[0010b] In another aspect, the present disclosure refers to a method for determining an effective dose of a semaphorin 4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof for treating a neurodegenerative or neuroinflammatory disease, disorder, or injury, comprising: (a) measuring the level of glucose uptake in a sample obtained from the subject's brain relative to a baseline level of glucose uptake in the subject's brain measured prior to administration of a starting dose of a SEMA4D antagonist antibody or antigen-binding fragment thereof; and (b) ~~determining that~~increasing the starting dose ~~must be adjusted~~ to provide an effective dose if an increase in glucose uptake over baseline is detected~~, the adjustment determined on the level of increase~~.

[0010c] In another aspect, the present disclosure refers to a method for determining whether a semaphorin 4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof will be effective in treating a neurodegenerative or neuroinflammatory disease, disorder, or injury, comprising: ~~ordering the measurement of~~measuring the level of glucose uptake in a sample obtained from the subject's brain relative to a baseline level of glucose uptake in the subject's brain measured prior to administration of the SEMA4D antagonist antibody or antigen-binding fragment thereof, wherein an increase in glucose uptake over baseline is indicative that the SEMA4D antagonist antibody or antigen-binding fragment thereof is effective in treating the neurodegenerative or neuroinflammatory disease, disorder, or injury.

[0011] In one example the method includes administering an effective amount of a SEMA4D antagonist antibody or antigen-binding fragment thereof to a subject having, suspected of having, or at risk of developing a neurodegenerative or neuroinflammatory disease, disorder, or injury; measuring the level of glucose uptake in the subject's brain relative to a baseline level of glucose uptake in the subject's brain measured prior to administration of the SEMA4D antagonist; and continuing administration of the SEMA4D antagonist antibody or fragment thereof if an increase in glucose uptake over baseline is detected; or discontinuing administration of the SEMA4D antagonist antibody or fragment thereof if no change or a decrease in glucose uptake relative to baseline is detected.

[0012] In another example the method includes measuring the baseline level of glucose uptake in the brain of a subject having, suspected of having, or at risk of developing a neurodegenerative or neuroinflammatory disease, disorder, or injury; administering an effective amount of a SEMA4D antagonist antibody or antigen-binding fragment thereof to the subject; remeasuring the level of glucose uptake in the subject's brain following

WHAT IS CLAIMED IS:

1. A method for determining whether a semaphorin 4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof will be effective in treating a neurodegenerative or neuroinflammatory disease, disorder, or injury, comprising:

(a) measuring the baseline level of glucose uptake in a sample obtained from the brain of a subject having, suspected of having, or at risk of developing a neurodegenerative or neuroinflammatory disease, disorder, or injury;

(b) remeasuring the level of glucose uptake in a sample obtained from the subject's brain after that subject was administered the SEMA4D antagonist antibody or antigen-binding fragment thereof;

wherein an increase in glucose uptake over baseline is indicative that the SEMA4D antagonist antibody or antigen-binding fragment thereof is effective in treating the neurodegenerative or neuroinflammatory disease, disorder, or injury.

2. A method for determining an effective dose of a semaphorin 4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof for treating a neurodegenerative or neuroinflammatory disease, disorder, or injury, comprising:

(a) measuring the level of glucose uptake in a sample obtained from the subject's brain relative to a baseline level of glucose uptake in the subject's brain measured prior to administration of a starting dose of a SEMA4D antagonist antibody or antigen-binding fragment thereof; and

(b) ~~determining that~~increasing the starting dose ~~must be adjusted~~ to provide an effective dose if an increase in glucose uptake over baseline is detected~~, the adjustment determined on the level of increase~~.

3. The method of claim 2, further comprising determining that the dose of SEMA4D antagonist antibody is to be increased relative to the dose tested in claim 2 and remeasuring the change in level of glucose uptake relative to a new baseline in a different previously untreated patient or in the same patient following withdrawal of treatment in the same patient for a period of time determined to allow accumulation of a historical

deficit in that neurodegenerative or neuroinflammatory disease, disorder, or injury, and further ~~adjusting~~ increasing the dose of the SEMA4D antagonist antibody if a further increase is detected.

4. A method for determining whether a semaphorin 4D (SEMA4D) antagonist antibody or antigen-binding fragment thereof will be effective in treating a neurodegenerative or neuroinflammatory disease, disorder, or injury, comprising:

~~ordering the measurement of~~measuring the level of glucose uptake in a sample obtained from the subject's brain relative to a baseline level of glucose uptake in the subject's brain measured prior to administration of the SEMA4D antagonist antibody or antigen-binding fragment thereof,

wherein an increase in glucose uptake over baseline is indicative that the SEMA4D antagonist antibody or antigen-binding fragment thereof is effective in treating the neurodegenerative or neuroinflammatory disease, disorder, or injury.

