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Chronic Rhinosinusitis: Advances in Phenotypes, Endotypes, and Clinical Treatment Options

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Chronic Rhinosinusitis

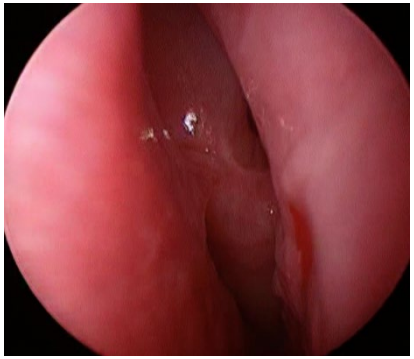
- Chronic inflammatory disorder of the paranasal sinuses

- Clinical symptoms (lasting for at least 12 weeks) include:
  - Anterior or posterior nasal rhinorrhea
  - Nasal congestion
  - Facial pressure/pain
  - Hyposmia

- Evidence of sinonasal inflammation on sinus CT scan and/or on nasal endoscopy

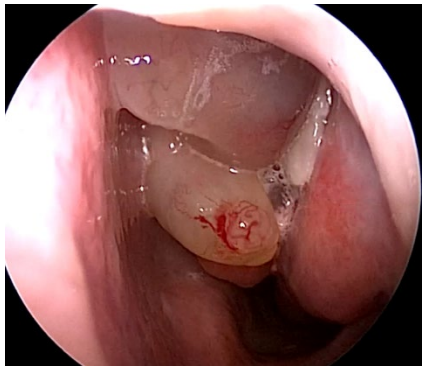
Chronic Rhinosinusitis: Phenotypes

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)



- Majority of patients with CRS (80%)
- 30% have comorbid asthma
- Mechanistically is less well-studied
- Fewer available treatment options

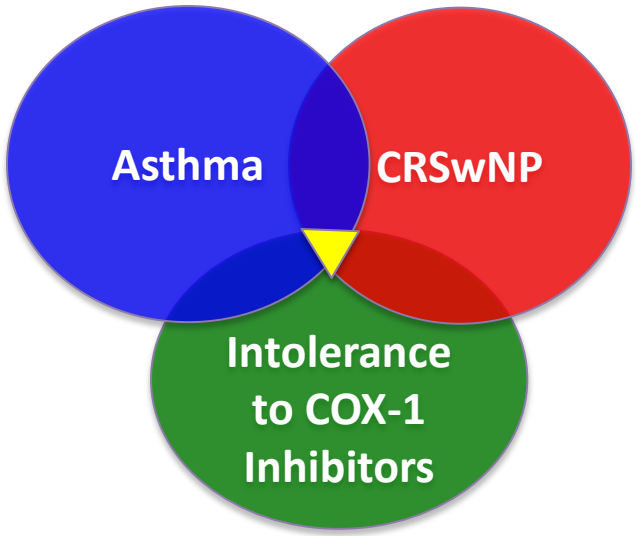
Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)



- Minority of patients with CRS (18-20%)
- More severe disease than CRSsNP
- 30% recurrence rate of polyps following sinus surgery
- 50-60% have comorbid asthma
- More mechanistic studies available
- Recent advances in treatment options

Benjamin M et al. JACI: IP. 2019 Mar;7(3):1010-1016.
Stevens WW et al. JACI: IP. 2017 Jul-Aug;5(4):1061-1070.

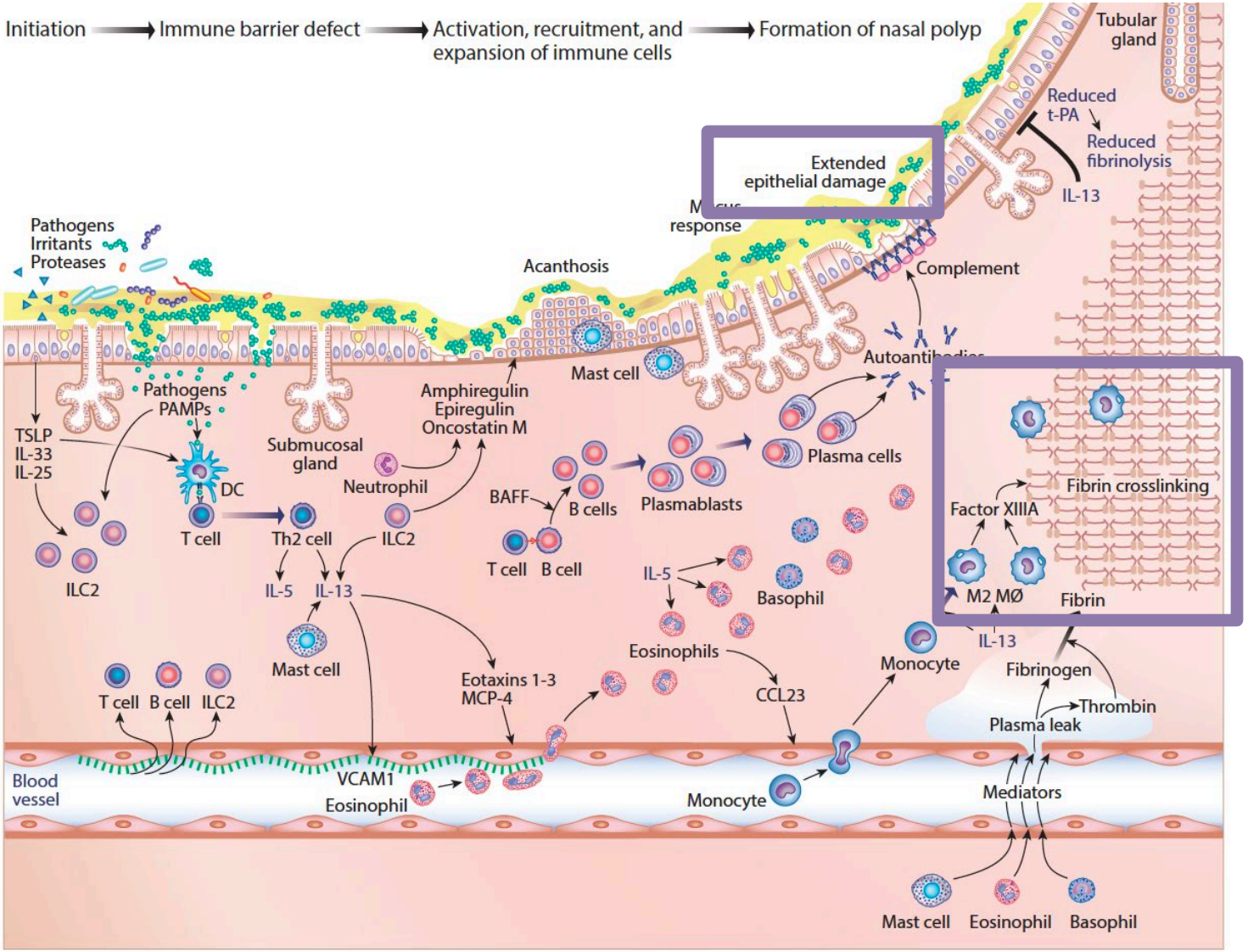
Aspirin Exacerbated Respiratory Disease (AERD)



- Clinical triad of CRSwNP, asthma, and intolerance to COX-1 inhibitors
- Observed in 12.4-15% of asthmatics
- Observed in 9.7-16% of patients with CRSwNP
- Typically is associated with more severe upper and lower respiratory disease
- Dysregulation of arachidonic acid metabolism thought to play a role in AERD pathogenesis
- Recent advances in treatment options

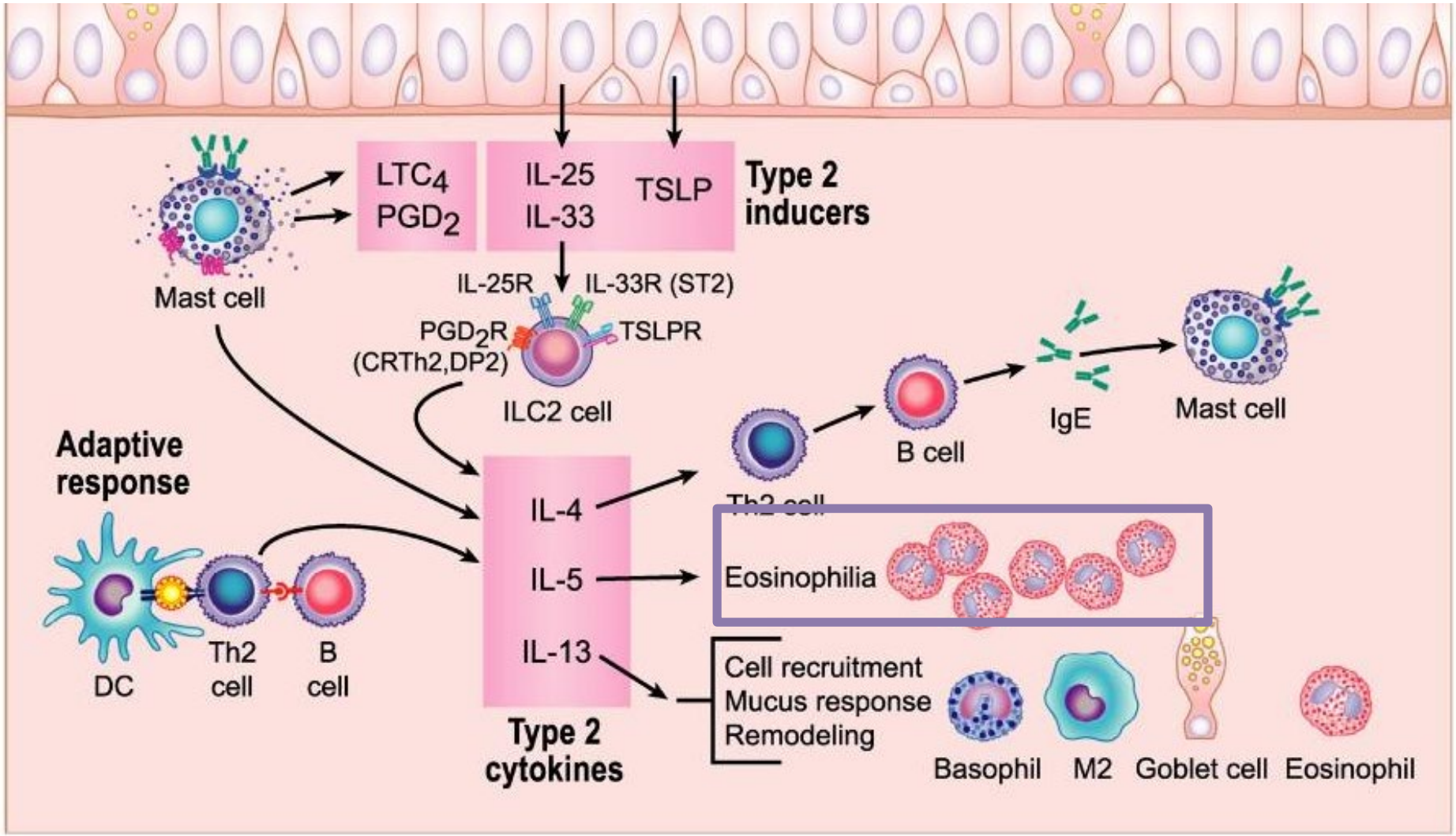
Rajan et al. JACI. 2015 Mar;135(3):676-81.
Stevens W et al. JACI: IP. 2017 Jul-Aug;5(4):1061-1070

Overview of CRSwNP pathogenesis



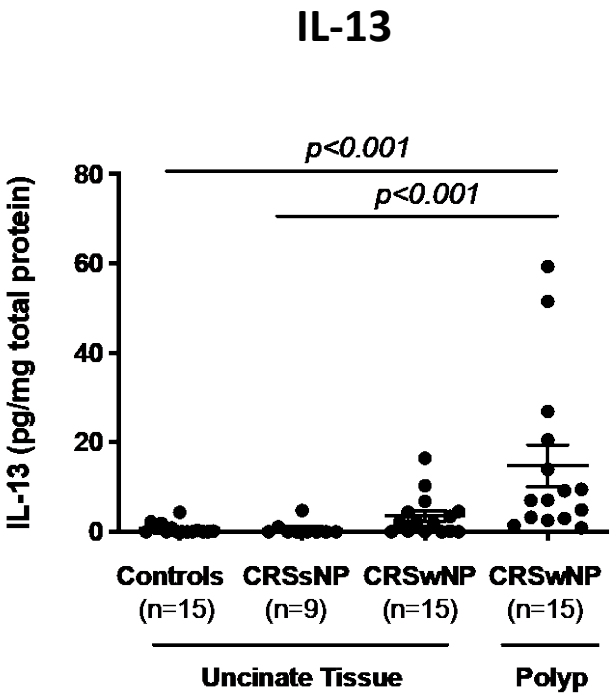
Schleimer RP. Annu Rev Pathol. 2017 Jan 24;12:331-357.

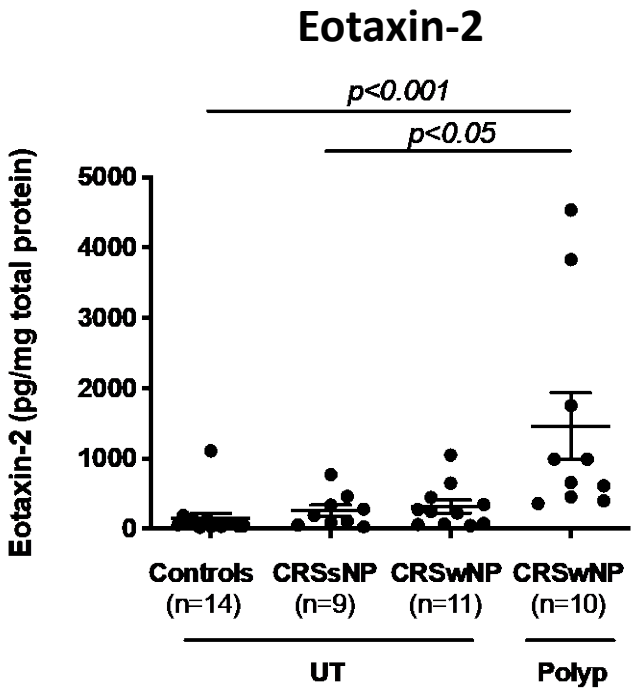
Simplified overview of CRSwNP pathogenesis

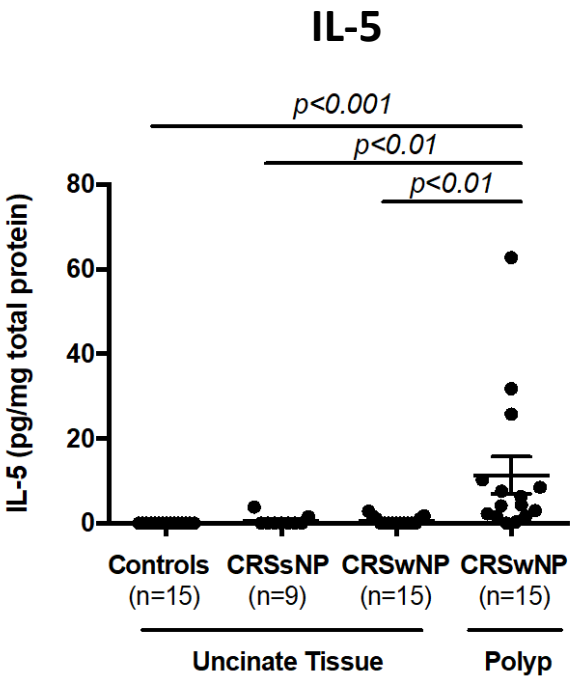


Hulse KE et al. Clin Exp Allergy. 2015 Feb;45(2):328-46.

Type 2 Inflammation in CRSwNP: Factors that promote eosinophil survival and chemotaxis





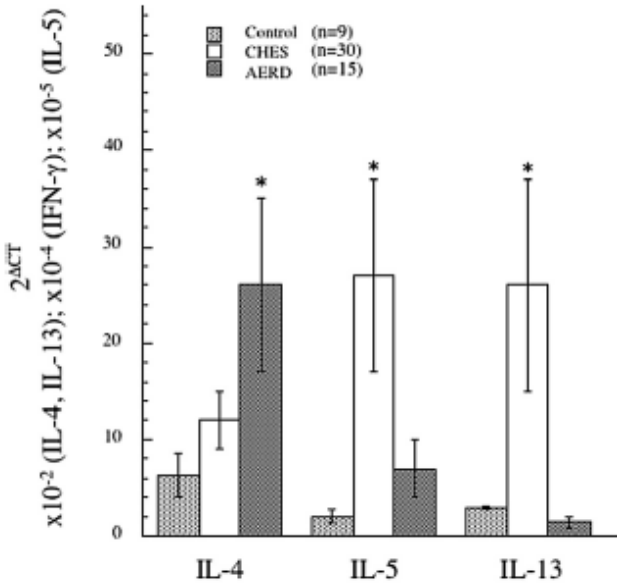


Stevens et al. Am J Respir Crit Care Med. 2015 Sep 15;192(6):682-94.

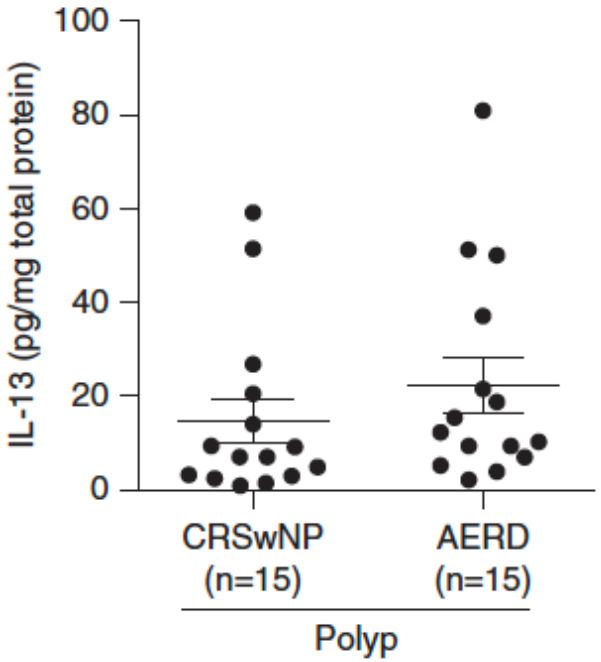
Type 2 Inflammation in CRSwNP and AERD

Nasal Polyp

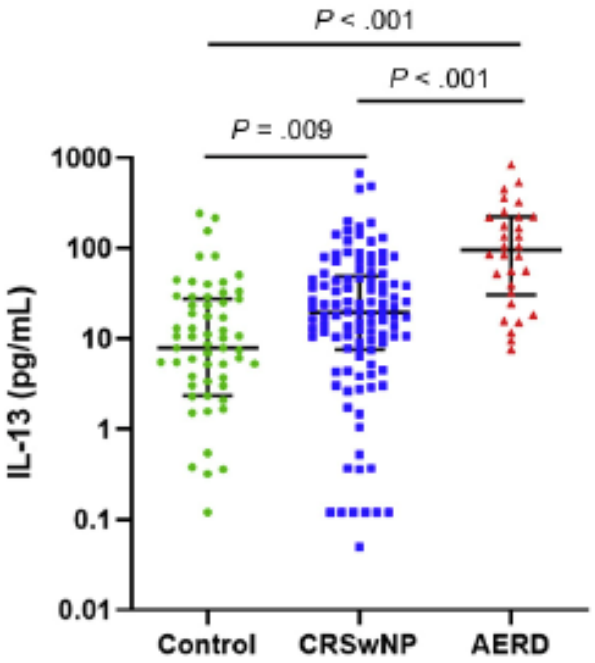
Gene Expression



Protein Levels

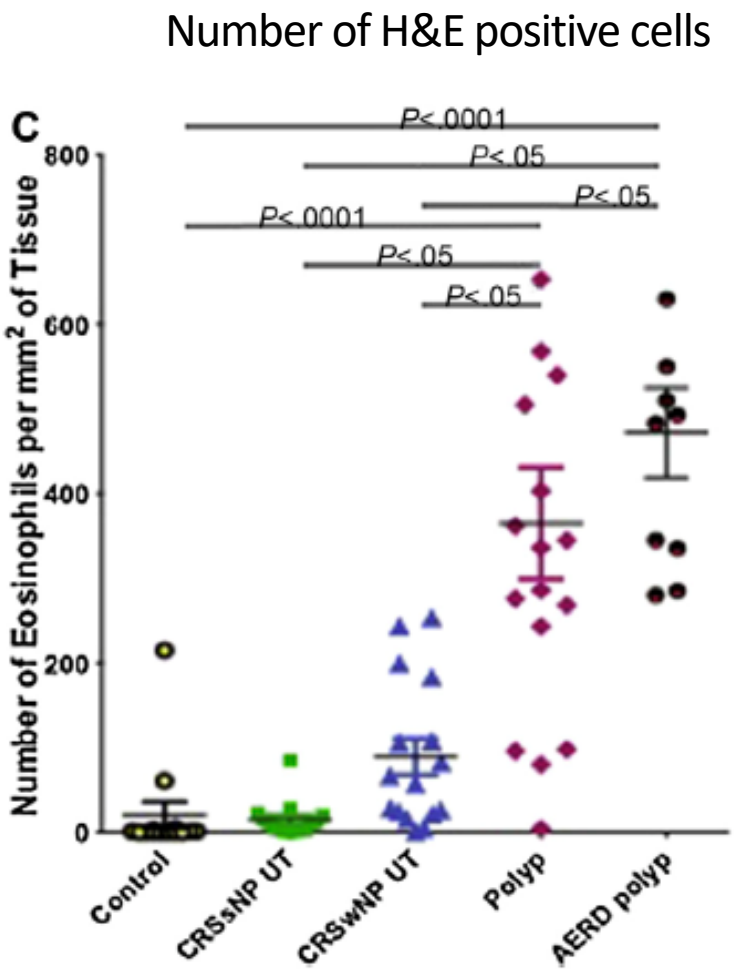


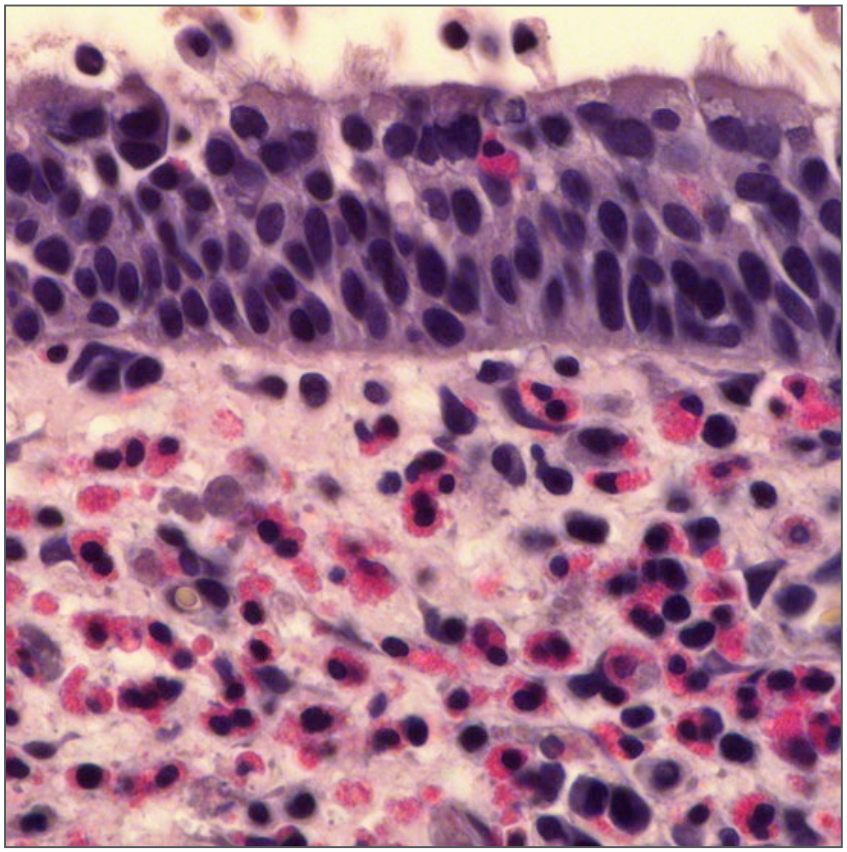
Nasal Secretions



Steinke et al. JACI. 2013 Oct;132(4):856-65.
Stevens et al. AJRCCM. 2015 Sep 15;192(6):682-94.
Scott et al. JACI.. 2021 Apr;147(4):1318-1328.

