Combining Neuroscience And Immunology: Exploring The Neuro-immune Circuitry Behind Itch And Inflammation By Targeting IL-13Rα1 With Eblasakimab

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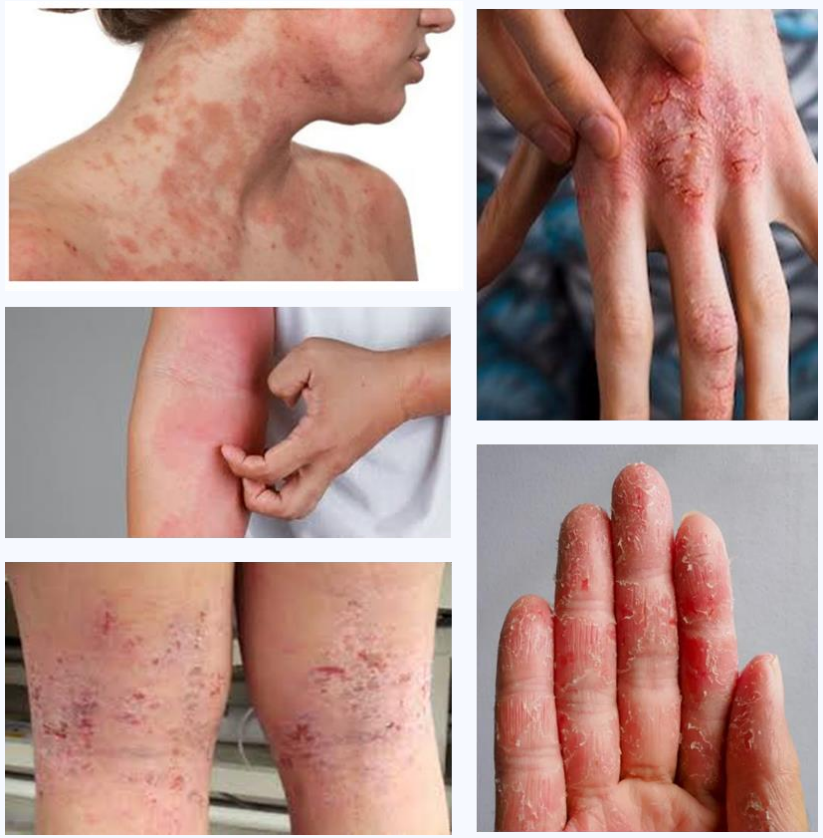
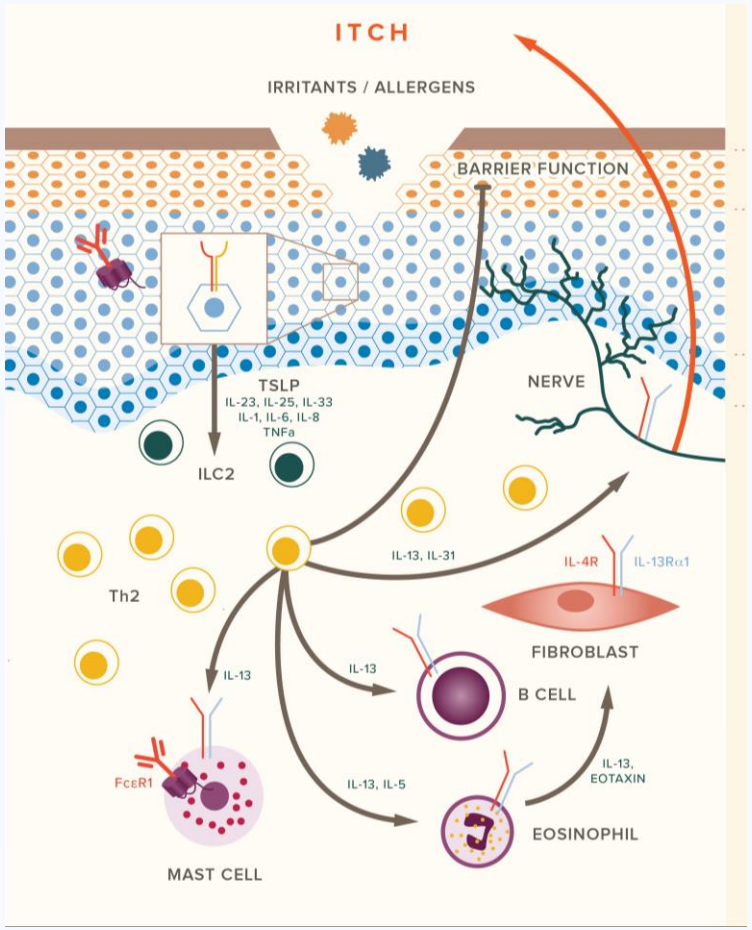
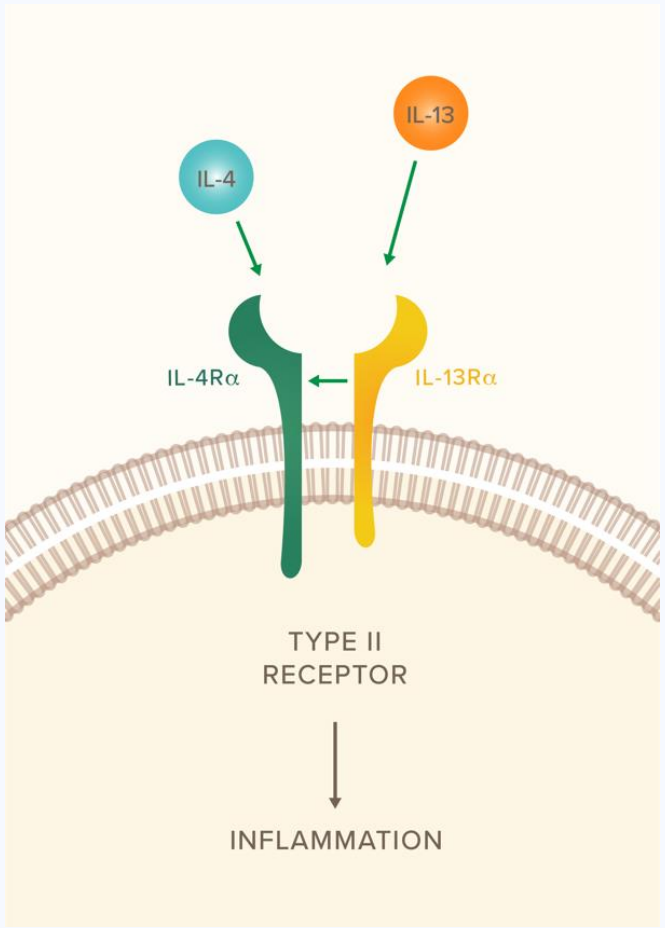
Atopic dermatitis (AD) is a common, chronic itchy and inflammatory skin disease



Up to 13% of children and 7% of adults in developed countries are affected. AD causes massive suffering for both patient and family.

Atopic dermatitis is a chronic inflammatory skin disease with a predominant Th2 cell polarisation

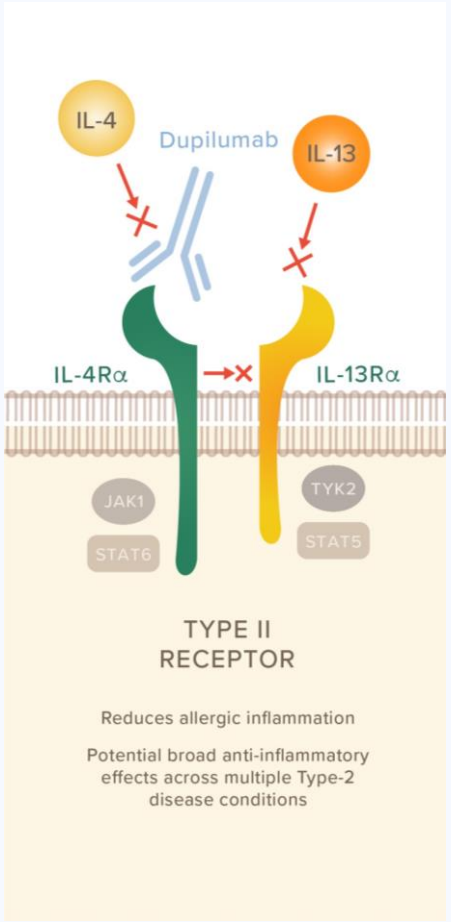


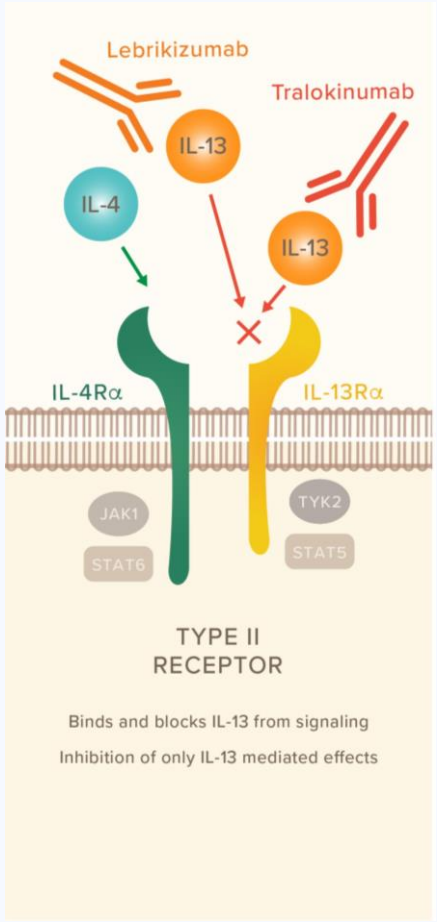


IL-4 and IL-13 are key cytokines of Th2 underlined diseases

- Signal through Type 2 receptor on immune and non-immune cells
- drive inflammatory responses in AD
- amplify itch responses through neuronal sensitization

