

IL-22. The antibody has a V_H domain comprising three complementarity determining regions (CDRs) with specific amino acid sequences of SEQ ID NOS: 602, 603, and 604, and a V_L domain comprising three CDRs with specific amino acid sequences of SEQ ID NOS: 605, 606, and 607.

[0009] U.S. Patent No. US 7,737,259 discloses compositions for the diagnosis and treatment of inflammatory disorders and autoimmune disorders. The compositions comprise an antibody that specifically binds to human IL-22. The antibody is (a) an antibody produced by a hybridoma selected from 3F11.3 (ATCC Accession No. PTA-7312), hybridoma 11H4.4 (ATCC Accession No. PTA-7315), and hybridoma 8E11.9 (ATCC Accession No. PTA-7319); (b) an affinity matured form of the antibody of (a); (c) an antigen-binding fragment of the antibody of (a) or (b); or (d) a humanized form of the antibody of (a), (b), or (c).

[0010] WO 2005/000897 discloses an isolated antibody and its antigen-binding fragment that specifically binds to IL-22. The antibody or fragment can reduce the binding of IL-22 to a complex comprising an IL-22 receptor (IL-22R) and interleukin-10 receptor 2 (IL-10R2). The antibody or its antigen-binding fragment may also reduce the direct interaction between IL-22 and an IL-22 receptor.

[0011] These antibodies were developed for binding to human IL-22 for treatment of diseases or disorders in humans. However, their binding to non-human mammalian IL-22, such as murine IL-22, was not measured or studied. An antibody intended to be used in humans to bind to human IL-22 must first be tested in animals for assessment of its safety and efficacy. To ensure that the animal testing is predictive of the safety and efficacy in humans, the antibody should ideally have a similar high binding affinity to both human IL-22 and at least the IL-22 of the test animal.

[0012] The present invention provides anti-IL-22 antibodies and their fragments that can bind to both human and mouse IL-22 with a high binding affinity, and which may be used to cause the same downstream biologic effects in both human and murine biologic systems.

SUMMARY OF THE DISCLOSURE

[0013] In one example, the present disclosure provides an anti-IL-22 antibody or antibody fragment comprising:

a light chain variable region including a light chain CDR1 having an amino acid sequence selected from SASSSVSX₁MH (SEQ ID NO:1), a light chain CDR2 having an amino acid sequence selected from X₂TX₃KLX₄S (SEQ ID NO:2), and a light chain CDR3 having an amino acid sequence of QQWSSNPYIT (SEQ ID NO:3); and

a heavy chain variable region including a heavy chain CDR1 having an amino acid sequence selected from GYIFX₅SYW₁H (SEQ ID NO:4), a heavy chain CDR2 having an amino acid sequence selected from RIYPGTGX₆TYYNX₇KFKG (SEQ ID NO:5), and a heavy chain CDR3 having an amino acid sequence selected from SYX₈X₉SVX₁₀Y (SEQ ID NO:6),

wherein X₁ is Y or K, X₂ is E or K, X₃ is S or R, X₄ is A or L, X₅ is T or R, X₆ is N or R, X₇ is E or R, X₈ is D or M, X₉ is S or Y, and X₁₀ is A or G.

[0013a] In one aspect, the present disclosure provides an anti-IL-22 antibody or antibody fragment comprising:

a light chain variable region including a light chain CDR1 (LCDR1) having an amino acid sequence selected from SASSSVSX₁MH (SEQ ID NO:1), a light chain CDR2 (LCDR2) having an amino acid sequence selected from X₂TX₃KLX₄S (SEQ ID NO:2), and a light chain CDR3 (LCDR3) having an amino acid sequence of QQWSSNPYIT (SEQ ID NO:3); and

