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

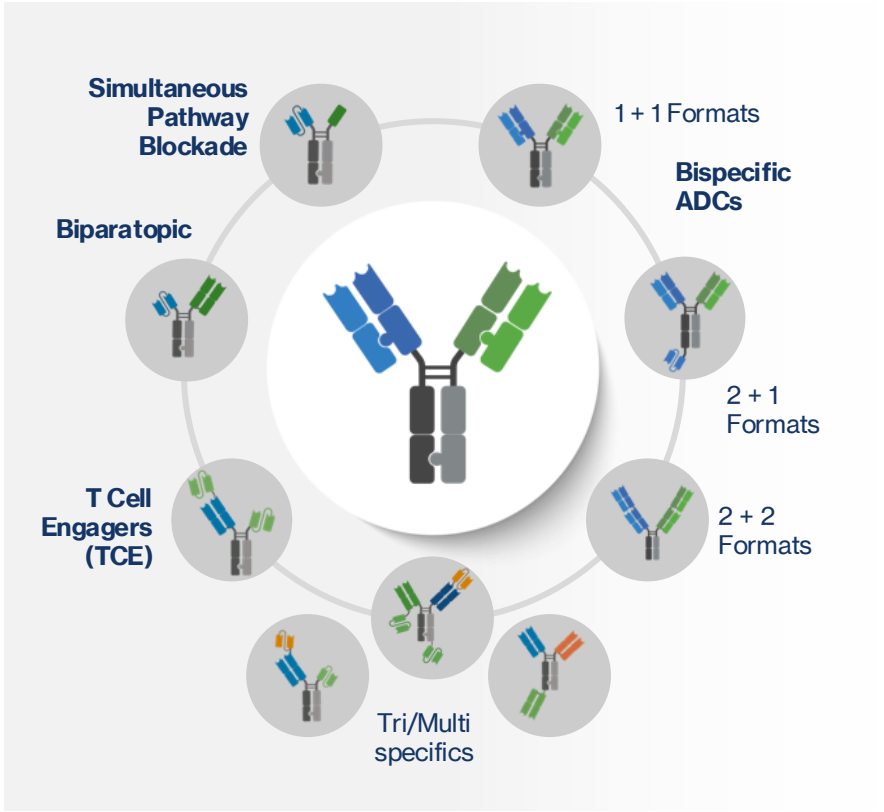
Can employ novel or existing antibody paratopes; human (IgG1, IgG2A, IgG4) and mouse frameworks; other CH2 and glyco-engineering approaches (eg YTE). Compatible with linker/payload conjugation

High-throughput Screening

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

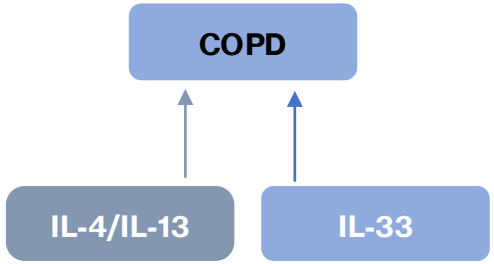
Highly Manufacturable

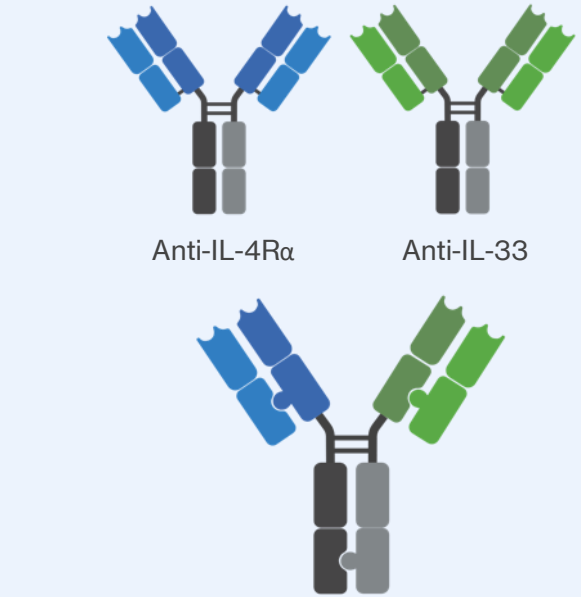
Antibody like yields/stability; leveraged by multiple pharma/biotech with various clinical stage programs in development



