XXX CONGRESSO NAZIONALE

SIAAIC

Società Italiana di Allergologia, Asma ed Immunologia Clinica

30° CONGRESSO NAZIONALE SIAAIC SINCE 1953

FIRENZE 6/9 APRILE 2017 | **WWW.SIAAIC2017.ORG**

Società Italiana di Allergologia, Asma ed immunologia Clinica

Agenti Biologici nell'Asma Eosinofilico

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and

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MASS TARGET ASTHMA THERAPY → **STRATIFIED ASTHMA PATHOGENESYs** → **PERSONALIZED ASTHMA THERAPY**

ICS
SABA
LABA
LAMA
AntiLTRs
OCS
Chromones

GINA GUIDELINES

AIT-*Allergen ImmunoTherapy*

TH_2 HIGH

Omalizumab
Ligelizumab
Quilizumab
Mepolizumab
Reslizumab
Benralizumab
Lebrikizumab
Tralokinumab
Anrukizumab
Dupilumab
Pitrakinra

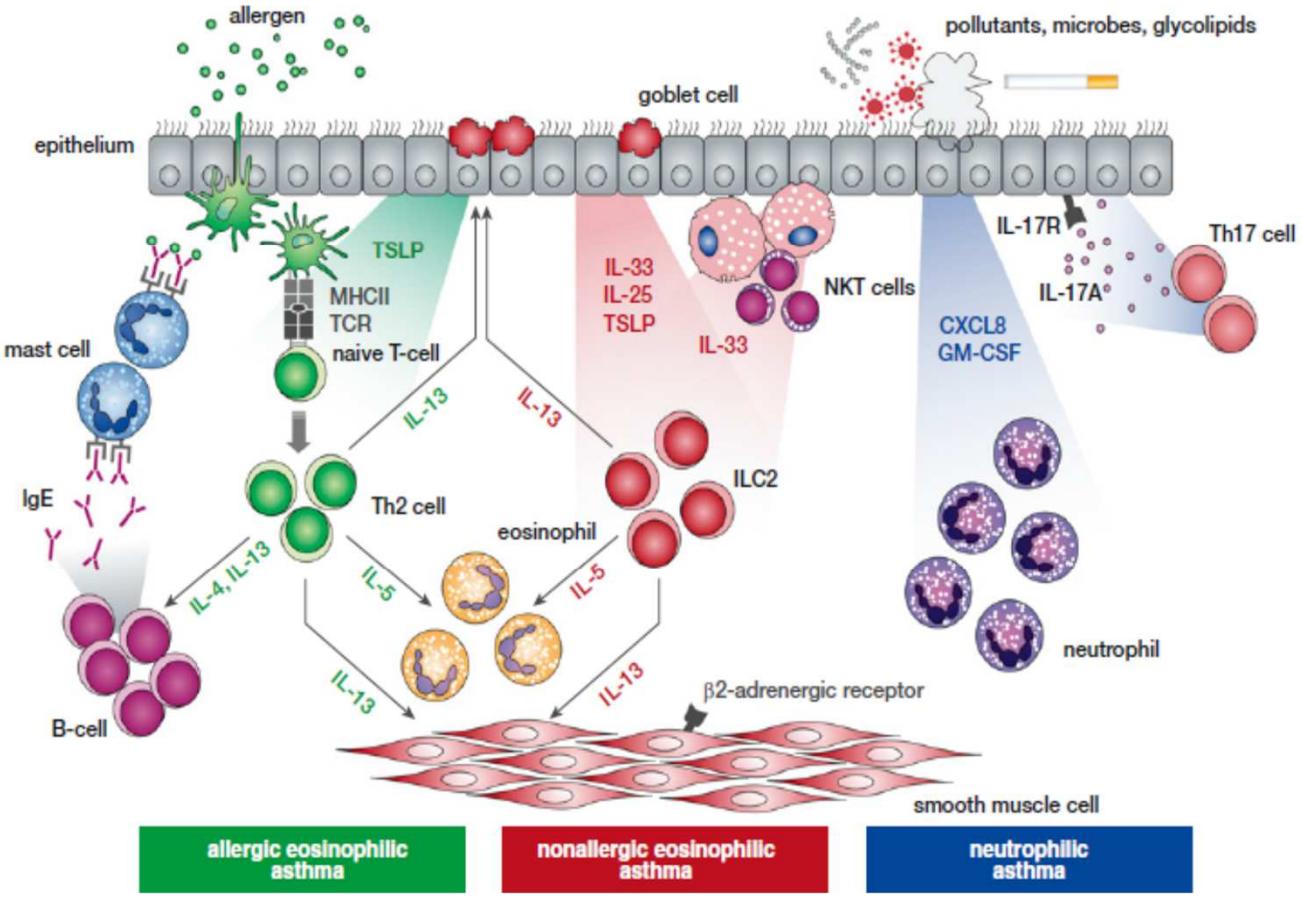
Biomarkers

TH_2 LOW

Brodalumab
α TSLP *(AMG 157)*
α $CRTH_2$
Macrolides

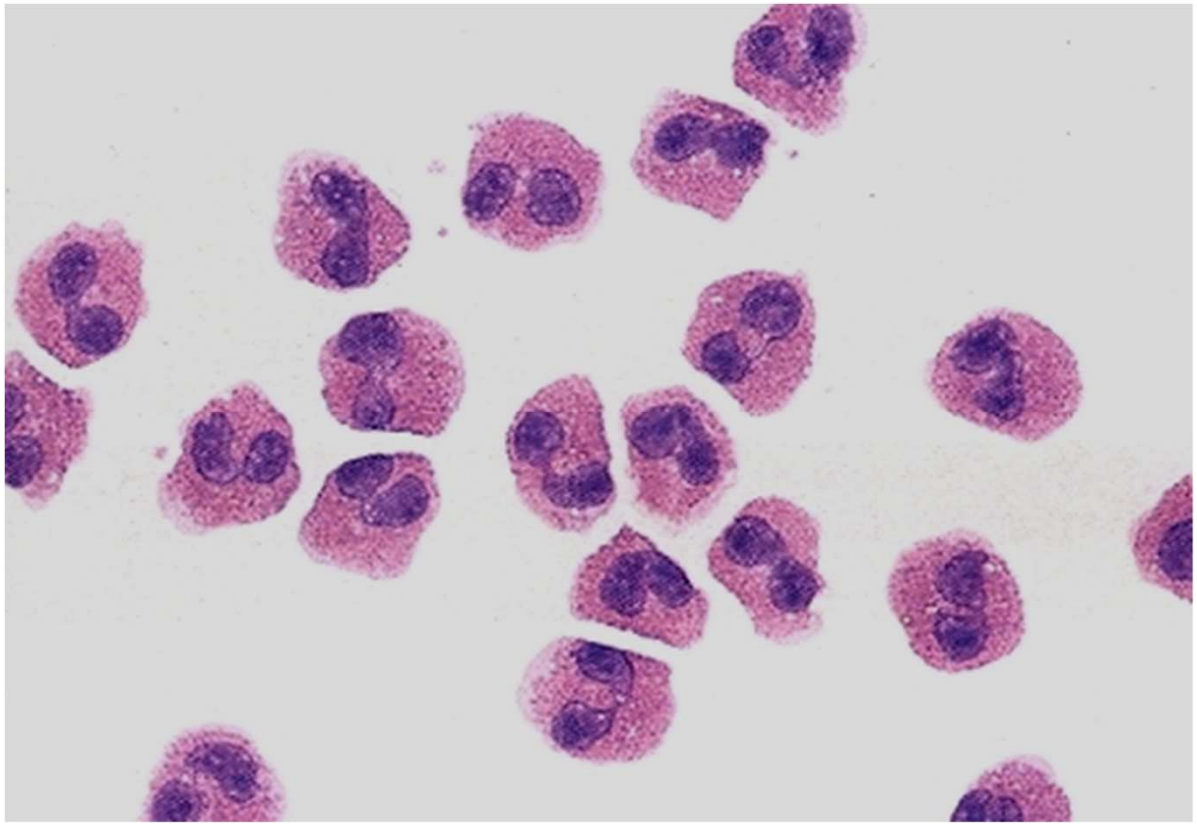
PREDICTIVE BIOMARKERS of RESPONSE

Bagnasco *et al.* Exp. Rev. Resp. Med. 2016;10:957-65

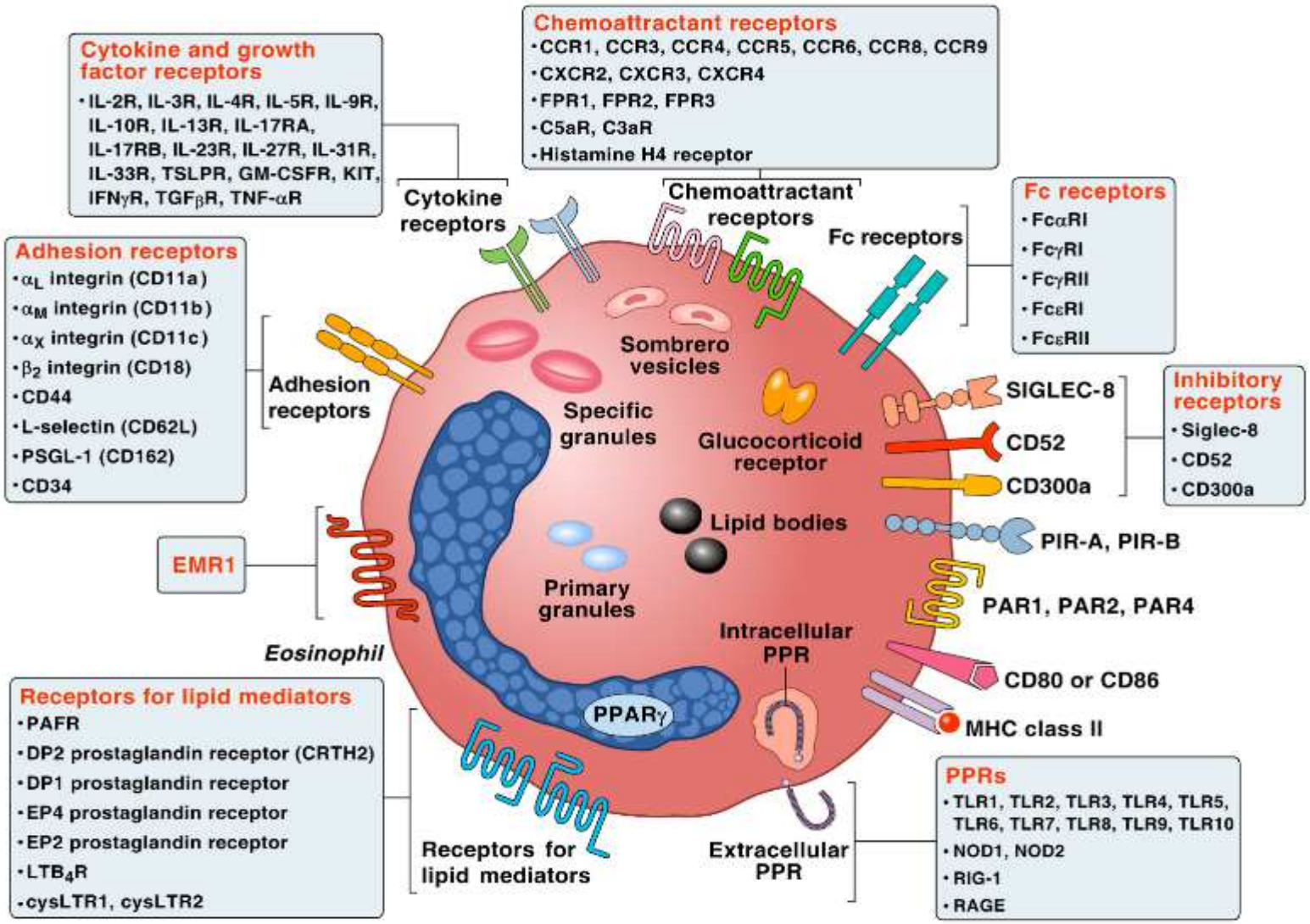


Brussel and Bracke, Ann. Am. Thorac. Soc. 2014;11:s322

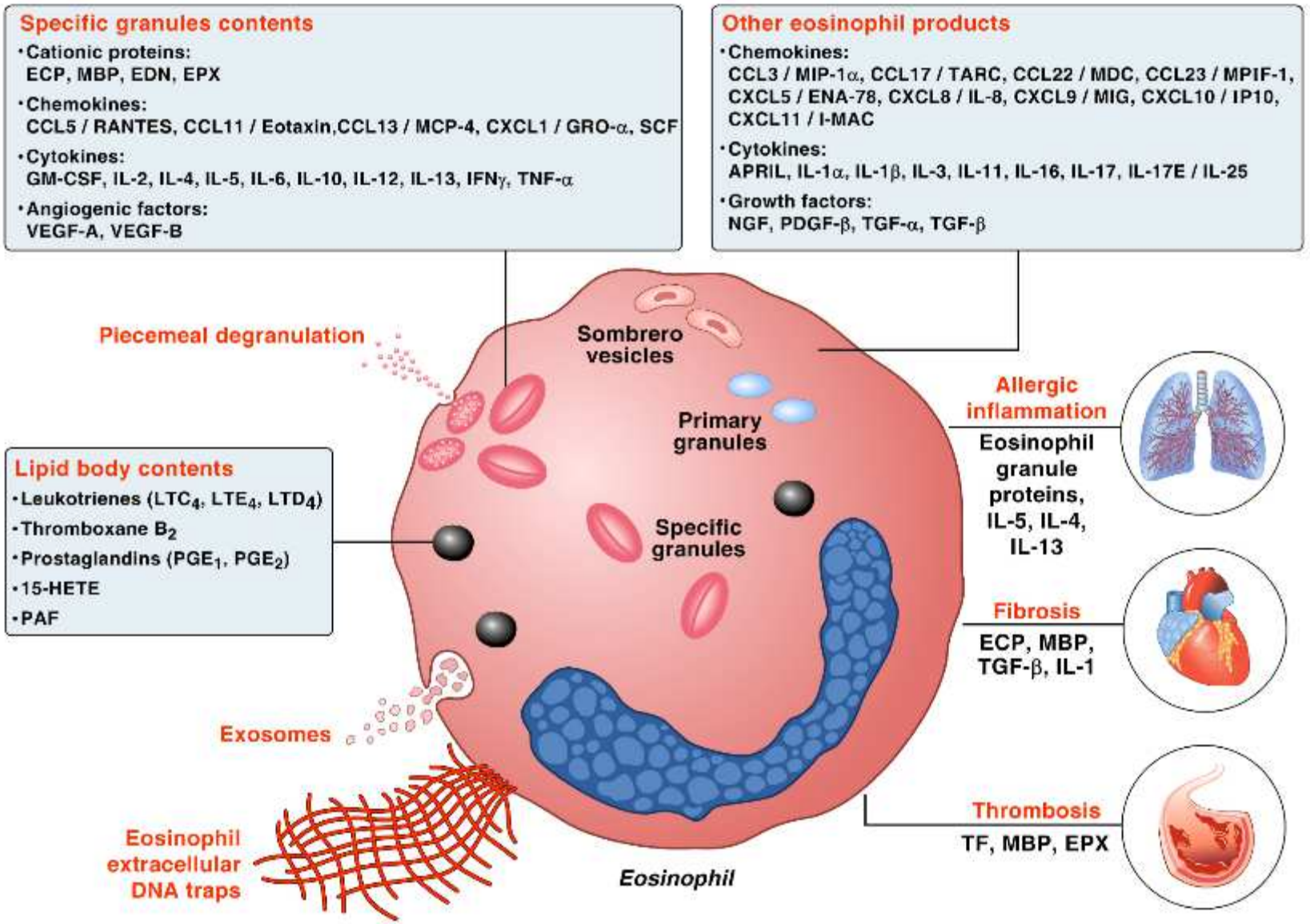
Eosinophils: 1-2% of leukocytes
< 350 cells/mm^3



Paul Ehrlich Nobel Prize in 1908
"in recognition of his work on immunity"

