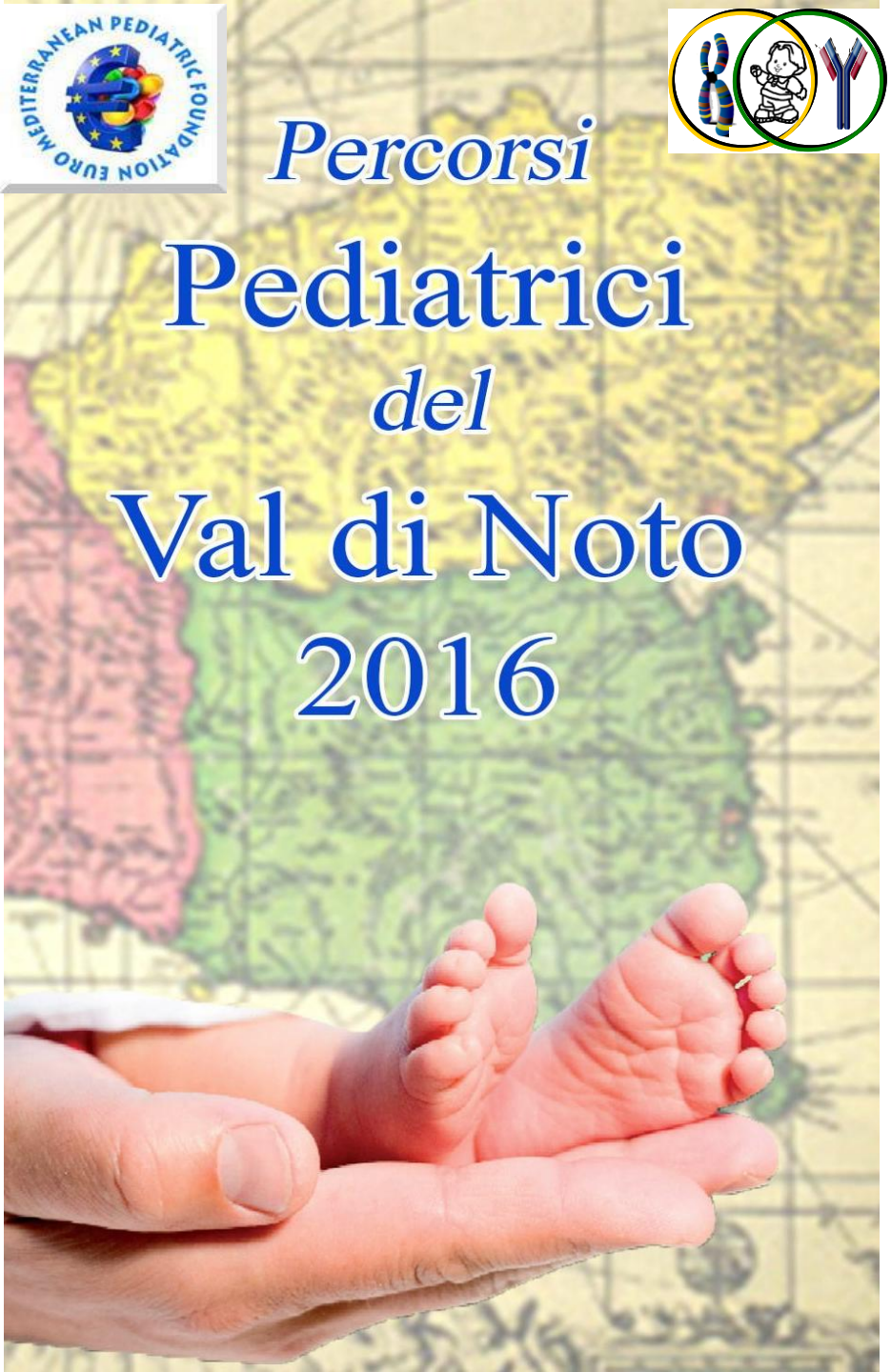
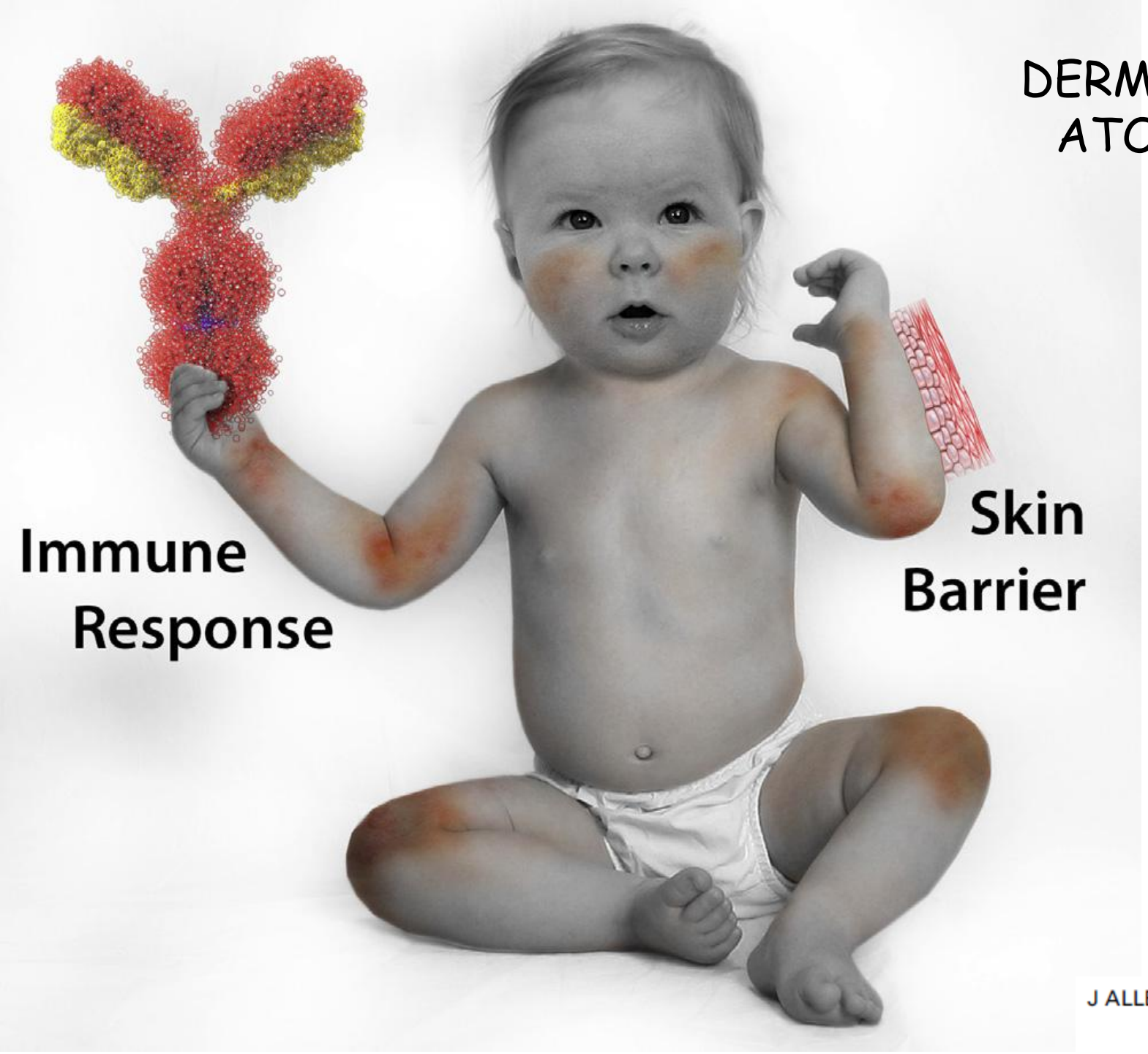


Università degli studi di Messina
Dip. di Scienze Pediatriche Mediche e Chirurgiche
U.O. C. di Genetica ed Immunologia Pediatrica
Centro di Riferimento Regionale per la Prevenzione, Diagnosi e Cura delle Malattie Genetiche
Direttore Prof. Carmelo Salpietro

DERMATITE ATOPICA: MECCANISMI IMMUNOLOGICI

Katia Cuppari

DERMATITE ATOPICA



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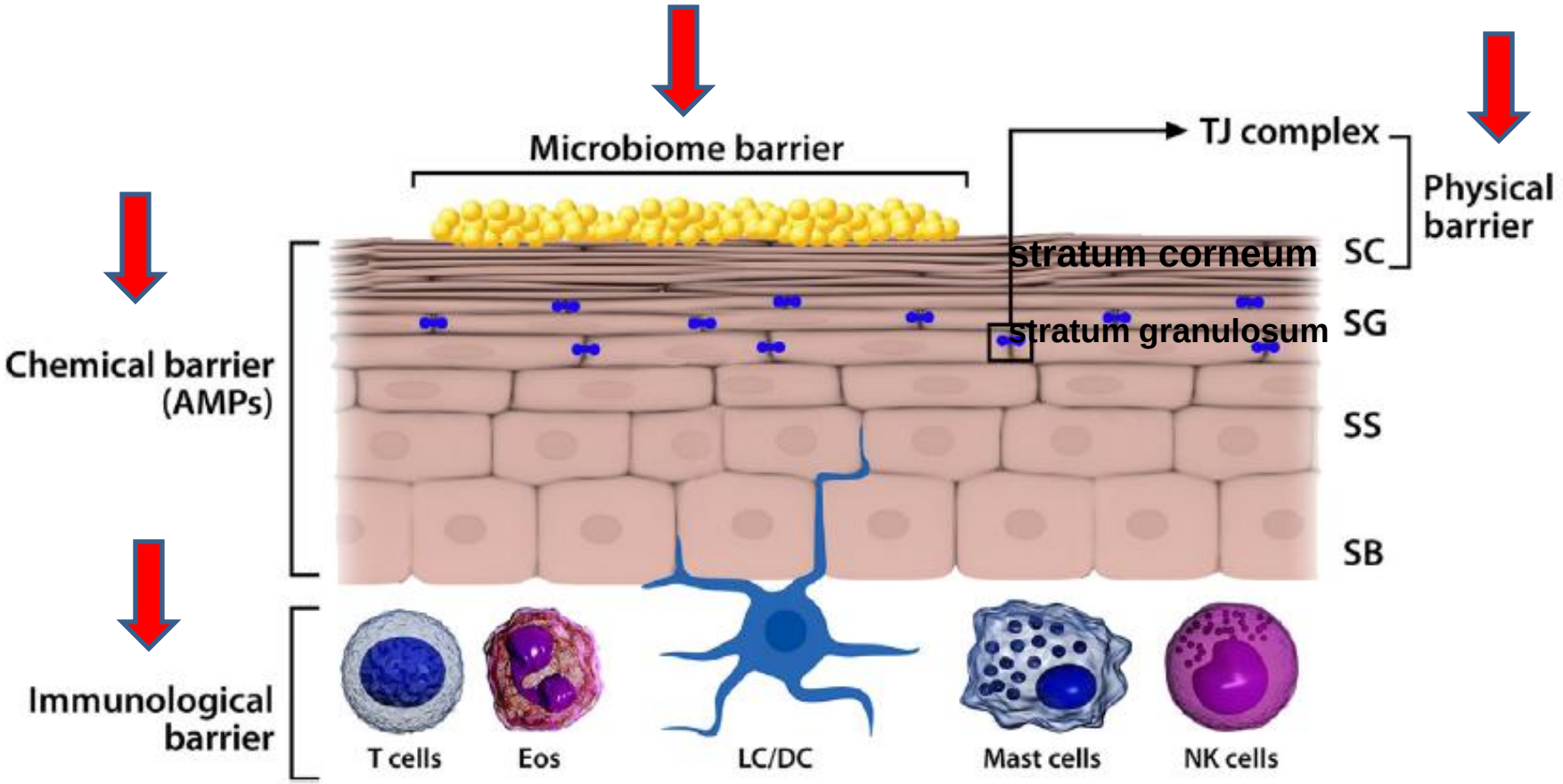
OCTOBER 2014

LE BARRIERE DELLA CUTE



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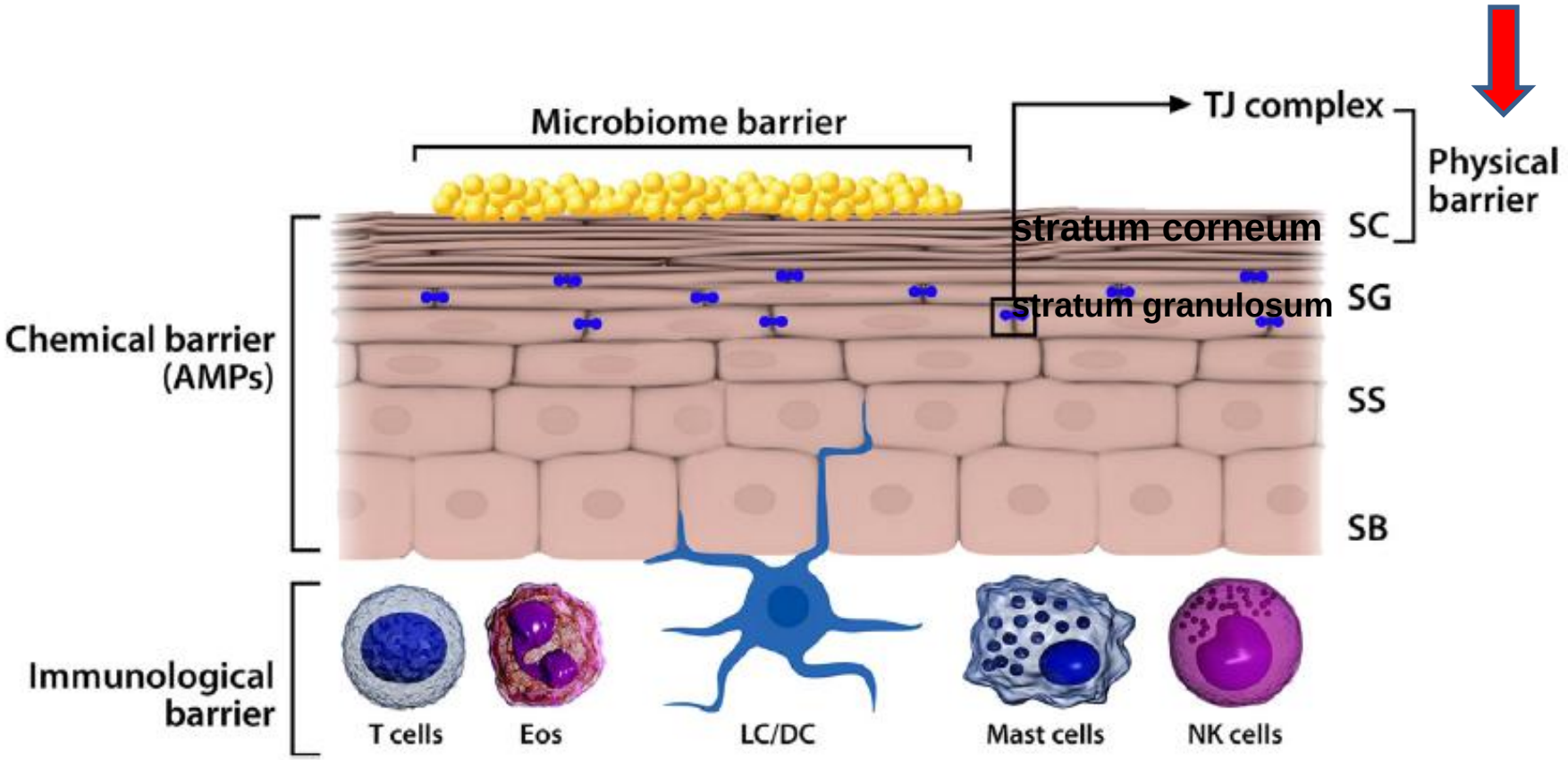
LE BARRIERE DELLA CUTE



