

antibodies or antigen-binding fragments thereof that specifically bind to SEMA4D. According to other examples of the disclosure illustrated herein, there is provided a method for treating a subject with an autoimmune disease, inflammatory disease, cancer, neuroinflammatory disease, and neurodegenerative disorder including administering to the subject an effective amount of an antibody or antigen-binding fragment which specifically binds to SEMA4D and neutralizes SEMA4D activity.

[0009] In certain examples, the antibody or antigen-binding fragment thereof that specifically binds to SEMA4D includes a heavy chain variable region (VH) and a light chain variable region (VL); wherein the VH includes complementarity determining regions (HCDRs) HCDR1, HCDR2, and HCDR3 that includes amino acid sequences identical or identical except for one, two, three, or four amino acid substitutions in one, two, or all three of the HCDRs to SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, respectively; and wherein the VL includes complementarity determining regions (LCDRs) LCDR1, LCDR2, and LCDR3 that includes amino acid sequences identical or identical except for one, two, three, or four amino acid substitutions in one, two, or all three of the LCDRs to SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively. In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprising a heavy chain variable region (VH) and a light chain variable region (VL); wherein the VH comprises complementarity determining regions (HCDRs) HCDR1, HCDR2, and HCDR3 comprising amino acid sequences identical to SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, respectively; and wherein the VL comprises complementarity determining regions (LCDRs) LCDR1, LCDR2, and LCDR3 comprising amino acid sequences identical to SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively.

[0010] In certain examples, the anti-SEMA4D antibody or antigen-binding fragment thereof includes VH complementarity determining regions HCDR1, HCDR2, and HCDR3 that includes amino acid sequences identical to SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, respectively, and VL complementarity determining regions LCDR1, LCDR2, and LCDR3 that includes amino acid sequences identical to SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively.

[0011] In certain examples, the anti-SEMA4D antibody or antigen-binding fragment thereof includes a VH that includes framework regions (HFWs) HFW1, HFW2, HFW3, and HFW4, and the VL that includes framework regions (LFWs) LFW1, LFW2, LFW3, and LFW4. In certain examples, the framework regions can be derived from a human antibody or from a non-human antibody.

[0012] In certain examples, the anti-SEMA4D antibody or antigen-binding fragment thereof includes a VH that includes the amino acid sequence SEQ ID NO: 1. In certain examples, the anti-SEMA4D antibody or antigen-binding fragment thereof includes a VL that includes the amino acid sequence SEQ ID NO: 5. In certain examples, the anti-SEMA4D antibody or antigen-binding fragment thereof includes a VH and VL that includes amino acid sequence SEQ ID NO: 1 and SEQ ID NO: 5, respectively.

[0013] In certain examples the VH of the anti-SEMA4D antibody or antigen-binding fragment thereof provided herein includes an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1. In certain examples, the VL of the anti-

SEMA4D antibody or antigen-binding fragment thereof provided herein includes an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 5. In certain examples the VH can include an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1, and the VL can include an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 5. In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprising a heavy chain variable region (VH) and a light chain variable region (VL); wherein the VH comprises SEQ ID NO: 1; or wherein the VL comprises SEQ ID NO: 5; or wherein the VH comprises SEQ ID NO: 1; and wherein the VL comprises SEQ ID NO: 5.

[0014] In certain examples, the anti-SEMA4D antibody or fragment thereof provided herein includes a heavy chain constant region or fragment thereof fused to the C-terminus of the VH. In certain examples the heavy chain constant region or fragment thereof is a human heavy chain constant region. In certain examples the heavy chain constant region or fragment thereof can be a human IgG4 constant region. In certain examples the heavy chain constant region or fragment thereof is a non-human constant region. In certain examples, the heavy chain constant region or fragment thereof is a murine IgG1 constant region. In certain examples, the anti-SEMA4D antibody or fragment thereof includes a VH and VL, wherein the light chain constant region or fragment thereof is fused to the C-terminus of the VL. In certain examples, the anti-SEMA4D antibody or fragment thereof provided herein includes a light chain constant region or fragment thereof fused to the C-terminus of the VL. In certain examples the light chain constant region is a human light chain constant region, *e.g.*, a human lambda or human kappa light chain constant region. In certain examples the light chain constant region is a non-human light chain constant region, *e.g.*, a murine lambda light chain constant region.

[0015] In certain examples, the anti-SEMA4D antibody or fragment thereof provided herein can be an Fab fragment, an Fab' fragment, an F(ab')₂ fragment, an Fd fragment, a single-chain Fv fragment (scFv), or a disulfide-linked Fv fragment (sdFv). In certain examples the anti-SEMA4D antibody or fragment thereof can be multi-specific, *e.g.*, bispecific.