Eosinophils are elevated in most nasal polyps





Currently, there is no uniform consensus for the number of eosinophils / hpf that defines "eosinophilic" CRSwNP

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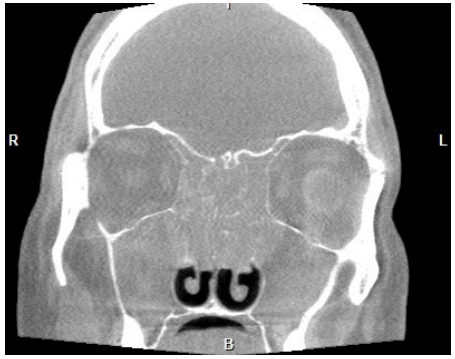
Mahdavinia et al., J Allergy Clin. Immunol. 2014. 133:1759.

What role do eosinophils play in CRSwNP?

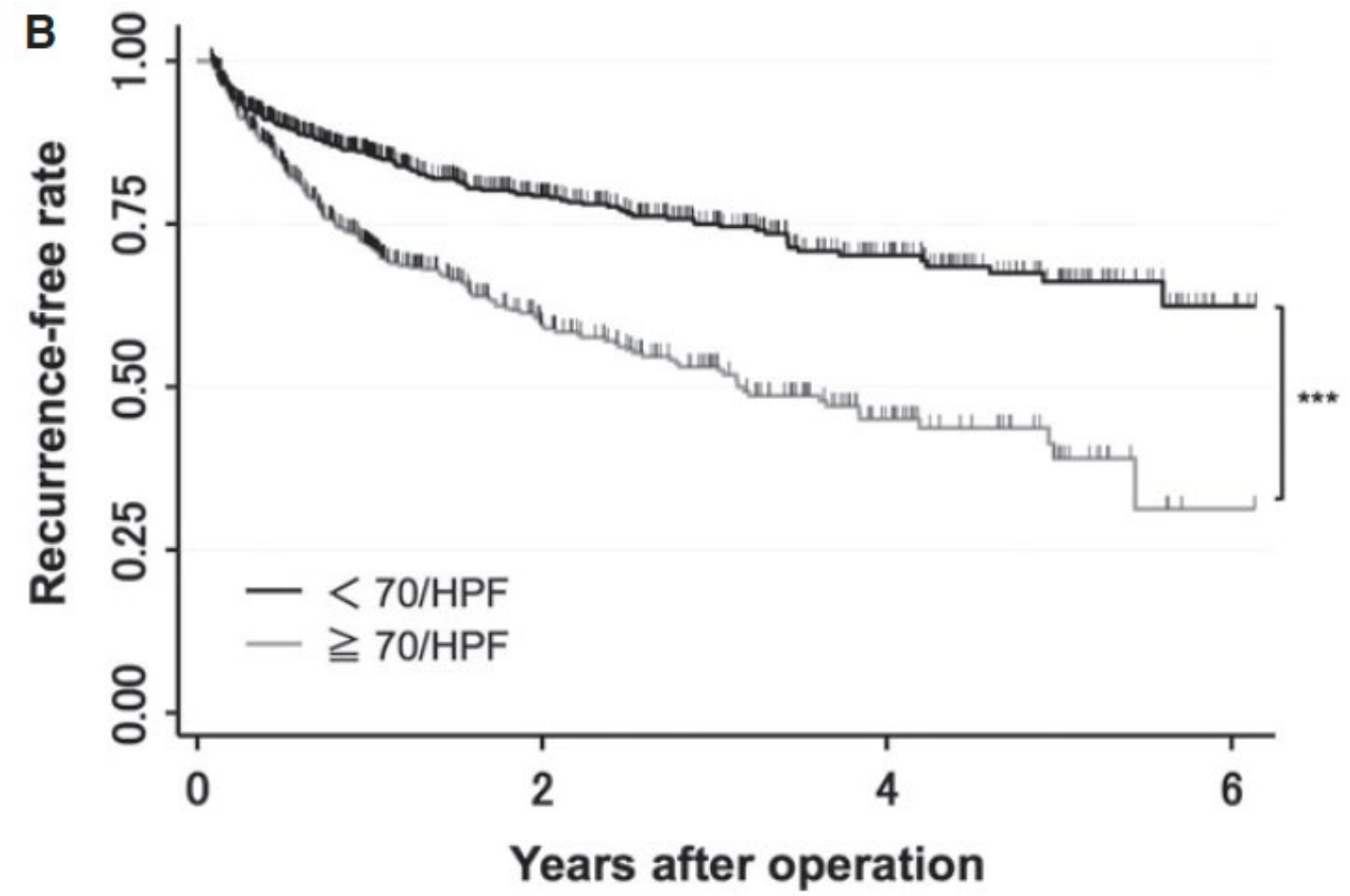


Objective Clinical Findings

Subjective Clinical Symptoms

Clinical Biomarker?

Tissue eosinophilia is associated with CRS recurrence



Tokunaga et al. Allergy. 2015 Aug;70(8):995-1003.

Peripheral eosinophilia is associated with CRS recurrence

Table 3 Multivariate Cox proportional hazards model: refractoriness of chronic rhinosinusitis

	Hazard ratio	*P* value
Peripheral blood eosinophils		
≤2%	1	
2< ≤5%	1.72 (0.95–3.10)	0.072
5< ≤10%	1.86 (1.49–3.32)	0.036*
10% <	2.12 (2.66–4.06)	0.024*
CT shadow: ethmoid ≥ maxillary	2.15 (1.22–3.79)	0.008**

CT, computer tomography. Values in parentheses are 95% confidence intervals. **P* value < 0.05; ***P* value < 0.01.

Tokunaga et al. Allergy. 2015 Aug;70(8):995-1003.

ECP and IL-5 are prognostic factors for polyp recurrence

TABLE II. Multivariate logistic regression analyses of the predictors in CRSwNP

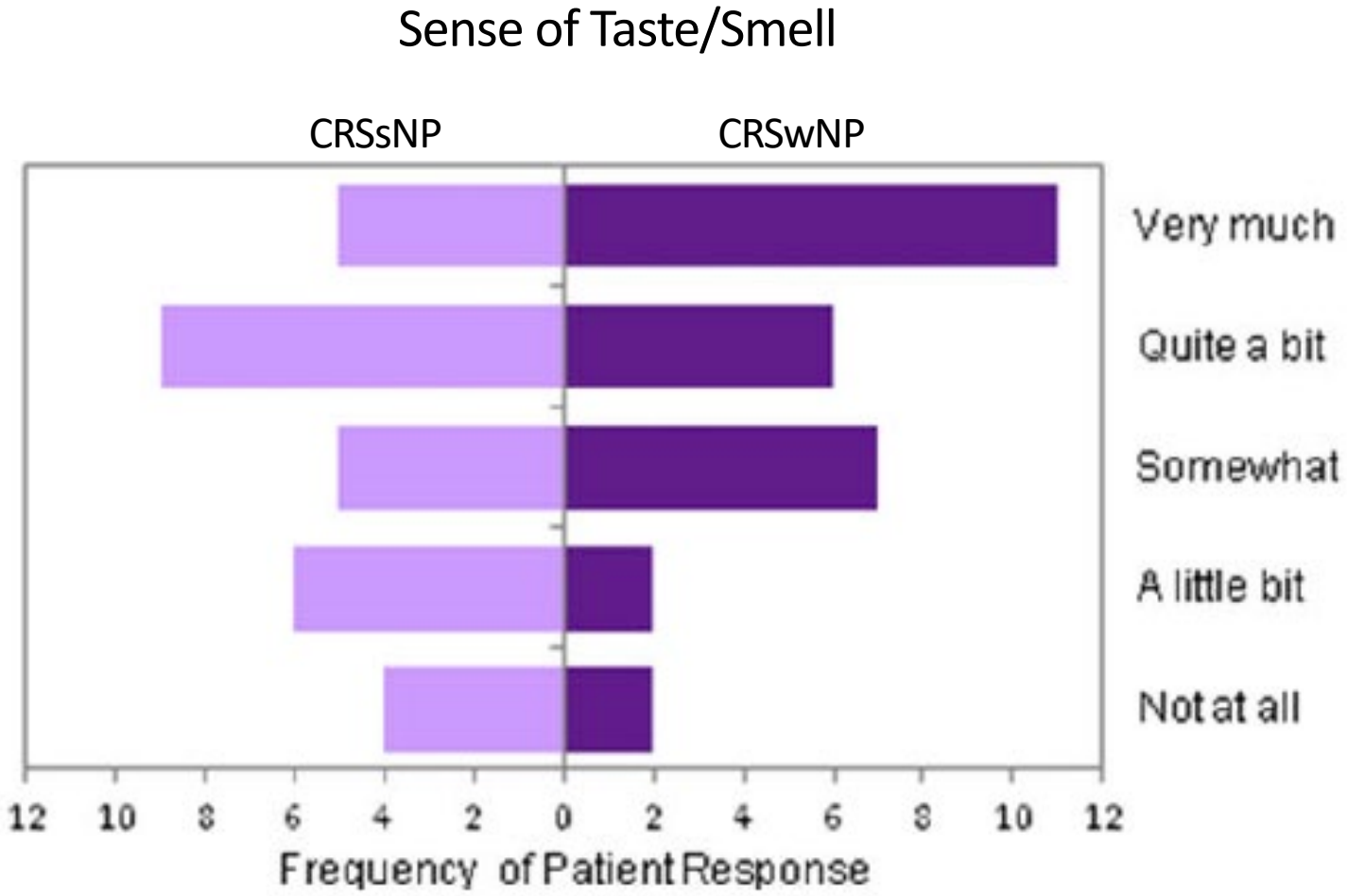
Analysis methods	Estimate	Std. Error	z value	P
Multivariate analysis [a]				
Clinical prediction model				
Pre-ESS MLM	0.07	0.03	2.46	* P < 0.05
Asthma	1.80	0.60	3.15	** P < 0.01
Biomarker prediction model				
log (ECP)	0.72	0.23	3.10	** P < 0.01
log (anti-dsDNA IgG)	0.44	0.27	1.63	* P < 0.05
log (IL-5)	0.17	0.19	0.93	* P < 0.05
Combined prediction model				
Pre-ESS MLM	0.08	0.03	2.29	* P < 0.05
Asthma	2.36	0.74	3.20	* P < 0.05
log (ECP)	0.44	0.27	1.60	* P < 0.05
log (anti-dsDNA IgG)	0.59	0.33	1.80	* P < 0.05
log (IL-5)	0.54	0.25	2.16	* P < 0.05

[a] Multivariate models were adjusted for age and sex.

ESS – endoscopic sinus surgery
MLM – modified Lund Mackay (radiographic measure of sinonasal disease severity)

Bai J et al. JACI. 2022 Aug;150(2):352-361.

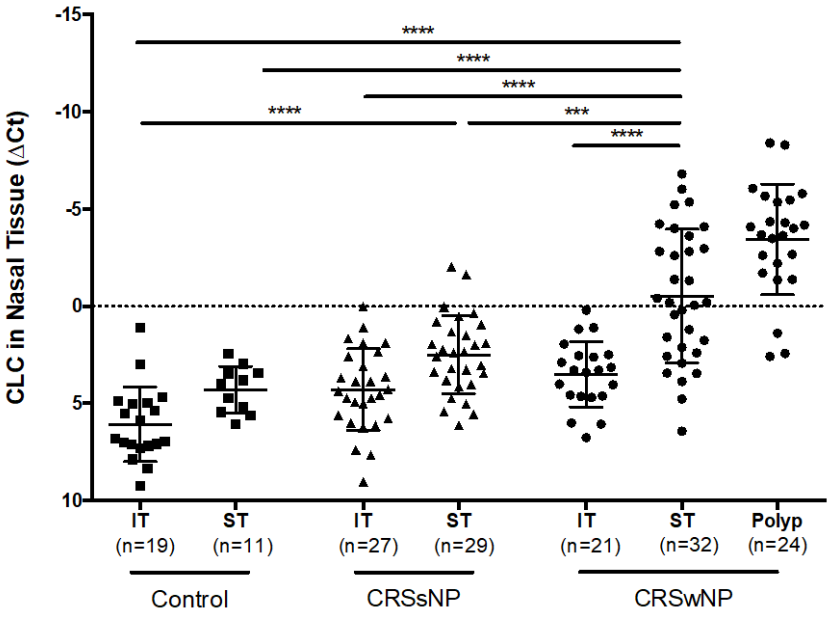
Reduced smell is a common clinical symptom of CRSwNP



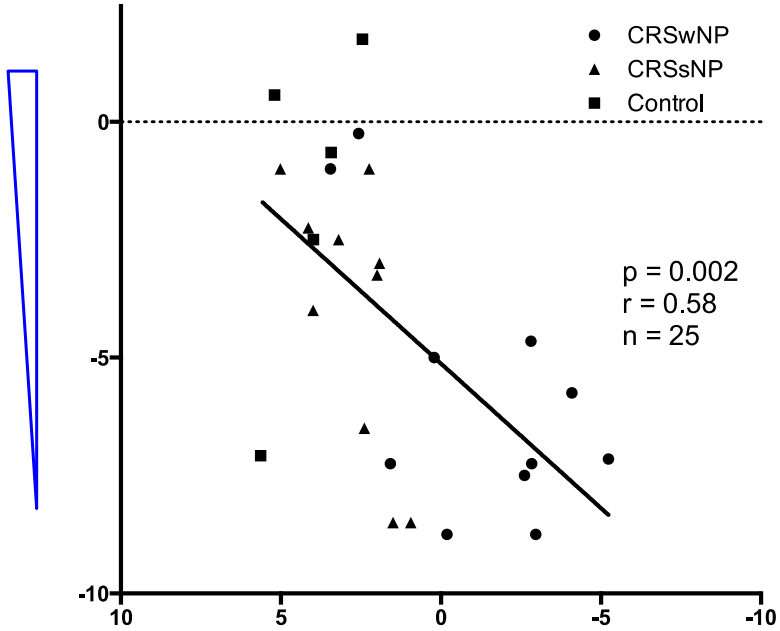
Thompson C et al. Int Forum Allergy Rhinol. 2016 May;6(5):500-7.

Olfactory eosinophilia correlated with olfaction function

CLC expression



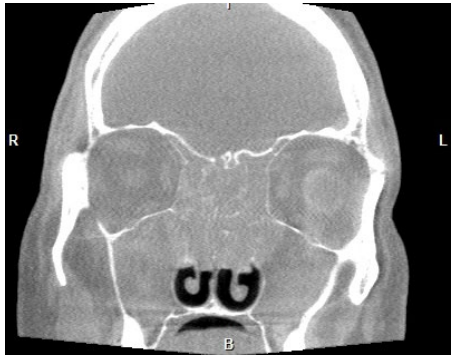
CLC expression vs Sense of Smell

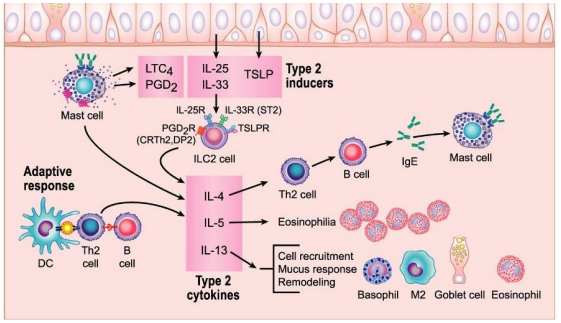


IT – inferior turbinate
ST – superior turbinate
NP – nasal polyp

Lavin J et al. Laryngoscope. 2017 Oct;127(10):2210-2218.

What role do eosinophils play in CRSwNP?





Objective Clinical Findings

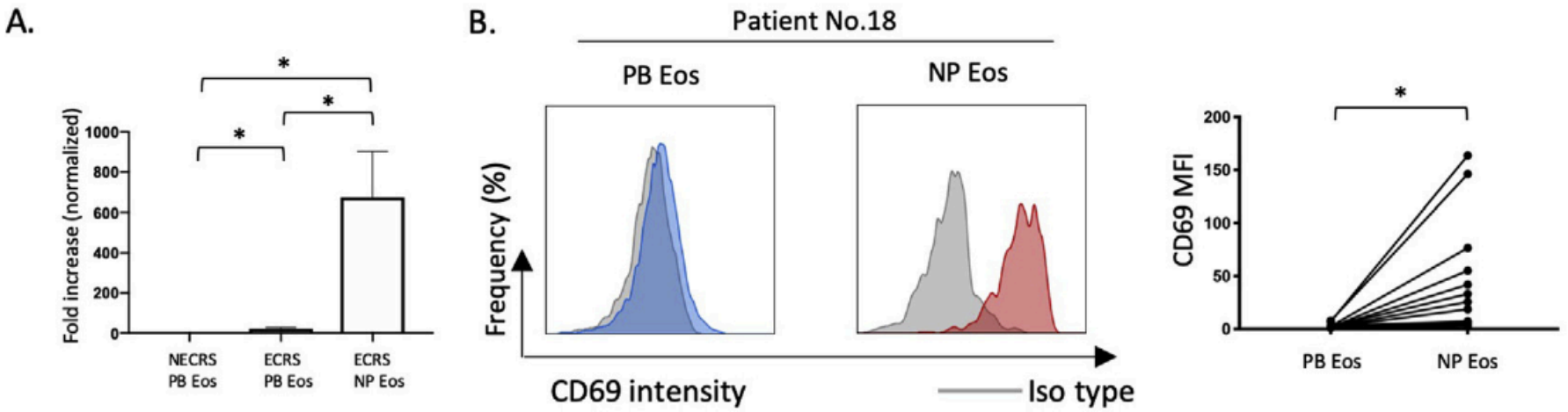
Subjective Clinical Symptoms

Disease Pathogenesis

Clinical Biomarker?

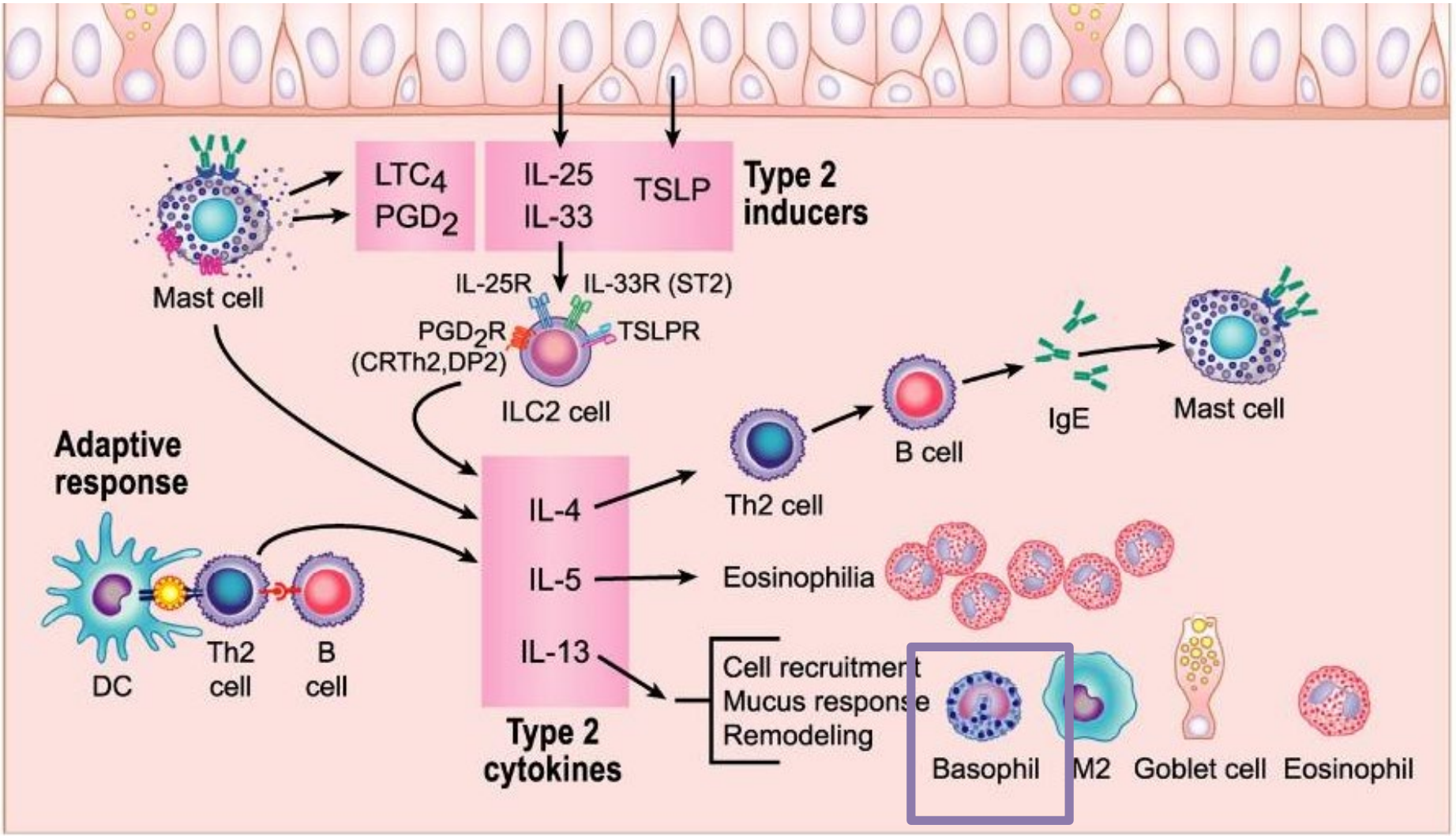
Direct Mediator?

CD69 surface expression on eosinophils is elevated in nasal polyps compared to peripheral blood



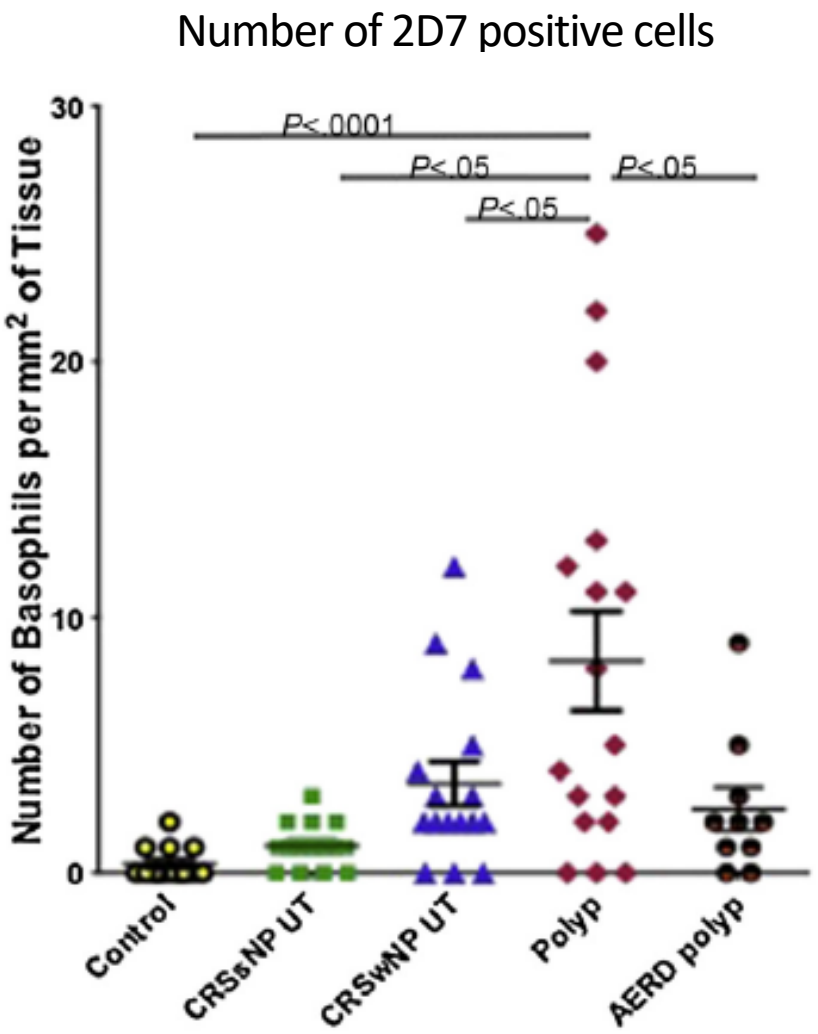
Yun Y et al. Allergol Int. 2020 Apr;69(2):232-238.

