



**34<sup>e</sup> cours**  
d'actualisation  
en dermato-allergologie

**GERDA 2013**

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# Allergologie et Immunologie clinique Lyon-Sud / Gerland



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Unité de recherche clinique  
Lyon-Sud →



# IMMUNOLOGY OF SKIN ALLERGY / SKIN VACCINATION

## Research activities

*Pathophysiological research*

**Skin allergic diseases**



Allergic contact dermatitis (ACD)



Atopic dermatitis (AD)

**ECZEMAS**



MILD - Exanthema



SEVERE - Blistering disease

**DRUG ALLERGY**

*Translational research*

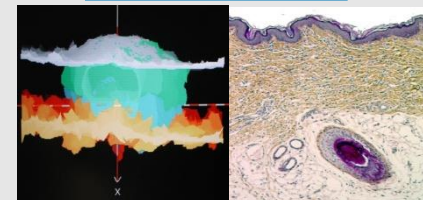
**New immunological assays**

*Diagnostic*



*Prediction of allergenicity*

**Intradermal vaccination**



# Fragrance allergy

We know very little!

1. Fragrances = allergens?
2. Some fragrances = allergens of concern?
3. Is it useful to ban allergens of concern?
4. Is it necessary to reduce the prevalence of ACD to fragrances?
5. Is it necessary to reduce the prevalence of fragrance contact allergy?
6. Fragrance contact allergy = positive patch tests could be irritation or allergy
7. Contact dermatitis to fragrance = eczema could be irritation or allergy

# Lack of evidence for allergenic properties of coumarin in a fragrance allergy mouse model

MARC VOCANSON<sup>1,2</sup>, MAGALIE VALEYRIE<sup>1</sup>, AURORE ROZIÈRES<sup>1,2</sup>, ANCA HENNINO<sup>1,2</sup>, FRANÇOIS FLOCH<sup>3</sup>,  
ARIELLE GARD<sup>3</sup> AND JEAN-FRANÇOIS NICOLAS<sup>1,2,4</sup>

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*Background:* There is controversy as to whether coumarin, an ingredient in cosmetics and fragrances, is a contact allergen involved in fragrance allergy. We recently showed that the purity of coumarin is a critical parameter for its allergenicity because coumarin preparations containing trace amounts of contaminants induced cell proliferation in the local lymph node (LN) assay whereas pure coumarin did not.

*Objective/Method:* In the present study, we analyzed the sensitizing properties of coumarin (purity > 99.9) and of dihydrocoumarin (DHC), in a recently developed model of fragrance allergy in mice.

*Results:* DHC was able to prime T cells in LNs draining the sensitization skin site and to induce a typical allergic contact dermatitis (ACD) reaction upon challenge, confirming that DHC is endowed with moderate sensitizing properties. In contrast, no T-cell activation and no ACD responses were obtained following sensitization and challenge with coumarin.

*Conclusion:* These results confirm that pure coumarin is endowed with very weak sensitizing capacities, if any, and suggest that the presence of contaminants in coumarin preparations may account for the previously reported allergenic properties of coumarin.

*Key words:* allergic contact dermatitis; coumarin; fragrance allergy; mouse ear-swelling test; murine model; T cell priming. © Blackwell Munksgaard, 2007.

*Accepted for publication 26 July 2007*

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# **The Skin Allergenic Properties of Chemicals May Depend on Contaminants – Evidence from Studies on Coumarin**

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F. Floc'h<sup>g</sup> C. Maliverney<sup>g</sup> A. Gard<sup>g</sup> J.F. Nicolas<sup>a, b, d, f</sup>

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**Table 3.** Clinical studies of the allergenicity of pure coumarin

Studies	Centers	Length of the study months	Patients	Contact dermatitis	ACD FM+ <sup>1</sup>	ACD perfume+ <sup>2</sup>	ACD atopy+ <sup>3</sup>	Coumarin+/ total <sup>4</sup>
Study 1 contact dermatitis	1	3	279 100	279 100	ND 3	ND 2	ND 12	0/279 0/100
Study 2 FM allergic	20	14	101		101	ND	22	1/101
Study 3 perfume allergic	7	12	30			30	5	0/30

ND = Not determined.

<sup>1</sup> Clinically relevant positive patch test to FM.

<sup>2</sup> Patients with a personal history of contact allergy to fragrances.

<sup>3</sup> Patients with a personal history of atopic diseases.

<sup>4</sup> Number of patients with a positive patch test to coumarin in the tested population.

**Table 4.** Frequency of positive patch test reactions to FM and coumarin over recent years in published studies on dermatological patients

Authors	Year	Patients	Positive patch test reactions, %
<i>FM</i>			
Uter et al. [27]	1992	6,700	7.4
	1996	9,600	10.3
Johansen et al. [28]	1985–1986	1,232	4.1
	1997–1998	1,267	9.9
Marks et al. [29]	1992–1994	3,509	11.4
	1994–1996	3,082	14.3
<i>Coumarin</i>			
Malten et al. [13]	1984	182	6.8
Kunkeler et al. [10]	1998	1,400	4.1
Frosch et al. [14]	2002	1,854	0.3
This study	2005	510	0.2

# ALLERGIC CONTACT DERMATITIS

## Contact Hypersensitivity

Repeated contact with skin sensitizers called haptens

### HAPTENS

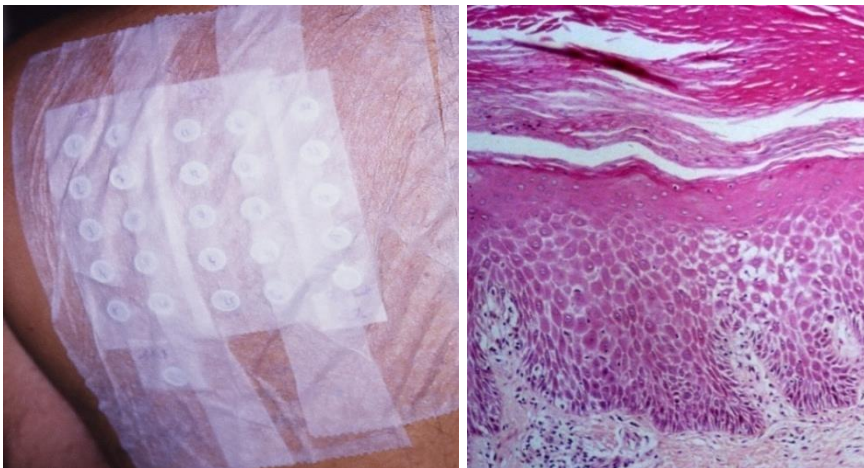
Non protein chemicals  
Interact with aminoacid residues

DNP et TNP: lysin  
Ni: histidin

- **Strong H**: DNP, TNP, oxazolone  
ACD in 90% of people

- **Weak H** : metals (Ni, Cr, Cu)  
ACD in 20% of people

- **Very weak H**: ACD in < 1%  
Professional ACD, drugs







Contact dermatitis/ eczema  
= skin inflammation

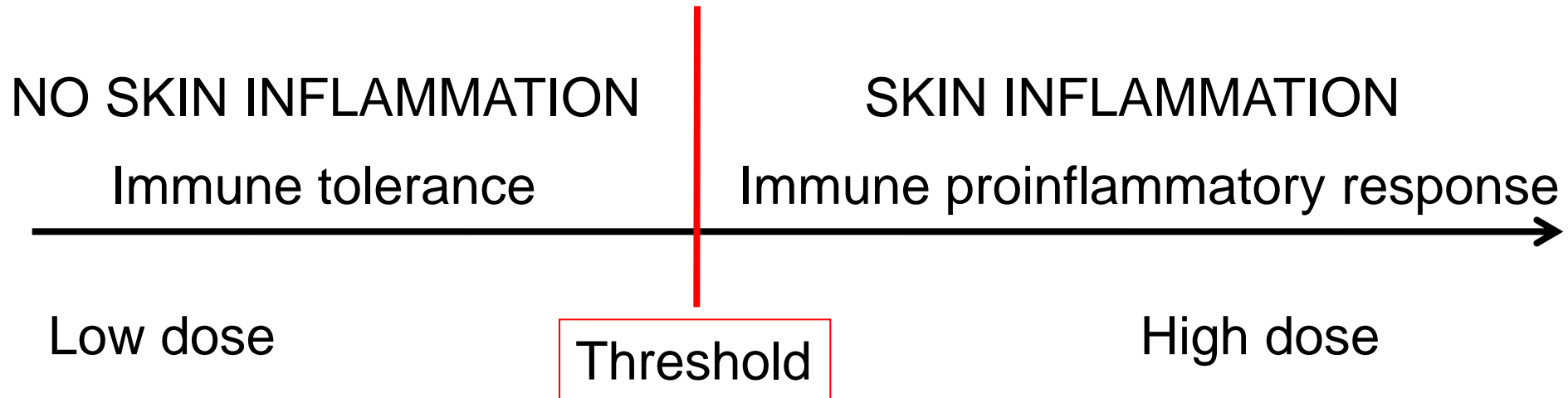
- |                                                                                                                                                                                          |                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• <b>Allergic CD</b></li> <li>• Specific T cells</li> <li>• CD8+ T cells/IFN<math>\gamma</math></li> <li>• Sensitization &amp; disease</li> </ul> | <ul style="list-style-type: none"> <li>• <b>Irritant CD</b></li> <li>• No specific T cells</li> <li>• No CD8+ T cells/IFN<math>\gamma</math></li> <li>• No sensitization</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



Pos patch test = Skin inflammation

- |                                                                                                                                                                                                                          |                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• <b>True +</b></li> <li>• Contact allergy = allergy to patch test</li> <li>• Specific T cells</li> <li>• CD8+ T cells/IFN<math>\gamma</math></li> <li>• Sensitization</li> </ul> | <ul style="list-style-type: none"> <li>• <b>False +</b></li> <li>• Contact irritation</li> <li>• No specific T cells</li> <li>• No CD8+ T cells/IFN<math>\gamma</math></li> <li>• No sensitization</li> </ul> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

