



ZW1528, a Bispecific Antibody Targeting IL-4Ra and IL-33 Potently Inhibits Key Mediators of Airway Inflammation

Alexey Berezhnoy

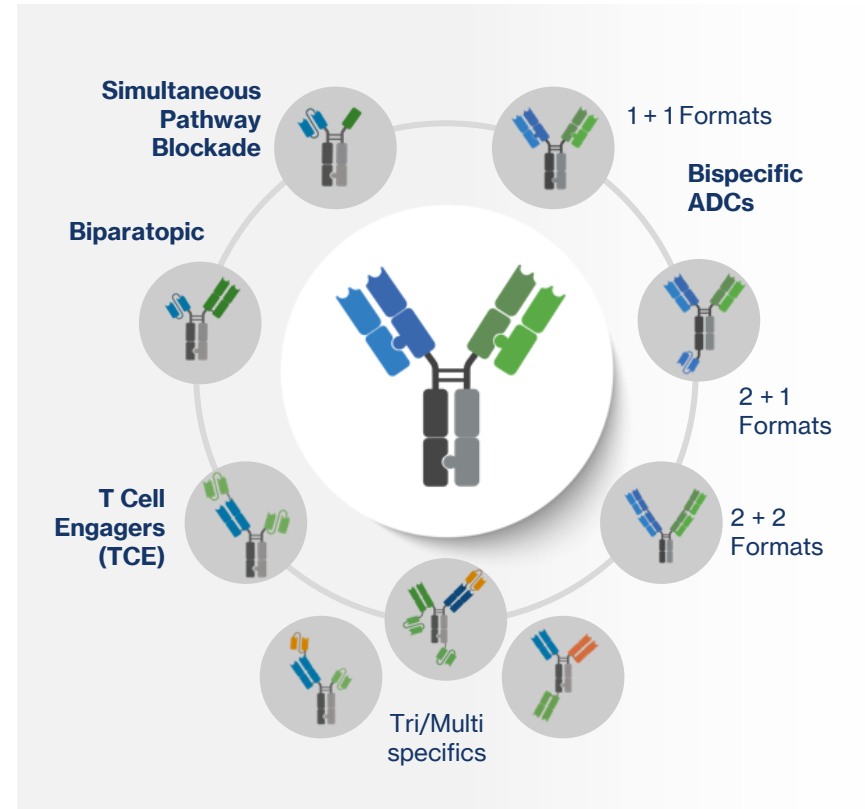
Senior Director, Immunology

World Bispecific & T Cell Engager Summit, South Korea

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Zymeworks Differentiated Pipeline of Multifunctional Therapeutics Enabled by the Azymetric™ Technology and Innovative Payloads

Program	Technology	Target
Solid Tumor Oncology: Antibody-Drug Conjugates (ADC)		
ZW191 Topoti ADC DAR 8 Fc WT	ZD06519 Payload	FRα
ZW251 Topoti ADC DAR 4 Fc WT	ZD06519 Payload	GPC3
ZW220 Topoti ADC DAR 4 Fc Mut	ZD06519 Payload	NaPi2b
ZW327* Topoti ADC DAR 8 Fc Mut	ZD06519 Payload	Ly6E
ZW427* RASi ADC DAR 8 Fc Silent	RASi Payload	Ly6E
ZW418* RASi ADC DAR 8 Biparatopic	RASi Payload	Biparatopic PTK7
ZW439* RASi ADC DAR 8 Fc Silent	RASi Payload	Claudin18.2
Solid Tumor Oncology: Multispecific Antibody Therapeutics (MSAT)		
Zanidatamab Bispecific	Azymetric™	HER2
ZW209 Trispecific TCE Tri-TCE Costim	Azymetric™, Novel anti-CD3 Conditional CD28	DLL3 x CD3 x CD28
ZW239 Trispecific TCE Tri-TCE Costim	Azymetric™, Novel anti-CD3 Conditional CD28	CLDN18.2 x CD3 x CD28
Autoimmune & Inflammatory Diseases		
ZW1528 Dual Cytokine Blocker	Azymetric™ Hetero-Fab YTE	IL4Rα x IL-33
ZW1572 Dual Cytokine Blocker	Azymetric™ Hetero-Fab YTE	IL4Rα x IL-31



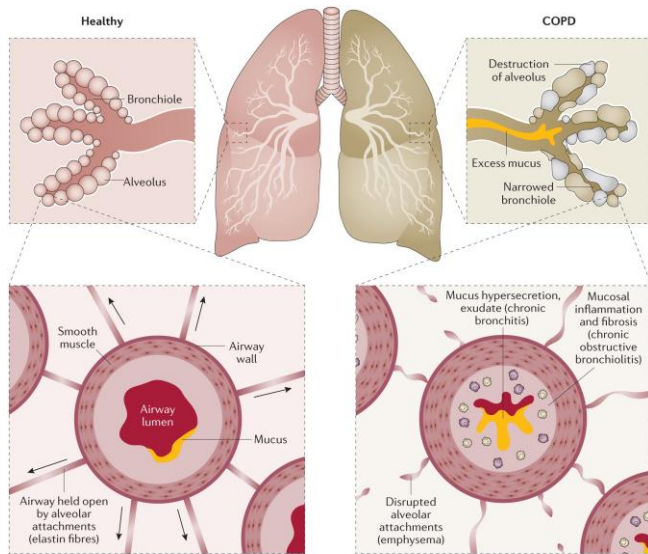
Chronic Obstructive Pulmonary Disease (COPD)

COPD burden

- COPD affects **~400 million people** worldwide
- Major risk factors include: advanced age, smoking, pollution, severe childhood lung infection
- Pharmacotherapy traditionally treated symptoms (bronchodilators & steroids)

