ZW1528: A Dual-Targeting Bispecific Antibody to Broadly Suppress Airway Inflammation by Inhibiting IL-4Ra and IL-33 Pathways

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Azymetric™ – Adaptable to Different Formats and Applications

Engineering

Set of transferable mutations supporting pure and stable Fc heterodimer formation with exclusive chain pairing during co-expression

Libraries of constant domain Fab mutations available for kappa/kappa, kappa/lamda and lambda/lambda bispecific LC combinations

Flexibility

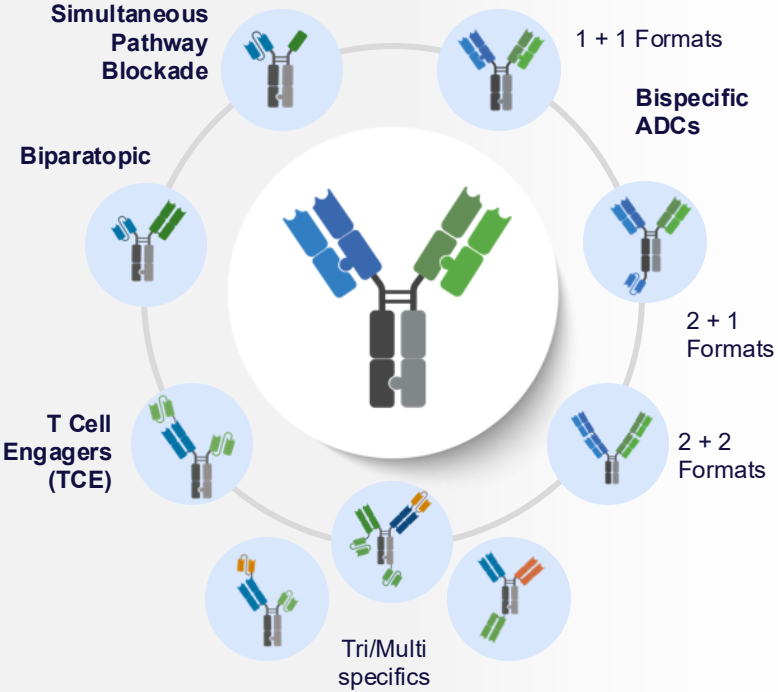
Can employ novel or existing antibody paratopes; human (IgG1, IgG2A, IgG4) and mouse frameworks; other CH2 and glyco-engineering approaches (eg YTE). Compatible with linker/payload conjugation

High-throughput Screening

Best-in-class activity requires screening of alternative targets, epitopes, sequences, target engagement geometries, and mechanisms of action (blocking, lytic, ADC)

Highly Manufacturable

Antibody like yields/stability; leveraged by multiple pharma/biotech with various clinical stage programs in development



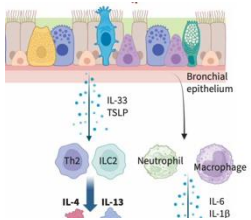
Differentiated Development of Multifunctional Therapeutics

Program	Technology	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
Solid Tumor Oncology: Antibody-Drug Conjugates (ADC)								
ZW191 Topo1i ADC | DAR 8 | Fc WT	ZD06519 Payload	FRα	Gynecological Thoracic			NCT06555744		
ZW220 Topo1i ADC |DAR 4 | Fc Mut	ZD06519 Payload	NaPi2b	Gynecological Thoracic					
ZW251 Topo1i ADC | DAR 4 | Fc WT	ZD06519 Payload	GPC3	Digestive System (HCC)				Phase 1 study planned to initiate in 2025	
Solid Tumor Oncology: Multispecific Antibody Therapeutics (MSAT)								
Zanidatamab Bispecific	Azymetric™	HER2	Multiple indications					Development partners: Jazz Pharmaceuticals and BeOne
ZW209 Trispecific TCE | Tri-TCE Costim	Azymetric™ Novel anti-CD3 Conditional CD28	DLL3 x CD3 x CD28	Thoracic				Anticipated IND 1H 2026	
ZW239 Trispecific TCE | Tri-TCE Costim	Azymetric™ Novel anti-CD3 Conditional CD28	CLDN18.2 x CD3 x CD28	Digestive System					
Autoimmune & Inflammatory Diseases								
ZW1528 Dual Cytokine Blocker	Azymetric™ Hetero-Fab | YTE	IL4Rα x IL-33				Anticipated IND 2H 2026		
ZW1572 Dual Cytokine Blocker	Azymetric™ Hetero-Fab | YTE	IL4Rα x IL-31						

Bispecific Antibody Therapeutics as the Answer to Complex Biology of Autoimmune and Inflammatory Diseases

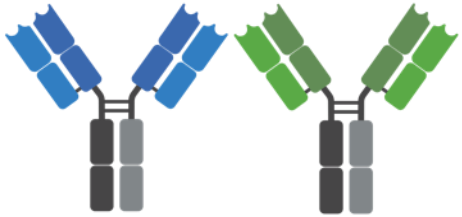
Patients

− Serious, difficult to treat diseases
− Large patient population
− Restricted access to advanced therapeutics



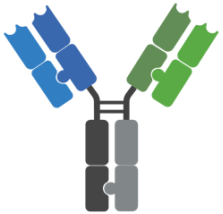
Clinical science

+ Clinically validated targets
+ Benefits of combination
− Inconvenience and cost of clinical implementation



