Elevating dermatological drug development through advanced inflammatory marker targeting methodology

- Focus of IL-17 in the pathophysiology of psoriasis and unmet medical need –

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Conflict of interest: AbbVie, Almirall, BMS, Celltrion, Janssen, Lilly, Novartis, UCB

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What is Psoriasis?[1-4]

- **Systemic, chronic inflammatory disorder**
- Affects **2–3%** of the fair-skinned population
- **Genetic** and **immunologic** basis, **can be triggered**
- Several **comorbid diseases** result in considerable **impairment of quality of life**
- **2016:** World Health Organization (WHO) publishes **Global Report on Psoriasis**[4]

WHO: World Health Organisation.

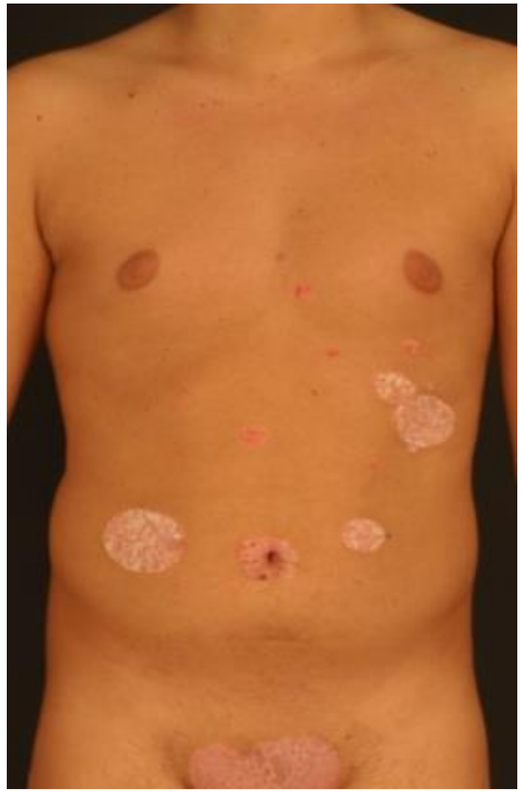
[1]National Psoriasis Foundation. About Psoriasis. Available at: https://www.psoriasis.org/about-psoriasis/. Accessed: 14/02/2024.

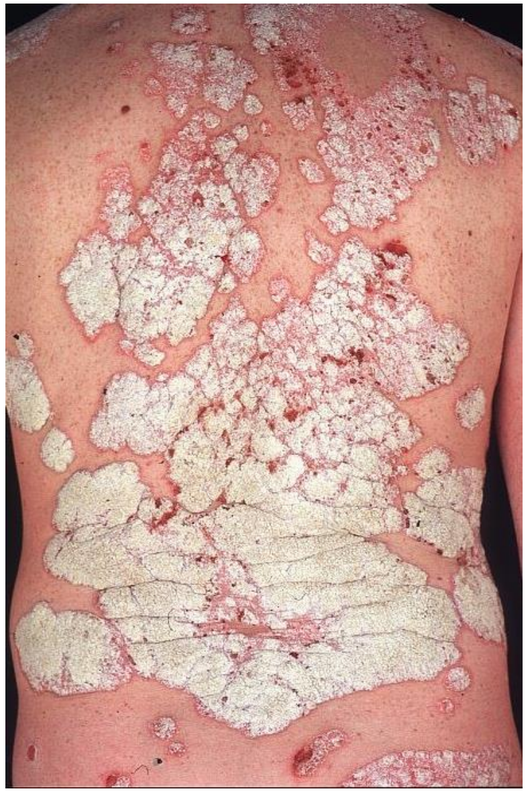
[2]Schön MP and Boehncke WH. N Engl J Med. 2005;352:1899–912.

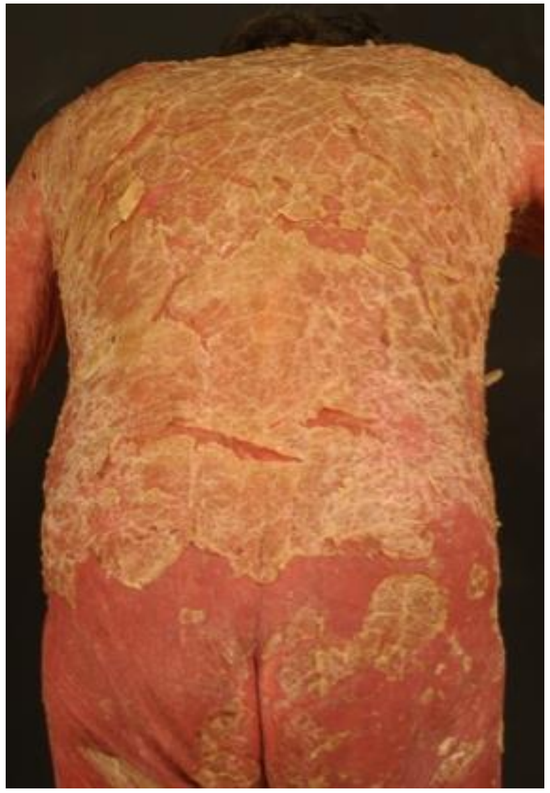
[3]Boehncke WH and Schön MP. Lancet. 2015;386:983–94.

[4]WHO Global Report on Psoriasis. Available at: https://apps.who.int/iris/bitstream/handle/10665/204417/9789241565189_eng.pdf?sequence=1&isAllowed=y. Accessed 14/02/2024.

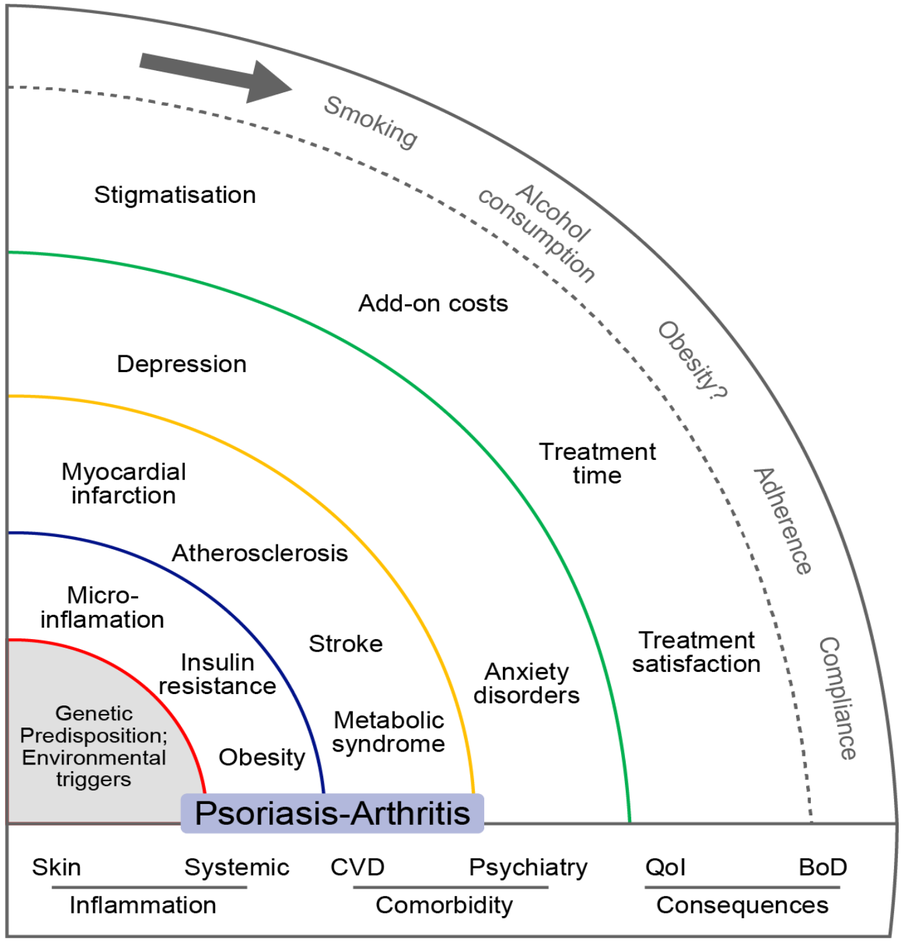
Psoriasis: comorbidity and general impact on the patients' lives







Boehncke WH and Schön MP, Lancet, 2015

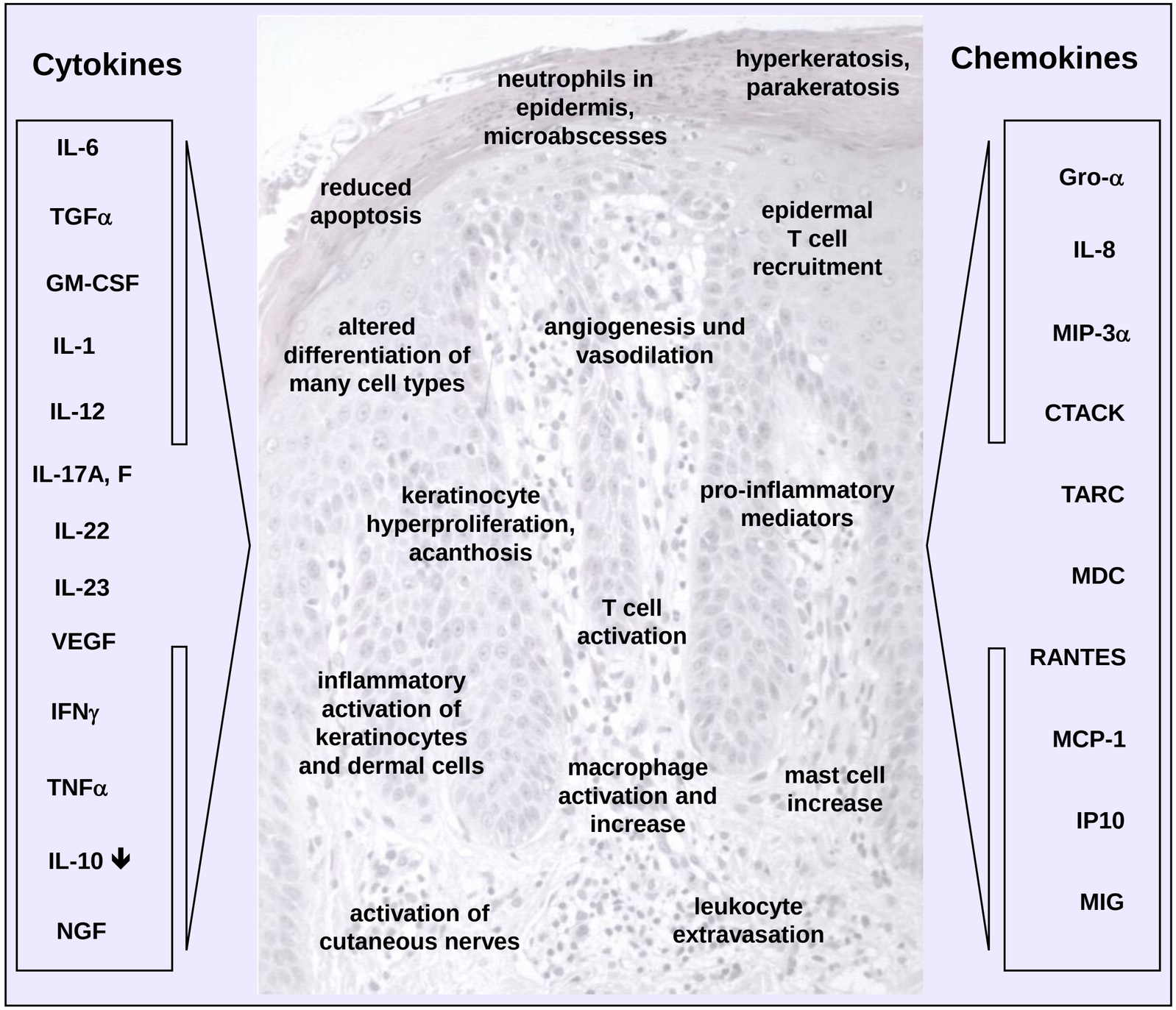


BoD: Burden of disease; CVD: Cardiovascular disease; QoL: Quality of life.

Adapted from WHO Global Report on Psoriasis. Available at: https://apps.who.int/iris/bitstream/handle/10665/204417/9789241565189_eng.pdf?sequence=1&isAllowed=y. Accessed 14/02/2024.

Microenvironment in psoriasis (I)

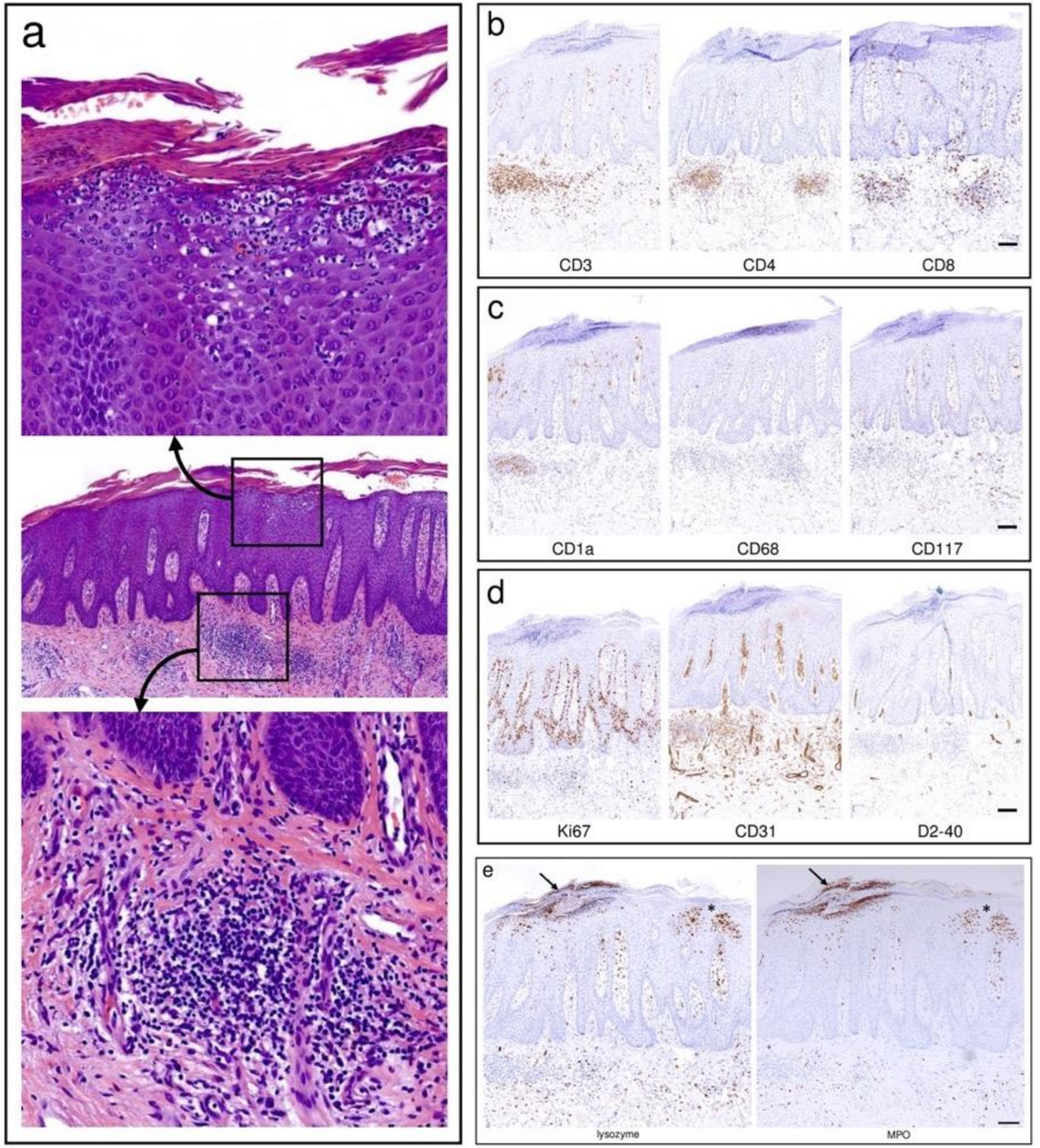
- altered expression of many **cytokines** and **chemokines** in psoriatic lesions
- known activities can explain many **pathological tissue changes**
- **increased expression** alone is **not sufficient** to predict the **therapeutic efficacy** of the inhibition



Adapted from:
Schön MP. Akt Dermatologie, 2006;32:169–75.
Boehncke WH and Schön MP. Lancet. 2015;386:983–94.
Schön MP and Wilsmann-Theis D: J Dtsch Dermatol Ges 2023;21(4):363-73

Microenvironment in psoriasis (II)

- **compartmentalization** of resident and immigrating cells
- **innate** and **adaptive immune system** contribute to pathogenesis
- infiltration of **dendritic cells** (DCs) and **T cells**, particularly Th17 and Th22 cells
- **complex immunological feedback loops** between antigen presenting cells, T cells, neutrophilic granulocytes, keratinocytes, endothelial cells and cutaneous nerves (and others)



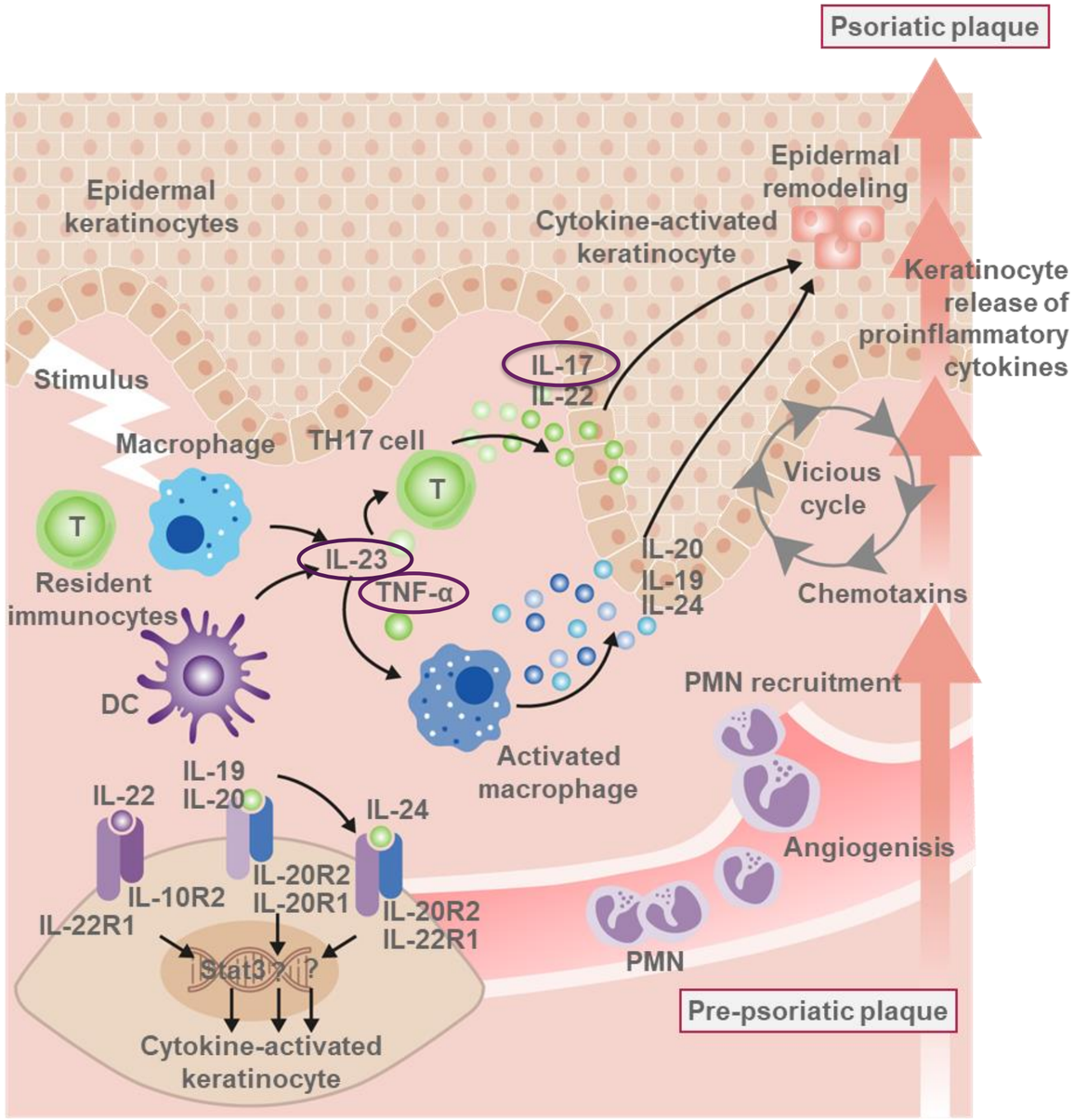
Schön MP. Adaptive and innate immunity in psoriasis and other inflammatory disorders. Front Immunol 10, 1764, 2019

