IL-17 and anti-IL-17 in asthma

정지예

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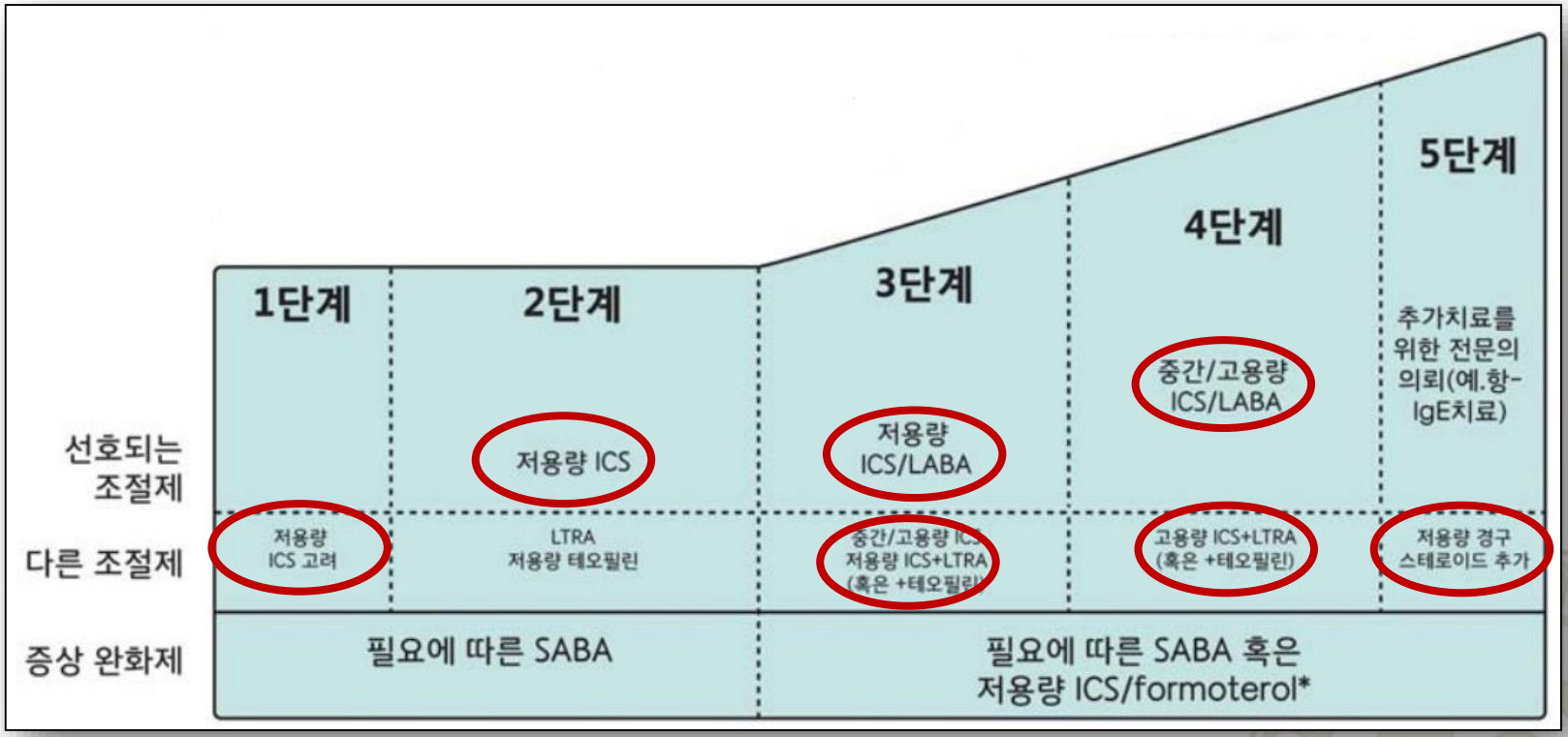
세브란스병원 호흡기내과

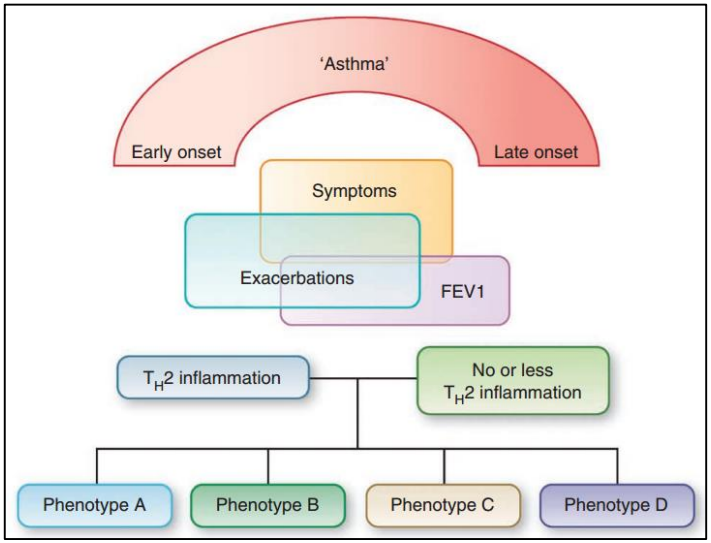
Current Treatment of Asthma

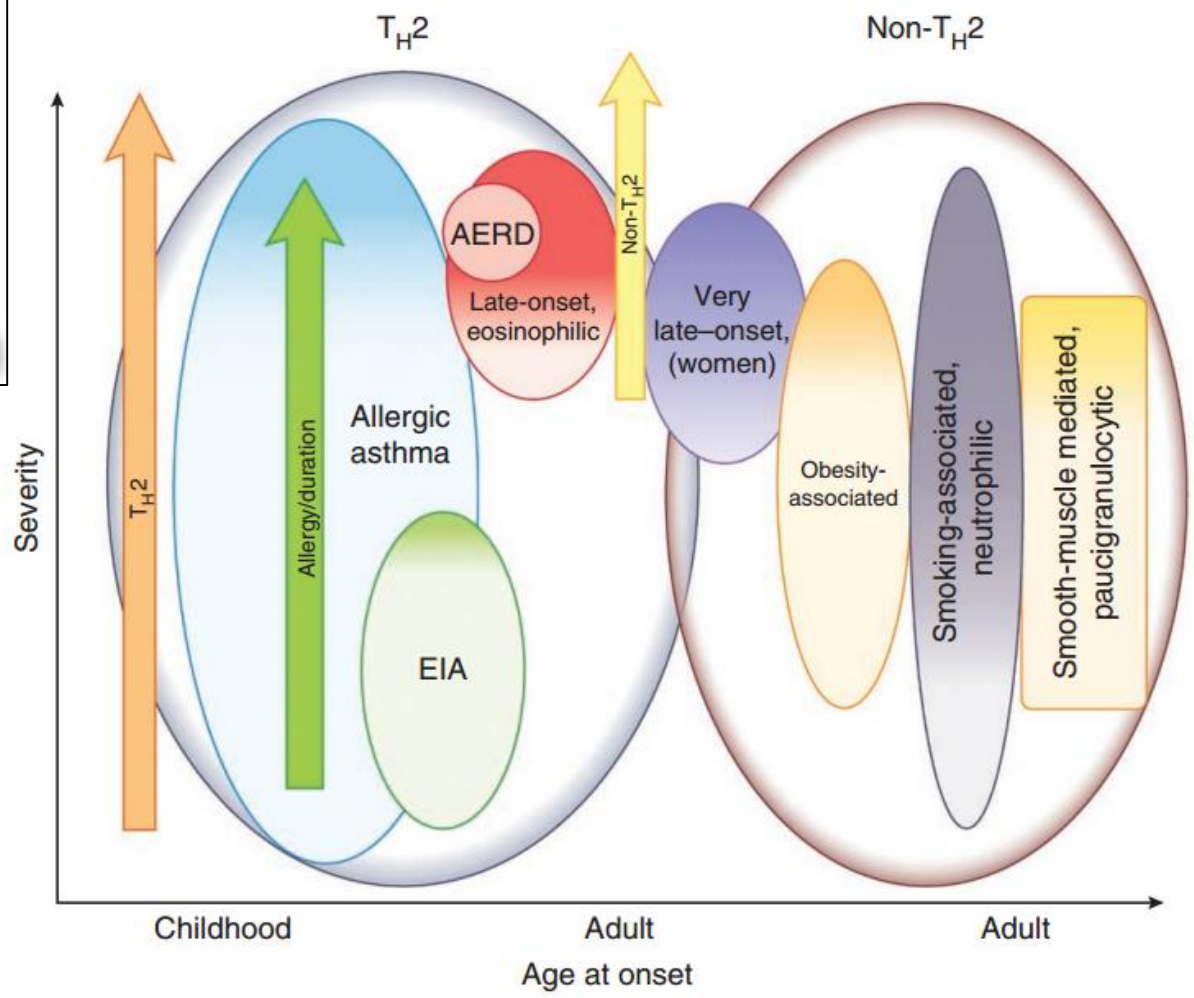


Oral corticosteroid, ICS, long-acting bronchodilators
Only current therapies typically used for **all types of asthma**

국내 천식 진료지침 2014

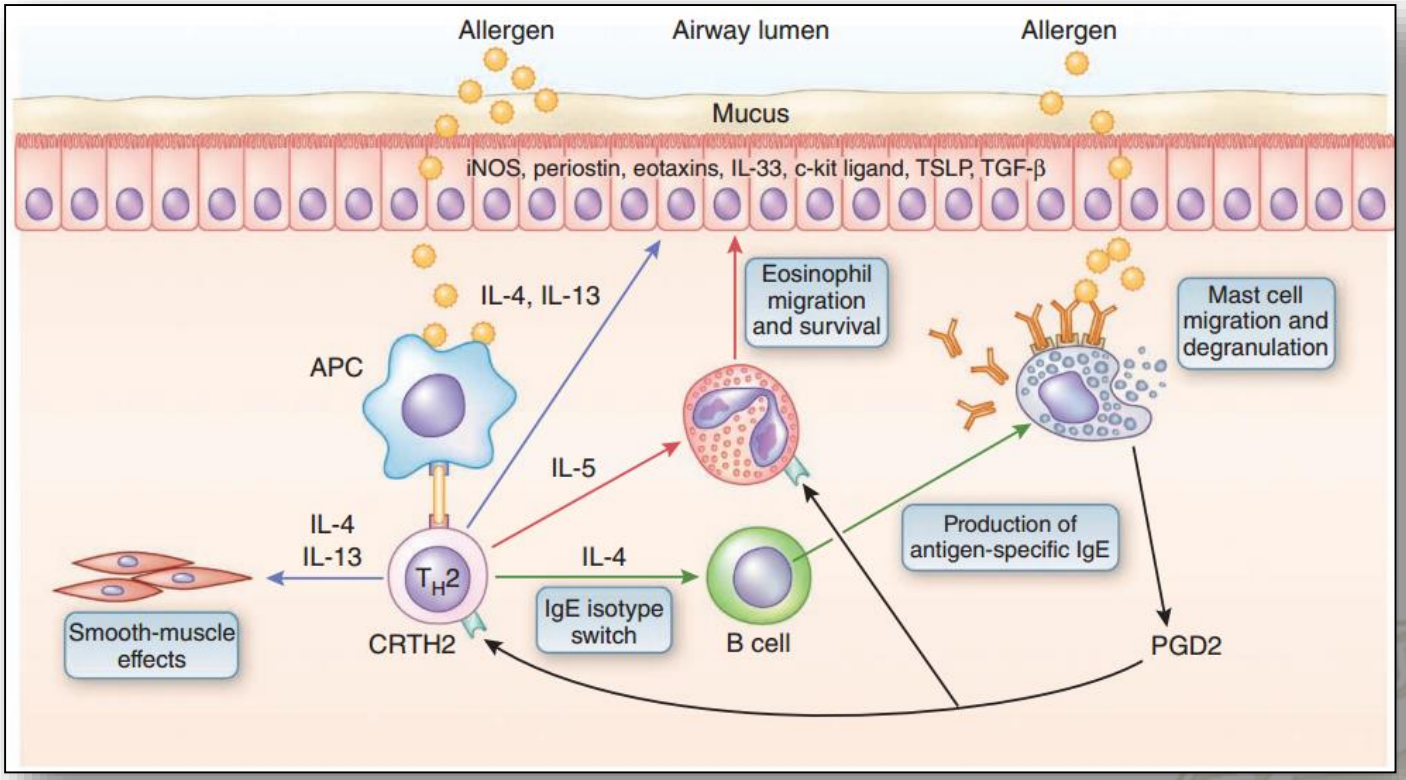
Asthma Phenotypes based on Th2





Wenzel at al. Nat Med 2012

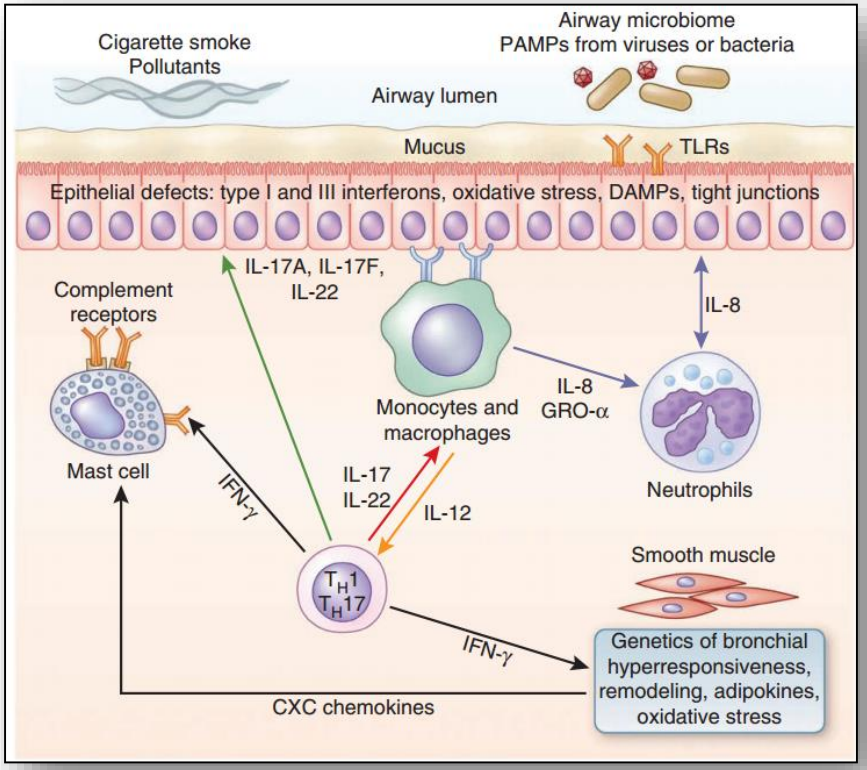
Th2-High Phenotype



Phenotypes	Biomarkers	Therapy
Early-onset allergic	Specific Ig E,	Corticosteroids, anti-IgE
Late-onset eosinophilic	Sputum eosinophilia, IL-5	Poor response to corticosteroids, anti-IL-5
Exercise induced	Mast cells	Leukotriene receptor antagonists, SABA

