Alopecia areata pathogenesis

Dr. Raghda Al Maashari

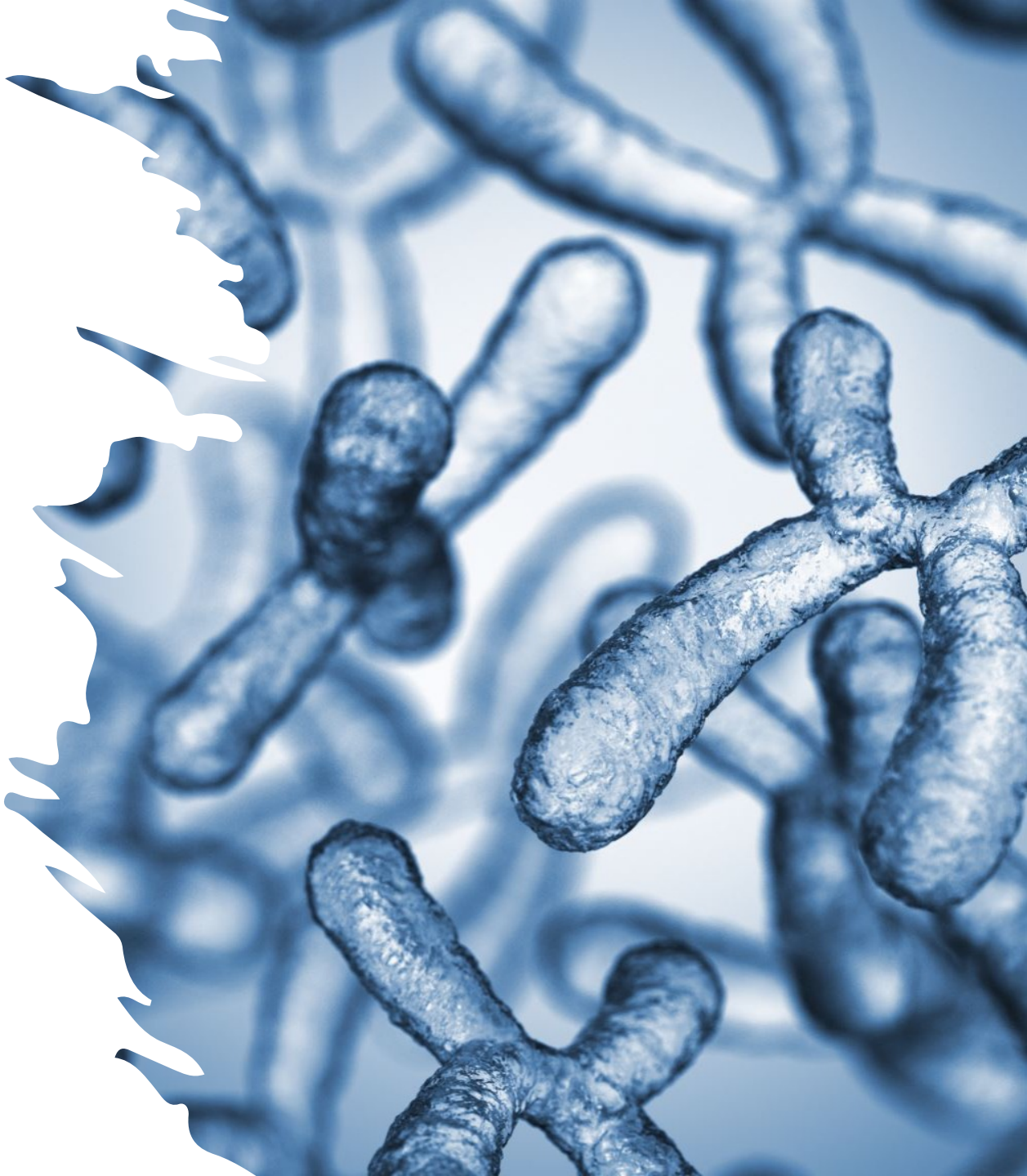
Objectives

- Introduction
- Evolution in the understanding of AA Pathogenesis
- Pathogenesis
  - Immune privilege concept
  - JAK STAT pathway
- Scoring system
  - SALT score
  - Alopecia areata scale
- 2024 EADV guideline

Alopecia areata (AA)

- AA is an autoimmune disorder of hair follicles, results in varying degrees of scalp, facial, and body hair loss
- Associated with psychosocial and quality-of-life impairments
- Unpredictable clinical course , with spontaneous remissions and relapses
- Current treatments are limited by their efficacy, safety, and high relapse rates after discontinuation

Evolution in the understanding of AA Pathogenesis



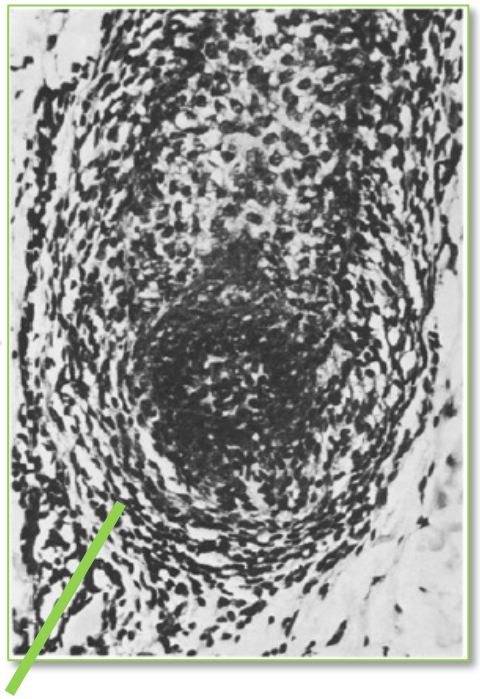
Evolution in the understanding of AA Pathogenesis (I)

1950[a]

Precipitating Cause of Attack

The commonest precipitating cause was found to be mental shock or acute anxiety. If alopecia followed a few weeks after such an event then that was taken to be the cause. In 27 cases (23%) the alopecia had been preceded by some form of mental stress. In a control series interviewed by members of the Scientific Advisory Committee of the Empire Rheumatism Council (1950) 9% of 292 subjects reported some form of mental trauma within three months previous to the investigation. A further 26 cases were obviously suffering from various degrees and forms of mental disturbance, or what the patients themselves called "nerves." They had, however, been in this state for years, and it was not related chronologically in any way to the appearance of the alopecia.

1982[b]



Hair bulb surrounded by lymphocytic infiltrate

Treatment of AA **in 2010**

- Intralesional corticosteroids
- Topical corticosteroids
- Topical minoxidil
- Topical immunotherapy

- Systemic corticosteroids
- Cyclosporine
- Methotrexate

STAT, signal transducer and activator of transcription; TCR, T cell receptor.

a. Anderson I. Br Med J. 1950;2:1250-1252; b. Perrett C, et al. Arch Dermatol Res. 1982;273:155-158; c. Divito SJ, et al. Nat Med. 2014;20:989-990; d. Xing L, et al. Nat Med. 2014;20:1043-1049; e. Alkhalifah A, et al. J Am Acad Dermatol. 2010;62:191-202.

Evolution in the understanding of AA Pathogenesis (II)

1950[a]

Precipitating Cause of Attack

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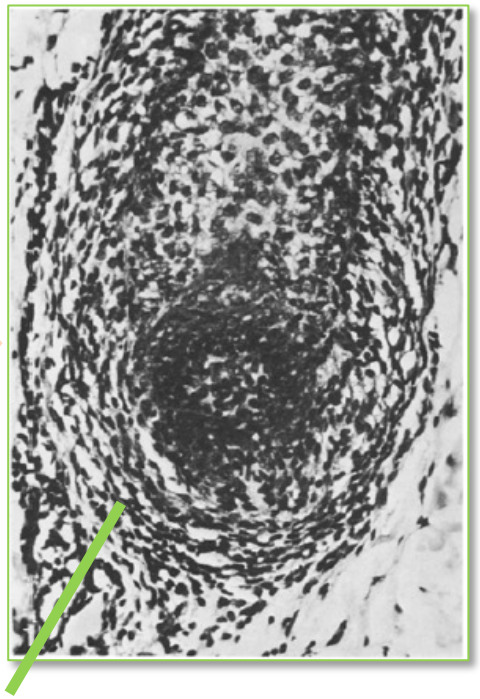
1982[b]



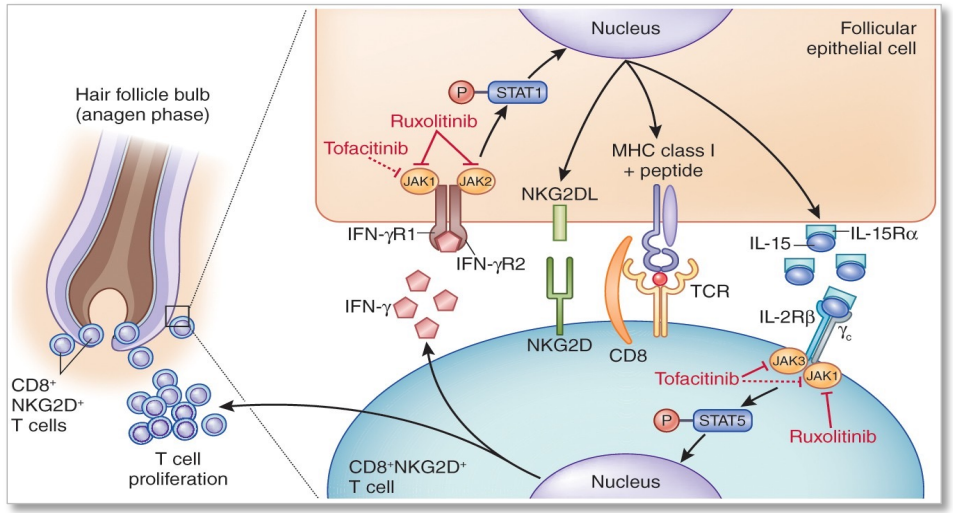
Hair bulb surrounded by lymphocytic infiltrate

2010[e]

Genome-wide association study in alopecia areata implicates both innate and adaptive immunity

Lynn Petukhova[1], Madeleine Duvic[2], Maria Hordinsky[3], David Norris[4], Vera Price[5], Yutaka Shimomura[1], Hyunmi Kim[1], Pallavi Singh[1], Annette Lee[6], Wei V. Chen[7], Katja C. Meyer[8], Ralf Paus[8,9], Colin A. B. Jahoda[10], Christopher I. Amos[7], Peter K. Gregersen[6] & Angela M. Christiano[1,11]

2014[c]



