(54) Title: USE OF ANTI-FAM19A5 ANTIBODIES FOR TREATING CANCERS

(57) Abstract: The present disclosure relates to the pharmaceutical use of antagonists (e.g., an antibody or antigen-binding portion thereof) that specifically bind to FAM19A5 to promote a blood vessel normalization and treat a disease (e.g., cancer) in a subject in need thereof, e.g., by promoting a blood vessel normalization.

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USE OF ANTI-FAM19A5 ANTIBODIES FOR TREATING CANCERS

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0001]   The content of the electronically submitted sequence listing in ASCII text file (Name: 3763.013PC01_SeqListing_ST25.txt; Size: 166,890 bytes; and Date of Creation: June 27, 2018) filed with the application is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002]   The present disclosure provides methods for the treatment or diagnosis of cancers in a subject (*e.g.*, a human) using antibodies that specifically bind to family with sequence similarity 19, member A5 (FAM19A5), or an antigen binding fragment thereof, or a composition comprising such antibodies or antigen binding fragment thereof.

BACKGROUND OF THE DISCLOSURE

[0003]   Angiogenesis (development and growth of blood vessels) plays an important role in many biological activity, including growth and development, as well as in wound healing. Under normal, healthy state, angiogenesis is a tightly regulated process. Carmeliet, P. and Jain, R.K., *Nature* 473(7347): 298-307 (2011). However, in cancers, defects in the control mechanisms allow for rampant angiogenesis to occur. This extensive neovasculature formation is a fundamental step in the transition of tumors from a benign to malignant state. Ferrara, N., *Nat Rev Cancer* 2(10): 795-803 (2002). The newly formed blood vessels are structurally abnormal and have increased permeability. Nagy J.A., *et al.*, *Br J Cancer* 100(6):865-869 (2009). This can cause hypoxia and the excessive accumulation of fibrous connective tissues in and around the tumor. Bottaro, D.P. and Liotta, L.A., *Nature* 423(6940):593-595 (2003); Wynn T.A., *et al.*, *Nat Med* 18(7):1028-1040 (2012). The morphological and molecular abnormalities associated with the tumor blood vessels can also contribute to the tumor's intrinsic resistance to host immune response. Ganss R., *et al.*, *Eur J Immunol* 34:2635-2641 (2004). Accordingly, therapeutic agents that can induce normalization of blood vessels can be an efficacious treatment option in many cancers, *e.g.*, when used in combination with chemoagent,

targeted therapy, immune-oncology therapy, or immune cell therapy (*e.g.*, CART, NK, Adoptive T cell therapy, *etc.*).

[0004]   Cancer immunotherapy has become well-established in recent years and is now one of the more successful treatment options available for patients with hematological malignancies and solid tumors. Scott, A.M., *et al.*, *Cancer Immun* 12:14 (2012). Despite such advances, patients with certain malignant tumors (*e.g.*, metastatic or refractory solid tumors) continue to have very poor prognosis (Rosenberg S A, *et al.*, Cancer immunotherapy in Cancer: Principles & Practice of Oncology (Eds DeVita V T, Lawrence T S and Rosenberg S A) 2011; 332-344 (Lippincott Williams & Wilkins, Philadelphia Pa.)). Only a subset of such patients actually experience long-term cancer remission, with many patients either not responding or initially responding but eventually developing resistance to the antibodies. Sharma, P., *et al.*, *Cell* 168(4): 707-723 (2017).

[0005]   Moreover, in addition to adaptive immunity, the innate immune response also plays an important role in the successful treatment of cancers. For instance, cells of the innate immune response (*e.g.*, macrophages and dendritic cells) is responsible for the phagocytic uptake of tumor antigens, the control of inflammation, and the induction of adaptive immune response by presenting the tumor antigens to the tumor-specific T cells. In many cancer patients, the innate immunity is also compromised. Currently, there are no therapeutic agents that can successfully enhance a cancer patient's innate immunity. Chanmee T., *et al.*, Cancers 6(3): 1670-1690 (2014); Gordon, S.R., *et al.*, Nature 545(7655): 495-499 (2017). Accordingly, there remains a need for more effective treatment options for many types of cancers.

BRIEF SUMMARY OF THE DISCLOSURE

[0006]   Provided herein is an antagonist against a family with sequence similarity 19, member A5 (FAM19A5) protein ("FAM19A5 antagonist") for promoting a blood vessel normalization in a tumor of a subject in need thereof.

[0007]   In some embodiments, the blood vessel normalization comprises (i) decreased blood vessel permeability, (ii) increased thickness of blood vessel wall, (iii) improved connectivity, (iv) increased blood flow rate, or (v) any combinations thereof. In some embodiments, the FAM19A5 antagonist (i) increases the number of blood vessels that extend into the tumor of the subject, (ii) increases the infiltration of an immune cell (*e.g.*,

macrophages, dendritic cells, or microglia) into the tumor of the subject, (iii) decreases the recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor of the subject, (iv) enhances the phagocytic activity and/or the mitochondrial membrane potential of an immune cell (*e.g.*, macrophages, dendritic cells, or microglia) in the tumor of the subject, or (v) any combination thereof.

[0008]   In some embodiments, the FAM19A5 antagonist is an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein ("anti-FAM19A5 antibody"), polynucleotide encoding the anti-FAM19A5 antibody, or a vector comprising the polynucleotide thereof. In certain embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 11, 12, and 13, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 23, 24, and 25, respectively. In other embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 14, 15, and 16, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 26, 27, and 28, respectively. In further embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 17, 18, and 19, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 29, 30, and 31, respectively. In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 20, 21, and 22, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 32, 33, and 34, respectively.

[0009]   Also disclosed herein is a method of *in vitro* diagnosing cancer comprising contacting an FAM19A5 antagonist with a biological sample of the subject and measuring a FAM19A5 protein level or a FAM19A5 mRNA level in the sample.

[0010]   In some embodiments, the anti-FAM19A5 antibody is a humanized antibody, a chimeric antibody, or a human antibody.

[0011]   In some embodiments, the FAM19A5 antagonist of the present disclosure is used in combination with an additional cancer agent comprising an immunotherapeutic agent,

chemotherapeutic agent, targeted therapeutic agent, or radiotherapeutic agent. In certain embodiments, the immunotherapeutic agent comprises a monoclonal antibody, chimeric antigen receptor (CAR) T-cell, NK-cell, dendritic cell (DC), adoptive cell transfer (ACT), immune checkpoint modulator, cytokine, cancer vaccine, adjuvant, oncolytic virus, or combination thereof. In some embodiments, the targeted therapeutic agent comprises tyrosine-kinase inhibitors, small molecule drug conjugates, serine-threonine kinase inhibitors, antibodies, or any combinations thereof.

[0012]   In some embodiments, the immunotherapeutic agent comprises a monoclonal antibody, which a signaling molecule selected from the group consisting of PD-1, PD-L1, CTLA-4, IDO, TIM-3, LAG-3, 4-1BB, OX40, MERTK, CD27, GITR, B7.1, TGF-β, BTLA, VISTA, Arginase, MICA, MICB, B7-H4, CD28, CD137, and HVEM. In certain embodiments, the monoclonal antibody is an anti-PD-1 antibody or an anti-PD-L1 antibody. In some embodiments, the anti-PD-1 antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD-L1 antibody is atezolizumab, durvalumab, or avelumab. In some embodiments, the monoclonal antibody increases penetration of a therapeutic agent into a tumor.

[0013]   In some embodiments, the chemotherapeutic agent comprises a drug comprising temozolomide, gemcitabine, paclitaxel, carboplatin, cisplatin, elotumumab, lenalidomide, dexamethasone, oxaliplatin, or any combination thereof.

[0014]   In some embodiments, the tumor comprises a carcinoma, sarcoma, or lymphoma. In certain embodiments, the tumor is derived from a cancer comprising melanoma, pancreatic cancer, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, ovarian cancer, or any combinations thereof.

EMBODIMENTS

[0015]   Embodiment 1. A method for treatment or amelioration of a tumor in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising an inhibitor of FAM19A5, wherein the inhibitor of FAM19A5 induces normalization of blood vessels.

[0016]   Embodiment 2. The method of Embodiment 1, wherein the inhibitor of FAM19A5 suppresses growth of the tumor.

[0017]   Embodiment 3.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 enhances infiltration of immune cells into the tumor.

[0018]   Embodiment 4.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 enhances phagocytic activity of macrophage or microglia.

[0019]   Embodiment 5.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 increases mitochondrial membrane potential of macrophages or microglia.

[0020]   Embodiment 6.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 reduces recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor.

[0021]   Embodiment 7.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 reduces necrosis and edema in the tumor.

[0022]   Embodiment 8.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 reduces tissue permeability of the tumor.

[0023]   Embodiment 9.   The method of Embodiment 1, wherein the inhibitor of FAM19A5 increases blood flow rate in the tumor.

[0024]   Embodiment 10.   The method of any one of Embodiments 1 to 9, wherein the inhibitor of FAM19A5 is selected from the group consisting of an antibody or an antigen binding portion thereof, a peptide, a nucleic acid, a compound, and any combination thereof.

[0025]   Embodiment 11.   The method of Embodiment 10, wherein the inhibitor of FAM19A5 is an antibody or an antigen binding portion thereof.

[0026]   Embodiment 12.   The method of Embodiment 11, wherein the inhibitor of FAM19A5 is a monoclonal antibody or an antigen binding portion thereof.

[0027]   Embodiment 13.   The method of any one of claims 1 to 12, wherein the tumor is selected from the group consisting of melanoma, pancreatic cancer, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, and ovarian cancer.

[0028]   Embodiment 14.   The method of Embodiment 13, wherein the tumor is melanoma.

[0029]   Embodiment 15.   The method of Embodiment 13, wherein the tumor is pancreatic cancer.

[0030]   Embodiment 16.   The method of Embodiment 13, wherein the tumor is lung cancer.

[0031]   Embodiment 17.   The method of Embodiment 1313, wherein the tumor is kidney cancer

[0032]   Embodiment 18.   The method of Embodiment 13, wherein the tumor is lymphoma.

[0033]   Embodiment 19.   The method of Embodiment 13, wherein the tumor is prostate cancer.

[0034]   Embodiment 20.   The method of Embodiment 13, wherein the tumor is adenocarcinoma.

[0035]   Embodiment 21.   The method of Embodiment 1, wherein the normalization of bleed vessels is evaluated by a marker of vascular endothelial cells.

[0036]   Embodiment 22.   The method of Embodiment 21, wherein the marker of vascular endothelial cells is selected from the group consisting of CD31, Collagen type IV, CD34, and CD146.

[0037]   Embodiment 23.   The method of Embodiment 22, wherein the marker of vascular endothelial cells is CD31.

[0038]   Embodiment 24.   The method of Embodiment 1, wherein the normalization of blood vessels is accompanied by changes in properties of the blood vessels comprising increased connectivity, increased wall thickness, reduced vessel diameter, more regular vessel direction and distribution pattern, increased vessel number, reduction of leakage and permeability, increased pericyte coverage and proximity on the vessel, increased oxygenation, or combination thereof.

[0039]   Embodiment 25.   The method of Embodiment 2, wherein the suppression of the growth of the tumor is evaluated by measuring a parameter selected from the group consisting of tumor mass, tumor volume, tumor size, tumor cell number, number of staining spots, and combination thereof.

[0040]   Embodiment 26.   The method of Embodiment 3, wherein the immune cells displaying increased infiltration into the tumor are selected from the group consisting of macrophages, dendritic cells, T lymphocytes, B lymphocytes, and natural killer (NK) cells.

[0041]   Embodiment 27.   The method of Embodiment 26, wherein the immune cells further display hypertrophy.

[0042]   Embodiment 28. The method of Embodiment 3, wherein the increased infiltration of immune cells into the tumor is further accompanied by increased infiltration of neuronal and stromal cells into the tumor.

[0043]   Embodiment 29.   The method of Embodiment 28, wherein the neuronal cells displaying increased infiltration into the tumor is selected from the group consisting of astrocytes and glial cells.

[0044]   Embodiment 30.   The method of Embodiment 1, wherein the pharmaceutical composition is administered in combination with a cancer therapy.

[0045]   Embodiment 31.   The method of Embodiment 1, wherein the pharmaceutical composition is administered in combination with a method selected from the group consisting of immunotherapy, chemotherapy, and radiotherapy.

[0046]   Embodiment 32.   The method of Embodiment 31, wherein the pharmaceutical composition is administered in combination with immunotherapy.

[0047]   Embodiment 33.   The method of Embodiment 32, wherein the immunotherapy comprises a monoclonal antibody, chimeric antigen receptor (CAR) T-cell, NK-cell, dendritic cell (DC), adoptive cell transfer (ACT), immune checkpoint modulator, cytokine, cancer vaccine, adjuvant, oncolytic virus, or combination thereof.

[0048]   Embodiment 34.   The method of Embodiment 33, wherein the monoclonal antibody modulates a signaling molecule selected from the group consisting of PD-1, PD-L1, CTLA-4, IDO, TIM-3, LAG-3, 4-1BB, OX40, MERTK, CD27, GITR, B7.1, TGF-β, BTLA, VISTA, Arginase, MICA, MICB, B7-H4, CD28, CD137, and HVEM.

[0049]   Embodiment 35.   The method of Embodiment 34, wherein the monoclonal antibody inhibits a signaling molecule selected from the group consisting of PD-1, PD-L1, CTLA-4, IDO, TIM-3, LAG-3, 4-1BB, OX40, MERTK, and CD27.

[0050]   Embodiment 36.   The method of Embodiment 35, wherein the monoclonal antibody inhibits PD-1.

[0051]   Embodiment 37.   The method of Embodiment 36, wherein the monoclonal antibody inhibiting PD-1 is selected from the group consisting of pembrolizumab and nivolumab.

[0052]   Embodiment 38.   The method of Embodiment 35, wherein the monoclonal antibody inhibits PD-L1.

[0053]   Embodiment 39.   The method of Embodiment 38, wherein the monoclonal antibody inhibiting PD-L1 is selected from the group consisting of atezolizumab, avelumab, and durvalumab.

[0054]   Embodiment 40.   The method of Embodiment 35, wherein the monoclonal antibody inhibits CTLA-4.

[0055]   Embodiment 41.   The method of Embodiment 40, wherein the monoclonal antibody inhibiting CTLA-4 is ipilimumab.

[0056]   Embodiment 42.   The method of Embodiment 31, wherein the pharmaceutical composition is administered in combination with chemotherapy.

[0057]   Embodiment 43.   The method of Embodiment 42, wherein the chemotherapy comprises a drug selected from the group consisting of temozolomide, gemcitabine, paclitaxel, carboplatin, cisplatin, elotumumab, lenalidomide, dexamethasone, and oxaliplatin.

[0058]   Embodiment 44.   The method of Embodiment 43, wherein the chemotherapy comprises gemcitabine.

[0059]   Embodiment 45.   The method of Embodiment 1, wherein the pharmaceutical composition is administered by a route selected from the group consisting of intradermal, subcutaneous, intravenous, intramuscular, and intrathecal.

[0060]   Embodiment 46.   The method of Embodiment 1, wherein the subject's response, or potential response, to treatment or amelioration of the tumor is assessed by the method comprising:

obtaining a sample from the subject;

detecting expression of FAM19A5 gene in the sample; and

based at least in part on the detection of the expression of FAM19A5 gene, assessing the subject's response, or potential response, to the treatment or amelioration of the tumor.

[0061]   Embodiment 47.   The method of any one of Embodiments 1 to 46 wherein the inhibitor of FAM19A5 cross-competes for binding to a human FAM19A5 epitope with a reference antibody comprising heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3,

(i)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 11, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 12, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 13, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 23, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 24, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 25;

(ii)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 28;

(iii)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 17, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 18, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 19, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 29, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 30, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 31; or

(iv)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 20, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 21, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 22, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 32, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 33, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 34.

[0062]   Embodiment 48. The method of any one of Embodiments 1 to 47, wherein the inhibitor of FAM19A5 binds to the same FAM19A5 epitope as a reference antibody comprising heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3,

(i)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 11, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 12, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 13, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 23, the light chain CDR2

comprises the amino acid sequence of SEQ ID NO: 24, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 25;

(ii)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 28;

(iii)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 17, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 18, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 19, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 29, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 30, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 31; or

(iv)   wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 20, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 21, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 22, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 32, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 33, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 34.

[0063]   Embodiment 49.   The method of Embodiment 48, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof binds to at least one FAM19A5 epitope, which is SEQ ID NO: 6 or SEQ ID NO: 9.

[0064]   Embodiment 50.   The method of Embodiment 48, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof binds only to an FAM19A5 epitope, which is SEQ ID NO: 6 or SEQ ID NO: 9.

[0065]   Embodiment 51.   The method of any one of Embodiments 48 to 50, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof further binds to an additional FAM19A5 epitope.

[0066]   Embodiment 52.   The method of Embodiment 51, wherein the additional FAM19A5 epitope is selected from the group consisting of SEQ ID NO: 5, SEQ ID NO:

6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, and any combination thereof.

[0067]   Embodiment 53. The method of any one of Embodiments 47 to 52, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR3 of the anti-FAM19A5 antibody or antigen-binding portion thereof comprises the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22.

[0068]   Embodiment 54. The method of Embodiment 53, wherein the heavy chain CDR1 of the anti-FAM19A5 antibody or antigen-binding portion thereof comprises the amino acid sequence of SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 17, or SEQ ID NO: 20.

[0069]   Embodiment 55. The method of Embodiment 53 or 54, wherein the heavy chain CDR2 of the anti-FAM19A5 antibody or antigen-binding portion thereof comprises the amino acid sequence of SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 18, or SEQ ID NO: 21.

[0070]   Embodiment 56. The method of any one of Embodiments 53 to 55, wherein the light chain CDR1 of the anti-FAM19A5 antibody or antigen-binding portion thereof comprises the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 26, SEQ ID NO: 29, or SEQ ID NO: 32.

[0071]   Embodiment 57. The method of any one of Embodiments 53 to 56, wherein the light chain CDR2 of the anti-FAM19A5 antibody or antigen binding portion thereof comprises the amino acid sequence of SEQ ID NO: 24, SEQ ID NO: 27, SEQ ID NO: 30, or SEQ ID NO: 33.

[0072]   Embodiment 58. The method of any one of Embodiments 53 to 57, wherein the light chain CDR3 of the anti-FAM19A5 antibody or antigen binding portion thereof comprises the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 28, SEQ ID NO: 31, or SEQ ID NO: 34.

[0073]   Embodiment 59. The method of any one of Embodiments 47 to 52, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein

(i)   the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 11, 12, and 13, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 23, 24, and 25, respectively;

(ii)   the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 14, 15, and 16, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 26, 27, and 28, respectively;

(iii)   the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 17, 18, and 19, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 29, 30, and 31, respectively; or

(iv)   the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 20, 21, and 22, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 32, 33, and 34, respectively.

[0074]   Embodiment 60. The method of any one of Embodiments 47 to 59, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NO: 35, 36, 37, or 38.

[0075]   Embodiment 61. The method of any one of Embodiments 47 to 60, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NO: 39, 40, 41, or 42.

[0076]   Embodiment 62. The method of any one of Embodiments 47 to 61, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

SEQ ID NO: 35, 36, 37, or 38; and wherein the light chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NO: 39, 40, 41, or 42.

[0077]   Embodiment 63. The method of any one of Embodiments 47 to 62, wherein the anti-FAM19A5 antibody is a chimeric antibody, a human antibody, or a humanized antibody.

[0078]   Embodiment 64. The method of any one of Embodiments 47 to 63, wherein the antigen-binding portion thereof is an Fab, an Fab', an F(ab')2, an Fv, or a single chain Fv (scFv).

[0079]   Embodiment 65. The method of any one of Embodiments 47 to 63, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, or a variant thereof.

[0080]   Embodiment 66. The method of Embodiment 65, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof is an IgG2, an IgG4, or a combination thereof.

[0081]   Embodiment 67. The method of Embodiment 65, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof comprises an IgG2/IgG4 isotype antibody.

[0082]   Embodiment 68. The method of any one of Embodiments 47 to 67, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof further comprising a constant region without the Fc function.

[0083]   Embodiment 69. The method of any one of Embodiments 47 to 48, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof is linked to a molecule having a second binding moiety, thereby forming a bispecific molecule.

[0084]   Embodiment 70. The method of any of Embodiments 47 to 49, wherein the anti-FAM19A5 antibody or antigen-binding portion thereof is linked to an agent, thereby forming an immunoconjugate.

[0085]   Embodiment 71. The method of any one of Embodiments 1 to 70, wherein the antagonist of the FAM19A5 protein is formulated with a pharmaceutically acceptable carrier.

[0086]   Embodiment 72. The method of any one of Embodiments 1 to 71, wherein the antagonist of the FAM19A5 protein is administered intravenously, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, intramuscularly, subcutaneously, intravitreally, or intraventricularly.

[0087]   Embodiment 73. The method of any one of Embodiments 1 to 72, wherein the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0088]   FIG. 1 show the immunohistochemistry analysis of the FAM19A5 protein expression in liver biopsies from three different liver cancer patients. As indicated, each of the patients had varying degree of fibrosis: (i) stage #0 (left column), (ii) stage #2 (middle column), and (iii) stage #4 (right column). The bottom row shows a higher magnification of the boxed region from the top row. The arrows indicate examples of FAM19A5-positive hepatic stellate cells.

[0089]   FIG. 2A shows the body weight (grams) of the animals as a function of time (weeks post inoculation). Some of the animals were inoculated with Hep3B cells alone and treated with either normal human immunoglobulin (circle, Group 1: "Hep3B + NHI", n = 3) or anti-FAM19A5 antibody (closed box, Group 2: "Hep3B + FAM19A5 Ab", n = 3). Other animals were inoculated with both Hep3B cells and human hepatic stellate cells (HHSteC) and treated with either normal human immunoglobulin (diamond, Group 3: "Hep3B+HHSteC + NHI", n = 3) or anti-FAM19A5 antibody (open box, Group 4: "Hep3B+HHSteC + FAM19A5 Ab", n = 3). Data are expressed as mean ± S.D.

[0090]   FIG. 2B shows the mean tumor volume observed in animals from the different groups as a function of time (weeks post inoculation). The groups shown are the same as those described in FIG. 2A, above. Tumor volume was calculated with the following equation: $0.5 \times \text{length} \times \text{width}^2 = \text{tumor volume (mm}^3)$. Data are expressed as mean ± S.D.

[0091]   FIGs 2C and 2D show a photographic image and the weight (grams), respectively, of the tumors isolated from the animals as described in FIG. 2A at 42 days post inoculation. In FIG. 2C, (i) the top left shows the tumors from the "Hep3B + NHI" group (n = 2); (ii) the top right shows the tumors from the "Hep3B+HHSteC + NHI" group (n = 2); (iii) the bottom left shows the tumors from the "Hep3B + FAM19A5 Ab" group (n =

3); and (iv) the bottom right shows the tumors from the "Hep3B+HHSteC + FAM19A5 Ab" group (n = 3). FIG. 2D shows the average weight (g) of the tumors isolated from the different groups.

[0092]   FIGs. 3A, 3B, and 3C show the anticancer effect of anti-FAM19A5 antibody in a melanoma tumor model. FIG. 3A provides a diagram showing the antibody administration schedule. FIG. 3B provides a comparison of the tumor volume (mm^3) in animals treated with either human IgG (black bar) or an anti-FAM19A5 antibody (gray bar), at different time points post birth. Day 56 post birth corresponds to the beginning of the antibody treatment (*i.e.*, week 8). FIG. 3C provides a comparison of the Braf^{V600E}-induced pigmented lesions in animals treated with either human IgG (left image) or the anti-FAM19A5 antibody (right image).

[0093]   FIG. 4 shows the distribution pattern of blood vessels (based on CD31 expression) in melanoma from animals treated with either the human IgG antibody (top image) or the anti-FAM19A5 antibody (bottom image). The arrow to the right of the images indicates the orientation of the tissue sample, with the epidermis at the top and the subcutaneous tissue toward the bottom.

[0094]   FIG. 5 show the distribution pattern of both blood vessels (based on CD31 expression) and macrophages (based on Iba1 expression) in melanoma from animals treated with either the human IgG antibody (top image) or the anti-FAM19A5 antibody (bottom image). The left column shows the CD31 expression alone. The middle column shows the Iba1 expression alone. The right column shows both the CD31 and Iba1 expression. The arrow to the right of the images indicates the orientation of the tissue sample, with the epidermis at the top and the subcutaneous tissue toward the bottom.

[0095]   FIGs. 6A, 6B, 6C, and 6D show the effect of anti-FAM19A5 antibody on the infiltration of macrophages and dendritic cells into tumors in a mouse melanoma model. FIG. 6A shows the distribution pattern of macrophages and dendritic cells (based on Iba1 and CD45 expression) in the melanoma of animals treated with the control (human IgG) antibody (left column) or the anti-FAM19A5 antibody (right column). Bottom images are magnified version of a representative region shown at the top row. FIG. 6B provides a comparison of the frequency of macrophages (shown as % Iba1$^+$ of total CD45+ cells within the melanoma) detected in the melanoma of animals treated with control human IgG antibody (white bar) or anti-FAM19A5 antibody (black bar). FIG. 6C provides a

comparison of the cellular volume of the macrophages (based on Voxel count) observed in the melanoma of animals treated with control human IgG antibody (white bar) or anti-FAM19A5 antibody (black bar). FIG. 6D shows a table providing the number of macrophages observed in a representative region of the melanoma isolated from the animals from the different groups.

[0096]   FIGs. 7A and 7B show the effect of anti-FAM19A5 antibody on the infiltration of T lymphocytes (based on CD3 and CD45 expression) into tumors in a mouse melanoma model. FIG. 7A shows immunohistochemical analysis of the T lymphocyte distribution. FIG. 7B shows a table providing the number of T lymphocytes observed in a representative region of the melanoma isolated from animals treated with either the control human IgG antibody or the anti-FAM19A5 antibody.

[0097]   FIGs. 8A and 8B show the effect of anti-FAM19A5 antibody on the infiltration of T lymphocytes (FIG. 8A) and myeloid-derived suppressor cells (FIG. 8B) into tumors in a mouse syngenic colon adenocarcinoma model. The animals were treated with either the control human IgG antibody ("Control") or the anti-FAM19A5 antibody ("FAM19A5Ab"). In FIG. 8A, the population of T lymphocytes is shown as percent CD3+ cells of total cells analyzed. Similarly, in FIG. 8B, the population of myeloid-derived suppressor cells is shown as percent Ly6G+ cells of total cells analyzed. Data are expressed as mean ± S.D.

[0098]   FIG. 9A shows both the experimental groups and the administration schedule for assessing the anticancer effect of anti-FAM19A5 antibody in a human pancreatic cancer xenograft animal model. Upon tumor inoculation, the animals received either the human IgG control antibody or the anti-FAM19A5 antibody, alone or in combination with gemcitabine. The control and anti-FAM19A5 antibodies were administered at days 10, 17, and 24 post tumor induction (dashed arrows). In animals that received gemcitabine, it was administered at days 12, 15, 19, 22, 26, and 29 post tumor induction (solid black arrows).

[0099]   FIGs. 9B and 9C compare the tumor weight (g) (FIG. 9B) and the relative collagen content (%) (FIG. 9C) in the human pancreatic cancer xenograft animal model treated with (i) human IgG antibody (hIgG), (ii) anti-FAM19A5 antibody (FAM19A5 Ab), (iii) gemcitabine (GEM), or (iv) anti-FAM19A5 antibody with gemcitabine (FAM19A5 Ab + GEM). In both FIGs. 9B and 9C, the data are shown as mean ± S.D.

[0100]   FIGs. 10A and 10B show the anti-tumor effects of anti-FAM19A5 antibody in a melanoma mouse model. FIG. 10A provides both the antibody administration schedule and the experimental groups. Upon tumor inoculation, the animals were treated with the following: (1) control human and rat IgG antibodies, (2) anti-FAM19A5 antibody + rat IgG antibody, (3) anti-PD-1 antibody + human IgG antibody, and (4) anti-PD-1 antibody + anti-FAM19A5 antibody. The anti-FAM19A5 antibody and the human IgG antibody were administered to the relevant animals at days 7 and 14 post tumor inoculation. The anti-PD-1 antibody and the rat IgG antibody were administered to the relevant animals at days 10 and 12 post tumor inoculation. FIG. 10B compares the anti-tumor efficacy in the different treatment groups: (i) anti-PD-1 antibody + human IgG antibody ("G3", group 3), (ii) anti-FAM19A5 antibody + rat IgG antibody ("G2", group 2), and (iii) anti-PD-1 antibody + anti-FAM19A5 antibody ("G4", group 4). The anti-tumor efficacy is shown as percent inhibition of tumor growth relative to the control group, *i.e.*, Group 1. The data are shown as mean ± S.D.

[0101]   FIG. 11 shows the tumor volume in pancreatic cancer animals treated with anti-FAM19A5 antibody, alone or in combination with anti-PD-1 antibody. The different treatment groups included: (i) human IgG antibody + mouse IgG antibody (G1); (ii) anti-FAM19A5 antibody + mouse IgG antibody (G2); (iii) human IgG antibody + mouse anti-PD-1 antibody (G3); and (iv) anti-FAM19A5 antibody + mouse anti-PD-1 antibody.

[0102]   FIGs. 12A and 12B show the effect of anti-FAM19A5 antibody on the phagocytic ability and/or membrane potential of different immune cells. FIG. 12A shows the percentage of Raw 264.7 cells (mouse macrophages) that were phagocytic after stimulation with LPS alone or LPS with anti-FAM19A5 antibody. Raw 264.7 cells treated with human IgG antibody or cytochalasin D were used as negative and positive controls, respectively. FIG. 12B shows the effect of anti-FAM19A5 on both the phagocytic ability (gray bars) and membrane potential (striped bars) of BV-2 cells (mouse microglia). The BV-2 cells treated with human IgG antibody or FAM19A5 protein were used as controls. The phagocytic and membrane potential data are shown as percent of the control.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0103]   The present disclosure shows that cancer can be controlled, treated, ameliorated, or reduced by administration of an anti-FAM19A5 antagonist, *e.g.*, an anti-FAM19A5

antibody. Not being bound by any theory, one possible mechanism of the efficacy can be due to the normalization of blood vessels induced by anti-FAM19A5 antagonists (also referred to as inhibitors). The FAM19A5 antagonists can thus suppress growth of the tumor, enhance infiltration of immune cells into the tumor, enhance phagocytic activity of macrophage or microglia, increase mitochondrial membrane potential of macrophages or microglia, reduce recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor, reduce necrosis and edema in the tumor, reduce tissue permeability of the tumor, and/or increase blood flow rate in the tumor.

[0104]   To facilitate an understanding of the disclosure disclosed herein, a number of terms and phrases are defined. Additional definitions are set forth throughout the detailed description.

I.   Definitions

[0105]   Throughout this disclosure, the term "a" or "an" entity refers to one or more of that entity; for example, "an antibody," is understood to represent one or more antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0106]   Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0107]   It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0108]   Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And

Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0109]   Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0110]   The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, *e.g.*, 10 percent, up or down (higher or lower).

[0111]   The terms "treat," "treating," and "treatment," as used herein, refer to any type of intervention or process performed on, or administering an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down or preventing the progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease. Treatment can be of a subject having a disease or a subject who does not have a disease (*e.g.*, for prophylaxis).

[0112]   As used herein, "administering" refers to the physical introduction of a therapeutic agent or a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. The different routes of administration for antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, intratracheal, pulmonary, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid,

intraventricle, intravitreal, epidural, and intrasternal injection and infusion, as well as *in vivo* electroporation. Alternatively, an antibody described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0113]   The term "therapeutically effective amount" as used herein refers to an amount of a drug, alone or in combination with another therapeutic agent, effective to "treat" a disease or disorder in a subject or reduce the risk, potential, possibility or occurrence of a disease or disorder (*e.g.*, a cancer). A "therapeutically effective amount" includes an amount of a drug or a therapeutic agent that provides some improvement or benefit to a subject having or at risk of having a disease or disorder (*e.g.*, a cancer disclosed herein). Thus, a "therapeutically effective" amount is an amount that reduces the risk, potential, possibility or occurrence of a disease or provides disorder or some alleviation, mitigation, and/or reduces at least one indicator (*e.g.*, cancer), and/or decrease in at least one clinical symptom of a disease or disorder.

[0114]   As used herein, the term "cancer" refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. A "cancer" or "cancer tissue" can include a tumor. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream. Following metastasis, the distal tumors can be said to be "derived from" the pre-metastasis tumor. For example, a "tumor derived from" a melanoma refers to a tumor that is the result of a metastasized melanoma. Because the distal tumor is derived from the pre-metastasis tumor, the "derived from" tumor can also comprise the pre-metastasis tumor, *e.g.*, a tumor derived from a melanoma can comprise a melanoma. As used herein, the term "cancer" excludes brain cancer (*e.g.*, glioma or glioblastoma.)

