production of other pro-inflammatory cytokines and the recruitment of immune cells (Deng, C. et al., Front. Immunol (2021) 12:691559).

**[0005]** On the other hand, IL-25 has been reported to play a role in autoimmune diseases as an anti-inflammatory cytokine and an inhibitor of both innate and adaptive immunity (Saadoun, D. et al., Current pharmaceutical design (2011) 17:3781–3785. For example, the anti-inflammatory and immunosuppressive activities of IL-25 in rheumatoid arthritis are attributed to an IL-13-dependent downregulation of the Th17 cell response (Liu, D. et al., Sci Rep (2016) 6:36002).

**[0006]** Additionally, the expression of IL-25 and its receptor have been dysregulated in various cancers compared with normal tissues. Therefore, it has been indicated that IL-25 might also play a Janus-faced role in cancer progression or regression. The tumor-suppressive role of IL-25 is mainly attributed to the infiltration of eosinophils and B cells into the tumor microenvironment and induction of apoptosis. In contrast, its tumor supportive roles rely on the deviation of immune responses and stimulation of EMT and cell growth (Gowhari Shabgah, A. et al., Cancer Med. (2021) 10: 5191– 5202).

**[0007]** Although the IL-25 pathway is a recognized therapeutic target, only a single Phase I clinical trial evaluating the safety, tolerability and pharmacokinetic characteristics IL-25 has been identified to date. Accordingly, there is an unmet need in the art for novel IL-25 antagonists, such as the anti-IL-25 antibodies disclosed herein, for the treatment of diseases or disorders associated with IL-25 expression and/or signaling.

## SUMMARY

**[0008]** The present disclosure addresses the above need by providing antibodies and antibody fragments thereof that bind to IL-25 including human IL-25. The antibodies and antibody fragments thereof are useful for the treatment of immune-mediated inflammatory diseases (IMIDs) (e.g., autoimmune diseases and inflammatory disorders) and cancer. The anti-IL-25 antibodies or antibody fragments thereof can either be used alone (e.g., as a monotherapy) or in combination with other immunotherapeutic agents. In an alternative example, an antibody fragment of an IL-25 antibody disclosed herein can be used as a component of a bispecific or multi-specific antibody or fusion protein.

**[0009]** In one aspect, the present disclosure provides an anti-IL-25 antibody comprising: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 49 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (LCDR1); the amino acid sequence of SEQ ID NO: 51 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3); (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 52 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (LCDR1); the amino acid sequence of SEQ ID NO: 51 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3); (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 11 (HCDR1); the amino acid sequence of SEQ ID NO: 12 (HCDR2); and the amino acid sequence of SEQ ID NO: 13 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (LCDR1); the amino acid sequence of SEQ ID NO: 15 (LCDR2); and the amino acid sequence of SEQ ID NO: 16 (LCDR3); (d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 17 (HCDR1); the amino acid sequence of SEQ ID NO: 18 (HCDR2); and the amino acid sequence of SEQ ID NO: 19 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 20 (LCDR1); the amino acid sequence of SEQ ID NO: 21 (LCDR2); and the amino acid sequence of SEQ ID NO: 22 (LCDR3); (e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 24 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 26 (LCDR1); the amino acid sequence of SEQ ID NO: 27 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3); (f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29 (HCDR1); the amino acid sequence of SEQ ID NO: 30 (HCDR2); and the amino acid sequence of SEQ ID NO: 31 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32 (LCDR1); the amino acid sequence of SEQ ID NO: 33 (LCDR2); and the amino acid sequence of SEQ ID NO: 34 (LCDR3);

or (g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35 (HCDR1); the amino acid sequence of SEQ ID NO: 36 (HCDR2); and the amino acid sequence of SEQ ID NO: 37 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 38 (LCDR1); the amino acid sequence of SEQ ID NO: 39 (LCDR2); and the amino acid sequence of SEQ ID NO: 40 (LCDR3).

**[0009a]** In another aspect, the present disclosure provides a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

**[0009b]** In another aspect, the present disclosure provides a use of the antibody as disclosed herein in the manufacture of a medicament for treating and/or preventing a Type 2 inflammation disease, autoimmune disease, allergic disorder, or cancer in a subject in need thereof.

**[0009c]** In another aspect, the present disclosure provides a composition of polynucleotides comprising: a) a first polynucleotide coding for a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, 3, 5, 7, 9, 44, or 47; and b) a second polynucleotide coding for a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 46, or 48.

**[0009d]** In another aspect, the present disclosure provides a composition of vectors comprising: a) a first vector comprising the first polynucleotide as disclosed herein; and b) a second vector comprising the second polynucleotide as disclosed herein.

**[0009e]** In another aspect, the present disclosure provides a cell comprising the polynucleotide composition as disclosed herein, or a vector composition as disclosed herein.

**[0009f]** In another aspect, the present disclosure provides a method for the production of an anti-IL-25 antibody as disclosed herein, the method comprising culturing the cell as disclosed herein in a culture media; and recovering the anti-IL-25 antibody from the media.

