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

Maladies autoimmunes
Maladies allergiques
Maladies inflammatoires chroniques

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department

Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- Généralités sur les Maladies Allergiques
- Hypersensibilités allergiques et non allergiques
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (**mastocyte**); type IV (**lymphocytes**)
- Classification de Gell & Coombs
  - Type I
  - Type II
  - Type III
  - Type IV

Physiopathologie de l’allergie

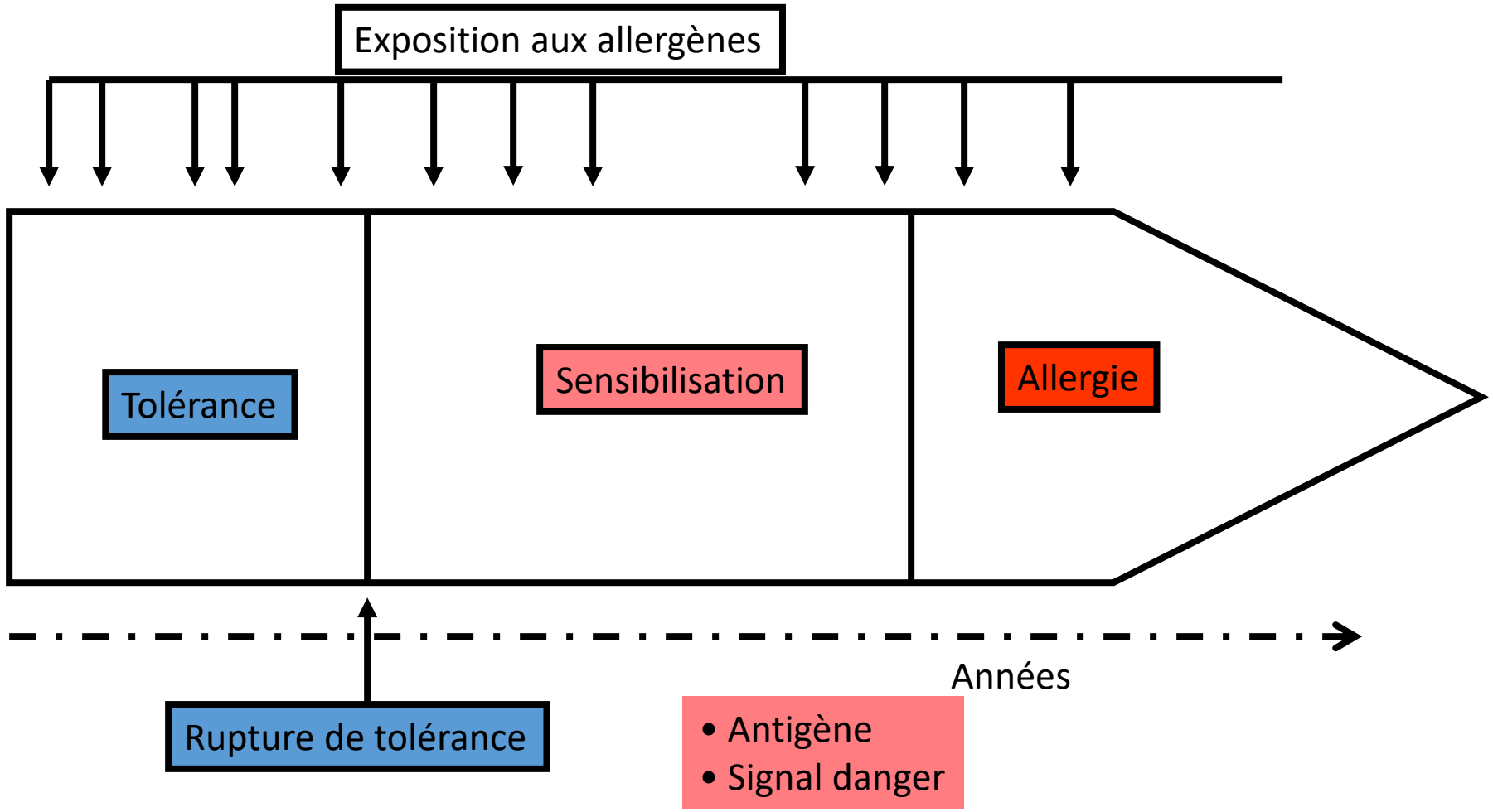
- La mise en place d’une maladie allergique obéit aux mêmes règles que la mise en place d’une réponse immunitaire vis à vis d’agents infectieux
- La physiopathologie des maladies allergiques est donc similaire à celle de la réponse anti-infectieuse

Allergie: rupture de tolérance

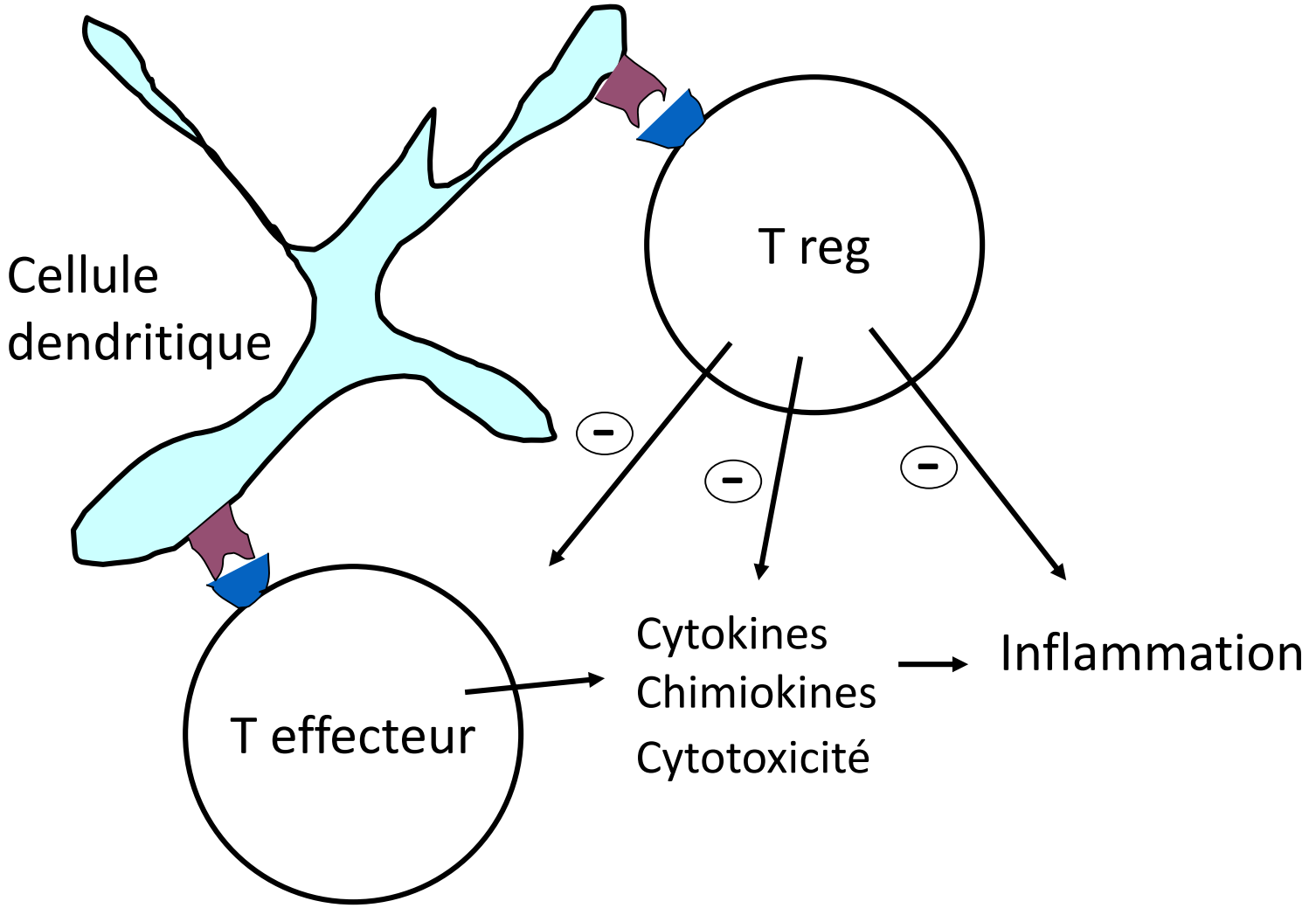
- Nous sommes tous en contact avec notre environnement
- Nous sommes tous sensibilisés vis à vis des antigènes de l'environnement
- Les sujets non allergiques développent une réponse immune tolérogène (régulatrice)
- Les sujets allergiques développent une réponse effectrice

ALLERGIE

Rupture de tolérance aux molécules de l'environnement



Allergie
Sensibilisation versus tolérance



Maladies allergiques

et
et
- *allergène naturel*
- *voie naturelle de contact*
- *sujet génétiquement prédisposé (ATCD familiaux)*

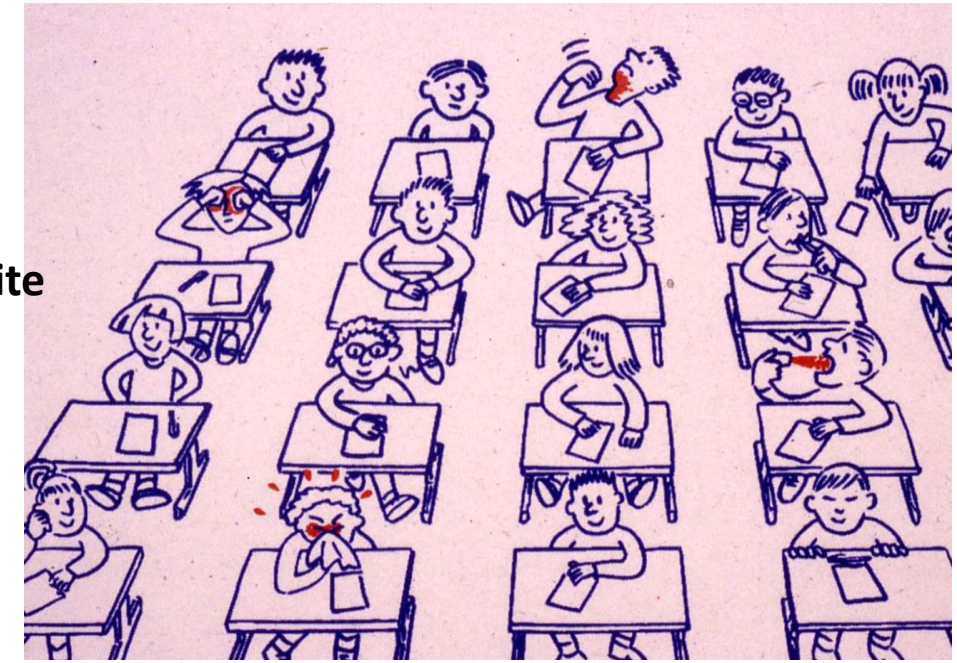
et/ou
et/ou
- *allergène chimique*
- *voie non naturelle de contact*
- *sujet non génétiquement prédisposé (ATCD familiaux)*

Allergènes

- Pneumallergènes
- Trophallergènes
- Injectables
- Contact cutané

maladie atopique

- **asthme**
- **rhinite**
- **conjonctivite**
- **eczéma**
- **aliments**
- **urticaire**



maladie non atopique

Venins guêpe
Médicaments
- **choc anaphylactique**
- **œdème de Quincke**

Allergènes cutanés
- **eczéma contact**

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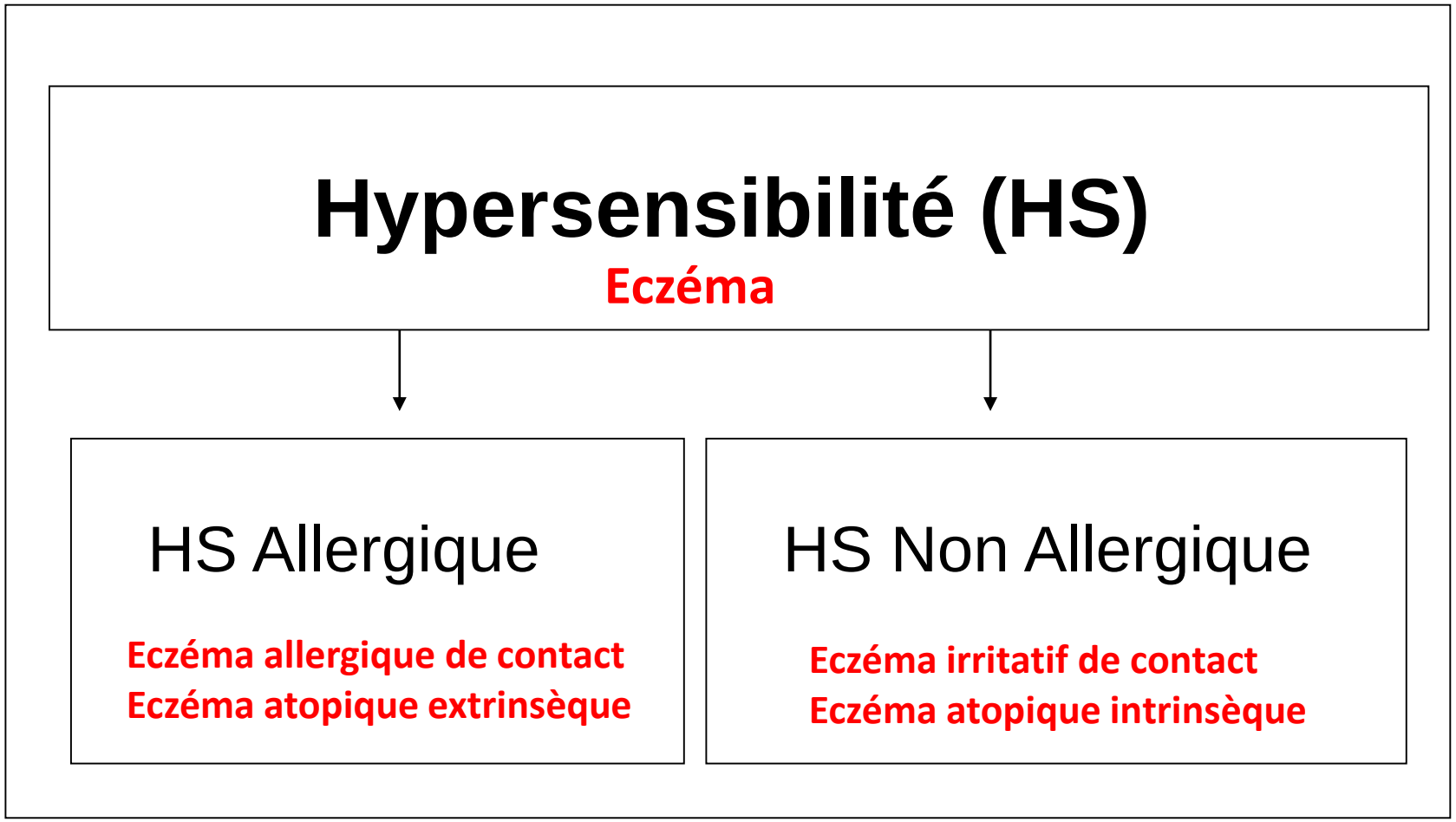
Terminologie