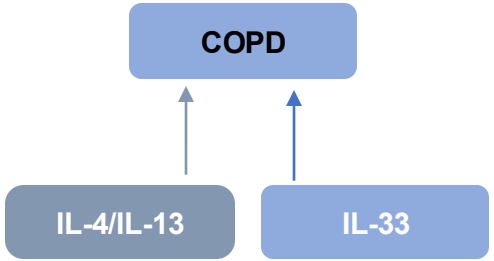
Technology

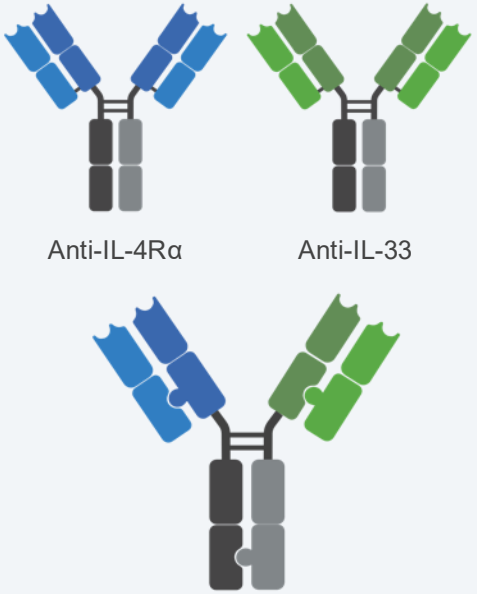
+ Clinically validated platform
+ Compatibility with Fc modifications (HLE)
+ High efficacy, convenient, cost-effective solution



Rationale for anti-IL-4Rα as an Anchor Arm

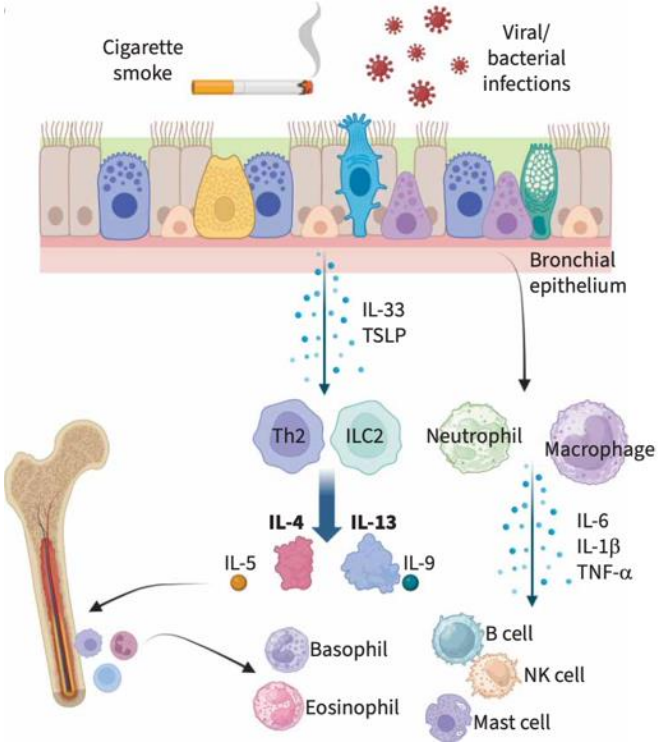
- Dupixent®/dupilumab is a highly successful mAb targeting IL-4Rα
  - Approved for multiple atopic and inflammatory diseases
- Blocking IL-4Rα inhibits both IL-4 and IL-13 signaling
  - Two key cytokines responsible for driving Type II inflammation
- Multiple cytokines drive pathology of respiratory inflammation
  - Add inhibition of an additional inflammatory pathway to augment or improve on monotherapy effects
  - **ZYME opportunity to develop more efficacious molecules**





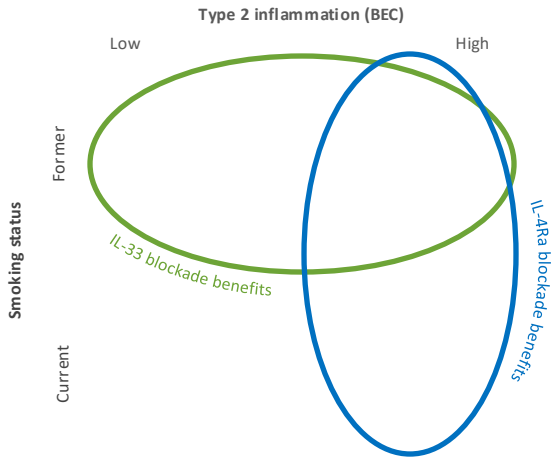
IL-33 as a Bispecific Arm in COPD and other Respiratory Diseases

- IL-33 is a tissue alarmin released in response to epithelial damage
  - Acts on a range of cells e.g., neutrophils, Th2 cells, eosinophils, and mast cells
- Initiates and amplifies inflammatory response / perpetuates chronic immune response
  - May also drive tissue remodelling in chronic inflammatory diseases e.g., COPD and asthma
- Clinical proof-of-concept for targeting IL-33
  - For former smokers with COPD, and in asthma
  - Phase III trials underway for anti-IL-33 mAbs itepekimab [Regeneron / Sanofi] and tozorakimab [AstraZeneca]



IL-4Rα x IL-33 Bispecific Provides Opportunity to Treat Broader Set of COPD Patients with Single Molecule

