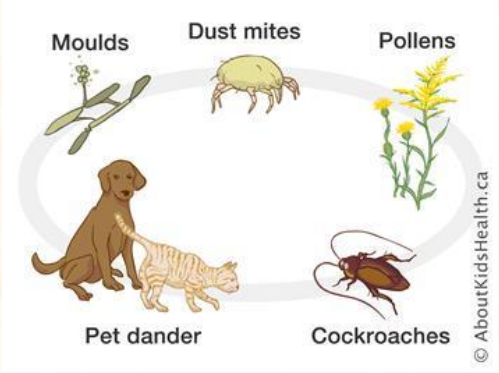
Immunopathology
2024’

Pathomechanism of allergic reactions
I.

Clinical manifestations of allergies

- Aero-allergies
- Food allergies
- Pollen and food allergy syndrome (PFAS)
- Drug allergies
- Contact dermatitis, eczema



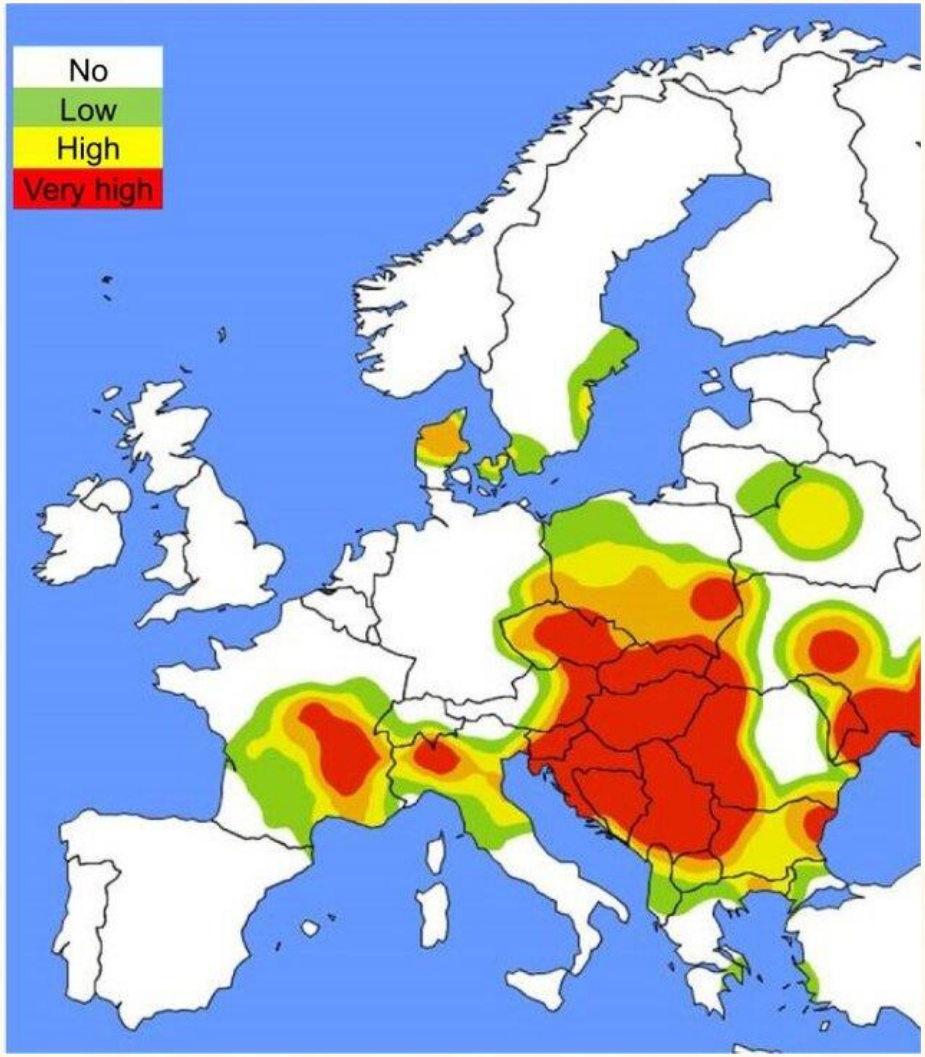
Immunopathological background

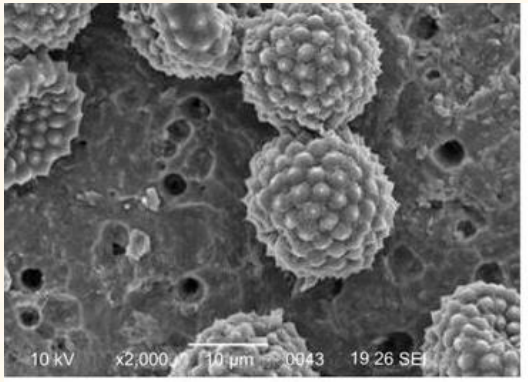
- Allergies are hypersensitive immune reactions
- Airborn and food allergies are dominantly IgE mediated (Type I) hypersensitivities
- Contact dermatitis is a Type IV hypersensitive reaction (DTH)
- Food sensitivities/intolerances are not immune-mediated diseases

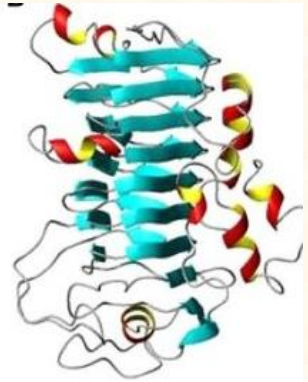

Ragweed
Rod Lym@NDSU


Mugwort

Ragweed pollen load map in Europe at mid-September





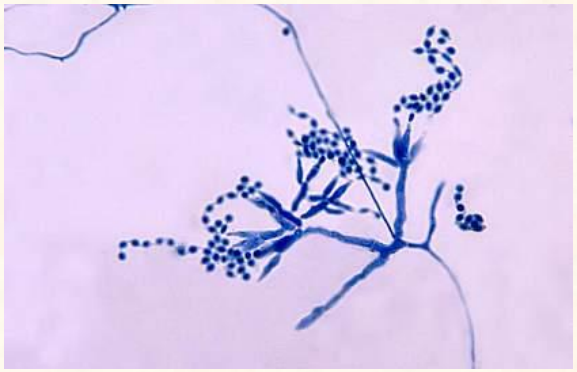


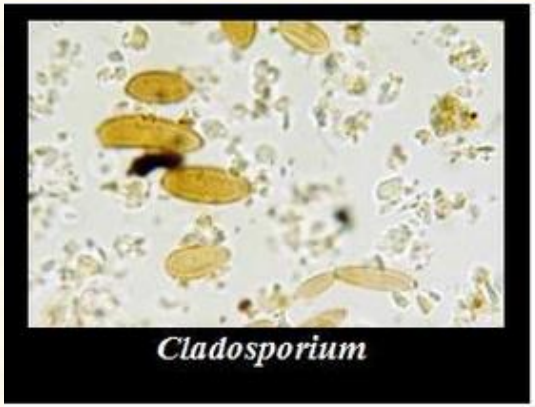
Ragweed (Ambrosia artemisiifolia) pollen