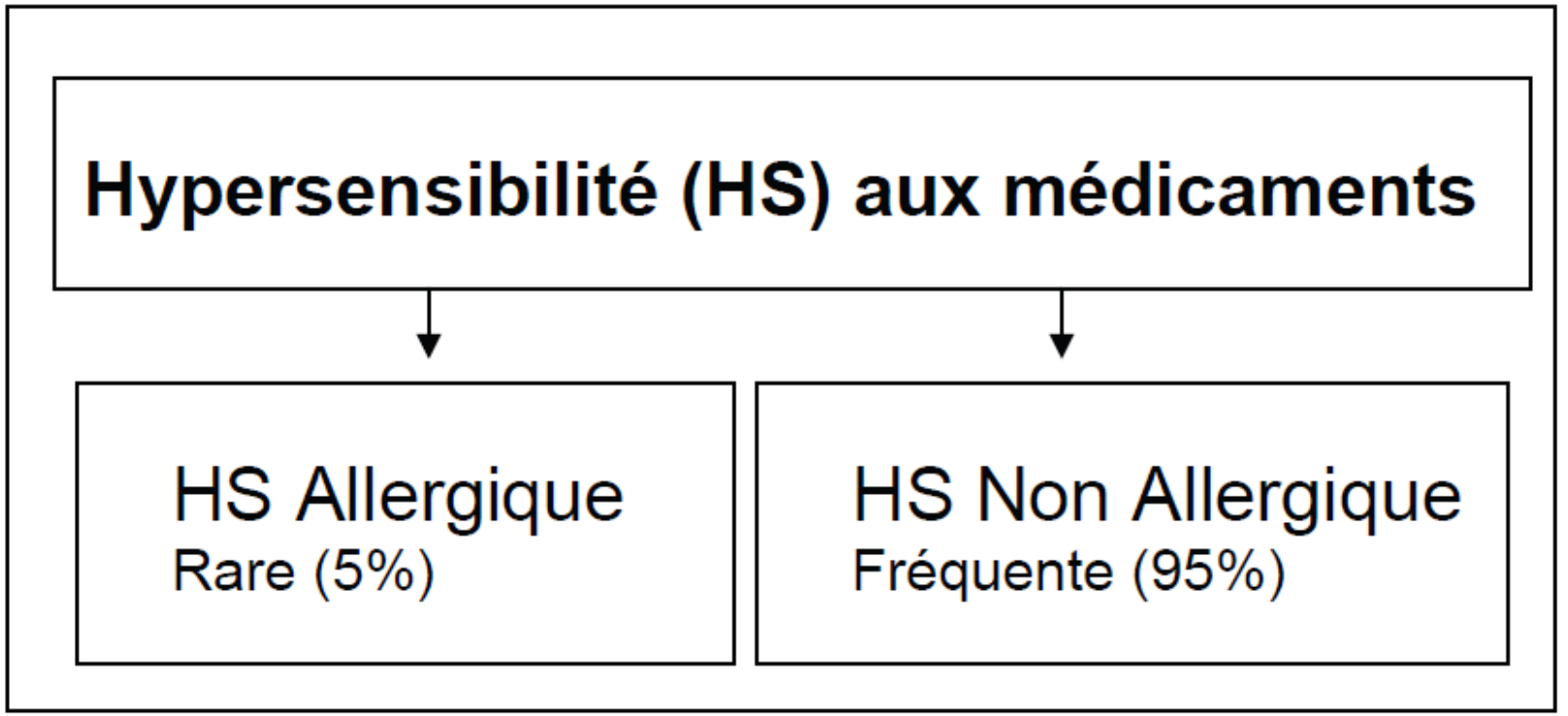
- **Allergie**
- **Hypersensibilité**
  - HS allergique
  - HS non allergique

Terminologie

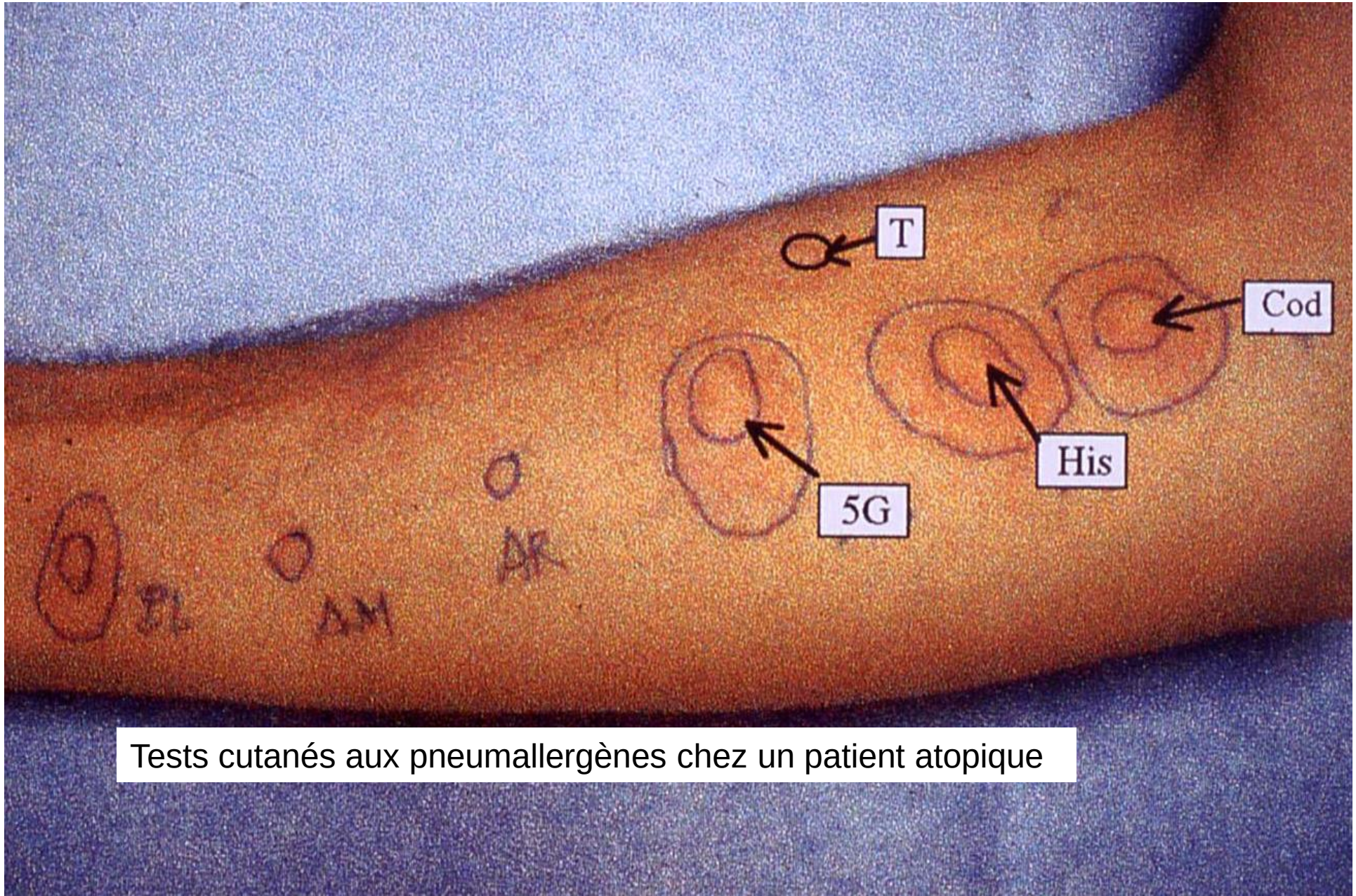
- Allergie (gell et coombs: immunité adaptative; immunité spécifique)
  - Type I:IgE
  - Type II: IgG
  - Type III:CIC
  - Type IV: lymphocytes T
- Hypersensibilité (immunité innée et adaptative)
  - HS allergique = Allergie
  - HS non allergique (immunité innée)

  (intolérance, pseudo-allergie, anaphylactoide, fausse allergie)
    - **HS immédiate: MASTOCYTES**
    - **HS retardée: LYMPHOCYTES**


Hypersensibilité (HS)
Eczéma
HS Allergique
Eczéma allergique de contact
Eczéma atopique extrinsèque
HS Non Allergique
Eczéma irritatif de contact
Eczéma atopique intrinsèque


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

HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

[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, après avoir passé un gel "erythrogel" 4 % sur ses boutons d'acné. Le 23 Mars dernier, il

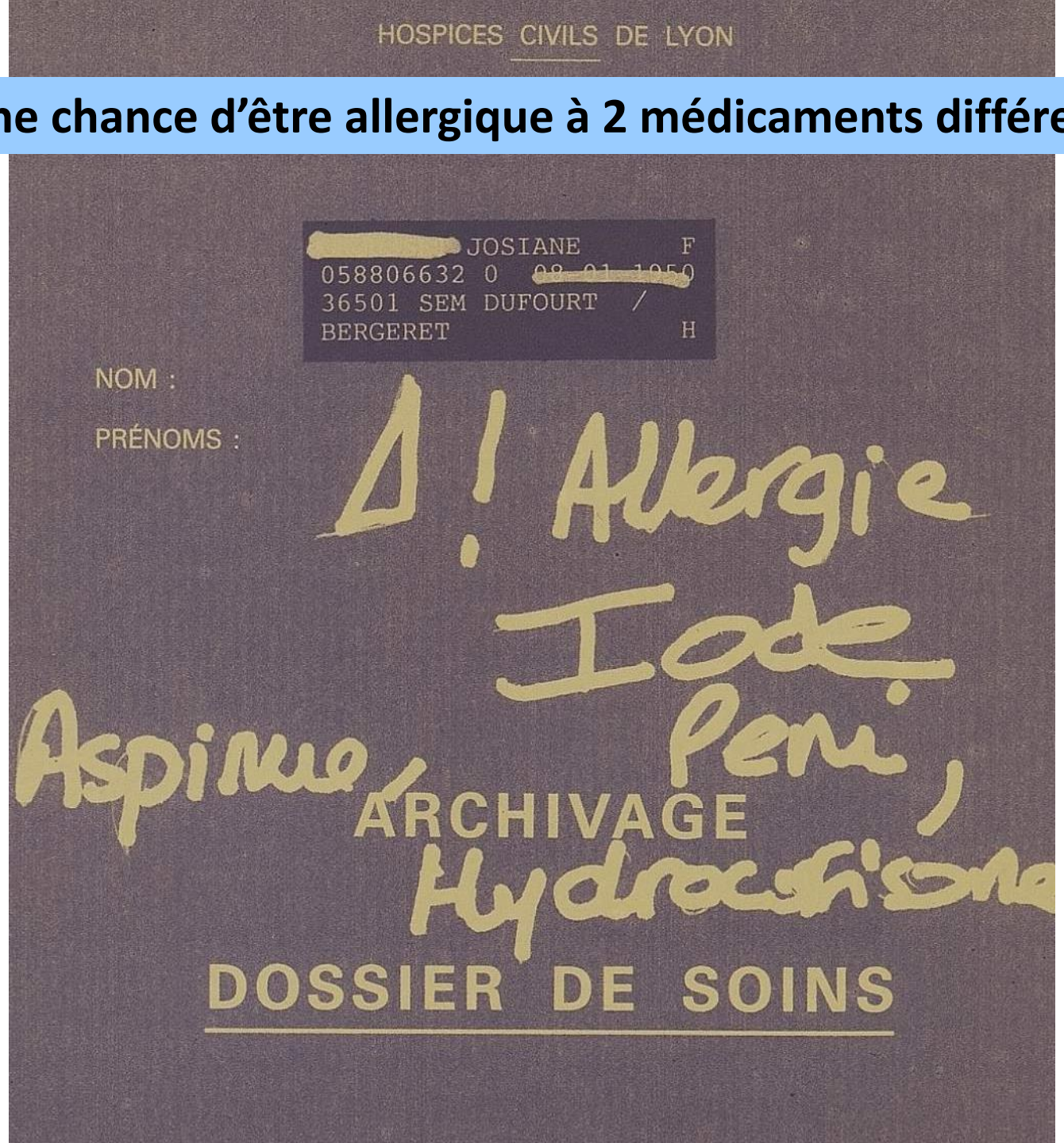
Quand on est allergique à tout, on est allergique à rien

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-

Aucune chance d'être allergique à 2 médicaments différents



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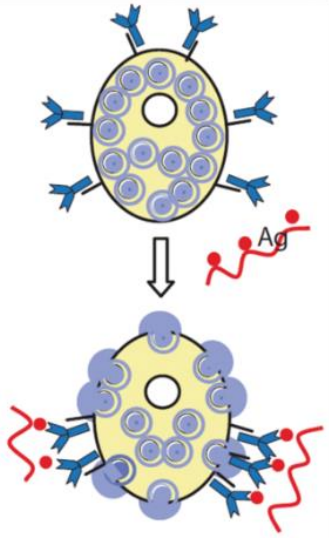
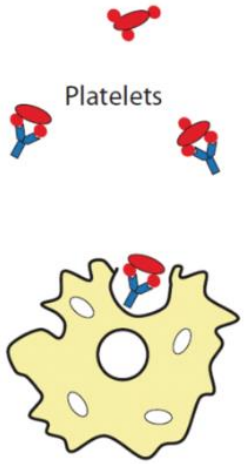
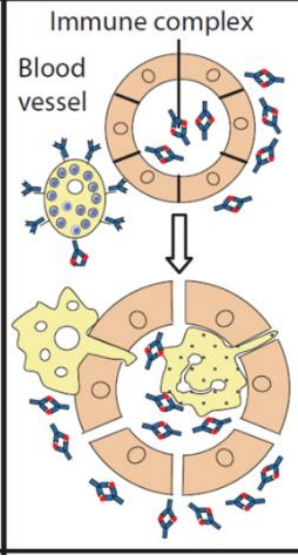
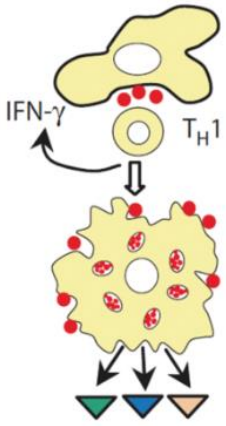
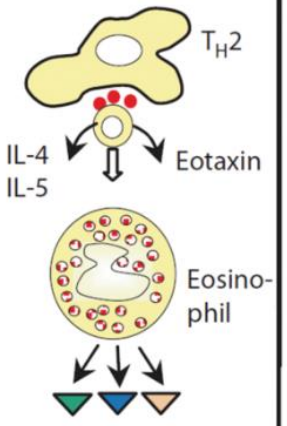
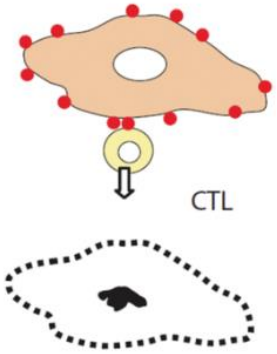
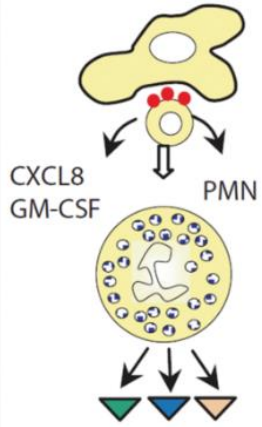
Hypersensibilités

