=eosinophils; FeNO=fractional exhaled nitric oxide; IgE=immunoglobulin E.

Denton E, et al. *J Allergy Clin Immunol Pract*. 2021;9(7):2680-2688.e7.

Cellular Phenotypes

- Neutrophilic
- Eosinophilic
- Pauciimmune

T2-Low and T2-High: Examples of Asthma Phenotypes[1,2]



IgE=immunoglobulin E; T2=T-helper cell type 2.

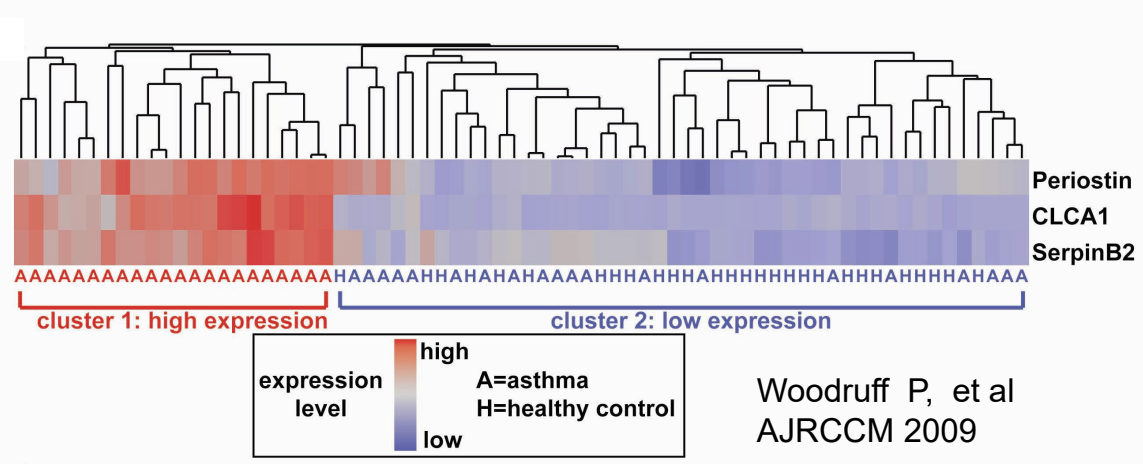
1. Fahy JV. *Nat Rev Immunol.* 2015;15(1):57-65.
2. Woodruff PG, et al. *Am J Respir Crit Care Med.* 2009;180:388-395.
3. Wenzel SE. *Nat. Med.* 2012;18(5):716-725.
4. Peters MC, et al. *J Allergy Clin Immunol.* 2014;133(2):388-394.

Sputum Cell Counts

- **Average cell counts (partial data – subset of baseline samples from each group):**

	Total cell counts (million)	Eos percent	Neut percent
Non-asthmatic controls	4.63	2.4%	44.4%
Well-controlled asthmatics	2.75	0.9%	19.1%
Not well-controlled asthmatics	4.08	1.7%	40.8%
Poorly controlled asthmatics	4.43	2.5%	74.8%

Molecular phenotyping supports a Th2/atopic phenotype

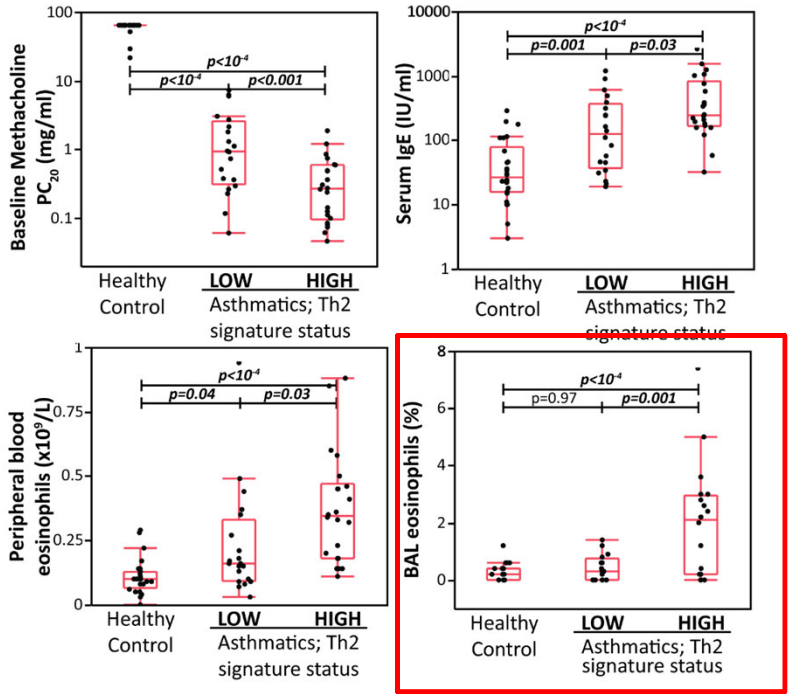


3 genes expressed *in vitro* in epithelial cells in response to IL-13 applied to *ex vivo* epithelial cells with:

- More BHR, atopy, eosinophils
- Identified by increases in epithelial periostin in particular

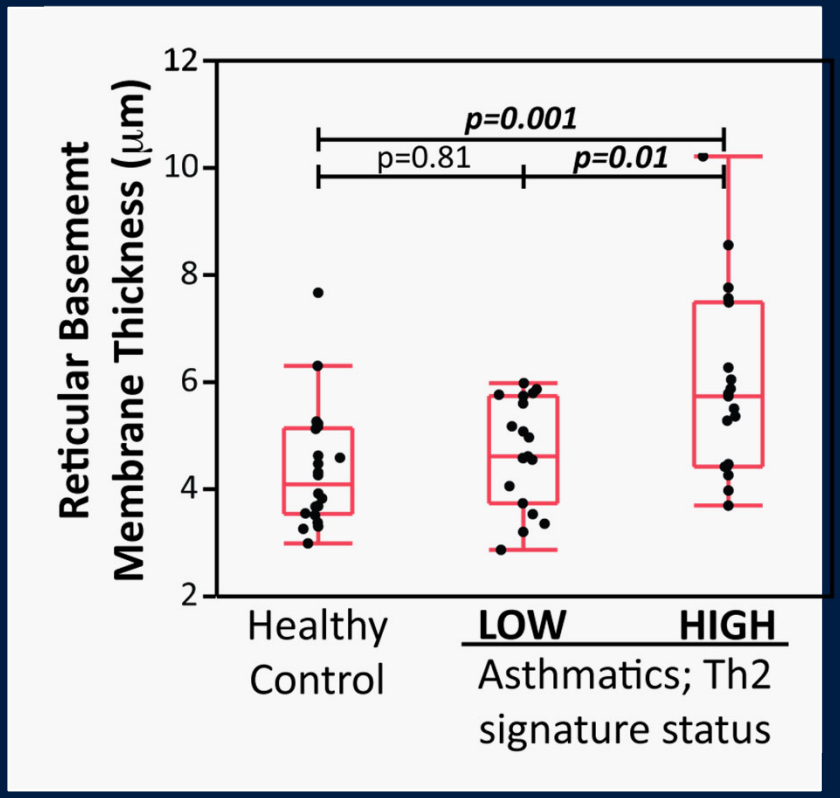
Woodruff et al. AJRCCM 2009

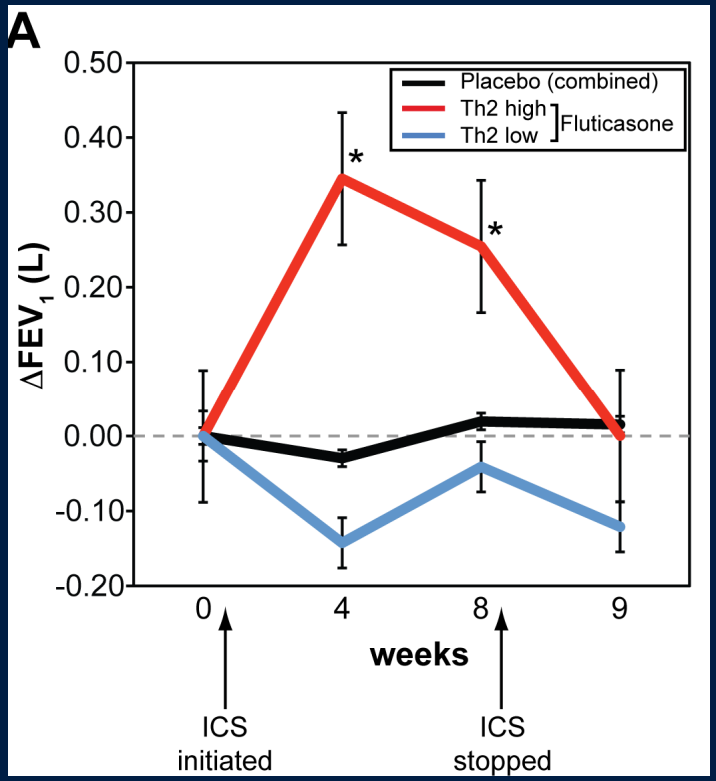
Clinical Features: Th2 High asthma has greater AHR, IgE levels and Eosinophilia



Woodruff et al. AJRCCM 2009

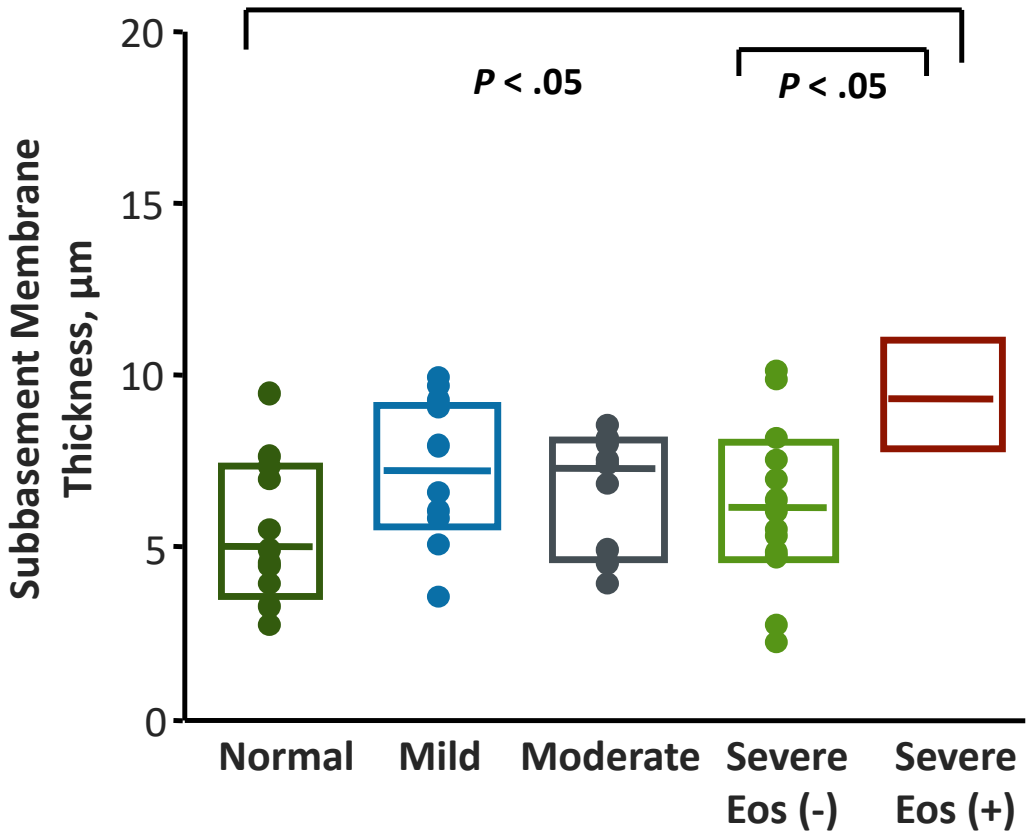
Th2 Hi: Thick SBM and Robust CS Response





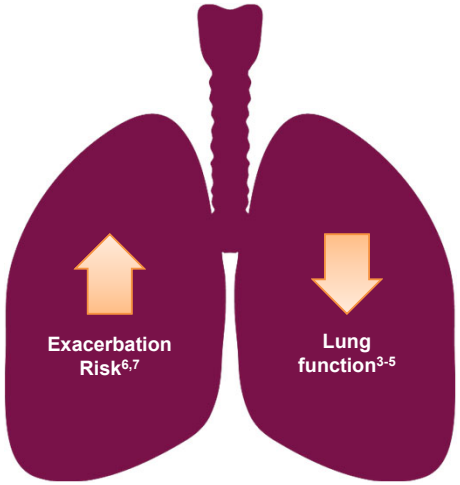
Woodruff P, et al AJRCCM 2009

SBM Thickness Associated With Eosinophilic Phenotype



Wenzel SE, et al. *Am J Respir Crit Care Med*. 1999;160:1001-1008.

