#WCD2019

AEDV HIGHLIGHTS

24th World Congress of Dermatology (WCD)

10-15 JUNIO 2019

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Patrocina:

janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Organiza:

ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA
AEDV 1909

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Systematic and autoimmune disease

Raquel Rivera

Dermatologia. HU 12 de Octubre MAdrid

Patrocina: Janssen Immunology

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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SY : Autoinflammatory Diseases

Plenary S: How Autoantigens Drive Cutaneous Disorders

Patrocina: Janssen Immunology

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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Classic hereditary fevers: FMF, TRAPS, mevalonato kinase deficiency: presentations and treatment.

Marco Gattorno

When to suspect an "inflammatory" periodic fever?

- Early onset (usually)
- Rapid appearance of fever without evident signs (and history) of respiratory or urinary tract infections
- Elevation of acute phase reactants with normalization in the inter-critical intervals
- Complete wellbeing in the inter-critical intervals
- Periodicity (not mandatory)/ lack of seasonality
- Stereotypic manifestations ("it is his/her typical episode!")

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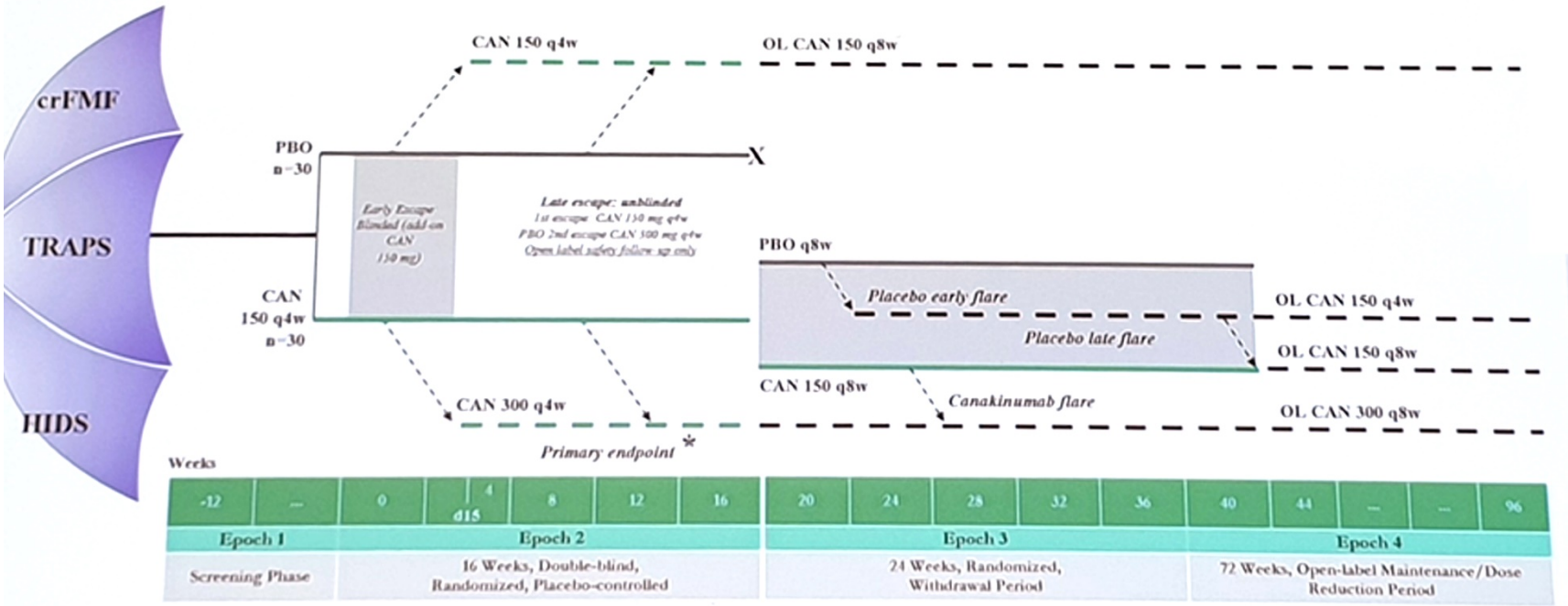
Classic hereditary fevers:FMF, TRAPS, mevalonato kinase deficiency: presentations and treatment.

Marco Gattorno

Cluster study (canakinumab)



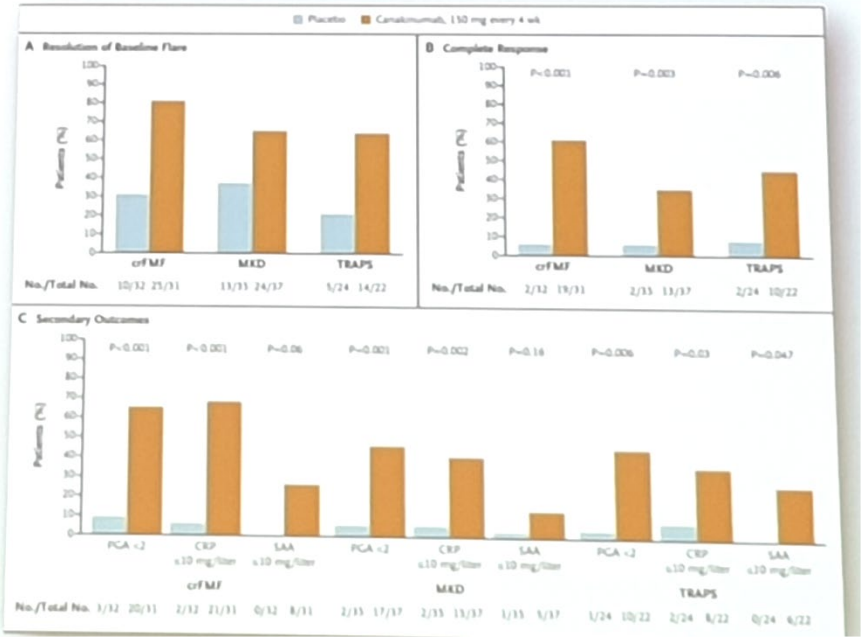
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes