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 3**
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
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

Hypersensibilités

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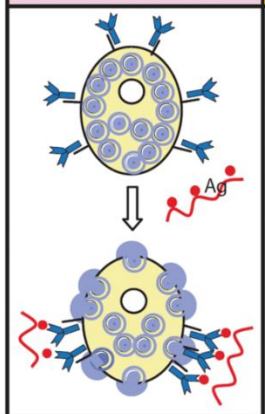
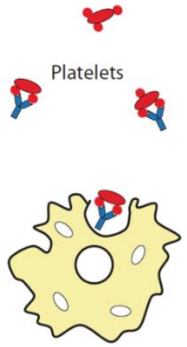
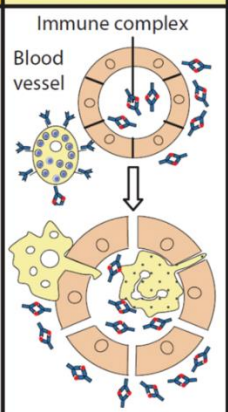
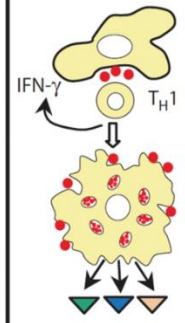
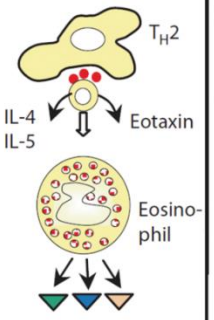
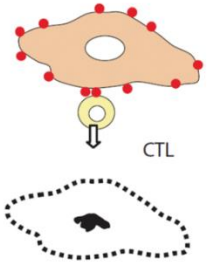
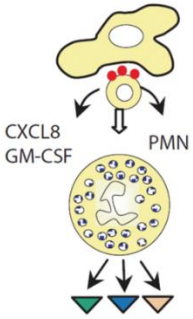
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
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Dermatoses autoimmunes et allergiques	**Urticaire contact**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Psoriasis**	**Dermatite atopique**	**Vitiligo Pelade Eczéma contact**	**Psoriasis**
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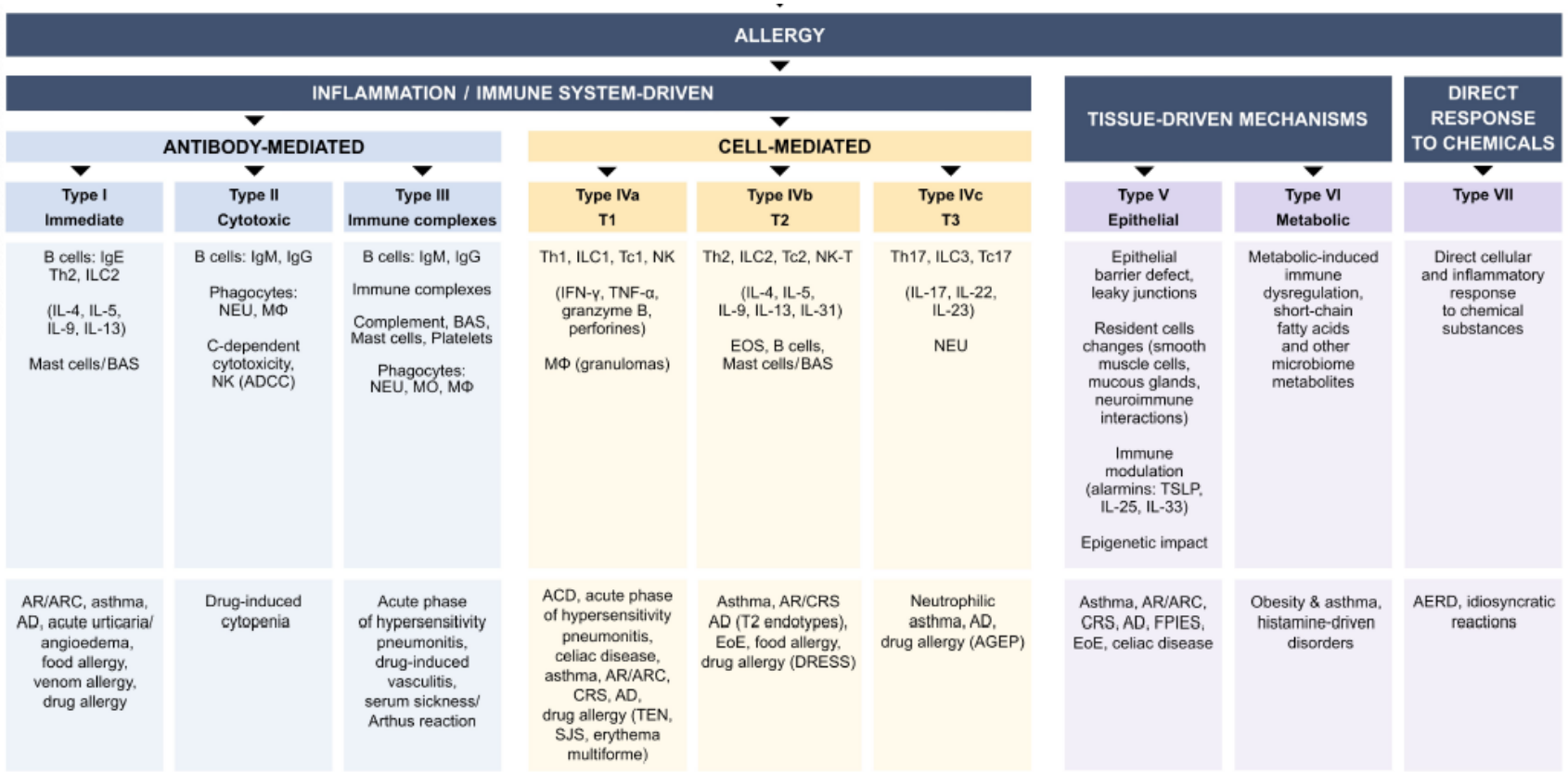
Nouvelle classification 2023

Joutel M. et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy 2023



ACD, allergic contact dermatitis; AD,atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; AR, allergic rhinitis;ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilicoesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; IFN-γ, interferon-gamma; Ig (E, G, M), immunoglobulin (type E, G, M); IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MO, monocyte; Mφ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Th, T helper lymphocytes; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha.

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Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

EAACI POSITION PAPER

Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper

Marek Jutel[1,2] | Ioana Agache[3] | Magdalena Zemelka-Wiacek[1] | Mübeccel Akdis[4] | Tomás Chivato[5] | Stefano del Giacco[6,7] | Pawel Gajdanowicz[1] | Ibon Eguiluz Gracia[8] | Ludger Klimek[9,10] | Antti Lauerma[11] | Markus Ollert[12,13] | Liam O'Mahony[14] | Jürgen Schwarze[15] | Mohamed H. Shamji[16,17] | Isabel Skypala[18,19] | Oscar Palomares[20] | Oliver Pfaar[21] | Maria Jose Torres[8] | Jonathan A. Bernstein[22] | Alvaro A. Cruz[23] | Stephen R. Durham[24] | Stephen J. Galli[25] | R. Maximiliano Gómez[26] | Emma Guttman-Yassky[27] | Tari Haahtela[28] | Stephen T. Holgate[29] | Kenji Izuhara[30] | Kenji Kabashima[31] | Désirée E. Larenas-Linnemann[32] | Erica von Mutius[33,34,35] | Kari C. Nadeau[36] | Ruby Pawankar[37] | Tomas A. E. Platts-Mills[38] | Scott H. Sicherer[39] | Hae-Sim Park[40] | Stefan Vieths[41] | Gary Wong[42] | Luo Zhang[43,44] | M. Beatrice Bilò[45] | Cezmi A. Akdis[4]

Hypersensibilités

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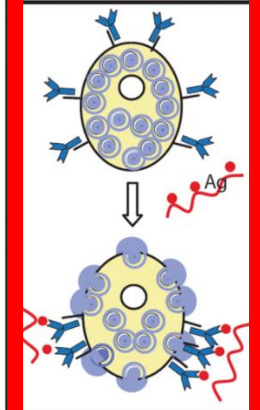
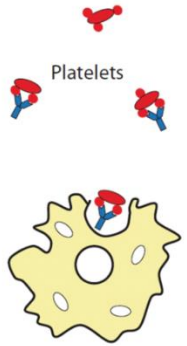
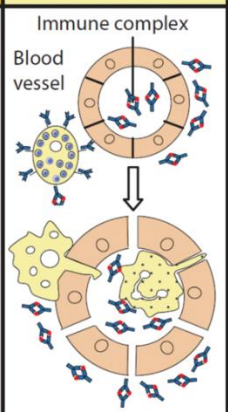
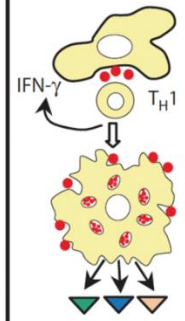
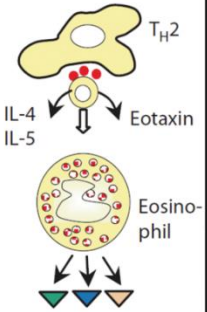
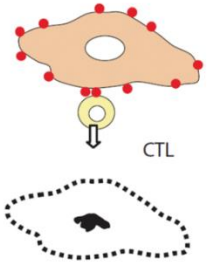
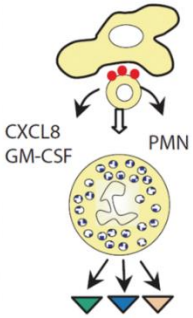
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
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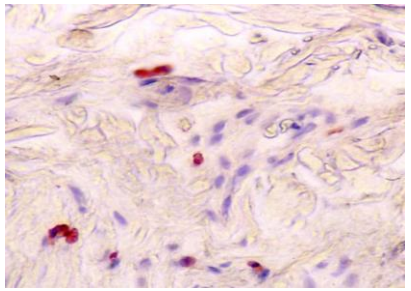
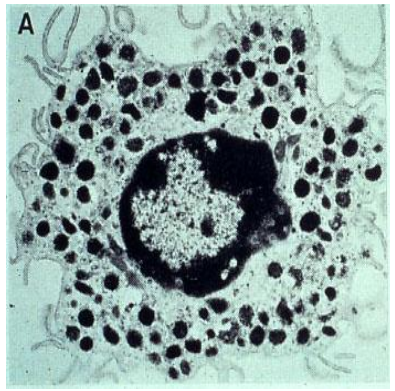
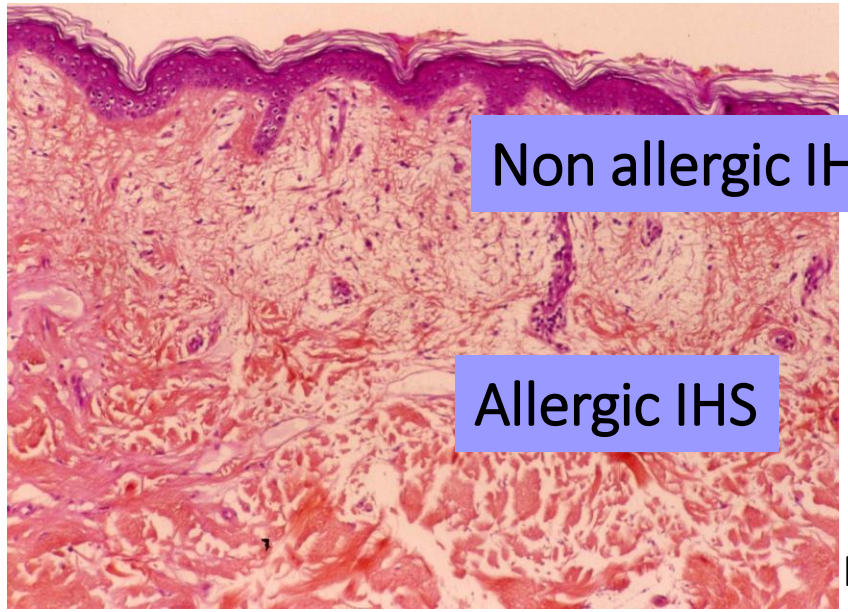
TYPE I HYPERSENSITIVITY

