Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department

Hypersensibilités allergiques et non allergiques

Audrey Nosbaum, Florence Hacard, Marie Tauber, Frédéric Bérard, Jean-François Nicolas, Marc Vocanson

Département Allergologie et Immunologie Clinique
INSER U1111/CIRI
Université Lyon1

http://allergolyon.fr

Hypersensibilités

Classification de Gell & Coombs

Antibody ← → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IIFN-γ, TNF-α **Th1/Type 1**	IL-5, IL-4/IL-13 **Th2/Type 2**	Perforin/ granzyme B **Cytotoxic**	**Th17/Type 17**
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
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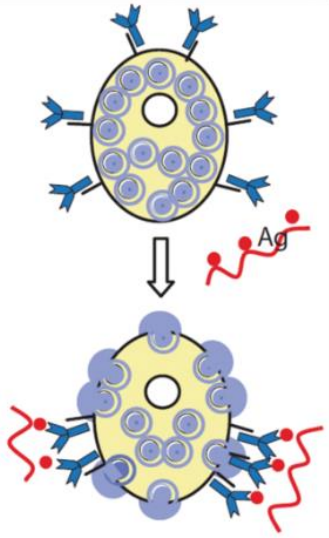
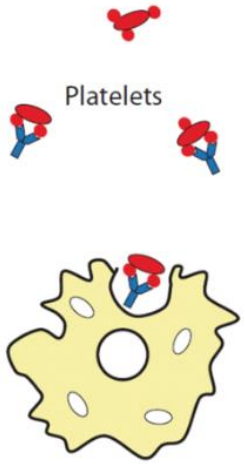
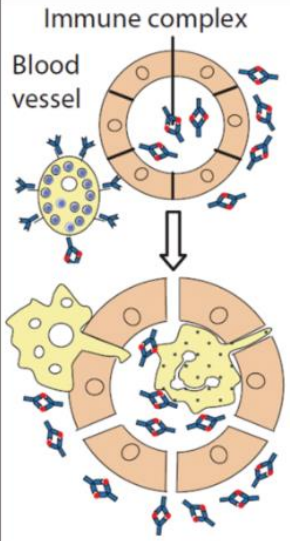
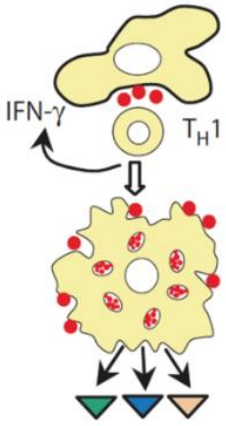
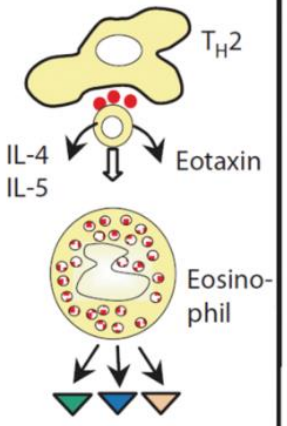
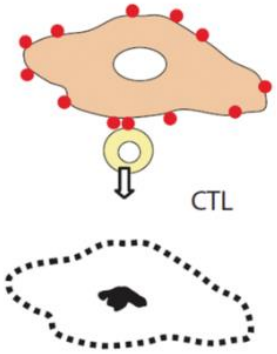
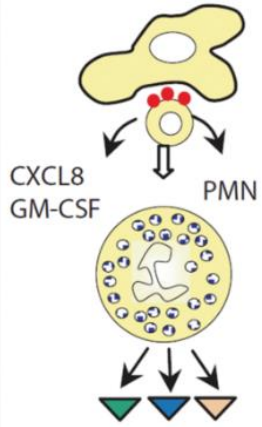
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

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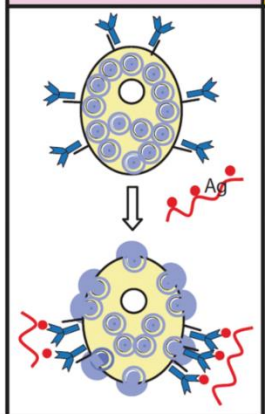
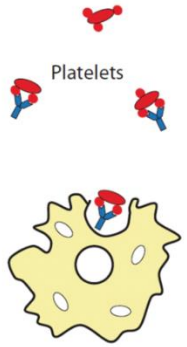
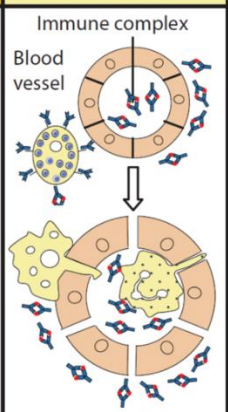
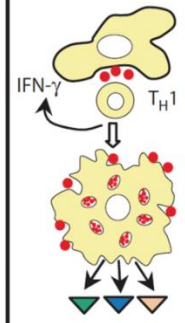
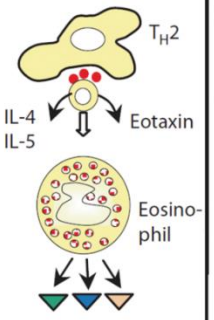
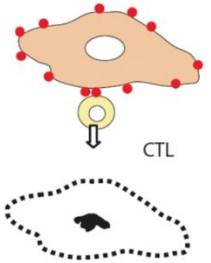
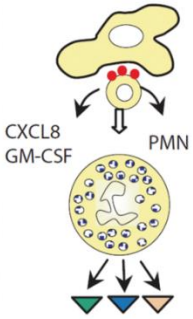
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Maladies autoimmunes et allergiques	**Anaphylaxie Rhinite allergique Asthme (crise)**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme chron. Rhinite chron.**	**Rejet de greffe Diabète SEP**	**Polyarthrite Sclérose en plaque Mal. de Crohn**
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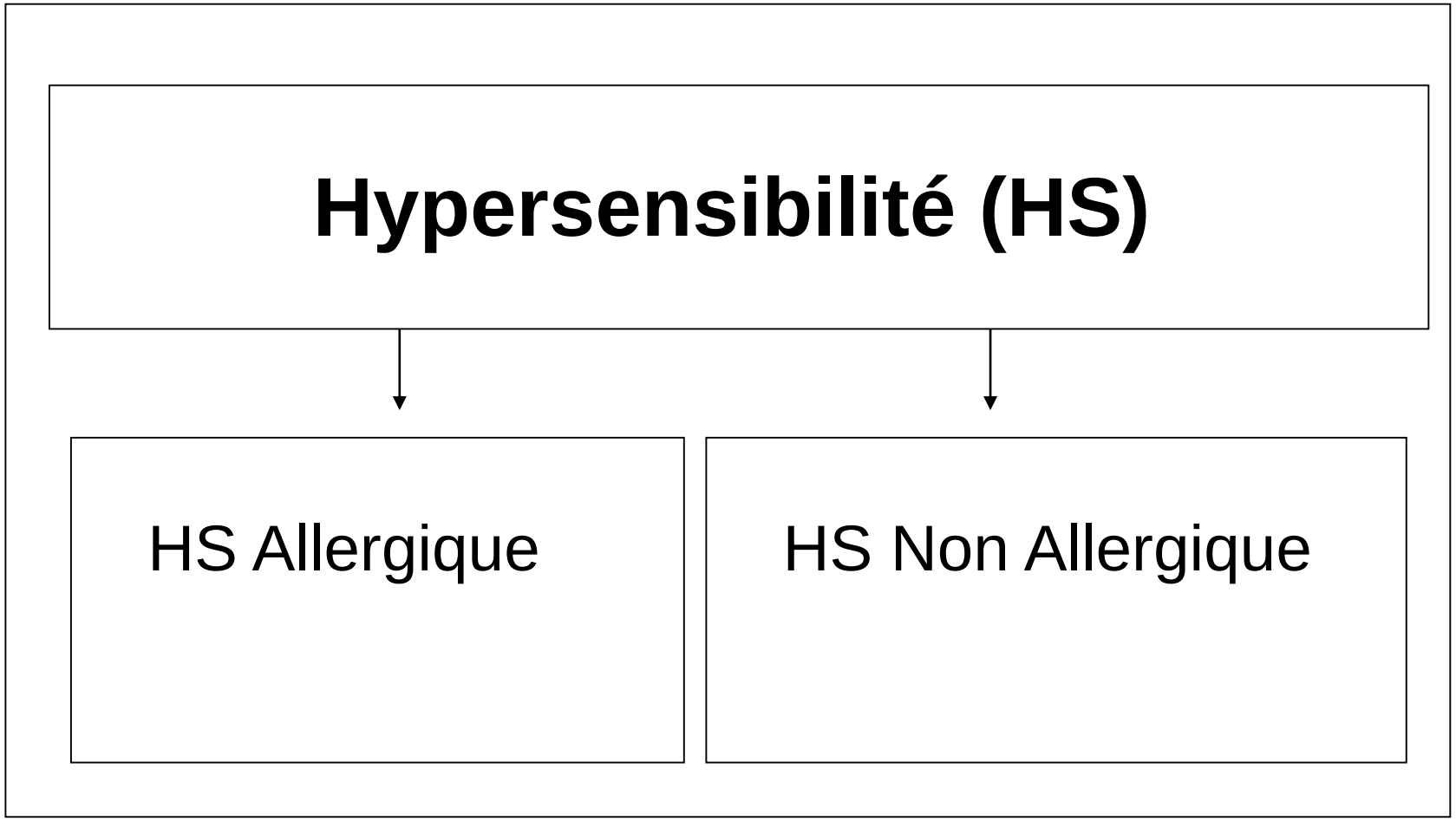
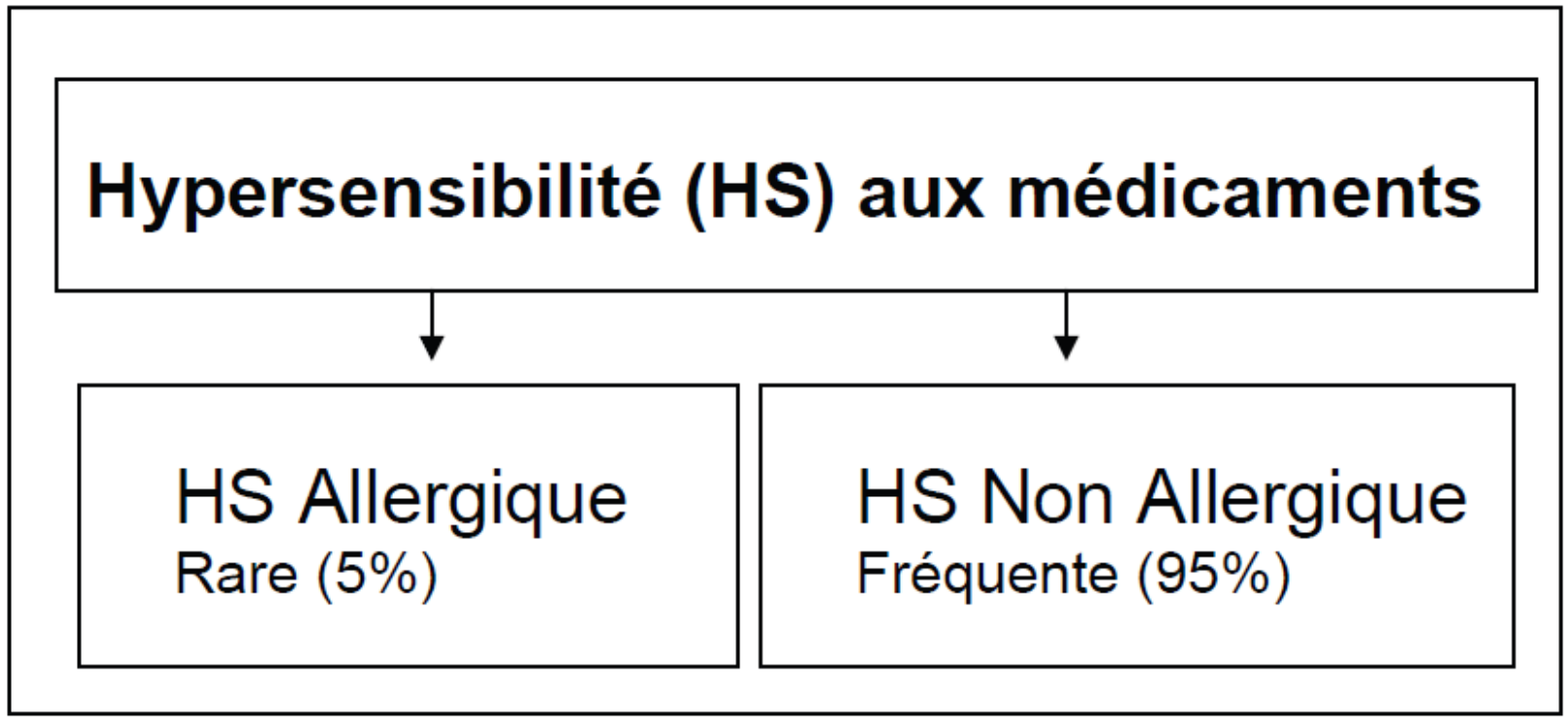
Allergies médicaments	**Choc anaphylactique**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème médic.**	**DRESS**	**Lyell Stevens-Johnson**	**Pustulose exanthématique aigue généralisée**