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

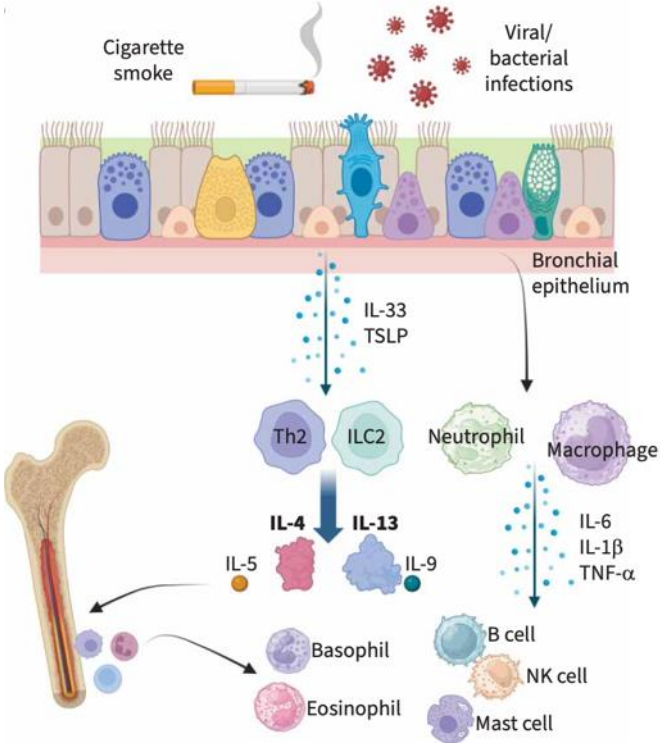
- Dupixent®/dupilumab is a highly successful mAb targeting IL-4Rα
  - Approved for multiple atopic and inflammatory diseases
- Blocking IL-4Rα inhibits both IL-4 and IL-13 signaling
  - Two key cytokines responsible for driving Type II inflammation
- Multiple cytokines drive pathology of respiratory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





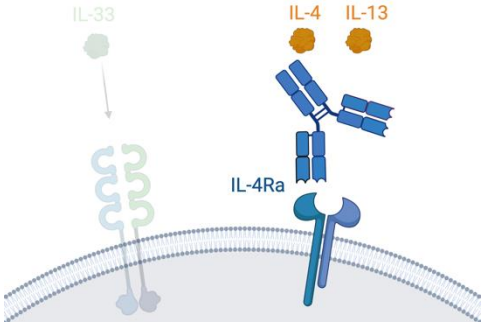
IL-33 as a Bispecific Arm in COPD and other Respiratory Diseases

- 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]