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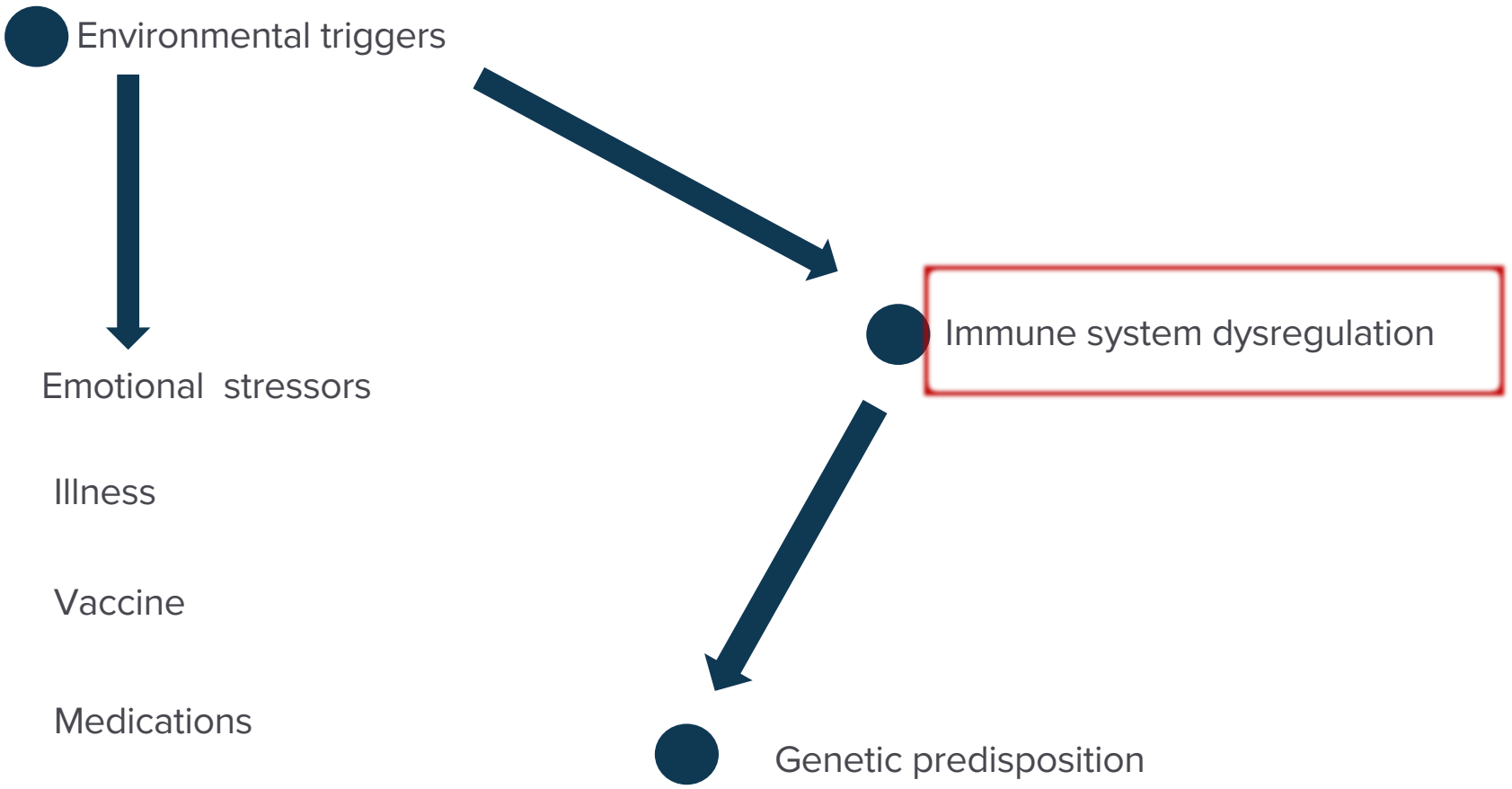
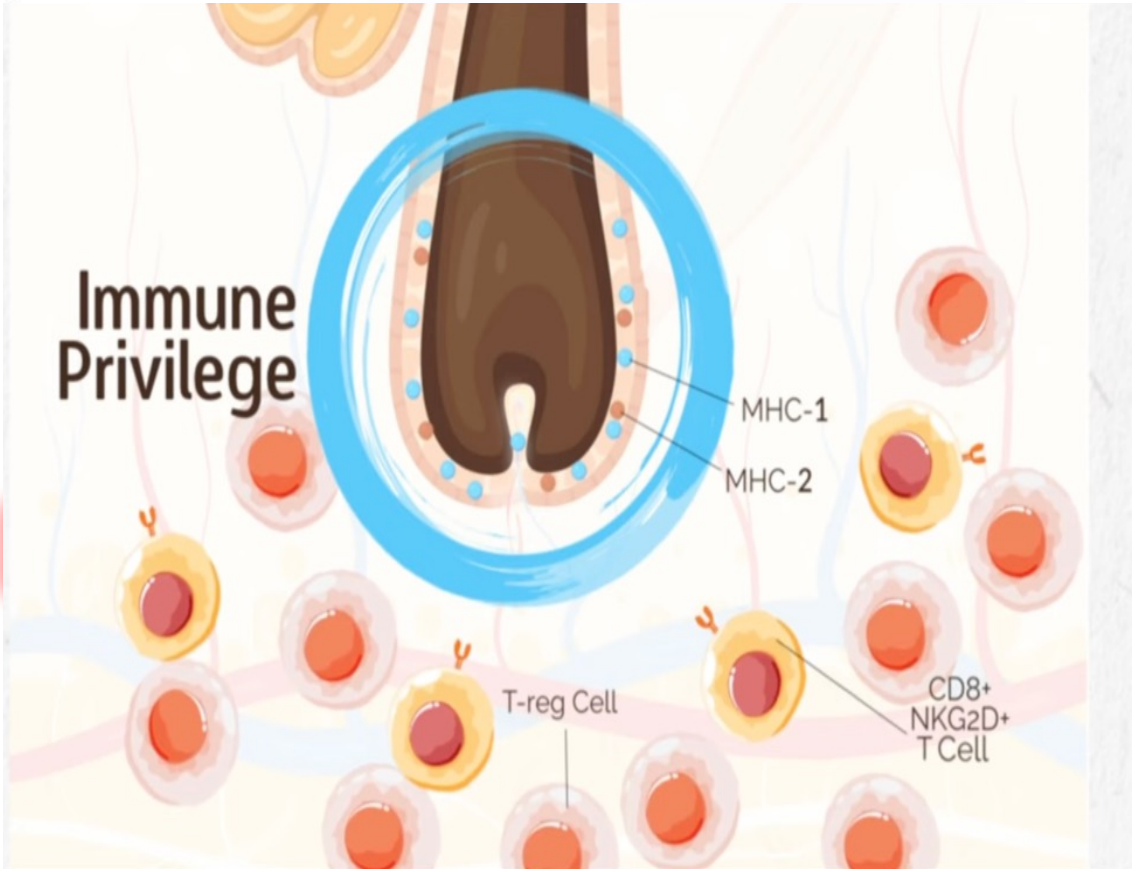
Pathogenesis of alopecia areata



Immune privilege (I)

Having immune privilege means these particular cells have the ability to endure exposure to antigens without eliciting an inflammatory immune response



Streilein, J. Ocular immune privilege: therapeutic opportunities from an experiment of nature. *Nat Rev Immunol* **3**, 879–889 (2003). https://doi.org/10.1038/nri1224

Immune privilege (II)

Immune privilege is believed to involve :

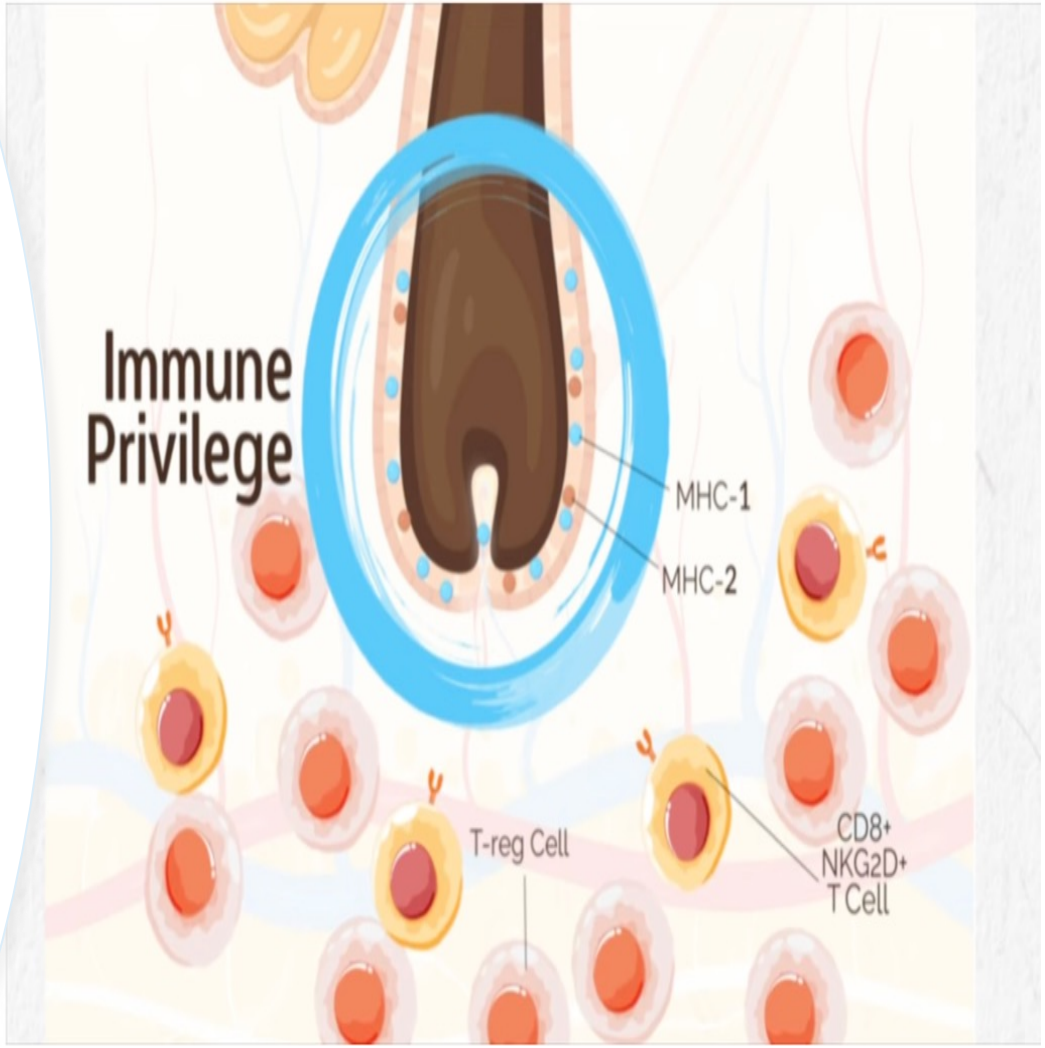
- Low level expression of major histocompatibility complex 1,2

-Presence of regulatory T cells

-Suppression of CD 8 +ve NKG2D +ve T cells

-Presence of anti-inflammatory cytokines/hormones (TGFβ, IL-10, α-MSH)

