Immunologie médicale
Inflammation et maladies inflammatoires

- Introduction: Présentation de l'équipe « Allergologie et Immunologie Clinique Lyon-Sud »
- Histoire naturelle des maladies inflammatoires
- Inflammation et maladies
- Système immunitaire et lymphatique
- Immunité en action : réponse immune anti-infectieuse
- **Hypersensibilité allergique et non allergique**
- Classification de Gell & Coombs
  - HS immédiate (mastocytes)
  - HS retardée (lymphocytes)
- Maladies allergiques atopiques et non atopiques

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

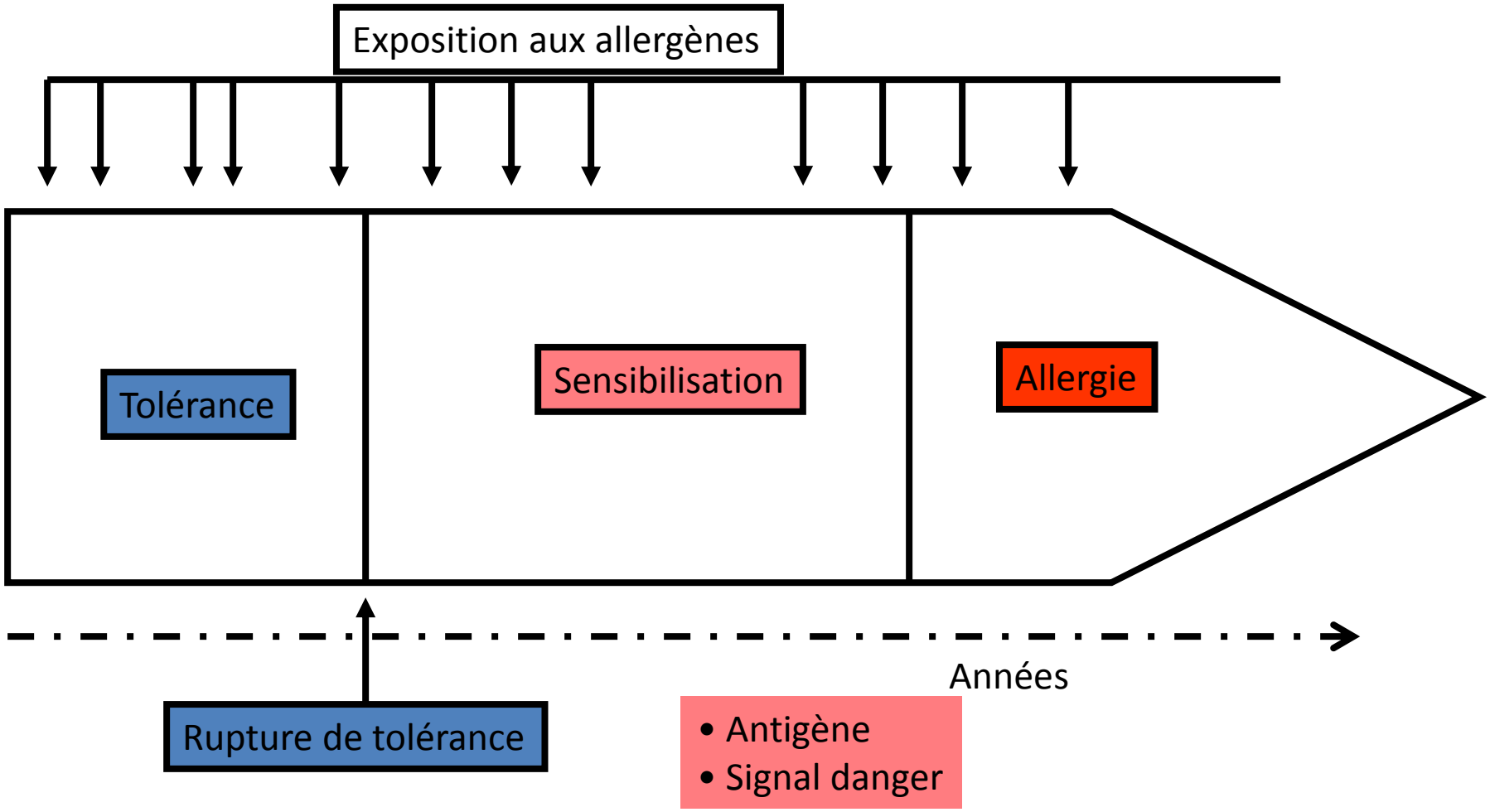
Physiopathologie de l'allergie

- 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

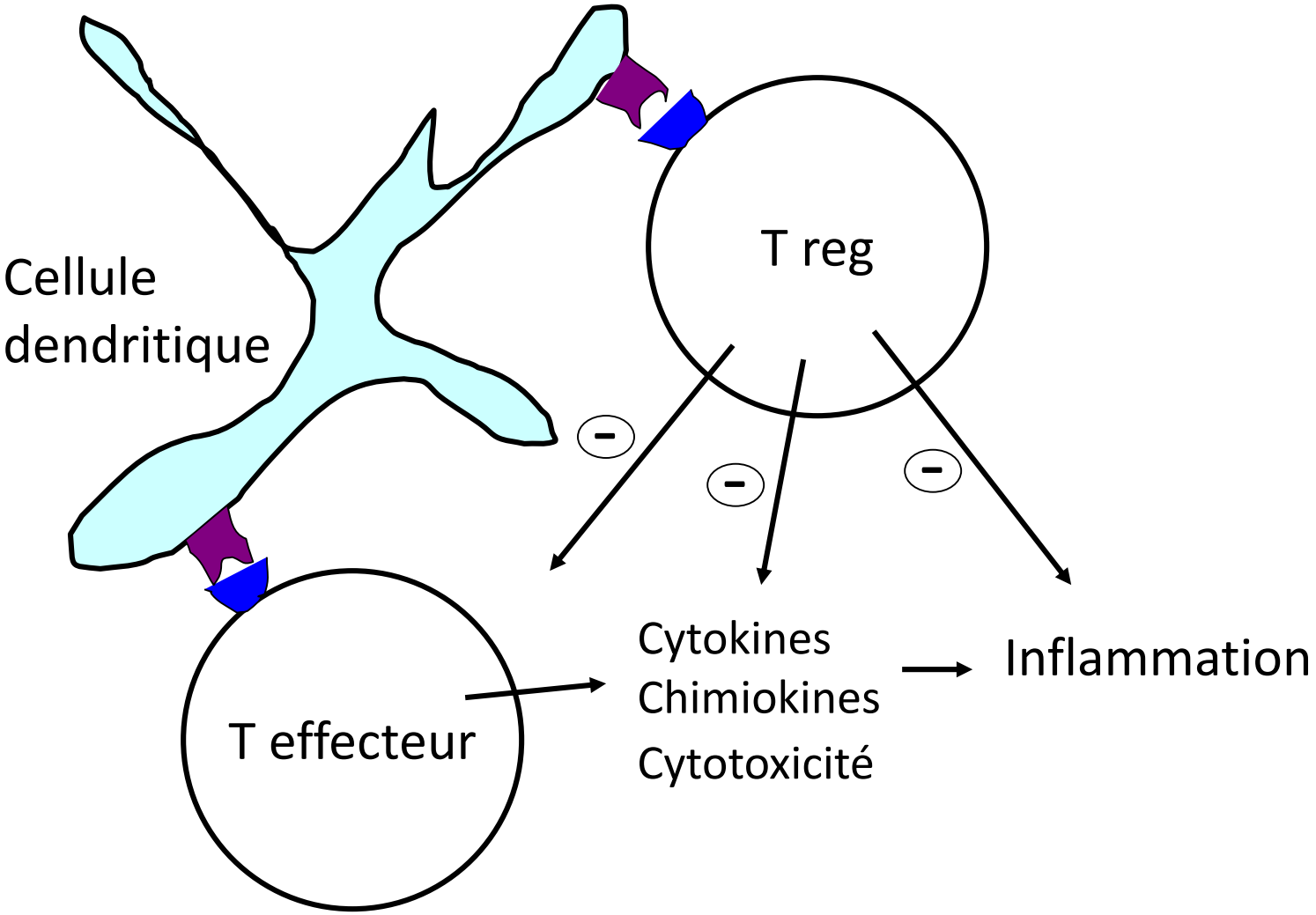
Allergie: rupture de tolérance

- 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)*

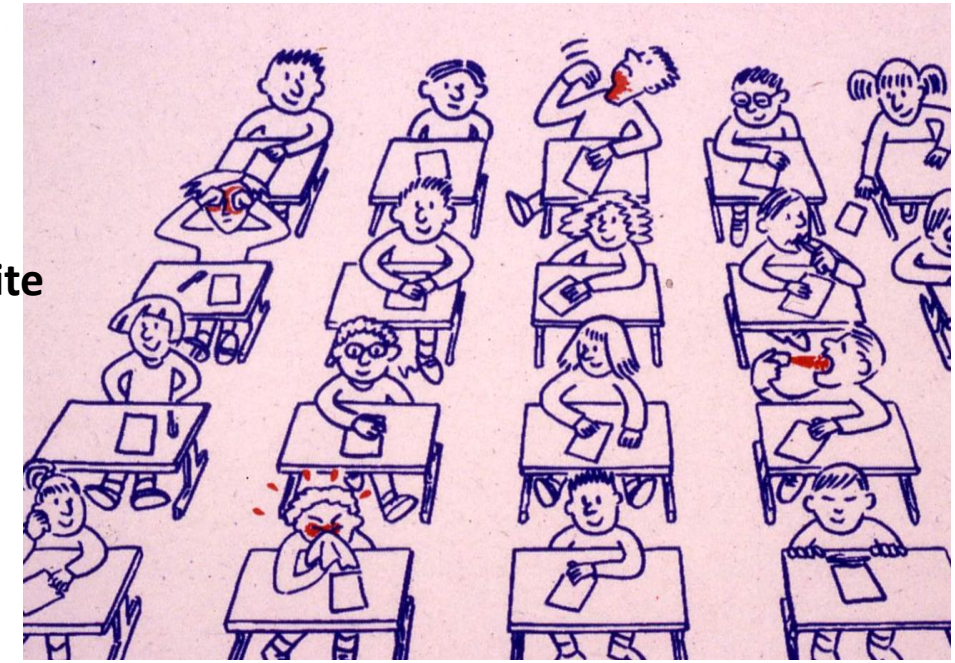
et/ou
et/ou
- *allergène chimique*
- *voie non naturelle de contact*
- *sujet non génétiquement prédisposé (ATCD familiaux)*

Allergènes

- Pneumallergènes
- Trophallergènes
- Injectables
- Contact cutané

maladie atopique

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

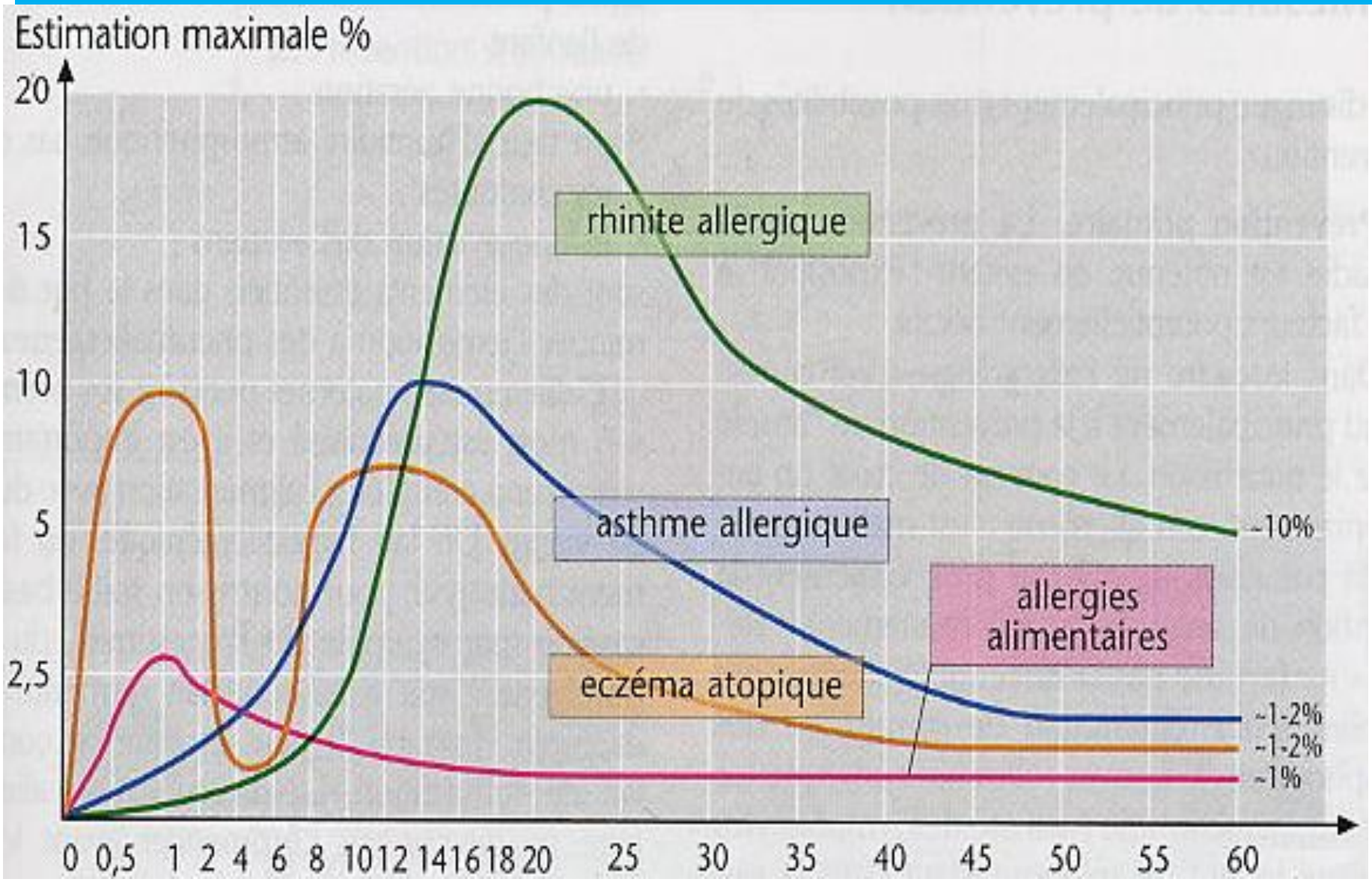


maladie non atopique

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

Allergènes cutanés
- **eczéma contact**

Histoire naturelle des maladies allergiques (atopiques)



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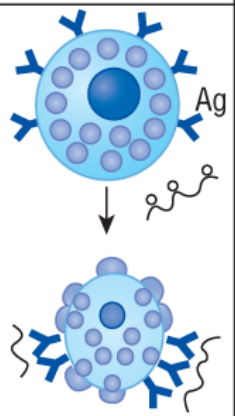
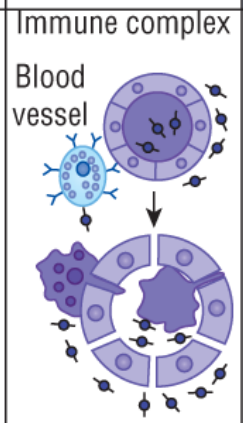
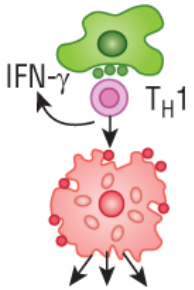
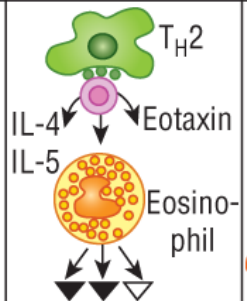
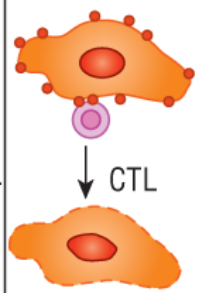
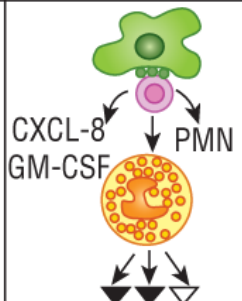
Physiopathologie des maladies autoimmunes et allergiques

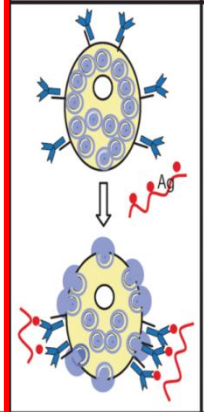
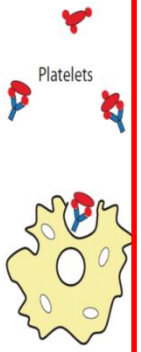
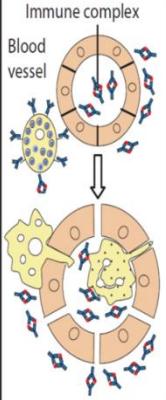
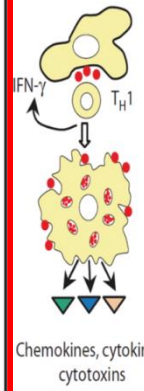
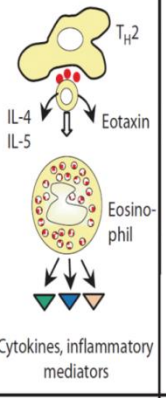
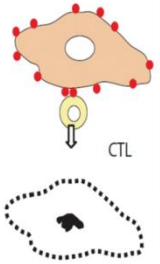
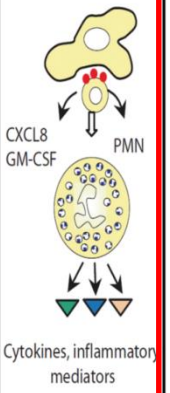
Classification de Gell & Coombs

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFNγ, TNFα (T_H1 cells)	IL-5,IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	CXCL-8, IL-17 GM-CSF (T-cells)
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
							
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Hemolytic anemia, thrombocytopenia (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behcet's disease

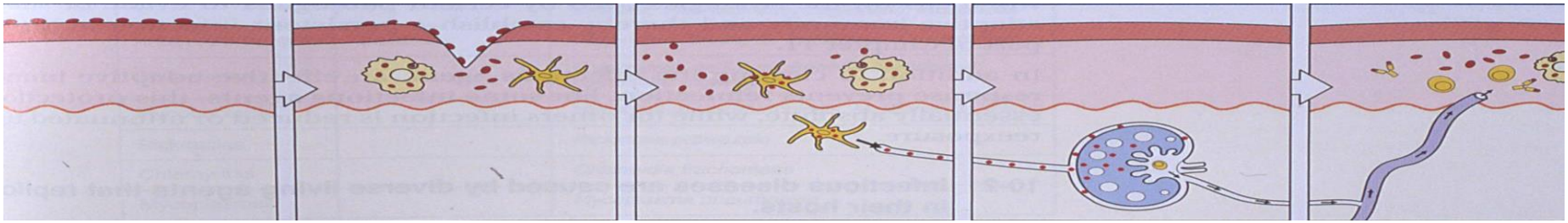
Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:*

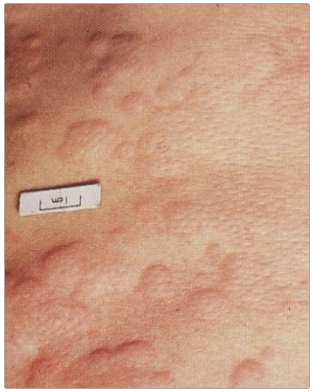
Hypersensibilités
Classification de Gell & Coombs

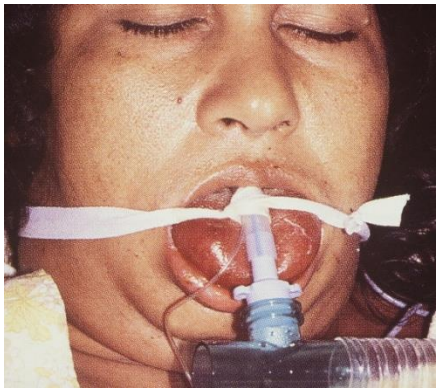
Antibody ← → T cells

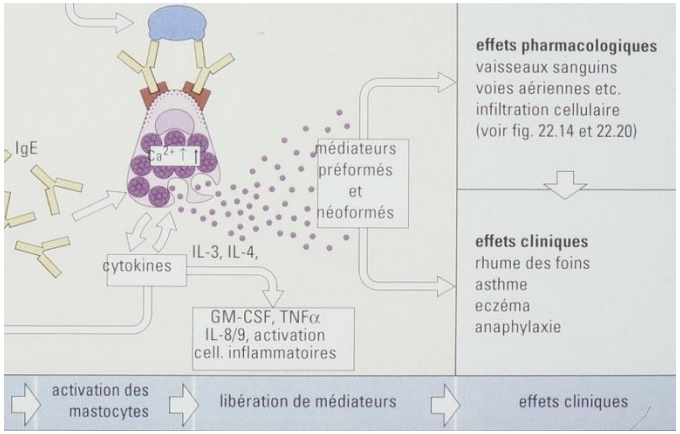
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IIFN-γ, TNF-α **Th1/Type 1**	IL-5, IL-4/IL-13 **Th2/Type 2**	Perforin/ granzyme B **Cytotoxic**	CXCL8, **Th17/Type 17**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented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