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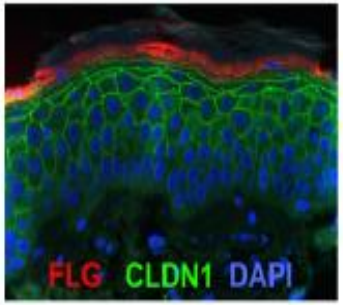
PROTEINE CUTANEE



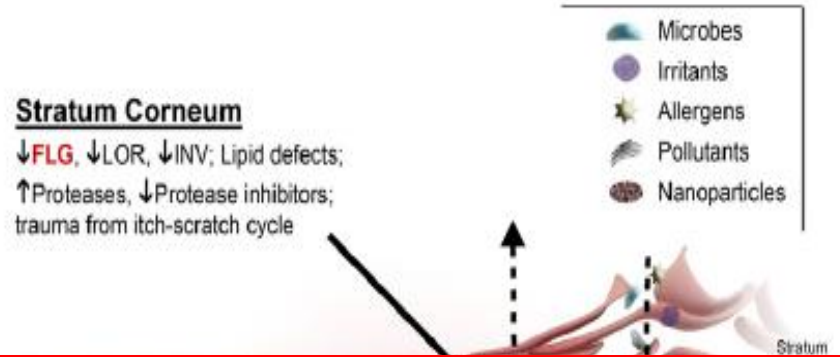
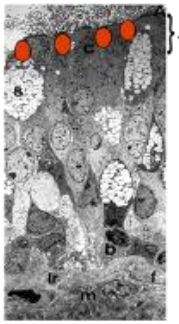
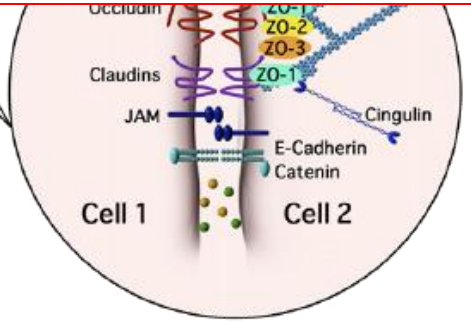


Table 1
Skin barrier–related genes associated with AD/AD-like dermatitis

Gene symbol	Gene name	Functions
Filaggrin system		
FLG	Filaggrin	Major constituent of keratohyalin granules; bundling keratin filament to form keratin pattern; degradation products are reported to have skin-moisturizing activity
Desquamation		
SPINK5	Serine peptidase inhibitor, Kazal type 5	pH-dependent inhibition of KLK5 and KLK7
KLK7[B]	Kallikrein-related peptidase 7	Digestion of corneodesmosin
CDSN	Corneodesmosin	Structural protein of corneodesmosomes
Others		
CSTA	Cystatin A	Cysteine protease inhibitor of house dust mite protease
CLDN1[D]	Claudin 1	Integral transmembrane protein of TJs





- adapter proteins (catenin, ZO 1-3) to the cytoskeleton (actin and cingulin).

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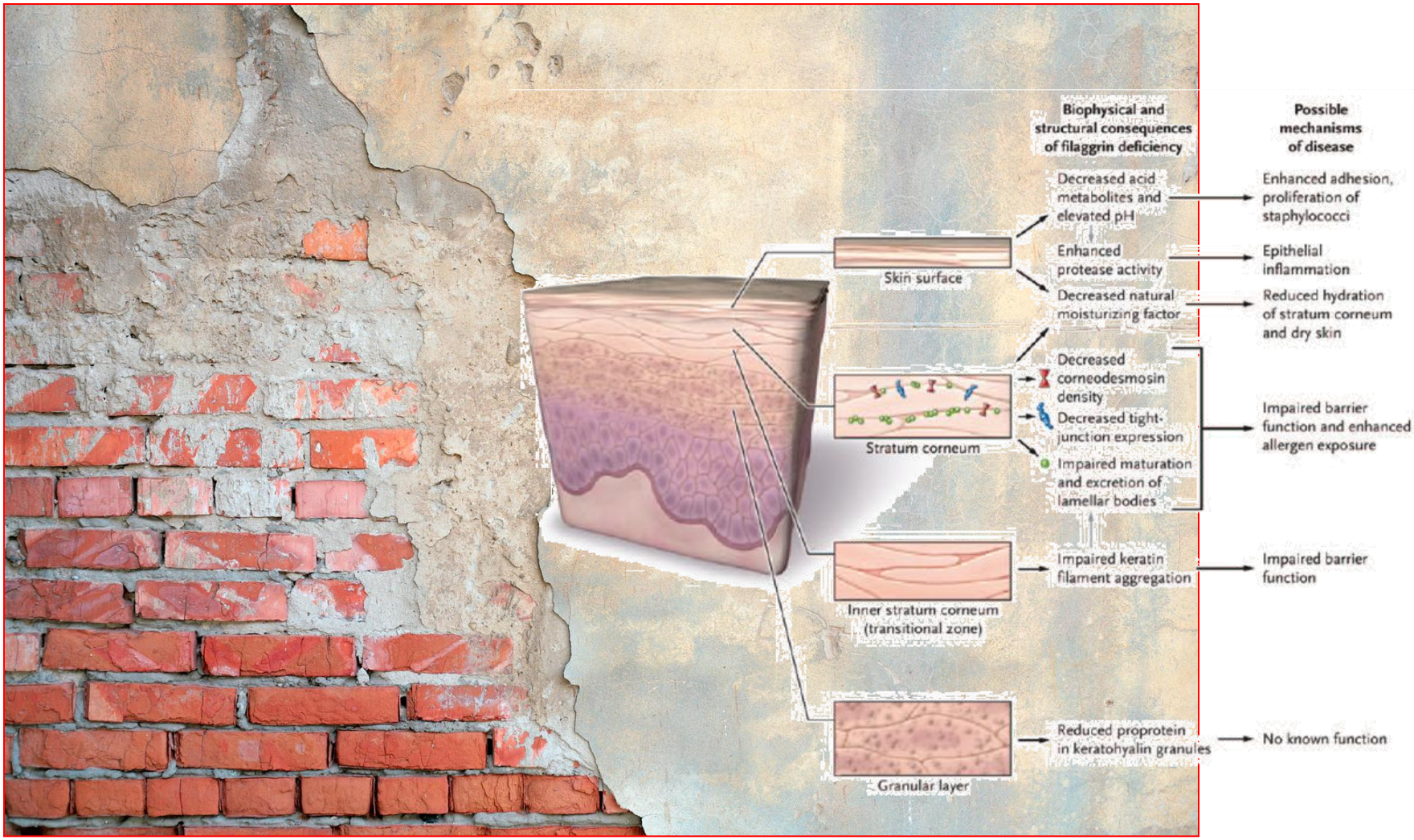
MARCH 2011

LE BARRIERE DELLA CUTE

BARRIERIA FISICA



The Journal of Clinical Investigation http://www.jci.org Volume 122 Number 2 February 2012

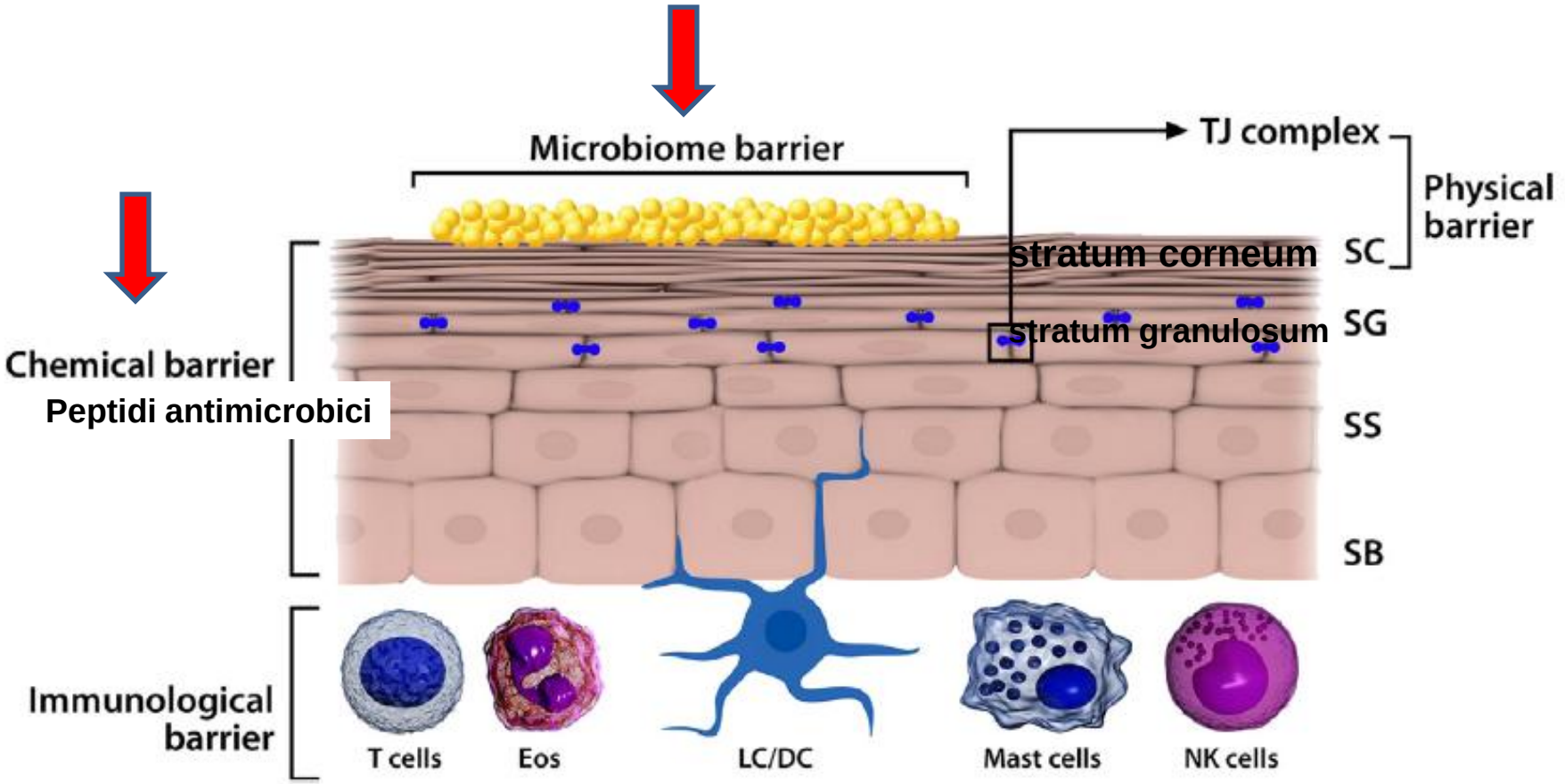
TABLE I. Comparison of clinical and biophysical features of patients with AD with (AD_{FLG}) and without ($AD_{NON\text{-}FLG}$) filaggrin mutations*

	Clinical features	Biophysical features
AD_{FLG}	Palmar hyperlinearity	Severe decrease in NMF
	More persistent	pH
	↑ Allergic sensitization	IL-1β
	↑ Risk of asthma	Type 1 interferon–mediated stress response
	↑ Severity of AD	
	↑ Eczema herpeticum	
$AD_{NON\text{-}FLG}$	No palmar hyperlinearity	Mild decrease in NMF
	Less persistent	pH lower compared with patients with AD_{FLG}
	Less allergic sensitization	IL-1β low compared with patients with AD_{FLG}
	Lower risk of asthma	Dysregulation of lipid metabolic processes

NMF, Natural moisturizing factor.

*Modified with permission from McAleer and Irvine.[28]

LE BARRIERE DELLA CUTE



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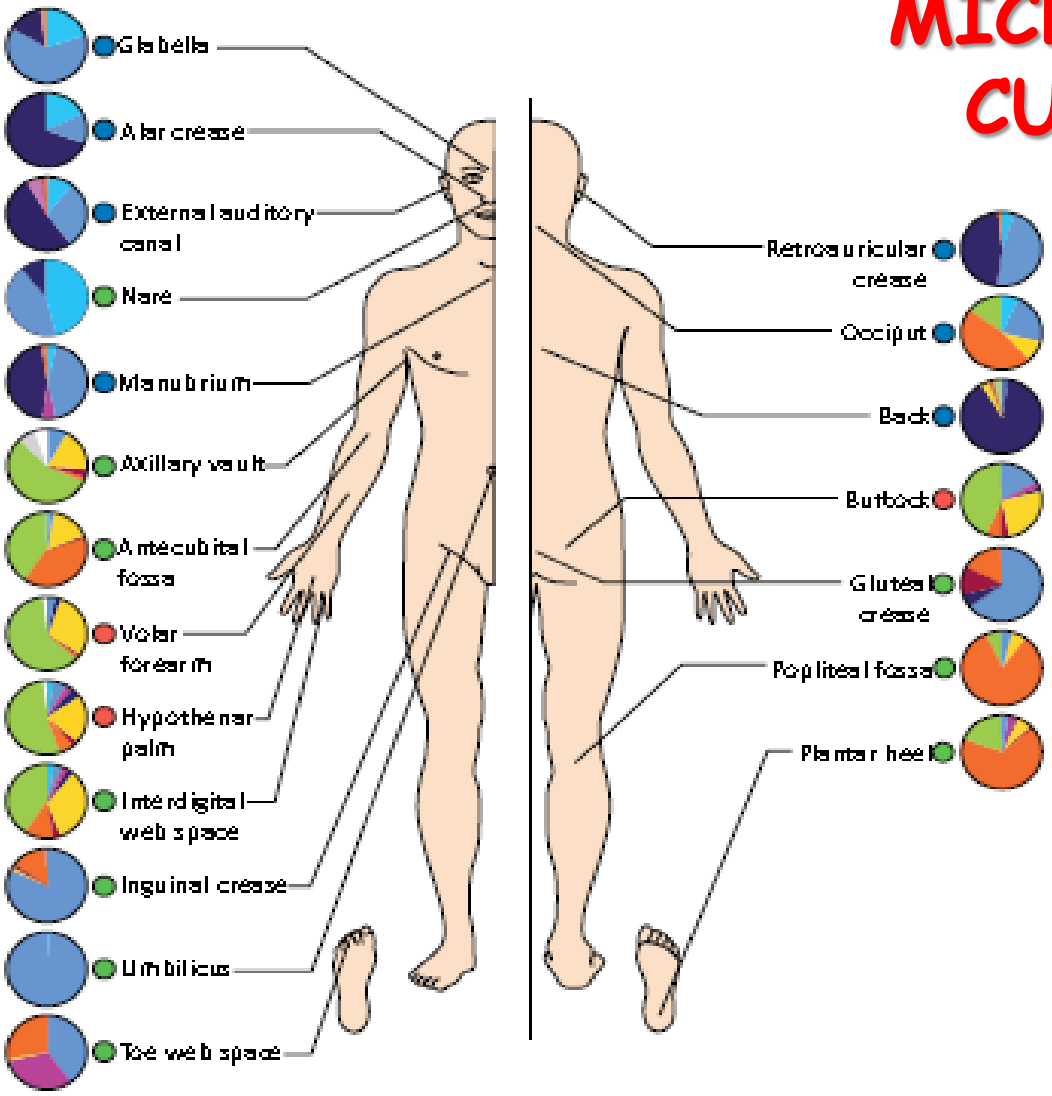
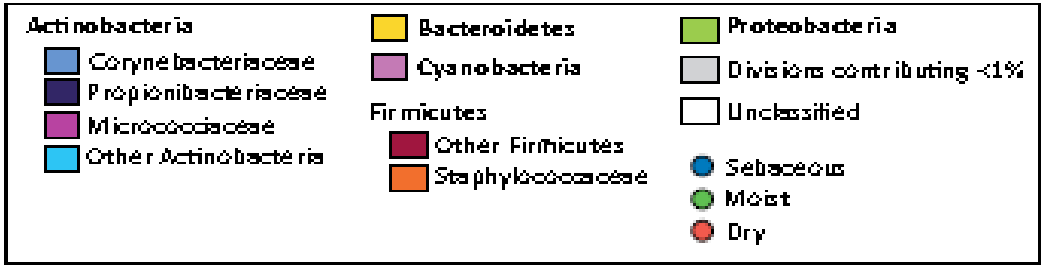
OCTOBER 2014

