Hypersensibilités allergiques et non allergiques

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Université Lyon1

http://allergolyon.fr

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

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department

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Physiopathologie de l’allergie

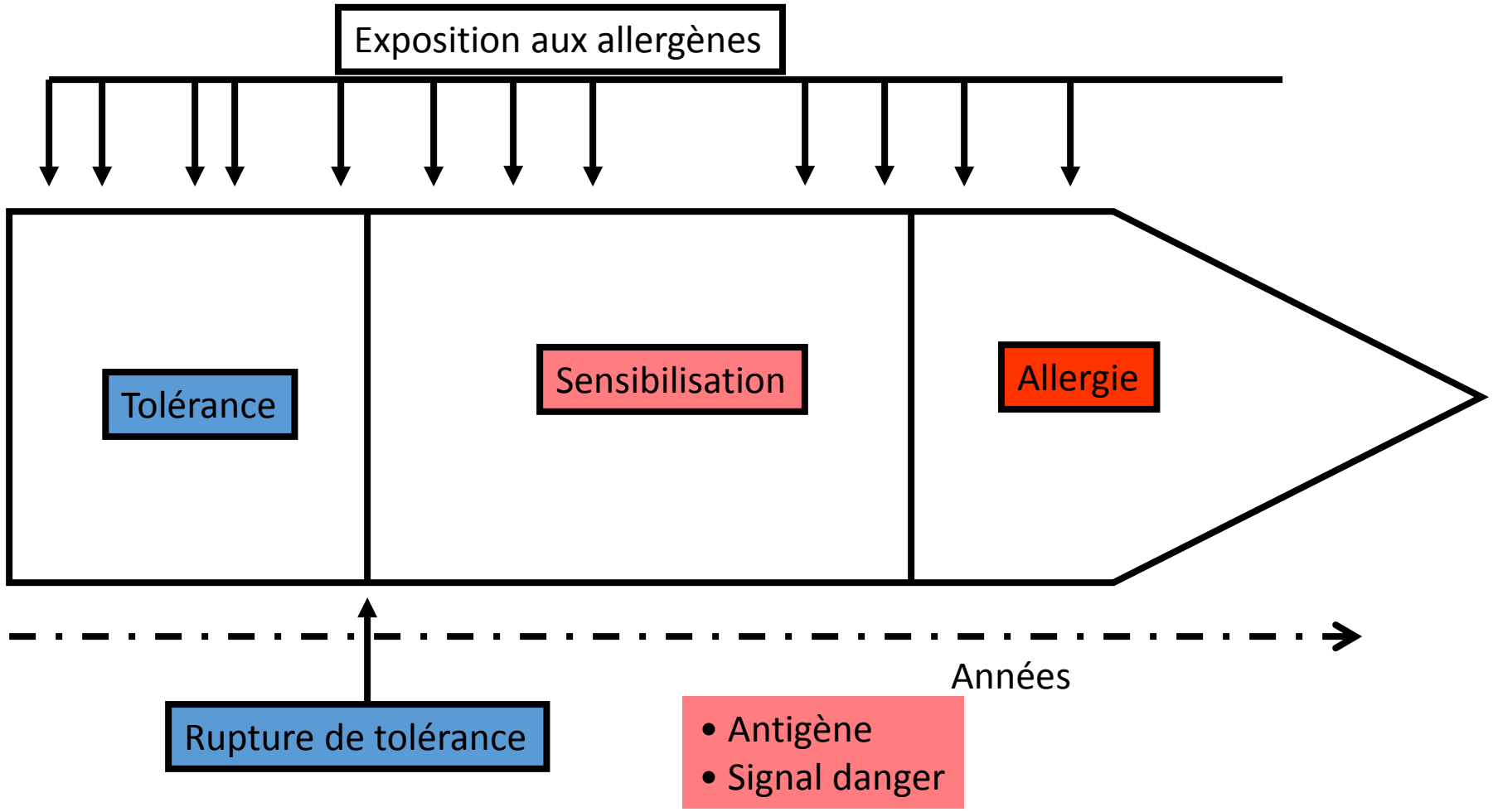
- La mise en place d’une maladie allergique obéit aux mêmes règles que la mise en place d’une réponse immunitaire vis à vis d’agents infectieux
- La physiopathologie des maladies allergiques est donc similaire à celle de la réponse anti-infectieuse

Allergie: rupture de tolérance

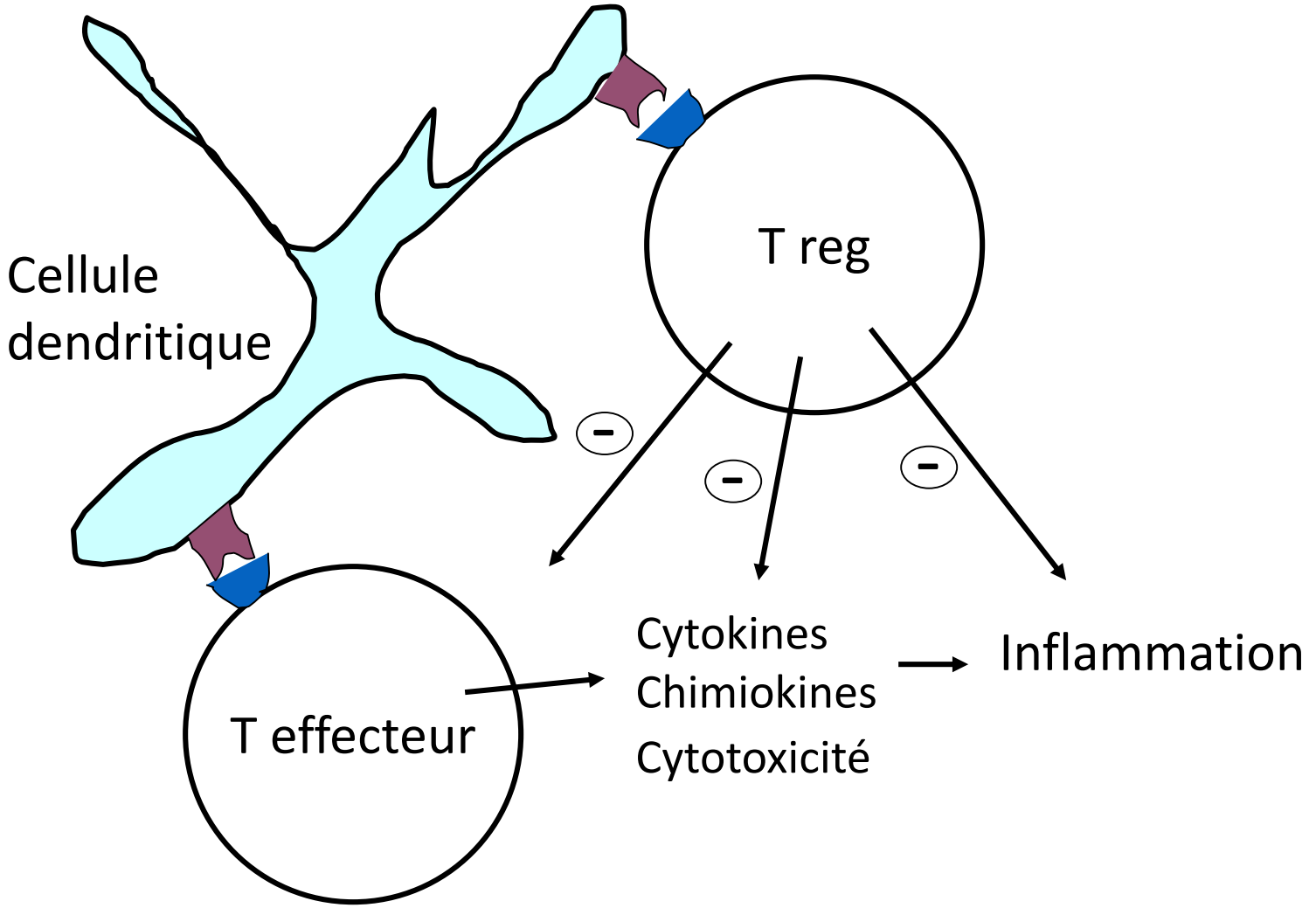
- Nous sommes tous en contact avec notre environnement
- Nous sommes tous sensibilisés vis à vis des antigènes de l'environnement
- Les sujets non allergiques développent une réponse immune tolérogène (régulatrice)
- Les sujets allergiques développent une réponse effectrice

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)*

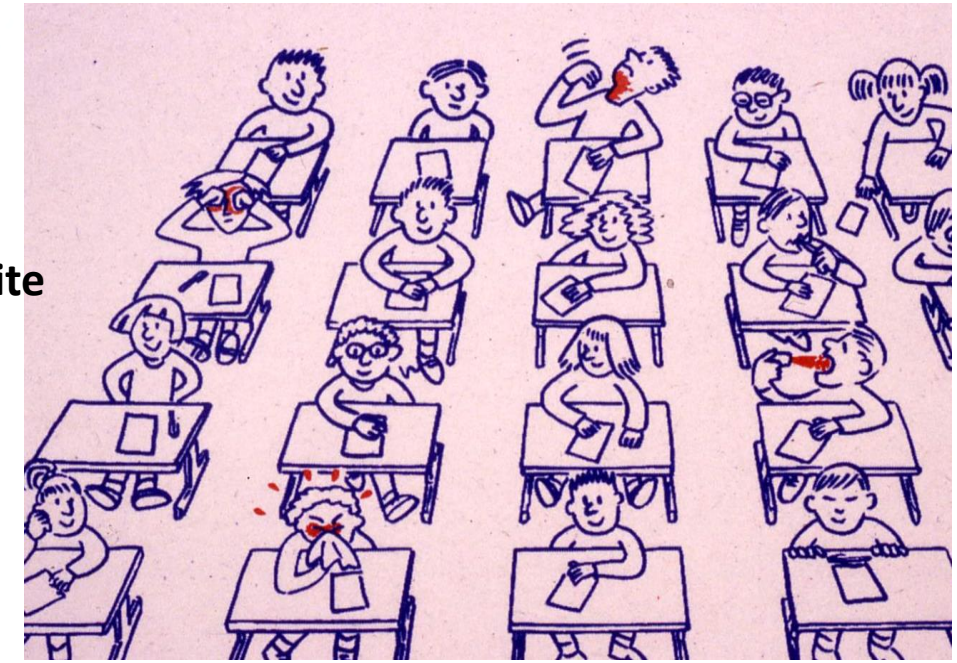
et/ou
et/ou
- *allergène chimique*
- *voie non naturelle de contact*
- *sujet non génétiquement prédisposé (ATCD familiaux)*

Allergènes

- Pneumallergènes
- Trophallergènes
- Injectables
- Contact cutané

maladie atopique

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

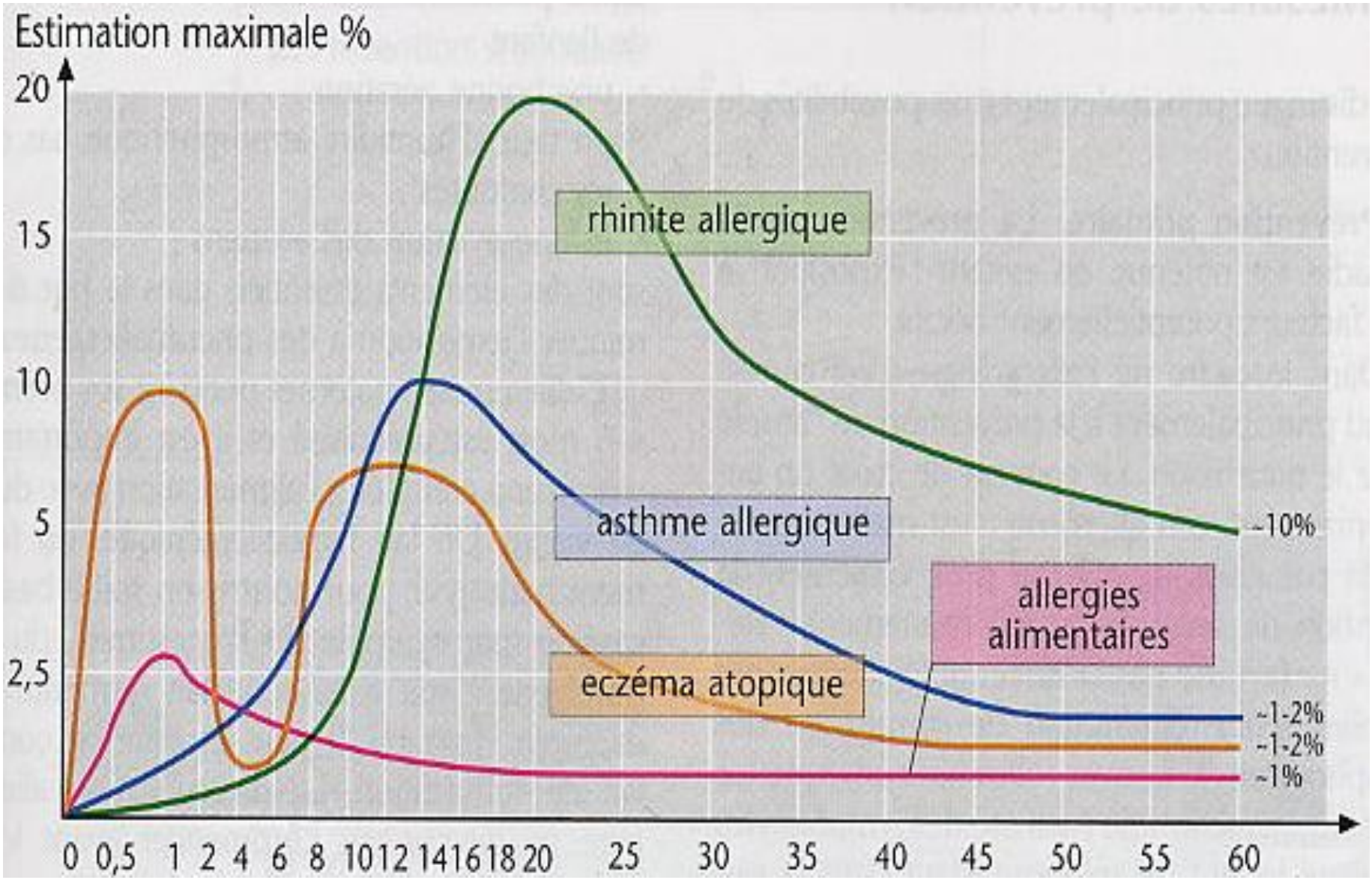


maladie non atopique

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

Allergènes cutanés
- **eczéma contact**

Histoire naturelle des maladies allergiques (atopiques)



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Terminologie

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

Hypersensitivity reactions

1. Immunology definition

   Hypersensitivity reactions = inappropriate and damaging immune response to an antigen caused by adaptive immunity (Igs and/or T cells)

   - Allergic diseases

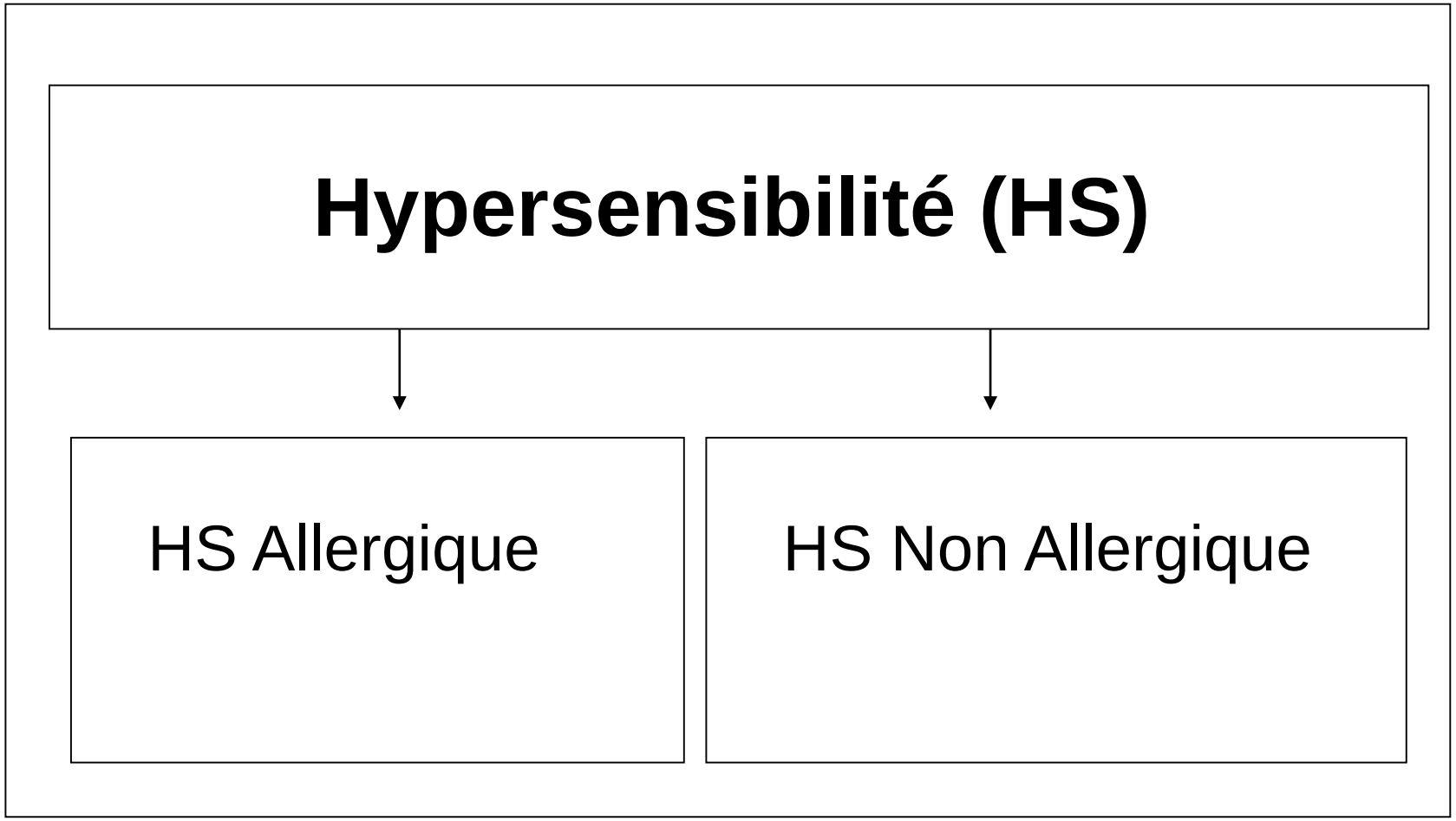
   - Autoimmune diseases

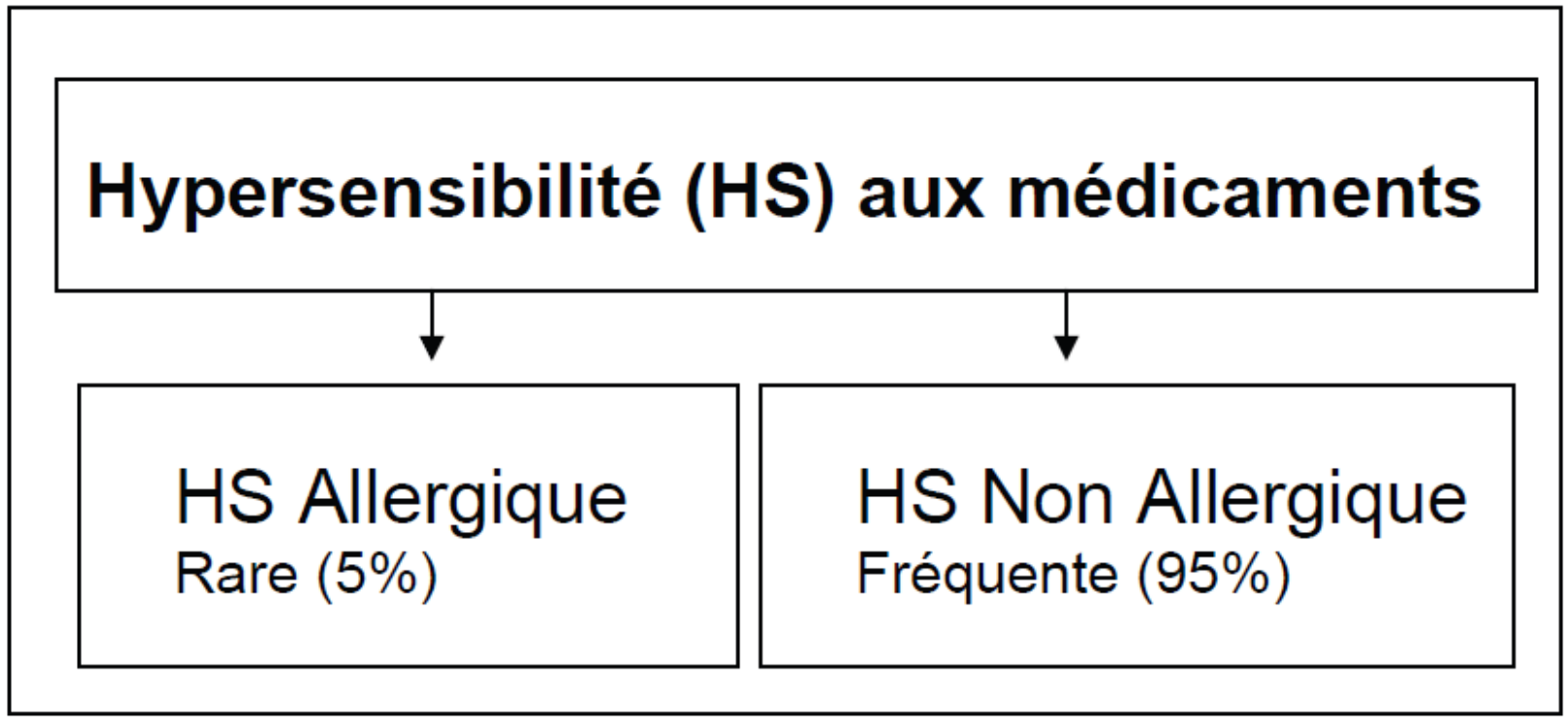
2. Allergy définition

   Hypersensitivity reactions = inappropriate and damaging immune response to a molecule caused by both innate and/or adaptive immunity