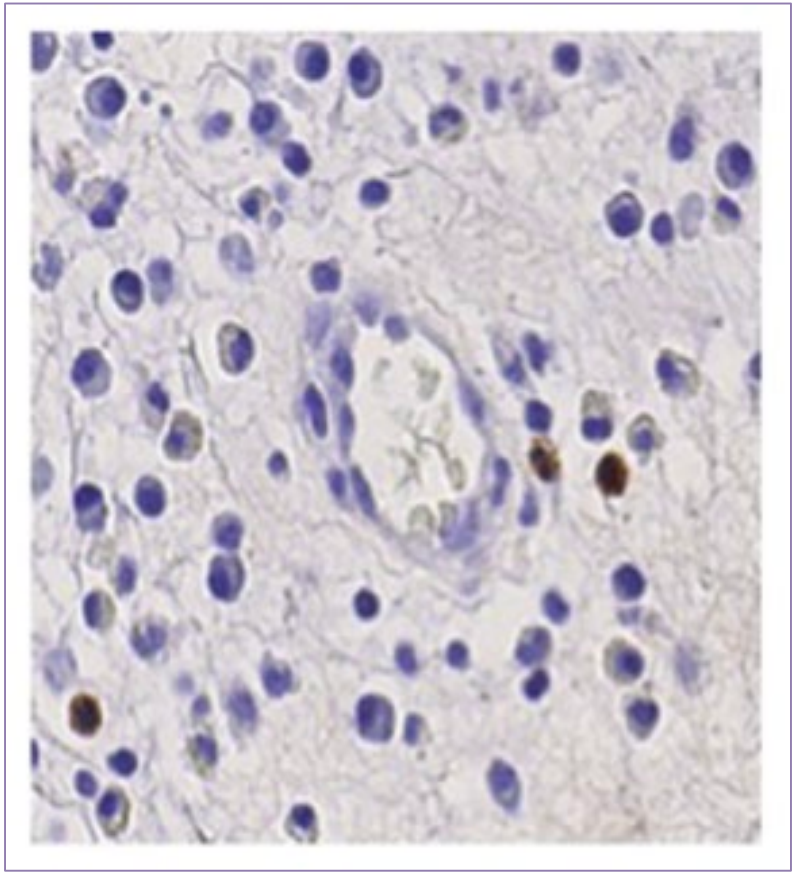
Simplified overview of CRSwNP pathogenesis



Hulse KE et al. Clin Exp Allergy. 2015 Feb;45(2):328-46.

Basophils are elevated in CRSwNP but not AERD nasal polyps

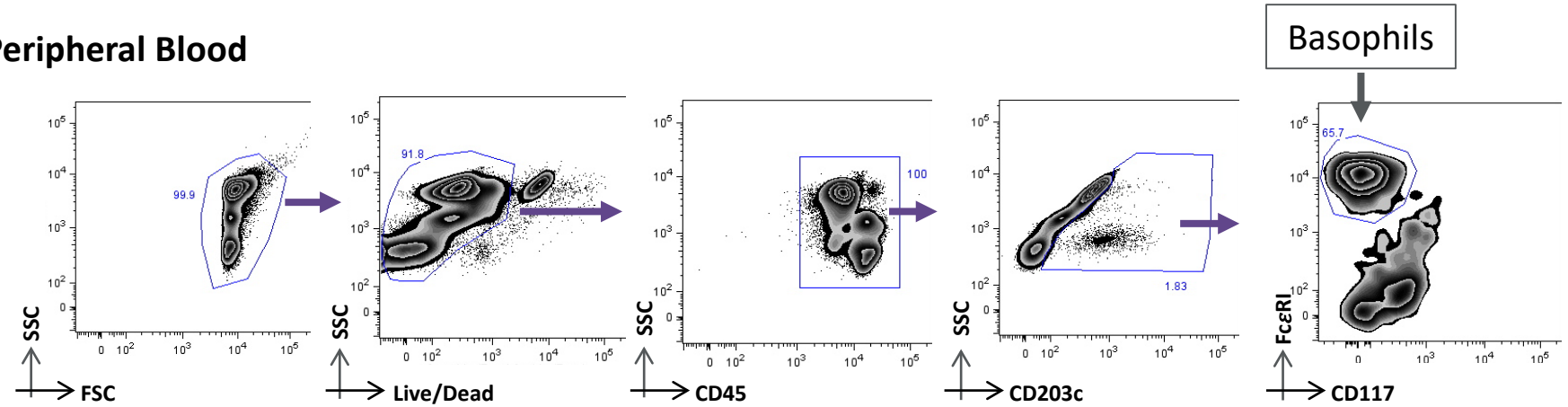




Mahdavinia M et al., JACI. 2014 Jun;133(6):1759-63.

Flow cytometry-based approach to identify basophils

Peripheral Blood



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Stevens W et al. JACI. 2021 Aug;148(2):439-449.

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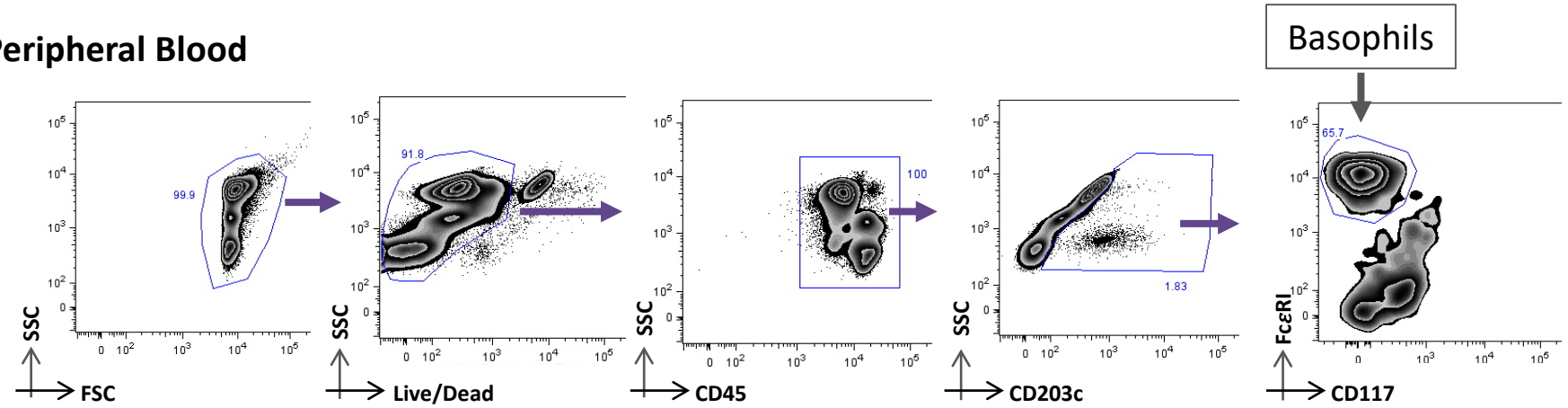
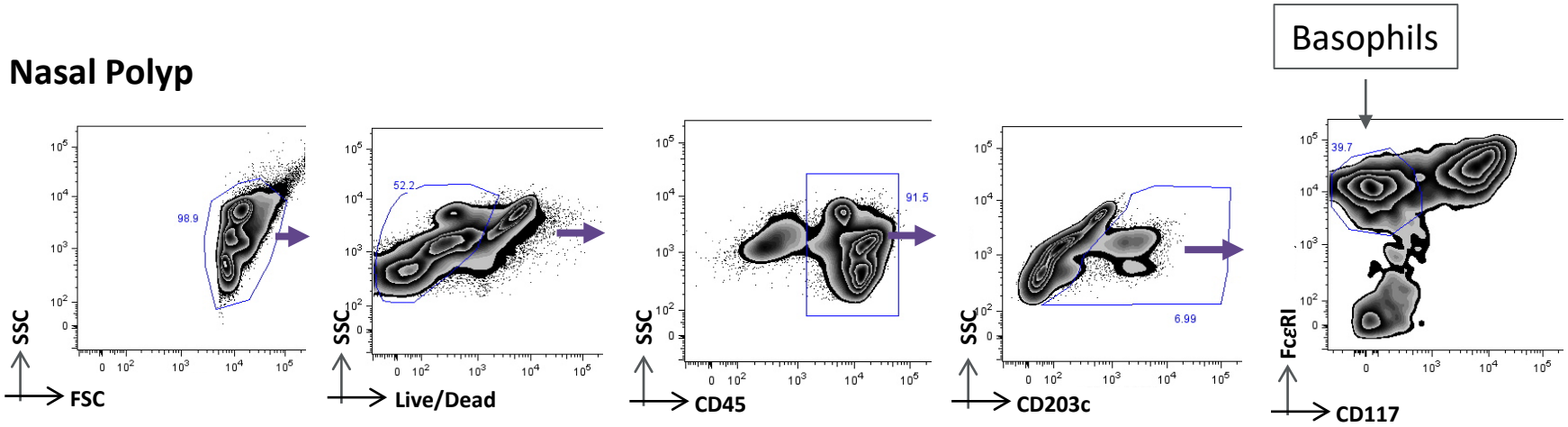


Nasal Polyp



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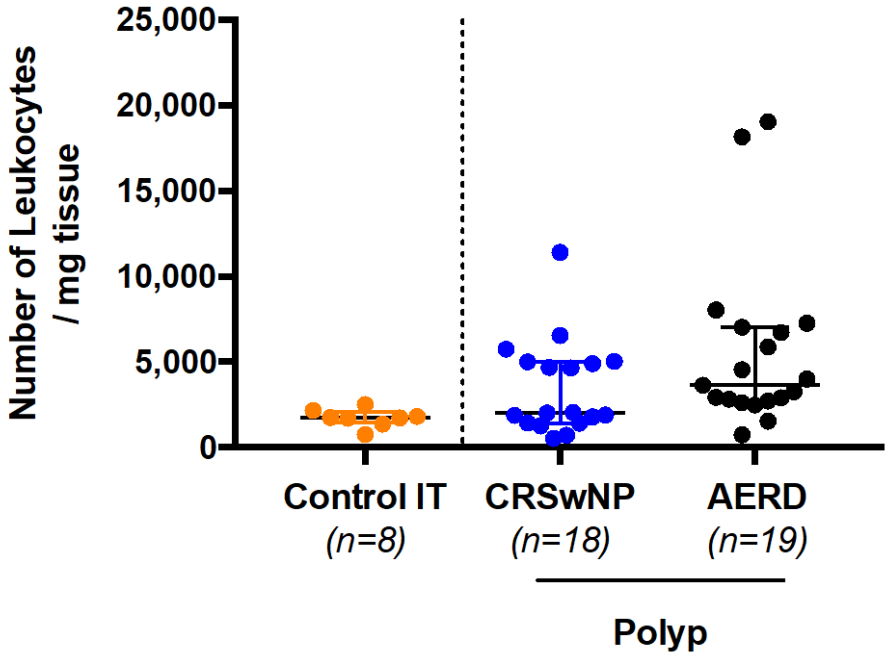
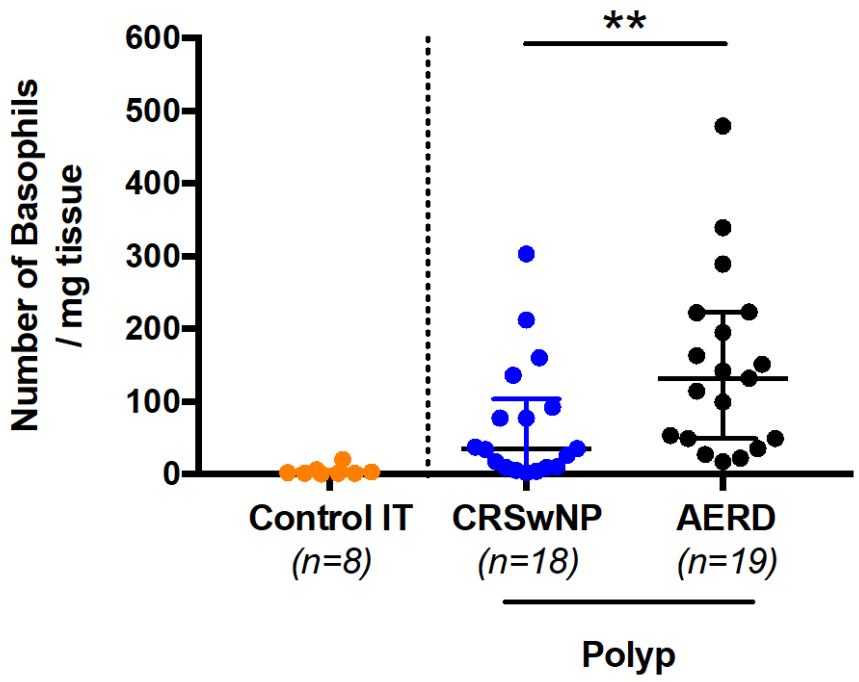
Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Basophils are elevated in nasal polyps of patients with AERD compared to CRSwNP

Total Leukocytes
(CD45$^+$ cells)



Basophils
(CD45$^+$ CD203c$^+$ FcεRI$^+$ CD117$^-$ cells)

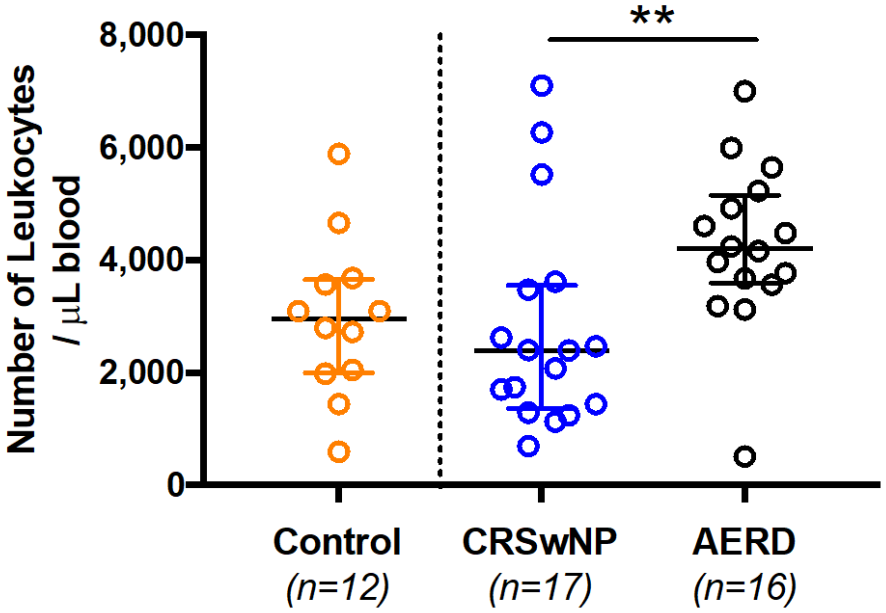


Mann-Whitney test, mean ± SEM

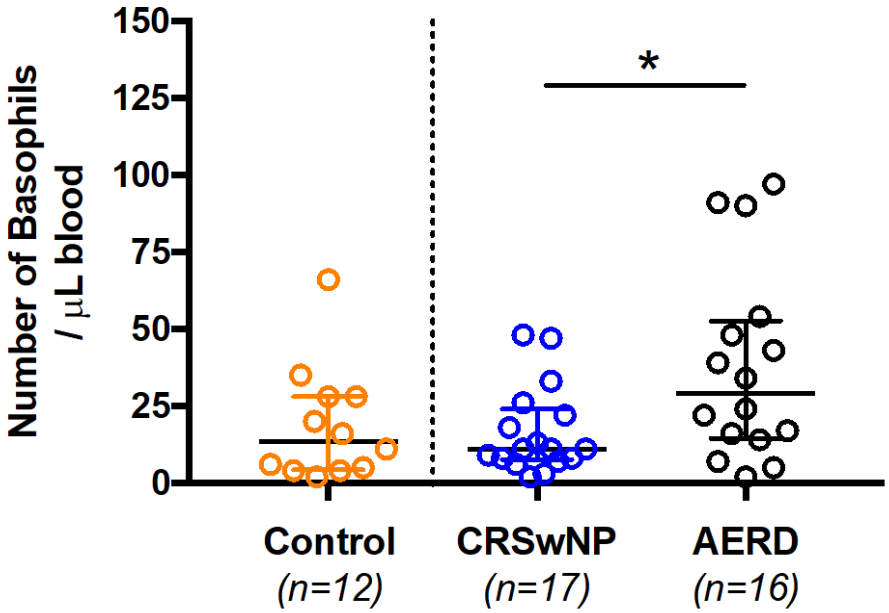
Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Basophils are also elevated in peripheral blood of patients with AERD compared to CRSwNP

Total Leukocytes
(CD45$^+$ cells)



Basophils
(CD45$^+$ CD203c$^+$ FcεRI$^+$ CD117$^-$ cells)

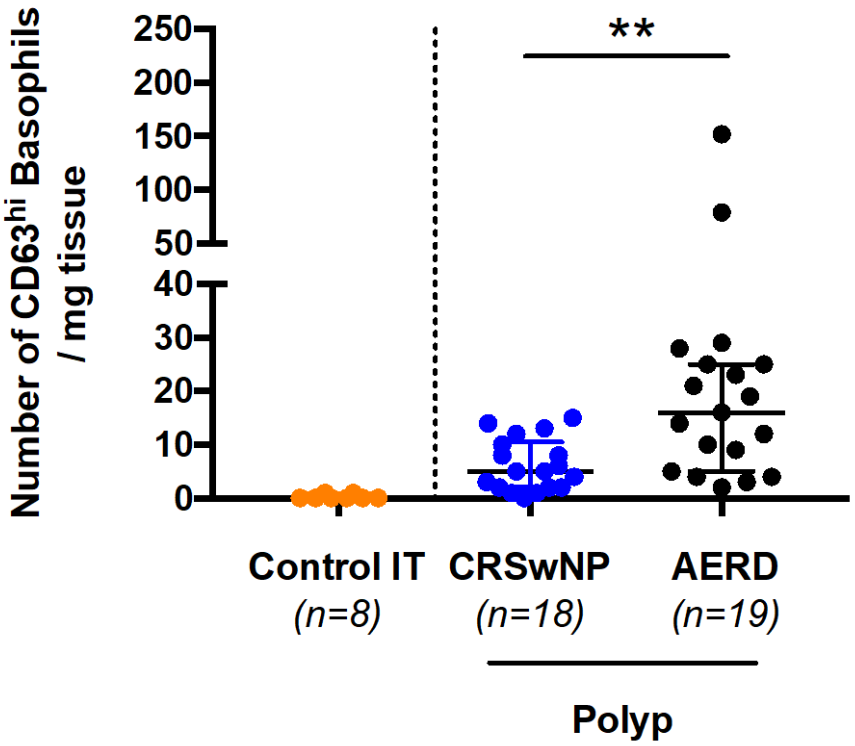


Mann-Whitney test, mean ± SEM

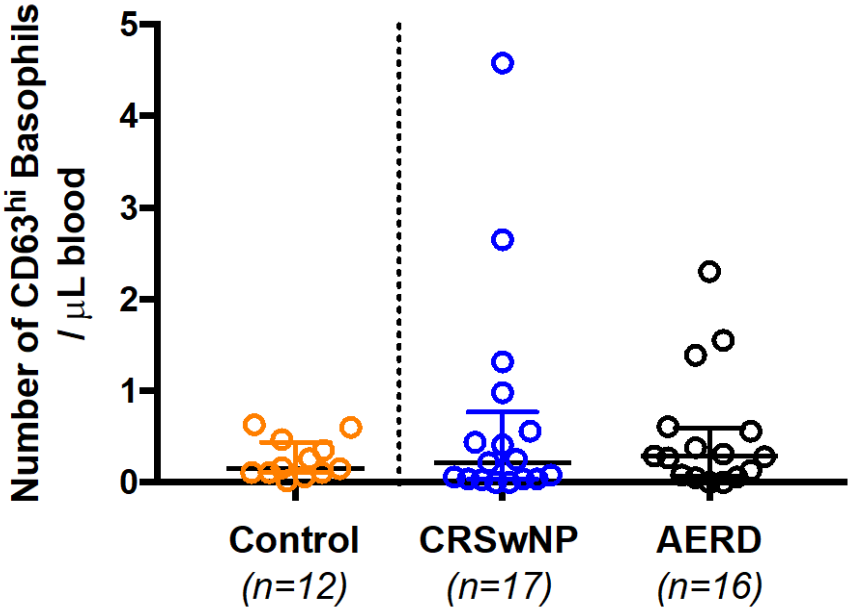
Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Increased number of activated (CD63^{+}) basophils in nasal polyps of patients with AERD compared to CRSwNP

Number of CD63^{+} Basophils Sinus Tissue



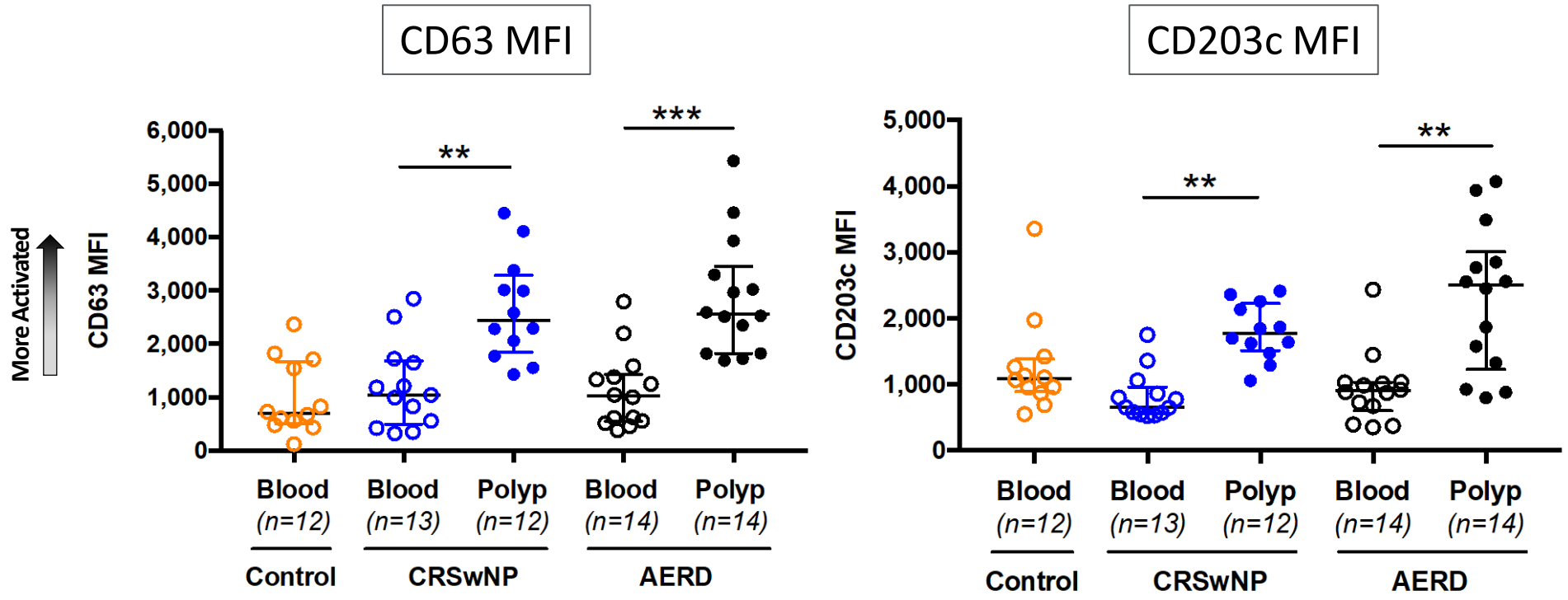
Number of CD63^{+} Basophils Peripheral Blood



Mann-Whitney test, mean ± SEM

Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Increased intensity of CD63 and CD203c staining on basophils in nasal polyps compared to peripheral blood

