ALLERGIES

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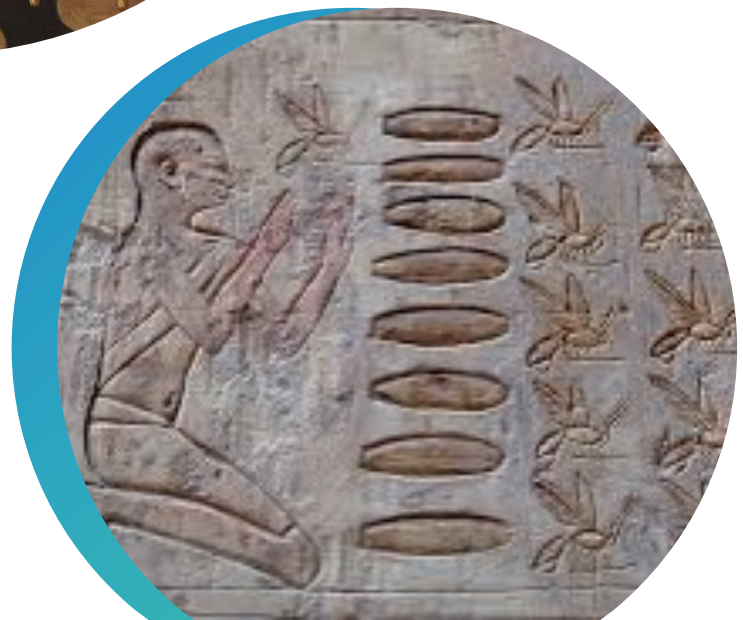
Northeastern University

Learning Objectives

- Understand what the term "*Allergy*"
- Understand the core mechanisms of allergic immunity
- Understand current theories behind development of allergy
- Understand how therapies relate to specific allergic mechanisms and the allergic diseases



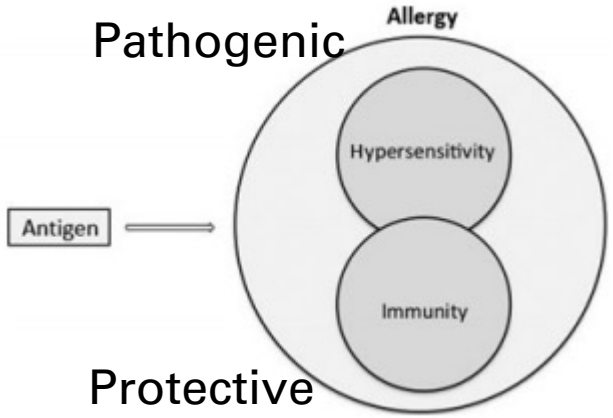
What is Allergy?

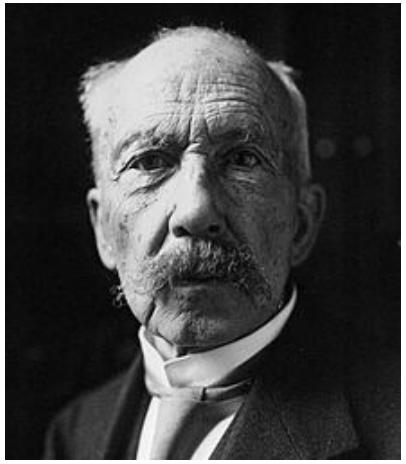
- King Menses of Egypt ~3300 BC
- Britannicus, son of Claudius ~10-54 BC
- *“would develop a rash and his eyes swelled to the extent that he could not see where he was going”- Seneca*

What is Allergy?—Pathogenic Hyperreaction of Immunity

Clemens von Pirquet
(1874–1929)

Allergie
1906





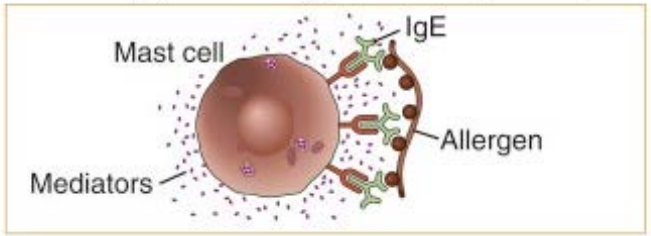
Charles Richet
(1850–1935)

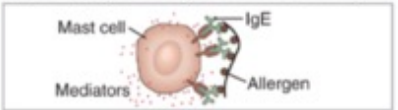
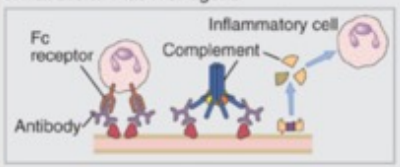
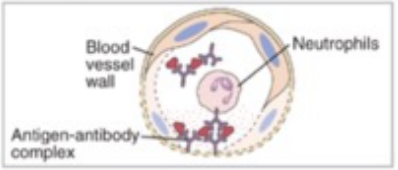
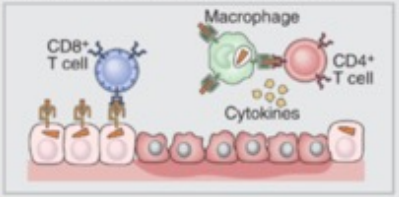
Aberrant hyperreactivity that threatens host

Protective mechanism for expulsion of noxious agent

J. M. Igea. *"The history of the idea of allergy"* 2013, Allergy, Aug;68(8):966-73.

Type 1 Hypersensitivity

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils, lymphocytes)

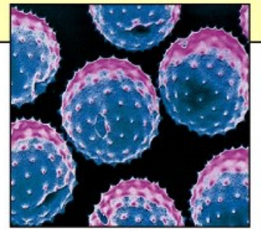
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	T_H2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g. hormone receptor signaling
Immune complex-mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement and Fc receptor-mediated recruitment and activation of leukocytes
T cell-mediated diseases (Type IV)	1. $CD4^+$ T cells (delayed type hypersensitivity) 2. $CD8^+$ CTLs (T cell-mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

WHAT ARE SOME COMMON ALLERGENS?

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
e.g., house dust mites


pollen


house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins


wasp


drugs

Ingested materials

Food
Orally administered drugs


peanuts


shellfish

Contacted materials

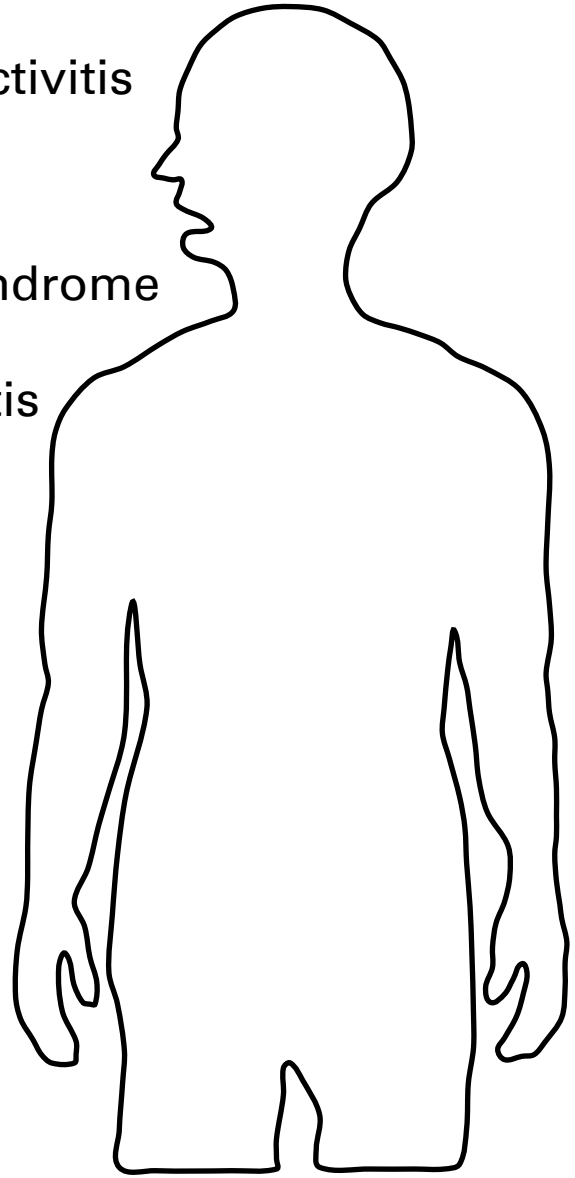
Plant leaves
Industrial products made from plants
Synthetic chemicals in industrial products
Metals


poison ivy

nickel coin

Figure 12.1 The Immune System, 3ed. (© Garland Science 2009)

Where do allergic reactions occur?



Allergic Conjunctivitis

Allergic Rhinitis

Oral Allergy Syndrome

Eosinophilic Esophagitis

Allergic Asthma

Atopic Dermatitis

Contact Dermatitis

Urticaria

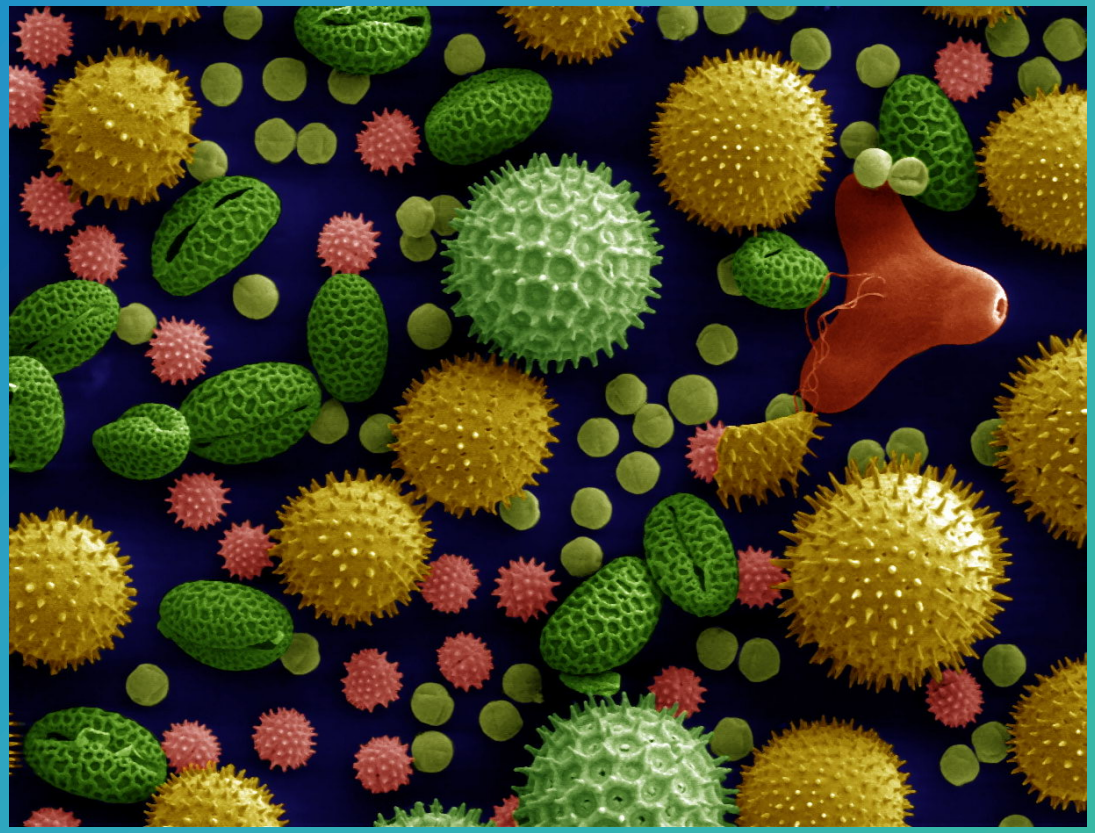
Food Allergy

Anaphylaxis

Drug Allergy

Core Mechanisms of Allergic Immunity

- Allergens
- Key Phases of Allergy
- Allergic Effector Cells
- Susceptibility Factors



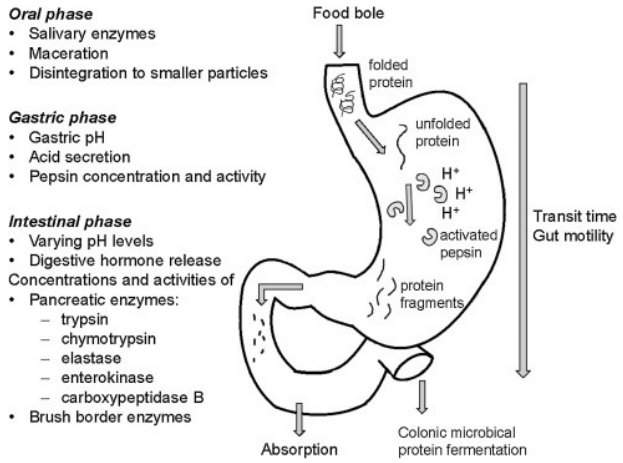
Allergens

- **<u>Proteins</u> within environmental substances**
- Chemicals that modify endogenous proteins
  - e.g. urushiol in poison ivy
- Most proteins are not allergens
  - Peanut contains only 17 defined allergens*

*WHO/IUIS Allergen Nomenclature Sub-committee

Common Features of Allergens

- **Low molecular weight (5-70kD)**
- **Highly soluble**
- **Highly glycosylated**
- **Enzymatic activity e.g. cysteine protease**
- **Stable**



