

# *The molecular diagnosis of contact allergy*

IDEA workshop  
12th december 2018

Team « Immunology of skin allergy & vaccination »  
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CIRI – INSERM U1111, Lyon - France



## MODAL project - MOlecular Diagnosis of skin ALlergy

### Contact Dermatitis (CD)



**Allergic (ACD)**  
Adaptive immunity  
T cells

**Non-allergic**  
Innate immunity

ALLERGY?  
ALLERGEN?



Dermatoallergy  
reference medical centre

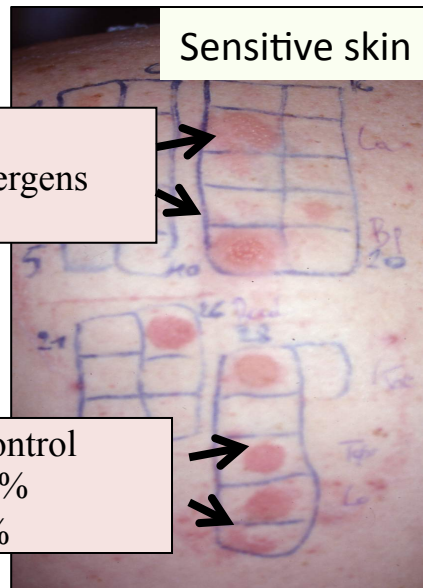
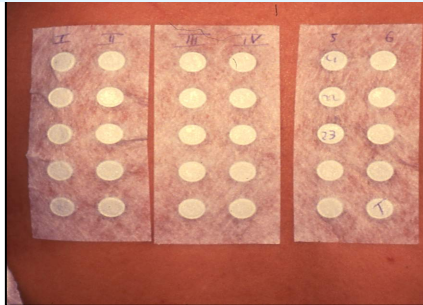


Patch-tests

### ■ Objectives

- To discover diagnostic & prognostic biomarkers in skin and blood of ACD patients
- To develop new tools that could help for the diagnosis of contact allergy

# When diagnosis turns out to be problematic?



Sensitive skin

Allergens

Irritant control  
SLS 0.25%  
SLS 0.5%

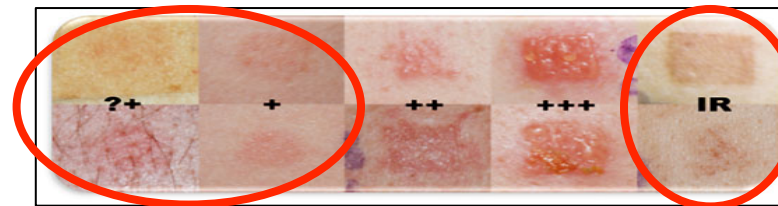
## How to differentiate irritation from allergy?

- Are they irritant or allergic?

## Are true positive tests clinically relevant?

- Strong reactions: Yes
- Low reactions: Poorly

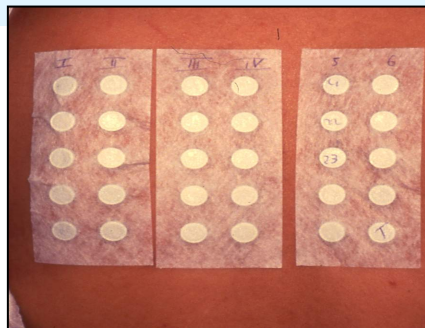
Scoring (ICDRG)



false positive ?

*Dittmar D, Contact Dermatitis, 2018  
Brasch J, J Am Acad Dermatol, 1994*

# How to circumvent problematic diagnosis?



Sensitive skin

Allergens

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## How to differentiate irritation from allergy?

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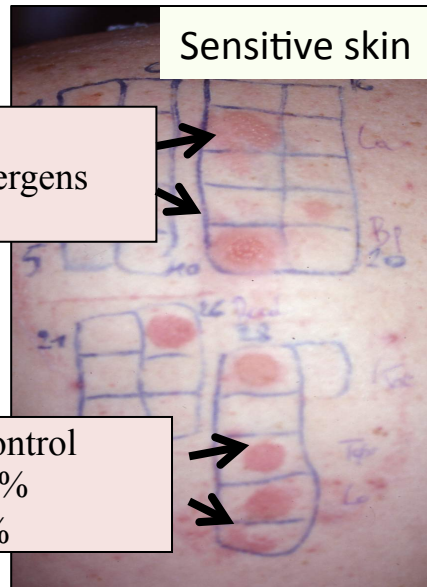
## Are true positive tests clinically relevant?

