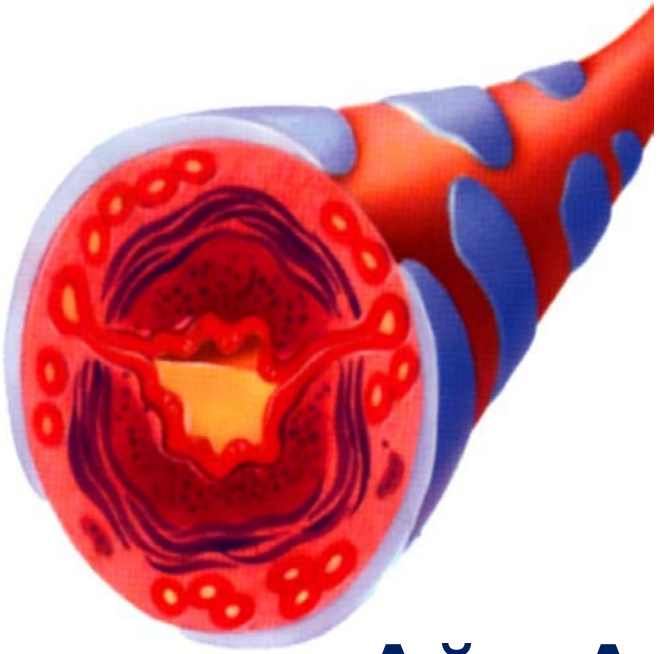


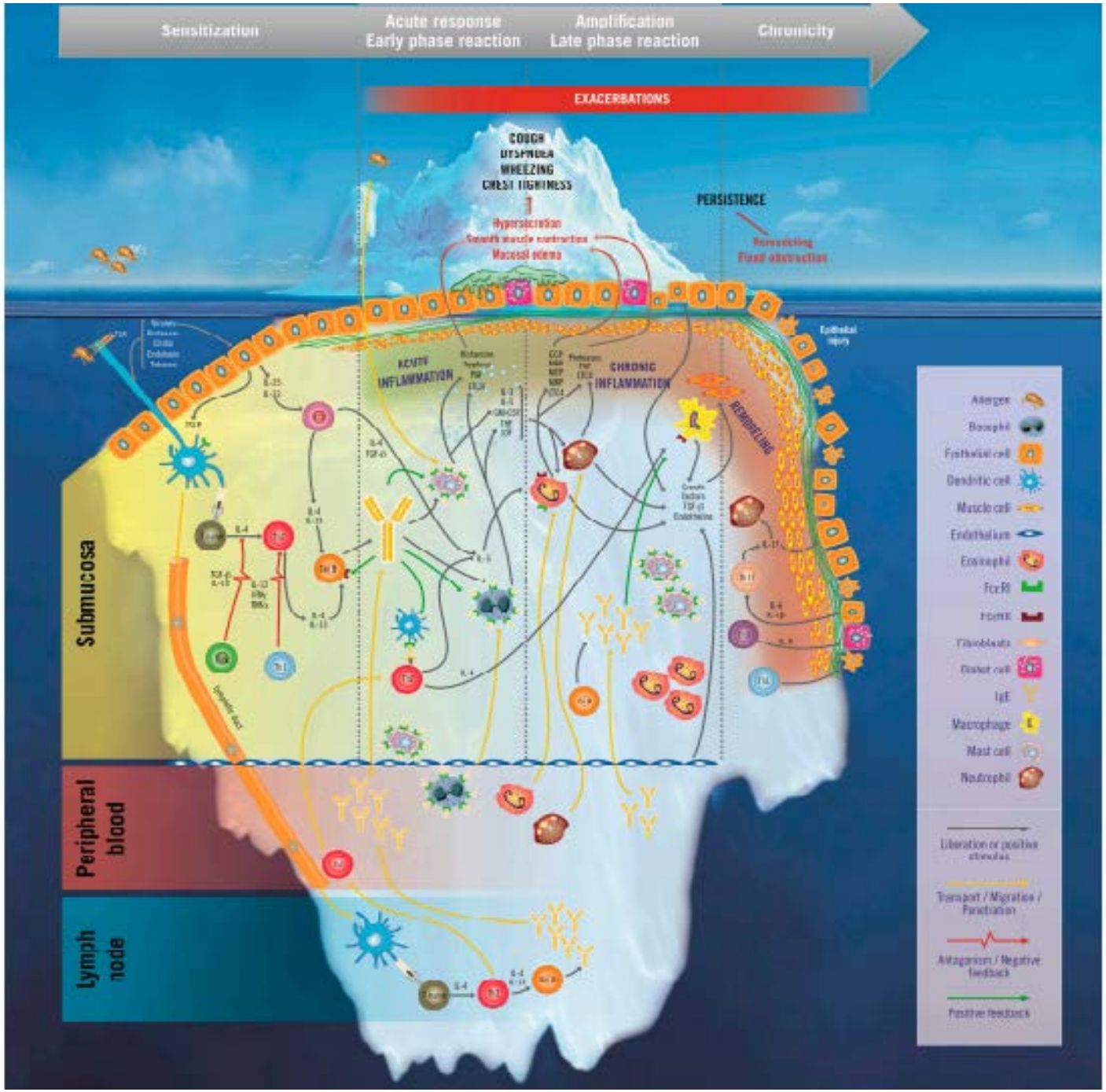
Ağır Astım Sempozyumu
Ağır Astım'da İmmünolojik Mekanizmalar: -Bildiklerimiz -

Prof. Dr. A. Füsun Kalpaklıoğlu

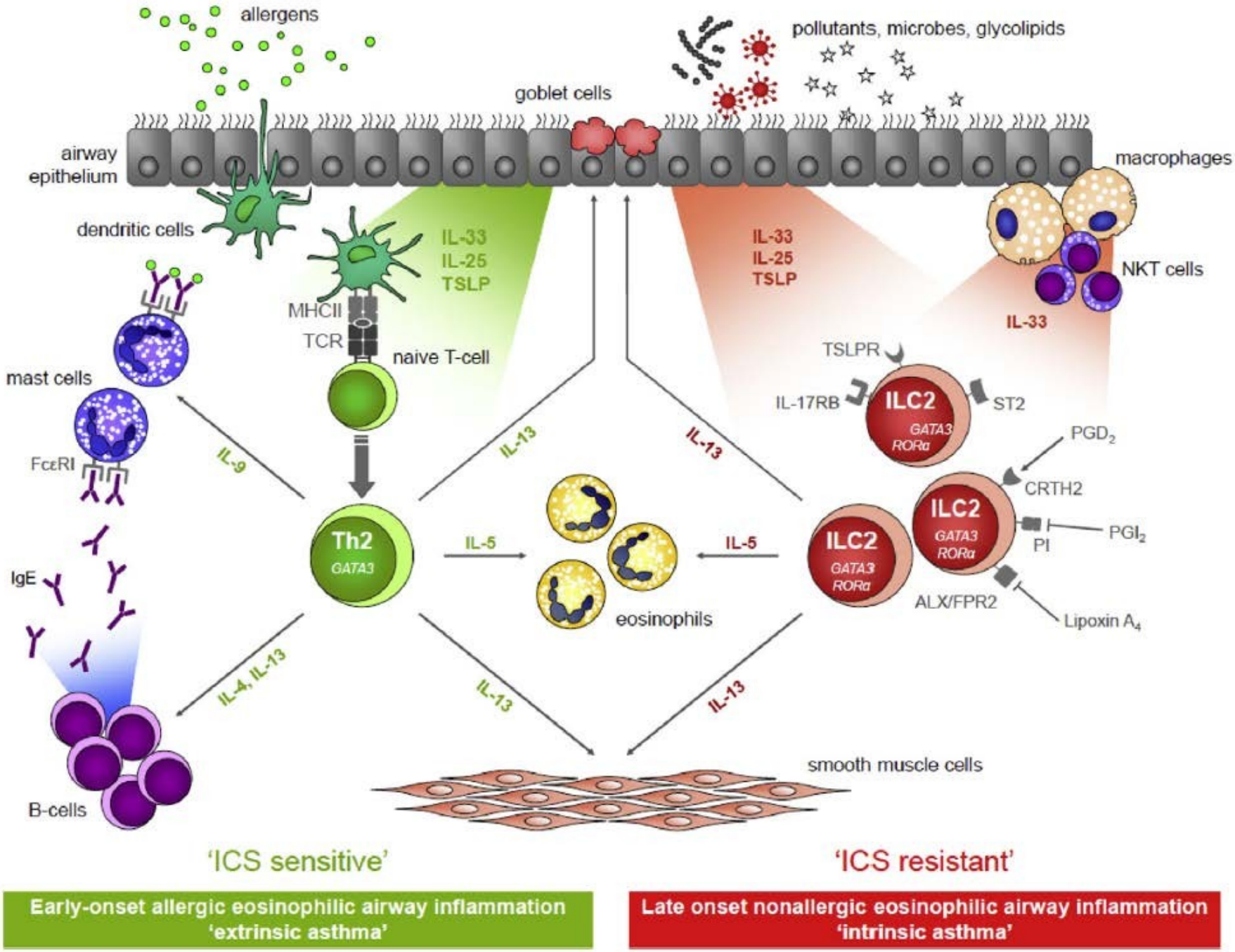
9 Haziran 2018, Koç Üniversitesi Hastanesi

Astım heterojen bir hastalıktır…

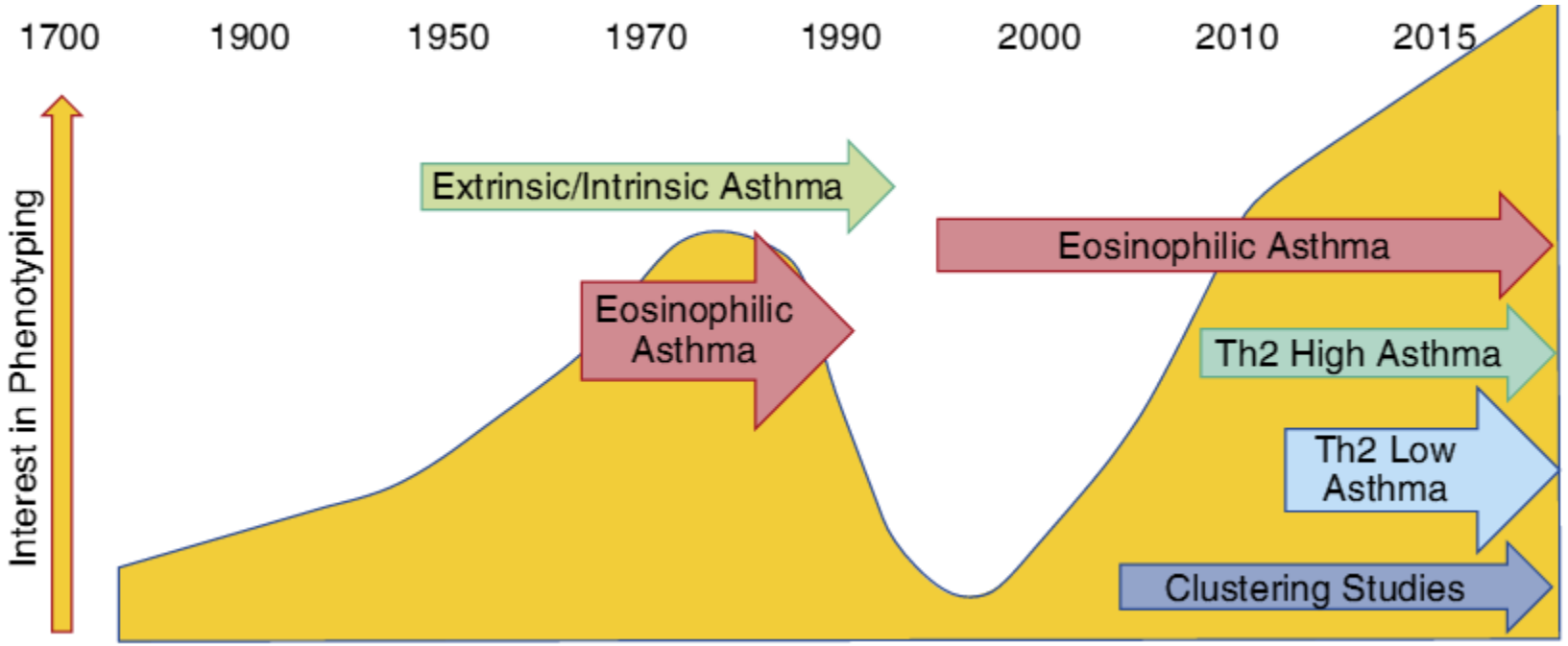
Çok çeşitli endotipler ve fenotipler vardır!



Palomares O, et al. Int J Mol Sci 2017; 18: 1-14

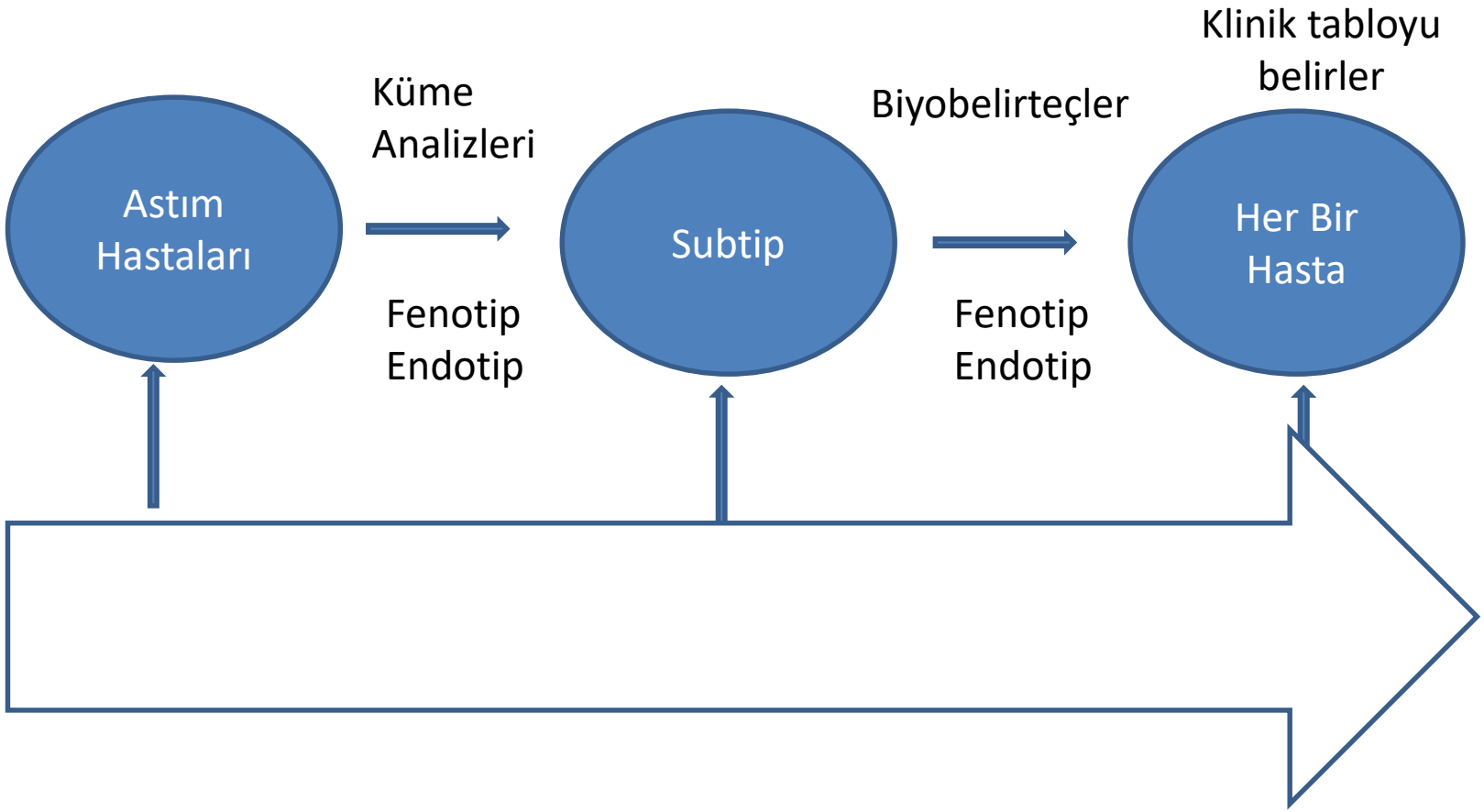

allergens
pollutants, microbes, glycolipids
goblet cells
airway epithelium
macrophages
dendritic cells
IL-33
IL-25
TSLP
IL-33
IL-25
TSLP
NKT cells
IL-33
MHCII
TCR
naive T-cell
TSLPR
IL-17RB
ILC2
GATA3
RORα
ST2
mast cells
FcεRI
IL-9
IL-13
IL-13
PGD2
CRTH2
ILC2
GATA3
RORα
PI
PGI2
Th2
GATA3
IL-5
IL-5
ILC2
GATA3
RORα
eosinophils
IgE
ALX/FPR2
Lipoxin A4
IL-4, IL-13
IL-13
IL-13
smooth muscle cells
B-cells
'ICS sensitive'
'ICS resistant'
Early-onset allergic eosinophilic airway inflammation
'extrinsic asthma'
Late onset nonallergic eosinophilic airway inflammation
'intrinsic asthma'

Astım/Fenotiplerin Gelişmesinde Temel Olaylar

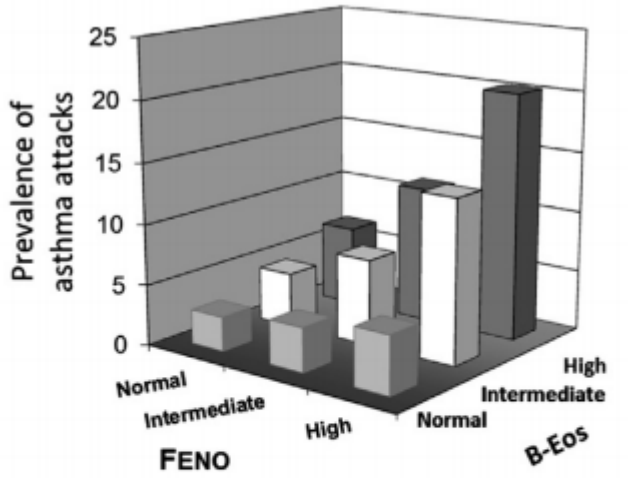


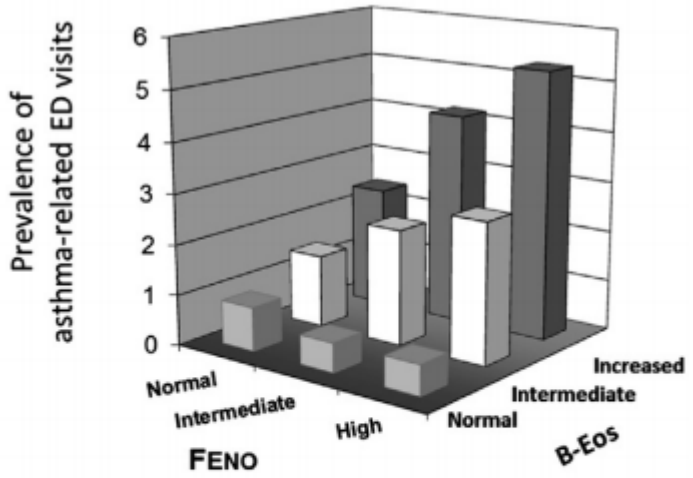
Gauthier M, et al. ARJCCM 2015; 192: 660-8