ZW1528 Design and Proposed Mechanism of Action

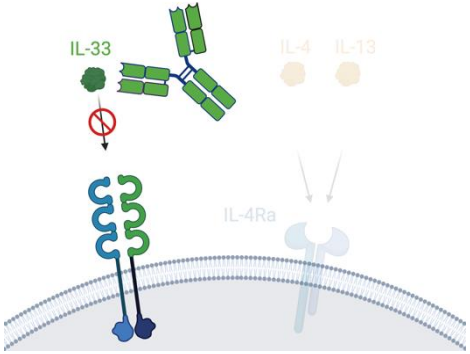
Dupilumab blocks IL-4Ra



Type 2 inflammation suppression

Approved in asthma, COPD

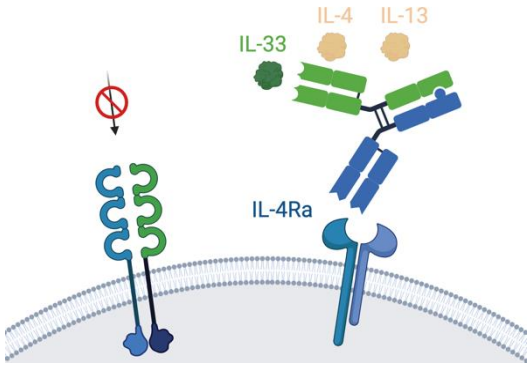
Itepekimab/tozorakimab block IL-33



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

Ph3 studies in COPD

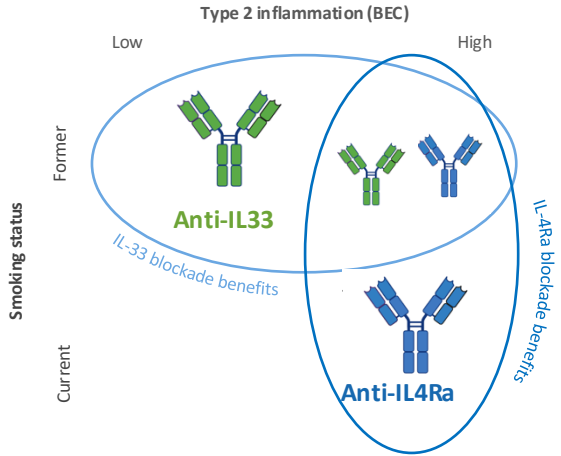
Dual blockade by ZW1528



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

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

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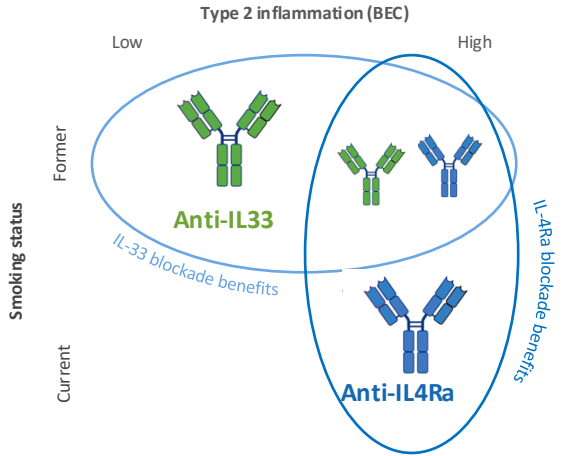

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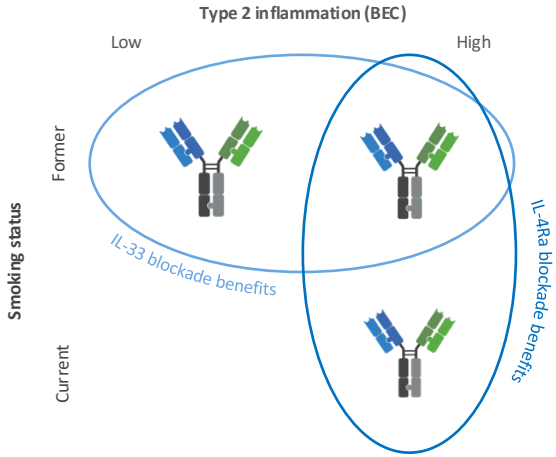
IL-4Rα x IL-33 bispecific provides opportunity to treat **broader set of COPD patients with single molecule**



- 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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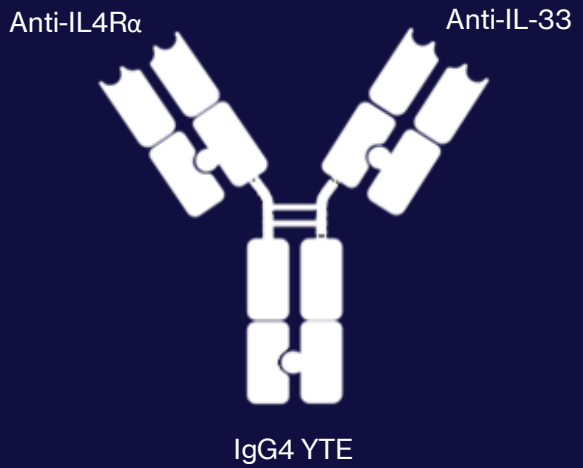


ZW1528
IL-4Rα x IL-33 Bispecific

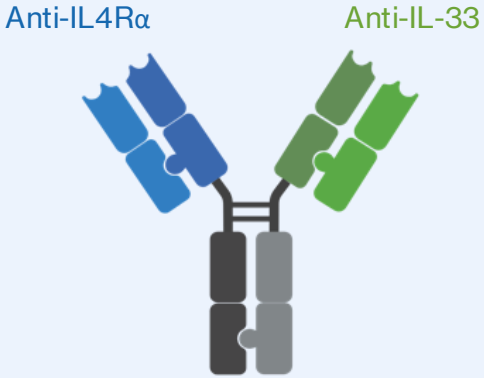
Inhibits Multiple Pathways within Complex Pathophysiology of Inflammation

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.

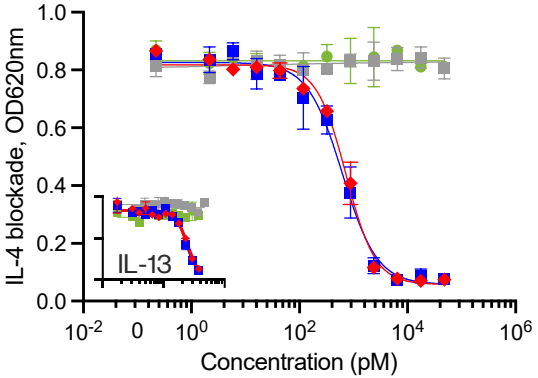
Mechanism
- Inhibition of 3 cytokines in single asset
- Potential advantages of **local retention**

Profile
- ZW1528 potently blocks two complementary pathways of respiratory inflammation

