(APCs), such as dendritic cells (DCs). Its expression, however, is upregulated in these cells following activation by various immunological stimuli. The release of soluble SEMA4D from immune cells is also increased by cell activation.

[0005] SEMA4D has been implicated in the development of neurodegenerative disorders, autoimmune diseases, demyelinating diseases, and certain cancers. However, the effect of blocking SEMA4D signaling on the organization and function of the central nervous system (CNS) including brain and spinal cord and on behaviors controlled by the CNS remains to be elucidated. This is important because changes in the CNS have a profound influence on a subject's behavior and quality of life. In particular, such changes can impact a subject's neuropsychiatric behavior, cognitive behavior, and motor skills. There remains, therefore, a need for treatments for neurodegenerative disorders that alleviate the symptoms associated with the disorder.

~~BRIEF~~ SUMMARY ~~OF THE DISCLOSURE~~

[0006] Methods for using semaphorin 4D binding molecules to alleviate symptoms in a subject having neurodegenerative disorders are disclosed herein. According to ~~aspects~~ embodiments of the disclosure illustrated herein, there is provided a method for improving symptoms in a subject with a neurodegenerative disorder including administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin 4D (SEMA4D) and inhibits, suppresses, prevents, reverses or slows the effect of SEMA4D.

[0007] According to ~~aspects~~ embodiments illustrated herein, there is provided a method of treating a subject with a neurodegenerative disorder including administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin 4D (SEMA4D), wherein the binding to SEMA4D acts to improve symptoms associated with the disorder.

[0008] In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for alleviating symptoms in a subject having a neurodegenerative disorder. Methods of alleviating symptoms in a subject having a neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D). In certain embodiments of the uses and methods, the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor. In certain embodiments of the uses and methods, the receptor is selected from the group consisting of Plexin-B1 and Plexin-

B2. In certain embodiments of the uses and methods, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In certain embodiments of the uses and methods, 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. In certain embodiments of the uses and methods, 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. In certain embodiments of the uses and methods, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In certain embodiments of the uses and methods, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67. In certain embodiments of the uses and methods, the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively. In certain embodiments of the uses and methods, the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18. In certain embodiments of any of the aforementioned uses and methods, the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof. In certain embodiments of any of the aforementioned uses and methods, the neurodegenerative disorder is Alzheimer's disease or Huntington's disease. In certain embodiments of any one of the aforementioned uses and methods, the symptoms are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof. In certain embodiments of any of the aforementioned uses and methods, the neuropsychiatric symptoms are selected from a group consisting of reducing anxiety-like behavior, improving spatial memory, increasing locomotion, and any combination thereof.

[0009] In one aspect, there is provided use of of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for alleviating symptoms in a subject having a neurodegenerative disorder, 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. Methods of alleviating symptoms in a subject having a neurodegenerative disorder are also provided, comprising administering to that 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.

In certain embodiments of the uses and methods, the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor. In certain embodiments of the uses and methods, the receptor is selected from the group consisting of Plexin-B1 and Plexin-B2. In certain embodiments of the uses and methods, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In certain embodiments of the uses and methods, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In certain embodiments of the uses and methods, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67. In certain embodiments of the uses and methods, the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively. In certain embodiments of the uses and methods, the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18. In certain embodiments of any of the aforementioned uses and methods, the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof. In certain embodiments of any of the aforementioned uses and methods, the neurodegenerative disorder is Alzheimer's disease or Huntington's disease. In certain embodiments of any one of the aforementioned uses and methods, the symptoms are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof. In certain embodiments of any of the aforementioned uses and methods, the neuropsychiatric symptoms are selected from a group consisting of reducing anxiety-like behavior, improving spatial memory, increasing locomotion, and any combination thereof.

[0010] Additional uses and methods of treating a subject having a neurodegenerative or neuroinflammatory disorder, or of effecting a desirable outcome in a subject having a neurodegenerative or neuroinflammatory disorder, are provided herein. In one aspect, there is provided use of of an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for treating a subject having a neurodegenerative disorder, wherein the binding to SEMA4D acts to alleviate symptoms associated with the disorder. Methods of treating a subject having a neurodegenerative disorder are also provided, comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D), wherein the binding to SEMA4D acts to alleviate symptoms associated with the disorder. In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for promoting myelination in a subject having a neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated activity of oligodendrocyte-myelin function. Methods of

promoting myelination in a subject having a neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated activity of oligodendrocyte-myelin function. In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing neural cell death in a subject having a neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated synaptic activity. Methods of preventing neural cell death in a subject having a neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated synaptic activity. In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing injury to the blood-brain barrier in a subject having a neuroinflammatory or neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier. Methods of preventing injury to the blood-brain barrier in a subject having a neuroinflammatory or neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier. In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing astrocyte activation in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier. Methods of preventing astrocyte activation in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier. In one aspect, there is provided use of of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for maintaining or restoring astrocyte-mediated trophic support of oligodendrocyte precursor cells (OPCs) in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disease, wherein the binding molecule prevents retraction of astrocyte processes and chemotactic movement of OPCs towards regions of damage. Methods of maintaining or restoring astrocyte-mediated trophic support of oligodendrocyte precursor cells (OPCs) in a subject having, determined to have, or suspected of having a neuroinflammatory or

neurodegenerative disorder are also provided, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule prevents retraction of astrocyte processes and chemotactic movement of OPCs toward regions of damage. In one aspect, there is provided use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for protecting inhibitory neurons from degeneration in early Alzheimer's disease in a subject having, determined to have, or suspected of having early Alzheimer's disease, wherein the binding molecule restores the number of somatostatin positive neurons, NYP-positive neurons, or both in the subject. Methods of protecting inhibitory neurons from degeneration in early Alzheimer's disease are also provided, comprising administering to a subject having, determined to have, or suspected of having early Alzheimer's disease an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule restores the number of somatostatin positive neurons, NYP-positive neurons, or both in the subject. In certain embodiments of the aforementioned uses and methods, the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor. In certain embodiments of the aforementioned uses and methods, the receptor is selected from the group consisting of Plexin-B1 and Plexin-B2. In certain

