cell proliferation, differentiation of B cells into plasma cells, induction of differentiation of naïve CD4 + T cells into Th2 effector cells, up-regulation of, MHC class II production, CD23, and IL-4Rα on B cells and myeloid lineage cells, such as monocytic cells, decrease in production of Th1 cells, macrophages, IFN-gamma, and dendritic cell IL-12. (Hershey et al., N. Engl. J. Med. 1997, 337 (24): 1720–5).

Human Interleukin-13 (also known as IL-13; P600) plays an important role in for example goblet cell metaplasia, smooth cell muscle contraction, and mucus production in the airway epithelium, for example, in allergic asthma. Binding of IL-13 complex to IL-4Rα initiates the activation of multiple transduction pathways including tyrosine kinase 2 (Tyk-2) and Janus kinase 1 (JAK1). As such, both IL-4 and IL-13 cytokines activate STAT6 transcription factor, promote B-cell class switching to IgE and chemotaxis of eosinophils, and have also been found to play a potential role in tumor proliferation, cell survival, cell adhesion, and metastasis. (Suzuki, A., et al., Cytokine 2015; 75(1): 79-88). IL-13 is expressed by multiple cell types including, B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells. (Hershey et al., N. Engl. J. Med. 1997, 337 (24): 1720–5).

Antibody therapeutics targeting Type 2 inflammatory diseases are known, and either approved or in clinical development. Such antibodies include, dupilumab which targets the IL-4Rα; pascolizumab that targets IL-4; lebrikizumab, anrukinzumab, and tralokinumab that target the IL-13 pathway. (Junttila, I., Frontiers in Immunology 2018, 9: 888). However, in spite of the development of these targeted therapies there remains a need for additional IL-4Rα antibodies, for use in patients having Type 2 inflammatory disorders such as, asthma, atopic dermatitis, and / or eosinophilic esophagitis (EoE), and for patients who remain resistant to treatment, or are non-durable responders of current therapies, such as dupilumab.

SUMMARY

In a first aspect of the present disclosure, there is provided an antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

the HCDR1 comprises SEQ ID NO: 1;
the HCDR2 comprises SEQ ID NO: 2;
the HCDR3 comprises SEQ ID NO: 3;
the LCDR1 comprises SEQ ID NO: 4;
the LCDR2 comprises SEQ ID NO: 5; and
the LCDR3 comprises SEQ ID NO: 6.

In another aspect of the present disclosure, there is provided an antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

the HCDR1 comprises SEQ ID NO: 42;
the HCDR2 comprises SEQ ID NO: 2;
the HCDR3 comprises SEQ ID NO: 3;
the LCDR1 comprises SEQ ID NO: 22;
the LCDR2 comprises SEQ ID NO: 5; and
the LCDR3 comprises SEQ ID NO: 6.

In yet another aspect of the present disclosure, there is provided an antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

the HCDR1 comprises SEQ ID NO: 19;
the HCDR2 comprises SEQ ID NO: 20;
the HCDR3 comprises SEQ ID NO: 3;
the LCDR1 comprises SEQ ID NO: 22;
the LCDR2 comprises SEQ ID NO: 5; and
the LCDR3 comprises SEQ ID NO: 24.

In a further aspect of the present disclosure, there is provided a nucleic acid comprising a sequence encoding SEQ ID NO: 9, 10, 13, 27, 28, 31, 33, 35, 37, 46, 47, 50, or 52.

In another aspect of the present disclosure, there is provided a vector comprising the nucleic acid as disclosed herein.

In yet another aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 9, 13, 31, 33, 35, 37, 46, 50, or 52 and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 10 or 47.

In a further aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 27, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 28.

In another aspect of the present disclosure, there is provided a cell comprising the vector as disclosed herein.

In yet another aspect of the present disclosure, there is provided a process of producing an antibody or antigen binding fragment thereof comprising culturing the cell as disclosed herein, under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

In a further aspect of the present disclosure, there is provided an antibody or antigen binding fragment thereof produced by the process as disclosed herein.

