Hypersensibilités et allergies cutanées

Gell & Coombs revisited

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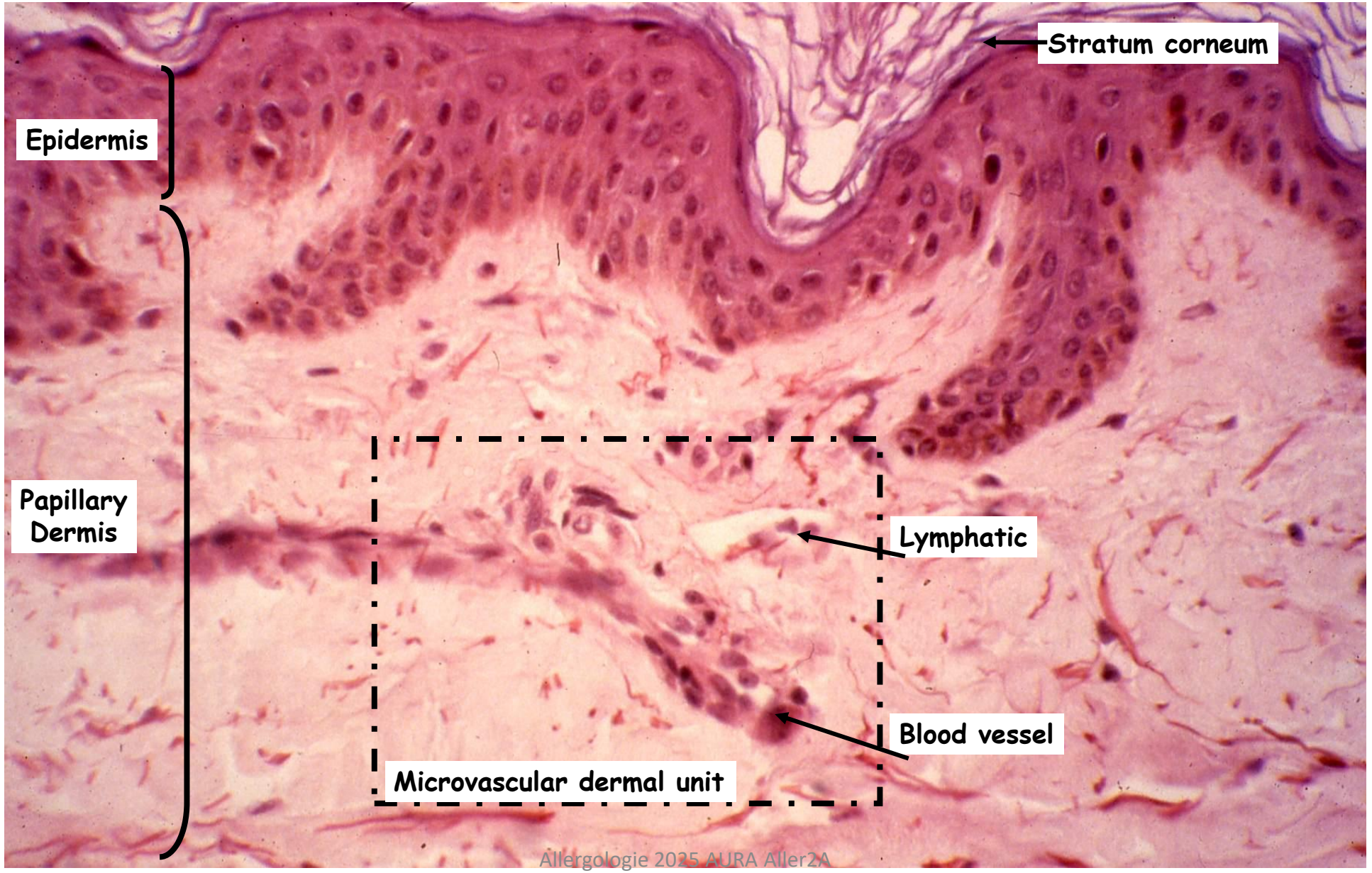
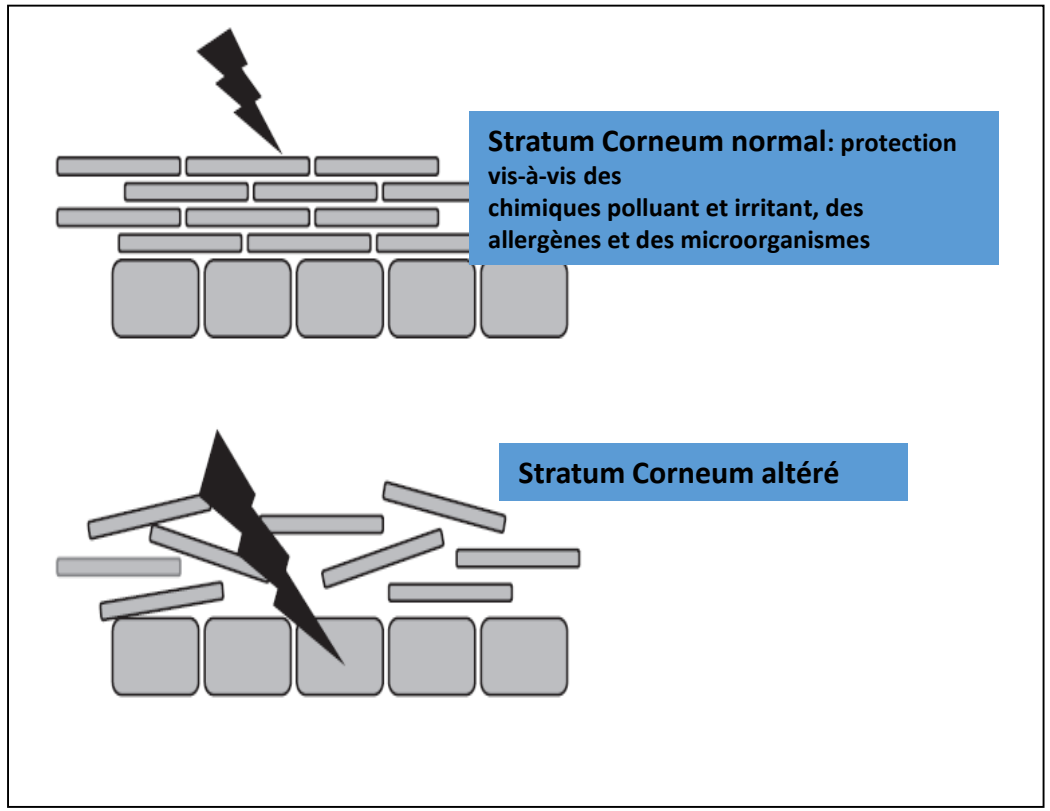
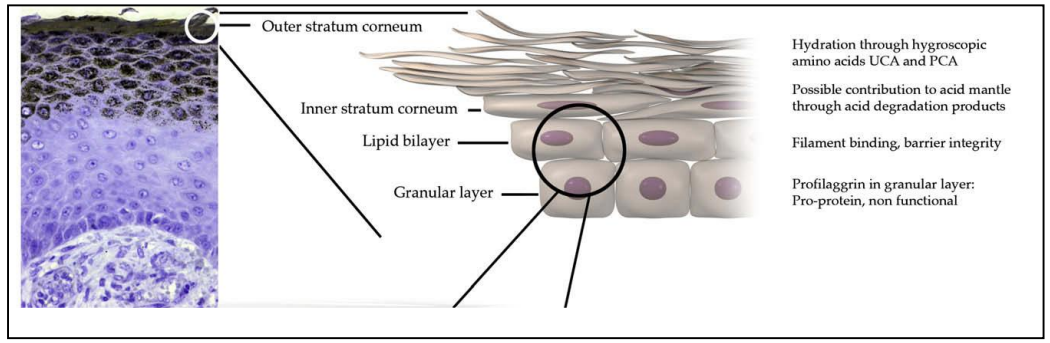
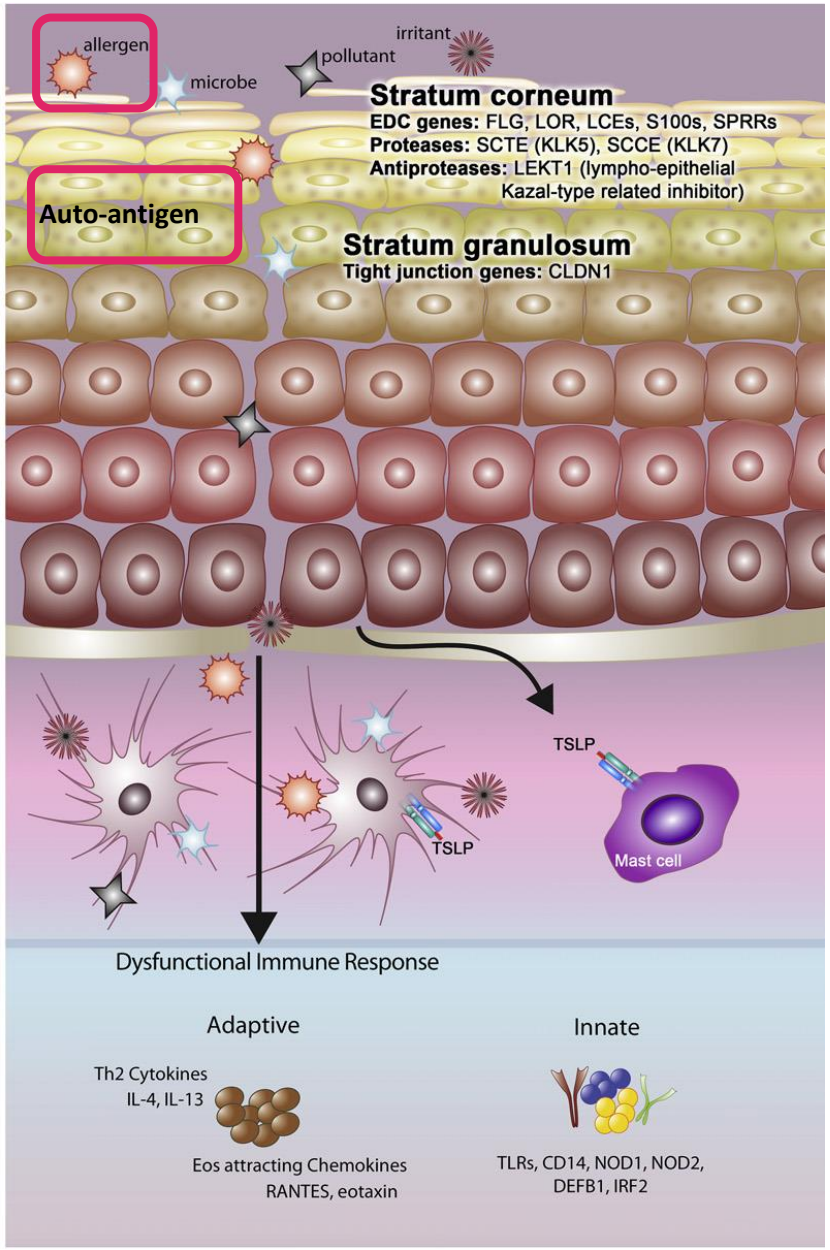
Skin anatomy and physiology



Epithelitis, source des maladies allergiques et autoimmunes







Plan

- Inflammation et maladies inflammatoires
- Hypersensibilités adaptatives et innées
- Classification des Hypersensibilités: Gell & Coombs
  - Type I (IgE), Type II (IgG), Type III (CIC), Type IV (lymphocytes T) (1975-2015)
  - Type I (mastocytes), Type II (IgG), Type III (CIC), Type IV (lymphocytes) (2015-2025)
- Hypersensibilités à expression cutanée
  - HSI: urticaire
  - HSR: inflammation T1, T2, T3
- Eczéma de contact allergique et inné

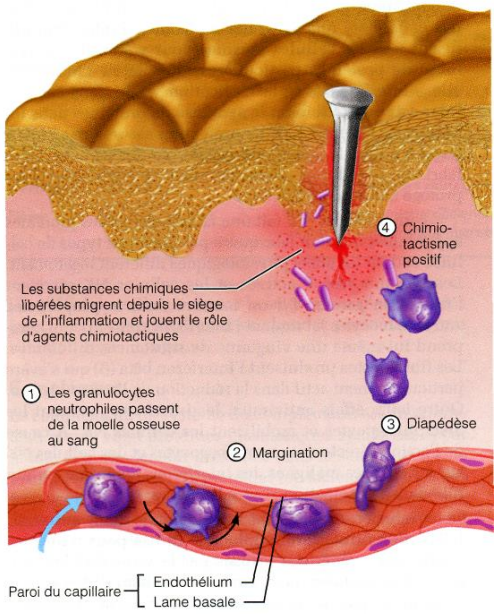
Inflammation et maladies inflammatoires

- **Inflammation** = mise en jeu de l'immunité innée et adaptative
  - Immunité adaptative: lymphocytes T et B
  - Immunité innée: leucocytes et toutes les cellules de l'organisme
- **Inflammation physiologique**
  - **Réponse immunitaire**
  - Réponse physiologique aux agressions
  - Ex: cicatrisation; guérison d'une infection
- **Inflammation pathologique: Maladies**
  - autoinflammatoires
  - inflammatoires chroniques

  } **Immunité innée**

  - autoimmunes
  - allergiques

  } **Immunité adaptative**



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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