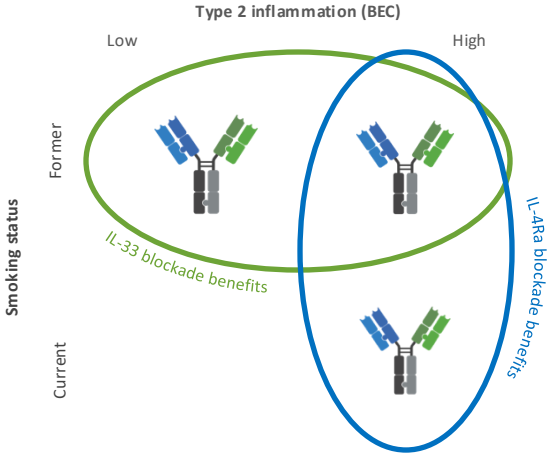
Anti-IL4Rα and anti-IL-33 therapeutics are being developed to treat different COPD populations



Anti-IL4Rα effective in Type 2 COPD (those with eosinophilia)

Anti-IL-33 may prove to be effective in former smokers

IL-4Rα x IL-33 bispecific provides opportunity to treat **broader set of COPD patients with single molecule**



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

Potential for **increased efficacy in monotherapy-responsive** patients

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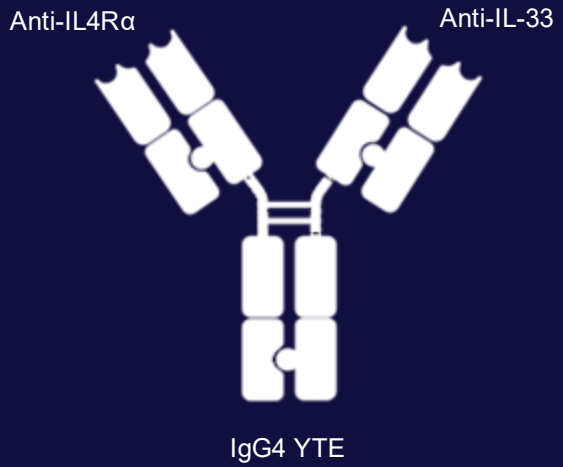


ZW1528
IL-4Rα x IL-33 Bispecific

Inhibits Multiple Pathways within Complex Pathophysiology of Inflammation

Design

- Native **IgG-like geometry**; highly manufacturable, compatible with half-life extending Fc modifications
- Clinically-validated targets
- Core arm mediates complete, prolonged IL-4Rα blockade. Second arm adds inhibition of IL-33, an upstream cytokine involved in perpetuating chronic inflammation.

Mechanism

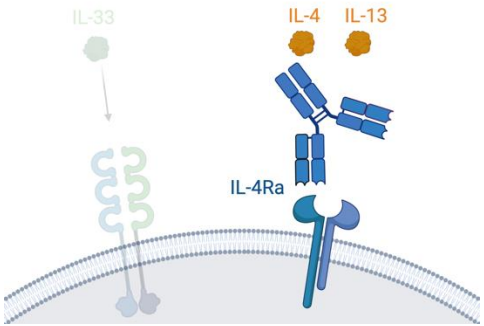
- Inhibition of 3 cytokines in single asset
- Potential advantages of **local retention**

Profile

- ZW1528 potently blocks two complementary pathways of respiratory inflammation

ZW1528 Design and Proposed Mechanism of Action

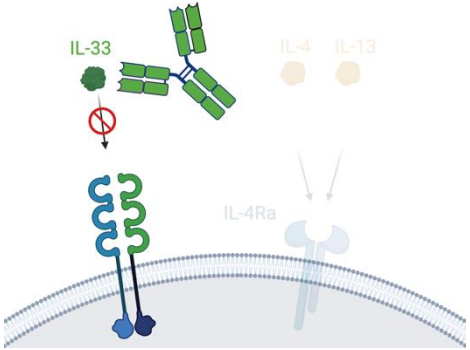
Dupilumab blocks IL-4Ra



Type 2 inflammation suppression

Approved in asthma, COPD

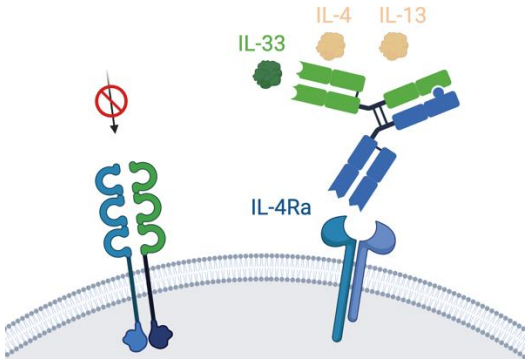
Itepekimab/tozorakimab block IL-33



Type 2 and non-T2 inflammation suppression. Improved tissue remodelling.

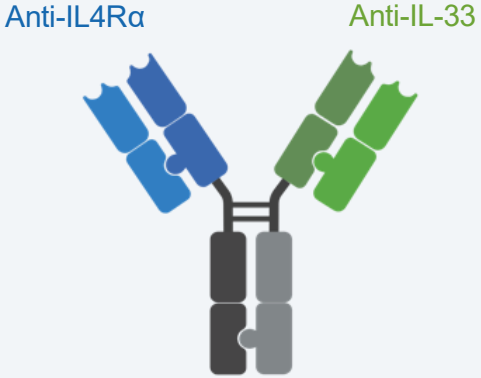
Ph3 studies in COPD

Dual blockade by ZW1528

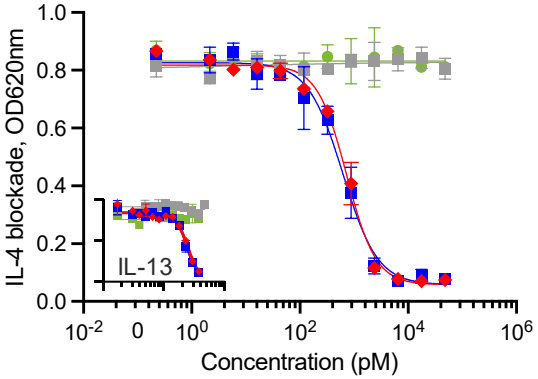


- Aim at complete, prolonged blockade of IL-4Rα
- Utilize potential advantages of local retention
- Take advantage of IgG-like geometry (PK, CMC)