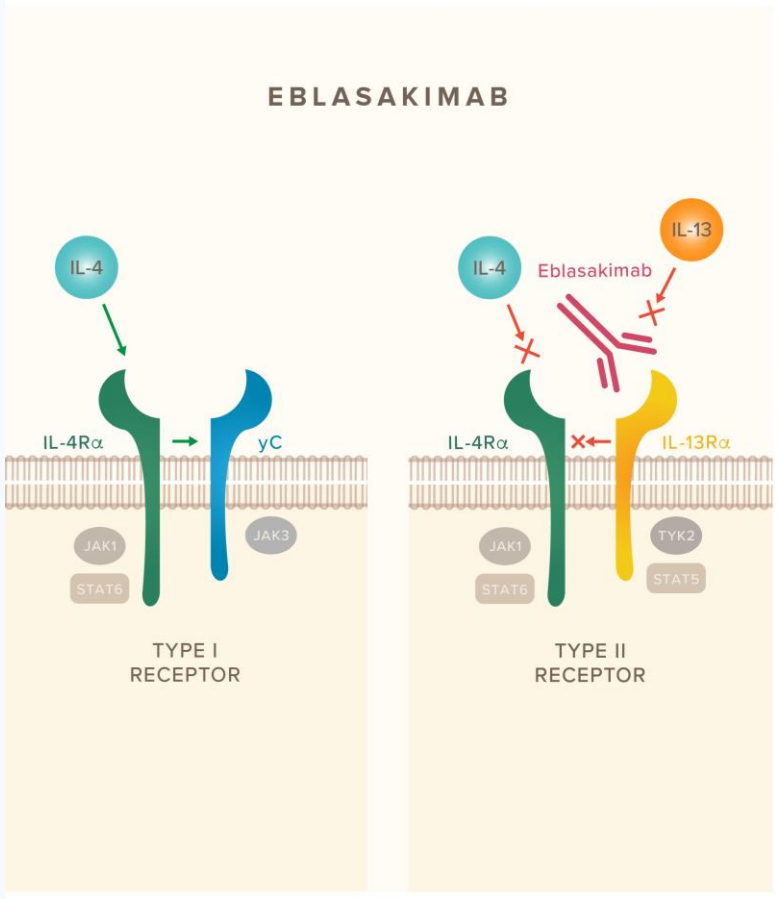
Targeting the IL-4 and IL-13 pathway in AD is a clinically proven approach





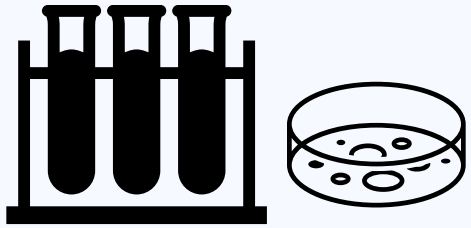
- Approved treatments in AD including dupilumab and tralokinumab block different aspects of the IL-4/ IL-13 pathway
- Blocking different parts of the receptor pathway can have different downstream signaling effects which may yield in
  - molecular differentiation between drugs
  - different downstream effects in disease

Eblasakimab has a unique MoA via its targeting of the IL-13Rα1 subunit

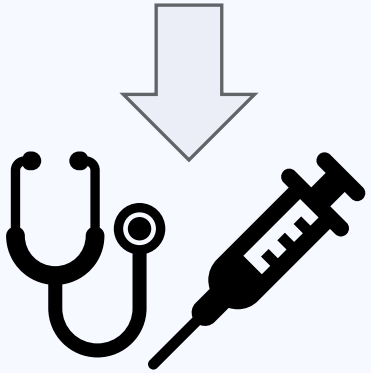


- Eblasakimab is a human IgG4 antibody which targets the human IL-13Rα1 subunit of the Type 2 receptor complex
- By blocking the IL-13Rα1, eblasakimab blocks IL-4 and IL-13 signaling through the Type 2 receptor only and does not interfere with the Type 1 receptor

Why unique translational models are needed to understand differentiation?



Bench



Bedside

- Monoclonal human-specific antibodies limit research with non-human species
- Utilizing human tissue or human-derived (healthy and patient) “inflamed” cells or neurons
- Translational gap between mouse and human neurons
- Emerging translational tools to advance mechanistic properties of eblasakimab and potentially compare/ differentiate to other pathway targets

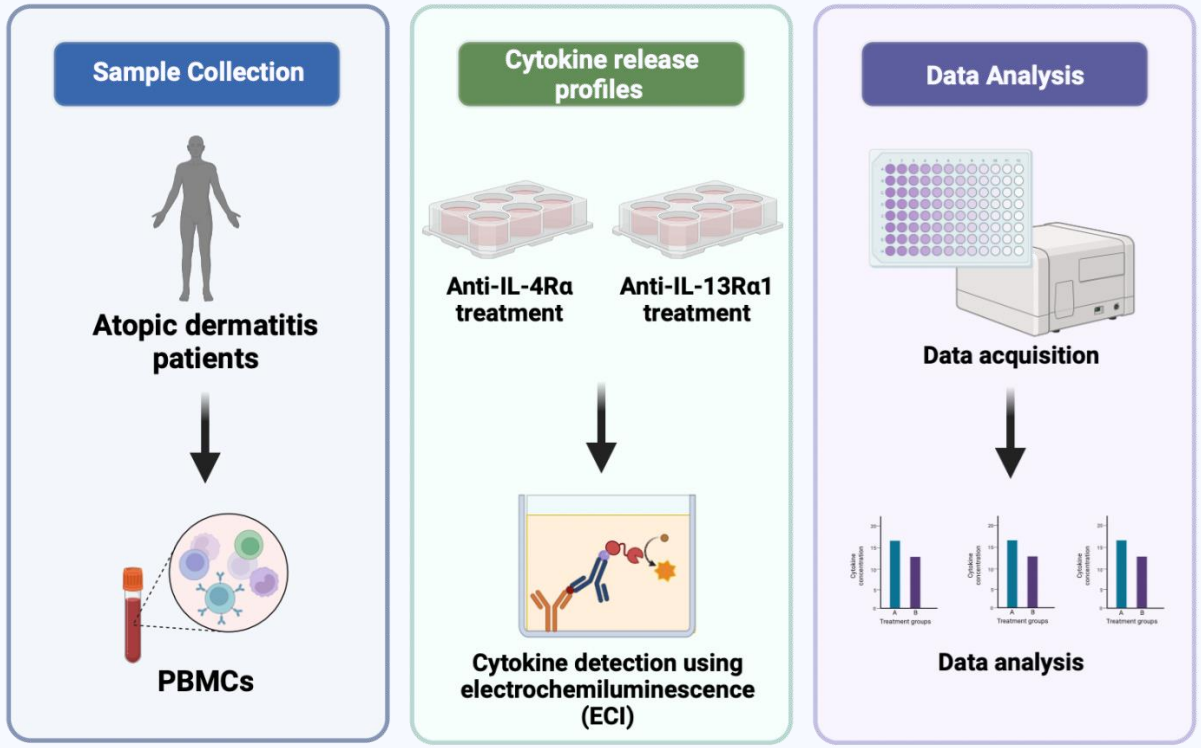
Translational research questions

What is the differentiated mechanism of eblasakimab targeting IL-13Rα1 versus IL-4Rα in skin diseases?

Can eblasakimab directly block neuronal multi-sensitized itch and provide rapid itch relief?

Can we expand eblasakimab *in other indications with translational science?*

What is the differential signaling between the Type 1 and Type 2 receptor pathways?