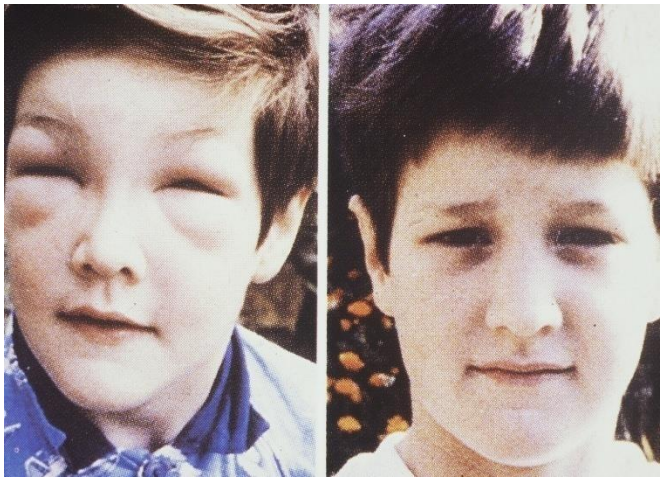
TYPE I HYPERSENSITIVITY

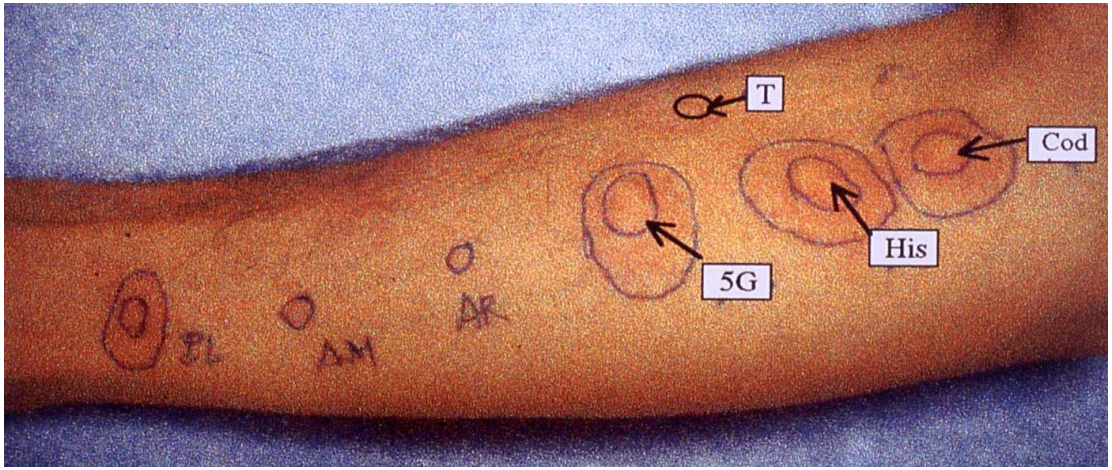




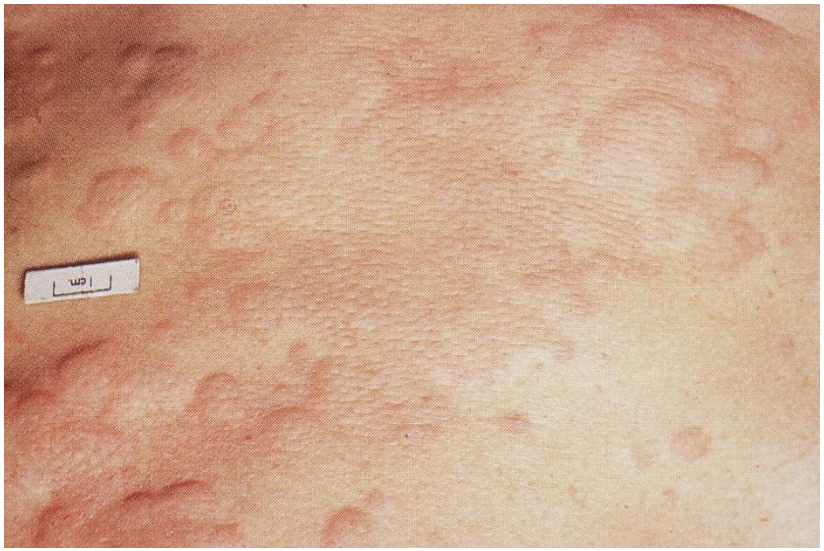




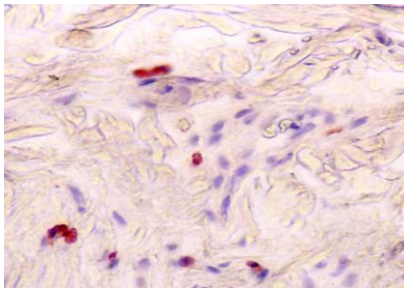


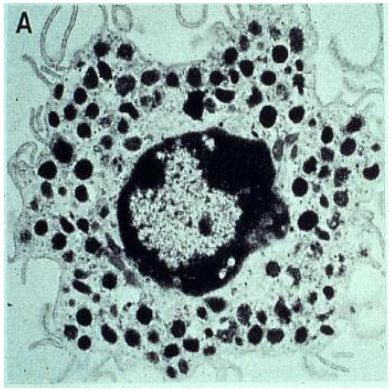


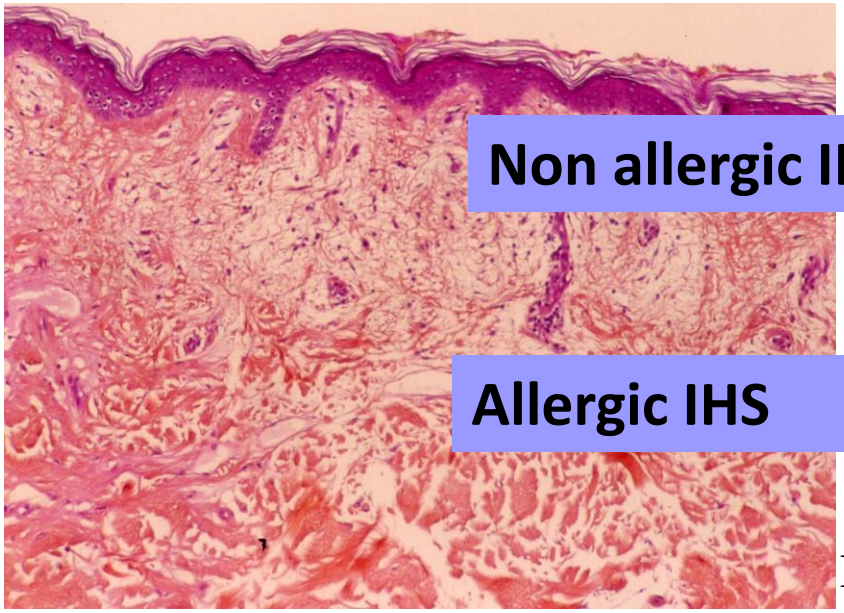
TYPE I HYPERSENSITIVITY



Œdème du derme / Vaisseaux

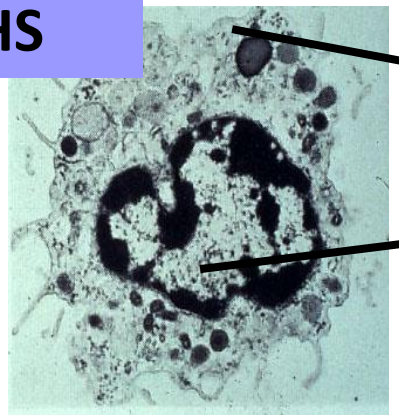




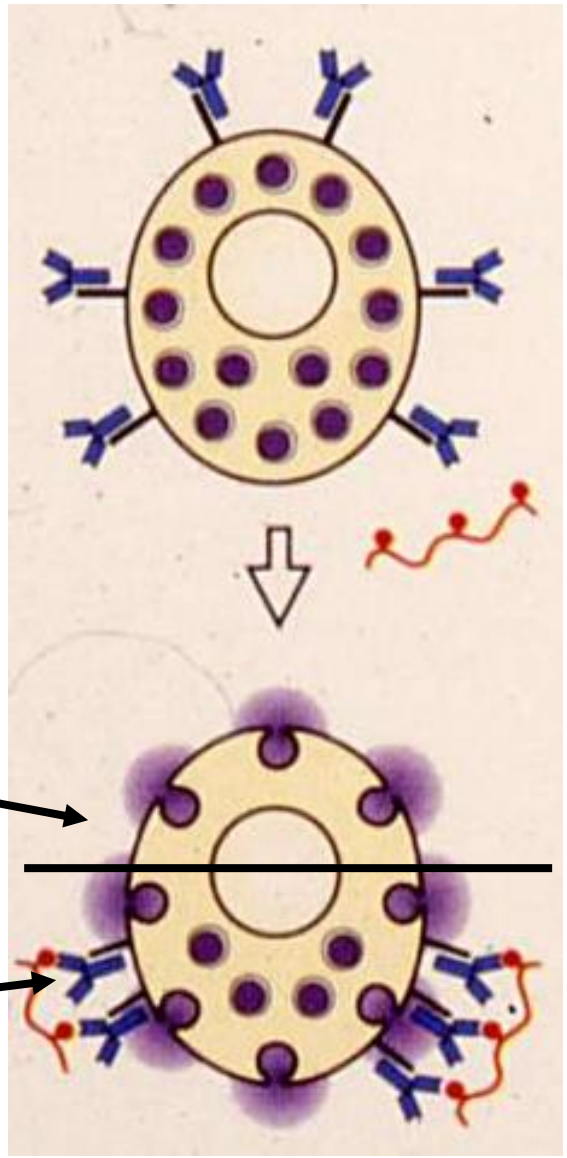


Non allergic IHS

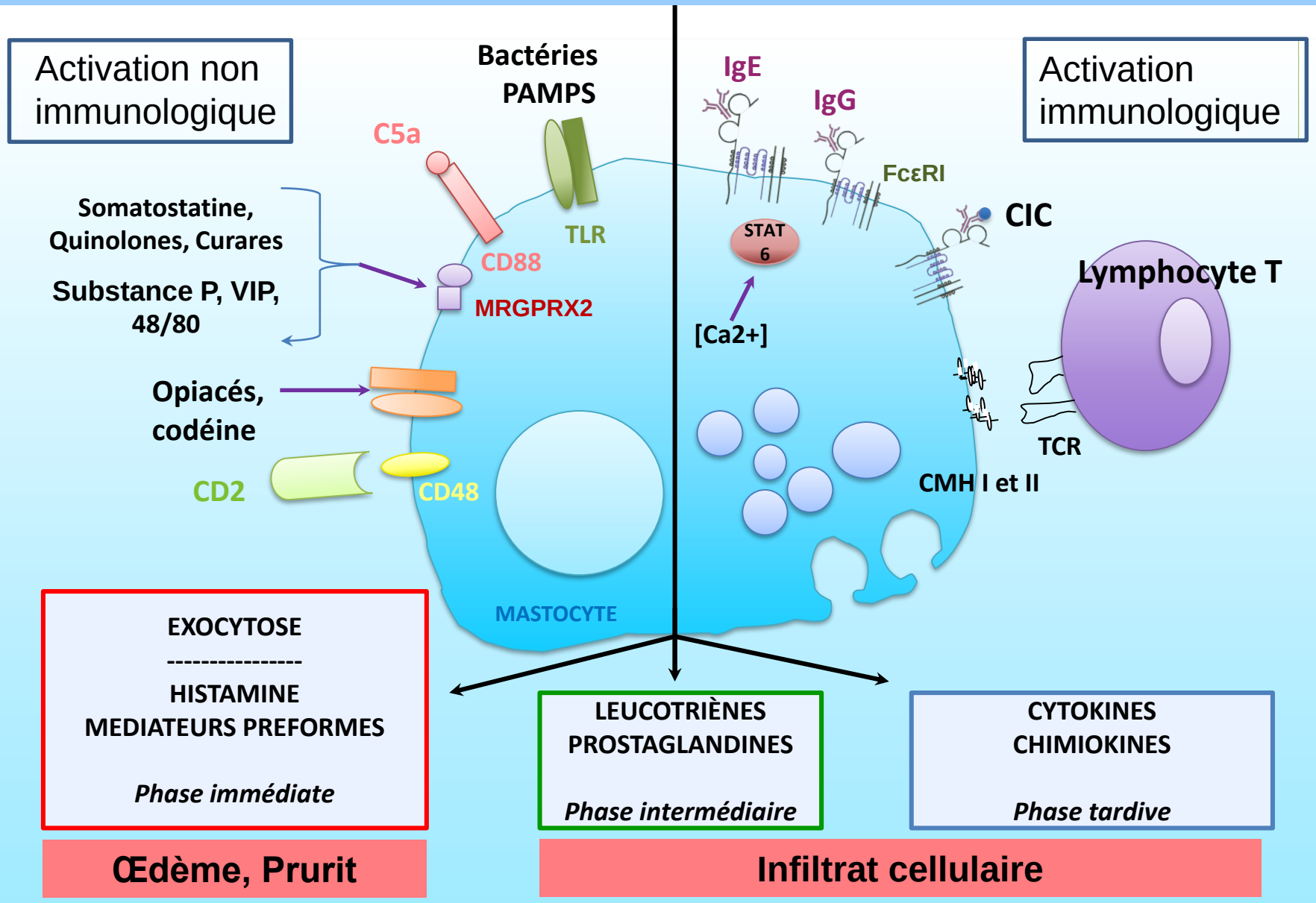
Allergic IHS



Mastocytes / Histamine



MASTOCYTES
Récepteurs et activation



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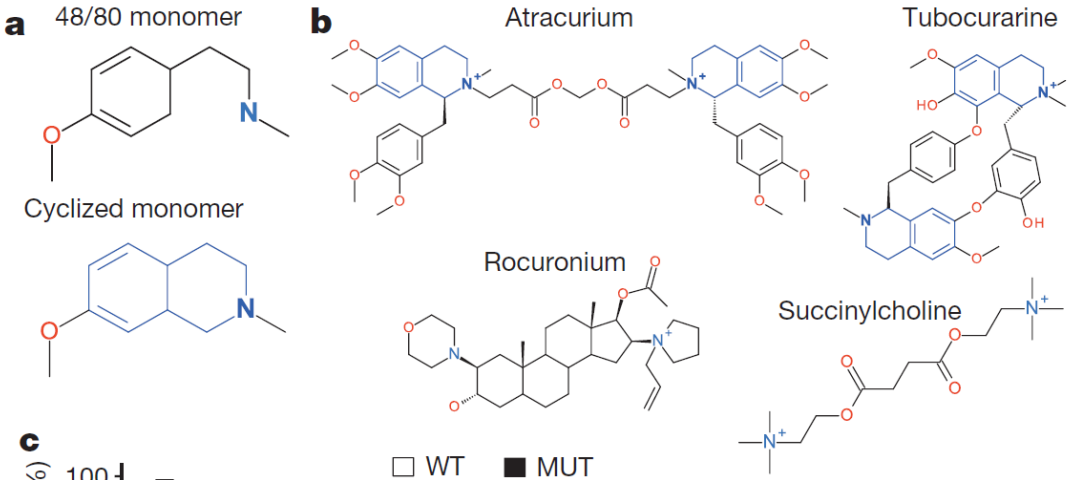
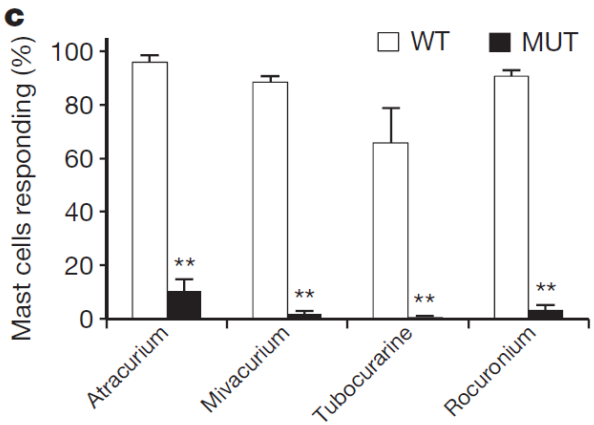
Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

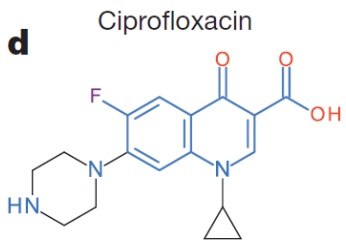
Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

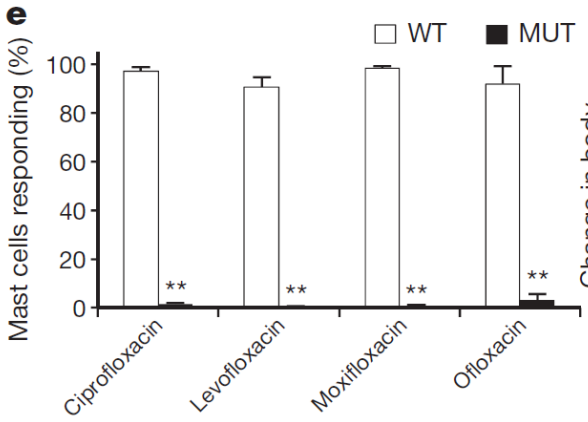
Mast cells are primary effectors in allergic reactions, and may have important roles in disease by secreting histamine and various inflammatory and immunomodulatory substances[1,2]. Although they are classically activated by immunoglobulin (Ig)E antibodies, a unique property of mast cells is their antibody-independent 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.

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









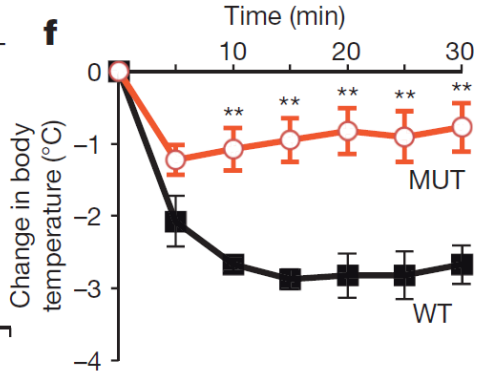


Figure 4 | Mrgprb2 mediates mast cell responsiveness and side effects of small-molecule therapeutic drugs. **a**, Structures of 48/80 and a cyclized variant. The THIQ motif is highlighted in blue. **b**, Structures of representative members of all NMBD classes (see Supplementary Information). THIQ motifs 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: $*P < 0.05$, $**P < 0.01$.