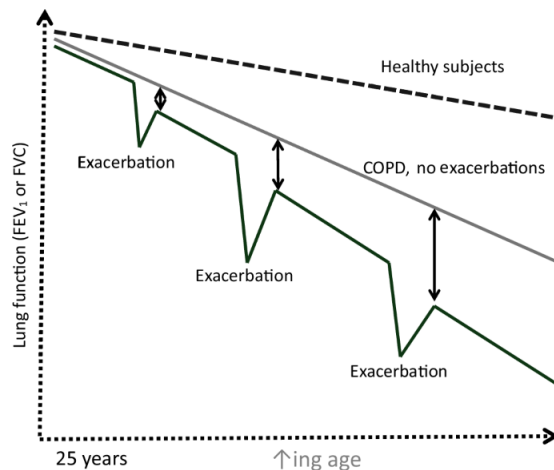
Enormous unmet need for disease modifying therapies

Progressive decline of lung function



Thickening of airway walls due to inflammation
Formation of plugs due to mucus hypersecretion

Exacerbations



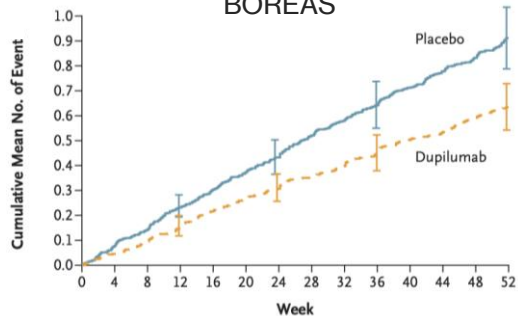
Acute worsening of symptoms requiring escalation in treatment

Type 2 and Non-Type 2 Inflammation Drives COPD

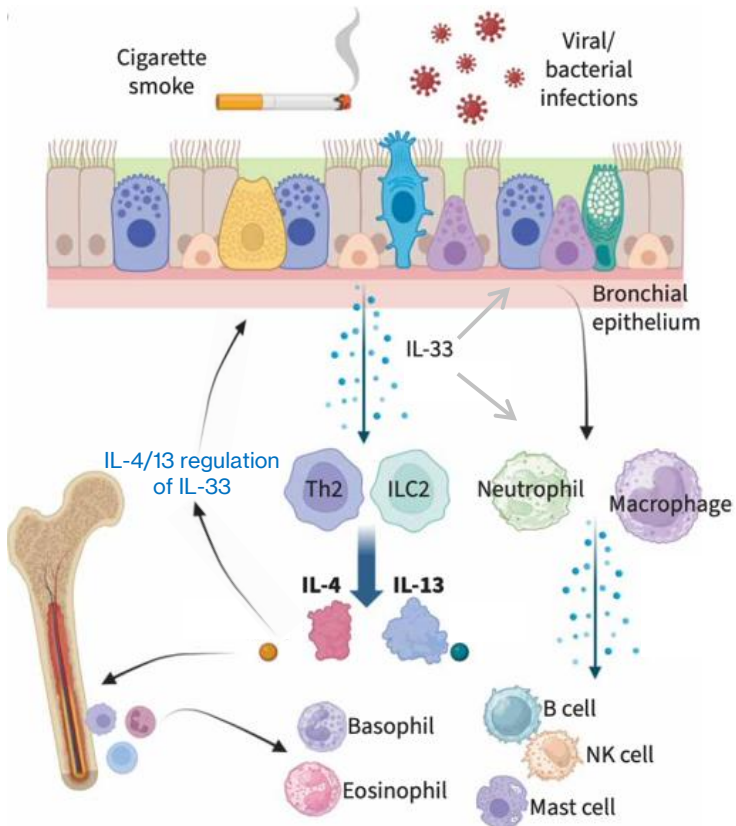
Multiple positive feedback loops getting established between IL-4/13 and IL-33



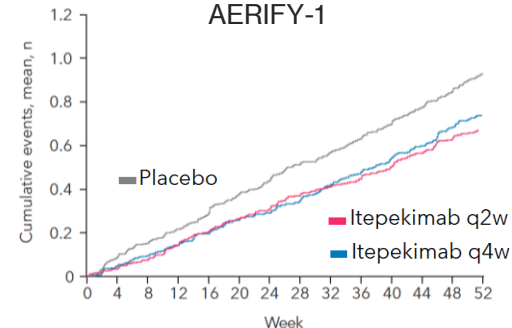
BOREAS



"Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts" ATS 2023



AERIFY-1

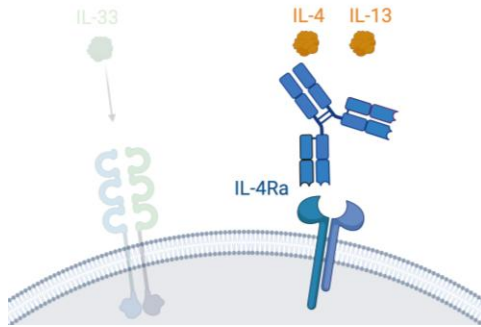


"Efficacy and Safety of Itepekimab in Former Smokers with Chronic Obstructive Pulmonary Disease: AERIFY-1 and AERIFY-2 Trials" ATS 2026

In addition, Tozorakimab COPD studies met primary endpoint of reducing exacerbations

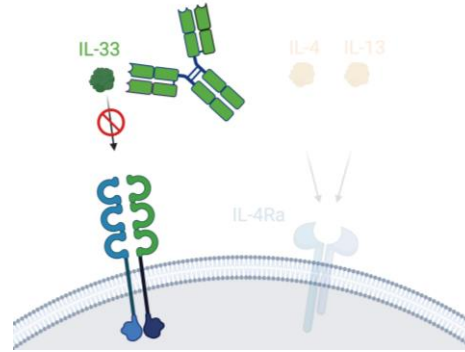
Anti-IL4R α and anti-IL-33 Therapeutics are being Developed to Target Different Aspects of COPD Pathology

Dupilumab blocks IL-4R α



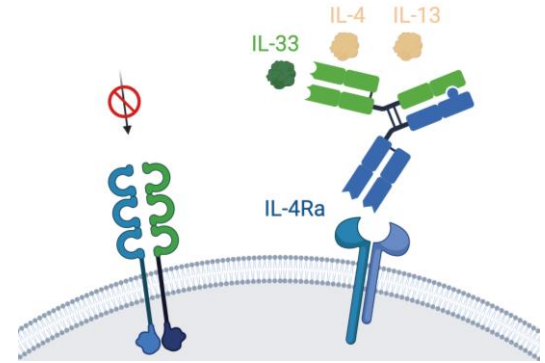
Type 2 inflammation suppression.