# Take home messages



# Scoring (ICDRG)



Négative



IR irritative



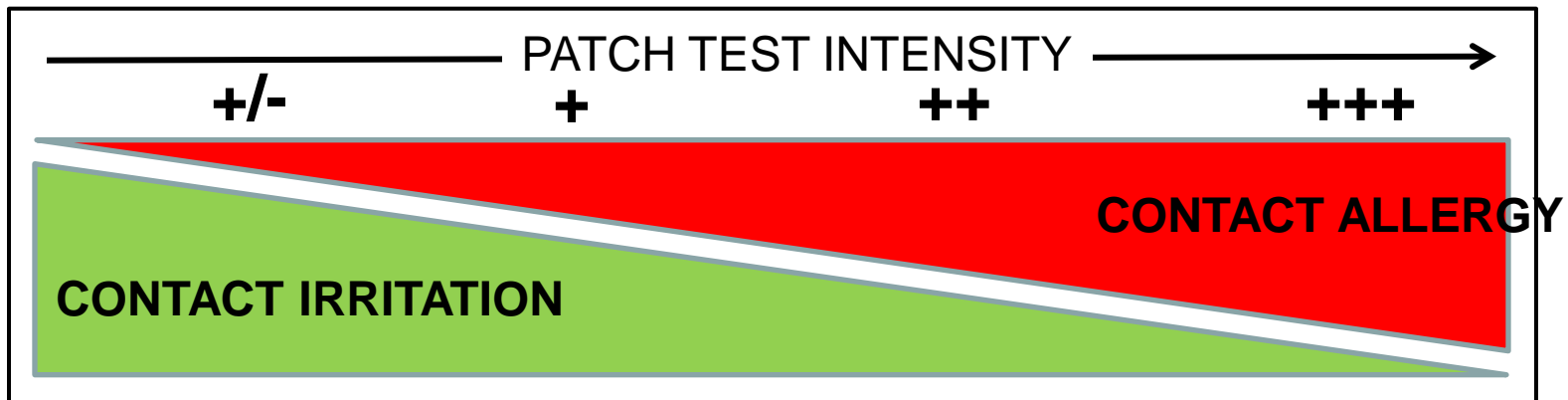
Positive +



Positive ++



Positive +++



# Fragrance Allergy

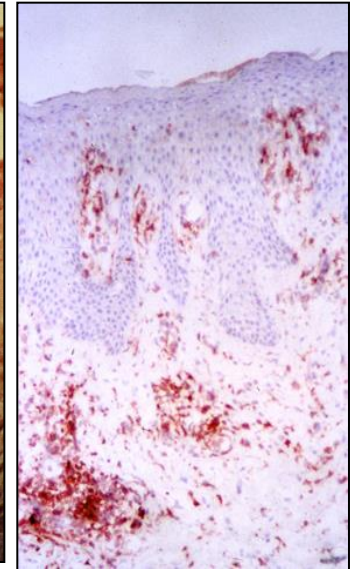
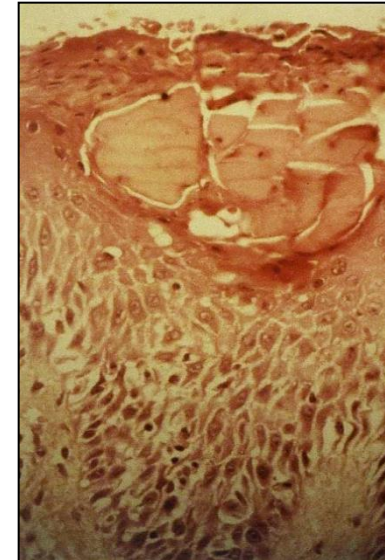
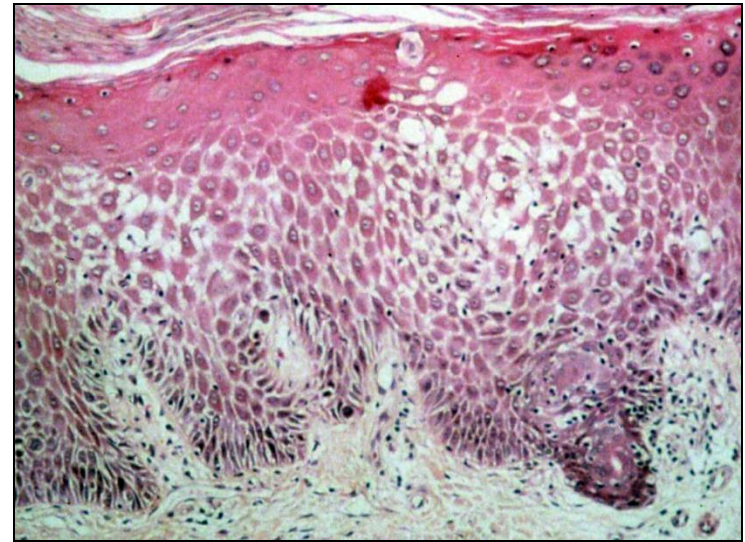
Contact allergy, allergic contact dermatitis or irritant contact dermatitis ?

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- Exposure to allergens promotes tolerance

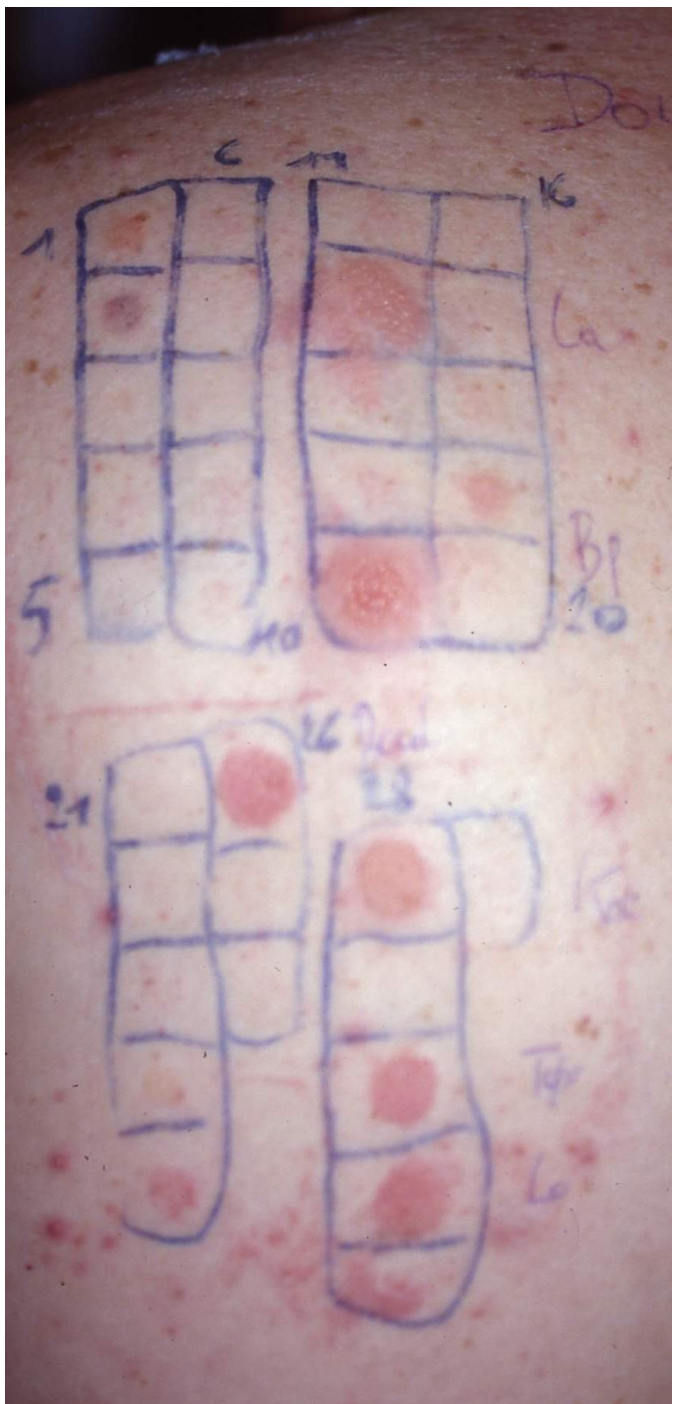
# SKIN INFLAMMATION ALLERGY OR IRRITATION ?

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- Exposure to allergens promotes tolerance

# Irritant versus Allergic Contact Dermatitis







## How to differentiate irritation from allergy?

- 10 positive patch tests
- Are there irritant or allergic ?
- Are true positive tests relevant ?

## By demonstrating the existence of an allergic reaction

### 1. Modify the patch testing protocol

- Patch-test applied for 24 hrs (12 hrs)
- Reading at 48/72 hrs

### 2. Characterize the skin DTH reaction: biopsy

- T cell infiltration
- T cell activation

### 3. Characterize circulating specific T cells

- LTT
- Elispot



## Strong and weak haptens

Nom	Source	Pouvoir sensibilisant
2,4-Dinitrochlorobenzène	Chimie	Fort
2,4-Dinitrofluorobenzène	Chimie	Strong/Fort
2,4-Dinitroiodobenzène	Chimie	Fort
Disperses Blue 124 ou 106	Textile (Colorants)	Faible
Dichromate de potassium	Bâtiment (ciment)	Modéré
Sulfate de nickel	Bâtiment, Bijoux fantaisie	Modéré
Formaldéhyde	Cosmétique, Textiles, Désinfectant	Faible
Glutaraldéhyde	Conservateur, Antiseptique	Faible
p- Phénylénédiamine	Cosmétique (colorant capillaire)	Faible
Eugénol	Cosmétique, Antiseptique	Weak/Faible
Hexylcinnamique aldéhyde	Cosmétique (parfum)	Weak/Faible
Hydroxycitronellal	Cosmétique (parfum)	Weak/Faible
Amoxicilline, Cyanamide, Cetrimide...	Médicament	Weak/Faible