Summary: Increased Eosinophils in Asthma



Elevated eosinophils were correlated with:

- Increased asthma severity[1,2]
- Worsening lung function[3-5]
- Increased risk of exacerbations[6,7]
- Increased rates of hospitalizations and ED visits[6]

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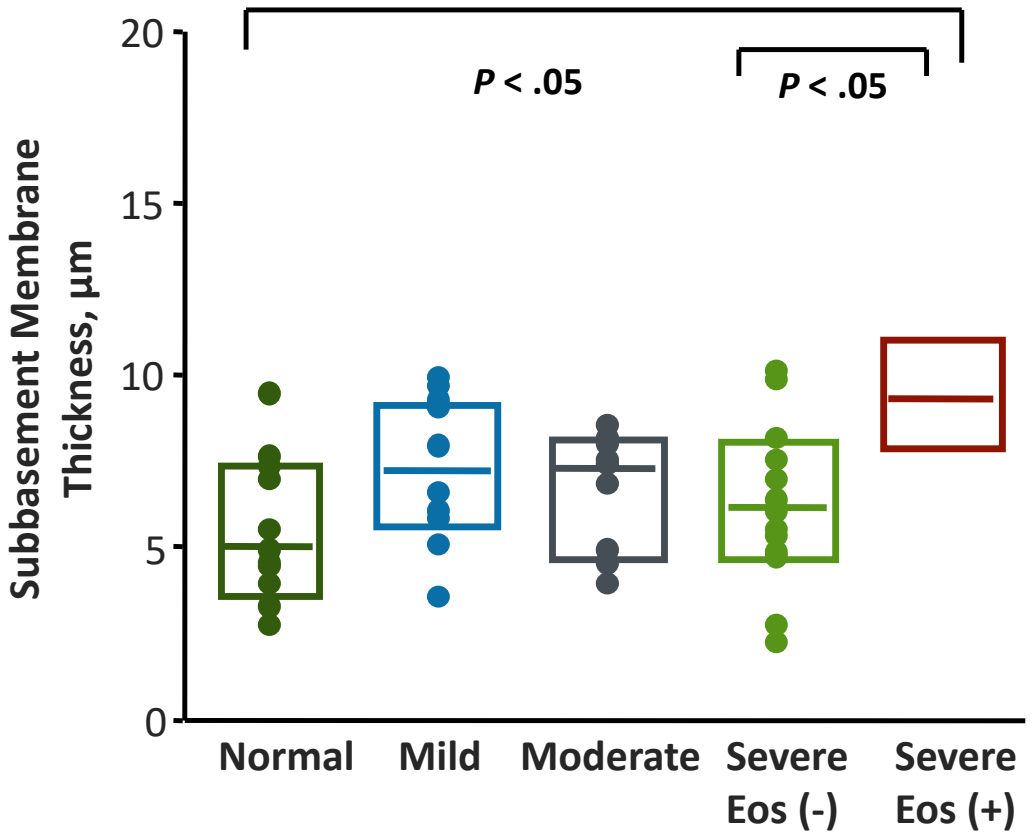

Wenzel SE, et al. *Am J Respir Crit Care Med*. 1999;160:1001-1008.

Increased Eosinophils in Sputum Are Strongly Associated With Increased Asthma Severity

	Eosinophils ($x10^3$/g)	
Group	**Median**	**Range**
Control	9	0-135
Intermittent asthma	45	4-220
Mild to moderate persistent asthma	199	4-2,227
Severe persistent asthma	305	12-10,800

p<0.05
p<0.001
p<0.001

- **Patients with severe asthma not treated with an OCS had a 44-fold higher median eosinophil count (p<0.0001) compared with individuals in the control group**
- **Despite treatment with high doses of ICS or with OCS, prominent eosinophilic inflammation was noted**

ICS = inhaled corticosteroids; OCS = oral corticosteroids.

Louis R et al. *Am J Respir Crit Care Med.* 2000;161:9-16.

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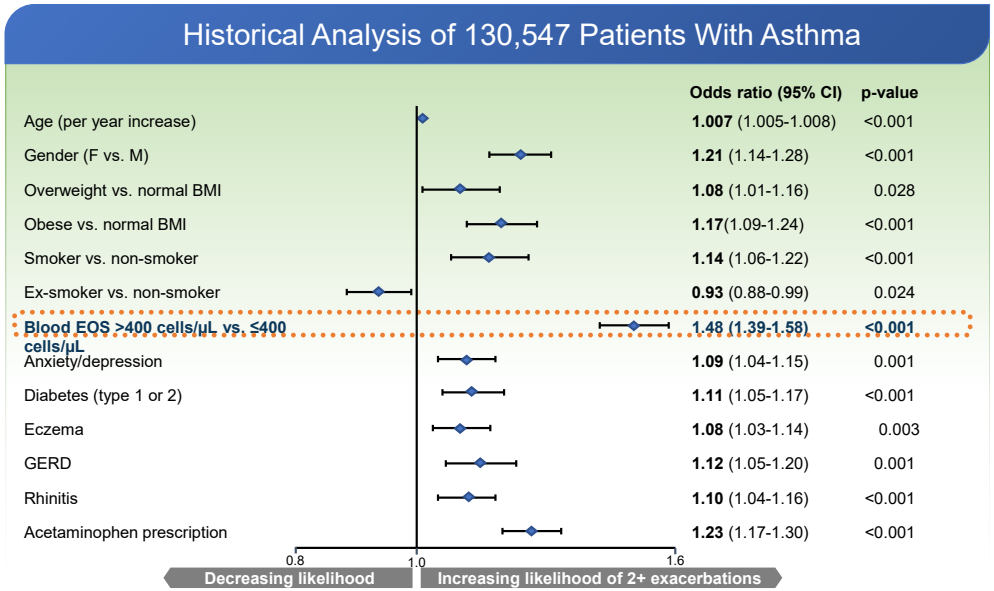
Increased Eosinophils in Asthma: Major Risk Factor for Exacerbations



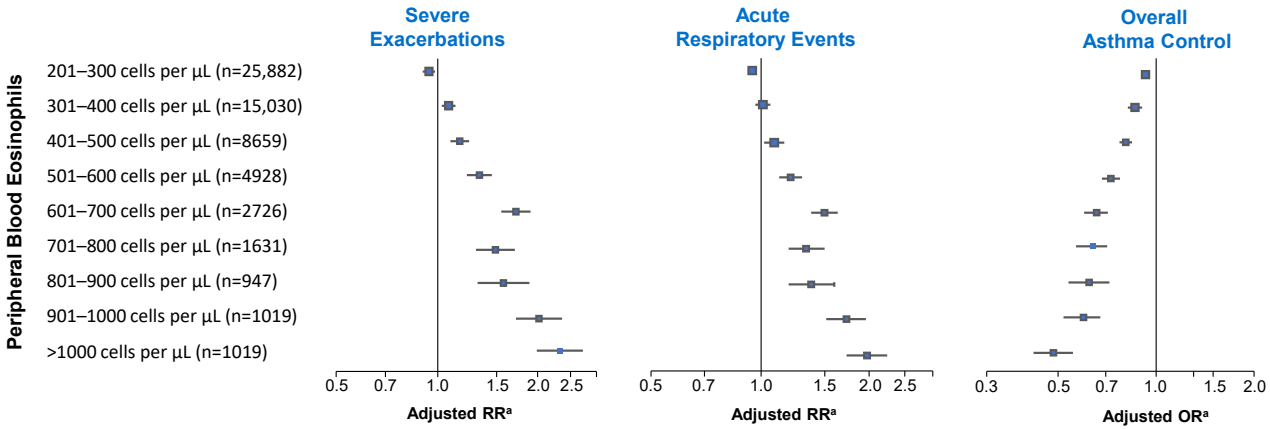
Adapted from Price D et al. *J Asthma Allergy*. 2016;9:1-12.

Blood eosinophil >400 cells/µL:

- **Single best predictor of multiple exacerbations**
- **↑ likelihood of ≥2 exacerbations by 1.5-fold**

BMI = body mass index; CI = confidence interval; EOS = eosinophils; F = female; GERD = gastroesophageal reflux disease; M = male.
Price D et al. J *Asthma Allergy*. 2016;9:1-12.

Peripheral Blood Eosinophil Levels Have Been Correlated With Both Asthma Severity and Control



Severe Exacerbation - an asthma-related hospitalization, attendance at an accident and an emergency department, or a prescription for acute oral OCS

Acute Respiratory Event - defined more broadly as an asthma-related hospital attendance or admission, or accident and an emergency department attendance, a prescription for acute OCS, or prescription for antibiotics in conjunction with an asthma-related primary care consultation

Overall Asthma Control - the absence of any acute respiratory event (as defined above) or asthma-related outpatient department visit with an average daily dose of 200 µg or less of salbutamol or 500 µg or less of terbutaline

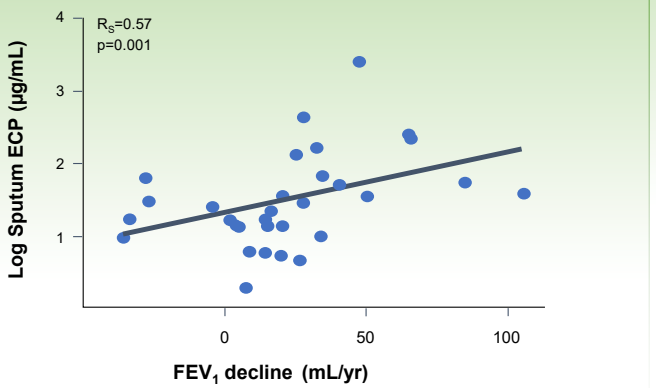
[a]Data from medical records of patients with asthma who were aged 12-80 years and had 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients were assigned to 9 eosinophil count categories and were compared with a reference category of ≤200 cells/µL (n=68,407). Data adjusted for age, gender, body mass index, smoking status, and Charlson comorbidity index score.

OCS = oral corticosteroids; OR = odds ratio; RR = rate ratio.

Price DB et al. *Lancet Respir Med.* 2015;3:849-858.

Eosinophilic Inflammation Correlates With Deterioration in Lung Function

Correlation of Sputum ECP Concentration With FEV_1 Decline[1]



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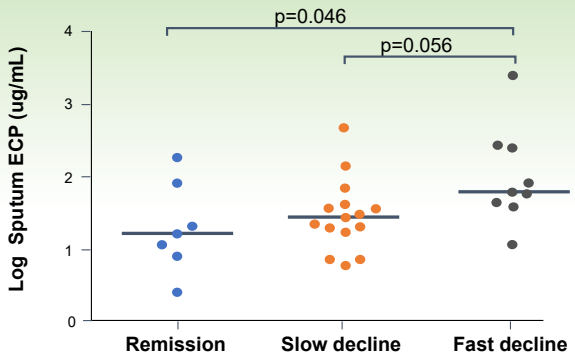

