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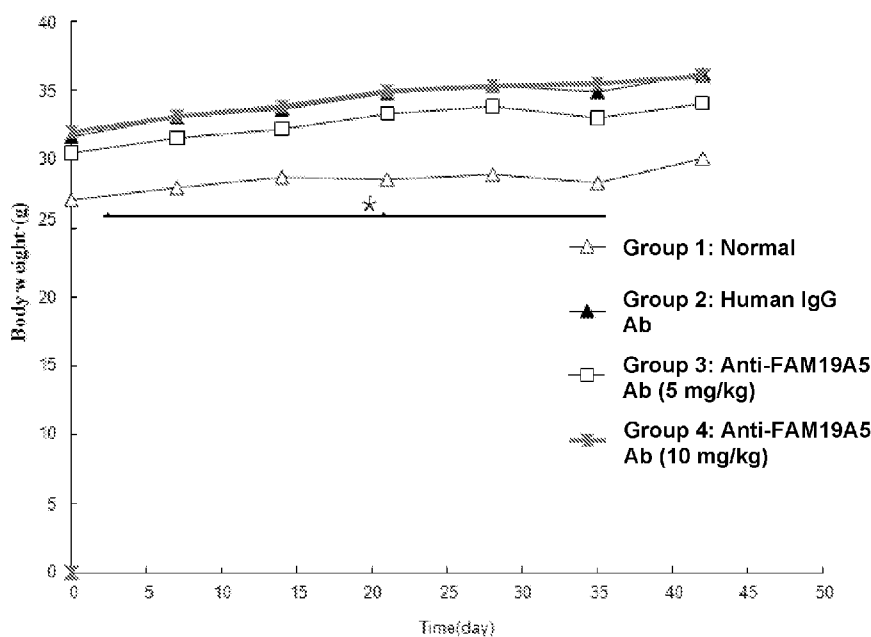


FIG. 1

(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 treat an atherosclerosis in a subject in need thereof.

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USE OF ANTI-FAM19A5 ANTIBODIES FOR TREATING ATHEROSCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the priority benefit of U.S. Provisional Application No. 62/785,569, filed December 27, 2018, which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The content of the electronically submitted sequence listing in ASCII text file (Name: 3763_015PC01_SeqListing_ST25.txt; Size: 262,323 bytes; and Date of Creation: December 26, 2019) filed with the application is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure provides methods for the treatment of atherosclerosis in a subject (*e.g.*, a human) using antagonists against family with sequence similarity 19, member A5 (FAM19A5) (*e.g.*, anti-FAM19A5 antibody) or a composition comprising such antagonists.

BACKGROUND OF THE DISCLOSURE

[0004] Atherosclerosis is a disease characterized by the narrowing of blood vessels (*e.g.*, artery) due to the accumulation of lipid-laden macrophages, resulting in lesion or plaque formation. Lu, H., *et al.*, *Arterioscler Thromb Vasc Biol* 35(3):485-491 (2015). Initially, there are usually no symptoms, but if left untreated, atherosclerosis can lead to coronary artery disease, stroke, peripheral artery disease, or kidney problems, depending on the arteries affected.

[0005] Atherosclerosis generally starts when a person is young and worsens with age. By the age of 65, almost all people are affected to some degree. Current treatment options generally include diet, exercise, and medications, such as agents that lower cholesterol (*e.g.*, statins), that regulate blood pressure (*e.g.*, antihypertensive drugs), and/or that decrease clotting (*e.g.*, aspirin). Bergheanu, S.C., *et al.*, *Neth Heart J* 25(4):231-242 (2017). In severe cases, more invasive procedures may be necessary (*e.g.*, percutaneous coronary intervention, coronary artery bypass graft, or carotid endarterectomy). Despite such treatment options, atherosclerosis remains the

number one cause of death and disability in the developed world. Herrington, W., *et al.*, *Circ Res* 118(4):535-46 (2016). Moreover, many of the available treatment options can have undesirable side effects. Stroes, E.S., *et al.*, *Eur Heart J* 36(17):1012-22 (2015).

[0006] Accordingly, there remains a need for more effective and comprehensive treatment options for atherosclerosis.

BRIEF SUMMARY OF THE DISCLOSURE

[0007] Provided herein is a method of increasing a phagocytosis of low density lipoprotein (LDL) by macrophages in a subject in need thereof, comprising administering to the subject an antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist").

[0008] In some embodiments, the phagocytosis of LDL by macrophages is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist). In certain embodiments, the increase in phagocytosis of LDL by macrophages occurs at an atherosclerotic lesion. In further embodiments, the LDL comprises oxidized LDL. In some embodiments, the atherosclerotic lesion site is in a blood vessel. In certain embodiments, the blood vessel comprises an artery, vein, capillaries, or combinations thereof. In some embodiments, the artery is an aorta.

[0009] Also disclosed herein is a method of increasing a migration and/or accumulation of macrophages at an atherosclerotic lesion site in a subject in need thereof, comprising administering to the subject an antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist").

[0010] In some embodiments, the migration and/or accumulation of macrophages at an atherosclerotic lesion site is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist). In further embodiments,

the increased migration and/or accumulation of macrophages at an atherosclerotic lesion site is associated with a decrease in a low density lipoprotein (LDL) level in the subject.

[0011] Present disclosure provides a method of reducing a low density lipoprotein (LDL) level in a subject in need thereof, comprising administering to the subject an antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist"). In some embodiments, the LDL level in the subject is reduced by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0012] In some embodiments, a subject disclosed herein (*e.g.*, treated with a FAM19A5 antagonist) exhibits one or more of the following properties: (i) an increased phagocytosis of LDL by macrophages; (ii) an increased migration and/or accumulation of macrophages to an atherosclerotic lesion site; and (iii) a reduced LDL level.

[0013] Provided herein is a method of treating an atherosclerosis in a subject in need thereof, comprising administering to the subject an antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist").

[0014] In some embodiments, the atherosclerosis is associated with a disease comprising coronary heart disease (CHD), carotid artery disease, peripheral artery disease, chronic kidney disease, stroke, retinal artery occlusion, abdominal pain caused by intestinal damage, peritonitis, or combinations thereof. In certain embodiments, the atherosclerosis is associated with a high fat and/or high cholesterol (hypercholesterolemic) diet. In further embodiments, the atherosclerosis is associated with an increased total cholesterol level, increased triglyceride level, increased LDL level, decreased HDL level, increased number and/or retention of oxo-LDL-induced foam cells within a plaque, or combinations thereof, compared to a subject without atherosclerosis (*e.g.*, a healthy subject).

[0015] In some embodiments, administering a FAM19A5 antagonist (*e.g.*, anti-FAM19A5 antibody) reduces a low density lipoprotein (LDL) level in the subject by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the

FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0016] In some embodiments, administering a FAM19A5 antagonist increases a migration and/or accumulation of macrophages at an atherosclerotic lesion site in an aorta of a subject by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0017] In some embodiments, administering a FAM19A5 antagonist increases a phagocytosis of LDL by macrophages by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist). In certain embodiments, the increase in phagocytosis of LDL by macrophages occurs at an atherosclerotic lesion site in a blood vessel. In some embodiments, the LDL comprises oxidized LDL. In certain embodiments, the blood vessel comprises an artery, vein, capillaries, or combinations thereof. In some embodiments, the artery is an aorta.

[0018] In some embodiments, the FAM19A5 antagonist is an antisense oligonucleotide, siRNA, shRNA, miRNA, dsRNA targeting FAM19A5, aptamer, PNA, or a vector including the same.

[0019] 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"). In certain embodiments, wherein the anti-FAM19A5 antibody exhibits a property selected from: (a) binds to soluble human FAM19A5 with a K_D of 10 nM or less as measured by enzyme-linked immunosorbent assay (ELISA); (b) binds to membrane bound human FAM19A5 with a K_D of 10 nM or less as measured by ELISA; and (c) both (a) and (b).

[0020] In some embodiments, the anti-FAM19A5 antibody cross-competes for binding to a human FAM19A5 epitope with a reference antibody, wherein the reference antibody is selected from the group consisting of the antibodies in TABLES 2-5. In certain embodiments, the reference antibody comprises heavy chain CDR1, CDR2, and CDR3 and light chain CDR1,

CDR2, and CDR3, wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.

[0021] In some embodiments, the anti-FAM19A5 antibody specifically binds to the same FAM19A5 epitope as a reference antibody, wherein the reference antibody is selected from the group consisting of TABLES 2-5. In certain embodiments, the reference antibody comprises heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3, wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.

[0022] In some embodiments, the anti-FAM19A5 antibody specifically binds to at least one FAM19A5 epitope, which is SEQ ID NO: 6 or SEQ ID NO: 9.

[0023] In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, (i) wherein the heavy chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in TABLE 2; (ii) wherein the heavy chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in TABLE 2; (iii) wherein the heavy chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in TABLE 2; (iv) wherein the light chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in TABLE 3; (v) wherein the light chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in TABLE 3; and/or (vi) wherein the light chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in TABLE 3.

[0024] In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, (i) wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14; (ii) wherein the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15; (iii) wherein the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16; (iv)

wherein the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26; (v) wherein the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27; and/or (vi) wherein the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.

[0025] 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 the amino acid sequence set forth as SEQ ID NOs: 14, 15, and 16, respectively, and the light chain CDR1, CDR2, and CDR3 comprises the amino acid sequence set forth as SEQ ID NOs: 26, 27, and 28, respectively.

[0026] In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth as SEQ ID NO: 36.

[0027] In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL), wherein the VH 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: 36. In certain embodiments, the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL), wherein the VL 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: 40.

[0028] In some embodiments, the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL), (i) wherein the VH 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: 36; and (ii) wherein the VL 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: 40.

[0029] In some embodiments, the anti-FAM19A5 antibody comprises a Fab, Fab', F(ab')₂, Fv, or single chain Fv (scFv). In certain embodiments, the anti-FAM19A5 antibody is

selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, and a variant thereof. In some embodiments, the anti-FAM19A5 antibody is an IgG2, an IgG4, or a combination thereof. In further embodiments, the anti-FAM19A5 antibody comprises an IgG2/IgG4 isotype antibody. In some embodiments, the anti-FAM19A5 antibody comprises a constant region without the Fc function. In some embodiments, the anti-FAM19A5 antibody is a chimeric antibody, a human antibody, or a humanized antibody.

[0030] In some embodiments, the FAM19A5 antagonist is linked to a molecule having a second binding moiety, thereby forming a bispecific molecule. In some embodiments, the FAM19A5 antagonist is linked to an agent, thereby forming an immunoconjugate.

[0031] In some embodiments, methods disclosed herein further comprise administering a therapeutic agent.

[0032] In some embodiments, the FAM19A5 antagonist disclosed herein is formulated with a pharmaceutically acceptable carrier. In some embodiments, the FAM19A5 antagonist is administered intravenously, subcutaneously, intramuscularly, orally, intravitreally, intrathecally, or combinations thereof.

[0033] In some embodiments, the subject being treated with the present disclosure is a human.

[0034] In some embodiments, methods disclosed herein further comprise administering a cholesterol lowering agent. In certain embodiments, the cholesterol lowering agent is administered subsequent to or concurrently with the FAM19A5 antagonist.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] FIG. 1 shows the effect of anti-FAM19A5 antibody on the body weight of hypercholesterolemic mice. The mice were treated with either human IgG control antibody (Group 2, black triangle) or anti-FAM19A5 antibody at two different concentrations, 5 mg/kg (Group 3, open square) or 10 mg/kg (Group 4). Normal mice (*i.e.*, regular diet; Group 1, open triangle) were used as a control. Body weight was measured at 7 different time points over a course of about 42 days.

[0036] FIG. 2 shows the effect of anti-FAM19A5 antibody on LDL level in hypercholesterolemic mice. The mice were treated with either human IgG control antibody (G2) or anti-FAM19A5 antibody at two different concentrations, 5 mg/kg (G3) or 10 mg/kg (G4). Normal mice (*i.e.*, regular diet; G1) were used as control. Data are shown as mean $\pm$ S.D.

[0037] FIGs. 3A, 3B, 3C, and 3D show an immunohistochemistry analysis of CD68 (left panel) and CD146 (right panel) expression in the aorta of mice from the different treatment groups. FIG. 3A show expression in normal mice (*i.e.*, regular diet). FIG. 3B show expression in hypercholesterolemic mice treated with a human IgG control antibody. FIGs. 3C and 3D show expression in mice treated with anti-FAM19A5 antibody at two different concentrations, 5 mg/kg and 10 mg/kg, respectively. Images shown are at 100x magnification.

[0038] FIGs. 4A and 4B show the effect of anti-FAM19A5 antibody treatment on the phagocytic ability of BV2 cells. FIG. 4A shows the phagocytic uptake of the PHRODO™ Green *E. coli* BioParticles over a course of 22 hours in BV2 cells treated with one of the following: (i) human Fc alone (“1”), (ii) human FAM19A5-Fc protein alone (“2”), or (iii) human FAM19A5-Fc protein in combination with varying concentrations (25 µg/mL (“6”), 12.5 µg/mL (“5”), 6.25 µg/mL (“4”), or 3.125 µg/mL (“3”)) of anti-FAM19A5 antibody. Data are shown as mean ± S.D. FIG. 4B provides representative immunofluorescence images of BV2 cells treated with one of the following: (i) human Fc alone (left panel), (ii) human FAM19A5-Fc protein alone (center panel), or (iii) human FAM19A5-Fc protein in combination with anti-FAM19A5 antibody (25 µg/mL) (right panel).

[0039] FIG. 5 shows the effect of anti-FAM19A5 antibody treatment on TNF-α production by BV2 cells. The different treatment groups shown include (from left to right): (1) LPS alone, (2) LPS + FAM19A5-Fc protein, (3) LPS + FAM19A5-Fc protein + 0.78125 µg/mL of anti-FAM19A5 antibody, (4) LPS + FAM19A5-Fc protein + 1.5625 µg/mL of anti-FAM19A5 antibody, (5) LPS + FAM19A5-Fc protein + 3.125 µg/mL of anti-FAM19A5 antibody, (6) LPS + FAM19A5-Fc protein + 6.25 µg/mL of anti-FAM19A5 antibody, (7) LPS + FAM19A5-Fc protein + 12.5 µg/mL of anti-FAM19A5 antibody, (8) LPS + FAM19A5-Fc protein + 25 µg/mL of anti-FAM19A5 antibody, (9) LPS + FAM19A5-Fc protein + 50 µg/mL of anti-FAM19A5 antibody, and (10) LPS + FAM19A5-Fc protein + 100 µg/mL of anti-FAM19A5 antibody. Data are shown as mean ± S.D. “****” above the bars indicate a statistically significant difference ($p < 0.005$) compared to LPS treated group. “####” above the bars indicate a statistically different difference ($p < 0.005$) compared to LPS + FAM19A5-Fc protein treated group.

[0040] FIGs. 6A and 6B show the effect of FAM19A5 signaling on the phagocytic ability of mouse bone marrow-derived macrophages (“BMDM”). Phagocytic ability is measured using flow cytometry and represented by the percentage of mouse BMDMs that are positive for PHRODO™ expression. FIG. 6A provides representative histogram plots for each of the different

treatment groups (value provided in the upper right quadrant represents the percentage of BMDMs that are positive for PHRODO™ expression). FIG. 6B provides a table summarizing the results from three independent experiments. The different BMDM treatment groups shown in FIGs. 6A and 6B include the following: (A1) mouse BMDMs only, (A2) mouse BMDMs + apoptotic thymocytes, (A3) mouse BMDMs + apoptotic thymocytes + control Fc (0.4 μM), (A4) mouse BMDMs + apoptotic thymocytes + control Fc (0.8 μM), (A5) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.4 μM), and (A6) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM).

[0041] FIGs. 7A and 7B show the effect of anti-FAM19A5 antibody treatment on the phagocytic ability of mouse bone marrow-derived macrophages (“BMDM”). Phagocytic ability is measured using flow cytometry and represented by the percentage of mouse BMDMs that are positive for PHRODO™ expression. FIG. 7A provides representative histogram plots for each of the different treatment groups (value provided in the upper right quadrant represents the percentage of BMDMs that are positive for PHRODO™ expression). FIG. 7B provides a table summarizing the results from three independent experiments. The different BMDM treatment groups shown in FIGs. 7A and 7B include the following: (B1) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + hIgG1 control antibody (25 nM), (B2) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + hIgG1 control antibody (50 nM), (B3) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + “3-2” anti-FAM19A5 antibody (25 nM), (B4) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + “3-2” anti-FAM19A5 antibody (50 nM), (B5) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + “1-65” anti-FAM19A5 antibody (25 nM), and (B6) mouse BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μM) + “1-65” anti-FAM19A5 antibody (50 nM).

[0042] FIG. 8 provides a graphical comparison of the results shown in FIGs, 6A, 6B, 7A, and 7B. Data are shown as mean ± S.D.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0043] 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

[0044] 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.

[0045] 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).

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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).

[0050] As used herein, the term "atherosclerosis," "atherosclerotic plaque," "plaque," or "atheroma" refers to the accumulation of one or more of lipids, cholesterol, collagen, and macrophages on the walls of a blood vessel. In some embodiments, such accumulation can result from an inflammatory process involving interaction among modified lipoproteins, monocyte-derived macrophages, T cells, and normal cellular elements of blood vessel walls. This inflammatory process can lead to the development of complex lesions or plaques along the walls of a blood vessel, resulting in the narrowing of the blood vessel lumen.

[0051] Non-limiting examples of risk factors for atherosclerosis can include hypertension, diabetes, hypercholesterolemia, elevated plasma low density lipoprotein (LDL) and triglycerides, smoking, obesity, family history, unhealthy diet, and combinations thereof.

[0052] As used herein, the term "HDL" refers to high-density lipoproteins.

[0053] As used herein, the term "LDL" refers to low-density lipoproteins. In some embodiments, LDL is oxidized ("oxidized LDL").

[0054] As used herein, the term "VLDL" refers to very low density lipoproteins.

[0055] The term "hypercholesterolemia," as used herein, refers to a condition characterized by very high levels of total cholesterol in the blood (*e.g.*, atherosclerosis). "Total cholesterol" refers to the sum of all the major plasma lipoproteins (*e.g.*, LDL, HDL, and VLDL) present in plasma.

[0056] In some embodiments, hypercholesterolemia is associated with a total cholesterol level of at least about 200 mg/dL, at least about 210 mg/dL, at least about 220 mg/dL, at least about 230 mg/dL, at least about 240 mg/dL, at least about 250 mg/dL, at least about 260 mg/dL, at least about 270 mg/dL, at least about 280 mg/dL, at least about 290 mg/dL or more. In certain embodiments, hypercholesterolemia is associated with a total cholesterol level of about 240 mg/dL or more.

[0057] In some embodiments, a hypercholesterolemic subject has an elevated LDL level in the blood. In certain embodiments, the LDL level in a hypercholesterolemic subject is at least about 130 mg/dL, at least about 140 mg/dL, at least about 150 mg/dL, at least about 160 mg/dL, at least about 170 mg/dL, at least about 180 mg/dL, at least about 190 mg/dL, at least about 200 mg/dL or more. In some embodiments, the LDL level in a hypercholesterolemic subject is about 160 mg/dL or more. In certain embodiments, the LDL level in a hypercholesterolemic subject is about 190 mg/dL or more.