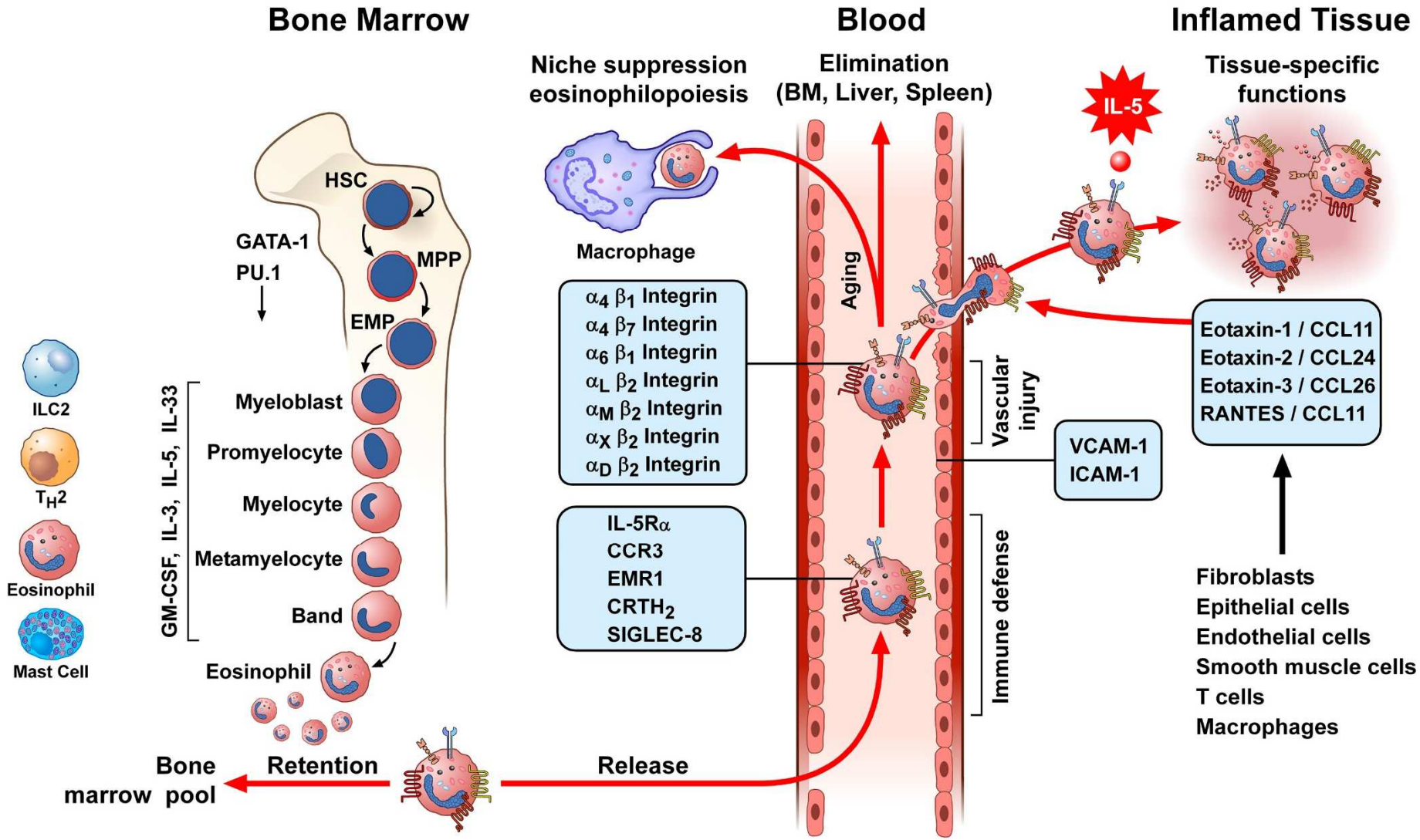


Varricchi *et al.*, Curr. Opin. Allergy Clin. Immunol. 2016;16:186-200

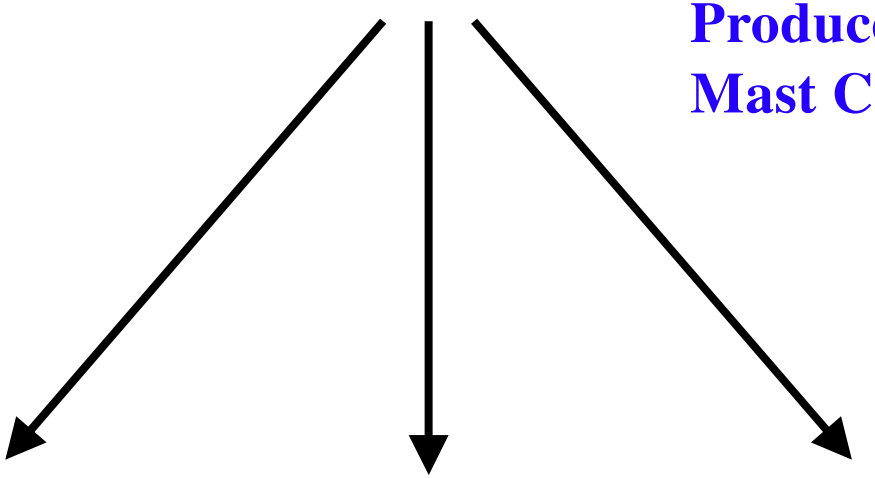


Varricchi *et al.*, Curr. Opin. Allergy Clin. Immunol. 2016;16:186-200

Life - Cycle Model of Eosinophils



Central Role of IL-5 in Human Eosinophil Growth, Differentiation, Survival and Apoptosis



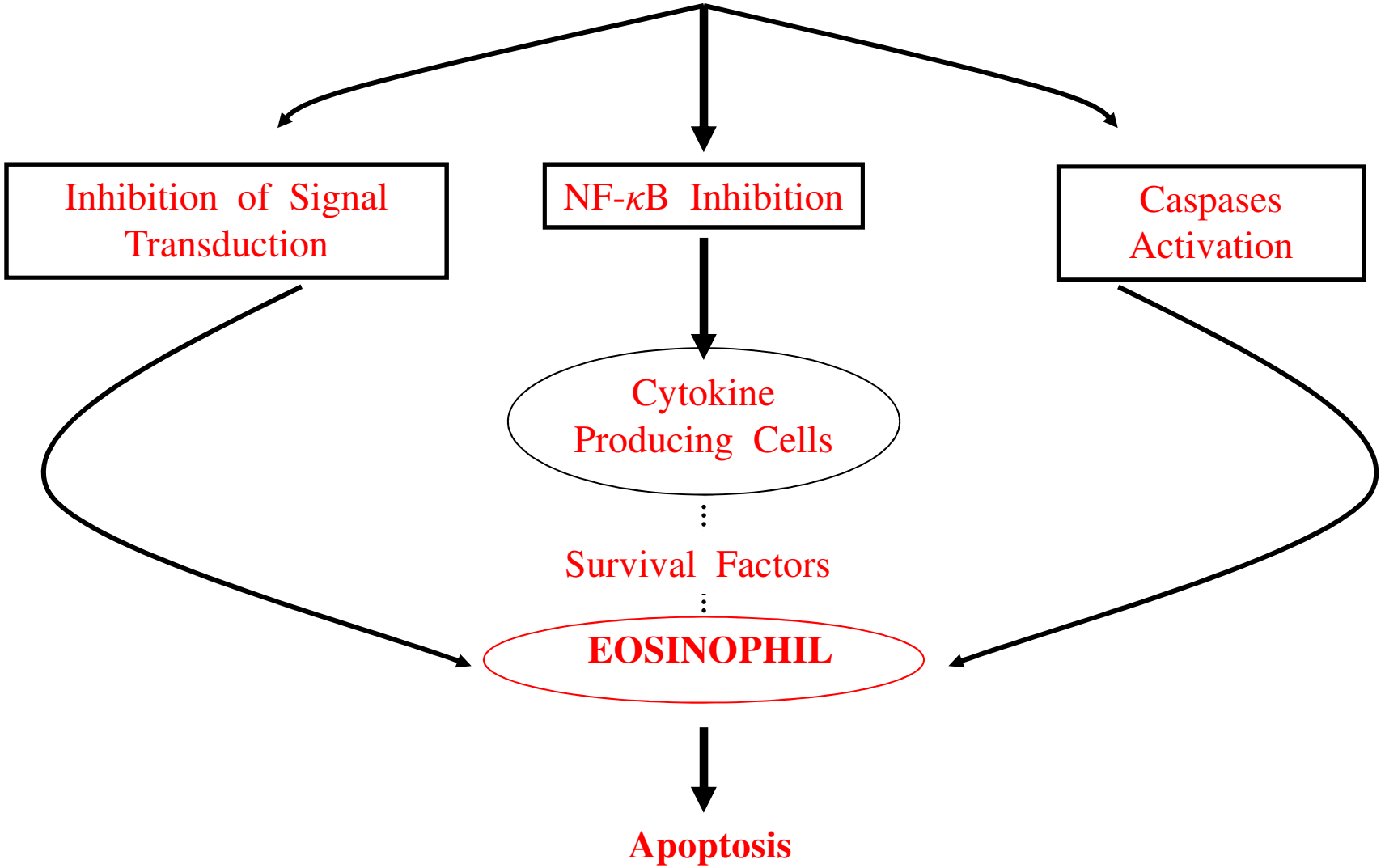
Produced by T Cells, ILC2, Mast Cells and Eosinophils

