

ISAD NOTTINGHAM MAY 23rd 2014

# DISEASE MODIFICATION STRATEGIES FOR AD

Alain Taïeb

Dept of Dermatology and Pediatric Dermatology  
[www.dermatobordeaux.fr](http://www.dermatobordeaux.fr)



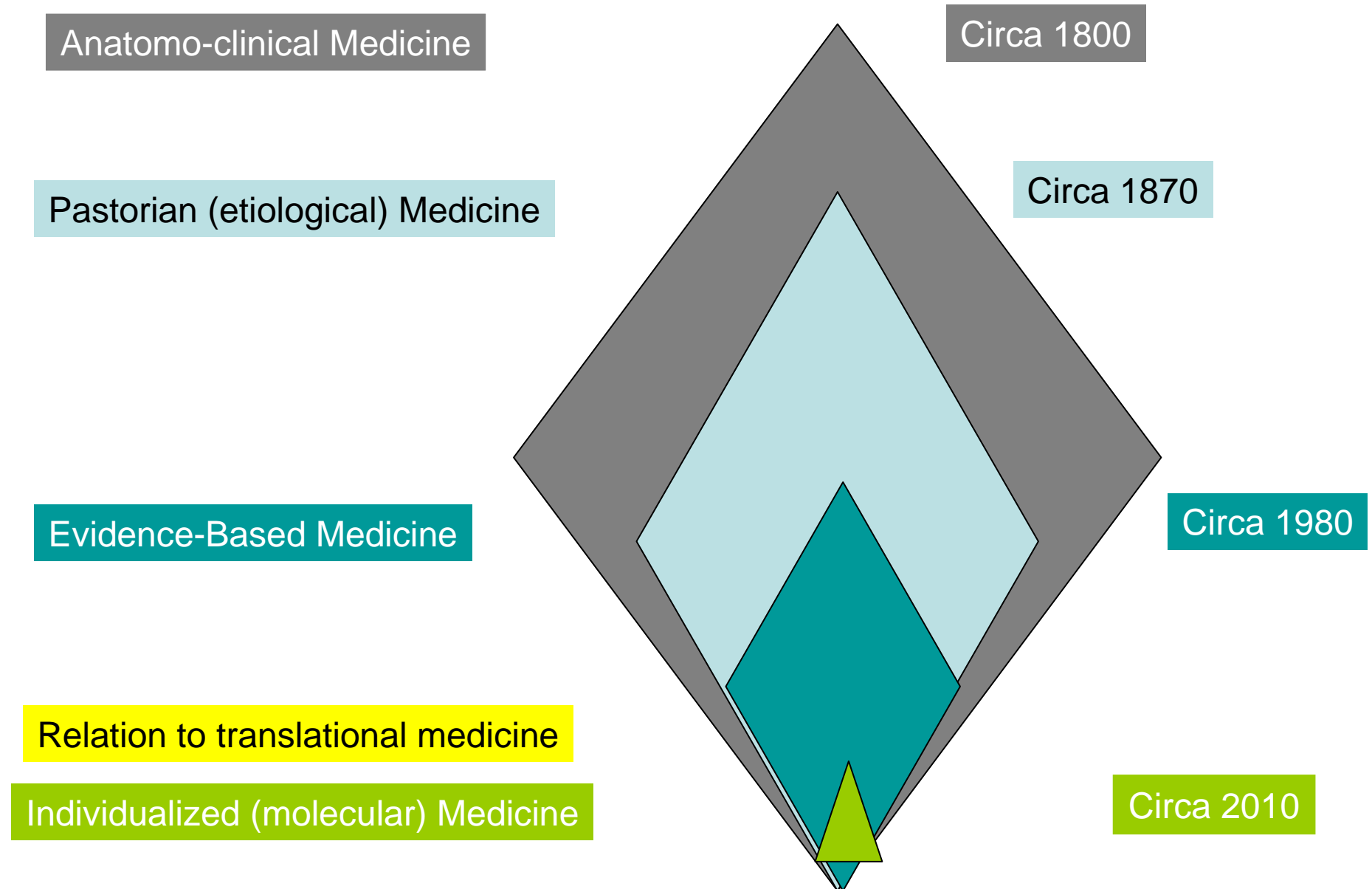
**Atopic dermatitis: pruritus  
constant but frequently omitted**



**Pruritic inflammation: hallmark of AD**

**Another frequently omitted point: Atopic dermatitis, a disease of the  
adult,...and of the elderly !**

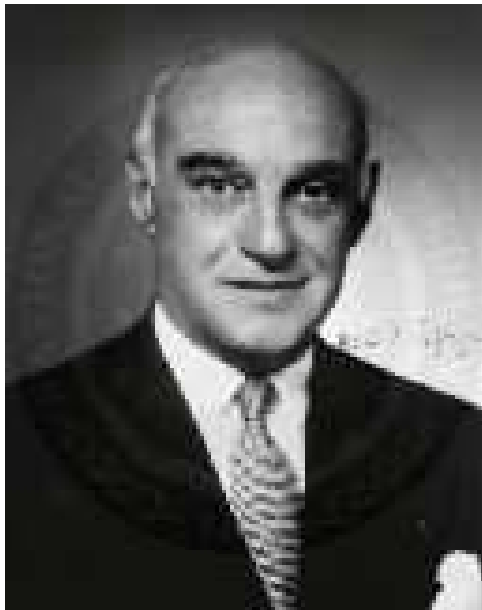
# Medicine: Evolution, not Revolution



# Translational medicine needed to implement personalized medicine

- **Translational medicine** is a discipline within biomedical and public health research that aims to improve the health of individuals and the community by “translating” findings into diagnostic tools, medicines, procedures, policies and education (*Wikipedia*)
- **Main objective: new cures for disease can be delivered faster to patients**
- **How it works:** multi-disciplinary, highly collaborative, “bench-to-bedside” approach.

## **Topical treatments: from topical hydrocortisone (1950s) to topical calcineurin inhibitors (1997)**



**Marion Baldur Sulzberger  
1895-1983**

Wise F, Sulzberger MB. 1933 Year Book of Dermatology and Syphilology ; 38-39.

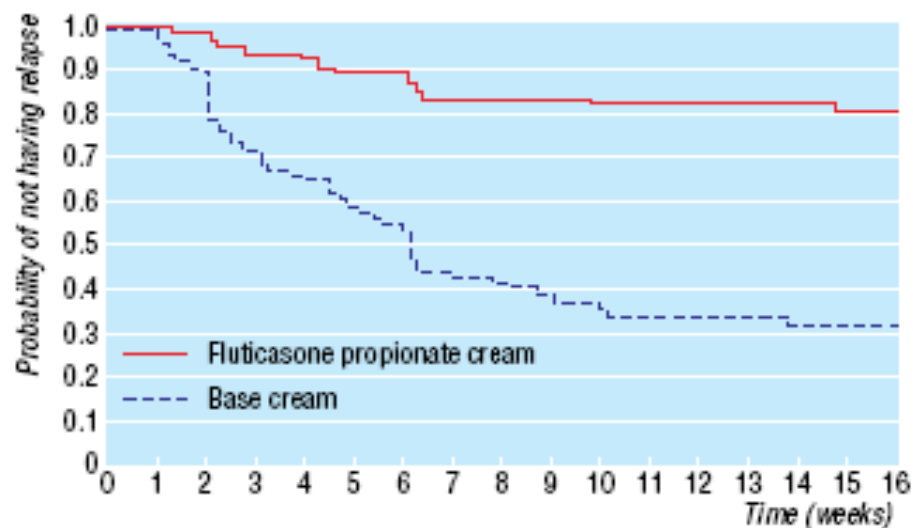
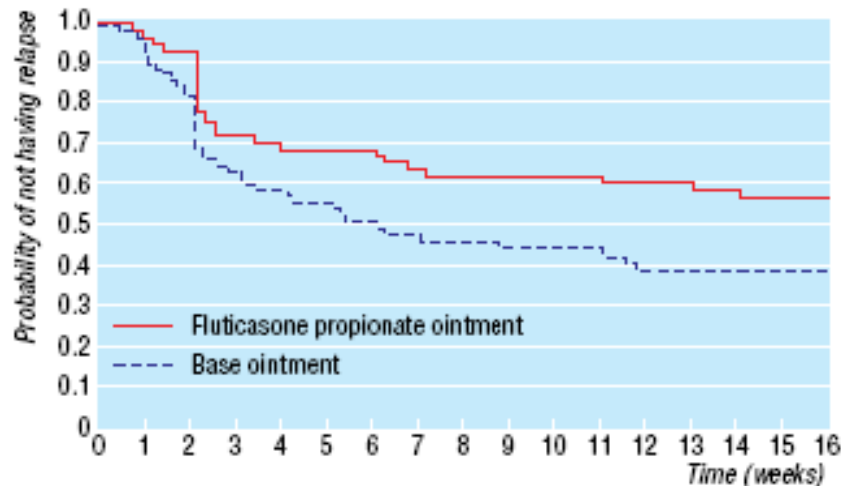
### **Definition of AD**