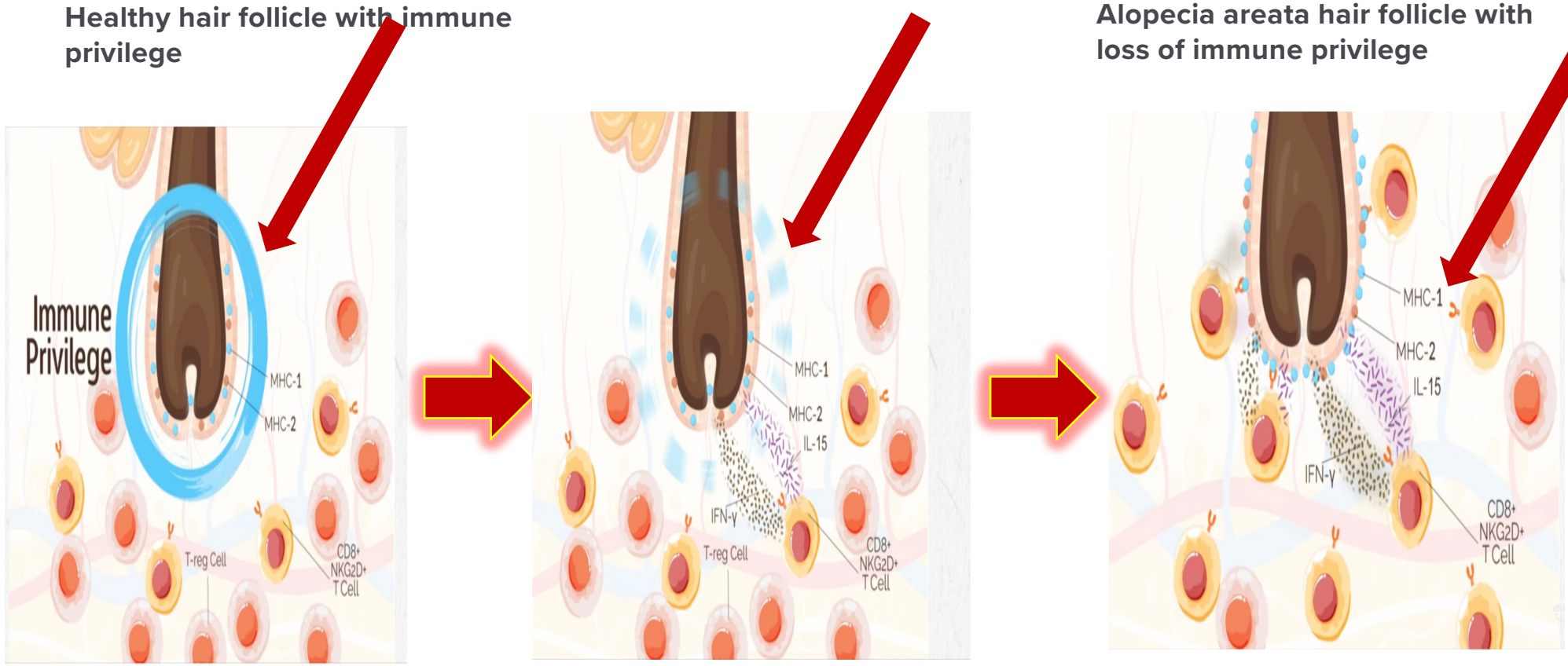
- A paucity of immune cell infiltrates



Immune privilege (III)

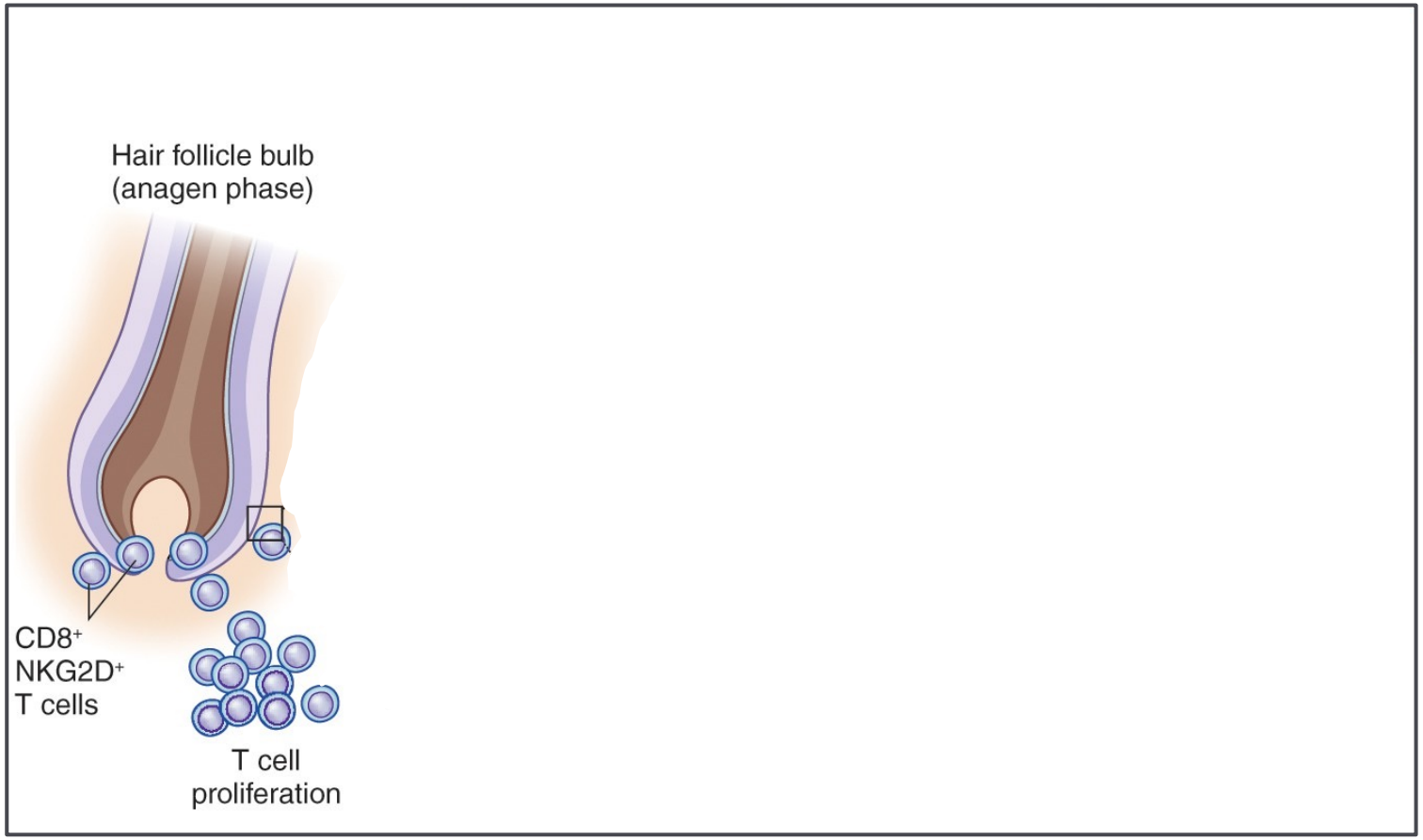
Healthy hair follicle with immune privilege

Alopecia areata hair follicle with loss of immune privilege



Alopecia Areata Pathogenesis –JAK STAT pathway (I)

[a]



CD, cluster of differentiation; HLA-D, human leukocyte antigen-DQB1*03; HLA-DR, HLA-D-related; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IGF-1, insulin-like growth factor 1; IL, interleukin; MHC, major histocompatibility complex; MSH, melanocyte-stimulating hormone; TGF-β1, human transforming growth factor beta 1; Th1, T helper type 1 (cells); Treg, T regulatory (cells).
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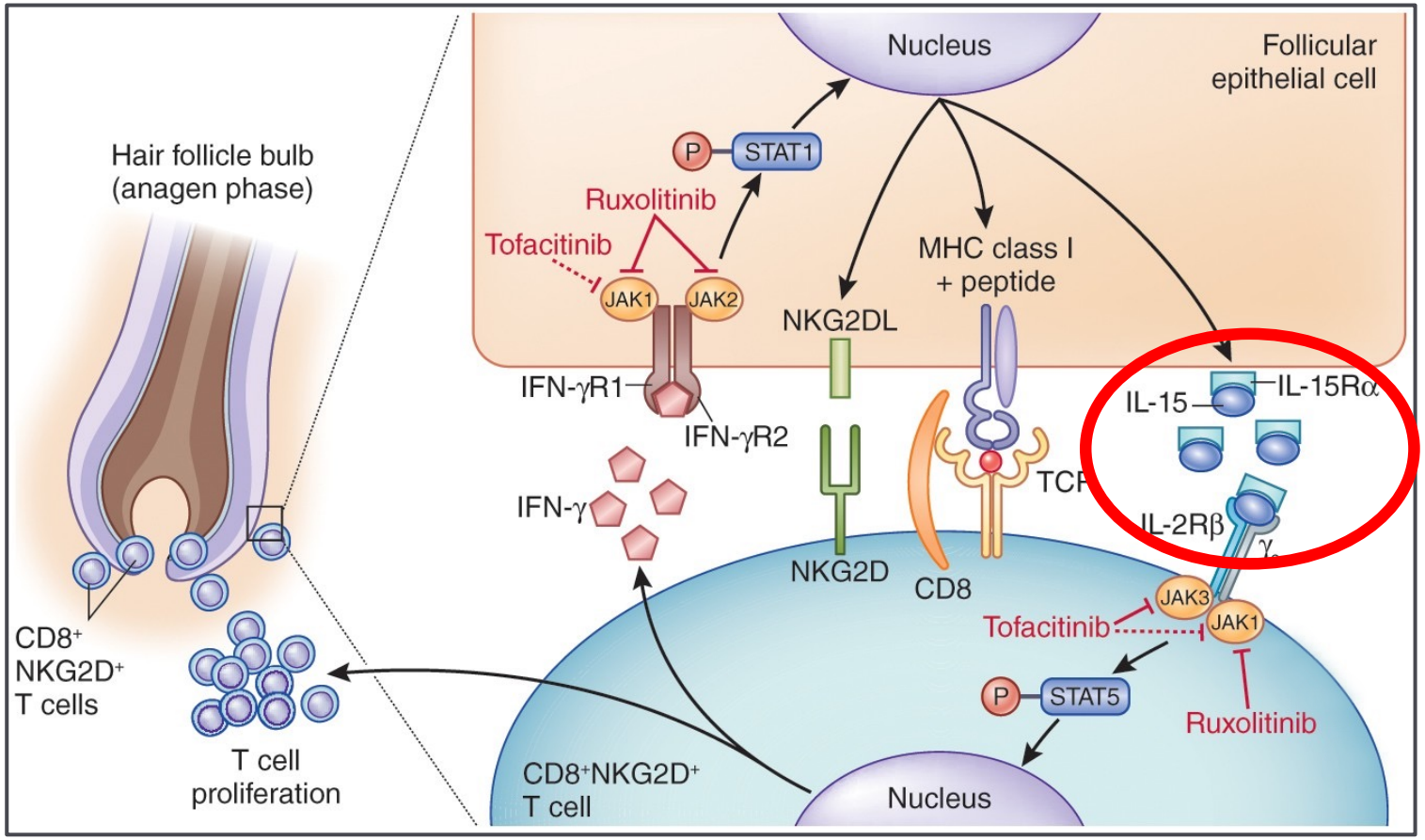
Alopecia Areata Pathogenesis –JAK STAT pathway (II)

[a]



- Secretion of IL-15 from follicular epithelial cells recruits and activates cytotoxic T cells

CD, cluster of differentiation; HLA-D, human leukocyte antigen-DQB1*03; HLA-DR, HLA-D-related; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IGF-1, insulin-like growth factor 1; IL, interleukin; MHC, major histocompatibility complex; MSH, melanocyte-stimulating hormone; TGF-β1, human transforming growth factor beta 1; Th1, T helper type 1 (cells); Treg, T regulatory (cells).

