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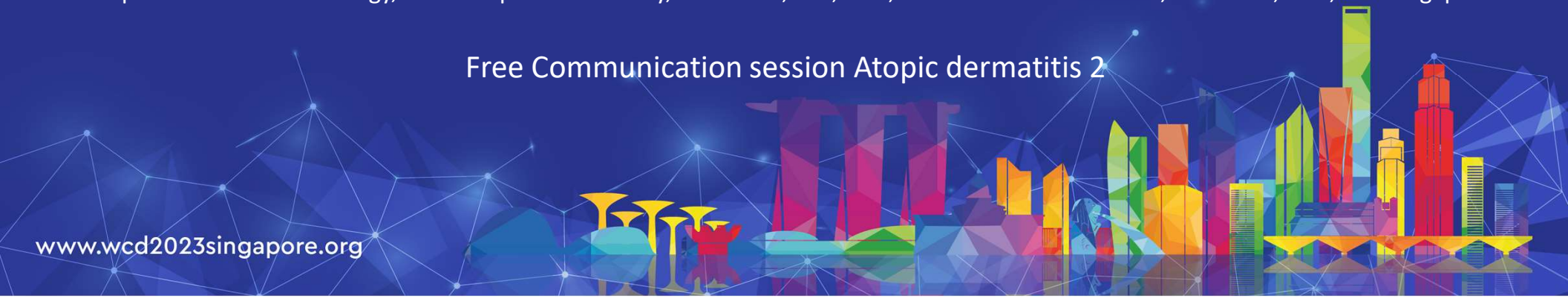
ILDS

IL-13Rα1 Signaling in Atopic Dermatitis

Sriya V. Reddy[1], Zachary Bordeaux[1], Ahmed Rajeh[2], Jackson Adams[1], Ferda Cevikbas[3], Shawn G. Kwatra[2], Madan M. Kwatra[1]

[1]Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA;
[2]Department of Dermatology, Johns Hopkins University, Baltimore, MD, USA; [3]ASLAN Pharmaceuticals, California, USA, and Singapore

Free Communication session Atopic dermatitis 2



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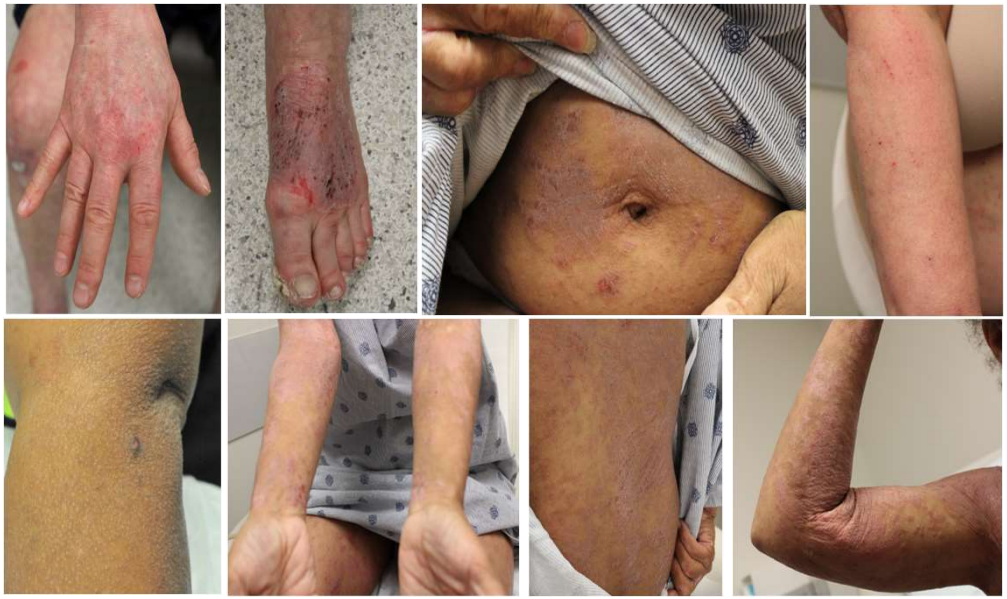
Disclosures

Dr. Ferda Cevikbas is an employee of ASLAN Pharmaceuticals.

Dr. Shawn G. Kwatra is an advisory board member/consultant for Abbvie, ASLAN Pharmaceuticals, Arcutis Biotherapeutics, Celldex Therapeutics, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi.