[0058] In some embodiments, a hypercholesterolemic subject has an elevated triglyceride level in the blood. In some embodiments, the triglyceride level in a hypercholesterolemic subject is at least about 150 mg/dL, at least about 175 mg/dL, at least about 200 mg/dL, at least about 225 mg/dL, at least about 250 mg/dL, at least about 275 mg/dL, at least about 300 mg/dL, at least about 325 mg/dL, at least about 350 mg/dL, at least about 375 mg/dL, at least about 400 mg/dL, at least about 425 mg/dL, at least about 450 mg/dL, at least about 475 mg/dL, at least about 500 mg/dL, at least about 525 mg/dL, at least about 550 mg/dL, at least about 575 mg/dL, at least about 600 mg/dL, at least about 625 mg/dL, at least about 650 mg/dL or more. In certain embodiments, the triglyceride level in a hypercholesterolemic subject is about 150 mg/dL or more. In other embodiments, the triglyceride level in a hypercholesterolemic subject is about 200 mg/dL or more. In further embodiments, the triglyceride level in a hypercholesterolemic subject is about 500 mg/dL or more.

[0059] In some embodiments, a hypercholesterolemic subject has a reduced HDL level in the blood. In certain embodiments, the HDL level in a hypercholesterolemic subject is less than about 50 mg/dL, less than about 45 mg/dL, less than about 40 mg/dL, less than about 30 mg/dL, less than about 20 mg/dL, less than about 10 mg/dL, or less than about 5 mg/dL.

[0060] As used herein, the term "foam cells" refers to a type of macrophage that localize to fatty deposits on blood vessel walls, where they ingest low-density lipoproteins (*e.g.*, oxidized LDL) and become laden with lipids, giving them a foamy appearance. These cells secrete various substances involved in plaque growth and their death promotes inflammation, thereby contributing to cardiovascular diseases. The accumulation of foam cells within the blood vessels can lead to formation of fatty streaks, which are the early atherosclerotic lesions.

[0061] 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).

[0062] 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, intravitreal, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, 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.

[0063] 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.*, atherosclerosis). 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.*, atherosclerosis). 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.*, increased inflammation or plaque formation), and/or decrease in at least one clinical symptom of a disease or disorder.

[0064] 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.

[0065] 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. 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 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.

[0066] FAM19A5 is believed to be important 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) 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. Antagonists against FAM19A5 (*e.g.*, anti-FAM19A5 antibody) 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.

[0067] However, for certain diseases, particularly those associated with blood vessel abnormalities, a recent study has suggested that FAM19A5 antagonists may not be a viable treatment option. Wang *et al.*, *Circulation* 138(1):48-63 (2018). Wang *et al.* showed that the adipose tissues of normal, healthy individuals produce FAM19A5, which signals through sphingosine-1-phosphate receptor 2 (S1PR2) to suppress the proliferation and migration of vascular smooth muscle cells (VSMCs) and to attenuate postinjury neointima formation. However, in obese individuals, there is a significant decrease in FAM19A5 expression (both mRNA and protein) in the adipose tissues. Wang *et al.* concludes that this decrease in FAM19A5 activity is responsible for the accelerated development of cardiovascular diseases observed in many obese individuals.

[0068] 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.

MAPSPRTGSR QDATAALPSMS STFWAFMILA SLLIAYCSQL AAGTCEIVTL DRDSSQPRRT
IARQTARCAK RKGQIAGTTR ARPACVDARI IKTKQWCDML PCLEGECDL LINRSGWTCT
QPGGRIKTTT VS (SEQ ID NO: 1)

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

MQLLKALWAL AGAALCCFLV LVIHAQFLKE GQLAAGTCEI VTLD RDSSQP RRTIARQTAR
CACRKGQIAG TTRARPACVD ARIIKTKQWC DMLPCLEGECD LLINRSGW TCTQPGGRIK
TTTVS (SEQ ID NO: 2)

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

MYHHREWPAP IIKTKQWCDM LPCLEGECD LLINRSGWTC TQPGGRIKTT TVS (SEQ ID
NO: 3)

[0069] 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 gatggcgcg cgggggccc cactggagg ccggcgcggg ggcgcgggca gggccggctg ctgagacgcg ctgctgcccc ccgcgcgggc gccgcggctt caatggcgcc atcgcccagg accggcagcc ggcaagatgc gaccgccttg ccagcatgt cctcaacttt ctgggcgttc atgacccctg ccagcctgct catcgccctac tgcagtcagc tggccgcggg cacctgtgag attgtgacct tggaccggga cagcagccag cctcggagga cgatcgcccc gcagaccgcc cgctgtgctg gtagaaagg gcagatcgcc ggcaccacga gagcccggcc cgctgtgtg gacgcaagaa tcatcaagac caagcagtgg tgtgacatgc ttccgtgtct ggagggggaa ggctgcgact tgttaataca

	ccggtcaggc tggacgtgca cgcagcccgg cgggaggata aagaccacca
	cggctctcctg acaaacacag cccctgaggg ggccccggga gtggccttgg
	ctccctggag agcccacgtc tcagccacag ttctccactc gcctcggact
	tcacccgttc tctgccgccc gccactccg tttccctgtg gtccgtgaag
	gacggcctca ggccttggca tcctgagctt cggctctgtcc agccgacccg
	aggaggccgg actcagacac ataggcgggg ggccggcacct ggcatcagca
	atacgcagtc tgtgggagcc cggccgcgcc cagccccgcg cgaccgtggc
	gttggccctg ctgtcctcag aggaggagga ggaggaggca gctccggcag
	ccacagaagg ctgcagccca gccgcctga gacacgacgc ctgccccagg
	ggactgtcag gcacagaagc ggctcctcc cgtgccccag actgtccgaa
	ttgcttttat tttcttatac tttcagtata ctccatagac caaagagcaa
	aatctatctg aacctggacg caccctcact gtcagggtcc ctggggtcgc
	ttgtgcgggc gggagggcaa tgggtggcaga gacatgctgg tggccccggc
	ggagcggaga gggcggccgt ggtggaggcc tccaccccag gagcaccgcc
	cacaccctcg gaggacgggc ttccggctgcg cggaggccgt ggcacacctg
	cgggaggcag cgacggcccc cacgcagacg ccgggaacgc aggccgcttt
	attcctctgt acttagatca acttgaccgt actaaaatcc ctttctgttt
	taaccagtta aacatgcctc ttctacagct ccatttttga tagttggata
	atccagtatc tgccaagagc atgttgggtc tcccgtgact gctgcctcat
	cgatacccca tttagctcca gaaagcaaag aaaactcgag taacacttgt
	ttgaaagaga tcattaaatg tattttgcaa agccccaaaa aaaaaaaaaa
	a

[0070] The term "antagonist against a FAM19A5 protein" refers to all antagonists that suppress and/or neutralize the expression and/or activity 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.

[0071] 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 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.

[0072] 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.

[0073] 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.

[0074] 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
		<u>(Kabat Numbering)</u>	
H1	H31-H35	H26-H35	H26-H32
		<u>(Chothia Numbering)</u>	
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] "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)).

[0081] 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.

[0082] As used herein, the terms "variable region" and "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 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).

[0083] 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).

[0084] As used herein, the term "heavy chain" (HC) 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.

[0085] As used herein, the term "light chain" (LC) 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.

[0086] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[0087] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[0088] As used herein, the terms "constant region" and "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.

[0089] 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, a 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 C γ 2 and C γ 3 and the hinge between C γ 1 and C γ 2. 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 a 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 a Fc-comprising protein polypeptide such as a "binding protein comprising a Fc region," also referred to as an "Fc fusion protein" (*e.g.*, an antibody or immunoadhesion).

[0090] A "native sequence Fc region" or "native sequence Fc" comprises an amino acid sequence that is identical to the amino acid sequence of a 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 Fcs (*see, e.g.,* Jefferis *et al.* (2009) *mAbs* 1:1; Vidarsson G. *et al. Front Immunol.* 5:520 (published online Oct. 20, 2014)).

[0091] 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 Fc γ R family, including allelic variants and alternatively spliced forms of these receptors. The Fc γ R family consists of three activating (Fc γ RI, Fc γ RIII, and Fc γ RIV in mice; Fc γ RIA, Fc γ RIIA, and Fc γ RIIA in humans) and one inhibitory (Fc γ RIIB) 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).

[0092] 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 a Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary "effector functions" include C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, Fc γ R-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.

[0093] 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 a 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.

[0094] 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).

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] "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).

[0100] 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."

[0101] 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.

[0102] "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®).

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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 FAM19A5) 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)).

[0107] 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.

[0108] The term "epitope mapping" refers to the process of identification of the molecular determinants for antibody-antigen recognition.

[0109] 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.

[0110] 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).

[0111] 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)).

[0112] 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).

[0113] 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.

[0114] 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).

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.*, atherosclerosis). A "therapeutically effective amount" includes an amount of a drug or a therapeutic agent (*e.g.*, anti-FAM19A5 antibodies disclosed herein) that provides some

improvement or benefit to a subject having or at risk of having a disease or disorder (*e.g.*, atherosclerosis). Thus, a "therapeutically effective" amount is an amount that reduces the risk, potential, possibility, or occurrence of a disease or disorder or provides some alleviation, mitigation, and/or reduces at least one indicator, and/or decrease in at least one clinical symptom of a disease or disorder (*e.g.*, atherosclerosis).

II. Methods of Treating Atherosclerosis

[0126] Disclosed herein are methods of treating a cardiovascular condition in a subject in need thereof. More specifically, the methods disclosed herein can be used to treat an atherosclerosis, including diseases and disorders associated with atherosclerosis. Non-limiting examples of such diseases and disorders include coronary artery disease, stroke, peripheral artery disease, kidney impairment, retinal artery occlusion, abdominal pain caused by intestinal damage, and peritonitis, or combinations thereof. As described *infra*, atherosclerosis is generally associated with abnormal levels of lipoproteins in the plasma. In certain embodiments, the term "lipoprotein" comprises total cholesterol, LDL, HDL, triglyceride, or combinations thereof. Abnormal levels of such lipoproteins can cause accumulation of lipid-laden macrophages (also known as foam cells), resulting in lesion or plaque build-up along blood vessel wall. Accordingly, the present disclosure also provides methods of modulating (*i.e.*, decreasing or increasing) the levels of one or more lipoproteins in a subject in need thereof (*e.g.*, having atherosclerosis). Also provided herein are methods for reducing a number of foam cells (*e.g.*, ox-LDL-induced foam cells) and/or retention of foam cells within a plaque in a subject in need thereof.

[0127] In some embodiments, methods disclosed herein comprise administering to the subject an antagonist against FAM19A5 protein ("FAM19A5 antagonist"). In some embodiments, the FAM19A5 antagonist is an antisense oligonucleotide, siRNA, shRNA, miRNA, dsRNA targeting FAM19A5, aptamer, PNA, 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 ("an anti-FAM19A5 antibody"), a polynucleotide encoding the anti-FAM19A5 antibody, or a vector comprising the polynucleotide thereof. In some embodiments, the anti-FAM19A5 antibody binds to FAM19A5 protein and reduces FAM19A5 activity.

[0128] Subjects that can be treated with the methods disclosed herein (*e.g.*, having atherosclerosis) can exhibit one or more of the following properties: (i) an increased total

cholesterol level, (ii) an increased triglyceride level, (iii) an increased LDL level, (iv) a reduced HDL level, (v) increased number of foam cells and/or retention of foam cells in a plaque, (vi) or combinations thereof, compared to a subject who does not have atherosclerosis (*e.g.*, a healthy subject).

[0129] Accordingly, not being bound by any single theory, a FAM19A5 antagonist disclosed herein (*e.g.*, anti-FAM19A5 antibody) can treat atherosclerosis by reducing, alleviating, and/or reversing one or more of the properties described above. In some embodiments, a FAM19A5 antagonist is capable of neutralizing a FAM19A5 protein, *e.g.*, a FAM19A5 neutralizing agent. In other embodiments, a FAM19A5 antagonist is an anti-FAM19A5 antibody. In some embodiments, the anti-FAM19A5 antibody is a neutralizing antibody.

[0130] In some embodiments, a FAM19A5 antagonist disclosed herein can reduce a total cholesterol level in a subject in need thereof. In certain embodiments, the total cholesterol level in the subject is reduced by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0131] In some embodiments, a FAM19A5 antagonist disclosed herein can reduce a triglyceride level in a subject in need thereof. In certain embodiments, the triglyceride level in the subject is reduced by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0132] In some embodiments, a FAM19A5 antagonist disclosed herein can reduce a low density lipoprotein (LDL) level in a subject in need thereof. In certain embodiments, the LDL level in the subject is reduced by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0133] In some embodiments, a FAM19A5 antagonist disclosed herein can increase a high density lipoprotein (HDL) level in a subject in need thereof. In certain embodiments, the HDL level in the subject is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0134] In some embodiments, a FAM19A5 antagonist disclosed herein (*e.g.*, anti-FAM19A5 antibody) can increase the migration and/or accumulation of macrophages to an atherosclerotic lesion site in a subject in need thereof. In certain embodiments, the migration and/or accumulation of macrophages at an atherosclerotic lesion site is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0135] In some embodiments, a FAM19A5 antagonist can increase the phagocytosis of low density lipoprotein (LDL) by macrophages (or other cells with phagocytic abilities, *e.g.*, dendritic cells) in a subject in need thereof. In certain embodiments, the phagocytosis of LDL by macrophages is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

[0136] Without wishing to be bound by any particular mechanism or theory, in some embodiments, (i) the increase in the migration and/or accumulation of macrophages at an atherosclerotic lesion site and/or (ii) the increase in the phagocytosis of LDL by the macrophages can reduce the level of LDL in the blood, and thereby treat atherosclerosis (or diseases or disorders associated with atherosclerosis). In some embodiments, the macrophages are lipid-laden macrophages (also known as foam cells).

[0137] In some embodiments, a FAM19A5 antagonist disclosed herein can induce a normalization of a blood vessel in a subject in need thereof. In certain embodiments, blood vessel

normalization comprises (i) increased number of blood vessels, (ii) improved connectivity of blood vessels, (iii) decreased blood vessel permeability, (iv) increased blood flow rate, or (v) any combinations thereof. In certain embodiments, normalization of a blood vessel is associated with reduced plaque build-up within the walls of the blood vessels.

[0138] As used herein, the term "blood vessel" refers to any of the vessels through which blood circulates in the body. The term "vessel" refers to any channel for carrying a fluid, such as an artery or vein. In some embodiments, a blood vessel comprises an artery, vein, or capillary. In certain embodiments, a blood vessel comprises an aorta.

[0139] As described *infra*, if not properly treated, atherosclerosis can lead to other cardiovascular diseases and disorders. Accordingly, in some embodiments, atherosclerosis that can be treated with the present methods is associated with a disease comprising coronary heart disease (CHD), carotid artery disease, peripheral artery disease, chronic kidney disease, stroke, retinal artery occlusion, abdominal pain caused by intestinal damage, and peritonitis, or combinations thereof. In some embodiments, the atherosclerosis is associated with a high fat and/or high cholesterol (hypercholesterolemic) diet. In certain embodiments, a high fat and/or high cholesterol diet comprises a total fat concentration of at least about 20%, at least about 25%, at least about 30%, at least 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 65%, at least about 70%, at least about 75%, at least about 80% or more. In some embodiments, a high fat and/or high cholesterol diet comprises a total fat concentration of about 42%. In other embodiments, the atherosclerosis is associated with an increased total cholesterol level, increased triglyceride level, increased LDL level, decreased HDL level, increased number and/or retention of oxo-LDL-induced foam cells within a plaque, or combinations thereof, compared to a subject without atherosclerosis (*e.g.*, a healthy subject).

[0140] In some embodiments, the term "reference," as used herein, refers to a corresponding subject (*e.g.*, having atherosclerosis) who did not receive a composition disclosed herein (*e.g.*, FAM19A5 antagonist, *e.g.*, anti-FAM19A5 antibody). The term "reference" can also refer to a same subject (*e.g.*, having atherosclerosis) but prior to the administration of a composition disclosed herein. In certain embodiments, the term "reference" refers to an average of a population of subjects (*e.g.*, having atherosclerosis).

[0141] In some embodiments, subject that can be treated with the present methods is a nonhuman animal, such as a rat or a mouse. In other embodiments, subject that can be treated with the methods disclosed herein is a human.

[0142] In some embodiments, a FAM19A5 antagonist (*e.g.*, anti-FAM19A5 antibody), a bispecific molecule, or an immunoconjugate, or a composition thereof disclosed herein, is delivered to a subject via intravenous administration. Non-limiting examples of other administration route include subcutaneously, intramuscularly, orally, intravitreally, intrathecally, or combinations thereof.

[0143] For administration of a FAM19A5 antagonist, or a composition thereof, disclosed herein (*e.g.*, anti-FAM19A5 antibody), dosage ranges from about 0.0001 to 100 mg/kg.

[0144] In some embodiments, a FAM19A5 antagonist, or a composition thereof, can be administered in combination with one or more additional agent (*e.g.*, therapeutic agent) for treating atherosclerosis. Non-limiting examples of such additional agent include (i) a cholesterol lowering agent, (ii) anti-platelet agent, (iii) beta-blocker, (iv) angiotensin-converting enzyme (ACE) inhibitor, (v) calcium channel blockers, (vi) diabetes drug, or (vii) combinations thereof.

[0145] In some embodiments, a cholesterol lowering agent comprises a statin (*e.g.*, atorvastatin (LIPITOR[®]), fluvastatin (LESCOL[®]), lovastatin, pitavastatin (LIVALO[®]), pravastatin (PRAVACHOL[®]), rosuvastatin calcium (CRESTOR[®]), and simvastatin (ZOCOR[®])). In other embodiments, a cholesterol lowering agent comprises a PCSK9 inhibitor (*e.g.*, alirocumab (PRALUENT[®]) and evolocumab (REPATHA[®])).

[0146] In some embodiments, an anti-platelet agent comprises acetylsalicylic acid or aspirin (ASPIRIN[®], ASAPHEN[®], ENTROPHEN[®], NOVASEN[®]), clopidogrel (PLAVIX[®]), prasugrel (EFFIENT[®]), or ticagrelor (BRILINTA[®]).

[0147] In some embodiments, a beta blocker comprises acebutolol (SECTRAL[®]), atenolol (TENORMIN[®]), bisoprolol (ZEBETA[®]), metoprolol (LOPRESSOR[®] and TOPROL-XL[®]), nadolol (CORGARD[®]), nebivolol (BYSTOLIC[®]), or propranolol (INDERAL LA[®] and INNOPRAN XL[®]).

[0148] In some embodiments, an ACE inhibitor comprises benazepril (LOTENSIN[®], LOTENSIN HCT[®]), captopril (CAPOTEN[®]), enalapril (VASOTEC[®]), fosinopril (MONOPRIL[®]), lisinopril (PRINIVIL[®], ZESTRIL[®]), moexipril (UNIVASC[®]), perindopril (ACEON[®]), quinapril (ACCUPRIL[®]), ramipril (ALTACE[®]), or trandolapril (MAVIK[®]).

[0149] In some embodiments, a calcium channel blocker comprises amlodipine (NORVASC), diltiazem (CARDIZEM[®], TIAZAC[®]), felodipine, isradipine, nifedipine, nifedipine (ADALAT CC[®], AFEDITAB CR[®], PROCARDIA[®]), nisoldipine (SULAR[®]), or verapamil (CALAN[®], VERELAN[®]).

