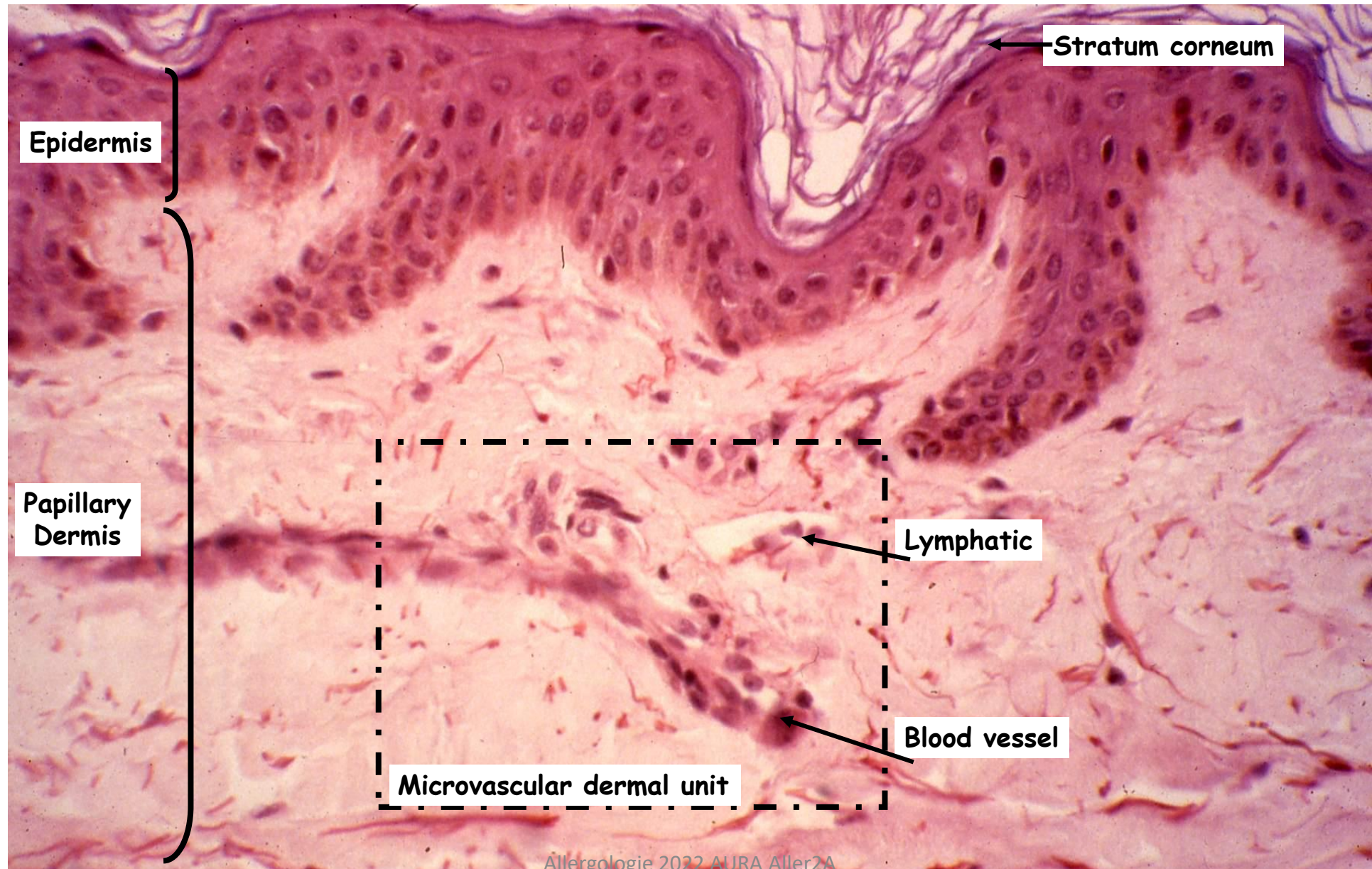


# Hypersensibilités et allergies cutanées

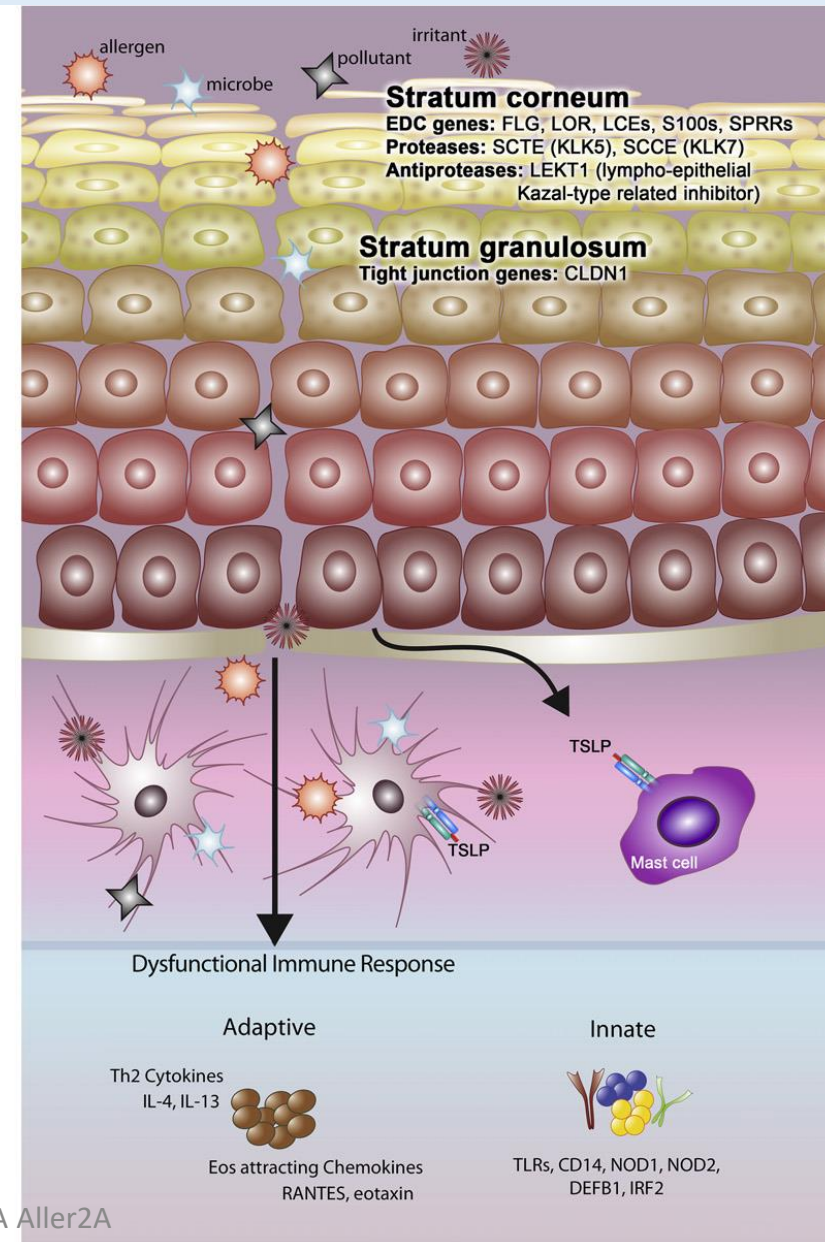
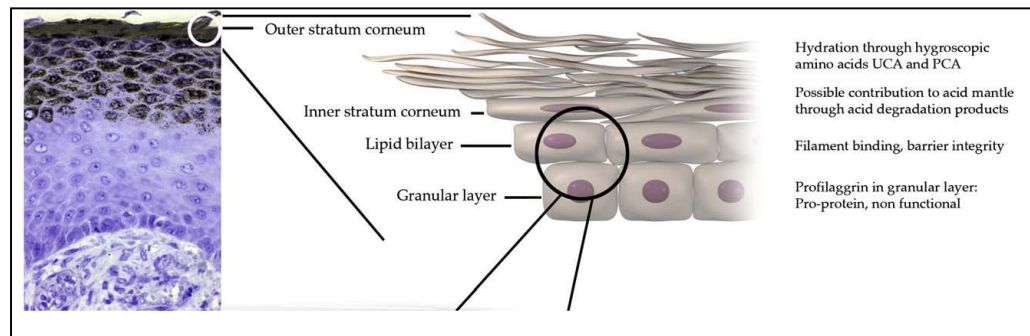
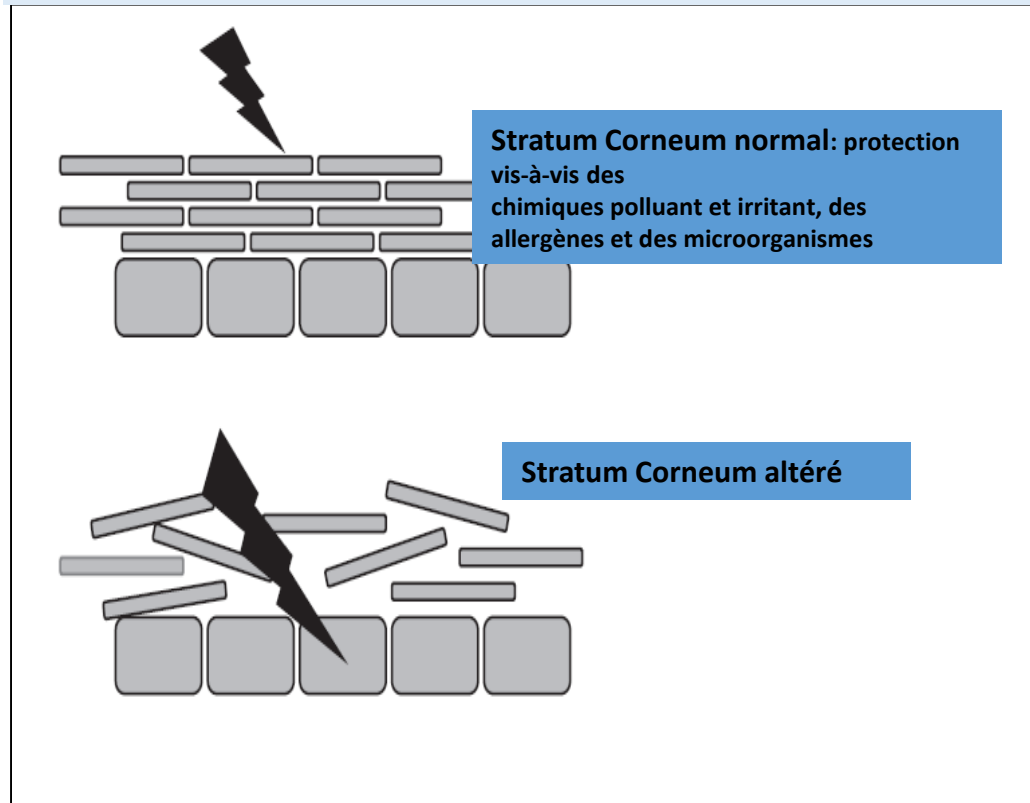
**Audrey NOSBAUM, Florence HACARD, Marc VOCANSON,  
Frédéric BERARD, Jean-François NICOLAS**

Allergologie et Immunologie Clinique,  
INSERM U1111-CIRI, CHU Lyon-Sud

# Skin anatomy and physiology



# ECZEMAS – Impairment of epidermal barrier



# Hypersensitivity reactions

## 1. Immunology definition – Gell & Coombs

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)

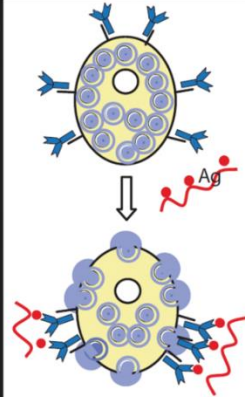
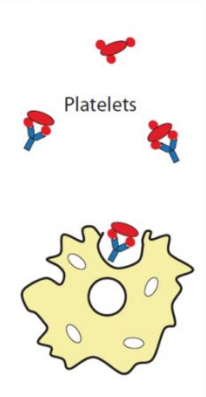
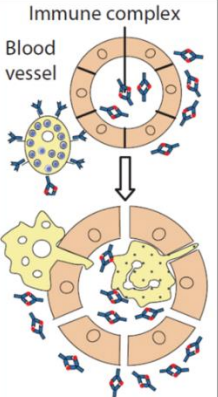
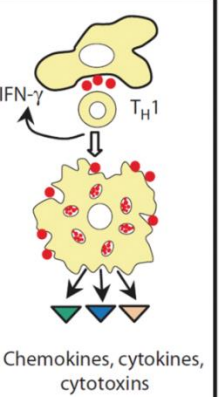
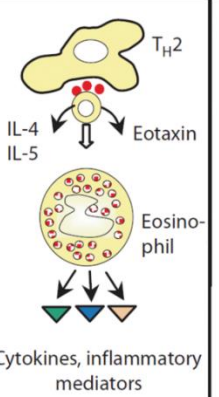
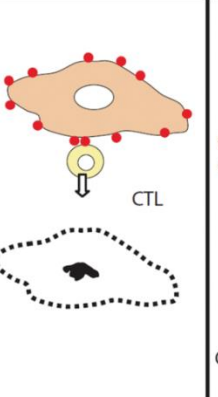
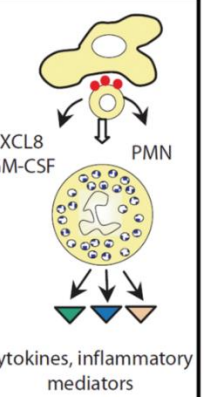
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graph TD; HS[Hypersensibilité (HS)] --> HS_A[HS adaptative Allergique]; HS --> HS_I[HS innée Non Allergique];
```

HS adaptative  
Allergique

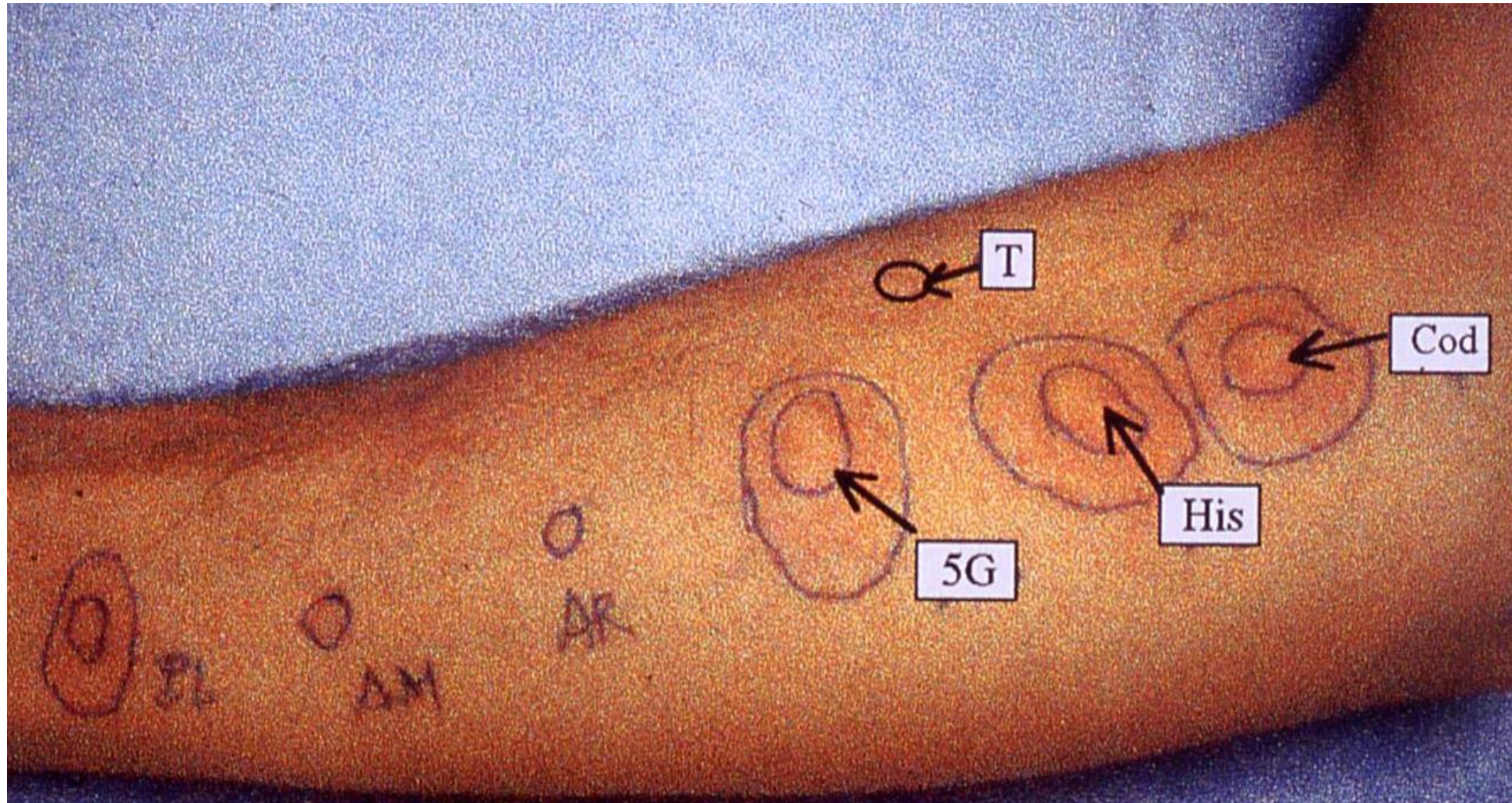
HS innée  
Non Allergique

# Hypersensibilités

## Classification de Gell & Coombs

	Antibody			T cells			
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN- $\gamma$ , TNF- $\alpha$ <b>Type 1</b>	IL-5, IL-4/IL-13 <b>Type 2</b>	Perforin/ granzyme B <b>Cytotoxic</b>	IL-17, IL-22 <b>Type 17/3</b>