**[0009g]** In some examples, the anti-IL-25 antibody or antibody fragment thereof binds to the IL-25 cytokine (IL-17E) with high affinity, and does not bind (e.g., specifically bind) to any other members of the IL-17 cytokine family.

**[0010]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO: 11, CDR2: SEQ ID NO: 12, and CDR3: SEQ ID NO: 13; and/or a light chain variable region comprising CDR1: SEQ ID NO: 14, CDR2: SEQ ID NO: 15, and CDR3: SEQ ID NO: 16.

**[0011]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO: 17, CDR2: SEQ ID NO: 18, and CDR3: SEQ ID NO: 19; and/or a light chain variable region comprising CDR1: SEQ ID NO: 20, CDR2: SEQ ID NO: 21, and CDR3: SEQ ID NO: 22.

**[0012]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO: 23, CDR2: SEQ ID NO: 24, and CDR3: SEQ ID NO: 25; and/or a light chain variable region comprising CDR1: SEQ ID NO: 26, CDR2: SEQ ID NO: 27, and CDR3: SEQ ID NO: 28.

**[0013]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO: 29, CDR2: SEQ ID NO: 30, and CDR3: SEQ ID NO: 31; and/or a light chain variable region comprising CDR1: SEQ ID NO: 32, CDR2: SEQ ID NO: 33, and CDR3: SEQ ID NO: 34.

**[0014]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO: 35, CDR2: SEQ ID NO: 36, and CDR3: SEQ ID NO: 37; and/or a light chain variable region comprising CDR1: SEQ ID NO: 38, CDR2: SEQ ID NO: 39, and CDR3: SEQ ID NO: 40.

**[0015]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO:23 CDR2: SEQ ID NO: 49, and CDR3: SEQ ID NO: 25; and/or a light chain variable region comprising CDR1: SEQ ID NO: 50 CDR2: SEQ ID NO:51, and CDR3: SEQ ID NO: 28.

**[0016]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region comprising CDR1: SEQ ID NO:23 CDR2: SEQ

ID NO: 52 and CDR3: SEQ ID NO: 25; and/or a light chain variable region comprising CDR1: SEQ ID NO: 50, CDR2: SEQ ID NO: 51, and CDR3: SEQ ID NO: 28.

**[0017]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, and 9.

**[0018]** In other examples, the anti-IL-25 antibody or antibody fragment thereof comprises a light chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, and 10.

**[0019]** In other examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, and 9 and a variable light chain sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8 and 10.

**[0020]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a humanized heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 44 and 47.

**[0021]** In other examples, the anti-IL-25 antibody or antibody fragment thereof comprises a humanized light chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 45, 46 and 48.

**[0022]** In other examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 44 and 47 and a variable light chain sequence selected from the group consisting of SEQ ID NOs: 45, 46 and 48.

**[0023]** In some examples, the anti-IL-25 antibody or antibody fragment thereof comprises a heavy chain variable region sequence and a light chain variable region sequence, selected from the following combinations:

(a) a variable heavy chain sequence comprising SEQ ID NO: 1 and a variable light chain sequence comprising SEQ ID NO: 2;

(b) a variable heavy chain sequence comprising SEQ ID NO: 3 and a variable light chain sequence comprising SEQ ID NO: 4;

(c) a variable heavy chain sequence comprising SEQ ID NO: 5 and a variable light chain sequence comprising SEQ ID NO: 6;

(d) a variable heavy chain sequence comprising SEQ ID NO: 7 and a variable light chain sequence comprising SEQ ID NO: 8;

(e) a variable heavy chain sequence comprising SEQ ID NO: 9 and a variable light chain sequence comprising SEQ ID NO: 10;

(f) a variable heavy chain sequence comprising SEQ ID NO: 44 and a variable light chain sequence comprising SEQ ID NO: 45;

(g) a variable heavy chain sequence comprising SEQ ID NO: 44 and a variable light chain sequence comprising SEQ ID NO: 46 or

(h) a variable heavy chain sequence comprising SEQ ID NO: 47 and a variable light chain sequence comprising SEQ ID NO: 48.

**[0024]** In some examples, the antibody is an human anti-IL-25 antibody.

**[0025]** In some examples, the antibody is a full-length antibody.

**[0026]** In some examples, the antibody is a full-length antibody comprising a human IgG1 constant region selected from SEQ ID NO: 55 or SEQ ID NO: 56.

**[0027]** In some examples, the antibody fragment is selected from the group consisting of: Fab, Fab, F(ab)2, Fd, Fv, scFv and scFv-Fc fragment, a single-chain antibody, a minibody, and a diabody.

