Downstream effects of IL-13Rα1 blockade on Th2-driven inflammation and Th1 immune axis activation in atopic dermatitis

Sriya V. Reddy[1], Zachary Bordeaux[1], Ahmad Rajeh[2], Darshan Sivaloganathan[2], Hannah Cornman[2], Anusha Kambala[2], Jackson Adams[1], Carl Firth[3], Ferda Cevikbas[3], Shawn G. Kwatra[2], Madan M. Kwatra[1]

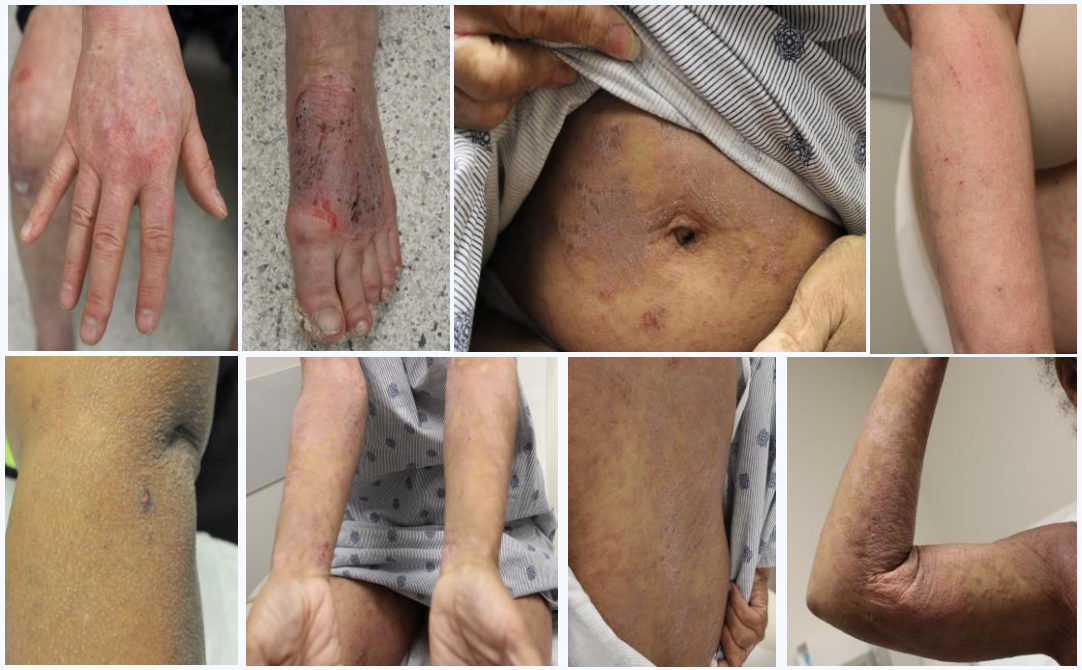
[1]Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA
[2]Department of Dermatology, Johns Hopkins University, Baltimore, MD, USA
[3]ASLAN Pharmaceuticals, San Mateo, California, USA, and Singapore

Disclosures

Drs. Ferda Cevikbas and Carl Firth are employees 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.