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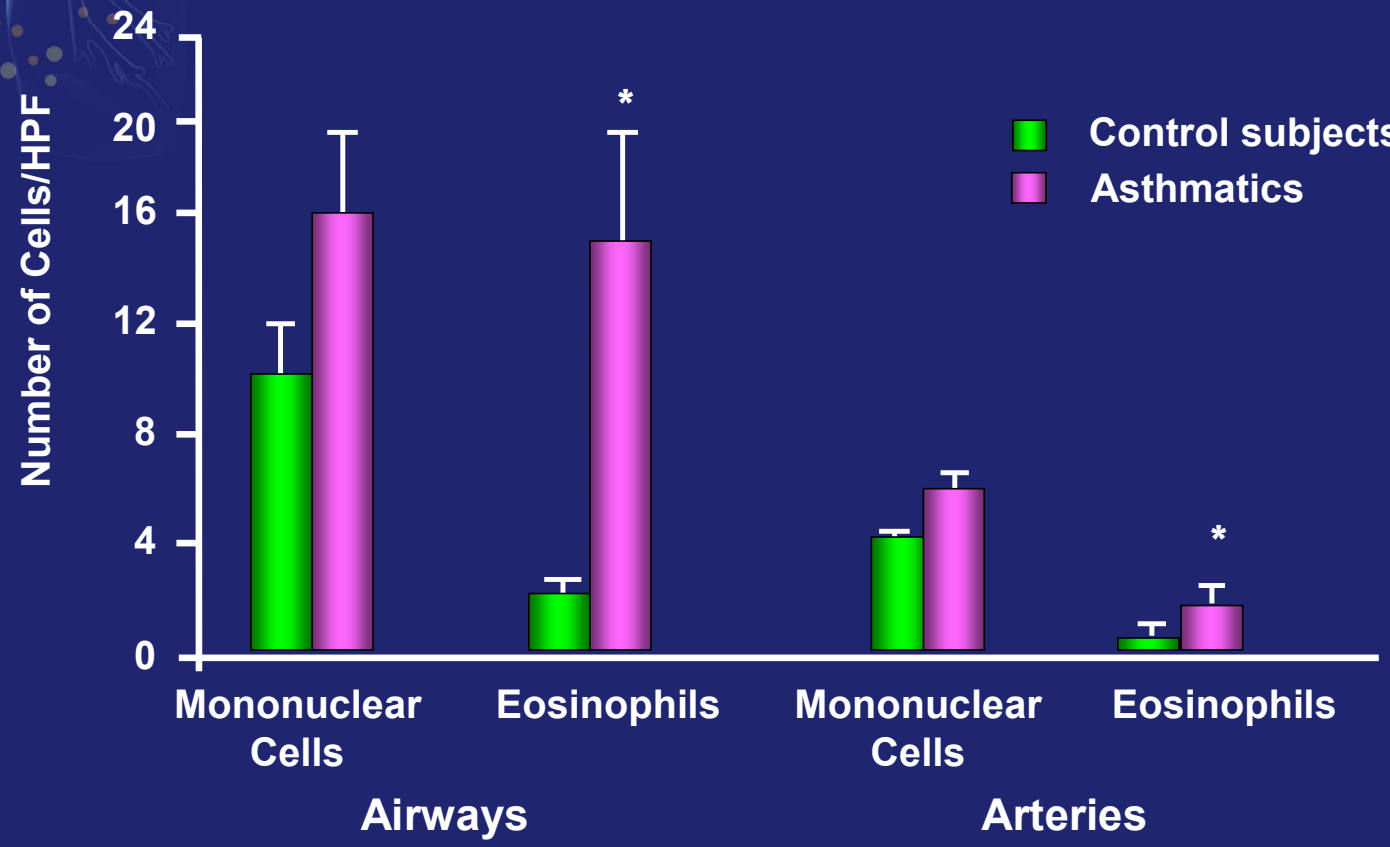
Note: Horizontal bars represent median values.

ECP is a protein released during degranulation of eosinophils that can be used as a biomarker of eosinophilic activity.[2]

ECP = eosinophil cationic protein; FEV_1 = forced expiratory volume in 1 second.

1. Broekema M et al. *Respir Med*. 2010;104:1254-1262; 2. Björk A et al. *Allergy.* 2000;55:442-448.

Eosinophils in Small Airways (Autopsies)

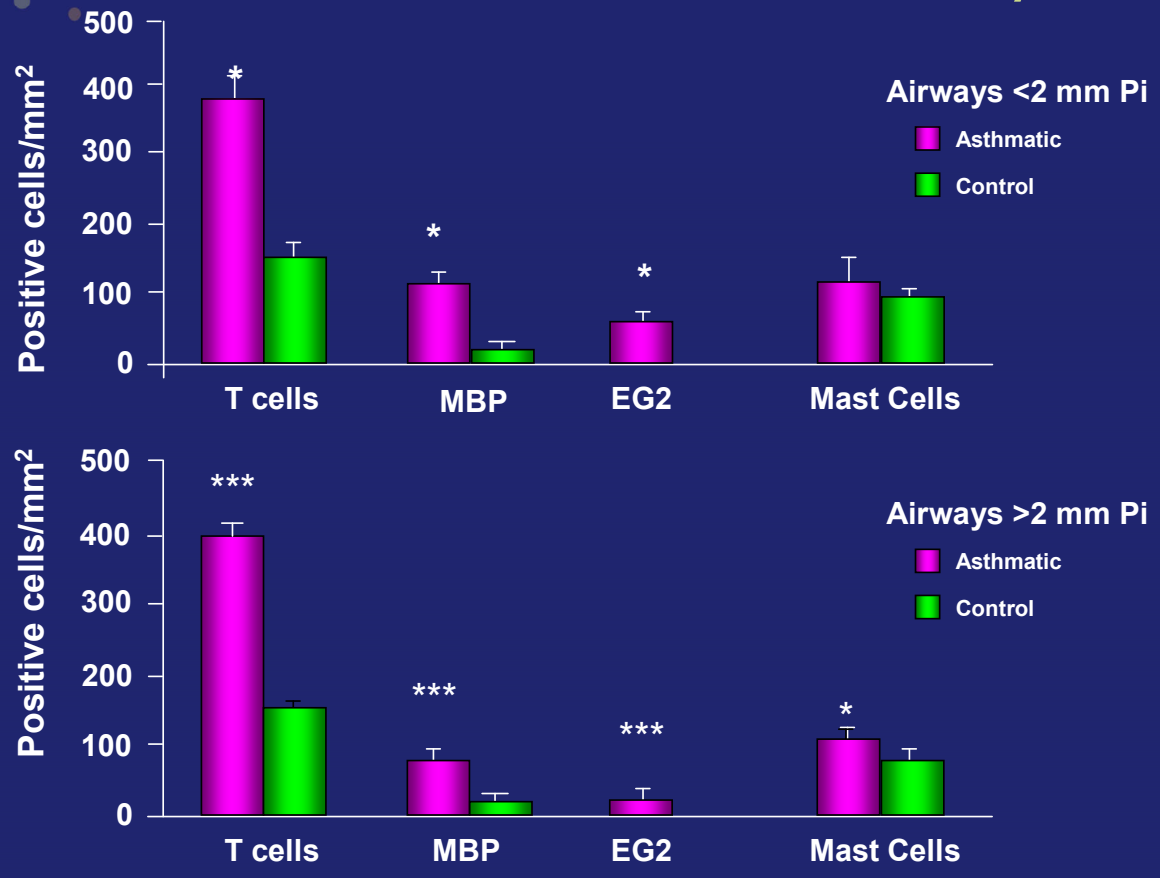


*$P<0.05$ vs. control subjects

HPF = High Power Field

Saetta M, et al. *Am Rev Respir Dis.* 1991;143:138-143.

The Inflammatory Response in Asthma Is ***Not*** Restricted to the Proximal Airways



Pi: internal perimeter; MBP: major basic protein (total eosinophils); EG2: activated eosinophils

Tulic MK. *Chest.* 2003;123:348-355. Hamid Q, et al. *J Allergy Clin Immunol*. 1997;100:44-51.

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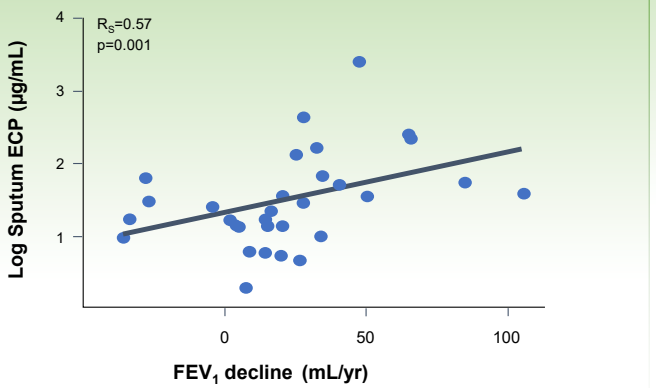

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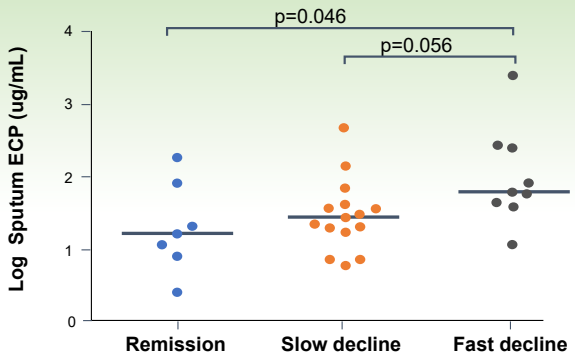

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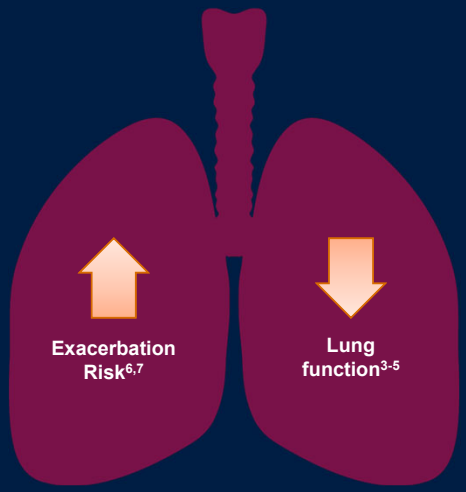

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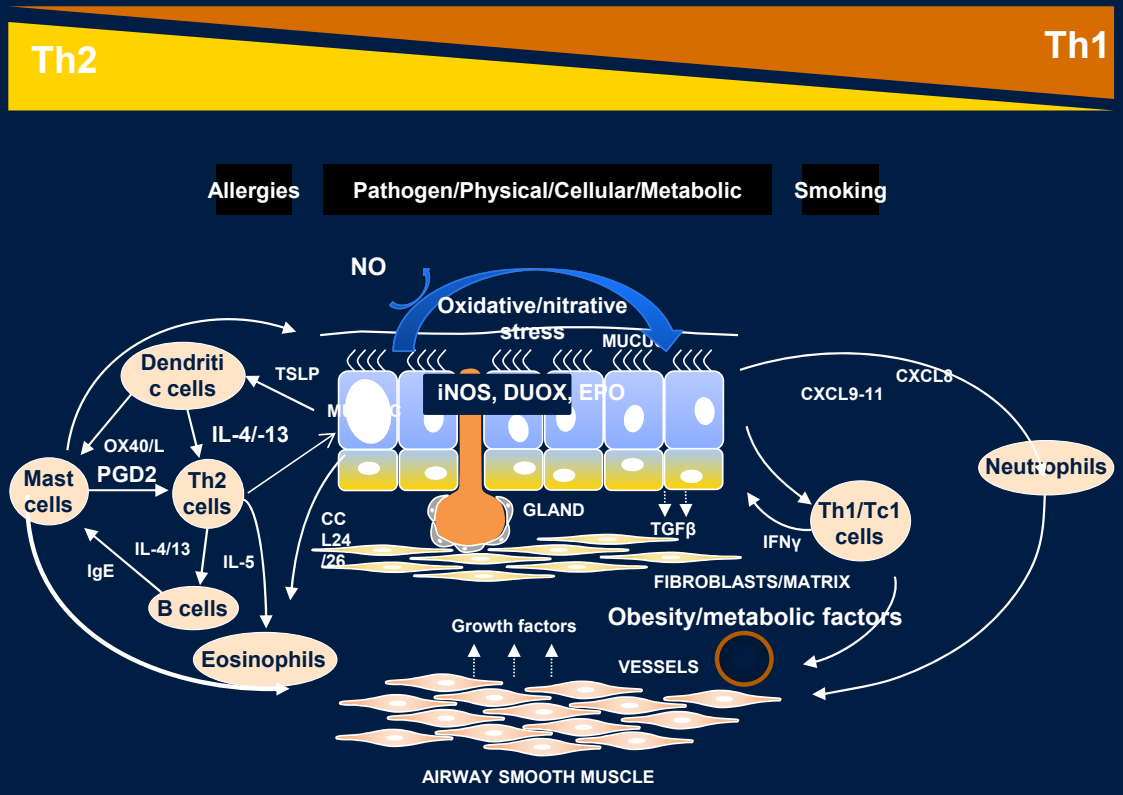
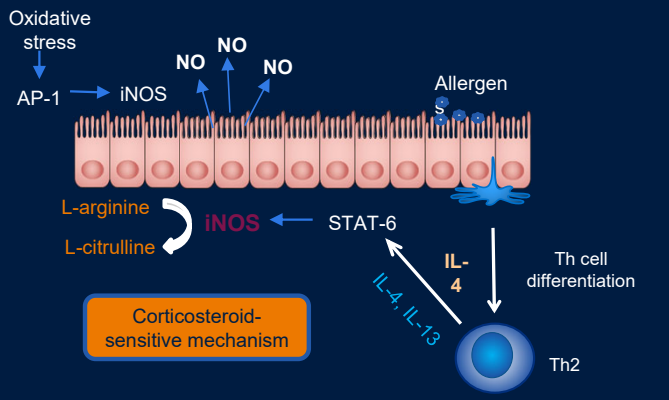
Pathobiology may involve multiple different immune/cellular pathways



