Φαινότυποι από το κλινικό στο μοριακό επίπεδο

Ν. Τζανάκης

4ο Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης – Ημέρες Άσθματος 2014, με θέμα "ΦΑΙΝΟΤΥΠΟΙ & ΕΝΔΟΤΥΠΟΙ ΑΣΘΜΑΤΟΣ " 14-16 Μαρτίου 2014, Ξενοδοχείο Negroponte, Ερέτρια

?

Simplicity Vs. Versatility

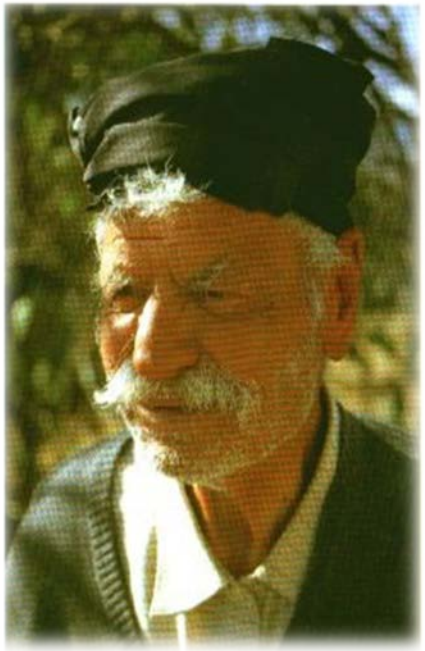
Examples

- 2 of my patients
- Cretans
- Age: 72 yrs
- FEV_1 (% pred): 34%

COPD A: The happy

Mr Manolis

COPD B: The unhappy



Mr Giannis

Examples: Their grandchildren

Asthma A: The happy

Manolis

- 2 of my patients
- Cretans
- Age: 8 yrs
- FEV_1 (% pred): 94%

Asthma B: The unhappy

Giannis

Phenotypes
Endotypes or
Personalized medicine

DEFINITION OF PHENOTYPE:

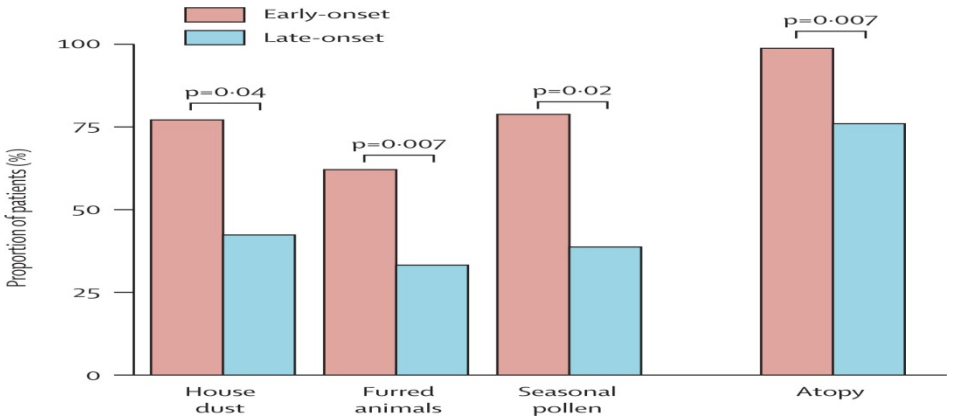
Observable properties of an organism that are produced by the interactions of the genotype and environment

Τι είναι κλινικός φαινότυπος

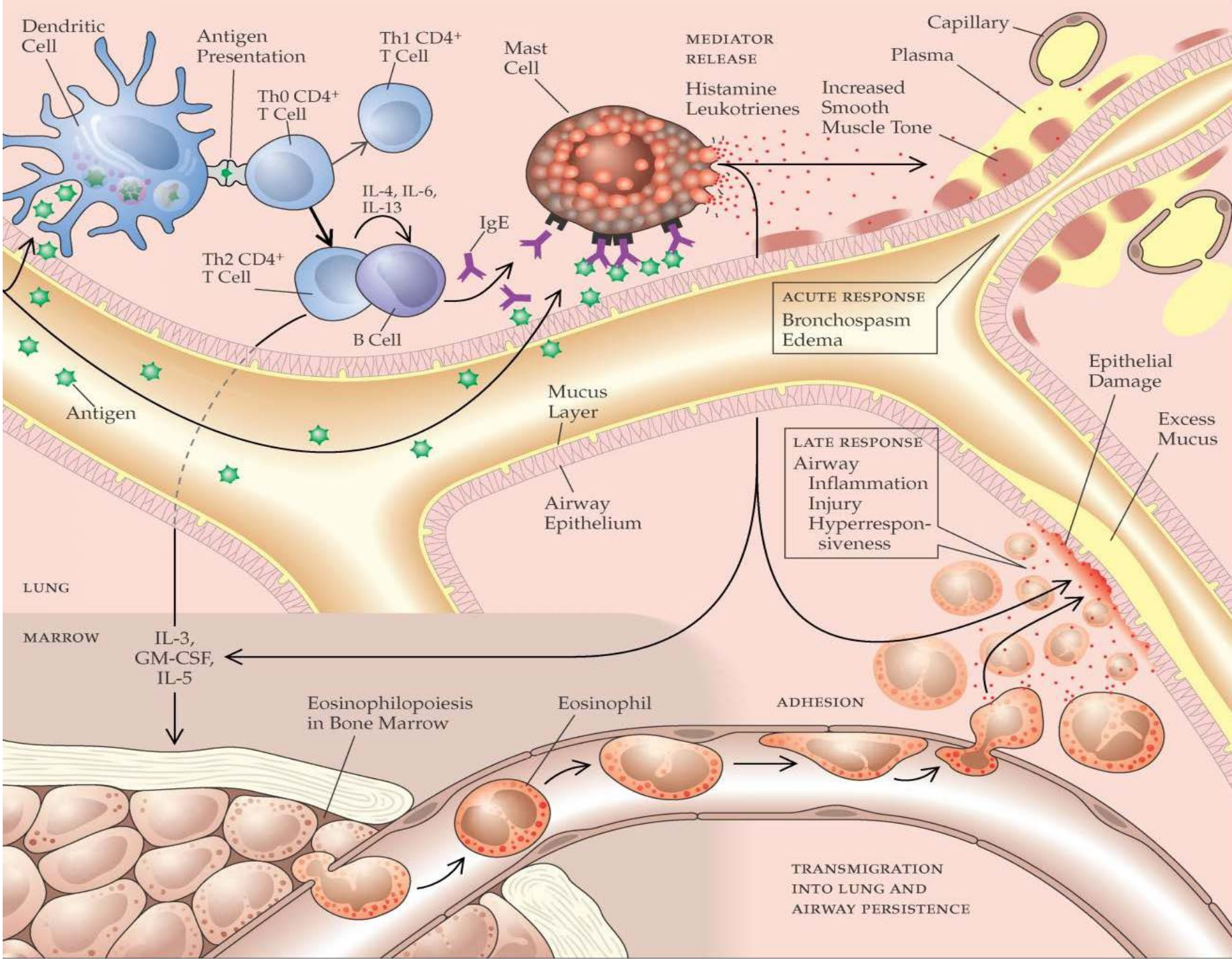
- Κάθε κλινικώς ενδιαφέρον χαρακτηριστικό που αποτελεί μέρος:
  - Της κλινικής εικόνας
  - Των λειτουργικών, βιοχημικών ή άλλων βιοδεικτών
  - Της συμπεριφοράς & τρόπου ζωής
- *Η συνύπαρξη ενός κρισίμου συνόλου αυτών των χαρακτηριστικών οδηγεί στην φαινοτυπική εκδήλωση που δυνατόν να διαχωρίζει τους ασθενείς σε ομάδες διαφορετικής πρόγνωσης και πιθανώς διαφορετικής θεραπευτικής παρέμβασης*

Οι πρώτοι φαινότυποι

- Ολλανδική υπόθεση
- Εξωγενές άσθμα
- Ενδογενές άσθμα
- Αλλεργικό
- Μη αλλεργικό
- Πρώιμης έναρξης (<20 ετών)
- Καθυστερημένης έναρξης



C Miranda, A Busacker, S Balzar, J Trudeau, SE Wenzel
Distinguishing severe asthma phenotypes: role of age at onset and eosinophillic inflammation J Allergy Clin Immunol, 113 (2004), pp. 101–108

