

Harbor Perspectives in Biology 3, a004440; Weiskopf et al., (2009). Transplant International 22, 1041-1050).

[0003] Thus, there is a need determine the factors driving aging-dependent regulation in neurons and the role of those factors in the control of axonal regeneration so that therapies that target such factors can be developed for the treatment of peripheral nervous system injuries.

FIELD

[0004] The invention relates to the use of CXCL13 neutralizing binding molecules, e.g., antibodies and antigen binding fragments thereof for the promotion of peripheral nerve regeneration in subjects with aging-dependent regeneration decline.

BRIEF SUMMARY OF THE DISCLOSURE

[0005] Methods for using CXCL13 binding molecules to promote peripheral nerve regeneration in a subject having aging-dependent regeneration decline are disclosed herein. According to aspects of the disclosure illustrated herein, there is provided a method for improving peripheral nerve regeneration in a subject with a peripheral nerve injury and aging-dependent regenerative decline including administering to the subject an effective amount of an isolated binding molecule which specifically binds to CXCL13 and inhibits, suppresses, prevents, reverses or slows the effect of CXCL13.

[0005a] In one aspect, provided herein is a use of an antibody or antigen-binding fragment thereof which specifically binds to CXCL13 in the manufacture of a medicament for treating peripheral nerve injury in a subject with aging-dependent regenerative decline.

[0005b] In another aspect, provided herein is a use of an isolated antibody or antigen-binding fragment thereof which specifically binds CXCL13 in the manufacture of a medicament for restoring axonal regeneration of sensory neurons following peripheral nerve injury in a subject with aging-dependent regenerative decline.

[0006] Methods for promoting nerve regeneration of an injured peripheral nerve in a subject with aging-dependent regenerative decline are provided, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof which

specifically binds CXCL13. In certain examples of the methods, the antibody or antigen-binding fragment thereof inhibits CXCL13 activity. In certain examples of the methods, the inhibited CXCL13 activity is recruitment of CXCR5+ CD8+ T cells to the dorsal root ganglion (DRG) of the injured peripheral nerve. In certain examples of the methods, the isolated antibody or antigen-binding fragment thereof inhibits CXCL13 interaction with its receptor. In certain examples of the methods, the CXCL13 receptor is CXCR5. In certain examples of the methods, the isolated antibody or antigen-

binding fragment thereof competitively inhibits a reference monoclonal antibody selected from the group consisting of Mab 5378, MAb 5261, MAb5080, MAb 1476, 3D2, 3C9, MAb 5091, MAb 1758, or MAb 0745 from specifically binding to CXCL13. In certain examples of any one of the aforementioned methods, the isolated antibody or antigen-binding fragment thereof specifically binds to the same CXCL13 epitope as a reference monoclonal antibody selected from the group consisting of Mab 5378, MAb 5261, MAb 5080, MAb 1476, 3D2, 3C9, MAb 5091, MAb 1758, or MAb 0745. In certain examples of the methods, the antibody or antigen-binding fragment thereof comprises (A) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs: 26, 30, and 33, respectively; (B) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:27, 30, and 33, respectively; (C) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:19, 22, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:28, 31, and 34, respectively; or (D) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:20, 23, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:29, 31, and 34, respectively. In certain examples, the VH and VL of the antibody or antigen-binding fragment thereof comprise amino acid sequences identical to VH and VL sequences selected from the group consisting of: (i) SEQ ID NO: 6 and SEQ ID NO:7, respectively; (ii) SEQ ID NO: 8 and SEQ ID NO: 9, respectively; (iii) SEQ ID NO: 10 and SEQ ID NO:11, respectively; (iv) SEQ ID NO:12 and SEQ ID NO:12, respectively; (v) SEQ ID NO:14 and SEQ ID NO:15, respectively; and (vi) SEQ ID NO:16 and SEQ ID NO:17,

respectively. In certain examples, the isolated binding molecule is MAb 5261, MAb 5091, or MAb 1476, MAb 1758. In certain examples of any one of the aforementioned methods, the injured peripheral nerve is selected from the group consisting of sciatic nerve, peroneal nerve, spinal accessory nerve, and brachial plexus. In certain examples of any of the aforementioned methods, the method regenerates the injured nerve totally or partially, reinnervates epidermal tissue, or results in complete or partial recovery of neurological function of the injured nerve, or a combination thereof.

