Eblasakimab Significantly Alleviates IL-4 and IL-13-Induced Bronchial Airway Constriction in COPD-Derived Lung Slices

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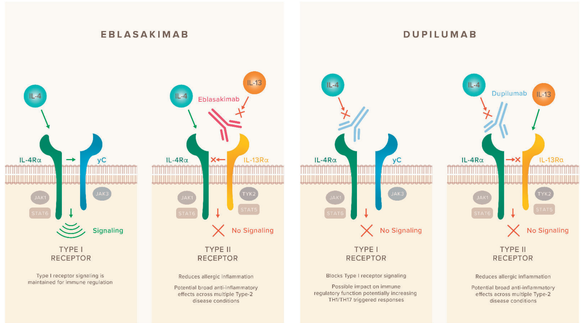
INTRODUCTION

- Patients with chronic obstructive pulmonary disorder (COPD) are vulnerable to acute exacerbations characterized by impaired airflow, obstruction, and dyspnea, underscoring the need for preventing exacerbations[1,2]
- Growing evidence indicates that Type 2 inflammation is observed during COPD exacerbations as well as during stable disease states in some patients[3]
  - In a Phase 3, double blind, randomized trial, COPD patients with Type 2 inflammation (indicated by elevated blood eosinophil counts) and a higher exacerbation risk treated with dupilumab had fewer exacerbations at week 52 compared to placebo-treated patients[4]
- Since interleukin-4 (IL-4) and interleukin-13 (IL-13) are central mediators of Type 2 inflammation,[5] and are implicated in various mechanisms of airway obstruction in asthma,[3] they may play an essential role in COPD[3]
- Therefore, blocking dual IL-4 and IL-13 signaling may have the potential to prevent bronchoconstriction evoked by the dual action of these proinflammatory cytokines
- IL-4 signaling is conducted through both Type I (IL-4Rα and γC) and Type II receptors (IL-4Rα and IL-13Rα1), while IL-13 signals through the Type II receptor[6]
- Dupilumab, an antibody approved for the treatment of multiple indications including atopic dermatitis and asthma, and eblasakimab, an antibody currently in clinical development for atopic dermatitis, are biologics that target different receptor subunits of the IL-4 and IL-13 signaling pathway
- While dupilumab functions by targeting IL-4Rα,[7] shared by both the Type I and II receptors, eblasakimab, a human IgG4 monoclonal antibody, targets the IL-13Rα1 subunit, uniquely blocking signaling through the Type II receptor complex and sparing the Type I receptor with the potential to block the Type II receptor more efficiently[8] (**Figure 1**)

FIGURE 1. EBLASAKIMAB AND DUPILUMAB MECHANISM OF ACTION



IL-4, interleukin-4; IL-13, interleukin-13; IL-4Rα, interleukin-4 receptor alpha; IL-13Rα, interleukin-13 receptor alpha 1.

OBJECTIVE

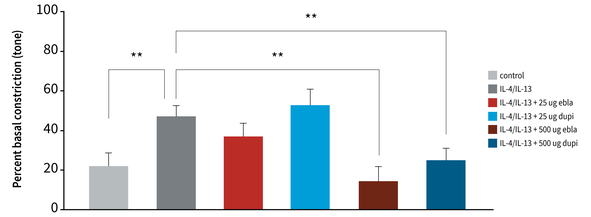
- Investigate the impact of eblasakimab on IL-4- and IL-13-induced bronchial airway constriction and compare the efficacy of eblasakimab with dupilumab in a human ex-vivo translational model for COPD.

KEY RESULTS: PRELIMINARY DATA INDICATE THAT EBLASAKIMAB HAS THE POTENTIAL TO SIGNIFICANTLY IMPROVE IL-4 AND IL-13-INDUCED BRONCHIAL AIRWAY CONSTRICTION