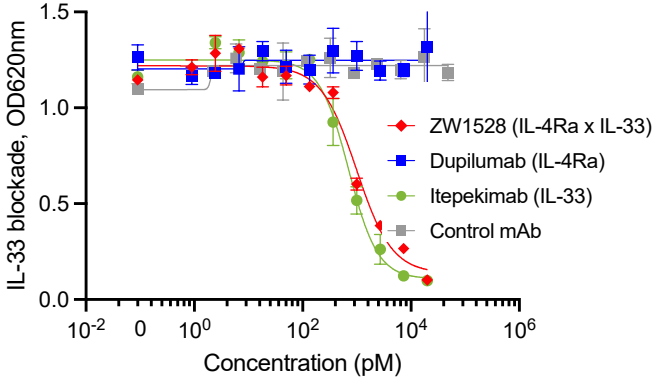
ZW1528 Effectively Blocks both IL-4/13 and IL-33 Signaling



Blockade of IL-4/13

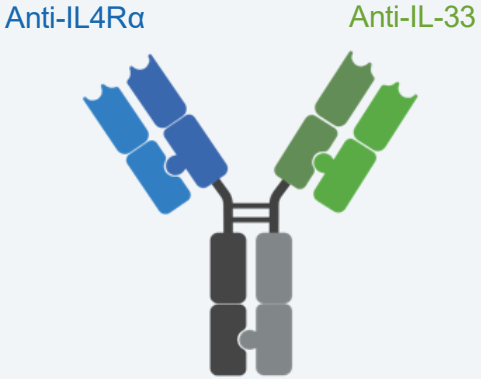


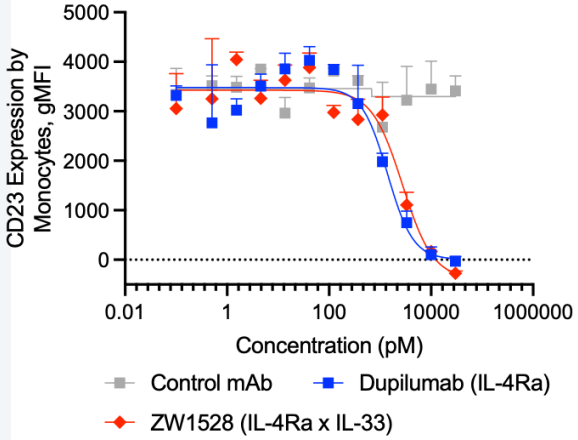
Blockade of IL-33

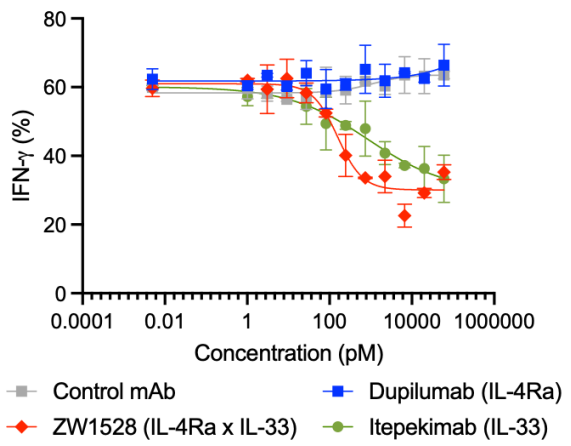


- Potency of ZW1528 similar to the _*bivalent*_ benchmark mAbs
- ZW1528 blocks both targets

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



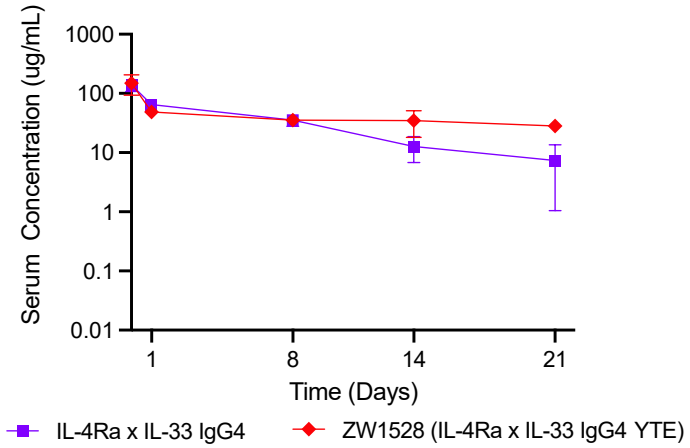




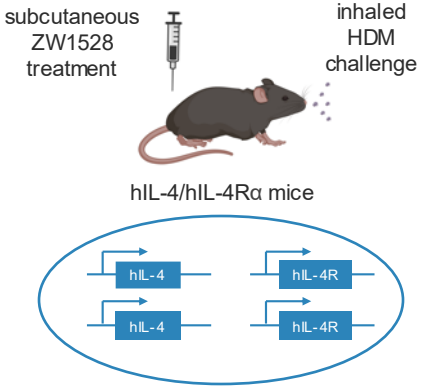
- ZW1528 effectively blocks IL-4Ra and IL-33 in PBMC of _*COPD patients*_ in vitro
- Enhanced blockade of IL-33 axis