- Strong reactions: Yes
- Low reactions: Poorly

## By demonstrating the existence of an allergic reaction

- Characterize the skin DTH reaction  
→ cell infiltration & activation using transcriptomic, immunohistochemistry...
- Characterize circulating specific T cells  
→ *in vitro* T cell reactivation using LTT, Elispot assays

# MODAL project - MOlecular Diagnosis of skin ALlergy

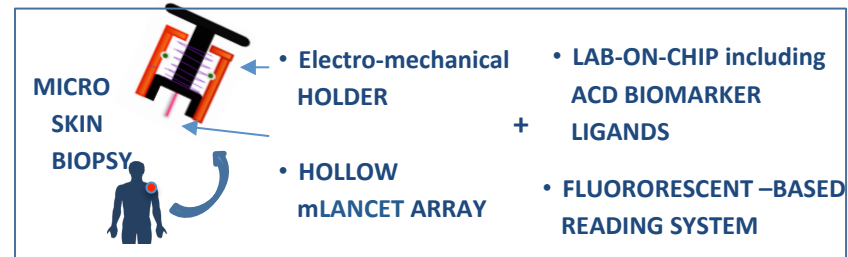


Sensitive skin

Allergens

Irritant control  
SLS 0.25%  
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## New medical device



Suspected skin allergic patient ?

Allergic patient

Non allergic patient

## Disease stratification / Clinical relevance



- ACD patient / Strong
- ACD asymptomatic patient / Low



## MODAL project - MOlecular Diagnosis of skin ALlergy

### Clinical study

- 48 patients suspected for skin allergy
- Positive patch-tests (+++, ++, +, +/-, -)
- Reference Allergens:
  - ✓ Nickel (n=10),
  - ✓ Linalool peroxyde (n=10),
  - ✓ Methylisothiazolinone (n=6)
  - ✓ Amoxicillin (n=6)
  - ✓ Diamox (n=1)
  - ✓ Tazocillin (n=1)
- Reference irritants:
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  - ✓ Cantharidin (n=8)
  - ✓ Nonanoïc acid (n=4)