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Maladies autoimmunes et allergiques	Anaphylaxie Rhinite allergique Asthme (crise)	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme chron. Rhinite chron.	Rejet de greffe Diabète SEP	Polyarthrite Sclérose en plaque Mal. de Crohn
Dermatoses autoimmunes et allergiques	Urticaire contact	Pemphigus Pemphigoïde Urticaire chroni.	Vascularites	Psoriasis	Dermatite atopique	Vitiligo Pelade Eczéma contact	Psoriasis
Allergies médicaments	Choc anaphylactique	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème médic.	DRESS	Lyell Stevens-Johnson	Pustulose exanthématique aigüe généralisée

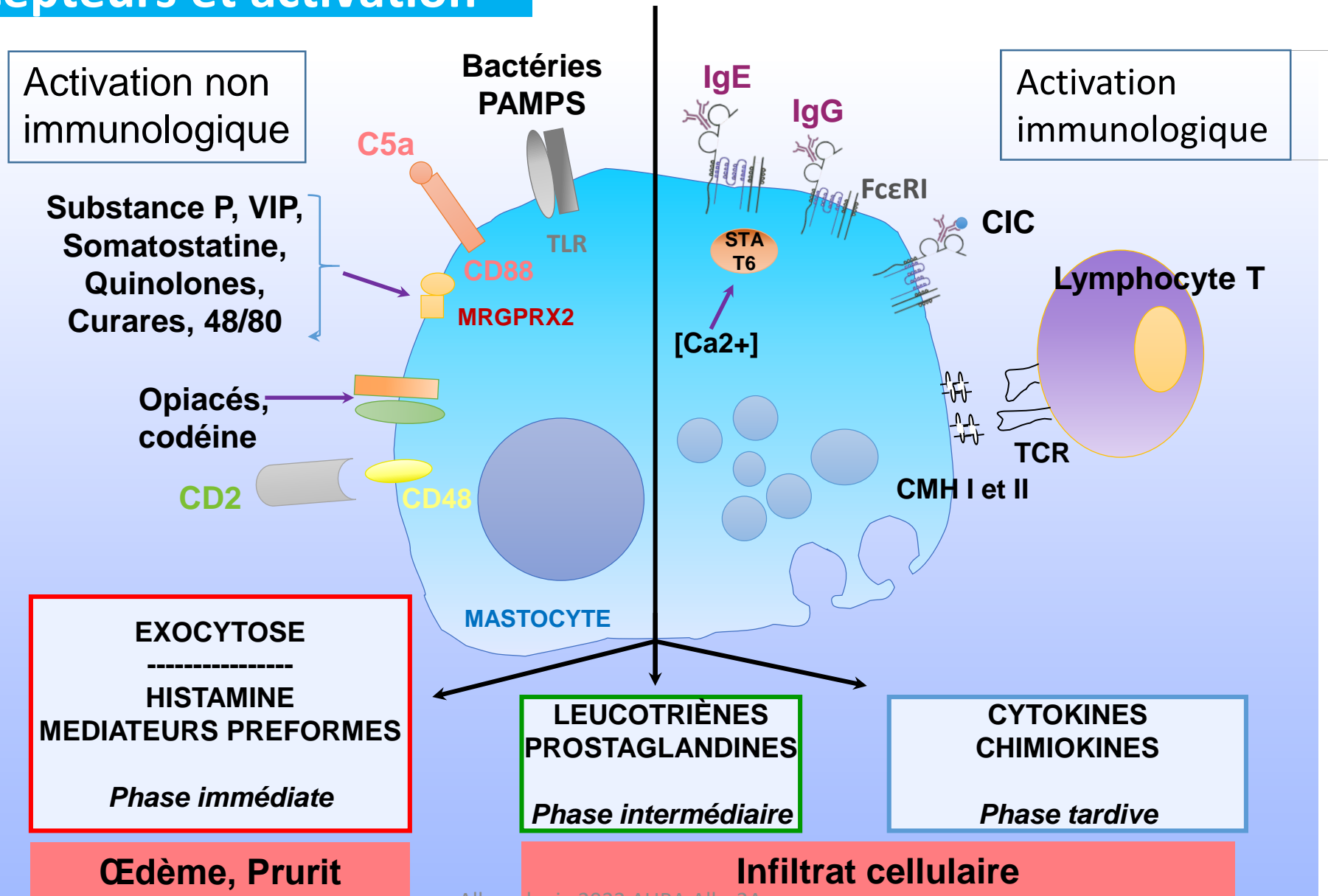
# HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

# MASTOCYTES

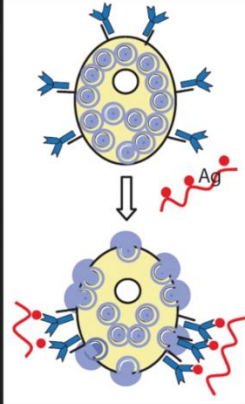
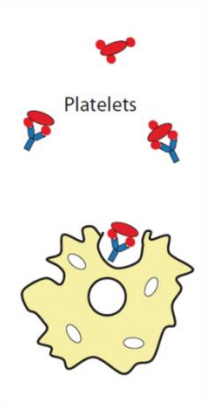
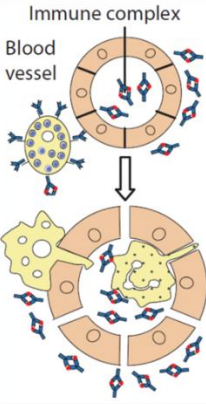
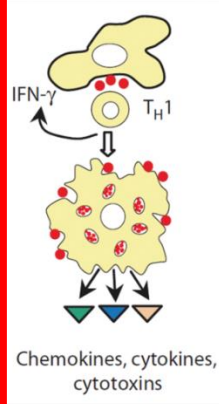
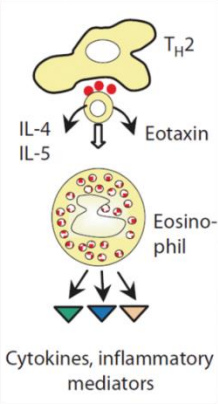
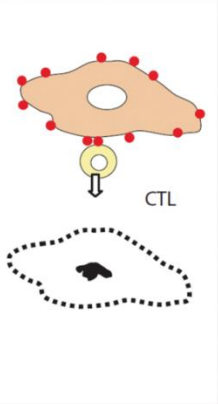
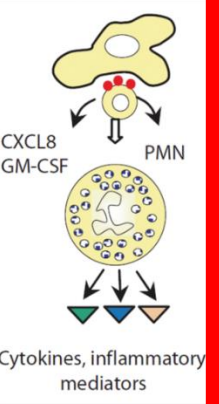
## Récepteurs et activation



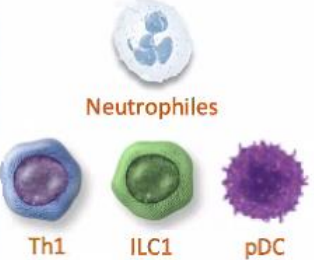




# Hypersensibilités

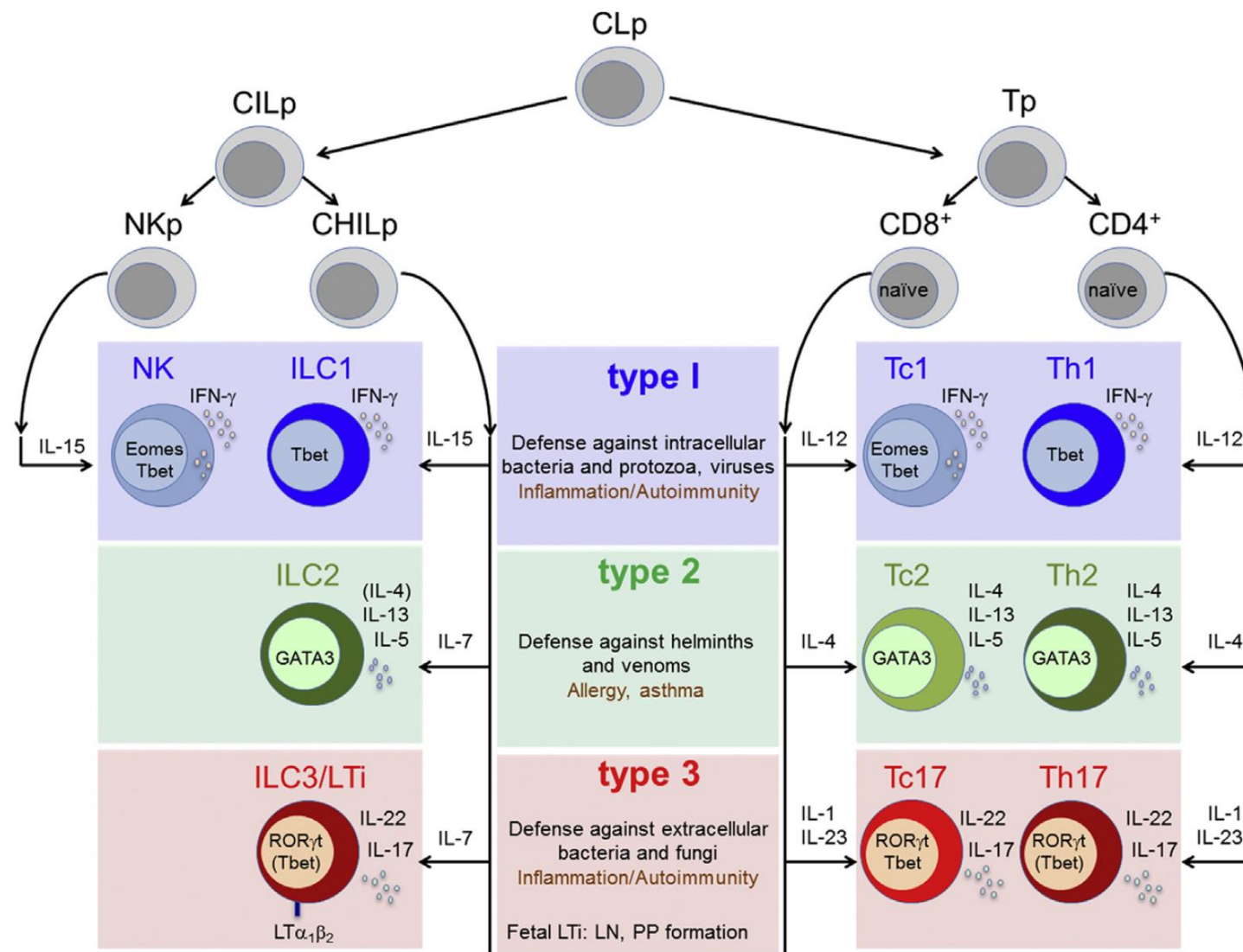
## Classification de Gell & Coombs

	Antibody			T cells			