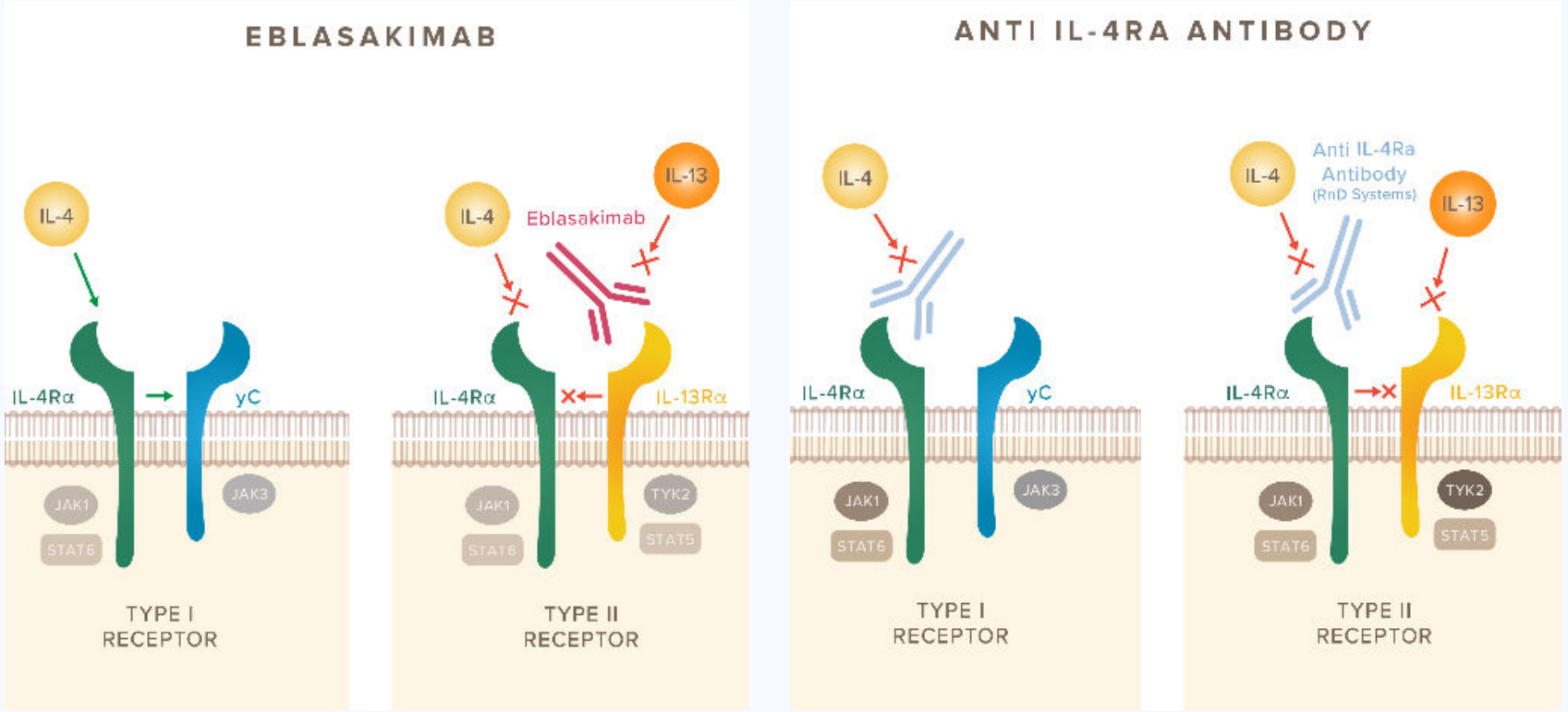
IL-4 and IL-13 cytokines are key to atopic dermatitis pathogenesis



- 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 the **Type 2 receptor** (IL-4Rα and IL-13Rα1) whereas IL-4 also engages the **Type 1 receptor** (IL-4Rα and common γ 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

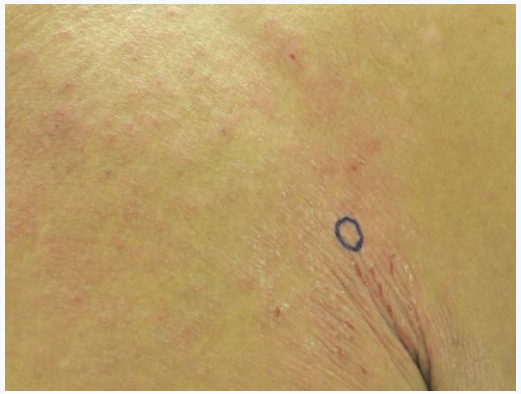
Analyze **Th1 and Th2 cytokine levels** upon IL-4Rα vs IL-13Rα1 receptor blockade

Study cohort demographic information

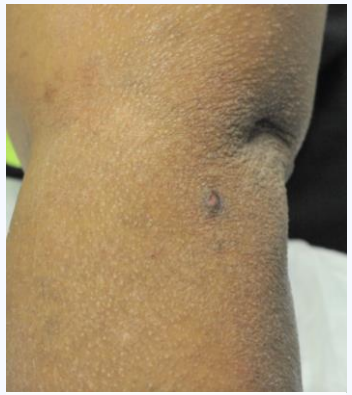
Patient with AD	Age	Sex	Race	Itch NRS	Disease Severity Score
1 AD	59	M	White	10	IGA: 4, SCORAD: 84.3
2 AD	24	F	AA	10	IGA: 4, SCORAD: 63.45
3 AD	25	F	White	7	IGA: 3, SCORAD: 40
4 AD	70	F	AA	10	IGA: 4, SCORAD: 49
5 AD	69	F	AA	10	IGA: 2, SCORAD: 21.2
6 AD	53	M	AA	9	IGA: 4, SCORAD: 35.5
7 AD	23	F	White	10	IGA: 4, SCORAD: 28.9
8 AD	60	F	White	10	IGA: 3, SCORAD: 41.5
9 AD	56	F	White	10	IGA: 4, SCORAD: 77
10 AD	60	F	AA	10	IGA: 4, SCORAD: 75.7

AA, African American; AD, atopic dermatitis; IGA, Investigator's Global Assessment Scale; NRS, Numerical Rating Scale; SNORAD, SCORing Atopic Dermatitis.