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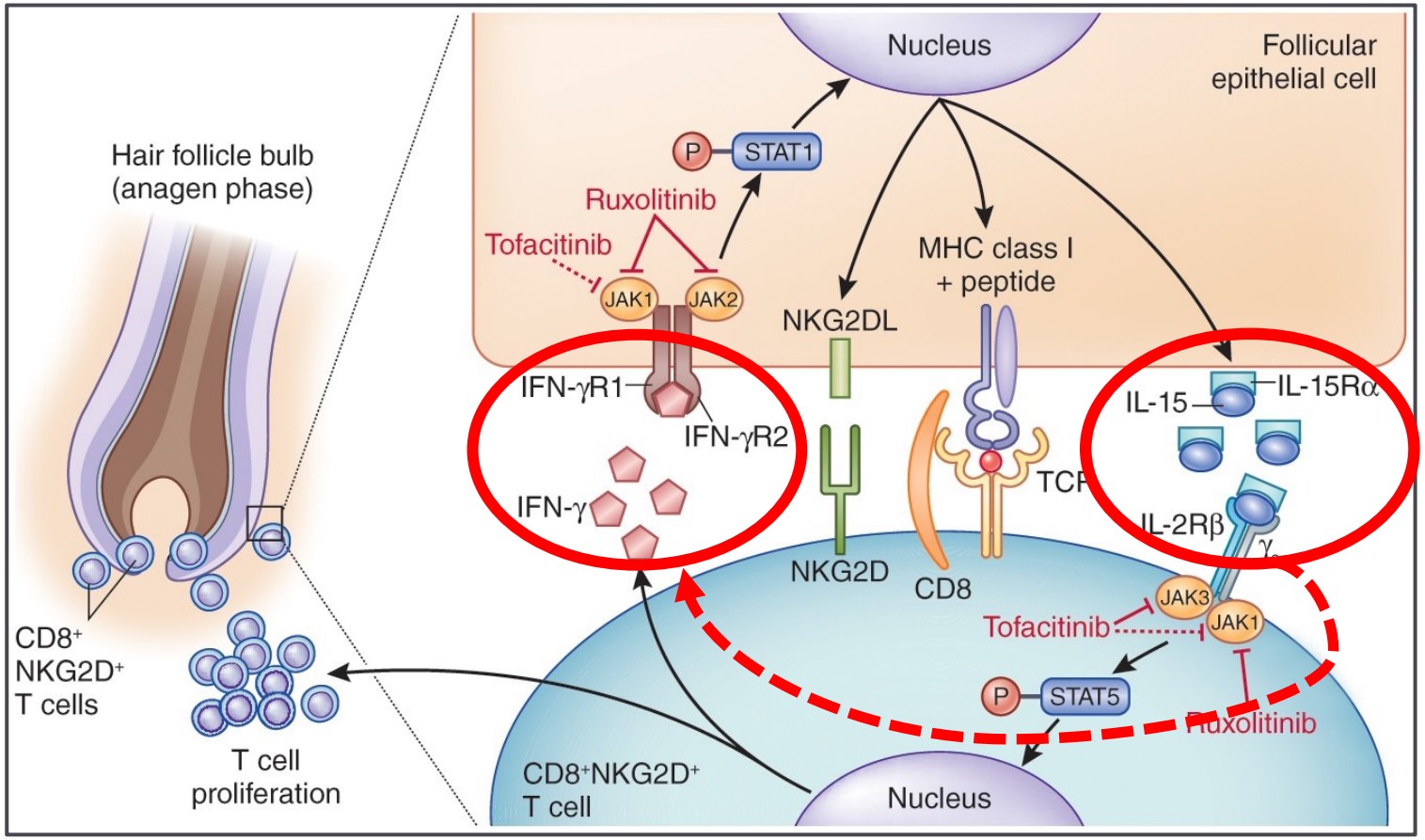

- Secretion of IL-15 from follicular epithelial cells recruits and activates cytotoxic T cells
- Cytotoxic T cells secrete IFN-**γ**, which binds its receptor on the follicular epithelial cell, leading to further secretion of IL-15

CD, cluster of differentiation; HLA-D, human leukocyte antigen-DQB1*03; HLA-DR, HLA-D-related; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IGF-1, insulin-like growth factor 1; IL, interleukin; MHC, major histocompatibility complex; MSH, melanocyte-stimulating hormone; TGF-β1, human transforming growth factor beta 1; Th1, T helper type 1 (cells); Treg, T regulatory (cells).

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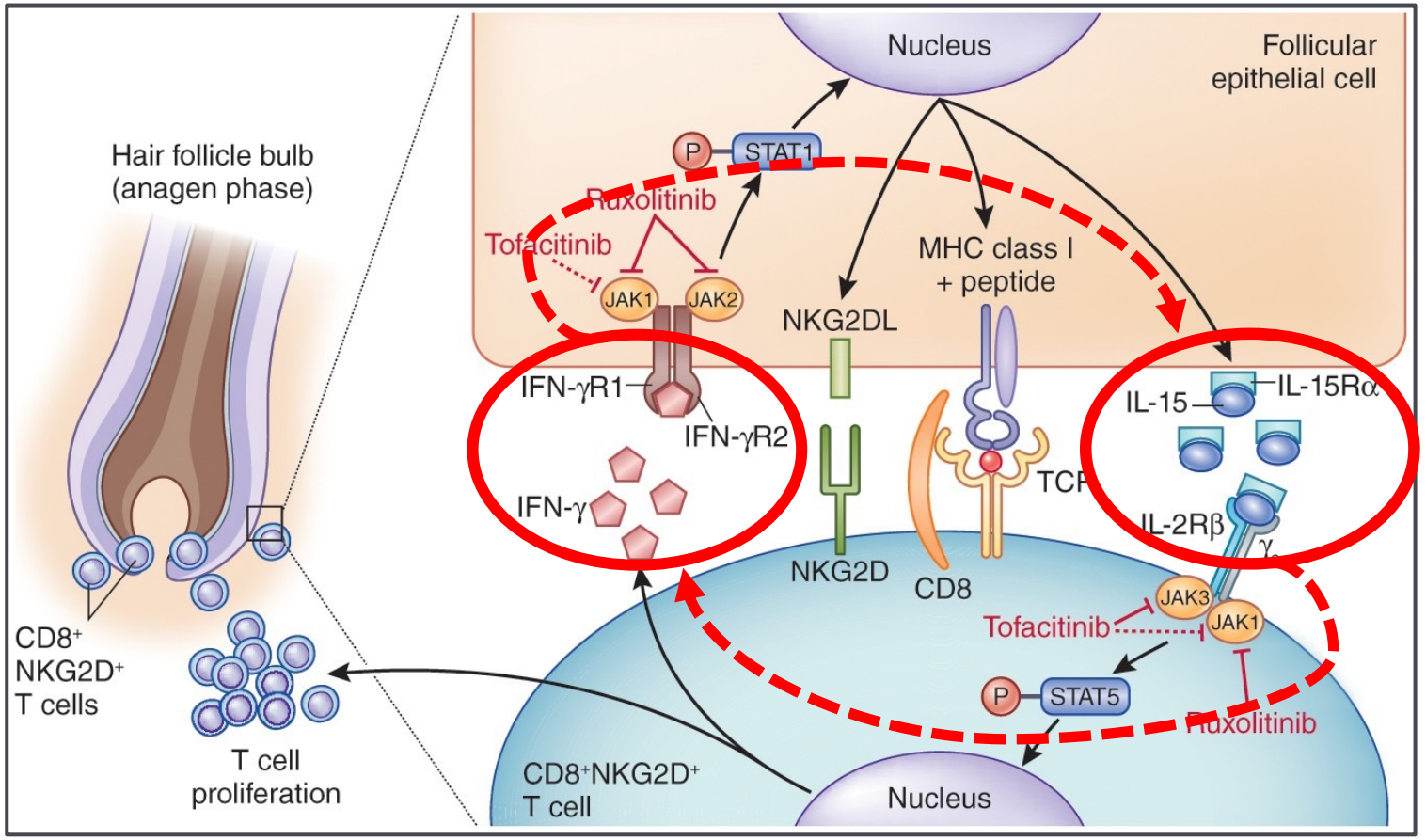
Alopecia Areata Pathogenesis –JAK STAT pathway (IV)

[a]



- Secretion of IL-15 from follicular epithelial cells recruits and activates cytotoxic T cells
- Cytotoxic T cells secrete IFN-**γ**, which binds its receptor on the follicular epithelial cell, leading to further secretion of IL-15
- This cyclical action leads to inflammation and subsequent hair loss[a,b]

CD, cluster of differentiation; HLA-D, human leukocyte antigen-DQB1*03; HLA-DR, HLA-D-related; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IGF-1, insulin-like growth factor 1; IL, interleukin; MHC, major histocompatibility complex; MSH, melanocyte-stimulating hormone; TGF-β1, human transforming growth factor beta 1; Th1, T helper type 1 (cells); Treg, T regulatory (cells).

