Field of the Invention

[0009] The invention relates to CXCL13 neutralizing binding molecules, *e.g.*, antibodies and antigen binding fragments thereof, *e.g.*, humanized monoclonal antibodies, methods of using the binding molecules, and methods for treatment of conditions and diseases associated with CXCL13-expressing cells.

BRIEF SUMMARY OF THE INVENTION

[0010] One aspect the invention relates to an isolated antibody or antigen-binding fragment thereof which specifically binds to human, murine, and cynomolgus monkey CXCL13, wherein said antibody or antigen-binding fragment is selected from the group consisting of: a) an antibody or antigen-binding fragment thereof comprising a heavy chain variable region (VH) comprising a heavy chain complementarity determining region-1 (VH-CDR1) amino acid sequence identical to SEQ ID NO: 4, a heavy chain complementarity determining region-2 (VH-CDR2) amino acid sequence identical to SEQ ID NO: 5, and a heavy chain complementarity determining region-3 (VH-CDR3) amino acid sequence identical to SEQ ID NO: 6; and a light chain variable region (VL) comprising a light chain complementarity determining region-1 (VL-CDR1) amino acid sequence identical to SEQ ID NO: 16 or 9, a light chain complementarity determining region-2 (VL-CDR2) amino acid sequence identical to SEQ ID NO: 10, and a light chain complementarity determining region-3 (VL-CDR3) amino acid sequence identical to SEQ ID NO: 11; b) an antibody or antigen-binding fragment thereof which specifically binds to the same CXCL13 epitope as the antibody or antigen-binding fragment thereof of a); and c) an antibody or antigen-binding fragment thereof that competitively inhibits the antibody or antigen-binding fragment thereof of a) from specifically binding to human, murine, and cynomolgus monkey CXCL13. Also disclosed is an isolated antigen binding molecule which specifically binds to the same CXCL13 epitope as a reference monoclonal antibody selected from the group consisting of MAb 5261, MAb 5378, MAb 5080, MAb 1476, 3D2, and 3C9. In certain examples, the antigen binding molecule specifically binds to the same CXCL13 epitope as MAb 5261 and MAb 5378.

[0011] Also disclosed is an isolated antigen binding molecule which specifically binds to CXCL13, wherein said binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of MAb 5261, MAb 5378, MAb 5080,

MAb 1476, 3D2, and 3C9 from specifically binding to CXCL13. In certain examples, the antigen binding molecule competitively inhibits MAb 5261 and MAb 5378. In another example, the antibody or fragment thereof is selected from the group consisting of MAb 5261, MAb 5378, MAb 5080, MAb 1476, 3D2, and 3C9.

[0012] In one example, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the heavy chain variable region (VH) of said antibody or fragment thereof comprises an amino acid sequence at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 13 and SEQ ID NO: 3. In another example, the light chain variable region (VL) of the antibody or fragment thereof comprises an amino acid sequence at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 17, and SEQ ID NO: 8.

[0013] In another example, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the VH of said antibody or fragment thereof comprises an amino acid sequence identical, except for 20 or fewer conservative amino acid substitutions, to a sequence selected from the group consisting of SEQ ID NO: 13 and

SEQ ID NO: 3. In another example, the VL of the antibody or fragment thereof comprises an amino acid sequence identical, except for 20 or fewer conservative amino acid substitutions, to a sequence selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 17, and SEQ ID NO: 8.

[0014] In certain examples, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the VH and VL of the antibody or fragment thereof comprise amino acid sequences at least 90% identical to VH and VL sequences selected from the group consisting of: (a) SEQ ID NO: 13 and SEQ ID NO: 15, respectively; (b) SEQ ID NO: 13 and SEQ ID NO: 17, respectively; and (c) SEQ ID NO: 3 and SEQ ID NO: 8, respectively. In yet another example, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13, wherein the VH and VL of said antibody or fragment thereof comprise amino acid sequences identical, except for 20 or fewer conservative amino acid substitutions each, to VH and VL sequences selected from the group consisting of: (a) SEQ ID NO: 13 and SEQ ID NO: 15, respectively; (b) SEQ ID NO: 13 and SEQ ID NO: 17, respectively; and (c) SEQ ID NO: 3 and SEQ ID NO: 8, respectively.