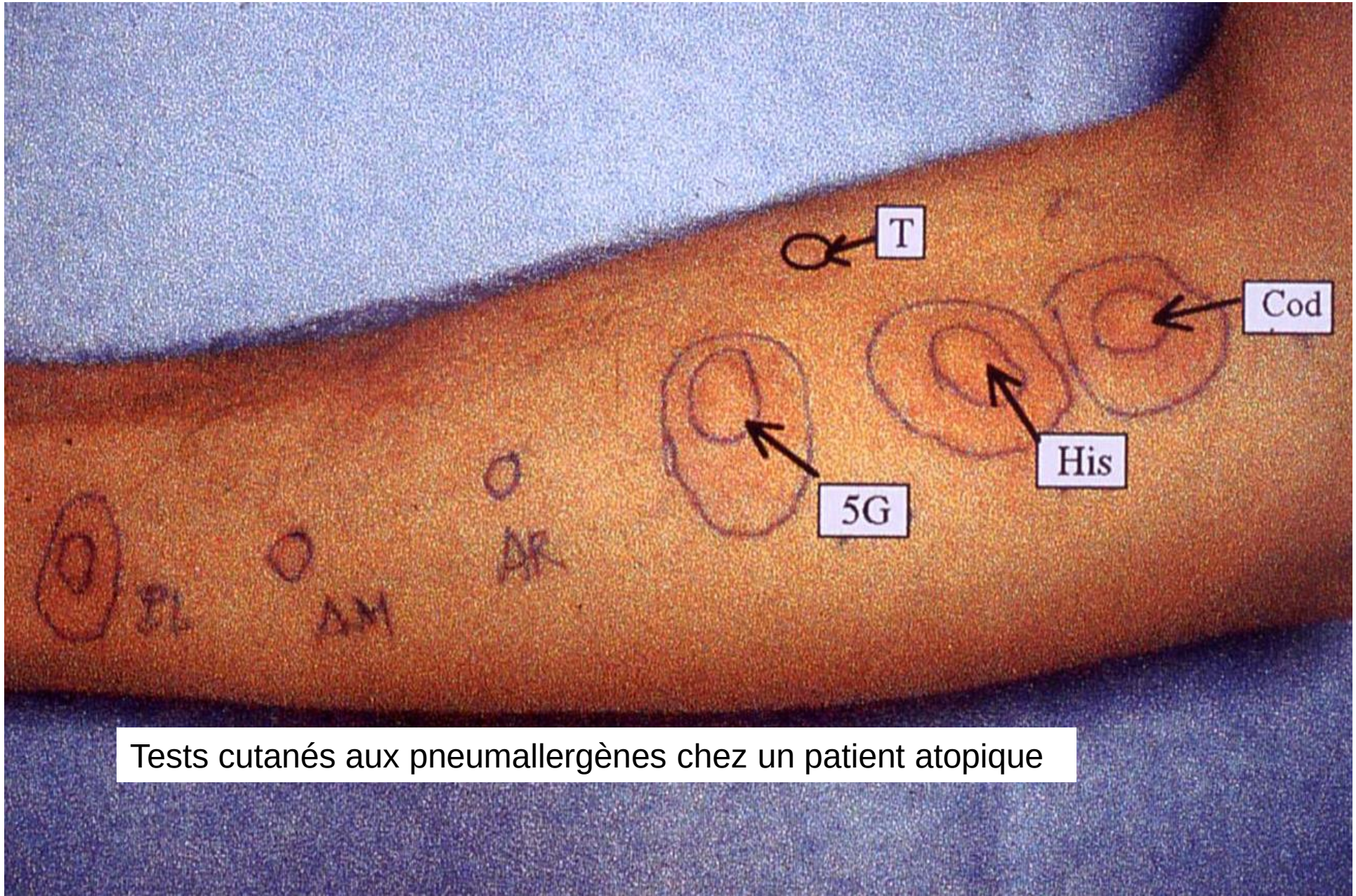
   - Allergic HS

   - Non allergic HS


Hypersensibilité (HS)
HS Allergique
HS Non Allergique


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

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,

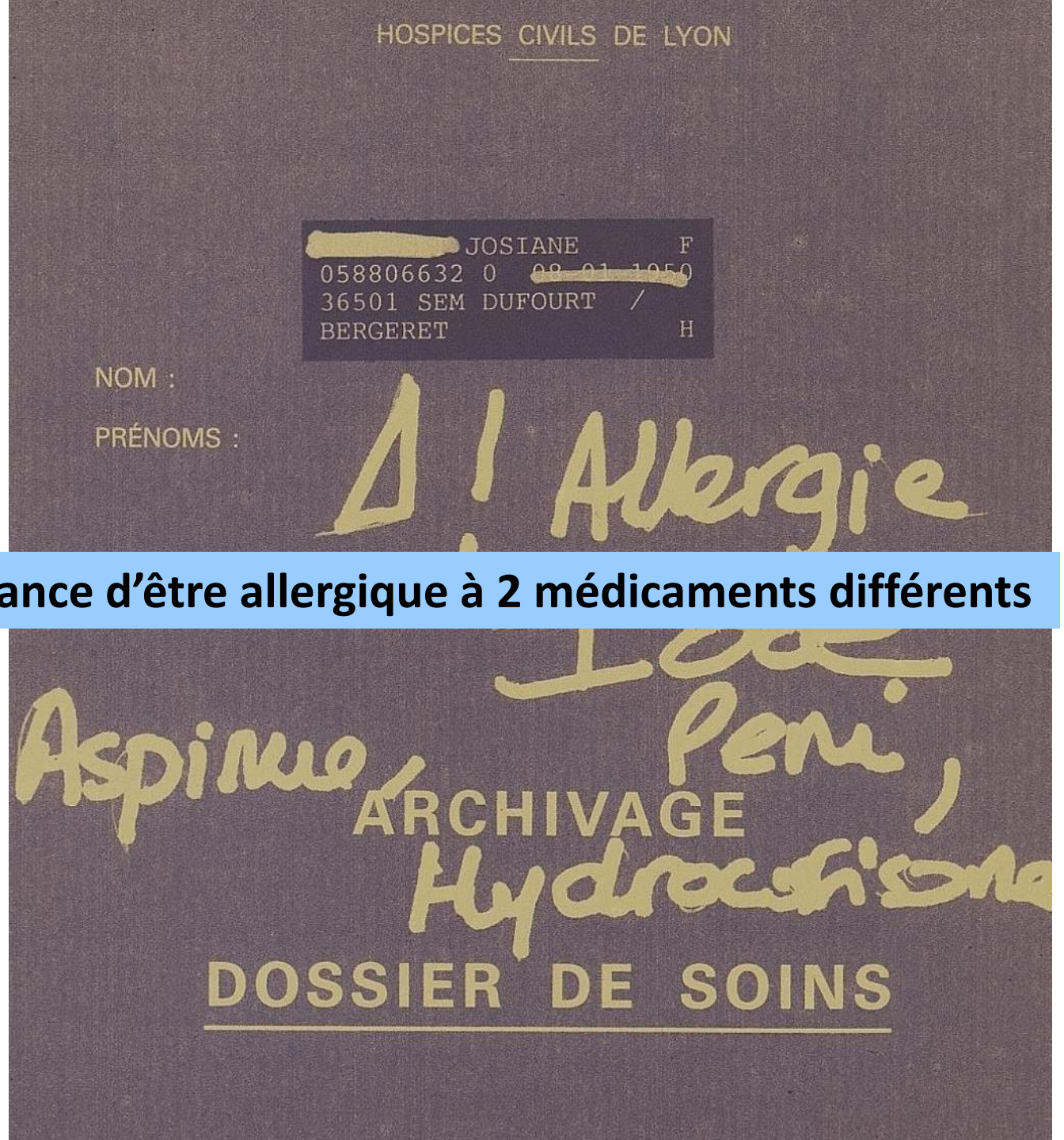
Mon fils Yves a rendez-vous le 25 Juin pour des tests. Il est né le 8 janvier 1983, et a fait un urticaire géant au Clamoxyl en 1986, donc on a évité cet antibiotique. Le 22 Décembre dernier, il a fait un oedème de Quincke,

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-



Aucune chance d'être allergique à 2 médicaments différents

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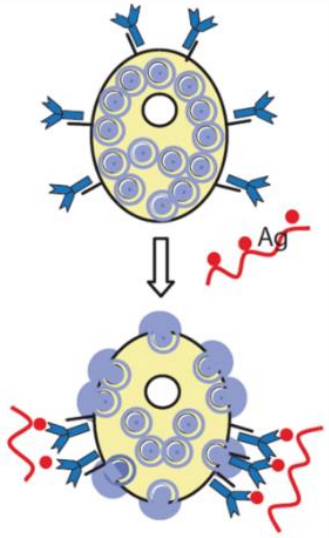
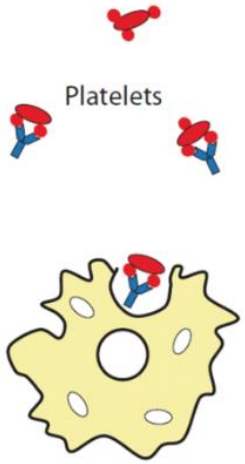
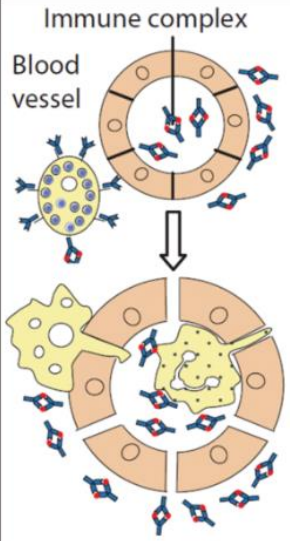
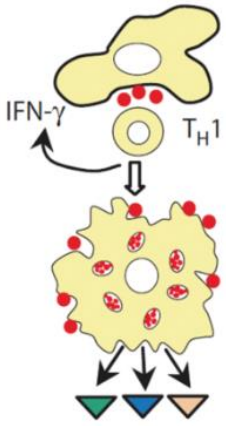
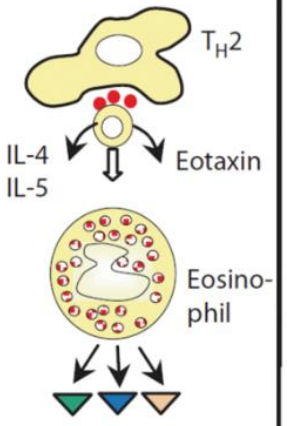
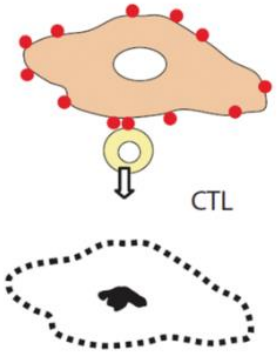
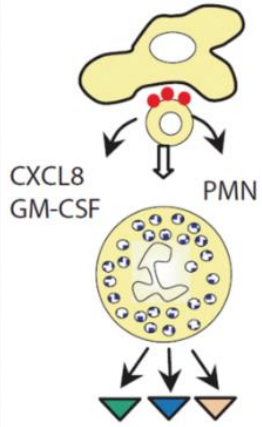
Hypersensibilités

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 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
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

Hypersensibilités

Classification de Gell & Coombs

Antibody ← → T cells →

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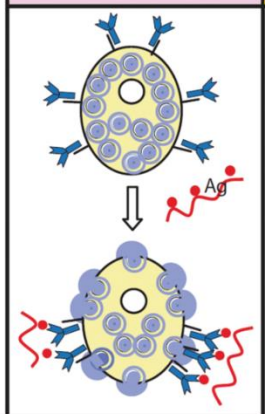
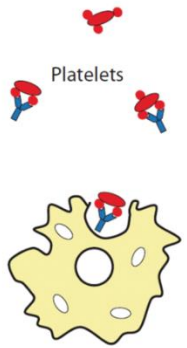
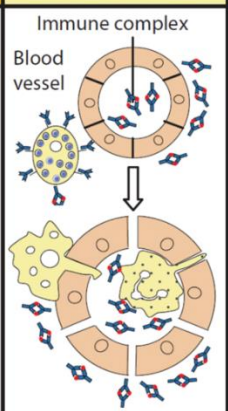
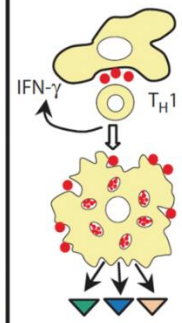
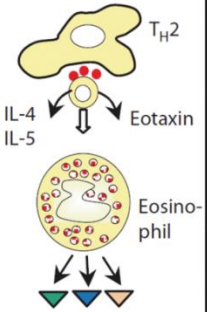
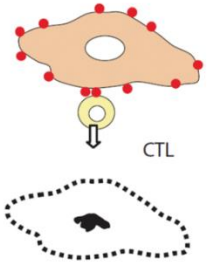
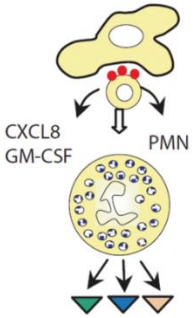
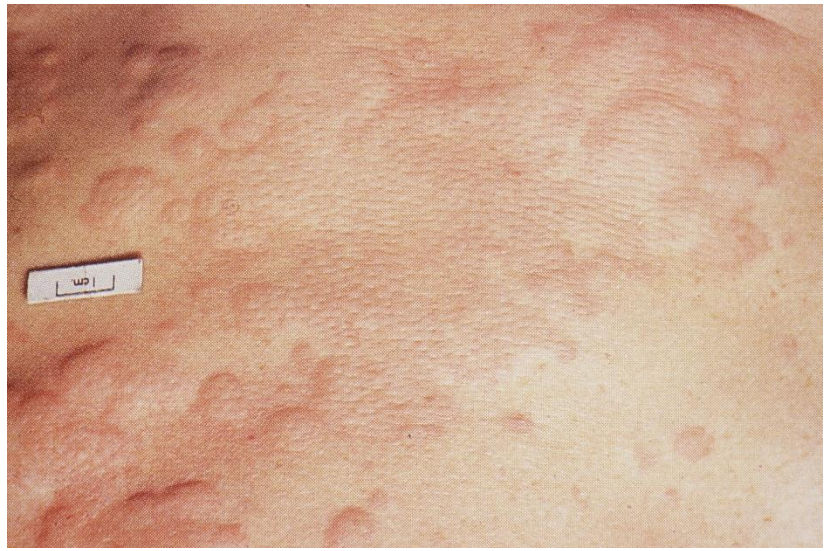
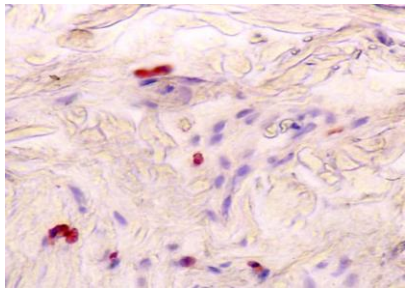
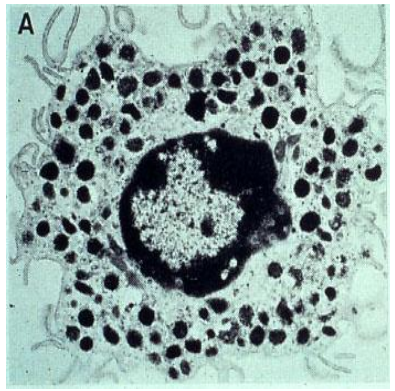
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Maladies autoimmunes et allergiques	**Anaphylaxie Rhinite allergique Asthme (crise)**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme chron. Rhinite chron.**	**Rejet de greffe Diabète SEP**	**Polyarthrite Sclérose en plaque Mal. de Crohn**
Dermatoses autoimmunes et allergiques	**Urticaire contact**	**Pemphigus Pemphigoide 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 aigue généralisée**

