

Neuromodulation beyond itch is blocked by targeting IL-13R α 1 with *eblasakimab*

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Disclosures

Drs. Ferda Cevikbas and Carl Firth are employees of ASLAN Pharmaceuticals.

Itch in meme culture

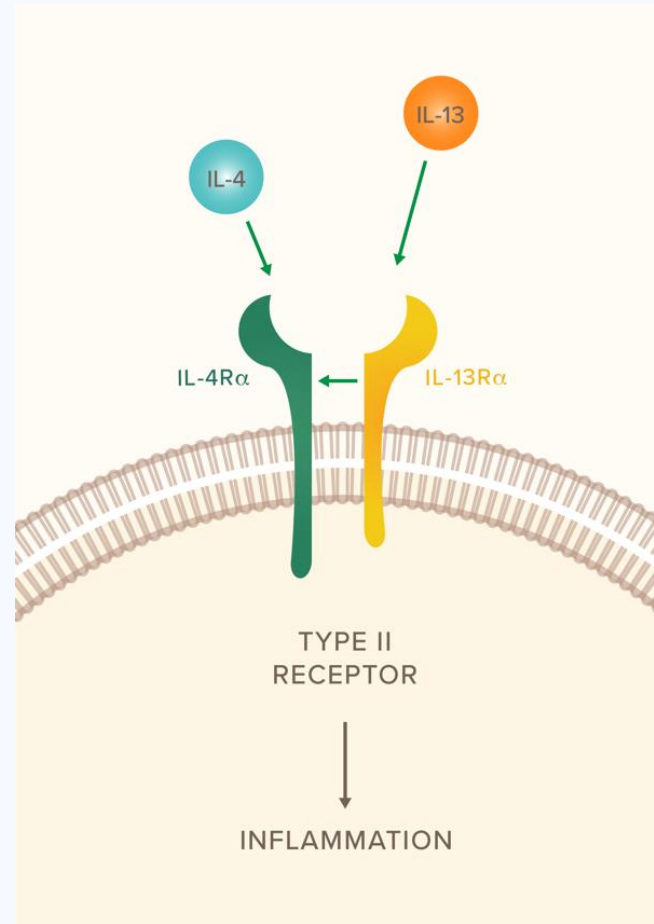
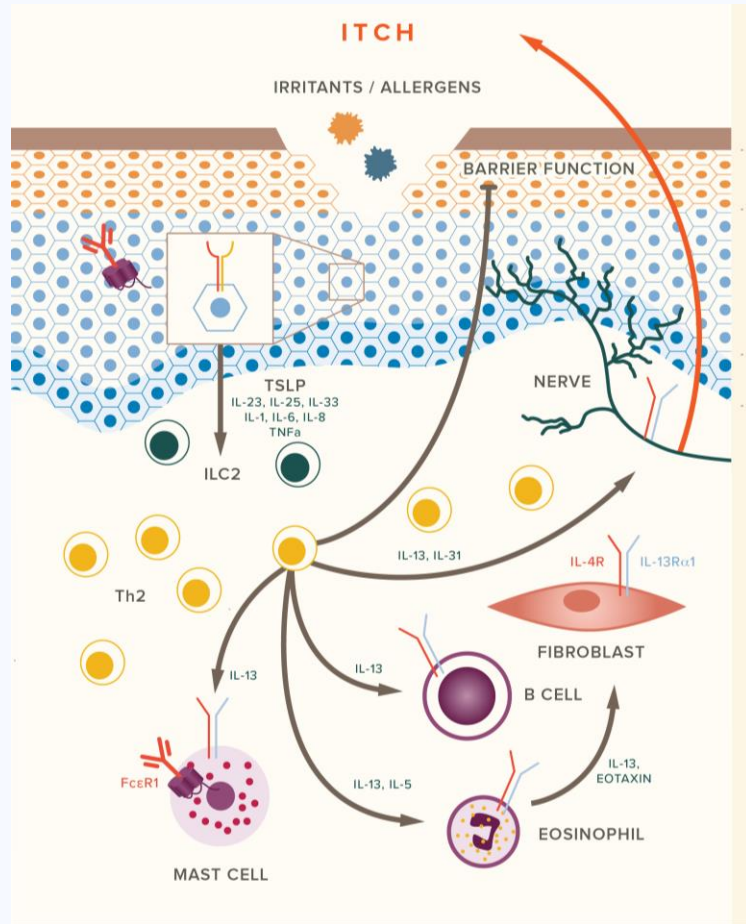