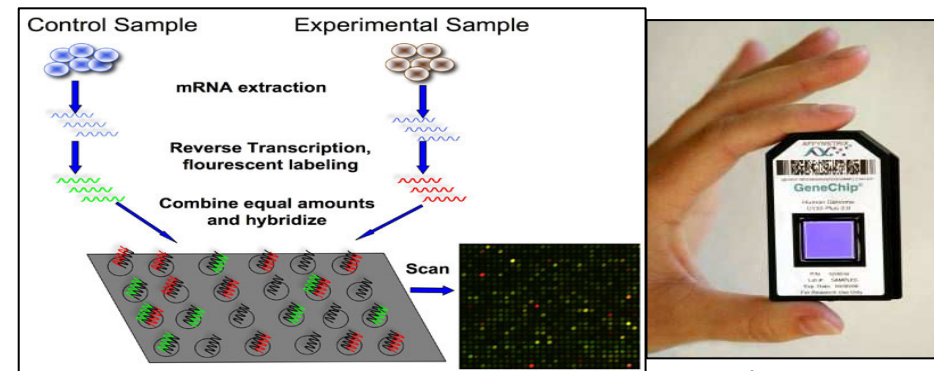
### Patch tests to induce skin allergy



72h

+++ , ++ , + , +/- Vehicle

### Microarrays generation



Affymetrix chip  
Human Genome U133  
Plus 2.0 Array  
> 22000 genes

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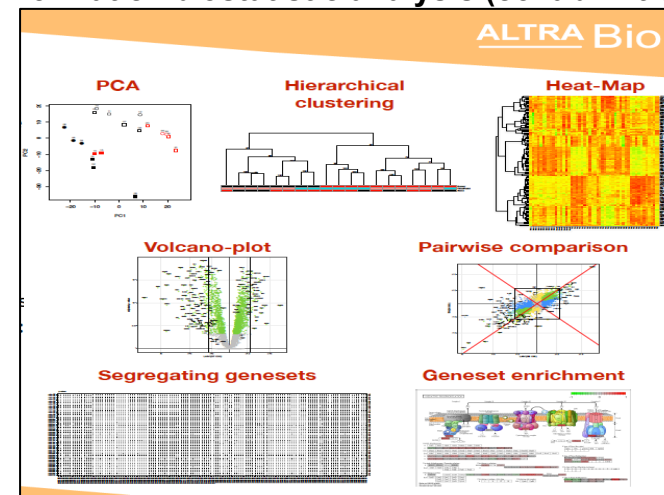
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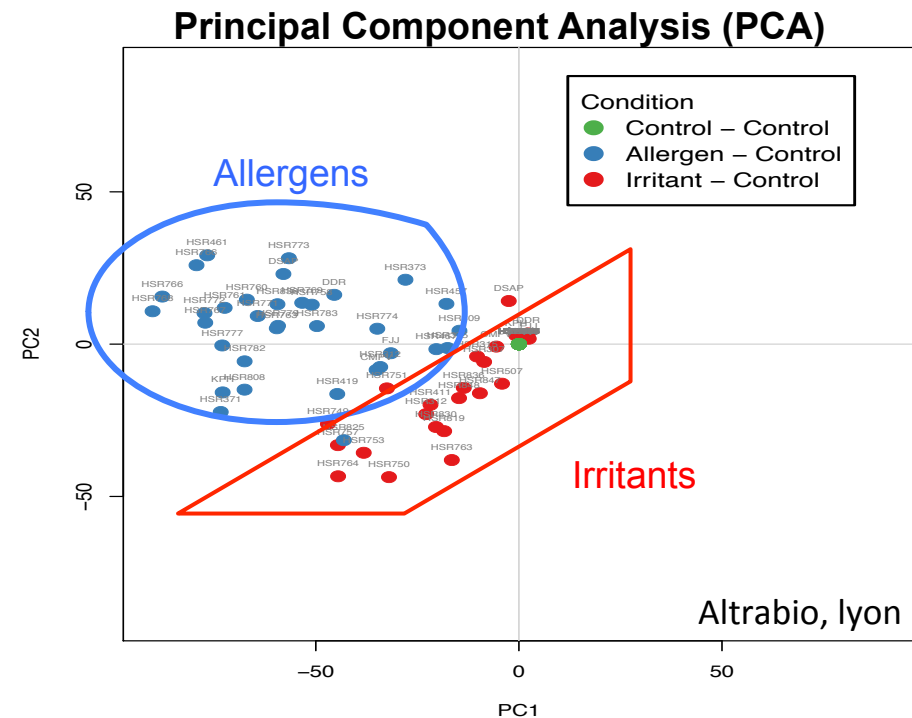
### Bioinformatic / biostatistic analysis (collab. AltraBio, Lyon)