Sulzberger MB., Witten VH

The effect of topically applied compound F in selected dermatoses, J. Invest. Dermatol. 1952, 19 : 101-102.

### **First data on topical steroids**

# From Sulzberger's introduction of TCS, more than 50 years to validate an active antiinflammatory maintenance treatment in AD



## What is already known on this subject

Atopic dermatitis is characterised by frequent, unpredictable relapses, and there is little evidence to support any of the commonly used practices for long term maintenance treatment of moderate to severe cases

## What this study adds

After stabilisation of an acute flare, adding fluticasone propionate cream or ointment twice weekly to daily emollient treatment significantly reduced the risk of patients experiencing a further relapse and extended remission time

This regimen seemed to be well tolerated, with a low risk of local adverse effects, and may paradoxically be steroid sparing since, by producing longer remission periods, it should reduce the need for intensive treatment with topical corticosteroids as is often required to control flares



# Circa 2010...



## The NEW ENGLAND JOURNAL of MEDICINE

« We expect to see more efficient clinical trials based on a more thorough understanding of the genetic basis of disease. *We also anticipate that some previously failed medications will be recognized as safe and effective and will be approved for subgroups of patients with specific genetic markers* »

Perspective  
JULY 22, 2010

### The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

*Scientific and policy challenges for steering patients to the best available personalized treatments*



Can I fish something here?



This is not evidence-based!

**ISAD Arcachon, 2005**



# How to adapt Evidence-Based Medicine?

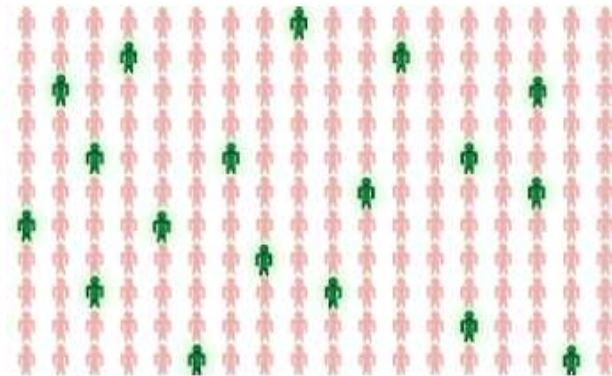
Strategy: begin with homogeneous populations

---

Fundamental Mechanism



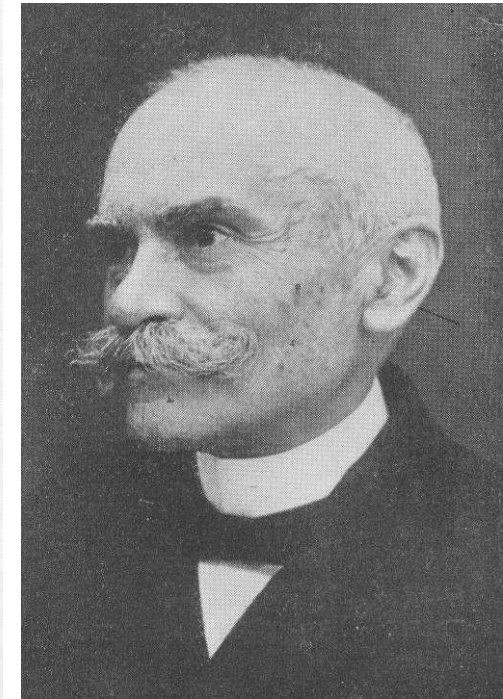
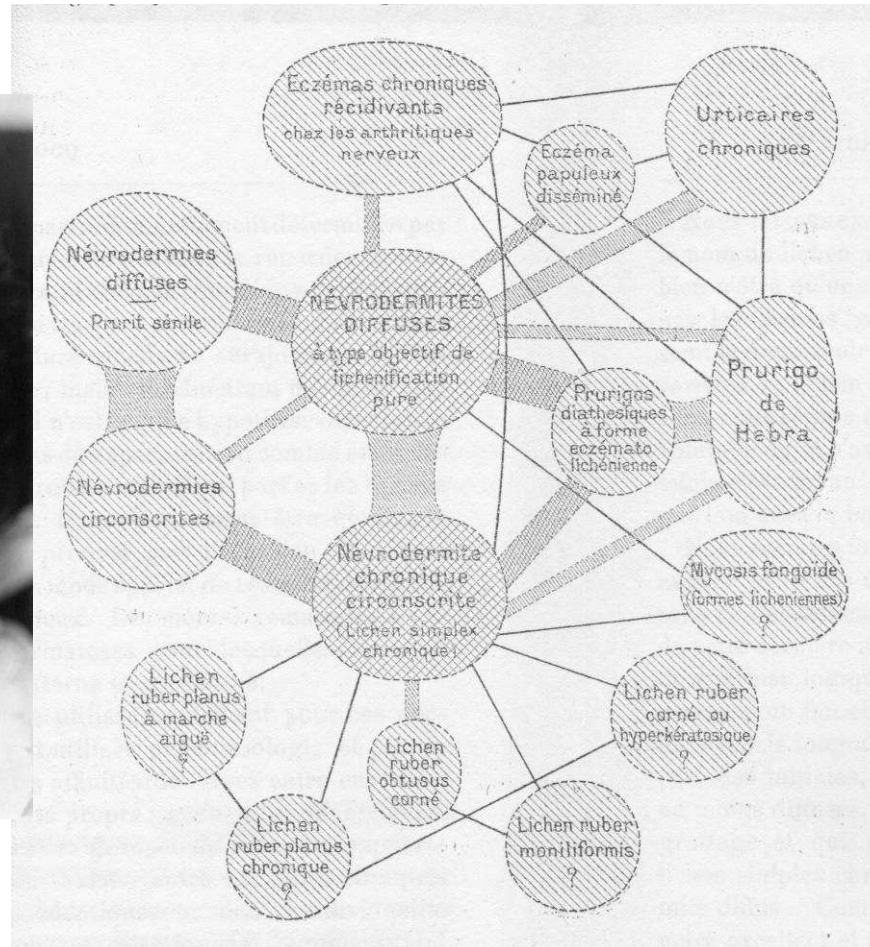
Sub-set of Broader Population



# Importance for AD therapy? One or several AD?



« ECZEMA »

