SUMMARY OF THE INVENTION

[0009] In accordance with certain ~~aspects~~ examples of the present disclosure, there are ~~provided~~ described monoclonal antibodies, or fragments thereof, that bind to Olfml-3 and inhibit the activity of Olfml-3 in angiogenesis. Thus, in some ~~embodiment~~examples, there is ~~provided~~described an isolated or recombinant monoclonal antibody that specifically binds to an Olfml-3 polypeptide. In certain ~~aspects~~examples, an antibody competes for the binding of an Olfml-3 polypeptide with a 46A9BO, 9F8BO or Z14A7 monoclonal antibody. Preferred antibodies compete for binding of the Olfml-3 polypeptide with the 46A9BO monoclonal antibody. In certain ~~aspects~~examples, the antibody may comprise all or part of the heavy chain variable region and/or the light chain variable region of the 46A9BO, 9F8BO or Z14A7 monoclonal antibodies. In a further ~~aspect~~example, the antibody may comprise an amino acid sequence that corresponds to a first, second, and/or third complementarity determining region (CDR) from the light variable and/or heavy variable chain of the monoclonal antibodies of the present ~~embodiment~~examples. In one aspect, the present invention refers to an isolated monoclonal antibody, wherein the antibody comprises (a) a first VH CDR at least 80% identical to VH CDR1 of 46A9BO (SEQ ID NO: 7), 9F8BO (SEQ ID NO: 21), or Z14A7 (SEQ ID NO: 13); (b) a second VH CDR at least 80% identical to VH CDR2 of 46A9BO (SEQ ID NO: 8), 9F8BO (SEQ ID NO: 22), or Z14A7 (SEQ ID NO: 14); (c) a third VH CDR at least 80% identical to VH CDR3 of 46A9BO (SEQ ID NO: 9), 9F8BO (SEQ ID NO: 23), or Z14A7 (SEQ ID NO: 15); (d) a first VL CDR at least 80% identical to VL CDR1 of 46A9BO (SEQ ID NO: 10), 9F8BO (SEQ ID NO: 24), or Z14A7 (SEQ ID NO: 16);(e) a second VL CDR at least 80% identical to VL CDR2 of 46A9BO (SEQ ID NO: 11), 9F8BO (SEQ ID NO: 25), or Z14A7 (SEQ ID NO: 17); and (f) a third VL CDR at least 80% identical to VL CDR3 of 46A9BO (SEQ ID NO: 12), 9F8BO (SEQ ID NO: 26), or Z14A7 (SEQ ID NO: 18). In another aspect, the present invention refers to a composition comprising an antibody as described herein in a pharmaceutically acceptable carrier. In a further aspect, the present invention refers to an isolated polynucleotide molecule comprising a nucleic acid sequence encoding an antibody as described herein. In yet another aspect, the present invention refers to a recombinant polypeptide comprising an antibody VH domain comprising CDRs 1-3 of the VH domain of 46A9BO (SEQ ID NOs: 7, 8 and 9); CDRs 1-3 of the VH domain of 9F8BO (SEQ ID NOs: 21, 22 and 23); or CDRs 1-3 of the VH domain of Z14A7 (SEQ ID NOs: 13, 14 and 15). In another aspect, the present invention refers to a recombinant polypeptide comprising an antibody VL domain comprising CDRs 1-3 of the VL domain of 46A9BO (SEQ ID NOs: 10, 11 and 12); CDRs 1-3 of the VL domain of 9F8BO (SEQ ID NOs: 24, 25 and 26); or CDRs 1-3 of the VL domain of

Z14A7 (SEQ ID NOs: 16, 5 and 6). In yet another aspect, the present invention refers to an isolated polynucleotide molecule comprising a nucleic acid sequence encoding a polypeptide as disclosed herein. In a further aspect, the present invention refers to a host cell comprising one or more polynucleotide molecule(s) encoding an antibody as disclosed herein or a recombinant polypeptide as described herein. In another aspect, the present invention refers to a method of manufacturing an antibody comprising (a) expressing one or more polynucleotide molecule(s) encoding a VL and VH chain of an antibody of any one of claims 1-12 in a cell; and (b) purifying the antibody from the cell. In a further aspect, the present invention refers to use of an antibody as disclosed herein in the manufacture of a medicament for treating an angiogenesis-related condition in a subject.