Itepekimab/tozorakimab block IL-33



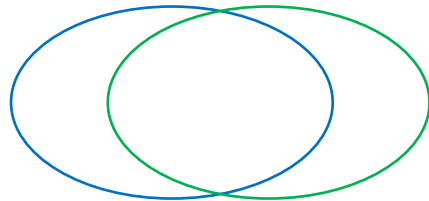
Type 2 and non-Type 2 inflammation suppression. Improved tissue remodelling.

Dual blockade by ZW1528



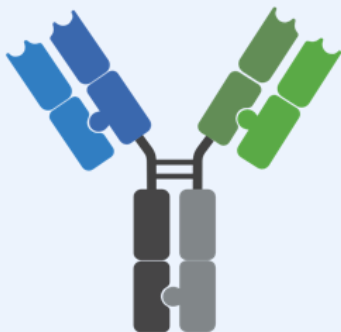
IL-4R α x IL-33 bispecific to combine the effects of two mAbs

Potential for increased efficacy in monotherapy-responsive patients






ZW1528 Binds IL-4R α and IL-33 with High Affinity

Anti-IL4R α Anti-IL-33



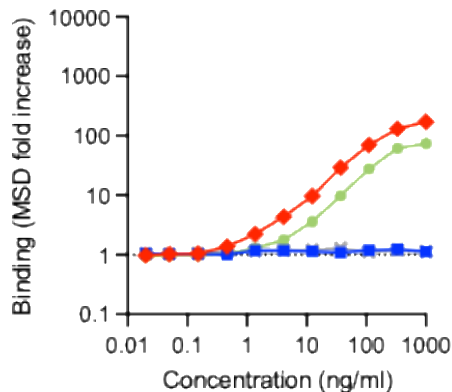
Azymetric™
IgG4
YTE

		IL-4Ra	IL-33	Fc
	Dupilumab	30 pM ¹	---	IgG4
	Itepekimab	---	42 pM ²	IgG4
	ZW1528	0.53 pM	0.7 pM	Azymetric IgG4 YTE

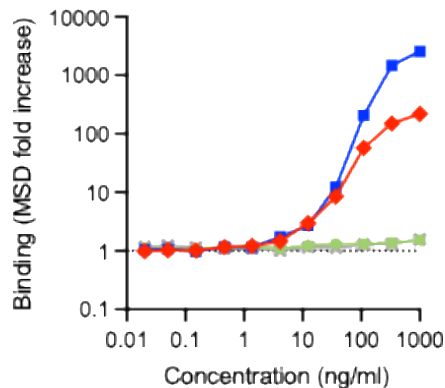
- ZW1528 binds to IL-4Ra and IL-33 with high affinity
- ZW1528 incorporates half-life extension for extended dosing intervals
- ZW1528 supports concentration to >150 mg/mL for subcutaneous administration

ZW1528 Simultaneously Binds IL-4Ra and IL-33

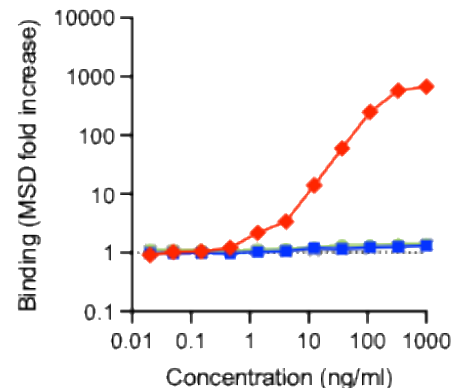
IL-33 Capture Fc Detection



IL-4Ra Capture Fc Detection

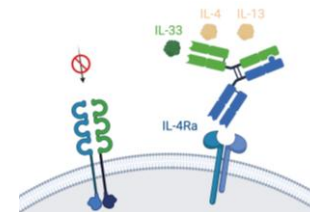


IL-33 Capture IL-4Ra Detection



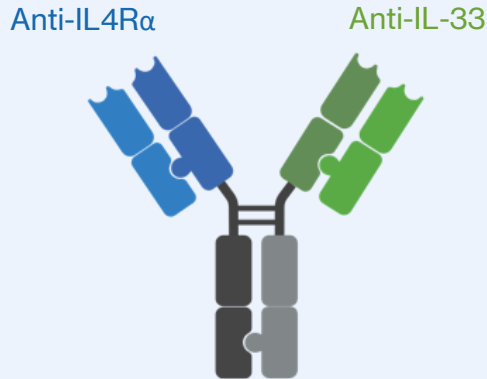
— Itepekimab (IL-33) — Dupilumab (IL-4Ra) — Control mAb — ZW1528 (IL-4Ra x IL-33)

- ZW1528 is capable of binding both targets at the same time
- Simultaneous binding could provide membrane tethering and increase local concentration of inhibitors in inflamed tissues

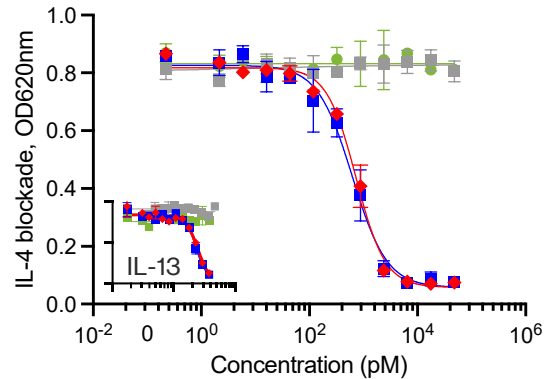


MSD plates were coated with IL-33 or IL-4Ra. ZW1528 (red), Dupilumab analog (blue), Itepekimab analog (green) and an isotype control (grey) were added to wells. Binding was confirmed by HuFc detection (A and B). Other wells had biotinylated IL-4Ra added and subsequently detected to measure the ability of antibodies already binding coated antigen to simultaneously bind the second target.