Nitric oxide production regulated by NOS enzymes, IL-4, and IL-13

- Derived endogenously from L-arginine[1]
- Synthesis catalyzed by 3 forms of the NO synthetase (NOS) enzyme: 2 constitutive forms and 1 inducible form[1]
- In asthma, iNOS expression is upregulated by IL-4 and IL-13, leading to increased levels of FeNO[1,2]
  - NO production by iNOS is corticosteroid sensitive[2]

NOS forms[1]	Expressed in:	Role
Constitutive NOS (eNOS, cNOS)	Platelets, neuronal, epithelial and endotelial cells	Physiological regulation of airway function
Inducible NOS (iNOS)	Macrophages, neutrophils, hepatocytes, epithelial, mesangial, endothelial and vascular smooth muscle cells	Produced in response to airway inflammation and in host defense against infection

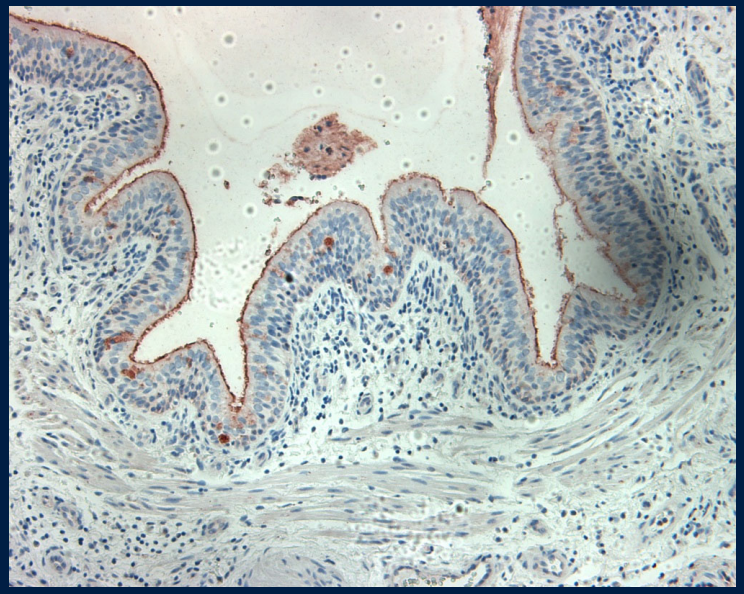


Adapted from Menzies-Gow,[1] Alving et al,[3] and Duong-Quy et al[4]

NO=nitic oxide; AP=activator protein; IL-interleukin; STAT=signal transducer and activator of transcription; Th2= T-helper cell type 2

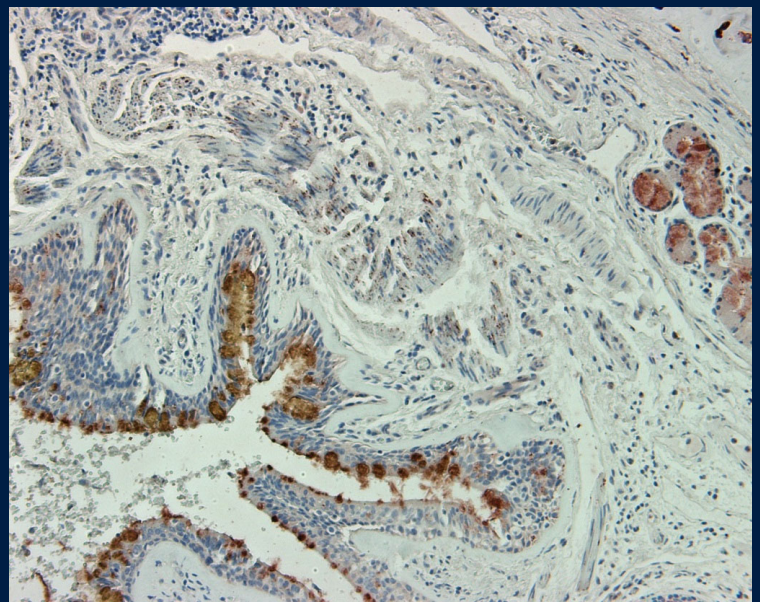
1. Menzies-Gow A et al. *Eur Respir J.* 2020; doi.org/10.1183/13993003.01633-2019. 2 Hoyte et al. *Immunol Allergy Clin N Am.* 2018; 38:573–585. 3. Alving K, Malinosvchi A. *Eur Respir Mon.* 2010;49: 1–31. 4. Duong-Quy C. *J Asthma Allergy.* 2019:12 331–341.