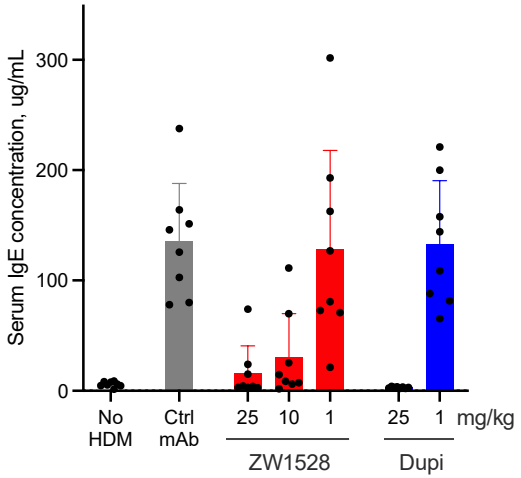
ZW1528 Demonstrates IgG-like PK and Blocks IL-4Rα in vivo

Half-life extension (Tg32 mice PK)



Suppression of IgE after inhaled allergen challenge

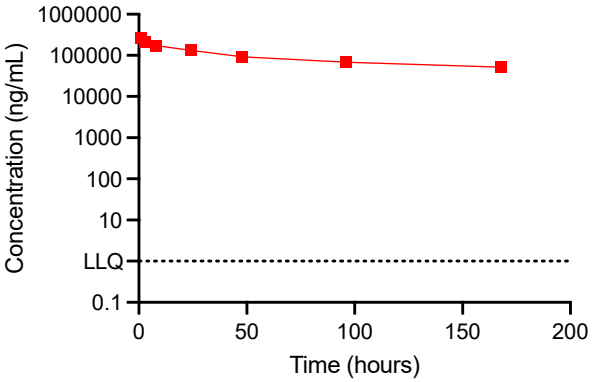




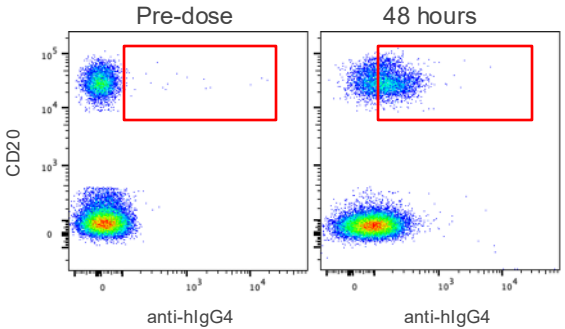
Left: PK in Tg32 mice after 5 mg/kg i.v. administration
Right: Challenge with house dust mite (HDM) inhalation

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

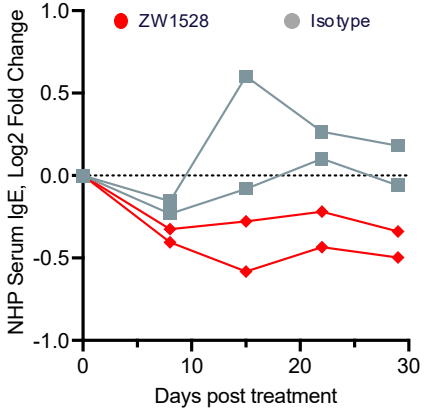
Pharmacokinetics



IL-4Rα Receptor Occupancy



Reduction of Serum IgE

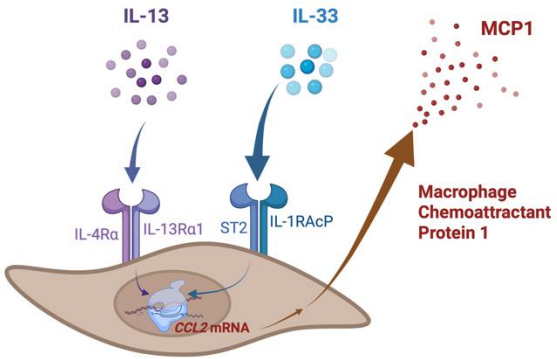


- IgG-like pharmacokinetics in non-human primates (NHP)
- Biomarkers of IL-4Rα/IL-33 blockade up to **6 weeks** after single administration

Cynomolgus monkey (N=2) were dosed with ZW1528 i.v. at 10 mg/kg

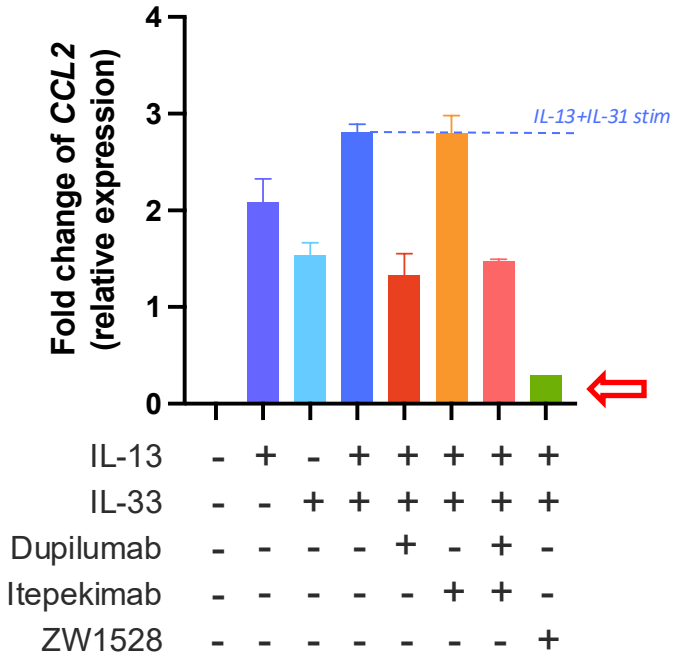
ZW1528-mediated Blockade of Primary Cell Activation is Superior to Dupilumab and Itepekimab