[0115]   An "immune response" is as understood in the art, and generally refers to a biological response within a vertebrate against foreign agents or abnormal, *e.g.*, cancerous cells, which response protects the organism against these agents and diseases caused by them. An immune response is mediated by the action of one or more cells of the immune system (for example, a T lymphocyte, B lymphocyte, natural killer (NK) cell,

macrophage, eosinophil, mast cell, dendritic cell or neutrophil) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from the vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues. An immune reaction includes, *e.g.*, activation or inhibition of a T cell, *e.g.*, an effector T cell, a Th cell, a CD4+ cell, a CD8+ T cell, or a Treg cell, or activation or inhibition of any other cell of the immune system, *e.g.*, NK cell.

[0116]   An "immunomodulator" or "immunoregulator" refers to an agent, *e.g.*, an agent targeting a component of a signaling pathway that can be involved in modulating, regulating, or modifying an immune response. "Modulating," "regulating," or "modifying" an immune response refers to any alteration in a cell of the immune system or in the activity of such cell (*e.g.*, an effector T cell, such as a Th1 cell). Such modulation includes stimulation or suppression of the immune system which can be manifested by an increase or decrease in the number of various cell types, an increase or decrease in the activity of these cells, or any other changes which can occur within the immune system. Both inhibitory and stimulatory immunomodulators have been identified, some of which can have enhanced function in a tumor microenvironment. In some embodiments, the immunomodulator targets a molecule on the surface of a T cell. An "immunomodulatory target" or "immunoregulatory target" is a molecule, *e.g.*, a cell surface molecule, that is targeted for binding by, and whose activity is altered by the binding of, a substance, agent, moiety, compound or molecule. Immunomodulatory targets include, for example, receptors on the surface of a cell ("immunomodulatory receptors") and receptor ligands ("immunomodulatory ligands").

[0117]   "Immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying the immune system or an immune response.

[0118]   As used herein, the phrase "inhibits growth of a tumor" includes any measurable decrease in the growth of a tumor, *e.g.*, , the inhibition of growth of a tumor by at least about 10%, for example, at least about 20%, at least about 30%, at least about 40%, at

least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 99%, or 100%.

[0119]   The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve a desired effect. A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A therapeutically effective amount or dosage of a drug includes a "prophylactically effective amount" or a "prophylactically effective dosage", which is any amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic agent to promote disease regression or inhibit the development or recurrence of the disease can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0120]   By way of example, an anti-cancer agent is a drug that promotes cancer regression in a subject. In some embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. "Promoting cancer regression" means that administering an effective amount of the drug, alone or in combination with an antineoplastic agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, a prevention of impairment or disability due to the disease affliction, or otherwise amelioration of disease symptoms in the patient. In addition, the terms "effective" and "effectiveness" with regard to a treatment includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

[0121]   By way of example, for the treatment of tumors, a therapeutically effective amount or dosage of the drug inhibits cell growth or tumor growth by at least about 20%, by at least about 40%, by at least about 60%, or by at least about 80% relative to untreated subjects. In some embodiments, a therapeutically effective amount or dosage of the drug completely inhibits cell growth or tumor growth, *i.e.,* inhibits cell growth or tumor growth by 100%. The ability of a compound to inhibit tumor growth can be evaluated using the assays described infra. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit cell growth, such inhibition can be measured *in vitro* by assays known to the skilled practitioner. In other embodiments described herein, tumor regression can be observed and continue for a period of at least about 20 days, at least about 40 days, or at least about 60 days.

[0122]   Some aspect of the present disclosure relates to the diagnosis of cancer in a subject in need thereof. In connection with the current disclosure, Applicant has found that upon damage to a tissue or an organ there is an increase in FAM19A5 expression both at the site of damage and in the peripheral blood of a subject with cancer. Accordingly, in some embodiments, the present disclosure provides a method of diagnosing a cancer in a subject in need thereof comprising contacting the monoclonal antibody or antigen-binding portion thereof, the bispecific molecule, or the immunoconjugate, disclosed herein, with a sample obtained from the subject and measuring the FAM19A5 expression level. In some embodiments, the level of FAM19A5 is increased in the sample of the subject as compared to the level of FAM19A5 in a reference sample of a subject without the cancer. *See infra.*

[0123]   The term "diagnosis" as used herein refers to methods that can be used to determine or predict whether a patient is suffering from a given disease or condition. A skilled artisan can make a diagnosis on the basis of one or more diagnostic marker (*e.g.,* FAM19A5), where the presence, absence, amount, or change in amount of the diagnostic marker is indicative of the presence, severity, or absence of the condition. In some embodiments, an increase in FAM19A5 expression, in a biological sample from a subject, is indicative of tumor. The term "diagnosis" does not refer to the ability to determine the presence or absence of a particular disease with 100% accuracy, or even that a given course or outcome is more likely to occur than not. Instead, the skilled artisan will

understand that the term "diagnosis" refers to an increased probability that a certain disease is present in the subject.

[0124]   The term "diagnostic marker" (*e.g.*, FAM19A5 expression) refers to a material capable of separately diagnosing tumors from normal cells, and includes organic bio-molecules such as polypeptides, or nucleic acids (for example, mRNA), lipids, glycolipids, glycoproteins, and sugars (monosaccharides, disaccharides, oligosaccharides, and the like) which increase or decrease in cells of tumors. The diagnostic marker provided in the present disclosure for cancer can be a protein that is expressed from FAM19A5 genes of which the expression increases in cells of tumors.

[0125]   The composition for diagnosing cancer includes an agent for measuring the expression level of mRNA of FAM19A5 genes or the amount of protein expressed. Such agents include oligonucleotides having a sequence complementary to FAM19A5 mRNA, a primer or a nucleic acid probe that specifically binds to FAM19A5 mRNA, and antibodies that specifically bind to the FAM19A5 protein.

[0126]   As used herein, the term "subject" includes any human or non-human animal. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

[0127]   The term "family with sequence similarity 19, member A5" or "FAM19A5" refers to a protein that belongs to the TAFA family (also known as FAM19 family) of five highly homologous proteins and is predominantly expressed in brain and the spinal cord. Tang T. Y. *et al.*, *Genomics* 83(4):727-34 (2004). These proteins contain conserved cysteine residues at fixed positions, and are distantly related to macrophage inflammatory protein 1-alpha (MIP-1-alpha), a member of the CC-chemokine family. The TAFA proteins are predominantly expressed in specific regions of the brain and the spinal cord. These proteins are believed to be generated and secreted by adult neural stem cells in neurogenesis processes. FAM19A5 is also known as TAFA5 or Chemokine-like protein TAFA-5.

[0128]   FAM19A5 is predominantly expressed in the brain of vertebrates and it is believed that FAM19A5 is important in for the development, differentiation, formation of a complete central nervous system. FAM19A5 also plays a significant role in the pathogenesis of many central nervous system damage and/or degenerative brain diseases (*e.g.*, Huntington's disease, Parkinson's disease, Alzheimer's disease, cerebrospinal

damage, strokes, and brain tumors). Upon damage to the central nervous system, neural stem cells produce FAM19A5, which induces the differentiation of normal astrocytes into reactive astrocytes. These reactive astrocytes (along with microglia) can express a wide array of ECMs (*e.g.*, proteoglycans, glycoproteins, and collagen) and induce the formation of glial scars, which can surround the damaged region of the central nervous system like a net and prevent the regeneration of the neurons. Antibodies against FAM19A5 can be used in the prevention and/or treatment of central nervous system injuries and/or diseases. *See* U.S. Patent No. 9,579,398.

[0129]   In humans, the gene encoding FAM19A5 is located on chromosome 22. There are three human FAM19A5 (UniProt: Q7Z5A7) isoforms, which are believed to be produced by alternative splicing: isoform 1 (UniProt: Q7Z5A7-1), which consists of 132 amino acids; isoform 2 (UniProt: Q7Z5A7-2), which consists of 125 amino acids; and isoform 3 (UniProt: Q7Z5A7-3), which consists of 53 amino acids. Human FAM19A5 protein is believed to exist as both membrane bound and soluble (secreted) forms. Isoform 1 is believed to be a membrane protein with one transmembrane region. Isoform 2, which was reported in Tang T. Y. *et al.*, *Genomics* 83(4):727-34 (2004) as a secreted protein (soluble), contains a signal peptide at amino acid positions 1-25. Isoform 3 is predicted based on EST data. Below are the amino acid sequences of the three known human FAM19A5 isoforms.

(I)   Isoform 1 (UniProt: Q7Z5A7-1, transmembrane protein): this isoform has been chosen as the canonical sequence.

MAPSPRTGSRQDATALPSMSSTFWAFMILASLLIAYCSQLAAGTCEIVTLDRDSSQPRRT
IARQTARCACRKGQIAGTTRARPACVDARIIKTKQWCDMLPCLEGEGCDLLINRSGWTCT
QPGGRIKTTTVS (SEQ ID NO: 1)

(II)   Isoform 2 (UniProt: Q7Z5A7-2, soluble protein):

MQLLKALWALAGAALCCFLVLVIHAQFLKEGQLAAGTCEIVTLDRDSSQPRRTIARQTAR
CACRKGQIAGTTRARPACVDARIIKTKQWCDMLPCLEGEGCDLLINRSGWTCTQPGGRIK
TTTVS (SEQ ID NO: 2)

(III)   Isoform 3 (UniProt: Q7Z5A7-3):

MYHHREWPARIIKTKQWCDMLPCLEGEGCDLLINRSGWTCTQPGGRIKTTTVS (SEQ ID
NO: 3)

[0130]   The term "FAM19A5" includes any variants or isoforms of FAM19A5 which are naturally expressed by cells. Accordingly, antibodies described herein can cross-react with different isoforms in the same species (*e.g.*, different isoforms of human FAM19A5), or cross-react with FAM19A5 from species other than human (*e.g.*, mouse FAM19A5). Alternatively, the antibodies can be specific for human FAM19A5 and cannot exhibit any cross-reactivity with other species. FAM19A5, or any variants and isoforms thereof, can either be isolated from cells or tissues which naturally express them or be recombinantly produced. The polynucleotide encoding human FAM19A5 has the GenBank Accession No. BC039396 and the following sequence:

Table 1A. Polynucleotide sequence of human FAM19A5

	Polynucleotide sequence (SEQ ID NO: 4)				
FAM19A5 (GenBank Accession No. BC039396)	ggcggcggag	gatggcgcgc	gcggggcccg	cacgtggagg	ccggcgcggg
	ggcgcgggca	gggccggctg	ctgagacgcg	ctgctgcccc	ccgcgcgggc
	gccgcggctt	caatggcgcc	atcgcccagg	accggcagcc	ggcaagatgc
	gaccgccctg	cccagcatgt	cctcaacttt	ctgggcgttc	atgatcctgg
	ccagcctgct	catcgcctac	tgcagtcagc	tggccgccgg	cacctgtgag
	attgtgacct	tggaccggga	cagcagccag	cctcggagga	cgatcgcccg
	gcagaccgcc	cgctgtgcgt	gtagaaaggg	gcagatcgcc	ggcaccacga
	gagcccggcc	cgcctgtgtg	gacgcaagaa	tcatcaagac	caagcagtgg
	tgtgacatgc	ttccgtgtct	ggaggggggaa	ggctgcgact	tgttaatcaa
	ccggtcaggc	tggacgtgca	cgcagccgg	cgggaggata	aagaccacca
	cggtctcctg	acaaacacag	cccctgaggg	ggccccggga	gtggccttgg
	ctccctggag	agcccacgtc	tcagccacag	ttctccactc	gcctcggact
	tcacccgttc	tctgccgccc	gcccactccg	tttccctgtg	gtccgtgaag
	gacggcctca	ggccttggca	tcctgagctt	cggtctgtcc	agccgacccg
	aggaggccgg	actcagacac	ataggcgggg	ggcggcacct	ggcatcagca
	atacgcagtc	tgtgggagcc	cggccgcgcc	cagcccccgc	cgaccgtggc
	gttggccctg	ctgtcctcag	aggaggagga	ggaggaggca	gctccggcag
	ccacagaagg	ctgcagccca	gcccgcctga	gacgacgc	ctgccccagg
	ggactgtcag	gcacagaagc	ggcctcctcc	cgtgccccag	actgtccgaa
	ttgcttttat	tttcttatac	tttcagtata	ctccatagac	caaagagcaa
	aatctatctg	aacctggacg	caccctcact	gtcagggtcc	ctggggtcgc
	ttgtgcgggc	gggagggcaa	tggtggcaga	gacatgctgg	tggccccggc
	ggagcggaga	gggcggccgt	ggtggaggcc	tccaccccag	gagcaccccg
	cacaccctcg	gaggacgggc	ttcggctgcg	cggaggccgt	ggcacacctg
	cgggaggcag	cgacggcccc	cacgcagacg	ccgggaacgc	aggccgcttt

	attcctctgt	acttagatca	acttgaccgt	actaaaatcc	ctttctgttt
	taaccagtta	aacatgcctc	ttctacagct	ccatttttga	tagttggata
	atccagtatc	tgccaagagc	atgttgggtc	tcccgtgact	gctgcctcat
	cgataccc a	tttagctcca	gaaagcaaag	aaaactcgag	taacacttgt
	ttgaaagaga a	tcattaaatg	tattttgcaa	agcccaaaaa	aaaaaaaaaa

[0131]   The term "antagonist against a FAM19A5 protein" refers to all antagonists that suppress the expression of the FAM19A5 protein. Such antagonist can be a peptide, nucleic acid, or a compound. More specifically, the antagonist can be an antisense-oligonucleotide, siRNA, shRNA, miRNA, dsRNA, aptamer, PNA (peptide nucleic acid) targeting FAM19A5, or a vector including the same. In some embodiments, the antagonist can be an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein.

[0132]   The terms "antibody" and "antibodies" are terms of art and can be used interchangeably herein and refer to a molecule with an antigen binding site that specifically binds an antigen. The terms as used to herein include whole antibodies and any antigen binding fragments (*i.e.*, "antigen-binding portions") or single chains thereof. An "antibody" refers, in one embodiment, to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. In another embodiment, an "antibody" refers to a single chain antibody comprising a single variable domain, *e.g.*, VHH domain. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. In certain naturally-occurring antibodies, the heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. In certain naturally-occurring antibodies, each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL.

[0133]   The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with

an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0134]   The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding portion thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (*see, e.g.*, Kabat EA & Wu TT (1971) *Ann NY Acad Sci* 190: 382-391 and Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[0135]   The phrases "amino acid position numbering as in Kabat," "Kabat position," and grammatical variants thereof refer to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991). Using this numbering system, the actual linear amino acid sequence can contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FW or CDR of the variable domain. For example, a heavy chain variable domain can include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy chain FW residue 82. *See* TABLE 1B.

TABLE 1B

Loop	Kabat	AbM	Chothia
L1	L24-L34	L24-L34	L24-L34
L2	L50-L56	L50-L56	L50-L56
L3	L89-L97	L89-L97	L89-L97
H1	H31-H35B	H26-H35B	H26-H32..34
		(Kabat Numbering)	
H1	H31-H35	H26-H35	H26-H33
		(Chothia Numbering)	
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[0136] The Kabat numbering of residues can be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. Chothia refers instead to the location of the structural loops (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software.

[0137] IMGT (ImMunoGeneTics) also provides a numbering system for the immunoglobulin variable regions, including the CDRs. *See, e.g.,* Lefranc, M.P. *et al., Dev. Comp. Immunol.* 27: 55-77(2003), which is herein incorporated by reference. The IMGT numbering system was based on an alignment of more than 5,000 sequences, structural data, and characterization of hypervariable loops and allows for easy comparison of the variable and CDR regions for all species. According to the IMGT numbering schema VH-CDR1 is at positions 26 to 35, VH-CDR2 is at positions 51 to 57, VH-CDR3 is at positions 93 to 102, VL-CDR1 is at positions 27 to 32, VL-CDR2 is at positions 50 to 52, and VL-CDR3 is at positions 89 to 97.

[0138] For all heavy chain constant region amino acid positions discussed in the present disclosure, numbering is according to the EU index first described in Edelman *et al.,* 1969, *Proc. Natl. Acad. Sci. USA* 63(1):78-85, describing the amino acid sequence of myeloma protein EU, which is the first human IgG1 sequenced. The EU index of

Edelman *et al.* is also set forth in Kabat *et al.*, 1991, Sequences of Proteins of Immunological Interest, 5th Ed., United States Public Health Service, National Institutes of Health, Bethesda. Thus, the phrases "EU index as set forth in Kabat" or "EU index of Kabat" and "position ... according to the EU index as set forth in Kabat," and grammatical variants thereof refer to the residue numbering system based on the human IgG1 EU antibody of Edelman et al. as set forth in Kabat 1991.

[0139]   The numbering system used for the variable domains (both heavy chain and light chain) and light chain constant region amino acid sequence is that set forth in Kabat 1991.

[0140]   Antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, or IgY), any class (*e.g.*, IgD, IgG2, IgG3, IgG4, IgA1, or IgA2), or any subclass (*e.g.*, IgG1, IgG2, IgG3, and IgG4 in humans; and IgG1, IgG2a, IgG2b, and IgG3 in mice) of immunoglobulin molecule. Immunoglobulins, *e.g.*, IgG1, exist in several allotypes, which differ from each other in at most a few amino acids. An antibody disclosed herein can be from any of the commonly known isotypes, classes, subclasses, or allotypes. In certain embodiments, the antibodies described herein are of the IgG1, IgG2, IgG3, or IgG4 subclass or any hybrid thereof. In certain embodiments, the antibodies are of the human IgG1 subclass or the human IgG2 or human IgG4 subclass.

[0141]   "Antibody" includes, by way of example, both naturally-occurring and non-naturally-occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human and non-human antibodies; wholly synthetic antibodies; single chain antibodies; monospecific antibodies; multispecific antibodies (including bispecific antibodies); tetrameric antibodies comprising two heavy chain and two light chain molecules; an antibody light chain monomer; an antibody heavy chain monomer; an antibody light chain dimer, an antibody heavy chain dimer; an antibody light chain-antibody heavy chain pair; intrabodies; heteroconjugate antibodies; monovalent antibodies; camelized antibodies; affybodies; anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti- anti-Id antibodies), and single-domain antibodies (sdAbs), which include binding molecules consisting of a single monomeric variable antibody domain that are fully capable of antigen binding (*e.g.*, a VH domain or a VL domain). Harmen M. M. and Haard H. J. *Appl Microbiol Biotechnol.* 77(1): 13–22 (2007)).

[0142]   The term "antigen-binding portion" of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen

(*e.g.*, human FAM19A5). Such "fragments" are, for example between about 8 and about 1500 amino acids in length, suitably between about 8 and about 745 amino acids in length, suitably about 8 to about 300, for example about 8 to about 200 amino acids, or about 10 to about 50 or 100 amino acids in length. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody, *e.g.*, an anti-FAM19A5 antibody described herein, include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL, and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, and disulfide-linked Fvs (sdFv); (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR) or (vii) a combination of two or more isolated CDRs which can optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv)); *see, e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

[0143]   As used herein, the terms "variable region" or "variable domain" are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its

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particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR).

[0144]   Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[0145]   As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG1, IgG2, IgG3 and IgG4.

[0146]   As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0147]   The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[0148]   The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[0149]   As used herein, the term "constant region" or "constant domain" are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[0150]   An "Fc region" (fragment crystallizable region) or "Fc domain" or "Fc" refers to the C- terminal region of the heavy chain of an antibody that mediates the binding of the immunoglobulin to host tissues or factors, including binding to Fc receptors located on various cells of the immune system (*e.g.*, effector cells) or to the first component (C1q) of the classical complement system. Thus, an Fc region comprises the constant region of an antibody excluding the first constant region immunoglobulin domain (*e.g.*, CH1 or CL). In IgG, IgA and IgD antibody isotypes, the Fc region comprises two identical protein fragments, derived from the second (CH2) and third (CH3) constant domains of the antibody's two heavy chains; IgM and IgE Fc regions comprise three heavy chain constant domains (CH domains 2-4) in each polypeptide chain. For IgG, the Fc region comprises immunoglobulin domains Cγ2 and Cγ3 and the hinge between Cγ1 and Cγ2. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position C226 or P230 (or amino acid between these two amino acids) to the carboxy-terminus of the heavy chain, wherein the numbering is according to the EU index as in Kabat. The CH2 domain of a human IgG Fc region extends from about amino acid 231 to about amino acid 340, whereas the CH3 domain is positioned on C-terminal side of a Cm domain in an Fc region, *i.e.*, it extends from about amino acid 341 to about amino acid 447 of an IgG. As used herein, the Fc region can be a native sequence Fc, including any allotypic variant, or a variant Fc (*e.g.*, a non-naturally-occurring Fc). Fc can also refer to this region in isolation or in the context of an Fc-comprising protein polypeptide such as a "binding protein comprising an Fc region," also referred to as an "Fc fusion protein" (*e.g.*, an antibody or immunoadhesion).

[0151]   A "native sequence Fc region" or "native sequence Fc" comprises an amino acid sequence that is identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region; native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally-occurring variants thereof. Native sequence Fc includes the various allotypes of Fes (*see, e.g.*, Jefferis *et al.* (2009) *mAbs* 1:1; Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014)).

[0152]   An "Fc receptor" or "FcR" is a receptor that binds to the Fc region of an immunoglobulin. FcRs that bind to an IgG antibody comprise receptors of the FcγR

family, including allelic variants and alternatively spliced forms of these receptors. The FcγR family consists of three activating (FcγRI, FcγRIII, and FcγRIV in mice; FcγRIA, FcγRIIA, and FcγRIIIA in humans) and one inhibitory (FcγRIIB) receptor. Human IgG1 binds to most human Fc receptors and elicits the strongest Fc effector functions. It is considered equivalent to murine IgG2a with respect to the types of activating Fc receptors that it binds to. Conversely, human IgG4 elicits the least Fc effector functions. Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014).

[0153]   The constant region can be manipulated, *e.g.*, by recombinant technology, to eliminate one or more effector functions. An "effector function" refers to the interaction of an antibody Fc region with an Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary "effector functions" include C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, FcγR-mediated effector functions such as ADCC and antibody dependent cell-mediated phagocytosis (ADCP), and down regulation of a cell surface receptor (*e.g.*, the B cell receptor; BCR). Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.*, an antibody variable domain). Accordingly, the term "a constant region without the Fc function" include constant regions with reduced or without one or more effector functions mediated by Fc region.

[0154]   Effector functions of an antibody can be reduced or avoided by different approaches. Effector functions of an antibody can be reduced or avoided by using antibody fragments lacking the Fc region (*e.g.*, such as a Fab, F(ab')₂, single chain Fv (scFv), or a sdAb consisting of a monomeric VH or VL domain). Alternatively, the so-called aglycosylated antibodies can be generated by removing sugars that are linked to particular residues in the Fc region to reduce the effector functions of an antibody while retaining other valuable attributes of the Fc region (*e.g.*, prolonged half-life and heterodimerization). Aglycosylated antibodies can be generated by, for example, deleting or altering the residue the sugar is attached to, removing the sugars enzymatically, producing the antibody in cells cultured in the presence of a glycosylation inhibitor, or by expressing the antibody in cells unable to glycosylate proteins (*e.g.*, bacterial host cells). *See, e.g.*, U.S. Pub. No. 20120100140. Another approach is to employ Fc regions from an IgG subclass that have reduced effector function, for example, IgG2 and IgG4 antibodies are characterized by having lower levels of Fc effector functions than IgG1 and IgG3.

The residues most proximal to the hinge region in the CH2 domain of the Fc part are responsible for effector functions of antibodies as it contains a largely overlapping binding site for C1q (complement) and IgG-Fc receptors (FcγR) on effector cells of the innate immune system. Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014). Accordingly, antibodies with reduced or without Fc effector functions can be prepared by generating, *e.g.*, a chimeric Fc region which comprises a CH2 domain from an IgG antibody of the IgG4 isotype and a CH3 domain from an IgG antibody of the IgG1 isotype, or a chimeric Fc region which comprises hinge region from IgG2 and CH2 region from IgG4 (*see, e.g.*, Lau C. *et al. J. Immunol.* 191:4769-4777 (2013)), or an Fc region with mutations that result in altered Fc effector functions, *e.g.*, reduced or no Fc functions. Such Fc regions with mutations are known in the art. *See, e.g.*, U.S. Pub. No. 20120100140 and U.S. and PCT applications cited therein and An *et al. mAbs* 1:6, 572-579 (2009); the disclosure of which are incorporated by reference to their entirety.

[0155]   A "hinge", "hinge domain" or "hinge region" or "antibody hinge region" refers to the domain of a heavy chain constant region that joins the CH1 domain to the CH2 domain and includes the upper, middle, and lower portions of the hinge (Roux *et al. J. Immunol.* 1998 161:4083). The hinge provides varying levels of flexibility between the binding and effector regions of an antibody and also provides sites for intermolecular disulfide bonding between the two heavy chain constant regions. As used herein, a hinge starts at Glu216 and ends at Gly237 for all IgG isotypes (Roux *et al.*, 1998 *J Immunol* 161:4083). The sequences of wild-type IgG1, IgG2, IgG3 and IgG4 hinges are known in the art. *See, e.g.*, Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014).

[0156]   The term "CH1 domain" refers to the heavy chain constant region linking the variable domain to the hinge in a heavy chain constant domain. As used herein, a CH1 domain starts at A118 and ends at V215. The term "CH1 domain" includes wildtype CH1 domains, as well as naturally existing variants thereof (*e.g.*, allotypes). CH1 domain sequences of IgG1, IgG2, IgG3, and IgG4 (including wildtype and allotypes) are known in the art. *See, e.g.*, Kabat EA *et al.*, (1991) *supra* and Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014). Exemplary CH1 domains include CH1 domains with mutations that modify a biological activity of an antibody, *e.g.*, half-life, *e.g.*,

described in U.S. Pub. No. 20120100140 and U.S. patents and publications and PCT publications cited therein.

[0157]   The term "CH2 domain" refers to the heavy chain constant region linking the hinge to the CH3 domain in a heavy chain constant domain. As used herein, a CH2 domain starts at P238 and ends at K340. The term "CH2 domain" includes wildtype CH2 domains, as well as naturally existing variants thereof (*e.g.*, allotypes). CH2 domain sequences of IgG1, IgG2, IgG3, and IgG4 (including wildtype and allotypes) are known in the art. *See, e.g.*, Kabat EA *et al.*, (1991) *supra* and Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014). Exemplary CH2 domains include CH2 domains with mutations that modify a biological activity of an antibody, *e.g.*, half-life and/or reduced Fc effector function, *e.g.*, described in U.S. Pub. No. 20120100140 and U.S. patents and publications and PCT publications cited therein.

[0158]   The term "CH3 domain" refers to the heavy chain constant region that is C-terminal to the CH2 domain in a heavy chain constant domain. As used herein, a CH3 domain starts at G341 and ends at K447. The term "CH3 domain" includes wildtype CH3 domains, as well as naturally existing variants thereof (*e.g.*, allotypes). CH3 domain sequences of IgG1, IgG2, IgG3, and IgG4 (including wildtype and allotypes) are known in the art. *See, e.g.*, Kabat EA *et al.*, (1991) *supra* and Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014). Exemplary CH3 domains include CH3 domains with mutations that modify a biological activity of an antibody, *e.g.*, half-life, *e.g.*, described in U.S. Pub. No. 20120100140 and U.S. patents and publications and PCT publications cited therein.

[0159]   As used herein, "isotype" refers to the antibody class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE antibody) that is encoded by the heavy chain constant region genes.

[0160]   "Allotype" refers to naturally-occurring variants within a specific isotype group, which variants differ in a few amino acids (*see, e.g.*, Jefferis *et al.* (2009) *mAbs* 1:1). Antibodies described herein can be of any allotype. Allotypes of IgG1, IgG2, IgG3, and IgG4 are known in the art. *See, e.g.*, Kabat EA *et al.*, (1991) *supra*; Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014); and Lefranc MP, *mAbs* 1:4, 1-7(2009).

[0161]   The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[0162]   An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds to FAM19A5 is substantially free of antibodies that specifically bind antigens other than FAM19A5). An isolated antibody that specifically binds to an epitope of FAM19A5 can, however, have cross-reactivity to other FAM19A5 proteins from different species.

[0163]   "Binding affinity" generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on} and is expressed as a molar concentration (M), whereas K_A is calculated from the quotient of k_{on}/k_{off}. k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as immunoassays (*e.g.*, enzyme-linked immunosorbent assay (ELISA)), BIACORE® or kinetic exclusion assay (KinExA®).

[0164]   As used herein, the terms "specifically binds," "specifically recognizes," "specific binding," "selective binding," and "selectively binds," are analogous terms in the context of antibodies and refer to molecules (*e.g.*, antibodies) that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen can bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIACORE®, KinExA® 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that specifically bind to an antigen bind to

the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind to another antigen.

[0165]   Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K_D) of 10^{-5} to 10^{-11} M or less. Any K_D greater than about 10^{-4} M is generally considered to indicate nonspecific binding. As used herein, an antibody that "binds specifically" to an antigen refers to an antibody that binds to the antigen and substantially identical antigens with high affinity, which means having a K_D of 10^{-7} M or less, preferably 10^{-8} M or less, even more preferably 10^{-9} M or less, and most preferably between 10^{-8} M and 10^{-10} M or less, when determined by, *e.g.*, immunoassays (*e.g.*, ELISA) or surface plasmon resonance (SPR) technology in a BIACORE™ 2000 instrument using the predetermined antigen, but does not bind with high affinity to unrelated antigens.

[0166]   As used herein, the term "antigen" refers to any natural or synthetic immunogenic substance, such as a protein, peptide, or hapten. An antigen can be FAM19A5 or a fragment thereof.

[0167]   As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non- linear, discontinuous, or non-contiguous epitope). Epitopes formed from contiguous amino acids are typically, but not always, retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 20 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*, epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from (*e.g.*, from FMAM19A5) are tested for reactivity with a given antibody (*e.g.*, anti-FAM19A5 antibody). Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography, 2-dimensional nuclear magnetic resonance and HDX-MS (*see, e.g.*, Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, G. E. Morris, Ed. (1996)).

[0168]   In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization can be accomplished using any of the known methods in the art (*e.g.*, Giege R *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson A (1990) *Eur J Biochem* 189: 1-23; Chayen NE (1997) *Structure* 5: 1269-1274; McPherson A (1976) *J Biol Chem* 251 : 6300-6303). Antibody:antigen crystals can be studied using well known X-ray diffraction techniques and can be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see, e.g., Meth Enzymol* (1985) volumes 114 & 115, eds Wyckoff HW *et al.*,; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) *Acta Crystallogr D Biol Crystallogr* 49(Pt 1): 37-60; Bricogne G (1997) *Meth Enzymol* 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) *Acta Crystallogr D Biol Crystallogr* 56(Pt 10): 1316-1323). Mutagenesis mapping studies can be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.*, (1995) *J Biol Chem* 270: 1388-1394 and Cunningham BC & Wells JA (1989) *Science* 244: 1081- 1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques.

[0169]   The term "epitope mapping" refers to the process of identification of the molecular determinants for antibody-antigen recognition.

[0170]   The term "binds to the same epitope" with reference to two or more antibodies means that the antibodies bind to the same segment of amino acid residues, as determined by a given method. Techniques for determining whether antibodies bind to the "same epitope on FAM19A5" with the antibodies described herein include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope and hydrogen/deuterium exchange mass spectrometry (HDX-MS). Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of

interest to affinity isolate specific short peptides from combinatorial phage display peptide libraries. Antibodies having the same VH and VL or the same CDR1, 2 and 3 sequences are expected to bind to the same epitope.

[0171]   Antibodies that "compete with another antibody for binding to a target" refer to antibodies that inhibit (partially or completely) the binding of the other antibody to the target. Whether two antibodies compete with each other for binding to a target, *i.e.*, whether and to what extent one antibody inhibits the binding of the other antibody to a target, can be determined using known competition experiments. In certain embodiments, an antibody competes with, and inhibits binding of another antibody to a target by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%. The level of inhibition or competition can be different depending on which antibody is the "blocking antibody" (*i.e.*, the cold antibody that is incubated first with the target). Competition assays can be conducted as described, for example, in Ed Harlow and David Lane, Cold Spring Harb Protoc; 2006; doi: 10.1101/pdb.prot4277 or in Chapter 11 of "Using Antibodies" by Ed Harlow and David Lane, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA 1999. Competing antibodies bind to the same epitope, an overlapping epitope or to adjacent epitopes (*e.g.*, as evidenced by steric hindrance).

[0172]   Other competitive binding assays include: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see* Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (*see* Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (*see* Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988)); solid phase direct label RIA using 1-125 label (*see* Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)).