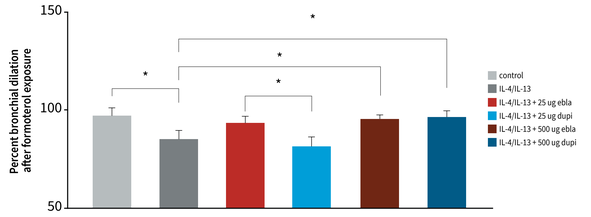
- In healthy PCLS, IL-4 and IL-13 combination treatment induced significantly higher percentages of bronchial airway constriction ($p<0.01$ vs control; **Figure 3A**), suppressed bronchial dilation levels stimulated by the relaxing agent formoterol ($p<0.05$ vs control; **Figure 3B**), and enhanced methacholine-induced airway constriction ($p<0.05$ vs control; **Figure 3C**)
- Both eblasakimab and dupilumab treatment significantly counteracted the constricting impacts of IL-4 and IL-13 cytokine exposure, restoring levels of airway constriction and dilation to levels observed in non-cytokine treated control slices (**Figures 3A-C**)
  - Both high and low doses of eblasakimab restored formoterol-induced acute dilation (5 minutes) in IL-4 and IL-13 pre-treated airways to levels observed in non-cytokine treated control slices (**Figure 3B**)
  - A low dose of eblasakimab was effective at inhibiting methacholine-induced constriction to levels observed in non-cytokine treated control slices (**Figure 3C**)
- In COPD-derived PCLS, exposure to IL-4 and IL-13 induced similar effects as in healthy tissue: significantly higher percentages of bronchial airway constriction ($p<0.01$ vs control; **Figure 4A**), numerically lower percentages of acute airway dilation in response to formoterol exposure compared to controls (**Figure 4B**), and increased constriction in response to methacholine ($p<0.001$ vs control; **Figure 4C**)
- Eblasakimab shows significant improvement compared with placebo across all measured bronchial outcomes in COPD-derived precision cut lung slices whereas dupilumab effects did not achieve statistical significance relative to placebo (**Figures 4A-C**)

FIGURE 3. BRONCHIAL AIRWAY RESPONSES TO VARIOUS TREATMENT CONDITIONS IN HEALTHY HUMAN PRECISION CUT LUNG SLICES

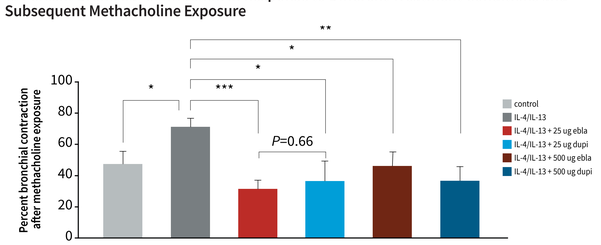
A. Percent Bronchial Contraction in Response to Different Treatment Conditions



B. Percent Bronchial Dilation in Response to Different Treatment Conditions and Subsequent Formoterol Exposure



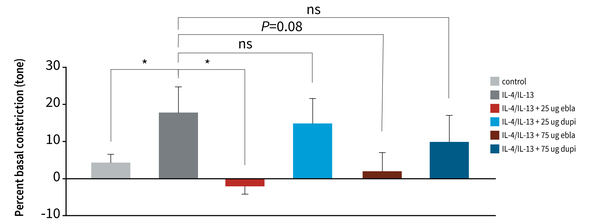
C. Percent Bronchial Contraction in Response to Different Treatment Conditions and Subsequent Methacholine Exposure



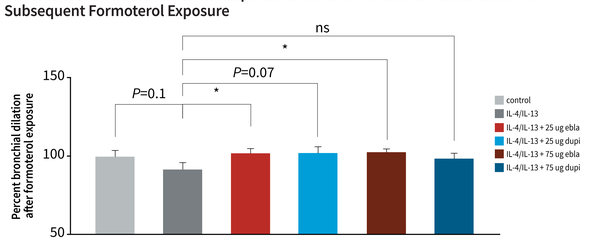
Dupi, dupilumab; ebla, eblasakimab; IL-4, interleukin-4; IL-13, interleukin-13.
n=6-13 airways per condition.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

FIGURE 4. BRONCHIAL AIRWAY RESPONSES TO VARIOUS TREATMENT CONDITIONS IN COPD-DERIVED PRECISION CUT LUNG SLICES

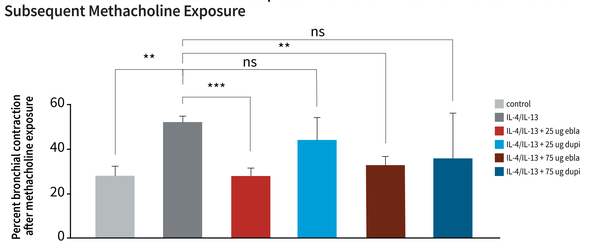
A. Percent Bronchial Contraction in Response to Different Treatment Conditions