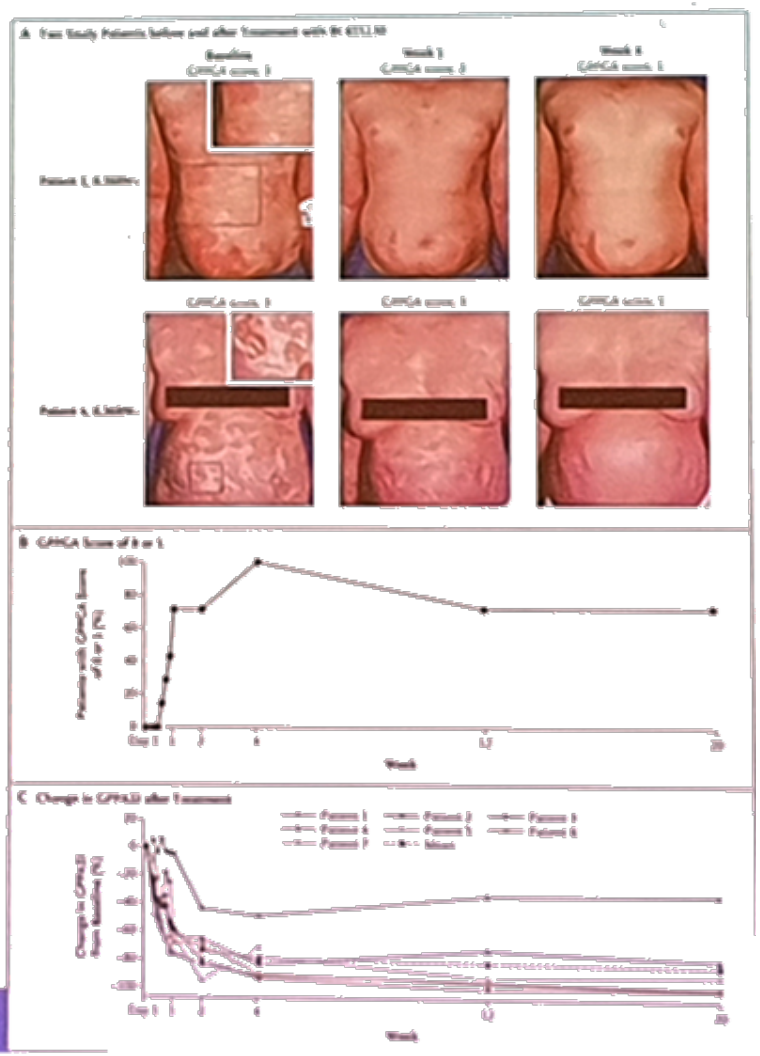
F. De Benedetti, M. Gattorno, J. Anton, E. Ben-Chetrit, J. Frenkel, H.M. Hoffman, I. Koné-Paut, H.J. Lachmann, S. Ozen, A. Simon, A. Zeft, I. Calvo Penades, M. Moutschen, P. Quartier, O. Kasapcopur, A. Shcherbina, M. Hofer, P.J. Hashkes, J. Van der Hilst, R. Hara, S. Bujan-Rivas, T. Constantin, A. Gul, A. Livneh, P. Brogan, M. Cattalini, L. Obici, K. Lheritier, A. Speziale, and G. Junge

N Engl J Med 2018;378:1908-19.
DOI: 10.1056/NEJMoa1706314



TARGEETING IL-36 IN DITRA SYNDROME

A phase 1 proof-of-concept study involving seven patients who presented with a generalized pustular psoriasis flare and were treated with a single, open-label, intravenous dose **of BI 655130, a monoclonal antibody against the interleukin-36 receptor**, at 10 mg per kilogram of body weight (ClinicalTrials.gov number, NCT02978690).



ibition of the Interleukin-36 Pathway for the Treatment of eralized Pustular Psoriasis.
helez H, et al. N Engl J Med. 2019 Mar 7;380(10):981-983.


IL-36R
SPESOLIMAB
Boehringer
Ingelheim

Type-1 interferon-mediated diseases and cutaneous signs of other rare autoinflammatory syndromes

Antonio Torrelo

Chronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature (CANDLE) syndrome

Antonio Torrelo, MD,[a] Sapna Patel, MD,[b] Isabel Colmenero, MD,[c] Dolores Gurbindo, MD,[d] Francisco Lendínez, MD,[e] Angela Hernández, MD,[a] Juan Carlos López-Robledillo, MD,[f] Ali Dadban, MD,[g] Luis Requena, MD,[h] and Amy S. Paller, MD[b]

Madrid and Almería, Spain; Chicago, Illinois; and Amiens, France

Several syndromes manifest as recurrent daily fevers, skin lesions, and multisystem inflammation. We describe 4 patients with early-onset recurrent fevers, annular violaceous plaques, persistent violaceous eyelid swelling, low weight and height, lipodystrophy, hepatomegaly, and a range of visceral inflammatory manifestations. Laboratory abnormalities included chronic anemia, elevated acute-phase reactants, and raised liver enzymes. Histopathologic examination of lesional skin showed atypical mononuclear infiltrates of myeloid lineage and mature neutrophils. Our patients have a distinctive early-onset, chronic inflammatory condition with atypical or immature myeloid infiltrates in the skin. We propose the acronym CANDLE (*c*hronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature) syndrome for this newly described disorder, which is probably genetic in origin. (J Am Acad Dermatol 2010;62:489-95.)

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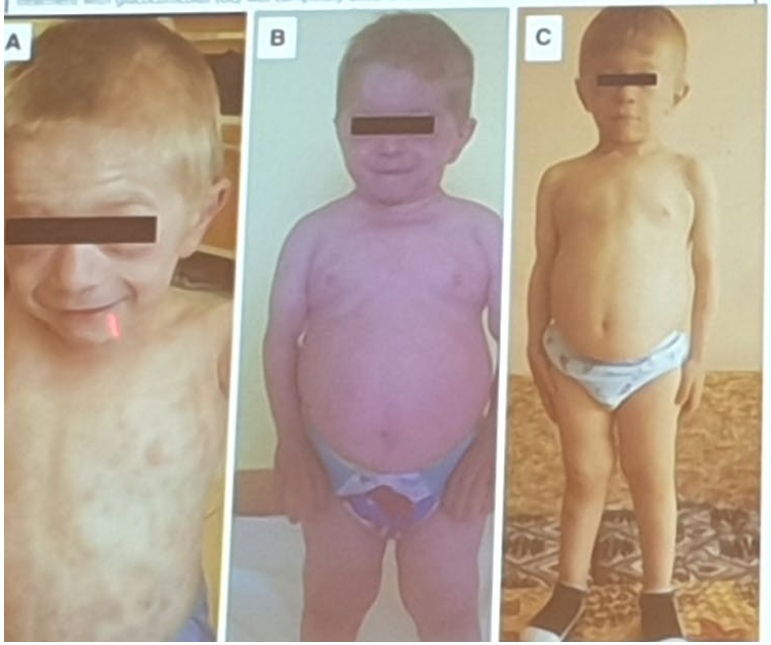
Disease course and treatment effects of a JAK inhibitor in a patient with CANDLE syndrome

M. Boyadzhiev[1], L. Marinov[2], V. Boyadzhiev[2], V. Ivtsova[3], I. Alexeritcjevich[3] and S. Hambleton[3]

Abstract

Background: CANDLE syndrome (an acronym for Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature) is a recently described rare autosomal recessive disorder characterized by systemic autoinflammation. Clinical manifestations include presentation in the first year of life, episodes of fever accompanied by erythematous skin lesions, progressive lipodystrophy, violaceous periorbital swelling and failure to thrive. This syndrome is caused by loss of function mutations and malfunction of the immunoproteasome complex. Most patients have biallelic mutations in the PSMB8 gene that encodes the β5i catalytic subunit of the immunoproteasome. Examples of digenic inheritance have been also described in CANDLE. CANDLE patients have strong type I interferon gene expression signature and they are responsive to treatment with JAK inhibitors. However, possible serious side-effects remain a concern. Here, we report another patient with CANDLE whose disease activity was well controlled by the treatment with baricitinib.