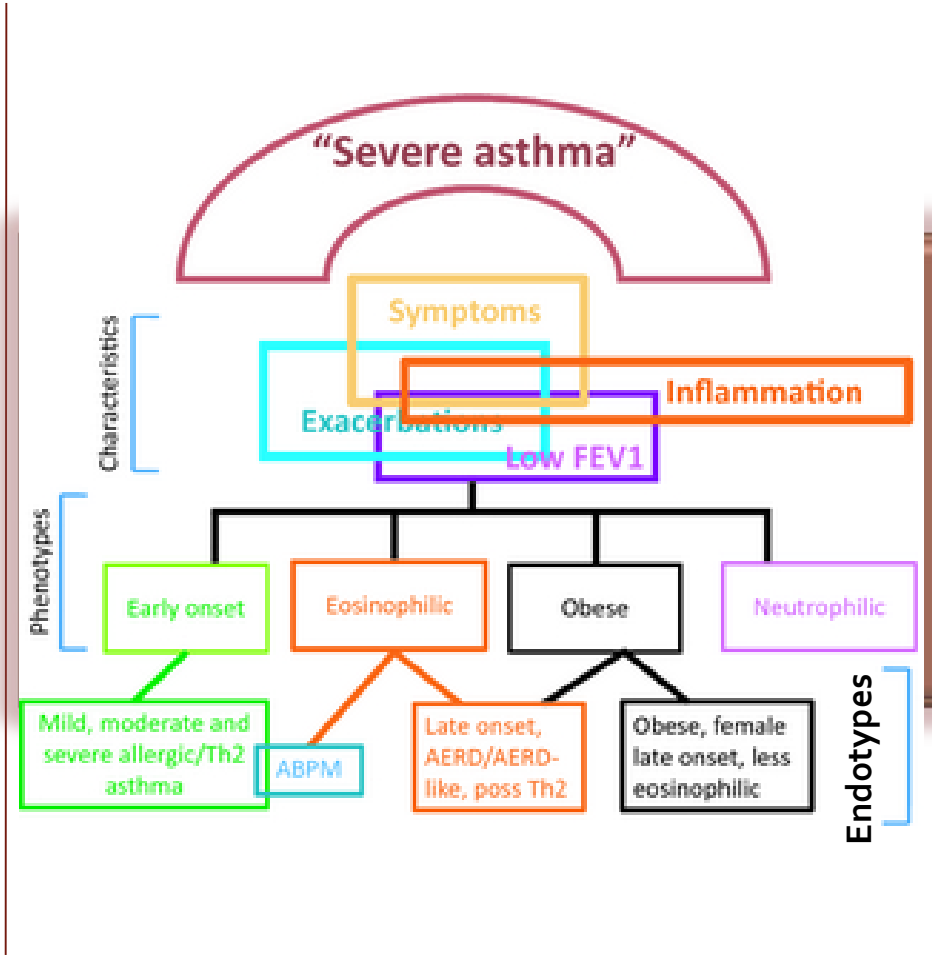

Dendritic Cell
Antigen Presentation
Th1 CD4+ T Cell
Th0 CD4+ T Cell
Mast Cell
MEDIATOR RELEASE
Histamine Leukotrienes
Increased Smooth Muscle Tone
Capillary
Plasma
IL-4, IL-6, IL-13
IgE
Th2 CD4+ T Cell
B Cell
ACUTE RESPONSE
Bronchospasm Edema
Epithelial Damage
Excess Mucus
Antigen
Mucus Layer
Airway Epithelium
LATE RESPONSE
Airway Inflammation Injury Hyperrespon-siveness
LUNG
MARROW
IL-3, GM-CSF, IL-5
Eosinophilopoiesis in Bone Marrow
Eosinophil
ADHESION
TRANSMIGRATION INTO LUNG AND AIRWAY PERSISTENCE

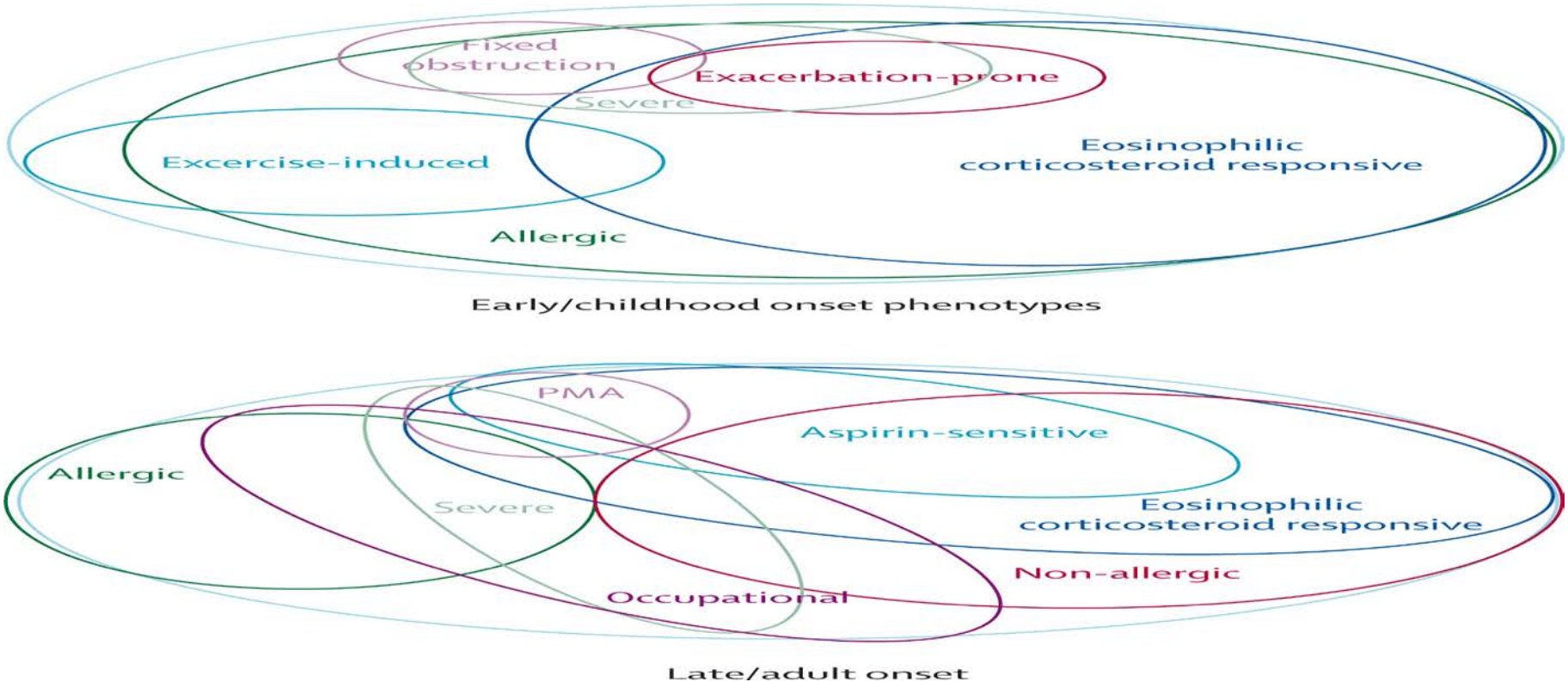
Large scale studies on difficult Asthma heterogeneity: Phenotypes vs. Endotypes

The ENFUMOSA
European multicentre study of the clinical phenotype of chronic severe asthma