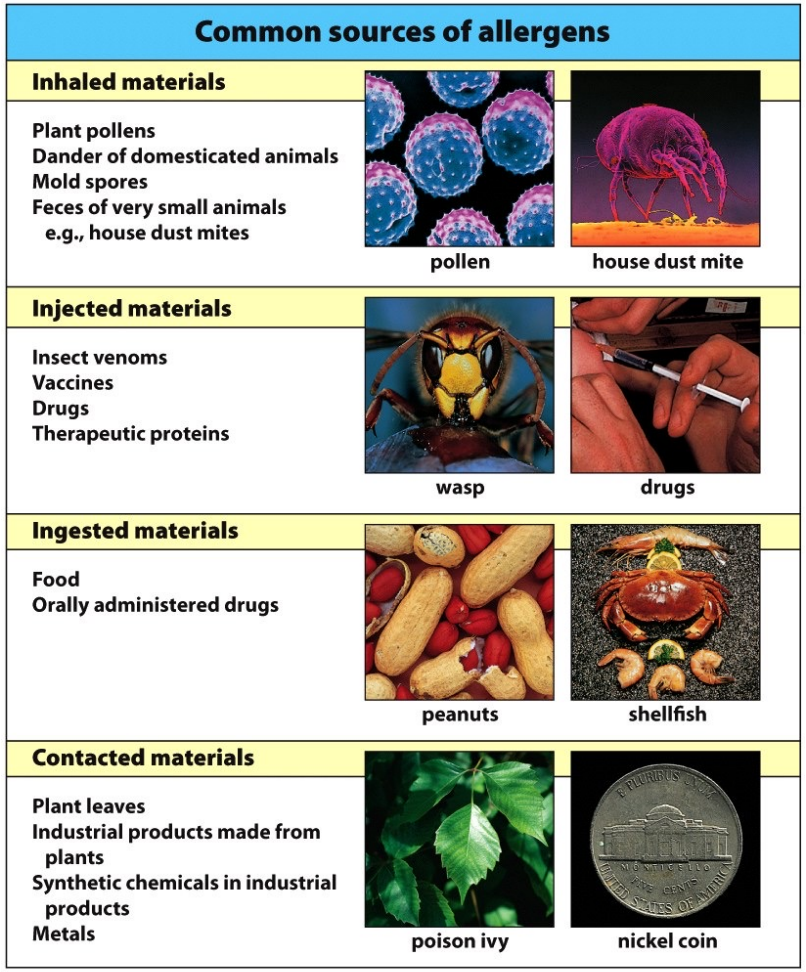
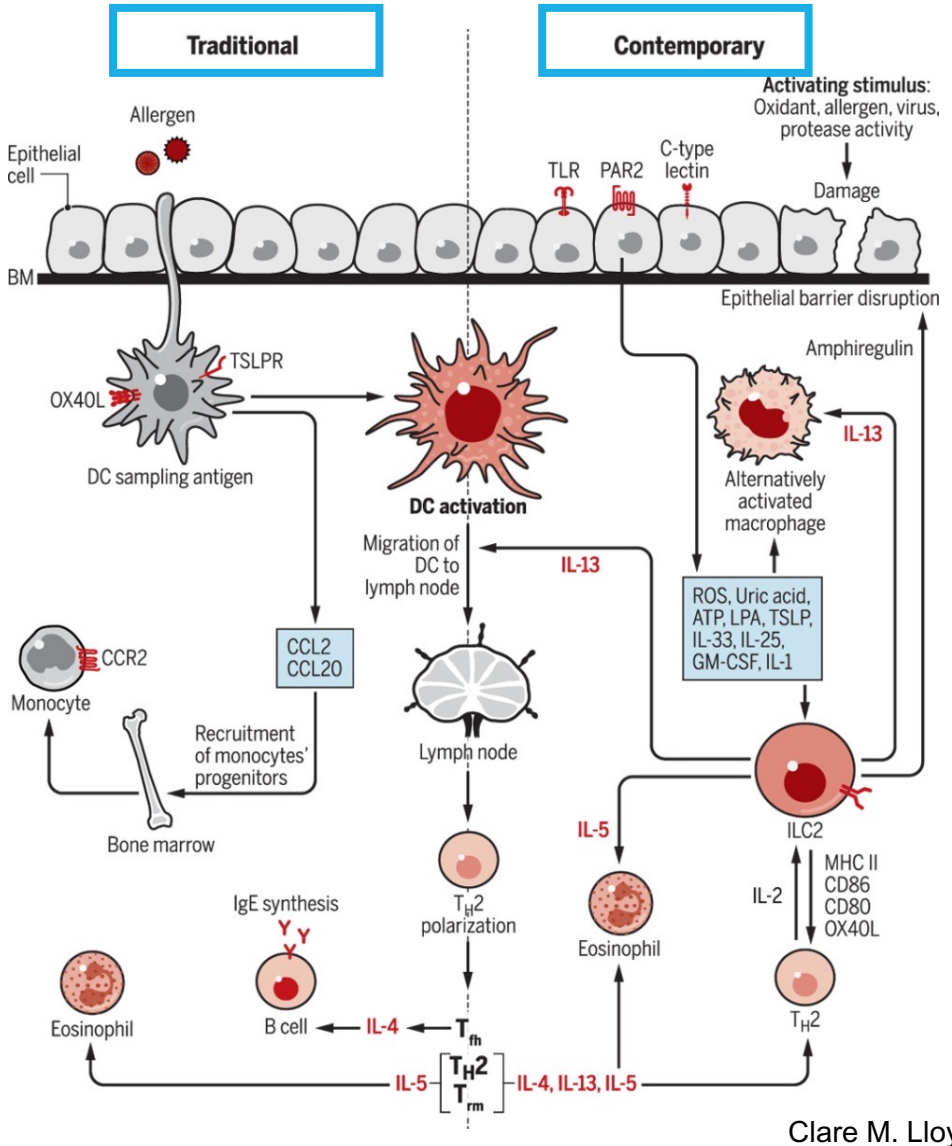


Figure 12.1 The Immune System, 3ed. (© Garland Science 2009)

Key Phases of Allergy

Step 1--Becoming Sensitized (***aka* loss of tolerance**)

Direct influence of allergen on Dendritic Cell



Stimulation of structural cells and innate cells to influence Dendritic Cell priming of T cells

CD4+ Th2 cell cytokines drive downstream responses

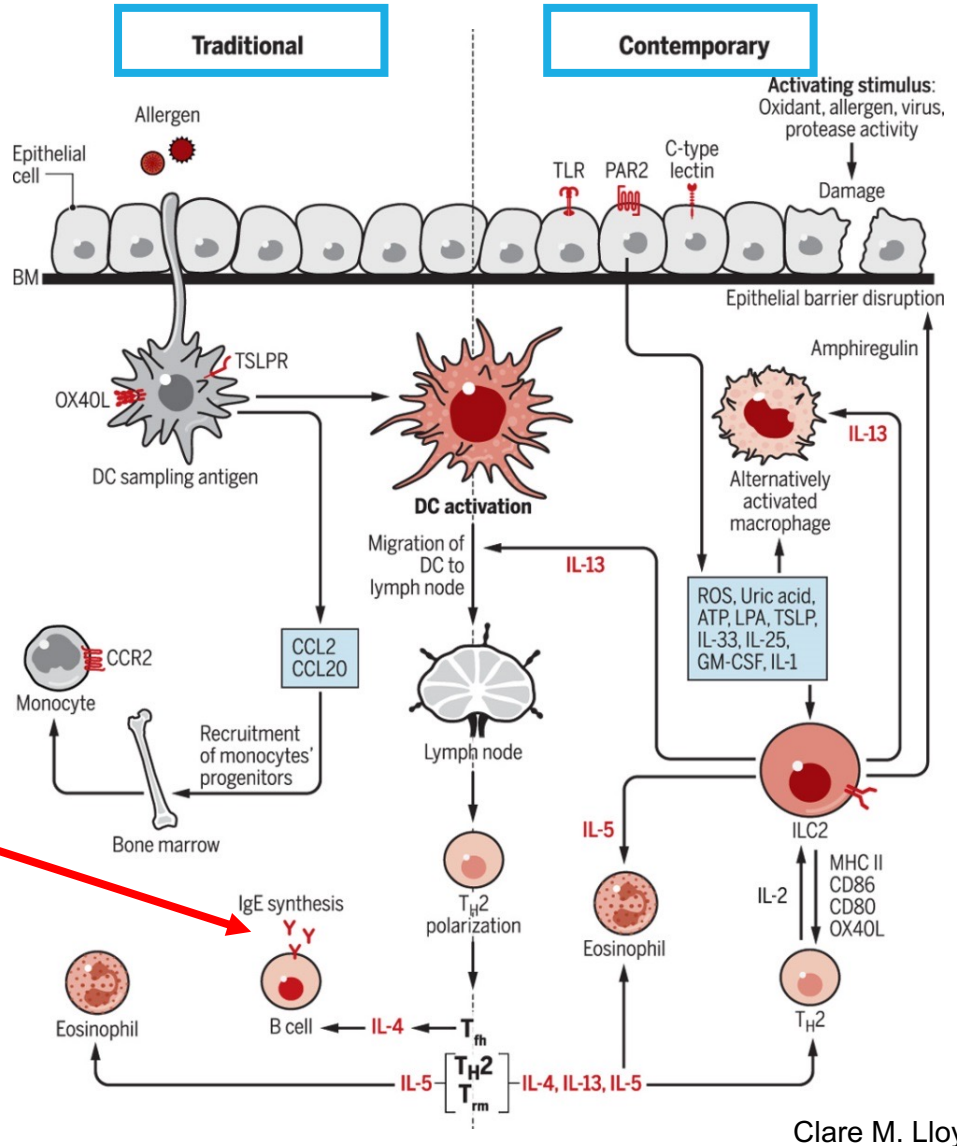
ILC2 cells cytokines contribute to drive downstream responses

Clare M. Lloyd, and Robert J. Snelgrove Sci. Immunol. 2018;3:eaat1604

Key Phases of Allergy

Step 1--Becoming Sensitized

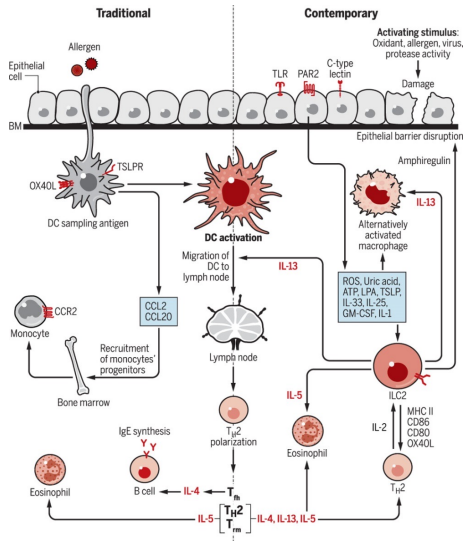
"Atopic"= Specific IgE has been produced



Clare M. Lloyd, and Robert J. Snelgrove Sci. Immunol. 2018;3:eaat1604

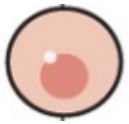
Key Phases of Allergy

Step 2– Re-exposure



Example Markers

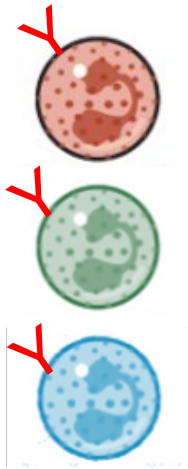
GATA3+
ST2+
CRTH2+
CD69+
CCR4+



Memory Th2 Cells
- Circulating
- Tissue-resident

→ IL-4, IL-5, IL-13

Late phase response several hours later



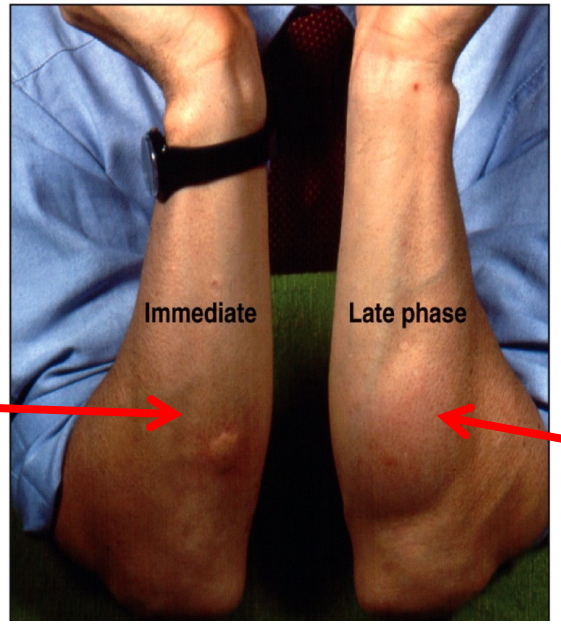
IgE Receptor Positive Cells

→ Granule Release

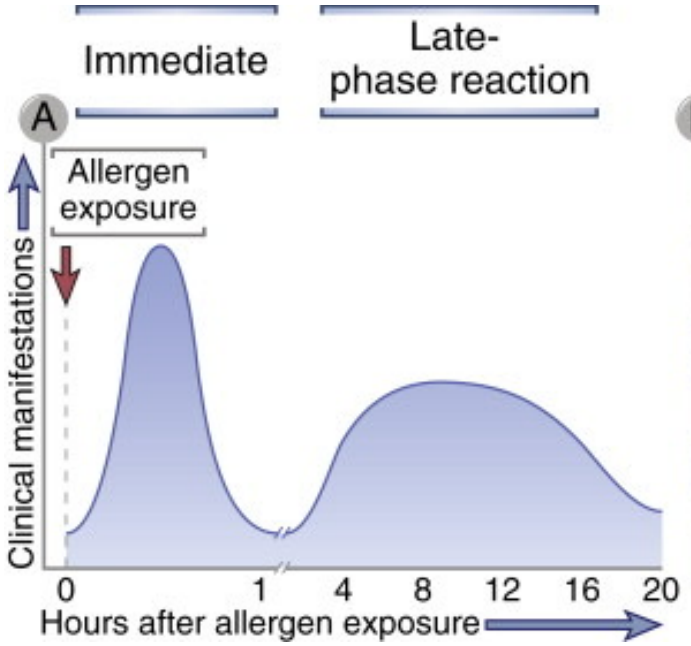
Immediate reactions within minutes

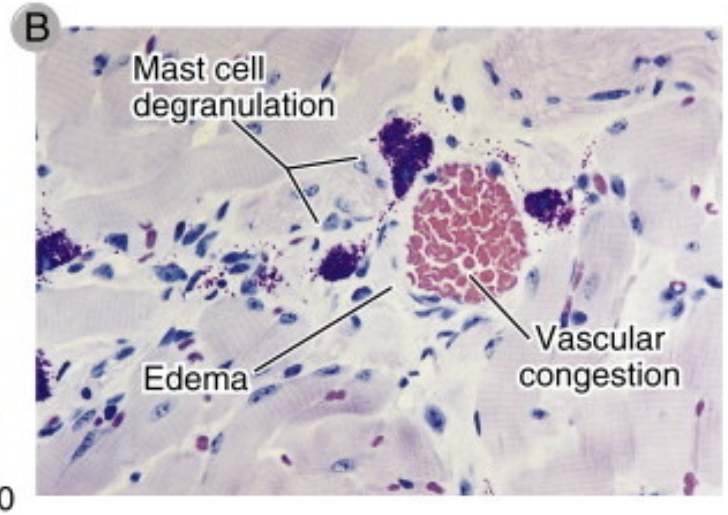
"Allergic"= Clinical manifestation on responses