Allergic grass pollen


Tree Pollen
Allergies

Allergic fungal spores

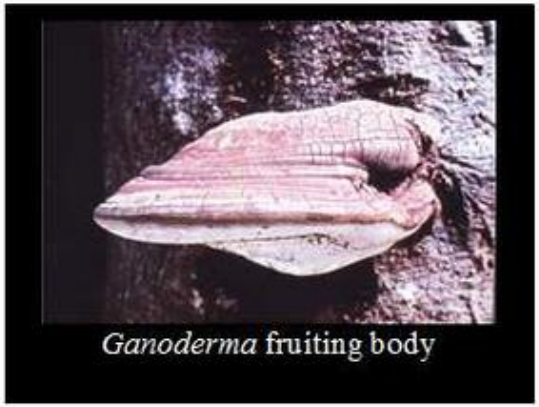


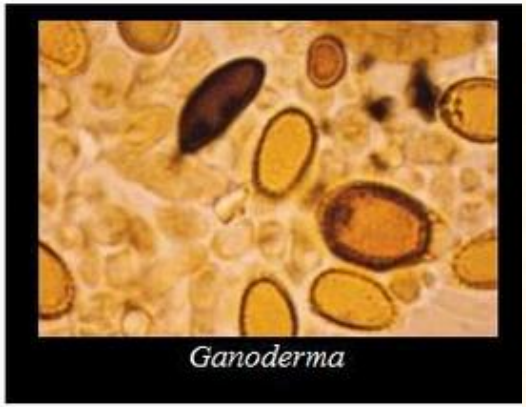

Cladosporium


Alternaria

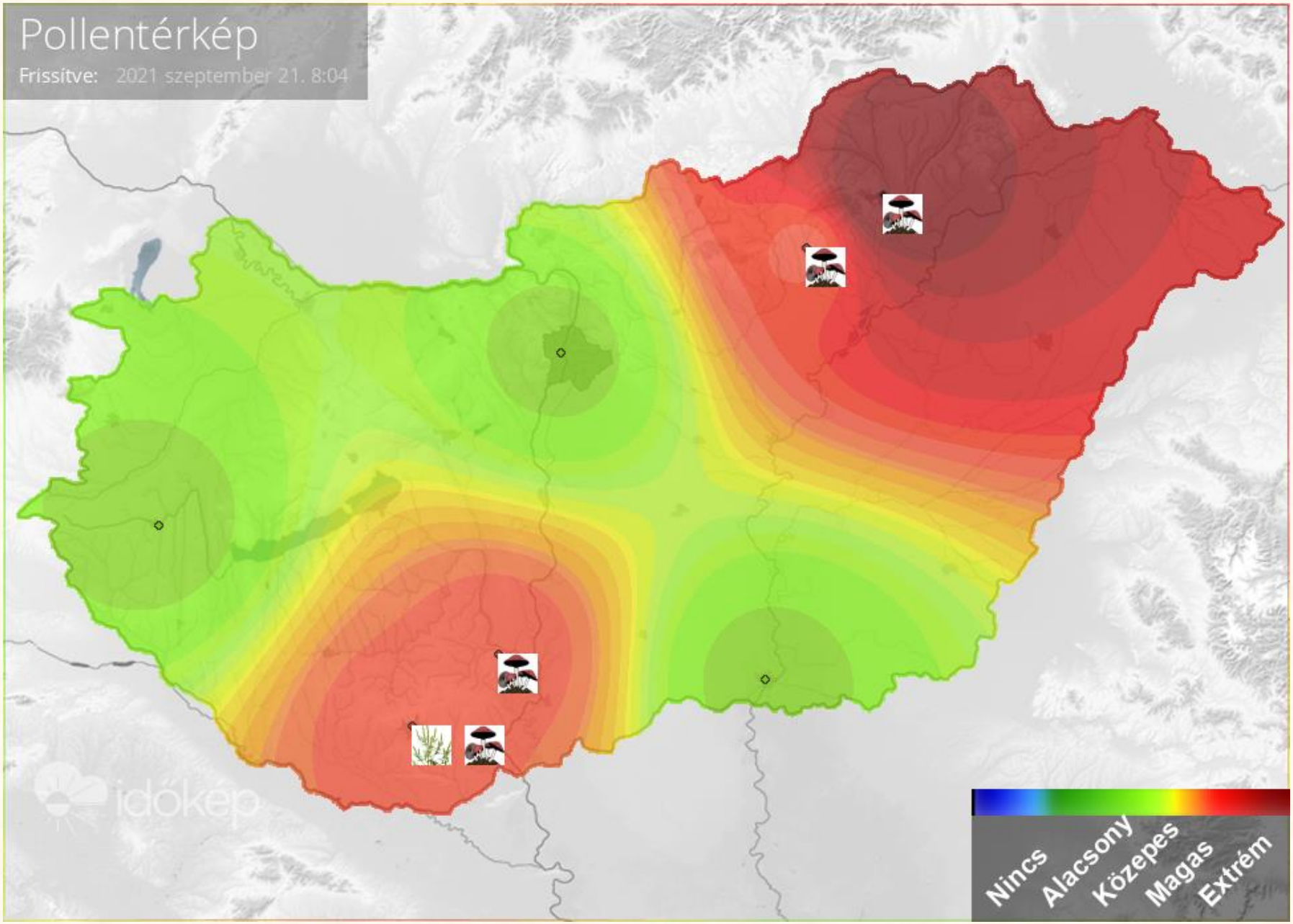

Ulocladium

Basidiospores

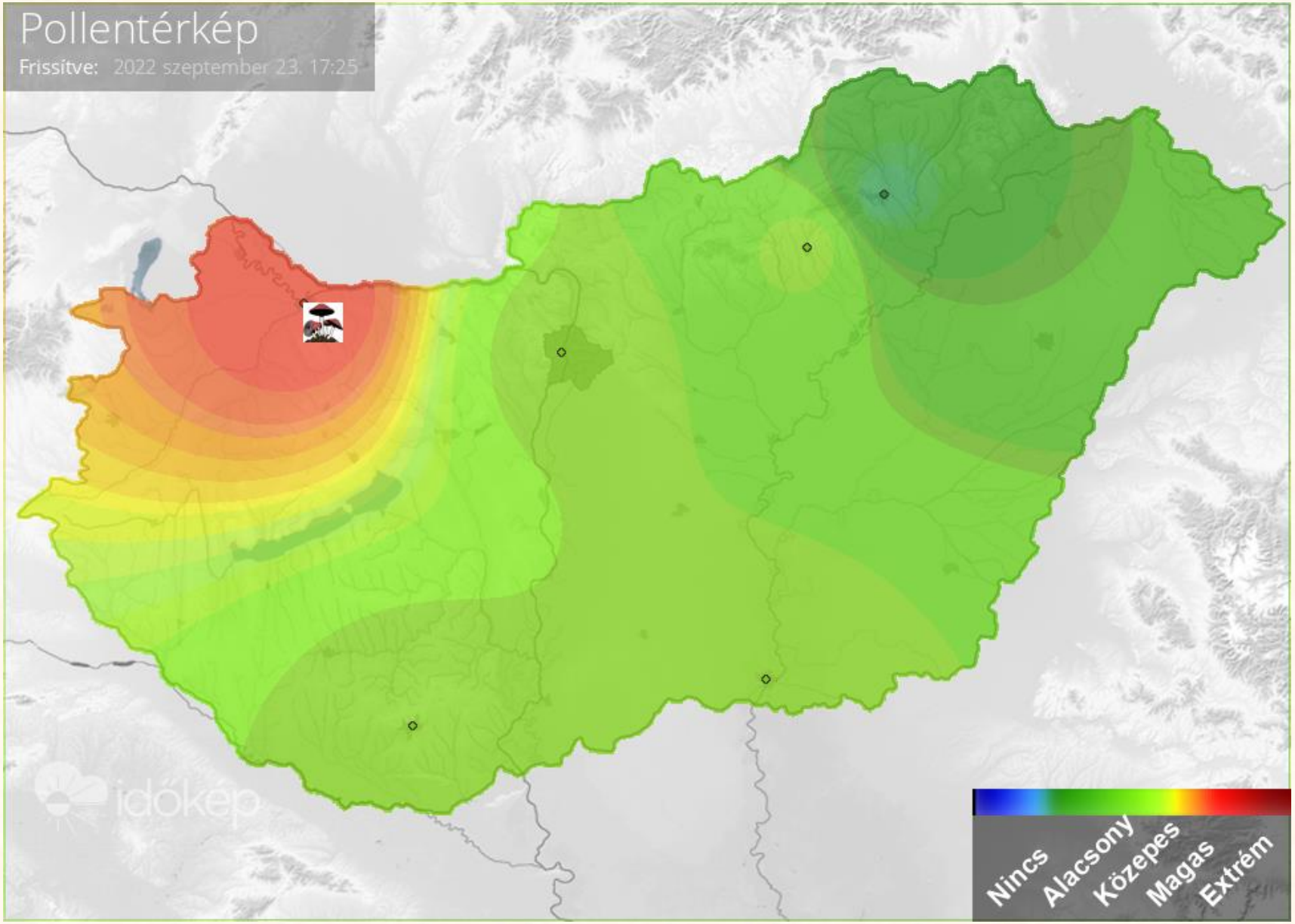

Ganoderma fruiting body


Ganoderma

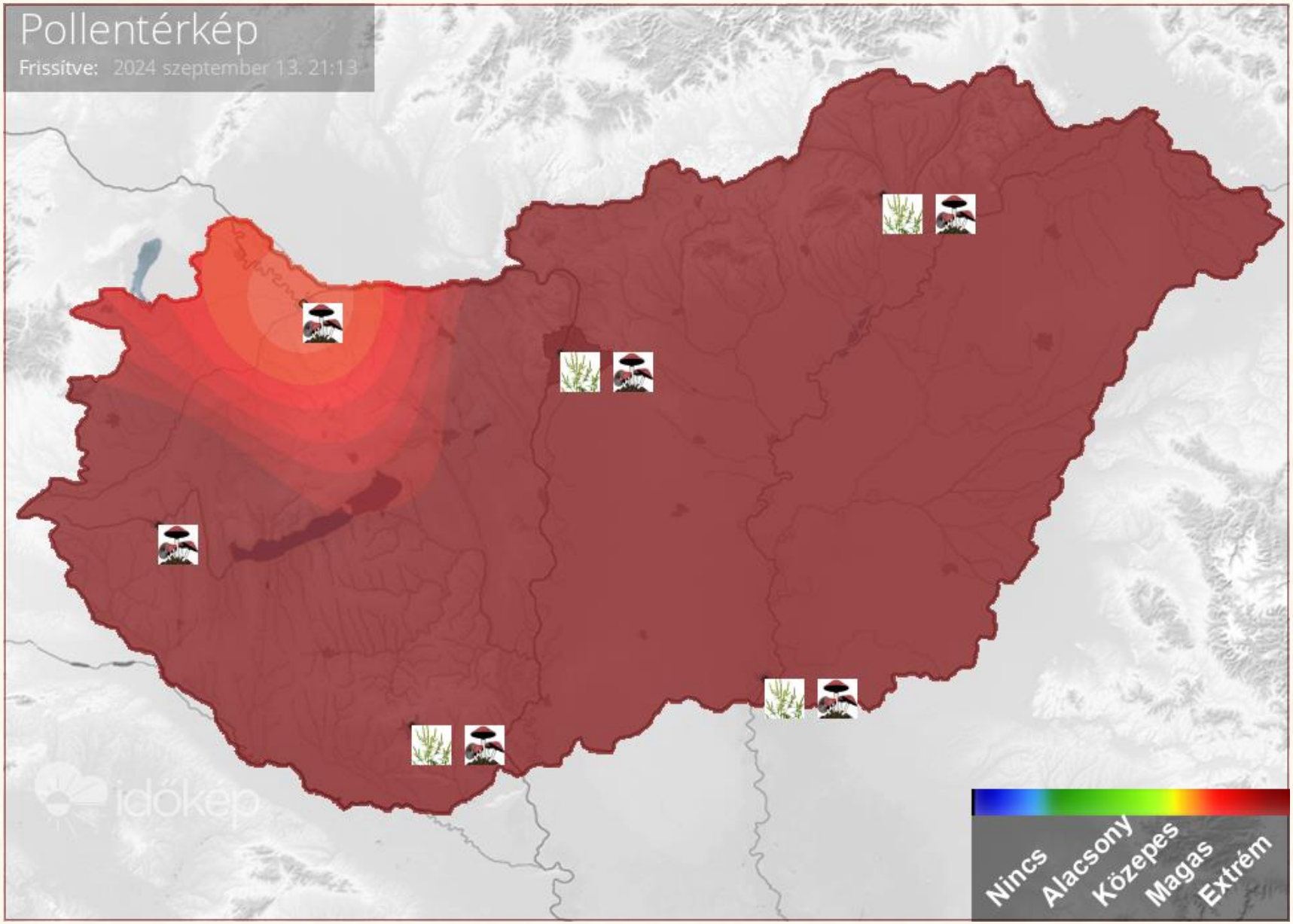
Pollen map of Hungary in 21st of September 2021



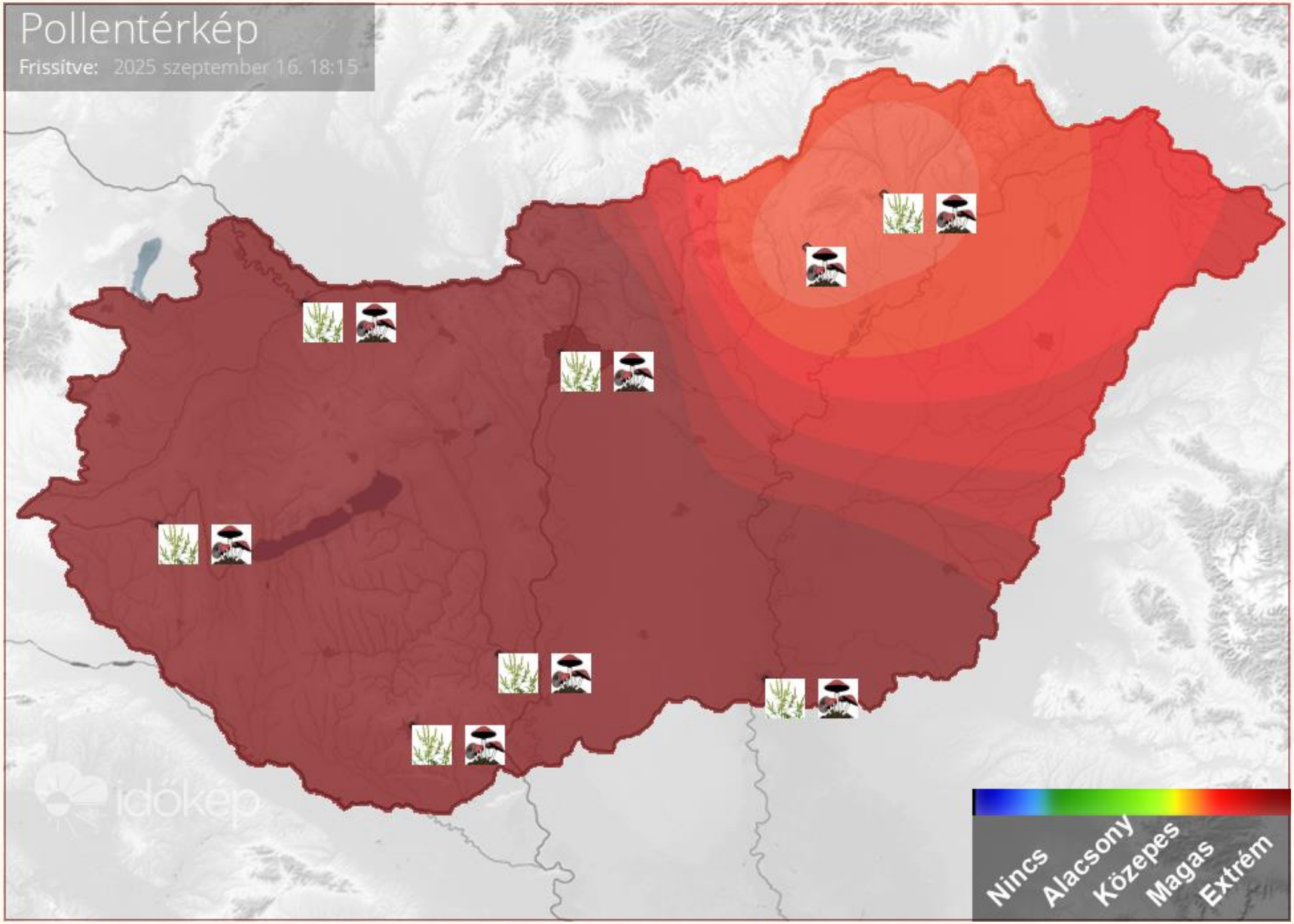
Pollen map of Hungary in 23rd of September 2022



Pollen map of Hungary in 13th of September 2024



Pollen map of Hungary in 16th of September 2025



Comparison of Different Types of hypersensitivity

	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	Exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	weal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
  eg house dust mites