# DRUG ALLERGY - INTRODUCTION



Mortality

Prevalence

- TEN: Toxic Epidermal Necrolysis
- DRESS: Drug Rash with Eosinophilia and Systemic symptoms
- AGEP: Acute Generalized Exanthematous Pustulosis
- FDE: Fixed Drug Eruption
- Erythema multiform
- Others severe reactions



**Drug allergy – DTH reactions or not ?  
What is the offending drug ?**

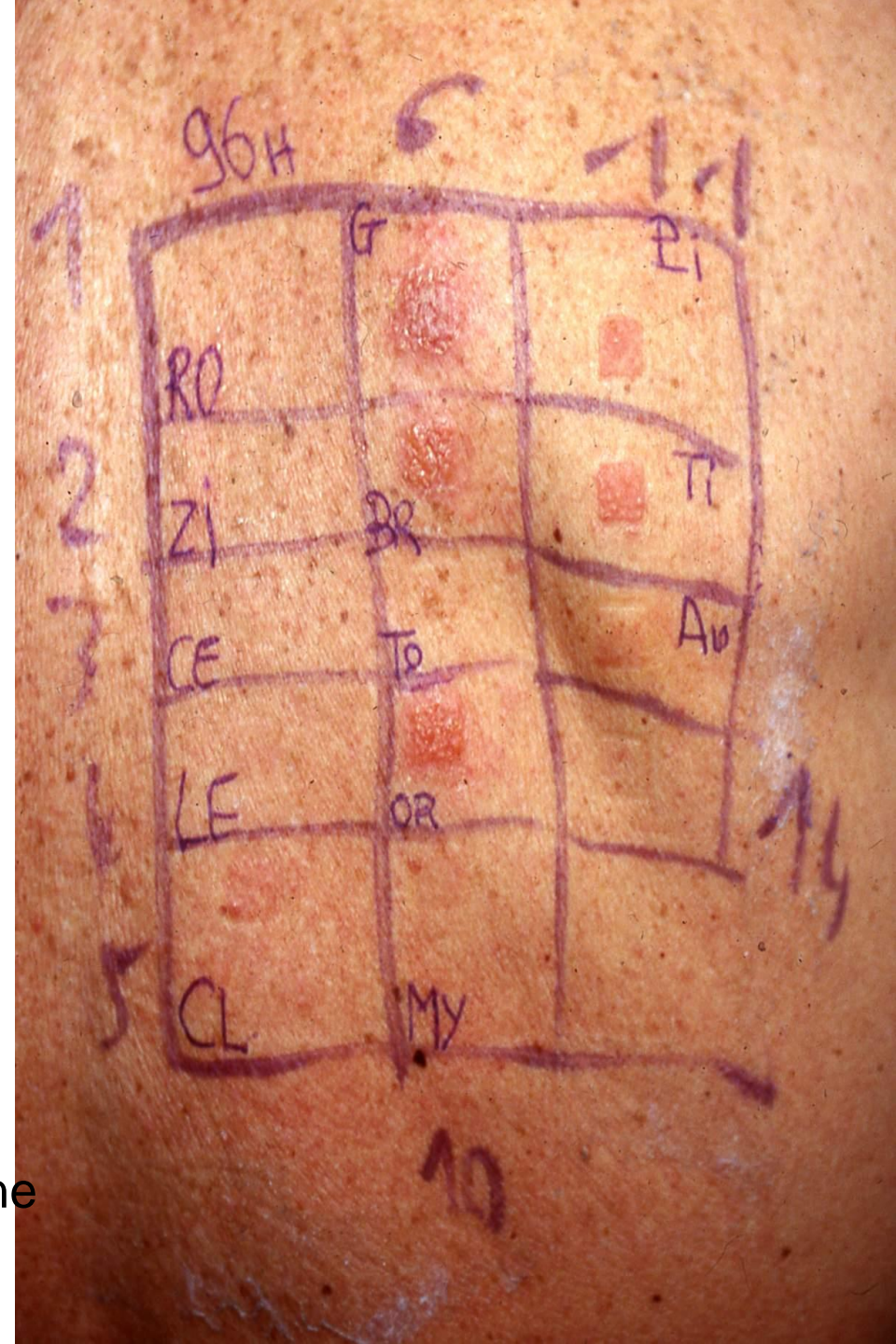


# Maculo-papular exanthema Clamoxyl (peni A)



MPE after clamoxyl + ibuprofene  
replaced by sulfamethoxazole +  
tenoxicam





MPE to peni M (Bristopen) + Oropivalone + ketoprofene + paracetamol

# FIRST PATCH TESTING – Allergic and irritant positive patch tests

Mr V.

Drug-induced maculo-papular exanthema

January 2004 – 5 days after a prostatectomy + GA

1st testing (patch removal 72h):

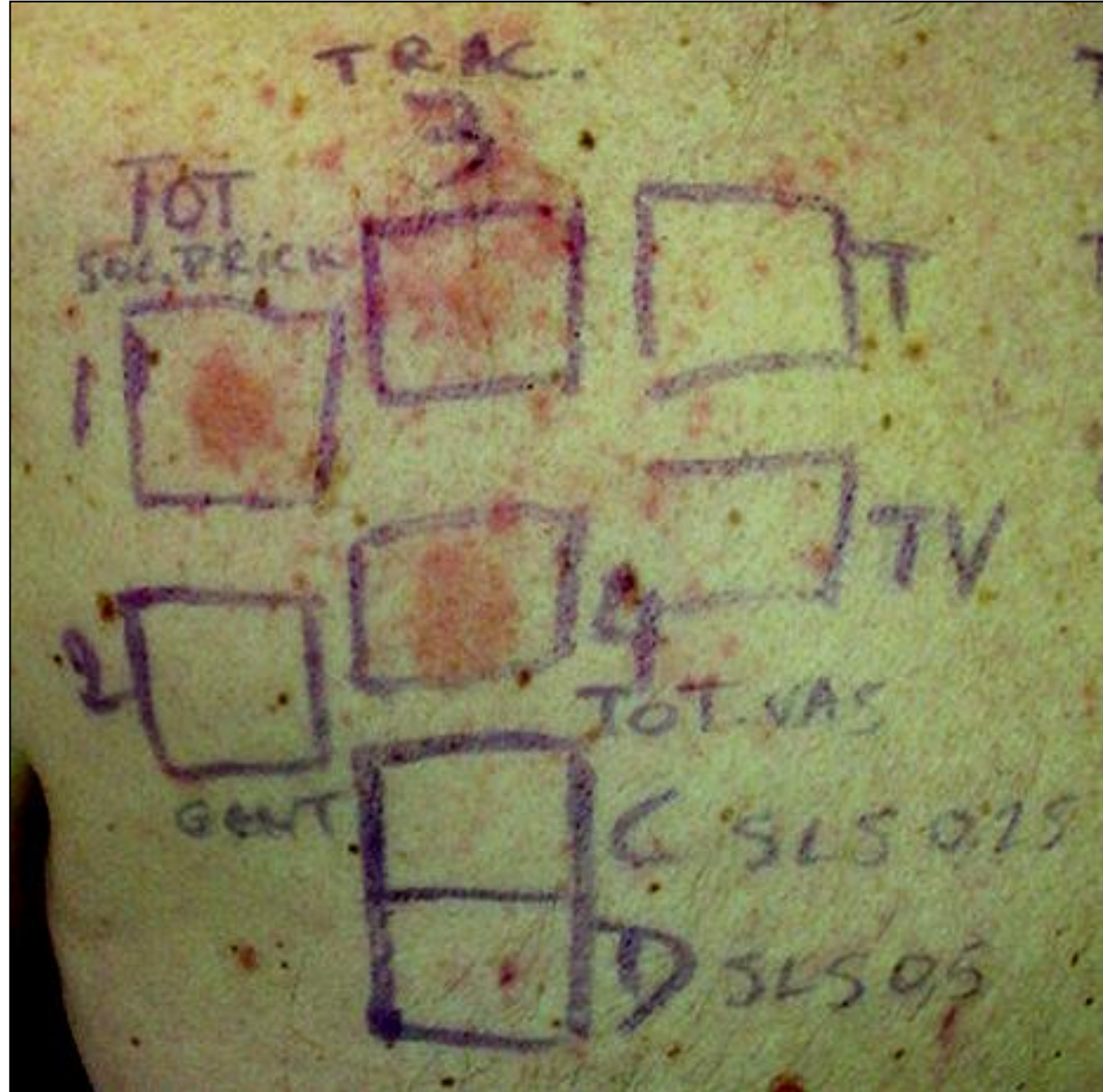
Tracrium +  
Ampicillin (IV solution + petrolatum)  
Gentamycin +  
SLS 0,5 et 0,25+

- Several positive patch tests
- Irritation control (SLS) positive
- No conclusion