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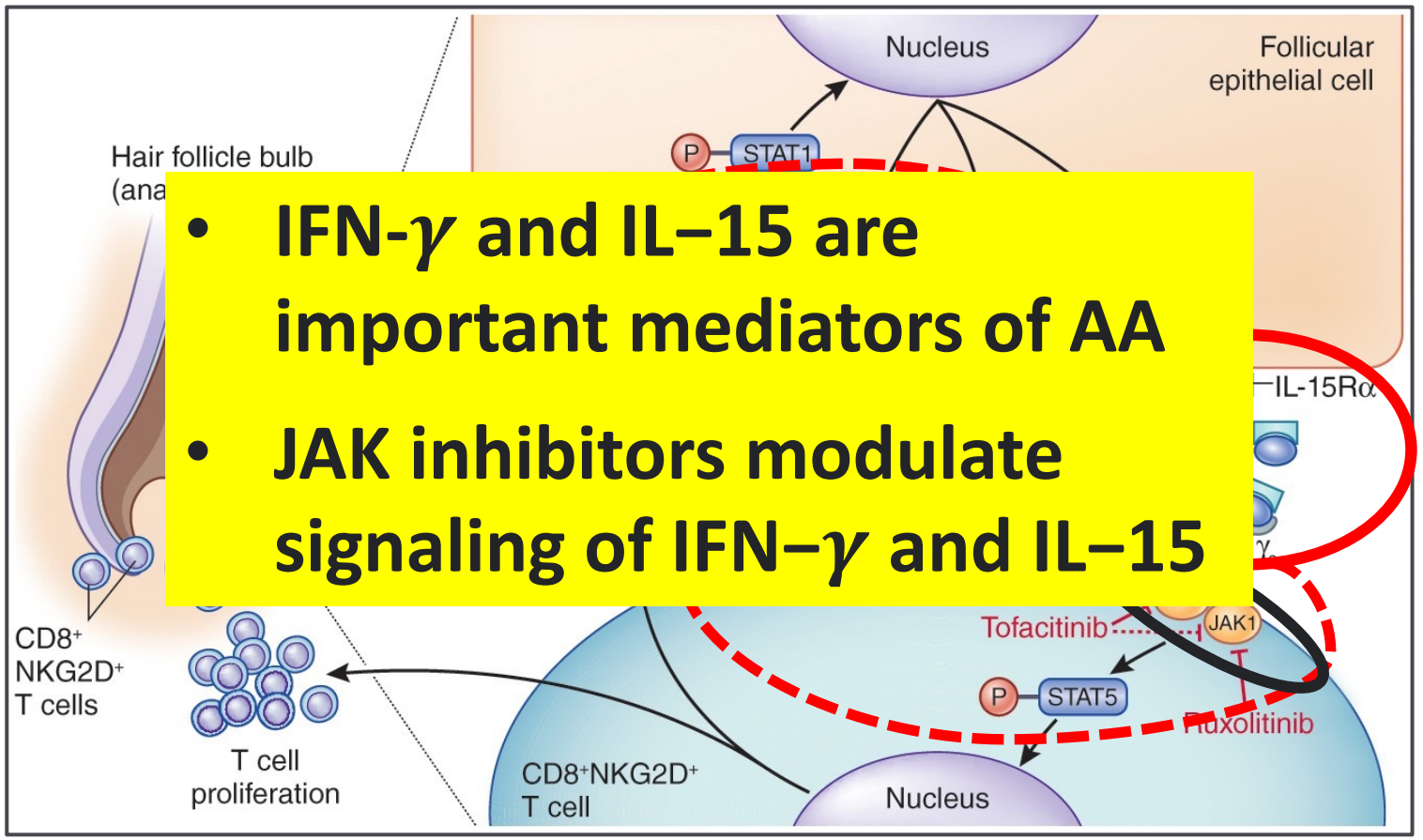
Alopecia Areata Pathogenesis –JAK STAT pathway (V)

[a]



- **IFN-γ and IL–15 are important mediators of AA**
- **JAK inhibitors modulate signaling of IFN–γ and IL–15**

- Secretion of IL-15 from follicular epithelial cells recruits and activates cytotoxic T cells
- Cytotoxic T cells secrete IFN-γ, which binds its receptor on the follicular epithelial cell, leading to further secretion of IL-15
- This cyclical action leads to inflammation and subsequent hair loss[a,b]
- **IFN-γ and IL–15 signal thru JAK proteins**

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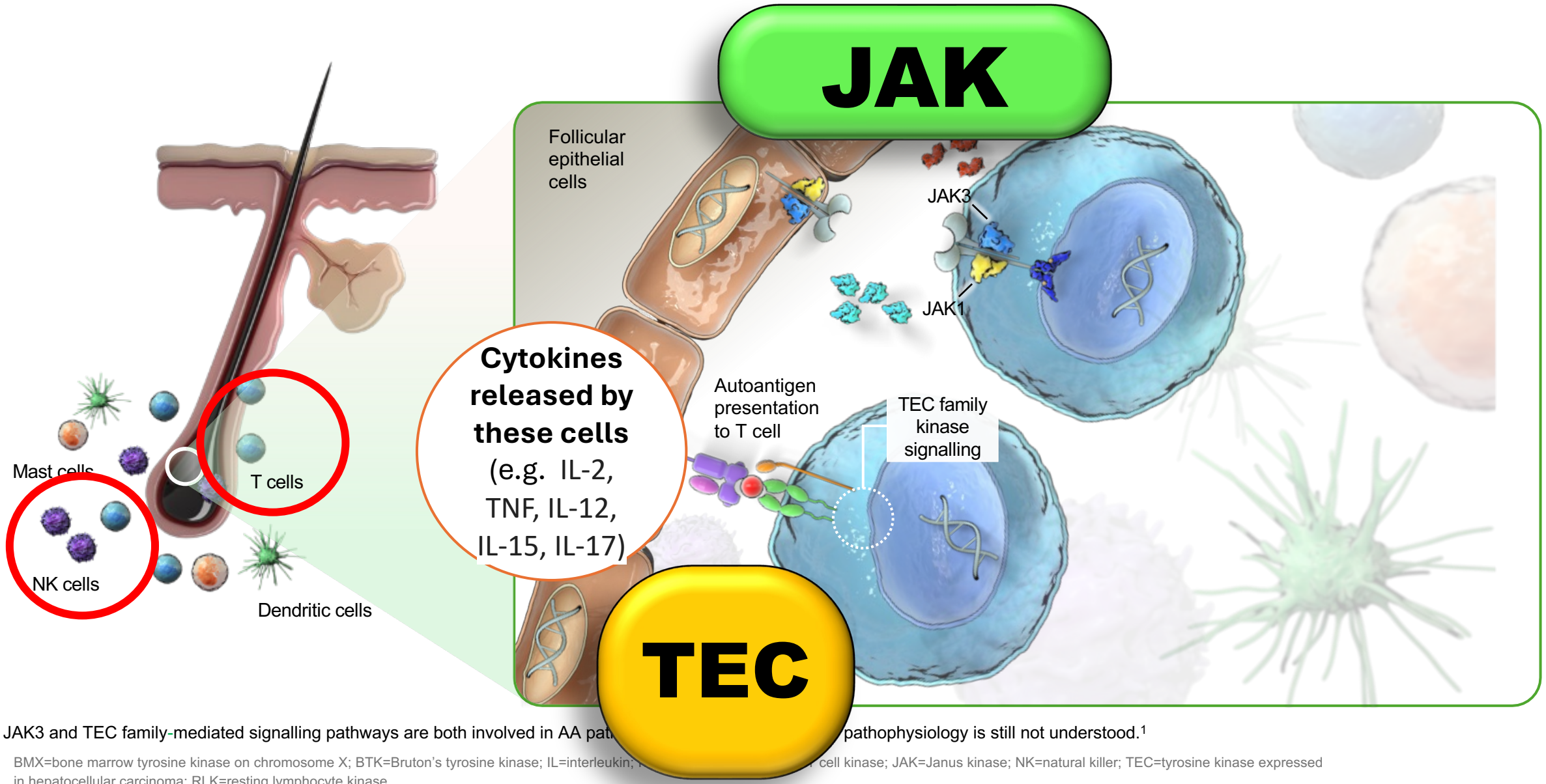
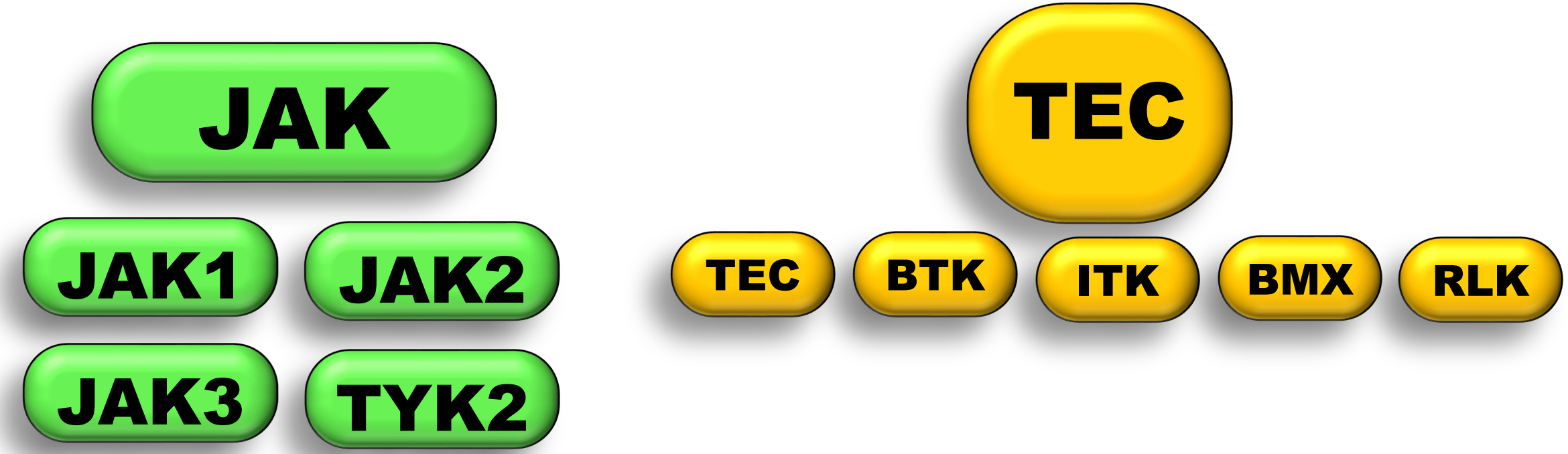


JAK3 and TEC family-mediated signalling pathways are both involved in AA pat… pathophysiology is still not understood.[1]

BMX=bone marrow tyrosine kinase on chromosome X; BTK=Bruton's tyrosine kinase; IL=interleukin; … cell kinase; JAK=Janus kinase; NK=natural killer; TEC=tyrosine kinase expressed in hepatocellular carcinoma; RLK=resting lymphocyte kinase.

1. LITFULO™ Summary of Product Characteristics. European Union. Pfizer Limited; 2024. **2.** Xu H, et al. *ACS Chem Biol.* 2019;14(6):1235-1242.