[0173]   A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.*, Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny *et al.*, *J. Immunol.* 148, 1547-1553 (1992).

[0174]   The term "monoclonal antibody," as used herein, refers to an antibody that displays a single binding specificity and affinity for a particular epitope or a composition of antibodies in which all antibodies display a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to an antibody or antibody composition that display(s) a single binding specificity and which has variable and optional constant regions derived from human germline immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0175]   The term "recombinant human antibody," as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (*see, e.g.*, Lonberg (2005) *Nature Biotech.* 23(9): 1117- 1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen cannot have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

[0176]   A "human" antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The antibodies described herein can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human" antibodies and "fully human" antibodies are used synonymously.

[0177]   A "humanized" antibody refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an antibody, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the antibody to bind to a particular antigen. A "humanized" antibody retains an antigenic specificity similar to that of the original antibody.

[0178]   A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

[0179]   The term "cross-reacts," as used herein, refers to the ability of an antibody described herein to bind to FAM19A5 from a different species. For example, an antibody described herein that binds human FAM19A5 can also bind another species of FAM19A5 (*e.g.*, mouse FAM19A5). As used herein, cross-reactivity can be measured by detecting a specific reactivity with purified antigen in binding assays (*e.g.*, SPR, ELISA) or binding to, or otherwise functionally interacting with, cells physiologically expressing FAM19A5. Methods for determining cross-reactivity include standard binding assays as described

herein, for example, by BIACORE® surface plasmon resonance (SPR) analysis using a BIACORE® 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or flow cytometric techniques.

[0180]   The term "naturally-occurring" as applied to an object herein refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

[0181]   A "polypeptide" refers to a chain comprising at least two consecutively linked amino acid residues, with no upper limit on the length of the chain. One or more amino acid residues in the protein can contain a modification such as, but not limited to, glycosylation, phosphorylation or disulfide bond formation. A "protein" can comprise one or more polypeptides.

[0182]   The term "nucleic acid molecule," as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule can be single- stranded or double- stranded, and can be cDNA.

[0183]   "Conservative amino acid substitutions" refer to substitutions of an amino acid residue with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.,* lysine, arginine, histidine), acidic side chains (*e.g.,* aspartic acid, glutamic acid), uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.,* threonine, valine, isoleucine) and aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan, histidine). In certain embodiments, a predicted nonessential amino acid residue in an anti-TIM3 antibody is replaced with another amino acid residue from the same side chain family. Methods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (*see, e.g.,* Brummell *et al., Biochem.* 32: 1180-1187 (1993); Kobayashi *et al. Protein Eng.* 12(10):879-884 (1999); and Burks *et al. Proc. Natl. Acad. Sci. USA* 94:412-417 (1997)).

[0184]   For nucleic acids, the term "substantial homology" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, at least about 90% to 95%, or at least about 98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

[0185]   For polypeptides, the term "substantial homology" indicates that two polypeptides, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate amino acid insertions or deletions, in at least about 80% of the amino acids, at least about 90% to 95%, or at least about 98% to 99.5% of the amino acids.

[0186]   The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[0187]   The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at worldwideweb.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (*CABIOS*, 4: 11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0188]   The nucleic acid and protein sequences described herein can further be used as a "query sequence" to perform a search against public databases to, for example, identify

related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. *See* worldwideweb.ncbi.nlm.nih.gov.

[0189]   The nucleic acids can be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids (*e.g.*, the other parts of the chromosome) or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. *See*, F. Ausubel, *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

[0190]   Nucleic acids, *e.g.*, cDNA, can be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, can affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

[0191]   The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian

vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, also included are other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0192]   The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell that comprises a nucleic acid that is not naturally present in the cell, and can be a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications can occur in succeeding generations due to either mutation or environmental influences, such progeny cannot, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0193]   As used herein, the term "linked" refers to the association of two or more molecules. The linkage can be covalent or non-covalent. The linkage also can be genetic (*i.e.*, recombinantly fused). Such linkages can be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

[0194]   The term "therapeutically effective amount" as used herein refers to an amount of a drug, alone or in combination with another therapeutic agent, effective to "treat" a disease or disorder in a subject or reduce the risk, potential, possibility or occurrence of a disease or disorder (*e.g.*, cancer). A "therapeutically effective amount" includes an amount of a drug or a therapeutic agent that provides some improvement or benefit to a subject having or at risk of having a disease or disorder associated with cancer. Thus, a "therapeutically effective" amount is an amount that reduces the risk, potential, possibility or occurrence of a disease or provides disorder or some alleviation, mitigation, and/or

reduces at least one indicator (*e.g.*, an onset of cancer or tumor formation), and/or decrease in at least one clinical symptom of a disease or disorder associated with cancer.

II.   Methods of Treating Cancer

[0195]   Disclosed herein are methods of treating a tumor (or a cancer) in a subject in need thereof, comprising administering to the subject an antagonist against FAM19A5. In some embodiments, the antagonist is an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein ("an anti-FAM19A5 antibody"), a polynucleotide encoding the anti-FAM19A5 antibody, or a vector comprising the polynucleotide thereof. In certain embodiments, the anti-FAM19A5 antibody specifically binds to FAM19A5 protein and reduces FAM19A5 activity.

[0196]   In some embodiments, administering a composition disclosed herein treats, reduces, ameliorates, controls, or inhibits a tumor in a subject in need thereof by promoting blood vessel normalization. As described *supra.*, the extensive angiogenesis that occurs in many cancers can result in the formation of blood vessels that are abnormal. Nagy J.A., *et al.*, *Br J Cancer* 100(6):865-869 (2009). For instance, such blood vessels can have increased permeability and/or decreased blood flow rate, which can interfere with the efficient delivery of oxygen and/or immune cells (*e.g.*, macrophages, microglia, and T lymphocytes) to the cancerous tissue. Accordingly, in certain embodiments, the methods disclosed herein promote blood vessel normalization by decreasing blood vessel permeability and/or increase the blood flow rate. In some embodiments, the blood vessel normalization is associated with the production of reactive oxygen species (ROS), and thus increases the delivery of oxygen and improves hypoxia. In some embodiments, the production of ROS and delivery of oxygen induced by an anti-FAM19A5 antibody increase the apoptosis of the tumor cells by chemoagents. In some embodiments, the blood vessel normalization is associated with reduced hypoxia and/or edema formation.

[0197]   In some embodiments, the methods disclosed herein also increase the number of blood vessels that extend into the tumors. In certain embodiments, the blood vessels that extend into the tumors are thicker and have improved connectivity, compared to reference blood vessels (*e.g.*, generated in the absence of anti-FAM19A5 treatment) present in a tumor. In some embodiments, the methods disclosed herein increase the number of blood vessels (with increased thickness and improved connectivity) that extend into the tumors by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or more. In

some embodiments, the increase in blood vessels in the tumor is associated with increase in collagen (*e.g.*, type IV) and/or CD31 expression within the tumor and/or production of reactive oxygen species (ROS) and/or increase in the delivery of oxygen and improves hypoxia within the tumor.

[0198]   In some embodiments, the methods disclosed herein increase the infiltration of immune cells into a tumor. In some embodiments, the infiltration of immune cells into a tumor is increased by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or more, compared to a reference (*e.g.*, number of immune cells present in a tumor not exposed to anti-FAM19A5 antibody). In certain embodiments, the immune cells comprise macrophages, dendritic cells, microglia, and T-lymphocytes. In certain embodiments, the methods disclosed herein can also increase the infiltration of other cells (*e.g.*, neuronal and/or stromal cells) into a tumor. Accordingly, in some embodiments, the infiltration of immune cells into a tumor is further accompanied by infiltration of other cells (*e.g.*, neuronal and/or stromal cells) in the tumor. In further embodiments, the methods disclosed herein increase the cellular volume of the immune cells present in a tumor. In certain embodiments, the cellular volume of the immune cells is increased by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or more, compared to a reference (*e.g.*, volume of immune cells present in a tumor not exposed to anti-FAM19A5 antibody). In certain embodiments, an increase in cellular volume of the immune cells is associated with maturation (*e.g.*, monocytes to macrophages) of the immune cells. In some embodiments, an increase in cellular volume of the immune cells is associated with increased effector function (*e.g.*, phagocytic activity) of the immune cells.

[0199]   In some embodiments, the methods disclosed herein increase the phagocytic activity and/or the membrane potential of immune cells in a tumor. In certain embodiments, the immune cells comprise macrophages or microglia. In some embodiments, the phagocytic activity and/or the membrane potential of the immune cells is increased by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or more, compared to a reference (*e.g.*, corresponding values in immune cells present in a tumor not exposed to anti-FAM19A5 antibody). In some embodiments, the increased phagocytic activity of immune cells by the present methods improves the tumor microenvironment, which allows for blood vessel normalization to occur. In some

embodiments, the increased phagocytic activity of immune cells enhances innate immunity (*e.g.*, clearance of tumor antigens, regulates inflammation, and tumor-antigen presentation to T cells).

[0200]   In some embodiments, the methods disclosed herein can also decrease the frequency of suppressor cells in a tumor. As used herein, the term "suppressor cells" refers to cells of the immune system that can inhibit or suppress the host immune response against an antigen (*e.g.*, tumor protein). In some embodiments, the suppressor cells comprise myeloid-derived suppressor cells. The term "myeloid-derived suppressor cells" (MDSCs) refers to a heterogeneous population of cells consisting of myeloid progenitor cells and immature myeloid cells (IMCs). In healthy individuals, IMCs that are quickly generated in the bone marrow differentiate into mature granulocytes, macrophages or dendritic cells (DCs). Interference with the differentiation of IMCs into mature myeloid cells results in the expansion of MDSC population. Accumulating evidence has shown that MDSCs contribute to the negative regulation of immune responses during cancer and other diseases. *See, e.g.*, U.S. Publ. No. 2015/0209404. In some embodiments, the methods disclosed herein decreases the frequency of suppressor cells in a tumor by at least at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, compared to a reference (*e.g.*, frequency of suppressor cells in a tumor not exposed to anti-FAM19A5 antibody).

[0201]   In some embodiments, the methods disclosed herein can improve an endogenous immune response against the tumor (*e.g.*, as described above). In some embodiments, the methods disclosed herein can improve and/or enhance an activity of a cancer immunotherapy (*e.g.*, chimeric antigen receptor T cells (CART), NK cell therapy, or cytokine-induced killer cells). Accordingly, as discussed *infra*, in certain embodiments, an anti-FAM19A5 antibody disclosed herein can be used in combination with one or more additional therapeutic agents to treat a cancer.

[0202]   In some embodiments, the methods disclosed herein inhibit and/or reduce tumor growth in a subject. In certain embodiments, the tumor growth (*e.g.*, tumor volume or weight) is reduced by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%, compared to a reference (*e.g.*, the corresponding tumor volume or weight in a subject that did not receive the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody). In some

embodiments, the methods disclosed herein increase a median tumor growth inhibition (TGI) by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%, compared to a reference (*e.g.*, the corresponding frequency in a subject that did not receive the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody). In some embodiments, administering the composition disclosed herein (*e.g.*, anti-FAM19A5 antibody) increases a median survival by at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days or more compared to a reference (*e.g.*, the corresponding value in a subject that did not receive the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody).

[0203]   In some embodiments, tumors that can be treated with the methods disclosed herein are derived from cancers that are typically responsive to immunotherapy and those that are not typically responsive to immunotherapy. In some embodiments, the cancers are cancers with solid tumors or blood malignancies (liquid tumors). In other embodiments, the cancers are derived from fibrosis associated tumors. As used herein, the terms "fibrosis associated tumors" and "tumors associated with fibrosis" refer to tumors that are accompanied by fibrosis. The term "fibrosis," as used herein, refer to the formation or presence of excess fibrous connective tissue (*e.g.*, due to increased accumulation of extracellular matrix proteins) in and/or around a tumor tissue.

[0204]   Non-limiting examples of cancers for treatment include squamous cell carcinoma, small-cell lung cancer, non-small cell lung cancer, squamous non-small cell lung cancer (NSCLC), nonsquamous NSCLC, gastrointestinal cancer, renal cancer (*e.g.*, clear cell carcinoma), ovarian cancer, liver cancer, colorectal cancer, endometrial cancer, kidney cancer (*e.g.*, renal cell carcinoma (RCC)), prostate cancer (*e.g.*, hormone refractory prostate adenocarcinoma), thyroid cancer, pancreatic cancer, cervical cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer (or carcinoma), gastric cancer, germ cell tumor, pediatric sarcoma, sinonasal natural killer, melanoma (*e.g.*, metastatic malignant melanoma, such as cutaneous or intraocular malignant melanoma), bone cancer, skin cancer, uterine cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue,

cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the ureter, carcinoma of the renal pelvis, tumor angiogenesis, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally-induced cancers including those induced by asbestos, virus-related cancers or cancers of viral origin (*e.g.*, human papilloma virus (HPV-related or -originating tumors)), and hematologic malignancies derived from either of the two major blood cell lineages, *i.e.*, the myeloid cell line (which produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells) or lymphoid cell line (which produces B, T, NK and plasma cells), such as all types of leukemias, lymphomas, and myelomas, *e.g.*, acute, chronic, lymphocytic and/or myelogenous leukemias, such as acute leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML), undifferentiated AML (MO), myeloblastic leukemia (Ml), myeloblastic leukemia (M2; with cell maturation), promyelocytic leukemia (M3 or M3 variant [M3V]), myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]), monocytic leukemia (M5), erythroleukemia (M6), megakaryoblastic leukemia (M7), isolated granulocytic sarcoma, and chloroma; lymphomas, such as Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), B cell hematologic malignancy, *e.g.*, B-cell lymphomas, T-cell lymphomas, lymphoplasmacytoid lymphoma, monocytoid B-cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, anaplastic (*e.g.*, Ki 1+) large-cell lymphoma, adult T-cell lymphoma/leukemia, mantle cell lymphoma, angio immunoblastic T-cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, primary mediastinal B-cell lymphoma, precursor T-lymphoblastic lymphoma, T-lymphoblastic; and lymphoma/leukaemia (T-Lbly/T-ALL), peripheral T- cell lymphoma, lymphoblastic lymphoma, post-transplantation lymphoproliferative disorder, true histiocytic lymphoma, primary effusion lymphoma, B cell lymphoma, lymphoblastic lymphoma (LBL), hematopoietic tumors of lymphoid lineage, acute lymphoblastic leukemia, diffuse large B-cell lymphoma, Burkitt's lymphoma, follicular lymphoma, diffuse histiocytic lymphoma (DHL), immunoblastic large cell lymphoma, precursor B - lymphoblastic lymphoma, cutaneous T-cell lymphoma (CTLC) (also called mycosis fungoides or Sezary syndrome), and lymphoplasmacytoid lymphoma (LPL) with Waldenstrom's macroglobulinemia; myelomas, such as IgG myeloma, light chain myeloma, nonsecretory myeloma, smoldering myeloma (also called indolent myeloma),

solitary plasmocytoma, and multiple myelomas, chronic lymphocytic leukemia (CLL), hairy cell lymphoma; hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma; seminoma, teratocarcinoma, tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscaroma, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoacanthoma, seminoma, thyroid follicular cancer and teratocarcinoma, hematopoietic tumors of lymphoid lineage, for example T-cell and B-cell tumors, including but not limited to T-cell disorders such as T-prolymphocytic leukemia (T-PLL), including of the small cell and cerebriform cell type; large granular lymphocyte leukemia (LGL) of the T-cell type; a/d T-NHL hepatosplenic lymphoma; peripheral/post-thymic T cell lymphoma (pleomorphic and immunoblastic subtypes); angiocentric (nasal) T-cell lymphoma; cancer of the head or neck, renal cancer, rectal cancer, cancer of the thyroid gland; acute myeloid lymphoma, and any combinations thereof.

[0205]   In some embodiments, tumors (*e.g.*, solid tumors) that can be treated with the present methods comprise carcinoma, sarcoma, or lymphoma. In certain embodiments, the solid tumors are carcinoma or sarcoma. As used herein, "sarcoma" refers to a type of cancer, *e.g.*, a connective tissue neoplasm, which is usually highly malignant and which is formed by proliferation of mesodermal cells (*i.e.*, tumor of mesenchymal origin). In some embodiments, sarcoma comprises Askin's tumor, sarcoma botryoides, angiosarcoma, bone sarcoma, chondrosarcoma, chodoma, desmoid-type fibromatosis, Ewing's sarcoma, fibroblastic sarcoma, gastrointestinal stromal tumors (GIST), giant cell tumor (GCT) of the bone, gynaecological sarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumor (MPNST), malignant hemangioendothelioma, osteosarcoma, retroperitoneal sarcoma, rhabdomyosarcoma, soft tissue Ewing's sarcoma, soft tissue sarcoma, synovial sarcoma, or any combinations thereof.

[0206]   In some embodiments, the sarcoma is a soft tissue sarcoma. In certain embodiments, soft tissue sarcoma comprises alveolar soft part sarcoma, angiosarcoma (also known as "hemangiosarcoma"), cystosarcoma phyllodes, dermatofibrosarcoma protuberans, desmoid tumor, desmoplastic small round cell tumor, epithelioid sarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, gastrointestinal stromal tumor, hemangiopericytoma (also known as "solitary fibrous tumor"), Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, plexiform

fibrohistiocytic tumor, rhabdomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, or any combinations thereof.

[0207]   In some embodiments, the solid tumors are lymphoma. As used herein, "lymphoma" refers to a group of blood cancers that develop from lymphocytes (a type of white blood cells). Dozens of subtypes of lymphomas are known in the art. In some embodiments, the lymphomas are Hodgkin's lymphomas (HL), non-Hodgkin lymphomas (NHL), multiple myeloma, or immunoproliferative diseases.

[0208]   In some embodiments, the tumor is associated with fibrosis. In certain embodiments, the tumor that is associated with fibrosis is derived from a cancer comprising liver cancer, lung cancer, renal cancer, breast cancer, pancreatic cancer, or any combination thereof.

[0209]   In some embodiments, the tumor (*e.g.*, solid tumor) that can be treated by the present methods is derived from or associated with a cancer comprising a breast cancer, lymphoma (*e.g.*, B-cell lymphoma), melanoma, lung cancer, pancreatic cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, ovarian cancer, or any combinations thereof. In other embodiments, the tumor treatable with the present methods is not a brain tumor. In certain embodiments, the tumor treatable with the present methods is not glioblastoma.

[0210]   In some embodiments, the methods described herein can also be used for treatment of metastatic cancers, unresectable, refractory cancers (*e.g.*, cancers refractory to previous cancer therapy, *e.g.*, immunotherapy, *e.g.*, with a blocking PD-(L)1 antibody), and/or recurrent cancers. In certain embodiments, the previous cancer therapy comprises a chemotherapy. In some embodiments, the chemotherapy comprises a platinum-based therapy. In some embodiments, the platinum-based therapy comprises a platinum-based antineoplastic selected from the group consisting of cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, satraplatin, and any combination thereof. In certain embodiments, the platinum-based therapy comprises cisplatin. In further embodiments, the platinum-based therapy comprises carboplatin.

[0211]   In some embodiments, the methods disclosed herein effectively increases the duration of survival of a subject in need thereof (*e.g.*, afflicted with a tumor). For example, the duration of survival of the subject is increased by at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5

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months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 1 year or more when compared to a reference individual (*e.g.*, another subject who was not treated with the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody). In still other embodiments, the methods disclosed herein increases the duration of survival of the subject at a level higher than (about one month higher than, about two months higher than, about three months higher than, about four months higher than, about five months higher than, about six months higher than, about seven months higher than, about eight months higher than, about nine months higher than, about ten months higher than, about eleven months higher than, or about one year higher than) the duration of survival of a reference subject (*e.g.*, another subject who was not treated with the another subject who was not treated with the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody).

[0212]   In some embodiments, the methods of the present disclosure effectively increases the duration of progression-free survival of the subject. For example, the progression free survival of the subject is increased by at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 1 year when compared to a reference subject (*e.g.*, another subject who was not treated with the another subject who was not treated with the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody).

[0213]   In some embodiments, the methods disclosed herein effectively increases the response rate in a group of subjects. For example, the response rate in a group of subjects is increased by at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at last about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 99% or at least about 100% when compared to a reference subject (*e.g.*, another subject who was not treated with the another subject who was not treated with the composition disclosed herein, *e.g.*, anti-FAM19A5 antibody).

[0214]   In some embodiments, the subject being treated in the method is a nonhuman animal such as a rat or a mouse. In some embodiments, the subject being treated in the method is a human.

[0215]   The present disclosure also includes methods of treating a cancer as described in this section in a subject in need thereof in combination with another cancer agent. In some embodiments, anti-FAM19A5 antibodies useful for the present methods can be administered in a combination therapy, *i.e.*, combined with at least one other anti-cancer and/or immunomodulating, *e.g.*, T-cell stimulating (*e.g.*, activating) agent. In some embodiments, anti-FAM19A5 antibodies useful for the present methods can be given in combination with other compounds, drugs, and/or agents used for the treatment of cancer. Such compounds, drugs, and/or agents can include, for example, chemotherapy drugs, small molecule drugs, or antibodies that stimulate the immune response to a given cancer. In some embodiments, the methods described herein are used in combination with a standard of care treatment (*e.g.*, surgery, radiation, and chemotherapy). In other embodiments, the methods described herein are used as a maintenance therapy, *e.g.*, a therapy that is intended to prevent the occurrence or recurrence of tumors.

[0216]   In some embodiments, anti-FAM19A5 antibodies useful for the present disclosure can be combined with more than one immuno-oncology agent, and can be, *e.g.*, combined with a combinatorial approach that targets multiple elements of the immune pathway, such as one or more of the following: a therapy that enhances tumor antigen presentation (*e.g.*, dendritic cell vaccine, GM-CSF secreting cellular vaccines, CpG oligonucleotides, imiquimod); a therapy that inhibits negative immune regulation *e.g.*, by inhibiting CTLA-4 and/or PD1/PD-L1/PD-L2 pathway and/or depleting or blocking Tregs or other immune suppressing cells (*e.g.*, myeloid-derived suppressor cells); a therapy that stimulates positive immune regulation, *e.g.*, with agonists that stimulate the CD-137, OX-40, and/or CD40 or GITR pathway and/or stimulate T cell effector function; a therapy that increases systemically the frequency of anti-tumor T cells; a therapy that depletes or inhibits Tregs, such as Tregs in the tumor, *e.g.*, using an antagonist of CD25 (*e.g.*, daclizumab) or by *ex vivo* anti-CD25 bead depletion; a therapy that impacts the function of suppressor myeloid cells in the tumor; a therapy that enhances immunogenicity of tumor cells (*e.g.*, anthracyclines); adoptive T cell or NK cell transfer including genetically modified cells, *e.g.*, cells modified by chimeric antigen receptors (CAR-T therapy); a therapy that

inhibits a metabolic enzyme such as indoleamine dioxigenase (IDO), dioxigenase, arginase, or nitric oxide synthetase; a therapy that reverses/prevents T cell anergy or exhaustion; a therapy that triggers an innate immune activation and/or inflammation at a tumor site; administration of immune stimulatory cytokines; or blocking of immuno repressive cytokines. In some instances, the additional anti-cancer agent that can be combined with anti-FAM19A5 antibodies useful for the disclosure can include, but are not limited to, one or more of an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-OX40 (also known as CD134, TNFRSF4, ACT35 and/or TXGP1L) antibody, an anti-CD137 antibody, an anti-LAG-3 antibody, an anti-GITR antibody, or any combination thereof.

[0217]   In some embodiments, anti-FAM19A5 antibodies useful for the present disclosure are administered in combination with an antagonist of the PD-1 pathway (*e.g.*, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies).

[0218]   An exemplary anti-PD-1 antibody that can be used with the anti-FAM19A5 disclosed herein is nivolumab (BMS-936558) or an antibody that comprises the CDRs or variable regions of one of antibodies 17D8, 2D3, 4H1, 5C4, 7D3, 5F4 and 4A11 described in WO 2006/121168. In certain embodiments, an anti-PD-l antibody is MK-3475 (Lambrolizumab) described in WO2012/ 145493; AMP-514 described in WO 2012/145493; or PDR001. Further known PD-1 antibodies and other PD-1 inhibitors include those described in WO 2009/014708, WO 03/099196, WO 2009/114335, WO 2011/066389, WO 2011/161699, WO 2012/145493, U.S. Patent Nos. 7,635,757 and 8,217,149, and U.S. Patent Publication No. 2009/0317368. Any of the anti-PD-1 antibodies disclosed in WO2013/173223 can also be used. An anti-PD-1 antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, as one of these antibodies can also be used in combination treatments of the present disclosure.

[0219]   An exemplary anti-PD-L1 antibody useful for the combination therapy disclosed herein is BMS-936559 (referred to as 12A4 in WO 2007/005874 and US Patent No. 7,943,743), or an antibody that comprises the CDRs or variable regions of 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 and 13G4, which are described in PCT Publication WO 07/005874 and US Patent No. 7,943,743. In certain embodiments, an anti-PD-L1 antibody is MEDI4736 (also known as durvalumab and Anti-B7-H1), MPDL3280A (also known as atezolizumab and RG7446), MSB0010718C (also known as

avelumab; WO2013/79174), or rHigM12B7. Any of the anti-PD-L1 antibodies disclosed in WO2013/173223, WO2011/066389, WO2012/ 145493, U.S. Patent Nos. 7,635,757 and 8,217,149 and U.S. Publication No. 2009/145493 can also be used. Anti-PD-L1 antibodies that compete with and/or bind to the same epitope as that of any of these antibodies can also be used in combination treatments.

[0220]   When used as a combination therapy, the composition disclosed herein has a greater anticancer effect than that observed when the individual therapeutic agents are administered alone. In certain embodiments, administering both anti-FAM19A5 antibody and an additional anti-cancer agent inhibits tumor formation by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, compared to anti-FAM19A5 antibody or the additional anti-cancer agent administration alone. In some embodiments, the administration of an anti-FAM19A5 antibody in combination with an anti-PD-(L)1 antibody results in greater tumor inhibition compared to administration of either of the antibodies alone. In certain embodiments, the administration of an anti-FAM19A5 antibody in combination with an anti-PD-(L)1 antibody increases the inhibition of a tumor growth by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, compared to a reference (*e.g.*, inhibition of tumor growth in a subject that did not receive the combination therapy, *e.g.*, monotherapy of either antibody).

[0221]   In some embodiments, the combination of the anti-FAM19A5 antibody and a second agent discussed herein (*e.g.*, anti-PD-(L)1 antibody) can be administered concurrently as a single composition in a pharmaceutically acceptable carrier, or concurrently as separate compositions with the anti-FAM19A5 antibody and the second agent in a pharmaceutically acceptable carrier. In other embodiments, the combination of the anti-FAM19A5 antibody and the second agent (*e.g.*, anti-PD-(L)1 antibody) can be administered sequentially.

[0222]   As discussed *supra*, in some embodiments, an anti-FAM19A5 antibody disclosed herein can be used in combination with one or more additional cancer agents comprising an immunotherapeutic agent, chemotherapeutic agent, targeted therapeutic agent, radiotherapeutic agent (radiation therapy), or any combinations thereof. Non-limiting examples of immunotherapeutic agents include: monoclonal antibodies (*e.g.*, those disclosed herein, *e.g.*, anti-PD-(L)1 antibody), chimeric antigen receptor (CAR) T-cell, NK-cell, dendritic cell (DC), adoptive cell transfer (ACT), immune checkpoint

modulator, cytokine, cancer vaccine, adjuvant, and oncolytic virus. Non-limiting examples of chemotherapeutic agents include: temozolomide, gemcitabine, paclitaxel, carboplatin, cisplatin, elotumumab, lenalidomide, dexamethasone, and oxaliplatin. As used herein, the term "targeted therapeutic agent" refers to molecules that specifically target and inhibit one or more oncogenic signaling proteins (*e.g.*, those involved in cell growth and survival). Non-limiting examples of such targeted therapeutic agents include: tyrosine-kinase inhibitors (*e.g.*, imatinib (GLEEVEC®), gefitinib (IRESSA®), erlotinib (TARCEVA®), sorafenib (NEXAVAR®), sunitinib (SUTENT®), dasatinib (SPRYCL®), lapatinib (TYKERB®), nilotinib (TASIGNA®), bortezomib (VELCADE®), tamoxifen (NOLVADEX®), tofacitinib (XELJANZ®), ALK inhibitors (*e.g.*, crizotinib), Bcl-2 inhibitors (*e.g.*, obatoclax, navitoclax, gossypol), PARP inhibitors (*e.g.*, iniparib, olaparib), PI3K inhibitors (*e.g.*, perifosine), apatinib, AN-152, Braf inhibitors (*e.g.*, trametinib, MEK162), CDK inhibitors (*e.g.*, PD-0332991, LEE011), Hsp90 inhibitors, salinomycin, VAL-083)); small molecule drug conjugates (*e.g.*, vintafolide); serine-threonine kinase inhibitors (*e.g.*, temsirolimus (TORISEL®), everolimus (AFINITOR®), vemurafenib (ZELBORAF®), trametinib (MEKINIST®), dabrafenib (TAFINLAR®)); antibodies (*e.g.*, anti-CD20 antibodies (*e.g.*, rituximab (RITUXAN®)), anti-HER2/neu antibodies (*e.g.*, trastuzumab (HERCEPTIN®)), alemtuxumab (CAMPATH®), anti-EGFR antibodies (*e.g.*, cetuximab, panitumumab), anti-VEGF antibodies (*e.g.*, bevacizumab (AVASTIN®)).

III.   Method of Diagnosing Cancer

[0223]   Currently, the most reliable method available for diagnosing a cancer is through tissue biopsy. But such method is often highly invasive and has various undesirable side effects (*e.g.*, hemorrhage at site of biopsy, pain and discomfort). Accordingly, disclosed herein are methods of diagnosing a cancer in a subject in need thereof of comprising contacting an anti-FAM19A5 antibody or antigen-binding portion thereof with a biological sample of the subject and measuring a protein level of FAM19A5 or an mRNA level encoding FAM19A5 protein in the sample. In some embodiments, the biological sample has at least 1.5 fold, at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 11 fold, at least 12 fold, at least 13 fold, at least 15 fold, at least 20 fold, at least 25 fold, or at least 30 fold increase in the protein level of FAM19A5 or an mRNA level encoding FAM19A5

protein compared to the protein level of FAM19A5 or an mRNA level encoding FAM19A5 protein in a reference sample (*e.g.*, sample of a subject who does not have a tumor).

[0224]   The method disclosed herein can be used to diagnose the presence of a tumor in a subject by measuring the subject's FAM19A5 expression level (protein and/or mRNA), where an increased expression as compared to a reference level (*e.g.*, FAM19A5 level in a subject without tumor) would suggest that the subject has a tumor. In some embodiments, the present disclosure can be used to confirm the presence of a tumor by measuring the FAM19A5 protein level in a subject who is suspected of having a tumor. In other embodiments, the disclosure provides measuring a subject's FAM19A5 protein level in combination with another assay that is used to diagnose a tumor.

[0225]   In some embodiments, the protein level of FAM19A5 is measured by an immunohistochemistry, a Western blotting, a radioimmunoassay, an enzyme linked immunosorbent assay (ELISA), a radioimmunodiffusion, an immunoprecipitation assay, an Ouchterlony immunodiffusion method, a rocket immunoelectrophoresis, a tissue immunostaining method, a complement fixation assay, FACS, or a protein chip. In one embodiment, the level of an mRNA encoding the FAM19A5 protein is measured by a RT-PCR, a real time polymerase chain reaction, or a Northern blot. In some embodiments, the biological sample comprises a tissue, cell, blood, serum, plasma, saliva, cerebro spinal fluid, intravitreal fluid, or urine. Not being bound by any theory, the FAM19A5 protein increasingly expressed in tumors can leak into the serum where the protein can be measured using any of the assays listed above. Therefore, the present disclosure provides a method of measuring the FAM19A5 protein expression in the serum of a subject who is suspected as having a cancer. This method can thus be more convenient and less intrusive than many of the currently available diagnostic methods (*e.g.*, biopsy).

V.   **FAM19A5 Antagonists Useful for the Disclosure**

[0226]   In some embodiments, the FAM19A5 antagonist useful for the present disclosure is an antisense oligonucleotide, siRNA, shRNA, miRNA, dsRNA, aptamer, PNA (peptide nucleic acid) that specifically targets FAM19A5, or a vector including the same. In other embodiments, the FAM19A5 antagonist is an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein ("anti-FAM19A5 antibody"), a

polynucleotide encoding the anti-FAM19A5 antibody, or a vector comprising the polynucleotide thereof.