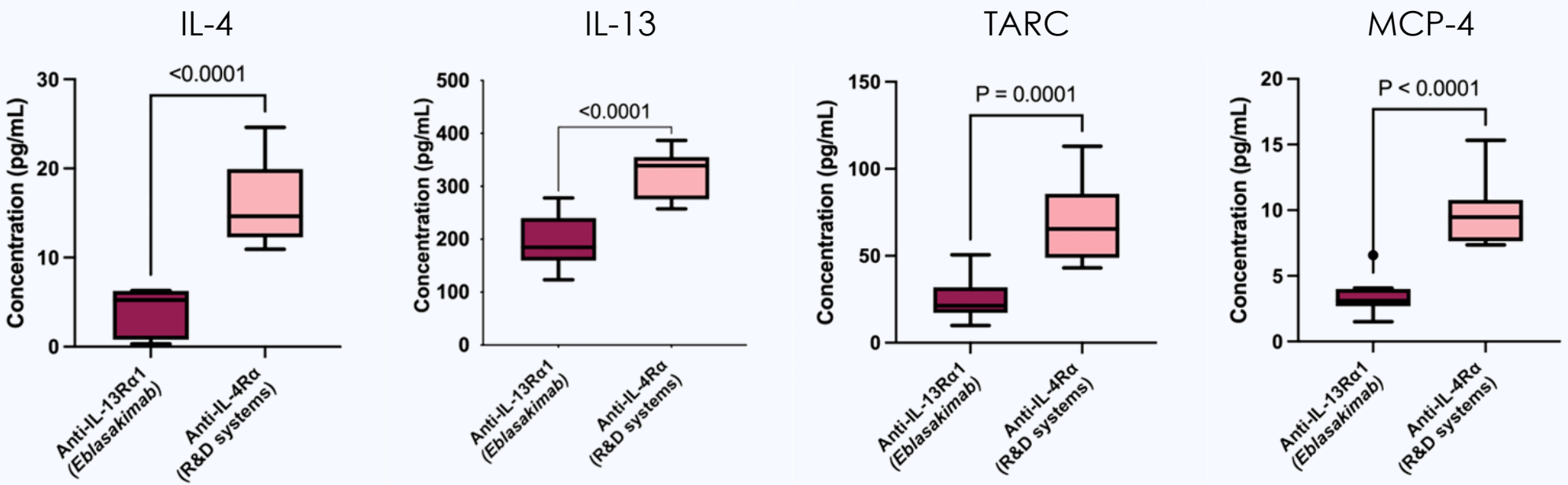
- **Th1 and Th2 cytokine levels** upon IL-4Rα vs IL-13Rα1 receptor blockade were analyzed with MesoScale Discovery Platform.
- PBMCs obtained from 10 patients with AD were treated with anti-IL-13Rα1 (eblasakimab) or anti-IL-4Rα (RnD Systems).

PBMC, peripheral blood mononuclear cells.

Duke University School of Medicine

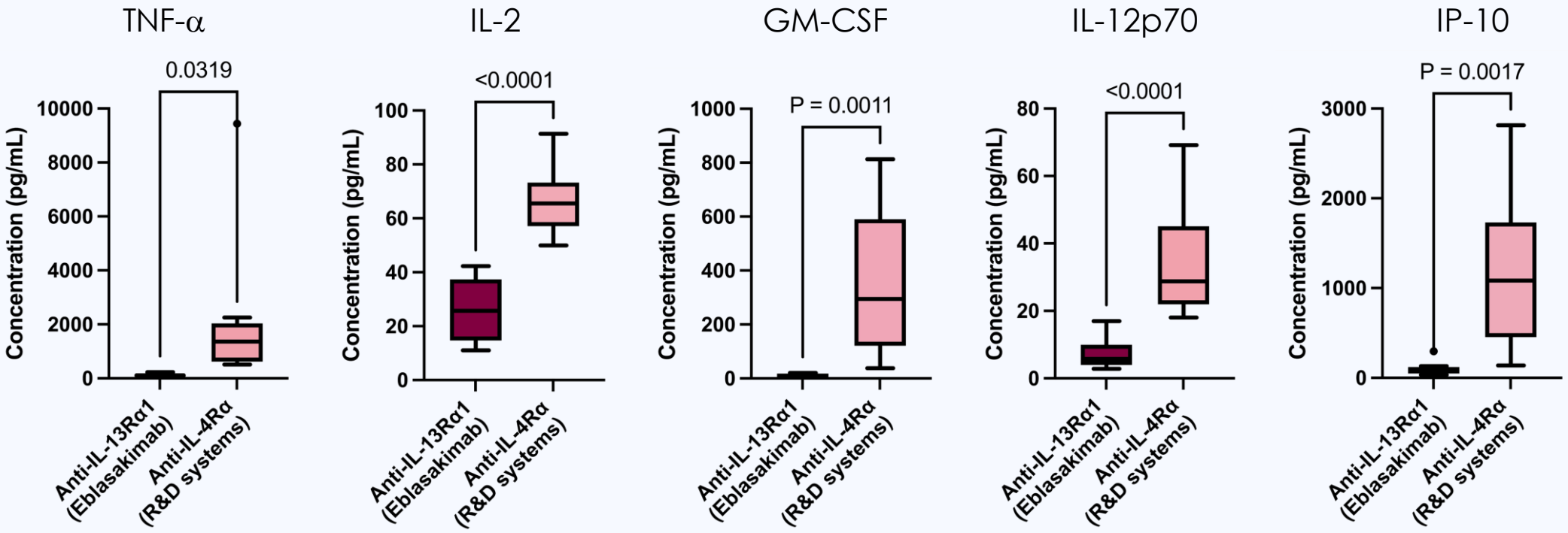
JOHNS HOPKINS MEDICINE

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



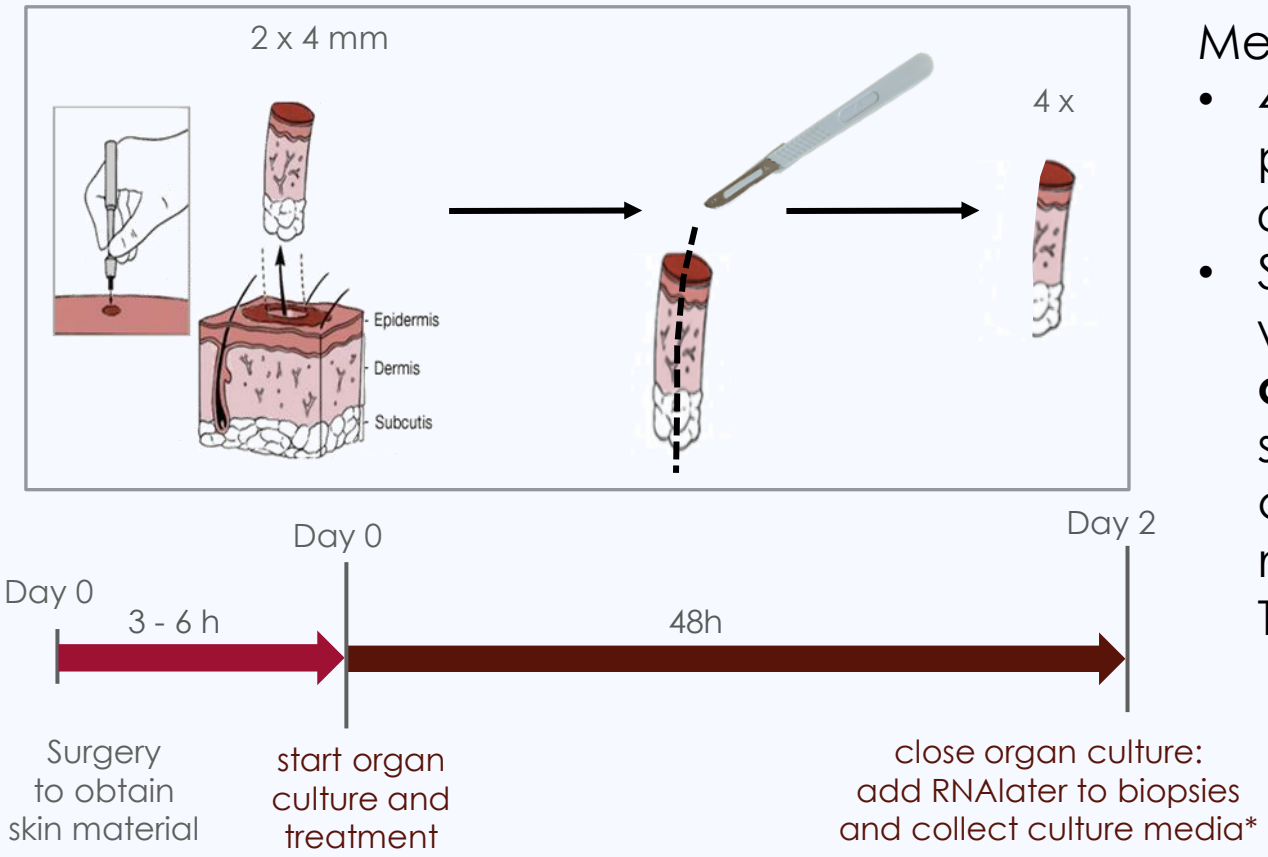
IL, interleukin; MCP, monocyte chemoattractant protein; TARC, thymus activation regulated chemokine.
Antibody targeting IL4Rα supplied by R&D Systems. Demonstrated to block IL-4 and IL-13 signaling through Type 1 and Type 2 receptors.