IL-2
IL-4
IL-7

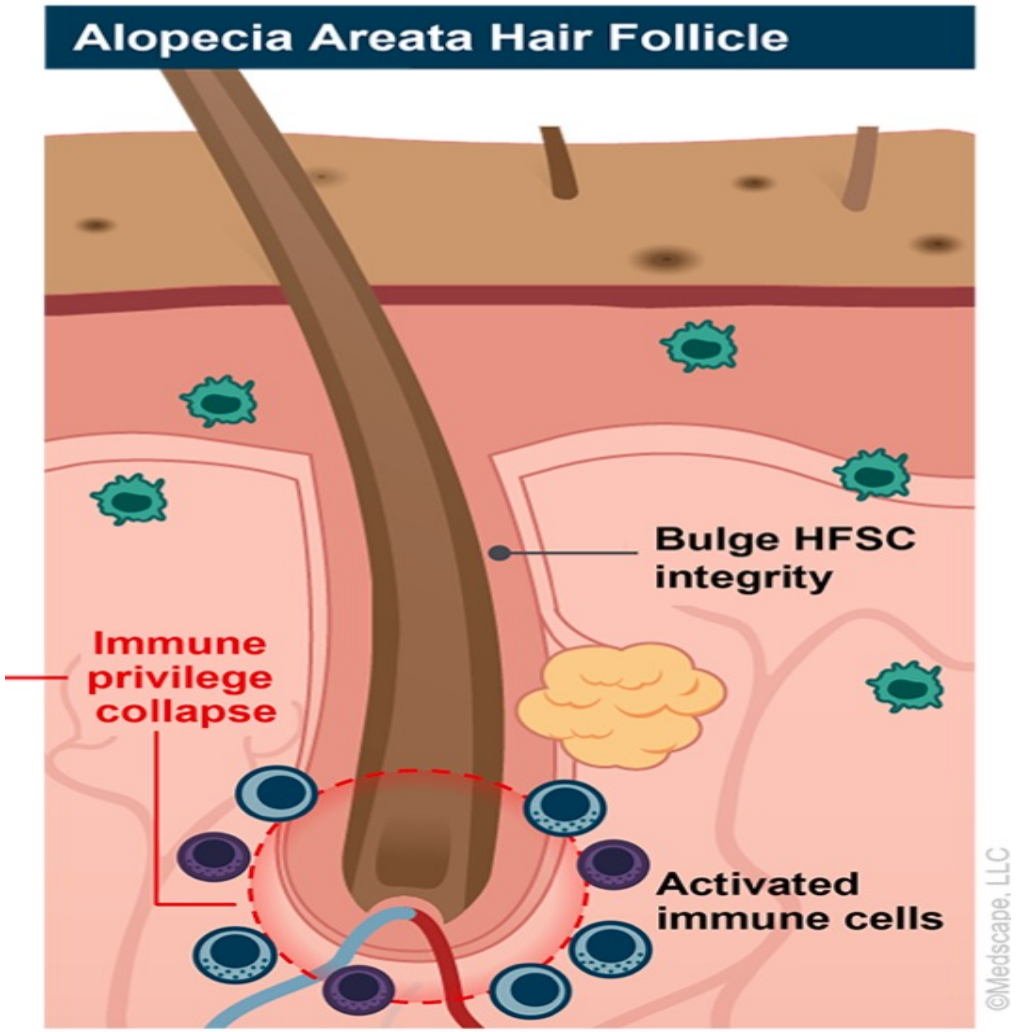
IL-15
IL-21

NK cells
CD8+ T cells.

Bansal A, Relhan V, Garg VK, Saran RK. A cross-sectional study of the histopathology and immunology of alopecia areata: Unearthing the role of the Janus kinase-signal transducer and activator of transcription pathway. Indian J Dermatol Venereol Leprol. 2019 Sep-Oct;85(5):455-461.

Xu H, Jesson MI, Seneviratne UI, Lin TH, Sharif MN, Xue L, Nguyen C, Everley RA, Trujillo JI, Johnson DS, Point GR, Thorarensen A, Kilty I, Telliez JB. PF-06651600, a Dual JAK3/TEC Family Kinase Inhibitor. ACS Chem Biol. 2019 Jun 21;14(6):1235-1242.

Kempson J, Ovalle D, Guo J, Wrobleski ST, Lin S, Spergel SH, Duan JJ, Jiang B, Lu Z, Das J, Yang BV, Hynes J Jr, Wu H, Tokarski J, Sack JS, Khan J, Schieven G, Blatt Y, Chaudhry C, Salter-Cid LM, Fura A, Barrish JC, Carter PH, Pitts WJ. Discovery of highly potent, selective, covalent inhibitors of JAK3. Bioorg Med Chem Lett. 2017 Oct 15;27(20):4622-4625.



Immune privilege collapse

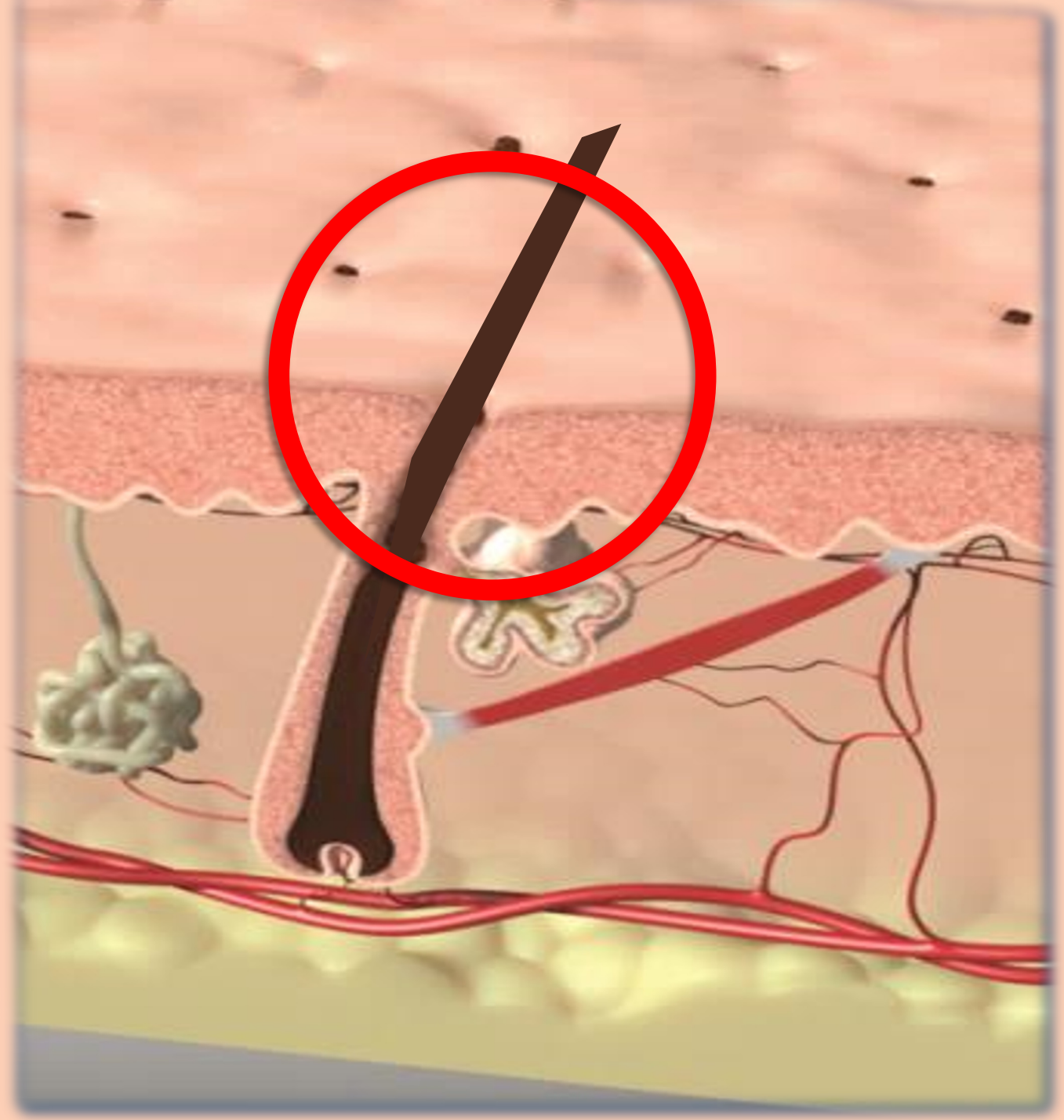
↓

IFNγ-driven inflammation (mediated by Janus kinase (JAK))

↓

Premature termination of the anagen phase leading to an acceleration of the follicle into the Catagen phase or telogen phase

Tosti A. Alopecia Areata: The Clinician and Patient Voice. J Drugs Dermatol. 2023 Oct 1;22(10):967-975. doi: 10.36849/JDD.SF396143. PMID: 37801523



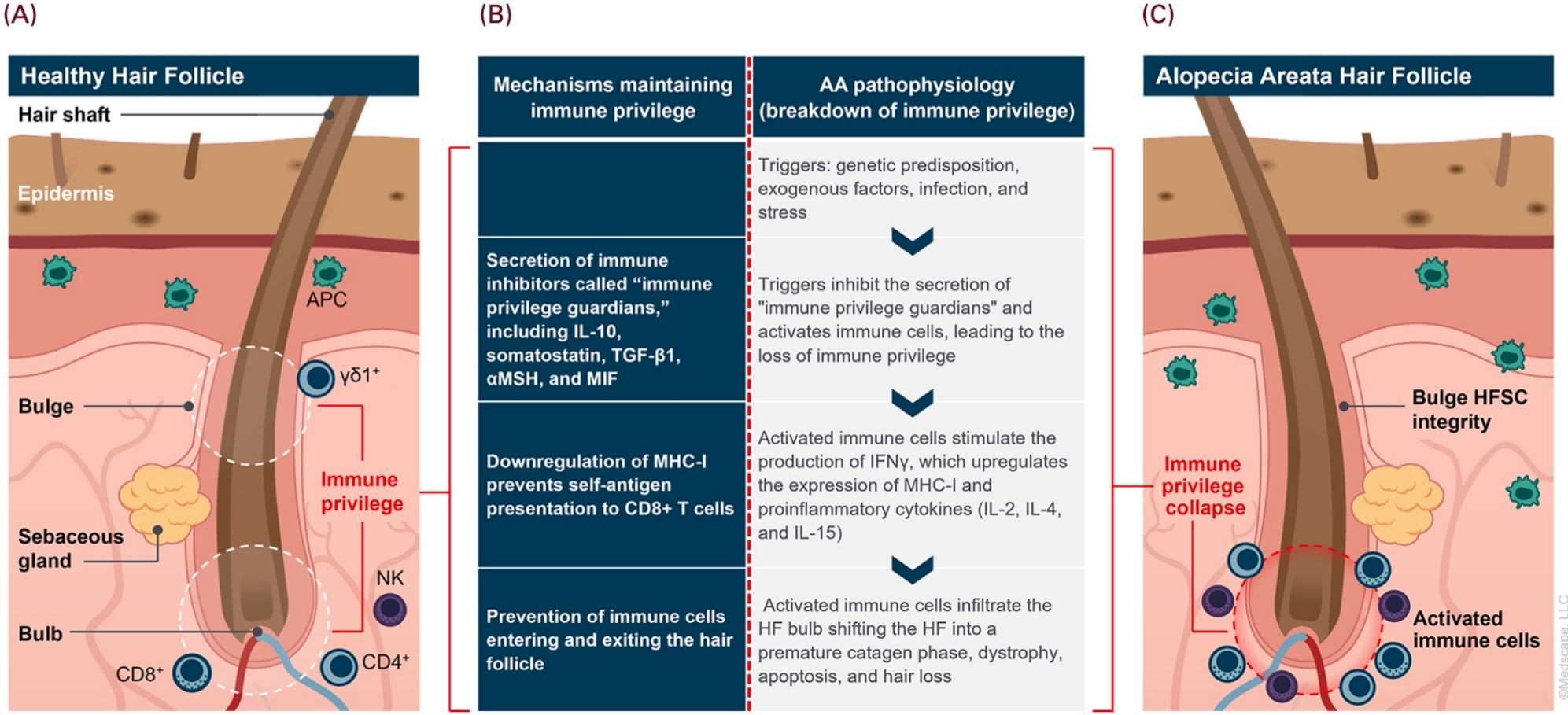
Alopecia areata is an autoimmune disease

Premature termination of the anagen (growing) phase of the hair

A lymphocytic infiltrate: **”swarm of bees”**

The perifollicular lymphocytes are the source of several **proinflammatory cytokines**

Summary of AA pathogenesis



Lintzeri DA, Constantinou A, Hillmann K, et al. Alopecia areata - Current understanding and management. *J Dtsch Dermatol Ges.* 2022;20:59–90. Copyright© 1999-2023 John Wiley & Sons, Inc. All rights reserved.