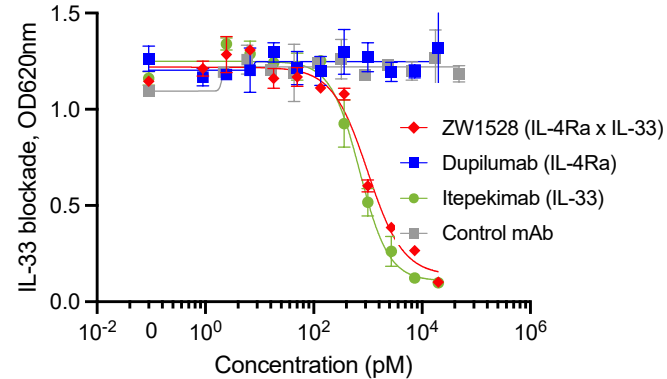
ZW1528 Effectively Blocks both IL-4/13 and IL-33 Signaling



Blockade of IL-4/13



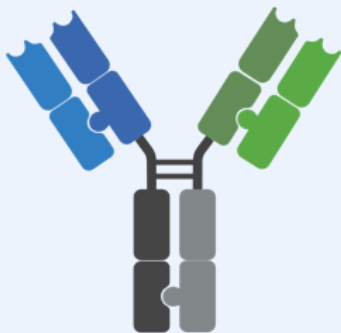
Blockade of IL-33



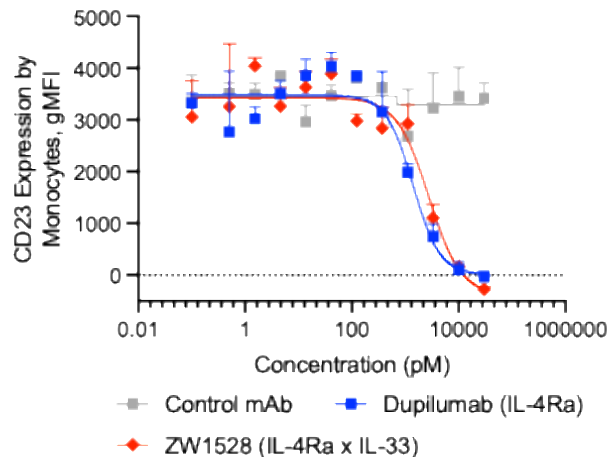
- Potency of ZW1528 similar to the ***bivalent*** benchmark mAbs
- ZW1528 blocks both targets

ZW1528 Blocks Two Complementary Pathways of Airway Inflammation in Primary Cells of COPD Patients

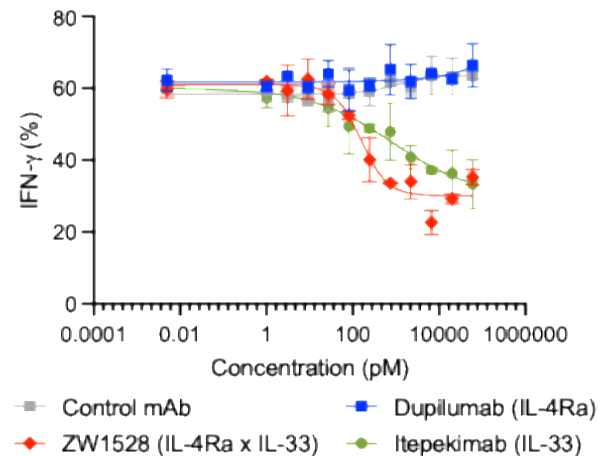
Anti-IL4R α Anti-IL-33



Blockade of IL-4



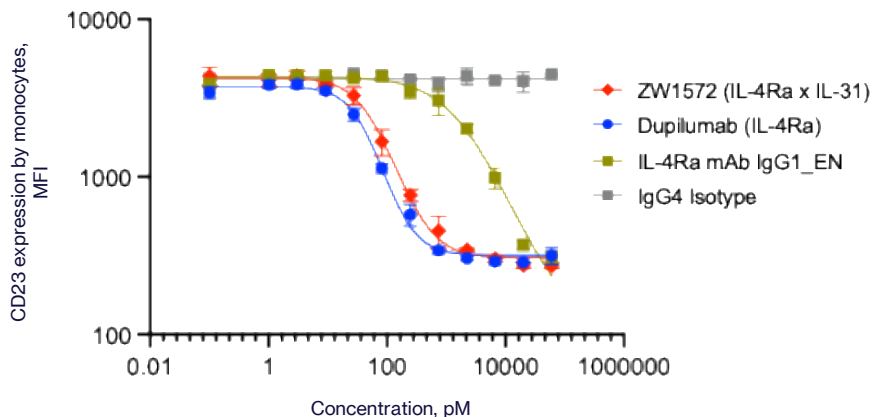
Blockade of IL-33



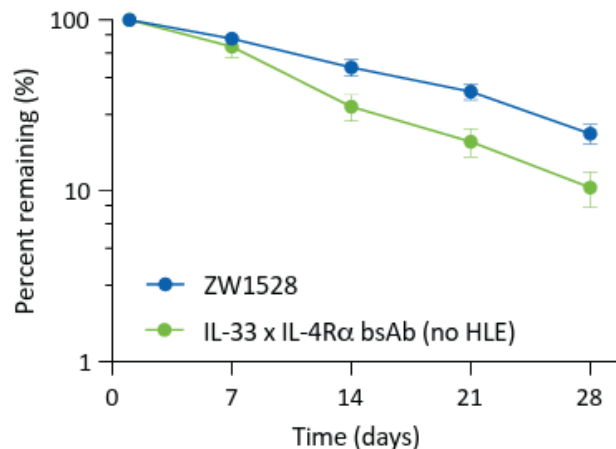
- ZW1528 effectively blocks IL-4Ra and IL-33 in PBMC of ***COPD patients*** in vitro
- Enhanced blockade of IL-33 axis