pollen

house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins

wasp

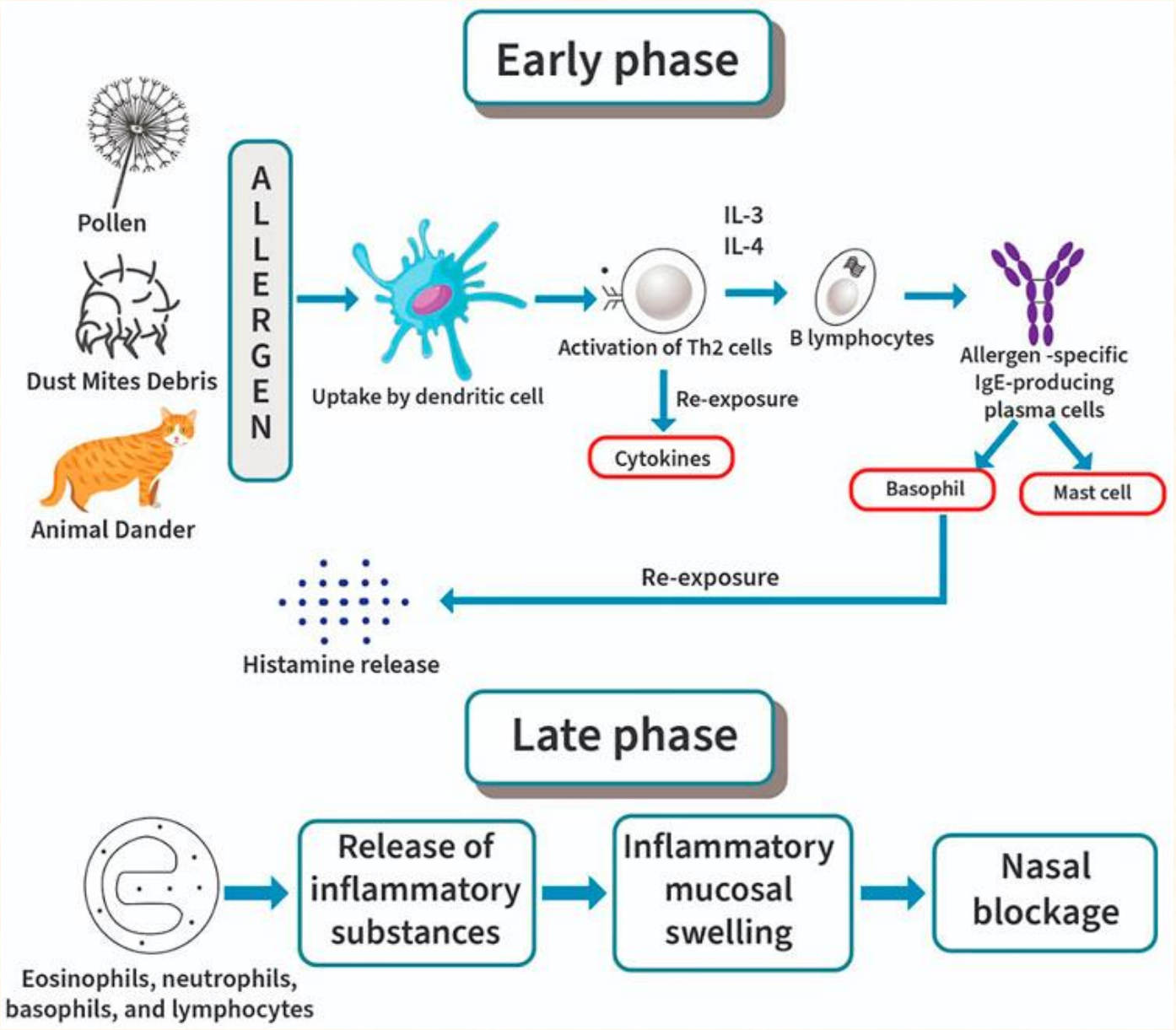
drugs

Dust mite

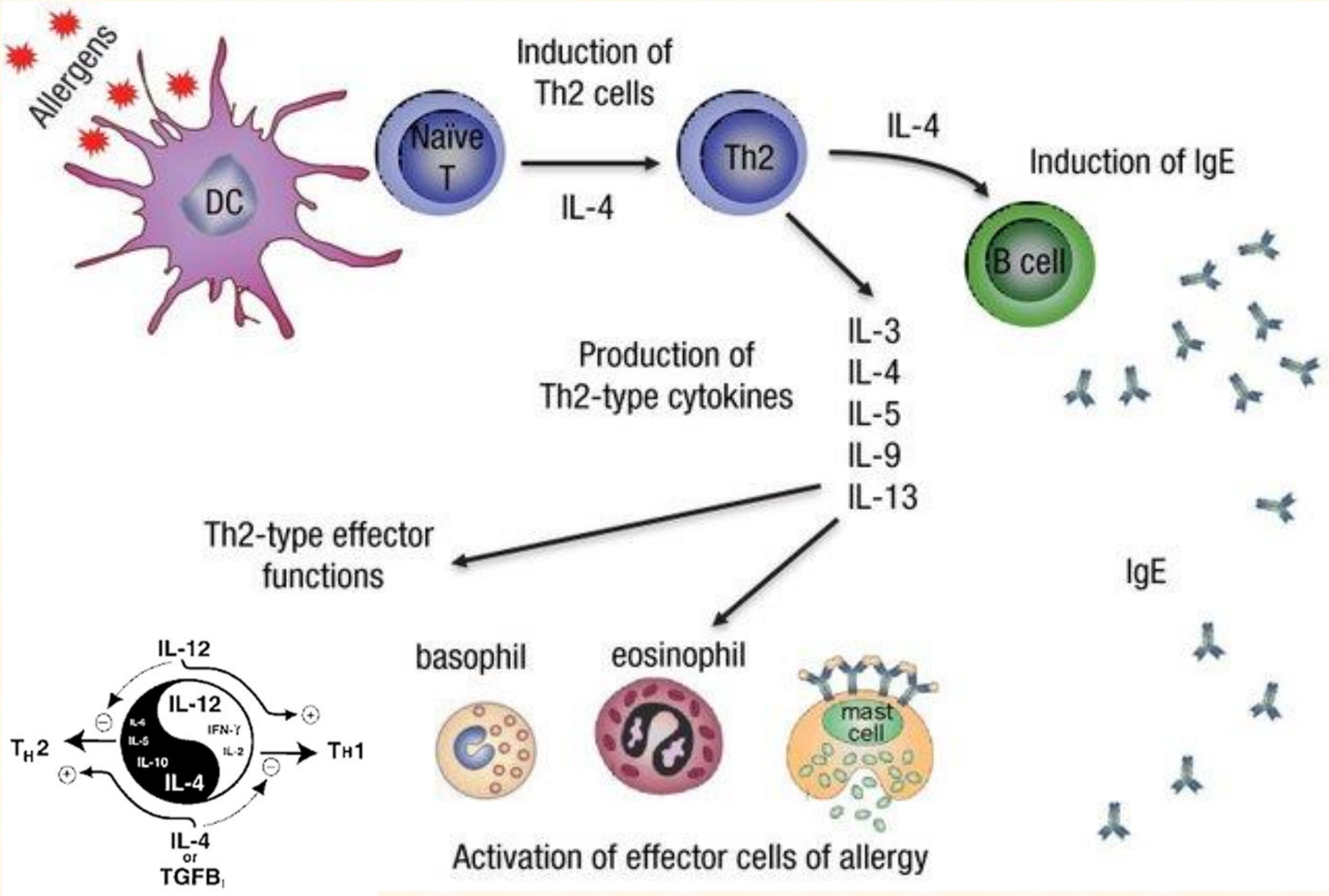
Dust mite allergy caused by the protein found in the fecal matter of the dust mite. The dust mite allergen is heavier than most other types of allergens. Therefore, it must be inhaled close to the source, usually in a stuffed toy, pillow or mattress. Dust mite allergy symptoms affect about ten percent of the population.

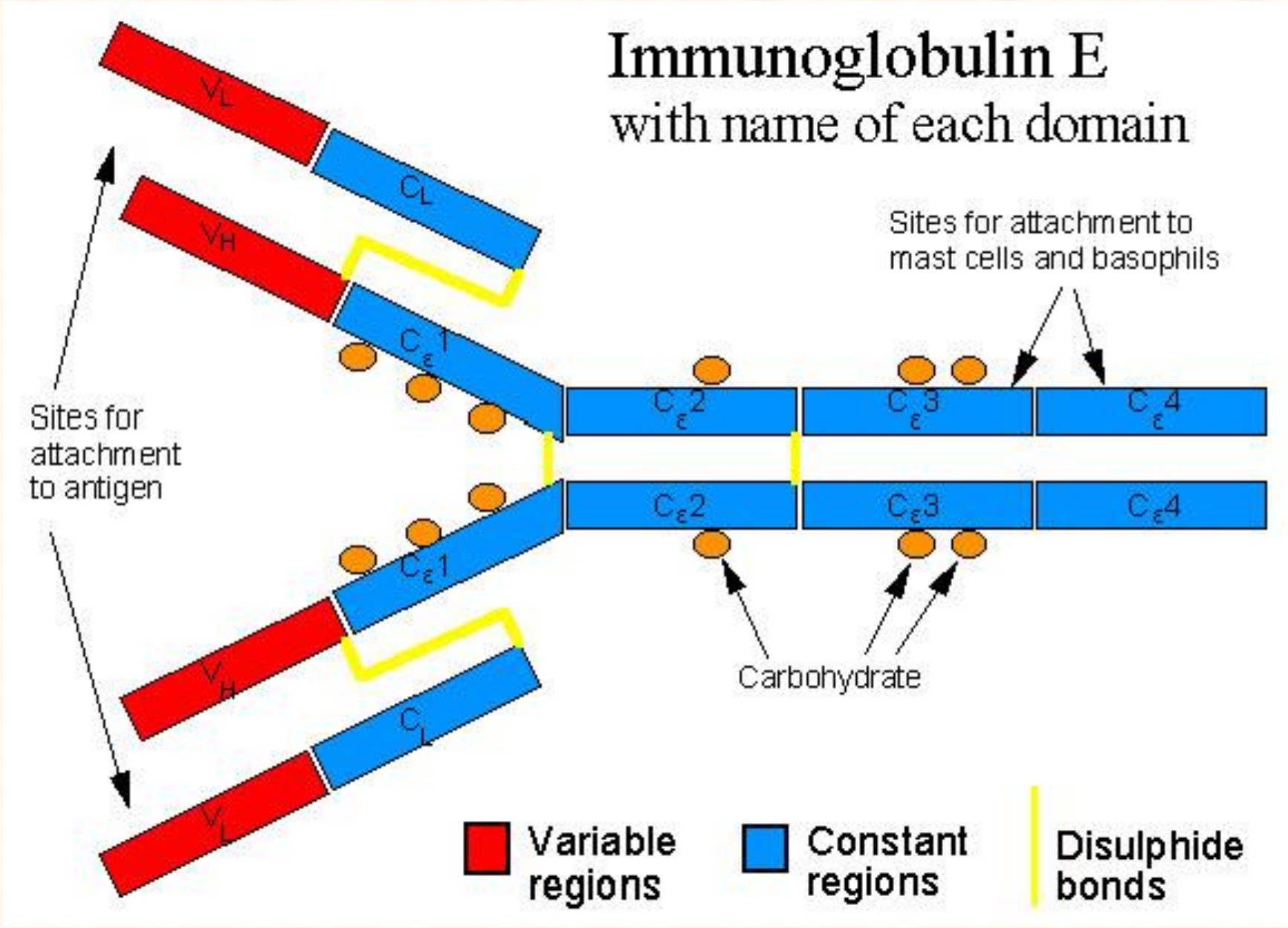
Dust mite allergy symptoms affect some people year-round. Some examples of dust mite allergy symptoms are: runny nose, eczema, persistent stuffy nose or ears, asthma, sitchy or watery eyes, and sneezing.

Mechanism of allergic rhinitis

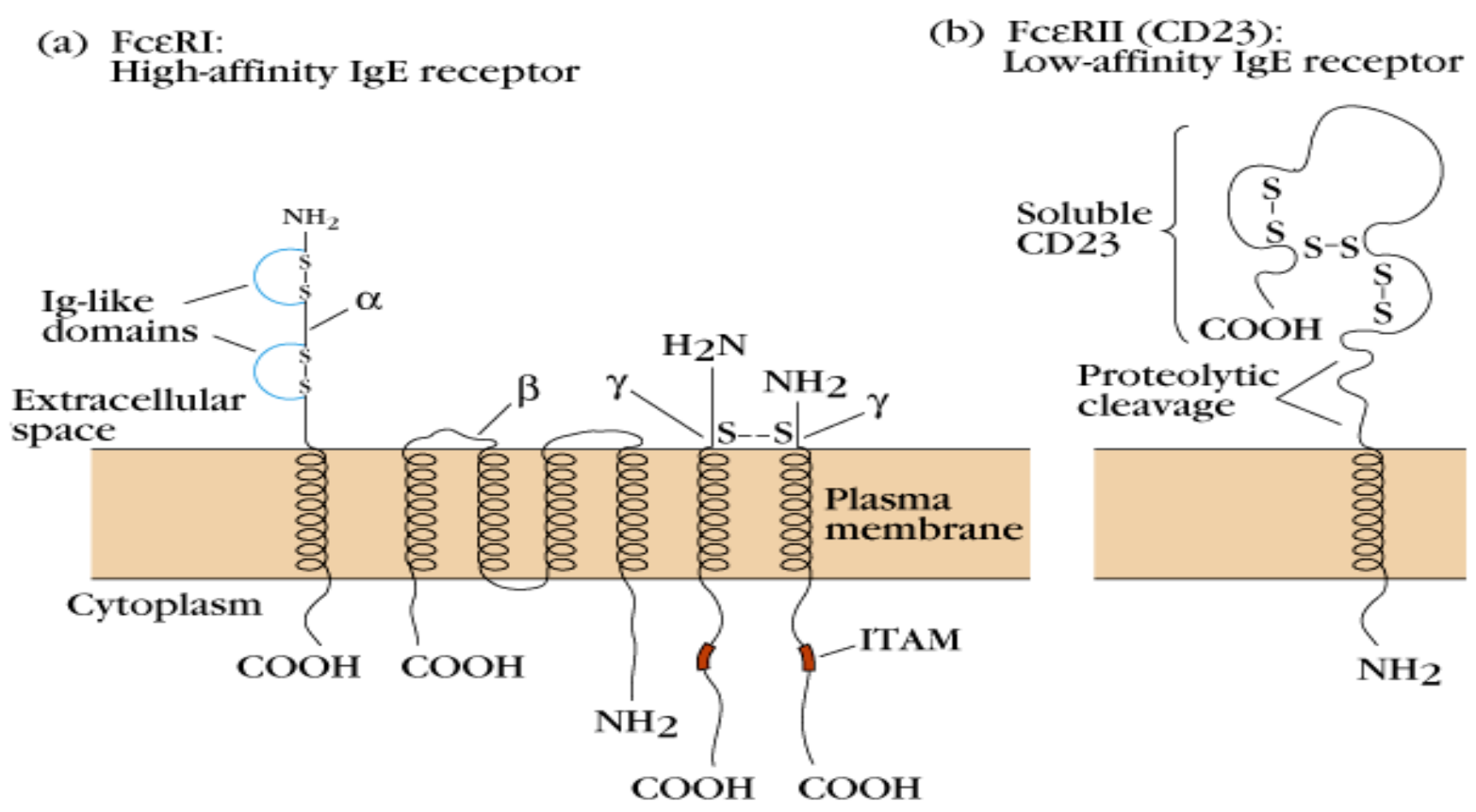


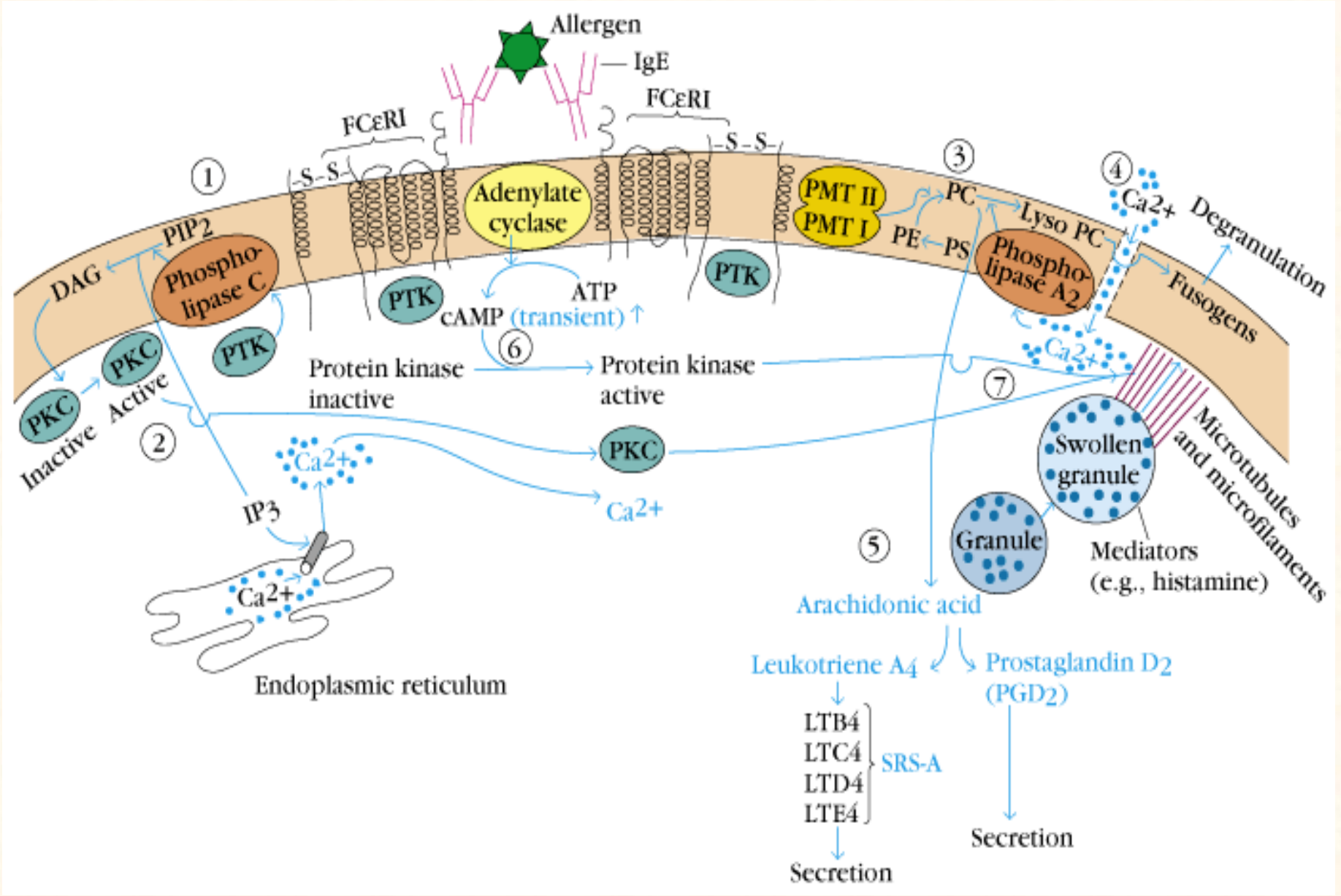
Role of mucosal IL-4 dominance in IgE production

