Neuromodulation Beyond Itch is Blocked by Targeting IL-13Rα1 with Eblasakimab

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INTRODUCTION

- Th2 associated cytokines interleukin-4 (IL-4) and IL-13 drive inflammation and sensitize neuronal responses to itch[1,2]
  - Both enhance neuronal itch via the Type 2 receptor
- Type 2 receptors are expressed on a range of immune and non-immune cells, including sensory neurons[1,4]
- Eblasakimab, a monoclonal human IgG4 antibody under investigation for treatment of moderate-to-severe atopic dermatitis (AD), binds to the human Type 2 receptor subunit IL-13Rα1 with high affinity, preventing signaling of IL-4 and IL-13 through IL-13Rα1 on a variety of cell types[3]
- Selective targeting of the IL-13Rα1 receptor in AD may lead to a more potent reduction in Th2-driven inflammation than blocking IL-4Rα (results presented at concurrent session LB1751)
- Sensitization of sensory neurons forms the cellular and molecular basis for multiple somatosensory disorders such as chronic itch, neurogenic inflammation, and forms of painful dysfunction[5]

OBJECTIVE

- To evaluate whether eblasakimab can potentially block cytokine-induced sensitization of neuronal itch responses and reduce spontaneous neuronal activity

METHODS

Sensitized Neuronal Itch Responses

- An *ex vivo* human neuronal model system was used to determine responses of human dorsal root ganglia (hDRG) neurons to itch signaling induced by pruritogens (bovine adrenal medulla 8-22 peptide [BAM8-22] and pro-adrenomedullin peptide 1-20 [PAMP-20]) under various conditions
- Cultured neurons were pretreated (1 hour) with either vehicle or eblasakimab, followed by the addition of cytokines for 24 hours. This was followed by pruritogen challenge.

Spontaneous Neuronal Activity

- The effects of IL-4 and IL-13 on spontaneous neuronal activity in hDRG neurons induced by inflammatory soup (IS) were measured with and without eblasakimab as a model for hypersensitization of sensory neurons in response to inflammatory conditions
- Cultured neurons were pretreated (1 hour) with vehicle or eblasakimab followed by the addition of cytokines for 72 hours
- Baseline activity was monitored over 20 minutes under test conditions; a change in internal calcium greater than 0.2 ΔF/F0 was identified as a spontaneous calcium spike event

Cell Culture and Calcium Imaging

- All hDRG neurons used for this study were isolated from organ donors in the United States after obtaining informed consent in accordance with state and federal regulations, and the United Network for Organ Sharing policies[6]
- Neuronal itch responses and spontaneous neuronal activity were captured by live cell calcium imaging
- Images were acquired at 0.2 Hz and analyzed using MetaMorph software from Molecular Devices

CONCLUSIONS

Sensitized Neuronal Itch Responses

- Eblasakimab significantly reduced the IL-4 and IL-13 induced sensitized neuronal itch responses to BAM8-22
- IL-13 sensitized hDRG neurons to PAMP-20, demonstrating that the itch-specific MRGPRX2 receptor is expressed and functional in human sensory neurons
- Eblasakimab significantly reduced the IL-13 driven sensitization effects on PAMP-20 induced neuronal itch responses, which may allow eblasakimab to reduce itch more broadly, even beyond AD
- These data suggest that Type 2 cytokines may have neuronal sensitization roles in a variety of chronic itch-associated diseases

Spontaneous Neuronal Activity

- The increased spontaneous neuronal activity induced by IL-4 was significantly reduced by eblasakimab

Overall Takeaways

- Intriguingly, our preliminary data revealed that IL-4 and IL-13 do not necessarily function as redundant cytokines in different sensitized itch mechanisms and amplification of spontaneous neuronal activity
- Unlike ligand-directed antibodies, eblasakimab potently inhibits IL-4- and IL-13-driven effects, which may be desirable to treat diseases driven by Type 2 inflammation
- These data provide a mechanistic basis for the reduction of itch observed in moderate-to-severe AD patients treated with eblasakimab in a phase 1b clinical trial