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN- $\gamma$ , TNF- $\alpha$ <b>Type 1</b>	IL-5, IL-4/IL-13 <b>Type 2</b>	Perforin/ granzyme B <b>Cytotoxic</b>	IL-17, IL-22 <b>Type 17</b>
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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Dermatoses autoimmunes et allergiques	Urticaire contact	Pemphigus Pemphigoïde Urticaire chroni.	Vascularites	Psoriasis	Dermatite atopique	Vitiligo Pelade Eczéma contact	Psoriasis
Allergies médicaments	Choc anaphylactique	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème médic.	DRESS	Lyell Stevens-Johnson	Pustulose exanthématique aigue généralisée

# Inflammation type 1, type 2, type 17

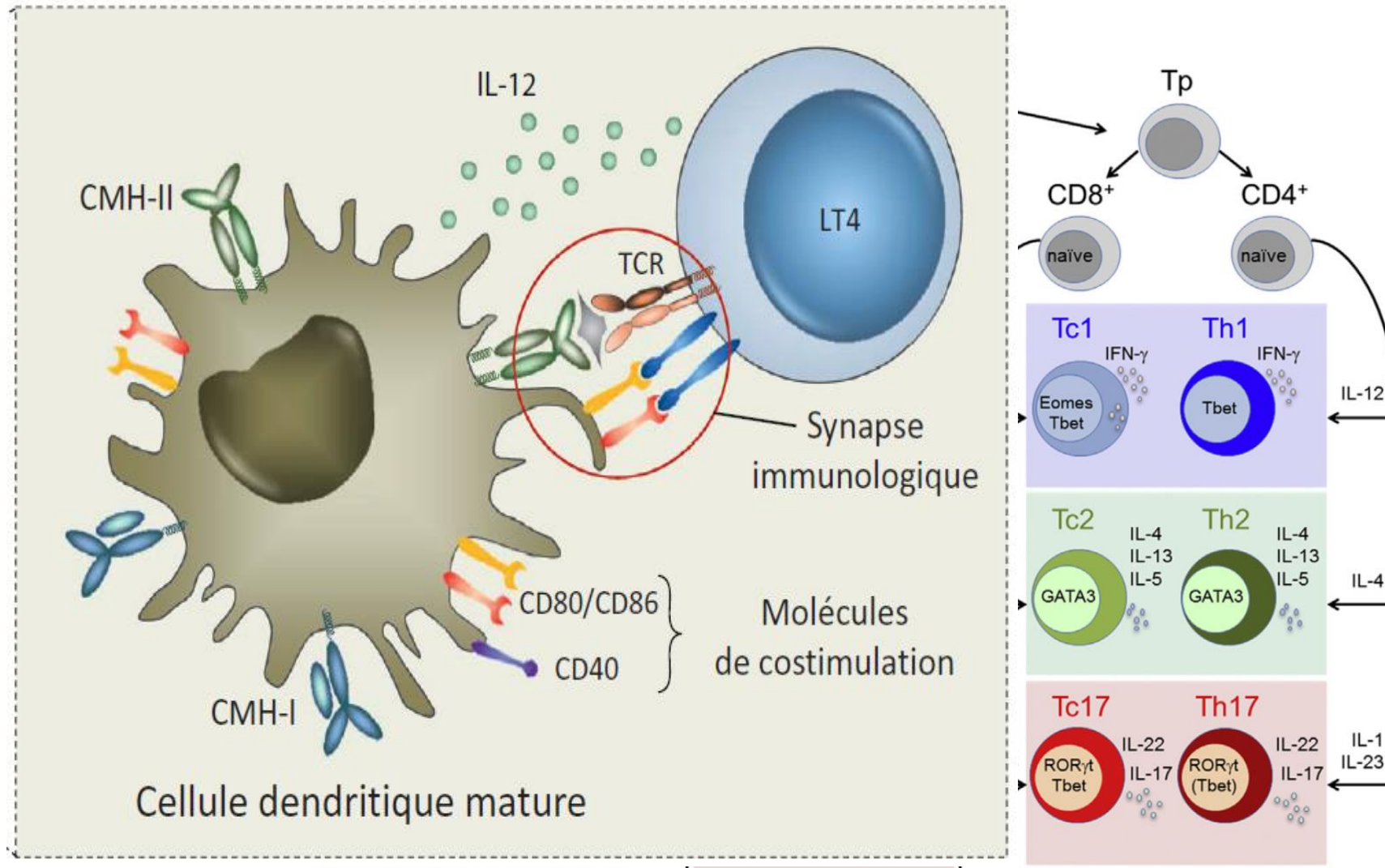
Voies Inflammatoires	Type 1	Type 2	Type 3
<b>Cellules Immunitaires<sup>1,2</sup></b>	 <p>Neutrophiles</p> <p>Th1 ILC1 pDC</p>	 <p>Th2 cell ILC2 Mast cell</p> <p>T<sub>fh</sub> Basophiles Eosinophiles</p>	 <p>Neutrophiles</p> <p>Th17 Th22 ILC3</p>
<b>Cytokines<sup>1-3</sup></b>	<p>IL-17 IFN<math>\gamma</math> IL-6</p> <p>IL-12 IL-2 TNF</p>	<p>IL-4 IL-5</p> <p>IL-13 IL-31</p>	<p>IL-17 IL-6</p> <p>IL-22 IL-23</p>
<b>Cibles<sup>1,3</sup></b>	<p>Virus</p> <p>Bactéries intracellulaires</p> <p>Cancer</p>	<p>Allergènes</p> <p>Parasites</p>	<p>Bactéries extracellulaires</p> <p>-Mycoses</p>