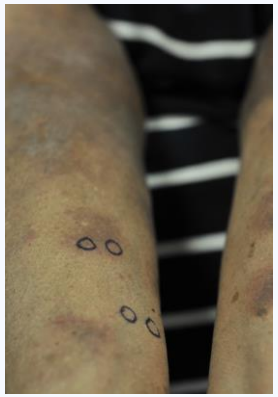
Study cohort patient photos



Patient: 1 AD

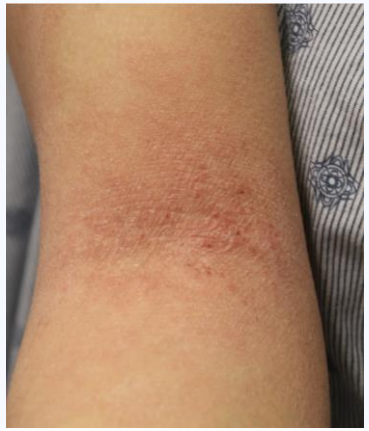


Patient: 2 AD



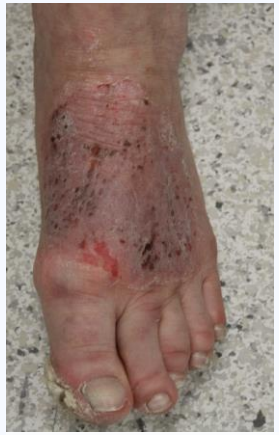
Patient: 5 AD

Patient: 6 AD



Patient: 7 AD

Patient: 8 AD



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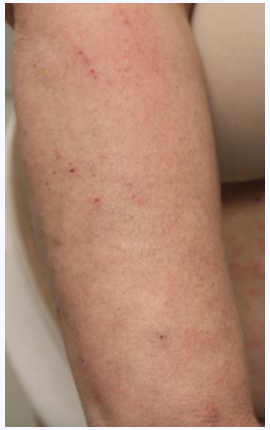
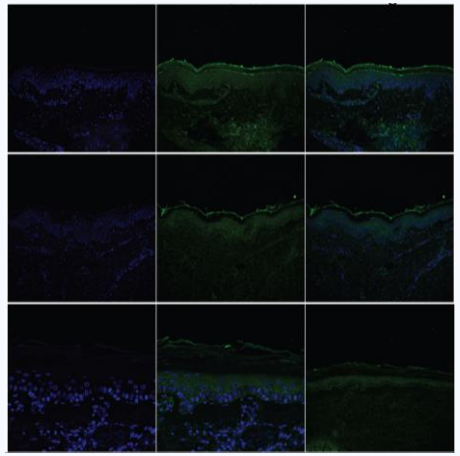


Patient: 9 AD

Photos courtesy of Shawn Kwatra, MD

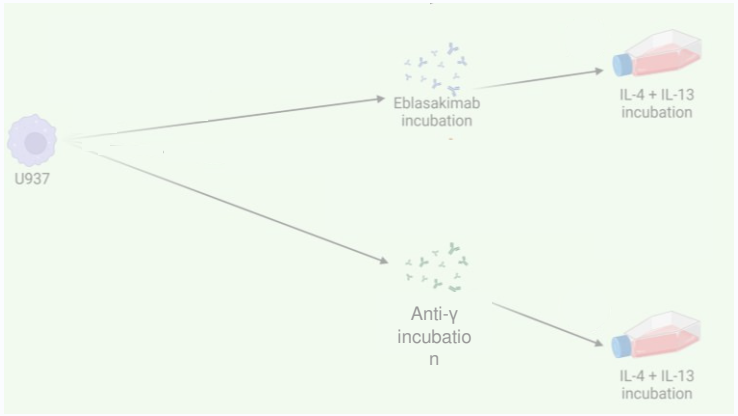
Methods

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



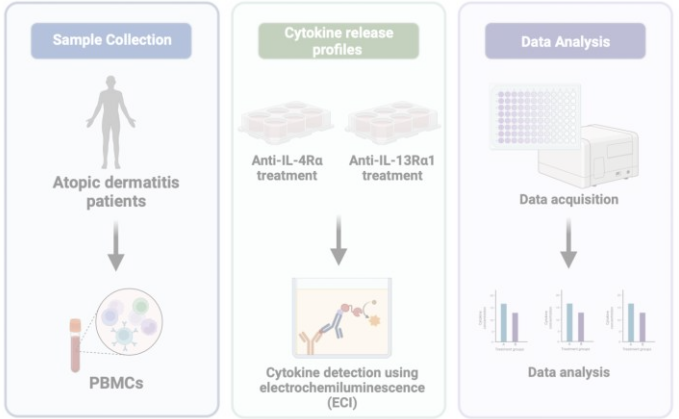
Skin samples from 14 patients with AD and 10 healthy controls were analyzed for IL-13Rα1 expression in sensory nerves, mast cells and eosinophils.

