

We claim:

1. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist, or use of an IL-4R antagonist in the manufacture of a medicament for use in combination with an IL-33 antagonist, for treating an inflammatory disease or disorder of the airway or lungs of a subject in need thereof, wherein the IL-33 antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 274 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 282, and wherein the IL-4R antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 337 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 338.

2. The use of claim 1, wherein the inflammatory disease or disorder is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), asthma and COPD overlap syndrome (ACOS), an allergic response of the airway or lungs, chronic bronchitis, emphysema, chronic rhinosinusitis with or without nasal polyps, hypersensitivity pneumonitis, allergic rhinitis, and pulmonary fibrosis.

3. The use of claim 1 or 2, wherein:

(a) the chronic obstructive pulmonary disease (i) is exacerbated by one or more of the following: asthma, a viral disease, a bacterial infection, an exposure to an allergen, an exposure to a chemical or chemical fumes, or an exposure to an environmental irritant or air pollution, or (ii) results from, or is exacerbated in part by cigarette smoke; or

(b) the asthma (i) is exacerbated by one or more of the following: a viral disease, a bacterial infection, an exposure to an allergen, an exposure to a chemical or chemical fumes, or an exposure to an environmental irritant or air pollution, or (ii) is eosinophilic asthma, non-eosinophilic asthma, steroid resistant asthma or steroid sensitive asthma.

4. The use of claim 1, wherein the inflammatory disease or disorder is asthma.

5. The use of claim 1, wherein the inflammatory disease or disorder is chronic obstructive pulmonary disease (COPD).

6. The use of claim 5, wherein the subject is a current smoker.

7. The use of claim 5, wherein the subject is a former smoker.

8. The use of any one of claims 1-7, wherein the IL-33 antagonist and the IL-4R antagonist are for use in combination with one or more additional therapeutic agents useful for alleviating the inflammatory disease or disorder, optionally wherein the one or more additional therapeutic agents is selected from the group consisting of a non-steroidal anti-inflammatory (NSAID), a corticosteroid, a bronchial dilator, an antihistamine, epinephrine, a decongestant, a thymic stromal lymphopoietin (TSLP) antagonist, an IL-1 antagonist, an IL-8 antagonist, an IL-13 antagonist, a different IL-4 antagonist, an IL-4/IL-13 dual antagonist, an IL-33/IL-13 dual antagonist, an IL-5 antagonist, an IL-6 antagonist, an IL-12/23 antagonist, an IL-22 antagonist, an IL-25 antagonist, an IL-17 antagonist, an IL-31 antagonist, a TNF inhibitor, an IgE inhibitor, a leukotriene inhibitor, an oral PDE4 inhibitor, a methylxanthine, nedocromil sodium, cromolyn sodium, a long-acting beta 2 agonist (LABA), a long acting muscarinic antagonist (LAMA), an inhaled corticosteroid (ICS) and another IL-33 antagonist, and optionally wherein the other IL-33 antagonist is selected from the group consisting of a different antibody to IL-33, a different IL-33 receptor based trap, an ST2 antibody, a soluble ST2 receptor, an antagonist to an IL-33 receptor other than ST2, an IL-1RAcP antagonist, and an antibody that interacts with an IL-33/ST2 complex.

9. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist, or use of an IL-4R antagonist in the manufacture of a medicament for use in combination with an IL-33 antagonist, for treating a pulmonary fibrotic disease or disorder, wherein the IL-33 antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 274 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 282, and wherein the IL-4R antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions

(HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 337 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 338.

10. The use of claim 4, wherein the pulmonary fibrotic disease or disorder is selected from the group consisting of idiopathic pulmonary fibrosis, fibrosis associated with acute lung injury or acute respiratory distress, silicosis, radiation-induced fibrosis, bleomycin-induced pulmonary fibrosis, asbestos-induced pulmonary fibrosis, and bronchiolitis obliterans syndrome.

11. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist, or use of an IL-4R antagonist in the manufacture of a medicament for use in combination with an IL-33 antagonist, for preventing or reducing the severity of an allergic response in the airway or lungs of a subject in need thereof, wherein the IL-33 antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 274 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 282, and wherein the IL-4R antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region (HCVR) sequence of SEQ ID NO: 337 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 338.

12. The use of any one of claims 1, 9, or 11, wherein the combination results in enhanced therapeutic efficacy, and the enhanced therapeutic efficacy is measured by any one or more of the following parameters:

- a) a reduction in the frequency of one or more of the following: eosinophils, activated B cells, activated CD8 T cells, or CD4/CD8 T cell ratio in a tissue sample, optionally wherein the tissue sample is obtained from the lung, or whole blood;
- b) a reduction in one or more of the following: interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-13 (IL-13), monocyte chemoattractant protein-1 (MCP-1), or tumor necrosis factor alpha (TNF α) levels in a tissue

sample, optionally wherein the tissue sample is obtained from the lung, liver, kidney, heart, or whole blood; or

c) a reduction in the gene expression level of one or more of the following: *Il4*, *Il5*, *Il6*, *Il9*, *Il13*, *Il1rl1*, *Il13ra2*, *tnf*, *Tgfb1*, *Ccl2*, *Ccl11*, *Ccl24*, *Col15a1* and/or *Col24a1* in a tissue sample, optionally wherein the tissue sample is obtained from the lung, liver, kidney, heart, or whole blood,

optionally wherein the enhanced therapeutic efficacy is further measured by any one or more of the following parameters:

- a) a reduction in serum IgE levels;
- b) a reduction in goblet cell metaplasia in the lung;
- c) an improvement in lung consolidation; or
- d) a decrease in sub-epithelial fibrosis in the lung.

13. The use of any one of claims 1-12, wherein the combination use of the IL-33 antagonist with the IL-4R antagonist results in an increase in a type 1 immune response, and/or a reduction in a type 2 immune response elicited by the disease, or by the causative agent of the disease or allergy.

14. The use of any one of claims 1-13, wherein the IL-4R antagonist is an antibody or antigen-binding fragment thereof that binds IL-4R α and prevents the interaction of IL-4 and/or IL-13 with a type 1 or type 2 IL-4 α receptor, optionally wherein the antibody or antigen-binding fragment thereof that binds IL-4R α prevents the interaction of IL-4 and/or IL-13 with both type 1 and type 2 IL-4 α receptors.

15. The use of any one of claims 1-14, wherein the IL-33 antagonist and the IL-4R antagonist are:

- (a) are formulated in separate compositions;
- (b) are co-formulated; or
- (c) are formulated for subcutaneous, intravenous, intramuscular, or intranasal use.

16. The use of any one of claims 1-15, wherein the IL-33 antagonist is a monoclonal antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282 and wherein the IL-4R antagonist is a monoclonal antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 337/338.

17. The use of claim 16, wherein the IL-33 antagonist comprises a human IgG4 heavy chain constant region.

18. The use of any one of claims 1-15, wherein the IL-33 antagonist is a monoclonal antibody comprising three HCDRs (HCDR1-HCDR2-HCDR3) having the amino acid sequences of SEQ ID NOs: 276-278-280, respectively and three LCDRs (LCDR1-LCDR2-LCDR3) having the amino acid sequences of SEQ ID NOs: 284-286-288, respectively and wherein the IL-4R antagonist is a monoclonal antibody comprising three HCDRs (HCDR1-HCDR2-HCDR3) having the amino acid sequences of SEQ ID NOs: 339-340-341, respectively and three LCDRs (LCDR1-LCDR2-LCDR3) having the amino acid sequences of SEQ ID NOs: 342-343-344, respectively.

19. The use of any one of claims 1-18, wherein the IL-33 antagonist is REGN3500 and wherein the IL-4R antagonist is dupilumab.