- **Hypersensibilité allergique et non allergique**
- Classification de Gell & Coombs
  - HS immédiate (mastocytes)
  - HS retardée (lymphocytes)

Pr JF Nicolas – janvier 2023
jean-francois.nicolas@chu-lyon.fr


Hypersensibilité (HS)
HS Allergique
HS Non Allergique


Hypersensibilité (HS) aux médicaments
HS Allergique
Rare (5%)
HS Non Allergique
Fréquente (95%)

[redacted] Danièle

7 Côte Carmagnac

69 [redacted]

tel

le 11 Mai 2003

Docteur Nicolas,

Mon fils Yves a rendez-vous le 25 Juin pour des tests. Il est né le 8 janvier 1983, et a fait un urticaire géant au Clamoxyl en 1986, donc on a évité cet antibiotique. Le 22 Décembre dernier, il a fait un oedème de Quincke,

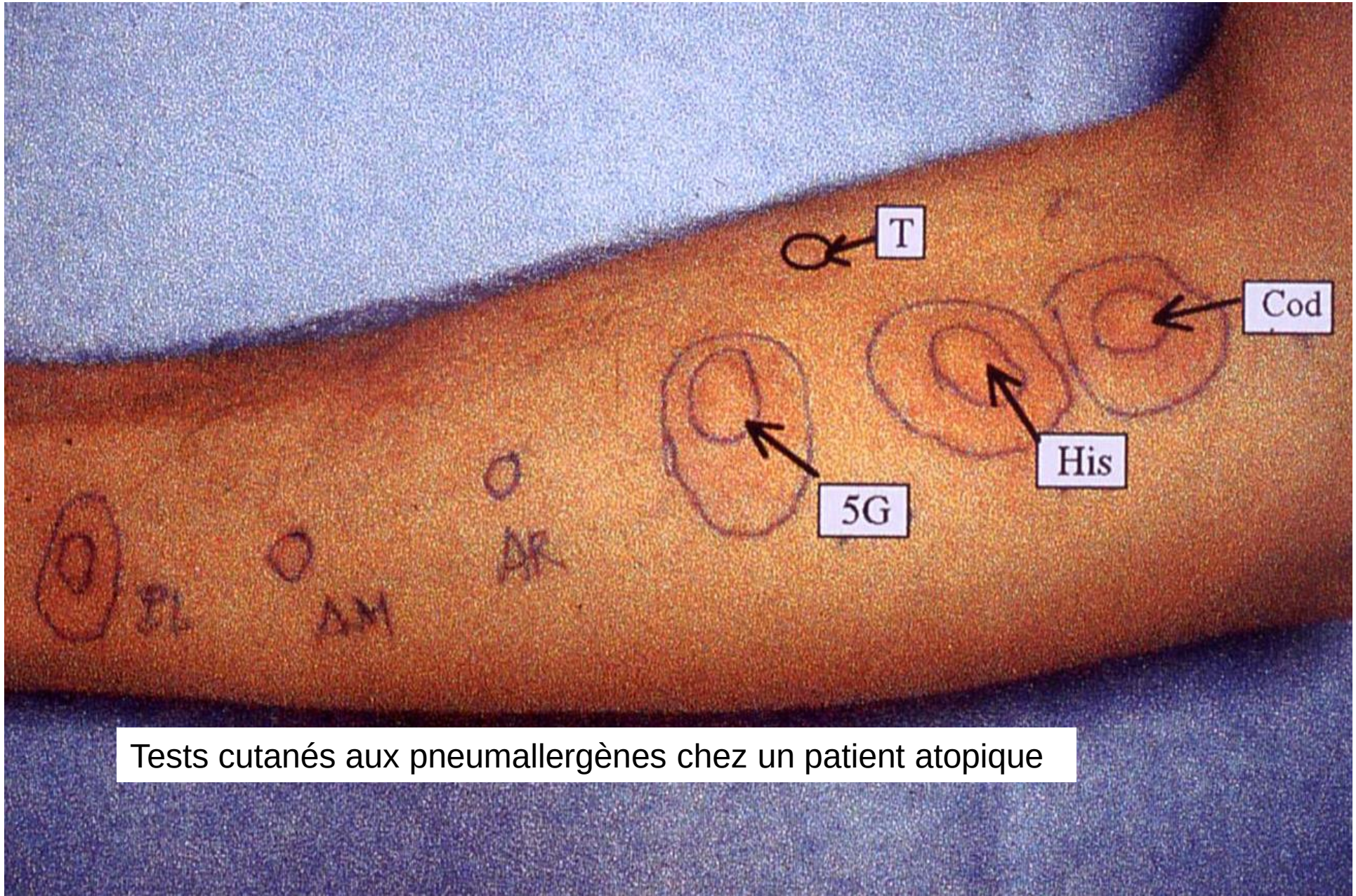
Quand on est allergique à tout, on est allergique à rien

n'avait pris ni clamoxyl, ni érythrogel, ni aucun médicament, et il a refait un oédème de Quincke. J'ai donc noté qu'il avait mangé = du nougat chinois, concombres, tomates, betteraves, magret de Canard, sauce au poivre vert, mangues, litchis, comté et pâtes.