The current concept in brief: TNF, Th17 cells, IL-17 and IL-23 [1-7]

Etanercept
Infliximab
Adalimumab
Certolizumab Pegol

Guselkumab
Risankizumab
Tildrakizumab
Ustekinumab (also IL-12)

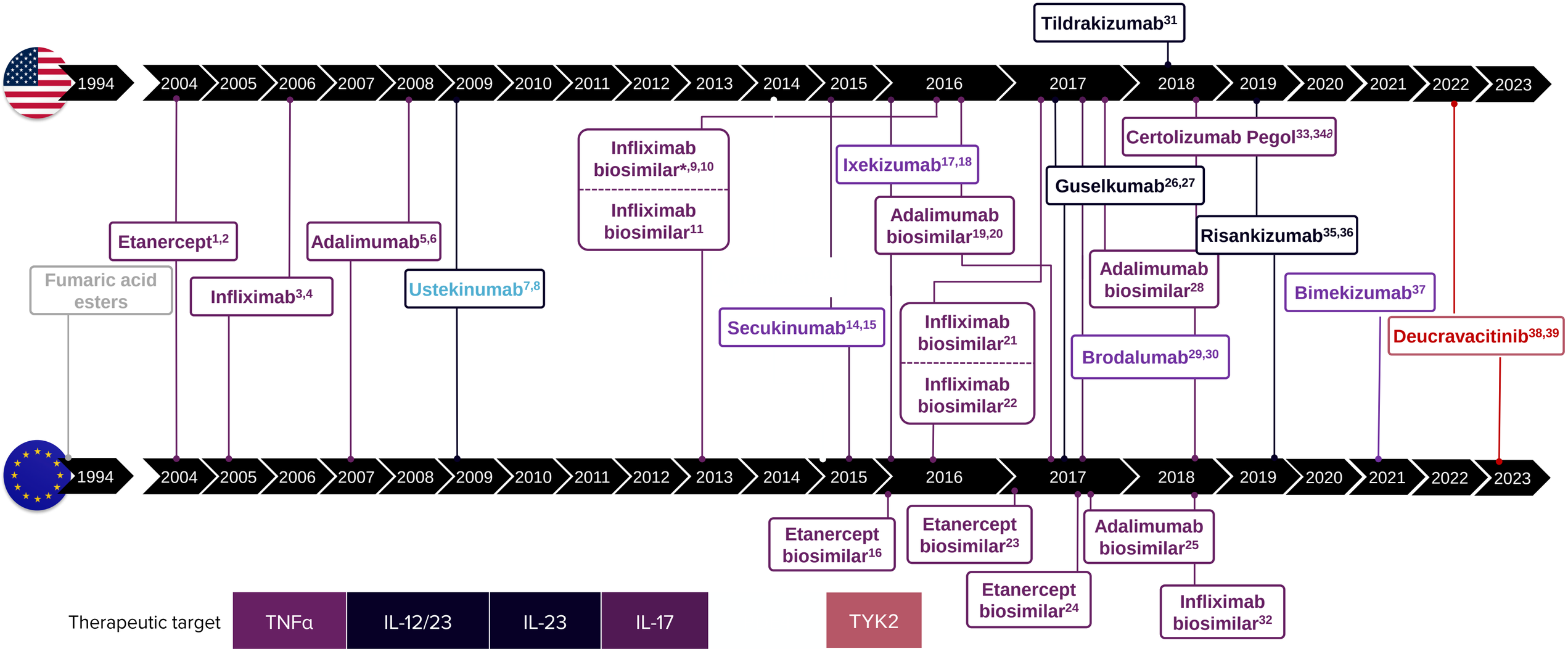
Secukinumab
Ixekizumab
Brodalumab
Bimekizumab



PMN: Polymorphonuclear leukocyte; STAT: Signal transducer and activator of transcription.

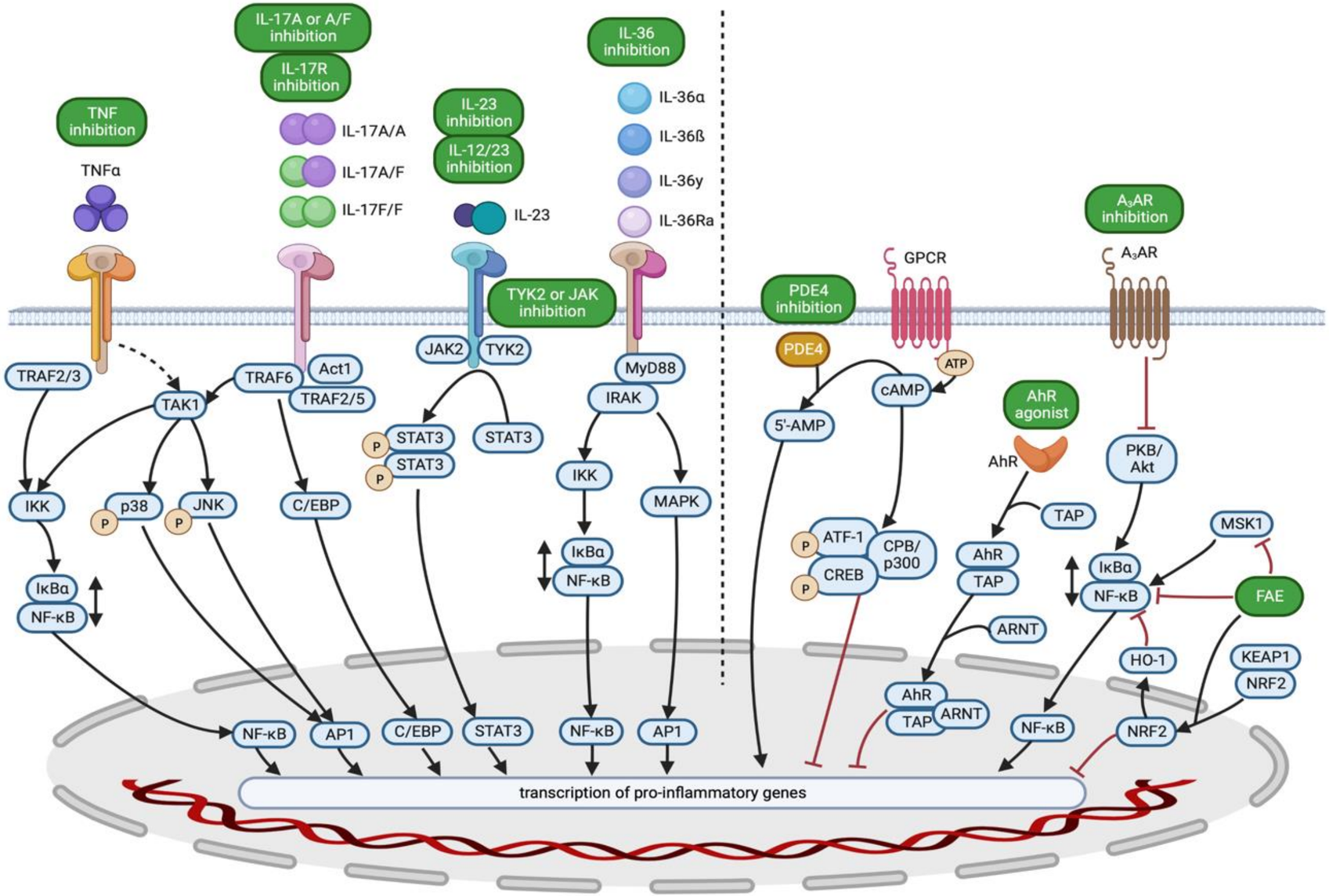
[1]Adapted from Dolgin E. Nat Biotechnol. 2016;34:1218–1219. [2]Boehncke WH and Schön MP. Lancet. 2015;386:983–994. [3]Nestle F et al. N Engl J Med. 2009;361:496–509. [4]Lowes MA et al. Nature. 2007;445:866–873. [5]Griffiths C and Barker J. Lancet. 2007;370:263–271. [6]Schön M and Boehncke WH.N Engl J Med. 2005;352:1899–1912. [7]Schön MP and Wilsmann-Theis D: J Dtsch Dermatol Ges 2023;21(4):363-73

Systemic therapies over the past three decades



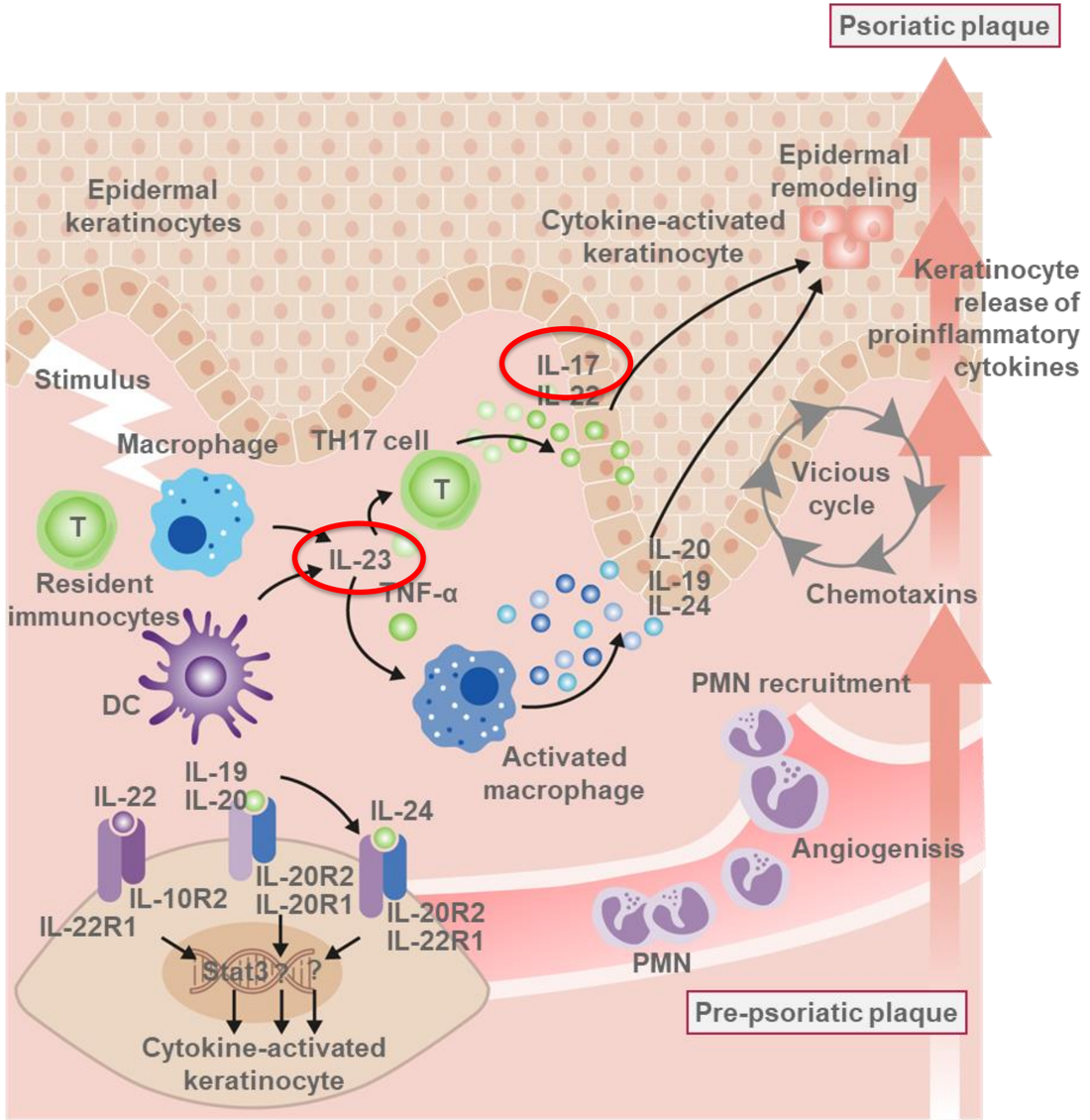
Also approved in the EU. [1]FDA. Enbrel PI. 2018. p4. [2]EMA. Enbrel SmPC. 2019. p3. [3]FDA. Remicade PI. 2018. p1. [4]EMA. Remicade SmPC. 2019. p3. [5]FDA. Humira PI. 2018. p1. [6]EMA. Humira SmPC. 2019. p89. [7]FDA. Stelara PI. 2019. p1. [8]EMA. Stelara SmPC. 2019. p19. [9]FDA. Inflectra PI. 2019. p1. [10]EMA. Inflectra SmPC. 2019. p3. [11]EMA. Remsima SmPC. 2019. p3. [12]FDA. Otezla PI. 2019. p1. [13]EMA. Otezla SmPC. 2019. p3. [14]FDA. Cosentyx PI. 2018. p1. [15]EMA. Cosentyx SmPC. 2018. p2. [16]EMA. Benepali SmPC. 2019. p3. [17]FDA. Taltz PI. 2019. p1. [18]EMA. Taltz SmPC. 2019. p2. [19]FDA. Amjevita PI. 2019. p1. [20]EMA. Amgevita SmPC. 2019. p3. [21]FDA. Renflexis PI. 2019. p1. [22]EMA. Flixabi SmPC. 2019. p3. [23]EMA. Erelzi SmPC. 2019. p3. [24]EMA. Lifmior SmPC. 2019. p3. [25]EMA. Imraldi SmPC. 2019. p3. [26]FDA. Tremfya PI. 2019. p1. [27]EMA. Tremfya SmPC. 2019. p2. [28]FDA. Cyltezo PI. 2019. p1. [29]FDA. Siliq PI. 2017. p2. [30]EMA. Kyntheum SmPC. 2019. p2. [31]FDA. Ilumya PI. 2018. p1. [32]EMA. Zessly SmPC. 2019. p3. [33]EMA. Cimzia SmPC. 2019. p3. [34]FDA. Cimzia PI. 2019. p1.[35]EMA. Skyrizi SmPC. 2019 p2. [36]FDA. Skyrizi PI. 2019 p1.

Current therapeutic targets in psoriasis



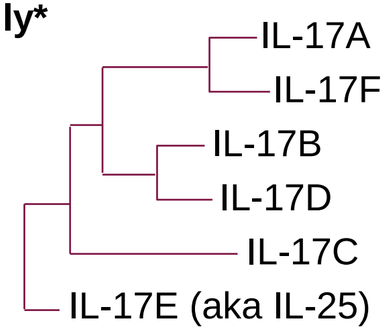
Schön MP and Wilsmann-Theis D: Current developments and perspectives in psoriasis. J Dtsch Dermatol Ges 2023;21(4):363-73

Inhibition of specific mediators: IL-23 and IL-17 [1-9]



Cytokine families

- Interleukins → **IL-17 family***
- Interferons
- Tumor Necrosis Factor
- Transforming Growth Factor
- Colony-stimulating Factors

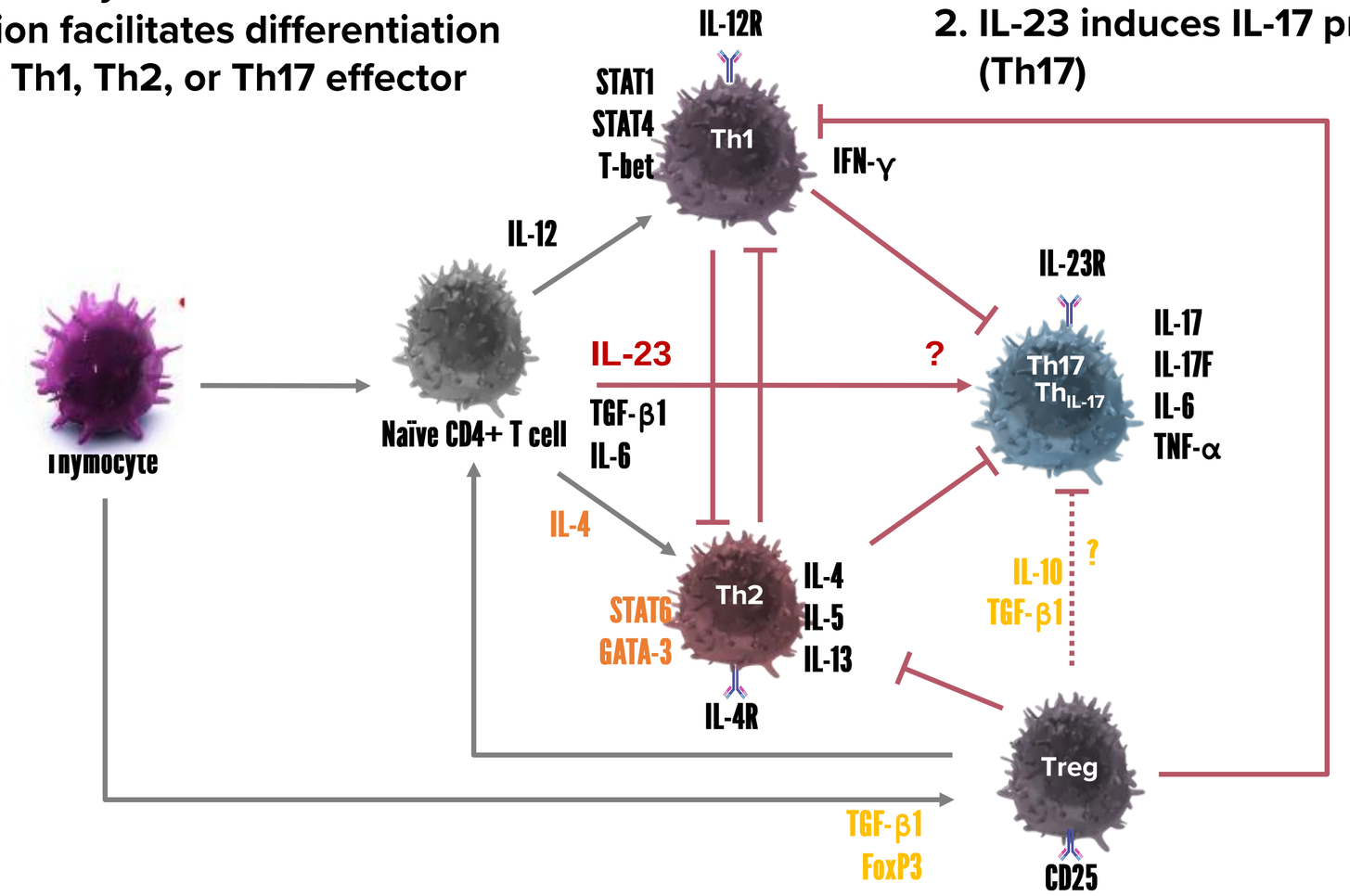


* IL-17F isoforms 1 and 2 have strongest homology with IL-17A (55% and 40%, resp.), followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (17%)[7]