**[0028]** In some examples, the antibody is a monoclonal antibody.

**[0029]** In some examples, the antibody is a human antibody (e.g, a fully human antibody).

**[0030]** In some examples, the antibody is a murine antibody.

**[0031]** In some examples, the antibody is a chimeric antibody.

**[0032]** In some examples, the antibody is a bispecific antibody.

**[0033]** In some examples, the antibody is a humanized antibody.

**WHAT IS CLAIMED IS:**

1. An anti-IL-25 antibody comprising:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 49 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (LCDR1); the amino acid sequence of SEQ ID NO: 51 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3);

(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 52 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (LCDR1); the amino acid sequence of SEQ ID NO: 51 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3);

(c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 11 (HCDR1); the amino acid sequence of SEQ ID NO: 12 (HCDR2); and the amino acid sequence of SEQ ID NO: 13 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (LCDR1); the amino acid sequence of SEQ ID NO: 15 (LCDR2); and the amino acid sequence of SEQ ID NO: 16 (LCDR3);

(d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 17 (HCDR1); the amino acid sequence of SEQ ID NO: 18 (HCDR2); and the amino acid sequence of SEQ ID NO: 19 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 20 (LCDR1); the amino acid sequence of SEQ ID NO: 21 (LCDR2); and the amino acid sequence of SEQ ID NO: 22 (LCDR3);

(e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 (HCDR1); the amino acid sequence of SEQ ID NO: 24 (HCDR2); and the amino acid sequence of SEQ ID NO: 25 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 26 (LCDR1); the amino acid sequence of SEQ ID NO: 27 (LCDR2); and the amino acid sequence of SEQ ID NO: 28 (LCDR3);

(f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29 (HCDR1); the amino acid sequence of SEQ ID NO: 30 (HCDR2); and the amino

acid sequence of SEQ ID NO: 31 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32 (LCDR1); the amino acid sequence of SEQ ID NO: 33 (LCDR2); and the amino acid sequence of SEQ ID NO: 34 (LCDR3); or

(g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35 (HCDR1); the amino acid sequence of SEQ ID NO: 36 (HCDR2); and the amino acid sequence of SEQ ID NO: 37 (HCDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 38 (LCDR1); the amino acid sequence of SEQ ID NO: 39 (LCDR2); and the amino acid sequence of SEQ ID NO: 40 (LCDR3).

2. The anti-IL-25 antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 1, 3, 5, 7, 9, 44 or 47; and a light chain variable region comprising the amino acid sequence of any one of SEQ ID NOs: 2, 4, 6, 8, 10, 45, 46 or 48.

3. The anti-IL-25 antibody of claim 1, wherein the antibody comprises:

(a) a heavy chain variable region sequence of SEQ ID NO: 44 and a light chain variable region sequence of SEQ ID NO: 45;

(b) a heavy chain variable region sequence of SEQ ID NO: 44 and a light chain variable region sequence of SEQ ID NO: 46;

(c) a heavy chain variable region sequence of SEQ ID NO: 47and a light chain variable region sequence of SEQ ID NO: 48;

(d) a heavy chain variable region sequence of SEQ ID NO: 1 and a light chain variable region sequence of SEQ ID NO: 2;

(e) a heavy chain variable region sequence of SEQ ID NO: 3 and a light chain variable region sequence of SEQ ID NO: 4;

(f) a heavy chain variable region sequence of SEQ ID NO: 5 and a light chain variable region sequence of SEQ ID NO: 6;

(g) a heavy chain variable region sequence of SEQ ID NO: 7 and a light chain variable region sequence of SEQ ID NO: 8; or

h) a heavy chain variable region sequence of SEQ ID NO: 9 and a light chain variable region sequence of SEQ ID NO: 10.

4. The anti-IL-25 antibody of claim 1, wherein the antibody is an anti-human anti-IL-25 antibody.

5. The anti-IL-25 antibody of claim 1, wherein the antibody is a full-length antibody comprising a human IgG1 constant region selected from SEQ ID NO: 55 or SEQ ID NO: 56.

6. The anti-IL-25 antibody of claim 1, wherein the antibody is an antibody fragment.

7. The anti-IL-25 antibody of claim 4, wherein the antibody fragment is selected from the group consisting of: Fab, Fab, F(ab)2, Fd, Fv, scFv and scFv-Fc fragment, a single-chain antibody, a minibody, and a diabody.

8. The anti-IL-25 antibody of claim 1, wherein the antibody is a monoclonal antibody.

9. The anti-IL-25 antibody of claim 1, wherein the antibody is a human antibody.

10. The anti-IL-25 antibody of claim 1, wherein the antibody is a murine antibody.

11. The anti-IL-25 antibody of claim 1, wherein the antibody is a chimeric antibody.

12. The anti-IL-25 antibody of claim 1, wherein the antibody is a bispecific or a multi-specific antibody.

13. The anti-IL-25 antibody of claim 1, wherein the antibody is a humanized antibody.

14. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

15. Use of the antibody of claim 1 in the manufacture of a medicament for treating and/or preventing a Type 2 inflammation disease, autoimmune disease, allergic disorder, or cancer in a subject in need thereof.

16. A composition of polynucleotides comprising:

a) a first polynucleotide coding for a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, 3, 5, 7, 9, 44, or 47; and

b) a second polynucleotide coding for a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 46, or 48.

17. A composition of vectors comprising:

a) a first vector comprising the first polynucleotide of claim 16; and

b) a second vector comprising the second polynucleotide of claim 16.

18. A cell comprising the polynucleotide composition according to claim 16, or a vector composition according to claim 17.

19. A method for the production of an anti-IL-25 antibody according to claim 1, the method comprising culturing the cell of claim 18 in a culture media; and recovering the anti-IL-25 antibody from the media.