Il y avait aussi un très gros bouquet de tulipes posé près de lui, avec des jonquilles.

Désolé d'avoir dû changer le rendez-

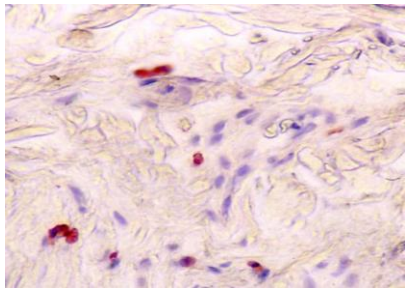
HSI allergique et non allergique

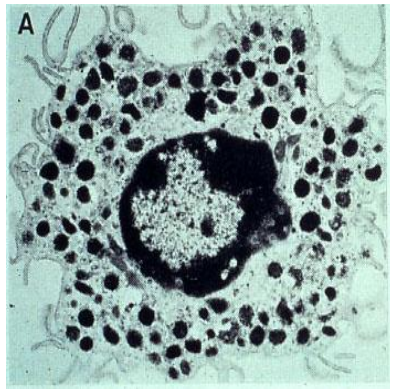


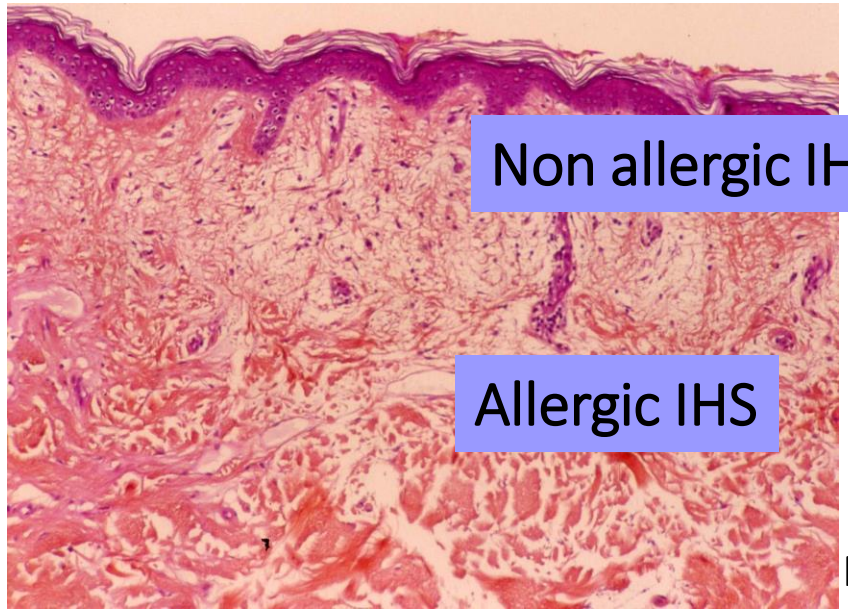
Tests cutanés aux pneumallergènes chez un patient atopique