15 min after injection



6 h after injection





Key Phases to Being "*Allergic*"

Loss of tolerance

Th2/ILC2 biased immune priming

Activation upon reexposure

Allergic Effector Cells

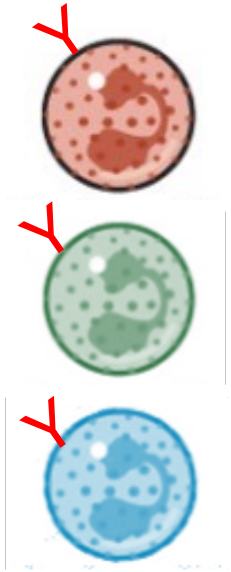
Example Markers

GATA3+
ST2+
CRTH2+
CD69+
CCR4+

Memory Th2 Cells
- Circulating
- Tissue-resident

IL-4
IL-5
IL-13

IgE Receptor Positive Cells



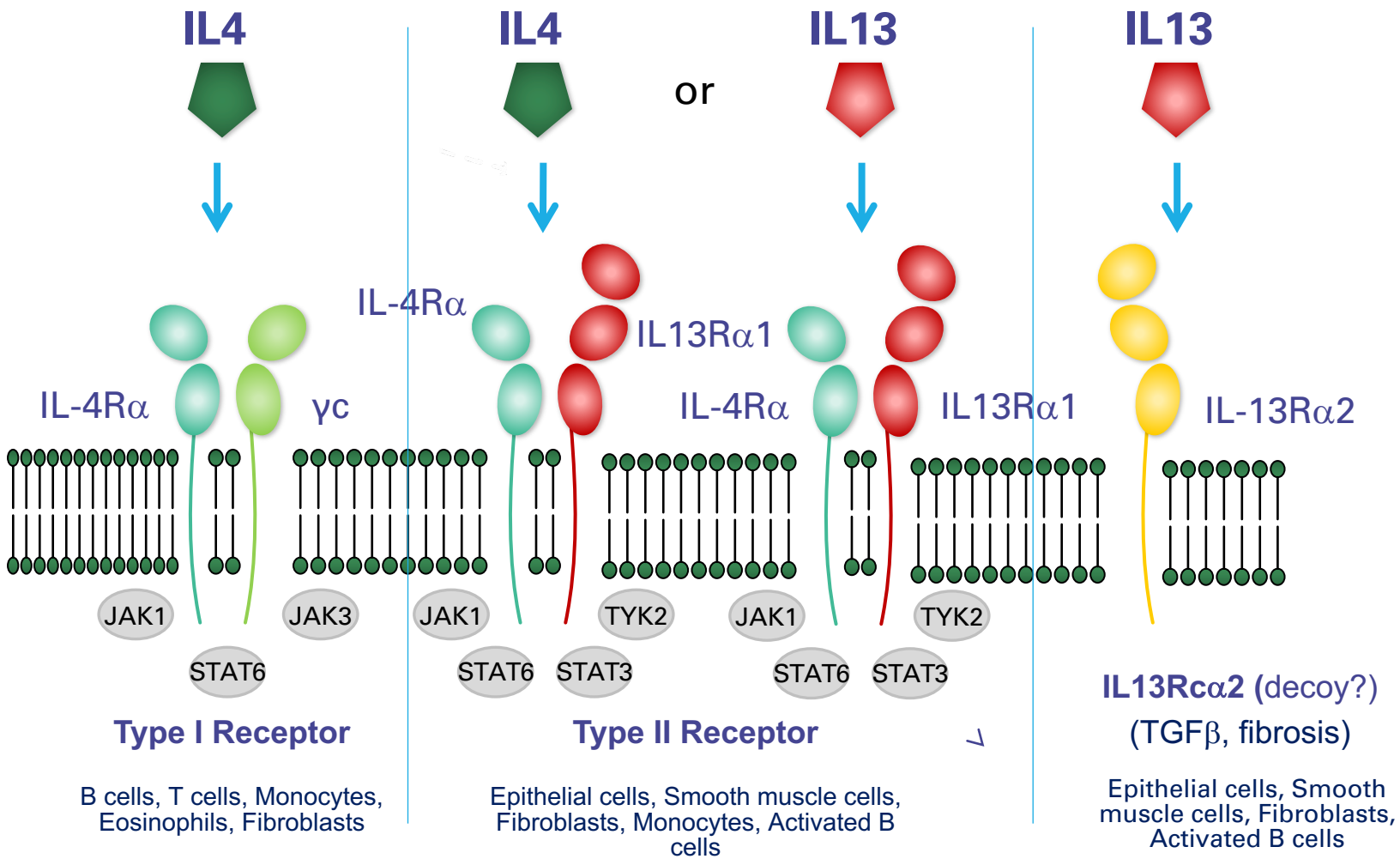
Eosinophil

Basophil

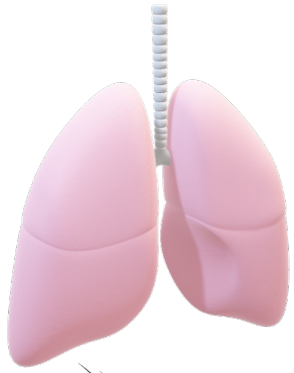
Mast Cell

Granule Release

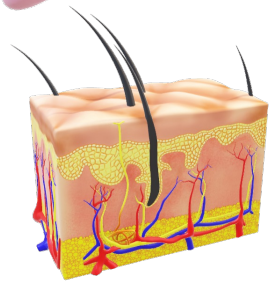
IL-4 & IL-13 Exhibit Broad Functions on Many Cell Types



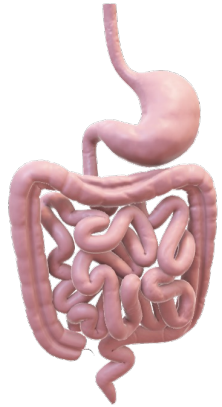
Tissue-Specific Effects of IL-4/IL-13



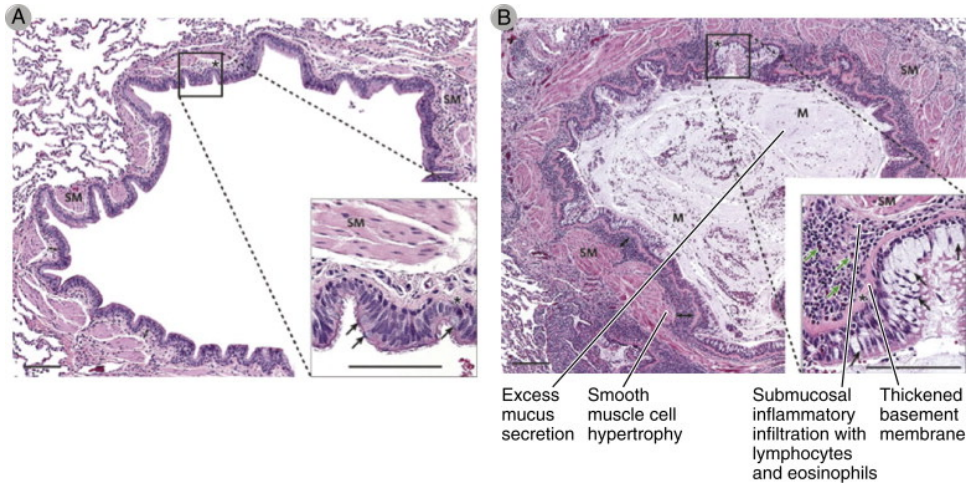
Mucus secretion
Smooth muscle hyperreactivity



Keratinocyte hyperproliferation
Loss of epithelial barrier
Itch



Permeability
Repair
Inflammation



Histopathologic features of bronchial asthma. Atopic bronchial asthma results from repeated immediate hypersensitivity reactions in the lungs with chronic late-phase reactions. A cross-section of a normal bronchus (A) and a cross-section of a bronchus from a patient with asthma (B) are shown. The diseased bronchus has excessive mucus (M) production, many submucosal inflammatory cells (including eosinophils), and smooth muscle (SM) hypertrophy, and many more goblet cells than in the normal bronchus (black arrows in insets). (From Galli SJ, Tsai M, Piliponsky AM: The development of allergic inflammation, Nature 454:445-454, 2008. Courtesy of G. J. Berry, Stanford University, California.)

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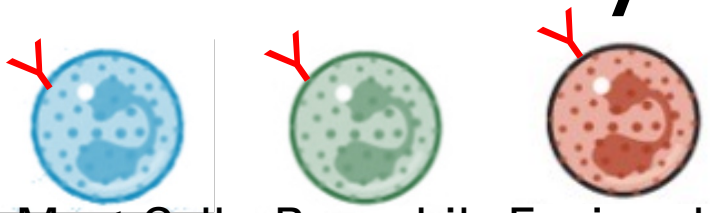
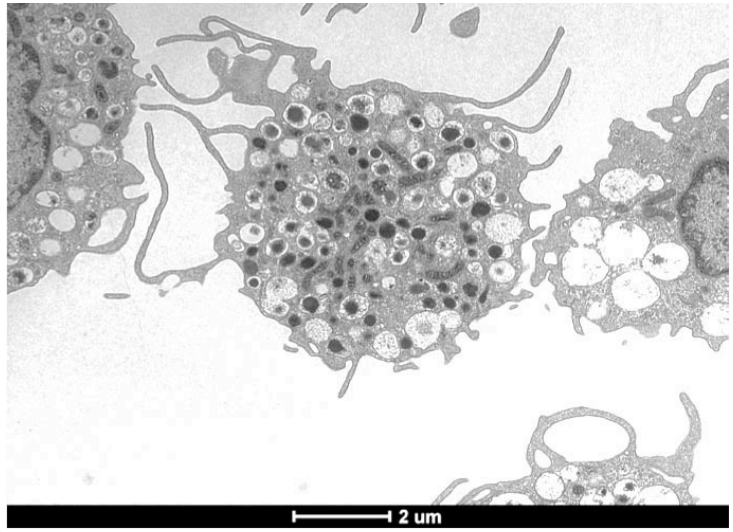
IgE Activated Granulocyte Cells



Mast Cell Basophil Eosinophil

Major site of maturation	Connective tissue	Bone marrow	Bone marrow
cells in circulation	No	Yes (0.5% of blood leukocytes)	Yes (~2% of blood leukocytes)
Mature cells recruited into tissues from circulation	No	Yes	Yes
Mature cells residing in connective tissue	Yes	No	Yes
Proliferative ability of mature cells	Yes	No	No
Life span	Weeks to months	Days	Days to weeks
Major development factor (cytokine)	Stem cell factor, IL-3	IL-3	IL-5
Expression of FcεRI	High levels	High levels	Low levels (function not clear)
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases	Histamine, chondroitin sulfate, protease	Major basic protein, eosinophil cationic protein, peroxidases, hydrolases, lysophospholipase

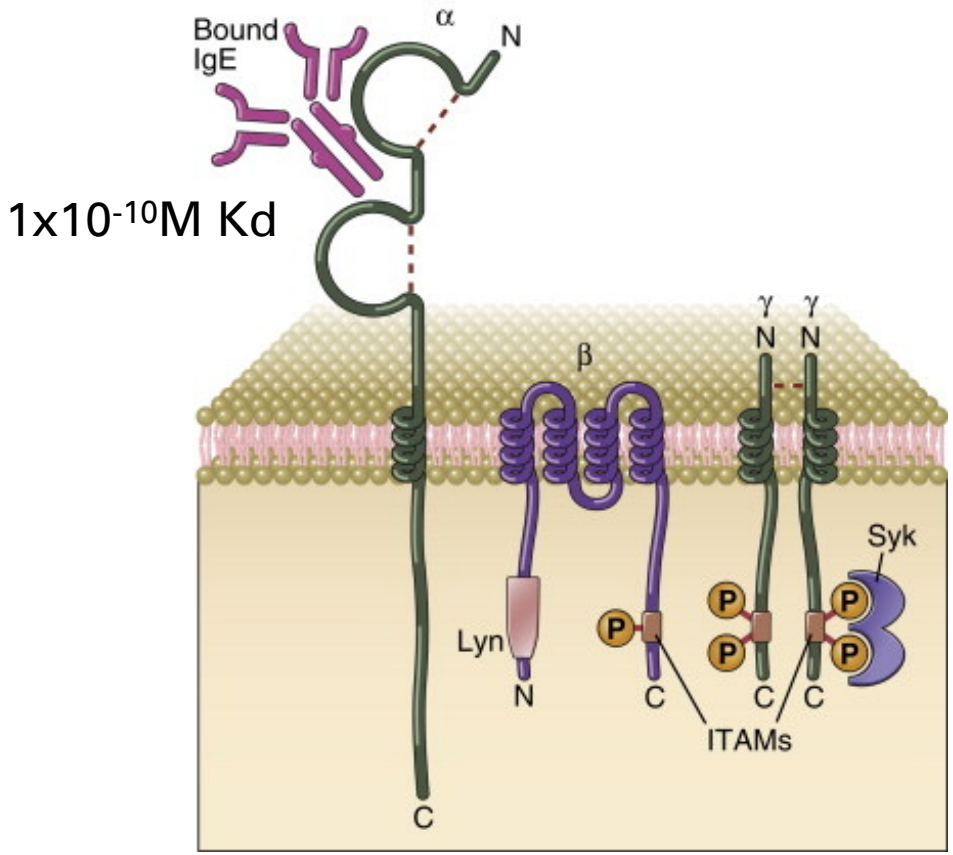
FcεRI, Fcε receptor type I; *IL*, interleukin.