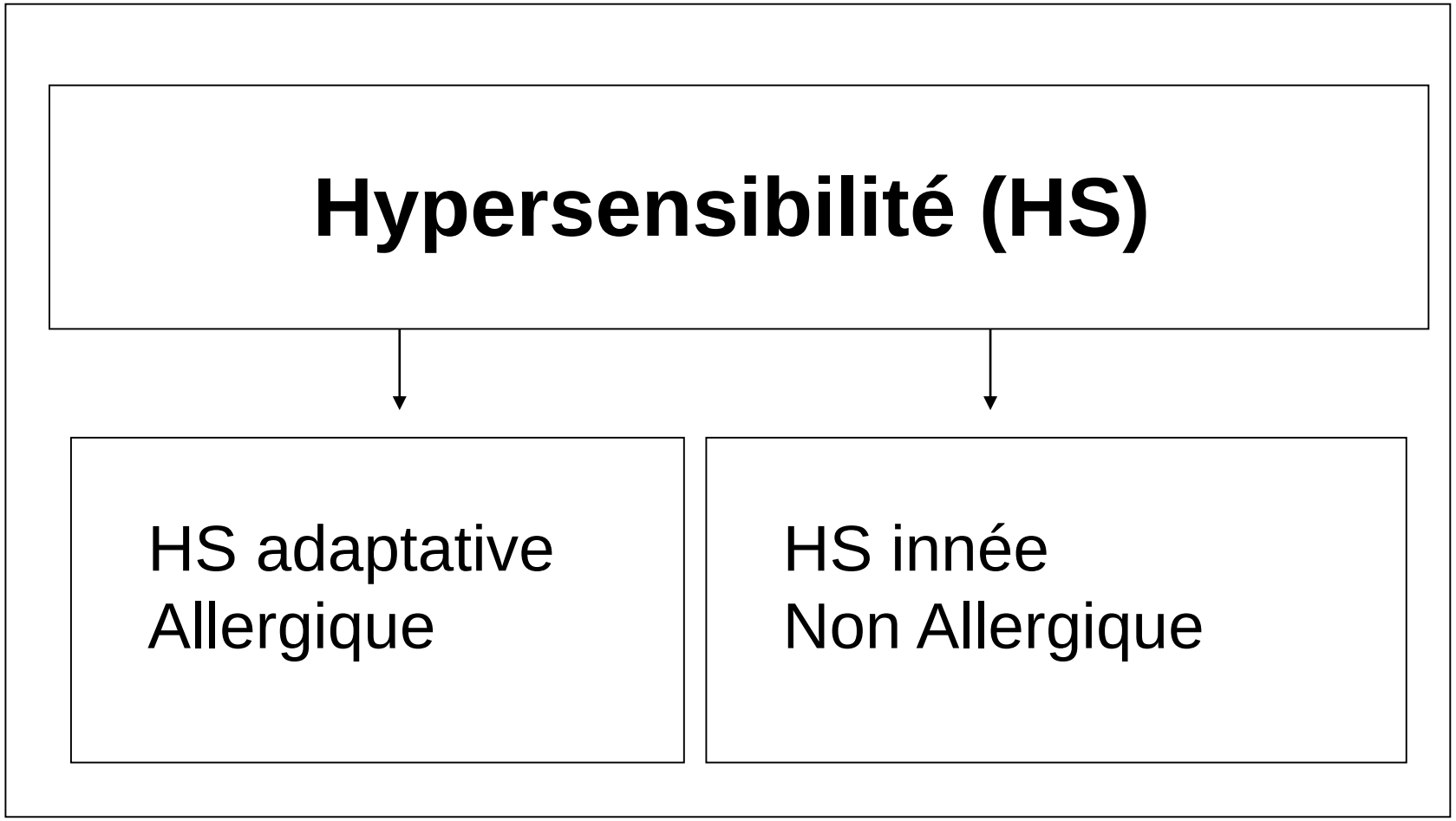
   - Autoimmune diseases

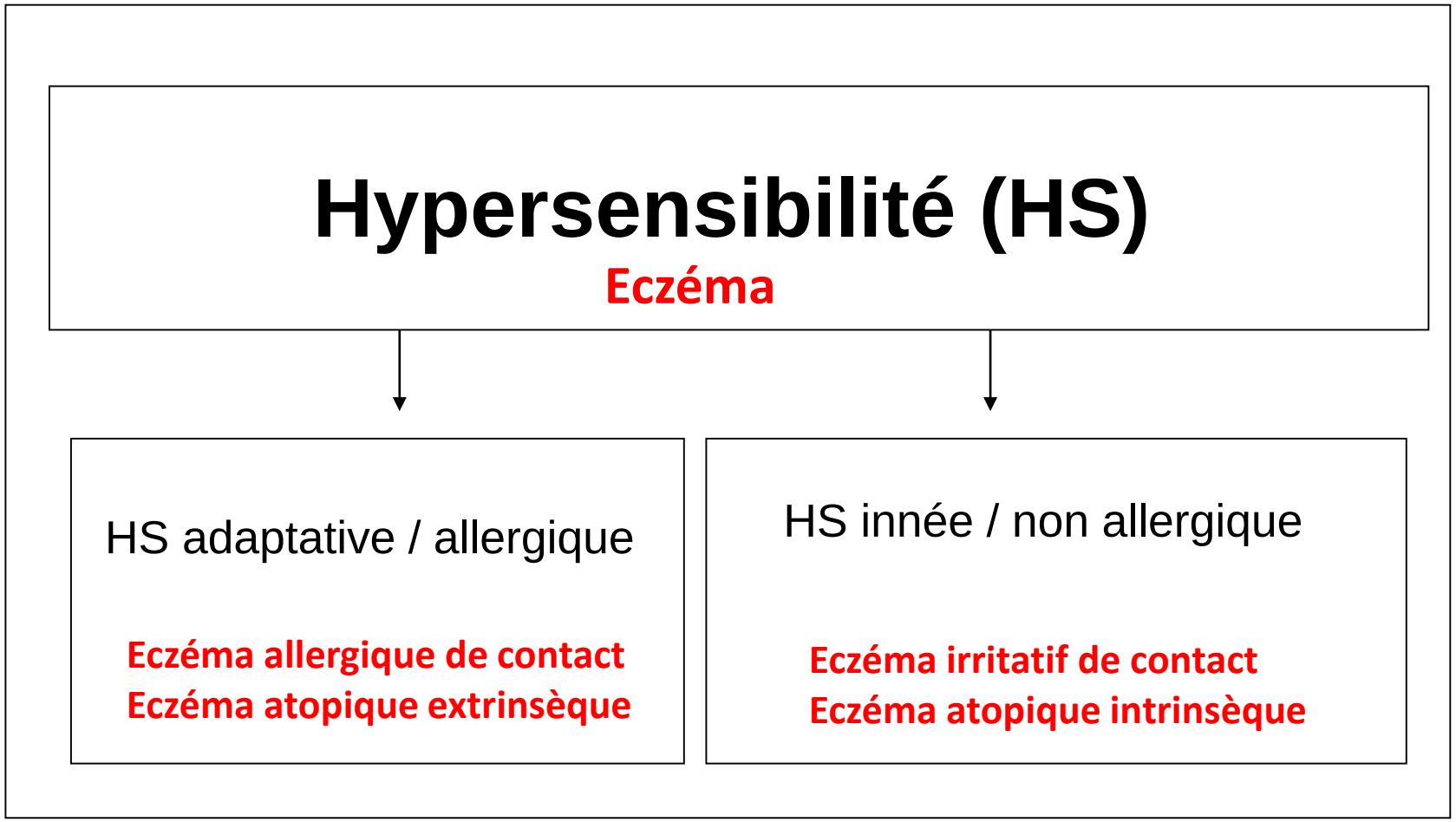
2. **Allergy définition**

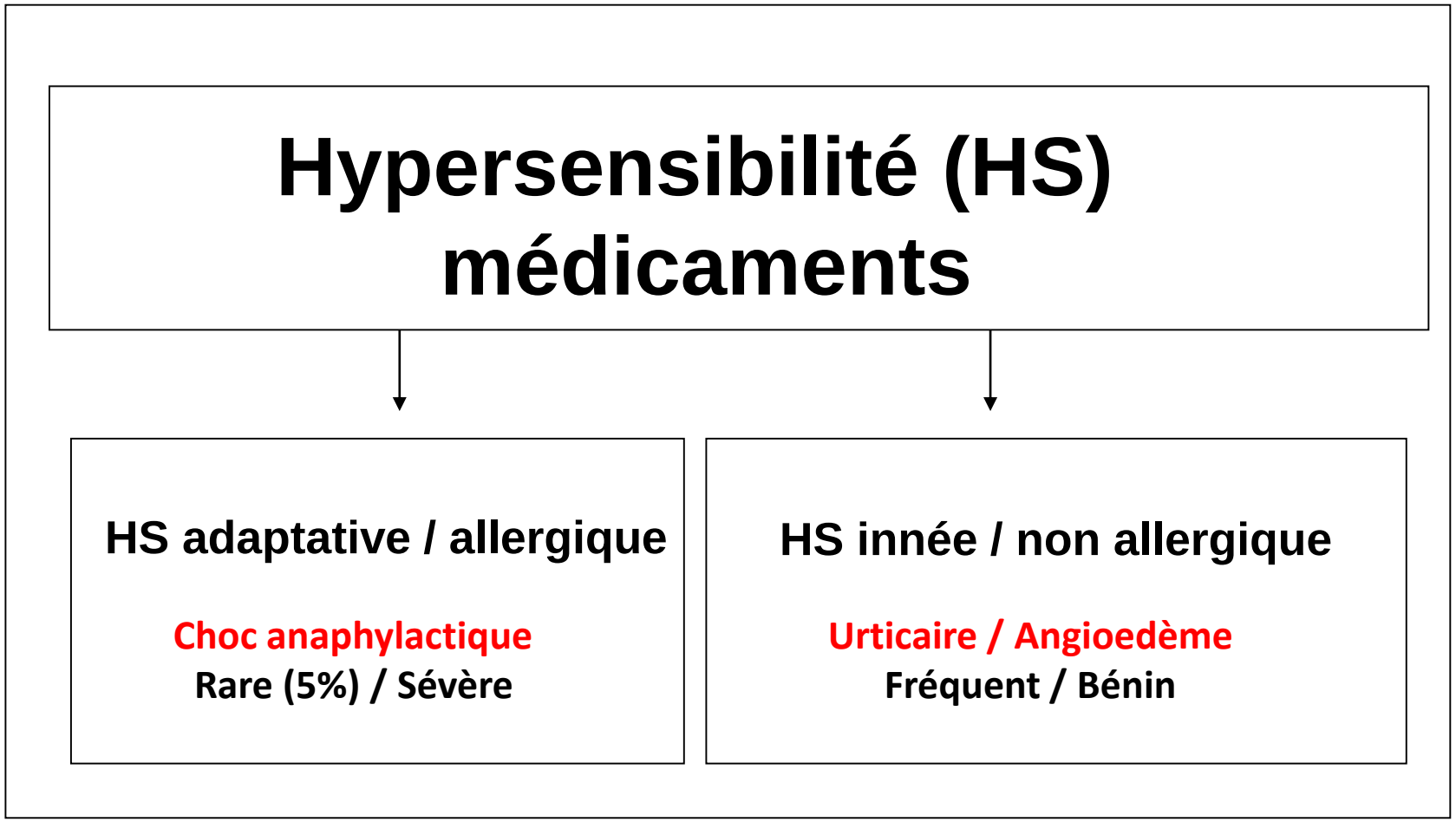
   Hypersensitivity reactions = inappropriate and damaging immune response to a molecule caused by both innate and/or adaptive immunity

   - Allergic HS

   - Non allergic HS


Hypersensibilité (HS)
HS adaptative
Allergique
HS innée
Non Allergique


Hypersensibilité (HS)
Eczéma
HS adaptative / allergique
Eczéma allergique de contact
Eczéma atopique extrinsèque
HS innée / non allergique
Eczéma irritatif de contact
Eczéma atopique intrinsèque


Hypersensibilité (HS) médicaments
HS adaptative / allergique
Choc anaphylactique
Rare (5%) / Sévère
HS innée / non allergique
Urticaire / Angioedème
Fréquent / Bénin

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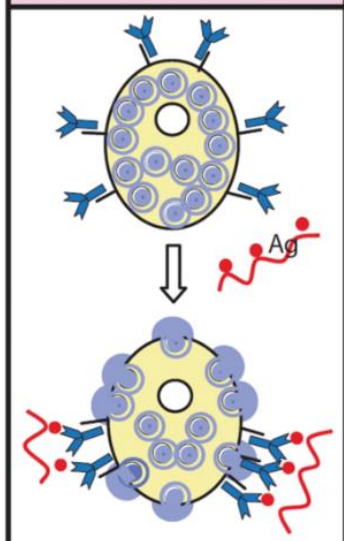
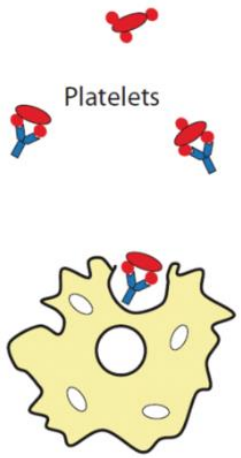
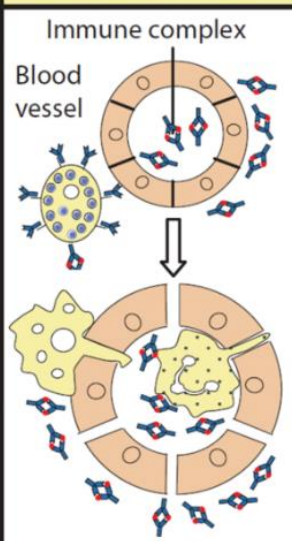
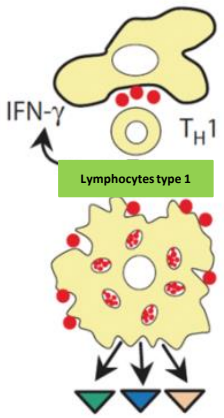
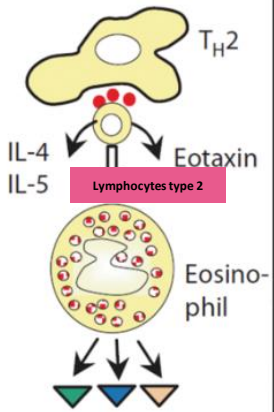
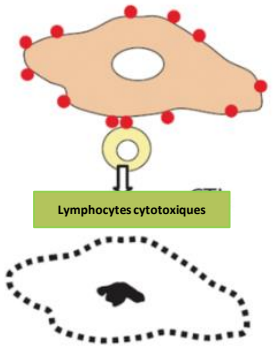
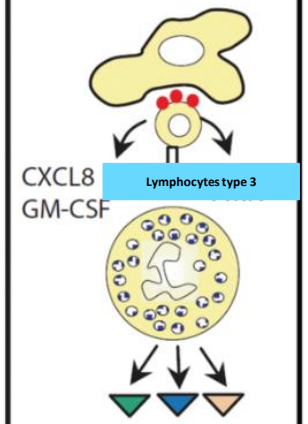
Hypersensibilités
Classification de Gell & Coombs

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**	IL-5, IL-4/IL-13 **Th2**	Perforin/ granzyme B **Cytotoxic**	IL-17, IL-22 **Th 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

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
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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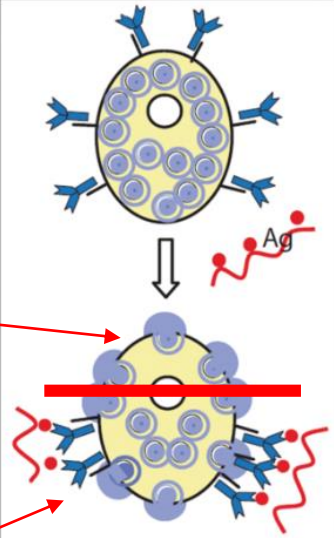
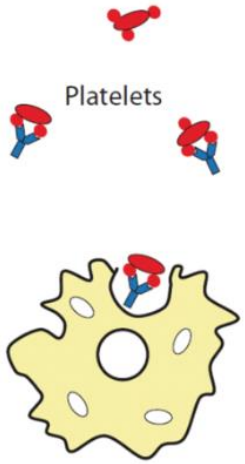
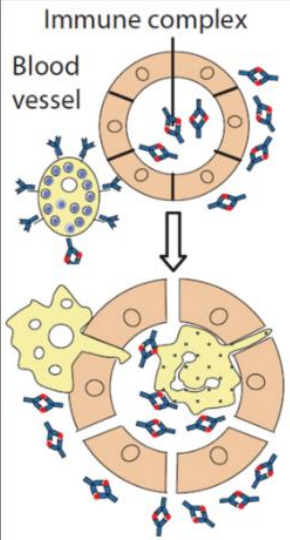
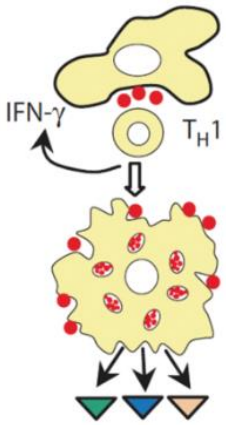
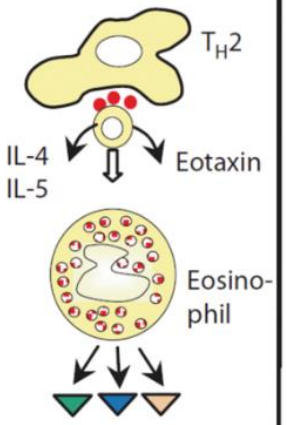
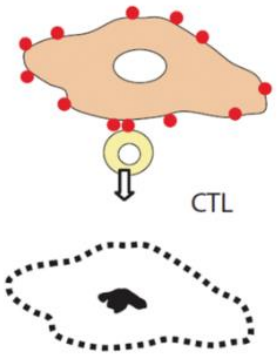
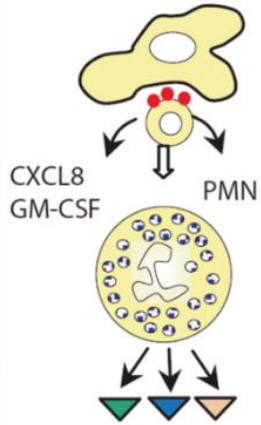
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