iNOS Staining



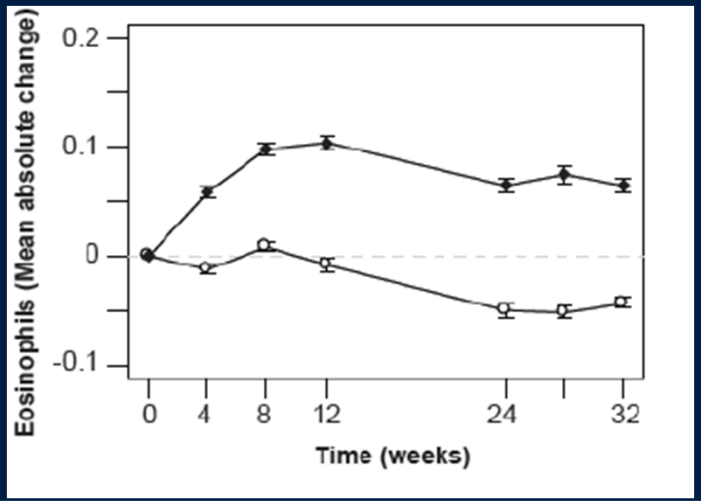
iNOS Stain in a Normal Subject

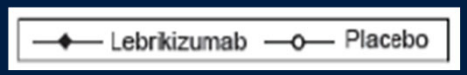
iNOS Stain in a Severe Asthmatic

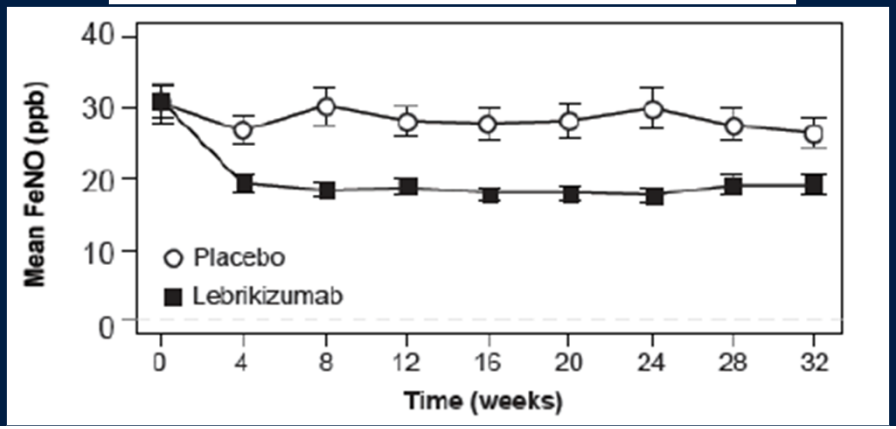


Courtesy Sally Wenzel and Silvana Balzar

FeNO and Eosinophils After Anti-IL-13 Treatment

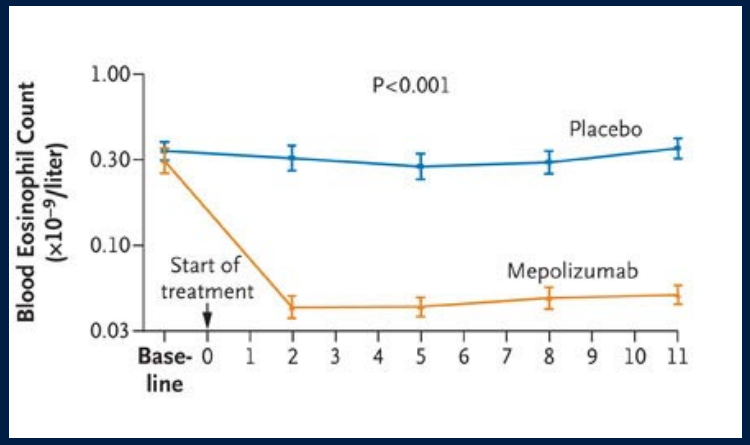


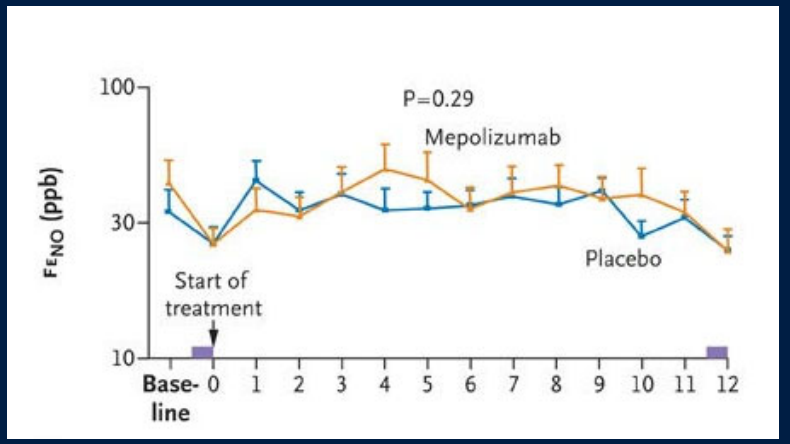




Adapted from Corren *et al* *NEJM* 2011; 365: 1088-98

FeNO and Eosinophils After Anti-IL-5 Treatment

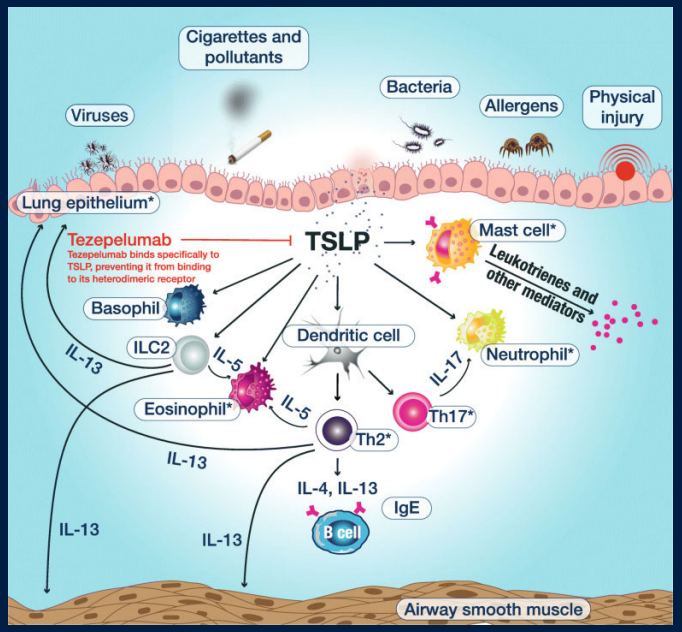




Adapted from Haldar et al; NEJM 2009; 360: 973-84

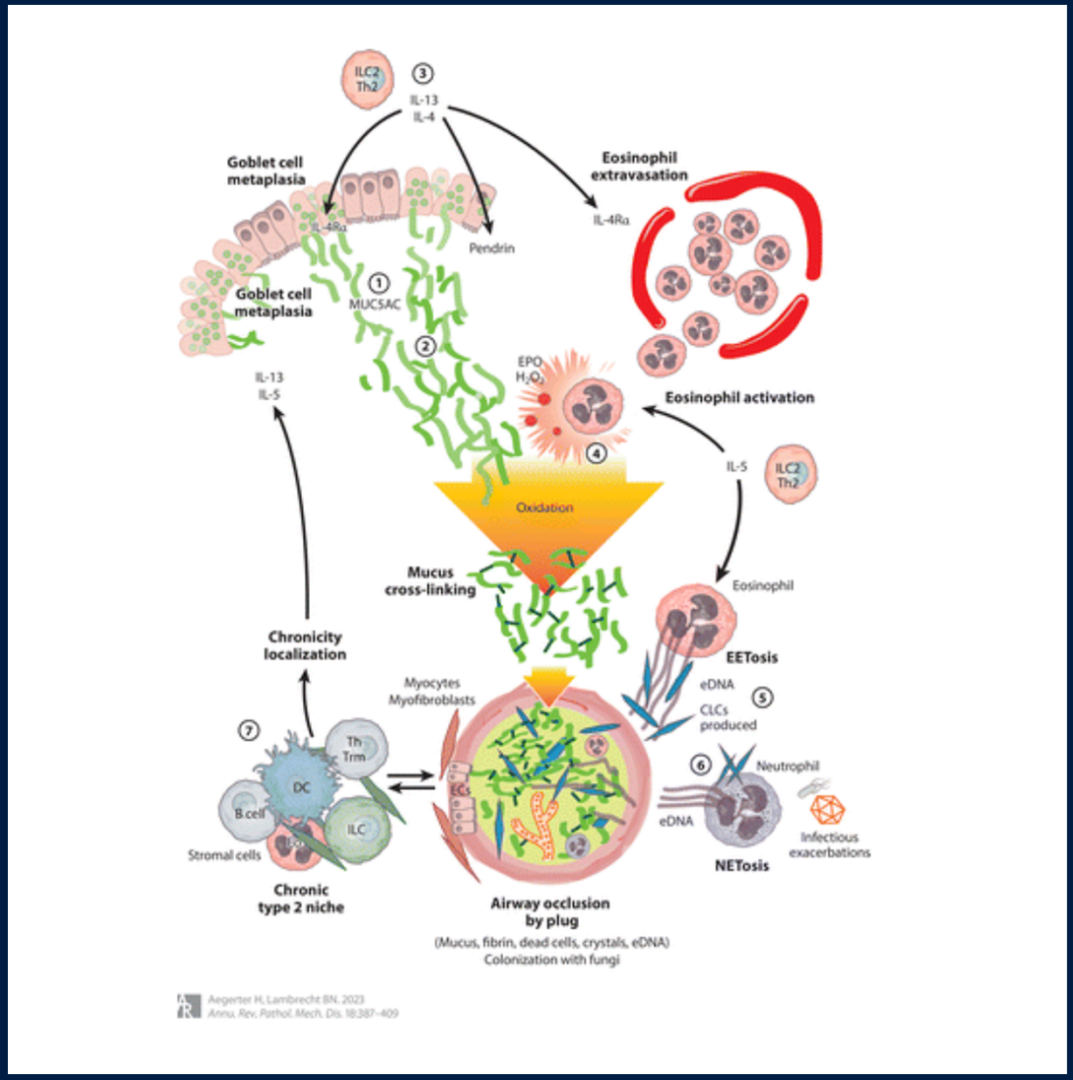
TSLP: A key epithelial cytokine in asthma

- Human TSLP is an epithelial-derived cytokine first described in 2001
- Variants at the TSLP gene loci have been associated with asthma risk
- TSLP expression:
  - higher in the airways of patients with asthma
  - correlates with Th2 cytokine and chemokine expression
  - correlates with disease severity

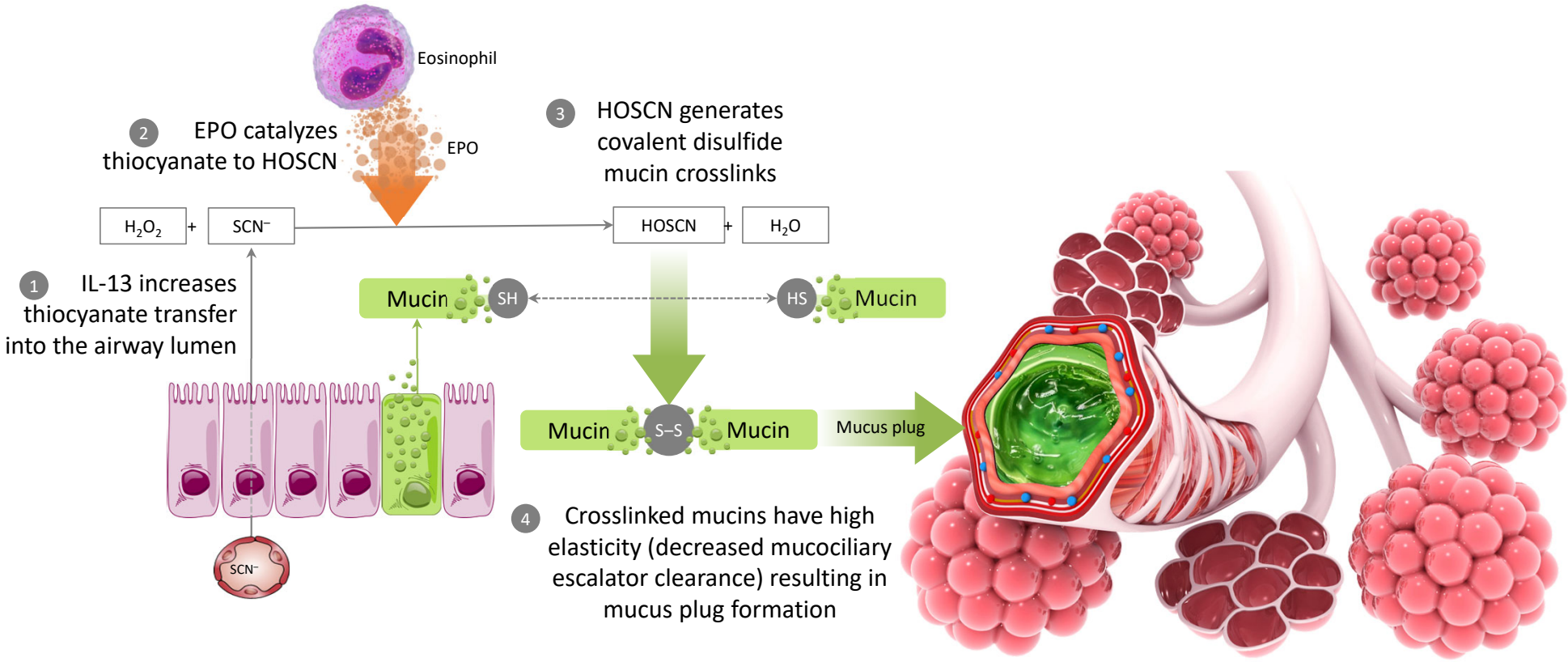


Emson, C., Diver, S., Chachi, L. *et al.* CASCADE: a phase 2, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effect of tezepelumab on airway inflammation in patients with uncontrolled asthma. *Respir Res* **21,** 265 (2020). https://doi.org/10.1186/s12931-020-01513-x

1. Ziegler and Artis. *Nat Immunol* 2010;11:289–293. 2. Soumelis, et al. *Nat Immunol* 2002;3:673–680. 3. Allakhverdi, et al. *J Exp Med* 2007;204:253–258. Ziegler, et al. *Adv Pharmacol* 2013;66:129–155. 4. Shikotra, et al. *J Allergy Clin Immunol* 2012;129:104-11 e1-9. 5. Ying, et al. *J Immunol* 2005;174:8183–8190. 6. Ying, O'Connor B, et al. *J Immunol* 2008;181:2790–2798.



Eosinophils Promote Mucus Plug Formation



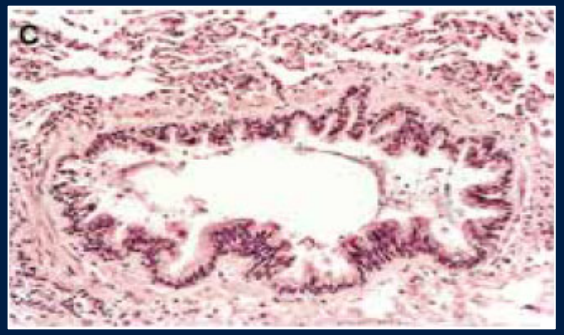
- EPO, eosinophil peroxidase; HOSCN, hypothiocyanous acid; SCN, thiocyanate

Dunican EM, et al. *J Clin Invest* 2018;128:997–1009.

Increased Eosinophils Contribute to Mucus Plugging

Elevated eosinophils in the lungs cause airway inflammation and damage

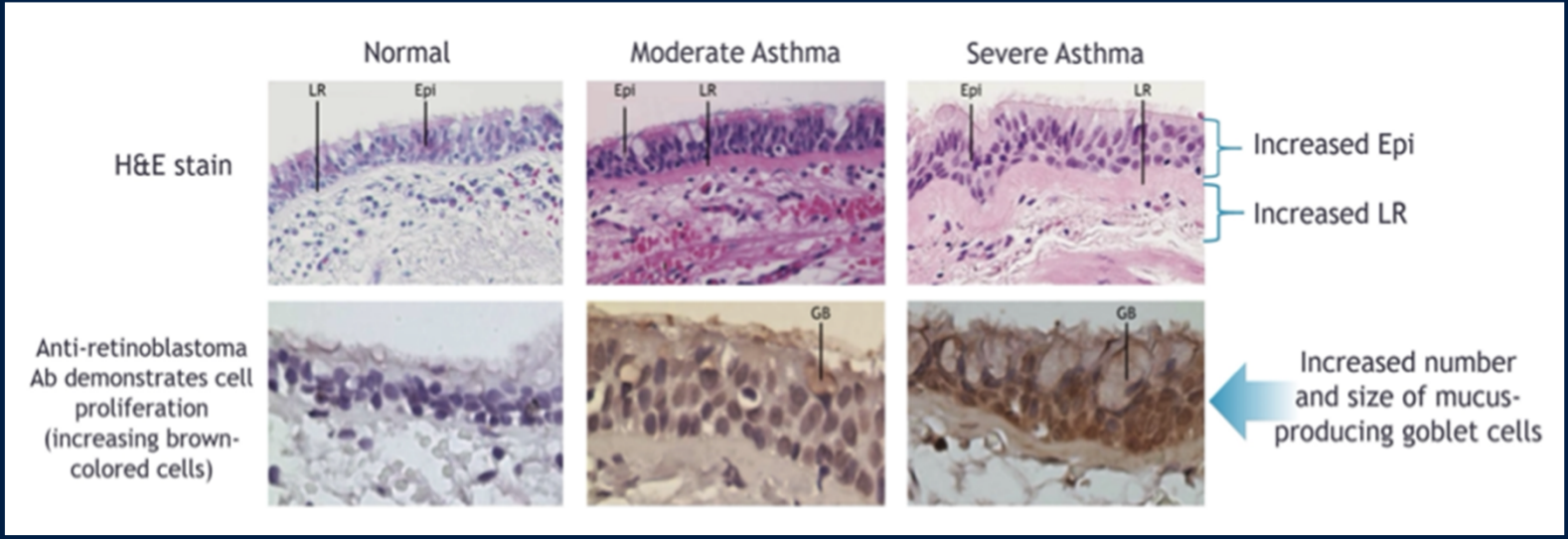
Normal airway[1]



Airway of patient with fatal asthma[1]

Reprinted from J Allergy Clin Immunol, Vol 106/issue 6,William W. Busse MDa, Susan Banks-Schlegel PhDb, Sally E. Wenzel MDc , Pathophysiology of severe asthma;1033-1042;2000, with permission from Elsevier.