[0015] In one example, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the VH of said antibody or fragment thereof comprises a Chothia-Kabat heavy chain complementarity determining region-1 (VH-CDR1) amino acid sequence identical, except for two or fewer amino acid substitutions, to SEQ ID NO: 4; a Kabat heavy chain complementarity determining region-2 (VH-CDR2) amino acid sequence identical, except for four or fewer amino acid substitutions, to SEQ ID NO: 5; a Kabat heavy chain complementarity determining region-3 (VH-CDR3) amino acid sequence identical, except for two or fewer amino acid substitutions, to SEQ ID NO: 6; a Kabat light chain complementarity determining region-1 (VL-CDR1) amino acid sequence identical, except for four or fewer amino acid substitutions, to SEQ ID NO: 16 or 9; a Kabat light chain complementarity determining region-2 (VL-CDR2) amino acid sequence identical, except for two or fewer amino acid substitutions, to SEQ ID NO: 10; or a Kabat light chain complementarity determining region-3 (VL-CDR3) amino acid sequence identical, except for two or fewer amino acid substitutions, to SEQ ID NO: 11.

[0016] In certain examples, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the VH of said antibody or fragment thereof comprises

VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences comprising SEQ ID NOs: 4, 5, and 6, respectively, except for four or fewer amino acid substitutions in one or more of said VH-CDRs. In another example, the isolated antibody or antigen-binding fragment thereof specifically binds to CXCL13 and the VL of said antibody or fragment thereof comprises VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences comprising SEQ ID NOs: 16 or 9, 10, and 11, respectively, except for four or fewer amino acid substitutions in one or more of said VL-CDRs.

[0017] In some examples, the antibody or fragment thereof of the invention inhibits CXCL13 from binding to a CXCL13 receptor. In certain examples, the CXCL13 receptor is CXCR5. In another example, the antibody or fragment thereof of the invention is humanized, primatized or chimeric.

[0018] Another aspect of the invention is directed to a composition comprising the antibody or fragment thereof of the invention, and a carrier.

[0019] A further aspect of the invention is directed to a composition comprising an isolated heavy chain variable region (VH) encoding polynucleotide and an isolated light chain variable region (VL) encoding polynucleotide, wherein said VH encoding polynucleotide encodes a VH polypeptide comprising heavy chain complementarity determining region-1 (VH-CDR1), heavy chain complementarity determining region-2 (VH-CDR2), and heavy chain complementarity determining region-3 (VH-CDR3) amino acid sequences consisting of SEQ ID NOs: 4, 5, and 6, respectively; wherein said VL encoding polynucleotide encodes a VL polypeptide comprising light chain complementarity determining region-1 (VL-CDR1), light chain complementarity determining region-2 (VL-CDR2), and light chain complementarity determining region-3 (VL-CDR3) amino acid sequences consisting of SEQ ID NOs: 9 or 16, 10, and 11, respectively; and wherein an antibody or fragment thereof encoded by said VH and VL encoding polynucleotides specifically binds human, murine, and cynomolgus monkey CXCL13. Also disclosed is an isolated polynucleotide comprising a nucleic acid encoding an antibody VH polypeptide, wherein the amino acid sequence of said VH polypeptide is at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 12 and SEQ ID NO: 2. In another example, the invention is directed to an isolated polynucleotide comprising a nucleic acid encodes an antibody VL polypeptide, wherein the amino acid sequence of said VL polypeptide is at least 90% identical to a sequence

selected from the group consisting of SEQ ID NO: 7 and SEQ ID NO14; and wherein an antibody or antigen binding fragment thereof comprising said VL polypeptide specifically binds to CXCL13.

[0020] In one example, the isolated polynucleotide comprises a nucleic acid encoding an antibody VH polypeptide, wherein the amino acid sequence of the VH polypeptide is identical, except for 20 or fewer conservative amino acid substitutions, to a sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 12. In another example, the isolated polynucleotide comprises a nucleic acid encoding an antibody VL polypeptide, wherein the amino acid sequence of the VL polypeptide is identical, except for 20 or fewer conservative amino acid substitutions, to a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 14, and SEQ ID NO: 18; and wherein an antibody or antigen binding fragment thereof comprising said VL polypeptide specifically binds to CXCL13.