HSI non allergique

HSI allergique

Hypersensibilités
Classification de Gell & Coombs

Antibody ← → Lymphocytes

- HS retardée
- Immunité médiation cellulaire
- Immunité lymphocytaire

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
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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	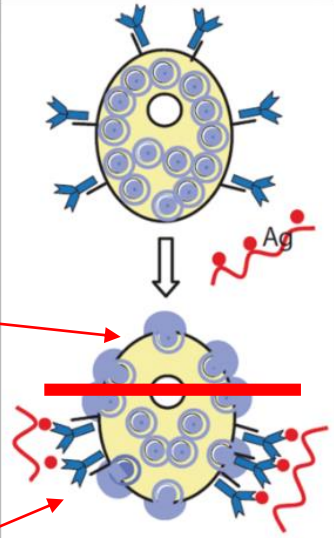	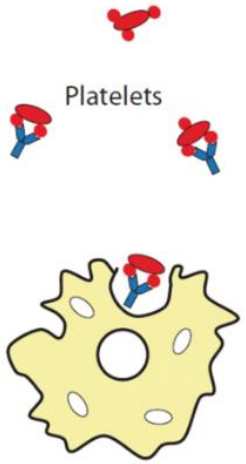	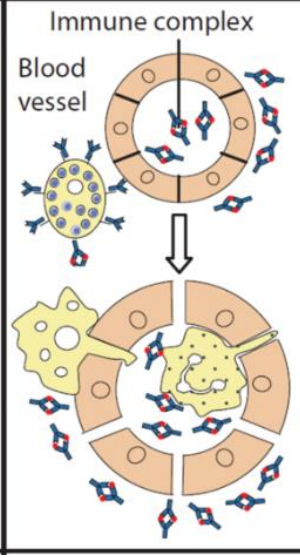	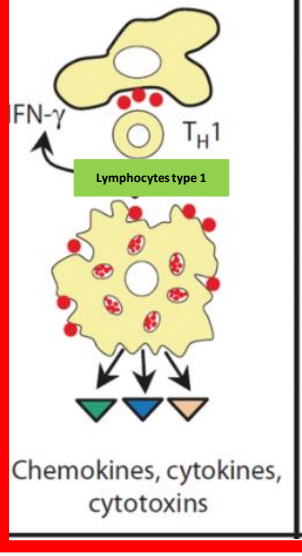	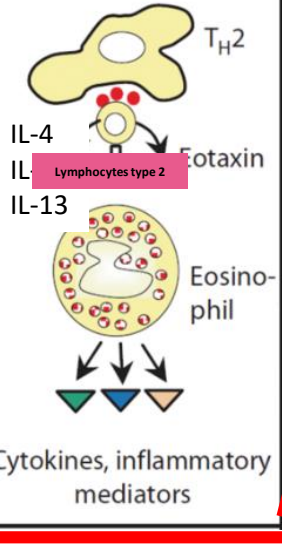	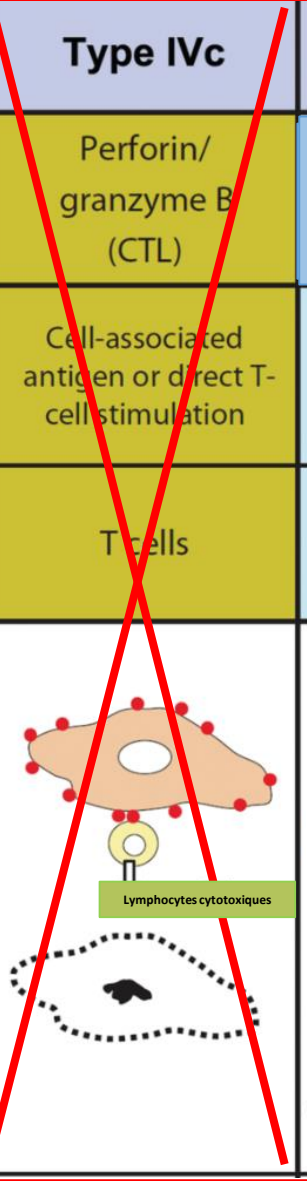	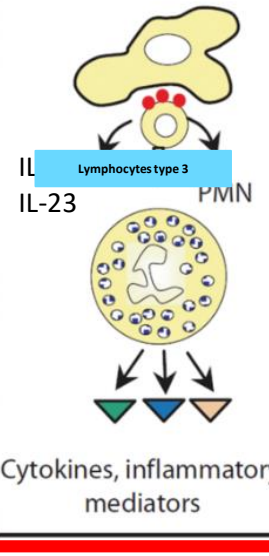
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Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin. Polypose NS**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis Hydradénite S. D. Séborrhéique**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

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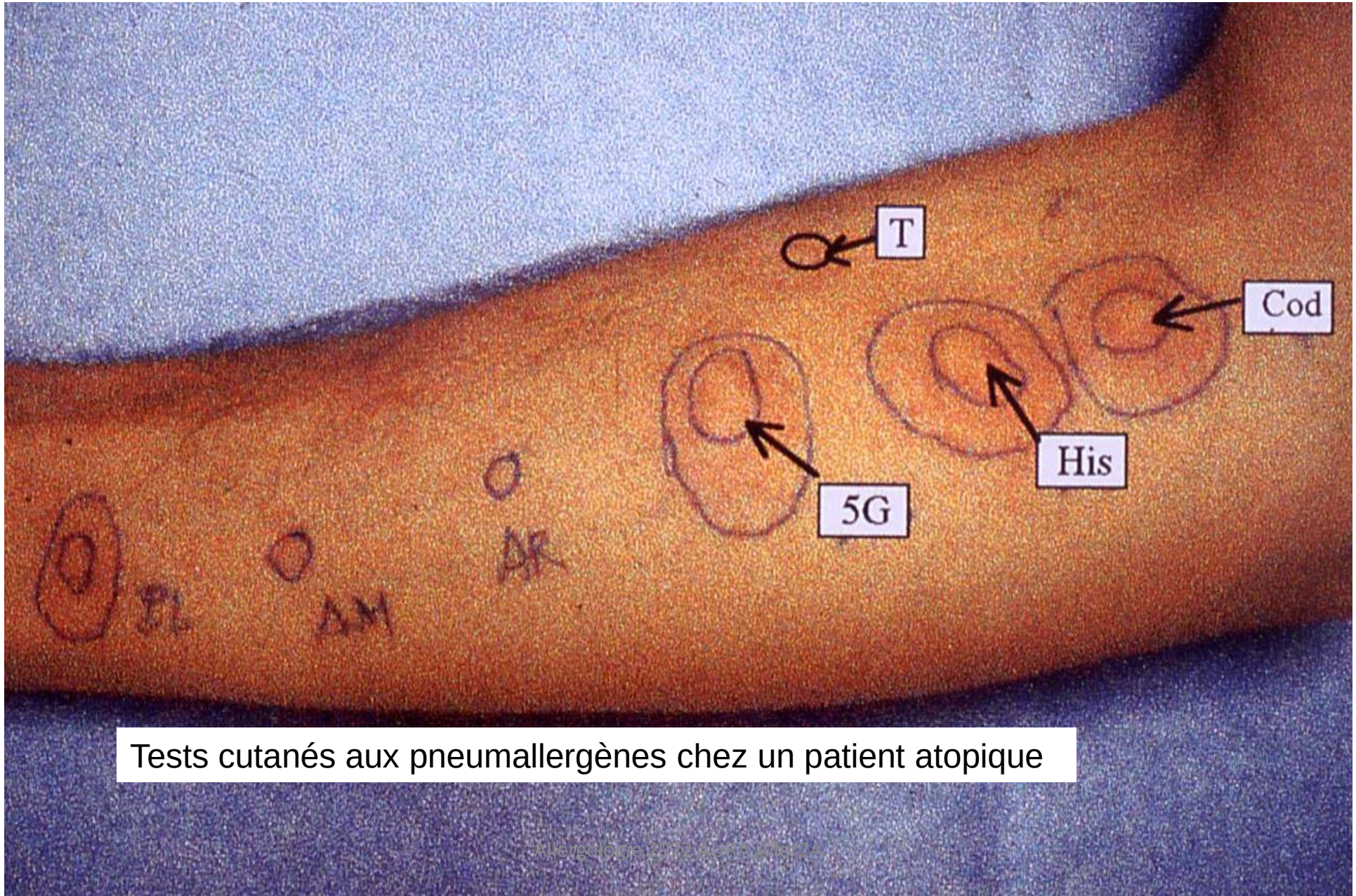
HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

Urticaire chronique

- Fréquente (2% population)
- Maladie inflammatoire chronique (pas une maladie allergique)

Diagnostic: facile

- Lésions erythémato-oedémateuses (<24h)
- Prurit
- 2 types: spontanée et induite
- 2 formes: plaques et angioedèmes
- Symptômes extra-cutanés fréquents

Pathophysiology : activation mastocytaire

- Mastocytes pré-activés

(UC auto-immune, UC atopique, UC auto-allergique)

- Activation complète induite par différents facteurs (aliments, médicaments, infections, stress, trauma, etc.)
- Maladie infl. de type 2 (Th2)
- FcεRI

Traitement: Chronique

- Anti-H1R efficaces
- Anti-IgE mAbs (omaluzimab)
- Pas de corticoides systémiques

L'urticaire spontanée n'est pas une maladie allergique

Investigative report

Eur J Dermatol 2011; 21(3): 349-53

Chronic spontaneous urticaria is not an allergic disease

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Benoit BENSAID
Audrey NOSBAUM
Frédéric BERARD
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The links between chronic urticaria, IgE sensitization and allergy have been much discussed but little studied. We investigated IgE sensitization and allergy in 128 adult chronic urticaria patients during 2006-2008. During a one-day hospitalisation, the patients answered a standardized questionnaire and underwent blood serum analysis, physical tests and skin prick-tests. IgE sensitization to environmental allergens was defined by the positivity of at least one skin prick test and/or elevated levels of serum IgE ≥ 300 Kui/L. The chronic urticaria was considered allergic if: i) a high correlation between positive skin prick tests to a clinically relevant allergen and the case history was found; ii) complete remission of urticaria occurred within two months of allergen withdrawal. Of 105 patients with interpretable skin prick tests, 46.7% were IgE sensitized. Two patients had clinically relevant positive skin prick tests but their chronic urticaria had many other triggering factors and neither was in complete remission after withdrawal of these allergens. IgE sensitization is higher in chronic urticaria patients than in the global adult population, suggesting that it is one important etiopathogenic factor in chronic urticaria. However, it cannot be considered as the expression of

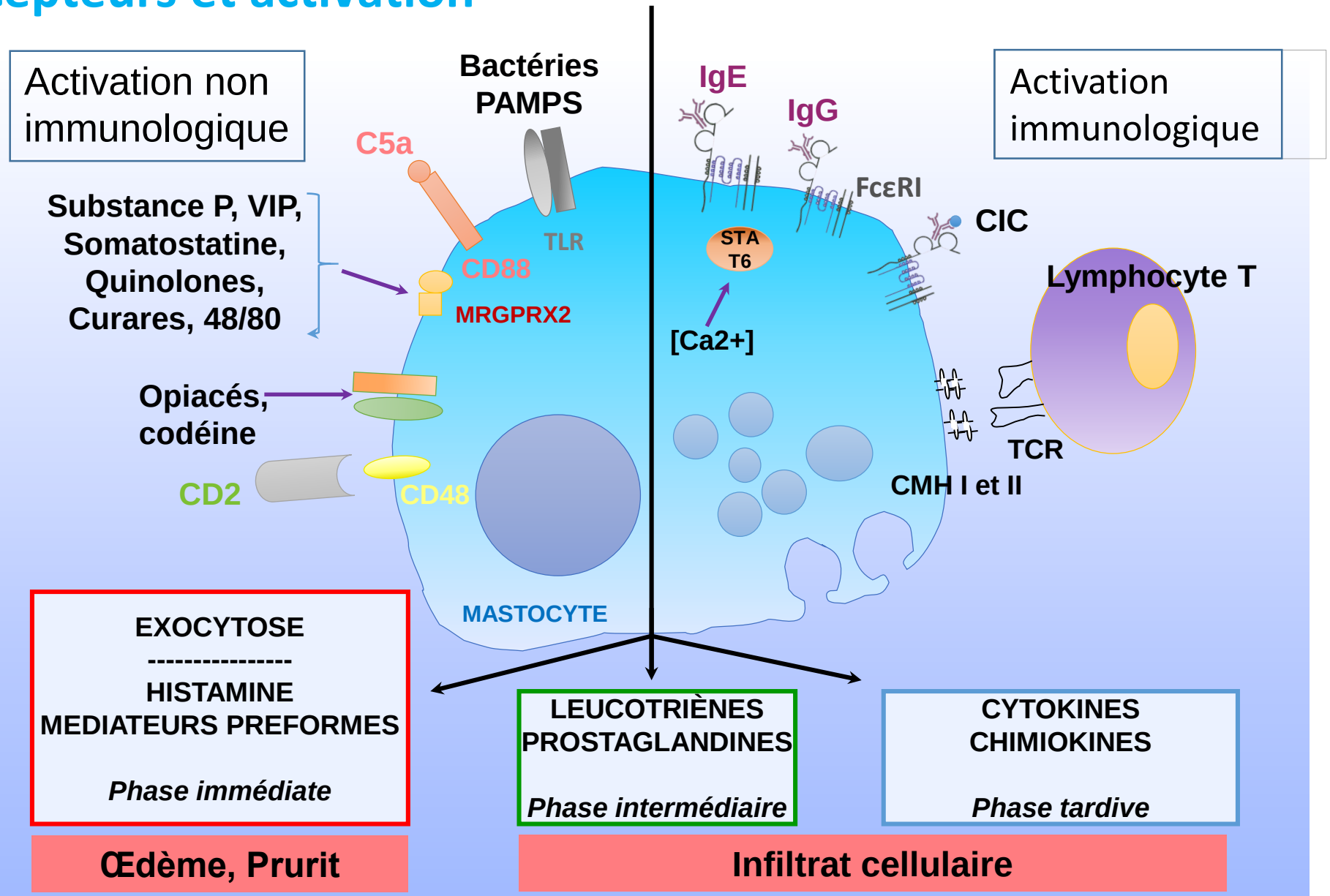
- Terrain atopique
  - 1 prick test + aeroallergens
  - Serum IgE > 300 kU/l
- Terrain autoimmun
  - AAN +
  - Ac anti-TPO +

Table 3. Number (and percentage) of patients with IgE sensitization** and/or autoimmune status*** among 105 prick-tested patients.

