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Christine Kühne – Center for Allergy Research and Education

Translational aspects in pathobiology of atopic dermatitis: Targeting molecular pathways

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Conflicts of interest

- AbbVie
- Allmiral
- AnaptysBio
- Arena
- Asana Biosciences
- Astellas
- BioVerSys
- Böhringer-Ingelheim
- Daichi-Sankyo
- Dermavant/Roivant
- DS Pharma
- FLX Bio
- Galapagos/MorphoSys
- Galderma
- Glenmark
- GSK
- Incytes
- Kymab
- LEO
- Lilly
- L´Oréal
- Novartis
- Pfizer
- Pierre Fabre
- Sanofi/Regeneron
- UCB

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N.B. Currently more than 72 companies with at least 1 new product in the pipeline

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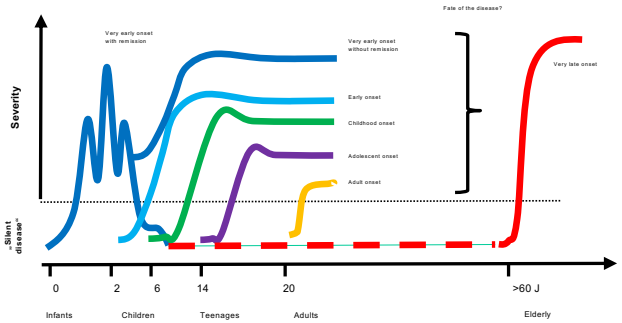
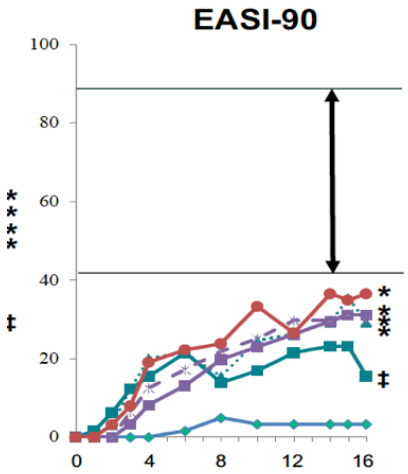


Different onsets and histories

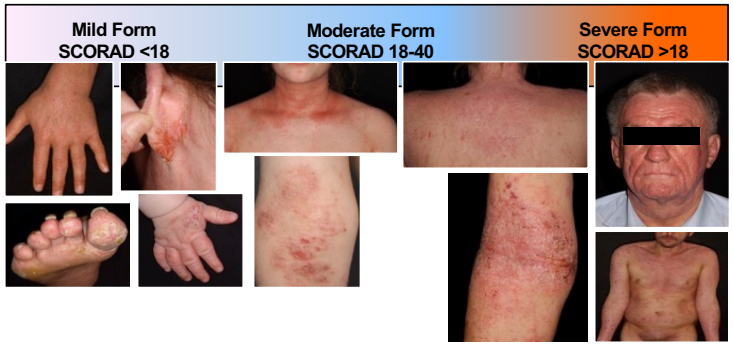
Caucasian China Tanzania

Differences due to ethnic background



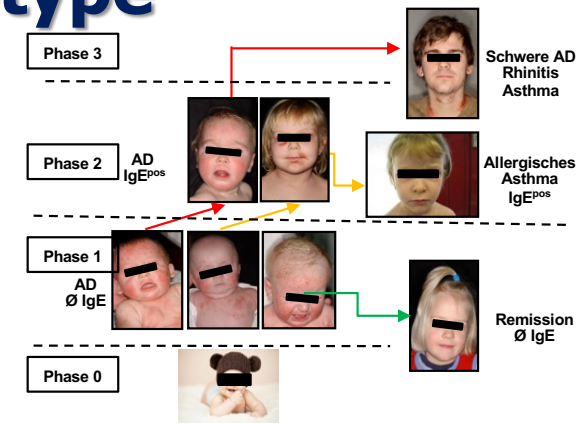
Differences in therapeutic response

Atopic Dermatitis:
A highly complex phenotype



Different severity forms

Risk for severe HSV complication



Different risk for atopic march

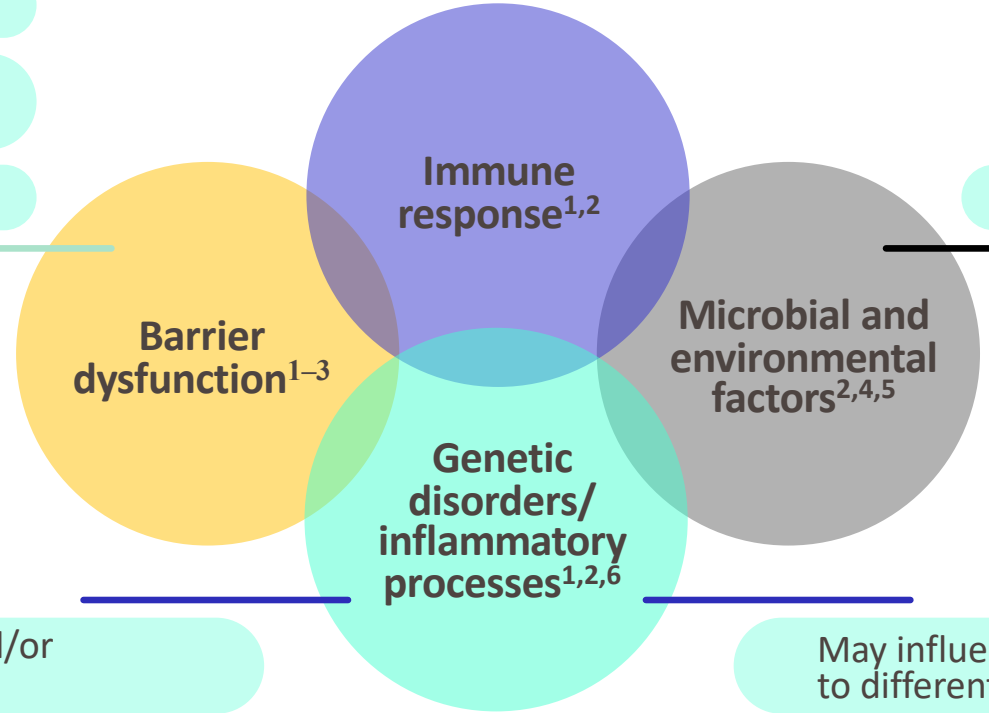
1. Bieber *et al. Journal of Allergy and Clinical Immunology,* 2017.
2. Bieber, In: *Personalized Treatment Options in Dermatology*, 2015.