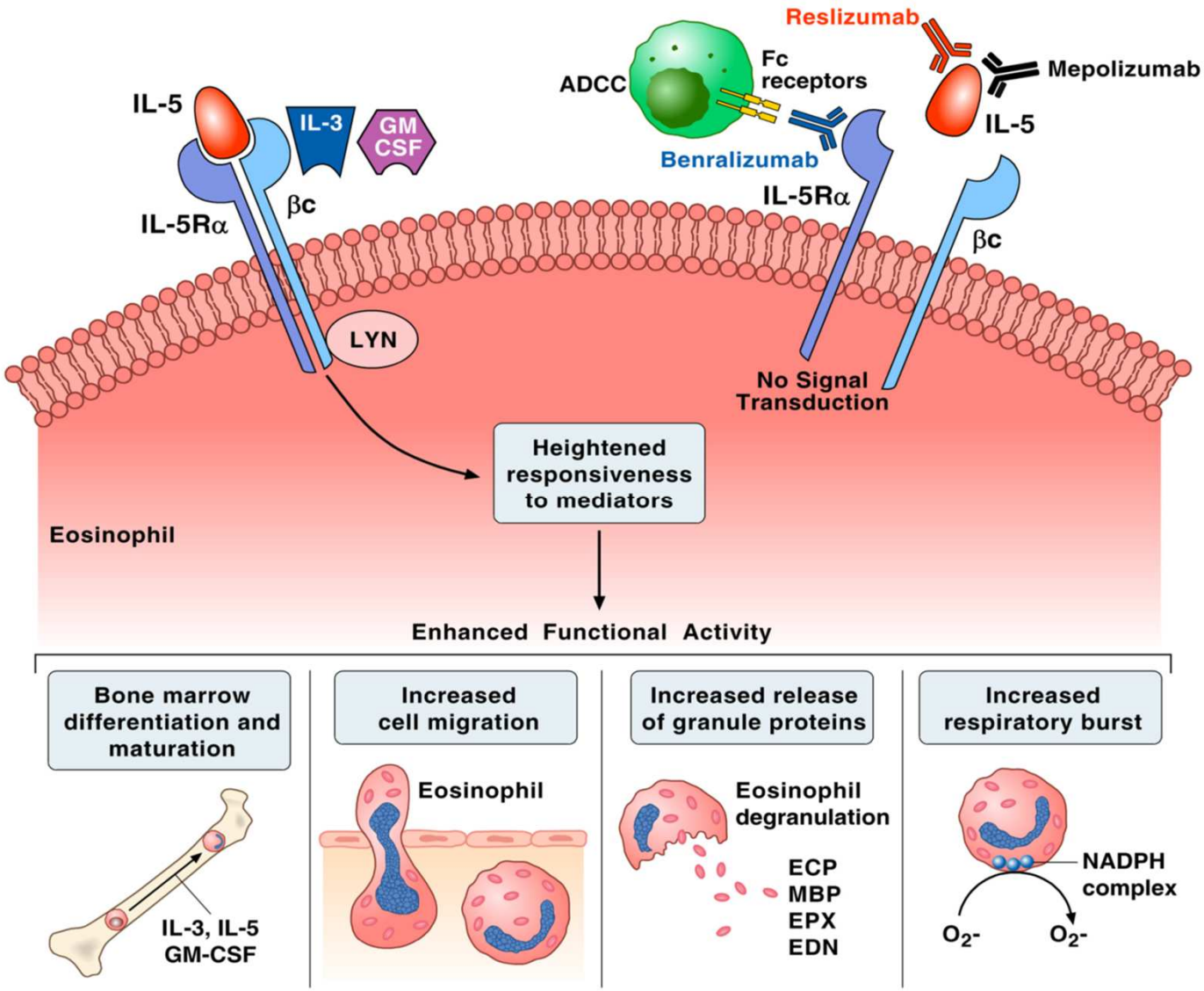
Induces Eosinophil Differentiation and Maturation

Increases Eosinophil Survival at Sites of Inflammation

Inhibits Eosinophil Apoptosis

Effects of Glucocorticoids in Eosinophilic Inflammation





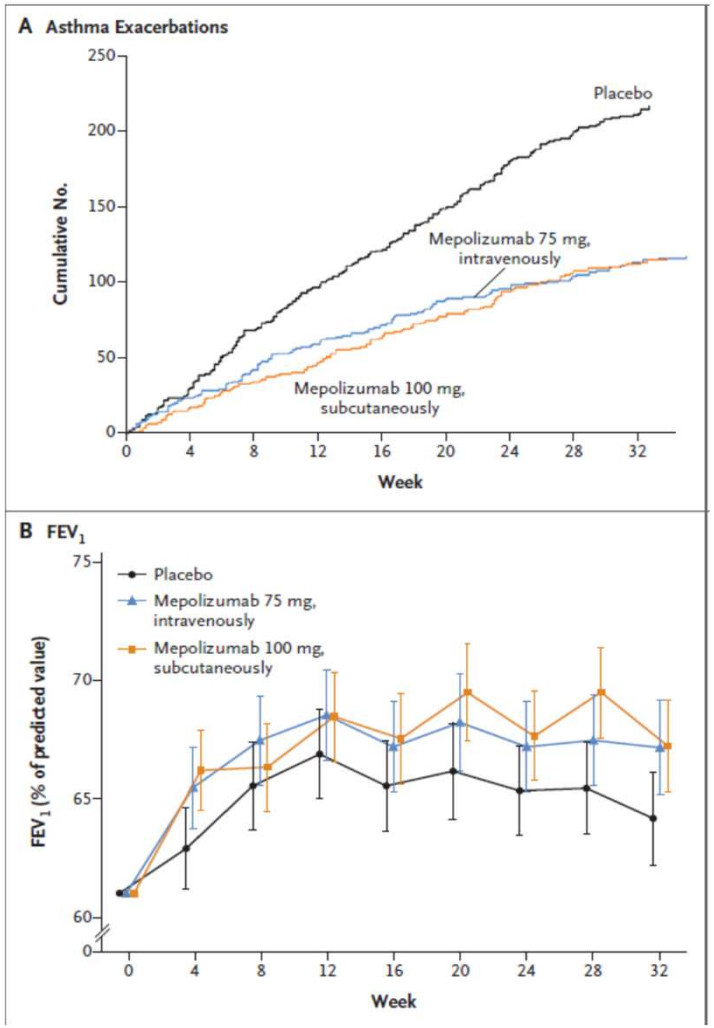
Varricchi *et al.*, Curr. Opin. Allergy Clin. Immunol. 2016;16:186-200

Anti-IL-5 and Anti-IL-5Rα MoAbs

MoAb	Target	Mode of Action	Recent Results
Mepolizumab	IL-5	Neutralizing MoAb IgG_1	Reduction of blood and sputum eosinophils. Reduction of exacerbations in EA
Reslizumab	IL-5	Neutralizing MoAb $IgG_{4/k}$	Reduction of blood and sputum eosinophils. Reduction of exacerbations in EA
Benralizumab	IL-5Rα	Cytotoxic MoAb $IgG_{1/k}$	Reduction of blood and sputum eosinophils and basophils. Reduction of exacerbations in EA

