

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>



Département Allergologie et Immunologie Clinique



Clinical Research Unit



INSERM translational research team



Allergy & 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

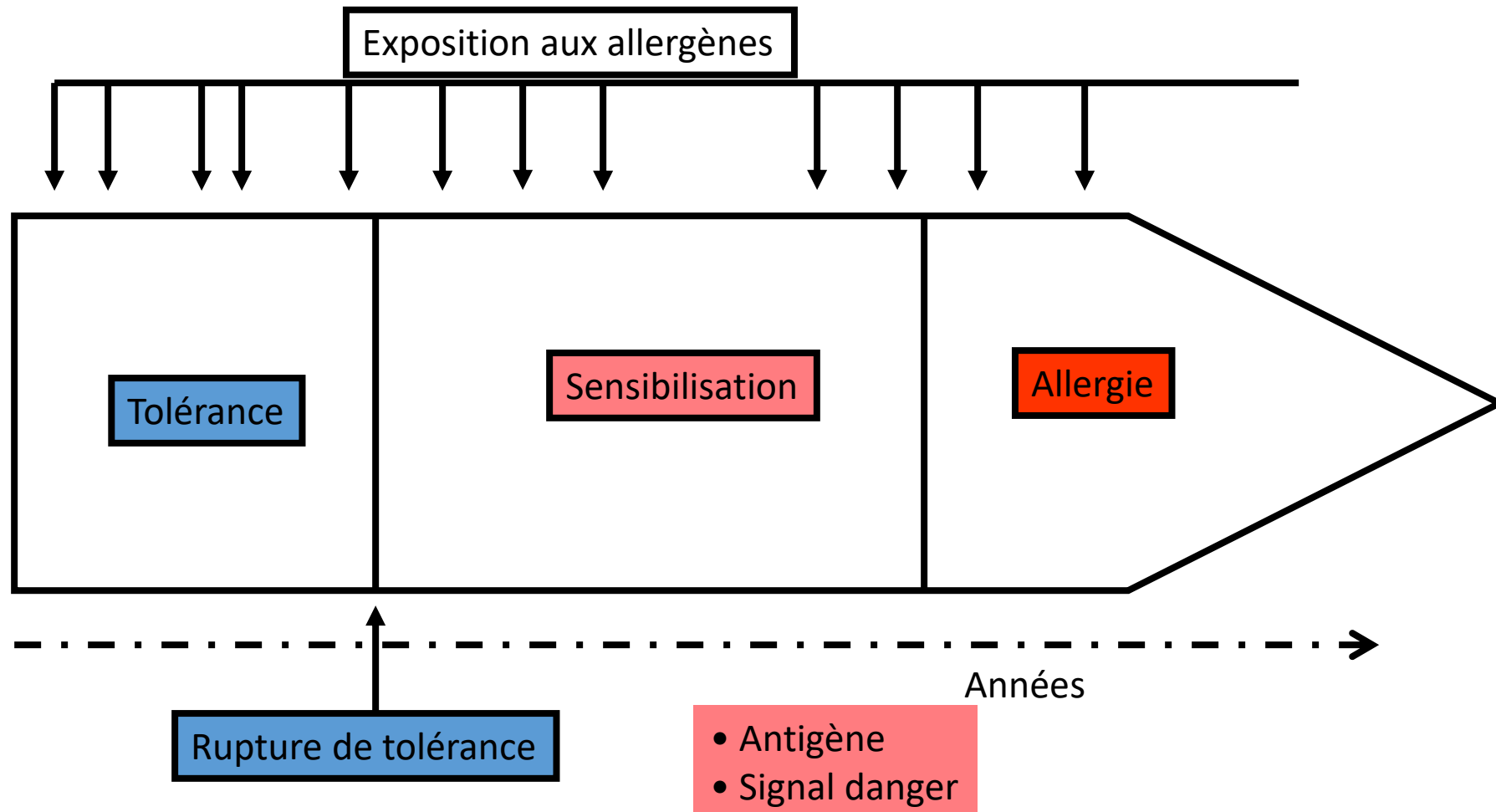
- La mise en place d'une maladie allergique obéit aux mêmes règles que la mise en place d'une réponse immunitaire vis à vis d'agents infectieux
- La physiopathologie des maladies allergiques est donc similaire à celle de la réponse anti-infectieuse

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

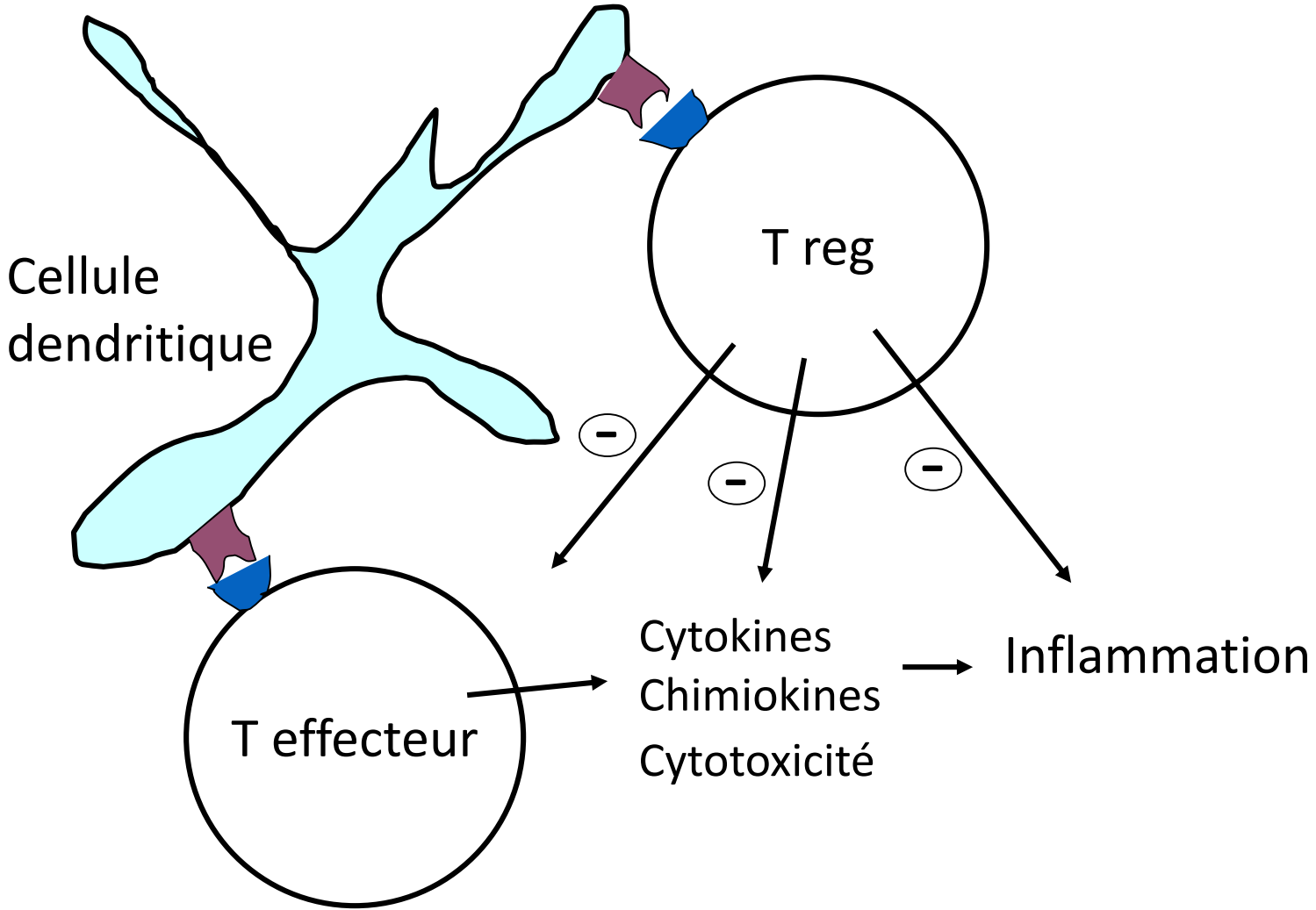
ALLERGIE

Rupture de tolérance aux molécules de l'environnement



Allergie

Sensibilisation versus tolérance



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

Terminologie

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

Terminologie

- Allergie (gell et coombs: immunité adaptative; immunité spécifique de médicaments)
 - 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, anaphylactoïde, fausse allergie)
 - **HS immédiate: MASTOCYTES**
 - **HS retardée: LYMPHOCYTES**

Hypersensibilité (HS)

```
graph TD; HS[Hypersensibilité (HS)] --> HS_A[HS Allergique]; HS --> HS_NA[HS Non Allergique]; HS_A --- EA[Eczéma allergique de contact]; HS_A --- EA2[Eczéma atopique extrinsèque]; HS_NA --- EI[Eczéma irritatif de contact]; HS_NA --- EA3[Eczéma atopique intrinsèque];
```

HS Allergique

Eczéma allergique de contact
Eczéma atopique extrinsèque

HS Non Allergique

Eczéma irritatif de contact
Eczéma atopique intrinsèque

Hypersensibilité (HS) aux médicaments

```
graph TD; A[Hypersensibilité (HS) aux médicaments] --> B[HS Allergique  
Rare (5%)]; A --> C[HS Non Allergique  
Fréquente (95%)]; B --- D[sévère]; C --- E[bénigne]
```