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.

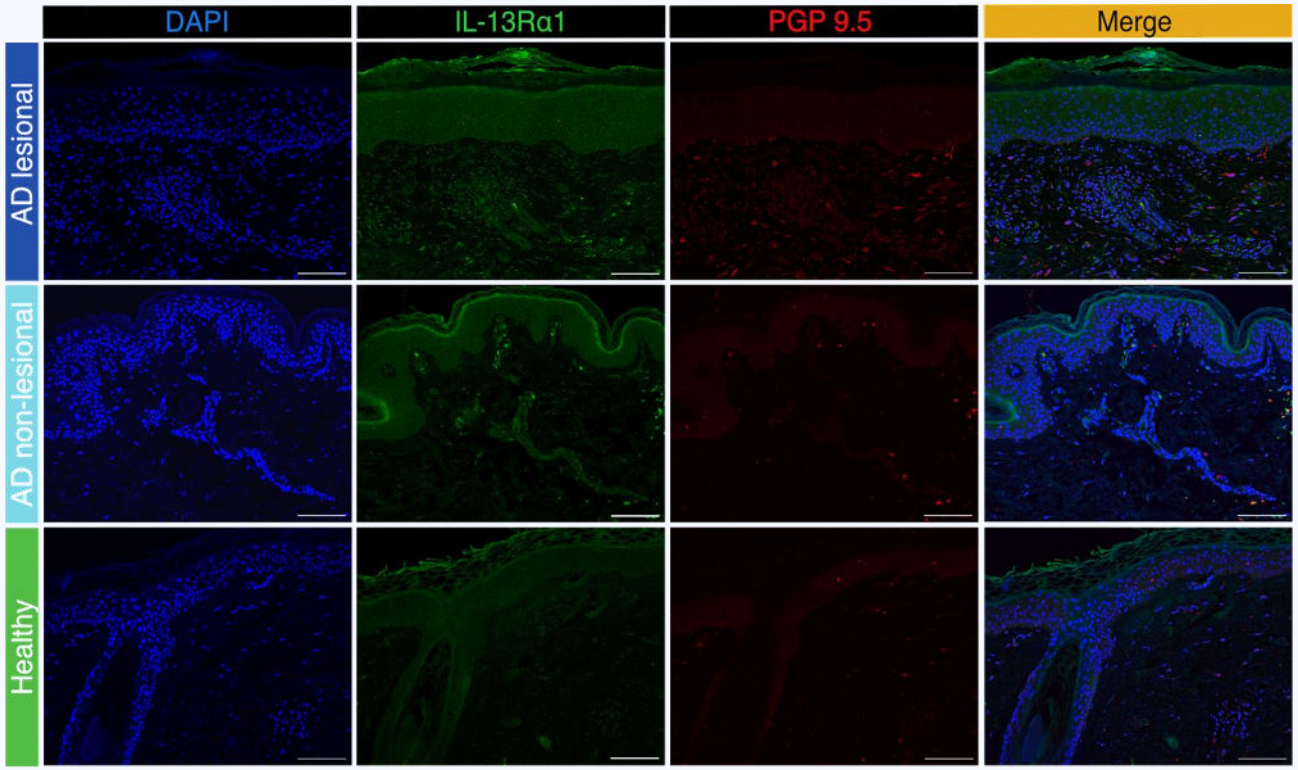
Comparison of Th1 and Th2 cytokine levels with anti-IL-4Rα vs eblasakimab