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AUTHOR DISCLOSURES

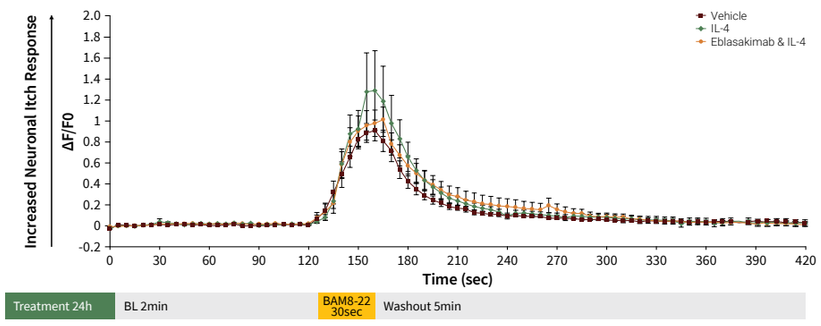
Y. Miron and P. E. Miller are employees of AnaBios Corporation; C. Firth and F. Cevikbas are employees of ASLAN Pharmaceuticals.

KEY RESULTS: IL-4 AND IL-13 HAVE DISTINCT EFFECTS ON ITCH PATHWAYS AND NEURONAL EXCITABILITY THAT CAN BE INHIBITED BY TARGETING IL-13Rα1 WITH EBLASAKIMAB

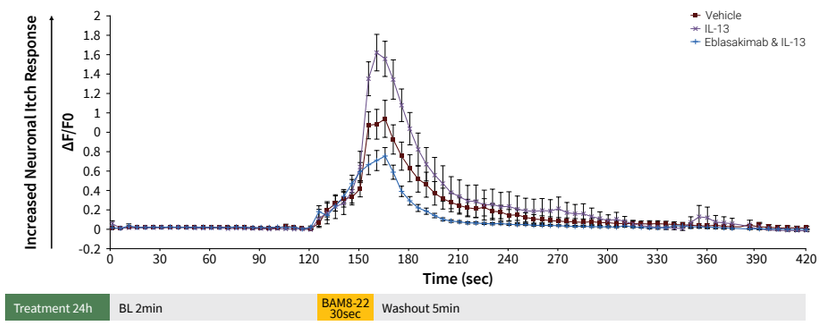
- Pre-stimulation of hDRG neurons with IL-4, IL-13, and IL-4 + IL-13 combined showed a neuronal enhancer effect with no obvious synergy on pruritic pathways (Figure 1A-D)
  - Eblasakimab significantly reduced the sensitized responses to BAM8-22 maximally up to 80% in single donors compared to control conditions (data not shown), with an average of 55% inhibition (p=0.0001) (Figure 1A-D)
- IL-13 sensitized hDRG neuronal responses to PAMP-20, a ligand for the Mas-related G-protein coupled receptor X2 (MRGPRX2), considered to be an itch-specific receptor[7-8] (Figure 2A-B)
  - IL-4 had no sensitizing effect in this set of neurons from a single donor (Figure 2A-B)
  - Eblasakimab significantly inhibited the IL-13 enhanced PAMP-20 neuronal responses in this donor (Figure 2A-B)
- Preliminary data showed that IL-4 directly induced spontaneous activity, but did not alter the IS-induced inflammatory activity in hDRG neurons (Figure 3A-D)
  - Eblasakimab reduced spontaneous activity induced by IL-4 treatment (Fig 3A-D)

Fig 1: Sensitized Neuronal Itch Responses to BAM8-22: Representative Time Courses