The SARP
Severe Asthma Research Network

The TENOR
Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens cohort

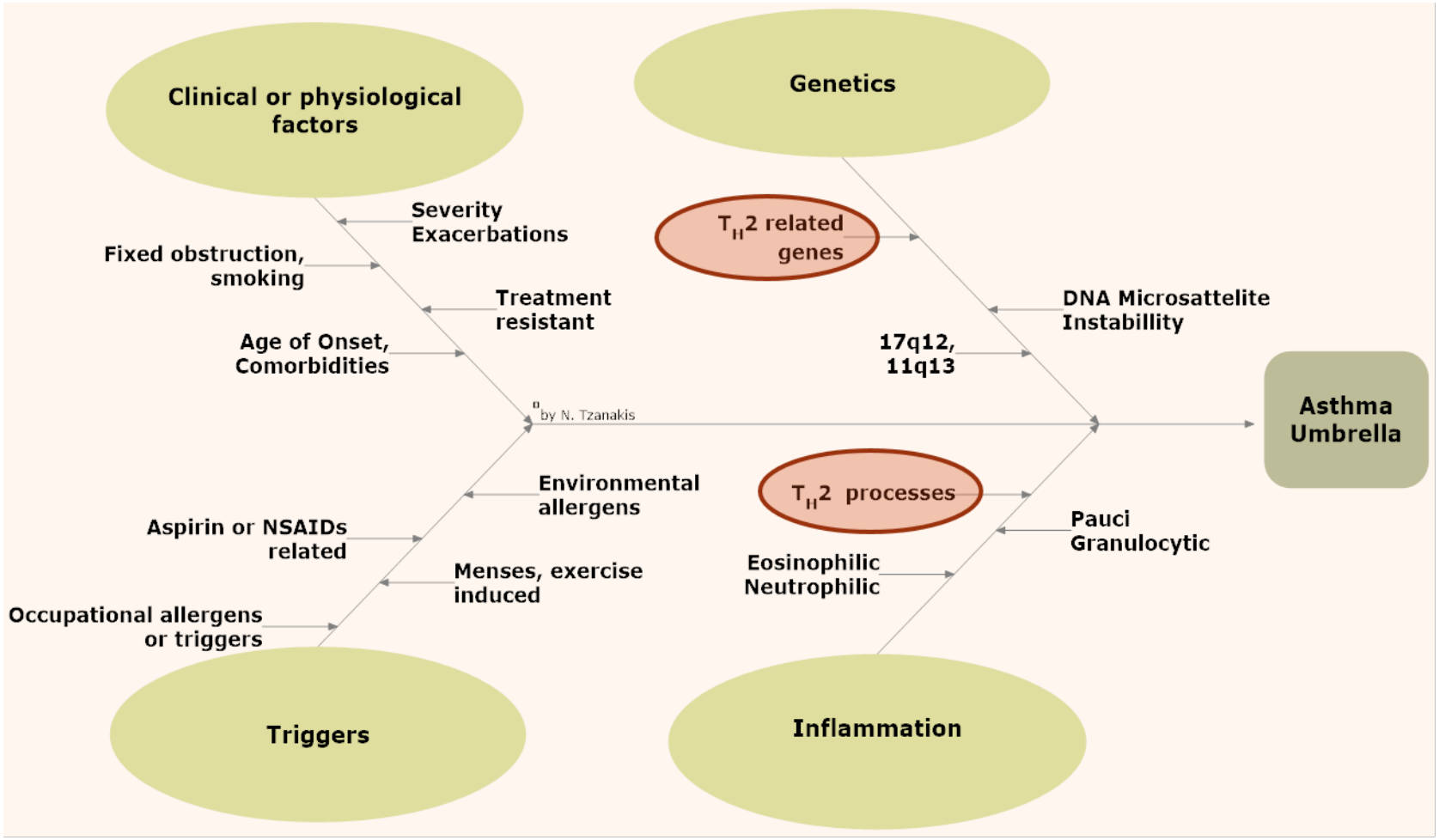




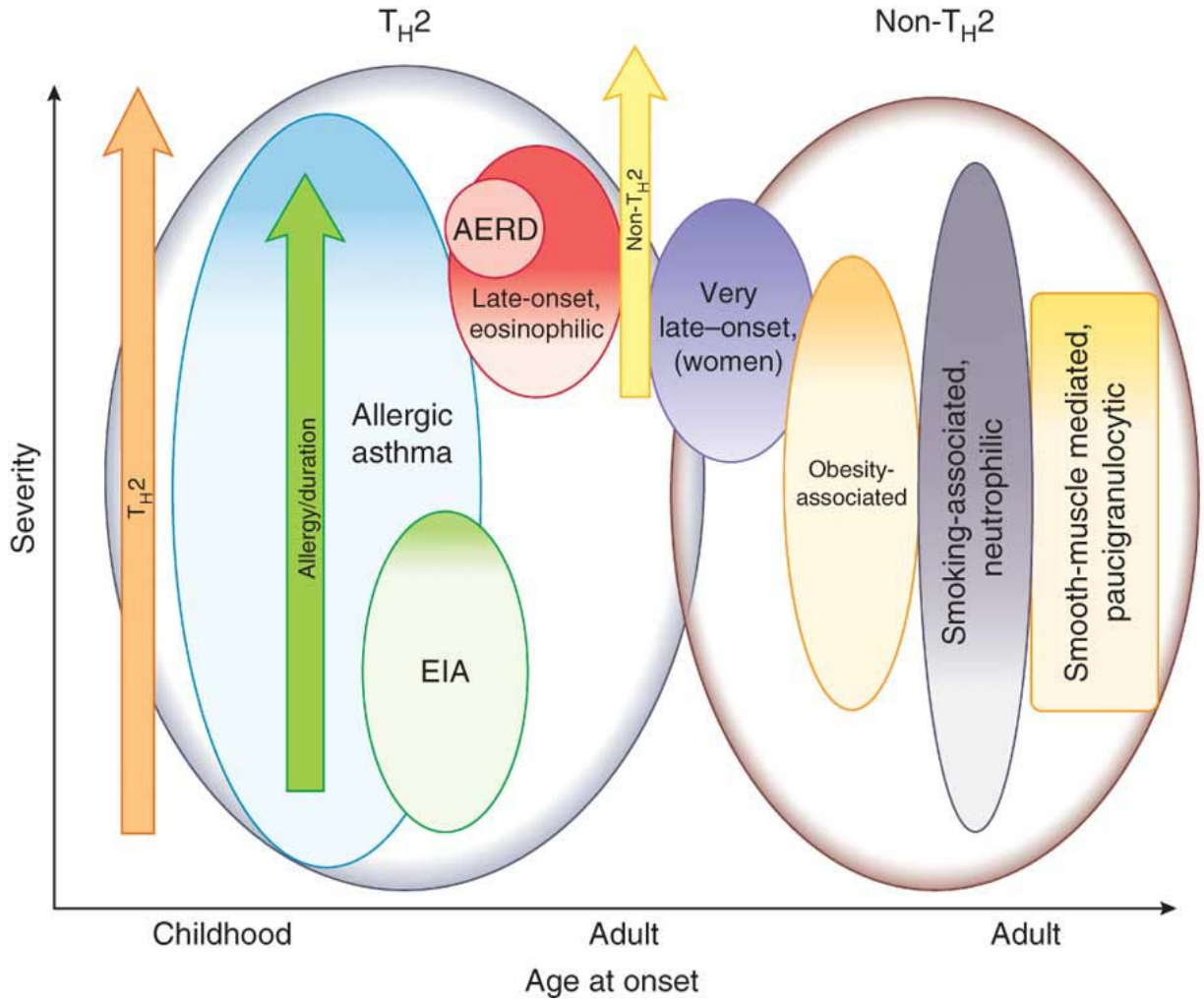
Venn diagram approach to identification of phenotypes of childhood-onset asthma and adult-onset asthma. PMA=perimenstrual asthma

Sally E Wenzel. **Asthma: defining of the persistent adult phenotypes.** The Lancet, Volume 368, Issue 9537, 2006, 804 - 813