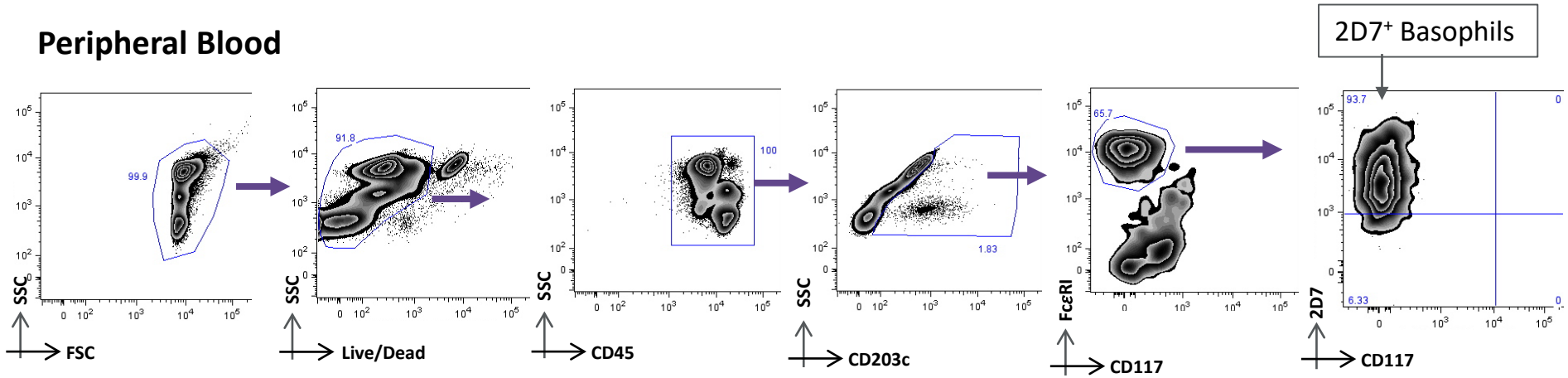


Kruskal-Wallis ANOVA, mean ± SEM

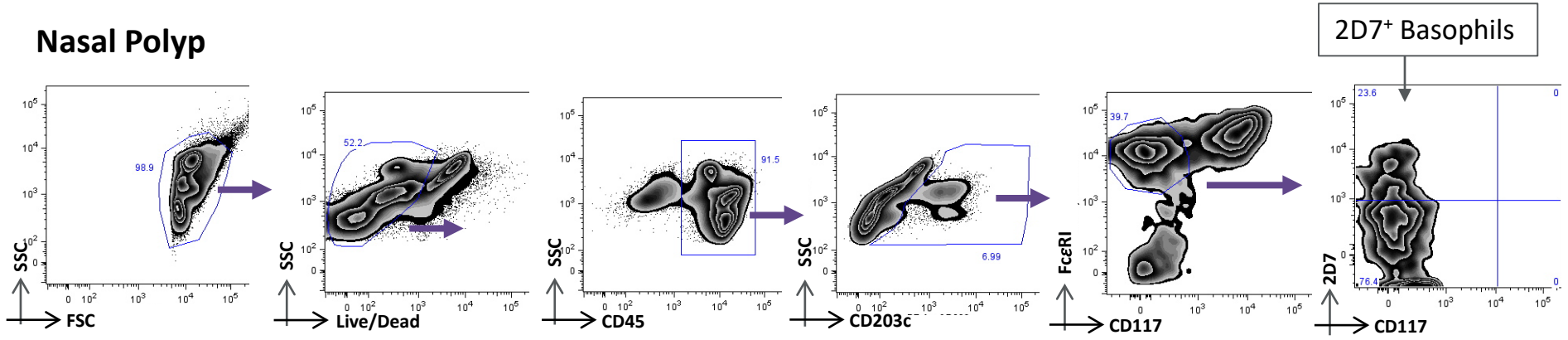
Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Flow cytometry-based approach to utilize 2D7 expression as a putative marker of basophil degranulation

Peripheral Blood

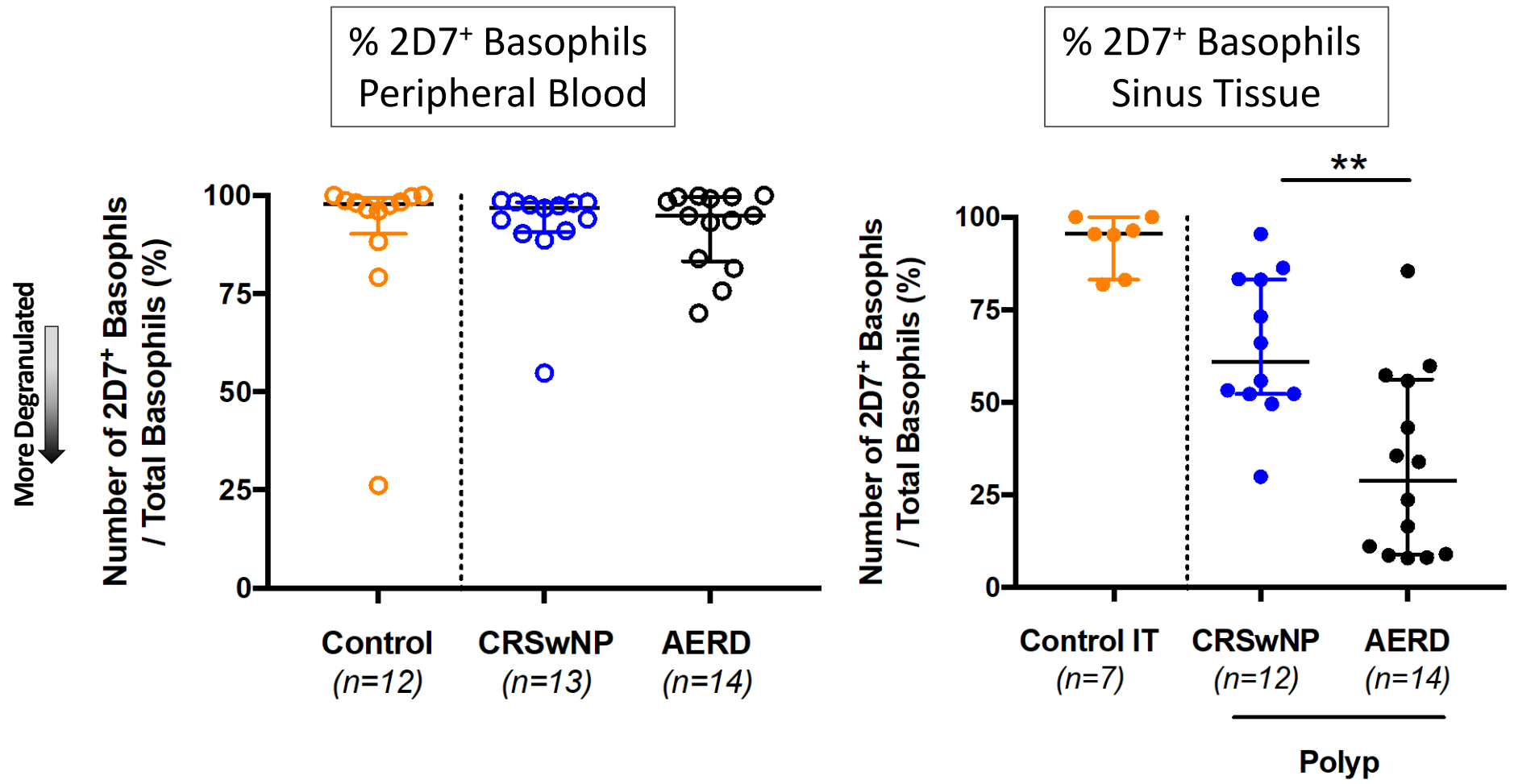


Nasal Polyp



Stevens W et al. JACI. 2021 Aug;148(2):439-449.

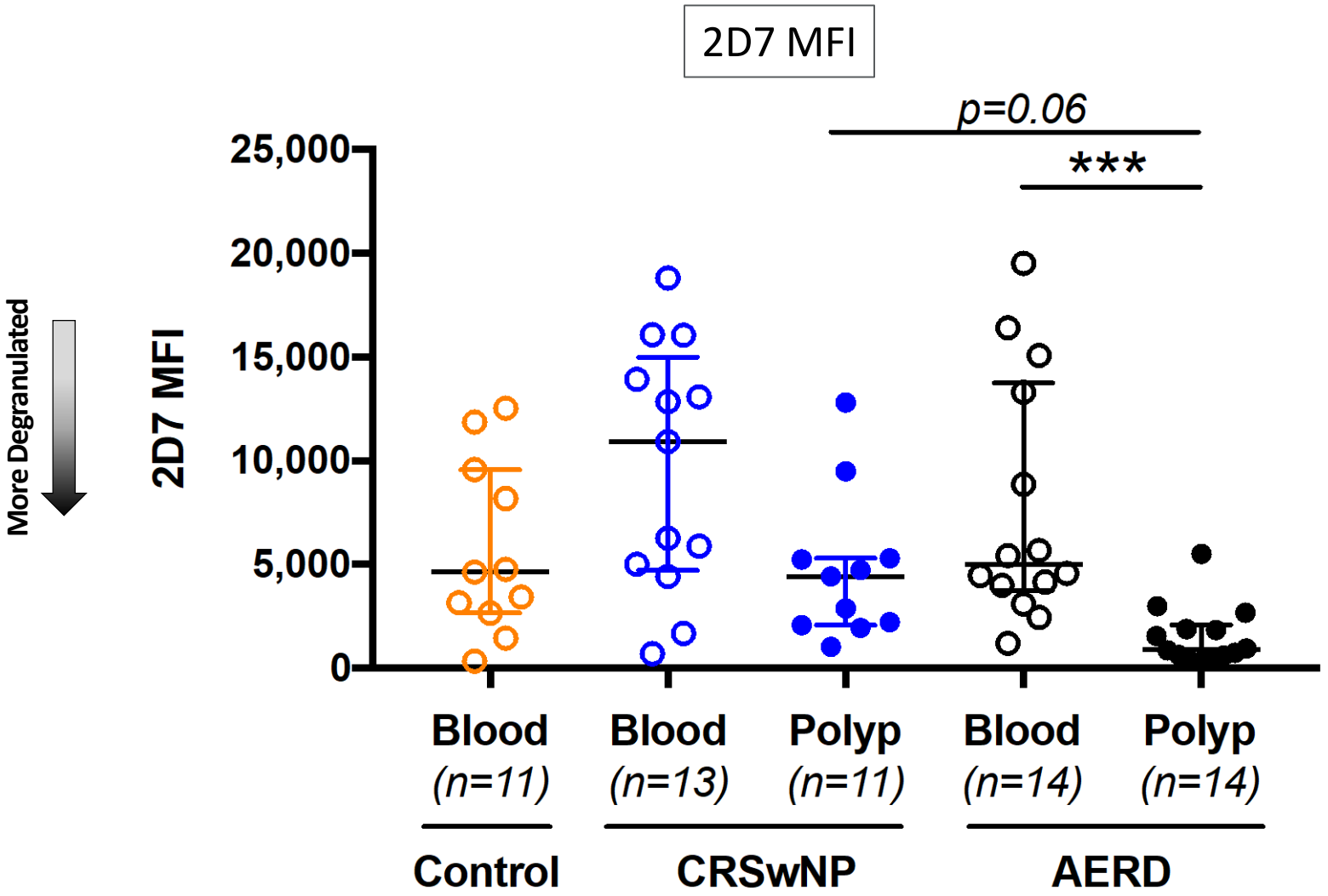
Reduction in percentage of 2D7^{+} basophils in nasal polyps of AERD compared to CRSwNP



Mann-Whitney test, mean ± SEM

Stevens W et al. JACI. 2021 Aug;148(2):439-449.

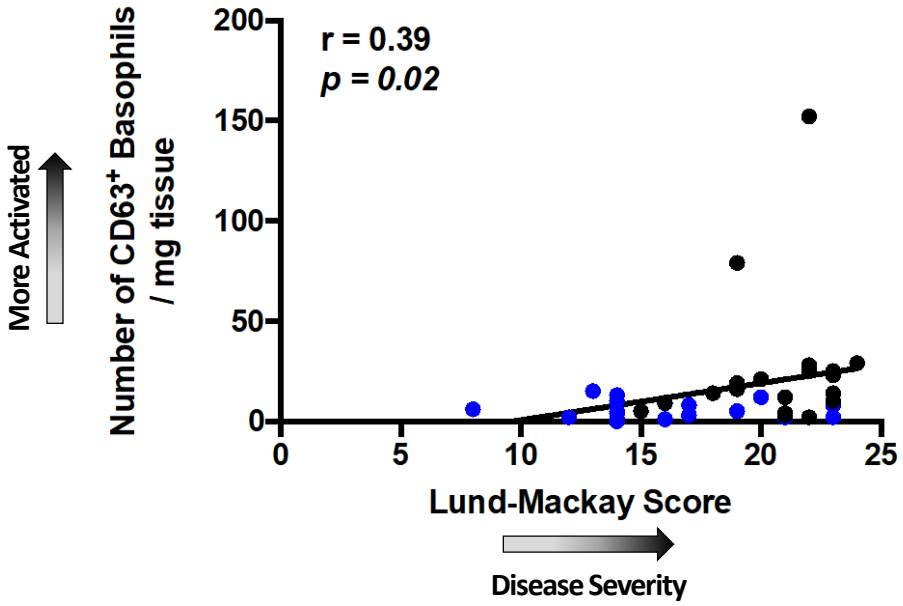
Reduced intracellular 2D7 staining in nasal polyp basophils from AERD compared to CRSwNP or AERD blood

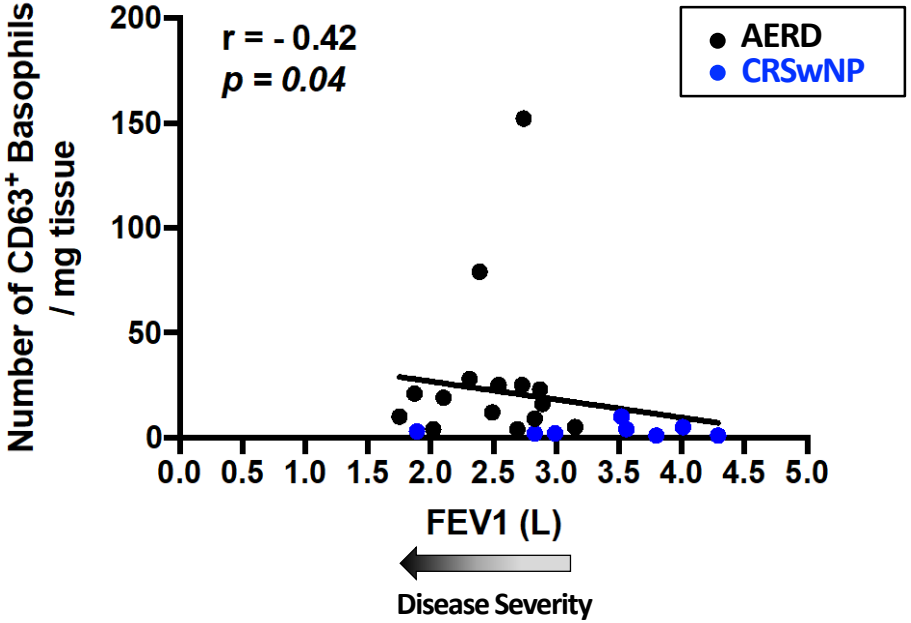


Kruskal-Wallis ANOVA, mean ± SEM

Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Measurements of basophil activation and degranulation correlate with enhanced disease severity

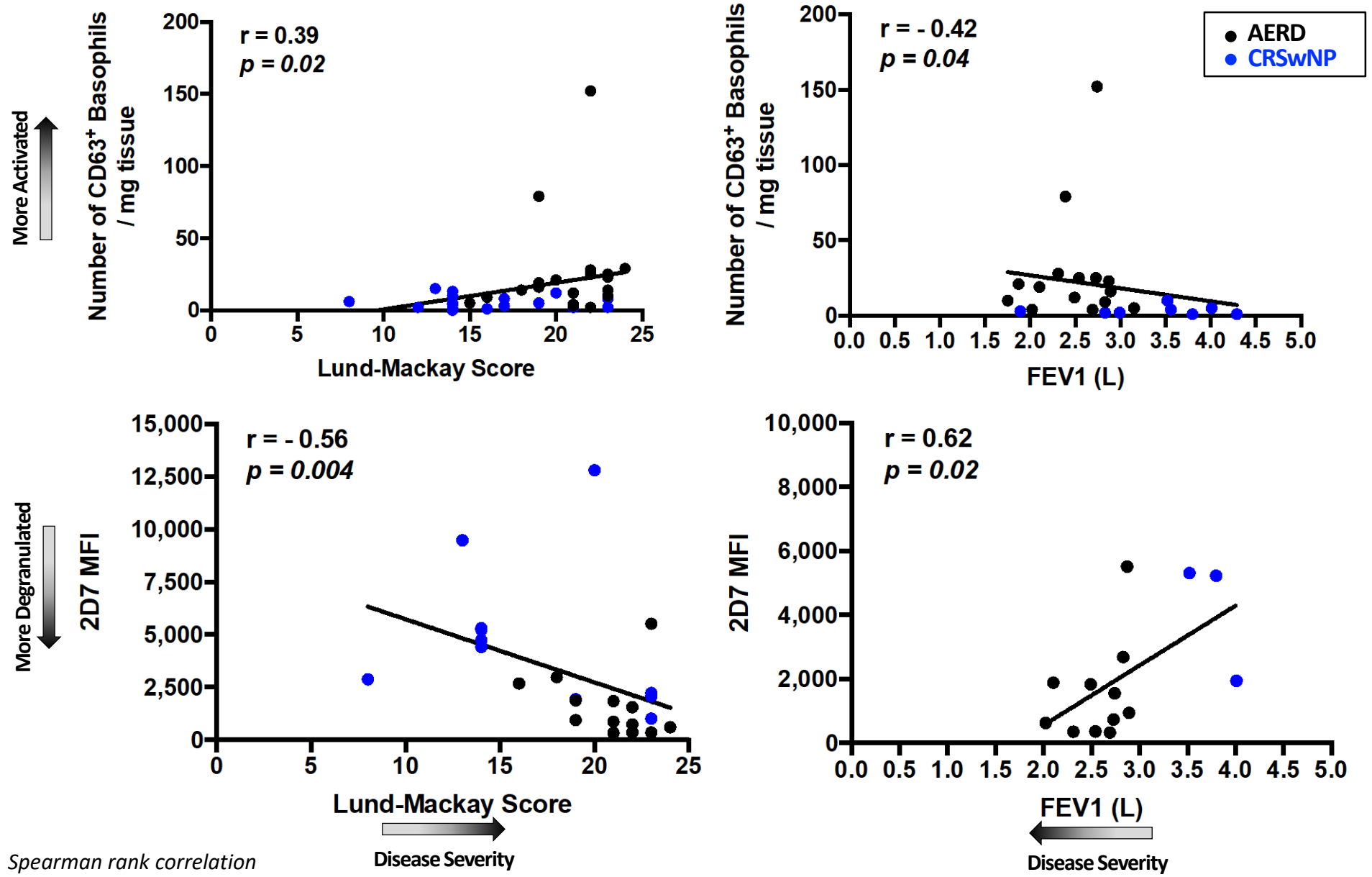




Spearman rank correlation

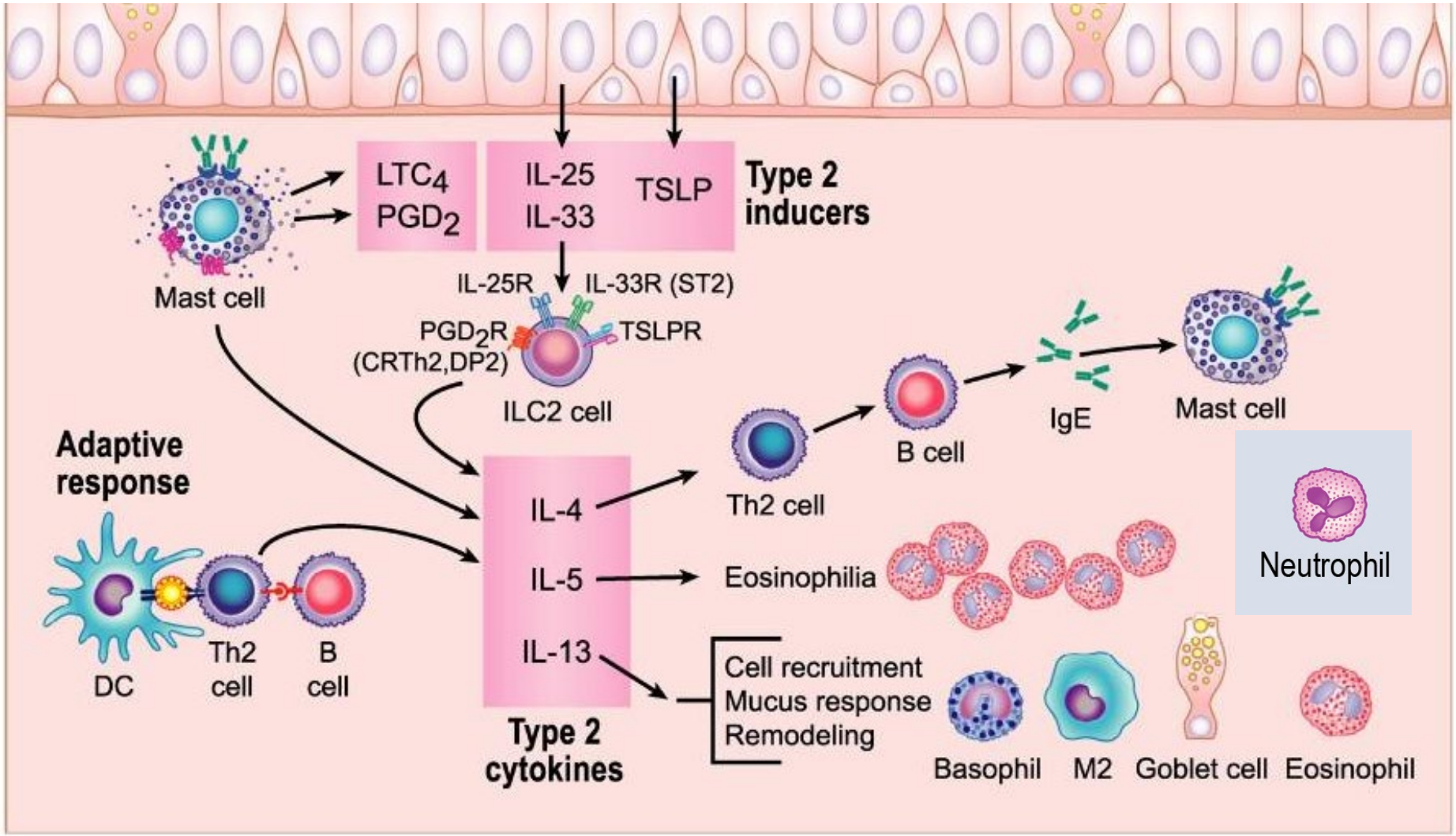
Stevens W et al. JACI. 2021 Aug;148(2):439-449.