	Autoimmune status +	Autoimmune status -	Total
IgE sensitization +	15 (14.3%)	34 (32.4%)	49 (46.7%)
IgE sensitization -	20 (19%)	36 (34.3%)	56 (53.3%)
Total	35 (33.3%)	70 (66.7%)	105 (100%)

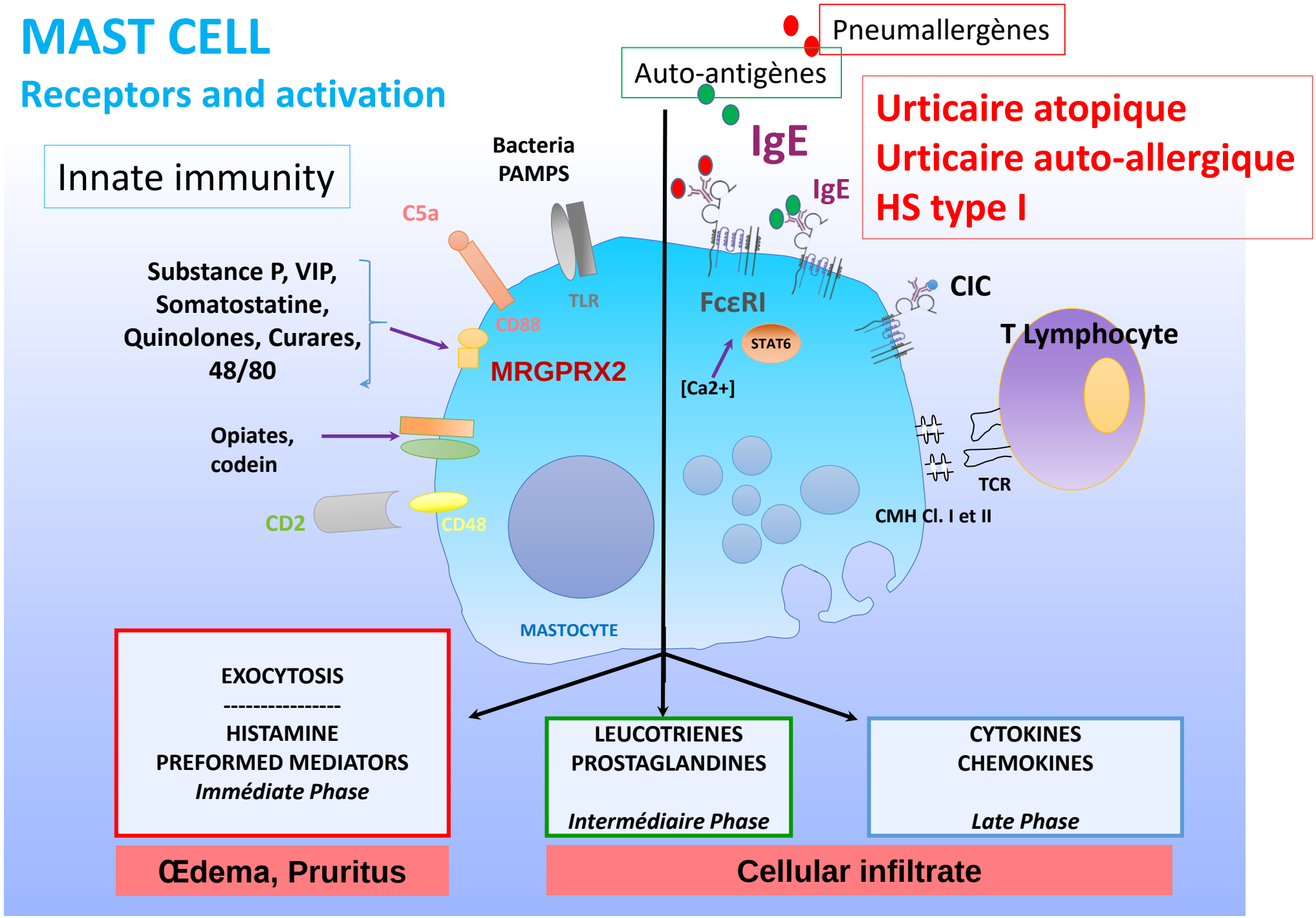
***At least one positive prick-test and/or IgE level ≥ 300 KU/L. ***ANA positivity ≥ 100 and/or antiTPO Abs ≥ 60 kU/L.*

MASTOCYTES
Récepteurs et activation



MAST CELL

Receptors and activation

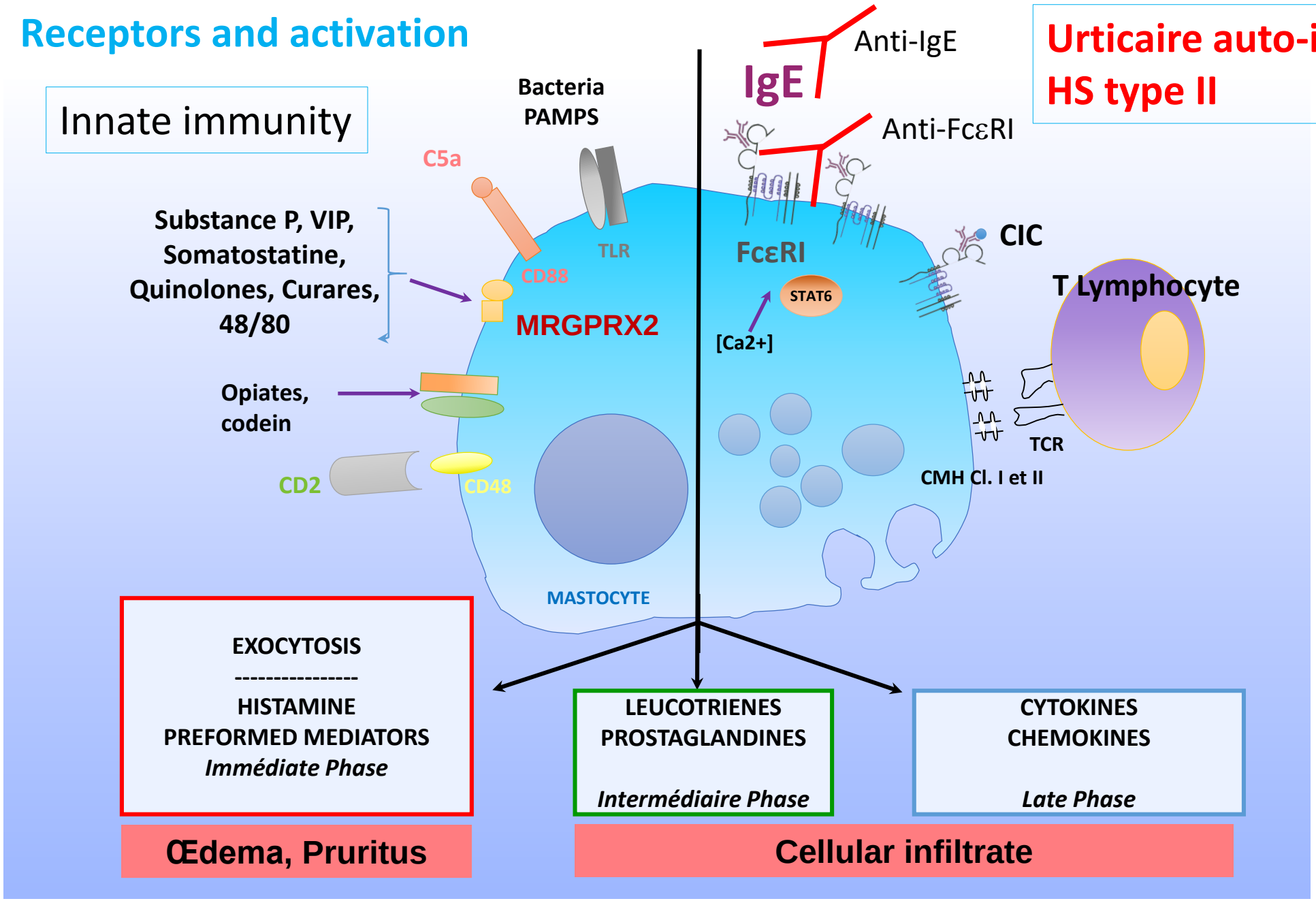


MAST CELL

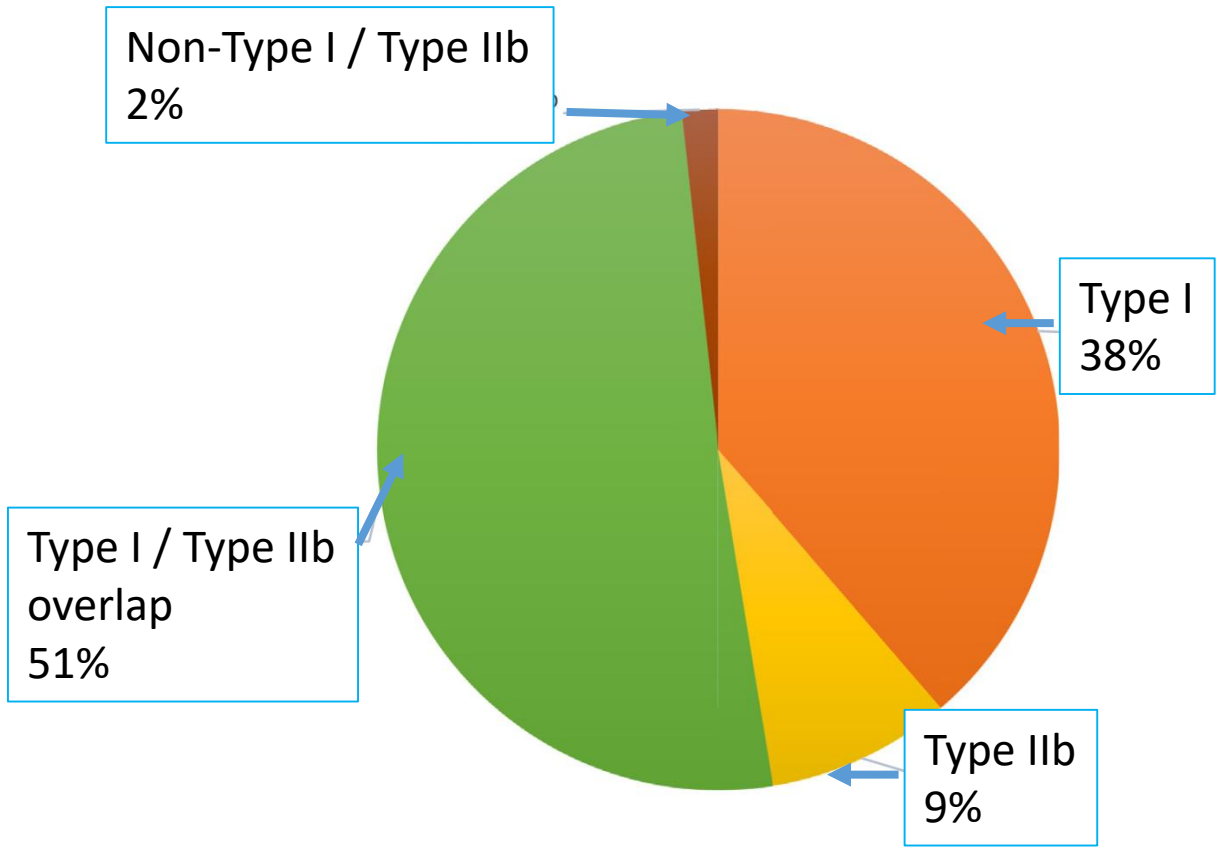
Receptors and activation

Innate immunity

Urticaire auto-immune
HS type II



Type I and Type IIb Urticaria (Gell & Coombs)
CSU Endotypes

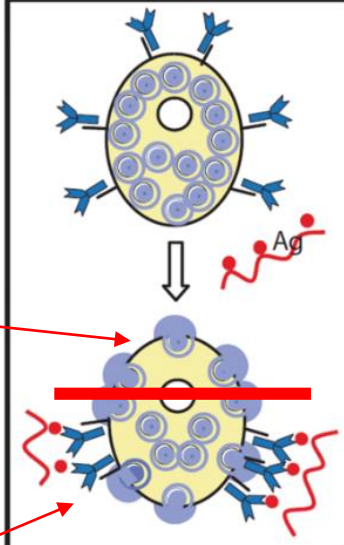
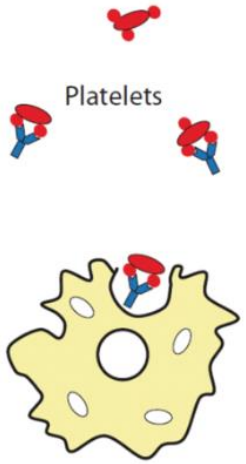
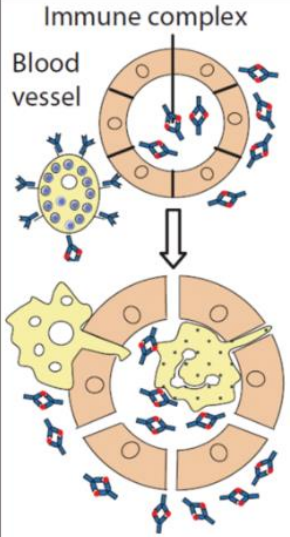
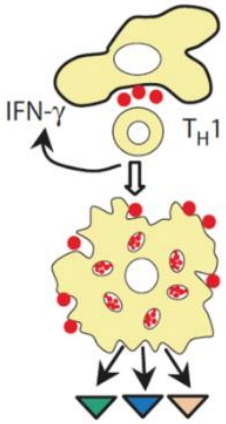
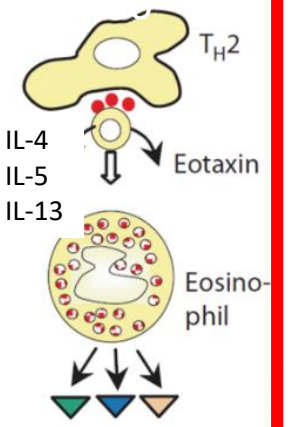
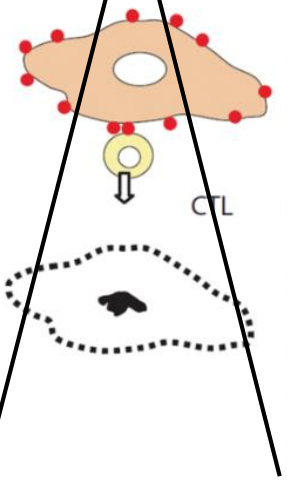
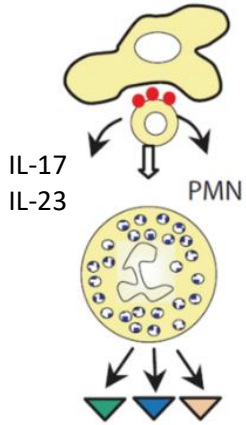


- Type I
  - Allergic diseases
  - Total IgE levels > 40 UI/l
  - Positive prick tests aeroallergens
- Type IIb
  - Autoimmune disease
  - Total IgE levels < 40 UI/l
  - Anti-nuclear antibodies > 1:160
  - Anti-peroxidase antibodies elevated
- Type I / Type IIb overlap
- Non-Type I / Type IIb

Sella JA et al.Type I and type IIb autoimmune chronic spontaneous urticaria: Using common clinical tools for endotyping patients with CSU. J Allergy Clin Immunol Global 2023;2:100159.

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

	Type I	Type II	Type III	Type IV / immunité à médiation cellulaire			
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Inflammation T1**	**Th2/Tc2/ILC2 Inflammation T2**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Inflammation T3 (T17)**
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

HSI non allergique

HSI allergique

Type IVb urticaria

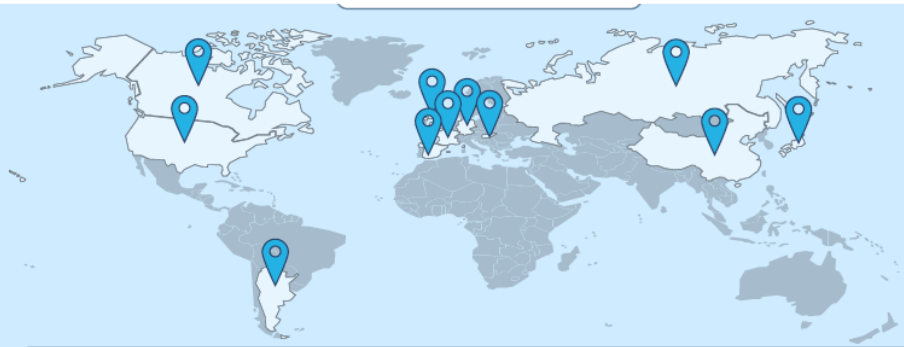
CUPID Study A

138 patients

Aged ≥ 6 years

Omalizumab-naïve

Anti-H1 non responders



The primary and key secondary endpoints were changes from BL to week 24 in UAS7[a] and ISS7[b] respectively, or vice versa depending on regional regulatory requirements.