Atopic dermatitis (AD) is a common, chronic itchy and inflammatory skin disease



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

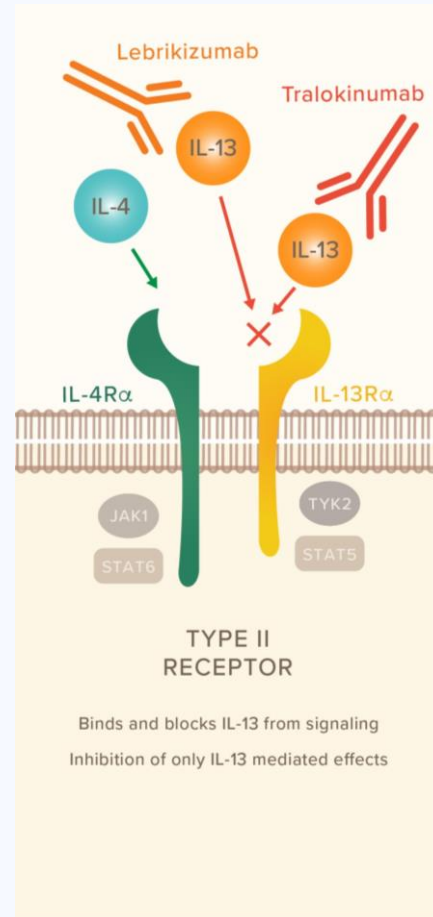
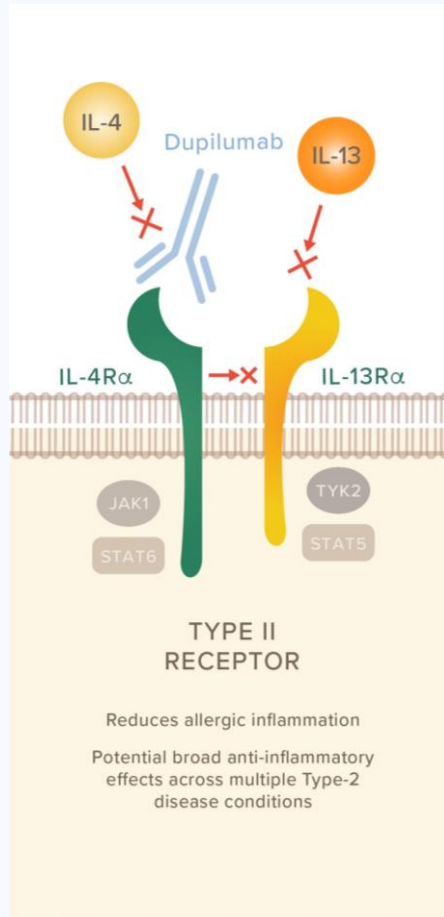
Atopic dermatitis is a chronic inflammatory skin disease with a predominant Th2 cell polarisation



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

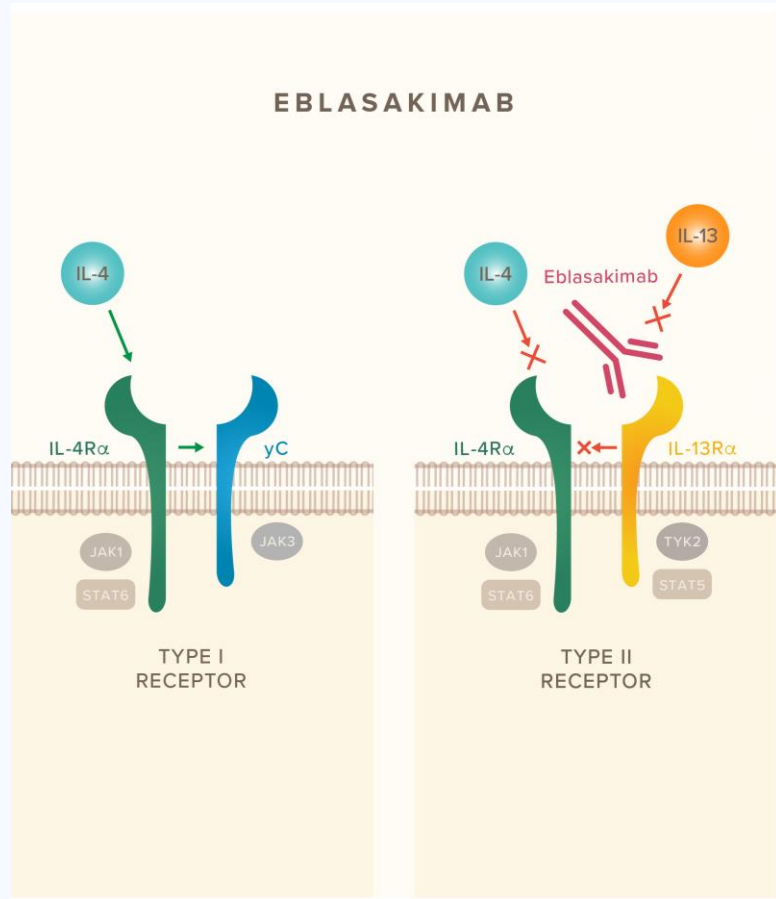
- Signal through Type 2 receptor on immune and non-immune cells
- drive inflammatory responses in AD
- amplify itch responses through neuronal sensitization