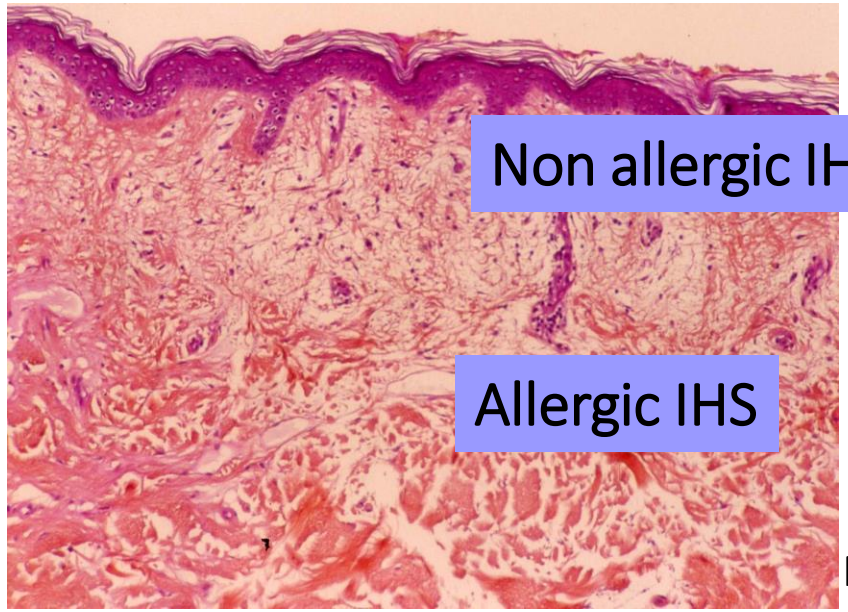
TYPE I HYPERSENSITIVITY

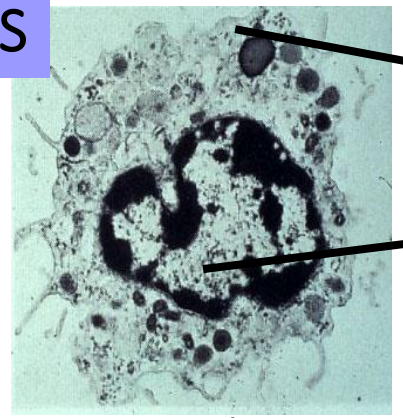


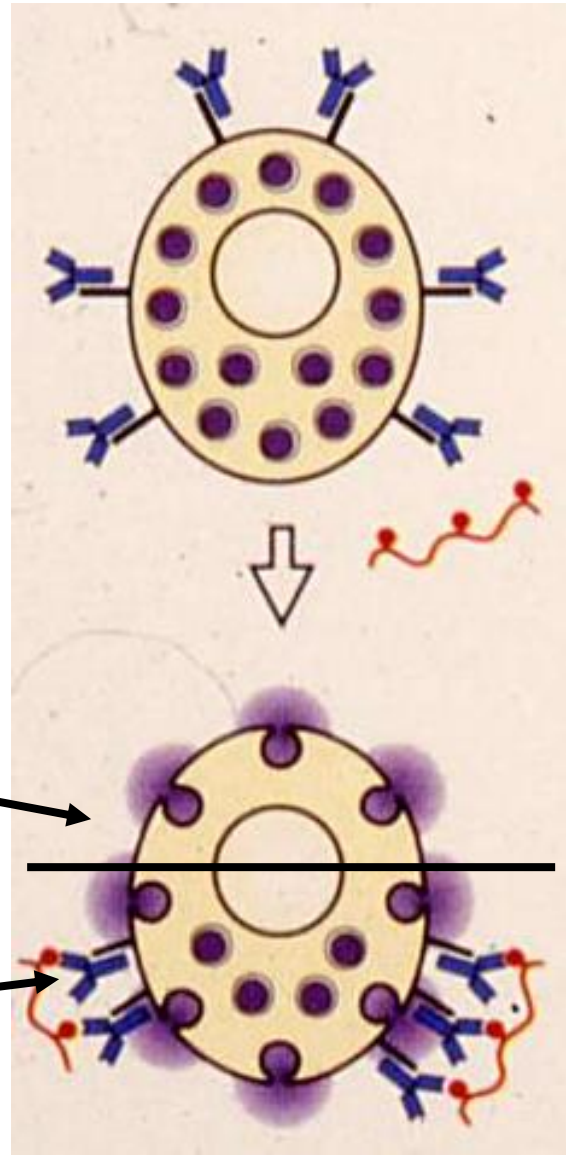
Œdème du derme / Vaisseaux





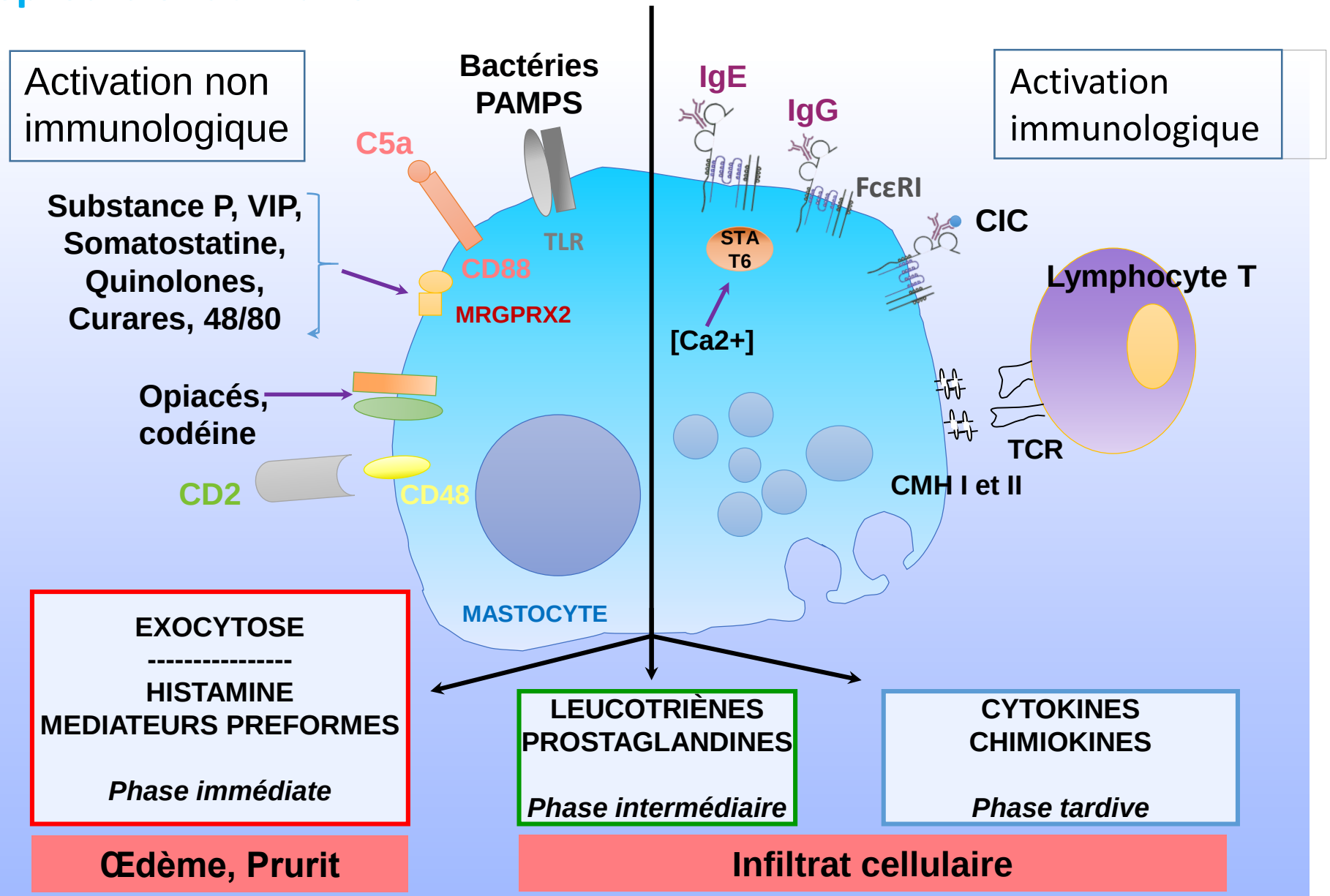






Mastocytes / Histamine

MASTOCYTES
Récepteurs et activation



LETTER 12 MARCH 2015 | VOL 519 | NATURE | 237

doi:10.1038/nature14022

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

Mast cells are primary effectors in allergic reactions, and may have important roles in disease by secreting histamine and various inflammatory and immunomodulatory substances[1,2]. Although they are classically activated by immunoglobulin (Ig)E antibodies, a unique property of mast cells is their antibody-independent responsiveness to a range of cationic substances, collectively called basic secretagogues, including inflammatory peptides and drugs associated with allergic-type reactions[1,3]. The pathogenic roles of these substances have prompted a decades-long search for their receptor(s). Here we report that basic secretagogues activate mouse mast cells *in vitro* and *in vivo* through a single receptor, Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2. Secretagogue-induced histamine release, inflammation and airway contraction are abolished in Mrgprb2-null mutant mice. Furthermore, we show that most classes of US Food and Drug Administration (FDA)-approved peptidergic drugs associated with allergic-type injection-site reactions also activate Mrgprb2 and MRGPRX2, and that injection-site inflammation is absent in mutant mice. Finally, we determine that Mrgprb2 and MRGPRX2 are targets of many small-molecule drugs associated with systemic pseudo-allergic, or anaphylactoid, reactions; we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

Responsiveness to basic secretagogues is conserved among mammals[4] and is also found in birds[5], indicating an ancient, fundamental role for its mechanism. Many basic secretagogues are endogenous peptides, often linked to inflammation; however, they activate connective tissue mast cells only at high concentrations and independent of their canonical receptors, so another mechanism of stimulation must exist[6]. Several candidate proteins that bind polycationic compounds have been proposed as basic secretagogue receptors[6–9]. Among these, MRGPRX2 has been screened with the most compounds[8,10–14], and short interfering RNA (siRNA) knockdown studies support at least a partial role for *MRGPRX2* in activation by four non-canonical basic secretagogues[11,13]. However, no direct *in vivo* study or knockout model has been employed for any candidate. The investigation of MRGPRX2 in mice is complicated because

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- Récepteur non sélectif
- Tous les mastocytes n'expriment pas MRGPRX2
- Variants avec gain ou perte de fonction de MRGPRX2
- Lie des peptides et molécules aux propriétés physico-chimiques particulières (Cationique, Hydrophobiques)
  - -Peptides toxines
  - -Neuropeptides
  - -Peptides anti-microbiens
  - -Other endogenous peptides: kallicreine
  - -Peptides médicaments
  - -Self-peptides dégradés des protéines

ell-specific receptor crucial reactions

Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

Substance	Mrgprb2 EC_{50}	MRGPRX2 EC_{50}
Compound 48/80	3.7 ± 0.5 μg/ml	470.1 ± 139.6 ng/ml
Substance P	54.3 ± 4.9 μM	152.3 ± 48.0 nM
Cortistatin-14	21.3 ± 0.9 μM	106.7 ± 39.3 nM
PAMP (9-20)	12.4 ± 1.6 μM	166.0 ± 35.7 nM
Mastoparan	24.0 ± 3.6 μM	3.9 ± 0.7 μM
Icatibant	32.5 ± 2.0 μg/ml	15.8 ± 2.7 μg/ml
Cetrorelix	23.4 ± 1.4 μg/ml	221.7 ± 63.1 ng/ml
Sermorelin	29.1 ± 1.2 μg/ml	4.5 ± 0.9 μg/ml
Octreotide	10.0 ± 1.1 μg/ml	6.6 ± 0.7 μg/ml
Leuprolide	152.0 ± 7.1 μg/ml	9.1 ± 0.7 μg/ml
Atracurium	44.8 ± 1.4 μg/ml	28.6 ± 2.4 μg/ml
Rocuronium	22.2 ± 3.3 μg/ml	261.3 ± 14.4 μg/ml
Ciprofloxacin	126.5 ± 5.1 μg/ml	6.8 ± 0.5 μg/ml
Moxifloxacin	14.1 ± 2.1 μg/ml	9.9 ± 0.6 μg/ml
Levofloxacin	807.6 ± 47.1 μg/ml	22.7 ± 0.4 μg/ml
Ofloxacin	225.0 ± 25.4 μg/ml	30.1 ± 1.5 μg/ml

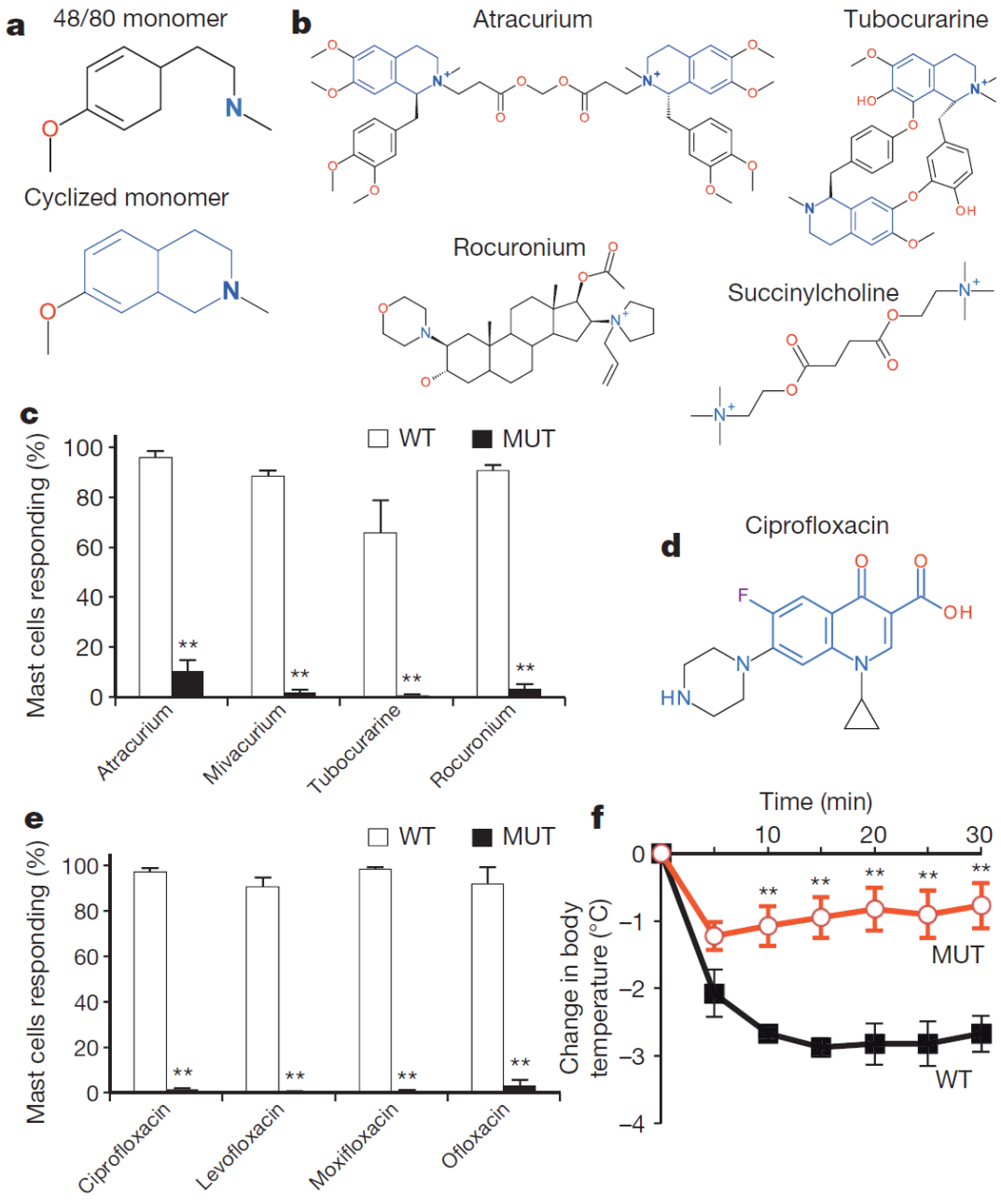
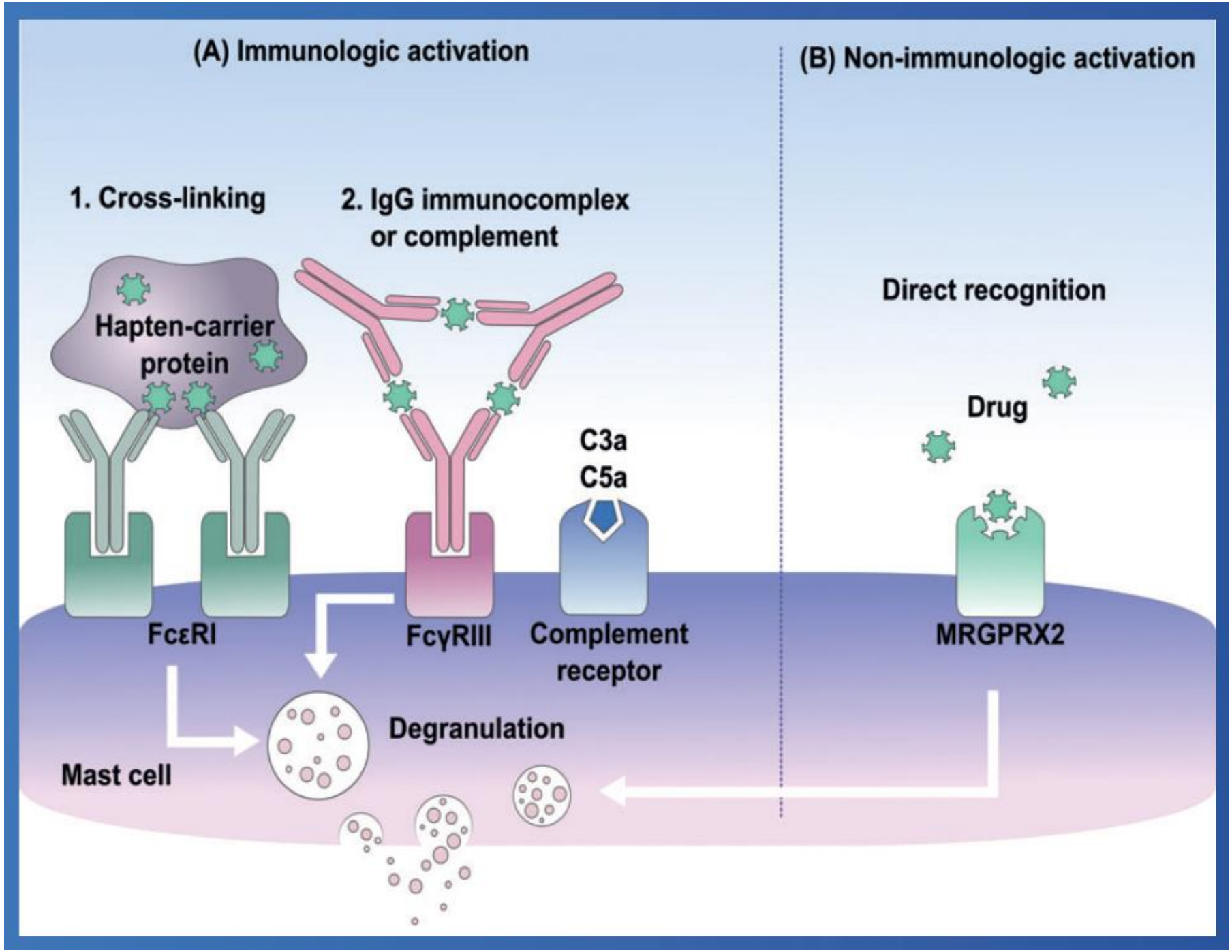


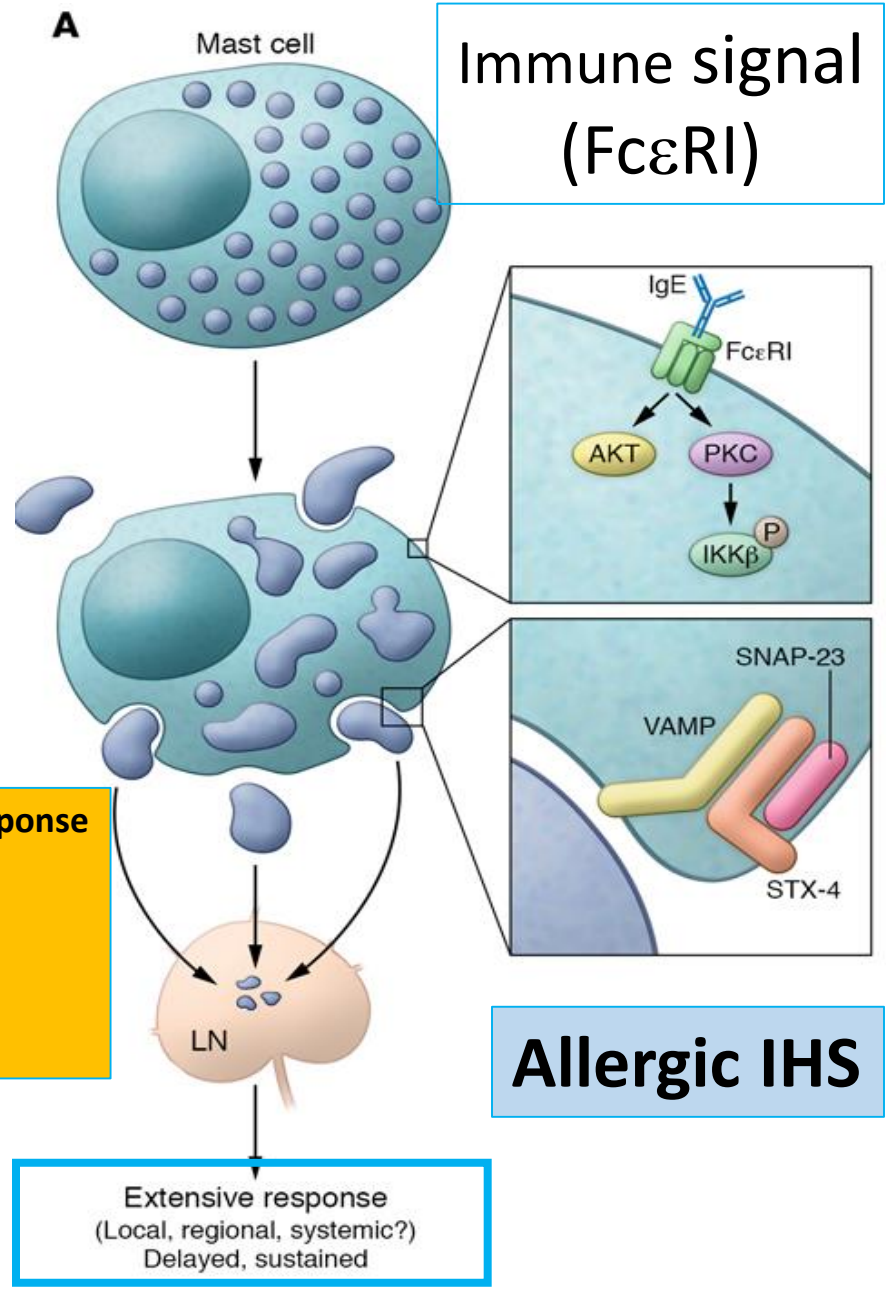
Figure 4 | Mrgprb2 mediates mast cell responsiveness and side effects of small-molecule therapeutic drugs. **a**, Structures of 48/80 and a cyclized variant. The THIQ motif is highlighted in blue. **b**, Structures of representative members of all NMBD classes (see Supplementary Information). THIQ motifs are highlighted in blue. Note that only succinylcholine lacks a bulky hydrophobic group. **c**, Percentage of responding cells from wild-type (WT) and Mrgprb2^{MUT} (MUT) peritoneal mast cells after application of various NMBDs, assayed using Fluo-4 imaging. Concentrations of drugs (in $\mu g\,ml^{-1}$): atracurium, 50; mivacurium, 20; tubocurarine, 30; rocuronium, 500. $n = 3$ mice per genotype; >150 cells counted per substance. **d**, Structure of ciprofloxacin, with the motif common to all fluoroquinolones highlighted in blue. Note the nitrogens close to the quinolone motif. **e**, Percentage of responding cells from wild-type and Mrgprb2^{MUT} peritoneal mast cells after fluoroquinolone application, assayed using Fluo-4 imaging. Concentrations of drugs (in $\mu g\,ml^{-1}$): ciprofloxacin, 200; levofloxacin, 500; moxifloxacin, 160; ofloxacin, 400. $n = 3$ mice per genotype; >150 cells counted per substance. **f**, Changes in body temperature after intravenous injection of ciprofloxacin (1.5 mg in 125 µl saline) at time 0. $n = 4$ mice per genotype. Data are presented as mean ± s.e.m. Two-tailed unpaired Student's *t*-test: $*P < 0.05$, $**P < 0.01$.