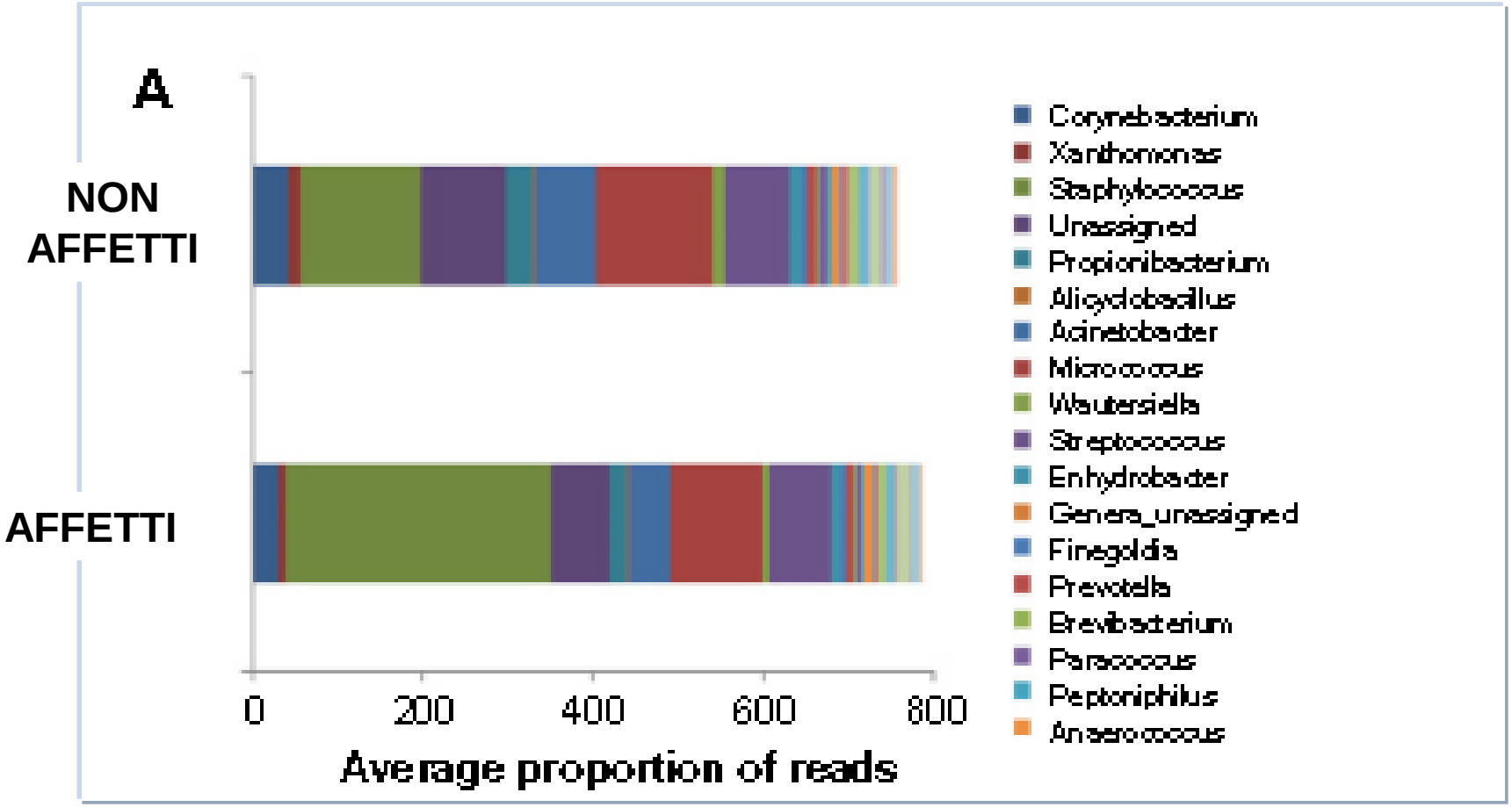
MICROBIOMA CUTANEO





Journal of Dermatology 2015; 42: 1–6

MICROBIOMA CUTANEO



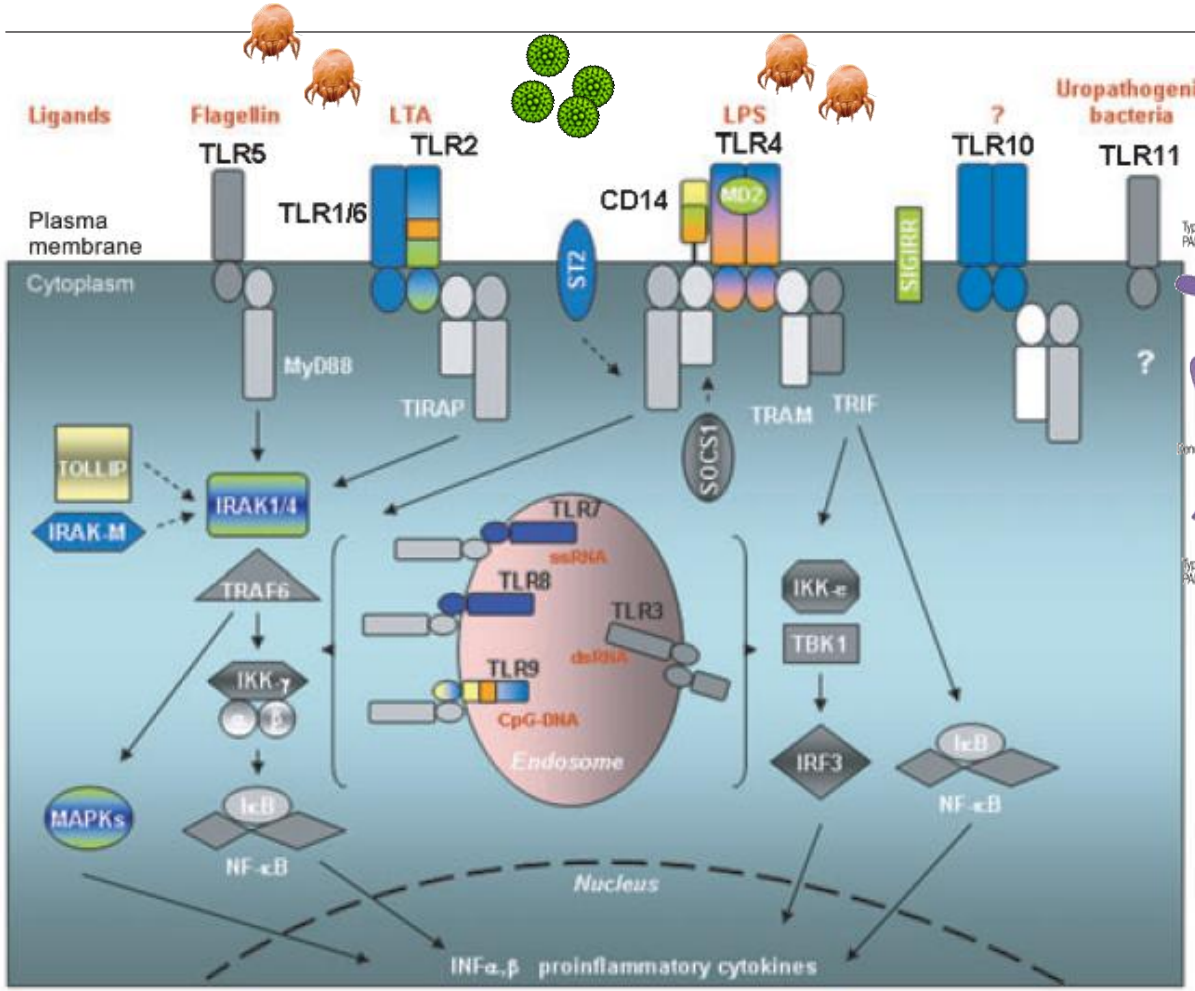
Clinical Cosmetic and Investigational Dermatology 2015:8

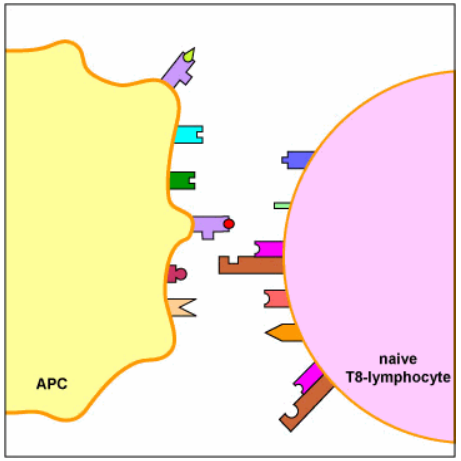
REVIEW ARTICLE

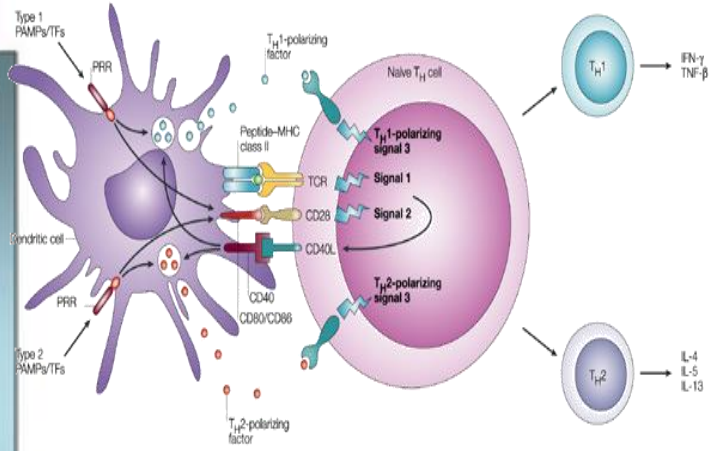
Genetic variations in toll-like receptor pathway genes influence asthma and atopy

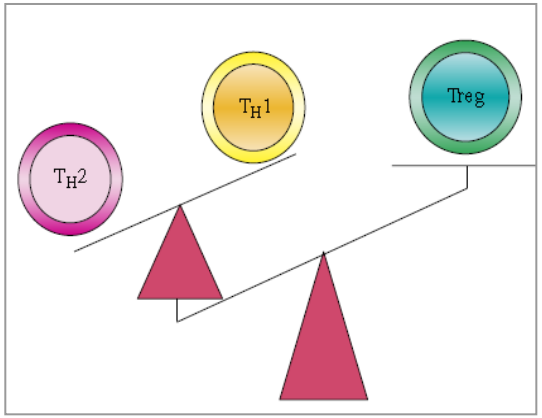
R. Tesse, R. C. Pandey & M. Kabesch

Center for Pediatrics, Clinic for Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany



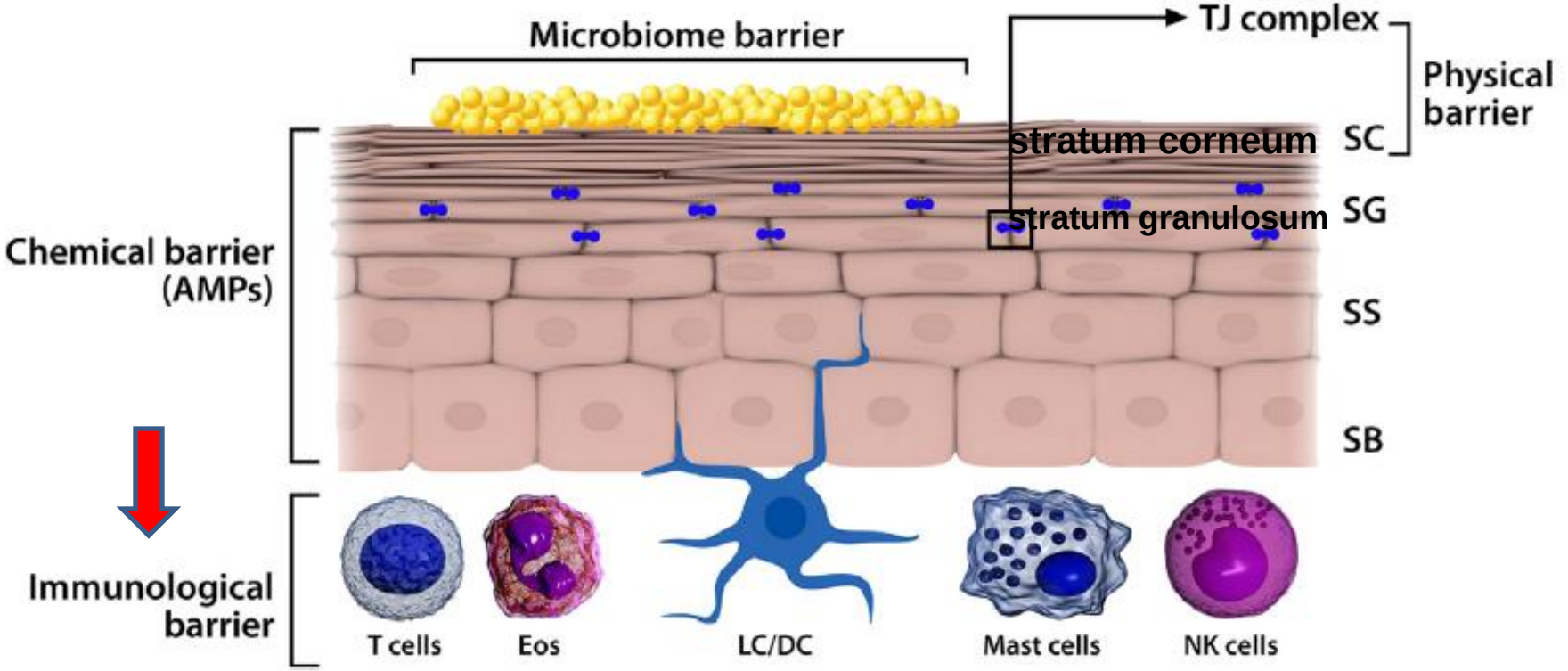






Asthma | Atopic eczema | Atopic sensitization | Others | None

LE BARRIERE DELLA CUTE



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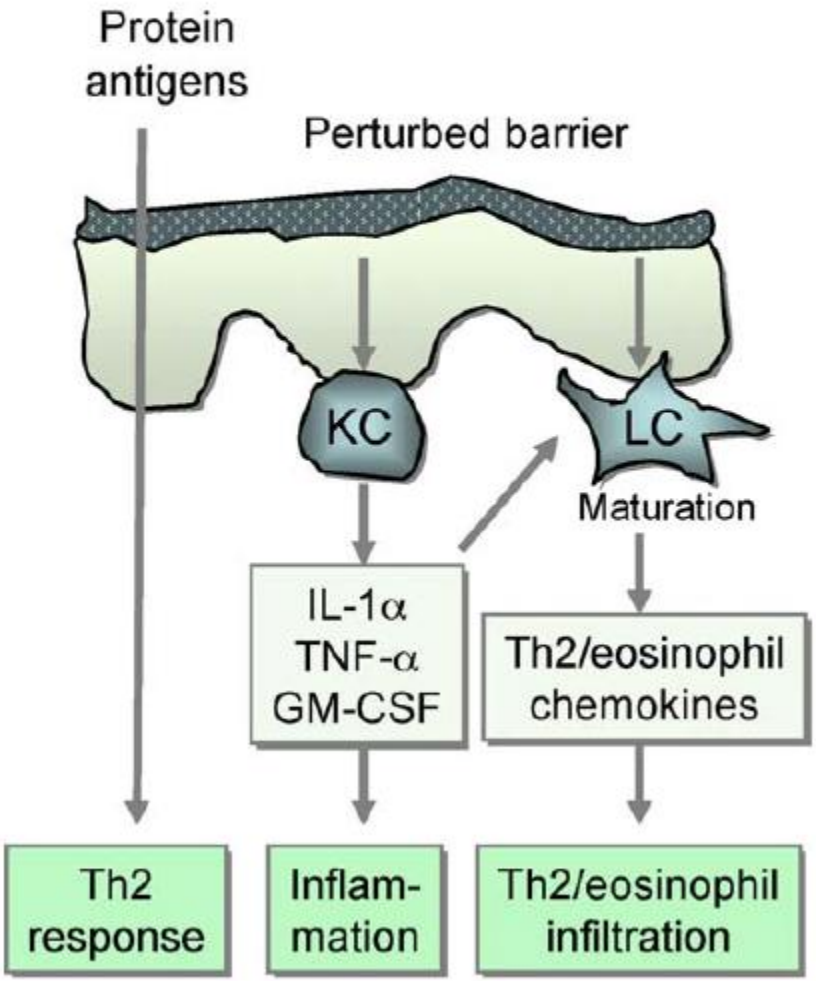
OCTOBER 2014

