

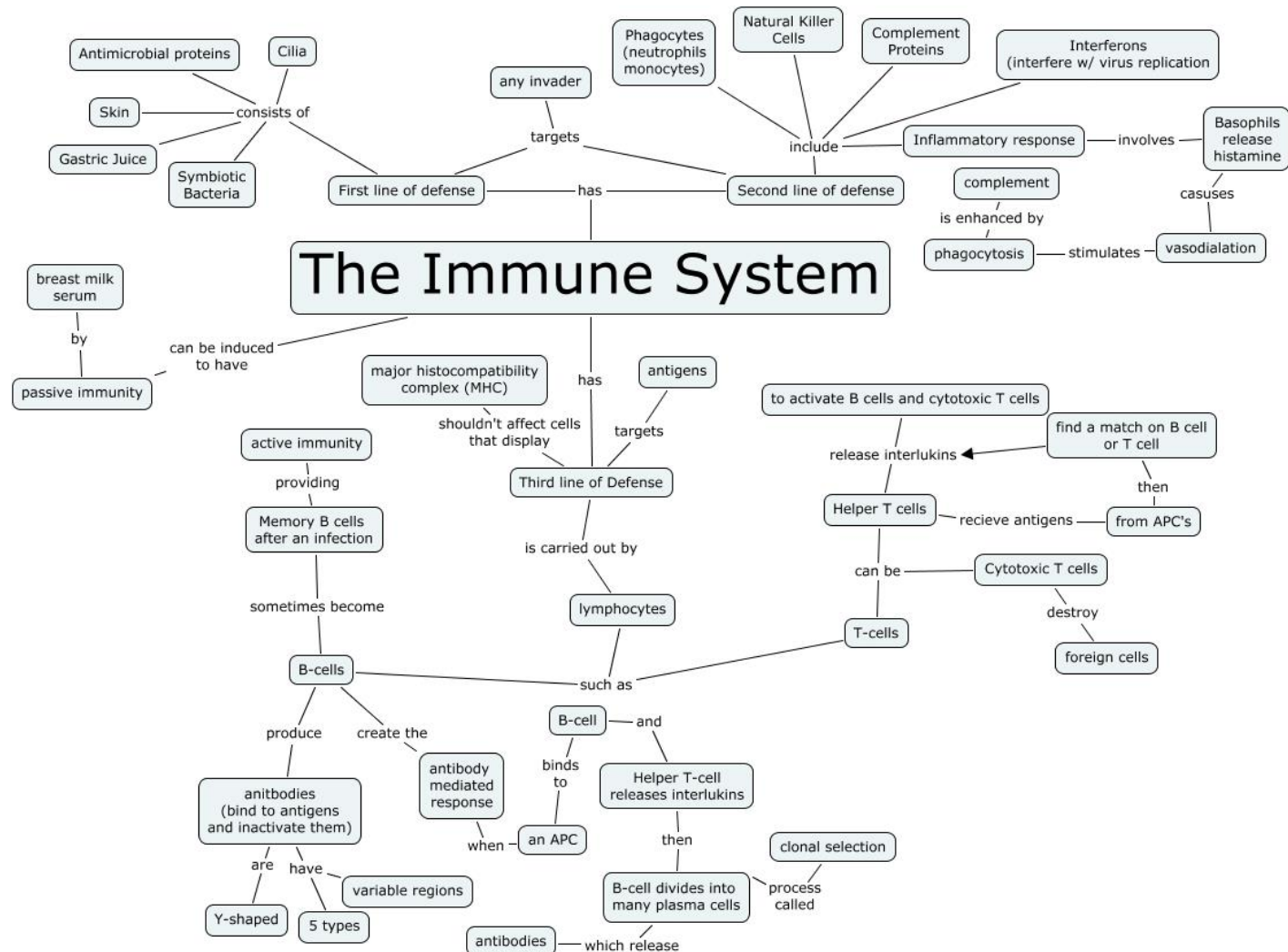
Classification, pathogenesis and diagnostics of allergic diseases

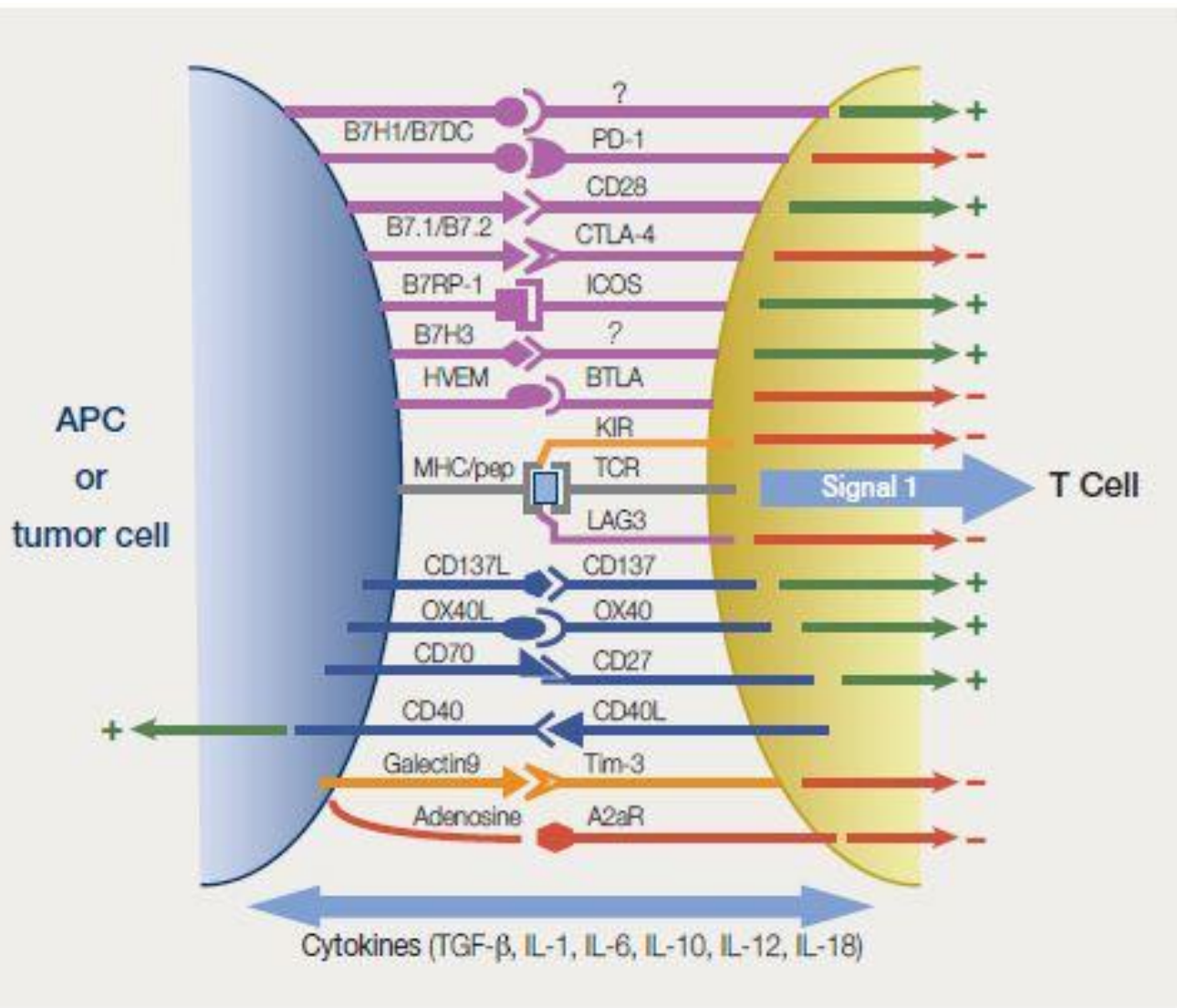
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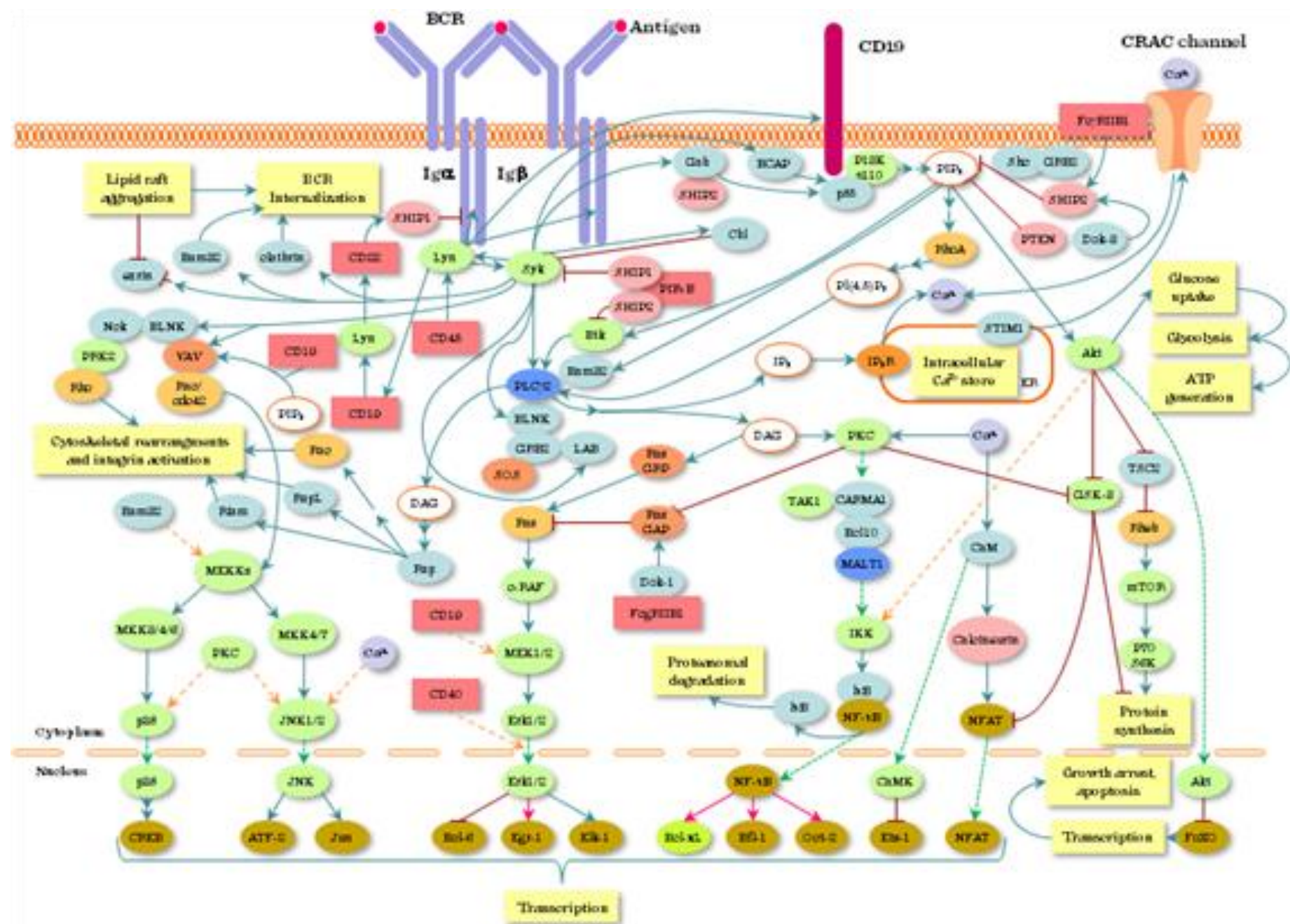


Of all the body's organs, the immune system may be the most challenging to coordinate. The system is collection of individual immune cells, immune cell aggregates, immune tissues, and immune organs.

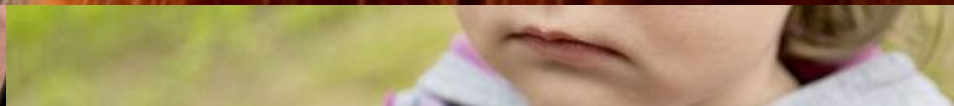


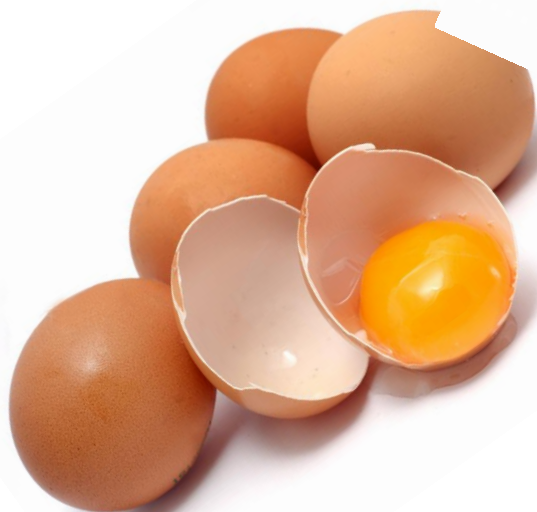


- Billions of immune cells communicate with each other.
- Functional integration of the immune system is accomplished mainly by cell-to-cell communication
- Every immune system cell is equipped with different surface molecules and is able to synthesize and release a variety of small molecules that travel to other cells and stimulate those cells to become either more active or less active



„know that I know nothing“
Socrates



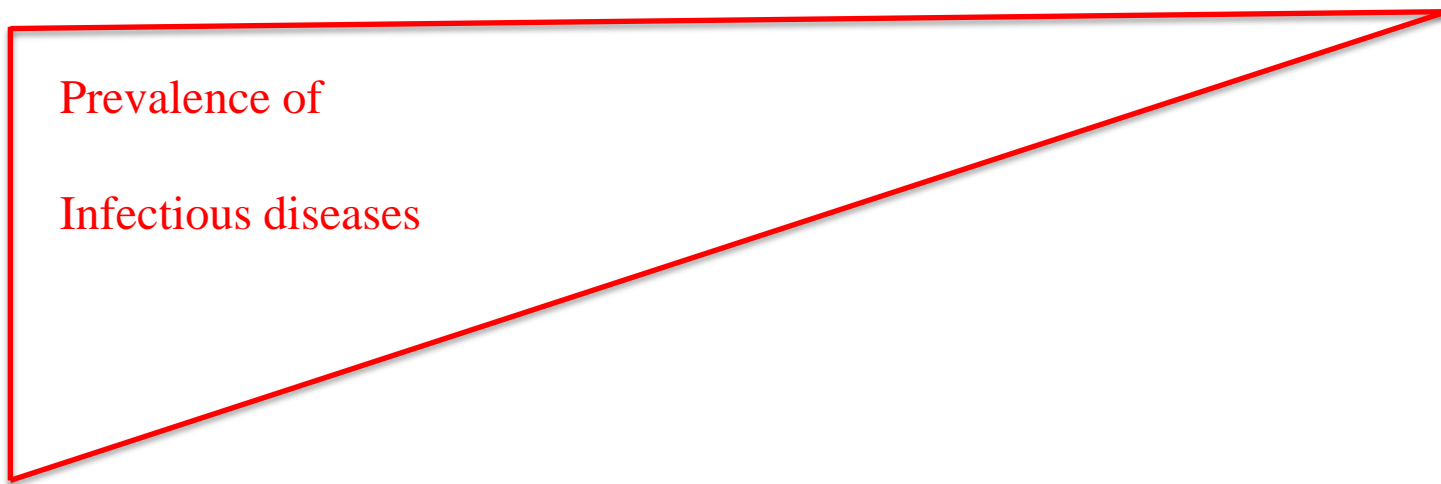
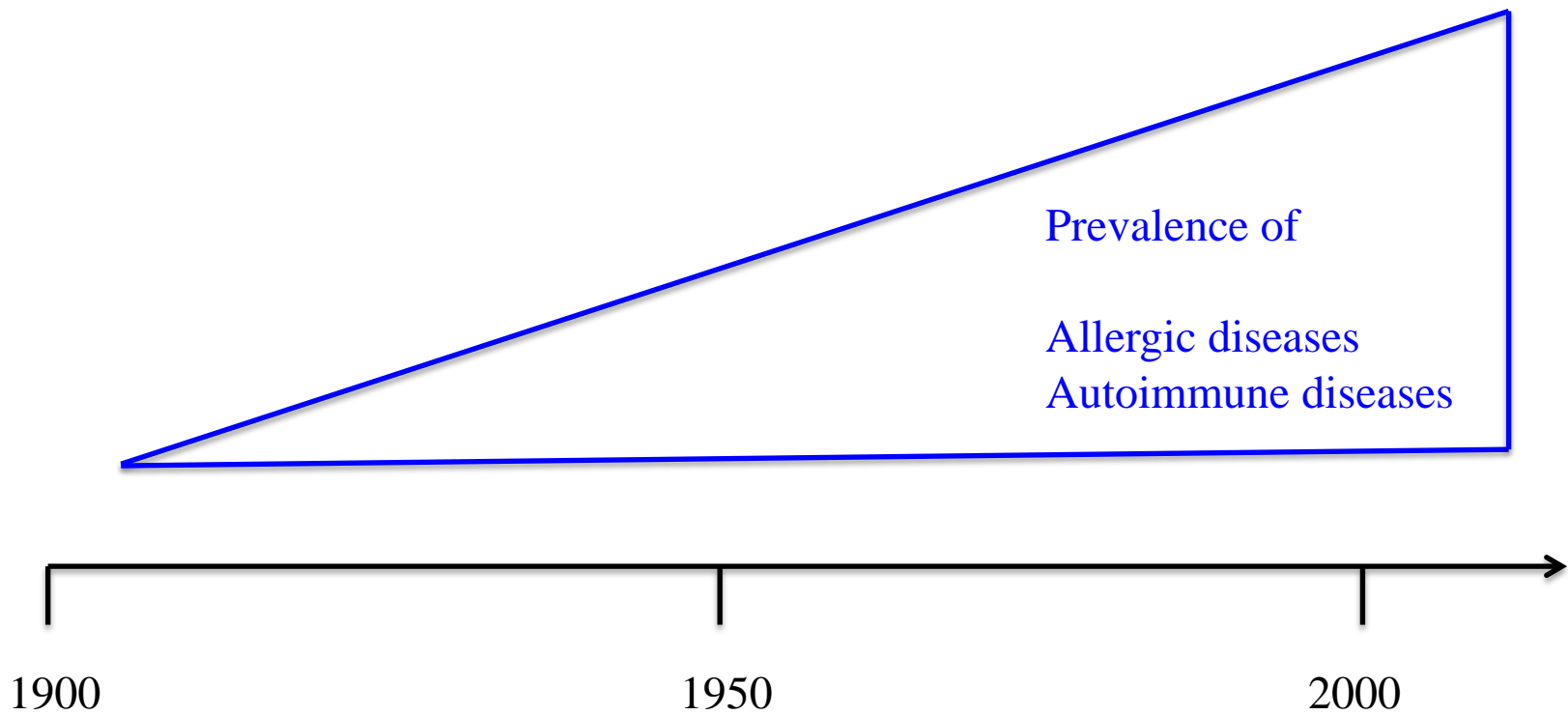




Prävalenzen von Allergien



	Welt	Europa	Schweiz
Allerg. Rhinitis	> 500 Mio.	90 Mio.	2 Mio.
Asthma	300 Mio.	25 Mio.	0,6 Mio.
Nahrungsmittelallergie	250 Mio.	17 Mio.	
Medikamentenallergie	5% hospitalisierter Patienten		



Overview

- Definitions (Allergy/Atopy and Allergens)
- Types of allergic reactions
- Immuncells and Mechanism involved in development of allergic reactions
- Diagnostic
- Treatment

Definitions

Atopy: genetic determined readiness to react by IgE formation to substances taken up via aerogen or gastro-intestinal routes

Sensitization: immune reaction to a foreign substance (proven in skin tests, serology, cellular tests...)

Allergy: immune reaction to a non replicating (harmless) substance (protein, chemical, drug, metal), which leads to clinical symptoms.

In contrast to infections: symptoms are caused almost exclusively by the immune reaction, not by the „bug“ (virus, bacteria, etc.)