MASTOCYTES

Récepteurs et activation



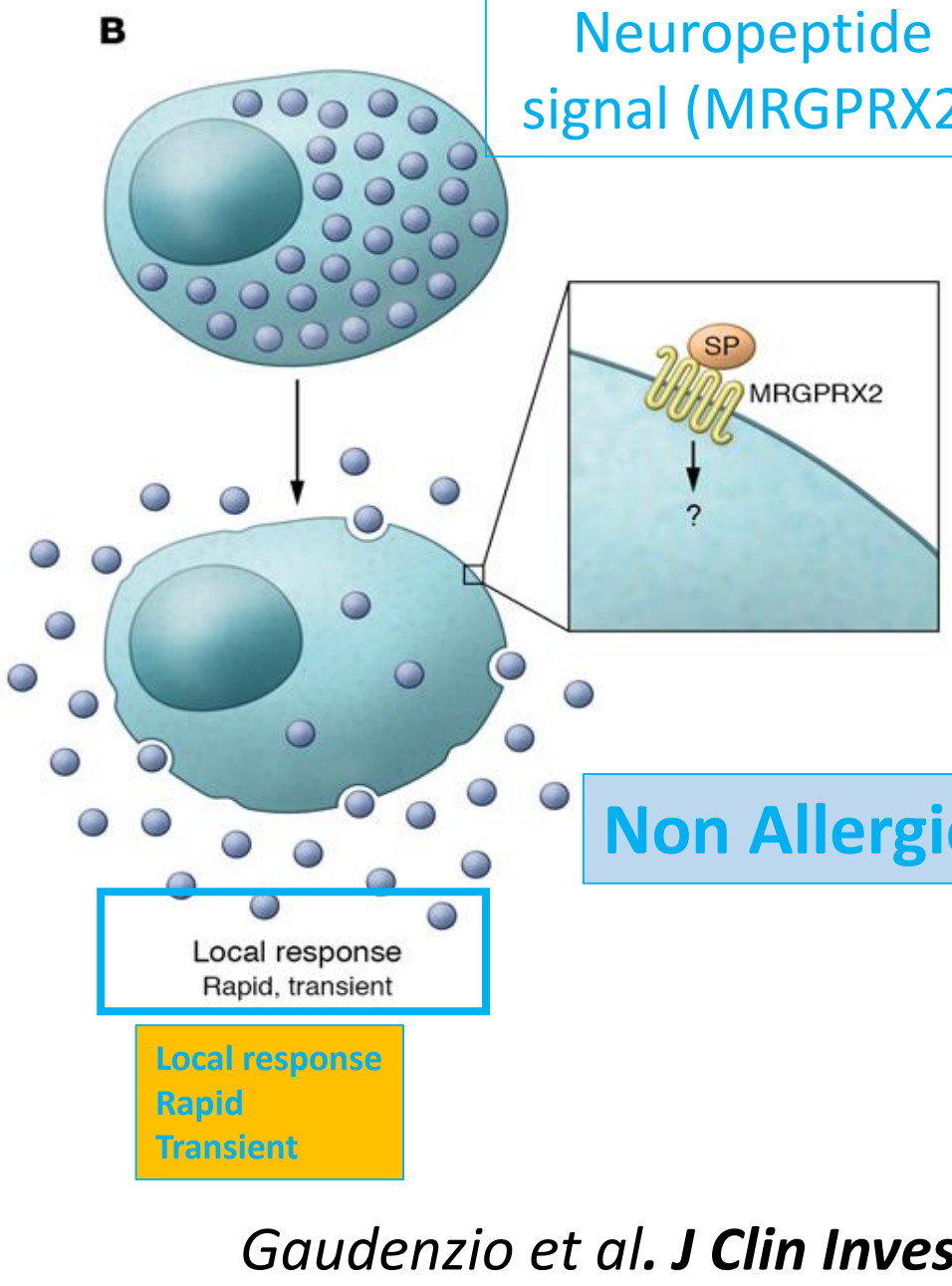
Two fundamental degranulation pathways in mast cells



Extensive response
- **Local**
- **Regional**
- **Systemic**

Delayed
Sustained

Allergic IHS



Non Allergic IHS

Local response
Rapid
Transient

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

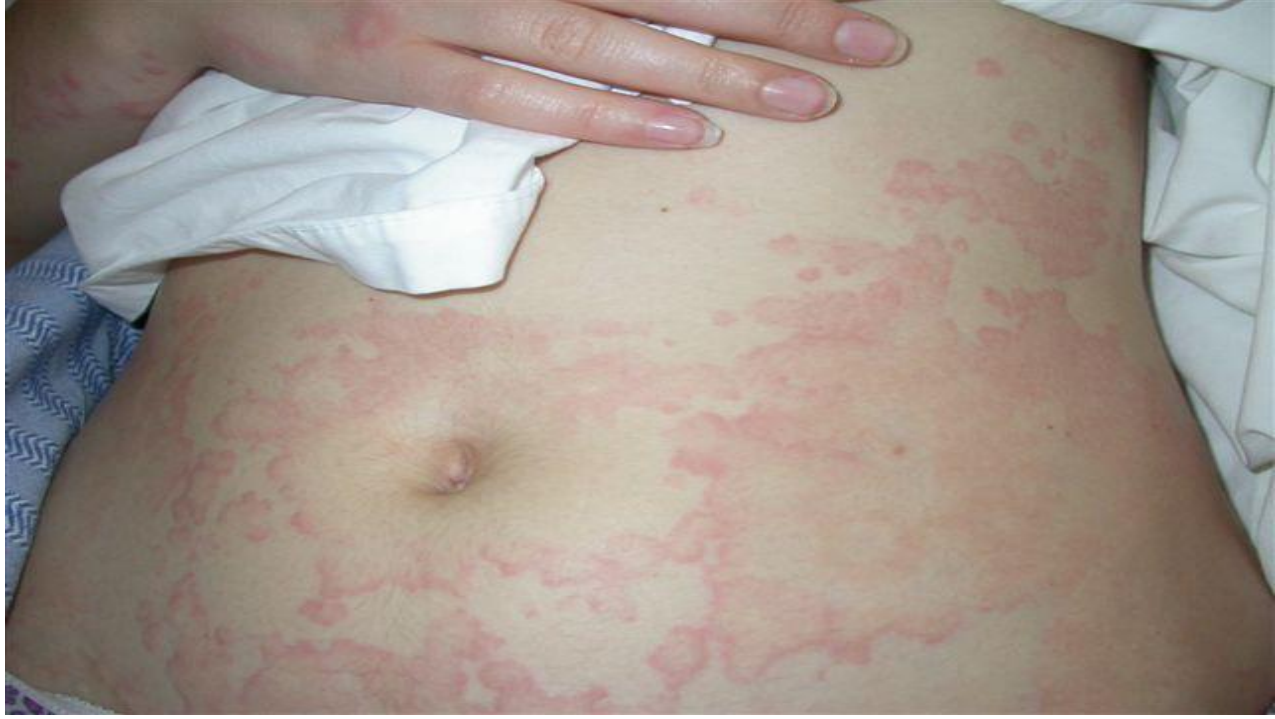
Drug-induced urticaria and angioedema

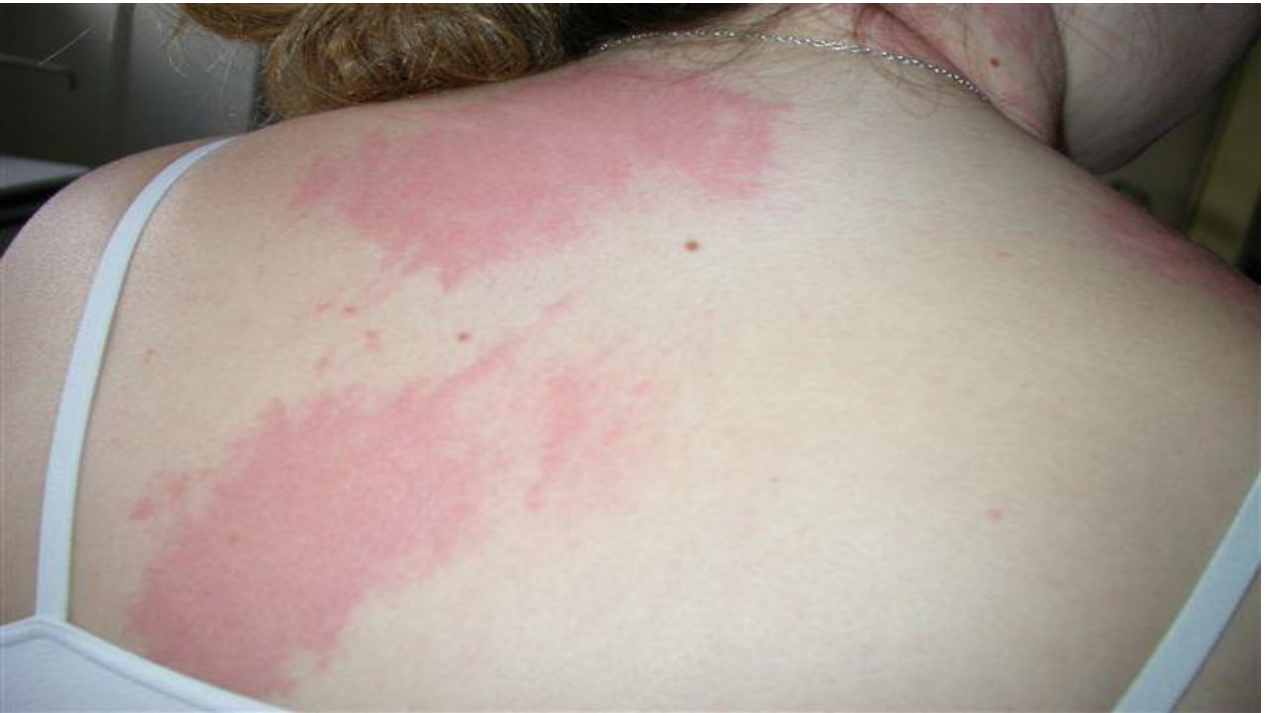
- **Allergic (IgE)**: rares (5%) and exceptionally isolated

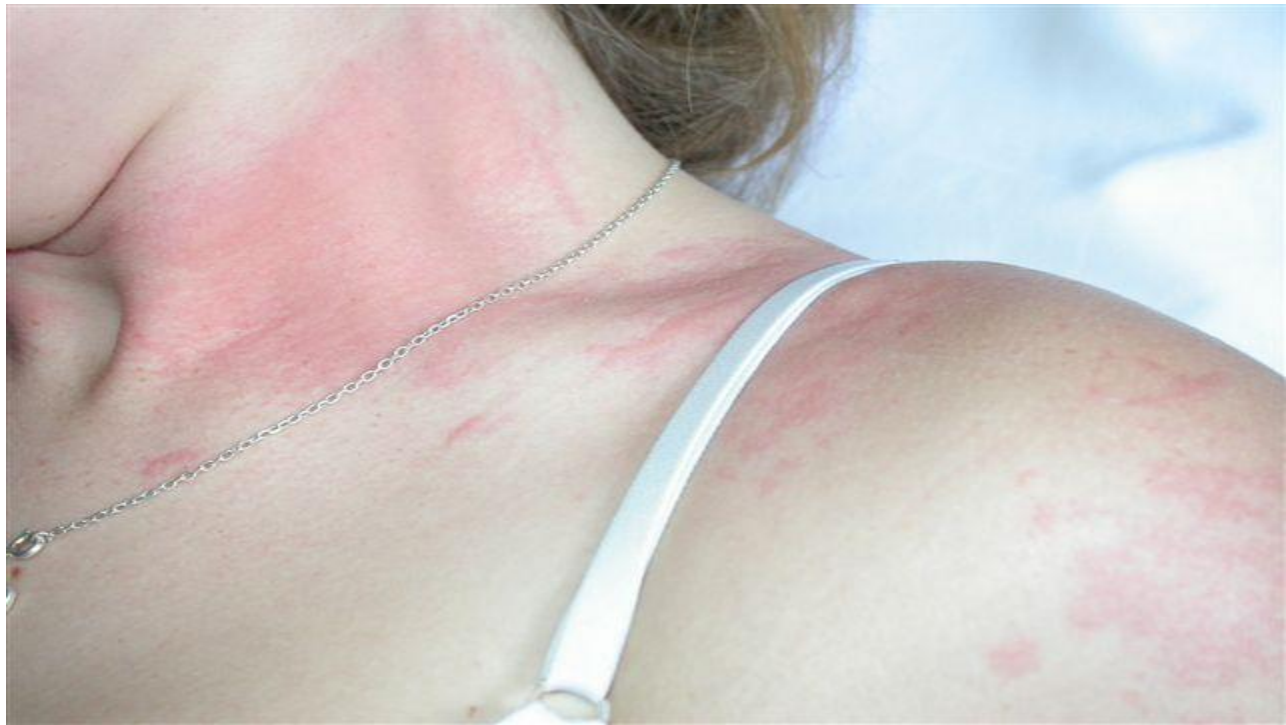
- **Non allergic**: frequent (95%) and almost always benign