Wenzel at al. Nat Med 2012

Th2-Low Phenotype



Phenotypes	Biomarkers	Therapy
Obesity related	Mast cells, adiponectin, Th1 cytokines	**Poor response to** corticosteroids, Weight loss, PPAR agonists
Neutrophilic	**Th17**, sputum neutrophilia	VitD, p38 MAPK inhibitors, macrolides **Poor response to** corticosteorids

Wenzel at al. Nat Med 2012

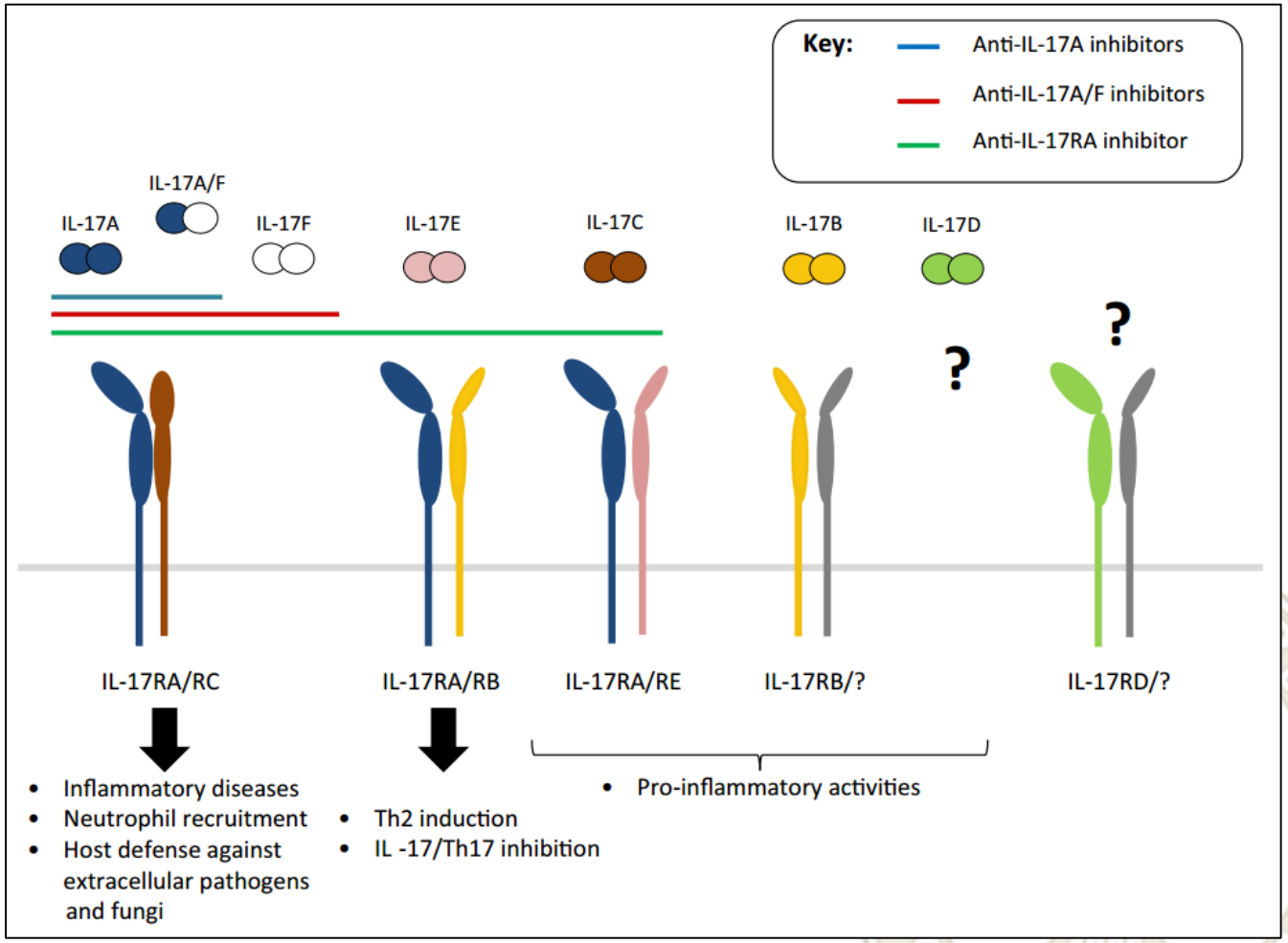
IL-17 Cytokine and Receptor Family

IL-17

- Human cytotoxic T lymphocyte-associated antigen 8 (CTLA8)
- identified in 1993
- named IL-17 in 1995
- IL-17A to IL-17F

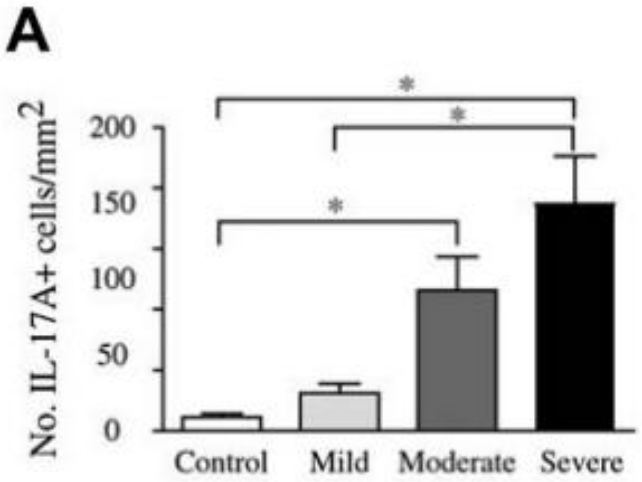
IL-17 Receptor

- Identified 1995
- Five subunits (IL-17RA to IL-17RE)

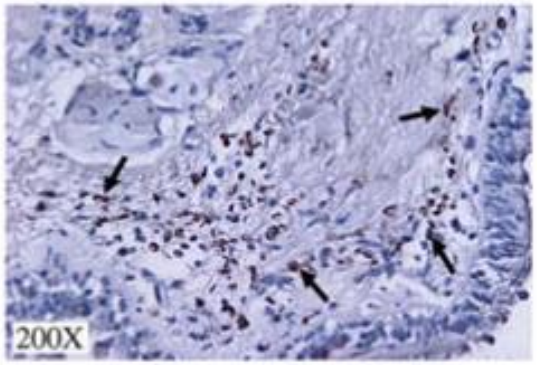


Beringer at al. Trends Mol Med 2016

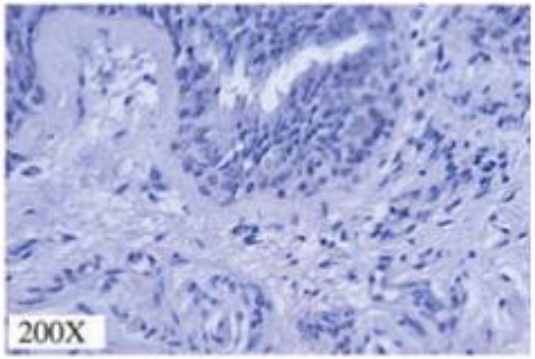
Immunostaining of IL-17 in lung tissue from asthma

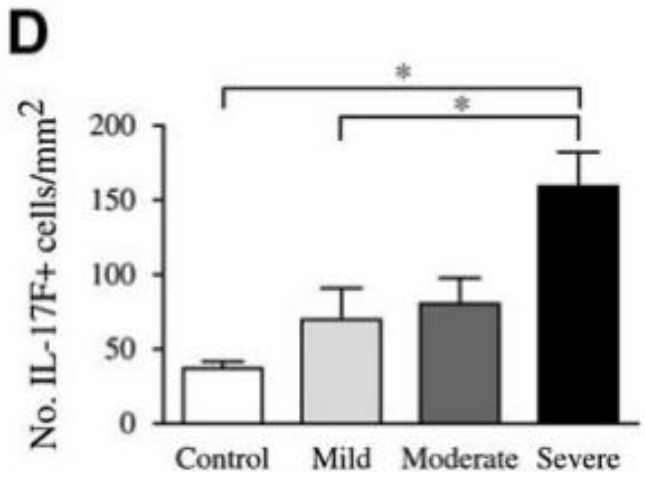


IL-17A

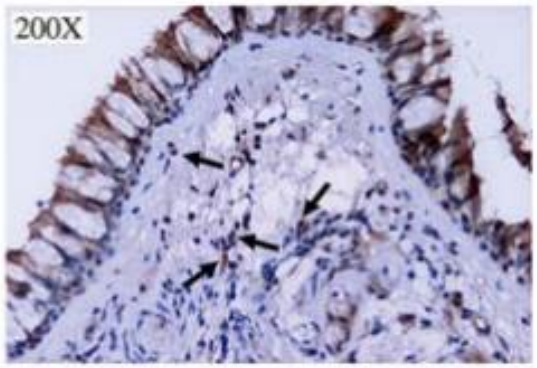


Negative control IgG

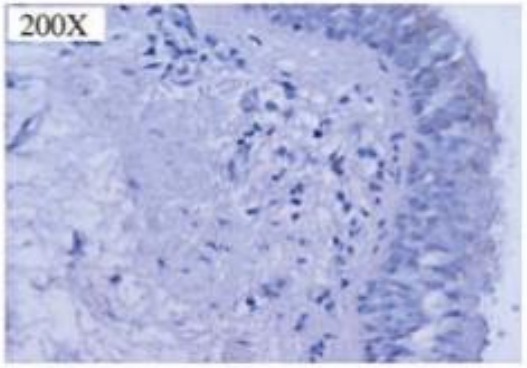




IL-17F

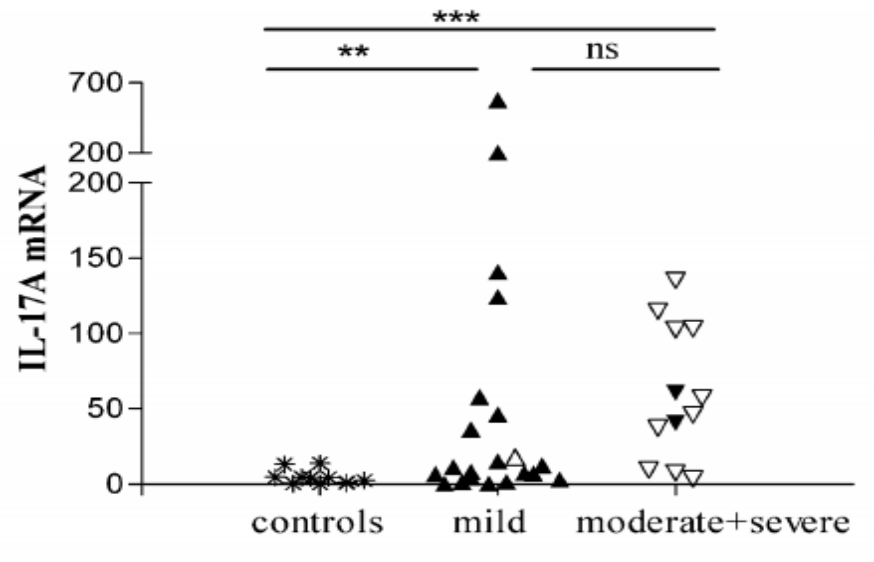


Negative control IgG

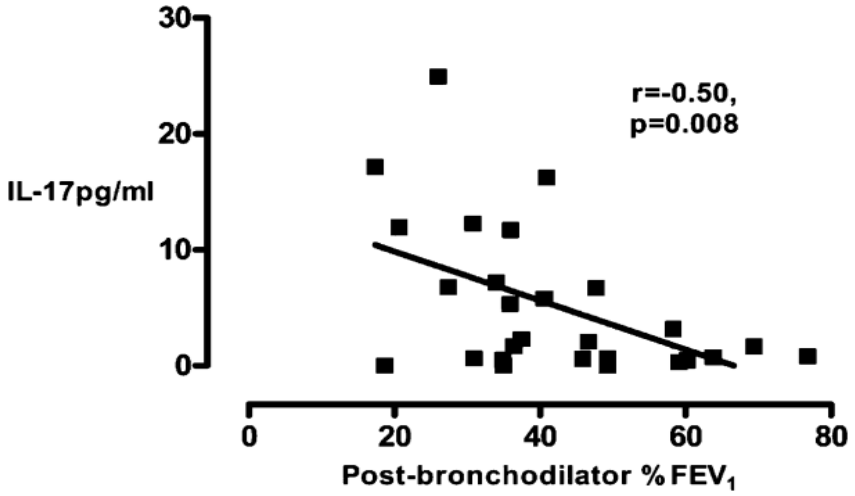


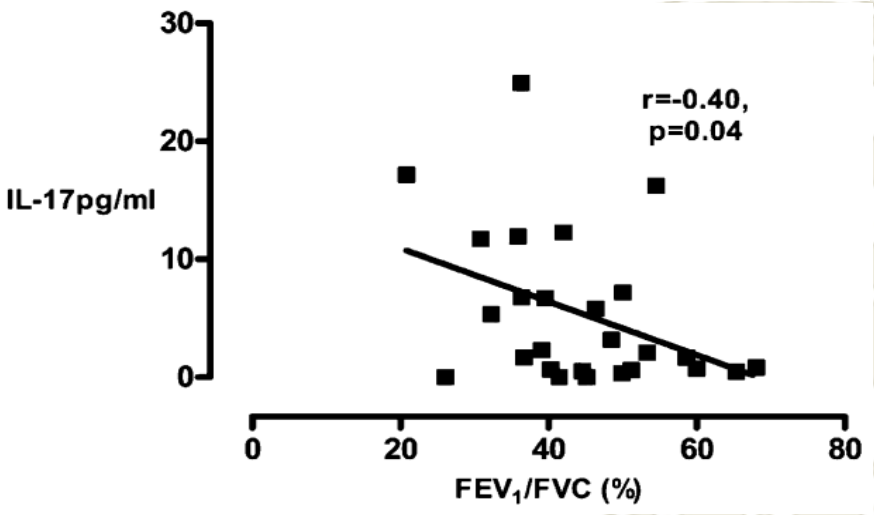
Al Ramli at al. J Allergy Clin Immunol 2009