[0150] In some embodiments, a diabetes drug comprises metformin (GLUCOPHAGE[®], GLUMETZA[®]), sulfonylureas (DIABETA[®], GLYNASE[®], GLUCOTROL[®], AMARYL[®]), meglitinides (PRANDIN[®], STARLIX[®]), thiazolidinediones (AVANDIA[®], ACTOS[®]), DPP-4 inhibitors (JANUVIA[®], ONGLYZA[®], TRADJENTA[®]), GLP-1 receptor agonists (BYETTA[®], VICTOZA[®]), SGLT2 inhibitors (INVOKANA[®], FARXIGA[®]), or insulin therapy.

[0151] Other currently available treatment options that can be used in combination with FAM19A5 antagonist, or a composition thereof, include, but are not limited to, surgery (*e.g.*, coronary artery bypass graft, or carotid endarterectomy) and controlling modifiable risk factors (*e.g.*, exercise, healthy diet, stopping tobacco use).

III. FAM19A5 Antagonists

[0152] In some embodiments, a 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, a 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.

[0153] 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 10 nM or less; or both (a) and (b).

[0154] 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 (10 nM) 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 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, 5×10^{-12} M, 10^{-11} M, 5×10^{-11} M, 10^{-10}

M, 5×10^{-10} M, 10^{-9} M, 5×10^{-9} M, 10^{-8} M, 5×10^{-8} M, 10^{-7} M, or 5×10^{-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®.

[0155] 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.

[0156] 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.

[0157] In certain embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof that is useful in the methods disclosed herewith 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.

[0158] 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; (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; (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; (xvi) 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: 208, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 209, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 210. In some aspects, the heavy chain CDR1, CDR2, and CDR3 of the reference antibody comprise a CDR1, CDR2, and CDR3 sequence as set forth in Table 2, respectively, and the light chain CDR1, CDR2, and CDR3 of the reference antibody comprise a CDR1, CDR2, and CDR3 sequence as set forth in Table 3, respectively.

[0159] 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; (o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively; (p) heavy and light chain variable region sequences comprising SEQ ID NOs: 211 and 212, respectively. In some aspects, the reference antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises an amino acid sequence as set forth in Table 4, and the VL comprises an amino acid sequence as set forth in Table 5.

[0160] 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.

[0161] 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, 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; (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; (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; or (xvi) 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: 208, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 209, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 210. In some aspects, the heavy chain CDR1, CDR2, and CDR3 of the reference antibody comprise a CDR1, CDR2, and CDR3 sequence as set forth in Table 2, respectively, and the light chain CDR1, CDR2, and CDR3 of the reference antibody comprise a CDR1, CDR2, and CDR3 sequence as set forth in Table 3, respectively.

[0162] 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; (o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively; (p) heavy and light chain variable region sequences comprising SEQ ID NOs: 211 and 212, respectively. In some aspects, the reference antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises an amino acid sequence as set forth in Table 4, and the VL comprises an amino acid sequence as set forth in Table 5.

[0163] 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.

[0164] 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 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 CDMLPCLEGECDLLINRSG (SEQ ID NO: 9 or amino acids 90 to 109 of SEQ ID NO: 2), *e.g.*, an epitope having at least 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.

[0165] 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.

[0166] 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.

[0167] 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 other 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: 5. 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: 10. In some embodiments, the anti-FAM19A5 antibody or antigen binding portion thereof binds to both glycosylated and unglycosylated human FAM19A5.

[0168] 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), TARCACRKGQIAGTTTARPA (SEQ ID NO: 7, epitope F3), ARPACVDARI I KTKQWCDML (SEQ ID NO: 8, epitope F4), CDMLPCLEGE GCDLLINRSG (SEQ ID NO: 9, epitope F5), or NRSGWTCTQPGGRIKTTTTS (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, or 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, 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, 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.

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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.*, an 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.

[0173] 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.

IV. Exemplary Anti-FAM19A5 Antibodies

[0174] 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 amino acid sequences for the VH and VL CDRs for the different anti-FAM19A5 antibodies are

provided in Tables 2 and 3, respectively. The CDRs for the following antibodies were identified using the Kabat numbering scheme (*see supra*): 1-65, 3-2, 2-13, 1-28, P2-C12, 13B4, 13F7, 15A9, P1-A03, P1-A08, P1-F02, P2-A01, P2-A03, P2-F07, P2-F11, SS01-13, SS01-13-s5, and S5-2.GKNG. The CDRs for the following antibodies were identified using the IMGT numbering system (*see supra*): 1-7A-IT, Low-PI, 1-30, 1-17, 1-32, 4-11, 6-10, 2-13D, 2-13D-37, 2-13D-37-1.5W-41, and 2-13D-37-3W-16. 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

Antibody	VH-CDR1	VH-CDR2	VH-CDR3
<i>According to Kabat System</i>			
Anti-FAM19A5 ("2-13")	SHGMF (SEQ ID NO: 11)	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	STYECPPGGFSCWGD TGQIDA (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)	IRSDG SNP (SEQ ID NO: 21)	AKDGN GYCALDAYRSGGYSCGVY PGSIDA (SEQ ID NO: 22)
Anti-FAM19A5 ("P2-C12")	TYAVT (SEQ ID NO: 89)	YINWRGGTSYANWAKG (SEQ ID NO: 90)	DASSGA AFGSYGM DP (SEQ ID NO: 91)
Anti-FAM19A5 ("13B4")	SSN WWS (SEQ ID NO: 95)	EIYHGGTTNYP SLKG (SEQ ID NO: 96)	WQLVGGLDV (SEQ ID NO: 97)
Anti-FAM19A5 ("13F7")	GYSWT (SEQ ID NO: 101)	EISHFGSANYNPSLKS (SEQ ID NO: 102)	ALRGTYSRFY YGMDV (SEQ ID NO: 103)
Anti-FAM19A5 ("15A9")	SYYWS (SEQ ID NO: 107)	YIYPSGSTNYNPSLKS (SEQ ID NO: 108)	VNPF GYYYAMDV (SEQ ID NO: 109)
Anti-FAM19A5 ("P1-A03")	SDYMS (SEQ ID NO: 113)	I IYPSSTTTYASWAKG (SEQ ID NO: 114)	GSNWSSGMNL (SEQ ID NO: 115)
Anti-FAM19A5 ("P1-A08")	TYYMS (SEQ ID NO: 119)	IVYPSGTTYANWAKG (SEQ ID NO: 120)	GDSFGYGL (SEQ ID NO: 121)
Anti-FAM19A5 ("P1-F02")	NYYMG (SEQ ID NO: 125)	I IYASGSTYYASWAKG (SEQ ID NO: 126)	IDIGVGDY GWAYDR LDL (SEQ ID NO: 127)
Anti-FAM19A5 ("P2-A01")	GYYMS (SEQ ID NO: 131)	I IYPSGSTDYASWAKG (SEQ ID NO: 132)	VAGYVG YGYETFFDI (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)	IIYPSGTTYAGWAKG (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)
Anti-FAM19A5 ("SS01-13")	SYQMG (SEQ ID NO: 17)	VINKSGSDTS (SEQ ID NO: 18)	GSASYITAATIDA (SEQ ID NO: 19)
Anti-FAM19A5 ("SS01-13- s5")	SYQMG (SEQ ID NO: 17)	AINKSGSDTS (SEQ ID NO: 252)	GSASYITAATIDA (SEQ ID NO: 19)
Anti-FAM19A5 ("S5- 2.GKNG")	SYQMG (SEQ ID NO: 17)	AINKGGSDTS (SEQ ID NO: 253)	GSASYITAATIDA (SEQ ID NO: 19)
<i>According to IMGT system</i>			
Anti-FAM19A5 ("1-7A-IT")	GFTFSSFNMF (SEQ ID NO: 218)	QISSSGSSTNYAPAVKG (SEQ ID NO: 219)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("Low-PI")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("1-30")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("1-17")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("1-32")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("4-11")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("6-10")	GFDFESFNMF (SEQ ID NO: 220)	QISSSEEDENYAPAVKG (SEQ ID NO: 221)	SSYDCPYGHCSSGVDSAGEIDA (SEQ ID NO: 16)
Anti-FAM19A5 ("2-13D")	GFTFSSHGMF (SEQ ID NO:	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	STYECPGGFSCWGD TGQIDA (SEQ ID NO: 13)

	222)		
Anti-FAM19A5 ("2-13D-37")	GFDFSSHGMF (SEQ ID NO: 223)	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	STYECPPGGFSCWGDTGQIDA (SEQ ID NO: 13)
Anti-FAM19A5 ("2-13D-37- 1.5W-41")	GFDFSSHGMF (SEQ ID NO: 223)	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	SSYVCPGGFSCWGDTGQIDA (SEQ ID NO: 246)
Anti-FAM19A5 ("2-13D-37- 3W-16")	GFDFSSHGMF (SEQ ID NO: 223)	EITNDGSGTNYGSAVKG (SEQ ID NO: 12)	SNYACPPGGFSCWGDTGQIDA (SEQ ID NO: 247)

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

Antibody	VL-CDR1	VL-CDR2	VL-CDR3
<i>According to Kabat System</i>			
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")	QASQSISYLS (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")	RSSQSLHNSNGYNYLD (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")	TADTLRSYAS (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)	AASSTLAS (SEQ ID NO: 153)	QGEFSCSSADCNA (SEQ ID NO: 154)
Anti-FAM19A5 ("SS01-13")	SGGASSGYGYG (SEQ ID NO: 208)	KDDERPS (SEQ ID NO: 209)	GNDDYSSDSGYVGV (SEQ ID NO: 31)
Anti-FAM19A5 ("SS01-13-S5")	SGGASSGYGYG (SEQ ID NO: 208)	KDSERPS (SEQ ID NO: 213)	GNDDYSSDSGYVGV (SEQ ID NO: 31)
Anti-FAM19A5 ("S5-2.GKNG")	SGGASSGYGYG (SEQ ID NO: 208)	KDSERPS (SEQ ID NO: 213)	GNDDYSSDSGYVGV (SEQ ID NO: 31)
<i>According to IMGT system</i>			
Anti-FAM19A5 ("1-7A-IT")	SGGGSYAGSYYYG (SEQ ID NO: 26)	ENNKRPS (SEQ ID NO: 224)	GSWDSSNGGI (SEQ ID NO: 28)
Anti-FAM19A5 ("Low-PI")	SGGGSEEEQYYYG (SEQ ID NO: 225)	EDEERPS (SEQ ID NO: 226)	GSWDSEDEDH (SEQ ID NO: 227)
Anti-FAM19A5 ("1-30")	SGGGSEEEQYYYG (SEQ ID NO: 225)	QDEERPS (SEQ ID NO: 228)	GSWDSEDEDH (SEQ ID NO: 227)
Anti-FAM19A5 ("1-17")	SGGGSYAGSYYYG (SEQ ID NO: 26)	EDEQRPS (SEQ ID NO: 229)	GSWDSEDEDH (SEQ ID NO: 227)
Anti-FAM19A5 ("1-32")	SGGGSYAGSYYYG (SEQ ID NO: 26)	QDEERPS (SEQ ID NO: 228)	GSWDSEDEDH (SEQ ID NO: 227)
Anti-FAM19A5 ("4-11")	SGGGSYAGSYYYG (SEQ ID NO: 26)	EDHERPS (SEQ ID NO: 230)	GSWDSSDEDH (SEQ ID NO: 231)
Anti-FAM19A5 ("6-10")	SGGGSYAGSYYYG (SEQ ID NO: 26)	QDLLRPS (SEQ ID NO: 232)	GSWDSLSSSH (SEQ ID NO: 233)

Anti-FAM19A5 ("2-13D")	SGGVYSYG (SEQ ID NO: 248)	WDDERPS (SEQ ID NO: 24)	GTEDISGTAGV (SEQ ID NO: 25)
Anti-FAM19A5 ("2-13D-37")	SGGVYSYG (SEQ ID NO: 248)	WDDERPS (SEQ ID NO: 24)	GTEDISGTAGV (SEQ ID NO: 25)
Anti-FAM19A5 ("2-13D-37- 1.5W-41")	SGGVYSYG (SEQ ID NO: 248)	WDDERPS (SEQ ID NO: 24)	GTEDISGTAGV (SEQ ID NO: 25)
Anti-FAM19A5 ("2-13D-37- 3W-16")	SGGVYSYG (SEQ ID NO: 248)	WDDERPS (SEQ ID NO: 24)	GTEDISGTAGV (SEQ ID NO: 25)

Table 4: Variable heavy chain amino acid sequence

Antibody	VH Amino Acid Sequence (SEQ ID NO)
Anti-FAM19A5 ("2-13")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSHGMFWVRQTPGKGLEYYVAEITNDGSGTNY GSAVKGRATISRDNQGSTVRLQLNNLRAEDTGTYFCARSTYECPPGFSCWGDTGQIDAWG HGTEVIVSS (SEQ ID NO: 35)
Anti-FAM19A5 ("3-2")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSFNMFWRQAPGKGLEYYVAQISSGSSSTNY APAVRGRATISRDNQGSTVRLQLNNPGAEDTGTYTCAKSSYDCPYGHCSSGVDSAGEIDA WGHGTEVIVSS (SEQ ID NO: 36)
Anti-FAM19A5 ("1-65")	AVTLDESGGGLQTPGGALSLVCKASGFTFSSYQMGWVRQAPGKGLEWVGVINKSGSDTSY GSAVKGRATISRDNQGSTVRLQLNNLRAEDTGTYFCAKGSASYITAATIDAWGHGTEVIV SS (SEQ ID NO: 37)
Anti-FAM19A5 ("1-28")	AVTLDESGGGLQTPGGALSLVCKASGFDSDYGMWVRQAPGKGLEWVAAIRSDGSNPSYGS KGRATISKDNGRSTVRLQLNNLRAEDTATYCAKDGNGYCALDAYRSGGYSCGVYPGSIDAWGHG TEVIVSS (SEQ ID NO: 38)
Anti-FAM19A5 ("P2-C12")	QSLEESGGRLVTPGTPLTLTCTVSGFSLSTYAVTWVRQAPGKGLEWIGYINWRGGTSYAN WAKGRFTISKTSSTTVDLKMTSPTTEDTATYFCARDASSGAAGFSYGMDFWGPGLTVTVS S (SEQ ID NO: 155)
Anti-FAM19A5 ("13B4")	QVQLQESGPGPLVKPSETLSLNCVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHGGTTNY NPSLKGRVTMSVDKTKNQFSLRLSSVTAVDTAVYYCARWQLVGGGLDVWGQGTITVTVSS (SEQ ID NO: 156)
Anti-FAM19A5 ("13F7")	QVQLQEWGAGLLKPSETLSLTCAINAESFNGYSWTWIRQTPGKGLEWIGIEISHFGSANYN PSLKSRATISADKSKNQFSLKLTSTAVDTAVYYCARALRGTYSRFYGMDFWVGQGTITVTV VSS (SEQ ID NO: 157)
Anti-FAM19A5 ("15A9")	QVQLQESGPGPLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGIYIPSGSTNYN PSLKSRVTISVDTSKNQFSLNLKSVTAVDTAVYYCARVNPFGYGYAMDFWVGQGTITVTVSS (SEQ ID NO: 158)
Anti-FAM19A5 ("P1-A03")	QSVEESGGRLVTPGTPLTLTCTVSGFSLSSDYMSWVRQAPGEGLEWIGIYIPSTTTYAS WAKGRFTISKTSSTTVELKMTSLTTEDTATYFCARGSNWSSGMNLWGPGLTVTVSS (SEQ ID NO: 159)
Anti-FAM19A5 ("P1-A08")	QSLEESGGRLVTPGTPLTLTCTASGFSLSTYYMSWVRQAPGKGLEWIGIVYPSGTTYAN WAKGRFTISTASTTVDLMTSPTTEDTATYFCARGDSFGYGLWGPGLTVTVSS (SEQ ID NO: 160)
Anti-FAM19A5 ("P1-F02")	QSLEESGGRLVTPGTPLTLTCTASGFSLSNYYMGWVRQAPGEGLEWIGIYASGSTYYAS WAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARIDIGVGDYGYWAYDRDLWVGQGTITVTV SS (SEQ ID NO: 161)
Anti-FAM19A5 ("P2-A01")	QEQLVESGGRLVTPGTPLTLTCTASGFFLSGYMSWVRQAPGKGLEWIGIYIPSGSTDYA SWAKGRFTISKTSSTTVDLKITPTTEDTATYFCARVAGYVGYGYETFFDIWGPGLTVTVS L (SEQ ID NO: 162)

Anti-FAM19A5 ("P2-A03")	QSVEESGGRLVTPGTPLTLTCTVSGFSLNNYDMSWVRQAPGKGLEYIGFMDTDGSAYYAT WAKGRFTISRTSTTVDLKMTSPTTEDTATYFCARRGSSYYGGIDIWGPPTVTVSL (SEQ ID NO: 163)
Anti-FAM19A5 ("P2-F07")	QSLEESGGRLVTPGTPLTLTCTASGFSLSSYYMNWVRQAPGKGLEWIGI IYPSGTTYAG WAKGRFTISKSTTVDLKITSPTSEDATYFCARTVSGYFDIWGPGLTVTVSL (SEQ ID NO: 164)
Anti-FAM19A5 ("P2-F11")	QEQLVESGGRLVTPGTTLTLTCTVSGFSLSSYGVSWVRQAPGKGLEWIGYIANNYNPHYA SWAKGRFTISKSTSTTVDLKMTSLTTEDTATYFCARDNYGMDPWGPGLTVTVSS (SEQ ID NO: 165)
Anti-FAM19A5 ("SS01-13")	AVTLDESGGGLQTPGGALSLSCASGFTFSSYQMGWVRQAPGKGLEWVGVINKSGSDTSY GSAVKGRATISRDNQSTLYLQMNNLRAEDTAVYFCAKGSASYITAATIDAWGHGTEVIV SS (SEQ ID NO: 211)
Anti - FAM19A5 ("SS01-13- s5")	AVTLDESGGGLQTPGGALRLSCKASGFTFSSYQMGWVRQAPGKGLEWVSAINKSGSDTSY GSAVKGRATISRDNQSTLYLQMNSLRAEDTAVYFCAKGSASYITAATIDAWGHGTEVIV SS (SEQ ID NO: 214)
Anti - FAM19A5 ("S5- 2.GKNG")	AVTLDESGGGLQTPGGALRLSCKASGFTFSSYQMGWVRQAPGKGLEWVSAINKSGSDTSY GSAVKGRATISRDNQSTLYLQMNSLRAEDTAVYFCAKGSASYITAATIDAWGHGTEVIV SS (SEQ ID NO: 249)
Anti - FAM19A5 ("1-7A-IT")	AVTLDESGGGLQTPGGALRLSCKASGFTFSSFNMFVRQAPGKGLEYVSQISSGSSTNY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 234)
Anti - FAM19A5 ("Low-PI")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5 ("1-30")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5 ("1-17")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5 ("1-32")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5 ("4-11")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5 ("6-10")	AVTLDESGGGLQTPGGALRLSCKASGFD FESFNMFVRQAPGKGLEYVSQISSSEEDENY APAVKGRATISRDNQSTLYLQMNSLRAEDTGTYYCAKSSYDCPYGHCSSGVD SAGEIDA WGHGTEVIVSS (SEQ ID NO: 235)
Anti - FAM19A5	AVTLDESGGGLQTPGGALRLSCSASGFTFSSHGMFVRQAPGKGLEYVSEITNDGSGTNY GSAVKGRATISRDNQSTLYLQMNSLRAEDTGTYFCARSTYECPPGFSCWGD TGQIDAWG HGTEVIVSS (SEQ ID NO: 236)