a heavy chain variable region including a heavy chain CDR1 (HCDR1) having an amino acid sequence selected from GYIFX₅SYW₁H (SEQ ID NO:4), a heavy chain CDR2 (HCDR2) having an amino acid sequence selected from RIYPGTGX₆TYYNX₇KFKG (SEQ ID NO:5), and a heavy chain CDR3 (HCDR3) having an amino acid sequence selected from SYX₈X₉SVX₁₀Y (SEQ ID NO:6),

wherein X₁ is Y or K, X₂ is E or K, X₃ is S or R, X₄ is A or L, X₅ is T or R, X₆ is N or R, X₇ is E or R, X₈ is D or M, X₉ is S or Y, and X₁₀ is A or G, with the proviso that
a) X₁ to X₁₀ cannot be Y, E, S, A, T, N, E, D, S, and A, respectively, at the same time; and
b) up to three of X₁ to X₄ can be other than Y, E, S, and A, respectively, at the same time, and up to five of X₅ to X₁₀ can be other than T, N, E, D, S, and A, respectively, at the same time.

[0014] In the previous example, the light chain variable region may have an amino acid sequence selected from SEQ ID NOS: 7-12, and the heavy chain variable region has an amino acid sequence selected from SEQ ID NOS: 13-18.

[0015] In any one of the previous examples, the antibody or antibody fragment may be selected from:

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 10 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 11 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 14;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 9 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 10 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 16;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 17;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 17; and

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 12 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 18.

[0016] In any one of the previous examples, the antibody or antibody fragment may bind to human IL-22 and a mammalian non-human IL-22.

[0017] In the previous example, the mammalian IL-22 may be mouse IL-22.

[0018] In any one of the previous two examples, the antibody or antibody fragment may bind to the human IL-22 and the mammalian IL-22 with affinities within $\pm 20\%$, $\pm 15\%$, $\pm 10\%$ or $\pm 5\%$ of each other.

[0019] In any one of the previous examples, the antibody or antibody fragment may be capable of inhibiting phosphorylation of Stat3.

[0020] In any one of the previous examples, the antibody or antibody fragment may be capable of inhibiting IL-22-induced cytokine production.

[0021] In any one of the previous examples, the antibody or antibody fragment may be capable of inhibiting an immune response in at least one animal or human.

[0022] In the previous example, the at least one animal may comprise a mammal.

[0023] In any one of the previous two examples, mammal may be a mouse.

[0024] In any one of the previous examples, the anti-IL-22 antibody or antibody fragment may be humanized.

[0025] In any one of the previous examples, the anti-IL-22 antibody or antibody fragment may comprise a modified Fc region.

[0026] In another example, the present disclosure provides a modified anti-IL-22 antibody or antibody fragment comprising the anti-IL-22 antibody or antibody fragment of any one of the previous examples and at least one moiety selected from oligosaccharides, non-proteinaceous moieties, a therapeutic agent, a prophylactic agent and a diagnostic agent. In one aspect, the present disclosure provides a modified anti-IL-22 antibody or antibody fragment comprising any one of the anti-IL-22 antibodies or antibody fragments disclosed herein and at least one moiety selected from oligosaccharides, non-proteinaceous moieties, a therapeutic agent, a prophylactic agent and a diagnostic agent.

[0027] In the previous example, the at least one moiety may be an oligosaccharide, at least one non-proteinaceous moiety, or selected from a therapeutic agent, a prophylactic agent and a diagnostic agent.

[0028] In the previous example, the at least one non-proteinaceous moiety may be selected from soluble polymers.

[0029] In any one of the previous two examples, the modified anti-IL-22 antibody or antibody fragment may comprise two agents selected from therapeutic agents, prophylactic agents and diagnostic agents.

[0030] In any one of the previous three examples, the antibody or antibody fragment and the therapeutic, prophylactic agent or diagnostic agent may be covalently bonded to a linker molecule.

[0031] In another example, the present disclosure provides pharmaceutical composition comprising the antibody or antibody fragment or the modified anti-IL-22 antibody or antibody fragment of any one of previous examples, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure provides a pharmaceutical composition comprising: any one of the antibodies or antibody fragments disclosed herein or any one of the modified anti-IL-22 antibodies or antibody fragments disclosed herein; and a pharmaceutically acceptable carrier.

