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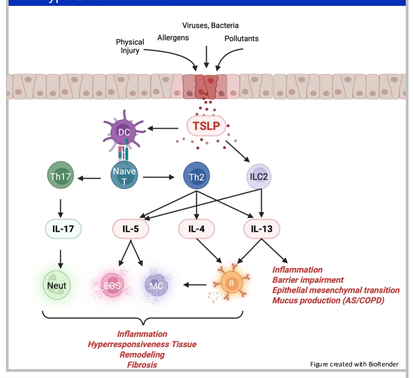
# *In vitro* characterization of solrikitug, a differentiated anti-TSLP antibody, provides distinct epitope binding profile and superior potency compared to tezepelumab

H. Kiyomi Komori Ph.D[1], Mlana Lore[2], Holly Postlethwaite[2], Volkan Manga MD[3], Lisa Wittmer PhD[3], Hector Ortega MD, ScD[1]
1- Uniquity Bio, San Diego CA, 2- Mosaic Biosciences, Boulder CO, 3- Uniquity Bio, Malvern PA

## Introduction

- Thymic stromal lymphopoietin (TSLP), a master regulator of type 2 inflammation, is an alarmin primarily secreted by barrier tissue epithelial cells in response to danger signals, infectious agents, food allergens, and environmental antigens[1]
- TSLP is an upstream mediator of inflammation in respiratory inflammatory diseases such as asthma and COPD (Figure 1)[2]
  - TSLP signals through a heterodimeric receptor comprised of TSLPR and IL-7RA (Figure 3)[1]
  - TSLP inhibition has proven to be a clinically effective therapeutic option for reducing exacerbations and symptom burden in asthma patients with type 2 and non-type 2 inflammation[3]
  - Solrikitug is a novel, potent, humanized IgG1 monoclonal antibody against TSLP in clinical development for the treatment of asthma (NCT06496607), COPD (NCT06496620), and EoE (NCT06598462)

**Figure 1:** TSLP is an upstream regulator of type 2 and non-type 2 inflammation




## Objectives

- Evaluate differences between solrikitug and tezepelumab and other anti-TSLP mAbs in TSLP binding epitopes and functional inhibitory potency

## Methods

- Human blood sample collection was performed with written informed consent from all donors and approved by local ethics committees
- Solrikitug, GSK5784283, ATI-045, WIN378, and verekitug were produced in house. Tezepelumab was commercially sourced
- Binding affinity, on- and off-rates were determined by surface plasmon resonance. Dissociation rates were evaluated over a 3 h dissociation phase
- Epitope binning was performed by biolayer interferometry with sequential antibody binding to TSLP
- Epitope mapping of solrikitug and tezepelumab was performed by deuterium exchange
- In vitro functional inhibition of TSLP activity evaluation:
  - PathHunterTSLPR/IL-7R dimerization cells were stimulated with TSLP for 16 h with and without inhibitory antibodies
  - PathHunter TSLP pSTAT5 reporter cells were stimulated with TSLP for 16 h with and without inhibitory antibodies
  - PBMC were purified from whole human blood by density centrifugation and cultured with 5 ng/ml human TSLP with or without anti-TSLP antibody for 5 days. TARC expression was evaluated by ELISA
  - Human dendritic cells were negatively selected from PBMCs. 3E5 cells were cultured with 5 ng/ml human TSLP for 48 h with or without anti-TSLP antibody

## Results

- Solrikitug binds to TSLP with similar affinity and kinetics as other anti-TSLP monoclonal antibodies (**Table 1**)

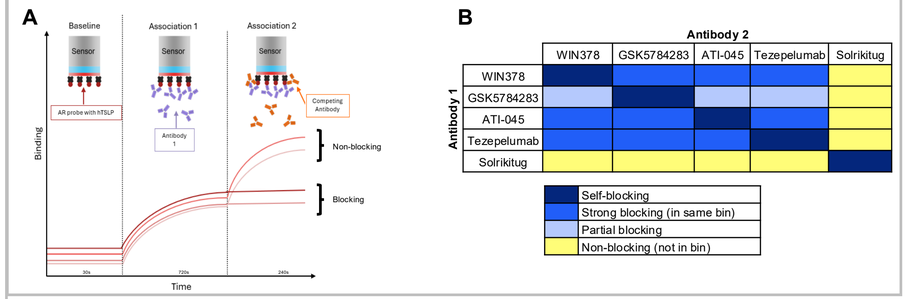
**Table 1:** Binding affinity, association and dissociation rates of anti-TSLP mAbs binding to TSLP as determined by surface plasmon resonance.

| | Parameter | Solrikitug | Tezepelumab | ATI-045 | GSK5784283 | WIN378 |
|---|---|---|---|---|---|---|
| $K_D$ | mean (pM) | 11.89 | 16.75* | 9.89 | 18.74 | 17.9 |
| | SD | 1.25 | 0.76 | 0.19 | 1.44 | 0.3 |
| | n | 4 | 4 | 2 | 2 | 2 |
| $k_a$ | mean ($M^{-1}s^{-1}$) | 7.44E5 | 3.95E5 | 1.93E5 | 8.51E5 | 4.48E5 |
| | SD | 5.47E4 | 2.25E4 | 3.54E3 | 6.51E4 | 7.07E3 |
| | n | 4 | 4 | 2 | 2 | 2 |
| $k_d$ | mean ($s^{-1}$) | 8.80E-6 | 6.61E-6 | 1.90E-6 | 1.59E-5 | 8.02E-6 |
| | SD | 3.46E-7 | 9.19E-8 | n/a | n/a | n/a |
| | n | 2 | 2 | 1 | 1 | 1 |