Multiple factors interact and contribute to the pathogenic and phenotypic complexity of atopic dermatitis[1–6]

Damage/repair failure

Abnormal innate immune responses

Allergen/pathogen entry



Sensitization

Predisposition to infection and/or effects on barrier homeostasis

May influence sensitization to different factors

➢ 1. Leung DYM, Guttman-Yassky E. *J Allergy Clin Immunol* 2014;134:769–779. 2. Lee S, Lane AP. *Curr Infect Dis Rep* 2011;13:159–168. 3. Kim BE *et al. Clin Immunol* 2008;126:332–337. 4. Darsow U *et al. J Eur Acad Dermatol Venereol* 2010;24:317–328. 5. Williams MR, Gallo RL. *Curr Allergy Asthma Rep* 2015;15:65. 6. Hoffjan S, Stemmler S. *Arch Dermatol Res* 2015;307:659–670.

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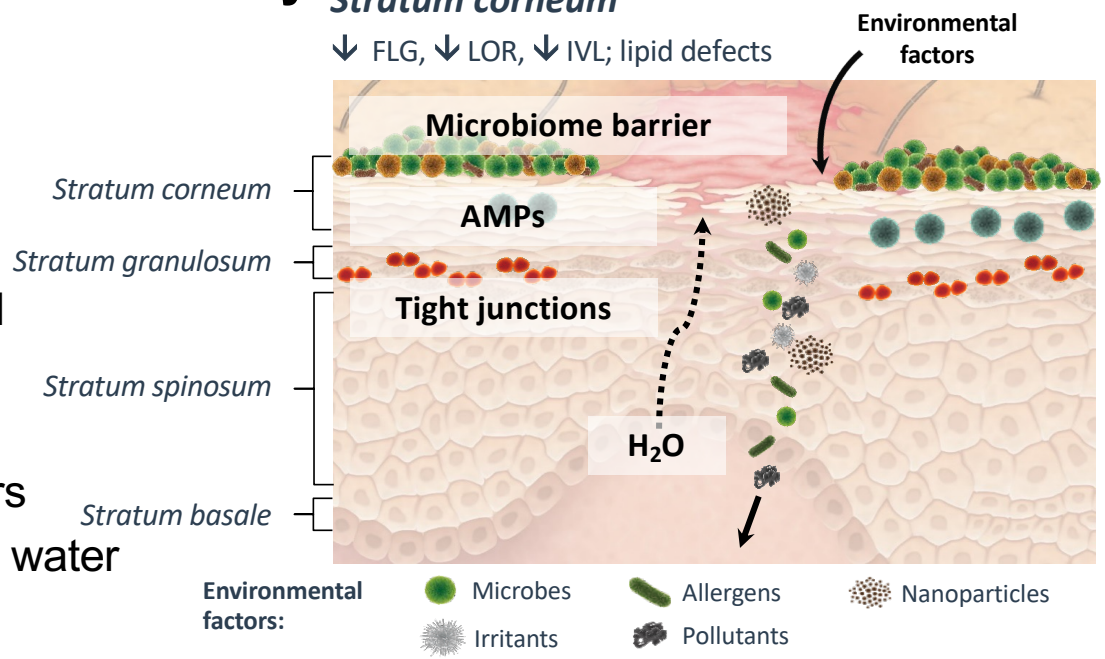
Epidermal Barrier Dysfunction in AD Has Multiple Causes

- **Epidermal barrier function can be affected by:**[1–6]
  - Genetic and epigenetic alterations[1–3]
  - **The underlying T2 inflammation**[3,4]
  - Commensal dysbiosis[5]
  - Lipid/structure defects[1,6]
  - Increased skin pH, facilitating microbial skin infections and barrier defects[2]
- **Barrier dysfunction**:[1]
  - Allows for entry of environmental factors
  - Reduces the ability of the skin to retain water



FLG, filaggrin; IVL, involucrin; LOR, loricrin.

Figure adapted from: Kuo I *et al. J Allergy Clin Immunol* 2013; and De Benedetto A *et al. J Allergy Clin Immunol* 2011.

1. De Benedetto A *et al. J Allergy Clin Immunol* 2011;127:773–786. 2. Kim BE *et al. Allergy Asthma Immunol Res* 2018;10:207–215. 3. Di ZH *et al. Chin Med J (Engl)* 2016;129:295–303. 4. Kuo I *et al. J Allergy Clin Immunol* 2013;131:266–278. 5. Williams MR *et al. Curr Allergy Asthma Rep* 2015;15:65. 6. Berdyshev E *et al. JCI Insight* 2018;3(4).