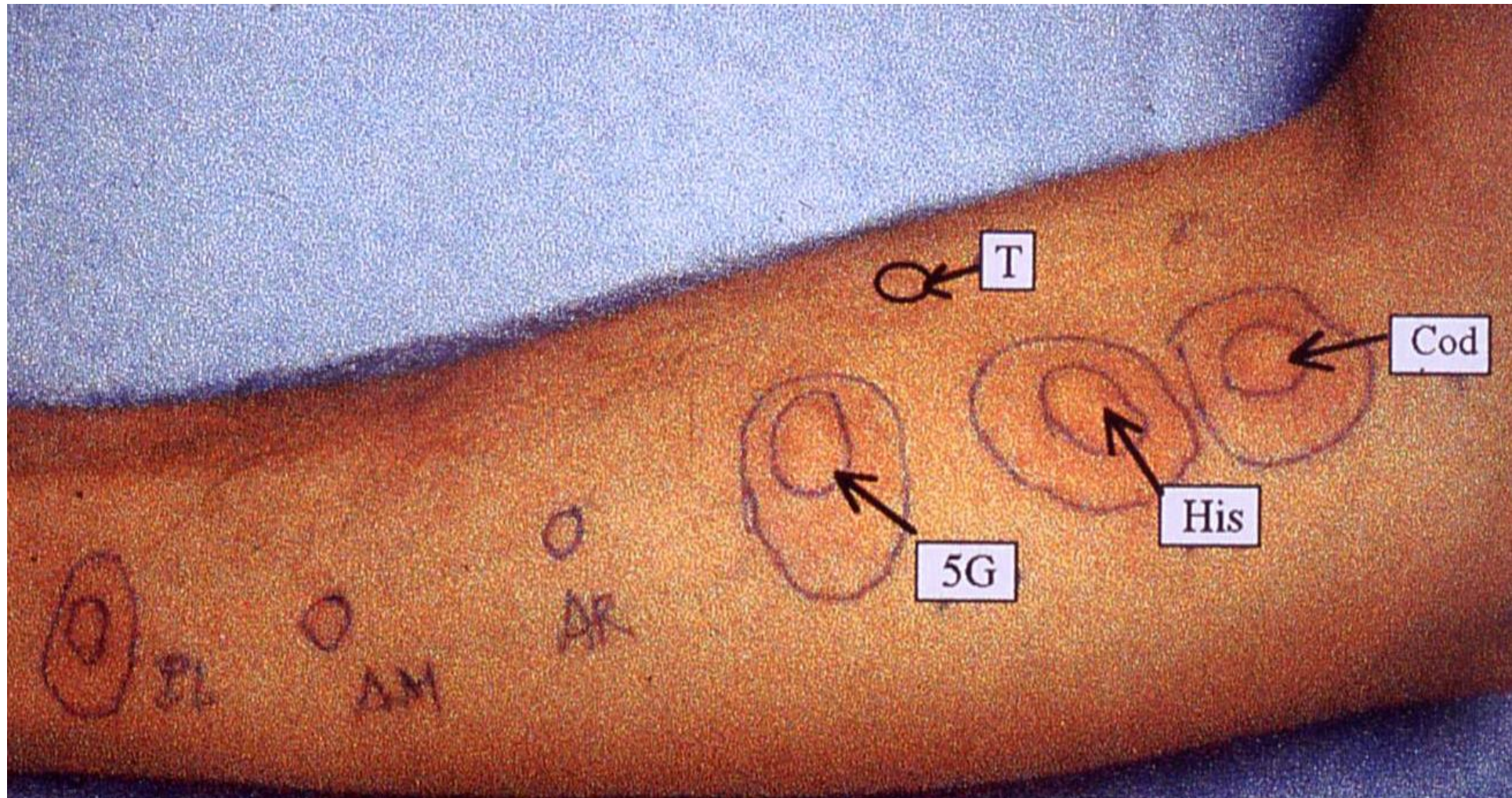
HS Allergique
Rare (5%)

sévère

HS Non Allergique
Fréquente (95%)

bénigne

HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

[redacted] Danièle
7 Cote Carmagnac
69 [redacted]
tel [redacted]

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 oedème de Quincke. J'ai donc noté qu'il avait mangé = du nougat chinois, concombres, tomates, betteraves, magret de Canard, sauce au poivre vert, mangues, lichies, crêpes 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

██████████ JOSIANE F
058806632 0 08 01 1950
36501 SEM DUFOURT /
BERGERET H

NOM :

PRÉNOMS :

Δ ! Allergie
Iode
Aspirine, Penic,
ARCHIVAGE
Hydrocortisone

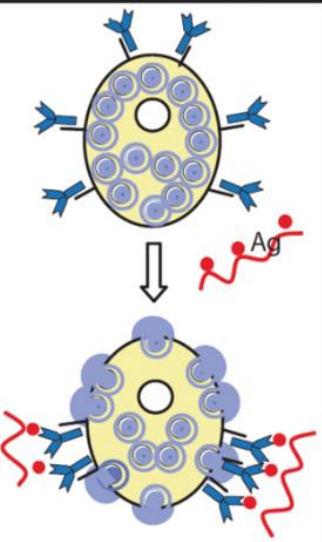
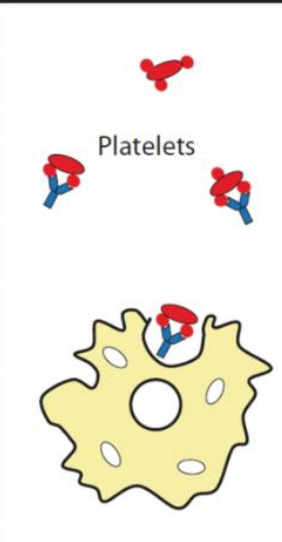
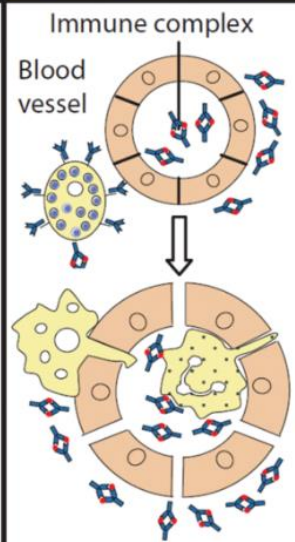
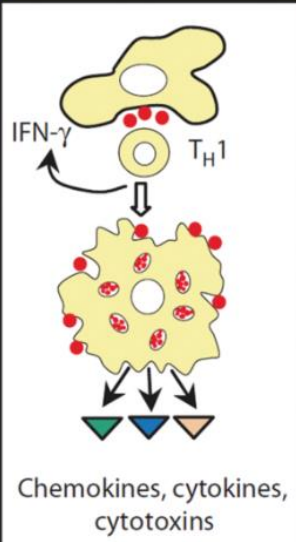
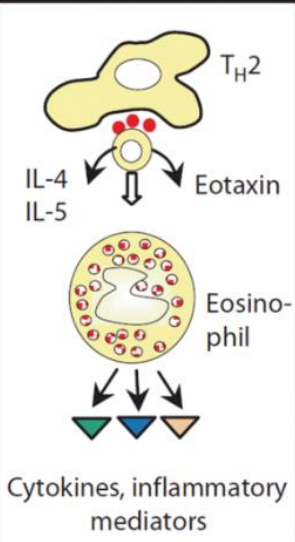
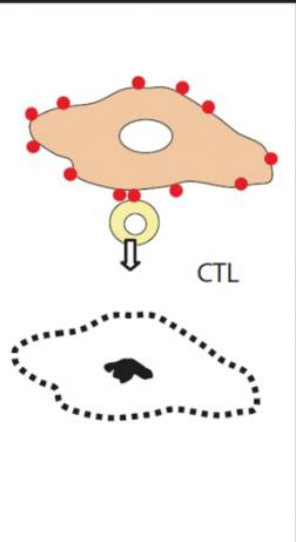
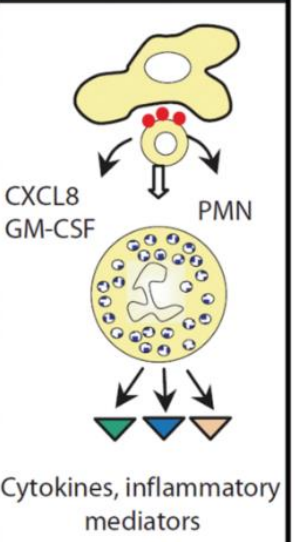
DOSSIER DE SOINS

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

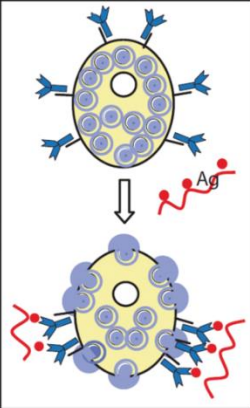
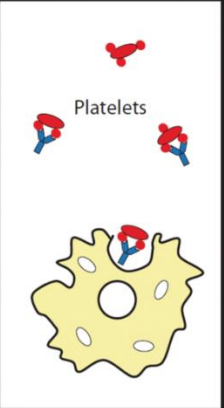
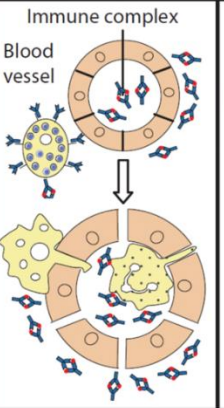
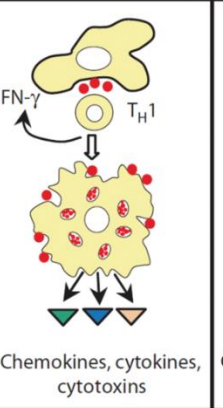
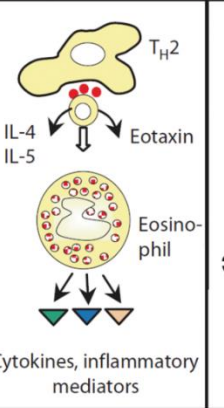
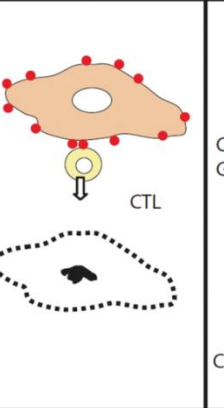
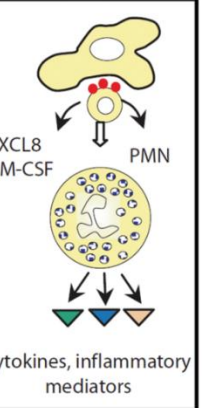
Hypersensibilités

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 | IFN- 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |

Hypersensibilités

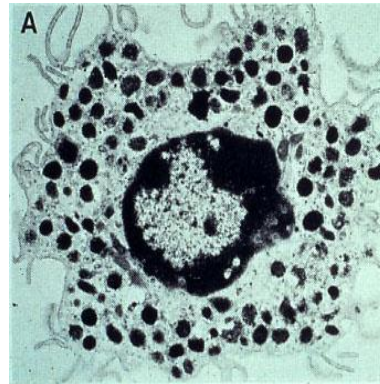
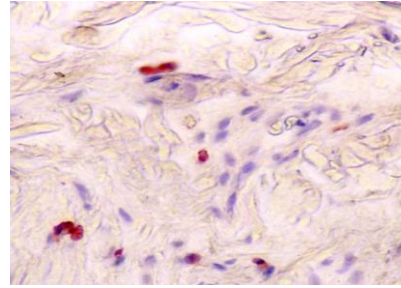
Classification de Gell & Coombs

| | Antibody | | | T cells | | | |
|---------------------------------------|--|---|--|--|--|--|--|
| | Type I | Type II | Type III | Type IVa | Type IVb | Type IVc | Type IVd |
| Immune reactant | IgE | IgG | IgG | IFN- γ , TNF- α Th1/Type 1 | IL-5, IL-4/IL-13 Th2/Type 2 | Perforin/ granzyme B Cytotoxic | CXCL8, 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |
| 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 |
| Dermatoses autoimmunes et allergiques | Urticaire contact | Pemphigus Pemphigoïde Urticaire chroni. | Vascularites | Psoriasis | Dermatite atopique | Vitiligo Pelade Eczéma contact | Psoriasis |
| Allergies médicaments | Choc anaphylactique | Cytopénies medic. | Vascularites immuno-allerg. | Exanthème médic. | DRESS | Lyell Stevens-Johnson | Pustulose exanthématique aigüe généralisée |