<b>Exemples de pathologies<sup>4-6</sup></b>	<p><b>Maladies auto-immunes</b></p> <p>Lupus</p> <p>Lichen</p> <p>Vitiligo-Pelade</p>	<p><b>Pathologies de type 2</b></p> <p>Dermatite Atopique</p> <p>Rhinite Allergique</p> <p>Asthme</p> <p>Polypose Nasale</p> <p>Oesophagite à éosinophiles</p> <p>Allergie alimentaire</p>	<p><b>Maladies auto-immunes</b></p> <p>Psoriasis</p> <p>Psoriatic arthritis</p> <p><b>Lupus</b></p>

Kaiko GE, et al. *Immunology*. Eyerich K, Eyerich S. *J Eur Acad Dermatol Venereol*. Raphael I, et al. *Cytokine*. 2015 Nakayama T, et al. *Annu Rev Immunol*. 2017. Coates LC, et al. *Semin Arthritis Rheum*. 2016 Gandhi NA, et al. *Expert Rev Clin Immunol*. 2017

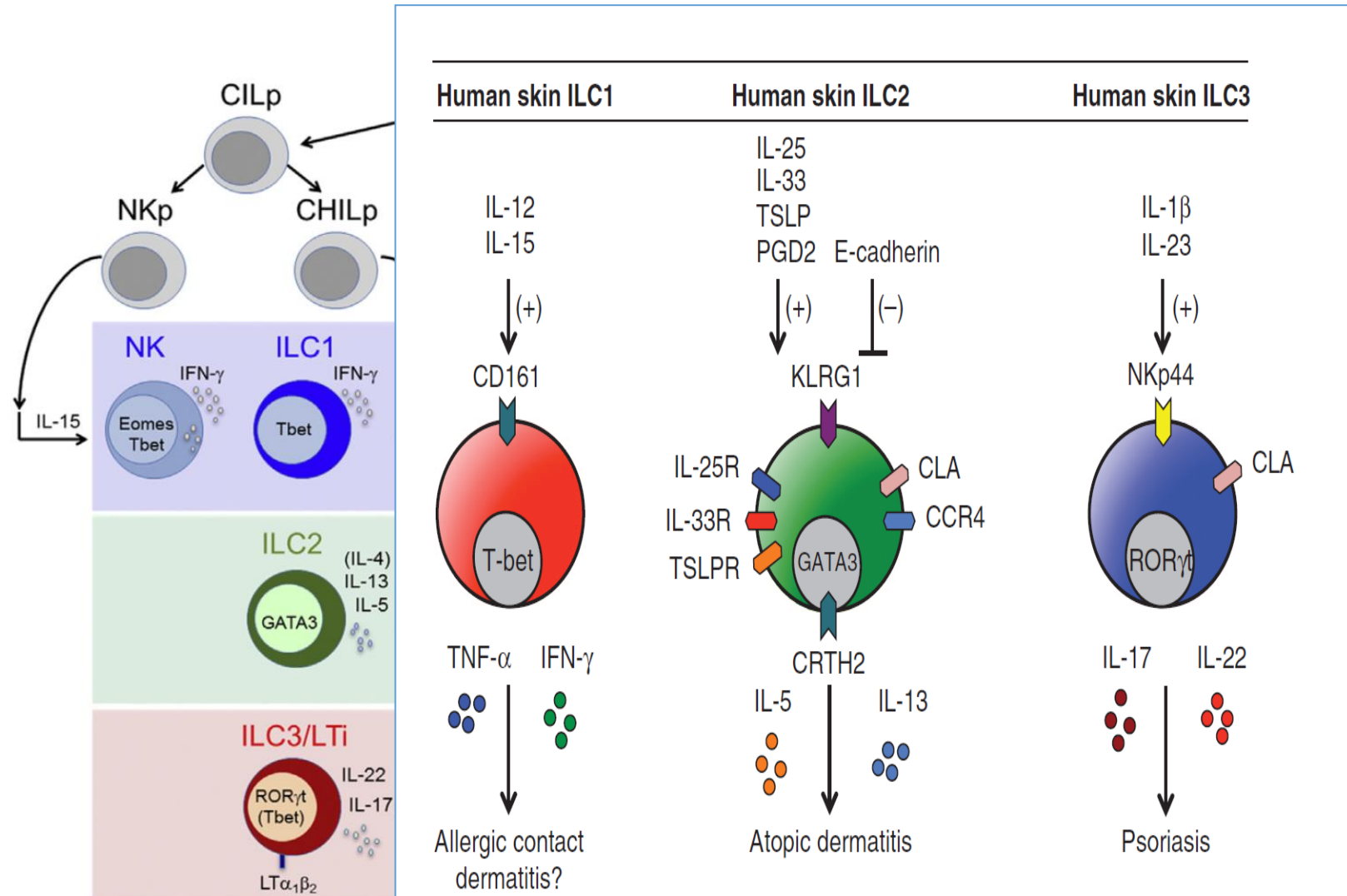


**FIG 1.** The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet<sup>+</sup> IFN- $\gamma$ -producing CD4<sup>+</sup> T<sub>H</sub>1 cells and ILC1s and T-bet<sup>+</sup>Eomes<sup>+</sup>CD8<sup>+</sup> T<sub>C</sub>1 and NK cells. Type 2 immunity is composed of GATA-3<sup>+</sup>CD4<sup>+</sup> T<sub>H</sub>2 cells, CD8<sup>+</sup> T<sub>C</sub>2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of ROR $\gamma$ t (RORC)<sup>+</sup>CD4<sup>+</sup>T<sub>H</sub>17 cells, CD8<sup>+</sup> T<sub>C</sub>17 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 immunity



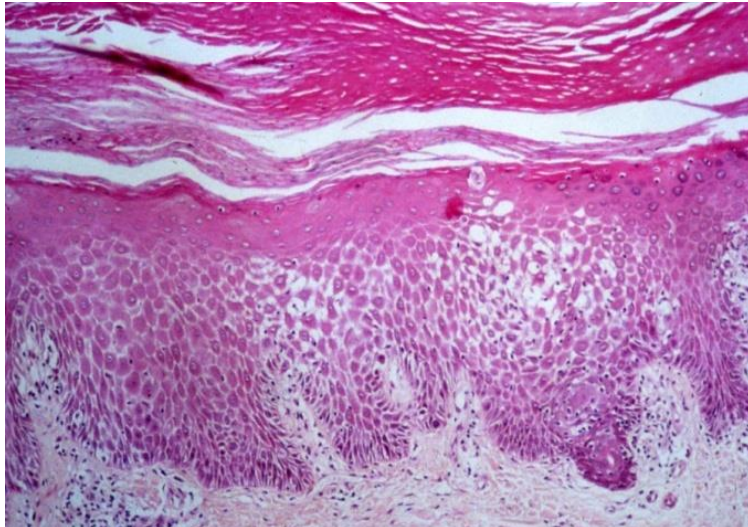
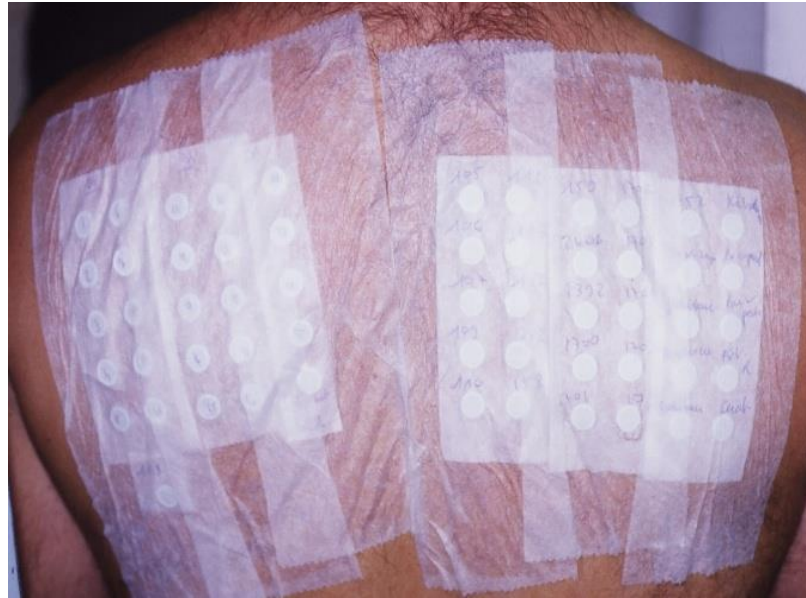
# The 3 major types of innate and adaptative cell-mediated immunity



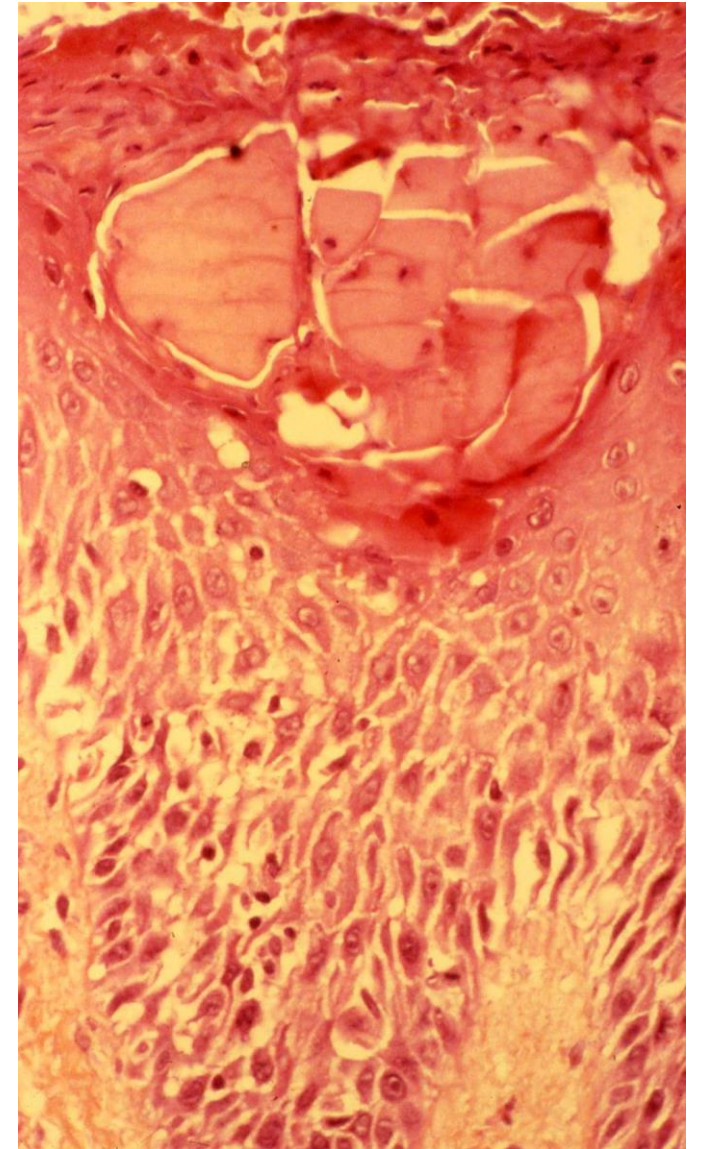