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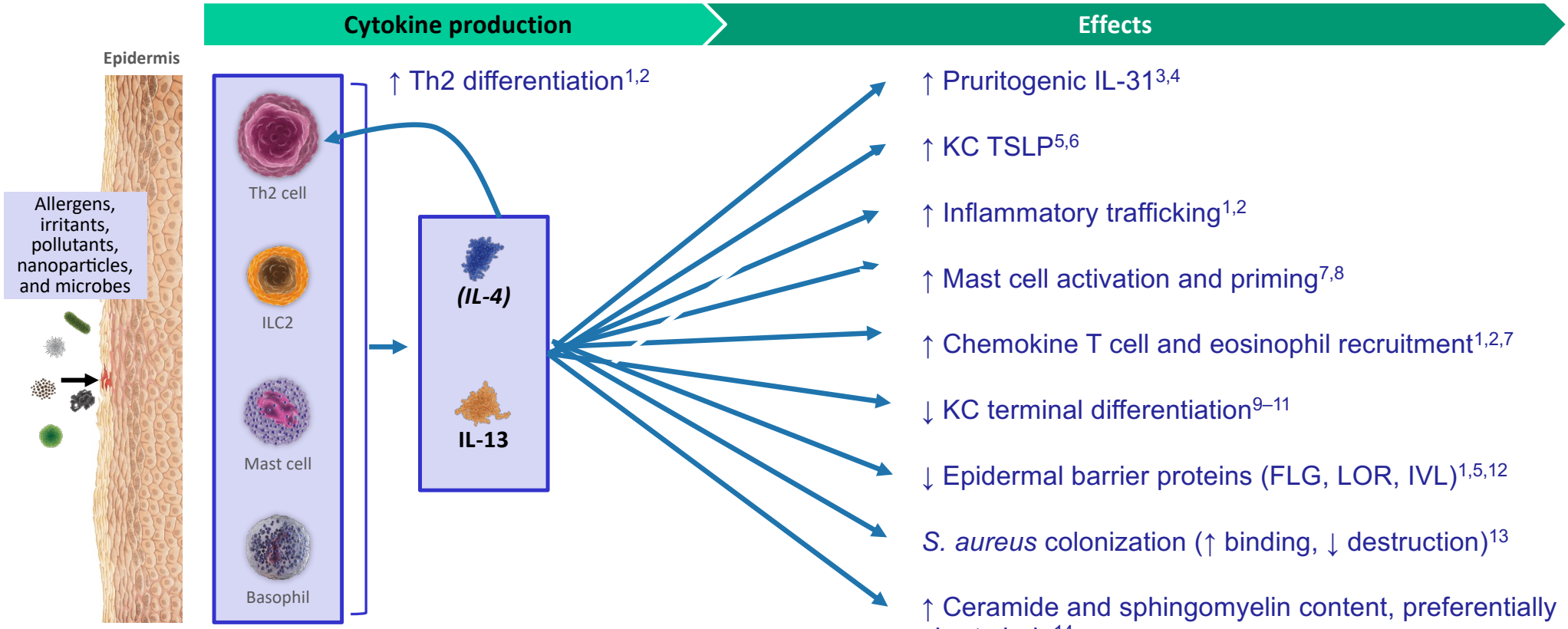
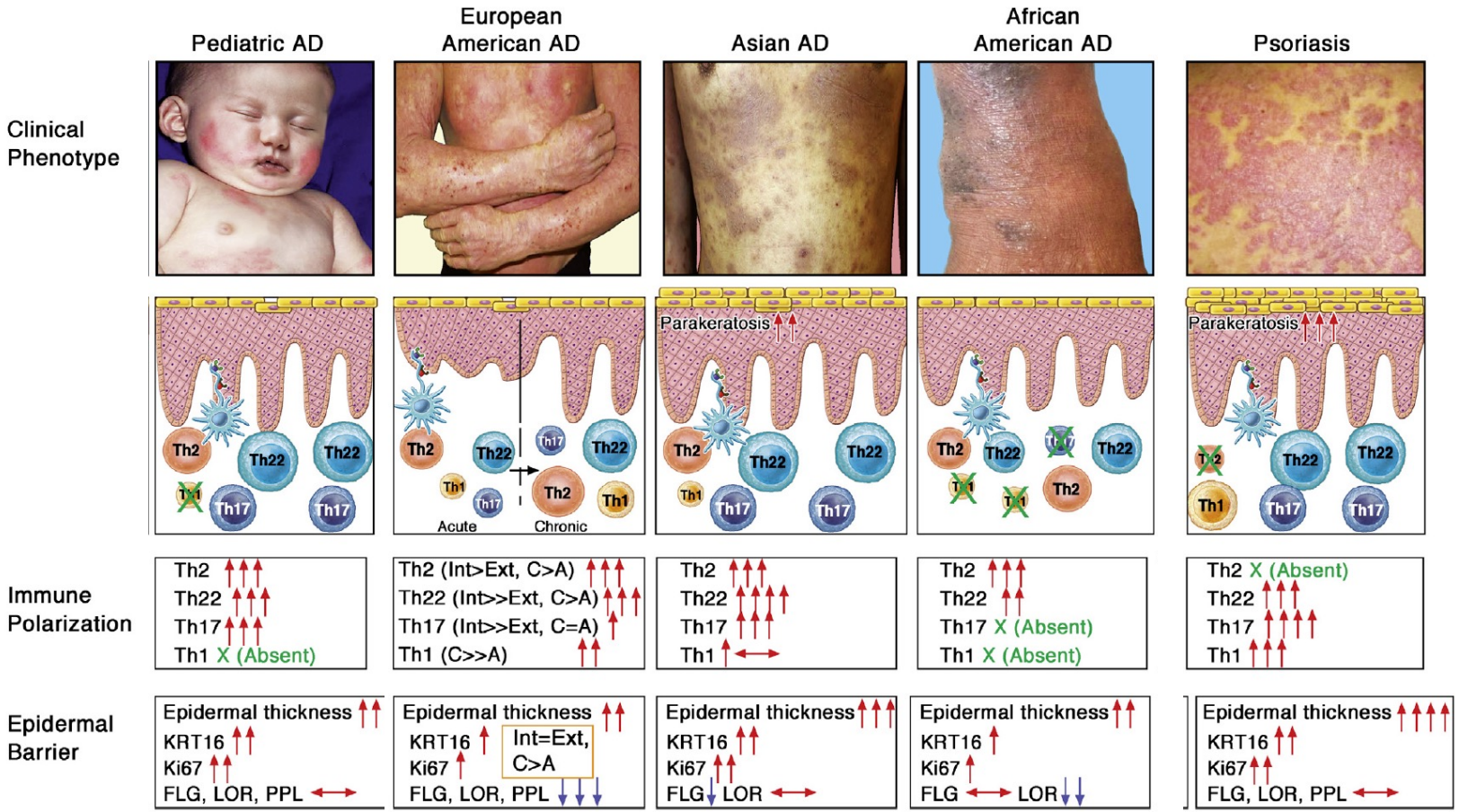
T2 cytokines Mediate Inflammation and Barrier Dysfunction in AD



