Allergy, atopy and asthma

Rich Locksley/Mark Ansel

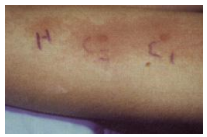
Micro 204

November 2018

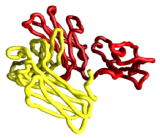
Allergy and asthma: cells and cytokines timeline

Anaphylaxis
Charles Richet

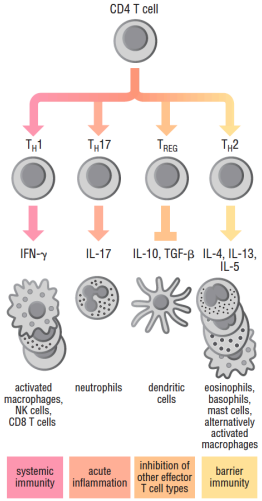
Eos, basos, mast cells
Paul Ehrlich



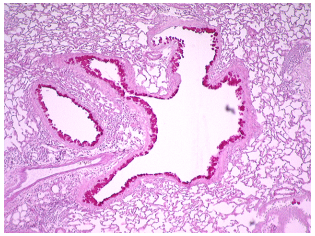
Prausnitz-Kustner



IgE
Ishizaka/ Bennich/ Johansson



Th2 cells
Mosmann, Coffman



Th2 cytokines in asthma lung biopsies

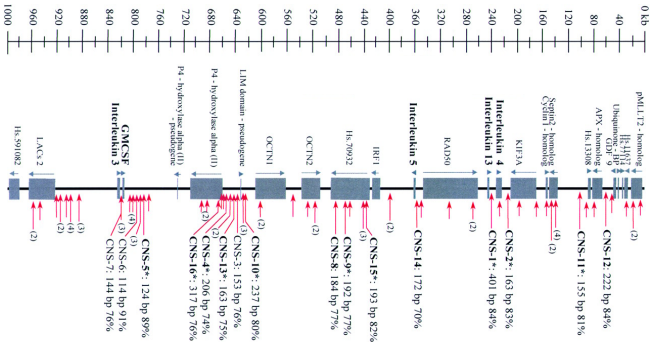
IL-5 ko mice

IL-13 ko mice

1879 1913 1921 1967 1983 1986 1991 1992 1998 2002 2009-

IL-4, IL-5, IL-13

IL-4 ko mice



IL-4/5/13 ko mice

αIL-5, αIL-4R

Global burden of allergic pathology

Developed Countries

Asthma and Allergy

>300 million worldwide

Asthma prevalence increased 75% from 1980-1994

>70% asthma patients have allergy

1:8-12 US children

4 of the top 50 prescribed drugs are used for allergic airway disease

>$20 billion/yr health care costs US

Developing Countries

Parasitic helminth infections

Intestinal nematodes (>2 billion)

Tissue filaria (>120 million)

Tapeworms (>2 million)

Schistosomes (>200 million)

Major causes of liver failure, bladder cancer, elephantiasis, blindness, epilepsy

(post-reproductive morbidity)

A word about helminths

Account for ~80% of all individual animals on earth

Estimates up to 10^6 species

Three major, two minor clades - all includes parasitic species

2.9 billion humans estimated infected

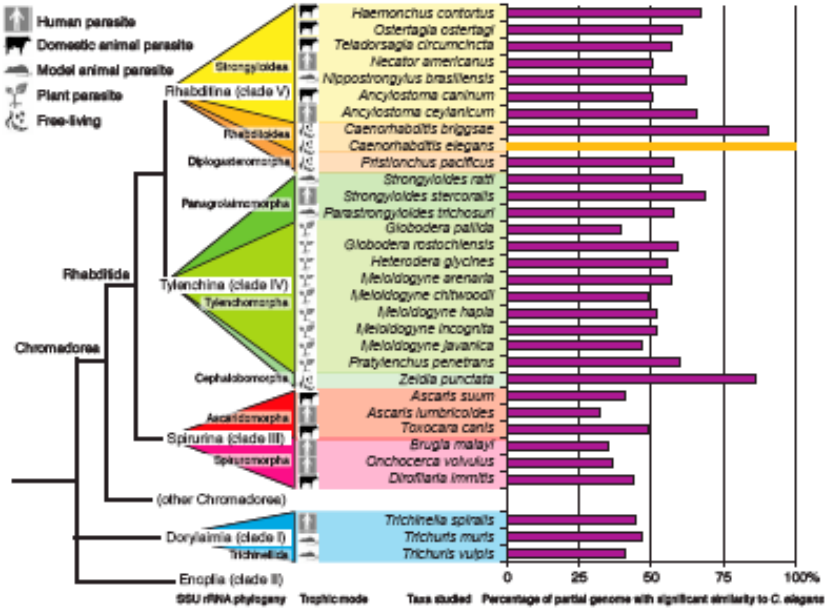
Universal in rural subtropical environments typical of human evolution

Essentially universal in feral vertebrates (mammals, birds, fish, reptiles, amphibians)

Genome size ~ 20,000

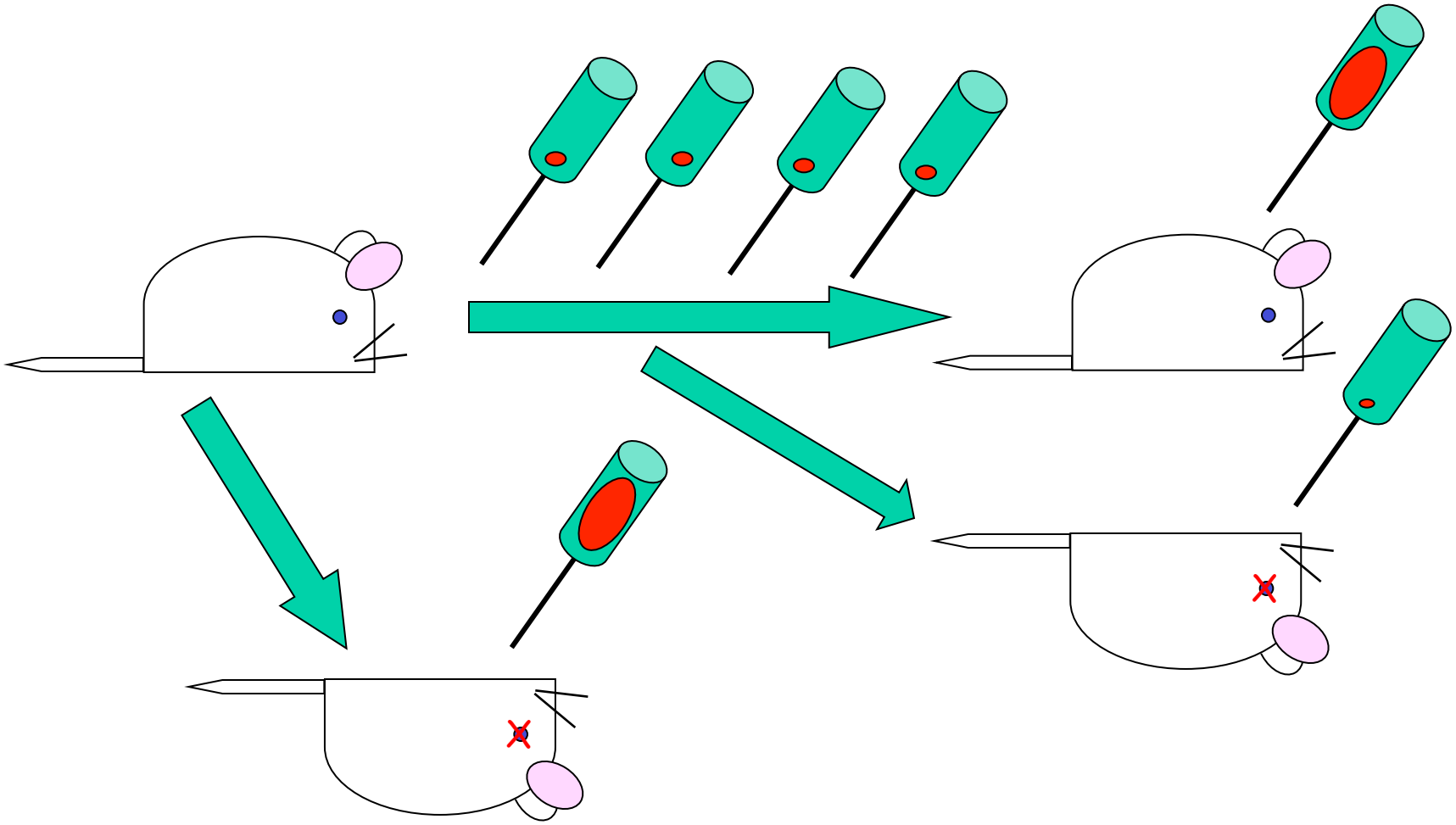
If type 2 immunity protects us from helminths, it doesn't do a very good job…

Maybe helminths exploit the pathway for other things…



Parkinson J, et al. 2004. A transcriptome analysis of the phylum Nematoda. Nature Genet 36:1259-67.

Ana - phylaxis: "Backwards Protection"



Richet: 1913 Nobel Prize

Allergy

An adverse immune response to environmental antigens (allergens).