Case presentation: We report a Bulgarian patient of the Turkish ancestry who carries biallelic mutations in the PSMB8 gene: p.Ala82Val and p.Lys105Gln. The pathogenic variant p.Ala82Val has not been previously described in patients with CANDLE. We also comment on the unusual feature in this patient, nephrolithiasis, that has not been described in other patients, however it might be related to the positive family history for kidney stones. We have treated the patient with the JAK inhibitor baricitinib for the past year and we observed a significant amelioration of his inflammatory episodes, skin and joint manifestations, and improvements in physical activities and growth. The treatment with glucocorticoids (GC) was completely discontinued. No side effects have been observed, however

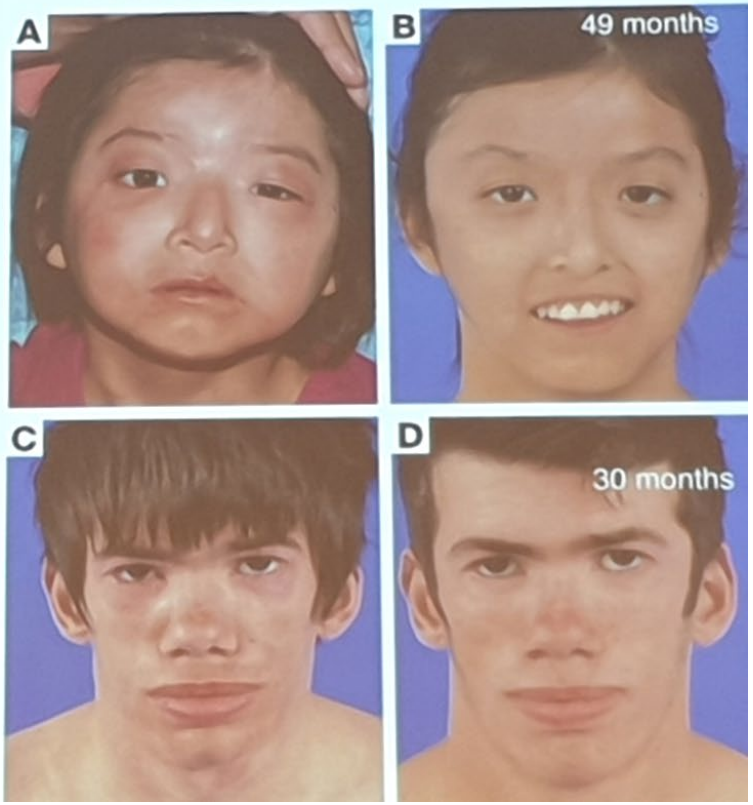


The Journal of Clinical Investigation

CLINICAL MEDICIN

JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies

Gina A. Montealegre Sanchez,[1] Adam Reinhardt,[1] Suzanne Ramsey,[1] Helmut Wittkowski,[1] Philip J. Hashkes,[1] Yackov Berkun,[2] Susanne Schalm,[1] Sara Murias,[1] Jason A. Dare,[1] Diane Brown,[1] Deborah L. Stone,[1] Ling Gao,[1] Thomas Klausmeier,[1] Dirk Foell,[3] Adriana A. de Jesus,[1] Dawn C. Chapelle,[1] Hanna Kim,[1] Samantha Dill,[1] Robert A. Colbert,[1] Laura Failla,[1] Bahar Kost,[1] Michelle O'Brien,[1] James C. Reynolds,[1] Les R. Folio,[1] Katherine R. Calvo,[1] Scott M. Paul,[1] Nargues Wein,[1] Alessandra Brofferio,[1] Arlene Sirdofsky,[1] Angelique Biancotto,[1] Edward W. Cowen,[1] John J. Oligiovanna,[1] Massimo Gadina,[1] Andrew J. Lipton,[1] Colleen Hadigan,[1] Steven M. Holland,[1] Joseph Fontana,[1] Ahmad S. Alawad,[1] Rebecca J. Brown,[1] Kristina I. Rother,[1] Theo Heller,[1] Kristina M. Brooks,[1] Parag Kumar,[1] Stephen R. Brooks,[1] Meryl Waldman,[1] Harsharan K. Singh,[1] Volker Nickeleit,[1] Maria Silk,[1] Apurva Prakash,[1] Jonathan M. Jones,[1] Seza Ozen,[1] Paul C. Wallin,[1] Paul A. Brogan,[1] William L. Macias,[1] and Raphaela Goldbach-Mansky[1]



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Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.

Karoline Krause

Neutrophilic Urticarial Dermatosis

A Variant of Neutrophilic Urticaria Strongly Associated With Systemic Disease. Report of 9 New Cases and Review of the Literature

Carine Kieffer, MD, Bernard Cribier, MD, PhD, and Dan Lipsker, MD, PhD

1. Clinically, the inclusion criteria were as follows:
   1.1. Patients with a recurrent or chronic cutaneous eruption consisting of macules, papules, or plaques,
   1.2. Individual lesions had to resolve within 48 hours,
   1.3. They could be pruritic or not.

2. Histopathologically, the following criteria had to be present:
   2.1. A diffuse neutrophilic infiltrate in the dermis, with interstitial involvement,
   2.2. Absence of significant vessel wall alteration (especially parietal necrosis),
   2.3. Absence of significant dermal edema.