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.

Validation of AD derived PBMC findings in AD skin biopsies

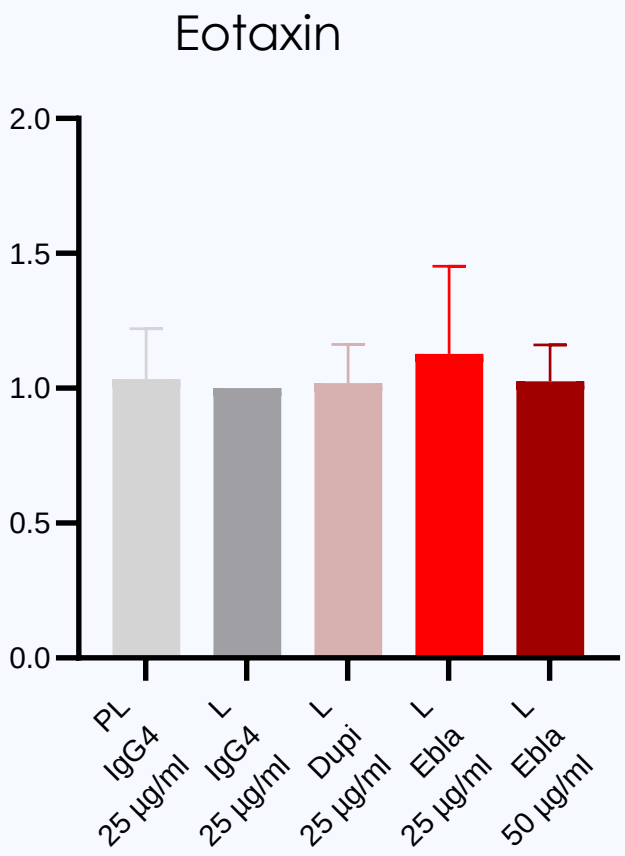


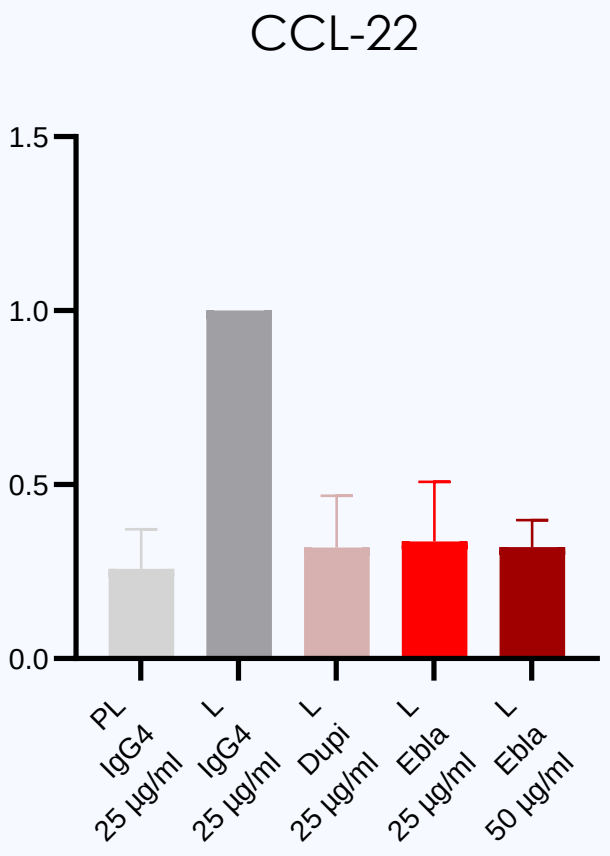
Methods:

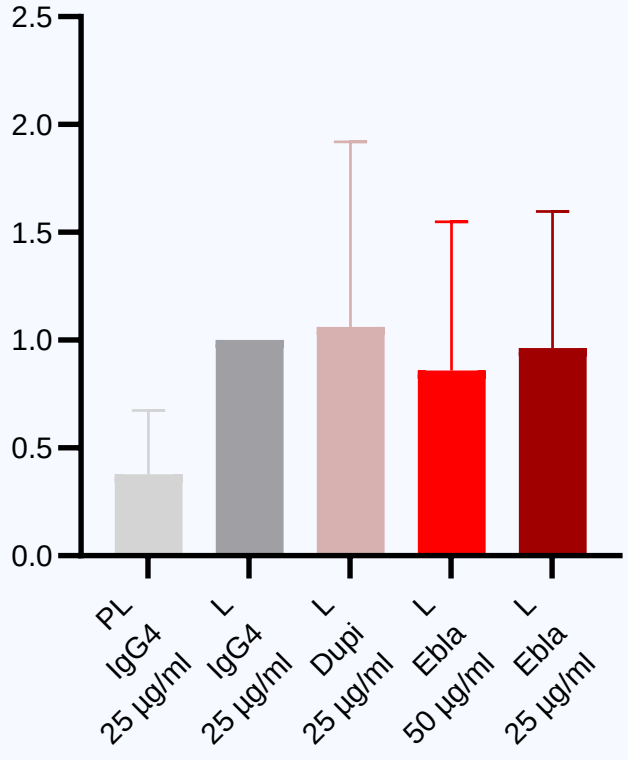
- 4mm skin punch biopsies from AD patients were collected for *ex vivo organ* culture.
- Skin punches were treated for 48h with either **eblasakimab, dupilumab or isotype** control to collect the supernatant for secreted cytokines/chemokines with a multiplex cytokine array (Eve Technologies).