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



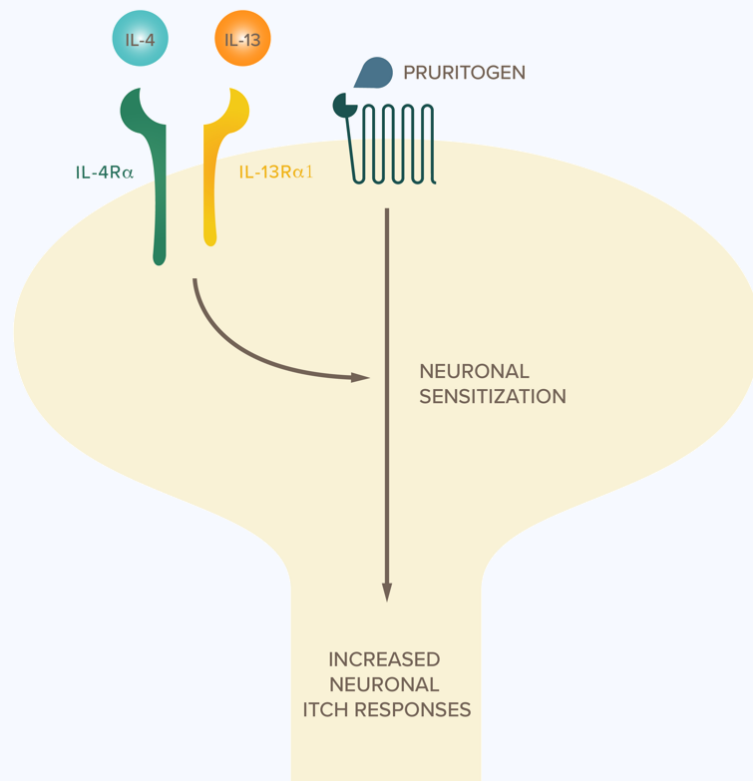
- Approved treatments in AD including dupilumab and tralokinumab block different aspects of the IL-4/ IL-13 pathway
- Blocking different parts of the receptor pathway can have different downstream signaling effects which may yield in
 - molecular differentiation between drugs
 - different downstream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

Eblasakimab has a unique MoA via its targeting of the IL-13R α 1 subunit



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

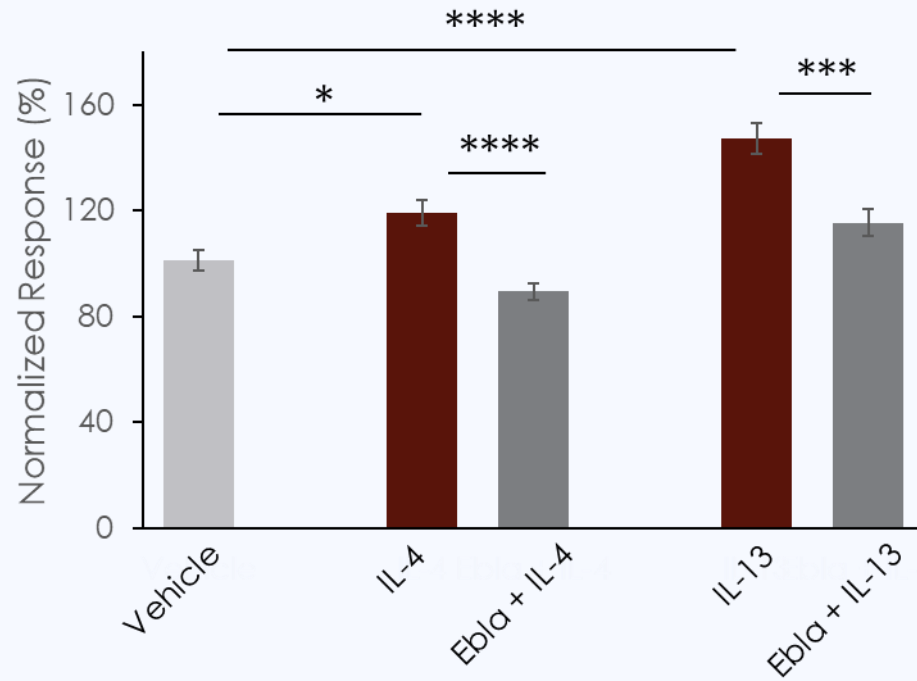
Can *eblasakimab* block cytokine-induced sensitization of neuronal itch responses? Do IL-4 and IL-13 exert redundant neuroactive roles?