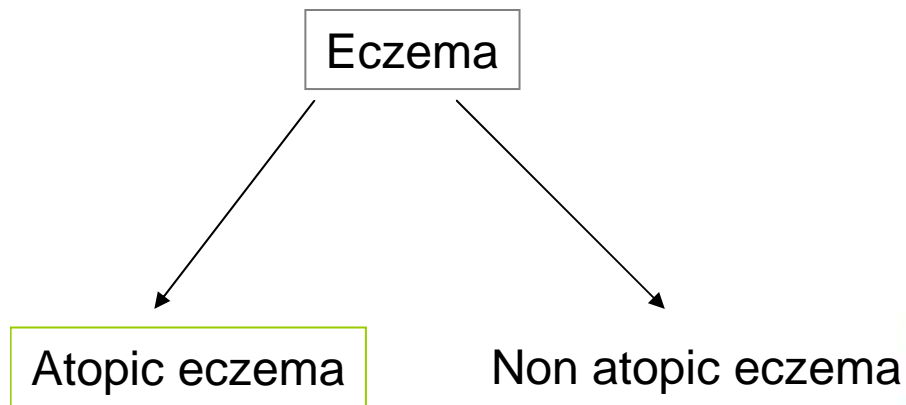


Louis Brocq 1856-1928

« nébuleuse » (Nebula) des névrodermites (neurodermatitis), 1896

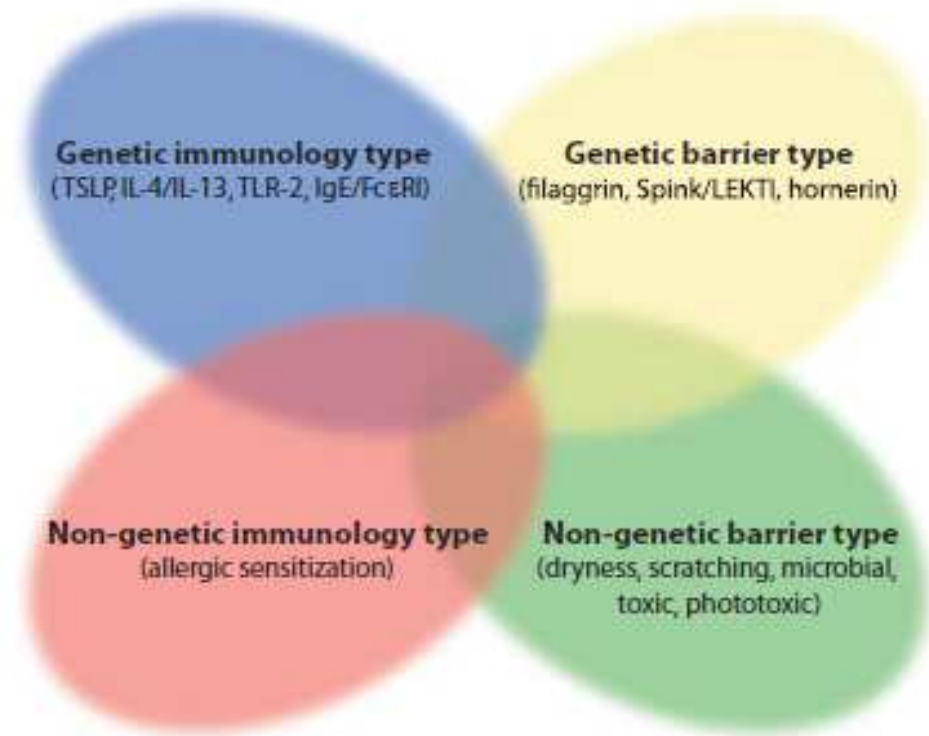
# Is the paradigm Atopic /Non atopic AD important for designing interventions?

*Johansson et al, JACI 2004*



**IgE**

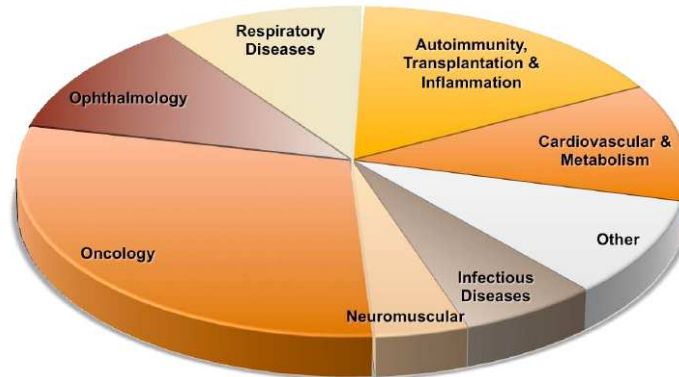
**2 endophenotypes??**



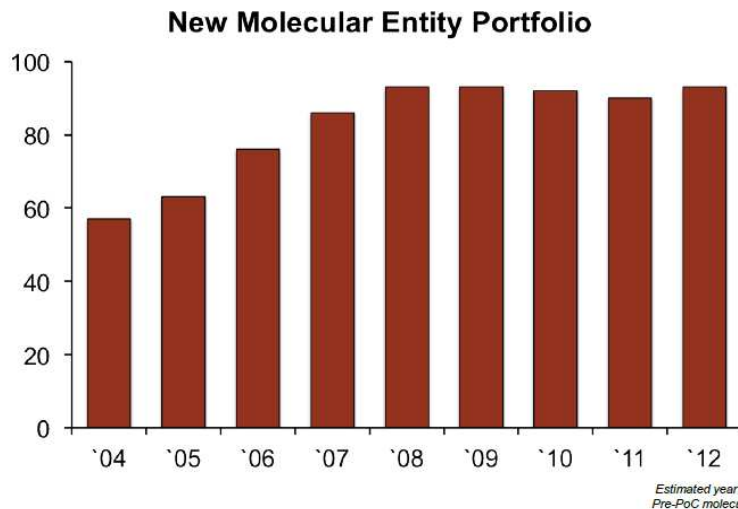
*Eyerich & Novak, 2013*

**4 endophenotypes??**

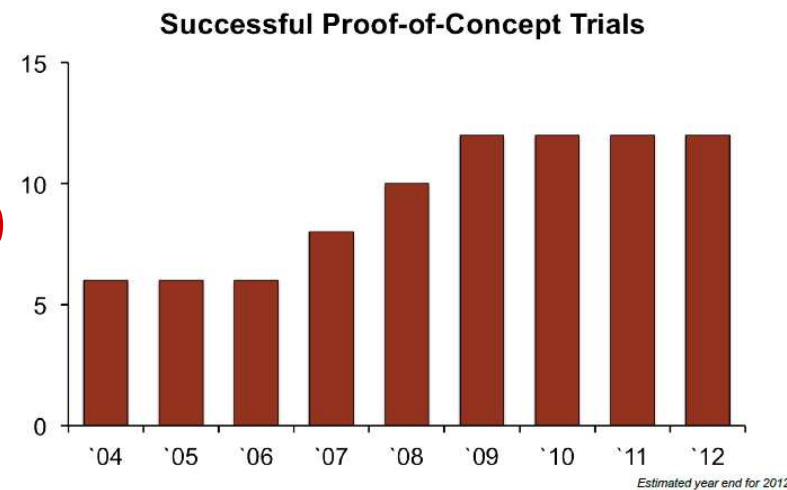
# Better translation: the perception from Pharma (e.g. Novartis)