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



Summary: ZW1528, an IL-4Rα 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-4Ra and IL-33, preliminary evidence of bispecific advantage

ZW1528 demonstrates favourable profile in vivo

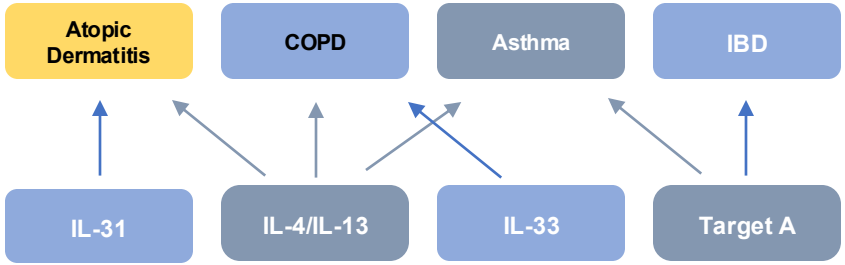
- good tolerability and PD of target blockade in NHP, extended PK in FcRn-humanized mice

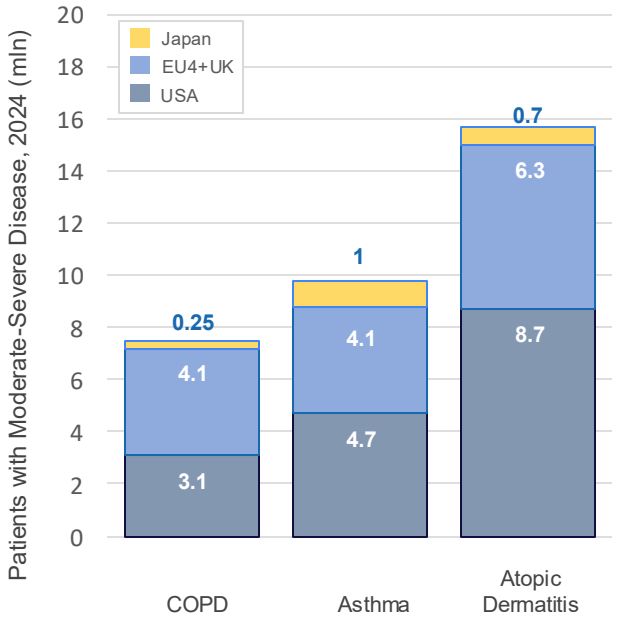
ZW1528 aligns with requirements for successful AIID therapeutics

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

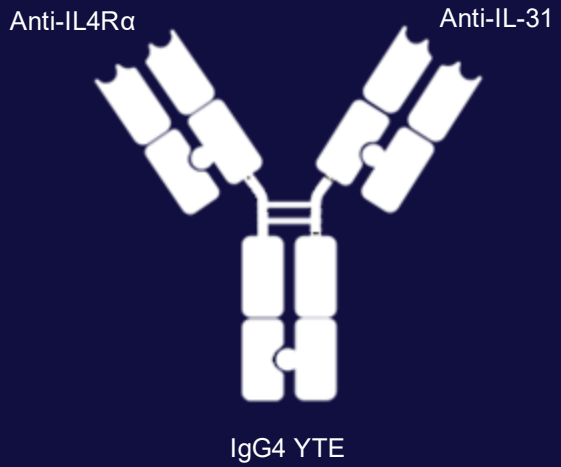
Multiple Therapeutic Programs Using Validated IL-4Rα Blocker

Program	Target Pair	Target Validation
ZW1528 (2026 IND/CTA)	IL4Rα x IL-33	Anti-IL4Rα approved in COPD Anti-IL33 in pivotal COPD phase 3 studies
ZW1572 (PCD ready)	IL4Rα x IL-31	Anti-IL4Rα approved in Atopic Dermatitis Anti-IL-31 validated clinically for itch control
Earlier stage asset	IL4Rα x Target A	Anti-IL4Rα approved in Asthma Target A efficacious in multiple AIIDs





Atopic Dermatitis: DataMonitor: Epidemiology: Atopic Dermatitis (May 2024); DataMonitor: Patient-Based Forecast Model: Atopic Dermatitis (Dec 2022)
Asthma: DataMonitor: Epidemiology: Asthma (Sep 2023); DataMonitor: Patient-Based Forecast Model: Asthma (Dec 2023)
COPD: DataMonitor: Patient-Based Forecast Model: COPD (Dec 2021); Evaluate Pharma Indication Sales Forecast (June 2024); UN Epidemiology forecast (medium variance); Koga Y, Deguchi S, Matsuo T, Suzuki A, Terashima G, Tajima T, Shibata Y, Sagara H. Underdiagnosis of COPD: The Japan COPD Real-World Data Epidemiological (CORE) Study. Int J Chron Obstruct Pulmon Dis. 2024;19:1011-1019doi:10.2147/COPD.S450270



ZW1572
IL-4Rα x IL-31 Bispecific

Inhibits Multiple Pathways within Complex Pathophysiology of Inflammation

Design

- Native **IgG-like geometry**; highly manufacturable, compatible with half-life extending Fc modifications
- Clinically-validated targets
- Core arm mediates complete, prolonged IL-4Rα blockade. Second arm adds inhibition of IL-31, a main driver of itch in atopic dermatitis.