[0227]   The anti-FAM19A5 antibodies that are useful in the methods disclosed herein include monoclonal antibodies, which are characterized by particular functional features or properties. For example, the antibodies specifically bind human FAM19A5, including soluble FAM19A5 and membrane bound FAM19A5. In addition to binding specifically to soluble and/or membrane bound human FAM19A5, the antibodies described herein also (a) binds to soluble human FAM19A5 with a K_D of 10 nM or less; (b) binds to membrane bound human FAM19A5 with a K_D of 1 nM or less; or both (a) and (b).

[0228]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof specifically binds to soluble human FAM19A5 or membrane-bound human with high affinity, for example, with a K_D of 10^{-7} M or less, 10^{-8} M or less, 10^{-9} M (1 nM) or less, 10^{-10} M (0.1 nM) or less, 10^{-11} M or less, or 10^{-12} M (1 pM) or less, $e.g.$, 10^{-12} M to 10^{-7} M, 10^{-11} M to 10^{-7} M, 10^{-10} M to 10^{-7} M, or 10^{-9} M to 10^{-7} M, $e.g.$, 10^{-12} M, 5 X 10^{-12} M, 10^{-11} M, 5 X 10^{-11} M, 10^{-10} M, 5 X 10^{-10} M, 10^{-9} M, 5 X 10^{-9} M, 10^{-8} M, 5 X 10^{-8} M, 10^{-7} M, or 5 X 10^{-7} M. Standard assays to evaluate the binding ability of the antibody toward human FAM19A5 of various species are known in the art, including for example, ELISAs, Western blots, and RIAs. Suitable assays are described in detail in the Examples. The binding kinetics ($e.g.$, binding affinity) of the antibodies also can be assessed by standard assays known in the art, such as by ELISA, BIACORE® analysis or KinExA®. Assays to evaluate the effects of the antibodies on functional properties of FAM19A5 ($e.g.$, ligand binding) are described in further detail infra and in the Examples.

[0229]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to soluble human FAM19A5 with a K_D, $e.g.$, as determined by ELISA, of 10^{-7} M or less, 10^{-8} M (10 nM) or less, 10^{-9} M (1 nM) or less, 10^{-10} M or less, 10^{-12} M to 10^{-7} M, 10^{-11} M to 10^{-7} M, 10^{-10} M to 10^{-7} M, 10^{-9} M to 10^{-7} M, or 10^{-8} M to 10^{-7} M. In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to soluble FAM19A5 with a K_D of 10 nM or less, $e.g.$, between 0.1 and 10 nM, between 0.1 and 5 nM, between 0.1 and 1 nM, between 0.5 and 10 nM, between 0.5 and 5 nM, between 0.5 and 1 nM, between 1 and 10 nM, between 1 and 5 nM, or between 5 and 10 nM. In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof specifically binds to soluble human FAM19A5 with a K_D of about 1 pM, 2 pM, 3

pM, 4 pM, 5 pM, 6 pM, 7 pM, 8 pM, 9 pM, 10 pM, 20 pM, 30 pM, 40 pM, 50 pM, 60 pM, 70 pM, 80 pM, 90 pM, 100 pM, 200 pM, 300 pM, 400 pM, 500 pM, 600 pM, 700 pM, 800 pM, or 900 pM, or about 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, or 9 nM, or about 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, or 90 nM, as determined by as determined by ELISA.

[0230]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to membrane-bound human with a K_D, $e.g.$, as determined by ELISA, of 10^{-7} M or less, 10^{-8} M (10 nM) or less, 10^{-9} M (1 nM) or less, 10^{-10} M or less, 10^{-12} M to 10^{-7} M, 10^{-11} M to 10^{-7} M, 10^{-10} M to 10^{-7} M, 10^{-9} M to 10^{-7} M, or 10^{-8} M to 10^{-7} M. In certain embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof specifically binds to membrane-bound human FAM19A5 with a K_D of 10 nM or less as determined by ELISA, $e.g.$, between 0.1 and 10 nM, between 0.1 and 5 nM, between 0.1 and 1 nM, between 0.5 and 10 nM, between 0.5 and 5 nM, between 0.5 and 1 nM, between 1 and 10 nM, between 1 and 5 nM, or between 5 and 10 nM. In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to membrane-bound human FAM19A5 with a K_D of about 1 pM, 2 pM, 3 pM, 4 pM, 5 pM, 6 pM, 7 pM, 8 pM, 9 pM, 10 pM, 20 pM, 30 pM, 40 pM, 50 pM, 60 pM, 70 pM, 80 pM, 90 pM, 100 pM, 200 pM, 300 pM, 400 pM, 500 pM, 600 pM, 700 pM, 800 pM, or 900 pM, or about 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, or 9 nM, or about 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, or 90 nM, as determined by as determined by ELISA.

[0231]   In certain embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof of useful in the methods disclosed herewith thereof cross-competes for binding to (or inhibits binding of) a human FAM19A5 epitope with an anti-FAM19A5 antibody comprising CDRs or variable regions disclosed herein.

[0232]   In certain embodiments, anti-FAM19A5 antibodies or antigen binding portions thereof inhibit binding of a reference antibody comprising heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3, (i) wherein the heavy chain CDR1, CDR2, and CDR3 of the reference antibody comprise the amino acid sequence of SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 13, respectively, and light chain CDR1, CDR2, and CDR3 of the reference antibody comprise the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively; (ii) wherein the heavy chain

CDR1 comprises the amino acid sequence of SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 15, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 28; (iii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 17, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 18, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 19, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 29, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 30, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 31; (iv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 20, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 21, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 22, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 32, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 33, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 34; (v) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 89, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 90, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 91, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 92, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 93, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 94; (vi) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 95, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 96, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 97, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 98, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 99, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 100; (vii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 101, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 102, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 103, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 104, the light chain CDR2

comprises the amino acid sequence of SEQ ID NO: 105, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 106; (viii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 107, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 108, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 109, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 110, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 111, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 112; (ix) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 113, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 114, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 115, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 116, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 117, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 118; (x) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 119, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 120, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 121, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 122, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 123, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 124; (xi) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 125, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 126, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 127, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 128, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 129, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 130; (xii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 131, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 132, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 133, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 134, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 135, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 136; (xiii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 137, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 138, the heavy

chain CDR3 comprises the amino acid sequence of SEQ ID NO: 139, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 140, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 141, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 142; (xiv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 143, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 144, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 145, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 146, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 147, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 148; or (xv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 149, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 150, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 151, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 152, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 153, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 154.

[0233]   In some embodiments, the reference antibody comprises (a) heavy and light chain variable region sequences comprising SEQ ID NOs: 35 and 39, respectively; (b) heavy and light chain variable region sequences comprising SEQ ID NOs: 36 and 40, respectively; (c) heavy and light chain variable region sequences comprising SEQ ID NOs: 37 and 41, respectively; (d) heavy and light chain variable region sequences comprising SEQ ID NOs: 38 and 42, respectively; (e) heavy and light chain variable region sequences comprising SEQ ID NOs: 155 and 166, respectively;; (f) heavy and light chain variable region sequences comprising SEQ ID NOs: 156 and 167, respectively;; (g) heavy and light chain variable region sequences comprising SEQ ID NOs: 157 and 168, respectively;; (h) heavy and light chain variable region sequences comprising SEQ ID NOs: 158 and 169, respectively;; (i) heavy and light chain variable region sequences comprising SEQ ID NOs: 159 and 170, respectively;; (j) heavy and light chain variable region sequences comprising SEQ ID NOs: 160 and 171, respectively;; (k) heavy and light chain variable region sequences comprising SEQ ID NOs: 161 and 172, respectively;; (l) heavy and light chain variable region sequences comprising SEQ ID NOs: 162 and 173, respectively;; (m) heavy and light chain variable region sequences

comprising SEQ ID NOs: 163 and 174, respectively;; (n) heavy and light chain variable region sequences comprising SEQ ID NOs: 164 and 175, respectively; or; or (o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively.

[0234]   In certain embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof inhibits binding of such a reference antibody to human FAM19A5 by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% or by 100%. Competing antibodies bind to the same epitope, an overlapping epitope or to adjacent epitopes (*e.g.*, as evidenced by steric hindrance). Whether two antibodies compete with each other for binding to a target can be determined using competition experiments known in the art such as RIA and EIA.

[0235]   In certain embodiments, the anti-FAM19A5 antibody or antigen binding portions thereof bind to the same FAM19A5 epitope as a reference antibody disclosed herein comprising heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3, (i) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 11, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 12, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 13, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 23, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 24, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 25; (ii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 15, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 28; (iii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 17, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 18, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 19, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 29, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 30, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 31; (iv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO:

20, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 21, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 22, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 32, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 33, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 34; (v) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 89, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 90, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 91, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 92, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 93, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 94; (vi) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 95, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 96, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 97, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 98, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 99, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 100; (vii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 101, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 102, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 103, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 104, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 105, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 106; (viii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 107, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 108, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 109, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 110, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 111, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 112; (ix) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 113, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 114, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 115, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 116, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 117,

and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 118; (x) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 119, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 120, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 121, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 122, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 123, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 124; (xi) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 125, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 126, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 127, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 128, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 129, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 130; (xii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 131, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 132, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 133, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 134, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 135, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 136; (xiii) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 137, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 138, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 139, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 140, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 141, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 142; (xiv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 143, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 144, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 145, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 146, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 147, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 148; or (xv) wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 149, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 150, the heavy chain CDR3 comprises the amino acid

sequence of SEQ ID NO: 151, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 152, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 153, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 154.

[0236] In some embodiments, the reference antibody comprises (a) heavy and light chain variable region sequences comprising SEQ ID NOs: 35 and 39, respectively; (b) heavy and light chain variable region sequences comprising SEQ ID NOs: 36 and 40, respectively; (c) heavy and light chain variable region sequences comprising SEQ ID NOs: 37 and 41, respectively; (d) heavy and light chain variable region sequences comprising SEQ ID NOs: 38 and 42, respectively; (e) heavy and light chain variable region sequences comprising SEQ ID NOs: 155 and 166, respectively; (f) heavy and light chain variable region sequences comprising SEQ ID NOs: 156 and 167, respectively; (g) heavy and light chain variable region sequences comprising SEQ ID NOs: 157 and 168, respectively; (h) heavy and light chain variable region sequences comprising SEQ ID NOs: 158 and 169, respectively; (i) heavy and light chain variable region sequences comprising SEQ ID NOs: 159 and 170, respectively; (j) heavy and light chain variable region sequences comprising SEQ ID NOs: 160 and 171, respectively; (k) heavy and light chain variable region sequences comprising SEQ ID NOs: 161 and 172, respectively; (l) heavy and light chain variable region sequences comprising SEQ ID NOs: 162 and 173, respectively; (m) heavy and light chain variable region sequences comprising SEQ ID NOs: 163 and 174, respectively; (n) heavy and light chain variable region sequences comprising SEQ ID NOs: 164 and 175, respectively; or (o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively.

[0237] Techniques for determining whether two antibodies bind to the same epitope include, e.g., epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope and hydrogen/deuterium exchange mass spectrometry (HDX-MS), methods monitoring the binding of the antibody to antigen fragments or mutated variations of the antigen, where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component, computational combinatorial methods for epitope mapping.

[0238]   An anti-FAM19A5 antibody or antigen binding portion thereof that would be useful in the methods disclosed herewith can bind to at least one epitope of mature human FAM19A5, as determined, *e.g.*, by binding of the antibodies to fragments of human FAM19A5. In some embodiments, anti-FAM19A5 antibodies or antigen binding portions thereof bind to a fragment located within the amino acid sequence of TLDRDSSQPRRTIARQTARC (SEQ ID NO: 6 or amino acid residues 42 to 61 of SEQ ID NO: 2), *e.g.*, an epitope having at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of SEQ ID NO: 6. In some embodiments, anti-FAM19A5 antibodies or antigen binding portion thereof bind to SEQ ID NO: 6 at one or more amino acids corresponding to amino acid residues 46 to 51 (*i.e.*, DSSQPR), *e.g.*, amino acid residues 46, 50, and 52 (*i.e.*, D---P-R), *e.g.*, amino acid residues 46, 47, 48, and 50 (*i.e.*, DSS-P) of SEQ ID NO: 2. In some embodiments, anti-FAM19A5 antibodies or antigen binding portions thereof bind to a fragment located within the amino acid sequence of CDMLPCLEGEGCDLLINRSG (SEQ ID NO: 9 or amino acids 90 to 109 of SEQ ID NO: 2), *e.g.*, an epitope having at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of SEQ ID NO: 9. In certain embodiments, anti-FAM19A5 antibodies or antigen binding portion thereof bind to SEQ ID NO: 9 at one or more amino acids residues 99 to 107 (*i.e.*, EGCDLLINR), *e.g.*, amino acid residues 102, 103, 105, and 107 (*i.e.*, DL-I-R), *e.g.*, amino acid residues 99, 100, 102, 103, 105, and 107 (*i.e.*, EG-DL-I-R), *e.g.*, amino acid residues 99, 100, and 107 (*i.e.*, EG------R) of SEQ ID NO: 4.

[0239]   In some embodiments, the at least one epitope has the amino acid sequence that is at least 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 6. In some embodiments, the at least one epitope has the amino acid sequence that is at least 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 9.

[0240]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to a human FAM19A5 epitope only, which is SEQ ID NO: 5, 6, 7, 8, 9, or 10, or a fragment located within the amino acid sequence of SEQ ID NO: 5, 6, 7, 8, 9, or 10, *e.g.*, an epitope having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of SEQ ID NO: 5, 6, 7, 8, 9, or 10.

[0241]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof of the present disclosure binds to SEQ ID NO: 6 or a fragment thereof in its native conformation (*i.e.*, un-denatured). In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof of the present disclosure binds to SEQ ID NO: 9 or a fragment thereof in its native conformation (*i.e.*, un-denatured). In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to both glycosylated and unglycosylated human FAM19A5.

[0242]   In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof further binds to one or more additional FAM19A5 epitopes. Therefore, certain anti-FAM19A5 antibodies or antigen binding portions thereof bind to an epitope of SEQ ID NO: 6 and an additional epitope or an epitope of SEQ ID NO: 9 and an additional epitope. Other anti-FAM19A5 antibodies or antigen binding portions thereof can bind to an epitope of SEQ ID NO: 5, SEQ ID NO: 9, and an additional epitope. In some embodiments, anti-FAM19A5 antibodies or antigen binding portions thereof bind to an epitope of SEQ ID NO: 6, an epitope of SEQ ID NO: 10, and an additional epitope. In some embodiments, the one or more additional FAM19A5 epitopes are selected from QLAAGTCEIVTLDR (SEQ ID NO: 5, epitope F1), TLDRDSSQPRRTIARQTARC (SEQ ID NO: 6, epitope F2), TARCACRKGQIAGTTRARPA (SEQ ID NO: 7, epitope F3), ARPACVDARIIKTKQWCDML (SEQ ID NO: 8, epitope F4), CDMLPCLEGEGCDLLINRSG (SEQ ID NO: 9, epitope F5), or NRSGWTCTQPGGRIKTTTVS (SEQ ID NO: 10, epitope F6), or a fragment located within the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, or any combination thereof. A fragment located within the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, includes a fragment having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of any of SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10. In some embodiments, the one or more additional FAM19A5 epitopes are selected from SEQ ID NO: 5, 6, 7, 8, 9, or 10, or a fragment located within the amino acid sequence of SEQ ID NO: 5, 6, 7, 8, 9, or 10, *e.g.*, a fragment having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of SEQ ID NO: 5, 6, 7, 8, 9, or 10, or any combination thereof. In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof of the disclosure binds to any of the one or more

additional epitopes in their native conformation (*i.e.*, un-denatured). In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to both glycosylated and unglycosylated of the one or more additional FAM19A5 epitopes.

[0243]   In some embodiments, anti-FAM19A5 antibodies or antigen binding portions thereof bind to at least one FAM19A5 epitope identified as EP2, EP4, and/or EP8, wherein EP2 comprises, consists essentially of, or consists of the amino acids DSSQP (SEQ ID NO: 66), wherein EP4 comprises, consists essentially of, or consists of the amino acids ARCACRK (SEQ ID NO: 68), and wherein EP8 comprises, consists essentially of, or consists of the amino acids TCTQPGGR (SEQ ID NO: 72). In some embodiments, the at least one epitope has the amino acid sequence that is at least 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to EP2, EP4, or EP8. In some embodiments, anti-FAM19A5 antibodies or antigen binding portion thereof only bind to EP2. In some embodiments, anti-FAM19A5 antibodies or antigen binding portion thereof bind to EP4 and EP8.

[0244]   In some embodiments, the anti-FAM19A5 antibody, or antigen binding portion thereof, binds to at least one FAM19A5 epitope identified as EP6, EP7, or EP8, wherein EP6 comprises the amino acids KTKQWCDML (SEQ ID NO: 70), wherein EP7 comprises the amino acids GCDLLINR (SEQ ID NO: 71), and wherein EP8 comprises the amino acids TCTQPGGR (SEQ ID NO: 72). In some embodiments, the at least one epitope has the amino acid sequence that is at least 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to EP6, EP7, or EP8. In some embodiments, the anti-FAM19A5 antibody, or antigen binding portion thereof, only binds to EP6, EP7, or EP8. In some embodiments, the anti-FAM19A5 antibody, or antigen binding portion thereof, binds to EP6, EP7, and EP8. In some embodiments, the anti-FAM19A5 antibody, or antigen binding portion thereof, binds to EP7 and EP8. In some embodiments, the anti-FAM19A5 antibody, or antigen binding portion thereof, binds to EP7.

[0245]   In some embodiments, anti-FAM19A5 antibodies or antigen binding portion thereof bind to one or more FAM19A5 epitopes selected from the group consisting of SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, and any combinations thereof.

[0246]   In certain embodiments, provided herein is an antibody or antigen binding portion thereof that binds to FAM19A5 (*e.g.*, human FAM19A5) with a 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or higher affinity than to another protein in the FAM19A family as measured by, *e.g.*, a immunoassay (*e.g.*, ELISA), surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, provided herein is an antibody or antigen binding portion thereof that binds to FAM19A5 (*e.g.*, human FAM19A5) with no cross reactivity with another protein in the FAM19A family as measured by, *e.g.*, an immunoassay.

[0247]   In certain embodiments, the anti-FAM19A5 antibodies are not native antibodies or are not naturally-occurring antibodies. For example, the anti-FAM19A5 antibodies have post-translational modifications that are different from those of antibodies that are naturally-occurring, such as by having more, less or a different type of post-translational modification.

V.   Exemplary Anti-FAM19A5 Antibodies

[0248]   Particular antibodies that can be used in the methods disclosed herein are antibodies, *e.g.*, monoclonal antibodies, having the CDR and/or variable region sequences disclosed herein, as well as antibodies having at least 80% identity (*e.g.*, at least 85%, at least 90%, at least 95%, or at least 99% identity) to their variable region or CDR sequences. The VH and VL amino acid sequences of different anti-FAM19A5 antibodies of the present disclosure are provided in Tables 4 and 5, respectively.

Table 2 Variable heavy chain CDR amino acid sequences (according to Kabat system)

Antibody	VH-CDR1	VH-CDR2	VH-CDR3
Anti-FAM19A5 ("2-13")	SHGMF (SEQ ID NO: 11)	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	STYECPGGFSCWGDTGQIDA (SEQ ID NO: 13)
Anti-FAM19A5 ("3-2")	SFNMF (SEQ ID NO: 14)	QISSSGSSTNYAPAVRG (SEQ ID NO: 15)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("1-65")	SYQMG (SEQ ID NO: 17)	VINKSGSDTS (SEQ ID NO: 18)	GSASYITAATIDA (SEQ ID NO: 19)
Anti-FAM19A5 ("1-28")	GFDFSDYG (SEQ ID NO: 20)	IRSDGSNP (SEQ ID NO: 21)	AKDGNGYCALDAYRSGGYSCGV YPGSIDA (SEQ ID NO: 22)

Anti-FAM19A5 ("P2-C12")	TYAVT (SEQ ID NO: 89)	YINWRGGTSYANWAKG (SEQ ID NO: 90)	DASSGAAFGSYGMDP (SEQ ID NO: 91)
Anti-FAM19A5 ("13B4")	SSNWWS (SEQ ID NO: 95)	EIYHGGTTNYNPSLKG (SEQ ID NO: 96)	WQLVGGLDV (SEQ ID NO: 97)
Anti-FAM19A5 ("13F7")	GYSWT (SEQ ID NO: 101)	EISHFGSANYNPSLKS (SEQ ID NO: 102)	ALRGTYSRFYYGMDV (SEQ ID NO: 103)
Anti-FAM19A5 ("15A9")	SYYWS (SEQ ID NO: 107)	YIYPSGSTNYNPSLKS (SEQ ID NO: 108)	VNPFGYYYAMDV (SEQ ID NO: 109)
Anti-FAM19A5 ("P1-A03")	SDYMS (SEQ ID NO: 113)	IIYPSTTTYYASWAKG (SEQ ID NO: 114)	GSNWSSGMNL (SEQ ID NO: 115)
Anti-FAM19A5 ("P1-A08")	TYYMS (SEQ ID NO: 119)	IVYPSGTTYYANWAKG (SEQ ID NO: 120)	GDSFGYGL (SEQ ID NO: 121)
Anti-FAM19A5 ("P1-F02")	NYYMG (SEQ ID NO: 125)	IIYASGSTYYASWAKG (SEQ ID NO: 126)	IDIGVGDYGWAYDRLDL (SEQ ID NO: 127)
Anti-FAM19A5 ("P2-A01")	GYYMS (SEQ ID NO: 131)	IIYPSGSTDYASWAKG (SEQ ID NO: 132)	VAGYVGYGYETFFDI (SEQ ID NO: 133)
Anti-FAM19A5 ("P2-A03")	NYDMS (SEQ ID NO: 137)	FMDTDGSAYYATWAKG (SEQ ID NO: 138)	RGSSYYGGIDI (SEQ ID NO: 139)
Anti-FAM19A5 ("P2-F07")	SYYMN (SEQ ID NO: 143)	IIYPSGTTYYAGWAKG (SEQ ID NO: 144)	TVSGYFDI (SEQ ID NO: 145)
Anti-FAM19A5 ("P2-F11")	SYGVS (SEQ ID NO: 149)	YIANNYNPHYASWAKG (SEQ ID NO: 150)	DNYGMDP (SEQ ID NO: 151)

Table 3 Variable light chain CDR amino acid sequences (according to Kabat system)

Antibody	VL-CDR1	VL-CDR2	VL-CDR3
Anti-FAM19A5 ("2-13")	SGGSYSYG (SEQ ID NO: 23)	WDDERPS (SEQ ID NO: 24)	GTEDISGTAGV (SEQ ID NO: 25)
Anti-FAM19A5 ("3-2")	SGGGSYAGSYYYG (SEQ ID NO: 26)	ESNKRPS (SEQ ID NO: 27)	GSWDSSNGGI (SEQ ID NO: 28)
Anti-FAM19A5 ("1-65")	SGGGSSGYGYG (SEQ ID NO: 29)	WNDKRPS (SEQ ID NO: 30)	GNDDYSSDSGYVGV (SEQ ID NO: 31)
Anti-FAM19A5 ("1-28")	GYGYG (SEQ ID NO: 32)	QND (SEQ ID NO: 33)	GSEDSSTLAGI (SEQ ID NO: 34)
Anti-FAM19A5 ("P2-C12")	QASQSISSYLS (SEQ ID NO: 92)	EASKLAS (SEQ ID NO: 93)	QQGYSSTNVWNA (SEQ ID NO: 94)

Anti-FAM19A5 ("13B4")	SGDKLGNVYAS (SEQ ID NO: 98)	QDNKRPS (SEQ ID NO: 99)	QAWDSSTAV (SEQ ID NO: 100)
Anti-FAM19A5 ("13F7")	RSSQSLLHSNGYNYLD (SEQ ID NO: 104)	LGSNRAS (SEQ ID NO: 105)	MQARQTPLT (SEQ ID NO: 106)
Anti-FAM19A5 ("15A9")	RASQSISTSLN (SEQ ID NO: 110)	GASTLQS (SEQ ID NO: 111)	QESASIPRT (SEQ ID NO: 112)
Anti-FAM19A5 ("P1-A03")	LASEDIYSGIS (SEQ ID NO: 116)	GASNLES (SEQ ID NO: 117)	LGGYSYSSTGLT (SEQ ID NO: 118)
Anti-FAM19A5 ("P1-A08")	TADTLSRSYAS (SEQ ID NO: 122)	RDTSRPS (SEQ ID NO: 123)	ATSDGSGSNYQYV (SEQ ID NO: 124)
Anti-FAM19A5 ("P1-F02")	LASEDIYSGIS (SEQ ID NO: 128)	GASNLES (SEQ ID NO: 129)	LGGYSYSSIT (SEQ ID NO: 130)
Anti-FAM19A5 ("P2-A01")	LASEDIYSGIS (SEQ ID NO: 134)	GASNLES (SEQ ID NO: 135)	LGGVTYSSTGTHLT (SEQ ID NO: 136)
Anti-FAM19A5 ("P2-A03")	QASQSIGGNLA (SEQ ID NO: 140)	RASTLAS (SEQ ID NO: 141)	QSPAYDPAAYVGNA (SEQ ID NO: 142)
Anti-FAM19A5 ("P2-F07")	LASEDIYSALA (SEQ ID NO: 146)	GTSNLES (SEQ ID NO: 147)	QGYSSYPLT (SEQ ID NO: 148)
Anti-FAM19A5 ("P2-F11")	QASQSVYNNKNLA (SEQ ID NO: 152)	AASTLAS (SEQ ID NO: 153)	QGEFSCSSADCNA (SEQ ID NO: 154)

Table 4: Variable heavy chain amino acid sequence

Antibody	VH Amino Acid Sequence (SEQ ID NO)
Anti-FAM19A5 ("2-13")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSHGMFWVRQTPGKGLEYVAEITNDGSGTNY GSAVKGRATISRDNGQSTVRLQLNNLRAEDTGTYFCARSTYECPGGFSCWGDTGQIDAWG HGTEVIVSS (SEQ ID NO: 35)
Anti-FAM19A5 ("3-2")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSFNMFWVRQAPGKGLEYVAQISSSGSSTNY APAVRGRATISRDNGQSTVRLQLNNPGAEDTGTYYCAKSSYDCPYGHCSSGVDSAGEIDA WGHGTEVIVSS (SEQ ID NO: 36)
Anti-FAM19A5 ("1-65")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSYQMGWVRQAPGKGLEWVGVINKSGSDTSY GSAVKGRATISRDNGQSTVRLQLNNLRAEDTGTYFCAKGSASYITAATIDAWGHGTEVIV SS (SEQ ID NO: 37)
Anti-FAM19A5 ("1-28")	AVTLDESGGGLQTPGGALSLVCKASGFDFSDYGMGWVRQAPGKGLEWVAAIRSDGSNPSY GSAVKGRATISKDNGRSTVRLQLNNLRAEDTATYYCAKDGNGYCALDAYRSGGYSCGVYP GSIDAWGHGTEVIVSS (SEQ ID NO: 38)
Anti-FAM19A5 ("P2-C12")	QSLEESGGRLVTPGTPLTLTCTVSGFSLSTYAVTWVRQAPGKGLEWIGYINWRGGTSYAN WAKGRFTISKTSSTTVDLKMTSPTTEDTATYFCARDASSGAAFGSYGMDPWGPGTLVTVS S (SEQ ID NO: 155)

Anti-FAM19A5 ("13B4")	QVQLQESGPGLVKPSGTLSLNCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHGGTTNY NPSLKGRVTMSVDKTKNQFSLRLSSVTAVDTAVYYCARWQLVGGLDVWGQGTTVTVSS (SEQ ID NO: 156)
Anti-FAM19A5 ("13F7")	QVQLQEWGAGLLKPSETLSLTCAINAESFNGYSWTWIRQTPGKGLEWIGEISHFGSANYN PSLKSRATISADKSKNQFSLKLTSVTAVDTAVYYCARALRGTYSRFYYGMDVWGQGTTVT VSS (SEQ ID NO: 157)
Anti-FAM19A5 ("15A9")	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYPSGSTNYN PSLKSRVTISVDTSKNQFSLNLKSVTAVDTAVYYCARVNPFGYYYAMDVWGQGTTVTVSS (SEQ ID NO: 158)
Anti-FAM19A5 ("P1-A03")	QSVEESGGRLVTPGTPLTLTCTVSGFSLSSDYMSWVRQAPGEGLEWIGIIYPSTTTYYAS WAKGRFTISKTSSTTVELKMTSLTTEDTATYFCARGSNWSSGMNLWGPGTLVTVSS (SEQ ID NO: 159)
Anti-FAM19A5 ("P1-A08")	QSLEESGGRLVTPGTPLTLTCTASGFSLSTYYMSWVRQAPGKGLEWIGIVYPSGTTYYAN WAKGRFTISTASTTVDLMITSPTTEDTATYFCARGDSFGYGLWGPGTLVTVSS (SEQ ID NO: 160)
Anti-FAM19A5 ("P1-F02")	QSLEESGGRLVTPGTPLTLTCTASGFSLSNYYMGWVRQAPGEGLEWIGIIYASGSTYYAS WAKGRFTISKTSTTVDLKMTSLTTEDTATYFCARIDIGVGDYGWAYDRLDLWGQGTLVTV SS (SEQ ID NO: 161)
Anti-FAM19A5 ("P2-A01")	QEQLVESGGRLVTPGTPLTLSCTASGFFLSGYYMSWVRQAPGKGLEWIGIIYPSGSTDYA SWAKGRFTISKTSTTVDLKITTPTTEDTATYFCARVAGYVGYGYETFFDIWGPGTLVTVS L (SEQ ID NO: 162)
Anti-FAM19A5 ("P2-A03")	QSVEESGGRLVTPGTPLTLTCTVSGFSLNNYDMSWVRQAPGKGLEYIGFMDTDGSAYYAT WAKGRFTISRTSTTVDLKMTSPTTEDTATYFCARRGSSYYGGIDIWGPGTPVTVSL (SEQ ID NO: 163)
Anti-FAM19A5 ("P2-F07")	QSLEESGGRLVTPGTPLTLTCTASGFSLSSYYMNWVRQAPGKGLEWIGIIYPSGTTYYAG WAKGRFTISKTSTTVDLKITSPTSEDTATYFCARTVSGYFDIWGPGTLVTVSL (SEQ ID NO: 164)
Anti-FAM19A5 ("P2-F11")	QEQLVESGGRLVTPGTTLTLTCTVSGFSLSSYGVSWVRQAPGKGLEWIGYIANNYNPHYA SWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARDNYGMDPWGPGTLVTVSS (SEQ ID NO: 165)

Table 5: Variable light chain amino acid sequence

Antibody	VL Amino Acid Sequence (SEQ ID NO)
Anti-FAM19A5 ("2-13")	ALTQPSSVSANPGETVKITCSGGSYSYGWFQQKSPGSALVTVIYWDDERPSDIPSRFSGA LSGSTNTLTITGVQADDEAVYFCGTEDISGTAGVFGAGTTLTVL (SEQ ID NO: 39)
Anti-FAM19A5 ("3-2")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKAPGSAPVTLIYESNKRPSDIPS RFSGSTSGSTATLTITGVQADDEAIYYCGSWDSSNGGIFGAGTTLTVL (SEQ ID NO: 40)
Anti-FAM19A5 ("1-65")	ALTQPSSVSANPGETVKITCSGGGSSGYGYGWYQQKSPSSAPLTVIYWNDKRPSDIPSRF SGSKSGSTHTLTITGVQAEDEAVYFCGNDDYSSDSGYVGVFGAGTTLTVL (SEQ ID NO: 41)
Anti-FAM19A5 ("1-28")	ALTQPSSVSANLEGTVEITCSGSGYGYGWYQQKSPGSAPVTVIYQNDKRPSDIPSRFSGS KSGSTGTLTITGVQVEDEAVYYCGSEDSSTLAGIFGAGTTLTVL (SEQ ID NO: 42)
Anti-FAM19A5 ("P2-C12")	ELDMTQTPSSVSAAVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYEASKLASGVPS RFSGSGYGTEFTLTISDLECADAATYYCQQGYSSTNVWNAFGGGTNVEIK (SEQ ID NO: 166)
Anti-FAM19A5 ("13B4")	SYELTQPLSVSVSPGQTASITCSGDKLGNVYASWYQQKPGQSPTLVIYQDNKRPSGIPER FSGSNSGKTATLTISGTQALDEADYYCQAWDSSTAVFGGGTKLTVL (SEQ ID NO: 167)
Anti-FAM19A5	DIVMTQTPLSLPVAPGEPASISCRSSQSLLHSNGYNYLDWYVQKPGQPPQLLIYLGSNRA SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPLTFGGGTKVEIK (SEQ ID

("13F7")	NO: 168)
Anti-FAM19A5 ("15A9")	DIQMTQSPSSLSASVGDRITISCRASQSISTSLNWYQQTPGKAPRLLIYGASTLQSGVPS RFSGGGSGTDFSLTITSLQPEDFATYYCQESASIPRTFGQGTKLDIK (SEQ ID NO: 169)
Anti-FAM19A5 ("P1-A03")	ELVMTQTPPSLSASVGETVRIRCLASEDIYSGISWYQQKPEKPPTLLISGASNLESGVPP RFSGSGSGTDYTLTIGGVQAEDAATYYCLGGYSYSSTGLTFGAGTNVEIK (SEQ ID NO: 170)
Anti-FAM19A5 ("P1-A08")	ELVLTQSPSVQVNLGQTVSLTCTADTLSRSYASWYQQKPGQAPVLLIYRDTSRPSGVPDR FSGSSSGNTATLTISGAQAGDEADYYCATSDGSGSNYQYVFGGGTQLTVT (SEQ ID NO: 171)
Anti-FAM19A5 ("P1-F02")	ELDMTQTPPSLSASVGETVRIRCLASEDIYSGISWYQQKPGKPPTLLIYGASNLESGVPP RFSGSGSGTDYTLTIGGVQAEDAATYYCLGGYSYSSITFGAGTNVEIK (SEQ ID NO: 172)
Anti-FAM19A5 ("P2-A01")	ELVMTQTPPSLSASVGETVRIRCLASEDIYSGISWYQQKPGKPPTLLIYGASNLESGVPP RFSGSGSGSDYTLTIGGVQAEDAATYYCLGGVTYSSTGTHLTFGAGTNVEIK (SEQ ID NO: 173)
Anti-FAM19A5 ("P2-A03")	ELDLTQTPASVSEPVGGTVTIKCQASQSIGGNLAWYQQKPGQPPKLLIYRASTLASGVPS RFKGSGSGTDFTLTISDLECADAATYYCQSPAYDPAAYVGNAFGGGTELEIL (SEQ ID NO: 174)
Anti-FAM19A5 ("P2-F07")	ELDLTQTPPSLSASVGGTVTINCLASEDIYSALAWYQQKPGKPPTLLISGTSNLESGVPP RFSGSGSGTDYTLTIGGVQAEDAATYFCQGYSSYPLTFGAGTNVEIK (SEQ ID NO: 175)
Anti-FAM19A5 ("P2-F11")	ELDLTQTPSSVSAAVGGTVTINCQASQSVYNNKNLAWYQQKPGQPPKLLIYAASTLASGV SSRFKGSGSGTQFTLTISDVQCDDAATYYCQGEFSCSSADCNAFGGGTELEIL (SEQ ID NO: 176)

[0249]   Accordingly, provided herein is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising heavy and light chain variable regions, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NOs: 35-38 or 155-165. In other embodiments, the isolated anti-FAM19A5 antibody, or an antigen binding portion thereof, comprises the CDRs of the heavy chain variable region selected from the group consisting of SEQ ID NOs: 35-38 or 155-165.