Operational definition:

↑ IgE

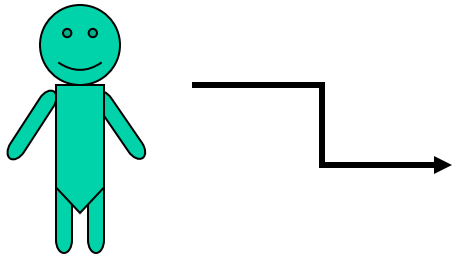
Manifestations: Anaphylaxis, Eczema, Hayfever, Asthma

Many Allergens Acquired Via the Mucosa

- Insect venoms
- Pollens
- Mite feces
- Animal danders
- Food
- Haptenylated drugs (penicillin)

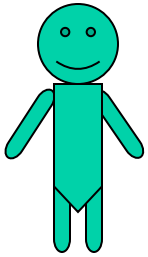
IgE = "Reagin" or "Reaginic Antibodies"

PCA: Passive Cutaneous Anaphylaxis



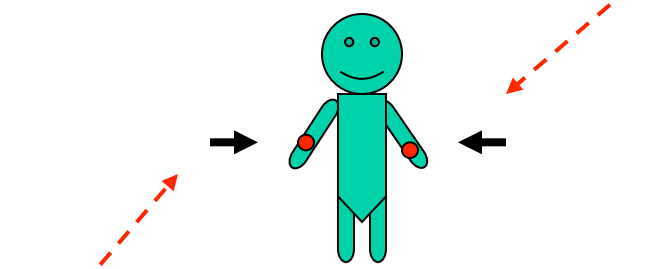
Serum (IgE) (Ishizaka, 1966)

Atopic to
Antigen X



Non-Atopic

αIgE

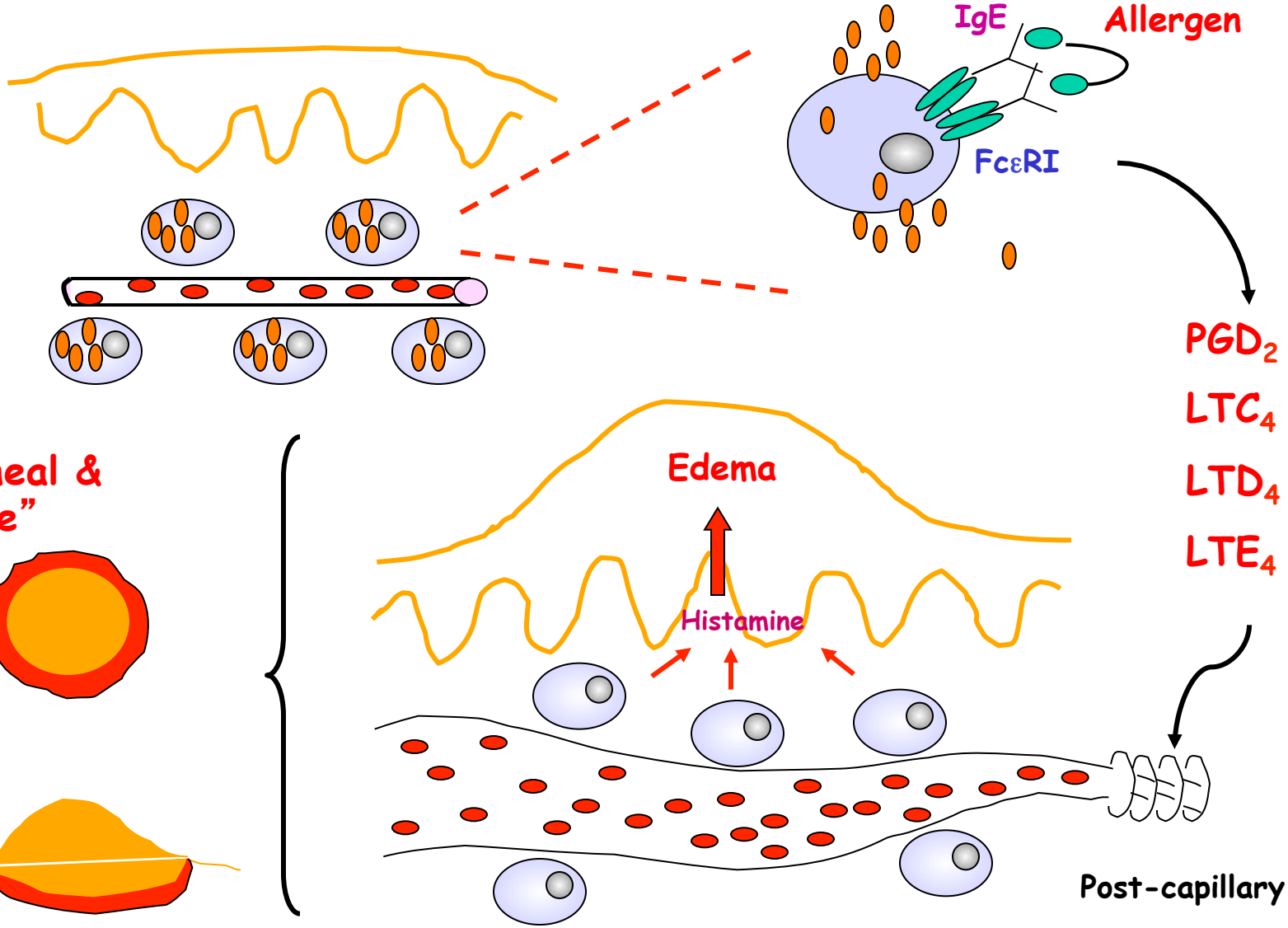


Antigen X

Immediate Hypersensitivity

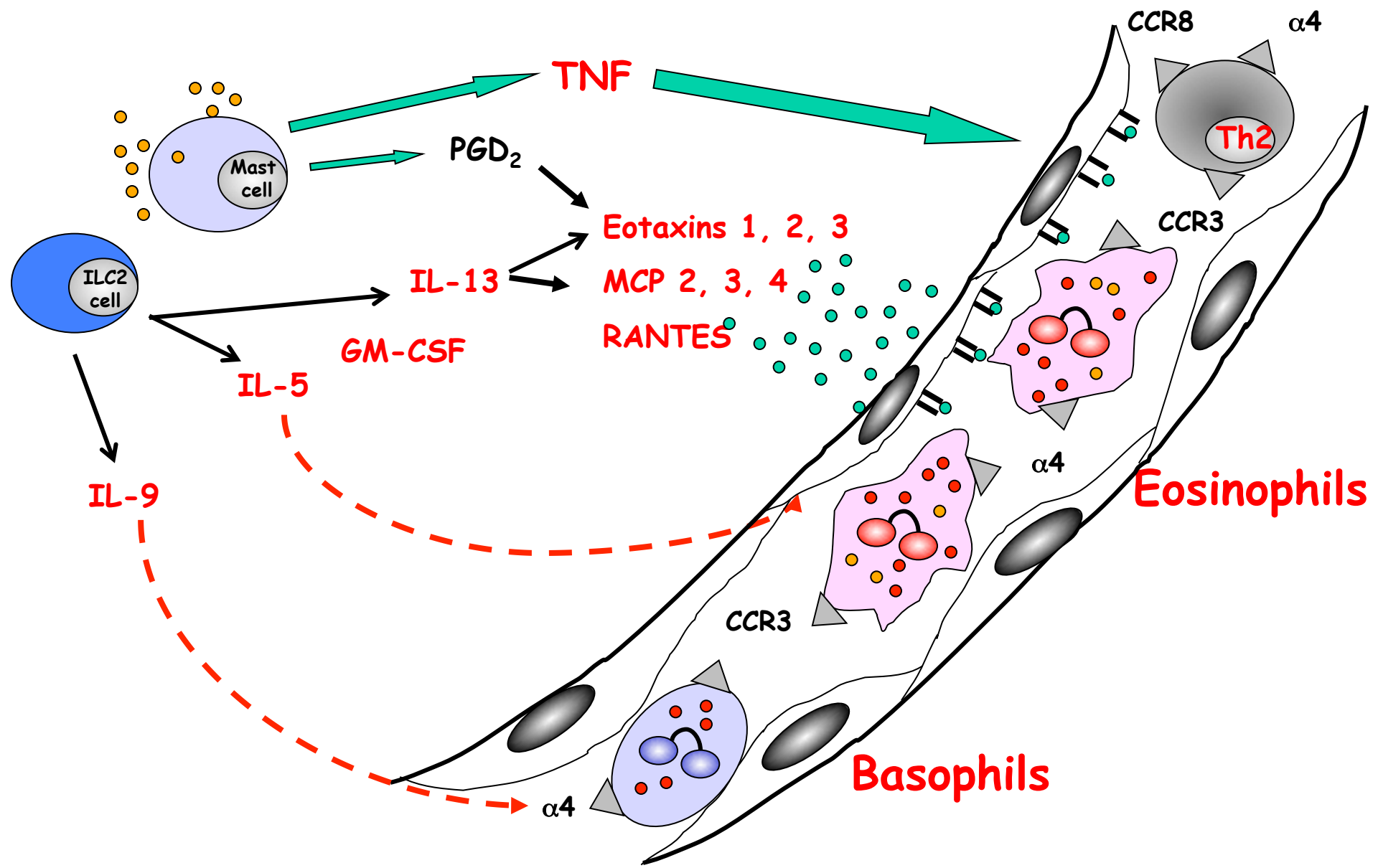
Stages of Allergy - I.