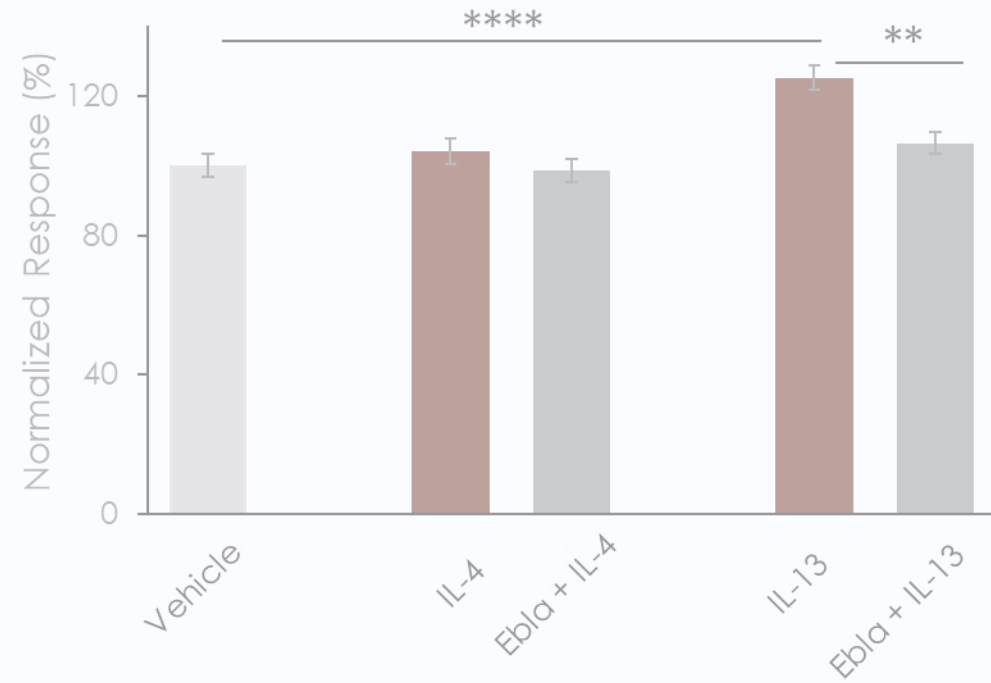
- An *ex vivo* human neuronal model system was used to determine responses of human dorsal root ganglia neurons to itch signaling induced by pruritogens **BAM8-22** and **PAMP-20**
- Cultured neurons were pretreated with either **vehicle** or ***eblasakimab***, followed by the addition of **IL-4** or **IL-13**. This was followed by pruritogen challenge
- Neuronal itch responses were captured by live cell calcium imaging