Allergens

- Non-reproducing foreign substances
- Mostly Proteins/Glykoproteins
 - Of animal or vegetable origin
 - Drugs/Chemicals



Pflanzen: > 3500 Arten Schweiz

Pilze: ~ 10'000 Arten Schweiz

Tiere: ~ 1,5 Millionen Welt

Hymenopteren: ~ 100'000 Welt

Berufsstoffe: > 400 beschrieben

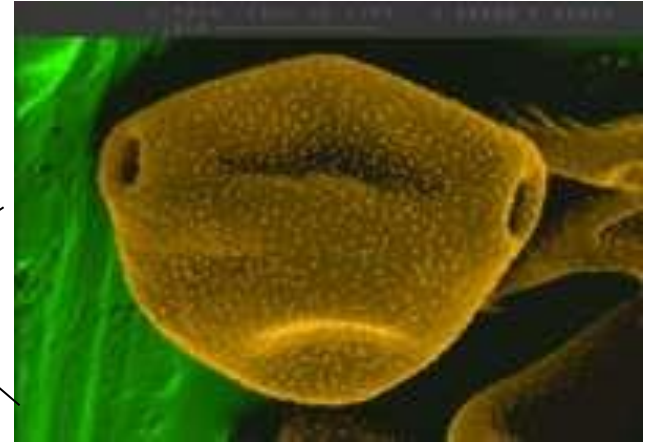
Arzneimittel: ~ 7000 Swissmedic

Allergens = 2% of proteins

Radauer et al. J Allergy Clin Immunol 2008

The allergy is **not** directed to pollen,
but to proteins within pollen !

Pollen = carrier (grain) + allergen (surface) + lipids

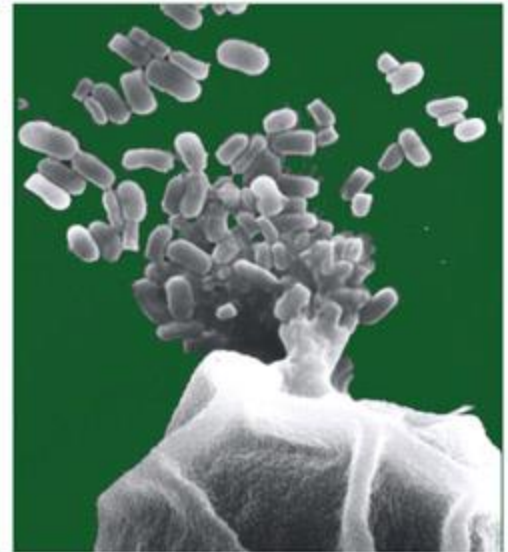
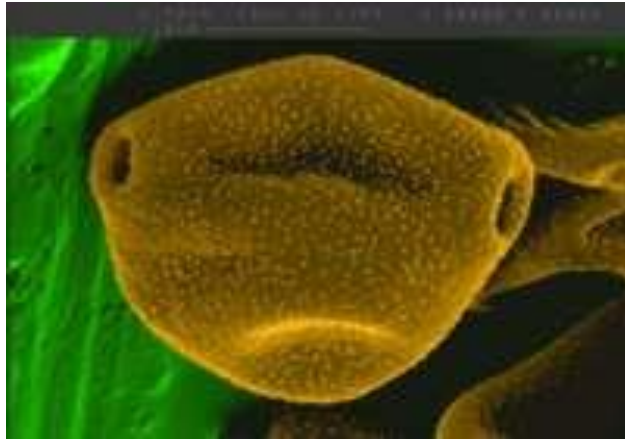
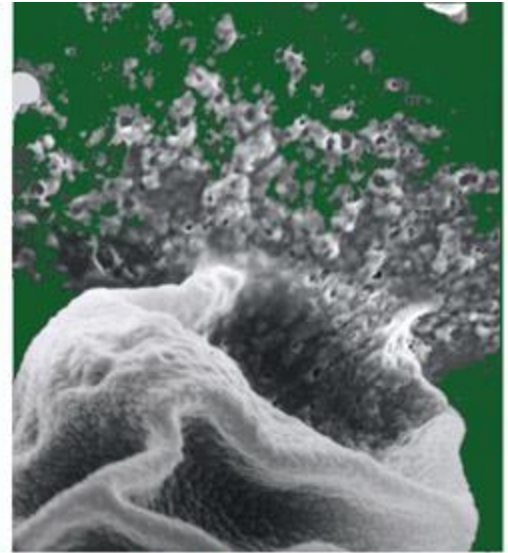
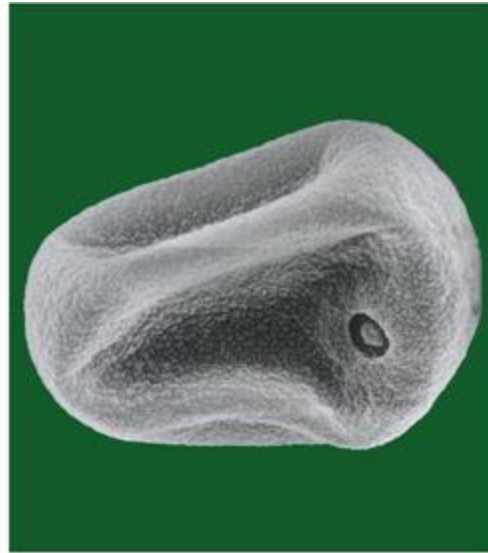
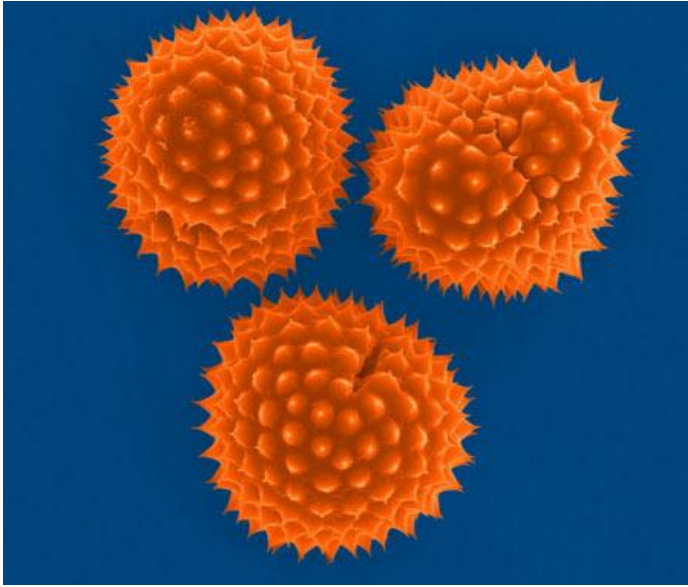


Betula verrucosa 1
Bet v 1

Major Allergen



Pollen



Early and late blooming flowers

www.pollenundallergie.ch / www.meteoschweiz.ch

Februar March April

May

June

July

August

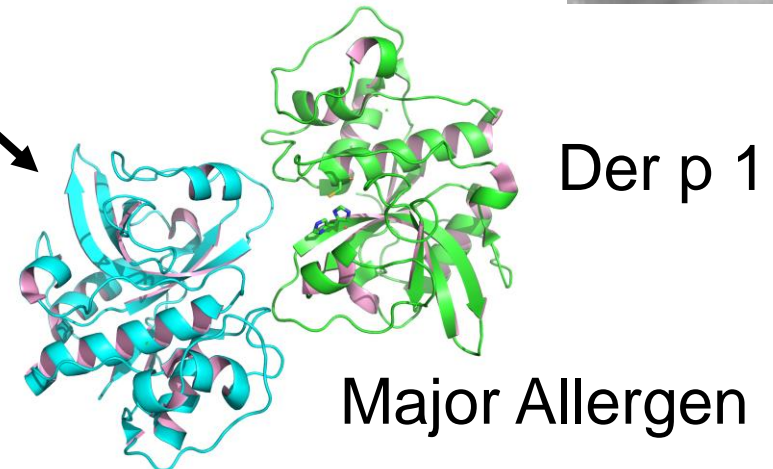
September



House dust mites allergens are a common cause of asthma and allergic symptoms worldwide

- *D. pteronyssinus* (european)
- *D. farinae* (american)
- feed on organic detritus, such as flakes of shed human skin

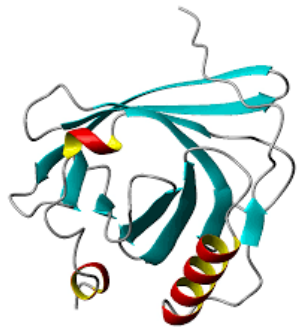
The mite's gut contains potent digestive enzymes (proteases) that persist in their feces



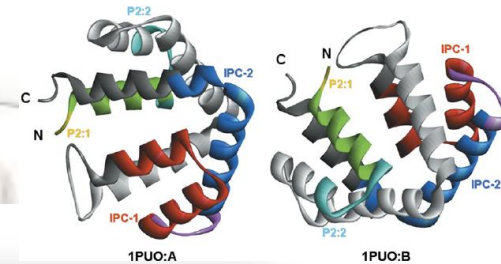
Allergic to your Pet?

Hilger C, Zahradnik E. Allergologie 2015;38:83-90

Can f 1
saliva

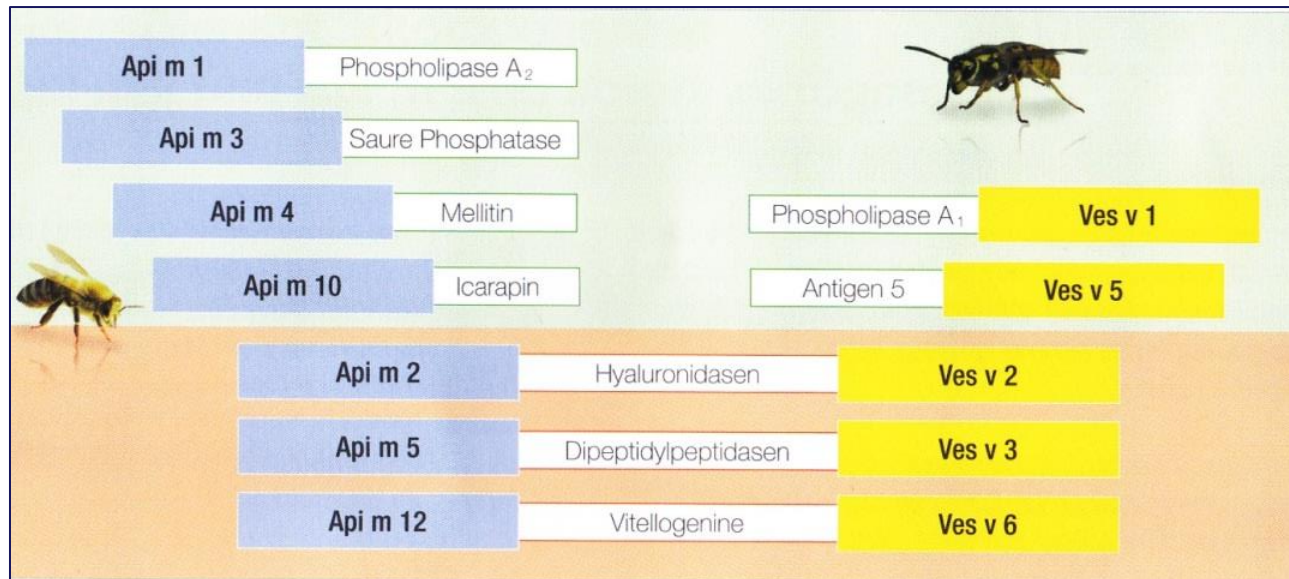


Fel d 1
saliva and skin

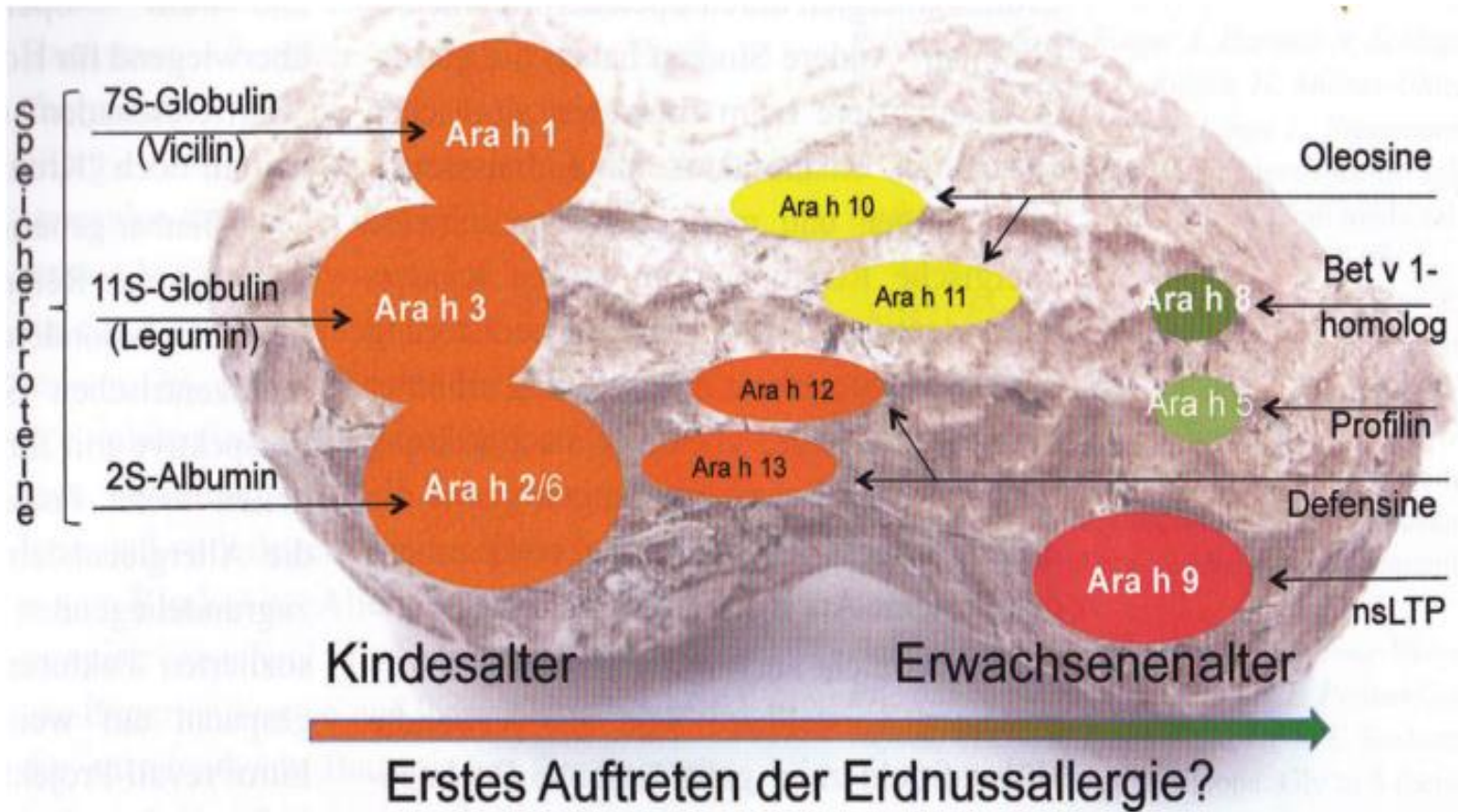


spezies	Allergen	Proteinfamilie	UniProtKB accession No	Apparentes MG in kDa	Allergenquelle	Sensibilisierungsrate in % ¹	In-vitro-Diagnostik verfügbar
Katze	Fel d 1	Sekretoglobin	P30438; P30440	18	Speicheldrüse, Haut	60 – 100	ja
	Fel d 2	Serumalbumin	P49064	69	Leber	14 – 23	ja
	Fel d 3	Cystatin	Q8WNR9	11	Haut	10	nein
	Fel d 4	Lipokalin	Q5VFH6	22	Speicheldrüse	63	ja
	Fel d 5	IgA	–	400	Speichel, Serum	38	nein
	Fel d 6	IgM	–	800 – 1000	Serum	–	nein
	Fel d 7	Lipokalin	E5D2Z5	17,5	Zunge	38	nein
	Fel d 8	Latherin	F6K0R4	24	Speicheldrüse	19	nein
Hund	Can f 1	Lipokalin	O18873	23 – 25	Zunge	50 – 75	ja
	Can f 2	Lipokalin	O18874	19	Zunge, Speicheldrüse	22 – 30	ja
	Can f 3	Serumalbumin	P49822	69	Leber	25 – 35	ja
	Can f 4	Lipokalin	D7PBH4	18	Zunge	35	nein
	Can f 5	Kallikrein	P09582	28	Urin	70	ja
	Can f 6	Lipokalin	H2B3G5	27 – 29	Speicheldrüse	61	nein

Bee / Wasp Allergy



Peanut allergy



Classification according to mechanisms

IgE mediated immune reactions:

e.g. rhinitis & conjunctivitis, asthma, urticaria, anaphylaxis

IgG mediated reactions:

vasculitis, immune hemolytic anemia, thrombocytopenia and granulocytopenia, Arthus reaction

T-cell reactions:

contact dermatitis, drug allergies, atopic dermatitis, asthma



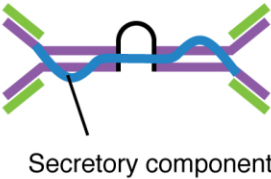


Immediate type Reaktion

< 1h

Type of Reaction	Time Before Clinical Signs	Characteristics	Examples
Type I (Anaphylactic)	<30 min	IgE binds to mast cells or basophils; causes degranulation of mast cell or basophil and release of reactive substances such as histamine	Anaphylactic shock from drug injections and insect venom; common allergic conditions, such as hay fever, asthma
Type II (Cytotoxic)	5–12 hours	Antigen causes formation of IgM and IgG antibodies that bind to target cell; when combined with action of complement, destroys target cell	Transfusion reactions, Rh incompatibility
Type III (Immune Complex)	3–8 hours	Antibodies and antigens form complexes that cause damaging inflammation	Arthus reactions, serum sickness
Type IV (Delayed Cell-Mediated, or Delayed Hypersensitivity)	24–48 hours	Antigens activate T _C that kill target cell	Rejection of transplanted tissues; contact dermatitis, such as poison ivy; certain chronic diseases, such as tuberculosis

delayed type Reaktion

> 24h

The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ϵ	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor



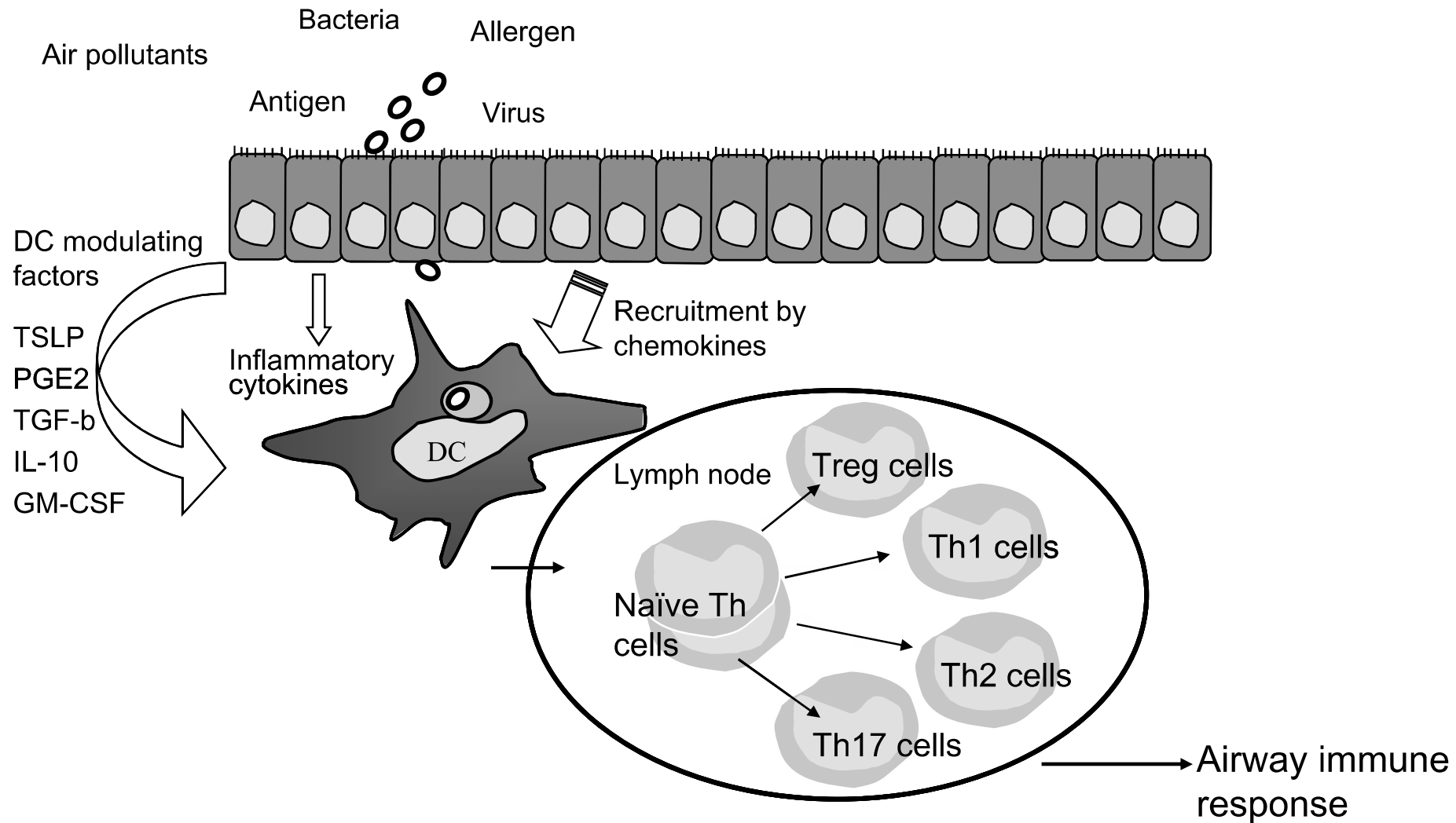
The immune system is highly specific and needs danger signals to become activated