→ mainly found to be associated with **Still's disease**, **Schnitzler's syndrome** and **systemic lupus erythematosus**

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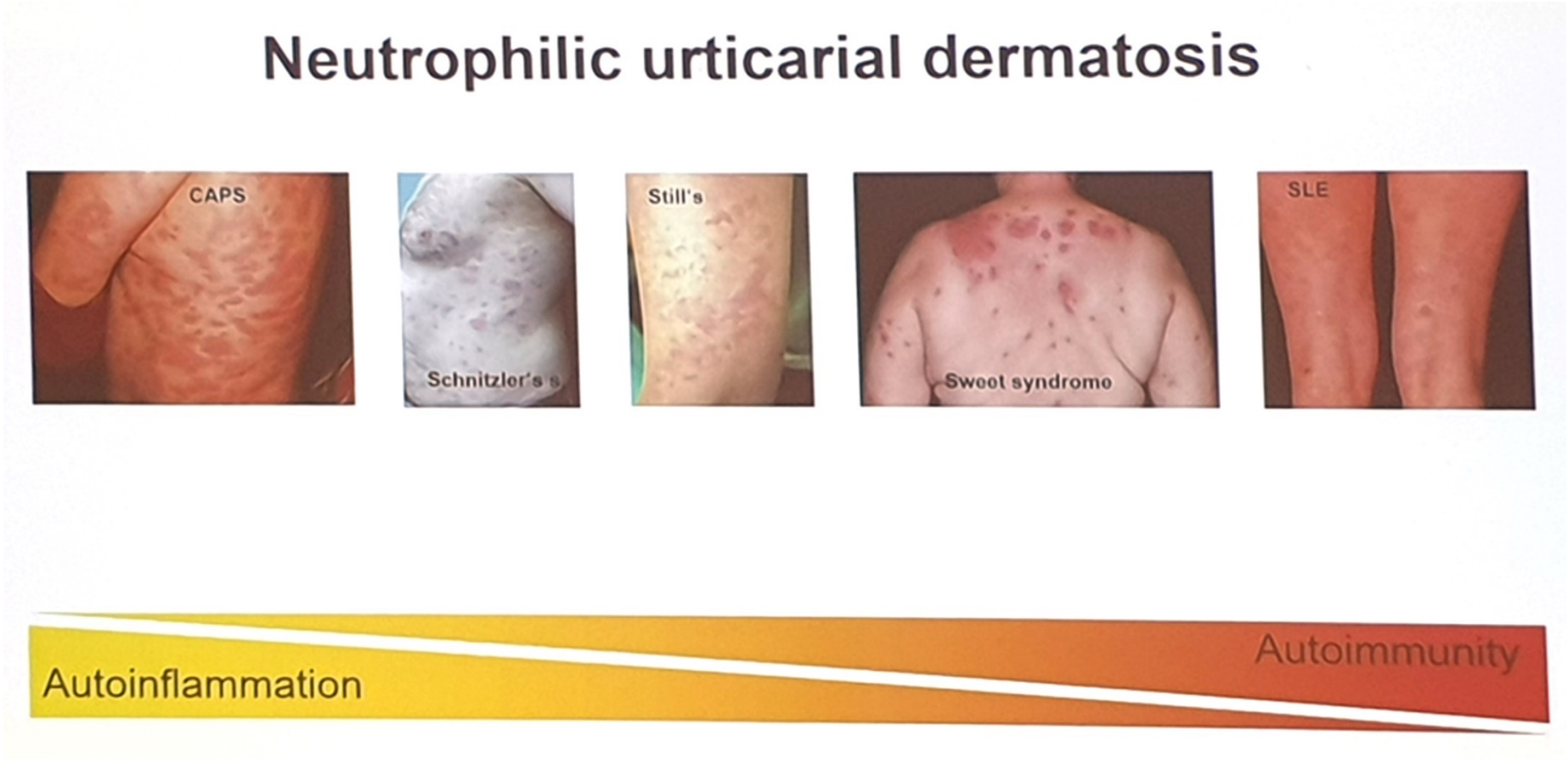
Karoline Krause

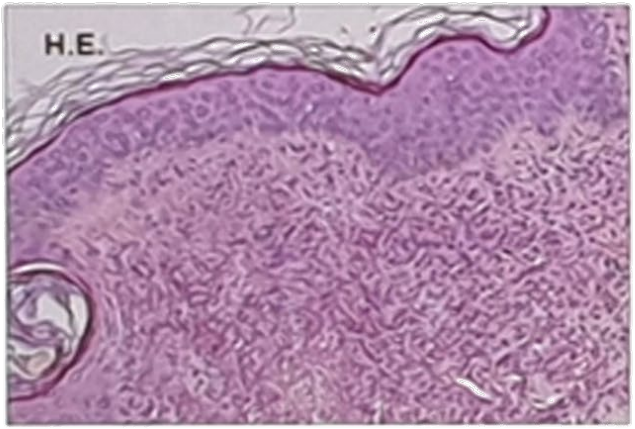


Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.

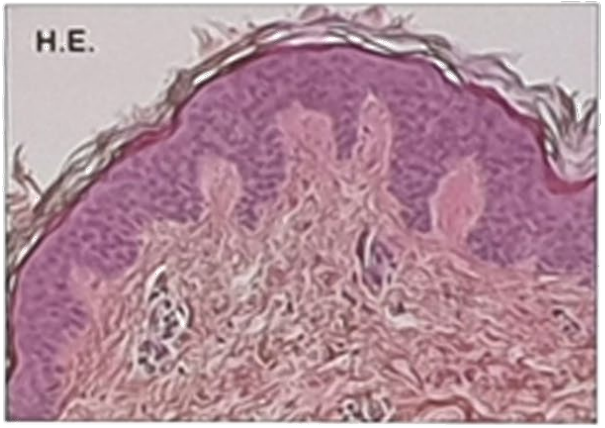
Karoline Krause

Histology: Neutrophil-dominated infiltrate

Schnitzler's syndrome



Urticaria

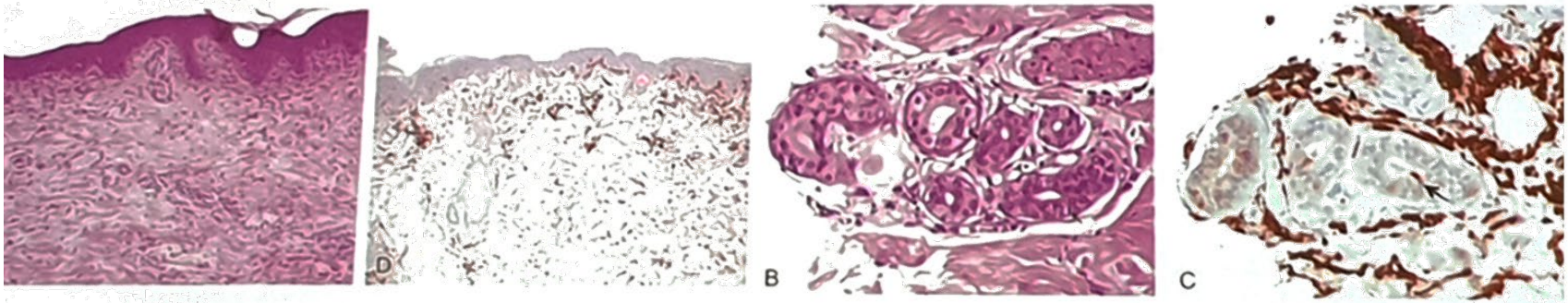


Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.