# Type IV hypersensitivity - Type 1



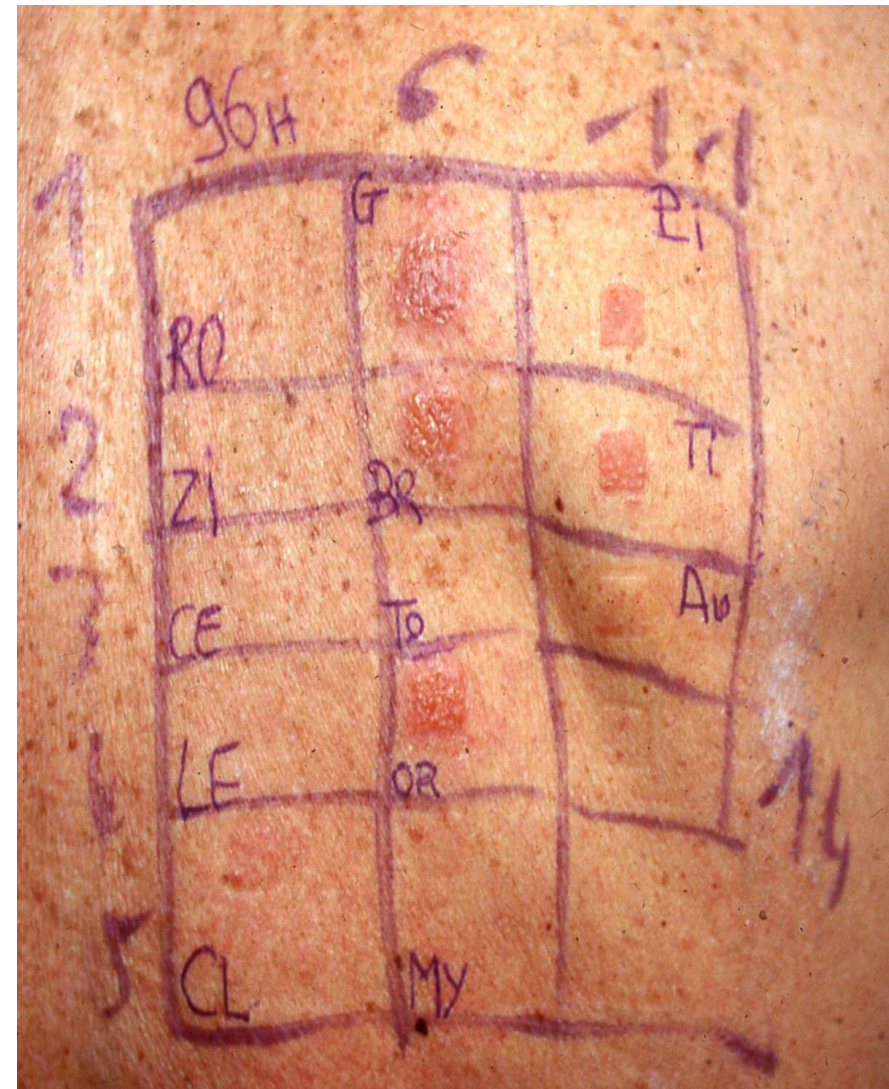
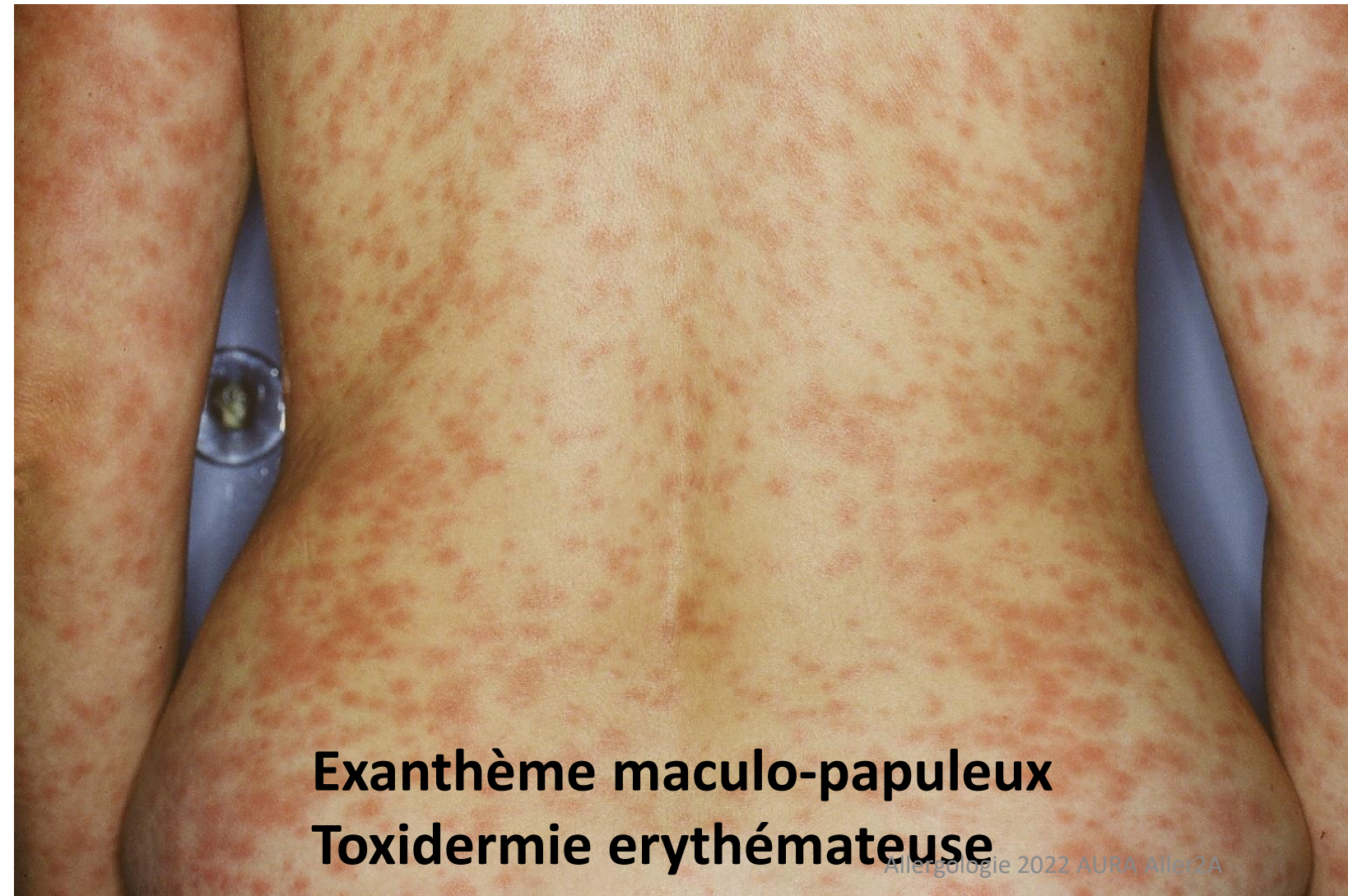
Eczéma allergique de contact



Allergologie 2022 AURA Aller2A

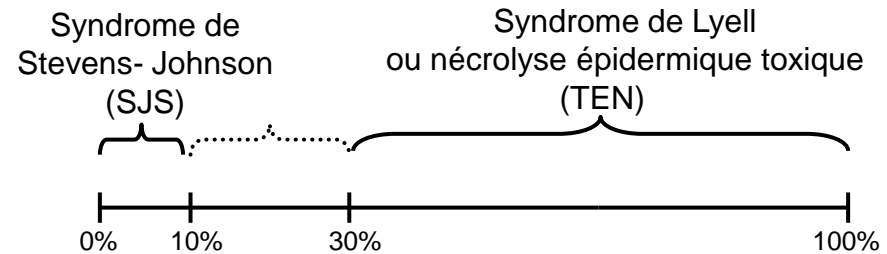
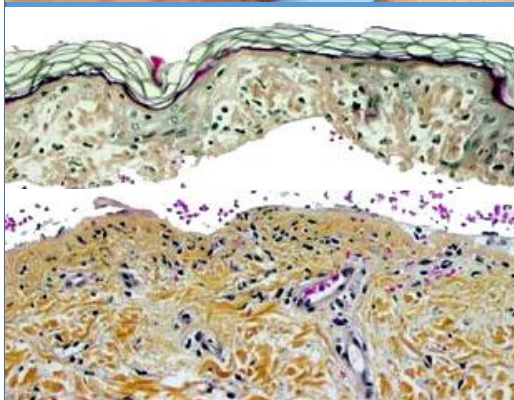


# Type IV hypersensitivity - Type 1



# Type IV hypersensitivity - Type 1 cytotoxic

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

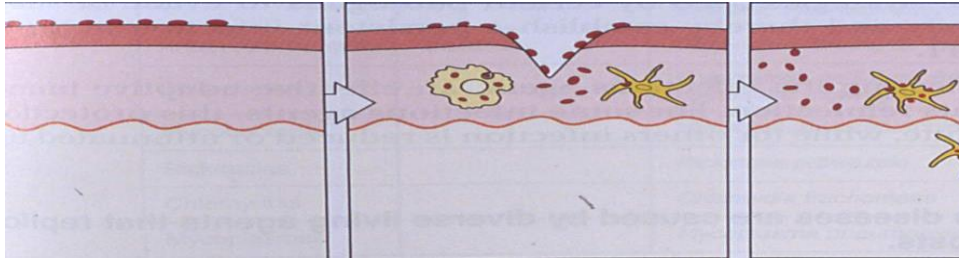


- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai :** 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie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

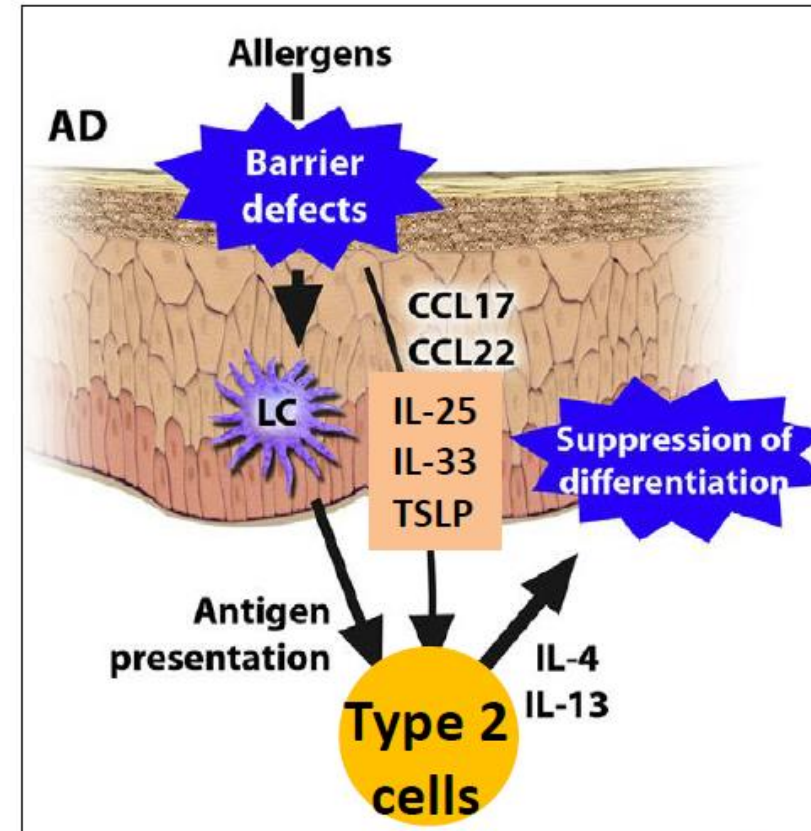


# Type IV hypersensitivity - Type 2 DERMATITE ATOPIQUE

Type 2



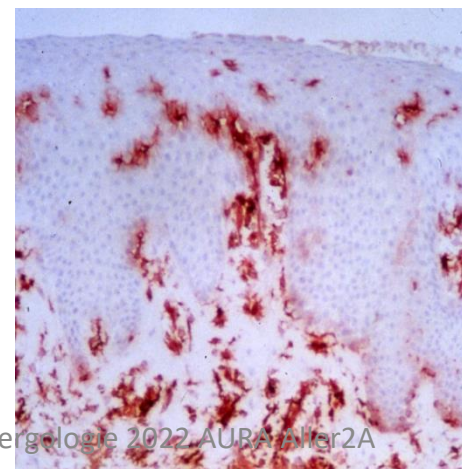
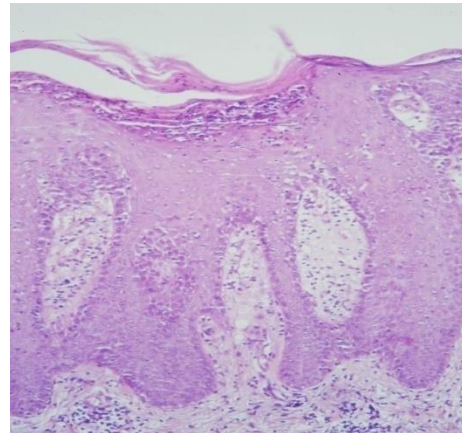
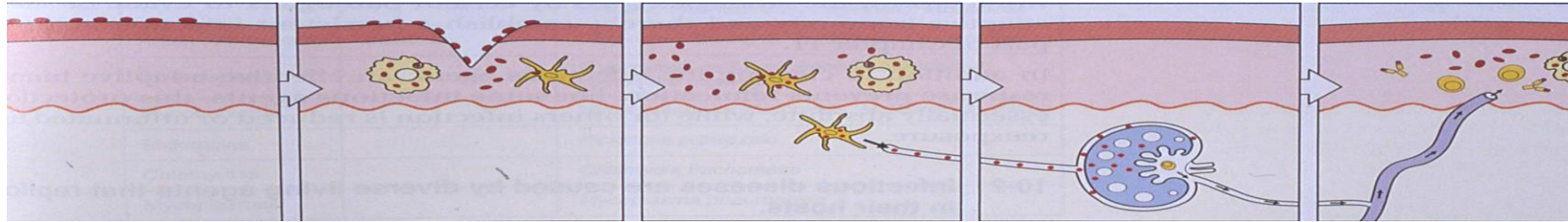
## Type 2 phenotype



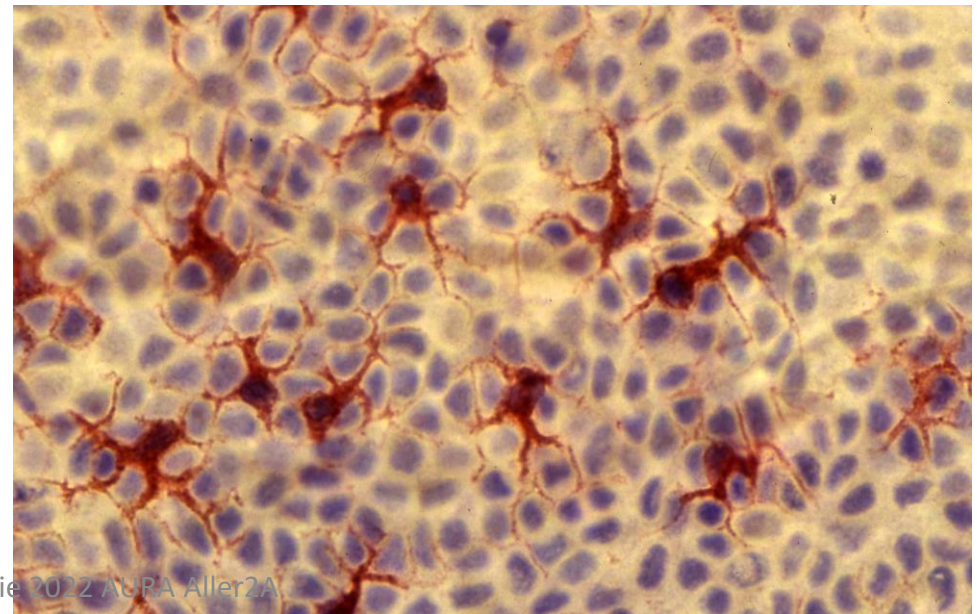
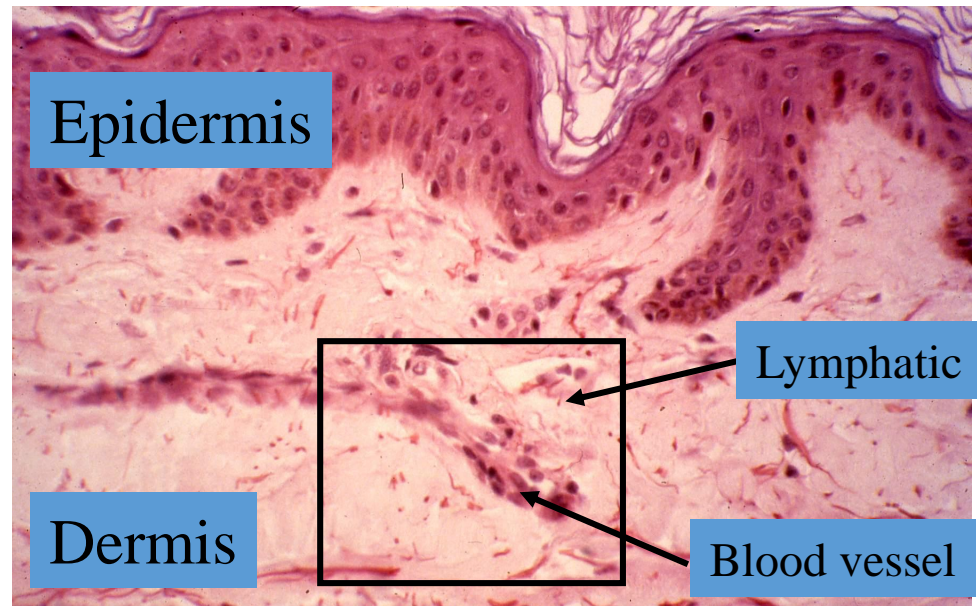
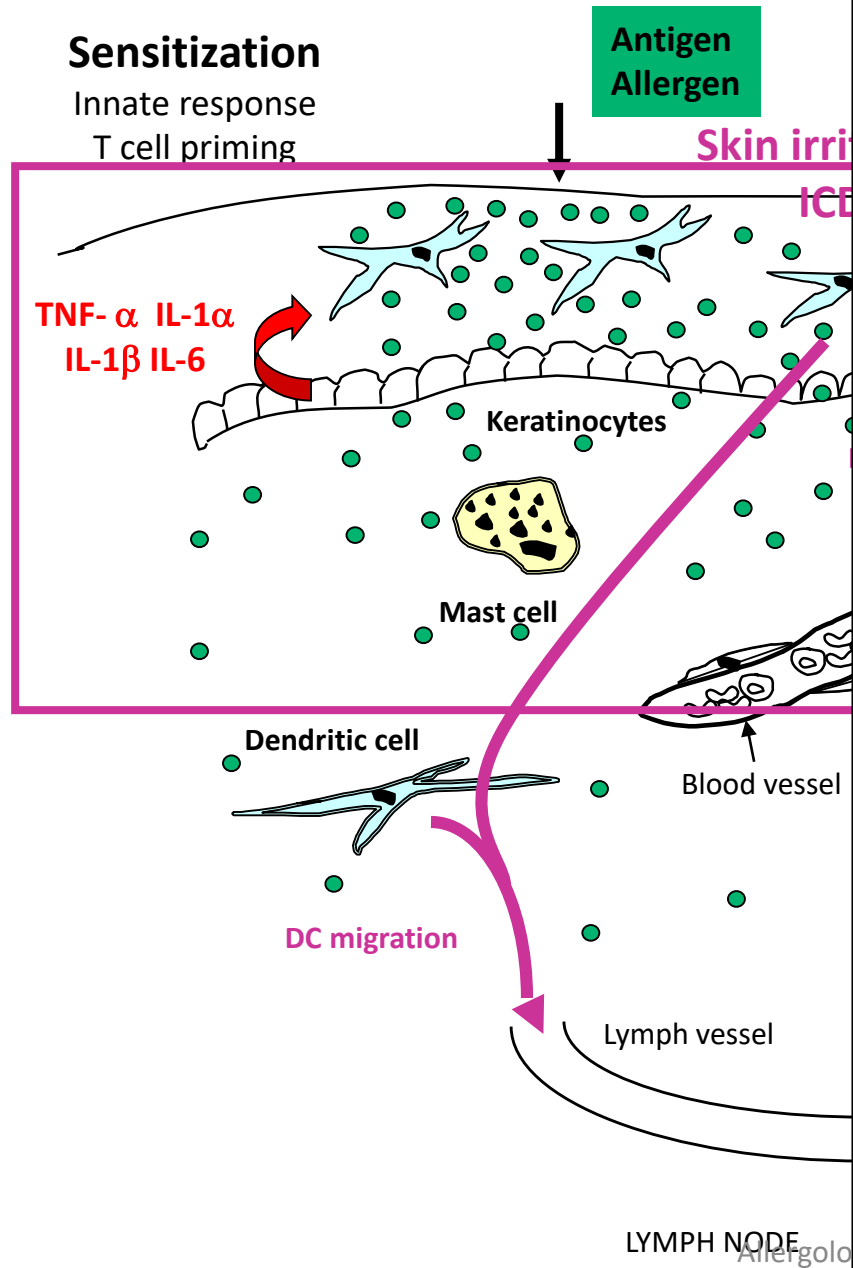
## Type 2 inflammation Type 2 immunity

# Type IV hypersensitivity - Type 3 Psoriasis

Type 17



# Immunology of eczemas



# Pathophysiology of skin inflammation

**EARLY (6-24h)**

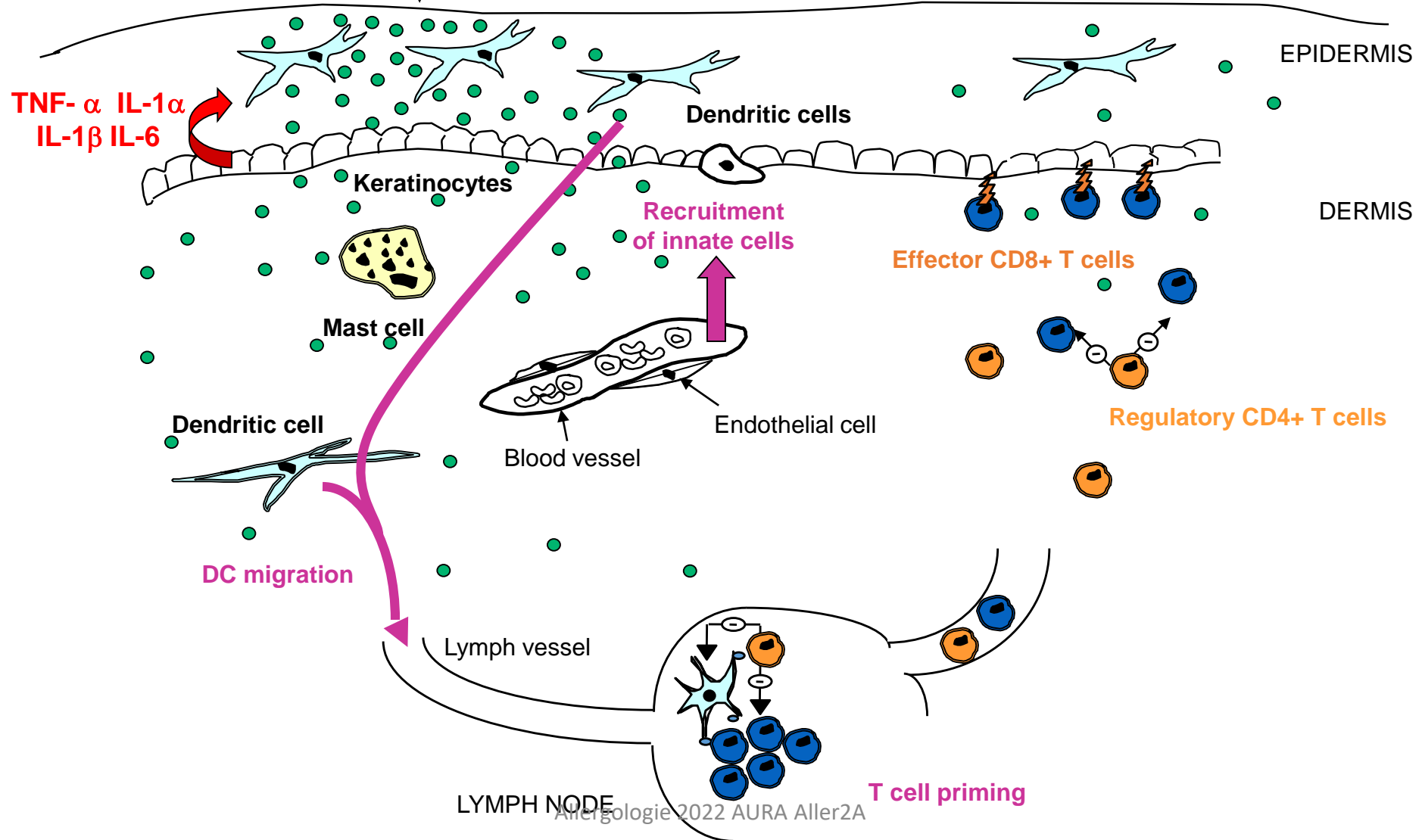
## Sensitization

Innate response  
T cell priming

**ANTIGEN (hapten, protein)**  
- Environmental antigen  
