

populations that direct adaptive immune responses to infection, inflammation and autoimmune disease outcomes. IL-12 and IL-23 are predominantly proinflammatory / prostimulatory cytokines that play roles in the development of Th1 and Th17 cells, respectively.

[0007] The functional IL-23 receptor is a heterodimer of the IL-12R β 1 subunit, which is shared with the IL-12 receptor and partnered with the signaling chain IL-23R (p19 subunit binding). The receptor for IL-23 is constitutively associated with Janus kinase 2 (Jak2) and predominantly activates STAT3. Expression of the IL-23 receptor is detected primarily on memory T-cells and NK cells. Monocytes, macrophages and dendritic cells also express IL-23 receptor at low levels.

[0008] There is substantial evidence that IL-23 responsive cells are associated with autoimmune inflammatory diseases and cancer and that the modulation of IL-23 activity can provide promising therapies. In particular, abnormal regulation of IL-23 is associated with immune-mediated inflammatory diseases (IMIDs), such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis. In addition, the balance of proinflammatory cytokines, including IL-23 and IL-12 plays a key role in shaping the development of antitumor or protumor immunity.

[0009] The IL-23/IL-12 pathways are implicated in the cellular mechanisms involved in the pathophysiology of multiple inflammatory diseases. Several therapeutic strategies have been designed to inhibit IL-23 activity and there is a continuing need for therapeutic agents that target the pro-inflammatory IL-23/IL-23 receptor signaling axis for treatment of immune-mediated inflammatory disorders. More specifically, there remains a need for selective IL-23p19 antagonist antibodies that bind with high affinity to the p19 subunit of IL-23, in particular, human IL-23, and do not bind to the p40 subunit of the related cytokine family member, IL-12.

SUMMARY

[0010] The present disclosure addresses the above need by providing antibodies and antibody fragments that bind to the cytokine p19 subunit of IL-23. The antibodies and antibody fragments are useful for the treatment of immune-mediated inflammatory diseases (IMIDs) (e.g., autoimmune diseases and inflammatory disorders), either alone (e.g., as a monotherapy) or in combination with other immunotherapeutic agents.

[0010a] In one aspect, the present disclosure refers to an anti-IL-23p19 antibody comprising: a heavy chain variable region comprising CDR1: SEQ ID NO: 15, CDR2: SEQ ID NO: 16, and CDR3: SEQ ID NO: 17; and a light chain variable region comprising CDR1: SEQ ID NO: 18, CDR2: SEQ ID NO: 19, and CDR3: SEQ ID NO: 20.

[0010b] In another aspect, the present disclosure refers to a bispecific antibody comprising the anti-IL-23p19 antibody as disclosed herein.

[0010c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[0010d] In yet another aspect, the present disclosure refers to the use of the antibody as disclosed herein in the manufacture of a medicament for treating an IL-23 mediated inflammatory disease.

[0011] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof bind to the cytokine p19 subunit of human IL-23. In a further [embodimentexample](#), the antibodies are fully human.

[0012] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a heavy chain variable region comprising CDR1: SEQ ID NO: 9, CDR2: SEQ ID NO: 10, and CDR3: SEQ ID NO: 11; and/or a light chain variable region comprising CDR1: SEQ ID NO: 12, CDR2: SEQ ID NO: 13, and CDR3: SEQ ID NO: 14.

[0013] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a heavy chain variable region comprising CDR1: SEQ ID NO: 15, CDR2: SEQ ID NO: 16, and CDR3: SEQ ID NO: 17; and/or a light chain variable region comprising CDR1: SEQ ID NO: 18, CDR2: SEQ ID NO: 19, and CDR3: SEQ ID NO: 20.

[0014] In some [embodimentexample](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a heavy chain variable region comprising CDR1: SEQ ID NO: 21, CDR2: SEQ ID NO: 22, and CDR3: SEQ ID NO: 23; and/or a light chain variable region comprising CDR1: SEQ ID NO: 24, CDR2: SEQ ID NO: 25, and CDR3: SEQ ID NO: 26.

[0015] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a heavy chain variable region comprising CDR1: SEQ ID NO: 27, CDR2: SEQ ID NO: 28, and CDR3: SEQ ID NO: 29; and/or a light chain variable region comprising CDR1: SEQ ID NO: 30, CDR2: SEQ ID NO: 31, and CDR3: SEQ ID NO: 32.

[0016] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a variable heavy chain sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, and 7.

[0017] In other [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a variable light chain sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, and 8.

[0018] In other [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a variable heavy chain sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, and 7, and a variable light chain sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, and 8.

[0019] In some [embodimentexamples](#), the anti-IL-23p19 antibody or antibody fragment comprises variable heavy chain and variable light chain sequences, 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; and
- (d) a variable heavy chain sequence comprising SEQ ID NO: 7 and a variable light chain sequence comprising SEQ ID NO: 8.