("2-13D")	
Anti-FAM19A5 ("2-13D-37")	AVTLDES GGG LQTPGGALRLSCSASGFD FSSHGMFWVRQAPGKGLEYVSEITNDGSGTNY GSAVKGRATISRDNQSTLYLQMNSLRAEDTGT YFCARSTYEC PGGFSCW GDTGQIDAWG HGTEVIVSS (SEQ ID NO: 250)
Anti-FAM19A5 ("2-13D-37-1.5W-41")	AVTLDES GGG LQTPGGALRLSCSASGFD FSSHGMFWVRQAPGKGLEYVSEITNDGSGTNY GSAVKGRATISRDNQSTLYLQMNSLRAEDTGT YFCARSSYVCPGGFSCW GDTGQIDAWG HGTEVIVSS (SEQ ID NO: 237)
Anti-FAM19A5 ("2-13D-37-3W-16")	AVTLDES GGG LQTPGGALRLSCSASGFD FSSHGMFWVRQAPGKGLEYVSEITNDGSGTNY GSAVKGRATISRDNQSTLYLQMNSLRAEDTGT YFCARSNYAC PGGFSCW GDTGQIDAWG HGTEVIVSS (SEQ ID NO: 251)

Table 5: Variable light chain amino acid sequence

Antibody	VL Amino Acid Sequence (SEQ ID NO)
Anti-FAM19A5 ("2-13")	ALTQPSSVSANPGETVKITCSGGSSYSGWFQQKSPGSALVTVIYWDDERPSDIPSRFSGA LSGSTNTLTITIGVQADDEAVYFCGTEDISGTAGVFGAGTTTLTVL (SEQ ID NO: 39)
Anti-FAM19A5 ("3-2")	ALTQPSSVSANPGETVKITCSGGSSYAGSYYYGWYQQKAPGSAPVTLIYESNKRPSDIPSRFSGSTSGSTATLTITIGVQADDEAIYYCGSWDSSNGGIFGAGTTTLTVL (SEQ ID NO: 40)
Anti-FAM19A5 ("1-65")	ALTQPSSVSANPGETVKITCSGGSSGYGYGWYQQKSPSSAPLTVIYWNDRPSDIPSRFSGSKSGSTHTLTITIGVQAEDEAVYFCGNDDYSSDSGYVGVFGAGTTTLTVL (SEQ ID NO: 41)
Anti-FAM19A5 ("1-28")	ALTQPSSVSANLEGTVEITCSGGSGYGYGWYQQKSPGSAPVTVIYQNDKRPSDIPSRFSGSKSGSTGTLTITIGVQVEDEAVYYCGSEDSSTLAGIFGAGTTTLTVL (SEQ ID NO: 42)
Anti-FAM19A5 ("P2-C12")	ELDMTQTPSSVSAAVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYEASKLASGVPS RFSGSGYGTEFTLTISDLCEADAATYYCQQGYSTNVWNAFGGGTNVEIK (SEQ ID NO: 166)
Anti-FAM19A5 ("13B4")	SYELTQPLSVSVSPGQTASITCSGDKLGNVYASWYQQKPGQSPTLVIYQDNKRPSGIPER FSGSNSGKTATLTISGTQALDEADYYCQAWDSSTAVFGGGTKLTVL (SEQ ID NO: 167)
Anti-FAM19A5 ("13F7")	DIVMTQTPPLSLPVAPGEPASISCRSSQSLLHSNGYNYLDWYVQKPGQPPQLLIYLGSNRA SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPLTFGGGTKVEIK (SEQ ID NO: 168)
Anti-FAM19A5 ("15A9")	DIQMTQSPSSLSASVGDRTISCRASQSIISTSLNHYQQTPGKAPRLLIYGASTLQSGVPS RFSGGGSGTDFSLTITSLQPEDFATYYCQESASIPRTFGQGTKLDIK (SEQ ID NO: 169)
Anti-FAM19A5 ("P1-A03")	ELVMTQTPPSSLSASVGETVIRICLASEDIYSGISWYQQKPEKPPTLLISGASNLESGVPP RFSGSGSGTDYTLTIGGVQAEDAATYYCLGGYSYSTGLTFGAGTNVEIK (SEQ ID NO: 170)
Anti-FAM19A5 ("P1-A08")	ELVLTQSPSPVQVNLGQTVSLTCTADTLRSYASWYQQKPGQAPVLLIYRDTSRPSGVDPDR FSGSSSGNTATLTISGAQAGDEADYYCATSDGSGSNYQYVFGGGTQLT VT (SEQ ID NO: 171)
Anti-FAM19A5 ("P1-F02")	ELDMTQTPPSSLSASVGETVIRICLASEDIYSGISWYQQKPGKPPTLLIYGASNLESGVPP RFSGSGSGTDYTLTIGGVQAEDAATYYCLGGYSYSTIFGAGTNVEIK (SEQ ID NO: 172)

Anti-FAM19A5 ("P2-A01")	ELVMTQTTPPSLSASVGETVIRIRCLASEDIYSGISWYQQKPGKPPTLLIYGASNLESGVPP RFGSGSGSDYTLTIGGVQAEDAATYYCLGGVTYSSTGTHLTFGAGTNVEIK (SEQ ID NO: 173)
Anti-FAM19A5 ("P2-A03")	ELDLTQTPASVSEPVGGTVTIKCQASQSIGGNLAWYQQKPGQPPKLLIYRASTLASGVPS RFKSGSGSDFTLTISDLECAATAATYYCQSPAYDPAAYVGNAGGGTELEIL (SEQ ID NO: 174)
Anti-FAM19A5 ("P2-F07")	ELDLTQTPPSLSASVGGTVTINCLASEDIYSALAWYQQKPGKPPTLLISGTSNLESGVPP RFGSGSGSDYTLTIGGVQAEDAATYFCQGYSSYPLTFGAGTNVEIK (SEQ ID NO: 175)
Anti-FAM19A5 ("P2-F11")	ELDLTQTPSSVSAAVGGTVTINCQASQSVYNNKNLAWYQQKPGQPPKLLIYAASLASGV SSRFKSGSGGTQFTLTISDVQCDDAATYYCQGEFSCSSADCNAGGGTELEIL (SEQ ID NO: 176)
Anti-FAM19A5 ("SS01-13")	ALTQPSSVSANPGETVRITCSGGASSGYGYGWYQQKPSSAPLTVIYKDDERPSDIPSRFS GSSSGSTHTLTITGVQAEDEAVYFCGNDDYSSDSGYVGVFGAGTTLTVL (SEQ ID NO: 212)
Anti-FAM19A5 ("SS01-13- s5")	ALTQPSSVSANPGETARITCSGGASSGYGYGWYQQKPSSAPLTVIYKDSERPSDIPSRFS GSSSGSTHTLTISGVQAEDEAVYFCGNDDYSSDSGYVGVFGAGTTLTVL (SEQ ID NO: 215)
Anti-FAM19A5 ("S5- 2.GKNG")	ALTQPSSVSANPGETARITCSGGASSGYGYGWYQQKPSSAPLTVIYKDSERPSDIPSRFS GSSSGSTHTLTISGVQAEDEAVYFCGNDDYSSDSGYVGVFGAGTTLTVL (SEQ ID NO: 215)
Anti-FAM19A5 ("1-7A-IT")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKPGSAPVTLIYENNKRPDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSSNGGIFGAGTTLTVL (SEQ ID NO: 238)
Anti-FAM19A5 ("Low-PI")	ALTQPSSVSANPGETVKITCSGGGSEEEQYYYGWYQQKPGSAPVTLIYEDEERPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSEDEDHFGAGTTLTVL (SEQ ID NO: 239)
Anti-FAM19A5 ("1-30")	ALTQPSSVSANPGETVKITCSGGGSEEEQYYYGWYQQKPGSAPVTLIYQDEERPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSEDEDHFGAGTTLTVL (SEQ ID NO: 240)
Anti-FAM19A5 ("1-17")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKPGSAPVTLIYEDEQRPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSEDEDHFGAGTTLTVL (SEQ ID NO: 241)
Anti-FAM19A5 ("1-32")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKPGSAPVTLIYQDEERPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSEDEDHFGAGTTLTVL (SEQ ID NO: 242)
Anti-FAM19A5 ("4-11")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKPGSAPVTLIYEDHERPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSSDEDHFGAGTTLTVL (SEQ ID NO: 243)
Anti-FAM19A5 ("6-10")	ALTQPSSVSANPGETVKITCSGGGSYAGSYYYGWYQQKPGSAPVTLIYQDLLRPSDIPSR FSGSTSGSTATLTITGVQAGDEADYYCGSWDSLSSSHFGAGTTLTVL (SEQ ID NO: 244)

Anti-FAM19A5 ("2-13D")	ALTQPSSVSANPGETAKITCSGGVYSYGWFQQKPGSALVTVIYWDDERPSDIPSRFSGAL SGSTNTLTITGVQAEDEADYYCGTEDISGTAGVFGAGTTTLTVL (SEQ ID NO: 245)
Anti-FAM19A5 ("2-13D-37")	ALTQPSSVSANPGETAKITCSGGVYSYGWFQQKPGSALVTVIYWDDERPSDIPSRFSGAL SGSTNTLTITGVQAEDEADYYCGTEDISGTAGVFGAGTTTLTVL (SEQ ID NO: 245)
Anti-FAM19A5 ("2-13D-37-1.5W-41")	ALTQPSSVSANPGETAKITCSGGVYSYGWFQQKPGSALVTVIYWDDERPSDIPSRFSGAL SGSTNTLTITGVQAEDEADYYCGTEDISGTAGVFGAGTTTLTVL ((SEQ ID NO: 245)
Anti-FAM19A5 ("2-13D-37-3W-16")	ALTQPSSVSANPGETAKITCSGGVYSYGWFQQKPGSALVTVIYWDDERPSDIPSRFSGAL SGSTNTLTITGVQAEDEADYYCGTEDISGTAGVFGAGTTTLTVL (SEQ ID NO: 245)

[0175] Accordingly, provided herein is an 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, 155-165, 211, 214, 234-237, or 249-251 (*see* Table 4). In other embodiments, the 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, 155-165, 211, 214, 234-237, or 249-251 (*see* Table 4).

[0176] Also provided is an 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, 166-176, 212, 215, or 238-245 (*see* Table 5). In other embodiments, the 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, 166-176, 212, 215, or 238-245 (*see* Table 5).

[0177] In certain embodiments, the 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, 155-165, 211, 214, 234-237, or 249-251 and the CDRs of the light chain variable region selected from the group consisting of SEQ ID NOs: 39-42, 166-176, 212, 215, or 238-245.

[0178] Also provided is an 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; (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; (xvi) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 211 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 212; (xvii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 214 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 215; (xviii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 249 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 215; (xix) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 234 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 238; (xx) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 239; (xxi) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 240; (xxii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 241; (xxiii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 242; (xxiv) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 243; (xxv) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 235 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 244; (xxvi) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 236 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 245; (xxvii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 250 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 245; (xxviii) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 237 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 245; or (xxix) wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 251 and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 245.

[0179] Provided herein is an 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, 155-165, 211, 214, 234-237, or 249-251 (*see* Table 4).

[0180] Also provided herein is an 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, 166-176, 212, 215, or 238-245 (*see* Table 5).

[0181] Also provided is an 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, 155-165, 211, 214, 234-237, or 249-251, 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, 166-176, 212, 215, or 238-245.

[0182] In some embodiments, the disclosure provides an 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;
- (o) heavy and light chain variable region sequences comprising SEQ ID NOs: 165 and 176, respectively;
- (p) heavy and light chain variable region sequences comprising SEQ ID NOs: 211 and 212, respectively;
- (q) heavy and light chain variable region sequences comprising SEQ ID NOs: 214 and 215, respectively;
- (r) heavy and light chain variable region sequences comprising SEQ ID NOs: 249 and 215, respectively;
- (s) heavy and light chain variable region sequences comprising SEQ ID NOs: 234 and 238, respectively;
- (t) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 239, respectively;

- (u) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 240, respectively;
- (v) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 241, respectively;
- (w) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 242, respectively;
- (x) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 243, respectively;
- (y) heavy and light chain variable region sequences comprising SEQ ID NOs: 235 and 244, respectively;
- (z) heavy and light chain variable region sequences comprising SEQ ID NOs: 236 and 245, respectively;
- (aa) heavy and light chain variable region sequences comprising SEQ ID NOs: 250 and 245, respectively;
- (bb) heavy and light chain variable region sequences comprising SEQ ID NOs: 237 and 245, respectively; or
- (cc) heavy and light chain variable region sequences comprising SEQ ID NOs: 251 and 245, respectively.

[0183] 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; (xv) the heavy chain CDR1, CDR2, and CDR3 of P2-F11, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of P2-F11, or any combinations thereof; (xvi) the heavy chain CDR1, CDR2, and CDR3 of SS01-13, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of SS01-13, or any combinations thereof; (xvii) the heavy chain CDR1, CDR2, and CDR3 of SS01-13-s5, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of SS01-13-s5, or any combinations thereof; (xviii) the heavy chain CDR1, CDR2, and CDR3 of S5-2.GKNG, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of S5-2.GKNG, or any combinations thereof; (xix) the heavy chain CDR1, CDR2, and CDR3 of 1-7A-IT, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-7A-IT, or any combinations thereof; (xx) the heavy chain CDR1, CDR2, and CDR3 of Low-PI, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of Low-PI, or any combinations thereof; (xxi) the heavy chain CDR1, CDR2, and CDR3 of 1-30, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-30, or any combinations thereof; (xxii) the heavy chain CDR1, CDR2, and CDR3 of 1-17, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-17, or any combinations thereof; (xxiii) the heavy chain CDR1, CDR2, and CDR3 of 1-32, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 1-32, or any combinations thereof; (xxiv) the heavy chain CDR1, CDR2, and CDR3 of 4-11, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 4-11, or any combinations thereof; (xxv) the heavy chain CDR1, CDR2, and CDR3 of 6-10, or

combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 6-10, or any combinations thereof; (xxvi) the heavy chain CDR1, CDR2, and CDR3 of 2-13D, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 2-13D, or any combinations thereof; (xxvii) the heavy chain CDR1, CDR2, and CDR3 of 2-13D-37, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 2-13D-37, or any combinations thereof; (xxviii) the heavy chain CDR1, CDR2, and CDR3 of 2-13D-37-1.5W-41, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 2-13D-37-1.5W-41, or any combinations thereof; or (xxix) the heavy chain CDR1, CDR2, and CDR3 of 2-13D-37-3W-16, or combinations thereof, and/or the light chain CDR1, CDR2, and CDR3 of 2-13D-37-3W-16, 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.

[0184] 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.

[0185] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0186] 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.

[0187] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0188] 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.

[0189] 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.

[0190] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0191] 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.

[0192] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0193] 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.

[0194] 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.

[0195] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0196] 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.

[0197] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0198] 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.

[0199] 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.

[0200] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0201] 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.

[0202] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0203] In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

- (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.

[0204] In specific embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof comprises one, two, three, four, five, or six of the CDRs above.

[0205] 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: 220 and/or
- (b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and/or
- (c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0206] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VH CDRs above.

[0207] 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: 225; and/or
- (b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 228; and/or
- (c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 227

[0208] In specific embodiments, the antibody or antigen-binding portion thereof comprises one, two, or all three of the VL CDRs above.

[0209] In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof, which specifically binds to human FAM19A5, comprises:

- (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 220;
- (b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 221;
- (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: 225;
- (e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 228; and/or
- (f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 227.

[0210] In specific embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof comprises one, two, three, four, five, or six of the CDRs above.

[0211] 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.

[0212] 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 a 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 a 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*.

[0213] 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*.

[0214] 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.

[0215] 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.*, a 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 a 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).

[0216] Thus, in some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof disclosed herein is a Fab, a Fab', a F(ab')₂, a Fv, a single chain Fv (scFv), or sdAb consisting of a monomeric VH or VL domain. Such antibody fragments are well known in the art and are described *supra*.

[0217] In some embodiments, the anti-FAM19A5 antibody or antigen-binding portion thereof disclosed herein comprises a 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 a 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.

V. Nucleic Acid Molecules

[0218] Another aspect described herein pertains to use of 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 use as part of whole cells, a cell lysate, or 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 useful for the present methods can be, for example, DNA or RNA and can or cannot contain intronic sequences. In certain embodiments, the nucleic acid useful for the methods is a cDNA molecule.

[0219] 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.

[0220] Certain nucleic acids molecules useful for the present methods 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. Additional exemplary DNA sequences encoding the VH sequence of anti-FAM19A5 antibodies are provided in Table 6 (below). Exemplary DNA sequences encoding the VL sequences of such antibodies are set forth in SEQ ID NOs: 47-50 and 178. Additional exemplary DNA sequences encoding the VL sequence of anti-FAM19A5 antibodies are provided in Table 7 (below).