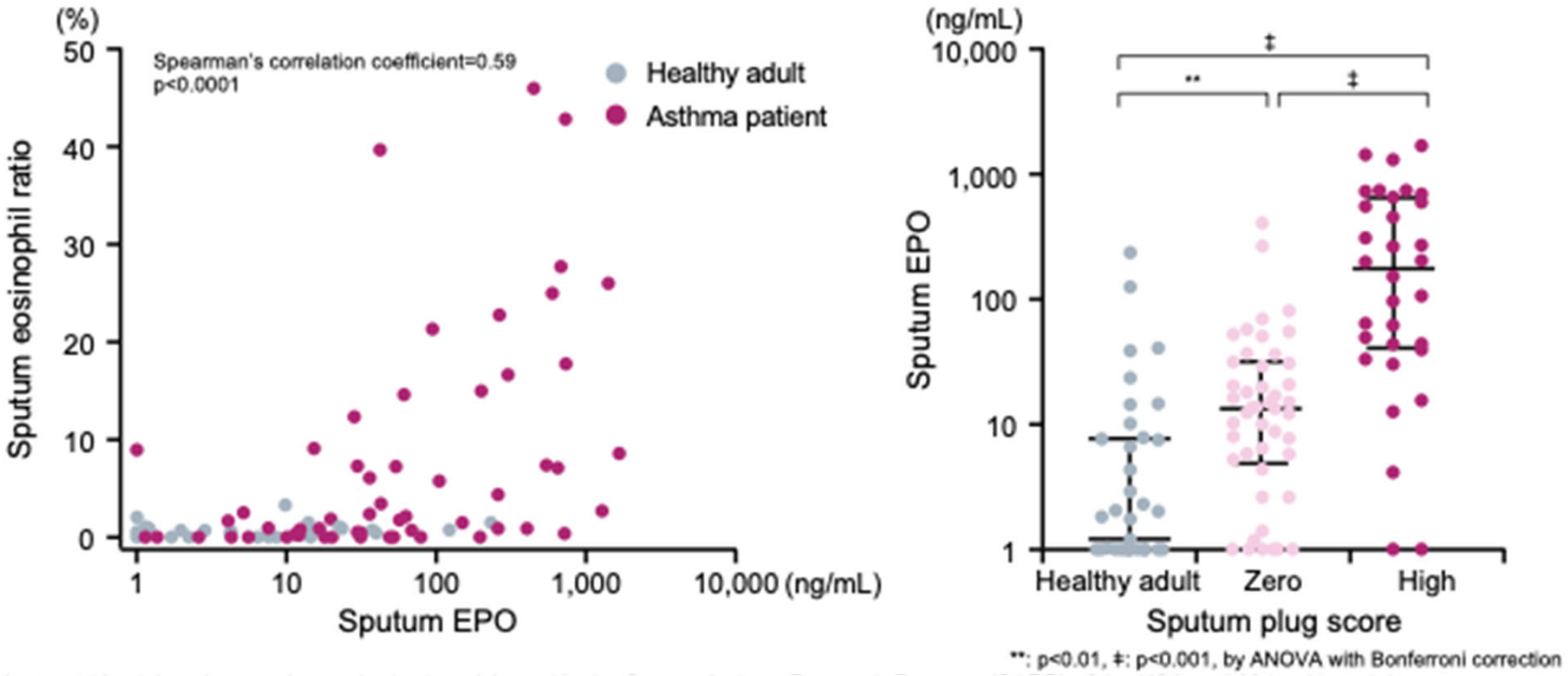
Mucus is Produced by Goblet Cells and Can Lead to Remodeling in Severe Asthma



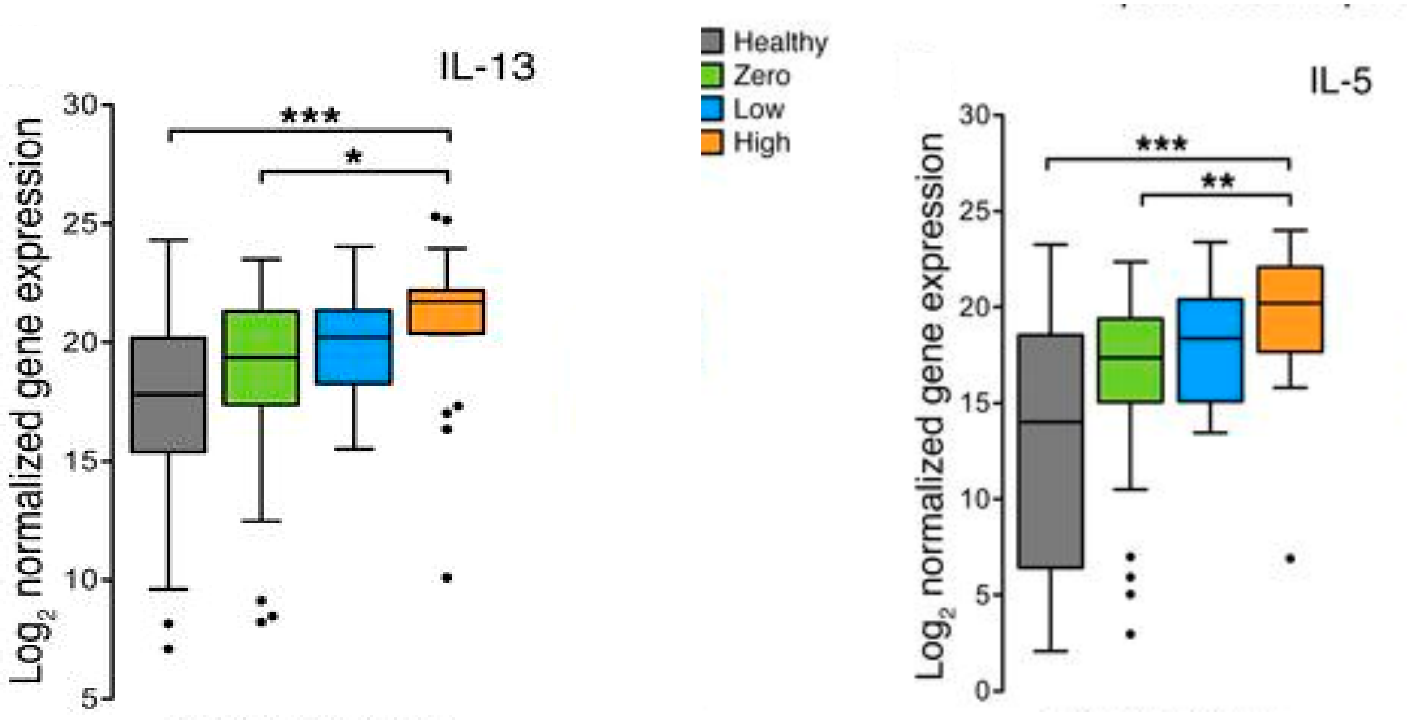
Shifren A et al. *J Allergy* (Cairo). 2012; 2012-316049.

Eosinophil products are associated with mucus plugging

- Patients with a higher mucus plug score had larger amounts of EPO in the sputum



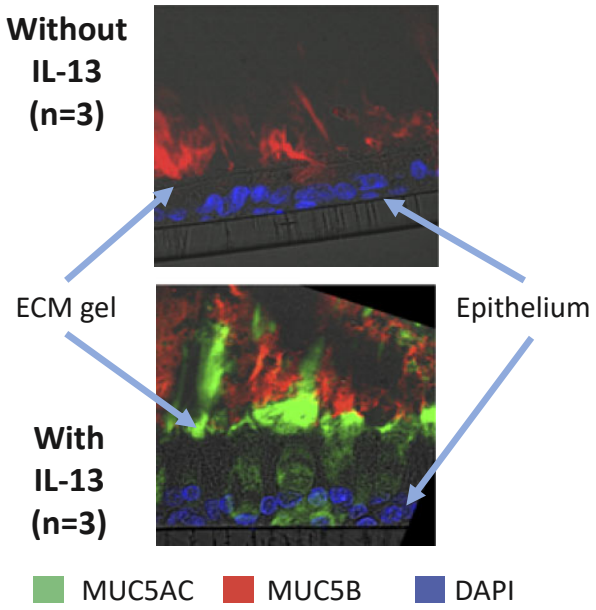
Type 2 Cytokine Expression is Associated with High Mucus Plug Scores



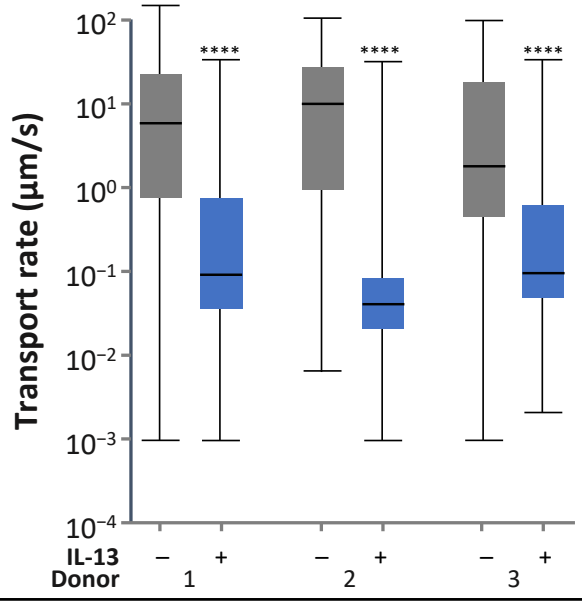
***P < 0.001; **P < 0.01; *P < 0.05. P values were determined by Kruskal-Wallis test with Dunn's correction

IL-13 Is a Key and Central Driver of Excess Mucus Production and Plugging

IL-13 Increases MUC5AC Expression (Cross-sectional Staining From HBE Cultures)[1]



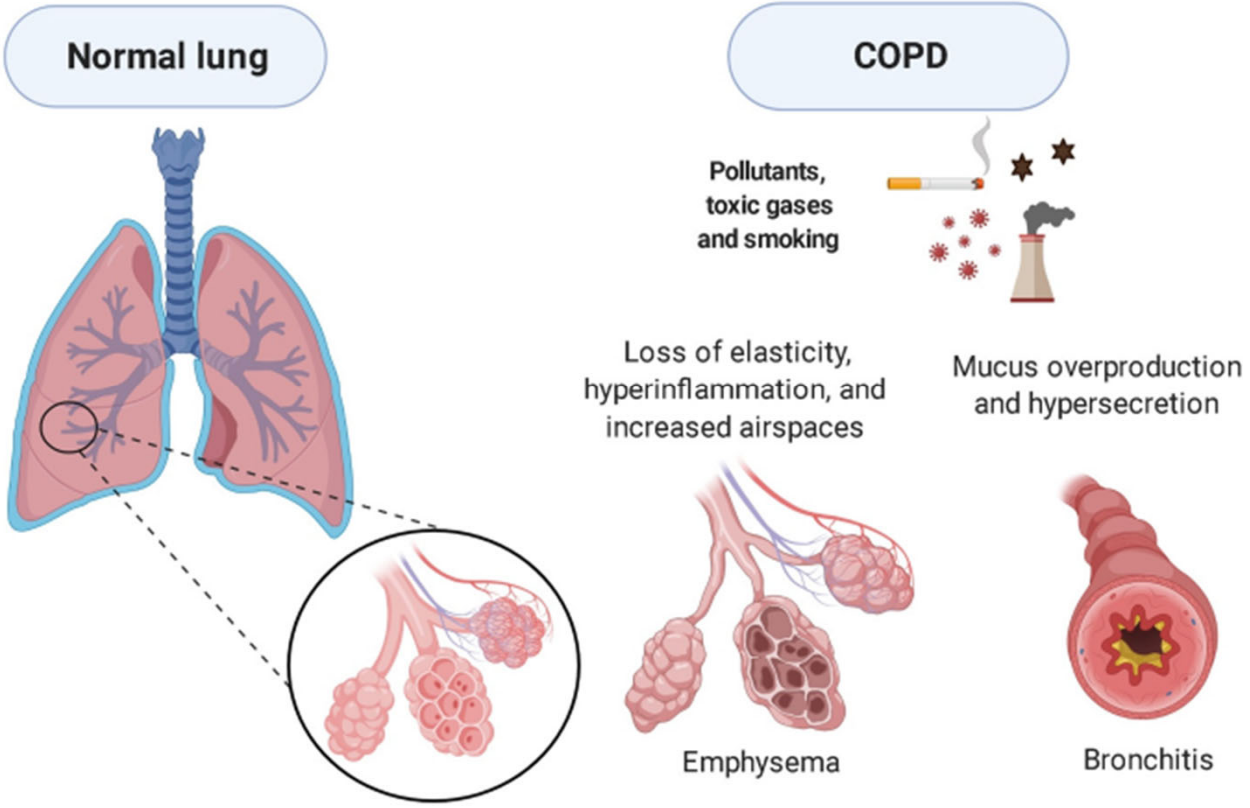
Mucus Transport Is Impaired When MUC5AC Is Overexpressed (IL-13 Stimulated HBE Cultures)[1]