Adapted from Dolgin E. Nat Biotechnol. 2016;34:1218–1219. [2]Boehncke WH and Schön MP. Lancet. 2015;386:983–994. [3]Nestle F et al. N Engl J Med. 2009;361:496–509. [4]Lowes MA et al. Nature. 2007;445:866–873. [5]Griffiths C and Barker J. Lancet. 2007;370:263–271. [6]Schön MP and Boehncke WH. N Engl J Med. 2005;352:1899–1912.; [7]Ivanov S and Linden A. Trends Pharmacol Sci. 2008;30:95-103; [8]Kolls J, Linden A. Immunity. 2004;21:467-476; [9]Gaffen S. Nat Rev Immunology. 2009/9:556-567

Cytokine network regulates T cell differentiation [1,2]

1. Antigen presentation by dendritic cells and cytokine stimulation facilitates differentiation of naïve T cells to Th1, Th2, or Th17 effector cells



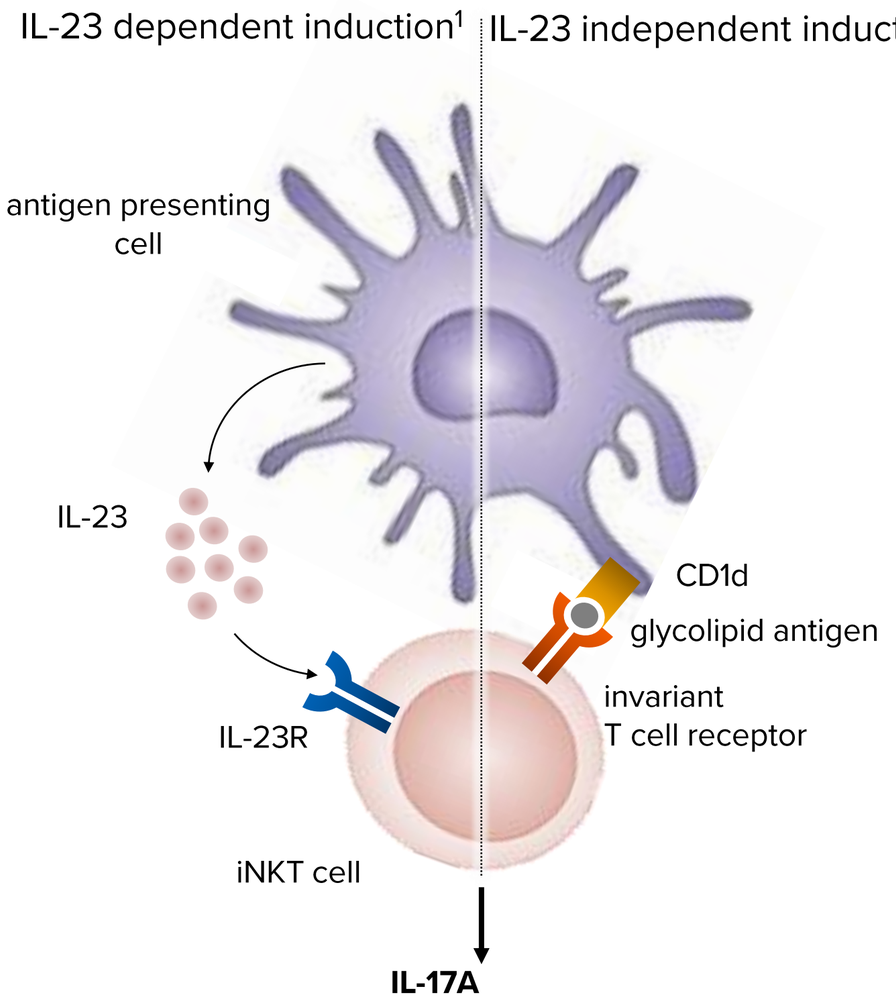
2. IL-23 induces IL-17 producing CD4$^+$ helper T cells (Th17)

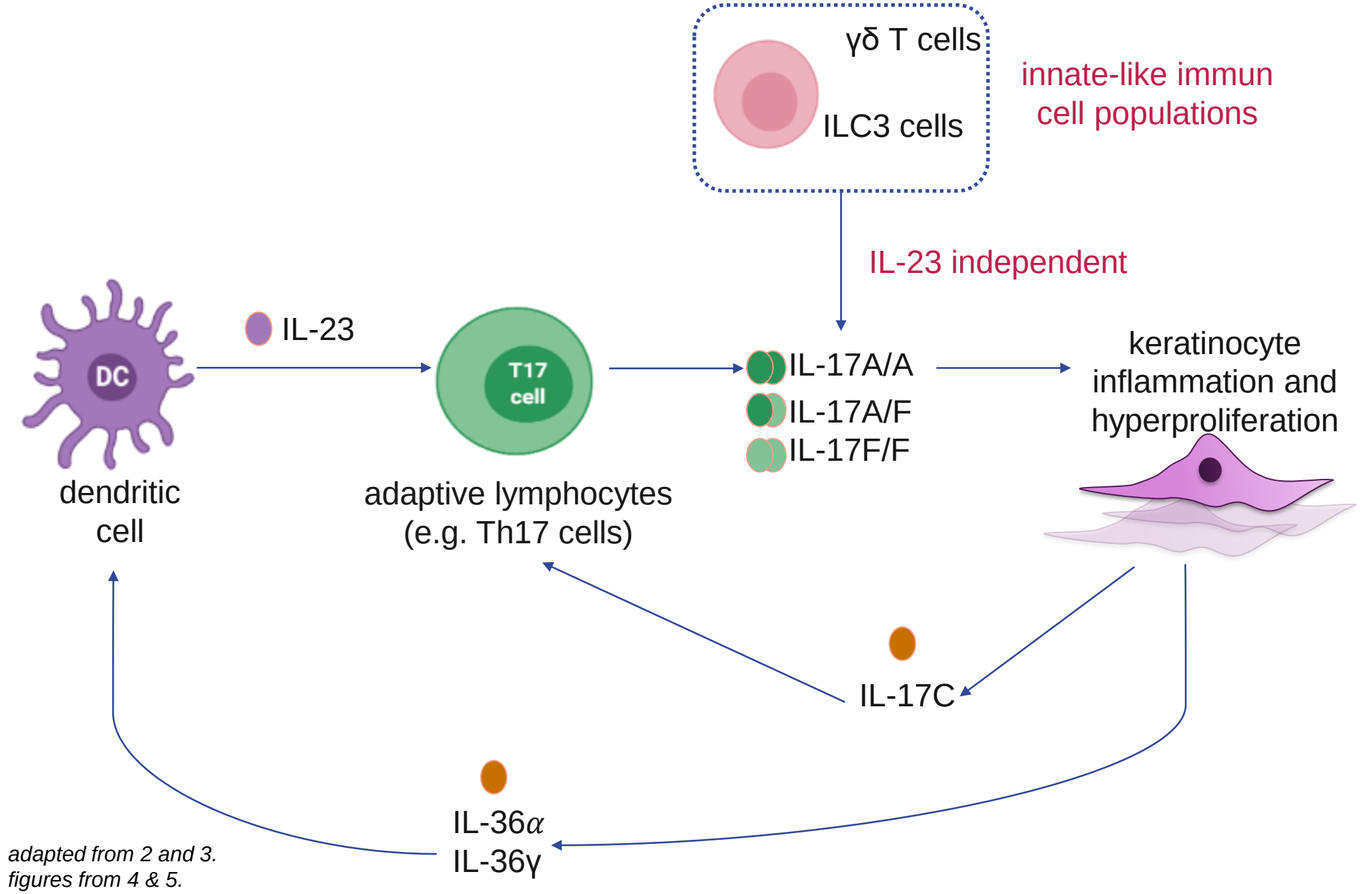
[1]Iwakura Y et al. J Clin Invest. 2006;116:1218–1222.

[2]Boehncke WH and Schön MP. Lancet. 2015;368:983–994.

3. T_{regs} inhibit differentiation and effector functions of Th1 and Th2 cells
4. Effect on Th17 cells (largely) unknown

There is more to IL-17 regulation...[1-3]

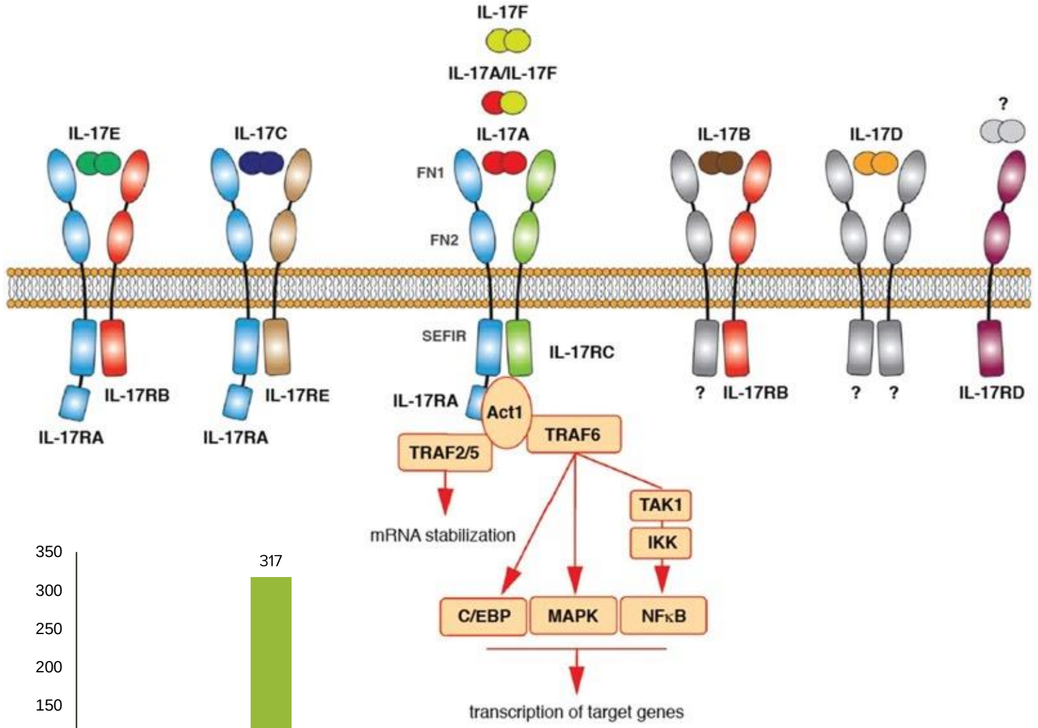




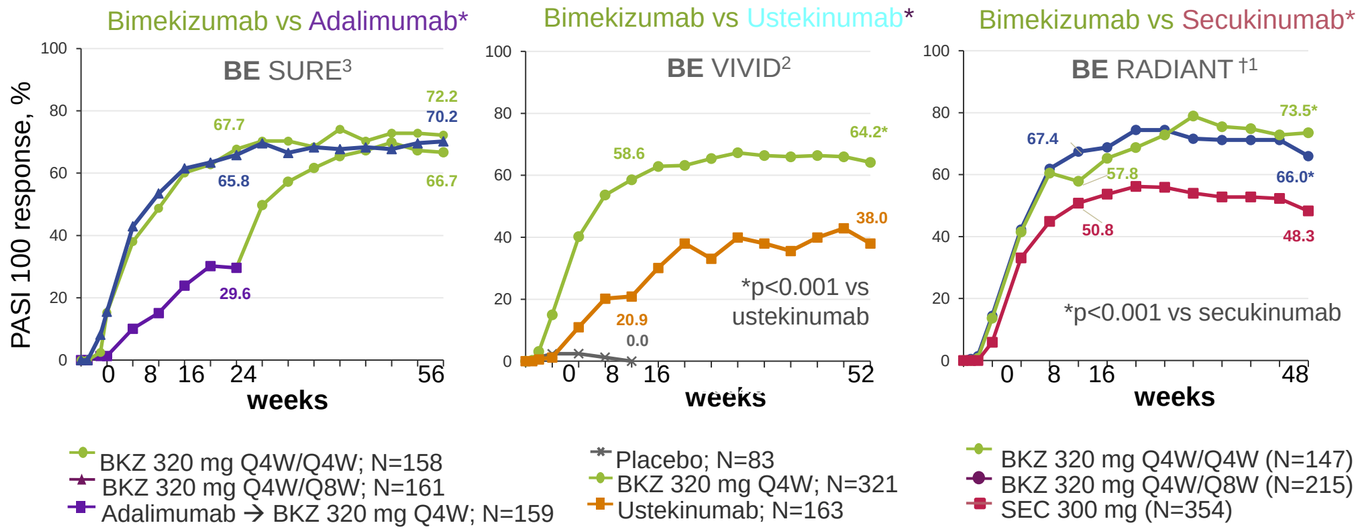
CD1d: antigen presenting glycoprotein; IL: Interleukin; iNKT-Zelle: invariant natural killer cell; Presentation also contains results from in vitro and animal studies;
1. Yoshiga, Int J Mol Med 2008.22:369-74; 2. Cua, Nat Rev Immunol 2010;10:479-89; 3. Nestle, N Engl J Med. 2009;361:496; 4. Lee, Immunity 2015;43:727–38

Exemplary representation of cell types. Not a complete list. 1. Lynde et al. J Am Acad Dermatol. 2014;71:141–50. 2. Krueger et al. Genome Informatics 2020;poster presentation. 3. Cole et al. Front Immunol. 2020 Nov 20;11:585134. 4. Gottlieb et al. PLoS One 2015;10:e0134703. 5 Johnson-Huang et al. PLoS One 2012;7:e30308.

IL-17 and IL-17 receptors [1-5]



IL-17 subtype	Receptor(s)	Producing cells	Effect on other cells	Associations with diseases
IL-17A	– IL-17-RA – IL-17-RC	– Th17 cells – γδ-T cells – ILC3 cells – Neutrophil granulocytes – Mast cells	– Proinflammatory effect on epithelial cells – IL-17F in synergy with IL-17A	– Psoriasis – Atopic eczema – Multiple sclerosis – Rheumatoid arthritis – Psoriatic arthritis – Chronic inflammatory intestinal diseases – Inflammation with acute coronary syndrome
IL-17F	– IL-17-RA – IL-17-RC	– Th17 cells – γδ-T cells – ILC3 cells	– Synergistic effect with IL-17A – Proinflammatory effect on epithelial cells	– Psoriasis – Atopic eczema – Multiple sclerosis – Rheumatoid arthritis – Psoriatic arthritis – Chronic inflammatory intestinal diseases

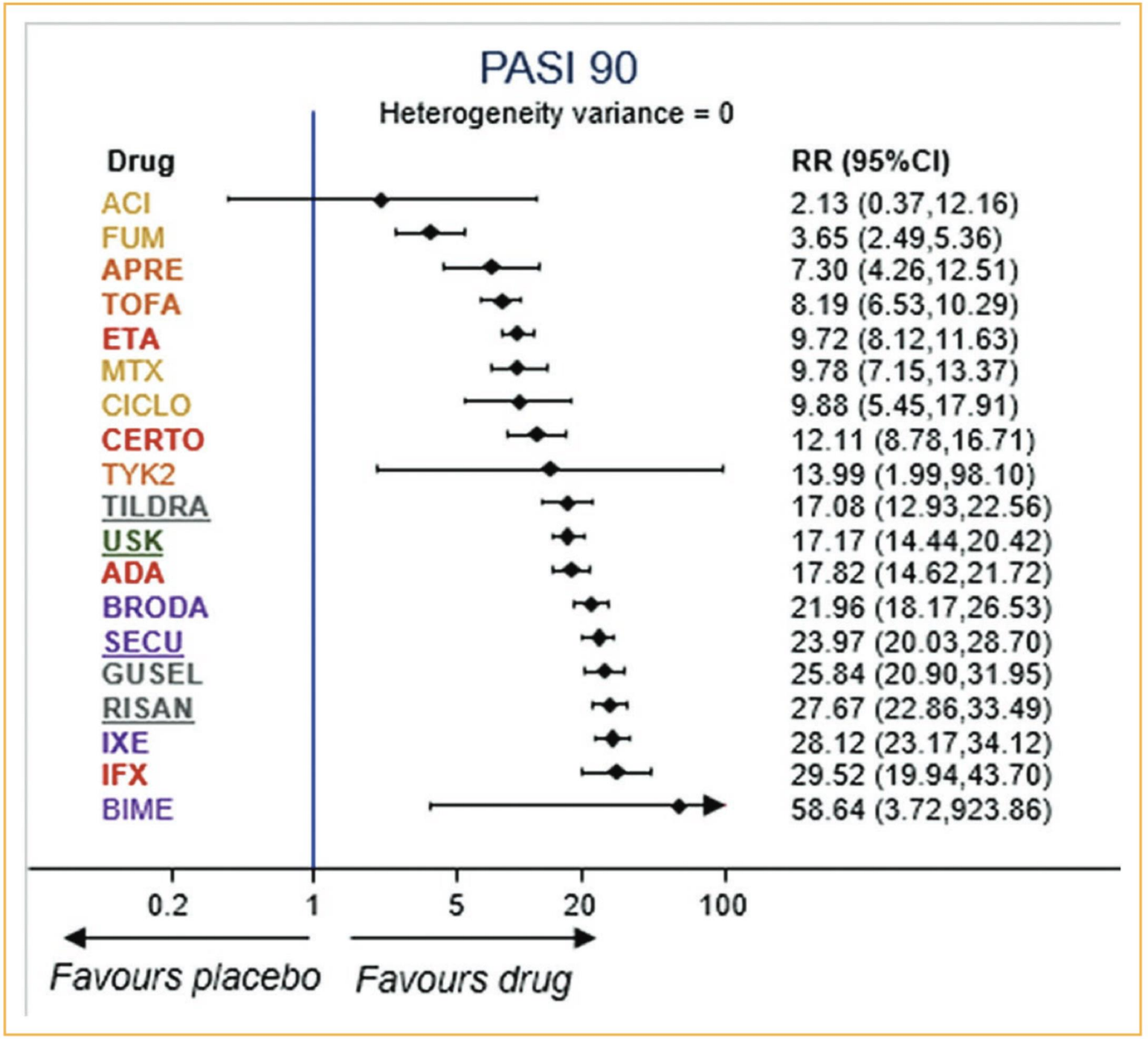


[1] Lauffer F, ..., Schön MP: J Dtsch Dermatol Ges. 18(7), 675-681, 2020
[2] Kolbinger et al. J Allergy Clin Immunol 2017;139:923–32
[3] Reich K, et al. N Engl J Med 2021;385:142-52;
[4] Reich K, et al. Lancet 2021;397:487-98;
[5] Warren RB, et al. N Engl J Med 2021;385:130-41.