Table 6: Variable heavy chain polynucleotide sequence

Antibody	Variable Heavy Chain Polynucleotide Sequence (SEQ ID NO)
Anti-FAM19A5 (2-13)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTACCTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGACG CCCCGCAAGGGGTGGAATATGTCGCTGAAATTACCAATGATGGTAGTGGCACAACTAC GGGTCCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACAGTGAGG CTGCAGCTGAACAACCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTACT TATGAATGTCCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 43)
Anti-FAM19A5 (3-2)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTACCTTCAGCAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCCGCAAGGGGCTGGAATACGTCGCTCAAATTAGCAGCAGTGGTAGTAGCACAACTAC GCACCCGCGGTGAGGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACAGTGAGG CTGCAGCTGAACAACCCGGGGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 44)
Anti-FAM19A5	GCCGTGACACTGGACGAATCTGGGGGAGGGCTGCAGACTCCAGGCGGAGCTCTGAGCCTG GTGTGCAAGGCATCCGGGTTACCTTTAGCTCCTACCAGATGGGATGGGTGCGGCAGGCA

(1-65)	CCAGGGAAGGGCCTGGAGTGGGTTCGGAGTGATCAACAAATCTGGGAGTGACACAAGCTAC GGCAGCGCCGTGAAGGGAAGGGCCACCATCAGCAGGGACAATGGCCAGAGTACCGTGCGG CTGCAGCTGAACAATCTGCGCGCTGAGGACACTGGCACCTACTTCTGTGCTAAGGGATCA GCAAGCTATATCACAGCCGCTACTATTGATGCATGGGGACACGGGACAGAAGTCATCGTG TCTAGT (SEQ ID NO: 45)
Anti-FAM19A5 (1-28)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCAGCCTC GTCTGCAAGGCCTCCGGGTTCTGACTTCAGCGATTATGGCATGGGTTGGGTGCGACAGGCT CCAGGCAAGGGGCTGGAGTGGGTGCTGCTATTAGAAGTGATGGTAGTAACCCATCATAAC GGGTTCGGCGGTGAAGGGCCGTGCCACCATCTCGAAGGACAACGGGCGAAGCACAGTGAGG CTGCAGCTGAACAACCTCAGGGCTGAGGACACCGCCACCTACTACTGCGCCAAGGATGGT AATGGTTACTGTGCTCTCGATGCTTATCGTAGTGGTGGTTATAGTTGTGGTGTCTTATCCT GGTAGCATCGACGCATGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 46)
Anti-FAM19A5 (P2-C12)	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACC TGCACCGTCTCTGGATTCTCCCTCAGTACCTATGCAGTGACCTGGGTCCGCCAGGCTCCA GGGAAGGGGCTGGAATGGATCGGATACATTAATTGGCGTGGTGGGACATCCTACGCGAAC TGGGCGAAAGGCCGATTACCATTCTCCAAACCTCGTCGACACCGTGGATCTGAAAATG ACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCTAGTAGTGGT GCTGCTTTTGGGTCTTACGGCATGGACCCCTGGGGCCCAGGGACCCCTCGTCACCGTCTCT TCA (SEQ ID NO: 177)
Anti-FAM19A5 (SS01-13)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCTCTCTC TCTTGCAAAGCCTCCGGGTTACCTTCAGCAGCTATCAGATGGGCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATGGGTGCGTGTTATTAACAAGTCTGGTAGTGACACATCATAAC GGGTTCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAC CTGCAGATGAACAACCTCAGGGCTGAGGACACCGCTGTTTACTTCTGCGCCAAAGGTTCT GCTAGTTACATAACTGCTGCTACCATCGACGCATGGGGCCACGGGACCGAAGTCATCGTC TCCTCC (SEQ ID NO: 271)
Anti-FAM19A5 (SS01-13-S5)	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCCGCCTC TCTTGCAAGGCCTCCGGGTTACCTTCAGCAGCTATCAGATGGGCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATGGGTGAGCGCGATTAATAAGAGCGGTAGTGACACATCATAAC GGGTTCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAC CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGCTGTTTACTTCTGCGCCAAAGGTTCT GCTAGTTACATAACTGCTGCTACCATCGACGCATGGGGCCACGGGACCGAAGTCATCGTC TCCTCC (SEQ ID NO: 216)
Anti-FAM19A5 ("S5-2.GKNG")	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCCGCCTC TCTTGCAAGGCCTCCGGGTTACCTTCAGCAGCTATCAGATGGGCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATGGGTGAGCGCGATTAATAAGGGCGGTAGTGACACATCATAAC GGGTTCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAC CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGCTGTTTACTTCTGCGCCAAAGGTTCT GCTAGTTACATAACTGCTGCTACCATCGACGCATGGGGCCACGGGACCGAAGTCATCGTC TCCTCC (SEQ ID NO: 269)
Anti-FAM19A5 ("1-7A-IT")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGGTTACCTTCAGCAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGGTAGTAGCACAACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 254)
Anti-FAM19A5 ("Low-PI")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGGTTACCTTCAGCAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGGTAGTAGCACAACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 255)
Anti-FAM19A5 ("1-30")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGCTTTGATTTTGAAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGAAGAAGATGAAAACCTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCGAGAGCACACTGTAT

	CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 256)
Anti-FAM19A5 ("1-17")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGCTTTGATTTTGAAAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGAAGAAGATGAAAACACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 256)
Anti-FAM19A5 ("1-32")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGCTTTGATTTTGAAAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGAAGAAGATGAAAACACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 256)
Anti-FAM19A5 ("4-11")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGCTTTGATTTTGAAAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGAAGAAGATGAAAACACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 256)
Anti-FAM19A5 ("6-10")	GCCGTGACGTTGGATGAATCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTC AGCTGCAAGGCCTCTGGCTTTGATTTTGAAAGCTTCAACATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGCTGGAATACGTCTCGCAGATTAGCAGCAGTGAAGAAGATGAAAACACTAC GCACCCGCGGTGAAAGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTGCGCGCTGAAGACACCGGCACCTACTACTGCGCCAAAAGTAGT TATGACTGTCCTTACGGTCATTGTAGTAGTGGTGTGATAGTGCTGGTGAGATCGACGCA TGGGGCCACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 256)
Anti-FAM19A5 ("2-13D")	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTT AGCTGCAGCGCCTCCGGGTTACCTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGTTGGAATATGTCTCGGAGATTACCAATGATGGTAGTGGCACAAACTAC GGGTCCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTACT TATGAATGTCCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 257)
Anti-FAM19A5 ("2-13D-37")	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTT AGCTGCAGCGCCTCCGGGTTGATTTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGTTGGAATATGTCTCGGAGATTACCAATGATGGTAGTGGCACAAACTAC GGGTCCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTACT TATGAATGTCCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 273)
Anti-FAM19A5 ("2-13D-37- 1.5W-41")	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTT AGCTGCAGCGCCTCCGGGTTGATTTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGTTGGAATATGTCTCGGAGATTACCAATGATGGTAGTGGCACAAACTAC GGGTCCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTTCT TATGTTTGTCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 258)
Anti-FAM19A5 ("2-13D-37-3W- 16")	GCCGTGACGTTGGACGAGTCCGGGGGCGGCCTCCAGACGCCCCGGAGGAGCGCTCCGCCTT AGCTGCAGCGCCTCCGGGTTGATTTTCAGCAGCCATGGCATGTTCTGGGTGCGACAGGCG CCCGGCAAGGGGTTGGAATATGTCTCGGAGATTACCAATGATGGTAGTGGCACAAACTAC GGGTCCGGCGGTGAAGGGCCGTGCCACCATCTCGAGGGACAACGGGCAGAGCACACTGTAT CTGCAGATGAACAGCCTCAGGGCTGAGGACACCGGCACCTACTTCTGCGCCAGATCTAAT TATGCTTGTCTGGTGGTTTTAGTTGTTGGGGTGATACTGGTCAAATAGACGCATGGGGC CACGGGACCGAAGTCATCGTCTCCTCC (SEQ ID NO: 259)

Table 7: Variable light chain polynucleotide sequence

Antibody	Variable Light Chain Polynucleotide Sequence (SEQ ID NO)
Anti-FAM19A5 (2-13)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATAACCTGC TCCGGGGGTAGCTATAGCTATGGCTGGTTCCAGCAGAAGTCTCCTGGCAGTGCCCTTGTC ACTGTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGCC CTATCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGACGACGAGGCTGTC TATTTCTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACC CTGACCGTCCTG (SEQ ID NO: 47)
Anti-FAM19A5 (3-2)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTACCAGCAGAAGGCACCT GGCAGTGCCCCGTGCTACTCTGATCTATGAAAGCAACAAGAGACCCTCGGACATCCCTTCA CGATTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCC GATGACGAGGCTATCTATTACTGTGGGAGCTGGGACAGTAGCAATGGTGGTATATTTGGG GCCGGGACAACCCTGACCGTCCTA (SEQ ID NO: 48)
Anti-FAM19A5 (1-65)	GCCCTGACTCAGCCCTCTTCCGTGTCAGCCAACCCTGGAGAACTGTGAAGATCACCTGC AGCGGAGGAGGGAGCTCCGGATACGGATATGGGTGGTATCAGCAGAAATCCCCATCTAGT GCCCCCTGACTGTGATCTATTGGAACGACAAGAGGCCTAGTGATATTCATCAAGATTC AGTGGATCAAAAAGCGGGTCCACTCACACCCTGACAATCACTGGCGTGCAGGCAGAGGAC GAAGCCGTCTACTTCTGCGGAAATGACGATTACTCAAGCGATTCTGGCTATGTGGGCGTC TTTGGCGCAGGAACCACACTGACAGTGCTG (SEQ ID NO: 49)
Anti-FAM19A5 (1-28)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCTGGAAGGAACCGTCGAGATCACCTGC TCCGGGAGTGGCTATGGTTATGGCTGGTATCAGCAGAAGTCTCCTGGCAGTGCCCTTGTC ACTGTGATCTATCAGAACGACAAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTTCC AAATCCGGCTCCACGGGCACATTAACCATCACTGGGGTCCAAGTCGAGGACGAGGCTGTC TATTACTGTGGGAGTGAAGACAGCAGCACTCTTGCTGGTATATTTGGGGCCGGGACAACC CTGACCGTCCTA (SEQ ID NO: 50)
Anti-FAM19A5 (P2-C12)	GAGCTCGATATGACCCAGACTCCATCCTCCGTGTCAGCTGTGGGAGGCACAGTCACC ATCAAGTGCCAGGCCAGTCAGAGCATTAGTAGCTACTTATCCTGGTATCAGCAGAAACCA GGGCAGCCTCCCAAGCTCCTGATCTATGAAGCATCCAACTGGCCTCTGGGGTCCCATCG CGGTTACAGCGGCAGTGGATATGGGACAGAGTTCACCTCTCACCATCAGCGACCTGGAGTGT GCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTAGTACTAATGTTTGAATGCT TTCGGCGGAGGCACCAATGTGGAATCAAA (SEQ ID NO: 178)
Anti-FAM19A5 (SS01-13)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCTGGGGAACTGTTCTGATCACCTGC TCCGGGGGTGCTAGCAGTGGCTATGGTTATGGCTGGTATCAGCAGAAGCCTAGCAGTGCC CCTCTCACTGTGATCTACAAAGACGACGAAAGACCCTCGGACATCCCTTCACGATTCTCC GGTTCCCTCTTCCGGCTCCACACACACATTAACCATCACTGGGGTCCAAGCCGAGGACGAG GCTGTATATTTCTGTGGGAATGATGACTACAGCAGTGATAGTGGATATGTCCGGTGTATTT GGGGCCGGGACAACCCTGACCGTCCTA (SEQ ID NO: 272)
Anti-FAM19A5 (SS01-13-S5)	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCTGGGGAACTGCGCGTATCACCTGC TCCGGTGGTGCTAGCAGTGGCTATGGTTATGGCTGGTATCAGCAGAAGCCTAGCAGTGCC CCTCTCACTGTGATCTACAAAGACTCTGAAAGACCCTCGGACATCCCTTCACGATTCTCC GGTTCCCTCTTCCGGCTCCACACACACATTAACCATCAGCGGGGTCCAAGCCGAGGACGAG GCTGTATATTTCTGTGGGAATGATGACTACAGCAGTGATAGTGGATATGTCCGGTGTATTT GGGGCCGGGACAACCCTGACCGTCCTA (SEQ ID NO: 270)
Anti-FAM19A5 ("S5-2.GKNG")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCTGGGGAACTGCGCGTATCACCTGC TCCGGTGGTGCTAGCAGTGGCTATGGTTATGGCTGGTATCAGCAGAAGCCTAGCAGTGCC CCTCTCACTGTGATCTACAAAGACTCTGAAAGACCCTCGGACATCCCTTCACGATTCTCC GGTTCCCTCTTCCGGCTCCACACACACATTAACCATCAGCGGGGTCCAAGCCGAGGACGAG GCTGTATATTTCTGTGGGAATGATGACTACAGCAGTGATAGTGGATATGTCCGGTGTATTT GGGGCCGGGACAACCCTGACCGTCCTA (SEQ ID NO: 270)
Anti-FAM19A5 ("1-7A-IT")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCCGTGCTACTCTGATCTATGAAAACAACAAGAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTAGCAATGGTGGTATATTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 261)

Anti-FAM19A5 ("Low-PI")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATGAAAACAACAAGAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTAGCAATGGTGGTATATTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 262)
Anti-FAM19A5 ("1-30")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCGAAGAAGAACAGTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATCAGGATGAAGAAAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTGAAGATGAAGATCATTTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 263)
Anti-FAM19A5 ("1-17")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATGAAGATGAACAGAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTGAAGATGAAGATCATTTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 264)
Anti-FAM19A5 ("1-32")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATCAGGATGAAGAAAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTGAAGATGAAGATCATTTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 265)
Anti-FAM19A5 ("4-11")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATGAAGACCACGAGAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTAGCGATGAAGATCATTTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 266)
Anti-FAM19A5 ("6-10")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGTCAAGATCACCTGC TCCGGGGGTGGCAGCTATGCTGGAAGTTACTATTATGGCTGGTATCAGCAGAAGCCTGGC AGTGCCCTGTCACTCTGATCTATCAGGATCTGCTGAGACCCTCGGACATCCCTTCACGA TTCTCCGGTTCACATCTGGCTCCACAGCCACACTAACCATCACTGGGGTCCAAGCCGGC GACGAGGCTGATTATTACTGTGGGAGCTGGGACAGTCTGAGCAGCAGCCATTTTGGGGCC GGGACAACCCTGACCGTCCTA (SEQ ID NO: 267)
Anti-FAM19A5 ("2-13D")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGCGAAGATAACCTGC TCCGGGGGTGTGTATAGCTATGGCTGGTTCCAGCAGAAGCCTGGCAGTGCCCTTGTCACT GTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGCCCTA TCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGAAGACGAGGCTGATTAT TATTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACCCTG ACCGTCCTG (SEQ ID NO: 268)
Anti-FAM19A5 ("2-13D-37")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGCGAAGATAACCTGC TCCGGGGGTGTGTATAGCTATGGCTGGTTCCAGCAGAAGCCTGGCAGTGCCCTTGTCACT GTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGCCCTA TCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGAAGACGAGGCTGATTAT TATTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACCCTG ACCGTCCTG (SEQ ID NO: 268)
Anti-FAM19A5 ("2-13D-37- 1.5W-41")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGCGAAGATAACCTGC TCCGGGGGTGTGTATAGCTATGGCTGGTTCCAGCAGAAGCCTGGCAGTGCCCTTGTCACT GTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGCCCTA TCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGAAGACGAGGCTGATTAT TATTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACCCTG ACCGTCCTG (SEQ ID NO: 268)
Anti-FAM19A5 ("2-13D-37-3W- 16")	GCCCTGACTCAGCCGTCCTCGGTGTCAGCAAACCCAGGAGAAACCGCGAAGATAACCTGC TCCGGGGGTGTGTATAGCTATGGCTGGTTCCAGCAGAAGCCTGGCAGTGCCCTTGTCACT GTGATCTACTGGGATGATGAGAGACCCTCGGACATCCCTTCACGATTCTCCGGTGCCCTA TCCGGCTCCACAAACACATTAACCATCACTGGGGTCCAAGCCGAAGACGAGGCTGATTAT TATTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACCCTG TATTGTGGGACTGAAGACATCAGCGGCACTGCTGGTGTATTTGGGGCCGGGACAACCCTG

ACCGTCCTG (SEQ ID NO: 268)

[0221] Once DNA fragments encoding VH and VL segments useful for the present methods 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.

[0222] The isolated DNA encoding the VH region useful for the present methods 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.

[0223] The isolated DNA encoding the VL region useful for the present methods 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.

[0224] 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).

[0225] In some embodiments, the present disclosure provides use of a vector comprising an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or antigen-binding portion thereof in the methods disclosed herein. In other embodiments, the vectors can be used for gene therapy.

[0226] Suitable vectors for the disclosed methods include expression vectors, viral vectors, and plasmid vectors. In one embodiment, the vector is a viral vector.

[0227] 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.

[0228] Expression vectors for the disclosed methods 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.

[0229] Viral vectors useful for the present methods 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., Clifton, N.J. (1991).

[0230] In one embodiment, the virus useful for the present methods is an adeno-associated virus or 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.

[0231] In other embodiments, the vector useful for the present methods is derived from lentivirus. In certain embodiments, the vector is a vector of a recombinant lentivirus capable of infecting non-dividing cells.

[0232] 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-1, HIV-2 and/or SIV).

[0233] 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.

[0234] However, the resulting mutant remains capable of directing the synthesis of all virion proteins. Also useful for the disclosure is 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.

[0235] 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.

[0236] 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.

[0237] The vector providing the viral env nucleic acid sequence is associated operably with regulatory sequences described elsewhere herein.

[0238] In certain embodiments, the vector useful for the methods 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.

[0239] 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.

[0240] 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.

[0241] 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.

[0242] Examples of the lentiviral vectors are disclosed in WO9931251, W09712622, W09817815, W09817816, and WO9818934, which are incorporated herein by reference in their entireties.

[0243] Other vectors useful for the present methods 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.

VI. Antibody Production

[0244] 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.

[0245] 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*.

VII. Pharmaceutical Compositions

[0246] Provided herein are compositions comprising an antibody or antigen-binding portion thereof useful for the present methods having the desired degree of purity in a physiologically acceptable carrier, excipient, and/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 dextrans; 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).

[0247] In some embodiments, pharmaceutical compositions useful for the present methods 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 some embodiments, pharmaceutical compositions comprise an effective amount of an antibody or antigen-binding portion thereof described herein, and optionally one or more additional prophylactic or 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 cardiovascular-related disease or disorder, such as atherosclerosis.

[0248] 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 carboxymethylcellulose, 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.

[0249] A pharmaceutical composition useful for the present methods can be formulated for any route of administration to a subject. Parenteral administration, characterized by either subcutaneous, intramuscular, intraperitoneal, 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.

[0250] 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.

[0251] 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.

[0252] 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.

[0253] 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.

[0254] An antibody or antigen-binding portion thereof useful for the present methods can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, in the form of gels, creams, and lotions. Topical administration is contemplated for transdermal delivery and also for administration to the mucosa or for inhalation therapies. Nasal solutions of the antibody alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0255] 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, 6,010,715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[0256] In certain embodiments, a pharmaceutical composition comprising an antibody or antigen-binding portion thereof useful for the present methods 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 one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will 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.

[0257] 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.

[0258] The antibodies or antigen-binding portions thereof, the bispecific molecule, or the immunoconjugate useful for the present methods 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 useful for the present methods can be used to treat an atherosclerosis and/or reduce, ameliorate, or inhibit one or more symptoms related to atherosclerosis (*e.g.*, increased total cholesterol, LDL, triglyceride levels, reduced HDL levels, and/or increased number and/or retention of oxo-LDL-induced foam cells within a plaque).

[0259] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

VIII. Kits

[0260] Provided herein are kits comprising one or more antibodies useful for the present methods, or antigen-binding portions thereof, bispecific molecules, or immunoconjugates thereof. In a specific embodiment, 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 useful for the present methods, 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 useful for the present methods and any prophylactic or therapeutic agent, such as those described herein.

EXAMPLES

Example 1: Evaluation of Body Weight After In Vivo Administration of Anti-FAM19A5 Antibody in a Mouse Model of Atherosclerosis

[0261] To begin assessing the effect of anti-FAM19A5 antibody treatment on atherosclerosis, atherosclerosis-prone C57BL/6 apolipoprotein E-deficient (Apoe ^{-/-}) mice (Jackson Laboratory, U.S.A.) were used. Briefly, the Apoe ^{-/-} mice were placed on a high-fat (hypercholesterolemic) diet (TD. 88137 Irradiated complete calories diet, 42% total fat, Halan Laboratories, Inc., U.S.A.) for 5 weeks to induce atherosclerosis. Then, either human IgG control antibody (10 mg/kg) or an anti-FAM19A5 antibody (clone "3-2") were intravenously administered once a week for a total of 6 weeks. The anti-FAM19A5 antibody was administered to the relevant mice at two different concentrations: (5 mg/kg) or (10 mg/kg). Normal (*i.e.*, regular diet (+40 RMM-SP-10 Irradiated complete diet, 15.2% protein, SAFE Inc., France)) healthy mice were used as a control. The normal and hypercholesterolemic mice remained on their respective diets for the entire duration of the experiment. Body weight and general clinical observations were monitored throughout the duration of the treatment. One week after the last antibody administration, the mice from the different treatment groups were sacrificed for further analysis. Table 8 provides the different treatment groups.