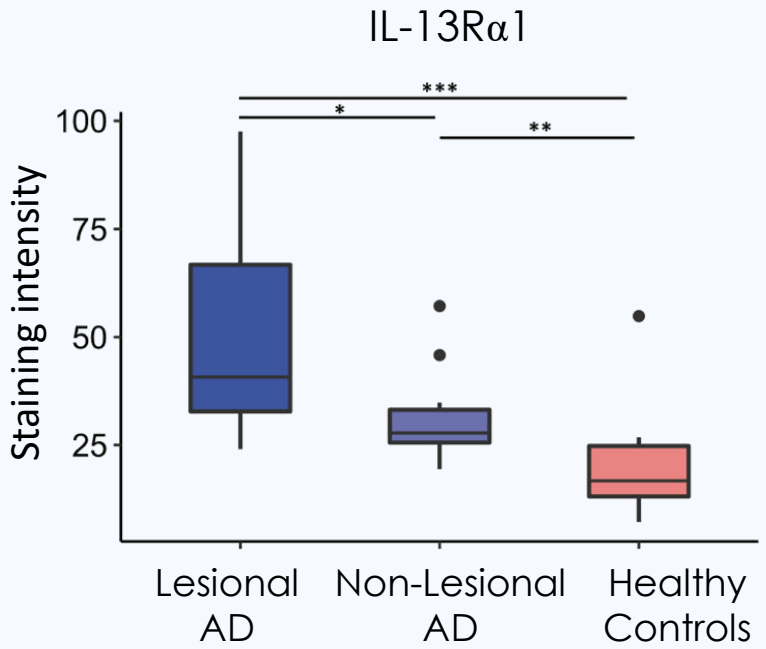


PBMCs obtained from 10 patients with AD were treated with anti-IL-13Rα1 (eblasakimab) or anti-IL-4Rα. Cytokine levels were measured with the MesoScale Discovery platform.

PBMC, peripheral blood mononuclear cells.

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

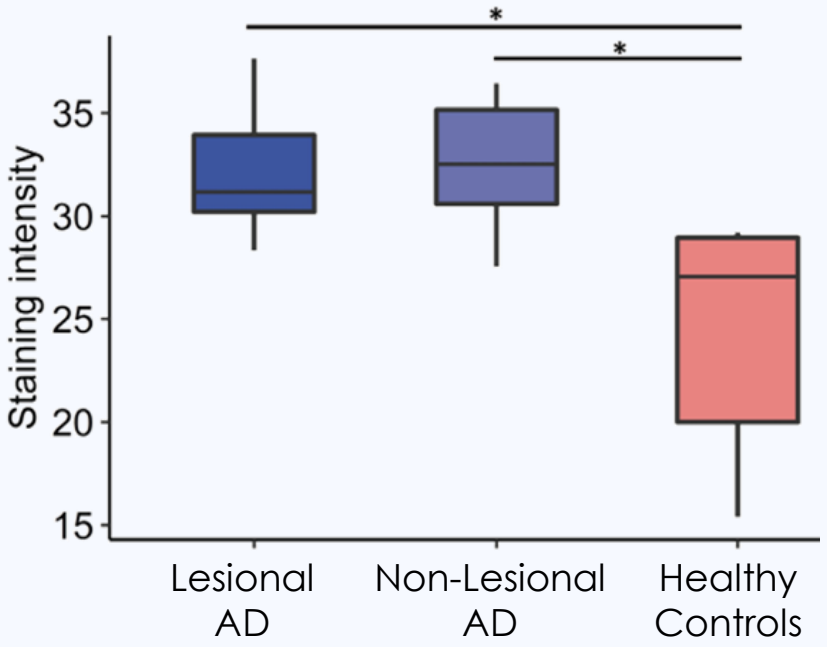




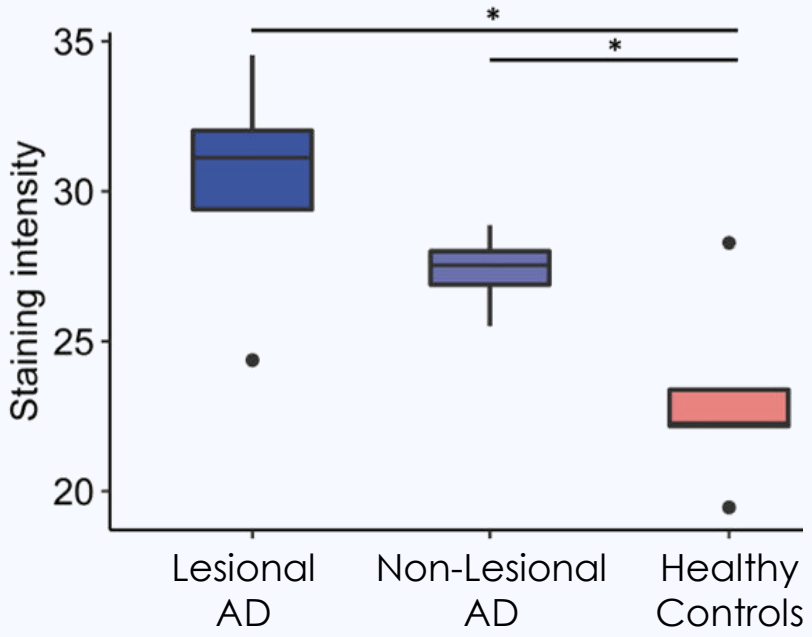
*P<0.05; **P<0.01; ***P<0.001
DAPI, 4′,6-diamidino-2-phenylindole; PGP9.5, protein gene product 9.5.