**From rare to common disorders: a paradigm shift in Pharma to improve the ratio NME-POC**



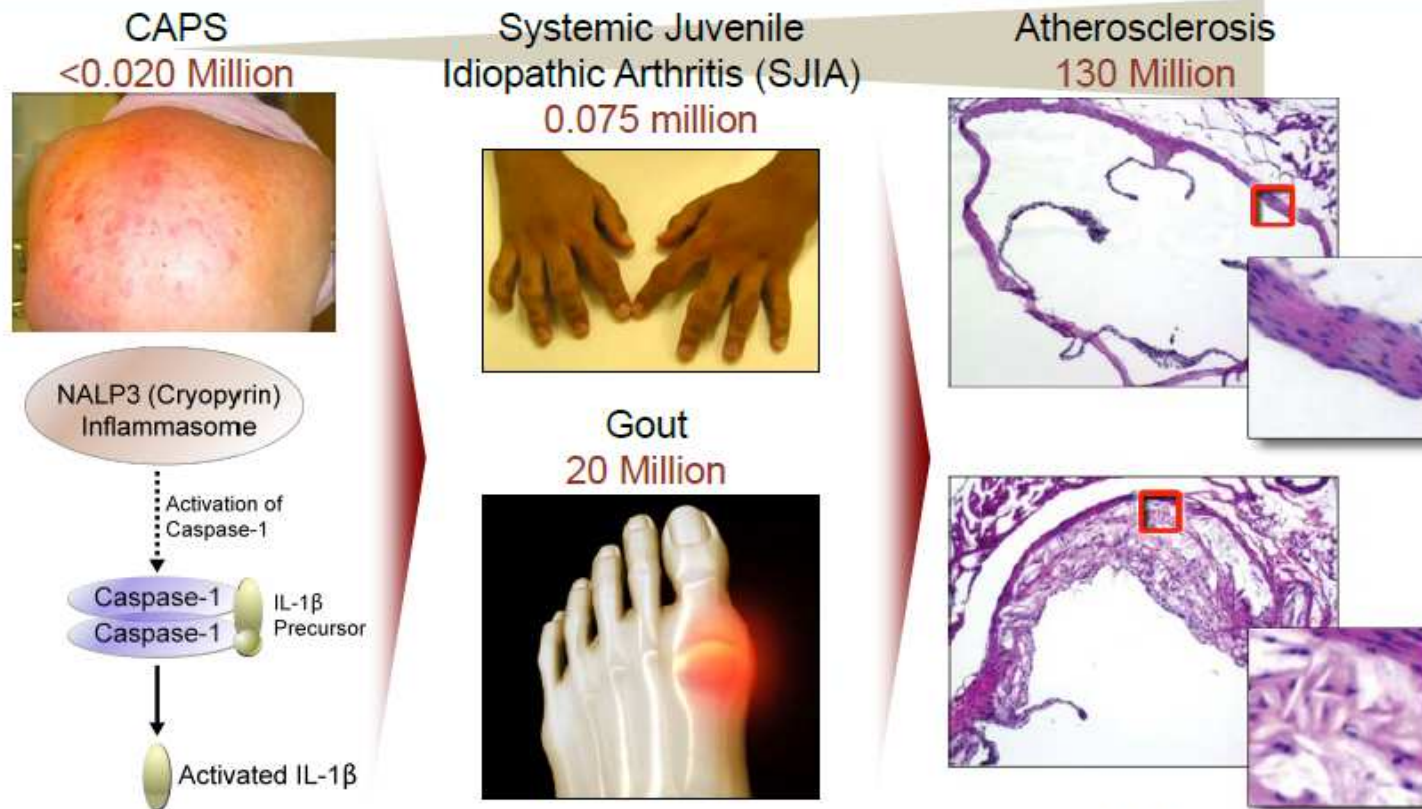
**1:10**





# Translational concept: from rare to common

ACZ885: anti IL-1 $\beta$  for inflammation



Investigational. Efficacy and safety have not been established

Latz, et al., Nature, Vol 464|29 April 2010

20 | Changing the Practice of Medicine | Mark C. Fishman, M.D. | November 8, 2012 | R&D Day

Source for patient numbers: global prevalence estimate from Patient Base

NOVARTIS

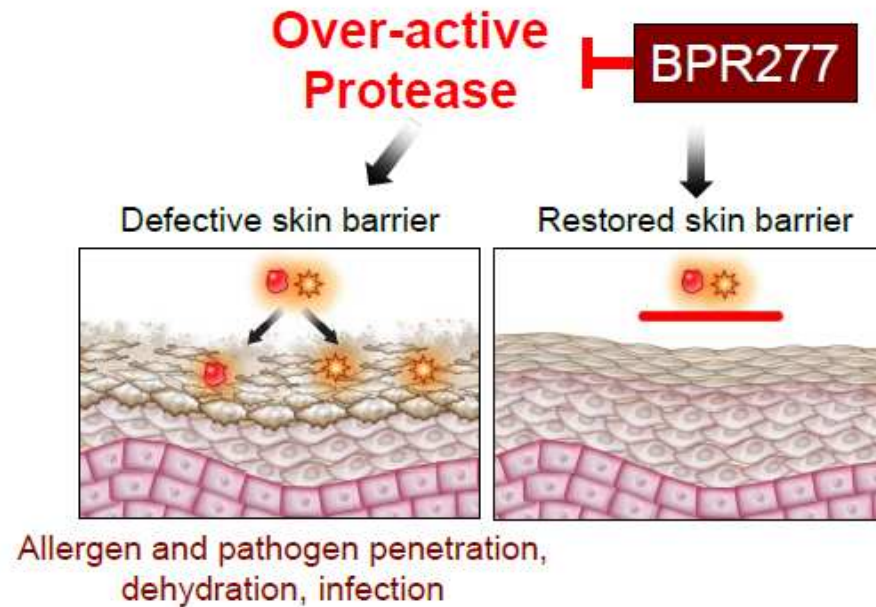
# Application of this strategy to AD

## Allergies

### Skin permeability



- Netherton syndrome is a genetic disorder. It is manifested by a severe impairment of the skin barrier function, with severe atopic dermatitis.



# 2014: current drug/device development for AD

- **315 studies found for:** atopic dermatitis | Exclude Unknown | Interventional Studies
- **58 studies found for:** atopic dermatitis | Open Studies | Exclude Unknown | Interventional Studies
- **22 studies found for:** atopic dermatitis | Completed | Exclude Unknown | Studies With Results | Interventional Studies
- **196 studies found for:** atopic dermatitis | Completed | Exclude Unknown | Studies Without Results | Interventional Studies

Clinicaltrials.gov, May 2014

# In development

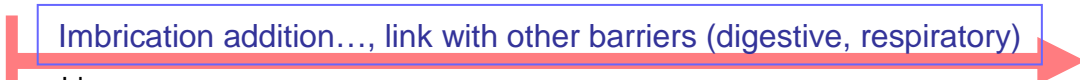
- **Barrier restoring devices** (emollients, antiproteases, urocanic acid, bacterial transplants...)
- **Itch controllers**
  - S-777469 cannabinoid receptor 2 selective agonist SHIONOGI INC.
  - VLY-686 neurokinin-1 receptor antagonist VANDA PHARMA
  - DNK 333 dual tachykinin NK1/NK2 receptor antagonist NOVARTIS
  - SB705498: TRPV1 antagonist, GSK
  - CT 327 TrkA kinase inhibitor (neurogenesis), CREABILIS SA
- **Oral/topical antiinflammatory drugs**
  - SEGRAs derived from corticosteroids, BAYER
  - Anti PDE4, GSK, EISAI, OTSUKA, DERMIRA, PRECISION DERM, ANACOR
  - CRTH2 (DP1, 2) antagonists, NOVARTIS, ATOPIX, TAISHO
  - Janus kinase inhibitors (tofacitinib) PFIZER ...