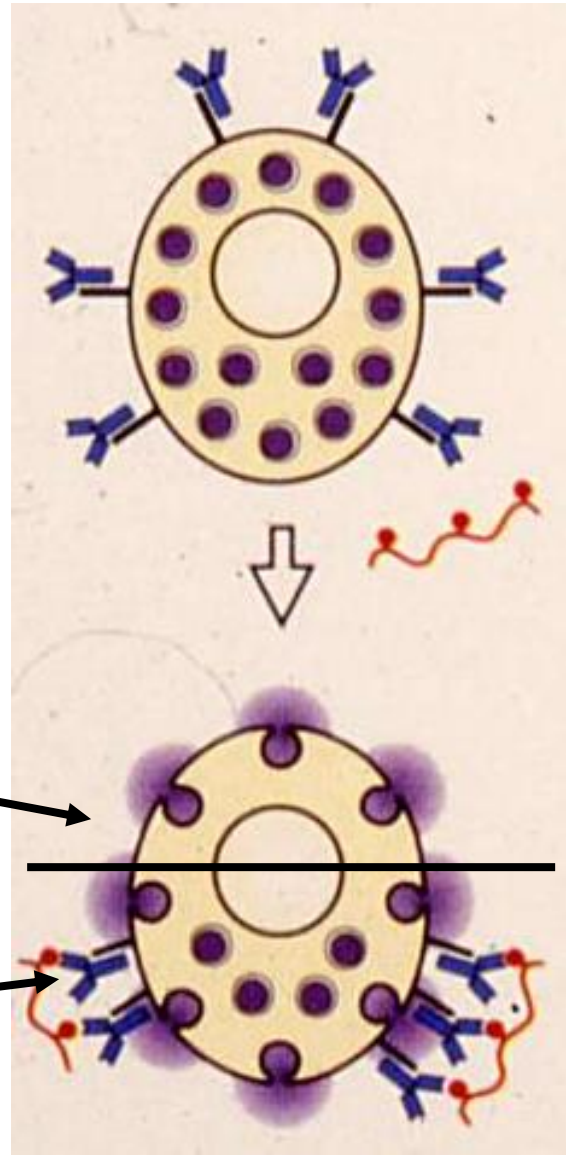
Œdème du derme / Vaisseaux





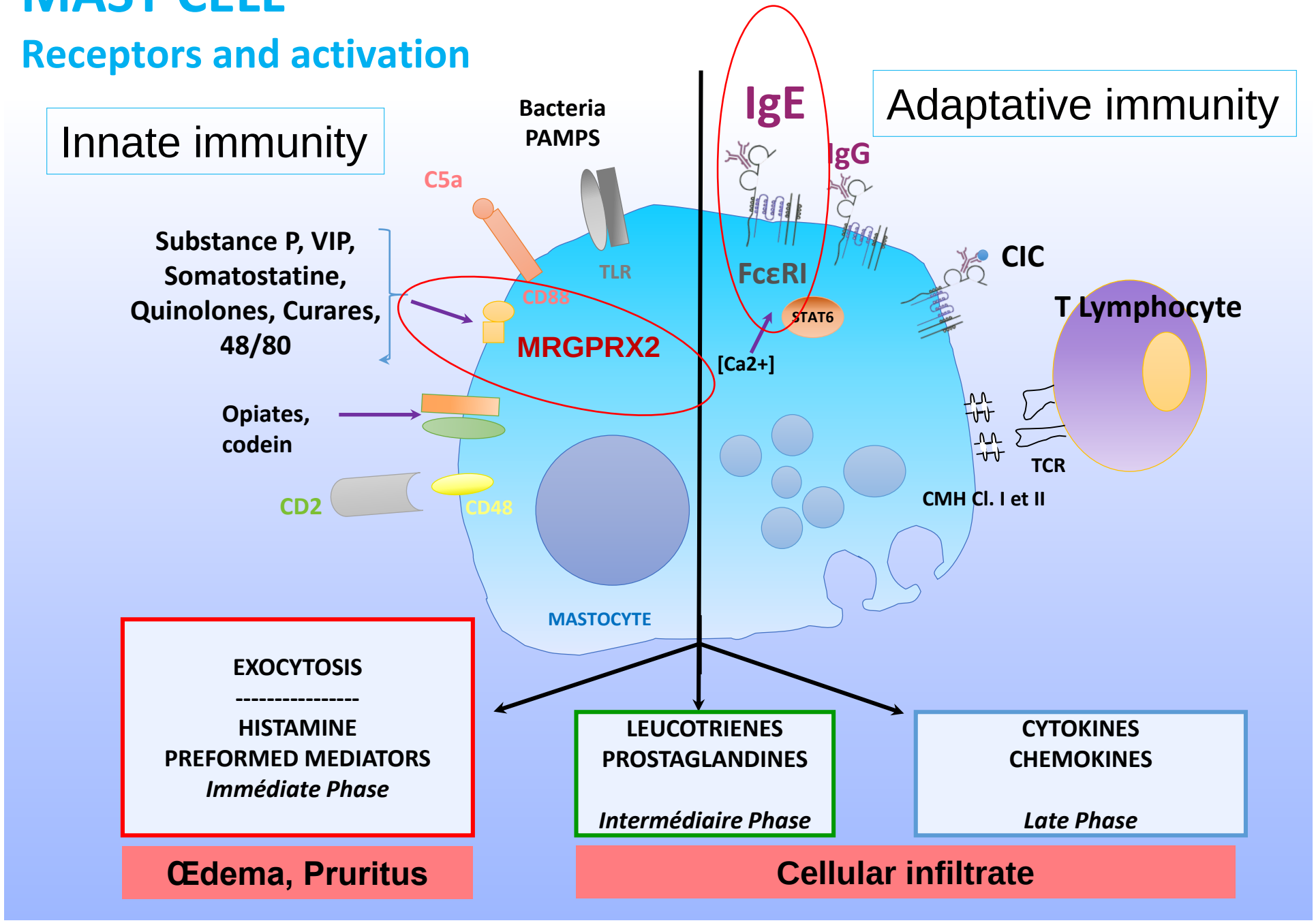


Mastocytes / Histamine



MAST CELL

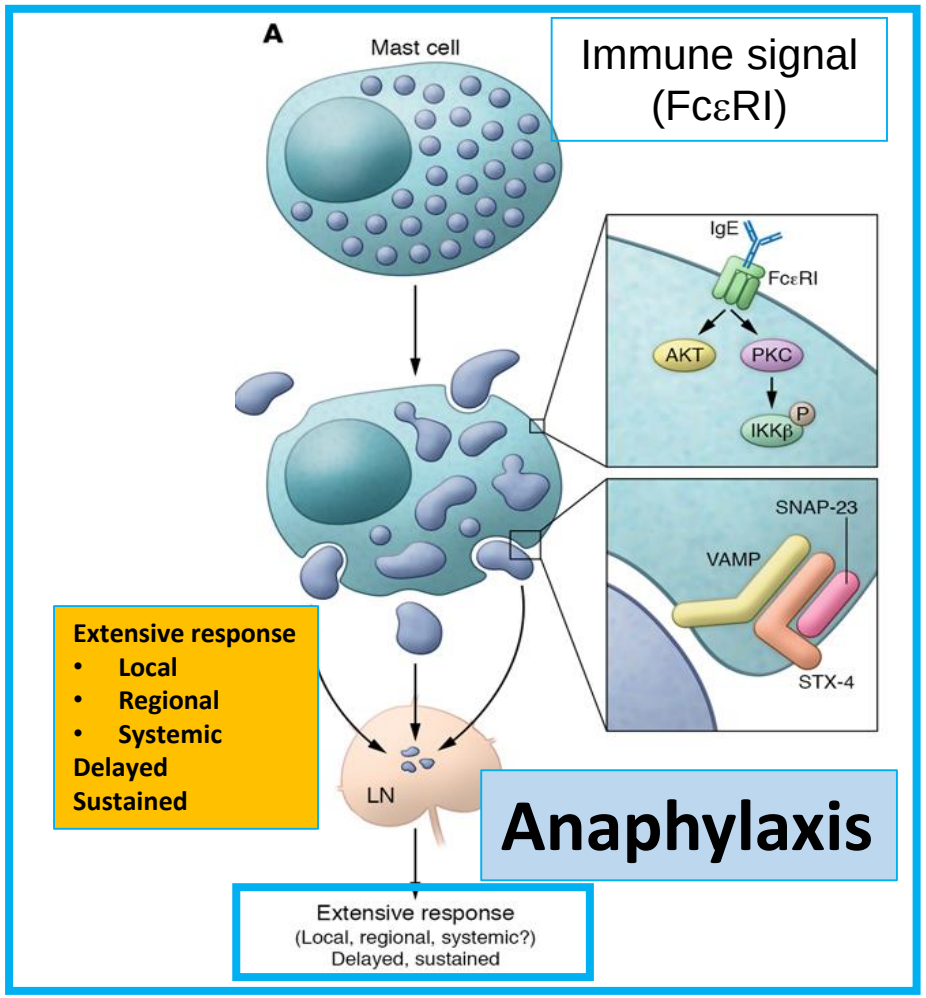
Receptors and activation

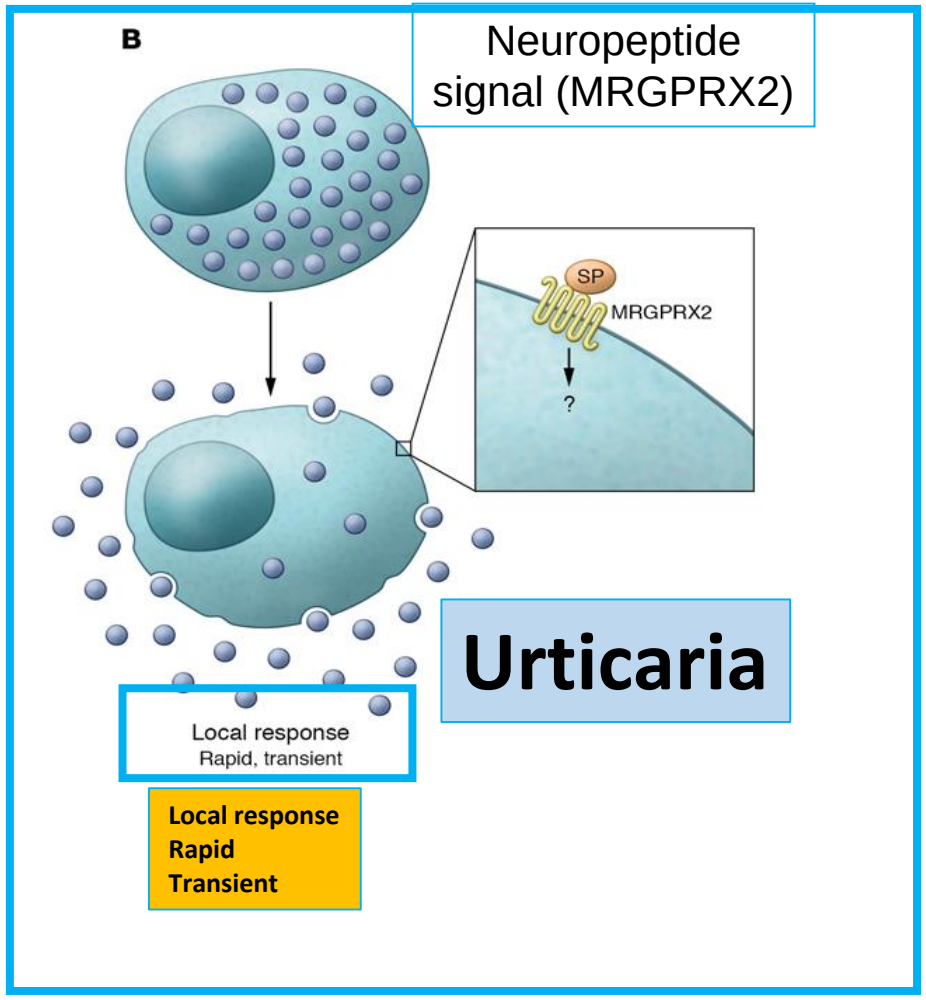


Two fundamental degranulation pathways in mast cells

IgE/FceRI

Other receptor





Gaudenzio et al. ***J Clin Invest*** *2016*

Drug-induced urticaria and angioedema

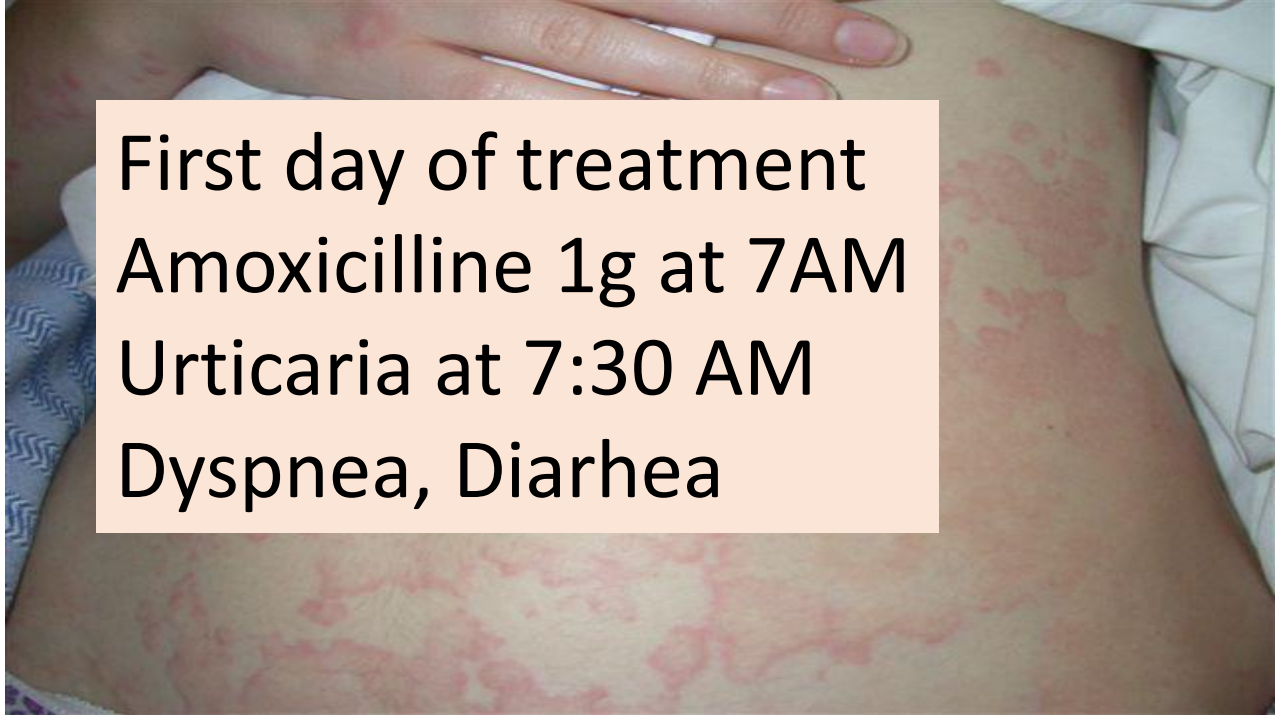
- **Allergic (IgE)**: rares (5%) and exceptionally isolated

