

CANCER ASSOCIATED ANTIBODY COMPOSITIONS AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/840638, filed April 30, 2019, U.S. Provisional Application No. 62/840640, filed April 30, 2019, U.S. Provisional Application No. 62/840644, filed April 30, 2019, U.S. Provisional Application No. 62/840648, filed April 30, 2019, U.S. Provisional Application No. 62/840855, filed April 30, 2019, U.S. Provisional Application No. 62/840858, filed April 30, 2019, U.S. Provisional Application No. 62/840860, filed April 30, 2019, U.S. Provisional Application No. 62/840861, filed April 30, 2019, U.S. Provisional Application No. 62/840864, filed April 30, 2019, U.S. Provisional Application No. 62/840870, filed April 30, 2019, U.S. Provisional Application No. 62/840875, filed April 30, 2019, U.S. Provisional Application No. 62/840880, filed April 30, 2019, U.S. Provisional Application No. 62/840893, filed April 30, 2019, U.S. Provisional Application No. 62/840904, filed April 30, 2019, U.S. Provisional Application No. 62/840909, filed April 30, 2019, U.S. Provisional Application No. 62/840917, filed April 30, 2019, U.S. Provisional Application No. 62/840938, filed April 30, 2019, U.S. Provisional Application No. 62/840950, filed April 30, 2019, U.S. Provisional Application No. 62/840957, filed April 30, 2019, U.S. Provisional Application No. 62/840970, filed April 30, 2019, U.S. Provisional Application No. 62/841036, filed April 30, 2019, U.S. Provisional Application No. 62/841044, filed April 30, 2019, U.S. Provisional Application No. 62/841047, filed April 30, 2019, and U.S. Provisional Application No. 62/841049, filed April 30, 2019; each of which application is incorporated herein by reference in their entirety.

REFERENCE TO A SEQUENCE LISTING

[0002] The present application includes a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 28, 2020, is named 54407_705_601_Sequence_Listing.txt and is 4,053,188 bytes in size.

BACKGROUND OF THE INVENTION

[0003] While the role of cytotoxic T cells in mediating immune responses against cancer is well established, the role of B cells is less known. In particular, the effect of antibodies identified in cancer patients is still unclear: while some studies suggested that such antibodies might promote tumor progression, others have reported that they might stimulate anti-tumor immunity.

SUMMARY

[0004] In one aspect, the present disclosure provides an antibody or antigen-binding fragment thereof that comprises: (a) a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein: (i) the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 794, (ii) the CDR-H2 comprises a

reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1336, and (iii) the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1878; and (b) a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, wherein: (i) the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1065, (ii) the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1607, and (iii) the CDR-L3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 2149.

[0004a] In one example, provided herein is an antibody or antigen-binding fragment thereof that comprises at least one of a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein: the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 543-813, the CDR-H2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1085-1355, and the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1627-1897.

[0005] In one example provided herein is an antibody or antigen-binding fragment thereof that comprises at least one of a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2 and a CDR-L3, wherein: the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 814-1084, the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1356-1626, and the CDR-L3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1898-2168.

[0006] In one example provided herein is an antibody or antigen-binding fragment thereof that comprises: a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein: the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 543-813, the CDR-H2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1085-1355, and the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1627-1897; and a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, wherein: the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 814-1084, the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one

renal papillary cell carcinoma sarcomatoid renal cell carcinoma, chromophobe renal cell carcinoma, renal medullary carcinoma, collecting duct renal cell carcinoma, unclassified renal cell carcinoma, renal oncocytoma, angiomyolipoma, or clear cell papillary carcinoma), a liver cancer (e.g., hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma, cholangiocarcinoma, mucinous cystic neoplasm, intraductal papillary biliary neoplasm, hepatoblastoma, cholangiocellular cystadenocarcinoma, angiosarcoma, hemangioendothelioma, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcomas, teratomas, yolk sac tumours, carcinoid tumours, lymphomas, or liver metastasis), a lung cancer (e.g., non-small cell lung carcinoma, small-cell lung carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, large cell carcinoma, carcinoid tumors, bronchial gland carcinoma, carcinosarcoma, pulmonary blastoma, giant or spindle cell carcinoma, or sarcomatoid carcinoma), a mesothelioma (e.g., malignant mesothelioma, or malignant pleural mesothelioma), a cystadenocarcinoma (e.g., ovarian serous cystadenocarcinoma) an adenocarcinoma (e.g., pancreatic adenocarcinoma), a pheochromocytoma or paraganglioma, a prostate adenocarcinoma, a sarcoma, a skin cutaneous melanoma, a stomach adenocarcinoma, a testicular germ cell cancer, a thyroid carcinoma, a uterine cancer (e.g., uterine carcinosarcoma, or uterine corpus endometrial carcinoma), a uveal melanoma.