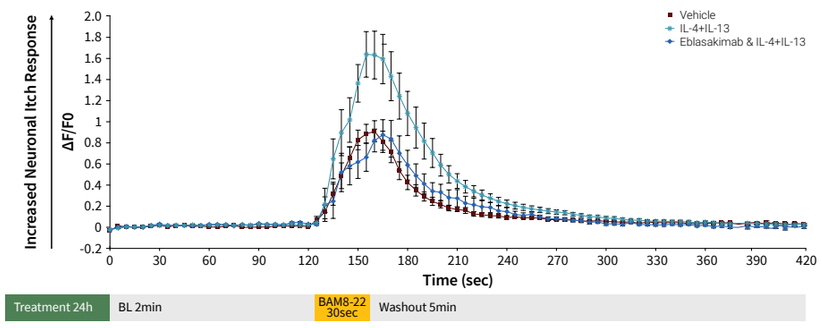
A. Prolonged Eblasakimab Exposure Reduced IL-4-Driven Neuronal Itch Sensitization to BAM8-22



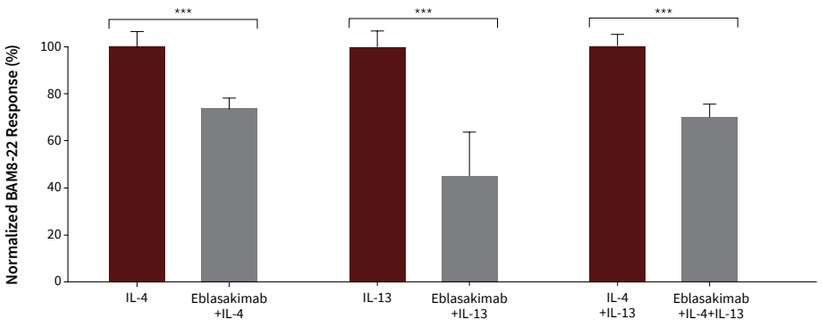
B. Prolonged Eblasakimab Exposure Reduced IL-13-Driven Neuronal Itch Sensitization to BAM8-22



C. Prolonged Eblasakimab Exposure Reduced Combined IL-4 and IL-13-Driven Neuronal Itch Sensitization to BAM8-22



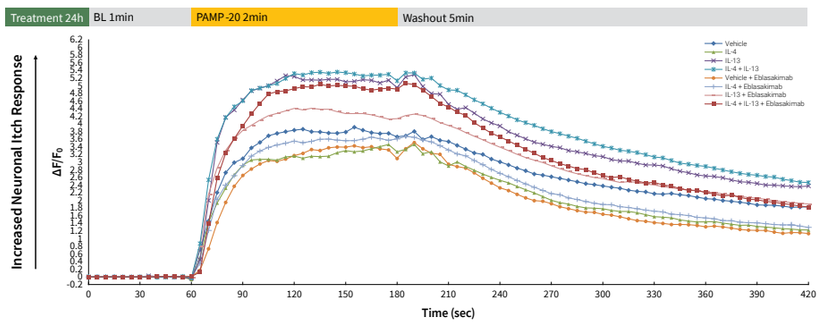
D. Summary of Cytokine + Eblasakimab Effects on Neuronal Responses to BAM8-22



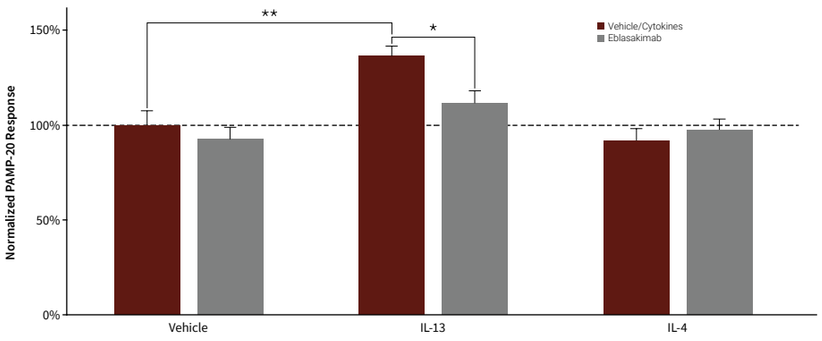
BAM8-22, bovine adrenal medulla 8–22 peptide; BL, baseline measurement; h, hours; IL-4, interleukin-4; IL-13, interleukin-13; sec, seconds.
Cells were pretreated with eblasakimab or vehicle for 1 hour followed by 24-hour cytokine treatment in the presence or absence of eblasakimab, and then challenged with pruritogen.
n = 3 donors, number of cells per experiment = 60-150
***p<0.0001. Error bars indicate standard error of mean.