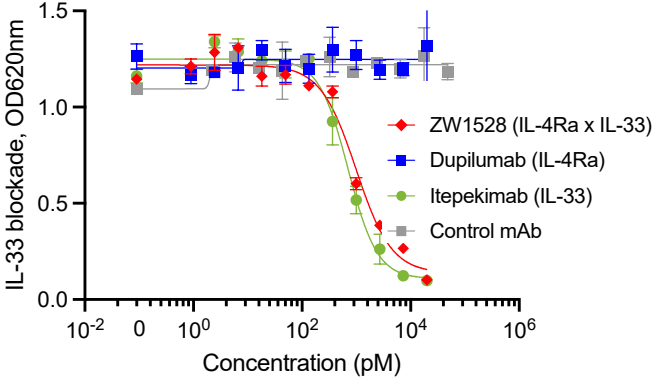
ZW1528 Effectively Blocks both IL-4/13 and IL-33 Signaling



Blockade of IL-4/13

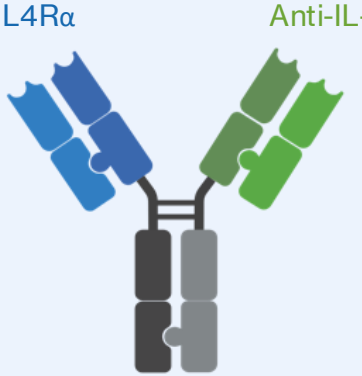


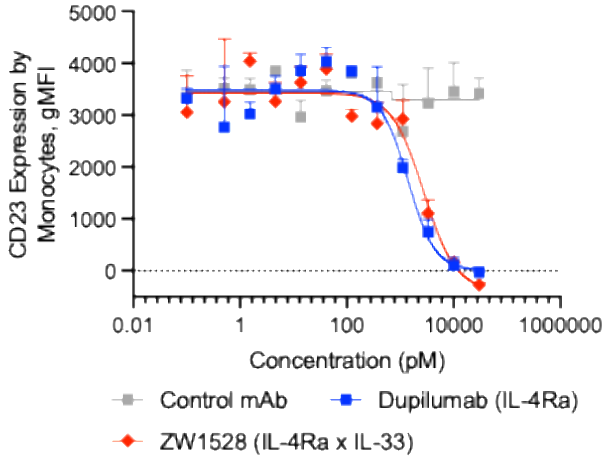
Blockade of IL-33

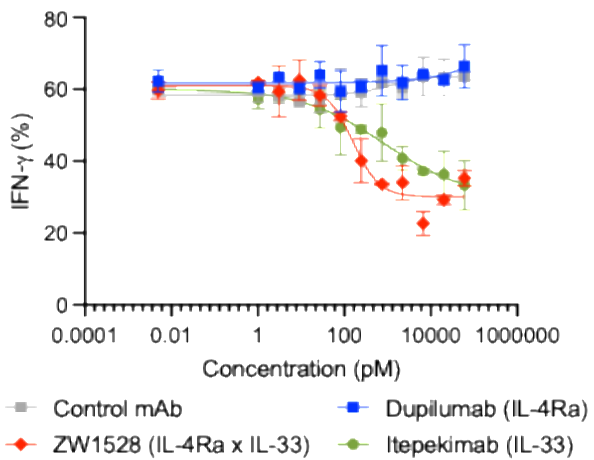


- Potency of ZW1528 similar to the _***bivalent***_ benchmark mAbs
- ZW1528 blocks both targets

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



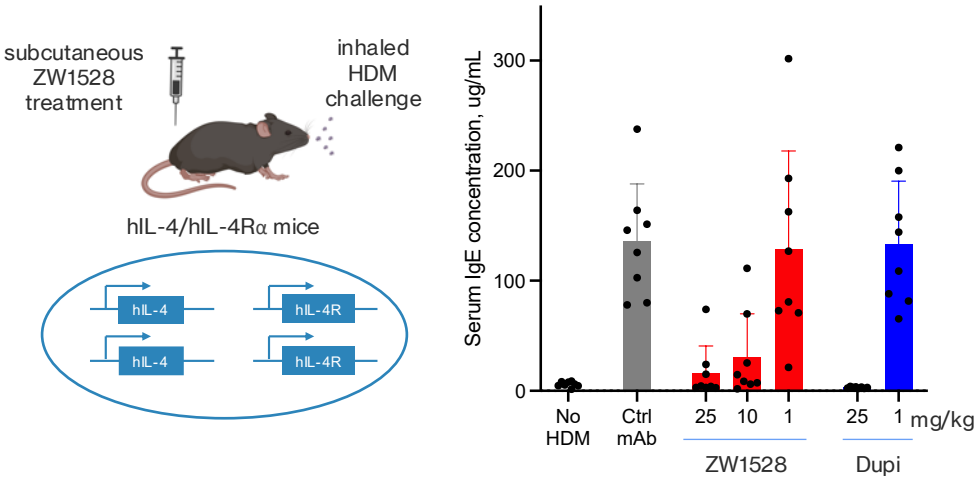




- ZW1528 effectively blocks IL-4Ra and IL-33 in PBMC of _***COPD patients***_ in vitro
- Enhanced blockade of IL-33 axis