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

Neuronal responses to BAM8-22



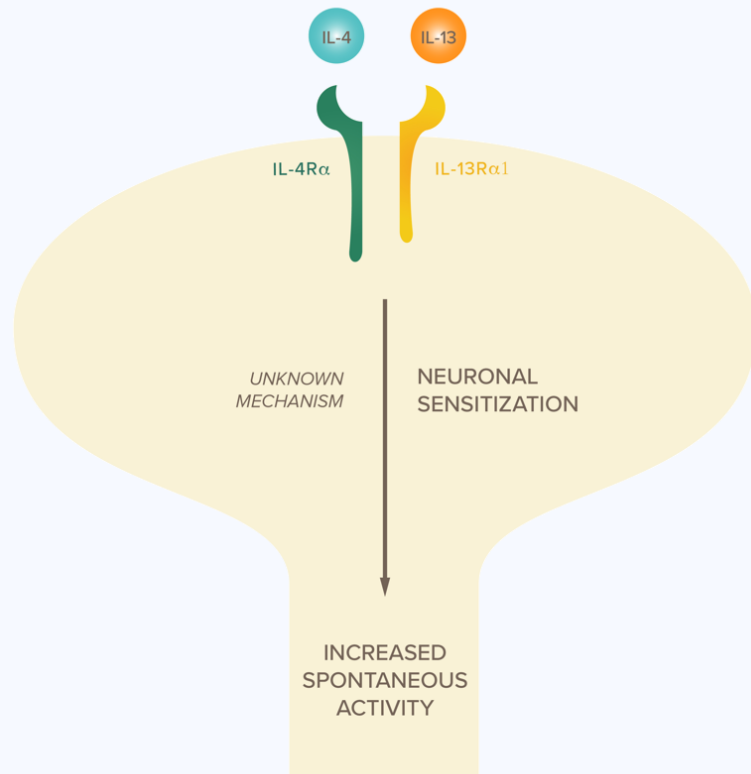
Neuronal responses to PAMP-20



ebla, eblasakimab.

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

Can *eblasakimab* reduce spontaneous neuronal activity?

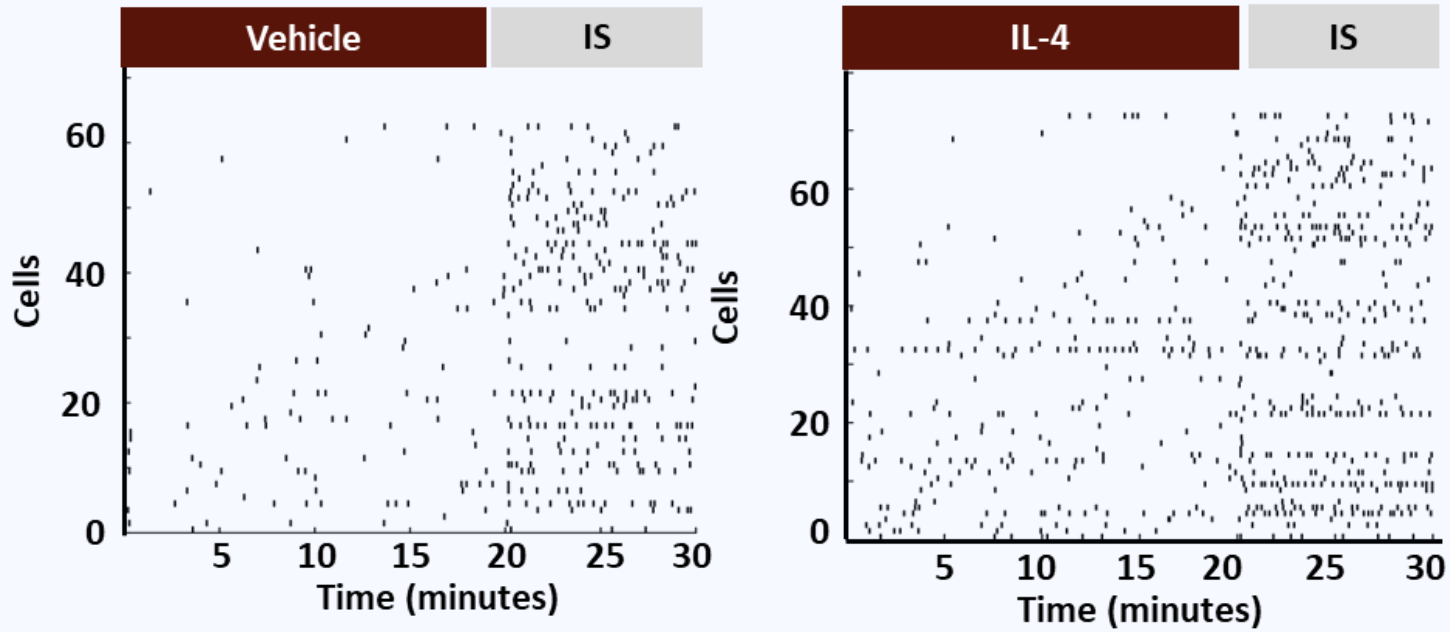


- The effects of IL-4 and IL-13 on spontaneous neuronal activity in human dorsal root ganglion neurons were measured with and without *eblasakimab* as a model for hypersensitization of neurons in response to inflammatory conditions
- Spontaneous neuronal activity was measured with live cell calcium imaging