EA: Eosinophilic Asthma

Mepolizumab Treatment in Adult Patients with Severe Eosinophilic Asthma



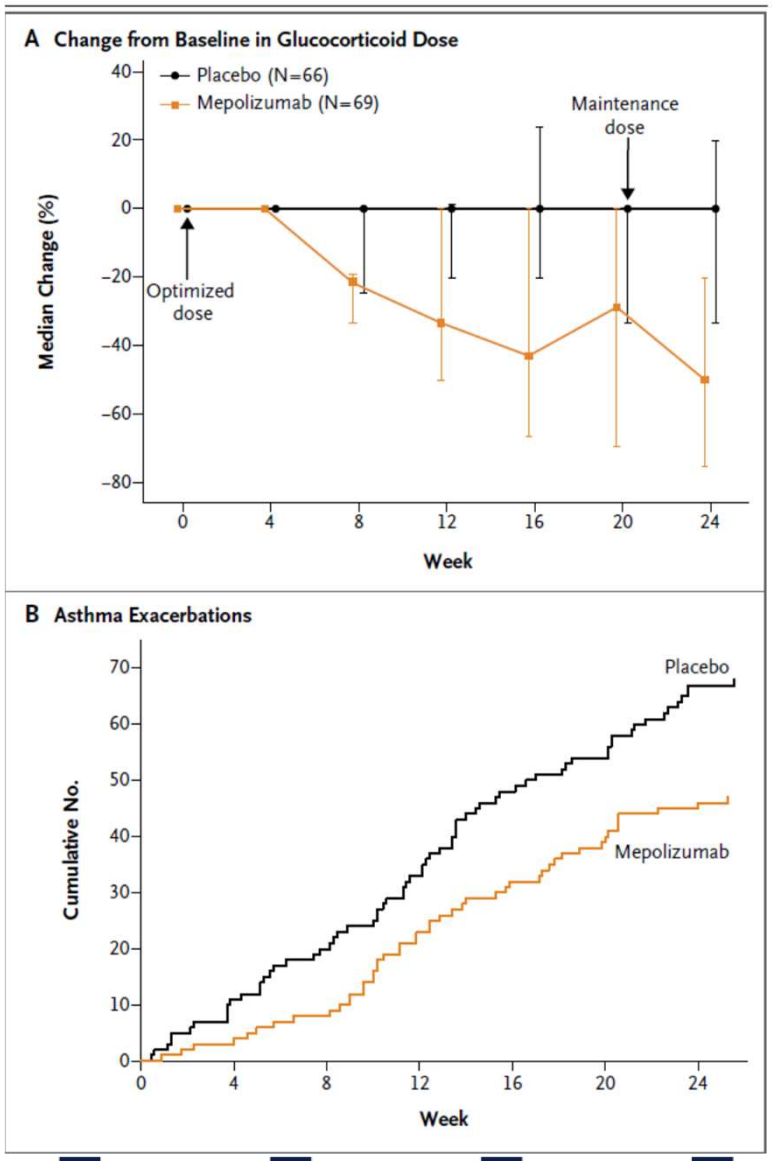
MENSA STUDY

576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high dose of inhaled corticosteroids.

Mepolizumab (75 mg i.v. or 100 mg s.c. every 4 weeks for 32 weeks) reduced blood and sputum eosinophils and exacerbations. Improvement of asthma symptoms.

Ortega *et al.*, N. Engl. J. Med. 2014;371: 1198-1207

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

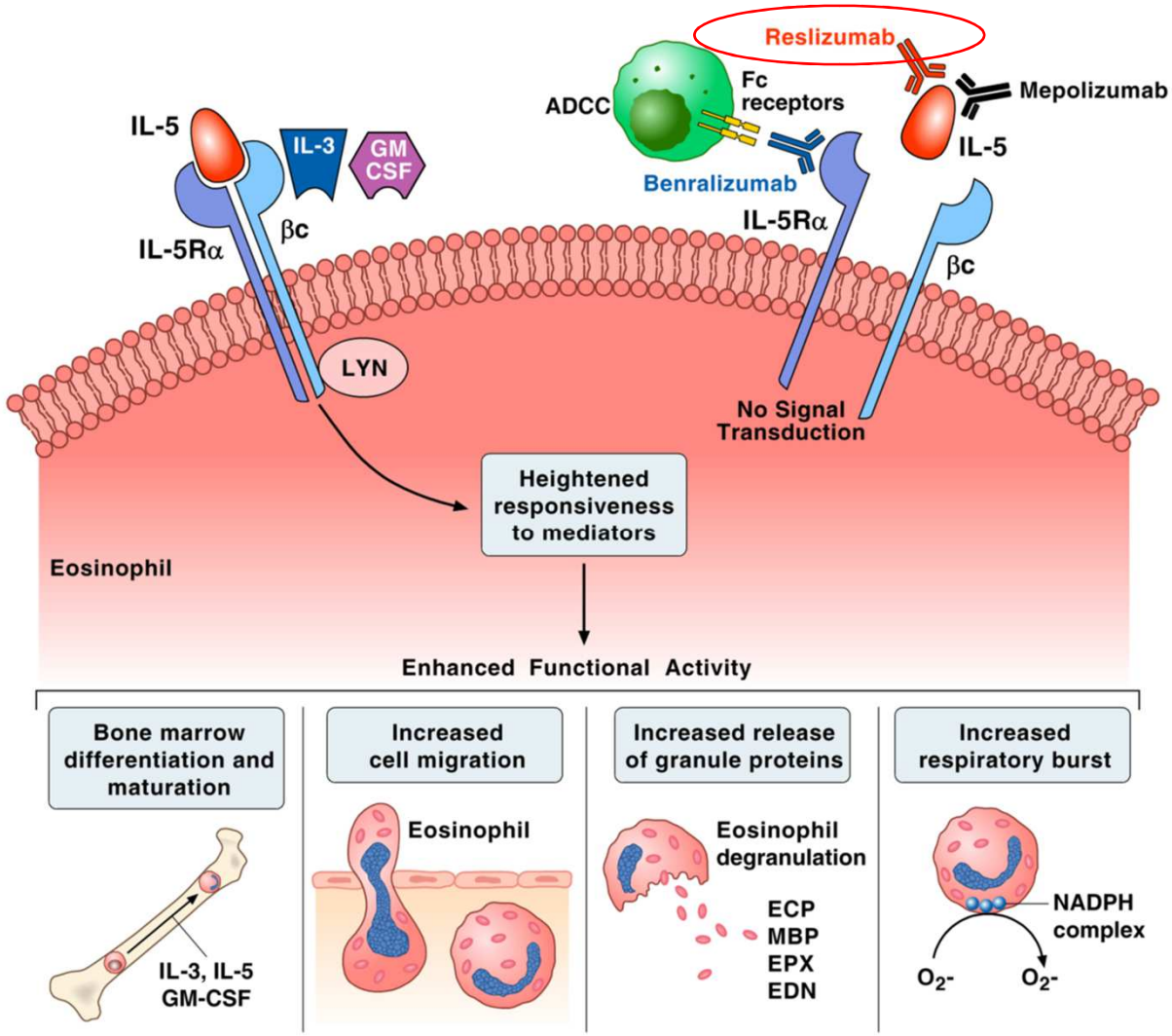


SIRIUS STUDY

135 patients with severe eosinophilic asthma.

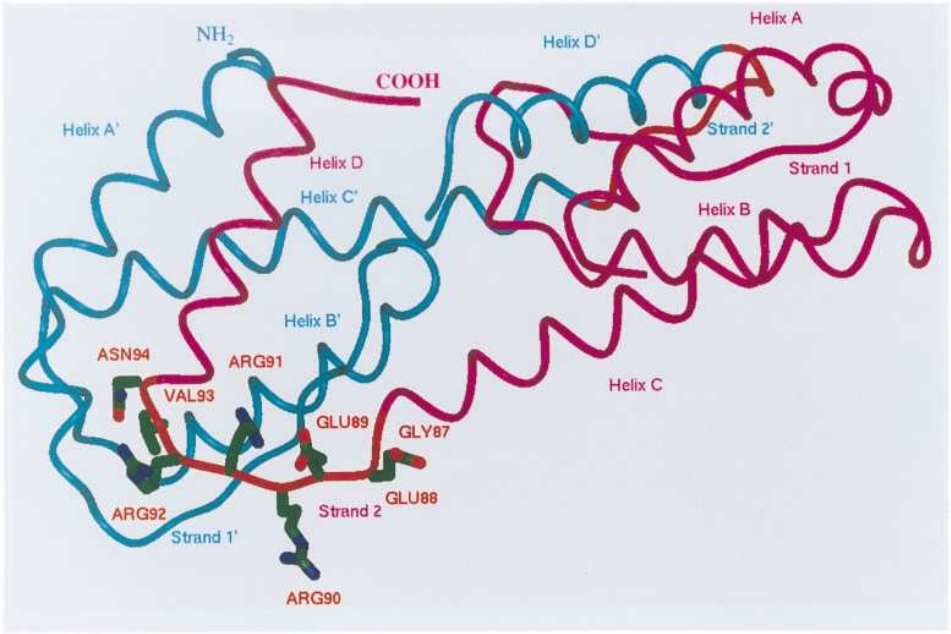
Mepolizumab (100 mg s.c. every 4 weeks for 8 months) had a significant glucocorticoid sparing effect, reduced exacerbations, blood eosinophilia and improved FEV_1 and QoL.