Be aware…

- Mast Cells, Basophils & Eosinophils can also be activated in many non-IgE dependent ways, including…
  - Innate cytokines, e.g. IL-33
  - DAMPs, e.g. extracellular ATP
  - Neural crosstalk, e.g. Substance P
  - Environment, e.g. temperature receptors (TRPs)

Binding of IgE to its high affinity receptor



Polypeptide chain structure of the high-affinity IgE Fc receptor (FcεRI). IgE (not drawn to scale) binds to the Ig-like domains of the α chain. The β chain and the γ chains mediate signal transduction. The ITAMs in the cytoplasmic region of the β and γ chains are similar to those found in the T cell receptor complex (see Fig. 7-5). Lyn and Syk are tyrosine kinases that bind to the β and γ chains and participate in signaling events. A model structure of FcεRI is shown in Chapter 12.

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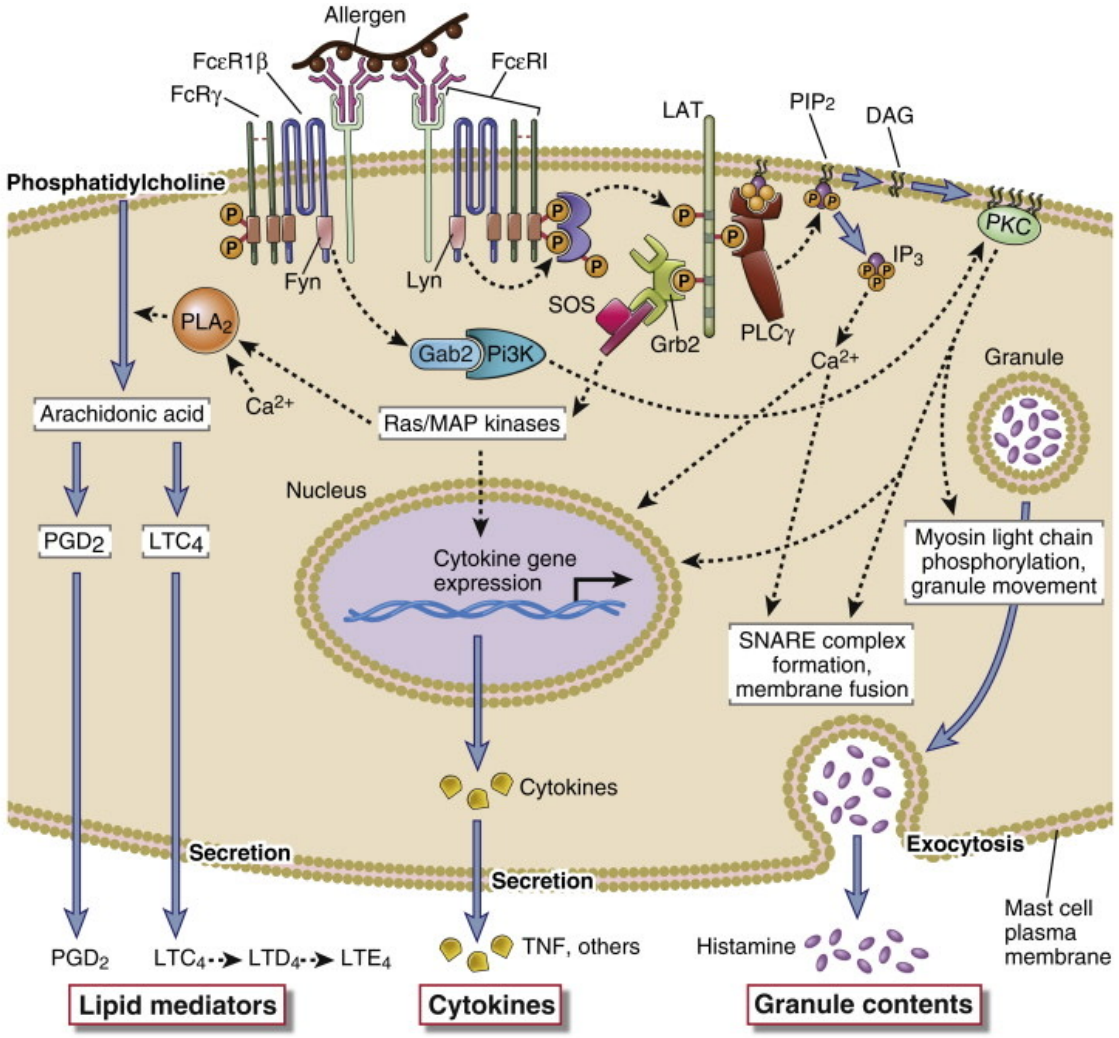

Biochemical events of mast cell activation. Cross-linking of bound IgE by antigen activates protein tyrosine kinases (Syk and Lyn), which in turn cause activation of a MAP kinase cascade and phospholipase Cγ (PLCγ). PLCγ catalyzes the release of IP3 and DAG from membrane PIP2. IP3 causes release of intracellular calcium from the endoplasmic reticulum. Calcium and DAG activate PKC, which phosphorylates substrates such as myosin light chain protein and thereby leads to the degradation and release of preformed mediators. Calcium and MAP kinases combine to activate the enzyme cytosolic phospholipase A2 (PLA2), which initiates the synthesis of lipid mediators, including prostaglandin D2 (PGD2) and leukotriene C4 (LTC4).

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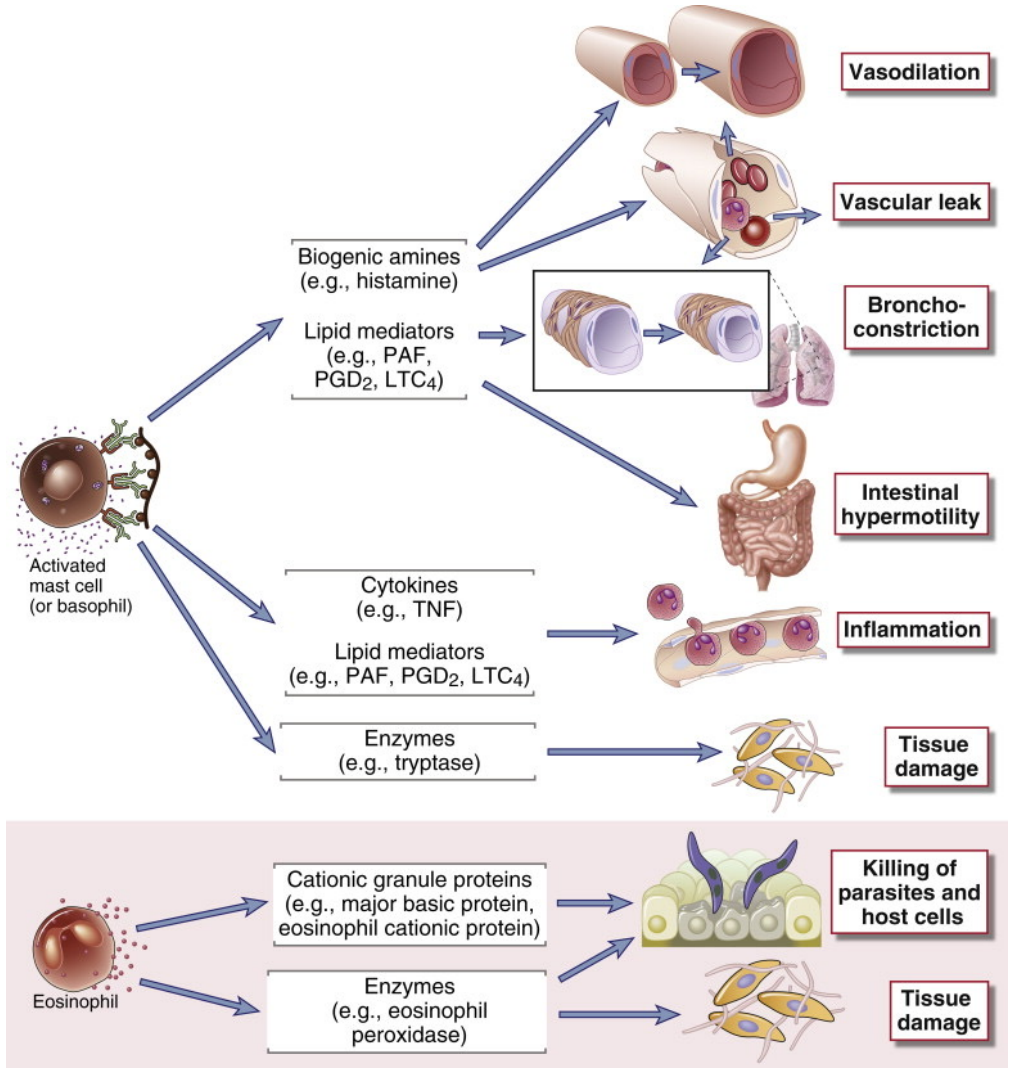

Tissue-specific consequences to granule release upon activation

Biologic effects of mediators of immediate hypersensitivity. Mast cells and basophil mediators include biogenic amines and enzymes stored preformed in granules as well as cytokines and lipid mediators, which are largely newly synthesized on cell activation. The biogenic amines and lipid mediators induce vascular leakage, bronchoconstriction, and intestinal hypermotility, all components of the immediate response. Cytokines and lipid mediators contribute to inflammation, which is part of the late-phase reaction. Enzymes probably contribute to tissue damage. Activated eosinophils release preformed cationic proteins as well as enzymes that are toxic to parasites and host cells. Some eosinophil granule enzymes probably contribute to tissue damage in chronic allergic diseases.

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Basophil Functions in Inflammation

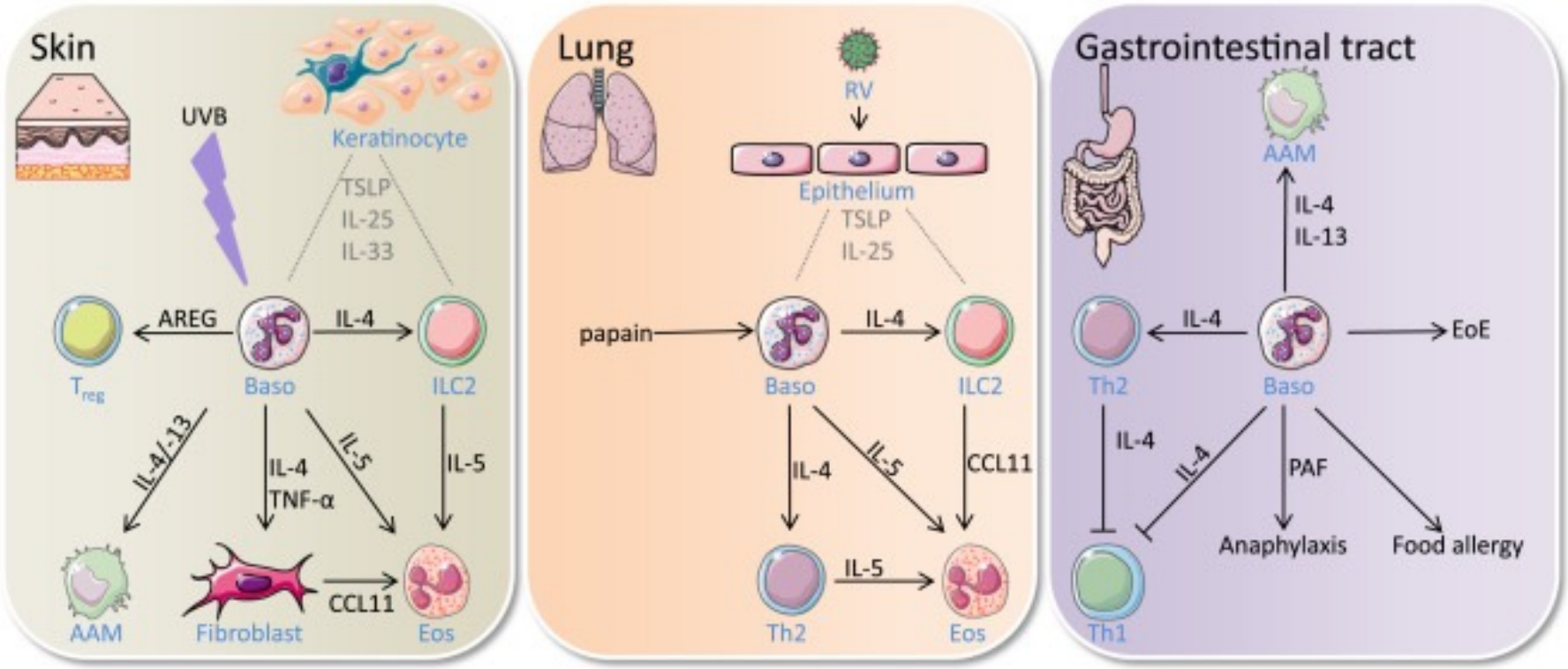
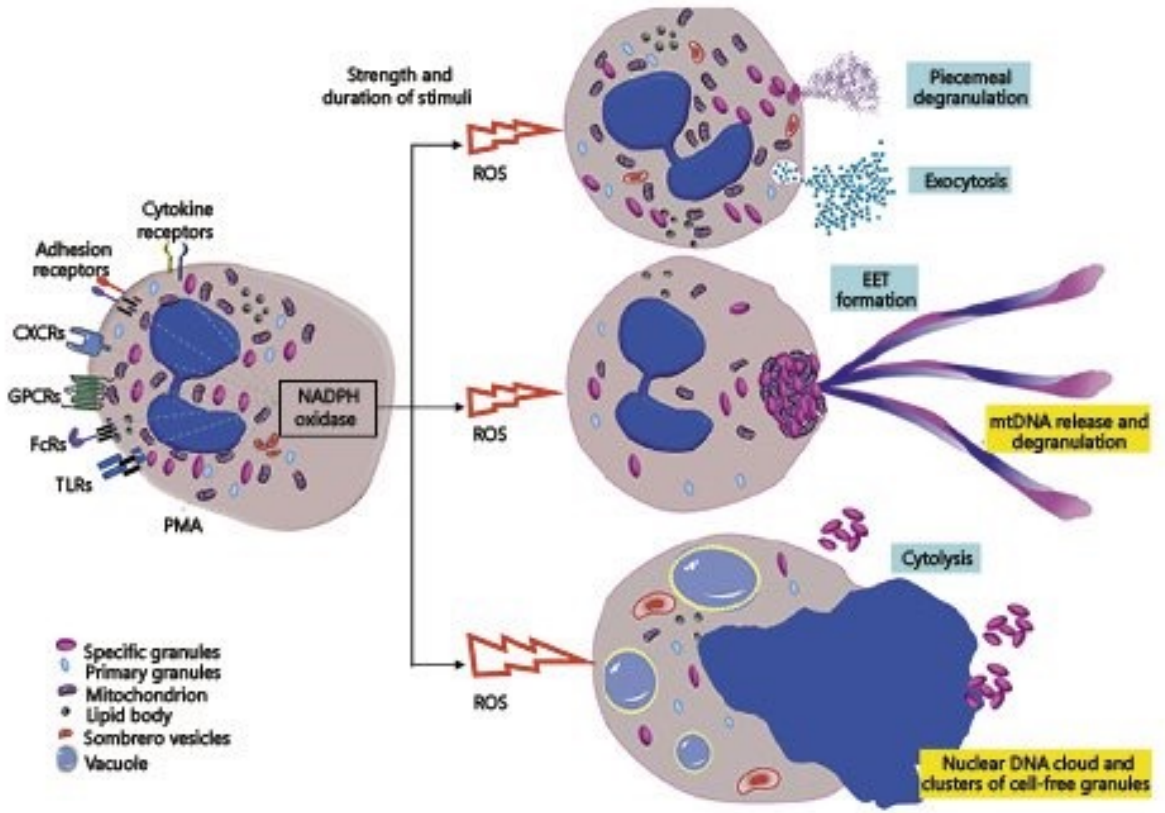