Asthma phenotypes and the related characteristics

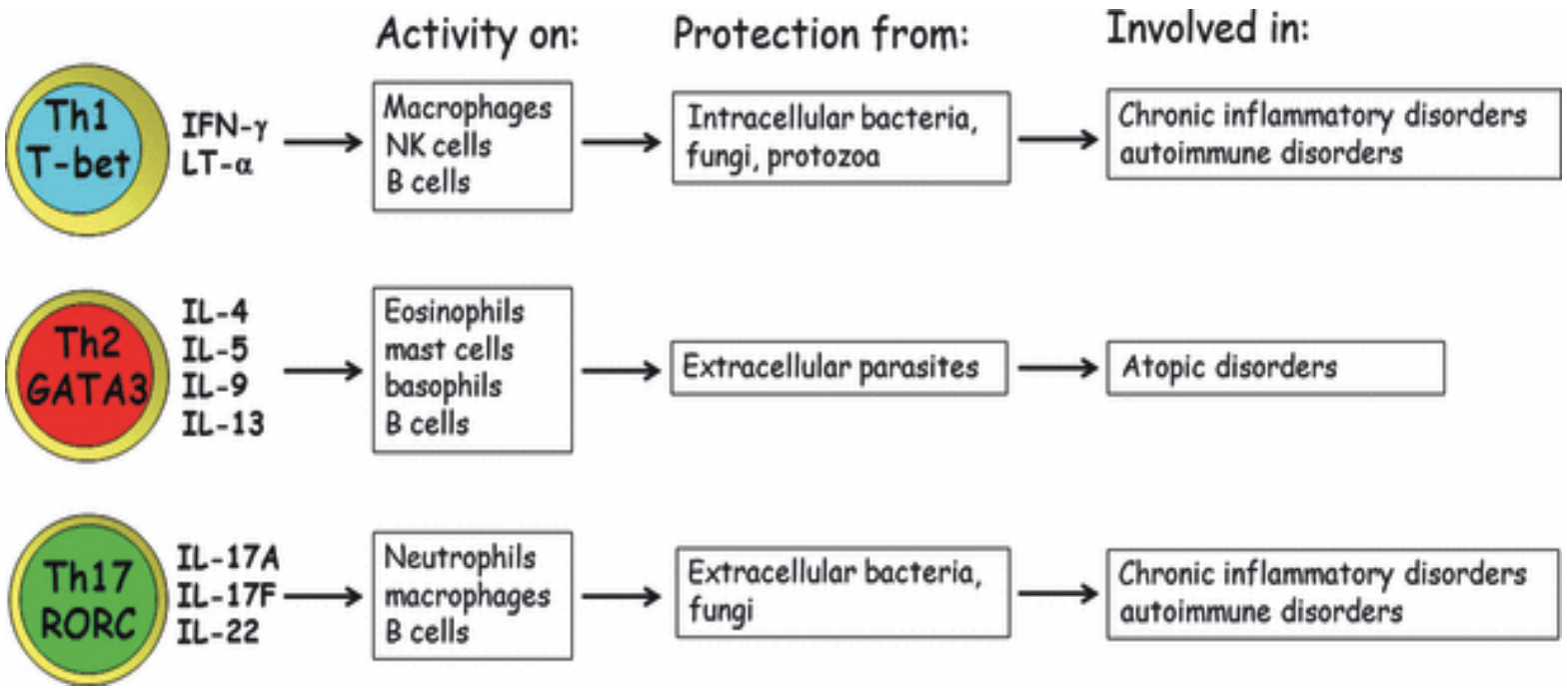


T_H2 / Non-T_H2 grouping

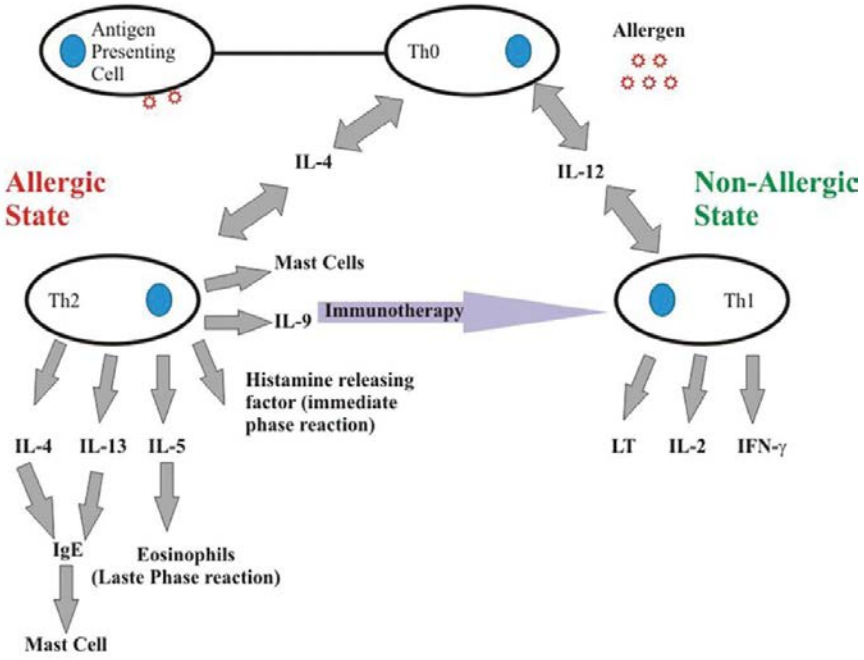


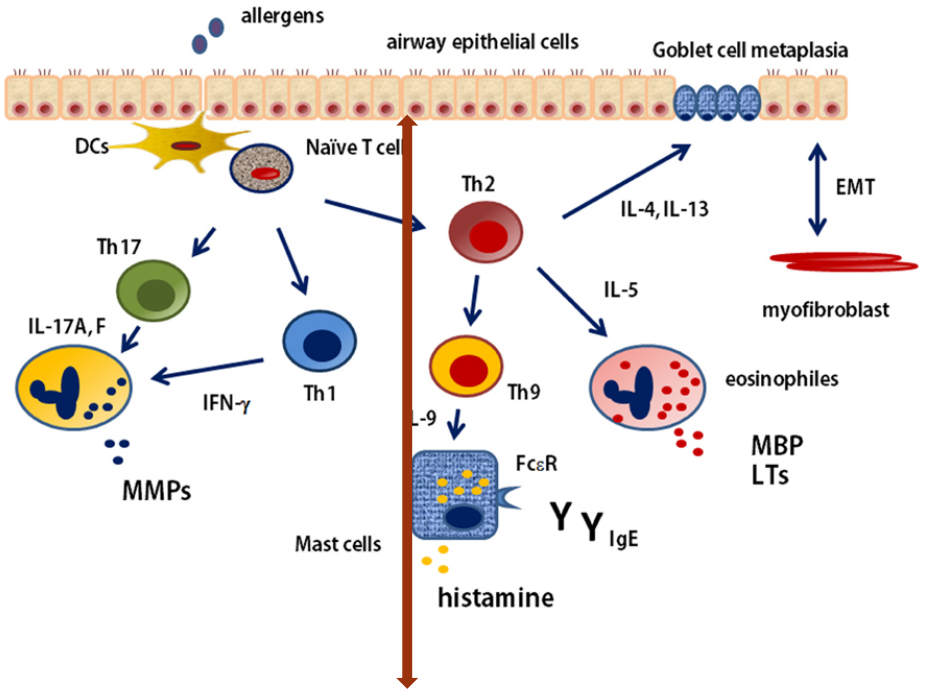
Wenzel S. Nature Medicine 2012

T helper subpopulation (T_H)