# SECOND PATCH TESTING – Early removal of patch tests decreases the irritation properties of chemicals

## FIRST PATCH TESTING



Patch removal at 12 hours

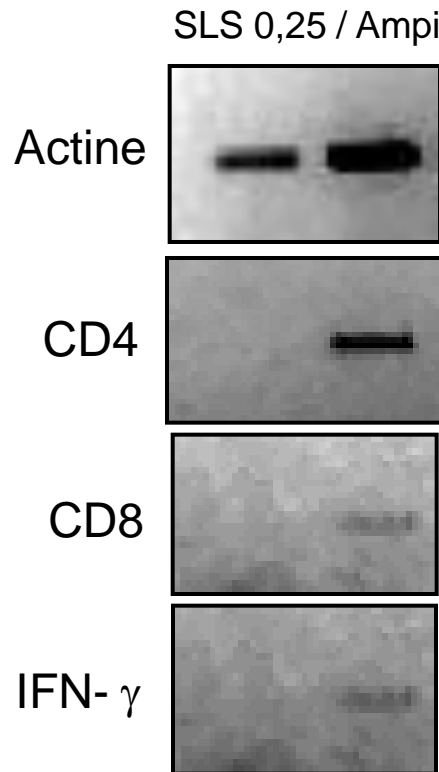
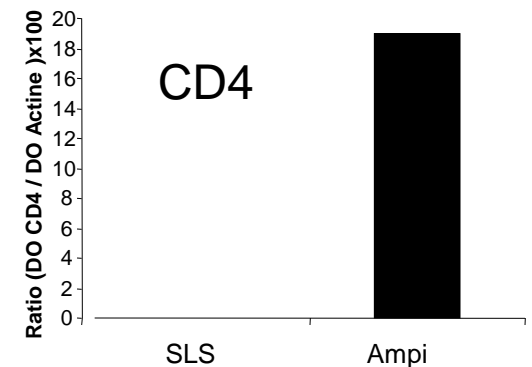
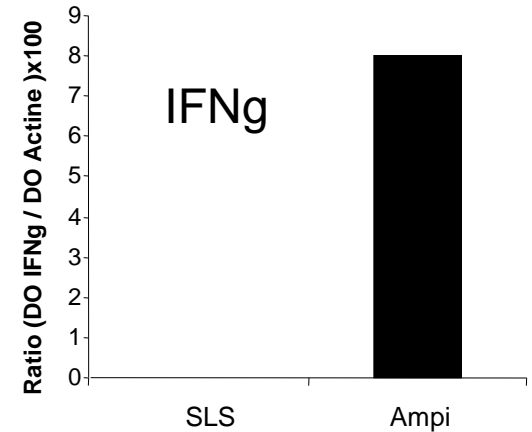
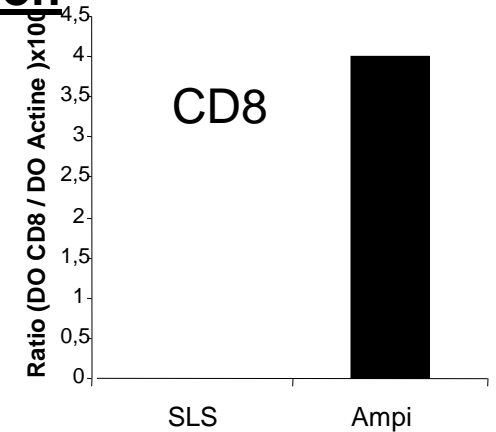
- Ampicillin solution ++
- Ampicillin petrolatum ++
- Tacrium patch: -
- Gentamycin patch: -
- SLS 0.25:-
- SLS 0.5:-

# SKIN BIOPSIES – Presence of T cells infiltrating the patch tests

## RT-PCR analysis of T cell infiltration and T cell activation

Skin Biopsies (4mm diameter). Deep frozen  
RNA extraction  
Probes for CD4, CD8 and IFN $\gamma$  (cDNA)  
Semi-quantitative RT-PCR

**Results: T cell infiltration/activation found only in ampicillin positive patch test**

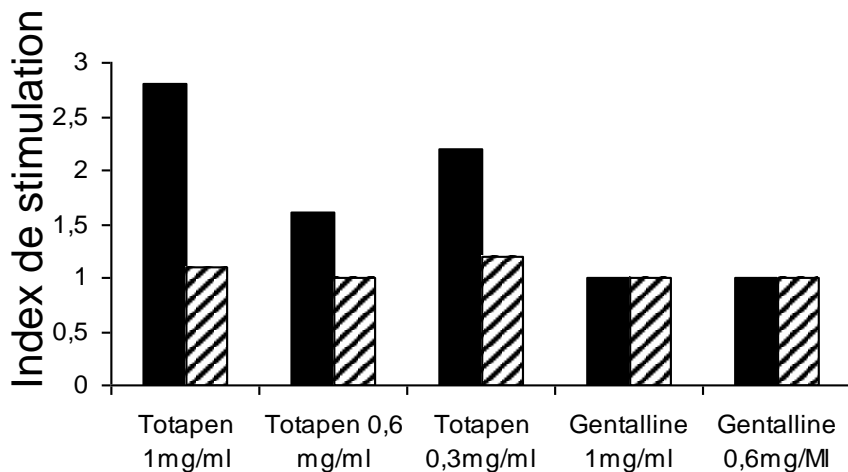




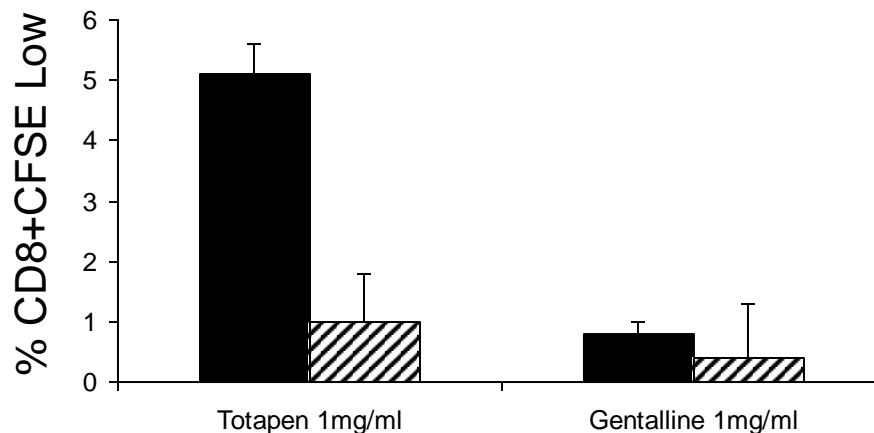
# BLOOD - Presence of hapten-specific T cells

## Detection and enumeration of hapten-specific T cells in blood

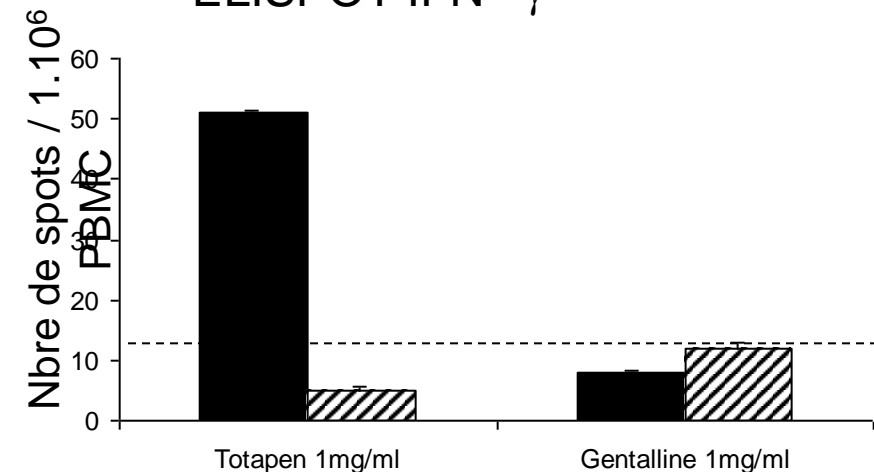
### LTT:



### CFSE



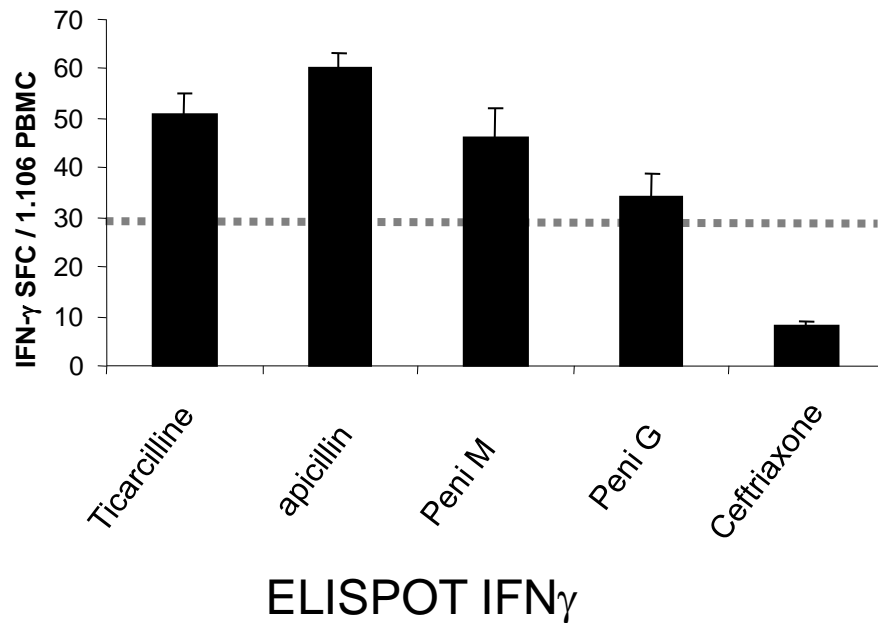
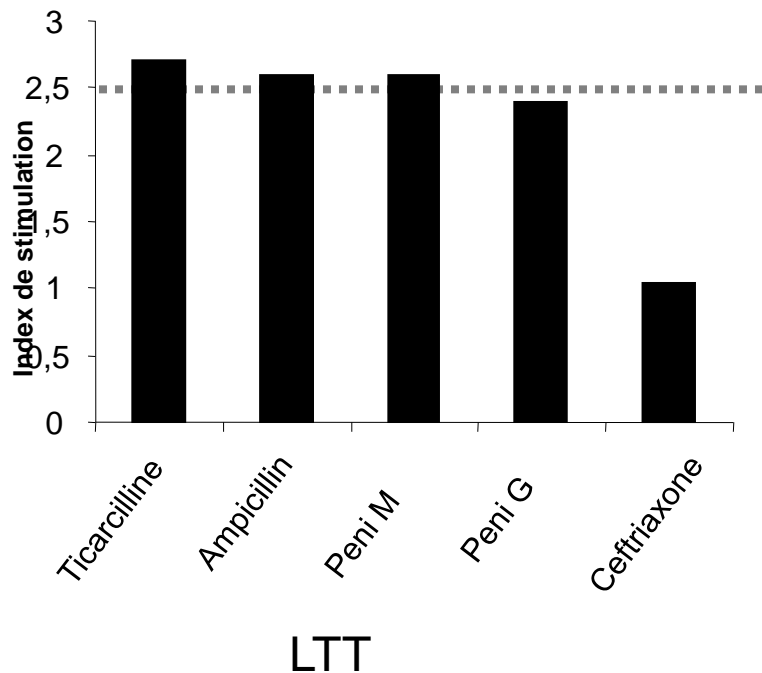
### ELISPOT IFN- $\gamma$



- LTT positive ampicillin SI=2,8 /
- CD8+CFSE low ampicillin 5,1%
- ELISPOT positive ampicillin 52 spots /  $1.10^6$  PBMC
- Tests negative for gentamycin

**CONCLUSION: presence of ampicillin-specific T cells in blood**

# BLOOD – Characterization of T cell cross-reactivities to different but related chemicals



⇒ **Cross-reactivity between ticarcillin, peni A, peni M, peni G:**  
**These antibiotics are contra-indicated**

⇒ **No cross-reactivity with ceftriaxon (Rocephine®)**

# ALLERGIC CONTACT DERMATITIS

## Contact Hypersensitivity



Question 1: IS THIS AN ECZEMA/DERMATITIS ?