Fig. 1. Illustration of basophil functions during inflammatory response in skin, lung and intestine. Symbols are derived from Servier medical art (Servier, Suresnes, France).

Eur J Pharmacol. 2016 May 5;778:90-5. doi: 10.1016/j.ejphar.2015.04.049. Epub 2015 May 7.
Schwartz C, Eberle JU, Voehringer D.

Eosinophil Functions (in inflammation)



Cationic granules highly toxic to both pathogens and neighboring cells

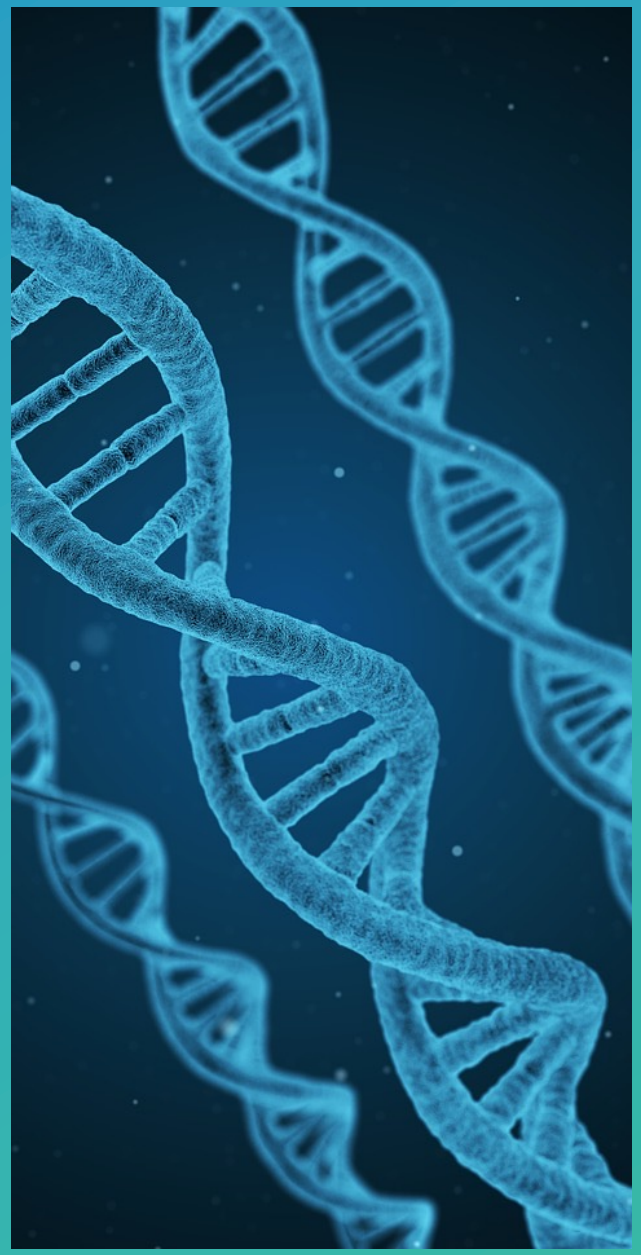
Charcot-Leyden crystal protein (CLC, also known as galectin 10) crosstalks to drive Th2 responses

Anti-pathogen (parasite and bacteria)

Regulation of adipose tissue

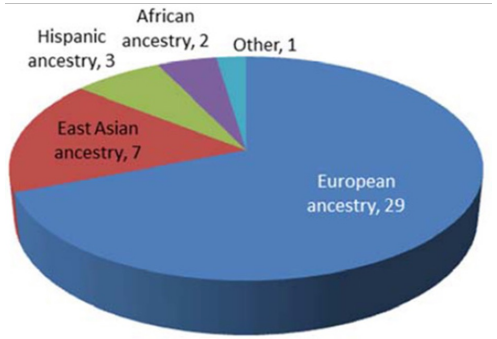
Int Arch Allergy Immunol. 2020;181(1):11-23. doi: 10.1159/000504847. Epub 2019 Nov 29.
The Cellular Functions of Eosinophils: Collegium Internationale Allergologicum (CIA) Update 2020.
Simon HU, Yousefi S, Germic N, Arnold IC, Haczku A, Karaulov AV, Simon D, Rosenberg HF.

SUSCEPTIBILITY FACTORS



Genetic Basis for Allergic Susceptibility

- Increased risk for allergy if mother is allergic
- GWAS associated SNPs in asthma
  - European ancestry dominated



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4415518/

TABLE 20-3

Examples of Genes Associated with Atopy and Asthma

Candidate Genes or Encoded Protein	Chromosomal Location	Disease Association	Putative Role of Gene Products in Disease
Genes in cytokine gene cluster (IL-4, IL-5, IL-13), CD14, β_2-adrenergic receptor	5q	Asthma	IL-4 and IL-13 promote IgE switching, IL-5 promotes eosinophil growth and activation; CD14 is a component of the LPS receptor that, through interaction with TLR4, may influence the balance between T_H1 and T_H2 responses to antigens; β_2-adrenergic receptor regulates bronchial smooth muscle contraction
Class II MHC	6p	Asthma	Some alleles may regulate T cell responses to allergens
FcεRI β chain	11q	Asthma	Mediates mast cell activation
Stem cell factor, interferon-γ, STAT6	12q	Asthma	Stem cell factor regulates mast cell growth and differentiation; interferon-γ opposes actions of IL-4; STAT6 mediates IL-4 signal transduction
IL-4 receptor α chain	16	Asthma	Subunit of both IL-4 and IL-13 receptors
ADAM33	20p	Asthma	Metalloproteinase involved in airway remodeling
DPP10	2q14	Asthma	Peptidase that may regulate chemokine and cytokine activity
PHF11	13q	Asthma	Transcriptional regulator involved in B cell clonal expansion and Ig expression
ORMDL3	17q	Asthma	ER stress inflammatory response
IL-1 receptor–like 1 (IL-33 receptor)	2q	Asthma	IL-33 induces T_H2 cytokines in T cells, mast cells, eosinophils, innate lymphoid cells
Phosphodiesterase 4D	5q	Asthma	Degrades cAMP and regulates airway smooth muscle contractility
Filaggrin	1q	Atopic dermatitis	Component of terminally differentiated keratinocytes important for epithelial barrier function

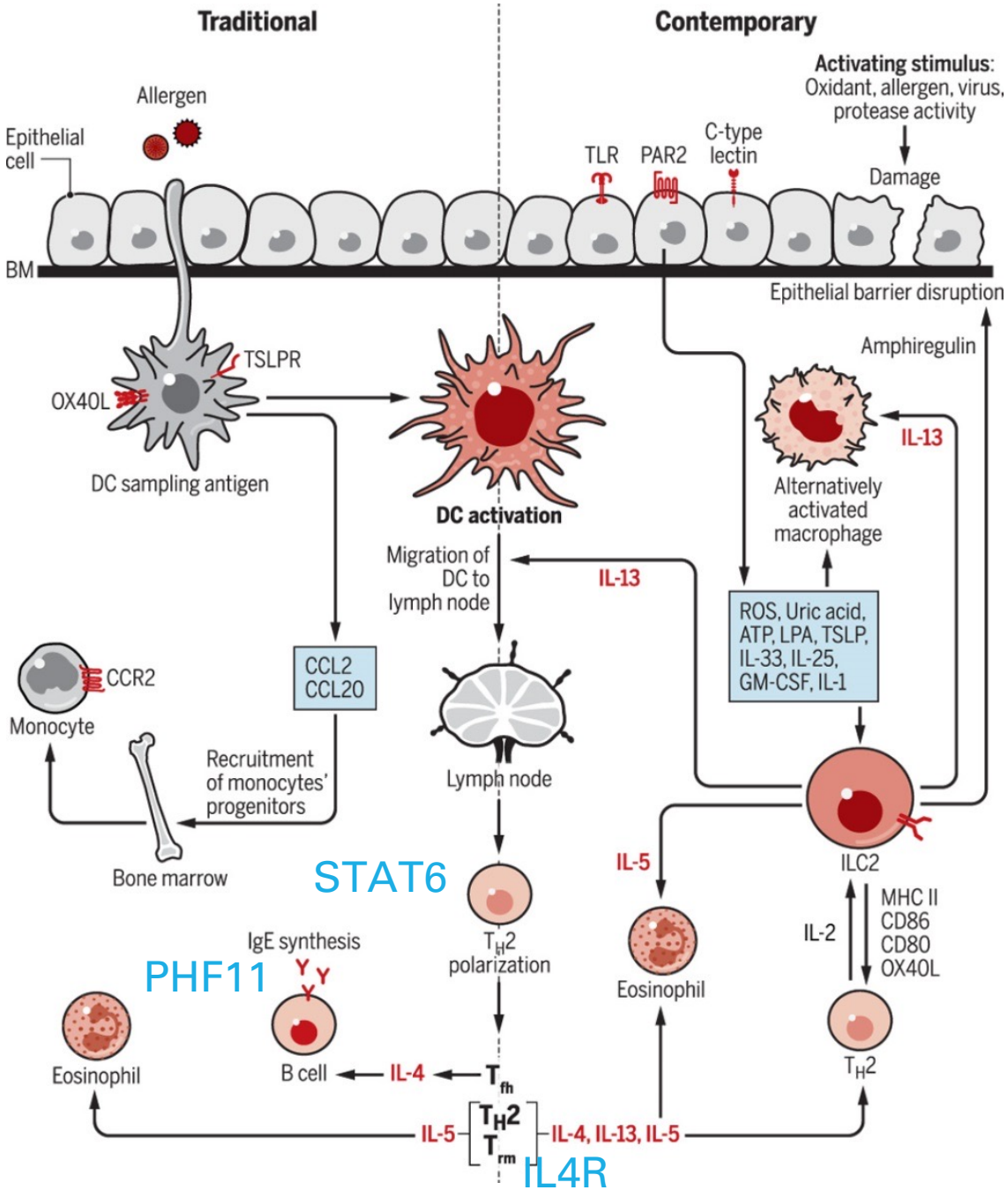
Clin Transl Immunology. 2017 Dec 15;6(12):e165. doi: 10.1038/cti.2017.54. eCollection 2017 Dec.

Lessons from ten years of genome-wide association studies of asthma.

Vicente CT[1], Revez JA[1], Ferreira MAR[1].