TYPE I HYPERSENSITIVITY

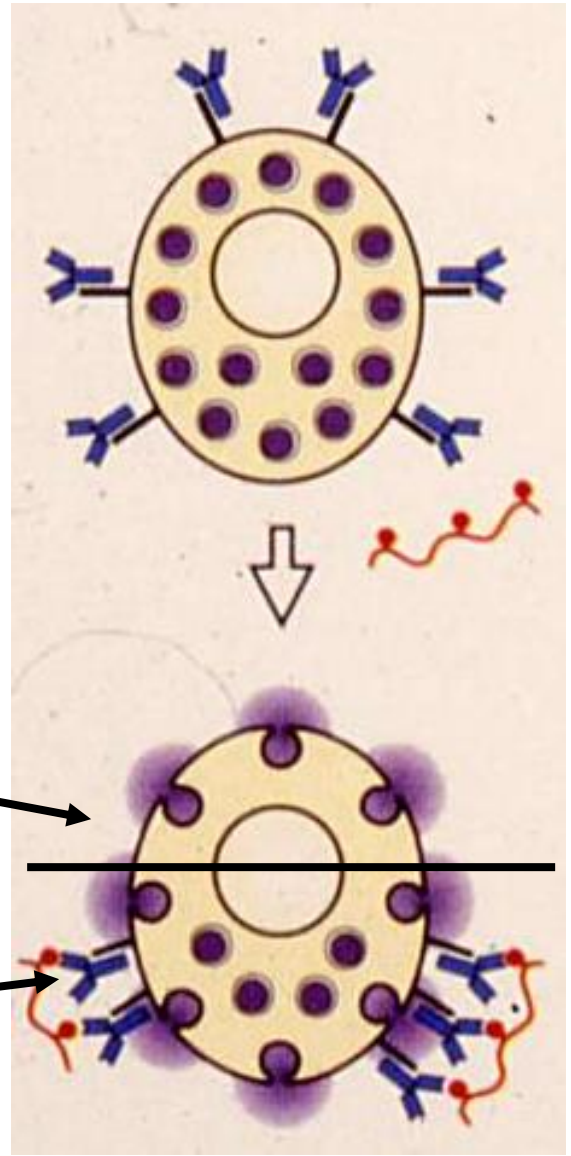
Œdème du derme / Vaisseaux



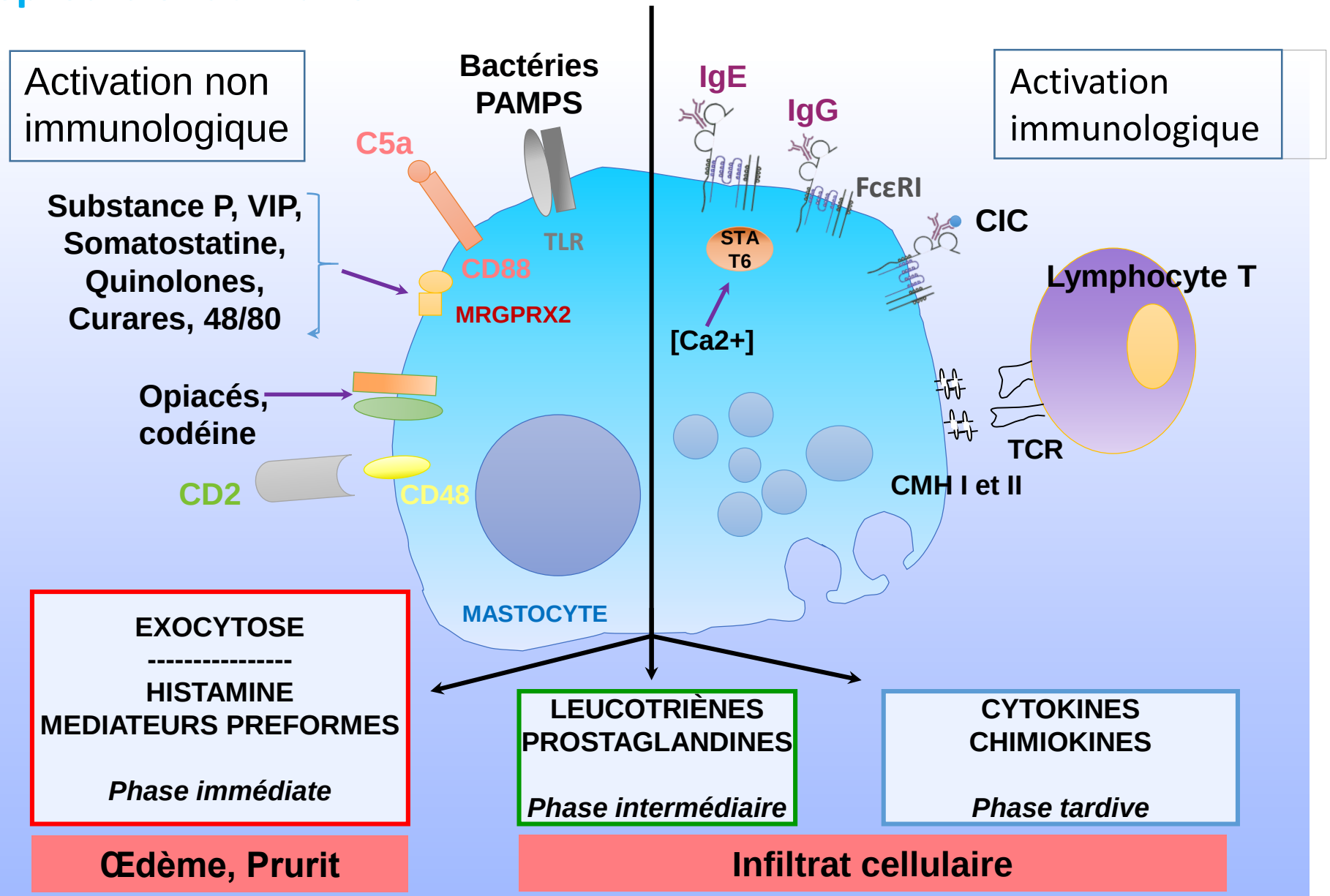




Mastocytes / Histamine



MASTOCYTES
Récepteurs et activation



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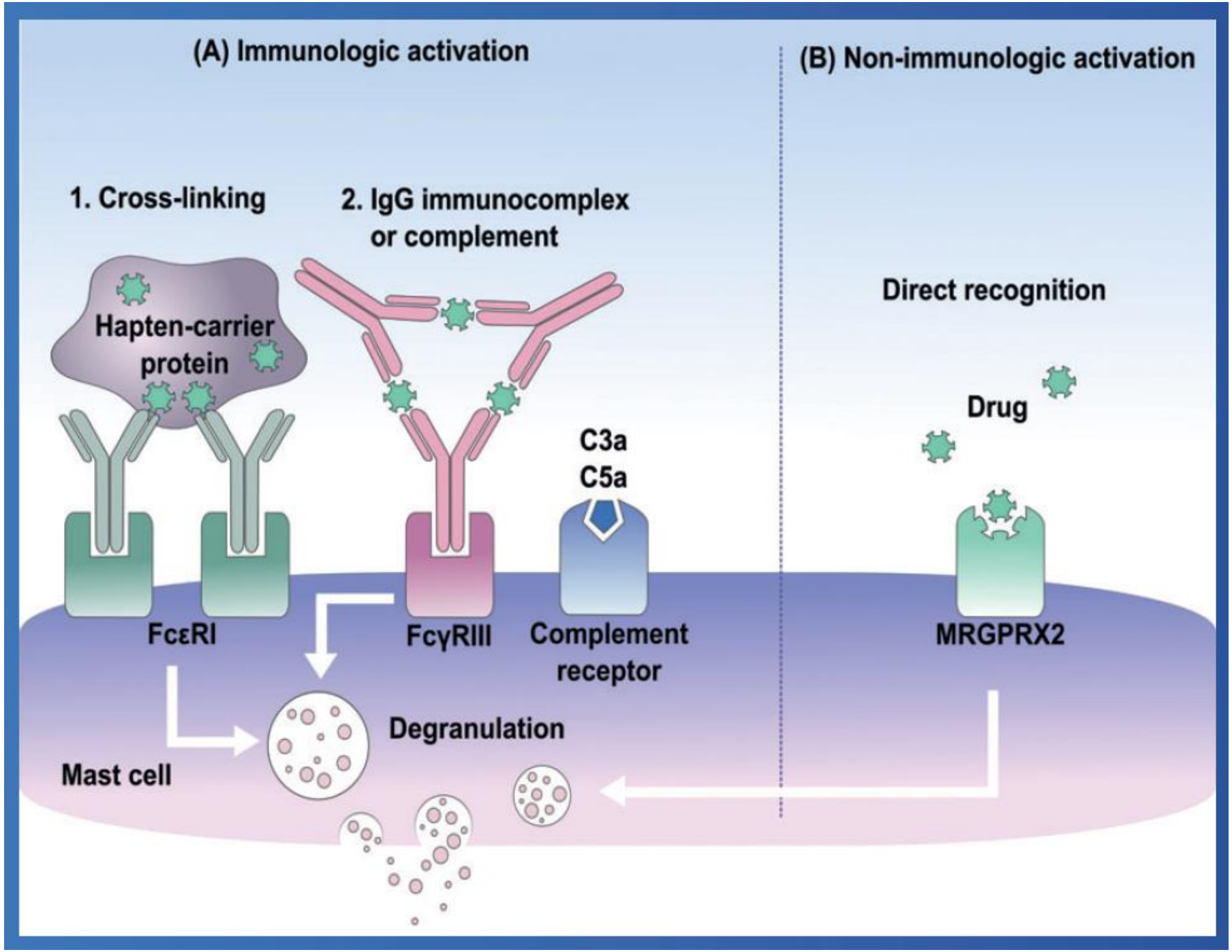


Drug-induced urticaria and angioedema

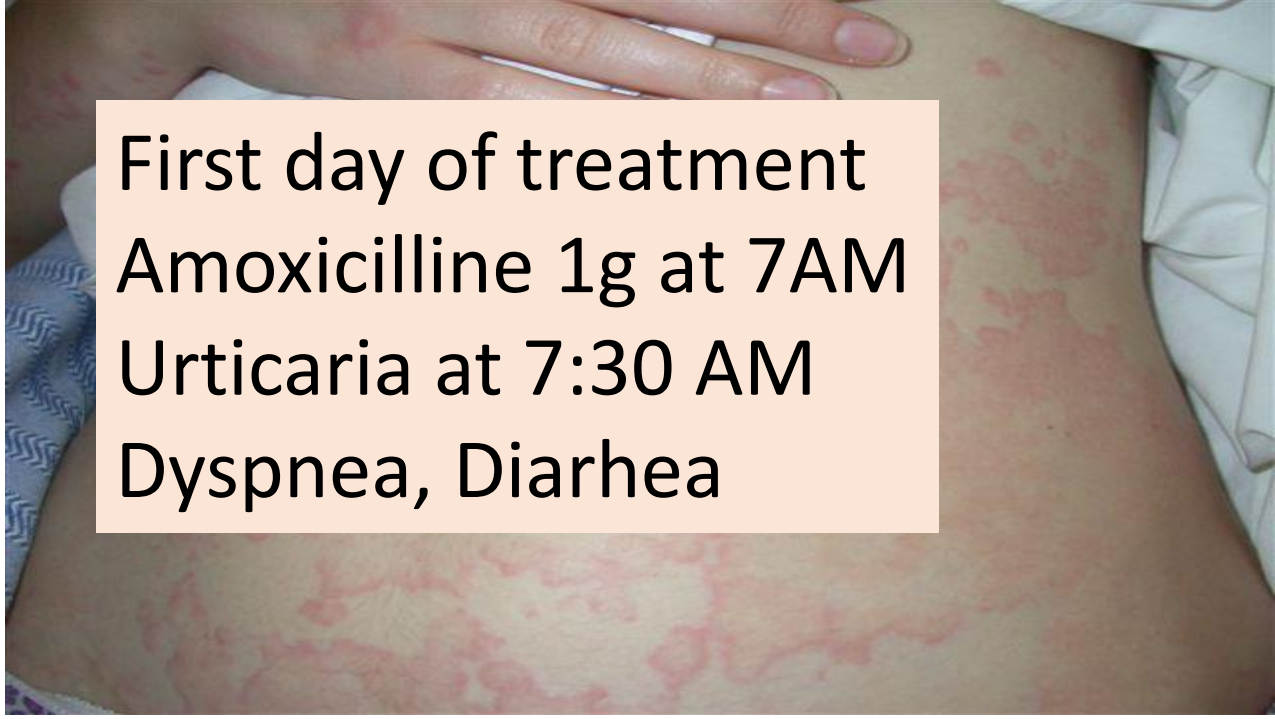
- **Allergic (IgE)**: rares (5%) and exceptionally isolated

- **Non allergic**: frequent (95%) and almost always benign

- Cousin F, Philips K, Favier B, Bienvenu J**,** Nicolas JF**.** Drug-induced urticaria. **Eur J Dermatol** 2001;11(3):181-7.