[0024] In some examples, the antibody or antigen-binding fragment thereof is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially. In some examples, the antibody or antigen-binding fragment thereof is administered to the subject in combination with a second therapeutic agent. In some examples, the second therapeutic agent comprises a cancer chemotherapeutic agent, radiation therapy, a cytotoxic agent, another antibody, a NSAID, a corticosteroid, a dietary supplement such as an antioxidant, or a combination thereof. In some examples, the anti-cancer agent is an anti-cancer antibody or a chemotherapeutic agent. In some examples, the second therapeutic agent is administered prior to, concurrently, or after administering the antibody or antigen binding fragment.

[0025] In yet another aspect, the present disclosure provides an isolated nucleic acid molecule encoding a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein: (i) the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 794, (ii) the CDR-H2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1336, and (iii) the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1878; and a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, wherein: (i) the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1065, (ii) the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1607, , and (iii) the CDR-L3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 2149.

[0025a] Provided herein is an isolated nucleic acid molecule comprising at least one of: a nucleic acid sequence encoding a CDR-H1, wherein the nucleic acid sequence is selected from SEQ ID NOs: 2711-2981; a nucleic acid sequence encoding a CDR-H2, wherein the nucleic acid sequence is selected from SEQ ID NOs: 3253-3523; a nucleic acid sequence encoding a CDR-H3, wherein the nucleic acid sequence is selected from SEQ ID NOs: 3795-4065; a nucleic acid sequence encoding a CDR-L1, wherein the nucleic acid sequence is selected from SEQ ID NOs: 2982-3252; a nucleic acid sequence encoding a CDR-L2, wherein the nucleic acid sequence is selected from SEQ ID NOs: 3524-3794; or a nucleic acid sequence encoding a CDR-L3, wherein the nucleic acid sequence is selected from SEQ ID NOs: 4066-4336.

[0026] In some examples, the nucleic acid sequence is selected from any one of SEQ ID NOs: 2169-2439.

[0027] In yet another example, provided herein is an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a light chain polypeptide of an antibody, wherein the nucleic acid sequence is selected from any one of SEQ ID NOs: 2440-2710.

[0028] In yet another aspect, provided herein is a vector comprising the isolated nucleic acid molecule as described herein.

[0029] The vector of claim 97, wherein the isolated nucleic acid is operably linked to a regulatory control sequence.

[0030] In yet another aspect, provided herein is a host cell comprising the vector described above or the isolated nucleic acid molecule described above.

[0031] In yet another aspect, provided herein is a method of producing an antibody or an antigen binding fragment thereof, the method comprising: culturing the host cell described above in a medium under conditions permitting expression of a polypeptide encoded by the isolated nucleic acid molecule and assembling of the antibody or an antigen binding fragment thereof; and purifying the antibody or antigen binding fragment thereof from the cultured cell or the medium of the cell.

[0032] Provided herein is a kit comprising a therapeutically effective amount of at least one of the antibody or antigen binding fragment thereof of any one of examples above. In some examples, the kit further comprises a therapeutically effective amount of a second therapeutic agent. In some examples, the second therapeutic agent is an anti-cancer agent, radiation therapy, a cytotoxic agent, a NSAID, a corticosteroid, a dietary supplement such as an antioxidant, or a combination thereof. In some examples, the anti-cancer agent is an anti-cancer antibody or a chemotherapeutic agent. In some examples, the antibody or antigen binding fragment thereof is in a lyophilized or an aqueous form. In some examples, the kit further comprises a reconstitution solution or a diluent.