[0250]   Also provided is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising heavy and light chain variable regions, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NOs: 39-42 or 166-176. In other embodiments, the isolated anti-FAM19A5 antibody, or an antigen binding portion thereof, comprises the CDRs of the light chain variable region selected from the group consisting of SEQ ID NOs: 39-42 or 166-176.

[0251]   In certain embodiments, the isolated anti-FAM19A5 antibody, or an antigen binding portion thereof, comprises the CDRs of the heavy chain variable region selected from the group consisting of SEQ ID NOs: 35-38 or 155-165 and the CDRs of the light chain variable region selected from the group consisting of SEQ ID NOs: 39-42 or 166-176.

[0252]   Also provided is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising heavy and light chain variable regions, (i) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 35 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 39; (ii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 36 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 40; (iii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 37 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 41; (iv) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 38 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 42; (v) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 155 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 166; (vi) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 156 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 167; (vii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 157 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 168; (viii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 158 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 169; (ix) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 159 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 170; (x) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 160 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 171; (xi) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 161 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 172; (xii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 162 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 173; (xiii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 163 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 174; (xiv) wherein the heavy chain variable

region comprises the amino acid sequence of SEQ ID NO: 164 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 175; and (xv) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 165 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 176.

[0253]   Provided herein is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NOs: 35-38 or 155-165.

[0254]   Also provided herein is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NOs: 39-42 or 166-176.

[0255]   Also provided is an isolated anti-FAM19A5 antibody, or an antigen-binding portion thereof, comprising heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NOs: 35-38 or 155-165, and wherein the light chain variable region comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as SEQ ID NOs: 39-42 or 166-176.

[0256]   In some embodiments, the disclosure provides an isolated anti-FAM19A5 antibody, or an antigen -binding portion thereof, comprising:

(a) heavy and light chain variable region sequences comprising SEQ ID NOs: 35 and 39, respectively;

(b) heavy and light chain variable region sequences comprising SEQ ID NOs: 36 and 40, respectively;

(c) heavy and light chain variable region sequences comprising SEQ ID NOs: 37 and 41, respectively;

(d) heavy and light chain variable region sequences comprising SEQ ID NOs: 38 and 42, respectively;

(e) heavy and light chain variable region sequences comprising SEQ ID NOs: 155 and 166, respectively;

(f) heavy and light chain variable region sequences comprising SEQ ID NOs: 156 and 167, respectively;

(g) heavy and light chain variable region sequences comprising SEQ ID NOs: 157 and 168, respectively;

(h) heavy and light chain variable region sequences comprising SEQ ID NOs: 158 and 169, respectively;

(i) heavy and light chain variable region sequences comprising SEQ ID NOs: 159 and 170, respectively;

(j) heavy and light chain variable region sequences comprising SEQ ID NOs: 160 and 171, respectively;

(k) heavy and light chain variable region sequences comprising SEQ ID NOs: 161 and 172, respectively;

(l) heavy and light chain variable region sequences comprising SEQ ID NOs: 162 and 173, respectively;

(m) heavy and light chain variable region sequences comprising SEQ ID NOs: 163 and 174, respectively;

(n) heavy and light chain variable region sequences comprising SEQ ID NOs: 164 and 175, respectively; or

(o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively.

[0257]   In certain embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof of the present disclosure comprises (i) the heavy chain CDR1, CDR2 and CDR3 of 2-13, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 2-13, or any combinations thereof; (ii) the heavy chain CDR1, CDR2 and CDR3 of 3-2, or

combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 3-2, or any combinations thereof; (iii) the heavy chain CDR1, CDR2 and CDR3 of 1-65, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-65, or any combinations thereof; (iv) the heavy chain CDR1, CDR2 and CDR3 of 1-28, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-28, or any combinations thereof; (v) the heavy chain CDR1, CDR2, and CDR3 of P2-C12, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P2-C12, or any combinations thereof; (vi) the heavy chain CDR1, CDR2, and CDR3 of 13B4, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 13B4, or any combinations thereof; (vii) the heavy chain CDR1, CDR2, and CDR3 of 13F7, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 13F7, or any combinations thereof; (viii) the heavy chain CDR1, CDR2, and CDR3 of 15A9, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 15A9, or any combinations thereof; (ix) the heavy chain CDR1, CDR2, and CDR3 of P1-A03, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P1-A03, or any combinations thereof; (x) the heavy chain CDR1, CDR2, and CDR3 of P1-A08, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P1-A08, or any combinations thereof; (xi) the heavy chain CDR1, CDR2, and CDR3 of P1-F02, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P1-F02, or any combinations thereof; (xii) the heavy chain CDR1, CDR2, and CDR3 of P2-A01, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P2-A01, or any combinations thereof; (xiii) the heavy chain CDR1, CDR2, and CDR3 of P2-A03, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P2-A03, or any combinations thereof; (xiv) the heavy chain CDR1, CDR2, and CDR3 of P2-F07, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P2-F07, or any combinations thereof; or (xv) the heavy chain CDR1, CDR2, and CDR3 of P2-F11, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of F2-F11, or any combinations thereof. The amino acid sequences of the VH CDR1, CDR2, and CDR3 for the different anti-FAM19A5 antibodies disclosed herein are provided in Table 2. The amino acid sequences of the VL CDR1, CDR2, and CDR3 for the different anti-FAM19A5 antibodies disclosed herein are provided in Table 3.

[0258]   The amino acid sequences of the VH CDR1, CDR2, and CDR3 for 2-13 are set forth in SEQ ID NOs: 11, 12, and 13, respectively. The amino acid sequences of the VL CDR1, CDR2s and CDR3 for 2-13 are set forth in SEQ ID NOs: 23, 24, and 25, respectively. The amino acid sequences of the VH CDR1, CDR2, and CDR3 for 3-2 are set forth in SEQ ID NOs: 14, 15, and 16, respectively. The amino acid sequences of the VL CDR1, CDR2s and CDR3 for 3-2 are set forth in SEQ ID NOs: 26, 27, and 28, respectively. The amino acid sequences of the VH CDR1, CDR2, and CDR3 for 1-65 are set forth in SEQ ID NOs: 17, 18, and 19, respectively. The amino acid sequences of the VL CDR1, CDR2s and CDR3 for 1-65 are set forth in SEQ ID NOs: 29, 30, and 31, respectively. The amino acid sequences of the VH CDR1, CDR2, and CDR3 for 1-28 are set forth in SEQ ID NOs: 20, 21, and 22, respectively. The amino acid sequences of the VL CDR1, CDR2s and CDR3 for 1-28 are set forth in SEQ ID NOs: 32, 33, and 34, respectively.

[0259]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof of the disclosure, which specifically binds to human FAM19A5, comprises:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 11; and/or

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and/or

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 13.

[0260]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0261]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

(a) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 23; and/or

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 24; and/or

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 25.

[0262]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0263]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprise:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 11;

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 12;

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 13;

(d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 23;

(e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 24; and/or

(f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 25.

[0264]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof of the disclosure, which specifically binds to human FAM19A5, comprises:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 14; and/or

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 15; and/or

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0265]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0266]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

(a) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 26; and/or

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 27; and/or

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 28.

[0267]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0268]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprise:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 14;

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 15;

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 26;

(e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 27; and/or

(f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 28.

[0269]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof of the disclosure, which specifically binds to human FAM19A5, comprises:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 17; and/or

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 18; and/or

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 19.

[0270]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0271]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

(a) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 29; and/or

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 30; and/or

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31.

[0272]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0273]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprise:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 17;

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 18;

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 19;

(d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 29;

(e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 30; and/or

(f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31.

[0274]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof of the disclosure, which specifically binds to human FAM19A5, comprises:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 20; and/or

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 21; and/or

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 22.

[0275]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0276]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

(a) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 32; and/or

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 33; and/or

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 34.

[0277]   In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0278]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprise:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 20;

(b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 21;

(c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 22;

(d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 32;

(e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 33; and/or

(f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 34.

[0279]   In specific embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof comprises one, two, three, four, five, or six of the CDRs above.

[0280]   A VH domain, or one or more CDRs thereof, described herein can be linked to a constant domain for forming a heavy chain, e.g., a full length heavy chain. Similarly, a VL domain, or one or more CDRs thereof, described herein can be linked to a constant domain for forming a light chain, e.g., a full length light chain. A full length heavy chain and full length light chain combine to form a full length antibody.

[0281]   Accordingly, in specific embodiments, provided herein is an antibody comprising an antibody light chain and heavy chain, e.g., a separate light chain and heavy chain. With respect to the light chain, in a specific embodiment, the light chain of an antibody described herein is a kappa light chain. In another specific embodiment, the light chain of an antibody described herein is a lambda light chain. In yet another specific embodiment, the light chain of an antibody described herein is a human kappa light chain or a human lambda light chain. In a particular embodiment, an antibody described herein, which specifically binds to an FAM19A5 polypeptide (e.g., human FAM19A5) comprises a light chain which comprises any VL or VL CDR amino acid sequences described herein, and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region. In a particular embodiment, an antibody described herein, which specifically binds to an FAM19A5 polypeptide (e.g., human FAM19A5) comprises a light chain which comprises a VL or VL CDR amino acid sequences described herein, and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Patent No. 5,693,780 and Kabat EA et al, (1991) supra.

[0282]   With respect to the heavy chain, in some embodiments, the heavy chain of an antibody described herein can be an alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In another specific embodiment, the heavy chain of an antibody described

can comprise a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In one embodiment, an antibody described herein, which specifically binds to FAM19A5 (*e.g.*, human FAM19A5), comprises a heavy chain which comprises a VH or VH CDR amino acid sequence described herein, and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region. In another embodiment, an antibody described herein, which specifically binds to FAM19A5 (*e.g.*, human FAM19A5), comprises a heavy chain which comprises a VH or VH CDR amino acid sequence disclosed herein, and wherein the constant region of the heavy chain comprises the amino acid of a human heavy chain described herein or known in the art. Non-limiting examples of human constant region sequences have been described in the art, *e.g.*, *see* U.S. Patent No. 5,693,780 and Kabat EA *et al.*, (1991) *supra*.

[0283]   In some embodiments, an antibody described herein, which specifically binds to FAM19A5 (*e.g.*, human FAM19A5) comprises a VL domain and a VH domain comprising the VH or VH CDRs and VL and VL CDRs described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule. In another specific embodiment, an antibody described herein, which specifically binds to FAM19A5 (*e.g.*, human FAM19A5) comprises a VL domain and a VH domain comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) of immunoglobulin molecule. In some embodiments, the constant regions comprise the amino acid sequences of the constant regions of a human IgG, which are naturally-occurring, including subclasses (*e.g.*, IgG1, IgG2, IgG3 or IgG4), and allotypes (*e.g.*, G1m, G2m, G3m, and nG4m) and variants thereof. *See, e.g.*, Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014) and Jefferis R. and Lefranc MP, *mAbs* 1:4, 1-7(2009). In some embodiments, the constant regions comprise the amino acid sequences of the constant regions of a human IgG1, IgG2, IgG3, or IgG4, or variants thereof.

[0284]   In certain embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof disclosed herein does not have Fc effector functions, *e.g.*, complement-dependent

cytotoxicity (CDC) and/or antibody-dependent cellular phagocytosis (ADCP). Effector functions are mediated by the Fc region and the residues most proximal to the hinge region in the CH2 domain of the Fc region are responsible for effector functions of antibodies as it contains a largely overlapping binding site for C1q (complement) and IgG-Fc receptors (FcγR) on effector cells of the innate immune system. Also, IgG2 and IgG4 antibodies have lower levels of Fc effector functions than IgG1 and IgG3 antibodies. Effector functions of an antibody can be reduced or avoided by different approaches known in the art, including (1) using antibody fragments lacking the Fc region (*e.g.*, such as a Fab, F(ab')$_2$, single chain Fv (scFv), or a sdAb consisting of a monomeric VH or VL domain); (2) generating aglycosylated antibodies, which can be generated by, for example, deleting or altering the residue the sugar is attached to, removing the sugars enzymatically, producing the antibody in cells cultured in the presence of a glycosylation inhibitor, or by expressing the antibody in cells unable to glycosylate proteins (*e.g.*, bacterial host cells, *see, e.g.*, U.S. Pub. No. 20120100140); (3) employing Fc regions from an IgG subclass that have reduced effector function (*e.g.*, an Fc region from IgG2 or IgG4 antibodies or a chimeric Fc region comprising a CH2 domain from IgG2 or IgG4 antibodies, *see, e.g.*, U.S. Pub. No. 20120100140 and Lau C. *et al. J. Immunol.* 191:4769-4777 (2013)); and (4) generating an Fc region with mutations that result in reduced or no Fc functions. *See, e.g.*, U.S. Pub. No. 20120100140 and U.S. and PCT applications cited therein and An *et al. mAbs* 1:6, 572-579 (2009).

[0285]   Thus, in some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof disclosed herein is an Fab, an Fab', an F(ab')2, an Fv, a single chain Fv (scFv), or a sdAb consisting of a monomeric VH or VL domain. Such antibody fragments are well known in the art and are described *supra*.

[0286]   In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof disclosed herein comprises an Fc region with reduced or no Fc effector function. In some embodiments, the constant regions comprise the amino acid sequences of the Fc region of a human IgG2 or IgG4, in some embodiments, the anti-FAM19A5 antibody is of an IgG2/IgG4 isotype. In some embodiments, the anti-FAM19A5 antibody comprises a chimeric Fc region which comprises a CH2 domain from an IgG antibody of the IgG4 isotype and a CH3 domain from an IgG antibody of the IgG1 isotype, or a chimeric Fc region which comprises a hinge region from IgG2 and a CH2 region from IgG4, or an Fc

region with mutations that result in reduced or no Fc functions. Fc regions with reduced or no Fc effector function include those known in the art. *See e.g.*, Lau C. *et al. J. Immunol.* 191:4769-4777 (2013); An *et al.*, *mAbs* 1:6, 572-579 (2009); and U.S. Pub. No. 20120100140 and the U.S. patents and publications and PCT publications cited therein. Also Fc regions with reduced or no Fc effector function can be readily made by a person of ordinary skill in the art.

VI.   Nucleic Acid Molecules

[0287]   Another aspect described herein pertains to one or more nucleic acid molecules that encode any one of the antibodies or antigen-binding portions thereof described herein. The nucleic acids can be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids (*e.g.*, other chromosomal DNA, *e.g.*, the chromosomal DNA that is linked to the isolated DNA in nature) or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, restriction enzymes, agarose gel electrophoresis and others well known in the art. *See,* F. Ausubel, *et al.* , ed. (1987) Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York. A nucleic acid described herein can be, for example, DNA or RNA and can or cannot contain intronic sequences. In a certain embodiments, the nucleic acid is a cDNA molecule.

[0288]   Nucleic acids described herein can be obtained using standard molecular biology techniques. For antibodies expressed by hybridomas (*e.g.*, hybridomas prepared from transgenic mice carrying human immunoglobulin genes as described further below), cDNAs encoding the light and heavy chains of the antibody made by the hybridoma can be obtained by standard PCR amplification or cDNA cloning techniques. For antibodies obtained from an immunoglobulin gene library (*e.g.*, using phage display techniques), nucleic acid encoding the antibody can be recovered from the library.

[0289]   Certain nucleic acids molecules described herein are those encoding the VH and VL sequences of the various anti-FAM19A5 antibodies of the present disclosure. Exemplary DNA sequences encoding the VH sequence of such antibodies are set forth in SEQ ID NOs: 43-46 and 177. Exemplary DNA sequences encoding the VL sequences of such antibodies are set forth in SEQ ID NOs: 47-50 and 178.

Table 6: Variable heavy chain polynucleotide sequence

Antibody	Variable Heavy Chain Polynucleotide Sequence (SEQ ID NO)
Anti-FAM19A5 (2-13)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCGGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTCACCTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGACG CCCGGCAAGGGGTTGGAATATGTCGCTGAAATTACCAATGATGGTAGTGGCACAAACTAC GGGTCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACAGTGAGG CTGCAGCTGAACAACCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTACT TATGAATGTCCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCCA (SEQ ID NO: 43)
Anti-FAM19A5 (3-2)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCGGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTCACCTTCAGCAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCGCTCAAATTAGCAGCAGTGGTAGTAGCACAAACTAC GCACCCGCGGTGAGGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACAGTGAGG CTGCAGCTGAACAACCCCGGGGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCCA (SEQ ID NO: 44)
Anti-FAM19A5 (1-65)	GCCGTGACACTGGACGAATCTGGGGGAGGGCTGCAGACTCCAGGCGGAGCTCTGAGCCTG GTGTGCAAGGCATCCGGGTTCACCTTTAGCTCCTACCAGATGGGATGGGTGCGGCAGGCA CCAGGGAAGGGCCTGGAGTGGGTCGGAGTGATCAACAAATCTGGGAGTGACACAAGCTAC GGCAGCGCCGTGAAGGGAAGGGCCACCATCAGCAGGGACAATGGCCAGAGTACCGTGCGG CTGCAGCTGAACAATCTGCGCGCTGAGGACACTGGCACCTACTTCTGTGCTAAGGGATCA GCAAGCTATATCACAGCCGCTACTATTGATGCATGGGGACACGGGACAGAAGTCATCGTG TCTAGT (SEQ ID NO: 45)
Anti-FAM19A5 (1-28)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCGGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTCGACTTCAGCGATTATGGCATGGGTTGGGTGCGACAGGCT CCAGGCAAGGGGCTGGAGTGGGTTGCTGCTATTAGAAGTGATGGTAGTAACCCATCATAC GGGTCGGCGGTGAAGGGCCGTGCCACCATCTCGAAGGACAACGGGCGAAGCACAGTGAGG CTGCAGCTGAACAACCTCAGGGCTGAGGACACCGCCACCTACTACTGCGCCAAGGATGGT AATGGTTACTGTGCTCTCGATGCTTATCGTAGTGGTGGTTATAGTTGTGGTGTTTATCCT GGTAGCATCGACGCATGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 46)
Anti-FAM19A5 (P2-C12)	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACC TGCACCGTCTCTGGATTCTCCCTCAGTACCTATGCAGTGACCTGGGTCCGCCAGGCTCCA GGGAAGGGGCTGGAATGGATCGGATACATTAATTGGCGTGGTGGGACATCCTACGCGAAC TGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATG ACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCTAGTAGTGGT GCTGCTTTTGGGTCTTACGGCATGGACCCCTGGGGCCCAGGGACCCTCGTCACCGTCTCT TCA (SEQ ID NO: 177)

Table 7: Variable light chain polynucleotide sequence

Antibody	Variable Light Chain Polynucleotide Sequence (SEQ ID NO)
Anti-FAM19A5 (2-13)	GGCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATAACCTG CTCCGGGGGTAGCTATAGCTATGGCTGGTTCCAGCAGAAGTCTCCTGGCAGTGCCCTTGT CACTGTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGC CCTATCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGACGACGAGGCTGT CTATTTCTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAAC CCTGACCGTCCTGGG (SEQ ID NO: 47)
Anti-FAM19A5 (3-2)	GGCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTG CTCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTACCAGCAGAAGGCACC TGGCAGTGCCCCTGTCACTCTGATCTATGAAAGCAACAAGAGACCCTCGGACATCCCTTC ACGATTCTCCGGTTCCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGC CGATGACGAGGCTATCTATTACTGTGGGAGCTGGGACAGTAGCAATGGTGGTATATTTGG GGCCGGGACAACCCTGACCGTCCTAGG (SEQ ID NO: 48)
Anti-FAM19A5	GCCCTGACTCAGCCCTCTTCCGTGTCAGCCAACCCTGGAGAAACTGTGAAGATCACCTGC AGCGGAGGAGGGAGCTCCGGATACGGATATGGGTGGTATCAGCAGAAATCCCCATCTAGT

(1-65)	GCCCCCCTGACTGTGATCTATTGGAACGACAAGAGGCCTAGTGATATTCCATCAAGATTC AGTGGATCAAAAAGCGGGTCCACTCACACCCTGACAATCACTGGCGTGCAGGCAGAGGAC GAAGCCGTCTACTTCTGCGGAAATGACGATTACTCAAGCGATTCTGGCTATGTGGGCGTC TTTGGCGCAGGAACCACACTGACAGTGCTG (SEQ ID NO: 49)
Anti-FAM19A5 (1-28)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCTGGAAGGAACCGTCGAGATCACCTGC TCCGGGAGTGGCTATGGTTATGGCTGGTATCAGCAGAAGTCTCCTGGCAGTGCCCCTGTC ACTGTGATCTATCAGAACGACAAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTTCC AAATCCGGCTCCACGGGCACATTAACCATCACTGGGGTCCAAGTCGAGGACGAGGCTGTC TATTACTGTGGGAGTGAAGACAGCAGCACTCTTGCTGGTATATTTGGGGCCGGGACAACC CTGACCGTCCTA (SEQ ID NO: 50)
Anti-FAM19A5 (P2-C12)	GAGCTCGATATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACC ATCAAGTGCCAGGCCAGTCAGAGCATTAGTAGCTACTTATCCTGGTATCAGCAGAAACCA GGGCAGCCTCCCAAGCTCCTGATCTATGAAGCATCCAAACTGGCCTCTGGGGTCCCATCG CGGTTCAGCGGCAGTGGATATGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGT GCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTAGTACTAATGTTTGGAATGCT TTCGGCGGAGGCACCAATGTGGAAATCAAA (SEQ ID NO: 178)

[0290]   A method for making an anti-FAM19A5 antibody as disclosed herewith can comprise expressing the relevant heavy chain and light chain of the antibody in a cell line comprising the nucleotide sequences encoding the heavy and light chains with a signal peptide, *e.g.*, SEQ ID NOs: 43 and 47, SEQ ID NOs: 44 and 48, SEQ ID NOs: 45 and 49, SEQ ID NOs: 46 and 50, SEQ ID NOs: 177 and 178, respectively. Host cells comprising these nucleotide sequences are encompassed herein.

[0291]   Once DNA fragments encoding VH and VL segments are obtained, these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

[0292]   The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (hinge, CH1, CH2 and/or CH3). The sequences of human heavy chain constant region genes are known in the art (*see, e.g.*, Kabat, E. A., *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD

constant region, for example, an IgG2 and/or IgG 4 constant region. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

[0293]   The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL. The sequences of human light chain constant region genes are known in the art (*see, e.g.*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region.

[0294]   To create a scFv gene, the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, *e.g.*, encoding the amino acid sequence (Gly4-Ser)3, such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (*see, e.g.*, Bird *et al.* (1988) *Science* 242:423-426; Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883; McCafferty *et al.*, (1990) *Nature* 348:552-554).

[0295]   In some embodiments, the present disclosure provides a vector comprising an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or antigen-binding portion thereof. In other embodiments, the vectors can be used for gene therapy.

[0296]   Suitable vectors for the disclosure include expression vectors, viral vectors, and plasmid vectors. In one embodiment, the vector is a viral vector.

[0297]   As used herein, an expression vector refers to any nucleic acid construct which contains the necessary elements for the transcription and translation of an inserted coding sequence, or in the case of an RNA viral vector, the necessary elements for replication and translation, when introduced into an appropriate host cell. Expression vectors can include plasmids, phagemids, viruses, and derivatives thereof.

[0298]   Expression vectors of the disclosure can include polynucleotides encoding the antibody or antigen-binding portion thereof described herein. In one embodiment, the coding sequences for the antibody or antigen-binding portion thereof is operably linked to an expression control sequence. As used herein, two nucleic acid sequences are operably

linked when they are covalently linked in such a way as to permit each component nucleic acid sequence to retain its functionality. A coding sequence and a gene expression control sequence are said to be operably linked when they are covalently linked in such a way as to place the expression or transcription and/or translation of the coding sequence under the influence or control of the gene expression control sequence. Two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a coding nucleic acid sequence if the gene expression sequence were capable of effecting transcription of that coding nucleic acid sequence such that the resulting transcript is translated into the desired antibody or antigen-binding portion thereof.

[0299]   Viral vectors include, but are not limited to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; lentivirus; adenovirus; adeno-associated virus; SV40-type viruses; polyomaviruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors well-known in the art. Certain viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (*i.e.*, capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell line with plasmid, production of recombinant retroviruses by the packaging cell line,

collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M., Gene Transfer and Expression, A Laboratory Manual, W.H. Freeman Co., New York (1990) and Murry, E. J., Methods in Molecular Biology, Vol. 7, Humana Press, Inc., Cliffton, N.J. (1991).

[0300]   In one embodiment, the virus is an adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus can be engineered to be replication-deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hematopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, the adeno-associated virus can integrate into human cellular DNA in a site-specific manner, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

[0301]   In other embodiments, the vector is derived from lentivirus. In certain embodiments, the vector is a vector of a recombinant lentivirus capable of infecting non-dividing cells.

[0302]   The lentiviral genome and the proviral DNA typically have the three genes found in retroviruses: gag, pol and env, which are flanked by two long terminal repeat (LTR) sequences. The gag gene encodes the internal structural (matrix, capsid and nucleocapsid) proteins; the pol gene encodes the RNA-directed DNA polymerase (reverse transcriptase), a protease and an integrase; and the env gene encodes viral envelope glycoproteins. The 5' and 3' LTR's serve to promote transcription and polyadenylation of the virion RNA's. The LTR contains all other cis-acting sequences necessary for viral replication. Lentiviruses have additional genes including vif, vpr, tat, rev, vpu, nef and vpx (in HIV-l, HIV-2 and/or SIV).

[0303]   Adjacent to the 5' LTR are sequences necessary for reverse transcription of the genome (the tRNA primer binding site) and for efficient encapsidation of viral RNA into particles (the Psi site). If the sequences necessary for encapsidation (or packaging of

retroviral RNA into infectious virions) are missing from the viral genome, the cis defect prevents encapsidation of genomic RNA.

[0304]   However, the resulting mutant remains capable of directing the synthesis of all virion proteins. The disclosure provides a method of producing a recombinant lentivirus capable of infecting a non-dividing cell comprising transfecting a suitable host cell with two or more vectors carrying the packaging functions, namely gag, pol and env, as well as rev and tat. As will be disclosed herein below, vectors lacking a functional tat gene are desirable for certain applications. Thus, for example, a first vector can provide a nucleic acid encoding a viral gag and a viral pol and another vector can provide a nucleic acid encoding a viral env to produce a packaging cell. Introducing a vector providing a heterologous gene, herein identified as a transfer vector, into that packaging cell yields a producer cell which releases infectious viral particles carrying the foreign gene of interest.

[0305]   According to the above-indicated configuration of vectors and foreign genes, the second vector can provide a nucleic acid encoding a viral envelope (env) gene. The env gene can be derived from nearly any suitable virus, including retroviruses. In some embodiments, the env protein is an amphotropic envelope protein which allows transduction of cells of human and other species.

[0306]   Examples of retroviral-derived env genes include, but are not limited to: Moloney murine leukemia virus (MoMuLV or MMLV), Harvey murine sarcoma virus (HaMuSV or HSV), murine mammary tumor virus (MuMTV or MMTV), gibbon ape leukemia virus (GaLV or GALV), human immunodeficiency virus (HIV) and Rous sarcoma virus (RSV). Other env genes such as Vesicular stomatitis virus (VSV) protein G (VSV G), that of hepatitis viruses and of influenza also can be used.

[0307]   The vector providing the viral env nucleic acid sequence is associated operably with regulatory sequences described elsewhere herein.

[0308]   In certain embodiments, the vector includes a lentiviral vector in which the HIV virulence genes env, vif, vpr, vpu and nef were deleted without compromising the ability of the vector to transduce non-dividing cells.

[0309]   In some embodiments, the vector includes a lentiviral vector which comprises a deletion of the U3 region of the 3' LTR. The deletion of the U3 region can be the complete deletion or a partial deletion.

[0310]   In some embodiments, the lentiviral vector of the disclosure comprising the FVIII nucleotide sequence described herein can be transfected in a cell with (a) a first nucleotide sequence comprising a gag, a pol, or gag and pol genes and (b) a second nucleotide sequence comprising a heterologous env gene; wherein the lentiviral vector lacks a functional tat gene. In other embodiments, the cell is further transfected with a fourth nucleotide sequence comprising a rev gene. In certain embodiments, the lentiviral vector lacks functional genes selected from vif, vpr, vpu, vpx and nef, or a combination thereof.

[0311]   In certain embodiments, a lentiviral vector comprises one or more nucleotide sequences encoding a gag protein, a Rev-response element, a central polypurine track (cPPT), or any combination thereof.

[0312]   Examples of the lentiviral vectors are disclosed in WO9931251, WO9712622, WO9817815, WO9817816, and WO9818934, which are incorporated herein by reference in their entireties.

[0313]   Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. *See, e.g.,* Sambrook *et al.,* Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells *in vivo* because of their inability to replicate within and integrate into a host genome. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operably encoded within the plasmid. Some commonly used plasmids available from commercial suppliers include pBR322, pUC18, pUC19, various pcDNA plasmids, pRC/CMV, various pCMV plasmids, pSV40, and pBlueScript. Additional examples of specific plasmids include pcDNA3.1, catalog number V79020; pcDNA3.1/hygro, catalog number V87020; pcDNA4/myc-His, catalog number V86320; and pBudCE4.1, catalog number V53220, all from Invitrogen (Carlsbad, CA.). Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids can be custom designed using standard molecular biology techniques to remove and/or add specific fragments of DNA.

VII.   Antibody Production

[0314]   Antibodies or fragments thereof that immunospecifically bind to FAM19A5 (*e.g.,* human FAM19A5) can be produced by any method known in the art for the synthesis of

antibodies, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. *See, e.g.*, Maniatis T *et al.*, (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B *et al.*, (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[0315]   In a specific embodiment, an antibody described herein is an antibody (*e.g.*, recombinant antibody) prepared, expressed, created or isolated by any means that involves creation, *e.g.*, via synthesis, genetic engineering of DNA sequences. In certain embodiments, such antibody comprises sequences (*e.g.*, DNA sequences or amino acid sequences) that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.*, human) in vivo.