Question 2: IS THIS A CONTACT DERMATITIS ?

Question 2: IS THIS AN ALLERGIC CD ?

# ALLERGIC CONTACT DERMATITIS

## Contact Hypersensitivity



**Question 1: irritation (false +)  
or allergy (real +) ?**

- irritation: non-specific inflammation
- allergy: specific, T cell-mediated, inflammation

**Question 2: Is the real + test  
clinically relevant ?**

- sensitization, DTH, chemical- specific T cells
- allergy to patch test
- patch testing is a maximization test and real+ patch means the existence of specific T cells
- real + patch test does not mean that these T cells could be activated in normal conditions of exposure to the chemical



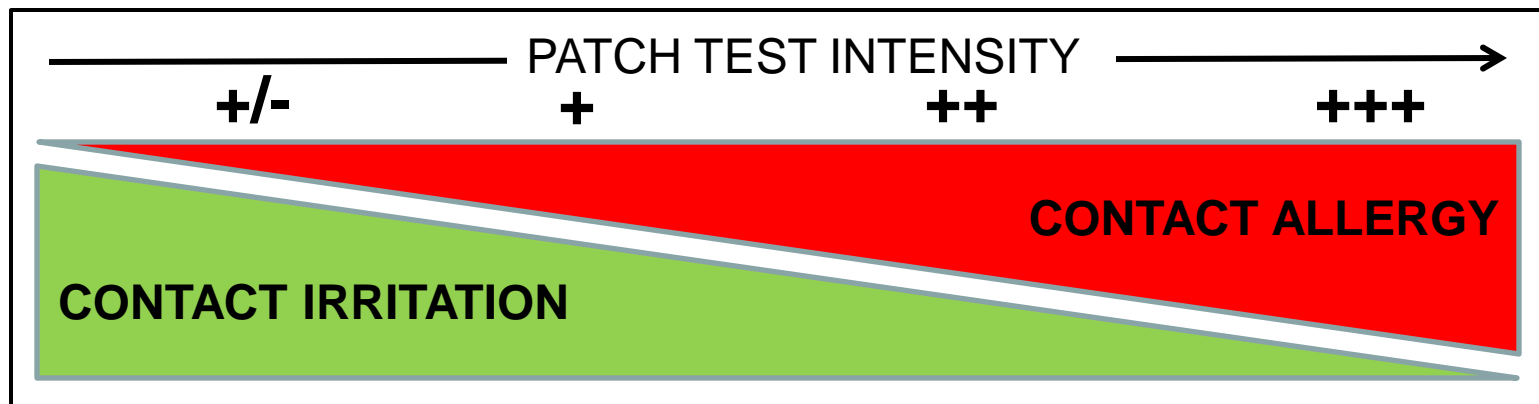
# SKIN INFLAMMATION ALLERGY OR IRRITATION ?

We know very little!

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- Exposure to allergens promotes tolerance
- Use of patch test to study the pathophysiology of contact allergy

# Contact Allergy to fragrances

- Prevalence of fragrance contact allergy: 10%
- Positive patch-test = Fragrance-induced skin inflammation
  - Innate immunity: contact irritation (inflammasome; IL-1 & other primary cytokines)
  - Adaptive immunity: contact allergy (T cell- mediated, CD8+ T cells, IFN $\gamma$ )
- What is the real prevalence of fragrance contact allergy ?
  - Which proportion of positive tests are true positive and represent allergic tests?
  - Which proportion of positive tests are false positive and represent irritative tests?
  - Open tests and repeated open tests (ROAT) are needed for diagnosis



# Contact Dermatitis to fragrances

- Clinical lesion of eczema
- Skin inflammation
  - Innate immunity: irritant CD  
(inflammasome; IL-1 & primary cytokines)
  - Adaptive immunity: allergic CD  
(T cell- mediated, CD8+ T cells, IFN $\gamma$ )
- Prevalence of CD to fragrances unknown
  - No strong epidemiological data
  - No cosmetovigilance data
- Prevalence of ACD to fragrances unknown  
Misinterpretation:
  - Irritant contact dermatitis
  - Atopic dermatitis (facial, eyelid eczema)
- Prevalence of ACD to fragrances probably lower  
(example though the coumarine studies)
- Studies needed on ACD to fragrances: epidemiology, cosmetovigilance, immunology etc..





- False + patch-tests
- Sensitization versus allergy
- Clinical relevance of skin tests
- Open tests et ROAT

# Allergic contact dermatitis from povidone-iodine: a re-evaluation study

JEAN-MARIE LACHAPELLE

Department of Dermatology, Louvain University, 30, Clos Chapelle-aux-Champs, UCL 3033,  
B-1200 Brussels, Belgium

500 consecutive patients were patch tested with a 10% povidone-iodine (PVP-I) solution, diluted 10 times in water. Readings were made at 2 and 4 days. 14 of the 500 (2.8%) showed a positive test to PVP-I. The 14 positive patients to PVP-I were subjected to a repeated open application test (ROAT) with a PVP-I solution, as is; 2 of the 14 were positive. The 12 negative patients were tested with 500 patients had true allergic contact dermatitis. The 12 patients were tested for more complete investigation, when tested with irritants and allergenic properties, such as PVP-I. The 12 patients were tested for reactions and to assess true clinical relevance.

*Key words:* allergic contact dermatitis; patch test; ROAT  
© Blackwell Munksgaard, 2005.

12/14 patch<sup>pos</sup>, roat<sup>neg</sup> ?

- irritants

- patch<sup>pos</sup> non pertinents

# Case #2

## Systemic allergic contact dermatitis to black cumin essential oil expressing as generalized erythema multiforme

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*EJD, vol. 21, n° 3, May-June 2011*

56 yr-old woman  
skin rash, 15 days after the daily  
intake and atrial application of black  
cumin essential oil (BCEO)



Positivity +++ to BCEO (at D3)



Positivity of ROAT test to BCEO (at D2)

→ eliminates an irritant patch test

→ confirms that the patient was strongly allergic to BCEO

# SKIN INFLAMMATION ALLERGY OR IRRITATION ?

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- Exposure to allergens promotes tolerance
- Use of patch test to study the pathophysiology of contact allergy

# Skin Contact Irritation Conditions the Development and Severity of Allergic Contact Dermatitis

Marlene Bonneville<sup>1</sup>, Cyril Chavagnac<sup>1</sup>, Marc Vocanson<sup>1</sup>, Aurore Rozieres<sup>1</sup>, Josette Benetiere<sup>1</sup>, Ingrid Pemet<sup>2</sup>, Alain Denis<sup>2</sup>, Jean-Francois Nicolas<sup>1,3,4</sup> and Ana Hennino<sup>1</sup>

Irritant contact dermatitis (ICD) is a frequent inflammatory skin disease induced by skin contact with low molecular weight chemicals such as haptens endowed with proinflammatory properties. Allergic contact dermatitis (ACD) is a frequent complication of ICD and is mediated by hapten-specific T cells primed in lymph nodes by skin emigrating dendritic cells. The aim of this study was to analyze the relationship between ICD and ACD to 2,4-dinitrofluorobenzene (DNFB) in C57BL/6 and BALB/C mice, which develop a severe and a moderate skin inflammation, respectively. Upon a single skin painting with DNFB, C57BL/6 developed within hours a more severe dose-dependent ICD response as compared to BALB/C mice, which was associated with enhanced upregulation of IL-1 $\beta$ , IL-6, and IL-10. Skin exposure to a low dose of DNFB resulted, in both strains, in a low ICD that resolved in a few hours. Alternatively, skin painting with either an intermediate or a high DNFB concentration induced an ICD that subsequently gave rise to an ACD reaction whose intensity was proportional to the magnitude of the ICD response and was more severe in C57BL/6 mice than in BALB/C mice. In conclusion, the hapten-induced skin contact irritation conditions the development and the severity of ACD.