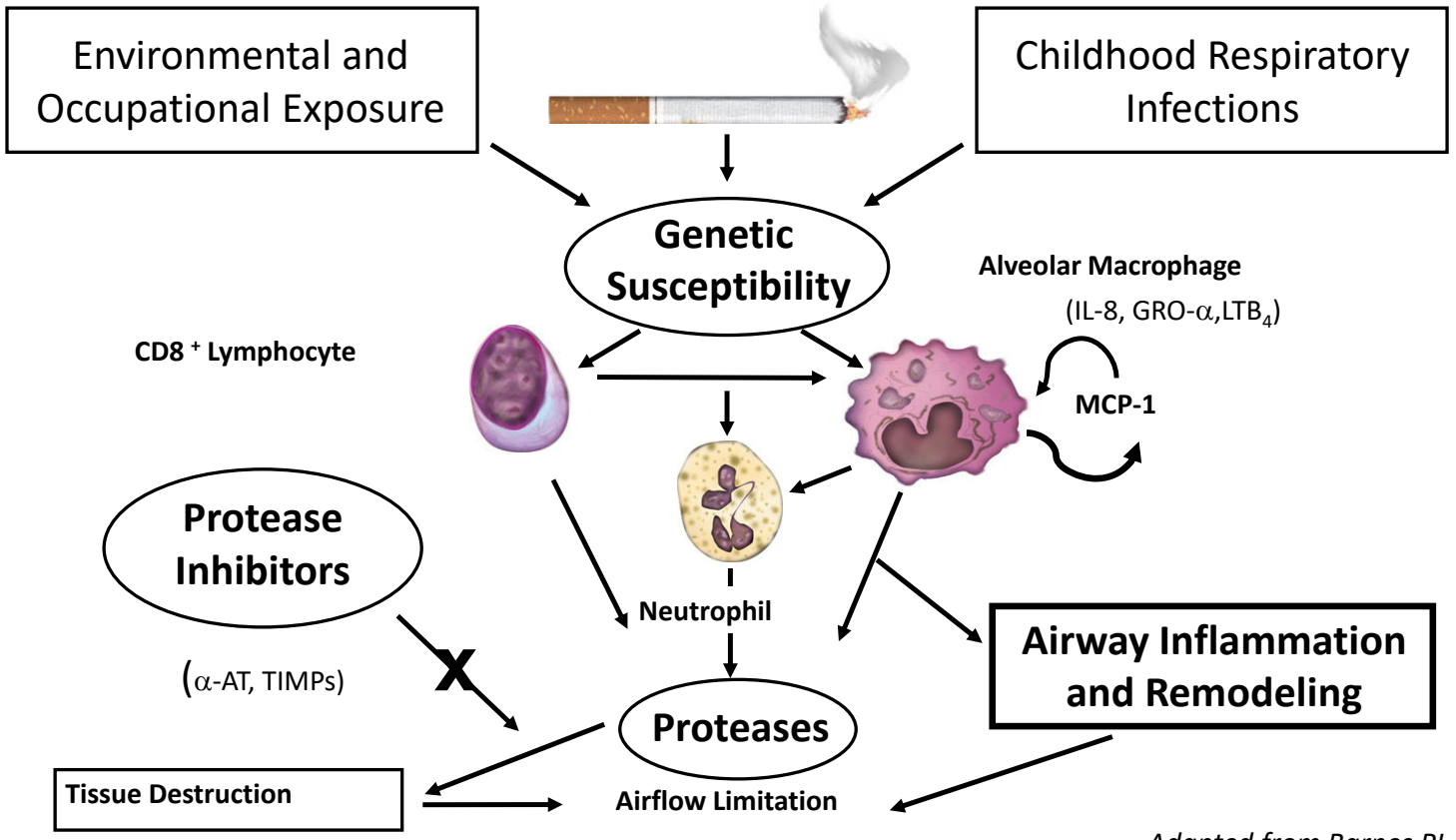
"Used with permission of American Society for Clinical Investigation, from Epithelial tethering of MUC5AC-rich mucus impairs mucociliary transport in asthma, Bonser LR, et al. J Clin Invest. 2016;126:2367–2371]; permission conveyed through Copyright Clearance Center, Inc."

p<0.05. ***p*<0.001. ****p*<0.0001. ECM, extracellular matrix; HBE, human bronchial epithelial; IL, interleukin.

Used with permission of American Society for Clinical Investigation, from Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction, Eleanor M Dunican, J Clin Invest 2018;128:997–1009 permission conveyed through Copyright Clearance Center, Inc.

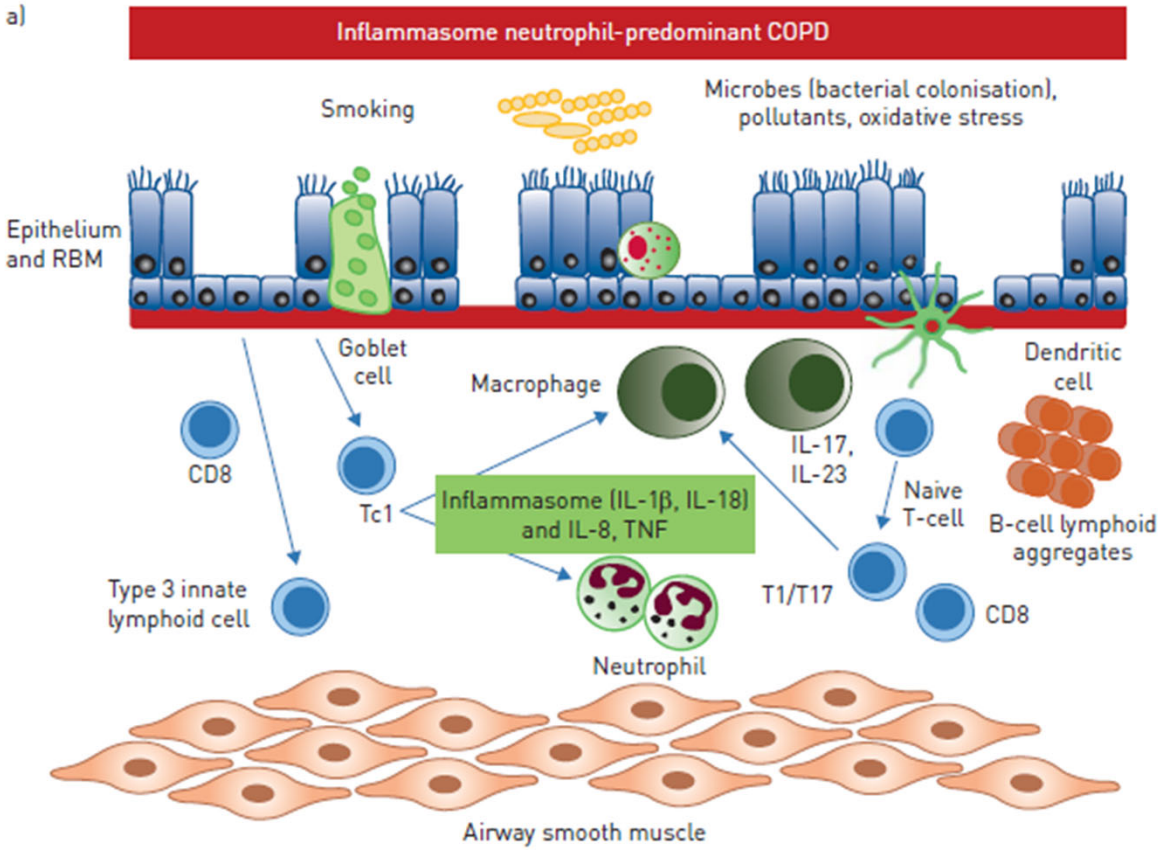


COPD Pathogenesis Leading to Tissue Destruction

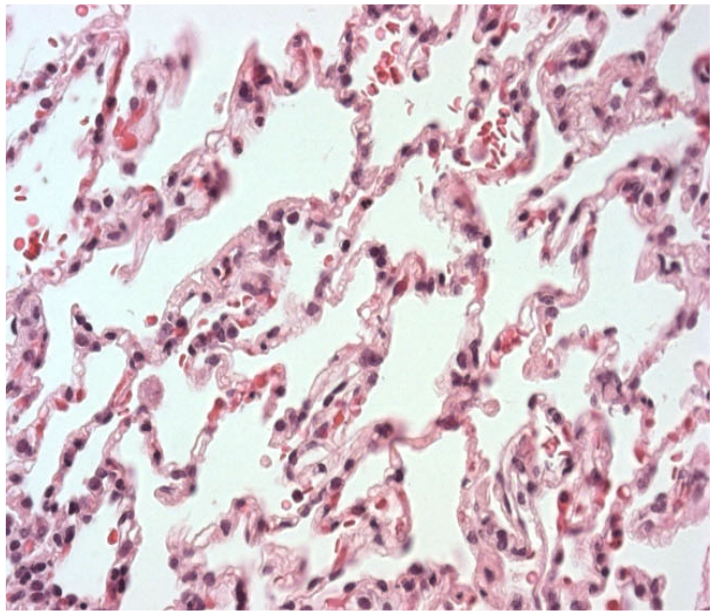


Adapted from Barnes PJ. Chest. 2000;117:10S

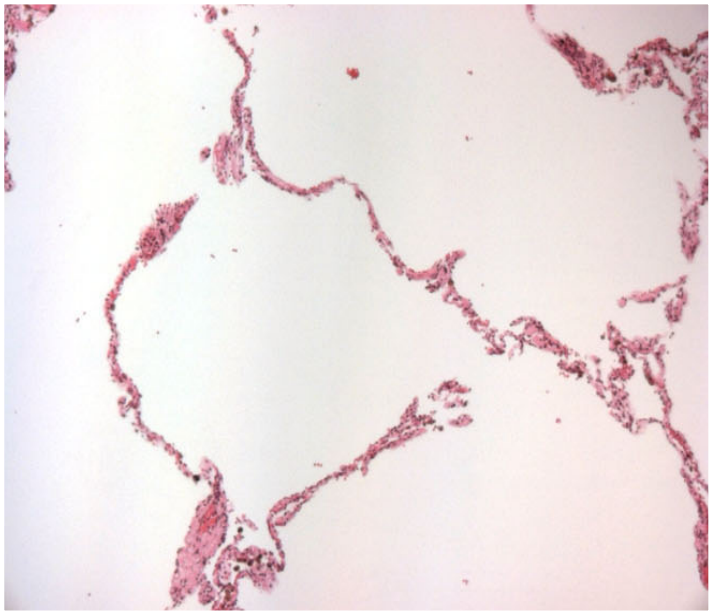
Non-T2: Inflammasome and T3 Inflammation