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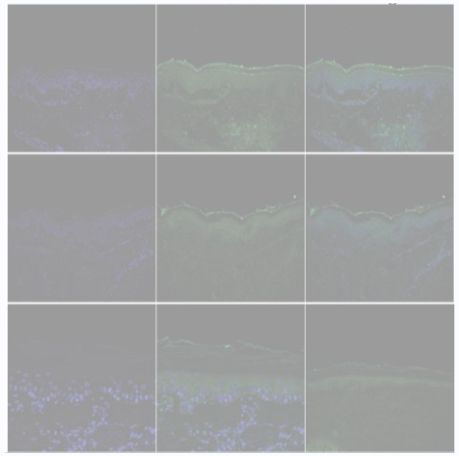
IL-13Rα1 expression pattern in lesional and non-lesional AD skin



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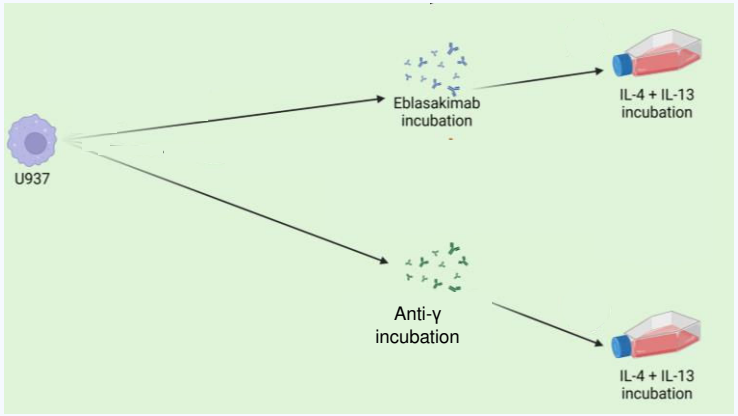

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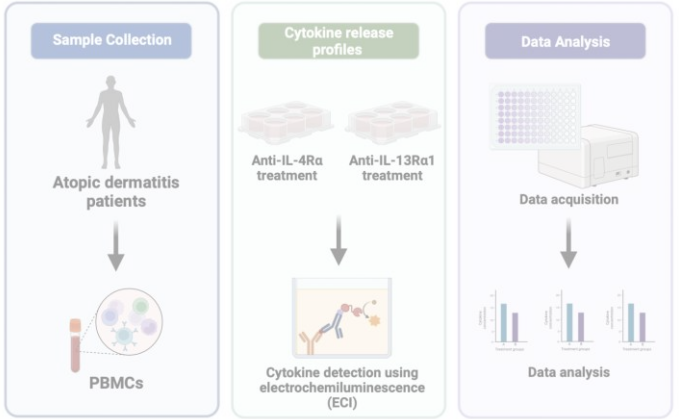

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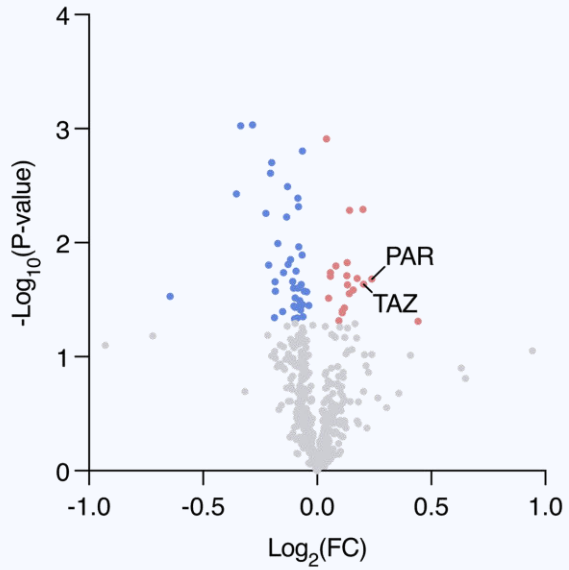
PBMC, peripheral blood mononuclear cells.

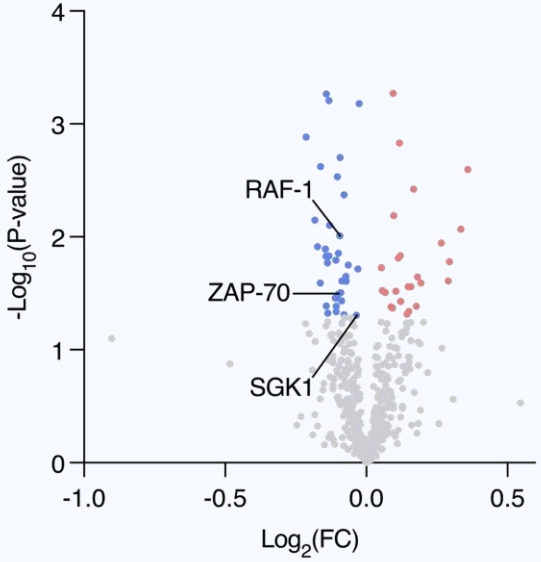
Differential protein expression was observed with blockade of the Type 1 vs Type 2 receptor in monocytes

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.