† Data from maintenance group. In BE SURE switch in BKZ Q4W/Q8W arm in week 16 from Q4W to BKZ Q8W, and in the adalimumab BKZ Q4W arm in week 24 von adalimumab to BKZ Q4W.
BKZ, Bimekizumab;
PASI 100, 100% improvement compared to baseline in PASI
Q4W, every 4 weeks; Q8W, every 8 weeks.

New guidelines expanded

- systemic therapies are usually approved only for moderate-to-severe disease
- i. e., PASI ≥ 10, BSA ≥ 10 and/or DLQI ≥ 10
- relative undertreatment of mild-to-moderate disease

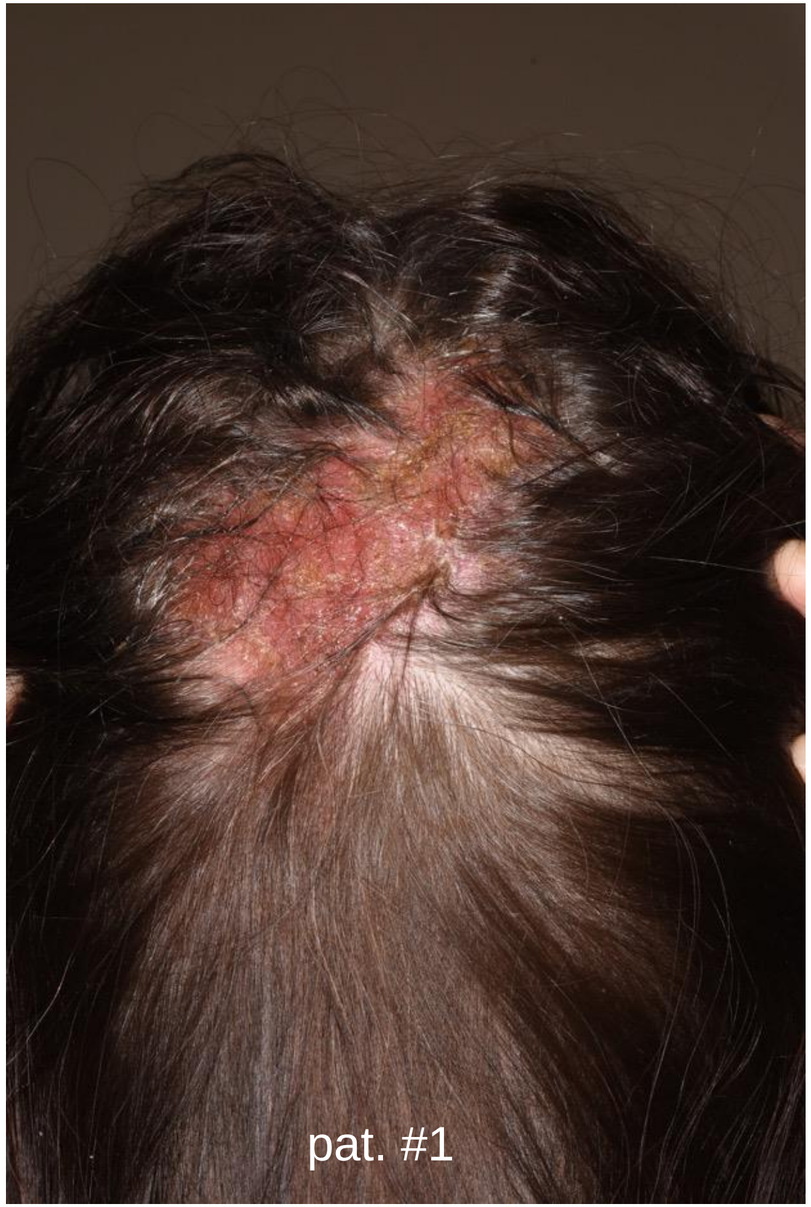


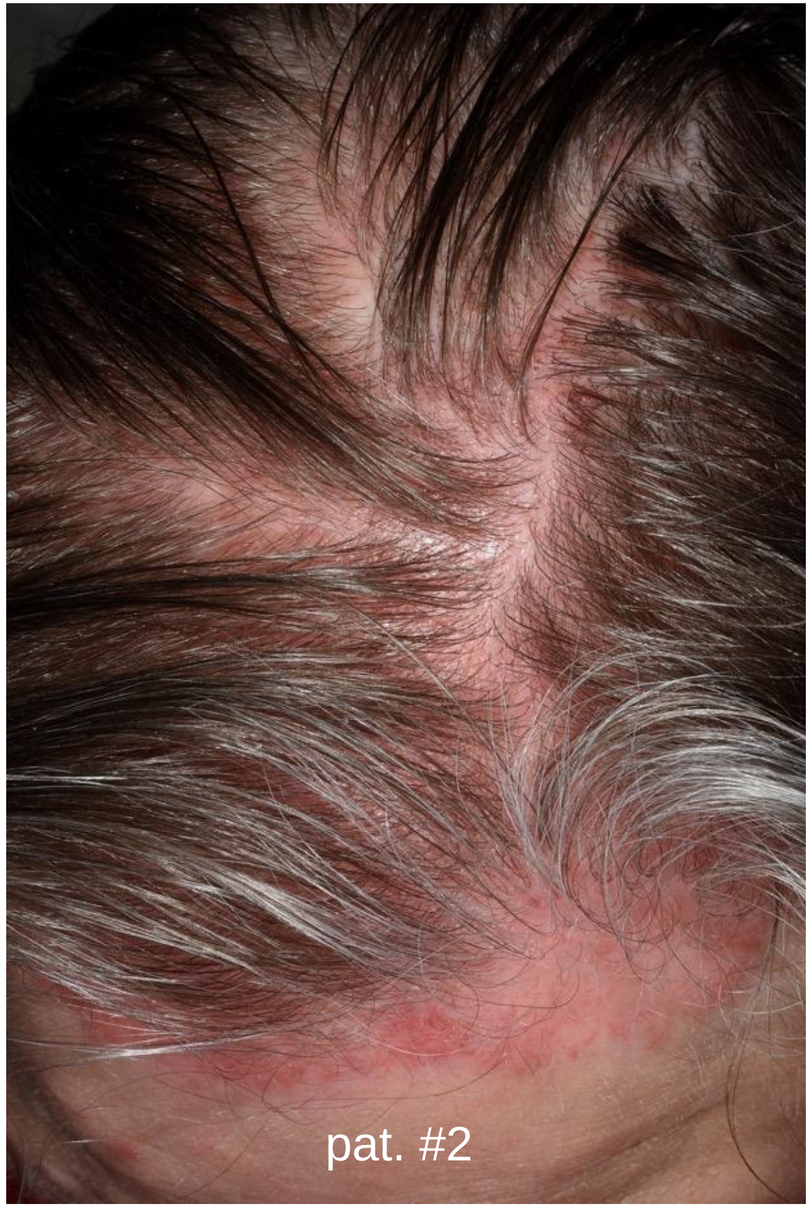
Nast A et al.: German S3 guideline treatment of psoriasis vulgaris.... J Dtsch Dermatol Ges. 19, 934-951, 2021

Why do we need more?

- not all patients achieve complete clearance (PASI90 or PASI100)
  - recalcitrant lesions that do not respond adequately
- some patients have psoriasis in difficult-to-treat areas
  - e.g. hands, feet, scalp, genitals...
- most patients are not eligible for systemic therapy (only moderate-to-severe disease)
  - lesions in visible or sensitive areas still cause considerable burden of disease
- individual preferences

Hard-to-treat lesions: scalp


pat. #1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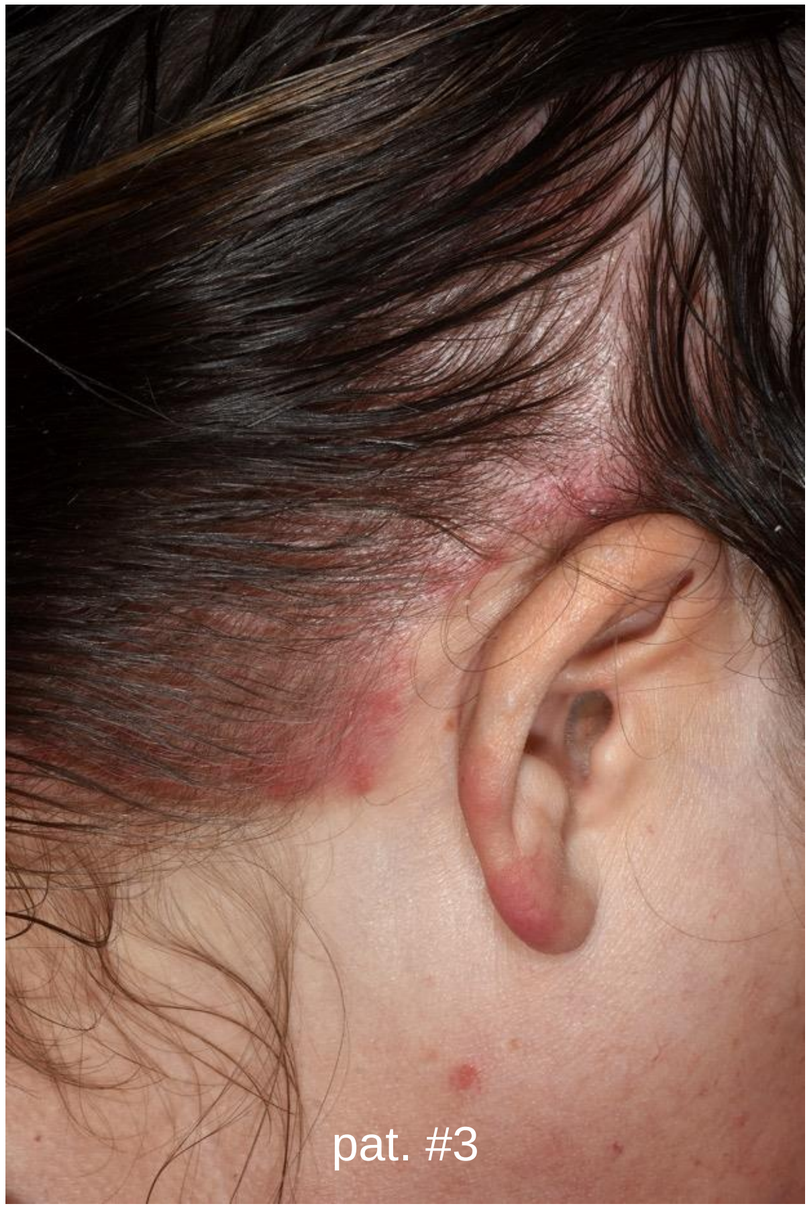
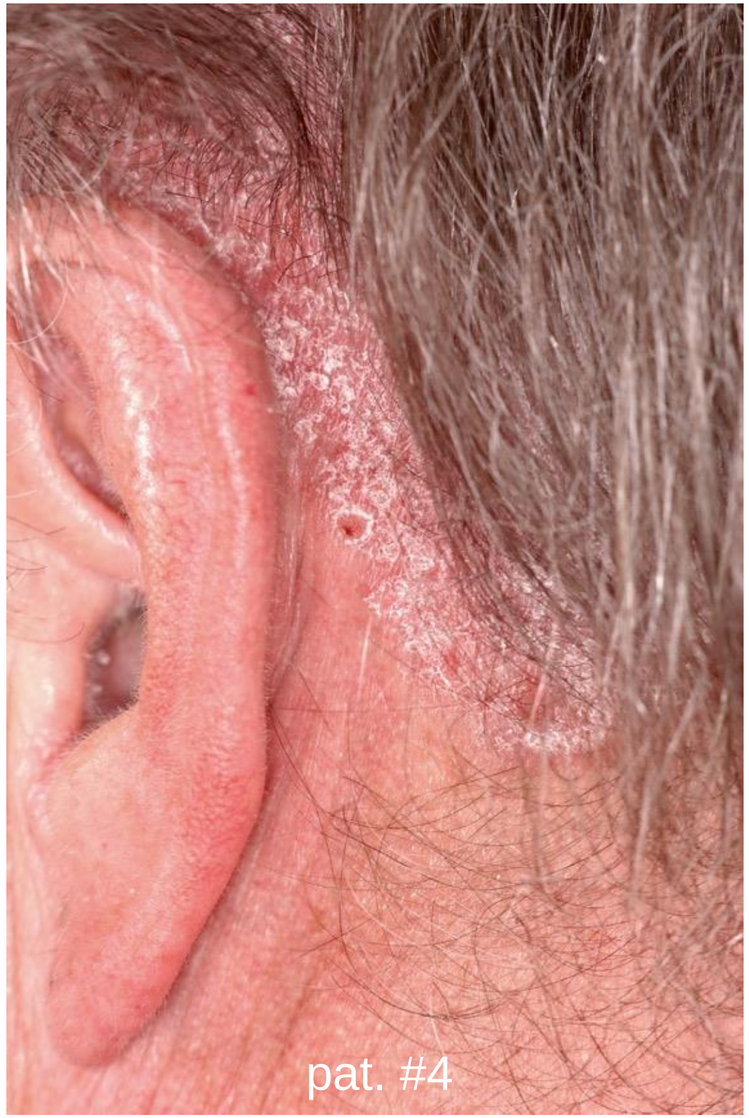

pat. #3

Hard-to-treat lesions: scalp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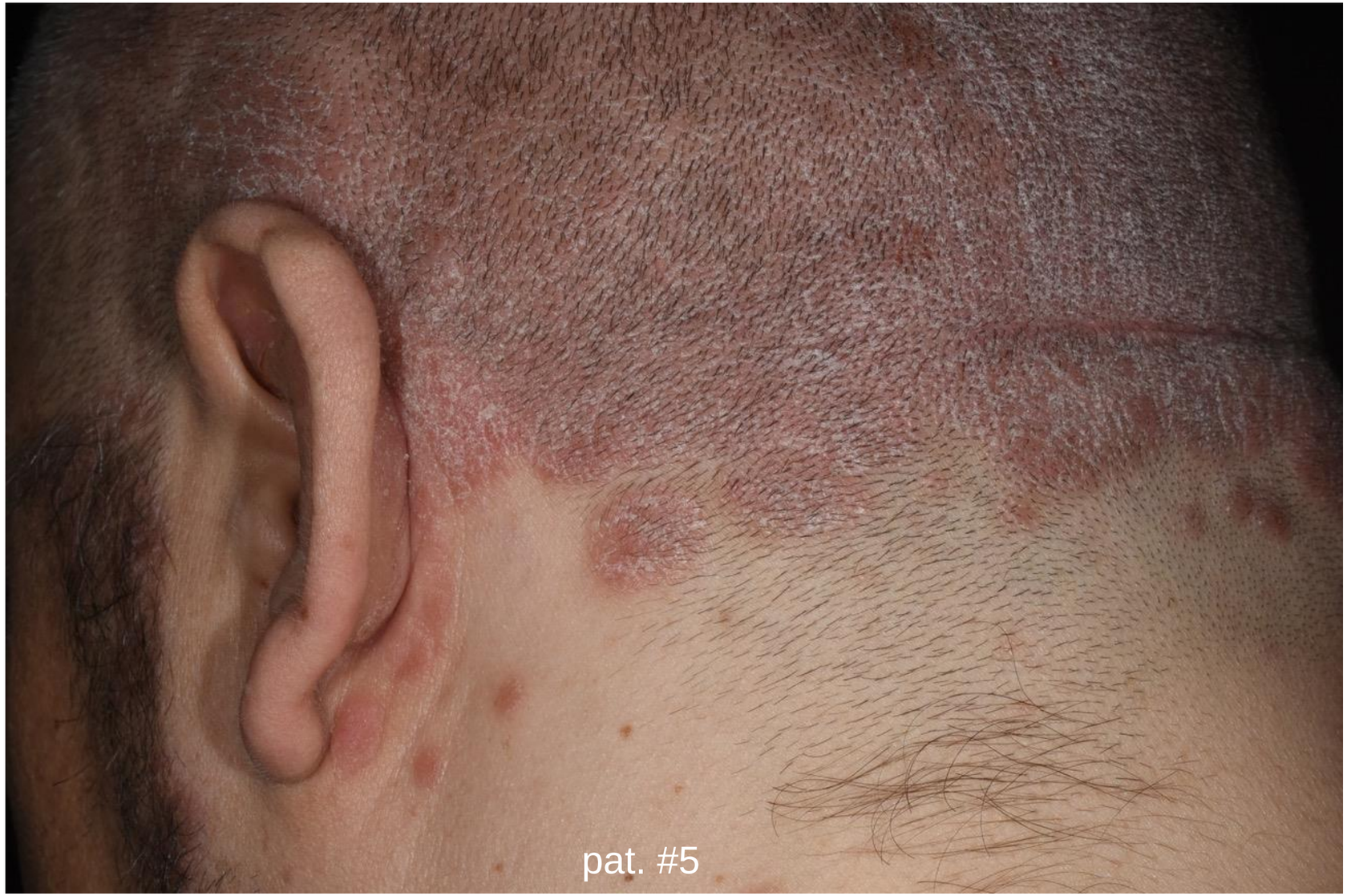
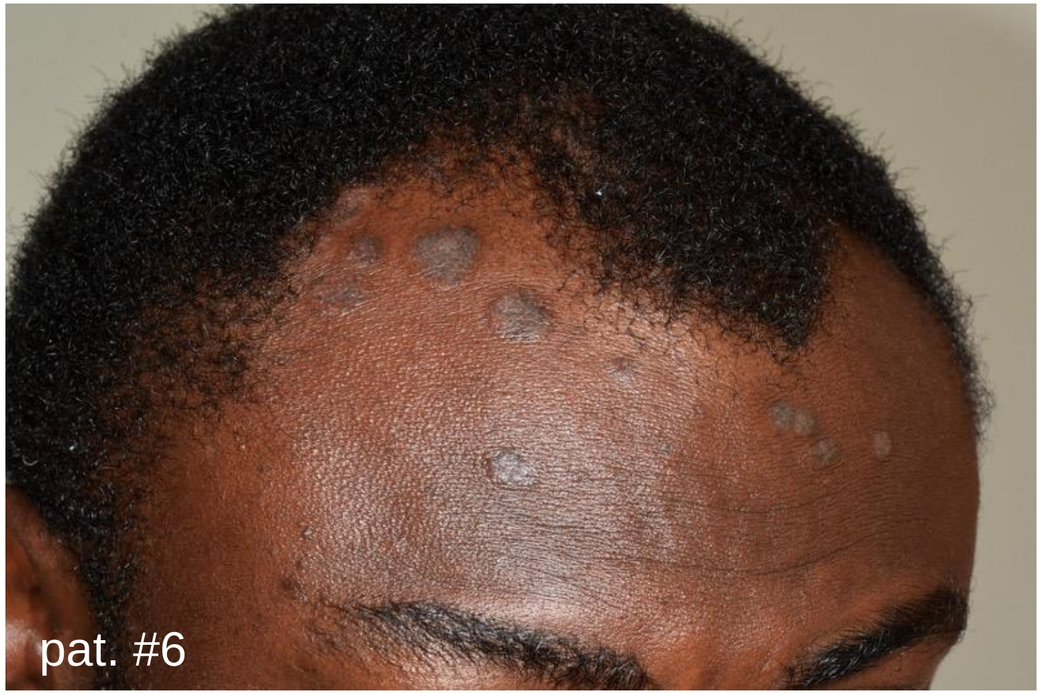
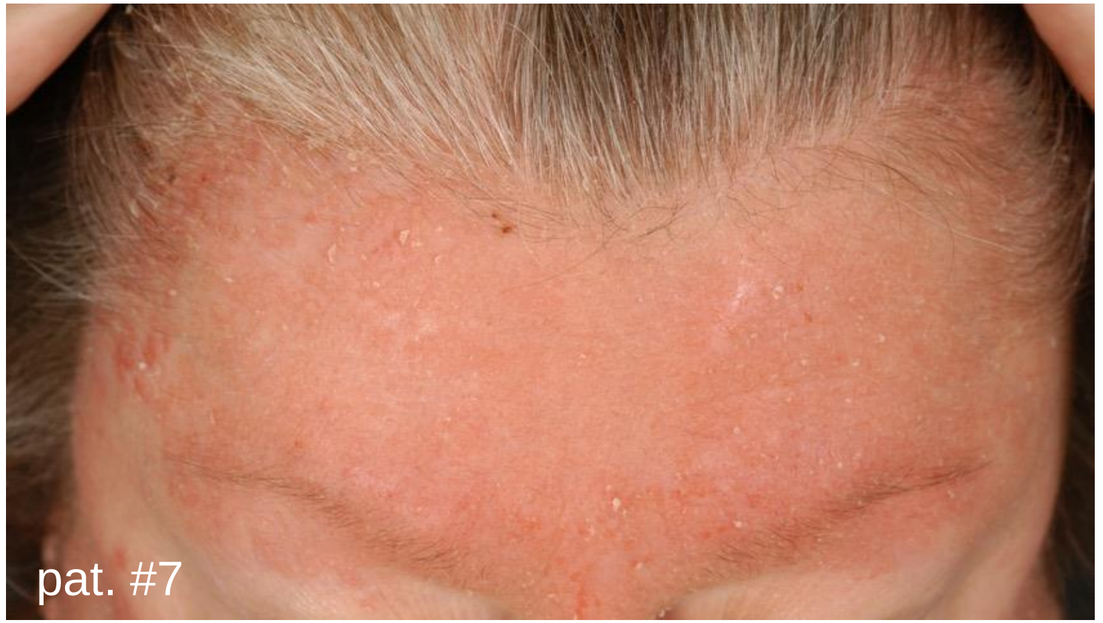
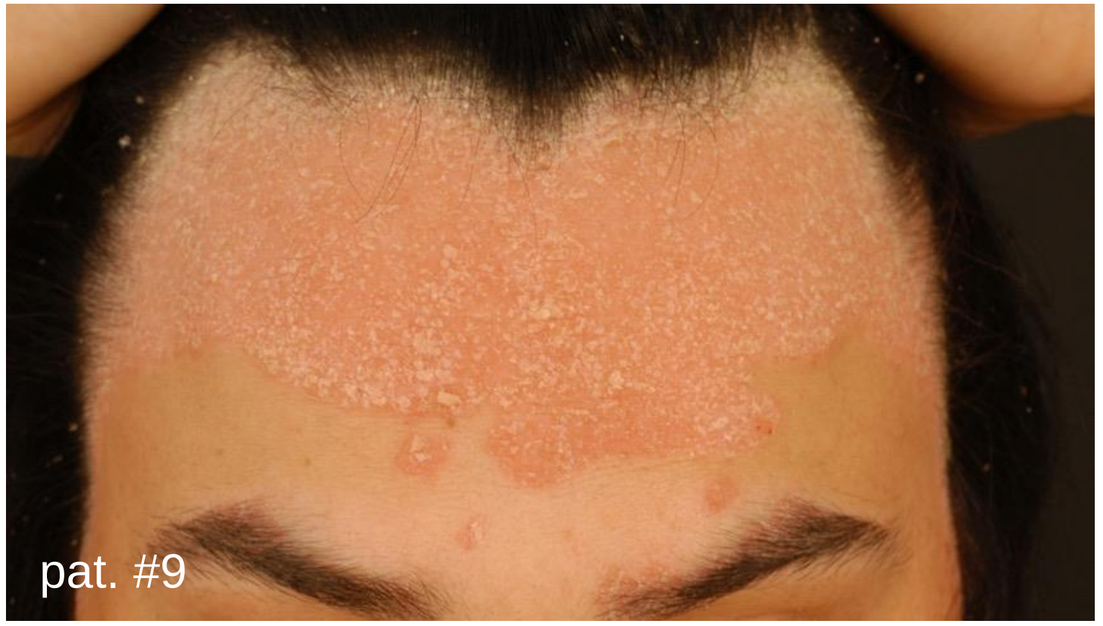