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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

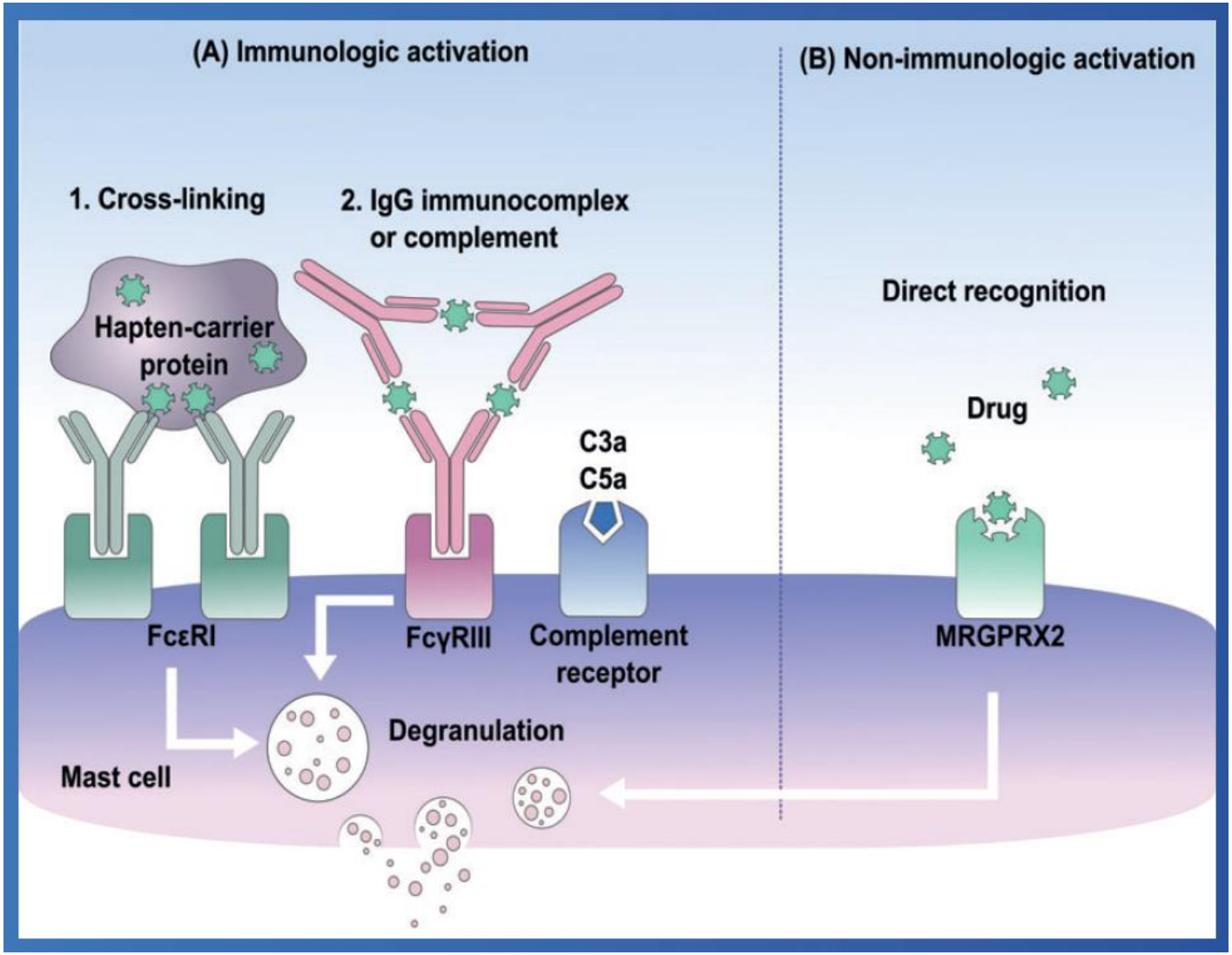
ell-specific receptor crucial reactions

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

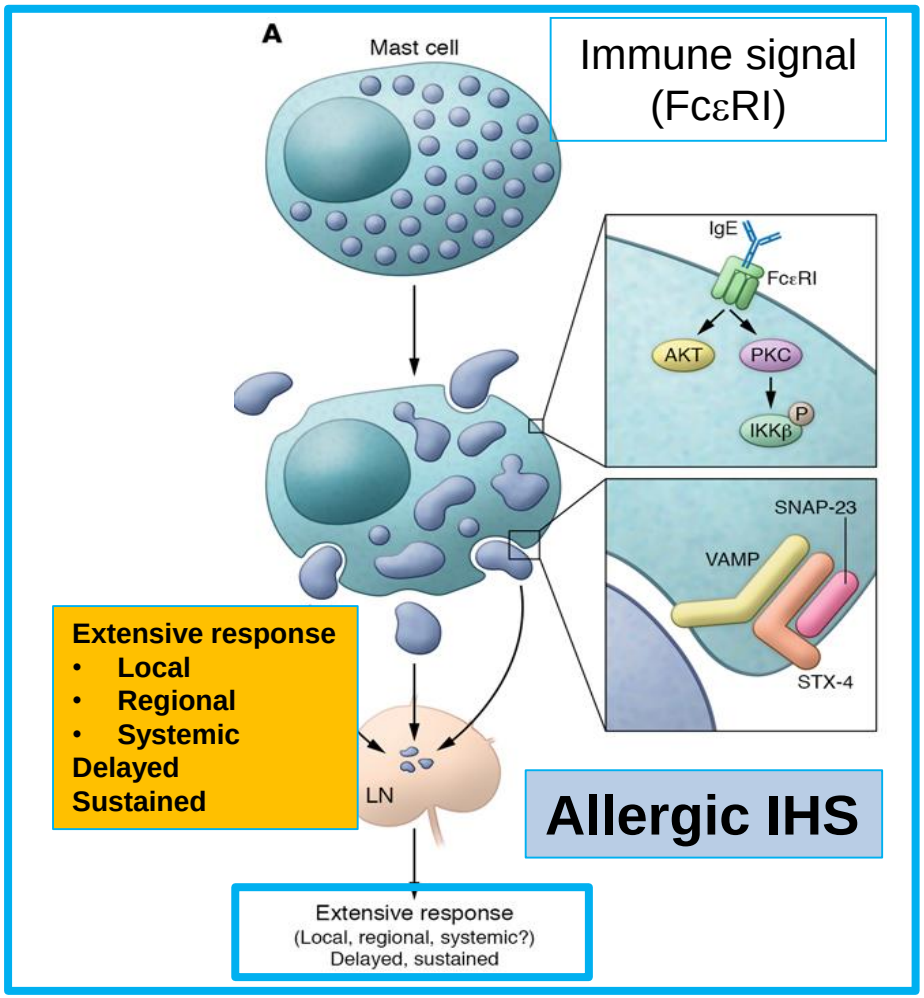
we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation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

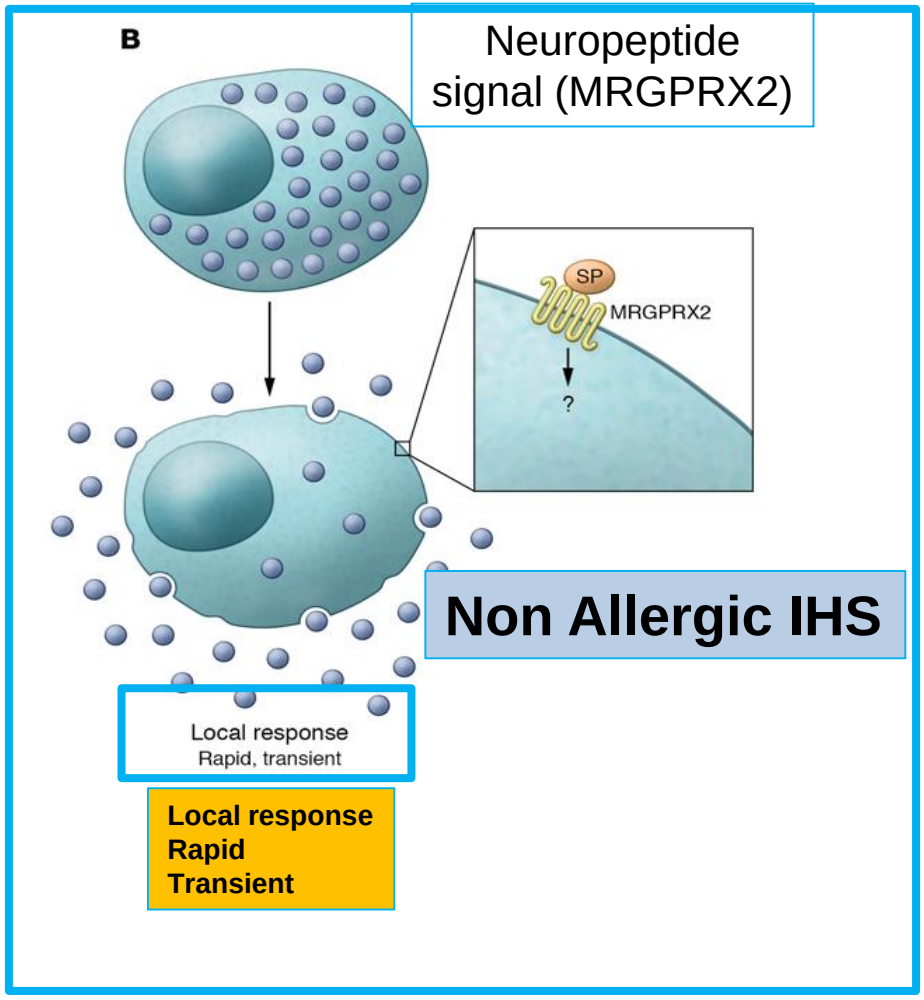
Substance	Mrgprb2 EC_{50}	MRGPRX2 EC_{50}
Compound 48/80	3.7 ± 0.5 μg/ml	470.1 ± 139.6 ng/ml
Substance P	54.3 ± 4.9 μM	152.3 ± 48.0 nM
Cortistatin-14	21.3 ± 0.9 μM	106.7 ± 39.3 nM
PAMP (9-20)	12.4 ± 1.6 μM	166.0 ± 35.7 nM
Mastoparan	24.0 ± 3.6 μM	3.9 ± 0.7 μM
Icatibant	32.5 ± 2.0 μg/ml	15.8 ± 2.7 μg/ml
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

MASTOCYTES
Récepteurs et activation



Two fundamental degranulation pathways in mast cells





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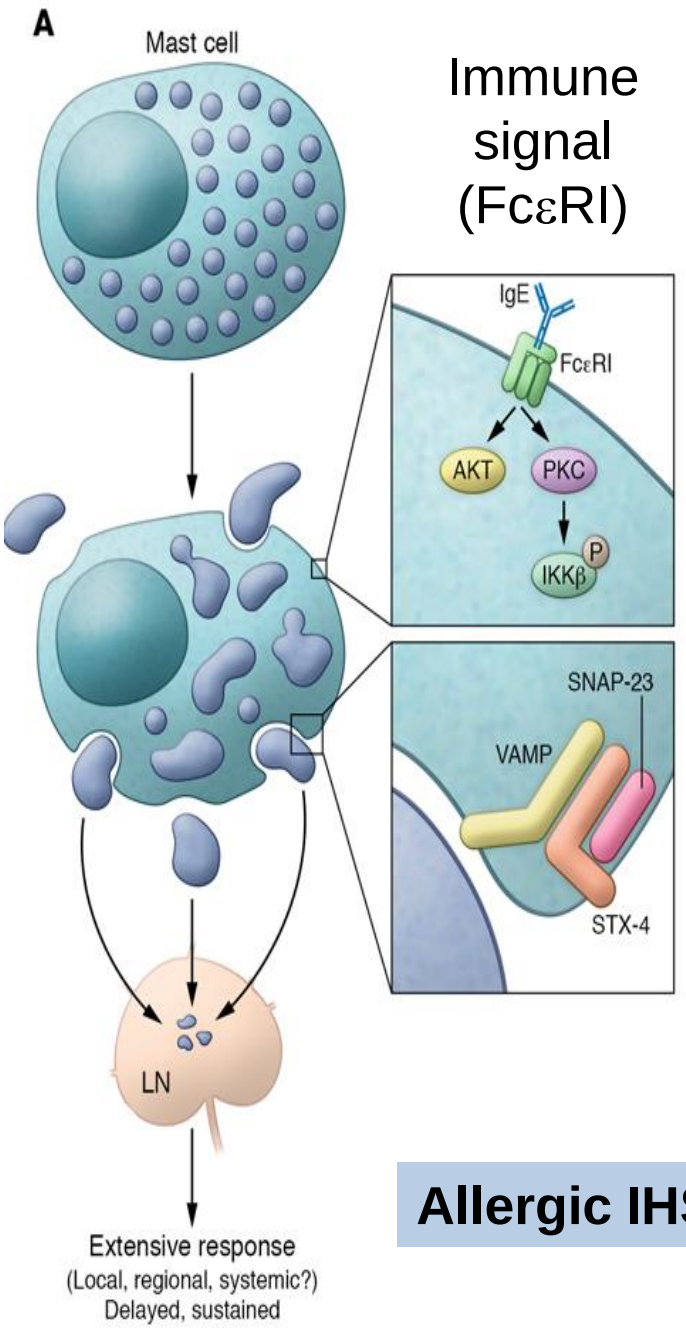
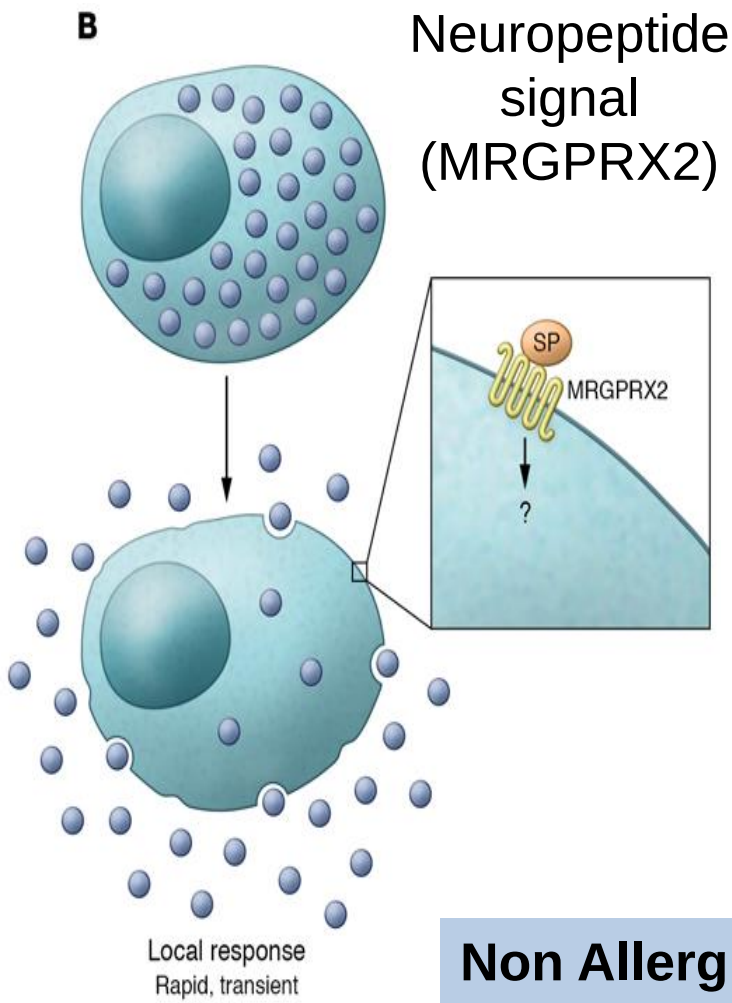


Allergic IHS



Non Allergic IHS

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

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
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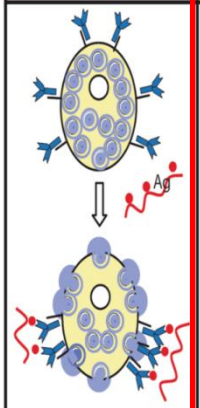
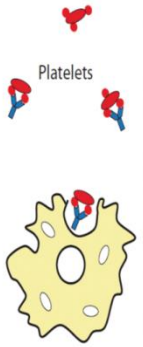
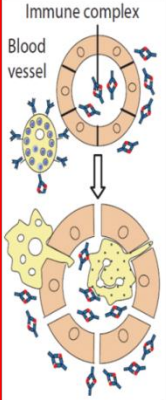
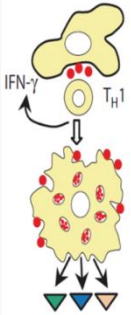
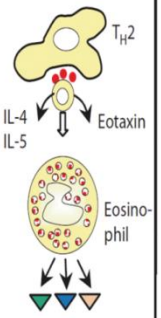
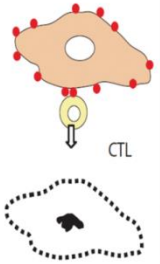
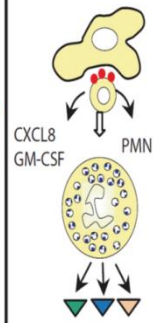
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
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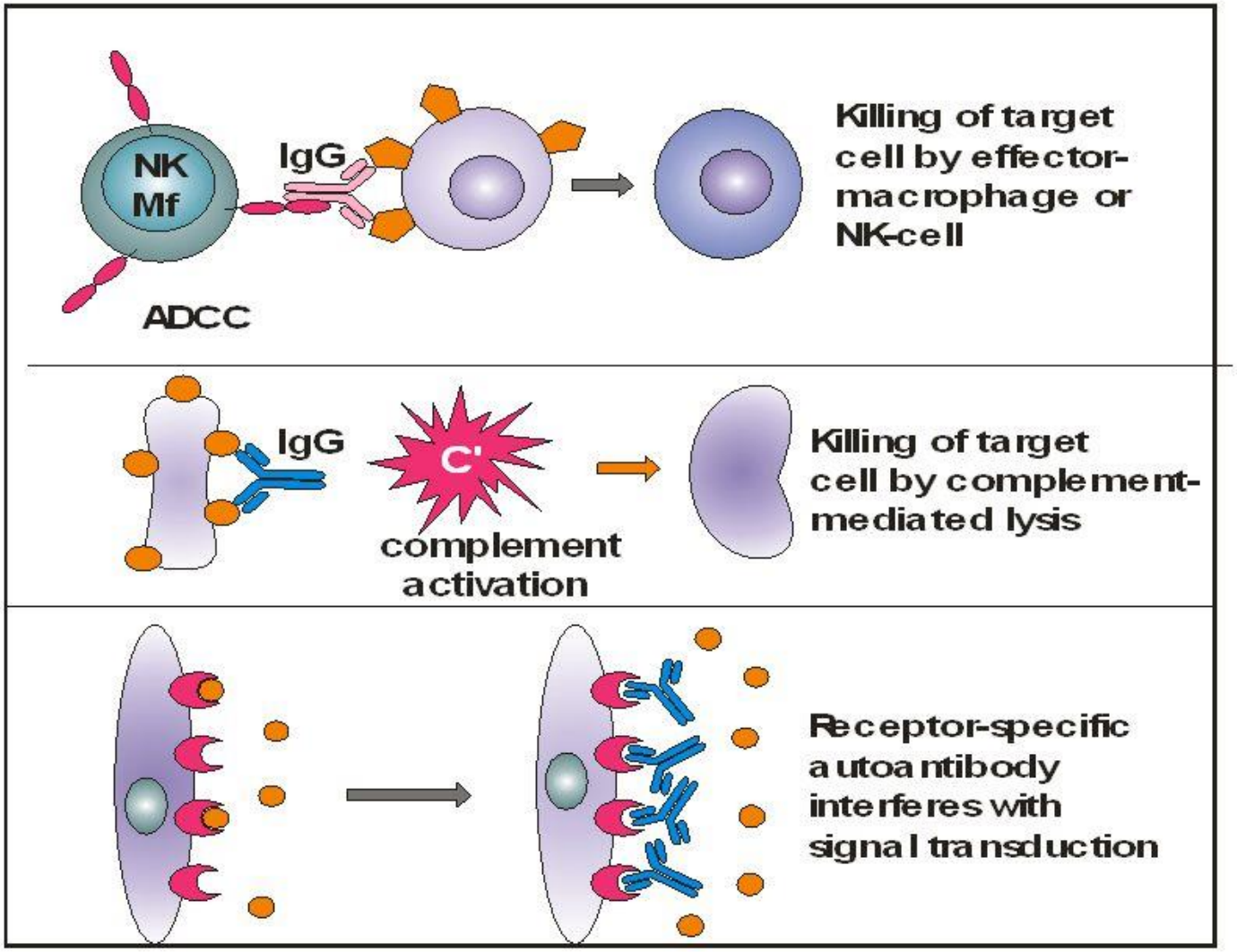
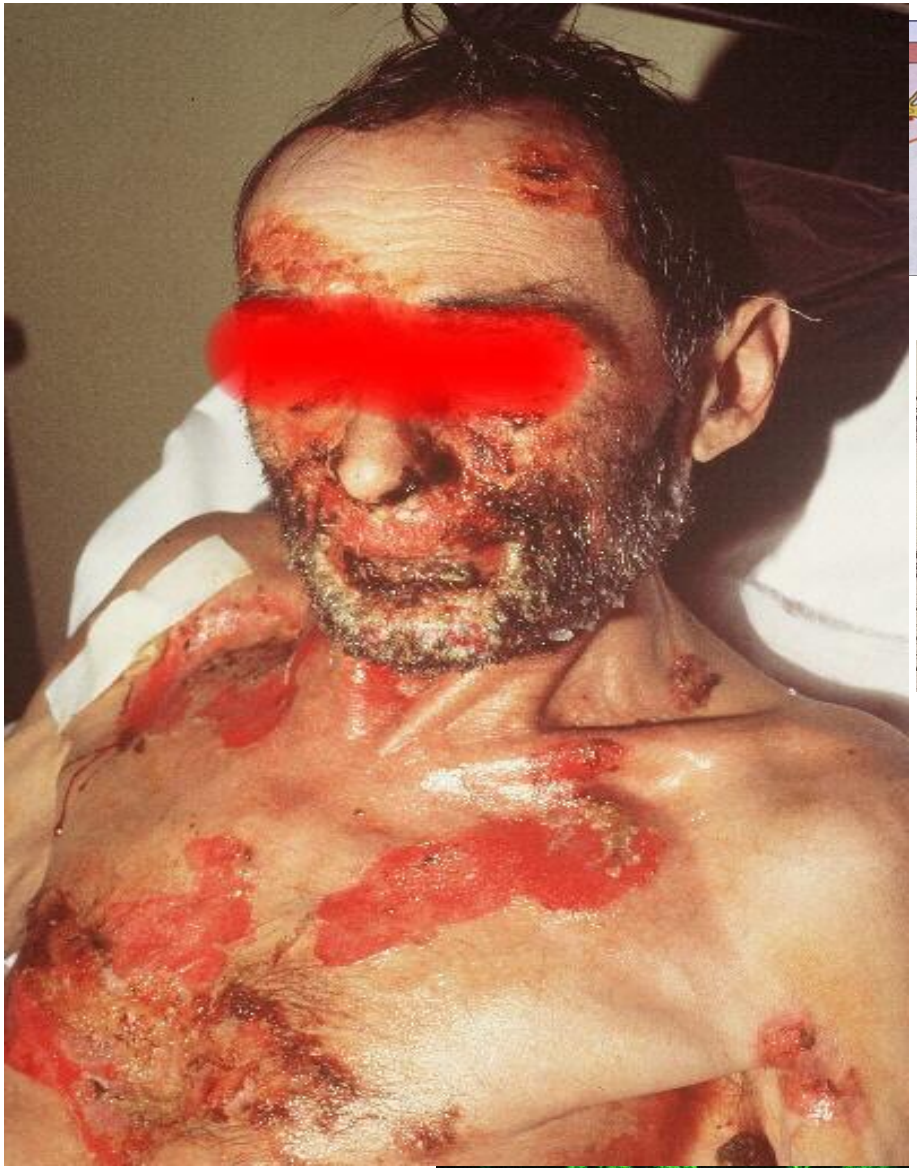
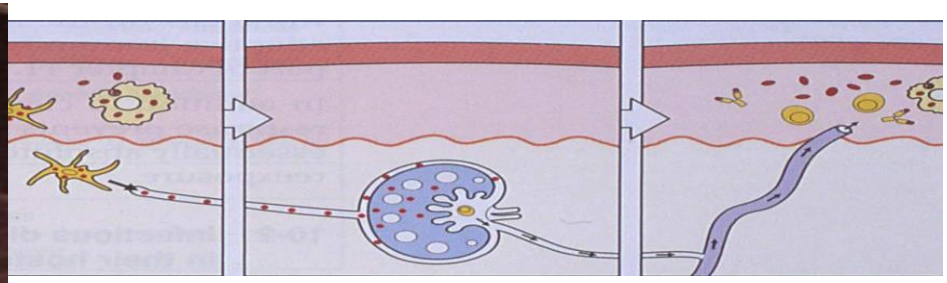
Dermatoses autoimmunes et allergiques	**Urticaire contact**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Psoriasis**	**Dermatite atopique**	**Vitiligo Pelade Eczéma contact**	**Psoriasis**
Allergies médicaments	**Choc anaphylactique**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème médic.**	**DRESS**	**Lyell Stevens-Johnson**	