ZW1528 Blocks IL-4Rα *in vivo*

Suppression of IgE after inhaled allergen challenge



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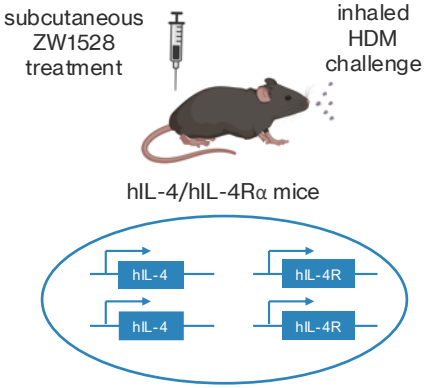
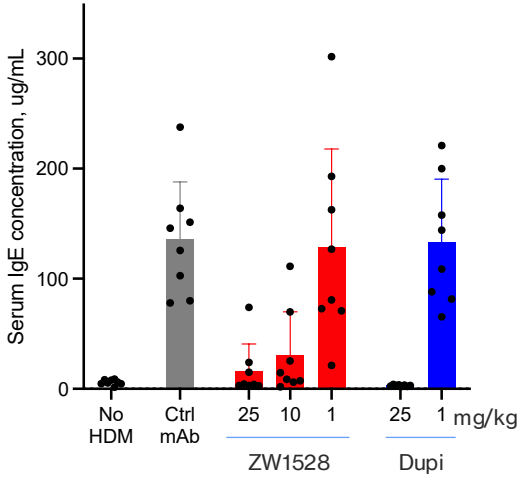
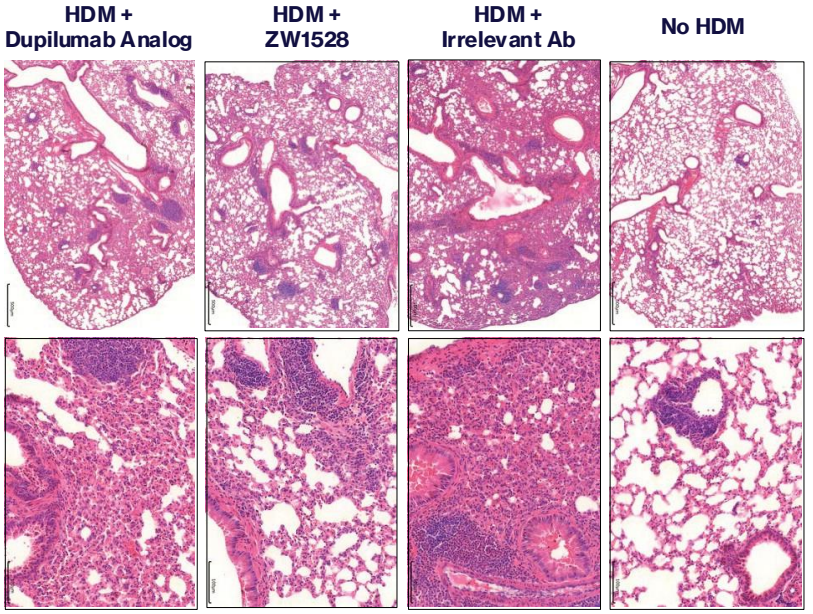
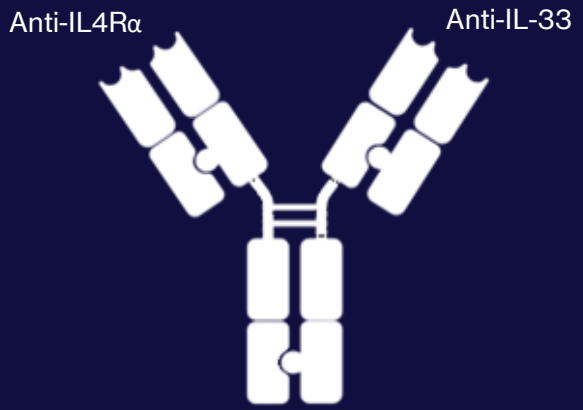