pat. #5

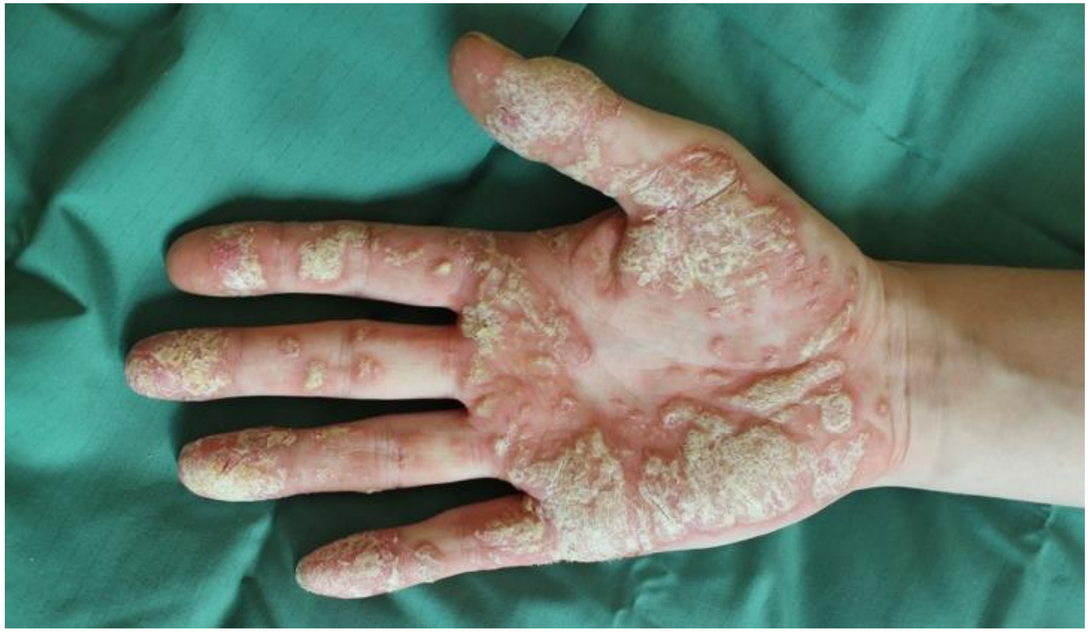
Visible areas with high burden of disease: face