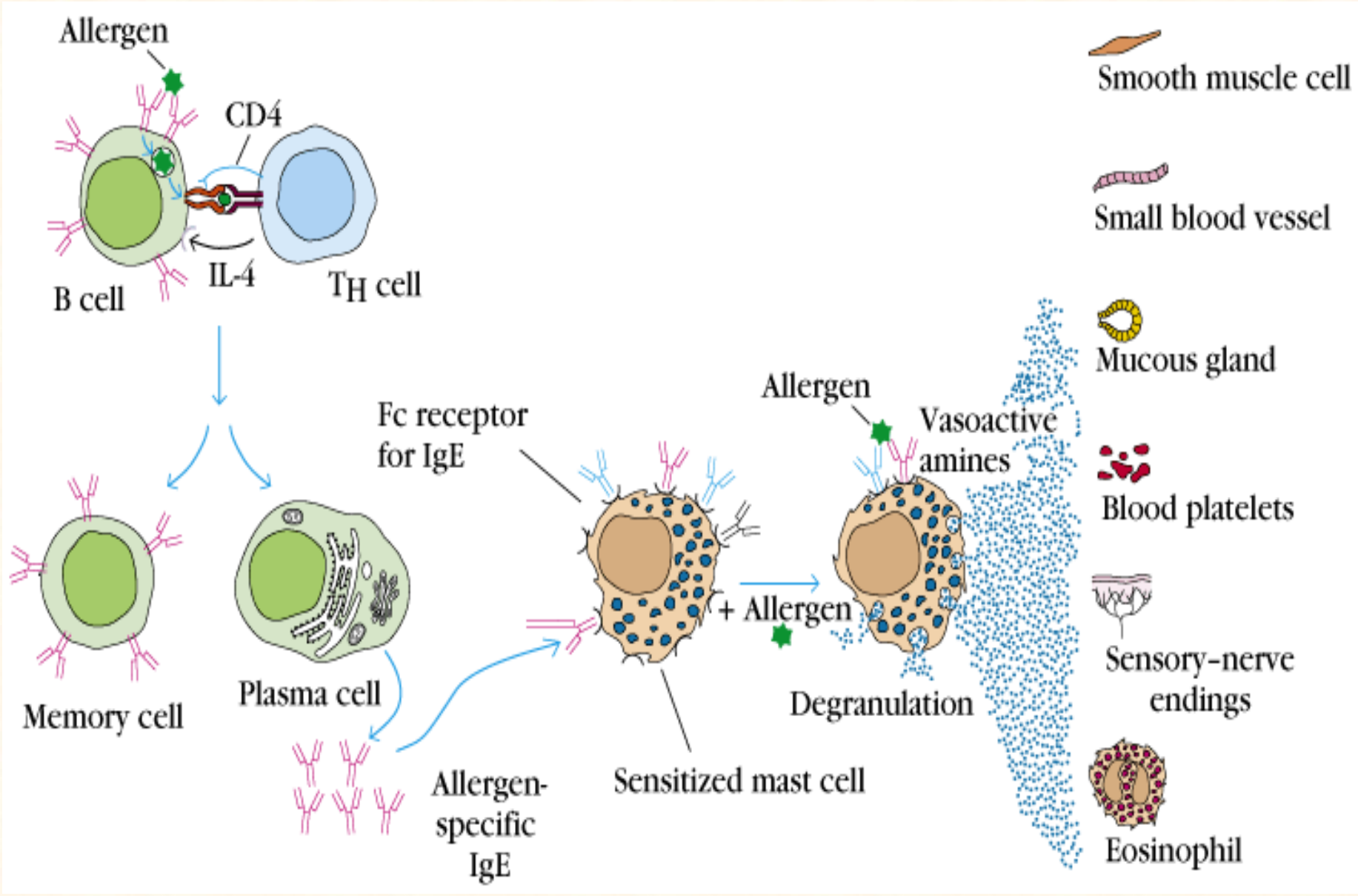



Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
Carbohydrate
Variable regions
Constant regions
Disulphide bonds

IgE binding receptors




Allergen
IgE
FCεRI
FCεRI
S–S
S–S
1
Adenylate cyclase
PMT II
PMT I
3
PC
Lyso PC
PE
PS
Phospho-lipase A2
4
Ca2+
Degranulation
Fusogens
PIP2
DAG
Phospho-lipase C
PTK
PTK
PTK
ATP
cAMP (transient)
6
Protein kinase inactive
Protein kinase active
PKC
Active
PKC
Inactive
2
Ca2+
IP3
PKC
Ca2+
Ca2+
7
Swollen granule
Microtubules and microfilaments
Granule
Mediators (e.g., histamine)
5
Arachidonic acid
Leukotriene A4
Prostaglandin D2 (PGD2)
LTB4
LTC4
LTD4
LTE4
SRS-A
Secretion
Secretion
Endoplasmic reticulum


Allergen
CD4
IL-4
B cell
TH cell
Memory cell
Plasma cell
Allergen-specific IgE
Fc receptor for IgE
Sensitized mast cell
+ Allergen
Allergen
Vasoactive amines
Degranulation
Smooth muscle cell
Small blood vessel
Mucous gland
Blood platelets
Sensory-nerve endings
Eosinophil

Pharmacologic Mediators of Immediate Hypersensitivity

Preformed mediators in granules

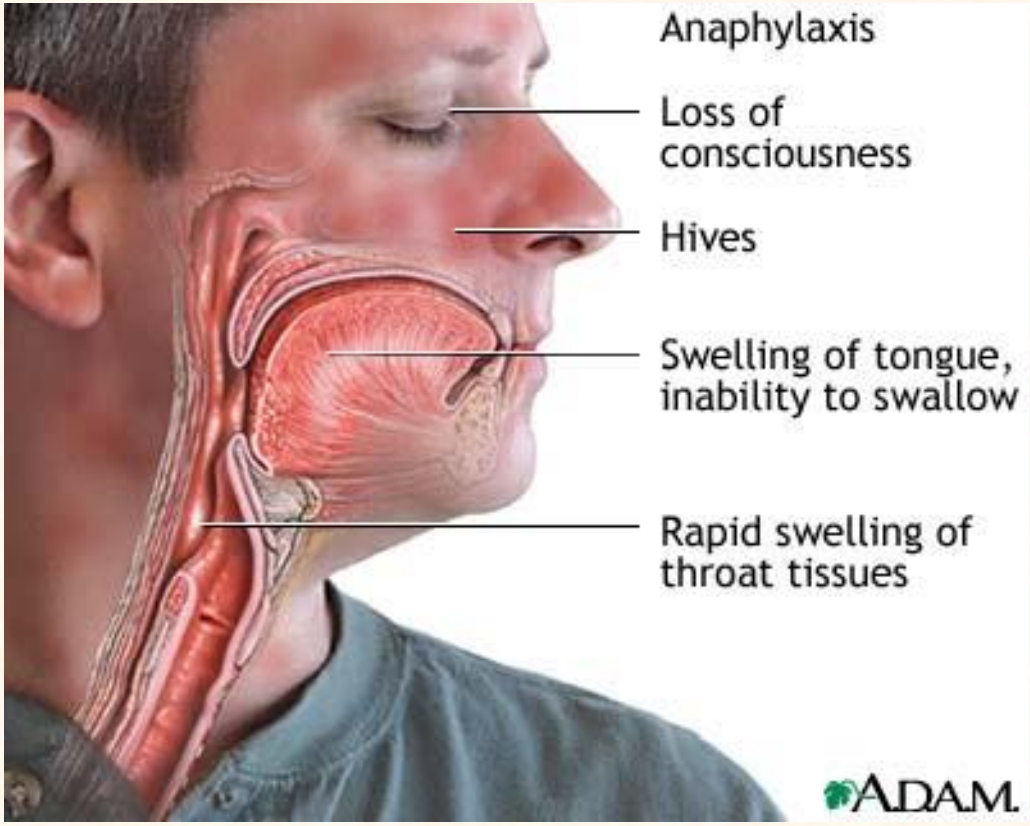
histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
tryptase	proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	attract eosinophil and neutrophils

Newly formed mediators

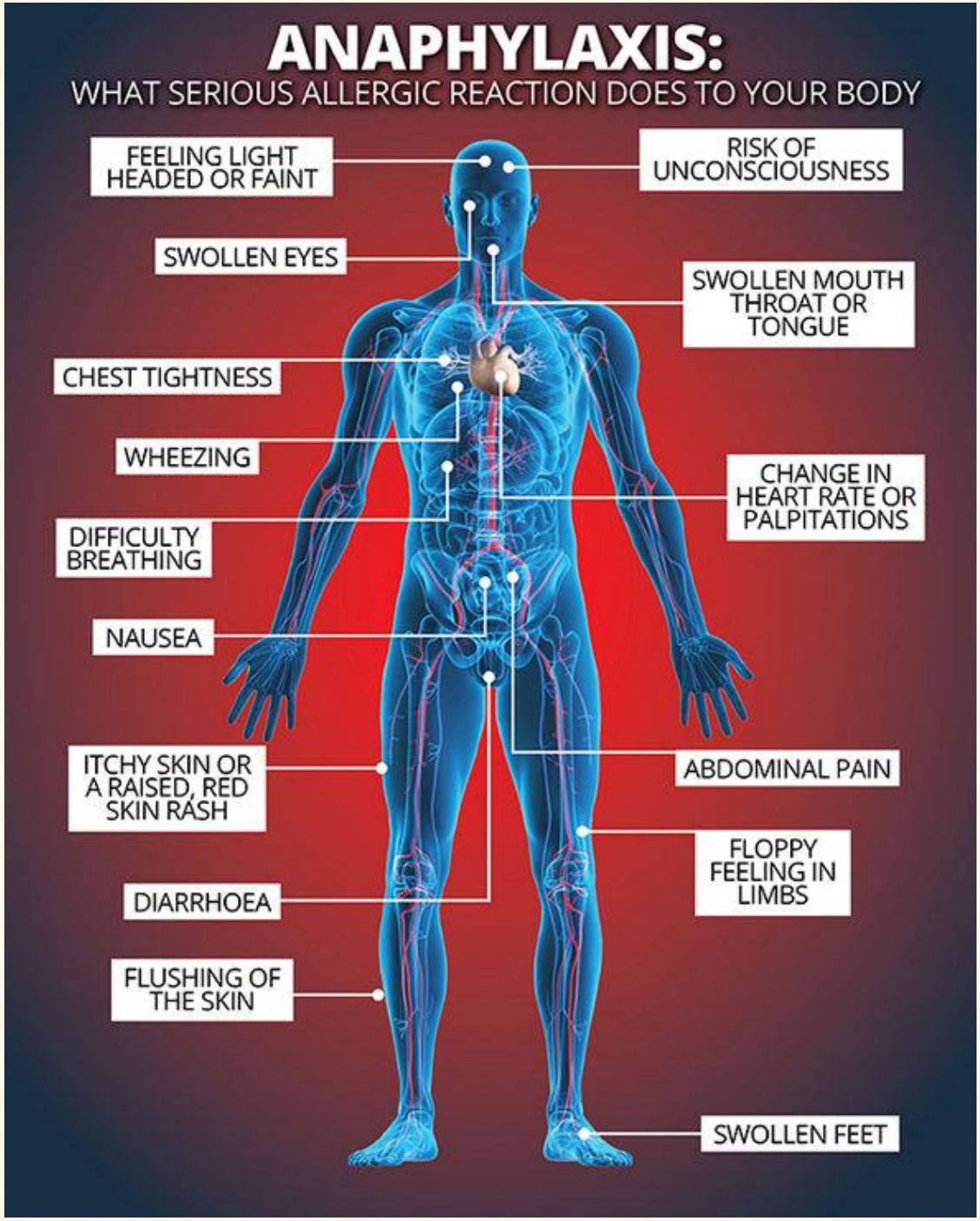
leukotriene B_4	basophil attractant
leukotriene C_4, D_4	same as histamine but 1000x more potent
prostaglandins D_2	edema and pain
PAF	platelet aggregation and heparin release: microthrombi

Clinical forms of allergic reactions

- Acute allergy – anaphylaxis
- Subacute and chronic allergies initiated by aeroallergens and food allergens
- Secondary organ failures caused by chronic allergies