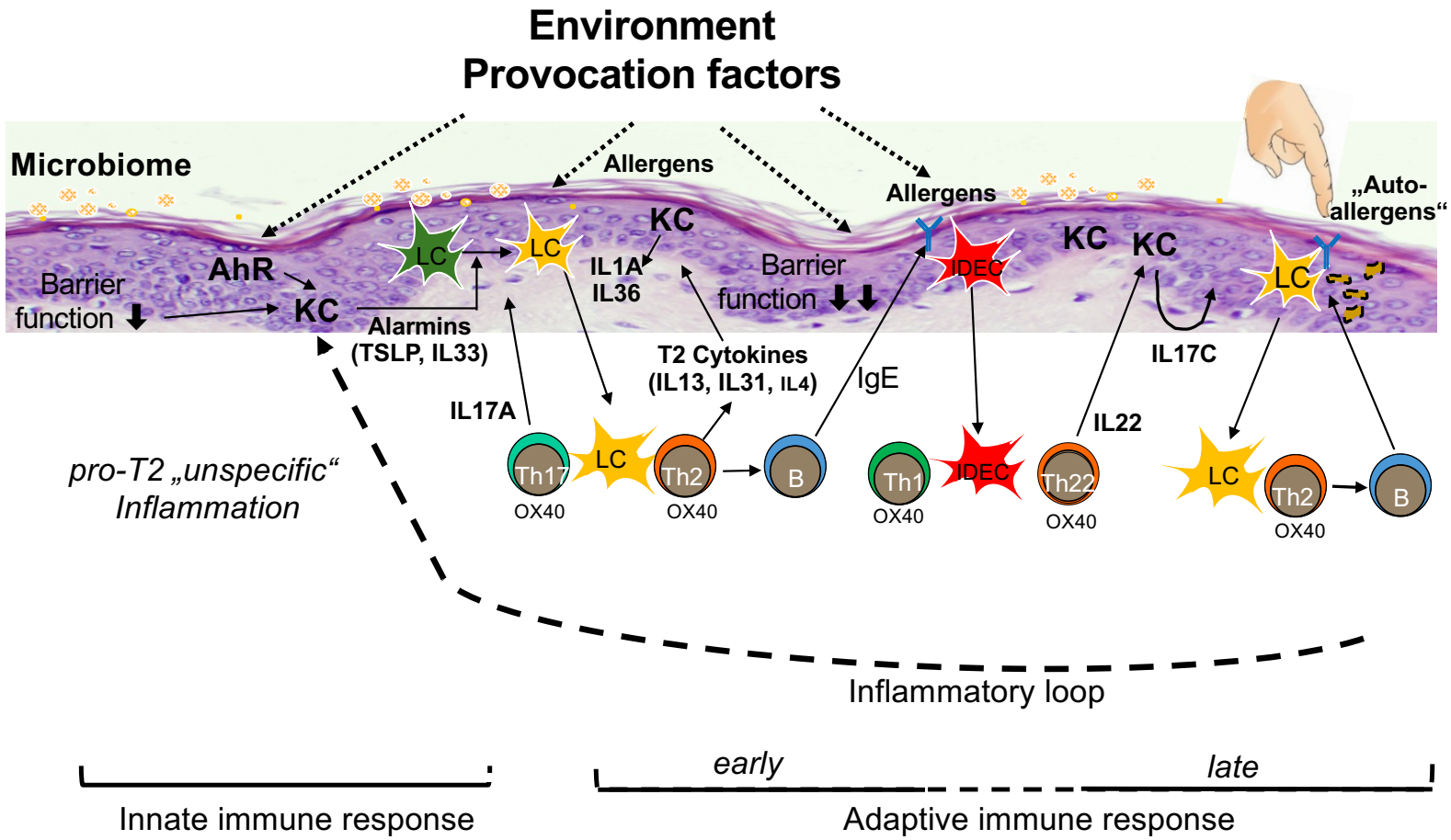
1. Brandt EB,et al. *J Clin Cell Immunol* 2011;2:110. 2. Gandhi NA *et al. Nat Rev Drug Discov* 2016;15:35–50. 3. Stott B *et al. J Allergy Clin Immunol* 2013;132:446–454. 4. Gutzmer R *et al. J Allergy Clin Immunol* 2009;23:619–625. 5. Danso MO *et al. J Invest Dermatol* 2014;134:1941–1950. 6. Gittler JK *et al. J Allergy Clin Immunol* 2013;131:300–313. 7. Zheng T *et al. J Invest Dermatol* 2009;129:742–751. 8. Chen L *et al. Clin Exp Immunol* 2004;138:375–387. 9. Noda S, et al,. *J Allergy Clin Immunol* 2015;135:324–336. 10. Leung DYM, et al *J Allergy Clin Immunol* 2014;134:769–779. 11. Howell MD *et al. J Invest Dermatol* 2008;128:2248–2258. 12. Kim BE *et al. Clin Immunol* 2008;126:332–337. 13. Huang YJ *et al. J Allergy Clin Immunol* 2017;139:1099–1110. 14. Berdyshev E *et al. JCI Insight* 2018;3:e98006.