VIII.   Pharmaceutical Compositions

[0316]   Further provided herein are compositions comprising an antibody or antigen-binding portion thereof described herein (*e.g.*, anti-FAM19A5 antibody) having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as

methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

[0317]   In some embodiments, pharmaceutical compositions comprise an antibody or antigen-binding portion thereof, a bispecific molecule, or a immunoconjugate described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In certain embodiments, pharmaceutical compositions comprise an effective amount of an antibody or antigen-binding portion thereof described herein, and optionally one or more additional prophylactic of therapeutic agents, in a pharmaceutically acceptable carrier. In some embodiments, the antibody is the only active ingredient included in the pharmaceutical composition. Pharmaceutical compositions described herein can be useful in reducing a FAM19A5 activity, and thereby treat a cancer.

[0318]   Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances. Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium

bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0319]   A pharmaceutical composition can be formulated for any route of administration to a subject. Specific examples of routes of administration include intranasal, oral, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, subcutaneously, or intraventricularly. Parenteral administration, characterized by either subcutaneous, intramuscular or intravenous injection, is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[0320]   Preparations for parenteral administration of an antibody include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions can be either aqueous or nonaqueous.

[0321]   If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0322]   Topical mixtures comprising an antibody are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension,

emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0323]   An antibody or antigen-binding portion thereof described herein can be formulated as an aerosol for topical application, such as by inhalation (*see, e.g.,* U.S. Patent Nos. 4,044,126, 4,414,209 and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[0324]   An antibody or antigen-binding portion thereof described herein can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the antibody alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0325]   Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer an antibody. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[0326]   In certain embodiments, a pharmaceutical composition comprising an antibody or antigen-binding portion thereof described herein is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions and other mixtures. It can also be reconstituted and formulated as solids or gels. The lyophilized powder is prepared by dissolving an antibody or antigen-binding portion thereof described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent can contain an excipient which improves the stability or other pharmacological component of the powder or

reconstituted solution, prepared from the powder. Excipients that can be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent can also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In some embodiments, the resulting solution can be apportioned into vials for lyophilization. Each vial can contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to room temperature.

[0327]   Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[0328]   The antibodies or antigen-binding portions thereof, the bispecific molecule, or the immunoconjugate described herein and other compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, *see, e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In a specific embodiment, the anti-FAM19A5 antibody or antigen-binding portion thereof described herein can be used treat a cancer.

[0329]   The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

IX.   Kits

[0330]   Provided herein are kits comprising one or more antibodies described herein, or antigen-binding portions thereof, bispecific molecules, or immunoconjugates thereof. In some embodiments, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies provided herein or an

antigen-binding portion thereof, optional an instructing for use. In some embodiments, the kits contain a pharmaceutical composition described herein and any prophylactic or therapeutic agent, such as those described herein.

Examples

[0331]   The following experimental methods and details are referenced in the Examples that follow.

Example 1 Expression and purification of human FAM19A5 protein

[0332]   Recombinant human FAM19A5 protein was produced and purified and the purified protein was used in an antibody screening assay based on binding affinity analysis. First, LPS-hT plasmid containing the FAM19A5 gene was transformed into bacteria and protein over-expression was induced. Once produced, the FAM19A5 protein was purified using an Ni-NTA affinity chromatography (Qiagen, Valencia, CA, USA). Using gradually higher concentration of imidazole, we removed the His-tagged FAM19A5 protein from the Ni-column. The protein expression in the solution is measured using Coomassie Brilliant Blue R-250 Dye. Taking only the FAM19A5 immidazole containing solution, we concentrated the FAM19A5 protein using PBS. When the concentration was complete, both the purity and concentration of the FAM19A5 protein were measured using a Western Blot assay. The concentrated protein was subsequently used to screen for FAM19A5-specific antibodies.

Example 2 Production of antibody libraries FAM19A5

[0333]   The FAM19A5 protein was used as antigen for immunization of a chicken. 50 µg of the synthetic peptide KLH conjugate was mixed in 750 µl phosphate buffered saline (PBS) and incubated at 37 °C for 30 minutes. Afterwards, the toxin is removed in a 2% squalene endotoxin MPL (monophosphorylate lipid A species) and mycobacteria (mycobacteria) of the cell wall components of TDW and CWS containing a water-in-oil emulsion adjuvant (RIBI + MPL + TDM + CWS adjuvant, Sigma, St. Louis, Mo, USA) in emulsified, which was then subcutaneously injected into three chickens. The chickens were immunized for a total of three times, approximately 2-3 weeks apart between immunization. The titer of the antibodies obtained from the immunized chickens was

measured via immune blotting using lysates of HEK293T cells which overexpressed the FAM19A5 protein. Sera from chickens that received the three immunizations were used as primary antibody. The secondary antibody used was anti-chicken IgG(Y) polyclonal antibody conjugated to HRP (Horseradish peroxidase) (Rabbit anti-chicken IgG (Y)-HRP, Millipore corporation, Billeria, MA, USA).

[0334]   Single-chain variable fragment (scFv) library was prepared from immunized chicken Using TRI reagent (Invitrogen, Carlsbad , CA USA), we extracted RNAs from the spleen, bone marrow, and synovial sac of the immunized chickens described above. Oligo-dT primers and SUPERSCRIPT™ III First-Strand Synthesis System (Invitrogen) were used to synthesize the first strand cDNA. For the cDNA obtained from the immune system of chickens, Expand High Fidelity PCR System (Roche Molecular Systems, IN, USA) was used to produce a single chain variable region library. In each reaction, 1 μL of cDNA, 60 pmol of each primer, 10 μL of 10 × reaction buffer solution, 8 μL of 2.5mM dNTP (Promega, Madison, WI , USA), and 0.5 μL of Taq DNA polymerase were mixed with water. The final volume was 100 μL PCR reaction was performed using the following conditions: 30 cycles of (i) 15 seconds at 94 °C (ii)30 seconds at 56 °C, and (iii) 90 seconds at 72 °C, followed by a final extension for 10 minutes at 72 °C. The PCR products comprising a fragment having a length of about 350bp were loaded onto a 1.5% agarose gel and after electrophoresis, QIAGEN Gel II Extraction Kit (QIAGEN, Valencia, CA, USA) was used to purify the nucleotide fragment. The purified PCR product was quantified by reading at OD 260nm. (1 unit OD = 50 μg/ml).

[0335]   Two VH and VL first products from the second PCR were connected randomly by the overlap extension PCR (Overlap extension PCR). Each PCR reaction was mixed with 100ng of the purified VL and VH products, 60 pmol of each primer, 10 μL 10 × reaction buffer, 8 μL of 2.5mM dNTP, 0.5 μL of Taq DNA polymerase, and water in a final volume of 100 μL of. PCR was performed under the following conditions: 25 cycles of (i) 15 seconds at 94 °C, (ii) 30 seconds at 56 °C, and (iii) 2 minutes at 72 °C, followed by final extension for 10 minutes at 72 °C. The PCR products comprising a single chain variable region fragment having a length of about 700bp were loaded onto a 1.5% agarose gel and after electrophoresis, QIAGEN II Gel Extraction Kit (QIAGEN) was used to purify the nucleotide fragment. The purified PCR product was quantified by reading at OD 260nm. (1 unit OD = 50 /ml).

[0336]   The scFv fragment of the PCR product and vector pComb3X - SS (The Scripps Research Institute, CA, USA) were digested with a Sfi I restriction enzyme. 10µg of the purified overlapping PCT product was mixed with 360 units of Sif I, (µg DNA per 16 units, Roche Molecular Systems, Pleasanton, CA, USA), 20 µL of a 10X reaction buffer, and water to the final volume with 200 µL. 20 µg of the pComb3X-SS vector was mixed with 120 units of Sfi I (µg DNA per 6 units), 20 µL of a10 × reaction buffer solution, and water to the final volume to 200 µL. The mixture was digested at 50 °C for 8 hours. Afterwards, the digested product comprising the scFv fragment (about 700bp) and the vector (about 3400 bp) was loaded onto a 1% agarose gel and purified using a Gel Extraction Kit II QIAGEN (QIAGEN, Valencia, CA, USA). 1400ng of the Sfi I-restricted pComb3X vector and 700ng of the digested scFv fragments were mixed with 5 × a ligase buffer, 10 µL of T4 DNA ligase (Invitrogen, Carlsbad, CA, USA), and water to a final volume of 200 µL. The mixture was incubated at 16 °C for 16 hours to perform the ligation.

[0337]   After precipitation with ethanol, the DNA pellet was dissolved in 15 µL of water. To produce a library, the ligation sample was transformed into *E.coli* strain ER2738 (New England Biolabs Inc., Hitchin, Hertfordshine, SG4 OTY, England, UK) via electroporation using the vibrator gene (Gene pulser: Bio - Rad Laboratories, Hercules, CA, USA). Cells were mixed in a 5ml Super Broth (SB) medium and incubated while stirring at 250rpm for one hour at 37 °C. Then, 3 µL of 100 mg/mL kanamycin was added to 10 mL of SB medium. To determine the library size, 0.1 µL, 1 µL and 10 µL of the culture sample were smeared onto Luria Broth (LB) agar plates containing 50 µg/mL of kanamycin. After stirring for 1 hour, 4.5 µL of 100 mg/mL kanamycin was added to the LB culture and further stirred for an additional 1 hour. Then, 2ml of the VCM13 helper phage in water (> 10^{11}cfu/ml) was added to the LB medium, along with pre-heated LB (183 mL) containing 92.5 µL of 100 mg/mL kanamycin. This mixture was stirred at 250rpm at 37 °C for an additional 2 hours. Next, 280 µL (50 mg/mL) of kanamycin was added to the culture and stirred overnight at 37 °C. The next day, the bacteria pellet was centrifuged using a high-speed centrifuge (Beckman, JA-10 rotor) at 3,000g, 4 °C. Afterwards, the bacterial pellet was used to extract phagemid DNA, while the supernatant was transferred to sterile centrifuge bottles. Next 8 grams of polyethylene glycol -8000 (PEG-8000, Sigma) and 6 grams of sodium chloride was added (NaCl,

Merck) to the supernatant, and then kept for 30 minutes in ice. Afterwards, the supernatant was centrifuged 15 minutes at 15,000g, 4 °C. The supernatant was then discarded, and the phage pellet Tris containing 1% BSA - reproduction was suspended in buffered saline (TBS).

Example 3 Library panning (Bio-panning) on an immobilized antigen

[0338]   Bio-panning was performed using magnetic beads (Dynabeads M - 270 Epoxy, Invitrogen). At room temperature, approximately 1×10^7 beads were coated with 5 µg of recombinant FAM19A5 protein by stirring, while rotating, the beads and the protein together for 20 hours at room temperature. Once the coating was done, the beads were washed 4 times with phosphate buffered saline (PBS) and blocked for one hour in PBS containing 3% BSA at room temperature. Then, the coated beads were cultured for two hours at room temperature with Phage-displayed scFv described above. To remove any phage that was not bound to the antigen coated beads, the beads were washed with 0.05% Tween20/PBS. Then the bound phages were eluted with 50 µL of 0.1M glycine/hydrogen chloride (0.1M Glycine-HCl, pH 2.2) and neutralized with 3 µL of 2M Tris with hydrogen chloride (tris-HCl, pH 9.1). This phage-containing supernatants were used to infect *E.coli* ER2738 cells and VCSM13 helper phage was used to amplify and rescue overnight. Also the input (input) and production (output) by phage titers from the phage-infected cultures were determined by blotting the phage-infected cultures on LB agar plates containing 50 µg/ml of kanamycin. The next day, PEG-8000 and NaCl were used to precipitate phages, which were used subsequently for bio-panning. Bio-panning was performed up to a total of five different times by repeating the above process. With each amplification, the phages were screened and selected for high affinity to the FAM19A5 protein.

Example 4 Selection of clone by phage ELISA

[0339]   To analyze the clones selected from the bio-panning, we randomly selected individual clones from the phase-displayed scFv and confirmed using ELISA that the clones bind to the FAM19A5 recombinant protein. The FAM19A5 recombinant protein was diluted in 0.1M NaHCO₃ buffer, and 100ng/well of the protein was used to coat 96-well microtiter plates at 4 °C for 16 hours. Next day, the plates were blocked with 3% BSA/PBS at 37 °C for 1 hour. Then, the phage supernatant was mixed with 6% BSA/PBS

and was cultured for 2 hours at 37 °C. The plates containing the supernatant were then washed with 0.05% Tween20/PBS. The HRP-conjugated M13 antibody (a-M13-HRP, Pierce Chemical Co, Rockford, IL, USA) was diluted to 1/5000. 50 μL of the diluted antibody was added to the plates and incubated for 1 hour at 37 °C. After the incubation and washing, the plates were added with 0.05M citrate buffer solution, 1 μg/ml of 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS, Amresco, Solon, OH, USA), and 0.1% H_2O_2 for color development. The absorbance for each well was measured at 405 nm.

[0340]   24 clones that bind to the FAM19A5 recombinant protein and show high absorbance were analyzed. From the 24 clones, we obtained 13 scFv clones having unique sequences. After further selecting the clones, we obtained clone 1-65 having the highest affinity.

Example 5 Production of anti-FAM19A5-IgG2/4 antibody

[0341]   Anti-FAM19A5 scFv was subcloned into a mammalian expression vector In the FAM19A5 scFv gene sequence, a human Cκ gene was connected to the light chain variable domain, and human immunoglobulin isotype IgG2/4 of CH1, CH2, and CH3 genes were connected to the heavy chain variable region. The antibody having each light chain and each heavy chain was synthesized by adding restriction sites (Genscript, USA). The synthesized gene was inserted into the mammalian cell expression vector having a modified restriction site to facilitate cloning. First, the light chain gene was inserted into the vector using Hind III and Xba I (New England Biolabs , UK) restriction enzymes and then adding the heavy chain gene to the vector by using NheI and BamHI (New England Biolabs , UK) restriction enzymes.

[0342]   In order to express and purify an anti-FAM19A5-IgG2/4 antibody, we used a mammalian cell transfection and overexpression injection system. We mixed 2 μg/ml of the mammalian expression vector with 4 μg of polyethyleneimine (PEI, Polysciences, Warrington, PA, USA) in 150mM sodium chloride (NaCl, Merck) corresponding to 1/10 of the cell culture volume. The mixture was allowed to stand for 15 minutes at room temperature. The mixture was added to HEK293F cells (2×10^6 cells/ml, Invitrogen), which were then incubated in the FREESTYLE™ 293 expression culture medium containing 100U/ml of penicillin and streptomycin (Invitrogen) at 7% CO_2 and 37 °C and in a stirring condition of 135rpm for six days. To purify the expressed anti-FAM19A5

IgG2/4 antibodies from the cell culture supernatant, we used Protein A bead (RepliGen, Waltham, MA, USA) affinity gel chromatography. The protein A chromatography was run on 4 ~ 12% Bis-Tris gradient gel electrophoresis. The size and yield of the protein was confirmed by the Coomassie Brilliant Blue staining.

Example 6 Human liver cancer patient analysis

[0343]   To assess FAM19A5 expression in liver cancer, FAM19A5 protein expression was measured in human liver biopsies using immunohistochemistry. Briefly, liver samples were obtained from liver cancer patients with varying degree of fibrosis (*i.e.*, stage #0 to stage #4). The tissue samples were immunostained with anti-FAM19A5 antibody and then counterstained with hematoxylin and eosin (H&E).

[0344]   As shown in FIG. 1, there was a significant increase in FAM19A5 protein expression in the liver tissue from stage #2 and stage #4 cancer patient as compared to stage #0 patient. The increased FAM19A5 expression was centralized primarily around areas of scar formation and in the hepatic stellate cells. The increase in FAM19A5 expression also correlated with disease progression, with stage #4 liver tissue expressing much higher levels of FAM19A5 as compared to stage #2 liver tissue. Collectively, this data demonstrates that FAM19A5 also plays an important role in human liver cancer.

Example 7 Analysis of the efficacy of anti-FAM19A5 antibody administration in liver cancer xenograft model

[0345]   To assess the anti-tumor efficacy of anti-FAM19A5 antibodies on human liver cancer, the xenograft mouse model of liver cancer was used. Briefly, nude mice were purchased and housed in specific pathogen-free (SPF) conditions. After approximately a week of adaptation period, the animals were injected subcutaneously with Hep3B cells and/or human hepatic stellate cells (HHSteC). To do so, the cells were first treated with trypsin to prepare a single cell suspension. Next, the cells were washed and approximately 5×10^6 of Hep3B and/or 0.4×10^6 HHSteC cells were resuspended in 100 µL of DMEM media. The cells were then injected subcutaneously into the right flank of the nude mice using an insulin syringe. About 3 weeks post-injection, the animals were observed for tumor formation.

[0346]   Upon tumor formation (~3 weeks after injection), the animals were injected intravenously with either normal human immunoglobulin (NHI, control) or 3-2 human

IgG1 anti-FAM19A5 antibody (2.5 mg/kg). The animals received the antibodies once a week for a total of 3 weeks. Both the body weight and tumor size were assessed each week. And at 42 days post inoculation, the animals were sacrificed and the tumors were further analyzed.

[0347]   As shown in FIG. 2A, the animals from all the different groups had similar body weight throughout the duration of the experiments. And as shown in FIGs 2B-2D, the administration of the anti-FAM19A5 antibody had minimal anti-tumor effect on animals inoculated with only Hep3B cells (*i.e.*, "Hep3B + NHI" and "Hep3B + FAM19A5 Ab"). But in animals inoculated with both Hep3B cells and HHSteC, the administration of the anti-FAM19A5 antibody resulted in significant reduction in tumor size/weight (*i.e.*, "Hep3B+HHSteC + NHI" v. "Hep3B+HHSteC + FAM19A5 Ab"). Such data shows that the interaction of anti-FAM19A5 antibody with the hepatocellular hepatic stellate cells in the tumor microenvironment can treat liver cancer.

Example 8 Evaluation of anticancer effect of anti-FAM19A5 antibody in an inducible mouse melanoma model

[0348]   To evaluate the anticancer effect of anti-FAM19A5 antibodies, melanoma was induced by crossbreeding male Tyr :: CreER; Braf+/+; Ptenlox/lox mice (Jackson Lab, USA) with female Tyr :: CreER; BrafCA/CA; Ptenlox/lox to produce Tyr :: CreER; BrafCA/+; Ptenlox/lox mice. Resulting crossbred mouse was a well-known animal model to mimic clinical manifestation of naturally occurring melanoma. *See* Dankort D., *et al.*, *Nat Genet* 41(5): 544-552 (2009). Melanoma was induced spontaneously from 7 weeks after birth, and each mouse was sorted according to their tumor volume and melanoma number.

[0349]   Following separation, either human IgG or anti-FAM19A5 antibody was intravenously injected at a dose of 5 mg/kg, from 8 weeks after birth, once a week, for a total of three injections (weeks 8, 9, and 10). At week 12 (*i.e.*, 4 weeks after initial antibody administration), volumetric analysis of mouse melanoma was performed with the use of Caliber (Caliber; Mitutoyo, Japan). *See* FIG. 3A.

[0350]   As shown in FIGs. 3B and 3C, the anti-FAM19A5 antibody-treated group showed significant inhibition of melanoma growth compared to the control human IgG-treated group in terms of both tumor volume (FIG. 3B) and area of pigmented regions (FIG. 3C).

Example 9 Vessel Normalization and promotion of immune cell infiltration following administration of anti-FAM19A5 antibodies in a mouse melanoma model

[0351]   Next, to assess the effect of anti-FAM19A5 on blood vessel normalization and immune cell infiltration into the melanoma, melanoma was induced in mice and either human IgG or anti-FAM19A5 antibody was administered as described in Example 8. Then, the mice were given intraperitoneal local anesthesia with 0.5 cc/100 g of urethane. The chest skin was incised and IV injected to the left cardia ventricle and 50 ml of 0.9% saline was administered to drain out the blood. Mice were fixed by perfusing with 50 ml of phosphate buffered saline (PBS) containing 4% paraformaldehyde (PFA).

[0352]   Melanoma was isolated from the skin of the fixed mice and post-fixed with phosphate buffered saline (PBS) containing 4% paraformaldehyde (PFA). After 24 hours, the melanoma was transferred into PBS and stored until used. For three-dimensional analysis, CLARITY and immunohistochemistry were used to observe blood vessel and immune cell distribution in the melanoma after anti-FAM19A5 antibody treatment. CD31 and IBA1 were used as markers for vascular endothelial cells and macrophages, respectively. Fluorescence image of samples prepared at about 700-750 μm were obtained using a confocal microscope (Leica).

[0353]   As shown in FIG. 4, the distribution pattern of blood vessels in the control group (top image) was similar to that observed in cancer tissues, with poor vessel connectivity and irregular vessel directions. In contrast, the anti-FAM19A5-antibody treated group demonstrated similar characteristics to those of normal tissues forming regular vessels with increased vessel connectivity and more regular vessel directions. *See* FIG. 4 (bottom image); *see also* FIG. 5 (images under the column labeled CD31).

[0354]   Moreover, macrophage distribution in the control group was intensively concentrated only within the subcutaneous tissue, with significantly decreased distribution in the epidermis (FIG. 5, upper middle panel). On the other hand, in the anti-FAM19A5 antibody-treated group, there was an even distribution of macrophages throughout the tissues (FIG. 5, lower middle panel).

[0355]   Again, without wishing to be bound by any particular mechanism or theory, these results indicated that therapeutic treatment with anti-FAM19A5 antibodies can mediate blood vessel normalization, which, in turn, can promote infiltration of immune cells into the melanoma.

Example 10 Promotion of immune cell infiltration following anti-FAM19A5 antibody
treatment in a spontaneous melanoma mouse model

[0356]   To further assess the effect of the anti-FAM19A5 antibody on immune cells,
melanoma was induced in the mice and either human IgG or anti-FAM19A5 antibody
was administered as described in Example 8. Then, mice were given intraperitoneal local
anesthesia with 0.5 cc/100 g of urethane. The chest skin was incised and IV injected to
the left cardia ventricle and 50 ml of 0.9% saline was administered to drain out blood.
Mice were fixed by perfusing with 50 ml of phosphate buffered saline (PBS) containing
4% paraformaldehyde (PFA). Melanoma was isolated from the skin of fixed mouse and
post-fixed with phosphate buffered saline (PBS) containing 4% paraformaldehyde (PFA).

[0357]   The melanoma was then incubated with PBS containing 30% sucrose for further
24 hours. The tissue was then placed in a tissue mold and frozen on dry ice with an
Optimal Cutting Temperature (OCT) composition containing 30% sugar solution. The
skin tissue was cut to 30 μm using a cryostat microtome. Immunohistochemistry was used
to analyze immune cell distribution in melanoma following anti-FAM19A5 antibody
treatment.

[0358]   In order to examine the distribution of immune cells in the melanoma tumor mass,
CD45, leukocyte common antigen marker, and Iba-1, macrophage marker, were co-
labeled to confirm macrophage and dendritic cell distribution, respectively. Also, CD45
and CD3, T lymphocyte markers, were co-labeled to confirm T lymphocyte distribution.

[0359]   Evident from the macrophage or dendritic cell distribution analysis (see FIG. 6A),
the distribution of macrophage or dendritic cell in the melanoma of anti-FAM19A5
antibody-treated group was similar to that of the human IgG-treated group (FIG. 6B).
However, the voxel intensity per macrophage and/or dendritic cell was significantly
increased in anti-FAM19A5 antibody-treated group compared to the human IgG-treated
group, indicating increase of cellular volume of the macrophage (FIGs. 6C and 6D).

[0360]   In addition, significantly higher infiltration of T lymphocytes was evident in the
anti-FAM19A5 antibody-treated group compared to those animals treated with human
IgG (FIGs. 7A and 7B).

[0361]   This result indicated that blood vessel normalization occurred within the
melanoma after anti-FAM19A5 antibody treatment, subsequently increasing the cellular
volume of the macrophages and T lymphocyte infiltration into the melanoma.

Example 11 Evaluation of the effect of anti-FAM19A5 antibody on immune cell
infiltration to the tumor tissue in mouse syngeneic colon adenocarcinoma model

[0362] Using a syngeneic tumor model of anticancer efficacy, the degree of immune cell infiltration into tumor tissue was evaluated by extraction of MC-38 colon adenocarcinoma model tumor from the animals. Briefly, colon adenocarcinoma tumor cells (5×10^5) were transplanted into each mouse. When tumor size reached about 80-100 mm3, the animals were separated into different groups. Then, either human IgG or anti-FAM19A5 antibody was administered (via intraperitoneal injection) to the animals from the relevant groups (twice daily for 2 weeks at a dose of 2.5 mg/kg). Ten days after the last antibody administration, mice were sacrificed and tumors harvested.

[0363] The harvested tumors of specific size were sieved through cell strainer for uniform single-cell suspension. The cells were washed with PBS and cells from each tumor were divided into three tubes, which were resuspended in 100 µl. Each tube was treated individually with 1 µg of anti-CD3 FITC antibody (abcam, ab34722), anti-Ly6G FITC antibody (abcam, ab25024), or rat IgG FITC antibody (abcam, ab37364) as isotype control. Antibody-cell suspensions were left at 4 °C for 30 minutes, and then washed with PBS for fluorescence-activated cell sorting (FACS) (Guava, Merck) analysis.

[0364] Mouse syngeneic colon adenocarcinoma model treated with the anti-FAM19A5 antibody (3-2), in comparison to animals that received the control human IgG, demonstrated an increase in T cell infiltration within the cancer tissue (FIG. 8A). Similarly, the anti-FAM19A5 antibody treated animals also had approximately 25% reduction in the frequency of myeloid-derived suppressor cells (MDSCs) within the cancer tissue, compared to the control animals (FIG. 8B).

[0365] These findings indicated that anti-FAM19A5 antibody administration can increase T cell infiltration while reducing MDSC recruitment to tumor tissue, causing modification of tumor tissue's immune suppressive environment and thereby leading to enhancement of anticancer efficacy.

Example 12 Evaluation of the anti-tumor effect of anti-FAM19A5 antibody in syngeneic
tumor growth models

[0366] The objective of this study was to evaluate the anti-tumor efficacy of an anti-FAM19A5 antibody (3-2) in different subcutaneous syngeneic murine tumor models. The tumor models tested included: 4T-1 tumor cells (Breast cancer), A20 tumor cells (B Cell

Lymphoma), B16F10 tumor cells (Melanoma), LLC tumor cells (Lung Cancer), Pan02 tumor cells (Pancreatic Cancer), Renca tumor cells (Kidney Cancer), RM-1 tumor cells (Prostate Cancer), WEHI-164 tumor cells (Fibrosarcoma), and MC-38 tumor cells (Colon adenocarcinoma).

[0367]   To induce the tumors, each mouse was inoculated subcutaneously at the right flank region with one of the mouse tumor cells provided below in 0.1 mL of PBS: (i) 4T-1 tumor cells (3×10^5), (ii) A20 tumor cells (5×10^5), (iii) B16F10 tumor cells (2×10^5), (iv) LLC tumor cells (3×10^5), (v) Pan02 tumor cells (3×10^6), (vi) Renca tumor cells (1×10^6), (vii) RM-1 tumor cells (1×10^6), (viii) WEHI-164 tumor cells (1×10^6), or MC-38 tumor cells (5×10^5).

[0368]   After the inoculation, tumor volume was measured twice a week in two dimensions using a caliper, and the measured volume was expressed in mm^3 by the formula: $V = 0.5 \times a \times b^2$, where a and b are the long and short diameters of the tumor, respectively. The antibody treatment began once tumor volume reached 80-100 mm^3. The animal numbers, dosage, dosage route and administration schedule of each study groups are shown in Table 8.

[0369]   Tumor growth inhibition was expressed as TGI (%) = 100 x (1-T/C), which is an indication of anti-tumor effectiveness. T and C are mean tumor volumes from the anti-FAM19A5 antibody treated group and the control (human IgG) treated group, respectively.

Table 8. Study Design

Group	N	Treatment	Dose (mg/kg)	Dosing Route	Schedule
1	8	hIgG	2.5	i.p.	BIW x 3 weeks
2	8	FAM19A5 Ab	2.5	i.p.	BIW x 3 weeks

[0370]   The TGI (%) of each syngeneic tumor growth model treated with the anti-FAM19A5 antibody in Table 9 was used to evaluate the anti-tumor effect of the anti-FAM19A5 antibody.

Table 9. TGI (%) of various syngenic tumor growth models treated with anti-FAM19A5 antibody

Tumor Type	4T-1	A20	B16F10	LLC	Pan02	Renca	RM-1	WEHI-164	MC-38
Days (post-tumor	29	27	21	34	32	31	20	22	21

inoculation)									
TGI%	10.92	15.2	6.03	11.83	19.00	16.98	15.00	41.00	11.89

[0371]   These results demonstrated that the growth of syngeneic tumor was inhibited in anti-FAM19A5 antibody-treated group when compared to the negative control human IgG-treated group.

Example 13 Evaluation of the anticancer effects of anti-FAM19A5 antibody in xenograft mouse model of human pancreatic cancer

[0372]   To further assess the anticancer effects of anti-FAM19A5 antibody, a human pancreatic cancer xenograft model was used. Briefly, MIA paca-2 cells (ATCC; Manassas, VA) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS), 2.5% horse serum, and 1% penicillin/streptomycin at 37 °C, 95% CO2. Cells were then harvested using 0.05% trypsin-0.02% EDTA, centrifuged (3 min at 1500 rpm), and resuspended in PBS at a concentration of 1 x 10^7 cells/0.1 mL. To induce tumor growth, nude mice were anesthetized with ketamine/xylazine and the left flank area was disinfected with 70% alcohol. An incision (0.7-1 cm) was made in the disinfected area to expose the pancreas. Then, the MIA paca-2 cells (1 x 10^7 cells / 0.1 mL) were injected into the pancreas using an insulin syringe (1 mL, 31G). Human IgG (negative control) or anti-FAM19A5 antibody (3-2) were administered intravenously to the animals, at a dose of 2.5 mg/kg at days 10, 17, and 24 post tumor induction. To assess the effect of the anti-FAM19A5 antibody in combination with gemcitabine, gemcitabine was also administered to the relevant animals at a dose of 50 mg/kg at days 12, 15, 19, 22, 26, and 29 post-tumor induction. After the last administration, the mice were sacrificed, bled, and pancreas harvested from the animals for analysis.

[0373]   The tumor tissues were weighed in 10% buffered neutral formalin solution. The pancreatic tissues were fixed, embedded with paraffin, and 4-5 μm tissue sections were prepared. The degree of fibrosis in the pancreatic cancer tissue was confirmed by the accumulation of extracellular matrix protein. The degree of fibrosis progression was evaluated with Sirius red staining, which specifically stained for collagen, a component of extracellular matrix. Images of the stained tissues were acquired and the relative collagen

content within the imaged area was determined (Image Pro Plus 7.0, MediaCybernetics, USA).

[0374]   As shown in FIG. 9B, animals that were treated with anti-FAM19A5 antibody alone did not have any significant on tumor growth (as measured by tumor weight) compared to the control animals (treated with human IgG antibody). However, anti-FAM19A5 antibody in combination with gemcitabine appeared to have a significant anti-tumor effect. Animals that received both anti-FAM19A5 antibody and gemcitabine had the smallest tumor weight among the different groups. Not to be bound by any single theory, the anti-FAM19A5 antibody is thought to promote blood vessel normalization, which allows for increased delivery of gemcitabine to the tumors.

[0375]   As for the effect on fibrosis progression, administration of anti-FAM19A5 antibody alone resulted in greater inhibition of fibrosis formation (as measured by relative collagen content) when compared to human IgG administration alone (FIG. 9C). When compared to gemcitabine alone, administering the combination of an anti-FAM19A5 antibody and gemcitabine had greater anti-fibrosis effect.

[0376]   These findings demonstrated that anti-FAM19A5 antibody, when administered alone or in combination with gemcitabine, can have a significantly higher anticancer effect when compared with the negative control (human IgG) and the positive control (gemcitabine alone) groups.

Example 14 Evaluation of the anti-tumor efficacy of anti-FAM19A5 antibody, alone or in combination and an anti-PD-1 antibody, in a melanoma animal model

[0377]   The mouse melanoma cancer cell line, B16F10, was purchased from Korea cell line bank (KCLB). To induce a mouse syngeneic melanoma model, 2×10^5 cells / 0.2 mL of cells were inoculated into each mouse's flank.

[0378]   On the 7th day after the inoculation, volume of each tumor was measured using caliper (Caliper; Mitutoyo, Japan). The measured volume was expressed in mm^3 by the formula: $V = 0.5 \times a \times b^2$, where a and b are the long and short diameters of the tumor, respectively.