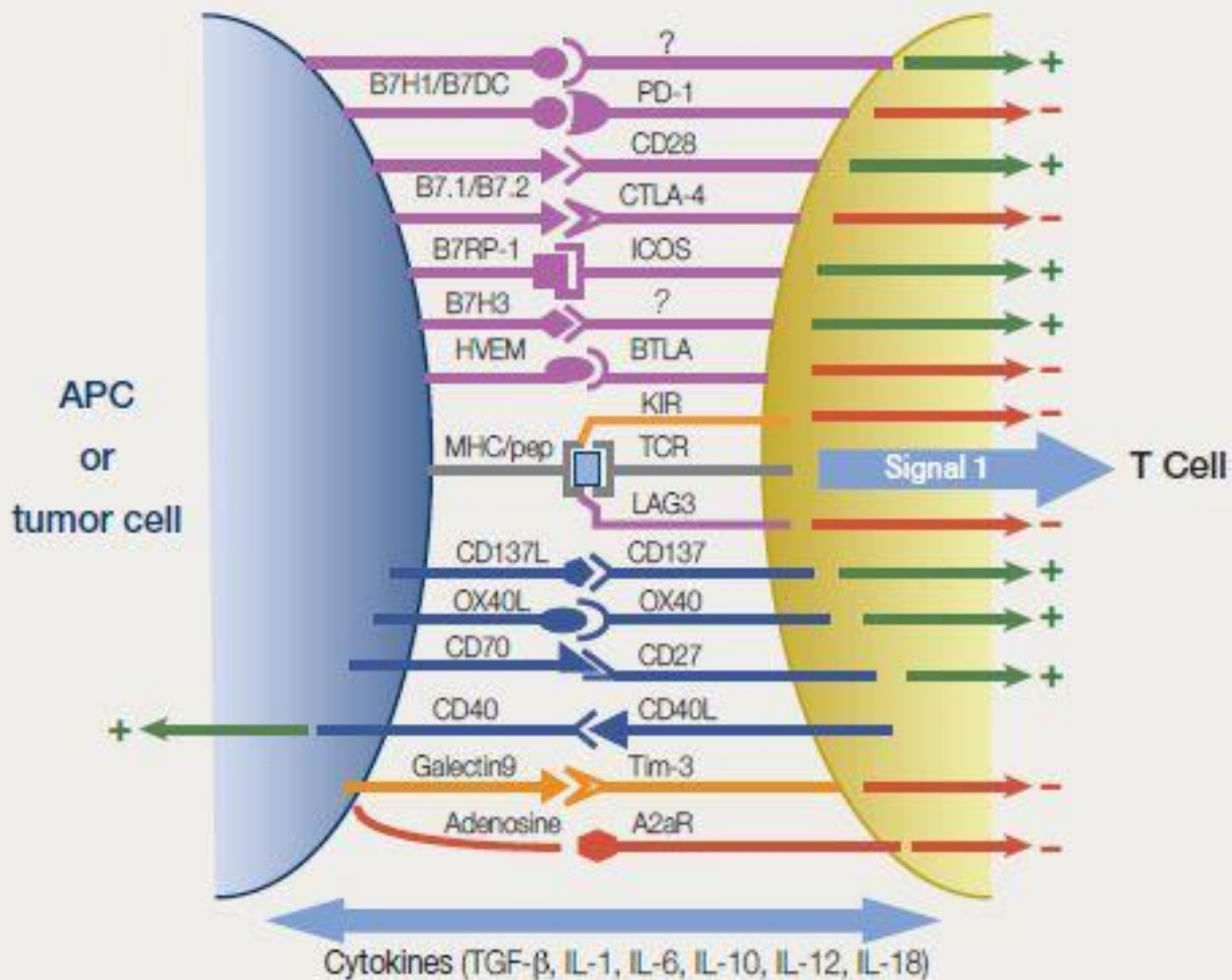
How can a harmless/innocuous substance like a pollen potentially induce an IgE mediated immune reaction ?

Ability of „innocuous“ proteins to activate immune system

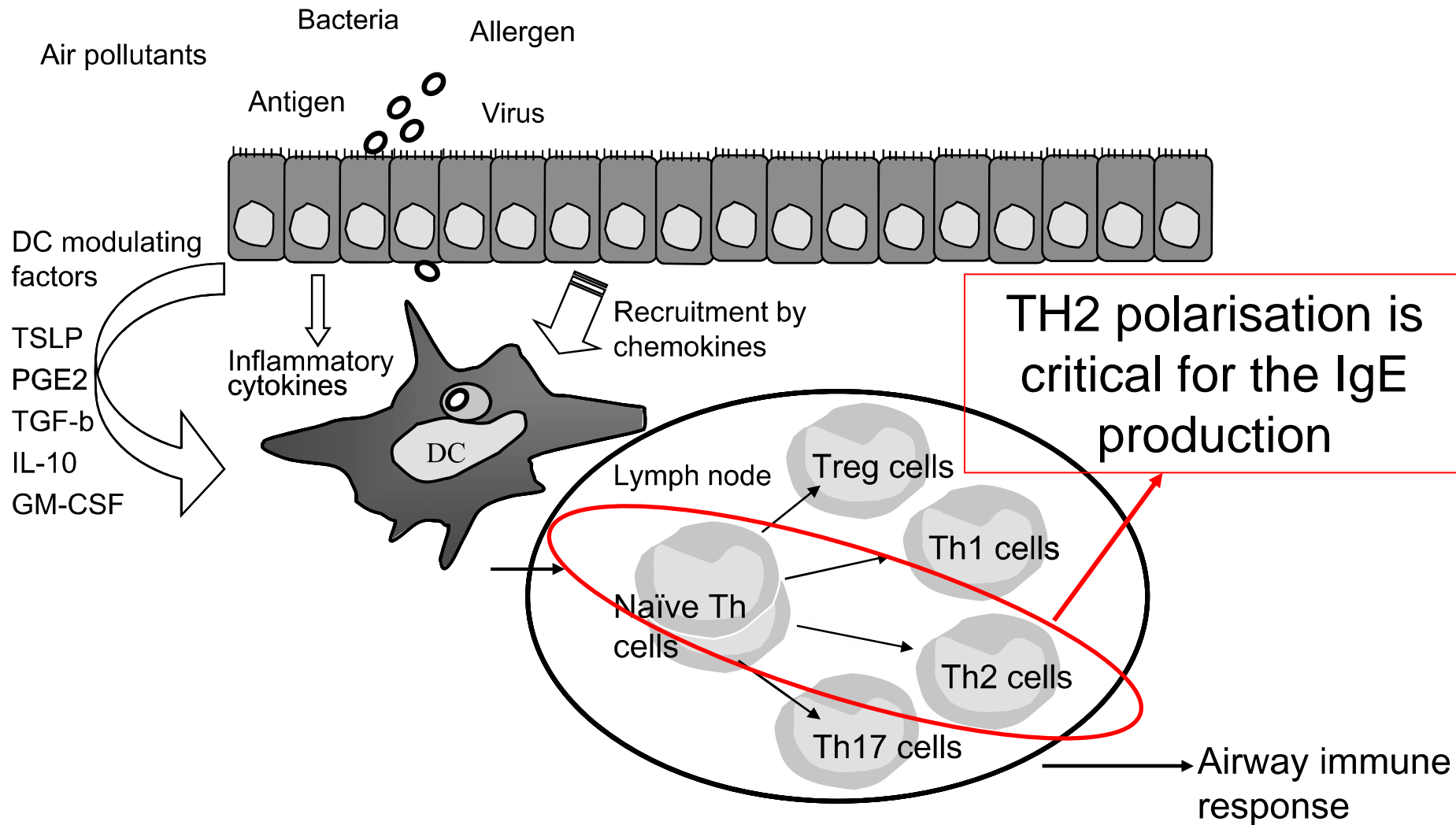
1. House dust mite allergen Der p1: cysteine protease cleaves tight junction protein occludin → Increased epithelial permeability and facilitating its entry into the tissue
2. House dust mite allergen Der p2: structural and functional homology with MD-2, LPS-binding component of TLR 4 signaling complex → facilitates signaling through direct interactions with the TLR4 complex
3. Pollen-associated lipid mediators (PALMs): When pollen grains are hydrated on the respiratory epithelia, they release allergens and eicosanoid lipids → so-called pollen-associated lipid mediators (PALMs) → act as stimulators of DC

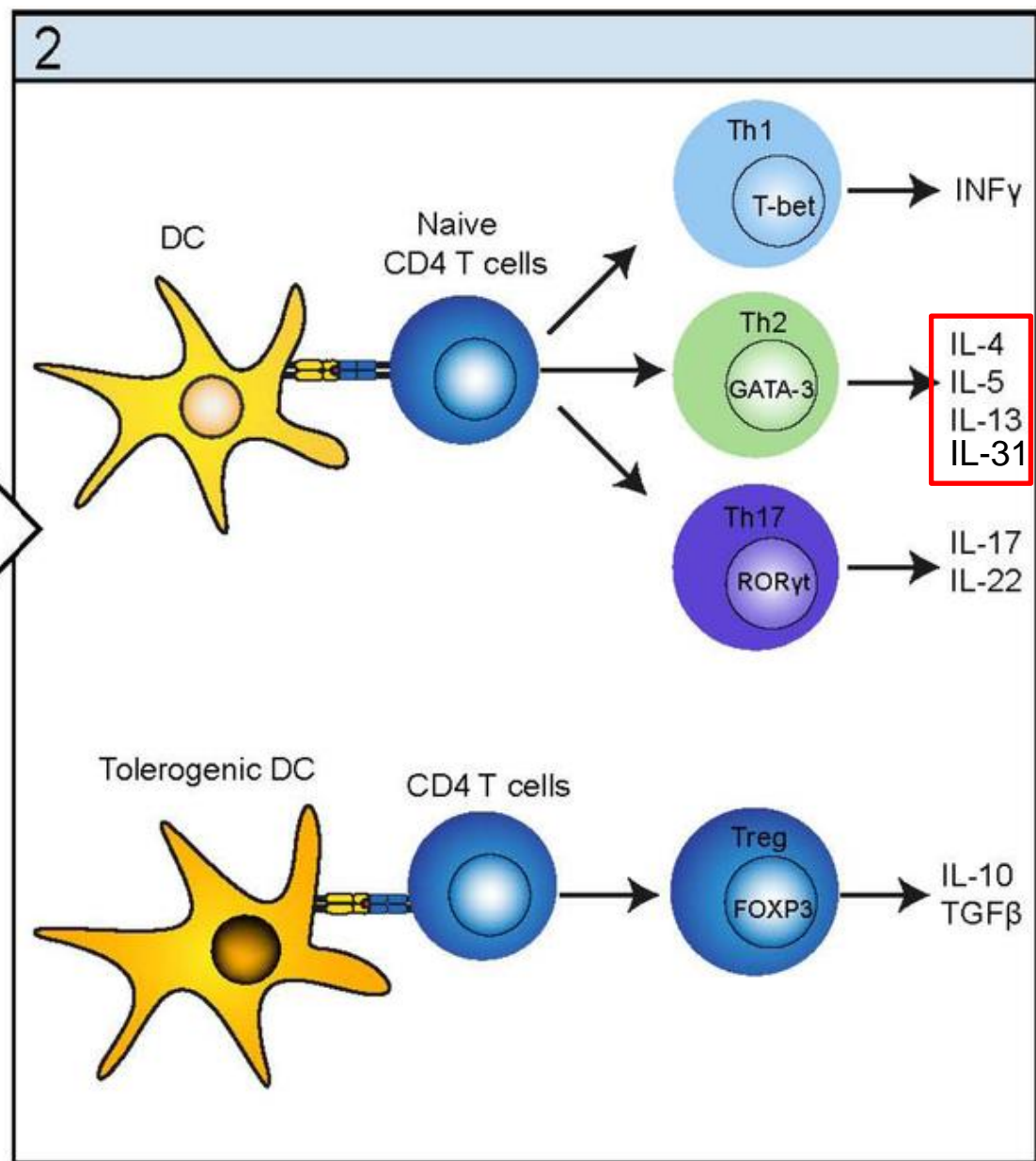
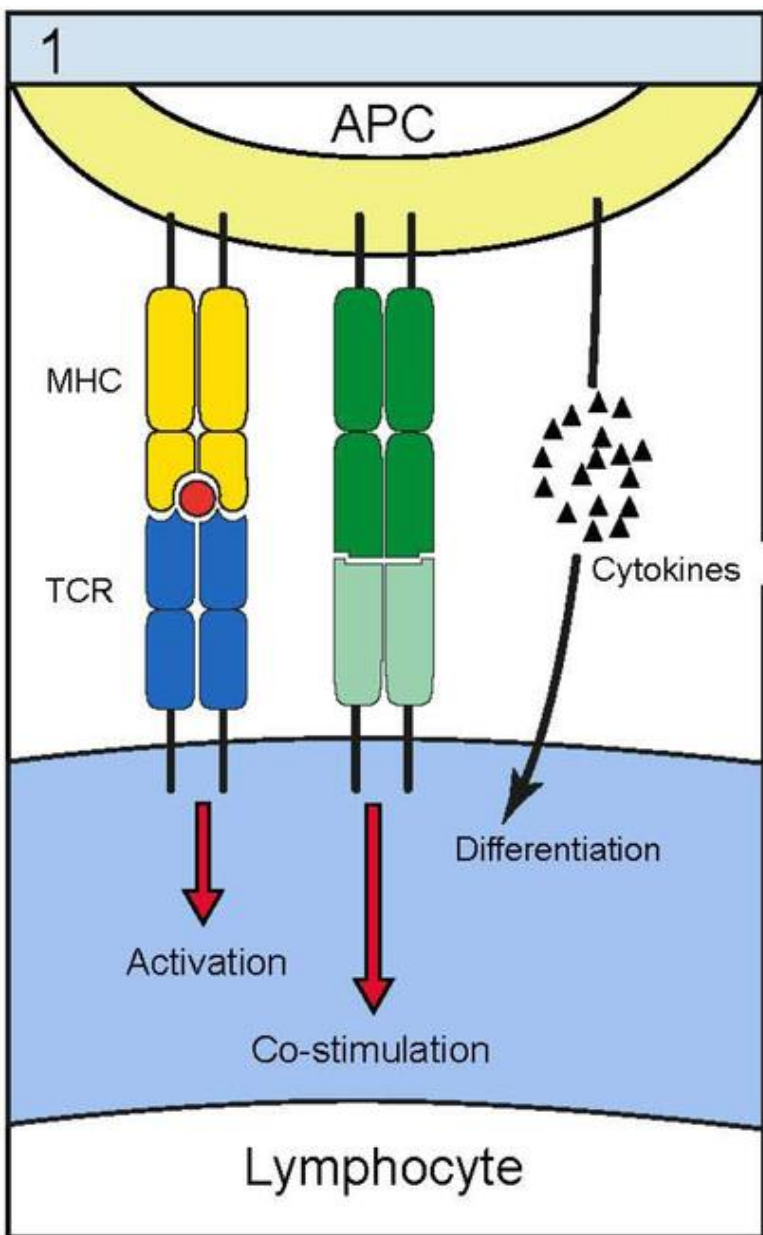
Airway immune response





Airway immune response





What drives Th2 polarisation ?

- antigen dose,
- nature of the antigen,
- direct cell-to-cell interaction with APCs
- the cytokine receptors available on the naive cell
- Genetic predisposition
- environmental factors
- gastrointestinal Flora

What drives Th2 polarisation ?

- **IL-2** proliferation and clonal expansion of T cells
- **IL-4** An autocrine of Th2 cells during their maturation
- **IL-6** is secreted by T cells and macrophages
- **IL-31** activated CD4+ T lymphocytes, in particular activated TH2 helper cells, mast cells, macrophages, and dendritic cells. IL-31 is believed to play a role in atopic dermatitis and eczema.
- **IL-33** is expressed by a wide variety of cell types, including fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells
- **TSLP** is produced mainly by non-hematopoietic cells such as fibroblasts, epithelial cells and different types of stromal or stromal-like cells