[0007] Methods for treatment of peripheral nerve injury in a subject with aging-dependent regenerative decline and a peripheral nerve injury are provided, comprising administering to the subject an effective amount of an isolated antibody or antigen-binding fragment thereof which specifically binds CXCL13. In certain examples of the methods, the peripheral nerve injury is the result of pressure, stretching or cutting of the peripheral nerve. In certain examples of the methods, the peripheral nerve injury is an injury of the sciatic nerve, brachial plexus, peroneal nerve, or spinal accessory nerve. In certain embodiments of the methods, the peripheral nerve injury is a sciatic nerve injury. In certain examples of any of the aforementioned methods, the antibody or antigen-binding fragment thereof inhibits CXCL13 interaction with its receptor. In certain examples of any of the aforementioned methods, the receptor is CXCR5. In certain examples of any of the aforementioned methods, the antibody or antigen-binding fragment thereof comprises: (A) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs: 26, 30, and 33, respectively; (B) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:27, 30, and 33, respectively; (C) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:19, 22, and 25, respectively; and a VL comprising

light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:28, 31, and 34, respectively; or (D) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:20, 23, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:29, 31, and 34, respectively. In certain examples of any of the aforementioned methods, the VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences identical to VH and VL sequences selected from the group consisting of: (i). SEQ ID NO: 6 and SEQ ID NO:7, respectively; (ii) SEQ ID NO: 8 and SEQ ID NO: 9, respectively; (iii) SEQ ID NO: 10 and SEQ ID NO:11, respectively; (iv) SEQ ID NO:12 and SEQ ID NO:12, respectively; (v) SEQ ID NO:14 and SEQ ID NO:15, respectively; and (vi) SEQ ID NO:16 and SEQ ID NO:17, respectively. In certain examples of any of the aforementioned methods, the isolated binding molecule is a human or humanized antibody that competitively inhibits a reference monoclonal antibody selected from the group consisting of Mab 5378, MAb 5261, MAb5080, MAb1476, MAb 5091, MAb 1758, 3D2 and 3C9 from specifically binding to CXCL13. In certain examples of any of the aforementioned methods, the isolated binding molecule is MAb 5261, MAb 5091, MAb 1476, or MAb 1758.

[0008]Methods for reversing aging-dependent regenerative decline in a subject in need thereof are provided, comprising administering to the subject an effective amount of an isolated antibody or antigen-binding fragment thereof which specifically binds CXCL13. In certain examples of the methods, the antibody or antigen-binding fragment thereof inhibits CXCL13 interaction with its receptor. In certain examples of the methods, the receptor is CXR5. In certain examples of any of the aforementioned methods, the isolated antibody or antigen-binding fragment thereof competitively inhibits a reference monoclonal antibody selected from the group consisting of Mab 5378, MAb 5261, MAb5080, MAb1476, MAb 5091, MAb 1748, 3D2 and 3C9 from specifically binding to CXCL13. In certain examples of any of the aforementioned methods, the antibody or antigen-binding fragment thereof comprises: (A) a VH comprising heavy chain

complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs: 26, 30, and 33, respectively; (B) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:27, 30, and 33, respectively; (C) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:19, 22, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:28, 31, and 34, respectively; or (D) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:20, 23, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:29, 31, and 34, respectively. In certain examples of any of the aforementioned methods, the VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences identical to VH and VL sequences selected from the group consisting of: (i). SEQ ID NO: 6 and SEQ ID NO:7, respectively; (ii) SEQ ID NO: 8 and SEQ ID NO: 9, respectively; (iii) SEQ ID NO: 10 and SEQ ID NO:11, respectively; (iv) SEQ ID NO:12 and SEQ ID NO:12, respectively; (v) SEQ ID NO:14 and SEQ ID NO:15, respectively; and (vi) SEQ ID NO:16 and SEQ ID NO:17, respectively. In certain examples of any of the aforementioned methods, the isolated binding molecule is MAb 5261, MAb 5091, MAb 1476, or MAb 1758. In certain examples of any of the aforementioned methods, the subject has a peripheral nerve injury. In certain examples of any of the aforementioned methods, the peripheral injury is a sciatic nerve injury, brachial plexus injury, spinal accessory nerve injury, or peroneal nerve injury. In certain examples of any of the aforementioned methods, the peripheral nerve injury is a sciatic nerve injury.