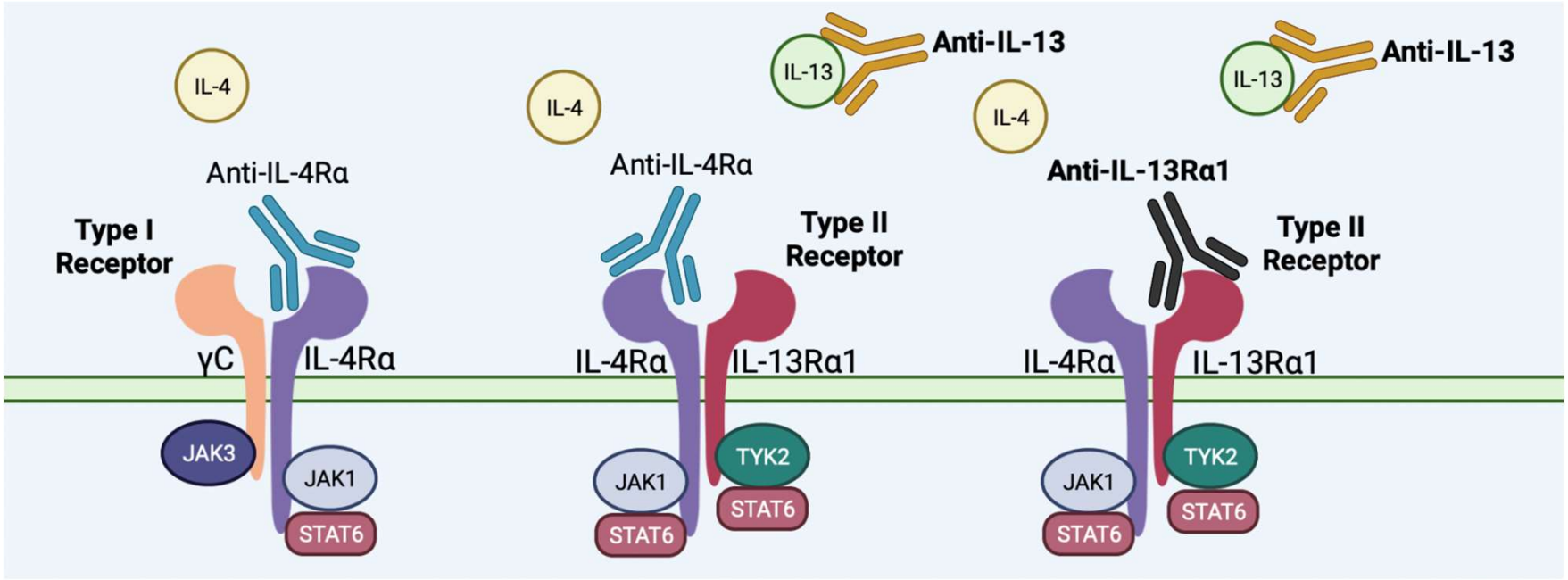
IL-13 and IL-4 cytokines are key to atopic dermatitis pathogenesis



- Both drive itch, inflammation, and skin barrier disruption
- IL-13 presents at higher levels in the skin and serum of patients with atopic dermatitis (AD)
- IL-4 and IL-13 signal through **Type 2 receptor** (composed of IL-4Rα and IL-13Rα1) whereas IL-4 also engages the **Type 1 receptor** (composed of IL-4Rα and the common gamma chain)

AD, atopic dermatitis; IL, interleukin, IL-4Rα, interleukin-4 receptor alpha; IL-13Rα1, interleukin-13 receptor subunit alpha 1.

Eblasakimab targets IL-13Rα1, blocking IL-4 and IL-13 via the Type 2 receptor while sparing the Type 1 receptor



IL-13Rα1, interleukin-13 receptor subunit alpha 1; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase.

What is the role of IL-13Rα1 in AD? What is the differential signaling between the Type 1 and Type 2 receptor pathways?