# Skin irritation conditions the severity of ACD

## Primary Allergic Contact Dermatitis

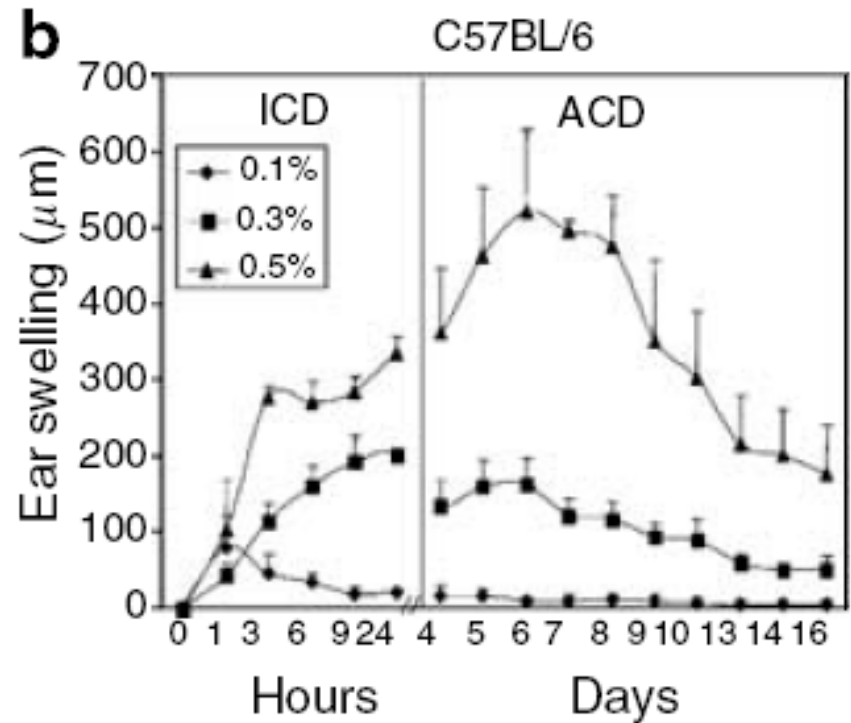
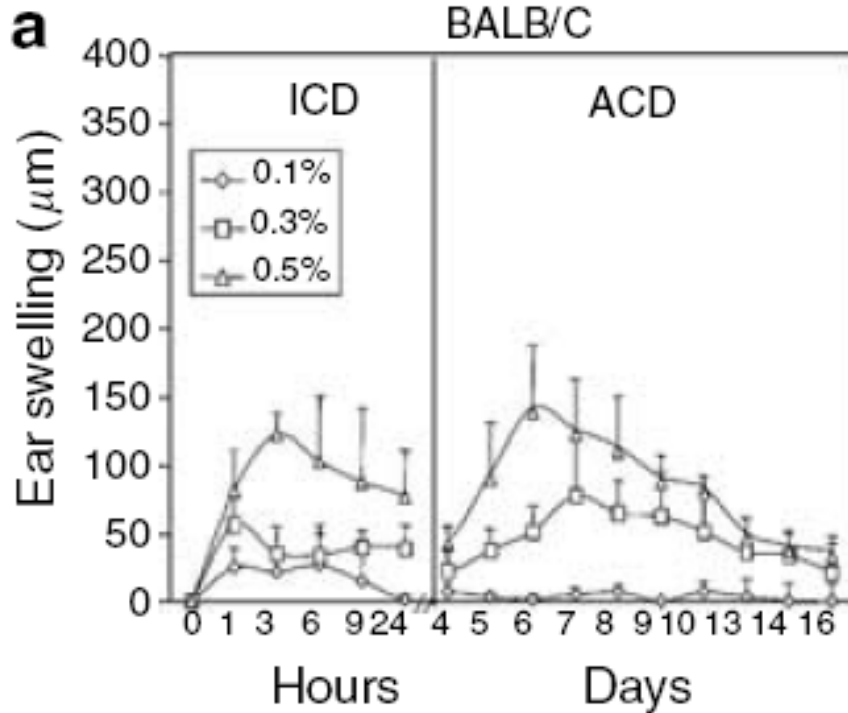
DNFB sur l'oreille  
gauche  
J0



Mesure de l'œdème  
de l'oreille  
H0 H3 H6 H9 H24



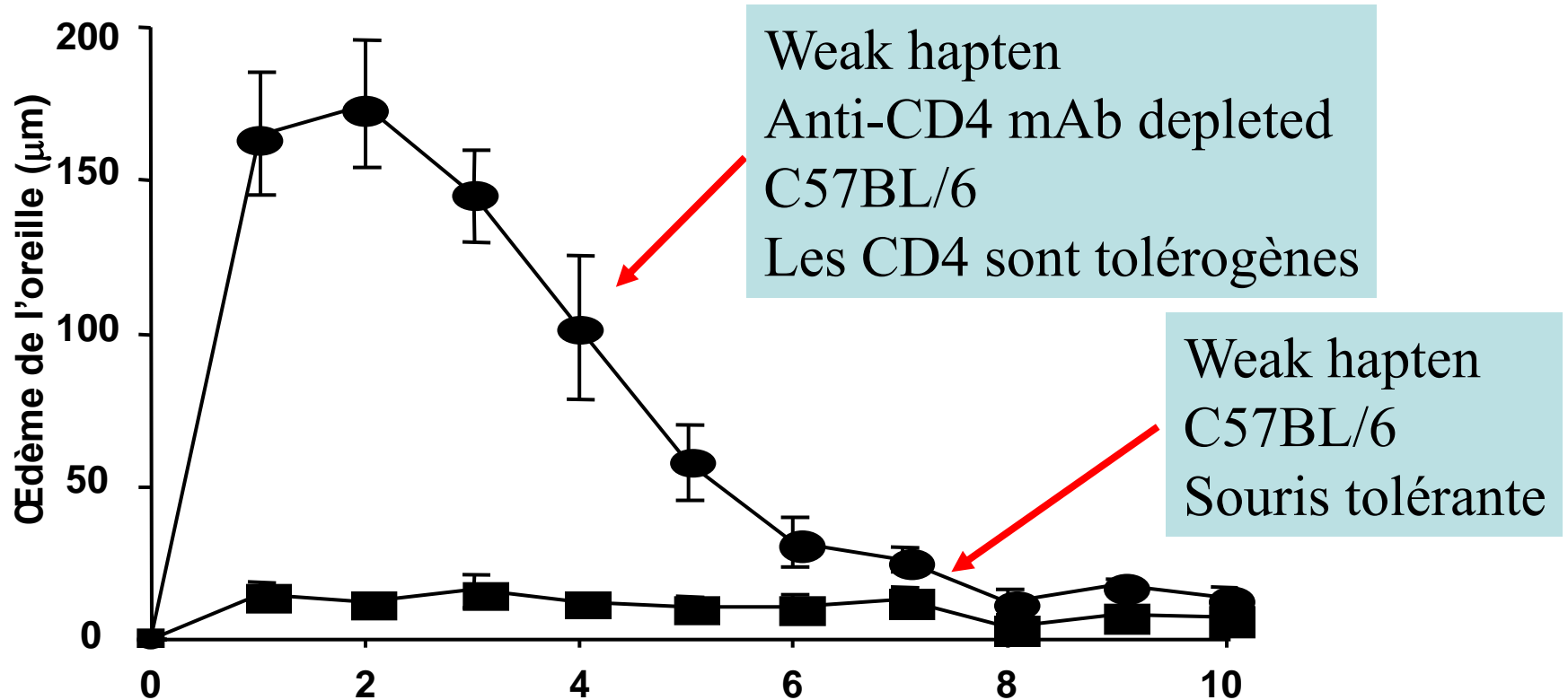
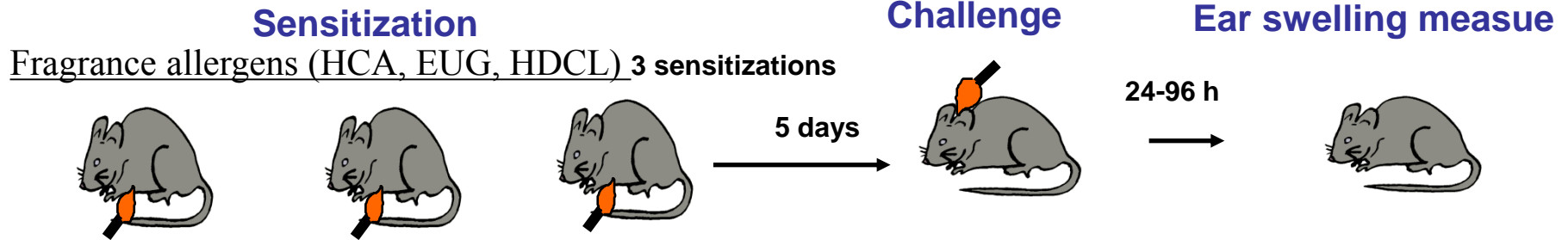
Mesure de l'œdème  
de l'oreille  
J5/J10