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

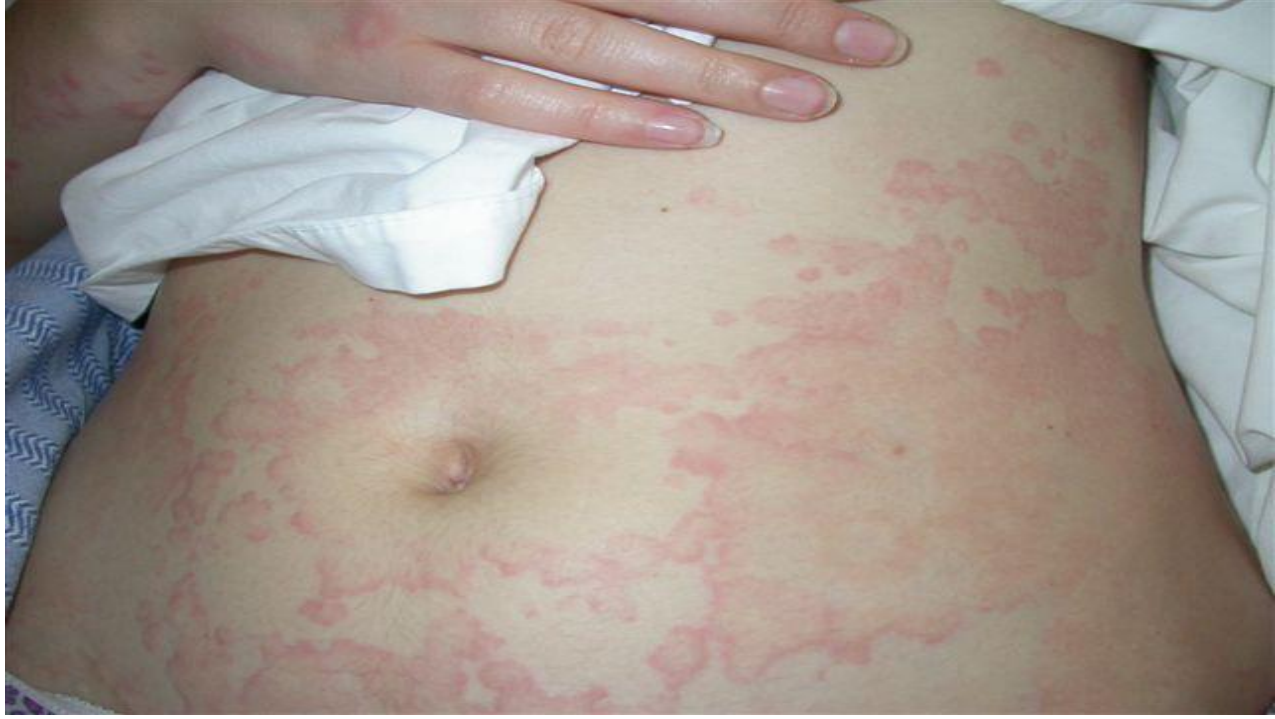

First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM

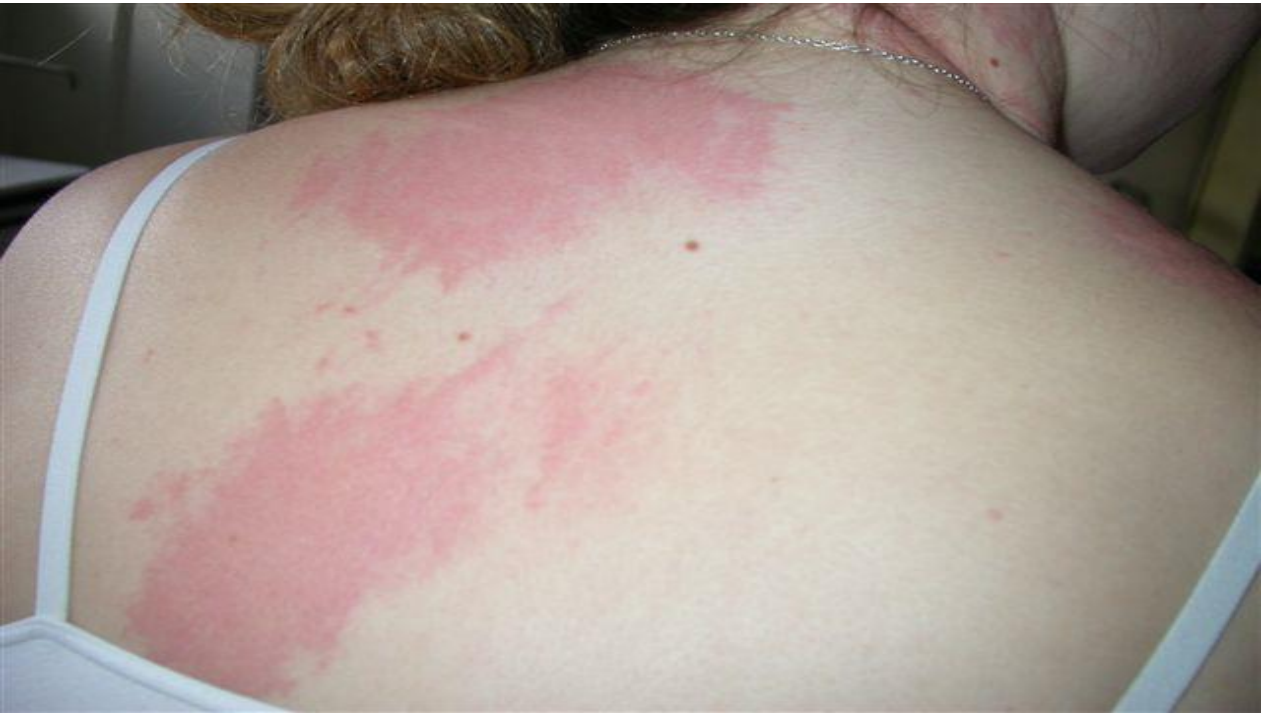


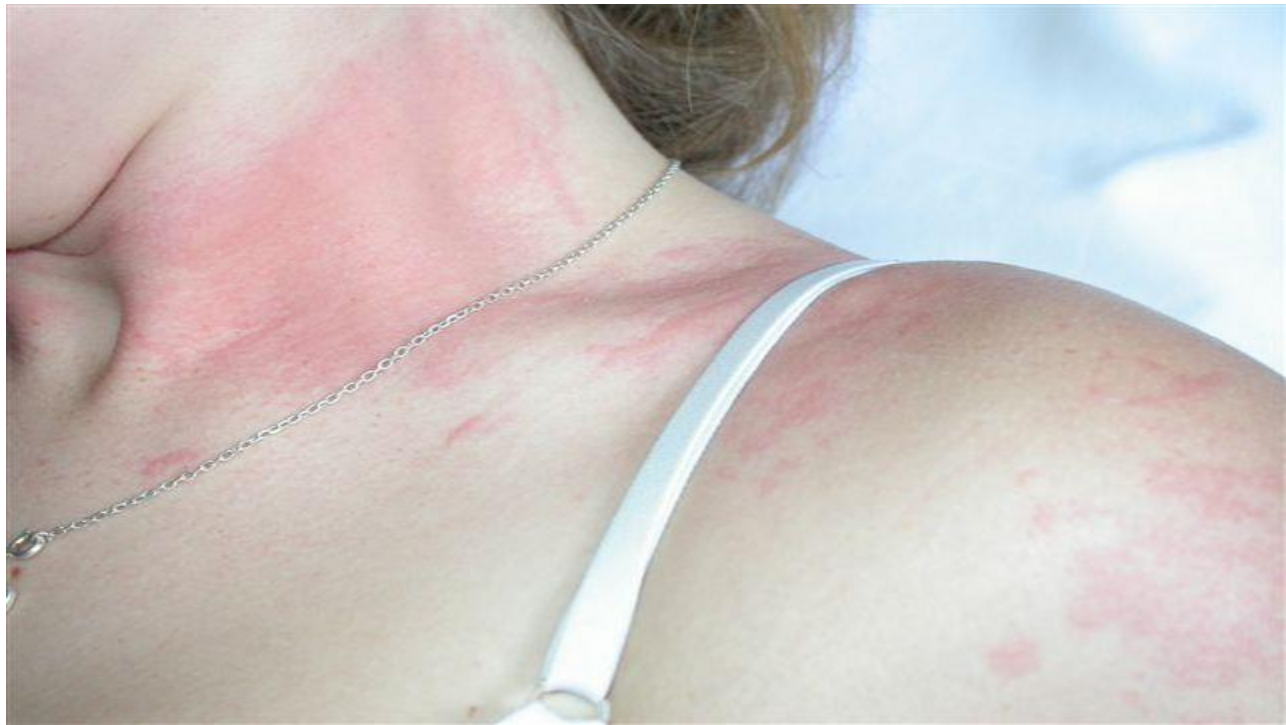


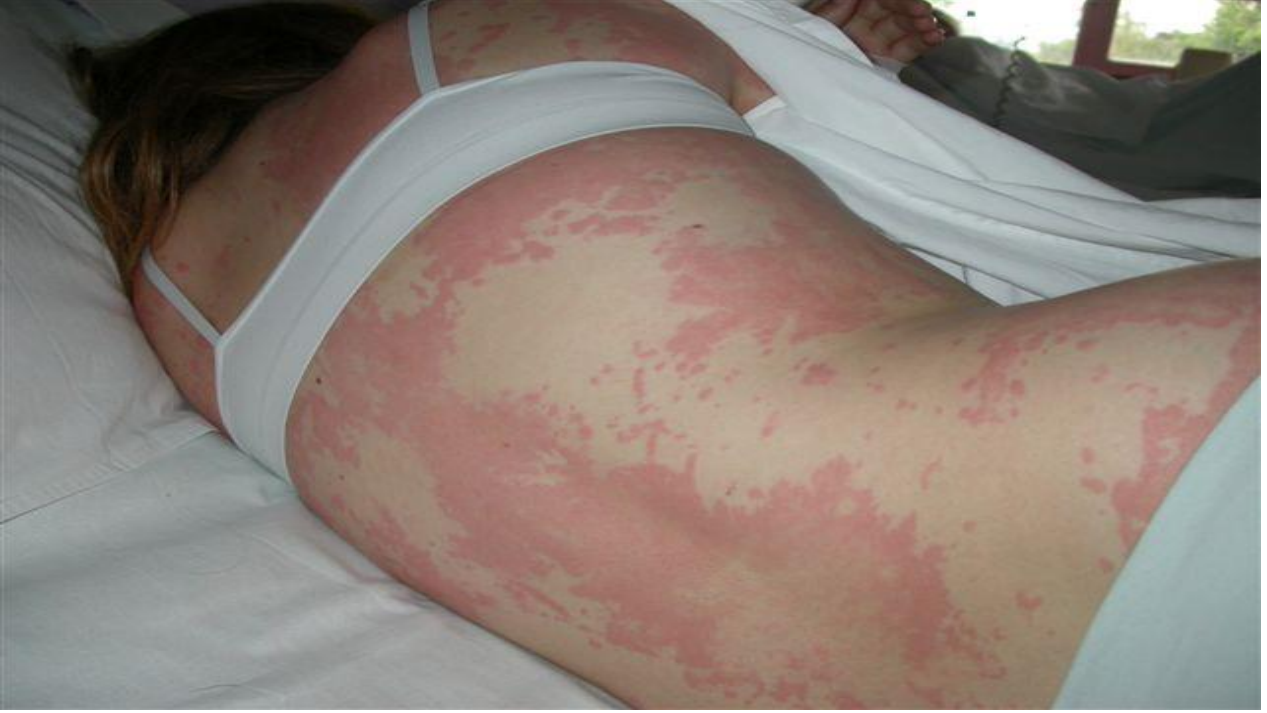


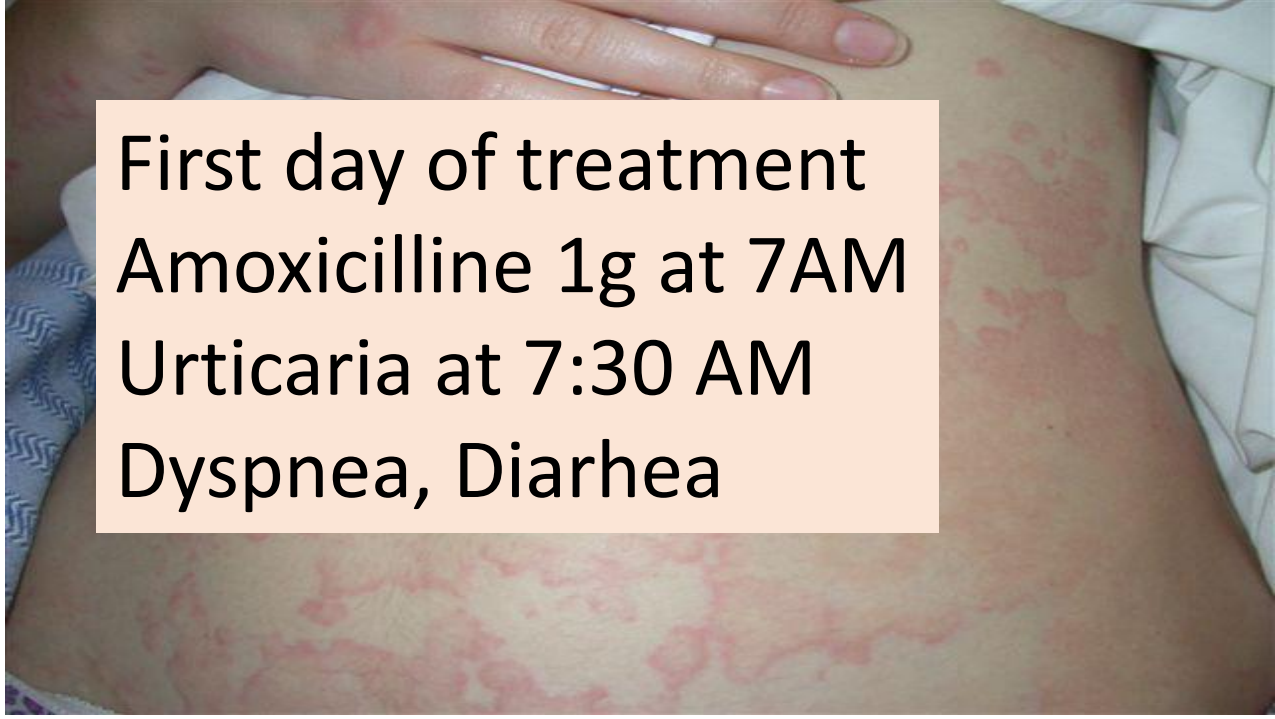

Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM



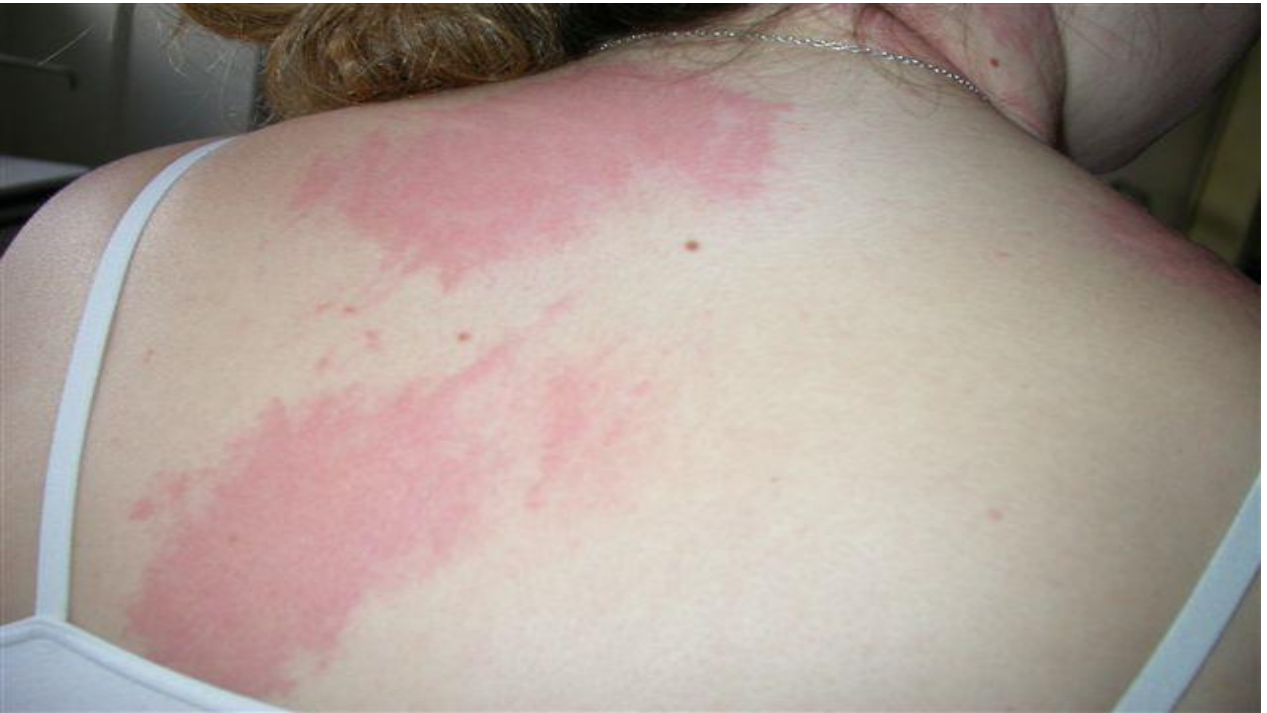


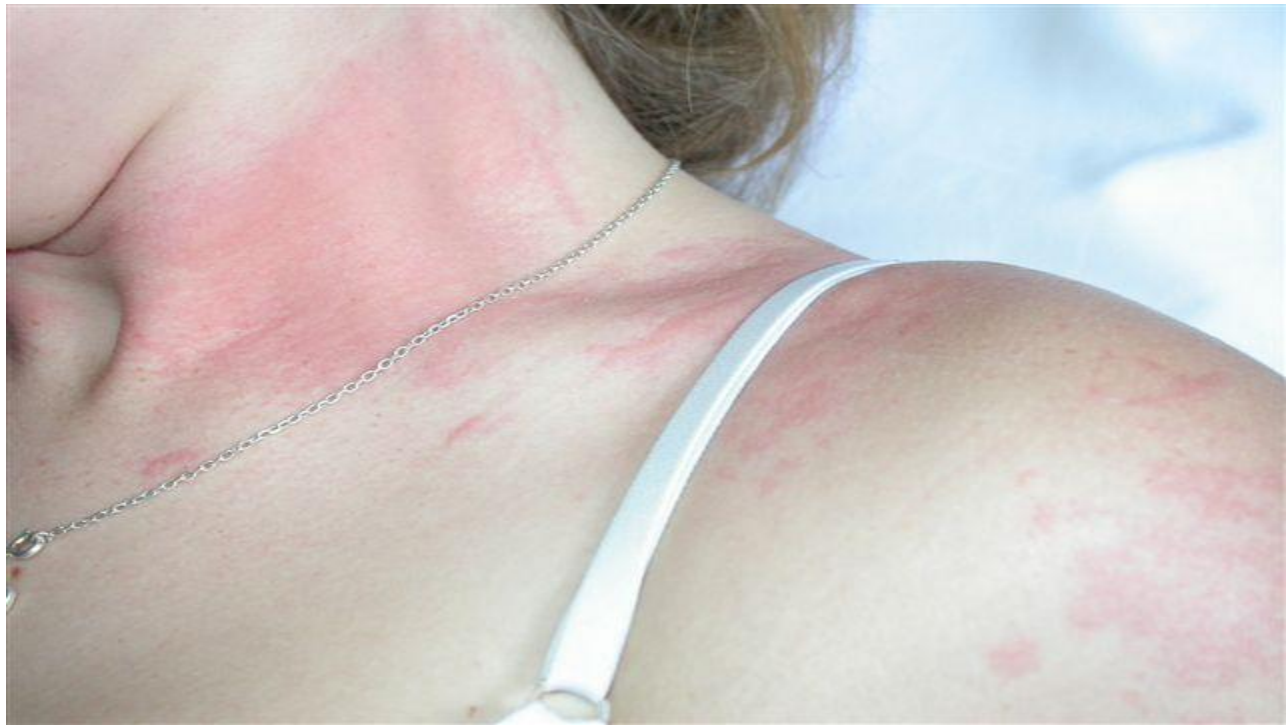


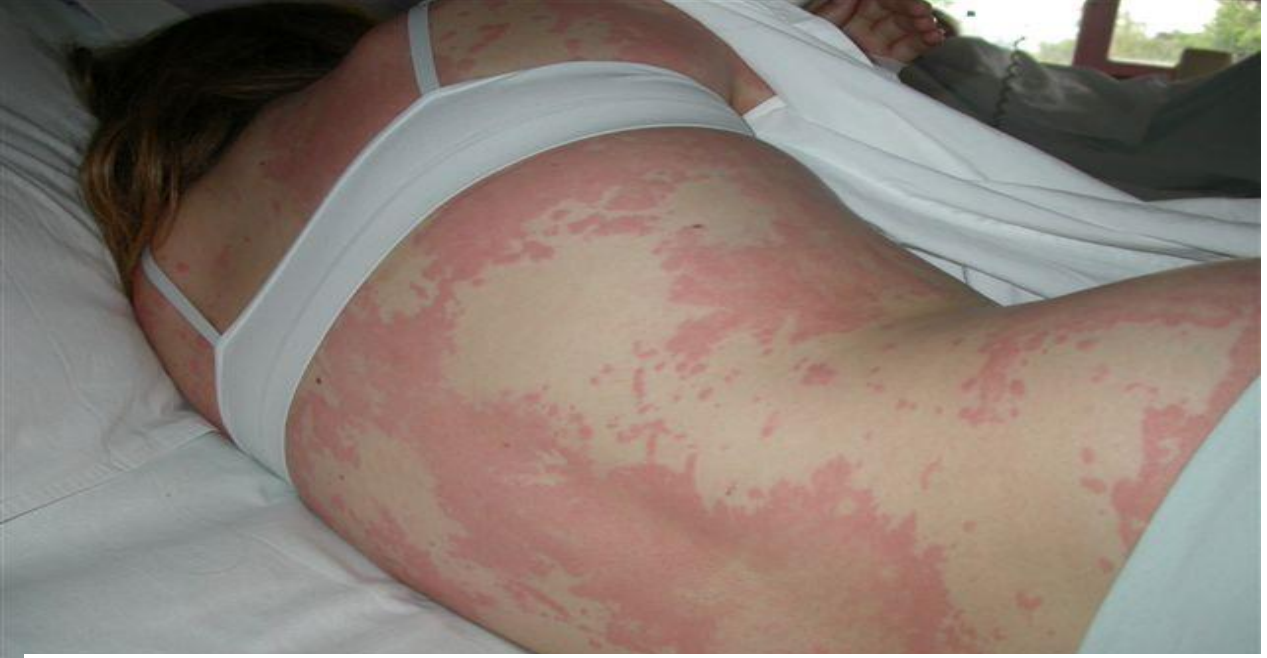


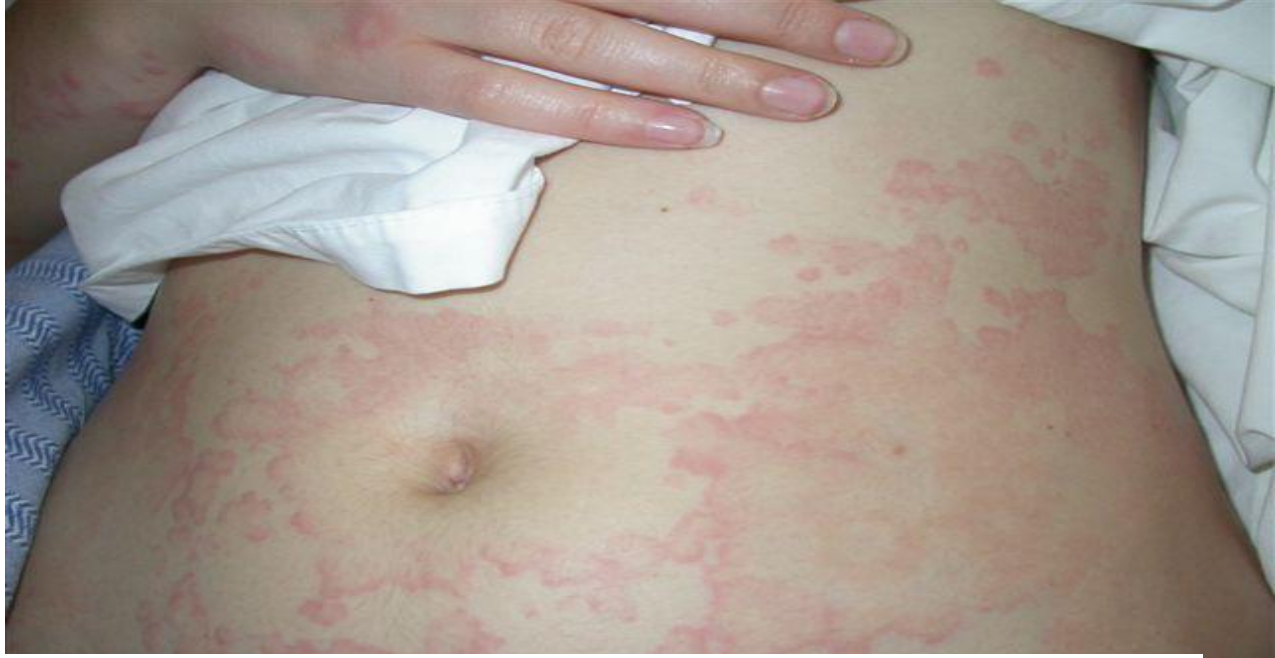


First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea

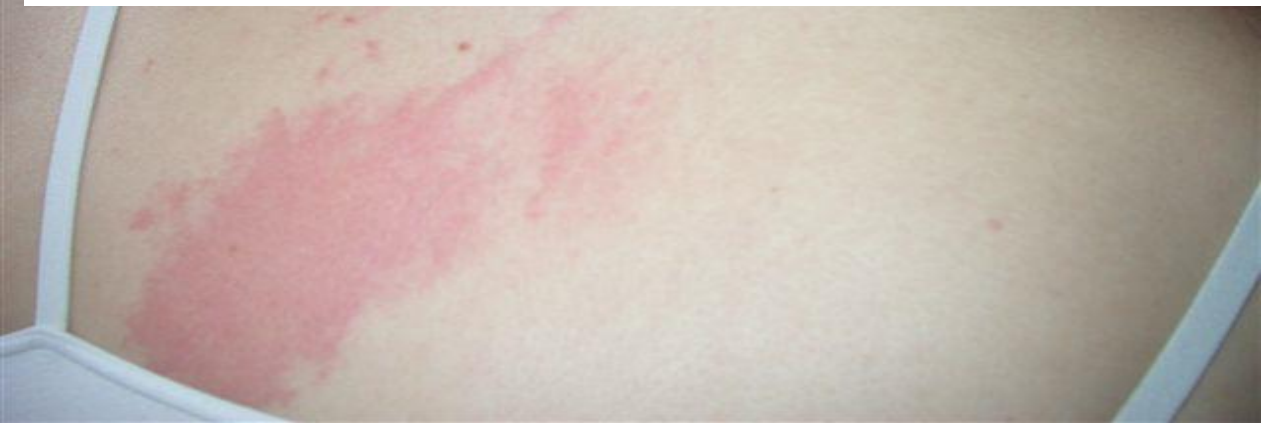


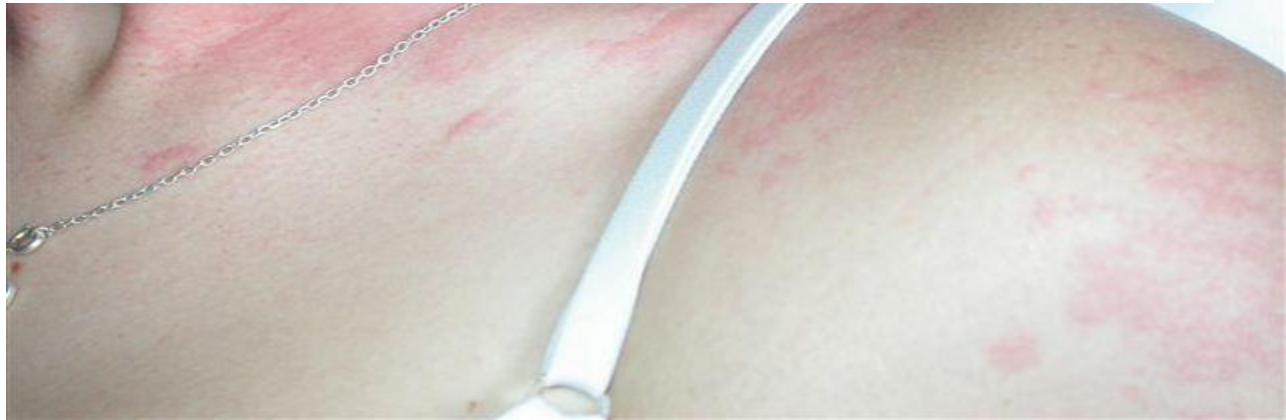






More a drug-induced reaction is severe, more it has a chance to be allergic

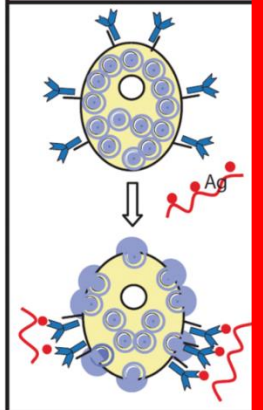
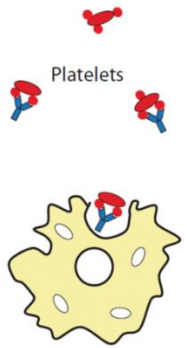
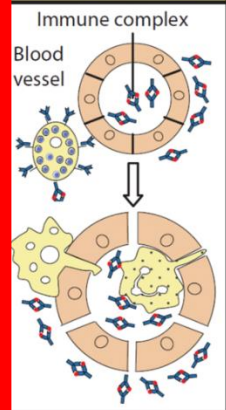
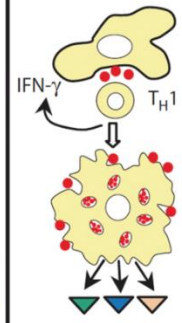
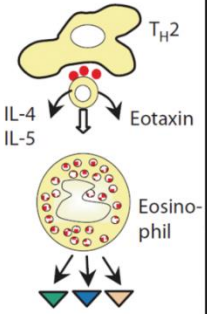
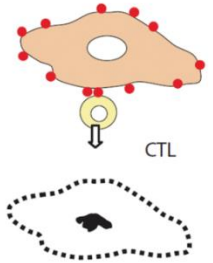
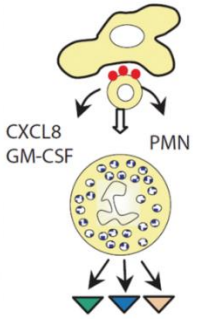




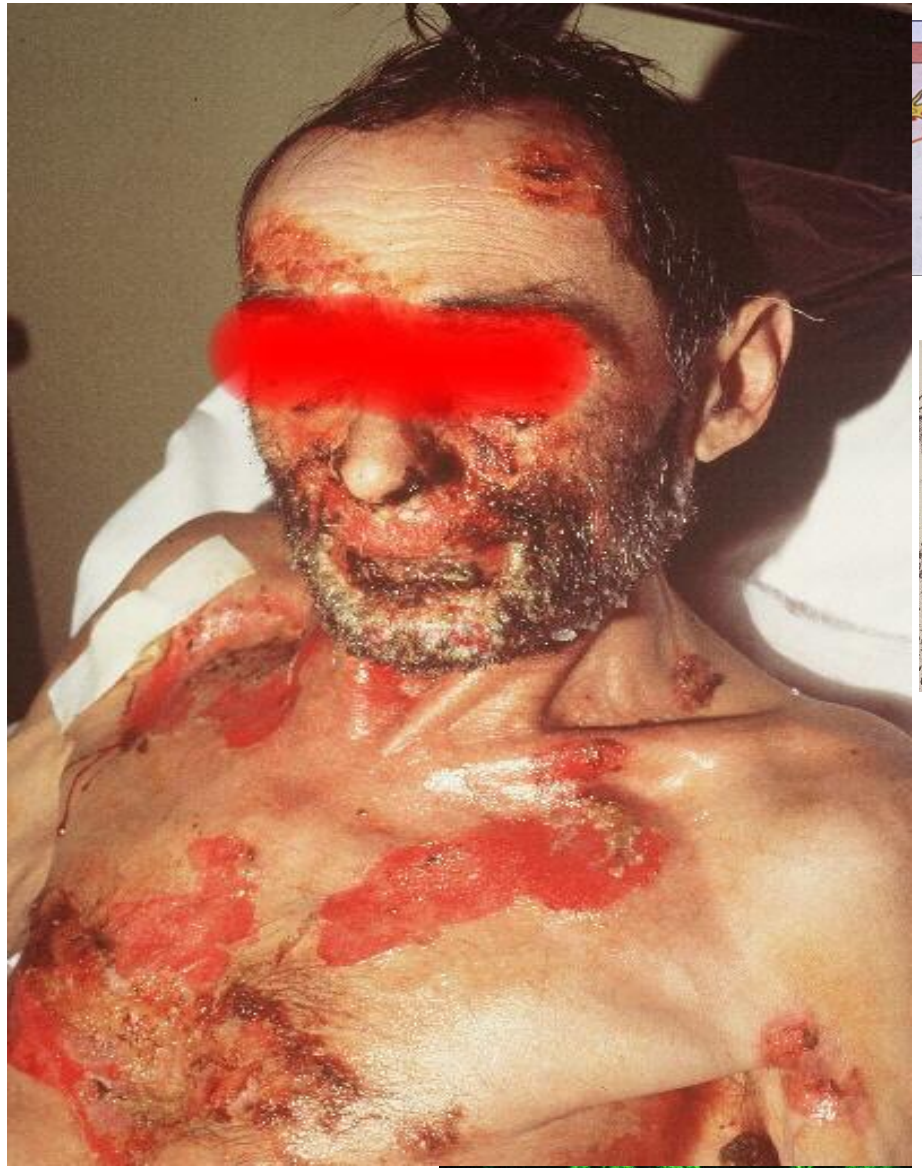
Hypersensibilités

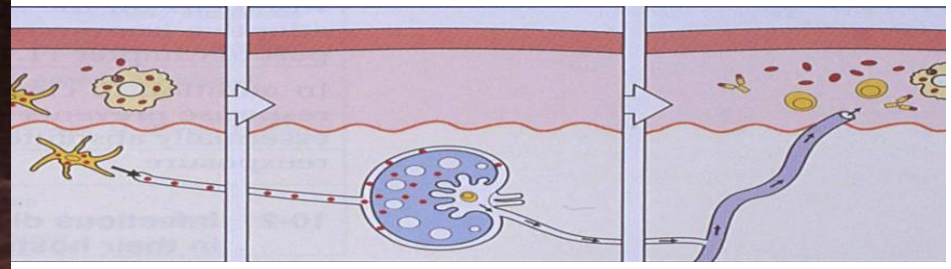
Classification de Gell & Coombs

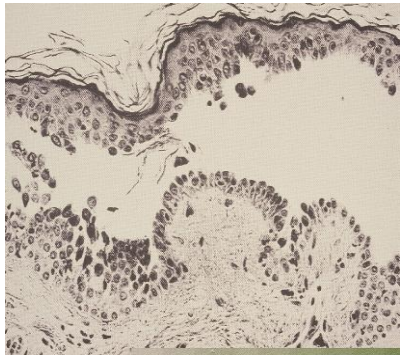
Antibody ← → T cells

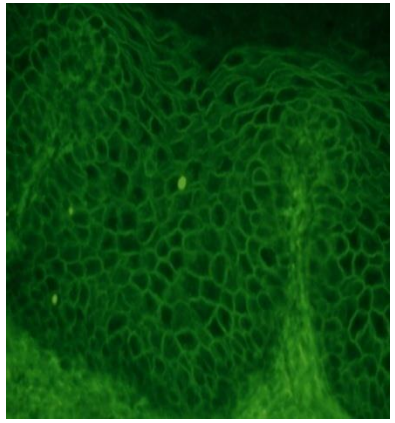