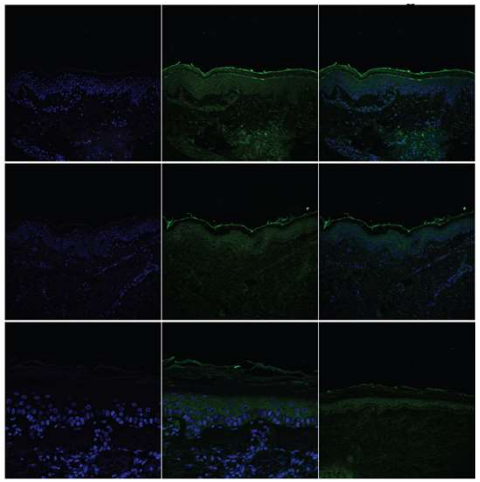
Determine the **expression pattern of IL-13Rα1** in lesional and non-lesional skin in patients with AD

Compare **RNA & protein profiles** upon Type 1 vs Type 2 receptor blockade

Analyze **Th1 and Th2 cytokine levels** upon IL-4Rα vs IL-13Rα1 receptor blockade

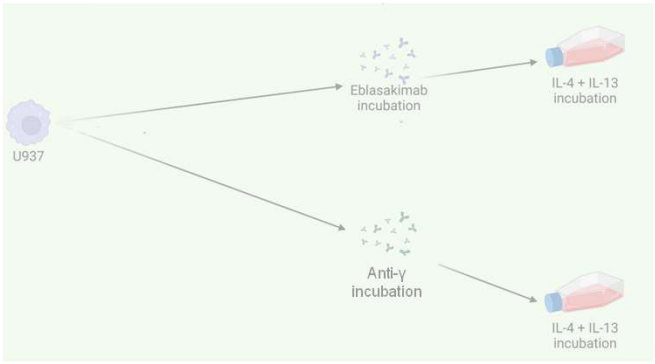
Methods

IL-13Rα1 expression pattern in lesional and non-lesional AD skin



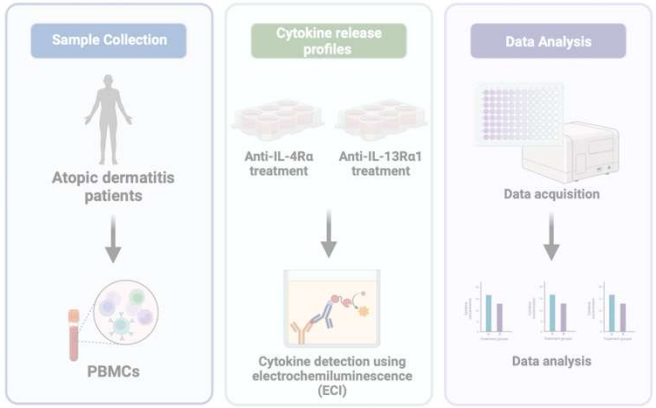
Immunohistochemistry was performed on skin from 14 AD patients and 10 matched healthy controls. Samples were stained for markers of sensory nerves, mast cells and eosinophils.

RNA and protein expression profiles upon Type 1 vs Type 2 receptor blockade



U937 monocytic cells were incubated with monoclonal antibodies to block Type 1 and 2 receptor components. Cells were subjected to RNA-seq or reverse phase protein array.