IL-17 in sputum from asthma



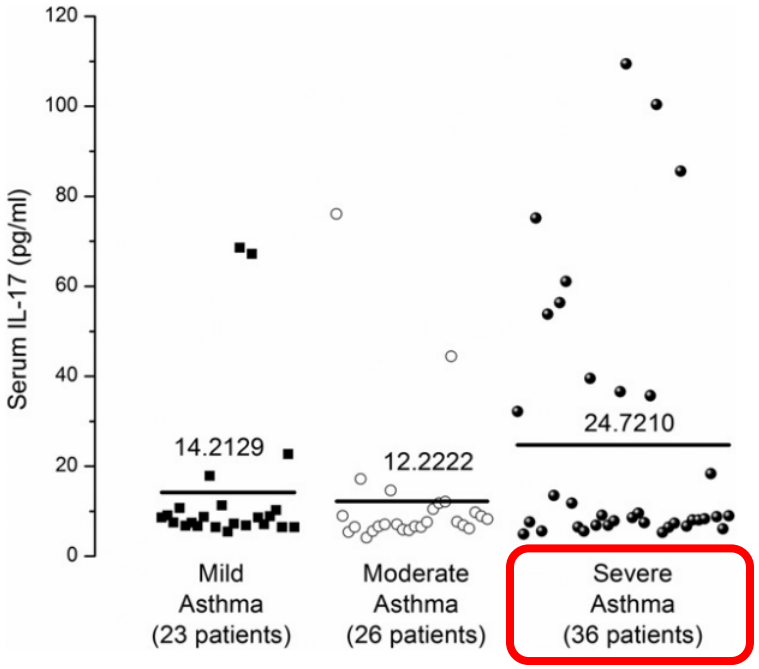
Sputum IL-17 and lung function in asthma and COPD





Bullens et al. Respir Res 2006
Doe et al. Chest 2010

Correlation between serum IL-17 and asthma severity

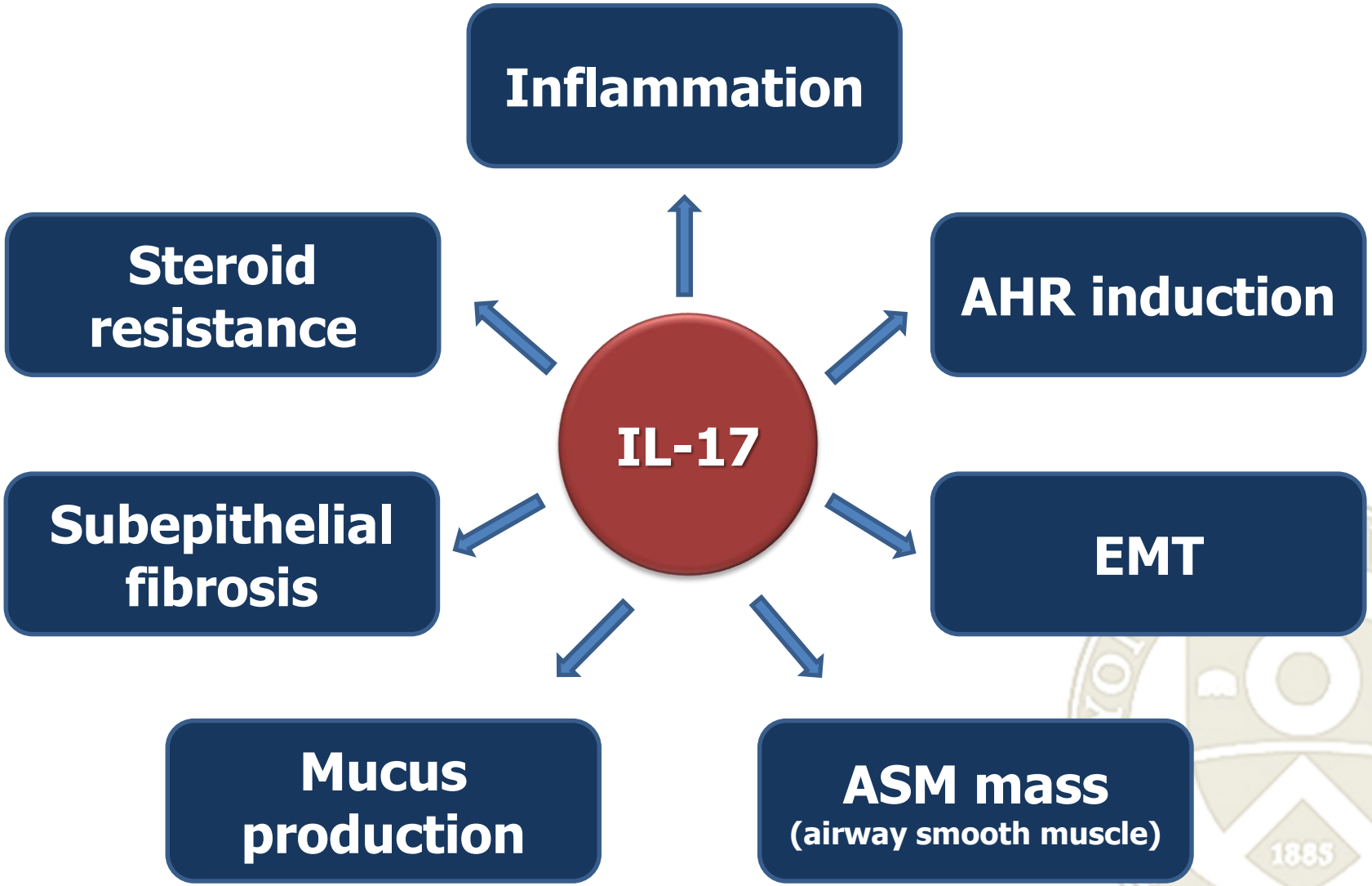


Risk factors for severe asthma in multiple regression analysis model

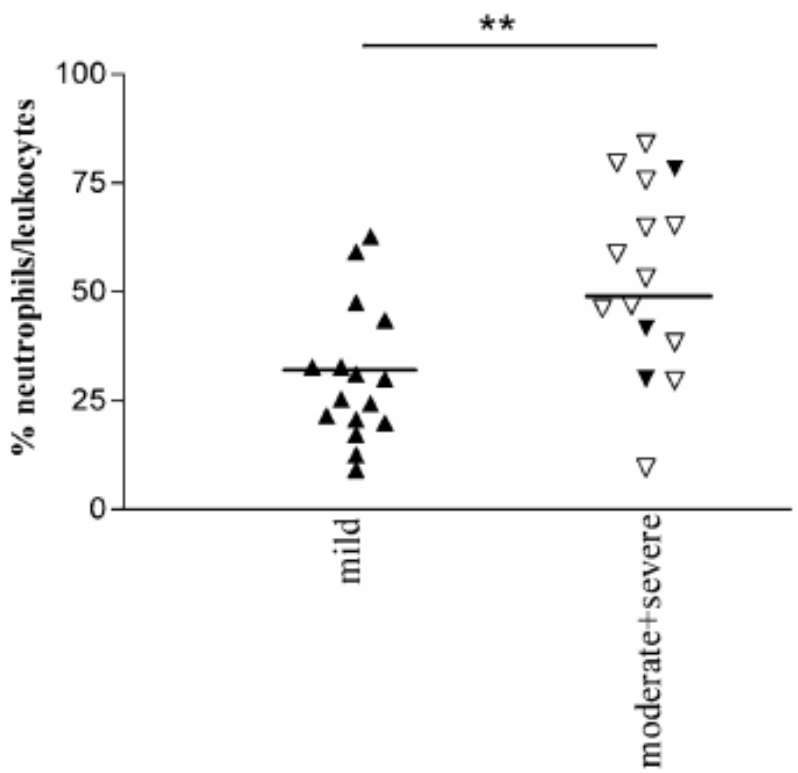
	Beta	p-level
Smoke	0.010273	0.911746
NSAID intolerance	0.346923	0.000649
Atopy	−0.076304	0.441099
Obesity	−0.002673	0.979728
Moderate/severe persistent rhinitis/chronic rhinosinusitis	−0.028323	0.773233
Blood eosinophilia	−0.094935	0.314731
$FEV_1 < 50\%$ predicted	0.400498	0.000043
IL-17 > 20 pg/ml	0.352762	0.000257

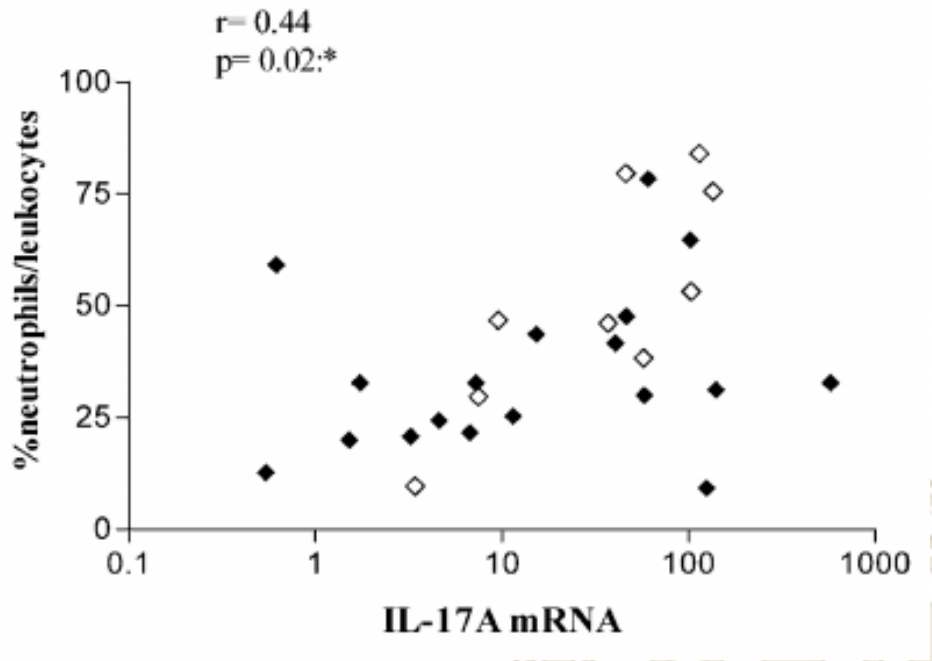
Agache at al. Respi Med 2010

IL-17 Effects in Asthma Pathophysiology



Correlation of IL-17 and neutrophil in Sputum of Asthmatic patient

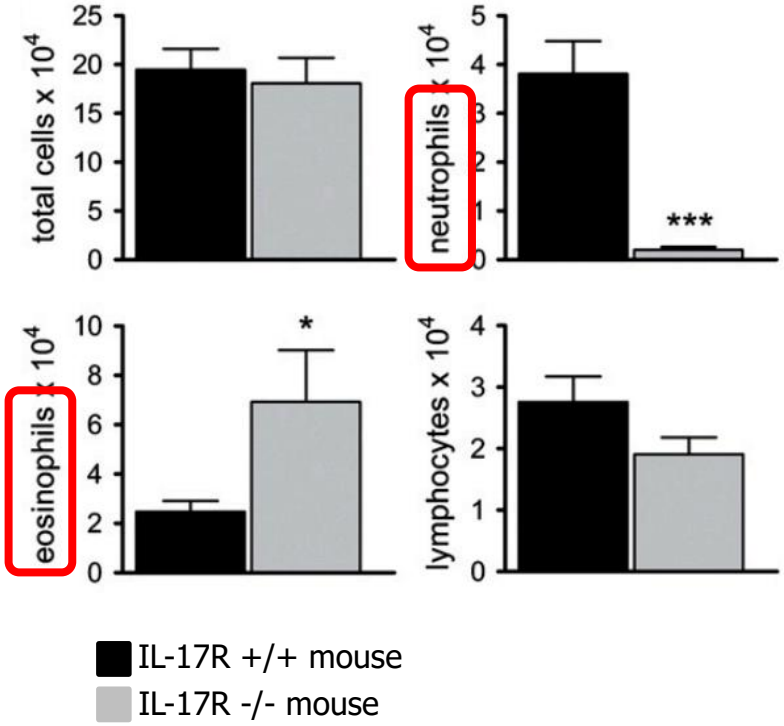




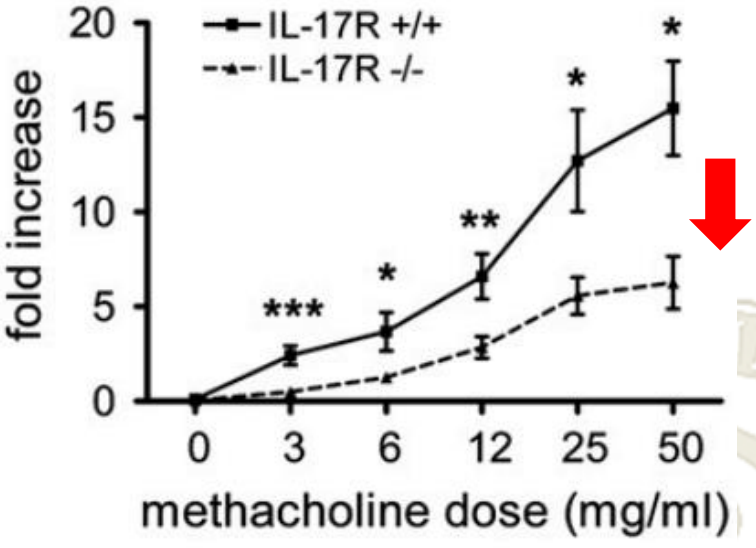
Bullens et al. Respir Res 2006

Airway neutrophilia and airway hyperreactivity in response to IL-17

BAL



Lung Resistance



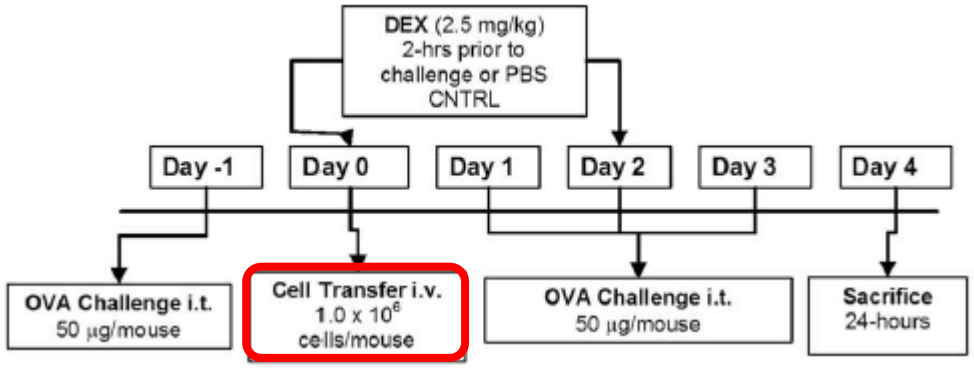
by Flexivent mechanical ventilator system