Early Phase Reaction - minutes



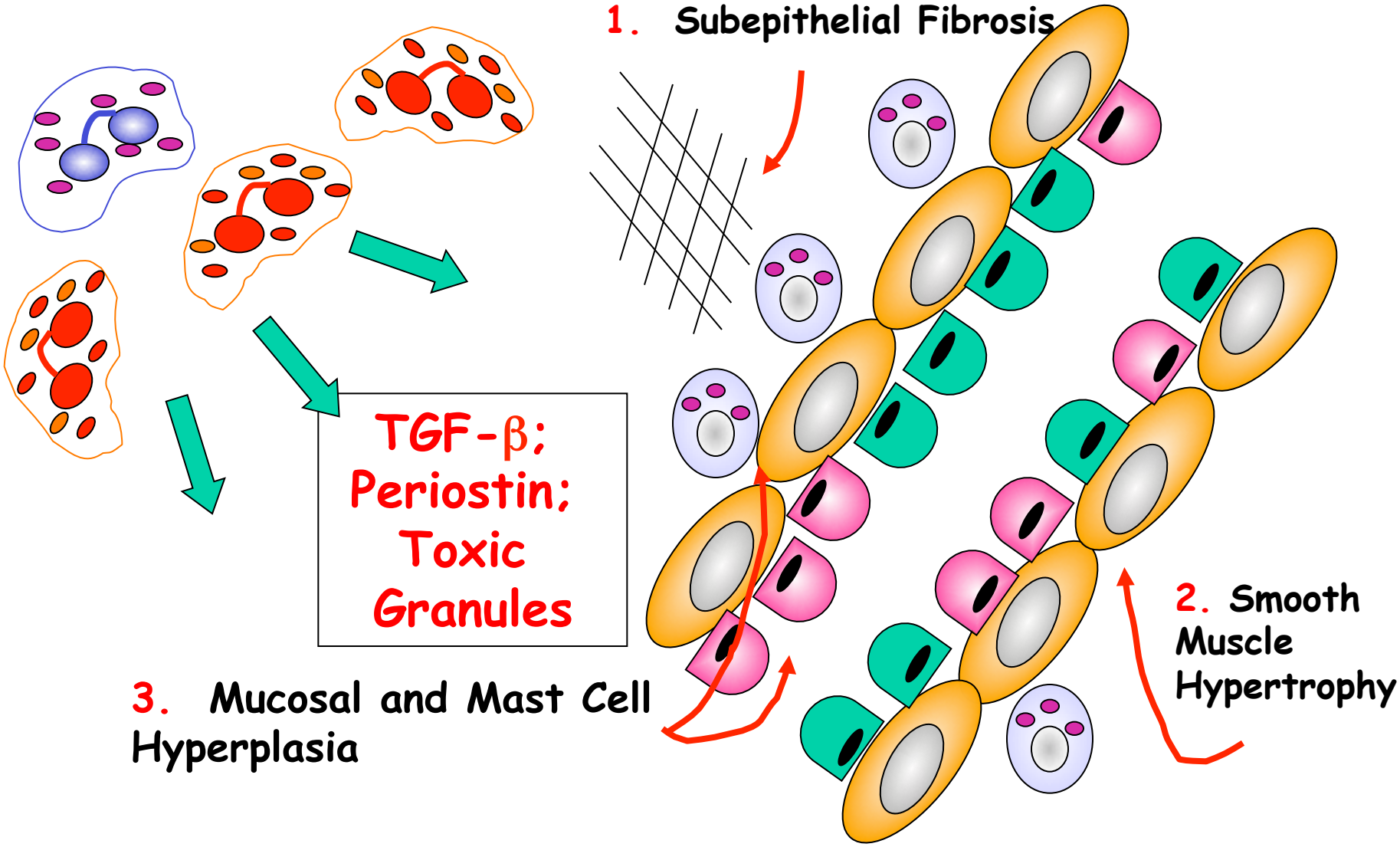
Stages of Allergy - II.

Late Phase Reaction - hours

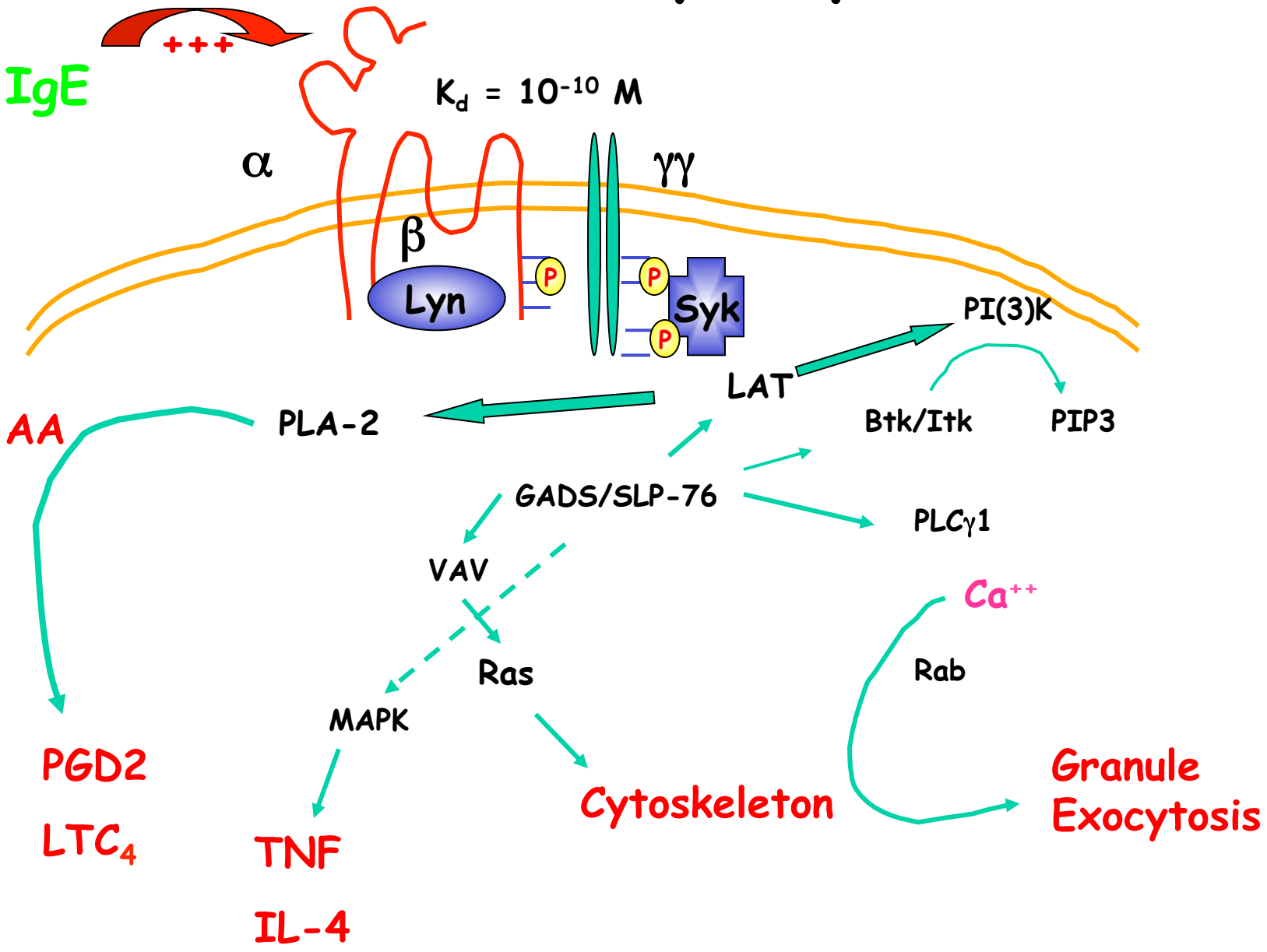


Stages of Allergy - III.

Chronic Phase Reaction - wks - yrs



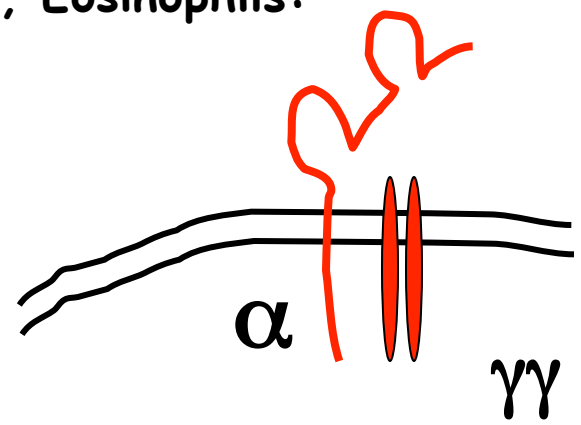
FcεRI: Key Player



Mouse ≠ Human

Mouse IgG1/FcγRIII on mast cells can trigger pathway (not present on human mast cells)

Human APC, Eosinophils:

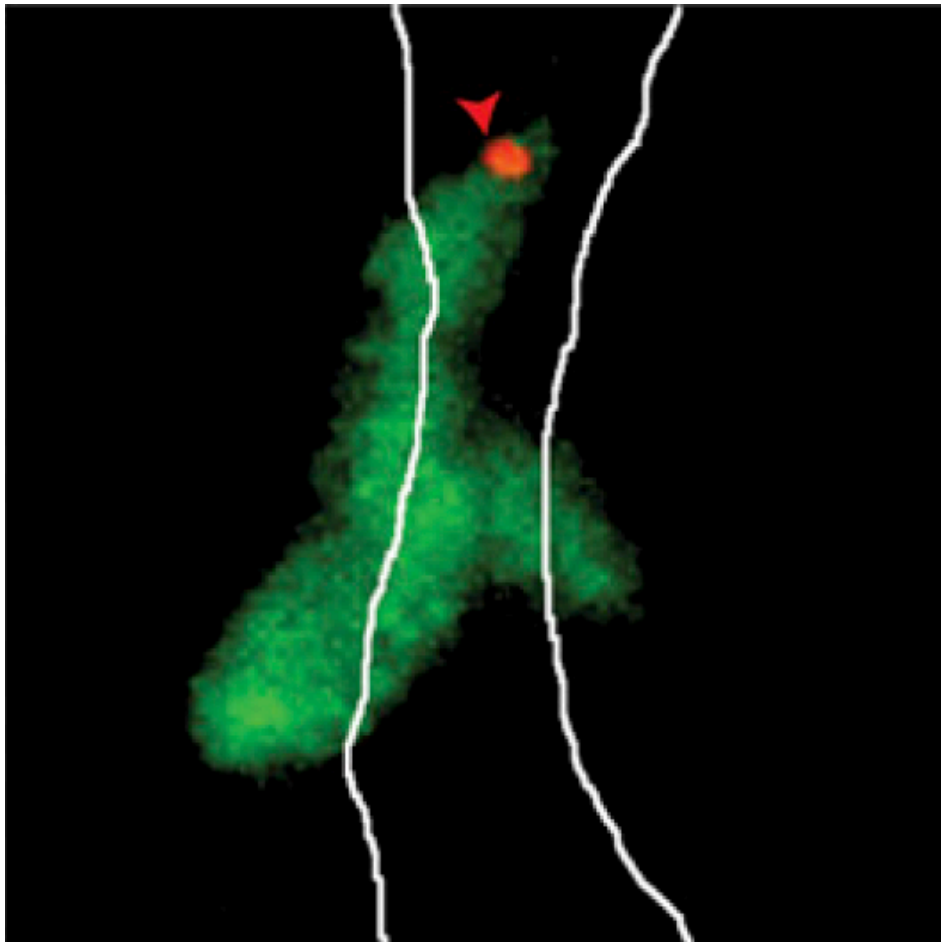


$\alpha\gamma_2$ FcεRI

IgE-linked antigen presentation in human

How do perivascular mast cells acquire serum IgE?