[0379]   The antibody treatment began once tumor volume reached 80-100 mm^3 as shown in FIG. 10A. Human IgG (negative control) or anti-FAM19A5 antibody were administered intravenously at a dose of 5 mg/kg once a week for 2 week period. Rat IgG (negative control) or anti-mouse PD-1 (mPD-1) antibody were administered

intraperitoneally twice a week for 1 week. On 17th day after tumor inoculation, tumor volume was measured and animals were sacrificed (FIG. 10A).

[0380]   Tumor growth inhibition (TGI), expressed as TGI (%) = 100 x (1-T/C), was used as an indication of anti-tumor effectiveness. T is the individual tumor volume of anti-FAM19A5 antibody administered mice and C is the mean tumor volume of the control group [human IgG + rat IgG]. As shown in FIG. 10B, no significant anti-tumor effect was observed in animals treated with anti-FAM19A5 antibody alone or anti-PD-1 antibody alone, compared to the control animals (human IgG + rat IgG treated group). However, mice that received both the anti-FAM19A5 antibody and the anti-PD-1 antibody showed reduction in tumor volume, compared to the control animals. FIG. 10B.

[0381]   These findings demonstrated that administration of an anti-FAM19A5 antibody in combination with mPD-1 antibody can result in a significant anti-tumor effect.

Example 15 Evaluation of the anti-tumor efficacy of anti-FAM19A5 antibody, alone or in combination with an anti-PD-1 antibody, in a pancreatic cancer animal model

[0382]   To further assess the anti-tumor efficacy of the combined use of anti-FAM19A5 antibody and anti-PD-1 antibody, a pancreatic cancer mouse model was used. Upon inducing pancreatic cancer in C57BL/6 mice through gene mutation ($Kras^{LSL-G12D/WT}$; $P53^{KO/KO}$; Pdx1-cre), the cancerous tissue was removed and transplanted into the pancreatic tissue of new C57BL/6 mice. After three days, the animals that received the cancerous tissue were separated into different groups and treated with the following: (i) control human and mouse IgG antibodies, (ii) anti-FAM19A5 antibody + mouse IgG antibody, (iii) human IgG antibody + anti-mouse PD-1 antibody, or (iv) anti-FAM19A5 antibody + anti-mouse PD-1 antibody. Human IgG (CrownBio, cat # C0001) and anti-FAM19A5 antibody (3-2 clone, Lot # 171123) were intravenously administered at a dose of 5 mg/kg, once a week, for 3 weeks. Mouse IgG (Bioxcell, cat # BE0089) and mouse anti-PD1 antibody (Bioxcell, cat # BE0146) were administered at a dose of 10 mg/kg, twice a week, for 3 weeks. Animals were sacrificed at week 3 post tumor inoculation and the anticancer effect of the different treatment regimens was assessed.

[0383]   As shown in FIG. 11, compared to the control group (G1: human IgG antibody + mouse IgG antibody), animals treated with anti-FAM19A5 antibody alone (G2) and animals treated with anti-PD-1 antibody alone (G3) had about 50% and 51% tumor inhibition, respectively. In agreement with the results from the mouse melanoma model

(*see* Example 14), animals treated with both anti-FAM19A5 antibody and anti-PD-1 antibody (G4) had the greatest tumor inhibition (~61% inhibition compared to the control group). This result confirms that the combined treatment of anti-FAM19A5 antibody and anti-PD-1 antibody may be an efficacious treatment for various cancers, including melanoma and pancreatic cancer.

Example 16 Impact of anti-FAM19A5 antibody on the phagocytosis of Raw 264.7
(Mouse macrophage cell) and BV-2 cell (mouse microglia)

[0384]   Raw 264.7 (Korean Cell Line Bank) cells were plated in 12 wells at $1*10^5$ cells / ml / well and cultured at 37 °C in 5% CO2 for 16 hours. Then, the cells were cultured with (i) no stimuli (control), (ii) cytochalasin D (5 mM), (iii) LPS (1 μg/ml) alone (sigma), or (iv) LPS with an anti-FAM19A5 antibody (1 μg/ml) at 37 °C and 5% CO2 for 24 hours. After removing the supernatant and PBS washing, the solution was treated with 0.05 mg / 300 μl / well of pHrodo *E. coli* bioparticles (Thermofisher, P35381) previously reacted with *E. coli* bioparticles opsonizing reagent (Thermofisher, E2870). After incubation at 37 °C for 1 hour, the supernatant was removed, and the cells were harvested after PBS washing. Using the GUAVA instrument (Merck), pHrodo expression, which become selectively fluorescent at low pH due to the fusion of lysosomes following phagocytosis, was analyzed.

[0385]   BV-2 cells were plated in 24 wells at $1*10^5$ / ml / well and incubated for 16 hours at 37 ° C and 5% CO2. After removing the supernatant and PBS washing, the solution was treated with 0.05 mg / 300 μl / well of pHrodo *E. coli* bioparticles (Thermofisher, P35381) previously reacted with *E. coli* bioparticles opsonizing reagent (Thermofisher, E2870). Each well was treated with (i) 1 μg/ml of FAM19A5 protein or (ii) 1 μg/ml of FAM19A5 protein with an anti-FAM19A5 antibody. To measure the mitochondrial membrane potential, the cells were further treated with Image-iT™ TMRM Reagent (tetramethylrhodamine methyl ester, mitochondrial membrane potential indicator; ThermoFisher, I34361) (at 100 nM concentration). After incubation at 37 °C for 1 hour, the supernatant was removed, and the cells were harvested after PBS washing. Using the GtmrmUAVA instrument (Merck) pHrodo expression, which becomes selectively fluorescent at low pH due to fusion of the lysosomes following phagocytosis, were analyzed in the B-Green channel, and TMRM was analyzed in the B-Yellow channel.

[0386]   As shown in FIG. 12A, FACS analysis showed that phagocytosis was inhibited when Raw 264.7 cells were treated with high-dose LPS alone for 24 hours, compared to the control. When the cells were treated with an anti-FAM19A5 antibody with the same concentration of LPS, the level of phagocytosis was increased about 67%. Similarly, treatment of BV-2 cells with FAM19A5 protein alone resulted in decreased phagocytosis and mitochondrial membrane potential (FIG. 12B). However, when BV-2 cells were further treated with anti-FAM19A5 antibody, the antibody increased the phagocytic activity of macrophages and microglia, typical phagocytes, and also increased mitochondrial membrane potential about 6% and 16%, respectively (FIG. 12B).

[0387]   It is to be appreciated that the Detailed Description section including the Summary and Abstract sections is intended to be used to interpret the claims. The Summary and Abstract sections can set forth one or more but not all exemplary embodiments of the present disclosure as contemplated by the inventor(s), and thus, are not intended to limit the present disclosure and the appended claims in any way.

[0388]   The present disclosure has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0389]   The foregoing description of the specific embodiments will so fully reveal the general nature of the disclosure that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present disclosure. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0390]   The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

[0391]   All publications, patents, patent applications, internet sites, and accession numbers/database sequences (including both polynucleotide and polypeptide sequences) cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, internet site, or accession number/database sequence were specifically and individually indicated to be so incorporated by reference.

[0392]   This PCT application claims the priority benefit of U.S. Provisional Application Nos. 62/525,633, filed June 27, 2017; 62/582,886, filed November 7, 2017, and 62/597,920, filed December 12, 2017, all of which are incorporated herein by reference in their entireties.

WHAT IS CLAIMED IS:

1.   An antagonist against a family with sequence similarity 19, member A5 (FAM19A5) protein ("FAM19A5 antagonist") for promoting a blood vessel normalization in a tumor of a subject in need thereof.

2.   The FAM19A5 antagonist for use of claim 2, wherein the blood vessel normalization comprises (i) decreased blood vessel permeability, (ii) increased thickness of blood vessel wall, (iii) improved connectivity, (iv) increased blood flow rate, or (iv) any combinations thereof.

3.   The FAM19A5 antagonist for use of claim 1 or 2, wherein the FAM19A5 antagonist (i) increases the number of blood vessels that extend into the tumor of the subject, (ii) increases the infiltration of an immune cell (*e.g.*, macrophages, dendritic cells, or microglia) into the tumor of the subject, (iii) decreases the recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor of the subject, (iv) enhances the phagocytic activity and/or the mitochondrial membrane potential of an immune cell (*e.g.*, macrophages, dendritic cells, or microglia) in the tumor of the subject, or (v) any combination thereof.

4.   The FAM19A5 antagonist for use of any one of claims 1 to 3, wherein the FAM19A5 antagonist is an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein ("anti-FAM19A5 antibody"), polynucleotide encoding the anti-FAM19A5 antibody, or a vector comprising the polynucleotide thereof.

5.   The FAM19A5 antagonist for use of claim 4, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 11, 12, and 13, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 23, 24, and 25, respectively.

6.   The FAM19A5 antagonist for use of claim 4, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and

CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 14, 15, and 16, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 26, 27, and 28, respectively.

7.   The FAM19A5 antagonist for use of claim 4, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 17, 18, and 19, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 29, 30, and 31, respectively.

8.   The FAM19A5 antagonist for use of claim 4, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 20, 21, and 22, respectively, and the light chain CDR1, CDR2, and CDR3 comprises SEQ ID NOs: 32, 33, and 34, respectively.

9.   A method of *in vitro* diagnosing cancer comprising contacting an FAM19A5 antagonist with a biological sample of the subject and measuring a FAM19A5 protein level or a FAM19A5 mRNA level in the sample.

10.   The pharmaceutical composition for use of any one of claims 4 to 8, wherein the anti-FAM19A5 antibody is a humanized antibody, a chimeric antibody, or a human antibody.

11.   The pharmaceutical composition for use of any one of claims 1 to 8, wherein the FAM19A5 antagonist is used in combination with an additional cancer agent comprising an immunotherapeutic agent, chemotherapeutic agent, targeted therapeutic agent, or radiotherapeutic agent.

12.   The pharmaceutical composition for use of claim 11, wherein the immunotherapeutic agent comprises a monoclonal antibody, chimeric antigen receptor (CAR) T-cell, NK-cell, dendritic cell (DC), adoptive cell transfer (ACT), immune checkpoint modulator, cytokine, cancer vaccine, adjuvant, oncolytic virus, or combination thereof.

13.   The pharmaceutical composition for use of claim 11, wherein the targeted therapeutic agent comprises tyrosine-kinase inhibitors, small molecule drug conjugates, serine-threonine kinase inhibitors, antibodies, or any combinations thereof.

14.   The pharmaceutical composition for use of claim 12, wherein the monoclonal antibody modulates a signaling molecule selected from the group consisting of PD-1, PD-L1, CTLA-4, IDO, TIM-3, LAG-3, 4-1BB, OX40, MERTK, CD27, GITR, B7.1, TGF-β, BTLA, VISTA, Arginase, MICA, MICB, B7-H4, CD28, CD137, and HVEM.

15.   The pharmaceutical composition for use of claim 13, wherein the monoclonal antibody is an anti-PD-1 antibody or an anti-PD-L1 antibody.

16.   The pharmaceutical composition for use of claim 14, wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.

17.   The pharmaceutical composition for use of claim 14, wherein the anti-PD-L1 antibody is atezolizumab, durvalumab, or avelumab.

18.   The pharmaceutical composition for use of claim 12, wherein the monoclonal antibody increases penetration of a therapeutic agent into a tumor.

19.   The pharmaceutical composition for use of claim 11, wherein the chemotherapeutic agent comprises a drug comprising temozolomide, gemcitabine, paclitaxel, carboplatin, cisplatin, elotumumab, lenalidomide, dexamethasone, oxaliplatin, or any combination thereof.

20.   The pharmaceutical composition for use of any one of claims 1 to 19, wherein the tumor comprises a carcinoma, sarcoma, or lymphoma.

21.   The pharmaceutical composition for use of any one of claims 1 to 20, wherein the tumor is derived from a cancer comprising melanoma, pancreatic cancer, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, ovarian cancer, or any combinations thereof.

FIG. 1

FIG. 2A

FIG. 2B

FIG. 2C

FIG. 2D

Tyr::CreER; BrafCA/WT
+ Pten^lox/lox mice

4 weeks
from initial
Ab treatment

Weeks: 0   8   9   10   12

Anti-FAM19A5 Ab (100ug/mice)
injection via I.V. route

Analysis

FIG. 3A

Days: 51   56   61   66   71

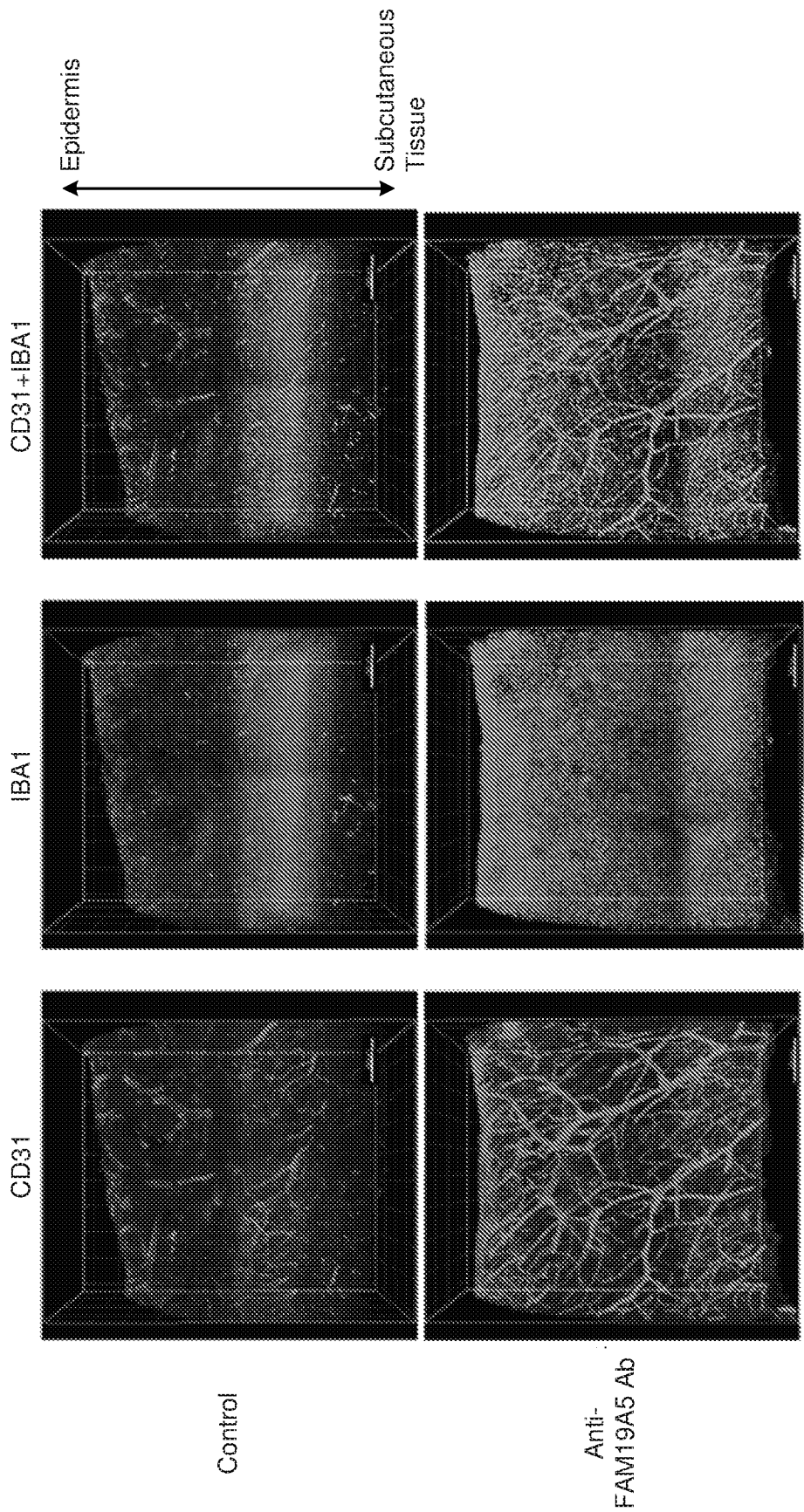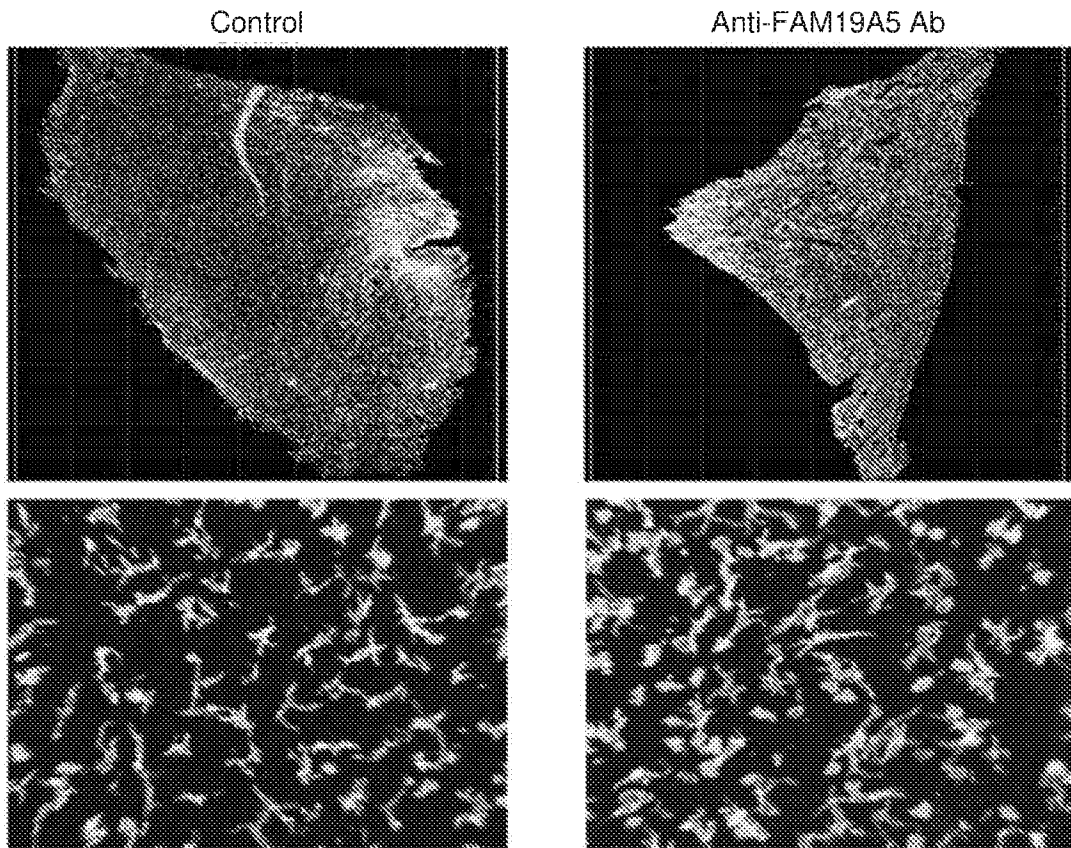Days after birth
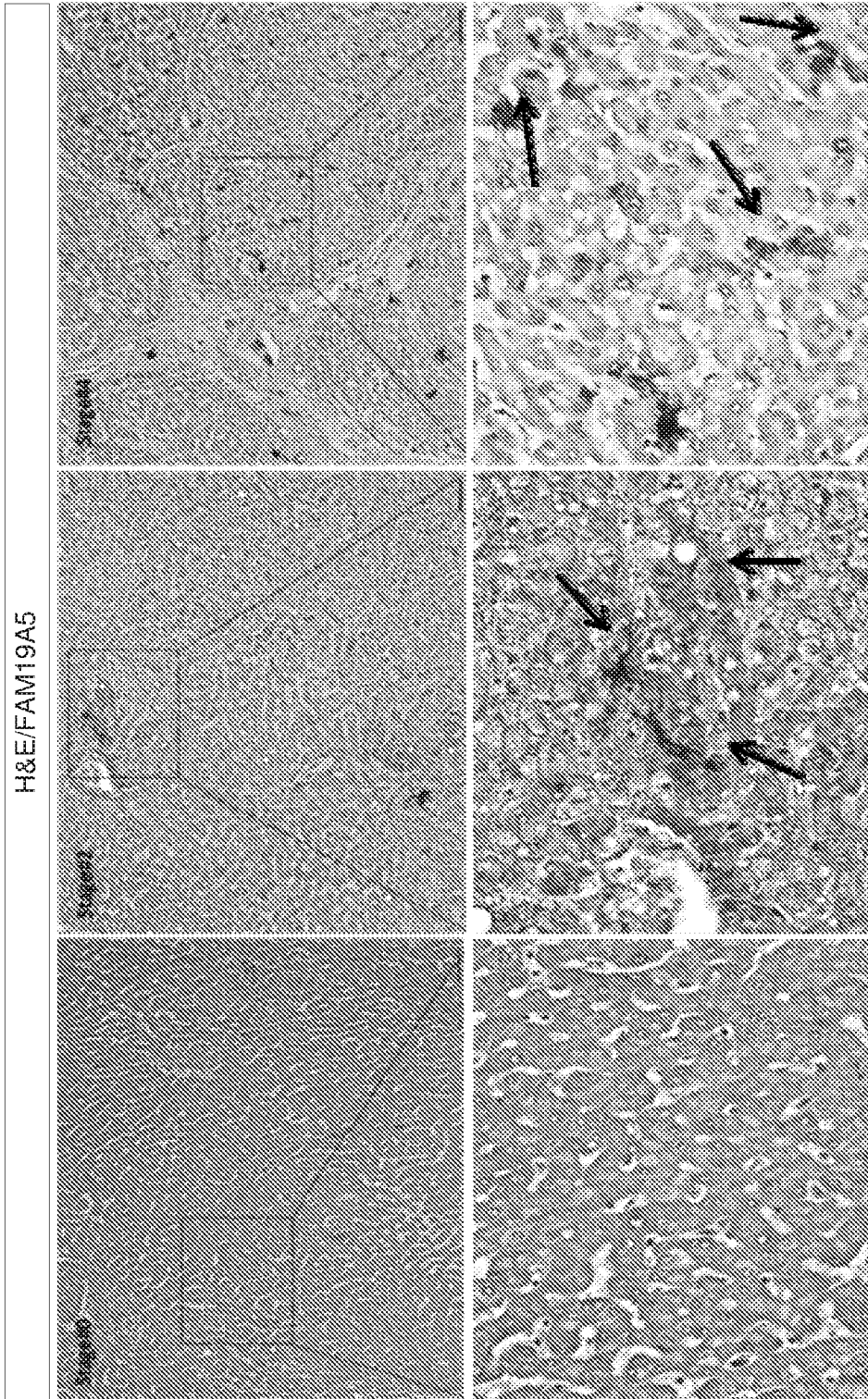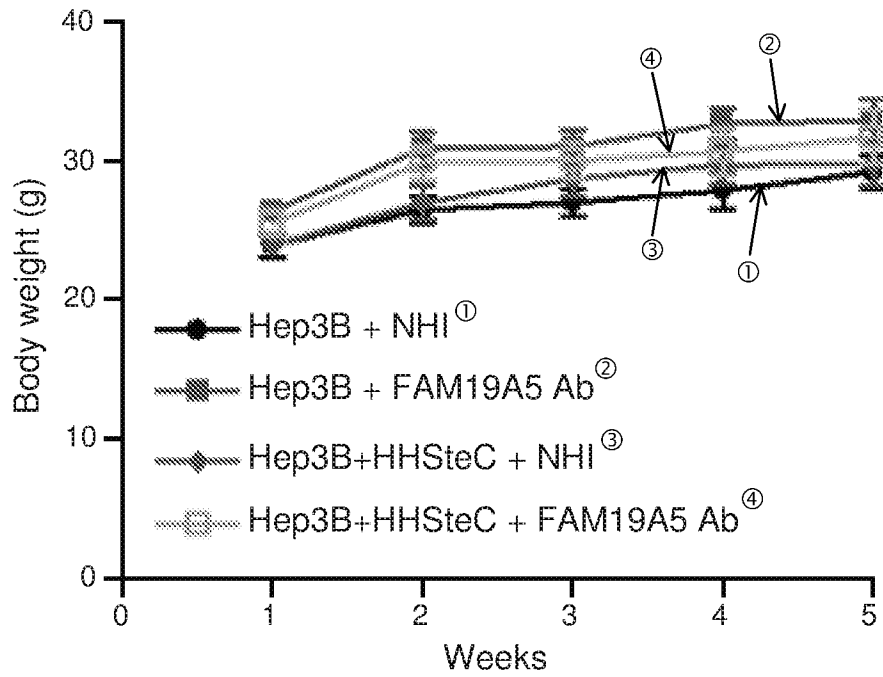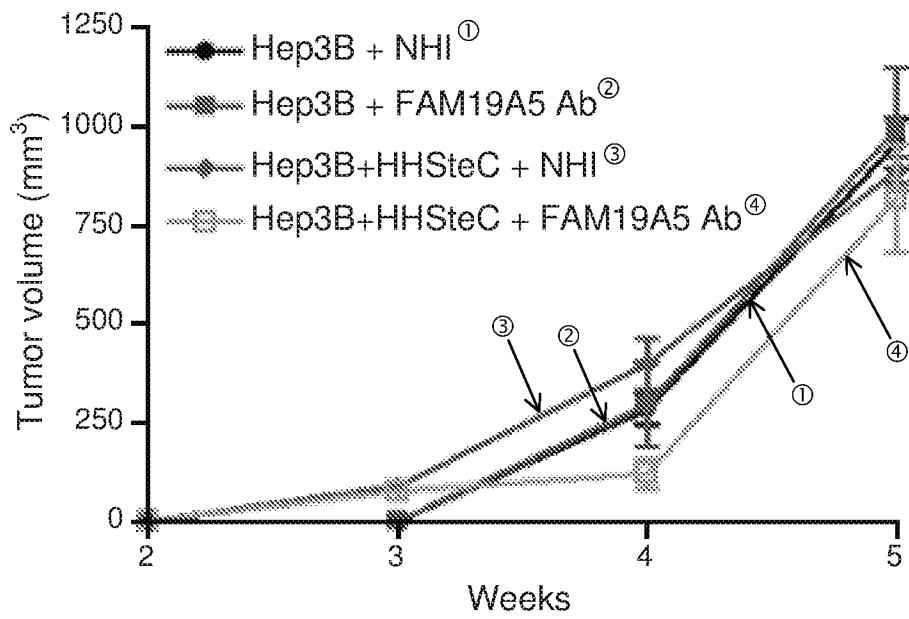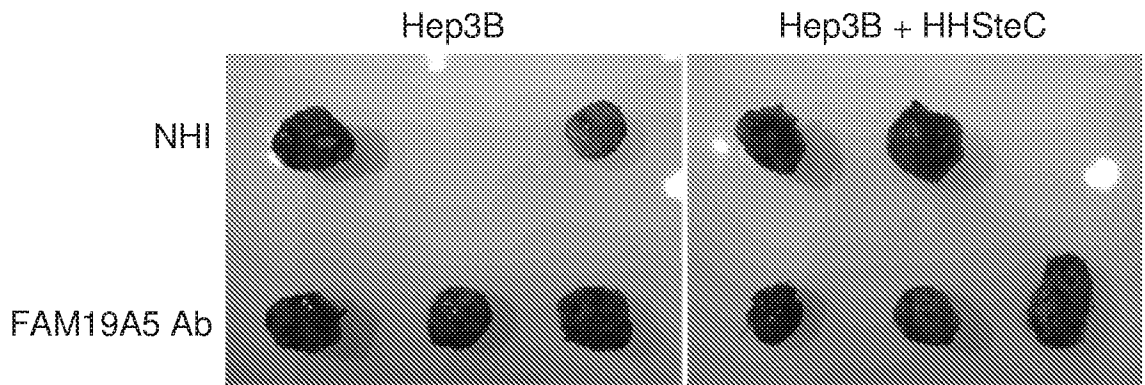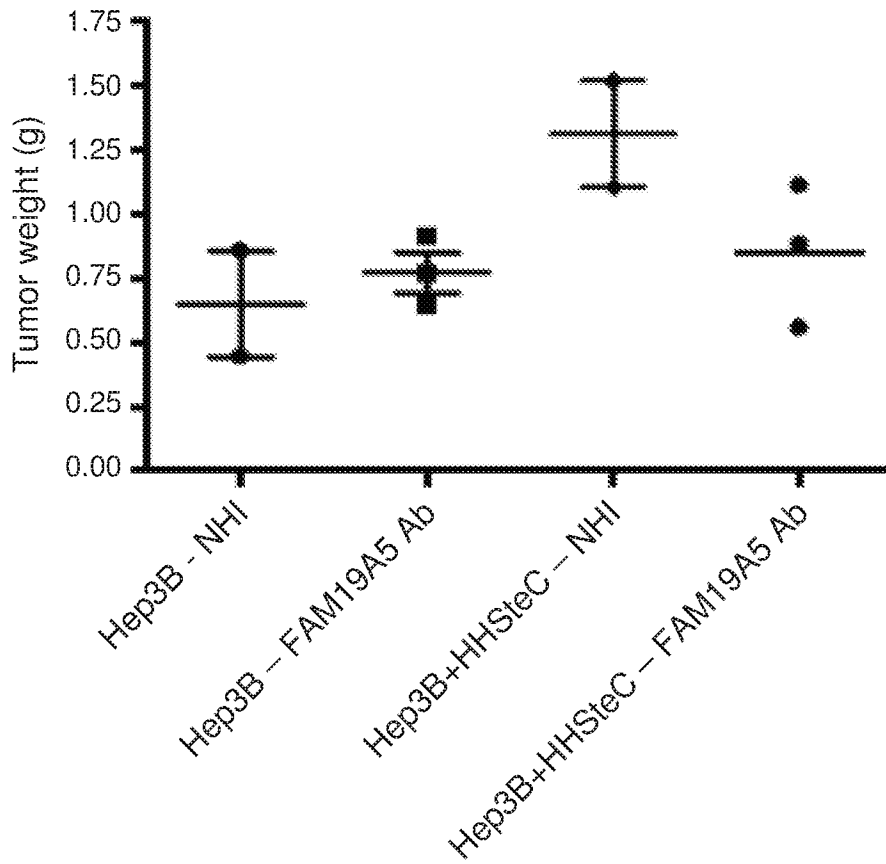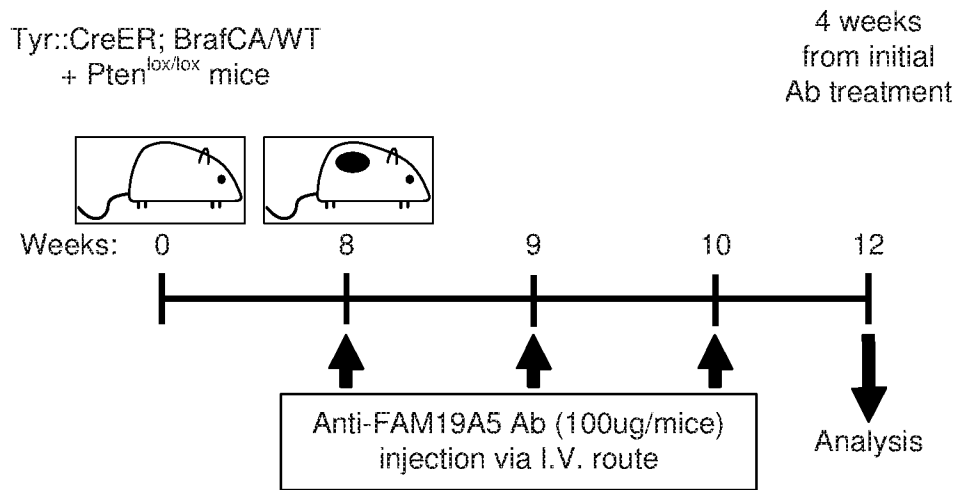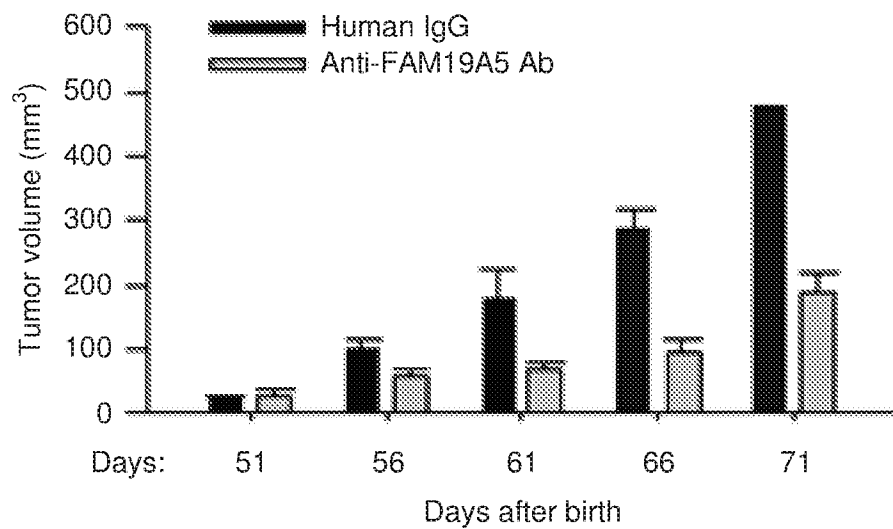
FIG. 3B

Braf^{V600E}-induced pigmented lesions

FIG. 3C

Scale bar = 500 µm.