Fig 2: Sensitized Neuronal Itch Responses to PAMP-20

A. Prolonged Eblasakimab Exposure Reduced IL-13-Driven Neuronal Itch Sensitization to PAMP-20: Representative Time Course



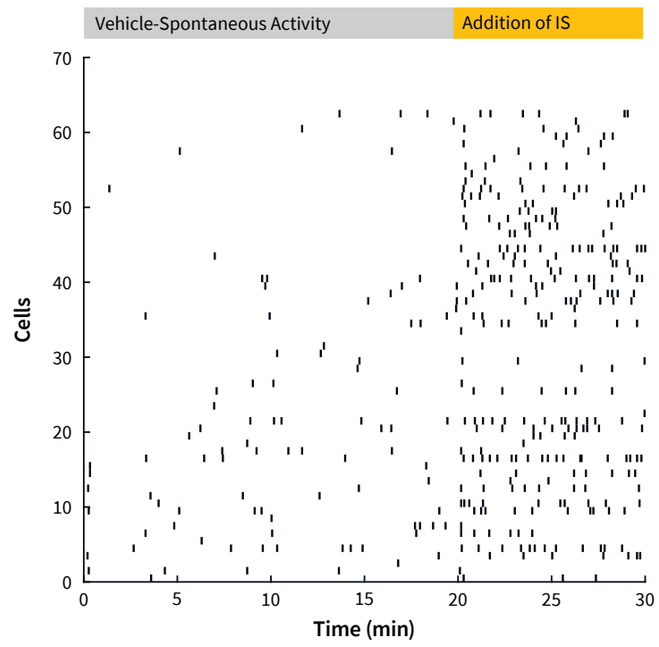
B. Summary of Vehicle and IL-4/IL-13 + Eblasakimab Effects on Neuronal Response to PAMP-20



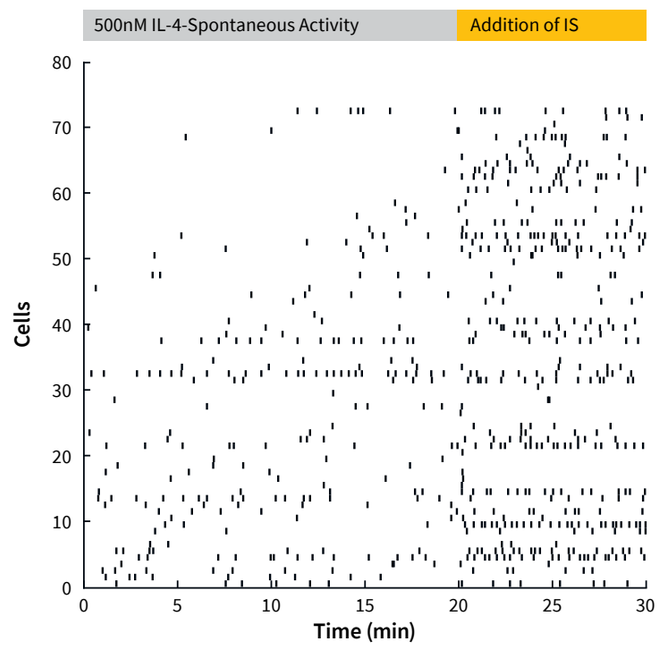
BL, baseline measurement; h, hours; IL-4, interleukin-4; IL-13, interleukin-13; min, minute; PAMP-20, pro-adrenomedullin peptide 1-20.
Cells were pretreated with eblasakimab or vehicle for 1 hour followed by 24-hour cytokine treatment in the presence or absence of eblasakimab, and then challenged with pruritogen.
n = 1 donor, number of cells per experiment = 60-150
*p<0.05, **p<0.01. Error bars indicate standard error of mean.