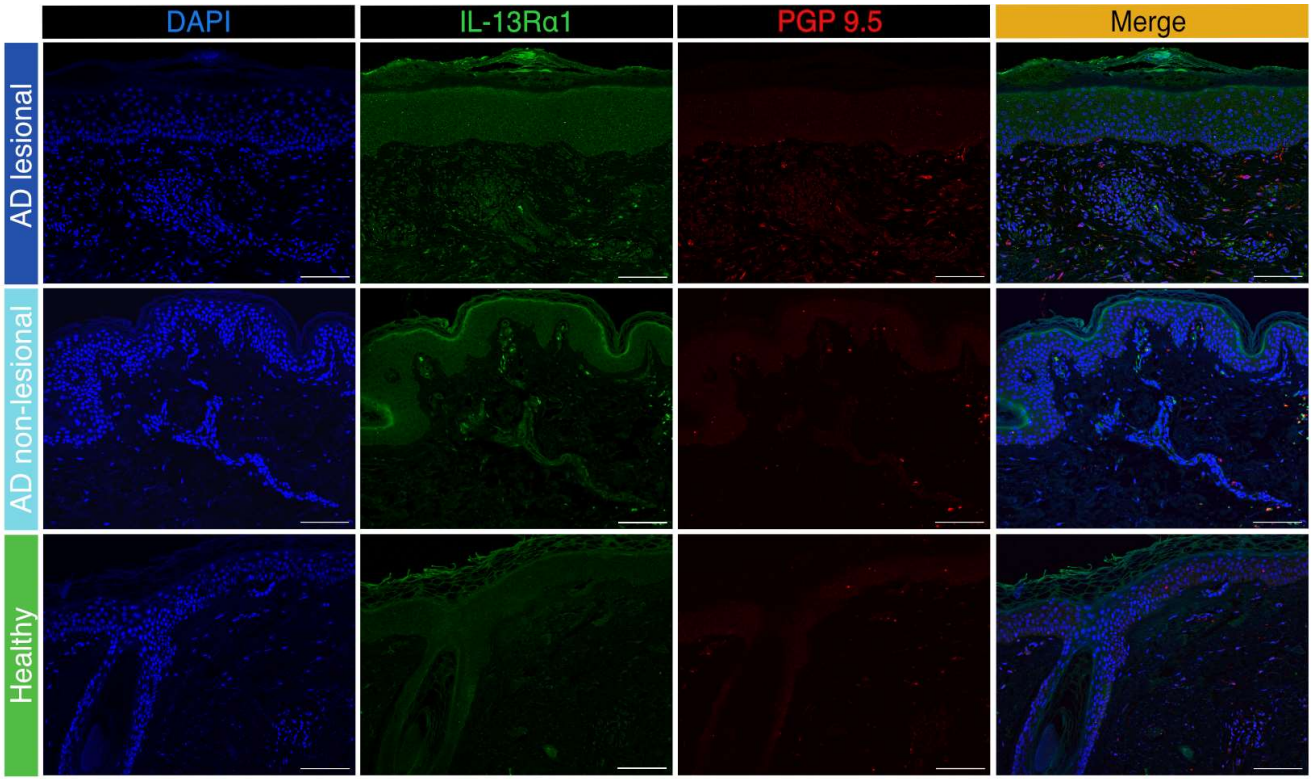
Comparison of Th1 and Th2 cytokine levels observed with anti-IL-4Rα vs eblasakimab

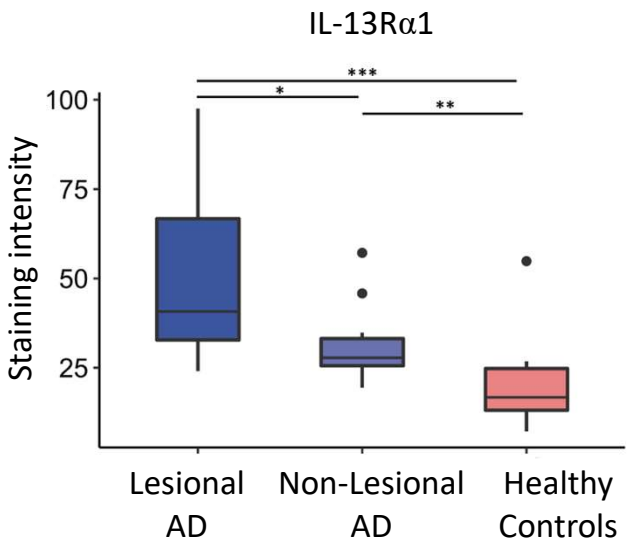


PBMCs obtained from 10 patients with AD were treated with either anti-IL-13Rα1 (eblasakimab) or anti-IL-4Rα (R&D Systems). The MesoScale Discovery platform was used to measure levels of cytokines.

PBMC, peripheral blood mononuclear cells.