[0021] A further aspect of the invention is directed to a method of producing an antibody or fragment thereof which specifically binds human, murine, and cynomolgus monkey CXCL13, comprising culturing the host cell of the composition as described herein, and recovering said antibody, or fragment thereof. Also disclosed is a vector comprising the polynucleotide of the invention. Another example is directed to a host cell comprising a vector of the invention. The disclosure is also directed to methods of producing an antibody or fragment thereof which specifically binds CXCL13, comprising culturing a host cell of the invention, and recovering said antibody, or fragment thereof. Another aspect of the invention is directed to a method of producing an antibody or fragment thereof which specifically binds human, murine, and cynomolgus monkey CXCL13, comprising co-culturing the separate host cells of the composition as described herein, and recovering said antibody, or fragment thereof. In a further aspect of the invention is directed to a method of producing an antibody or fragment thereof which specifically binds human, murine, and cynomolgus monkey CXCL13, comprising separately culturing the separate host cells of the composition as described herein, combining said VH and VL encoding polypeptides, and recovering said antibody, or fragment thereof. Another aspect of the invention is directed to an antibody or fragment thereof which specifically binds human, murine, and cynomolgus monkey CXCL13, produced by the method as described herein.

[0022] Another aspect of the invention is directed to methods for neutralizing CXCL13 in an animal, comprising administering to said animal a composition comprising: an isolated antibody or fragment thereof or a composition of the invention; and a pharmaceutically acceptable carrier.

[0023] Further embodiments of the invention are directed to use of a composition comprising: (a) the isolated antibody or fragment thereof of any one of claims 1 to 40 or the composition of claim 41 or 42; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for neutralizing CXCL13 in an animal. Also disclosed is methods for treating an autoimmune disease or an inflammatory disease or cancer in an animal in need of treatment, comprising administering to said animal a composition comprising: an isolated antibody or fragment thereof or a composition of the invention; and a pharmaceutically acceptable carrier. Another aspect of the invention is directed to use of a composition comprising: (a) the isolated antibody or fragment thereof as

described herein or the composition as described herein; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating an autoimmune disease or an inflammatory disease in an animal in need of treatment. Another aspect of the invention is directed to use of a composition comprising: (a) the isolated antibody or fragment thereof as described herein or the composition as described herein; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating a cancer in an animal in need of treatment. Another aspect of the invention is directed to use of a composition comprising: (a) the isolated antibody or fragment thereof as described herein or the composition as described herein; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for inhibiting gastric lymphoid follicles in an animal. Another aspect of the invention is directed to use of a composition comprising: (a) the isolated antibody or fragment thereof as described herein or the composition as described herein; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for preventing or treating mucosa-associated lymphoid tissue (MALT) lymphoma in an animal in need of prevention or treatment. Another aspect of the invention is directed to use of a composition comprising: (a) the isolated antibody or fragment thereof as described herein or the composition as described herein; and (b) a pharmaceutically acceptable carrier, in the manufacture of a medicament for preventing or treating a gastric or duodenal ulcer in an animal in need of prevention or treatment. In some examples, the autoimmune disease or said inflammatory disease is multiple sclerosis, Systemic Lupus Erythematosis (SLE), or arthritis, *e.g.*, rheumatoid arthritis.

[0024] Also disclosed are directed to methods for reducing or inhibiting gastric lymphoid follicles in an animal, comprising administering to said animal a composition comprising an isolated antibody or fragment thereof of the invention and a pharmaceutically acceptable carrier. A further example of the invention is directed to a method for preventing or treating mucosa-associated lymphoid tissue (MALT) lymphoma or a gastric or duodenal ulcer in an animal in need of prevention or treatment, comprising administering to said animal a composition comprising an isolated antibody or fragment thereof of the invention and a pharmaceutically acceptable carrier. In one example, the animal has been infected with a *Heliobacter* bacterium. In one example the *Heliobacter* bacterium is *H. pylori* or *H. heilmannii*.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0025] Figure 1. Specificity ELISA results showing the binding of mouse anti-human CXCL13 antibodies (3D2 and 3C9) to recombinant human CXCL13 (1A), recombinant mouse CXCL13 (1B), and recombinant cynomolgus monkey CXCL13 (1C) compared to antibody controls (mouse MAb 801 and/or rat MAb 470). EC50 values are shown and