Astım heterojen bir hastalıktır…



Eozinofilik İnflamasyon Biyomarkerları ve Risk





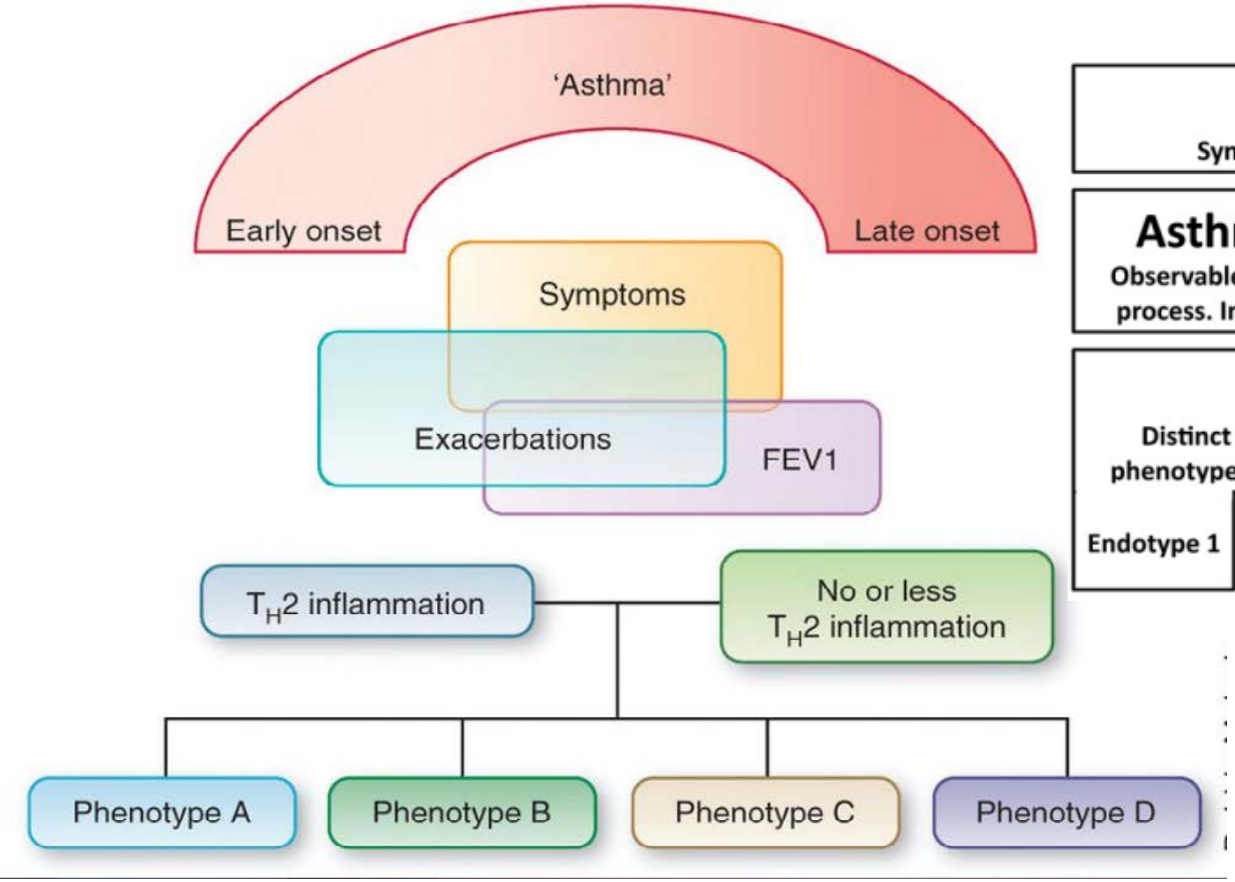
Number of subjects per group (n), according to levels of FENO and B-Eos.

7,827	1,042	167	Normal B-Eos
1,806	478	215	Intermediate B-Eos
498	168	207	High B-Eos
Normal FENO	Intermediate FENO	High FENO	

Malinovschi A, et al. JACI 2013;132:821-7.

Schematic representation of the umbrella term 'asthma'

Endotip: Hastalığın farklı fizyopatolojik mekanizmasına sahip alt grubu



The Asthma Syndrome

Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics

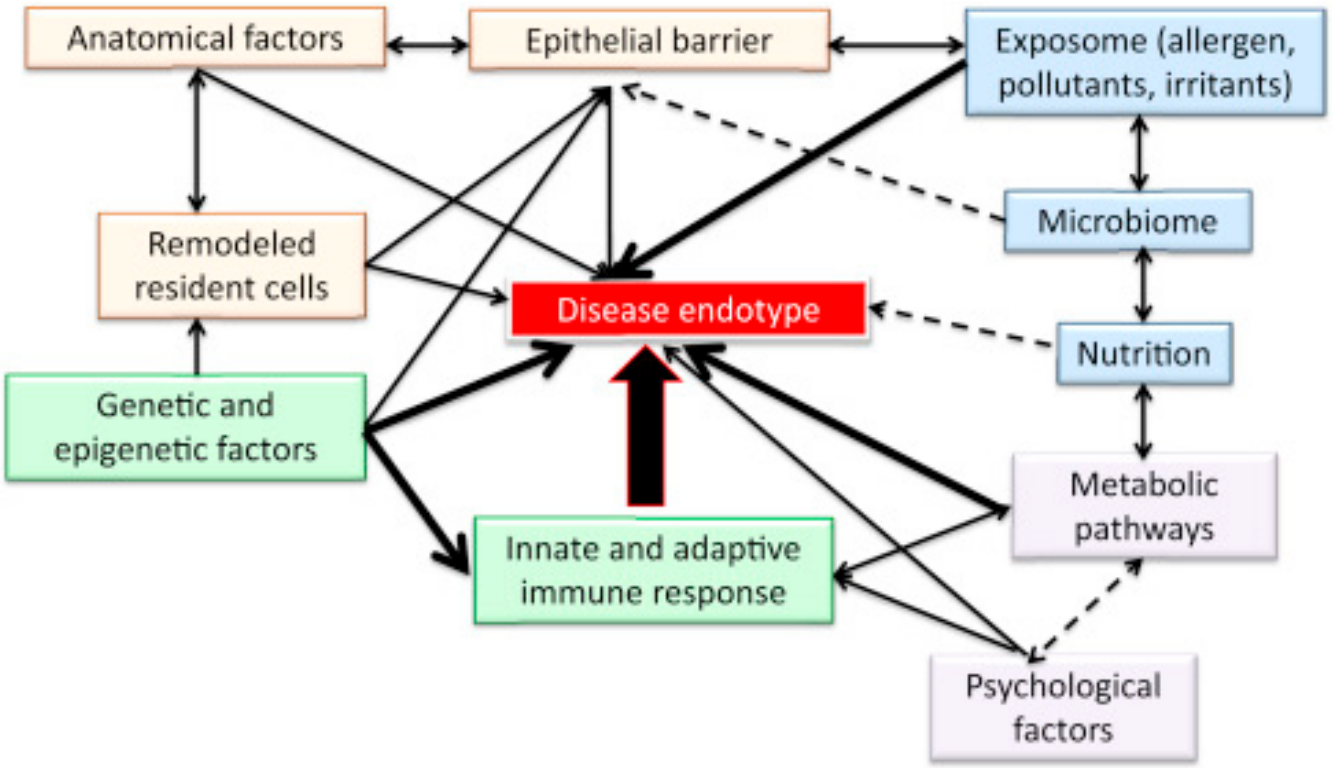
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes

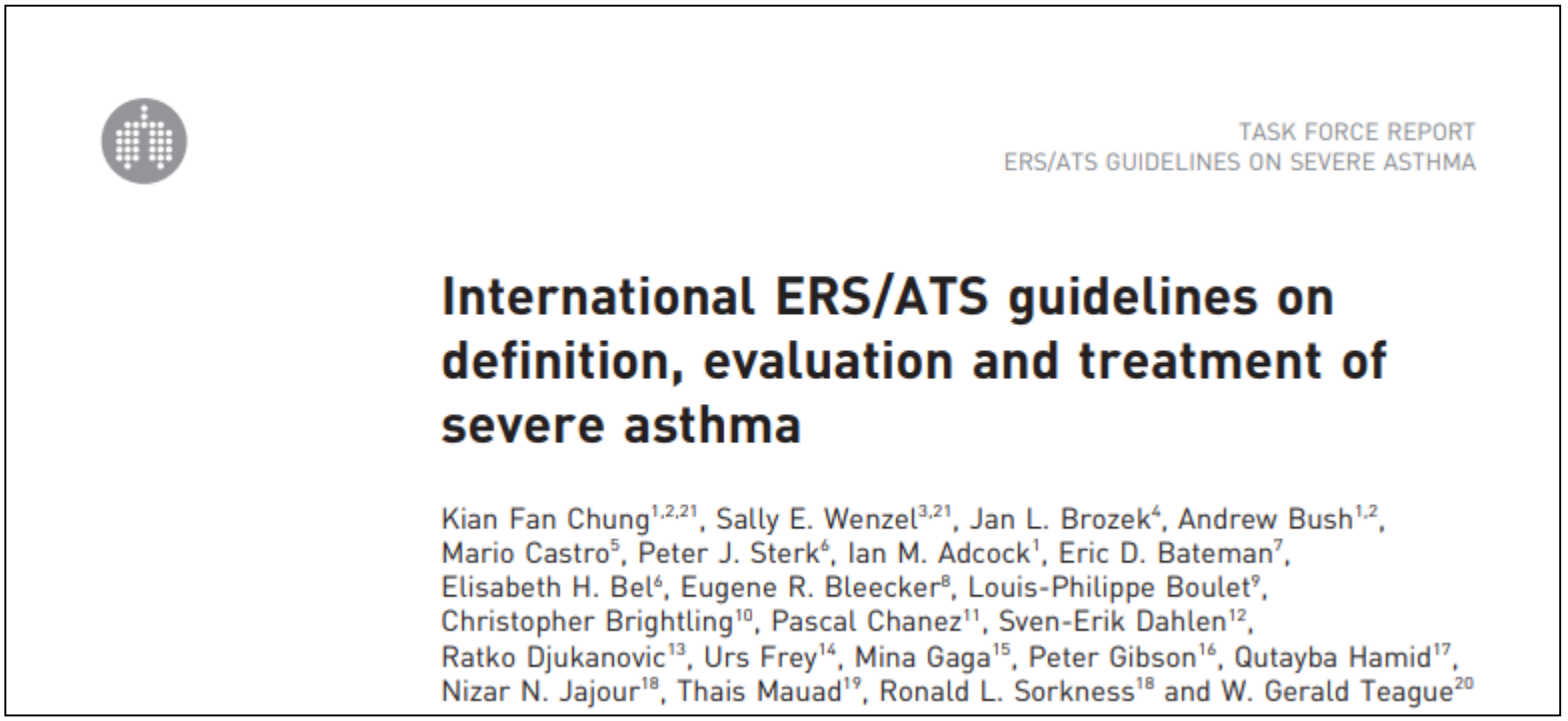
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1 | Endotype 2 | Endotype 3 | Endotype 4 | Endotype 5

Astımda Endotipi Belirleyen Faktörler



Agache I, et al. Allergology International 2016;65:243-52



TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

Ağır Astım:

- Yüksek doz IKS ile birlikte ikinci bir kontrol edici ilaç (LABA, LTRA, Teofilin) ve/veya

  -<u>Kontrol altına alınamayan</u>

  veya

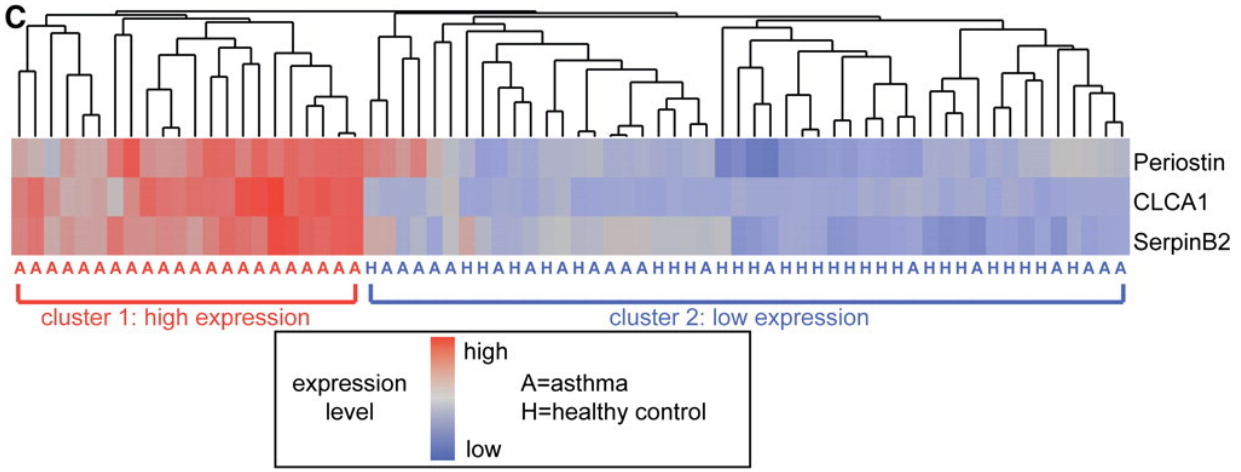
  -<u>Bu tedavi ile kontrol edilebilen astım</u>

- Önceki yıla göre >%50 sistemik steroide rağmen

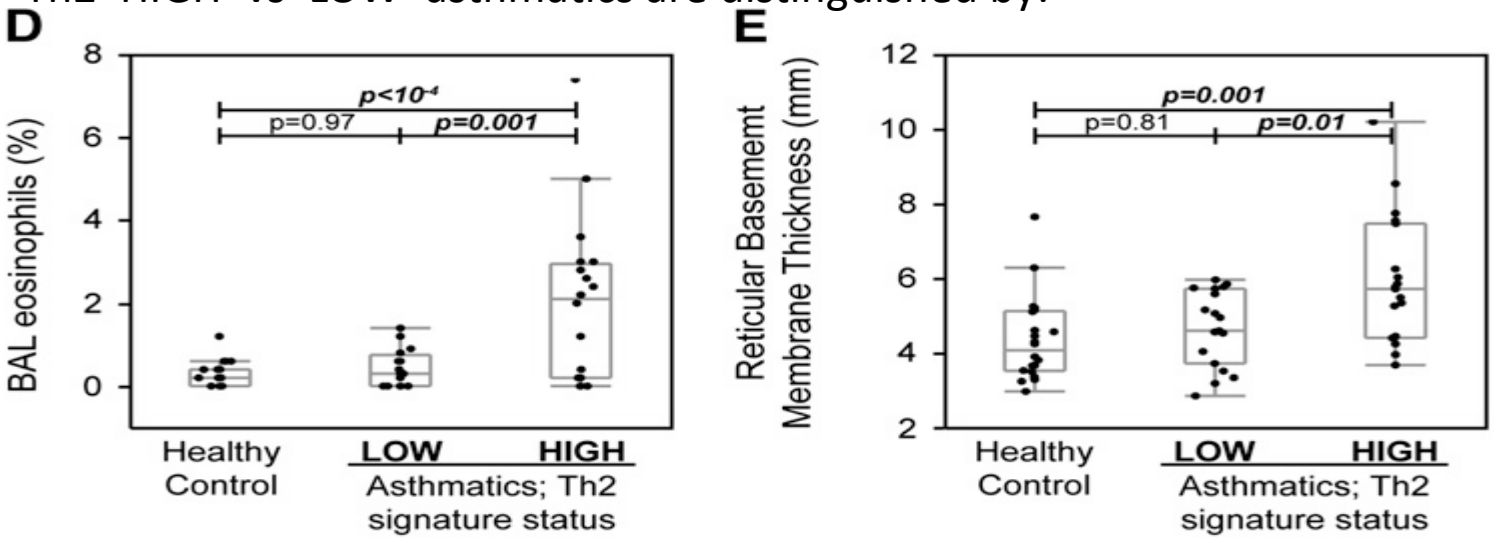
Eur Respir J 2014; 43: 343–373 | DOI: 10.1183/09031936.00202013

Bronş Epitel Gen Analizi ile Astımdaki 2 Grup

IL-13 responsive gen signature in bronchial epithelium



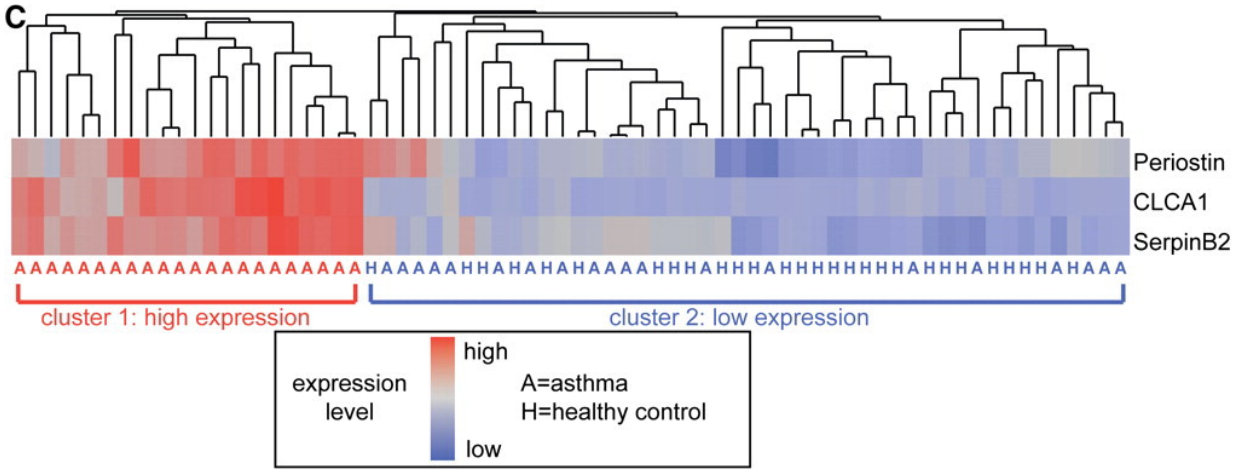
Th2 'HİGH' vs 'LOW' asthmatics are distinguished by:

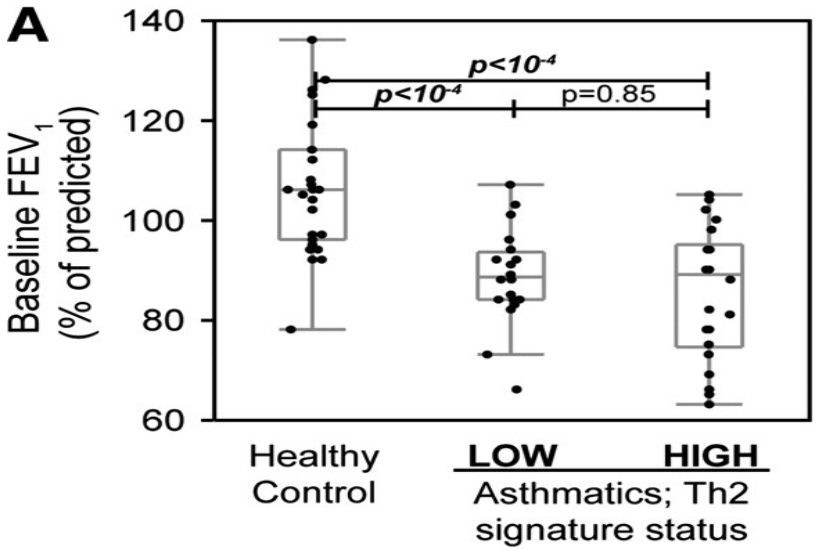


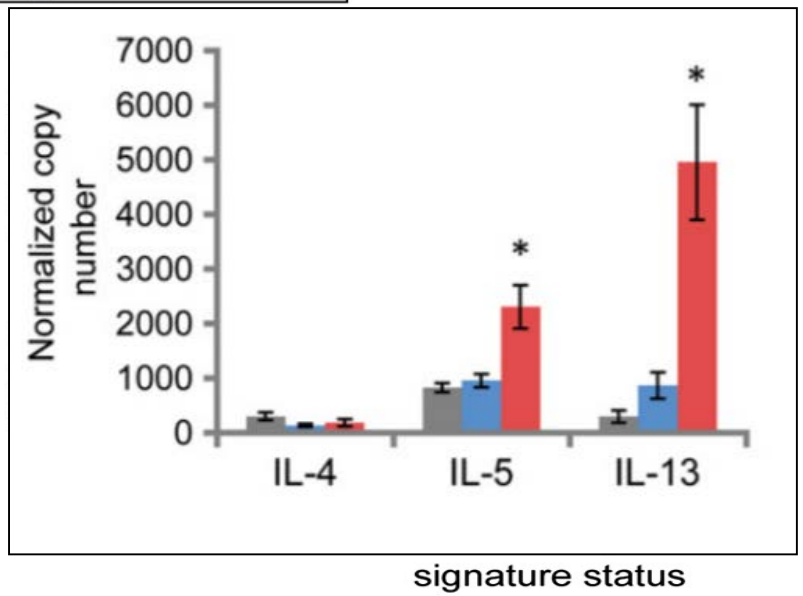
Woodruff P, et al. AJRCCM 2009;180: 388-95

Bronş Epitel Gen Analizi ile Astımdaki 2 Grup

IL-13 responsive gen signature in bronchial epithelium

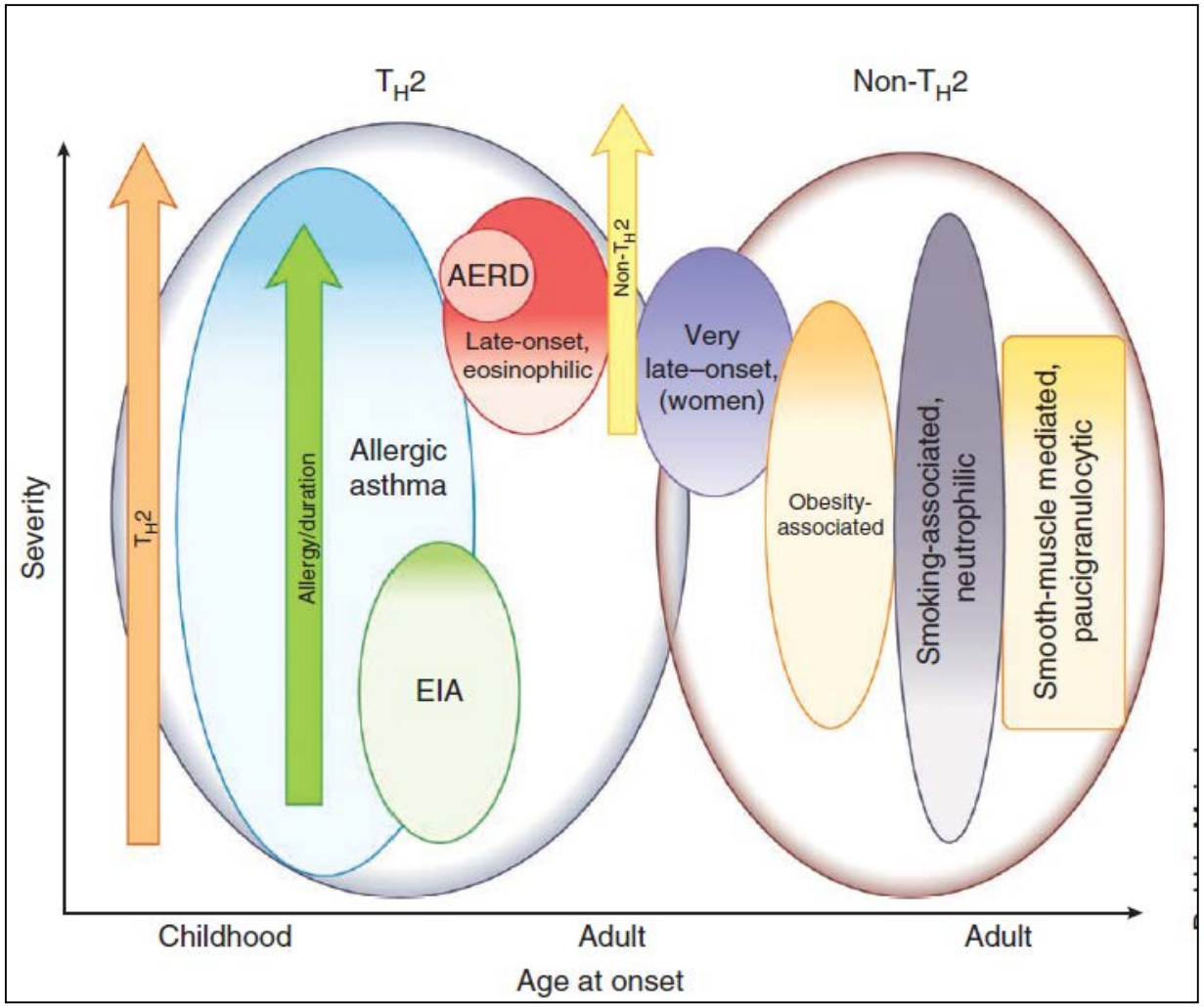






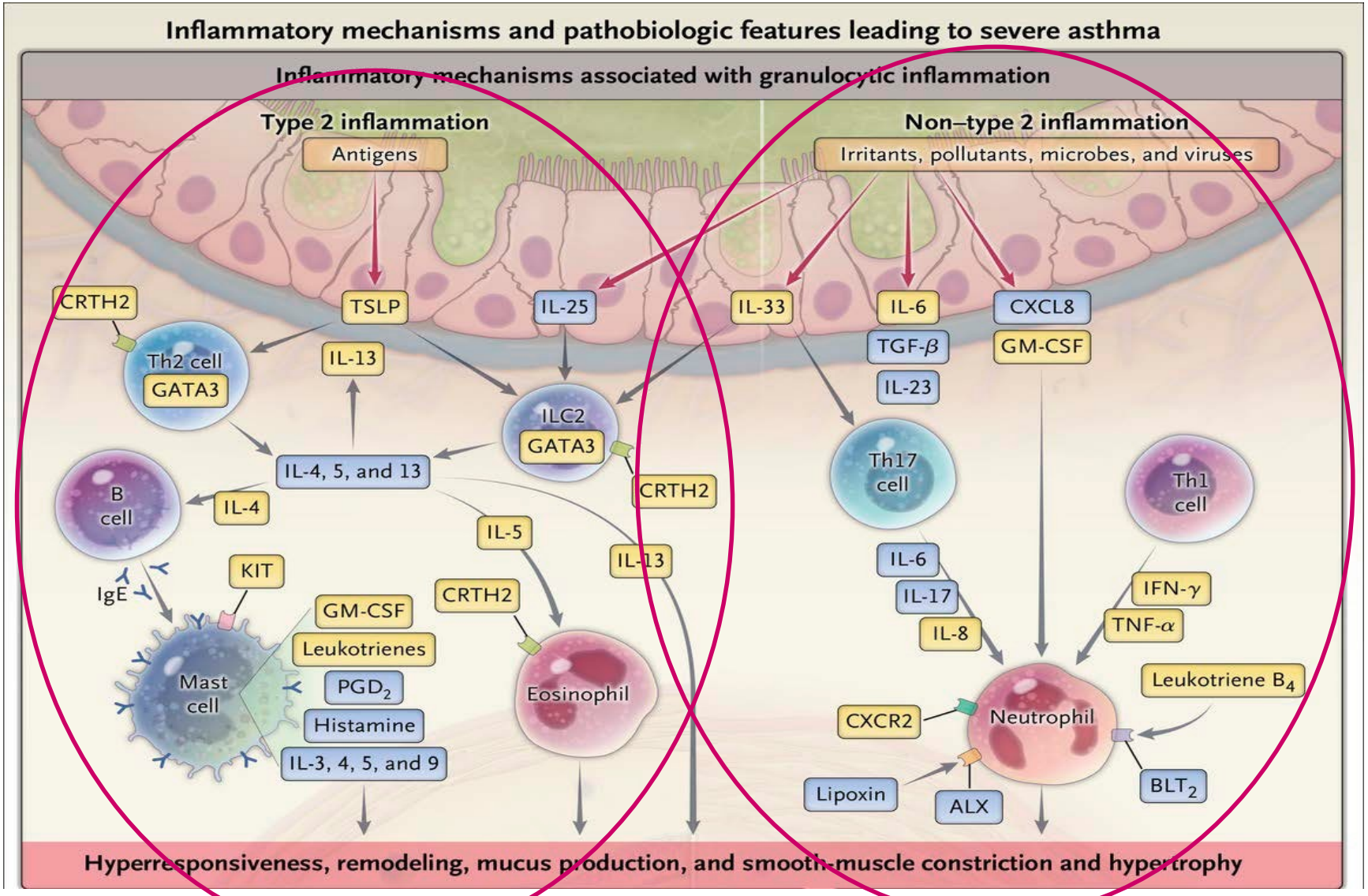
Woodruff P, et al. AJRCCM 2009;180: 388-95

Astım Endotipleri: Astım sendromu içinde farklı hastalıkları sınıflamak için yeni bir yaklaşım



Wenzel S, Nat Med 2012:18;716–25

Ağır Astımda İnflamatuar Mekanizmalar



Israel E, et al. N Engl J Med 2017;377:965-76

The NEW ENGLAND JOURNAL of MEDICINE

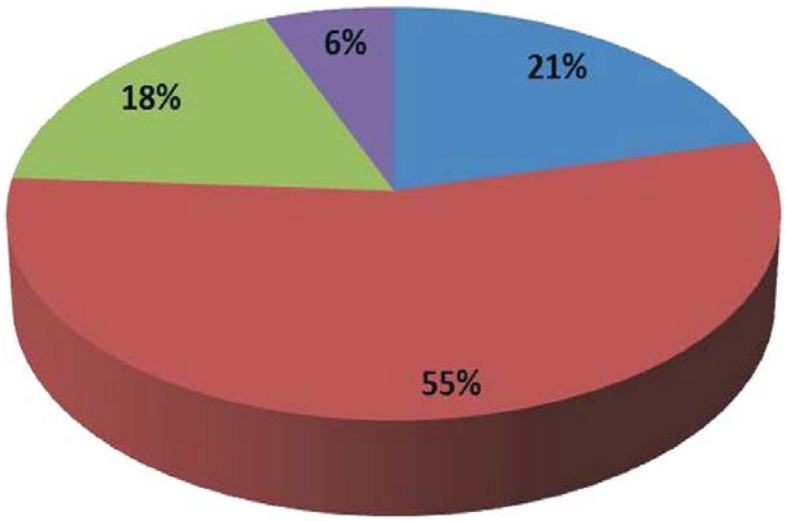
Respiratory Medicine (2014) 108, 1723–1732

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR)



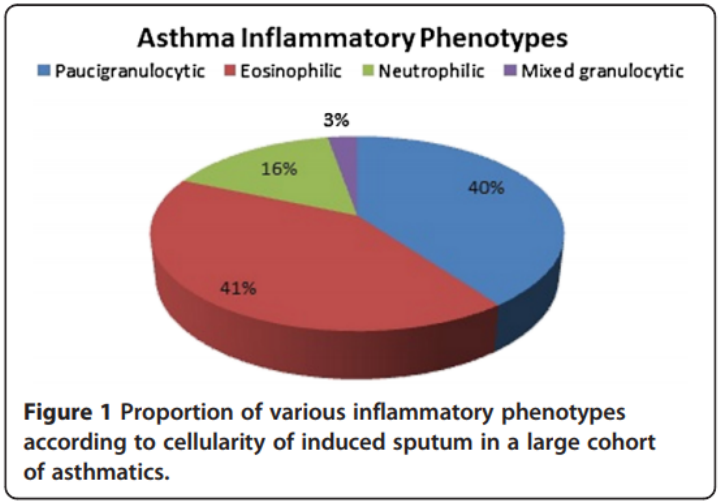


Figure 1 Proportion of various inflammatory phenotypes according to cellularity of induced sputum in a large cohort of asthmatics.

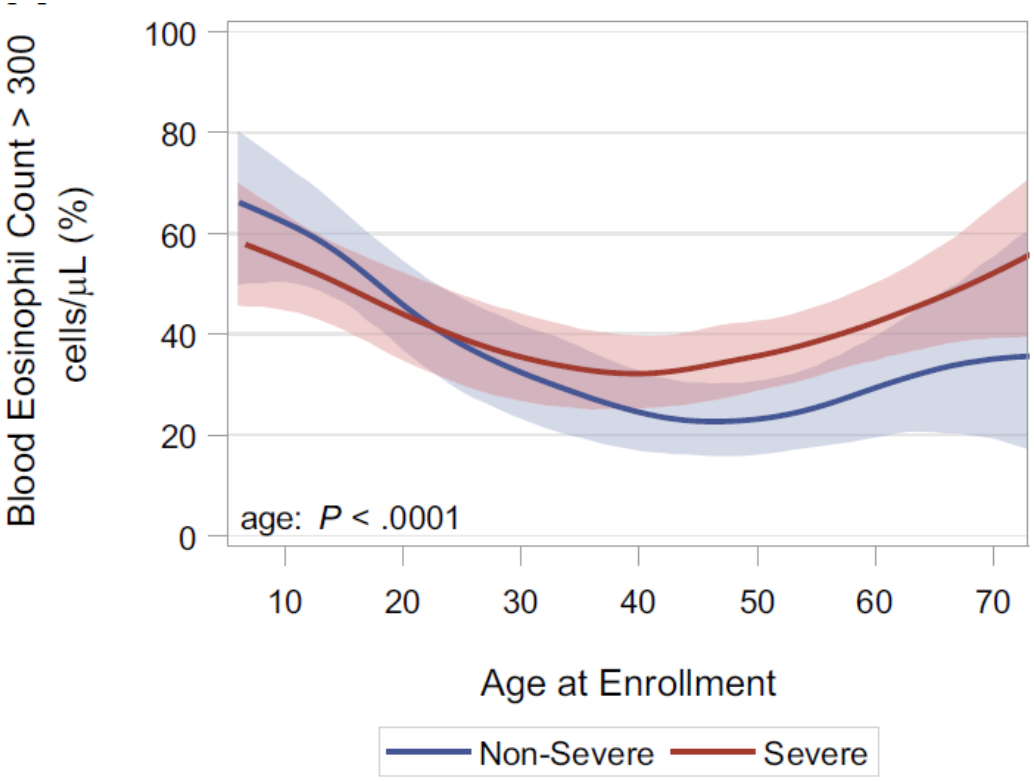
- Neutrophilic → <%3 eos + ≥%76 neutro
- Eosinophilic → ≥%3 eos + <%76 neutro
- Paucigranulocytic → <%3 eos + <%76 neutro
- Mixed Granulocytic → ≥%3 eos + ≥%76 neutro

Schleich F, et al. Respir Med 2014;108: 1723-32
BMC Pulm Med 2013; 13:11

Original Article

Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age

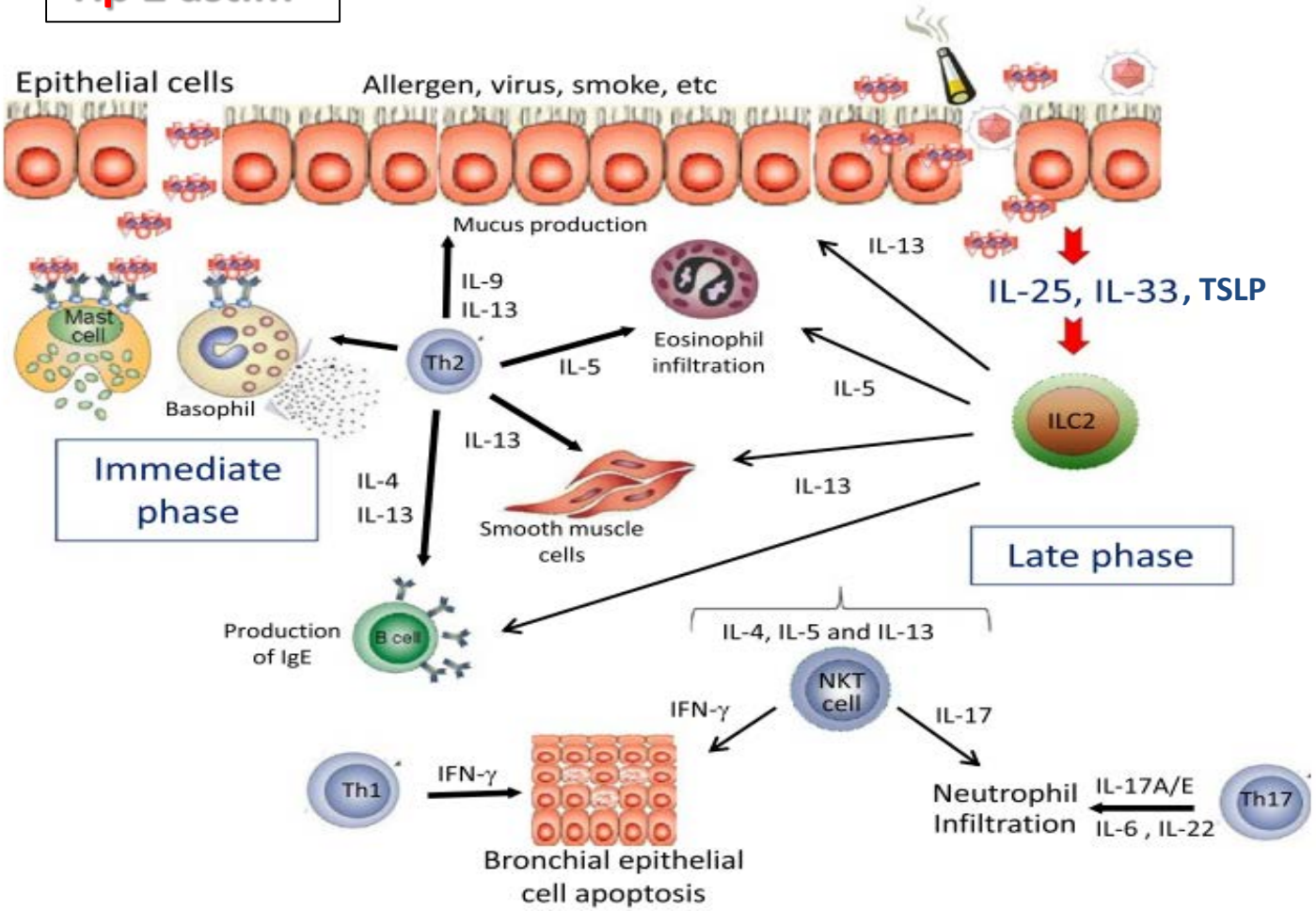
NIH/NHLBI'nın desteklediği bu programda ağır astımın farklı moleküler, biyokimyasal ve hücresel İnflamatuar özelliklerinin yanısıra yapısal/fonksiyonel anormallikler gösteren bir heterojen sendrom olduğu ortaya konmuştur.