Optimized Fc Portion Enhances IL-4Ra Pathway Blockade and Pharmacokinetics

Blockade of IL-4-driven activation *in vitro*

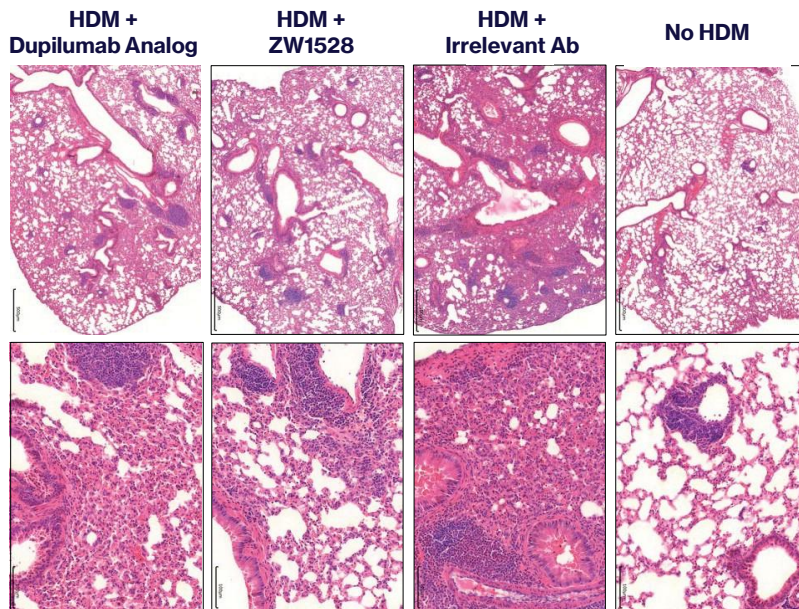
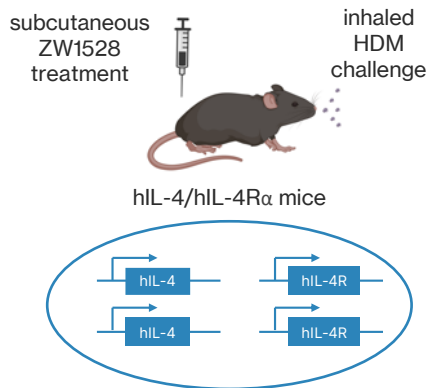


Extended half-life in humanized FcRn (Tg32) mice

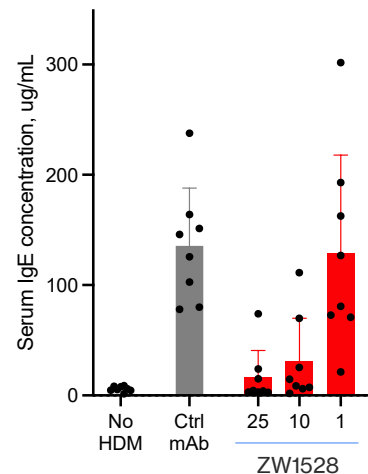


- Azymetric™ Fc platform is compatible with IgG4 Fc isotype and YTE mutations
- Selected Fc isotype/modifications demonstrate favorable profile in vitro and in vivo
 - superior target blockade compared to unmodified effector-negative IgG1
 - superior PK relative to unmodified IgG4

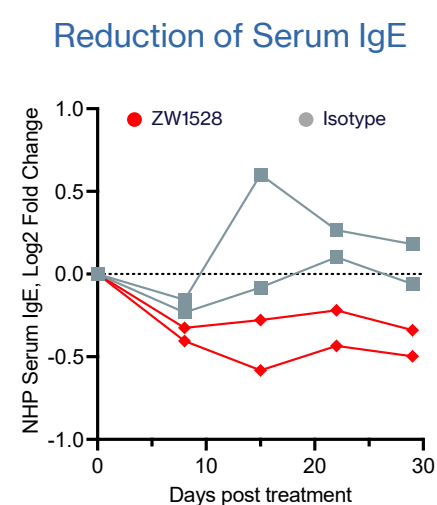
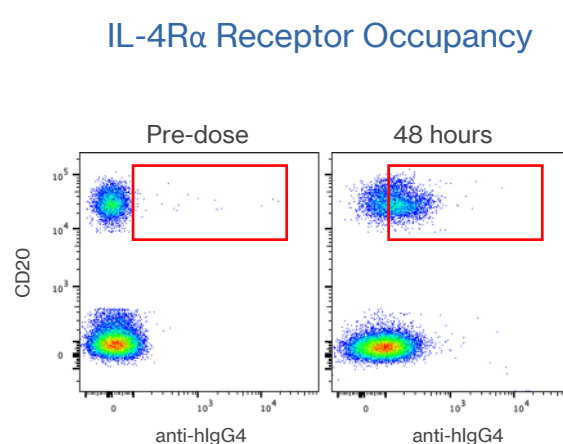
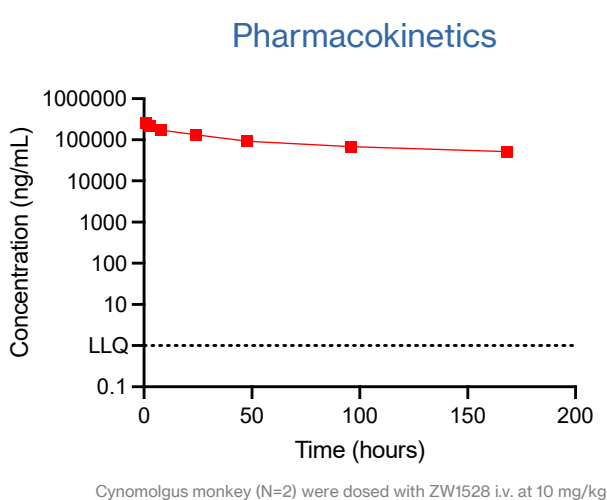
ZW1528 Blocks IL-4R α in vivo Comparable to Dupilumab