Mechanism

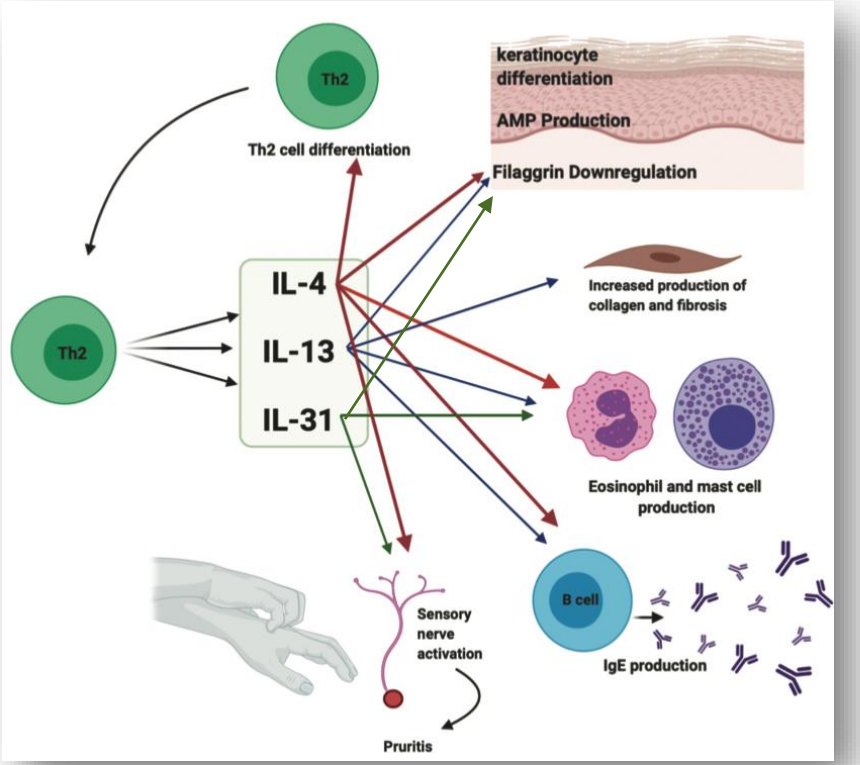
- Inhibition of 3 cytokines in single asset
- Potential advantages of **local retention**

Profile

- ZW1572 potently blocks two complementary pathways of inflammation

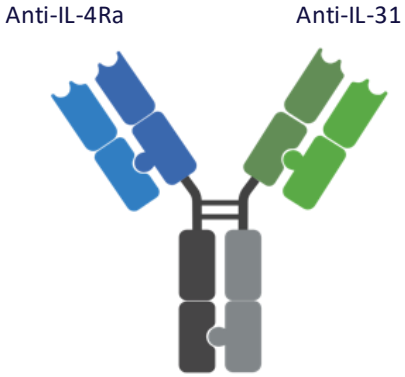
IL-4, IL-13 and IL-31 Act Synergistically in Atopic Dermatitis to Drive Inflammation, Pruritis and Skin Barrier Defects

- IL-4 promotes differentiation of naïve T cells to Th2 cells
- IL-4 and IL-13 maintain the Th2 response
  - Drive recruitment of eosinophils and mast cells
  - Stimulate B cells to make IgE
  - Inhibit production of barrier proteins e.g., filaggrin, and promote keratinocyte hyperplasia
- IL-31 drives eosinophil and mast cell production, plus
  - Impairs keratinocyte differentiation & production of filaggrin
  - Activates keratinocytes to produce cytokines that amplify skin inflammation and itch
  - Acts on sensory nerves and contributes to pruritis / itch
- Several genes are regulated by IL-4/IL-13 and IL-31 in an additive or synergistic manner



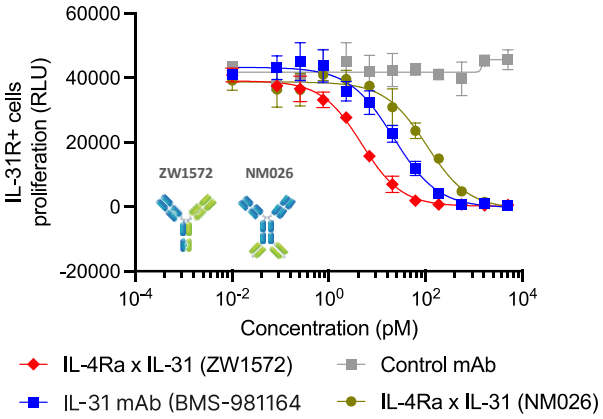
Sources: Dubin, C., Del Duca, E., & Guttman-Yassky, E. (2021). Expert Review of Clinical Immunology, 17(8), 835–852. Cornelissen, C et al, J Allergy Clin Immunol 2012;129:426-33