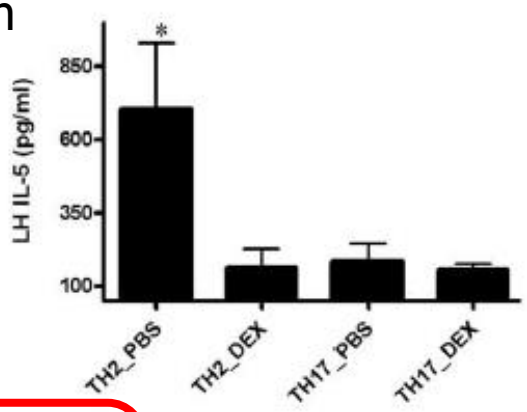
Wilson et al. AJRCCM 2009

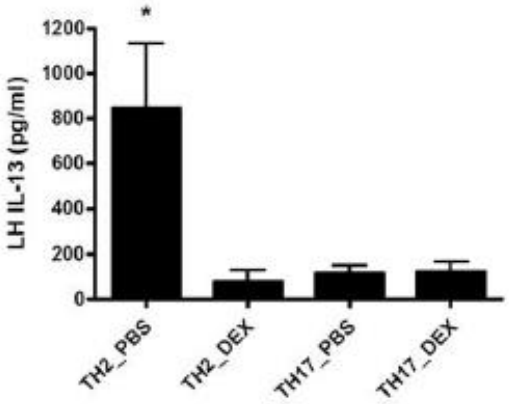
Role of IL-17 in Steroid Insensitivity

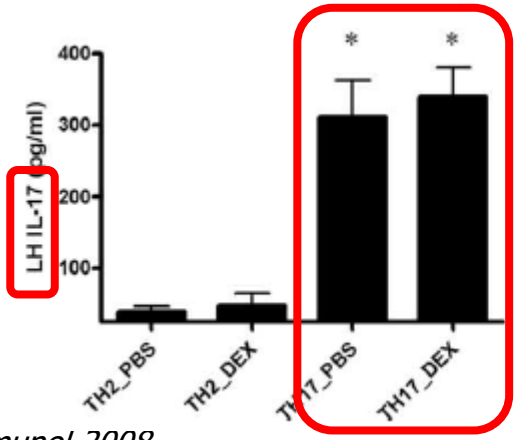
Cytokine/chemokine profiles induced by Th2 & Th17 cell transfer & allergen provocation