Teague WG, et al. JACI Practice 2018;6:545-54.

Ağır Astımda İmmünolojik Mekanizmalar

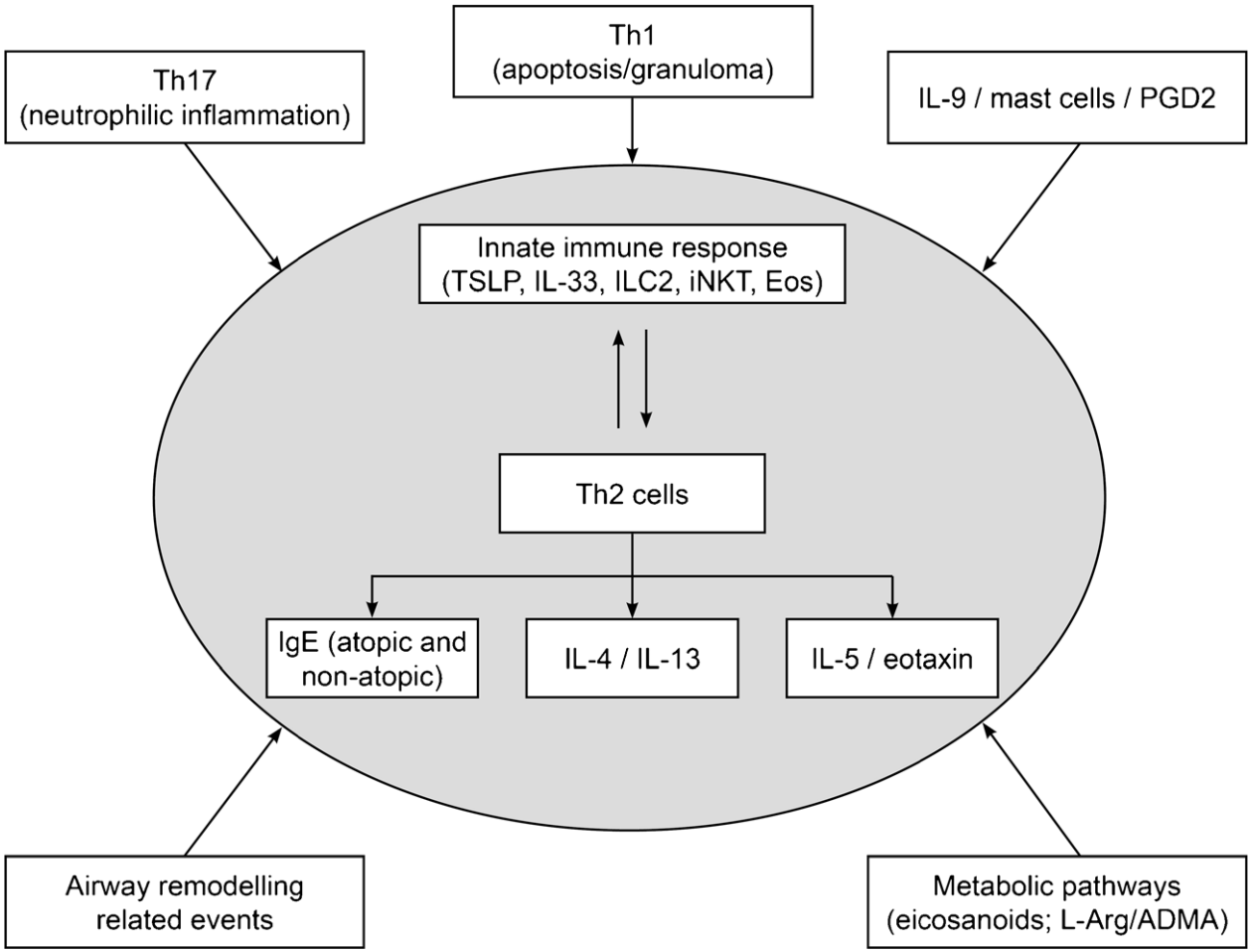
Tip 2 astım



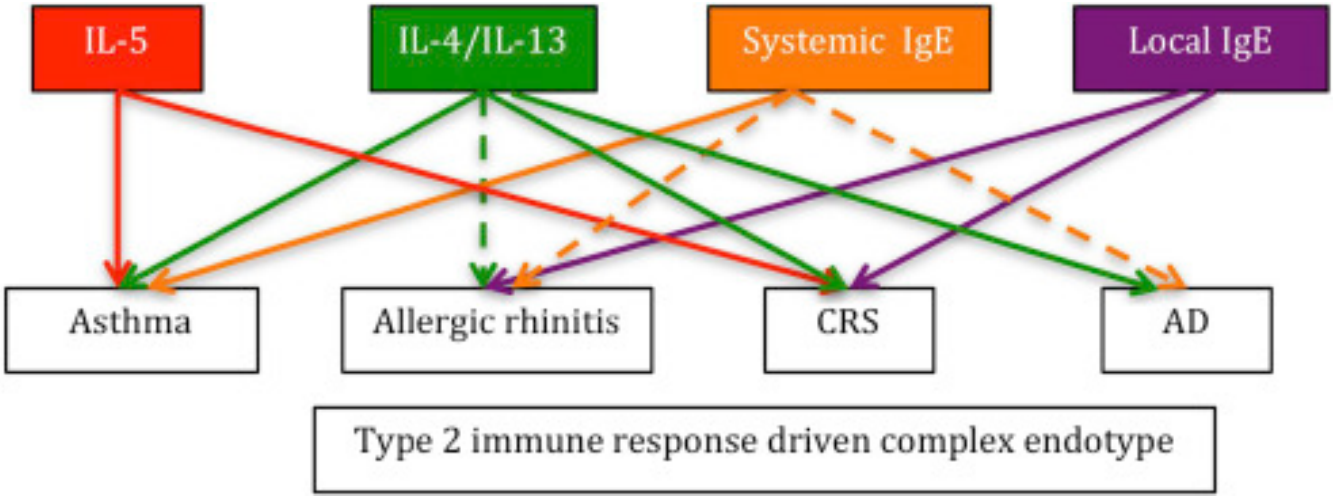
Palomares O, et al. Immunol Rev 2017;278:219-36

T_h2 Astım Fenotipi Komplekstir

Th2
IL2
NK
Bazofil
Eozinofil
Mast h

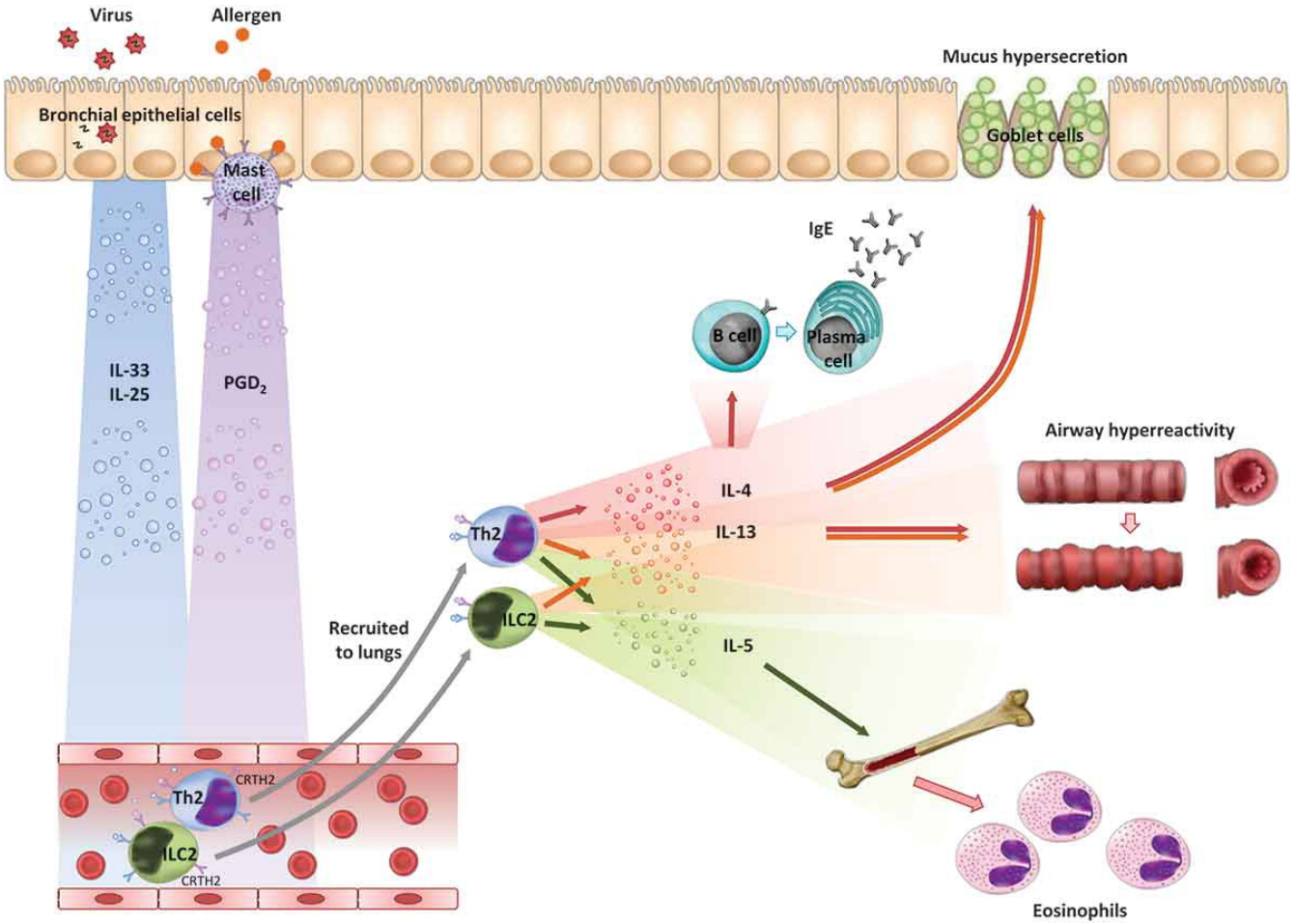


Agache I, et al. Curr Allergy Asthma Rep 2015; 15:29



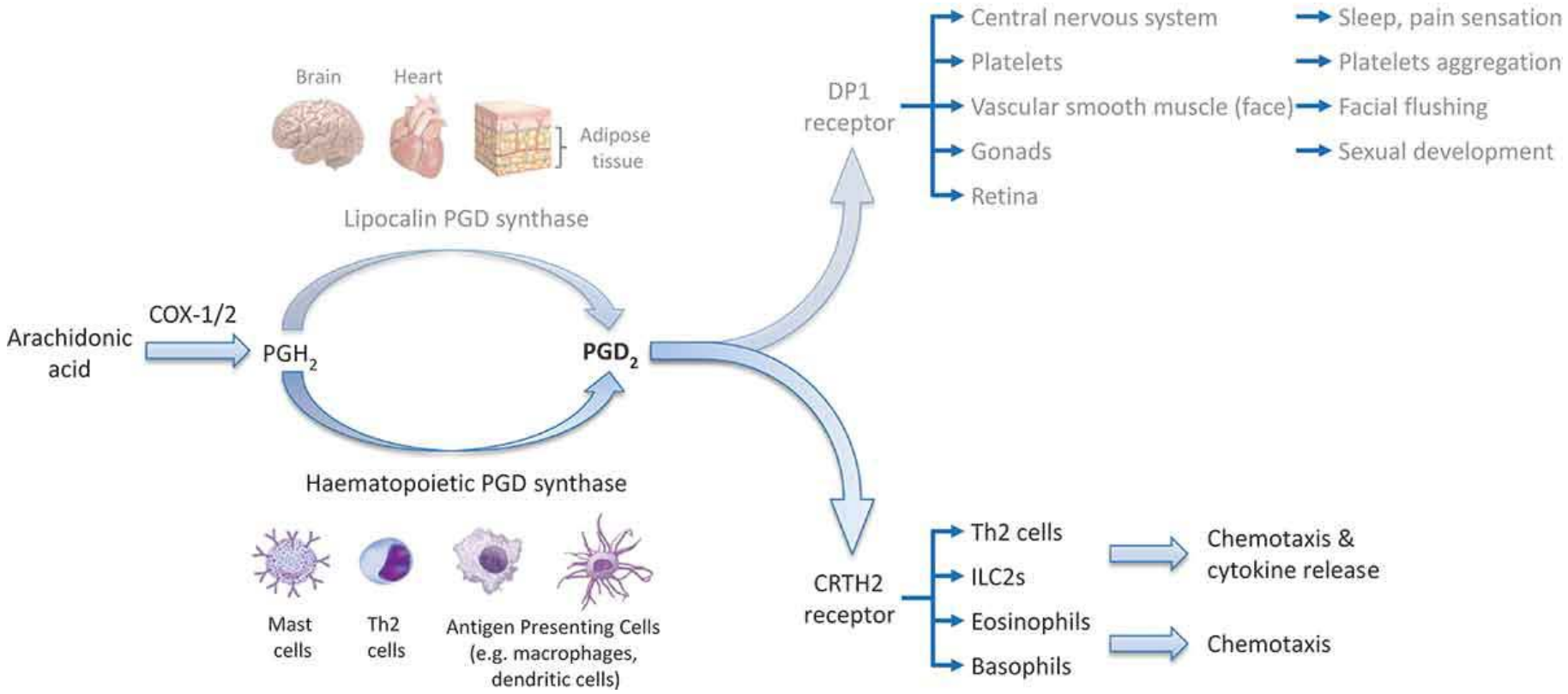
Agache I, et al. Allergology International 2016;65:243-52

Astımda PGD2'lerin Rolü



Farne H, et al. Expert Opin Emerging Drugs 2016;21:359-64

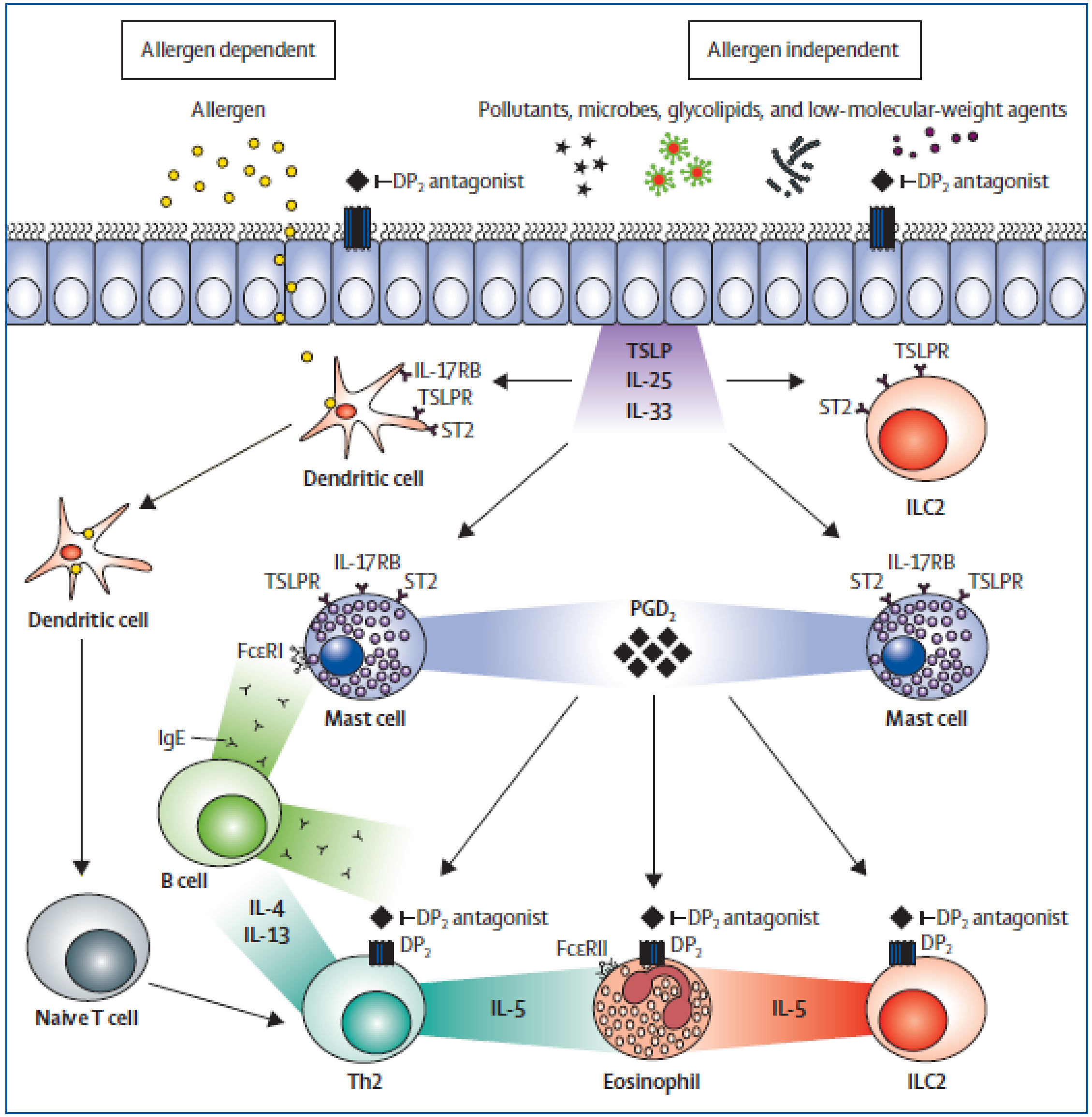
PGD_2 Biyolojisi



CRTH2; chemoattractant receptor– homologous molecule expressed on TH2 lymphocytes