First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM


Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM



First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea

More a drug-induced reaction is severe, more it has a chance to be allergic

Hypersensibilités

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	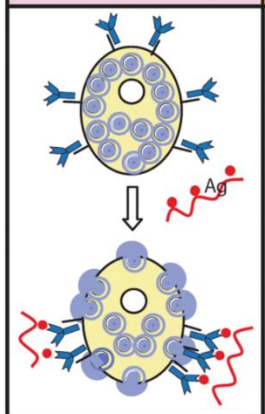	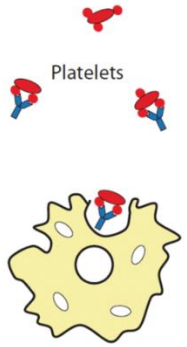	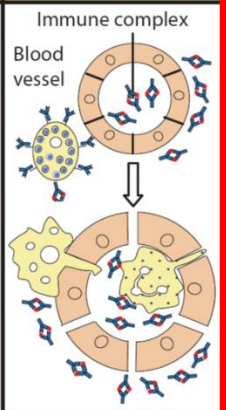	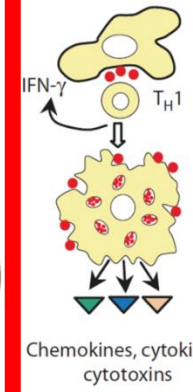	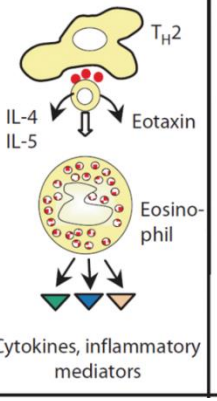	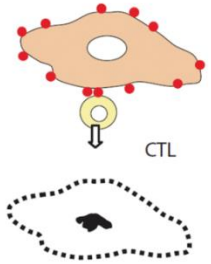	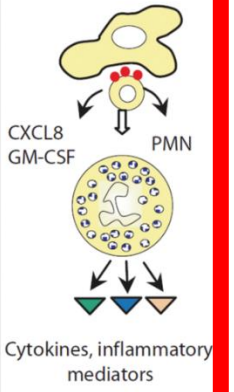
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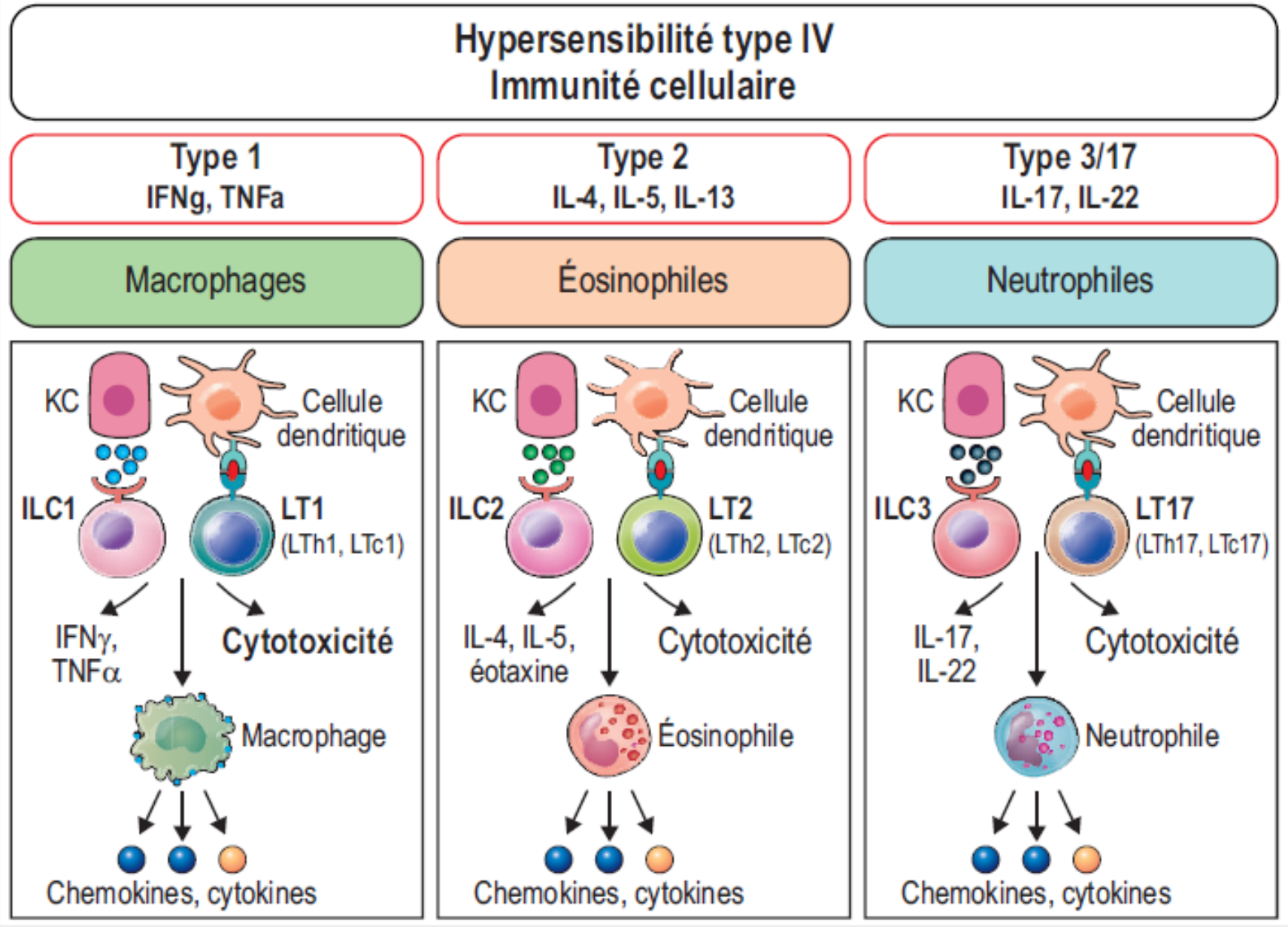


Table 1
Classification des réactions immunitaires cellulaires (hypersensibilité retardée de type IV de Gell & Coombs)

The 3 major types of innate and adaptive cell-mediated effector immunity

Francesco Annunziato, PhD,[a] Chiara Romagnani, MD, PhD,[b] and Sergio Romagnani, MD[a] *Florence, Italy, and Berlin, Germany*

The immune system has tailored its effector functions to optimally respond to distinct species of microbes. Based on emerging knowledge on the different effector T-cell and innate lymphoid cell (ILC) lineages, it is clear that the innate and adaptive immune systems converge into 3 major kinds of cell-mediated effector immunity, which we propose to categorize as type 1, type 2, and type 3. Type 1 immunity consists of T-bet$^+$ IFN-γ–producing group 1 ILCs (ILC1 and natural killer cells), CD8$^+$ cytotoxic T cells (T_C1), and CD4$^+$ T_H1 cells, which protect against intracellular microbes through activation of mononuclear phagocytes. Type 2 immunity consists of GATA-3$^+$ ILC2s, T_C2 cells, and T_H2 cells producing IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation, as well as IgE antibody production, thus protecting against helminthes and venoms. Type 3 immunity is mediated by retinoic acid–related orphan receptor γt$^+$ ILC3s, T_C17 cells, and T_H17 cells producing IL-17, IL-22, or both, which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi. On the other hand, type 1 and 3 immunity mediate autoimmune diseases, whereas type 2 responses can cause allergic diseases. (J Allergy Clin Immunol 2015;135:626-35.)

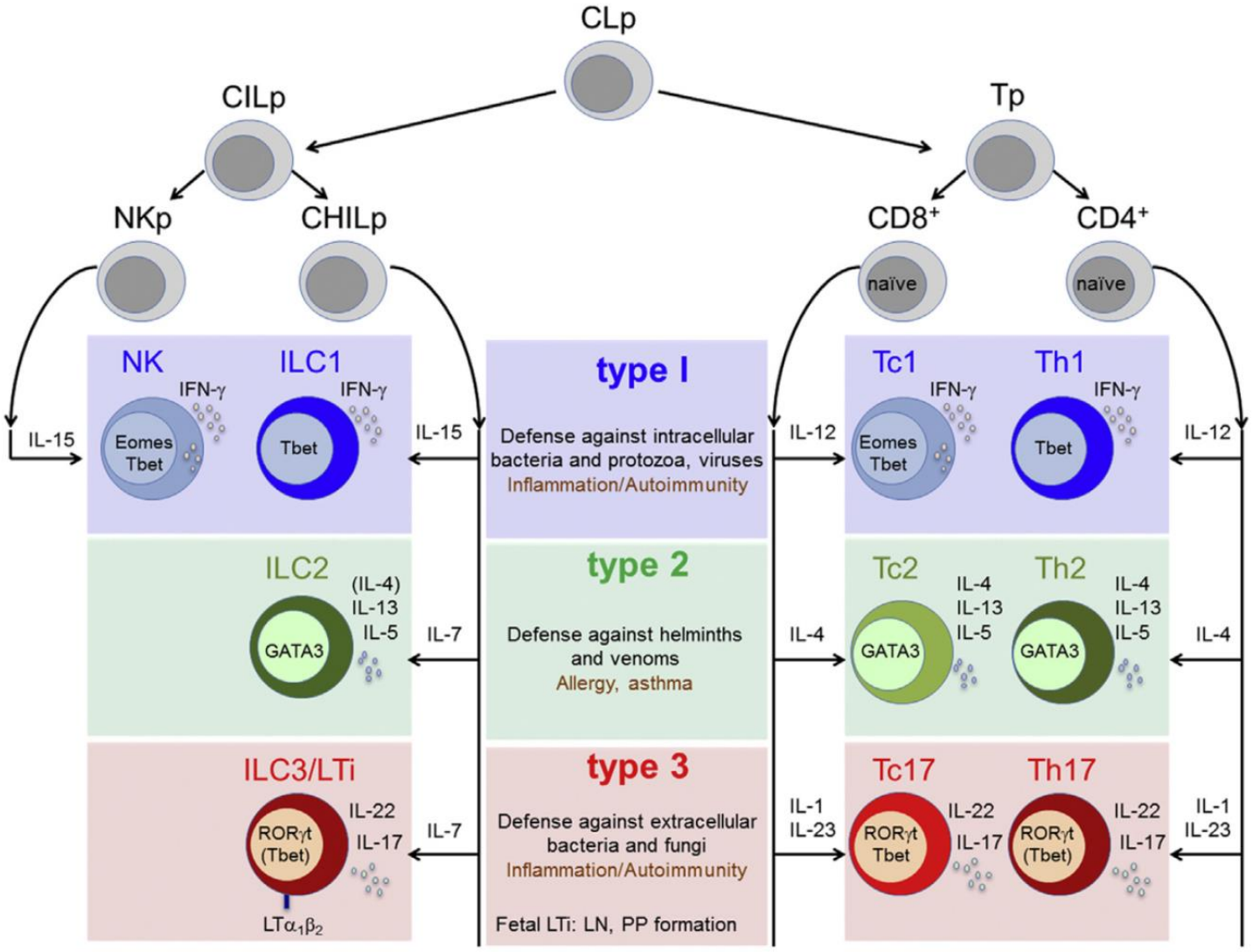
Key words: *Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22*