Heterogeneity in immune response depending on age and ethnic background



(Czarnowicki et al, *JACI* 2019)

Translational perspective of the pathophysiology of AD



(Bieber T, JDDG 2019)

The pharmacological strategies to control inflammation in AD

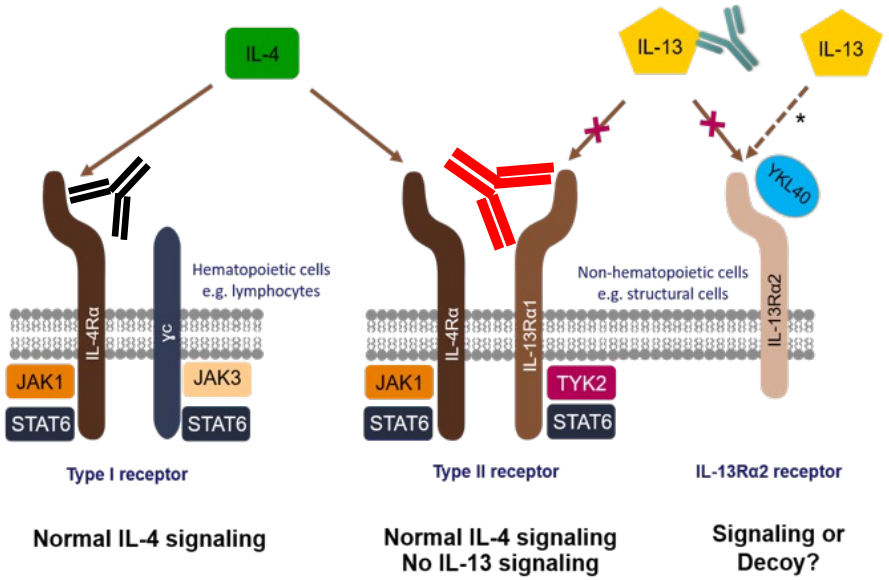
The targeted approach

Biologicals

The broad approach

Small molecules (JAKi)

Targeted therapy against T2 cytokines



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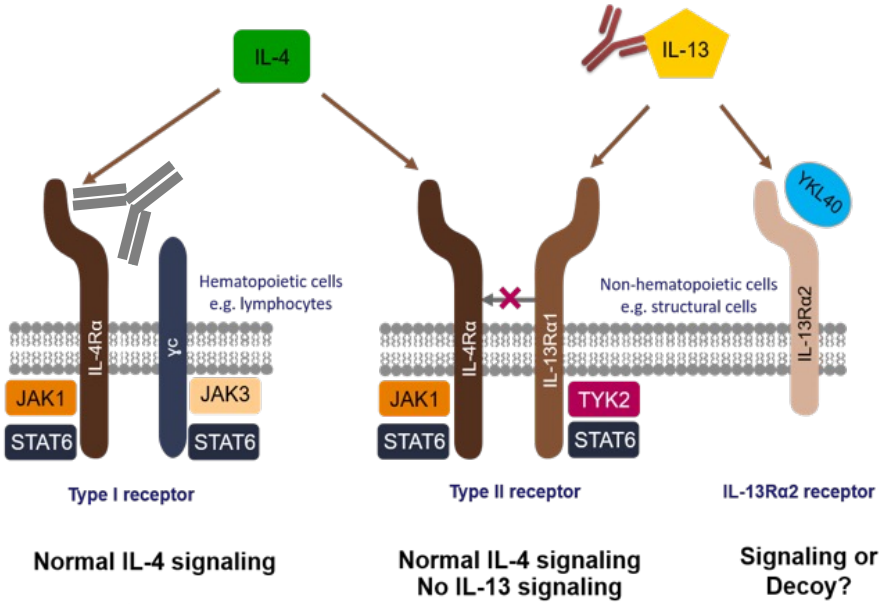

Dupilumab

Tralokinumab und RPC4046

Lebrikizumab and anrukizumab

Eblasakimab (ASLAN004)

CBP-201

(Bieber T. *Allergy* 2019)

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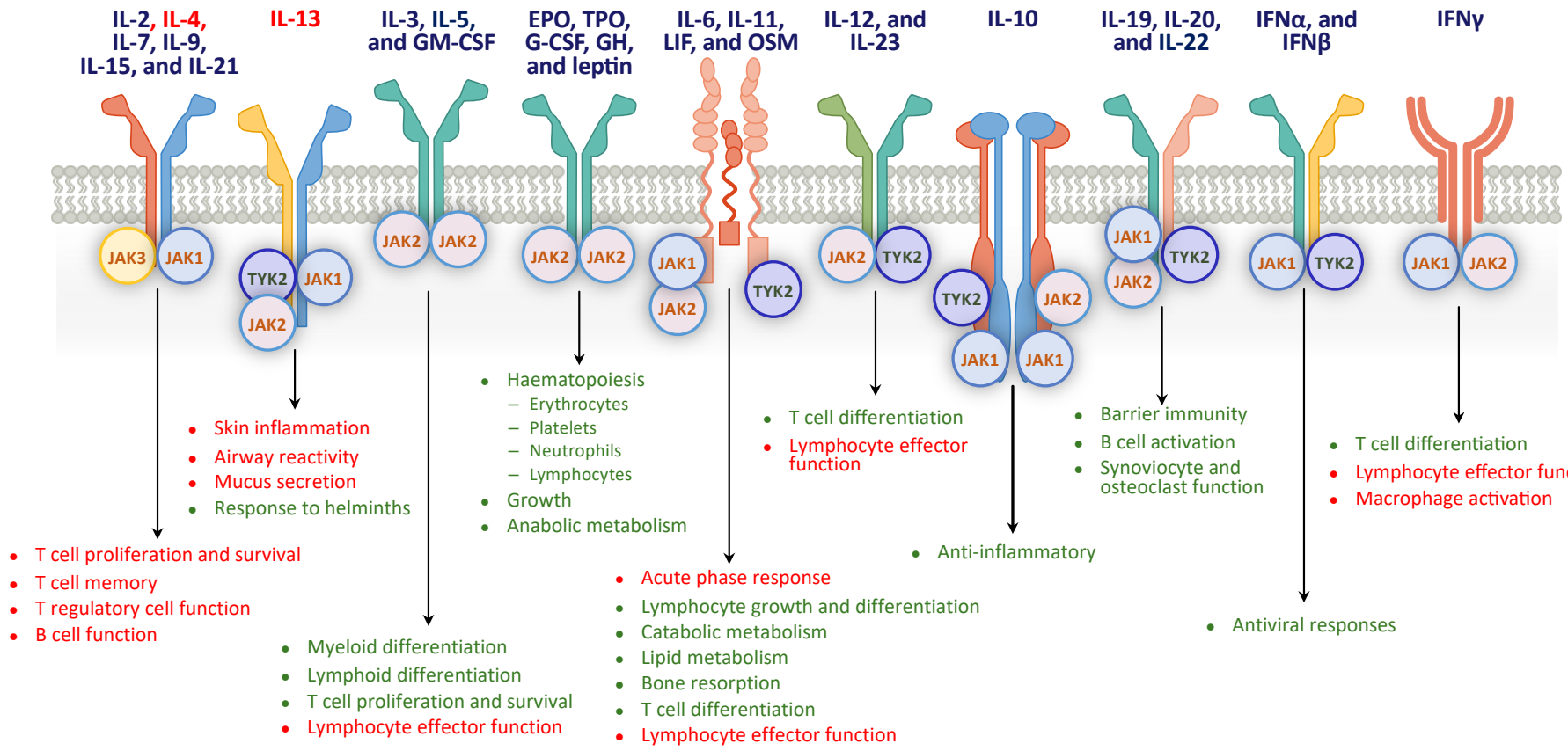
Janus kinases as therapeutic targets