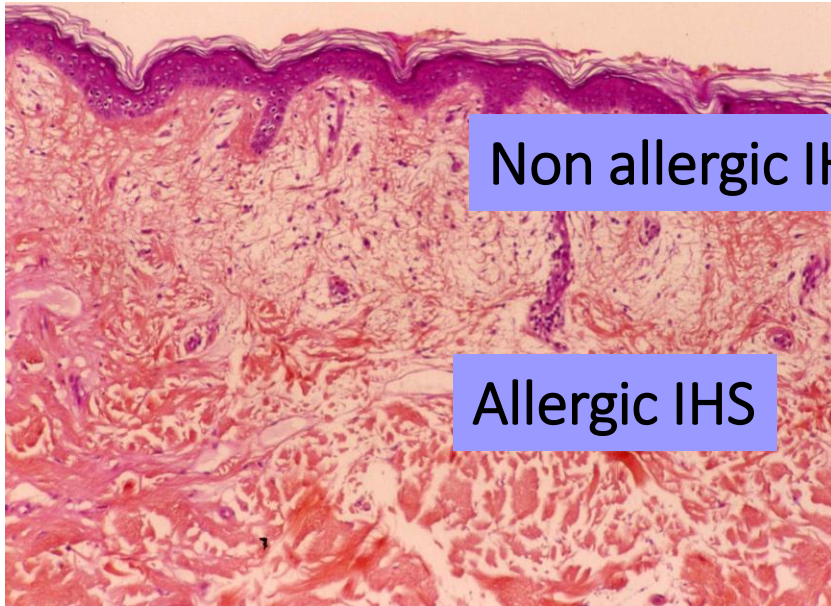
TYPE I HYPERSENSITIVITY



Œdème du derme / Vaisseaux

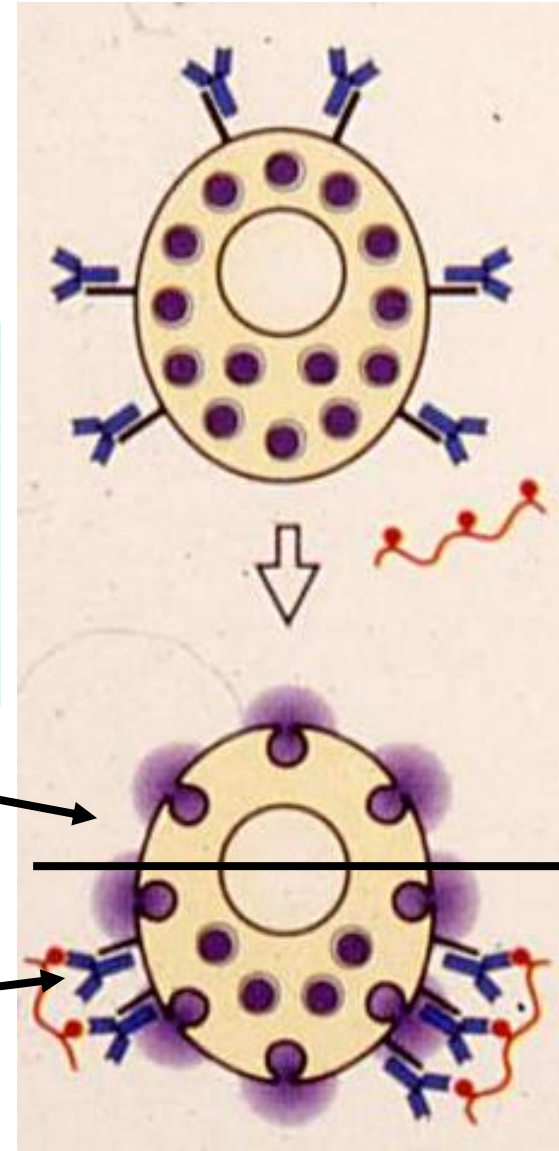


Mastocytes / Histamine



Non allergic IHS

Allergic IHS

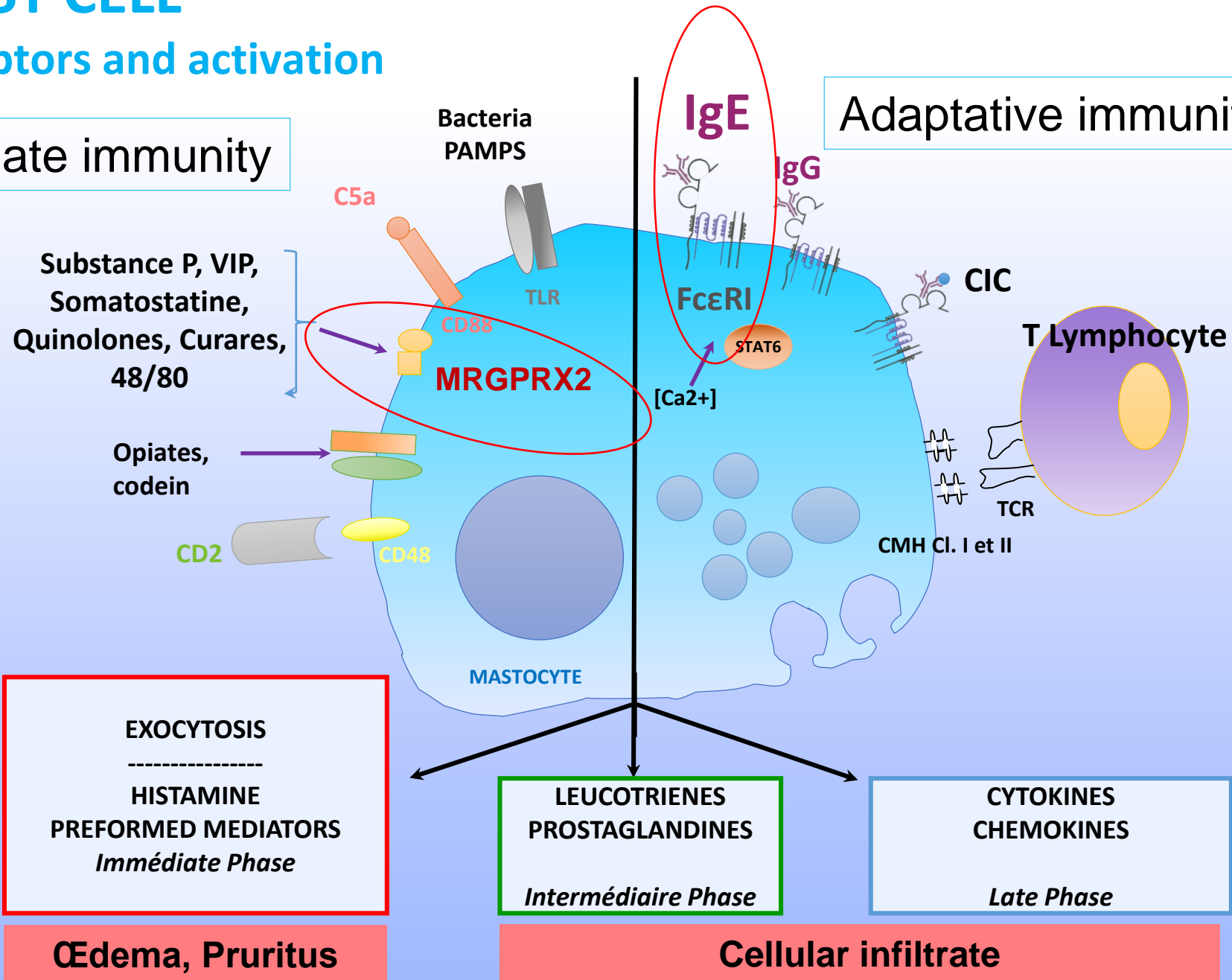


MAST CELL

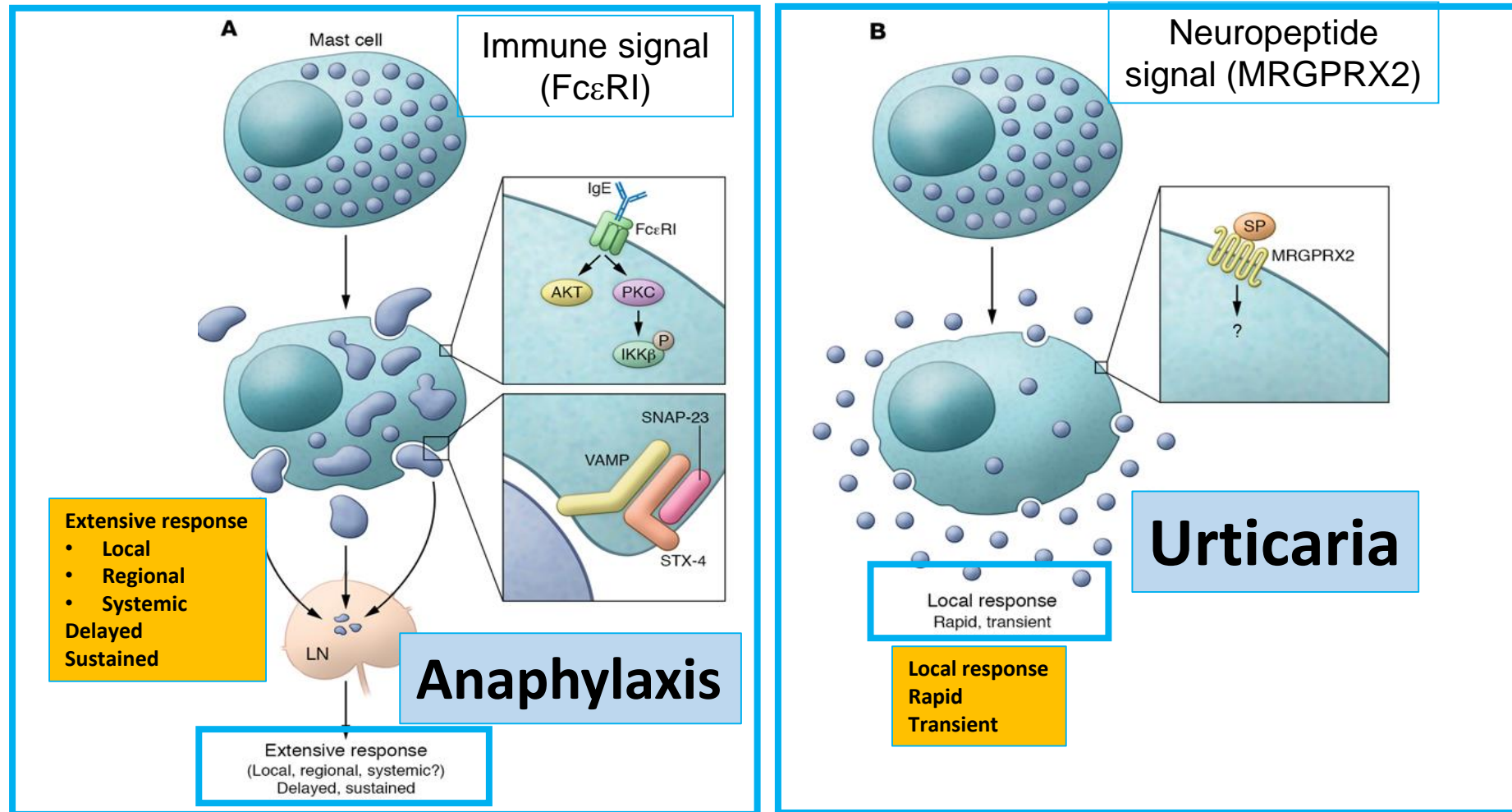
Receptors and activation

Innate immunity

Adaptative immunity



Two fundamental degranulation pathways in **IgE/FcεRI** mast cells **Other receptor**



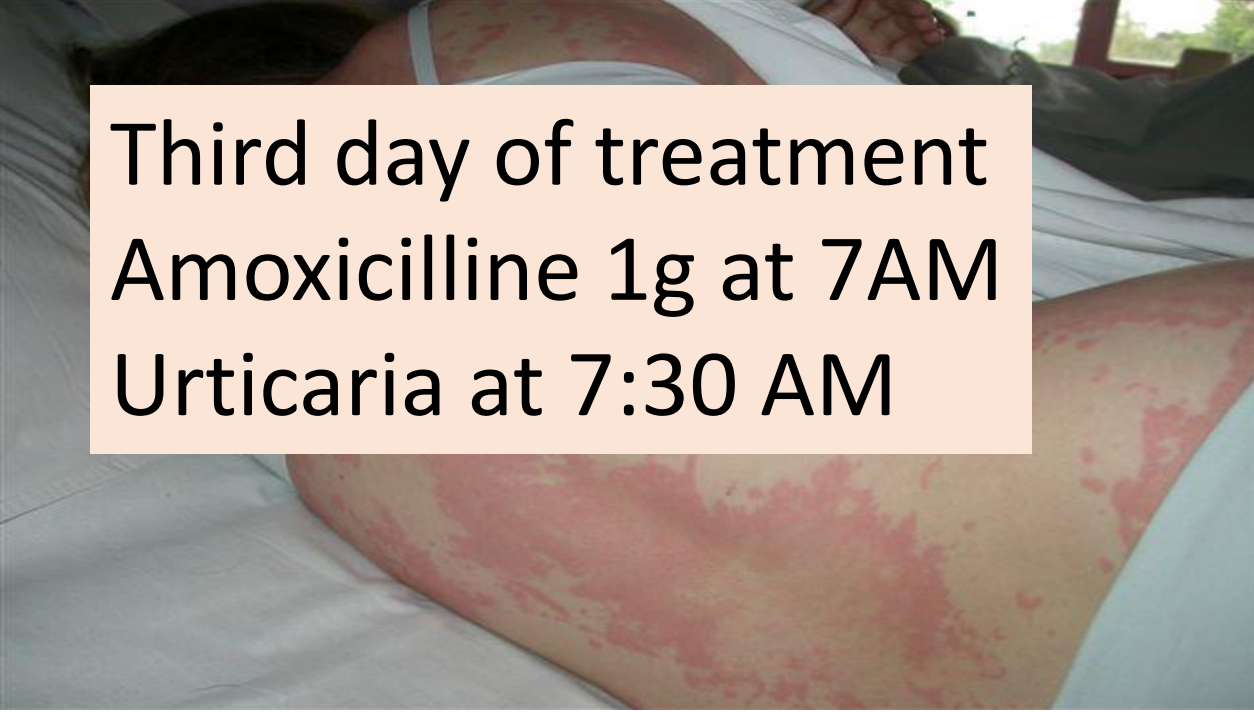
Drug-induced urticaria and angioedema