[0020] In some [embodimentexamples](#), the anti- IL-23p19 antibodies (e.g., antagonist antibodies) bind with high affinity to the p19 subunit of IL-23 and do not bind to the p40 subunit of the related cytokine family member, IL-12.

[0021] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof exhibit one or more of the following characteristics: (a) is specific for human IL-23p19 and has the ability to block IL-23 binding to its receptor (IL-23R); (b) inhibits, interferes with, or modulates IL-23p19 interaction with IL-23 receptor signal transduction; (c) inhibits STAT3 activation induced by IL-23 in DB cells; (d) inhibits IL-17 production induced by human IL-23 in mouse splenocytes; (e) inhibits IL-17 production induced by human IL-23 in activated human PBMC; (f) does not inhibit IL-23 interaction with IL-12R β 1 signal transduction; (g) does not inhibit human IL-12 induced interferon gamma production in human activated T-cells (PBMC) (h) does not inhibit cynomolgus monkey IL-12 induced interferon gamma production in human activated T-cells (PBMC); and (i) inhibits skin inflammation induced by human IL-23 in a murine psoriasis-like model.

[0022] In one [aspectexample](#), the disclosed antibodies and isolated antigen binding agents can be used to inhibit IL-23p19 induced IL-23 receptor signaling networks (e.g., of the inflammatory microenvironment that promote autoimmune diseases).

[0023] The anti-IL-23p19 antibodies or antibody fragments thereof may exhibit one or more of the following properties:

- (a) is specific for human IL-23p19 and has the ability to block IL-23 binding to its receptor IL-23 receptor (e.g., blocker);
- (b) inhibits, interferes with, or modulates IL-23/IL-23 receptor-mediated signal transduction;

- (c) blocks IL-23-induced STAT3 activation induced by IL-23 in DB cells;
- (d) inhibits IL-23- induced IL-17 production in mouse splenocytes;
- (e) inhibits IL-23-induced IL-17 production in human PBMC;
- (f) does not inhibit IL-23 interaction with IL-12R β 1 signal transduction;
- (g) does not block human IL-12-induced interferon- γ production in human PBMC;
- (h) does not inhibit cynomolgus monkey IL-12-induced interferon gamma productions in human PBMC; and
- (i) inhibits IL-23-induced skin-inflammation in a murine psoriasis-like model.

[0024] In some [embodimentexamples](#), the anti-IL-23p19 antibodies or antibody fragments thereof comprise a combination of CDR sequences derived from a variable heavy chain sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, and 7, and a variable light chain sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, and 8.

[0025] In some [embodimentexamples](#), the anti-IL-23p19 antibodies and antibody fragments thereof comprise one or more heavy chain variable region CDRs disclosed in Table 1 and/or one or more light chain variable region CDRs disclosed in Table 2.

[0026] In some [embodimentexamples](#), the anti-IL-23p19 antibody or antibody fragment is a recombinant antibody (e.g., a chimeric antibody or a humanized antibody) and comprises six (6) CDRs, all derived from the VH or VL domain of a single anti-IL-23p19 antibody disclosed herein. For example, a binding agent may comprise all six of the CDR regions of the anti-IL-23p19 antibody designated Hu-2.18006B (for a human antibody). In a representative example an antibody or antibody fragment thereof may comprise the amino acid sequences of SEQ ID NOs: 9-11 and SEQ ID NOs: 12-14, representing the CDR1, CDR2 and CDR3 of the variable heavy chain region and the CDR1, CDR2 and CDR3 of the variable light chain region of the Hu-2.18006B antibody.

[0027] In some [embodimentexamples](#), the anti-IL-23p19 antibody is a full-length antibody.

[0028] In some [embodimentexamples](#), the anti-IL-23p19 antibody is an antibody fragment. In further [embodimentexamples](#), 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.

[0029] In some [embodimentexamples](#), the anti-IL-23p19 antibody is a monoclonal antibody.

[0030] In some [embodimentexamples](#), the anti-IL-23p19 antibody is a human antibody. In some [embodimentexamples](#), the anti-IL-23p19 antibody is a murine antibody.

[0031] In some [embodimentexamples](#), the anti-IL-23p19 antibody is a chimeric antibody. In some [embodimentexample](#)s, the anti-IL-23p19 antibody is a bispecific antibody. In some [embodimentexamples](#), the anti-IL-23p19 antibody is a humanized antibody.

[0032] The anti-IL-23p19 antibodies and antibody fragments thereof may be used for the treatment or prevention of an immune-mediated inflammatory disease (IMID), such as an autoimmune diseases or inflammatory disorders, or cancer. Such methods for the treatment or prevention of an IMID or cancer comprise administering a composition or formulation that comprises an anti-IL-23p19 antibody or antibody fragment thereof to a subject in need thereof. In a further [embodimentexample](#), the anti-IL-23p19 antibody or antibody fragment thereof may be administered either alone (e.g., as a monotherapy) or in combination with other immunotherapeutic agent and/or a chemotherapy. The IMID may be selected from the group consisting of, psoriasis, psoriatic arthritis, inflammatory bowel diseases (e.g., ulcerative colitis or Crohn's disease) ankylosing spondylitis, systemic lupus erythematosus, hidradenitis suppurativa, atopic dermatitis, asthma and familial adenomatous polyposis (FAP).