# **AD Clinical Trials registered biologics**

- **Dupilumab anti recept IL4/13 Regeneron**
- **QGE031 Anti IgE Novartis**
- **MEDI4212 Anti IgE MedImmune**
- **Ustekinumab JANSSEN**
- **ILV-094 anti IL-22 Antibody**
- **AMG 157 anti TSLP receptor AMGEN**
- **Anti-Interleukin 31 Bristol-Myers Squibb**
- **CIM331 CHUGAI Anti-IL-31 receptor humanized monoclonal**
- **FURESTEM-AD mesenchymal stem cells KANG STEM BIOTECH CO., LTD. Korea**

# Importance of the medical perspective: several phases, several strategies

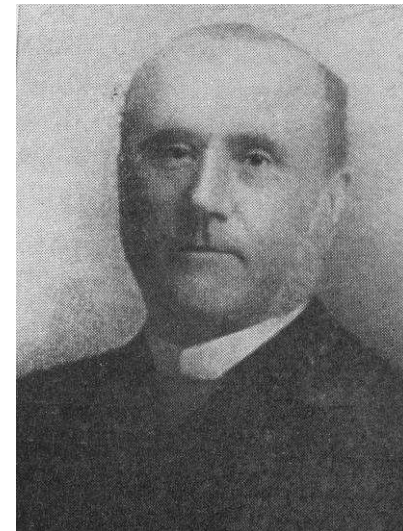
	Initiation phase	Revelation phase	Chronic phase	Extracutaneous phase
<b>clinical</b>	No symptom /dry skin	Pruritus+++ «contact » AD Reversible	Pruritus+++ Flexural stable AD	Asthma/rhinitis
<b>Key factors</b>	<div style="border: 1px solid red; padding: 2px;">Epidermal barrier impaired (FLG)</div> Skin innate immunity (TLR, peptides)	Antigens Tolerance yes/no Eosinophils, T cells	Cutaneous immune system Autoinflammation Unmasking autoAg T cells, Macrophages	Resp epithelial barrier Innate immunity (resp) Basophils, eosinophils, T cells, Macroph, Mast cells
<b>regulation</b>	Epigenetics Skin microflora Others:pH, temperature... Stress Dendr cells/Macroph	<div style="border: 1px solid blue; padding: 2px; display: inline-block;">Imbrication addition..., link with other barriers (digestive, respiratory)</div> 		Link with skin ? TSLP
<b>strategies</b>	Primary prevention Barriers, microflora	Local Antiinflammatoiy drugs Immunotherapies (skin) Prevention extracutaneous involvement	Immunosuppressive drugs Targeted biologics (TSLP, IL31, IL22, ustekinumab...)	Local antiinflammatory drugs antihistamines Immunotherapy(resp)

**Situating interventions according to phases +++**

(Taieb et al, JDDG, 2011)

# Initiation phase: before drug intervention, some basic issues not solved, e.g. bathing

- Vienna school (Hebra, Kaposi):
  - major importance of local treatments and water use, bathing, showers
- Besnier (1897) :
  - "Baths of any kind should be given to children with eczema **sparingly**, based on specific indications"
- Marfan (1928) :
  - "**Do not bathe the infant with eczema** (...) You just wash integuments with warm boiled water or better with an emollient water as bran in water, then dried thoroughly with sterilized cotton wool."
- Babonneix (1935) :
  - « **Just omit bathing** »



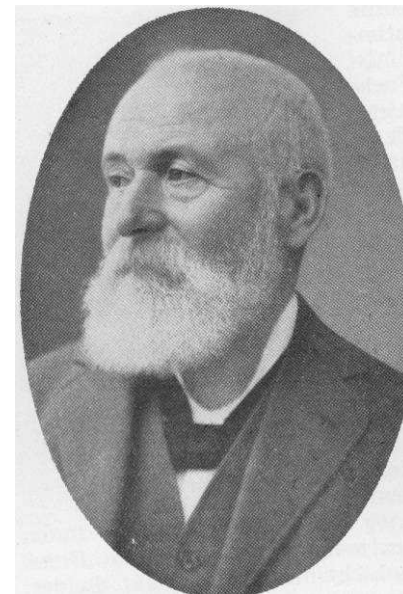
**Ernest Besnier**  
**1831-1909**

# Common to all clinical phases: need to fight itch

- *"Let's remember that the clinical benefit of the patient must prevail ... **trying to find an effective way to combat the itch of eczema**. This point should be considered at the next Congress"*

*Excerpted of the proceedings of Paris 1900 WCD about the theory of Unna*

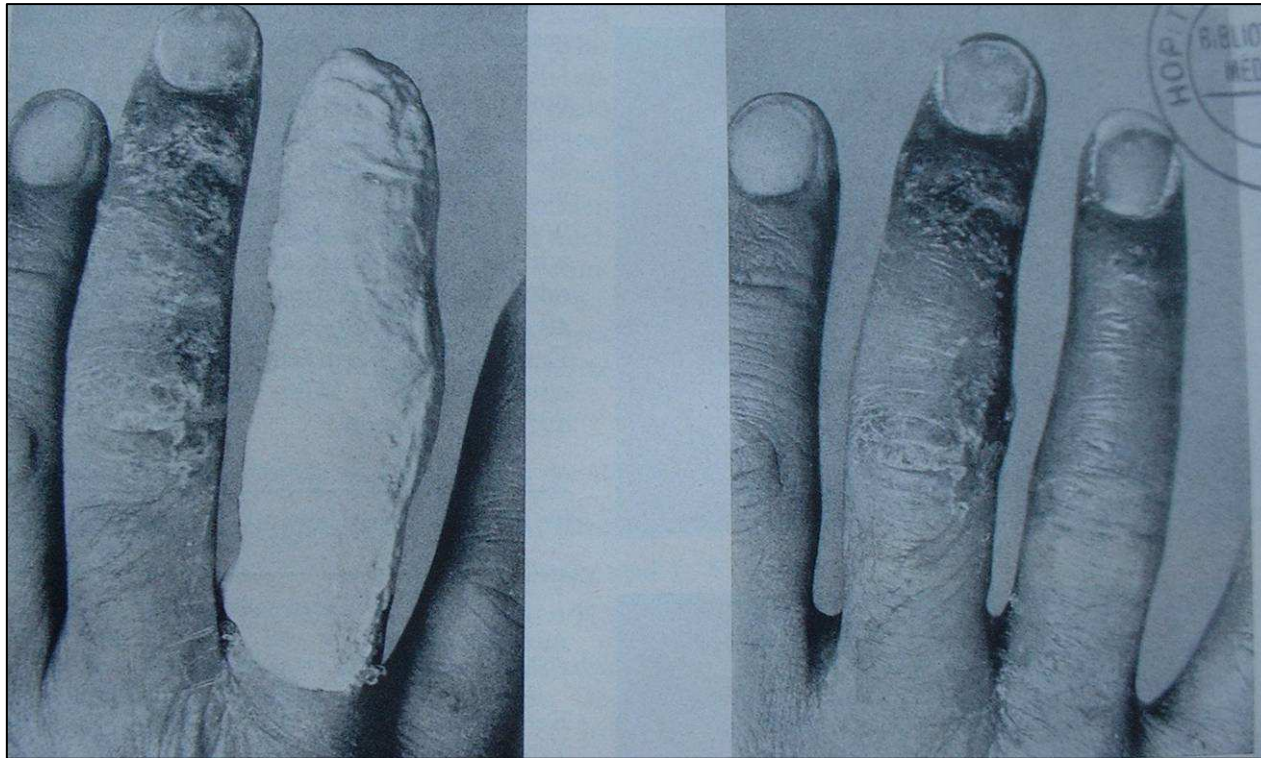
**Current perspective: can itch be understood  
From the perspective of « allergic » inflammation?**



**Paul Gerson Unna  
1850-1929 and the microbial  
theory of eczema**



# « Neurodermatitis » from Jacquet's experiment to current intervention strategies



Jacquet's experiment of 1892 replicated in Germany, 1957: Simons RDG.,  
Weitere Studien über den Einfluss von Abschluss und Ruhigstellung durch  
Gipsverband auf Ekzeme, *Der Hautarzt*, 1957, 2 : 65-69.