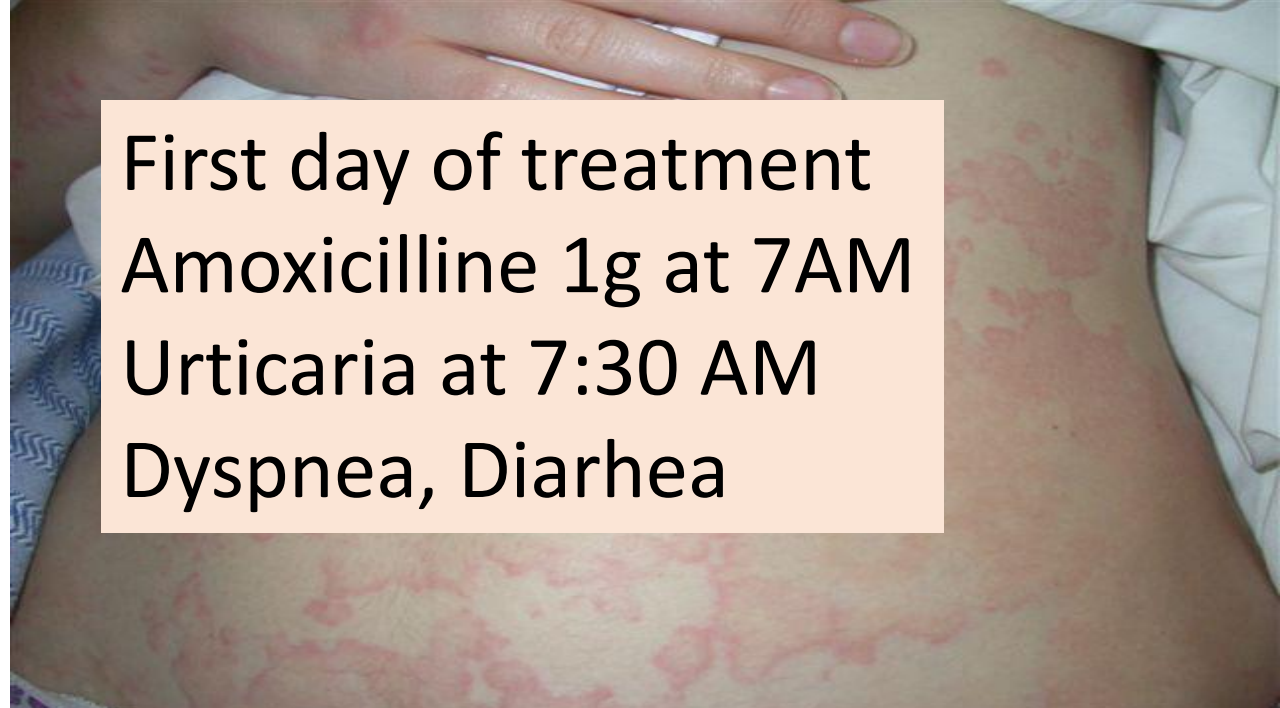
- **Allergic (IgE):** rares (5%) and exceptionally isolated
- **Non allergic:** frequent (95%) and almost always benign

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



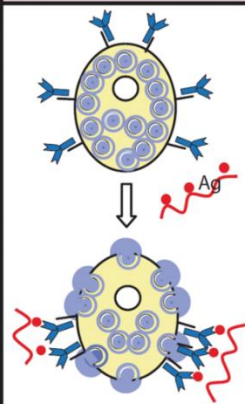
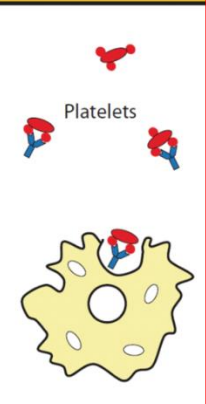
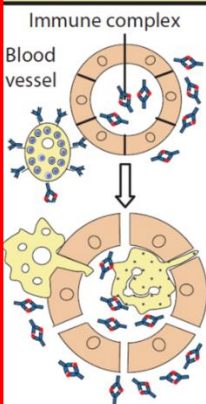
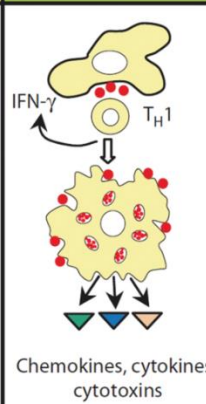
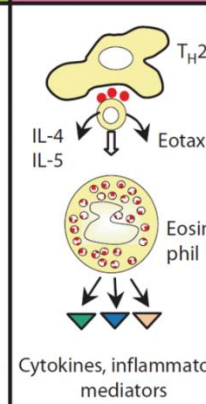
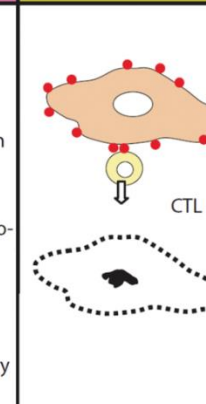
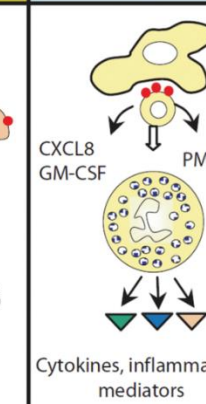