- Vaccine antigen

## Elicitation

Effector T cell response  
Skin inflammation



# Pathophysiology of skin inflammation

**LATE (48-72h)**

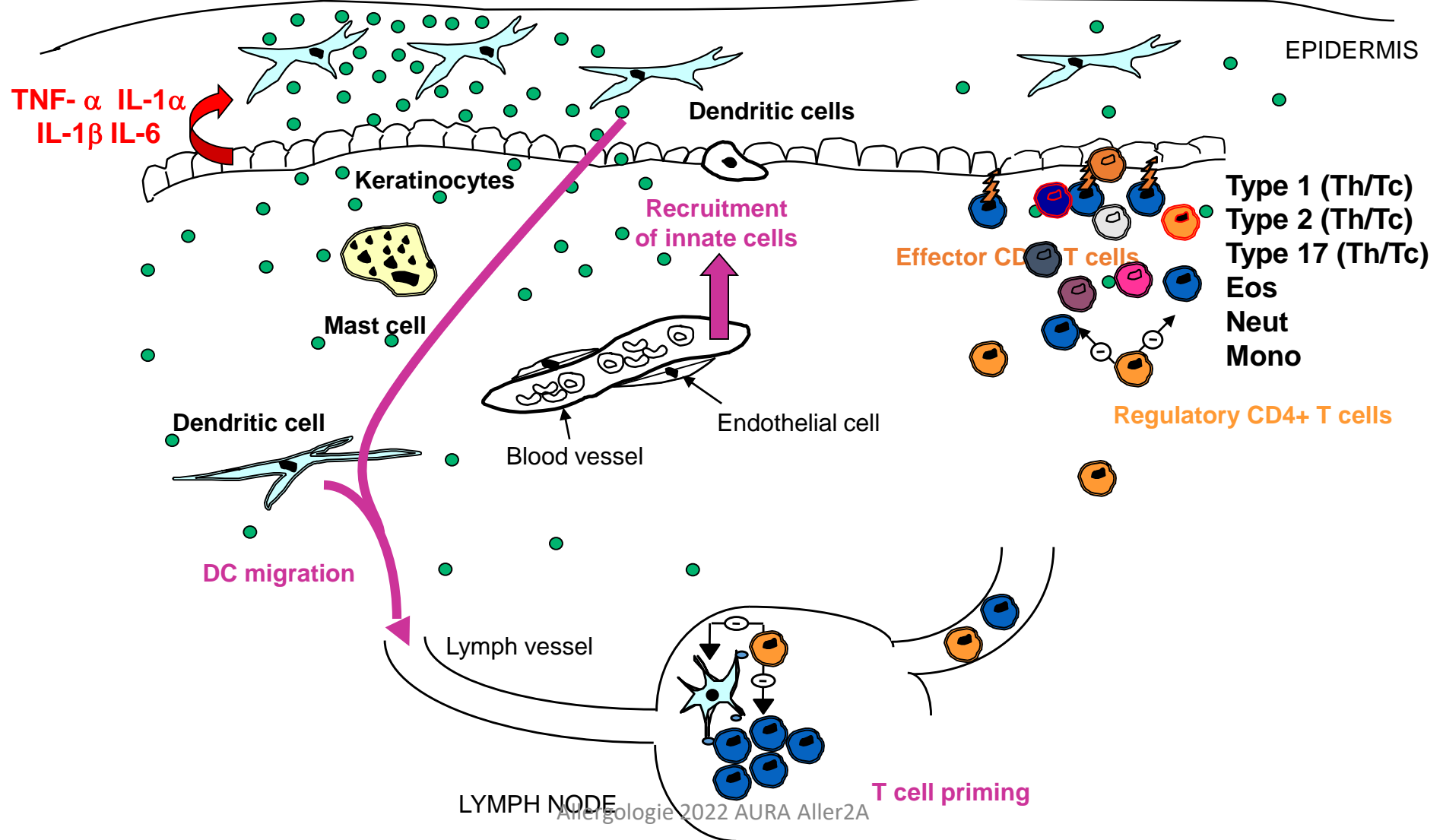
## Sensitization

Innate response  
T cell priming

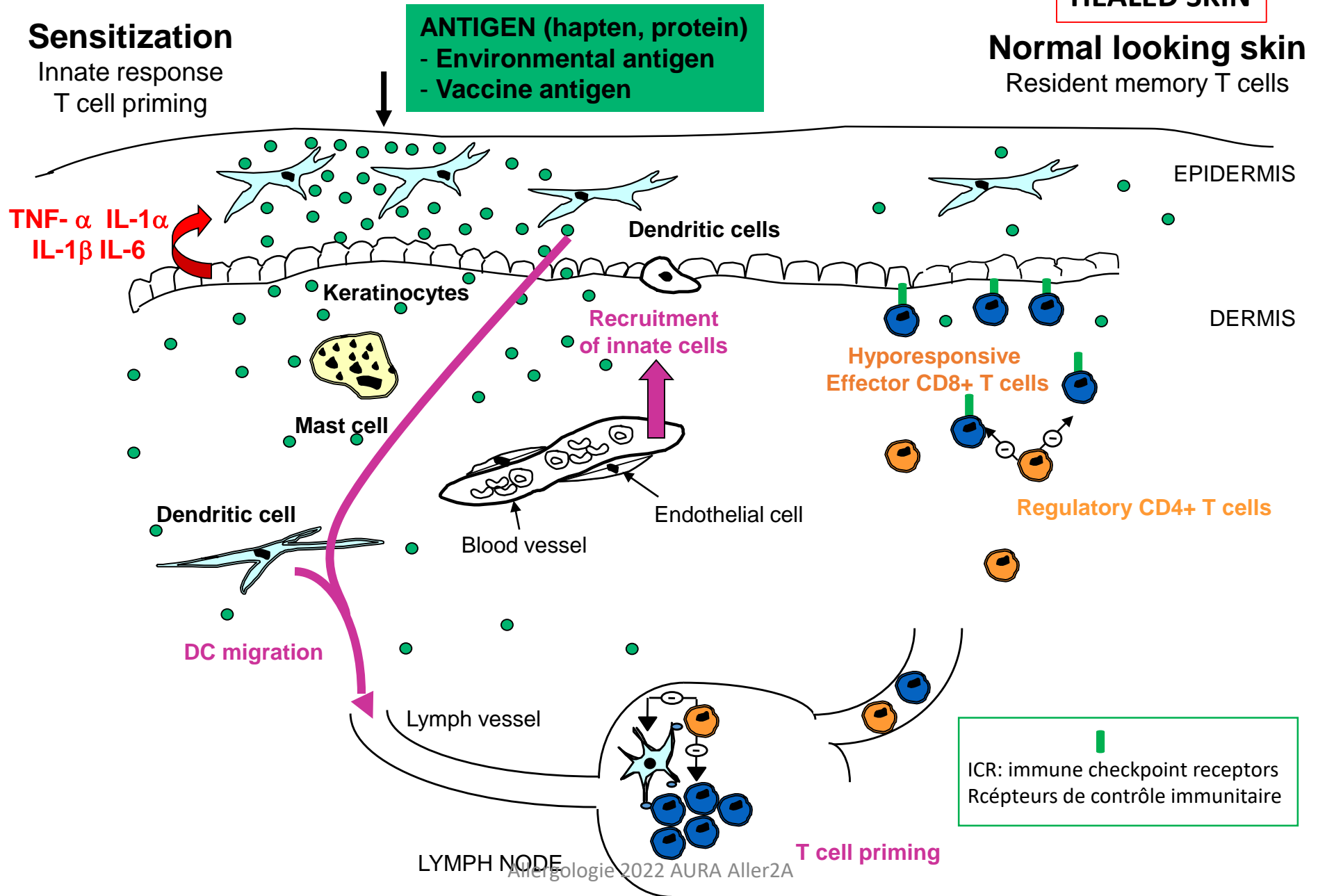
**ANTIGEN (hapten, protein)**  
- Environmental antigen  
- Vaccine antigen

## Elicitation

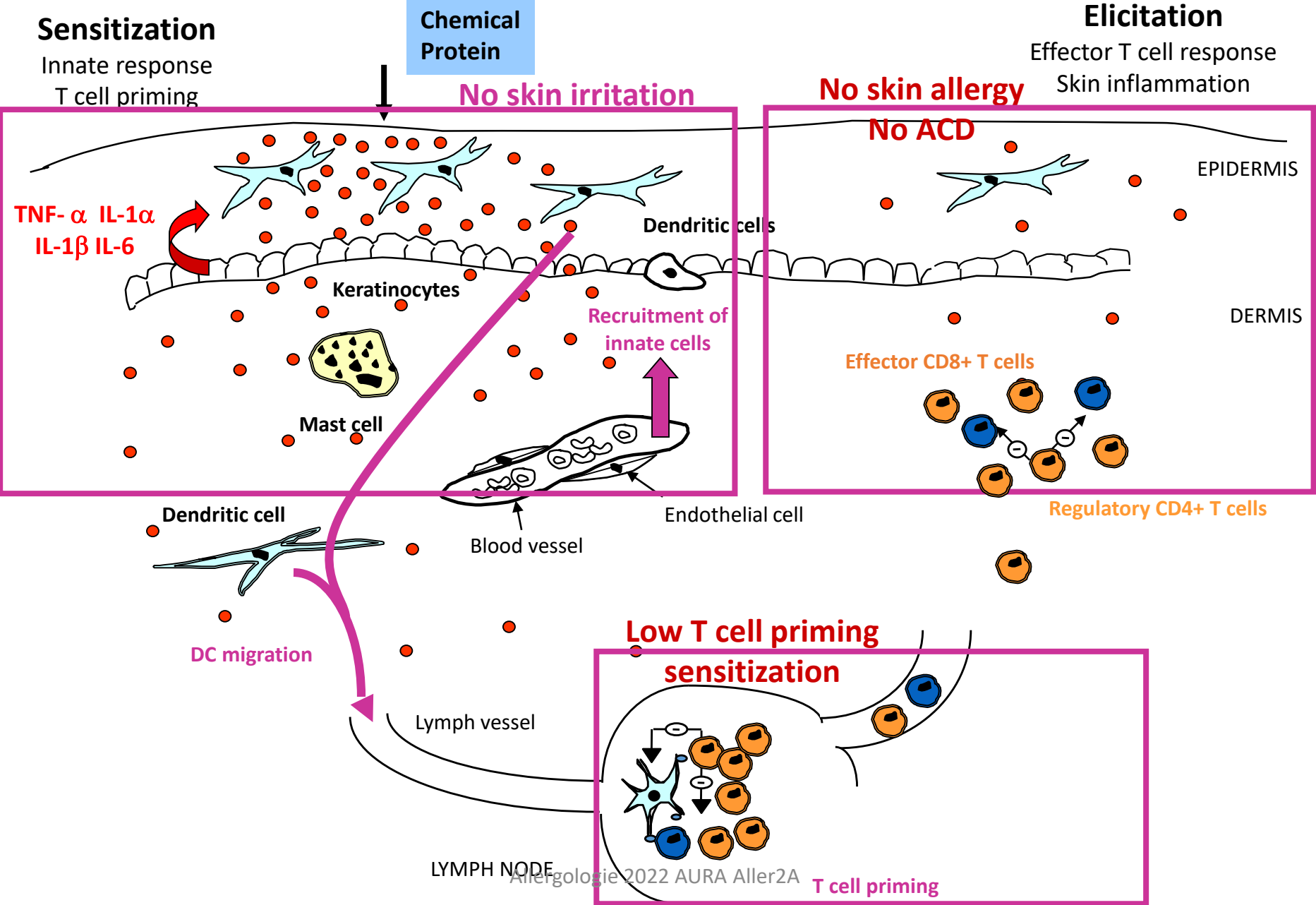
Effector T cell response  
Skin inflammation



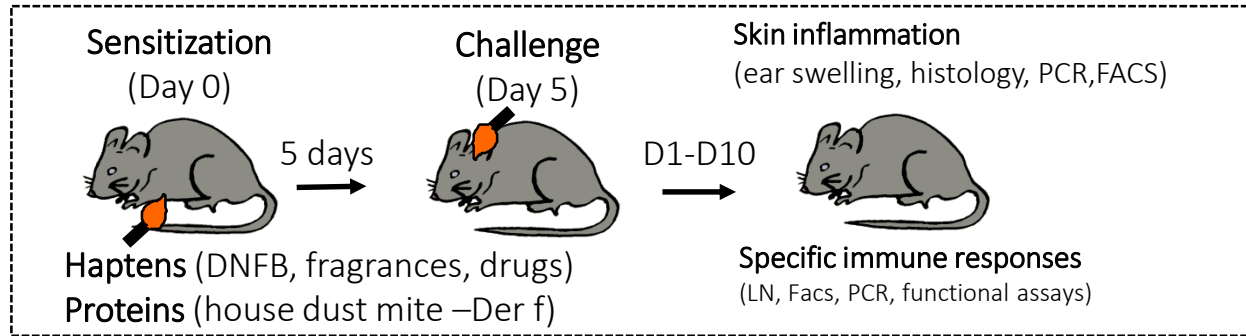
# Pathophysiology of skin inflammation



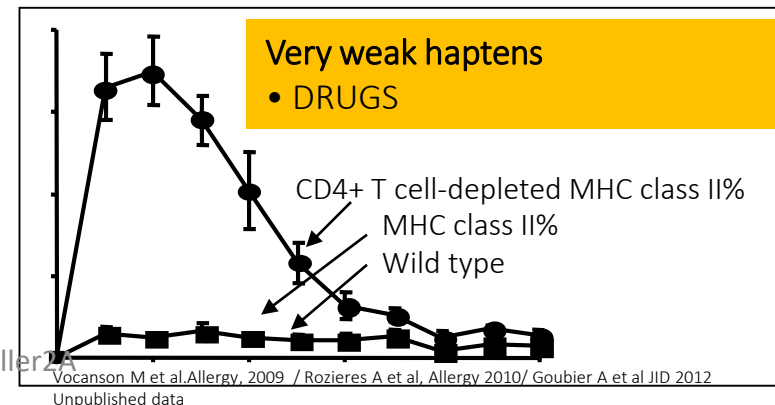
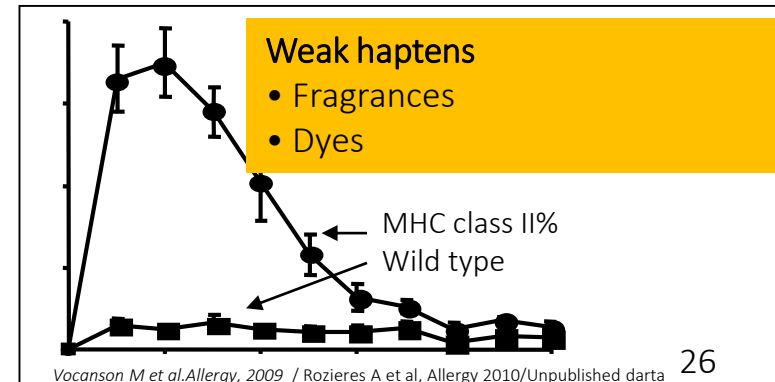
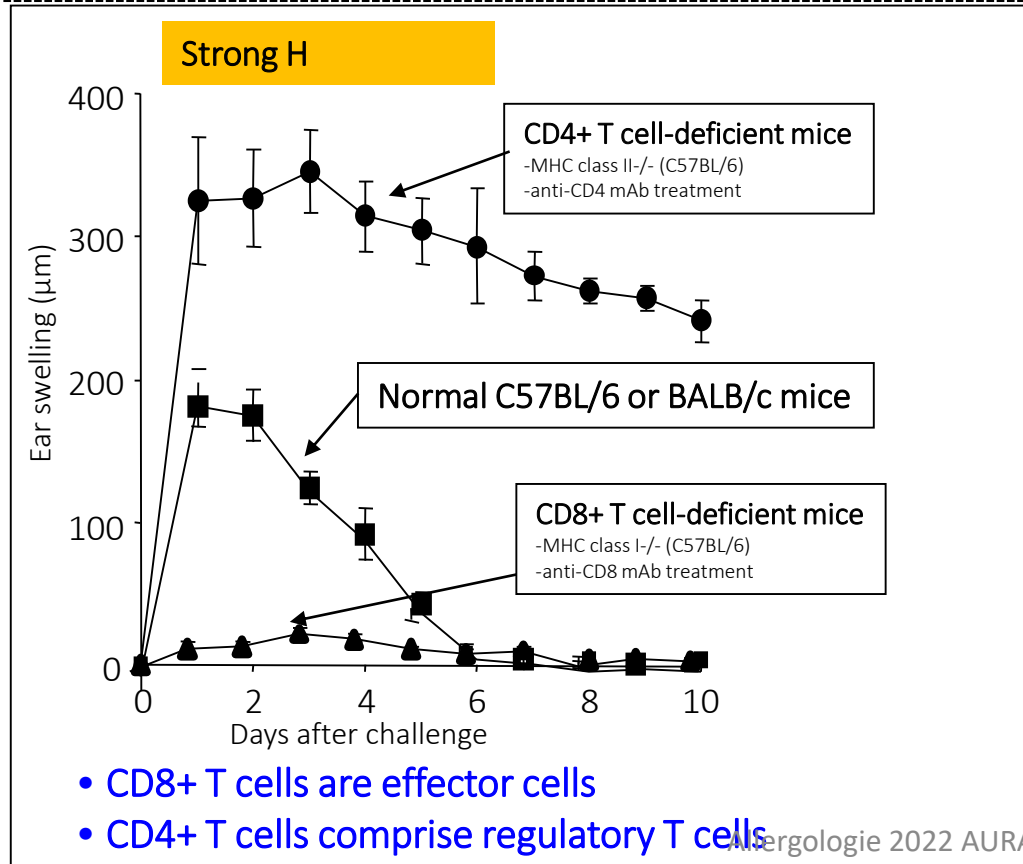
# Non allergic individual



# EFFECTOR and REGULATORY MECHANISMS IN ACD



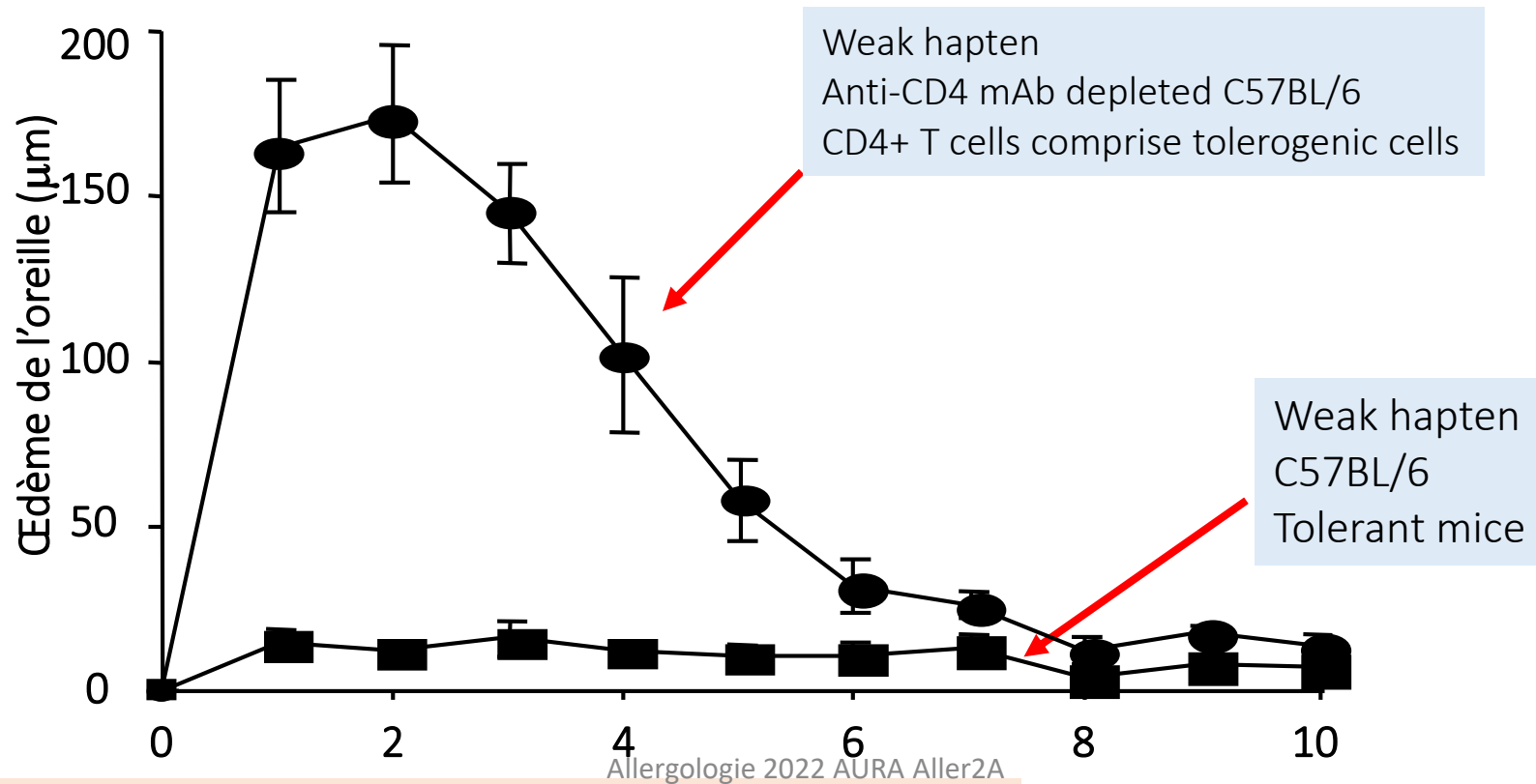
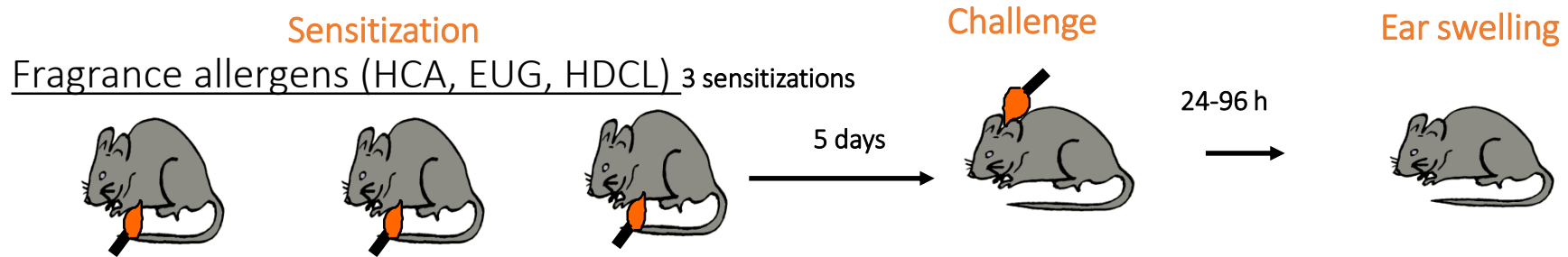
BOUR et al., Eur J Immunol, 1995  
 KRASTEVA et al., J Immunol, 1998  
 KEHREN et al., J Exp Med, 1999  
 AKIBA et al., J Immunol, 2002  
 SAINT-MEZARD et al. J Immunol, 2003  
 VOCANSON et al. J Invest Dermatol, 2006  
 BONNEVILLE et al. J Invest Dermatol, 2007  
 HENNINO et al J Immunol, 2007  
 ROZIERES et al, Allergy, 2009  
 VOCANSON et al, J Allergy Clin Immunol, 2010  
 HENNINO et al. J Allergy Clin Immunol, 2011  
 ROUZAIRE et al. Eur J Immunol, 2012  
 GOUBIER et al. J Invest Dermatol, 2013  
 ACHACHI et al. J Invest Dermatol, 2015  