αMSH, melanocyte-stimulating hormone alpha; AA, alopecia areata; APC, antigen-presenting cell; HF, hair follicle; HFSC, hair follicle stem cell; IFNγ, interferon gamma; IL, interleukin; MHC-I, major histocompatibility complex I; MIF, migration inhibitory factor; NK, natural killer; TGF-β1, transforming growth factor beta-1.

- Tosti A. Alopecia Areata: The Clinician and Patient Voice. J Drugs Dermatol. 2023 Oct 1;22(10):967-975. doi: 10.36849/JDD.SF396143. PMID: 37801523.

systemic activation of the immune system

IFN-γ

IL-15

IL-6

IL-2

IL-17A

IL- 17F

IL-12

IL- 23

IFN-γ

IL-15

IL-2

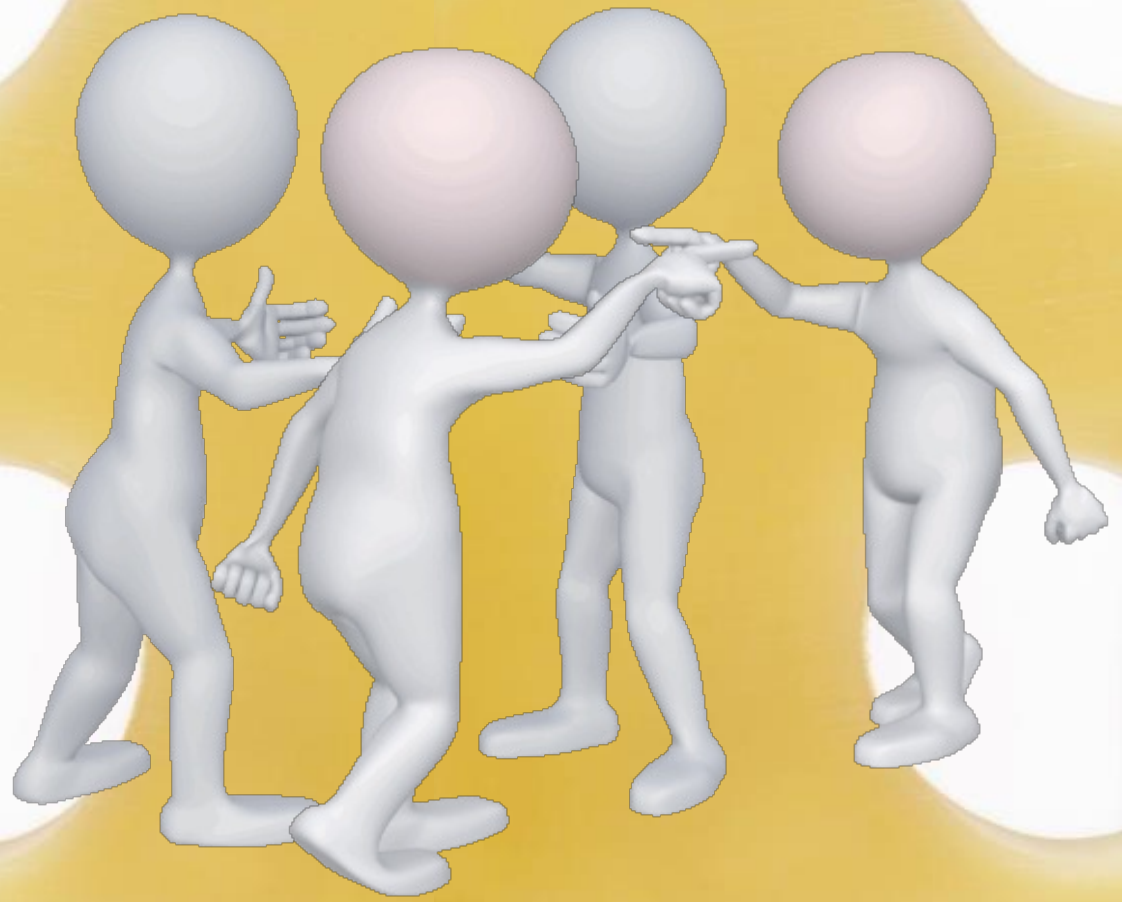
IL-17A

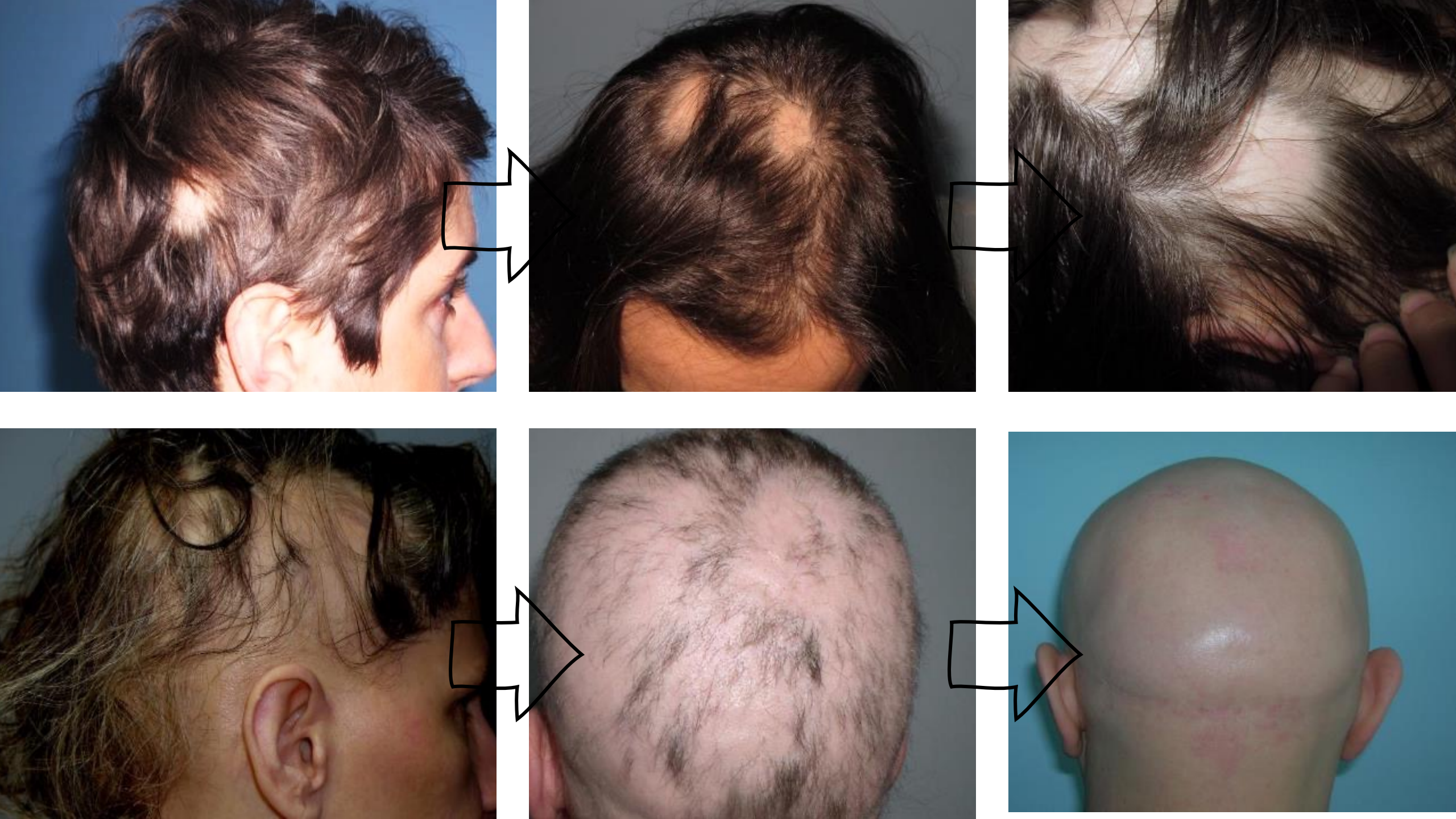
IL-2

TNF

IL-15

Many gaps in the knowledge about in the pathogenesis of alopecia areata





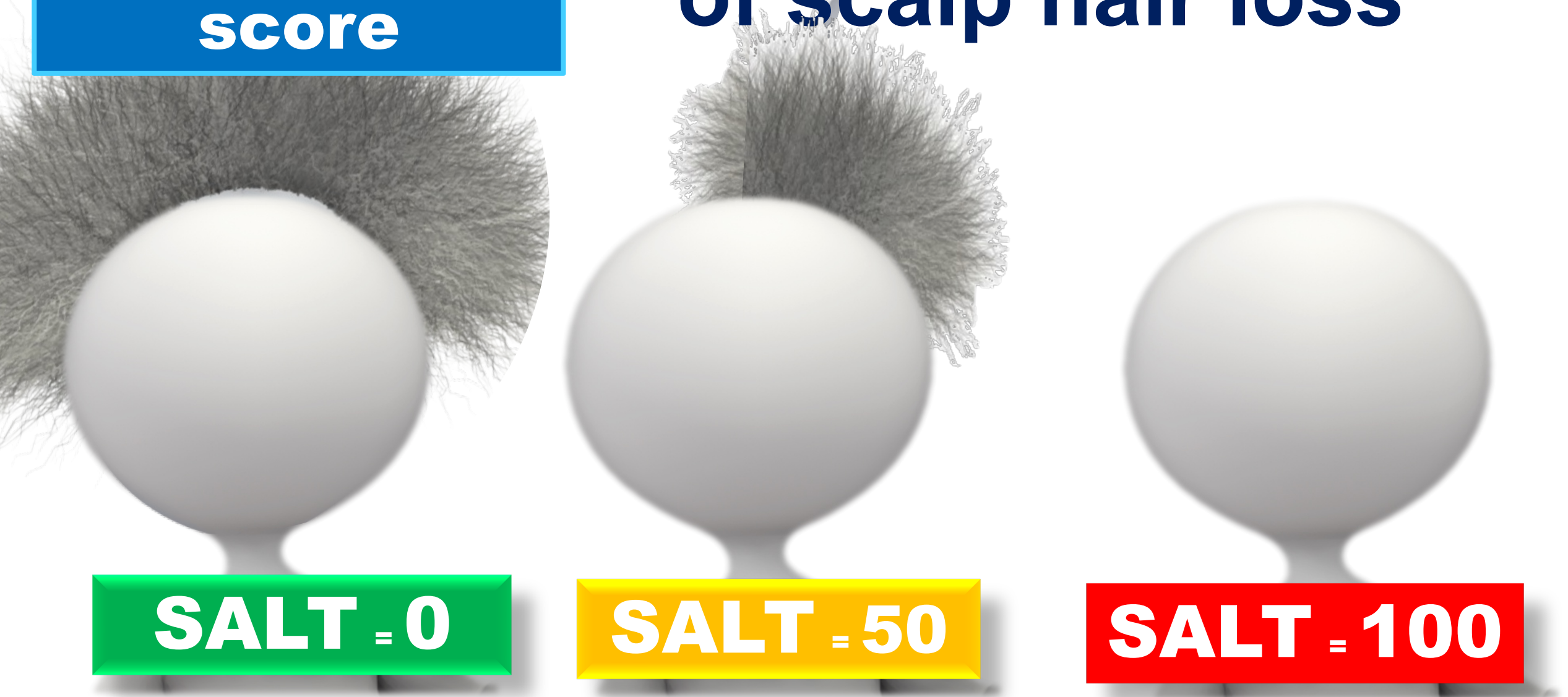
Measuring treatment efficacy

SALT score

Severity of **AL**opecia **T**ool

SALT score

= % percentage of scalp hair loss



SALT = 0

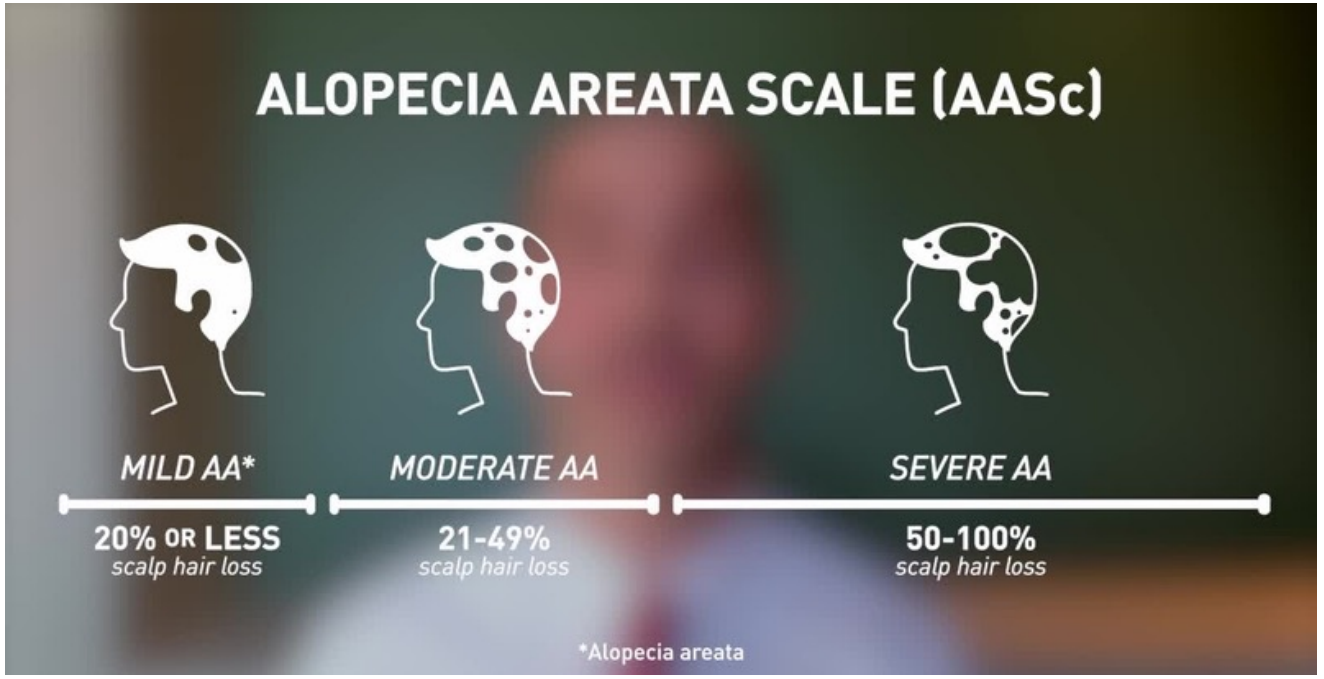
SALT = 50

SALT = 100

Alopecia Areata Scale (2022)

1. Mild — SALT ≤ 20%
2. Moderate — SALT 21-49%
3. Severe — SALT 50-100%

- **Negative** psychological impact
- **Loss** of eyelashes or eyebrows
- **No adequate** treatment response (6 months)
- **Diffuse** positive pull test



ALOPECIA AREATA SCALE (AASc)

A Multidimensional Assessment Tool for Clinical Use

ALOPECIA AREATA SCALE (AASc)

Primary Criterion—Severity of Scalp Hair Loss

Mild AA	Moderate AA	Severe AA
20% or less scalp hair loss	21-49% scalp hair loss	50-100% scalp hair loss

Secondary Criteria

- Negative impact on psychosocial functioning resulting from AA
- Noticeable involvement of eyebrows or eyelashes
- Inadequate response after at least 6 months of treatment
- Diffuse (multifocal) positive hair pull test consistent with rapidly progressive AA

If any secondary criteria are present, increase severity rating by one level.