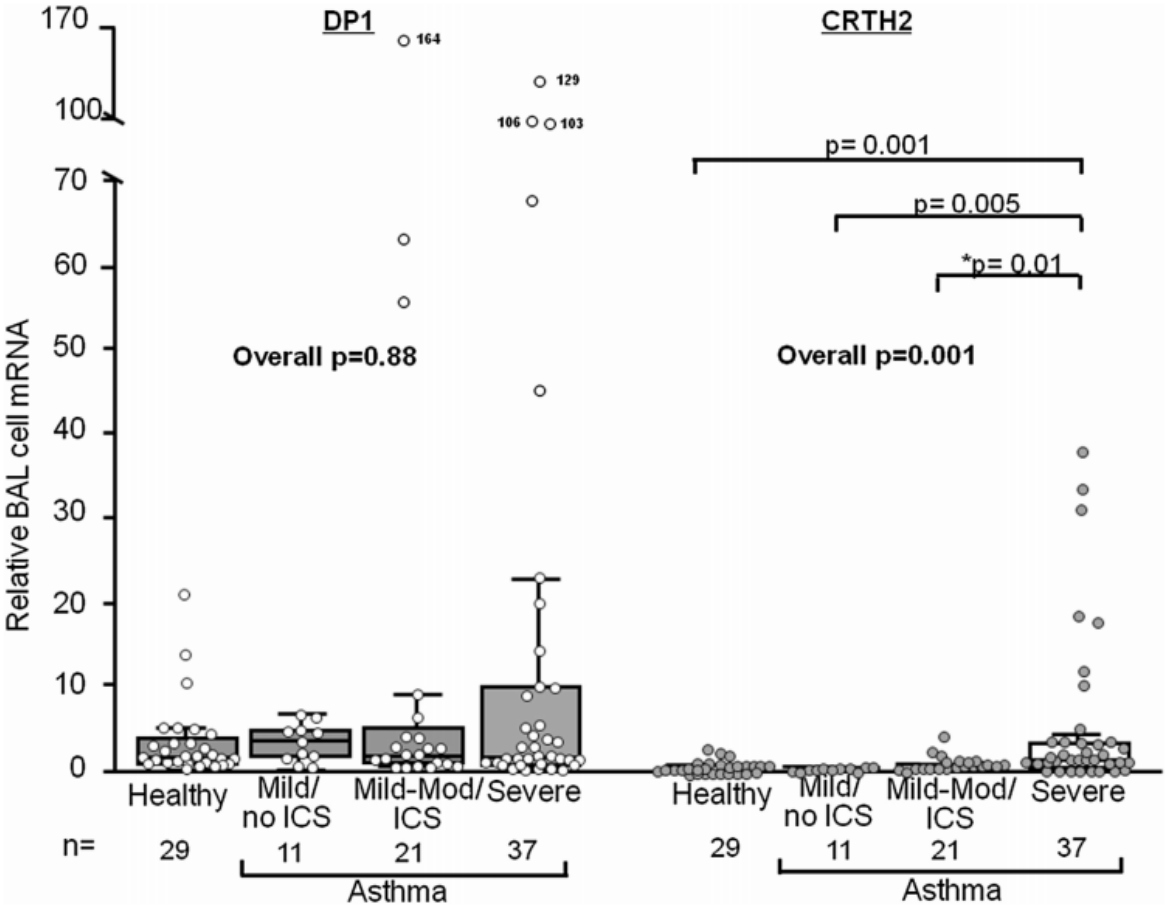
Farne H, et al. Expert Opin Emerging Drugs 2016;21:359-64

Astımda PGD2-DP2 Yolağı



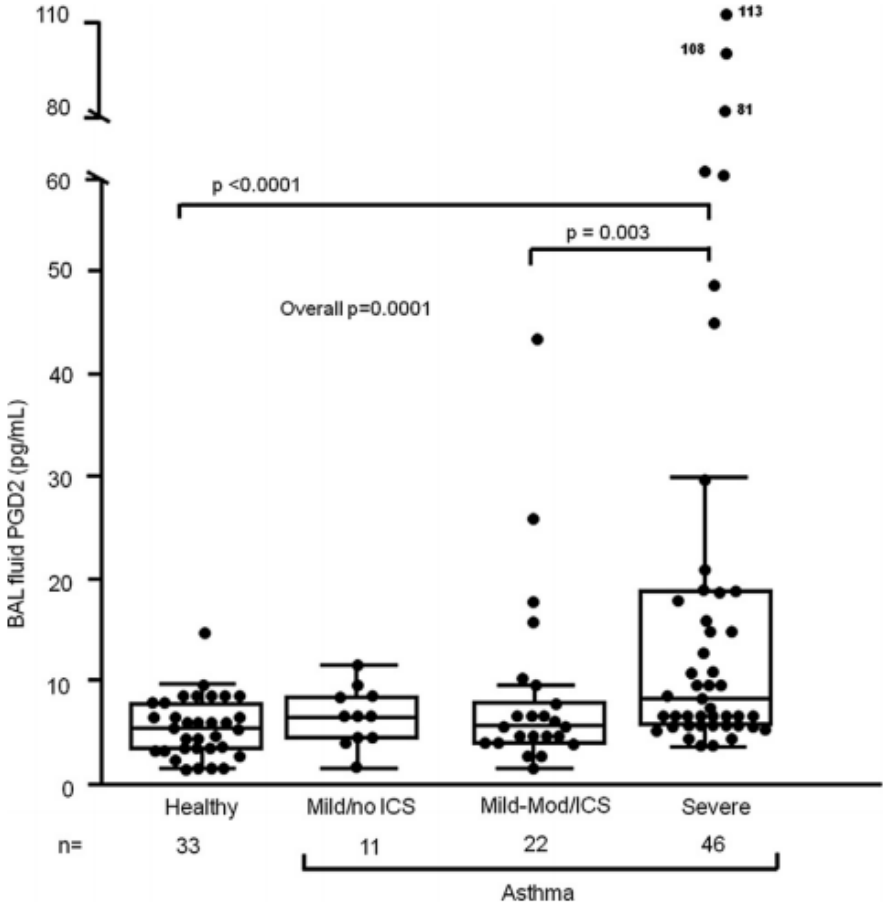
Brusselle GG, et al. Lancet Respir Med 2016:4:676-77

PGD_2 pathway upregulation;
Astım şiddeti, kontrolu ve TH_2 inflamasyon ilişkisi



Fajt ML, et al. JACI 2013; 131:1504-12

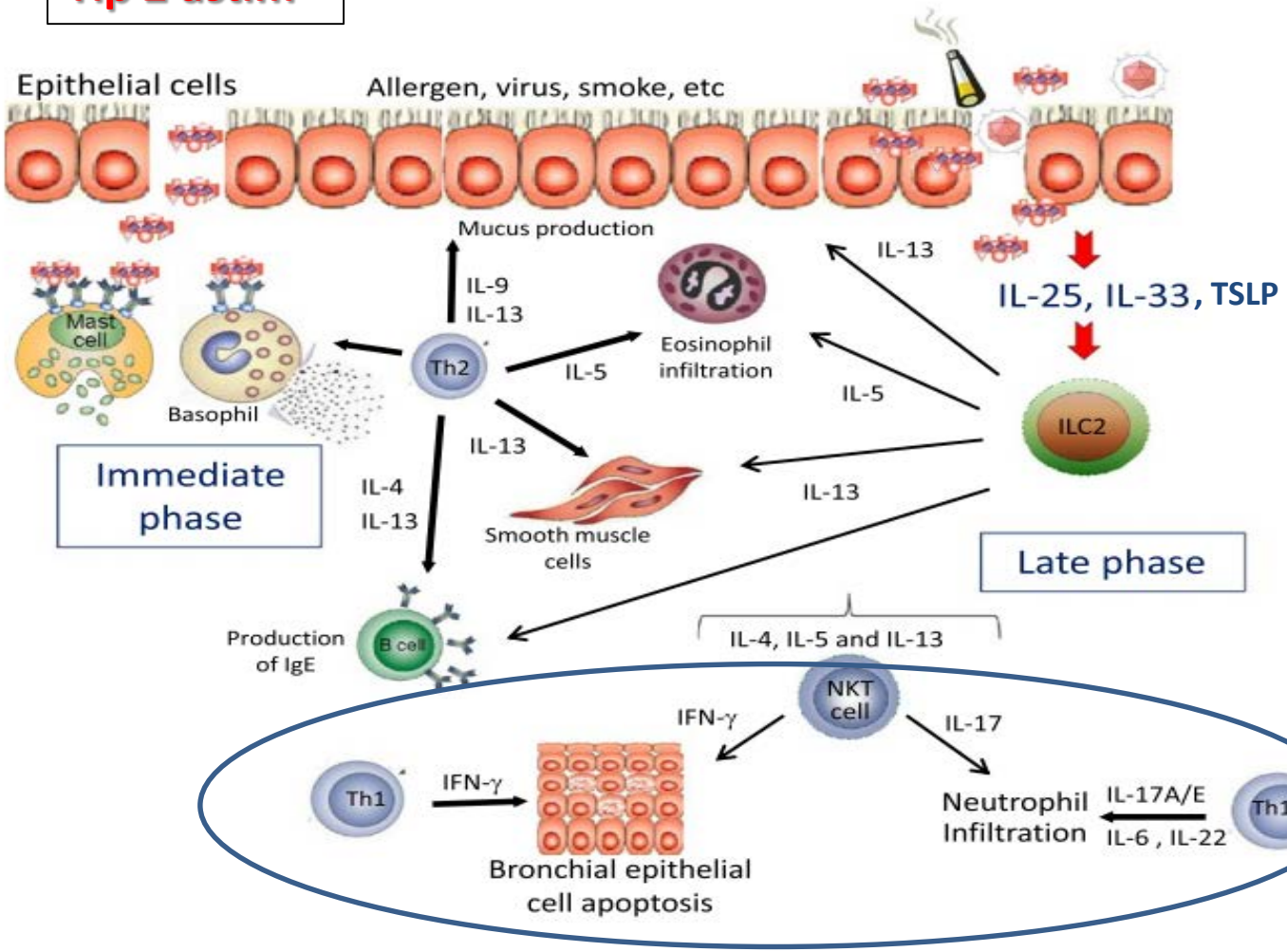
PGD_2 pathway upregulation;
Astım şiddeti, kontrolu ve TH_2 inflamasyon ilişkisi



Fajt ML, et al. JACI 2013; 131:1504-12

Ağır Astımda İmmünolojik Mekanizmalar

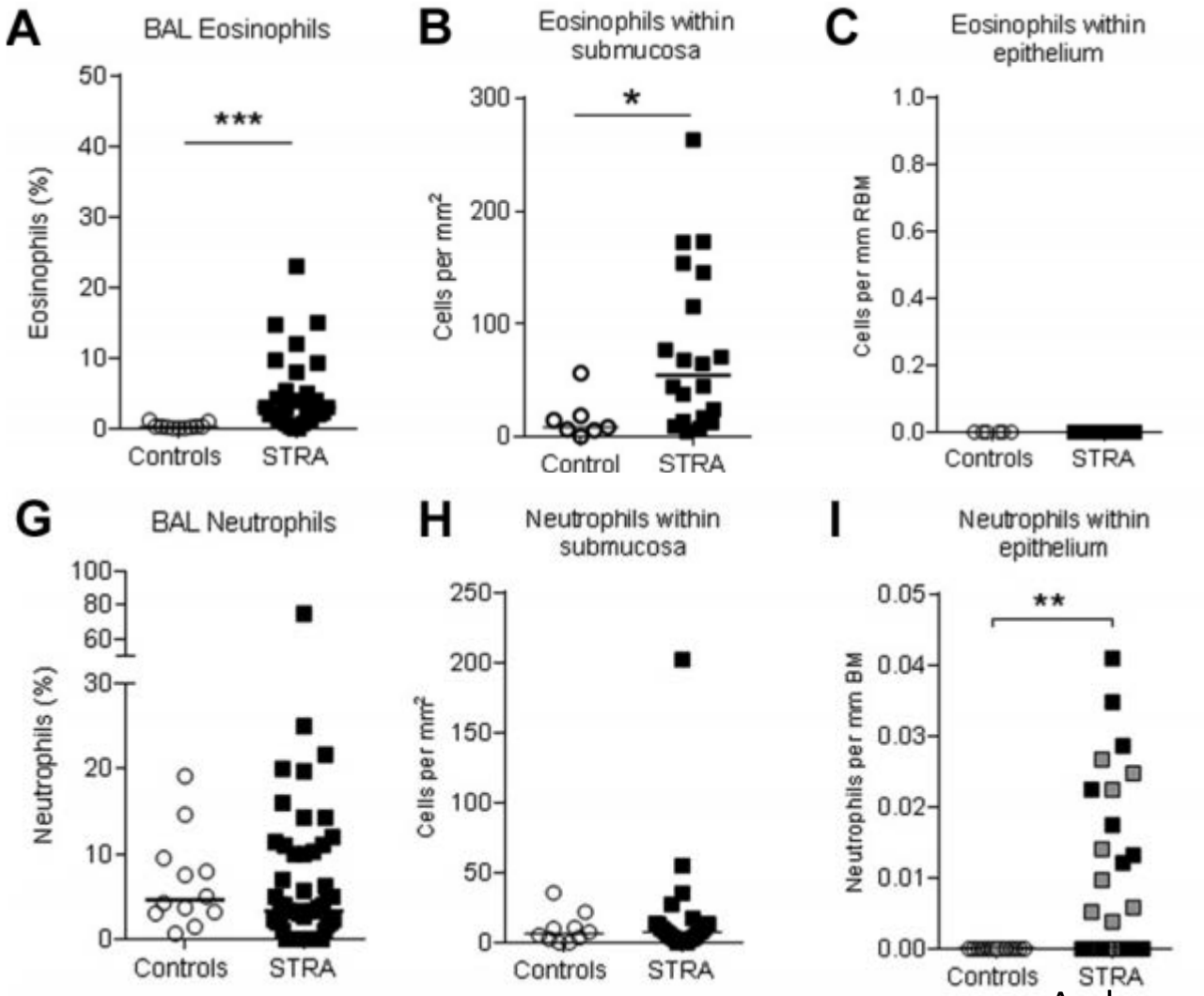
Tip 2 astım



Non Tip 2 astım

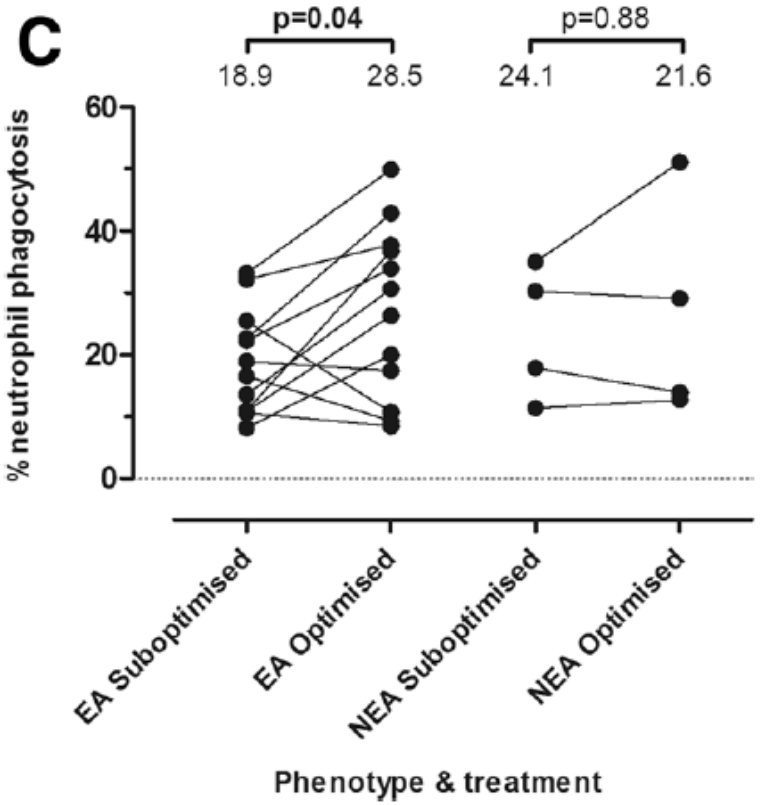
Palomares O, et al. Immunol Rev 2017;278:219-36

Ağır Astımda Nötrofillerin Rolü (Ne dereceye kadar?)



Andersson CK, et al. JACI 2017;1819-29

Nötrofillerin Rolü Var mı?



Artmış balgam nötrofil oranı:

1. İnflamasyondaki artışı
2. Eozinofil ve makrofajlar gibi diğer inflamatuar hücrelerdeki kısmi azalmayı
3. Doku ve lümen arasındaki nötrofil dağılımındaki değişikliği
4. IL-17 aracılı nötrofil göçündeki artışı gösterir.

Brooks CR. BMC Pulm Med 2017;17:169

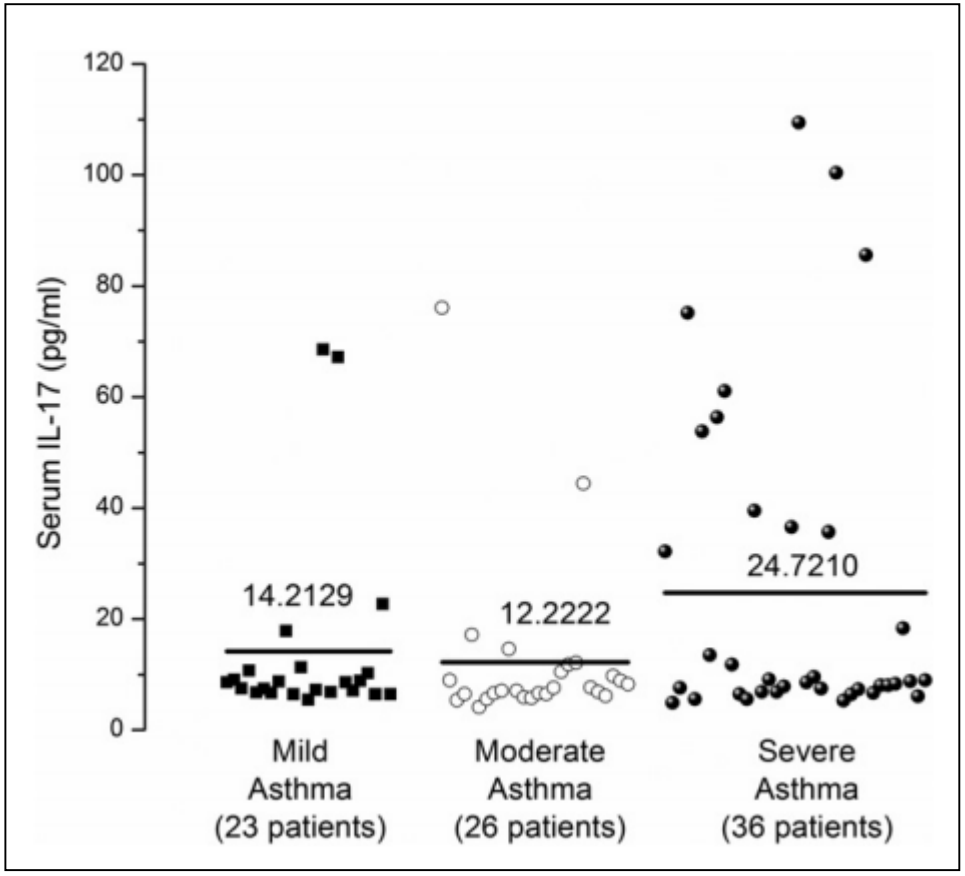
Nötrofillerin Rolü Var mı? (Ne dereceye kadar?)

Artmış balgam nötrofil oranı:

1. İnflamasyondaki artışı
2. Eozinofil ve makrofajlar gibi diğer inflamatuar hücrelerdeki kısmi azalmayı
3. Doku ve lümen arasındaki nötrofil dağılımındaki değişikliği
4. IL-17 aracılı nötrofil göçündeki artışı gösterir.

Anatomik lokalizasyonu (intraepitelyal, lamina propria veya lümen içi), aktivasyon durumunu ve fonksiyonel fenotiplerin belirlenmesi çok önemlidir.