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The foregoing summary, as well as the following detailed description of the disclosure, will be better understood when read in conjunction with the appended figures. For the purpose of illustrating the disclosure, shown in the figures are embodiments which are presently preferred. It should be understood, however, that the disclosure is not limited to the precise arrangements, examples and instrumentalities shown.

[0034] **Figures 1A-1D** provide the amino acid sequences of the VH and VL domains of the anti-IL-23p19 antibodies and their respective CDR sequences. Sequence identifiers are provided and the CDRs are underlined in the context of the variable domain sequence.

[0035] **Figures 2A, 2B, 2C, 2D and 2E** show the binding profiles of the anti-IL-23p19 antibodies to human IL-23, a recombinant cytokine comprising human p19 and murine p40 subunits, human IL-12 and human p40 subunit, determined by BIAcore.

[0036] **Figures 3A, 3B and 3C** show dose-dependent binding of the selected representative IL-23p19 antibodies to human IL-23 and a recombinant cytokine comprising human p19 and murine p40 subunits determined by ELISA.

WHAT IS CLAIMED IS:

1. An anti-IL-23p19 antibody comprising:

~~(a) a heavy chain variable region comprising CDR1: SEQ ID NO: 9, CDR2: SEQ ID NO: 10, and CDR3: SEQ ID NO: 11; and a light chain variable region comprising CDR1: SEQ ID NO: 12, CDR2: SEQ ID NO: 13, and CDR3: SEQ ID NO: 14;~~

~~(b) a heavy chain variable region comprising CDR1: SEQ ID NO: 15, CDR2: SEQ ID NO: 16, and CDR3: SEQ ID NO: 17; and a light chain variable region comprising CDR1: SEQ ID NO: 18, CDR2: SEQ ID NO: 19, and CDR3: SEQ ID NO: 20;~~

~~(c) a heavy chain variable region comprising CDR1: SEQ ID NO: 21, CDR2: SEQ ID NO: 22, and CDR3: SEQ ID NO: 23; and a light chain variable region comprising CDR1: SEQ ID NO: 24, CDR2: SEQ ID NO: 25, and CDR3: SEQ ID NO: 26; or~~

~~(d) a heavy chain variable region comprising CDR1: SEQ ID NO: 27, CDR2: SEQ ID NO: 28, and CDR3: SEQ ID NO: 29; and a light chain variable region comprising CDR1: SEQ ID NO: 30, CDR2: SEQ ID NO: 31, and CDR3: SEQ ID NO: 32.~~

2. The anti-IL-23p19 antibody of claim 1, wherein the antibody comprises:

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

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

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

~~(d) a heavy chain variable region sequence of SEQ ID NO: 7 and a light chain variable region sequence of SEQ ID NO: 8.~~

~~3. The anti-IL-23p19 antibody of claim 1, wherein the antibody is an anti-human IL-23p19 antibody.~~

34. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a full-length antibody.

54. The anti-IL-23p19 antibody of claim 1, wherein the antibody is an antibody fragment.

56. The anti-IL-23p19 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.

67. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a monoclonal antibody.

78. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a human antibody.

~~9. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a murine antibody.~~

810. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a chimeric antibody.

119. The anti-IL-23p19 antibody of claim 1, wherein the antibody is an anti-human IL-23p19 antibody ~~a bispecific antibody~~.

~~12. The anti-IL-23p19 antibody of claim 1, wherein the antibody is a humanized antibody.~~

1310. The anti-IL-23p19 antibody of claim 1, wherein the antibody does not bind the p40 subunit of IL-12.

11. A bispecific antibody comprising the anti-IL-23p19 antibody of claim 1.

1214. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

~~1513. Use of the antibody of claim 1 in the manufacture of a medicament for A method of treating or preventing an immune-IL-23 mediated inflammatory disease, the method comprising administering the antibody of claim 1 to a patient in need thereof.~~

~~16. An isolated polynucleotide comprising a sequence encoding an anti-IL-23p19 antibody according to claim 1.~~

~~17. An isolated polynucleotide according to claim 16, encoding a sequence as set forth in any one of SEQ ID NOs. 1, 3, 5, or 7.~~

~~18. A vector comprising a polynucleotide according to claim 16.~~

~~19. A cell comprising a polynucleotide according to claim 16, and/or a vector according to claim 17.~~

~~20. A method for the production of an anti-IL-23p19 antibody according to claim 1, the method comprising culturing the cell of claim 19.~~