Suppression of IgE after inhaled allergen challenge

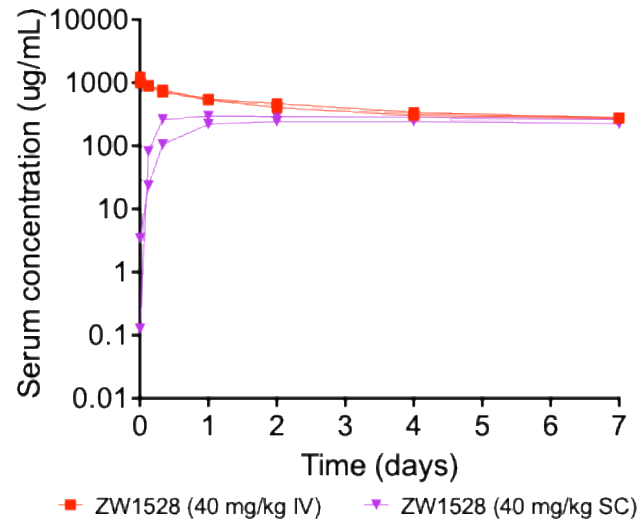
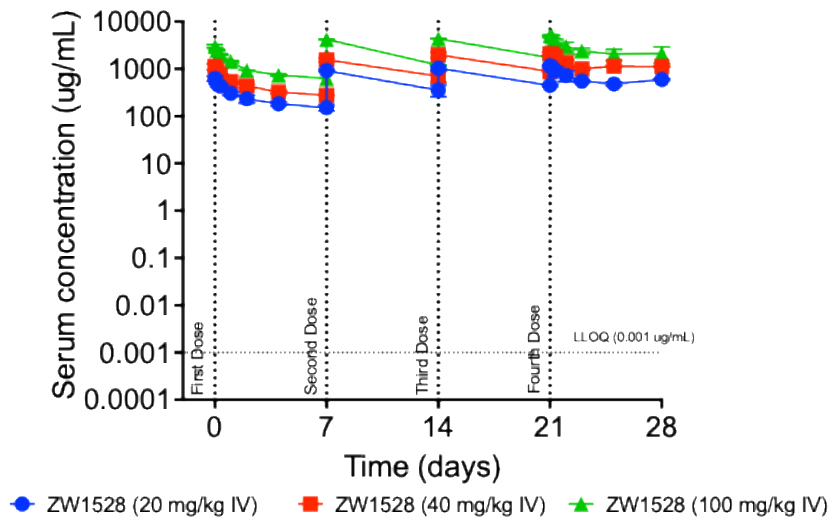


ZW1528 Demonstrates Biomarkers of IL-4R α /IL-33 Blockade in NHP



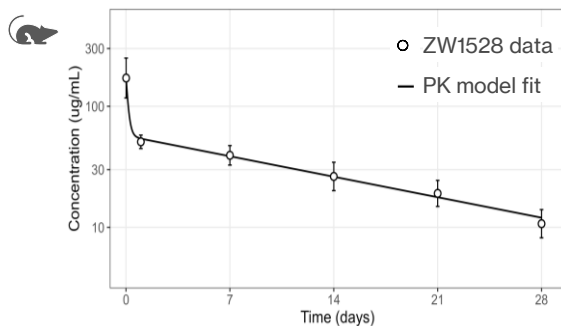
- IgG-like pharmacokinetics in non-human primates (NHP); exposure is maintained.
- Biomarkers of IL-4R α /IL-33 blockade up to **6 weeks** after single administration
- Well tolerated with no adverse effects up to 200 mg/kg/dose in a multidose study

ZW1528 Exhibited Dose Dependent PK with SC Dosing Supporting Similar Exposure to IV Dosing



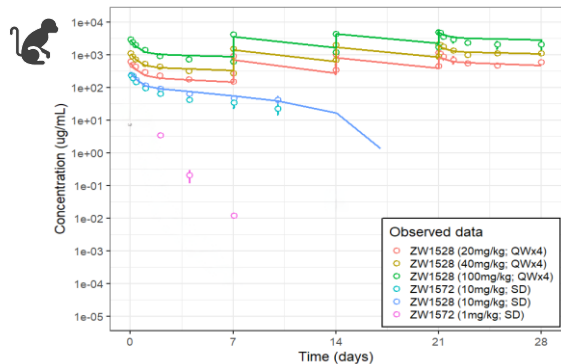
- Exposure maintained for all groups across study
- No observed impact of ADA status seen on TAb PK
- SC dosing achieved similar C_{max} and PK to IV dosing

ZW1528 Human PK Prediction Supports Long Dosing Interval



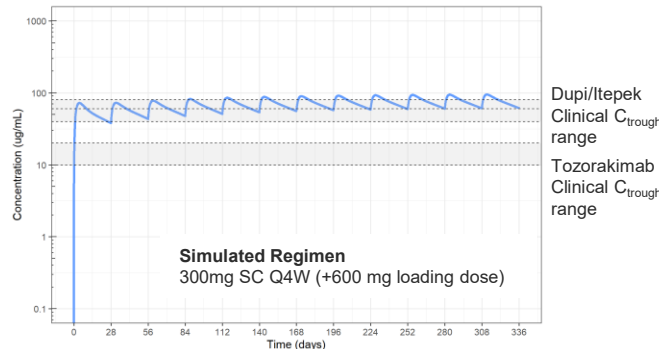
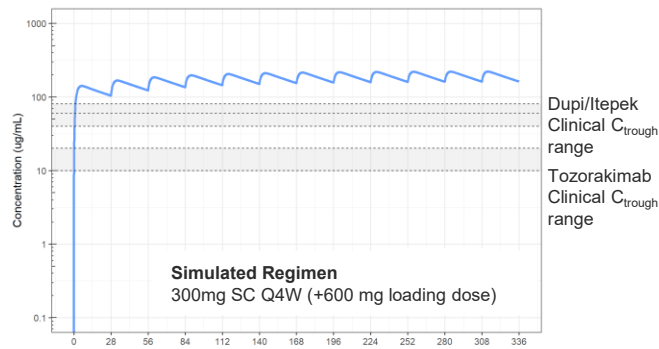
Allometric Scaling