Measurements of basophil activation and degranulation correlate with enhanced disease severity



Spearman rank correlation

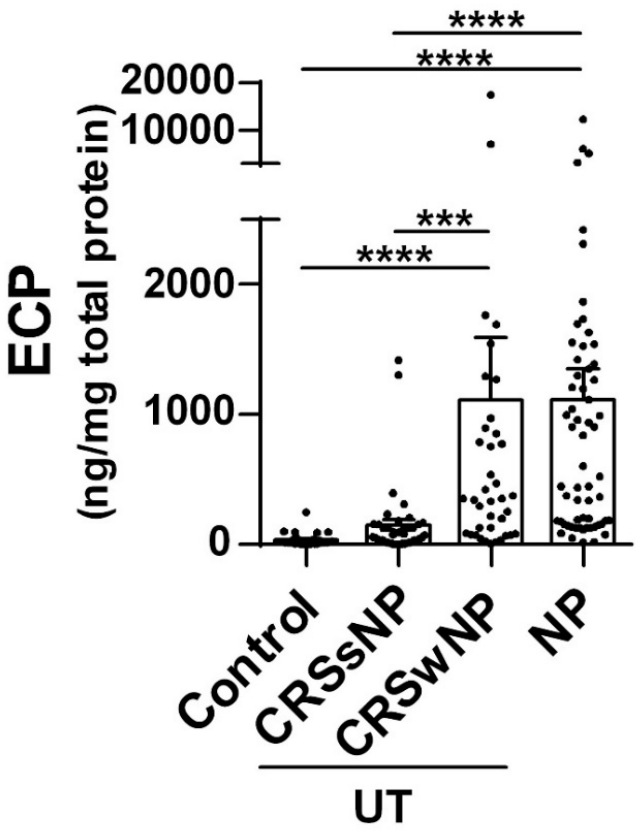
Simplified overview of CRSwNP pathogenesis



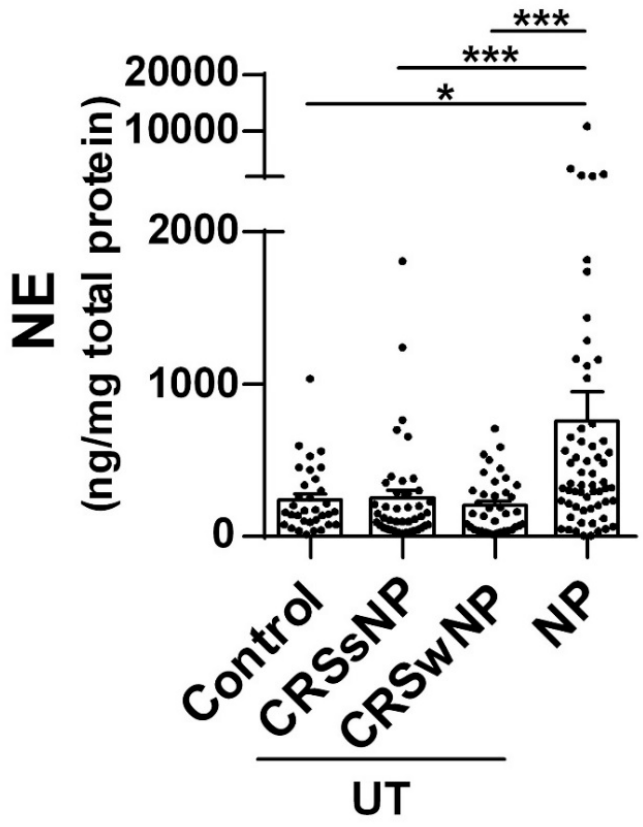
Hulse KE et al. Clin Exp Allergy. 2015 Feb;45(2):328-46.

Elevation of neutrophils in a subset of eosinophilic nasal polyps

Eosinophil Cationic Protein
(eosinophil marker)



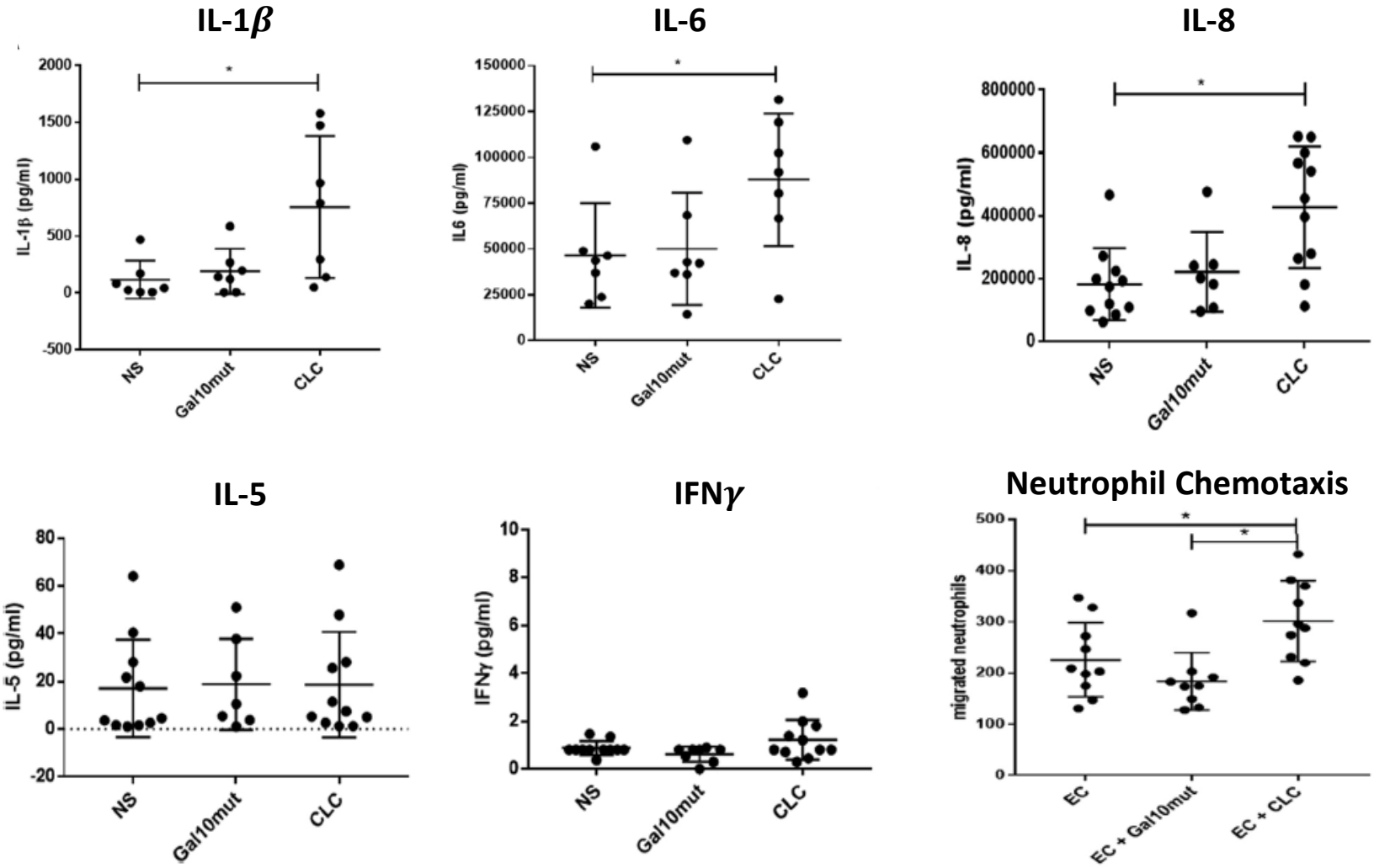
Neutrophil elastase
(neutrophil marker)



ECP: Eosinophil cationic protein
NE: Neutrophil elastase
UT: Uncinate tissue

Poposki JA et al. JACI 2022 May;149(5):1666-1674.

Charcot-Leyden crystals can induce a pro-inflammatory response in nasal polyps and recruit neutrophils



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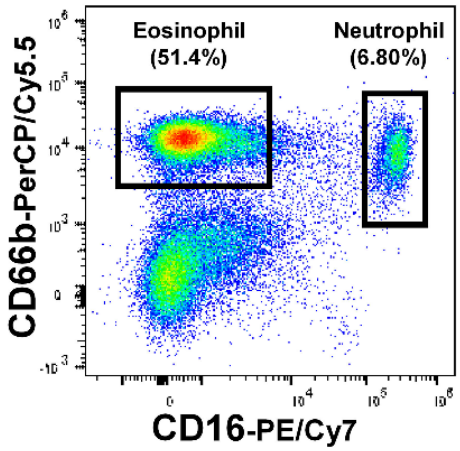
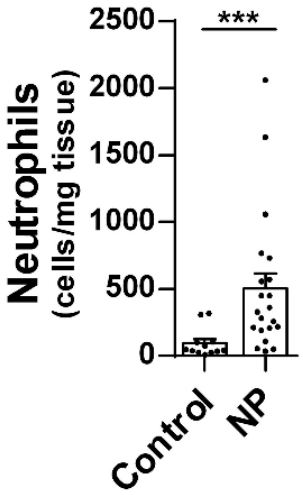
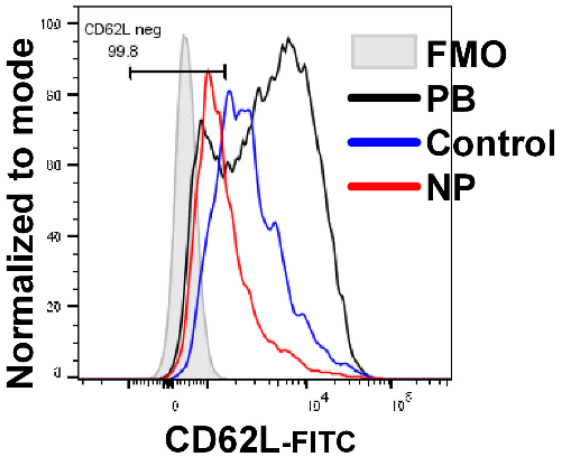
Gevaert et al. J Allergy Clin Immunol. 2020 Jan;145(1):427-430.

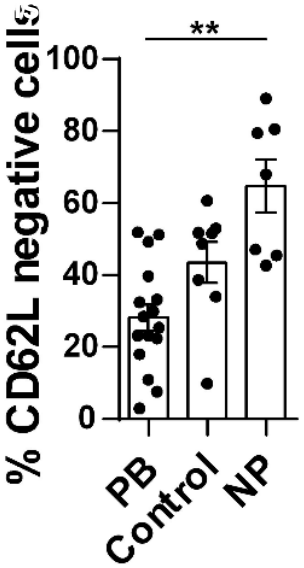
Elevated neutrophils in nasal polyps have an activated phenotype





12 Control inferior turbinate
21 NP



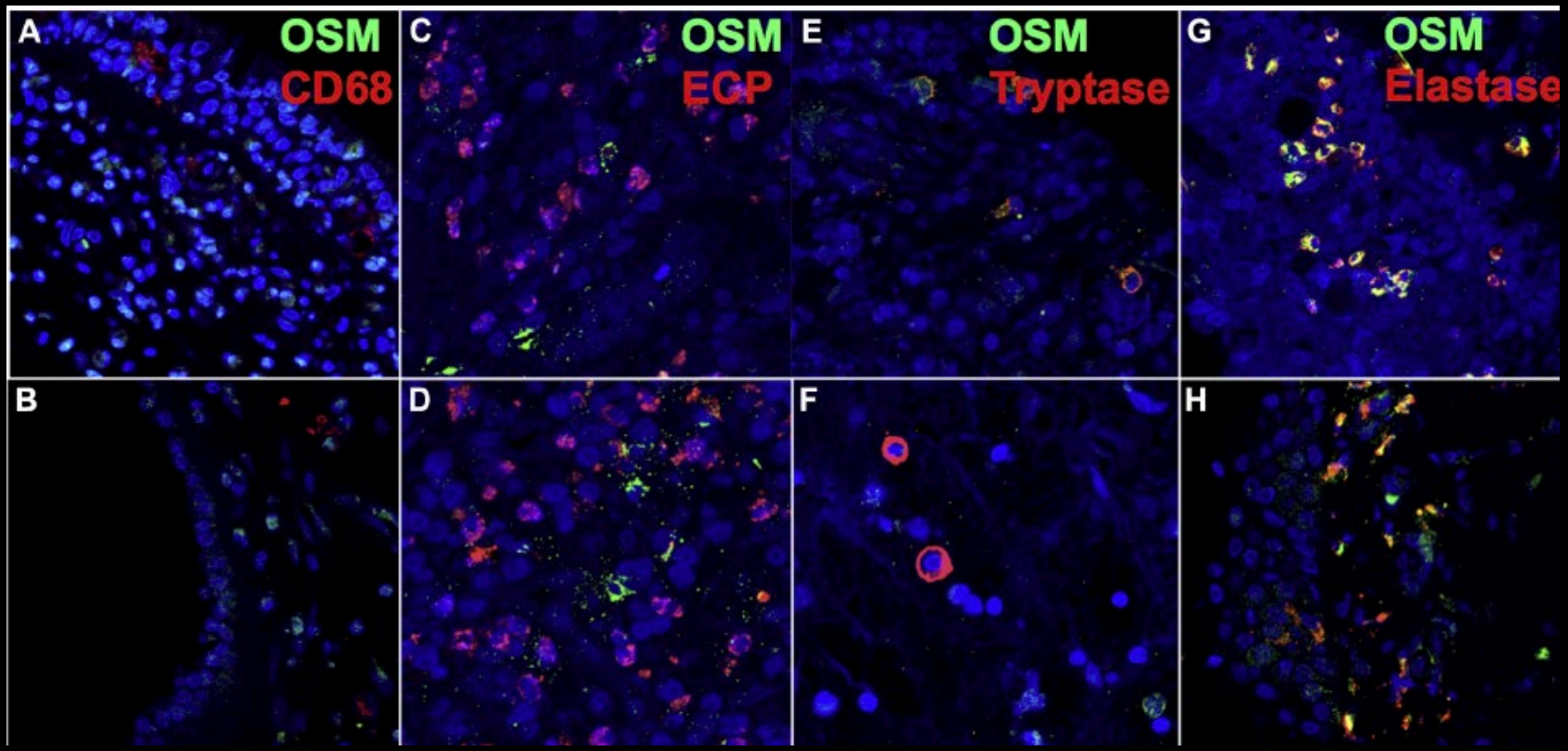


16 Peripheral blood (PB) neutrophils
8 Control inferior turbinate neutrophils
7 NP neutrophils

Poposki JA et al. JACI 2022 May;149(5):1666-1674.

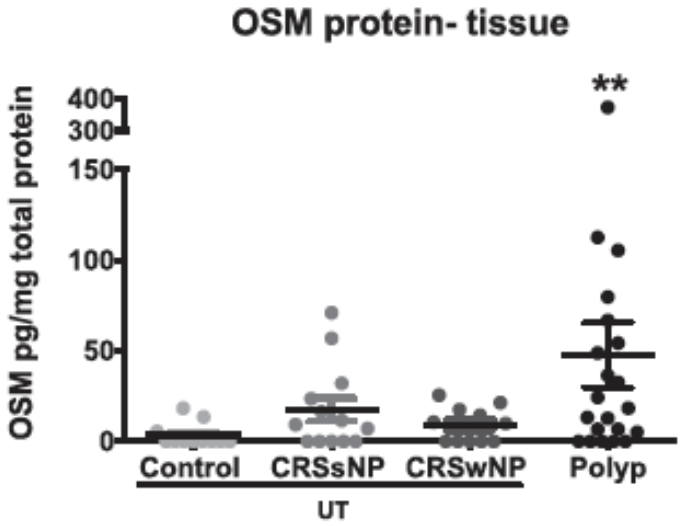
Neutrophils are the predominant cellular source of Oncostatin M in nasal polyps

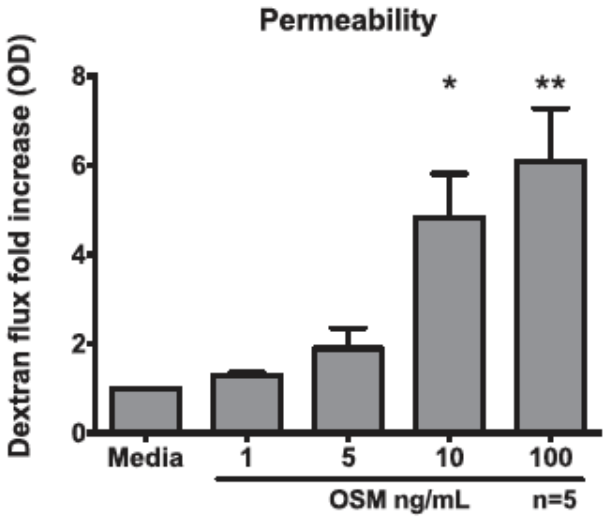
Macrophages Eosinophils Mast cells Neutrophils

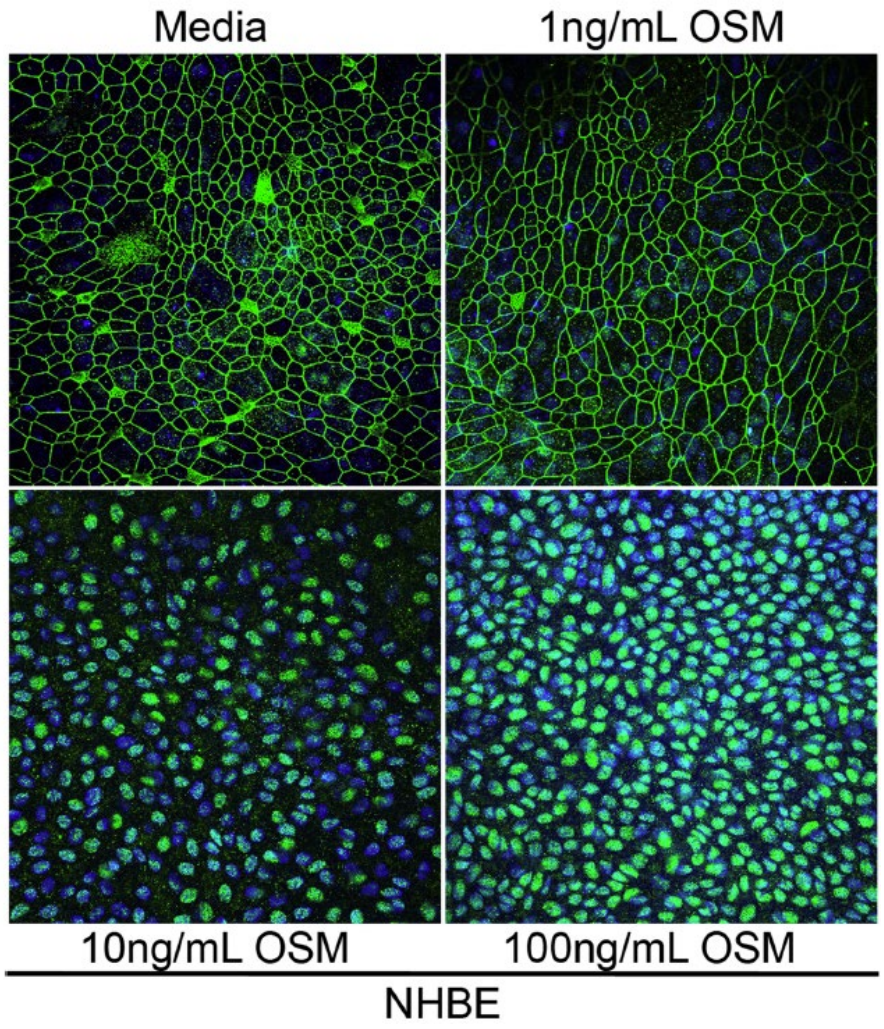


Stevens et al. JACI. 2017 Jun;139(6):1966-1978.

Oncostatin M promotes epithelial barrier dysfunction and is elevated in CRSwNP





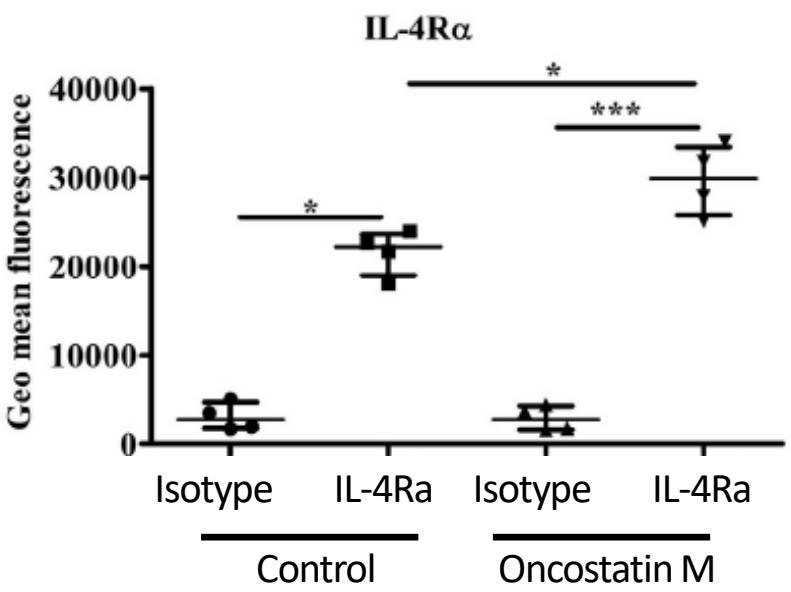


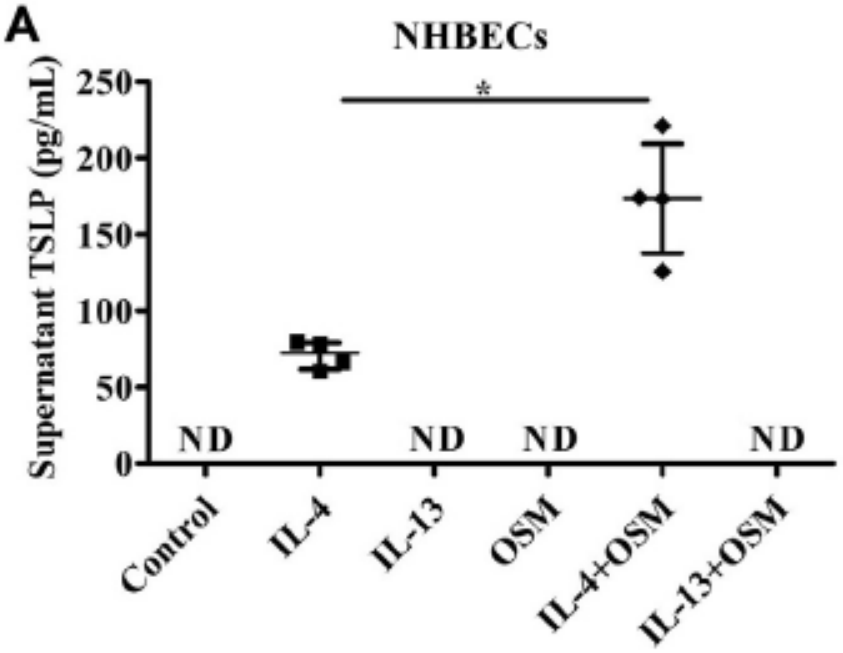
Green – Occludin (tight junction)

Pothoven et al. J Allergy Clin Immunol. 2015 Sep;136(3):737-

Oncostatin M synergizes with IL-4 signaling to induce TSLP expression in CRSwNP

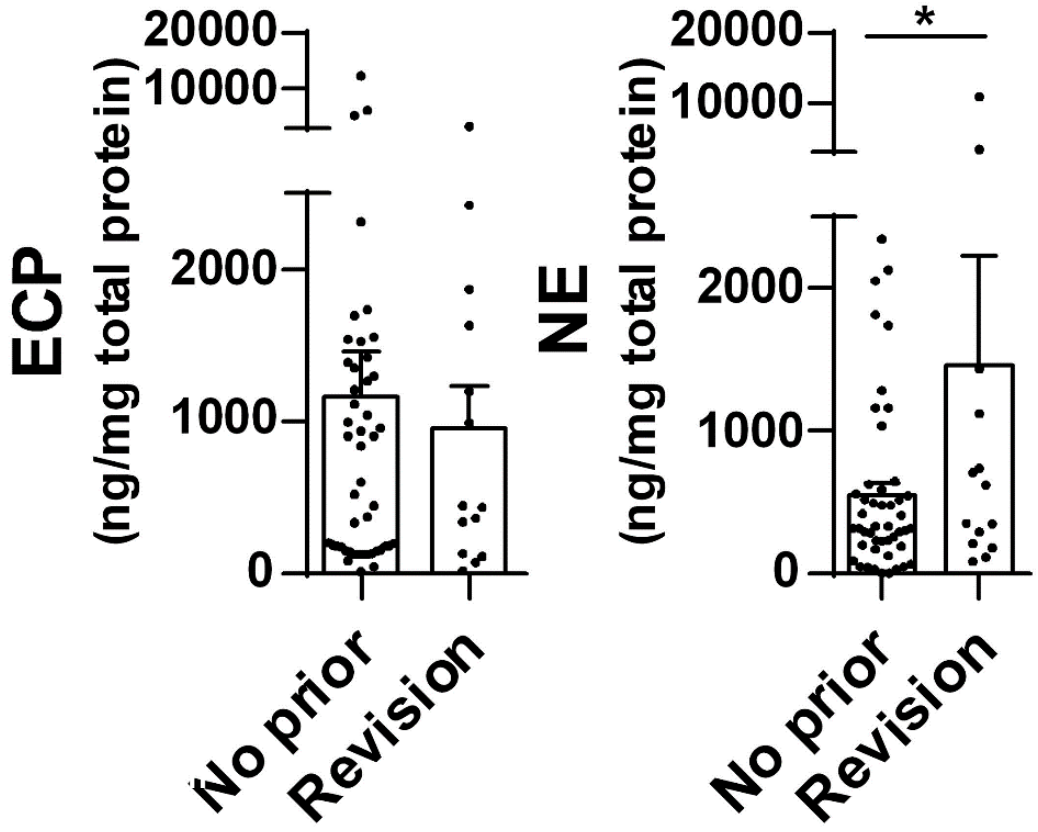
Nasal Epithelial Cells





Wang et al. JACI. 2023 Jan 6 epub.