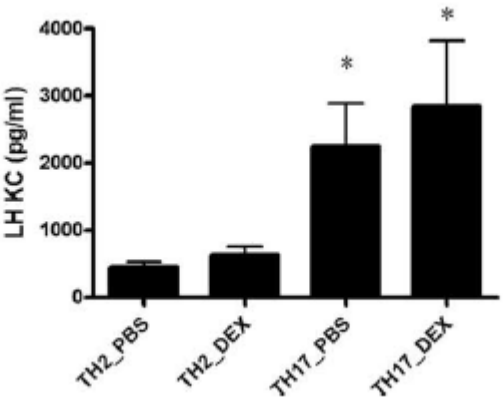
LH: lung homogenate sample

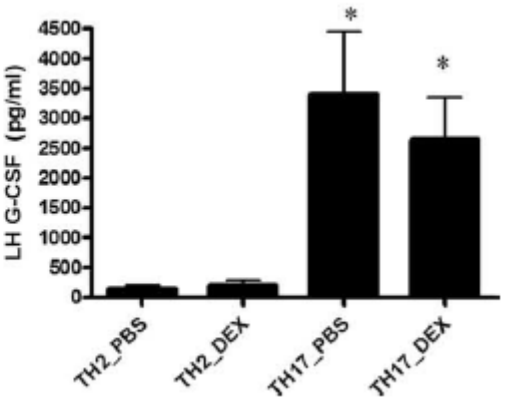






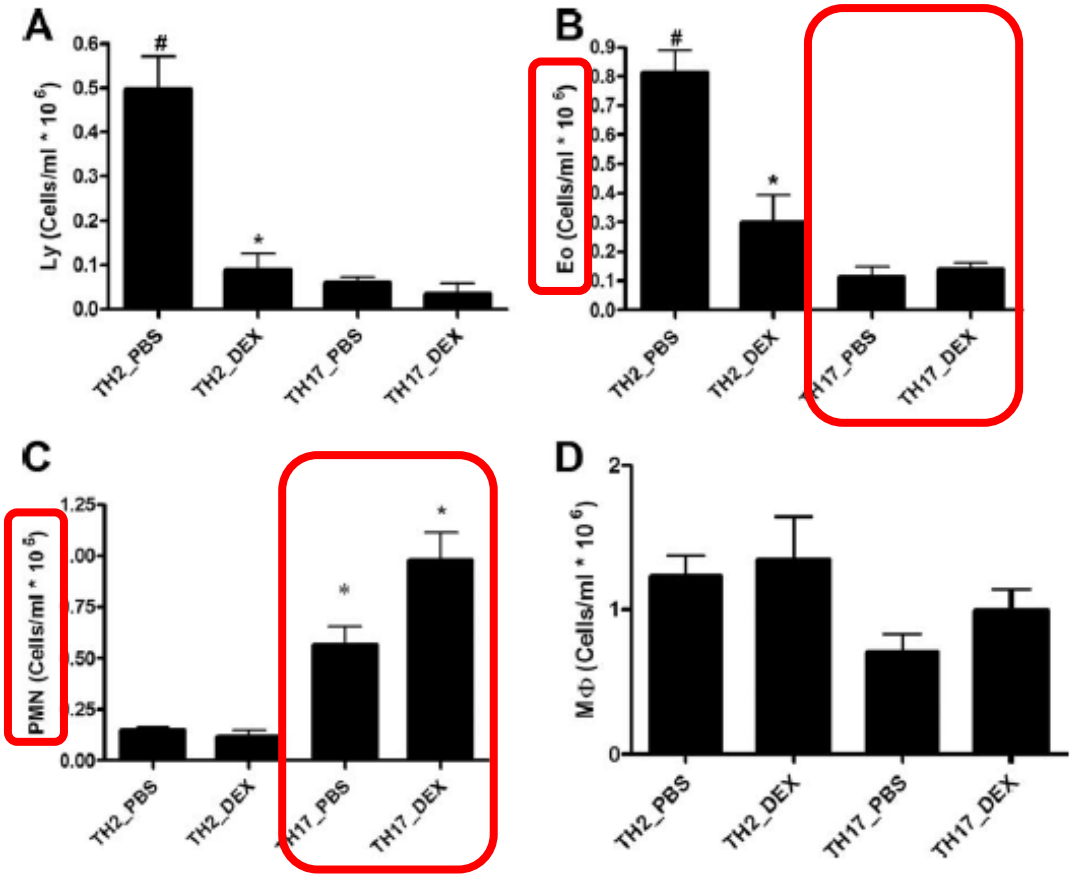




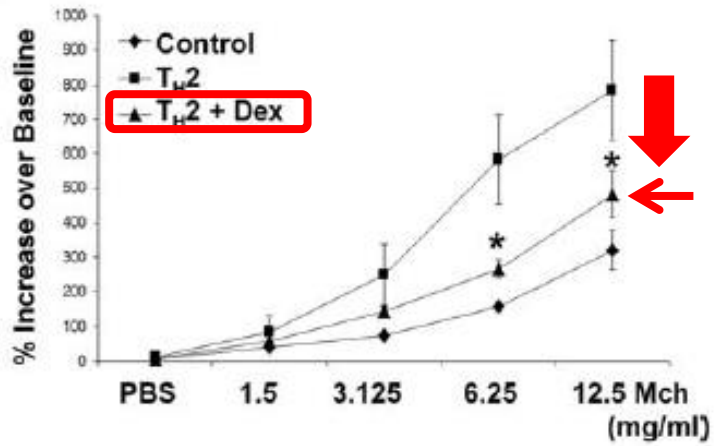


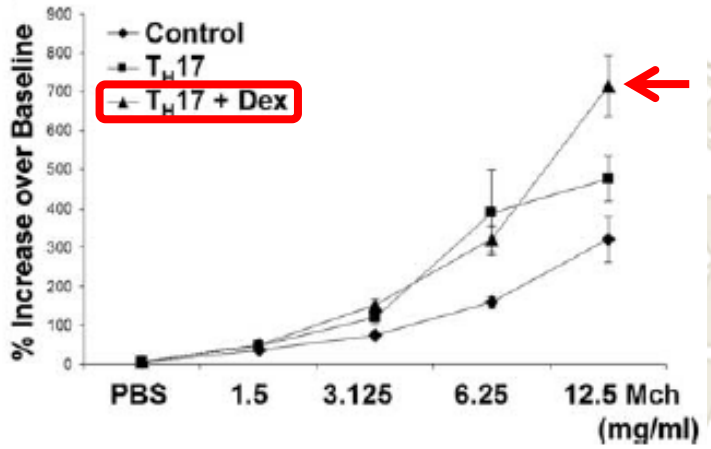
McKinley et al. J Immunol 2008

TH2- and TH17-mediated airway inflammation in BAL



Methacholine dose-response curves

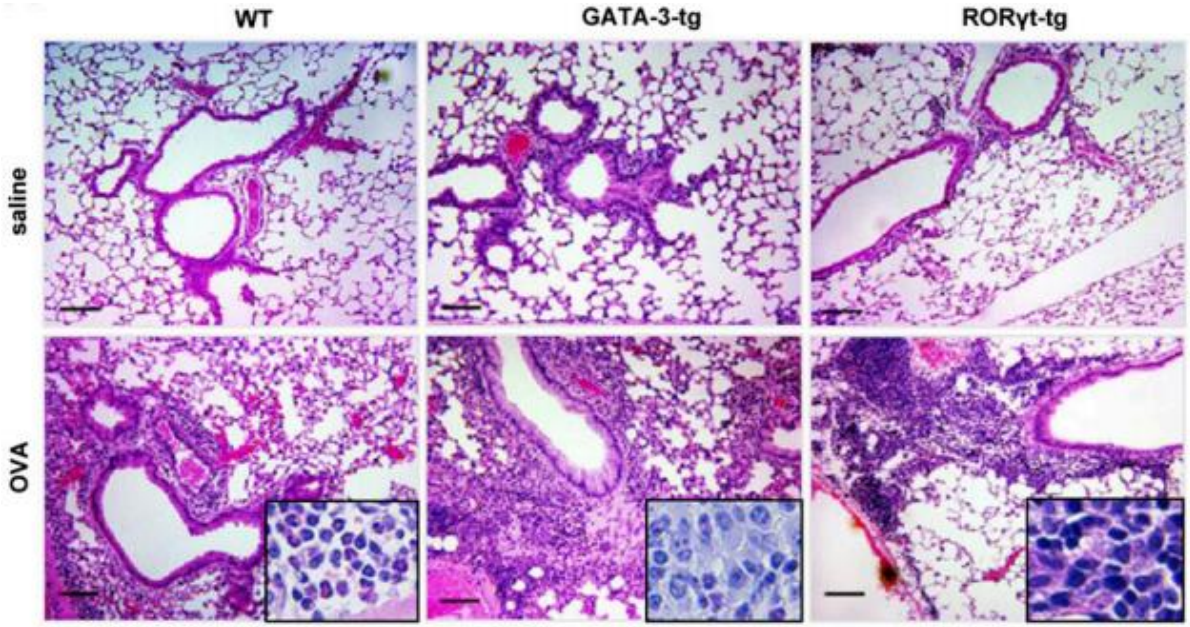




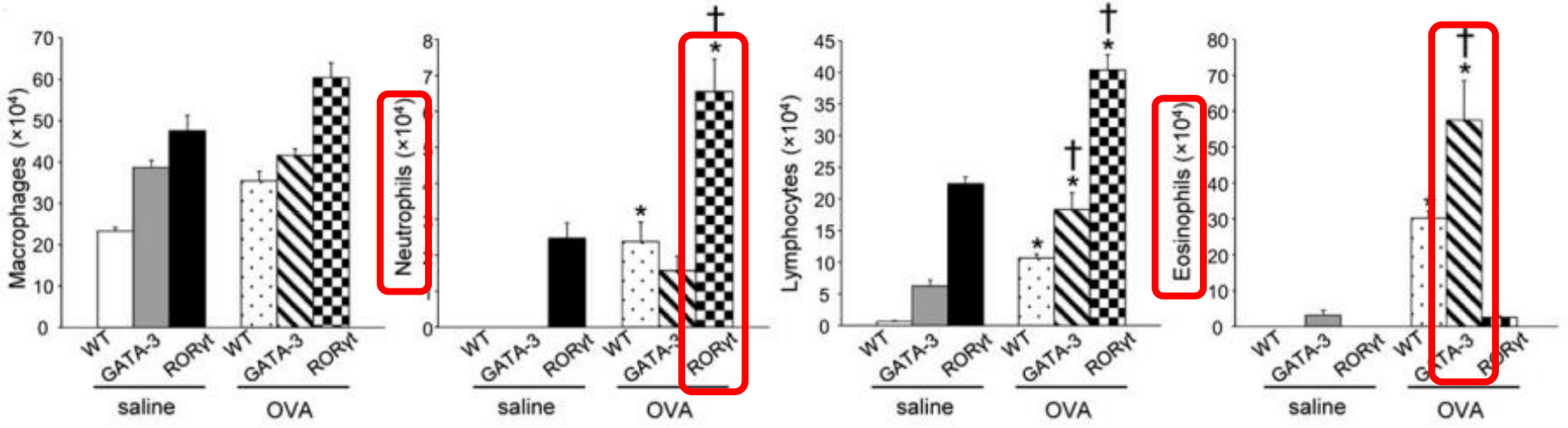
McKinley et al. J Immunol 2008

Role of IL-17 in Steroid Insensitivity

GATA-3; Th2 differentiation
RORγt; Th17 differentiation

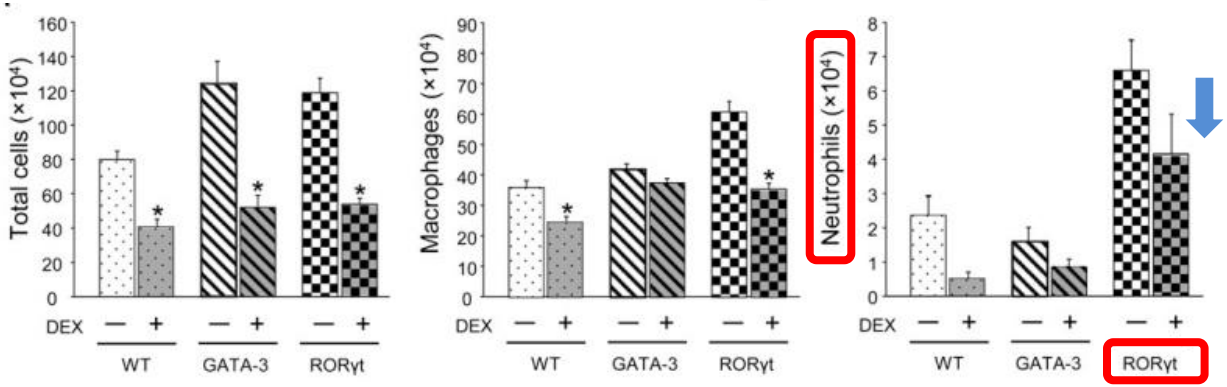


BAL

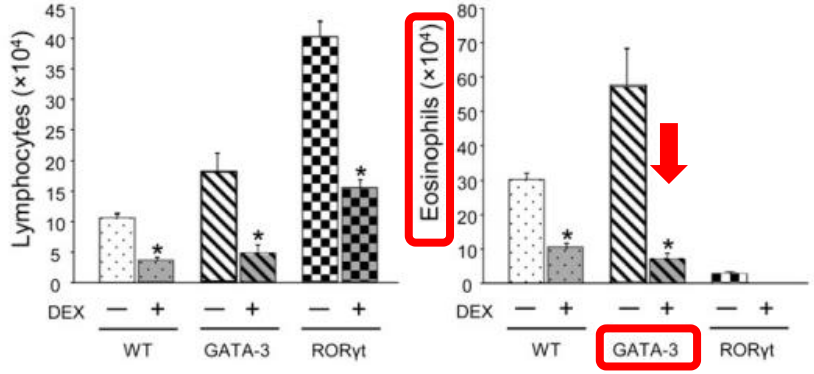


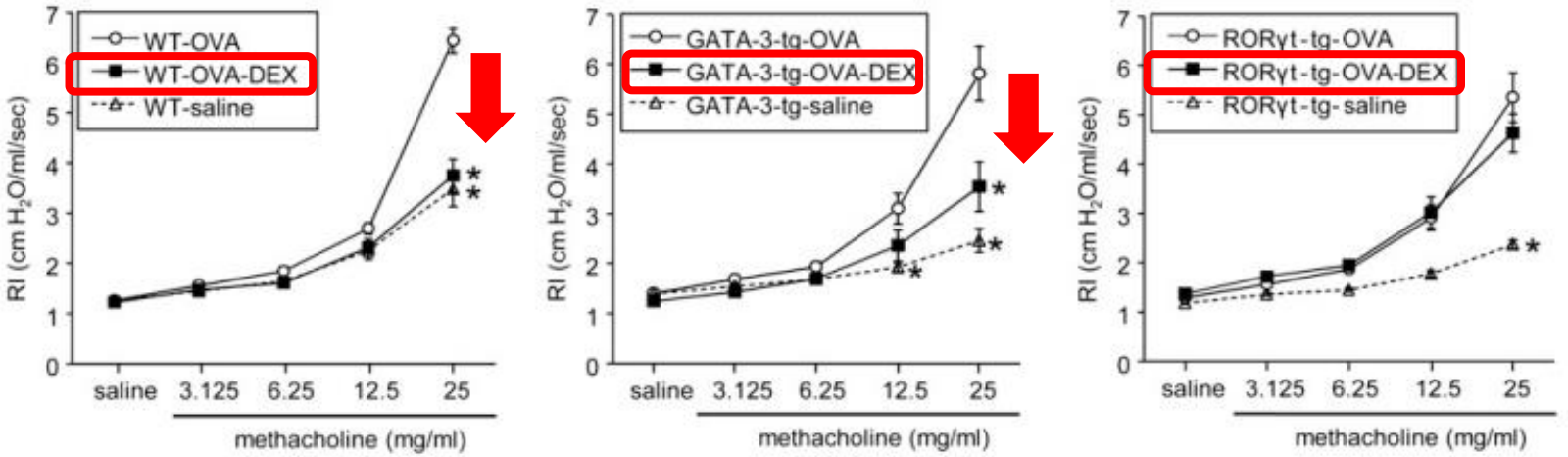
Ano et al. Jr Immunol 2013

Airway inflammation



Airway Hyper-responsiveness

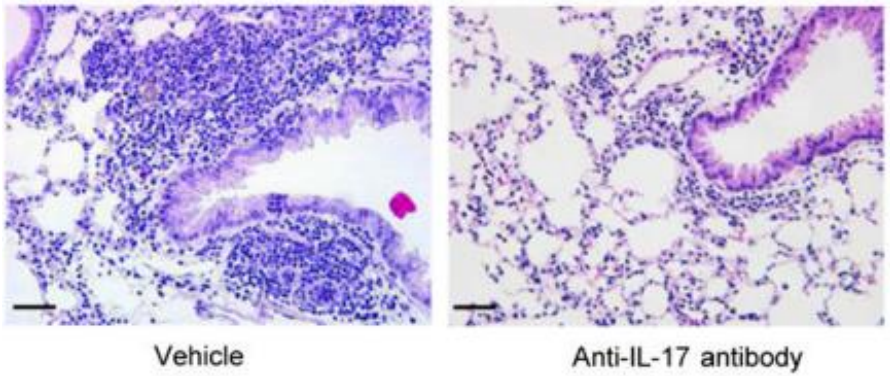


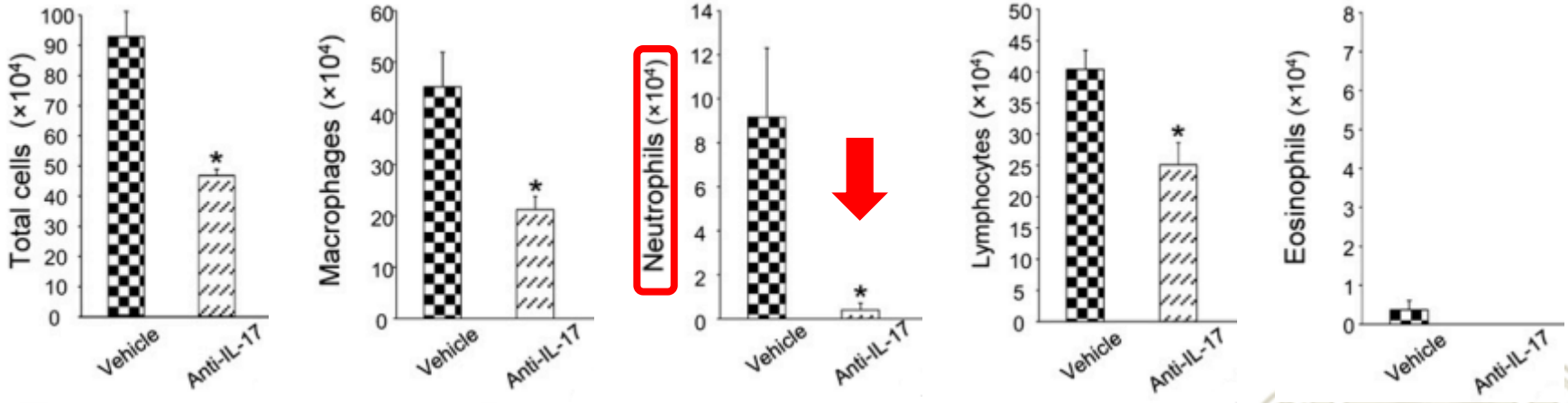


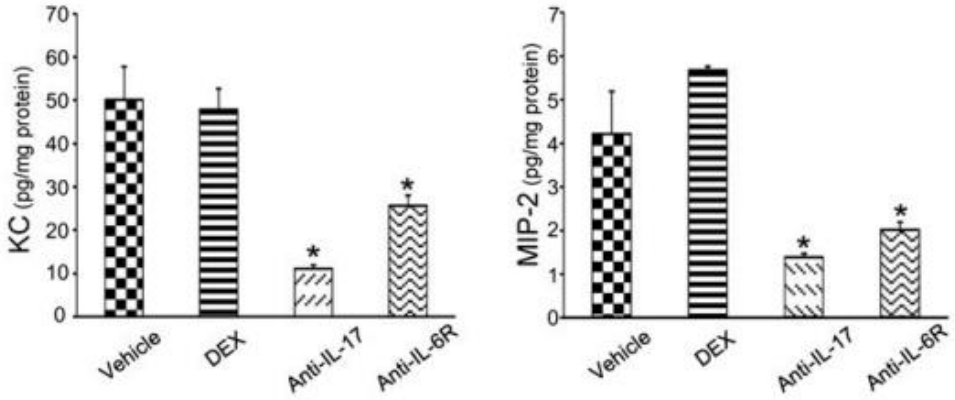
Ano et al. Jr Immunol 2013

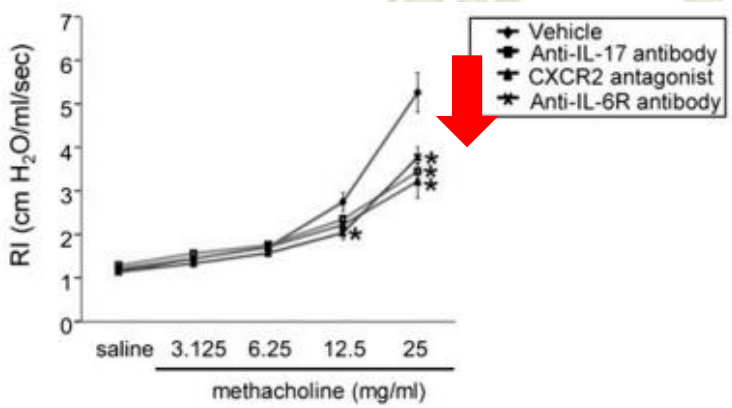
Role of Anti-IL17 Ab

RORδt-tg mice



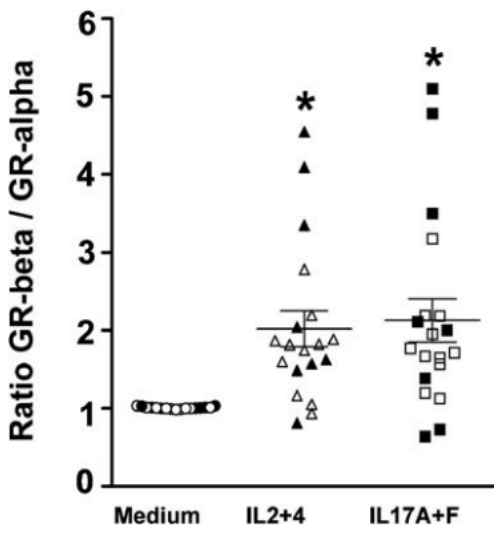






Ano et al. Jr Immunol 2013

Glucocorticoid Receptor-beta Up-regulation

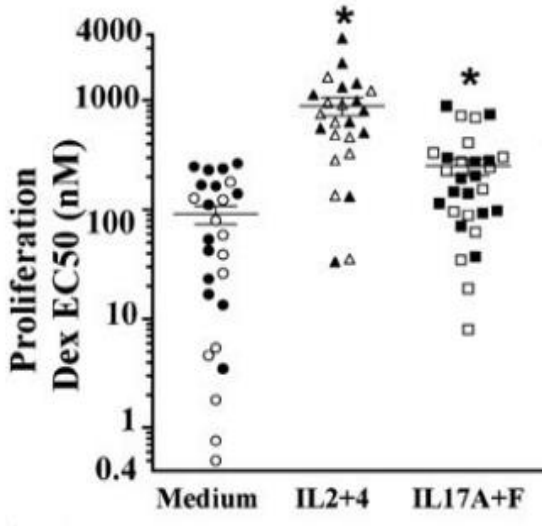


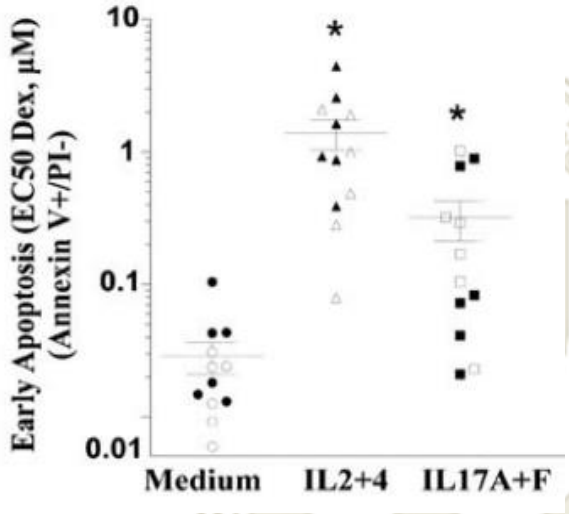
Steroid resistance
Linked to increased expression of glucocorticoid receptor **beta**

PBMC from normal and asthmatic patients

Inhibition of PBMC **proliferation** by Dexa is **decreased**

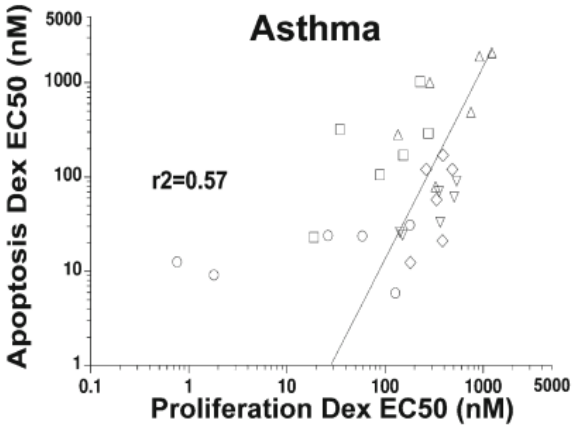
Induction of PBMC **apoptosis** by Dexa is **decreased**

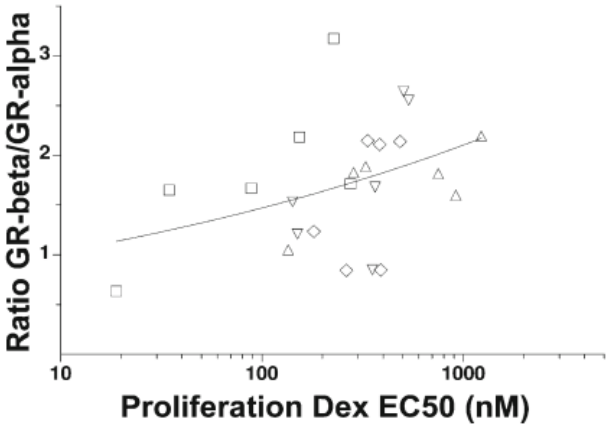




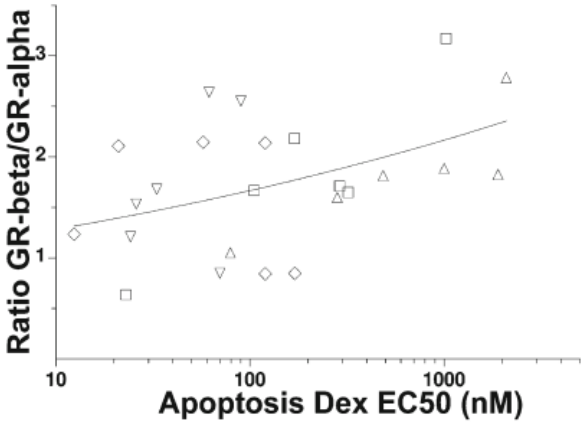
Vazquez-Tello et al. J Clin Immunol 2013