embodiments of the aforementioned uses and methods, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In certain embodiments of the aforementioned uses and methods, 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. In certain embodiments of the aforementioned uses and methods, 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. In certain embodiments of the aforementioned uses and methods, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In certain embodiments of the aforementioned uses and methods, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67. In certain embodiments of the aforementioned uses and methods, the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively. In certain embodiments of the aforementioned uses and methods, the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18. In certain embodiments of the aforementioned uses and methods, the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof. In certain embodiments of the aforementioned uses and methods, the neurodegenerative disorder is Alzheimer's disease or Huntington's disease. In certain embodiments of the aforementioned uses and methods, symptoms of the subject that are alleviated by the uses and methods are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof. In certain embodiments of the aforementioned uses and methods, the neuropsychiatric symptoms of the subject that are alleviated by the uses and methods are selected from a group consisting of reducing anxiety-like behavior, improving spatial memory, increasing locomotion, and any combination thereof. In certain embodiments of the aforementioned uses and methods, the subject is determined to have the neurodegenerative disorder by processing a sample or image from the subject.

WHAT IS CLAIMED IS:

1. A method of alleviating symptoms in a subject having a neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D).

2. A method of preventing astrocyte activation in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier.

3. A method of maintaining or restoring astrocyte-mediated trophic support of oligodendrocyte precursor cells (OPCs) in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule prevents retraction of astrocyte processes and chemotactic movement of OPCs toward regions of damage.

4. A method of treating a subject having a neurodegenerative disorder, comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D), wherein the binding to SEMA4D acts to alleviate symptoms associated with the disorder.

5. A method of alleviating symptoms in a subject having a neurodegenerative disorder, comprising administering to that 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.

6. A method of promoting myelination in a subject having a neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated activity of oligodendrocyte-myelin function.

7. A method of preventing neural cell death in a subject having a neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated synaptic activity.

8. A method of preventing injury to the blood-brain barrier in a subject having a neuroinflammatory or neurodegenerative disorder, comprising administering to that subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier.

9. A method of protecting inhibitory neurons from degeneration in early Alzheimer's disease, comprising administering to a subject having, determined to have, or suspected of having early Alzheimer's disease an effective amount of an isolated binding

molecule which specifically binds to SEMA4D, wherein the binding molecule restores the number of somatostatin positive neurons, NYP-positive neurons, or both in the subject.

10. The method of any one of claims 1-9, wherein the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor.

11. The method of any one of claims 1-9, wherein the receptor is selected from the group consisting of Plexin-B1 and Plexin-B2.

12. The method of any one of claims 1-9, wherein the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction.

13. The method of any one of claims 1-9, 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.

14. The method of any one of claims 1-4 or 6-9, 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.

15. The method of any one of claims 1-9, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

16. The method of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67.

17. The method of claim 16, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively.

18. The method of claim 17, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18.

19. The method of any one of claims 1-9, wherein the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof.

20. The method of any one of claims 1, 4, or 5, wherein the symptoms are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof.

21. The method of claim 20, wherein the neuropsychiatric symptoms are selected from a group consisting of reducing anxiety-like behavior, improving spatial memory, increasing locomotion, and any combination thereof.

WHAT IS CLAIMED IS:

1. Use of an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for alleviating symptoms in a subject having a neurodegenerative disorder.

2. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing astrocyte activation in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier.

3. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for maintaining or restoring astrocyte-mediated trophic support of oligodendrocyte precursor cells (OPCs) in a subject having, determined to have, or suspected of having a neuroinflammatory or neurodegenerative disease, wherein the binding molecule prevents retraction of astrocyte processes and chemotactic movement of OPCs towards regions of damage.

4. Use of an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for treating a subject having a neurodegenerative disorder, wherein the binding to SEMA4D acts to alleviate symptoms associated with the disorder.

5. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for alleviating symptoms in a subject having a neurodegenerative disorder, 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.

6. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for promoting myelination in a subject

having a neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated activity of oligodendrocyte-myelin function.

7. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing neural cell death in a subject having a neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated synaptic activity.

8. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for preventing injury to the blood-brain barrier in a subject having a neuroinflammatory or neurodegenerative disorder, wherein the binding molecule modulates astrocyte-mediated maintenance of the integrity of the blood-brain barrier.

9. Use of an effective amount of an isolated binding molecule which specifically binds to SEMA4D in the preparation of a medicament for protecting inhibitory neurons from degeneration in early Alzheimer's disease in a subject having, determined to have, or suspected of having early Alzheimer's disease, wherein the binding molecule restores the number of somatostatin positive neurons, NYP-positive neurons, or both in the subject.

10. The use of any one of claims 1-9, wherein the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor.

11. The use of any one of claims 1-9, wherein the receptor is selected from the group consisting of Plexin-B1 and Plexin-B2.

12. The use of any one of claims 1-9, wherein the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction.

13. The use of any one of claims 1-9, 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.

14. The use of any one of claims 1-4 or 6-9, 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.

15. The use of any one of claims 1-9, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

16. The use of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67.

17. The use of claim 16, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively.

18. The use of claim 17, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18.

19. The use of any one of claims 1-9, wherein the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof.

20. The use of any one of claims 1, 4, or 5, wherein the symptoms are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof.

21. The use of claim 20, wherein the neuropsychiatric symptoms are selected from a group consisting of reducing anxiety-like behavior, improving spatial memory, increasing locomotion, and any combination thereof.