Does not include any TMDD



Allometric Scaling

Assumes Dupi-like TMDD

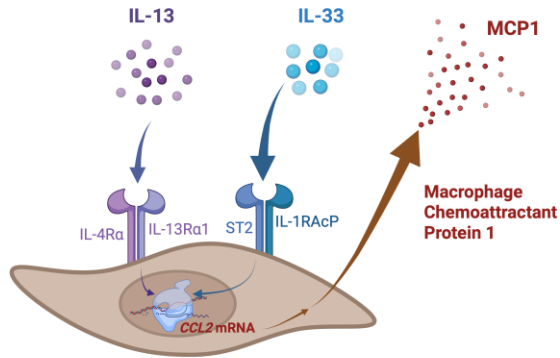


Dupilumab steady-state C_{trough} ranged from 55.3±34.3 to 80.2±35.3 $\mu\text{g/mL}$ for 300mg SC Q2W; DUPIXENT USPI Itepekimab steady-state C_{trough} are 60.8 and 35.2 $\mu\text{g/mL}$ for 300mg SC Q2W and Q4W, respectively; Kosloski, Matthew P et al. 2024 Tozorakimab C_{trough} was 12.8 $\mu\text{g/mL}$ following the 3rd dose of 300mg SC Q2W; Reid et al. 2023

Assuming 150mg/mL x 2mL injection volume = 300mg flat dose
Assuming 60% of SC dose reaches bloodstream

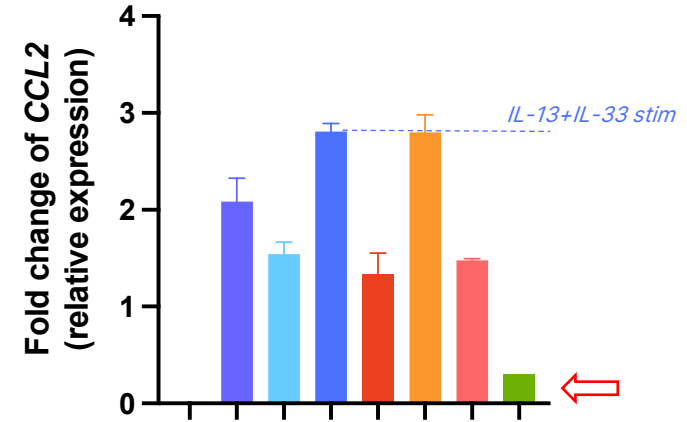
ZW1528-mediated Blockade of Primary Cell Activation is Superior to Dupilumab and Itepekimab

IL-33 and IL-13 activate human epithelial cells



- IL-13 and IL-33 treatment induces disease-relevant genes in primary cells
- ZW1528-mediated blockade is superior to dupilumab, itepekimab and combo

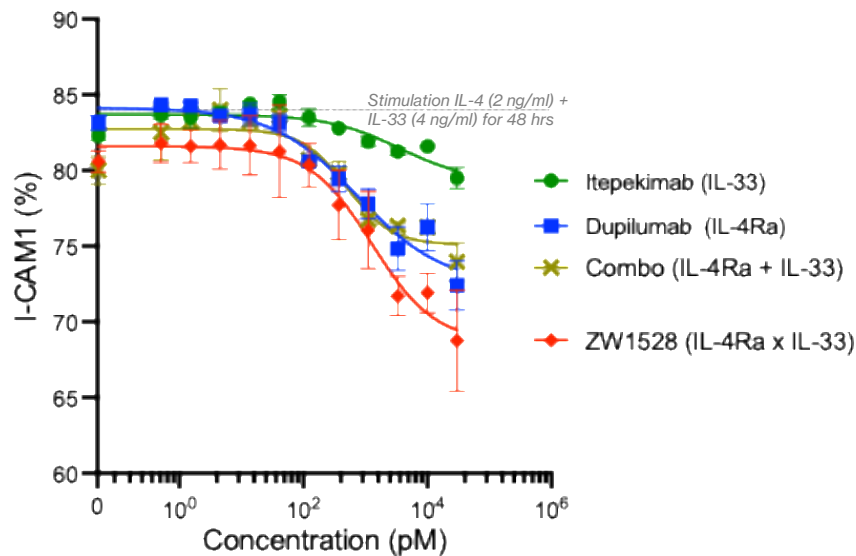
ZW1528 blocks activation



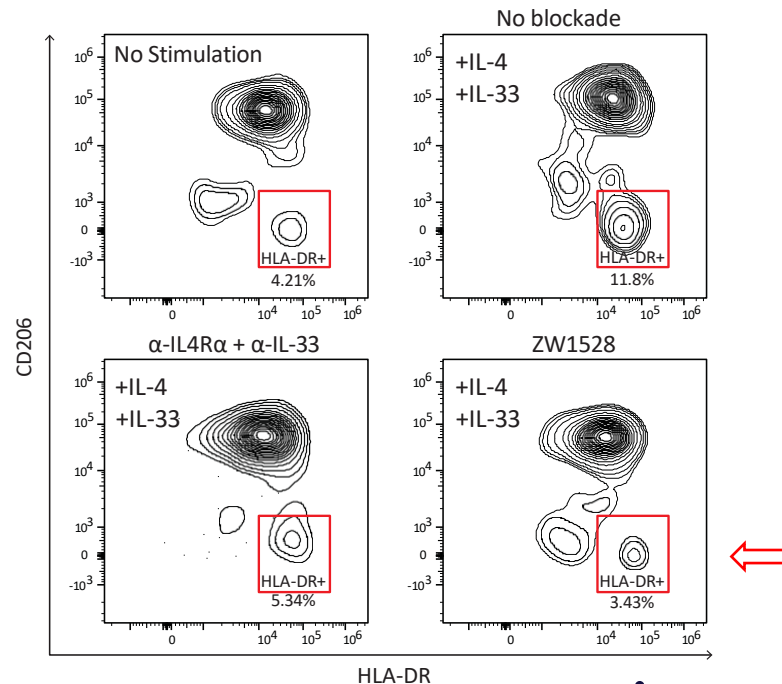
IL-13	-	+	-	+	+	+	+	+
IL-33	-	-	+	+	+	+	+	+
Dupilumab	-	-	-	-	+	-	+	-
Itepekimab	-	-	-	-	-	+	+	-
ZW1528	-	-	-	-	-	-	-	+