CUPID Study B

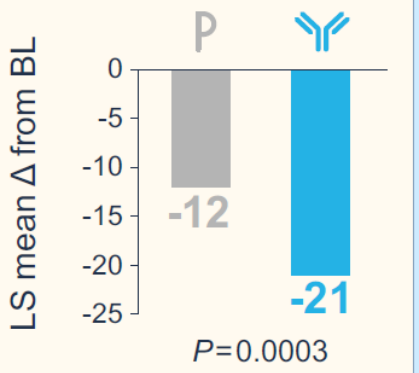
108 patients

Aged ≥ 12 years

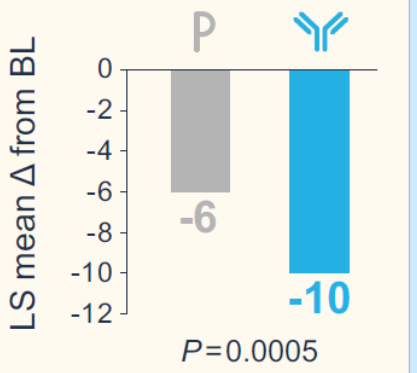
Omalizumab-intolerant/ incomplete responders

RESULTS AT WEEK 24

UAS7

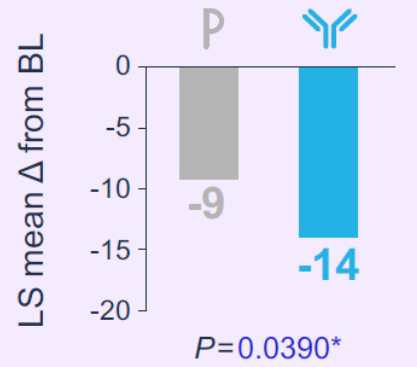


ISS7

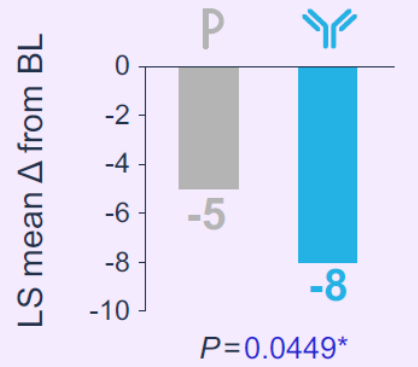


In Study A, both UAS7 and ISS7 improved significantly with dupilumab vs placebo at week 24.

UAS7



ISS7



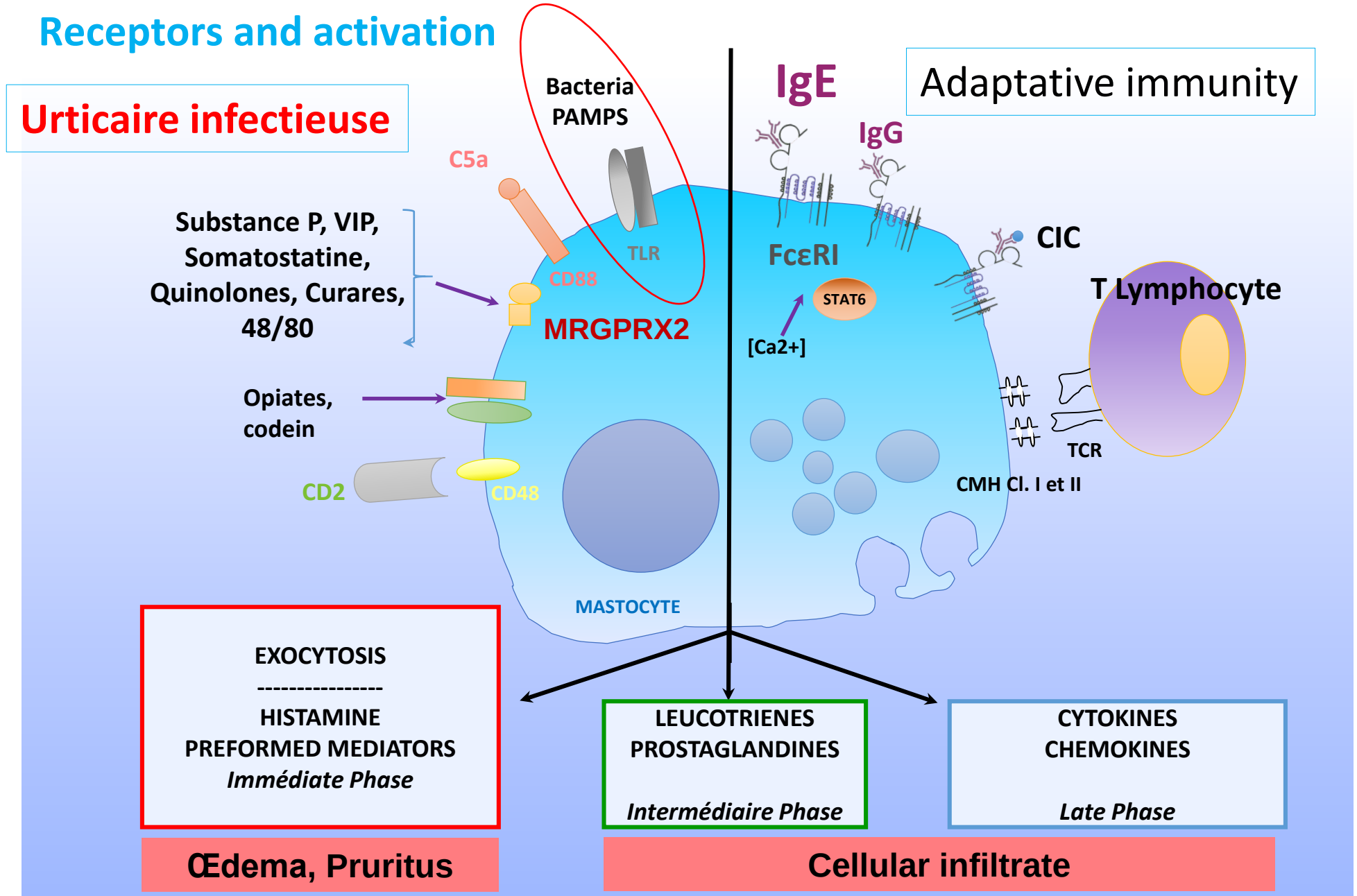
In Study B, UAS7 improved significantly (primary endpoint for EU countries), with a numerical, non-significant trend of improvement in ISS7 (primary endpoint for non-EU countries).

Maurer M et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials. J Allergy Clin Immunol 2024

MAST CELL

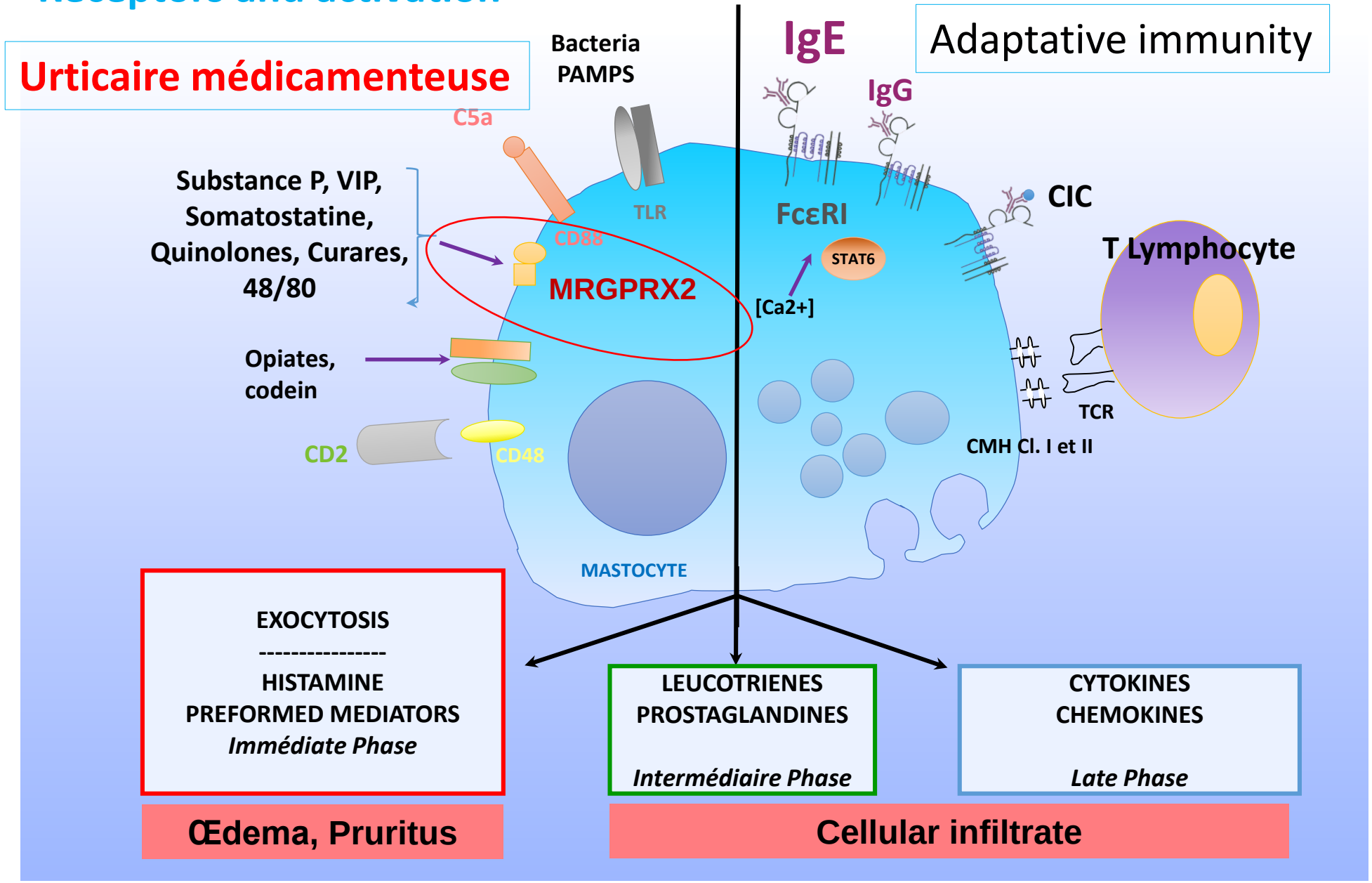
Receptors and activation

Urticaire infectieuse



MAST CELL

Receptors and activation



Plan

- Inflammation et maladies inflammatoires
- Hypersensibilités adaptatives et innées
- Classification des Hypersensibilités: Gell & Coombs
  - Type I (IgE), Type II (IgG), Type III (CIC), Type IV (lymphocytes T) (1975-2015)
  - Type I (mastocytes), Type II (IgG), Type III (CIC), Type IV (lymphocytes) (2015-2025)
- **Hypersensibilités à expression cutanée**
  - HSI: urticaire
  - **HSR: inflammation T1, T2, T3**
- Eczéma de contact allergique et inné

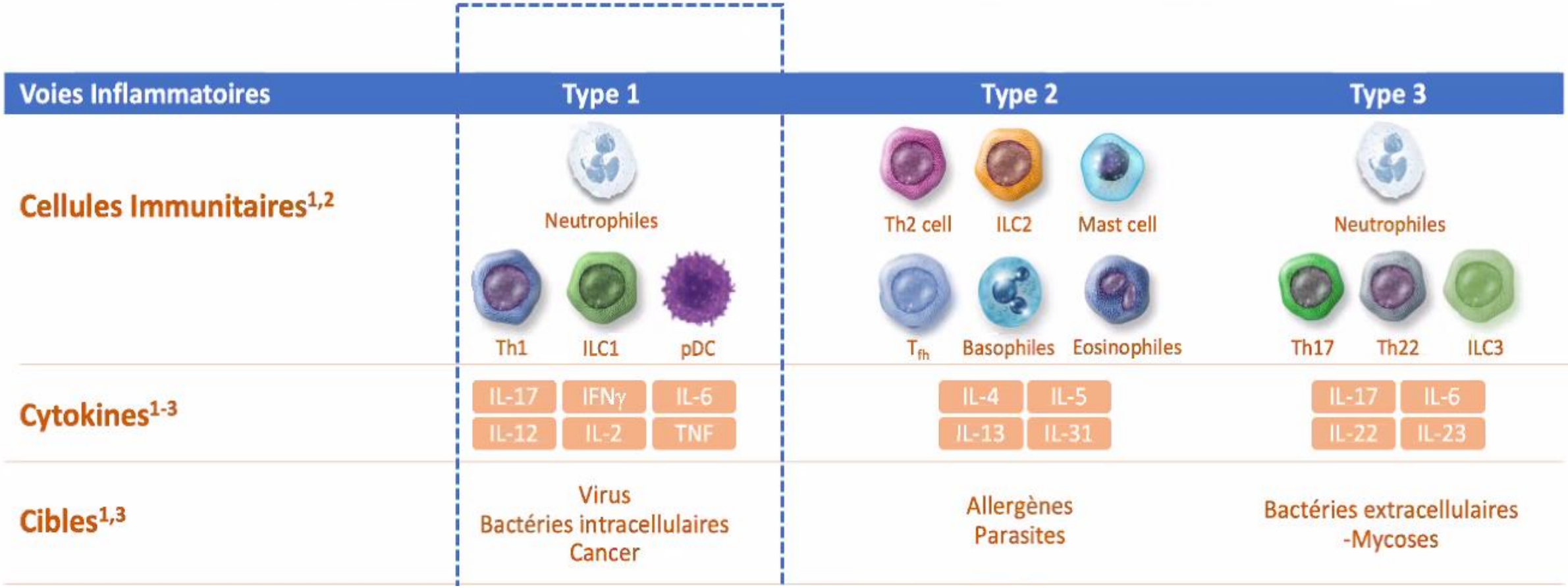
Hypersensibilités
Classification de Gell & Coombs

Antibody ← → Lymphocytes

- HS retardée
- Immunité médiation cellulaire
- Immunité lymphocytaire

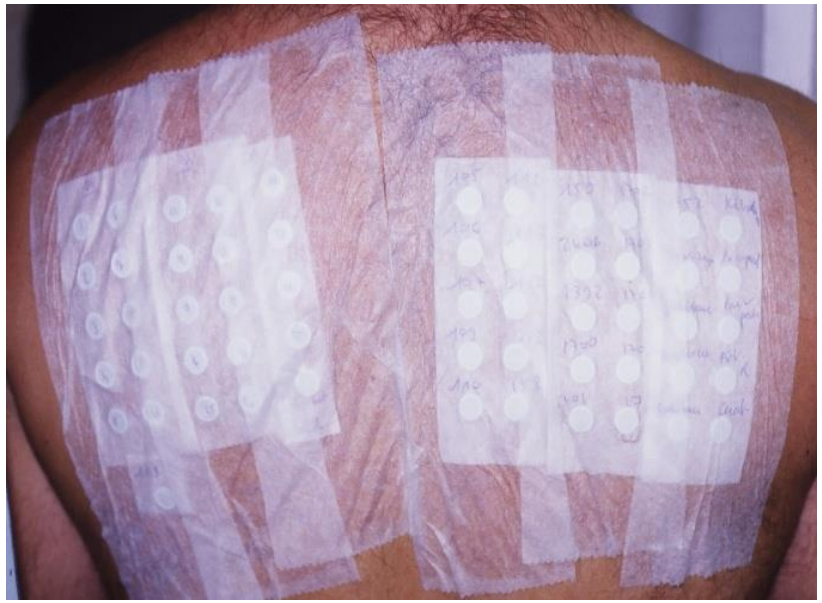
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble 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, allergiques et HS	Anaphylaxie Rhinite Asthme	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme T2 Rhinite, Conjonctivite Œsophagite eosin. Polypose NS		Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.
Dermatoses autoimmunes, allergiques et HS	Urticaire SAMa	Pemphigus Pemphigoide Urticaire chroni.	Vascularites	Vitiligo Pelade Eczéma contact	Dermatite atopique Prurigo nodulaire Urticaire chronique		Psoriasis Hydradénite S. D. Séborrhéique
Allergie et HS médicaments	Choc anaphylactique Urticaire aux médicaments	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème Lyell Stevens-Johnson	DRESS		Pustulose exanthématique aigue généralisée