Fig 3: Spontaneous Neuronal Activity: Representative Raster Plots

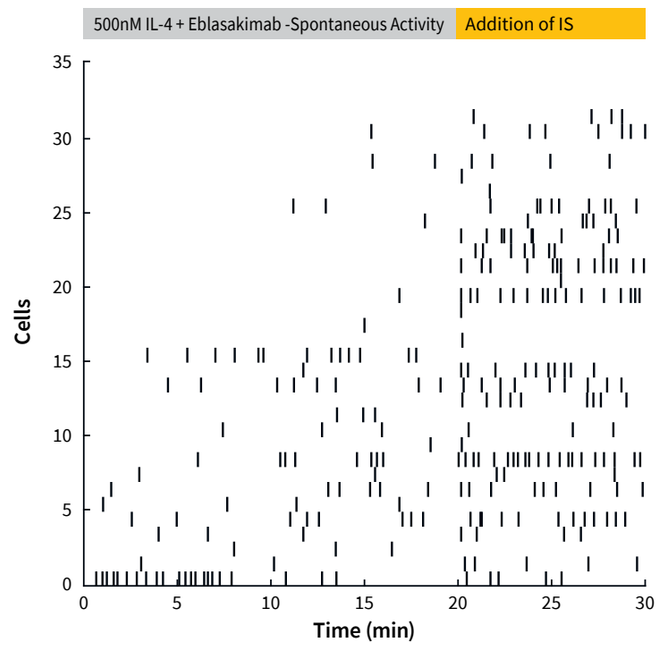
A. Vehicle



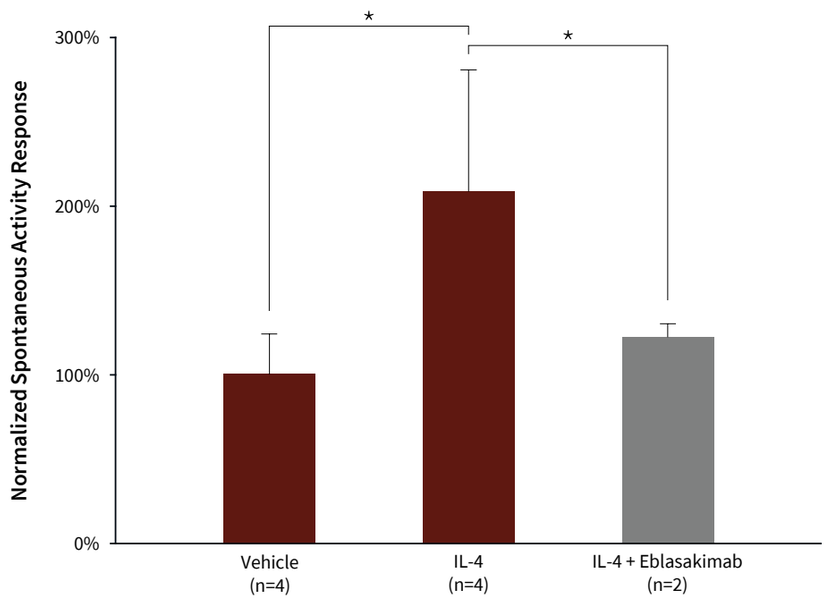
B. IL-4



C. IL-4 and Eblasakimab



D. Summary Of Spontaneous Neuronal Activity Induced by IL-4 With and Without Eblasakimab



BL, baseline measurement; IL-4, interleukin-4; IL-13, interleukin-13; IS, inflammatory soup; min, minute; SA, spontaneous activity.
Cells were pretreated with eblasakimab or vehicle for 1 hour followed by 72-hour cytokine treatment in the presence or absence of eblasakimab, and then exposed to IS.
n = number of donors, number of cells per experiment = 60-150
*p<0.05. Error bars indicate standard error of mean.

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