Several unidimensional assessments are used in Alopecia Areata (AA), including those that measure the percentage of scalp hair loss or extent of eyebrow or eyelash involvement. However, they do not fully characterize the clinical spectrum of disease severity and its manifestations. **To facilitate a more comprehensive assessment of disease severity in AA, eyebrow and eyelash involvement, treatment-refractory disease, rapid progression, and psychosocial impact should also be considered.**

Clinical Scale for Assessing Severity in AA

The Alopecia Areata Scale (AASc) is a multidimensional assessment tool designed to more effectively and consistently evaluate the severity of AA in clinical practice.

Developed by a consensus of 22 disease area experts and unanimously endorsed, the AASc incorporates exam findings and elements of patient history into a descriptive severity rating that is relevant to clinical practice. It prioritizes the amount of scalp hair loss as the primary determinant of disease severity in AA. The severity rating increases if any of the secondary criteria are present (see table above).

Assessing Psychosocial Impact in AA

The psychosocial impact of disease is frequently mentioned by patients with AA during clinical encounters. Direct questioning may be helpful in cases where this is less clear.

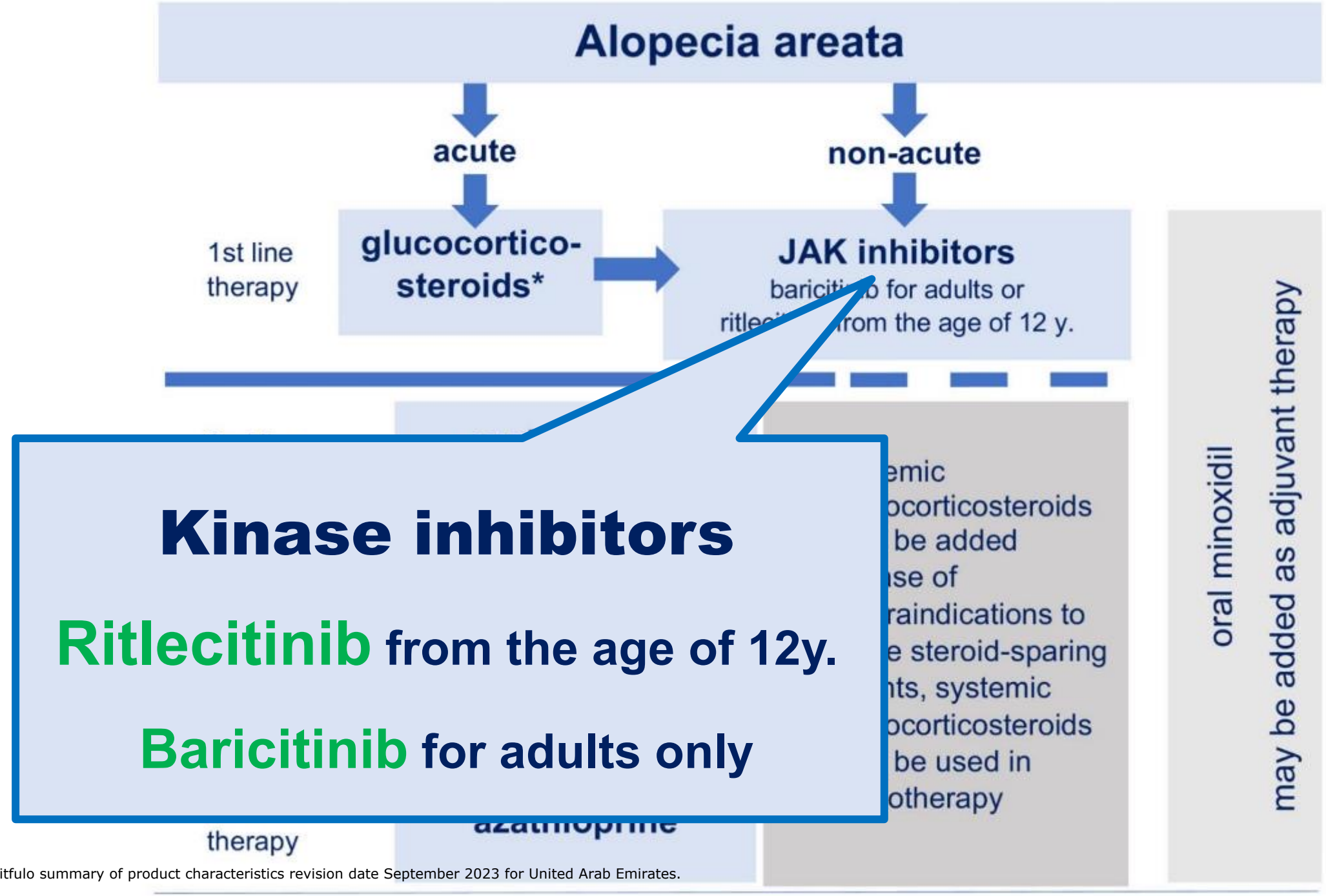
How would you rate the impact of AA on your quality of life on a scale of 0 (none) to 10 (very negative impact)? Scores of 6 or above are indicative of a significant psychosocial impact.

How has AA affected your daily activities? Age-related activities (i.e., school, sports, interaction with peers, job performance, dating, and relationships) may also demonstrate psychosocial impact.

Scan to learn more about the AASc from International Thought Leaders

SALT ≤ 20 is considered by some experts the treatment goal

(Alternative: SALT ≤ 10)



Litfulo summary of product characteristics revision date September 2023 for United Arab Emirates.

Rudnicka et al. JEADV 2024

EMA/FDA approved JAK/kinase inhibitors

Ritlecitinib (JAK 3 / TEC)

- 50 mg/d
- adults
- children ≥ 12 y.o.

Baricitinib (JAK 1 / JAK 2)

- 4 mg/d
- adults

Thank you