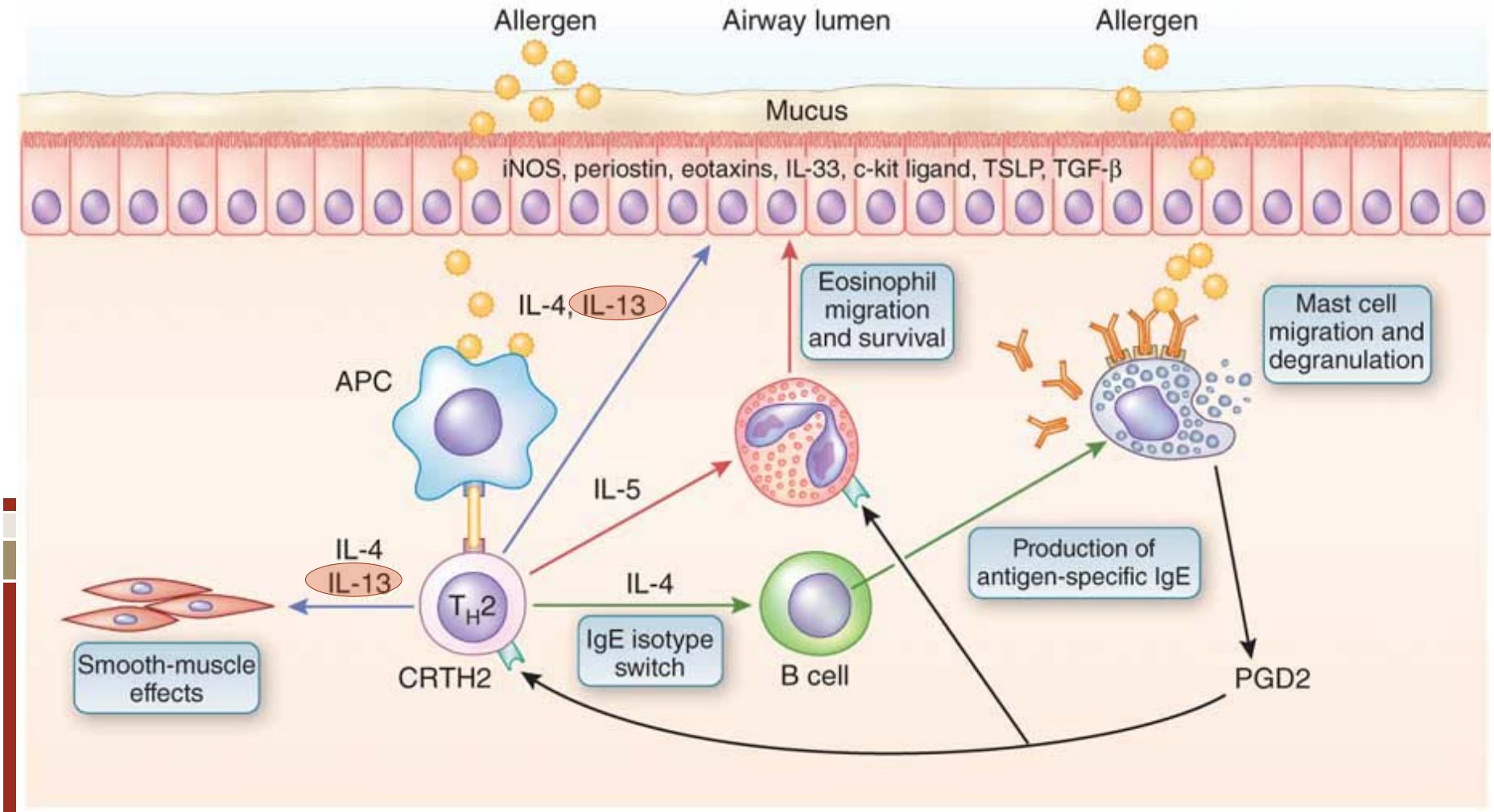


Innate Immune Responses in asthma

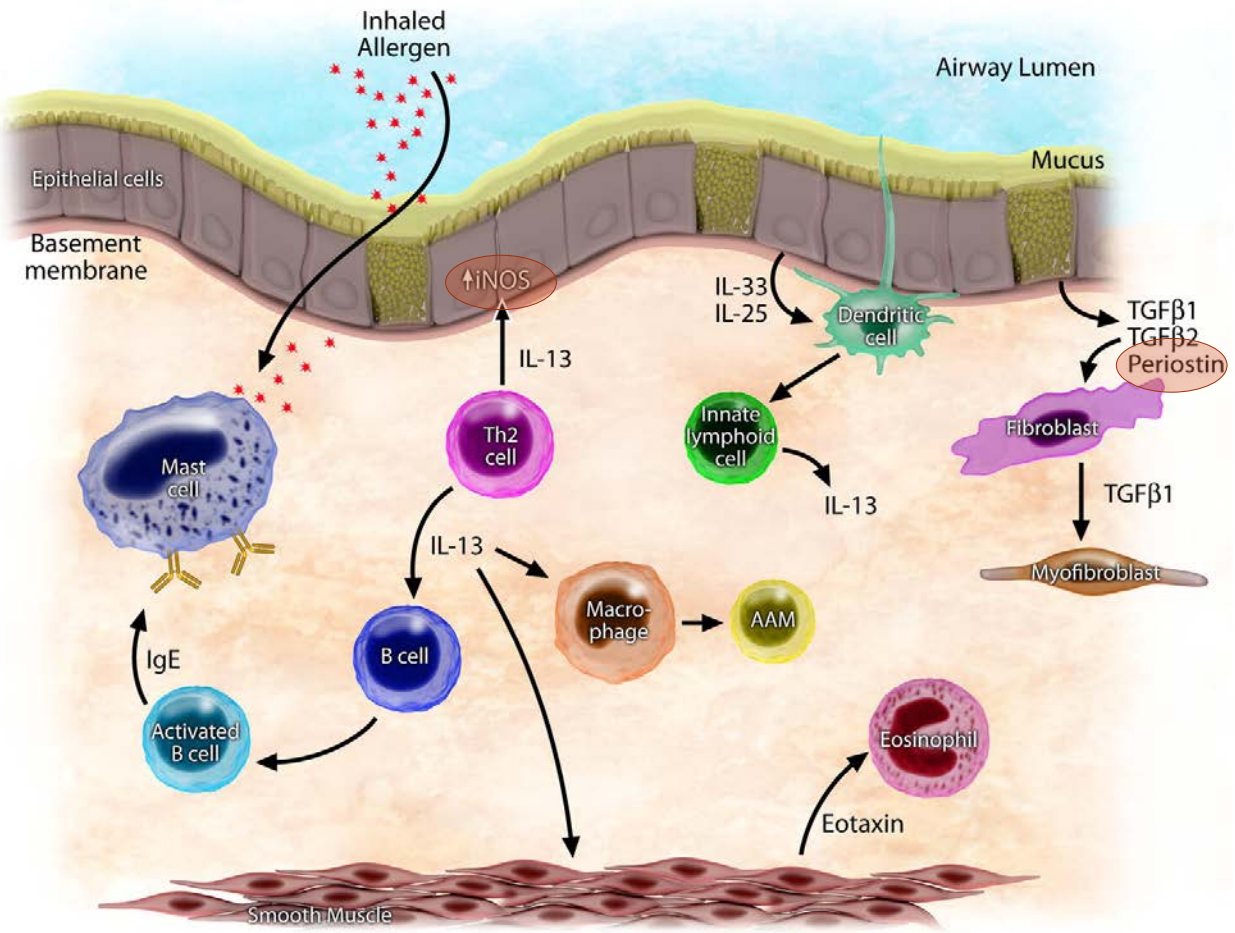




Classic T_H2 responses

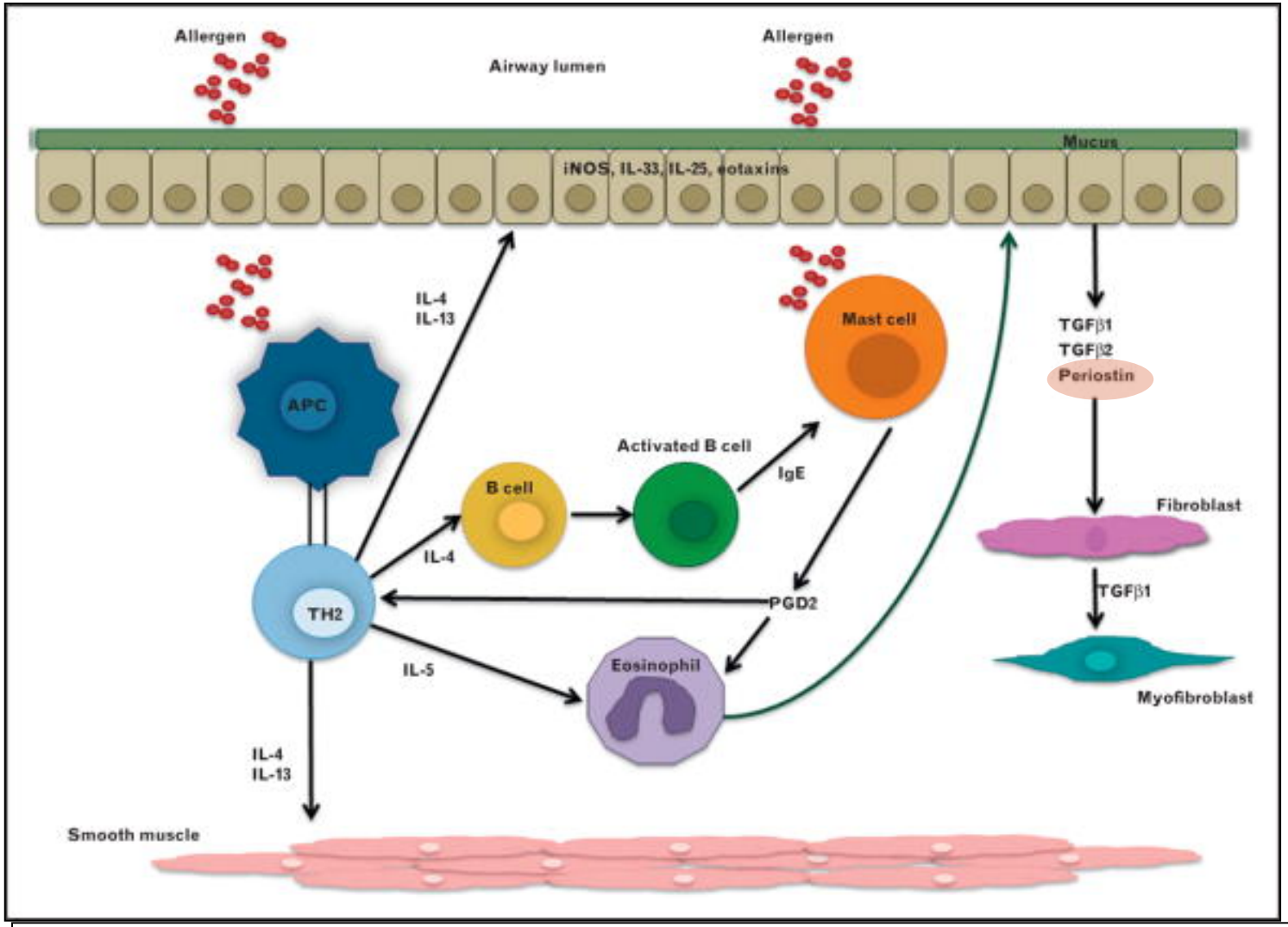


IL-13 in asthma and allergic disease



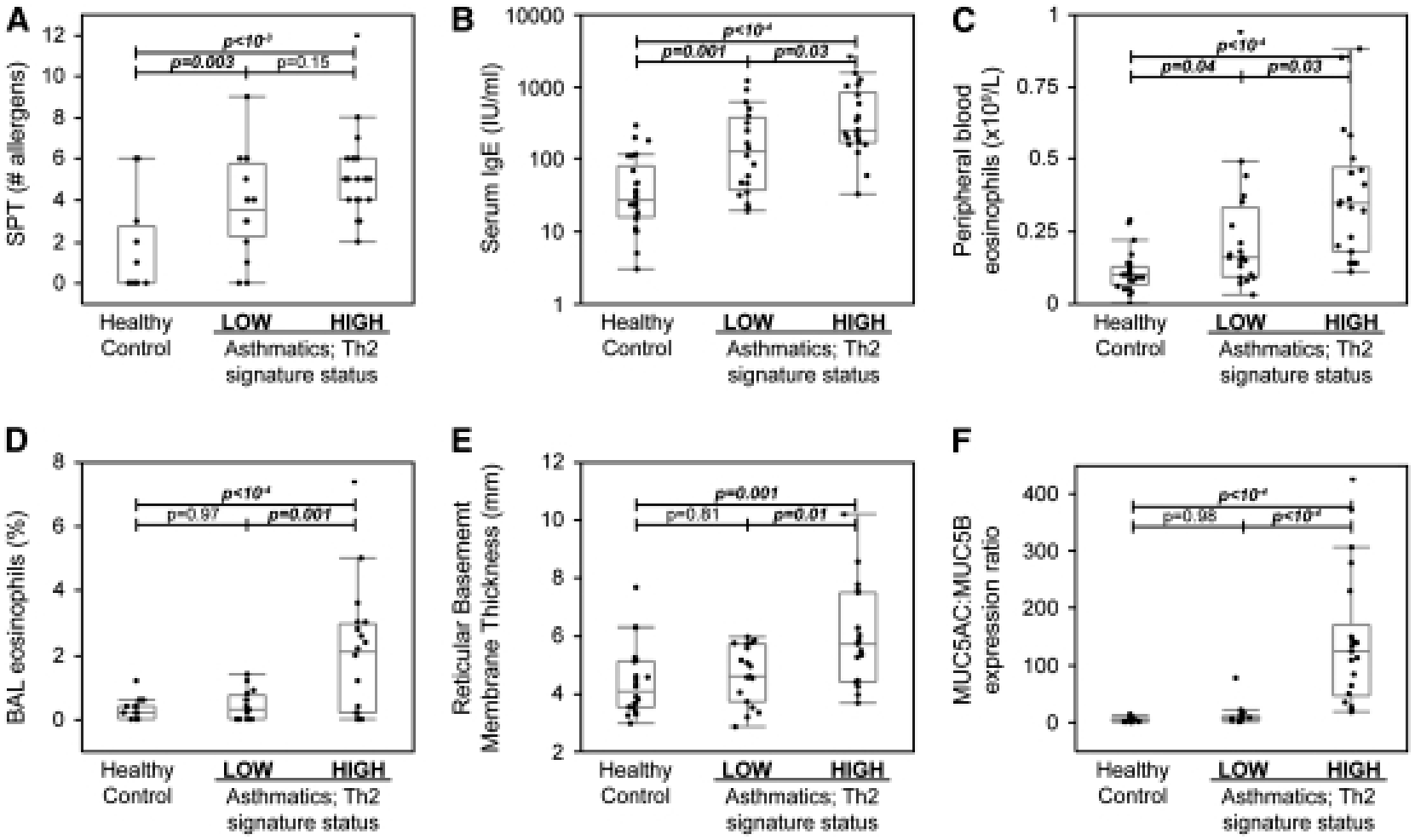
Jennifer L. Ingram, & Monica Kraft, Journal of Allergy and Clinical Immunology, Volume 130, Issue 4, Pages 829-842 (October 2012)

