ZB-168 Potently Inhibits Thymic Stromal Lymphopoietin–Mediated Inflammation

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Abstract

Background: Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine synthesized in response to various stimuli including allergens and invading pathogens. Biological functions of TSLP require heterodimer formation between the TSLP receptor (TSLPR) and IL-7 receptor-a (IL-7Rα), which polarize dendritic cells to induce type 2 inflammation and directly expand and/or activate Th2 cells, group 2 innate lymphoid cells, basophils, and other immune cells. Stimulation with TSLP has previously been shown to potently induce thymus and activation-regulated chemokine (CCL17/TARC) and macrophage-derived chemokine (CCL22/MDC) which recruit T cells to the site of inflammation. This study evaluated the potency of ZB-168, a fully human anti-IL-7Rα antibody, in TSLP-mediated chemokine production.

Materials and Methods: Whole blood was collected from 3 healthy donors for use in these studies. Purified CD14+ monocytes were subsequently stimulated with TSLP in the presence/absence of ZB-168 (anti-IL-7Rα), anti-TSLPR, or anti-TSLP for 24 hours. Levels of CCL17/TARC and CCL22/MDC were assessed in culture supernatants using a Quantikine® ELISA. All participants provided written consent before enrollment.

Results: TSLP dose-dependently stimulated the secretion CCL17/TARC and CCL22/MDC. Treatment with ZB-168 significantly inhibited the TSLP-mediated induction of CCL17/TARC and CCL22/MDC in a dose-dependent manner with IC50s of 0.05nM and 0.07nM, respectively. In comparison, the IC50s for anti-TSLP and anti-TSLPR were significantly greater than ZB-168.

Conclusion: These studies demonstrate that ZB-168 (anti-IL-7Rα) potently inhibits TSLP mediated inflammation and warrants further clinical exploration in TSLP mediated inflammatory diseases.

Targeting IL-7 and TSLP

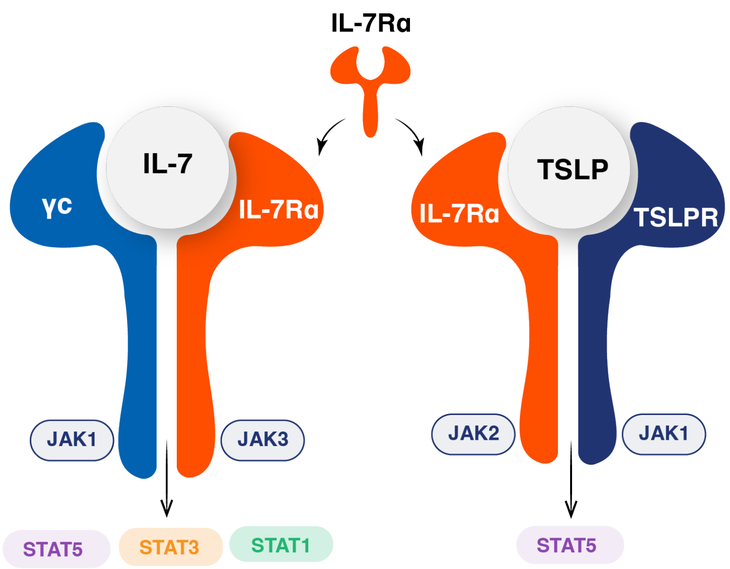
IL-7Rα is a key receptor in immune regulation, central to the signaling of cytokines ***IL-7*** and ***TSLP***

IL-7

IL-7Rα collaborates with the common gamma chain (γc) to establish the IL-7 receptor complex

Triggers a sequence of cellular events, notably **JAKs & STATs**

Vital for the growth, sustenance, and balance of T-cells



TSLP

TSLPR collaborates with IL-7Rα to create a composite complex for TSLP

This assembled complex **initiates pathways** primarily linked to **type 2 immunity**

Commonly tied to allergic responses and specific inflammatory scenarios

Methods

Blood Collection from Healthy Volunteers

PBMC Isolation

TSLP stimulation of total PBMC, CD4+ T cells, CD8+ T cells, or CD14+ monocytes in the presence/absence of blocking antibodies