Abbreviations used

APC:	Antigen-presenting cell
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T_H2 cells
DC:	Dendritic cell
Eomes:	Eomesodermin
IBD:	Inflammatory bowel disease
IL-7R:	IL-7 receptor
ILC:	Innate lymphoid cell
LT:	Lymphotoxin
MP:	Mononuclear phagocyte
MS:	Multiple sclerosis
NK:	Natural killer
NKp:	Natural killer progenitor
PB:	Peripheral blood
RA:	Rheumatoid arthritis
ROR:	Retinoic acid–related orphan receptor
STAT:	Signal transducer and activator of transcription
T_C:	Cytotoxic T
TSLP:	Thymic stromal lymphopoietin

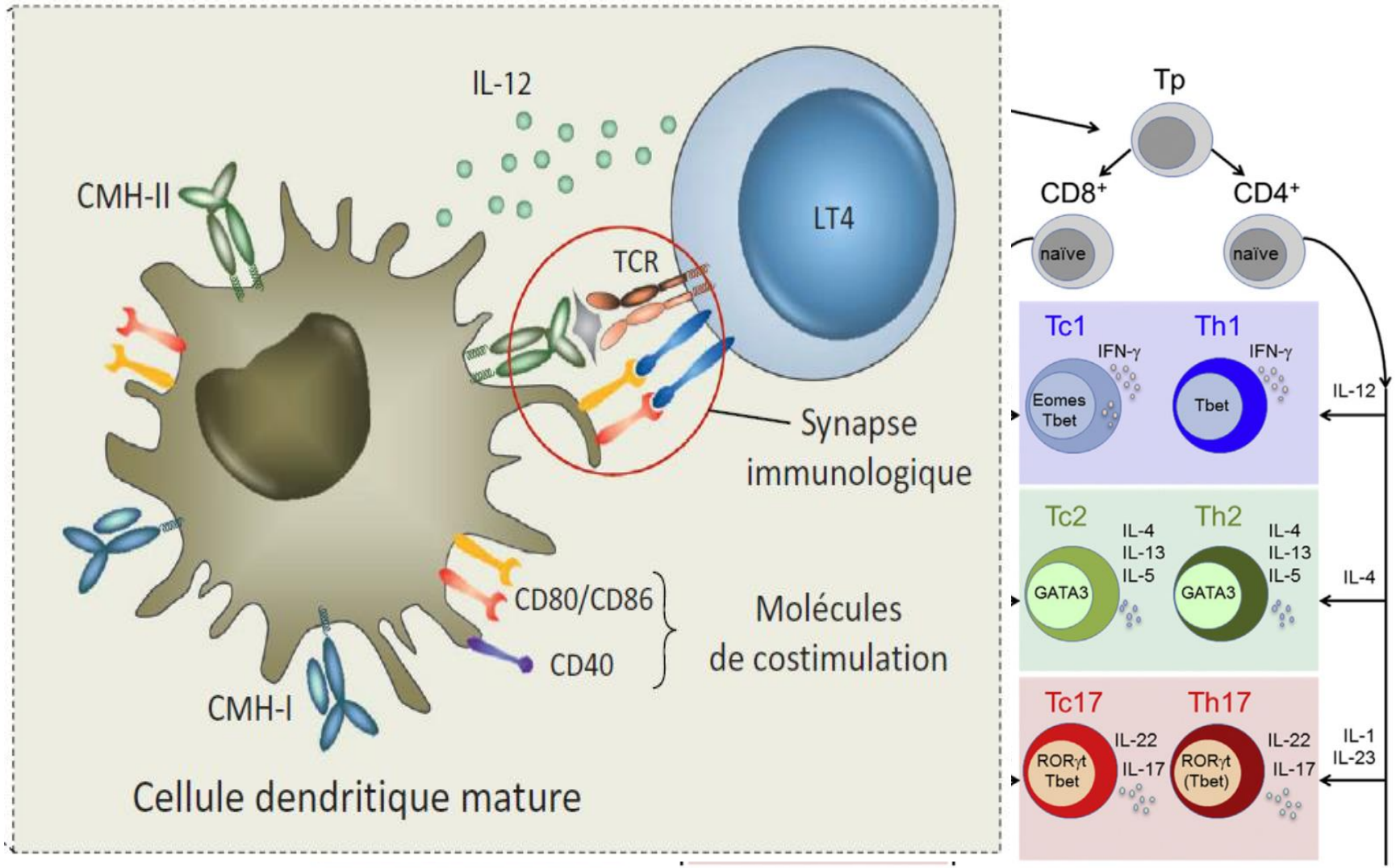
whereas T_H2 cells produce IL-4, IL-5, and IL-13.[3] Subsequently, a similar dichotomy within the CD8$^+$ cytotoxic T (T_C) cell population was discovered in both mice and human subjects, and the 2 subsets were named T_C1 and T_C2,

The 3 major types of innate and adaptative cell-mediated immunitv



Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

The 3 major types of innate and adaptative cell-mediated immunity



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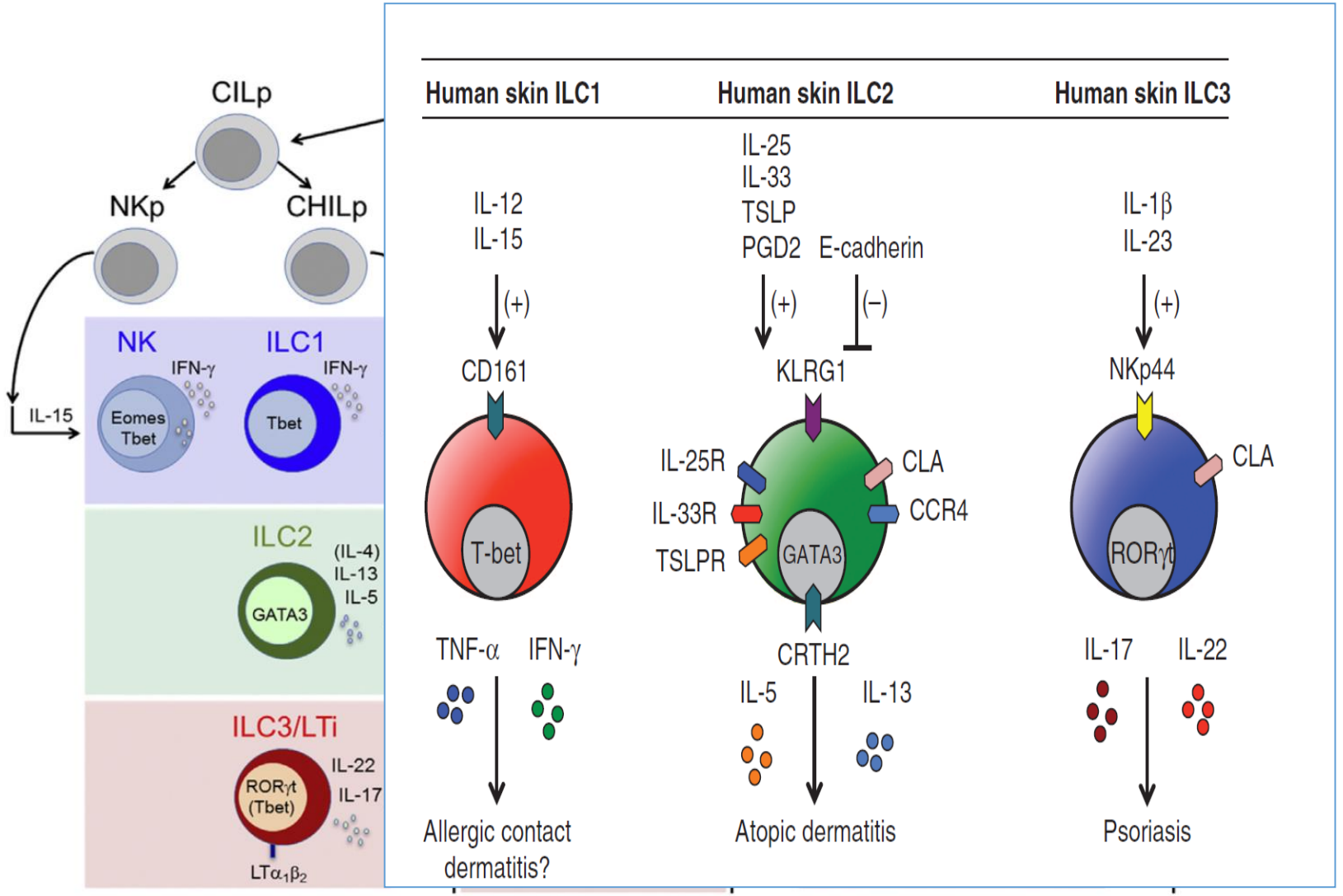
The 3 major types of innate and adaptative cell-mediated immunity