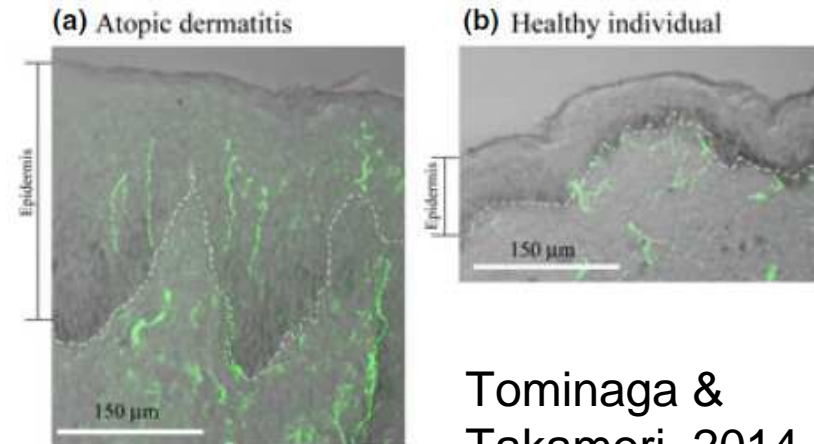
# Pruritus, nerves, inflammation

## 1. Peripheral mediators

Source	Mediators	Receptors
Mast cells	Histamine	H1 (H4?)
Nerves	Substance P	
Eosinophils	Reactive oxygen	
Fibroblasts	Artemin	
Keratinocytes	Nerve growth factor, semaphorin 3A	
T cells	IL-2	IL-2 receptor
	IL-31	IL-31 receptor
Endothelial cells	Endothelin	
	Acetylcholine	ACh receptor

## 2. Central mediators

Mediators	Receptors
Enkephalin	
Morphine/opioid	$\mu$ receptor (pruritogenic) $\kappa$ receptor (anti-pruritogenic)



Tominaga & Takamori, 2014

Kabashima, 2013

**TSLP, a newcomer**  
**Wilson et al, 2013**

# Intervention on epidermal nerve sprouting?

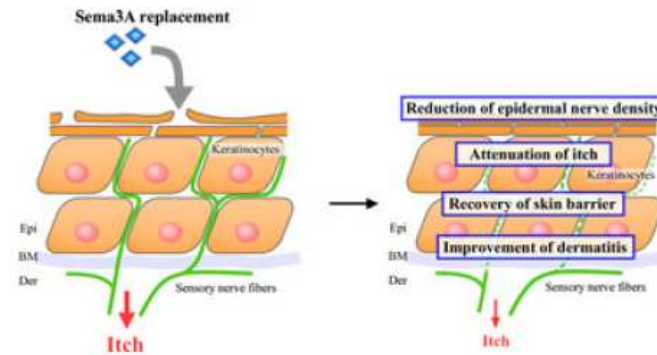
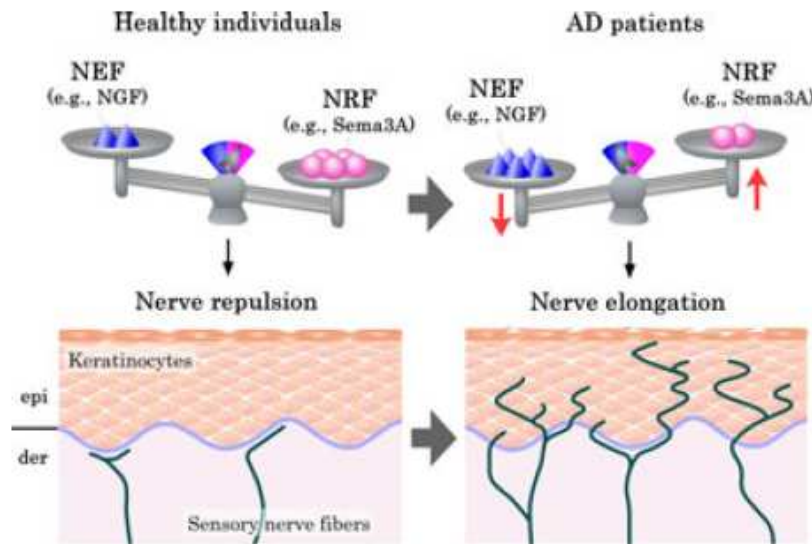


Figure 5. Strategy of semaphorin 3A (Sema3A) replacement. Rescue of Sema3A function using Sema3A-containing ointment or intradermal injection may reduce the nerve density in the epidermis and attenuate itch. In addition, this treatment may recover skin barrier function and improve dermatitis.

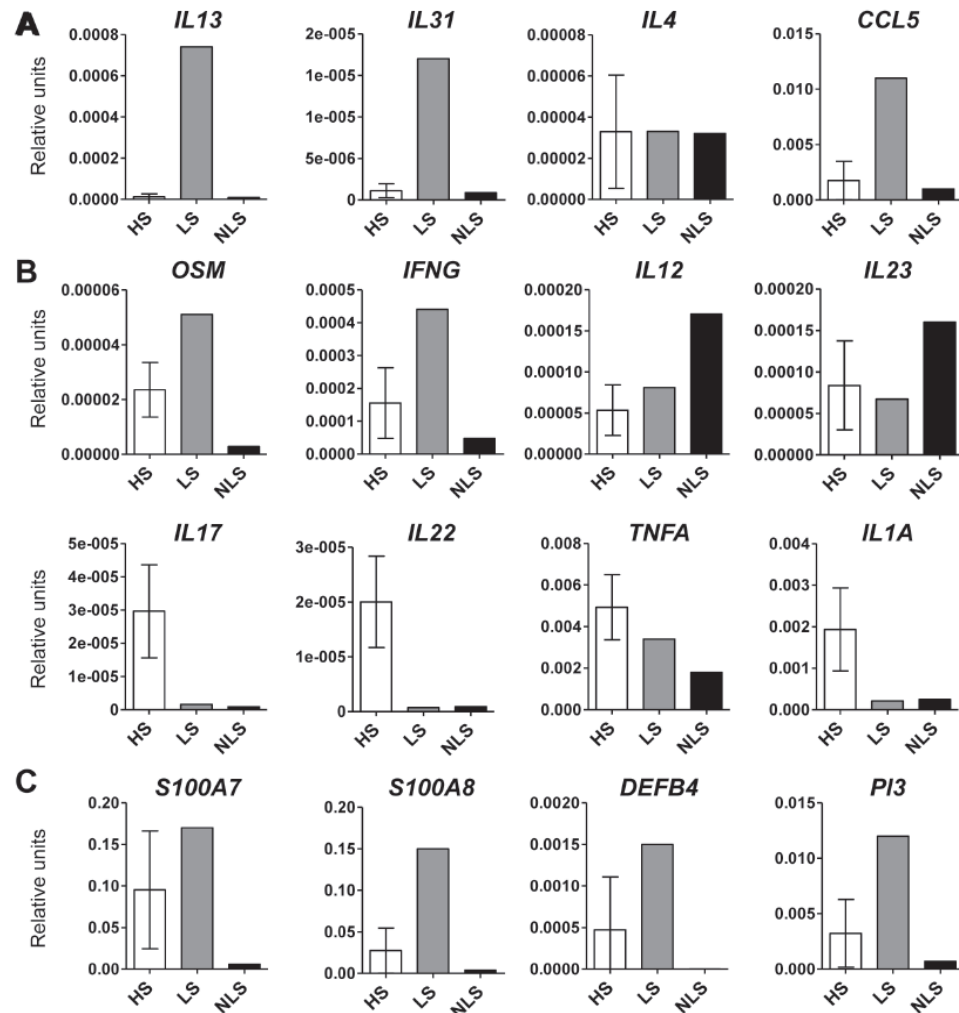
## Itch and nerve fibers with special reference to atopic dermatitis: Therapeutic implications