Extrinsic AD

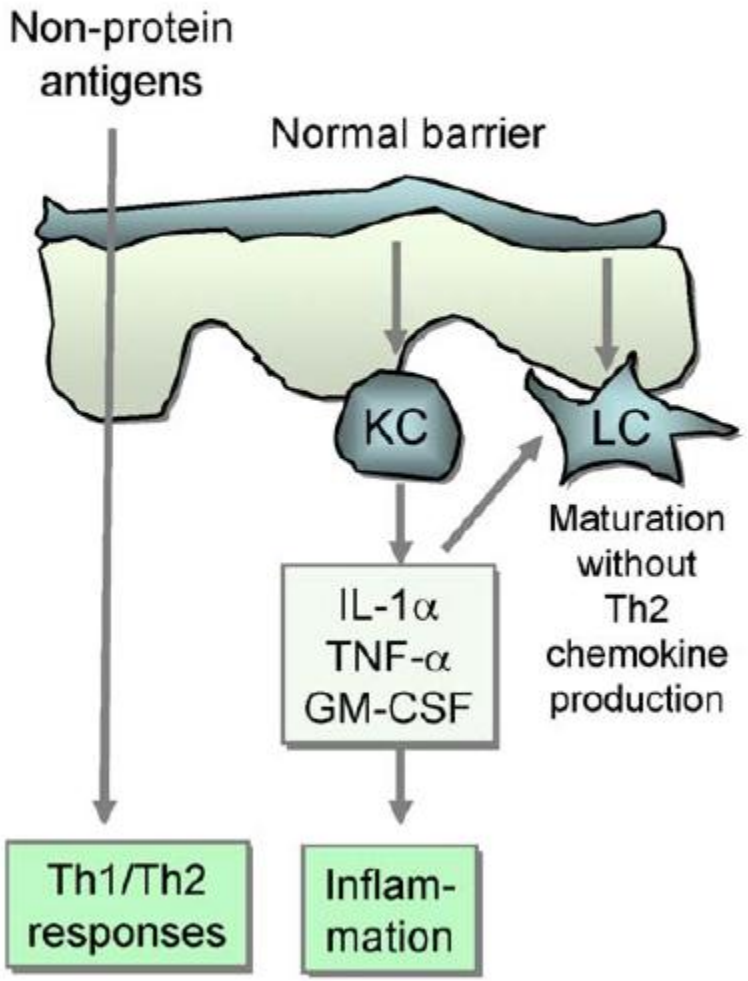
80%

elevation of total serum IgE



IL-4, IL-5 ,IL-13
eosinophil counts

Intrinsic AD



Y. Tokura / Journal of Dermatological Science 58 (2010) 1–7

EAACI Nomenclature

J ALLERGY CLIN IMMUNOL
MAY 2004

ATOPIC ECZEMA/DERMATITIS SYNDROME

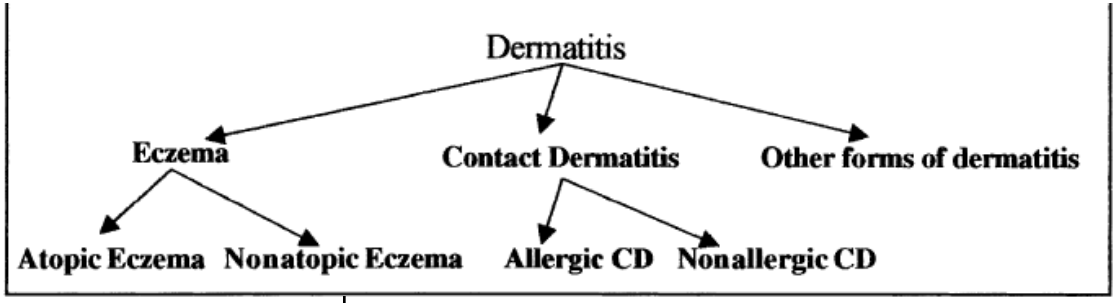


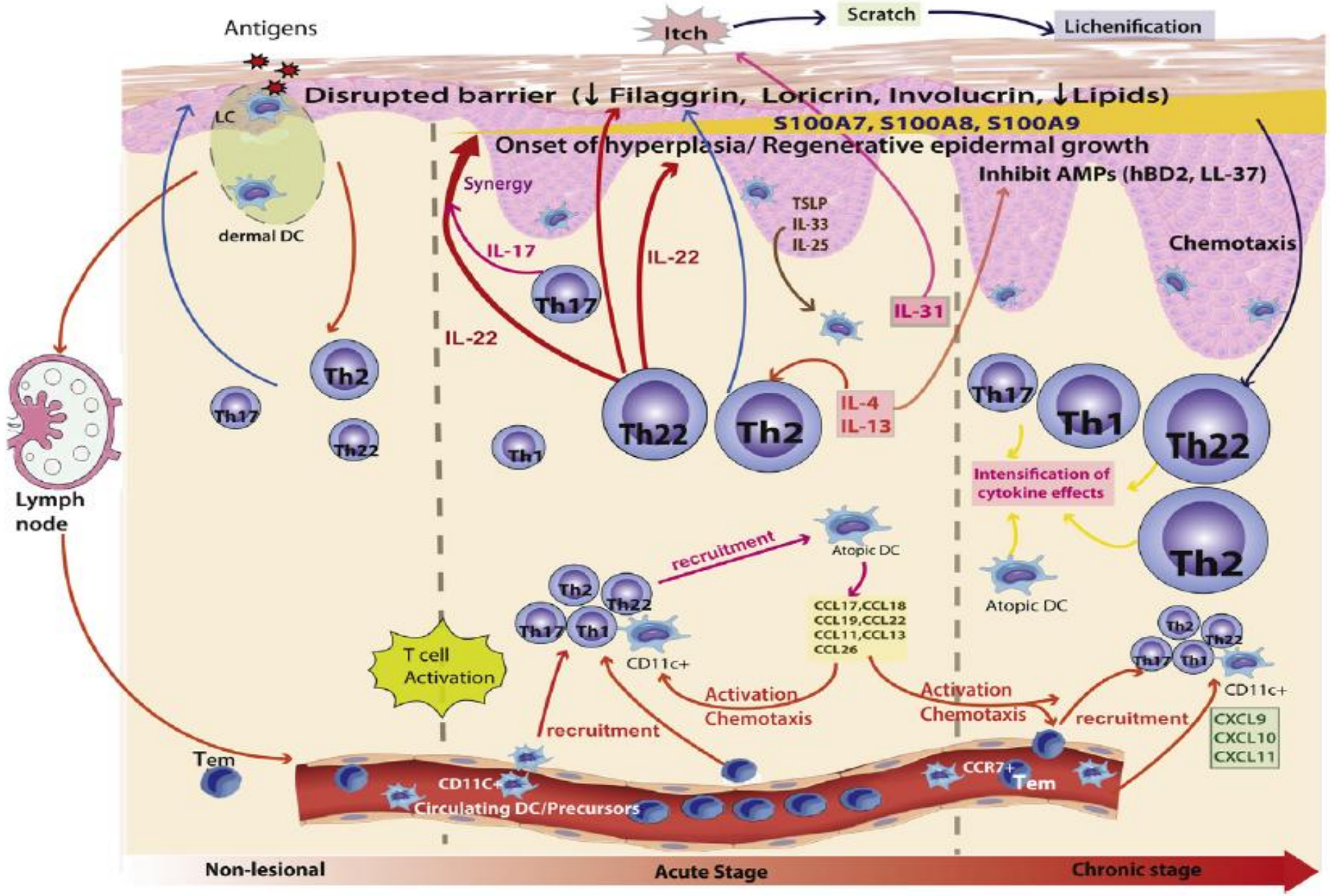
FIG 2. Under the umbrella *dermatitis, eczema* is now the agreed term to replace the transitional term atopic eczema/dermatitis syndrome (AEDS). Atopic eczema is eczema in a person of the atopic constitution.

the intrinsic type is termed **non-allergic AEDS**, which shows
- normal IgE levels,
- No specific IgE,
- no association with respiratory diseases (bronchial
- asthma or allergic rhinitis),
- negative skin-prick tests to common aeroallergens or food allergens

Table 2
Subsets of CD4T cells associated with skin.

Subset	Inducing cytokine	Master regulator	Effector cytokine	Inhibitors	Function	Host defense	Pathology
Th1	IFN-γ, IL-12	T-bet	INF-γ	IL-4	Activation of MF, Ig class switch to IgG1/G3 (human) or IgG2a/G3 (mouse)	Intracellular pathogens	Granulomatous disease
Th2	IL-4	GATA3	IL-4, -5, -10, -13	IFN-γ	Activation of MC, Bas, Eos, M2MF, barrier function, Ig class switch to IgE	Helminths	AD
Non-pathogenic Th17	IL-6, TGF-β	RORγt	IL-17, IL-10	IL-2, -4, IFN-γ, Foxp3, T-bet	Recruitment of neutrophils (?)	Undefined	Undefined
Pathogenic Th17	IL-6, IL-23, IL-1β, TGF-β3	RORγt, T-bet	IL-17, IL-22, IFN-γ, GM-CSF	Ditto and TGF-β1(?)	Recruitment of neutrophils	Extracellular bacteria and fungi	Psoriasis, RA, MS, AD
Th22	IL-6, TNF-α	Undefined	IL-22	TGF-β1	Induction of defensins	*Klebsiella pneumoniae* *Candida albicans*	Psoriasis, AD, chloracne
Th9	IL-4, TGF-β	PU.1, IRF4	IL-9	Undefined	Activation of skin-tropic T cells to produce IFN-γ, IL-9, -13, and -17		Allergy, psoriasis
Treg	IL-2, TGF-β	Foxp3	TGF-β, IL-10, IL-35	IL-6, RORγt, HIF1a	Peripheral tolerance, tuning of immune response	Tuning of inflammation	Cancer, chronic infection
Tr1	IL-27, TGF-β	c-Maf	IL-10	Undefined	Ditto	Ditto	Undefined
Th3	Undefined	Undefined	TGF-β	Undefined	Ditto	Ditto	Undefined
LAG3 Treg	Undefined	Undefined	IL-10	Undefined	Ditto	Ditto	Undefined

MF, macrophages; M2MF, M2 macrophage; MC, mast cells; Bas, basophils; Eos, eosinophils; AD, atopic dermatitis; Ig, immunoglobulin; RA, rheumatoid arthritis; MS, multiple sclerosis; Ditto, same as above.



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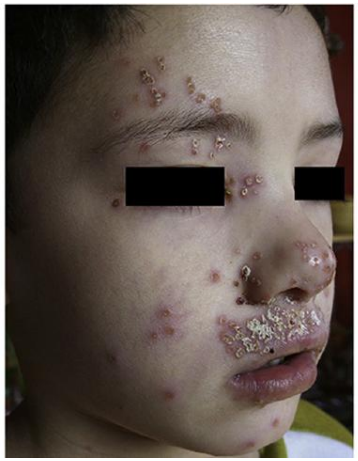

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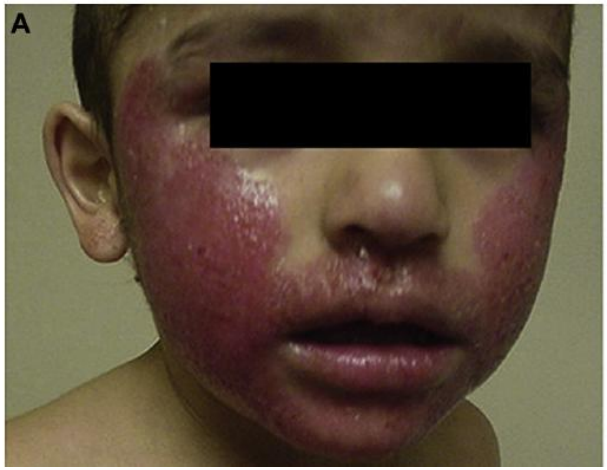

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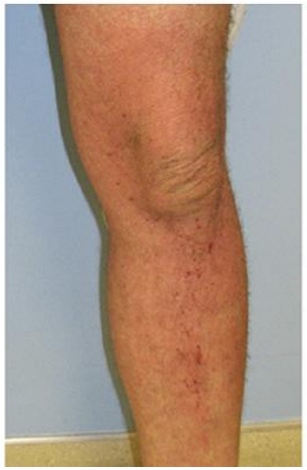


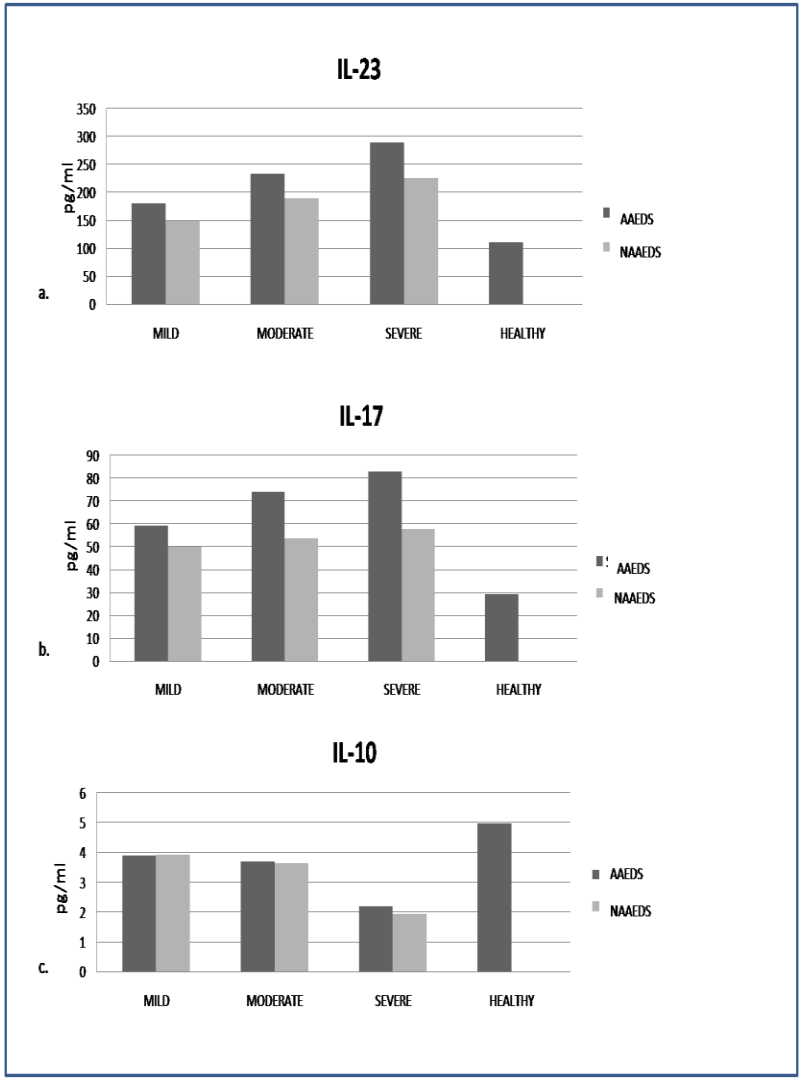
TABLE III. Summary of cytokine effects on the epidermis in patients with AD