**More a drug-induced reaction is severe,
more it has a chance to be allergic**

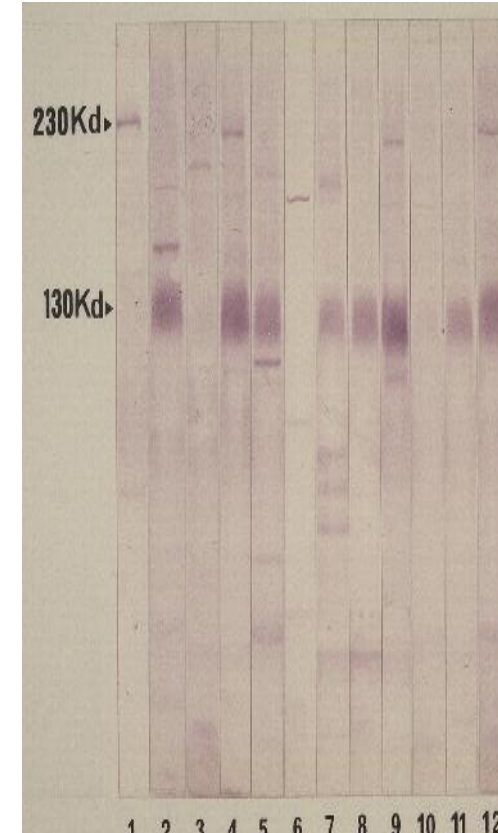
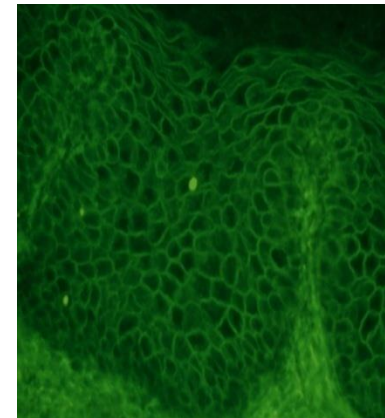
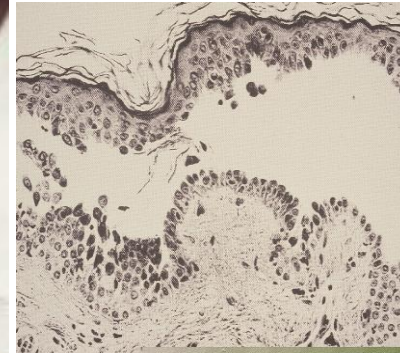
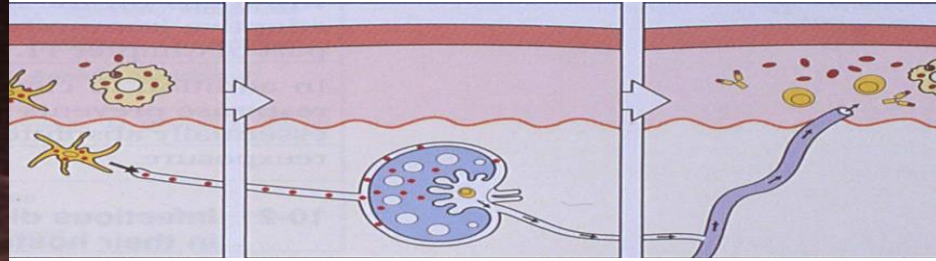


Hypersensibilités

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 | IFN- γ , TNF- α Th1/Type 1 | IL-5, IL-4/IL-13 Th2/Type 2 | Perforin/ granzyme B Cytotoxic | CXCL8, 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |
| 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 |
| Dermatoses autoimmunes et allergiques | Urticaire contact | Pemphigus Pemphigoïde Urticaire chroni. | Vascularites | Psoriasis | Dermatite atopique | Vitiligo Pelade Eczéma contact | Psoriasis |
| Allergies médicaments | Choc anaphylactique | Cytopénies medic. | Vascularites immuno-allerg. | Exanthème médic. | DRESS | Lyell Stevens-Johnson | Pustulose exanthématique aigüe généralisée |

Hypersensibilité de type II due à des IgG spécifiques PEMPHIGUS



Hypersensibilités

Classification de Gell & Coombs

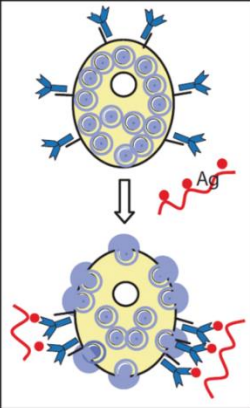
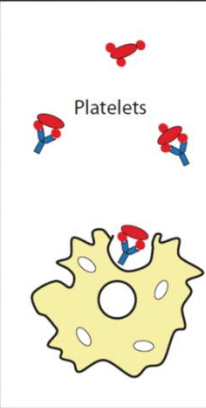
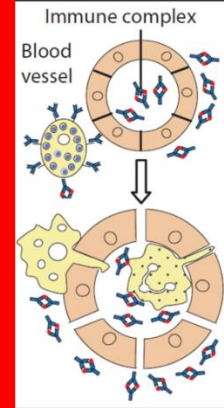
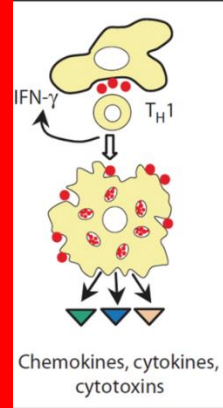
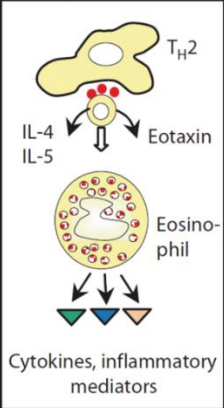
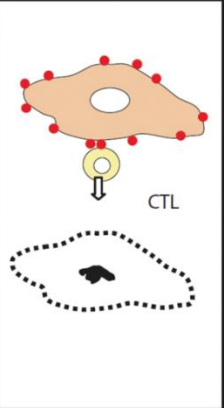
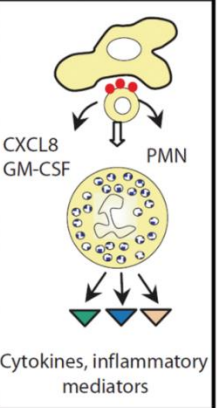
| | Antibody | | | T cells | | | |
|---------------------------------------|--|---|--|--|--|--|--|
| | Type I | Type II | Type III | Type IVa | Type IVb | Type IVc | Type IVd |
| Immune reactant | IgE | IgG | IgG | IFN- γ , TNF- α Th1/Type 1 | IL-5, IL-4/IL-13 Th2/Type 2 | Perforin/ granzyme B Cytotoxic | CXCL8, 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |
| 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 |
| Dermatoses autoimmunes et allergiques | Urticaire contact | Pemphigus Pemphigoïde Urticaire chroni. | Vascularites | Psoriasis | Dermatite atopique | Vitiligo Pelade Eczéma contact | Psoriasis |
| Allergies médicaments | Choc anaphylactique | Cytopénies medic. | Vascularites immuno-allerg. | Exanthème médic. | DRESS | Lyell Stevens-Johnson | Pustulose exanthématique aiguë généralisée |