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IIFN-γ, TNF-α **Th1/Type 1**	IL-5, IL-4/IL-13 **Th2/Type 2**	Perforin/ granzyme B **Cytotoxic**	CXCL8, **Th17/Type 17**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented 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 Pemphigoide 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 aigue généralisée**

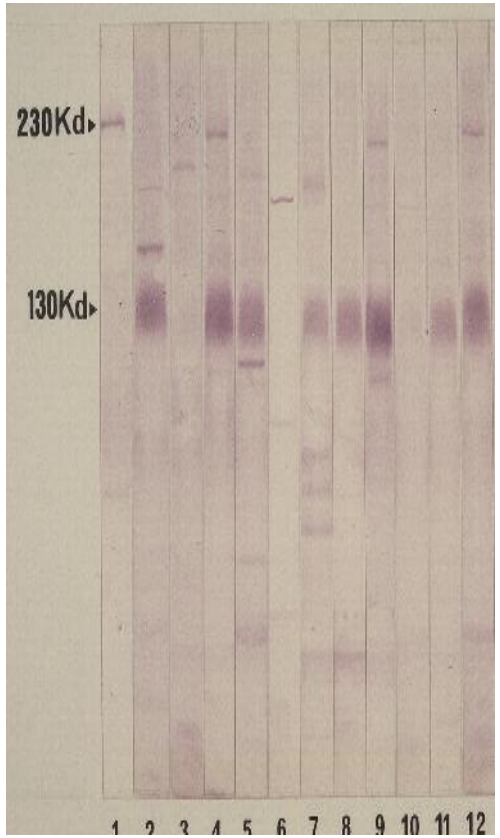
Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS







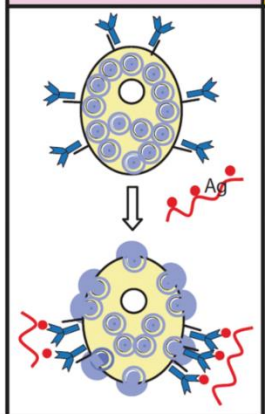
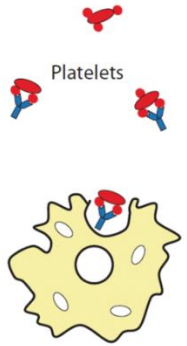
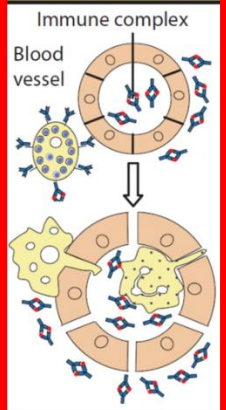
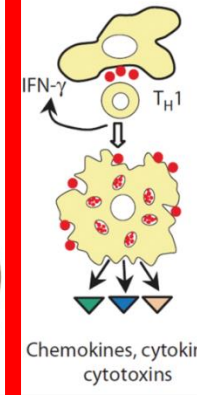
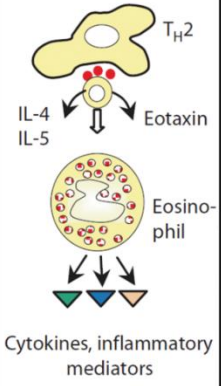
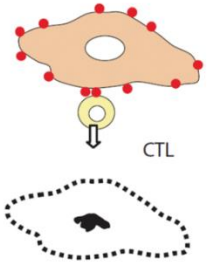
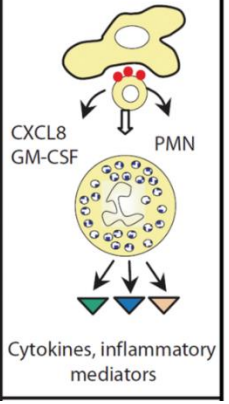




Hypersensibilités

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 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**
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Allergies médicaments	**Choc anaphylactique**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème médic.**	**DRESS**	**Lyell Stevens-Johnson**	**Pustulose exanthématique aigue généralisée**

Fig

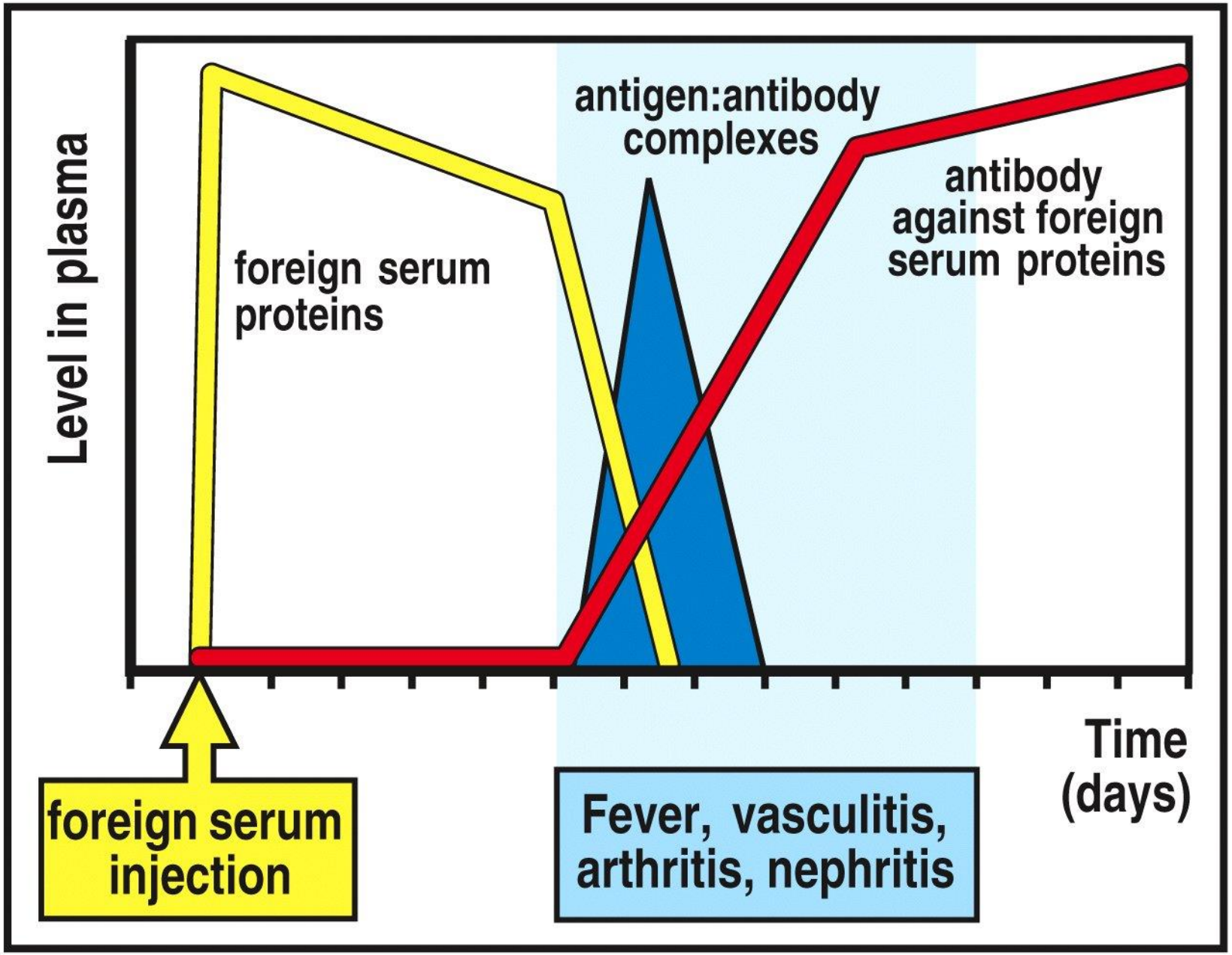
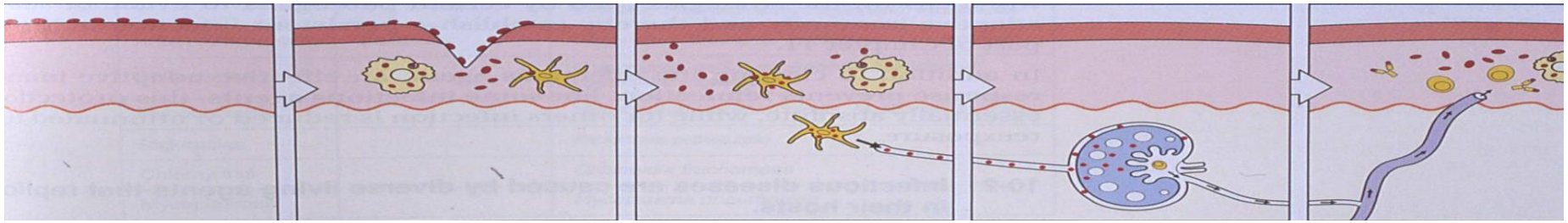
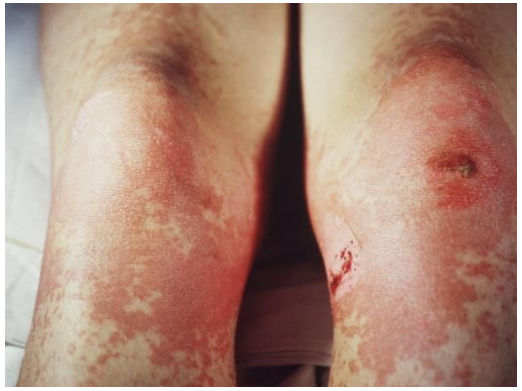
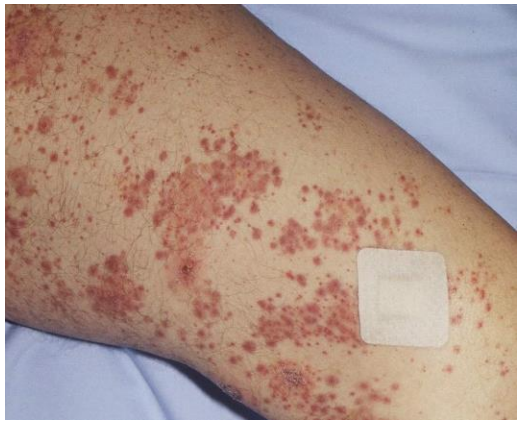


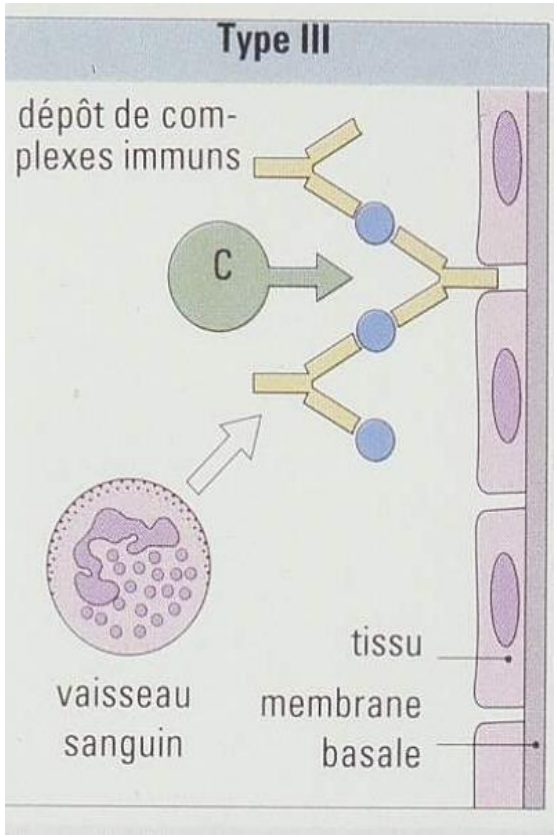
Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

