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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

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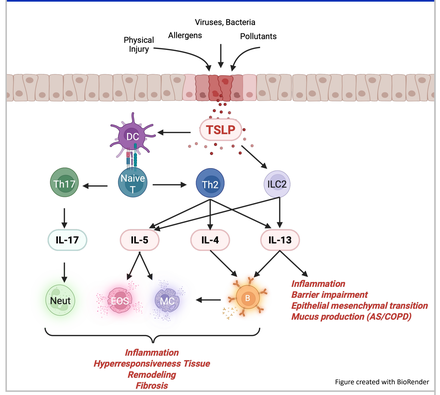
Introduction

- 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**)

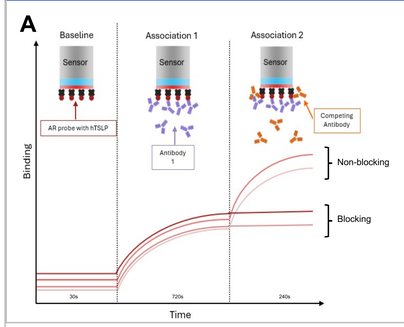
Table 1: Binding affinity, association and dissociation rates of anti-TSLP mAbs binding to TSLP as determined by surface plasmon resonance.

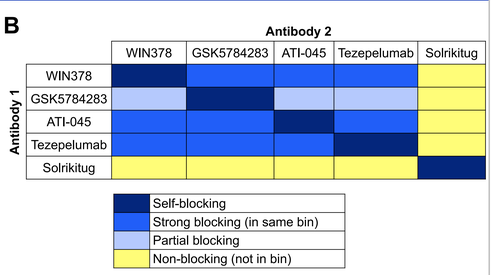
	Parameter	Solrikitug	Tezepelumab	ATI-045	GSK5784283	WIN378
K_D	mean (pM)	11.89	16.75*	9.89	18.74	17.9
	SD	1.25	0.76	0.19	1.44	0.3
	n	4	4	2	2	2
k_a	mean ($M^{-1}s^{-1}$)	7.44E5	3.95E5	1.93E5	8.51E5	4.48E5
	SD	5.47E4	2.25E4	3.54E3	6.51E4	7.07E3
	n	4	4	2	2	2
k_d	mean (s^{-1})	8.80E-6	6.61E-6	1.90E-6	1.59E-5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

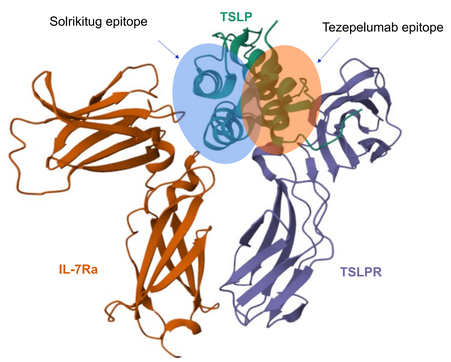
Figure 2: Epitope binning of solrikitug and other anti-TSLP monoclonal antibodies. (**A**) Epitope binning experimental design (**B**) Solrikitug binds a unique epitope on TSLP and does not inhibit binding of other anti-TSLP monoclonal antibodies





- 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 IC_{50} (mean ng/ml)	147.4	2,190.0	n.t.	n.t.	n.t.	335.0
pSTAT5 Inhibition n=5 IC_{50} (mean [95% CI] ng/ml)	638.7 [290.3 to 427.1]	4,201.0 [1379 to 2167]	n.t.	n.t.	n.t.	939.8 [491.2 to 806.6]
TARC Expression (human PBMC) n=5 IC_{50} (mean [SD] ng/ml) Maximum % Inhibition [SD]	16.8 [12.2] 97.1% [1.6]	149.5 [111.9] 87.6% [12.9]	57.5 [54.8] 90.8% [3.5]	43.3 [18.3] 90.9% [5.4]	55.8 [63.6] 51.2% [18.8]	281.5 [410.1] 92.8% [3.8]
TARC Expression (human DC) n=4 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