Hygien-Hypothesis

«Western» Lifestyle

Traditional Lifestyle

r

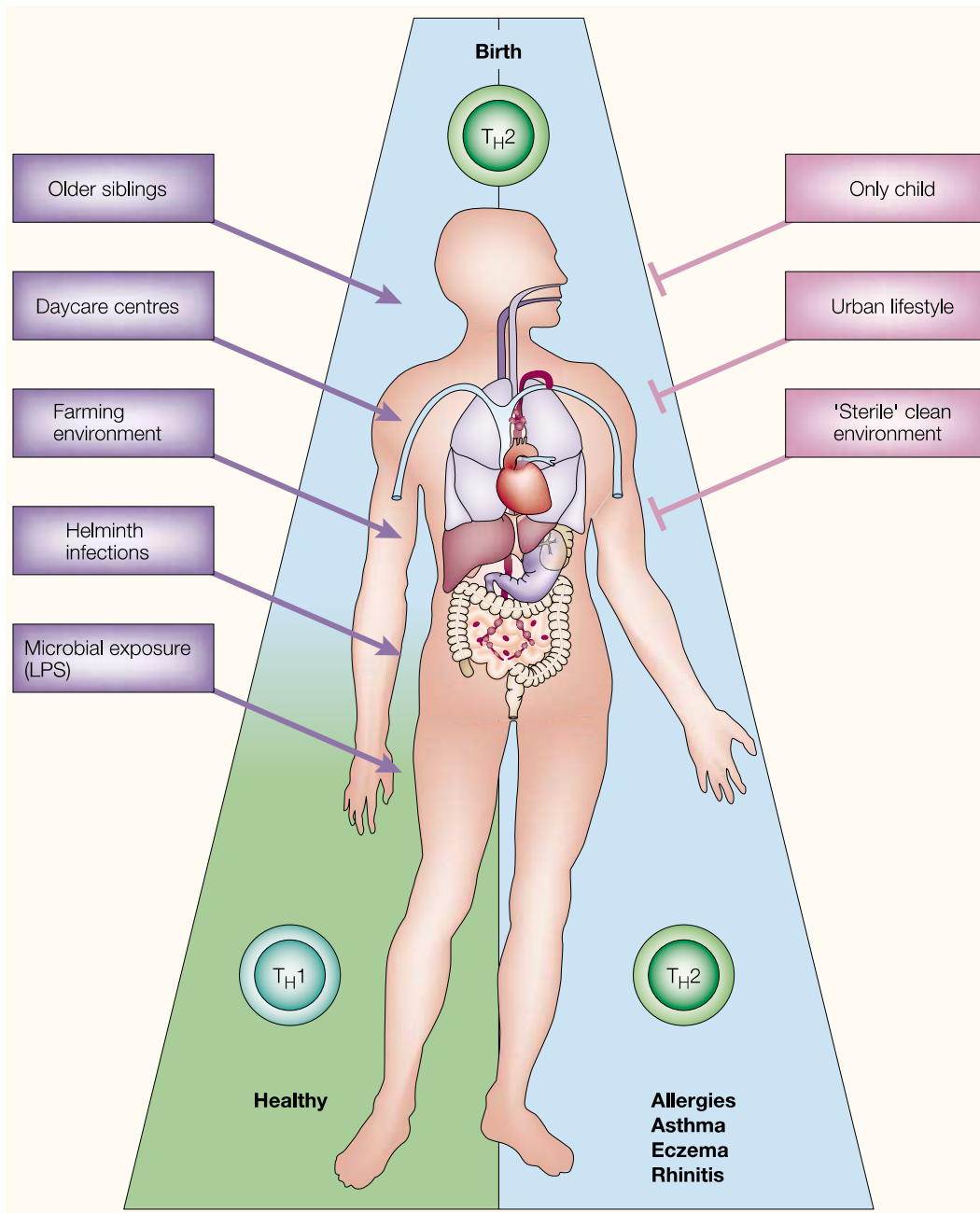
Th2

IL-4, IL-5

Allergy-Epidemic

Allergy-Prevention





→ Microbial exposure boosts Th1 response

→ Microbial exposure alters Th2 response

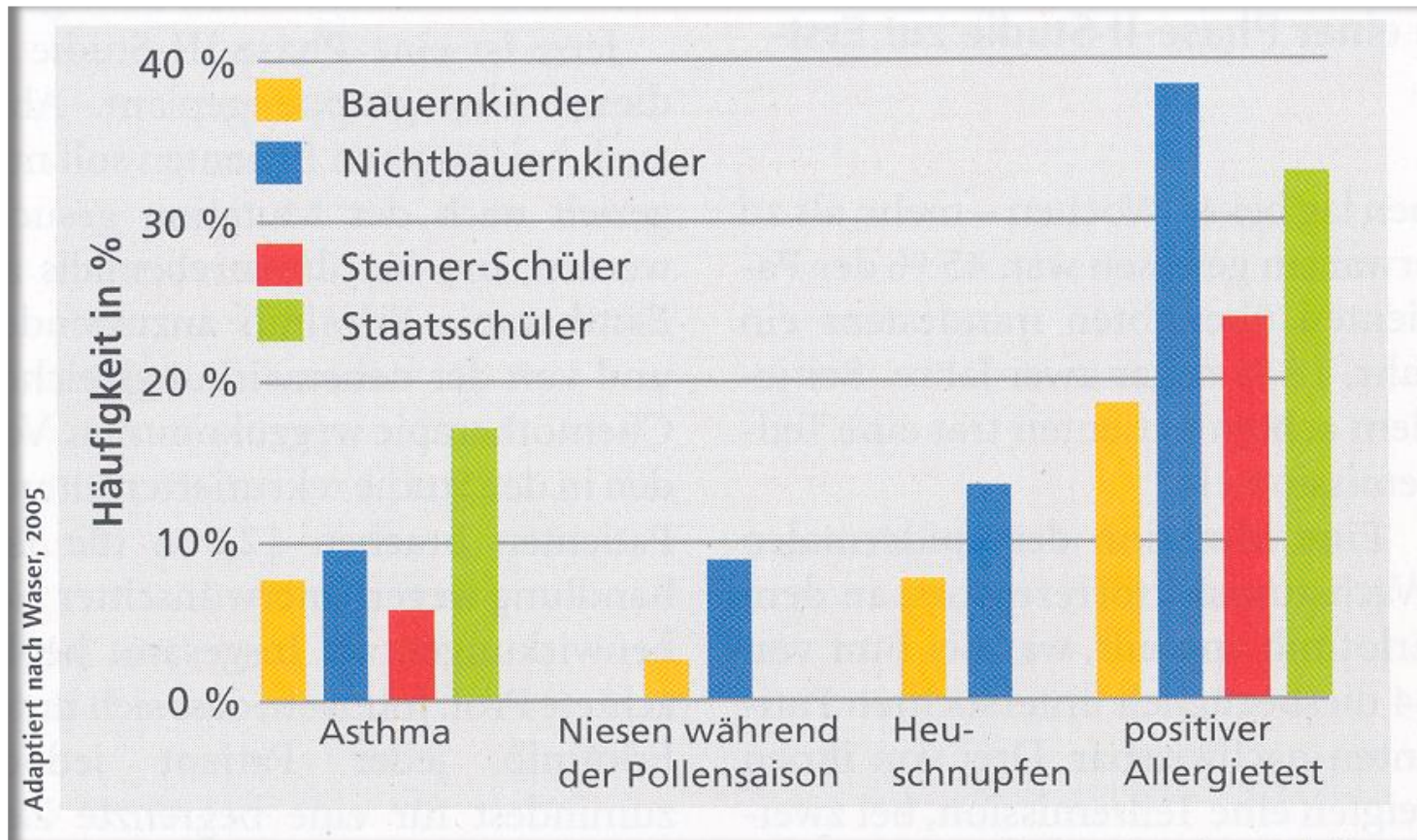
Response starts *in utero*

Protective effect of the farm environment

Protective effect by parasite infection

PARSIFAL Studie

Braun-Fahrländer C et al, J Allergy Clin Immunol 2006; 117:59-66

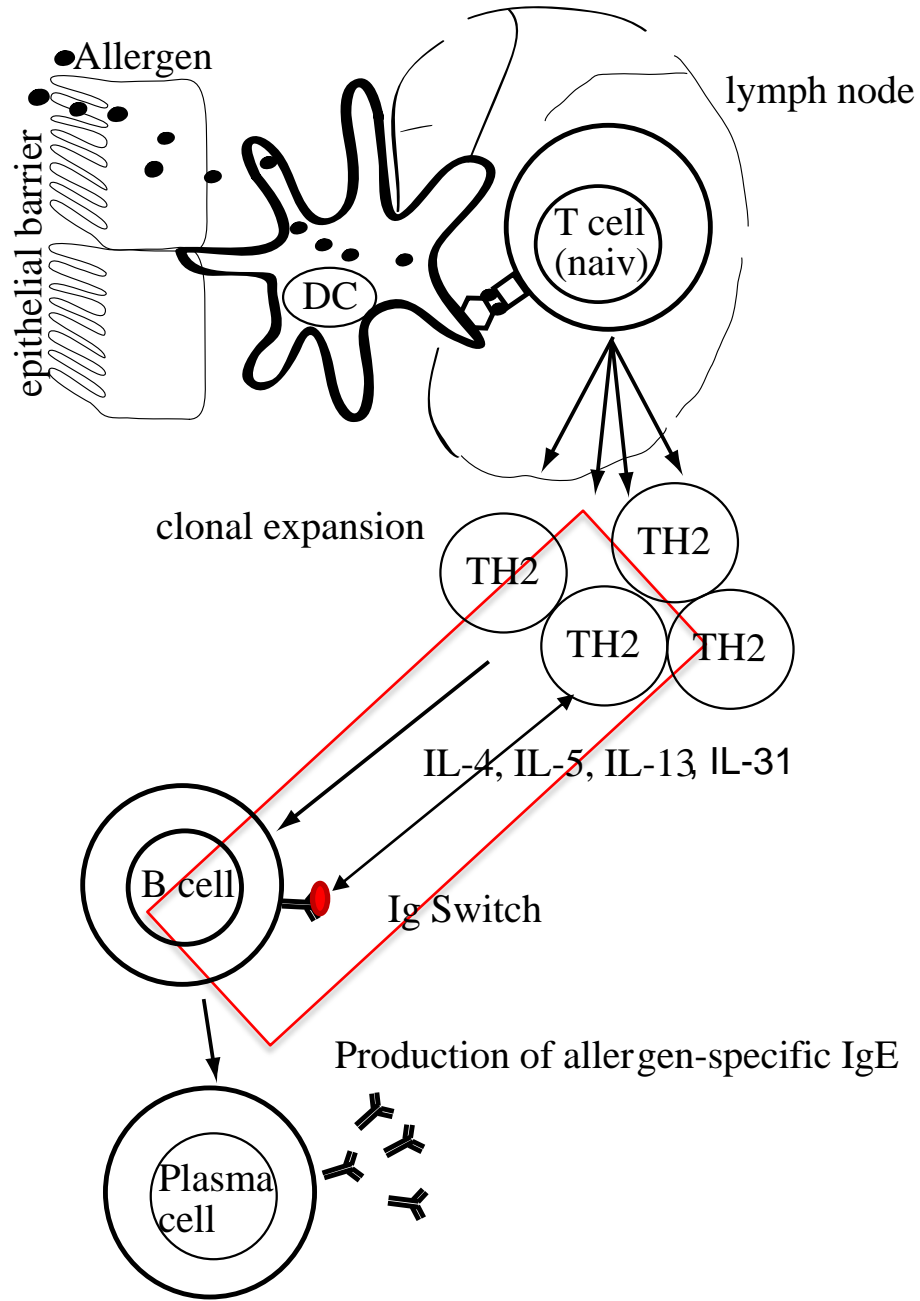


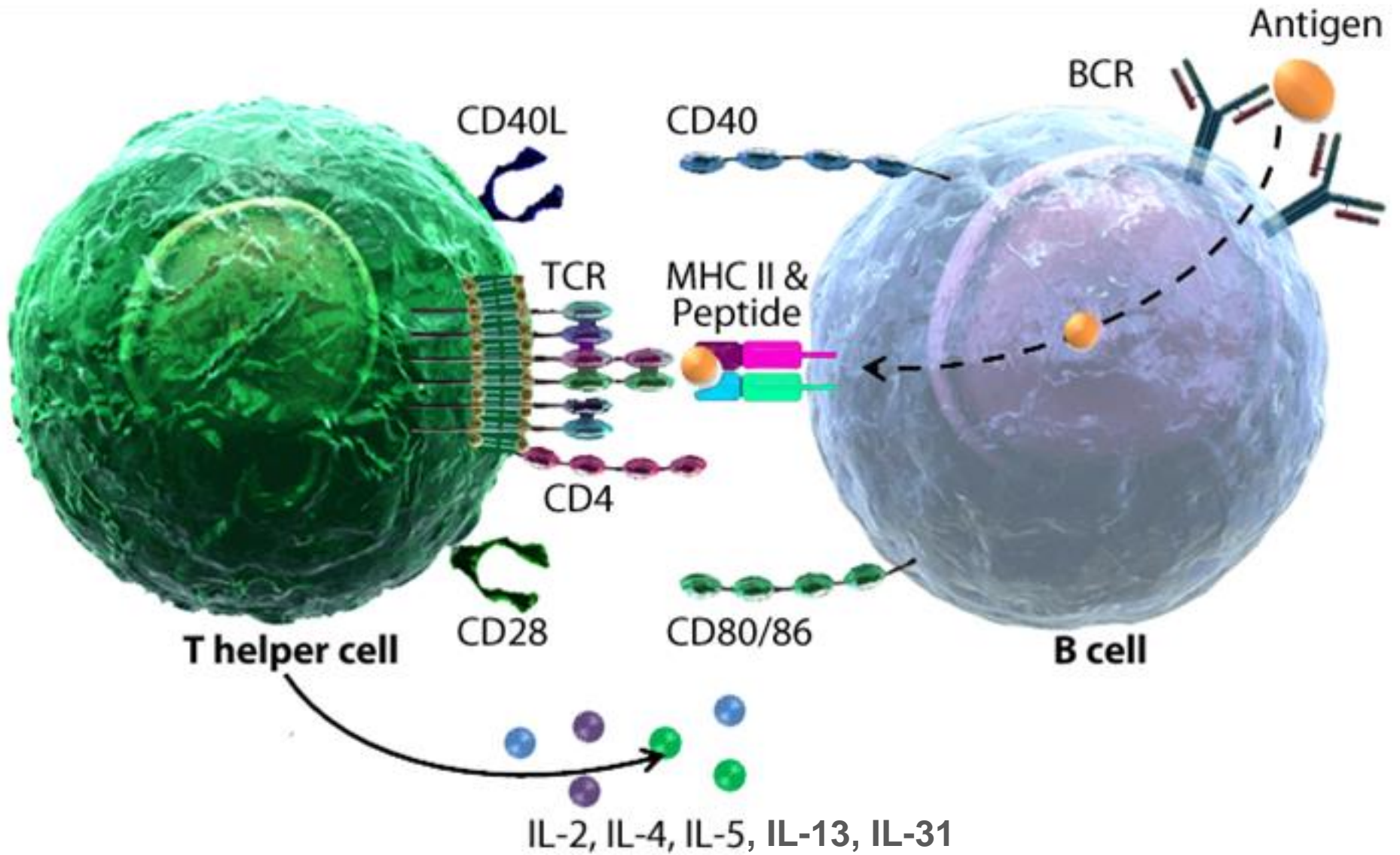
Too much hygiene is harmful for horses !!!!

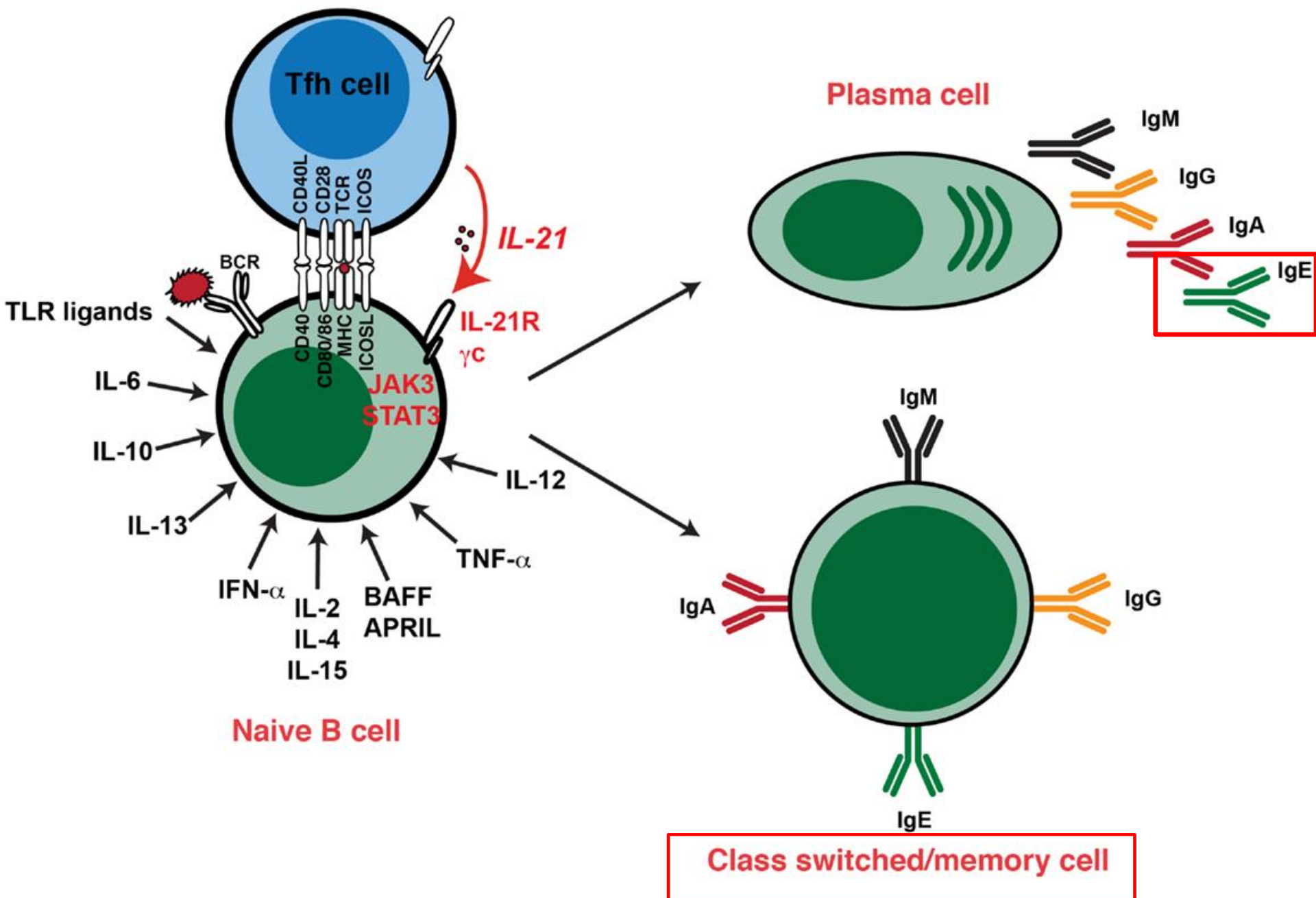
- Clean stables increase allergic diseases in horses.
- - in Switzerland every 10th horse has Asthma to Hay-/stables

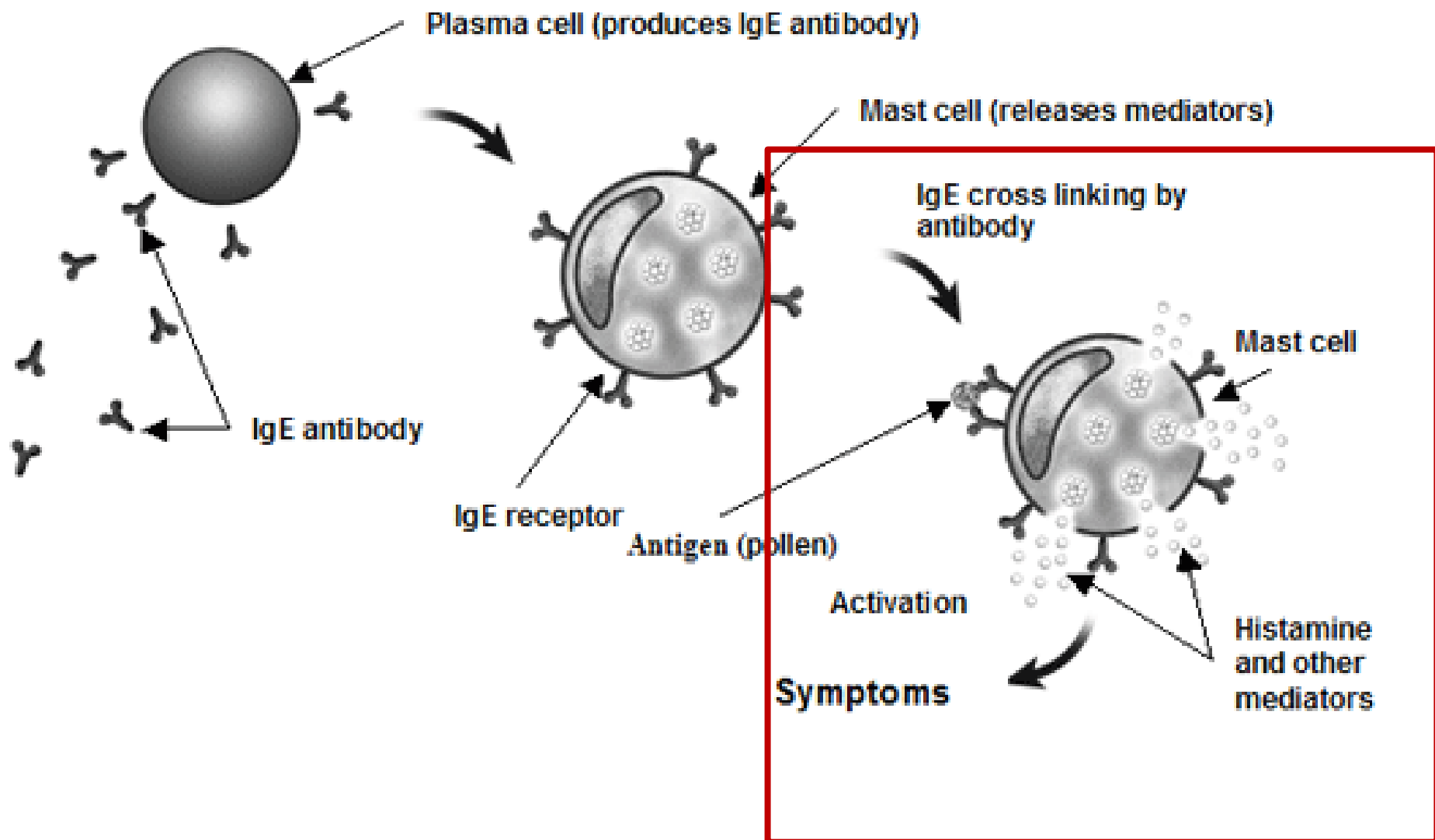
Prof. Vinzenz Gerber, Head of Clinics for Horses University of Bern, 2009