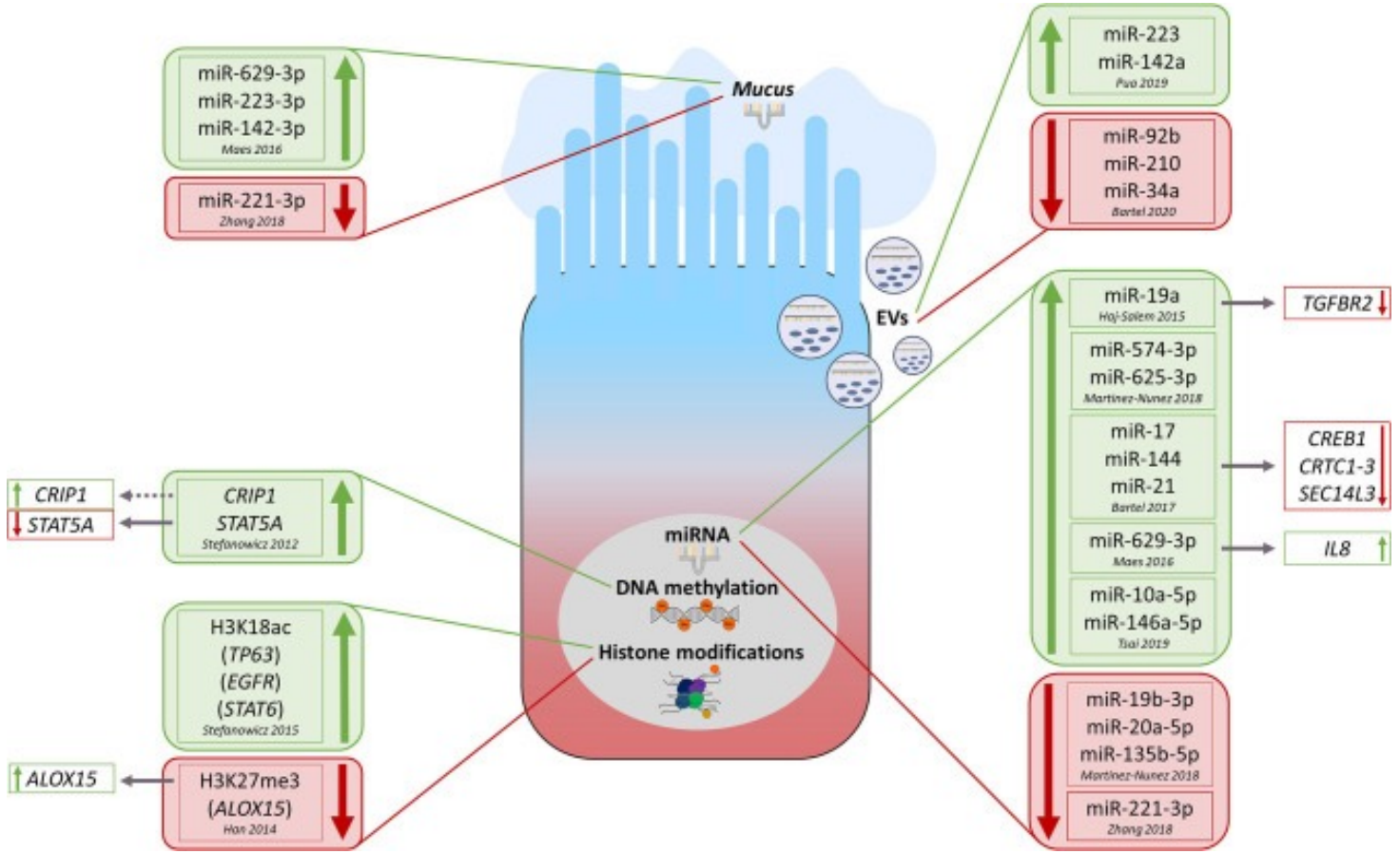
Fillagrin

CD14/MHC



IL-33

Evolving Understanding of Epigenetic Modifications

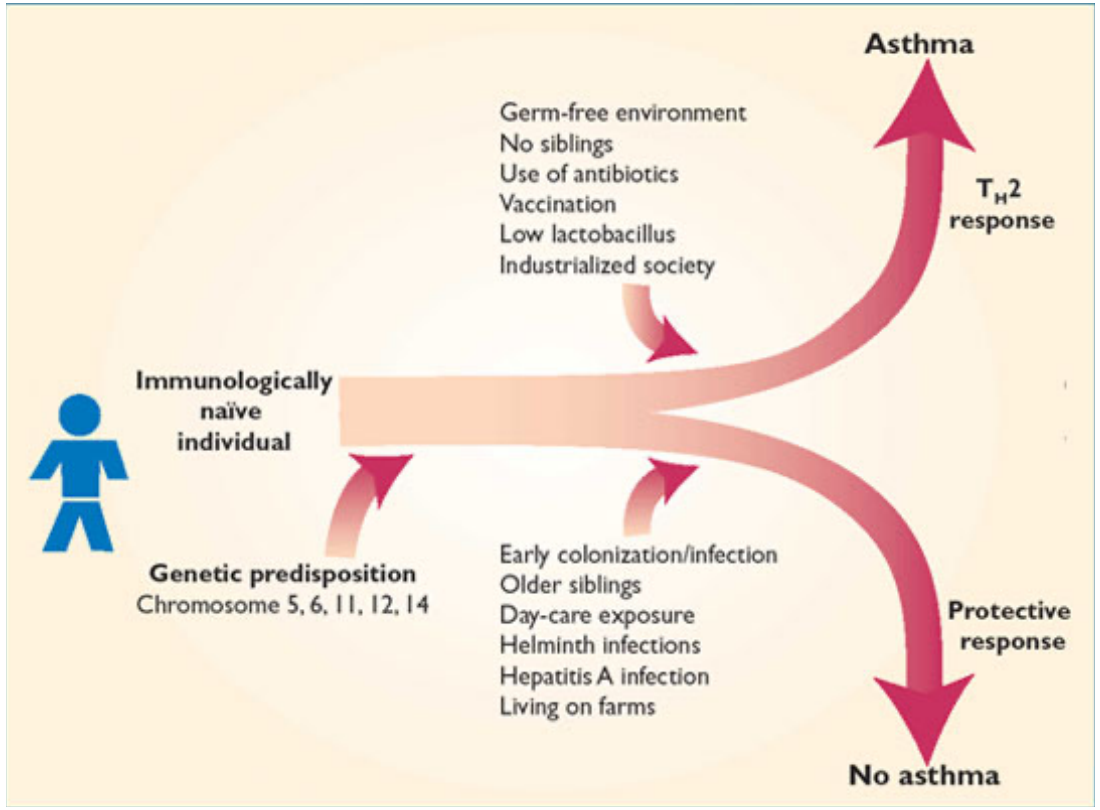


Overview of currently known key epigenetic modifications observed in lower airway epithelial cells from asthma/allergic airway inflammation conditions and—if known—associated functional consequences.

The green color always indicates upregulation of the respective modification in asthmatics vs. healthy while red color identifies opposite regulation. EVs, extracellular vesicles; miRNA, microRNA; H3K18ac, histone H3K18 acetylation; H3K27me3, histone H3K27me3 trimethylation.

Epigenetic Regulation of Airway Epithelium Immune Functions in Asthma. Front Immunol. 2020 Aug 18;11:1747.

Environmental Influences over Allergic Susceptibility



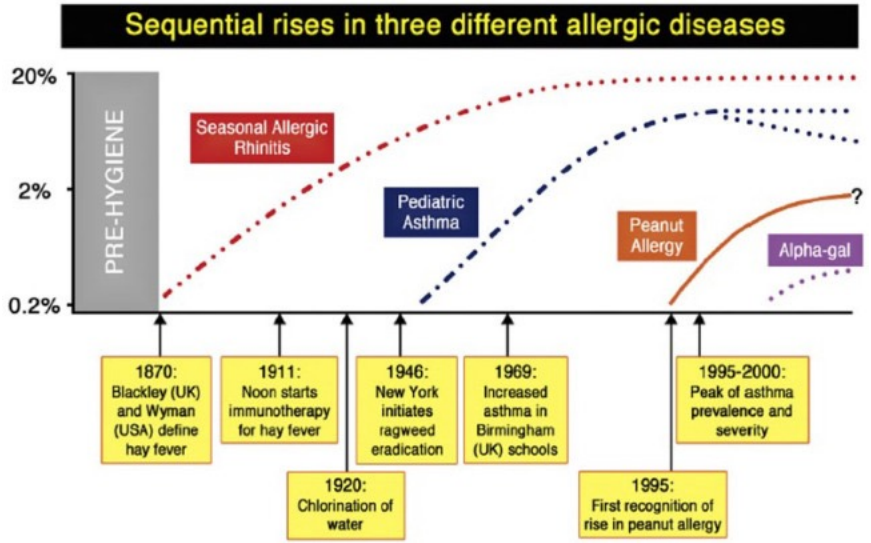
The *"Hygiene"* Hypothesis

Exposure to *"good"* infection prevents allergy

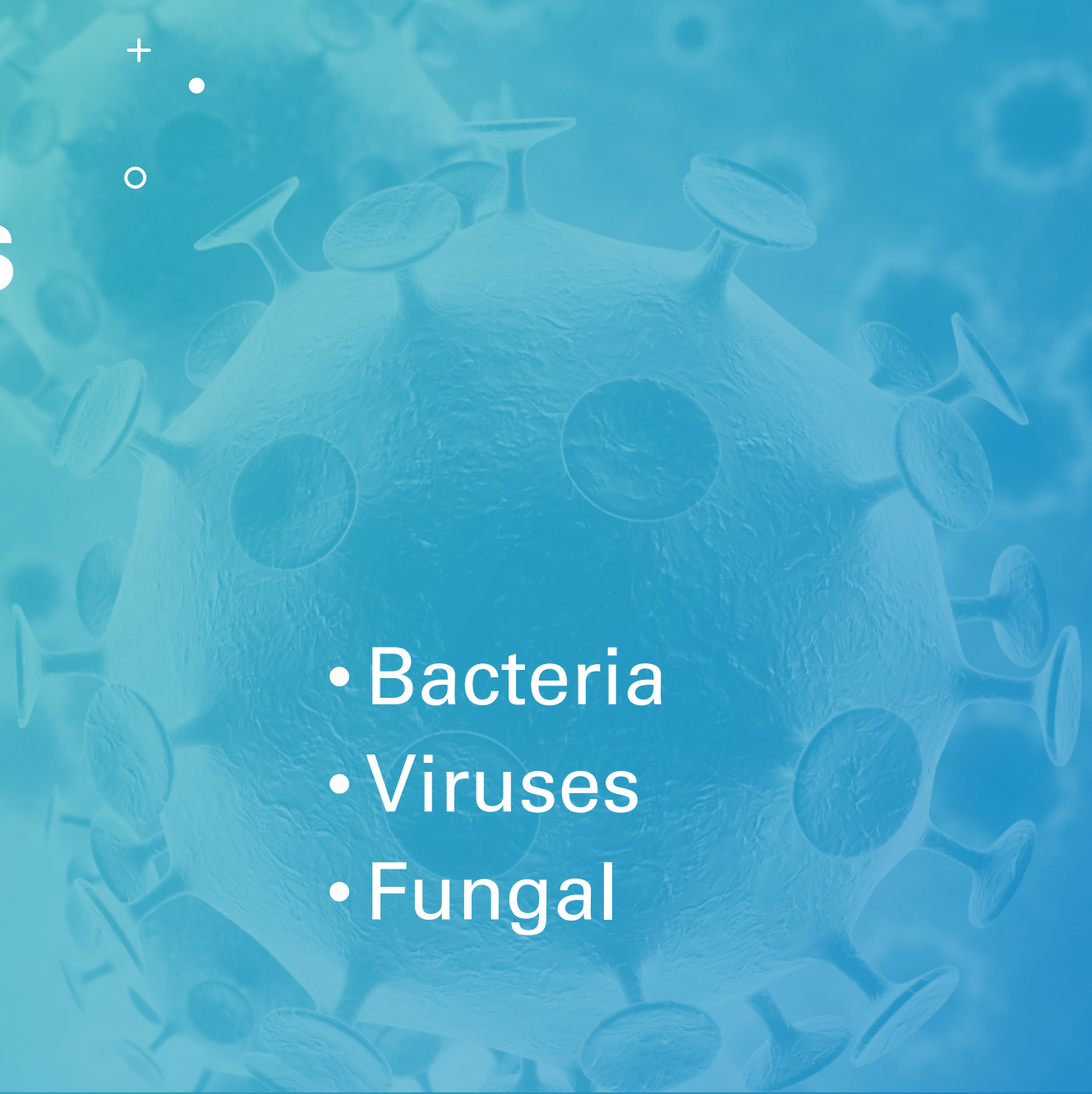
› Perspect Public Health. 2016 Jul;136(4):213-24. doi: 10.1177/1757913916650225.

Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene

Sally F Bloomfield [1], Graham Aw Rook [2], Elizabeth A Scott [3], Fergus Shanahan [4], Rosalind Stanwell-Smith [5], Paul Turner [6]



Pathogen Associations in Allergic Diseases



- Bacteria
- Viruses
- Fungal

Pathogens Associate with Disease Susceptibility & Severity

Bacteria

Staphylococcus aureus colonization is present on >90% of skin of Atopic Dermatitis patients & enriched in lesions

- Relationship with commensal Staph species[1]

Viruses

Early life infection with Rhinoviruses increases risks for asthma development in later life

Initiates a ”pathogenic” lung microbiome environment[2]

Fungal

Aspergillus fungal species associate with severe allergic disease forms

[1]Host-microbiome interactions in the holobiome of atopic dermatitis. 2022. Burger E, Gallo RL PMID: 36509150

[2]Rhinovirus Infections and Their Roles in Asthma: Etiology and Exacerbations. 2022. Jackson D, Gern J. PMID: 35074599

FUNGUS & ALLERGIES

Common Fungal Species in Allergy

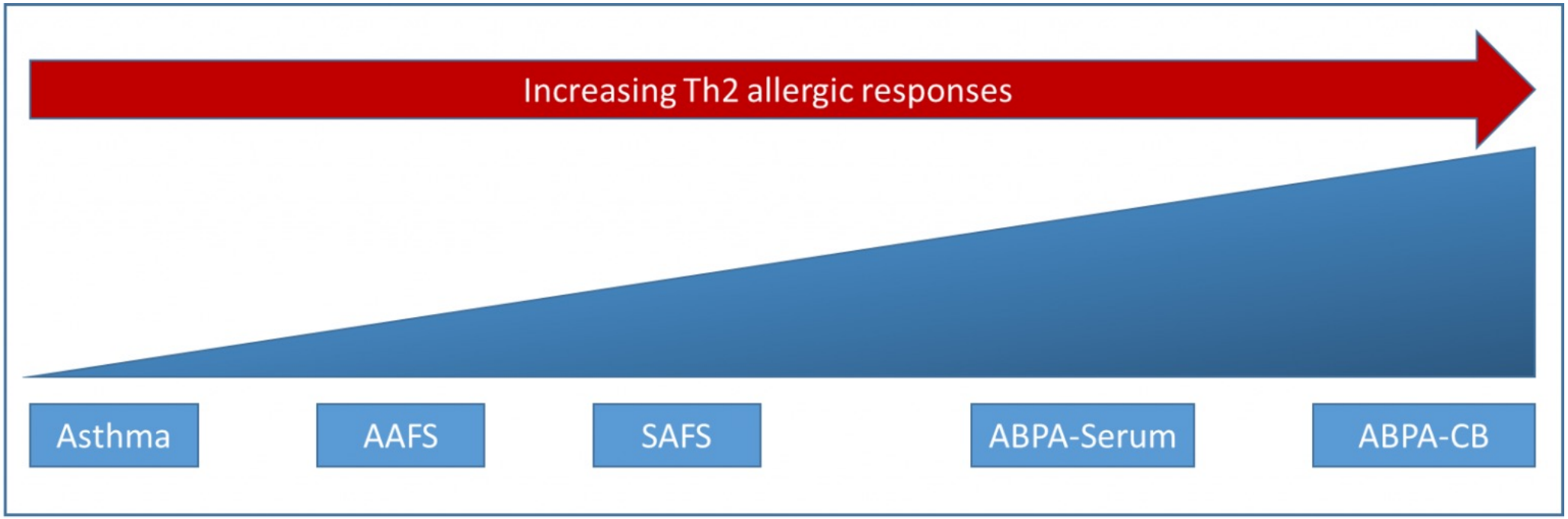
- Penicillium (29%, +127%)
- Aspergillus (10%, +42%)
- Alternaria (12%, +36%)
- Curvularia (20%, +137%)
- Rhizopus (10%, +57%)

(% SPT +ve/total patients during 2008-2017, % change from last decade)

Sensitization against Fungi in Patients with Airway Allergies over 20 Years in Germany. Forkel et al. Int Arch Allergy Immunol. 2021 May; 182(6): 515–523.

Various fungi including Penicillium and Aspergillus spp. growing in axenic culture. Image source:Wikipedia, Dr. David Midgley Cultures: Dr. David Midgley University of Sydney, Australia, Creative Commons Attribution ShareAlike 2.5 License.

Fungal Colonization Associates with Asthma Severity

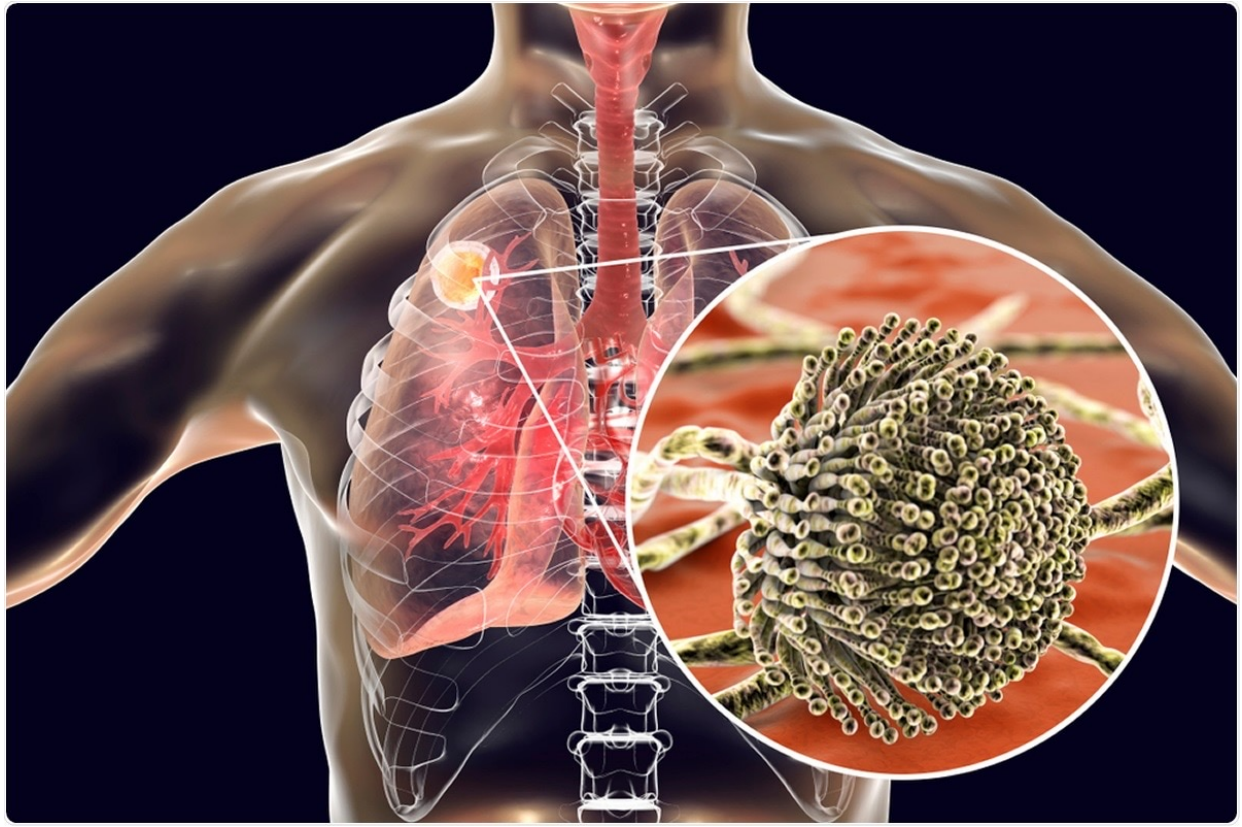


AAFS Asthma Associated with Fungal Sensitization
SAFS Severe Asthma with Fungal Sensitization
ABPA-S Seropositive Allergic Bronchopulmonary Aspergillosis
ABPA-CB Allergic Bronchopulmonary Aspergillosis with Central Bronchiectasis

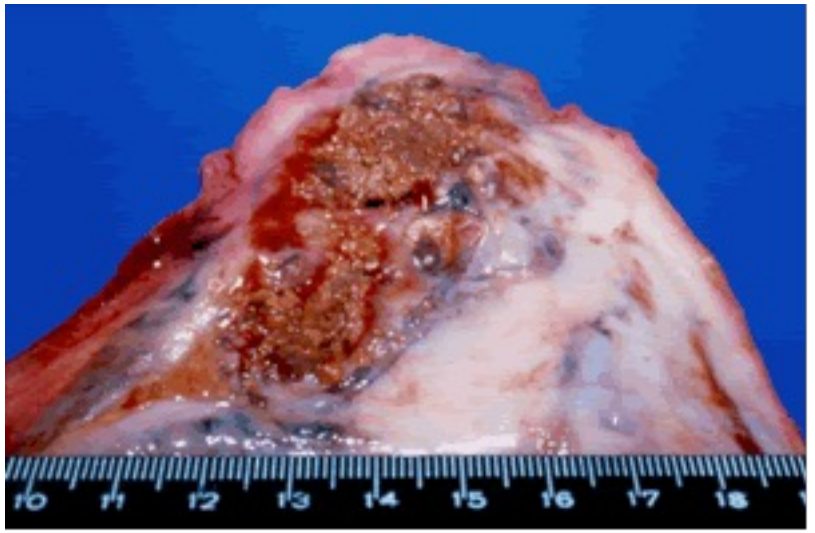
https://mft.nhs.uk/wythenshawe/services/respiratory-and-allergy/national-aspergillosis-centre/about-aspergillosis/allergic-aspergillosis/

Opportunistic Lung Infection by Aspergillus

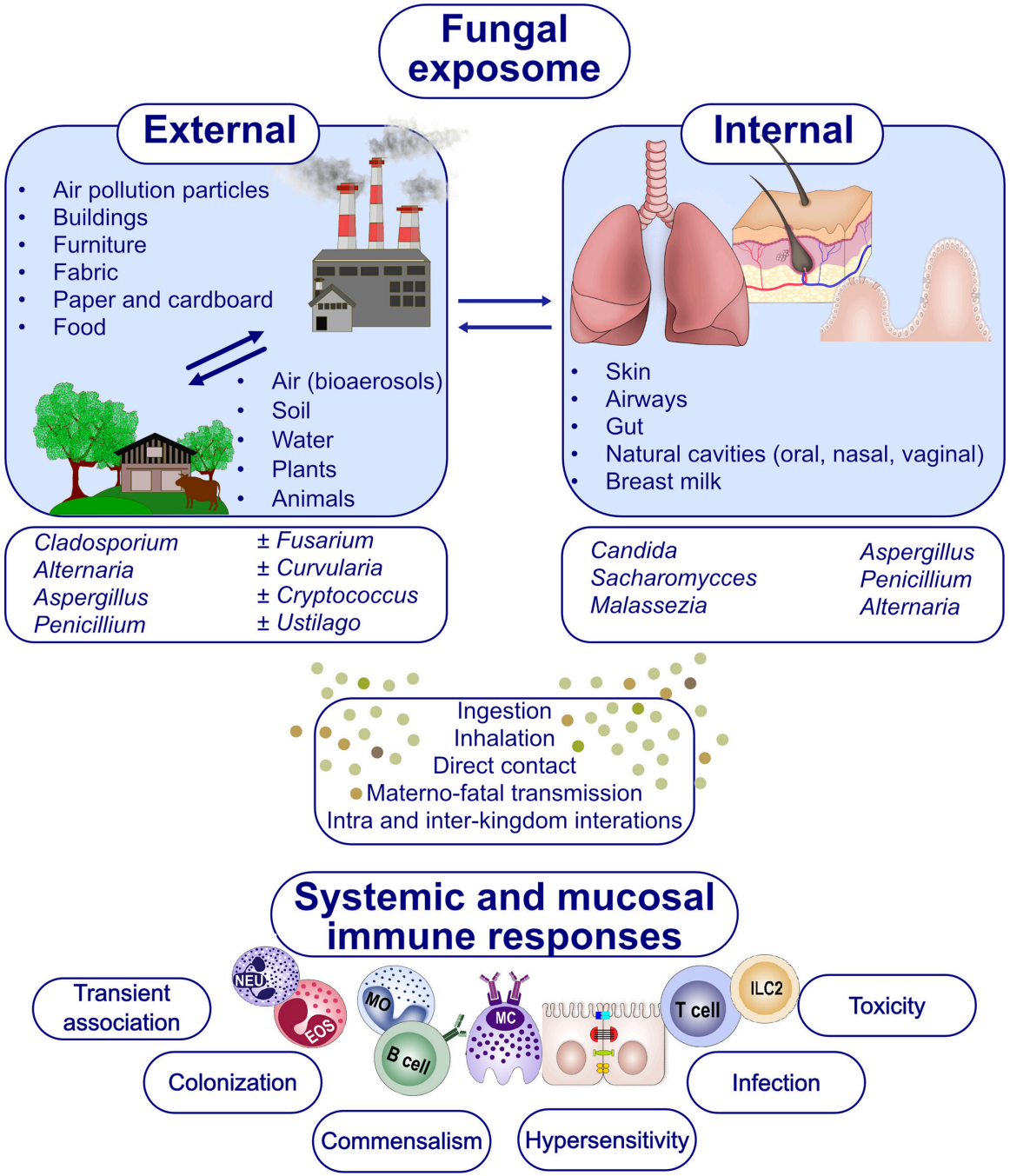
Development of fungal balls within damaged lung tissues



https://www.news-medical.net/news/20201110/COVID-19-associated-pulmonary-aspergillosis-caused-by-aspergillus-fumigatus.aspx



www.aspergillus.org.uk



Fungal exposome, human health, and unmet needs: A 2022 update with special focus on allergy

Allergy, Volume: 77, Issue: 11, Pages: 3199-3216, First published: 17 August 2022, DOI: (10.1111/all.15483)