The mixed eosinophilic and neutrophilic endotype may be associated with severe disease in CRS



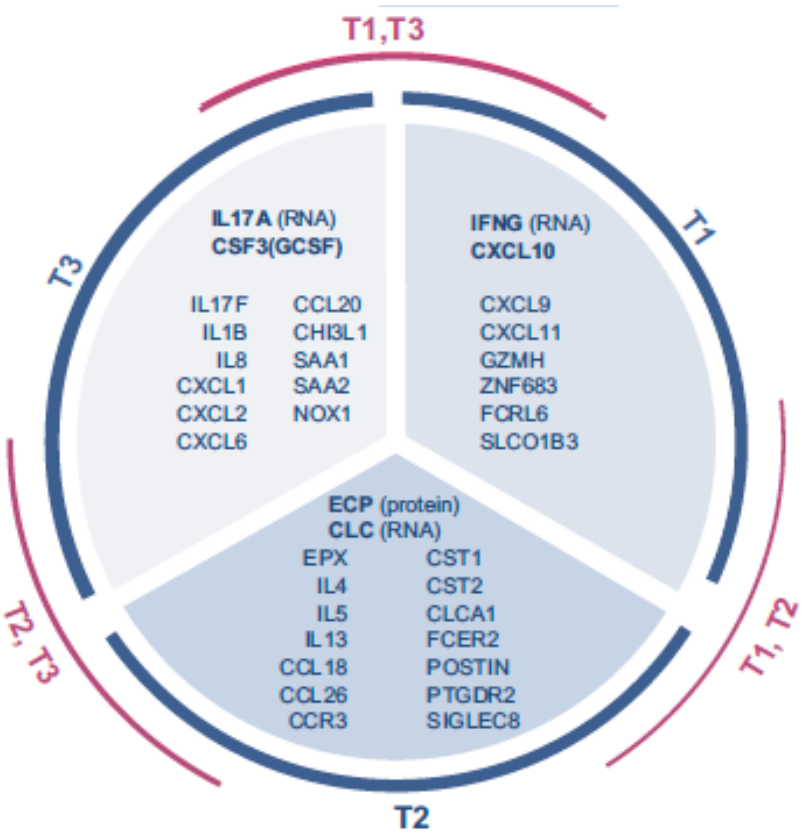
Poposki JA et al. JACI 2022 May;149(5):1666-1674.

Mixed eosinophilic and neutrophilic inflammation is associated with more severe sinonasal disease

	Paucigranulocytic	Neutrophilic	Eosinophilic	Mixed granulocytic	*P*-value
No.	33	23	73	35	
Age (years)	50.3 ± 14.0	54.1 ± 16.6	48.1 ± 13.5	47.5 ± 13.6	.26
Sex, no. (% female)	17 (52)	7 (30)	33 (45)	15 (43)	.47
Race, no. (% white)	29 (88)	20 (87)	60 (82)	30 (86)	.87
Current smoker, no. (%)	2 (6)	2 (9)	5 (7)	1 (3)	.80
BMI (kg/m^2)	30.5 ± 11.2	30.4 ± 6.7	30.5 ± 6.0	28.6 ± 6.4	.68
Nasal polyps, no. (%)	6 (15)	11 (48)	55 (75)	26 (74)	<.0001
Asthma, no. (%)	9 (27)	9 (39)	26 (36)	18 (51)	.21
Allergic rhinitis, no. (%)	19 (58)	12 (52)	45 (62)	26 (74)	.20
AERD, no. (%)	0 (0)	1 (4)	10 (14)	5 (14)	.09
AFRS, no. (%)	1 (3)	1 (4)	12 (16)	7 (20)	.08
NCS, no. (%)	25 (86)	19 (83)	59 (81)	28 (80)	.92
LTR, no. (%)	4 (12)	5 (22)	21 (29)	11 (31)	.22
SNOT-22 score	43.0 ± 19.5	47.0 ± 20.3	41.2 ± 18.5	56.2 ± 21.7	.03
Rhinologic	11.8 ± 5.0	12.4 ± 5.8	11.8 ± 5.2	14.7 ± 4.7	.18
Extranasal	7.9 ± 3.6	8.7 ± 2.9	7.0 ± 3.6	8.0 ± 3.3	.36
Ear/Facial	8.2 ± 4.8	8.0 ± 5.1	7.4 ± 5.2	11.0 ± 5.3	.06
Psychological	11.5 ± 8.8	12.7 ± 6.9	11.2 ± 7.9	17.1 ± 9.0	.05
Sleep	10.4 ± 7.0	12.4 ± 6.4	10.4 ± 6.7	14.1 ± 7.0	.17
CT score	11.0 (8.0 to 14.0)	15.0 (7.5 to 19.0)	16.5 (13.0 to 20.5)	17.0 (14.0 to 21.0)	<.0001
SIT score	-3.0 (−7.0 to −1.0)	-9.0 (−19.5 to −1.5)	-13.0 (−26.0 to −3.0)	-14.0 (−25.5 to −4.0)	.04
Mucopurulence, no. (%)	11 (33)	14 (61)	12 (16)	9 (26)	.0005
Prior surgery, no. (%)	8 (24)	8 (35)	29 (40)	17 (49)	.21

Succar et al. Allergy. 2020 Mar;75(3):713-716.

Variation in defining inflammatory endotypes



Inflammatory mediator expression

- CLC, ECP, IL-5, IL-13,
- IFNg, CXCL10
- IL-17, GCSF

Cellular composition

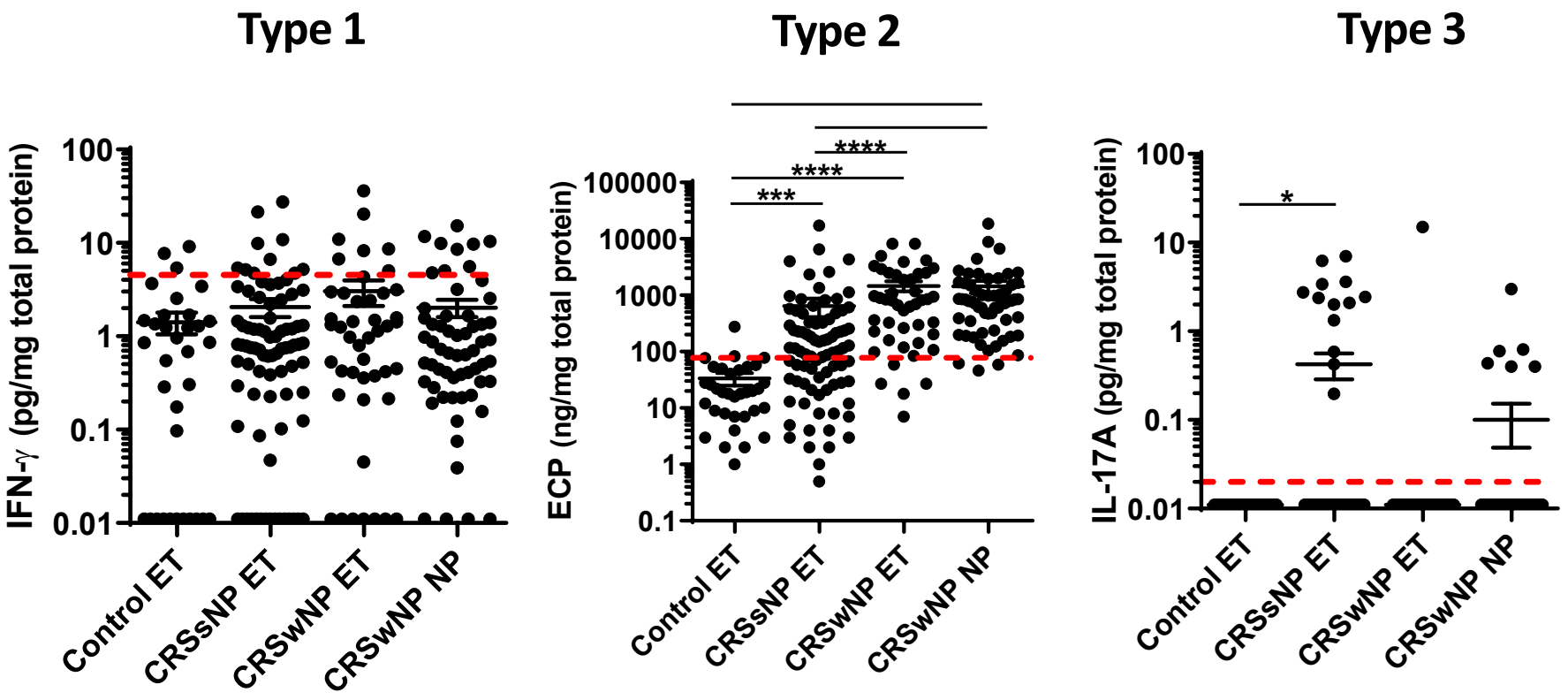
- Number of neutrophils versus eosinophils

Location, location, location

- Nasal polyp tissue
- Nasal lavage
- Nasal secretions

Kato et al. Allergy. 2022 Mar;77(3):812-826.

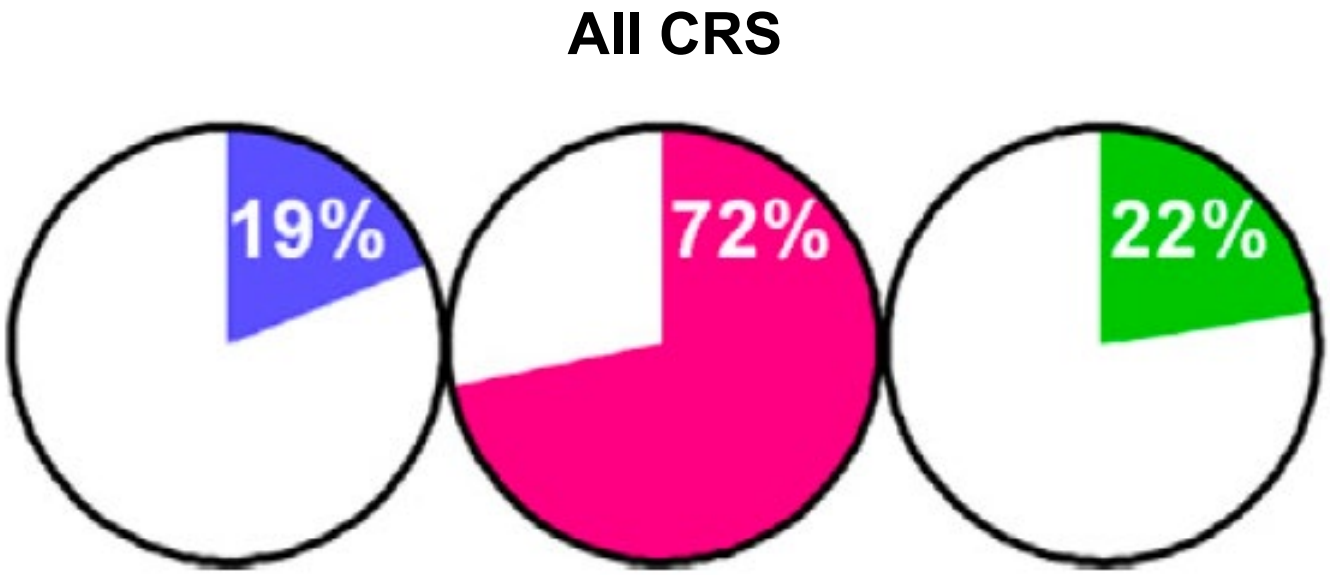
CRS inflammatory endotypes determined by cytokine profiles



Red dotted line: 90th percentile of the expression measured in control ethmoid tissue

Adapted from Tan et al. J Allergy Clin Immunol. 2017 Feb;139(2):699-703.

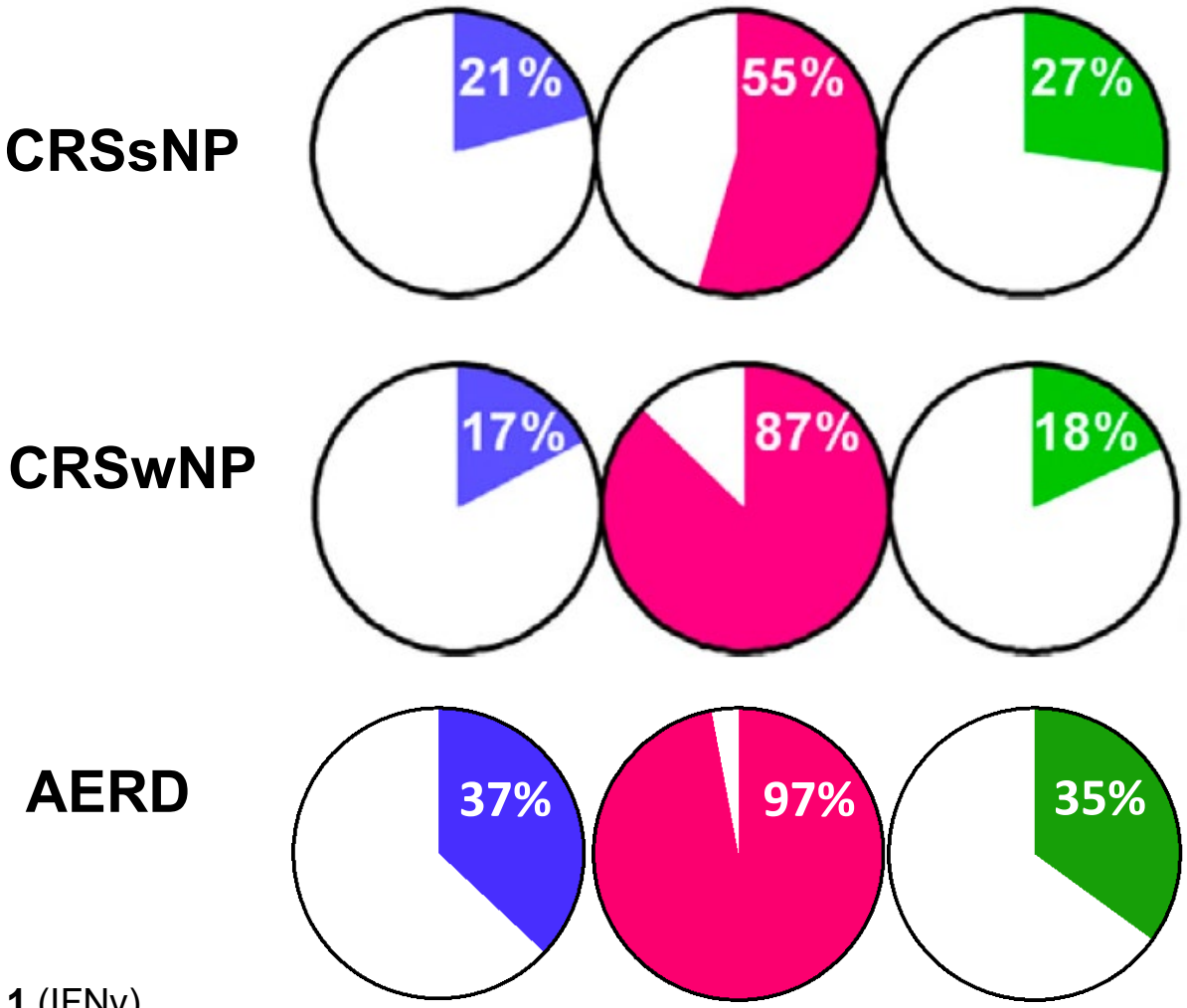
Type 2 inflammatory endotype of CRS patients in Chicago



Greater than the 90th percentile expression in control ET

Stevens et al. J Allergy Clin Immunol Pract. Nov-Dec 2019;7(8):2812-2820.

Type 2 inflammatory endotype of CRS patients in Chicago



Type 1 (IFNγ)

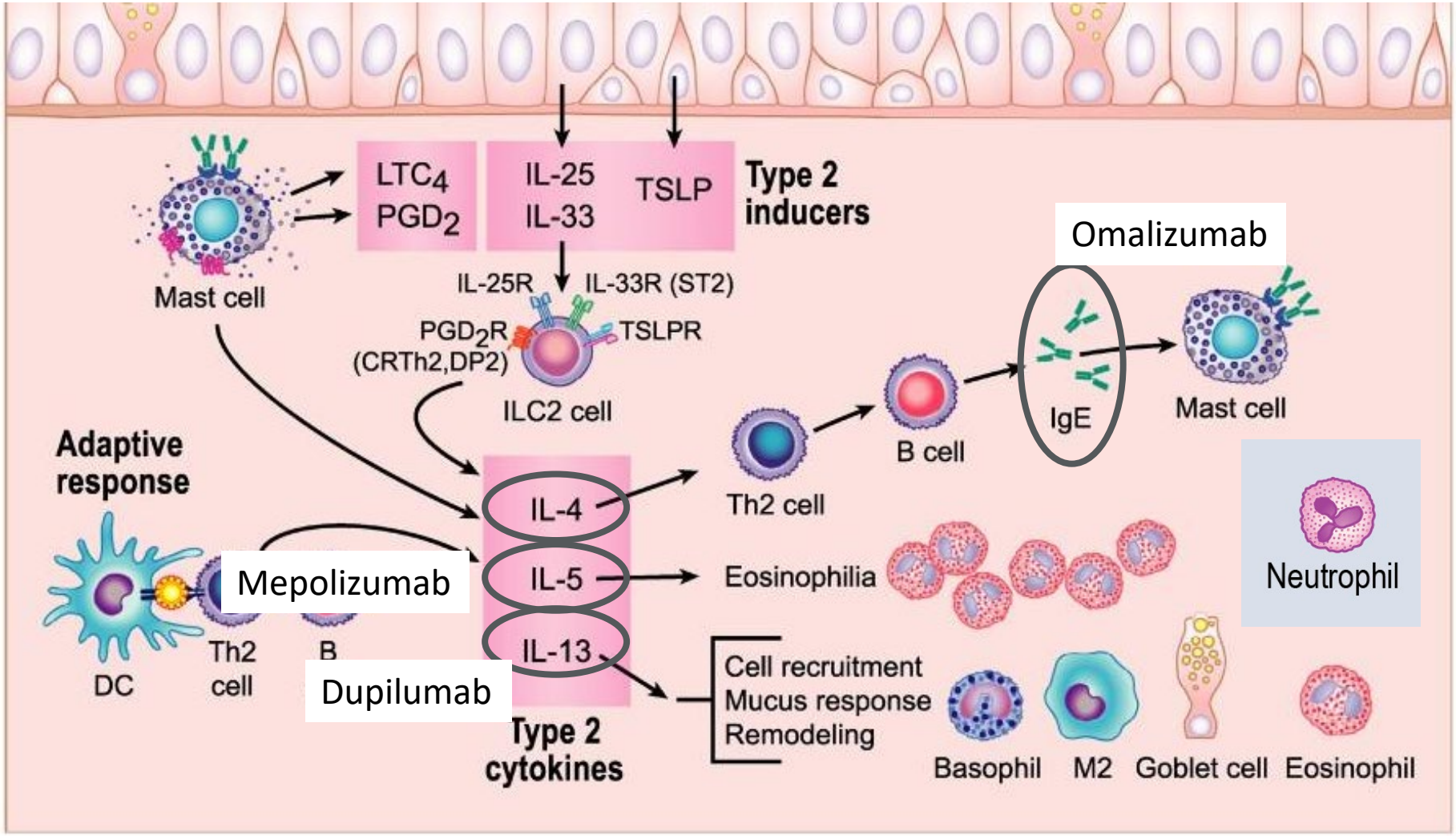
Type 2 (CLC and ECP)

Type 3 (IL-17A)

Greater than the 90th percentile expression in control ET

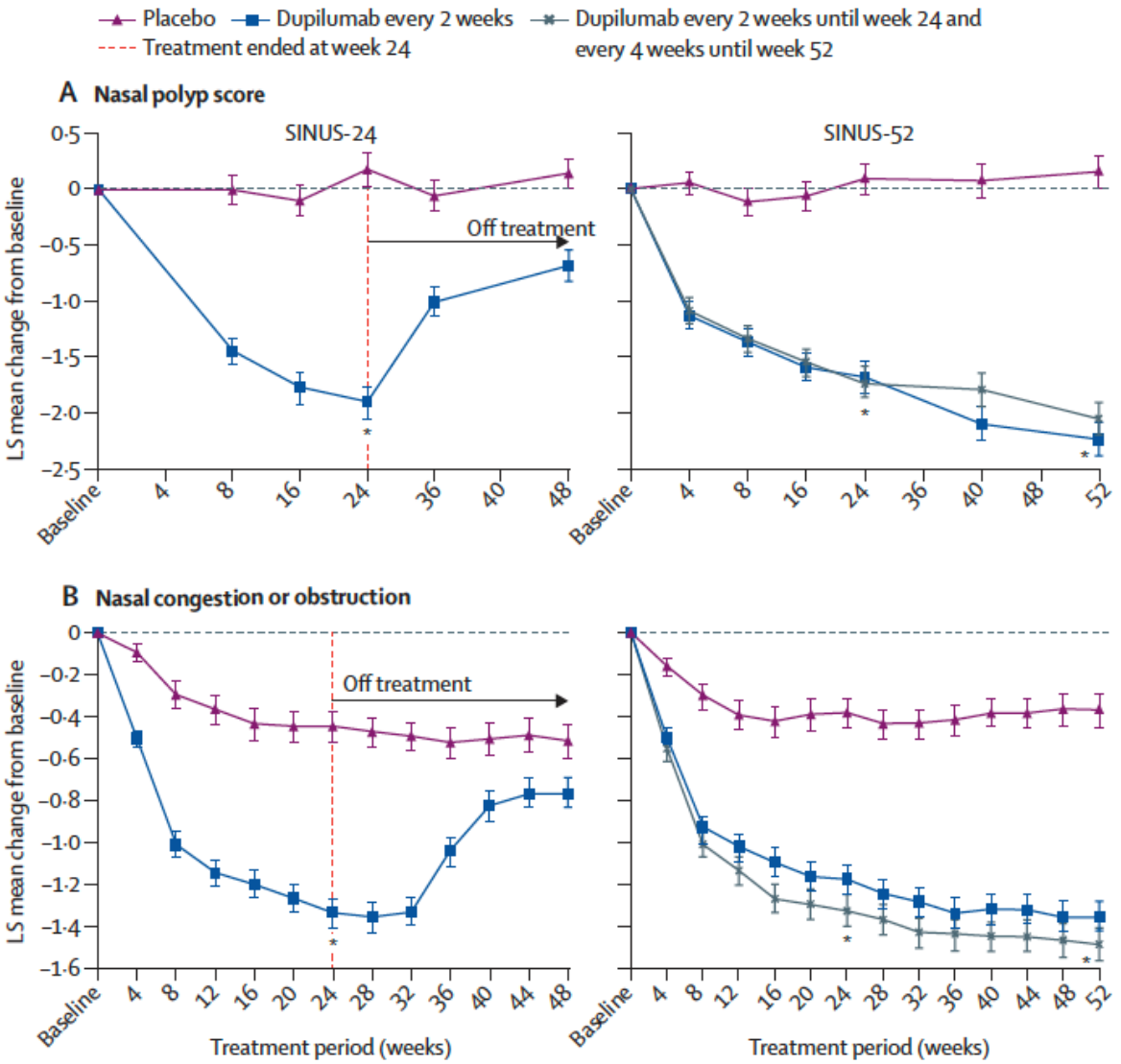
Stevens et al. J Allergy Clin Immunol Pract. Nov-Dec 2019;7(8):2812-2820.
Stevens et. al unpublished 2023.