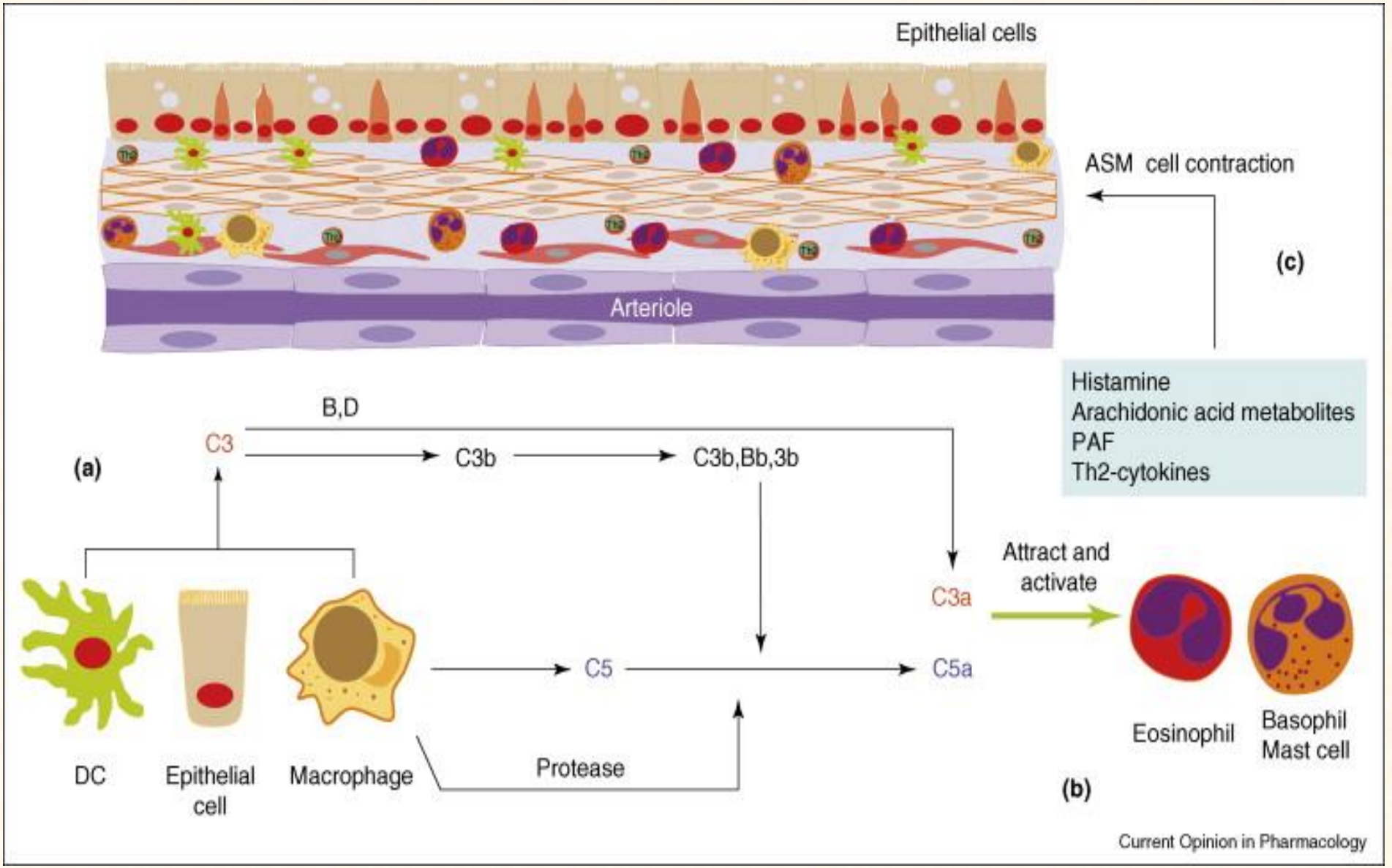
Anaphylaxis is a serious acute allergic reaction that is rapid in onset and may lethal.


ANAPHYLAXIS:
WHAT SERIOUS ALLERGIC REACTION DOES TO YOUR BODY
FEELING LIGHT HEADED OR FAINT
RISK OF UNCONSCIOUSNESS
SWOLLEN EYES
SWOLLEN MOUTH THROAT OR TONGUE
CHEST TIGHTNESS
WHEEZING
CHANGE IN HEART RATE OR PALPITATIONS
DIFFICULTY BREATHING
NAUSEA
ITCHY SKIN OR A RAISED, RED SKIN RASH
ABDOMINAL PAIN
FLOPPY FEELING IN LIMBS
DIARRHOEA
FLUSHING OF THE SKIN
SWOLLEN FEET

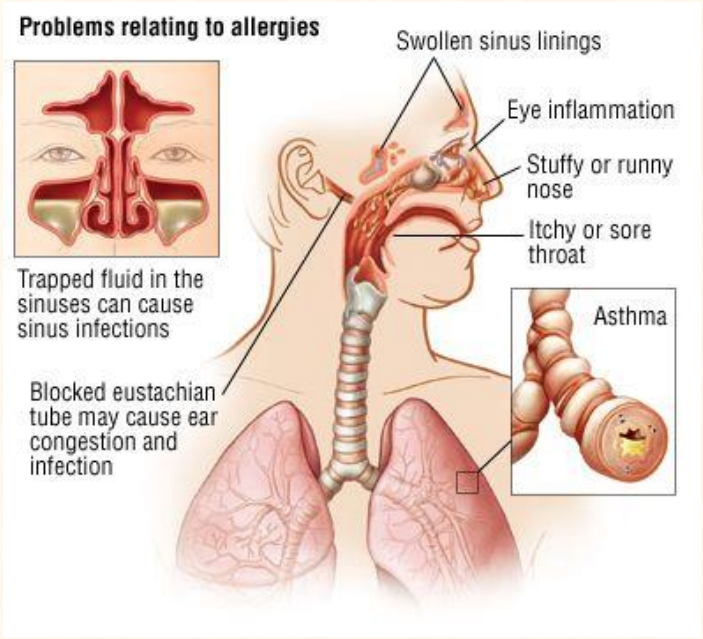
IgG mediated anaphylaxis

- More antigen-specific IgG produced as IgE and FcγRIIIA and FcγRIV on neutrophils can activate anaphylaxis in mouse model.
- Human neutrophils, but also mast cells and basophils, express neither FcγRIIIA nor FcγRIV, but FcγRIIA triggers allergic reactions.
- FcγRIIB have dominant inhibitory effect over positive signals triggered by FcγRIIA.
- Co-engagement of FcεRI with FcγR (both inhibitory and triggering) induces FcγRIIB-dependent inhibition of IgE-induced responses of human basophils.
- IgG antibodies can develop antagonistic roles when engaging low-affinity IgG receptors on granulocytes, but they can trigger allergic reactions by engaging with FcγRIIA expressed by neutrophils, monocytes, macrophages and mast cells, but inhibitory effect if expressed in basophils.

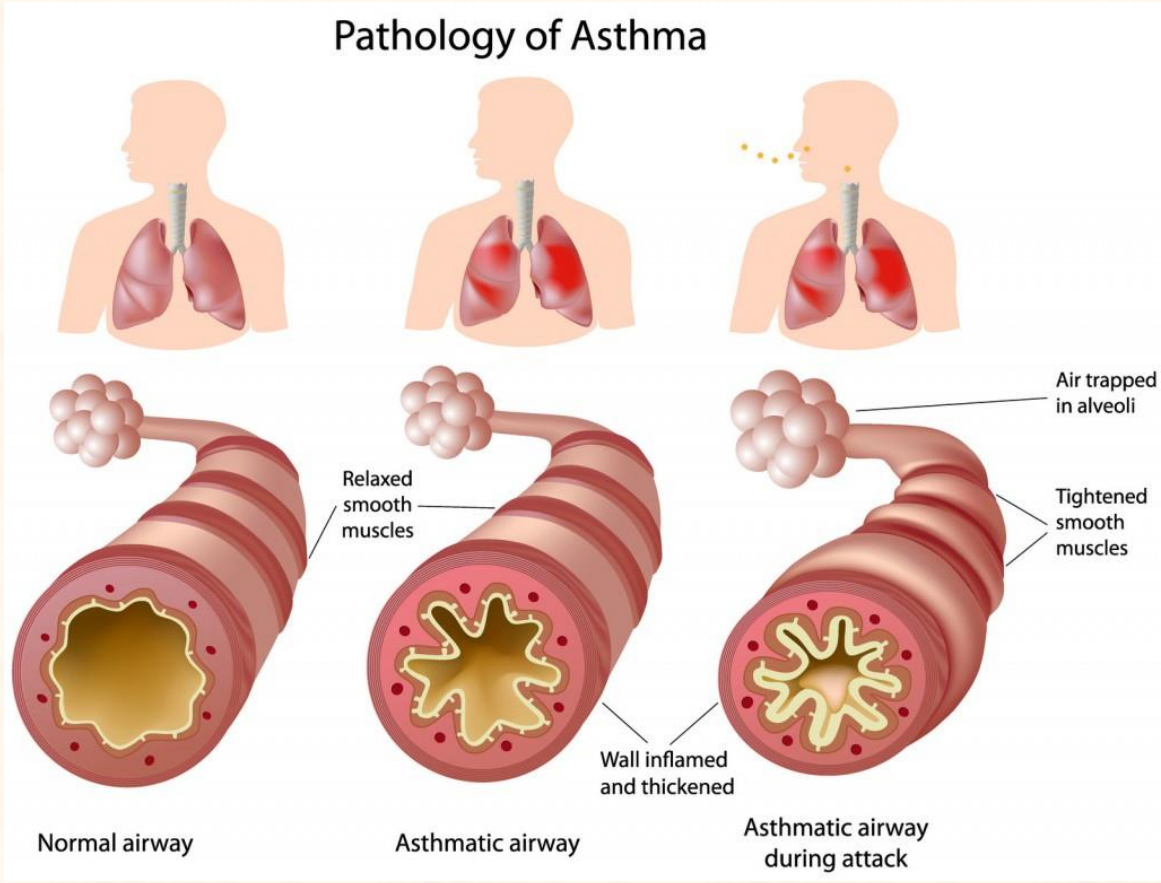
Complement induced allergic asthma



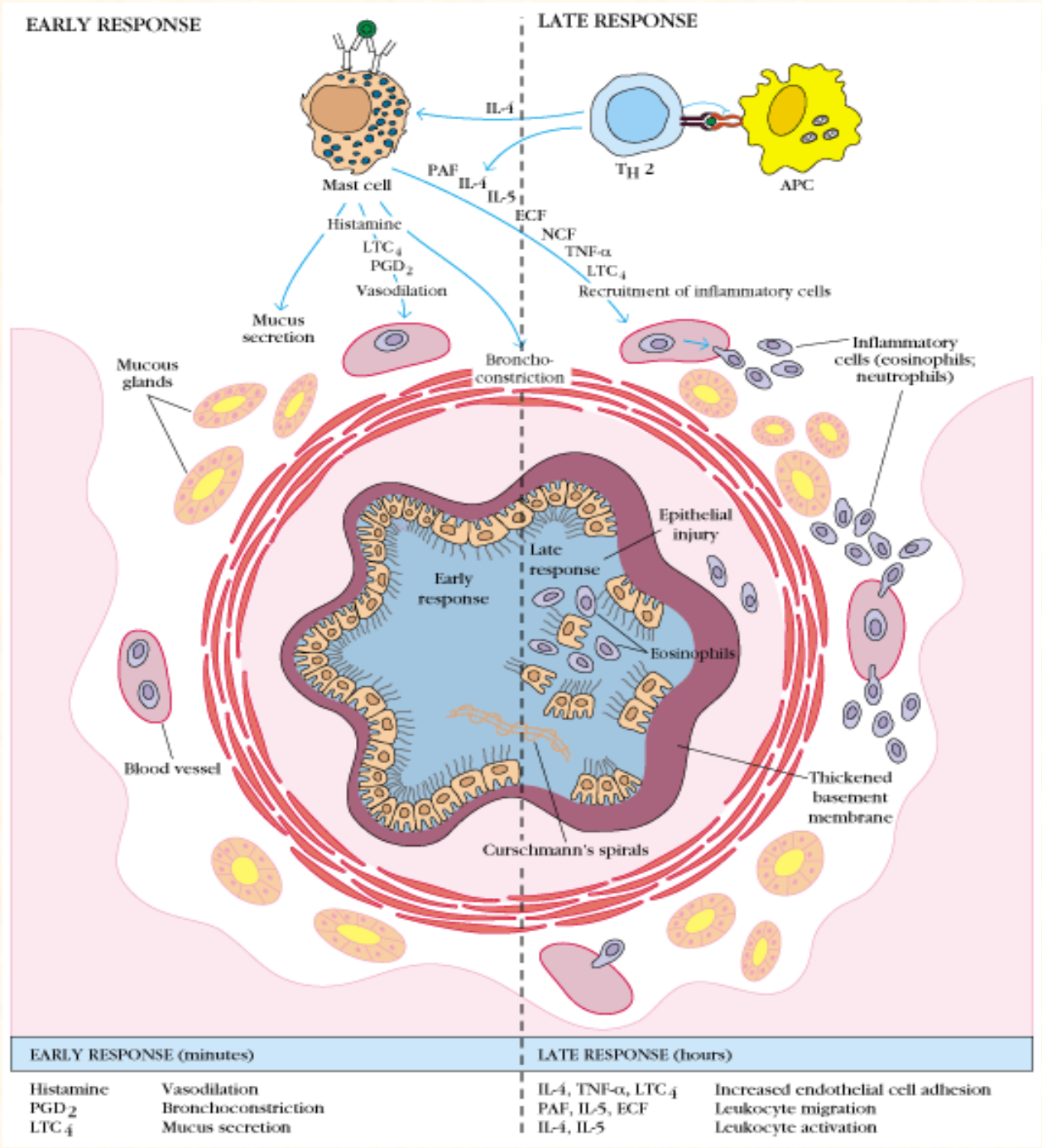
Consequences of chronic respiratory allergy