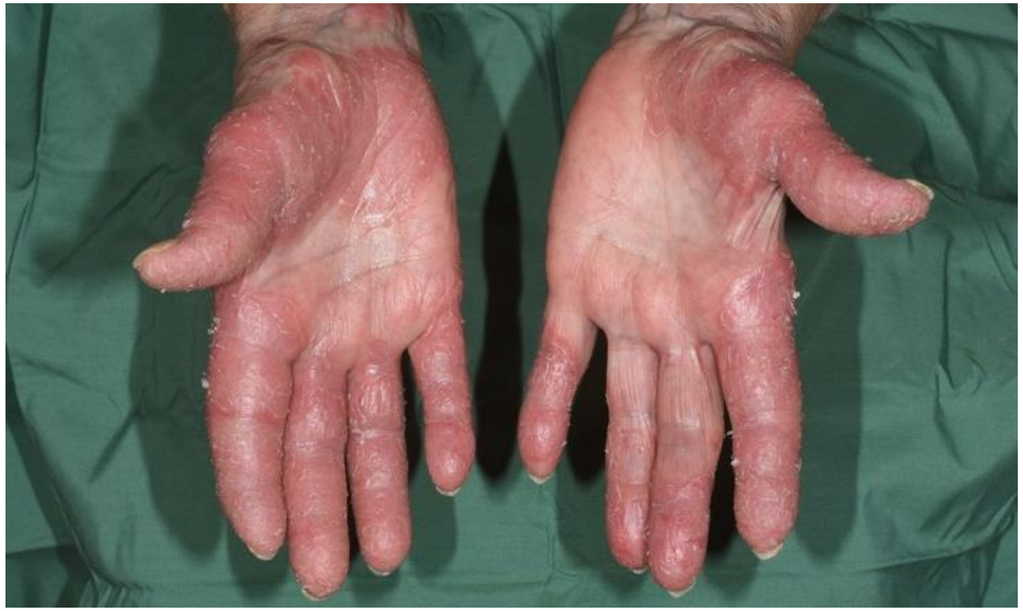


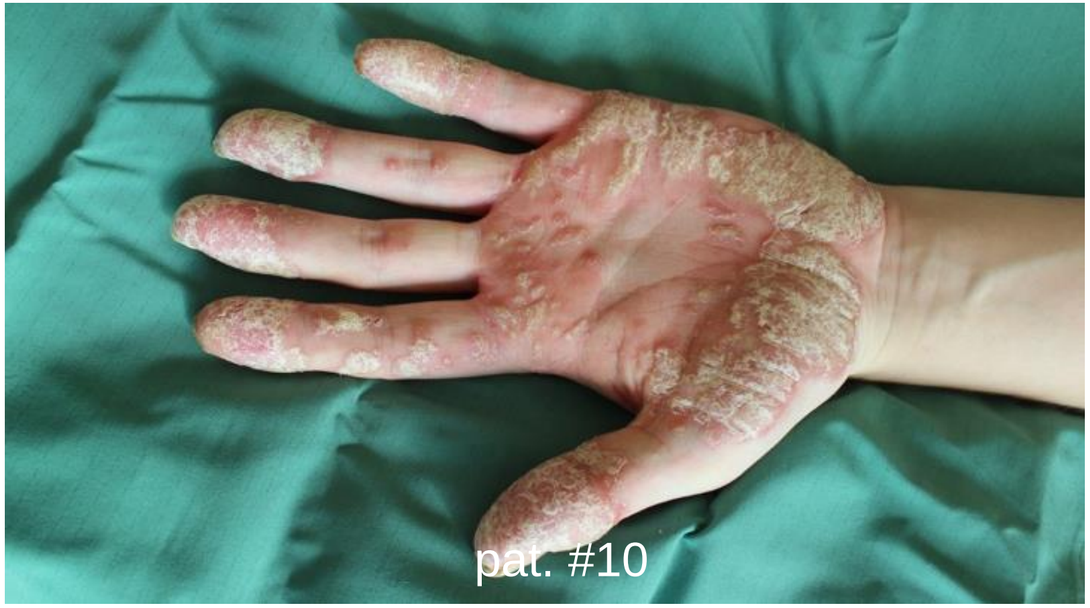




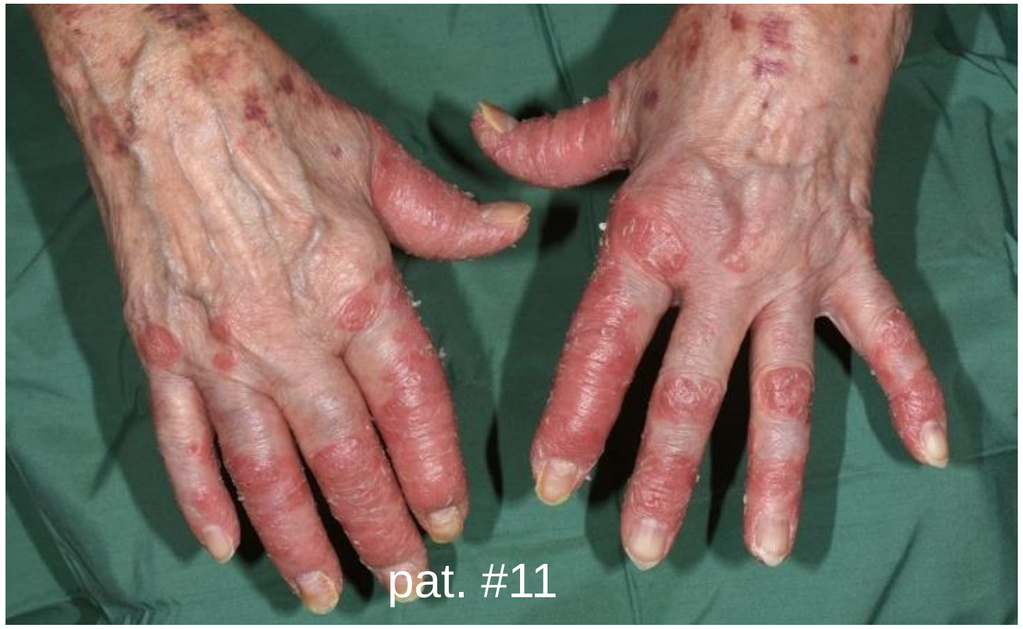
Hard-to-treat lesions: hands





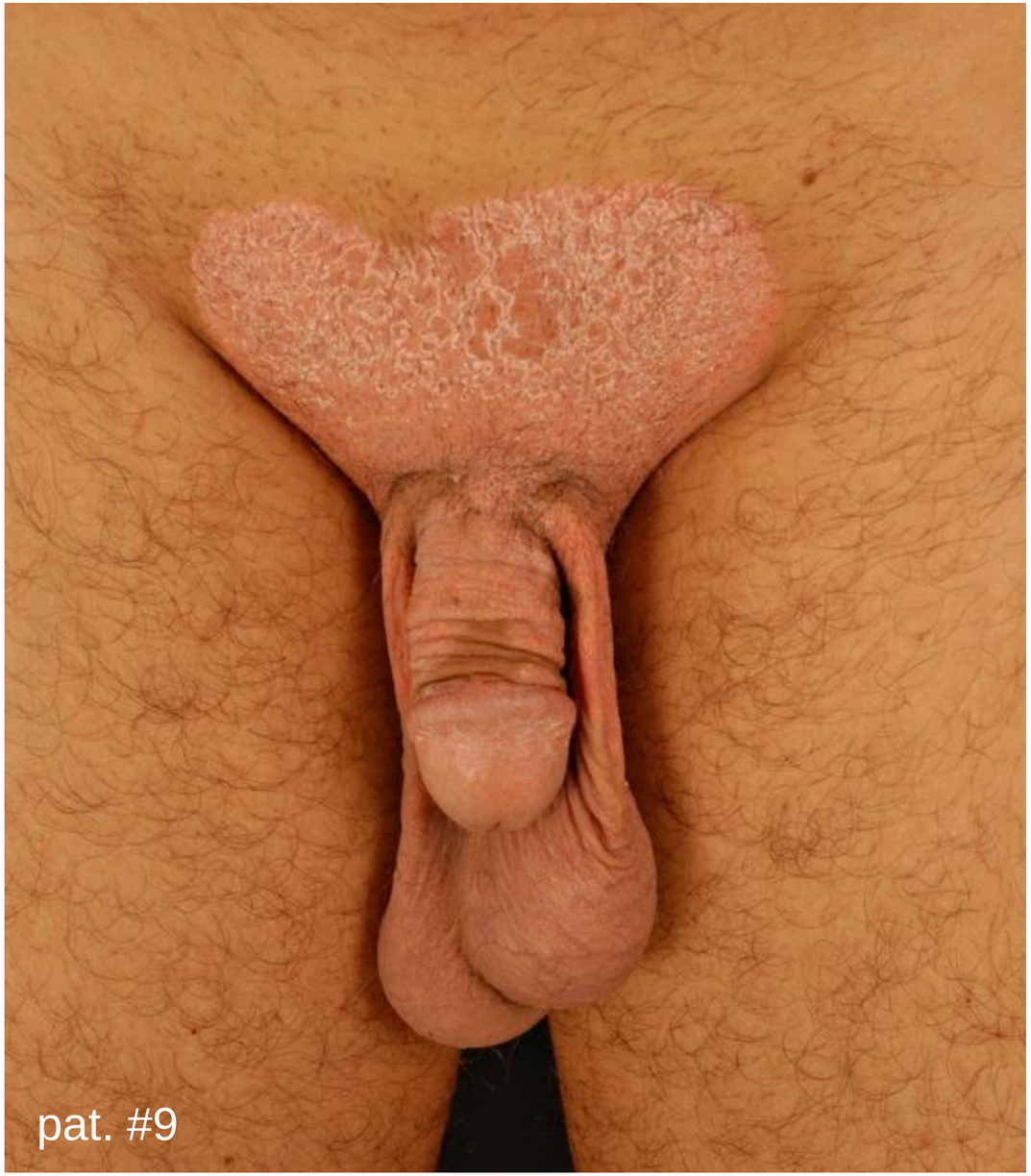


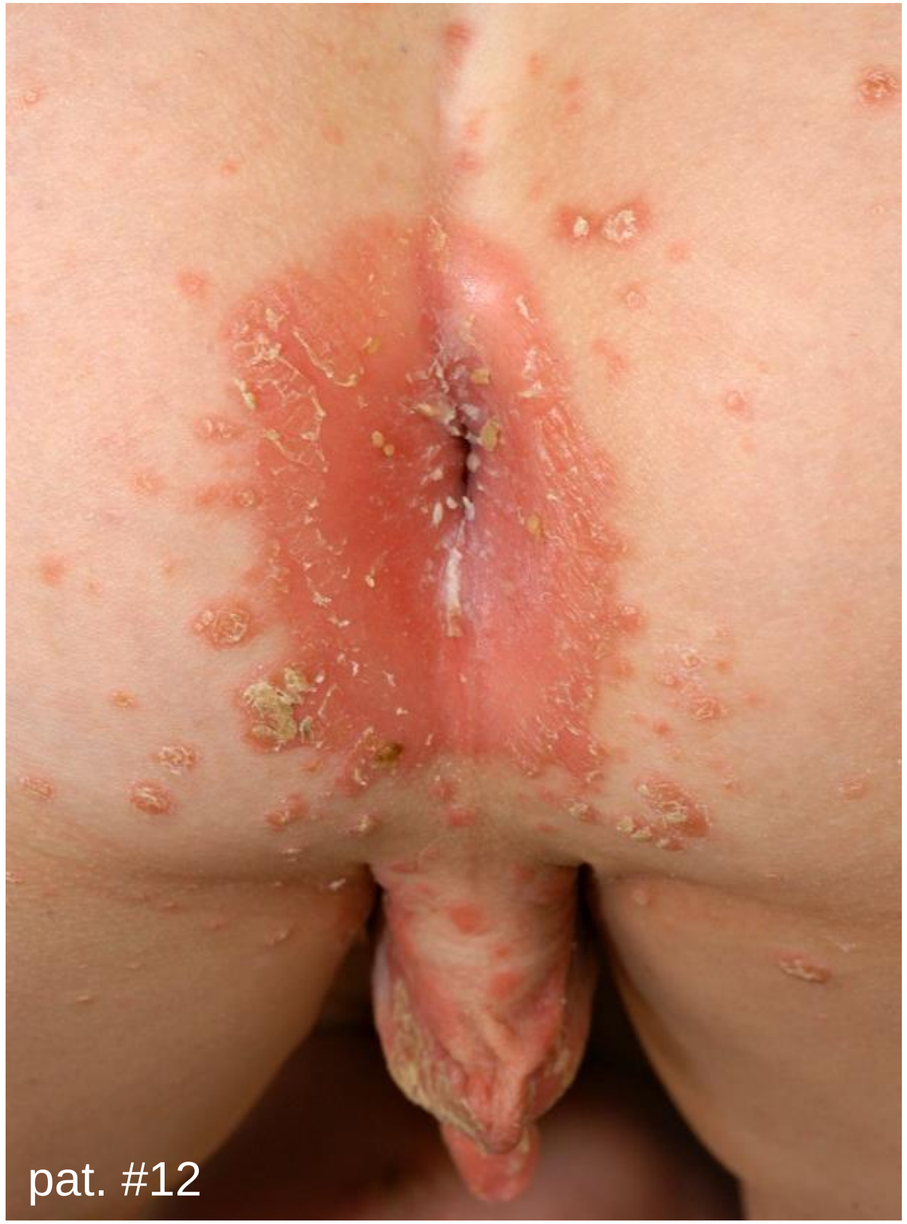
pat. #10



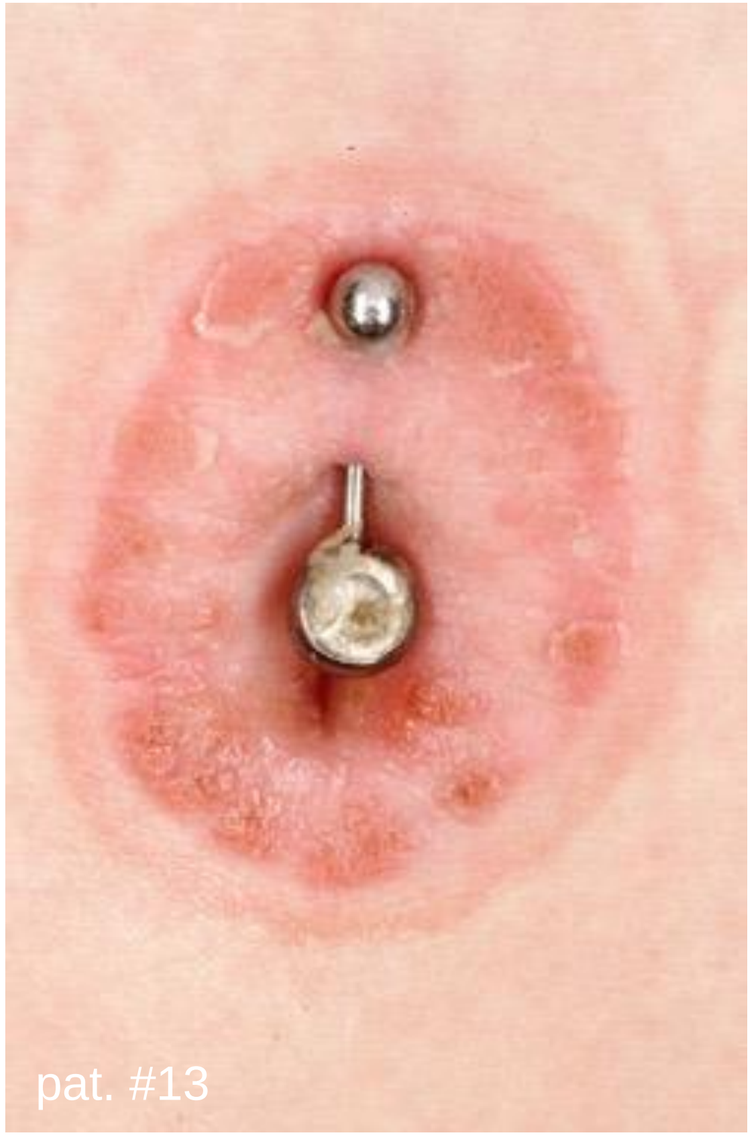
pat. #11

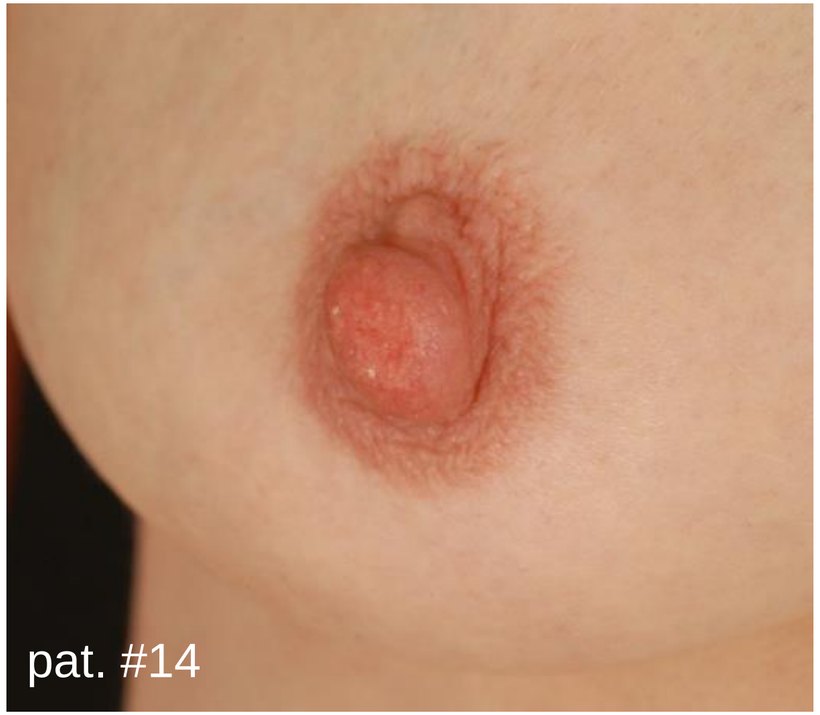
Sensitive areas with high burden of disease: ano-genital region





Special locations: navel and nipples





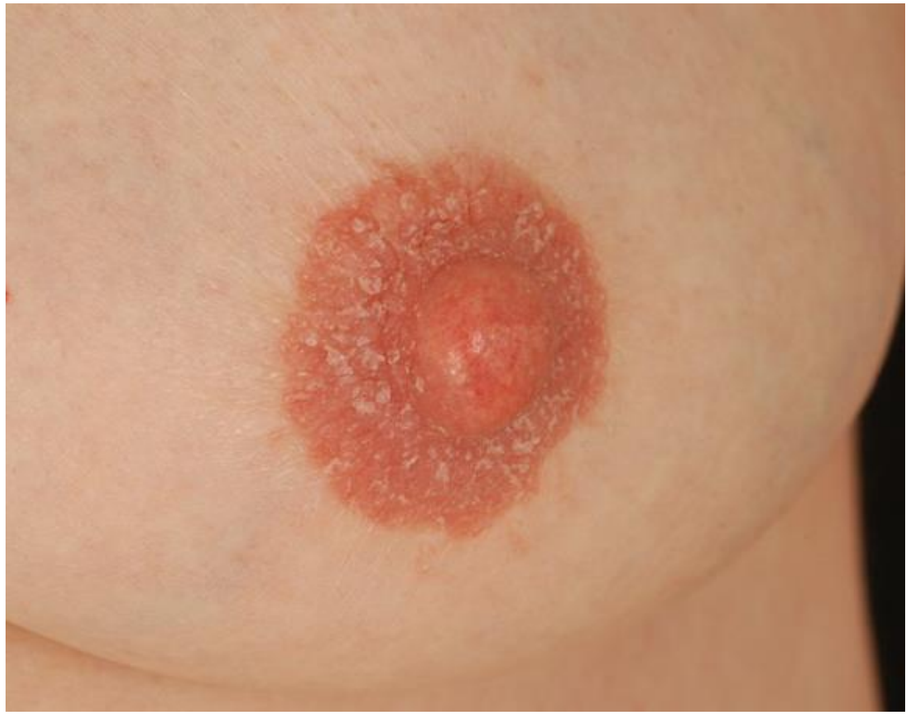
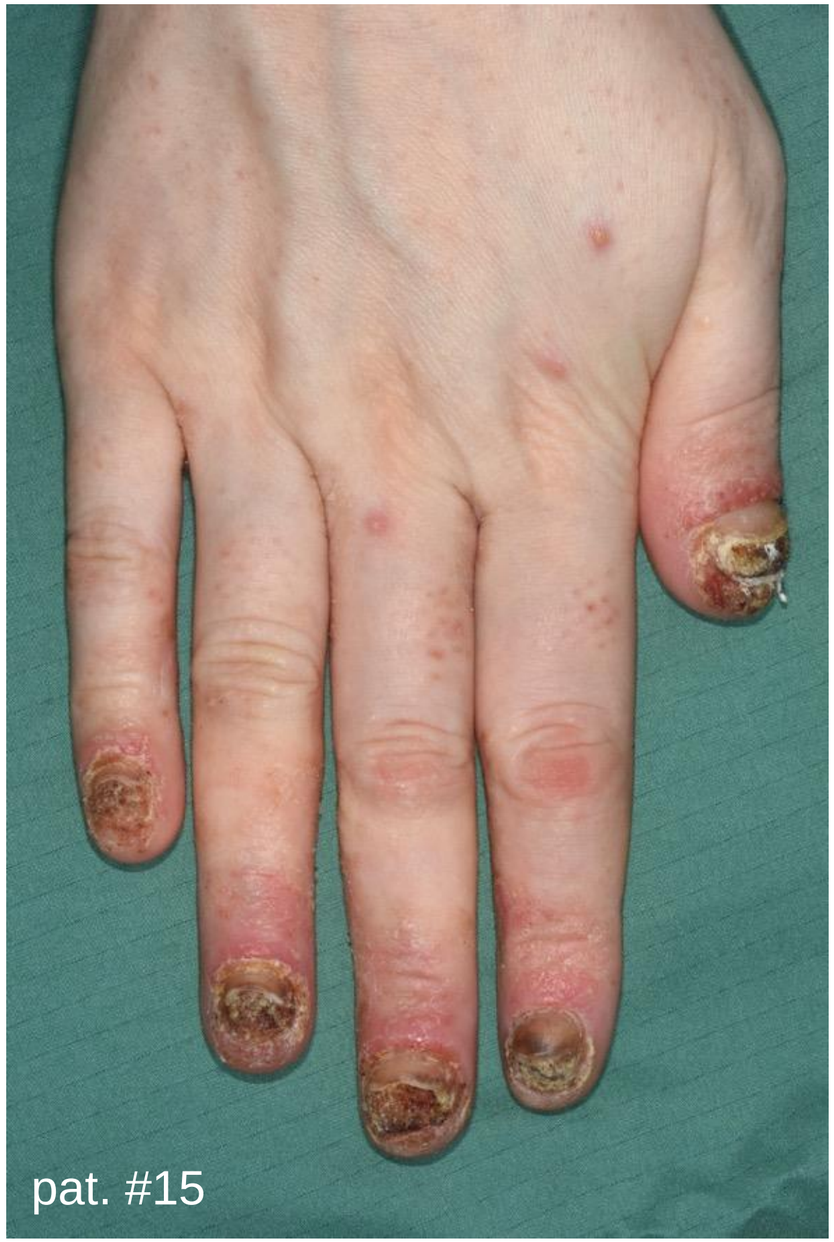
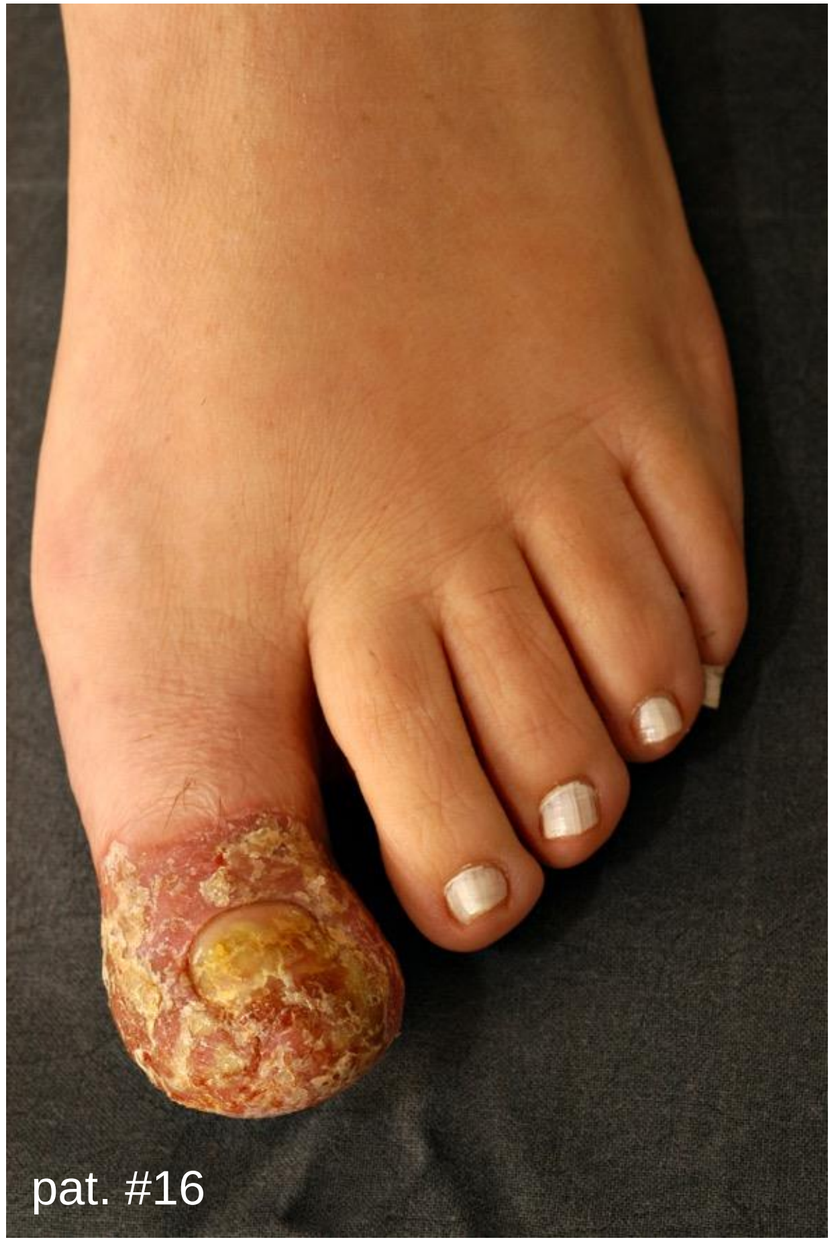
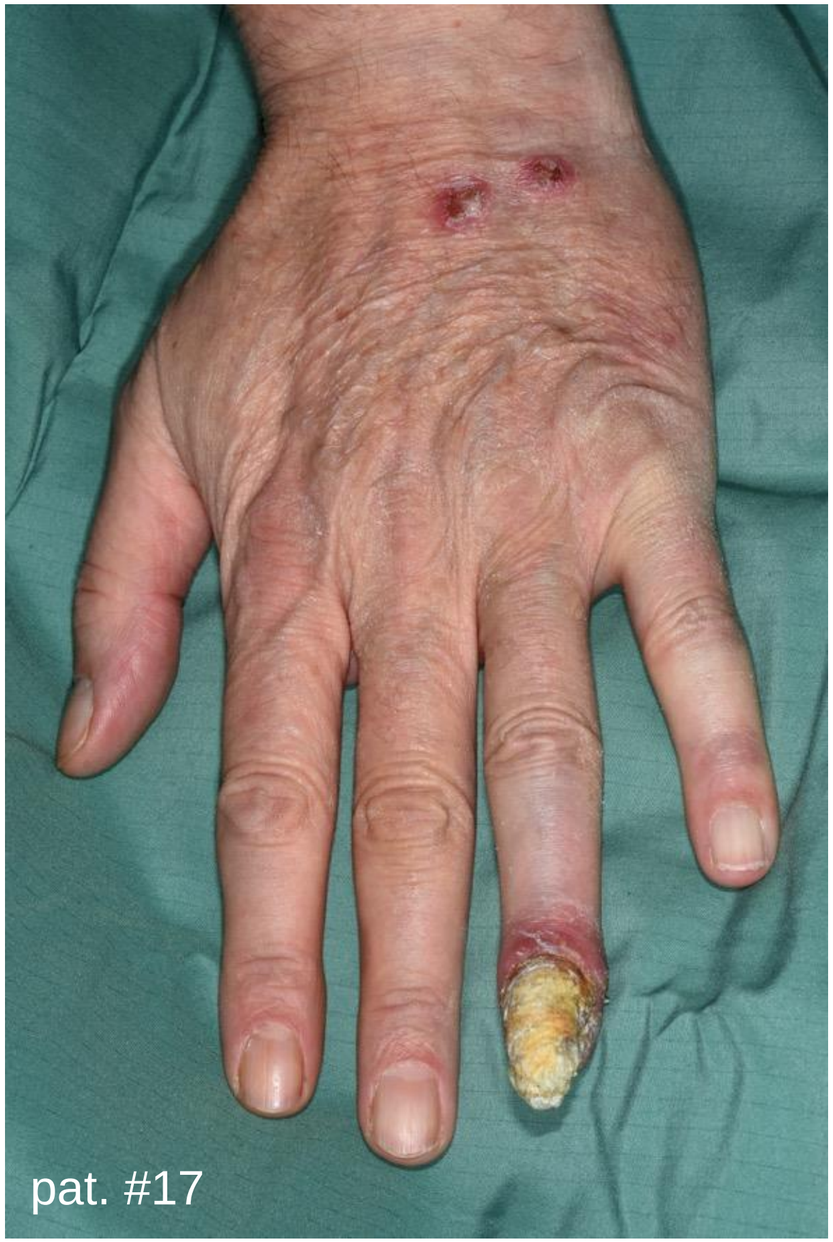