Karoline Krause

Neutrophilic Epitheliotropism Is a Histopathological Clue to Neutrophilic Urticarial Dermatosis

Sigrid M. C. Broekaert, MD, Almut Böer-Auer, MD,† Katrin Kerl, MD,‡ Ilka Herrgott, MD,* Xenia Schulz, MSc,§ Gisela Bonsmann, MD,* Randolf Brehler, MD,* and Dieter Metze, MD**



Epidermal neutrophils:
sensitivity 61%, specificity 76%

Neutrophils in epithelial sweat glands:
sensitivity 64%, specificity 94%

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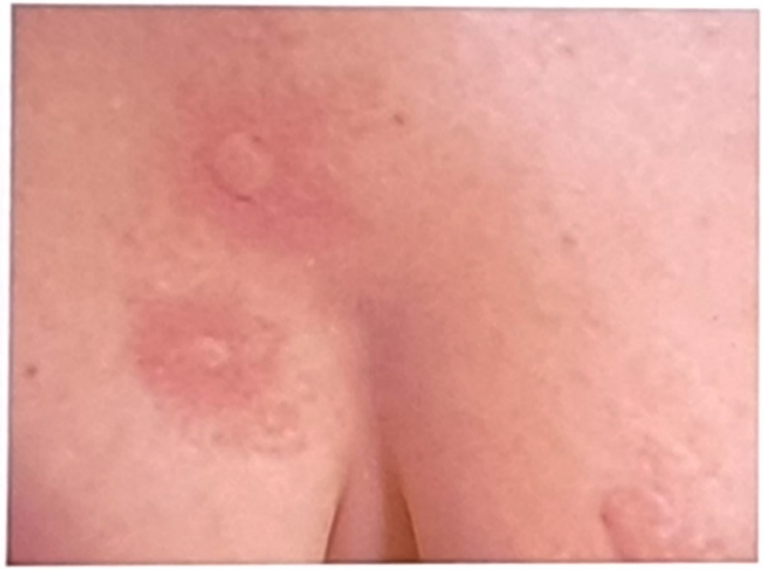
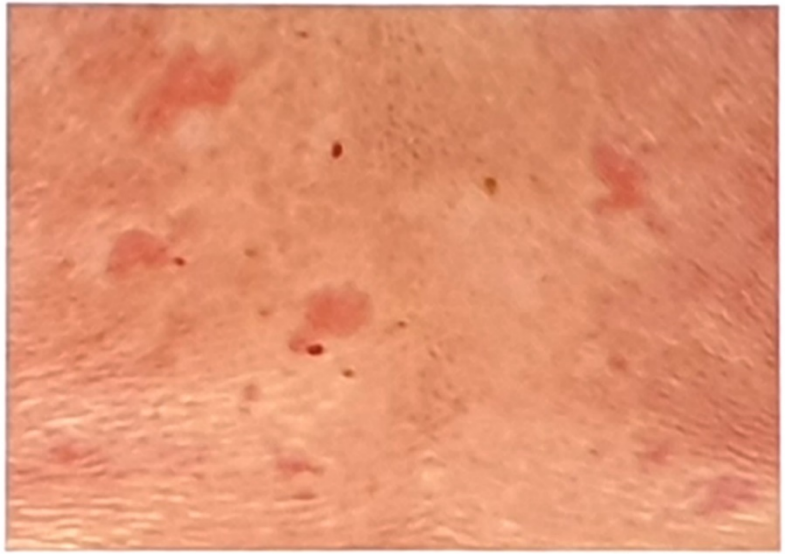
Appearance of urticarial lesions

Common acute or chronic spontaneous urticaria



Wheal and flare

CAPS



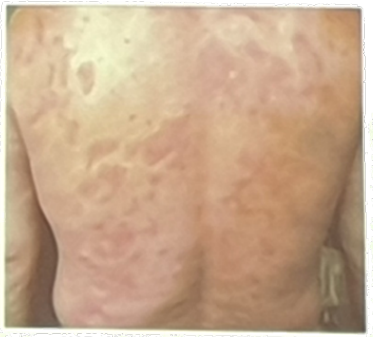
Flat wheals, erythematous patches

Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.

Karoline Krause

Autoinflammation: Clinical clues

Spontaneous wheals…



+ No or little pruritus
+ Absence of angioedema
+ Diurnal pattern
+ Systemic symptoms and high inflammatory markers
+ No response to antihistamines or anti-IgE

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Pyoderma gangrenosum and other rarer neutrophilic dermatoses as paradigm of autoinflammation

Angelo Valerio Marzano

Neutrophilic dermatoses

TABLE II.—*Classification of neutrophilic dermatoses.*

Epidermal	Dermal	Hypodermal	Epidermal/dermal/hypodermal
Subcorneal pustulosis (Sneddon-Wilkinson's disease)	Sweet's syndrome	Pyoderma gangrenosum	Overlapping forms
Amicrobial pustulosis of the folds	Erythema elevatum diutinum	Hidradenitis suppurativa	PAPA/PASH/SAPHO syndrome
Amicrobial pustulosis of the scalp/leg	Rheumatoid neutrophiilc dermatosis	Behçet's disease	Bowel-bypass syndrome
Acute exanthematic generalized pustulosis (AGEP)	Acneiform eruption due to EGFRIs	Neutrophilic panniculitis	
Pustular psoriasis		Aseptic abscesses syndrome	
IgA pemphigus			

IgA: immunoglobulin A; EGFRIs: epidermal growth factor receptor inhibitors; PAPA: pyogenic arthritis, pyoderma gangrenosum and acne; PASH: pyoderma gangrenosum, acne and hidradenitis suppurativa; SAPHO: synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis.

Marzano AV et al. *G Ital Dermatol Venereol* 2013; 148: 185-96
Marzano AV et al *Clin Rev Allergy Immunol.* 2018; 54:114-30