Bel *et al.*, N. Engl. J. Med. 2014;371:1189-1197



Varricchi *et al.*, Curr. Opin. Allergy Clin. Immunol. 2016;16:186-200

Structure of IL-5 by X-ray Crystallography

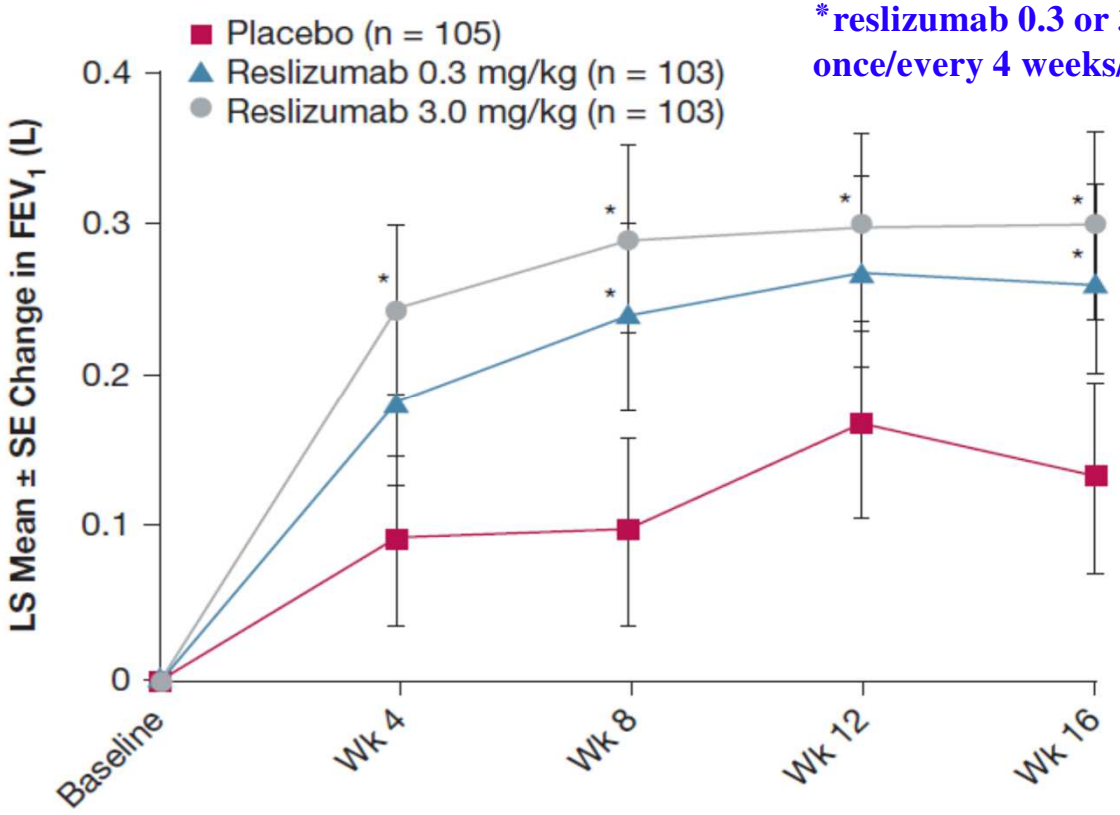


Human IL-5 has a dimeric core and two four-helix bundles formed by two identical polypeptide chains joined covalently by disulfide bonds.
Reslizumab binds to amino acids 89-93 of IL-5 occupying a region essential for its interaction with IL-5Rα.

Zhang *et al.* Int. Immunol. 1999;11:1935-1943
Varricchi *et al.* Front.Immunol. DOI:10.3389/fimmu.2017.00242

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

*reslizumab 0.3 or 3.0 mg/kg or placebo once/every 4 weeks/16 weeks.



Bjermer *et al.* CHEST 2016;150-789-798

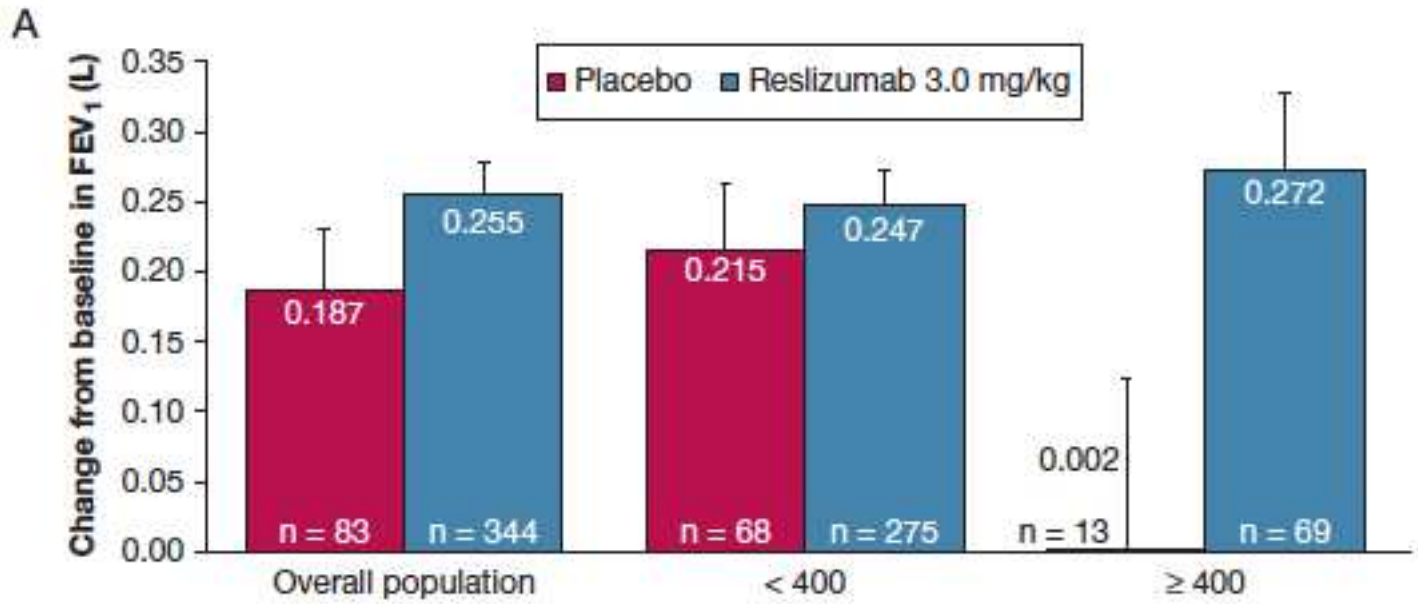
[Original Research Asthma]