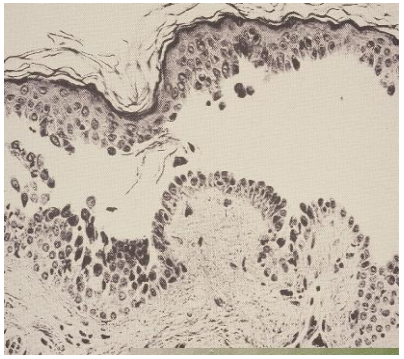
MECHANISMS OF TYPE II HYPERSENSITIVITY REACTIONS

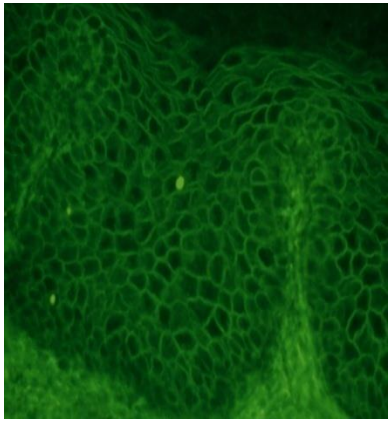


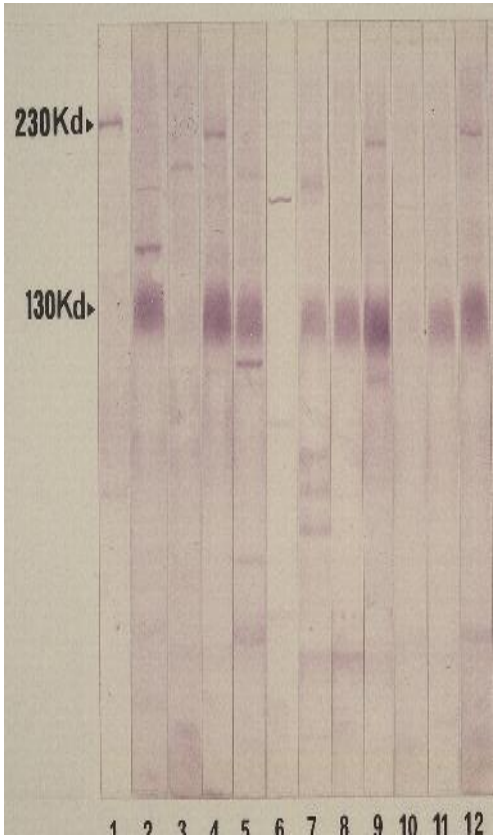
Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS











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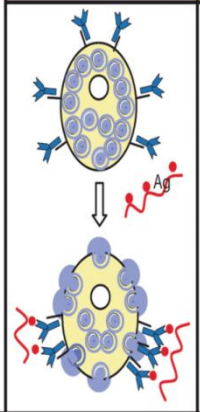
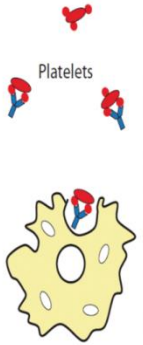
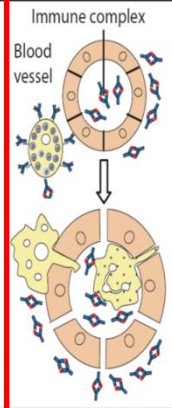
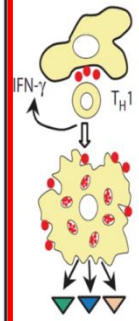
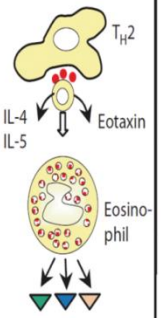
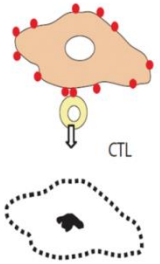
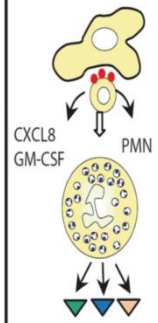
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
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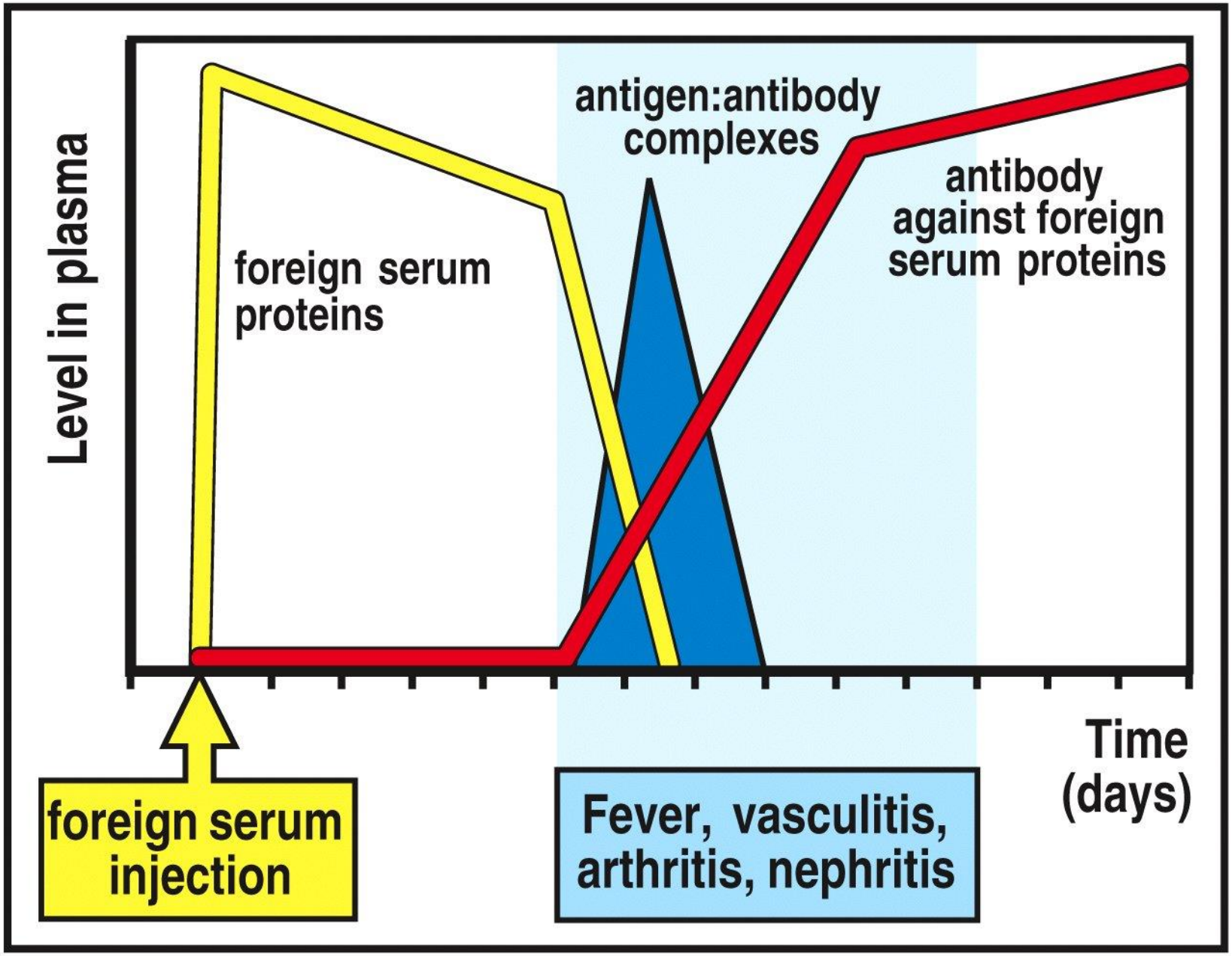
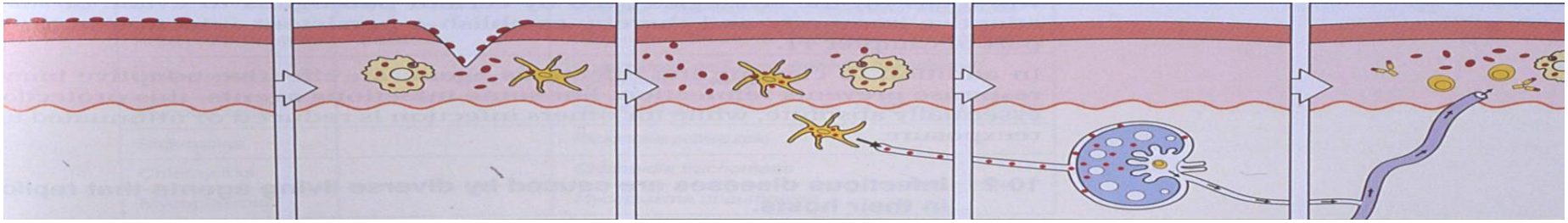
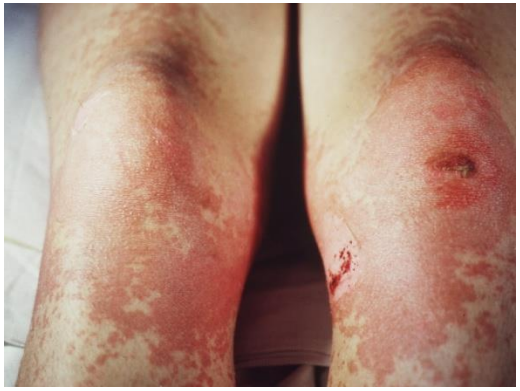
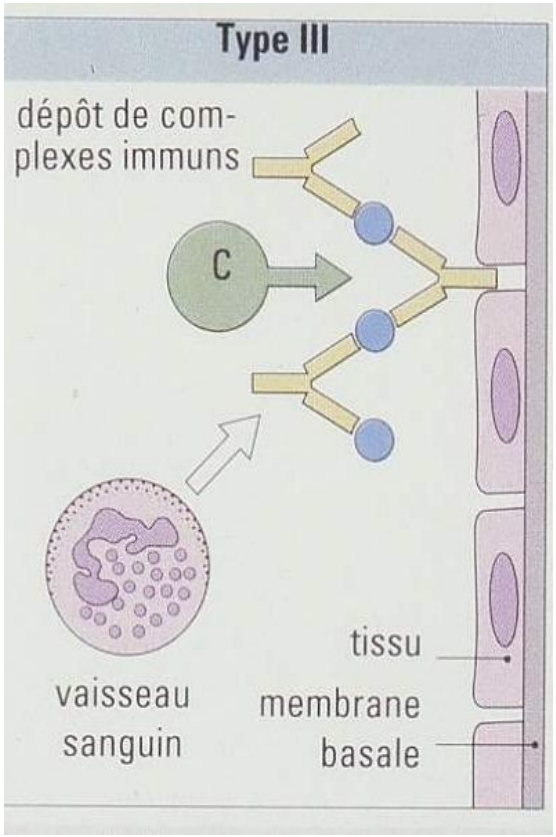


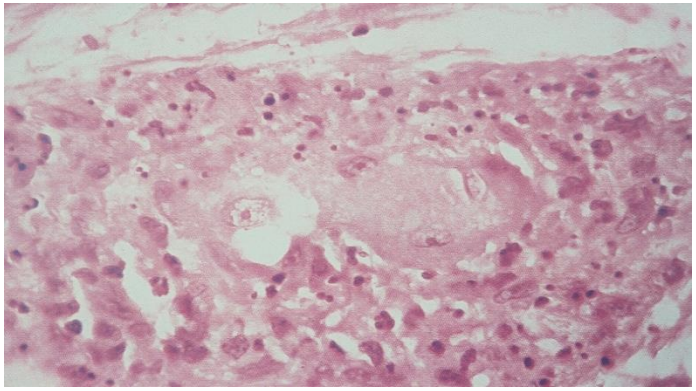
Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

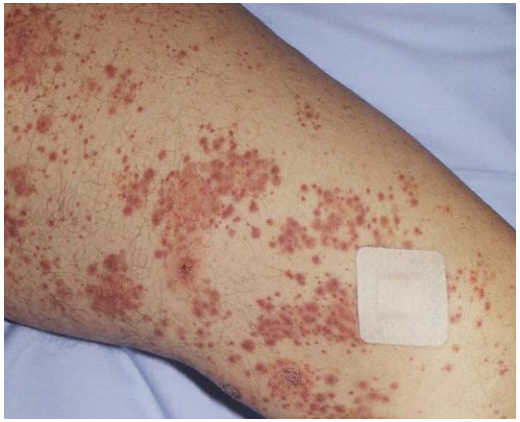
Hypersensibilité de type III due à des complexes immuns
VASCULITES – PURPURA RHUMATOIDE

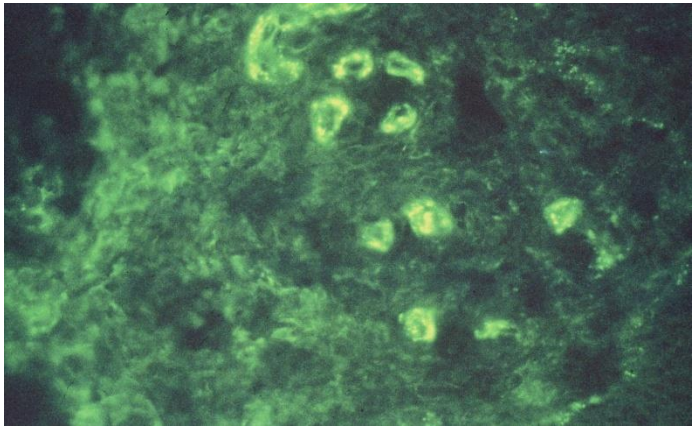












HS de type III aux antigènes inhalés
Alvéolites allergiques

- 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

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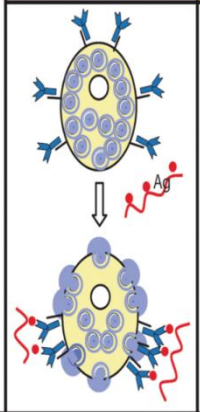	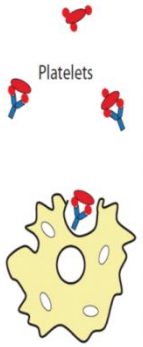	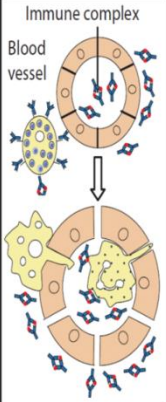	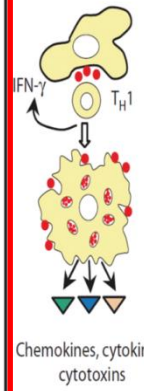	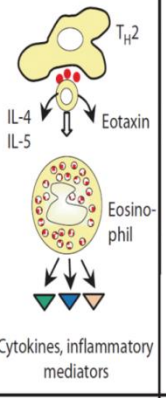	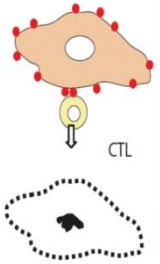	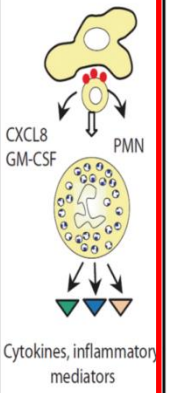
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The 3 major types of innate and adaptive cell-mediated effector immunity

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

In 1986, Mosmann et al[1] demonstrated that murine CD4$^+$ T_H cells can be classified into 2 major functionally different subsets on the basis of the different cytokines they produce (ie, T_H1 and T_H2). The first clear evidence for the existence of T_H1 and T_H2 cells in human subjects was provided only 5 years later.[2] As known, T_H1 cells produce IFN-γ and lymphotoxin (LT) α, 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, respectively.[4] In 2005, a third subset of murine CD4$^+$ T_H cells was identified and named T_H17 cells because of the unique ability of these cells to produce IL-17.[5] Two years later, T_H17 cells were found to exist in human subjects.[6,7] Likewise, CD8$^+$ T cells producing IL-17 were identified and named T_C17 cells.[8] In the last few years, the existence of innate lymphoid cells (ILCs), which differ from classic T cells because they lack the T-cell receptor, has been reported both in mice and

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

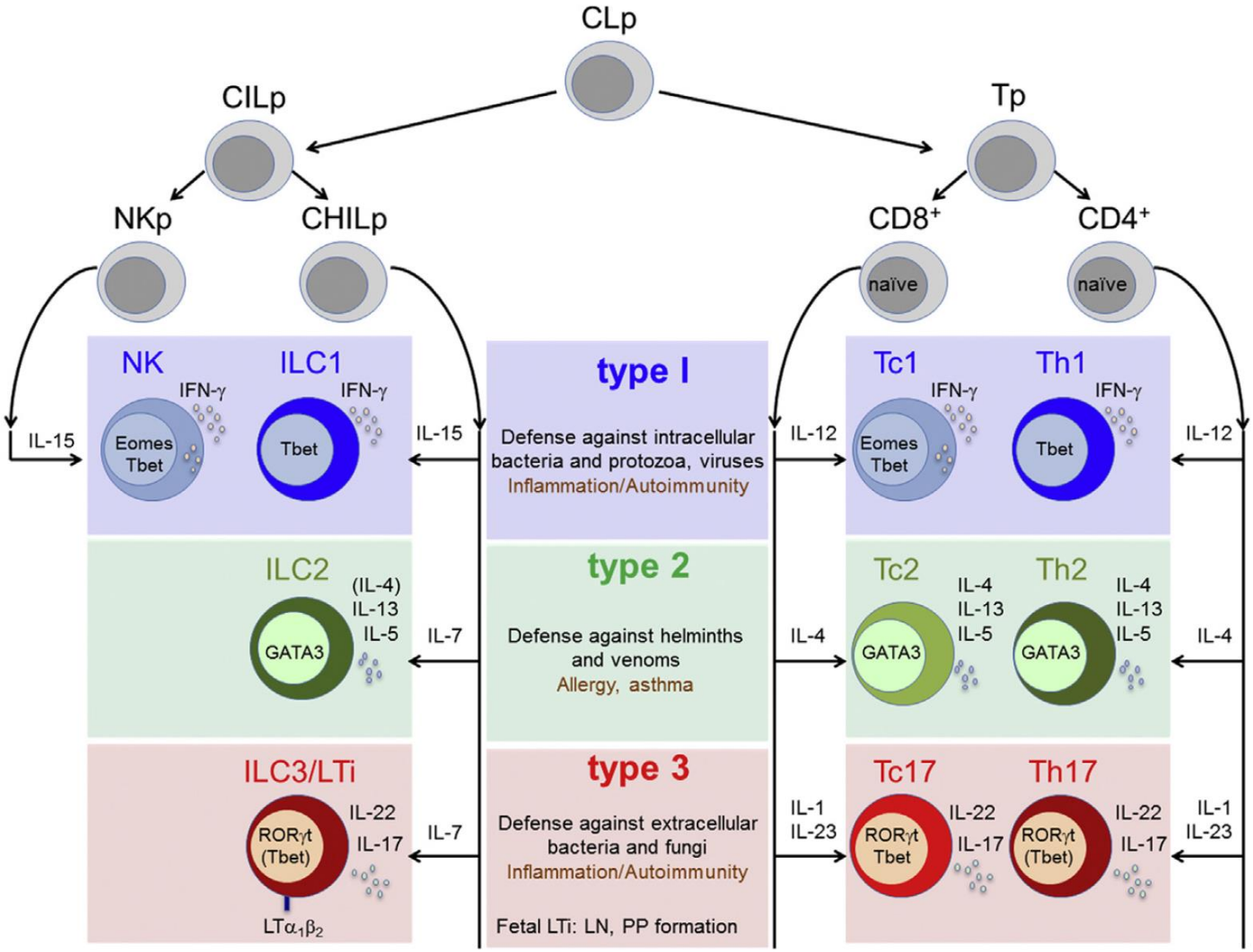
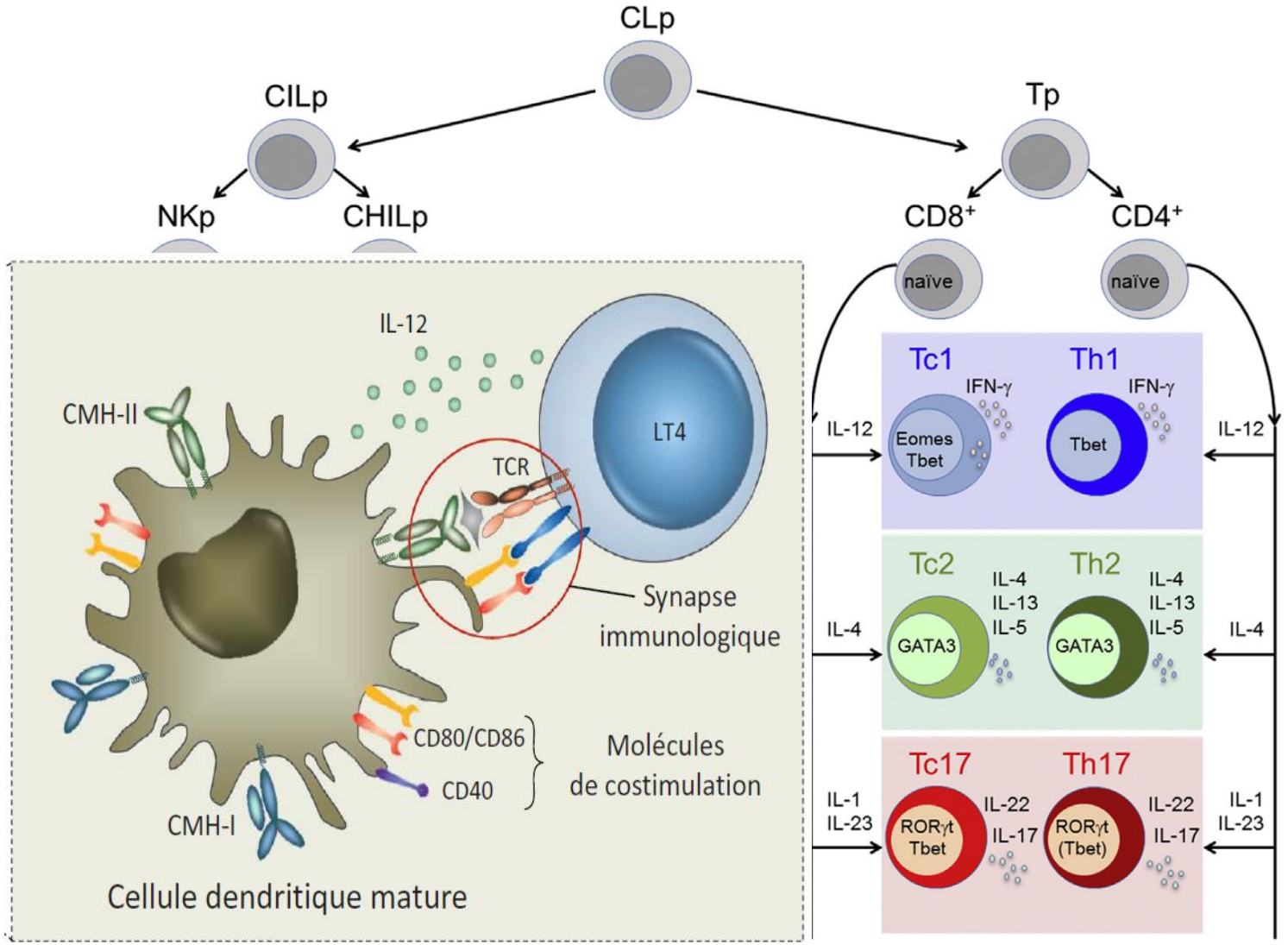