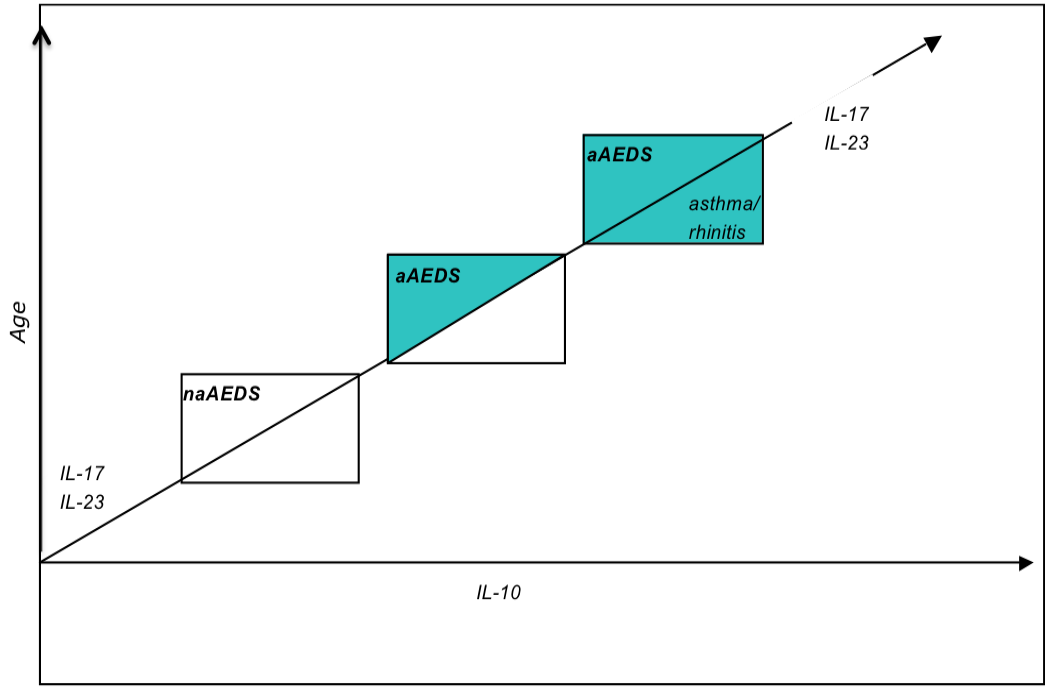
- Induce epidermal hyperplasia (IL-22)
- Induce spongiosis (T_H2 cytokines IL-4/IL-13 and TNF)
- Inhibit keratinocyte terminal differentiation (IL-4, IL-13, IL-31, IL-25/T_H2, IL-22/T_H22, and TNF) with potential for feedback hyperplasia
- Inhibit synthesis of AMPs (T_H2 cytokines IL-4, IL-13, and IL-33)
- Inhibit lipid synthesis (T_H2 cytokines IL-4/IL-13, IL-31, and TNF)
- Increase expression of S100A7, S100A8, and S100A9 (IL-22 plus IL-17)
- Induce TSLP production in KCs (IL-4/IL-13 and TNF)
- Promote itch (IL-31 and TSLP)
- Promote antiviral responses (IFN-γ, IFN-α, and IL-29)

KCs, Keratinocytes; *TSLP*, thymic stromal lymphopoietin.

Interleukin-17, interleukin-23, and interleukin-10 serum levels in children with AEDSand their relationship with clinical severity

Leonardi Salvatore, Cuppari Caterina, Manti Sara, Filippelli Martina, Borgia Francesco, Briuglia Silvana, Cannavò Patrizia, Salpietro Annamaria, Arrigo Teresa, SalpietroCarmelo





Allergy and *Asthma* Proceedings in press

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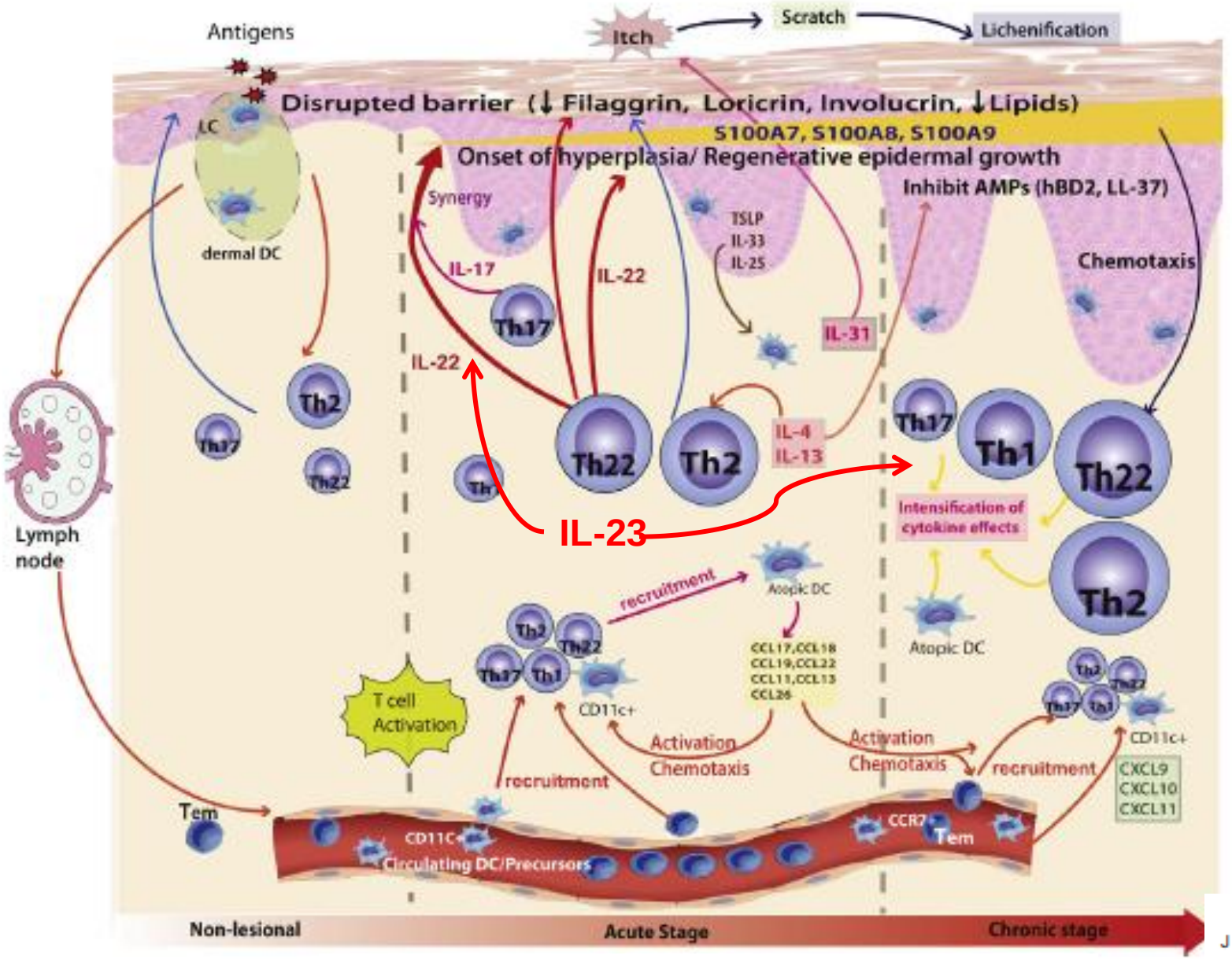

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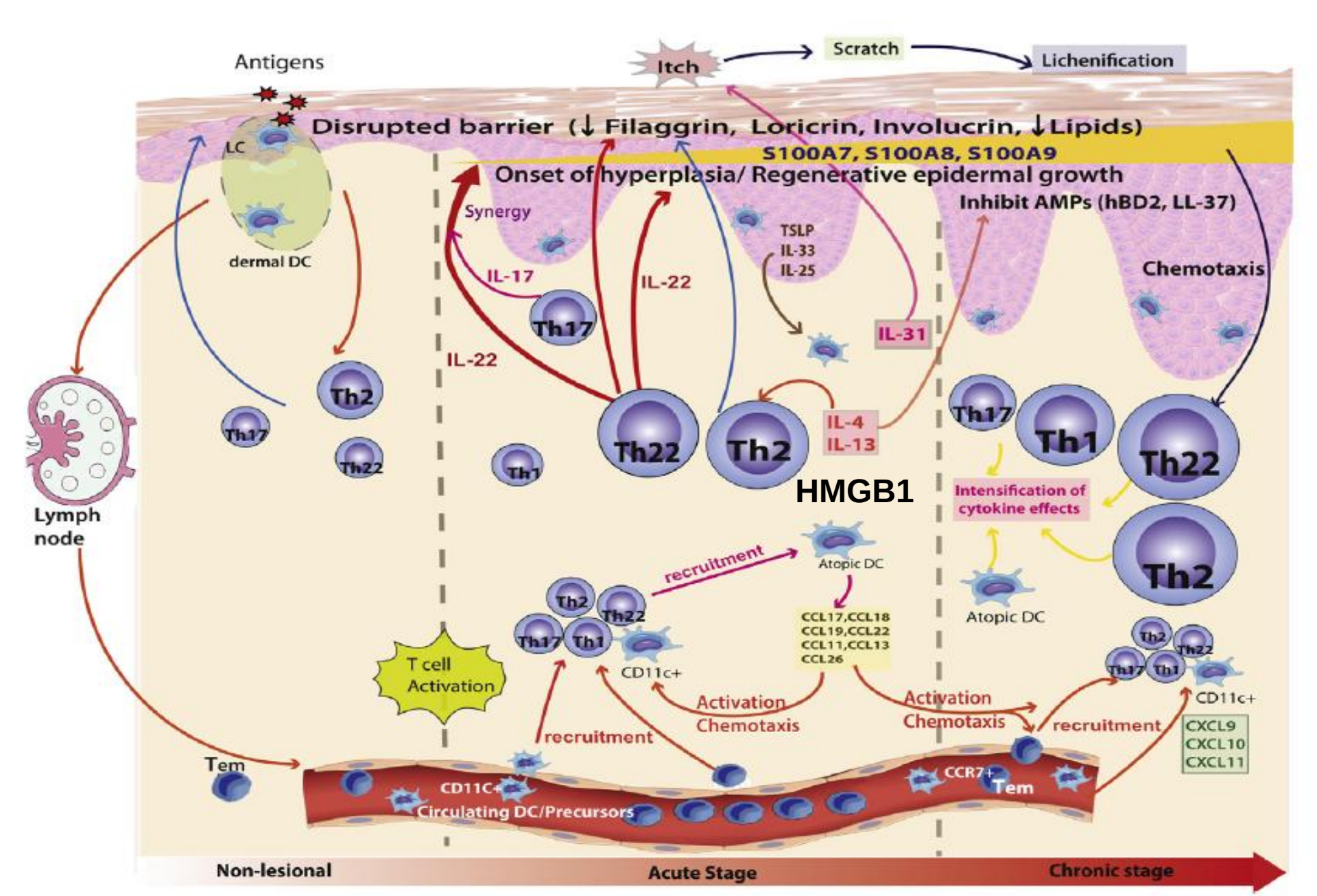
Donald Y. M. Leung, MD, PhD,[a] and Emma Guttman-Yassky, MD, PhD[b]



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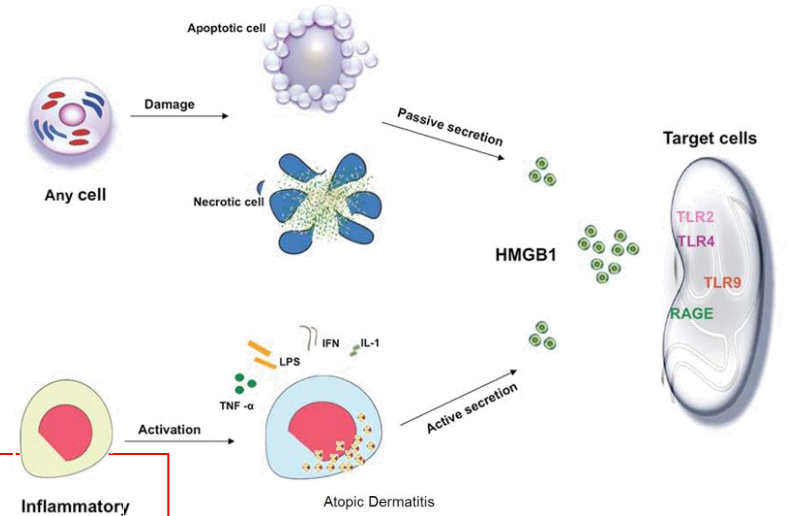
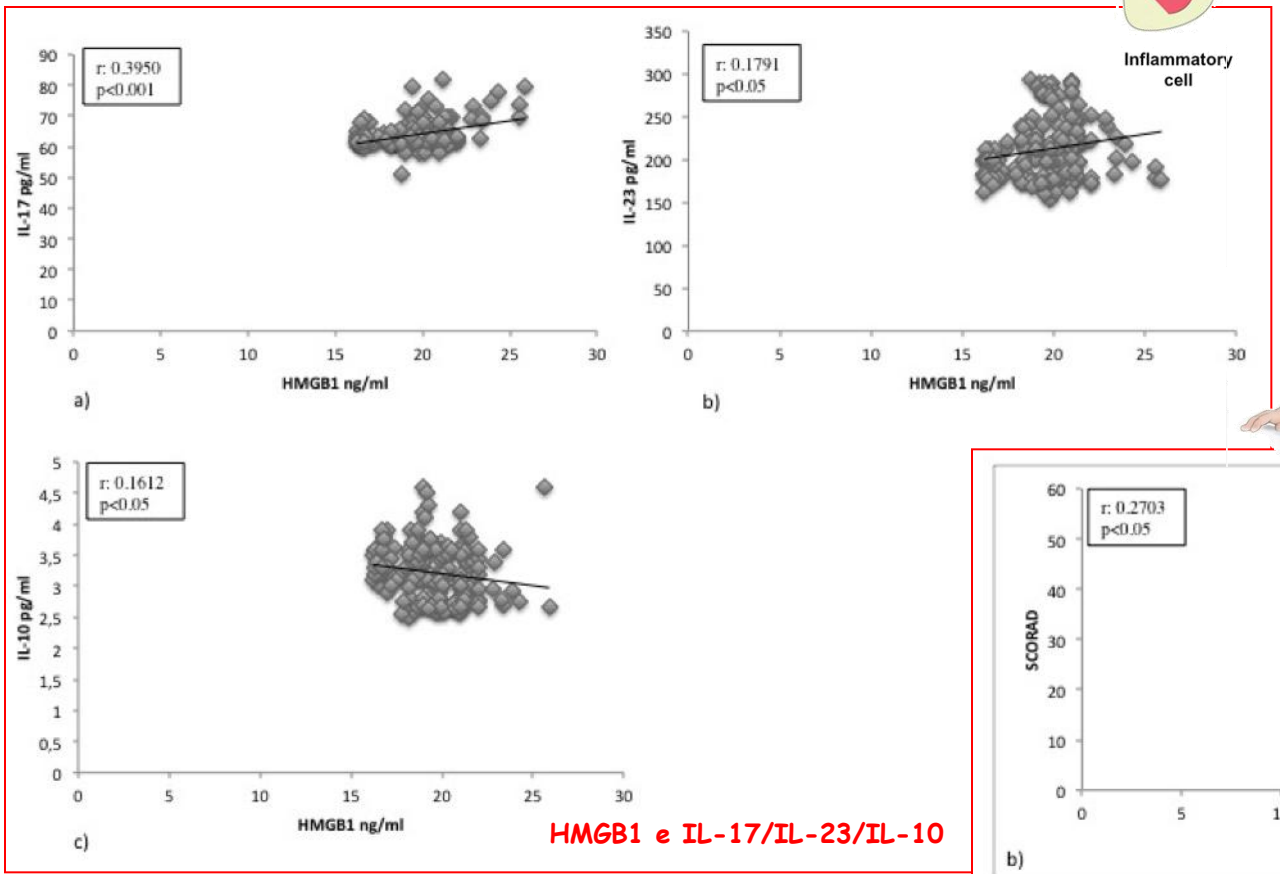
HMGB1 levels in children with atopic eczema/dermatitis syndrome (AEDS)

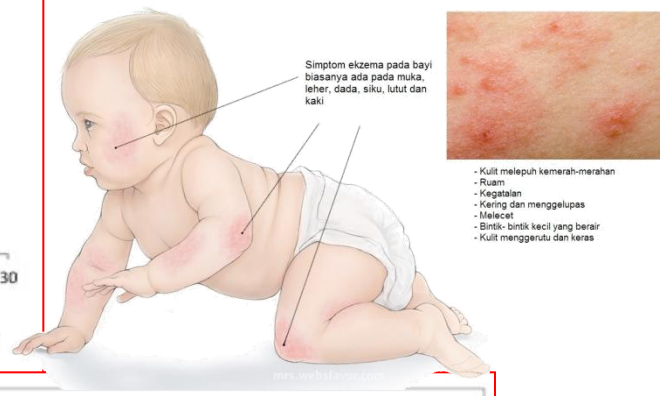
C. Cuppari, S. Manti, A. Salpietro, S. Valenti, A. Capizzi, T. Arrigo, C. Salpietro, S. Leonardi.