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Neutrophilic dermatoses

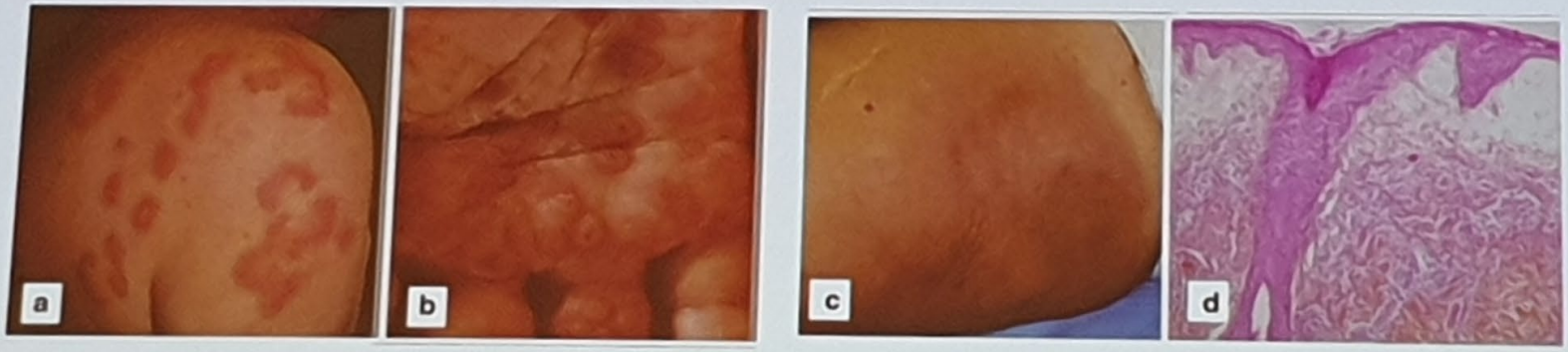
SpringerLink

Clinical Reviews in Allergy & Immunology
February 2018, Volume 54, Issue 1, pp 114–130 | Cite as

A Comprehensive Review of Neutrophilic Diseases

Authors | Authors and affiliations

Angelo V. Marzano ✉, Alessandro Borghi, Daniel Wallach, Massimo Cugno



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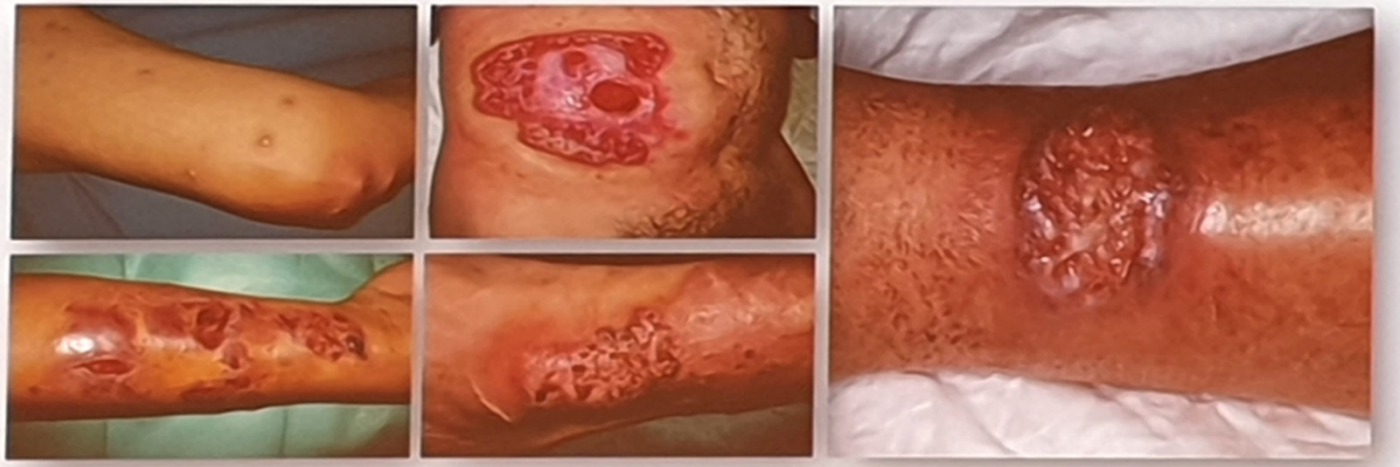
Pyoderma gangrenosum

Table 1 Diagnostic criteria for pyoderma gangrenosum

Major		
	Clinical:	Ulcer with violaceous and undermined borders or nodular, pustular, bullous, or vegetating lesions
	Histological:	Neutrophilic infiltration of the dermis and hypodermis with a variable number of lymphocytes and macrophages and ulceration/necrosis of the epidermis
	Microbiological:	Negative cultures from intact or recent-onset lesions
Minor		
	Clinical:	Presence of hematologic or solid neoplasia or inflammatory bowel diseases or rheumatological diseases
		Absence of diabetes mellitus and chronic venous disease
	Laboratory:	Presence of various circulating autoantibodies

The diagnosis requires three major criteria and at least one minor criterion



Marzano AV et al. *Clin Rev Allergy Immunol* 2013; 45: 202-10

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Pyoderma gangrenosum

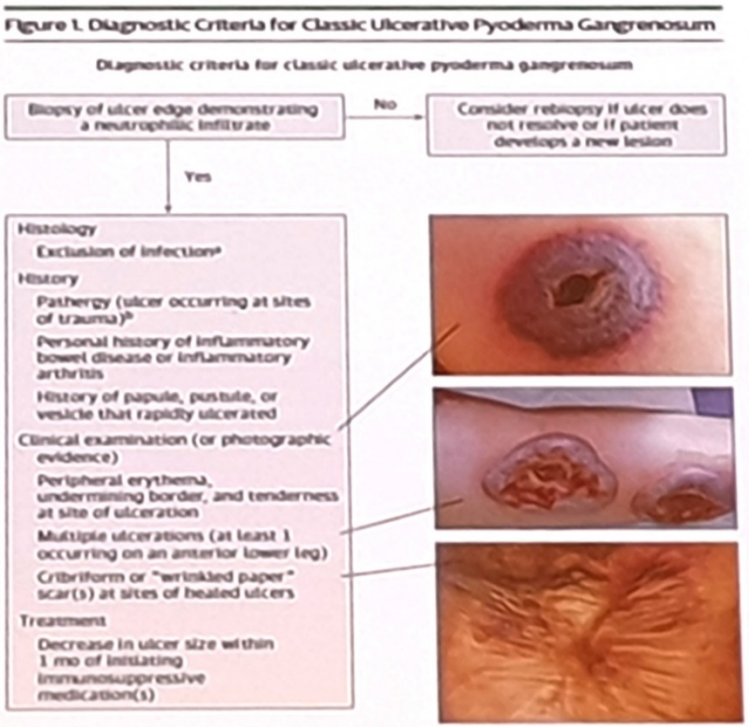
JAMA Dermatology | Consensus Statement

The JAMA Network
JAMA Dermatology

Diagnostic Criteria of Ulcerative Pyoderma Gangrenosum
A Delphi Consensus of International Experts

Emanual Maverakis, MD; Chelsea Ma, MD; Kanade Shinkai, MD, PhD; David Fiorentino, MD, PhD; Jeffrey P. Callen, MD; Uwe Wollina, MD; Angelo Valerio Marzano, MD; Daniel Wallach, MD; Kyoungmi Kim, PhD; Courtney Schadt, MD; Anthony Ormerod, MD; Maxwell A. Fung, MD; Andrea Steel, BA; Forum Patel, MD; Rosie Qin, MD; Fiona Craig, MRCP; Hywel C. Williams, DSc; Frank Powell, FRCP; Alexander Merkeev, PhD; Michelle Y. Cheng, MD

Figure 1. Diagnostic Criteria for Classic Ulcerative Pyoderma Gangrenosum



In addition to a biopsy demonstrating a neutrophilic infiltrate, patients must have at least 4 minor criteria to meet diagnostic criteria.