Correlation of GR-beta/GR-alpha ratio with EC50 for apoptosis and proliferation





IL17 A+F stimulation
r^2=0.53 *P*=0.13



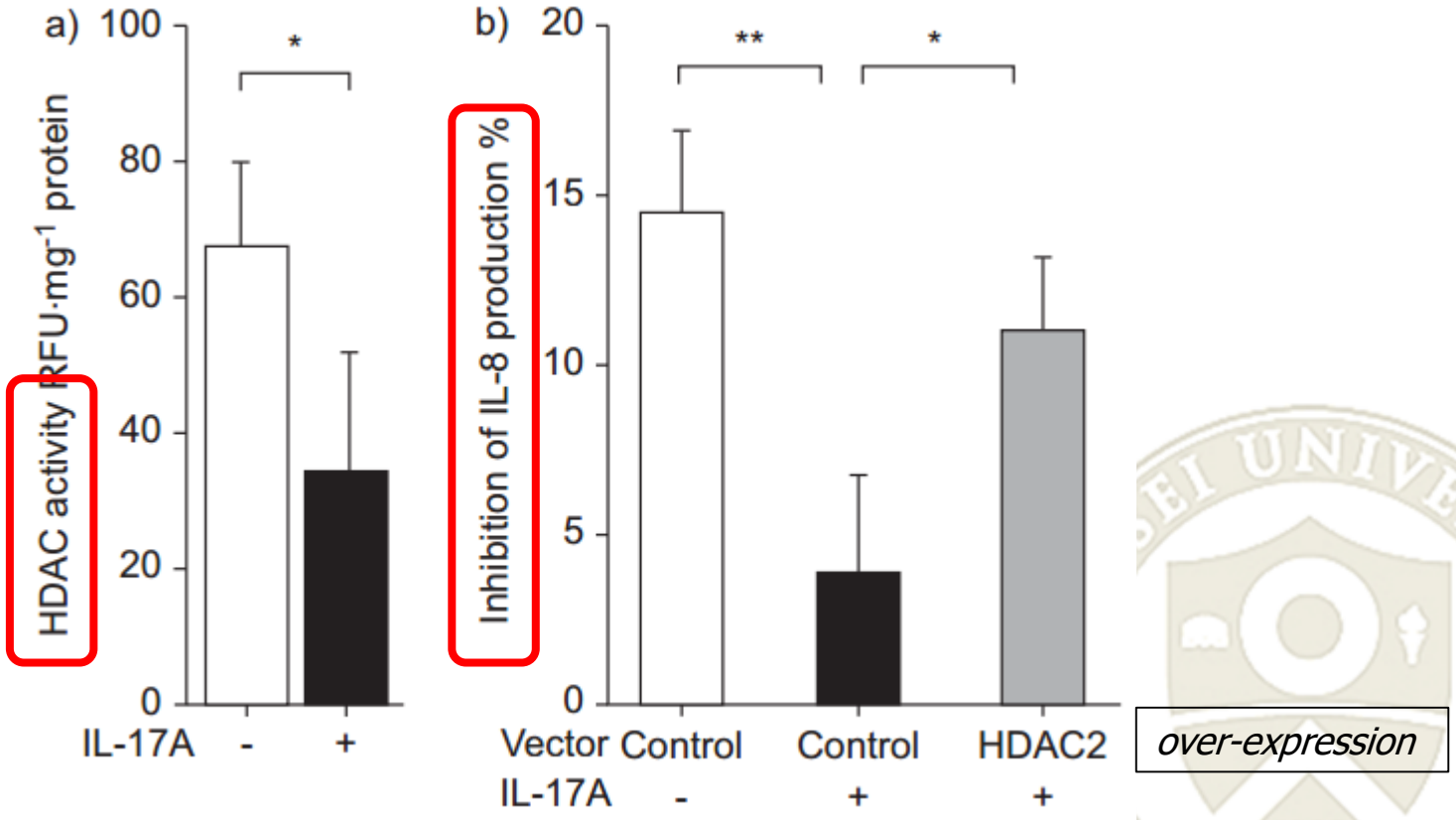
IL17 A+F stimulation
r^2=0.81 *P*=0.03

Relative increased of GR-beta expression by IL17 A+F stimulation
⇒ Lower response of cells to dexamethasone-induced apoptosis

Vazquez-Tello et al. J Clin Immunol 2013

IL17 and glucocorticoid insensitivity

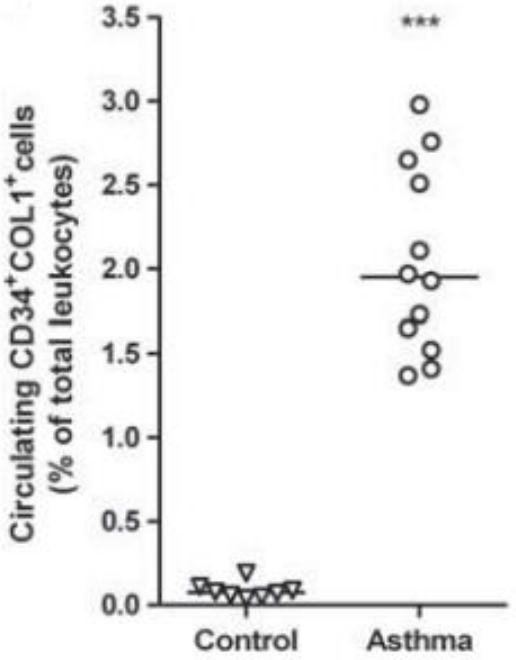
Human bronchial epithelial cell

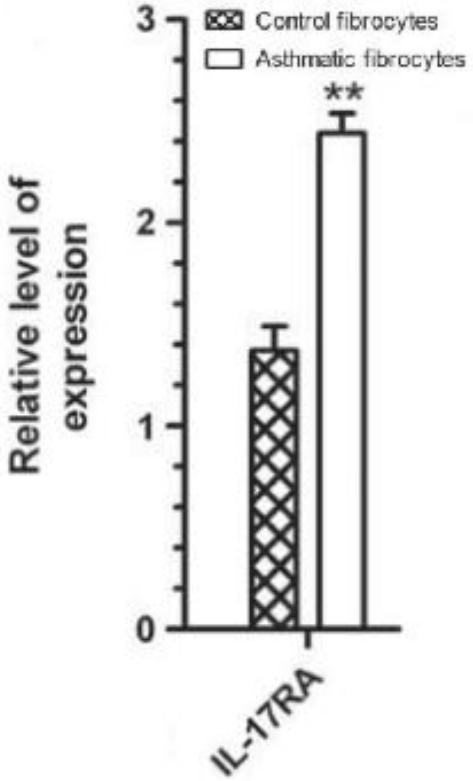


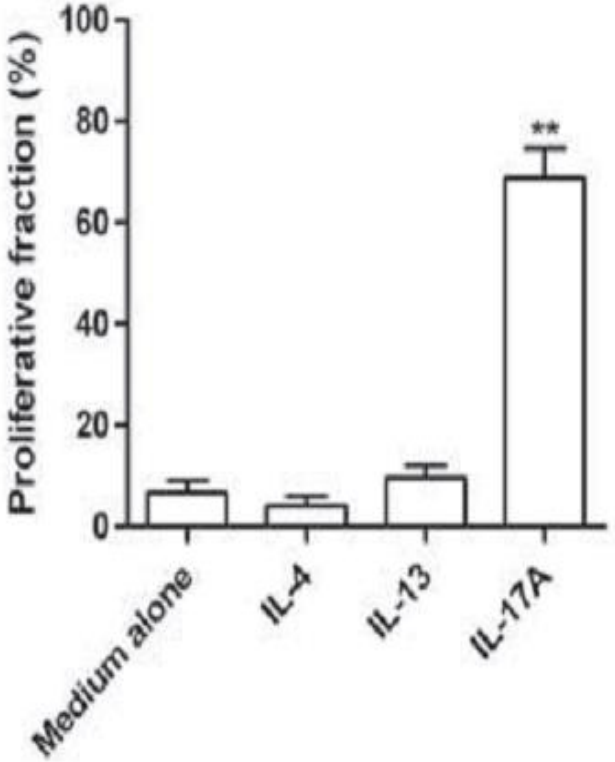
* HDAC Histone deacetylase

Zijlstra et al. Eur Respir J 2012

Profibrotic function of IL-17A in Asthma







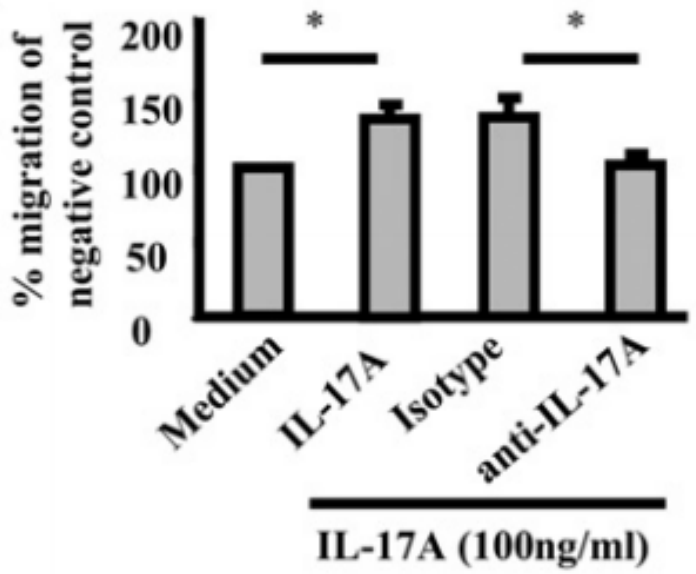
Blood

Isolated fibrocyte

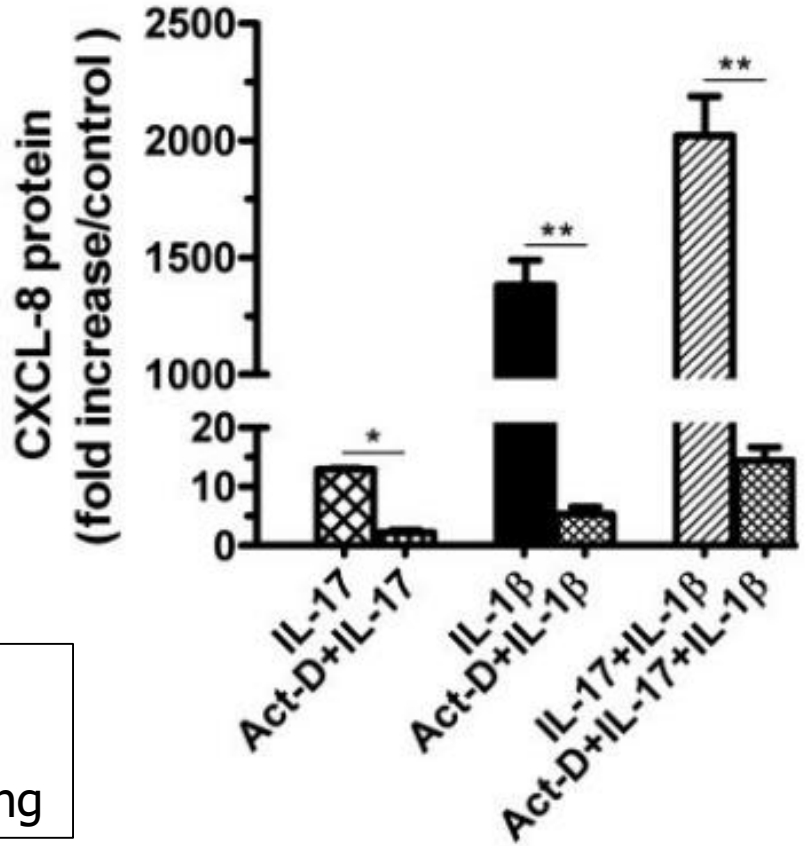
Proliferative responses to stimulation in fibrocyte from asthma patient

Bellini et al. Mucosal Immuno 2012

IL-17 induces HASMC migration



IL-17 enhances IL-1β-mediated CXCL-8 release from HASMC



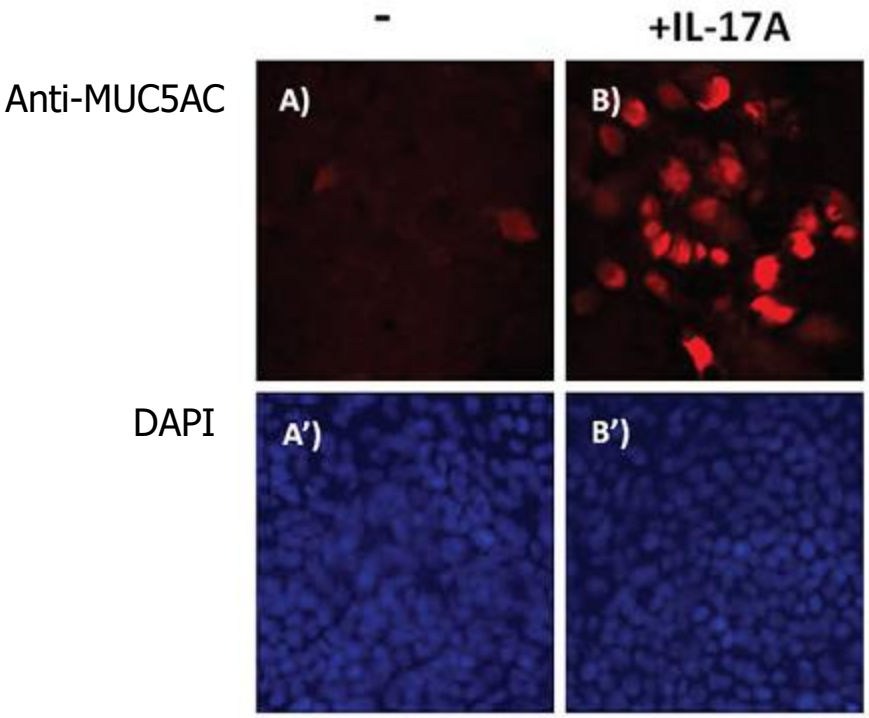
IL-8(CXCL-8)
HASMC contraction/migration
Mediating airway responsiveness/remodeling

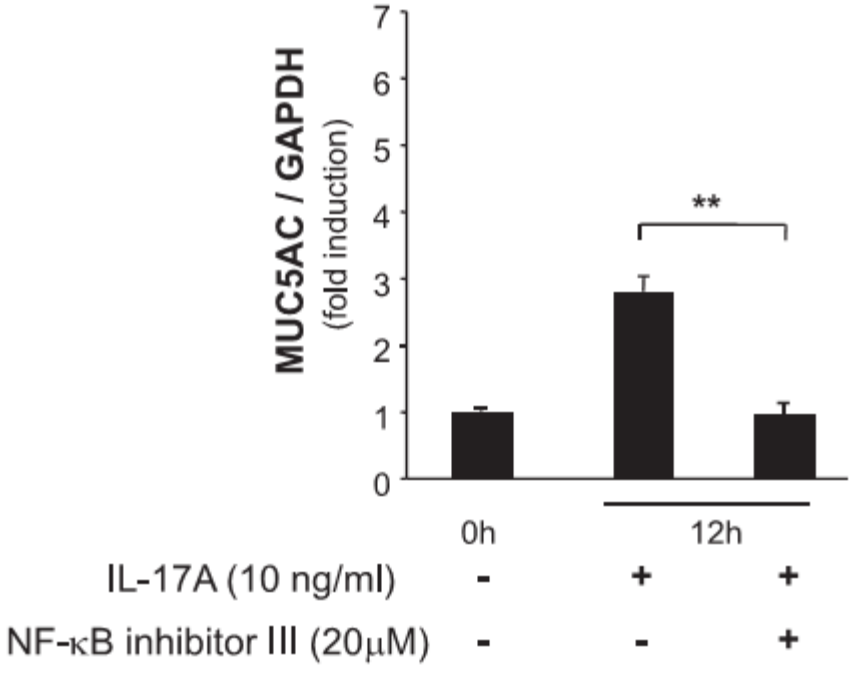
- HASMC human airway smooth muscle cell
- Act-D actinomycin