MONASTERIUM LABORATORY
A QIMA Life Sciences Company

Similar inhibitory effects were observed for Eotaxin, CCL-22 and CCL-5

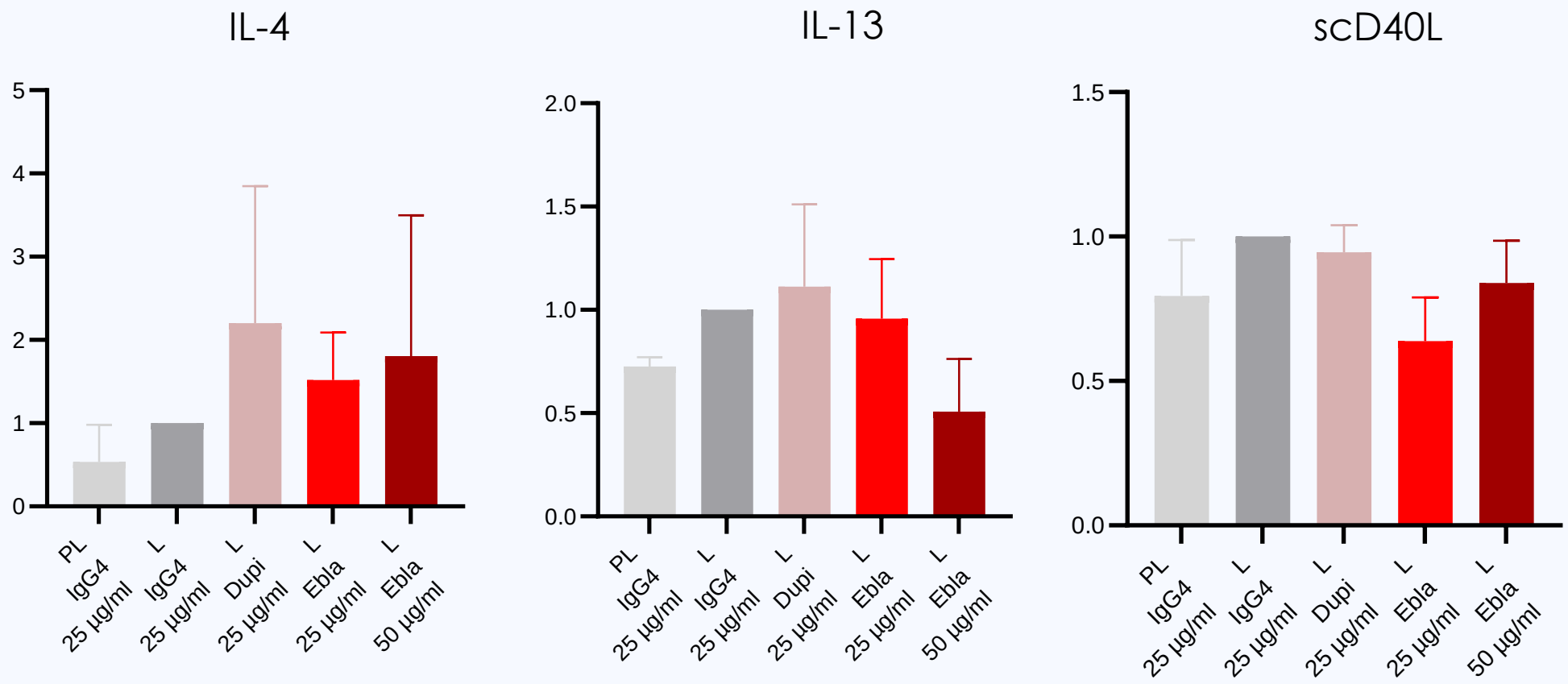






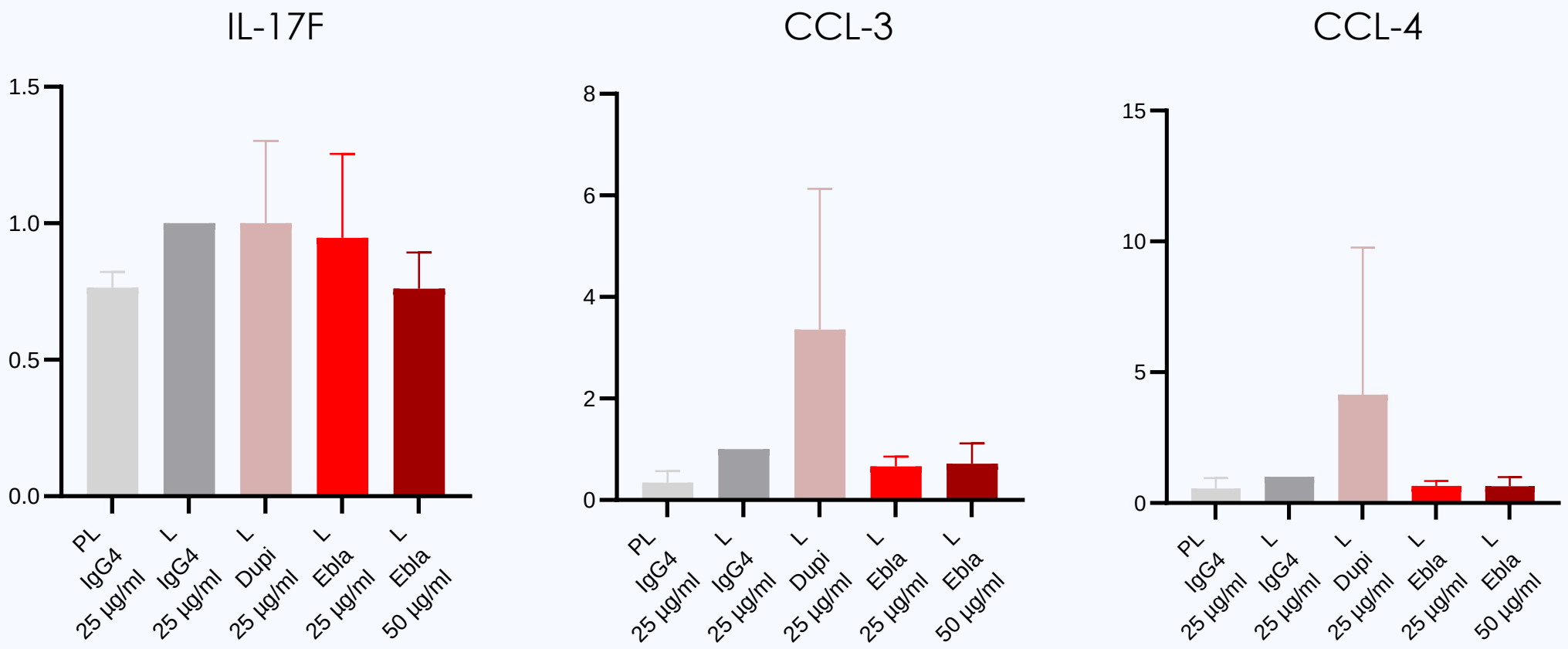
Preliminary data from ongoing experiments

Pro-inflammatory TH2 cytokines reduced more by eblasakimab as compared to dupilumab



Preliminary data from ongoing experiments

Other AD relevant mediators were tendentially downregulated by eblasakimab in AD lesional skin



Preliminary data from ongoing experiments

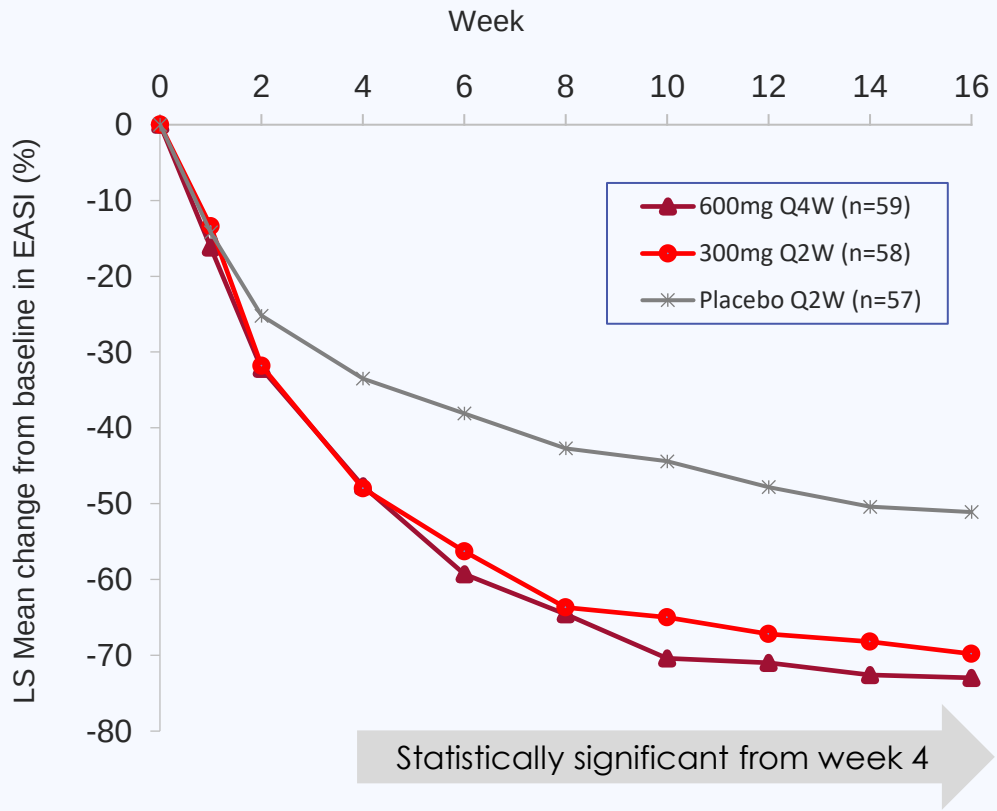
Clinical Significance

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 **potentially more efficient blockade of the Type 2 receptor and sparing the Type 1 receptor**

Translation to the clinic: Eblasakimab monthly dosing regimen achieved comparable efficacy to dosing every 2 weeks in the Phase 2b AD study



- A Phase 2b dose-ranging dose study evaluated the safety and tolerability for eblasakimab vs placebo in adult patients with moderate-to-severe AD
- Improvement of EASI scores was significantly greater for eblasakimab at week 16 for eblasakimab doses 600mg Q4W doses, 300mg Q2W vs placebo
- Efficacy in monthly dosing is supported by translational data on differentiated and unique MoA

EASI, eczema area and severity index; LS, least squares; Q2W, every 2 weeks; Q4W, every 4 weeks. All dosing arms not shown