[0032] In the previous example, the pharmaceutical composition may comprise at least one additional excipient.

[0033] In any one of previous two examples, the pharmaceutical composition may further comprise at least one additional therapeutic agent, and/or a pharmaceutically acceptable preservative.

[0034] In another example, the present disclosure provides a method of treating an immune-related disease or cancer comprising a step of administering the antibody or antibody fragment, the modified anti-IL-22 antibody or antibody fragment, or the pharmaceutical composition of any one of the previous examples, to a subject. In one aspect, the present disclosure provides use of any one the antibodies or antibody fragments disclosed herein, any one of the modified anti-IL-22 antibodies or antibody fragments disclosed herein, or any one of the pharmaceutical compositions disclosed herein, in the manufacture of a medicament for treating an immune-related disease or cancer.

[0035] In another example, the present disclosure provides a kit for diagnosis or treatment, said kit comprising the antibody or antibody fragment, the modified anti-IL-22 antibody or antibody fragment, or the pharmaceutical composition of any one of previous examples; and instructions for using the antibody or antibody fragment, the modified the antibody or antibody fragment, or the pharmaceutical composition for diagnosis or treatment. In one aspect, the present disclosure provides a kit for diagnosis or treatment, said kit comprising: any one of the antibodies or antibody fragments disclosed herein, any one of the modified anti-IL-22 antibodies or antibody fragments disclosed herein, or any one of the pharmaceutical compositions disclosed herein; and instructions for using the antibody or antibody fragment, the modified the antibody or antibody fragment, or the pharmaceutical composition for diagnosis or treatment.

[0036] In another example, the present disclosure provides an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 7-12; and a heavy chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 13-18. In one aspect, the present disclosure provides an antibody or antibody fragment comprising: a light chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 7-12; and a heavy chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 13-18.

[0037] In the previous example, the light chain variable region may have three complementarity determining regions that are identical to complementarity determining

regions of a light chain variable region having an amino acid sequence selected from SEQ ID NOS: 7-12.

[0038] In any one of the previous two examples, the heavy chain variable region may be three complementarity determining regions that are identical to complementarity determining regions of a heavy chain variable region having an amino acid sequence selected from SEQ ID NOS: 13-18.

[0039] In any one of the previous three examples, the the light and heavy chains may have at least 95% sequence identity, at least 98% sequence identity, or at least 99% sequence identity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 shows the structure of the light and heavy chains of a humanized monoclonal antibody against human IL-22 (hum10) that was used as the parent antibody to evolve the antibodies of the present invention. The CDRs are shown as thicker portions in the diagrams with their starting and ending positions in the light and heavy chains labelled. Some of the mutations and their positions in the CDRs that were made to the parent antibody to provide antibodies of the present invention are labeled within the CDRs.

[0041] FIGS. 2A-2B show sequence alignments of the light chains of hum10 and antibodies of the present invention.

[0042] FIGS. 3A-3B show sequence alignments of the heavy chains of hum10 and antibodies of the present invention.

[0043] FIG. 4 shows certain purified antibodies on a sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gel as single bands under a non-reducing condition (left side) and two bands of heavy and light chains respectively under a reducing condition (right side), demonstrating the purity of the antibodies.

[0044] FIGS. 5A-5C show the single peak obtained by size exclusion chromatography (SEC) analyses of the purified antibodies (CPS02 and CPS09) in comparison to the SEC analysis of a control standard human IgG antibody.

[0045] FIG. 6 shows the specificity of the antibodies of the present invention to human and mouse IL-22, as well as other related antigens.

[0046] FIG. 7A shows the reduced level phosphorylation of Stat3 protein caused by inhibition of human IL-22 in HepG2 cells using antibodies of the present invention.