- **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

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**	CXCL8, **Th17/Type 3** (T cells)
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	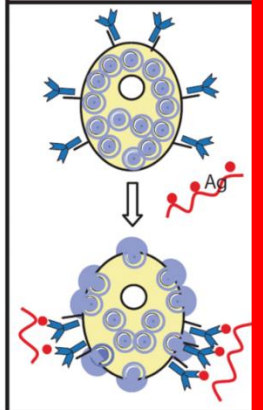	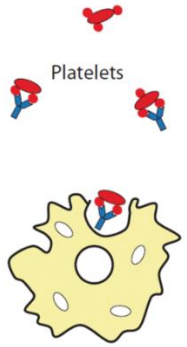	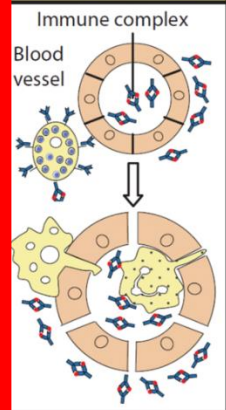	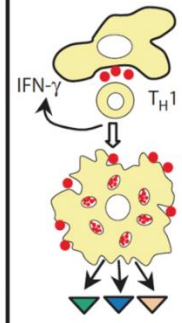	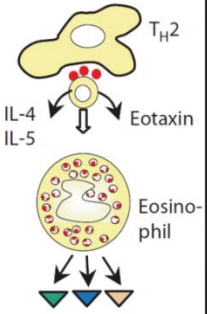	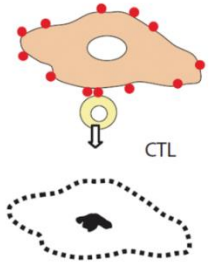	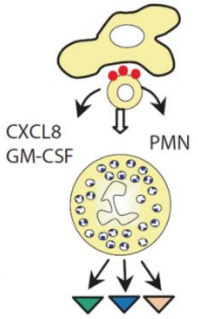
Maladies autoimmunes et allergiques	**Anaphylaxie Rhinite allergique Asthme (crise)**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme chron. Rhinite chron.**	**Rejet de greffe Diabète SEP**	**Polyarthrite Sclérose en plaque Mal. de Crohn**
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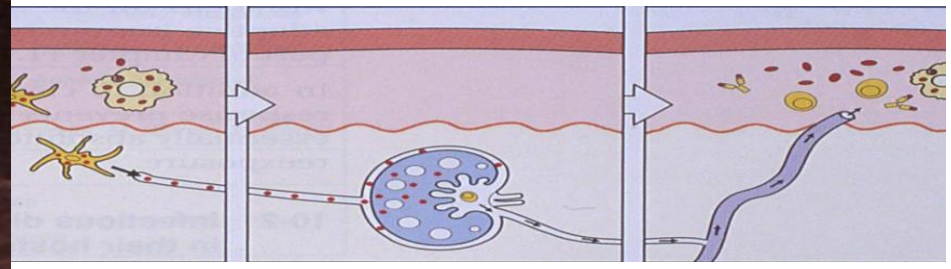
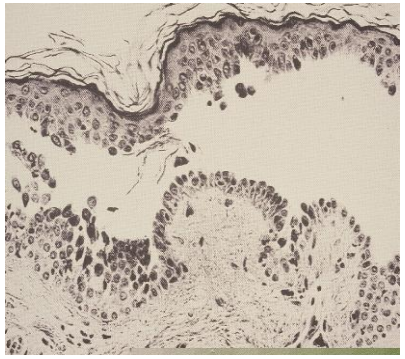
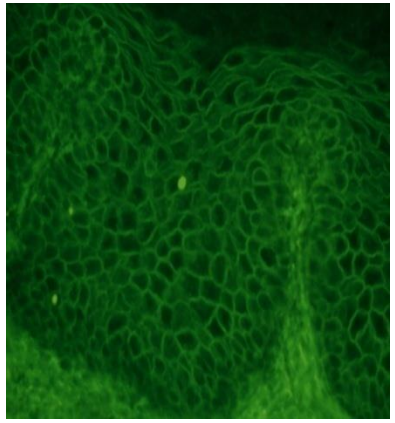
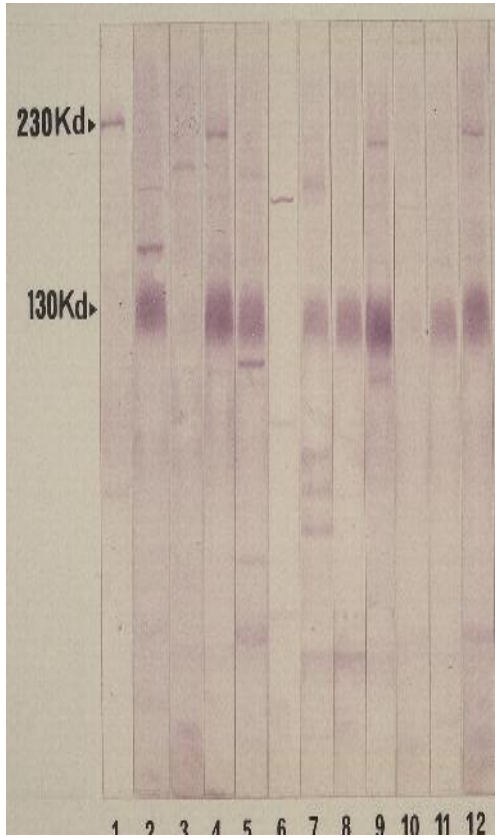
Allergies médicaments	**Choc anaphylactique**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème médic.**	**DRESS**	**Lyell Stevens-Johnson**	**Pustulose exanthématique aigue généralisée**

Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS









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**	CXCL8, **Th17/Type 3** (T cells)
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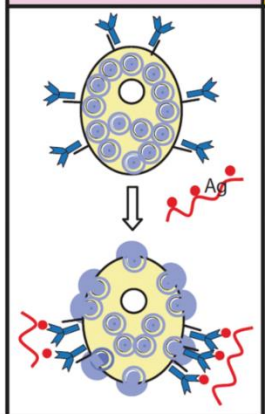
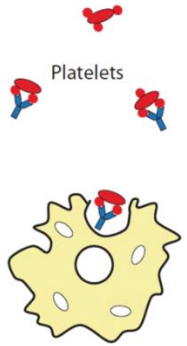
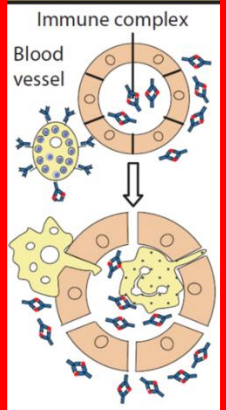
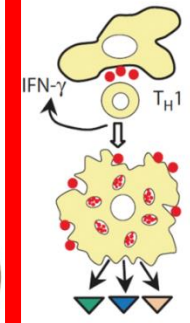
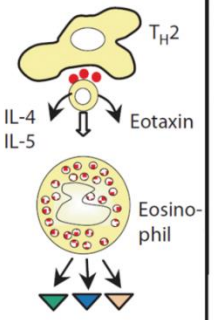
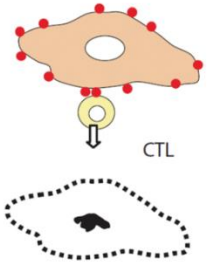
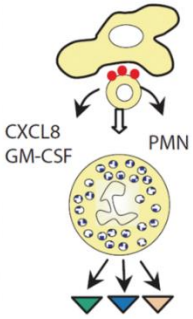
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Maladies autoimmunes et allergiques	**Anaphylaxie Rhinite allergique Asthme (crise)**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine 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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Fig

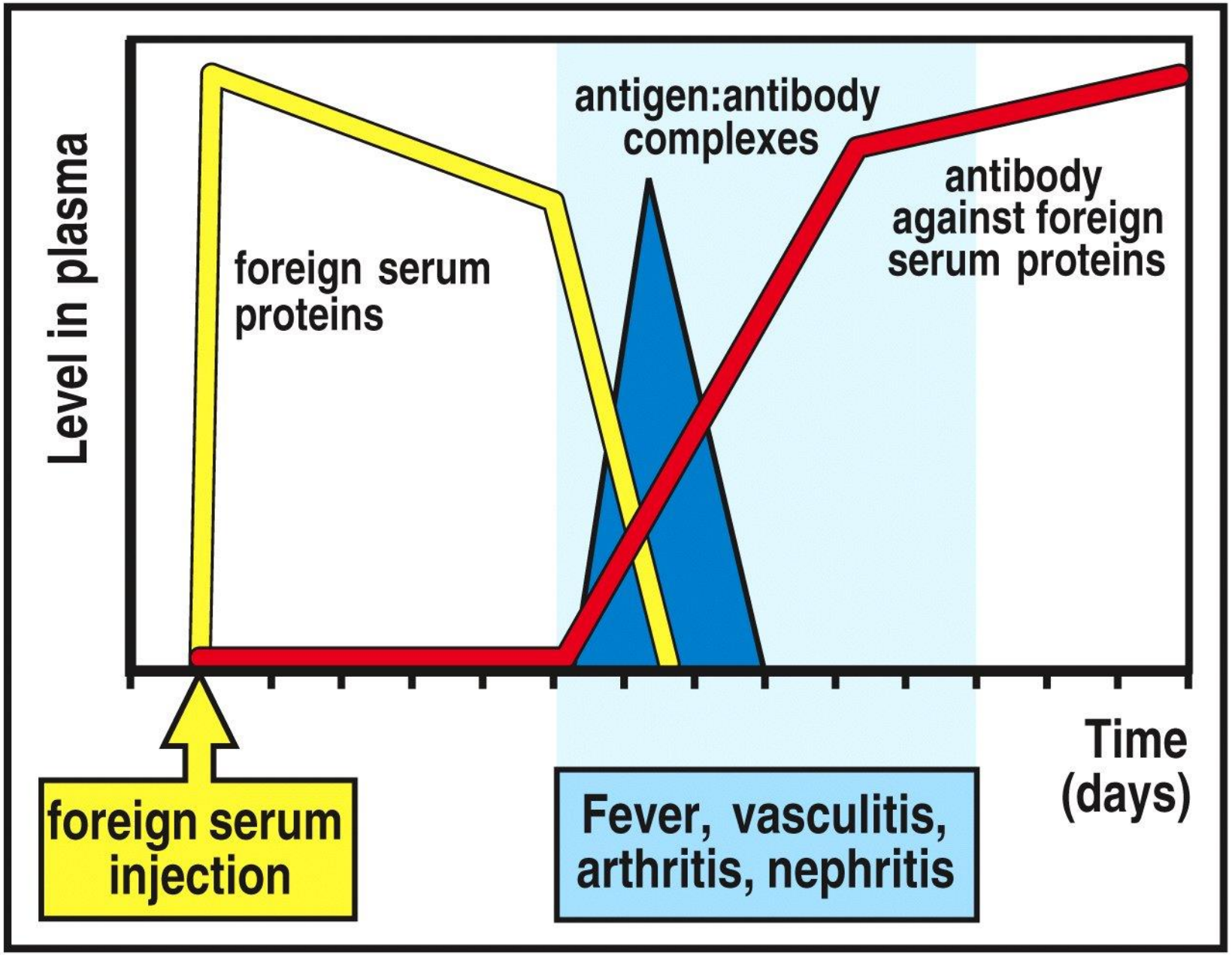
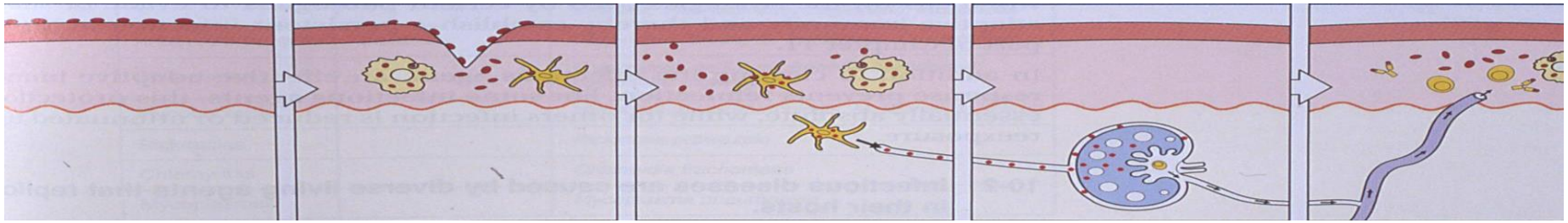
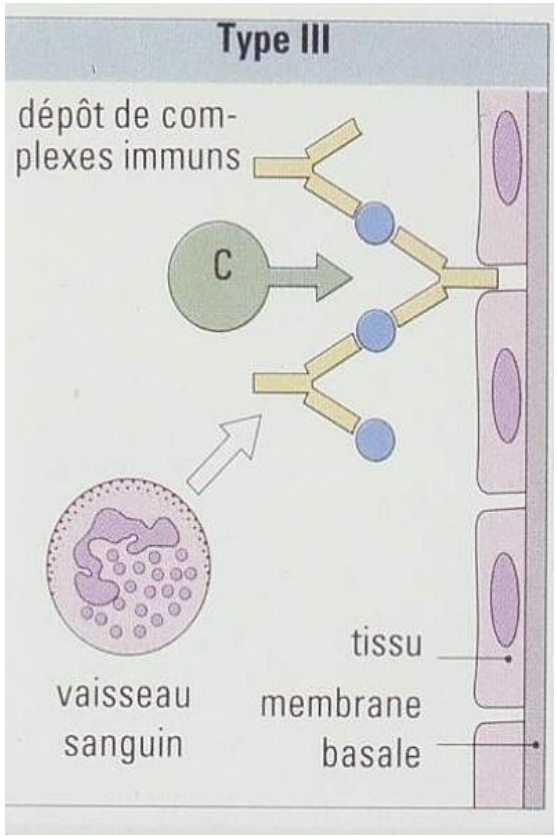
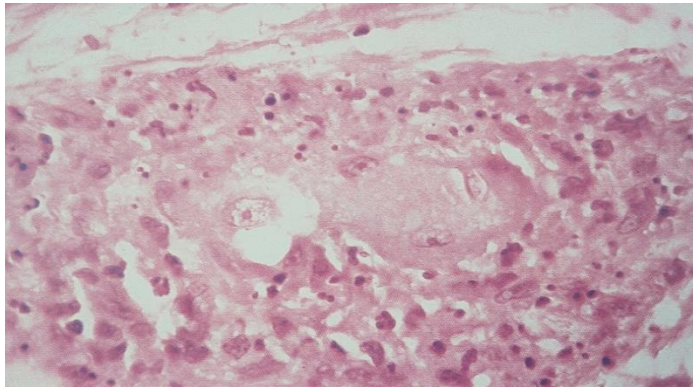


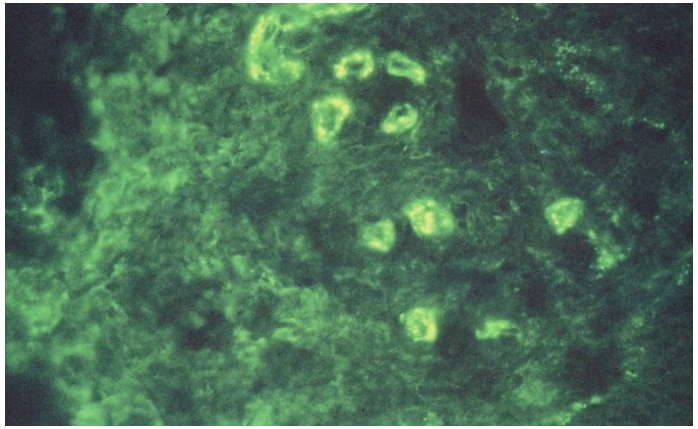
Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

Hypersensibilité de type III due à des complexes immuns
VASCULITES – PURPURA RHUMATOIDE









HS de type III aux antigènes inhalés

Alvéolites allergiques

- Poumon de fermier: poussière de foin moisi: actinomyces
- Maladie des éleveurs de pigeons: poussière de fiente séchée
- Maladie des manipulateurs de rats: protéines éliminées dans l'urine
- Maladie des laveurs de fromages: spores de penicillum casei
- Maladie des fourreurs: protéines de la fourrure de renard
- Maladie des écorceurs d'érable: spores de cryptostroma

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**	CXCL8, **Th17/Type 3** (T cells)
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	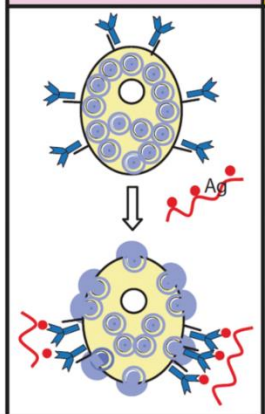	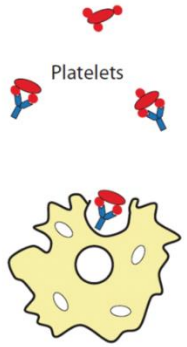	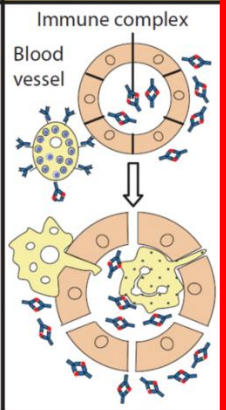	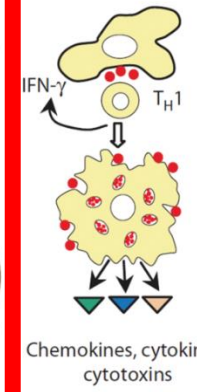	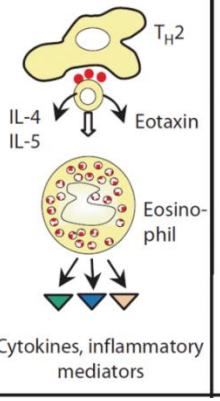	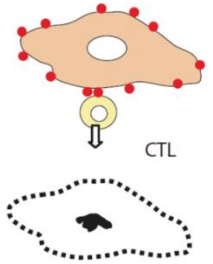	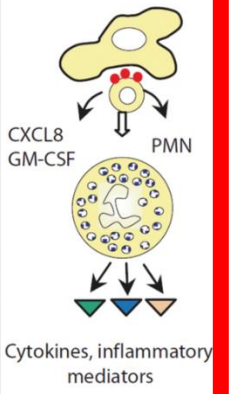
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The 3 major types of innate and adaptive cell-mediated effector immunity

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.)