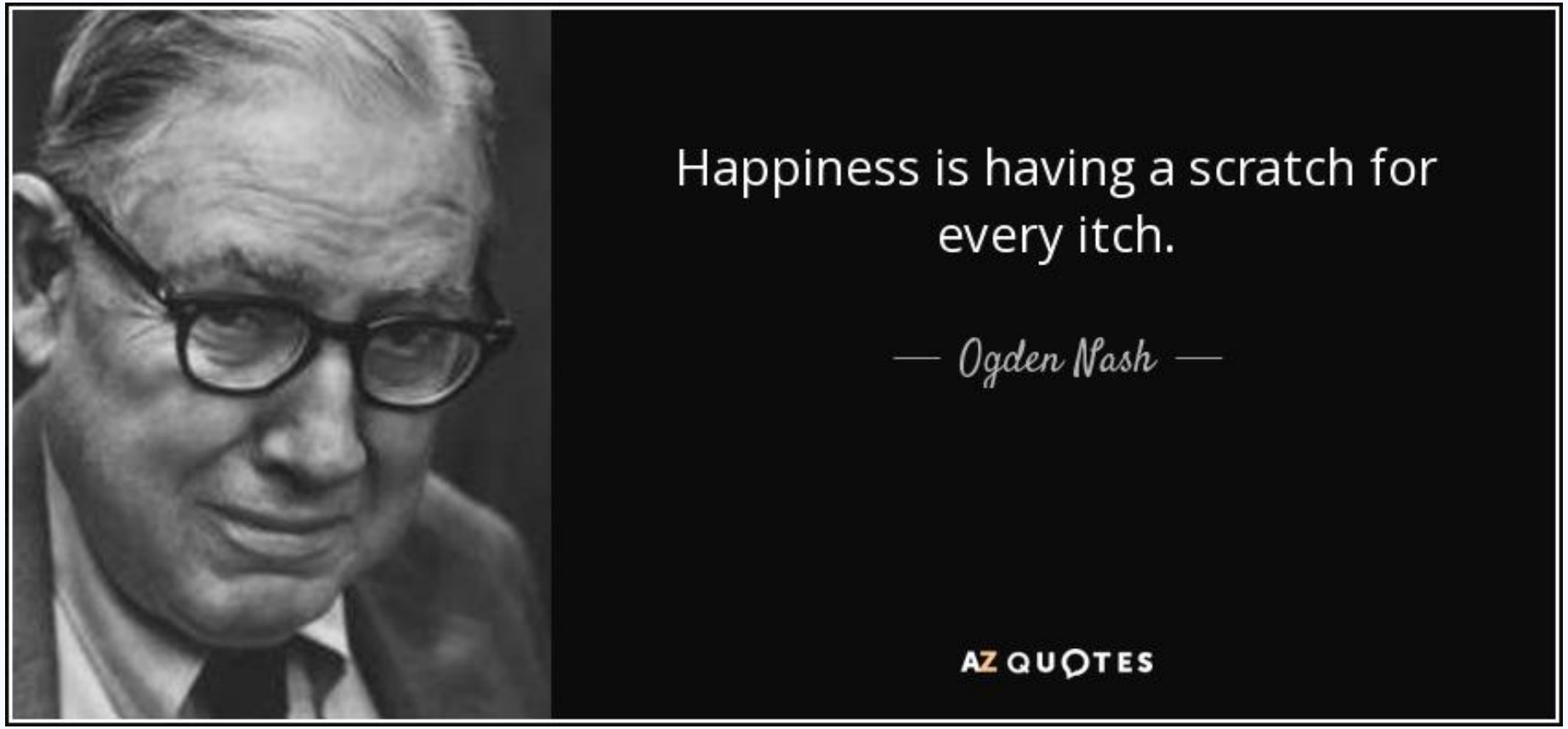
Translational research questions

What is the differentiated mechanism of eblasakimab targeting IL-13Rα1 versus IL-4Rα in skin diseases?

Can eblasakimab directly block neuronal multi-sensitized itch and provide rapid itch relief?

Can we expand eblasakimab *in other indications with translational science?*

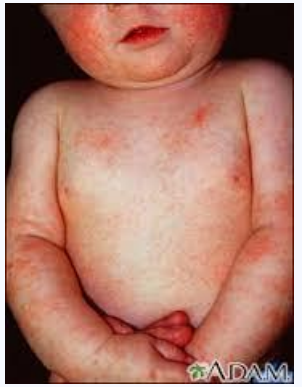
Itch from a philosophical view



Chronic itch is a persistent sensation lasting more than 6 weeks

Impacts on quality of life

- Sleep disruptions
- Impaired daytime activities
- Decreased school performance in children
- Increased rates of ADHD

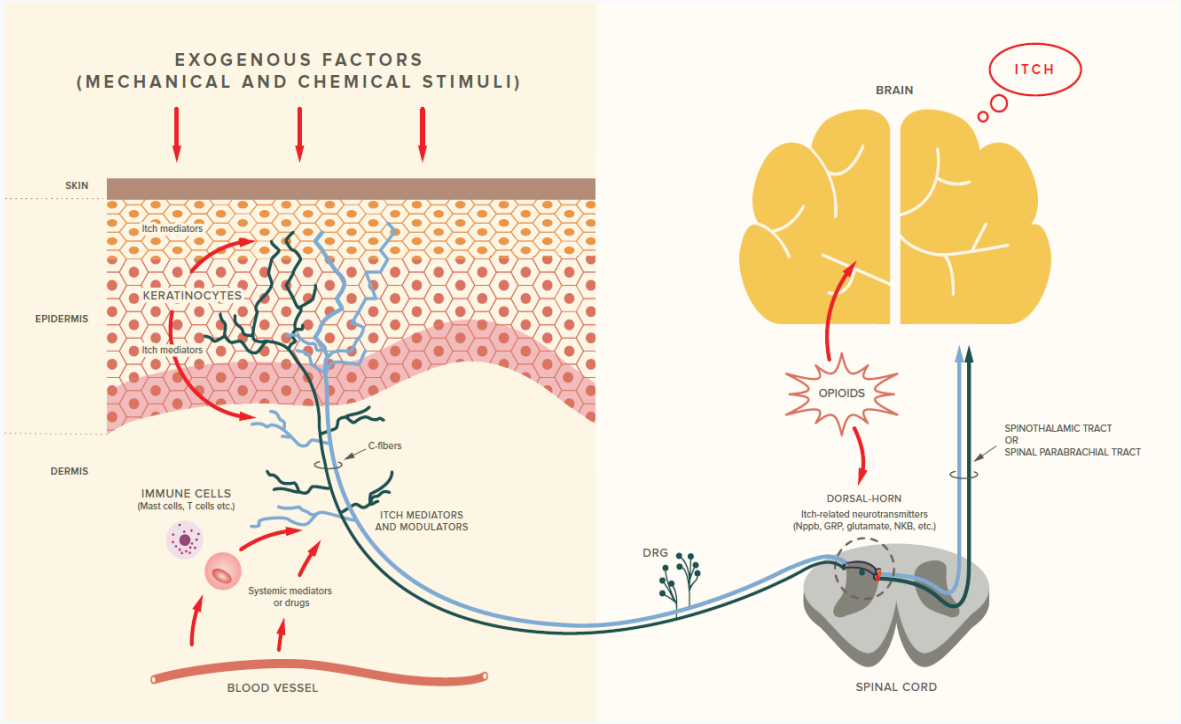


Causes

Neuropathic	Dermatological
Psychogenic	Systemic

ADHD, attention-deficit/hyperactivity disorder; HIV, human immunodeficiency virus

Sensing itch in the skin



The sensation of itch is carried by unique sensory neurons called **unmyelinated C-fibers**

Cutaneous sensory neurons, which innervate the skin, transmit itch & carry the signal along axons to the spinal cord and brain

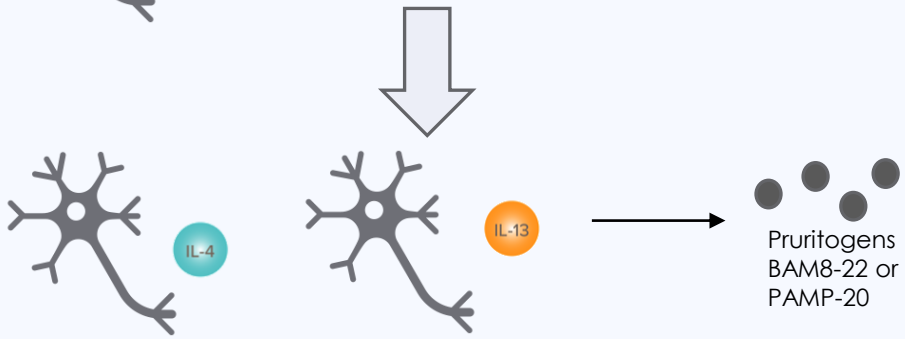
These neurons are a **subset of pain-transmitting** primary afferents

The process entails **complex inhibitory and excitatory control between itch and pain** circuitry

Modified from Cevikbas F, Lerner EA. *Physiol Rev*. 2020;100(3):945-982.