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Type 2 Immunity

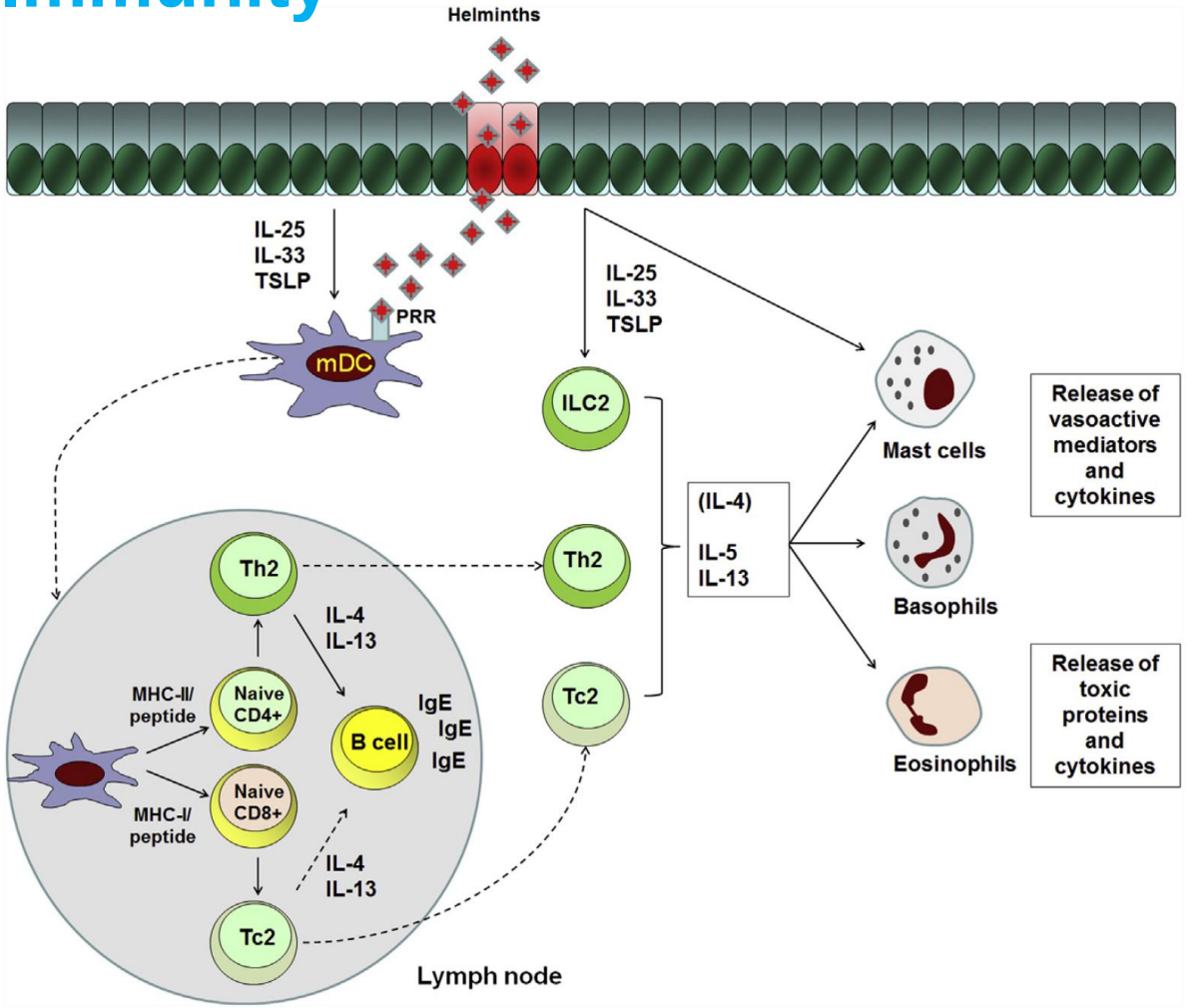
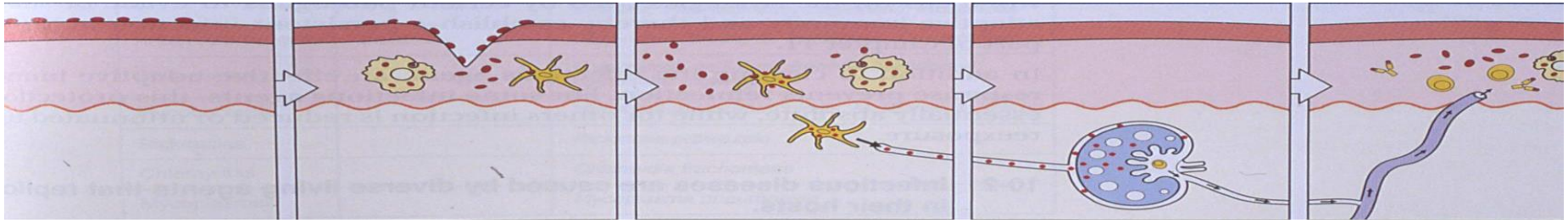
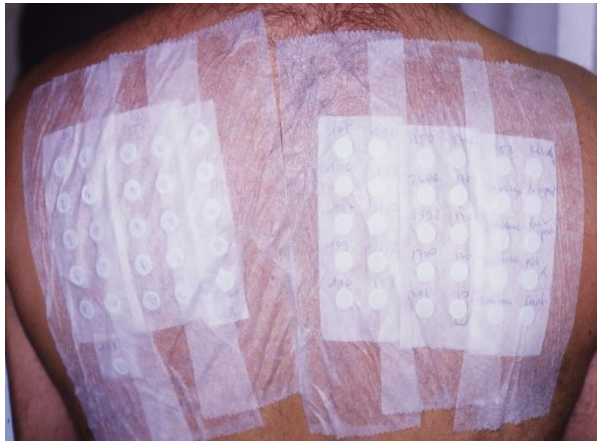


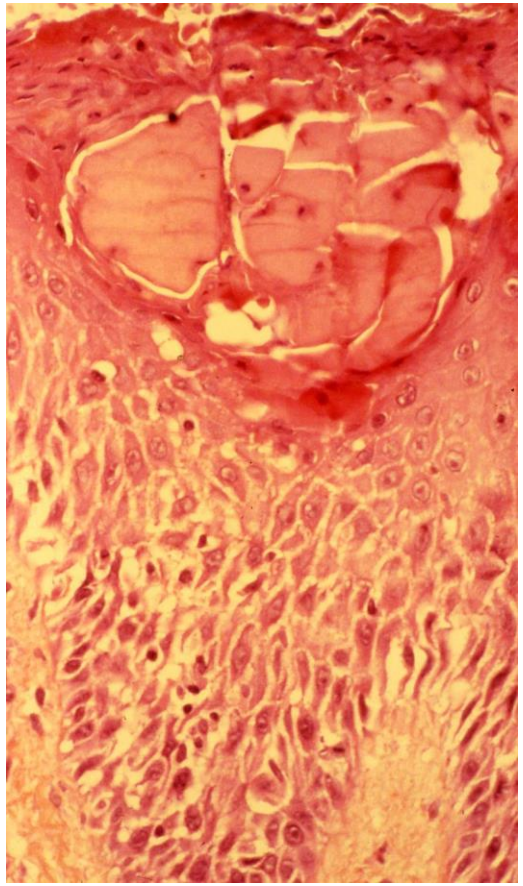
FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin *(TSLP)* release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated DCs in the presence of IL-4 induce naive T cells to develop into T_H2 and T_C2 cells producing IL-4, IL-5, and IL-13. IL-4 and IL-13 allow IgE production by B lymphocytes, whereas IL-5 promotes eosinophil recruitment. *mDC*, Myeloid dendritic cell; *PRR*, pathogen recognition receptors.

