# Lebrikizumab Directly Reverses IL-13 Driven Neuronal Gene Regulation and Neuronal Excitability

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**Introduction:** Atopic dermatitis (AD) is a chronic, inflammatory, relapsing skin disease with a preponderance of type 2 immune cells, which release cytokines (i.e., IL-4, IL-13, and IL-31) that orchestrate the multi-faceted downstream effects of the disease. A clinical hallmark is chronic, persistent, and highly prevalent severe itch impacting the quality of life of AD patients. Our key objective is to understand the mechanistic basis of chronic itch and gain insight into the efficacy of lebrikizumab, a monoclonal investigational anti-IL-13 antibody that is in development for the treatment of moderate-to-severe AD.

**Methods:** To ascribe a laboratory surrogate to chronic itch, we employed a primary human dorsal root ganglion (hDRG) tissue culture model and stimulated these sensory neurons with IL-13 along with different pruritic as well as other inflammatory agents (with or without lebrikizumab).

**Results:** Live-cell calcium measurements demonstrate that acute as well as prolonged exposure of sensory neurons to IL-13 amplifies the neuronal responses to a multitude of signals. These arrays of neuronal potentiation elicited by IL-13 were attenuated by lebrikizumab. Additional studies with electric field stimulation suggest that acute and prolonged exposure of IL-13 increases neuronal excitability in the DRG, which is reversed by lebrikizumab underlining a direct neuro-modulatory role and may be complementary to potentiation of itch responses.

**Discussion:** To highlight the possible molecular basis of neuronal activity, we measured the downstream transcriptional targets of IL-13 using RNA Seq. Dominant transcripts that were differentially regulated by IL-13 include immune-regulatory and neuroinflammatory genes that are related to the AD disease and itch signature. AD associated gene transcripts induced by IL-13 were reversed by lebrikizumab providing the mechanistic basis for lebrikizumabs' ability to counteract the IL-13 driven neuroactive effects in this hDRG culture model. Canonical type-2 cytokine IL-13 is a neuronal enhancer of itch pathways in human sensory neurons driving sensitization of neuronal activity. The neuromodulatory effects to increase neuronal activity and the upregulation of multiple AD-associated gene transcripts suggest broad neuro-immune active roles of IL-13 which are key features of AD pathophysiology. Lebrikizumab's efficacy to reverse the neuronal driven effects of IL-13 suggest a broad effect of lebrikizumab's MoA in AD linking immune with the neuronal axis.

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