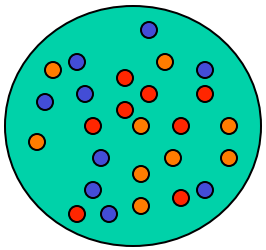
…..they reach in and take it



Mast cell (green) around a blood vessel (white outline) extending a process into the lumen to bind an IgE-coated bead.

Cheng et al, Immunity 38:166-75, 2013

Mast Cell Granules



Histamine: Vasodilator → Edema*

- Heparin: Bonds constituents (negative charge)

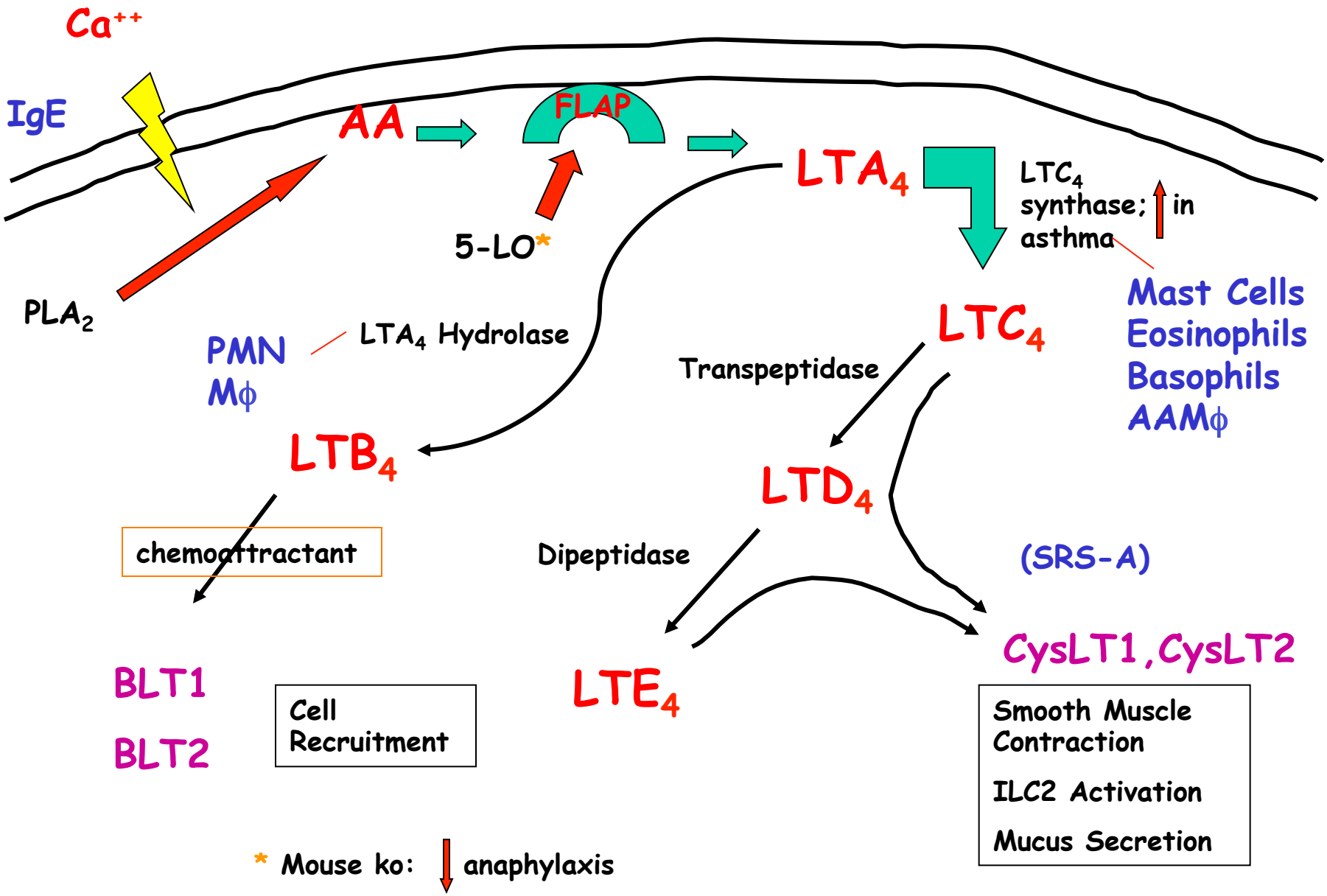
Neutral Serine Proteases:

Tryptase	All
Chymase	
Carboxypeptidase	C.T. > mucosal
Cathepsin G	C.T. > mucosal

- Knock-out: no mast cell granules

*Dudeck A et al, Immunity 34:973-84, 2011

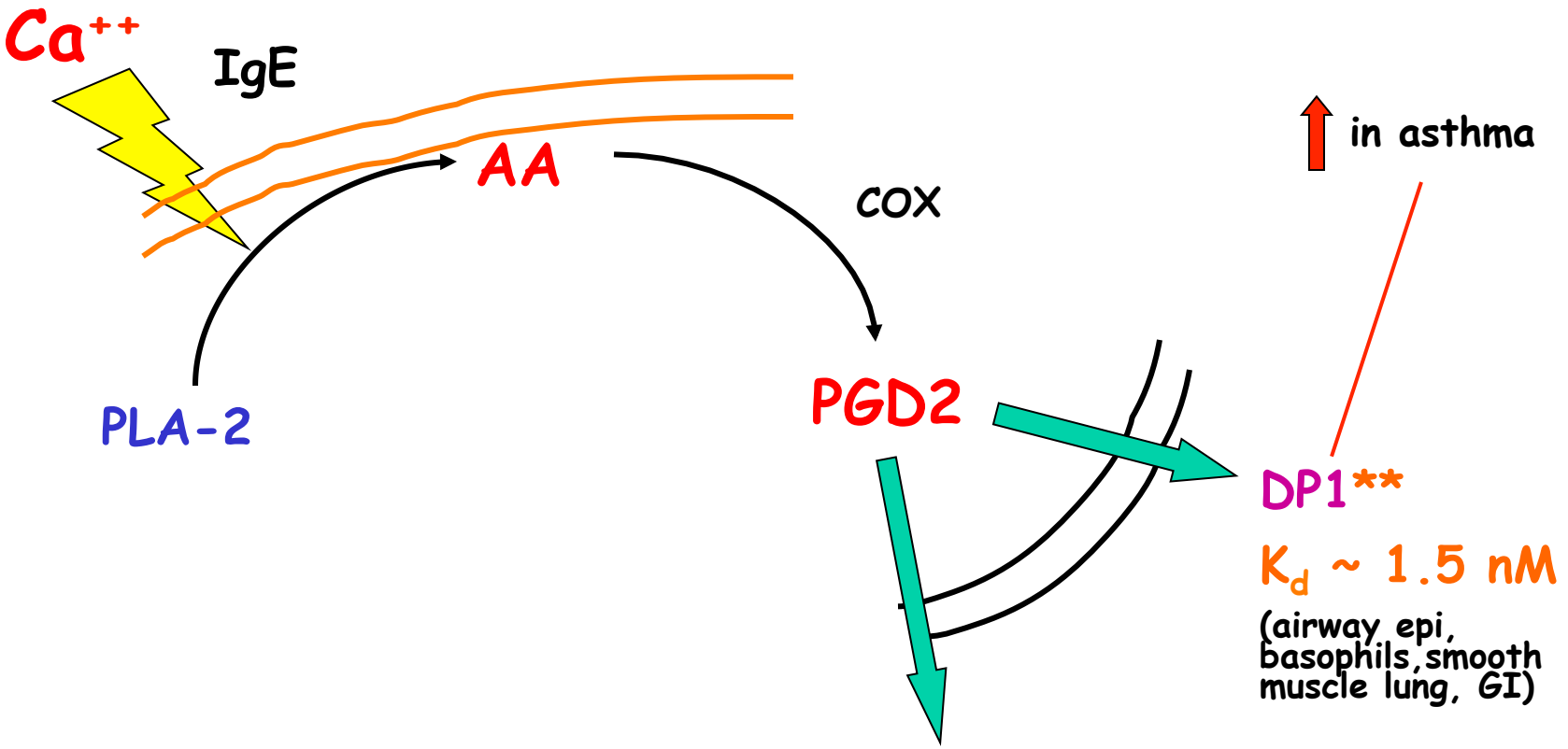
Mast Cell Eicosanoids (also tuft cells)