Chang et al. J Allergy Clin Immunol 2011
Dragon et al. Am J Physiol Lung Cell Mol Physiol 2007

Regulation of MUC5AC expression by IL-17A

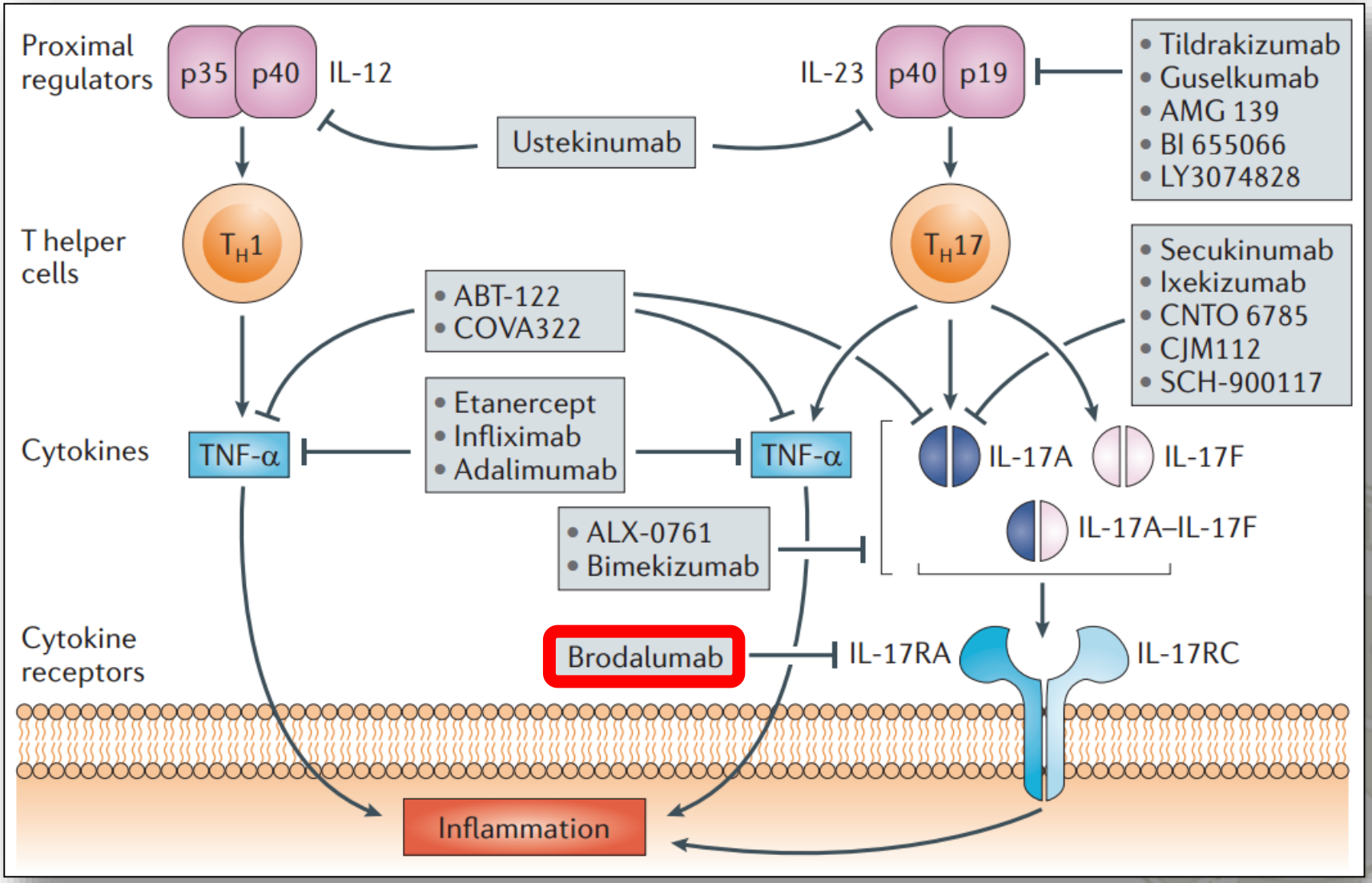
Normal human bronchial epithelial cell





Fujisawa et al. Jr Immunol 2009

Targeting the IL-17–TH 17 pathway



Bartlett et al. Nat Rev Drug 2015

Brodalumab (AMG827)

Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma

William W. Busse[1], Stephen Holgate[2], Edward Kerwin[3], Yun Chon[4], JingYuan Feng[4], Joseph Lin[4], and Shao-Lee Lin[4]

[1]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [2]University of Southampton, Southampton, United Kingdom; [3]Clinical Research Institute of Southern Oregon, PC, Medford, Oregon; and [4]Amgen Inc., Thousand Oaks, California

- a human, anti–IL-17RA IgG2 monoclonal antibody
- Blocking the biologic activity of IL-17A, -17F, -17A/F heterodimer, and -17E (IL-25)

- Subjects aged 18 - 65 years with inadequately controlled moderate to severe asthma on stable ICS (>200 and<1,000 mg/d of fluticasone powder or equivalent for >3 mo) with or without additional LABAs
- Subcutaneously at Day 1 and Weeks 1, 2, 4, 6, 8, and 10

Busse at al. AJRCCM 2013

Brodalumab (AMG827)

Placebo (n=76)	Brodalumab 140mg (n=74)	Brodalumab 210mg (n=76)	Brodalumab 280mg (n=76)

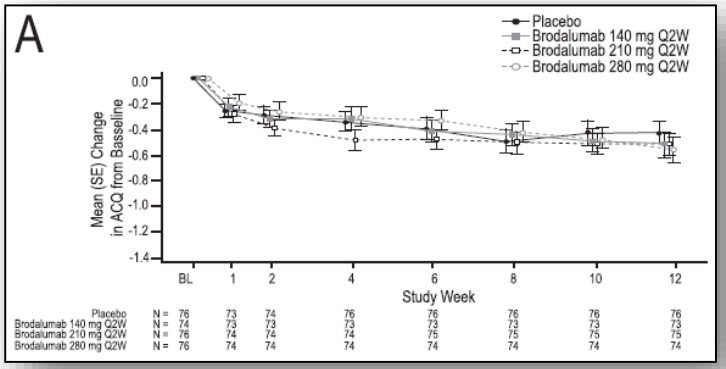
- **Primary endpoint**
  - ACQ total score (long-form ACQ-7) change from baseline to Week 12
  - ≥ 0.5 considered clinically meaningful changes

- **Secondary endpoint**
  - changes from baseline in pre- and post-bronchodilator FEV_1, morning peak expiratory flow (AM PEF), rescue SABA use, daily asthma symptom score, and symptom-free days

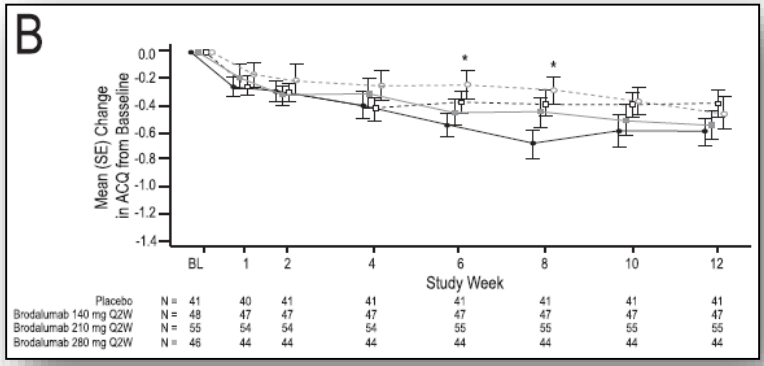
Busse at al. AJRCCM 2013

Change in ACQ score

Overall Study Population

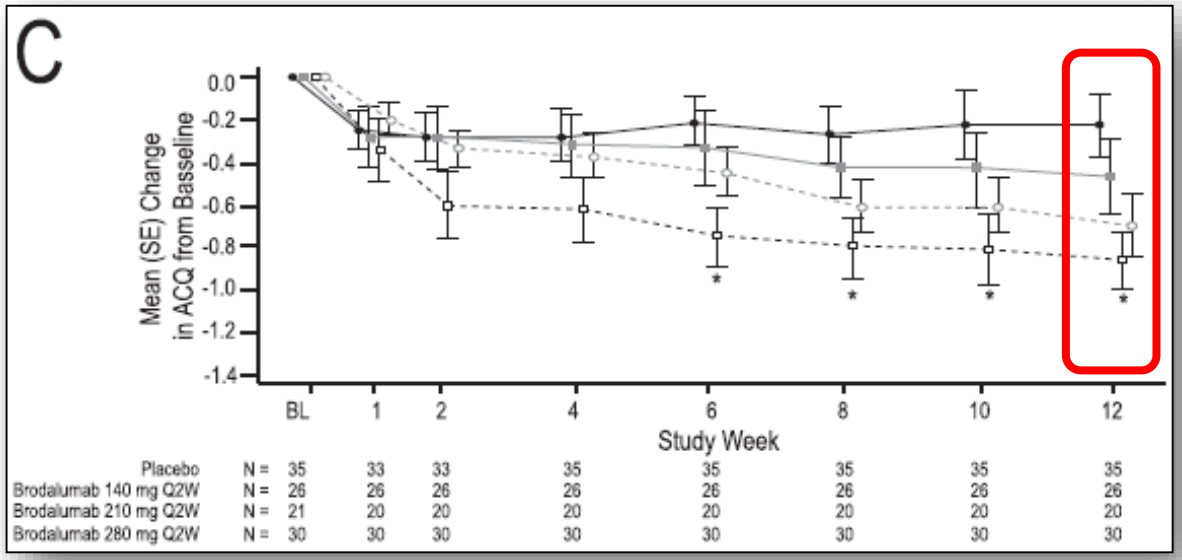


Low-Reversibility Subgroup



FEV_1 improvement >20% after BD

High-reversibility subgroup



***P*=0.02**, linear trend test

Placebo
Brodalumab 140 mg
Brodalumab 280 mg
Brodalumab 210 mg

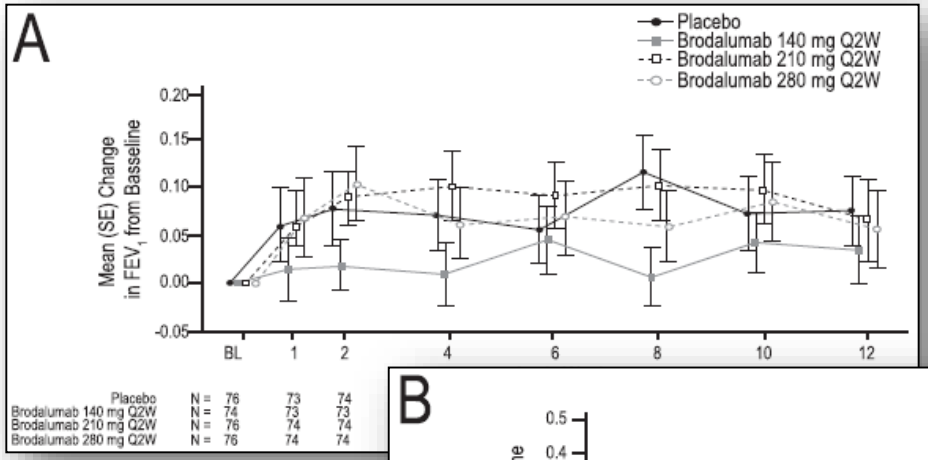
Busse at al. AJRCCM 2013

CLINICAL RESPONSES AT WEEK 12 BY TREATMENT GROUP IN FULL STUDY POPULATION

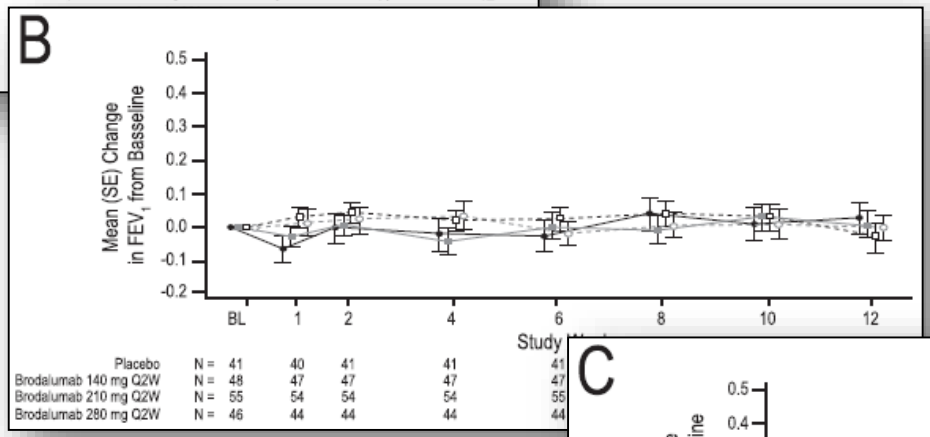
Response (Change from Baseline)	Placebo (*N* = 76)	Brodalumab Q2W 140 mg (*N* = 74)	Brodalumab Q2W 210 mg (*N* = 76)	Brodalumab Q2W 280 mg (*N* = 76)	*P* Value*
ACQ	n = 76	n = 73	n = 75	n = 74	
LS mean	−0.431	−0.498	−0.506	−0.544	0.3731
FEV_1, prebronchodilator	n = 76	n = 73	n = 75	n = 74	
LS mean	0.056	0.009	0.034	0.037	0.8521
AM PEF	n = 76	n = 74	n = 76	n = 75	
LS mean	1.490	−15.357	−5.234	−3.999	0.7834
SABA use	n = 76	n = 74	n = 76	n = 75	
LS mean	−0.561	−0.230	−0.795	−0.759	0.469
Daily symptom score, % change	n = 76	n = 74	n = 76	n = 75	
LS mean	−10.59	−29.37	−24.47	−23.33	0.5603
Nighttime symptom score, % change	n = 76	n = 74	n = 76	n = 75	
LS mean	−39.01	−16.83	−26.67	−24.52	0.4528
Symptom-free days	n = 76	n = 74	n = 76	n = 76	
LS mean	0.243	0.181	0.226	0.201	0.5147