[0033] Provided herein is an antibody or an antigen binding fragment thereof that selectively binds to R-spondin 1, transcript variant 2 (RSPO1) or a variant thereof, comprising at least one of: a variable heavy chain region, wherein the variable heavy chain region comprises a complementarity-determining region

CLAIMS

What is Claimed Is:

1. An antibody or antigen-binding fragment thereof that comprises:
 - (a) a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein:
 - (i) the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 794,
 - (ii) the CDR-H2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1336, and
 - (iii) the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1878; and
 - (b) a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, wherein:
 - (i) the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1065,
 - (ii) the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1607, and
 - (iii) the CDR-L3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 2149.
2. The antibody or antigen-binding fragment of claim 1 comprising:
 - (i) a variable heavy chain, wherein the variable heavy chain comprises a reconstructed polypeptide consensus sequence having at least 95% sequence identity to an amino acid sequence selected from any one of SEQ ID NOs: 252; and/or
 - (ii) a variable light chain, wherein the variable light chain comprises a reconstructed polypeptide consensus sequence having at least 95% sequence identity to an amino acid sequence selected from any one of SEQ ID NOs: 523.
3. The antibody or antigen-binding fragment thereof of any of claims 1-2, wherein the antibody comprises a chimeric antibody, a humanized antibody, a human antibody, a monoclonal antibody, a deimmunized antibody, a bispecific antibody, a multispecific antibody, a multivalent antibody, or a combination thereof.
4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antigen-binding fragment comprises a Fab, Fab', Fab'-SH, Fv, scFv, F(ab')₂, a diabody, a linear antibody, or a multi-specific antibody formed from antibody fragments.
5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment thereof is cytolytic to a tumor cell or a cancer cell.

6. The antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof inhibits tumor growth or cancer cell growth.
7. A fusion protein that comprises the antibody or antigen-binding fragment thereof of any one of claims 1-6.
8. An immunoconjugate comprising the antibody or the antigen binding fragment thereof of any one of claims 1-6, and a therapeutic agent.
9. A pharmaceutical composition or a medicament that comprises the antibody or antigen-binding fragment thereof of any one of claims 1-6 and a pharmaceutically acceptable carrier, excipient or diluent.
10. Use of the antibody or antigen binding fragment thereof of any one of claims 1-6 or immunoconjugate of claim 8 in the manufacture of a medicament for treating cancer.
11. An isolated nucleic acid molecule encoding

a variable heavy chain complementarity-determining region 1 (CDR-H1), a CDR-H2 and a CDR-H3, wherein:

- (i) the CDR-H1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 794,
- (ii) the CDR-H2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1336, and
- (iii) the CDR-H3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1878; and

a variable light chain complementarity-determining region 1 (CDR-L1), a CDR-L2, and a CDR-L3, wherein:

- (i) the CDR-L1 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1065,
- (ii) the CDR-L2 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 1607, and
- (iii) the CDR-L3 comprises a reconstructed polypeptide consensus sequence selected from any one of SEQ ID NOs: 2149.

12. The isolated nucleic acid molecule of claim 11, wherein the nucleic acid sequence encoding a heavy chain polypeptide of an antibody is selected from any one of SEQ ID NOs: 2420.
13. The isolated nucleic acid molecule of claim 11, wherein the nucleic acid sequence encoding a light chain polypeptide of an antibody is selected from any one of SEQ ID NOs: 2691.
14. A vector comprising the isolated nucleic acid molecule of any one of claims 11-13.
15. The vector of claim 14, wherein the isolated nucleic acid is operably linked to a regulatory control sequence.

16. A host cell comprising the vector of any one of claims 14-15 or the isolated nucleic acid molecule of any one of claims 11-13.
17. A method of producing an antibody or an antigen binding fragment thereof, the method comprising:
- (i) culturing the host cell of claim 16 in a medium under conditions permitting expression of a polypeptide encoded by the isolated nucleic acid molecule and assembling of the antibody or an antigen binding fragment thereof; and
 - (ii) purifying the antibody or antigen binding fragment thereof from the cultured cell or the medium of the cell.