ZW1572: Bispecific Inhibitor of IL-4Ra and IL-31 for Atopic Dermatitis



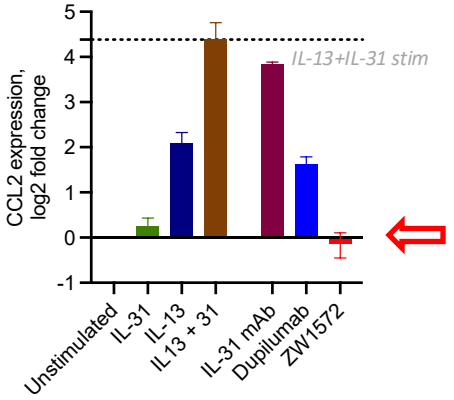
IgG4 YTE

Enhanced blockade of IL-31



Superior IL-31 blockade vs (bivalent) clinical benchmarks

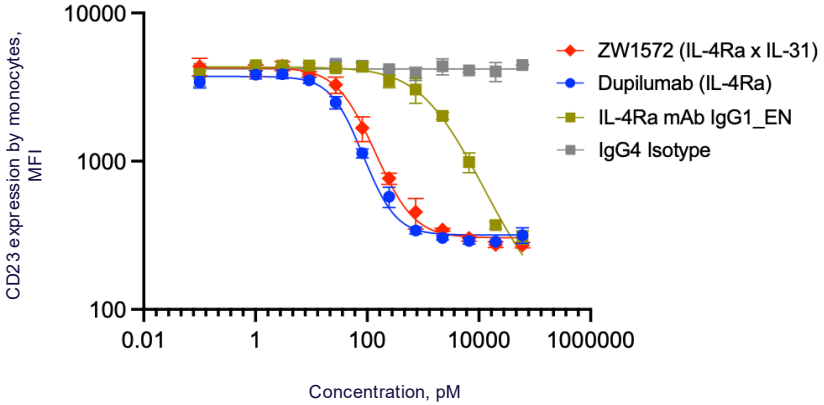
Suppression of CCL2 induction in keratinocytes



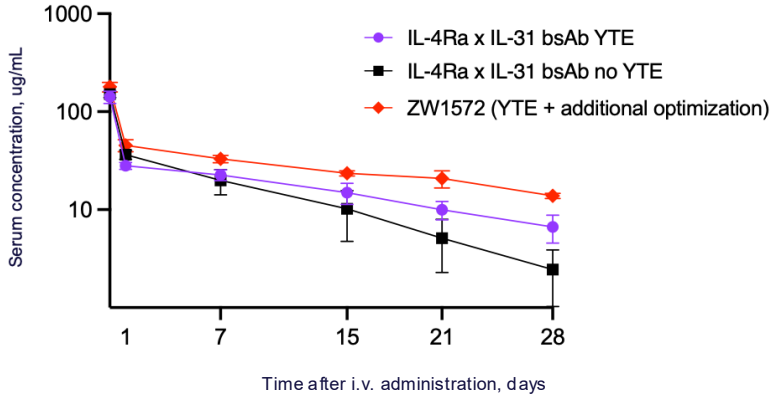
Superior potency vs individual mAbs in primary cells

Optimized Fc Portion Enhances IL-4Ra Pathway Blockade and Pharmacokinetics of ZW1572

Blockade of IL-4-driven activation
in vitro



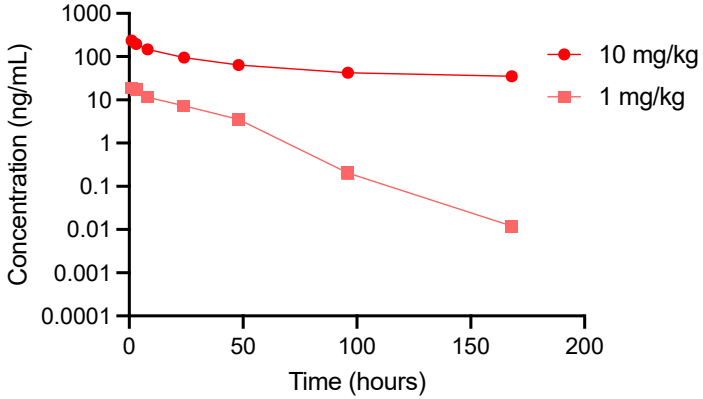
Extended half-life in humanized
FcRn (Tg32) mice



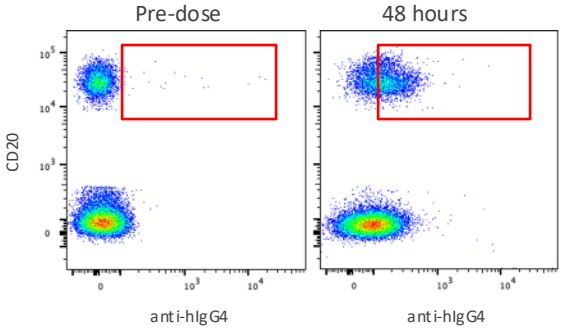
- Azymetric™ Fc platform is compatible with IgG4 Fc isotype and YTE mutations
- Selected Fc isotype/modifications demonstrate favorable profile in vitro and in vivo
  - superior target blockade compared to unmodified effector-negative IgG1
  - superior PK relative to unmodified IgG4

ZW1572 Demonstrates Antibody-like PK and RO in NHP

Pharmacokinetics



IL-4Rα Receptor Occupancy



- IgG-like pharmacokinetics and biomarkers of IL-4Rα blockade in non-human primates (NHP)

Cynomolgus monkey (N=2) were dosed with ZW1572 i.v. at 10 or 1 mg/kg

Benefits of Bispecific Therapeutics for AIID Patients: Blockade of Multiple Cytokines by a Single Molecule for Patients Convenience and Better Outcomes

Opportunity to benefit patients with autoimmune and inflammatory diseases

- Blockade of complementary pathways of autoimmunity could enhance therapeutic benefits for patients with mixed-type disease
- Single therapeutic molecule could address multiple subsets of AIID, such as type 2 and non-type 2 driven inflammation
- Computationally-guided protein optimization enables low-volume subcutaneous administration and less frequent dosing