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and 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.

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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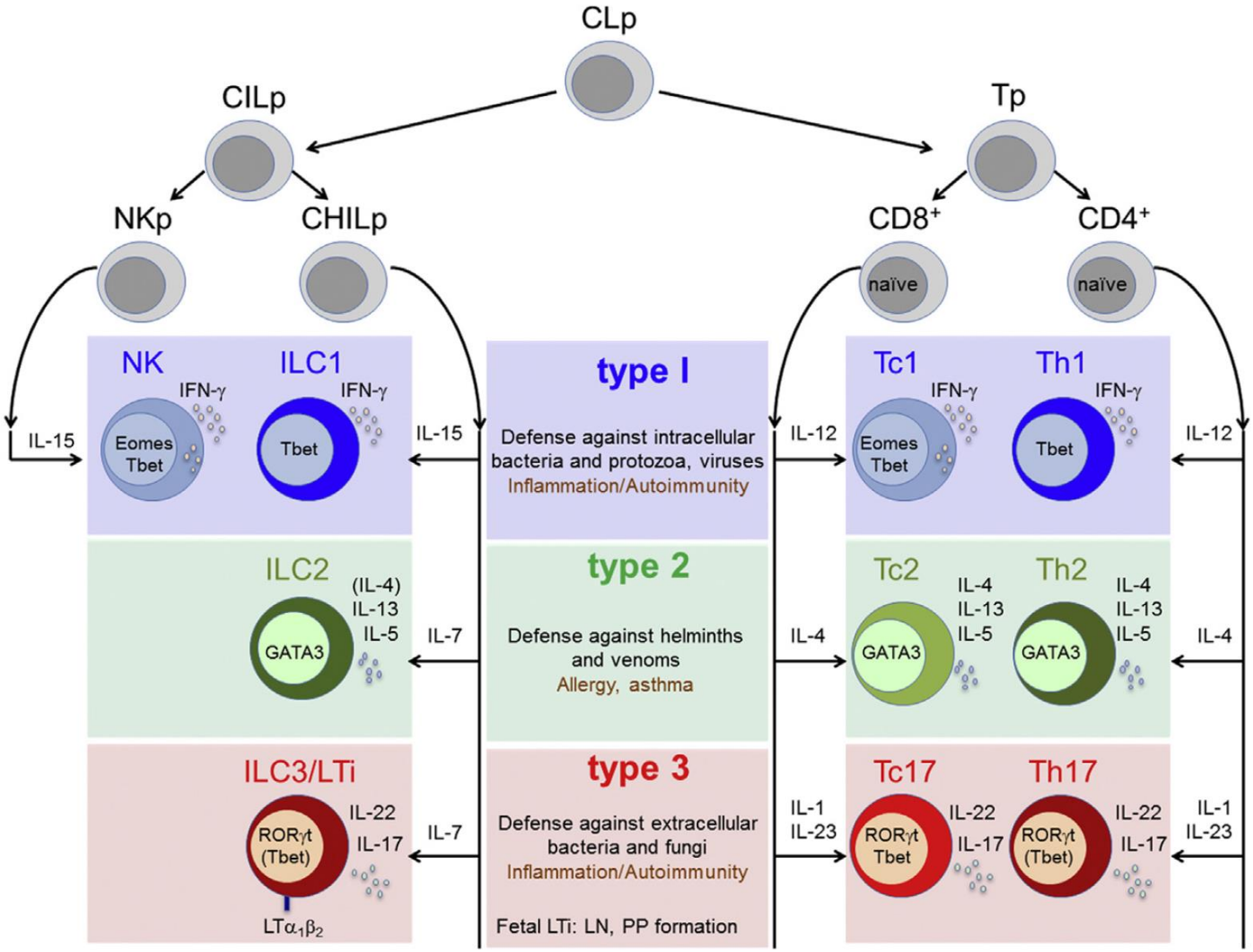

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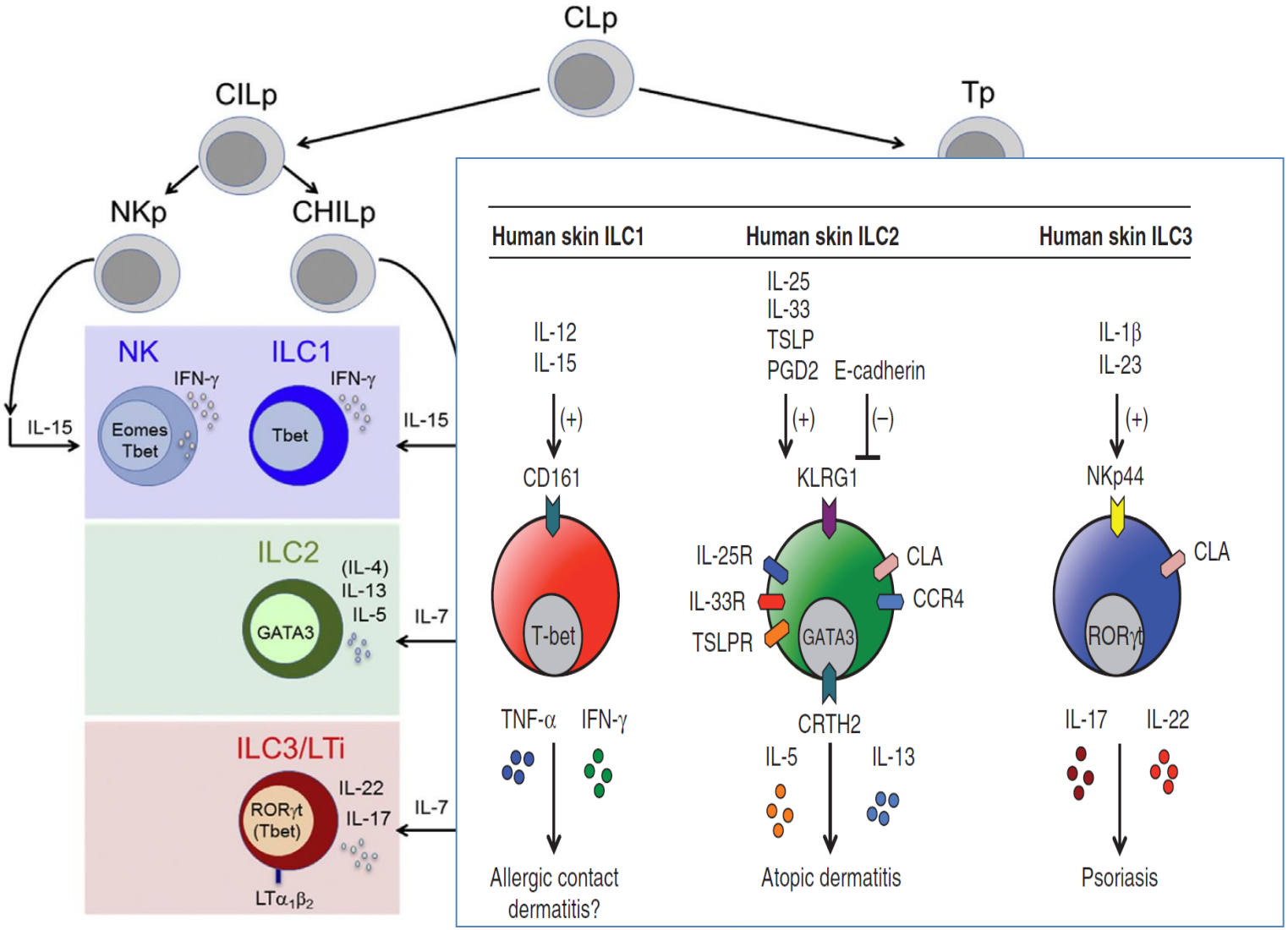

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Type 1/ Th1 Immunity

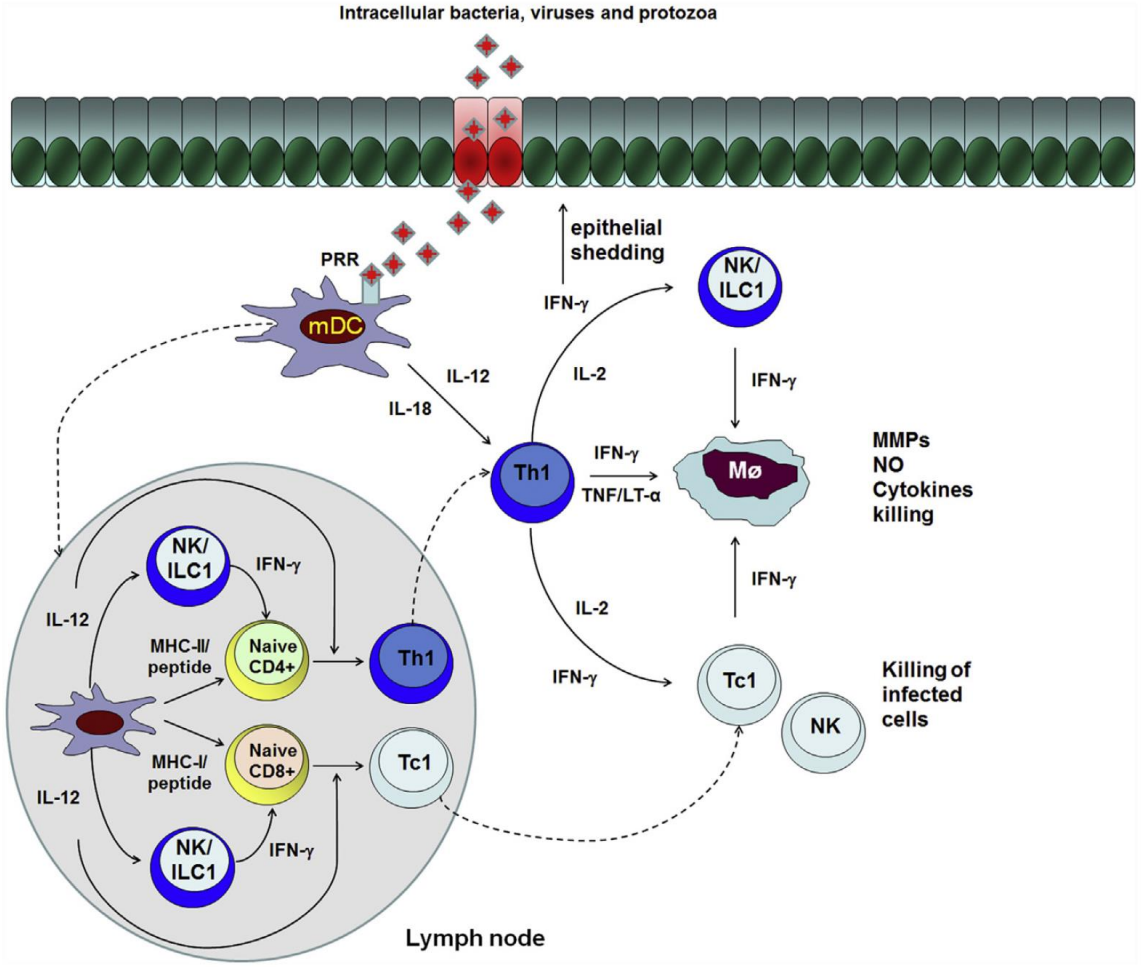


FIG 2. Cells, cytokines, and effectors of type 1 immunity. Intracellular microbes interacting with pathogen recognition receptors *(PRR)* on DCs in the presence of DC-derived IL-12 and IL-18 and of NK/ILC1-derived IFN-γ induce T_H1 or T_C1 development from naive T cells. T_C1 and NK cells kill virus-infected 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/ Th2 Immunity

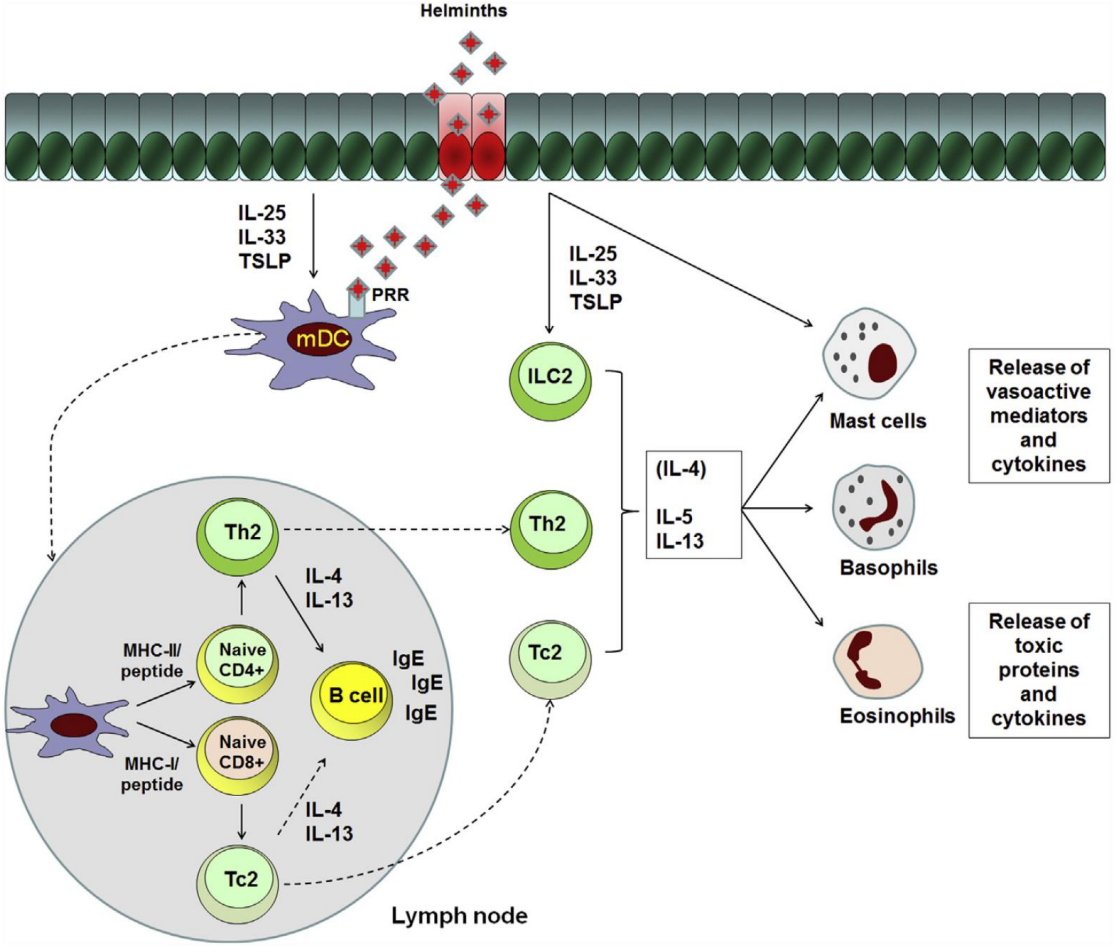


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin *(TSLP)* release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated 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/Th17 Immunity