IL-17 Ağır Astımda Önemli Bir Biomarkerdır



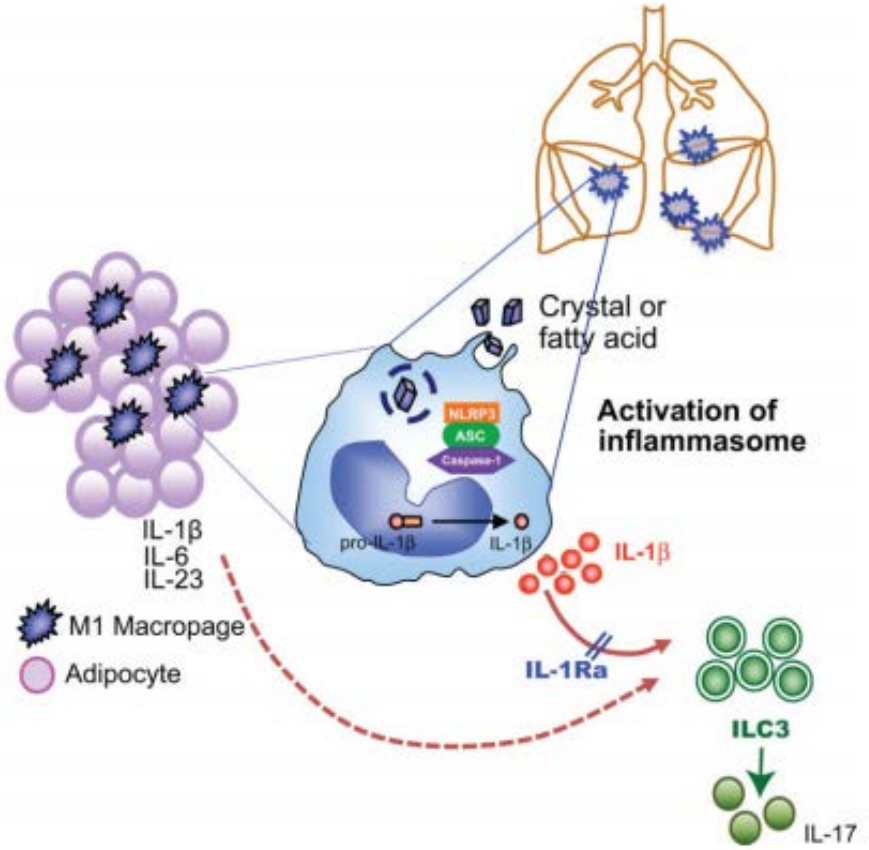
- IL-17A;
  - Nötrofilik havayolu inflamasyonu
  - Mukus gland hiperplazisi
  - Havayolu aşırı cevabı
  - Steroid “rezistansı”ndan sorumludur

Agache I, et al. Respir Med 2010; 104, 1131-7

Th17 Yolağı

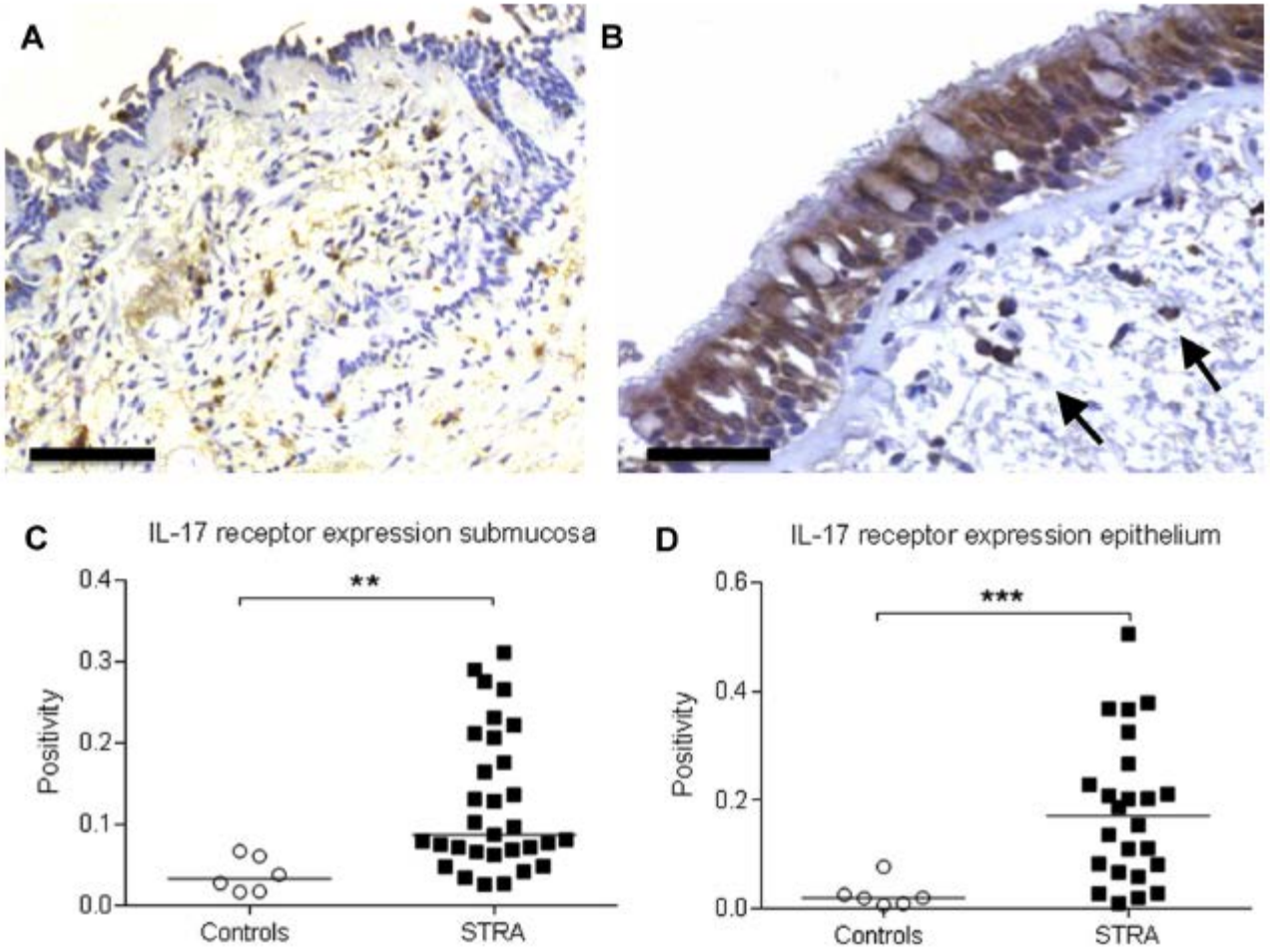
IL-17 Kaynakları

- Th17 hücreleri
- ILC3 (obez ağır astımda BAL'da artmıştır)



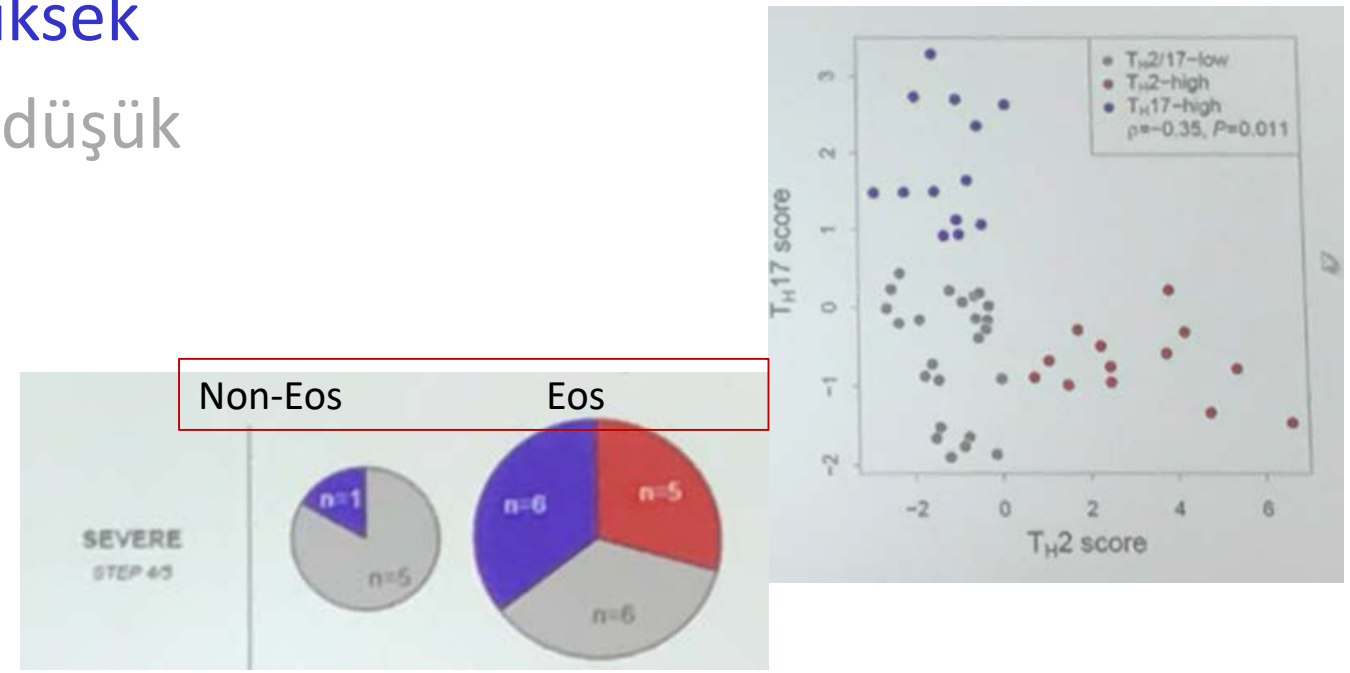
Kim HY, et al. Nat Med 2014;20:54-61

Havayolları IL-17'ye çok duyarlıdır



Andersson CK, et al. JACI 2017;1819-29

- IL-13 ve IL-17A Bronş Epitel hücrelerinde Th2 ve IL-17 signature genlerini indükte eder
- Buna göre 3 astım subgrubu tanımlanmıştır
  - Th2-yüksek
  - Th17-yüksek
  - Th2/17-düşük



Choy D, et al. Sci Transl Med 2015;301: 301

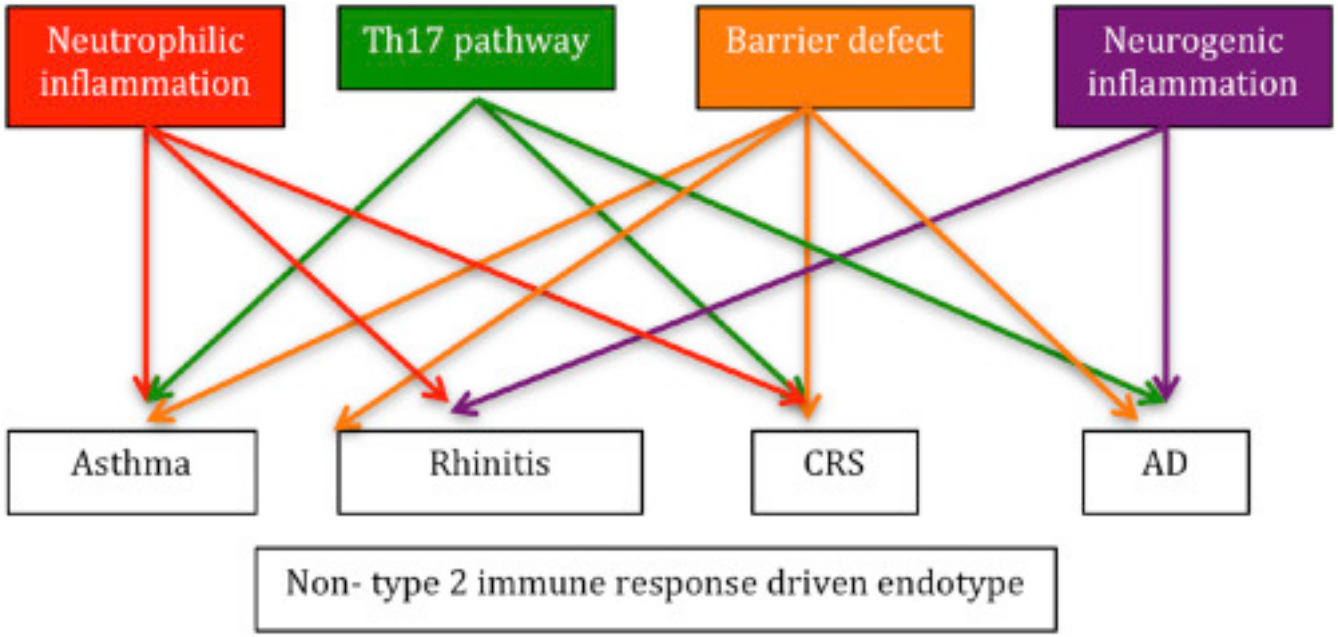
The Journal of Immunology

IL-17A Promotes the Exacerbation of IL-33–Induced Airway Hyperresponsiveness by Enhancing Neutrophilic Inflammation via CXCR2 Signaling in Mice

Nobuaki Mizutani,* Takeshi Nabe,† and Shin Yoshino*

- IL-17A ile birlikte CXCR2 sinyali üzerinden nötrofilik inflamasyonu arttırarak BHR'yi tetikler
- CXCR2 sinyal-aracılı TH2 cevapları arttırır

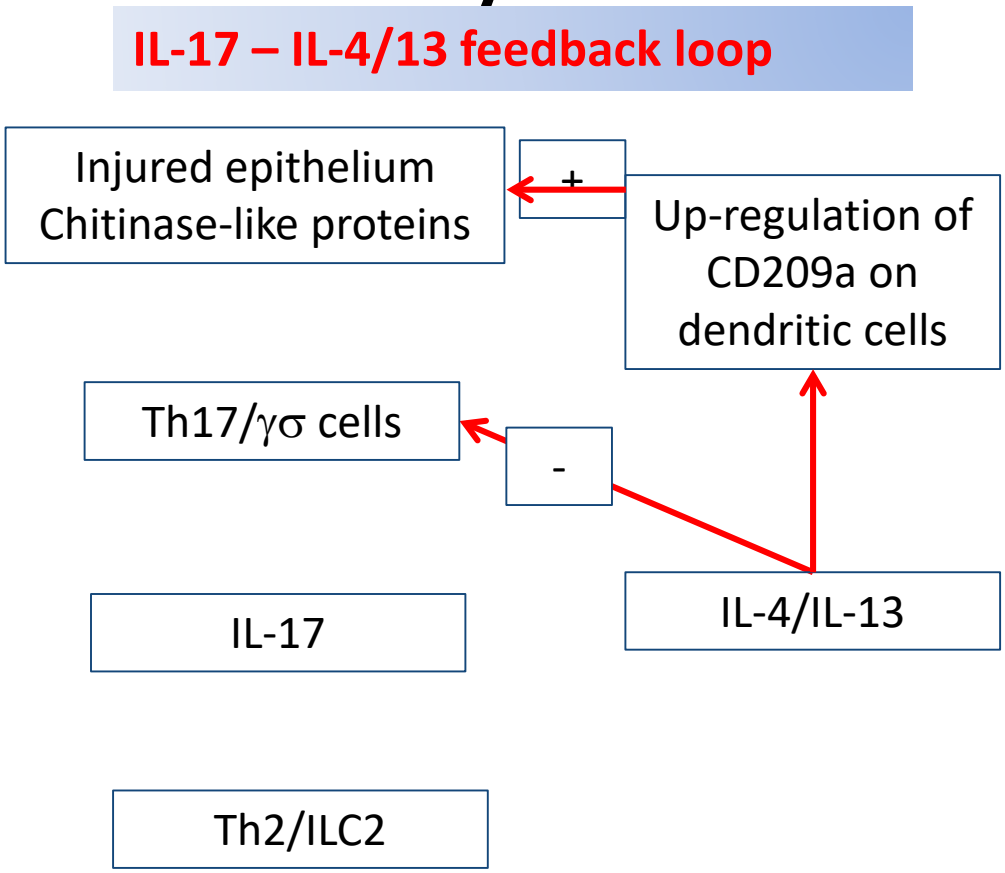
Mizutani N, et al. J Immunol 2014;192:1372-84



Agache I, et al. Allergology International 2016;65:243-52

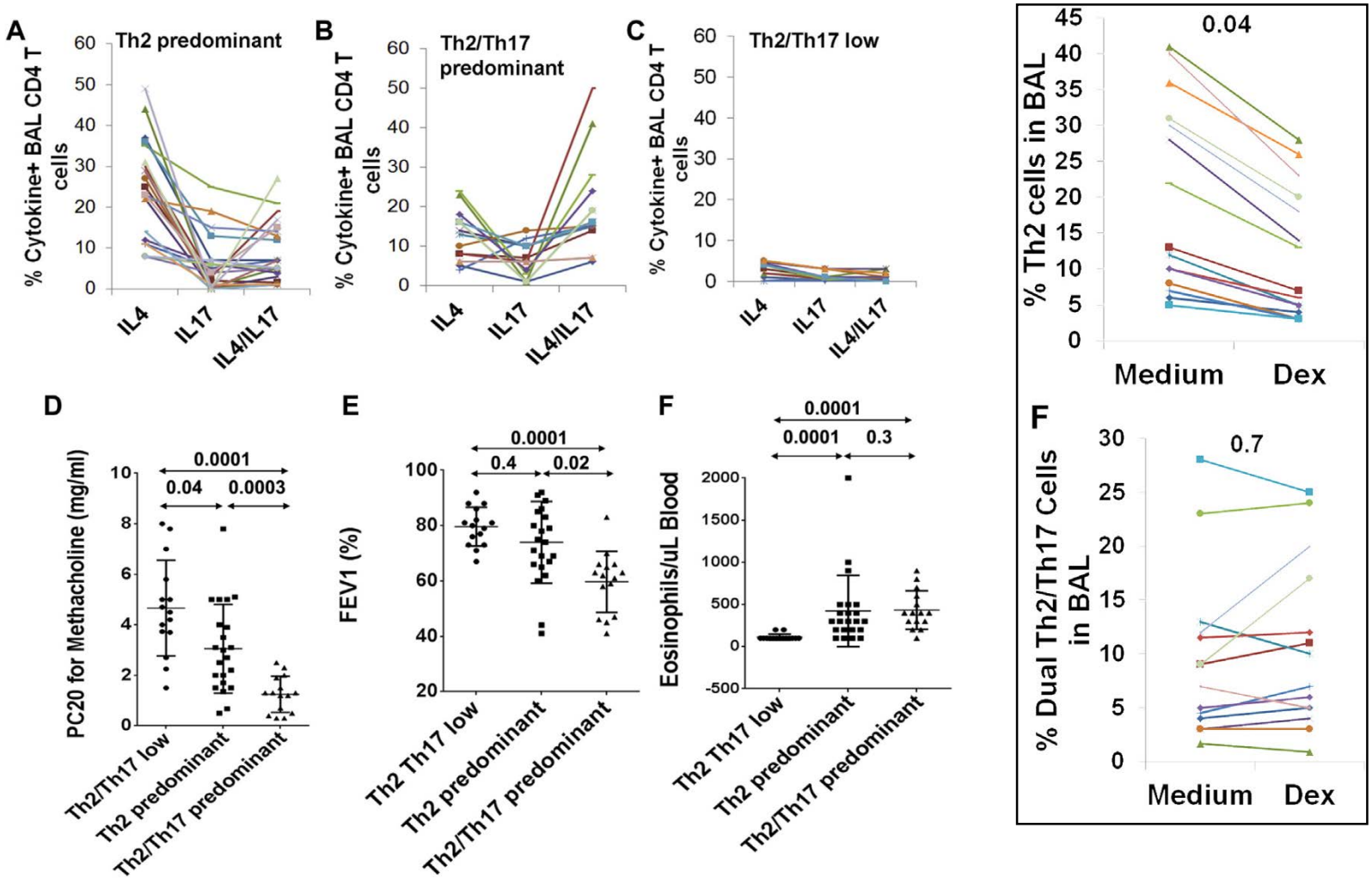
Miks Th17/Th2 aktivasyonu

- Astımda bazı Th2 hücreler dual-pozitif hücrelere diferansiye olur
- Dual-pozitif Th2/Th17 grubunda steroid rezistansı vardır.
- En fazla havayolu obstrüksiyonu ve hiperreaktivitesi bu grupta görülür.