# Unsupervised analysis « Principal component analysis (PCA) »

## Clinical study

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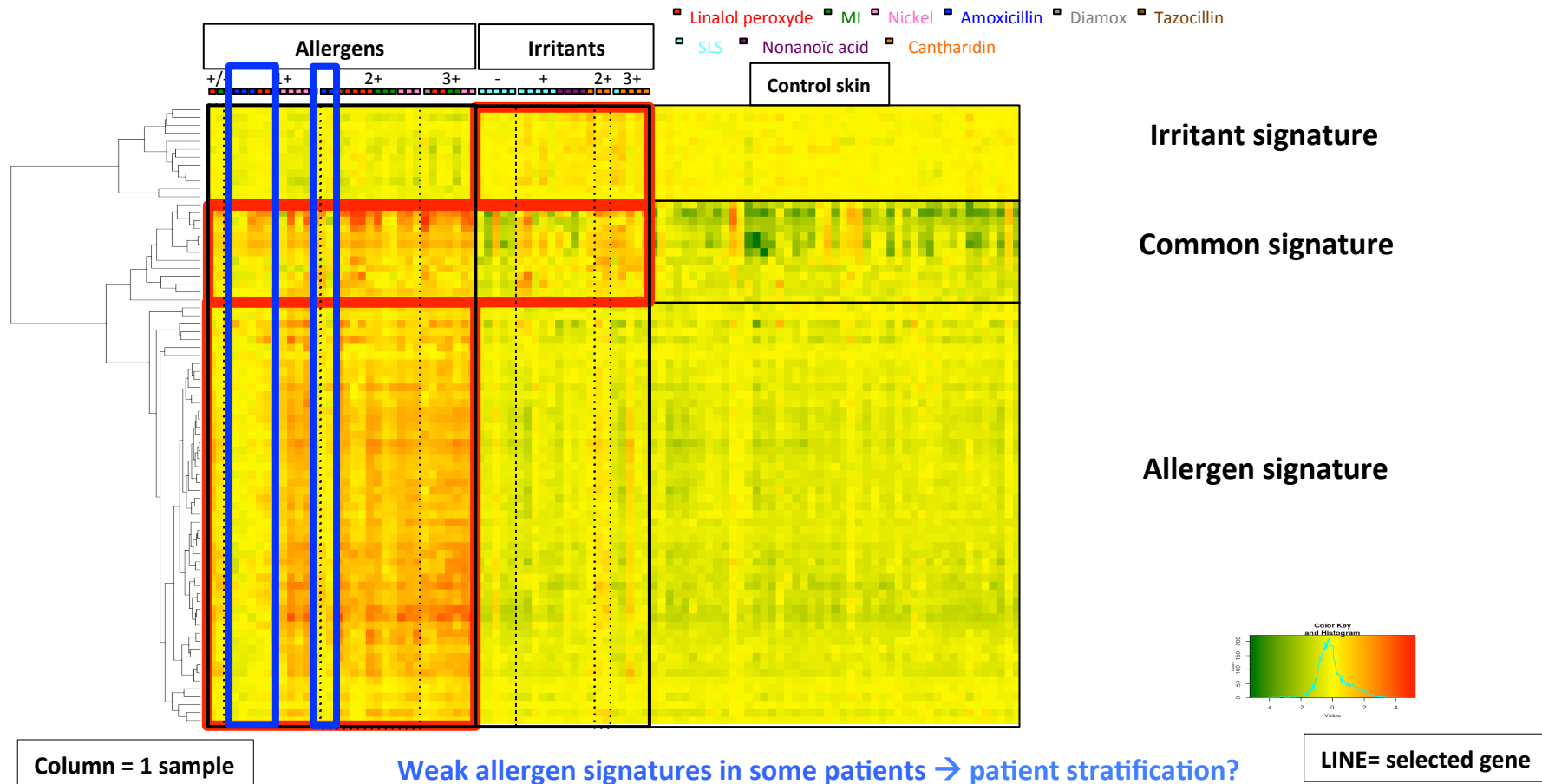


The molecular signatures of allergens are clearly distinct from those of irritants



# Heatmap

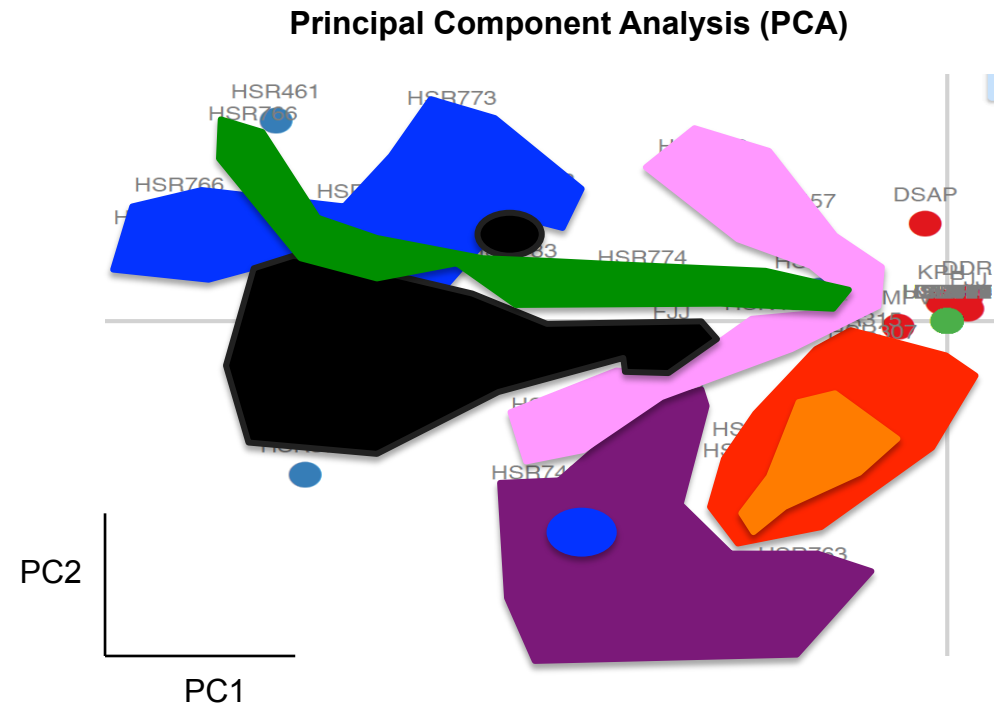
## Over-expressed genes in allergen/irritant samples