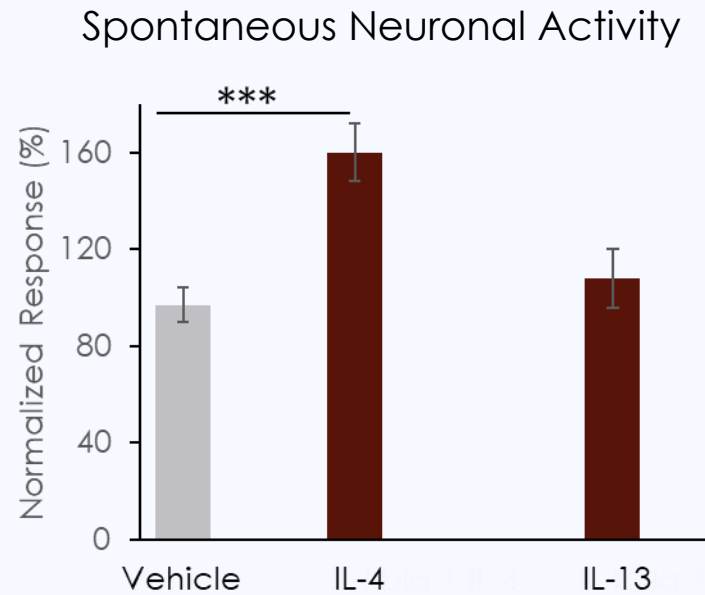
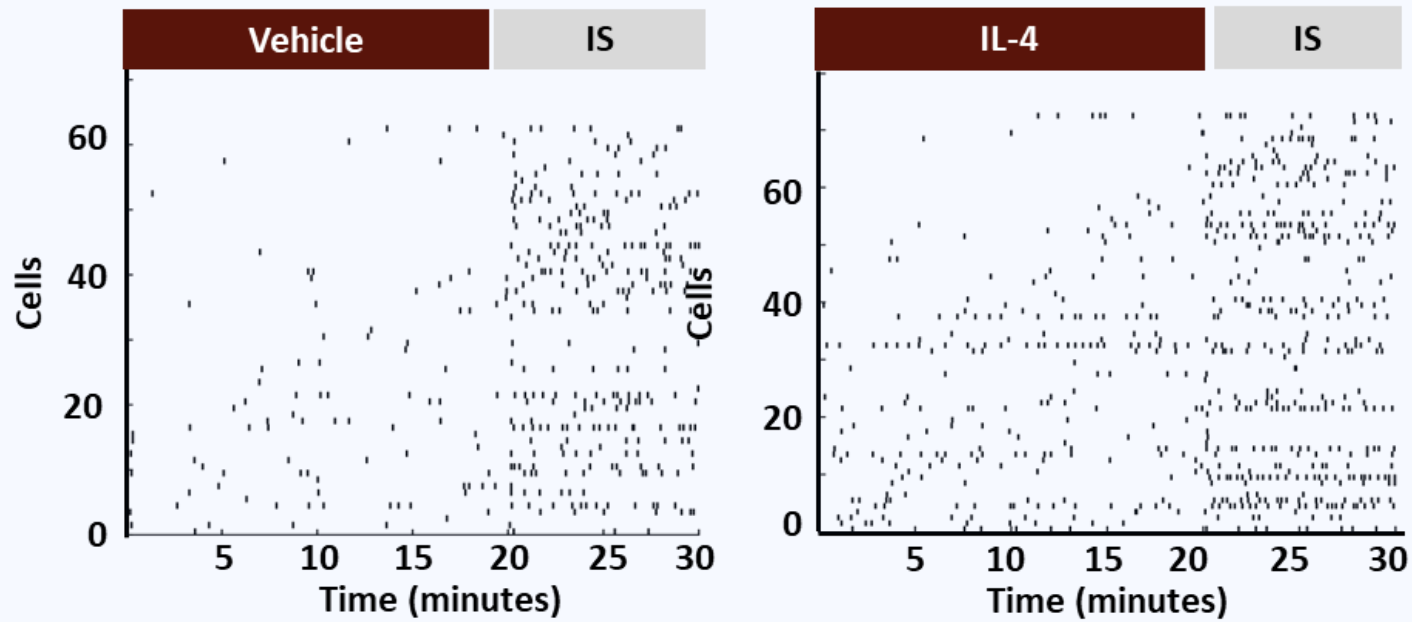
Hypothesis

- Th2 cytokines induce spontaneous increased neuronal activity in sensory neurons and form the **basis of hypersensitization** to touch and other non-painful or non-itchy stimuli in AD patients
- If these are mediated by IL-4 and/or IL-13, *eblasakimab* may block spontaneous neuronal activity