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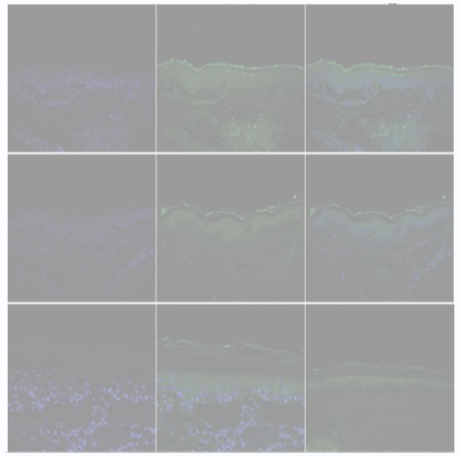

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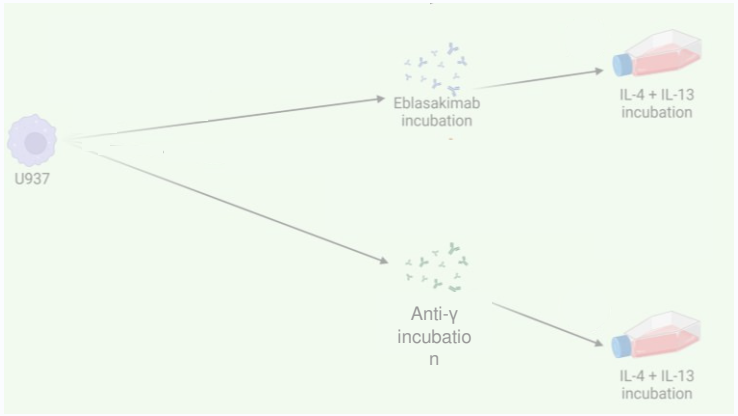

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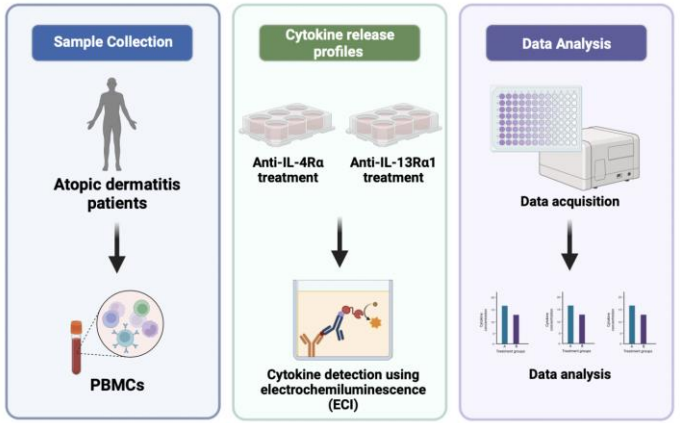