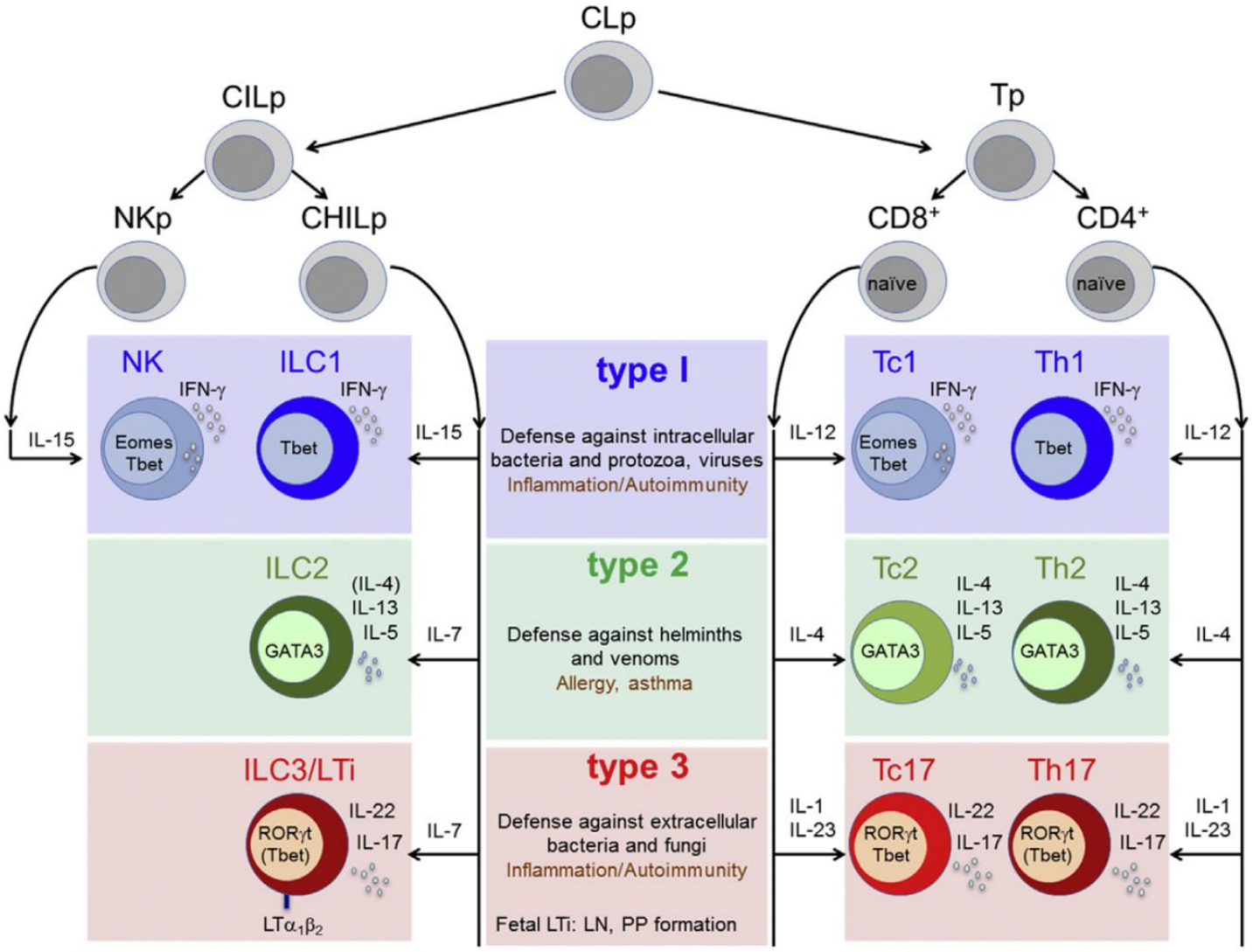
Key words: *Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22*

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

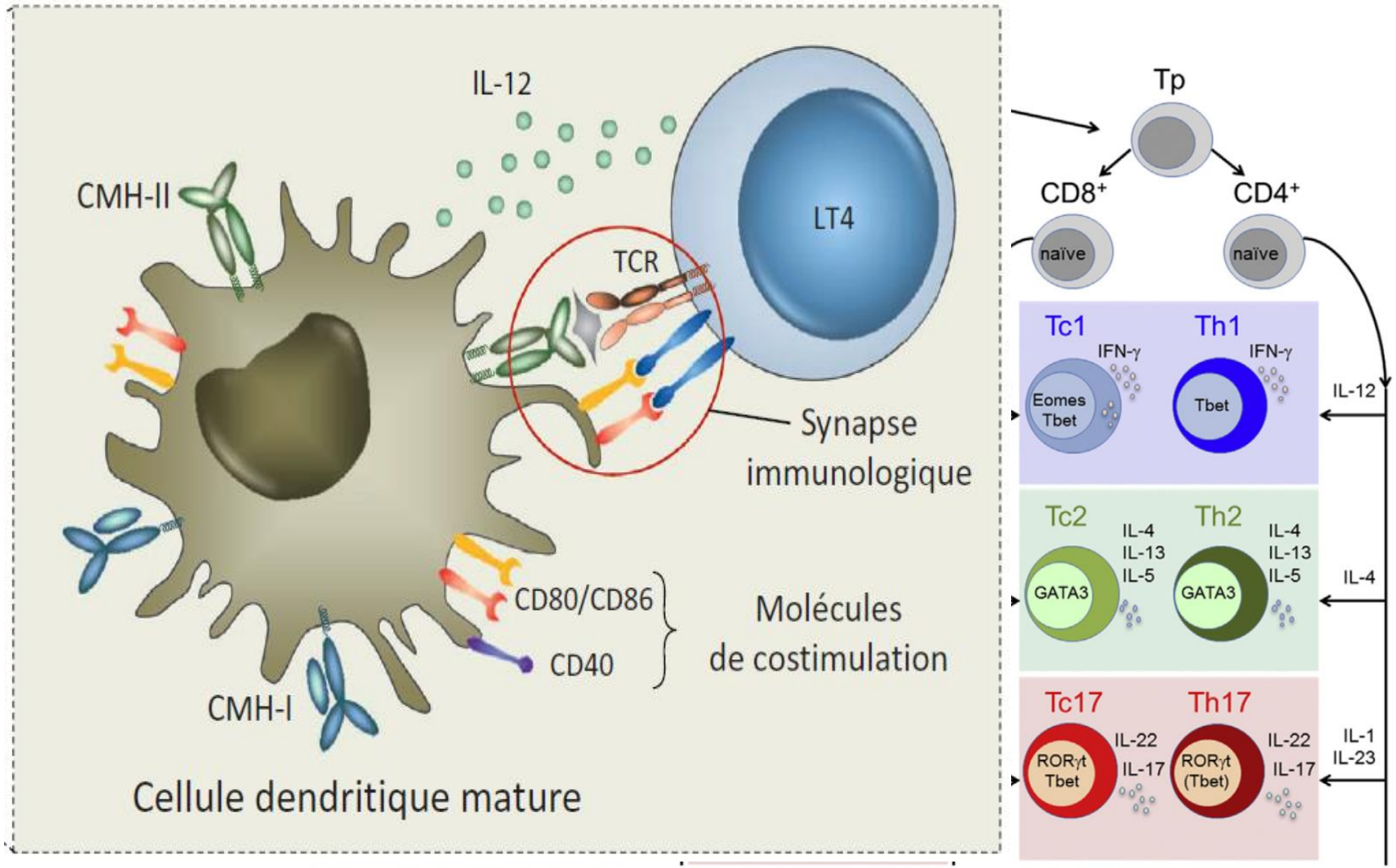
whereas T_H2 cells produce IL-4, IL-5, and IL-13.[3] Subsequently, a similar dichotomy within the CD8$^+$ cytotoxic T (T_C) cell population was discovered in both mice and human subjects, and the 2 subsets were named T_C1 and T_C2,

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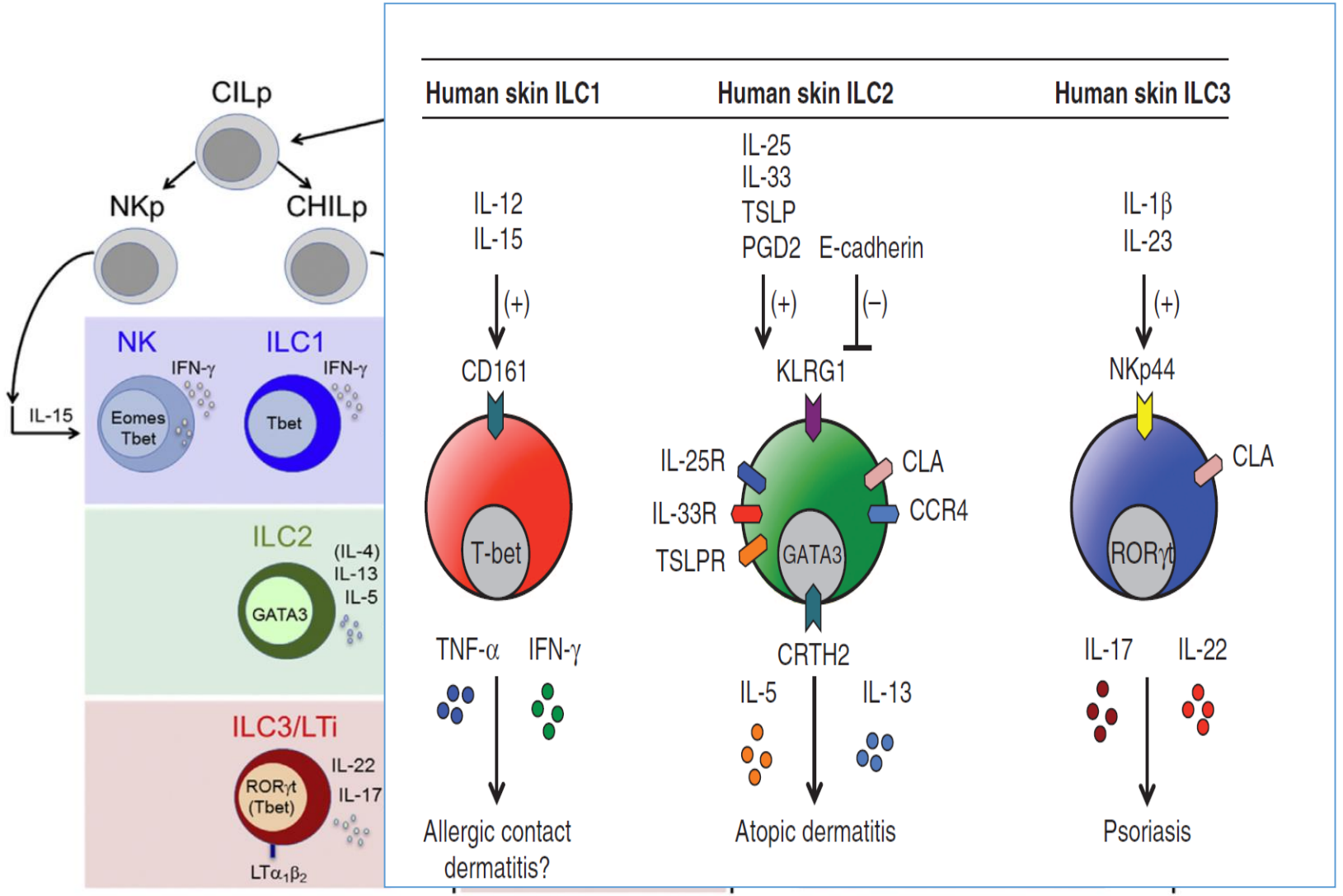
The 3 major types of innate and adaptative cell-mediated immunity



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.