ZW1528-mediated Blockade of Immune Cell Activation Driven by IL-4 and IL-33

ZW1528 blocks activation of EoL1 cells

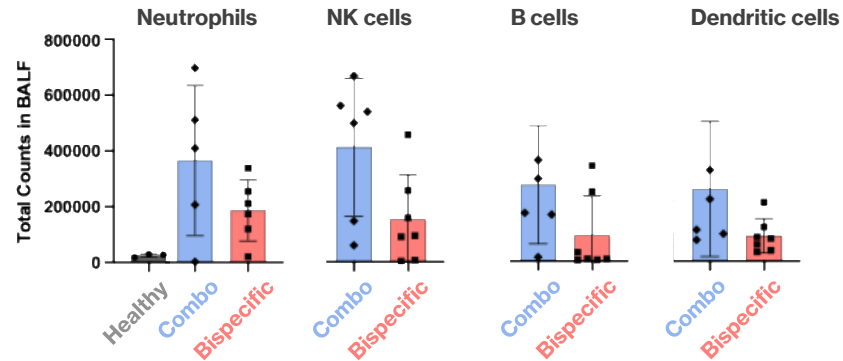
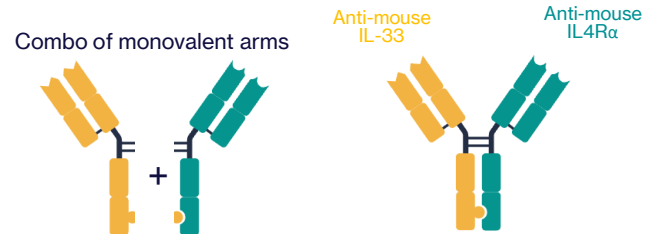
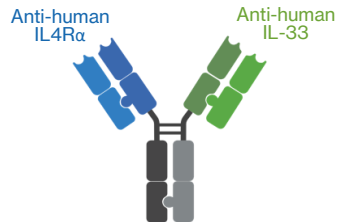
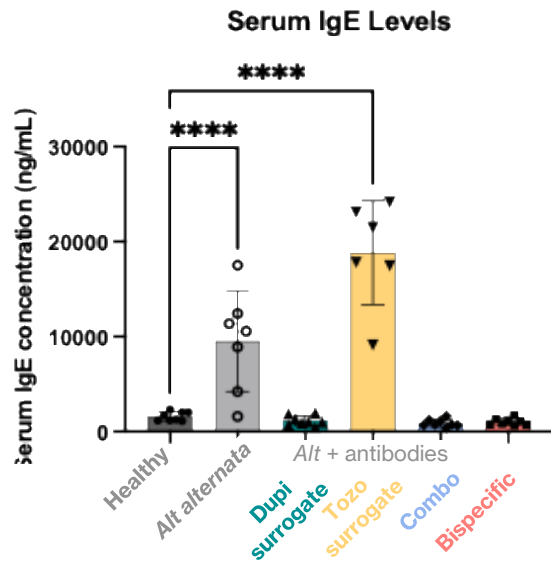
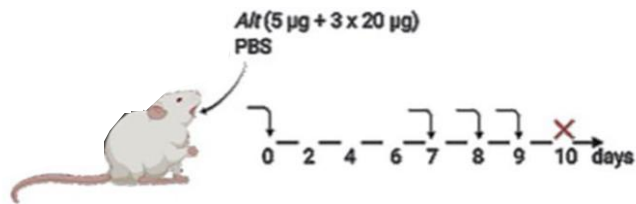


ZW1528 blocks activation of human monocytes



Monocytes were enriched from PBMCs by adhesion to cell culture dishes. Enriched monocyte cultures were incubated for 72 hours with IL-4, IL-33, and relevant antibodies.

Evaluation of IL-4Ra x IL-33 Mouse Homologous Agent in Alternaria-induced Lung Inflammation



Mice were dosed with 10 mg/kg of surrogate antibodies or 25+25 mg/kg of combination of individual monovalent arms or 25 mg/kg of bispecific protein.

Summary: ZW1528, an IL-4R α x IL-33 Bispecific Antibody has the Potential to be a Significant New Treatment Option for Patients with COPD

ZW1528 potently blocks two complementary pathways of respiratory inflammation

- dual blockade of IL-4R α and IL-33, preliminary evidence of bispecific advantage

ZW1528 demonstrates favourable profile in vivo

- potent suppression of inflammation in humanized respiratory models
- extended PK in FcRn-humanized mice
- well tolerated with evidence of target blockade in NHP

ZW1528 aligns with requirements for successful AIID therapeutics

- easy-to-manufacture IgG-like molecule
- designed to allow subcutaneous administration and less frequent dosing

Acknowledgements – A global Team Effort

Multi-specific Antibody Therapeutics (MSAT)



ZW1528, a Bispecific Antibody Targeting IL-4R α and IL-33, Potently Inhibits Key Mediators of Airway Inflammation

Blair K. Hardman, Purva P. Bhojane, Maya C. Poffenberger, Bing C. Wu, Janessa Li, Keshu Patel, Tristan S. Philip, Kurt Stahl, Veronica Luu, Omar Kassas, Steve Booth, Hani Maroki, Shang-Chiung Chen, Nichole K. Escalante, Diana Canals Hernaez, Andrew Sharon, Larissa Patlan Ramirez, Anam Nan Nan Liu, Rachel Guo, Richard Kunze, Gavin Storoschuk, Maya Nathani-Sim, Jenny R. Lu, Paul A. Moore, Thomas Spreter von Kreudenstein, Alexey Berezhnoy

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