Novel T_H2 biomarker



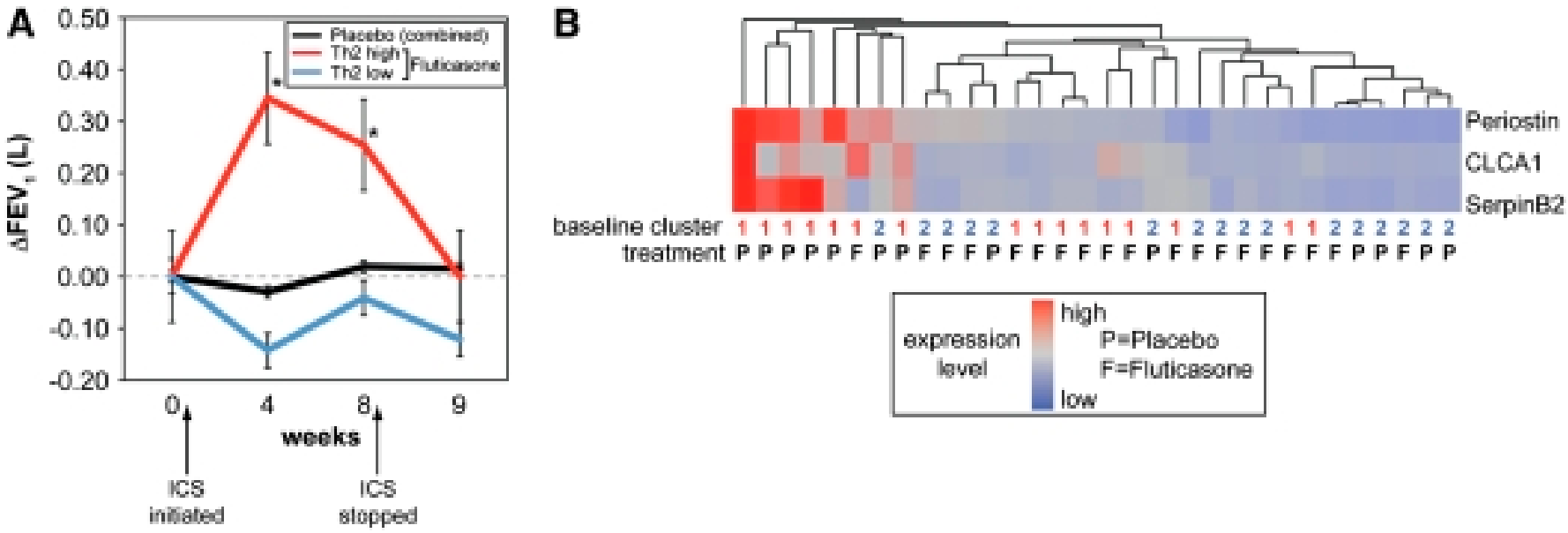
Periostin, a novel biomarker of TH2-driven asthma. Parulekar, Amit; Atik, Mustafa; Hanania, Nicola, Current Opinion in Pulmonary Medicine. 20(1):60-65, January 2014.

TH2 high/low phenotype (periostin gene classification)



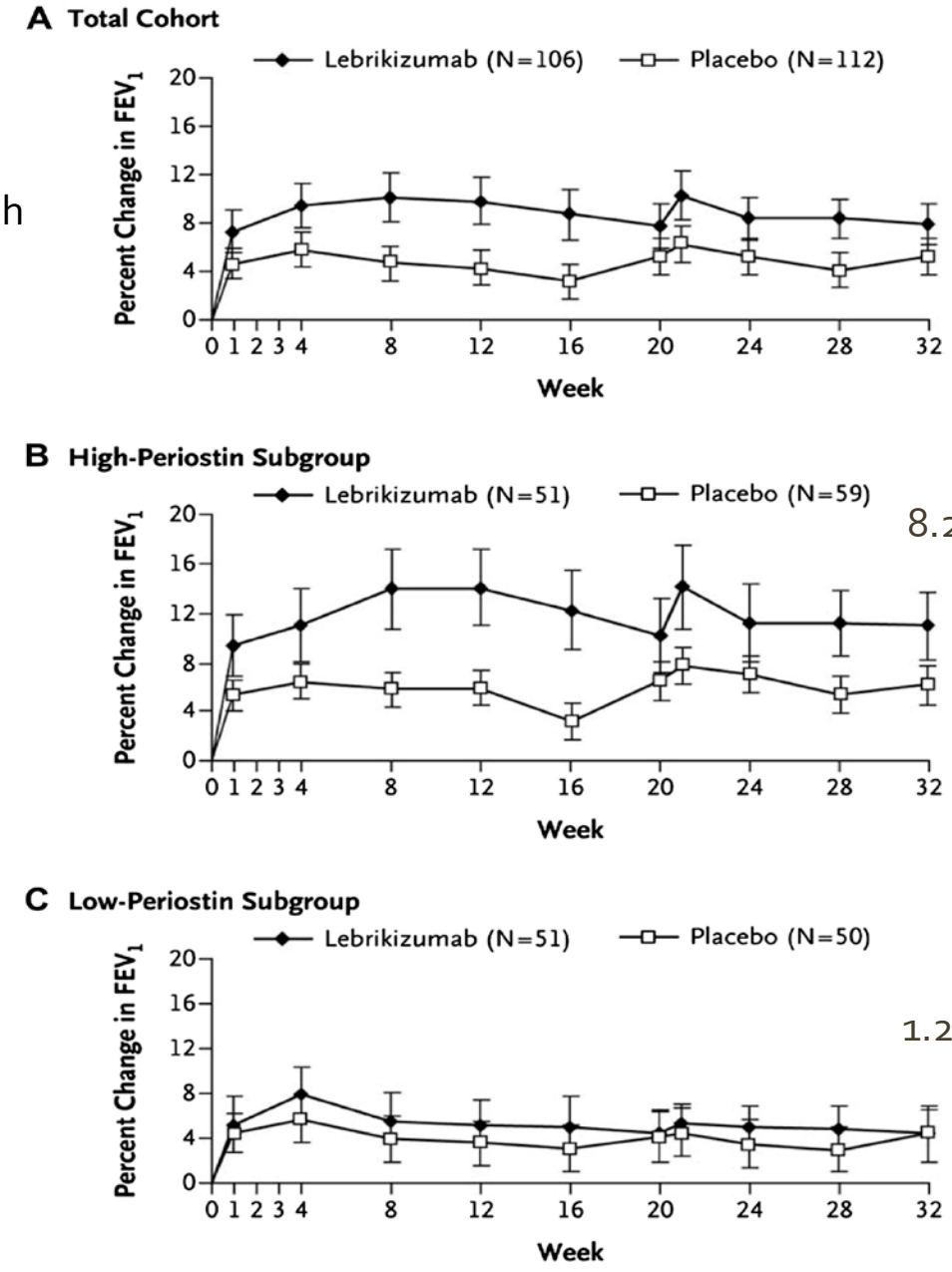
T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma: Woodruff et al, AJRCC M 2009

TH2 high/low phenotype (periostin gene classification): ICS



T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma: Woodruff et al, AJRCC M 2009

- RCT in 219 uncontrolled asthmatics (high dose ICS)
- Monoclonal antibody to IL-13 (Lebrikizumab)



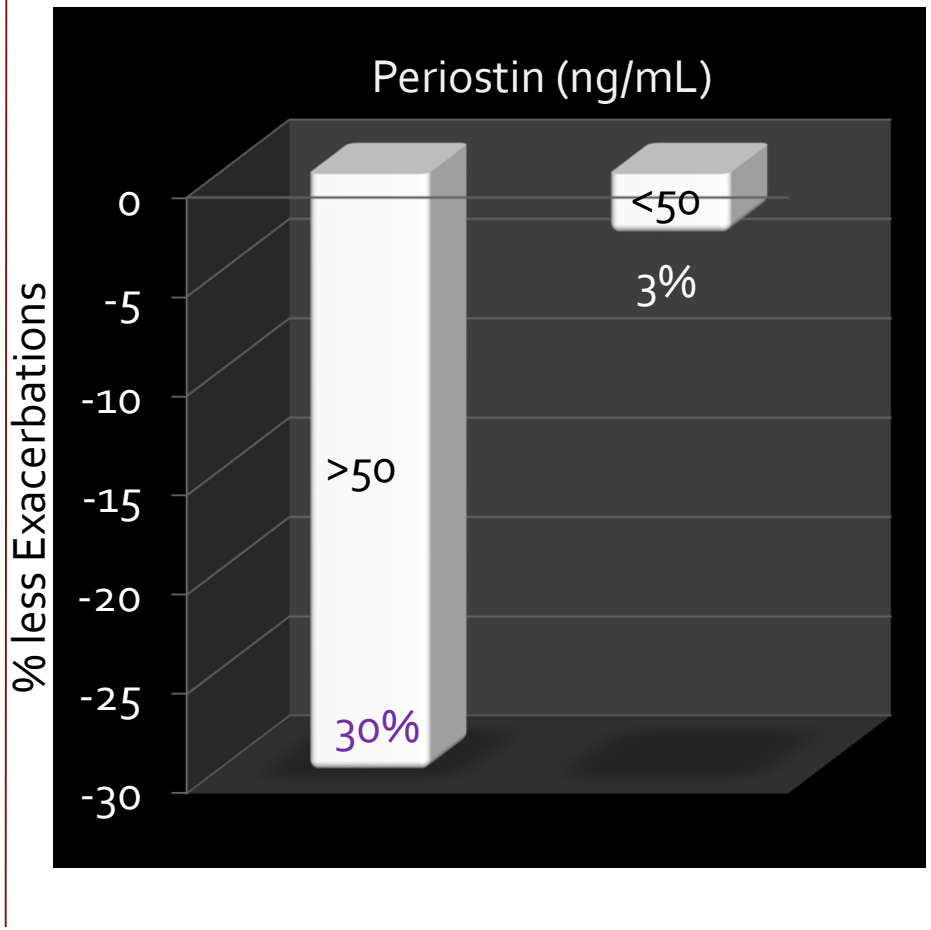
Coren et al: JACI2012; 130:829-842

Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Hanania et alW. Am J Respir Crit Care Med. 2013 Apr 15;187(8):804-11