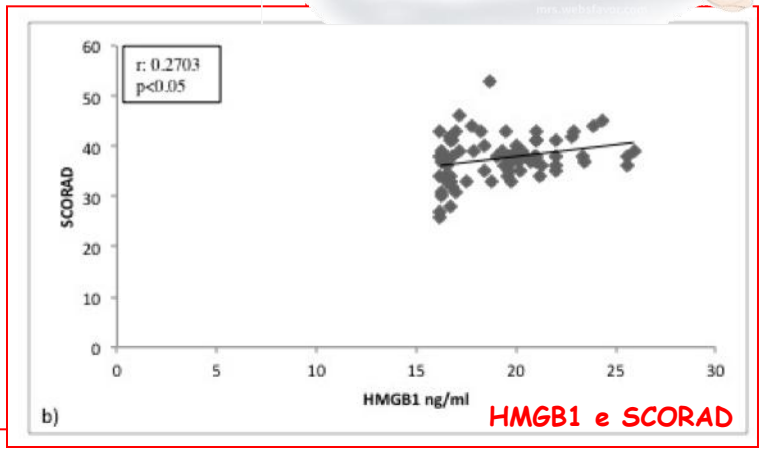
Pediatric Allergy and Immunology





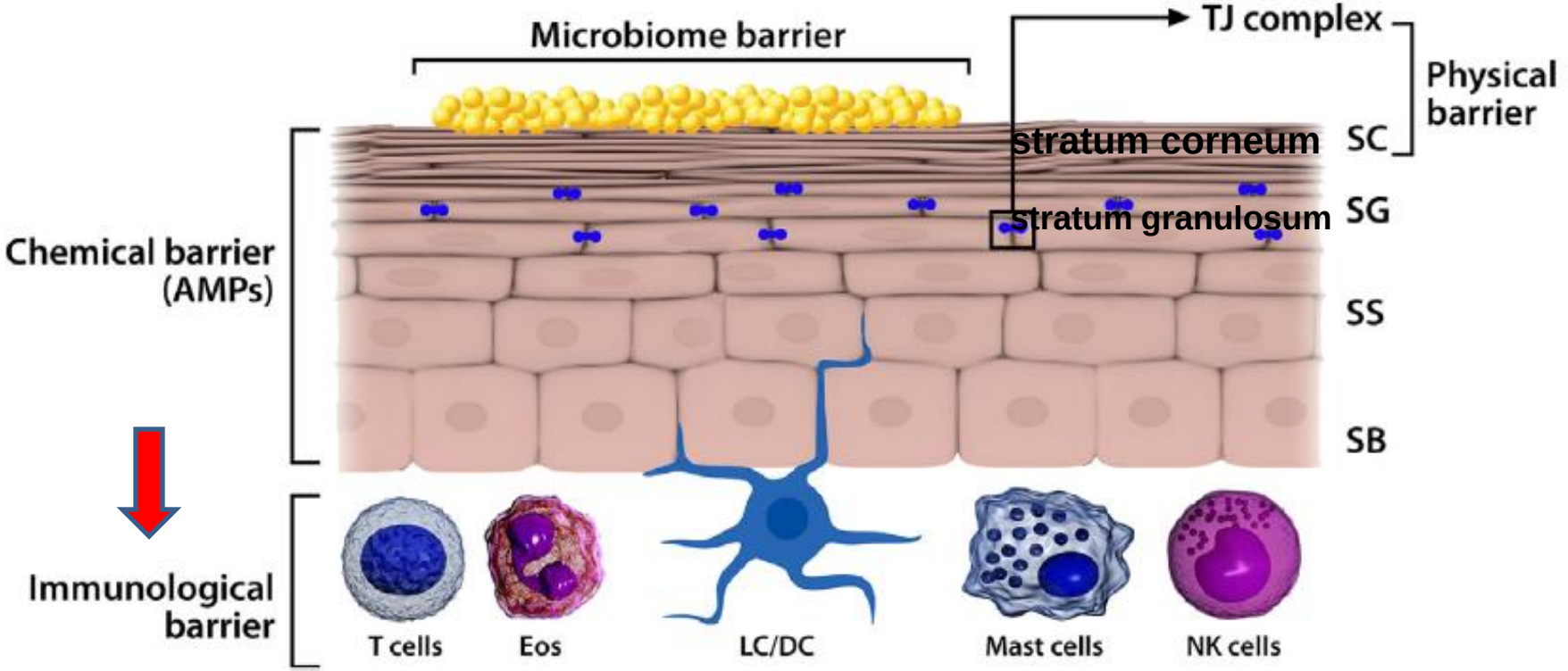
HMGB1 e IL-17/IL-23/IL-10





HMGB1 e SCORAD

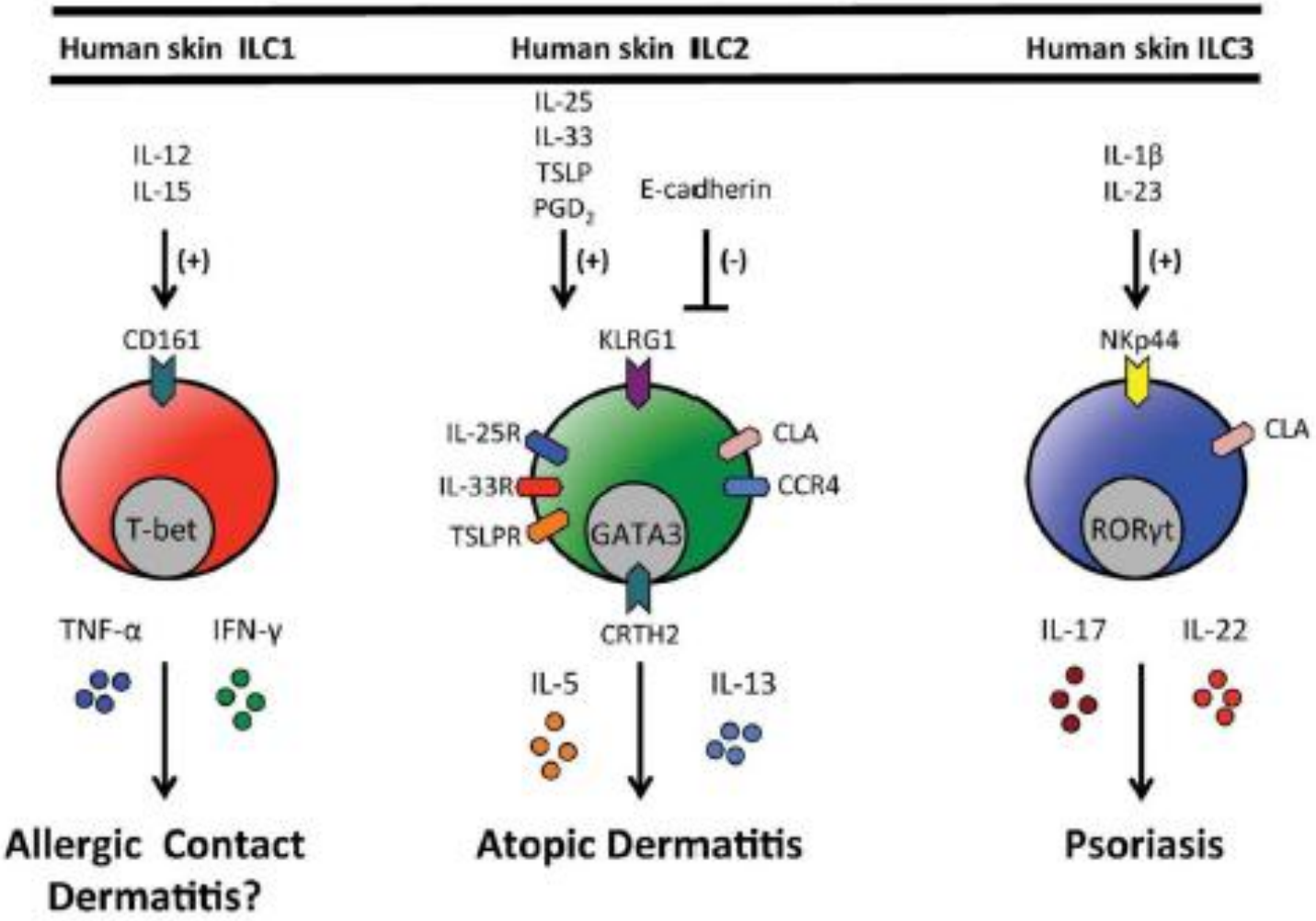
LE BARRIERE DELLA CUTE



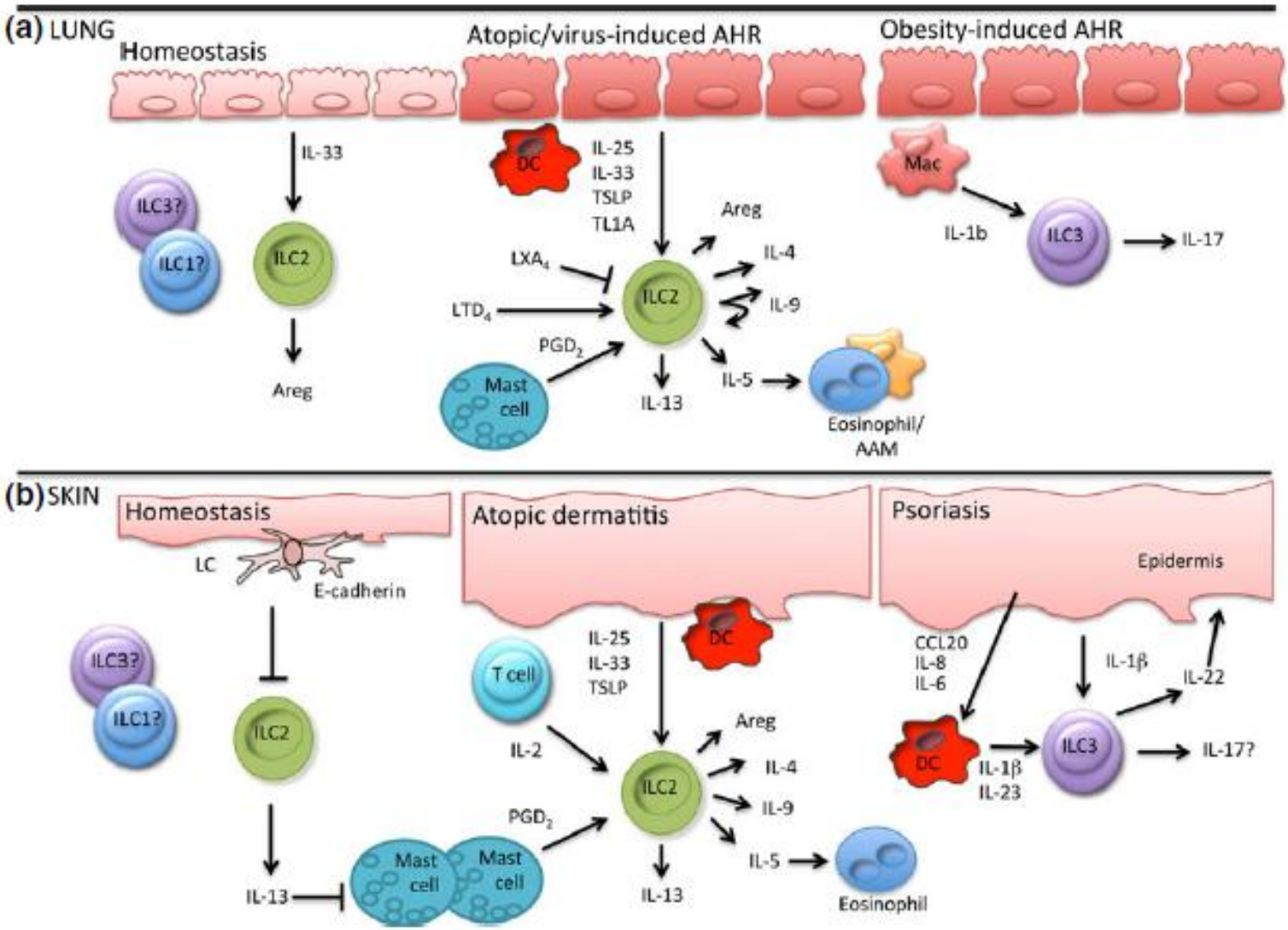
CELLULE LINFOIDI INNATE

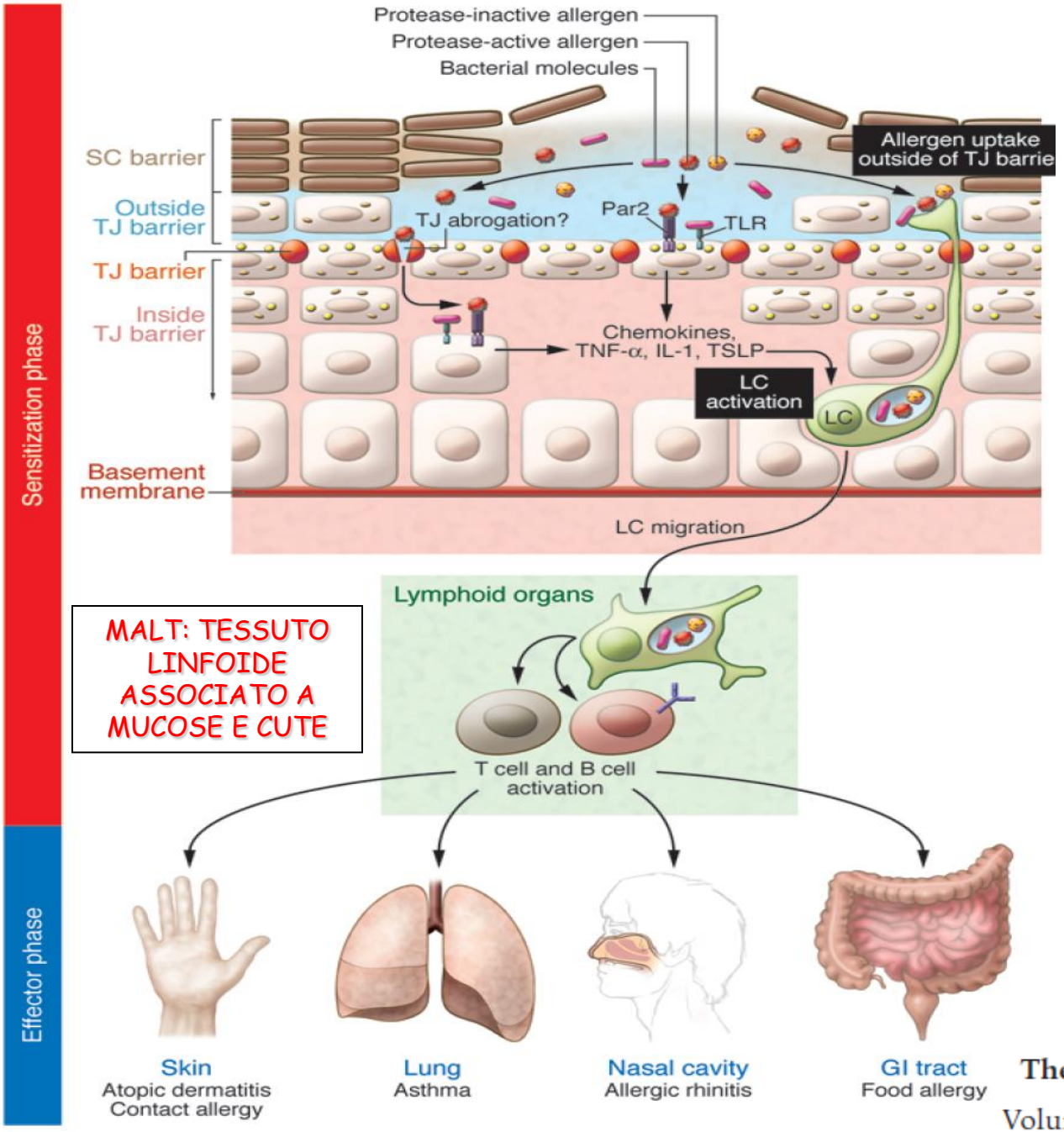
J ALLERGY CLIN IMMUNOL
OCTOBER 2014

Regulation and function of human skin ILC responses



CELLULE LINFOIDI INNATE (ILC)