## Specific molecular signature for each molecule?

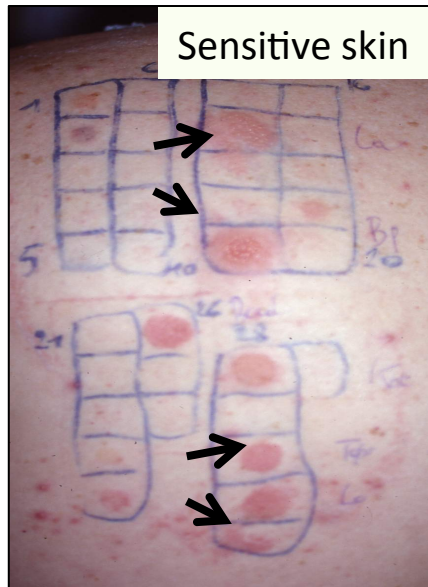
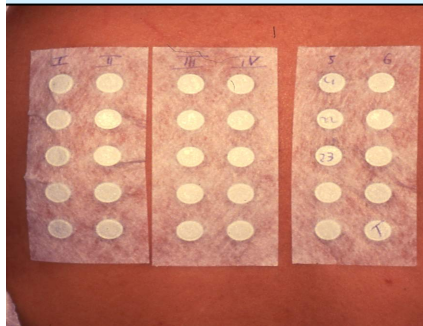
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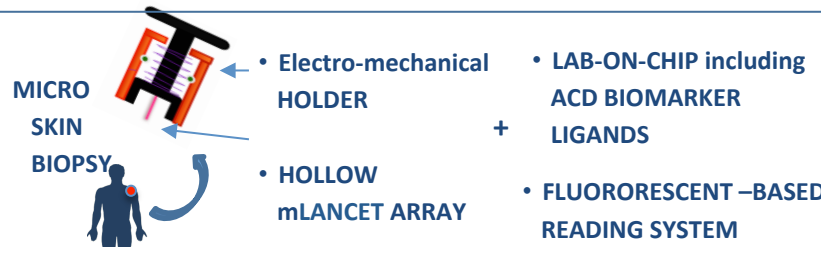


Specific signature for certain groups of molecules?

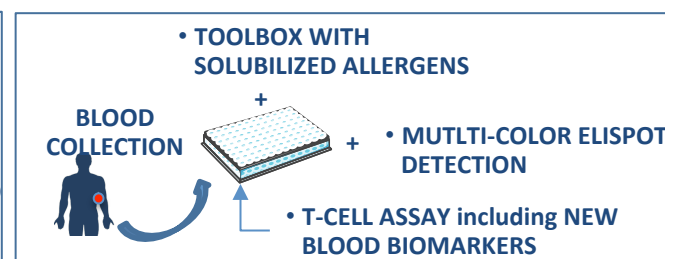
# MODAL project (MOlecular Diagnosis of skin ALlergy)