IL-4 induced spontaneous neuronal activity

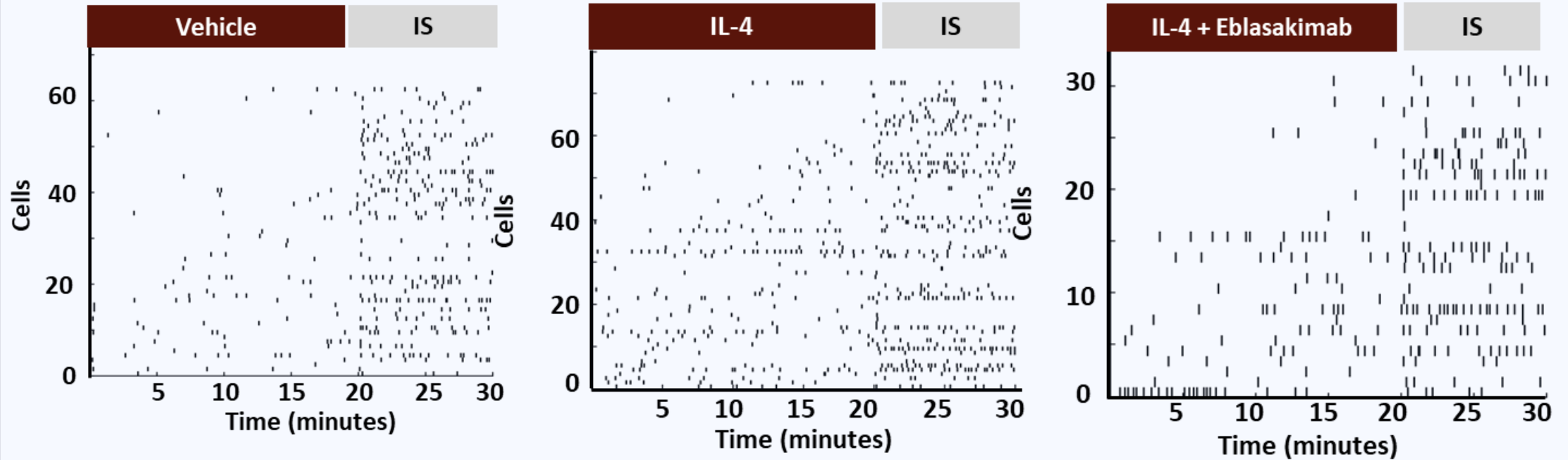


IL-4 induced spontaneous neuronal activity



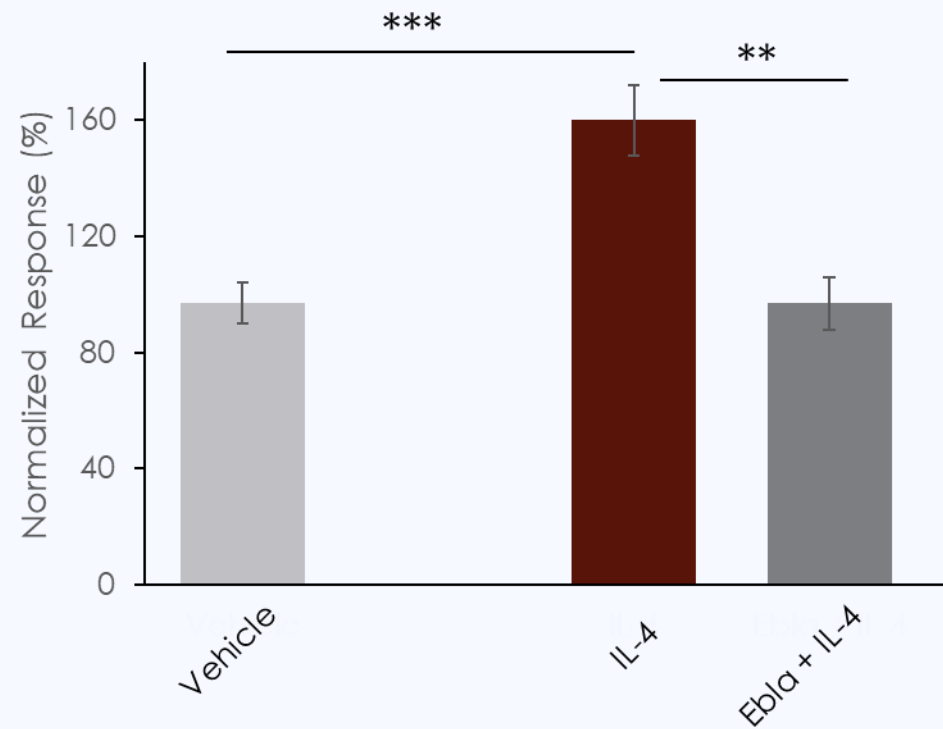
p < 0.01, * p < 0.001; error bars indicate standard error of mean; n > 200