Brightling et al. *Eur Resp J* 2019; 54:1-14

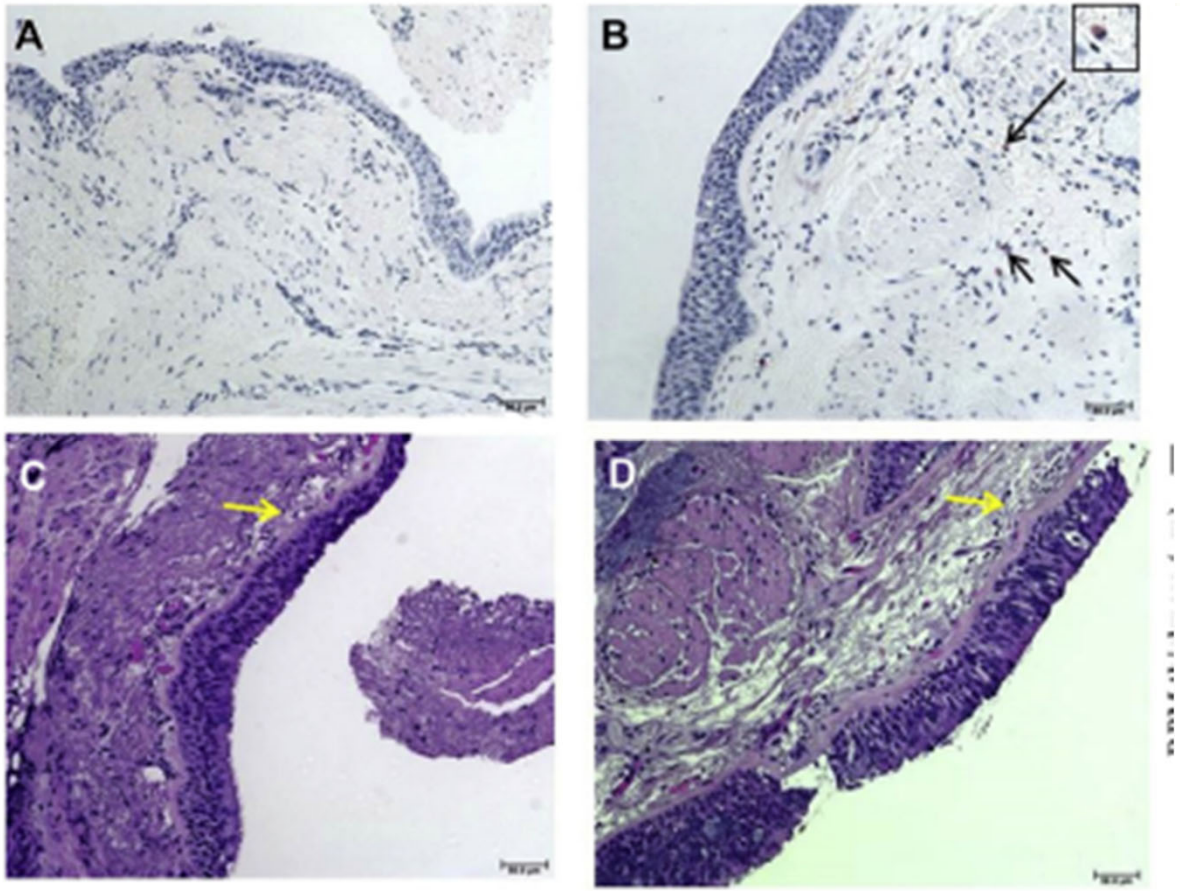


Normal Lung



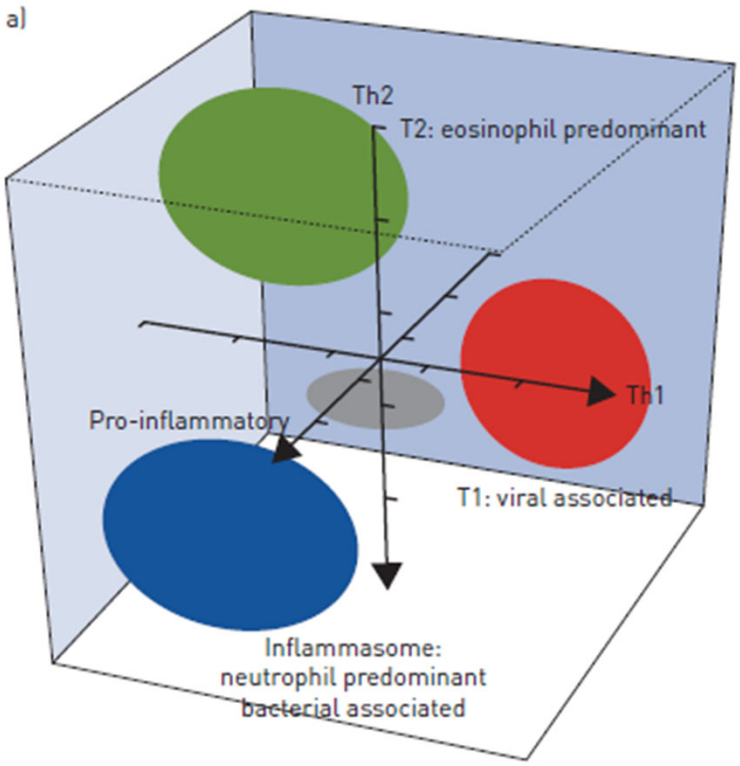
Parenchymal Changes of Emphysema

With permission from Rubin Tuder, MD, Johns Hopkins Medical Institute and Carlyne Cool, MD, National Jewish Medical and Research Center

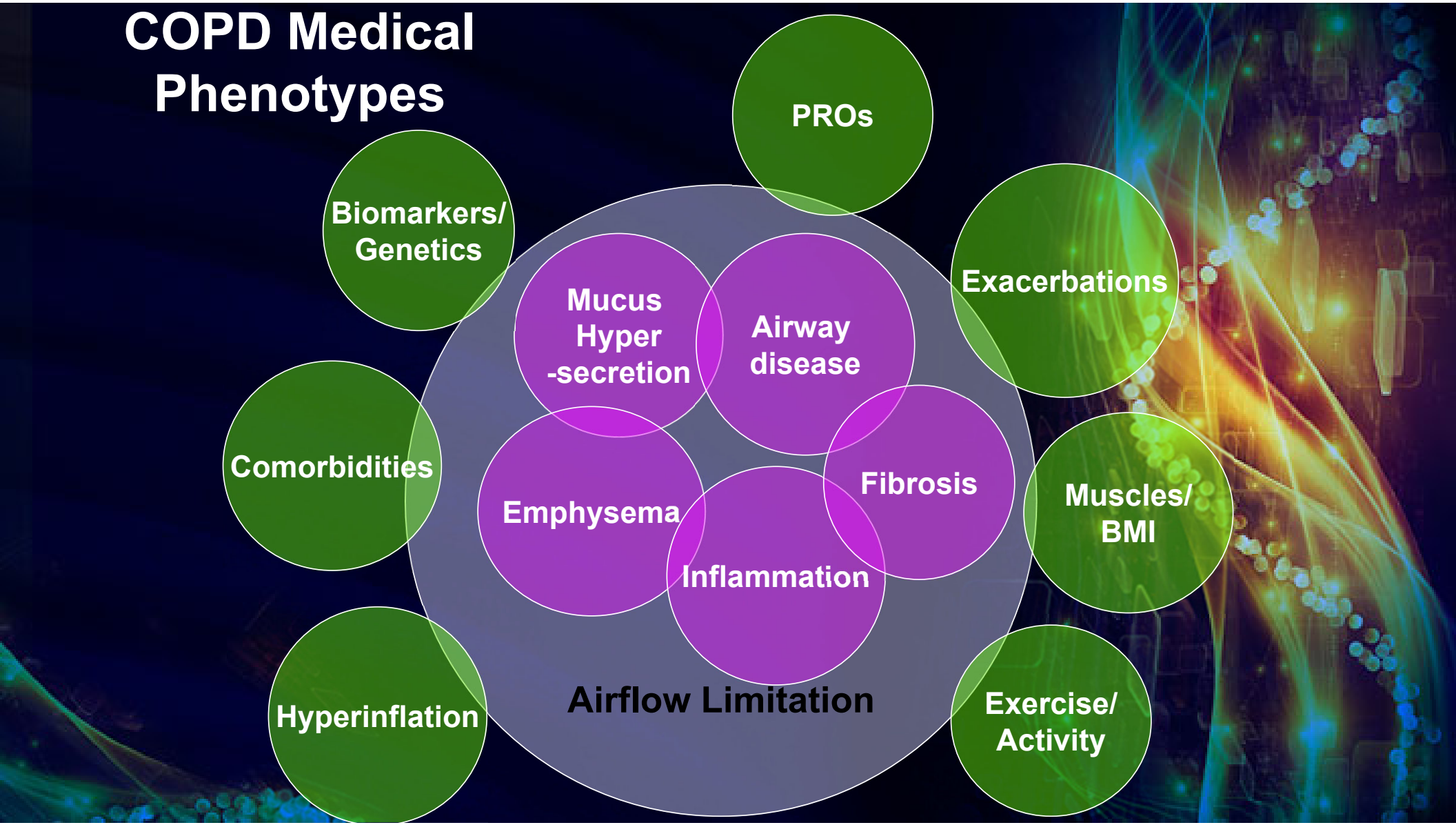


Kolsum U, Damera G, Pham TH, et al. Pulmonary inflammation in patients with chronic obstructive pulmonary disease with higher blood eosinophil counts. J Allergy Clin Immunol. 2017;140:1181-1184.e7

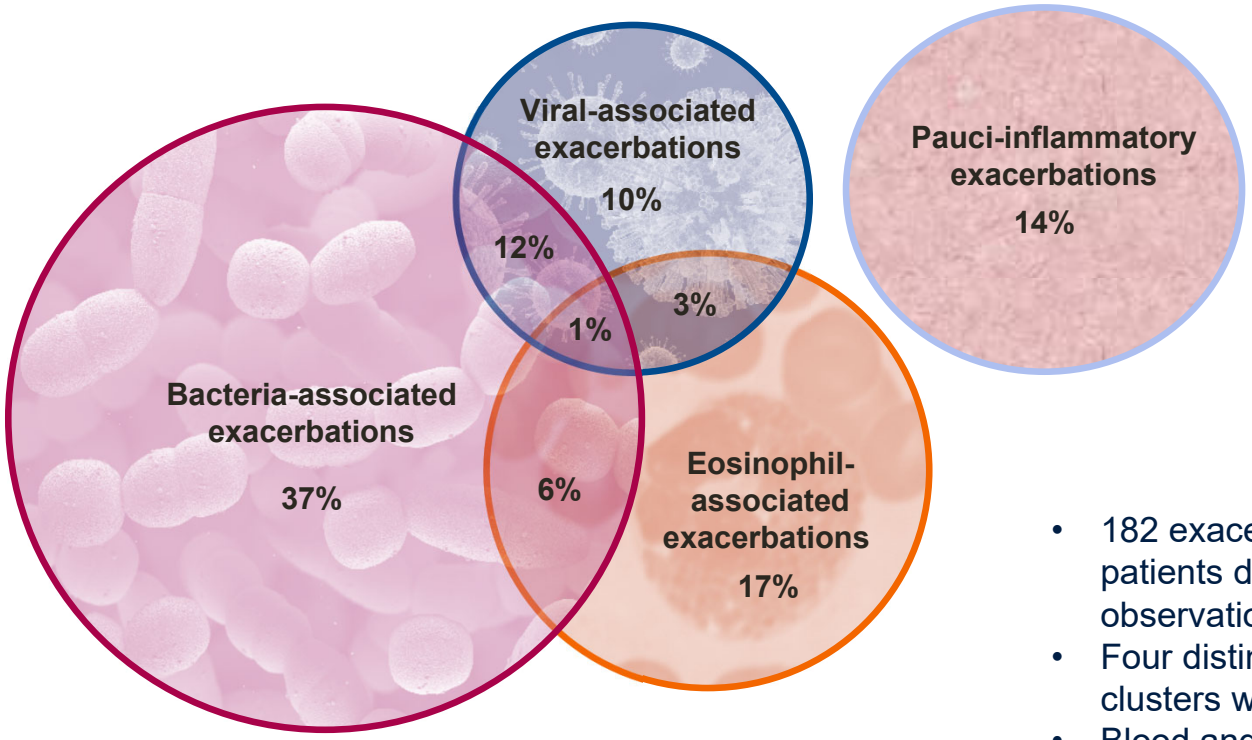
Inflammatory Phenotype/Endotype



Brightling et al. *Eur Resp J* 2019; 54:1-14



Etiologic and inflammatory causes of COPD exacerbations



- 182 exacerbations were captured from 86 patients during a 12-month, prospective, observational study
- Four distinct biologic exacerbation clusters were identified
- Blood and sputum neutrophils were increased in bacteria-associated exacerbations

Adapted from: Bafadhel M, et al. *Am J Respir Crit Care Med.* 2011;184:662–671.

Blood eosinophil counts as a predictor of readmission

Outcome	Eosinophil-associated COPD (n = 55)	Non-eosinophil-associated COPD (n = 112)	Crude OR	Adjusted OR
	No. (%)	No. (%)		
12-month COPD-related readmission	26 (47.3)	28 (25.0)	2.54 [1.27–5.08]*	3.59 [1.65–7.82]*
12-month all-cause readmission	37 (67.3)	60 (53.6)	1.68 [0.85–3.31]	2.32 [1.10–4.92]†
	Median [IQR]	**Median [IQR]**	**Crude exp(β)**	**Adjusted exp(β)**
Length of stay, days	5 [2–6]	5 [3–7]	1.15 [0.88–1.50]	1.19 [0.91–1.55]

Eosinophil/non-eosinophil matched for age, race, gender, FEV_1, ICS use. Model adjusted for age, race. OR (logistic regression) or exp(β) (negative binomial regression) [95% CI].
IQR = interquartile range. *p <0.01. † p <0.05.

Based on a 12-month observational study following patients who were hospitalized for COPD exacerbation, higher blood eosinophil counts may be a biomarker in severe COPD exacerbations for predicting higher readmission rates.

Reference: Couillard S, et al. *Chest.* 2017;151:366–373.