Busse at al. AJRCCM 2013

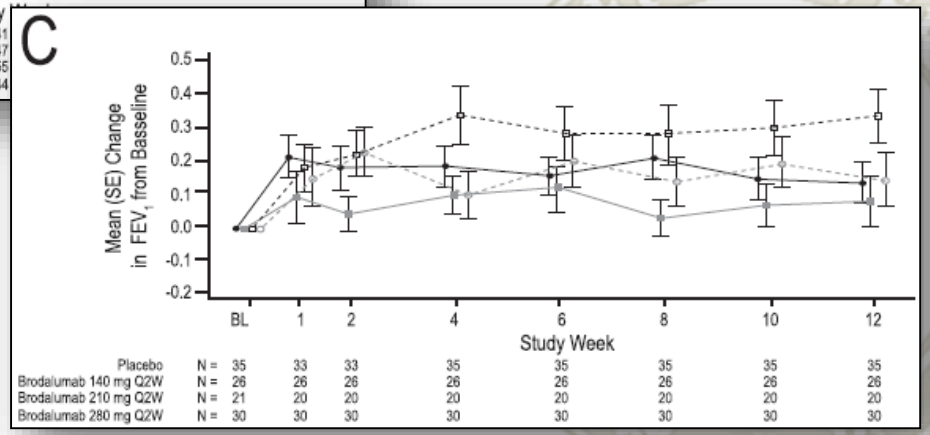
Change in prebronchodilator FEV_1



Overall Study Population



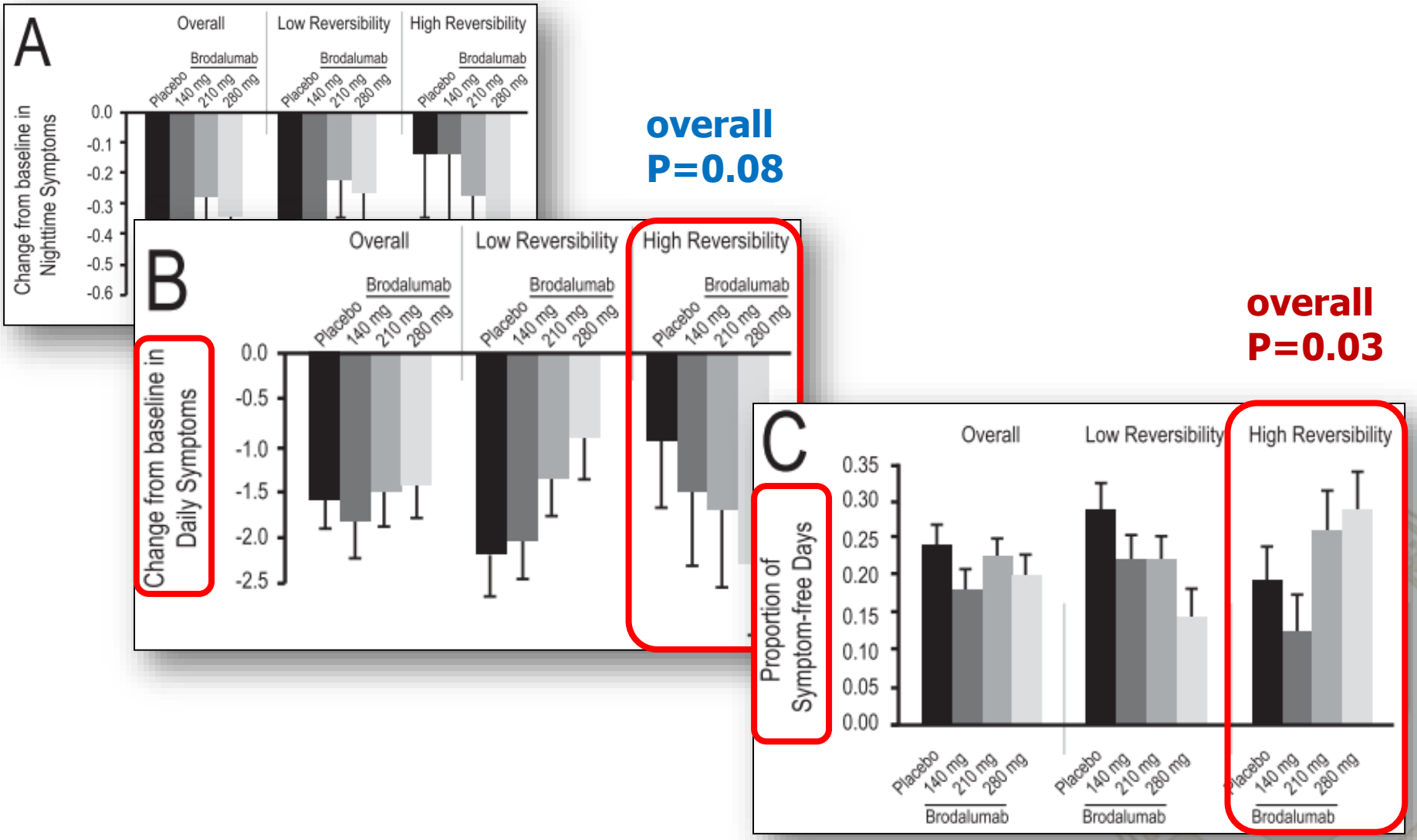
Low-Reversibility Subgroup



High-Reversibility Subgroup

Busse at al. AJRCCM 2013

Change in asthma symptoms



overall P=0.08

overall P=0.03

Busse at al. AJRCCM 2013

Limitation of Study

- inadequate selection of patients with asthma
- selected based on sputum neutrophilia, a biomarker for neutrophilic asthma, or the quantity of IL-17 in BAL, serum, or sputum to enrich the population of responding individuals
- inclusion of many patients with Th2 high asthma in the trial who are less likely to respond to an IL-17–targeted therapy

Chesne et al. AJRCCM 2014

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Status	Study

Study of Efficacy and Safety of Brodalumab Compared With Placebo in Inadequately Controlled Asthma Subjects With High Bronchodilator Reversibility

Condition: Asthma

Interventions: Biological: Placebo; Biological: 210 mg brodalumab

Inclusion Criteria:

- Diagnosis of asthma, and presently has reversibility over pre-bronchodilator FEV1 of ≥ 20% at screening
- Percent of predicted FEV1 ≥ 40% and ≤ 80% at screening
- ICS ≥ 200 and ≤ 1000/μg/day fluticasone powder or equivalent
- Ongoing asthma symptoms with ACQ composite score at screening and baseline ≥ 1.5 points

This study has been terminated.

(The decision to stop the study was due to a lack of observed efficacy in a pre-specified interim analysis. The decision was not related to safety concerns.)

SUMMARY

- Pathologic role of IL-17-producing cell in asthma
  - Severity
  - Neutrophilic inflammation
  - Steroid resistance
  - Immediate response to bronchodilators
- Different among various patient subgroups
- Ex-vivo quantification of pathogenic IL-17-procuding cells
  - from blood or BAL
  - in combination with potent biomarkers
  - patients with Th17^{predominant} asthma

Thank U

Thank U

Glucocorticoid refractory asthma

- High doses of ICS and sometimes OCS cannot control severe asthma in some patients
- Steroid-insensitive or partially sensitive patients are found in some of these subgroups
- Precise description of disease and categorization into – well-characterized subpopulations could facilitate development of stratified and targeted therapies

	Natural history	Clinical and physiological features	Pathobiology and biomarkers
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases	Specific IgE; T_H2 cytokine thick SBM
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic	Corticosteroid-refractory eosinophilia; IL-5
Exercise-induced		Mild; intermittent with exercise	Mast-cell activation; T_H2 cytokines; cysteinyl leukotrienes
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear	Lack of T_H2 biomarkers; oxidative stress
Neutrophilic		Low FEV1; more air trapping	Sputum neutrophilia; T_H17 pathways; IL-8

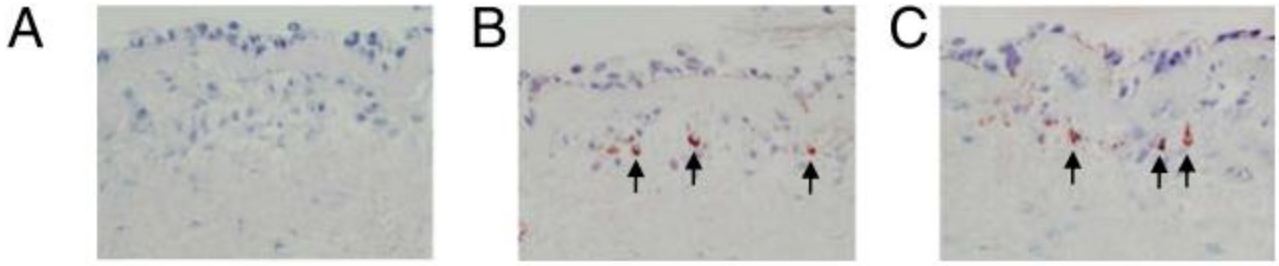
Wenzel at al. Nat Med 2012

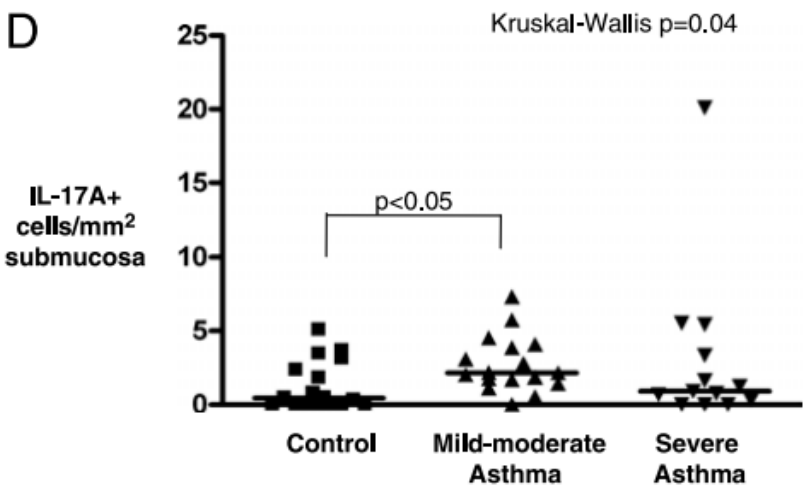
Neutrophilia in asthma

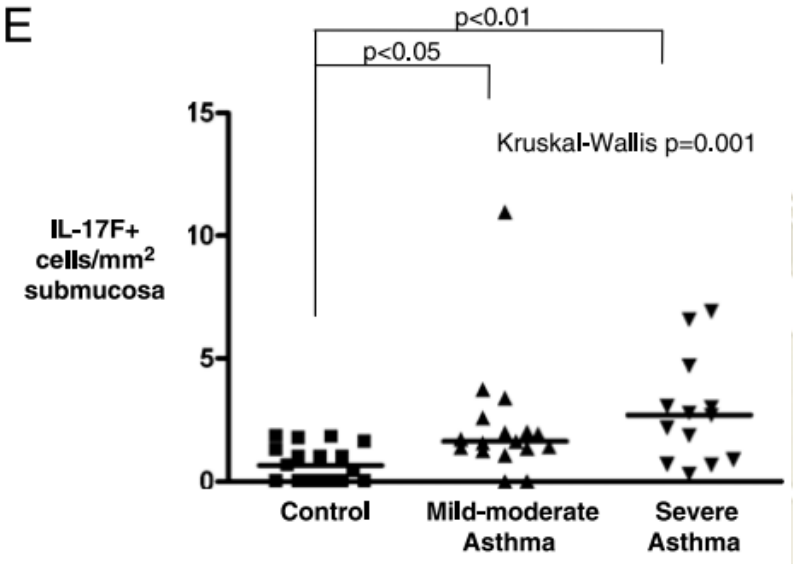
- Neutrophilia in noneosinophilic asthma
- Correlation with asthma severity

Wenzel at al. Nat Med 2012

Correlation between IL-17 and asthma severity







Doe at al. Chest 2010

Drug Candidates targeting IL-17 or its Receptor IL-17RA

Drug	Manufacturer	Psoriasis	PsA	AS	RA	Other Indications
IL-17A Inhibitors						
Secukinumab (AIN457), Consentyx™	Novartis	Approved	Approved	Approved	Phase III	
Ixekizumab (LY2439821)	Lilly	Submitted	Phase III		Phase II	
CNTO 6785	Janssen				Phase II	COPD (Phase II)
CJM112	Novartis	Phase I/II				Hidradenitis suppurativa (Phase II)
BCD 085	Biocad					Healthy subjects (Phase I)
IL-17A and IL-17F Inhibitors						
Bimekizumab (UCB-4940)	UCB	Phase I	Phase I		Phase II	
ALX-0761 (MSB 0010841)	Merck Serono Ablynx	Phase I				
IL-17A and TNFα Inhibitors						
ABT-122	AbbVie		Phase II		Phase II	
COVA322	Janssen/ Covagen	Phase I/II	Preclinical	Preclinical	Preclinical	
IL-17RA Inhibitors						
Brodalumab (AMG 827)	Valeant Pharmaceuticals	Phase III		Phase III	Phase II	

Bartlett et al. Nat Rev Drug 2015

Demographics and baseline characteristics

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Placebo (*N* = *76*)	Brodalumab (*N* = *226*)
Sex, female, n (%)	53 (70)	126 (56)
Race, n (%)		
White	69 (91)	185 (82)
Black	5 (7)	26 (12)
Asian	2 (3)	8 (4)
American Indian or Alaskan Native	0 (0)	2 (1)
Hispanic or Latino	3 (4)	17 (8)
Multiple	0 (0)	4 (2)
Other	0 (0)	1 (0)
Age, yr	46.8 (11.2)	45.4 (11.5)
Weight, kg	84.1 (19.0)	86.9 (22.0)
Height, cm	167.6 (8.6)	169.2 (9.9)
ACQ score	2.48 (0.65)	2.52 (0.66)
AQLQ score	4.44 (0.99)	4.56 (1.04)
Atopic,* n (%)	60 (79)	190 (84)
FEV_1, prebronchodilator, L	2.06 (0.50)	2.20 (0.60)
% Predicted FEV_1, prebronchodilator	64.7 (8.7)	65.4 (8.5)
FEV_1, post-bronchodilator, L	2.49 (0.62)	2.60 (0.72)
% Predicted FEV_1, post-bronchodilator	78.2 (12.9)	77.3 (10.9)
% Reversibility	21.1 (12.7)	18.9 (13.5)
Duration of asthma, yr	24.8 (16.1)	24.3 (13.5)
Baseline ICS dose, μg/d fluticasone equivalent	541 (270)	497 (251)
Daily rescue β-agonist use, puffs/d	4.34 (7.34)	3.86 (5.06)
Previous LABA use, yes, n (%)	58 (76)	153 (68)
AM PEF, L/min	318.7 (97.2)	358.7 (114.8)
Daily asthma symptom scores	5.52 (3.86)	5.82 (3.41)
Nighttime asthma symptom scores	1.00 (1.01)	1.10 (1.10)
eNO, median (IQR), parts/billion	22.0 (13.0, 29.5)	24.0 (16.0, 38.3)
Peripheral eosinophils, median (IQR), %	2.9 (1.7, 4.5)	2.9 (1.9, 4.3)
Total serum IgE, median (IQR), IU/ml	141 (44, 311)	122 (60, 320)

Busse at al. AJRCCM 2013