Mitsutoshi TOMINAGA,<sup>1</sup> Kenji TAKAMORI<sup>1,2</sup>

J Dermatol 2014



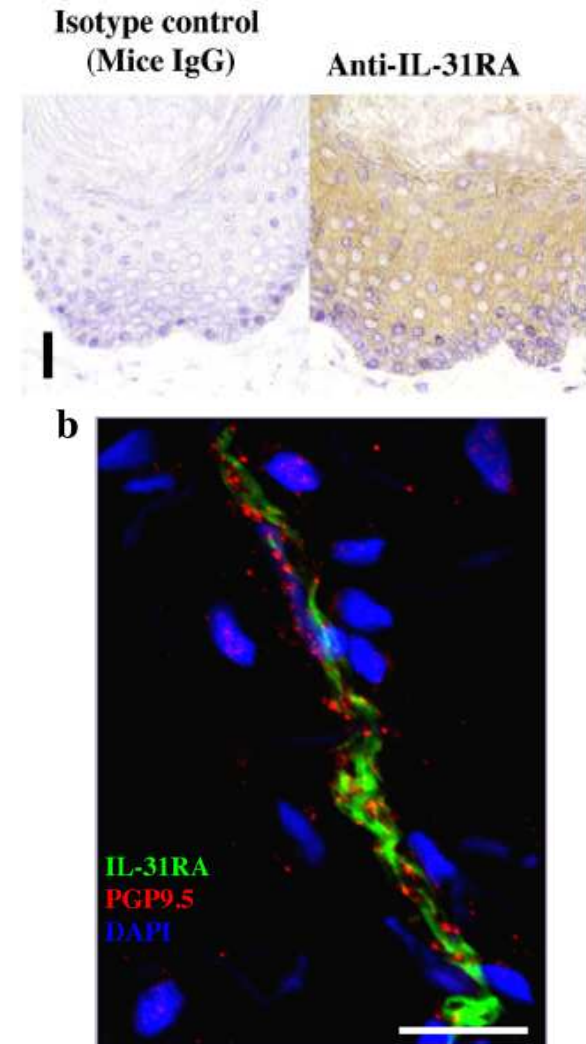
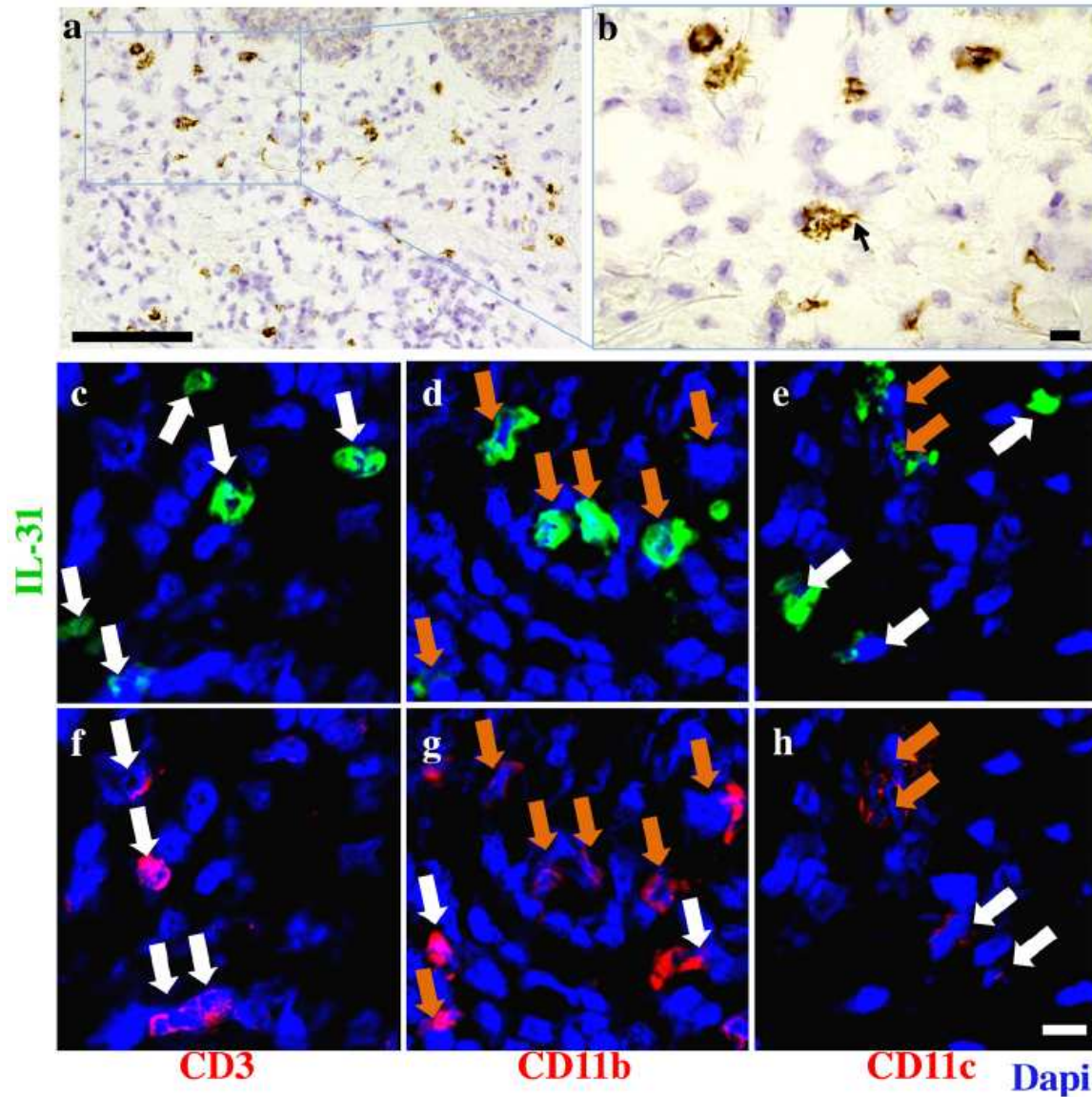
# Link to « allergic » cytokines? Monogenic dermatological model: lichen amyloidosis and IL31-OSM



Dousset et al, 2014

# IL-31 and IL-31R in AD skin

Kato et al, JDS, 2014

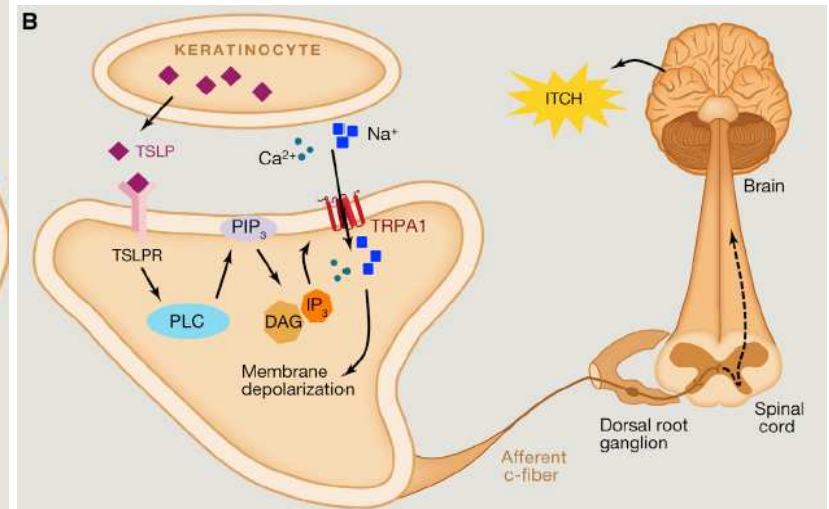
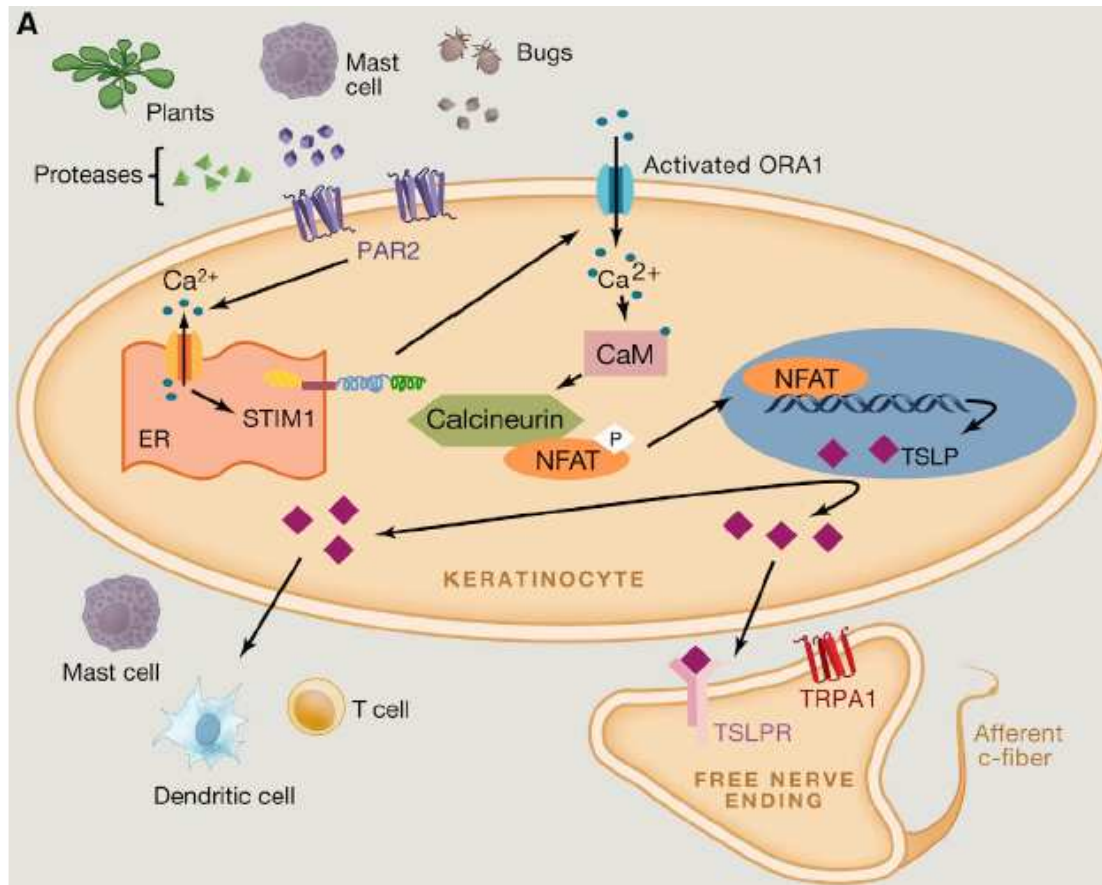