Novel treatment options for CRSwNP



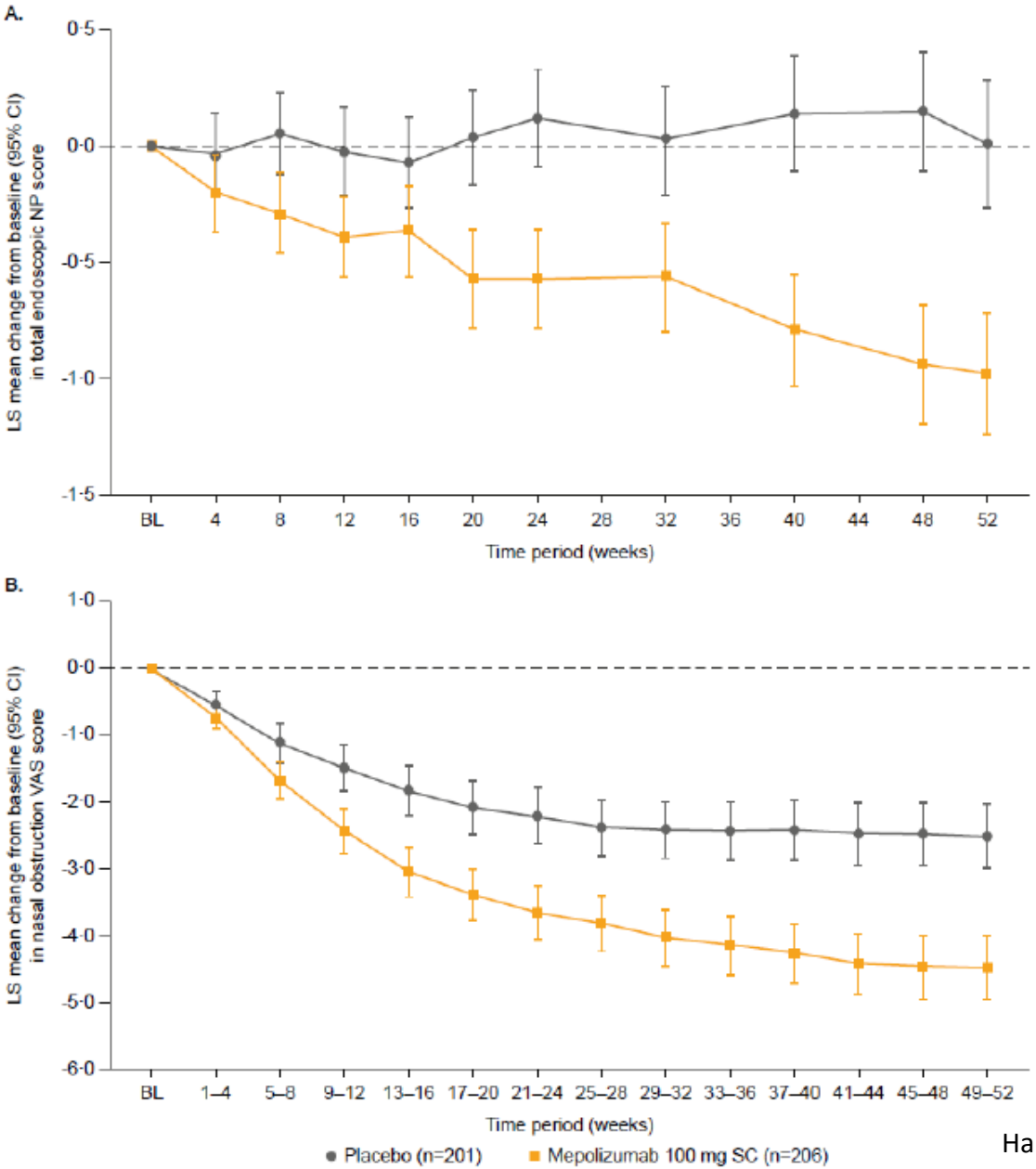
Hulse KE et al. Clin Exp Allergy. 2015.

Dupilumab and CRSwNP (SINUS-24 & SINUS-52)



Bachert et al. Lancet. 2019 Nov 2;394(10209):1638-1650.

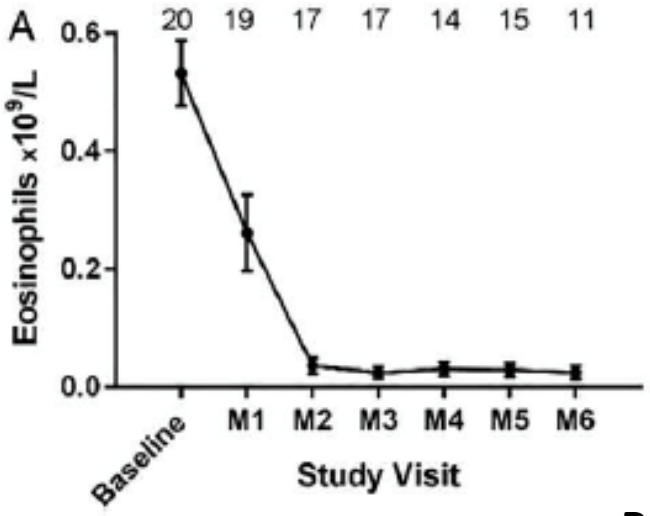
Mepolizumab and CRSwNP (SYNAPSE)



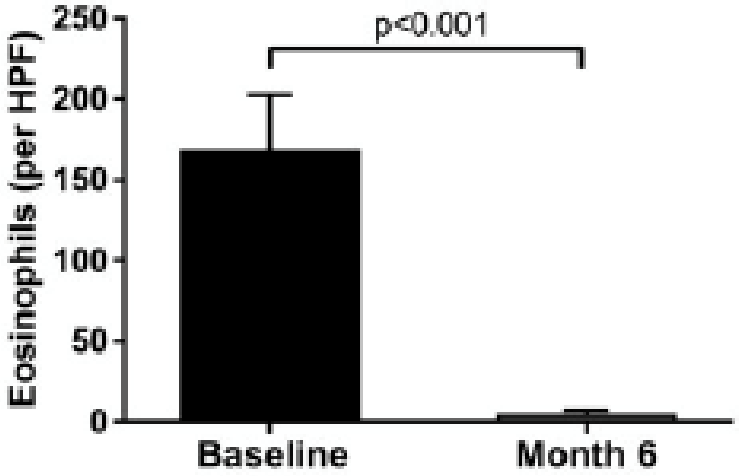
Han et al. Lancet Respir Med. 2021 Oct;9(10):1141-1153.

Dexpramipexole treatment was associated with a reduction in eosinophils but not nasal polyp size

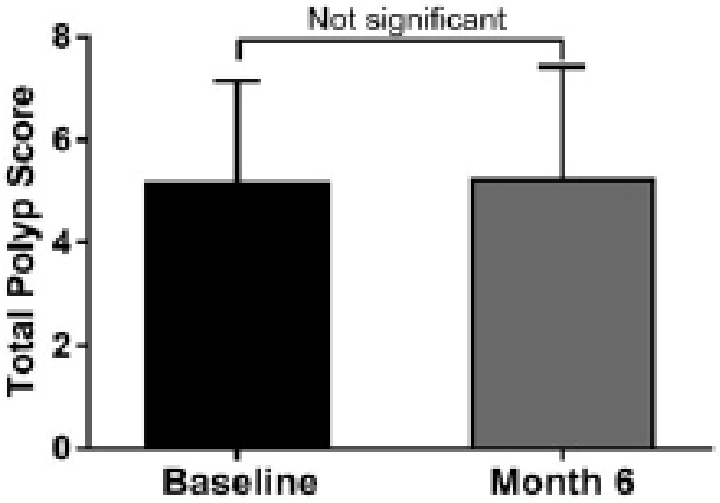
Peripheral Eosinophils



Polyp Eosinophils



Polyp Score (Size)



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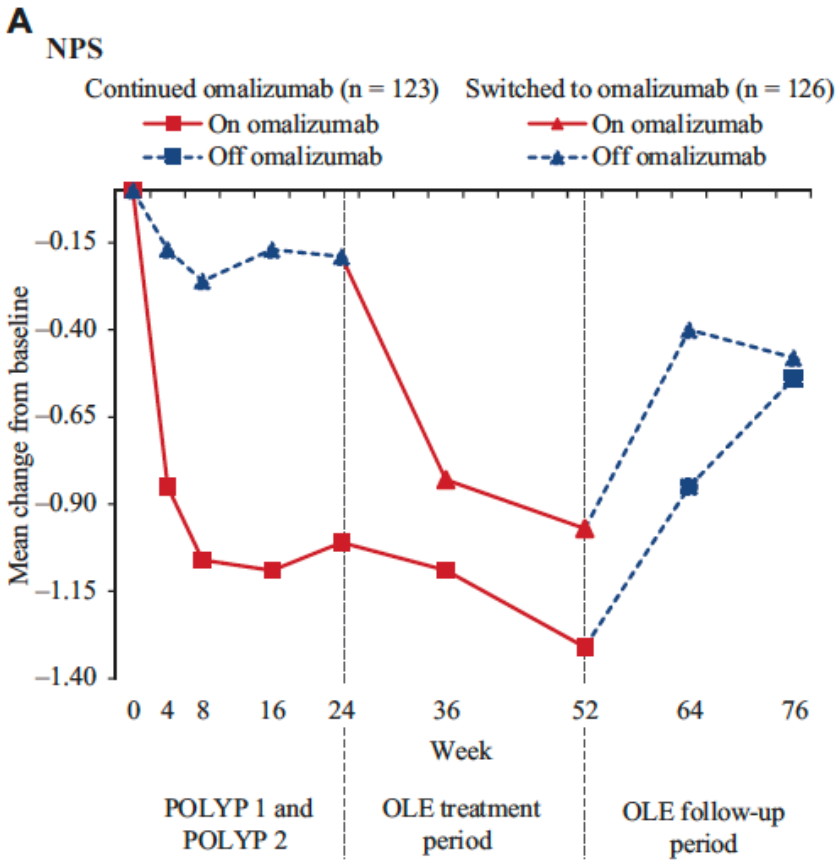
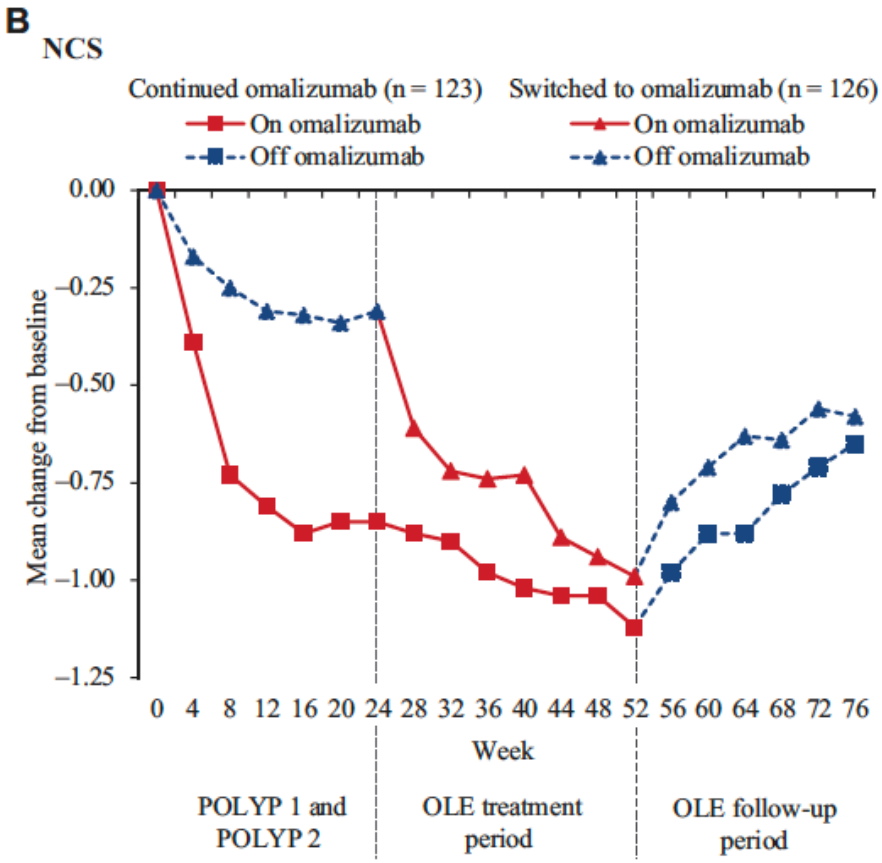
Laidlaw T. et al. Laryngoscope. 2019 Feb;129(2):E61-E66.

Omalizumab and CRSwNP (52-week extension)

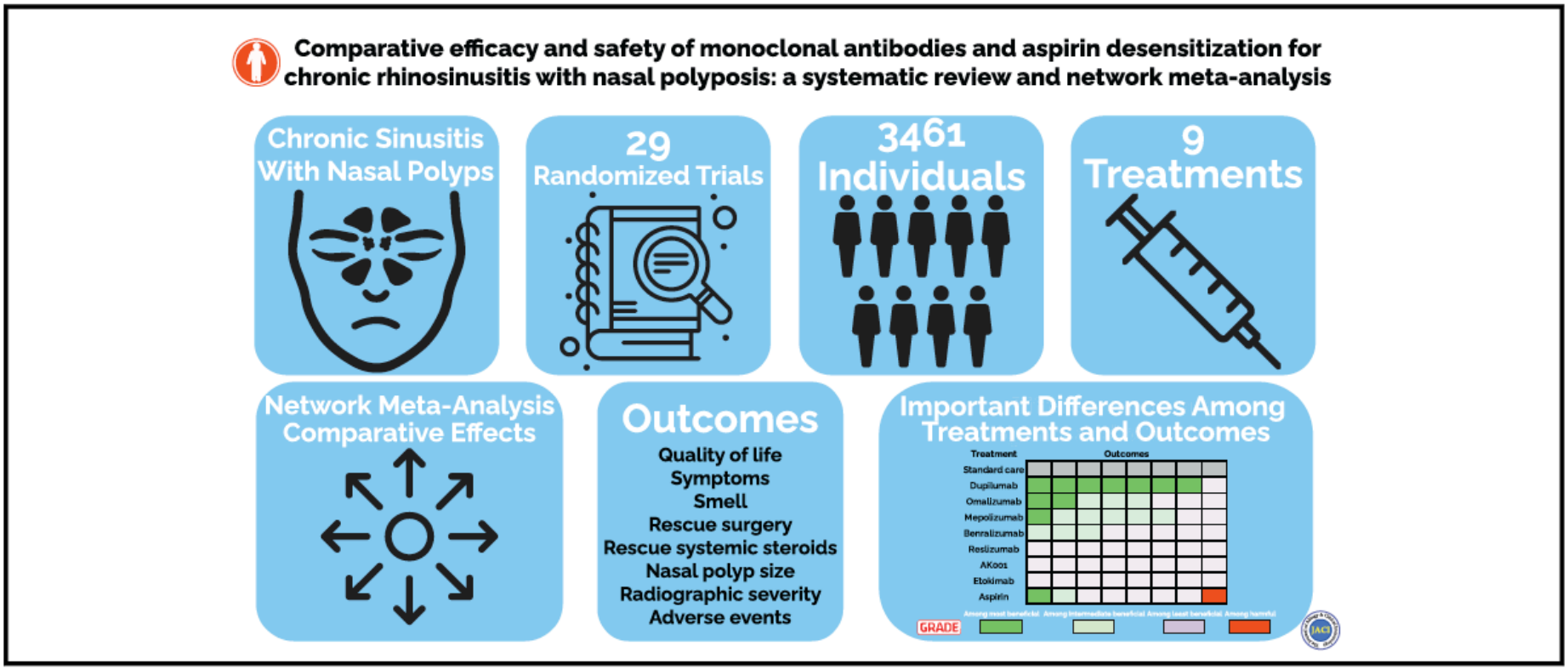




Gevaert et al. JACI. 2022 Mar;149(3):957-965

Which biologic is better? No head-to-head comparisons but… there are indirect treatment comparisons

GRAPHICAL ABSTRACT



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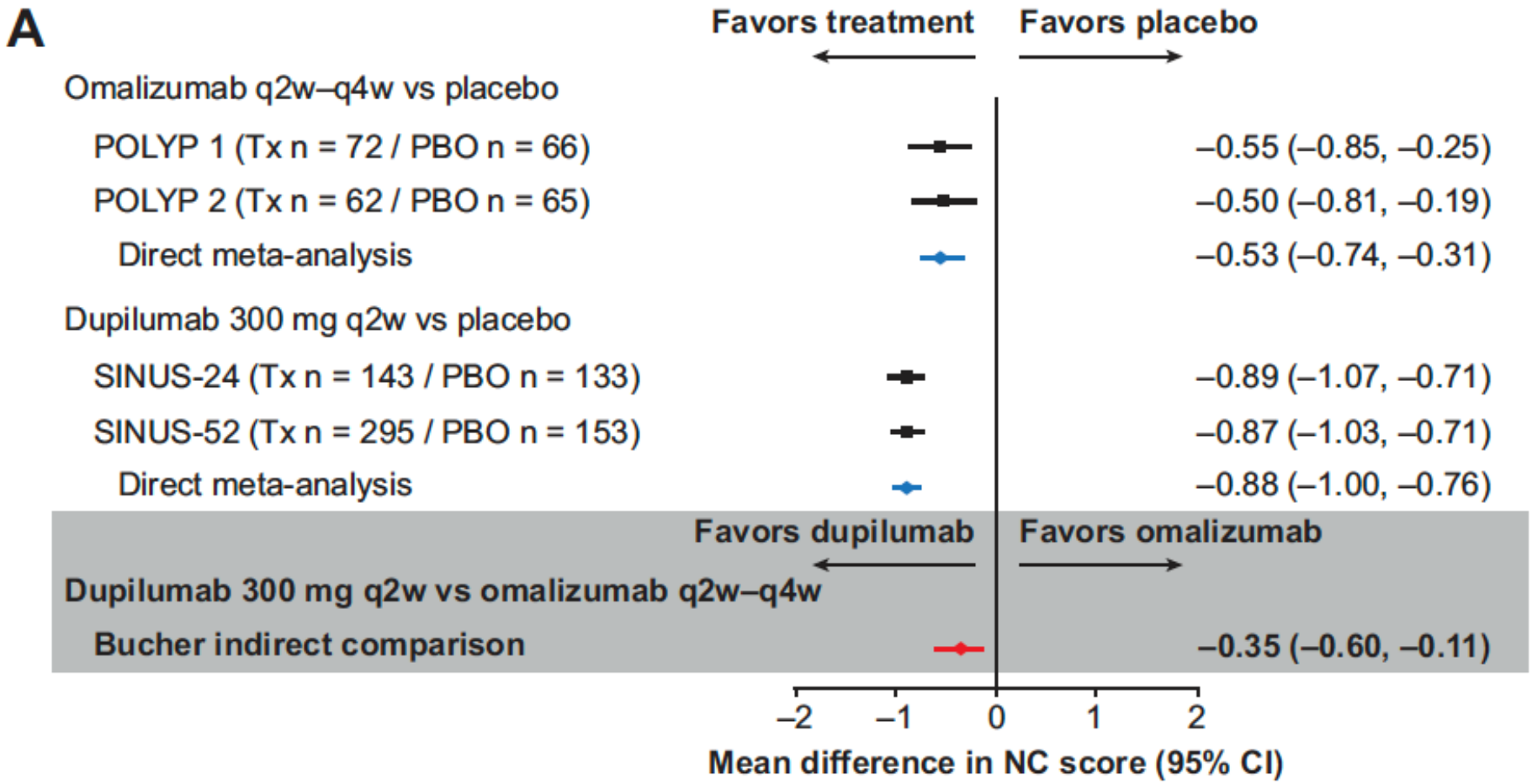
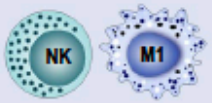
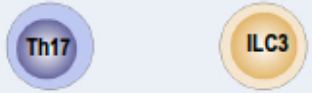
Oykhman P et al. JACI. 2021 Sep 17;S0091-6749(21)01393-2.

Which biologic is better? No head-to-head comparisons but… there are indirect treatment comparisons



Peters et al. J Allergy Clin Immunol Pract. 2021 Jun;9(6):2461-2471.e5.

Summary

Endotype	Primary cytokines	Source cells	Effector cells	Immune targets	Specific clinical features	Potential clinical treatments
Tun	None	None	None	None	Undefined to date	Undefined to date
T1	IFN-γ			Viruses	Undefined to date	Undefined to date
T2	IL-4 IL-5 IL-13			Parasites	Asthma, smell loss, NP formation	May be more responsive to corticosteroids, consider type 2 biologicals
T3	IL-17			Bacteria Fungi	Pus	Consider antibiotics

Kato et al. Allergy. 2022 Mar;77(3):812-826.

Unmet needs

- What are the roles for eosinophils, basophils, and neutrophils in CRS- *clinical biomarker or mediator in pathogenesis or both*?
- What is the "best" method to define inflammatory endotypes?
- What is the clinical significance of inflammatory endotypes?
- How can we improve clinical management of CRS?
  - *How do you select which patient to start on a biologic?*
  - *Which biologic do you start?*
  - *What about sinus surgery?*
  - *What about patients with CRSsNP or non-type 2 inflammation?*
- Can further investigation of the cellular basis of chronic rhinosinusitis predict the role of biologics?

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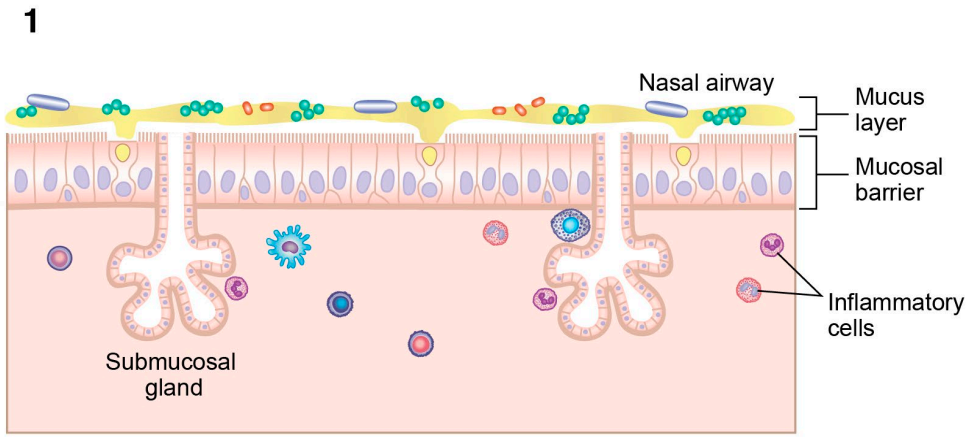
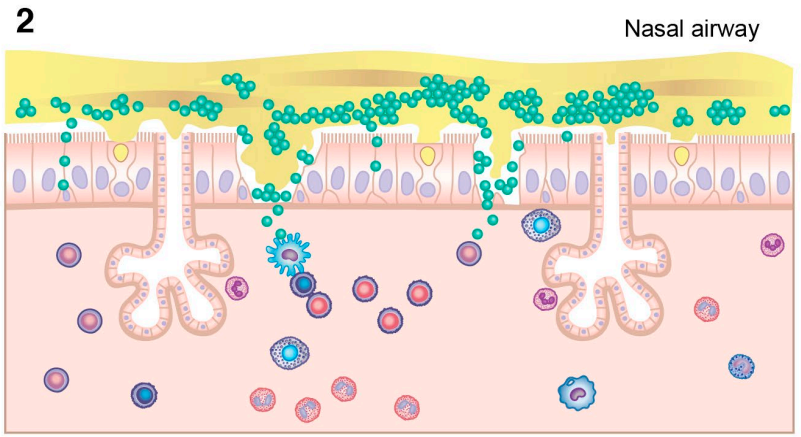
Thank you!