Leukotriene Receptors

BLT1	LTB4 (K_d~0.5 nM)	Gene duplication 14q (h)	Myeloid, lymphoid cells ILC2s, eos	Tissue recruitment
BLT2	LTB4 (K_d~23 nM), other eicosanoids		More widely	
CysLT1	LTD4>C4=E4	X (h)	PBL, lung smooth muscle, lung macrophages, small intestine ILC2s, eos	Vascular relaxation; smooth muscle contraction; cell activation
CysLT2	LTC4=LTD4>E4	13q14 (h)	PBL, lung, heart, brain	Cell activation

Mast Cell PGD2 (also tuft cells)

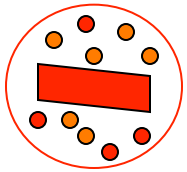


**Mouse ko = ↓ lung inflammation, ↓ bronchial hyperreactivity

*Mouse ko = ↓ skin allergic hypersensitivity

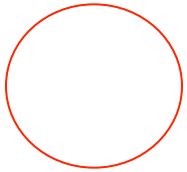
Eosinophil Granules

Specific



- Major Basic Protein
- Eosinophil Cationic Protein (RNase3)
- Eosinophil Peroxidase
- Eosinophil-derived Neurotoxin (Rnase 2)

Primary

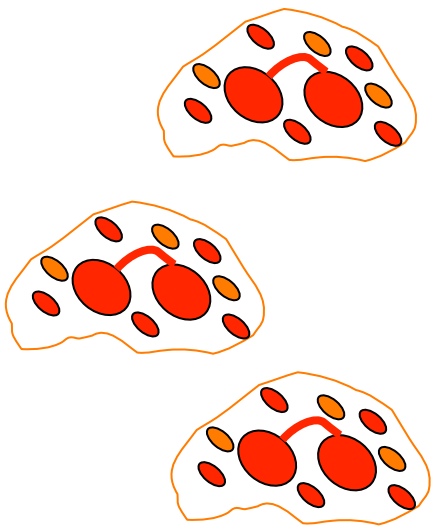


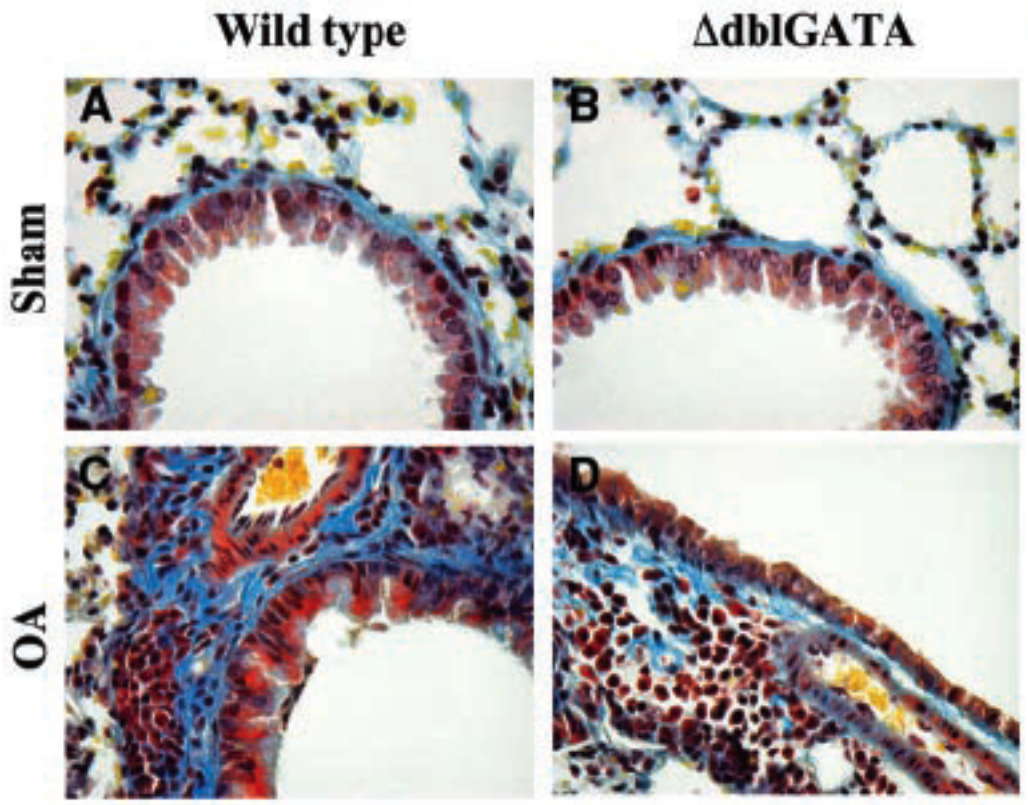
- Lysophospholipase
- (Charcot-Leyden crystals)

CYTOTOXICITY

(multi-system toxicity in patients with idiopathic HES)

Eosinophils and airway remodeling





Less subepithelial and interstitial collagen deposition in sensitized mice lacking eosinophils (Humbles et al., Science 305:1776, 2004)

Asthma

Prevalence:

>300 million worldwide

1/6 U.S. children

Cost in U.S. > $6 billion/yr

 ing Developed > Nondeveloped Countries

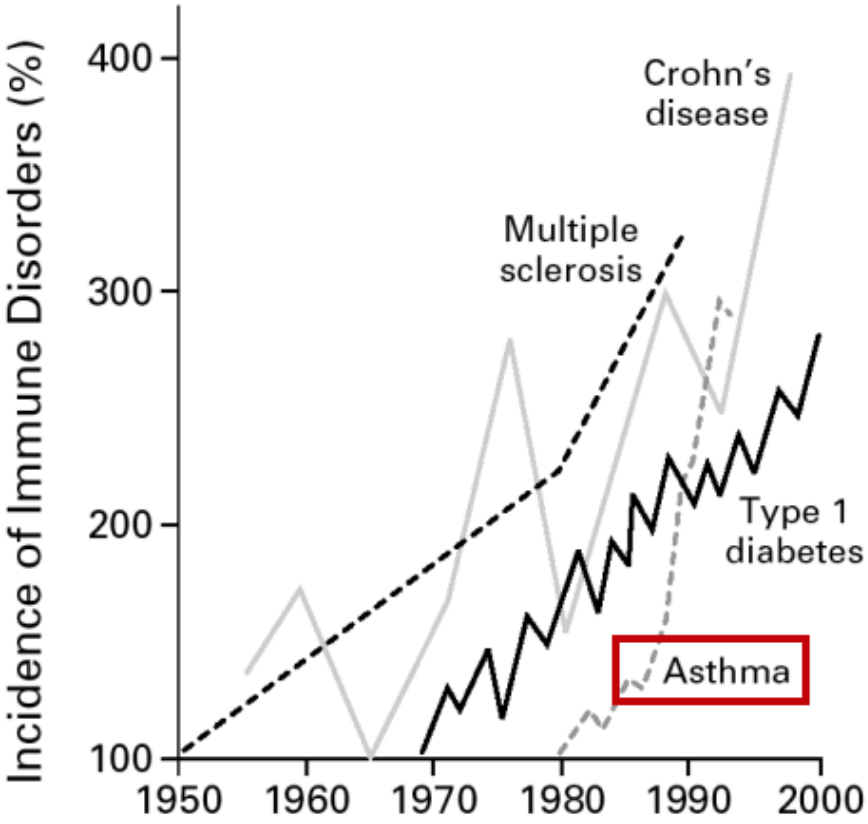
Hygiene Hypothesis

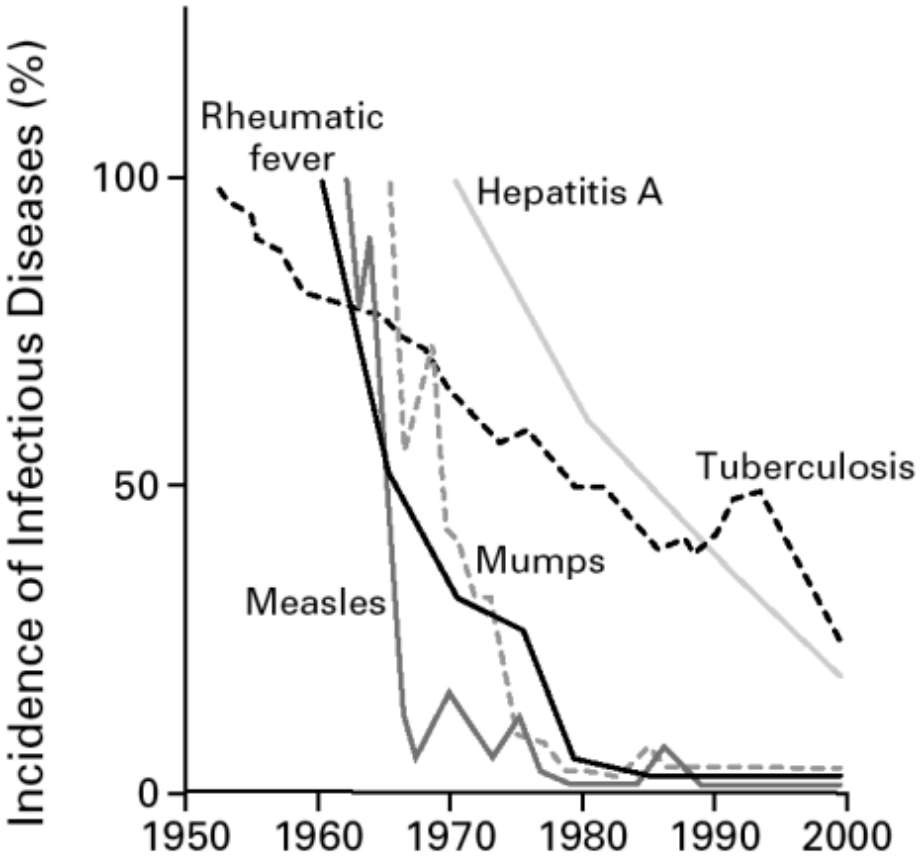
Reflects developmental evolution of mucosal/regulatory immune system, possibly through effects on establishing the commensal flora

?Worms, ectoparasites, childhood infections

Asthma: an epidemic in the absence of infection…

Inverse relationship between infections and immune disorders





Bach JF. 2002. N Engl J Med. 347:911.

