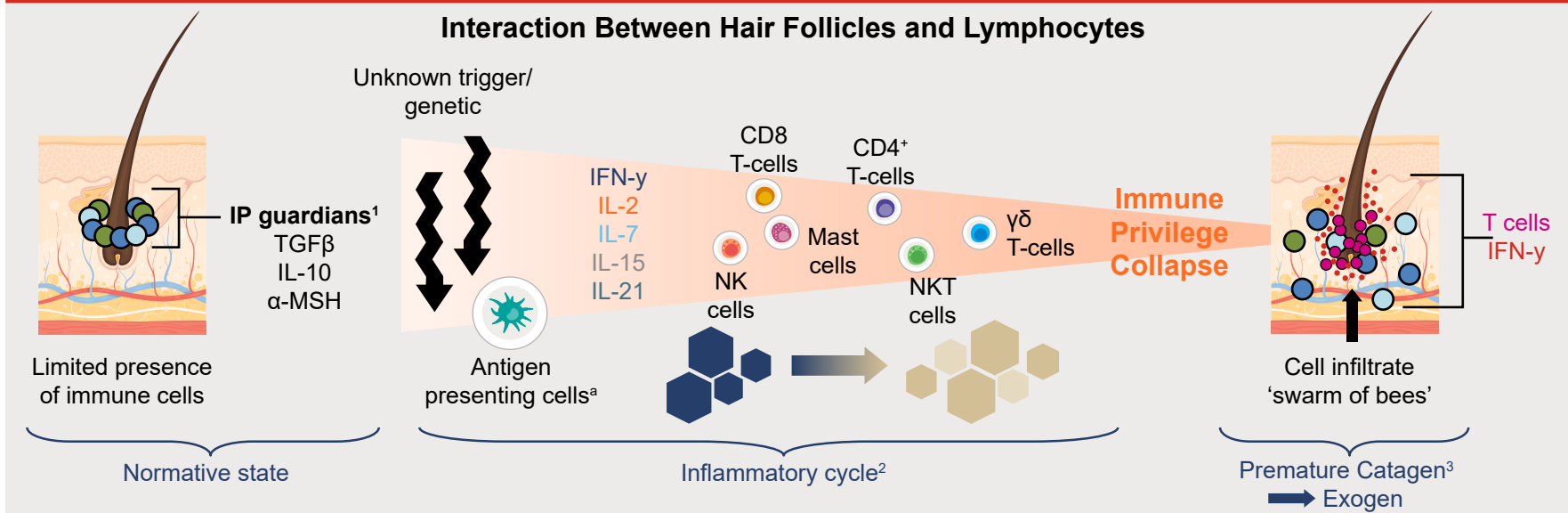
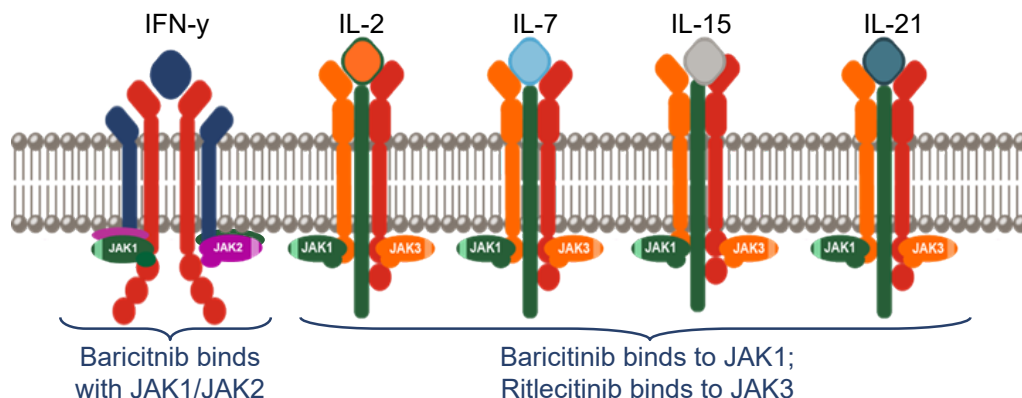


Mechanism of Action of JAK Inhibitors in Alopecia Areata

Alopecia Areata Results from Collapse of the Immune Privilege in Hair Follicle



JAK Inhibitors Reduce Inflammation by Regulating Cytokines that Communicate through the JAK-STAT Pathway⁴⁻⁷



Ritlecitinib also binds to the TEC family of kinases through the cysteine site shared by both JAK3 and TEC kinases^{8,9}