Fig 80

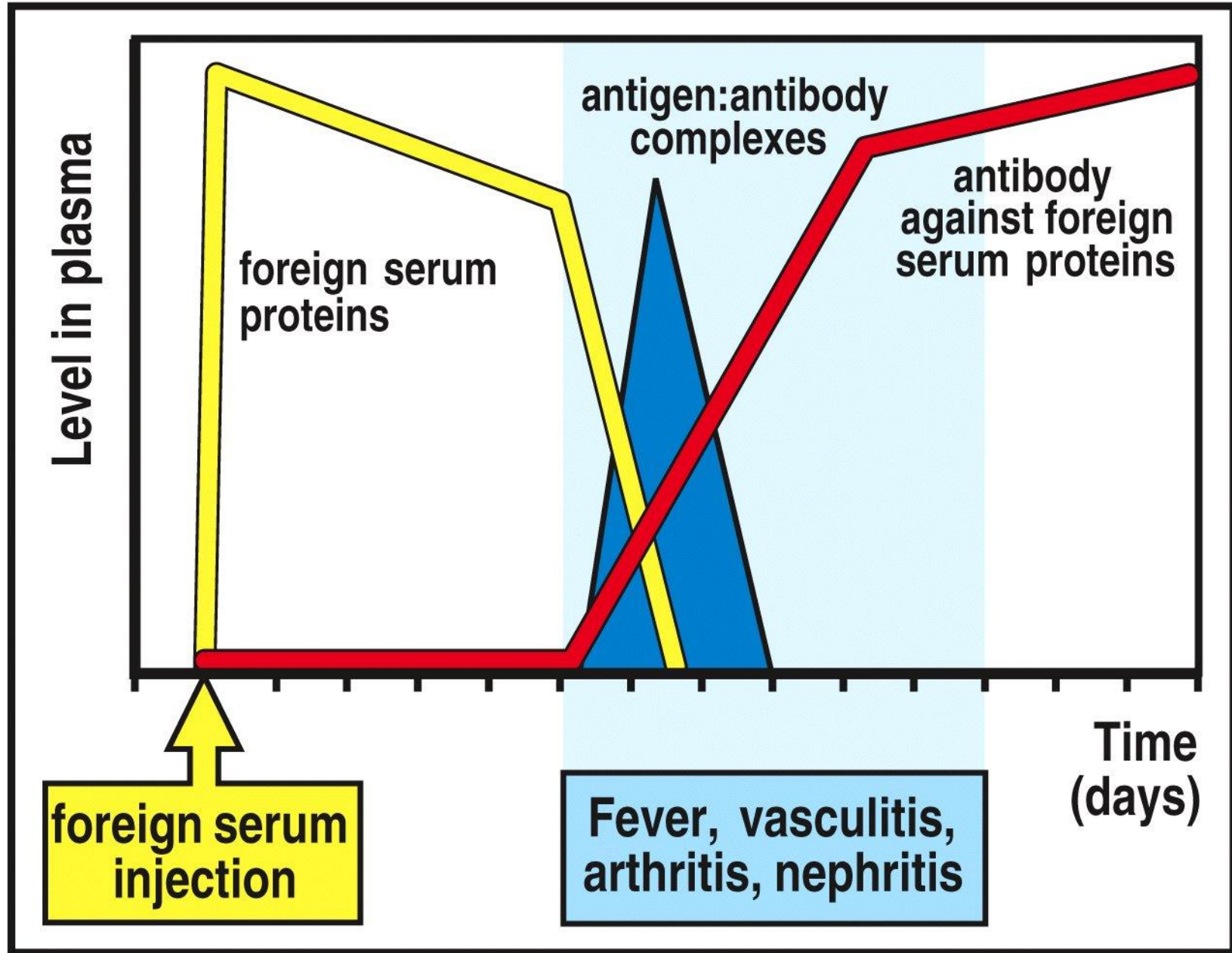
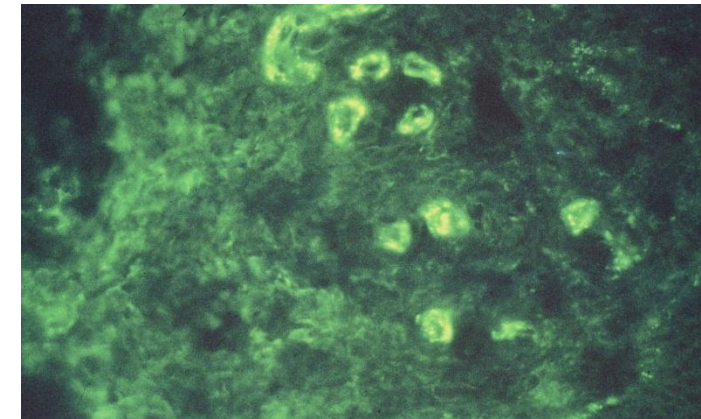
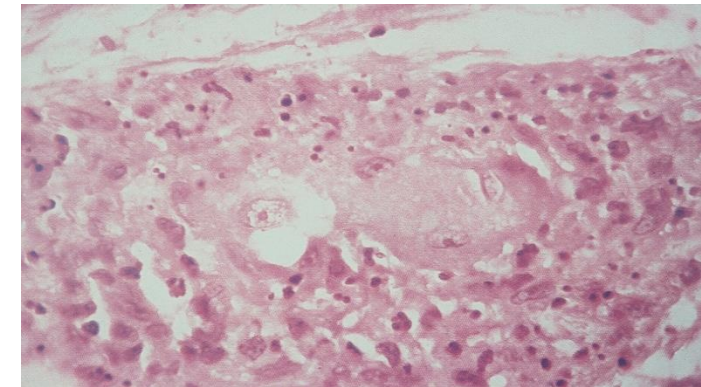
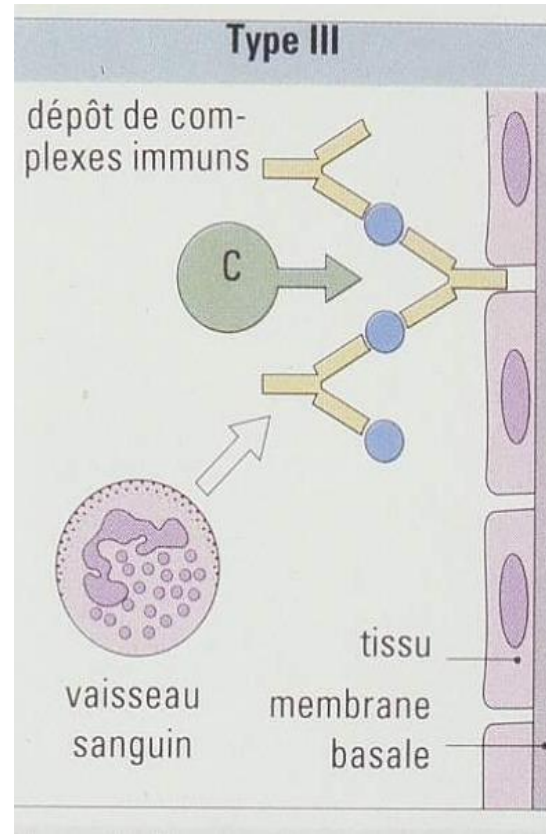
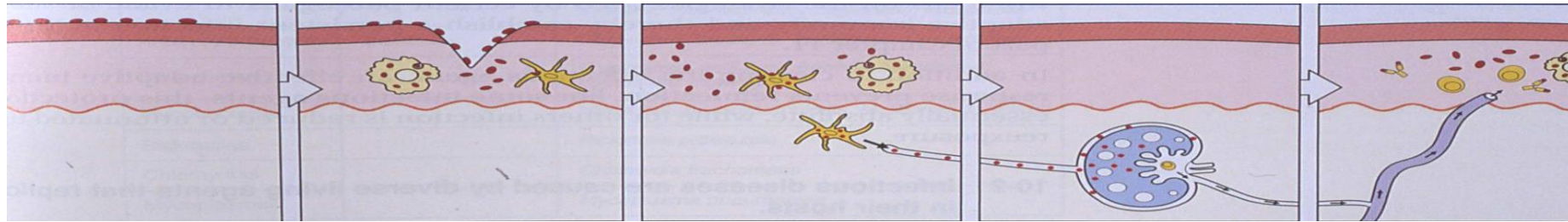


Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

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



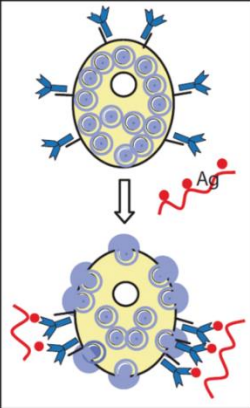
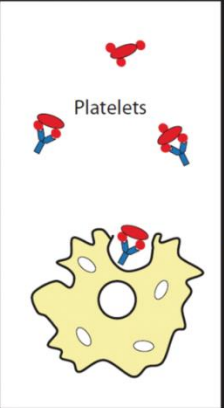
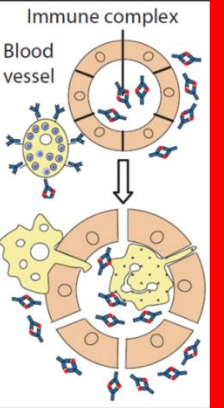
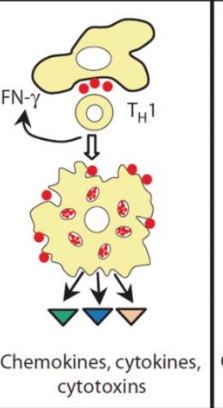
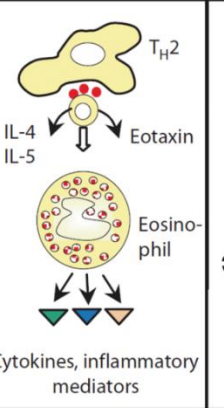
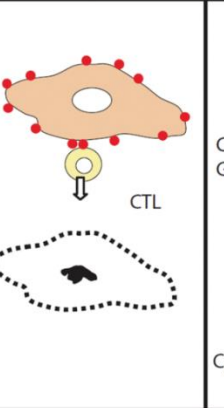
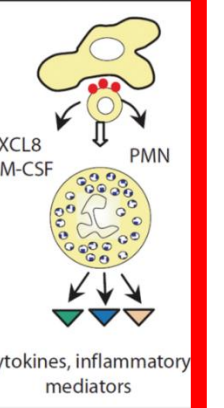
HS de type III aux antigènes inhalés

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

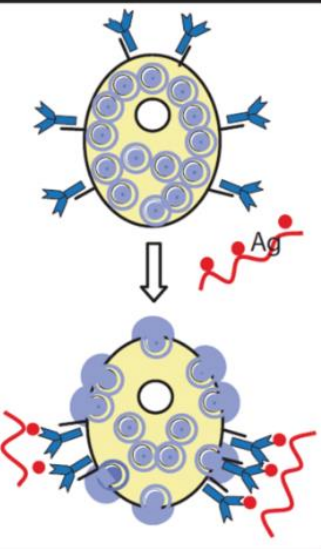
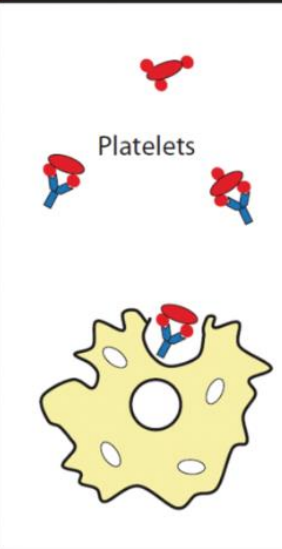
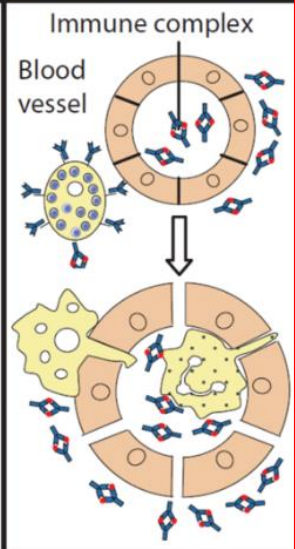
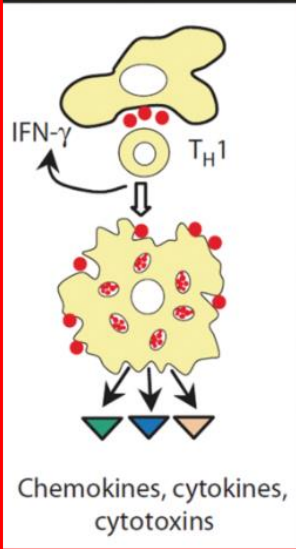
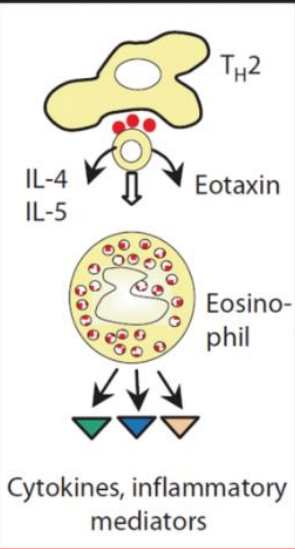
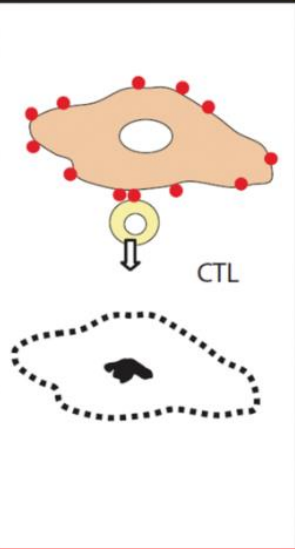
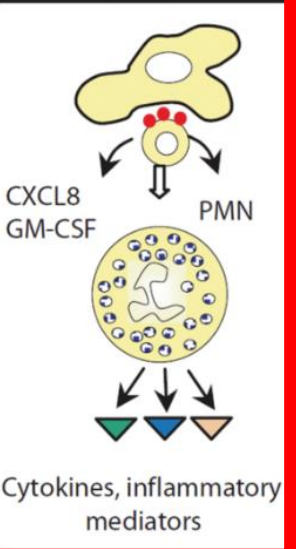
Hypersensibilités

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 | IFN- γ , TNF- α Th1/Type 1 | IL-5, IL-4/IL-13 Th2/Type 2 | Perforin/ granzyme B Cytotoxic | CXCL8, 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |
| 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 |
| Dermatoses autoimmunes et allergiques | Urticaire contact | Pemphigus Pemphigoïde Urticaire chroni. | Vascularites | Psoriasis | Dermatite atopique | Vitiligo Pelade Eczéma contact | Psoriasis |
| Allergies médicaments | Choc anaphylactique | Cytopénies medic. | Vascularites immuno-allerg. | Exanthème médic. | DRESS | Lyell Stevens-Johnson | Pustulose exanthématique aigüe généralisée |

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 | IFN- 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 |
| Effector | Mast cell activation | FcR+ cells (phagocytes, NK cells) | FcR+ cells Complement | Macrophage activation | Eosinophils | T cells | Neutrophils |
| |  |  |  |  |  |  |  |

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 γ t⁺ 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.)