image courtesy of Prof. D. Thaci, Lübeck

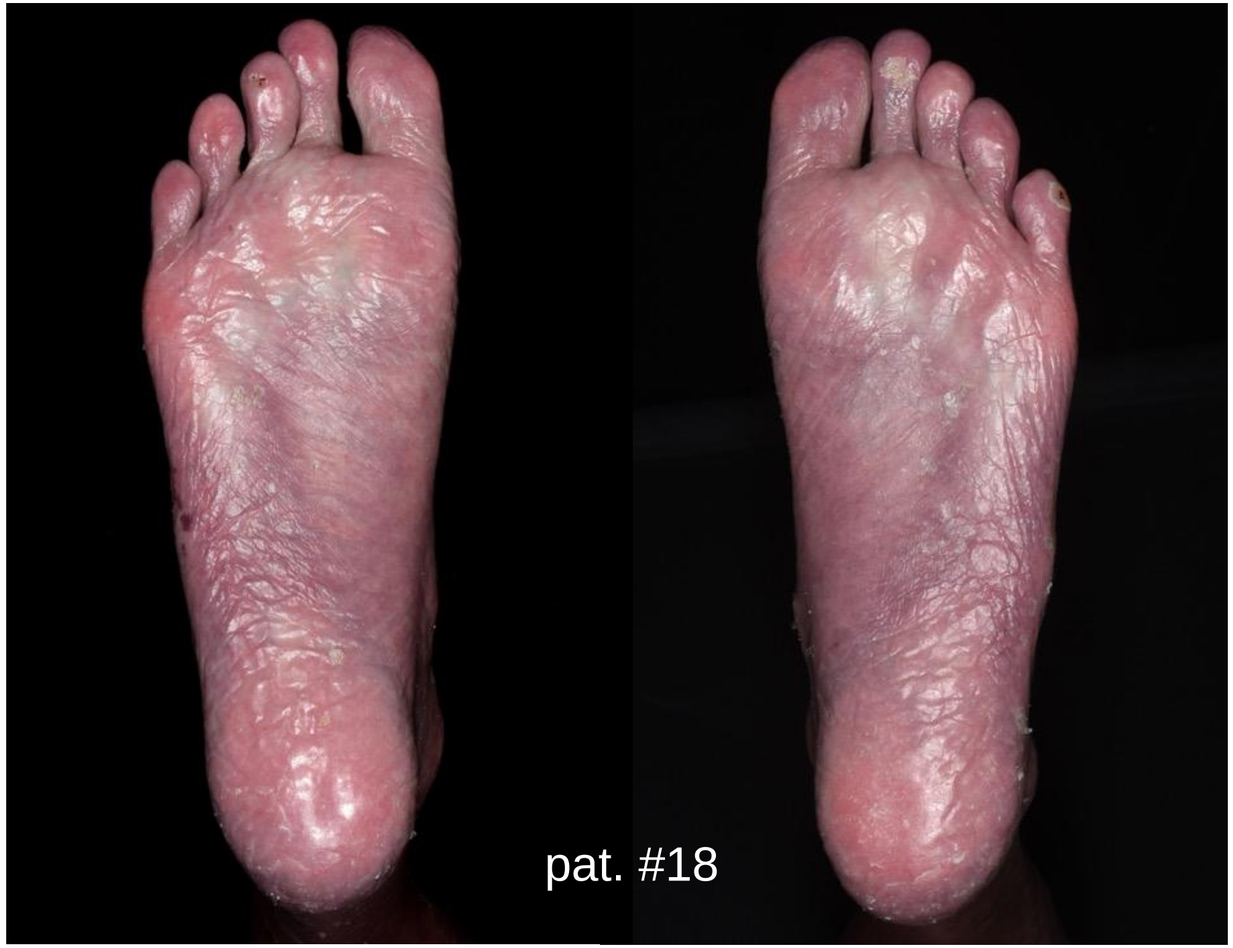
Recalcitrant isolated lesions

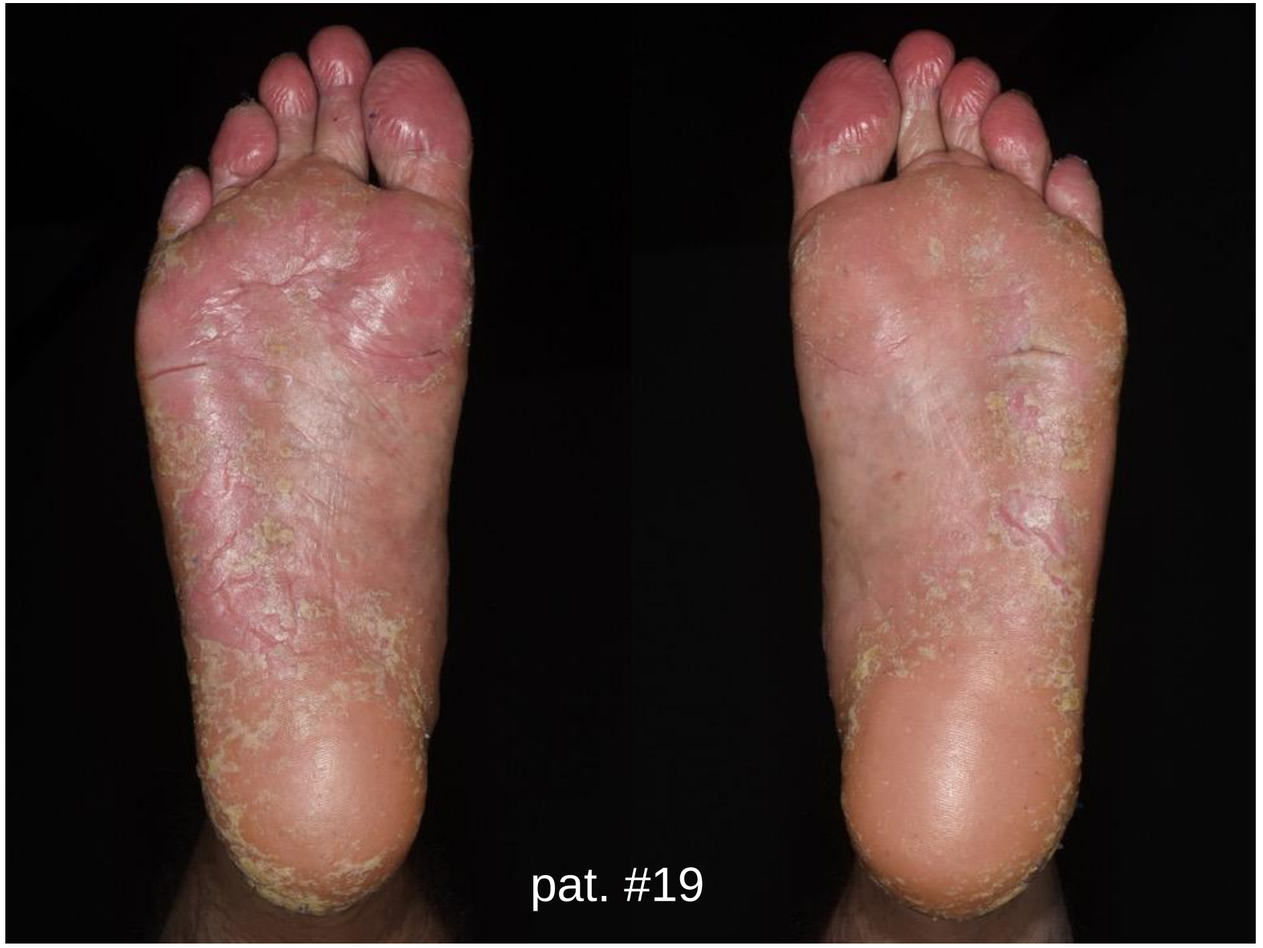

pat. #15


pat. #16


pat. #17

Pretreated lesions with therapy side effects: soles





Summary

- psoriasis is a systemic chronic inflammatory disorder with high burden of disease
- complex (immuno)pathogenesis with involvement of both innate and adaptive immune mechanisms, prominent role of IL-23/IL-17 axis
- pathogenesis-oriented therapies have greatly improved therapy
- yet, need for further developments, especially for certain localized treatments

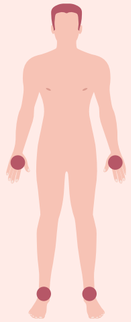
Thank you!

Plaque Psoriasis: a large unmet need with the mild and moderate

Current biological therapies targeted to moderate & severe patients and are administered systemically

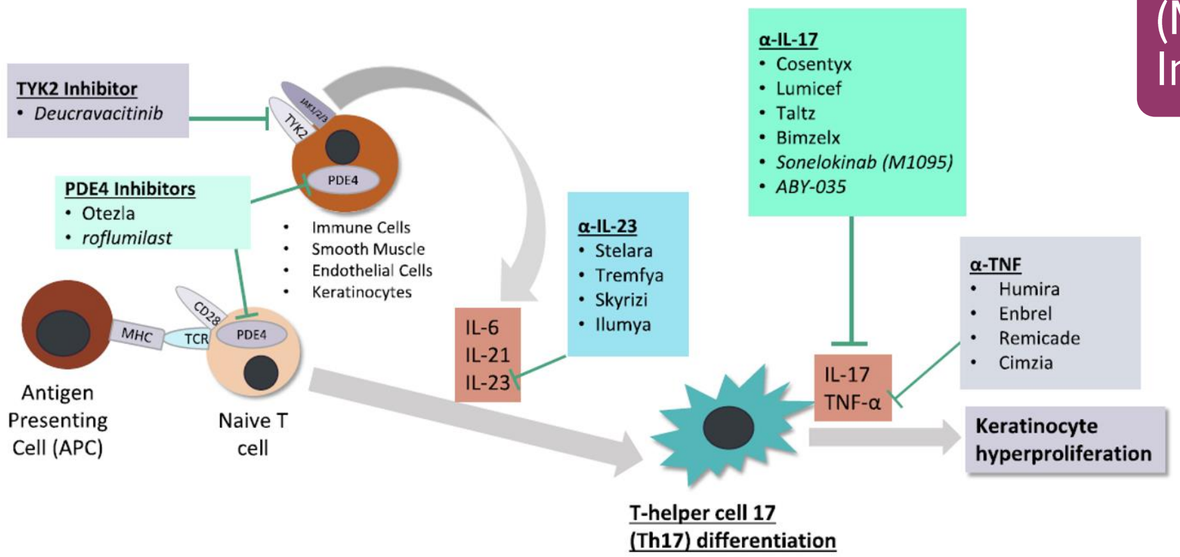
- 125 million patients globally, of them 15.7 million in the 7 major markets (US, EU5 and Japan)
- 80-90% with plaque psoriasis
- Mild patients may suffer from considerable and visible lesions which may be uncomfortable, painful, and impact social and mental well-being
- Mild patients are ineligible for biological treatments in most cases; and moderate psoriatic patients are often reluctant to receive systemic biological treatments due to side effects and costs.

Psoriasis prevalence and severity

MILD	MODERATE	SEVERE
		
50% **of patients.**	**28%** **of patients.**	**22%** **of patients.**
<3% of the body Typically occasional effect on quality of life e.g., aesthetic discomfort	3-10% of the body Generally affects quality of life	>10% of the body Typically has a severe impact on quality of life

Sources: Canadian Psoriasis Network; National Psoriasis Foundation; https://link.springer.com/article/10.1007/s13555-021-00518-8

CURRENT PLAQUE PSORIASIS TREATMENTS



Corticosteroid creams, vitamin E+A, vitamin D derivatives

Phototherapy

1st line systemic immunosuppressants (Methotrexate and Cyclosporine) & Immunomodulators (Otezla)

2nd line systemic Immunomodulators (e.g., Sotyktu)

Injectable biologics (anti- TNFα, IL-17, IL-23)

NANOABs ADDRESS UNMET NEED

Designed to be convenient, safe, affordable, effective biologic for mild and moderate patients

Current treatment shortcomings

Corticosteroids

- Side effects including: Skin thinning (bruising) & Lightening of skin color
- Development of tolerance
- An ointment that is inconvenient for use

Phototherapy

- Requires 20-35 sessions, 3 times a week

1st line systemic immunosuppressants & Immunomodulators

- E.g. Methotrexate (5.8M prescriptions in the USA in 2020) and Cyclosporin (2.2 million prescriptions) come with concerns for health risks and adverse effects. Otezla (PDE4 Inhibitor) has limited efficacy and requires daily dosing.

2nd line systemic Immunomodulators (e.g. Sotyktu)

- Expensive
- Limited efficacy (lower than Biologics)
- Systemic and chronic, with systemic side effects

Injectable Biologics (mAbs)

- Limited to moderate-to-severe patients
- Very expensive
- Systemic and chronic; Increased risk of infections especially oral candida and developing side effects such as psychological illness (suicidal thoughts) and inflammatory bowel disease.

The need for a novel local therapeutic

- There has not been any novel local treatment in the last 25 years.
- Significant patient preference for local therapies, compared to systemic drugs.
- Corticosteroids are not suitable for long-term management of PsO due to adverse safety profiles, development of tolerance and inconvenient treatment procedure for the patients.
- If innovator local treatments could provide increased efficacy with a superior safety profile early in the disease progression, PsO patients may never need to escalate to the injectable biologics.

Source: Global Data Plaque Psoriasis Market Analysis 2021-2030

The need: why develop an anti-IL-17 nanoab?

Strong business and clinical potential for development and commercialization

IL-17 is a cytokine that plays a key role in the development of psoriatic lesions, which are in essence **an acute, local (dermis) flareup of a chronic underlying disease**. It allows for local (rather than systemic) administration of anti – IL-17 drugs to stop the cytokine cascade.

Success Factor	Rationale
IL-17 is a well-established target in psoriasis	IL-17 as a molecular target in psoriasis is well understood and has been validated by existing therapies, e.g., Cosentyx, Siliq, Taltz and Bimzelx.
Antibodies targeting IL-17A and IL-17F isoforms are more effective in treating plaque psoriasis	IL-17 F is highly expressed in the skin. UCB's Bimzelx and MoonLakes' Sonelokimab both target IL-17A and F showed superior PASI 90 scores vs. anti-IL-17A only antibodies
There is clinical evidence of IL-17 being responsive to nanobodies in treating psoriasis	MoonLake's Sonelokimab, showed positive Phase II results in treating patients with **moderate to severe** psoriasis
Specific physicochemical characteristics of our drug candidate make it optimal for treatment of **mild to moderate** psoriasis patients (78% of psoriatic patients)	Most novel oral and biological treatments tend to focus on **moderate to severe** psoriasis segment, are administered chronically via a systemic RoA (cost and risk for AE) while **Mild to moderate** patients seek for local treatments that are specific, efficacious and safe and that do not require chronic use.

Local ID injection of Anti-IL-17A/F VHH antibody fragment

- **A novel way to using VHH antibodies -** Most other entities working with VHHs (nanobodies®) aim to mimic mAbs “playbook” and hence are competing for the same patient populations and are using the same routes of administration.

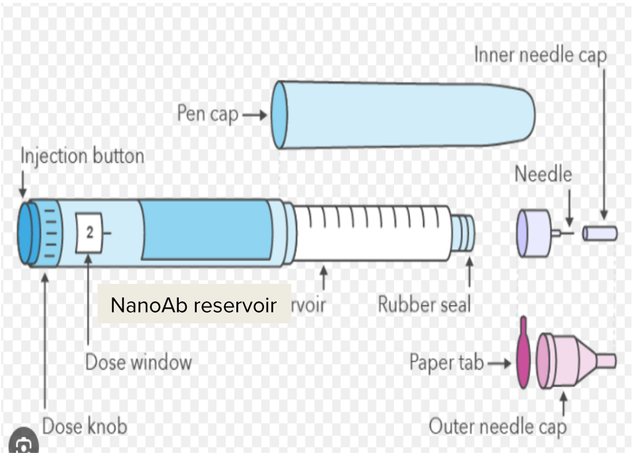
- **Making biologics available for the mild to moderate patients**: Current biologics treatments are approved only for moderate to severe psoriasis patients since they are provided systemically and come with associated risks for severe adverse effects (e.g. infections, exacerbation of IBD, heart diseases). Scinai’s nanoAb is for local administration for local action. No systemic impact

- **Improves patient’s convenience** by sparing the need for twice a day application of creams and ointments that makes day to day activities cumbersome (e.g. wearing cloths after application or getting into bed without getting bed sheets dirty) or the need to attend three times a week a phototherapy center for 10 weeks long.

The product

An intradermal pen filled with a liquid, sustained release formulation of Scinai's anti-IL-17A/F nanoAb given every 3 to 6 months at the doctor's office.

- Upon a patient's visit, a reusable pen injector will be loaded by the physician with a sterile cartridge filled with 1.5 to 3ml of Scinai's formulated nanoAb drug.
- A disposable and sterile ID needle of 1-2mm long will be mounted to the pen
- The physician (or nurse) will apply the drug in aliquots of 30 microliters each (per "click") per 7 sq/cm.
- A pen will therefore be sufficient for 50/100 aliquots (50/100 clicks on the pen) depending whether a 1.5 or a 3ml pen was used covering up to 350/700 sq cm of skin.
- As the needle is short the injection will be painless.
- A session will be up to three pens per patient covering up to 10% of the skin surface of an adult's body.
- Such a session will last 5-10 minutes and will be required every 3 to 6 months depending on the clinical results



Generating incentives for the customers – the three P's

Patients: Mild to moderate plaque psoriasis patients.

- Currently treated with corticosteroids and are unhappy :
  - Inconvenience of use (e.g. twice a day, use of ointments/creams).
  - Development of tolerance
  - Development of side effects – thinning of the skin and changes in color of the skin.
- Cannot do phototherapy:
  - Location of lesion
  - Low compliance with phototherapy schedule
- Are pushing the physician to receive biologics
- Do not want to take daily systemic orals (Otezla or Sotyktu)
- Prefer a local, non painful treatment 2-3 times per year that saves daily treatments and at lower costs than once a month systemic biologics and without the risks of systemic immunosuppressants.

Providers

- Dermatologists
- Don't want to prescribe biologics off label to mild patients (risks).
- Prefer a solution that would allow them to charge for the visit, the drug dispensing and the injection.

Payers

- Prefer lower costs vs. systemic biologics especially when used off label
- Provide their clients a superior solution vs. corticosteroids and safer than systemic biologics at a lower deductible to the patient.

Where is the money?

		2030	CAGR (2020–2030)
Drug Sales, Mild PsO ($m)	$	1,841,500,335.5	12.1%
TNF inhibitors	$	123,915,881.2	0.4%
Enbrel (etanercept)	$	21,197,962.4	-5.2%
etanercept biosimilar	$	17,987,481.0	31.2%
Humira (adalimumab)	$	31,022,633.0	-8.8%
adalimumab biosimilar	$	50,177,132.4	58.9%
Remicade (infliximab)	$	1,940,221.9	-3.4%
infliximab biosimilars	$	900,856.4	8.4%
Cimzia (certolizumab pegol)	$	307,903.1	-0.5%
certolizumab biosimilars	$	381,690.9	N/A
IL-12/IL-23 inhibitors	$	92,770,995.3	0.2%
Stelara (ustekinumab)	$	43,015,881.4	-7.2%
ustekinumab biosimilars	$	49,755,113.9	N/A
IL-23 inhibitors	$	540,126,396.7	19.7%
Tremfya (guselkumab)	$	395,863,978.0	26.8%
Ilumya (tildrakizumab)	$	44,223,187.6	9.9%
Skyrizi (risankizumab)	$	100,039,231.0	10.9%
IL-17 inhibitors	$	269,947,325.1	17.5%
Cosentyx (secukinumab)	$	63,619,131.3	3.8%
secukinumab biosimilars	$	32,516,667.7	N/A
Taltz (ixekizumab)	$	28,460,732.8	11.9%
ixekizumab biosimilars	$	6,159,350.6	N/A
Siliq (brodalumab)	$	1,514,817.9	8.0%
Bimzelx (bimekizumab)	$	63,359,429.7	N/A
sonelokimab (M1095)	$	42,537,922.2	N/A
izokibep/ABY-035	$	31,779,272.9	N/A
PDE4 inhibitors	$	233,629,627.9	10.3%
Otezla (apremilast)	$	141,509,024.3	4.9%
generic apremilast	$	86,829,302.6	N/A
roflumilast	$	5,291,301.0	N/A
AhR Agonists	$	4,511,596.3	N/A
tapinarof	$	4,511,596.3	N/A
Kinase inhibitors	$	259,505,982.9	N/A
Deucravacitinib (BMS-986165)	$	259,505,982.9	N/A
NF-kappa B inhibitors	$	63,077,343.7	N/A
tepilamide fumarate/PPC-06	$	63,077,343.7	N/A
Other Systemic therapies	$	130,772,138.5	14.2%
Methotrexate	$	1,537,772.3	-0.6%
Cyclosporine	$	34,459,452.4	0.5%
Piclidenoson	$	94,774,913.9	N/A
Topical therapies	$	123,243,047.9	0.9%
Wynzora (calcipotriene + betamethasone dipropionate)	$	1,253,390.2	N/A
generic calcipotriene + betamethasone dipropionate	$	15,497,482.0	0.9%
Rx Topical Corticosteroids	$	60,251,381.7	0.8%
Rx Vitamin D derivatives	$	31,849,172.6	0.8%
Rx Vitamin A/Retinoid derivatives	$	14,391,621.4	0.6%

- Total sales of drugs in the 7MM for mild psoriasis expected to be $1.8B in 2030
- $1.3B is expected to come from prescription of biologics and $259M from TYK2 inhibitor
- This is the market where the topicals and phototherapy do not help.
- This is the unmet need, which represents approx. 300K monthly prescriptions of expensive drugs not planned for use with mild patients
- Pay attention that topicals and immunosuppressants sell altogether $250M annually in the 7MM.