IgG4 YTE

ZW1528
IL-4Rα x IL-33 Bispecific

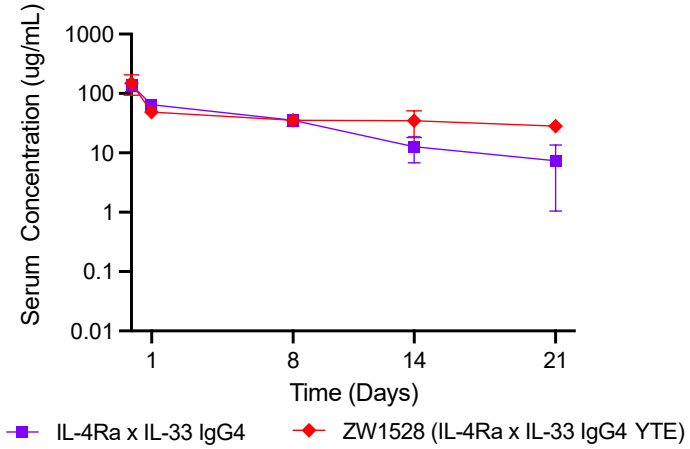
Inhibits Multiple Pathways within Complex Pathophysiology of Inflammation

Mechanism

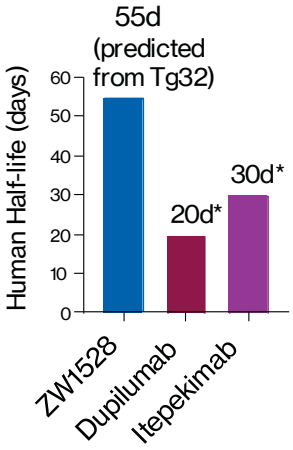
- Inhibition of 3 cytokines in single asset
- Potential advantages of local retention
- **YTE mutations:** a triple amino acid substitution in the Fc region of antibodies that significantly extend serum half-life by enhancing binding to the neonatal Fc receptor (FcRn) at acidic pH.

ZW1528 Demonstrates IgG-like PK *in vivo*

Half-life extension (Tg32 mice PK)



Allometric scaling to predict half life in patients based on Tg32 data

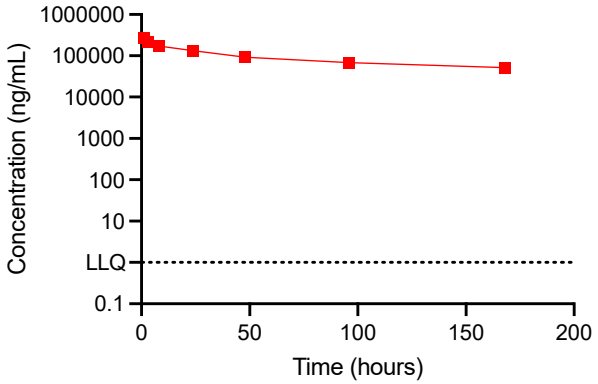


*based on literature values

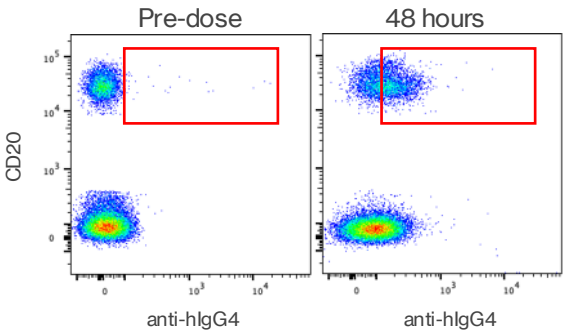
PK in Tg32 mice after 5 mg/kg i.v. administration