[a] Including histologically indicated stains and tissue cultures.

[b] Ulcer should extend past area of trauma.

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How Autoantigens Drive Cutaneous Autoimmune Disoerders
Michell Gilliet

Autoimmune diseases

- A clinical syndrome caused by:
  - Activated T cells +/-B cells
  - In absence of an ongoing infection
  - Recognizing host-derived autoantigens

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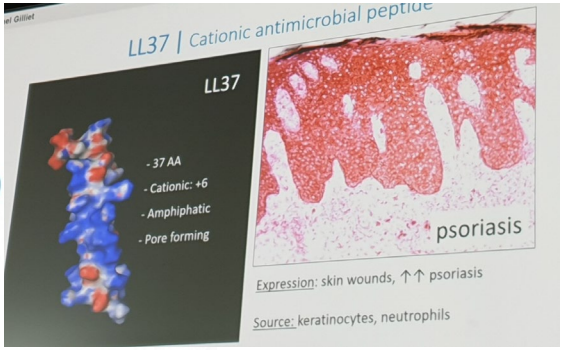
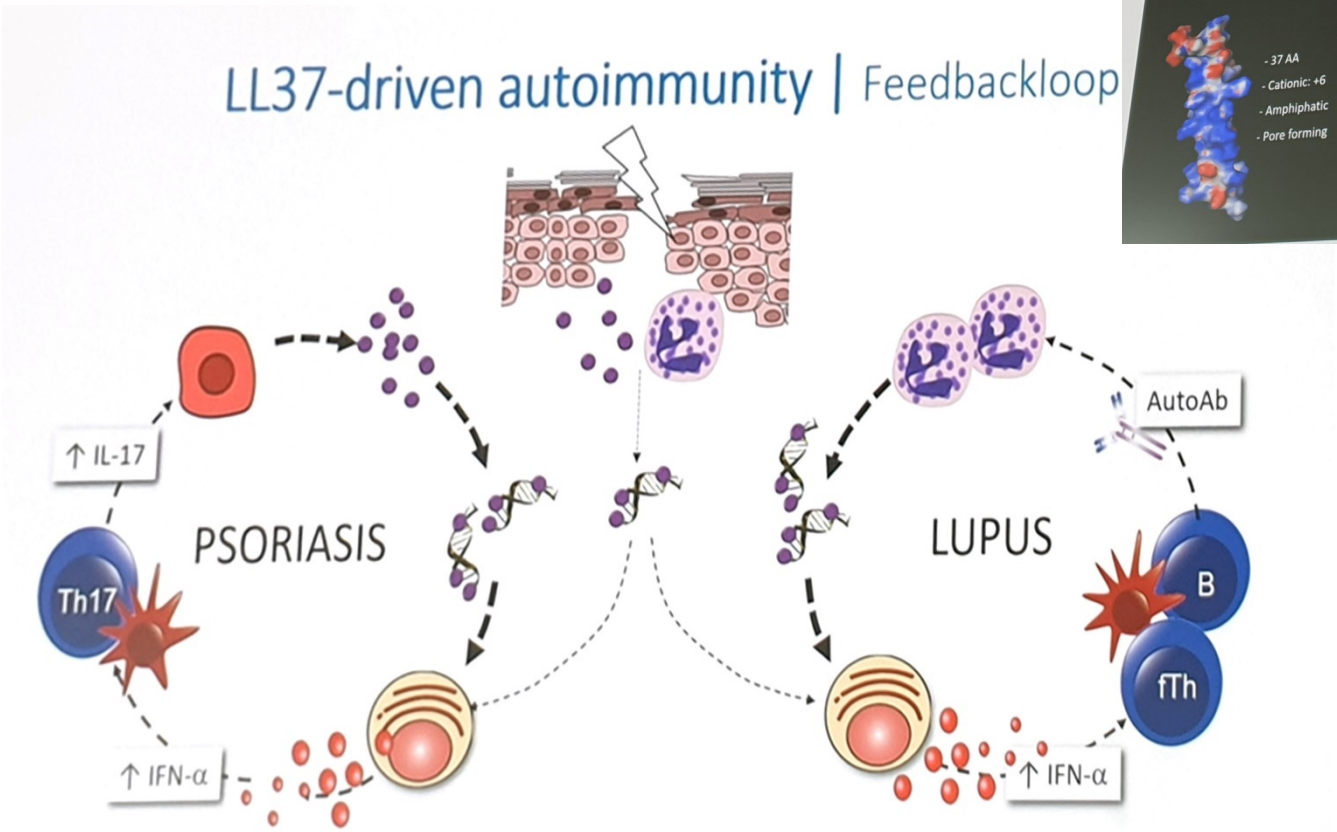
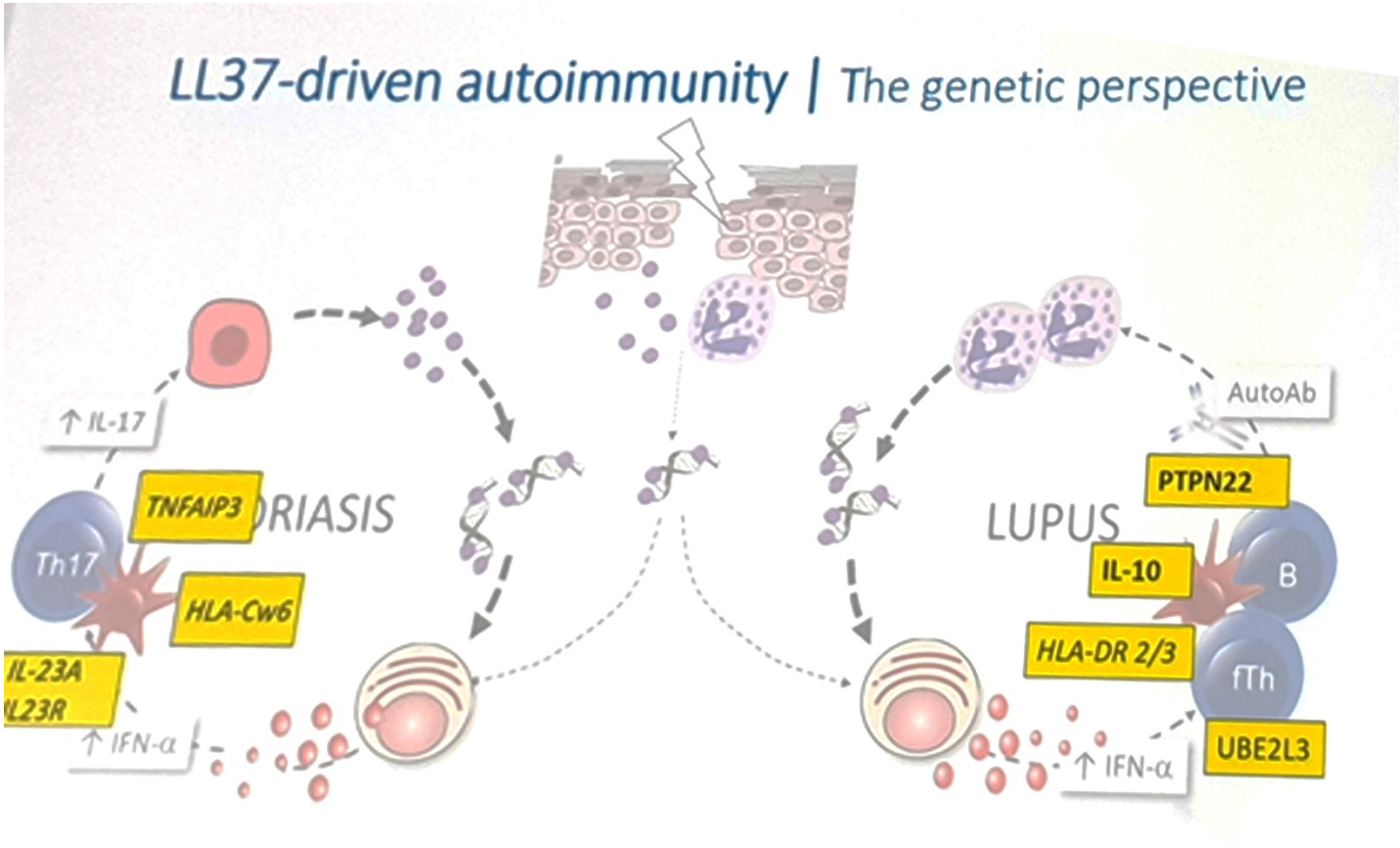
How Autoantigens Drive Cutaneous Autoimmune Disoerders
Michell Gilliet