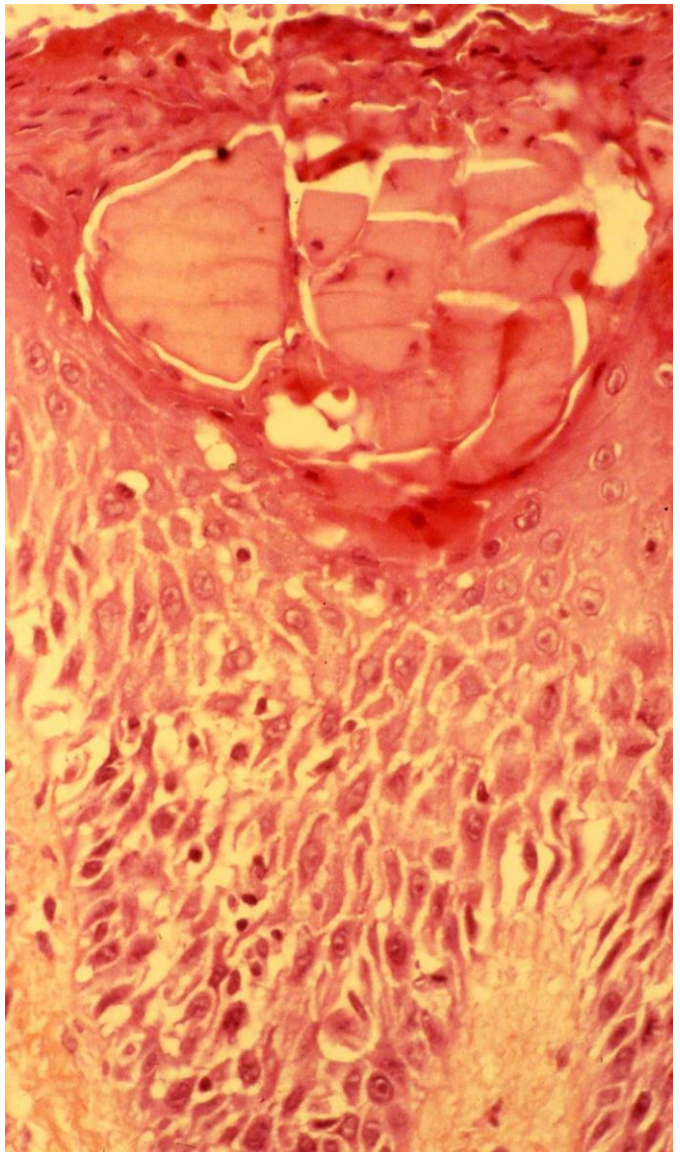
Inflammation type 1, type 2, type 3

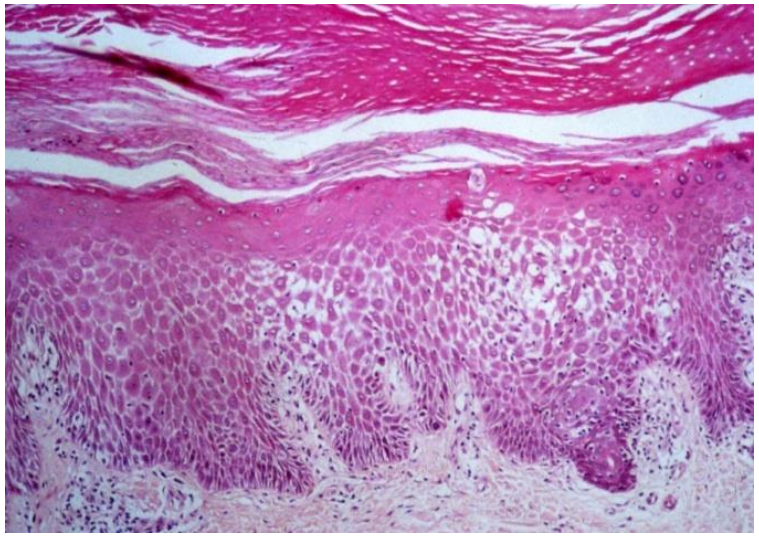


Kaiko GE, et al. *Immunology.* Eyerich K, Eyerich S. *J Eur Acad Dermatol Venereol.* Raphael I, et al. *Cytokine.* 2015 Nakayama T, et al. *Annu Rev Immunol.* 2017. Coates LC, et al. *Semin Arthritis Rheum.* 2016 Gandhi NA, et al. *Expert Rev Clin Immunol.* 2017

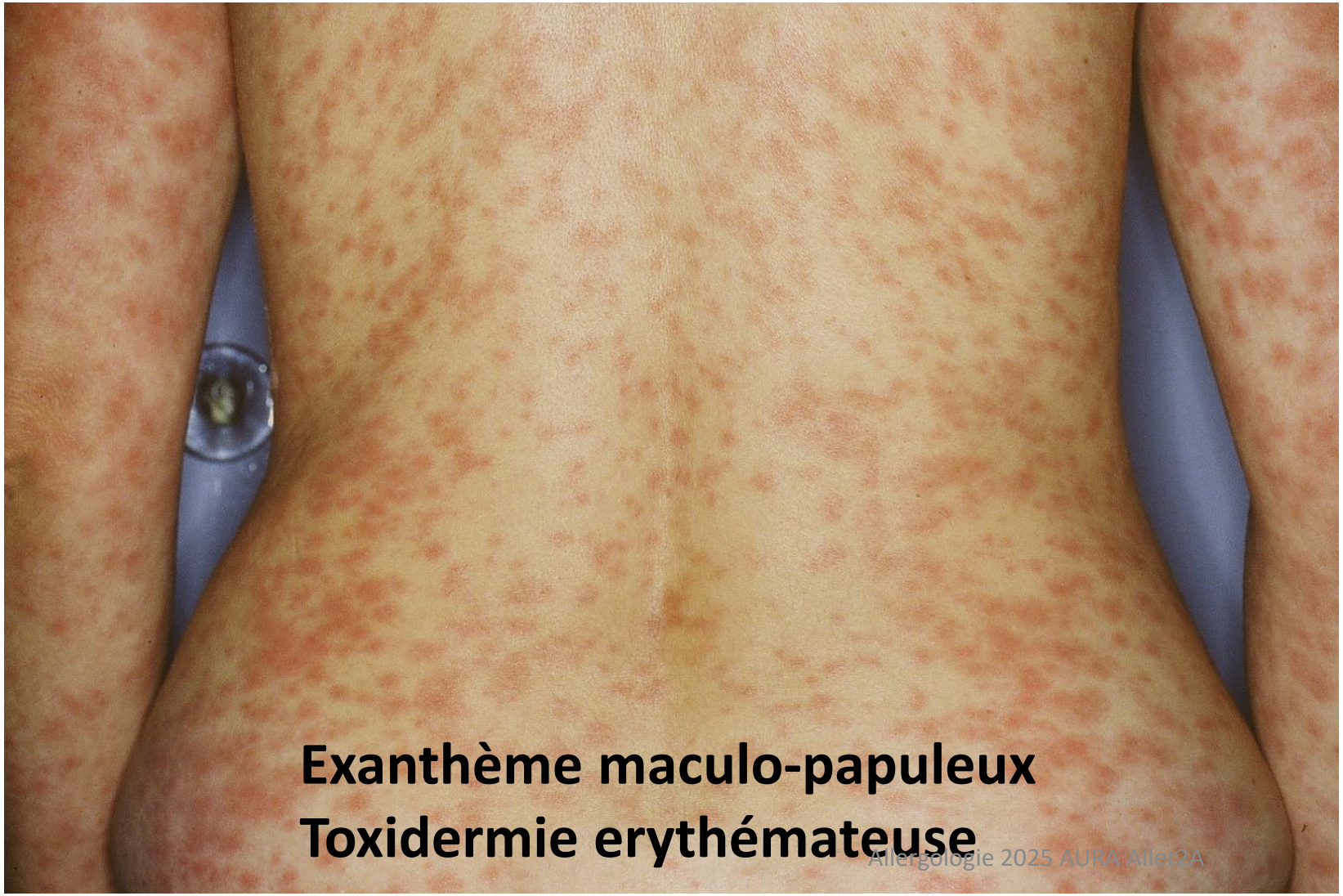
Type IV hypersensitivity - T1



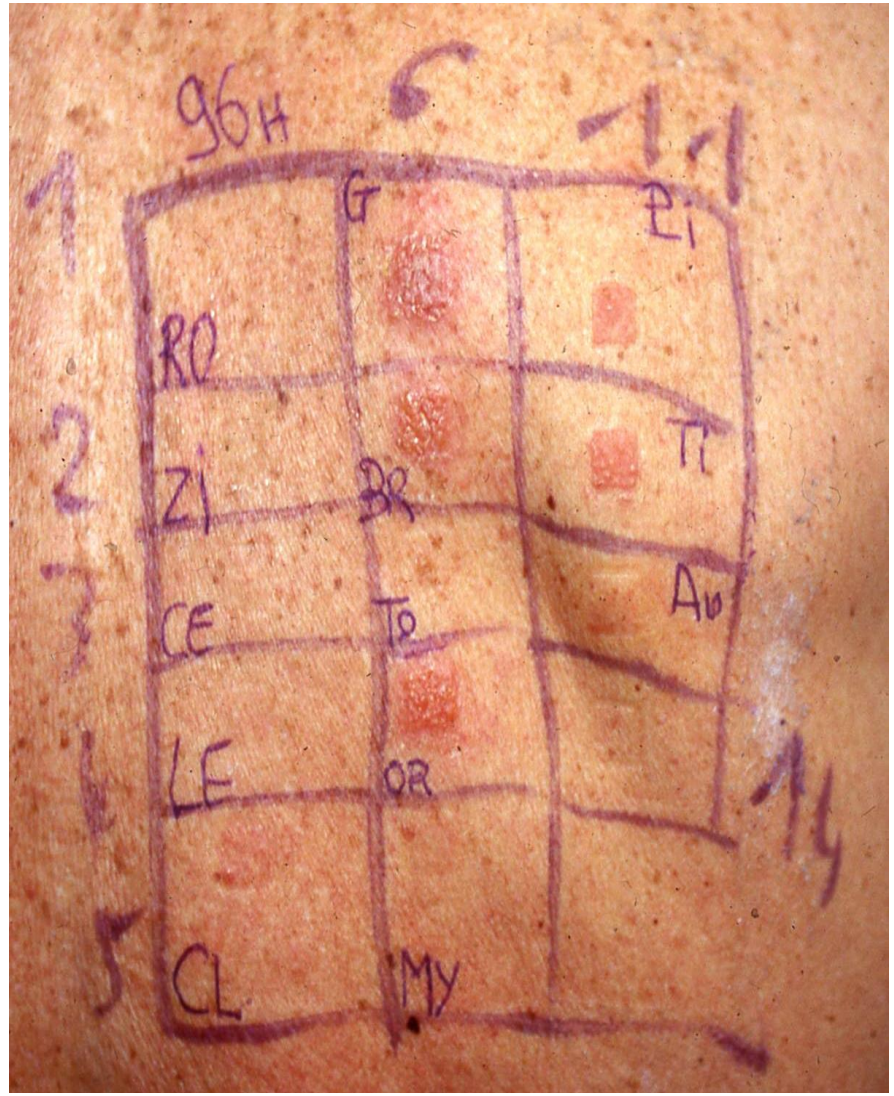




Type IV hypersensitivity - T1

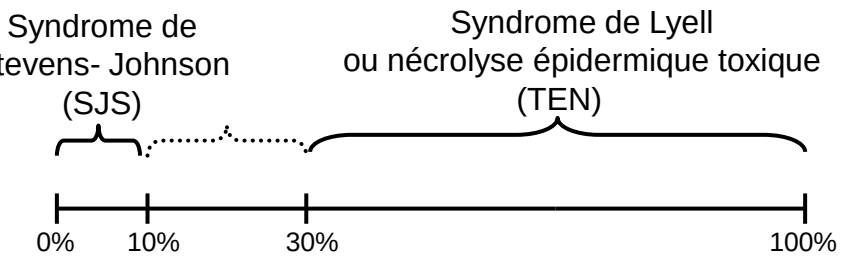


Exanthème maculo-papuleux
Toxidermie erythémateuse



Type IV hypersensitivity - T1 cytotoxic

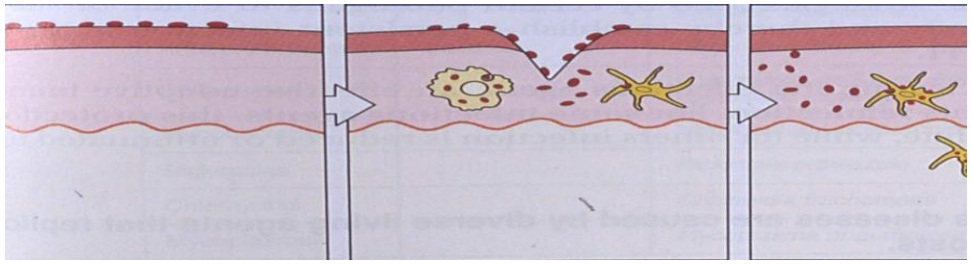
Nécrolyse épidermique toxique – Sd de Stevens-Johnson – Sd de Lyell



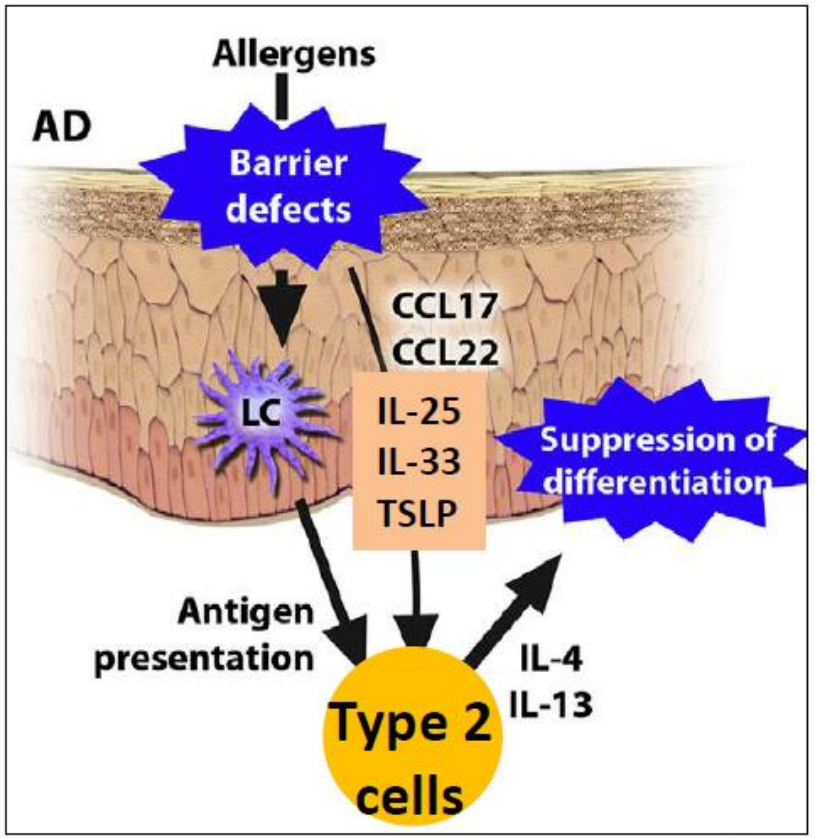
- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie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