A highly complex interaction requesting a balanced act in drug development



1. Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;16(12):843-862.

JAK inhibitors in the management of AD

JAKi

Systemic

Gusacitinib (pan JAK/SYK)

Baricitinib (JAK1/2; Olumiant®)*

Abrocitinib (JAK1; Cibinqo®)*

Upadacitinib (JAK1; Rinvoq®)*

SHR0302 (JAK1)

Delgocitinib/JTE-052 (pan JAKi; Corectim®)**

Ruxolitinib (JAK1/2; Opzelura®)***

Cerdulatinib (pan JAK/SYK)

Brepocitinib (JAK1/TYK2)

ATI-1777 (JAK1/JAK3)

CEE321 (pan-JAKi), ...

Topic

* approved in EU
** approved in Japan
*** approved in USA

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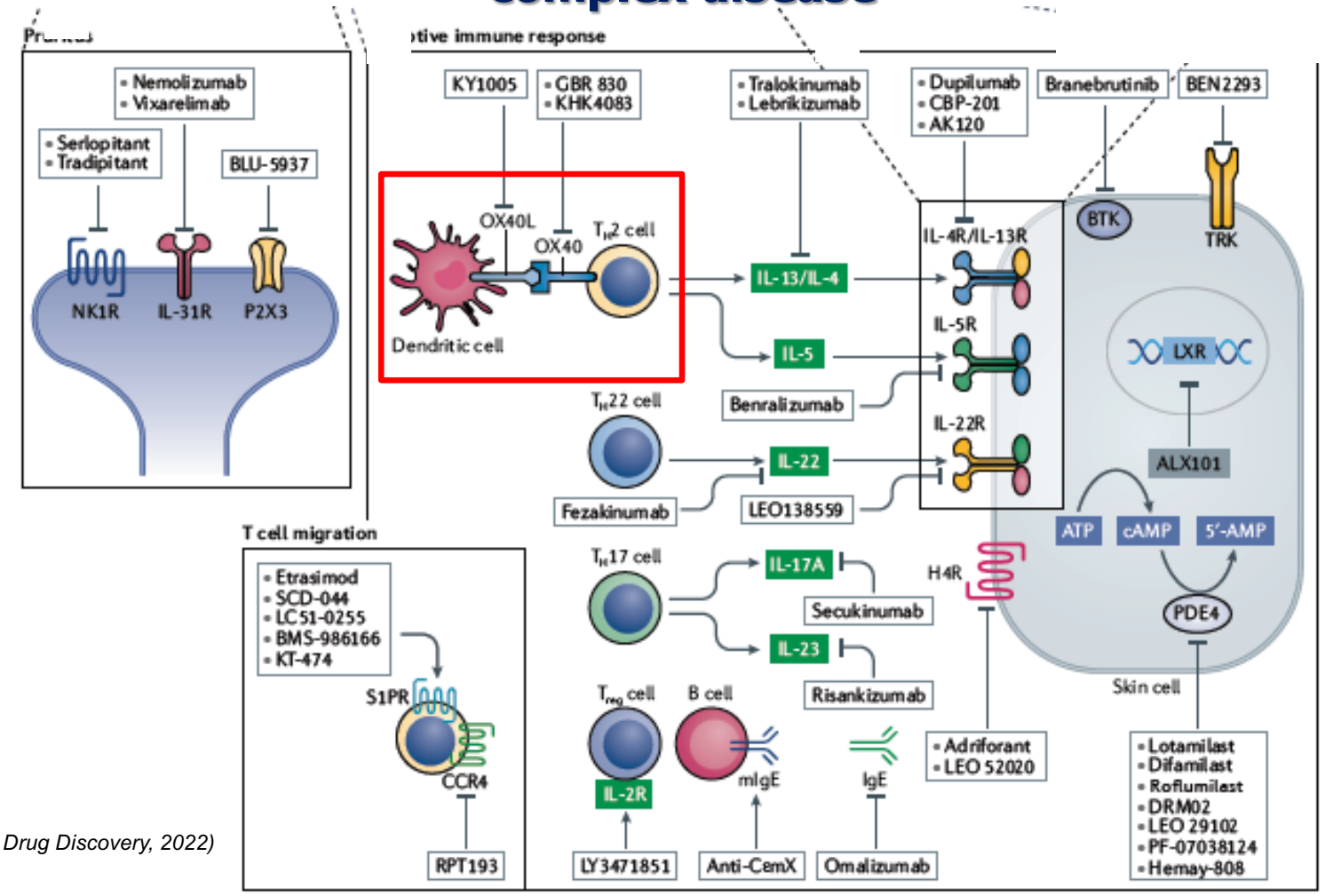
Atopic dermatitis: an expanding therapeutic pipeline for a complex disease