Irvin L, et al. J Allergy Clin Immunol 2014;134: 1175-86

Miks Th17/Th2 aktivasyonu

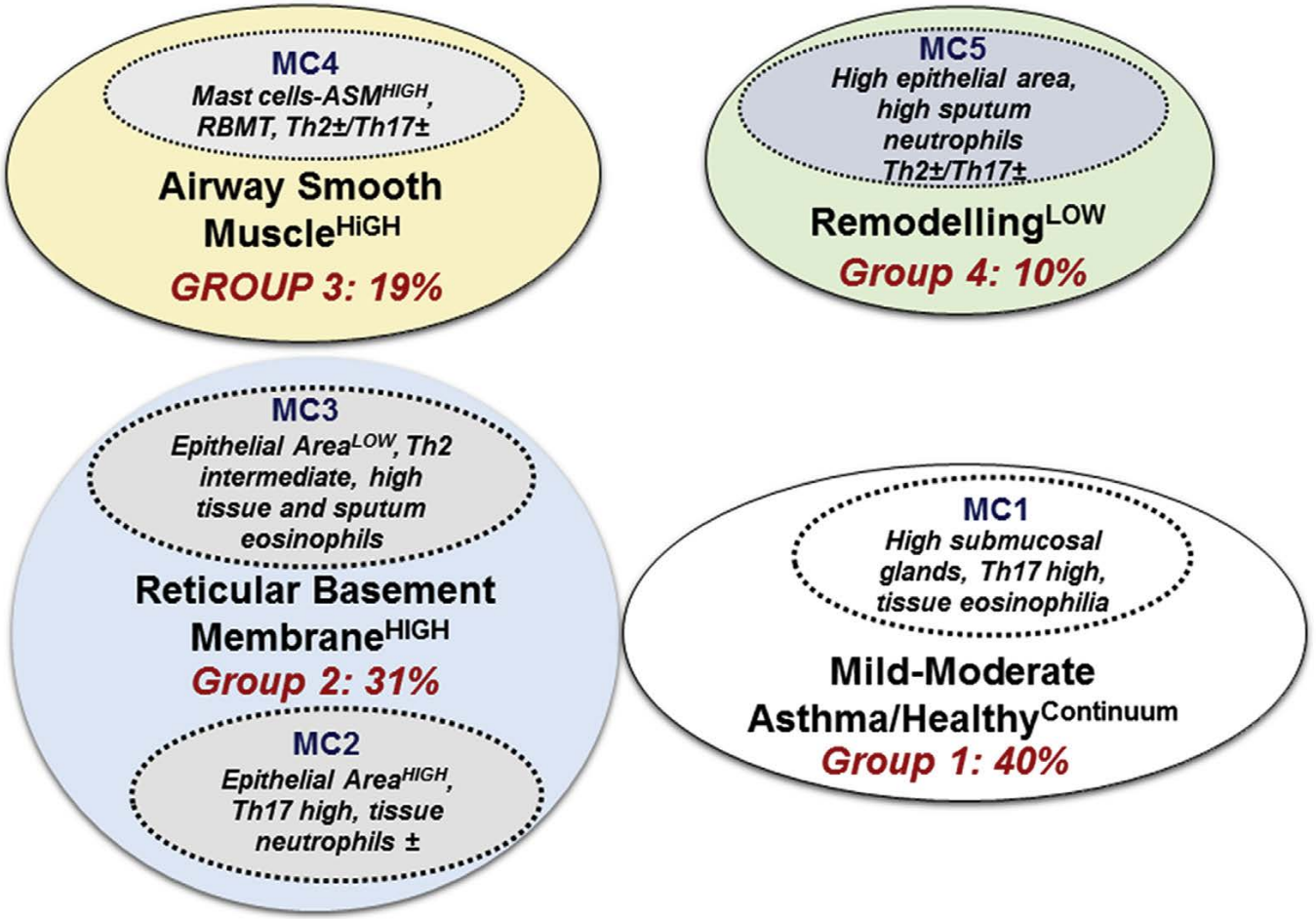


Irvin L, et al. JACI 2014;134: 1175-86

Ağır Astım'da İnflamasyon

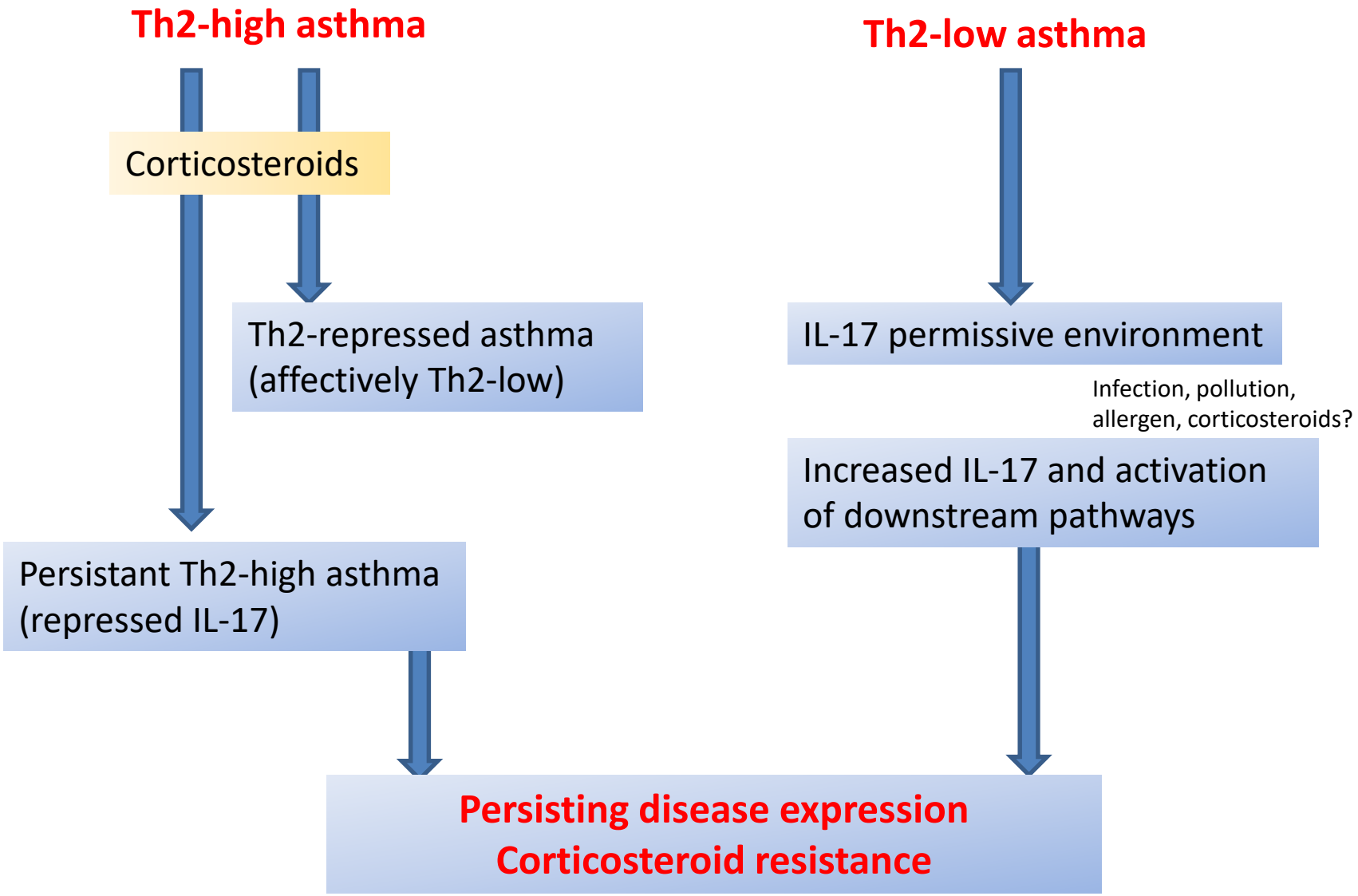
Choy D, et al. Sci Transl Med 2015;301: 301
Irvin L, et al. JACI 2014;134: 1175-86

Ağır Astımda Immunofenotipleme



Siddiqui S, JACI 2018

Tip 2 vs IL-17 Astım Özeti



T1/T2 Mikst Inflamasyon

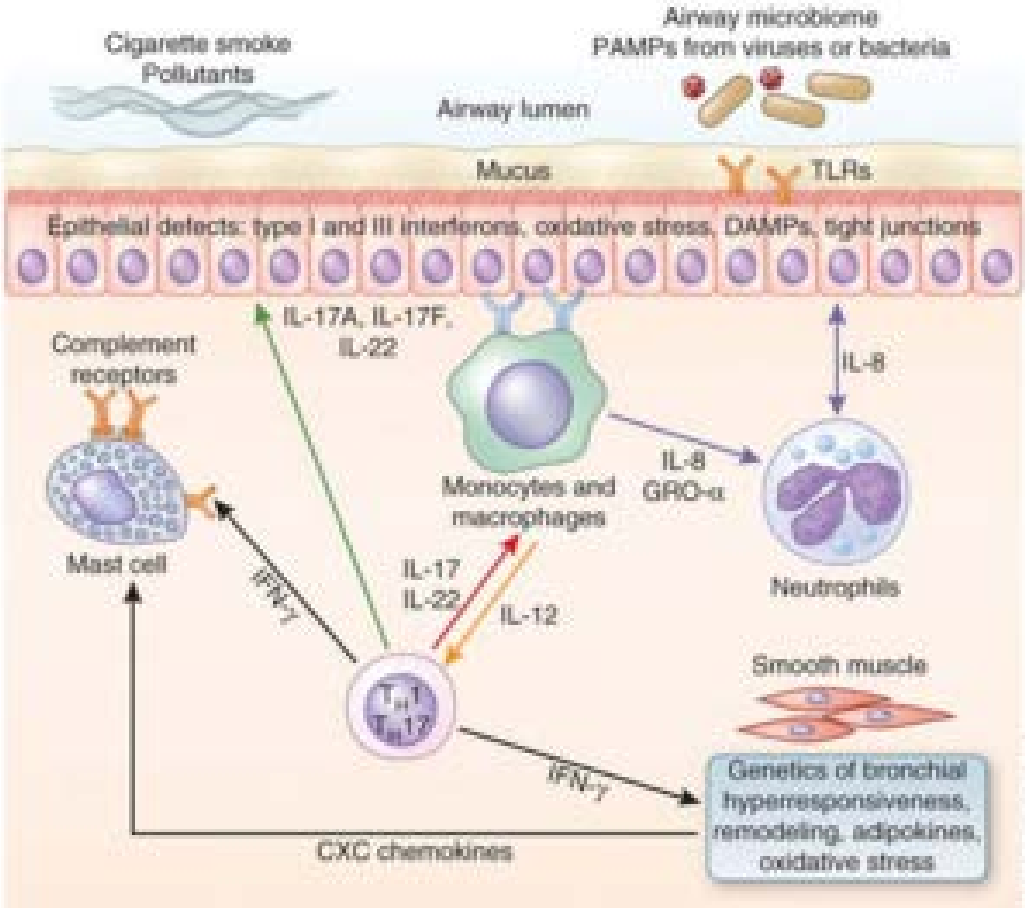
- Obezite/HDM miks lokalize inflamatuar cevapları başlatır (T1 ve T2)

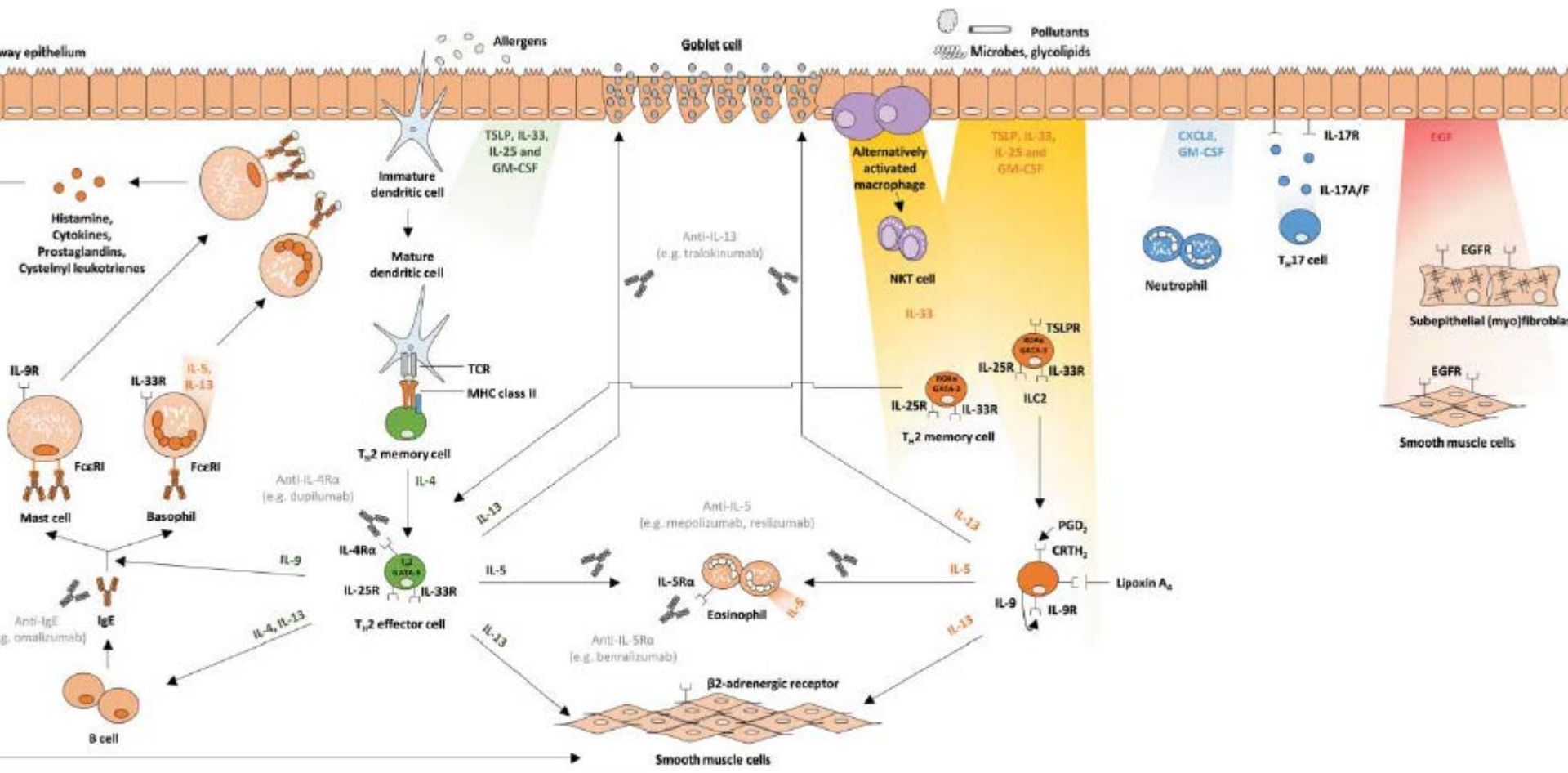
  Diaz J. Immunol Res 2015;63:197-208

T1/T17 Mikst Inflamasyon

Çocukluk astımında transkriptomik kümeler:

Yeh EL, et al. Clin Exp Allergy 2018; 14





Low Eos+Low FeNO

(a) Allergic eosinophilic asthma	(b) Nonallergic eosinophilic asthma	(c) Neutrophilic asthma	(d) Paucigranulocytic asthma
(A) Type 2 asthma		(B) Non-type 2 asthma	