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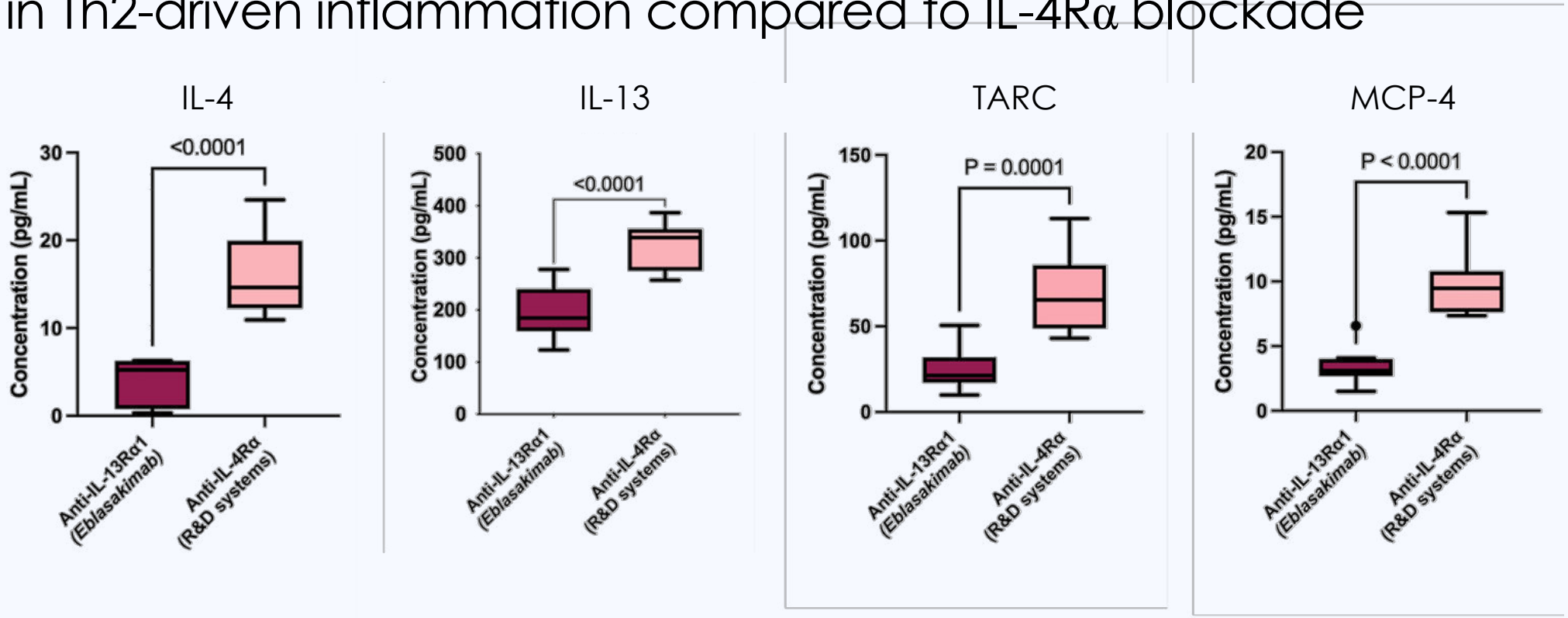
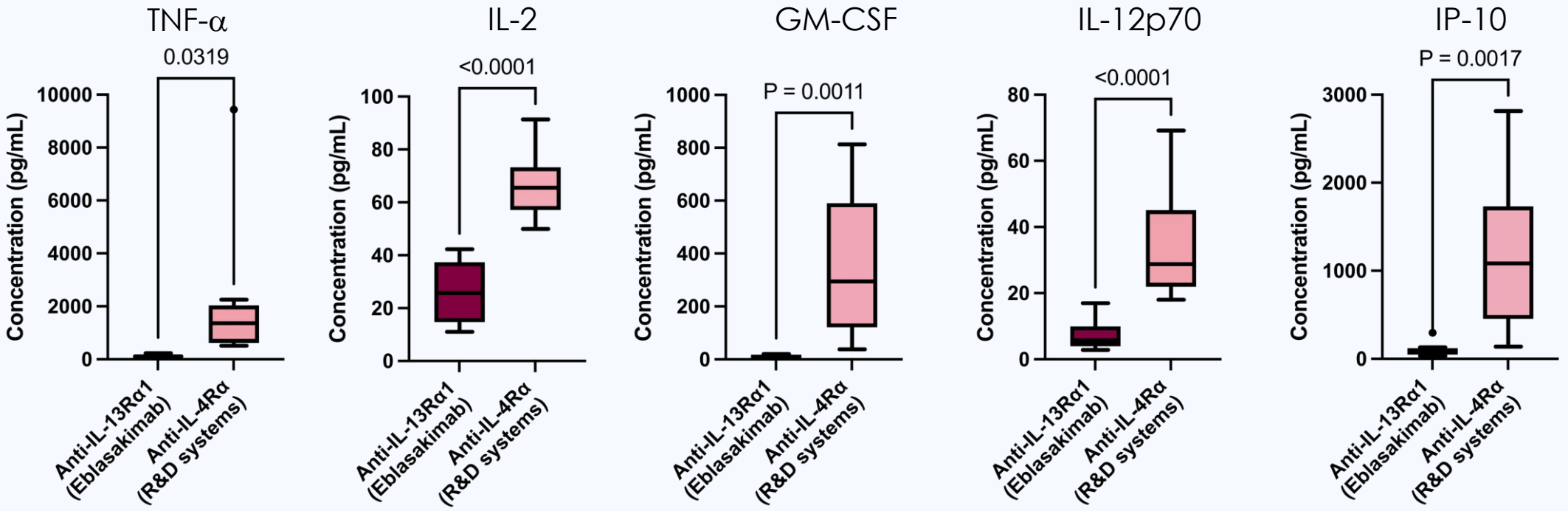
PBMC, peripheral blood mononuclear cells.

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



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

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 **circumvents increased 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