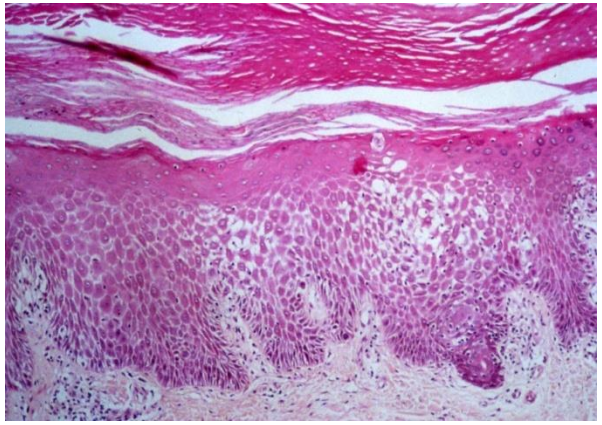
Hypersensibilité de type IV (HS retardée) due à des LT1
ECZEMA DE CONTACT

Th1
Type 1









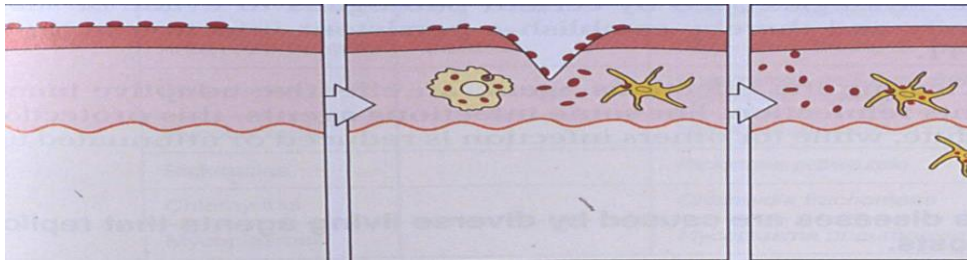
Skin tests represent experimental models of allergic type IV DTH reactions

Hypersensibilité de type IV (HS retardée) due à des LT1
EXANTHEMES MEDICAMENTEUX

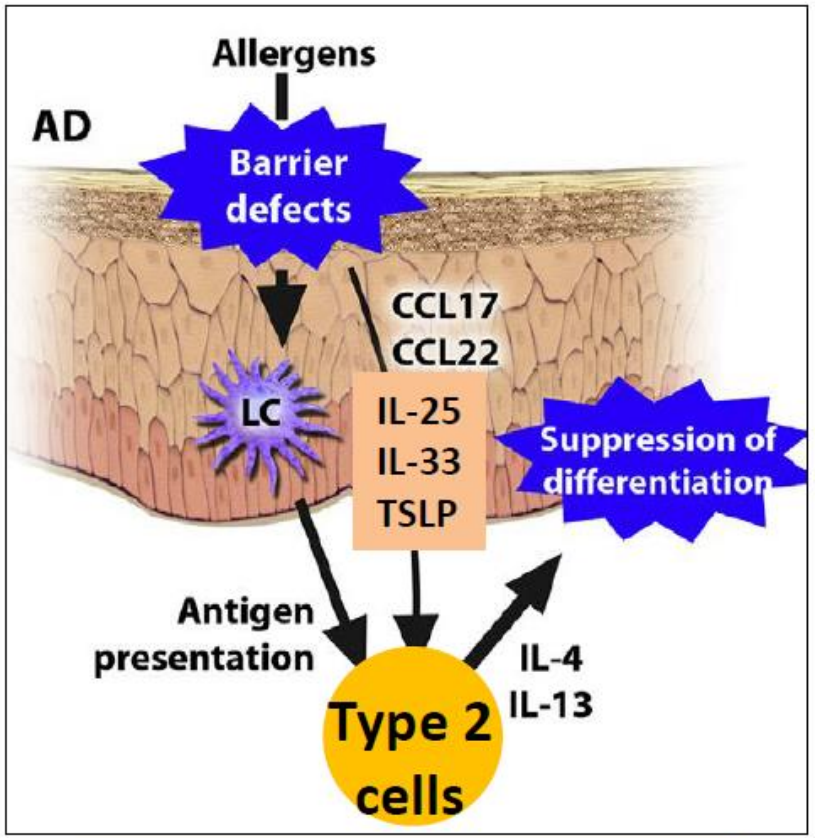
Th1
Type 1

Hypersensibilité de type IV (HS retardée) due à des LT2
DERMATITE ATOPIQUE

Th2
Type 2



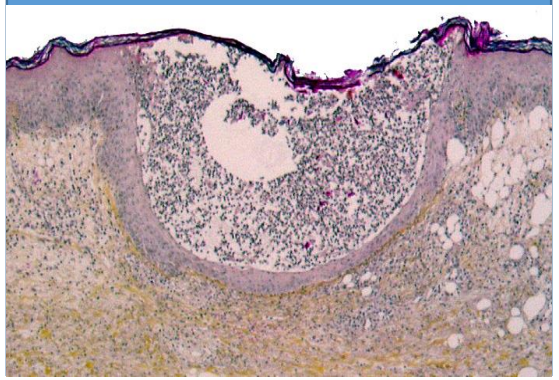
Type 2 phenotype



Type 2 inflammation
Type 2 immunity

Hypersensibilité de type IV (HS retardée) due à des LT 17
PEAG pustulose exanthématique aigue généralisée

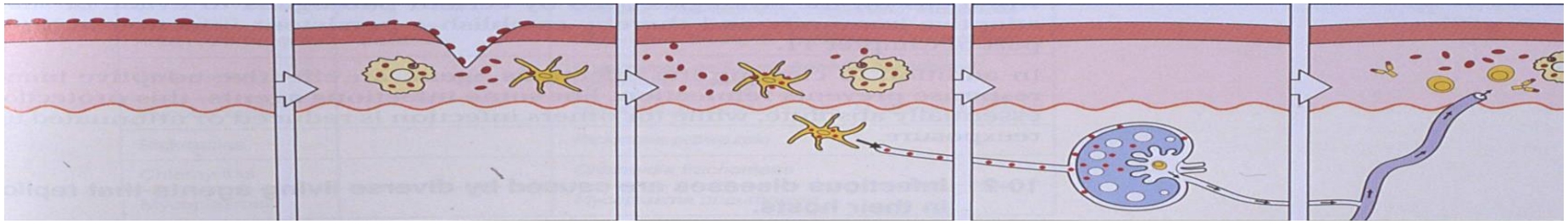
Th17
Type 17

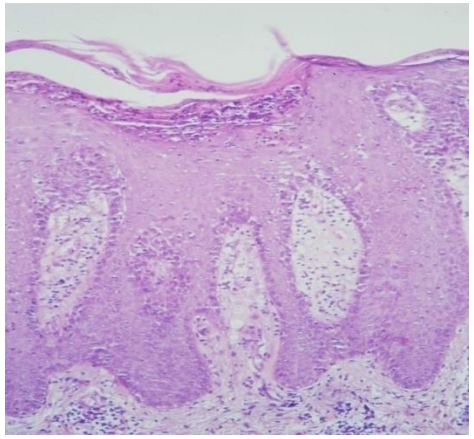


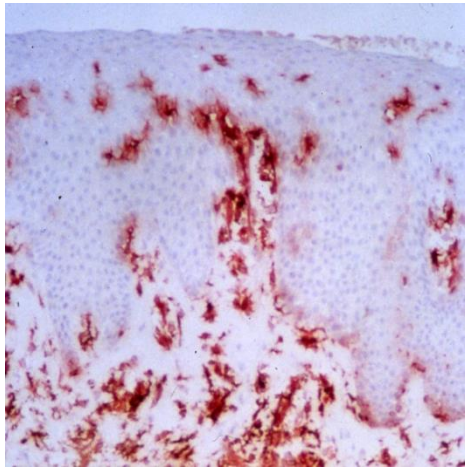
- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre,
  - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
  - Hyperleucocytose à PNN ou PNE,
  - Hypocalcémie
- **Atteinte viscérale:** foie, rein
- **Histologie:** pustules intraépidermiques ou sous cornées
- **Médicaments :** pénicillines, macrolides, carbamazépine, inhibiteurs calciques, terbinafine
- **Guérison** rapide (7 jours)
- **Mortalité:** 5%

Hypersensibilité de type IV (HS retardée) due à des LT 17
PSORIASIS

Th17
Type 17



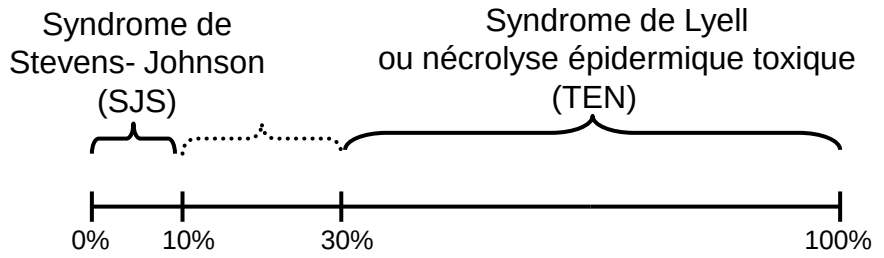




Hypersensibilité de type IV (HS retardée) due à des LT cytotoxiques

Nécrolyse épidermique toxique – Sd de Stevens-Johnson – Sd de Lyell

Tc1
Type 1



- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie fréquente
- **Atteinte viscérale:** rénale, pulmonaire, digestive, foie
- **Histologie:** nécrolyse épidermique totale
- **Médicaments: allopurinol+++,** lamotrigine, carbamazépine, sulfamethoxazole, AINS (oxicams), nevirapine,…
- **Mortalité:** 30-35% (estimée par le SCORTEN)

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department