

PREDICTIVE OUTCOME PROFILING FOR USE OF AN ANTI-SEMAPHORIN-4D BINDING MOLECULE TO TREAT NEURODEGENERATIVE DISORDERS

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

- [0001] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 27, 2021, is named 8555_040_SL.txt and is 32KB bytes in size.

BACKGROUND OF THE DISCLOSURE

- [0002] Semaphorin 4D (SEMA4D), also known as CD100, is a transmembrane protein (*e.g.*, SEQ ID NO: 1 (human); SEQ ID NO: 2 (murine)) that belongs to the semaphorin gene family. SEMA4D is expressed on the cell surface as a homodimer, but upon cell activation SEMA4D can be released from the cell surface via proteolytic cleavage to generate sSEMA4D, a soluble form of the protein, which is also biologically active. See Suzuki *et al.*, *Nature Rev. Immunol.* 3:159-167 (2003); Kikutani *et al.*, *Nature Immunol.* 9:17-23 (2008). SEMA4D has been implicated in the development of neurodegenerative disorders, autoimmune diseases, demyelinating diseases, and certain cancers.
- [0003] 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.
- [0004] Neurodegenerative and neuroinflammatory disorders are recognized as a highly heterogeneous diseases that develop from diverse causes and progression of the disorder is highly likely to have an effect on treatment outcome. Thus, there is a need to help predict response to treatment for patients with neurodegenerative and neuroinflammatory disorders.

BRIEF SUMMARY OF THE DISCLOSURE

- [0004a] In one aspect, provided herein is a method of selecting subjects having, determined to have, or suspected of having a neurodegenerative disorder for treatment with an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D), said method comprising: (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and (ii) selecting the subject for treatment if the score satisfies a predetermined value

indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment, or Stage I or Stage II Huntington's disease.

[0004b] In another aspect, provided herein is a method for predicting whether a semaphorin-4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D will be effective in treating a subject having, diagnosed as having, or suspected of having a neurodegenerative disorder, comprising: (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and (ii) predicting a positive response to treatment if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment or Stage I or Stage II Huntington's disease.

[0004c] In another aspect, provided herein is a use of an isolated antibody or antigen-binding fragment thereof which specifically binds to semaphorin-4D (SEMA4D) in the manufacture of a medicament for treating a subject that has, is suspected of having or is diagnosed with a neurodegenerative disorder, wherein the subject is assessed to have a cognitive impairment assessment score in one or more standard cognitive assessment tests that is indicative of mild cognitive impairment, mild dementia or moderate cognitive impairment or is assessed to have a functional impairment assessment score in one or more standard functional assessment tests that is indicative of Stage I or Stage II Huntington's disease.

[0005] Methods for selecting a subject having, determined to have, or suspected of having a neurodegenerative disorder for treatment with an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) are provided. The methods comprise (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and (ii) selecting the subject for treatment if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI),

mild dementia, moderate cognitive impairment, or Stage I or Stage II Huntington's disease. In certain examples, the one or more standard cognitive assessment tests are selected from the Montreal Cognitive Assessment (MoCA), the Total Functional Capacity (TFC), Clinical Global Impression of Change (CGIC), and the Clinical Global Impression of Severity (CGIS). In certain examples, the one or more standard cognitive assessment test is the TFC and the cognitive impairment assessment score for the subject is in the range of 7-12, 8-12 or 8-11. In other examples, the one or more standard cognitive assessment test is the MoCA and the cognitive impairment assessment score for the subject is in the range of from 10-25, such as 10-21, 11-25, 19-25, or 11-21. In certain examples, the method is applied to subjects having, suspected of having, or diagnosed with 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, mild dementia, moderate cognitive impairment or a combination thereof. In other examples, the method is applied to subjects having, suspected of having, or diagnosed with Alzheimer's disease or Huntington's disease.

[0006] In the methods of this examples of the disclosure, the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D may comprise 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 or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively. In other examples, the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor. In further examples, the receptor is selected from Plexin-B1 and Plexin-B2 and in certain examples, the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction.

[0007] Another example of the disclosure provides methods for predicting whether a semaphorin-4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof will be effective in treating a subject having, determined to have, or suspected of having a neurodegenerative disorder. This method comprises (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and (ii) predicting a positive response to treatment if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment, or Stage I or Stage II Huntington's disease. In certain examples, the one or more standard cognitive assessment tests are selected from the Montreal Cognitive Assessment (MoCA), the Total Functional Capacity (TFC), Clinical Global Impression of Change (CGIC), and the Clinical Global Impression of Severity (CGIS). In certain other examples, the one or more standard cognitive

assessment test is the TFC and the cognitive impairment assessment score for the subject is in the range of 7-12, 8-12 or 8-11. In other examples, the one or more standard cognitive assessment test is the MoCA and the cognitive impairment assessment score for the subject is in the range of from 10-25, such as 10-21, 11-25, 19-25, or 11-21. In certain examples, the method is applied to subjects having, suspected of having, or diagnosed with 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, mild dementia, moderate cognitive impairment or a combination thereof. In other examples, the method is applied to subjects having, suspected of having, or diagnosed with Alzheimer's disease or Huntington's disease.