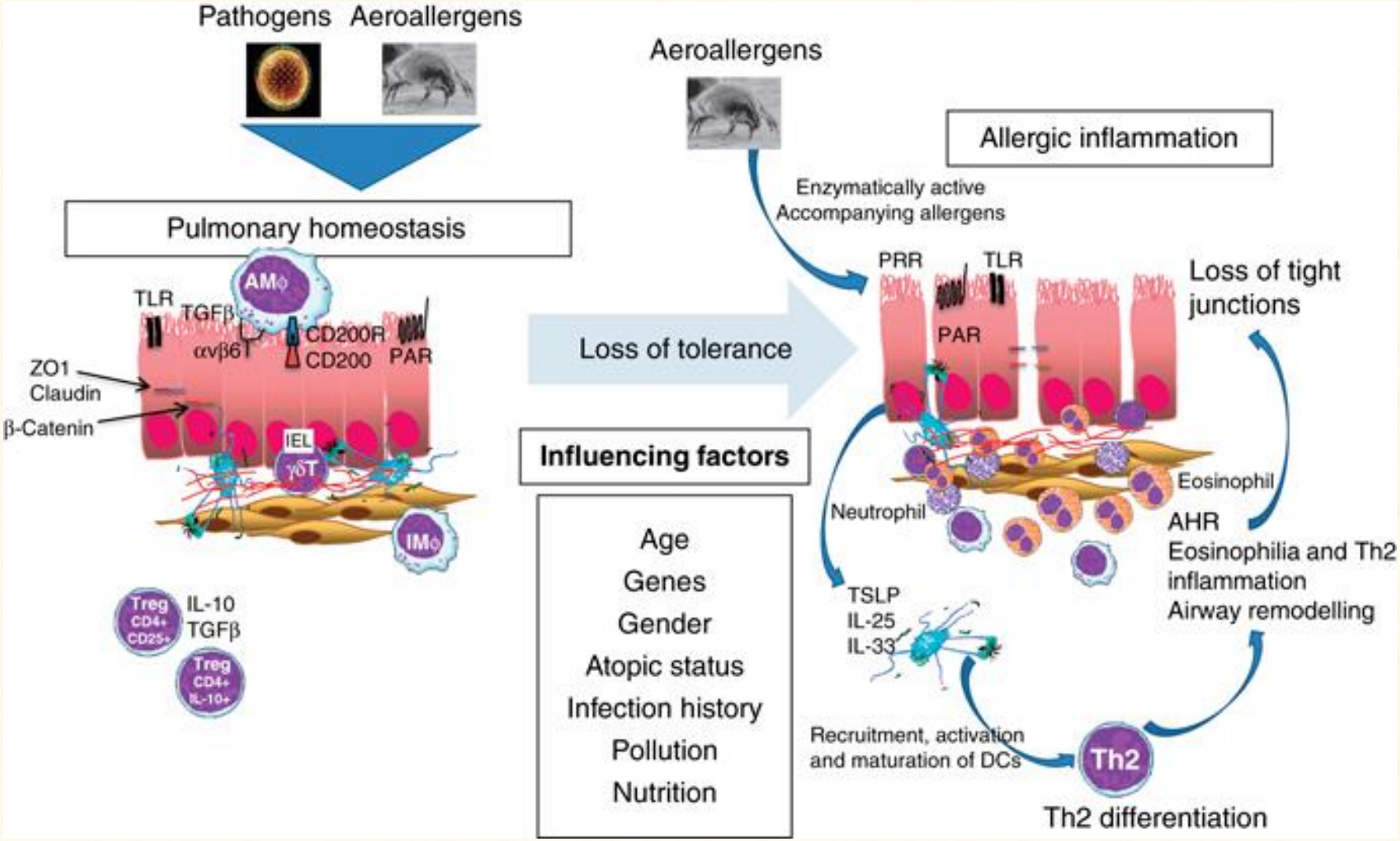
Chronic sinusitis and rhinitis, middle ear, eye and lacrimal gland inflammations



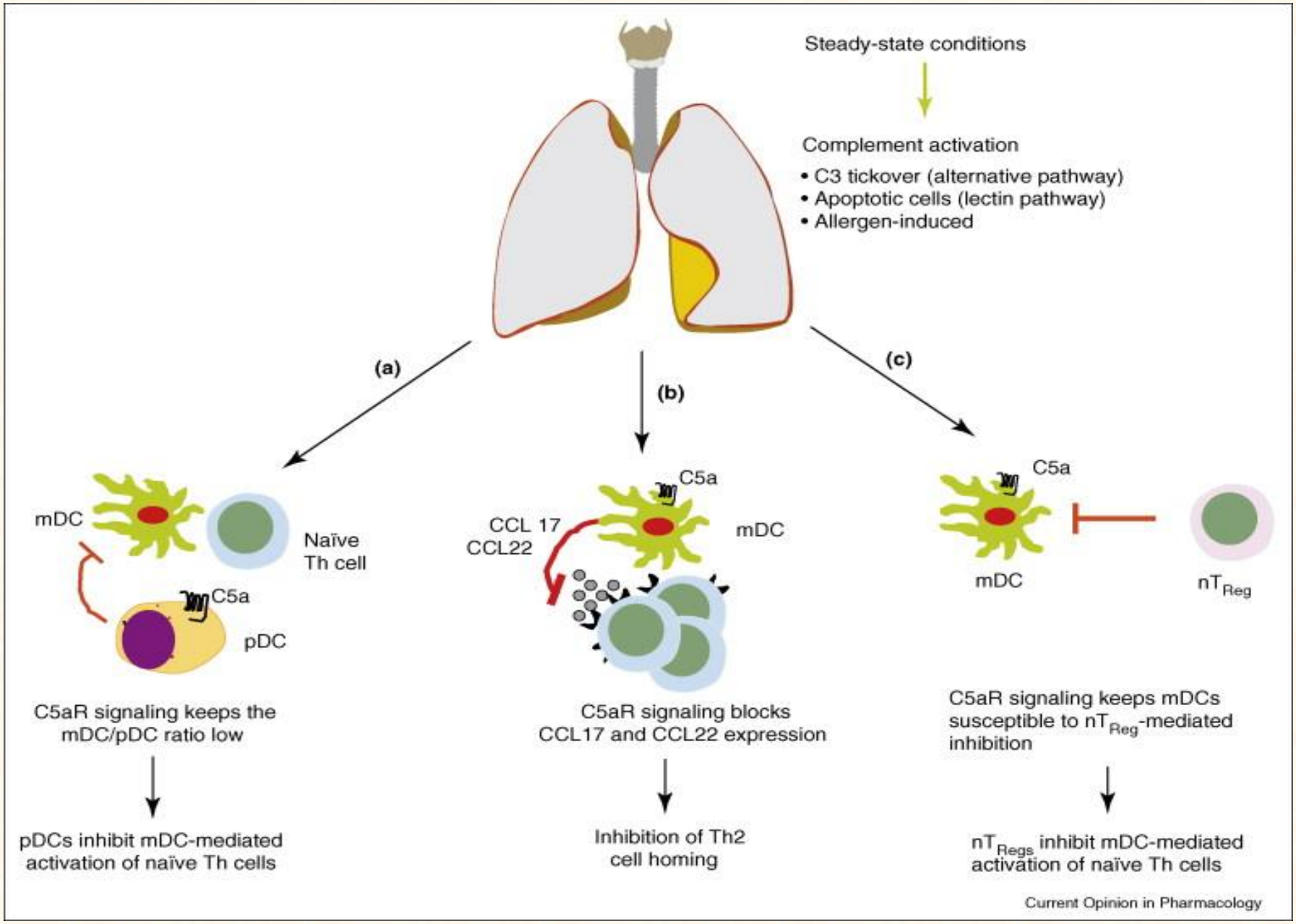
Asthma bronchiale


EARLY RESPONSE
LATE RESPONSE
IL-4
PAF
IL-4
IL-5
Mast cell
T_H 2
APC
ECF
NCF
TNF-α
LTC_4
Recruitment of inflammatory cells
Histamine
LTC_4
PGD_2
Vasodilation
Mucus secretion
Broncho-constriction
Mucous glands
Inflammatory cells (eosinophils; neutrophils)
Epithelial injury
Late response
Early response
Eosinophils
Blood vessel
Thickened basement membrane
Curschmann's spirals
EARLY RESPONSE (minutes)
LATE RESPONSE (hours)
Histamine
PGD_2
LTC_4
Vasodilation
Bronchoconstriction
Mucus secretion
IL-4, TNF-α, LTC_4
PAF, IL-5, ECF
IL-4, IL-5
Increased endothelial cell adhesion
Leukocyte migration
Leukocyte activation

Pulmonary allergy



Protective role of C5aR signaling in allergic asthma



Pollen and Food Allergy Syndrome: cross-reactivity between aeroallergens and food allergens

In respiratory allergy, cross-reactivity between aeroallergens and foods may induce food allergy symptoms ranging from oral allergy syndrome to severe anaphylaxis. Clinical entities due to IgE sensitization to cross-reactive aeroallergen and food allergen components are described for many sources of plant origin (pollen-food syndromes and associations, such as birch-apple, cypress-peach and celery-mugwort-spice syndromes, and mugwort-peach, mugwort-chamomile, mugwort-mustard, ragweed-melon-banana, goosefoot-melon associations), fungal origin (Alternaria-spinach syndrome), and invertebrate, mammalian or avian origin (mite-shrimp, cat-pork, and bird-egg syndromes). Clinical cases of allergic reactions to ingestion of food products containing pollen grains of specific plants, in patients with respiratory allergy to Asteraceae pollen, especially mugwort and ragweed, are also mentioned, for honey, royal jelly and bee polen dietary supplements, along with allergic reactions to foods contaminated with mites or fungi in patients with respiratory allergy to these aeroallergens.

Popescu FD: World J Methodol. 2015

celery-mugwort-spice-syndrome

Apiaceae

Solanaceae

Piperaceae

Anacardiaceae

Liliaceae

mugwort-mustard-syndrome

Cruciferae

*Leguminosae**

*Rosaceae**

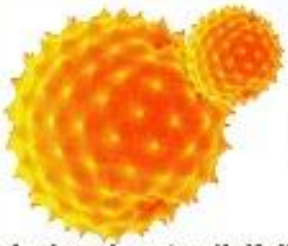
Artemisia vulgaris

mugwort-peach-association

Rosaceae

mugwort-chamomile-association

Asteraceae



Ambrosia artemiisifolia

ragweed-melon-banana-association

Cucurbitaceae

Musaceae

Therapeutic relevances

1. **Acute intervention**

(adrenalin, corticosteroid)

EpiPen®

2. **Prevention**

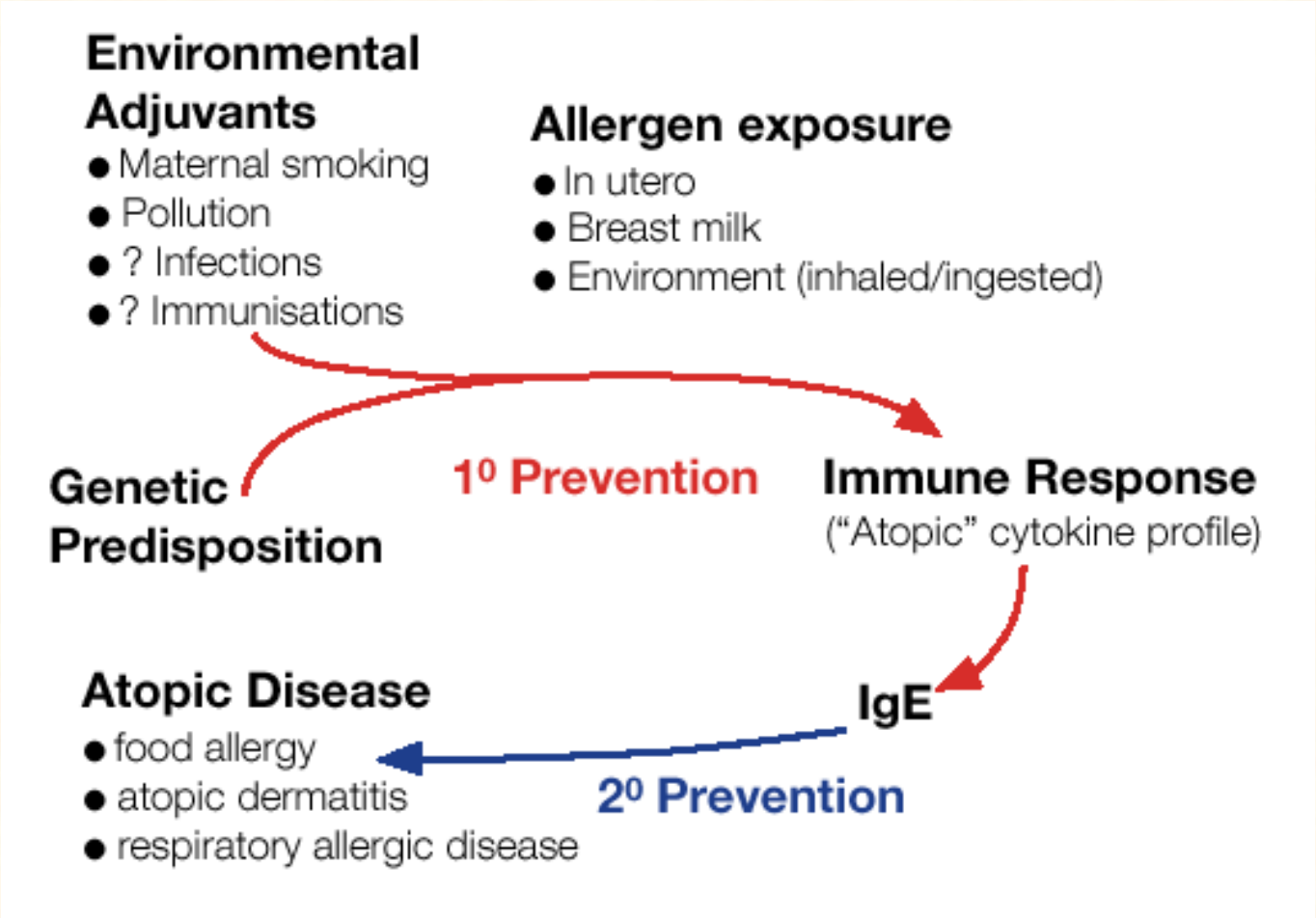
- **Allergen free environment**
- **Desensibilization**