Type IV hypersensitivity - T2
DERMATITE ATOPIQUE

Type 2



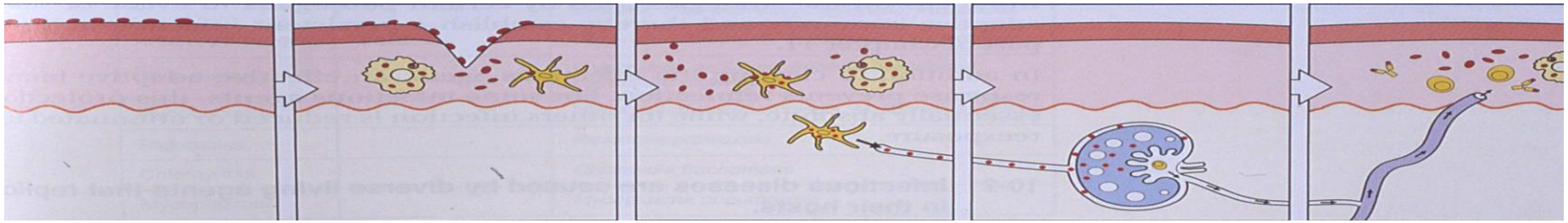
Type 2 phenotype

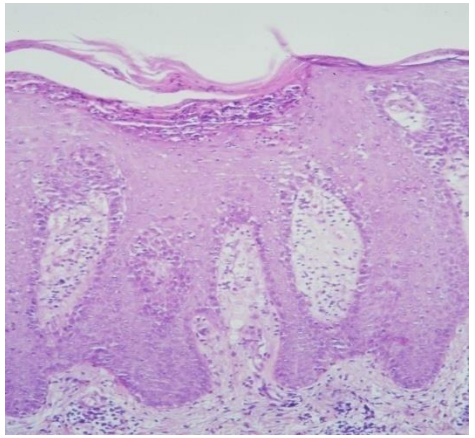


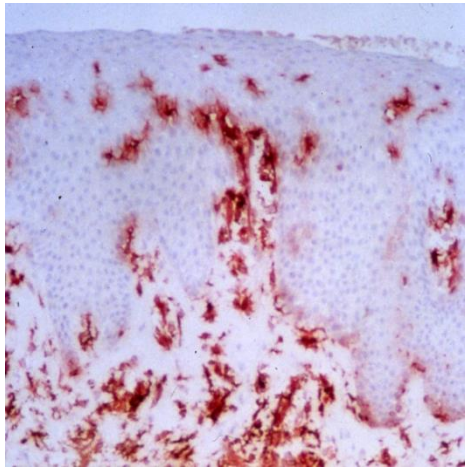
Type 2 inflammation
Type 2 immunity

Type IV hypersensitivity - T3
Psoriasis

Type 17







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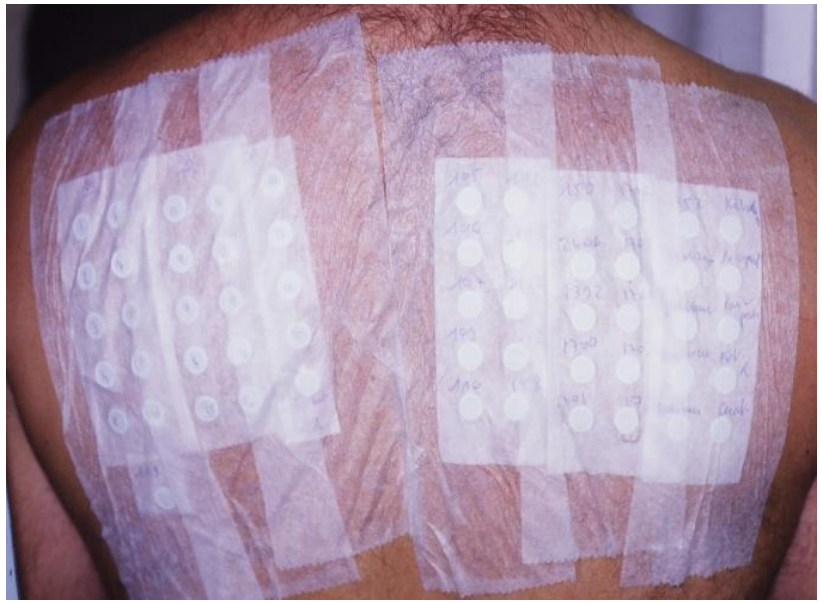
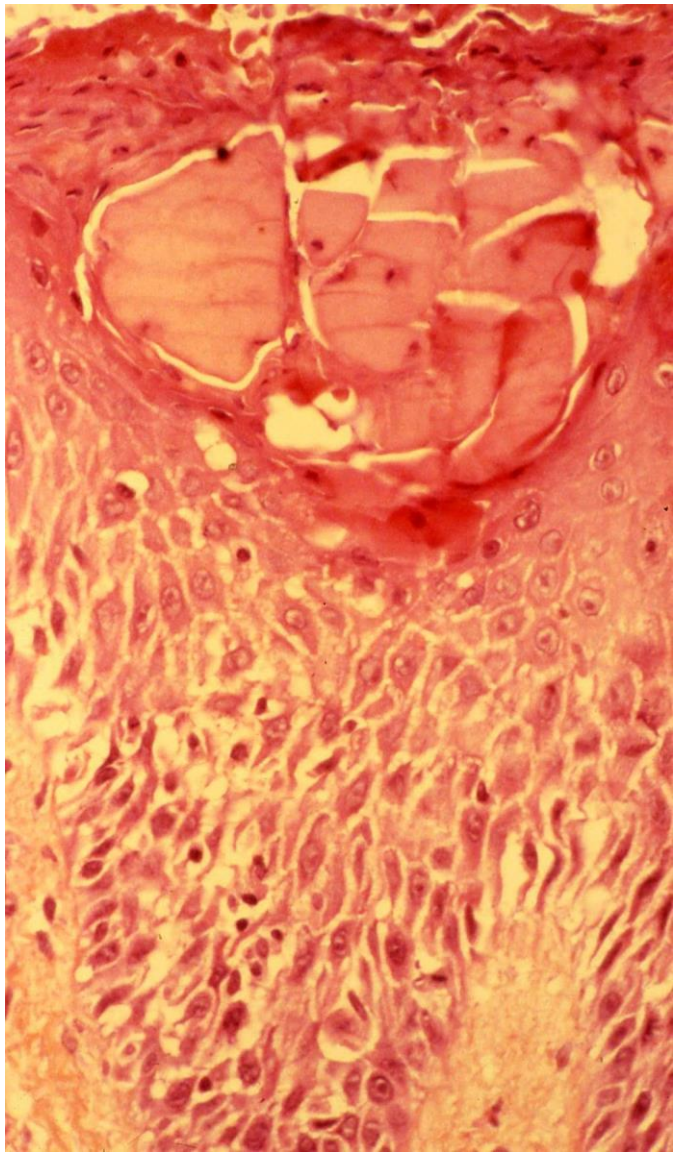
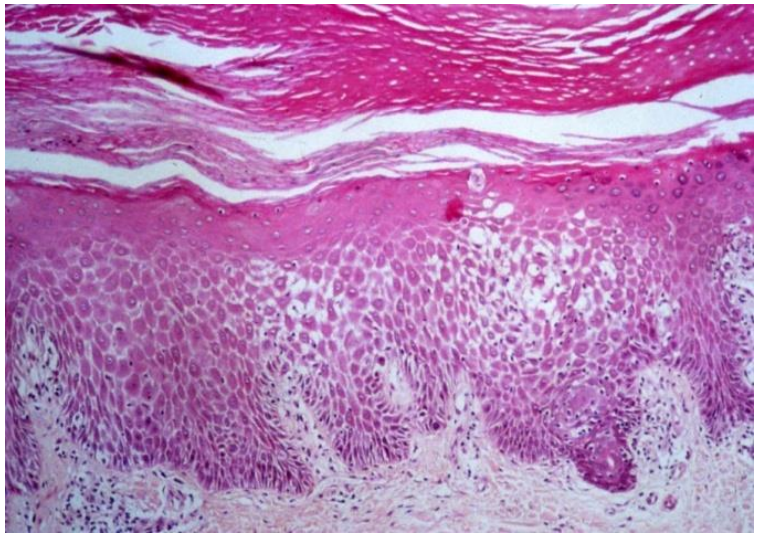
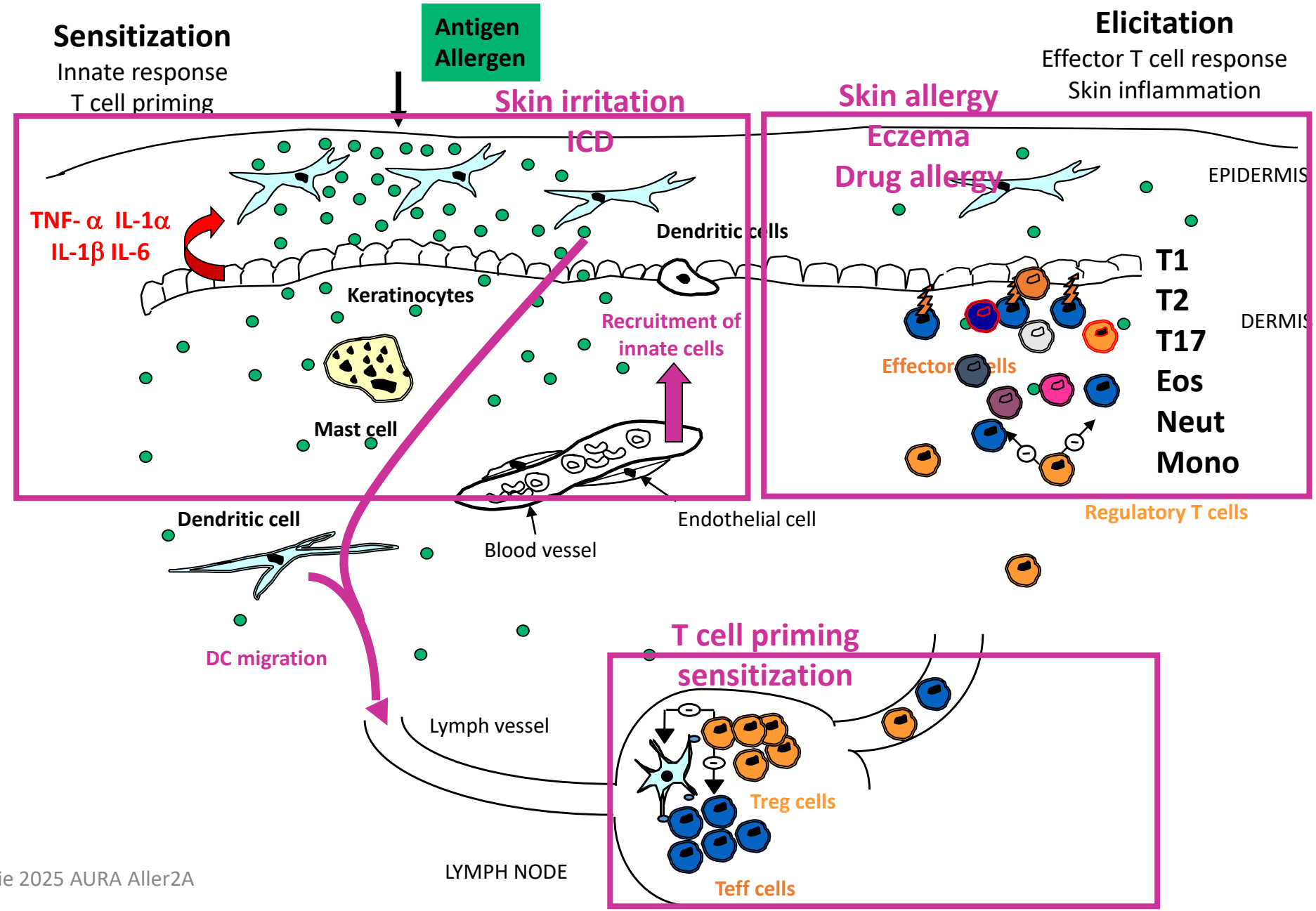
Type IV hypersensitivity - T1