5. The method of any one of claims 1 to 4, wherein the SEMA4D antagonist antibody or antigen-binding fragment thereof inhibits SEMA4D interaction with its receptor.

6. The method ~~or the use~~ of claim 5, wherein the receptor is Plexin-B1, Plexin-B2, or CD72.

7. The method of any one of claims 1 to 6, wherein the SEMA4D antagonist antibody or antigen-binding fragment thereof inhibits SEMA4D-mediated Plexin-B1 signal transduction.

8. The method of any one of claims 1 to 7, wherein the SEMA4D antagonist antibody or antigen-binding fragment thereof competitively inhibits a reference antibody comprising a variable heavy chain region (VH) comprising the amino acid sequence SEQ ID NO: 1 and a variable light chain region (VL) comprising the amino acid sequence SEQ ID NO: 5 from binding to SEMA4D.

9. The method of any one of claims 1 to 8, wherein the SEMA4D antagonist antibody or antigen-binding fragment thereof binds to the same SEMA4D epitope as a reference antibody comprising a VH comprising the amino acid sequence SEQ ID NO: 1 and a VL comprising the amino acid sequence SEQ ID NO: 5.

10. The method of claim 8 or claim 9, wherein the SEMA4D antagonist antibody comprises a VH and a VL, wherein the VH comprises three complementarity determining regions (CDRs) HCDR1, HCDR2, and HCDR3, wherein the VL comprises three CDRs LCDR1, LCDR2, and LCDR3, and wherein the CDRs comprise the amino acid sequences SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively except for at least one or two single conservative amino acid substitutions in one or more of the CDRs.

11. The method of claim 8 or 9, wherein the SEMA4D antagonist antibody comprises a VH and a VL, wherein the VH comprises three complementarity determining regions (CDRs) HCDR1, HCDR2, and HCDR3, wherein the VL comprises three CDRs LCDR1, LCDR2, and LCDR3, and wherein the CDRs comprise the amino acid sequences SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively.

12. The method of any one of claims 8 to 11, wherein the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 1 and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 5.

13. The method of claim 12 wherein the VH comprises the amino acid sequence SEQ ID NO: 1 and the VL comprises the amino acid sequence SEQ ID NO: 5.

14. The method of any one of claims 1 to 13, wherein a first dose of the SEMA4D antagonist antibody is to be administered, and then the SEMA4D antagonist antibody is to be administered at least once every week, at least once every two weeks, at least once every three weeks, at least once a month, or at least once every two months thereafter.

15. The method ~~or use~~ of claim 14, wherein the change in glucose uptake relative to baseline is measured at least one week after the first dose, at least two weeks after the first dose, at least one month after the first dose, at least two months after the first dose, at least three months after the first dose, at least four months after the first dose, at least five months after the first dose, at least six months after the first dose, or any combination thereof.

16. The method of any one of claims 1 to 15, wherein glucose uptake in the subject's brain is measured by 18F- Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) imaging.

17. The method of any one of claims 1 to 16, wherein the subject is a human.

18. The method of any one of claims 1 to 17, wherein the neurodegenerative or neuroinflammatory disease, disorder or injury is Alzheimer's disease, Parkinson's disease, Huntington's disease, Down syndrome, ataxia, amyotrophic lateral sclerosis (ALS), multiple sclerosis, (MS), epilepsy, meningitis, brain edema, spinal cord injury, traumatic brain injury, frontotemporal dementia (FTD), HIV-related cognitive impairment, CNS Lupus, mild cognitive impairment, or a combination thereof.

19. The method of claim 18, wherein the neurodegenerative or neuroinflammatory disease, disorder or injury is Huntington's disease (HD).

20. The method of claim 19, wherein the subject is at risk of developing HD due to familial history of HD or genetic testing.

21. The method of claim 20, wherein genetic testing reveals 36 or more CAG repeats in the subject's HTT gene.

22. The method of any one of claims 19 to 21, wherein the subject is suspected of having HD due to mild motor dysfunction, mild cognitive impairment, or mild neuropsychiatric features.

23. The method of any one of claims 19 to 22, wherein the subject is diagnosed as having HD due to brain atrophy, an elevated Uniform Huntington's Disease Rating Scale score (UHDRS), an increased Huntington's Disease Cognitive Assessment Battery (HD-CAB) score, an increased Huntington's Disease Quantitative Motor Assessment score or a combination thereof.

24. The method of claim 23, wherein the subject is in the presymptomatic, early prodromal, late prodromal, early manifest, moderate manifest, or advanced manifest stage of HD.