Asthma Triad

1. **Reversible episodes of airway obstruction**

   (↑mucus, eosinophils, T cells with IL-4, IL-5, IL-13, GM-CSF, etc.)

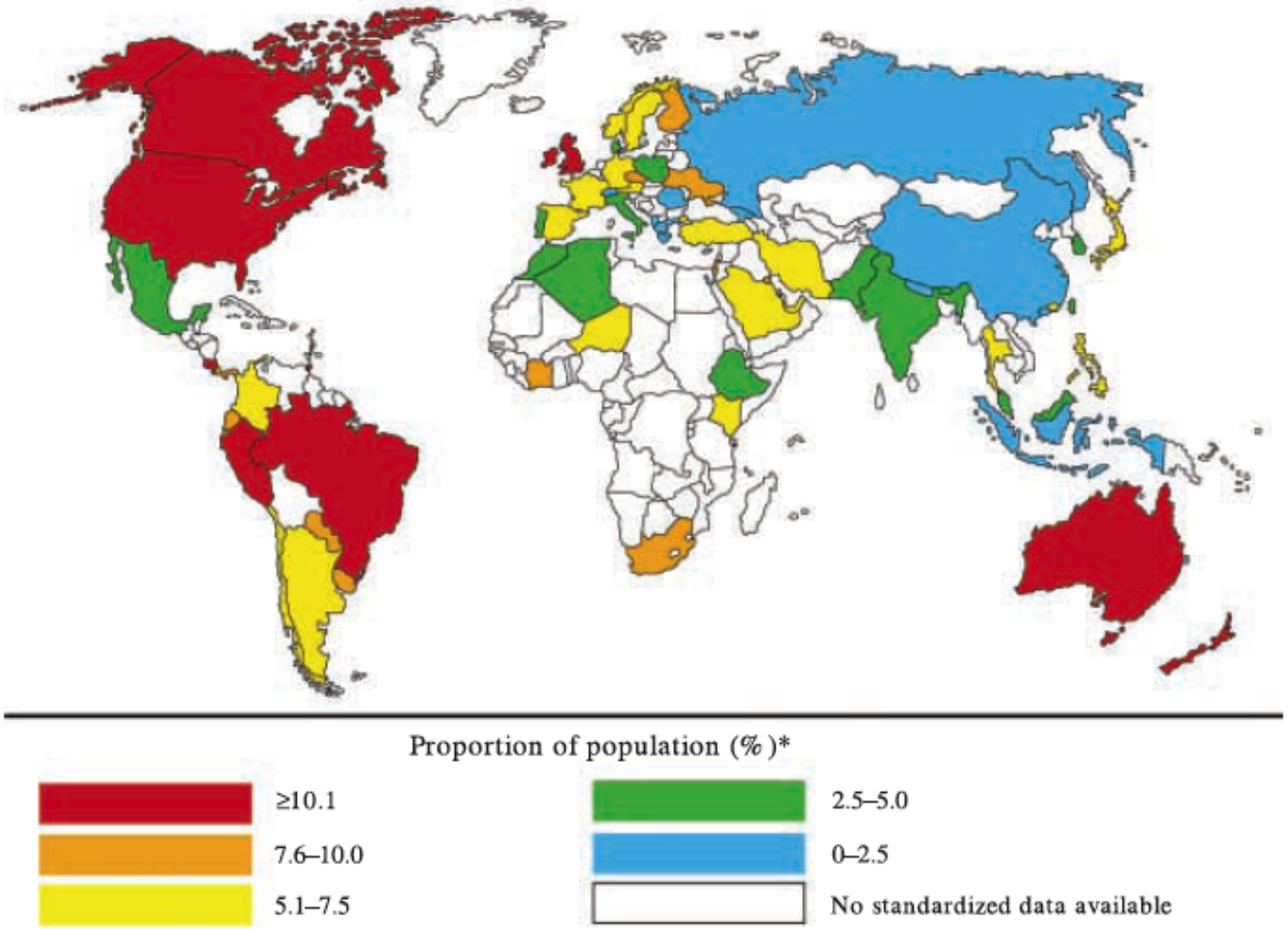
2. **Chronic airway inflammation**

   (↑T cells, eosinophils with ↑ type 2 cytokines; chronic subepithelial, epithelial changes with mucus cell hyperplasia)

3. **Bronchial hyperreactivity with provocative agents**

The global epidemic of asthma

Masoli et al., The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy 59:469-78, 2004



A disease of persistent Th2-associated airway inflammation

The New England
Journal of Medicine

Volume 326:298-304 January 30, 1992 Number 5

Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma

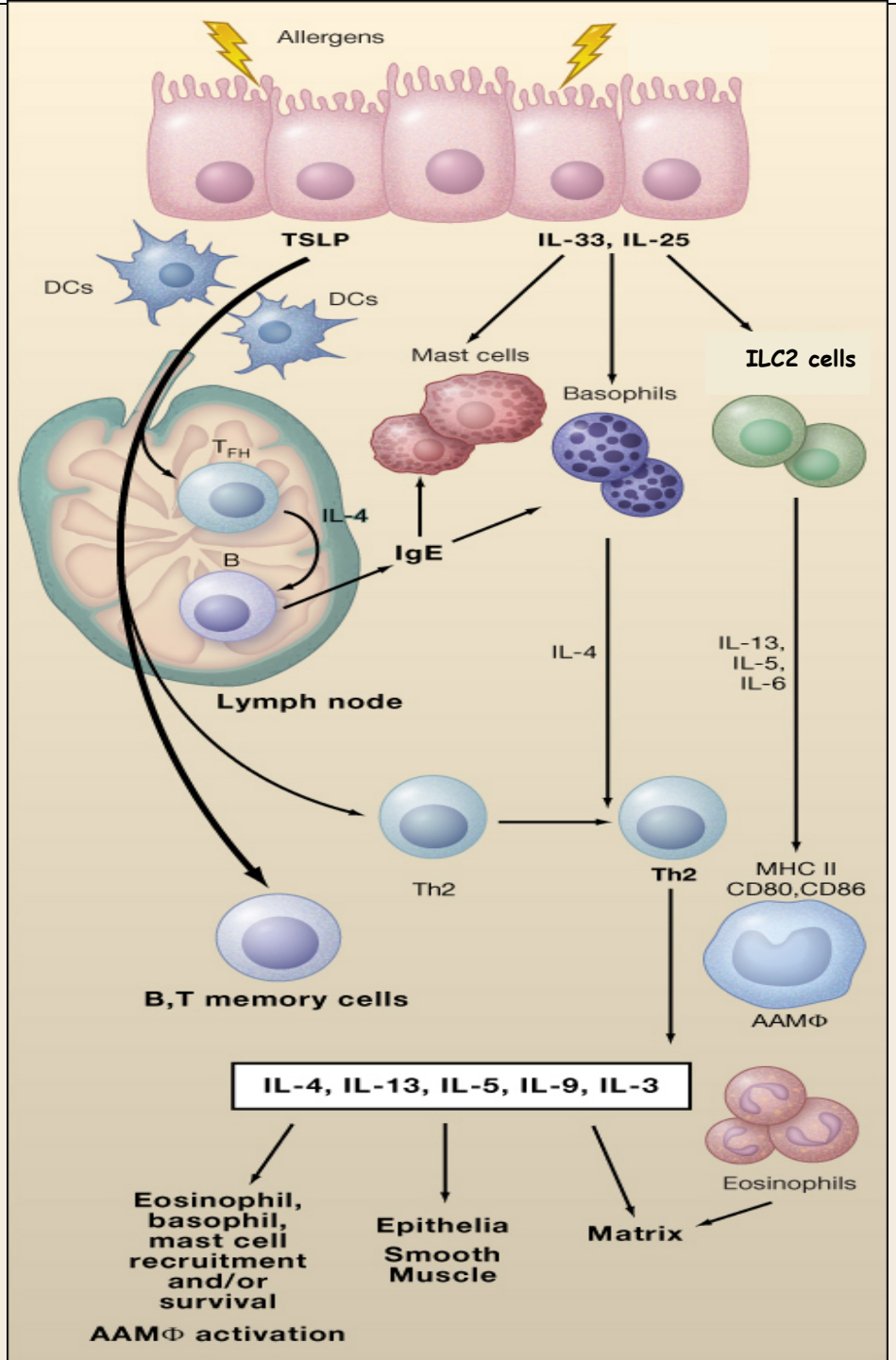
DS Robinson, Q Hamid, S Ying, A Tsicopoulos, J Barkans, AM Bentley, C Corrigan, SR Durham, and AB Kay

Abstract

BACKGROUND. In atopic asthma, activated T helper lymphocytes are present in bronchial-biopsy specimens and bronchoalveolar-lavage (BAL) fluid, and their production of cytokines may be important in the pathogenesis of this disorder. Different patterns of cytokine release are characteristic of certain subgroups of T helper cells, termed TH1 and TH2, the former mediating delayed-type hypersensitivity and the latter mediating IgE synthesis and eosinophilia. The pattern of cytokine production in atopic asthma is unknown. METHODS. We assessed cells obtained by BAL in subjects with mild atopic asthma and in normal control subjects for the expression of messenger RNA (mRNA) for interleukin-2, 3, 4, and 5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon gamma by in situ hybridization with 32P-labeled complementary RNA. Localization of mRNA to BAL T cells was assessed by simultaneous in situ hybridization and immunofluorescence and by in situ hybridization after immunomagnetic enrichment or depletion of T cells. RESULTS. As compared with the control subjects, the subjects with asthma had more BAL cells per 1000 cell that were positive for mRNA for interleukin-2 (P less than 0.05), 3 (P less than 0.01), 4 (P less than 0.001), and 5 (P less than 0.001) and GM-CSF (P less than 0.001). There was no significant difference between the two groups in the number of cells expressing mRNA for interferon gamma. In the subjects with asthma, mRNA for interleukin-4 and 5 was expressed predominantly by T lymphocytes. CONCLUSIONS. Atopic asthma is associated with activation in the bronchi of the interleukin-3, 4, and 5 and GM-CSF gene cluster, a pattern compatible with predominant activation of the TH2-like T-cell population.