Translational neuronal itch models to assess anti-pruritic effects

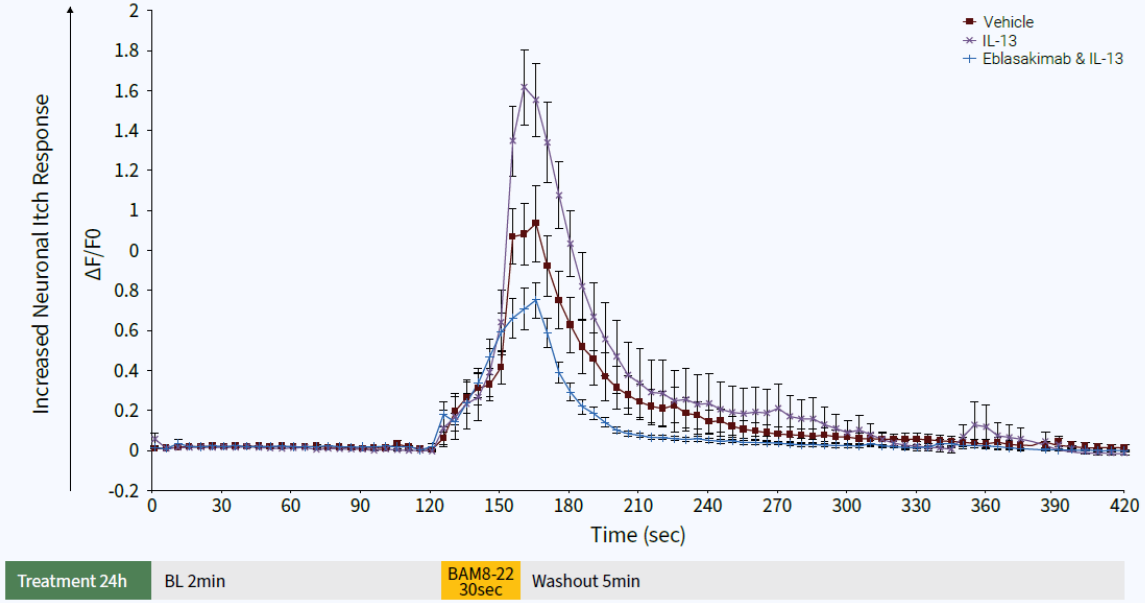
Cultured neurons were pre-treated with vehicle or eblasakimab



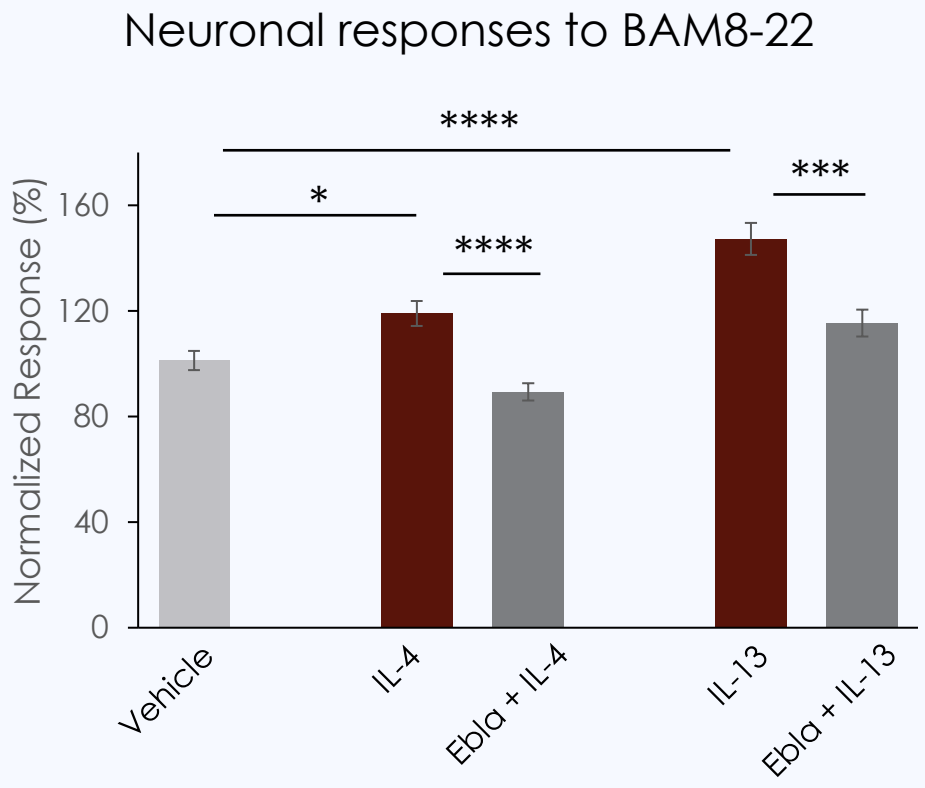
Neurons were exposed to IL-4 / IL-13, followed by pruritogen challenge, loaded with fluorophore

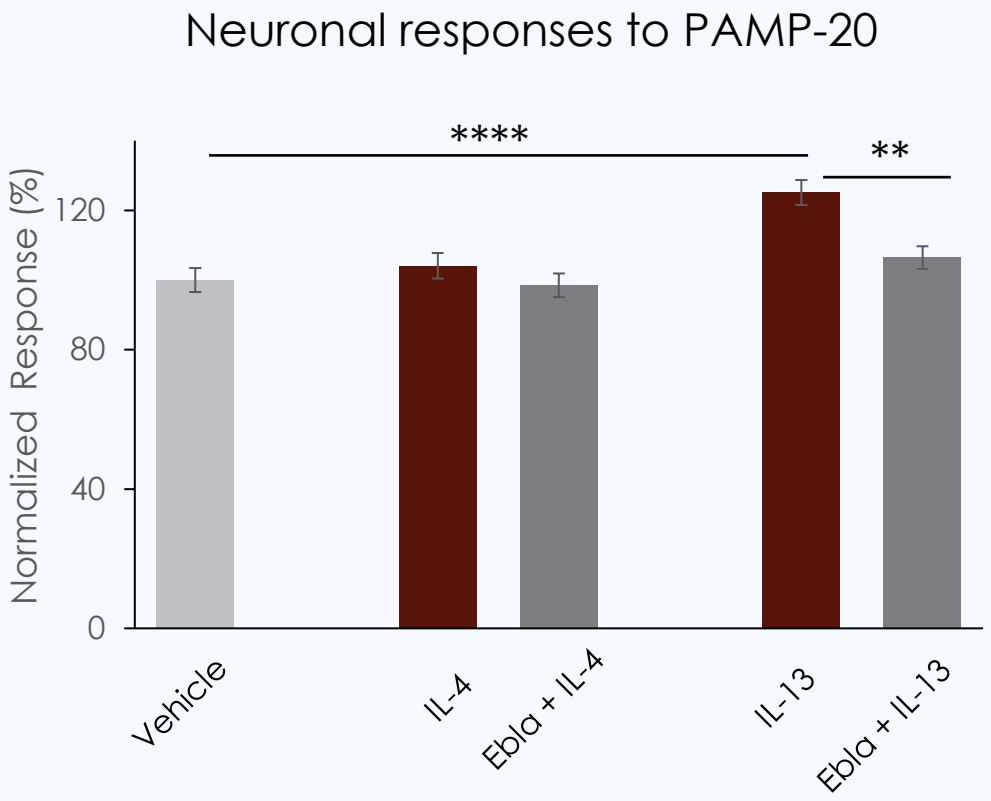
Neuronal itch responses were captured by live cell calcium imaging

Live-cell calcium imaging output: Neuronal responses



Eblasakimab reduced enhanced neuronal itch responses to IL-4 and IL-13





ebla, eblasakimab.
*p< 0.05, *** p<0.001, ****p<0.0001; error bars indicate standard error of mean

Conclusions

- Human sensory neurons are sensitized by Th2 cytokines to pruritogens
- IL-4 and IL-13 **do not necessarily function as redundant cytokines**
- Eblasakimab **potently inhibits both IL-4 and IL-13-** driven effects

Data provide **a mechanistic basis for the reduction of itch observed in patients** with moderate-to-severe AD and potentially suggests broad anti-pruritic efficacy across different Th2 inflammatory diseases