In another aspect of the present disclosure, there is provided an antibody drug conjugate comprising the antibody as disclosed herein.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody or antigen binding fragment thereof as disclosed herein, and a pharmaceutically acceptable excipient, diluent, or carrier.

In a further aspect of the present disclosure, there is provided a use of the antibody or antigen binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating an IL-4R associated disorder.

In another aspect of the present disclosure, there is provided the antibody or antigen binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in therapy.

DETAILED DESCRIPTION

The present disclosure provides antibodies that specifically bind human IL-4Rα and inhibit IL-4R, IL-4 and / or IL-13 mediated responses (e.g., B cell proliferation, STAT-6 phosphorylation, CD23 expression), compositions comprising such IL-4Rα antibodies, and methods of using such IL-4Rα antibodies. Particularly, the present disclosure provides human IL-4Rα antibodies that bind a novel epitope spanning the n-terminal fibronectin type-III domains 1 and 2 of the human and / or cynomolgus monkey

CLAIMS:

1. An antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

    the HCDR1 comprises SEQ ID NO: 1;
    the HCDR2 comprises SEQ ID NO: 2;
    the HCDR3 comprises SEQ ID NO: 3;
    the LCDR1 comprises SEQ ID NO: 4;
    the LCDR2 comprises SEQ ID NO: 5; and
    the LCDR3 comprises SEQ ID NO: 6.

2. The antibody or antigen binding fragment thereof of Claim 1, wherein the VH comprises SEQ ID NO: 7 and the VL comprises SEQ ID NO: 8.

3. An antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

    the HCDR1 comprises SEQ ID NO: 42;
    the HCDR2 comprises SEQ ID NO: 2;
    the HCDR3 comprises SEQ ID NO: 3;
    the LCDR1 comprises SEQ ID NO: 22;
    the LCDR2 comprises SEQ ID NO: 5; and
    the LCDR3 comprises SEQ ID NO: 6.

4. The antibody or antigen binding fragment thereof of Claim 3, wherein the VH comprises SEQ ID NO: 44 and the VL comprises SEQ ID NO: 45.

5. The antibody or antigen binding fragment thereof of any of Claims 1 to 4, wherein the antibody comprises:
    i. a heavy chain (HC) comprising SEQ ID NO: 33 and a light chain (LC) comprising SEQ ID NO: 10;
    ii. a heavy chain (HC) comprising SEQ ID NO: 35 and a light chain (LC) comprising SEQ ID NO: 10;
    iii. a heavy chain (HC) comprising SEQ ID NO: 9 and a light chain (LC) comprising SEQ ID NO: 10;
    iv. a heavy chain (HC) comprising SEQ ID NO: 13 and a light chain (LC) comprising SEQ ID NO: 10;
    v. a heavy chain (HC) comprising SEQ ID NO: 31 and a light chain (LC) comprising SEQ ID NO: 10;
    vi. a heavy chain (HC) comprising SEQ ID NO: 37 and a light chain (LC) comprising SEQ ID NO: 10;
    vii. a heavy chain (HC) comprising SEQ ID NO: 52 and a light chain (LC) comprising SEQ ID NO: 10;
    viii. a heavy chain (HC) comprising SEQ ID NO: 50 and a light chain (LC) comprising SEQ ID NO: 10; or
    ix. a heavy chain (HC) comprising SEQ ID NO: 46 and a light chain (LC) comprising SEQ ID NO: 47.

6. The antibody or antigen binding fragment thereof of any one of Claims 1 to 4, wherein the antibody comprises a human IgG1 isotype.

7. The antibody or antigen binding fragment thereof of Claim 6, wherein the antibody comprises an alanine at amino acid residue 322 (EU numbering).

8. The antibody or antigen binding fragment thereof of any one of Claims 1 to 4, wherein the antibody comprises a human IgG4 isotype.

9. The antibody or antigen binding fragment thereof of Claim 8, wherein the antibody comprises one or more of the following:

a glycine at amino acid residue 137 (EU numbering);

an asparagine at amino acid residue 203 (EU numbering);

a lysine at amino acid residue 274 (EU numbering);

an arginine at amino acid residue 355 (EU numbering); or

a glutamine at amino acid residue 419 (EU numbering).