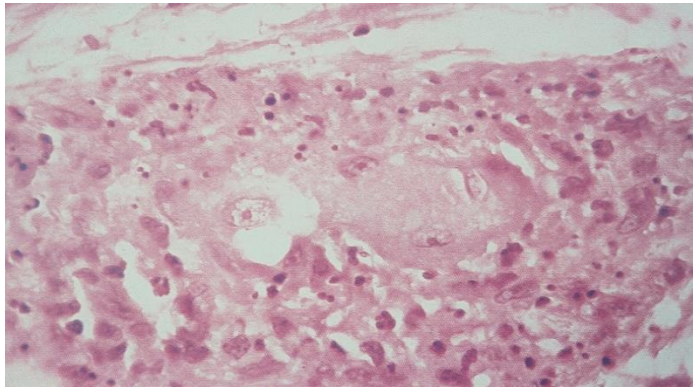
Hypersensibilité de type III due à des complexes immuns
VASCULITES – PURPURA RHUMATOIDE

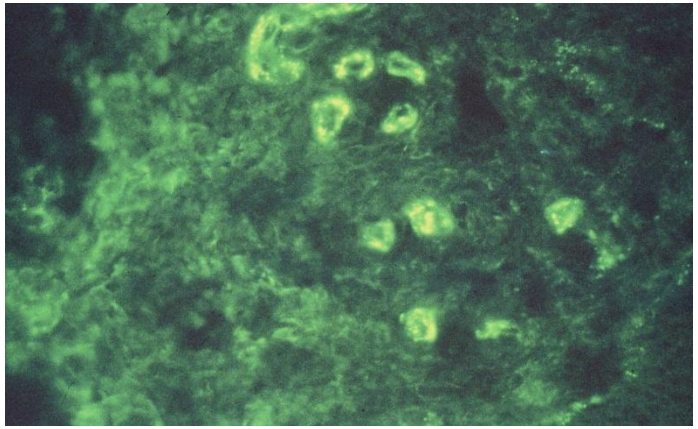












HS de type III aux antigènes inhalés

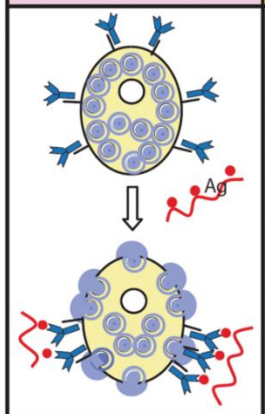
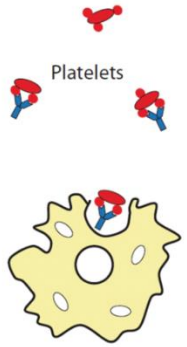
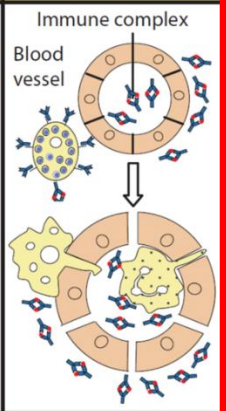
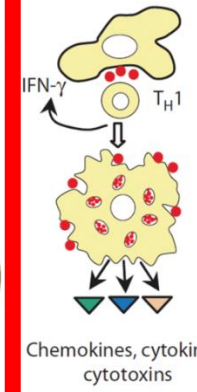
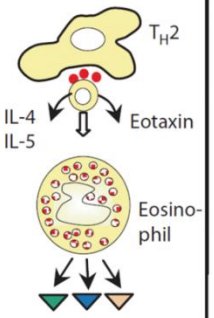
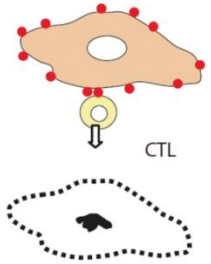
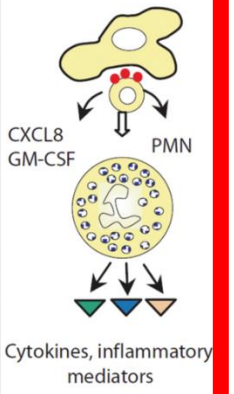
Alvéolites allergiques

- 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 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 Pemphigoide 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 aigue généralisée**

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

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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,

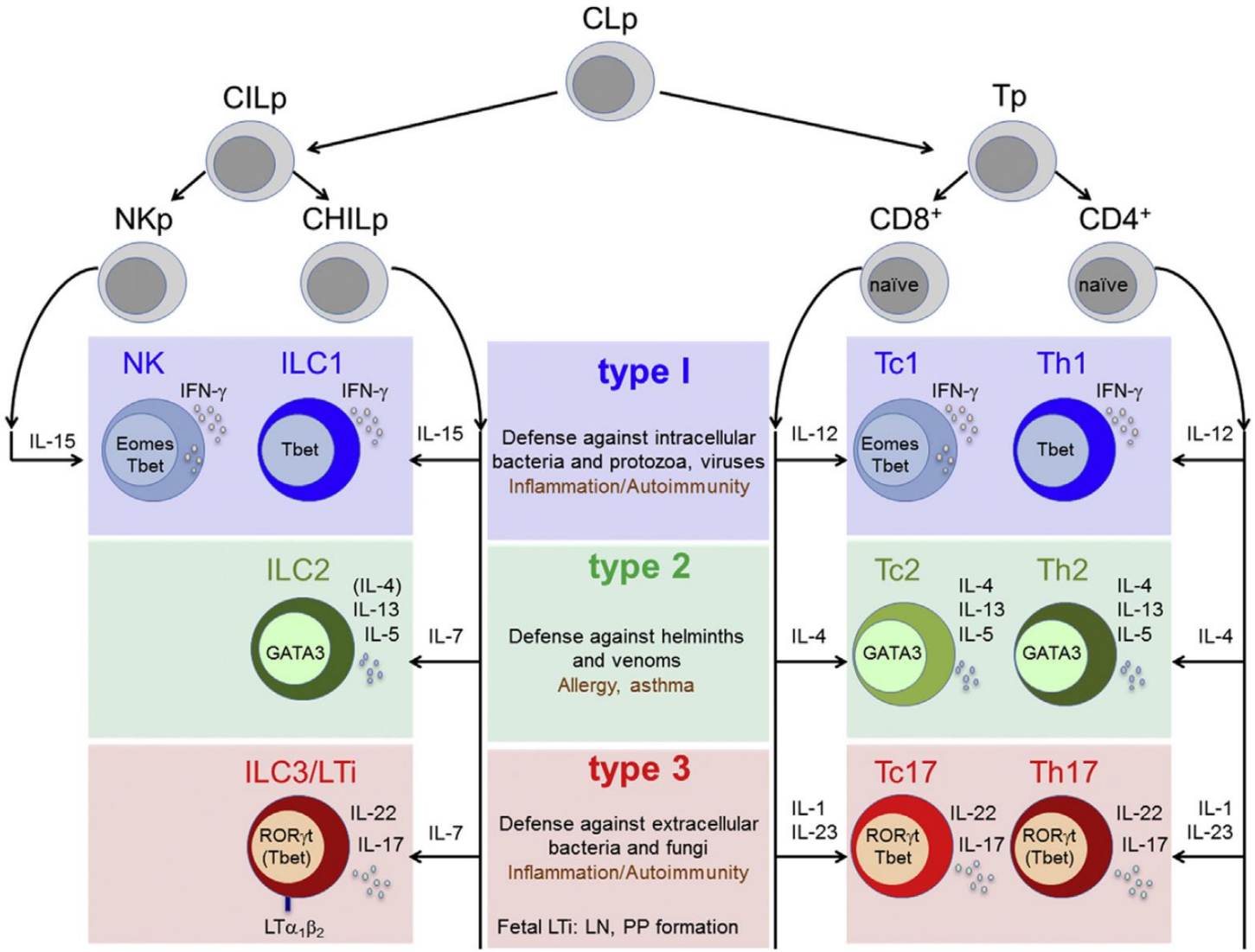
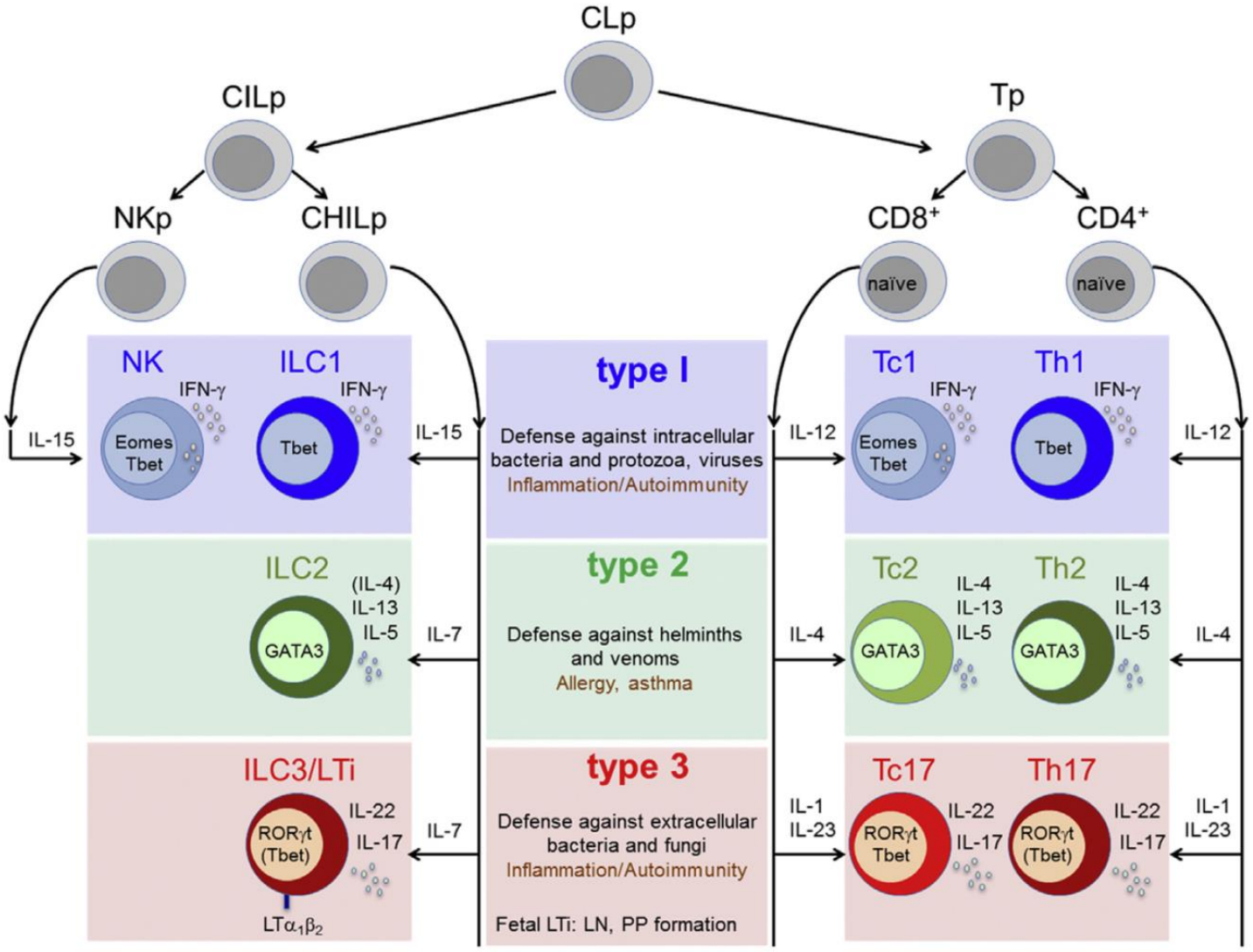


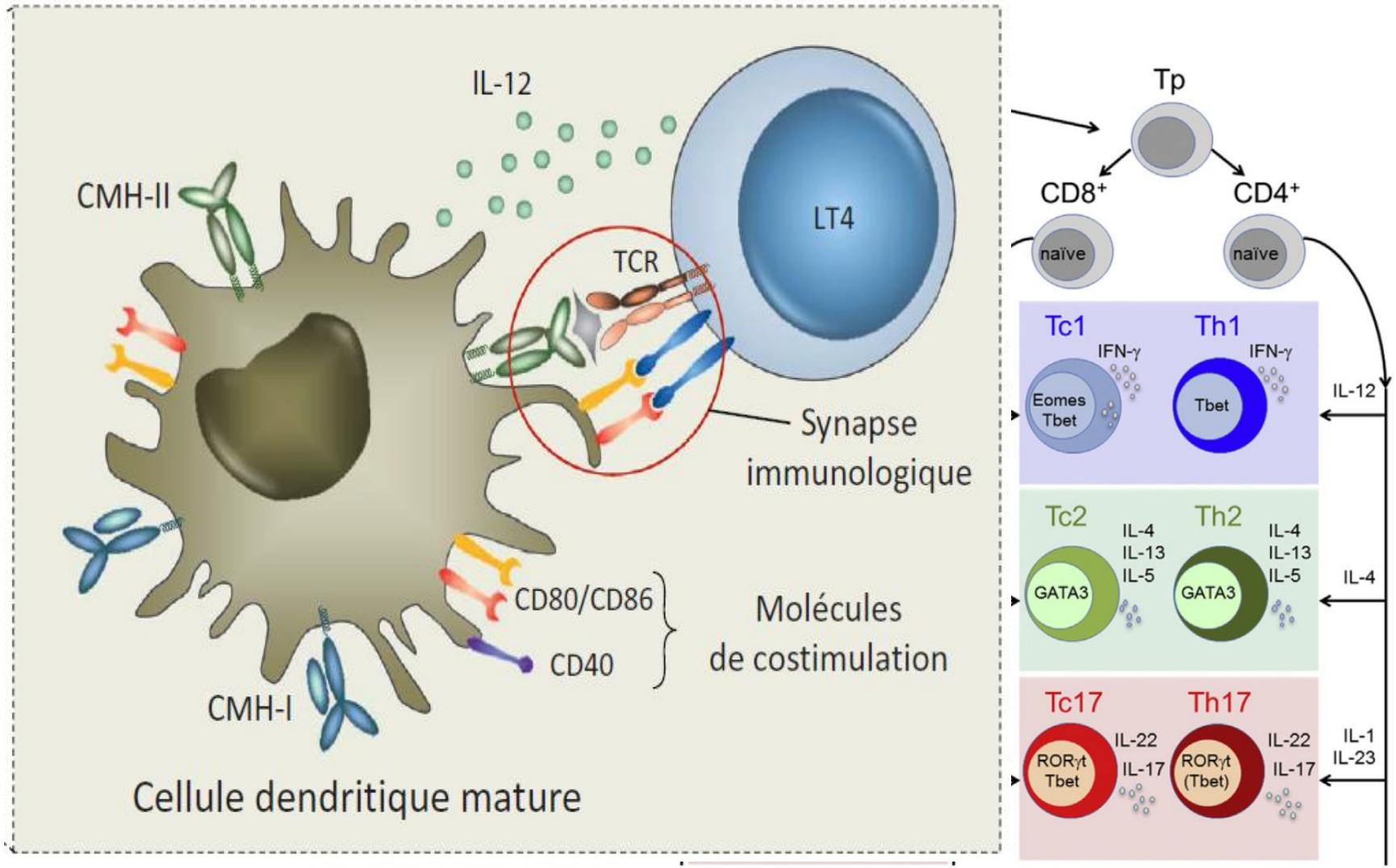
FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of RORγt *(RORC)*$^+$CD4$^+$$T_H17$ cells, CD8$^+$ T_C17 cells, and ILC3s, producing IL-17, IL-22, or both. *CILp*, Common innate lymphoid precursor; *CLp*, common lymphoid precursor; *LN*, lymph node; *LTi*, lymphoid tissue inducer; *PP*, Peyer patch; *Tp*, T-cell progenitor.

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



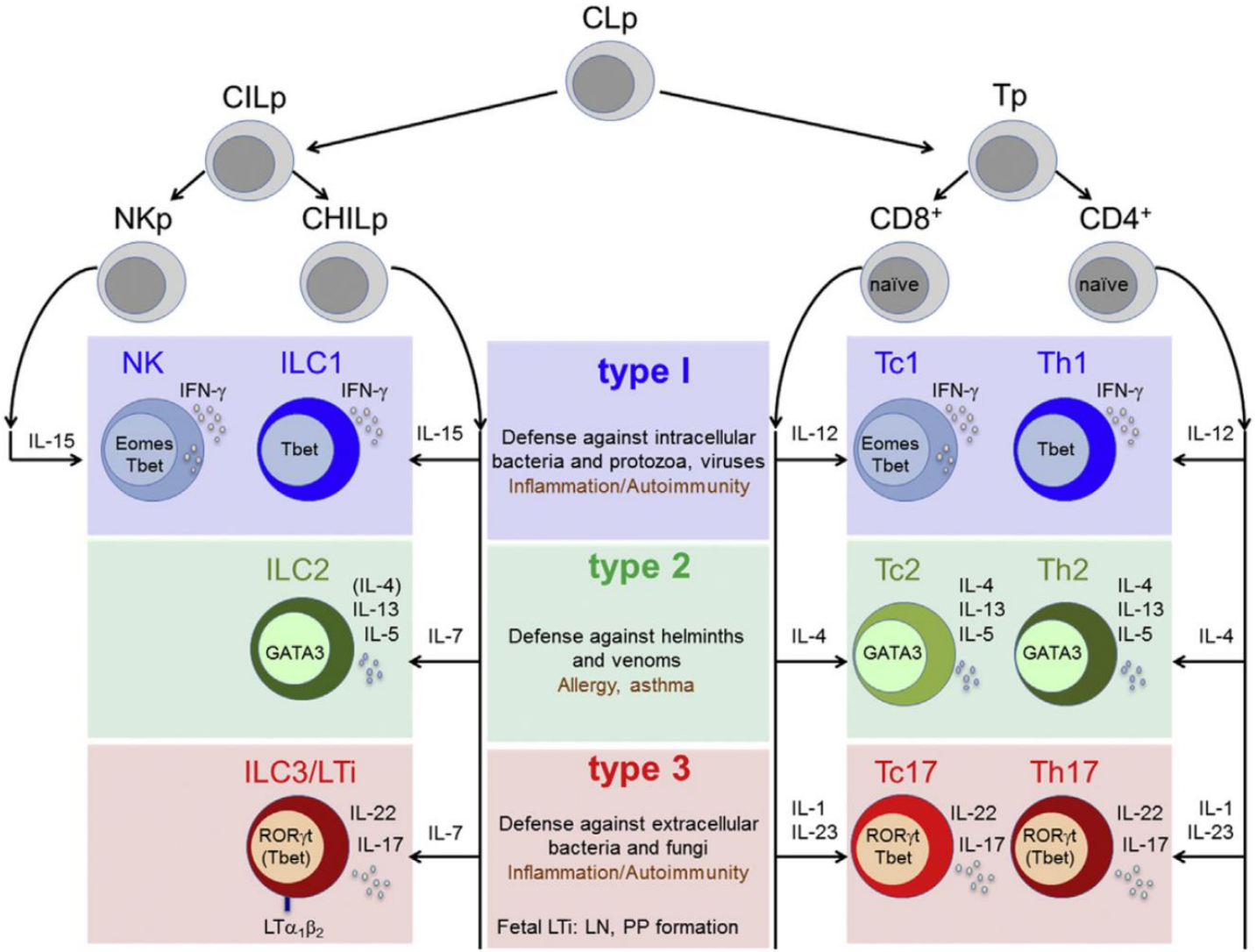
Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