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

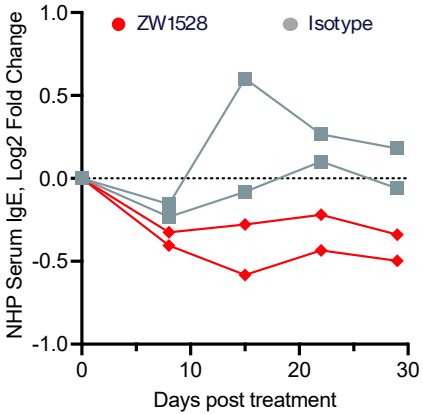
Pharmacokinetics



IL-4Rα Receptor Occupancy

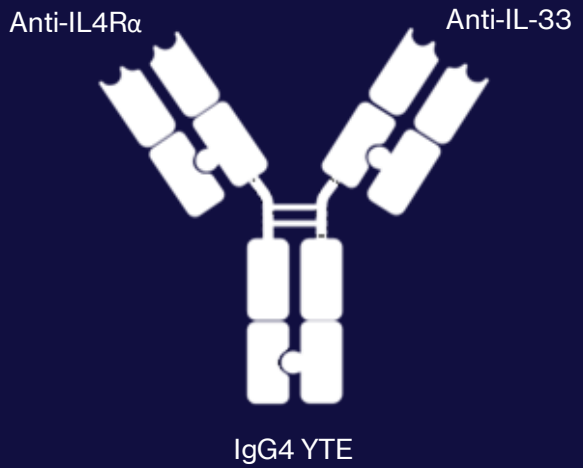


Reduction of Serum IgE



- IgG-like pharmacokinetics in non-human primates (NHP); exposure is maintained.
- 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



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IL-4Rα x IL-33 Bispecific

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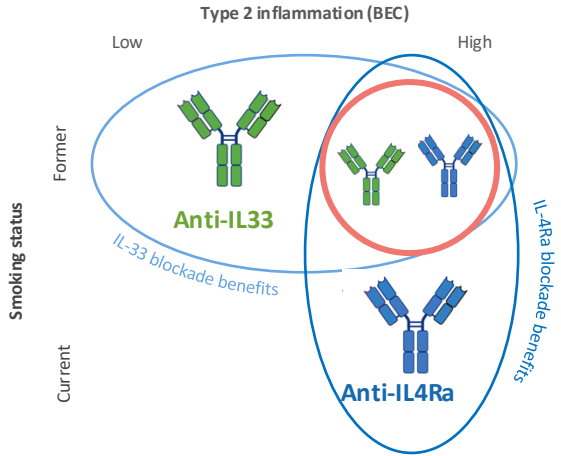
Mechanism

- Inhibition of 3 cytokines in single asset.
- Potential advantages of local retention.
- YTE mutations extend serum half-life.
- **Bispecific advantage:** Potential for increased efficacy than combination monotherapy treatment in patients.

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



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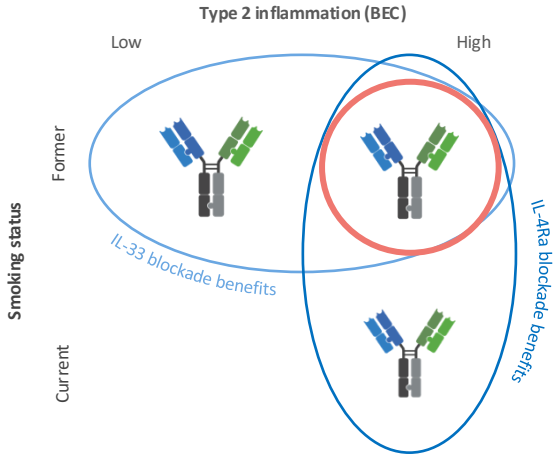
IL-4Rα x IL-33 bispecific provides opportunity to treat **broader set of COPD patients with single molecule**



- IL-4Rα x IL-33 bispecific to **combine the effects of two mAbs**
- Potential for **increased efficacy in monotherapy-responsive** patients
- Potential for **increased efficacy than combination monotherapy treatment** (*bispecific advantage*)

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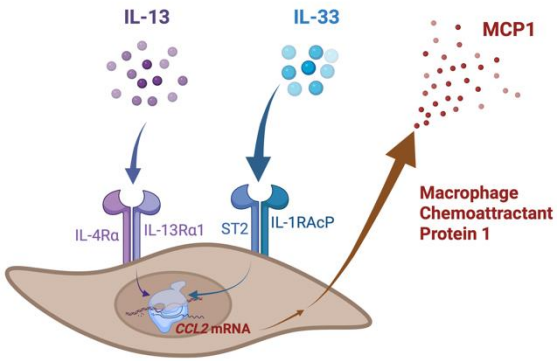
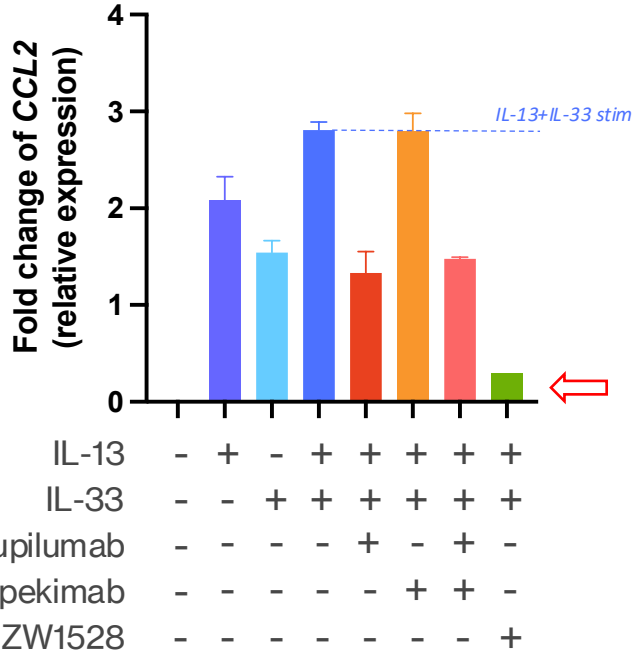
ZW1528-mediated Blockade of Primary Cell Activation is Superior to Dupilumab and Itepekimab