Source: GlobalData

MAX PLANCK, UMG, SCINAI COLLABORATION

Covering discovery and initial characterization of NanoAbs aimed at predefined list of molecular targets.

Designed to create significant clinical and commercial advantages.

Scinai brings…

- Recombinant protein drug development experience from lab to Phase 3 clinical trial
- Manufacturing, quality, international regulatory experience
- GMP biologics manufacturing facility
- Best-in-class equipped labs
- Top-tier big pharma & biotech leadership expertise

The Max Planck Institute & UMG[1] bring…

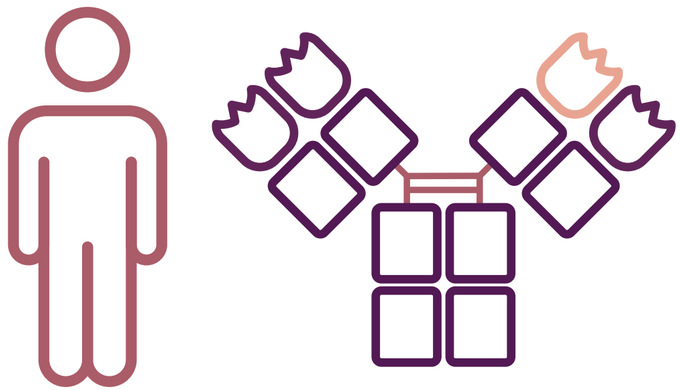
- World-class science & access to leading scientists
- NanoAb platform for the development of promising potent therapeutics
- Patents covering NanoAbs & their manufacturing

Professor Dr Dirk Görlich
Director of Max Planck Institute for Multidisciplinary Sciences
Winner of inaugural World Laureates Association (WLA) Prize in Life Sciences or Medicine

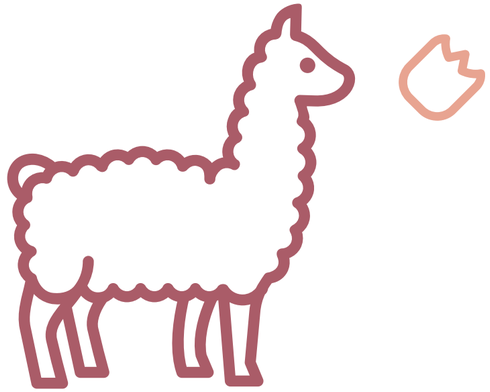
Professor Dr Matthias Dobbelstein
Fellow at Max Planck Institute for Multidisciplinary Sciences
UMG Head of Department

1. Max Planck Institute for Multidisciplinary Sciences and the University Medical Center Göttingen (UMG)

NANOSIZED ANTIBODY PIPELINE: HUGE OPPORTUNITY



HUMAN ANTIBODY (mAb)



ALPACA-DERIVED ANTIBODY (NanoAb)

Alpaca-derived nanosized antibodies (NanoAbs) are also known as VHH antibodies or nanobodies[1]

mAb therapeutic market size is ~$205 billion[2] including Cosentyx for psoriasis $4.8 billion (2022)[3]

NanoAbs: Human monoclonal antibody (mAb)'s biobetter

1. VHH antibody is trademarked by ABLYNX N.V., a wholly owned subsidiary of Sanofi, as Nanobody. Scinai has no affiliation with and is not endorsed by Sanofi.

2. https://www.researchandmarkets.com/reports/5791212/monoclonal-antibody-therapeutics-market-source (accessed 14.Aug.2023)

3. https://www.reporting.novartis.com/2022/novartis-in-society/performance-in-2022/financial-performance.html (Accessed 7.Jan.2024)

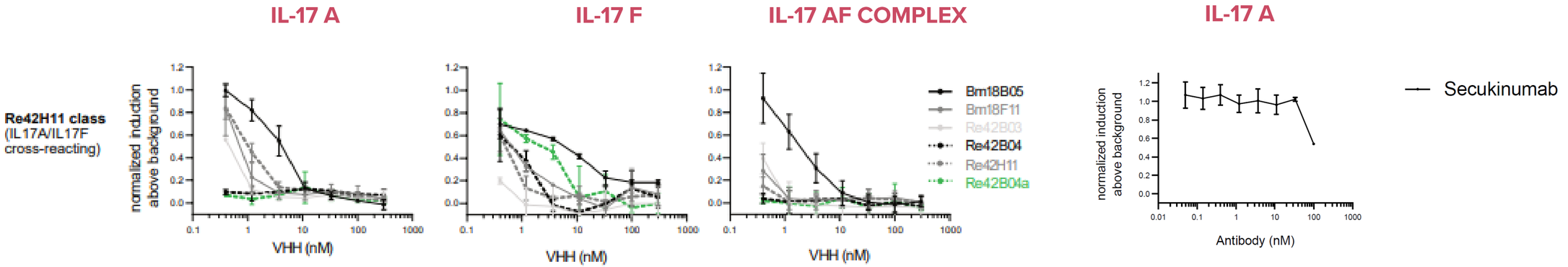
Anti-IL-17 Nanoab: A better neutralizer

Cytokine	NanoAb	Secukinumab*
IL17A	0.56nM	0.2nM
IL17F	1.00nM	µM
IL17AF	0.25nM	2.0nM

* Cosentyx, INN-sekukinumab (europa.eu)

Single NanoAb neutralizes IL-17 A, F, and AF complex

Whereas the affinity for NanoAb is comparable to that of Cosentyx (for IL-17A), the neutralization shows a significantly better efficacy of the NanoAb Neutralization assays



Mode of Action:

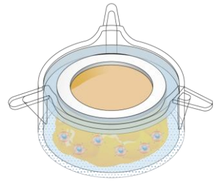
By Blocking IL-17, the interactions with the IL-17 receptors expressed on keratinocytes, fibroblast-like synoviocytes, endothelial cells, chondrocytes and osteoblasts downstream cascade of events in the epidermis and expression of Psoriasis-related markers is avoided.

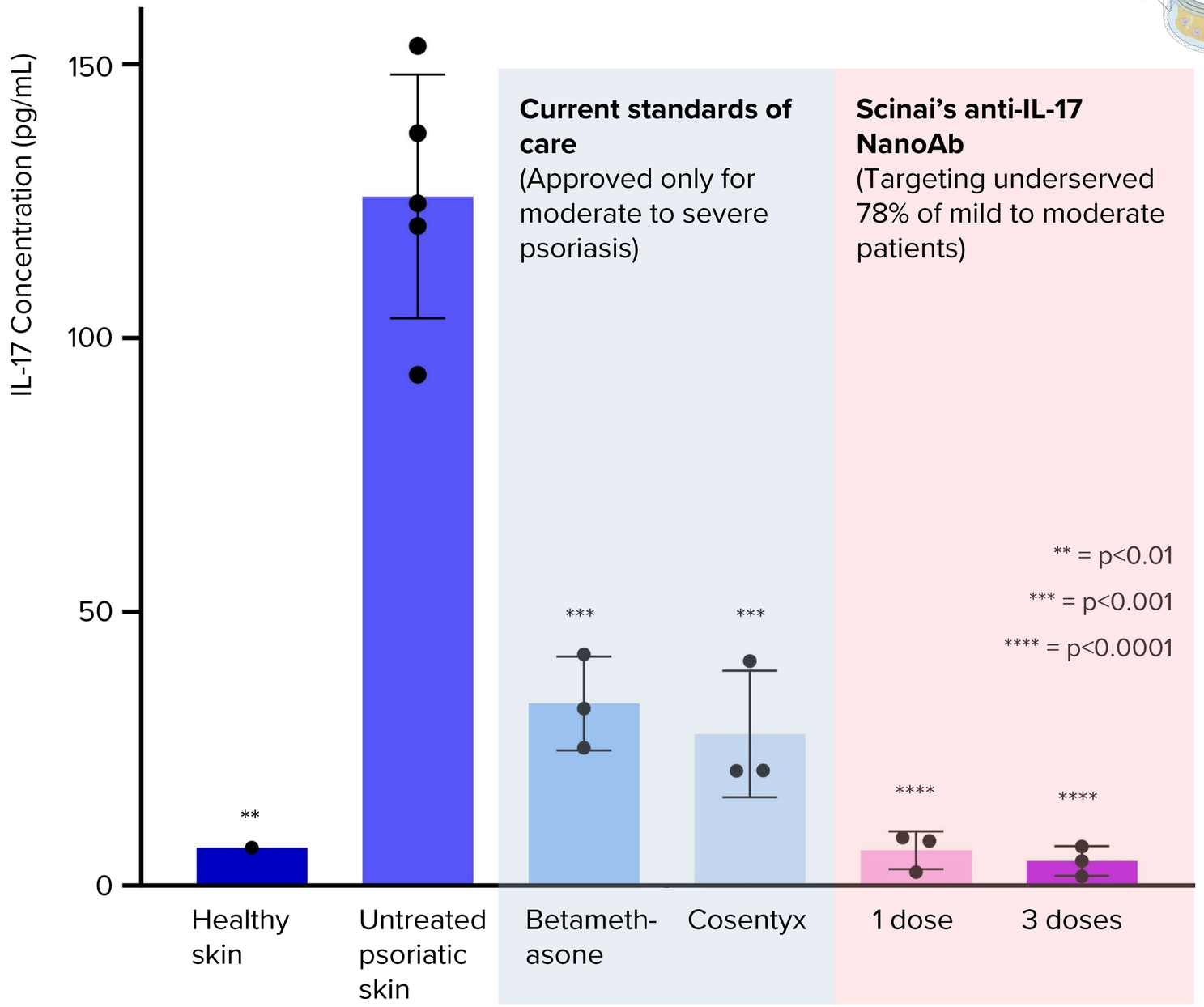
The NanoAb neutralizes IL-17 isoforms at nM concentrations, x100 better than the mAb

EX-VIVO PROOF OF CONCEPT: NANOABS SHOWN TO BLOCK IL-17

Impact of ID injected nanoAb in comparison to current leading treatments Betamethasone and Cosentyx

Designed to be local, less frequent use, safer, more convenient and more affordable





Preliminary PK: limited systemic exposure

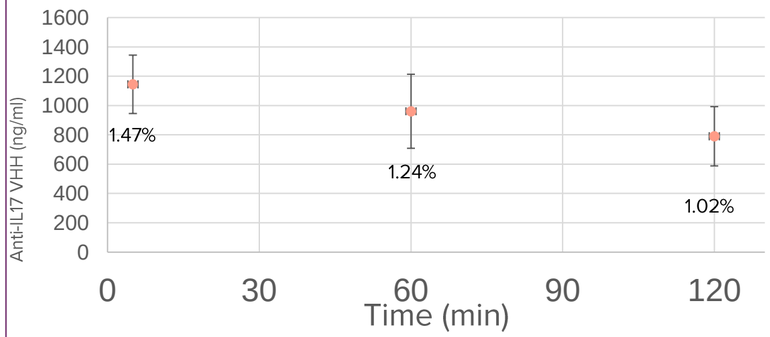
PK Study design

Healthy mice were injected ID with biotinylated anti IL-17 nanoAbs, blood samples removed periodically post administration.

Limited systemic exposure will contribute to safety
T1/2 in the dermis is ~6h, in the blood - ~2h

Nanoabs' presence in dermis was measured by digital morphology analysis. In plasma their presence was measured by Bio-Layer Interferometry (BLI) using Octet.

Minimal % NanoAb in the plasma upon ID administration



Implications:

2 potential modes of action:

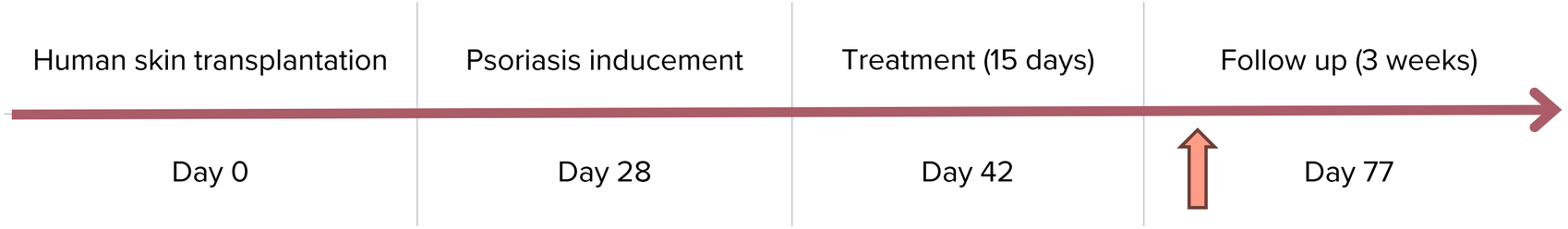
1. An acute and efficient blockage of IL-17 can shut down the downstream inflammatory cascade. Hence a single local injection of the NanoAb without sustained release formulation will suffice. The next flare up will appear independently, possibly few months later.

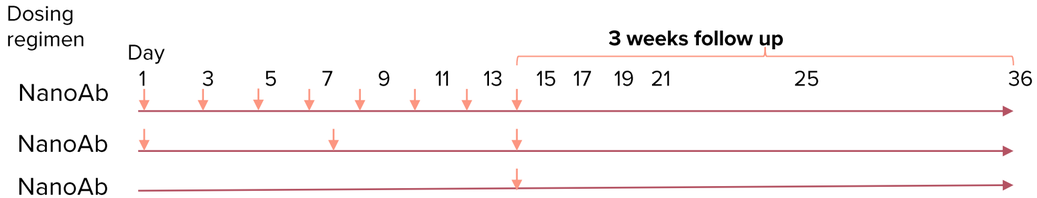
2. A prolonged pressure on the inflammatory process is needed to block the cascade, hence, a longer local exposure of the IL-17 blocking nanoAb will be achieved by formulating the injected NanoAb in a slow-release formulation.

In vivo PoC: Human xenograft skin (1/2)

Animal model: Normal human skin will be engrafted into SCID BEIGE mouse and disease will be induced by injection of IL-2 activated PBMC's from psoriatic patients

Experiment timeline





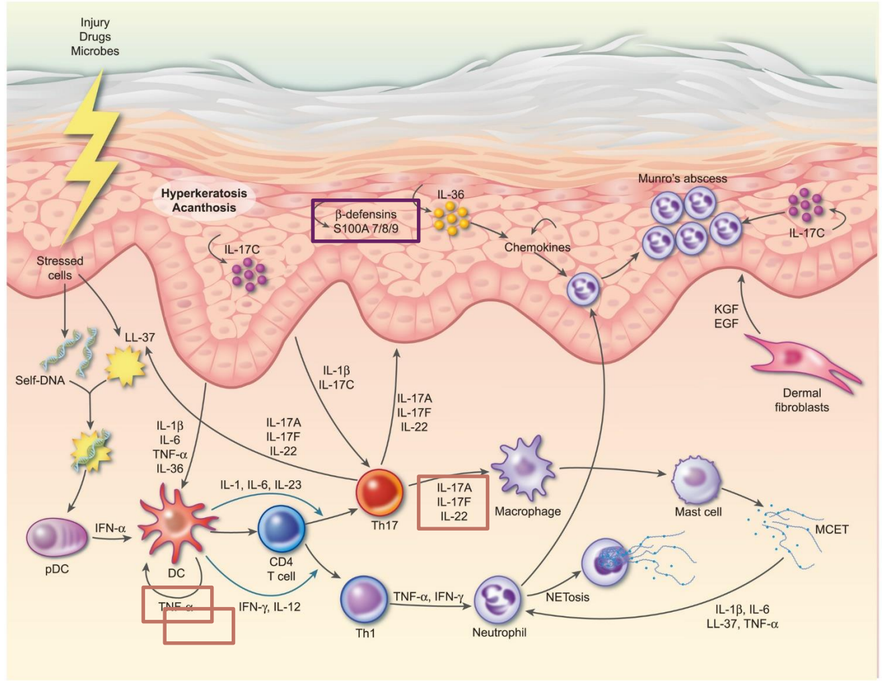
Study design

#	Role	Compound	Route	Frequency	Follow up	N
1	Negative control	Irrelevant VHH	ID	Once a week for 3 weeks	2 weeks	8
2	Positive control - model	Dexamethasone	Topical	Twice/day for 5 weeks	NA	8
3	Positive control – comparable antibody	Cosentyx	SC	Once a week for 3 weeks	2 weeks	8
4	Positive control – standard of care for mild to moderate	Betamethasone	Topical	Twice/day for 3 weeks	2 week	8
5	Scinai's NanoAb	Test item high dose	ID	Every other day	2 weeks	8
6	Scinai's NanoAb	Test item high dose	ID	Once a week for 3 weeks	2 weeks	8
7	Scinai's NanoAb	Test item high dose	ID	Once	2 weeks	8

Major outcome measures

- Epidermis thickness scoring
- Macroscopic evaluation
- Immunohistochemical analysis of Psoriasis markers

In vivo PoC: Human xenograft skin (2/2)



Source: IL-17 in inflammatory skin diseases psoriasis and hidradenitis suppurativa - Fletcher - 2020 - Clinical & Experimental Immunology - Wiley Online Library

What is being studied? The impact of local psoriasis treatments by efficacy parameters:

- ✓ Clinical evaluation by medical photographs.
- ✓ Macroscopic evaluation, epidermis thickness scoring & Histological analysis.
- ✓ IHC analysis for Ki-67, (proliferative marker of keratinocytes).
- ✓ IHC analysis: HLA-DR (High DR characterizes Psoriasis), epidermal human beta-defensin-2 (BD-2 serum levels correlate with IL-17A and PASI, it is decreased after IL-17A blockade).
- ✓ Psoriasin (S100A7), CD8 & CD4 (increase in inflammation), IL-17, IL-22 (parallel to IL17), TNF-a, CD31 (angiogenesis marker)

- ✓ Results expected in Q2 2024

Summary

- There is a need for a better treatment for patients with mild to moderate Psoriasis and for specific lesions that are hard to treat with current therapies.
- Biological drugs are the safest and most efficient, yet – they are administered systemically and are expensive.
- Blocking IL-17A and IL-17F isoforms is an effective mechanism to control Psoriasis
- Scinai's NanoAbs, administered locally ID already showed superior neutralization of IL-17 in cell culture, and ex-vivo in human Psoriatic skin.
- Scinai's upcoming in vivo study will compare schedules of administration and show the duration of the therapeutic effect
- Next steps: Toxicology and First in Human clinical trial

SCINAI

IMMUNOTHERAPEUTICS

THANK YOU