to the tumor microenvironment, the question of what role SEMA4D can play in migration, survival, differentiation and organization of the different cell types that constitute the tumor stroma remains to be addressed.

BRIEF SUMMARY

[0004] This application addresses the need for safe and effective cancer treatments that serve either as a single agent that inhibits, reduces, suppresses, prevents, slows or delays the progression of, shrinks, or directly attacks tumor cells or that can act in combination with other immune modulating therapies to enhance their therapeutic benefit. In particular, SEMA4D was shown to play a role in the infiltration, maturation and organization of immune cells and macrophage that either promote or inhibit tumor growth, which can contribute to development of effective methods for reducing tumor growth and metastases in a subject with cancer.

[0004a] In one aspect, the present disclosure refers to a method of selecting subjects with cancer for treatment with an isolated antibody or antigen-binding fragment thereof which specifically binds to semaphorin-4D (SEMA4D) in combination with at least one other immune modulating therapy, the method comprising: (a) determining the number of B cells and/or T cells in a sample obtained from a subject with cancer; and (b) selecting said subject for treatment if the number of B cells and/or T cells in the sample exceeds a predetermined threshold level.

[0005] Certain examples of the application are directed to a method for inhibiting, delaying, or reducing tumor growth or metastases or both tumor growth and metastases in a subject with cancer comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy.

[0006] In some examples, the binding molecule inhibits SEMA4D interaction with its receptor (e.g., Plexin-B1). In some examples, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In some examples, the inhibition, delay, or reduction of metastases occurs independently of primary tumor growth inhibition, delay, or reduction. In some example, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer,

brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some examples, the subject has elevated levels of either B cells, T cells or both B cells and T cells when compared to other cancer subjects.

[0007] In some examples, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503 and 67. In some examples, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some examples, the antibody or antigen-binding fragment thereof comprises the six complementarity determining regions (CDRs) of monoclonal antibody VX15/2503 or 67.

[0008] In some examples, the immune modulating therapy is selected from the group consisting of a cancer vaccine, an immunostimulatory agent, adoptive T cell or antibody therapy, immune checkpoint blockade and a combination thereof. In some examples, the immune modulating agent is selected from the group consisting of interleukins, cytokines, chemokines, antagonists of immune checkpoint blockades and a combination thereof. In some examples, the immune modulating therapy can be a cancer therapy. In some examples, the cancer therapy is selected from the group consisting of surgery or surgical procedures, radiation therapy, chemotherapy or a combination thereof. In some examples, the isolated binding molecule and the immune modulating agent or immune modulating therapy are administered separately or concurrently.

[0009] In some examples, methods for inhibiting, delaying, or reducing tumor growth in a subject with cancer are provided that comprise administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy. In some examples, the binding molecule inhibits SEMA4D interaction with its receptor. In some examples, the receptor is Plexin-B1. In some examples, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In some examples, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some examples, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody VX15/2503 or 67. In some examples, the isolated binding

molecule competitively inhibits a reference monoclonal antibody VX15/2503 or 67 from specifically binding to SEMA4D. In some examples, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some examples, 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 some examples, 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 some examples, the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof. In some examples, the immune modulating therapy comprises an immune checkpoint blockade inhibitor. In some examples, wherein the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof. In some examples, the immune modulating therapy comprises administration of a cancer vaccine. In some examples, the Treg modulator is cyclophosphamide. In some examples, the isolated binding molecule and the immune modulating therapy are administered separately or concurrently. In some examples, administration of the combination of the isolated binding molecule and the immune modulating therapy results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the immune modulating therapy alone. In some examples, the subject has an elevated level of B cells, T cells or both B cells and T cells when compared to other cancer subjects. In some examples, the level of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer patients. In some examples, the level of B cells and/or T cells per microliter of blood in the subject ranges from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., ,when compared to other cancer patients. In some examples, the subject has B cell and/or T cell levels that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examples, the B cell and/or T cell levels per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 or more, respectively, e.g., ,when compared to healthy, non-cancer patients.

[0010] In some examples, methods for treating a subject having cancer with immunotherapy are provided that comprise: (a) determining the number of B cells and/or T cells in a subject with cancer; and (b) administering to the subject an effective amount of an isolated binding

molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy if the number of B cells and/or T cells in the subject exceeds a predetermined threshold level. In some examples, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer patients. In some examples, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., when compared to other cancer patients. In some examples, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examples, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650, or more, respectively, e.g., when compared to healthy, non-cancer patients.