Eblasakimab blocked IL-4 induced spontaneous neuronal activity

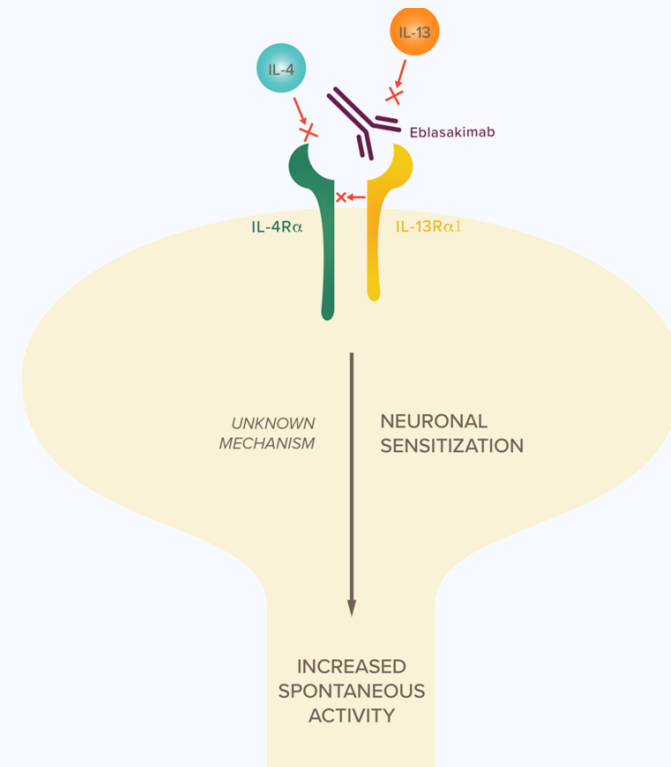


Eblasakimab blocked IL-4 induced spontaneous neuronal activity

Spontaneous Neuronal Activity



p < 0.01, * p < 0.001; error bars indicate standard error of mean; n > 200



Conclusions

- Human sensory neurons are sensitized by Th2 cytokines to pruritogens
- IL-4 and IL-13 **do not necessarily function as redundant cytokines**
- IL-13 sensitizes neurons to PAMP-20
- IL-4 enhances spontaneous neuronal activity in human sensory neurons
- Eblasakimab **potently inhibits both IL-4 and IL-13**-driven neuronal effects

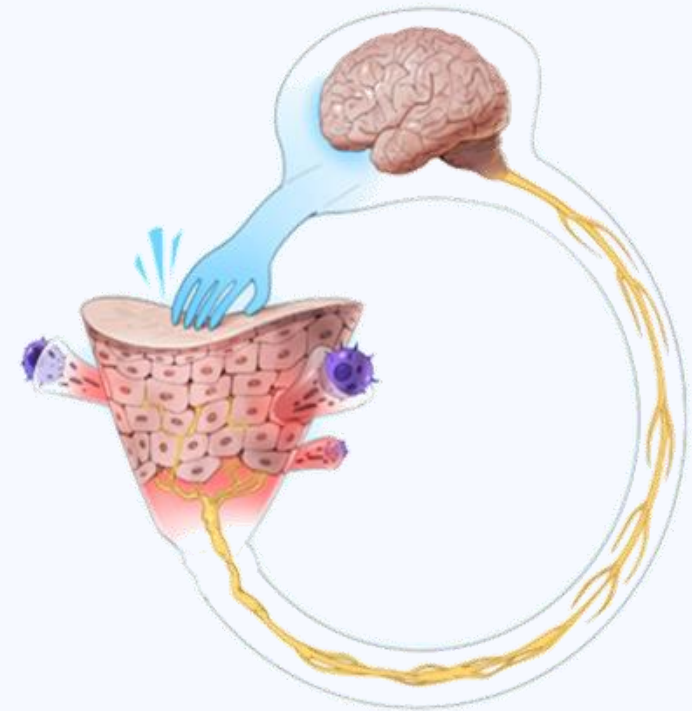
Data provide **a mechanistic basis for the reduction of itch observed in patients** with moderate-to-severe AD and potentially suggests broad anti-pruritic efficacy across different Th2 inflammatory diseases

Acknowledgements

ASLAN Pharmaceuticals

Dani Guralnick

Prescott Medical Communications Group



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