A Novel Preclinical Mouse Model of Neutrophilic Asthma: Advancing Mechanistic Studies and Therapeutic Development

Xu Bai[1], Xiaoyue Chen[1], Chao Yao[1*]
1 WuXi Biology, WuXi AppTec, Shanghai, China.

WuXi Biology

INTRODUCTION

Neutrophilic Asthma (NA): Airway neutrophil infiltration

Key Features

- Chronic, often severe, corticosteroid-resistant phenotype
- ~20–30% of asthma patients; more frequent in severe asthma
- Limited targeted therapies compared to eosinophilic asthma

Current Challenges

- Scarcity of robust preclinical models
- Hinders evaluation of novel anti-inflammatory interventions
- Delays bench-to-bedside translation

Strategic Opportunity

- Develop validated, reproducible experimental models
- Elucidate mechanisms of neutrophilic airway inflammation
- Enable targeted therapeutic testing
- Improve outcomes in refractory asthma

METHOD

TSLP/TSLPR/IL7R humanized mice

Administration Time (TBD)

Day 0 — Day 14 — Day 24 — Day 29 — Day 30

Sensitization (D0–D14)
- OVA/CFA administration

Challenge (D24–D29)
- OVA/LPS exposure

Assessments

- **Inflammatory cells**: Flow cytometry of BALF
- **Lung function**: Whole-body plethysmography (WBP)
- **Inflammatory cytokines**: Measured in BALF and blood
- **Histopathology**: Lung tissue sections stained with HE and PAS

Whole Body Plethysmography

- Detect basic respiratory function parameters (e.g., PenH, Tvb, frequency)
- Non-invasive; automatic data collection

Resistance & Compliance

- Collects invasive resistance, compliance, and elastance data across breathing conditions
- Prolonged data collection with heated bed

Pulmonary Function Test

- Comprehensive pulmonary function assessment completed in minutes

Inhalation Tower

- Multi-species inhalation platform (mice, rats, guinea pigs); IA & AIA compatible

RESULTS

Inflammatory Cell Counts in BALF-FACS

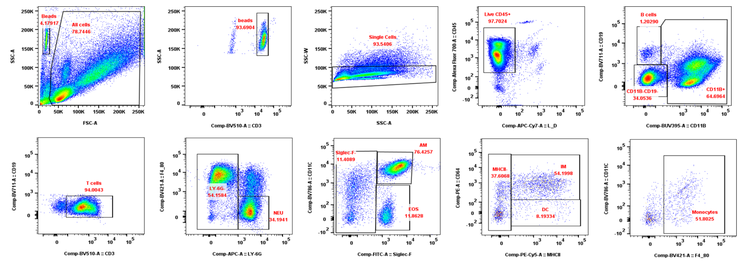

Figure 1. FACS settings for cell counting in BALF

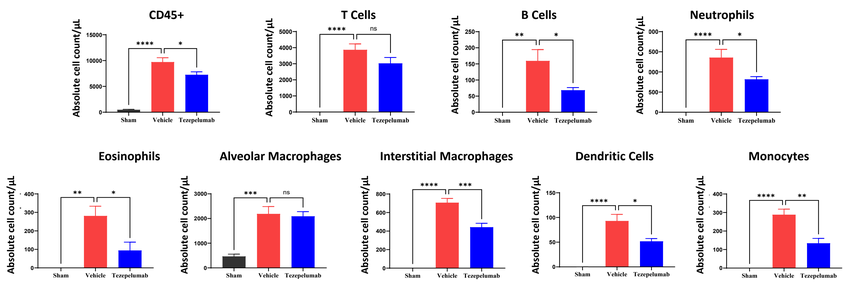

Figure 2. Number of inflammatory cells in BALF was significantly reduced following Tezepelumab treatment. *N=12/group, mean±SEM, ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05 vs. vehicle; One-Way ANOVA*