IL-13Rα1 expression is higher in skin of patients with AD vs healthy controls



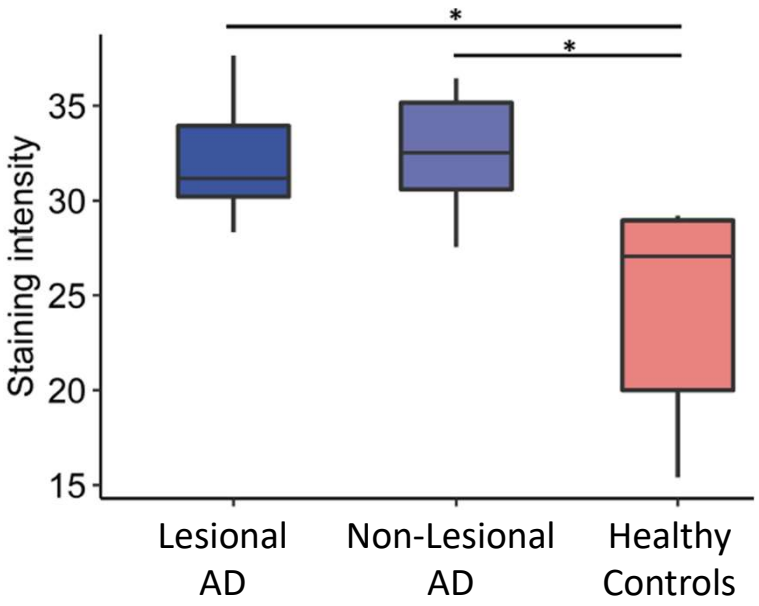


*P<0.05; **P<0.01; ***P<0.001

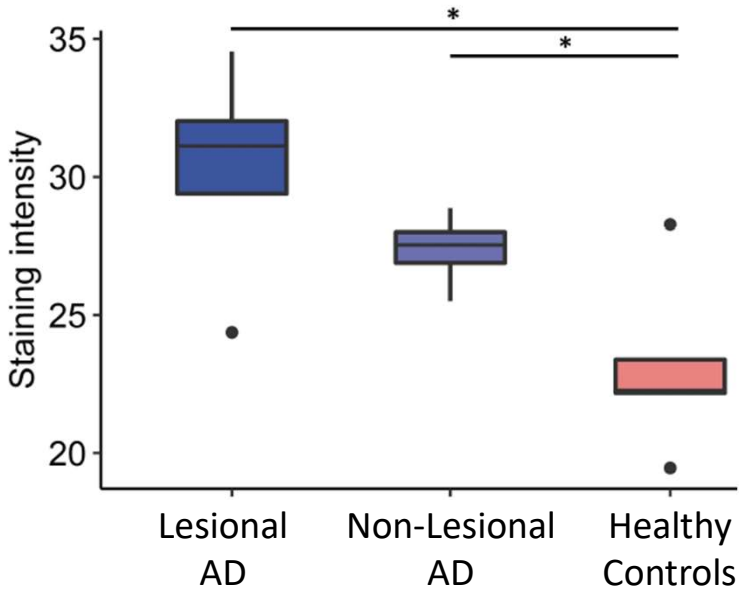
DAPI, 4',6-diamidino-2-phenylindole; PGP9.5, protein gene product 9.5.

IL-13Rα1 expression is higher in mast cells and eosinophils in the skin of patients with AD vs healthy controls

IL-13Rα1 in Mast Cells



IL-13Rα1 in Eosinophils



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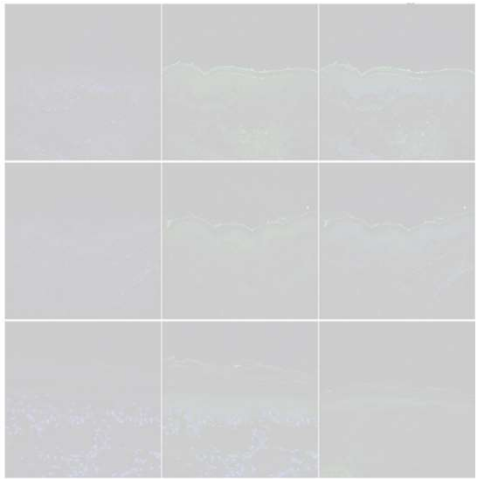
Methods

IL-13Rα1 expression pattern in lesional and non-lesional AD skin



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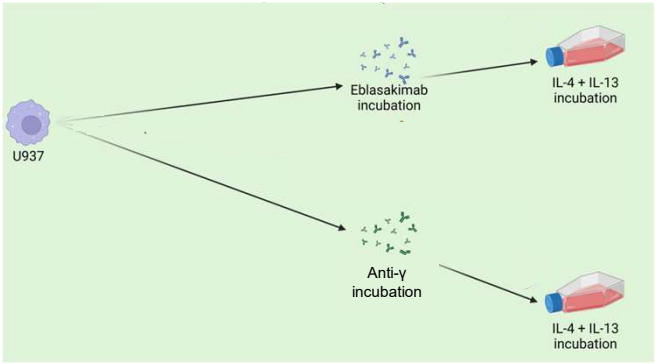