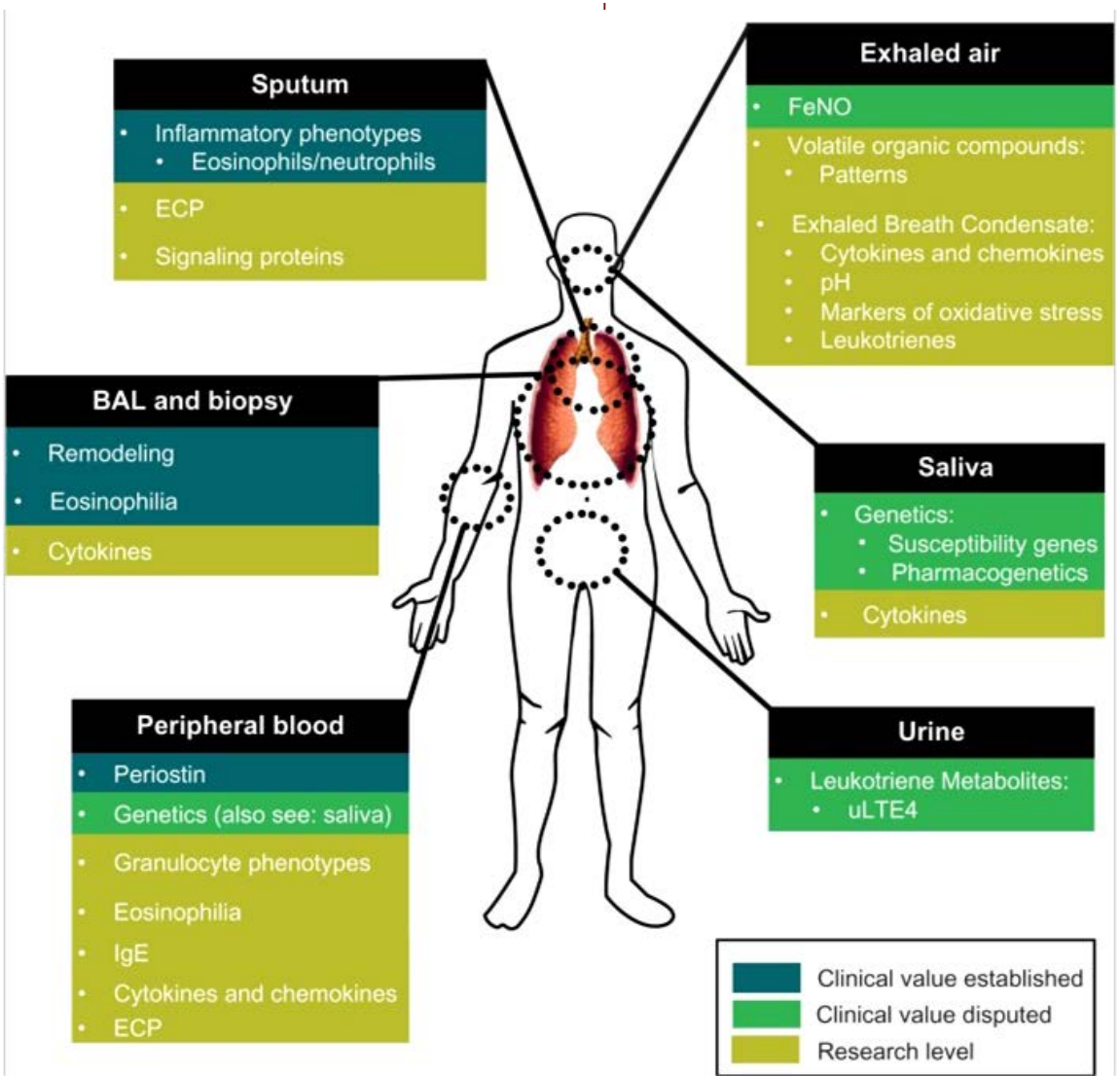
- PostHoc analysis
- 534 uncontroled asthmatics
- Omalizumab for 48 mo

- 2 groups according to (high/low) serum periostin level, F_{NO} & Eos sputum

Δ-Acute Exacerbation rate%
-For F_{NO} grouping: 53 vs 16
-For Eos grouping: 32 vs 9



Asthma biomarkers: T_H2 meter

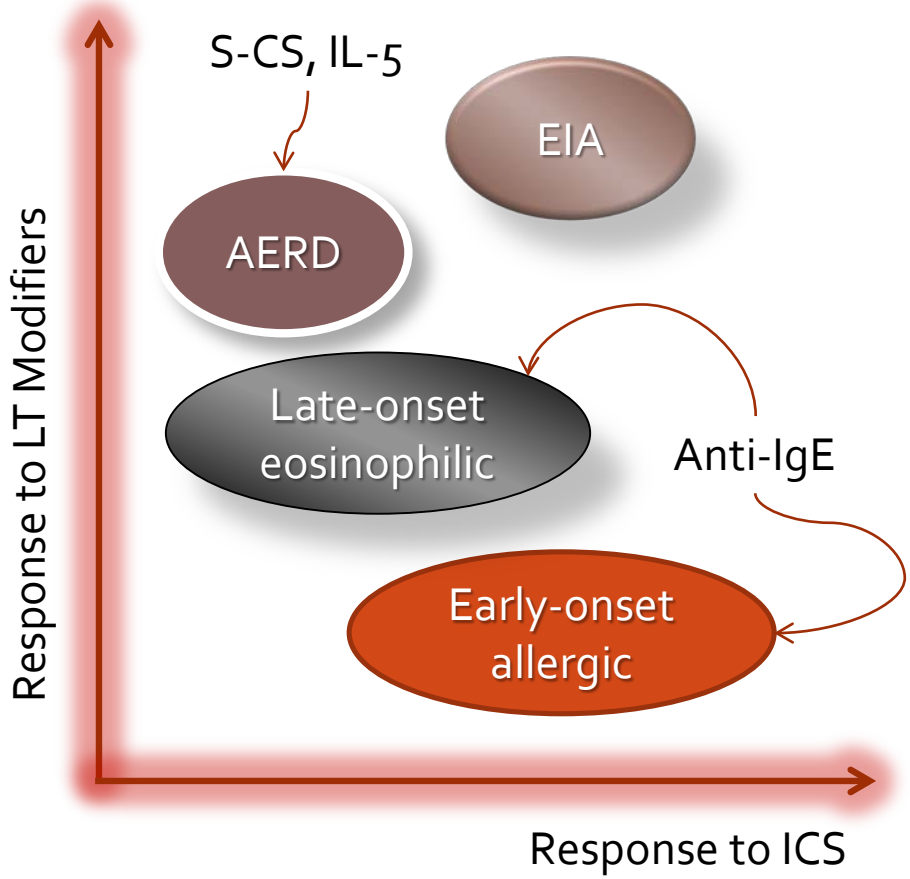


Biomarkers of T_H2 asthma in clinical practice

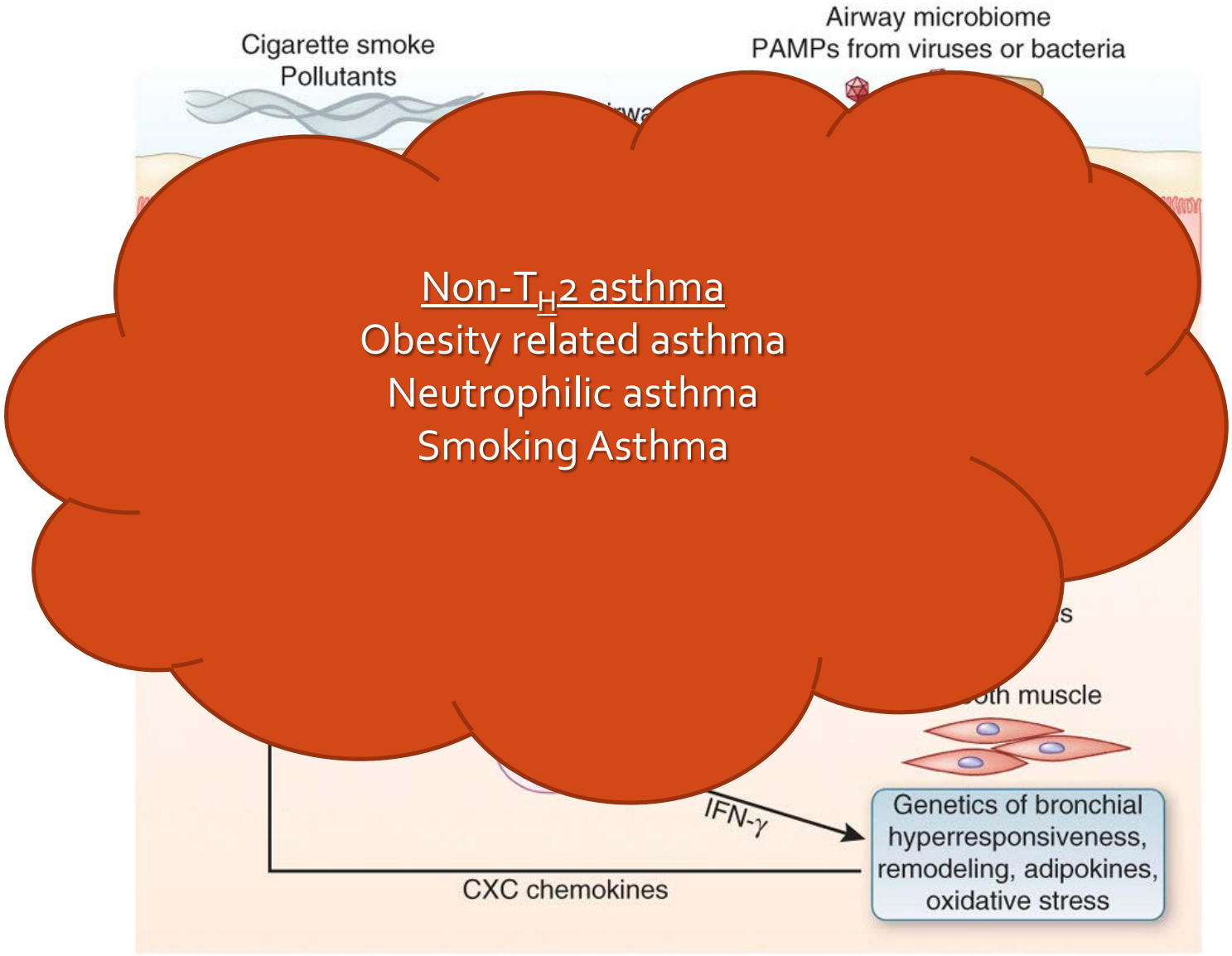
- Sputum Eos >2% of inflammatory cells
- F_{NO} > 30 ppb
- Periostin 50 ng/m?
- Atopy (skin or serum indices)
- Of extremely importance: Not a single cut-off rather a classification of High T_H2 to Low T_H2