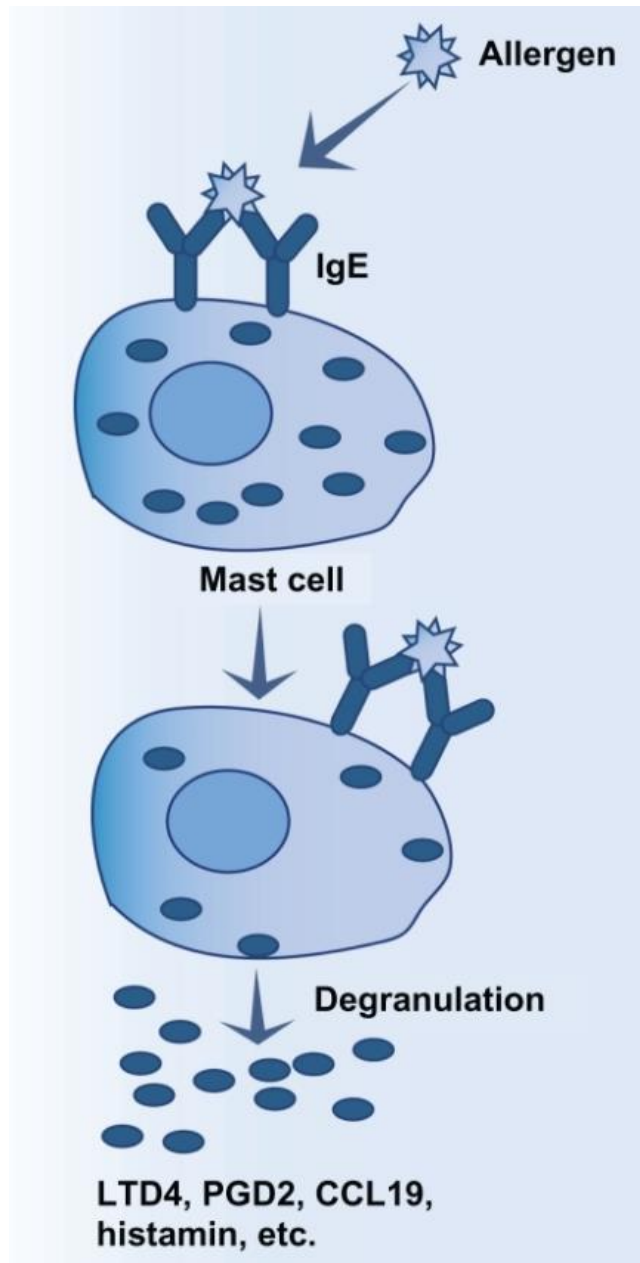
Sensitization Phase





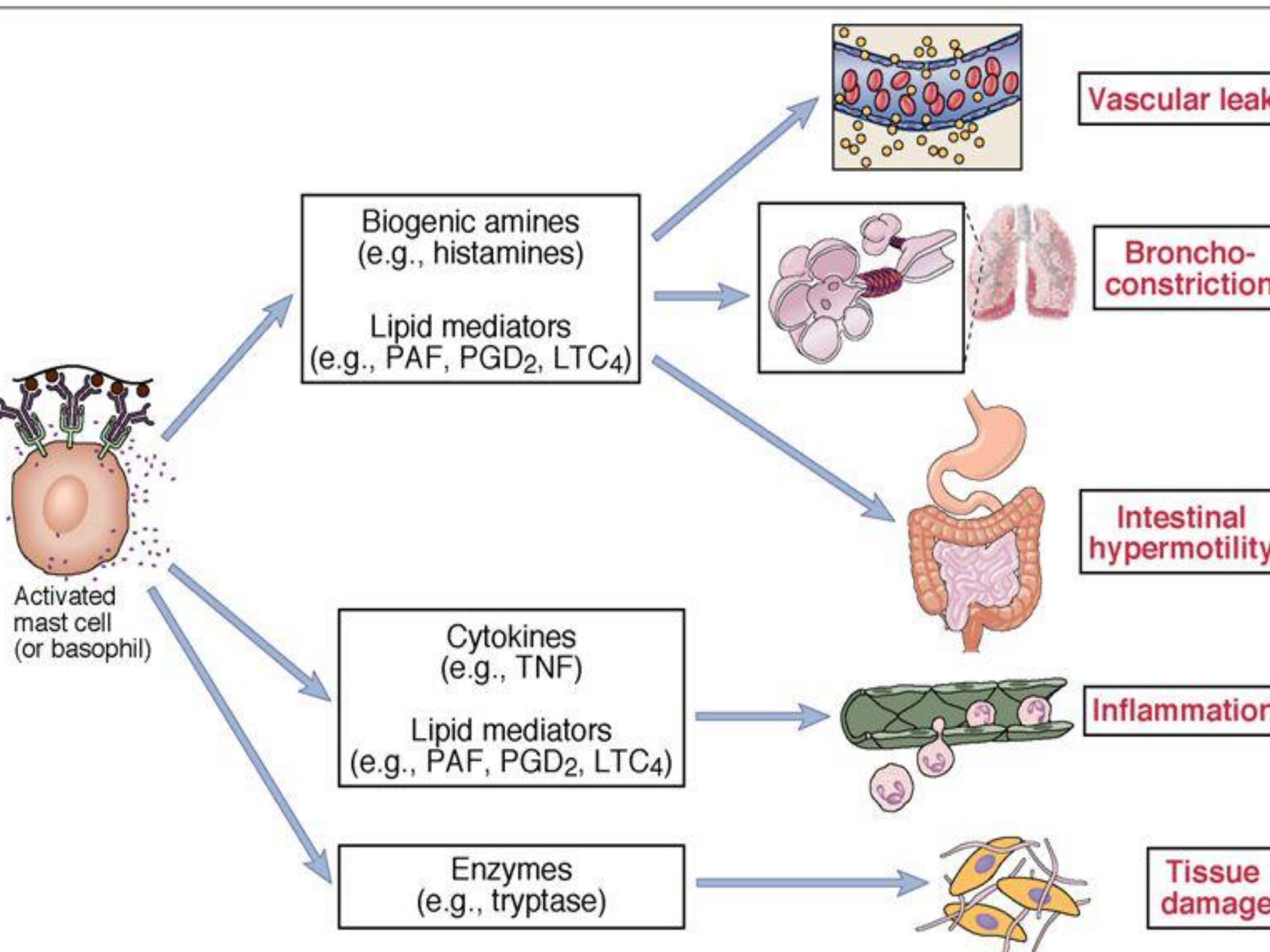




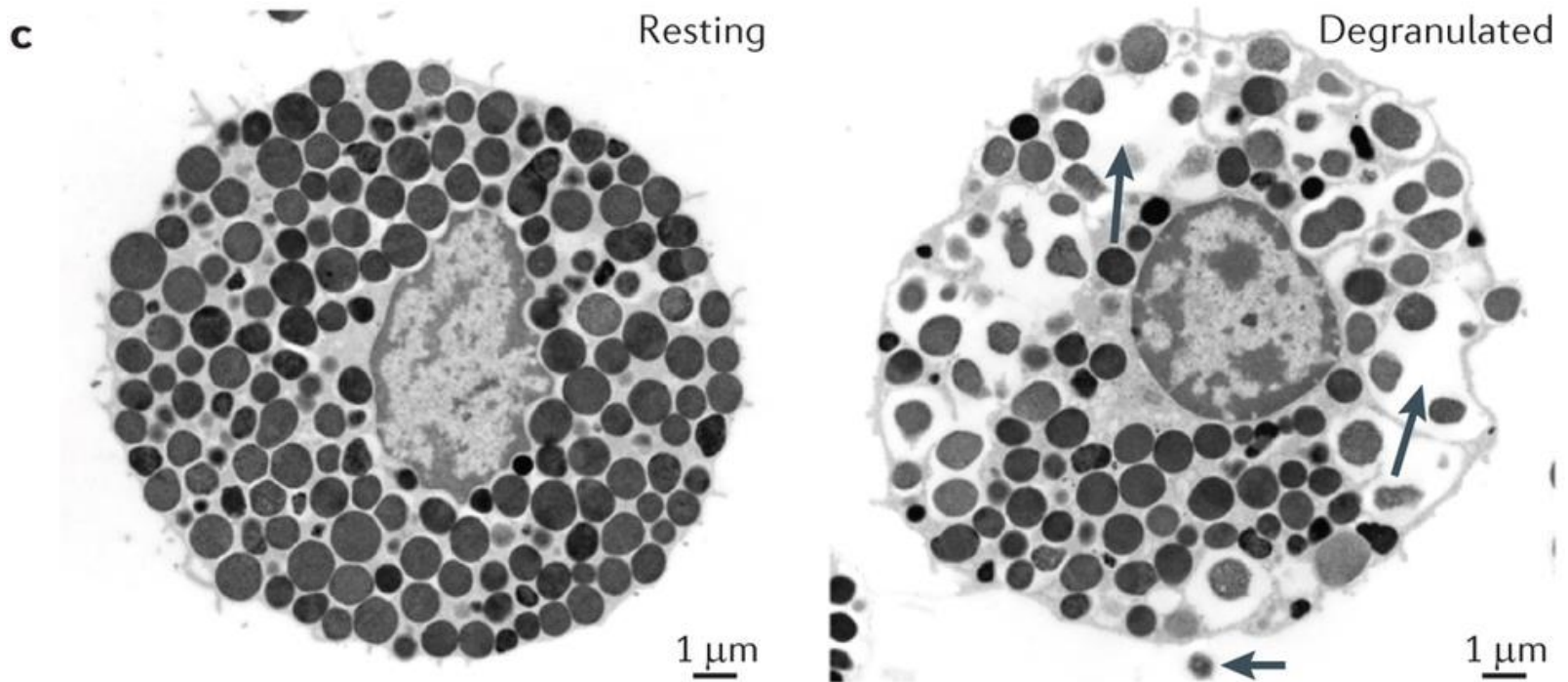


Cross linking of 2 Fc-IgE-RI
Is required for mast cell activation

Mediator release



Mast cell



symptoms of immediate reaction

Eyes:
Conjunctivitis



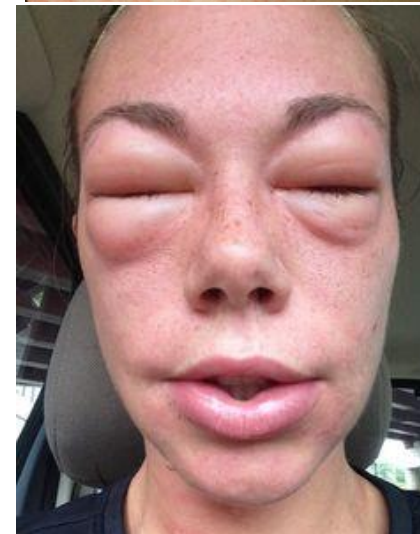
Nose:
Rhinitis



Lungs:
Asthma



Skin:
Urticaria
Angioedema



Anaphylaxis

= potentially life threatening situation; rapid onset

Massive mediator release

different organs are involved (skin, respiratory, cardiovascular system)

most frequent cause in Switzerland: hymenoptera venom allergy, drug allergy, food allergy

Symptoms of IgE induced late reaction

chronic

- Swelling
- Infiltration by inflammatory cells
- Damage to epithelia
- Thickening of basal membrane, restructuring of lung tissue
- Mucus production

(LT, cytokine, PG, PAF,
ECP, EPO, EDN,... IL-13,
TNFa)

blocked nose

bronchial hyper reactivity

reduced lung function

Adverse reaction Food

1. Toxic

2. Nontoxic

A) Immune mediated

- IgE mediated

- Non-IgE mediated

B) Non immune mediated (food intolerance)

- enzymatic (e.g. lactase deficiency)

- pharmacological (abnormal reactivity to substances e.g. amines)

- undefined (e.g. food additive intolerance)

2 Groups of food allergy



```
graph TD; A["2 Groups of food allergy"] --> B["Food sensitization develops as a consequence of sensitization to airborne allergens"]; A --> C["Food sensitization occurs by gastrointestinal tract (often stable proteins)"];
```

Food sensitization develops as a consequence of sensitization to airborne allergens

Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

Mostly in children
“real food allergy”

Oral allergy syndrome

Sensitization to heat/pepsine labile plant-derived proteins in patients with pollen allergy

Cross reactivity between homologous plant derived proteins and pollen proteins

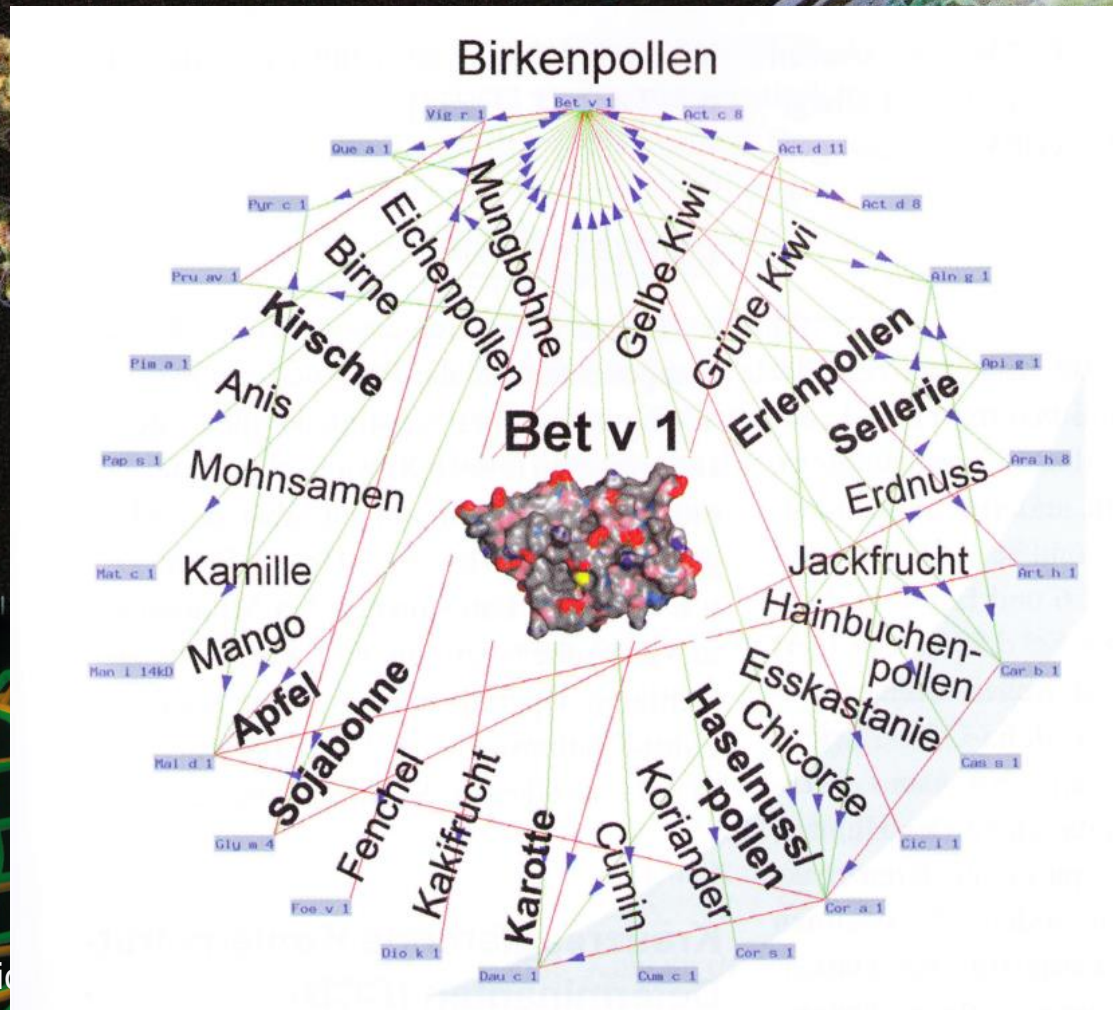
Bet v1 → nuts, apple, kiwi

heated normally well tolerated



Allergen cross reactivity seems to be due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or present evolutionarily conserved structures

Allergen cross reactivity structurally similar epitopes on different proteins



Crystallographic

Pru a1 and Bet v1

Neudecker P et al. Biochem J 2005



Birch



Apple Peach Plum Pear Cherry Apricot Almond
Rosaceae



Carrot Celery Parsley Caraway Fennel Coriander Aniseed
Apiaceae



Soybean Peanut
Fabaceae
(old Leguminosae)



Hazelnut
Betulaceae



Ragweed



Cantaloupe Honeydew Watermelon Zucchini Cucumber
Cucurbitaceae



Banana
Musaceae



Mugwort



Celery Carrot Parsley Caraway Fennel Coriander Aniseed
Apiaceae



Bell pepper
Solanaceae



Black pepper
Piperaceae



Mustard Cauliflower Cabbage Broccoli
Brassicaceae



Garlic Onion
Liliaceae



Peach
Rosaceae



Orchard



Cantaloupe Honeydew Watermelon
Cucurbitaceae



Peanut
Fabaceae
(old Leguminosae)



White potato Tomato
Solanaceae



Swiss chard
Amaranthaceae



Orange
Rutaceae

Food allergy - crossreaktiviti

celery-birch-mugwort-spices syndrome

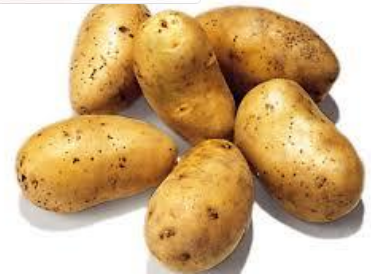
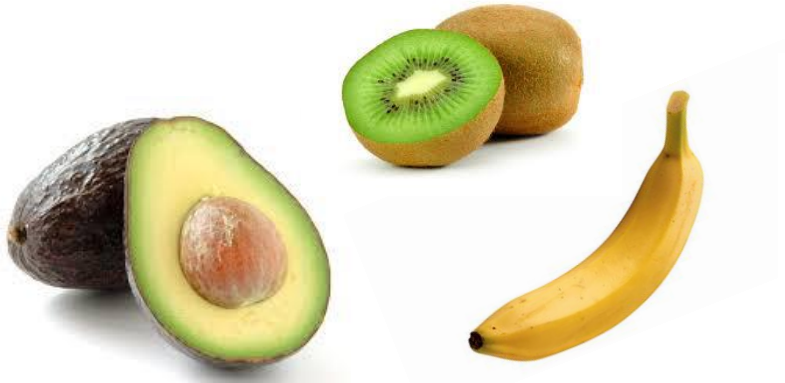


shellfish and dust mite allergy



Food allergy - crossreaktivity

Latex-fruit syndrome

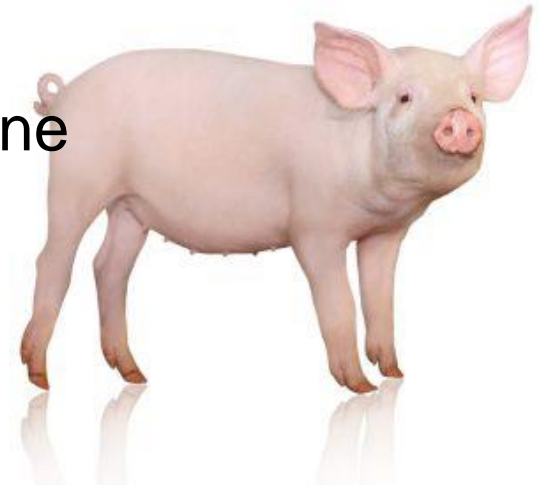


Cat-pork syndrome

Fel d 2



Pig serum albumine



2 Groups of food allergy



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```

Food sensitization develops as a consequence of sensitization to airborne allergens

Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

Mostly in children
“real food allergy”

Lipid transfer proteins

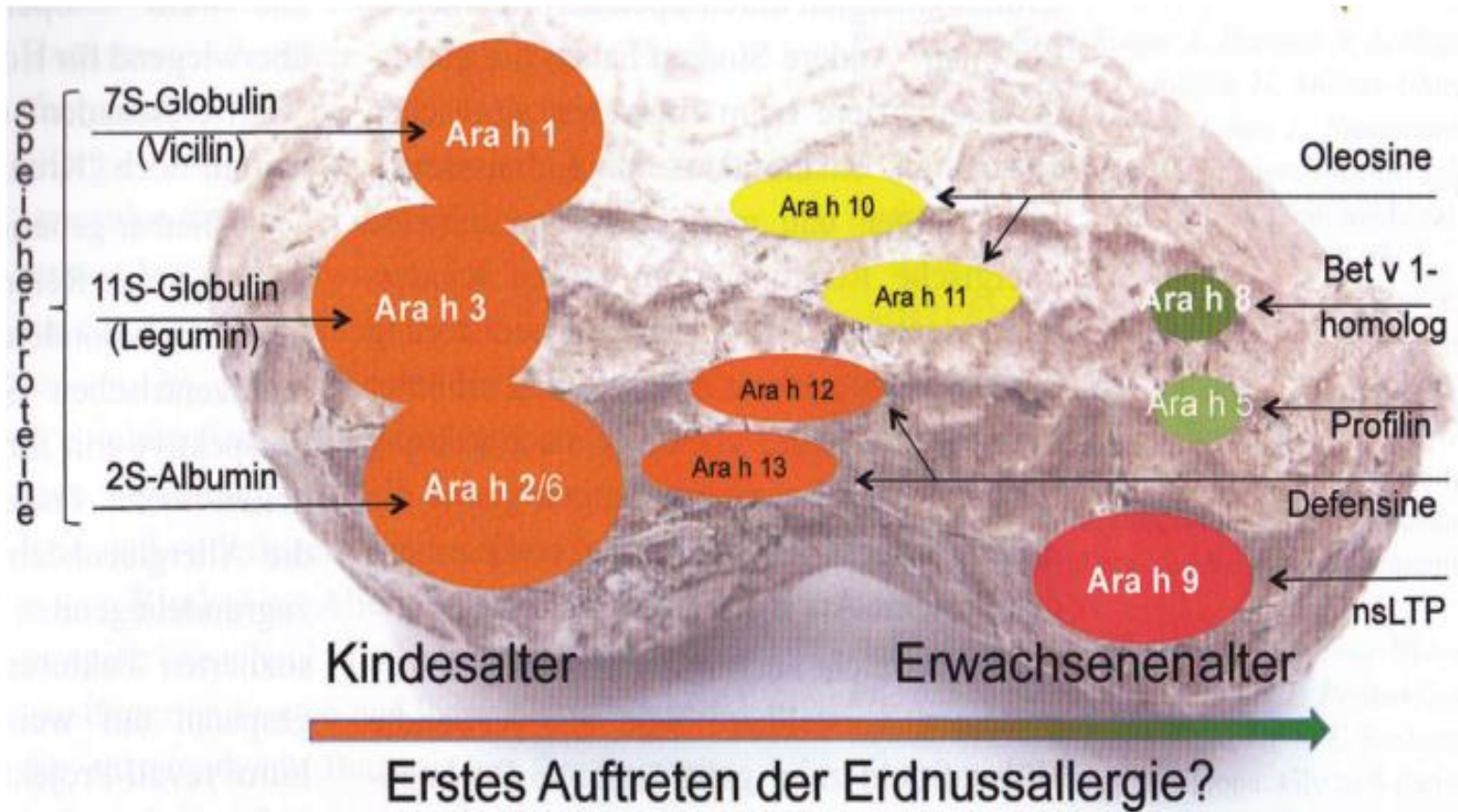
Role in defence against fungi and bacteria