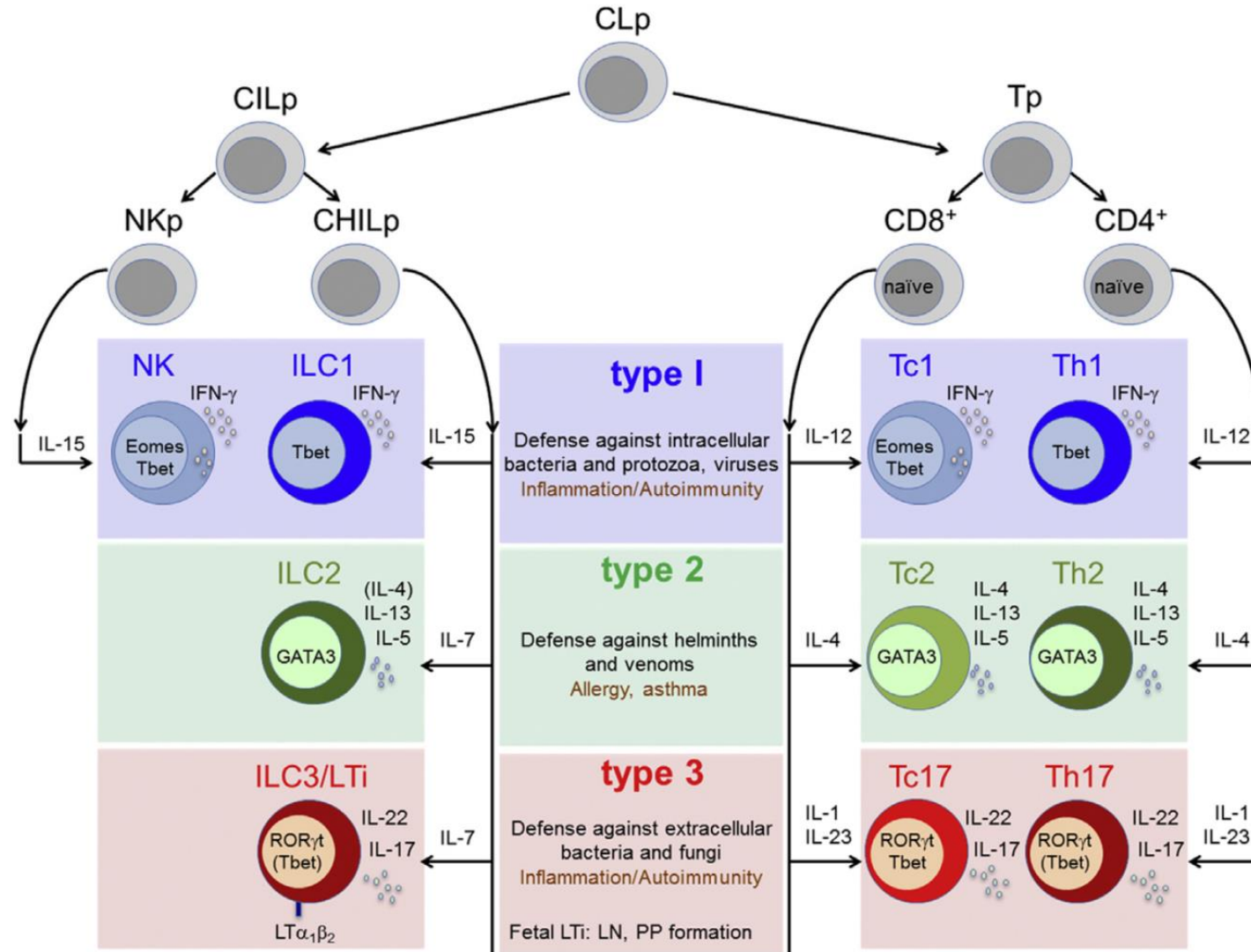
Key words: Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22

Abbreviations used

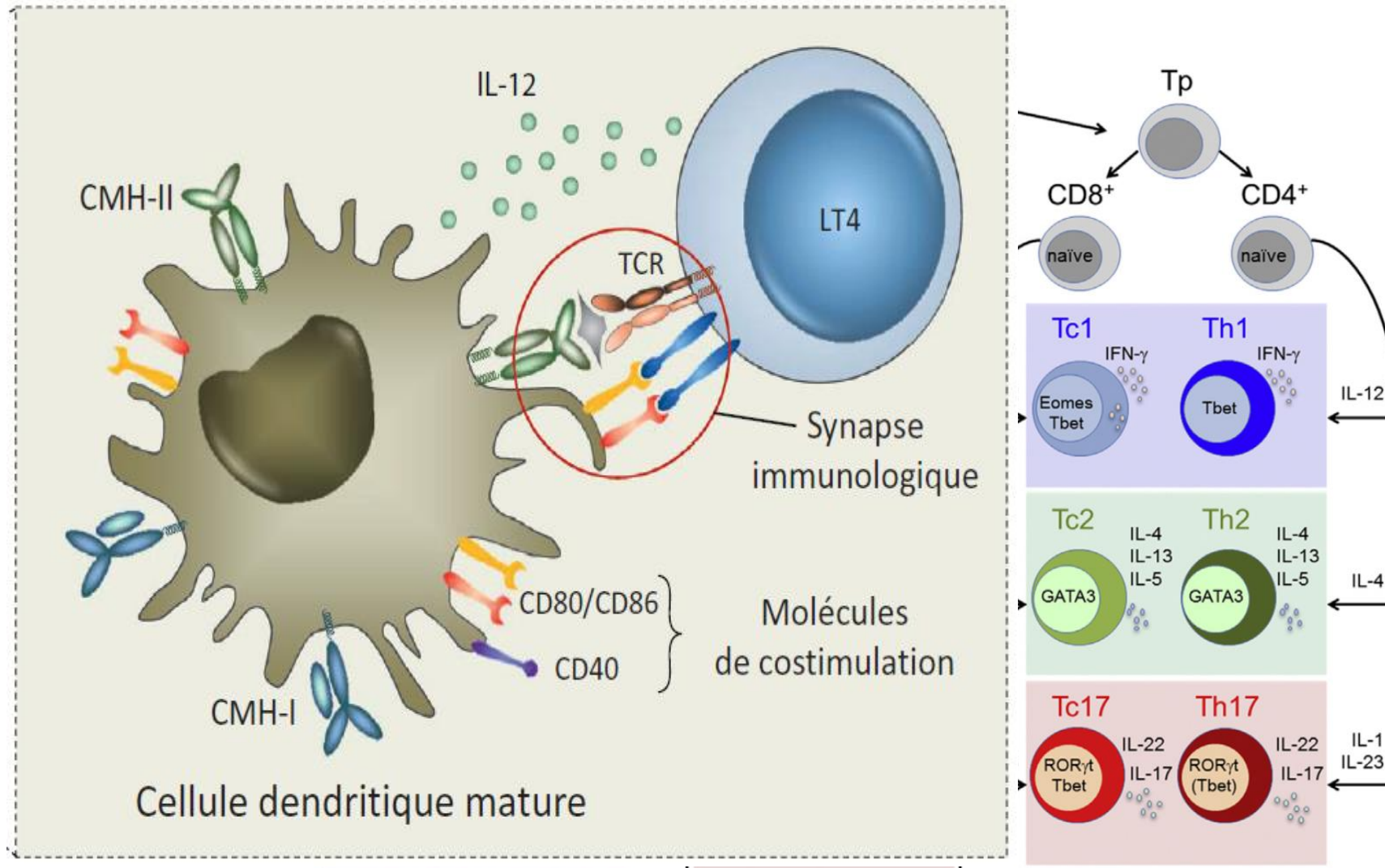
APC: Antigen-presenting cell
CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 cells
DC: Dendritic cell
Eomes: Eomesodermin
IBD: Inflammatory bowel disease
IL-7R: IL-7 receptor
ILC: Innate lymphoid cell
LT: Lymphotoxin
MP: Mononuclear phagocyte
MS: Multiple sclerosis
NK: Natural killer
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,