What is claimed is:

1. Use of an antibody or antigen-binding fragment thereof which specifically binds to CXCL13 in the manufacture of a medicament for treating peripheral nerve injury in a subject with aging-dependent regenerative decline.
2. The use of claim 1, wherein the antibody or antigen-binding fragment thereof inhibits CXCL13 activity.
3. The use of claim 2, wherein the inhibited CXCL13 activity is recruitment of CXCR5+ CD8+ T cells to the dorsal root ganglion (DRG) of the injured peripheral nerve.
4. The use of claim 1, wherein the antibody or antigen-binding fragment thereof inhibits CXCL13 interaction with its receptor.
5. The use of claim 4, wherein the CXCL13 receptor is CXCR5.
6. The use of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof comprises
 - (A) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs: 26, 30, and 33, respectively;
 - (B) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:27, 30, and 33, respectively;
 - (C) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:19, 22, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:28, 31, and 34, respectively; or
 - (D) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:20, 23, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:29, 31, and 34, respectively.

7. The use of any one of claims 1-5, wherein the VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences identical to VH and VL sequences selected from the group consisting of: (i) SEQ ID NO: 6 and SEQ ID NO:7, respectively; (ii) SEQ ID NO: 8 and SEQ ID NO: 9, respectively; (iii) SEQ ID NO: 10 and SEQ ID NO:11, respectively; (iv) SEQ ID NO:12 and SEQ ID NO:13, respectively; (v) SEQ ID NO:14 and SEQ ID NO:15, respectively; and (vi) SEQ ID NO:16 and SEQ ID NO:17, respectively.
8. The use of any one of claims 1-7, wherein the peripheral nerve injury is selected from the group consisting of sciatic nerve injury, peroneal nerve injury, spinal accessory nerve injury, and brachial plexus injury.
9. The use of claim 8, wherein said use results in regeneration of the injured nerve totally or partially, reinnervation of epidermal tissue, or results in complete or partial recovery of neurological function of the injured nerve, or a combination thereof.
10. The use of claim 1, wherein the peripheral nerve injury is a result of pressure, stretching or cutting of the peripheral nerve.
11. The use of claim 8, wherein the peripheral nerve injury is a sciatic nerve injury.
12. The use of any one of claims 1-11, wherein the antibody or antigen-binding fragment thereof is a human or humanized antibody that competitively inhibits a reference monoclonal antibody selected from the group consisting of Mab 5378, Mab 5261, MAb5080, MAb1476, MAb 5091, MAb 1758, 3D2 and 3C9 from specifically binding to CXCL13.
13. Use of an isolated antibody or antigen-binding fragment thereof which specifically binds CXCL13 in the manufacture of a medicament for restoring axonal regeneration of sensory neurons following peripheral nerve injury in a subject with aging-dependent regenerative decline.
14. The use of claim 13, wherein the antibody or antigen-binding fragment thereof inhibits CXCL13 interaction with its receptor.
15. The use of claim 14, wherein the receptor is CXR5.
16. The use of any one of claims 13-15, wherein the antibody or antigen-binding fragment thereof comprises:
 - (A) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs: 26, 30, and 33, respectively;
 - (B) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID

NOs:18, 21, and 24, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:27, 30, and 33, respectively;

(C) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:19, 22, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:28, 31, and 34, respectively; or

(D) a VH comprising heavy chain complementarity determining region 1 (VH-CDR1), VH-CDR2, and VH-CDR3 amino acid sequences set forth as SEQ ID NOs:20, 23, and 25, respectively; and a VL comprising light chain complementarity determining region 1 (VL-CDR1), VL-CDR2, and VL-CDR3 amino acid sequences set forth as SEQ ID NOs:29, 31, and 34, respectively.

17. The use of any one of claims 13-16, wherein the VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences identical to VH and VL sequences selected from the group consisting of: (i). SEQ ID NO: 6 and SEQ ID NO:7, respectively; (ii) SEQ ID NO: 8 and SEQ ID NO: 9, respectively; (iii) SEQ ID NO: 10 and SEQ ID NO:11, respectively; (iv) SEQ ID NO:12 and SEQ ID NO:13, respectively; (v) SEQ ID NO:14 and SEQ ID NO:15, respectively; and (vi) SEQ ID NO:16 and SEQ ID NO:17, respectively.
18. The use of any one of claims 13-17, wherein the antibody or antigen-binding fragment thereof is a human or humanized antibody or antigen-binding fragment thereof.
19. The use of claim 13-18, wherein the peripheral injury is a sciatic nerve injury, brachial plexus injury, spinal accessory nerve injury, or peroneal nerve injury.
20. The use of claim 19, wherein the peripheral nerve injury is a sciatic nerve injury.