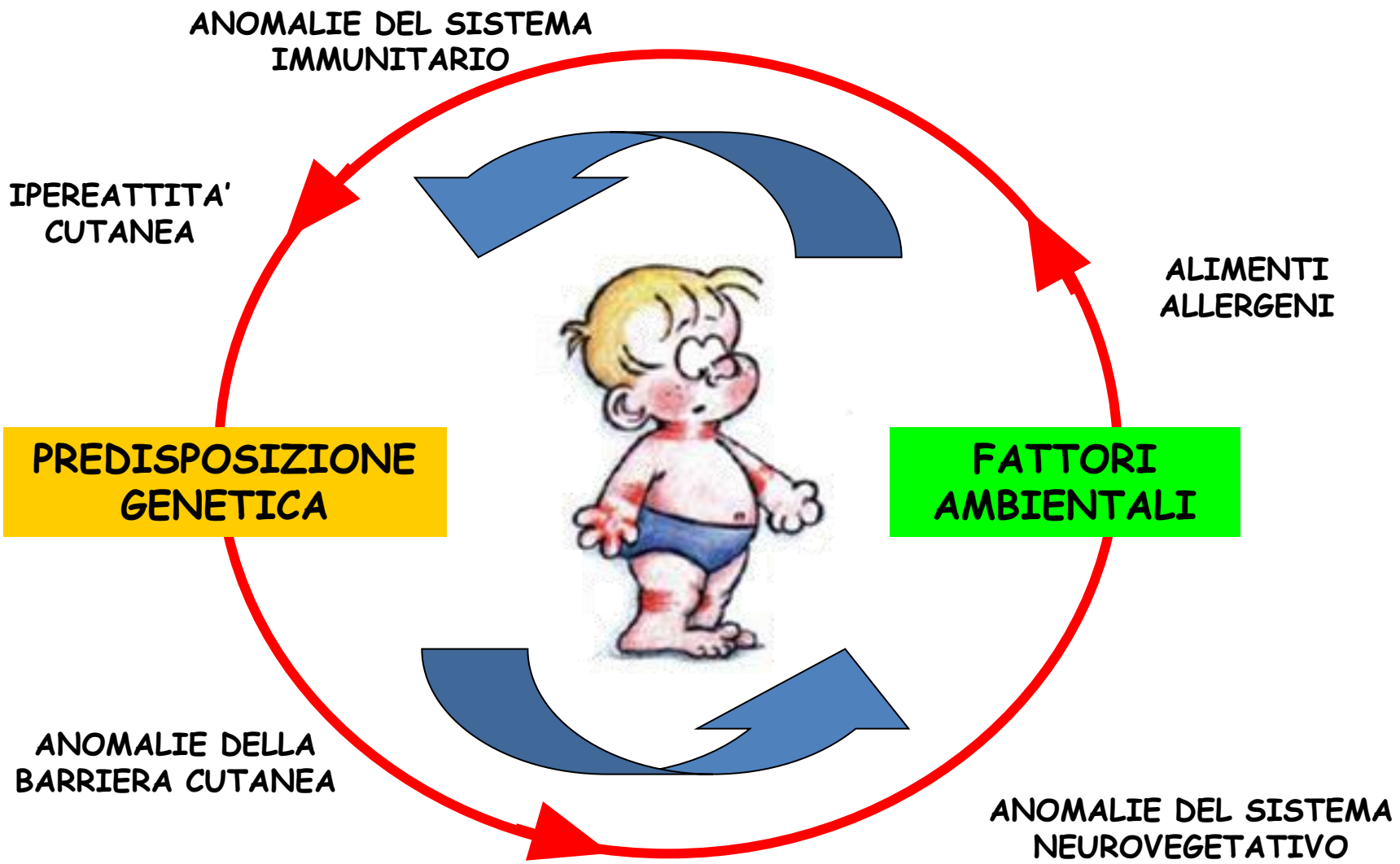


MALT: TESSUTO LINFOIDE ASSOCIATO A MUCOSE E CUTE

A model of barrier disruption and consequences of percutaneous sensitization. SC barrier damages induce danger signals in the epidermis. After SC barrier abrogation, protease-active allergens and uncontrolled intrinsic proteases, as well as bacterial molecules such as lipoteichoic acid of gram-positive bacteria, might agonize Par2 and TLRs on keratinocytes, respectively Keratinocytes then produce TNF-α, IL-1, and thymic stromal lymphopoietin (TSLP) in response to which LCs become activated . Alternatively, protease-active allergens might directly obscure the TJ barrier and then penetrate the epidermis, where they directly or indirectly activate LCs. Upon SC perturbation, dendrites of activated LCs penetrate the TJs to take up protease-active or -inactive antigens from the extra-TJ environment.

The Journal of Clinical Investigation
Volume 122 Number 2 February 2012

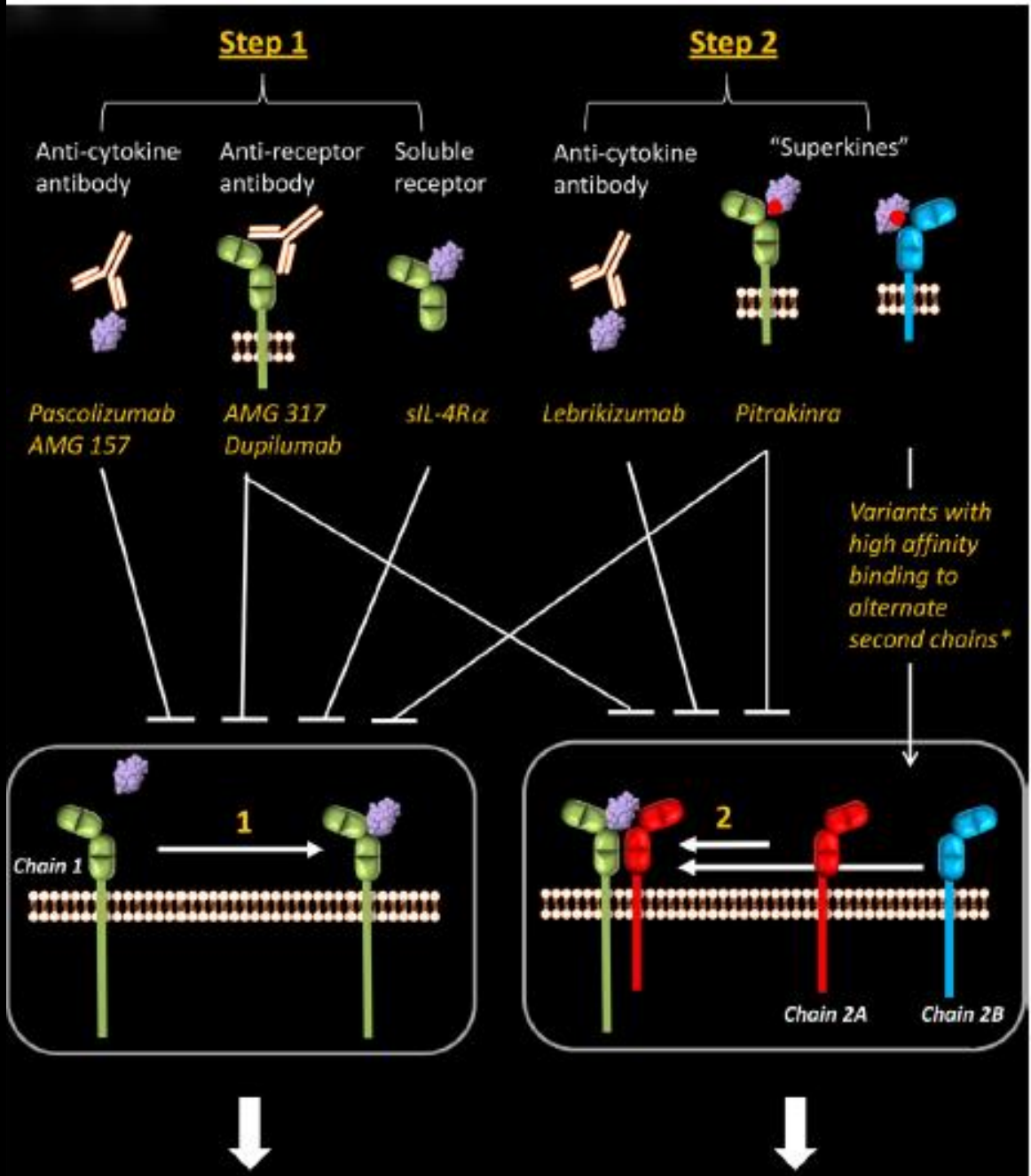
DERMATITE ATOPICA: TRA GENI ED AMBIENTE



COSTITUZIONE IMMUNOGENETICA

FENOTIPO

TERAPIA PERSONALIZZATA



J ALLERGY CLIN IMMUNOL
APRIL 2014

Eczema management algorithm adapted from NICE[5]

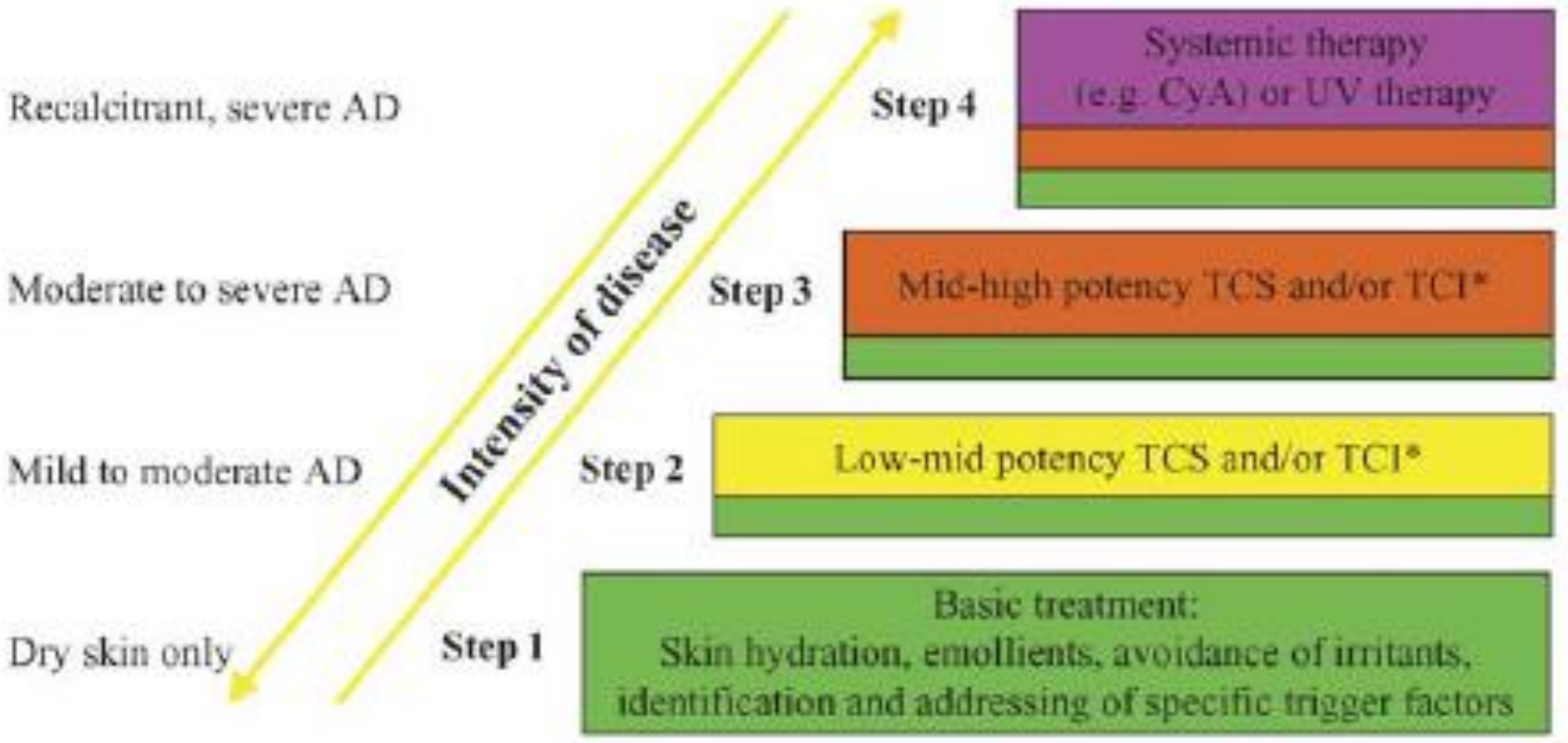
Clear:	Mild:	Moderate:	Severe:
■ Normal skin ■ No evidence of active eczema	■ Areas of dry skin ■ Infrequent itching (with or without small areas of redness)	■ Areas of dry skin ■ Frequent itching ■ Redness (with or without excoriation and localised skin thickening)	■ Widespread areas of dry skin ■ Incessant itching ■ Redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of skin pigment)
Emollients	Emollients	Emollients	Emollients
	Mild topical corticosteroids	**Moderate** potency topical corticosteroids*	**Potent** topical corticosteroids**
			Consider **wet wraps** (see page 30) and referral for systemic therapies

* Avoid use on face, neck, genitals or axillae for longer than 7–14 days

** Avoid use on face, neck, genitals or axillae

STEPWISE MANAGEMENT OF PATIENT WITH DA

STRATEGIE TERAPEUTICHE



TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A

* Over the age of 2 years

Diagnosis and treatment of atopic dermatitisin children and adults: European Academy of Allergology and Clinica Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus ReportJ Allergy Clin Immuno 2006;118:152-69

Table 1. Recent randomized clinical trials on the efficacy of probiotics in the treatment of pediatric atopic dermatitis yield mixed results

First author	Study population	Probiotic	Results	Country
Yang [51]	*n* 100, ages 2 9	*Lactobacillus* and *Bifidobacterium*	Cytokine levels not significantly different at week 6 (IL-4, *P* 0.50; *P* 0.58; TNF-α, *P* 0.82). Improved clinical severity in both intervention and placebo groups at 6 weeks.	Korea
Wickens[46]	*n* 425, maternal supplementation 35 weeks gestation to 6 weeks, infant supplementation for first 2 years	*Lactobacillus rhamnosus* or *Bifidobacterium animalis*	Decreased cumulative prevalence of dermatitis by 4 years, hazard ratio 0.57 (95% CI 0.39 0.83) with *L. rhamnosus*. Non-significant reductions in SCORAD scores >10 (HR 0.74 [95% CI 0.52 1.05]).	New Zealand
Han[52]	*n* 118, ages 12 months to 13 years	*Lactobacillus plantarum CJLP133*	SCORAD at week 14 was lower in the probiotic group than placebo (*P* 0.044). Eosinophil count, IFN-γ and IL-4 significantly decreased from baseline in intervention group.	Korea
Gore[53]	*n* 208, ages 3 6 months	*Bifidobacterium lactis* or *Lactobacillus paracasei*	No significant difference between SCORAD in placebo and each probiotic group.	UK
Wu[54]	*n* 60, ages 2 14 years, moderate to severe	*Lactobacillus salivarius*	At 8 and 10 weeks, treatment (synbiotic) group SCORAD scores (27.4 ± 12.7) were significantly lower than controls (prebiotic) (36.3 ± 14.9). (*P* 0.022)	Taiwan
van der Aa[55]	*n* 90, ages <7 months	*Bifidobacterium breve*	No significant differences between the symbiotic and the placebo groups in cytokine production and circulating regulator T-cell percentage.	Netherlands

CI, confidence interval; HR, hazard ratio; IFN, interferon; IL, interleukin; SCORAD, Scoring Atopic Dermatitis severity score; TNF, tumor necrosis factor.