B. Percent Bronchial Dilation in Response to Different Treatment Conditions and Subsequent Formoterol Exposure



C. Percent Bronchial Contraction in Response to Different Treatment Conditions and Subsequent Methacholine Exposure



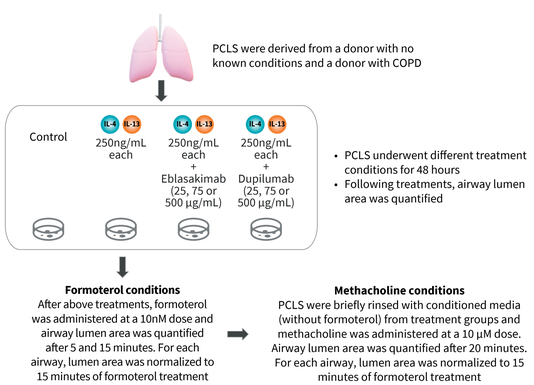
COPD, chronic obstructive pulmonary disease; dupi, dupilumab; ebla, eblasakimab; ns, not significant.
n=6-13 airways per condition.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

METHODS

Translational Lung Model

- Precision-cut lung slices (PCLS) from a 66-year-old male with no known history of lung diseases and a 67-year-old female with COPD were used to test constriction and dilation responses in response to different treatment conditions
- PCLS were assigned to the following treatment groups, each administered for 48 hours: untreated control, cytokine-stimulated with combination IL-4 and IL-13 treatment (250ng/mL IL-4 + 250ng/ml IL-13), or cytokine-stimulated and co-treated with different concentrations of eblasakimab or dupilumab as shown in the graphs (either 25 µg/mL, 75 µg/mL, or 500 µg/mL doses) (**Figure 2**)
  - Drug concentrations were selected to be within range of steady-state serum concentrations of dupilumab;[9] concentrations were used to develop a head-to-head eblasakimab vs dupilumab study design
  - A minimum of 6 PCLS were tested for each treatment condition
- PCLS were individually placed in separate wells of 6-well plates grouped by the experimental treatment conditions described above; the multi-well plates were mounted on a computer-controlled translation stage and imaged using an inverted microscope (DMI6000B; Leica Microsystems)
- Following 48-hour treatment, PCLS were sequentially treated with 10nM of the broncho-dilating agent formoterol, briefly rinsed with conditioned medium (without formoterol), then treated with 10µM of the constricting agent methacholine
- PCLS were imaged at baseline, 5 and 15 minutes after formoterol treatment, and 20 minutes after methacholine treatment
- From the acquired images, airway luminal area was quantified (Image J software; National Institutes of Health, Bethesda, MD) and its magnitude normalized to 15 minutes of formoterol treatment

FIGURE 2. SCHEMATIC OF TRANSLATIONAL LUNG MODEL



COPD, chronic obstructive lung disease; IL-4, interleukin-4; IL-13, interleukin-13; PCLS, precision-cut lung slices.

Statistical Analysis

- Unpaired t-tests assuming parametric distribution were performed to compare treatment groups, with $p<0.05$ considered statistically significant.

CONCLUSIONS

- In both healthy and COPD-derived lung tissues, eblasakimab significantly reduced IL-4- and IL-13-induced bronchial airway constriction, both pre- and post- methacholine stimulation
- In IL-4 and IL-13 pre-treated healthy and COPD-derived lung tissues, eblasakimab further restored formoterol-induced airway dilation and improved methacholine-induced constriction
- Results suggest a therapeutic benefit of eblasakimab in reducing IL-4- and IL-13-induced airway hyperresponsiveness and that eblasakimab may provide relief in situations of acute airway constriction
- Eblasakimab showed significant improvement across all measured bronchial outcomes whereas dupilumab did not achieve statistical significance relative to placebo for all measures, suggesting that eblasakimab may potentially provide stronger relief against bronchoconstriction as well as improved dilatory function in COPD compared to dupilumab
  - These results may be attributed to the potential of eblasakimab to inhibit the Type II receptor complex more efficiently, resulting in greater reduction in Th2 cytokine activity
- As airway hyperresponsiveness is clinically shared across asthma, COPD, and other lung disorders, eblasakimab has the potential to improve airway function in various Th2-driven lung conditions
- Taken together, these preliminary results support further investigation of eblasakimab as a potential therapeutic option for COPD with potentially more effective blockade of Type-2 mediated effects in lung tissue

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AUTHOR DISCLOSURES

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