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; wherein the predetermined threshold levels of B cells range from 147 to 588 per microliter of blood and the predetermined level of T cells in the subject are from 1173 to 3910 per microliter of blood; and wherein the at least one other immune modulating therapy comprises an immune checkpoint blockade inhibitor, a T cell (Treg) modulator comprising cyclophosphamide, or a combination thereof, and wherein the cancer is a solid tumor.

[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 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,

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;
wherein the predetermined threshold levels of B cells range from 147 to 588 per microliter of blood and the predetermined level of T cells in the subject are from 1173 to 3910 per microliter of blood; and wherein the at least one other immune modulating therapy comprises an immune checkpoint blockade inhibitor, a T cell (Treg) modulator comprising cyclophosphamide, or a combination thereof, and wherein the cancer is a solid tumor.

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 antibody or antigen-binding fragment thereof 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, 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 claim 5, wherein the cancer is head and neck cancer.

7. The method of claim 5, wherein the cancer is non-small cell lung cancer.

8. The method of any one of claims 1-7, 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.

9. The method of claim 8, 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.

10. The method of claim 1, wherein the immune modulating therapy comprises an immune checkpoint blockade inhibitor selected from the group consisting of an anti-Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA4) antibody, 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.

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

12. The method of claim 1, wherein the Treg modulator is cyclophosphamide.

13. 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.

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