Target	Drug
Anti-IL-7R	ZB-168
Anti-CD127	Analog of ADX-914
Anti-TSLP	Analog of Tezepelumab
Anti-TSLPR	Analog of UPB-101

- TSLP-induced STAT phosphorylation in CD4+ & CD8+ T cells
- TSLP-induced CCL17 and CCL22 in Monocytes
- Alarmin-induced IL-5 and IL-13 in PBMC

Characterizing the Anti-Inflammatory Properties of ZB-168

TSLP-Induced pSTAT5

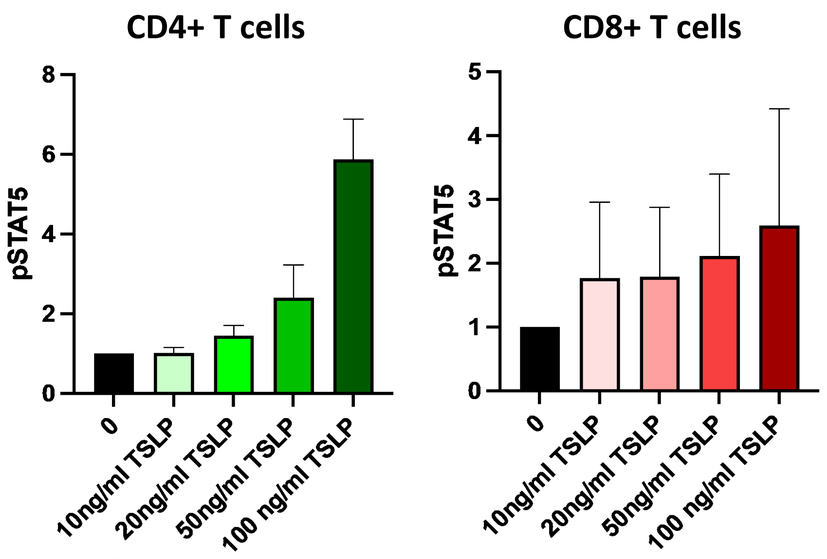


Figure 1. Purified CD4+ and CD8+ T cells were activated with anti-CD3 and anti-CD28; then stimulated with TSLP for 10 minutes. Phosphorylated STAT5 levels were assessed using flow cytometric analysis. N=3 healthy volunteers. Data presented as mean +/- standard error.

TSLP-Induced Chemokines

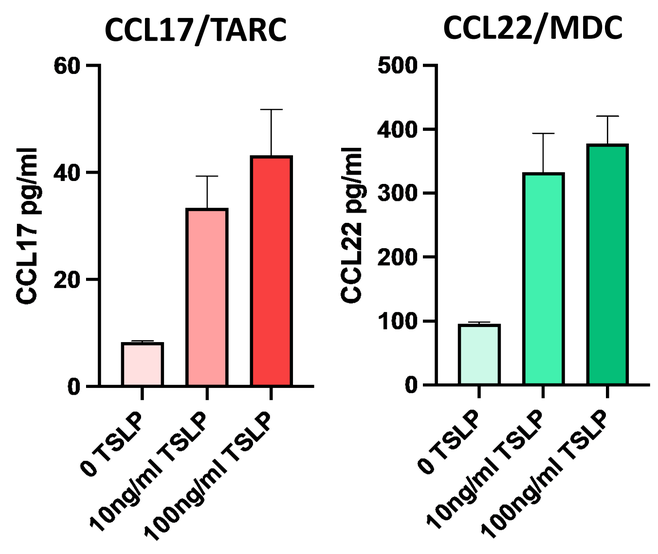


Figure 2. Purified monocytes (CD14+) were stimulated with TSLP to assess the production of CCL17/TARC and CCL22/MDC by ELISA. N=3 healthy volunteers. Data presented as mean +/- standard error.