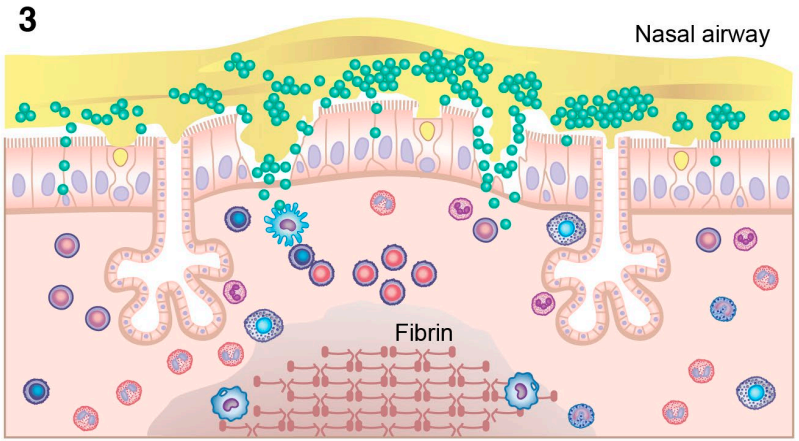
Nasal Polyp Formation Overview



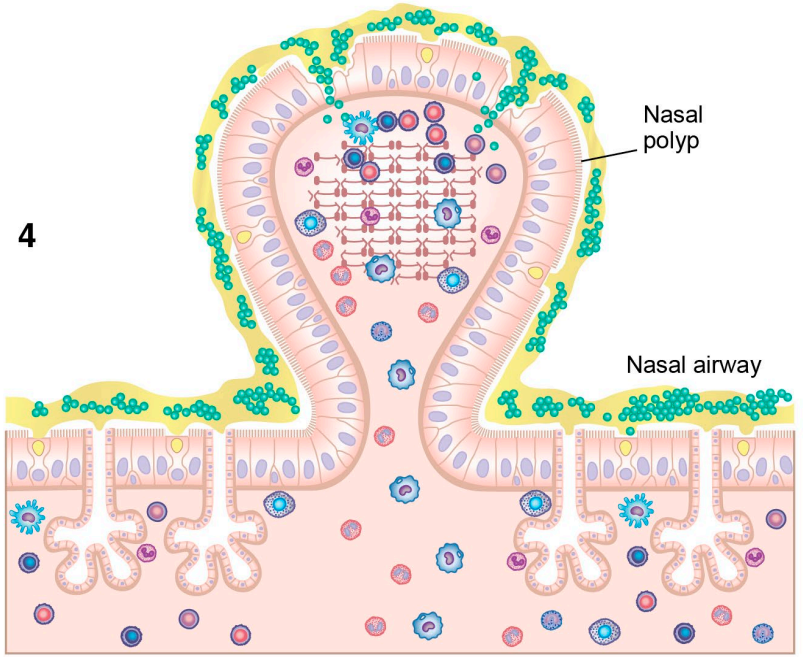
Normal nasal mucosa and colonization with microbes



Loss of barrier with increased abundance and decreased diversity of microbes



Recruitment and expansion of inflammatory cells, tissue swelling, inflammation, and deposition of crosslinked fibrin



Tissue remodeling with loss of submucosal glands in polyp and profound inflammatory cell expansion

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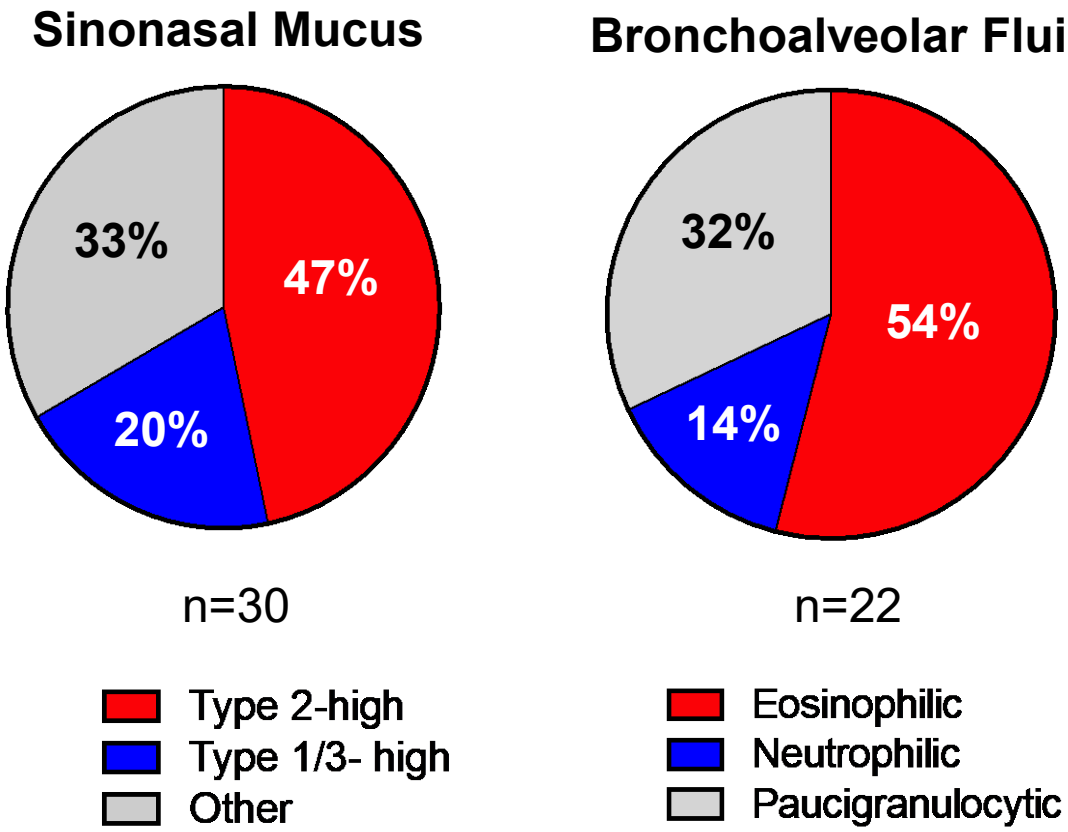
Stevens WW et al. J Allergy Clin Immunol Pract. 2016 Jul-Aug;4(4):565-72.

AERD pathogenesis: mixed inflammatory endotypes



Scott WC et al. , JACI. 2021;147(4):1318-28.
Jakiela B et al. JACI. 2021;147(4):1269-80
Jakiela B et al. JACI 2022. in press.
Stevens and Cahill. JACI. 2023. in press.

Estimated prevalence of AERD in the United States

0.6% - 2.5%

General Population

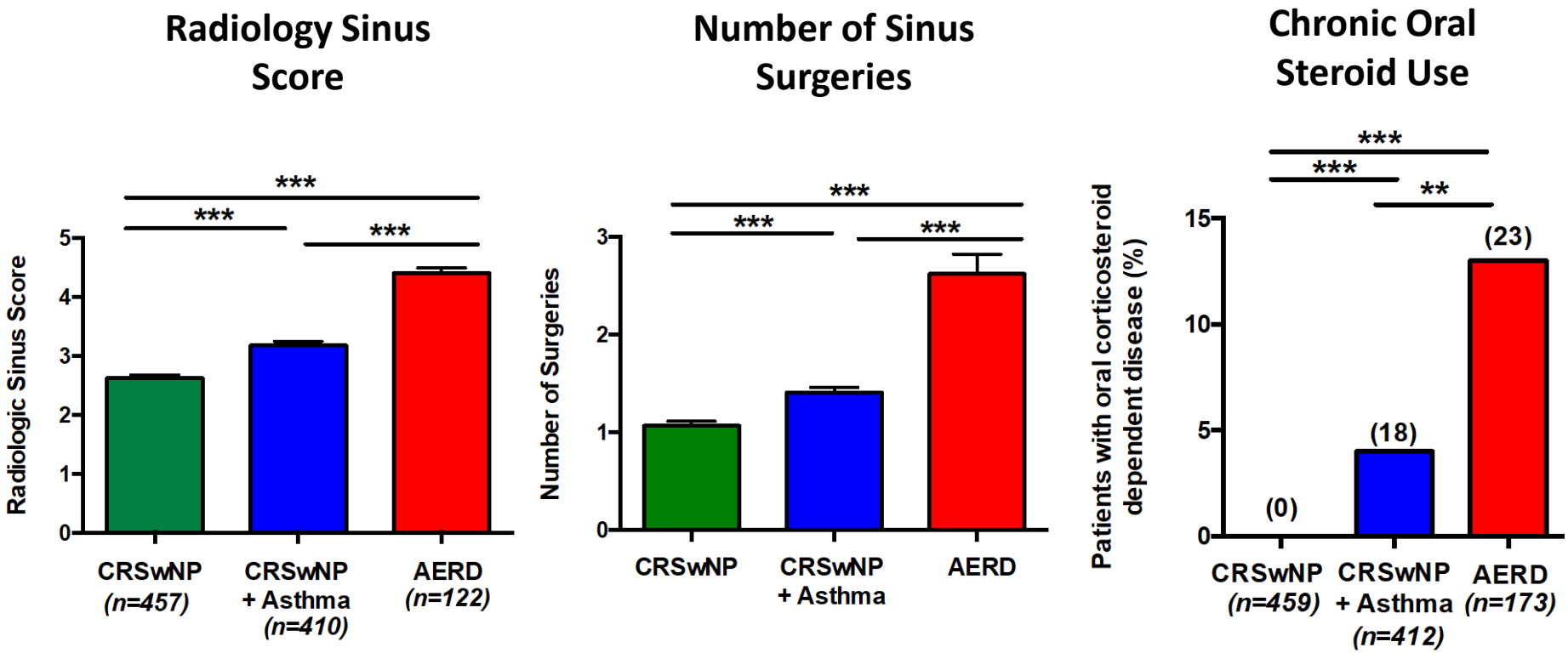
12.4% - 14.9%
Asthmatics

9.7% - 16%
Nasal Polyps

15% of patients with AERD may not be able to identify if they are intolerant to COX-1 inhibitors

Rajan *et al.* J Allergy Clin Immunol; 2015
Stevens *et al.* J Allergy Clin Immunol Pract. 2017
Szczeklik *et al.* Eur Resp J. 2000
White *et al.* Semin Respir Crit Care Med; 2012
Cahill *et al.* J Allergy Clin Immunol. 2017

Patients with AERD tend to have more severe disease



*AERD patients, on average, are significantly younger at the time of first sinus surgery (40yrs) than CRSwNP (43yrs) or CRSwNP+Asthma (42yrs)

*** p<0.01; *** p<0.001; Chi-squared*

Stevens W et al. JACI: IP. 2017 Jul-Aug;5(4):1061-1070

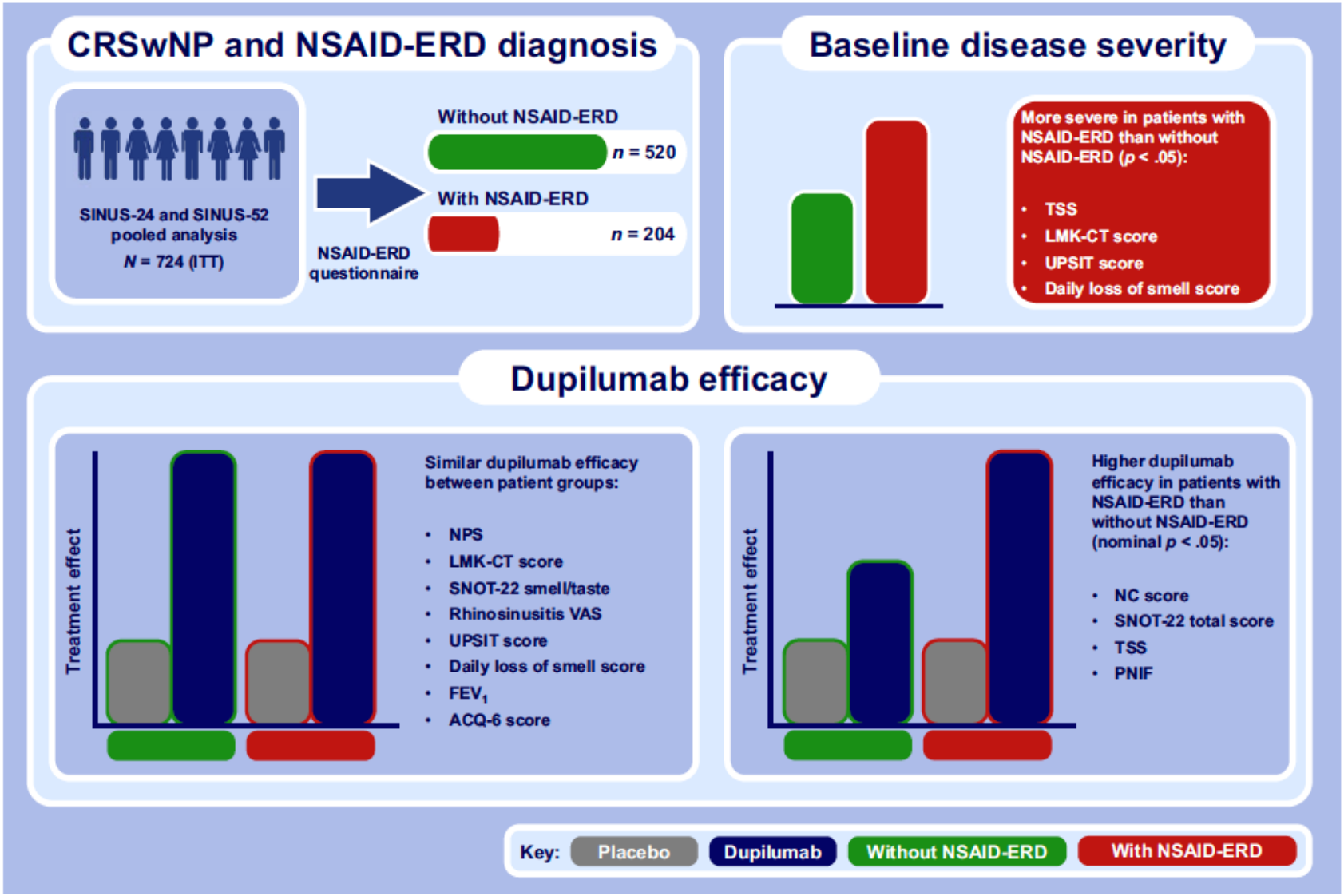
Post-hoc analysis of AERD (SINUS-24 & SINUS-52)

	SINUS-24			SINUS-52		
Patients with comorbid NSAID-ERD	**Placebo (n=38)**	**Dupilumab 300 mg q2w (n=46)**	**LS mean difference (95% CI)**	**Placebo (n=44)**	**Dupilumab 300 mg q2w (n=76)**	**LS mean difference (95% CI)**
Nasal polyp score — scale 0–8	0.21 (0.27)	−1.41 (0.26)	−1.62 (−2.28 to −0.97)	0.27 (0.23)	−1.82 (0.19)	−2.10 (−2.61 to −1.58)
			p<0.0001			*p*<0.0001
Nasal congestion/obstruction score — scale 0–3	−0.37 (0.14)	−1.39 (0.14)	−1.02 (−1.37 to −0.68)	−0.18 (0.13)	−1.43 (0.11)	−1.25 (−1.54 to −0.96)
			p<0.0001			*p*<0.0001
Lund-Mackay CT score — scale 0–24	−0.71 (0.74)	−7.37 (0.68)	−6.66 (−8.37 to −4.95)	−0.14 (0.61)	−6.26 (0.50)	−6.13 (−7.48 to −4.78)
			p<0.0001			*p*<0.0001

In AERD patients, dupilumab was associated with significant improvement in nasal polyp score, nasal congestion score, and CT score compared to placebo

Bachert et al. Lancet. 2019 Nov 2;394(10209):1638-1650.

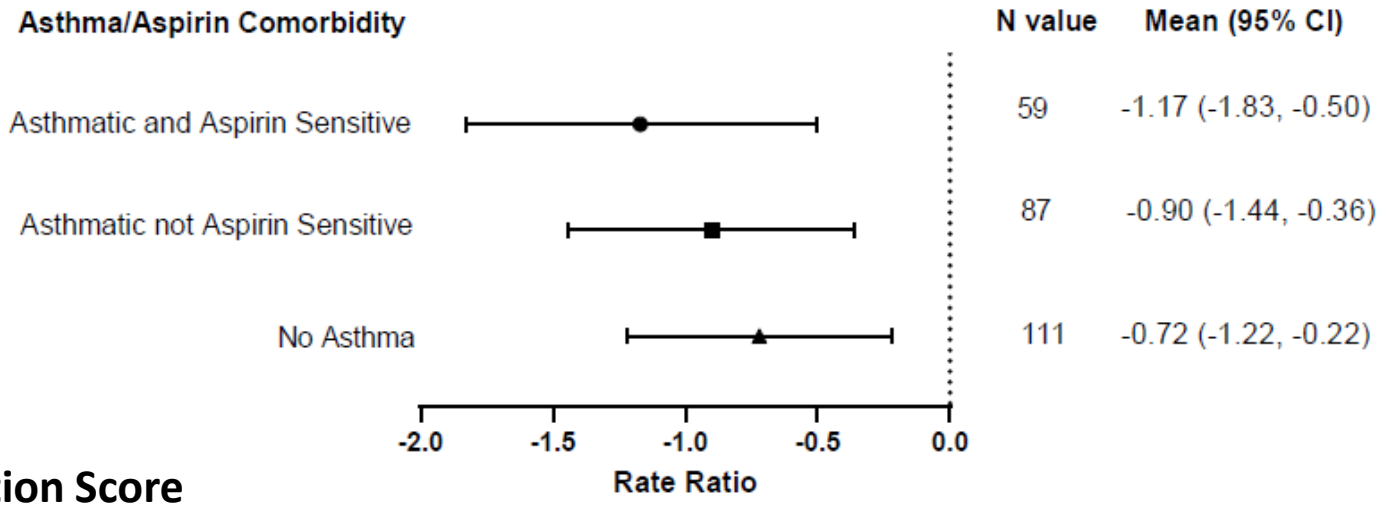
Post-hoc analysis of AERD vs CRSwNP (SINUS-24 & SINUS-52)



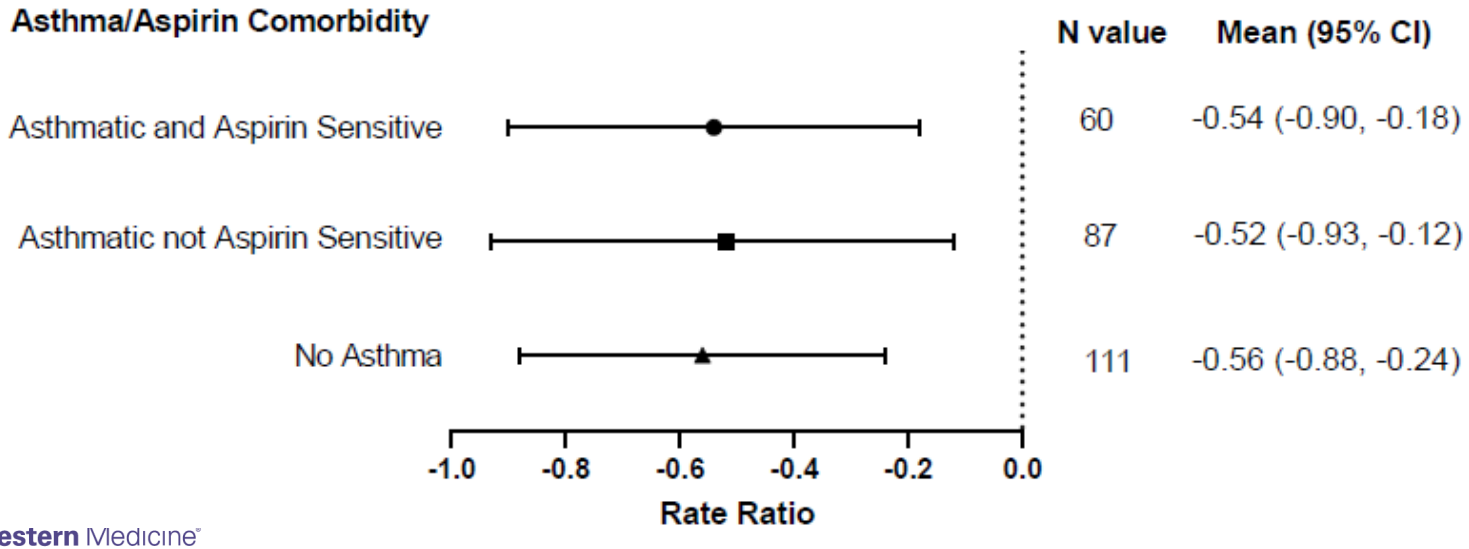
Mullol et al. Allergy. 2022 Apr;77(4):1231-1244.

Post-hoc analysis of AERD (POLYP 1 and POLYP 2)

Nasal Polyp Score

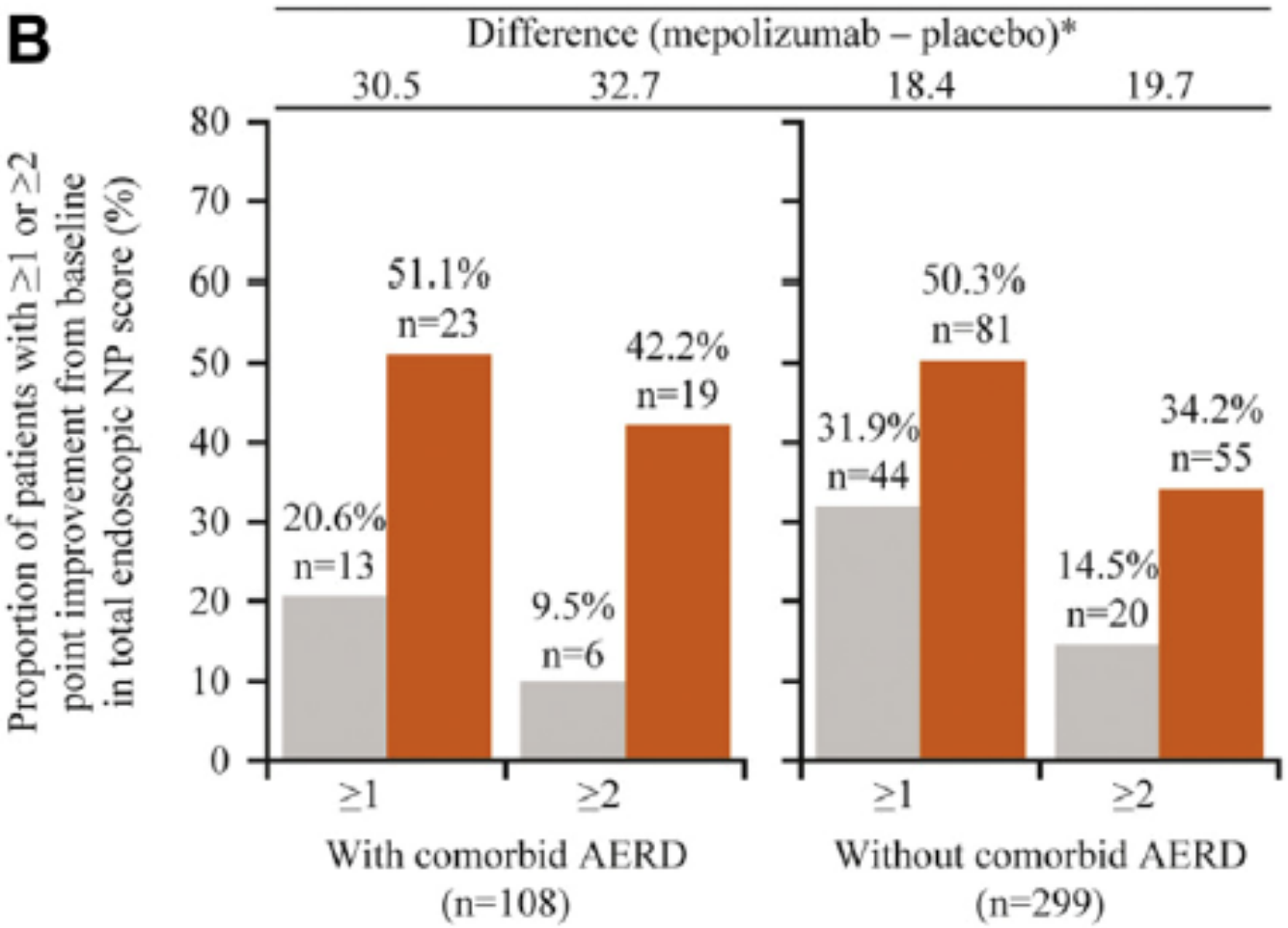


Nasal Congestion Score



Gevaert et al. J Allergy Clin Immunol. 2020

Post-hoc analysis of AERD (SYNAPSE) – nasal polyp score



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