Table 8. Treatment Groups

Group	Treatment
Group 1	Untreated; healthy animals
Group 2	Anti-IgG control antibody (10 mg/kg)

Group 3	Anti-FAM19A5 antibody (5 mg/kg)
Group 4	Anti-FAM19A5 antibody (10 mg/kg)

[0262] As shown in Table 9 (below) and FIG. 1, compared to animals placed on a regular diet (Group 1), animals that received the high-fat diet all gained weight during the course of the experiment. All the animals from Groups 1, 3, and 4 survived the entire duration of the experiment (*i.e.*, 42 days). However, in Group 2 (hypercholesterolemic mice treated with the control human IgG antibody), 3/10 mice had died by the end of the experiment. Two of the dead mice exhibited abnormal symptoms prior to their death (*e.g.*, spasms and gait disorders). There were no other significant abnormalities observed among the mice from the different treatment groups.

Table 9. Mean Body Weight

Groups	Days						
	0	7	14	21	28	35	42
G1	27.1 ± 1.4	27.9 ± 1.3	28.7 ± 1.3	28.5 ± 1.8	28.9 ± 1.6	28.3 ± 1.2	30.1 ± 1.7
G2	31.7 ± 2.2*	33.1 ± 1.9*	33.7 ± 1.6*	34.8 ± 1.9*	35.4 ± 2.1*	34.9 ± 2.3	36.3 ± 2.1
G3	30.5 ± 2.4*	31.6 ± 2.1*	32.2 ± 2.1*	33.3 ± 2.6*	33.9 ± 2.8*	33.0 ± 4.1	34.1 ± 4.7
G4	32.0 ± 1.2*	33.1 ± 1.1*	33.8 ± 1.1*#	35.0 ± 1.4*	35.3 ± 1.6*	35.5 ± 1.6	36.1 ± 3.1

Significantly different from G1 vs G2~G4 (ANOVA, Fisher's PLSD *post-hoc* tests: *, $p < 0.05$)

[0263] The above results suggest that the administration of the anti-FAM19A5 antibody does not significantly affect body weight in hypercholesterolemic animals. However, anti-FAM19A5 treatment can promote survival as evidenced by the three mice that had died in the hypercholesterolemic group treated with the control anti-human IgG control antibody.

Example 2: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on LDL Level

[0264] To assess the effect of anti-FAM19A5 antibody treatment on the LDL level, hypercholesterolemic mice described in Example 1 were also used herein. Briefly, the mice from the different groups were sacrificed approximately a week after the last antibody administration

(*i.e.*, week 7 post-initial antibody administration). Blood (~1 mL) was collected from the abdominal vein, treated with EDTA-2K, and centrifuged (~3000 rpm for 10 minutes at room temperature) to remove the plasma. Then, the LDL levels of the mice were measured.

[0265] As shown in Table 10 (below), the LDL level was modestly reduced in hypercholesterolemic mice treated with anti-FAM19A5 antibody (both Groups 3 and 4) compared to mice treated with the human IgG control antibody (Group 2). (*see* also FIG. 2).

Table 10. Plasma Levels of LDL

Groups	LDL (mg/dL)
G1	179.2 ± 26.8
G2	828.6 ± 66.7
G3	757.4 ± 153.0
G4	757.8 ± 100.1

[0266] The above results suggest that anti-FAM19A5 treatment can help treat atherosclerosis by lowering LDL levels in the blood of hypercholesterolemic animals. This decrease in LDL levels can translate to reduced total cholesterol level in the blood.

Example 3: Immunohistochemistry Analysis of the Effect of Anti-FAM19A5 Antibody Treatment on Migration of Macrophages to Atherosclerotic Lesion Sites on Aorta

[0267] Phagocytosis by macrophage of dead cell and oxidized LDL is important for the clearance of atherosclerotic plaque. Therefore, to determine whether anti-FAM19A5 treatment has any effect on the accumulation and/or phagocytic properties of monocyte/macrophages in atherosclerotic lesion sites on blood vessels, the expression of CD68 and CD146 was assessed in the aorta of hypercholesterolemic mice described above in Example 1. CD68 and CD146 are markers commonly used to detect fat-laden macrophages (foam cells) within tissues.

[0268] Briefly, the mice from the different groups were sacrificed approximately a week after the last antibody administration (*i.e.*, week 7 post-initial antibody administration). Prior to isolating the heart and aorta from the animals, cardiac perfusion was performed with PBS and then with 4% paraformaldehyde. The heart and aorta were collected and fixed in 10% neutral formalin. Then, the tissue samples were stained with CD68 and CD146, and the presence of foam cell or fat-laden macrophage of the total lesion area of the tissues samples was determined.

[0269] As shown in FIGs. 3A-3D, there was an increase in CD68 and CD146 expression in the aorta of hypercholesterolemic mice (Groups 2, 3, and 4) compared to normal healthy mice (Group 1). This increase was much more profound in hypercholesterolemic mice treated with anti-FAM19A5 antibody.

[0270] This result suggests that anti-FAM19A5 antibody can promote the migration and activation of CD68 and CD146 expressing fat-laden macrophages (foam cells) to atherosclerotic lesion sites within the aorta of hypercholesterolemic animals.

Example 4: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on the Phagocytic Ability of BV2 Cells

[0271] To assess whether anti-FAM19A5 antibody treatment has an effect on macrophage function, BV cells (an immortalized murine microglial cell line) was used. Briefly, the BV2 cells (4×10^3 /100 μ L/well) were plated onto a 96 well plate and incubated at 37°C 5% CO₂ for 6 hours. Then, the BV2 cells were treated with human FAM19A5-Fc protein (0.25 μ M, Lot# 170815) alone or in combination with varying concentrations (25 μ g/mL, 12.5 μ g/mL, 6.25 μ g/mL, or 3.125 μ g/mL) of anti-FAM19A5 antibody (clone "1-30"; Lot# A5m180831). The treated cells were incubated for an additional 16 hours at 37°C 5% CO₂. After the incubation, PHRODO™ Green *E. coli* BioParticles (Thermofisher, P35366) were added to the cells (15 μ g/100 μ L/well). INCUCYTE® (Sartorius) was then used to observe the phagocytic uptake of the BioParticles by measuring green fluorescence intensity every 1 hour.

[0272] As shown in FIGs. 4A and 4B, treatment of BV2 cells with human FAM19A5-Fc protein inhibited the phagocytic ability of the BV2 cells. However, treatment of BV2 cells with the combination of human FAM19A5-Fc protein and anti-FAM19A5 antibody restored phagocytosis in a concentration-dependent manner. At approximately 9 hours post treatment with the BioParticles, compared to the control group (*i.e.*, human FAM19A5-Fc protein alone), phagocytosis observed with 3.125, 6.25, 12.5, and 25 μ g/mL anti-FAM19A5 antibody was 66%, 68%, 80%, 91%, and 104%, respectively.

[0273] The above results demonstrate that anti-FAM19A5 antibody can effectively restore the phagocytic ability of the BV2 cells after FAM19A5 protein treatment. Collectively, the above Examples suggest that anti-FAM19A5 antibody treatment can enhance both the migratory (*e.g.*, to atherosclerotic lesion sites on blood vessel walls) and functional (*e.g.*, phagocytosis) properties of lipid-laden macrophages in hypercholesterolemic animals. Not to be

bound by any one theory, such macrophages can be important in the uptake of LDL from circulation and thereby, reduce the level of LDL in the blood.

Example 5: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on the Phagocytosis of Oxidized LDL by BV2 Cells

[0274] To further assess the effect of anti-FAM19A5 antibody on macrophage function, the ability of BV2 cells to phagocytose oxidized LDL after anti-FAM19A5 antibody treatment will be assessed. BV2 cells will be plated onto a 96 well plate and treated with human FAM19A5-Fc protein (0.25 μ M, Lot# 170815) alone or in combination with varying concentrations of anti-FAM19A5 antibody. The BV2 cells will be incubated at 37°C 5% CO₂. Then, Ox-LDL (purchased from AbD Serotec, Kidlington, Oxford, UK) will be added to the cells. The cellular content of Ox-LDL will be measured by using Oil Red O. INCUCYTE[®] (Sartorius) will be used to observe the phagocytic uptake of Ox-LDL by measuring Oil Red O intensity every 1 hour.

Example 6: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on Plaque Formation

[0275] To assess the effect that anti-FAM19A5 antibody has on plaque formation associated with atherosclerosis, atherosclerosis-prone C57BL/6 apolipoprotein E-deficient (Apoe^{-/-}) mice (Jackson Laboratory, U.S.A.) will be used. As described in Example 1, atherosclerosis will be induced in the animals with a high-fat diet and then, treated with either human IgG control antibody or anti-FAM19A5 antibody. After the last treatment, the mice will be sacrificed and plaque build-up along blood vessel walls will be assessed using Oil Red O staining.

Example 7: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on TNF- α Secretion by BV2 Cells

[0276] To further understand the effect of anti-FAM19A5 antibody treatment on macrophages associated with atherosclerosis, BV2 cells were plated onto a 96 well plate (5 x 10³ cells/well) and incubated for 6 hours at 37°C in 5% CO₂ environment. The cells were then treated with the following: (i) 5 μ L LPS (0.5 μ g/mL) alone, (ii) 5 μ L LPS (0.5 μ g/mL) + 5 μ L FAM19A5-Fc protein (10 μ g/mL), and (iii) 5 μ L LPS (0.5 μ g/mL) + 5 μ L FAM19A5-Fc protein (10 μ g/mL) + varying concentrations of anti-FAM19A5 antibody (clone "1-30"). The final

concentrations for the anti-FAM19A5 antibody were as follows: 100 µg/mL, 50 µg/mL, 25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, 3.125 µg/mL, 1.5625 µg/mL, and 0.78125 µg/mL. The treated cells were incubated for an additional 16-18 hours at 37°C in 5% CO₂ environment. After the incubation, the cells were centrifuged at 3,000 rpm for 3 minutes. Then, supernatant from the different wells was collected and the concentration of TNF-α present in the sample was assessed using Quantikine ELISA mouse TNF-α immunoassay (R&D biosystems, cat# SMTA00B).

[0277] As shown in FIG. 5, FAM19A5-Fc protein greatly increased the amount of TNF-α produced by the BV2 cells after stimulation with LPS, compared to control cells (*i.e.*, cells treated with LPS alone). This enhanced effect was inhibited when the anti-FAM19A5 antibody was added to the cells. The inhibitory effect was observed starting at a concentration of 12.5 µg/mL of the anti-FAM19A5 antibody (IC₅₀ = 11.5 µg/mL).

[0278] The above results demonstrate that an anti-FAM19A5 antibody disclosed herein can effectively neutralize FAM19A5 protein activity and thereby, inhibit and/or reduce the pro-inflammatory inducing effects that FAM19A5 protein can have on macrophages associated with atherosclerosis.

Example 8: Evaluation of the Effect of Anti-FAM19A5 Antibody Treatment on Peripheral Macrophages

[0279] To assess the effect of anti-FAM19A5 antibody treatment on peripheral macrophages, the ability of mouse bone marrow-derived macrophages (“m-BMDMs”) to phagocytize apoptotic cells was assessed.

[0280] To generate the apoptotic cells, thymocytes were isolated from mice and exposed 2 Gy of ionizing radiation with constant cell concentration of 1.0×10^6 thymocytes/mL. The apoptotic state of the cells was assessed using annexin V–positive and propidium iodide-negative staining or TUNEL staining by flow cytometry. When approximately 60-70% of the cells were apoptotic, the cells were labeled with PHRODO™ (Invitrogen) and used in the phagocytic assay as described below.

[0281] To measure phagocytosis, m-BMDMs were plated onto a 24-well plate (2×10^5 cells/well) and incubated overnight. Then, the cells were starved for 30 min with DMEM/F12 containing 2% FBS and incubated with PHRODO™-labeled apoptotic thymocytes (described above) (4.0×10^6 cells/well) in the presence of one of the following: (i) control Fc, (ii) FAM19A5-Fc protein, (iii) human IgG control antibody, (iv) 3-2 anti-FAM19A5 antibody, and (v) 1-65 anti-

FAM19A5 antibody. The different treatment groups are shown in Table 11 (below). After the incubation, the cells were washed with PBS, trypsinized, resuspended in cold medium containing 1% NaN₃, and analyzed by flow cytometry. Forward and side-scatter parameters were used to distinguish unengulfed targets from phagocytes. The data were analyzed using FlowJo software. Fluorescent signal-positive BMDMs were considered to be phagocytes engulfing targets.

Table 11. Treatment Groups

Group	Treatment
A1	m-BMDMs only (negative control)
A2	m-BMDMs + apoptotic thymocytes
A3	m-BMDMs + apoptotic thymocytes + control Fc (0.4 μ M)
A4	m-BMDMs + apoptotic thymocytes + control Fc (0.8 μ M)
A5	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.4 μ M)
A6	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M)
B1	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + hIgG1 control antibody (25 nM)
B2	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + hIgG1 control antibody (50 nM)
B3	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + “3-2” anti-FAM19A5 antibody (25 nM)
B4	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + “3-2” anti-FAM19A5 antibody (50 nM)
B5	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + “1-65” anti-FAM19A5 antibody (25 nM)
B6	m-BMDMs + apoptotic thymocytes + FAM19A5-Fc (0.8 μ M) + “1-65” anti-FAM19A5 antibody (50 nM)

[0282] As shown in FIGs. 6A, 6B, and 8, FAM19A5-Fc protein inhibited the ability of the m-BMDMs to phagocytize the apoptotic thymocytes, compared to m-BMDMs that were not treated to FAM19A5-Fc protein (*see, e.g.*, A3 and A4 vs. A5 and A6 in FIG. 6A). However, when the cells were also treated with the anti-FAM19A5 antibody (both the 3-2 and the 1-65 antibodies), the phagocytic ability of the m-BMDMs was comparable to the corresponding cells that were not treated with FAM19A5-Fc protein (*see, e.g.*, B5 and B6 in FIG. 7A vs. A3 and A4

in FIG. 6A), suggesting that the anti-FAM19A5 antibodies (particularly at a concentration of 50 nM) effectively neutralized the activity of the FAM19A5-Fc protein.

[0283] The above results confirm the results observed earlier with the BV2 cells (*see* Example 4) and demonstrate that the administration of an anti-FAM19A5 antibody (such as those disclosed herein) can also improve the functional properties (*e.g.*, phagocytosis) of peripheral macrophages, which could be useful in the treatment of atherosclerosis.

[0284] It is to be appreciated that the Detailed Description section, and not 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.

[0285] 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.

[0286] 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.

[0287] 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.

[0288] 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.

WHAT IS CLAIMED IS:

1. An antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist") for increasing a phagocytosis of low density lipoprotein (LDL) by macrophages in a subject in need thereof.
2. The FAM19A5 antagonist for use of claim 1, wherein the phagocytosis of LDL by macrophages is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).
3. The FAM19A5 antagonist for use of claim 1 or 2, wherein the increase in phagocytosis of LDL by macrophages occurs at an atherosclerotic lesion.
4. The FAM19A5 antagonist for use of any one of claims 1 to 3, wherein the LDL comprises oxidized LDL.
5. The FAM19A5 antagonist for use of claim 3 or 4, wherein the atherosclerotic lesion site is in a blood vessel.
6. The FAM19A5 antagonist for use of claim 5, wherein the blood vessel comprises an artery, vein, capillaries, or combinations thereof.
7. The FAM19A5 antagonist for use of claim 6, wherein the artery is an aorta.
8. An antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist") for increasing a migration and/or accumulation of macrophages at an atherosclerotic lesion site in a subject in need thereof.
9. The FAM19A5 antagonist for use of claim 8, wherein the migration and/or accumulation of macrophages at an atherosclerotic lesion site is increased by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).
10. The FAM19A5 antagonist for use of claim 8 or 9, wherein the increased migration and/or accumulation of macrophages at an atherosclerotic lesion site is associated with a decrease in a low density lipoprotein (LDL) level in the subject.

11. An antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist") for reducing a low density lipoprotein (LDL) level in a subject in need thereof.
12. The FAM19A5 antagonist for use of claim 11, wherein the LDL level in the subject is reduced by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).
13. The FAM19A5 antagonist for use of any one of claims 1 to 12, wherein the subject exhibits one or more properties:
 - (i) an increased phagocytosis of LDL by macrophages;
 - (ii) an increased migration and/or accumulation of macrophages to an atherosclerotic lesion site; and
 - (iii) a reduced LDL level.
14. An antagonist against a family with sequence similarity 19, member A5 ("FAM19A5") protein ("FAM19A5 antagonist") for treating an atherosclerosis in a subject in need thereof.
15. The FAM19A5 antagonist for use of claim 14, wherein the atherosclerosis is associated with a disease comprising coronary heart disease (CHD), carotid artery disease, peripheral artery disease, chronic kidney disease, stroke, retinal artery occlusion, abdominal pain caused by intestinal damage, peritonitis, or combinations thereof.
16. The FAM19A5 antagonist for use of claim 14 or 15, wherein the atherosclerosis is associated with a high fat and/or high cholesterol (hypercholesterolemic) diet.
17. The FAM19A5 antagonist for use of any one of claims 14 to 16, wherein the atherosclerosis is associated with an increased total cholesterol level, increased triglyceride level, increased LDL level, decreased HDL level, increased number and/or retention of oxo-LDL-induced foam cells within a plaque, or combinations thereof, compared to a subject without atherosclerosis (*e.g.*, a healthy subject).
18. The FAM19A5 antagonist for use of any one of claims 14 to 17, wherein administering the FAM19A5 antagonist reduces a low density lipoprotein (LDL) level in the subject by at least about 5%, at least about 10%, 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%, or at least about 90% or

more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

19. The FAM19A5 antagonist for use of any one of claims 14 to 18, wherein administering the FAM19A5 antagonist increases a migration and/or accumulation of macrophages at an atherosclerotic lesion site in an aorta of a subject by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

20. The FAM19A5 antagonist for use of any one of claims 14 to 19, wherein administering the FAM19A5 antagonist increases a phagocytosis of LDL by macrophages by at least about 5%, at least about 10%, 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%, or at least about 90% or more, compared to a reference (*e.g.*, corresponding value in a subject that did not receive the FAM19A5 antagonist or corresponding value in the subject prior to administering the FAM19A5 antagonist).

21. The FAM19A5 antagonist for use of claim 20, wherein the increase in phagocytosis of LDL by macrophages occurs at an atherosclerotic lesion site in a blood vessel.

22. The FAM19A5 antagonist for use of claim 20 or 21, wherein the LDL comprises oxidized LDL.

23. The FAM19A5 antagonist for use of claim 21 or 22, wherein the blood vessel comprises an artery, vein, capillaries, or combinations thereof.

24. The FAM19A5 antagonist for use of claim 23, wherein the artery is an aorta.

25. The FAM19A5 antagonist for use of any one of claims 1 to 24, wherein the FAM19A5 antagonist is an antisense oligonucleotide, siRNA, shRNA, miRNA, dsRNA targeting FAM19A5, aptamer, PNA, or a vector including the same.

26. The FAM19A5 antagonist for use of any one of claims 1 to 24, wherein the FAM19A5 antagonist is an antibody, or an antigen-binding portion thereof, that specifically binds to the FAM19A5 protein ("anti-FAM19A5 antibody").