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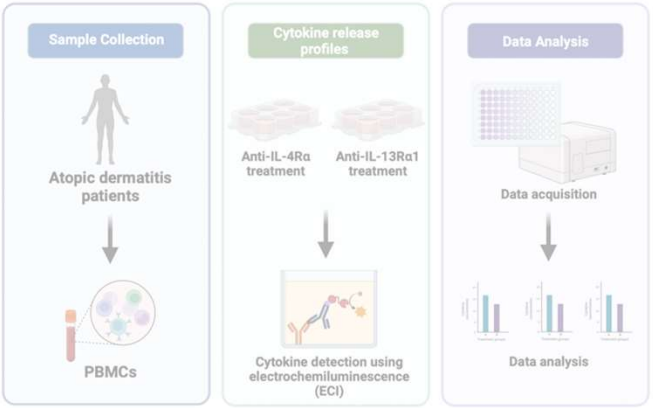

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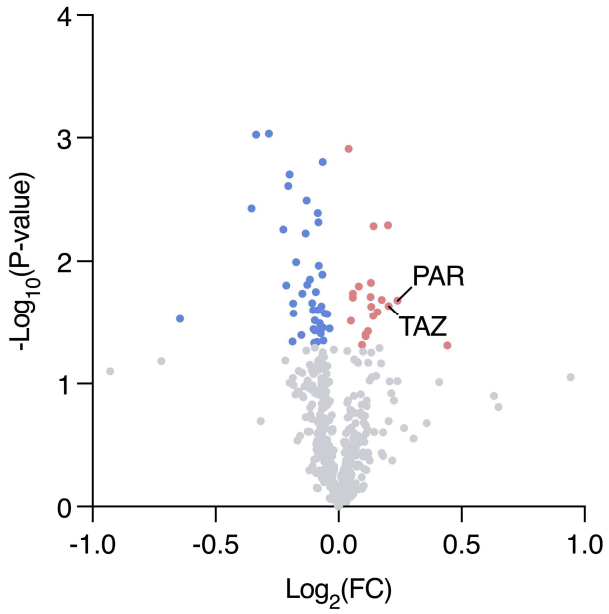
PBMC, peripheral blood mononuclear cells.

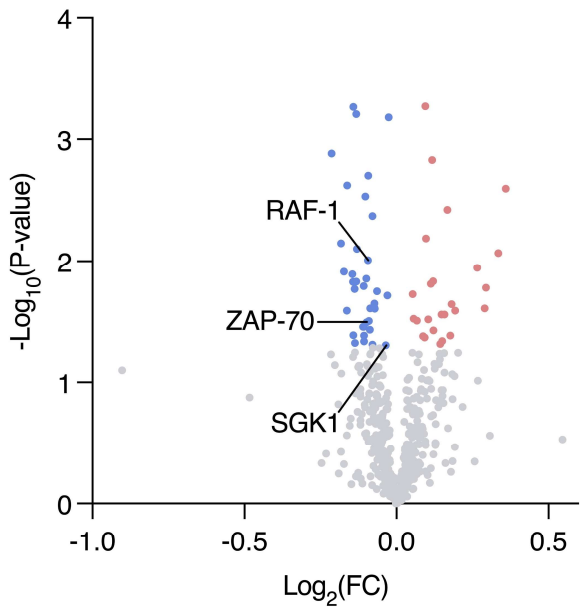
Differential protein expression was observed with blockade of the Type 1 vs Type 2 receptor in monocytes

Type 1 receptor blockade with anti-common γ chain[a]



Type 1 receptor blockade **upregulated** PAR and TAZ, proteins implicated in promoting inflammation and pruritus

Type 2 receptor blockade with eblasakimab



Type 2 receptor blockade **suppressed** ZAP70 and RAF1 (enhance nerve growth factor production) and SGK1 (promotes sodium-rich environment)

[a]R&D systems.