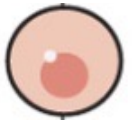
Therapeutic Strategies

- Medications
- Immunotherapy
- Biologics

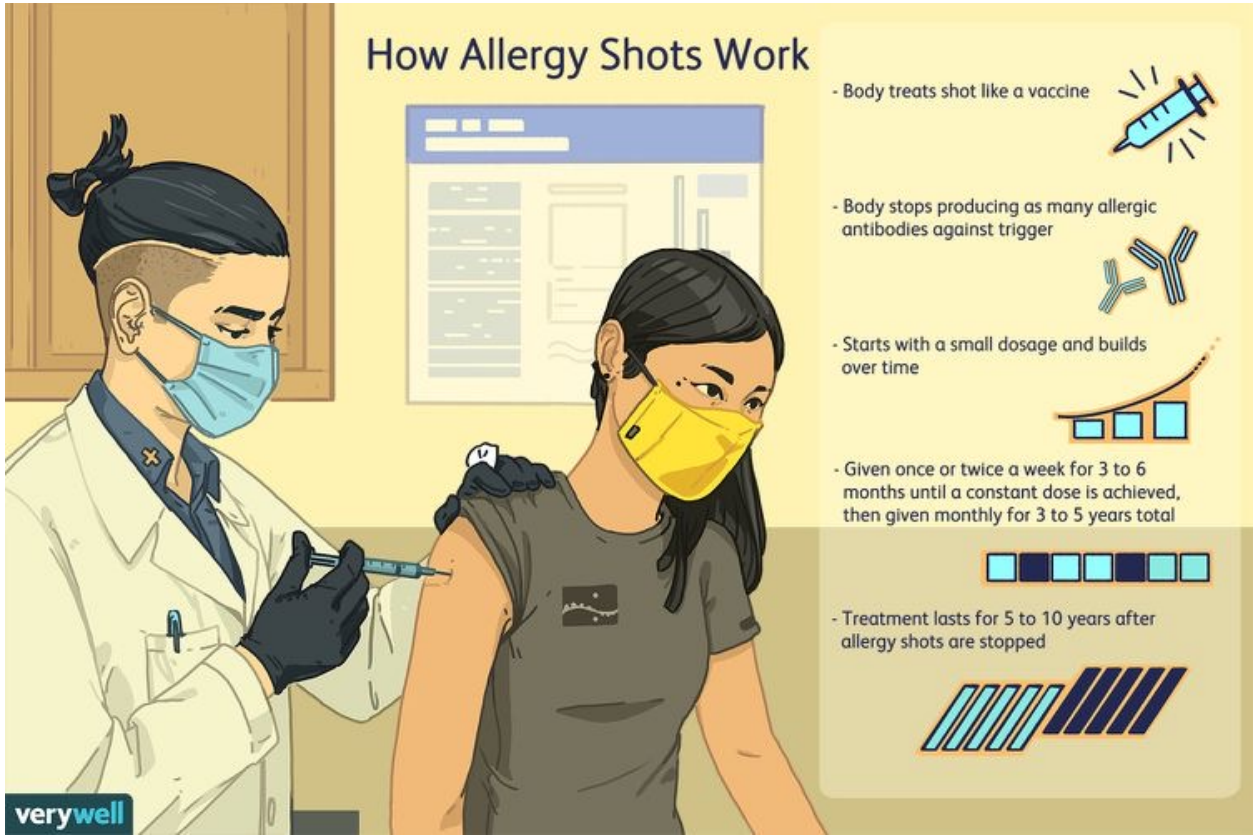
Medications

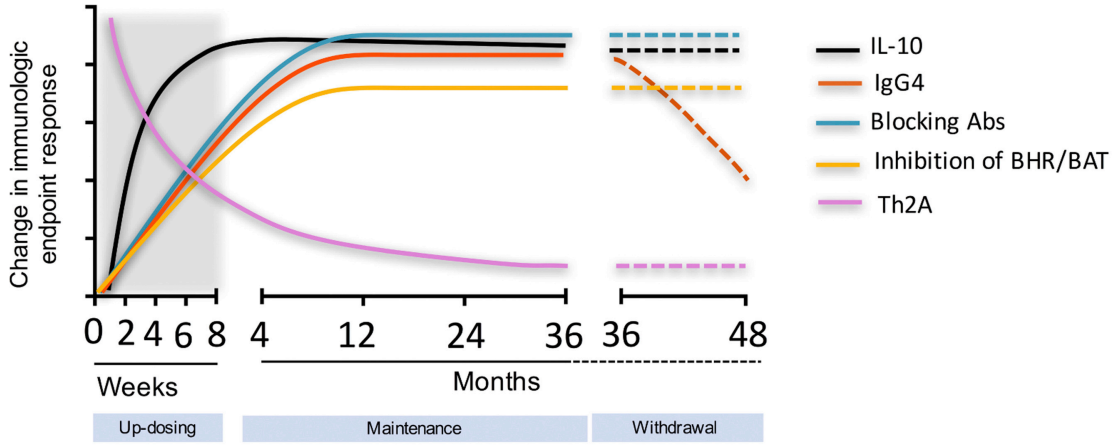
- Antihistamines
- Mast cell stabilizer
  - E.g Cromolyn sodium
- Corticosteroids
- Leukotriene Inhibitors
- Life-sparing

Mast Cell	Eosinophil	Th2	
✓	✗	✗	Rhinitis
✓	✗	✗	Conjunctivitis
✗	✓	✓	Asthma
✓	✓	✗	Rhinitis & Asthma
✗	✗	✗	Food Allergy



Immunotherapy—multiple mechanisms in play



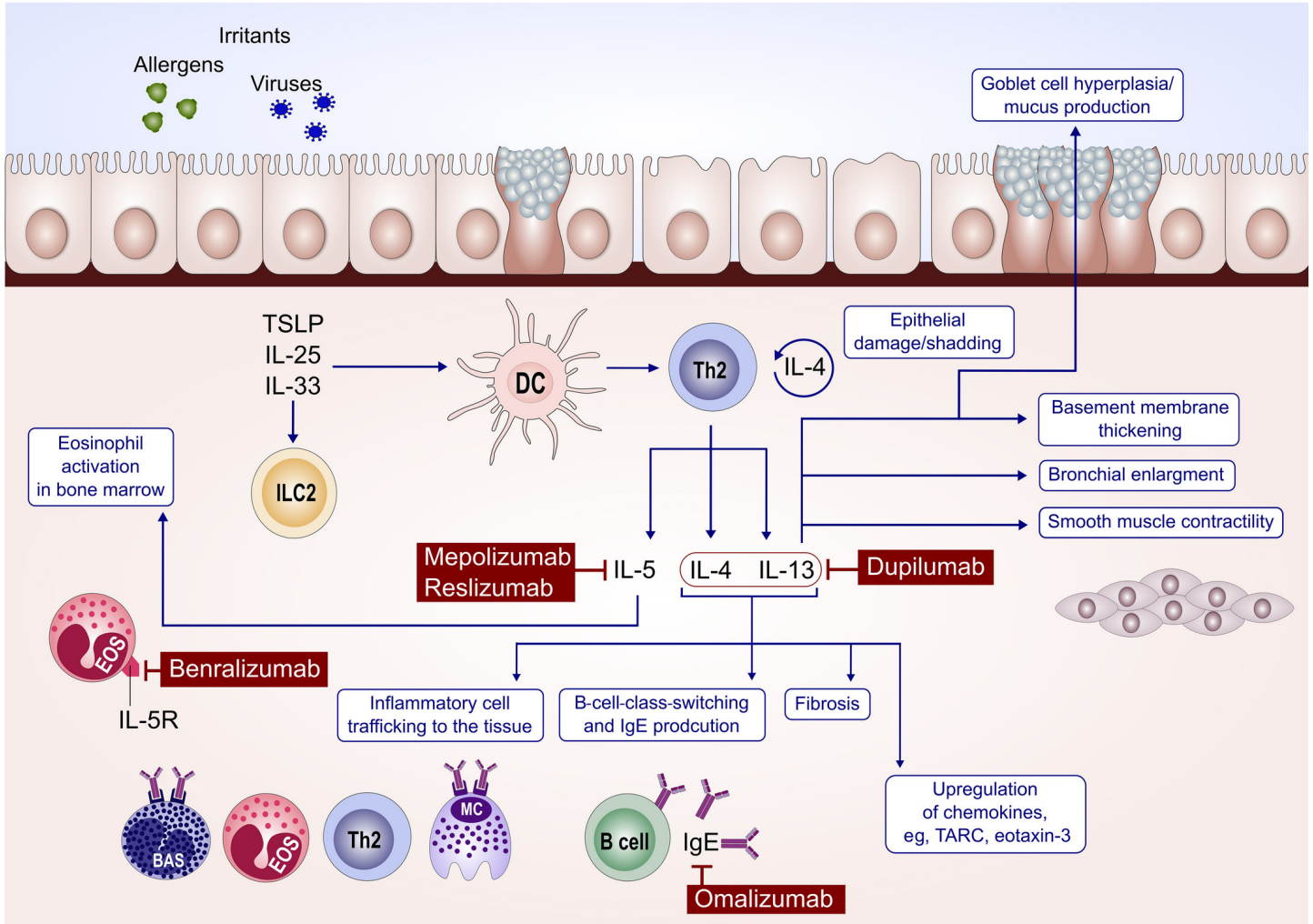


Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers

Mohamed H. Shamji, PhD, FAAAI, Stephen R. Durham, MD, FRCP

Journal of Allergy and Clinical Immunology
Volume 140, Issue 6, Pages 1485-1498 (December 2017)
DOI: 10.1016/j.jaci.2017.10.010

Biologics in Asthma Treatment



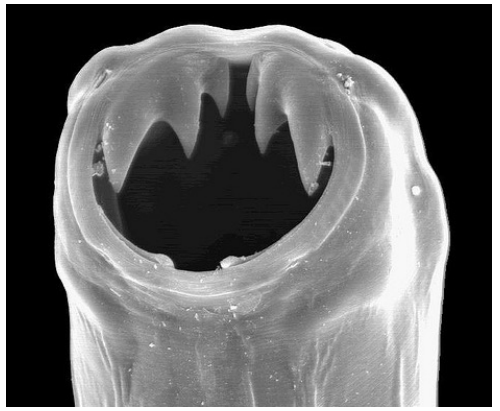
Allergy, Volume: 75, Issue: 7, Pages: 1582-1605, First published: 22 April 2020, DOI: (10.1111/all.14318)

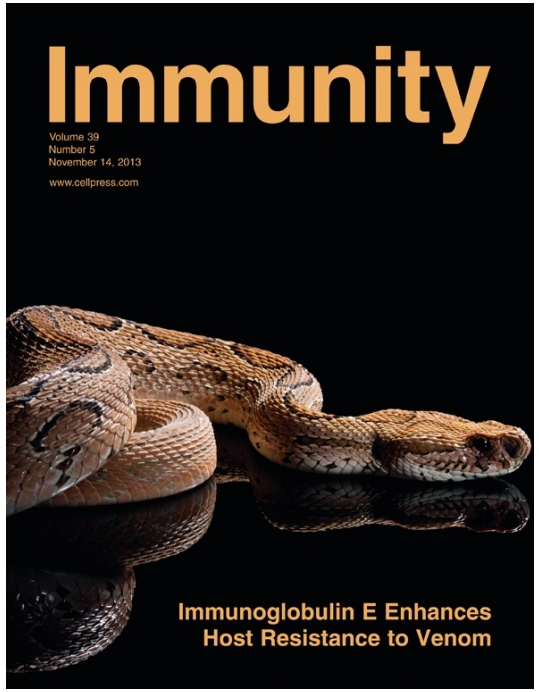
Learning Objectives

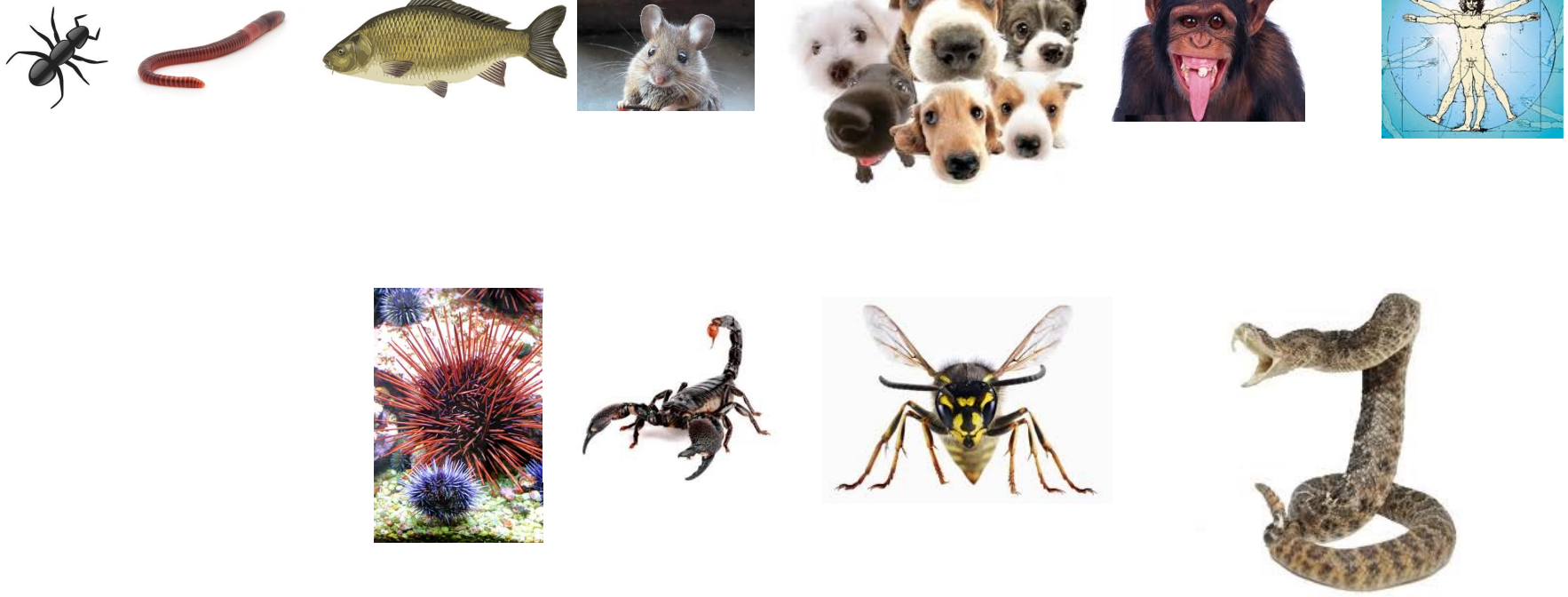
- Understand what the term "*Allergy*"
- Understand the core mechanisms of allergic immunity
- Understand current theories behind development of allergy
- Understand how therapies relate to specific allergic mechanisms and the allergic diseases

Why?

- Helminth infection immunity
- Wound healing & foreign body reaction
- Venom degradation







Thanks!


I SNEEZE EVEN INSIDE THE CLEAN ROOM, DOCTOR... I DON'T KNOW WHAT TO DO!
HMM...
ALLERGIES USUALLY OCCUR WHEN YOU'VE BEEN OVER-EXPOSED TO SOMETHING IRRITATING OR UPSETTING.
YOU MEAN-
JORGE CHAM © 2010
YOU'RE ALLERGIC TO YOUR THESIS.
I KNEW IT!
LET'S TRY IT: WHAT ARE THE MAJOR CONTRIBUTIONS OF YOUR WORK?
I- ACHOO!
ACHOO!
ACHOO!
WWW.PHDCOMICS.COM