27. The FAM19A5 antagonist for use of claim 26, wherein the anti-FAM19A5 antibody exhibits a property selected from the group consisting of:

- (a) binds to soluble human FAM19A5 with a KD of 10 nM or less as measured by enzyme-linked immunosorbent assay (ELISA);
 - (b) binds to membrane bound human FAM19A5 with a KD of 10 nM or less as measured by ELISA; and
 - (c) both (a) and (b).
28. The FAM19A5 antagonist for use of claim 26 or 27, wherein the anti-FAM19A5 antibody cross-competes for binding to a human FAM19A5 epitope with a reference antibody, wherein the reference antibody is selected from the group consisting of the antibodies in TABLES 2-5.
29. The FAM19A5 antagonist for use of any one of claims 26 to 28, wherein the reference antibody comprises heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3,
- wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.
30. The FAM19A5 antagonist for use of any one of claims 26 to 29, wherein the anti-FAM19A5 antibody specifically binds to the same FAM19A5 epitope as a reference antibody, wherein the reference antibody is selected from the group consisting of TABLES 2-5.
31. The FAM19A5 antagonist for use of any one of claims 26 to 30, wherein the reference antibody comprises heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3,
- wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14, the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15, the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16, the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26, the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27, and the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.
32. The FAM19A5 antagonist for use of any one of claims 26 to 31, wherein the anti-FAM19A5 antibody specifically binds to at least one FAM19A5 epitope, which is SEQ ID NO: 6 or SEQ ID NO: 9.

33. The FAM19A5 antagonist for use of any one of claims 26 to 32, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3,

- (i) wherein the heavy chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in TABLE 2;
- (ii) wherein the heavy chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in TABLE 2;
- (iii) wherein the heavy chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in TABLE 2;
- (iv) wherein the light chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in TABLE 3;
- (v) wherein the light chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in TABLE 3; and/or
- (vi) wherein the light chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in TABLE 3.

34. The FAM19A5 antagonist for use of any one of claims 26 to 33, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3,

- (i) wherein the heavy chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 14;
- (ii) wherein the heavy chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 15;
- (iii) wherein the heavy chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 16;
- (iv) wherein the light chain CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 26;
- (v) wherein the light chain CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 27; and/or
- (vi) wherein the light chain CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 28.

35. The FAM19A5 antagonist for use of any one of claims 26 to 34, 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 the amino acid sequence set forth as SEQ ID NOs: 14, 15, and 16, respectively, and the light chain CDR1, CDR2, and CDR3 comprises the amino acid sequence set forth as SEQ ID NOs: 26, 27, and 28, respectively.

36. The FAM19A5 antagonist for use of any one of claims 26 to 35, wherein the anti-FAM19A5 antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth as SEQ ID NO: 36.

37. The FAM19A5 antagonist for use of any one of claims 26 to 35, wherein the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL), wherein the VH 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: 36.

38. The FAM19A5 antagonist for use of any one of claims 26 to 35, wherein the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL), wherein the VL 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: 40.

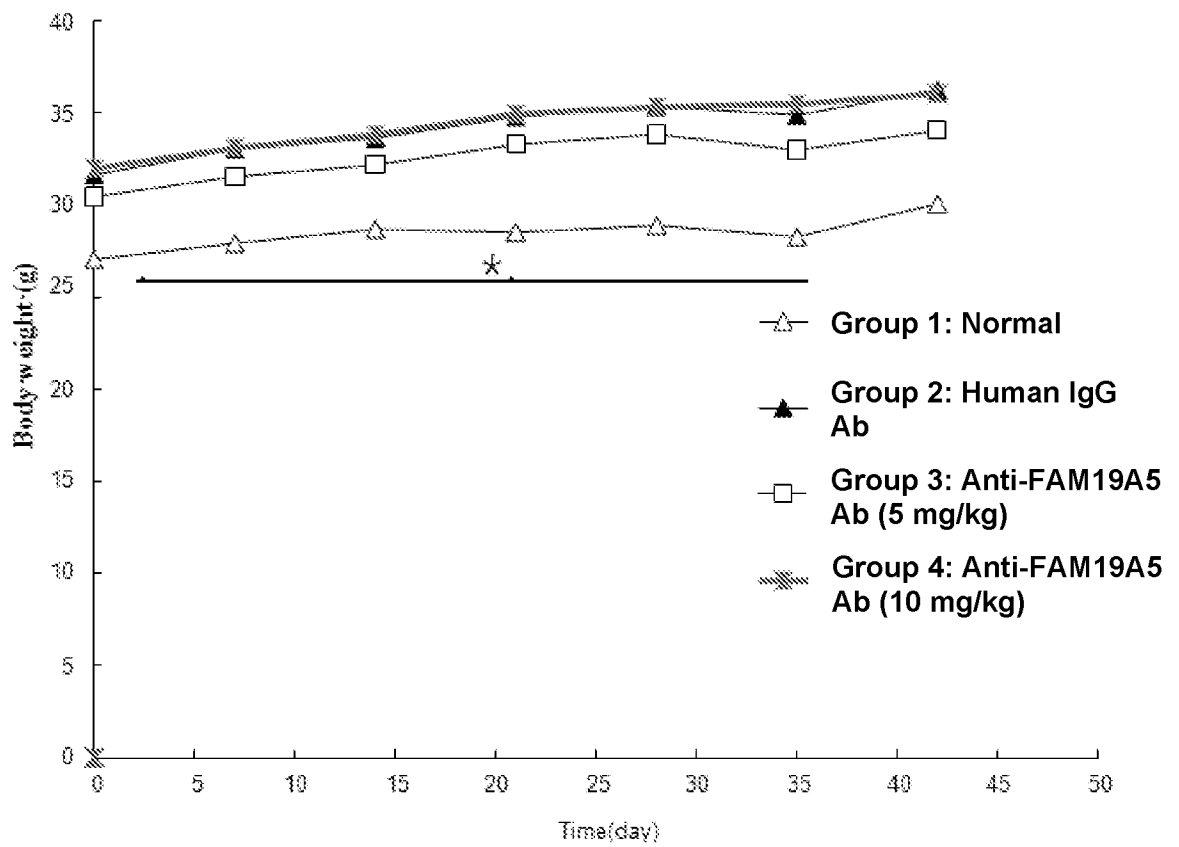
39. The FAM19A5 antagonist for use of any one of claims 26 to 35, wherein the anti-FAM19A5 antibody comprises a heavy chain variable region(VH) and a light chain variable region (VL),

(i) wherein the VH 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: 36; and

(ii) wherein the VL 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: 40.

40. The FAM19A5 antagonist for use of any one of claims 26 to 39, wherein the anti-FAM19A5 antibody comprises a Fab, Fab', F(ab')₂, Fv, or single chain Fv (scFv).

41. The FAM19A5 antagonist for use of any one of claims 26 to 40, wherein the anti-FAM19A5 antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, and a variant thereof.
42. The FAM19A5 antagonist for use of claim 41 wherein the anti-FAM19A5 antibody is an IgG2, an IgG4, or a combination thereof.
43. The FAM19A5 antagonist for use of claim 42, wherein the anti-FAM19A5 antibody comprises an IgG2/IgG4 isotype antibody.
44. The FAM19A5 antagonist for use of any one of claims 26 to 43, wherein the anti-FAM19A5 antibody comprises a constant region without the Fc function.
45. The FAM19A5 antagonist for use of any one of claims 26 to 44, wherein the anti-FAM19A5 antibody is a chimeric antibody, a human antibody, or a humanized antibody.
46. The FAM19A5 antagonist for use of any one of claims 26 to 45, wherein the FAM19A5 antagonist is linked to a molecule having a second binding moiety, thereby forming a bispecific molecule.
47. The FAM19A5 antagonist for use of any one of claims 1 to 46, wherein the FAM19A5 antagonist is linked to an agent, thereby forming an immunoconjugate.
48. The FAM19A5 antagonist for use of any one of claims 1 to 47, further comprising administering a therapeutic agent.
49. The FAM19A5 antagonist for use of any one of claims 1 to 48, wherein the FAM19A5 antagonist is formulated with a pharmaceutically acceptable carrier.
50. The FAM19A5 antagonist for use of any one of claims 1 to 49, wherein the FAM19A5 antagonist is administered intravenously, subcutaneously, intramuscularly, orally, intravitreally, intrathecally, or combinations thereof.
51. The FAM19A5 antagonist for use of any one of claims 1 to 50, wherein the subject is a human.
52. The FAM19A5 antagonist for use of any one of claims 1 to 51, further comprising administering a cholesterol lowering agent.
53. The FAM19A5 antagonist for use of claim 52, wherein the cholesterol lowering agent is administered subsequent to or concurrently with the FAM19A5 antagonist.

**FIG. 1**

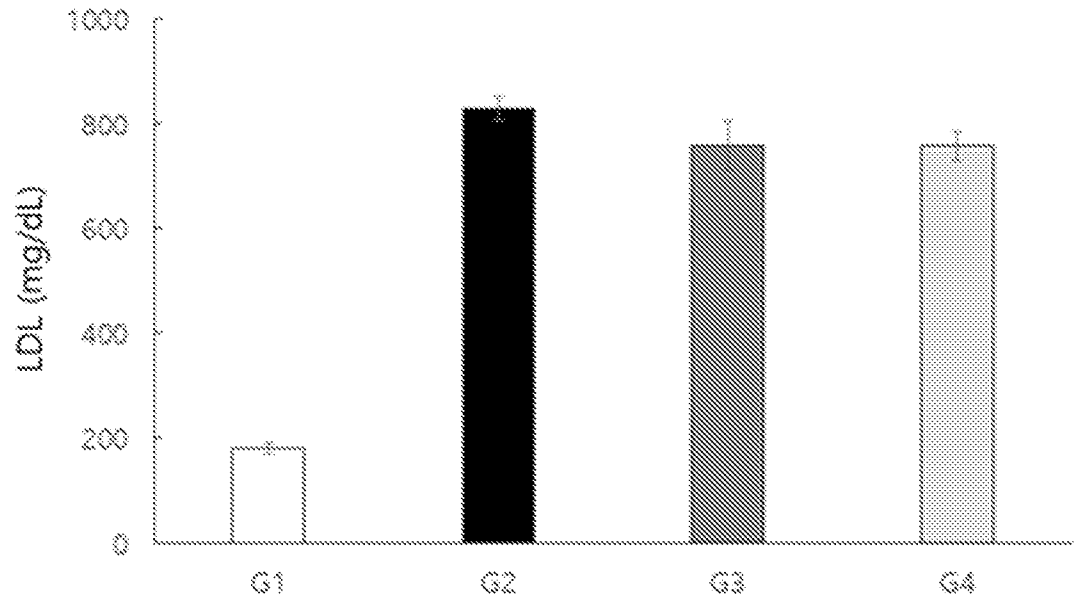
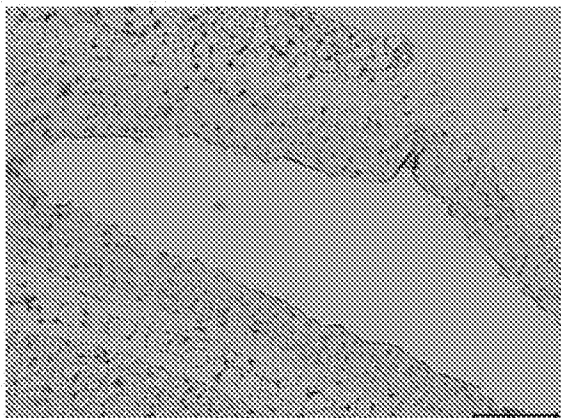


FIG. 2

CD68



CD146

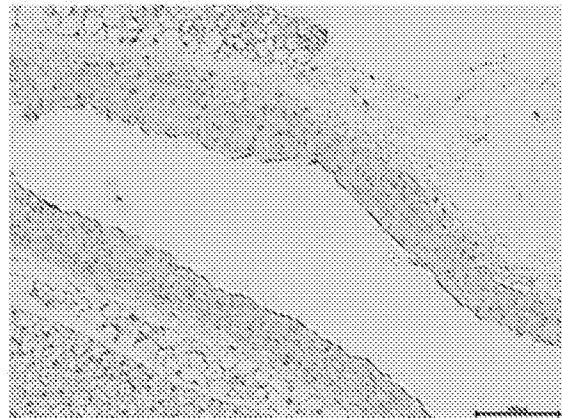
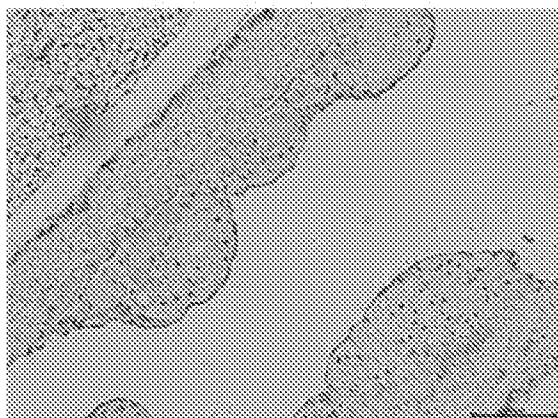


FIG. 3A

CD68



CD146

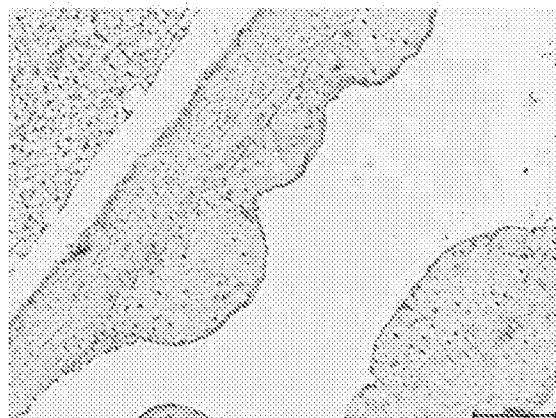
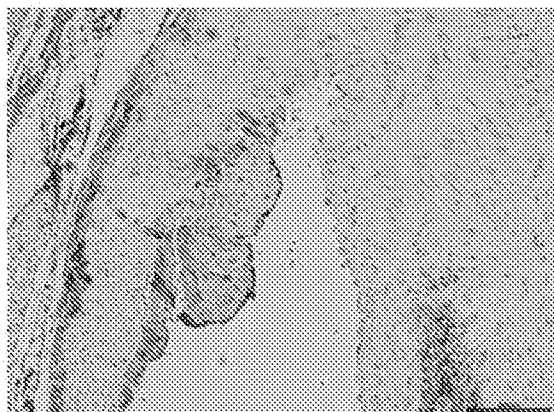


FIG. 3B

CD68



CD146

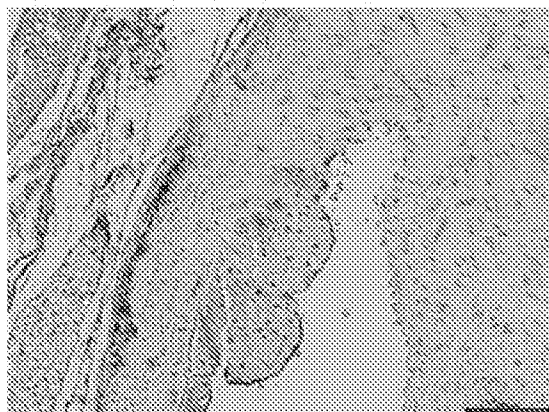
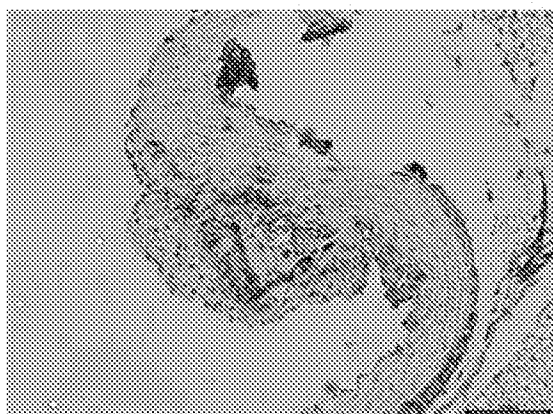