[0008] In the methods of this example of the disclosure, the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D may comprise 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 or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively. In other examples, the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor. In further examples, the receptor is selected from Plexin-B1 and Plexin-B2 and in certain examples, the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction.

[0009] In another example of the disclosure, methods for using semaphorin 4D binding molecules to alleviate symptoms in a subject having, determined to have, or suspected of having a neurodegenerative disorder are provided. According to this example of the disclosure illustrated herein, there is provided a method for treating a subject having, determined to have, or suspected of having a neurodegenerative disorder including determining (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and (ii) administering a therapeutically effective amount of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment, or Stage I or Stage II Huntington's disease. In certain examples of this example of the disclosure, the one or more standard cognitive assessment tests are selected from the Montreal Cognitive Assessment (MoCA), the Total Functional Capacity (TFC), the Clinical Global Impression of Change (CGIC) test, and the Clinical Global Impression of Severity (CGIS) test. In other examples, the one or more standard cognitive assessment test is the TFC and the cognitive impairment assessment score for the subject is in the range of 7-12, such as 7-11, 8-12 or 8-11. In

yet other examples, the one or more standard cognitive assessment test is the MoCA and the cognitive impairment assessment score for the subject is in the range of from 10-25, such as 10-21, 11-25, 19-25, or 11-21. In certain examples, the method is applied to subjects having, suspected of having, or diagnosed with 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, mild dementia, moderate cognitive impairment or a combination thereof. In other examples, the method is applied to subjects having, suspected of having, or diagnosed with Alzheimer's disease or Huntington's disease.

[00010] In the methods of this example of the disclosure, the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D may comprise 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 or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively. In other examples, the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor. In further examples, the receptor is selected from Plexin-B1 and Plexin-B2 and in certain examples, the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction.

[00011] In further examples of this example of the disclosure, the treatment results in a decrease, reduction, slowing or stopping of the incidence of symptoms associated with the neurodegenerative disorder; a decrease, reduction or lessening of the severity of symptoms associated with the neurodegenerative disorder; or improves the quality of life of the subject. In certain examples, the symptoms are selected from neuropsychiatric symptoms, cognitive symptoms, motor dysfunction and any combination thereof.

[00012] In another example of the disclosure, there is provided an isolated antibody or antigen-binding fragment thereof which specifically binds to semaphorin-4D (SEMA4D) for use in a method of treating a subject that has, is suspected of having or is diagnosed with a neurodegenerative disorder, wherein the subject is assessed to have a cognitive and/or functional impairment assessment score in one or more standard cognitive and/or functional assessment tests that is indicative of mild cognitive impairment, mild dementia or moderate dementia, or Stage I or Stage II Huntington's disease. In certain examples of this example, the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D may comprise 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 or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light

chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively. In other examples, the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor. In further examples, the receptor is selected from Plexin-B1 and Plexin-B2 and in certain examples, the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction. The isolated antibodies of this example may be used in any of the methods of the disclosure.

BRIEF DESCRIPTION OF THE FIGURES

- [00013] FIGURE 1: shows categorical changes in the Clinical Global Impression of Change (CGIC) of early manifest patients treated with placebo (PBO) or an anti-SEMA4D antibody (Pepinemab; PEPI) during the primary analysis period from baseline to Months 3, 5, 11, and 17 by subgroup with baseline Unified Huntington Disease Rating Scale (UHDRS) Total Functional Capacity score (HDRS-TFC) of 11 or 12-13. Fig. 1A shows the categorical change in CGIC of subjects with a baseline TFC score of 11. Fig. 1B shows the categorical change in CGIC of subjects with a baseline TFC score of 12 and 13.
- [00014] Figure 2: Huntington Disease Cognitive Assessment Battery (HD-CAB) composite test results. Fig. 1A shows the change (CHG) from baseline (mean + standard error of measurement (SEM)) of HD-CAB composite score in patients with early manifest HD having a baseline MoCA score < 26 treated with placebo (PBO) or an anti-SEMA4D antibody (Pepinemab; PEPI B1) over a period of 18 months. Fig. 1B shows the change (CHG) from baseline (mean + standard error of measurement (SEM)) of HD-CAB composite score in patients with early manifest HD having a baseline MoCA score of ≥ 26 treated with placebo or an anti-SEMA4D antibody (Pepinemab; PEPI) over a period of 18 months.
- [00015] Figure 3: Total Motor Score (TMS) stratified by MoCA. Fig. 1A shows the change (CHG) from baseline in the TMS (mean + standard error of measurement (SEM)) in patients with early manifest HD having a baseline MoCA score of < 26 treated with placebo (PBO) or an anti-SEMA4D antibody (Pepinemab; PEPI) over 18 months. Fig. 1B shows the change (CHG) from baseline (mean + standard error of measurement (SEM)) in patients with early manifest HD having a baseline MoCA score of ≥ 26 treated with placebo or an anti-SEMA4D antibody (Pepinemab; PEPI) over 18 months.