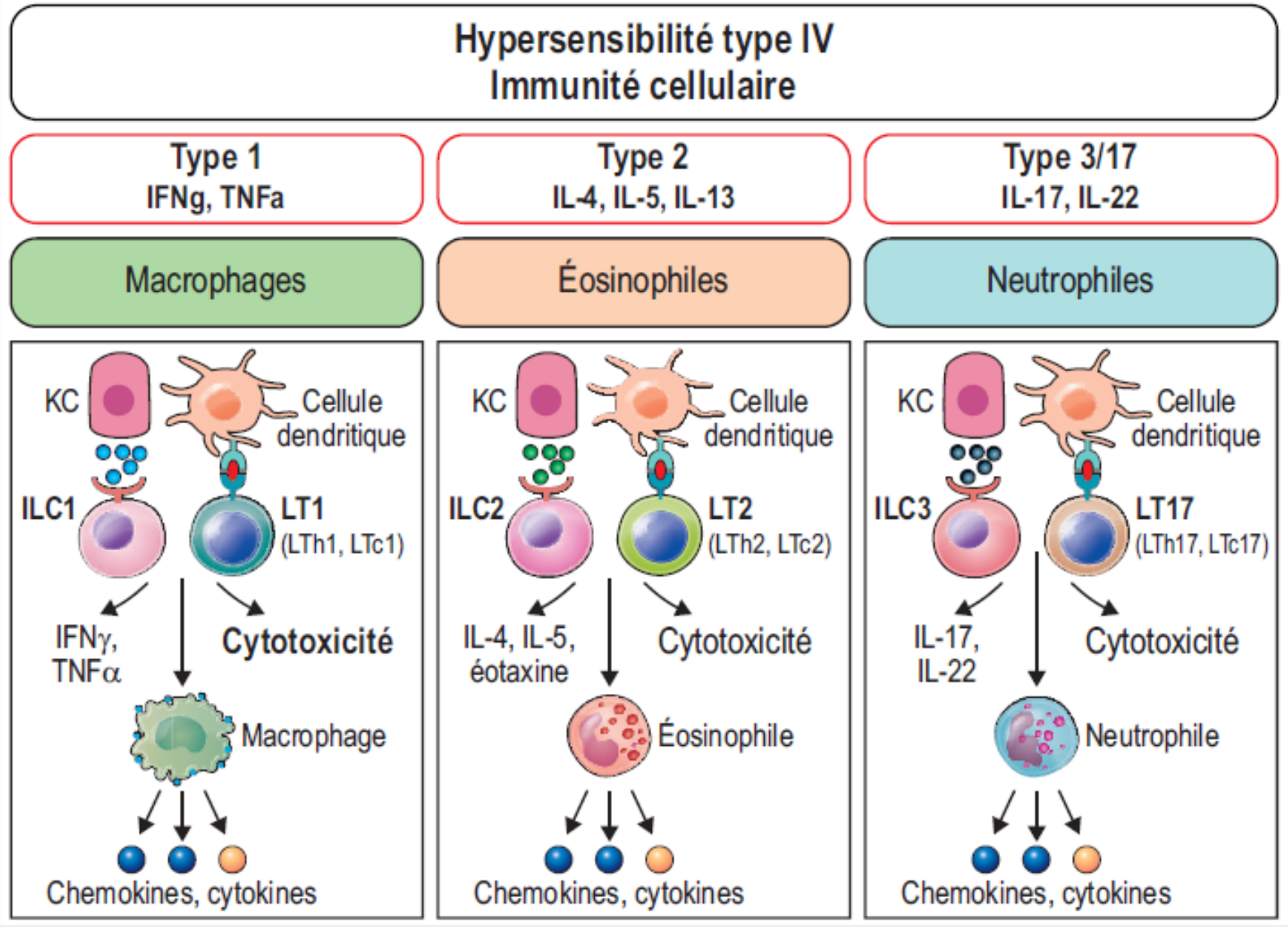


Table 1
Classification des réactions immunitaires cellulaires (hypersensibilité retardée de type IV de Gell & Coombs)

Type 1 Immunity

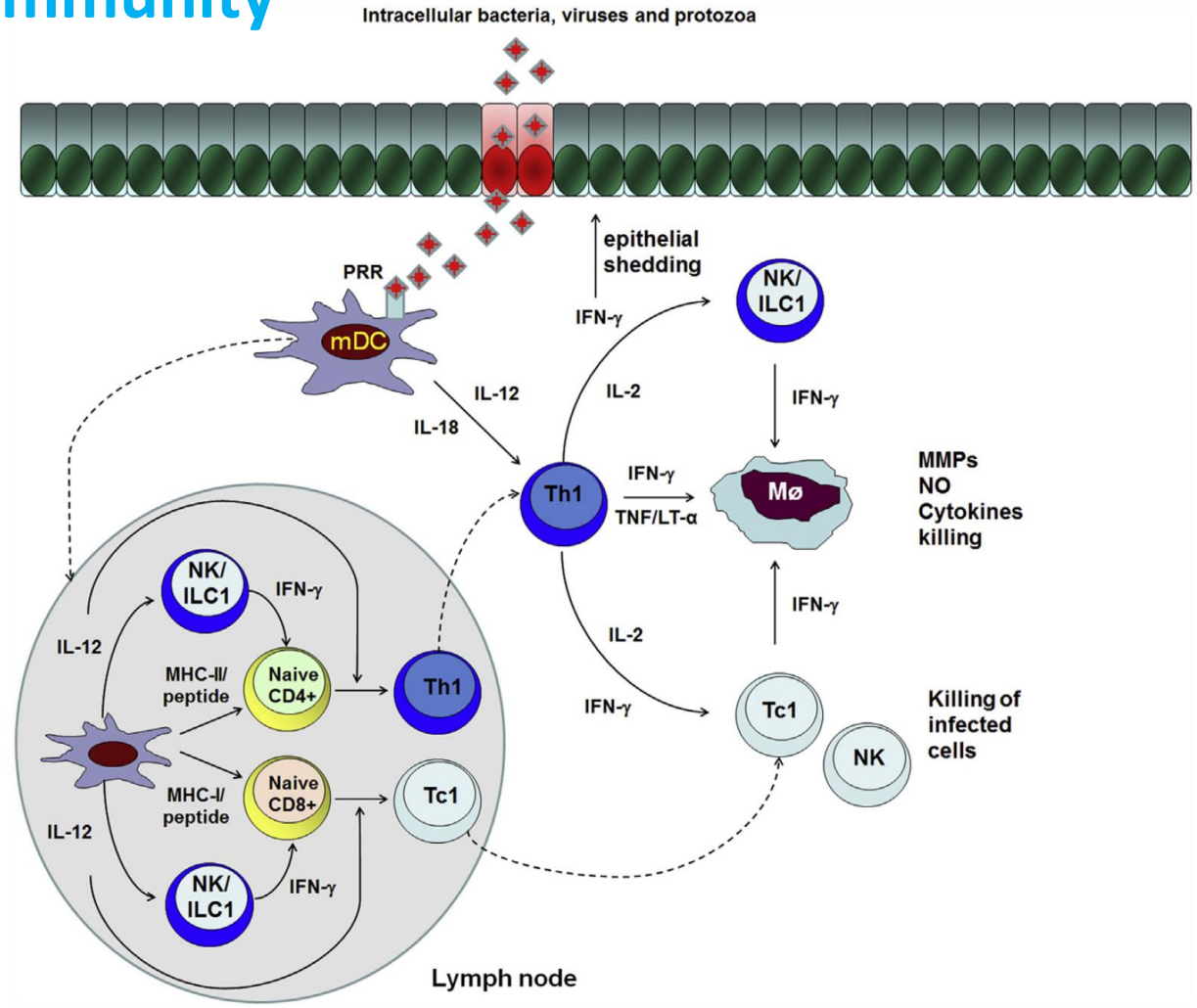


FIG 2. Cells, cytokines, and effectors of type 1 immunity. Intracellular microbes interacting with pathogen recognition receptors *(PRR)* on DCs in the presence of DC-derived IL-12 and IL-18 and of NK/ILC1-derived IFN-γ induce T_H1 or T_C1 development from naive T cells. T_C1 and NK cells kill virus-infected cells. T_H1 cell–, T_C1 cell–, and ILC1-derived cytokines activate MPs to produce the matrix metallopeptidase *(MMPs)*, nitric oxide *(NO)*, and cytokines that allow engulfment and killing of microbial invaders. *mDC*, Myeloid dendritic cell.

Type 2 Immunity

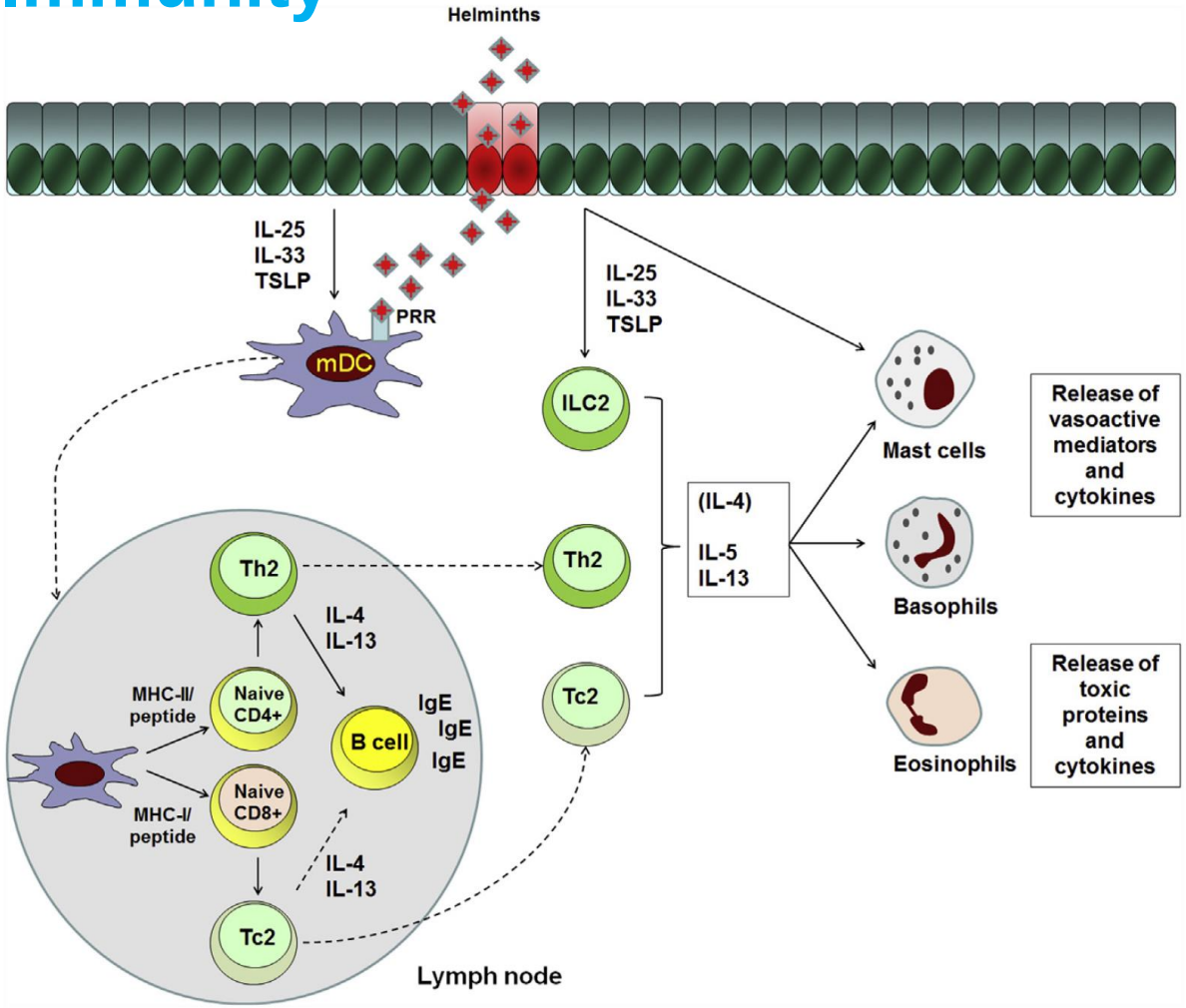


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin *(TSLP)* release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated 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.

Type 3/ type 17 Immunity

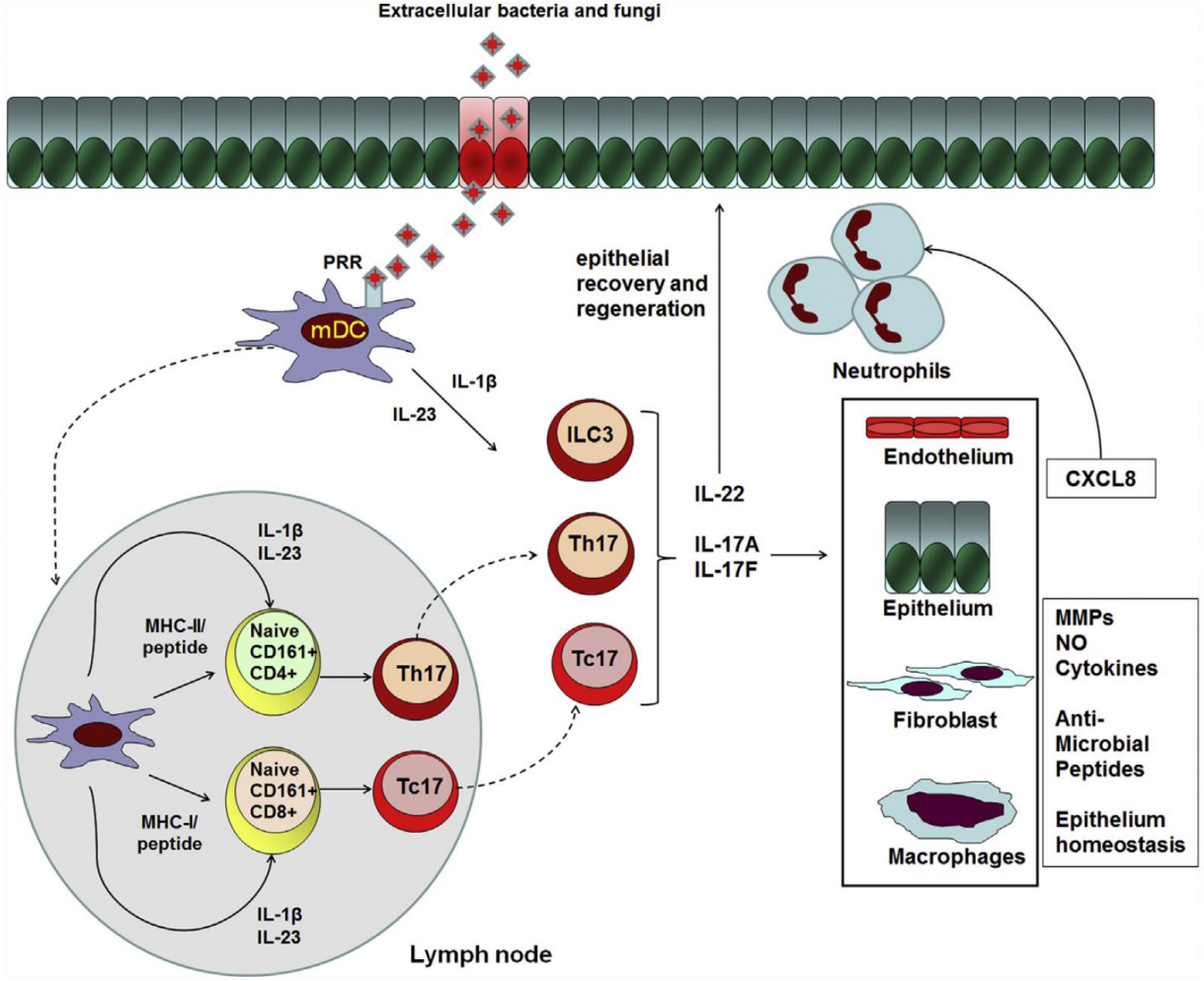
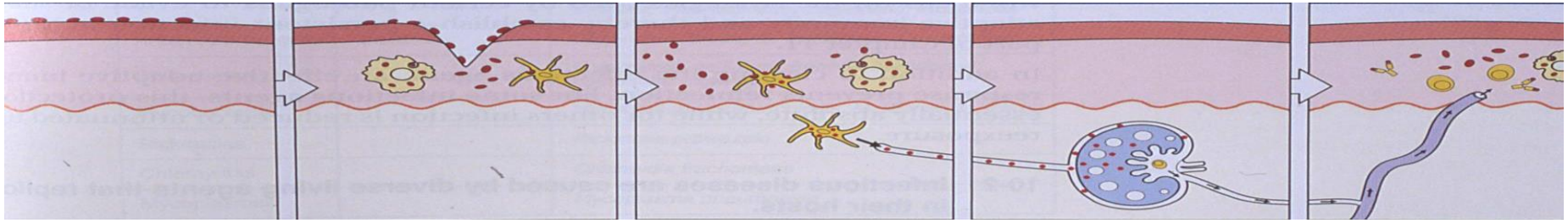
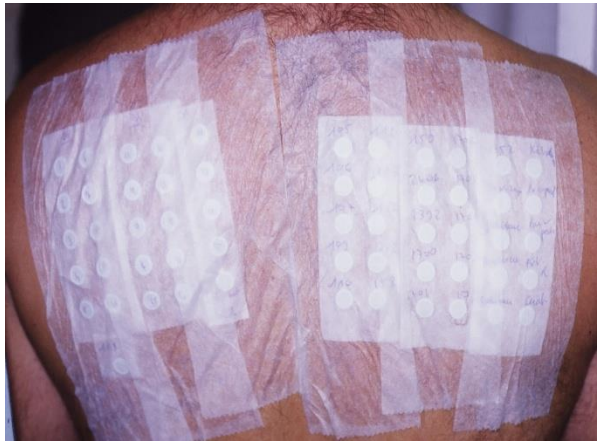