Heat stable, begin to unfold above 95°, protein refold on cooling

More severe allergic reactions



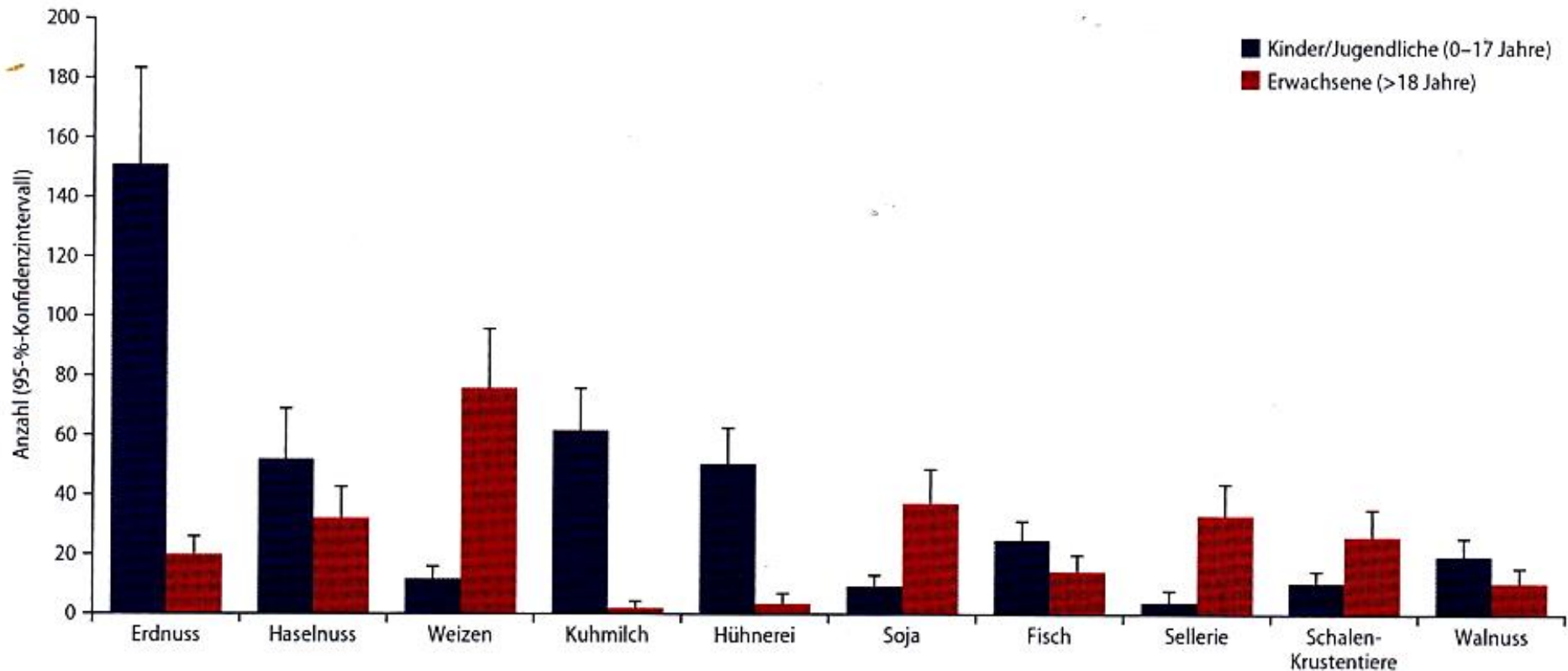
Peanut allergy

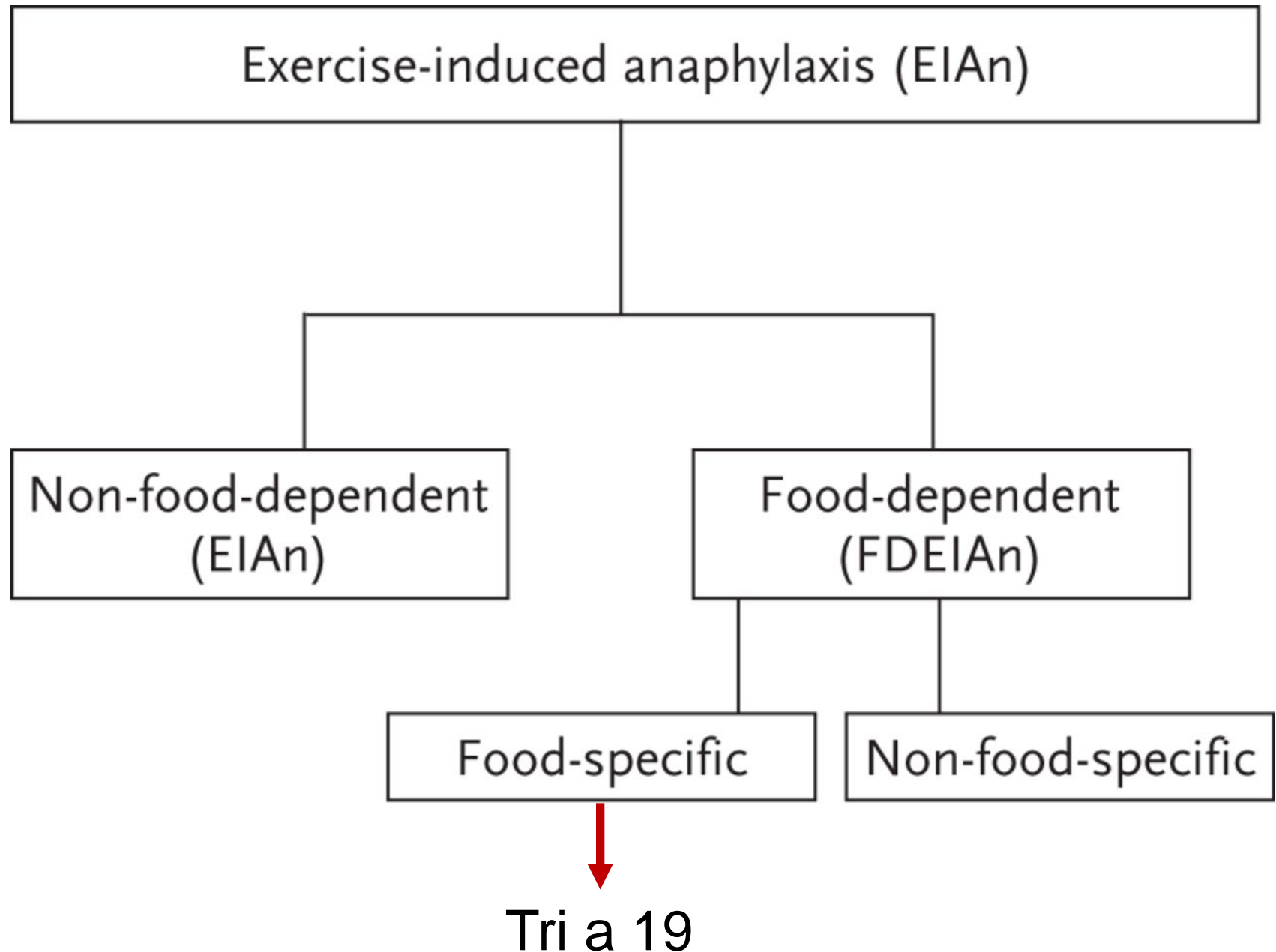


Triggers of food allergy - age groups

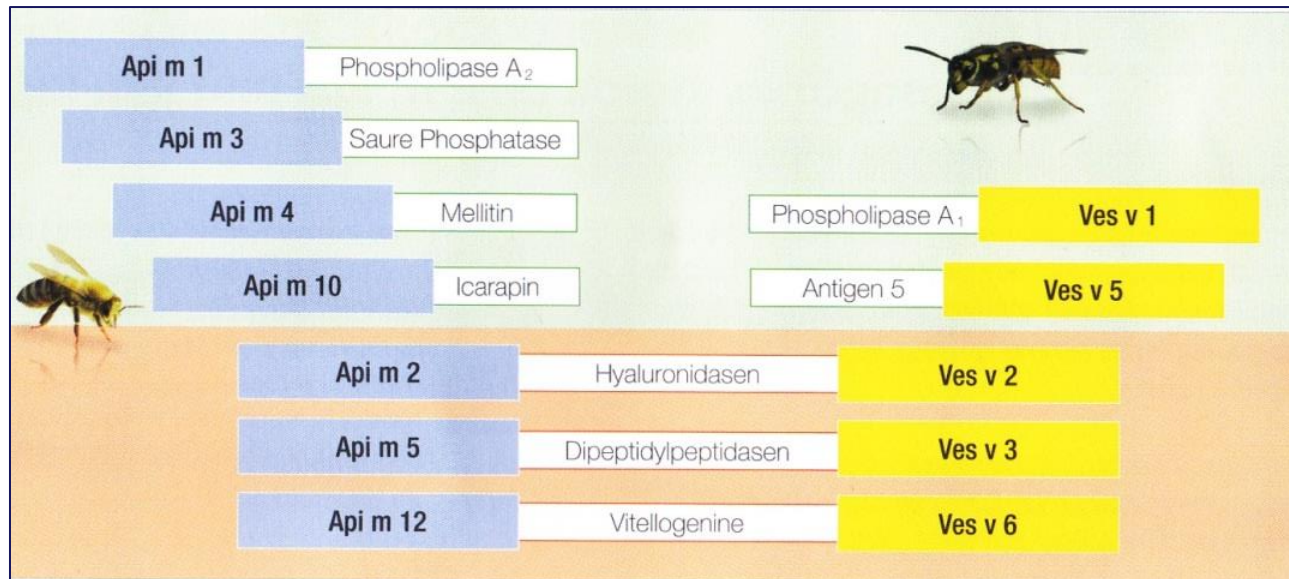
Worm M et al. Dtsch Arzteblatt Int 2014;111: 367-75

Worm M et al. Allergo J Int 2015;24:256-93



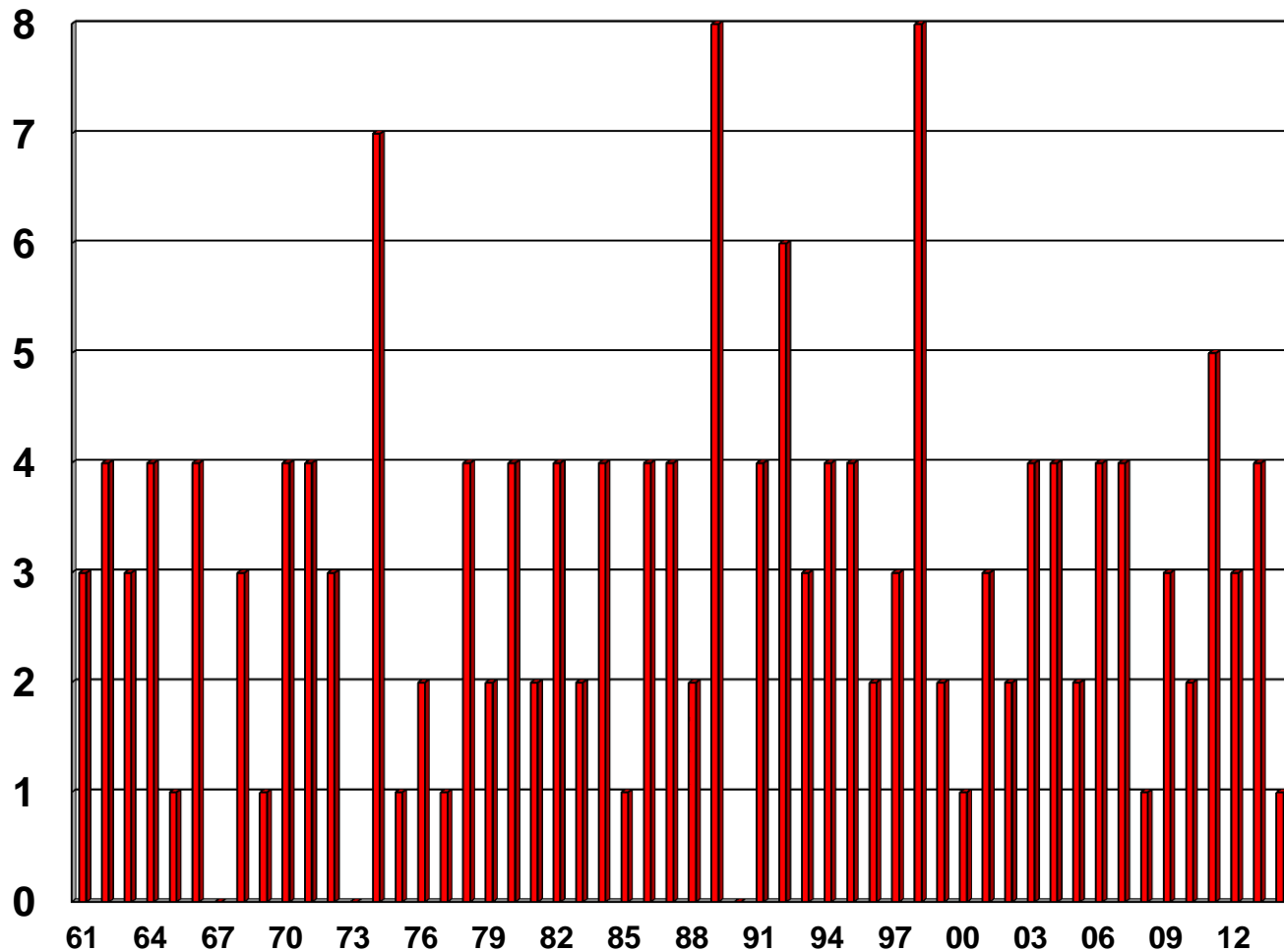


Bee / Wasp Allergy



Mortality due to bee /wasp sting in Switzerland 1961 – 2012

Erwin K. Wüest, EDI BFS



Local reactions after hymenoptera stings

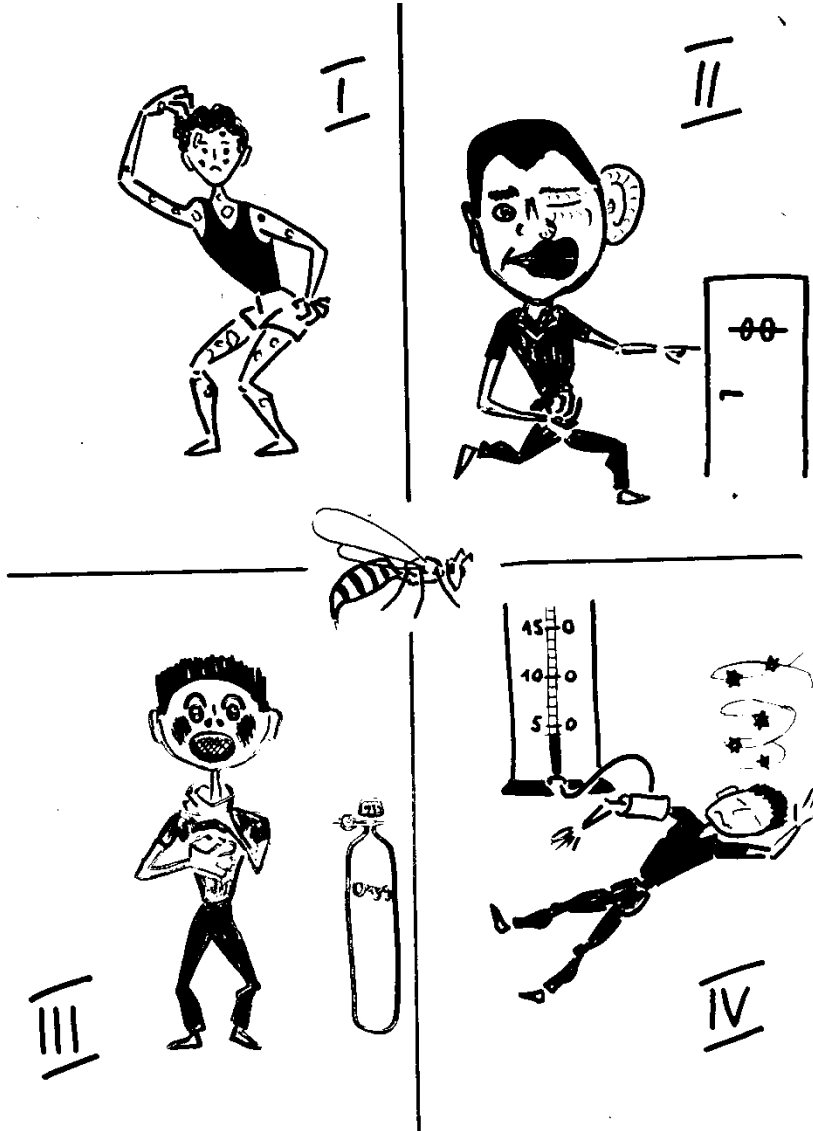


Large local reaction=
Swelling exceeding 10 cm

Not an Allergy !

Classification of hymenoptera allergic reactions

Classification according to Mueller



Drug allergy

Haptens

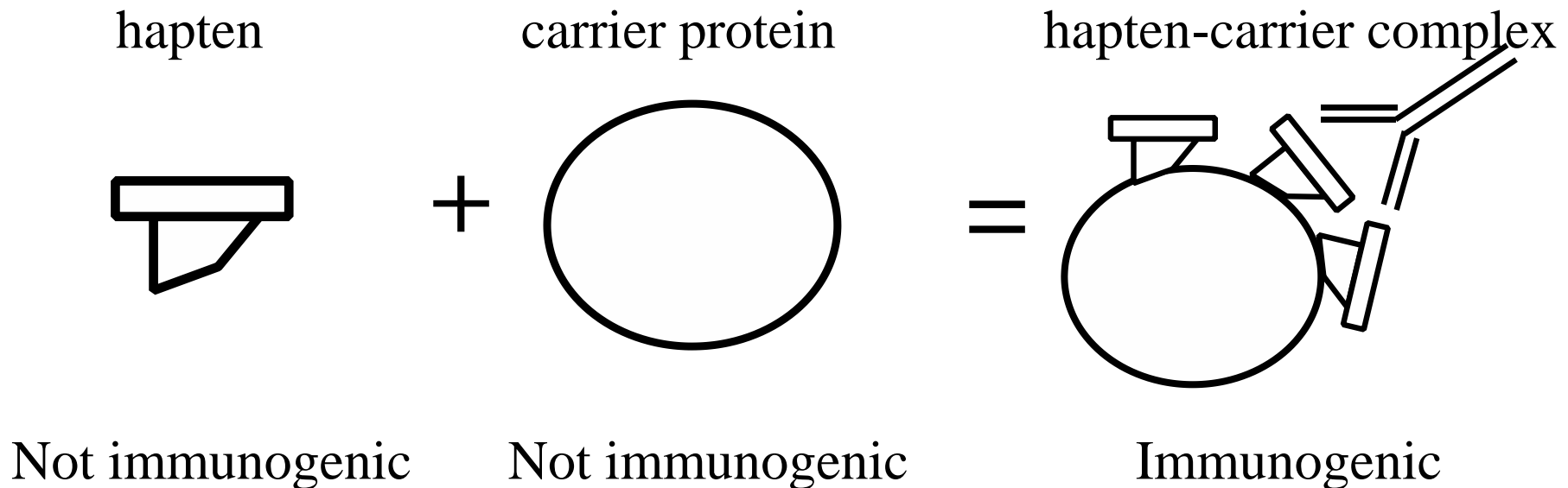
Small molecules alone are not immunogenic!