% Inhibition of TSLP-Induced CCL17

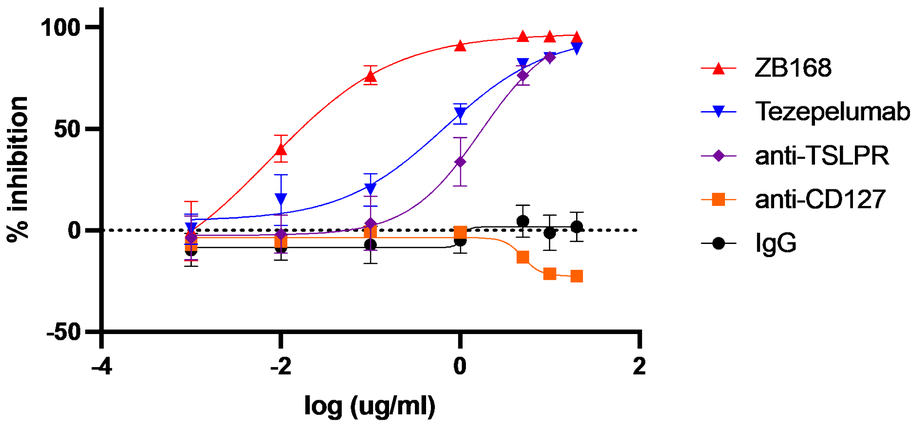


Figure 3. Purified monocytes (CD14+) were stimulated with TSLP for 24 hours in the presence/absence of anti-CD127, anti-TSLPR, Tezepelumab (anti-TSLP) and ZB-168 (anti-IL-7Rα) for 24 hours. N=3 healthy volunteers. Data presented as mean +/- standard error.

% Inhibition of Alarmin-Induced Cytokine Production

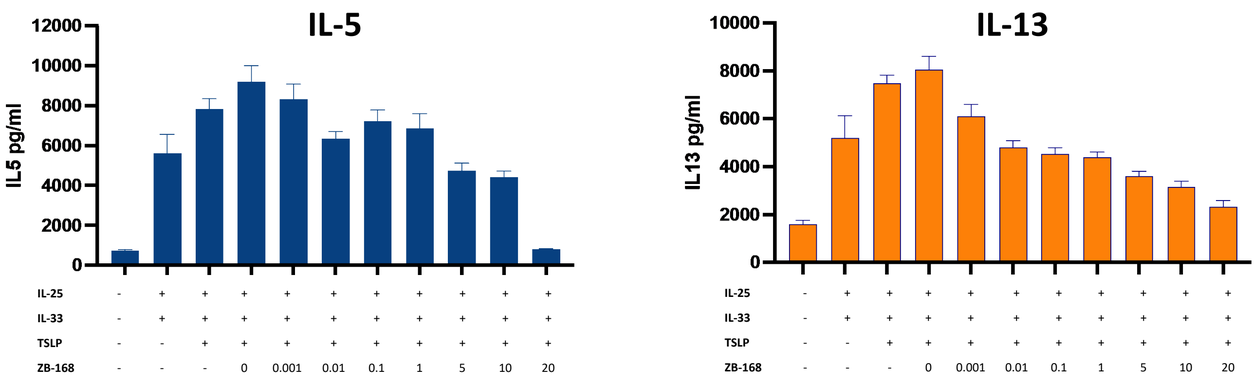


Figure 4. PBMC were stimulated with IL-25, IL-33, and TSLP in the presence/absence of ZB-168 (μg/mL) to assess the ability of ZB-168 to prevent induction of the Th2 cytokines IL-5 and IL-13. Data presented as mean +/- standard error.

Conclusions

- ZB-168 (anti-IL-7Rα) potently inhibits TSLP-mediated inflammation with potential best-in-class activity and warrants further clinical exploration in TSLP mediated inflammatory diseases

References

- Markovic and Savvides. 2020. Modulation of Signaling Mediated by TSLP and IL-7 in Inflammation, Autoimmune Diseases, and Cancer. *Frontiers in Immunology*.
- Nakajima S, Kabata H, et al. 2020. Anti-TSLP antibodies: Targeting a master regulator of type 2 immune responses. *Allergology International.*