IL-33 and IL-13 activate human epithelial cells



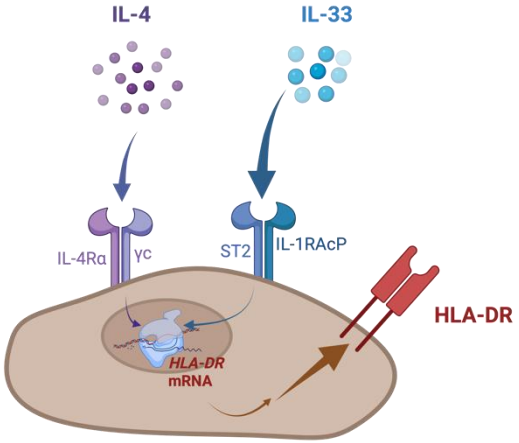
- IL-13 and IL-33 treatment induces disease-relevant genes in primary cells
- ZW1528-mediated blockade is superior to dupilumab, itepekimab and combo

ZW1528 blocks activation



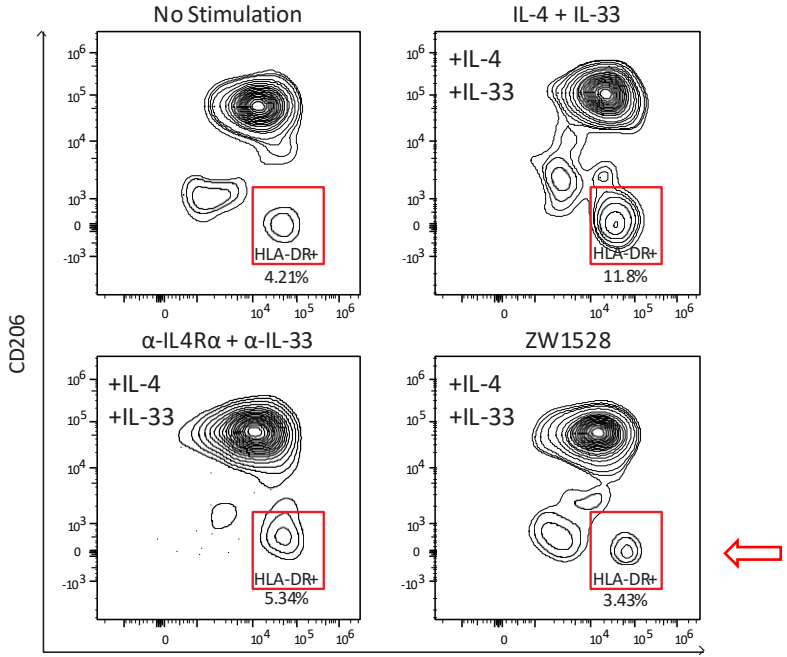
ZW1528-mediated Blockade of Primary Cell Activation is Superior to Dupilumab and Itepekimab

IL-33 and IL-4 activate human monocytes



- IL-4 and IL-33 treatment induces monocytes to differentiate into suppressive macrophages expressing HLA-DR
- 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

Acknowledgements

Project Team			
Team Leads	Meghan Verstraete Purva Bhojane Blair Hardman Robert Nechanitzky	**Business Development**	David Kroeger Elena Topchiy Steve Seredick
Immunology	Janessa Li Omar Kassas Veronica Luu Yunfan Lyu Scott Lien Maya Poffenberger	**LCMS Analytics**	Diego Alonzo Edward Lau
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Translational Sciences	Steve Booth	**Advisors & Oversight**	
Intellectual Property	Emma Macfarlane	Alexey Berezhnoy, Nina Weisser, Thomas Spreter von Kreudenstein Charles Chen, Diana Papove, Adam Schayowitz, Paul Moore, and many more	
Toxicology	Kurt Stahl		
Project Management	Michelle Chakraborti Alyssa Mudryk		