Summary: T_H2 ASTHMA

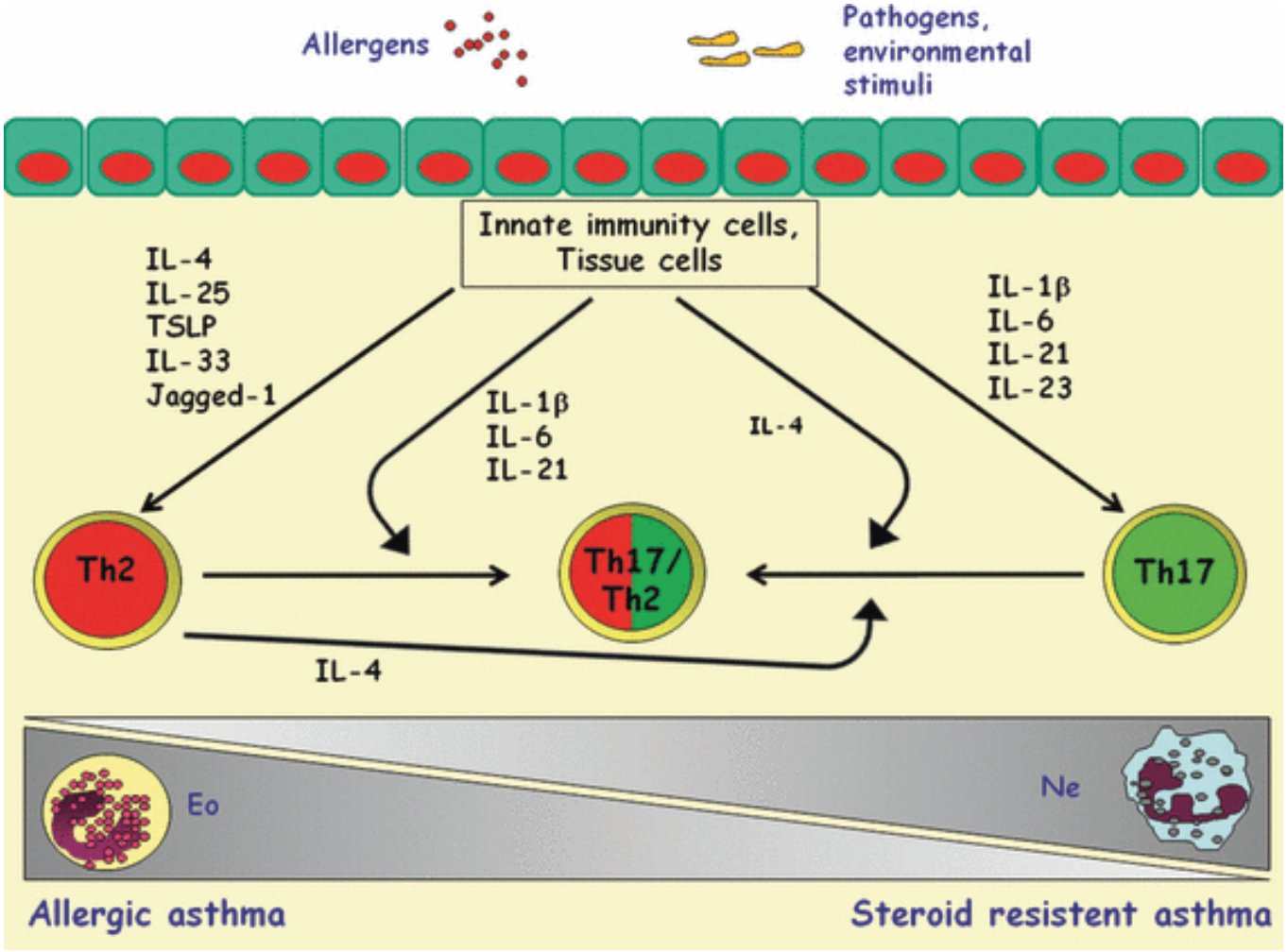
- Early-onset allergic, Late-onset eosinophilic, EIA, AERD
- F_{NO}, Eos, Periostin biomarkers
- T_H2 high or low



Non-T_H2 asthma

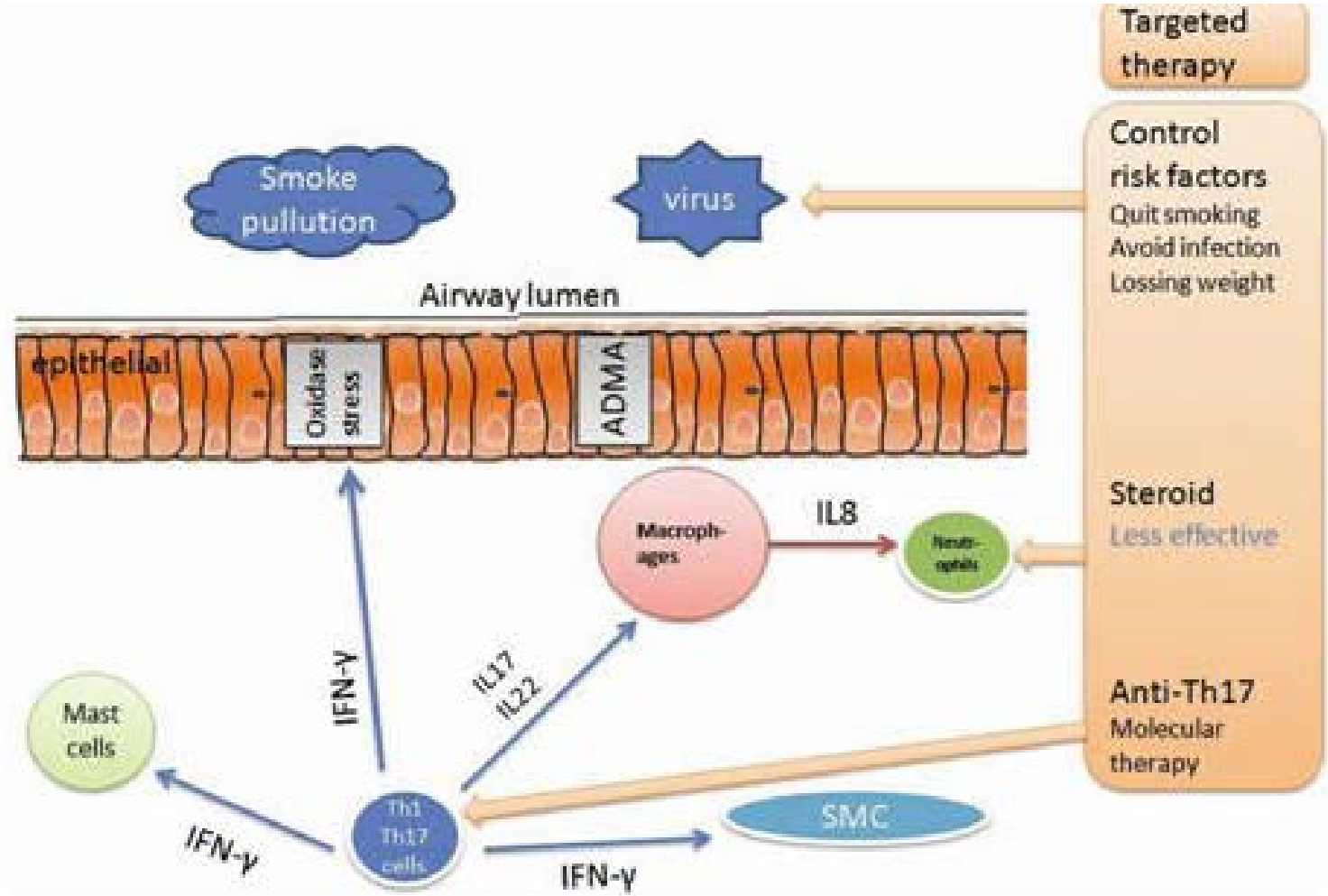


Th17 cells: new players in asthma pathogenesis



Cosmi et al. Allergy 66: 2011

Non-TH2 associated asthma: Therapy



Xie & Wenzel, Chin Med J 2013;126

Φαινότυποι από το κλινικό στο μοριακό επίπεδο: Συμπεράσματα

- Οι βασικοί μοριακοί μηχανισμοί που εμπλέκονται στην φαινοτυπική έκφραση των ασθματικών ασθενών είναι πλέον απαραίτητοι
- Ο διαχωρισμός σε T_H2/Non-T_H2 ασθματική συνδρομή είναι εφικτός στην καθημερινή πράξη με εύκολους και φθηνούς βιοδείκτες
- Ο προσεκτικός χαρακτηρισμός, με βάση τα παραπάνω, των ασθενών που συμμετέχουν στις RCTs θα προσδώσει ακρίβεια/αποτελεσματικότητα στην εκτίμηση των ενδείξεων των παλιών αλλά και των νέων στοχευμένων παρεμβάσεων