 CORTIAL et al. Nanomedicine, 2015





# CD4+ T cells prevent ACD

## Weak haptens



# 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



irritation

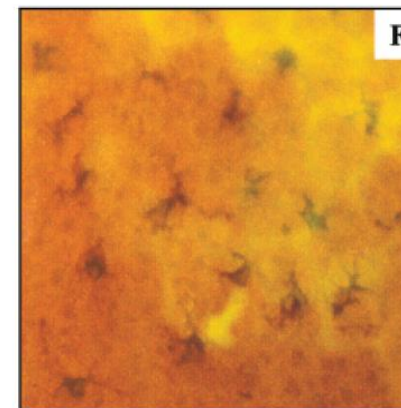
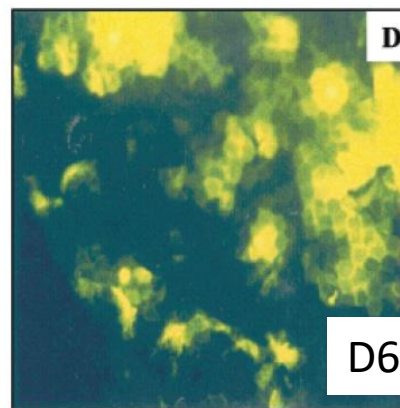
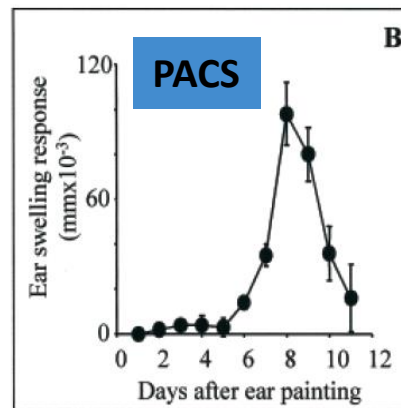
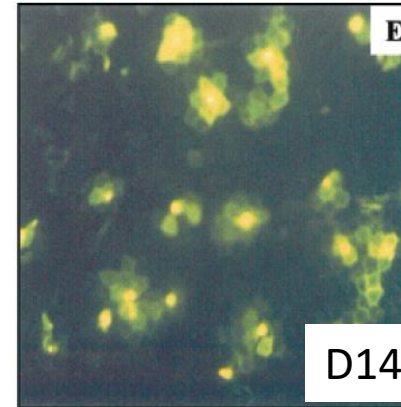
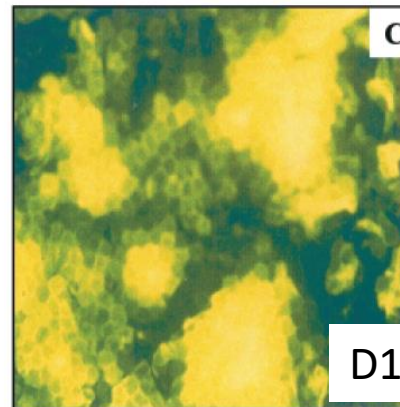
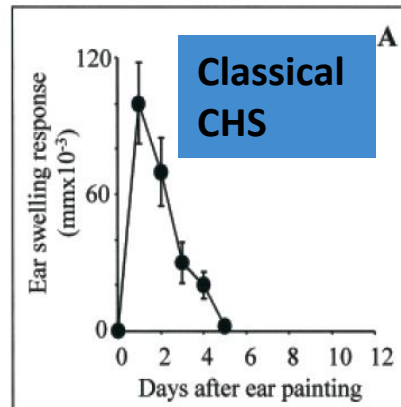
Ear inflammation  
DAYS 1 to 10



allergy

Bonneville M et al. Skin Contact Irritation Conditions the Development and Severity of Allergic Contact Dermatitis. *J Invest Dermatol.* 2007, 127:1430-7.

Saint-Mezard P et al. Afferent and efferent phases of allergic contact dermatitis (ACD) can be induced after a single skin contact with haptens: evidence using a mouse model of primary ACD. *J Invest Dermatol.* 2003 Apr;120(4):641-7.



# Skin irritation conditions the severity of ACD

## Primary Allergic Contact Dermatitis

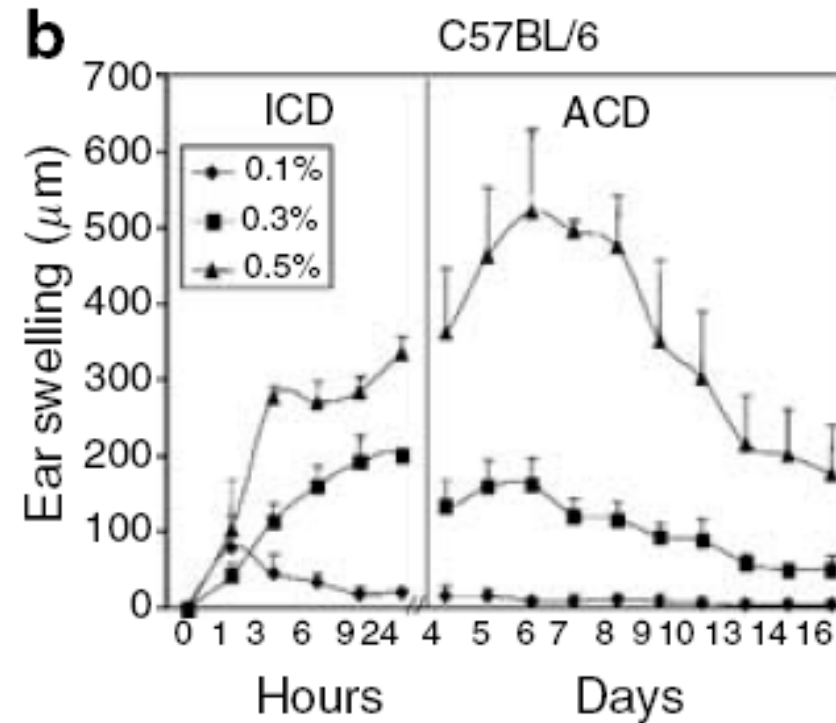
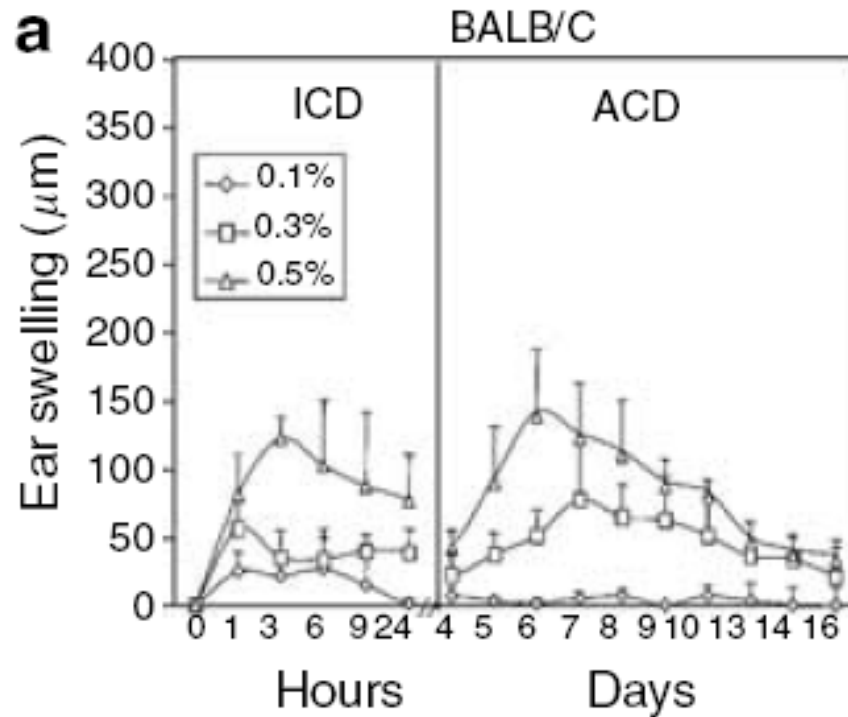
DNFB  
D0 once only on naive ear



Ear inflammation  
HOURS 1 to 24



Ear inflammation  
DAYS 1 to 10



# D.I.U Immunopathologie

**Approche clinicobiologique transversale de l'immunologie appliquée en pathologie humaine**

**Mécanismes physiopathologiques**  
Rappel des principes fondamentaux impliqués dans les différents cadres nosologiques