Biomarkers in BALF

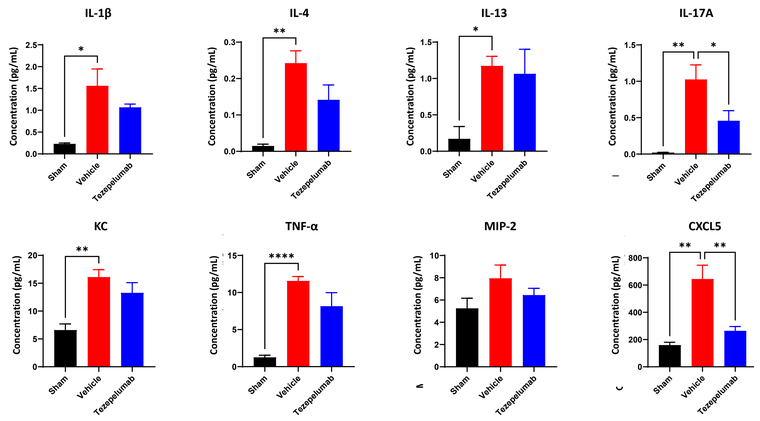

Figure 3. Level of different inflammatory biomarkers in BALF supernatant. *N=12/group, mean± SEM, ****p<0.0001, **p<0.01, *p<0.05 vs. vehicle; One-Way ANOVA.*

RESULTS

Lung function- AHR Test and Total IgE in Serum

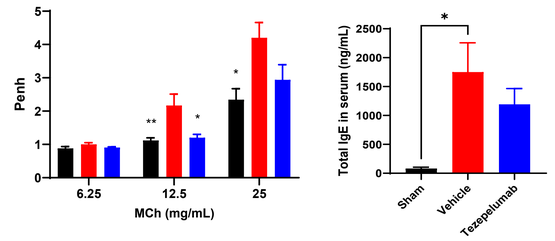

Figure 4. Lung function test at different dose of MCh and level of total IgE in serum. *N=12/group, mean±SEM, **p<0.01 and *p<0.05 vs. vehicle; One-Way ANOVA.*

H&E and PAS Staining of Lung Section (200 ×)

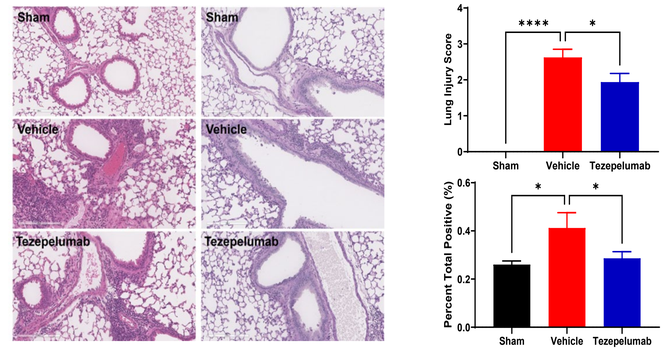

Figure 5. Lung injury and PAS-positive area were significantly reduced following Tezepelumab treatment. *N=12/group, mean±SEM, ****p<0.0001 and *p<0.05 vs. vehicle; One-Way ANOVA.*

CONCLUSION

We have developed a validated, reproducible **preclinical model** that **faithfully recapitulates key features of neutrophilic airway inflammation**:

- ✓ BALF cytology confirmed **predominant neutrophil population**, significantly elevated vs. sham
- ✓ **Inflammation**, **mucus hypersecretion**, and **goblet cell metaplasia** were **elevated** in the model group
- ✓ Increased **airway resistance** and **airflow limitation** were reversed following **tezepelumab treatment**

→ This model provides **a translationally relevant** platform for mechanistic studies and targeted therapeutic evaluation in **neutrophil-driven airway disease**.

REFERENCES

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2. De Volder J, Bontinck A, De Grove K, et al. Trajectory of neutrophilic responses in a mouse model of pollutant-aggravated allergic asthma. Environ Pollut. 2023;329:121722. doi:10.1016/j.envpol.2023.121722

WuXi AppTec

Contact Us

USA: mahnaz_arjomand@wuxiapptec.com
EU/UK/Israel: dave_madge@wuxiapptec.com
Japan: fumio_itoh@wuxiapptec.com
Korea: sycho@wuxiapptec.com
China/Singapore/Australia: xu_longji@wuxiapptec.com