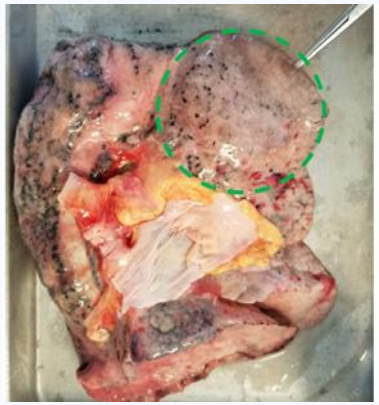
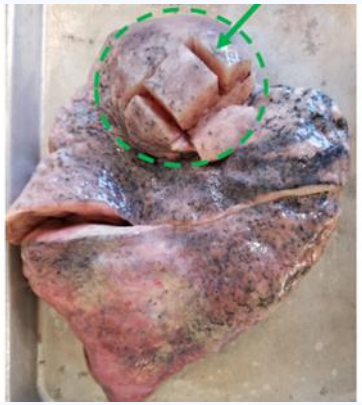
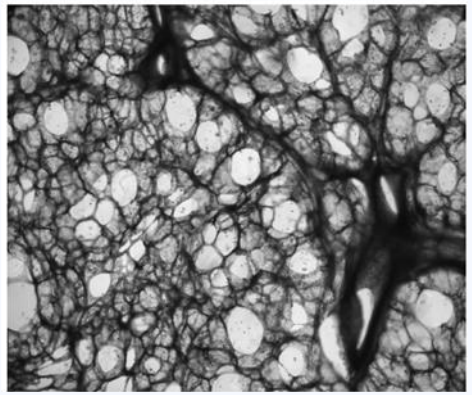
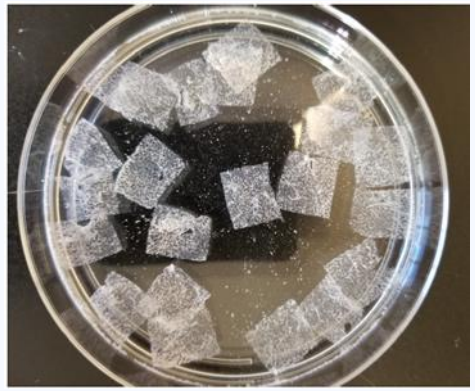
Translational research questions

What is the differentiated mechanism of eblasakimab targeting IL-13Rα1 versus IL-4Rα in skin diseases?

Can eblasakimab directly block neuronal multi-sensitized itch and provide rapid itch relief?

Can we expand eblasakimab in other indications with translational science?

The PCLS model: Precision Cut Lung Slices

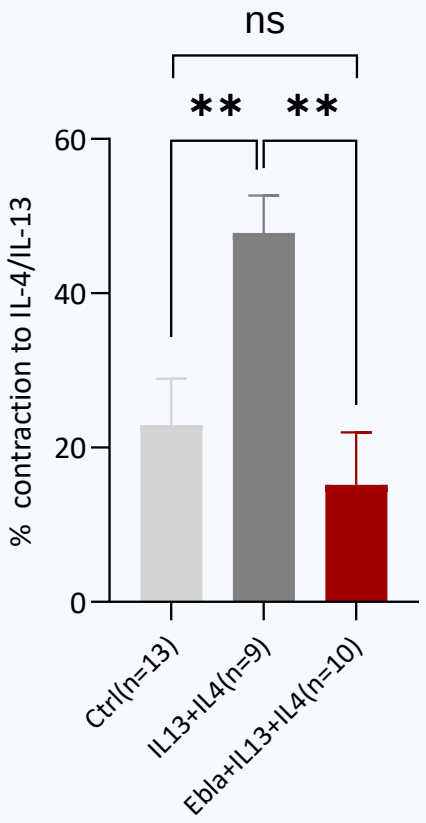





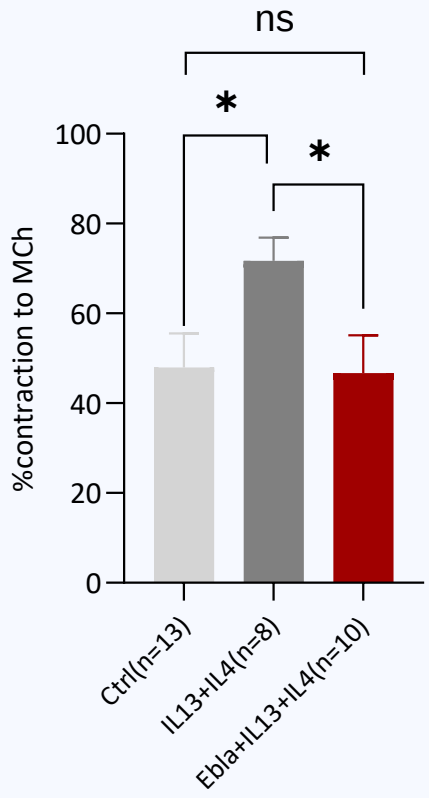
Human PCLS from healthy donors were treated for 48 hours with cytokines

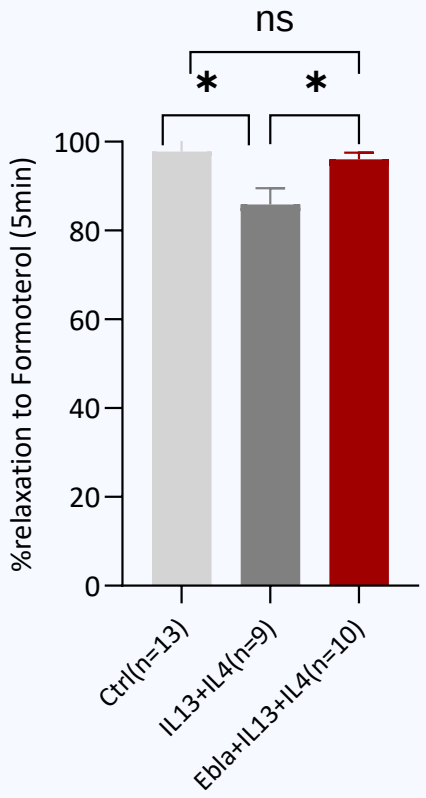
Airway responsiveness was tested with increasing doses of Methacholine (MCh), followed by a single dose of Formoterol (therapy for dilation)

Chronic **O**bstructive **P**ulmonary **D**isease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the:
Airways (bronchitis, bronchiolitis), and/or Alveoli (emphysema) which causes persistent, often progressive, airflow obstruction

Eblasakimab reduces airway constriction and enhances dilation in PCLS from healthy donors







Preliminary data from ongoing experiments

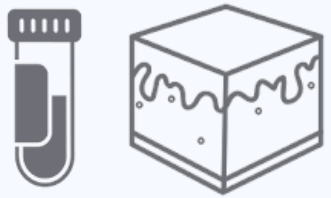
Significance of COPD model

IL-4 and IL-13 combined pre-treatment of PCLS results in **increased bronchoconstriction of the airways** tested in the PCLS with Methacholine

Both cytokines **delay the kinetics of airway dilation to Formoterol** suggesting rapid changes of airway responsiveness with 48 hours of treatment

Eblasakimab significantly blocks the IL-4/IL-13 increased bronchoconstriction as well as rapidly improves responses to Formoterol as compared to cytokine- treated PCLS

Translational models help elucidate the unique mechanism of action and differentiated effects of eblasakimab

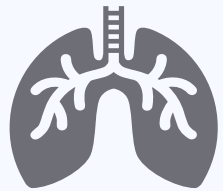


Blood cells and skin biopsy from patients with AD

Differentiated therapeutic approach through unique MoA – potential for more efficient blockade and sparing Type 1 receptor

Cultured human dorsal root ganglion neurons

Eblasakimab reduced IL-4 and IL-13-induced neuronal sensitization to itch and neuronal hyperactivity



COPD model: human precision cut lung slices

Eblasakimab significantly blocked the IL-4/IL-13 increased bronchoconstriction and enhanced dilation in human PCLS

Acknowledgements

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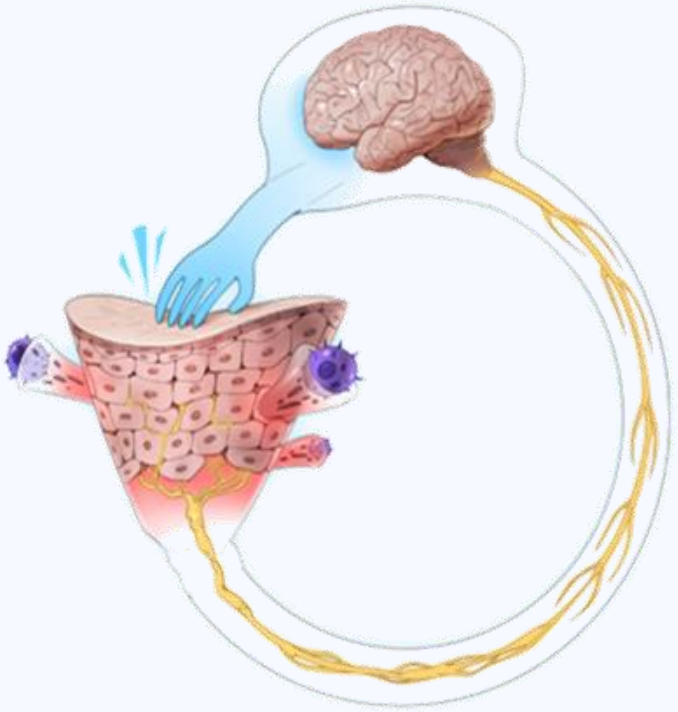

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