FIG. 4

Scale bar = 300 μm.

FIG. 5
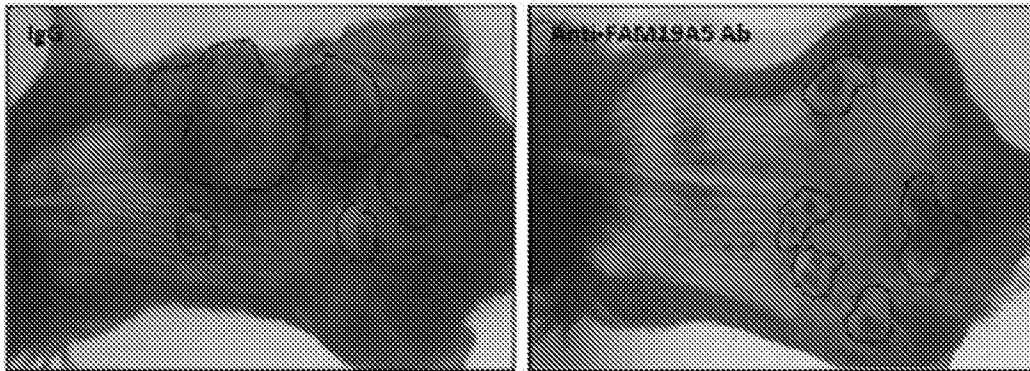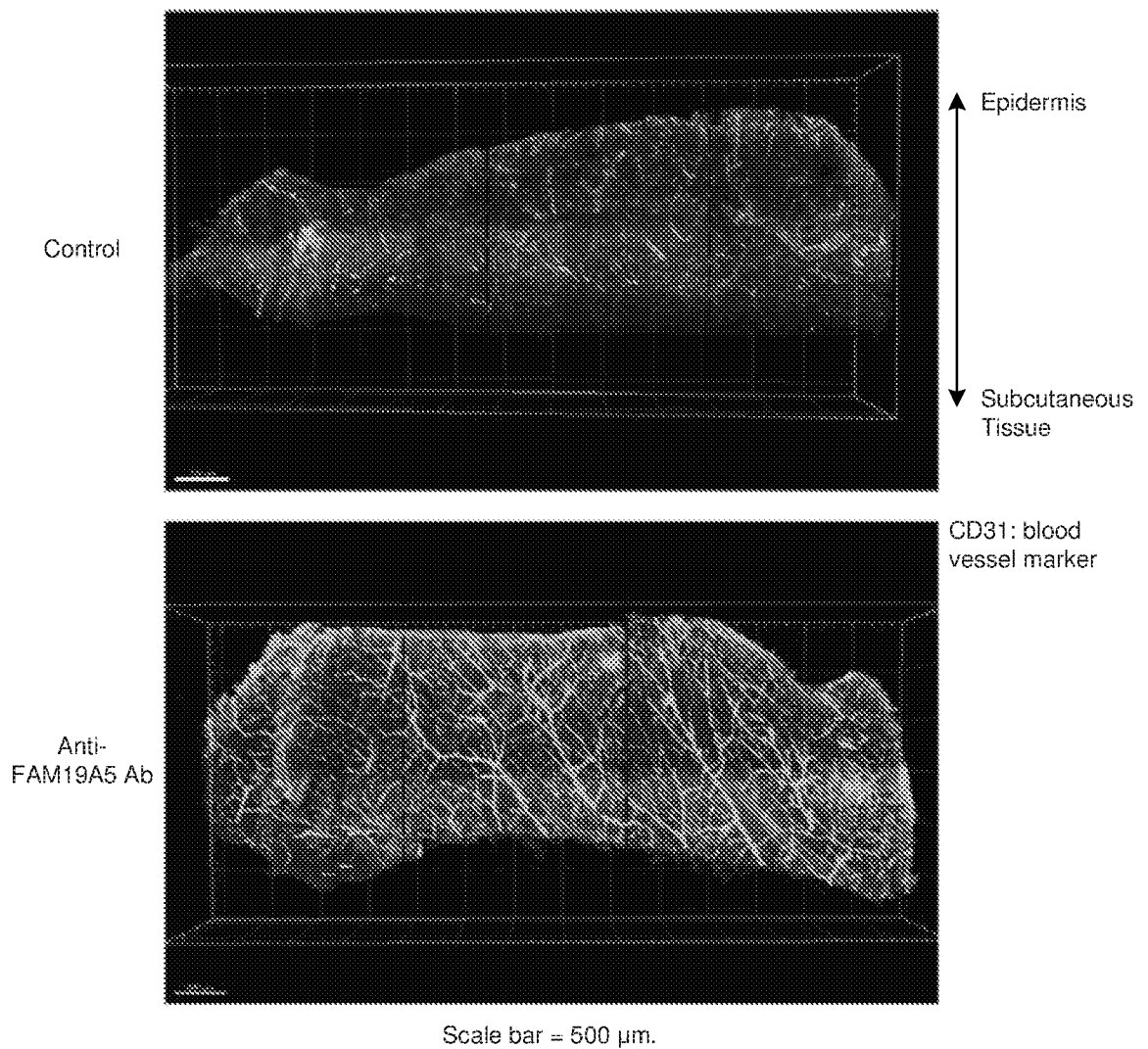
Control   Anti-FAM19A5 Ab

FIG. 6A
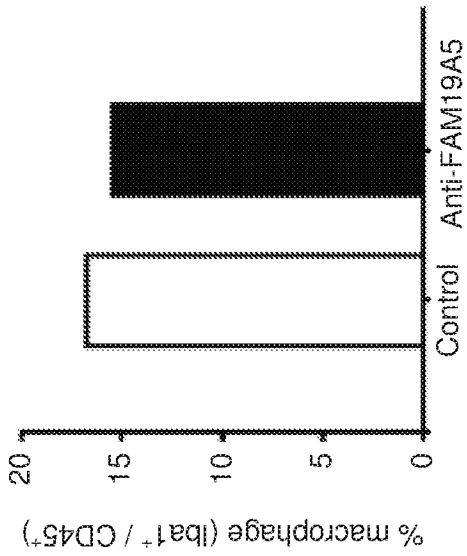
FIG. 6B

FIG. 6C

	Control	Anti-FAM19A5
% total	16.7370735	15.4766097
/cell	82.86607279	169.9912664
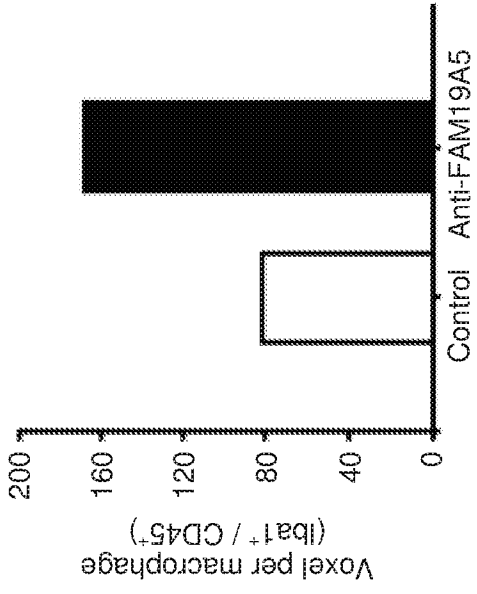
FIG. 6D

	Control	Anti-FAM19A5
Number of DAPI	156945	72503
Number of macrophage (Iba1+ and CD45+)	26268	11221
Voxel of Macrophage (Iba1+ and CD45+)	2176726	1907472

Control   Anti-FAM19A5 Ab
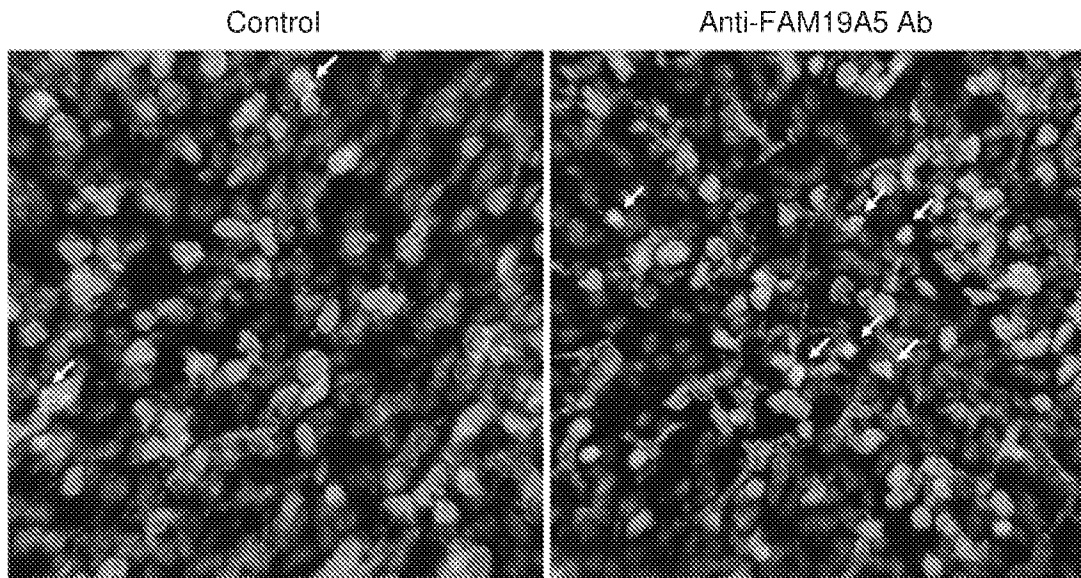
FIG. 7A

	Control	Anti-FAM19A5			Control	Anti-FAM19A5
# of DAPI$^+$ Cells	136313	63187				
# of T cells (CD3$^+$ and CD45$^+$)	265	850		% Total	0.194405523	1.345213414

FIG. 7B
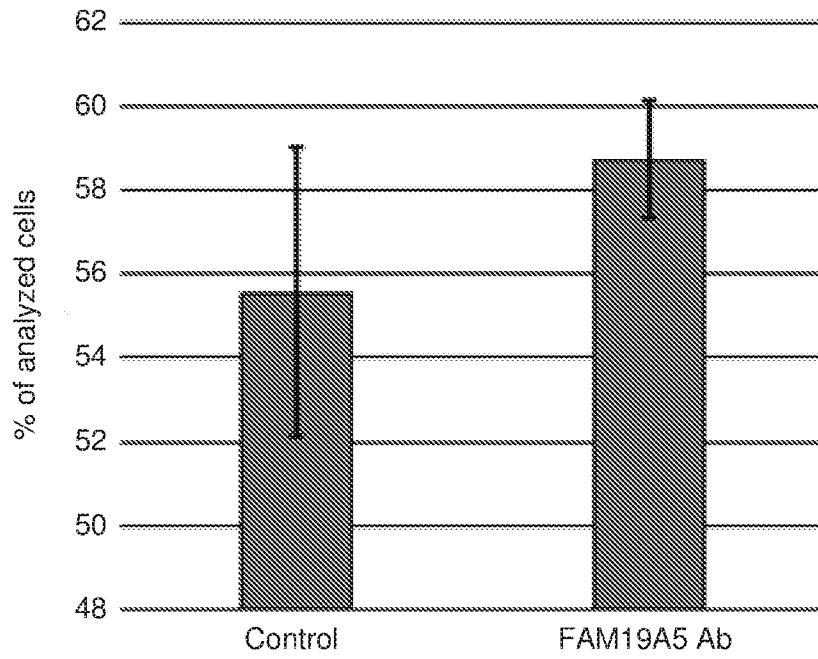
FIG. 8A
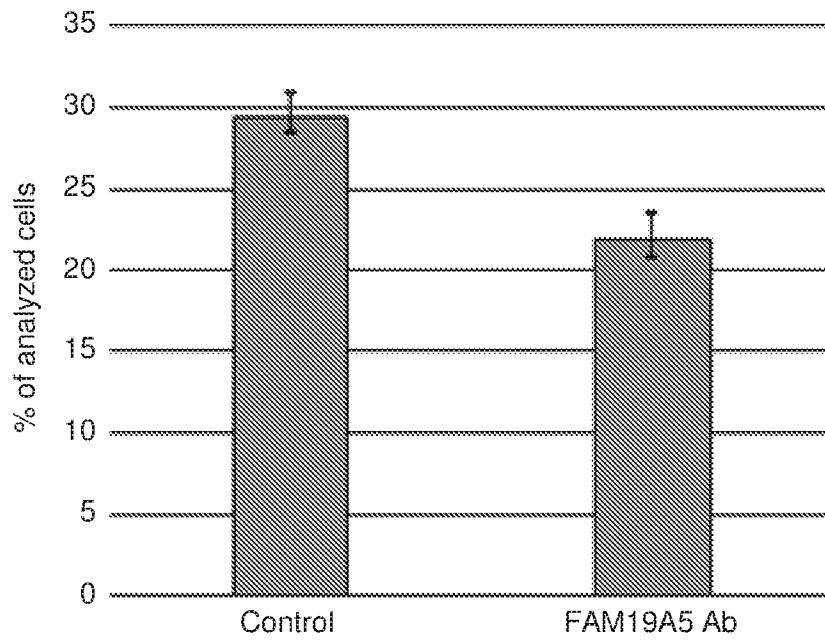
FIG. 8B
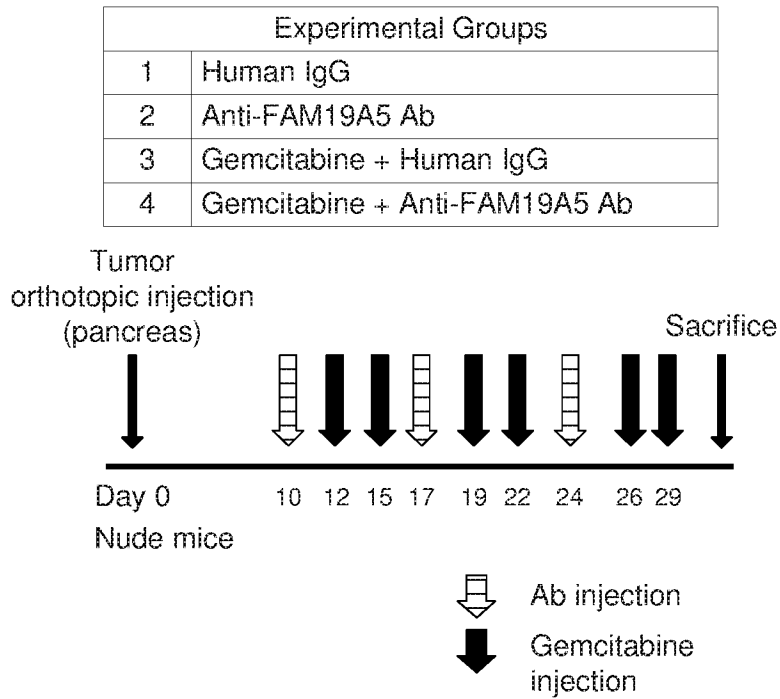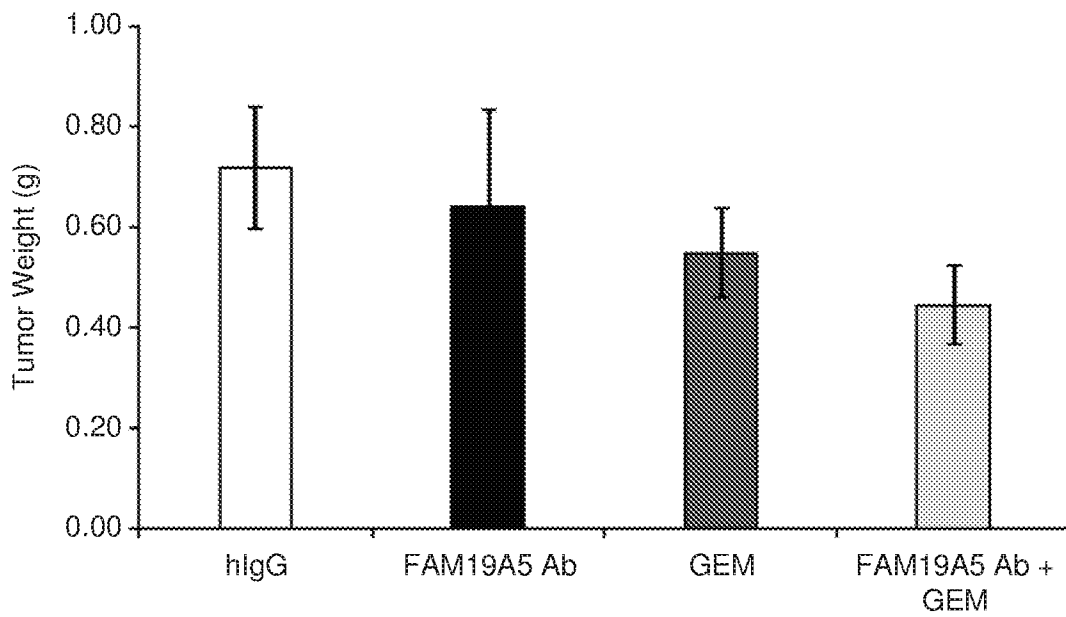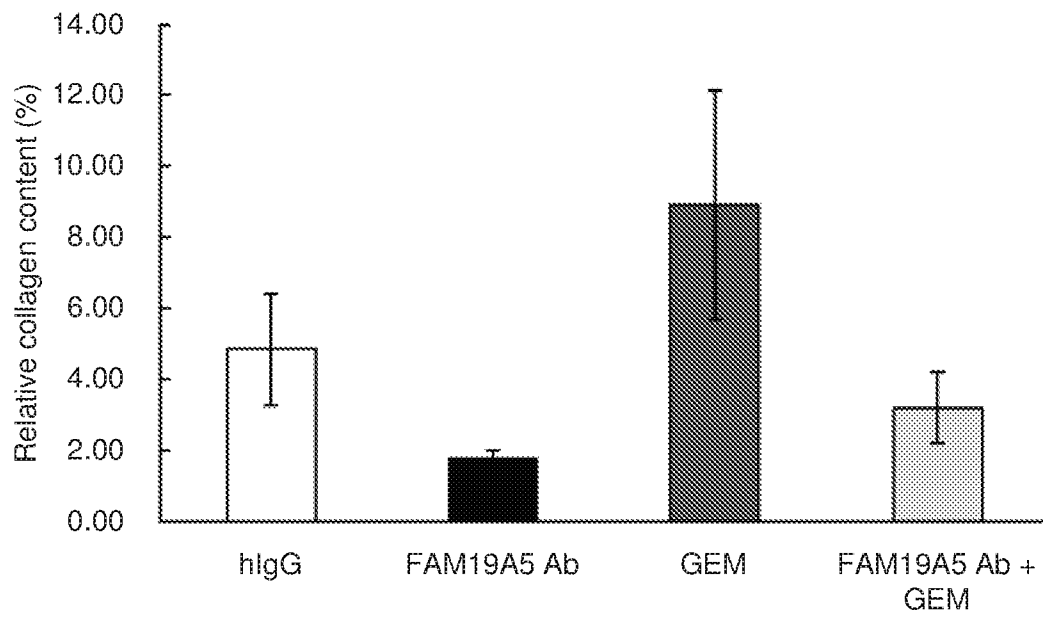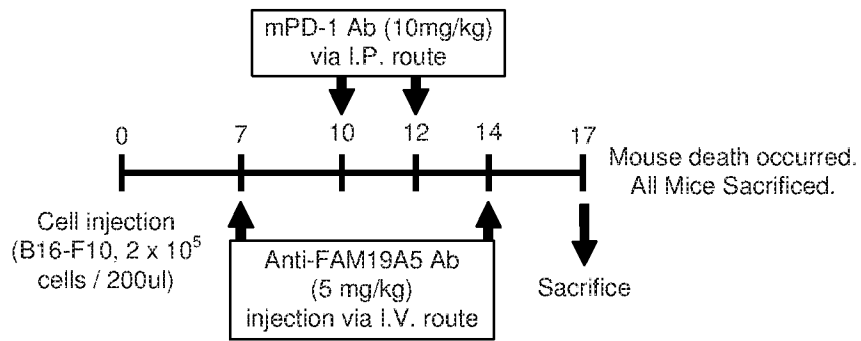
Experimental Groups	
1	Human IgG
2	Anti-FAM19A5 Ab
3	Gemcitabine + Human IgG
4	Gemcitabine + Anti-FAM19A5 Ab

FIG. 9A

FIG. 9B

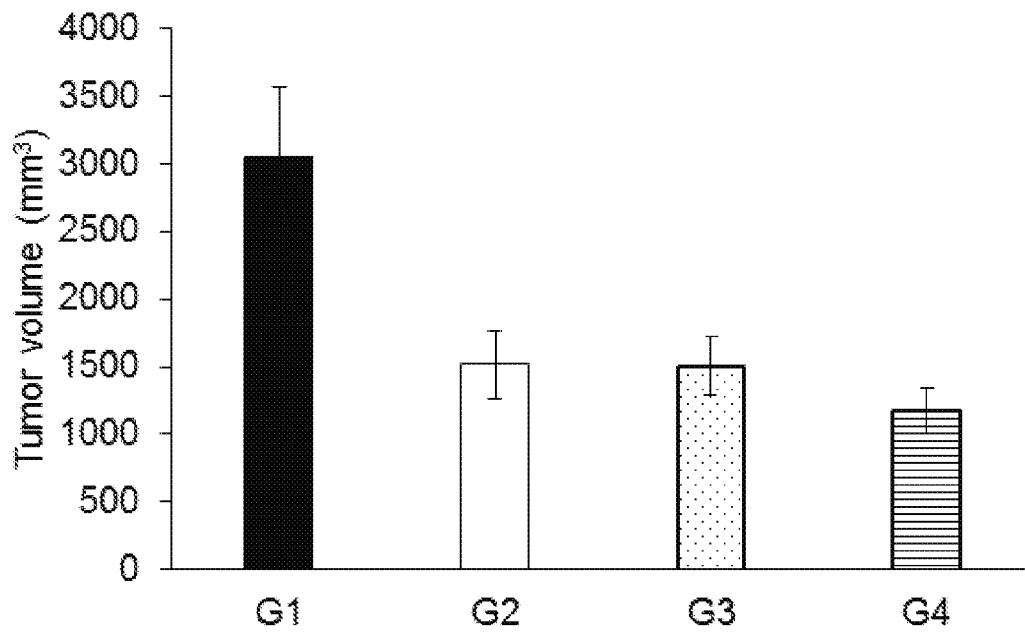FIG. 9C
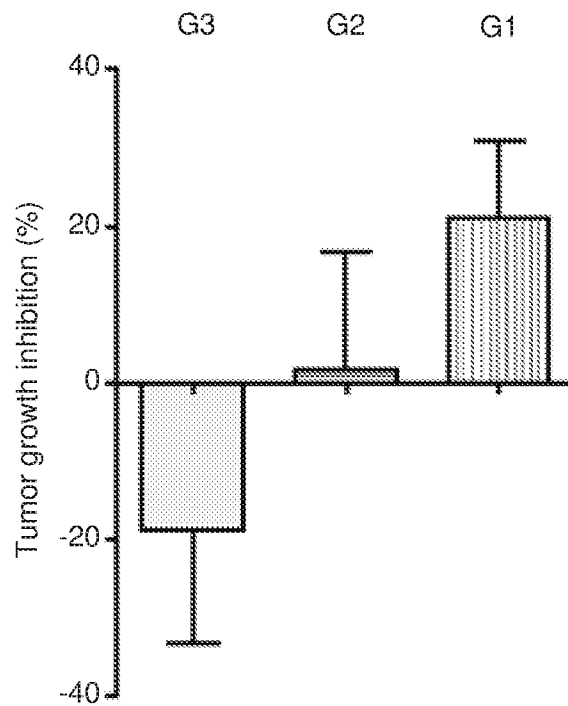
FIG. 10A
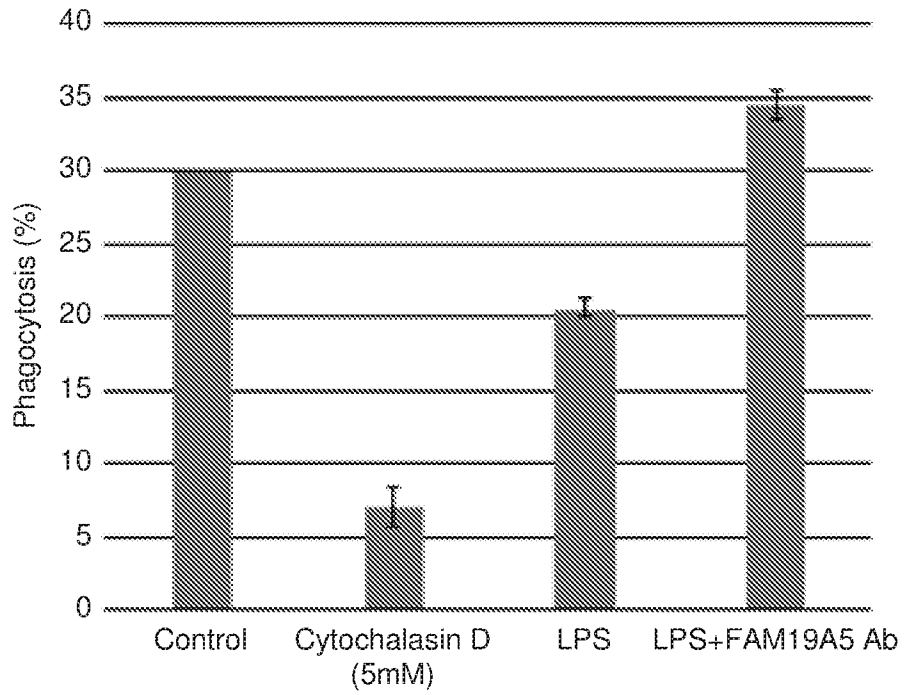

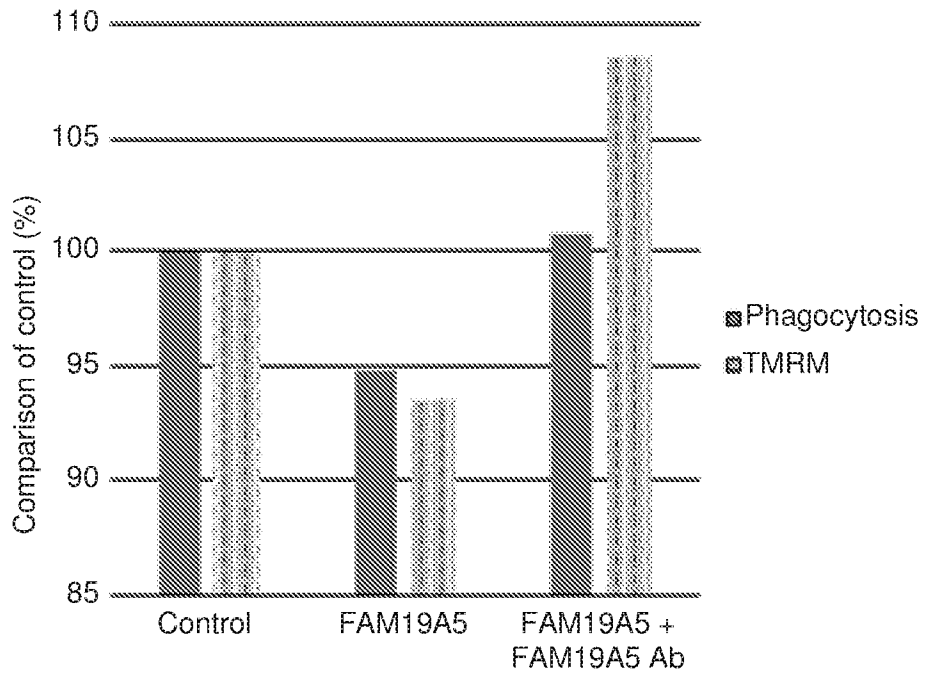**FIG. 10B**

FIG. 11

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FIG. 12A

FIG. 12B

A. CLASSIFICATION OF SUBJECT MATTER

A61K 39/395(2006.01)i, A61P 35/00(2006.01)i, A61K 39/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 39/395; A61K 48/00; C07K 16/18; C12Q 1/68; G06F 19/24; A61P 35/00; A61K 39/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: FAM19A5, antagonist, antibody, tumor, cancer, blood vessel normalization

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015-0118230 A1 (KOREA UNIVERSITY RESEARCH AND BUSINESS FOUNDATION) 30 April 2015 See paragraphs [0017], [0076], [0095], [0099].	1-3,9
A	US 2016-0060705 A1 (ALMAC DIAGNOSTICS LIMITED) 03 March 2016 See claims 51-56.	1-3,9
A	WO 2015-015000 A1 (UNIVERSITE CATHOLIQUE DE LOUVAIN) 05 February 2015 See pages 7, 34; claims 1-3; and table 1.	1-3,9
A	US 2009-0221670 A1 (BORGLUM, ANDERS et al.) 03 September 2009 See paragraphs [0036]-[0047].	1-3,9
A	TANG, Y. TOM et al., 'TAFA: a novel secreted family with conserved cysteine residues and restricted expression in the brain', Genomics, 2004, Vol. 83, pp. 727-734 See abstract; and page 732.	1-3,9

☐ Further documents are listed in the continuation of Box C.	☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2018 (16.11.2018)	**16 November 2018 (16.11.2018)**

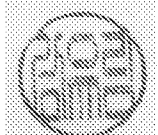| Name and mailing address of the ISA/KR	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	KAM, Yoo Lim
Facsimile No. +82-42-481-8578	Telephone No. +82-42-481-3516

Form PCT/ISA/210 (second sheet) (January 2015)

Box No. II	Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 5-8,12-19
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   Claims 5-8 and 12-19 are not clear because they refer to multiple dependent claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4,10,11,20,21
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015-0118230 A1	30/04/2015	CN 104254343 A	31/12/2014
		CN 107019800 A	08/08/2017
		EP 2815769 A1	24/12/2014
		EP 2815769 A4	19/08/2015
		KR 10-1406393 B1	13/06/2014
		KR 10-2013-0094255 A	23/08/2013
		US 2017-0121401 A1	04/05/2017
		US 9579398 B2	28/02/2017
		WO 2013-122408 A1	22/08/2013
US 2016-0060705 A1	03/03/2016	AU 2011-302004 A1	04/04/2013
		AU 2011-302004 B2	29/10/2015
		AU 2016-200494 A1	07/04/2016
		AU 2016-200494 B2	16/11/2017
		BR 112013006207 A2	24/10/2017
		CA 2811015 A1	22/03/2012
		CN 103299188 A	11/09/2013
		CN 103299188 B	15/03/2017
		CN 106978480 A	25/07/2017
		EA 201390370 A1	30/07/2013
		EP 2619574 A2	31/07/2013
		EP 2619574 A4	12/03/2014
		EP 2975399 A1	20/01/2016
		HK 1216665 A1	25/11/2016
		JP 2013-537045 A	30/09/2013
		JP 2017-093440 A	01/06/2017
		KR 10-2013-0115250 A	21/10/2013
		MX 2013002879 A	17/05/2013
		MX 344636 B	04/01/2017
		MY 166040 A	21/05/2018
		NZ 608459 A	30/10/2015
		NZ 620799 A	30/10/2015
		NZ 712823 A	26/05/2017
		SG 10201610027V A	27/01/2017
		SG 188397 A1	30/04/2013
		US 2014-0031260 A1	30/01/2014
		US 2014-0051591 A1	20/02/2014
		US 2017-0198360 A1	13/07/2017
		US 9670547 B2	06/06/2017
		US 9677140 B2	13/06/2017
		WO 2012-037378 A2	22/03/2012
		WO 2012-037378 A3	05/07/2012
		ZA 201301567 B	28/04/2016
WO 2015-015000 A1	05/02/2015	CA 2920062 A1	05/02/2015
		EP 3027770 A1	08/06/2016
		US 2016-0186270 A1	30/06/2016
US 2009-0221670 A1	03/09/2009	AU 2006-246116 A1	16/11/2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CA 2651376 A1	16/11/2006
		EP 1888773 A2	20/02/2008
		EP 2287340 A2	23/02/2011
		EP 2287340 A3	30/03/2011
		EP 2305837 A1	06/04/2011
		WO 2006-119775 A2	16/11/2006
		WO 2006-119775 A3	28/06/2007