Methods

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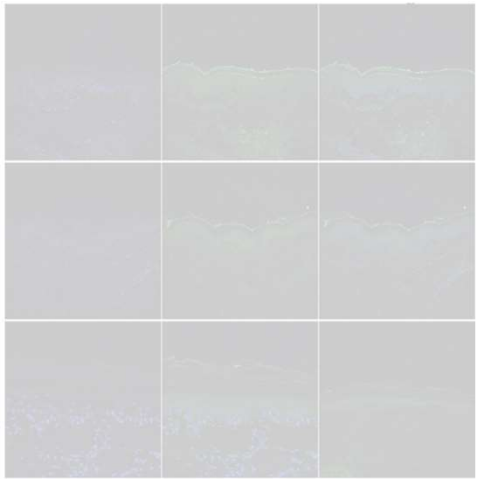

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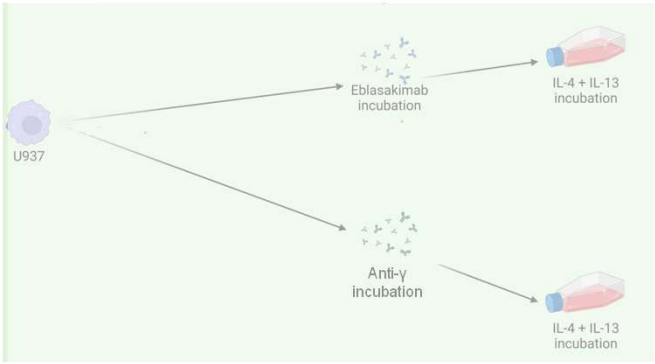

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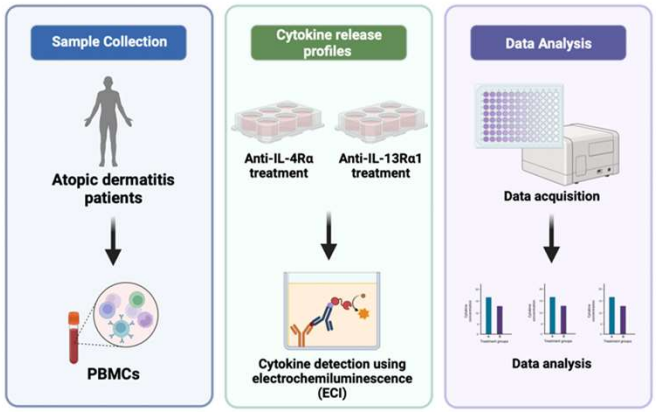

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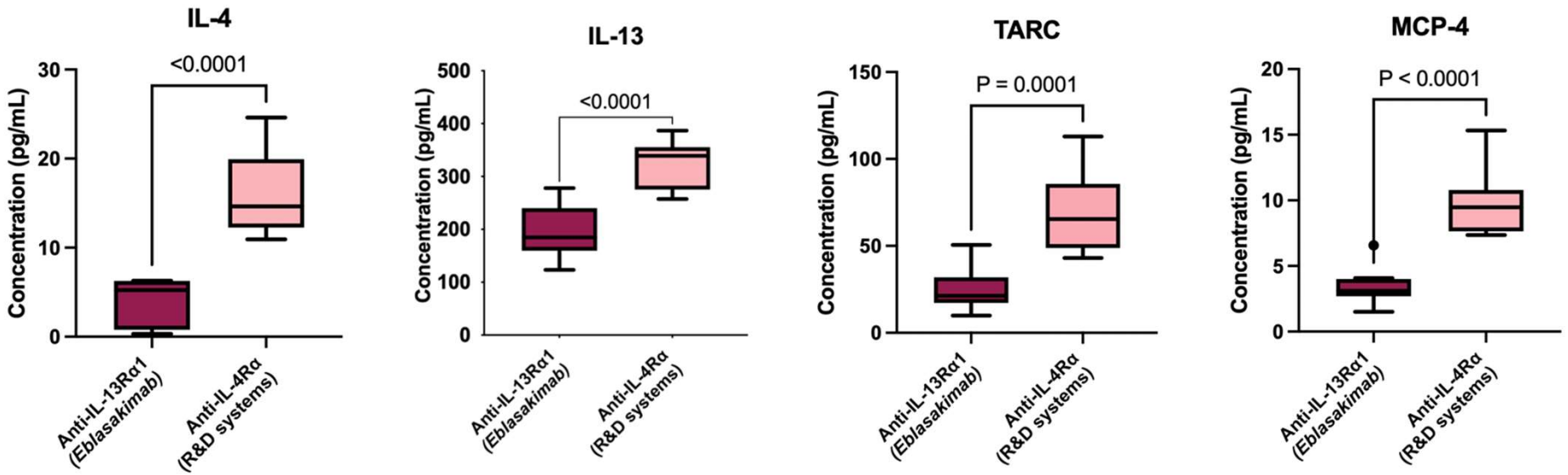
PBMC, peripheral blood mononuclear cells.