DETAILED DESCRIPTION OF THE DISCLOSURE

Definitions

- [00016] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "an anti-SEMA4D antibody" is understood to represent one or more anti-SEMA4D antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

WHAT IS CLAIMED IS:

1. A method of selecting subjects having, determined to have, or suspected of having a neurodegenerative disorder for treatment with an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D), said method comprising:

(i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and

(ii) selecting the subject for treatment if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment, or Stage I or Stage II Huntington's disease.

2. The method of claim 1, wherein the one or more standard cognitive assessment and/or functional assessment tests are selected from the Montreal Cognitive Assessment (MoCA), the Total Functional Capacity (TFC), Clinical Global Impression of Change (CGIC), the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog Test), Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB), and the Clinical Global Impression of Severity (CGIS).

3. The method of claim 1 or 2, wherein the one or more standard functional assessment test is the TFC and wherein the functional impairment assessment score for the subject is in the range of 7-12, 8-12 or 8-11.

4. The method of claim 1 or 2, wherein the one or more standard cognitive assessment test is the MoCA and wherein the cognitive impairment assessment score for the subject is in the range of from 10-25, 19-25, or 11-21.

5. The method of any one of claims 1-4, 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 to moderate cognitive impairment, or a combination thereof.

6. The method of claim 5, wherein the neurodegenerative disorder is Alzheimer's disease (AD) or Huntington's disease (HD).

7. The method of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D 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, or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively.

8. The method of any one of claims 1-7, wherein the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor.
9. The method of claim 8, wherein the receptor is selected from Plexin-B1 and Plexin-B2.
10. The method of claim 8 or 9, wherein the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction.
11. A method for predicting whether a semaphorin-4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D will be effective in treating a subject having, diagnosed as having, or suspected of having a neurodegenerative disorder, comprising:
 - (i) determining the cognitive and/or functional impairment assessment score for the subject in one or more standard cognitive and/or functional assessment tests; and
 - (ii) predicting a positive response to treatment if the score satisfies a predetermined value indicative of mild cognitive impairment (MCI), mild dementia, moderate cognitive impairment or Stage I or Stage II Huntington's disease.
12. The method of claim 11, wherein the one or more standard cognitive and/or functional assessment tests are selected from the Montreal Cognitive Assessment (MoCA), the Total Functional Capacity (TFC), Clinical Global Impression of Change (CGIC), the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog Test), Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB), and the Clinical Global Impression of Severity (CGIS).
13. The method of claim 11 or 12, wherein the standard functional assessment test is the TFC and wherein the functional impairment assessment score for the subject is in the range of from 7-12, from 8-12, or from 8-11.
14. The method of claim 11 or 12, wherein the standard cognitive assessment test is the MoCA and wherein the cognitive impairment assessment score for the subject is in the range of from 10-25, from 19-25, or from 11-21.
15. The method of any one of claims 11 to 14, 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 to moderate cognitive impairment, or a combination thereof.
16. The method of claim 15, wherein the neurodegenerative disorder is Alzheimer's disease (AD) or Huntington's disease (HD).
17. The method of any one of claims 11 to 16, wherein the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D 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 or comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 42, 43, and 44, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 46, 47, and 48, respectively.

18. The method of any one of claims 11 to 17, wherein the antibody or antigen binding fragment thereof inhibits SEMA4D binding to its receptor.

19. The method of claim 18, wherein the receptor is selected from Plexin-B1 and Plexin-B2.

20. The method of claim 18 or 19, wherein the antibody or antigen binding fragment thereof inhibits SEMA4D-mediated signal transduction.

21. Use of an isolated antibody or antigen-binding fragment thereof which specifically binds to semaphorin-4D (SEMA4D) in the manufacture of a medicament for treating a subject that has, is suspected of having or is diagnosed with a neurodegenerative disorder, wherein the subject is assessed to have a cognitive impairment assessment score in one or more standard cognitive assessment tests that is indicative of mild cognitive impairment, mild dementia or moderate cognitive impairment or is assessed to have a functional impairment assessment score in one or more standard functional assessment tests that is indicative of Stage I or Stage II Huntington's disease.

22. The method of claim 1 or 11 or the use of claim 21, wherein the neurodegenerative disorder is Alzheimer's disease.

23. The method of claim 22, wherein the one or more standard cognitive and/or functional assessment tests is the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog Test), or the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB).

24. The method of claim 23, wherein the test score for the CDR-SOB is in the range of from 4.5 to 9.0 or from 9.5 to 15.5, the test score for the MMSE is < 24, and/or the test score for the ADAS-COG indicates mild cognitive impairment (MCI).