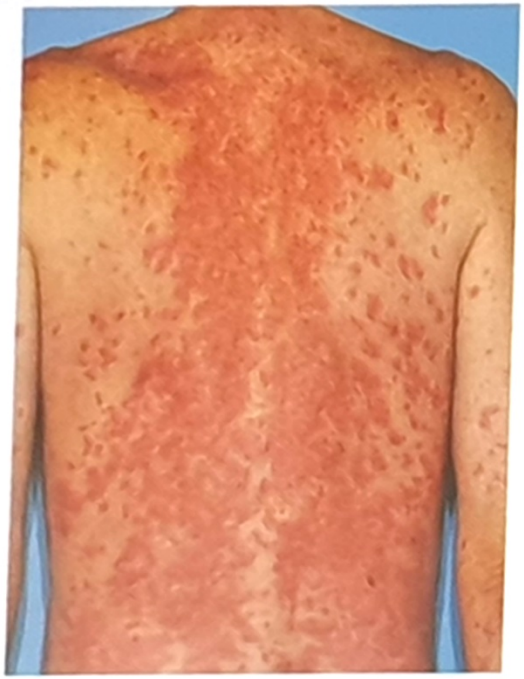




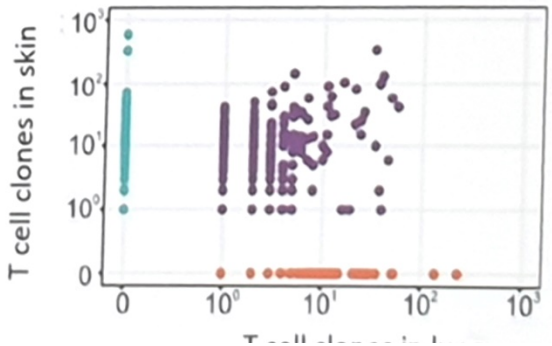
How Autoantigens Drive Cutaneous Autoimmune Disoerders
Michell Gilliet



Anti-PD1-induced rash | LL37-driven autoimmunity?



- Lichenoid skin rash associates with clinical responses
- Shared T cell clones in lung and skin specific for LL37, maspin, desmocollin, keratin 14
- Th1/Tc1 phenotype



er et al. JAMA Oncology. 207:2921 (2019)

How Autoantigens Drive Cutaneous Autoimmune Disoerders
Michell Gilliet

- LL-37 is an autoantigen that induces potent virus-like immune activation
  - Forms DNA complexes that trigger intracellular nucleic acid receptors
  - Unleashes IFN-mediated CD4 and CD8 T cell responses (autoimmunity)

- Early unspecific driver of autoimmunity T cell polarization depends on genetic predisposition/tissue microenviroment:
  - Th17 for psoriasis, fTh antibodies for lupus, TH1 for cancer/anti-PD1

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Clinical relevance| Early therapeutic targeting

Inhibitors of AMP production:

NET inhibitors (PAD4 antagonists)

Targeting AMPs:

Structural AMP Competitors (anionic, spacing)

AMP inhibitors?

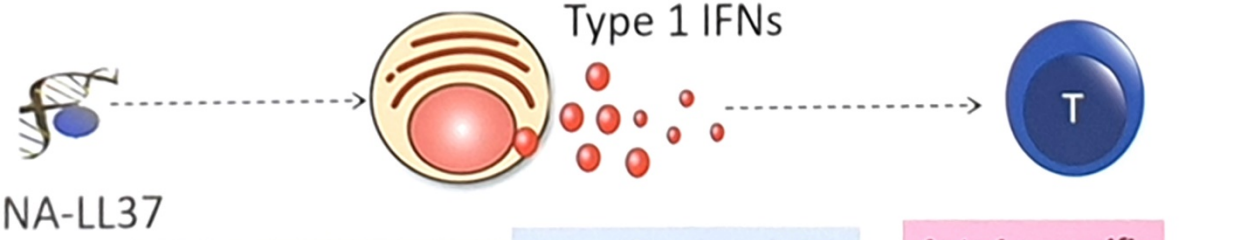
Targeting nucleic acids:

Dnase/Rnase-Fc

pDC inhibition:

Anti-ILT-7

Anti-BDCA2



TLR/STING antagonists:

TLR7/9 inhibitors

TLR7/9 antagonists

STING antagonists

Neutralization of IFN IFNAR signalling:

Anti-IFN-α Ab
Anti-IFNAR Ab

JAK-1 Inhibitors

AutoAg specific T cell control

Tolerogenic vaccines
CAR-T cells targeting the AutoAg

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