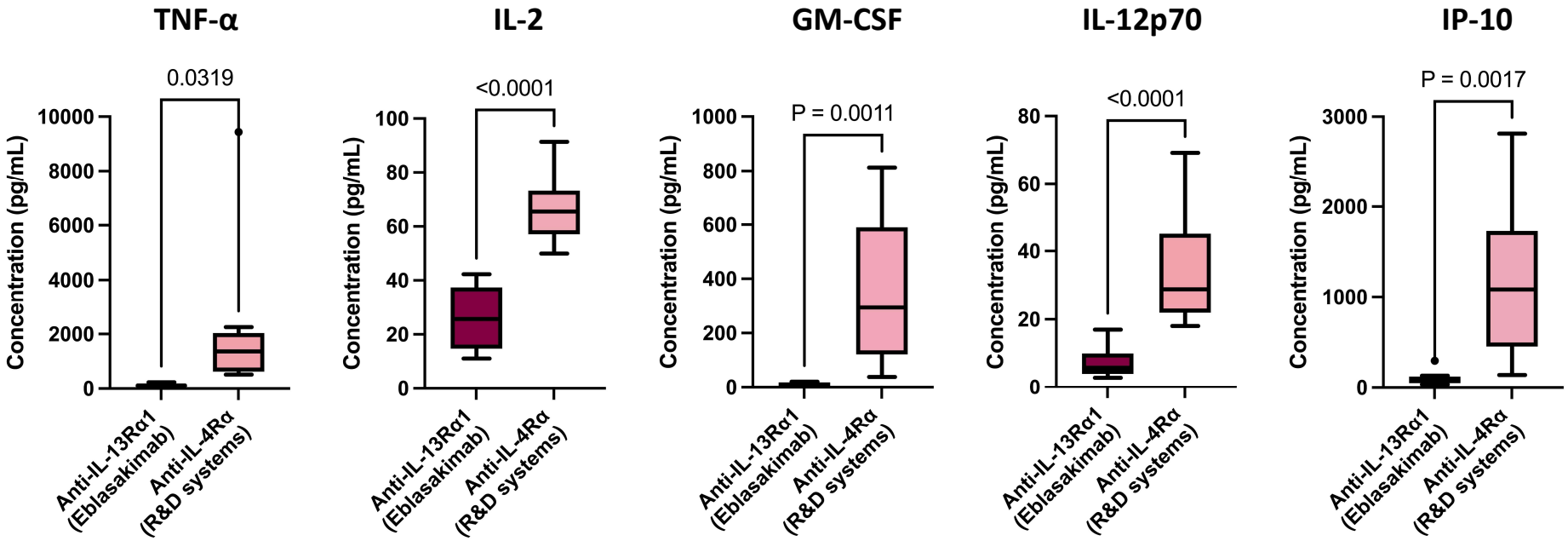
IL-13Rα1 blockade results in lower levels of key cytokines implicated in Th2-driven inflammation compared to IL-4Rα blockade



MCP, monocyte chemoattractant protein; TARC, thymus activation regulated chemokine.

[a]Antibody targeting IL4Rα supplied by R&D Systems. Demonstrated to block IL-4 and IL-13 signaling through Type 1 and Type 2 receptors.

IL-13Rα1 blockade prevents subsequent expression changes of Th1 cytokines



GM-CSF, granulocyte-macrophage colony-stimulating factor; IP, Interferon gamma-induced protein; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.
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Clinical Significance

These results suggest that ***targeting different subunits of the same molecular pathway*** can lead to different clinical outcomes

Selective blockade of the IL-13Rα1 subunit by eblasakimab is a promising therapeutic approach compared to IL-4Rα blockade as it does **not increase levels of Th1 and Th2 cytokines**

Eblasakimab may offer a **differentiated therapeutic approach** to treat AD by **sparing the Type 1 receptor** and the effects seen with targeting IL-4Rα

Acknowledgments