(Bieber T. *Nature Review Drug Discovery, 2022)*

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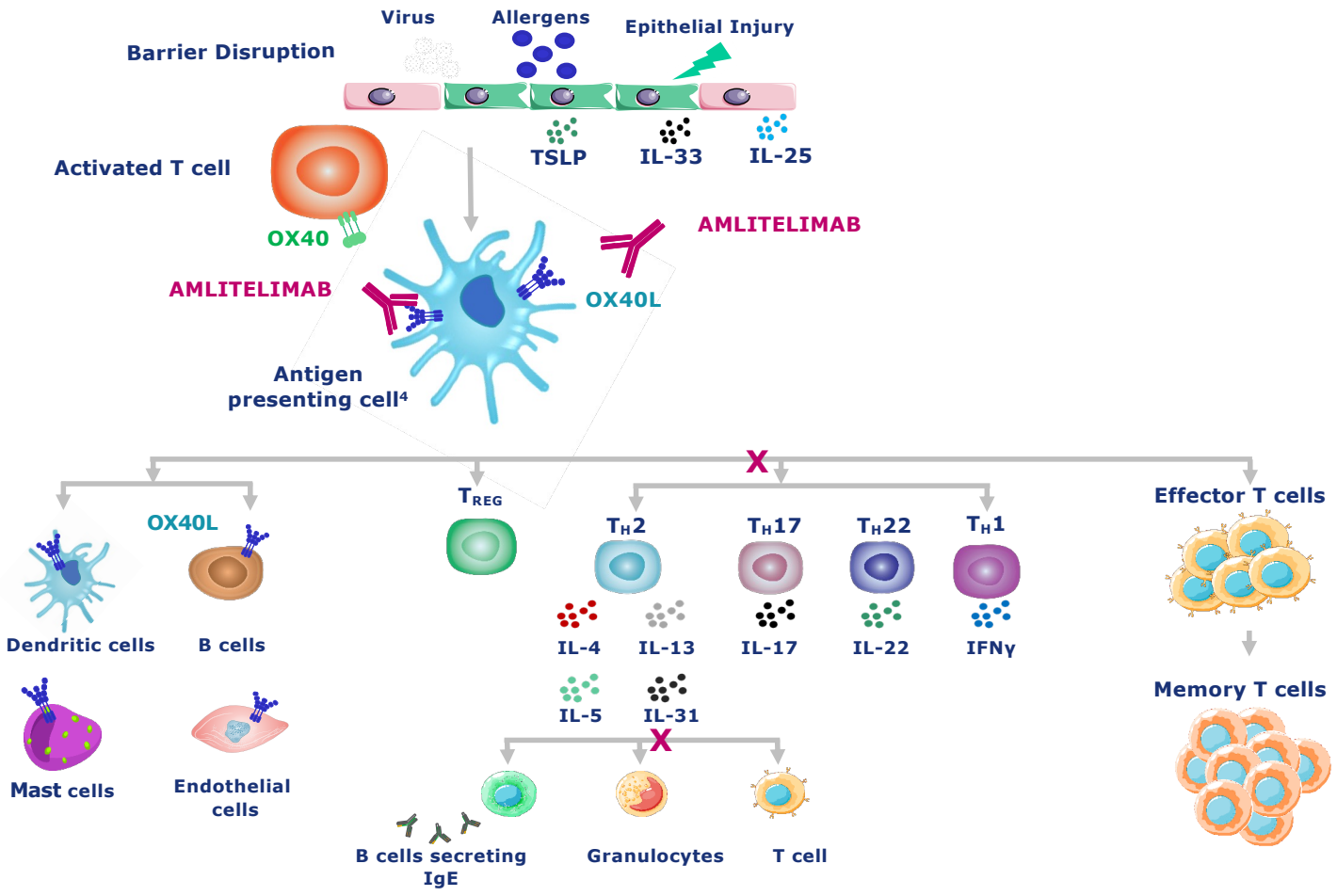
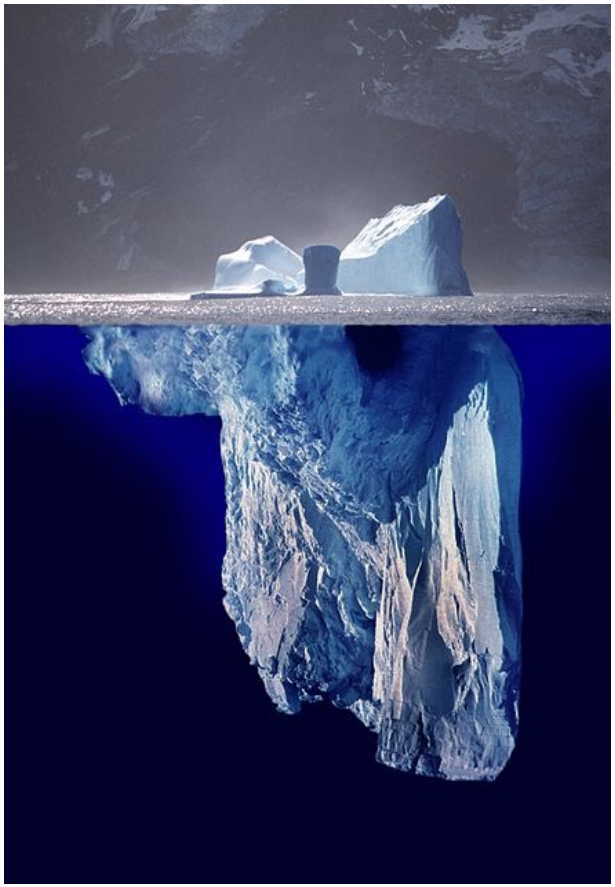
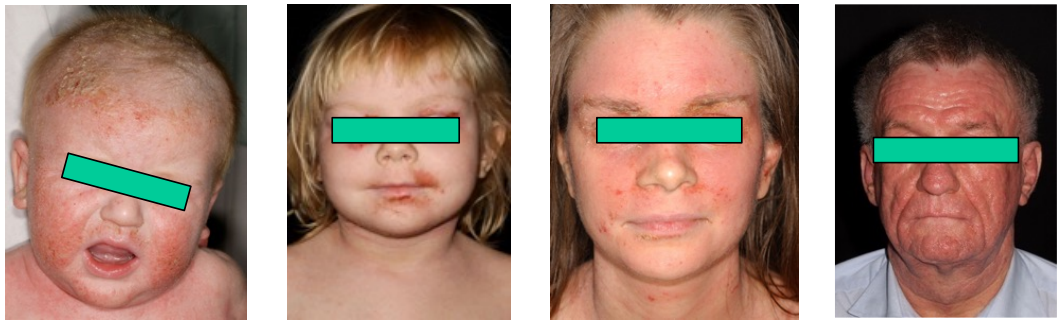
Amlitelimab: the first in class targeted therapy acting "upstream" of the inflammatory reaction