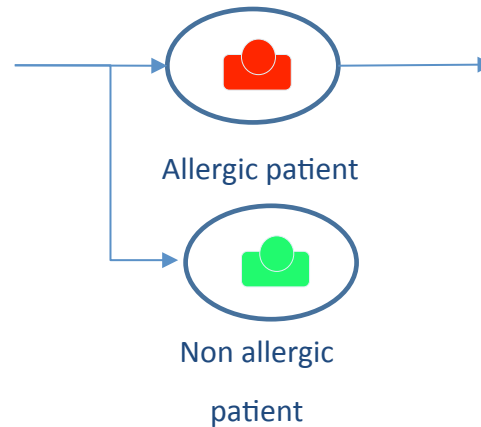
## New medical device



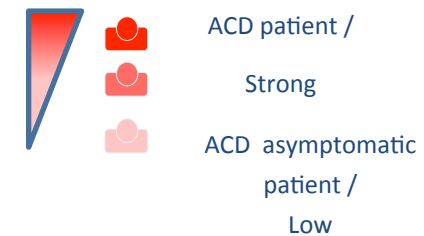
## New T cell assay



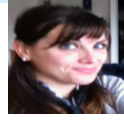
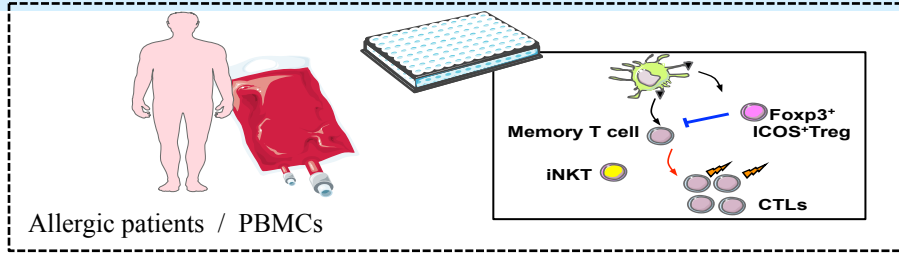
Suspected skin allergic patient ?



## Disease stratification / Clinical relevance



# in vitro diagnosis of ACD (T cell assay)



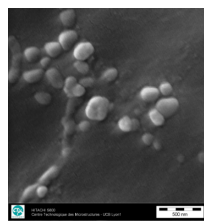
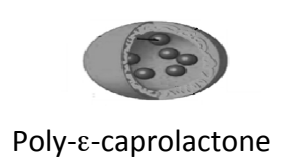
Nanomedicine: Nanotechnology, Biology, and Medicine  
11 (2015) 1029–1033



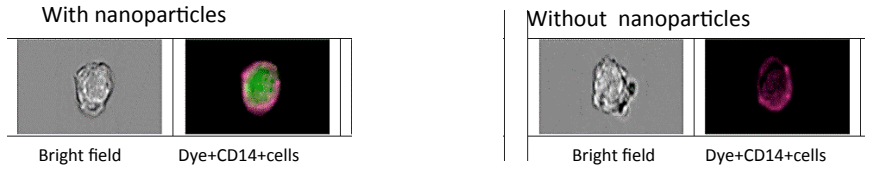
A. Cortial

Encapsulation of hydrophobic allergens into nanoparticles improves the *in vitro* immunological diagnosis of allergic contact dermatitis  
 Angèle Cortial, PhD<sup>a,b,c,d,e,f,1</sup>, Audrey Nosbaum, MD-PhD<sup>b,c,d,e,f,h,1,2</sup>, Aurore Rozières, PhD<sup>b,c,d,e,f</sup>, Marie Baeck, MD-PhD<sup>g</sup>, Laurence de Montjoye, MD<sup>g</sup>, Sophie Grande, MD<sup>h</sup>, Stéphanie Briançon, PhD<sup>g</sup>, Jean-François Nicolas, MD, PhD<sup>b,c,d,e,f,h</sup>, Marc Vocanson, PhD<sup>b,c,d,e,f,\*</sup>