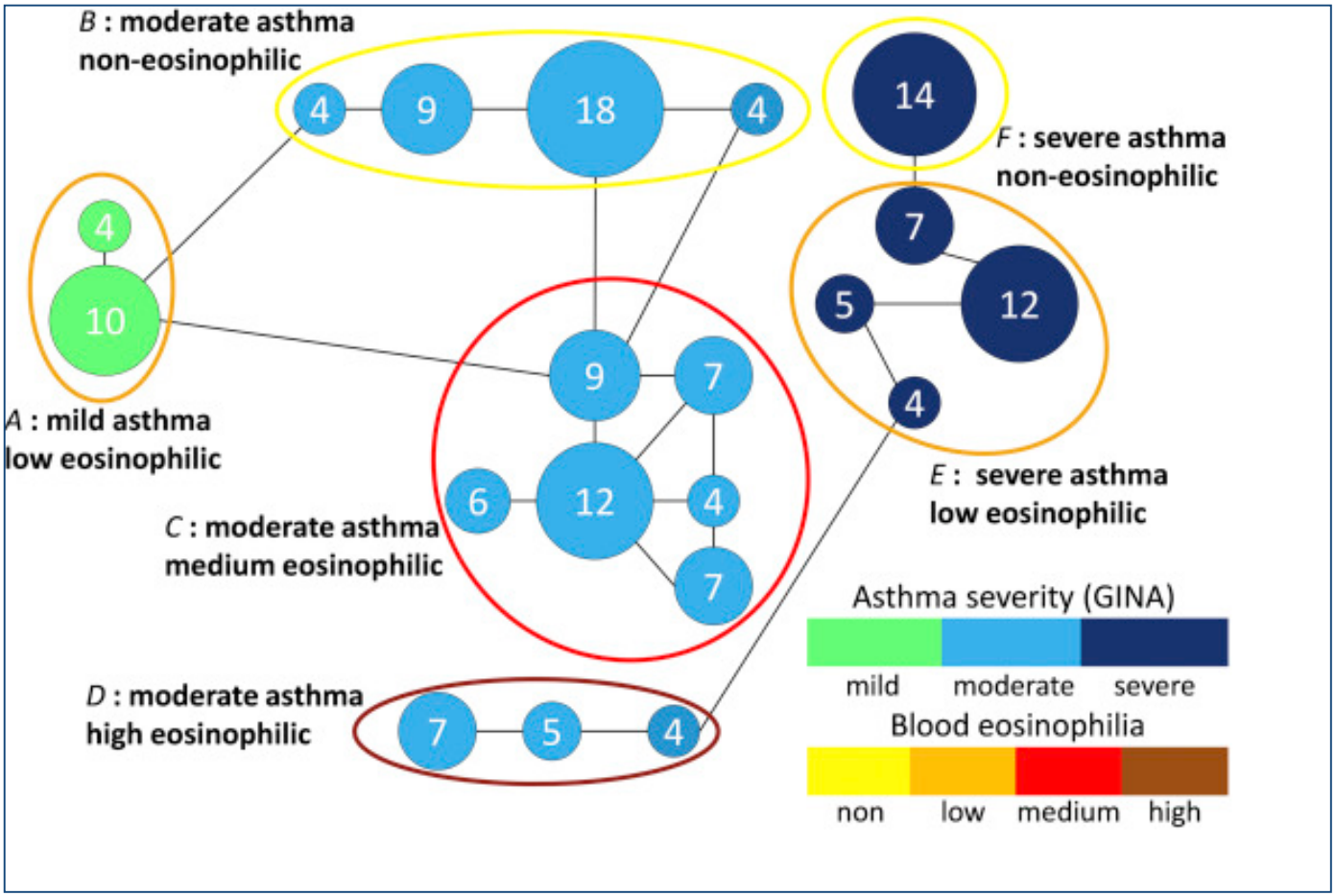
Th2/mast h
Eozinofilik inflamasyon
IgE

NKT, ILC2, IL-5,
Eoz/Nötrofilik
inflamasyon

IL-17, CXCL8

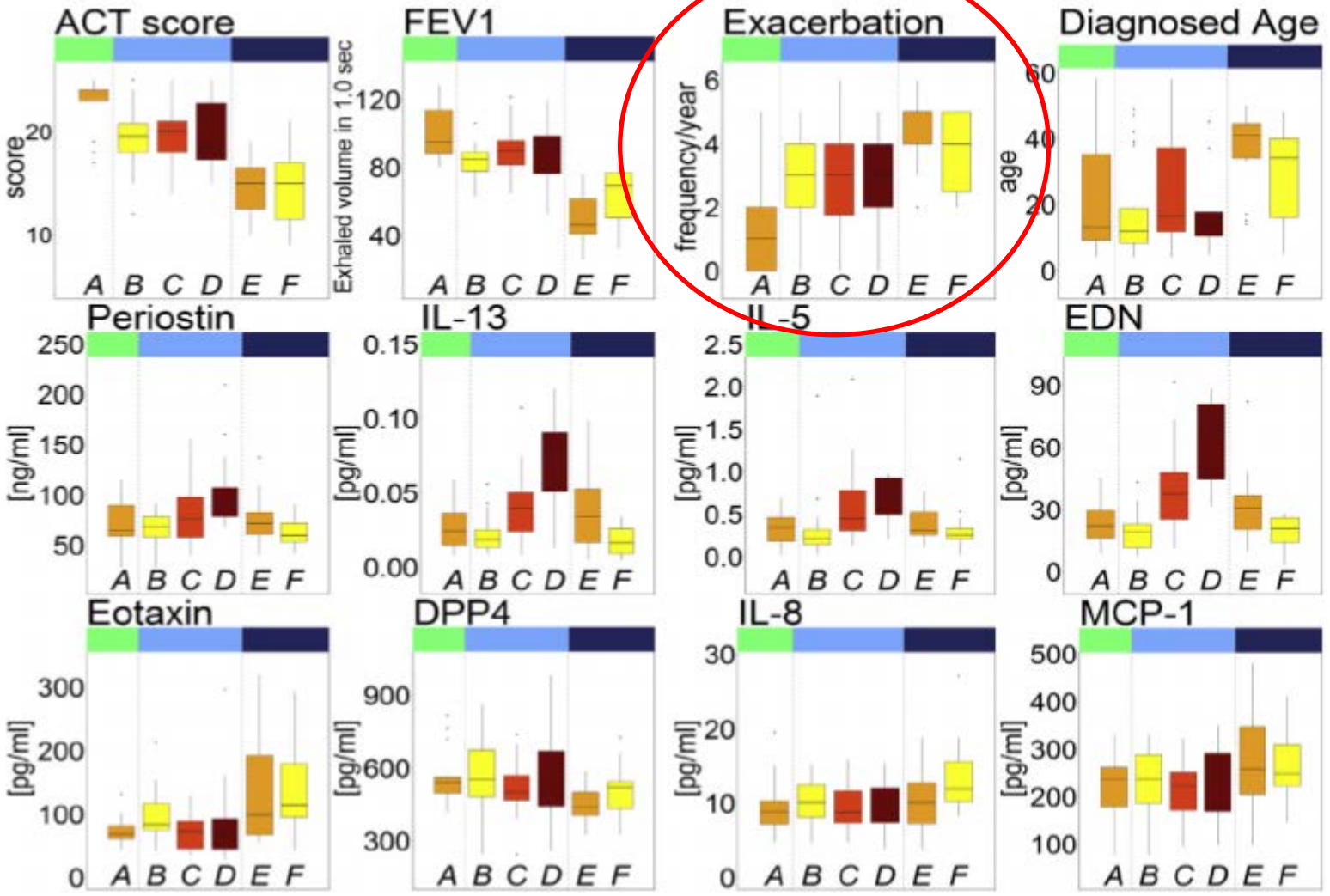
Inflamasyon?

Godar M, et al. MABS 2018; 10:34–45



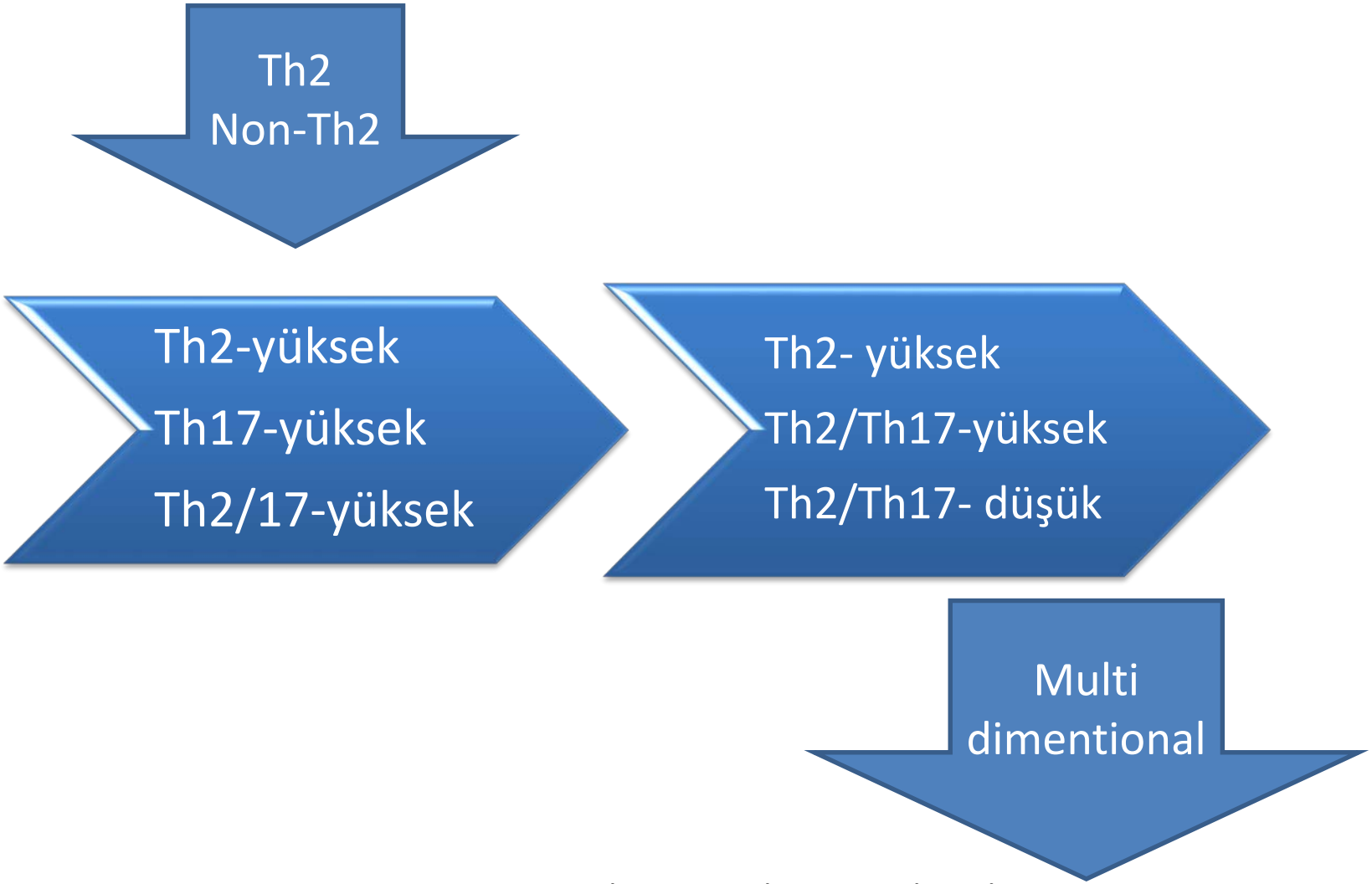
Agache I, et al. J Allergy Clin Immunol 2018;141:442-5

Çok yönlü endotipleme



Agache I, et al. J Allergy Clin Immunol 2018;141:442-445

Ağır Astım'da İnflamasyon



Choy D, et al. Sci Transl Med 2015;301: 301
Irvin L, et al. JACI 2014;134: 1175-86

Ağır Astım'da İmmünolojik Mekanizmalar: -Bilmediklerimiz-

- IL-17 _IL-4/13 feed-back loop'u neyin regüle ettiğini bilmiyoruz.

- Mast hücresinin IL-33 aracılı Th2 sitokinlerinin, öz. IL-13, sentezine neden olan uyarı mekanizması bilinmemektedir.

- Prostaglandin D2'nin bir reseptörü olan CRTHS insan ILC2 üzerinde mevcuttur. Ancak CRTH2'nin bu hücreler üzerindeki fonksiyonları net değildir.

Allergy
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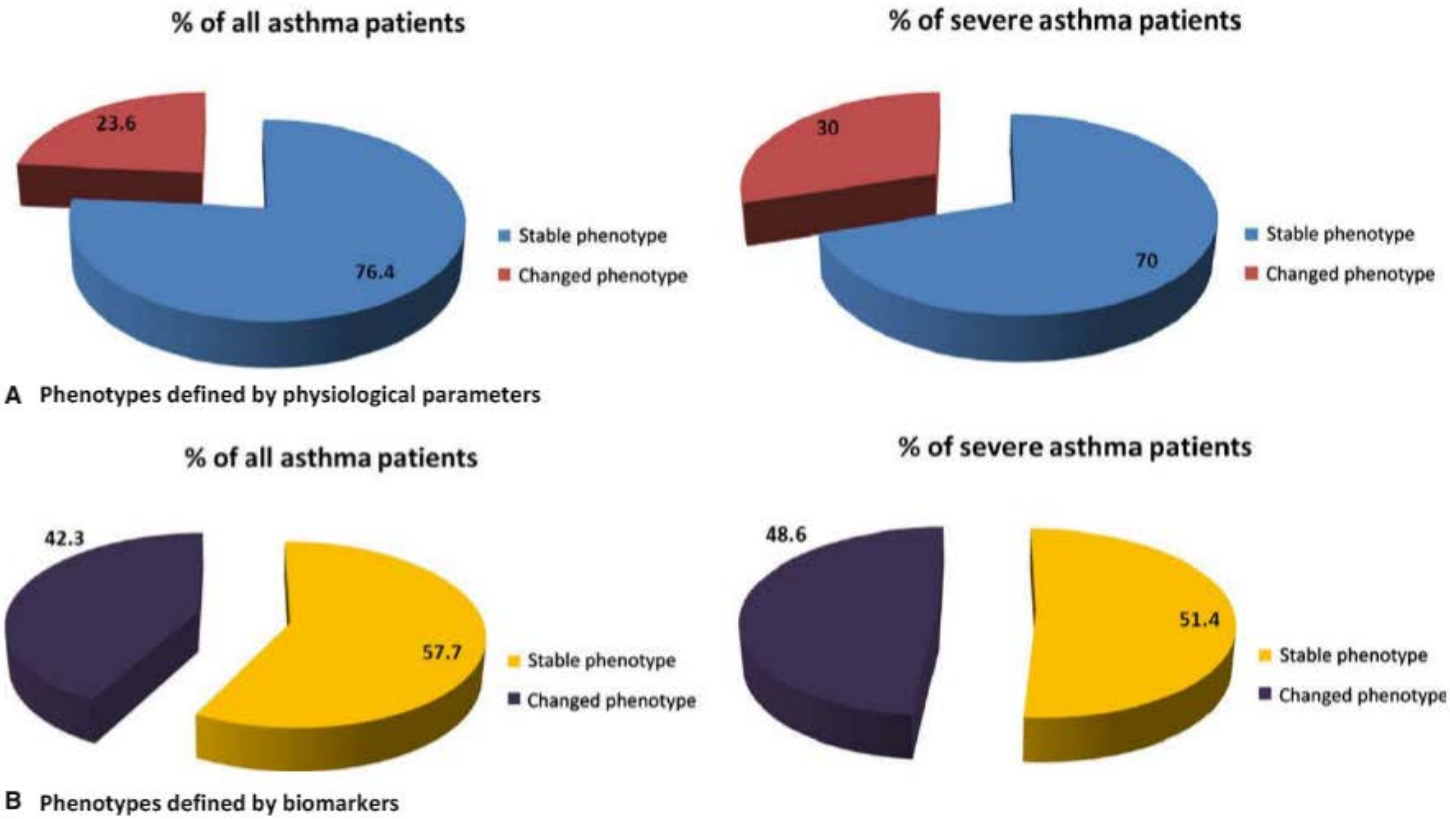
EAACI Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

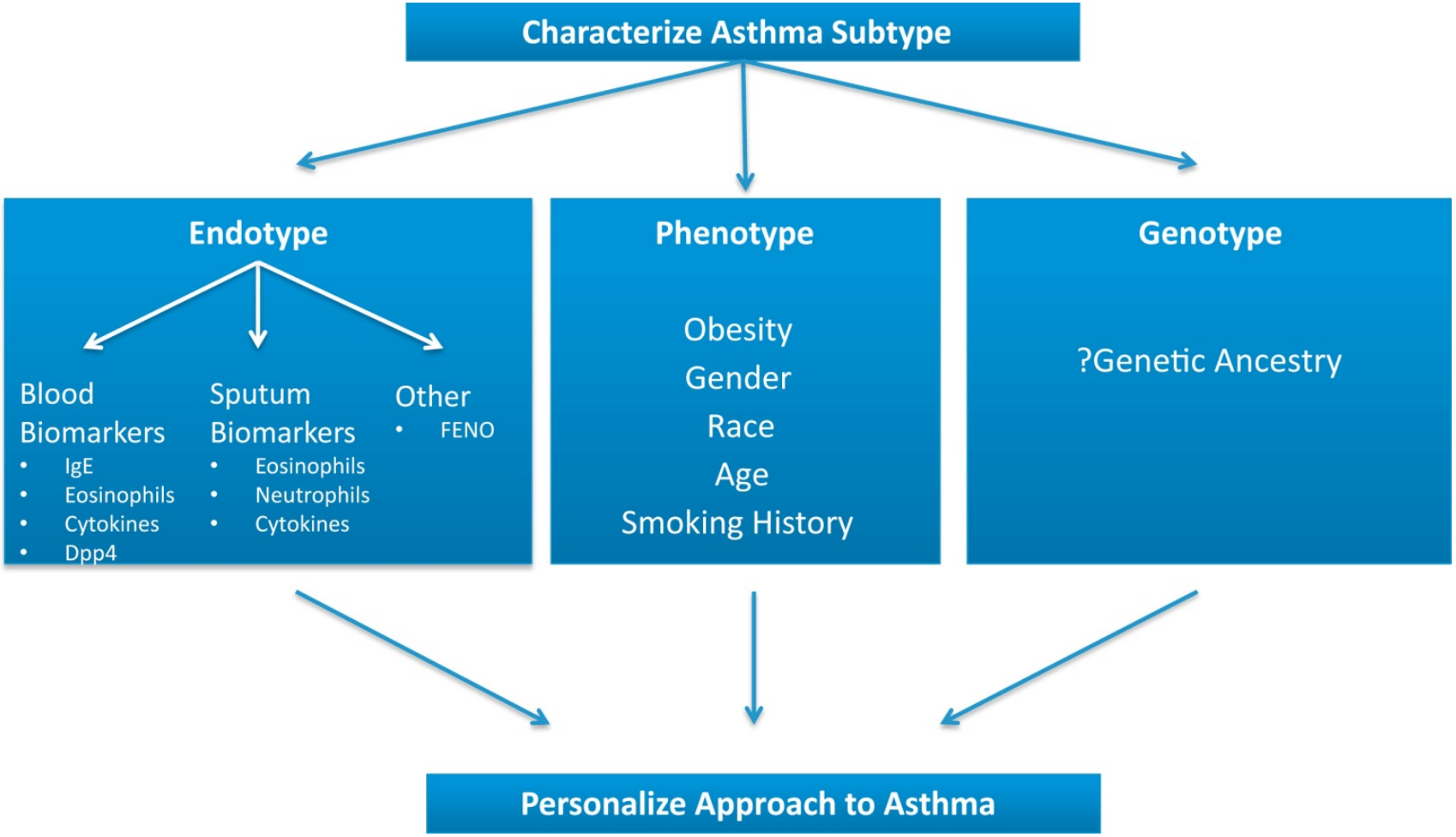
Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma



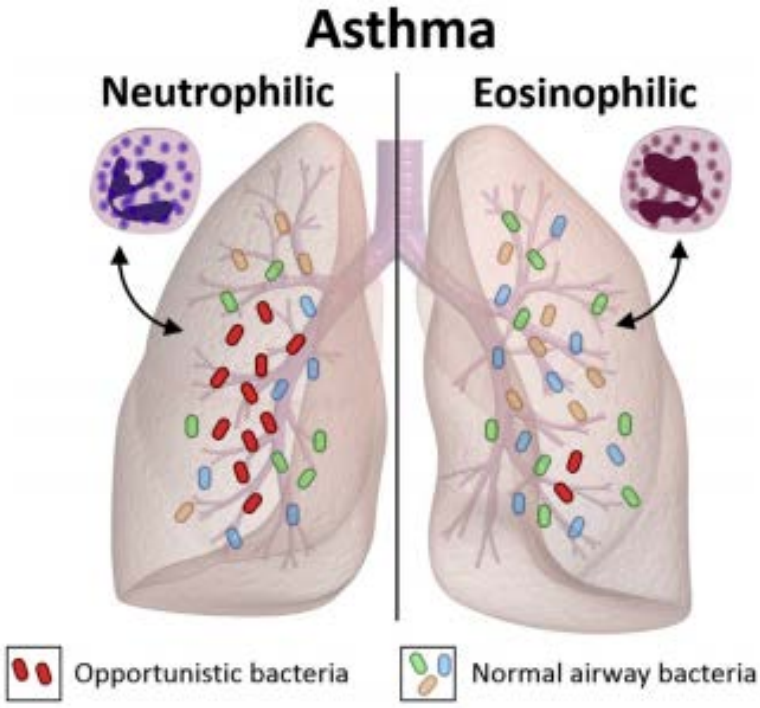
Kupczyk M, et al. Allergy 2014; 69:1198-1204

Fenotip ve Endotipten Genotipe Geçiş

-Refractory asthma? Characterize subtype-



Dunn RM, et al. JACI 2016;5:1370-52


Asthma
Neutrophilic
Eosinophilic
Opportunistic bacteria
Normal airway bacteria

Sir John Bell,
Professor of Medicine
at Oxford University

"The best example of precision medicine in my opinion does not come from cancer, it comes from asthma. For this condition, we have gone more than 20 years without a new drug, because the disease was not defined very well"