[0011] In some examples, methods of treating a subject having cancer with immunotherapy are provided that comprise: administering a combination of an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy to a subject with cancer, wherein administration of the combination results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the other immune modulating therapy alone. In some examples, the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof. In some examples, the immune modulating therapy comprises an immune checkpoint blockade inhibitor. In some examples, the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof. In some examples, the immune modulating therapy comprises administration of a cancer vaccine. In some examples, the Treg modulator is cyclophosphamide. In some examples, the isolated binding molecule and the immune modulating therapy are administered separately or concurrently. In some examples, the subject has elevated levels of either B cells, T cells or both B cells and T cells when compared to other cancer subjects. In some examples, the levels of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer

patients. In some examples, the levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., when compared to other cancer patients. In some examples, the subject has levels of B cells and/or T cells that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examples, the levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650, or more, respectively, e.g., when compared to healthy, non-cancer patients. In some examples, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some examples of any of the aforementioned 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 some examples of any of the aforementioned 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 some examples, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some examples, the antibody or antigen-binding fragment thereof comprises the six complementarity determining regions (CDRs) of monoclonal antibody VX15/2503 or 67. In some examples, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67.

[0012] Also provided are methods for inhibiting, delaying, or reducing growth of tumor cells expressing Her2 and Plexin B1, Plexin B2, or a combination thereof, comprising contacting the tumor cells with an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D), wherein growth of the tumor cells is inhibited, delayed, or reduced. In some examples, the contacting comprises administration of the SEMA4D binding molecule to a subject with cancer, wherein the subject’s cancer cells express Her2 and Plexin B1, Plexin B2, or a combination thereof. In some examples, the cancer is breast cancer, ovarian cancer, lung cancer, or prostate cancer.

WHAT IS CLAIMED IS:

1. A method of selecting subjects with cancer for treatment with an isolated antibody or antigen-binding fragment thereof which specifically binds to semaphorin-4D (SEMA4D) in combination with at least one other immune modulating therapy, the method comprising:

(a) determining the number of B cells and/or T cells in a sample obtained from a subject with cancer; and

(b) selecting said subject for treatment if the number of B cells and/or T cells in the sample exceeds a predetermined threshold level.

2. The method of claim 1, wherein the antibody or antigen-binding fragment thereof inhibits SEMA4D interaction with its receptor.

3. The method of claim 2, wherein the receptor is Plexin-B1, Plexin-B2, CD72, or a combination thereof.

4. The method of any one of claims 1-3, wherein the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction.

5. The method of any one of claims 1-4 , wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, ·salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof.

6. The method of any one of claims 1-5, 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.

7. The method of claim 6, 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.

8. The method of any one of claims 1-7, wherein the at least one other immune modulating therapy is selected from the group consisting adoptive T cell or antibody therapy, f an immune checkpoint blockade inhibitor, a regulatory T cell (Treg) modulator, and a combination thereof.

9. The method of claim 8, wherein the immune modulating therapy comprises an immune checkpoint blockade inhibitor selected from the group consisting of an anti-Programmed Cell Death 1 (PD-1) antibody, an anti-Programmed Death-Ligand 1 (PD-L1) antibody, an anti-Lymphocyte Activation Gene 3 (LAG3) antibody, an anti-B7-H3 antibody, an antigen-binding fragment thereof, and a combination thereof .

10. The method of claim 9, wherein the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof.

11. The method of claim 8, wherein the Treg modulator is cyclophosphamide.

12. The method of any one of claims 1-11, wherein the predetermined threshold level of B cells and/or T cells per microliter of blood in the subject is about 1.5 to about 5 times the mean number of B cells and/or T cells in circulation in other cancer patients.

13. The method of claim 12, wherein the level of B cells and/or T cells per microliter of blood in the subject ranges from about 147 to about 588 and from about 1173 to about 3910, respectively.

14. The method of any one of claims 1-12, wherein the subject has B cell and/or T cell levels that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients.

15. The method of claim 13, wherein the B cell and/or T cell levels per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 or more, respectively.