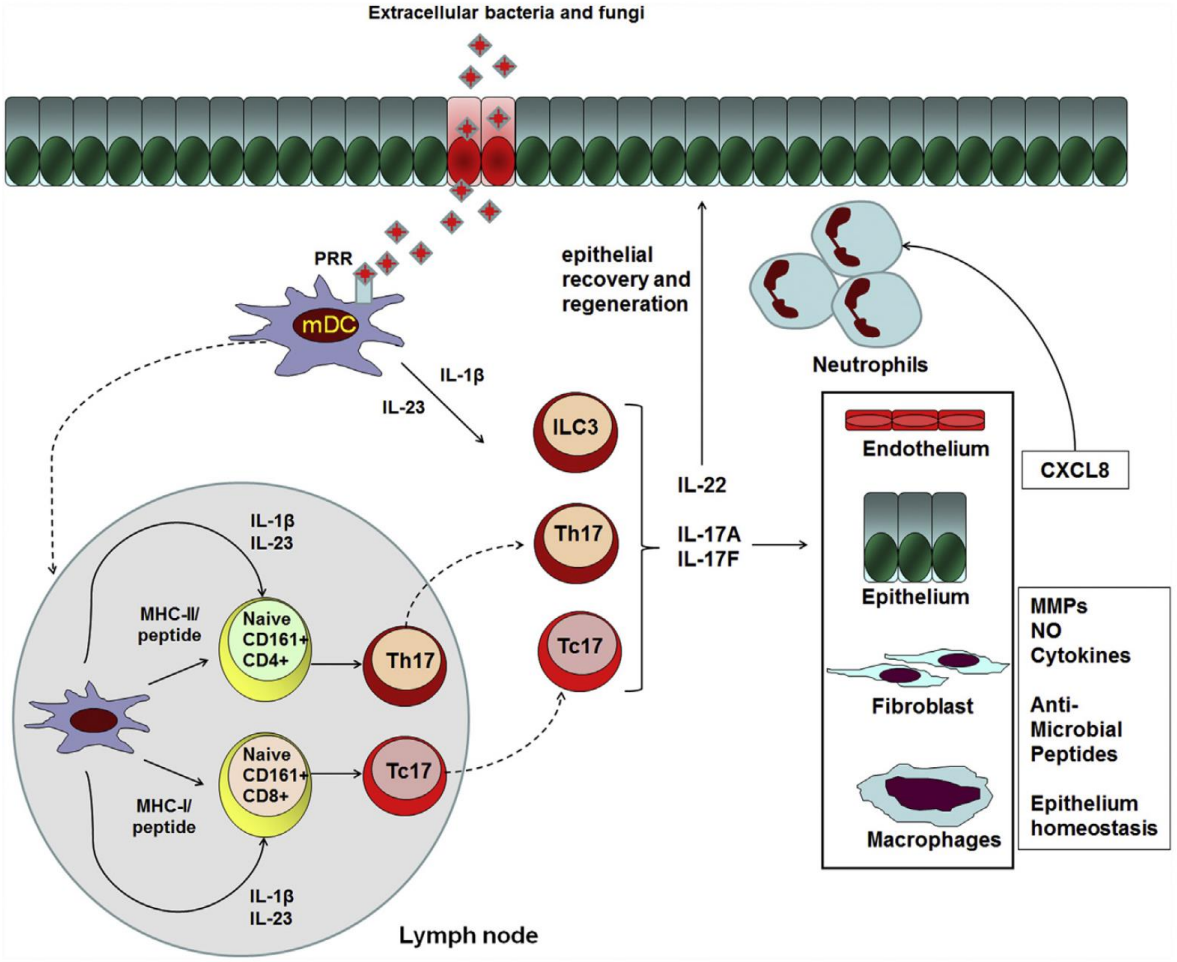
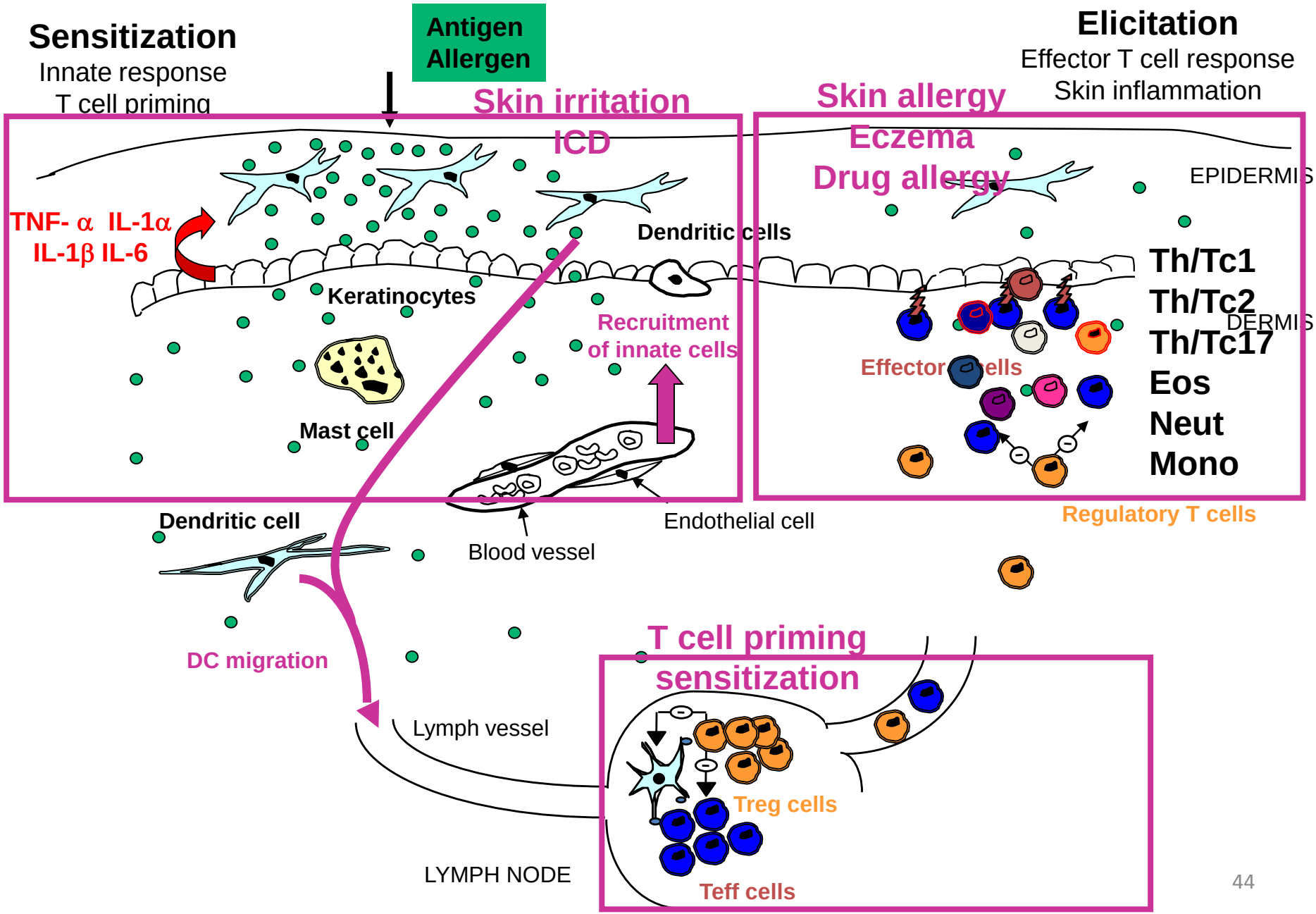


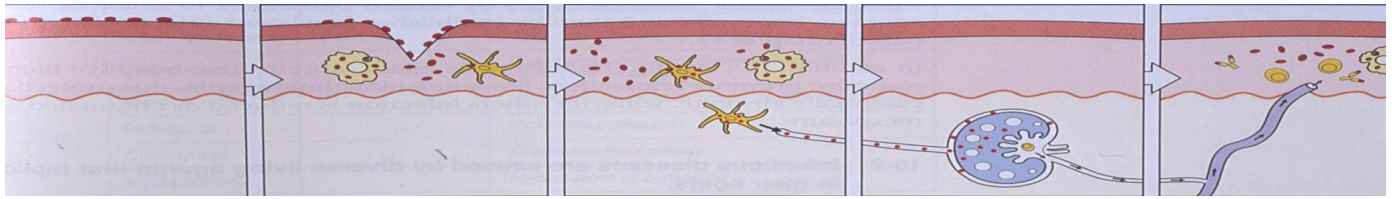
FIG 4. Cells, cytokines, and effectors of type 3 immunity. Extracellular bacteria and fungi induce myeloid dendritic cells *(mDC)* to produce IL-1β and IL-23, which allow T_H17 or T_C17 development from naive $CD161^+$ T cells and trigger cytokine production by ILC3s. IL-17A, IL-17F, and IL-22 from ILC3s 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.

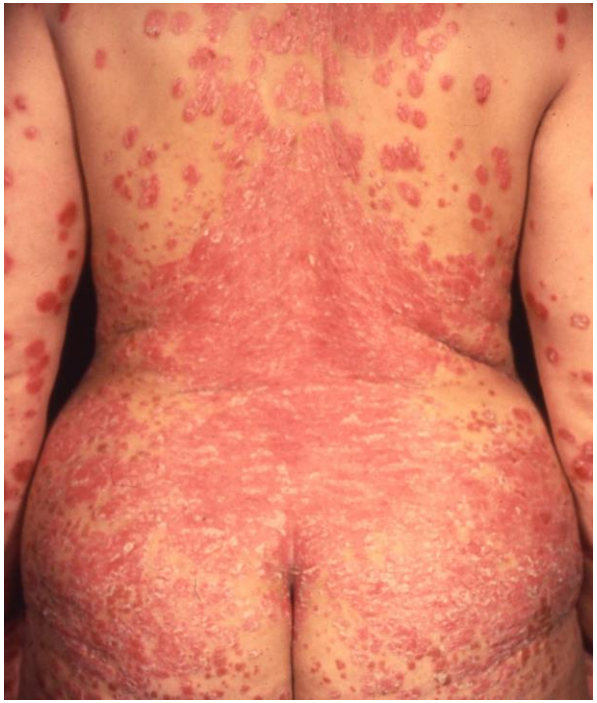
Immunology of eczemas

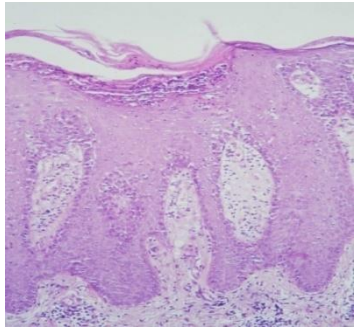


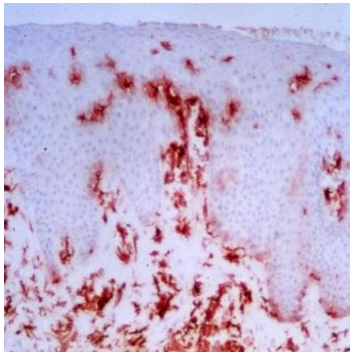
Hypersensibilité de type IV (HS retardée) due à des LT
PSORIASIS

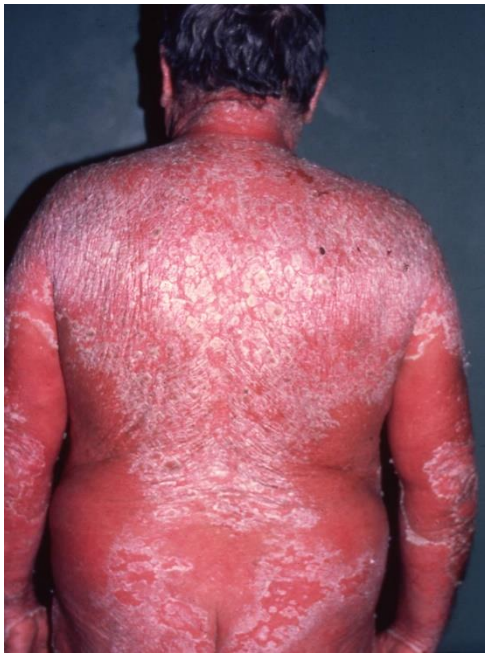
Th17
Type
17





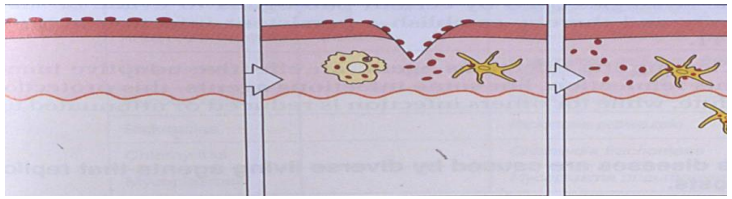


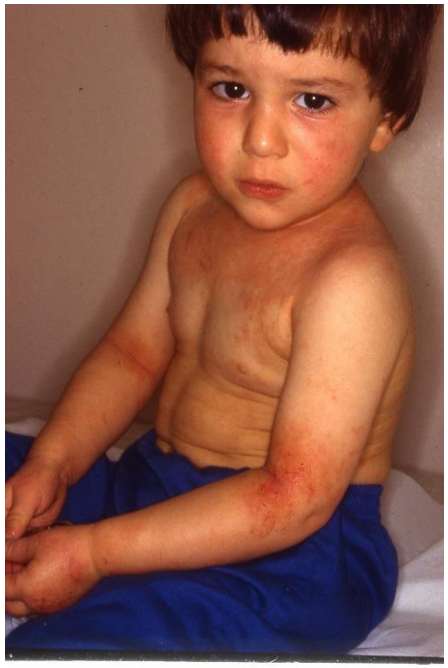


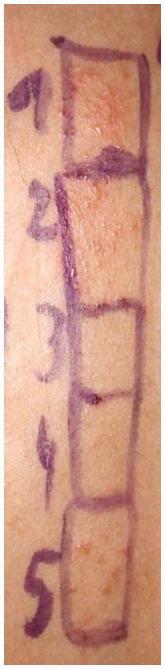


Hypersensibilité de type IV (HS retardée) due à des LT
DERMATITE ATOPIQUE

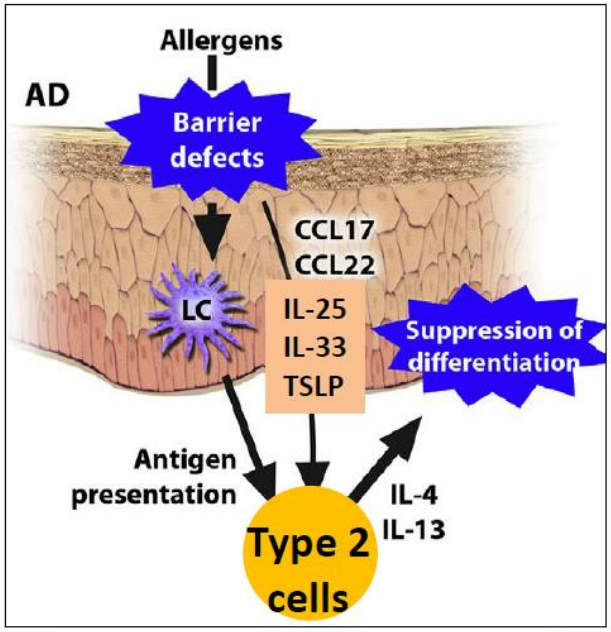
Th2
Type 2







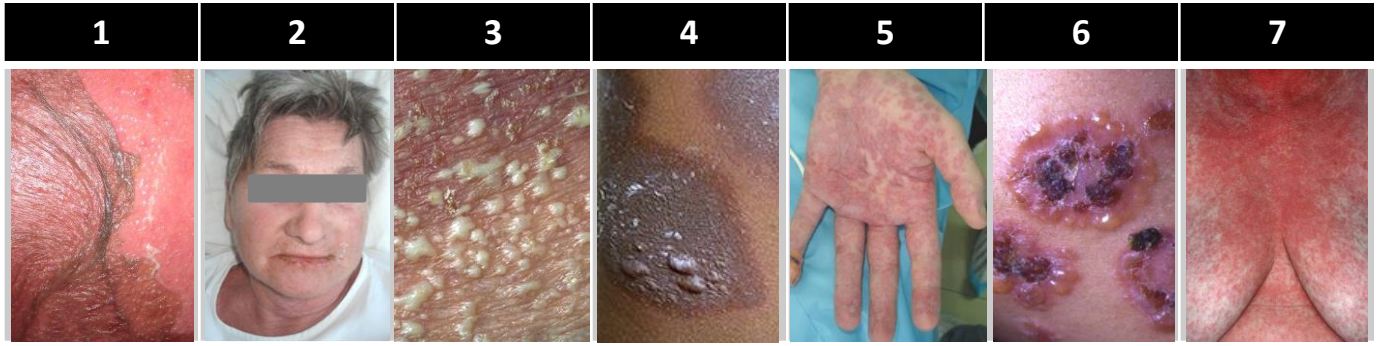
Type 2 phenotype



Type 2 inflammation
Type 2 immunity

Toxidermies – Drug allergy

Cytotoxic



Severity

Prevalence

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

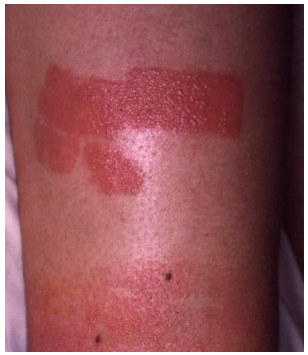
6 - Linear IgA Dermatosis

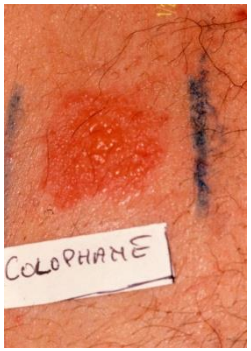
MILD

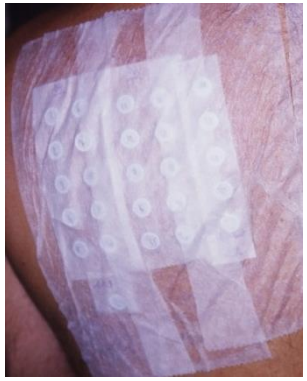
7 - MPE: Maculo-papular exanthema

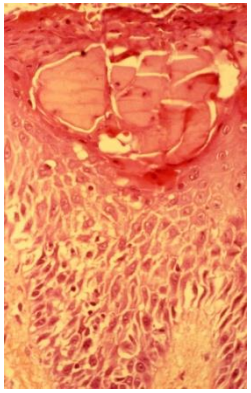
ECZEMAS/DERMATITES DE CONTACT

Allergic Contact dermatitis

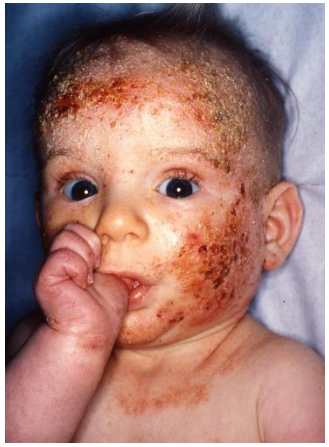


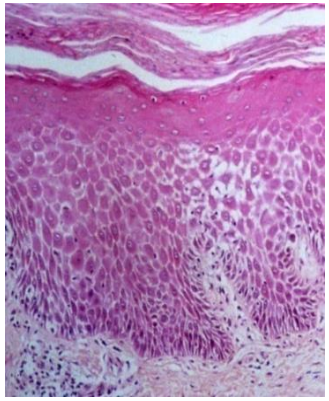


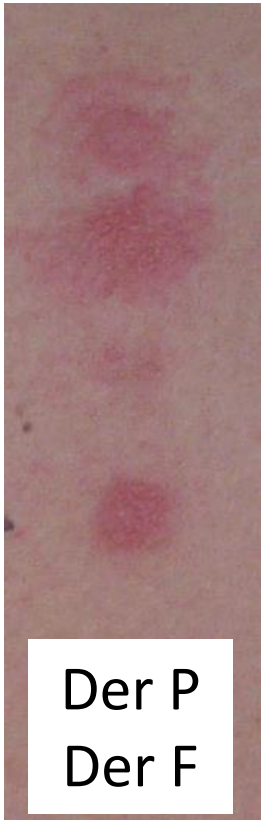




Atopic eczema

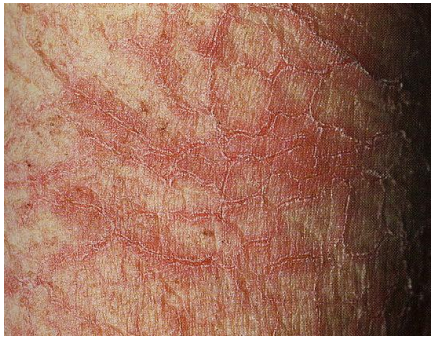


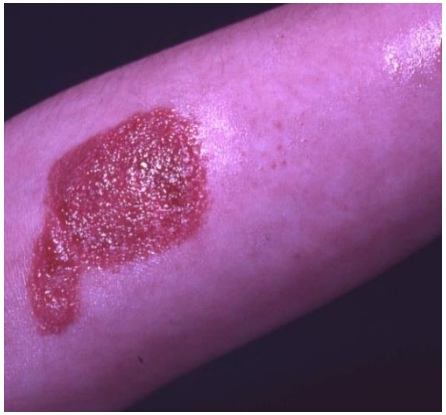




Adaptive Immunity
- hapten, allergen
- DTH – type IV Gell and Coombs
- T cell mediated