[0016] In certain examples, the anti-SEMA4D antibody or fragment thereof provided herein can specifically bind to human SEMA4D, mouse SEMA4D, rat SEMA4D, and/or non-human primate SEMA4D, *e.g.*, cynomolgus monkey SEMA4D and/or marmoset SEMA4D. In certain examples, the anti-SEMA4D antibody or fragment thereof provided herein can bind to SEMA4D, *e.g.*, human SEMA4D, mouse SEMA4D, rat SEMA4D,

WHAT IS CLAIMED IS:

1. An antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprising a heavy chain variable region (VH) and a light chain variable region (VL); wherein the VH comprises complementarity determining regions (HCDRs) HCDR1, HCDR2, and HCDR3 comprising amino acid sequences identical to SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, respectively; and wherein the VL comprises complementarity determining regions (LCDRs) LCDR1, LCDR2, and LCDR3 comprising amino acid sequences identical to SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively.
2. The antibody or fragment thereof of claim 1, wherein the VH further comprises framework regions (HFWs) HFW1, HFW2, HFW3, and HFW4, and wherein the VL further comprises framework regions (LFWs) LFW1, LFW2, LFW3, and LFW4.
3. The antibody or fragment thereof of claim 2, wherein the framework regions are derived from a human antibody.
4. The antibody or fragment thereof of claim 2, wherein the framework regions are derived from a non-human antibody.
5. The antibody or fragment thereof of any one of claims 1 to 3, wherein the VH comprises the amino acid sequence SEQ ID NO: 1; or wherein the VL comprises the amino acid sequence SEQ ID NO: 5; or , wherein the VH comprises the amino acid sequence SEQ ID NO: 1 and the VL comprises the amino acid sequence SEQ ID NO: 5.
6. An antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprising a heavy chain variable region (VH) and a light chain variable region (VL); wherein the VH comprises SEQ ID NO: 1; or wherein the VL

comprises SEQ ID NO: 5; or wherein the VH comprises SEQ ID NO: 1; and wherein the VL comprises SEQ ID NO: 5.

7. The antibody or fragment thereof of any one of claims 1 to 6, further comprising a heavy chain constant region or fragment thereof fused to the C-terminus of the VH, wherein the constant region or fragment thereof is a human or non-human heavy chain constant region.

8. The antibody or fragment thereof of claim 7, wherein the heavy chain constant region or fragment thereof is a human IgG4 constant region.

9. The antibody or fragment thereof of claim 7, wherein the heavy chain constant region or fragment thereof is a murine IgG1 constant region.

10. The antibody or fragment thereof of any one of claims 1 to 9, further comprising a light chain constant region or fragment thereof fused to the C-terminus of the VL, wherein the constant region or fragment thereof is a human or non-human light chain constant region.

11. The antibody or fragment thereof of claim 10, wherein the light chain constant region or fragment thereof is a human lambda light chain constant region.

12. The antibody or fragment thereof of claim 10, wherein the light chain constant region or fragment thereof is a murine lambda light chain constant region.

13. The antibody or fragment thereof of any one of claims 1 to 12, which is an Fab fragment, an Fab' fragment, an F(ab')₂ fragment, an Fd fragment, a single-chain Fv fragment (scFv), or a disulfide-linked Fv fragment (sdFv).

14. The antibody or fragment thereof of any one of claims 1 to 13, which is multispecific.

15. The antibody of any one of claims 1 to 14, which can specifically bind to human SEMA4D, mouse SEMA4D, rat SEMA4D, or non-human primate SEMA4D.

16. The antibody or fragment thereof of any one of claims 1 to 15, which can inhibit SEMA4D from binding to a SEMA4D receptor.

17. The antibody or fragment thereof of claim 16, wherein the SEMA4D receptor is Plexin-B1, Plexin-B2, CD72, or a combination thereof.

18. A composition comprising the antibody or fragment thereof of any one of claims 1 to 17, and a carrier.

19. An isolated polynucleotide or combination of polynucleotides comprising one or more nucleic acid sequences encoding the antibody or fragment thereof of any one of claims 1 to 17, or a subunit thereof.

20. A host cell comprising the polynucleotide or combination of polynucleotides of claim 19, or a vector or vectors comprising the polynucleotide or combination of polynucleotides of claim 19.

21. A method for producing the antibody or fragment thereof of any one of claims 1 to 17, comprising culturing the host cell of claim 20 and recovering the antibody or fragment thereof.

22. Use of the antibody or fragment thereof according to any one of claims 1-17 in the manufacture of a medicament for neutralizing SEMA4D in a human subject, wherein the human subject is in need of treatment for a disease or disorder selected from the group consisting of an autoimmune disease or disorder, an inflammatory disease or disorder, cancer, a neuroinflammatory disease or disorder, a neurodegenerative disease or disorder, or any combination thereof.

23. The use of claim 22, wherein the disease or disorder is stroke, 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, multiple sclerosis, arthritis, rheumatoid arthritis or a combination thereof.