Haptens = reactive proteins binding to a larger protein →
hapten-carrier complex

→ resistant to intracellular processing

→ danger signal (activation of innate immunity e.g. DC's)

→ forms neo-antigenic determinants able to induce both a T-cell and B-cell immune response.



TCR

HLA

HLA peptide TCR complex

p-i concept:

a) the drug binds first to the TCR (by non covalent bonds; not restricted to a HLA-allele)

or

b) the drug binds first to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR
(HLA-class I restricted, CD8)

IgE mediated drug allergies (immediate reactions)

Anaphylactic IgE-mediated reactions Flushing, pruritus, urticaria, angioedema, laryngeal edema, rhinorrhea, conjunctivitis, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, hypotension	Antibiotics <u>Beta-lactams</u> Penicillins, cephalosporins, amino-penicillins <u>Fluroquinolones</u> Ciprofloxacin, levofloxacin	Sepsis Meningitis Pneumonia Pyelonephritis
	Chemotherapy drugs <u>Platins</u> Carboplatin, cisplatin, oxaliplatin	Primary and recurrent metastatic cancers (breast, ovarian, colon)
	Monoclonal antibodies Rituximab, trastuzumab	Chronic inflammatory diseases, cancers (leukemias, breast, ovarian)

Desensitization often possible!!!

Non-IgE mediated drug allergies (immediate reactions)

Anaphylactoid Direct mast cell/basophil, complement, and leukotriene metabolism reactions Flushing, pruritus, urticaria, angioedema, throat tightness, shortness of breath, nausea, vomiting, diarrhea, hypotension, hypertension, back and/or abdominal pain	Aspirin/NSAIDs	Cardiac protection, asthma w/ nasal polyposis, chronic inflammatory diseases (RA, Crohn's)
	Vancomycin	MRSA
	Chemotherapy drugs <u>Taxenes</u> Paclitaxel, docetaxel	Primary and recurrent metastatic cancers (breast, ovarian, colon)

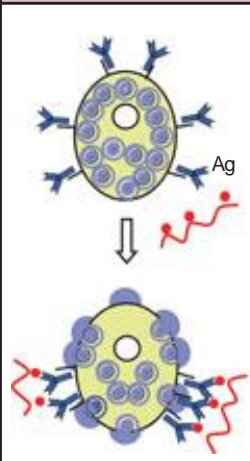
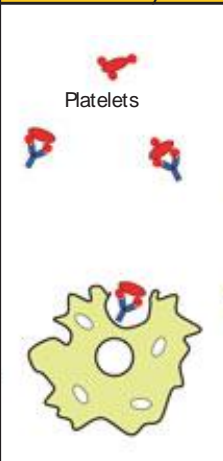
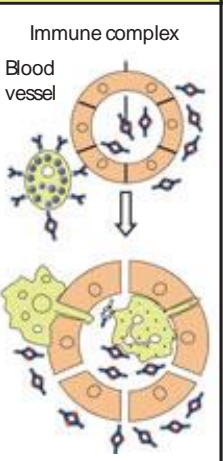
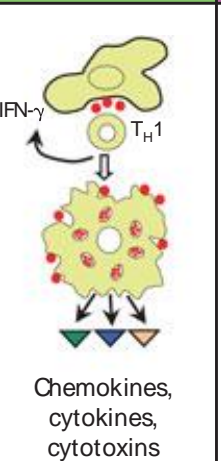
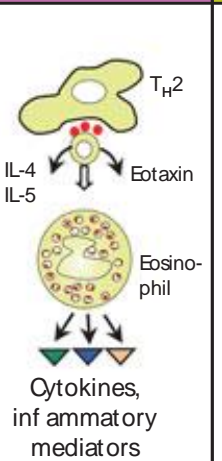
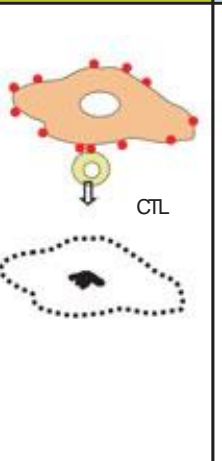
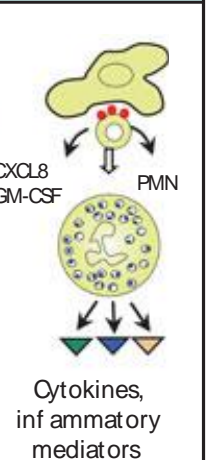
Pseudo-allergic reactions radio contrast media: direct membrane effects related to the osmolarity of contrast media solution

Symptoms of T cell mediated drug allergy

- Makulo-papular Exanthem
- bullous Exanthem
- Acute generalized exanthematous Pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) toxic-epidermal Necrolysis (TEN)
- DRESS, Hepatitis, interstitial Nephritis, Pneumonitis



Antibody (I–III) and T cell-orchestrated
hypersensitivity reactions (IVa–d)

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN γ , TNF α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/granzymeB (CTL)	CXCL-8, IL-17 GM-CSF (T cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Hemolytic anemia, thrombocytopenia (e.g. penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

Contact Dermatitis

non-infectious reaction of the skin to external substances



Allergic contact dermatitis

T- Zell mediated immune response to contactallergens like:

- Nickel, lanolin, Peru balsam or potassium dichromate
- jewellery, medication cosmetics, dyes impregnating agents



Irritative contact dermatitis

Non immune mediated response to physical, chemical irritants and physical influences

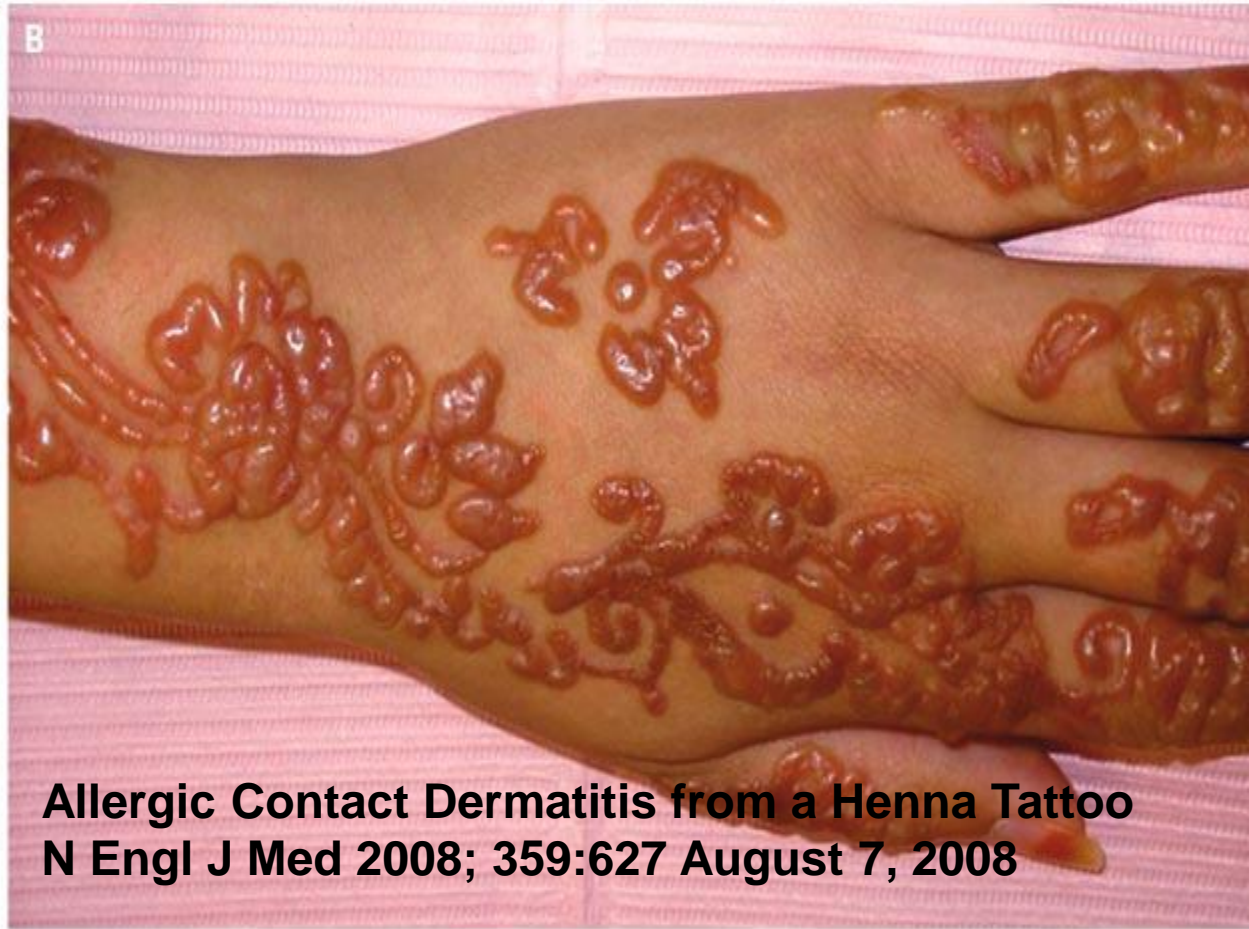
- rubbing, pressure, heat and cold or UV rays
- water, soap, disinfectants,

Allergic Contact Dermatitis

- The reaction usually occurs 24–48 hours after contact with the allergenic substance.
- The skin is inflamed and reddened, it may swell up and blisters or papules may appear.
- The skin reaction appears at the site of the body where the skin came into contact with the irritant, but may also spread to nearby or remote regions of the skin.



Allergic Contact Dermatitis



Allergic Contact Dermatitis from a Henna Tattoo
N Engl J Med 2008; 359:627 August 7, 2008

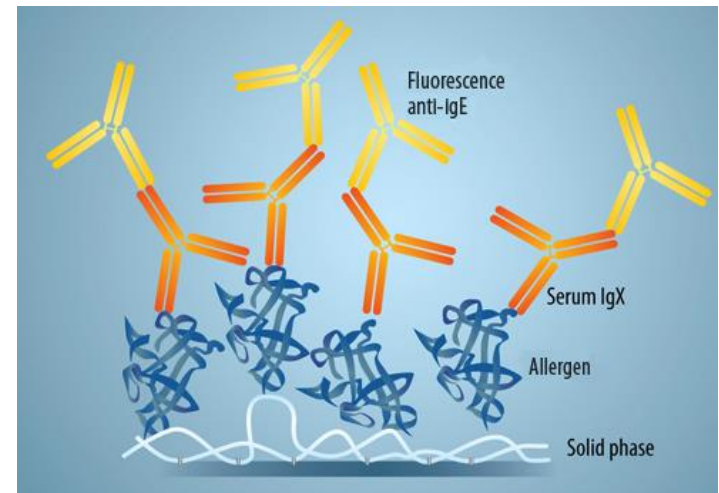
Allergy diagnosis

Allergy = sensitization + clinical symptoms

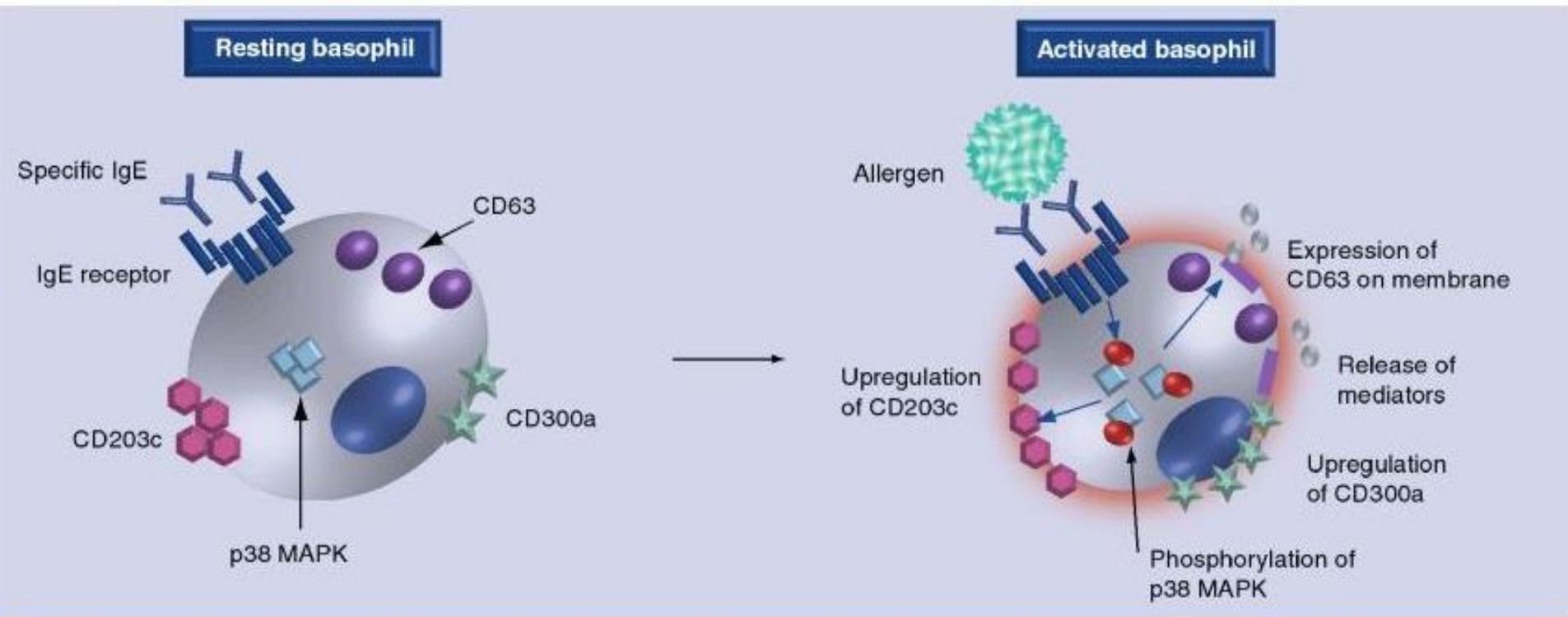
Skin pricktest



Serum IgE



Basophil activation Test



Conjunctival provocation tests (CPT, allergen solution)



No standardization of CPT; no grading of ocular reactions

Digital image analysis possesses the potential of being an objective evaluation method compared to the wide-spread subjective