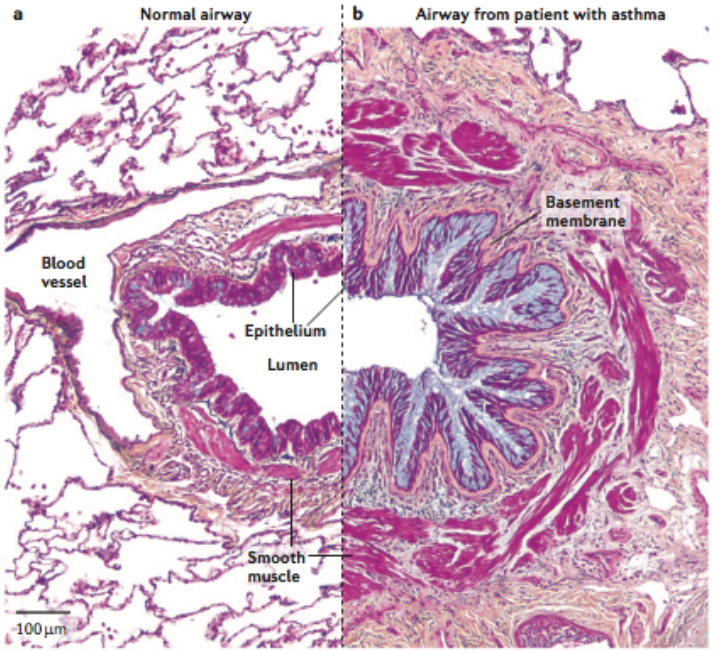
Type 2 immunity as a confluence of innate and adaptive responses to epithelial insults…

…and why no Treg function? (prominent in helminth infection)

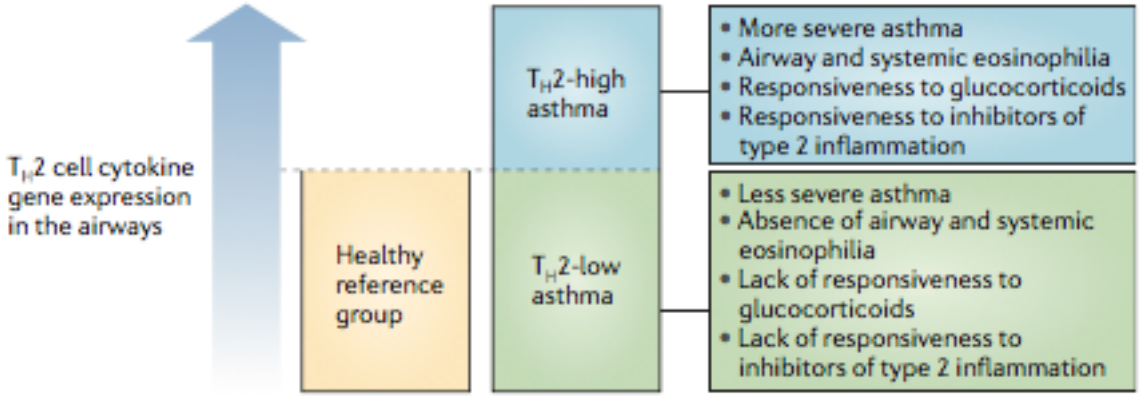


Locksley, Cell 140:777-783, 2010

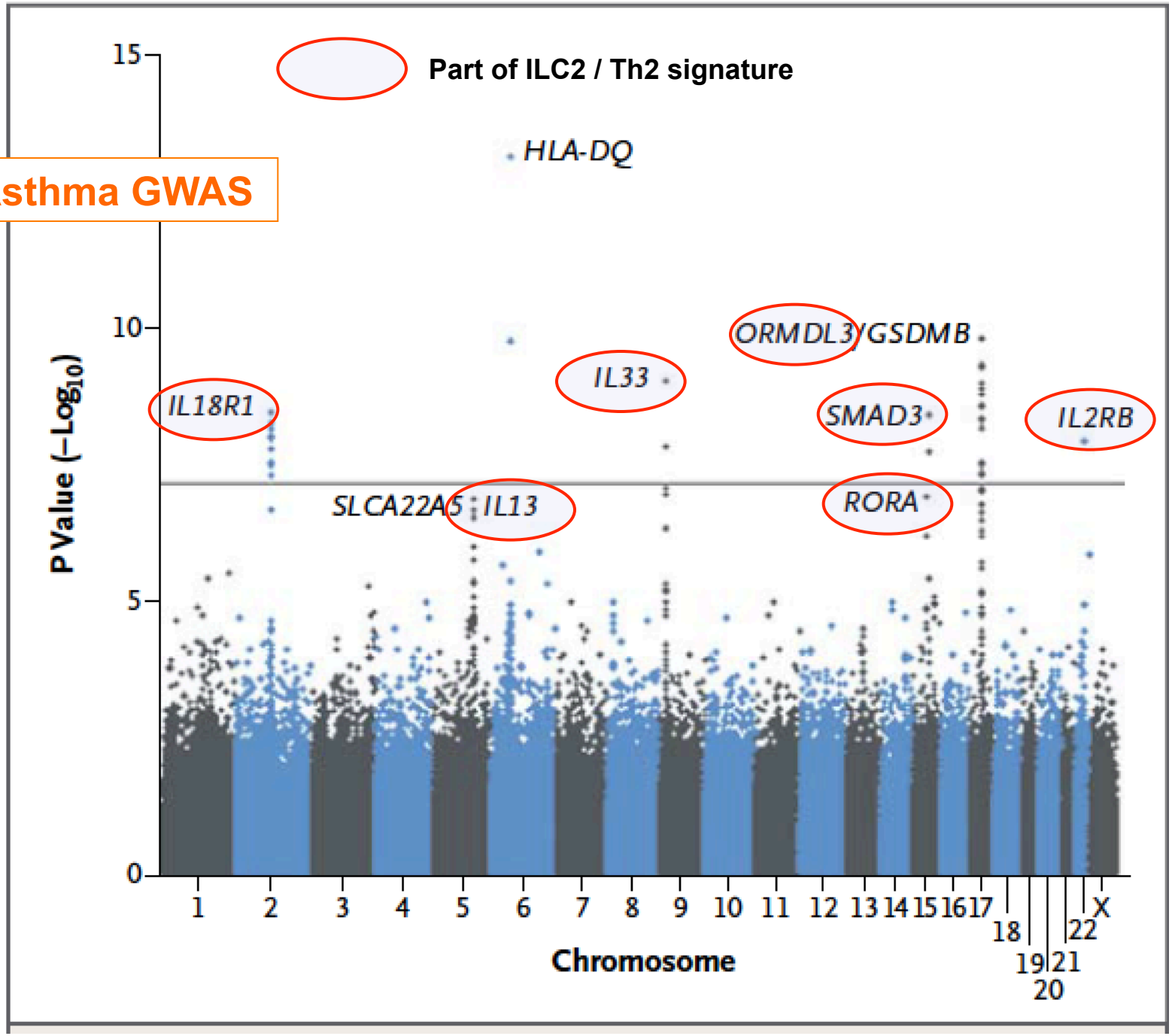
Th2 in most, not all…



'Endotypes'

