New Insights Into Neuronal Itch Mechanisms by Targeting IL-13Rα1 With Eblasakimab

Yannick Miron,1 Paul Miller,1 Carl Firth,2 and Ferda Cevikbas2
1 AnaBios Corporation, 3030 Bunker Hill St., Suite 312, San Diego, CA 92109
2 ASLAN Pharmaceuticals, 101 Jefferson Drive, Menlo Park, CA 94025

INTRODUCTION

- Chronic itch is a cardinal feature of multiple type-2 inflammation-associated skin disorders such as atopic dermatitis (AD).1
- Itch signaling in AD has been recently postulated to be amplified by inflammatory cytokines present in the skin, which exacerbate immune responses, disrupt the skin barrier, and drive disease pathology.2
- Recently, it has been shown that interleukin-13 (IL-13) acts as a neuronal enhancer for a multitude of different itch pathways in human neurons.3

A prior murine study established that interleukin-4 (IL-4) and IL-13 do not induce itch but rather sensitize neuronal itch responses;2,4 additionally, the study showed a direct effect of IL-4 in human sensory neurons.3

Eblasakimab, a first-in-class, fully human monoclonal antibody under investigation for the treatment of moderate-to-severe AD, binds the human IL-13 receptor α1 subunit (IL‑13Rα1) with high affinity and blocks the pre-stimulated IL-13-mediated signaling in human neurons.5

Figure 1. Eblasakimab Mechanism of Action

OBJECTIVE

To determine the impact of targeting the IL-13Rα1 receptor with eblasakimab on neuronal itch responses

METHODS

- An ex vivo human neuronal model system was used to determine neuronal responses of human dorsal root ganglia (hDRG) neurons to itch signaling induced by the pruritogen BAM22 under various conditions (Figure 4)
- Neuronal responses were captured by live cell calcium imaging, with a minimum of 50 hDRG neurons used per assay
- 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
- hDRG cells were loaded with Fluo-8-AM for 30 minutes and placed under the microscope to measure cytoplasmic calcium
- Images were acquired at 0.2 Hz and analyzed using MetaMorph software from Molecular Devices

RESULTS

1. Incubation of human sensory neurons with IL-4, IL-13, and IL-4 + IL-13 combined elicited an enhanced pruritic neuronal effect profile in response to the pruritogen BAM22 (Figure 2A-C)
2. Eblasakimab attenuated the IL-4- and IL-13-driven enhanced responses (Figure 2A-C)
3. Simultaneous application of both IL-4+IL-13 produced no obvious synergy or combined additive enhancer effects on pruritic pathways (Figure 2A-C)

CONCLUSIONS & OUTLOOK

- Human sensory neurons pre-stimulated with IL-4, IL-13, and their combination showed enhanced neuronal itch effect profiles
- Observed differences in the neuronal sensitization effects between IL-4 and IL-13 warrant further investigation
- Eblasakimab significantly reduced neuronal itch responses to IL-4, IL-13, and their combination
- Results suggest that both IL-4 and IL-13 cytokines may play a role in amplifying neuronal itch responses via type 2 IL-13Rα1 receptors

The finding that eblasakimab treatment reduced pruritogenic neuronal responses sensitized by cytokines below vehicle controls suggests that IL-13Rα1 may play an additional role in neuro-immune modulation beyond the cytokine-related neuronal itch sensitization

Future studies could further investigate the molecular basis of the neuro-immune modulatory effects driven by eblasakimab’s binding to neuronally expressed IL-13Rα1

These results suggest a mechanistic basis for the improvement in pruritus observed with eblasakimab treatment in participants with moderate-to-severe AD in the Phase 2b clinical trial.

The observed dual inhibitory effects of IL-4 and IL-13 by targeting IL-13Rα1 with eblasakimab could possibly benefit other type-2 immune disorders in which neuronal sensitization might be part of the disease pathology.

KEY RESULTS: EBLASAKIMAB SIGNIFICANTLY REDUCED CYTOKINE-ENHANCED NEURONAL ITCH RESPONSES

- Quantification of relative neuronal response showed eblasakimab significantly reduced neuronal responses to IL-4, IL-13, and their combination by an average of up to 40% (p<0.001) (Figure 3A), with some responses demonstrating inhibition up to 100% (Figure 2B, C)
- Eblasakimab treatment in the presence of cytokines reduced pruritic neuronal responses below vehicle conditions (Figure 3B)

REFERENCES


ACKNOWLEDGEMENTS

This work was funded by ASLAN Pharmaceuticals Pte LTD. Writing, editorial, and graphic assistance provided by Prescott Medical Communications Group (Chicago, IL).