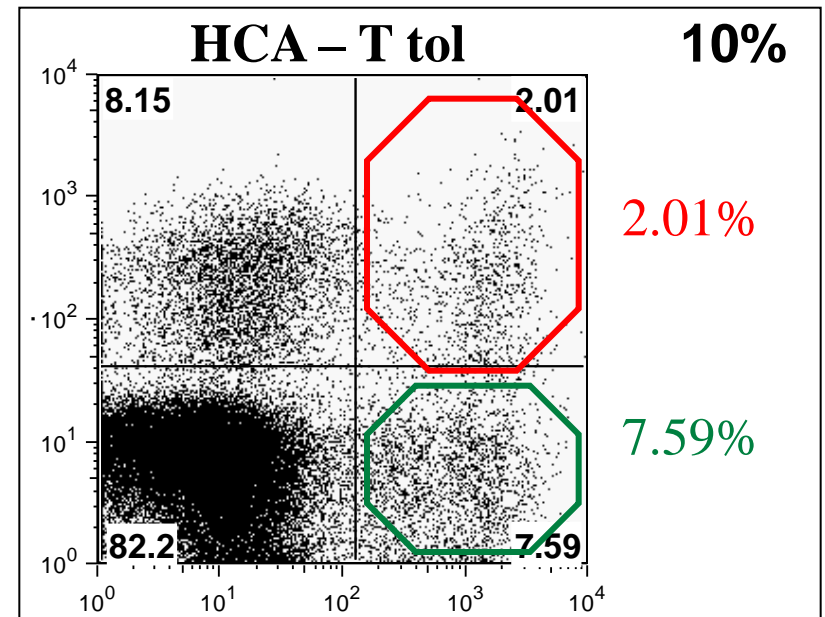
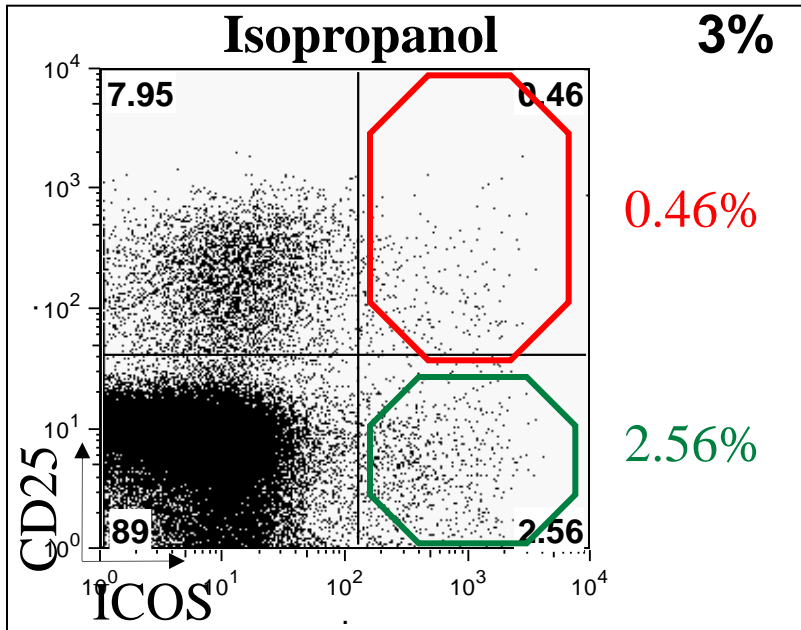
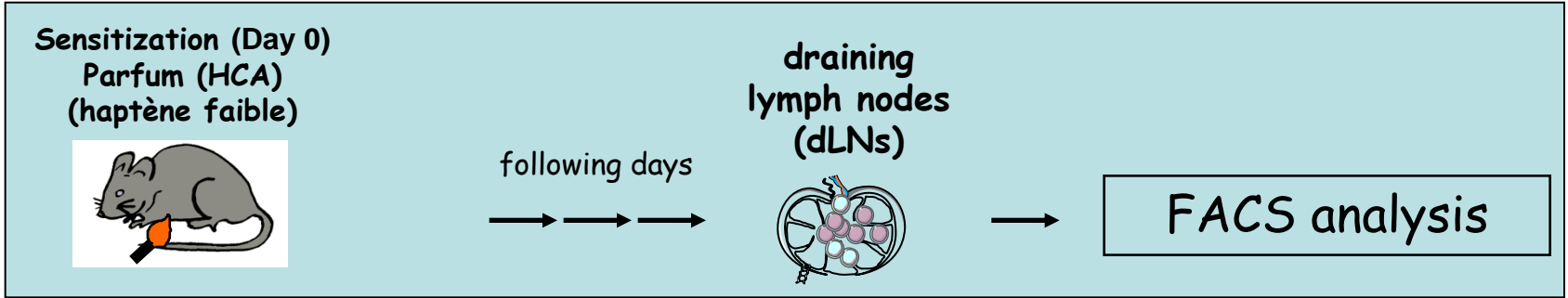
# SKIN INFLAMMATION ALLERGY OR IRRITATION ?

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- **Exposure to allergens promotes tolerance**
- Use of patch test to study the pathophysiology of contact allergy

# Allergic contact dermatitis - Weak Haptens



# Weak haptens (fragrances) activate Tregs which prevent Effector T cell priming (sensitization) and therefore the development of ACD





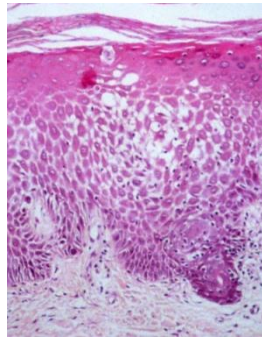
# SKIN INFLAMMATION ALLERGY OR IRRITATION ?

- Pathophysiology of skin irritation and allergy
- How to differentiate allergy from irritation ?
- How to differentiate allergy to patch test from clinically relevant allergy ?
- Exposure to allergens promotes tolerance
- Use of patch test to study the pathophysiology of contact allergy

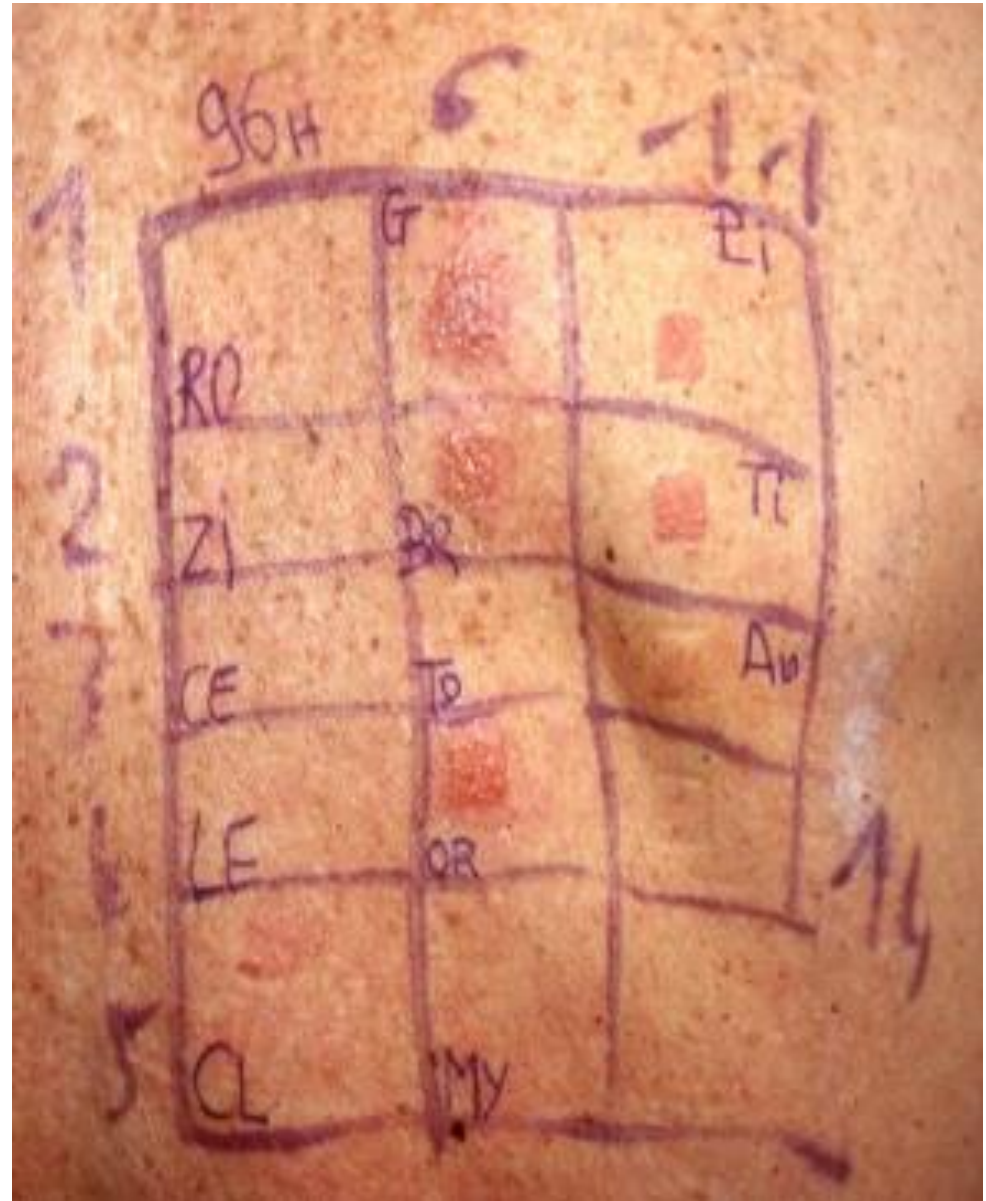
# 1. EFFECTOR MECHANISMS

CD8+ T cells - Human studies - ACD to drugs

EXANTHEMA - mild severity



- Frequent & non severe - high morbidity
- Apoptosis of epidermal cells
- Pathophysiology not well known



# 1. EFFECTOR MECHANISMS - RESULTS

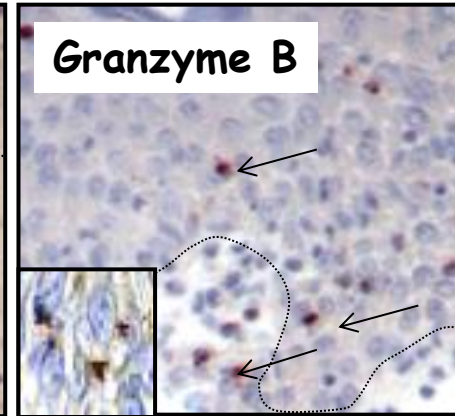
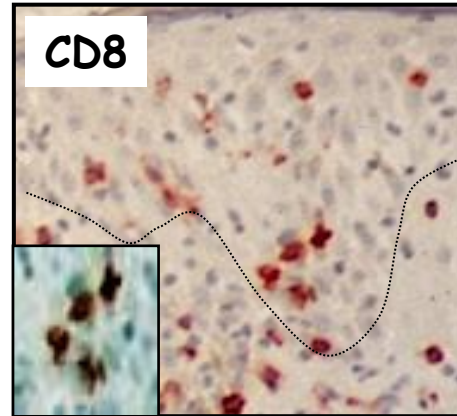
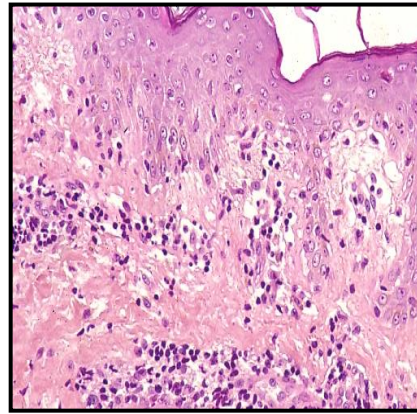
## CD8+ T cells - Human studies - DRUG ALLERGY