CHEST

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma

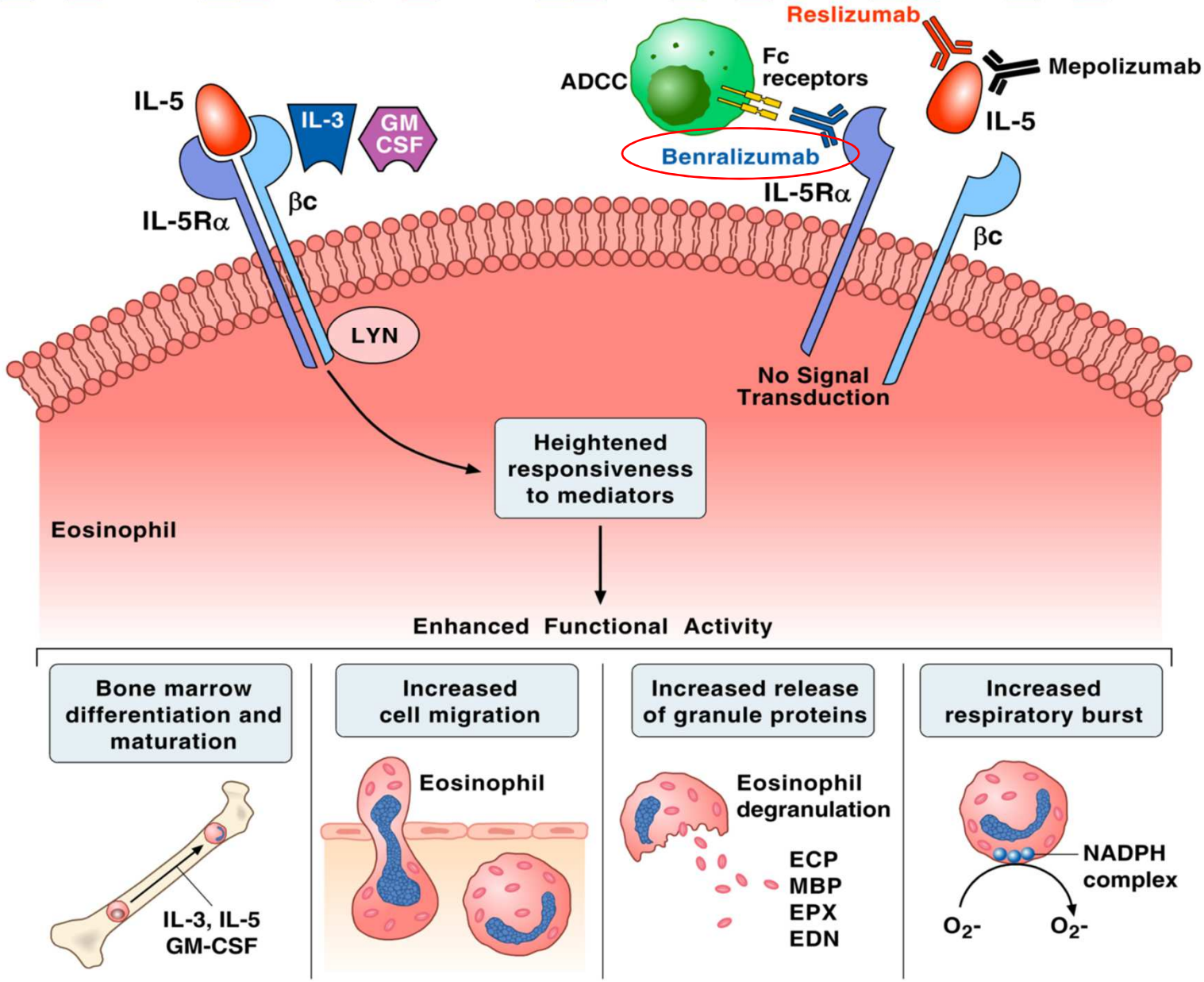
Effects Across a Broad Range of Eosinophil Counts

Jonathan Corren, MD; Steven Weinstein, MD; Lindsay Janka, MS; James Zangrilli, MD; and Margaret Garin, MD



Corren *et al.*, Chest 150: 799, 2016

***Reslizumab 3 mg/kg i.v. every 4 weeks per 4 months was administered in adults with severe eosinophilic asthma: reslizumab improved lung functions (FEV_1), and ACQ only in patients with ≥ 400 eosinophils/μL**


Reslizumab
Mepolizumab
IL-5
ADCC
Fc receptors
Benralizumab
IL-5
IL-3
GM CSF
IL-5Rα
βc
IL-5Rα
βc
LYN
No Signal Transduction
Heightened responsiveness to mediators
Eosinophil
Enhanced Functional Activity
Bone marrow differentiation and maturation
IL-3, IL-5 GM-CSF
Increased cell migration
Eosinophil
Increased release of granule proteins
Eosinophil degranulation
ECP
MBP
EPX
EDN
Increased respiratory burst
NADPH complex
O2-
O2-

Benralizumab, an anti-IL-5Rα monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA)

Blood eosinophils ≥300 cells/μL

Blood eosinophils ≤300 cells/μL

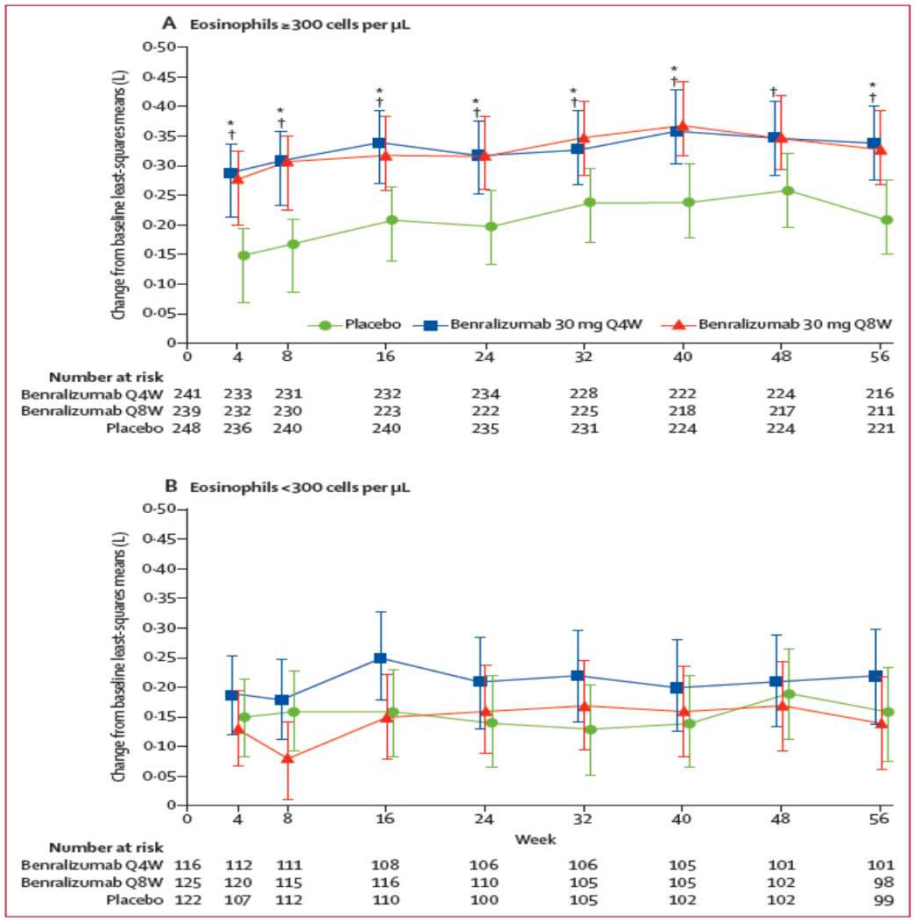


Figure 3: **Change from baseline in pre-bronchodilator FEV_1 for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils (A) 300 cells per μL or greater and (B) less than 300 cells per μL**

FitzGerald *et al.* Lancet 2016;388:2128-2141

Benralizumab

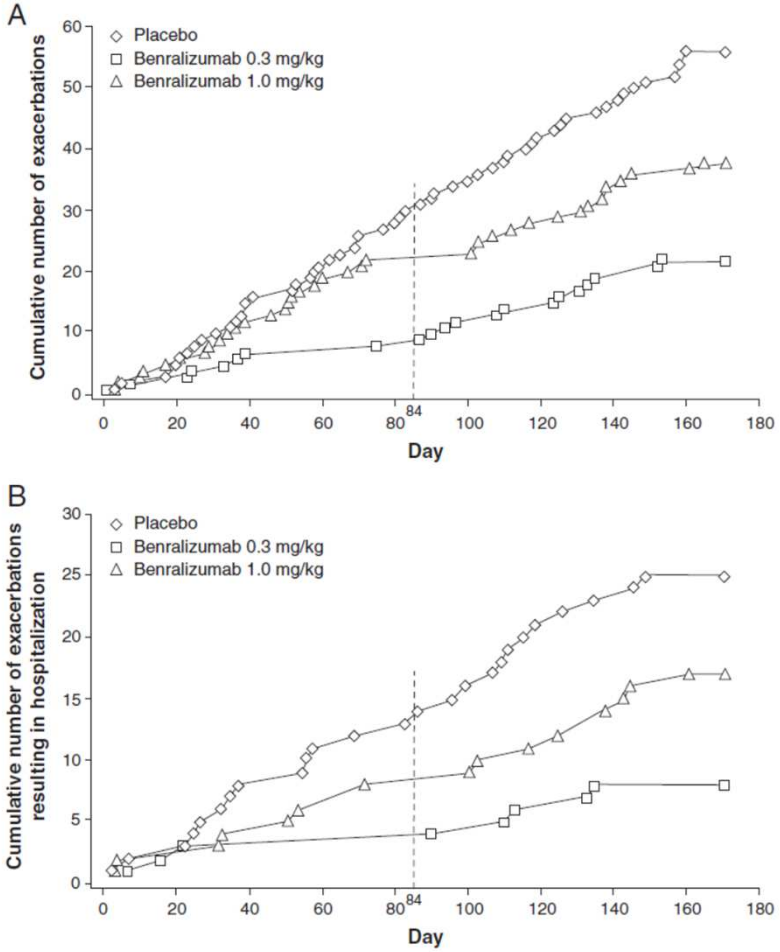
- **In a randomized, double-blind, parallel-group, placebo-controlled phase 3 study at 374 sites in 17 Countries (SIROCCO STUDY), benralizumab (30 mg s.c. every 4 or every 8 weeks per 12 months) was administered in adults with severe eosinophilic asthma: both regimens reduced asthma exacerbations, improved lung function and quality of life, particularly in patients with ≥ 300 eosinophils/μL**