[0047] FIG. 7B shows the reduced level phosphorylation of Stat3 protein caused by inhibition of mouse IL-22 in HepG2 cells using antibodies of the present invention.

WHAT IS CLAIMED IS:

1. An anti-IL-22 antibody or antibody fragment comprising:
 - a light chain variable region including a light chain CDR1 (LCDR1) having an amino acid sequence selected from SASSSVSX₁MH (SEQ ID NO:1), a light chain CDR2 (LCDR2) having an amino acid sequence selected from X₂TX₃KLX₄S (SEQ ID NO:2), and a light chain CDR3 (LCDR3) having an amino acid sequence of QQWSSNPYIT (SEQ ID NO:3); and
 - a heavy chain variable region including a heavy chain CDR1 (HCDR1) having an amino acid sequence selected from GYIFX₅SYWIIH (SEQ ID NO:4), a heavy chain CDR2 (HCDR2) having an amino acid sequence selected from RIYPGTGX₆TYYNX₇KFKG (SEQ ID NO:5), and a heavy chain CDR3 (HCDR3) having an amino acid sequence selected from SYX₈X₉SVX₁₀Y (SEQ ID NO:6),
 - wherein X₁ is Y or K, X₂ is E or K, X₃ is S or R, X₄ is A or L, X₅ is T or R, X₆ is N or R, X₇ is E or R, X₈ is D or M, X₉ is S or Y, and X₁₀ is A or G, with the proviso that
 - a) X₁ to X₁₀ cannot be Y, E, S, A, T, N, E, D, S, and A, respectively, at the same time; and
 - b) up to three of X₁ to X₄ can be other than Y, E, S, and A, respectively, at the same time, and up to five of X₅ to X₁₀ can be other than T, N, E, D, S, and A, respectively, at the same time.
2. The anti-IL-22 antibody or antibody fragment of claim 1, wherein the light chain variable region has an amino acid sequence selected from SEQ ID NOS: 7-12, and the heavy chain variable region has an amino acid sequence selected from SEQ ID NOS: 13-18.
3. The anti-IL-22 antibody or antibody fragment of claim 2, wherein the antibody or antibody fragment is selected from:
 - an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13;
 - an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 10 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 11 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 14;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 9 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 10 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 16;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 17;

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 17; and

an antibody or antibody fragment comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 12 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 18.

4. The anti-IL-22 antibody or antibody fragment of any one of claims 1-3, wherein the antibody or antibody fragment binds to human IL-22 and a mammalian non-human IL-22.
5. The anti-IL-22 antibody or antibody fragment of claim 4, wherein the mammalian IL-22 is mouse IL-22.

6. The anti-IL-22 antibody or antibody fragment of any one of claims 4-5, wherein the antibody or antibody fragment binds to the human IL-22 and the mammalian IL-22 with affinities within $\pm 20\%$, $\pm 15\%$, $\pm 10\%$ or $\pm 5\%$ of each other.
7. The anti-IL-22 antibody or antibody fragment of any one of claims 1-6, wherein the antibody or antibody fragment is capable of inhibiting phosphorylation of Stat3.
8. The anti-IL-22 antibody or antibody fragment of any one of claims 1-7, wherein the antibody or antibody fragment is capable of inhibiting IL-22-induced cytokine production.
9. The anti-IL-22 antibody or antibody fragment of any one of claims 1-8, wherein the antibody or antibody fragment is capable of inhibiting an immune response in at least one animal or human.
10. The anti-IL-22 antibody or antibody fragment of claim 9, wherein the at least one animal comprises a mammal.
11. The anti-IL-22 antibody or antibody fragment of any one of claims 9-10, wherein the mammal is a mouse.
12. The anti-IL-22 antibody or antibody fragment of any one of claims 1-11, wherein the anti-IL-22 antibody or antibody fragment is humanized.
13. The anti-IL-22 antibody or antibody fragment of any one of claims 1-12, wherein the anti-IL-22 antibody or antibody fragment comprises a modified Fc region.
14. A modified anti-IL-22 antibody or antibody fragment comprising the anti-IL-22 antibody or antibody fragment of any one of claims 1-13 and at least one moiety selected from oligosaccharides, non-proteinaceous moieties, a therapeutic agent, a prophylactic agent and a diagnostic agent.
15. The modified anti-IL-22 antibody or antibody fragment of claim 14, wherein the at least one moiety is an oligosaccharide.