What´s next?

Atopic dermatitis:
Did we only focused on the tip of the iceberg?





Food allergy
Allergic rhinitis
Allergic Asthma

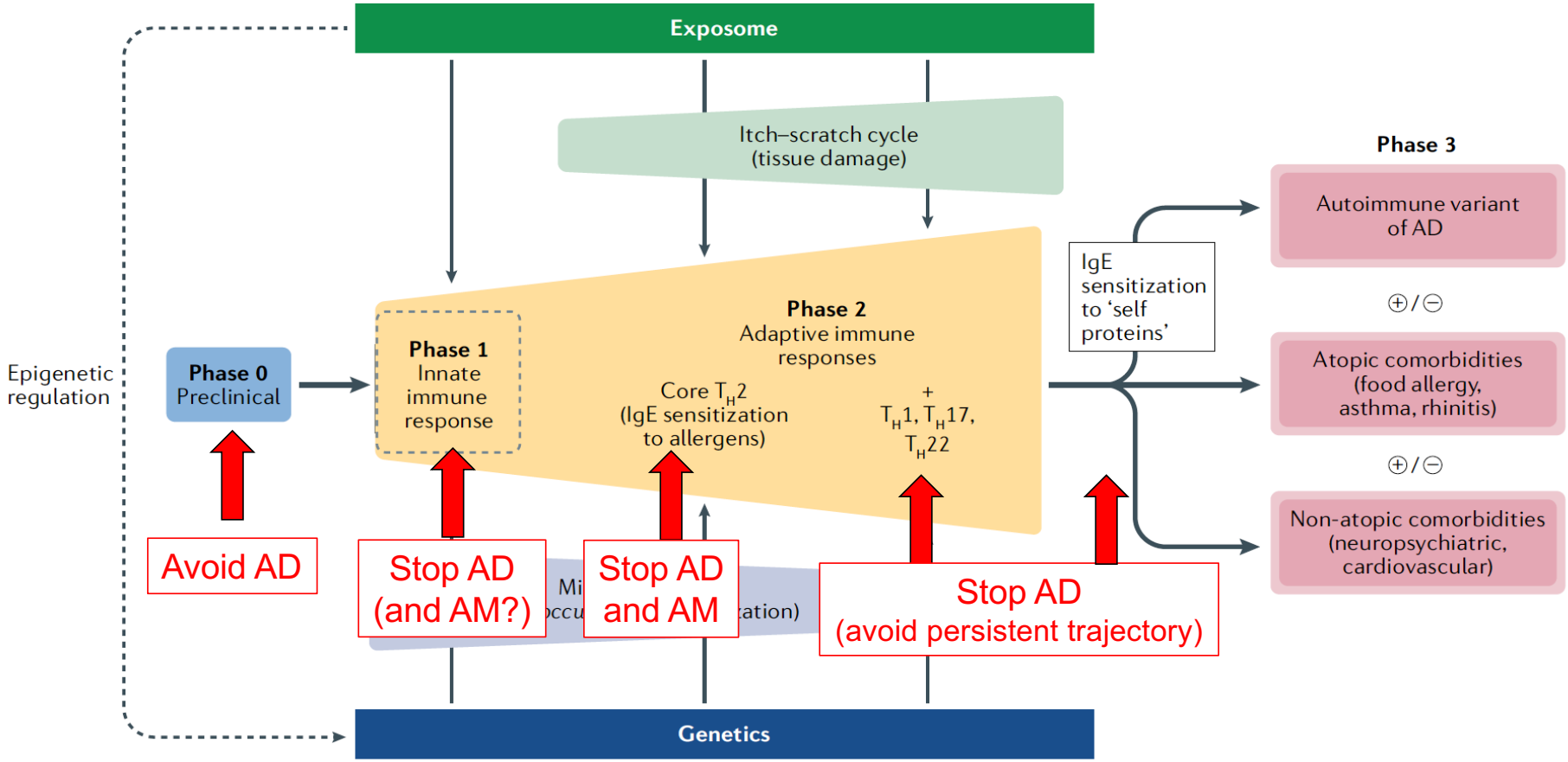
„Atopic march“

Psycho/Neurologic comorbidities

Cardio-vascular comorbidities

Photos provided by Prof. Bieber

The new challenge in the management of AD
Various strategies to reach "disease modification"



Bieber T. *Nature Review Drug Discovery, 2022*

Thank you for your attention!