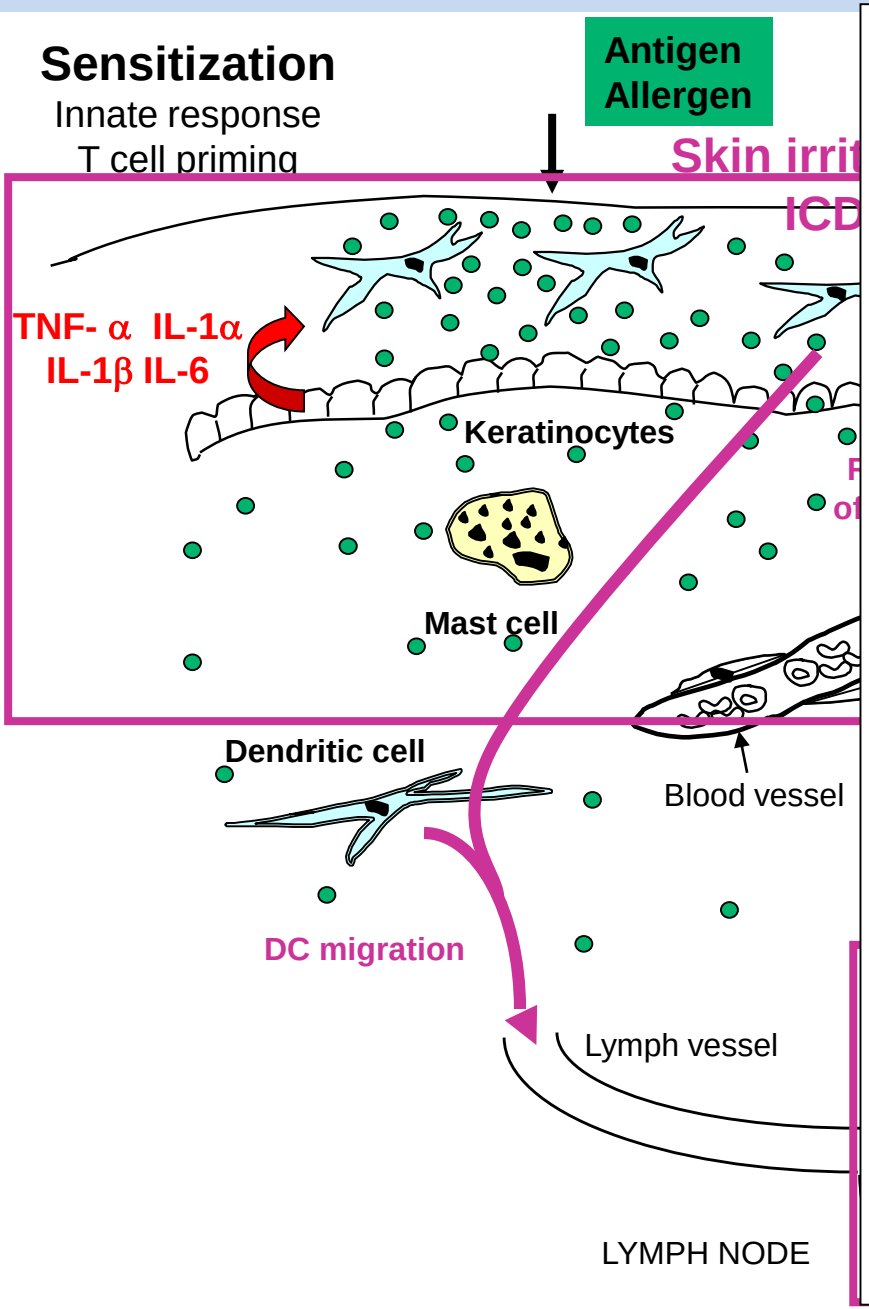
Irritant Contact Dermatitis

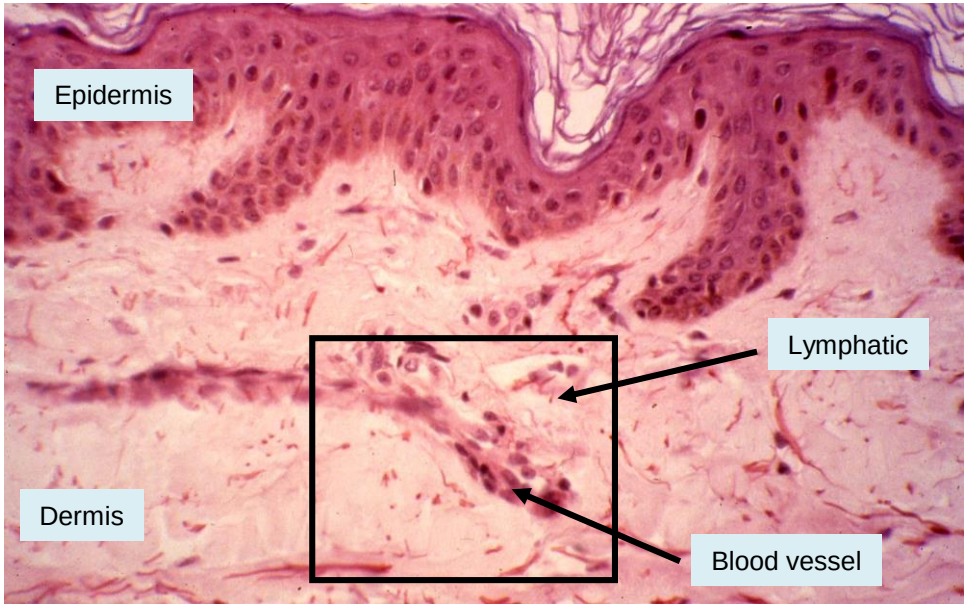


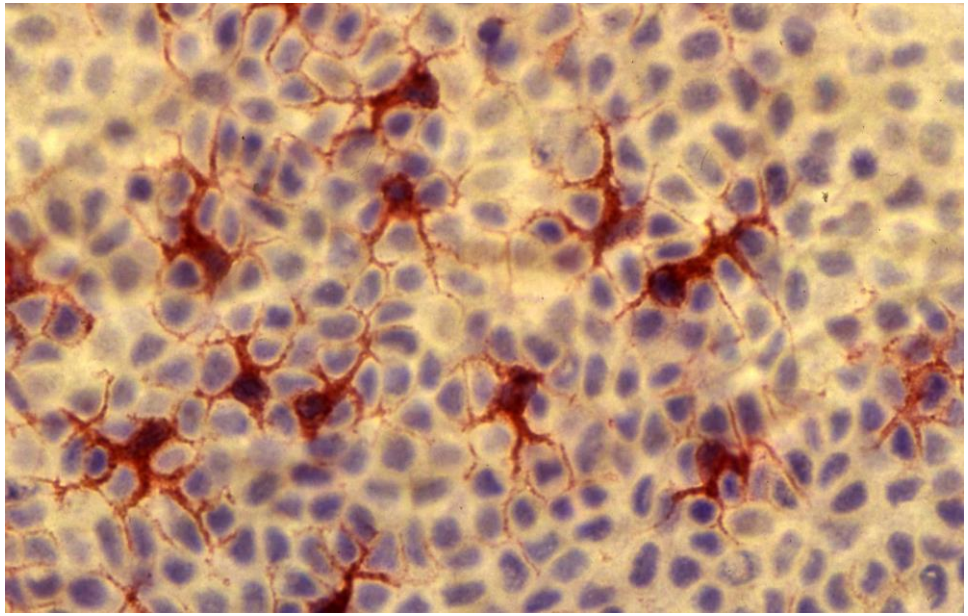


Innate Immunity
- Inflammatory properties
- TLR- and inflammasome-mediated

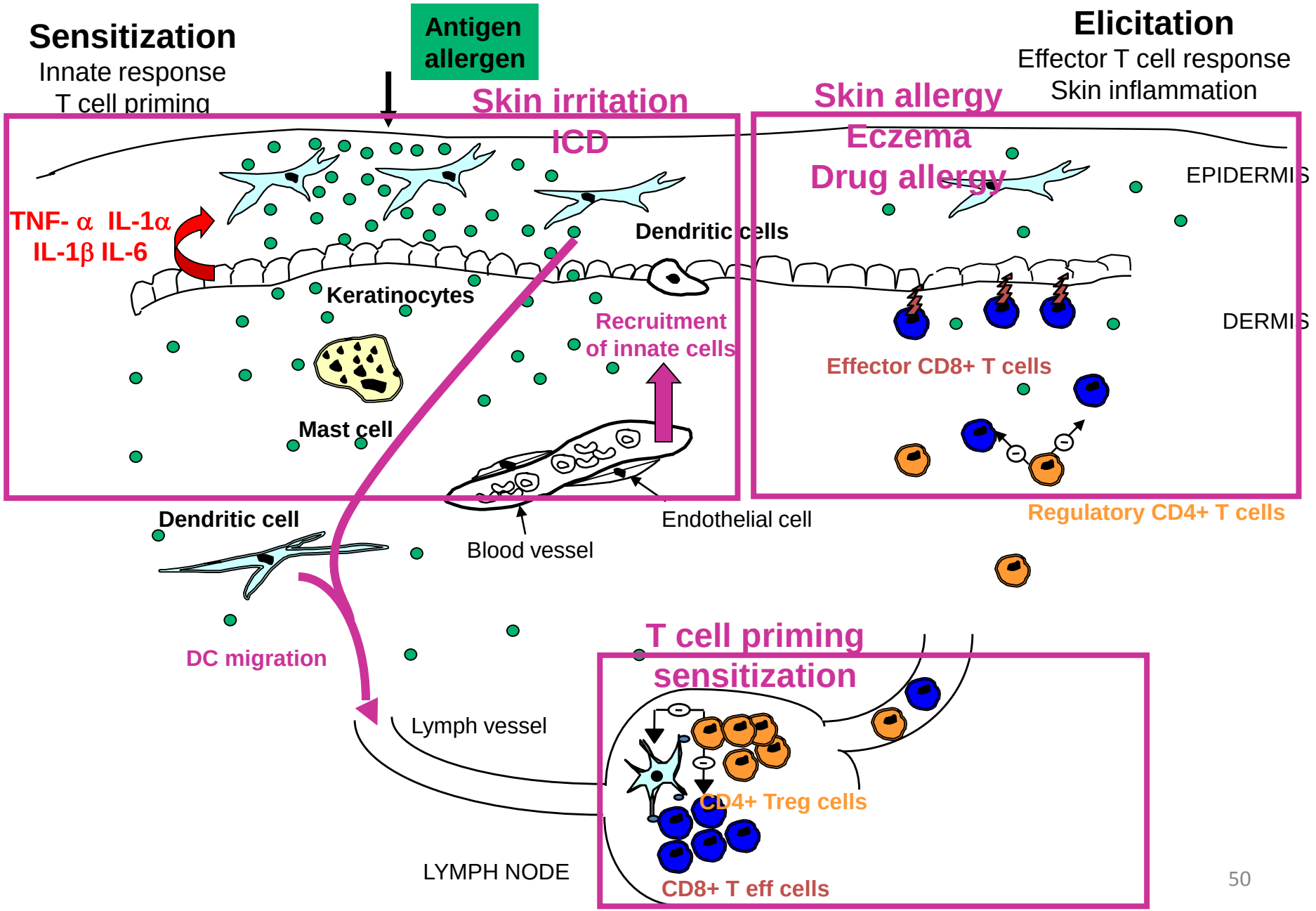
Immunology of eczemas







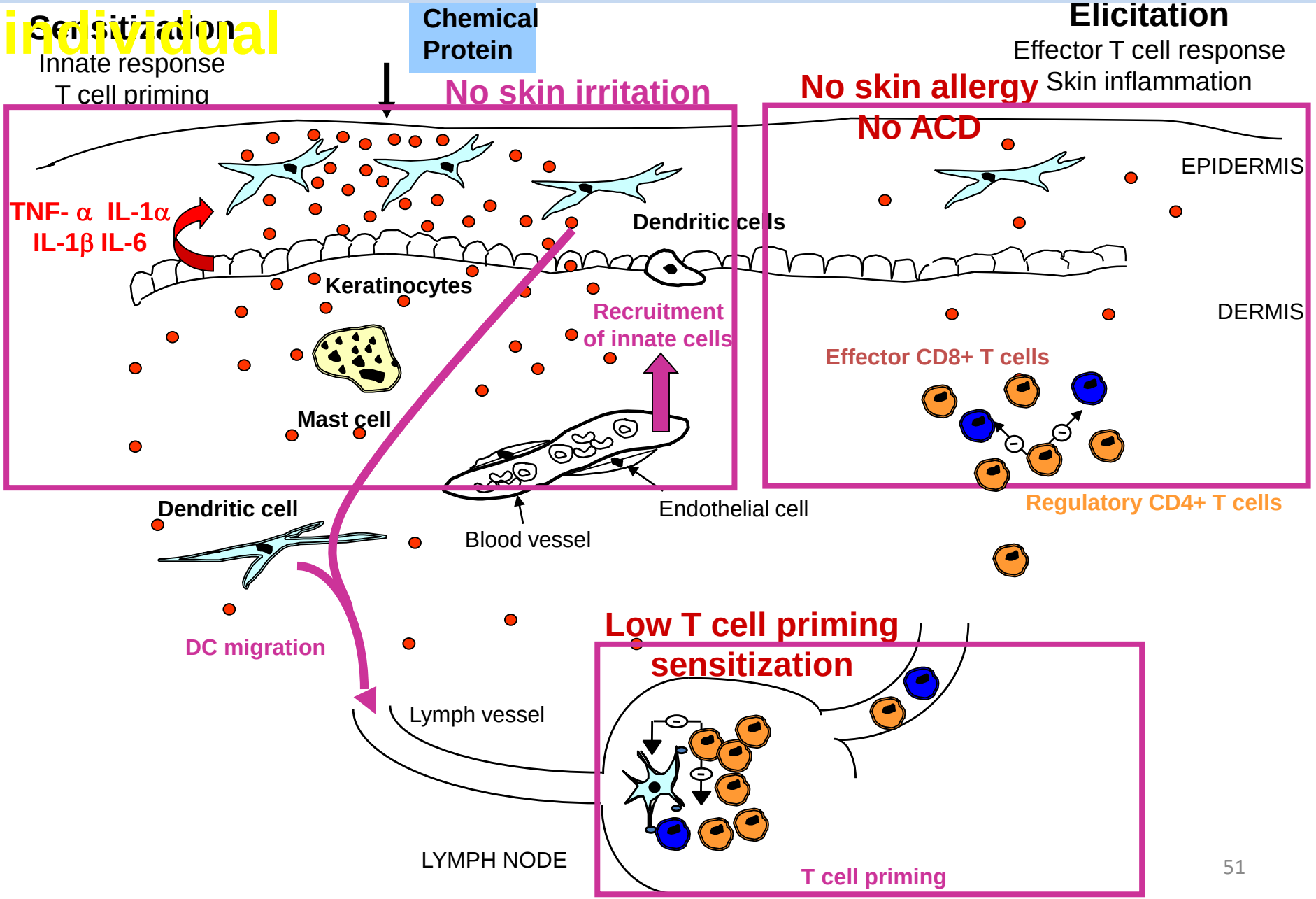
Pathophysiology of eczemas



Pathophysiology of eczemas

Non allergic

individual



Pathophysiology of eczemas

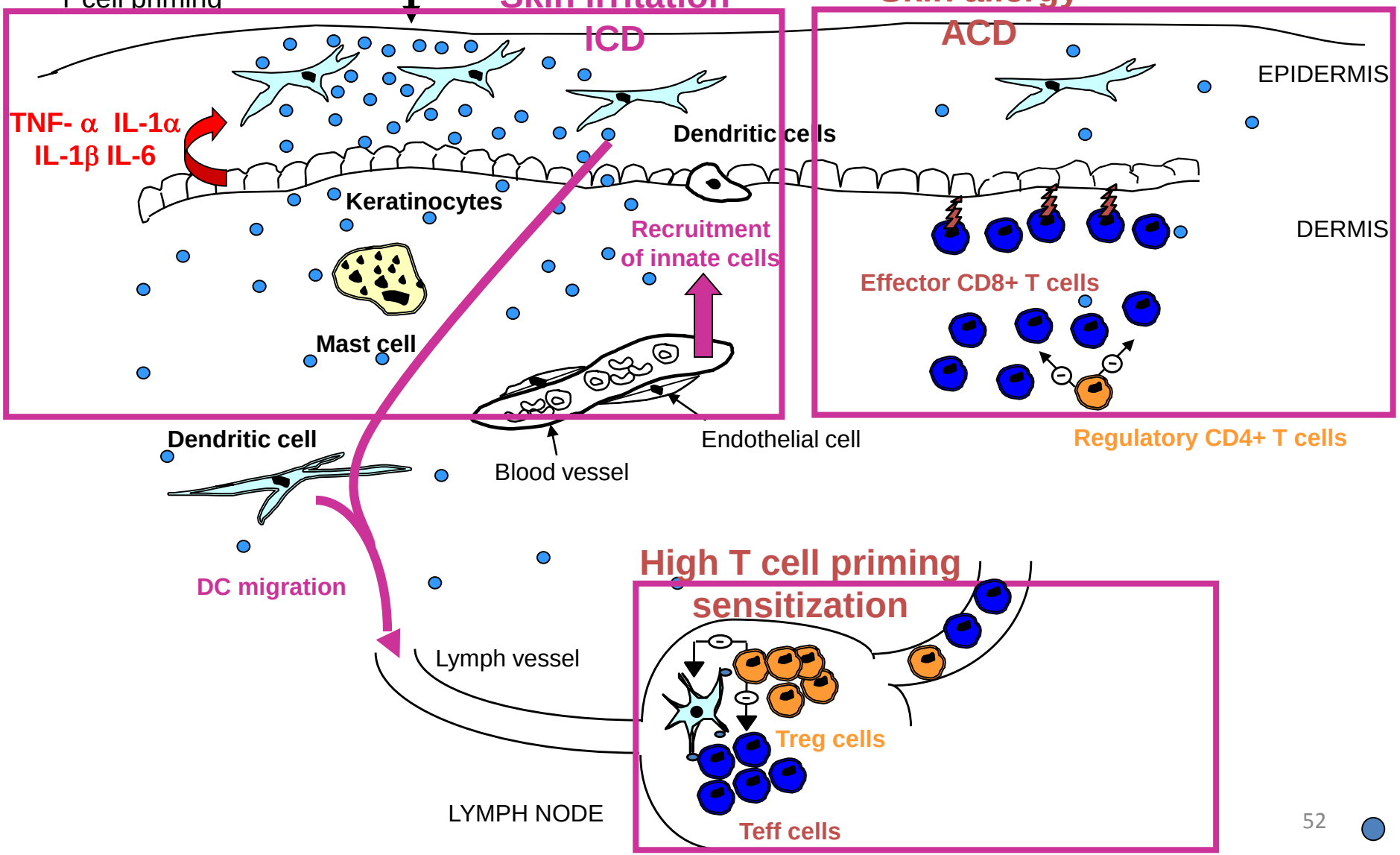
ACD

patient

Sensitization
Innate response
T cell priming

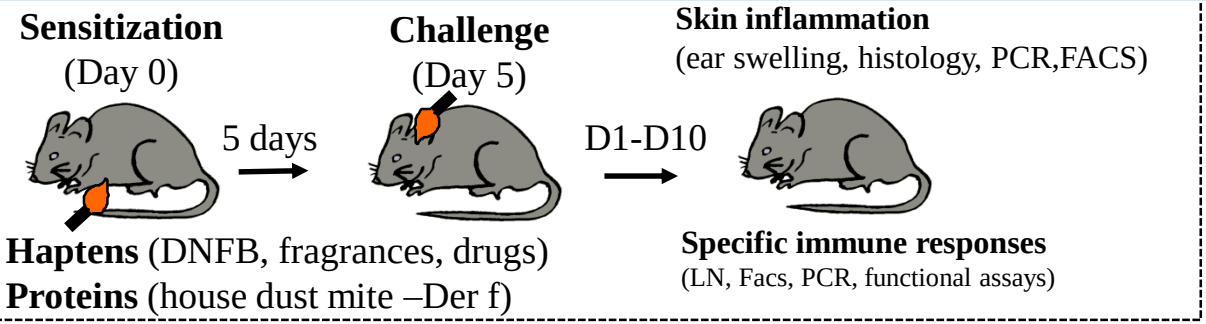
Chemical
Protein

Elicitation
Effector T cell response
Skin inflammation



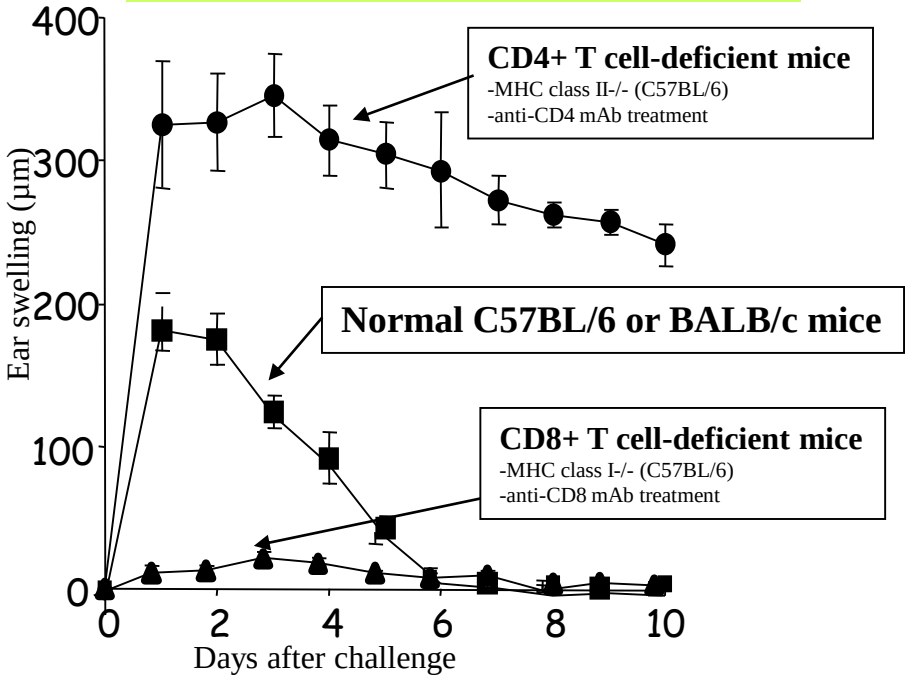
CONTACT DERMATITIS

CD8+ T cells are mandatory for Allergic CD and Atopic Dermatitis



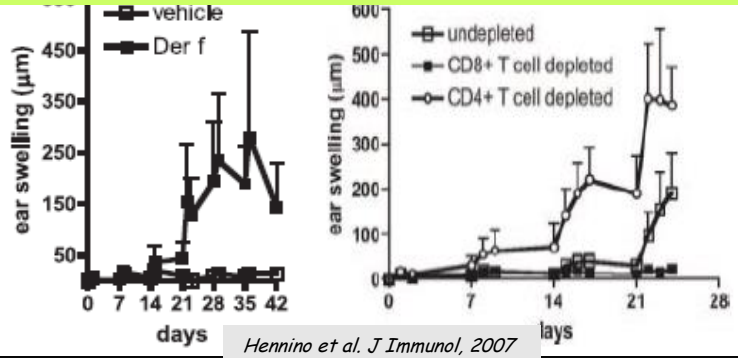
Hélène BOUR et al., Eur J Immunol, 1995
Maya KRASTEVA et al., J Immunol, 1998
Jeanne KEHREN et al., J Exp Med, 1999
Hitoshi AKIBA et al., J Immunol, 2002
Pierre SAINT-MEZARD et al,. J Immunol, 2003
Marc VOCANSON et al., J Invest Dermatol, 2006
Anca HENNINO et al., J Immunol, 2007
Marc VOCANSON et al., Allergy, 2009
Marc VOCANSON et al., JACI, 2010
Aurore ROZIERES et al., Allergy, 2010
Béatrice VANDERBLIET, JACI, 2011