16. The modified anti-IL-22 antibody or antibody fragment of claim 14, wherein the at least one moiety is at least one non-proteinaceous moiety.
17. The modified anti-IL-22 antibody or antibody fragment of claim 15, the at least one non-proteinaceous moiety is selected from soluble polymers.
18. The modified anti-IL-22 antibody or antibody fragment of claim 14, wherein the at least one moiety is selected from a therapeutic agent, a prophylactic agent and a diagnostic agent.
19. The modified anti-IL-22 antibody or antibody fragment of claim 18, wherein the therapeutic agent, prophylactic agent or diagnostic agent is conjugated to the anti-IL-22 antibody or antibody fragment and is selected from a chemotherapeutic agent, a radioactive atom, a detectable label, a prodrug activating enzyme, a cytostatic agent and a cytotoxic agent.
20. The modified anti-IL-22 antibody or antibody fragment of any one of claims 18-19, comprising two agents selected from therapeutic agents, prophylactic agents and diagnostic agents.
21. The modified anti-IL-22 antibody or antibody fragment of any one of claims 18-20, wherein the antibody or antibody fragment and the therapeutic, prophylactic agent or diagnostic agent are covalently bonded to a linker molecule.
22. A pharmaceutical composition comprising:
 - the antibody or antibody fragment of any one of claims 1-13 or the modified anti-IL-22 antibody or antibody fragment of any one of claims 14-21; and
 - a pharmaceutically acceptable carrier.
23. The pharmaceutical composition of claim 22, further comprises at least one additional excipient.

24. The pharmaceutical composition of any one of claims 22-23, further comprising at least one additional therapeutic agent.
25. Use of the antibody or antibody fragment of any one of claims 1-13, the modified anti-IL-22 antibody or antibody fragment of any one of claims 14-21, or the pharmaceutical composition of any one of claims 22-24, in the manufacture of a medicament for treating an immune-related disease or cancer.
26. A kit for diagnosis or treatment, said kit comprising:
the antibody or antibody fragment of any one of claims 1-13, the modified anti-IL-22 antibody or antibody fragment of any one of claims 14-21, or the pharmaceutical composition of any one of claims 22-24; and
instructions for using the antibody or antibody fragment, the modified the antibody or antibody fragment, or the pharmaceutical composition for diagnosis or treatment.
27. An antibody or antibody fragment comprising:
a light chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 7-12; and
a heavy chain variable region having an amino acid sequence that has at least 90% sequence identity to one of amino acid sequences with SEQ ID NOS: 13-18.
28. The antibody or antibody fragment of claim 27, wherein the light chain variable region has three complementarity determining regions that are identical to complementarity determining regions of a light chain variable region having an amino acid sequence selected from SEQ ID NOS: 7-12.
29. The antibody or antibody fragment of any one of claims 27-28, wherein the heavy chain variable region has three complementarity determining regions that are identical to complementarity determining regions of a heavy chain variable region having an amino acid sequence selected from SEQ ID NOS: 13-18.

30. The antibody or antibody fragment of any one of claims 27-29, wherein the light and heavy chains have at least 95% sequence identity, at least 98% sequence identity, or at least 99% sequence identity.
31. The pharmaceutical composition of claims 22-24, further comprising a pharmaceutically acceptable preservative.
32. The anti-IL-22 antibody or antibody fragment of claim 2, wherein the antibody or antibody fragment comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 10 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13.
33. The anti-IL-22 antibody or antibody fragment of claim 2, wherein the antibody or antibody fragment comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 15.