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Atopic Dermatitis is Characterized by Enrichment in a BTLA Transcriptomic Signature

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Introduction & Objectives: B and T lymphocyte attenuator (BTLA) is a co-inhibitory immune checkpoint receptor present on T cells, B cells, and dendritic cells (DCs). ANB032 is an investigational BTLA agonist antibody currently in a Phase 2b study in atopic dermatitis (AD) and has been shown to reduce the proliferation of activated T cells, reduce cytokine secretion by T helper cells, and modulate DC function in vitro. In this study, transcriptomic data from preclinical models with a focus on T cell genes were used to study the immune effects of ANB032-mediated BTLA agonism. This signature was applied to transcriptomic data from AD tissues.

Materials & Methods: Xenogeneic graft-versus-host disease (GvHD) studies were used to study human immune cell biology with bulk RNA-sequencing to capture the differential transcriptome signals between ANB032-treated and control groups. Purified human PBMCs were adoptively transferred into irradiated NOD-scid IL2Rγnull mice and cohorts were treated with ANB032 or isotype control. At the study midpoint, gene signatures of sorted human T cells were profiled. To generate a robust BTLA signature, the most differentially expressed genes from this study were combined with previously identified genes altered by BTLA agonism in B and T lymphocytes (Stienne et al. 2022). Next, enrichment of this BTLA signature in skin from AD patients and healthy controls using a published data set was probed (Guttman-Yassky et al. 2019).

Results: ANB032 downregulated multiple inflammatory pathways in the GvHD model and reduced expansion of human T cells. ANB032-treated cohorts decreased immune pathways including T cell activation and proliferation, T-helper cell differentiation, co-stimulatory receptor signaling, TLR signaling, and type 1 IFN signaling compared to controls. Downregulated genes of interest included those encoding OX40, IL-4R, IL-2Ra, IL-18RAP, NFKBIA, T-bet, and granzyme B. These same pathways were upregulated in AD lesional skin compared to healthy skin. In AD lesional skin, BTLA levels were elevated, and HVEM (a natural BTLA agonist ligand) levels were decreased suggesting insufficient agonism. Gene set variation analysis (GSVA) using the BTLA signature showed significant enrichment in AD patients compared to healthy controls (p-value = 6.58 x 10-14) (Figure 1).

Conclusion: A BTLA transcriptomic signature was derived from experimental data to study the relevance of the BTLA pathway in human disease. Significant overlap between genes modulated by BTLA agonism via ANB032 and clinically validated immune genes/pathways in AD patient skin was demonstrated. Furthermore, this BTLA signature was enriched in AD skin highlighting the potential role for this pathway in the pathogenesis of AD. These human translational data, additional in vitro data, and results from a Phase 1 healthy volunteer study support the ongoing double-blind, placebo-controlled, global Phase 2b study of ANB032 in moderate-to-severe AD (NCT05935085).

References:

Guttman-Yassky E, et al. J Allergy Clin Immunol 2019;143:155-72.

Stienne C, et al. Cell Rep 2022;38:110553.

Figure 1. BTLA signature gene set enrichment shows statistically significant increase in AD lesional skin compared to healthy skin

