[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 ~~OF THE INVENTION~~

[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 ~~aspects~~embodiments of the ~~invention~~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 ~~aspects~~embodiments of the ~~invention~~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 aspect, 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.

[0008] According to ~~aspects~~embodiments of the ~~invention~~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 aspect, 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 ~~aspects~~embodiments of the ~~invention~~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

isolated binding molecule which specifically binds to and/or inhibits to semaphorin-4D (SEMA4D), wherein the binding to SEMA4D acts to alleviate the symptom.

[0009a] In one aspect, there is provided the use of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the manufacture of a medicament for treating stroke in a patient

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0010] FIGURE 1: Schematic of experimental protocol for middle cerebral artery (MCA) occlusion described in the Examples.

[0011] FIGURES 2A-2E: Show neural stem/precursor cells in brain samples stained for Nestin/Sox2 in the areas indicated in 2E following occlusion of the middle cerebral artery (MCAO) and treatment with either isotype control ("Control IgG", 2A and 2C) or MAb 67-2 ("Anti-Sema4D-Ab", 2B and 2D). The brain samples were prepared 7 days after MCAO.

[0012] FIGURES 3A-3D: Show (A) mRNA expression by RT-PCR with quantitative analysis for (B) Sox2, (C) nestin, and (D) PLP relative to actin control in brain tissue of MCAO mice treated with isotype control ("Control IgG") or MAb 67-2 ("Anti-SEMA4D"). Brain tissue was isolated 7 days after MCAO. Nestin and Sox2 are markers of neural stem precursor cells. PLP is a marker of myelination.

[0013] FIGURES 4A-4D: Show relative total volume of brain and striatum in treated and untreated hemispheres in MCAO mice treated with isotype control or MAb 67-2. Measurements were taken 30 days after MCAO. FIGS. 4A-4B show brain sections stained with NeuN from (A) 1 representative isotype control ("Control IgG") mouse and (B) 1 representative anti-SEMA4D antibody-treated ("Anti-SEMA4D") mouse. Brain volume is represented by the volume of the striatum (solid line) and the hemisphere (dotted line). FIGS. 4C-4D show the calculated ratio (L/R) of striatum and hemispheric volume, respectively, for isotype control ("IgG") mouse and anti-SEMA4D antibody-treated ("SEMA") mouse.

[0014] FIGURES 5A-5B: Show expression of the mature neuronal cell marker, NeuN, in MCAO mice (A) MAb 67-2 ("Sema4D-Ab") or (B) isotype control ("Control IgG") at 30 days after MCAO. The striatum at the border of cerebral infarction is indicated with arrows.

[0015] FIGURES 6A-C: Shows light and dark phase open-field locomotor activity of mice following MCAO and treatment with isotype control ("IgG") or MAb 67-2 ("SEMA4D")

WHAT IS CLAIMED IS:

1. ~~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~~ 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.

2. The ~~method~~use of claim 1, wherein the isolated binding molecule inhibits SEMA4D activity.

3. The ~~method~~use of claim 1, wherein the inhibited SEMA4D activity is dimerization.

4. The ~~method~~use of claim 1, wherein the isolated binding molecule inhibits SEMA4D interaction with a receptor or a portion of the receptor.

5. The ~~method~~use of claim 4, wherein the receptor is selected from the group consisting of Plexin-B1, Plexin-B2 or CD72.

6. The ~~method~~use of claim 1, wherein the isolated binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67 from specifically binding to SEMA4D.

7. The ~~method~~use of claim 1, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67.

8. The ~~method~~ use of claim 1, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

9. The ~~method~~use of claim 8, wherein the antibody or antigen-binding fragment thereof is or is derived from monoclonal antibody VX15/2503 or 67.

10. The ~~method~~use of claim 8, wherein the antibody is chimeric, human or humanized.

1 1. The ~~method~~use of claim 8, wherein the antibody comprises the six CDRs from monoclonal antibody VX15/2503 or 67.

12. The ~~method~~use of claim 1 wherein the central nervous system disorder is selected from the group consisting of a neurodegenerative disorder, acute brain injury, and certain CNS dysfunctions.

13. The ~~method~~use of claim 12 wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Huntington's Disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, and multiple sclerosis.

~~Misnumbered claim [13] has been renumbered [23].~~

14. The ~~method~~use of claim 12 wherein the CNS dysfunction is selected from the group consisting of depression, epilepsy, and schizophrenia.

15. The ~~method~~ use of claim 1, wherein the method increases the number of, enhances differentiation of, and/or increases survival of progenitor cells.

16. ~~A method for increasing the number of progenitor cells in a subject with a central nervous system disorder comprising administering to the subject an effective amount of an~~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.

17. The ~~method~~use of claim 16, wherein the method reduces the burden of the central nervous system disorder in the subject.

18. ~~A method for treating stroke in a patient comprising administering to the subject in need thereof an effective amount of~~ Use of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the manufacture of a medicament for treating stroke in a patient.

19. The ~~method~~use of claim 18, wherein the isolated binding molecule specifically binds to SEMA4D.

20. The ~~method~~use of claim 18, wherein the isolated binding molecule inhibits SEMA4D interaction with a receptor or a portion of the receptor.

21. The ~~method~~use of claim 18, wherein the isolated binding molecule is an antibody or an antigen-binding fragment thereof.

22. The ~~method~~use of claim 17, wherein the an antibody or an antigen-binding fragment thereof that specifically binds to SEMA4D comprises a variable heavy domain having the sequence set forth in SEQ ID NO: 1 or 3 and a variable light domain having the sequence set forth in SEQ ID NO: 2 or 4.

23. The ~~method~~use of claim 12 wherein the acute brain injury is selected from the group consisting of stroke, head injury, cerebral palsy, cerebral infarction, spinal cord injury, and traumatic injury.