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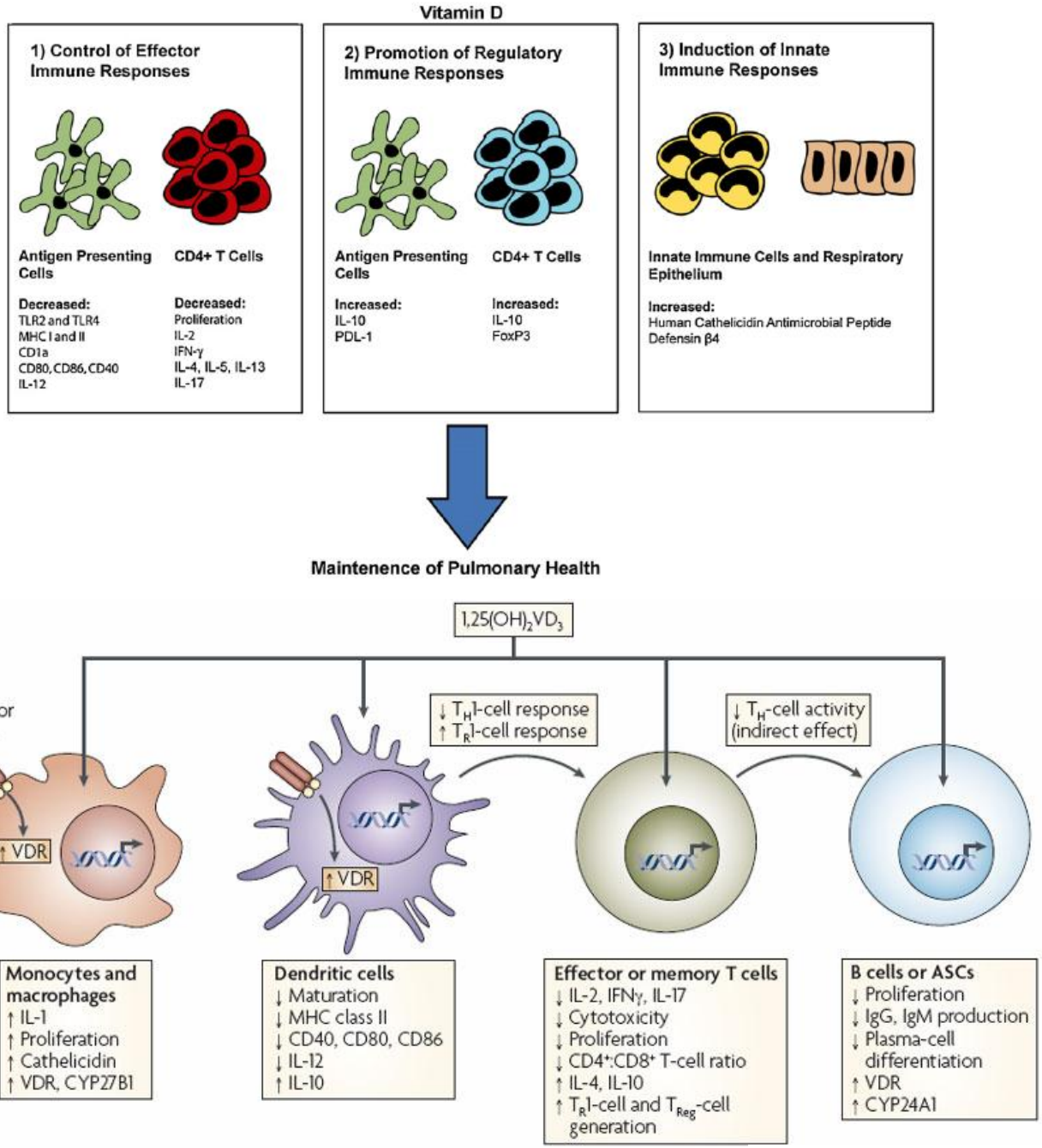
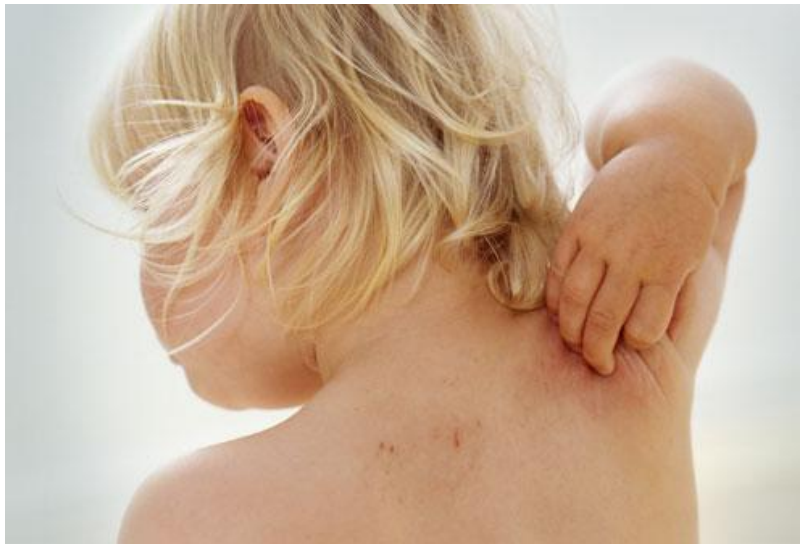


S. Dimeloe et al. / Journal of Steroid Biochemistry & Molecular Biology 120 (2010) 86–95

Table 2. Present and future of immunomodulatory therapy for atopic dermatitis

Present	Future
· Transient symptomatic treatment	· Long-term clinical remission
· Pharmacological therapy	· Biological therapy
· Non-specific immune suppression	· Induction of immune tolerance. Correction of immune dysfunction and hypersensitivity.
· Monotherapy with single immunomodulatory modality	· Combinations of multiple antigen-specific and non-specific immunomodulatory modalities
· Treatment of patients with atopic dermatitis	· Prevention of development of atopic dermatitis in high risk subjects



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Ann Dermatol Vol. 27, No. 4, 2015

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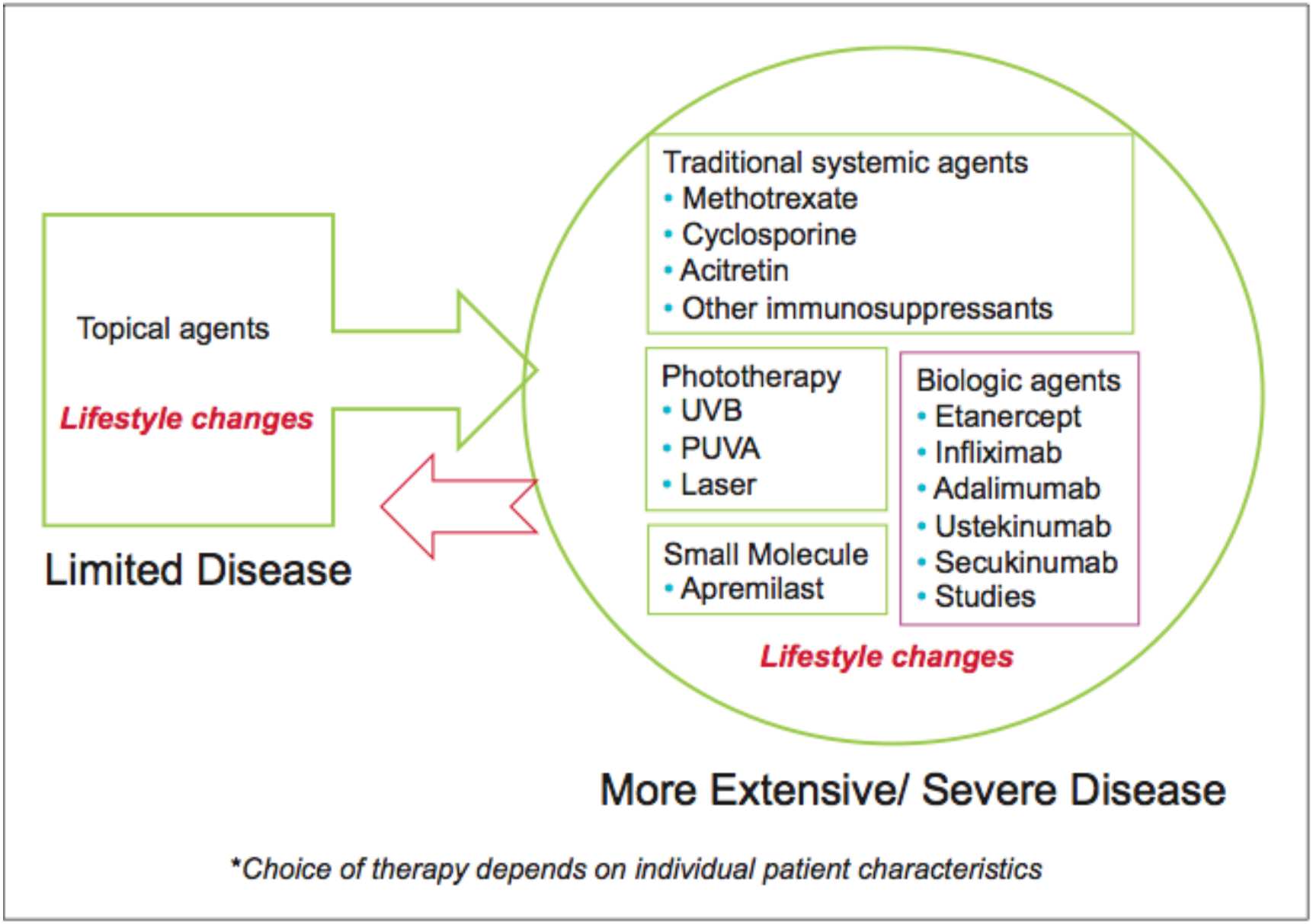

Figure 1. Not all treatment options work for every patient.

TABLE 1: EMERGING TREATMENTS FOR ATOPIC DERMATITIS		
Therapy	**Mechanism of Action**	**Phase of Drug Development**
Biologics		
CIM331	Antibody against IL-31 receptor	2
ILV-094	Antibody against IL-22	2
Tralokinumab	Antibody against IL-13	2
Ustekinumab	Antibody against IL-12 & IL-23	2
Dupilumab	Antibody against IL-4 receptor	3
Anti-pruritics		
CT327	Tropomyosin receptor kinase A kinase inhibitor	2
VLY-686	Neurokinin 1 receptor antagonist	2
Adapted from the National Eczema Association's "Eczema Drugs in Development" chart.[20]		

J Clin Med. 2015 Apr; 4(4): 593–613.

J Pharmacol Sci **126**, 85 – 91 (2014)

Journal of Pharmacological Sciences

Current Perspective

Interleukin (IL)-33: New Therapeutic Target for Atopic Diseases

Takeshi Nabe[1,*]

Abstract. Interleukin (IL)-33, a member of the IL-1 family of cytokines, is produced when epithelial and endothelial cells are exposed to stimuli. Hematopoietic cells such as macrophages also produce IL-33. IL-33 is considered to function as an 'alarmin', activating various immune cells through its receptor ST2, which leads to the production of various molecules. The IL-33-induced production of pro-inflammatory cytokines is a critical event that aggravates atopic diseases such as asthma, atopic dermatitis, and pollenosis and suggests that IL-33-blocking agents could represent new therapeutic drugs. The anti-IL-33 antibody was effective in allergic models,

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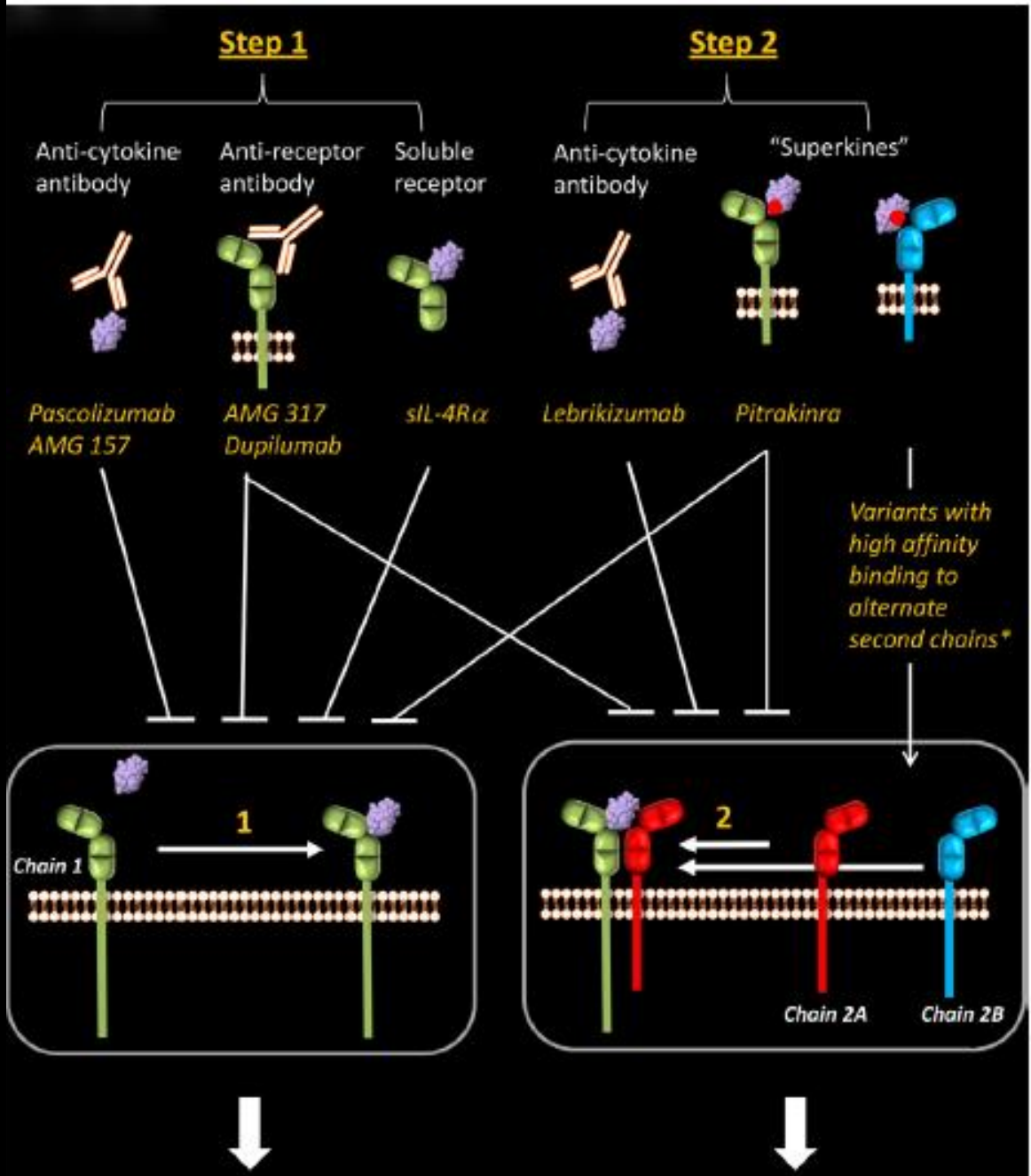

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