FIG. 3C

CD68



CD146

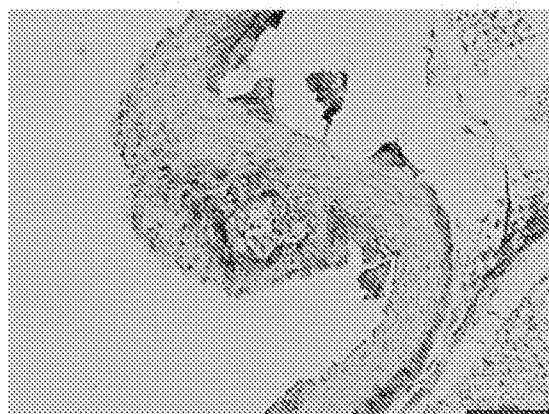


FIG. 3D

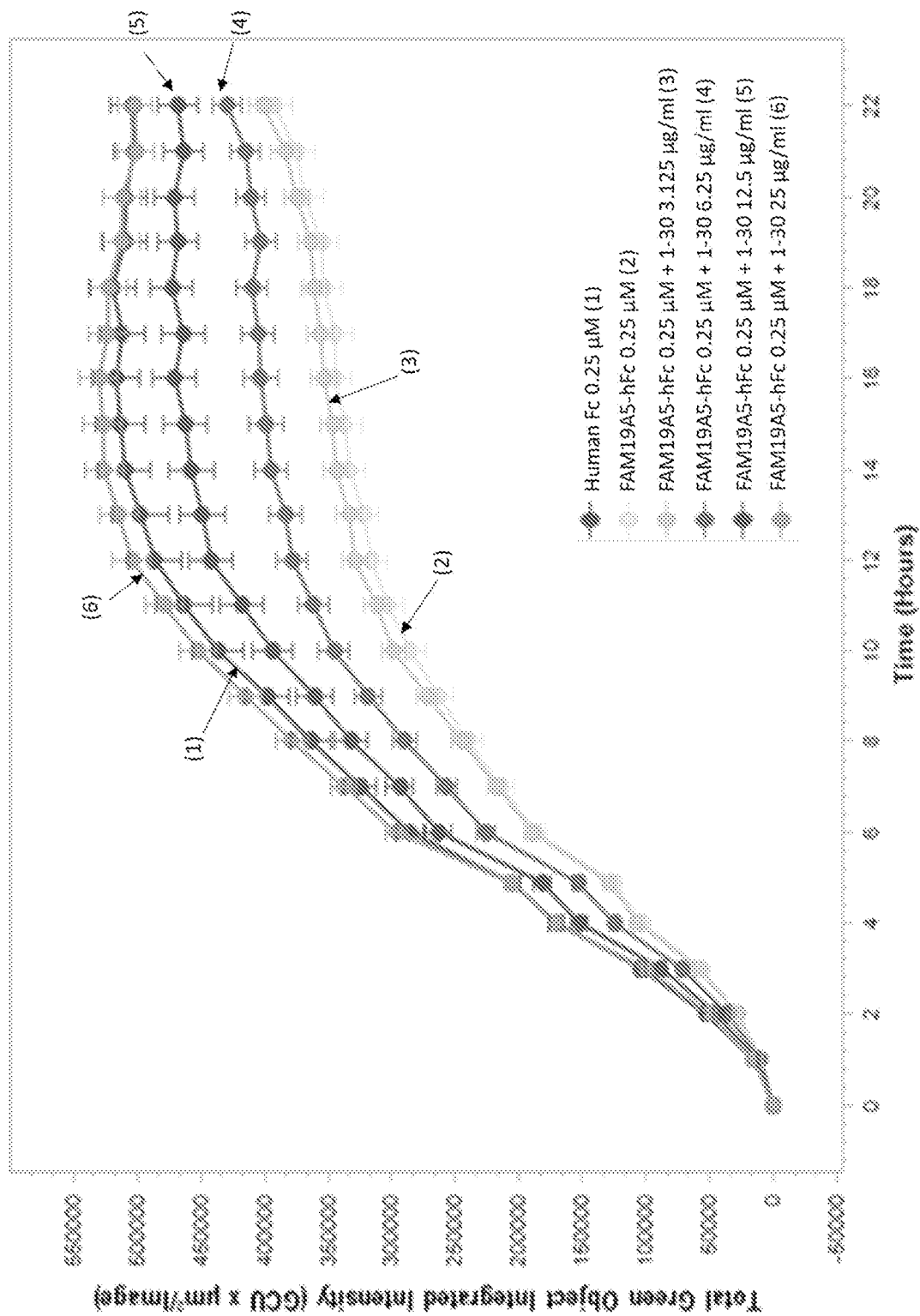


FIG. 4A

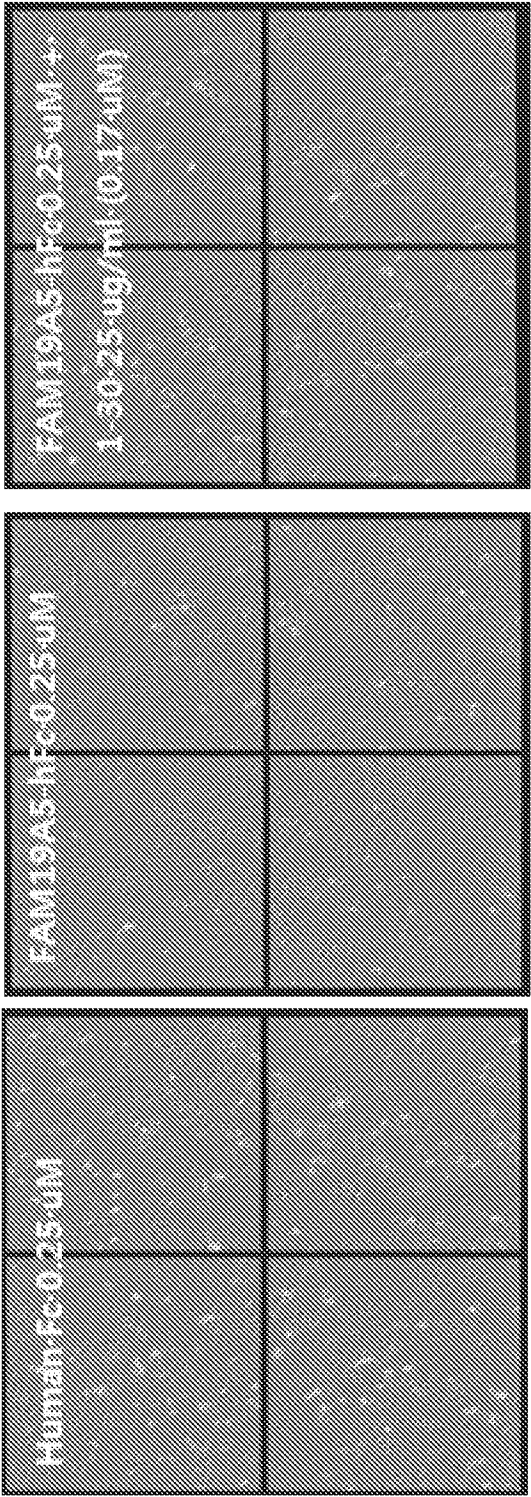


FIG. 4B

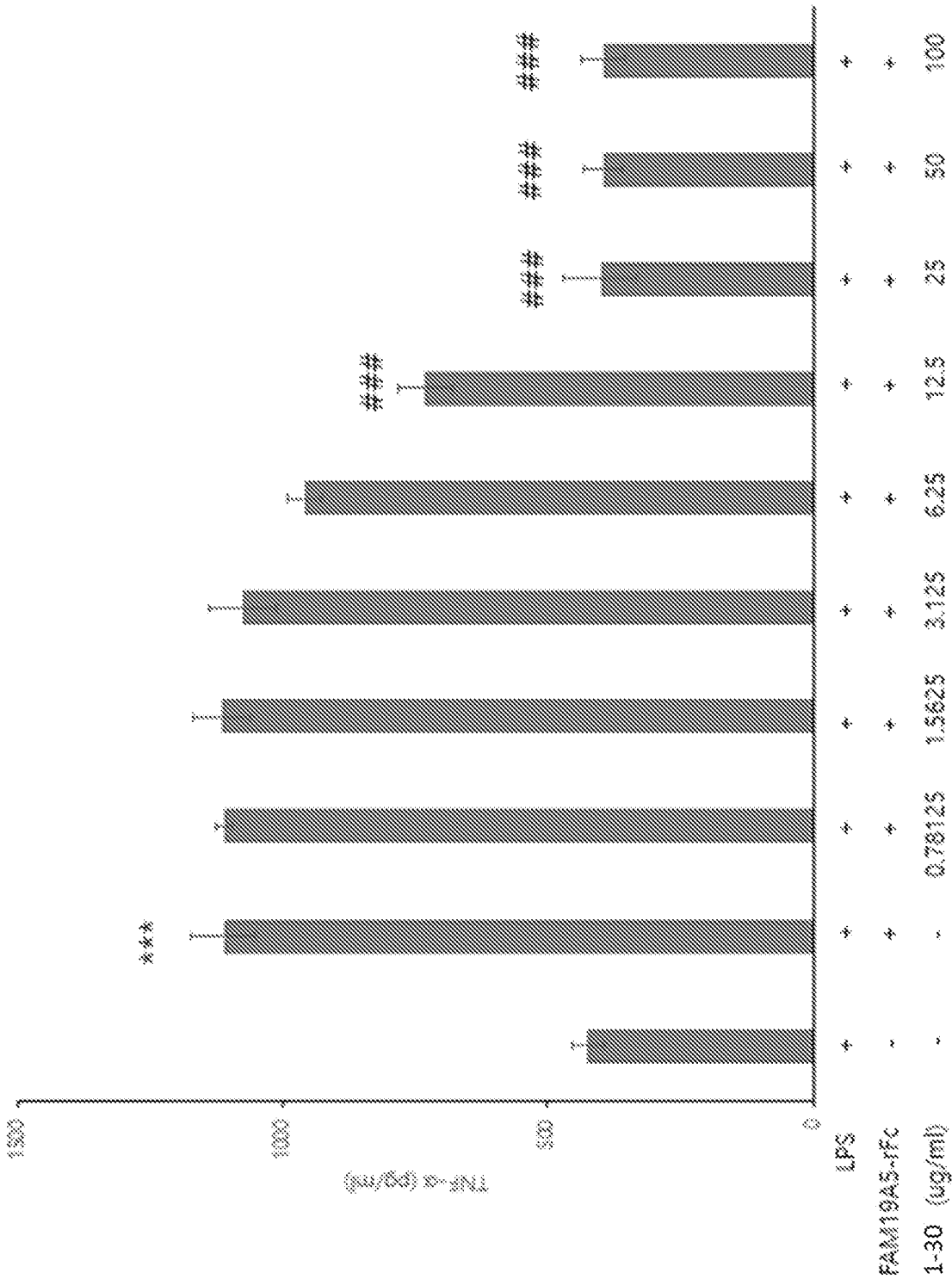


FIG. 5

FIG. 6A

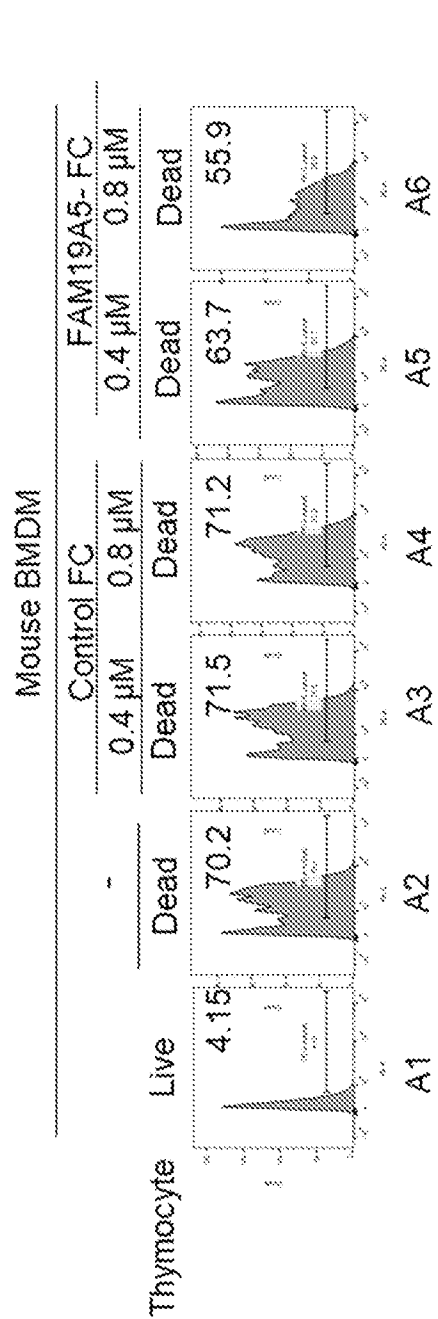


FIG. 6B

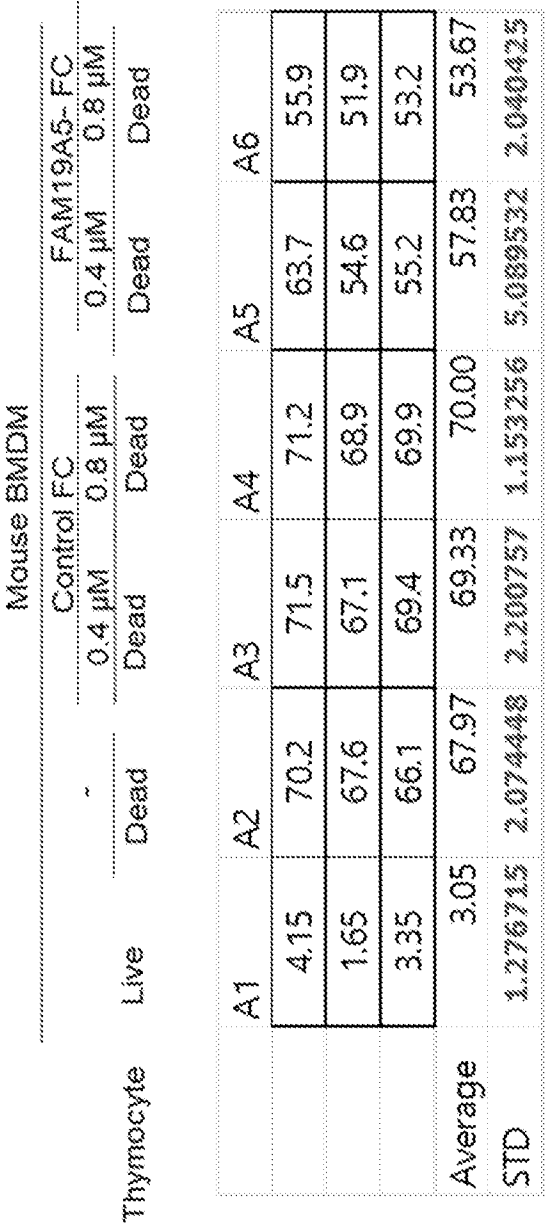


FIG. 7A

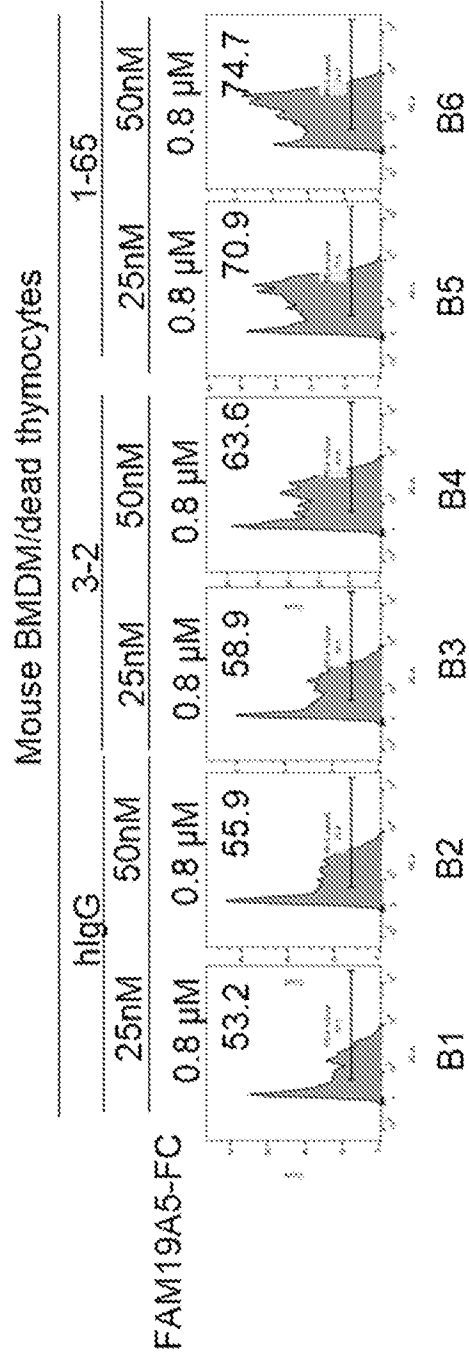
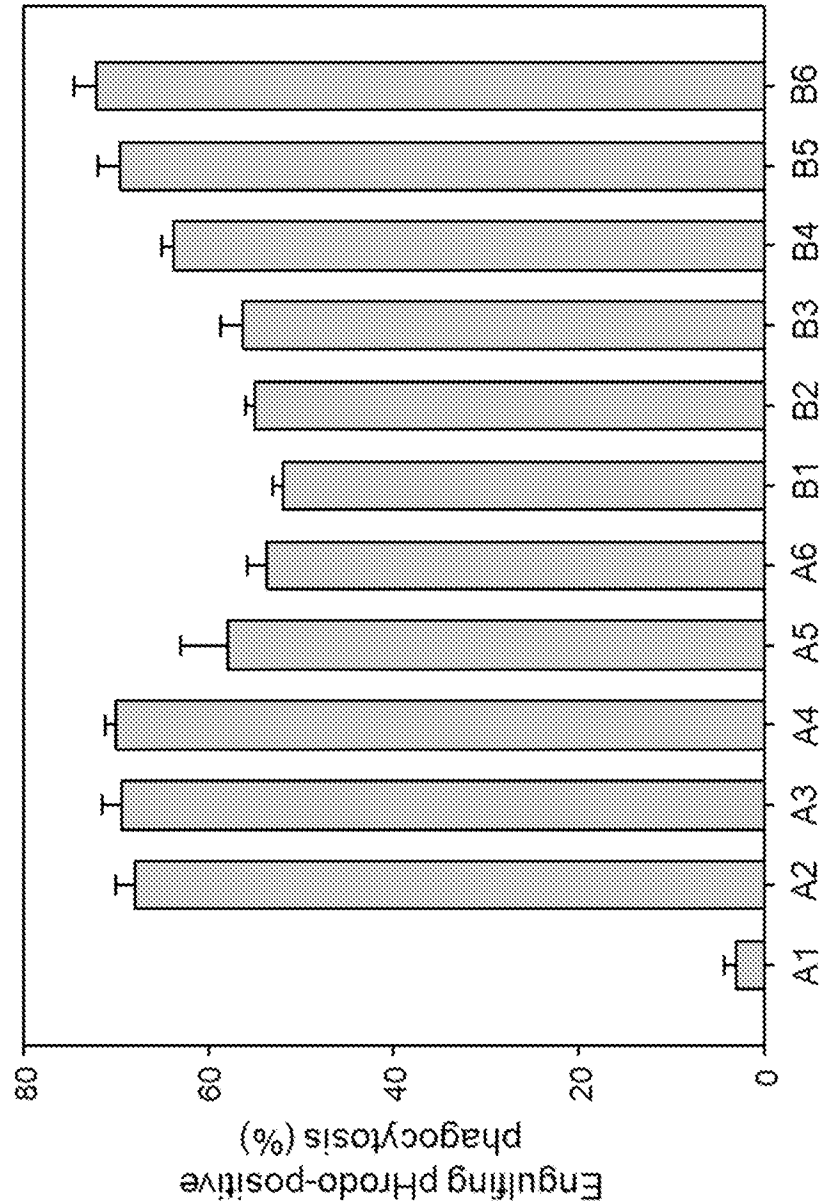


FIG. 7B

Mouse BMDM/dead thymocytes						
hlgG		3-2			1-65	
25nM	50nM	25nM	50nM	25nM	50nM	50nM
0.8 μ M	0.8 μ M	0.8 μ M	0.8 μ M	0.8 μ M	0.8 μ M	0.8 μ M
B1	B2	B3	B4	B5	B6	
53.2	55.9	58.9	63.6	70.9	74.7	
51.1	55	55.5	65.2	66.9	70.3	
51.3	54.1	54.2	62.6	71	71.6	
Average	51.87	55.00	56.20	63.80	69.60	72.20
STD	1.159023	0.9	2.426932	1.311488	2.338803	2.260531

FIG. 8



A. CLASSIFICATION OF SUBJECT MATTER**C07K 16/24(2006.01)i, A61P 9/10(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)

C07K 16/24; A61K 39/395; A61P 25/00; C07K 14/705; C07K 16/18; C07K 16/46; C07K 7/00; C12Q 1/68; A61P 9/10; 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: atherosclerosis, low density lipoprotein (LDL), FAM19A5, antagonist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018-083538 A1 (NEURACLE SCIENCE CO., LTD.) 11 May 2018 claims 1-16	1-3, 8-12, 14-16
A	US 9579398 B2 (NEURACLE SCIENCE CO., LTD.) 28 February 2017 the whole document	1-3, 8-12, 14-16
A	WO 2017-216559 A1 (ALMAC DIAGNOSTICS LIMITED) 21 December 2017 the whole document	1-3, 8-12, 14-16
A	WO 2017-123556 A1 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 20 July 2017 the whole document	1-3, 8-12, 14-16
A	US 2014-0051591 A1 (O'DONNELL, J. et al.) 20 February 2014 the whole document	1-3, 8-12, 14-16



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

"D" document cited by the applicant in the international application

"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

23 April 2020 (23.04.2020)

Date of mailing of the international search report

23 April 2020 (23.04.2020)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea

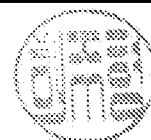


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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/061377

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.: 6, 7, 21, 24, 27, 42, 43, 53
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 6, 7, 21, 24, 27, 42, 43, 53 are regarded to be unclear because it refers to claims 5, 6, 20, 23, 26, 41, 42, 52 which does not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4, 5, 13, 17-20, 22, 23, 25, 26, 28-41, 44-52
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 additional 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2019/061377

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018-083538 A1	11/05/2018	AU 2019-353939 A1 CA 3042989 A1 EP 3535294 A1 KR 10-2019-0077366 A	06/06/2019 11/05/2018 11/09/2019 03/07/2019
US 9579398 B2	28/02/2017	CN 104254343 A CN 107019800 A EP 2815769 A1 KR 10-1406393 B1 KR 10-2013-0094255 A US 2015-0118230 A1 US 2017-0121401 A1 WO 2013-122408 A1	31/12/2014 08/08/2017 24/12/2014 13/06/2014 23/08/2013 30/04/2015 04/05/2017 22/08/2013
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