Verekitug not tested for TSLP binding as it binds to TSLPR
* Tezepelumab published $K_D$= 15.8 pM[4]

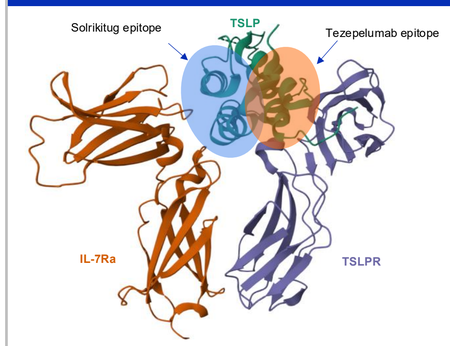
- Epitope binning demonstrates that solrikitug is in a different epitope bin than the other tested anti-TSLP antibodies

**Figure 2:** Epitope binning of solrikitug and other anti-TSLP monoclonal antibodies. (**A**) Epitope binning experimental design (**B**) Solrikitug binds a unique epitope on TSLP and does not inhibit binding of other anti-TSLP monoclonal antibodies




- Solrikitug binds to an epitope on TSLP required for binding to IL-7RA and assembly of the full signal transducing complex (**Figure 3**)
- Tezepelumab binds to an epitope that is required for binding to TSLPR
- ATI-045, GSK5784283 and WIN378 are predicted to bind similar or overlapping epitopes to tezepelumab (**Figure 2B**)

**Figure 3:** Structural representation of solrikitug and tezepelumab epitopes on TSLP




- TSLP signaling requires dimerization of TSLPR and IL-7R
  - Solrikitug is 15X more potent at inhibiting receptor dimerization compared to tezepelumab (**Table 2**)
- TSLP signals through the JAK/STAT pathway
  - Solrikitug is 6X more potent than tezepelumab at inhibiting STAT5 phosphorylation (**Table 2**)
- TSLP stimulation of PBMCs activates dendritic cells and induces expression of TARC (CCL17)
  - Solrikitug demonstrated 10X greater inhibition of TARC expression than tezepelumab in human PBMC and purified human dendritic cells (**Table 2**)

**Table 2:** Anti-TSLP and anti-TSLPR antibodies inhibit TSLP-induced receptor dimerization and downstream signaling

| Name | Solrikitug | Tezepelumab | ATI-045 | GSK5784283 | WIN378 | Verekitug |
|---|---|---|---|---|---|---|
| **Target** | TSLP | TSLP | TSLP | TSLP | TSLP | TSLPR |
| **TSLPR/IL-7R Dimerization** n=2<br>$IC_{50}$ (mean ng/ml) | 147.4 | 2,190.0 | n.t. | n.t. | n.t. | 335.0 |
| **pSTAT5 Inhibition** n=5<br>$IC_{50}$ (mean [95% CI] ng/ml) | 638.7<br>[290.3 to 427.1] | 4,201.0<br>[1379 to 2167] | n.t. | n.t. | n.t. | 939.8<br>[491.2 to 806.6] |
| **TARC Expression (human PBMC)** n=5<br>$IC_{50}$ (mean [SD] ng/ml)<br>Maximum % Inhibition [SD] | 16.8 [12.2]<br>97.1% [1.6] | 149.5 [111.9]<br>87.6% [12.9] | 57.5 [54.8]<br>90.8% [3.5] | 43.3 [18.3]<br>90.9% [5.4] | 55.8 [63.6]<br>51.2% [18.8] | 281.5 [410.1]<br>92.8% [3.8] |
| **TARC Expression (human DC)** n=4<br>$IC_{50}$ (mean [SD] pM) | 244 [55] | 3006 [1689] | n.t. | n.t. | n.t. | n.t. |

n.t. not tested

## Conclusions

- While anti-TSLP antibodies may bind to TSLP with similar affinities, differences in epitope location may lead to differentiated inhibition of TSLP-induced function
- Solrikitug binds a unique epitope on TSLP and disrupts downstream signaling by blocking the TSLP/IL-7RA interaction rather than the TSLP/TSLPR interaction
  - Disruption of the TSLP/IL-7RA interaction may provide more complete hinderance of TSLP signaling by more potently inhibiting TSLPR/IL-7RA dimerization
- Solrikitug is 6-15X more potent at inhibiting TSLP-induced signaling compared to tezepelumab across multiple in vitro assays
- Solrikitug is ≥ 2X more potent at inhibiting TSLP-induced signaling compared to other anti-TSLP monoclonal antibodies in development
- Solrikitug is 2-17X more potent than an anti-TSLPR monoclonal antibody in development across multiple assays
- These data indicate that solrikitug is a highly potent TSLP inhibitor that has the potential to demonstrate clinical efficacy in patients with TSLP-driven diseases

1- Ebina-Shibuya and Leonard. Nat Rev Immunol 2023;23:24-37 2- Porsbjerg et al. Lancet 2023;401:858-73 3- Menzies-Gow et al. N Engl J Med 2021;384:1800-9. 4- Tezepelumab prescribing information

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**Disclosure of interest**
HKK, VM, LW & HO are employees and shareholders of Uniquity Bio
ML & HP are employees of Mosaic Biosciences