# The Epithelial Cell-Derived Atopic Dermatitis Cytokine TSLP Activates Neurons to Induce Itch

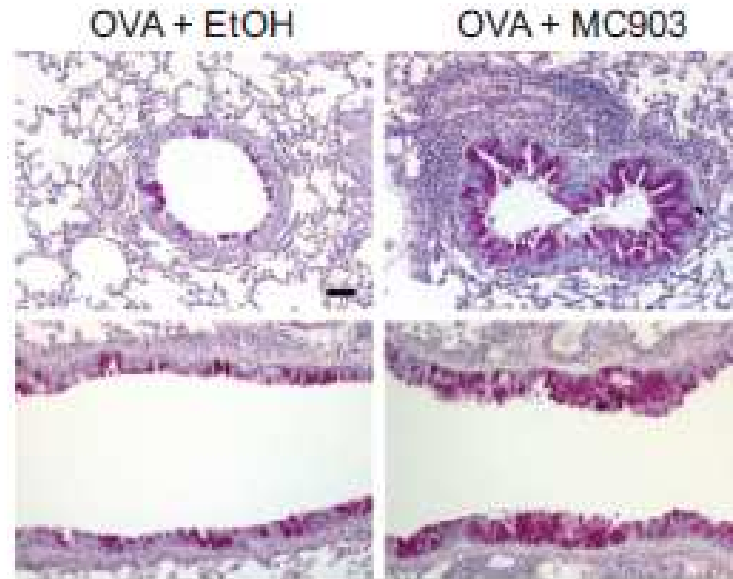
Sarah R. Wilson,<sup>1,2,3</sup> Lydia Thé,<sup>1,3</sup> Lyn M. Batia,<sup>1</sup> Katherine Beattie,<sup>1</sup> George E. Katibah,<sup>1</sup> Shannan P. McClain,<sup>1</sup> Maurizio Pellegrino,<sup>1</sup> Daniel M. Estandian,<sup>1</sup> and Diana M. Bautista<sup>1,2,\*</sup>

Cell, 2013

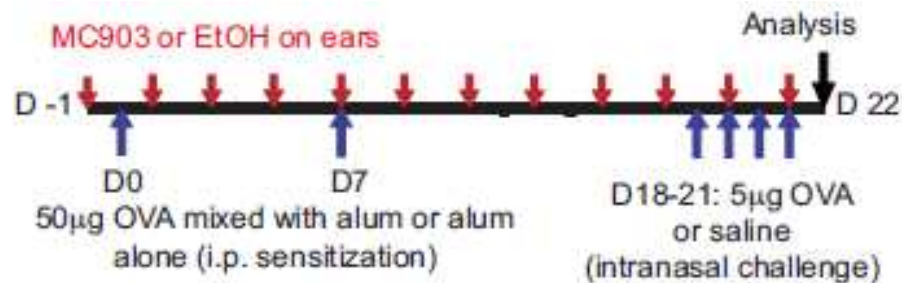


A missing link ?

# Calcipotriol-induced mouse AD and TSLP



Effect abolished in TSLP<sup>-/-</sup> mouse



Zhang et al, PNAS 2009

Adjunctive effect of epidermal TSLP on distant airways allergic sensitization

# What can be translated from non-allergic inflammation?

- **T cell–mediated allergic disease probably involves multiple chemokines and their receptors, the relative roles of which will vary depending**
  - on the affected organ
  - on the temporal phase of the disease.
- **Test of existing drugs used in non allergic inflammatory diseases recommended in recalcitrant AD as POC**

## Biologics and targeted therapies: significant failures and ongoing development in AD

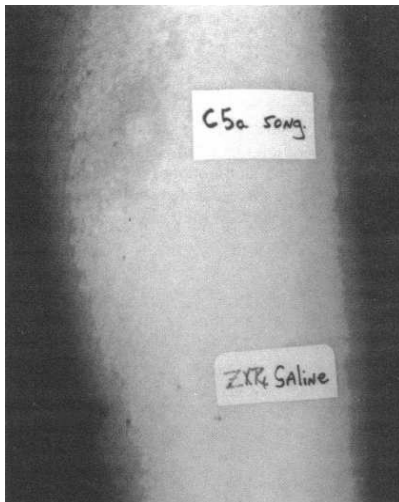
- Anti-IgE (competes with IgE high affinity receptor): **omalizumab** others in development (Novartis, Medimmune)
  - Pathogenic role of IgE unclear in AD
- Anti T Cell recruitment/trafficking/activation: **efalizumab, alefacept, anti PD2 receptors**
- Anti B cell: rituximab (anti CD 20)\*
- Anti TNF: **infliximab**
- Anti IL4-IL13 (TH2 cytokines) and receptor: **nuvance, pitrakinra, dupilumab, librikizumab**
- Anti IL5 (eosinophils): **mepolizumab, (anti PD2 receptors)**

\*Simon et al, JACI 2008, 6 patients treated

# How to translate faster crucial lab data on pruritogenic inflammation into practice?

Increased Epidermal Cell Proliferation in Normal Human Skin *in Vivo* Following Local Administration of Interferon- $\gamma$  1993

Jonathan N. W. N. Barker,\* John R. Goodlad,<sup>†</sup>  
Elizabeth L. Ross,\* Carmen C. Yu,<sup>‡</sup>  
Richard W. Groves,\* and  
Donald M. MacDonald\*



**Studies of Human C5a as a Mediator of Inflammation in Normal Human Skin**

Kim B. Yancey, Carl H. Hammer, Liana Harvath, Lois Renfer, Michael M. Frank, and Thomas J. Lawley 1984



# Summary and conclusions

- Therapy according to stage of natural history of AD in addition to severity.
- Therapy according to genetic subtype???
- Prevention: public health dimension of the problem for food allergy and asthma +++
- (Too?) many druggable targets, many existing products not yet tested to fight pruritic inflammation: justification of ongoing and future POC pilot trials (e.g : anti IL6, anakinra IL1R)
- Need of faster POC studies