  (Bleecker *et al.*, Lancet 388: 2115, 2016)

- **In a randomized, double-blind, parallel-group, placebo-controlled phase 3 study at 303 sites in 11 Countries (CALIMA), benralizumab (30 mg s.c. every 4 or every 8 weeks per 14 months) was administered in adults with severe eosinophilic asthma: both regimens reduced asthma exacerbations, improved lung function and quality of life, particularly in patients with ≥ 300 eosinophils/μL**

  (FitzGerald *et al.*, Lancet 388: 2128, 2016)

A Randomized Trial of Benralizumab an Anti-Interleukin 5 Receptor α Monoclonal Antibody after Acute Asthma



1 i.v. dose of Benralizumab reduced the rate and severity of exacerbations experienced over 12 weeks by subjects who presented to the ED with acute asthma

Novak *et al.* Am. J. Emerg. Med. 33: 14, 2015

Anti-IL-5/IL-5Rα in Adult Eosinophilic Asthma

Author/year	MoAb	Administration	Blood Eosinophil Cut-off
Pavord/2012	Mepolizumab	i.v.	≥ 300 μL
Bel/2014	Mepolizumab	s.c.	≥ 150 μL at screening
			≥ 300 μL previous year
Ortega/2014	Mepolizumab	s.c.	≥ 150 μL at screening
			≥ 300 μL previous year
Castro/2015	Reslizumab	i.v.	≥ 400 μL
Bjermer/2016	Reslizumab	i.v.	≥ 400 μL
Corren/2016	Reslizumab	i.v.	≥ 400 μL
Bleecker/2016	Benralizumab	s.c.	≥ 300 μL
FitzGerald/2016	Benralizumab	s.c.	≥ 300 μL

Conclusions

- **Targeting IL-5 or IL-5Rα appeared an interesting approach to the treatment of patients with severe eosinophilic asthma**
- **Mepolizumab, Reslizumab and Benralizumab have been found to be well-tolerated in adult patients with severe eosinophilic asthma for periods of 3 months to approximately 1 year**
- **The blood eosinophil count at screening appears to be closely associated with a clinical response to IL-5 pathway inhibition in adult patients with eosinophilic asthma**
- **Looking toward elevated blood eosinophil counts, as aiming for a high cut-off is most likely the best way we shall achieve success**

Unmet needs

- **Identification of novel biomarkers, in addition to blood eosinophilia will allow a more selective identification of patients responsive to these treatments**

- **The possible role of other cytokines (e.g. IL-33, IL-3) in the control of eosinophil homeostasis and functions needs to be investigated**

- **The long-term safety of these agents in chronic respiratory disorders is an important issue and a major concern**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Dott. Diego Bagnasco
Dott. Matteo Ferrando

Reslizumab

- **In a randomized, double-blind, parallel-group, placebo-controlled phase 3 study conducted at 68 sites, reslizumab (3 mg/kg i.v. every 4 weeks per 4 months) was administered in adults with severe eosinophilic asthma: reslizumab improved lung functions (FEV_1, FVC), ACQ, and AQLQ ≥ 400 eosinophils/μL**

  (Bjermer *et al.*, Chest 150: 789, 2016)

- **In a randomized, double-blind, parallel-group, placebo-controlled phase 3 study conducted at 66 US sites, reslizumab (3 mg/kg i.v. every 4 weeks per 4 months) was administered in adults with severe eosinophilic asthma: reslizumab improved lung functions (FEV_1), and ACQ only in patients with ≥ 400 eosinophils/μL**

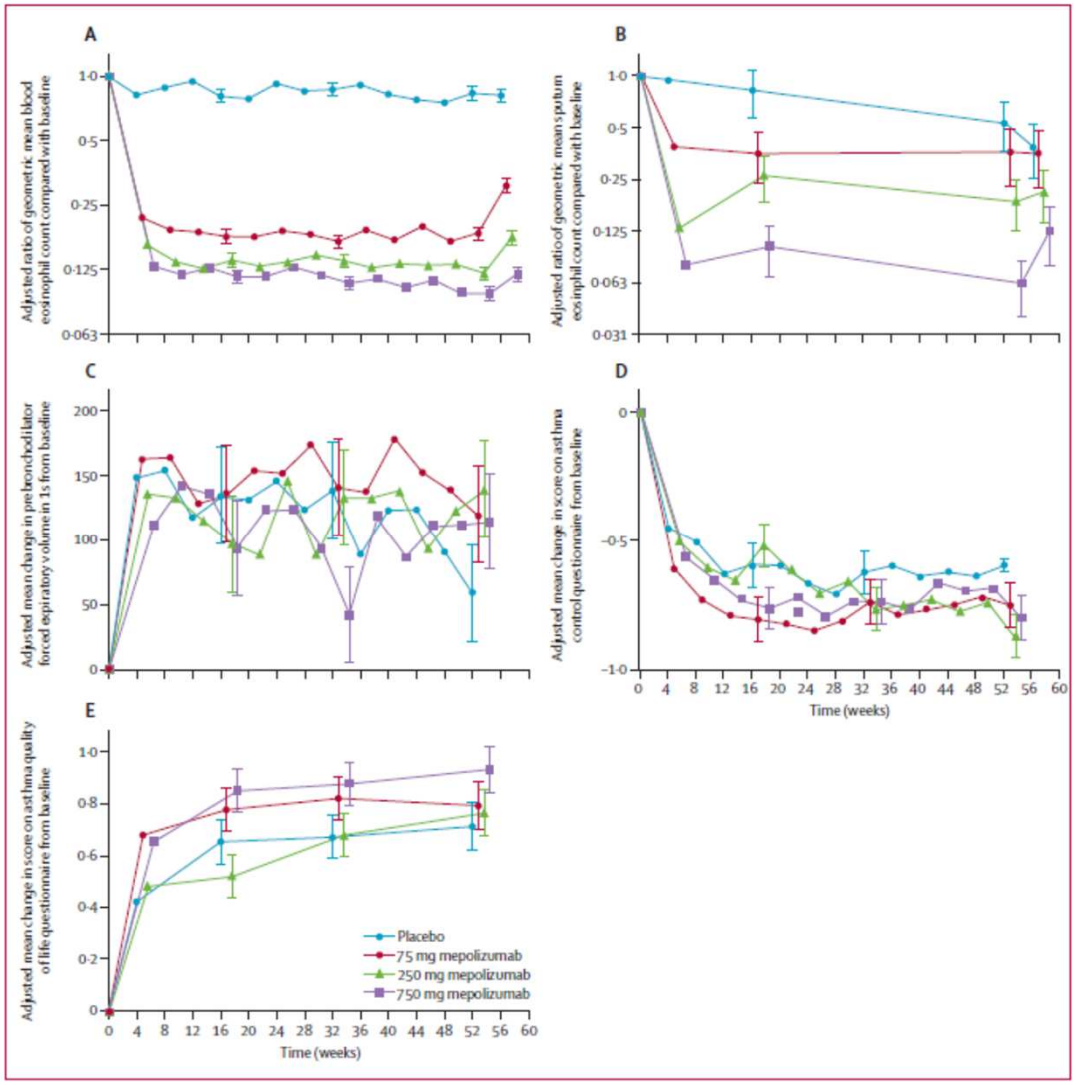
  (Corren *et al.*, Chest 150: 799, 2016)

1. **An incorrect selection of patients with mild or moderate asthma without significant eosinophilia**

2. **The small cohorts of patients treated with mepolizumab**

3. **The i.v. administration of mepolizumab: there is evidence that s.c. administration of human polyclonal immunoglobulins (IgGs) provides more prolonged serum levels of IgGs compared with i.v. infusion (Spadaro *et al.*, Clin. Immunol. 2016)**

Mepolizumab for Severe Eosinophilic Asthma (DREAM):



DREAM STUDY

Mepolizumab (75 mg, 250 mg or 750 mg i.v. every 4 weeks for 13 mo) in 462 patients reduced blood and sputum eosinophilis.

No changes in FEV_1 and QoL.

Pavord et al., Lancet 380: 651, 2012