Haptens Allergic contat dermatitis (ACD)



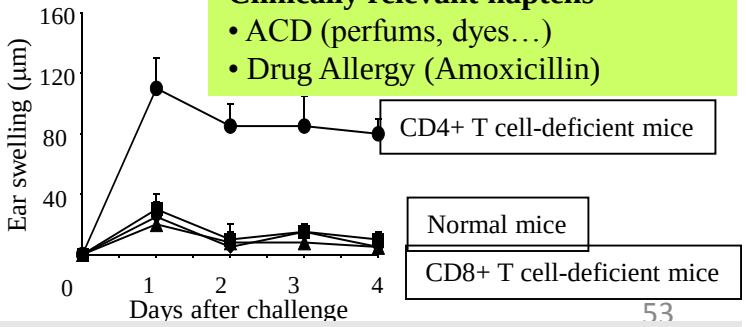
- CD8+ T cells are effector cells
- CD4+ T cells comprise regulatory T cells

Protein allergens (Dermatophagoïdès farinae)
Atopic Dermatitis



Hennino et al. J Immunol, 2007

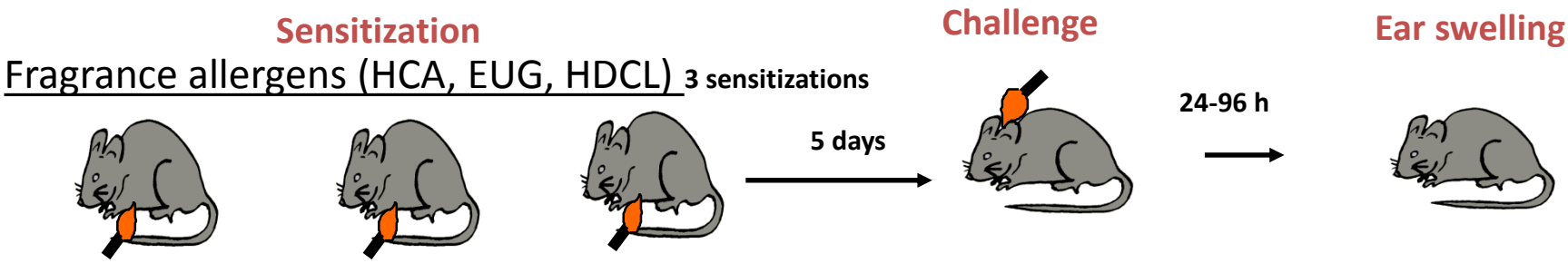
Clinically relevant haptens
- ACD (perfums, dyes…)
- Drug Allergy (Amoxicillin)

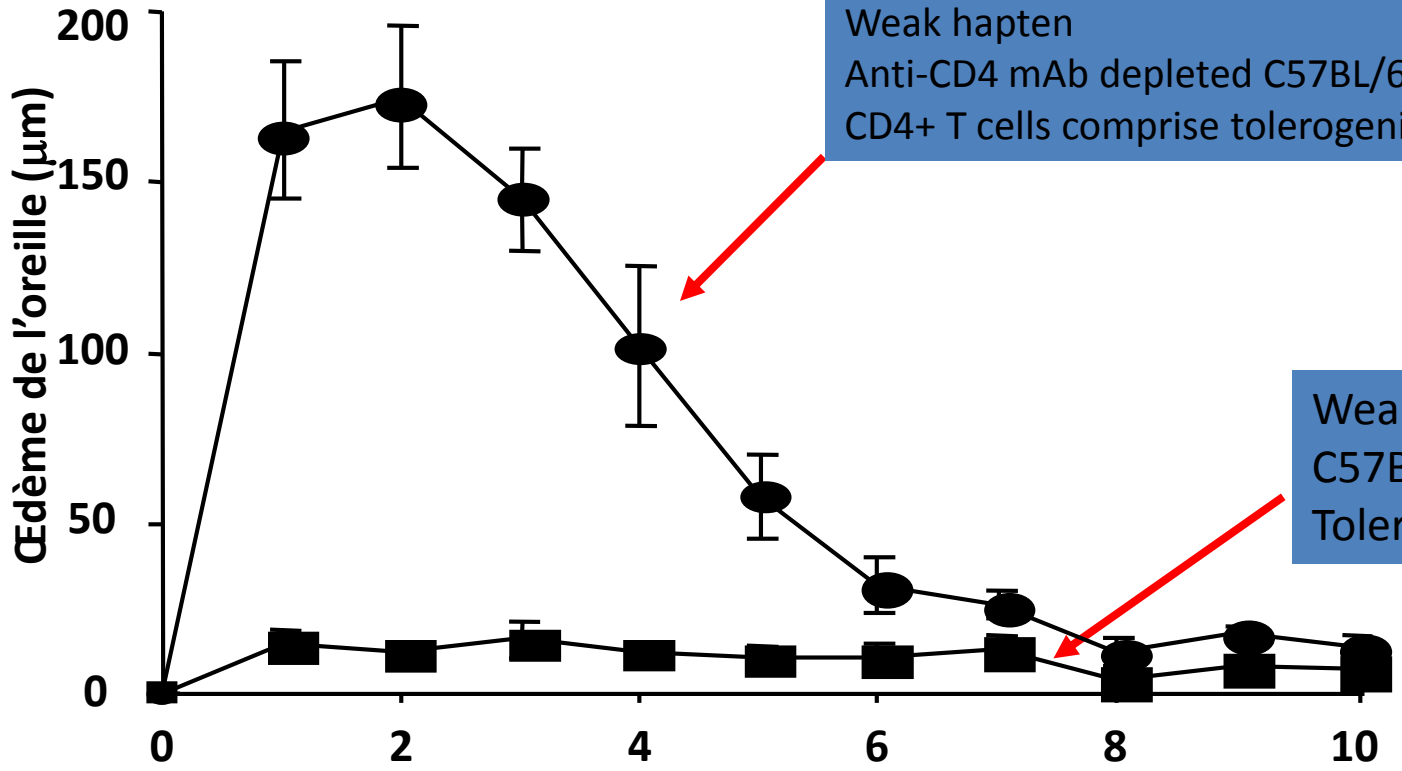


Vocanson M et al.Allergy, 2009 / Rozieres A et al, Allergy 2010

3. CD4+ T cells prevent ACD

Weak haptens





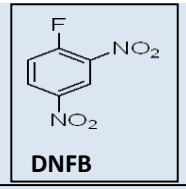
Weak hapten
Anti-CD4 mAb depleted C57BL/6
CD4+ T cells comprise tolerogenic cells

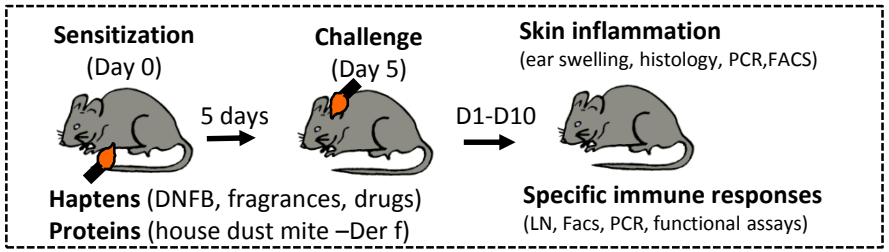
Weak hapten
C57BL/6
Tolerant mice

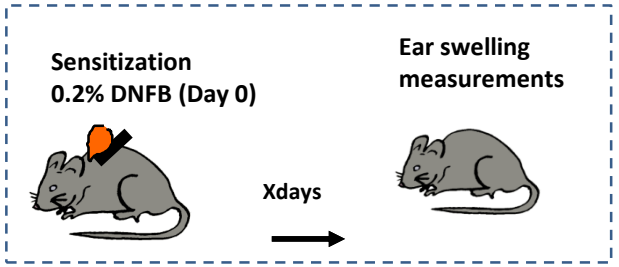
Vocanson et al., J Invest Dermatol 2008 & 2009; J Allergy Clinical Immunol 2010 & 2011

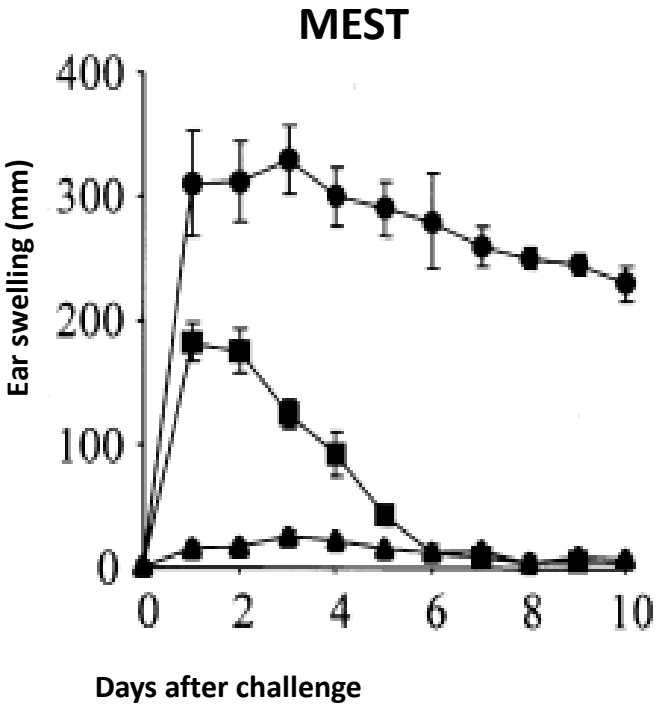
CONTACT DERMATITIS

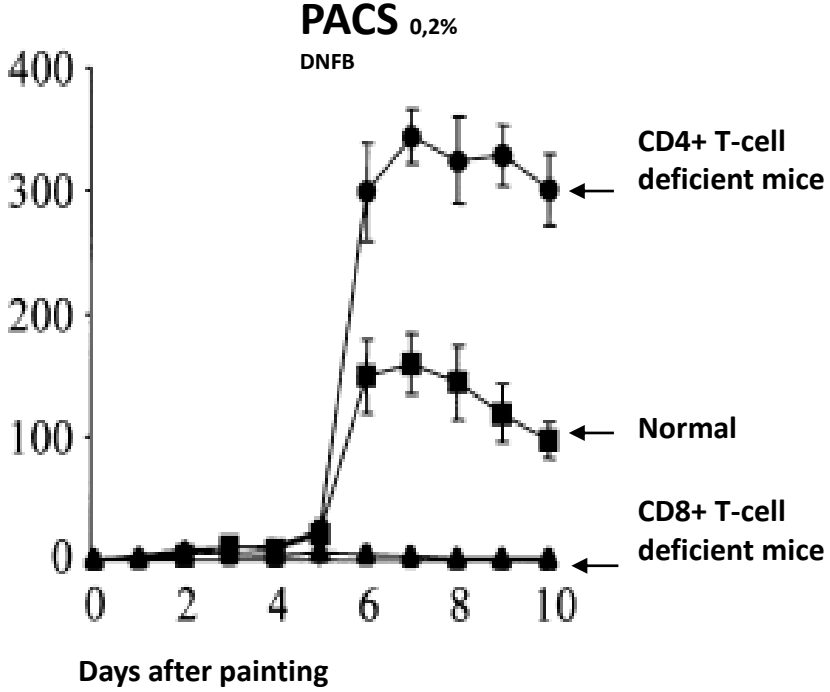
Primary Allergic Contact Sensitivity (PACS) protocol











Eczematous lesion can develops after a single epicutaneous painting

Pierre ST MEZARD et al., J Invest Dermatol, 2003

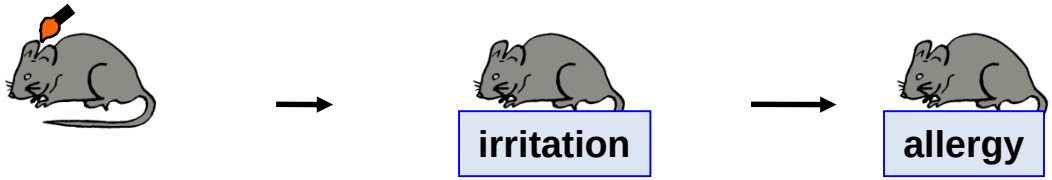
PACS : Primary Allergic Contact Sensitivity

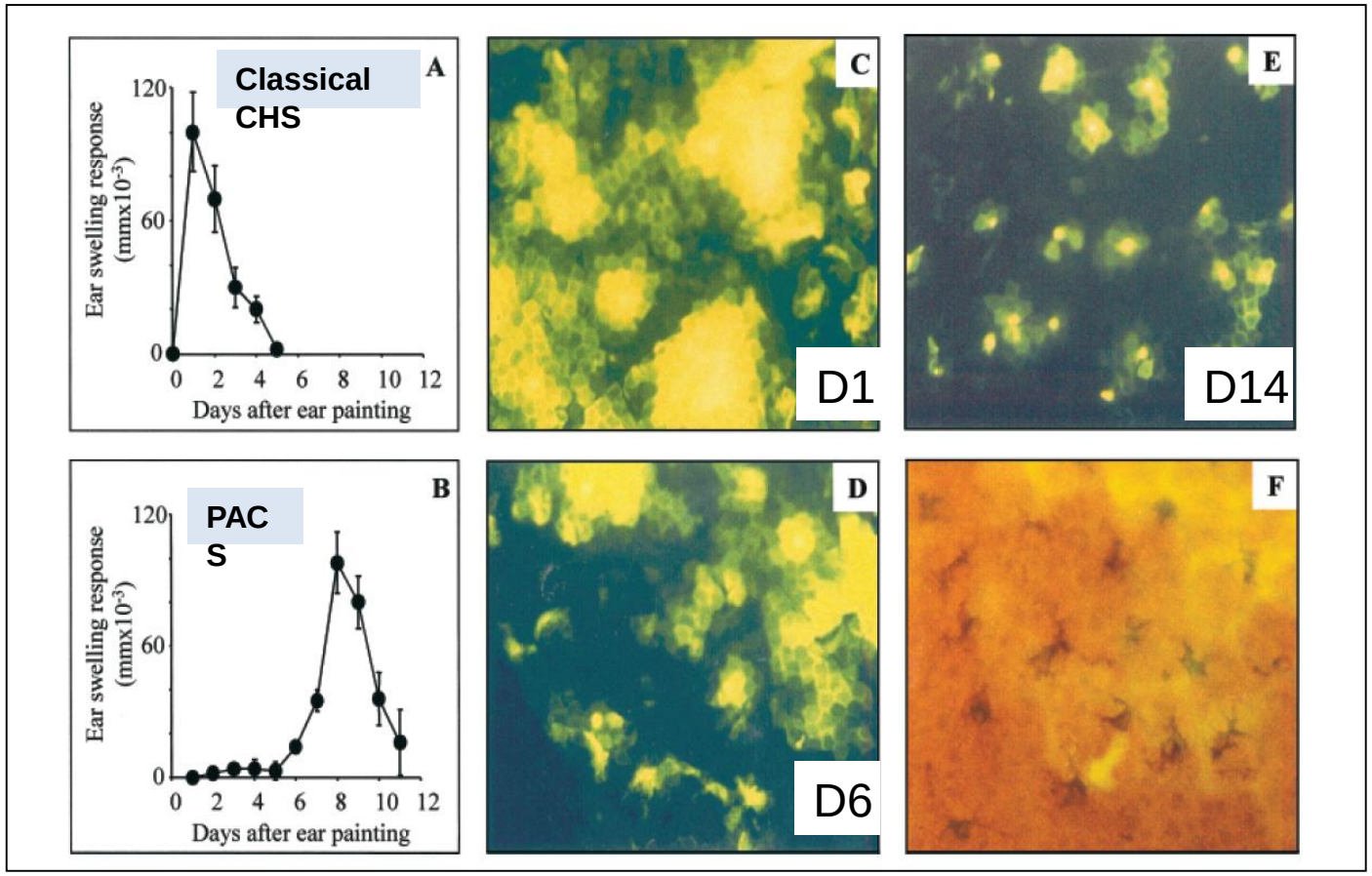
Model to study the relationship between dose, sensitization and elicitation of eczema

DNFB
D0 once only on naive ear

Ear inflammation
HOURS 1 to 24

Ear inflammation
DAYS 1 to 10



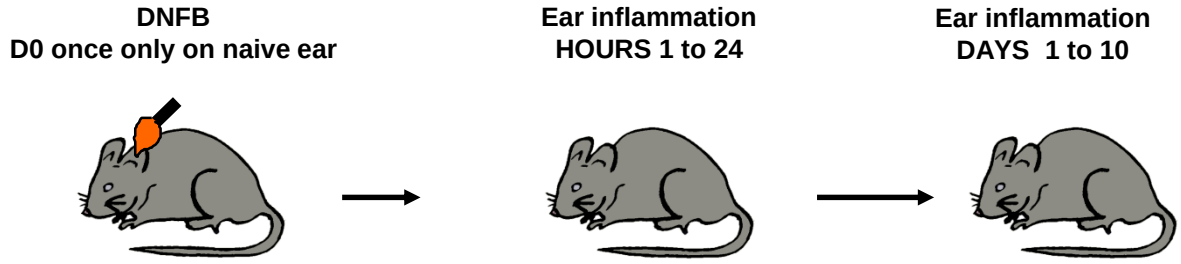


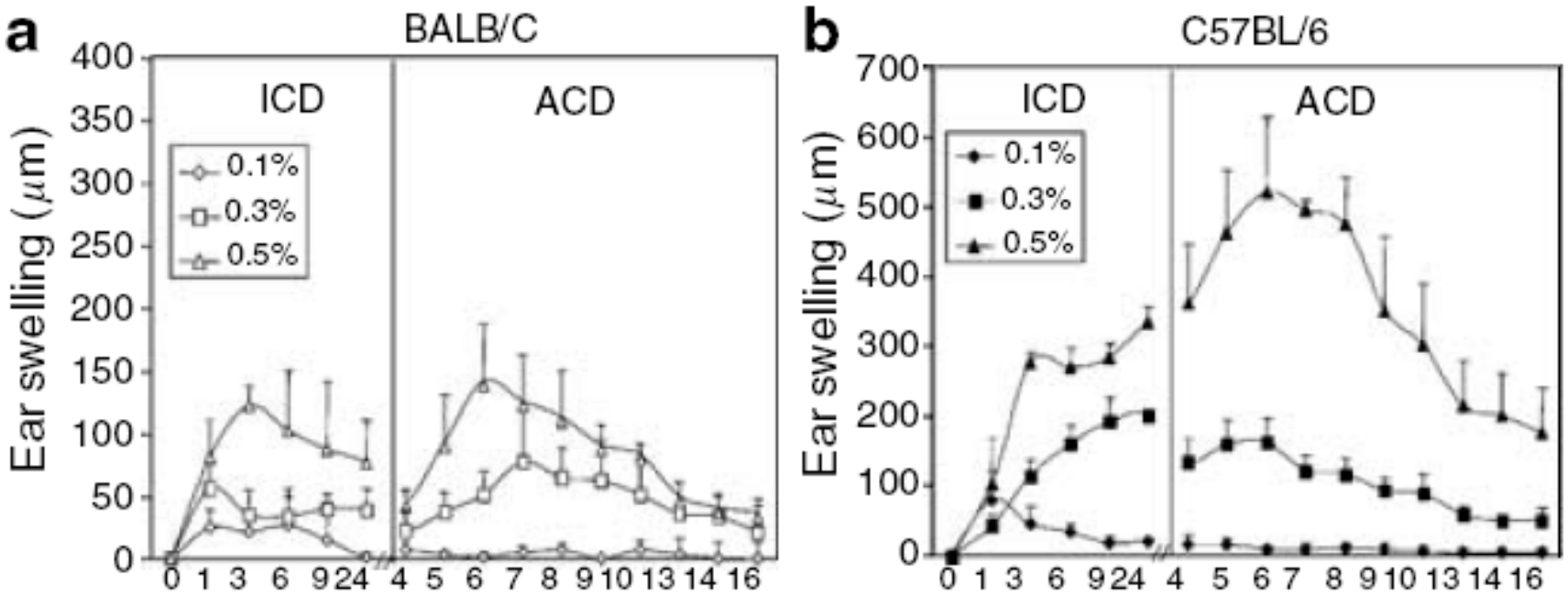
Saint-Mezard P et coll, JInvestDermatol, 2003

Bonneville M et coll, JInvestDermatol, 2007

Skin irritation conditions the severity of ACD

Primary Allergic Contact Dermatitis





Preventing skin irritation is the best prevention strategy for eczema

Saint-Mezard P et coll, JInvestDermatol, 2003

Bonneville M et coll, JInvestDermatol, 2007

Immunologie médicale
Inflammation et maladies inflammatoires

- Introduction: Présentation de l'équipe « Allergologie et Immunologie Clinique Lyon-Sud »
- Histoire naturelle des maladies inflammatoires
- Inflammation et maladies
- Système immunitaire et lymphatique
- Immunité en action : réponse immune anti-infectieuse
- Hypersensibilité allergique et non allergique
- Classification de Gell & Coombs
  - HS immédiate (mastocytes)
  - HS retardée (lymphocytes)
- Maladies allergiques atopiques et non atopiques