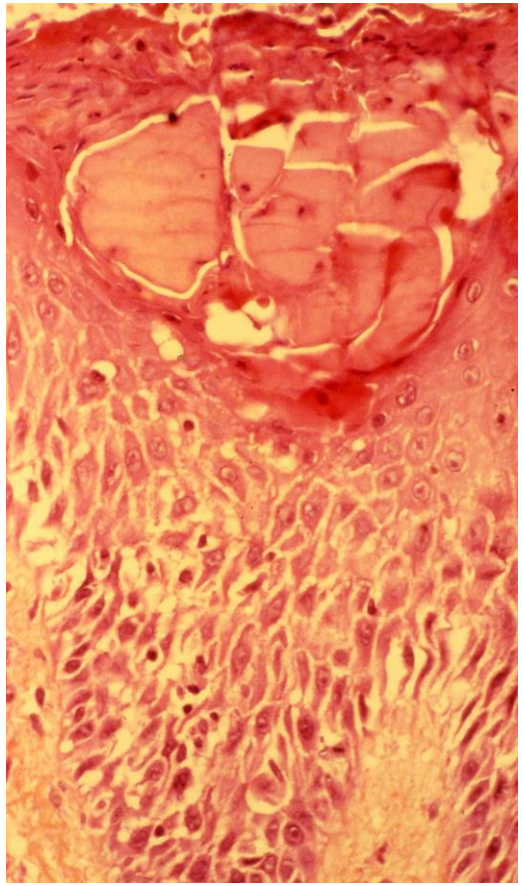
FIG 4. Cells, cytokines, and effectors of type 3 immunity. Extracellular bacteria and fungi induce myeloid dendritic cells *(mDC)* to produce IL-1β and IL-23, which allow T_H17 or T_C17 development from naive $CD161^+$ T cells and trigger cytokine production by ILC3s. IL-17A, IL-17F, and IL-22 from ILC3s and T_H17 and T_C17 cells activate nonimmune and immune cells to produce matrix metallopeptidases *(MMPs)*, nitric oxide *(NO)*, cytokines, antimicrobial peptides, and the neutrophil recruiter CXCL8. IL-22, especially that produced by ILC3s, promotes epithelial proliferation and restrains the gut microflora. *PRR*, Pathogen recognition receptors.

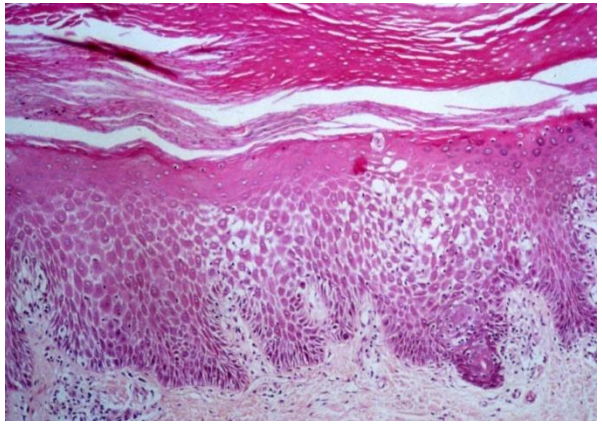
Hypersensibilité de type IV (HS retardée) due à des LT1
ECZEMA DE CONTACT

Th1
Type 1









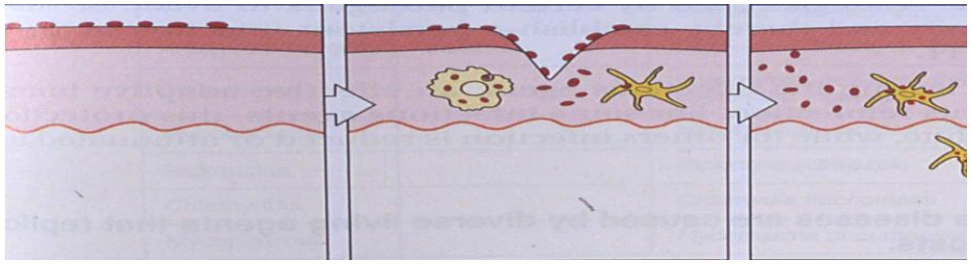
Skin tests represent experimental models of allergic type IV DTH reactions

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

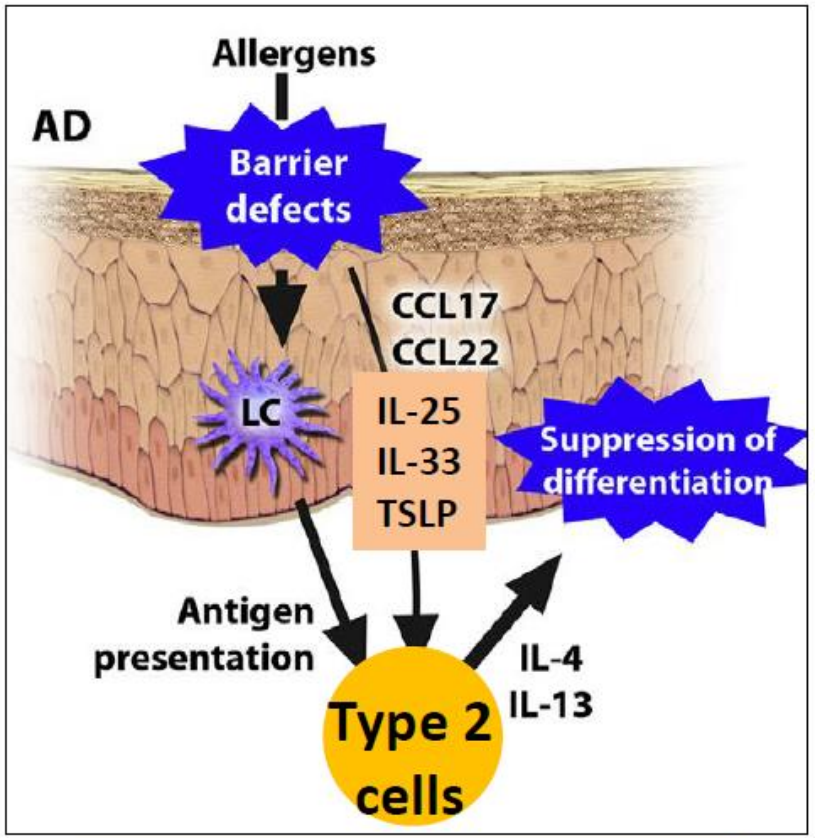
Th1
Type 1

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

Th2
Type 2



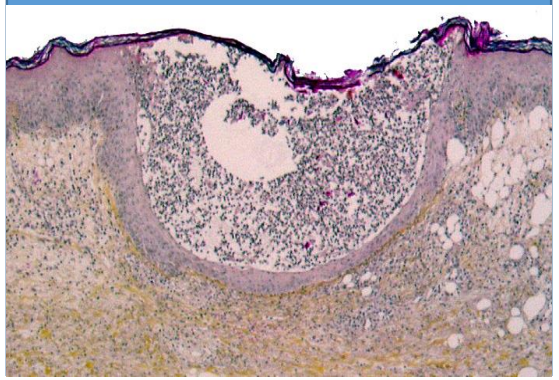
Type 2 phenotype



Type 2 inflammation
Type 2 immunity

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

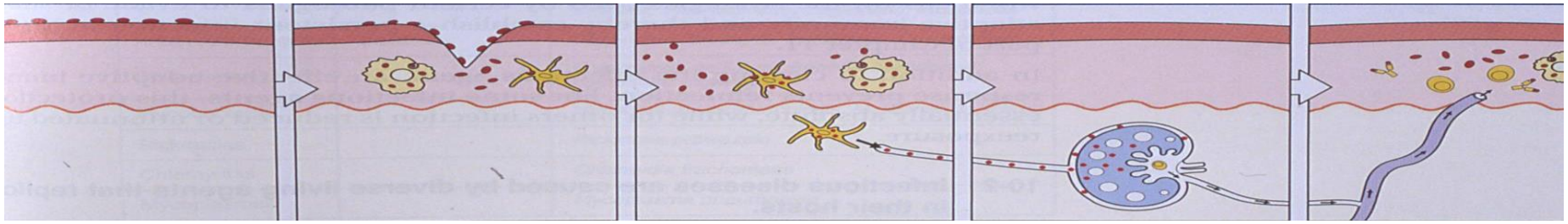
Th17
Type 3

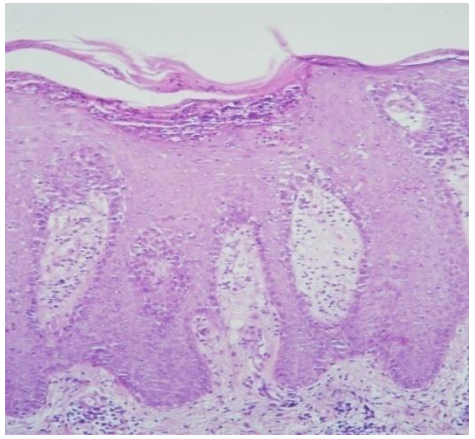


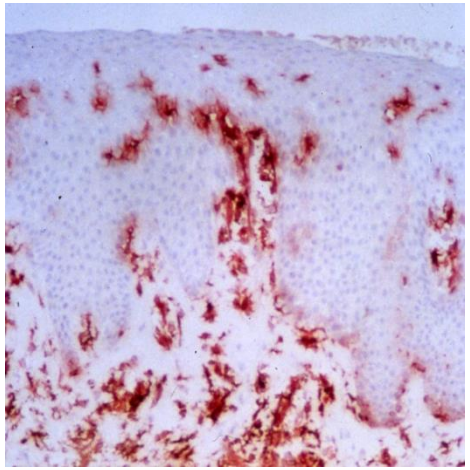
- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre,
  - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
  - 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 3



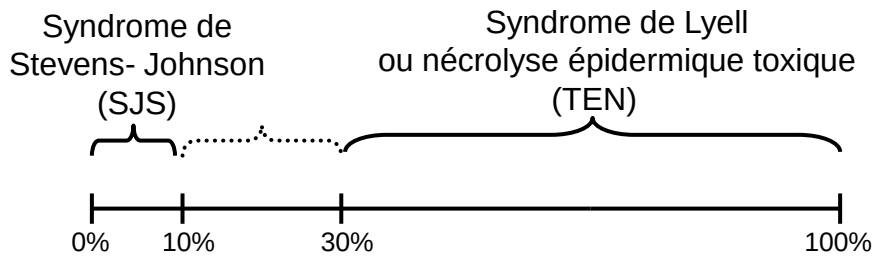




Hypersensibilité de type IV (HS retardée) due à des LT cytotoxiques

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)

Toxidermies – Drug allergy

Cytotoxic

SEVERE

1 - TEN: Toxic Epidermal Necrolysis

MODERATE

2 - DRESS: Drug Rash with Eosino &Systemic symptoms

3 - AGEP: Acute Generalized Exanthematous Pustulosis

4 - FDE: Fixed Drug Eruption

5 - Generalized Erythema multiform

6 - Linear IgA Dermatosis

MILD

7 - MPE: Maculo-papular exanthema

Exanthèmes médicamenteux et toxidermies sévères

Signes généraux et muqueux imposent l'arrêt immédiat du médicament

Les hypersensibilités retardées aux médicaments peuvent toucher tous les organes mais la peau est certainement celui le plus fréquemment atteint. Elles surviennent quelques heures, jours ou semaines après la prise de médicaments et se manifestent par un exanthème, plus ou moins œdémateux, la survenue de bulles et/ou de décollements cutanés. On parle souvent de « toxidermies » pour décrire ces atteintes cutanées. Le tableau (*v.* p. 982) donne les caractéristiques des principales toxidermies. Le bilan allergologique qui comprend des tests cutanés (patch-tests et intradermoréactions), des tests biologiques (tests de prolifération et/ou d'activation lymphocytaire) et des tests de réintroduction dans les formes bénignes, permet de différencier hypersensibilité retardée allergique et non allergique et de proposer aux patients des alternatives thérapeutiques.

symptoms) ou une nécrolyse épidermique toxique.

L'évolution est en général favorable en 1 à 4 semaines après arrêt et élimination du médicament, laissant la place à une desquamation sans séquelle.

Tous les médicaments peuvent induire un exanthème, en particulier les antibiotiques et plus spécialement les pénicillines.

Diagnostic différentiel

Dans tous les cas il est important d'éliminer un exanthème infectieux, en particulier viral (infection par le virus de l'immunodéficience humaine [VIH] chez l'adulte jeune ou mononucléose infectieuse),[2] en sachant que l'infection et la fièvre sont des cofacteurs souvent nécessaires au développement d'un exanthème médicamenteux. Cette association infection virale et exanthème aux pénicillines est classique au cours de la primo-infection par le virus d'Epstein-Barr (EBV ou *human herpes virus*-4 [HHV4]).

BENOÎT BENSAÏD*
LAURENCE VALEYRIE-ALLANORE**
BÉNÉDICTE LEBRUN-VIGNES***
JEAN-FRANÇOIS NICOLAS*

* Service allergologie et immunologie clinique, CHU de Lyon, centre de compétences « allergie aux médicaments », université Lyon 1, Inserm U1111-CIRI, Hôpitaux de Lyon,

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department