3. **Treatments**

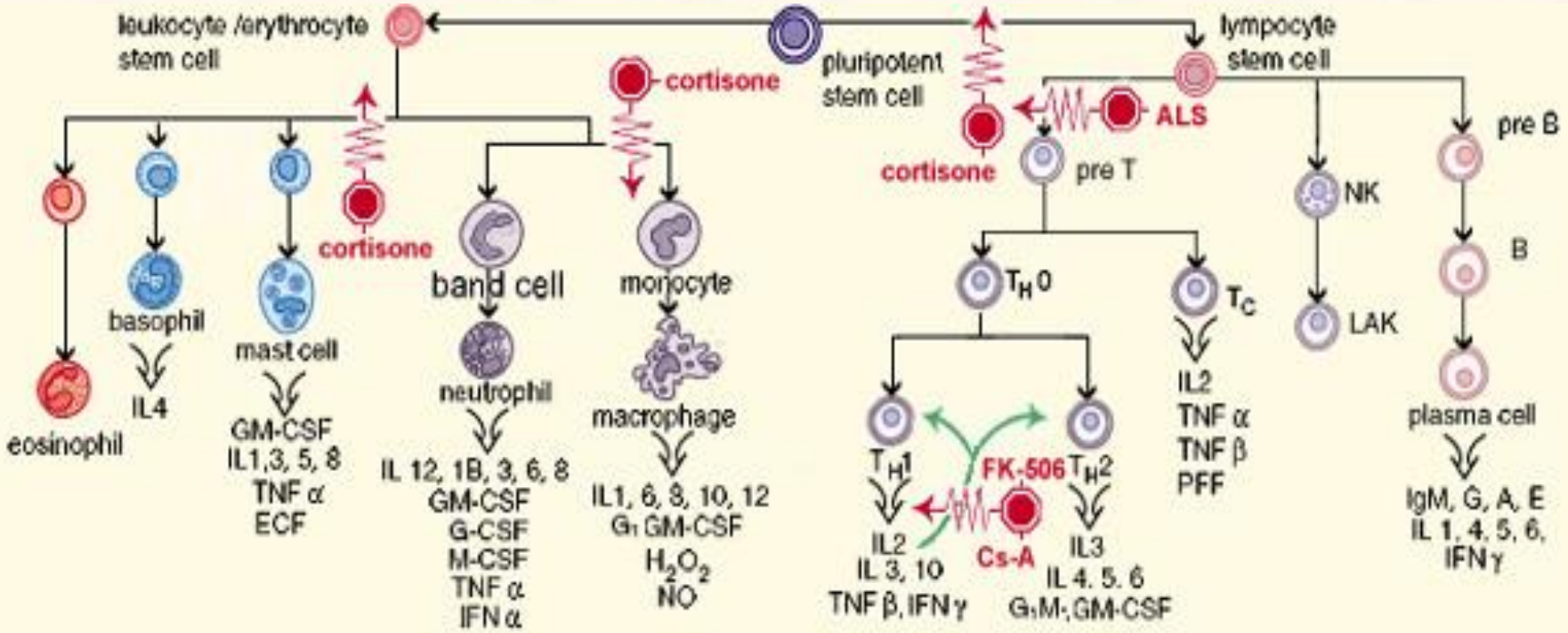
- **Antihistamins**
- **Non-specific immunosuppression**

Prevention

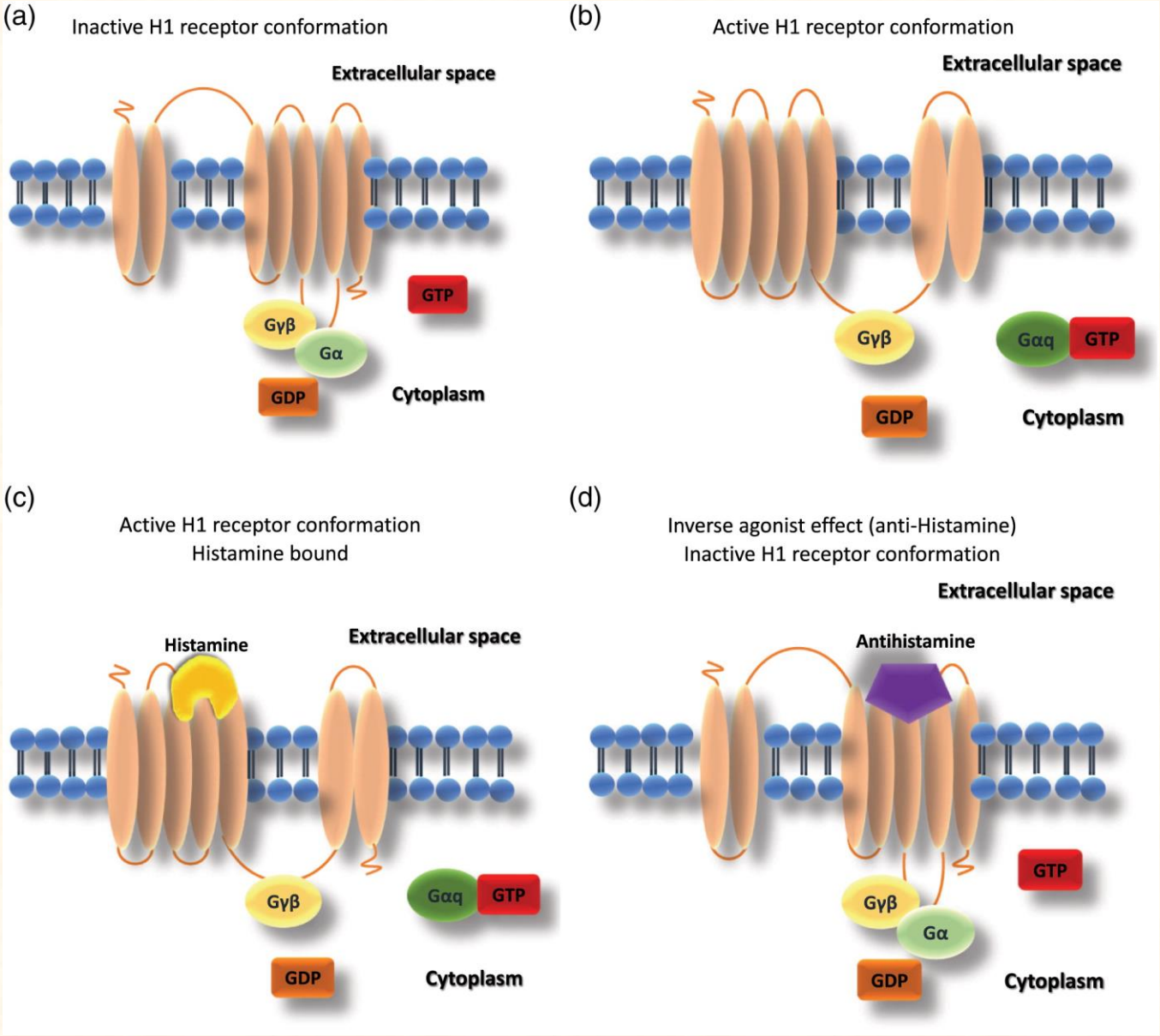
- **Allergen free environment**
- **Primary and secondary prevention**