## Nanoparticles + fragrance mixture

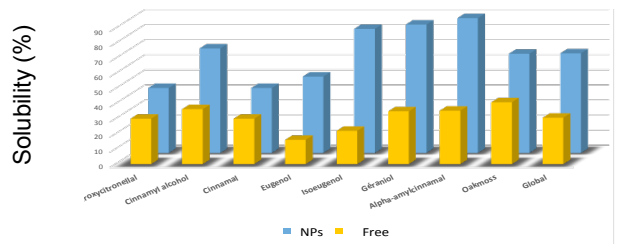


## Enhanced uptake by blood cells



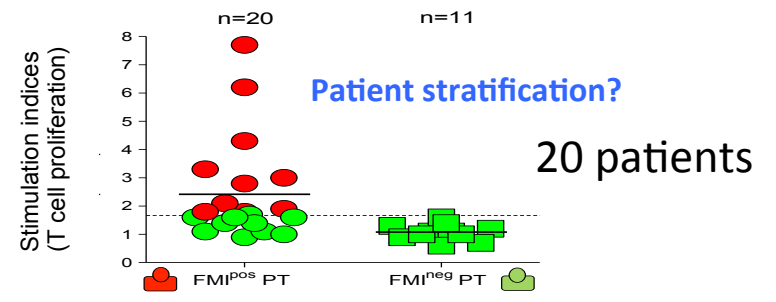
Imagestream

## Increased solubilisation



The encapsulation of hydrophobic allergens improves the detection of specific T cells circulating in the blood of allergic patients to fragrances

## In vitro diagnosis of fragrance allergy



# Project **MODAL**

## Conclusions & **perspectives**



- **Molecular analysis reveals distinct signatures between :**
  - **allergens and irritants**
  - **allergy and irritancy (to be confirmed!)**
- **The use of NPs allows for the sensitive detection of hydrophobic chemicals/mixtures in routine T cell assays**
- ✓ **To determine the predictive value of molecular signatures in patients with highly sensitive skin**
- ✓ **To combine molecular signatures / T cell assays / use-test responses to stratify contact allergy patients, and improve clinical relevance assessment**
- ✓ **To develop new test systems (minimally invasive, low cost)**

# Acknowledgements



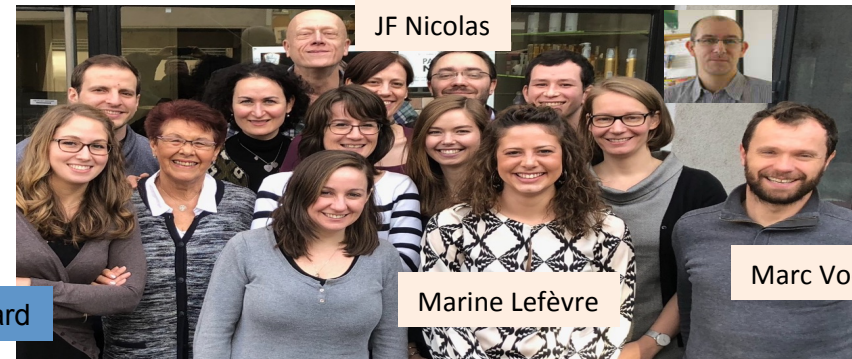
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David Bottiglioli

**Clinical research unit, Lyrec- Lyon-sud hospital**



# Acknowledgements



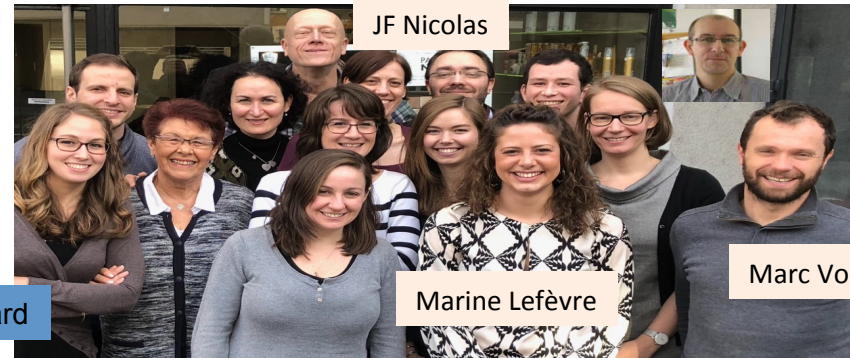
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 C. Svedman/L. Ljungberg/M. Bruze / Skane, Malmoe

