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 another aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and at least one other immune modulating agent in the preparation of a medicament for inhibiting, delaying, or reducing tumor growth in a subject with a solid tumor; wherein the at least one other immune modulating agent comprises: (a) an adoptive T cell therapeutic agent comprising tumor-infiltrating lymphocytes (TIL) recovered from the tumor microenvironment (TME) of the subject with a tumor after administration of the antibody or fragment thereof to the subject, (b) an immune checkpoint blockade inhibitor comprising 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, or a combination thereof, or (c) a regulatory T cell (Treg) modulator comprising cyclophosphamide; and wherein the medicament can provide enhanced therapeutic efficacy relative to anti-SEMA4D antibody or fragment thereof alone or the at least one other immune modulating agent alone.

WHAT IS CLAIMED IS:

1. Use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and at least one other immune modulating agent in the preparation of a medicament for inhibiting, delaying, or reducing tumor growth in a subject with a solid tumor; wherein the at least one other immune modulating agent comprises: (a) an adoptive T cell therapeutic agent comprising tumor-infiltrating lymphocytes (TIL) recovered from the tumor microenvironment (TME) of the subject with a tumor after administration of the antibody or fragment thereof to the subject, (b) an immune checkpoint blockade inhibitor comprising 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, or a combination thereof, or (c) a regulatory T cell (Treg) modulator comprising cyclophosphamide; and wherein the medicament can provide enhanced therapeutic efficacy relative to anti-SEMA4D antibody or fragment thereof alone or the at least one other immune modulating agent alone.

2. The use of claim 1, wherein the recovered TIL have been expanded *in vitro*.

3. The use of claim 2, wherein the *in vitro* expansion comprises incubating the recovered TIL with allo-reactive feeder cells, interleukin-2 (IL-2), anti-CD3 antibody, or any combination thereof.

4. The use of claim 2 or claim 3, wherein the *in vitro* expansion enriches for cytotoxic CD8+ T cells.

5. The use of any one of claims 1 to 4, wherein the anti-SEMA4D antibody or fragment thereof and the at least one immune modulating agent are formulated for separate administration.

6. The use of any one of claims 1 to 4, wherein the anti-SEMA4D antibody or fragment thereof and the at least one immune modulating agent are formulated for concurrent administration.

7. The use of any one of claims 1 to 6, wherein the subject has elevated levels of B cells, T cells or both B cells and T cells in circulation when compared to other patients with solid tumors.

8. The use of claim 7, wherein the 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 patients with solid tumors.

9. The use of claim 7, 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 individuals.

10. The use of any one of claims 1 to 9, wherein the anti-SEMA4D antibody or fragment thereof inhibits SEMA4D interaction with its receptor.

11. The use of claim 10, wherein the receptor is Plexin-B1.

12. The use of claim 11, wherein the anti-SEMA4D antibody or fragment thereof inhibits SEMA4D-mediated Plexin-B1 signal transduction.

13. The use of any one of claims 1 to 12, wherein the anti-SEMA4D antibody or 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.

14. The use of claim 13, 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.

15. The use of any one of claims 1 to 14, wherein the solid tumor is 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, or a combination thereof.

16. The use of claim 15, wherein the solid tumor expresses Her2 and either Plexin B1 or Plexin B2.