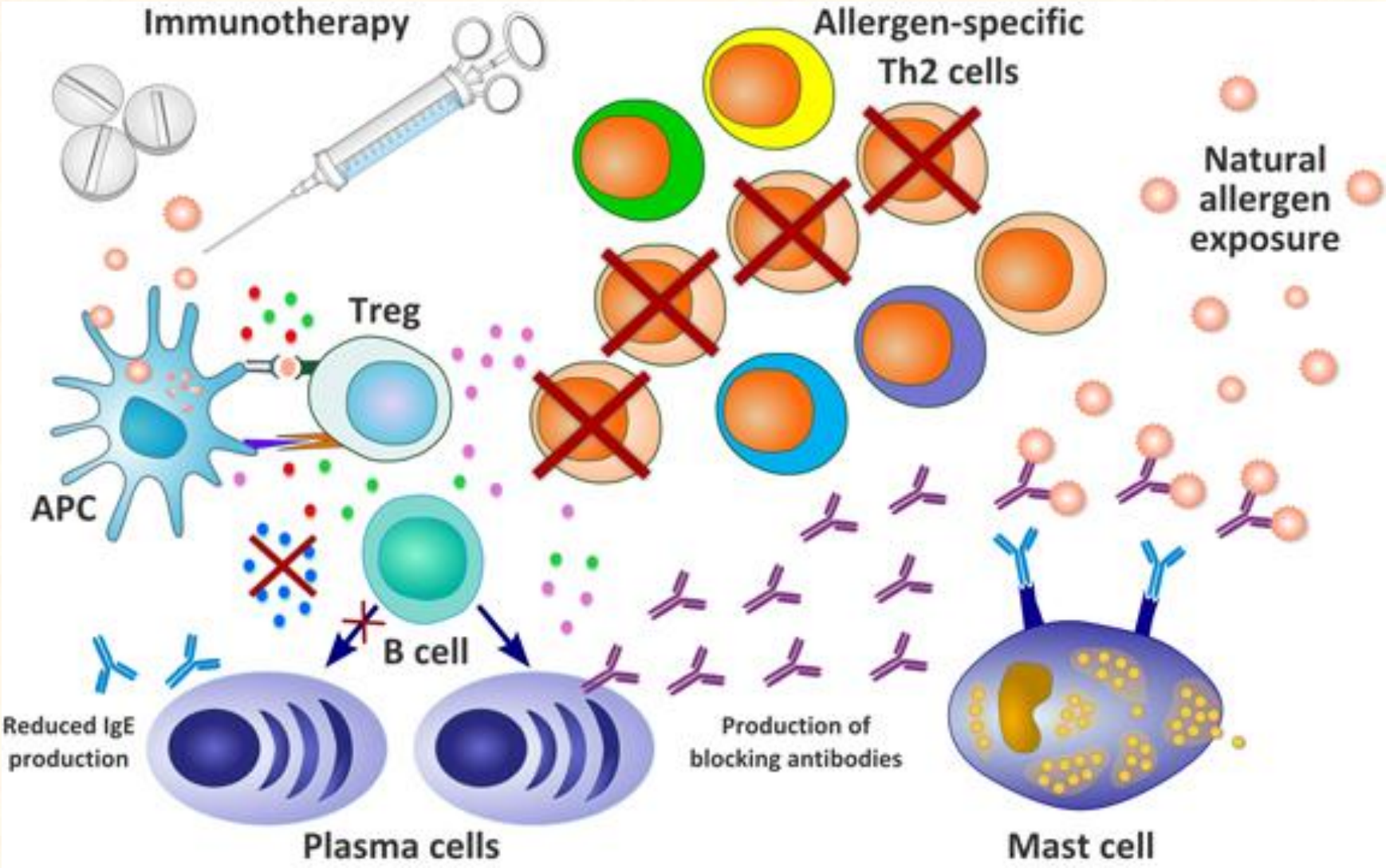
Immunosuppression



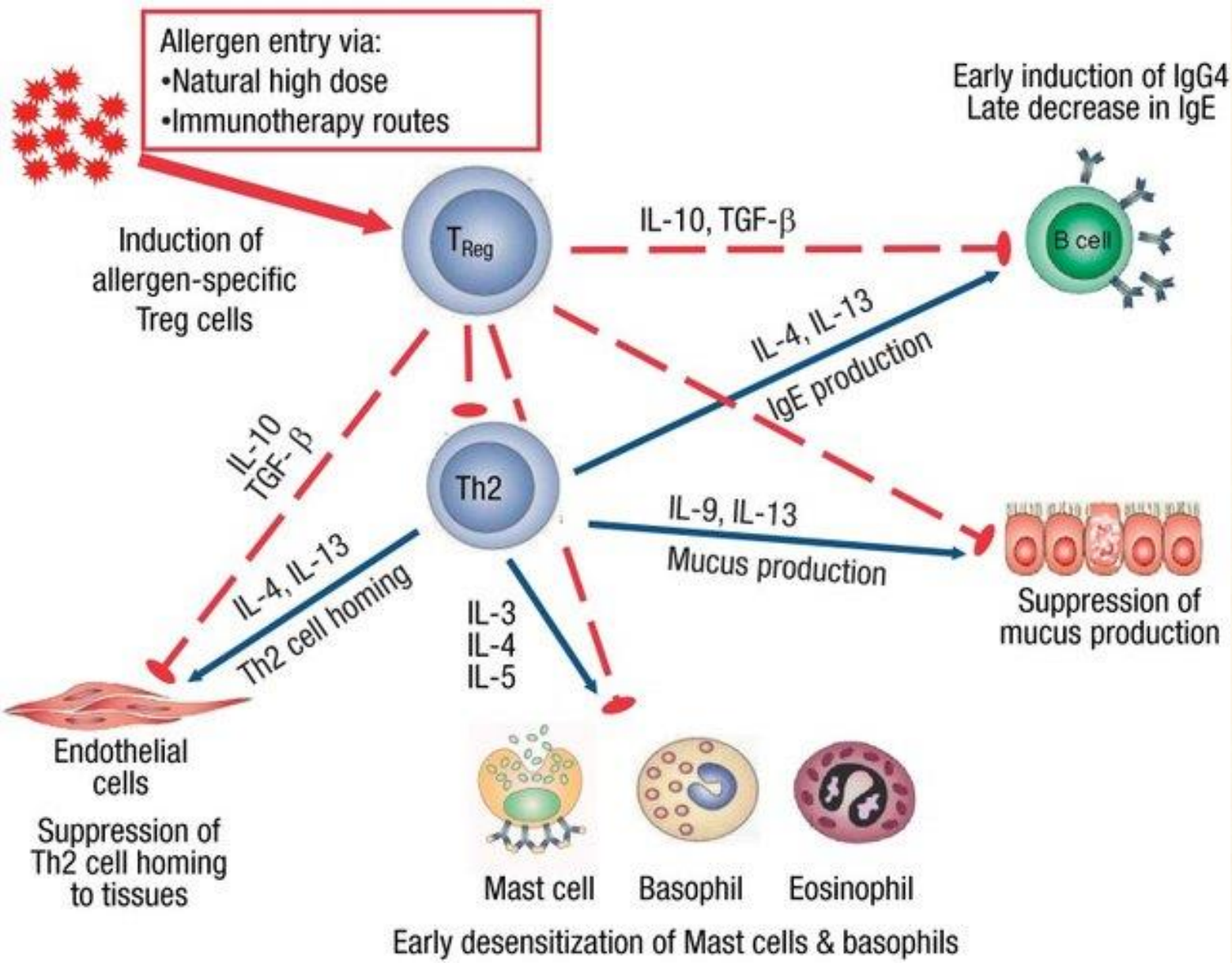
Mechanism of action of antihistamines



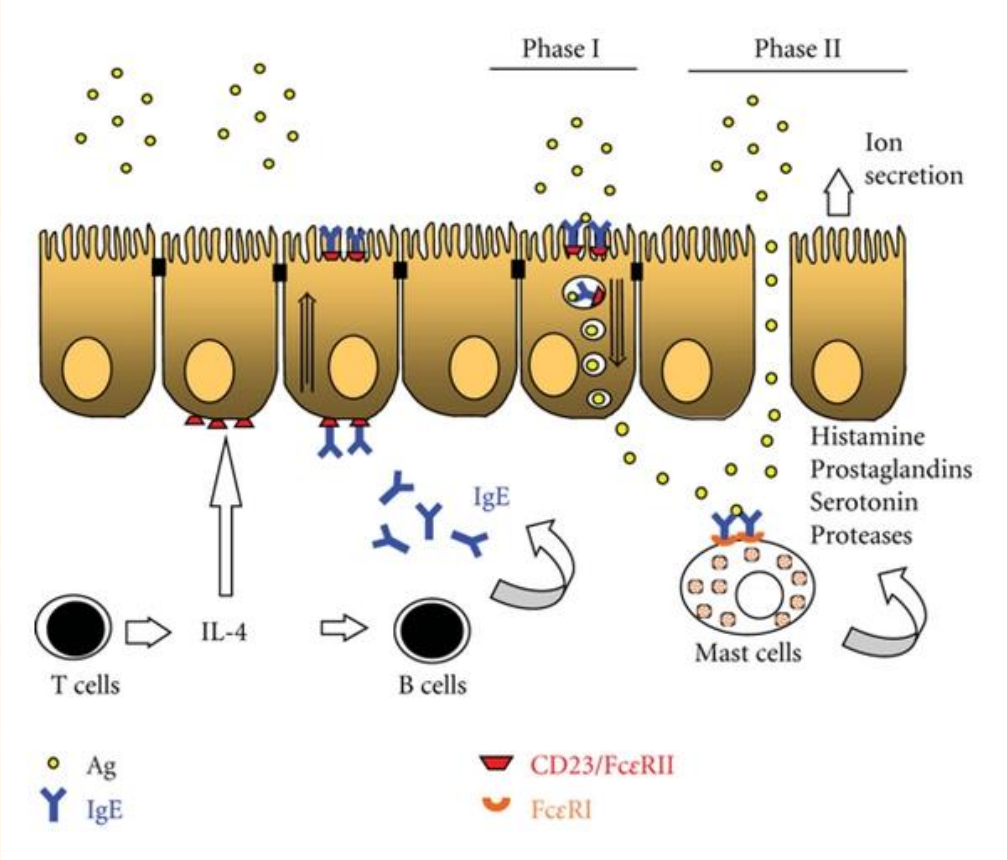
Desensibilisation



Mechanisms of tolerance to allergens



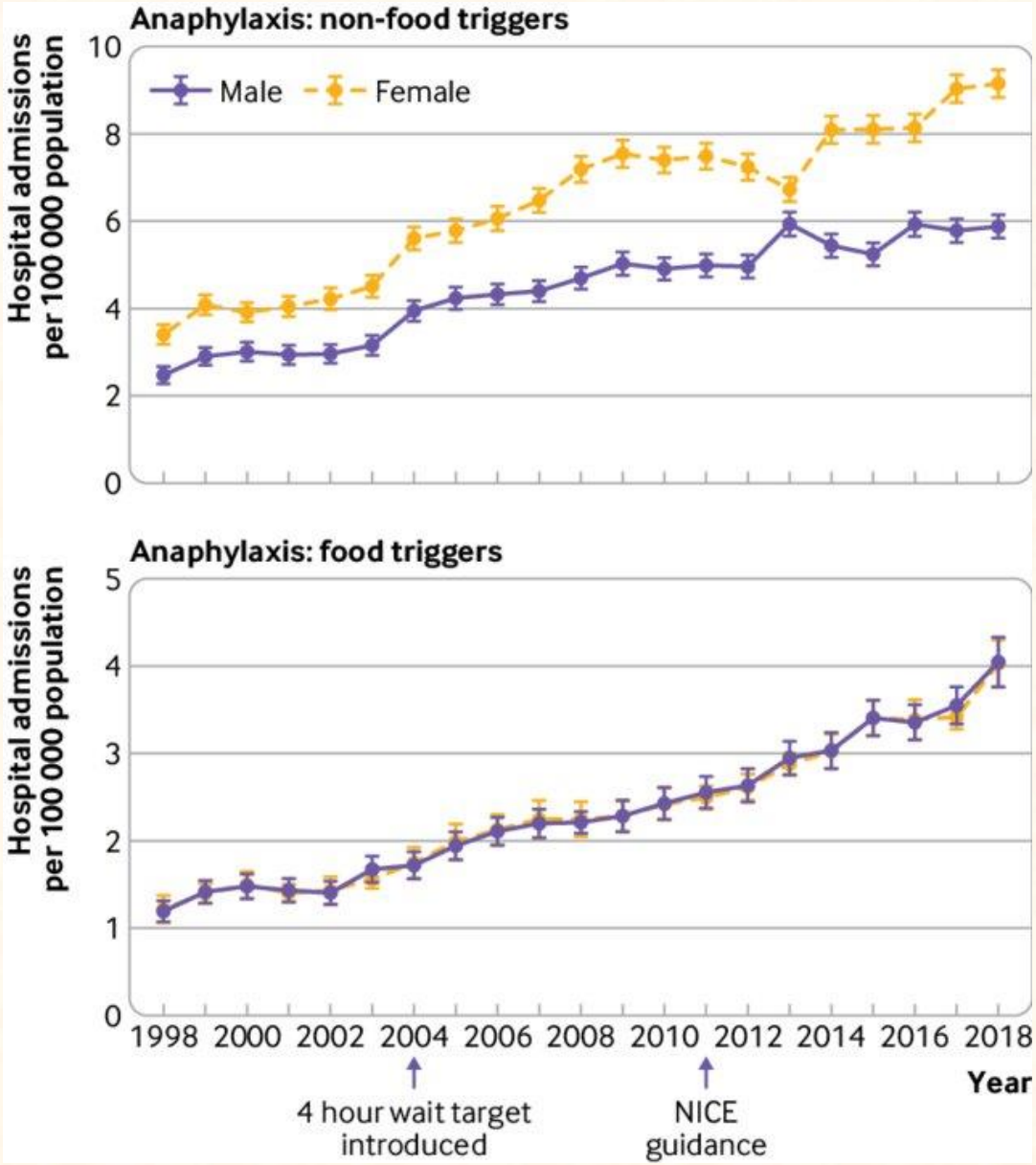
In vivo intranasal anti-CD23 treatment inhibits allergic responses in a murine model of allergic rhinitis



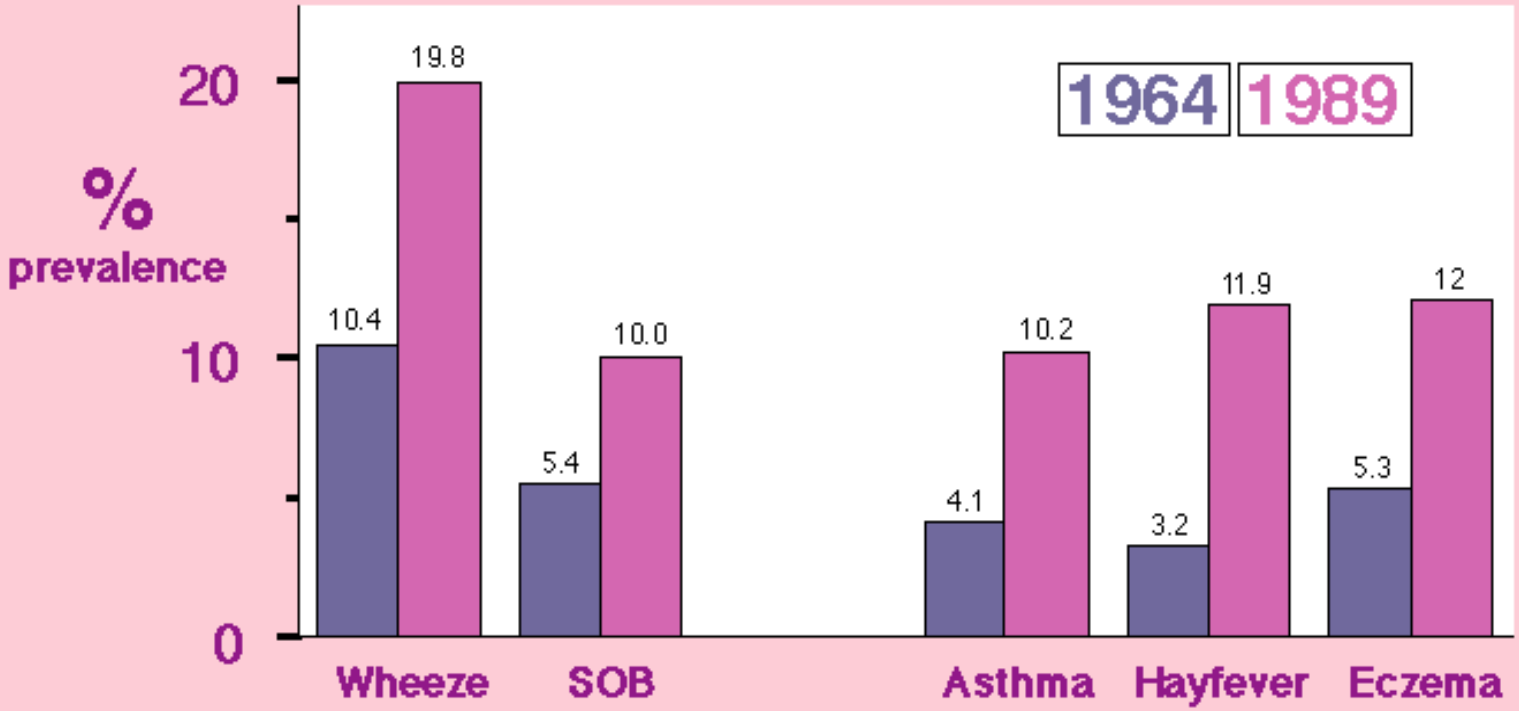
CD23-dependent transcytosis of IgE and IgE-derived immune complexes across respiratory epithelial cells is likely to play a pivotal role in the initiation and development of airway allergic inflammation and suggest that the targeting of CD23 could be used as a means of therapeutic intervention.

Zhou M1, Du D, Zhao K, Zheng C. : J Mol Histol. 2013

Incidence of anaphylaxis in the United Kingdom between 1998 - 2018

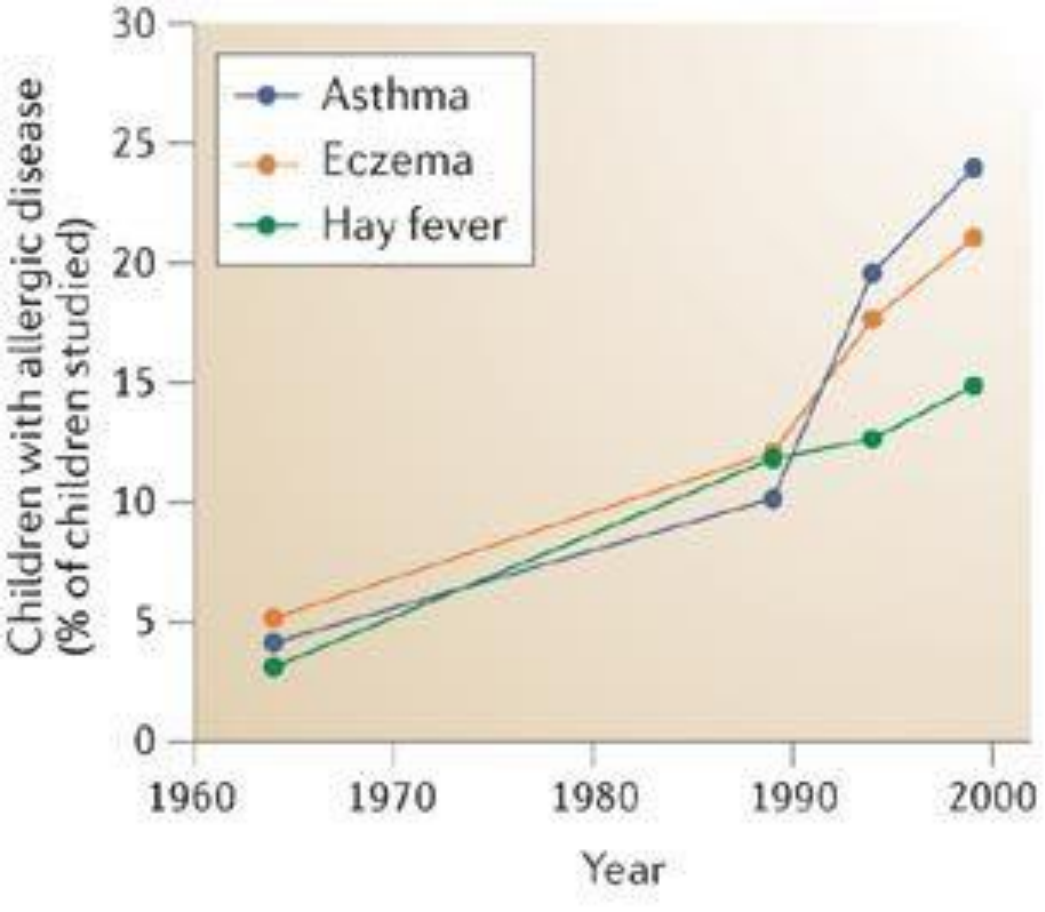


Increasing prevalence of asthma & atopy
Aberdeen 1964 - 1989
schoolchildren aged 8 - 13 yrs inclusive



Ninan TK, Russell G. BMJ 1992;304:873-5

Prevalence of allergic diseases increasing in the industrialized countries continuously



- Diet
- Maternnal diet during pregnancy
- Smoking
- Alterations in microbiota
- Antibiotic treatments
- ?
- ?
- ?

Continuation of the Aberdeen Study

Devereux G.: **Nat Rev Immunol. 2006**