## 4 modules communs

- Module 1 : Bases fondamentales (21-22/10/2021)
- Module 2 : Immunopathologie générale & explorations biologiques (18-19 et 25-26/11/2021)
- Module 3 : Immunothérapie (2-3/12/2021)
- Module 4 : Maladies inflammatoires systémiques (6-7/01/2022)

## 3 modules au choix parmi :

- Module 5 : Néphrologie (27-28/01/2022)
- Module 6 : Pneumologie (03-04/03/2022)
- Module 7 : Hématologie (10-11/03/2022)
- Module 8 : Dermatologie (24-25/03/2022)
- Module 9 : Neurologie (28-29/04/2022)
- Module 10 : Infectiologie (19-20/05/2022)
- Module 11 : Hépto-gastroentérologie/Endocrinologie (02-03/06/2022)
- Module 12 : Oncologie (09-10/06/2022)



**Volume horaire total ~ 100 heures**

**Modules : du 21 octobre 2021 au 10 juin 2022**

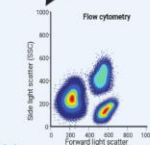


## Examens :

- Tronc commun : Lecture Critique d'Article (20-21 janvier 2022)
- Modules spécifiques : Un article ou module à commenter (24 juin 2022)

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## Applications diagnostiques et thérapeutiques



Flow cytometry



Biothérapies et thérapies ciblées



Vaccins, CAR-T cells...



# Département Allergologie et Immunologie Clinique



Clinical Research Unit



INSERM translational research team



Allergy & Clinical Immunology Department

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