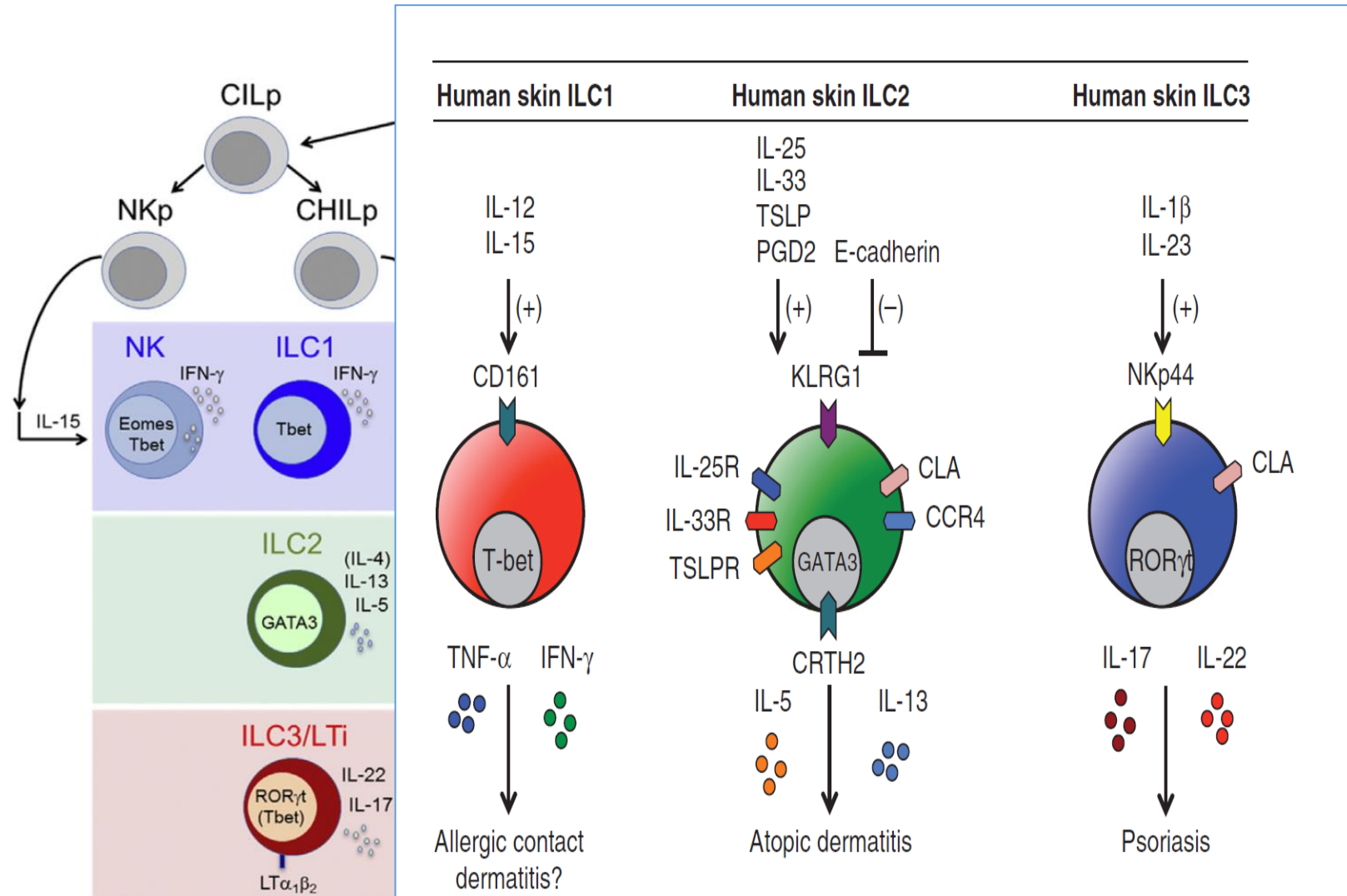
The 3 major types of innate and adaptive cell-mediated immunity



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



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



Hypersensibilité type IV Immunité cellulaire

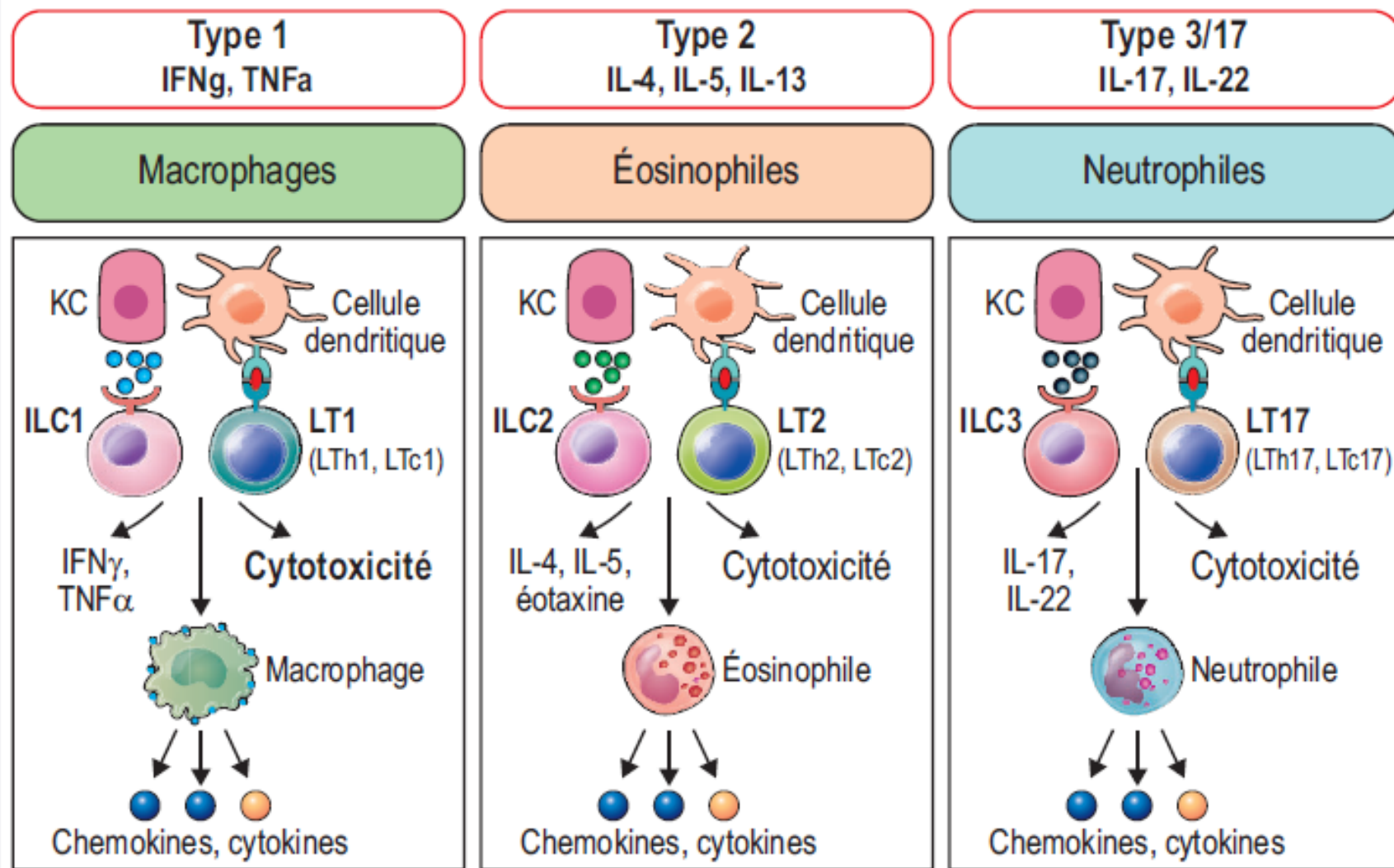


Table 1
Classification des réactions immunitaires cellulaires
(hypersensibilité retardée de type IV de Gell & Coombs)

Type 2 Immunity

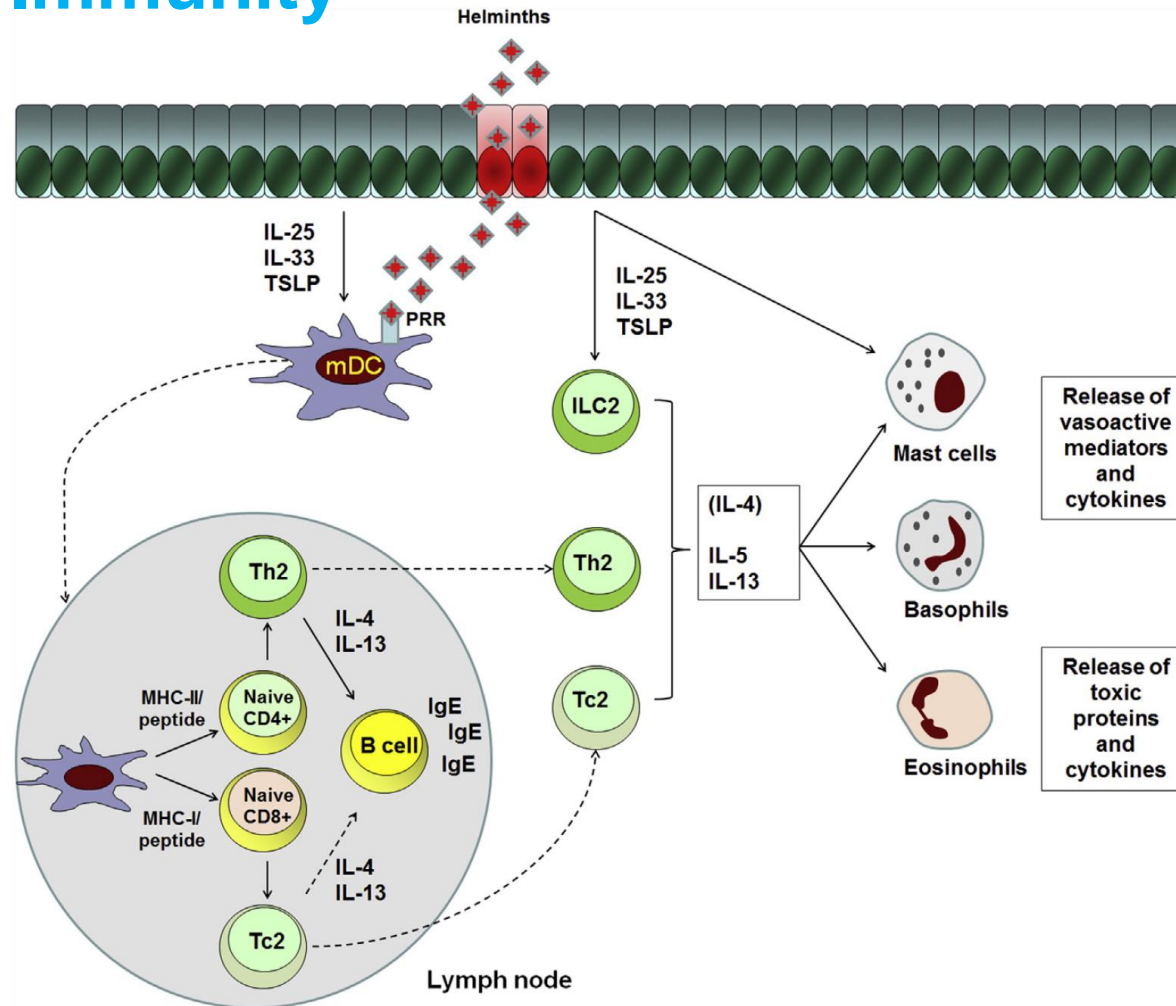


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin (*TSLP*) release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated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