10. The antibody or antigen binding fragment thereof of Claim 8, wherein the antibody comprises:

a lysine at amino acid residue 274 (EU numbering), an arginine at amino acid residue 355, and a glutamine at amino acid residue 419 (EU numbering).

11. The antibody or antigen binding fragment thereof of Claim 8, wherein the antibody comprises:

a glycine at amino acid residue 137 (EU numbering), an asparagine at amino acid residue 203 (EU numbering), a lysine at amino acid residue 274 (EU numbering), an arginine at amino acid residue 355, and a glutamine at amino acid residue 419 (EU numbering).

12. An antibody or antigen binding fragment thereof that specifically binds human IL-4Rα, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein:

the HCDR1 comprises SEQ ID NO: 19;

the HCDR2 comprises SEQ ID NO: 20;

the HCDR3 comprises SEQ ID NO: 3;

the LCDR1 comprises SEQ ID NO: 22;

the LCDR2 comprises SEQ ID NO: 5; and

the LCDR3 comprises SEQ ID NO: 24.

13. The antibody or antigen binding fragment thereof of Claim 12, wherein the VH comprises SEQ ID NO: 25 and the VL comprises SEQ ID NO: 26.

14. The antibody or antigen binding fragment thereof of any one of Claims 12 or 13, wherein the antibody comprises a HC comprising SEQ ID NO: 27 and a LC comprising SEQ ID NO: 28.

15. The antibody or antigen binding fragment thereof of any one of Claims 5-11 or 14, wherein the antibody comprises:

a cysteine at amino acid residue 124 (EU numbering);

a cysteine at amino acid residue 378 (EU numbering); or

a cysteine at amino acid residue 124 (EU numbering) and cysteine at amino acid residue 378 (EU numbering).

16. A nucleic acid comprising a sequence encoding SEQ ID NO: 9, 10, 13, 27, 28, 31, 33, 35, 37, 46, 47, 50, or 52.

17. A vector comprising the nucleic acid of claim 16.

18. The vector of Claim 17, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 9, 13, 31, 33, 35, 37, 46, 50, or 52 and a second nucleic acid sequence encoding SEQ ID NO: 10 or 47.

19. The vector of Claim 17, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 27, and a second nucleic acid sequence encoding SEQ ID NO: 28.

20. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 9, 13, 31, 33, 35, 37, 46, 50, or 52 and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 10 or 47.

21. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 27, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 28.

22. A cell comprising the vector of any one of Claims 17 or 19.

23. The cell of Claim 22, wherein the cell is a mammalian cell.

24. A process of producing an antibody or antigen binding fragment thereof comprising culturing the cell of any one of Claims 22 to 23, under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

25. An antibody or antigen binding fragment thereof produced by the process of Claim 24.

26. An antibody drug conjugate comprising the antibody of any one of Claims 1 to 15, or 25.

27. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof of any one of Claims 1 to 15, or 25, and a pharmaceutically acceptable excipient, diluent, or carrier.

28. Use of the antibody or antigen binding fragment thereof of any one of Claims 1 to 15, or 25, or the pharmaceutical composition of Claim 27, in the manufacture of a medicament for treating an IL-4R associated disorder.

29. The use of Claim 28, wherein IL-4R associated disorder is an immune inflammatory disorder.

30. The use of Claim 29, wherein the immune inflammatory disorder is a Type 2 inflammatory disorder.

31. The use of Claim 30, wherein the Type 2 inflammatory disorder is selected from atopic dermatitis, eosinophilic esophagitis, nasal polyposis, asthma, chronic rhinosinusitis (CRS), allergic disease, chronic obstructive pulmonary disease (COPD), or chronic spontaneous urticaria (CSU).

32. The antibody or antigen binding fragment thereof of any one of Claims 1 to 15, or 25, or the pharmaceutical composition of claim 27, for use in therapy.

5