### SKIN PATCH TESTS

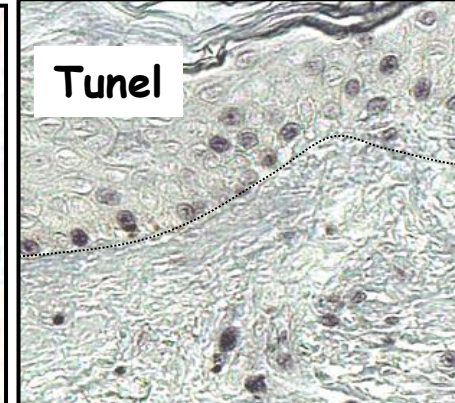
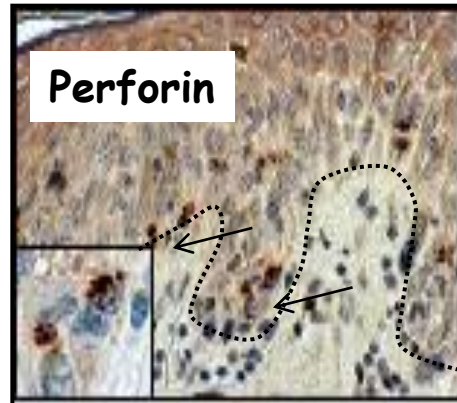
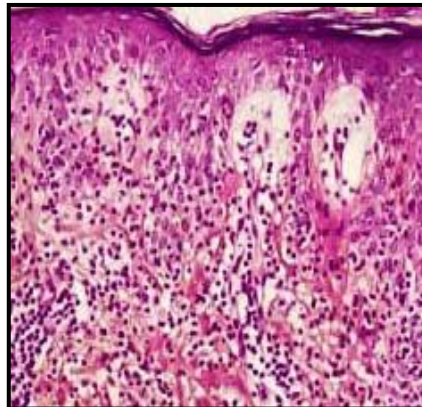
12 hrs



AMOX 12H



AMOX 48H



48/72 hrs

Histology

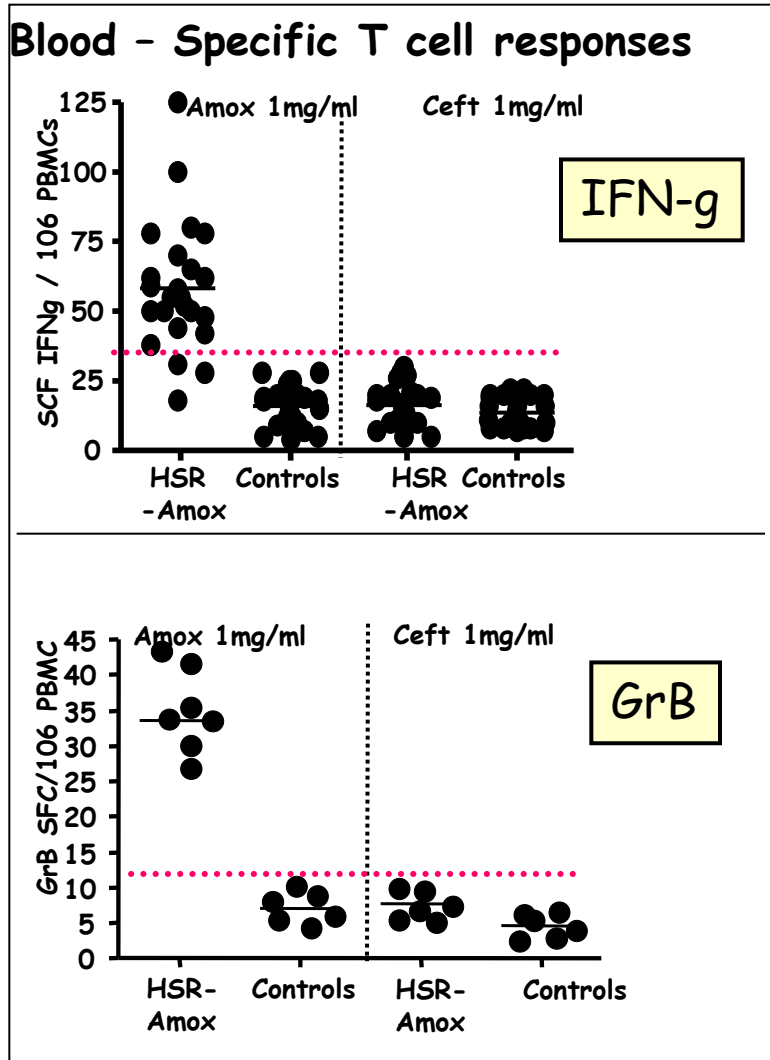
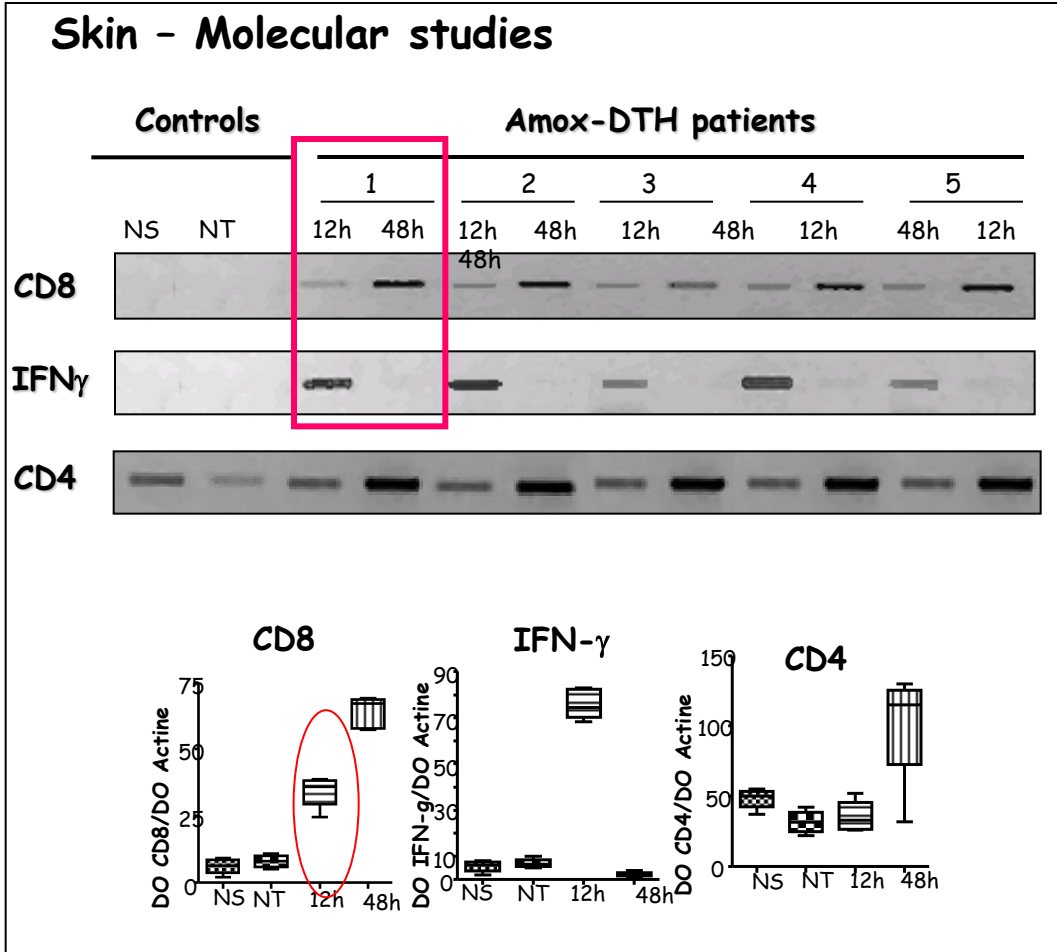
12 hrs negative skin patch test

► CD8+ Tc1 cells are rapidly recruited in the amox-challenged skin before CD4+ T cells

# 1. EFFECTOR MECHANISMS - RESULTS

## CD8+ T cells - Human studies - DRUG ALLERGY

- ▶ TC1 cells infiltrate the skin
- ▶ Specific TC1 cells circulate in the blood of patients
- ▶ Development of an immunobiological assay for the diagnosis of drug allergy



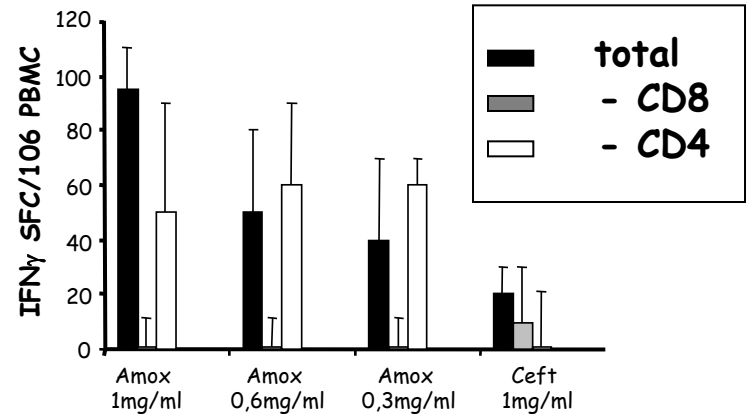
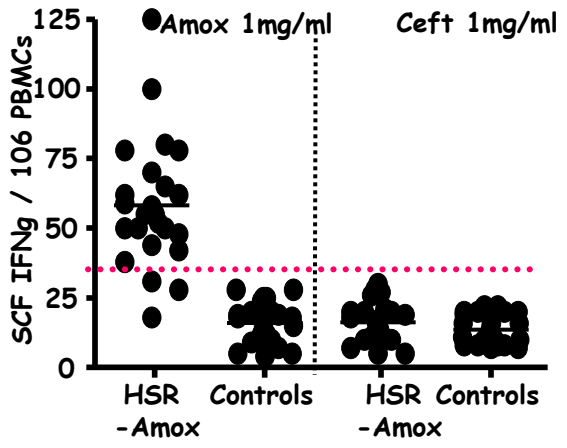
# 1. EFFECTOR MECHANISMS

## CD8+ T cells - Human studies - DRUG ALLERGY

### BLOOD T CELLS

► Drug-specific IFN $\gamma$ + GrB+ cells are CD8+ T cells

IFN- $\gamma$  ELISPOT



► Immunological assay for the diagnosis of drug allergy





**34<sup>e</sup> cours**  
d'actualisation  
en dermato-allergologie

**GERDA 2013**

Lyon, 25-28 septembre

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2013/09/10

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# Thank you!



**T cell priming group** (Lyon, July 29-30, 2013)

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