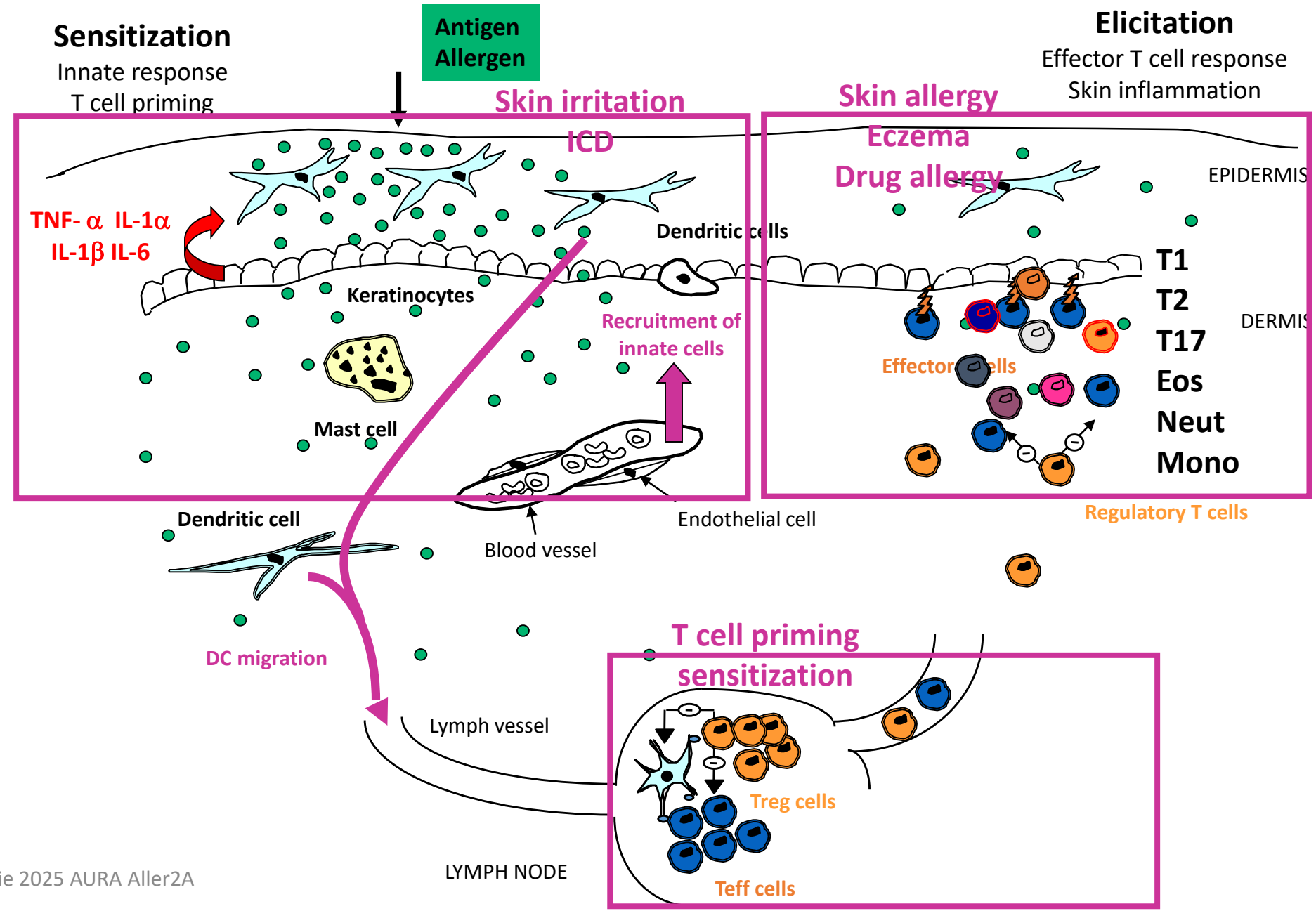




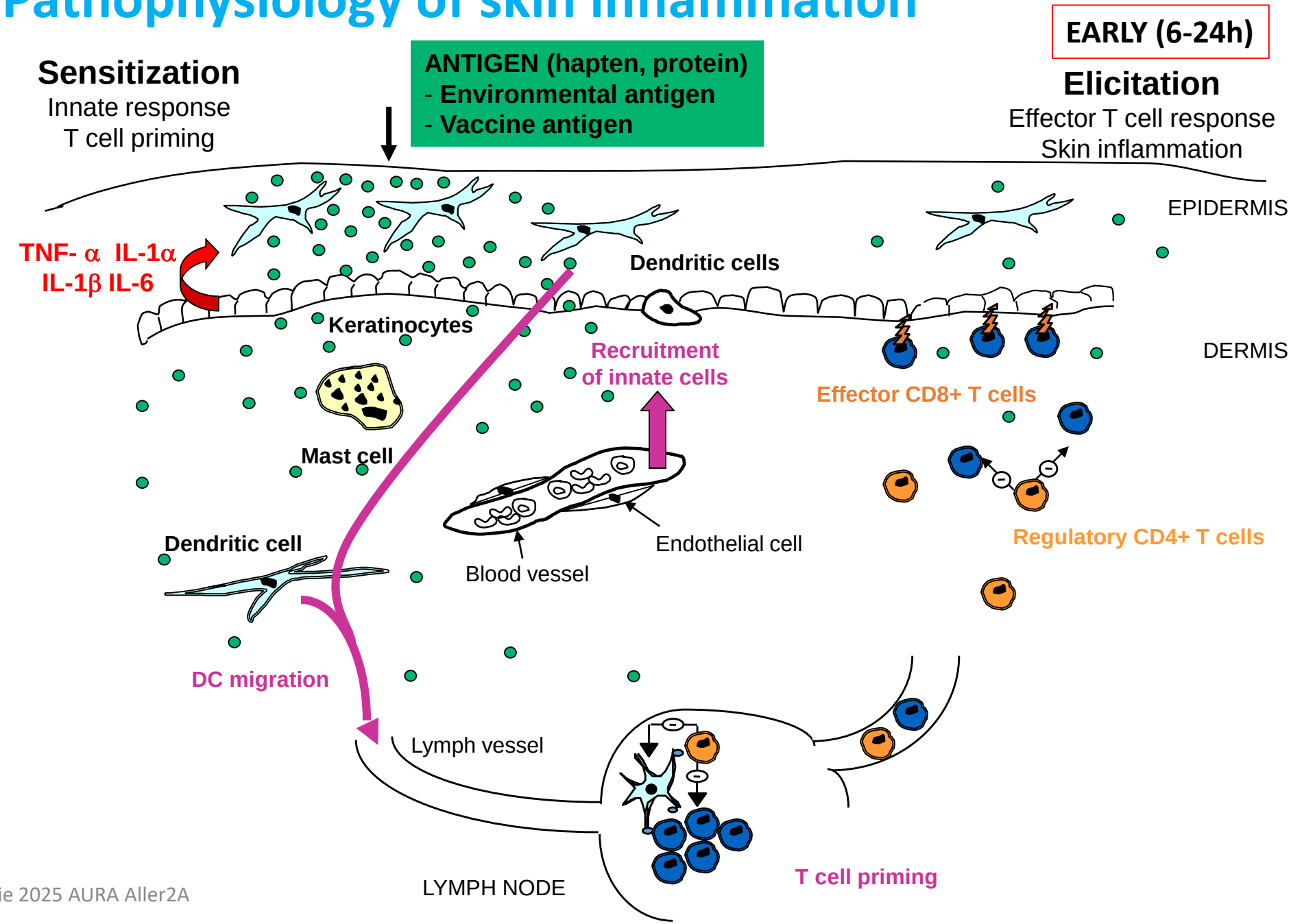
Immunology of eczemas



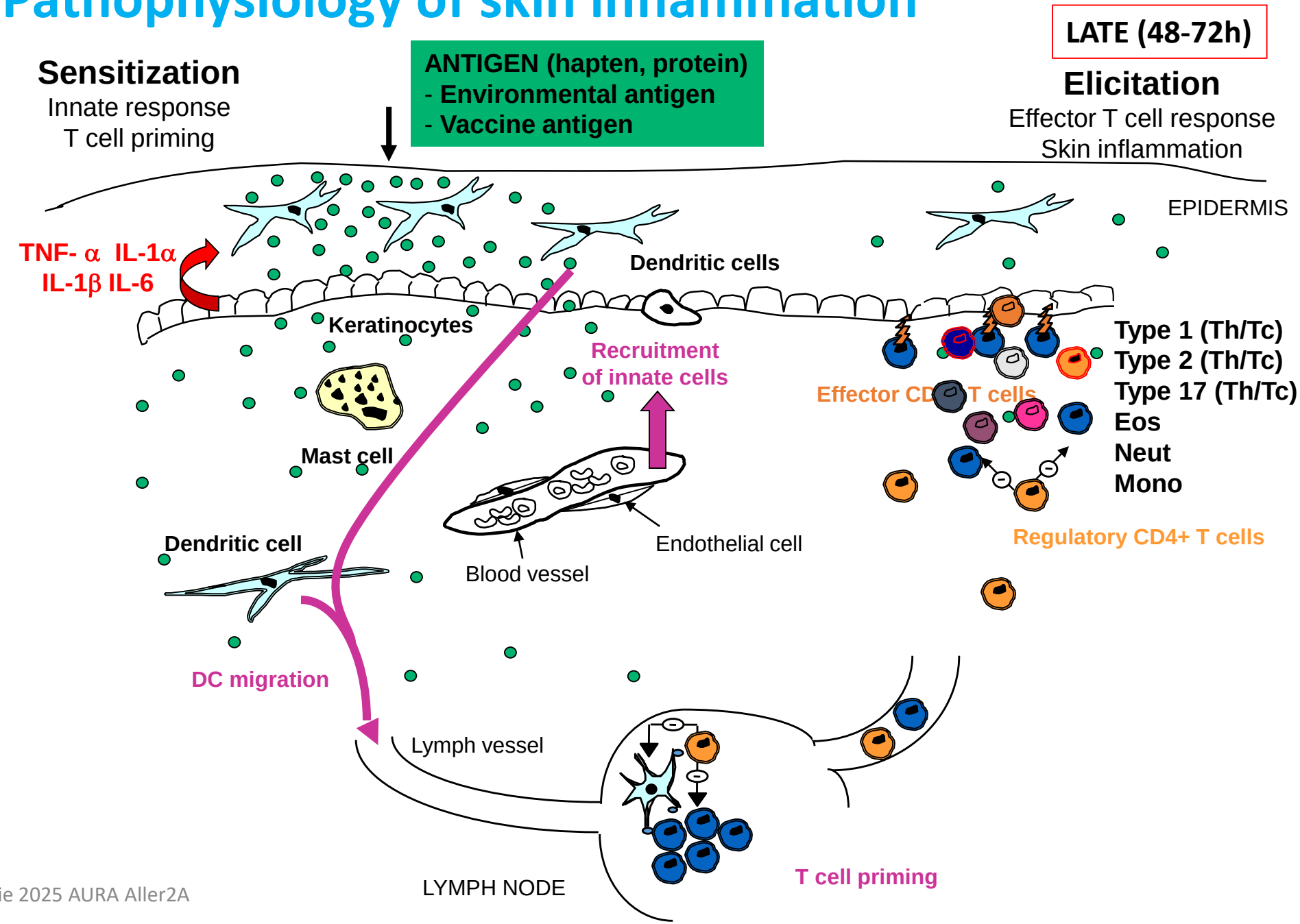
Immunology of eczemas



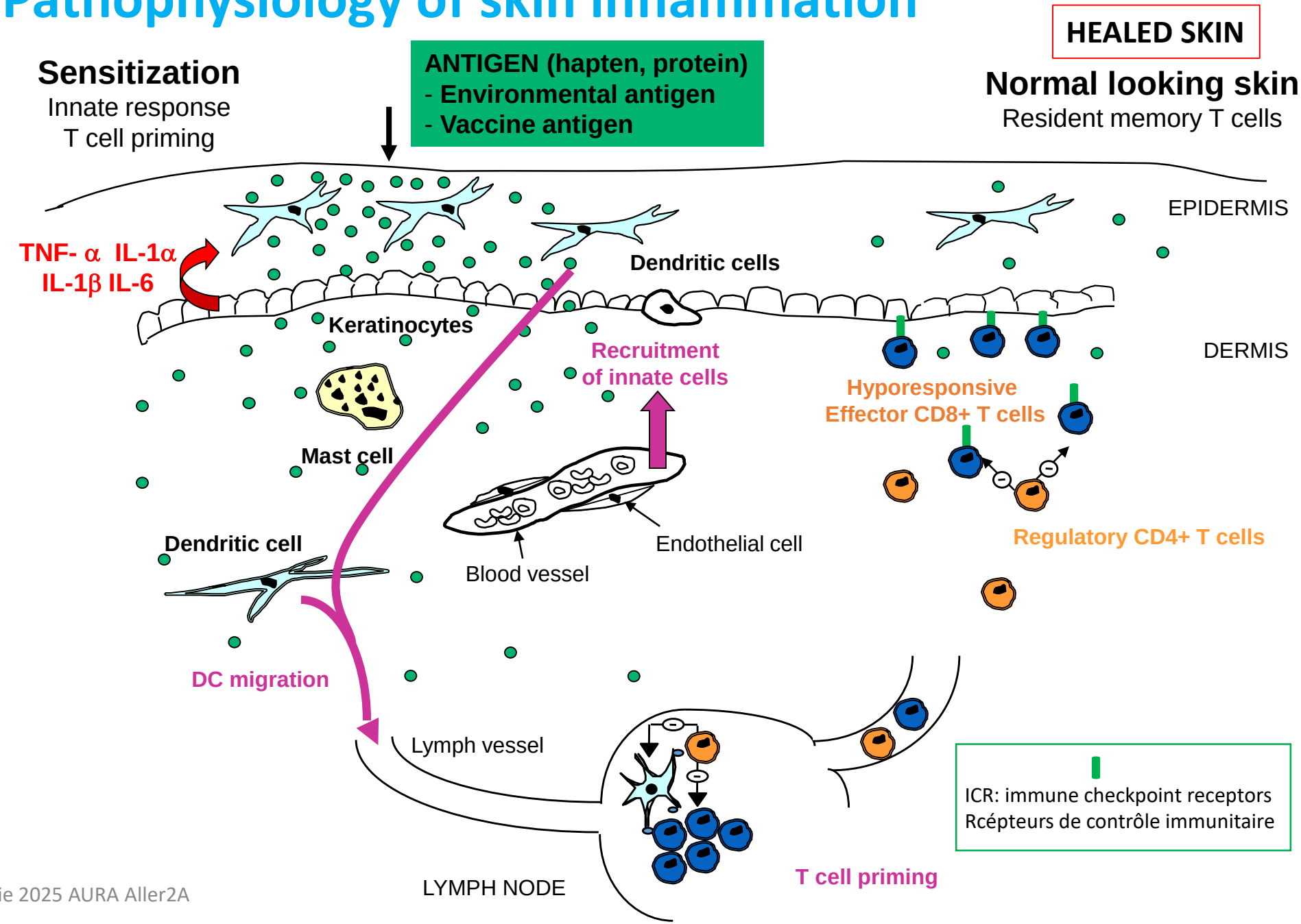
Pathophysiology of skin inflammation



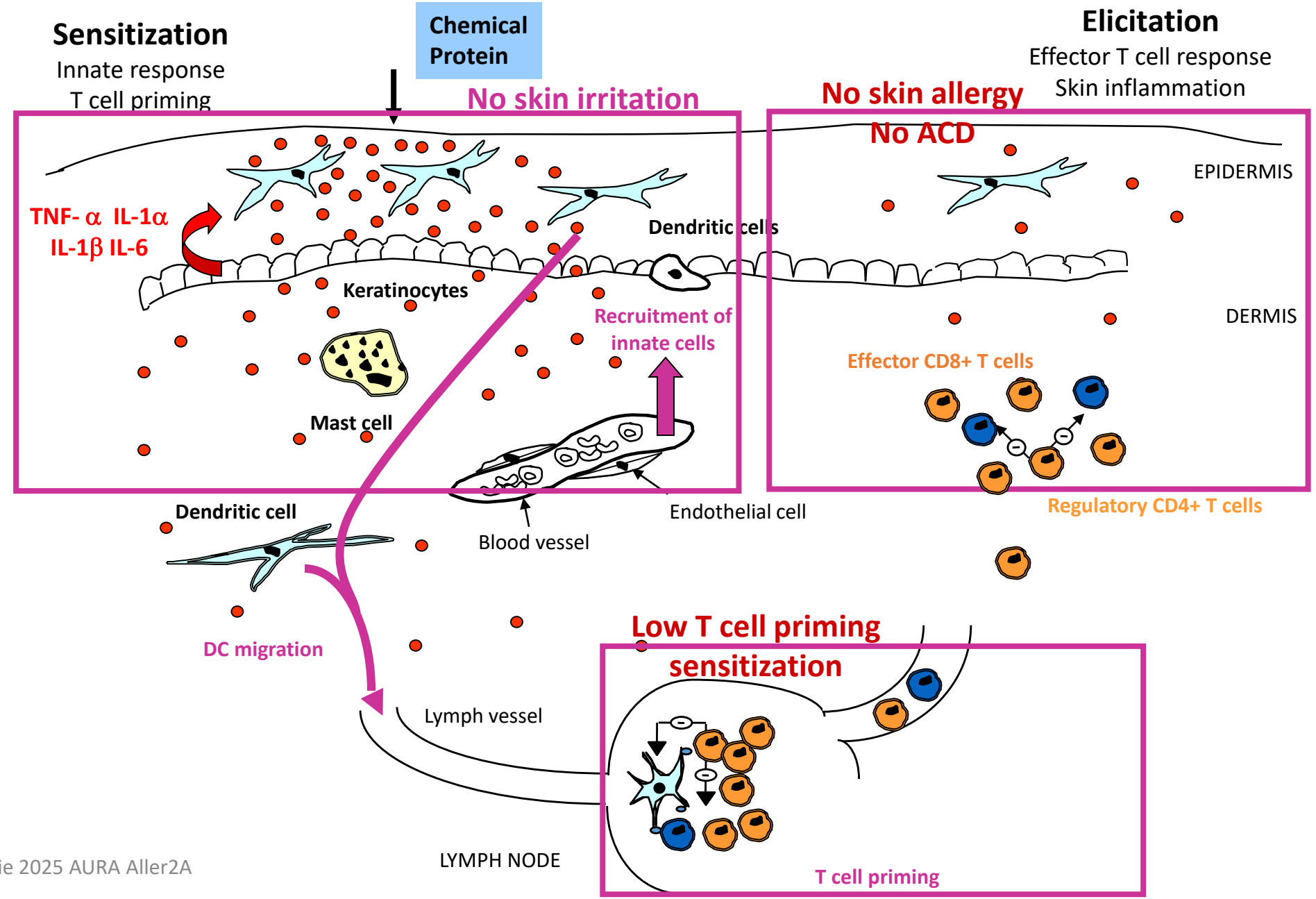
Pathophysiology of skin inflammation



Pathophysiology of skin inflammation



Non allergic individual



Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department