[0005] SEMA4D has been implicated in the development of autoimmune demyelinating diseases such as multiple sclerosis and certain cancers. The failure of the mammalian nervous system to completely regenerate after injury is a major clinical problem. Neural damage as a result of stroke or trauma to the brain, as well as neurodegenerative diseases such as Alzheimer's disease, are a leading cause of death and disability. While the role of SEMA4D signaling through its receptors, e.g., Plexin-B1, on angiogenesis is well-recognized, the effect of SEMA4D signaling on promoting neurogenesis remains unclear. There remains, therefore, a need to provide a solution to the unmet medical need for therapeutic means of neuroregeneration.

BRIEF SUMMARY

[0006] Methods for using Semaphorin-4D binding molecules for promotion of neurogenesis are disclosed herein. Evidence is presented demonstrating that SEMA4D can compromise the ability of neural cells to regenerate. According to embodiments of the disclosure illustrated herein, there is provided a method for promoting neurogenesis in neural tissue of a patient exhibiting at least one symptom of a central nervous system disorder, the method comprising administering to a subject in need thereof an effective amount of an isolated binding molecule which specifically binds to and/or inhibits semaphorin-4D (SEMA4D).

[0007] According to embodiments of the disclosure illustrated herein, there is provided a method for increasing the number of progenitor cells in a subject with a disorder of the central nervous system comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorm-4D (SEMA4D), wherein the binding to SEMA4D acts to increase the number of progenitor cells.

[0007a] In one embodiment, there is provided the use of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the manufacture of a medicament for increasing the number of progenitor cells in a subject with a central nervous system disorder.

[0007b] In one aspect, there is provided the use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for treating stroke~~, wherein administration of an effective amount of the antibody or fragment thereof can promote neurogenesis~~ in a subject in need of neural ~~tissue of a subject following~~ regeneration as a result of the stroke ~~injury~~, ~~and~~ wherein administration of an effective amount of the antibody or fragment thereof ~~to the subject can~~ increases one or more of proliferation, differentiation, or migration of neural progenitor cells.

[0008] According to embodiments of the disclosure illustrated herein, there is provided a method for promoting neurogenesis in neural tissue of a patient exhibiting at least one symptom of a central nervous system disorder, comprising administering to a subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67 from specifically binding to SEMA4D.

[0008a] In one embodiment, there is provided the use of an isolated binding molecule which specifically binds semaphorin-4D (SEMA4D) in the manufacture of a medicament for promoting neurogenesis in neural tissue of a patient exhibiting at least one symptom of a central nervous system disorder.

[0009] According to embodiments of the disclosure illustrated herein, there is provided a method for alleviating a symptom of a disease or disorder of the central nervous system, such as stroke, in a patient comprising administering to the subject an effective amount of an

WHAT IS CLAIMED IS:

1. Use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for treating stroke, wherein administration of an effective amount of the antibody or fragment thereof can promote neurogenesis in neural tissue of a subject following stroke injury, and wherein administration of an effective amount of the antibody or fragment thereof to the subject can increase one or more of proliferation, differentiation, or migration of neural progenitor cells.

2. The use of claim 1, wherein the antibody or fragment thereof can inhibit SEMA4D interaction with a receptor or a portion of the receptor.

3. The use of claim 2, wherein the receptor is selected from the group consisting of Plexin-B1, Plexin-B2, and CD72.

4. The use of claim 1, wherein the antibody or fragment thereof:

a. competitively inhibits a reference monoclonal antibody comprising: a variable domain of a heavy chain (VH) comprising the amino acid sequence SEQ ID NO: 1, and a variable domain of a light chain (VL) comprising the amino acid sequence SEQ ID NO: 2; or

b. binds to the same epitope as a reference monoclonal antibody comprising: a VH comprising the amino acid sequence SEQ ID NO: 1, and a VL comprising the amino acid sequence SEQ ID NO: 2.

5. The use of claim 4, wherein the antibody or fragment thereof comprises: a VH comprising the VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences SEQ ID NOs: 5, 6, and 7, respectively; and a VL comprising the VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences SEQ ID NOs: 8, 9, and 10, respectively.

6. The use of claim 5, wherein the antibody or fragment thereof comprises a VH comprising the amino acid sequence SEQ ID NO: 1 and a VL comprising the amino acid sequence SEQ ID NO: 2.

7. The use of claim 5, wherein the antibody or fragment thereof comprises a VH comprising the amino acid sequence SEQ ID NO: 3 and a VL comprising the amino acid sequence SEQ ID NO: 4.

8. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is to be administered to the blood side of the blood brain barrier.

9. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is to be administered to the brain side of the blood brain barrier.

10. The use of any one of claims 1 to 7, wherein the subject exhibits an increase in differentiation of neural progenitor cells.

11. The use of any one of claims 1 to 7, wherein the subject is human.

12. The use of any one of claims 1 to 7, wherein administration of an effective amount of the antibody or fragment thereof to the subject results in an increase in expression of a neural precursor or progenitor cell marker in the subject.

13. The use of claim 12, wherein the marker is Sox2 and/or nestin.

14. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is an IgG isotype.

WHAT IS CLAIMED IS:

1. Use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for treating stroke in a subject in need of neural regeneration as a result of the stroke, wherein administration of an effective amount of the antibody or fragment thereof increases one or more of proliferation, differentiation, or migration of neural progenitor cells.

2. The use of claim 1, wherein the antibody or fragment thereof inhibits SEMA4D interaction with a receptor or a portion of the receptor.

3. The use of claim 2, wherein the receptor is selected from the group consisting of Plexin-Bl, Plexin-B2, and CD72.

4. The use of claim 1, wherein the antibody or fragment thereof:

a. competitively inhibits a reference monoclonal antibody comprising: a variable domain of a heavy chain (VH) comprising the amino acid sequence SEQ ID NO: 1, and a variable domain of a light chain (VL) comprising the amino acid sequence SEQ ID NO: 2; or

b. binds to the same epitope as a reference monoclonal antibody comprising: a VH comprising the amino acid sequence SEQ ID NO: 1, and a VL comprising the amino acid sequence SEQ ID NO: 2.

5. The use of claim 4, wherein the antibody or fragment thereof comprises: a VH comprising the VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences SEQ ID NOs: 5, 6, and 7, respectively; and a VL comprising the VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences SEQ ID NOs: 8, 9, and 10, respectively.

6. The use of claim 5, wherein the antibody or fragment thereof comprises a VH comprising the amino acid sequence SEQ ID NO: 1 and a VL comprising the amino acid sequence SEQ ID NO: 2.

7. The use of claim 5, wherein the antibody or fragment thereof comprises a VH comprising the amino acid sequence SEQ ID NO: 3 and a VL comprising the amino acid sequence SEQ ID NO: 4.

8. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is to be administered to the blood side of the blood brain barrier.

9. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is to be administered to the brain side of the blood brain barrier.

10. The use of any one of claims 1 to 7, wherein the subject exhibits an increase in differentiation of neural progenitor cells.

11. The use of any one of claims 1 to 7, wherein the subject is human.

12. The use of any one of claims 1 to 7, wherein administration of an effective amount of the antibody or fragment thereof to the subject increases expression of a neural precursor or progenitor cell marker in the subject.

13. The use of claim 12, wherein the marker is Sox2 and/or nestin.

14. The use of any one of claims 1 to 7, wherein the antibody or fragment thereof is an IgG isotype.