TEC Family

BMX Bone marrow X kinase

BTK Bruton's tyrosine kinase

ITK Interleukin-2 inducing T cell kinase

RLK Resting lymphocyte kinase

TEC Tyrosine protein expressed in hepatocellular carcinoma

The role of the TEC family of kinases has not been established in AA

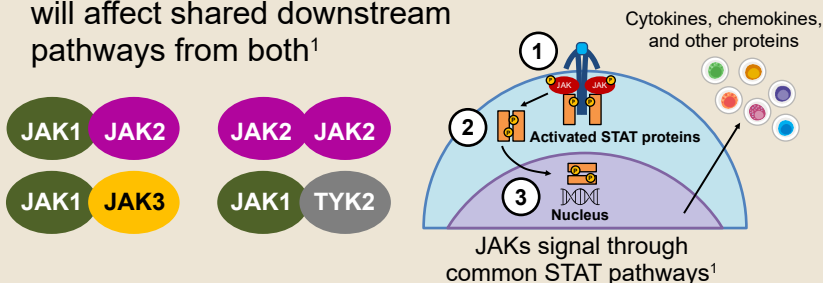
^aAntigen presenting cells may be dendritic, macrophages, T-cells, or other unknown cells. α-MSH=Alpha-Melanocyte-Stimulating Hormone; γδ=Gamma Delta; AA=Alopecia Areata; CD=Cluster of Differentiation; IFN-γ=Interferon Gamma; IL=Interleukin; IP=Immune Privilege; JAK=Janus Kinase; JAK-STAT=Janus Kinase-Signal Transducers and Activators of Transcription; NK=Natural Killer; NKT=Natural Killer T; TEC=Hepatocellular Carcinoma; Th=T-Helper; TGFβ=Transforming Growth Factor Beta; TNF=Tumor Necrosis Factor.

1. Lensing M, Jabbari A. *Front Immunol.* 2022;13:955035. 2. Divito SJ, Kupper TS. *Nat Med.* 2014;20(9):989-990. 3. Bertolini M, et al. *Exp Dermatol.* 2020;29(8):703-725. 4. Triyankulsri K, Suchonwanit P. *Review Drug Des Devel Ther.* 2018;12:2323-2335. 5. O'Shea JJ, Plenge R. *Immunity.* 2012;36(4):542-550. 6. O'Shea JJ, et al. *Annu Rev Med.* 2015;66:311-328. 7. King B, et al. *N Engl J Med.* 2022;386(18):1687-1689. 8. Xu H, et al. *ACS Chem Biol.* 2019;14(6):1235-1242. 9. Ramirez-Marín HA, Tosti A. *Drug Des Devel Ther.* 2022;16:363-374.

Understanding Selectivity in Context of JAK Inhibitor Therapies

What is Selectivity & How Does it Impact Therapy?

JAK **receptors** signal in **pairs** – selectivity for either will affect shared downstream pathways from both¹



JAK inhibitors target specific pathways with broad relevance

“Targeting the Inflammatory Milieu”



Broad pathways:

- General immunosuppression
- Examples: steroids, cyclosporine

Selective receptors:

- Modulated immunotherapy
- Examples: JAK-STAT pathway, JAK inhibitors

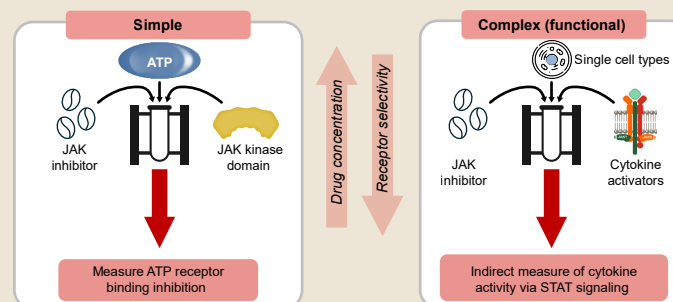
Specific molecule:

- Modulated immunotherapy
- Examples: monoclonal antibodies

JAK **selectivity** is NOT the same as **specificity** related to monoclonal biologics

How is selectivity determined?

By various laboratory assays, selectivity is assigned and will vary based on **type and complexity of assay** and **drug concentration**²⁻⁴



What are the limits of selectivity?

Metabolism

Pharmacokinetics

Pharmacodynamics

Drug absorption

Human body more complex than assays

Regulatory labeling:
“The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known”

Efficacy and safety outcomes ultimately reflect a drug's clinical effects

^aTYK2 is not TEC.

ATP= Adenosine Triphosphate; JAK=Janus Kinase; JAK-STAT=Janus Kinase-Signal Transducers and Activators of Transcription; STAT=Signal Transducers and Activators of Transcription; TYK2=Tyrosine Kinase 2.

1. Passeron T, et al. *Front Immunol.* 2023;14:1243556. 2. Fridman JS, et al. *J Immunol.* 2010;184(9):5298-5307. 3. Schwartz DM, et al. *Nat Rev Drug Discov.* 2017;16(12):843-862. 4. Yamaoka K, et al. *Genome Biol.* 2004;5(12):253.



Lilly