Dogan et al. Int Arch Allergy Immunol 2014;163:59–68

Diagnosis of food allergy



Prick-to-prick Test



Detection of specific IgE Antibodys

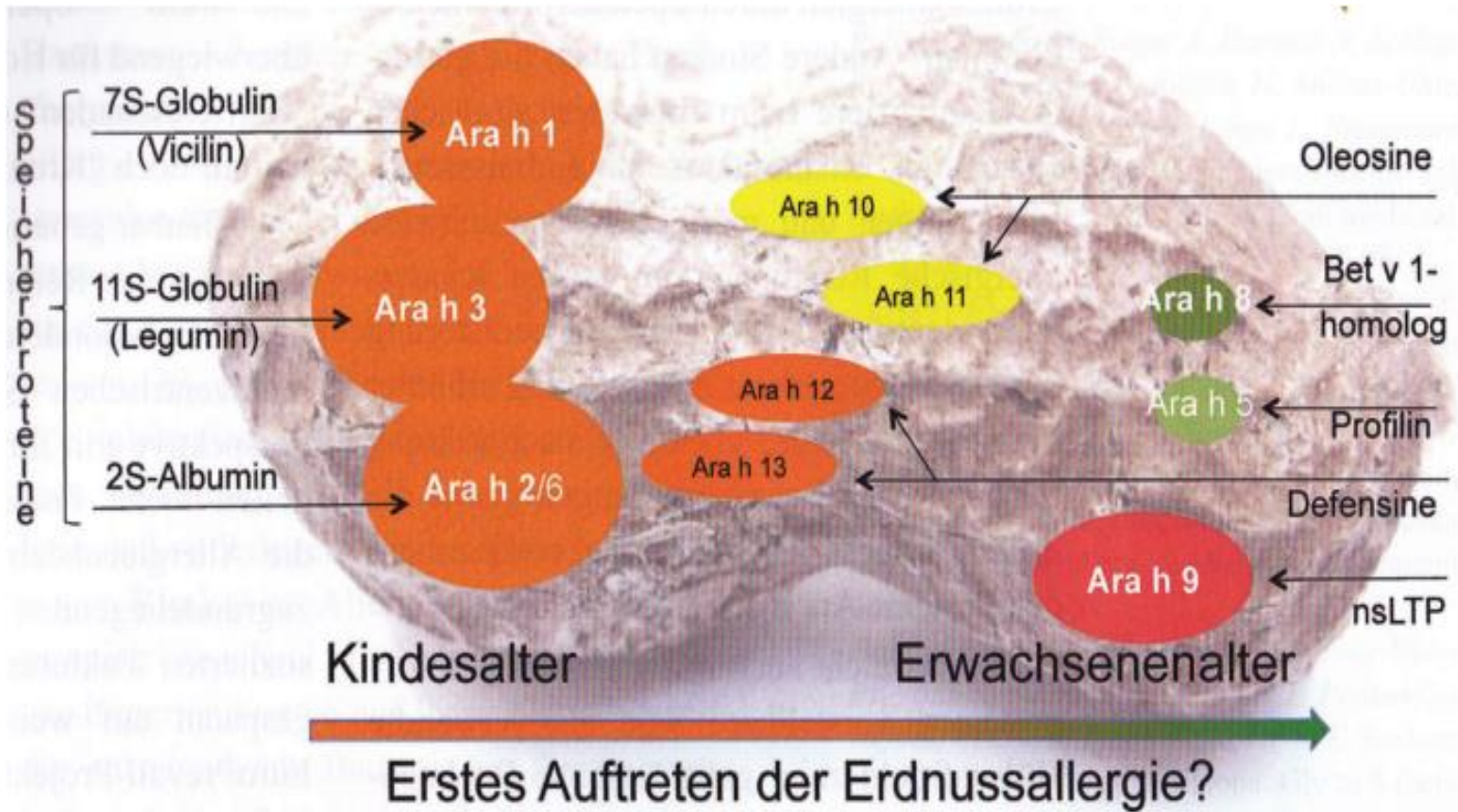
Bet v 1 versus **Pru p 3**



Food challenge Tests



Peanut allergy



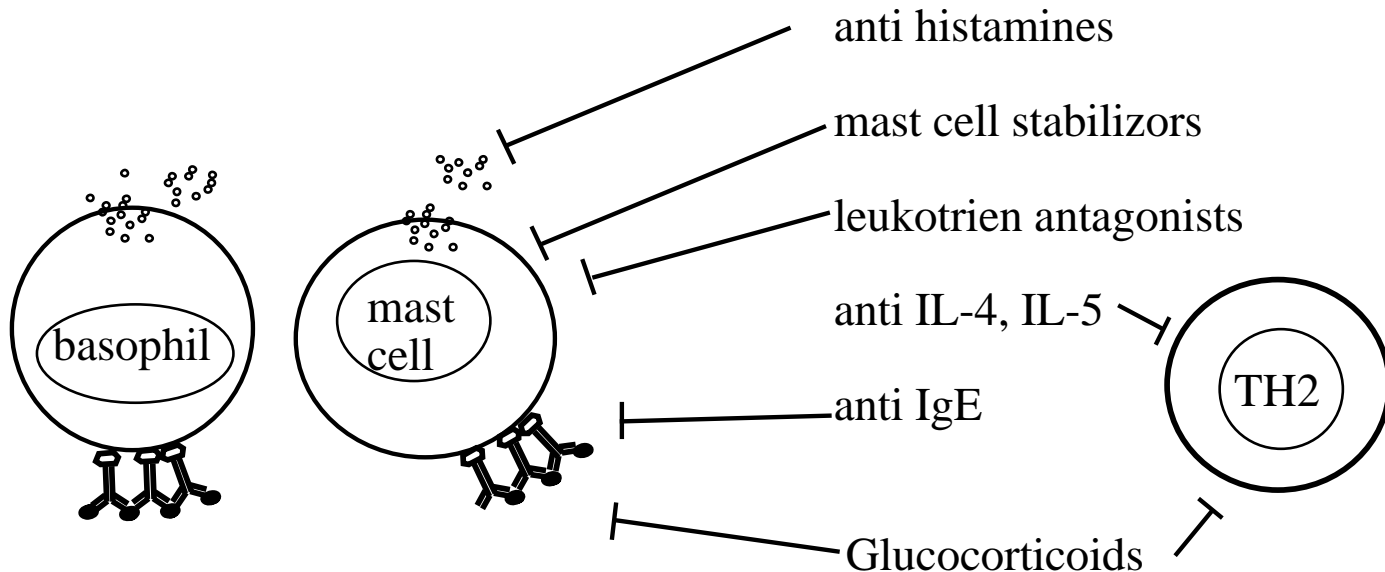
Patch Tests



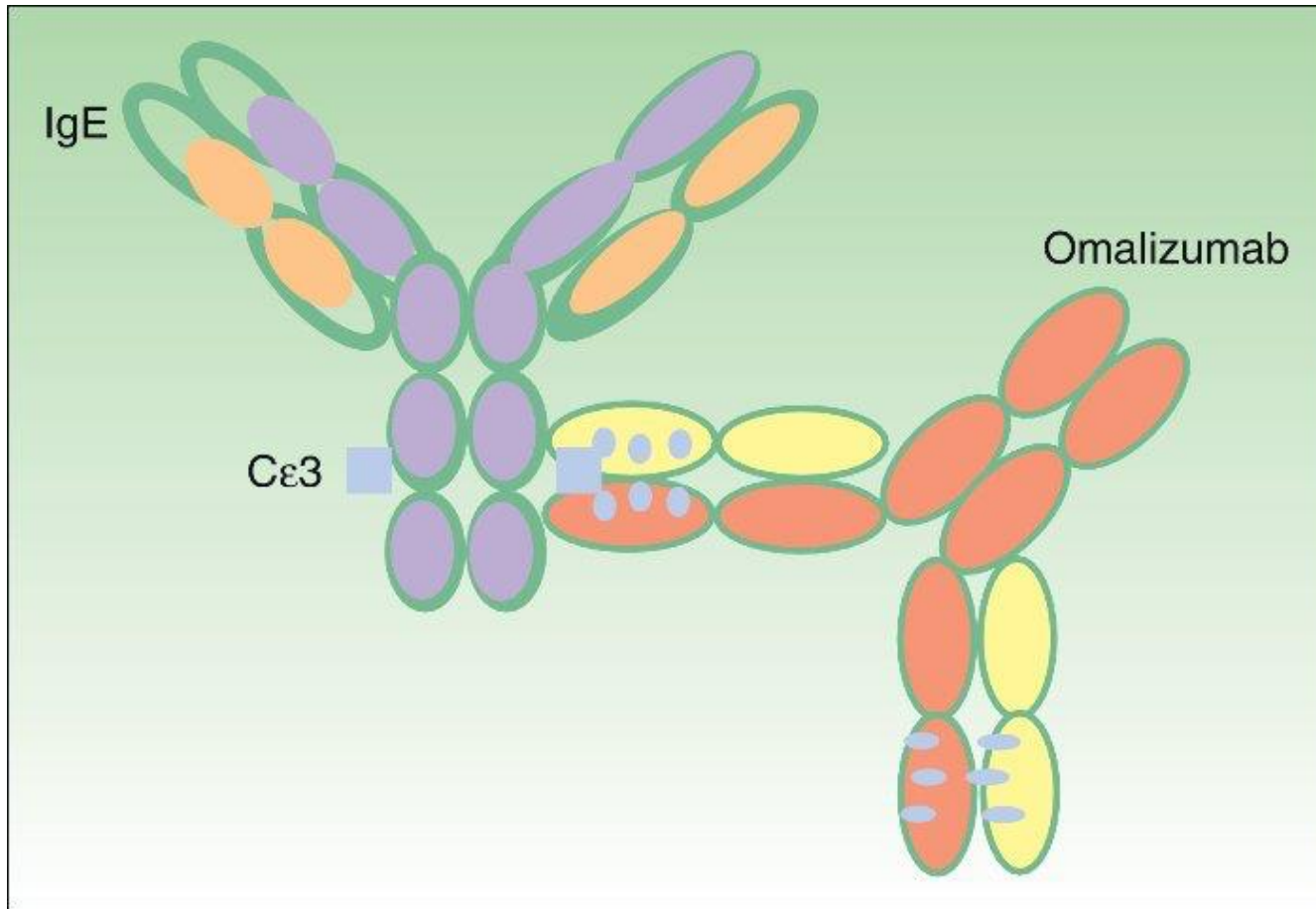
Therapy principles

1. Symptomatic therapy
 - antihistamines
 - corticosteroids
 - leukotrien antagonists
 - antiasthmatics (inhalativ medication)
 - biologics (Omalizumab anti-IgE, Mepolizumab anti-IL5)

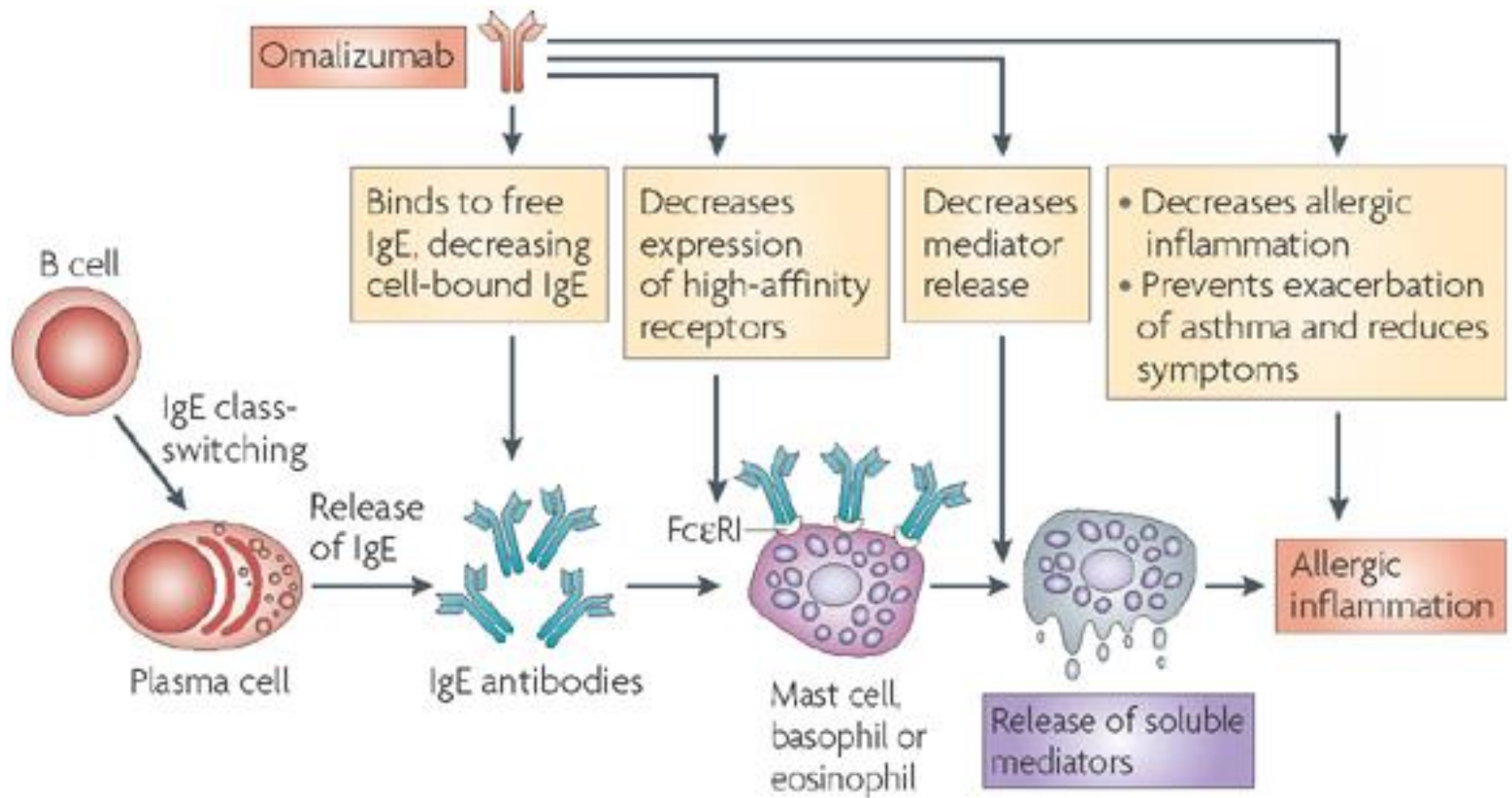
Inhibition of inflammatory mediatores released during ef fector phase:



Anti IgE therapy (omalizumab)



Binding of omalizumab to the $\text{C}\epsilon 3$ domain of IgE.



Nature Reviews | Immunology

Therapy principles

2. Specific /causal therapy

Allergen-specific Immunotherapy = alters course of disease

Bee keepers



Systemic reactions in 45% of
beekeepers with <15 bee
sting / year

No/less systemic reactions in
Beekeepers with
> 200 bee sting / year

Why???

Allergen-specific Immunotherapy

The only causal therapy of allergic Diseases

1998 WHO accepts the therapy

Bousquet, Lockey Malling. WHO position paper. J Allergy Clin Immunol 1998;102:55-62



Reduktion allergischer Symptome

Calderon et al. JACI 2011;127:30-8

Radulovic et al. Allergy 2011;66:740-52

Asthma prevention

Douglas et al. Pediatrics 1968; 42: 793

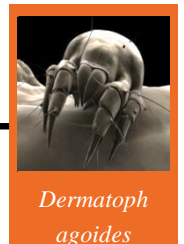
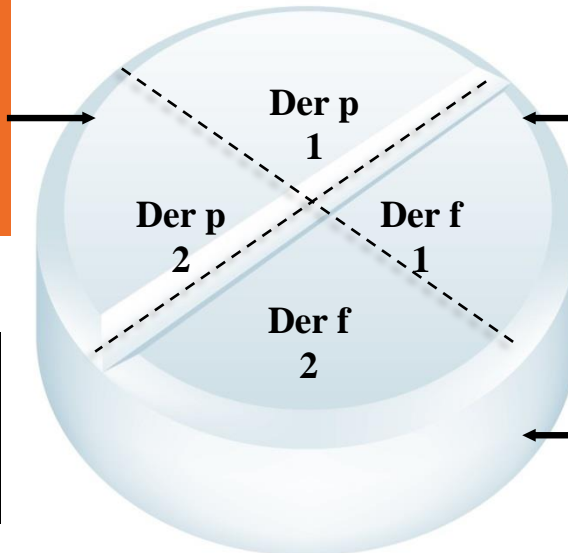
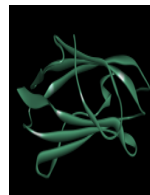
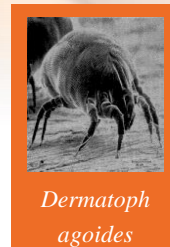
Jacobsen et al. Allergy 2007;62:943-8

Möller et al. JACI 2002; 109: 251-256

Schmitt J et al. JACI 2015;136:1511-6

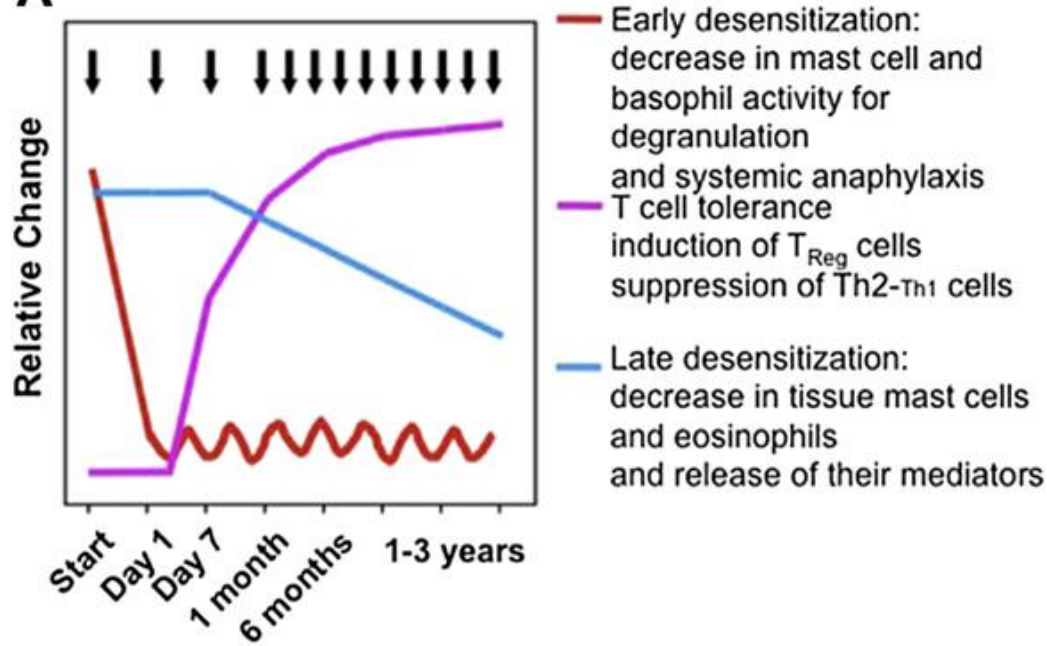
Sublingual Immunotherapy SLIT

Passalacqua et al. JACI 2007;119:881-91

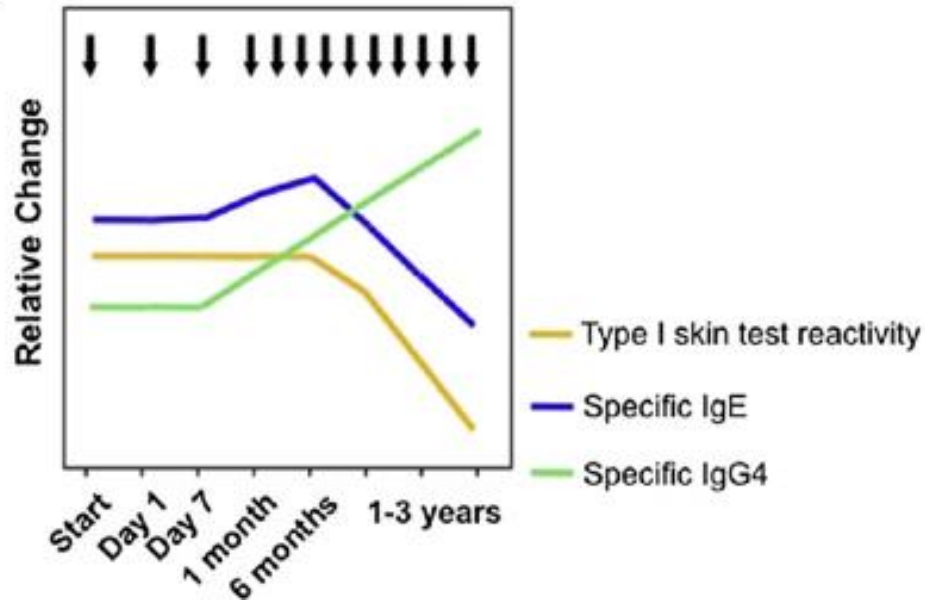


Mechanisms of SIT

A



B



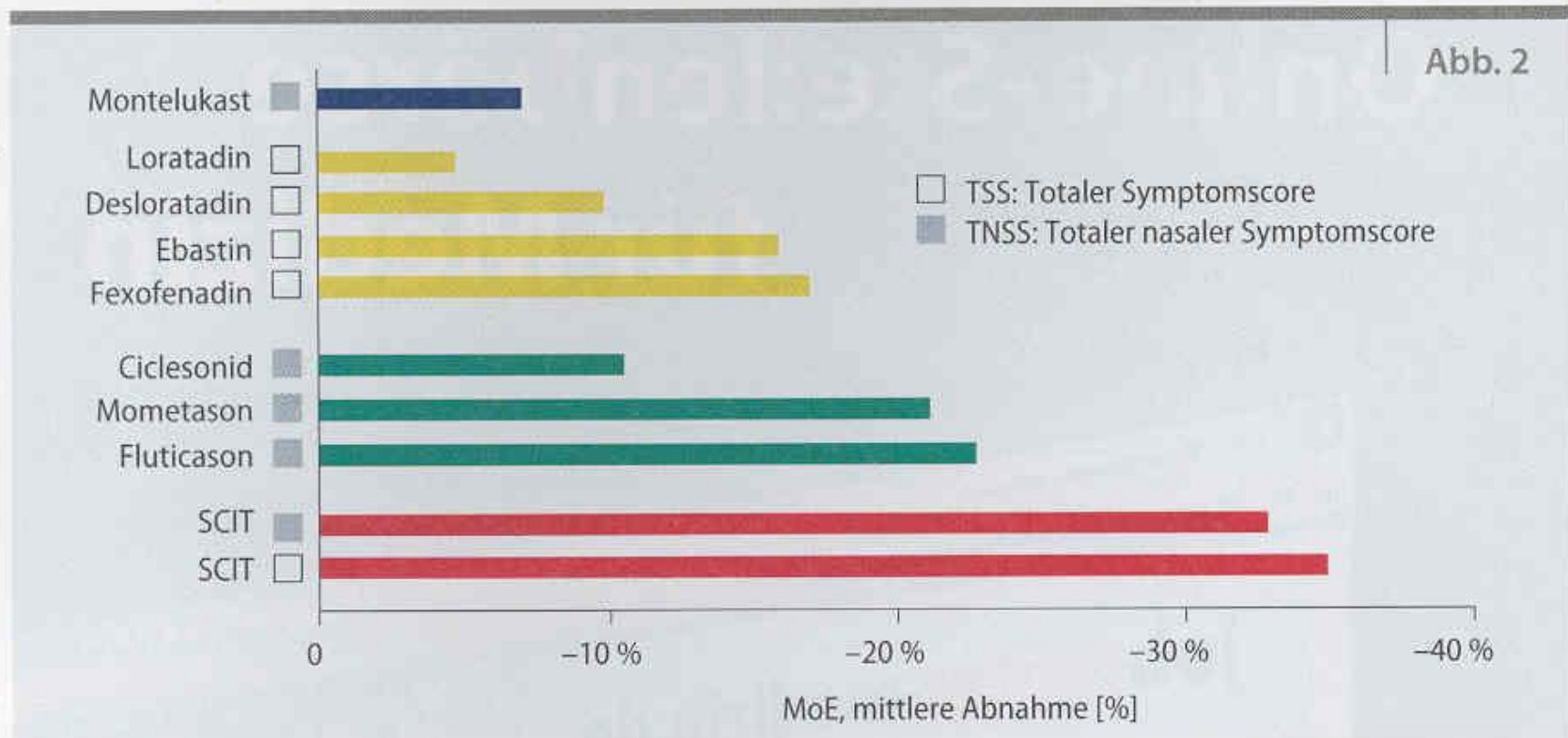
Burks et al. J

Allergy Clin Immunol 2013;131:1288-96.

Efficacy of different Interventions in seasonal allergic Rhinitis (1. year)

Matricardi et al. J Allergy Clin Immunol 2011;128:791-9

Mod. nach Matricardi PM et al. J Allergy Clin Immunol. In press 2011



Side effects of SCIT

Severity of side effects: Mild symptoms to life-threatening anaphylaxis and even death

Table 2. Systemic Reactions (SRs) per 10,000 Injection Visits^a between July 2008 and 2010

	Year 1 (7/1/2008– 7/31/2009)	Year 2 (8/1/2009– 7/31/2010)
Any type of SR	10.2	9.7
Grade 1 (mild SRs)	7.6	6.7
Grade 2 (moderate SRs)	2.3	2.7
Grade 3 (severe SRs)	0.3	0.4

Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy–year 2

Tolly G. Epstein et al. *Ann Allergy Asthma Immunol.* 2011;107:426–431.

SLIT has a better safety profile than SCIT (home administration possible)

Summary

Allergy?

specific immune reaction to harmless foreign substances with clinical symptoms

Sensitisation and Atopy \neq Allergy

Type 1 hypersensitivity

Key Players:

Allergen-specific IgE

Allergen

Eosinophils

B cells

TH2

Cytokines
(IL-4, IL-5, IL-13)

APC

Tissue Mast cells

Chemokines

Are IgE antibodies needed for Mast cell
activation ?

Yes

No

Is allergen needed to induce anaphylaxis?

Yes

No

Which antibody is blocked by omalizumab (Xolair)
?

IgE

IgM

IgG

IgA

What is the only causal therapy for allergic diseases ?

Corticosteroids ?

Xolair ?

Antihistamines?

Allergen-specific immunotherapy ?