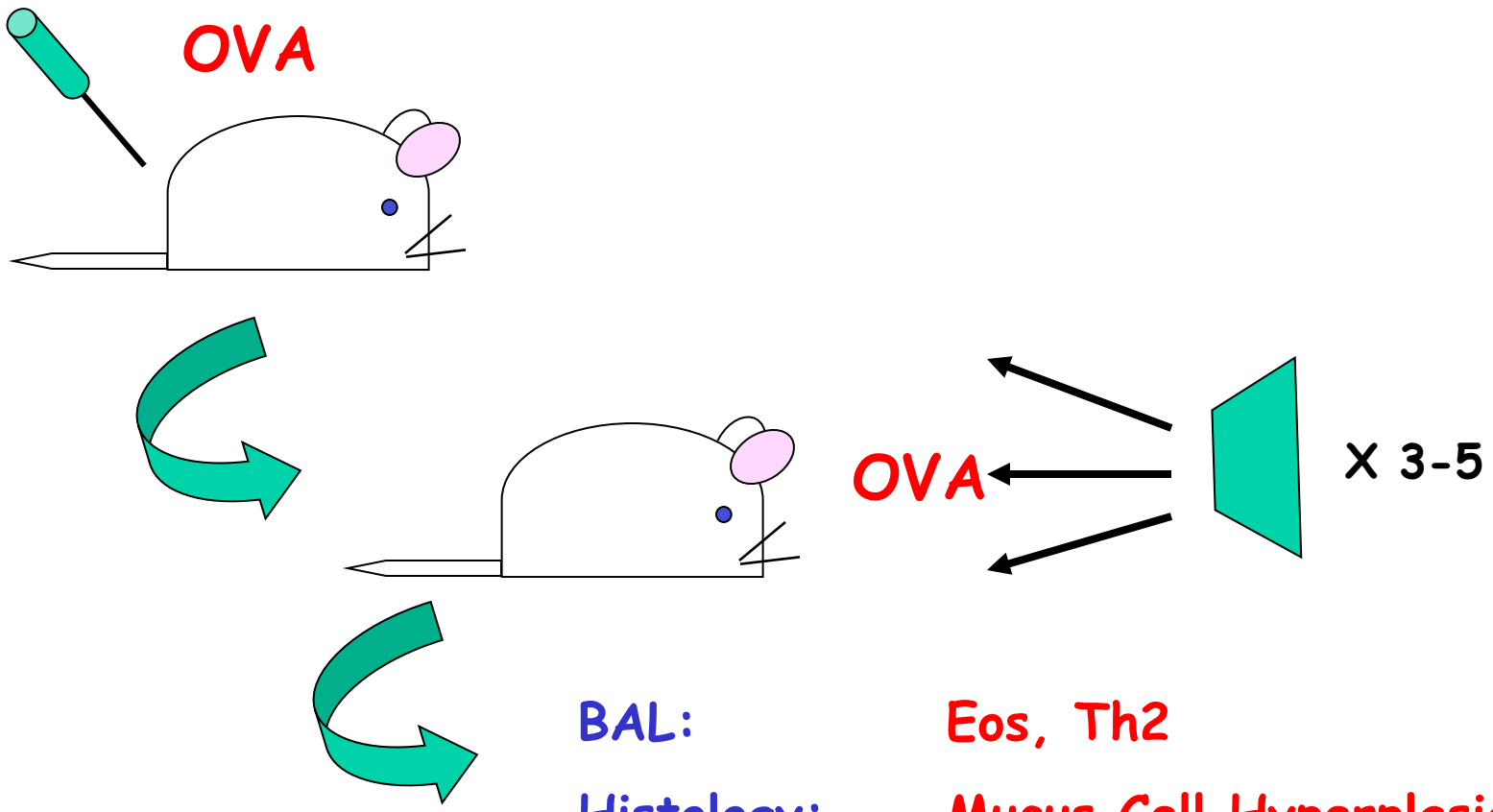


Fahy JV. 2015. Type 2 inflammation in asthma – present in most, absent in many. Nat Rev Immunol 15:57-65.



Moffat MM et al, NEJM 363:1211-21, 2012

Mouse 'Asthma'



BAL: Eos, Th2

Histology: Mucus Cell Hyperplasia, Inflammation (BALT's)

Physiology: Airway Hyperreactivity

Therapy of human asthma

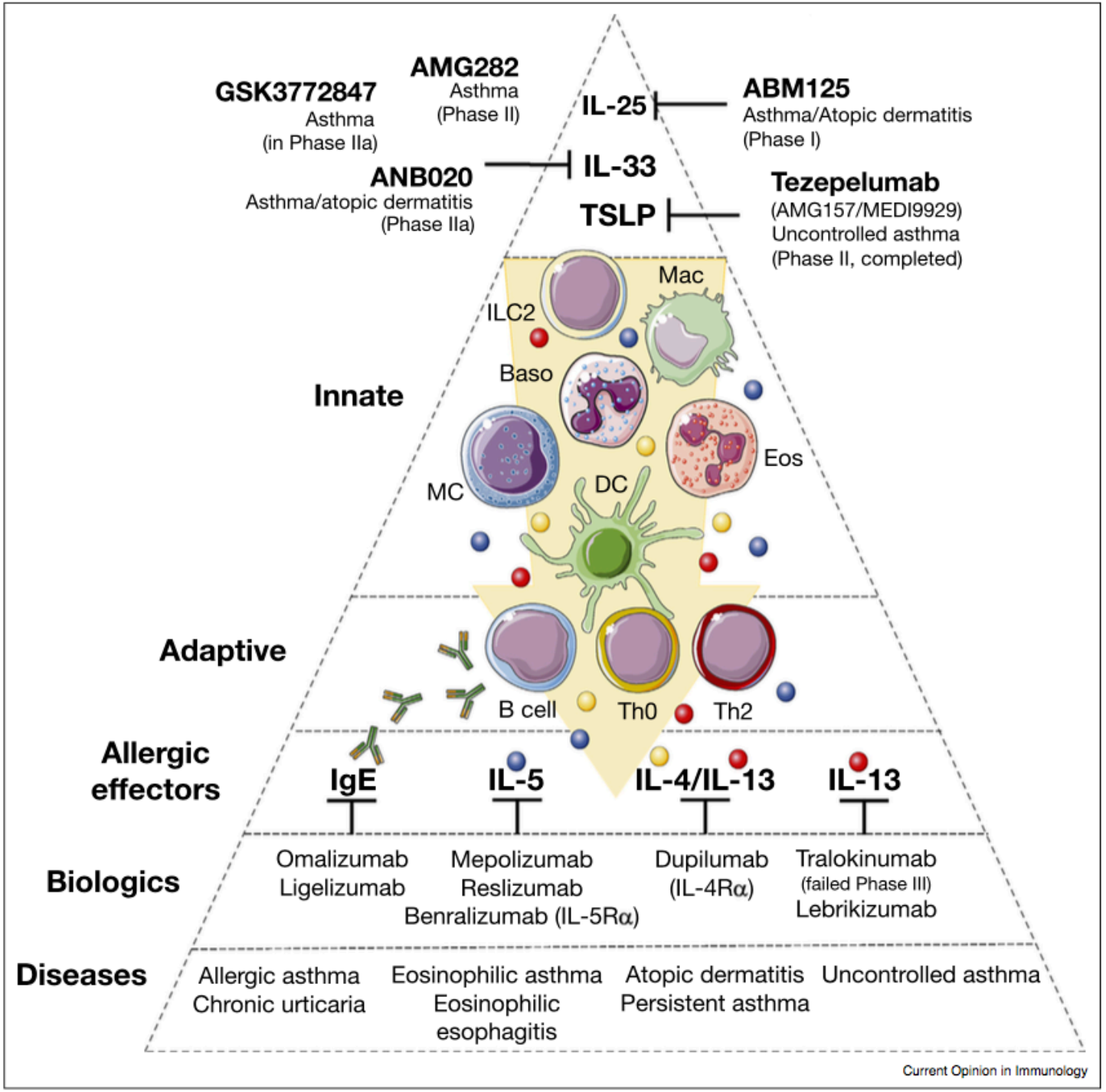
Approved in clinic

- **Steroids and beta-agonists (long- and short-acting) - mainstay**
- **5-LO inhibitors (LTA4 synthesis blockers)**
- **CysLTI antagonists (LTD4 blockers)**
- **Monoclonal humanized anti-IgE mAb (E25)**
- **Anti-IL-5 (decrease disease in high-eo subsets, usually steroid-resistant); Anti-IL-5R**
- **IL-4 receptor (IL-4 and IL-13 blockade; approved for eczema)**

In development/testing:

- **anti-TSLP (clinical trial worked)**
- **Anti-IL-13**
- **Suplatast tosilate (suppresses IL-4, IL-5 from Th2 cells)**
- **CDP840, phosphodiesterase type 4 inhibitor**
- **anti-TNF (steroid resistant asthma), IL-17 inhibitors (didn't work)**
- **anti-IL-33**

Mechanical: Bronchial thermoplasty


GSK3772847
Asthma
(in Phase IIa)
AMG282
Asthma
(Phase II)
IL-25
ABM125
Asthma/Atopic dermatitis
(Phase I)
ANB020
Asthma/atopic dermatitis
(Phase IIa)
IL-33
TSLP
Tezepelumab
(AMG157/MEDI9929)
Uncontrolled asthma
(Phase II, completed)
Innate
Adaptive
Allergic effectors
Biologics
Diseases
Mac
ILC2
Baso
MC
DC
Eos
B cell
Th0
Th2
IgE
IL-5
IL-4/IL-13
IL-13
Omalizumab
Ligelizumab
Mepolizumab
Reslizumab
Benralizumab (IL-5Rα)
Dupilumab
(IL-4Rα)
Tralokinumab
(failed Phase III)
Lebrikizumab
Allergic asthma
Chronic urticaria
Eosinophilic asthma
Eosinophilic esophagitis
Atopic dermatitis
Persistent asthma
Uncontrolled asthma
Current Opinion in Immunology

Topics for discussion

Asthma reaches prevalence levels of 8%-12% in some urban Westernized populations. Allergic asthma is predominantly a disease of childhood. Consider the impact of genetics, environment and development in constructing a model to explain the immunologic underpinnings explaining the increasing prevalence of asthma. How would you proceed to validate and/or intervene therapeutically based on your conclusions?

Food allergy, like asthma, is increasingly prevalent in developed countries. For over a decade, food avoidance was encouraged by pediatricians to prevent the subsequent development of intolerance, with little effects on the steady increase in prevalence. A controlled trial of peanut intervention at early age showed that early introduction of peanuts to individuals at risk for food allergy decreased the subsequent development of intolerance (De Toit et al. 2015. Randomized trial of peanut consumption in infants at risk for peanut allergy. New Engl J Med 372:803-813). Discuss mechanisms that might account for the trial outcome and experiments you would suggest to test the hypotheses that you develop. (A comprehensive review of genetic causes of human atopy if you have time: Lyons JJ, Milner JD. 2018. Primary atopic disorders. J Exp Med 215:1009-22)