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



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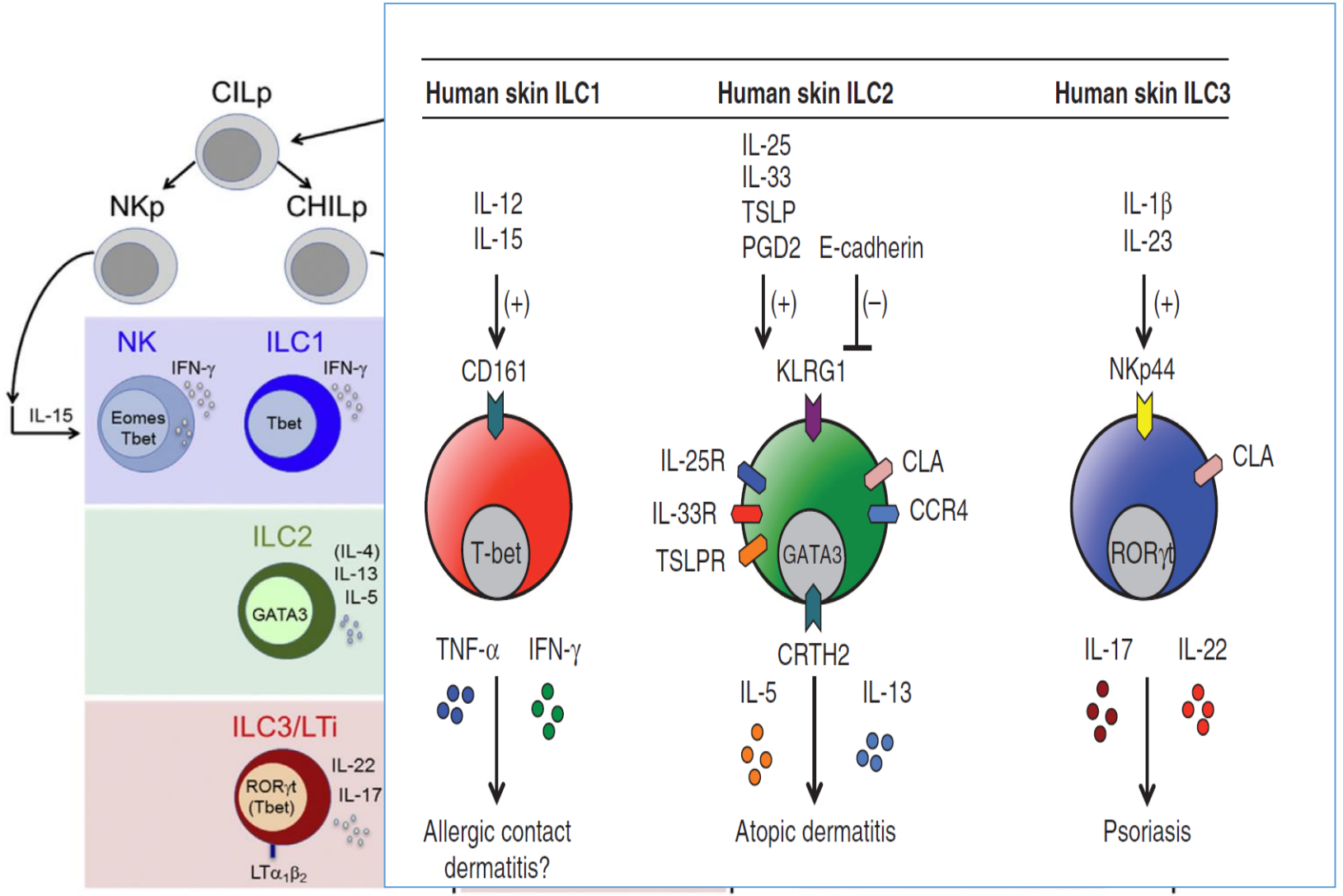
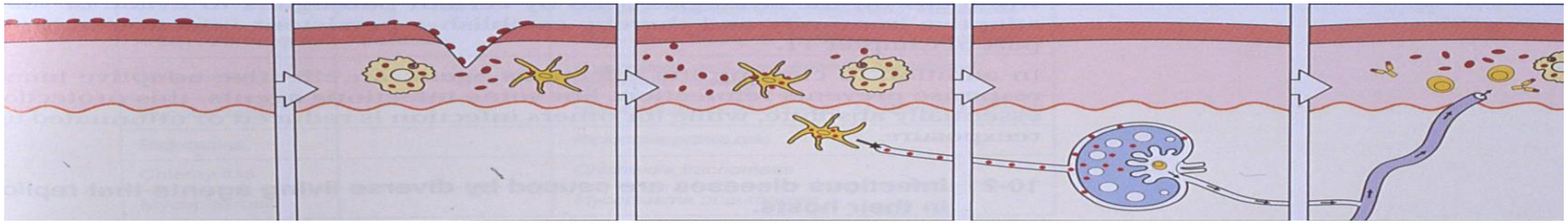
The 3 major types of innate and adaptative cell-mediated immunity

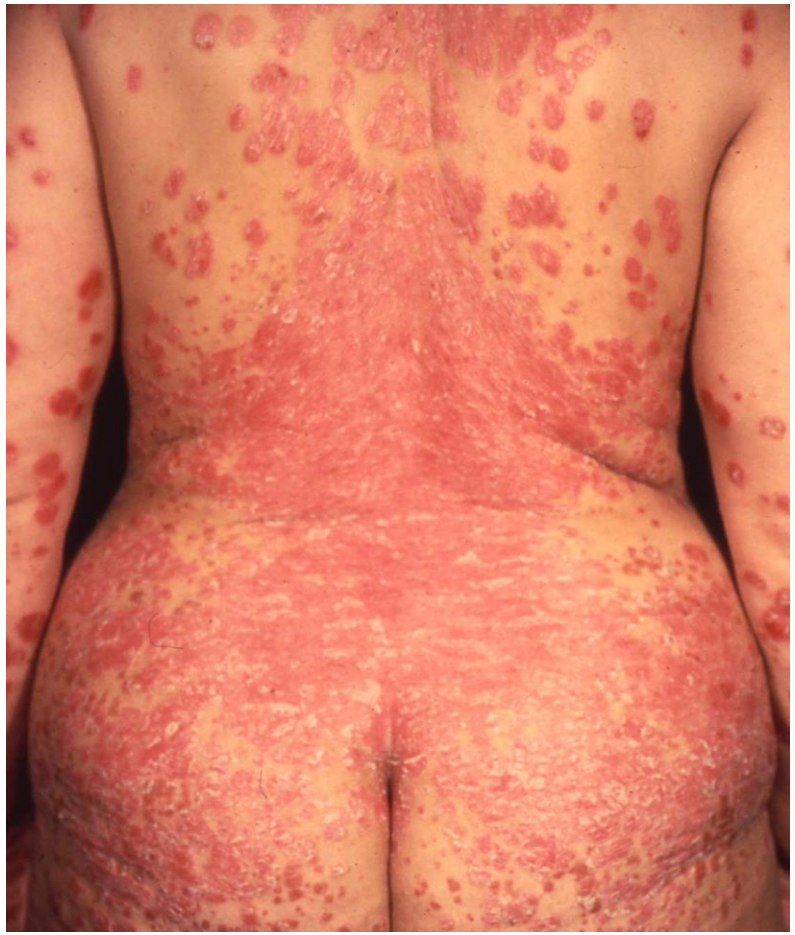


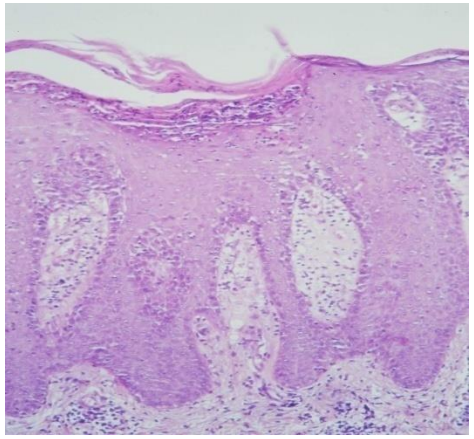
Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

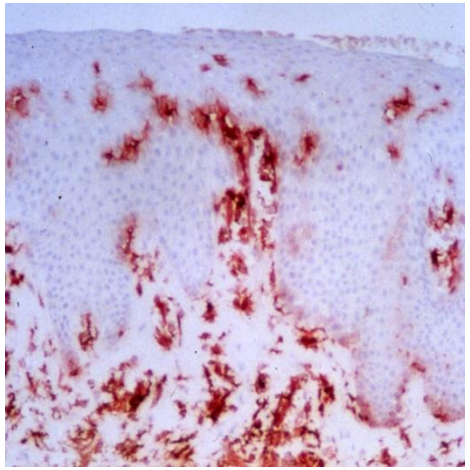
Hypersensibilité de type IV (HS retardée) due à des LT 17
PSORIASIS

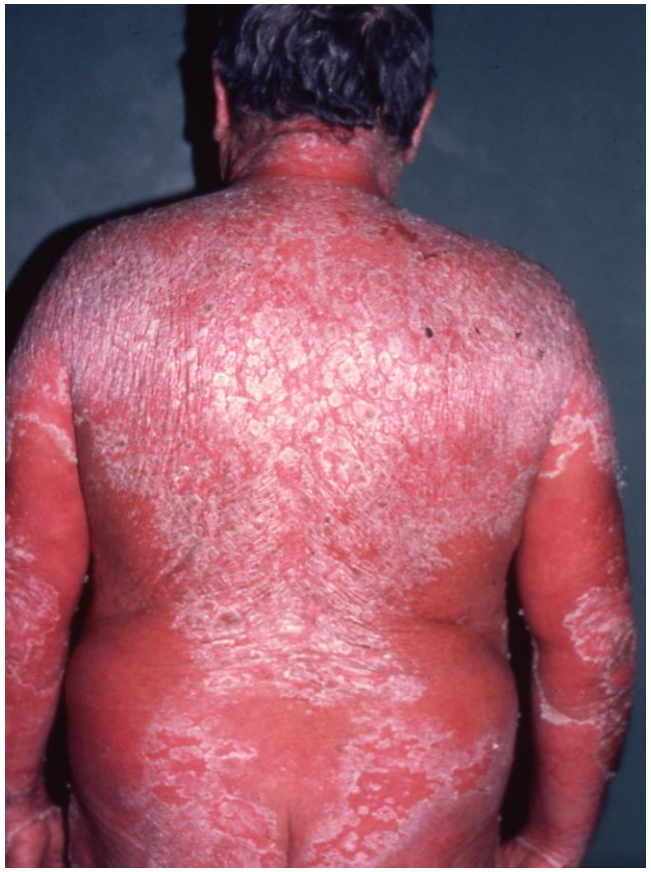
Th17
Type 17





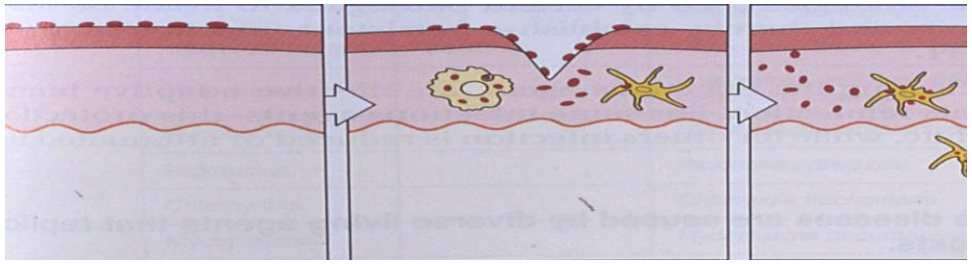


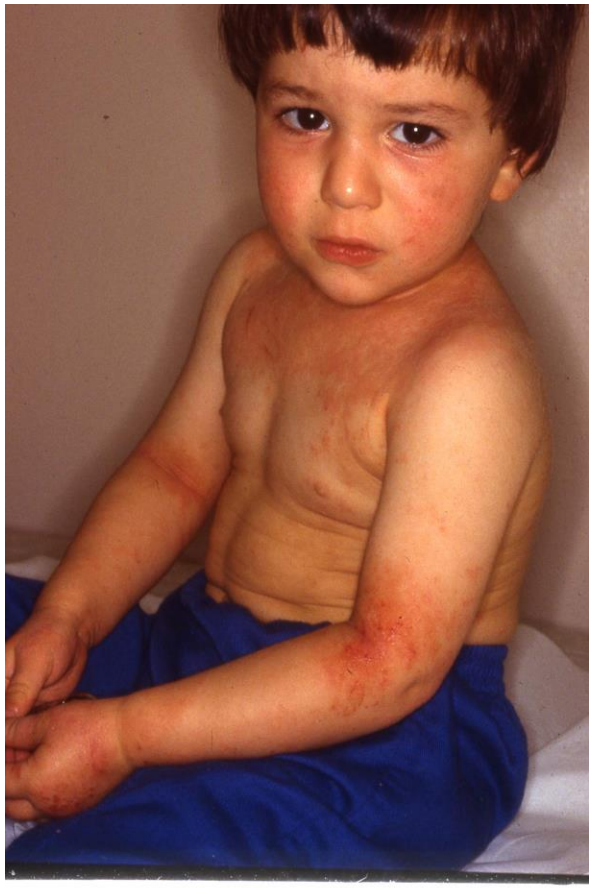


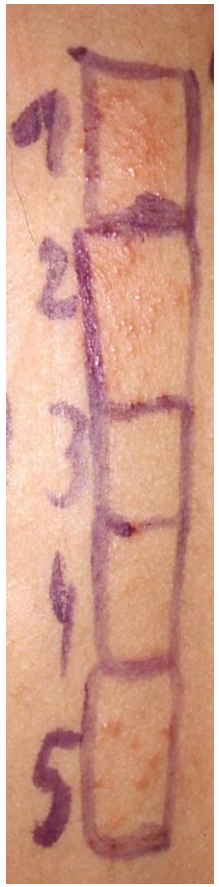


Hypersensibilité de type IV (HS retardée) due à des LT2
DERMATITE ATOPIQUE

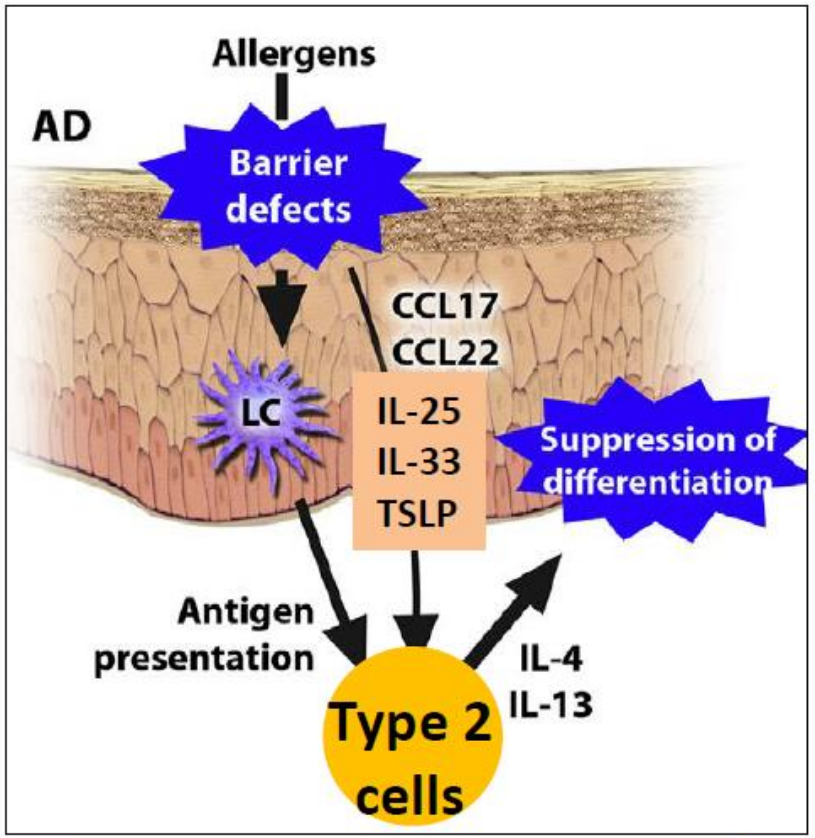
Th2
Type 2







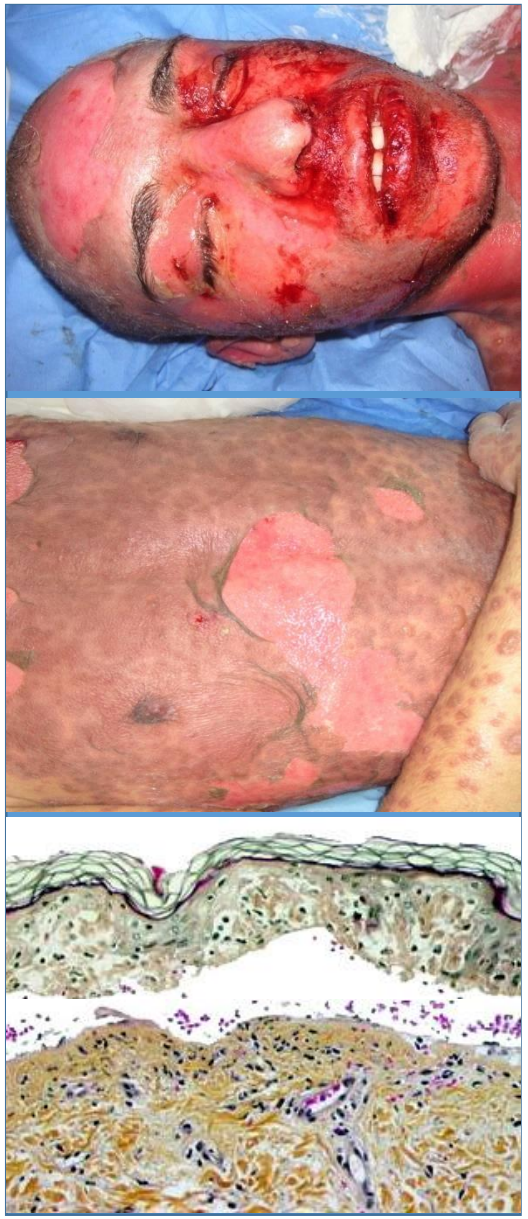
Type 2 phenotype

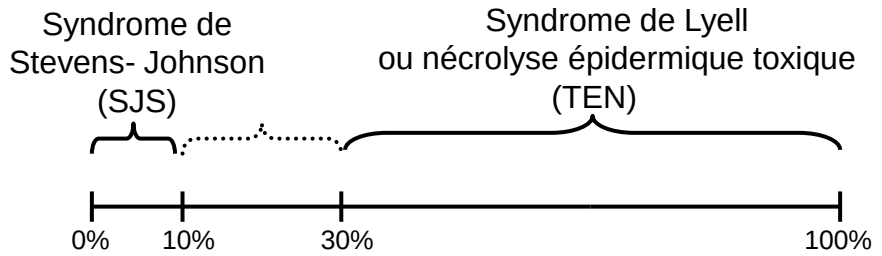


Type 2 inflammation
Type 2 immunity

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

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

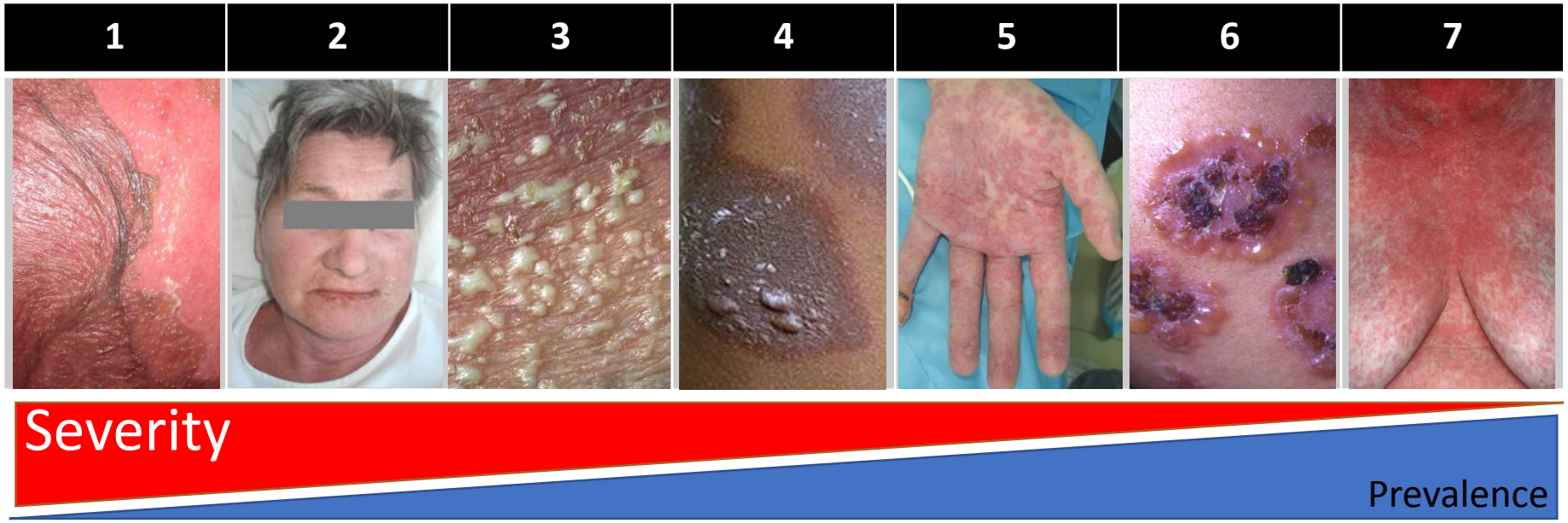




- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie 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

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department