[0010] Thus, in certain ~~aspects~~examples, an isolated or recombinant antibody of the ~~embodiment~~examples comprises CDR sequences at least 80%, 90% or 95% identical to the CDR regions of the 46A9BO, 9F8BO or Z14A7 heavy and light chain amino acid sequences. In further ~~aspect~~examples, an antibody comprises CDR regions identical to the 46A9BO, 9F8BO or Z14A7 CDRs, except for one or two amino acid substitutions, deletions or insertions at one, two, three or more of the CDRs. For example, the antibody can comprise CDRs wherein the CDR sequences comprise 1 or 2 amino acid substitutions in the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2 and/or VL CDR3 relative to the CDRs of a 46A9BO, 9F8BO or Z14A7 monoclonal antibody. Thus, in some specific ~~aspects~~examples, an antibody of the ~~embodiments~~ examples comprises (a) a first VH CDR at least 80% identical to VH CDR1 of 46A9BO (SEQ ID NO: 7), or Z14A7 (SEQ ID NO: 13); (b) a second VH CDR at least 80% identical to VH CDR2 of 46A9BO (SEQ ID NO: 8), or Z14A7 (SEQ ID NO: 14); (c) a third VH CDR at least 80% identical to VH CDR3 of 46A9BO (SEQ ID NO: 9), or Z14A7 (SEQ ID NO: 15); (d) a first VL CDR at least 80% identical to VL CDR1 of 46A9BO (SEQ ID NO: 10), or Z14A7 (SEQ ID NO: 16); (e) a second VL CDR at least 80% identical to VL CDR2 of 46A9BO (SEQ ID NO: 11), or Z14A7 (SEQ ID NO: 17); and (f) a third VL CDR at least 80% identical to VL CDR3 of 46A9BO (SEQ ID NO: 12), or Z14A7 (SEQ ID NO: 18). In a further ~~aspect~~example, an antibody of the ~~embodiments~~ example comprises (a) a first VH CDR at least 80% identical to VH CDR1 of 9F8BO (SEQ ID NO: 21); (b) a second VH CDR at least 80%

identical to VH CDR2 of 9F8BO (SEQ ID NO: 22); (c) a third VH CDR at least 80% identical to VH CDR3 of 9F8BO (SEQ ID NO: 23); (d) a first VL CDR at least 80% identical to VL CDR1 of 9F8BO (SEQ ID NO: 24); (e) a second VL CDR at least 80% identical to VL CDR2 of 9F8BO (SEQ ID NO: 25; and (f) a third VL CDR at least 80% identical to VL CDR3 of 9F8BO (SEQ ID NO: 26).

[0011] In further ~~aspect~~example, an isolated or recombinant antibody comprises a first VH, a second VH, a third VH, a first VL, a second VL, and a third VL CDR sequence at least 80%, 85%, 90%, or 95% identical to the corresponding CDR sequence of monoclonal antibody 46A9BO, which are represented by SEQ ID NOs: 7, 8, 9, 10, 11, and 12, respectively. In one ~~aspect~~example, the isolated antibody comprises CDR sequences that are identical to the CDR sequences of monoclonal antibody 46A9BO. In further ~~aspect~~examples, the antibody is an IgG2b antibody.

[0012] In another ~~aspect~~example, the isolated antibody comprises a VH domain at least about 80%, 85%, 90%, or 95% identical to the VH domain of 46A9BO (SEQ ID NO: 1) and a VL domain at least about 80%, 85%, 90%, or 95% identical to the VL domain of 46A9BO (SEQ ID NO: 2). In further ~~aspect~~examples, the isolated antibody comprises VH and VL domains identical to those of monoclonal antibody 46A9BO.

[0013] In still further ~~aspect~~examples, an isolated or recombinant antibody comprises a first VH, a second VH, a third VH, a first VL, a second VL, and a third VL CDR sequence at least 80%, 85%, 90%, or 95% identical to the corresponding CDR sequence of monoclonal antibody 9F8BO, which are represented by SEQ ID NOs: 21, 22, 23, 24, 25, and 26, respectively. In one ~~aspect~~example, the isolated antibody comprises CDR sequences that are identical to the CDR sequences of monoclonal antibody 9F8BO. In further ~~aspect~~examples, the antibody is an IgG2b antibody.

[0014] In yet another ~~aspect~~example, the isolated antibody comprises a VH domain at least about 80%, 85%, 90%, or 95% identical to the VH domain of 9F8BO (SEQ ID NO: 19) and a VL domain at least about 80%, 85%, 90%, or 95% identical to the VL domain of 9F8BO (SEQ ID NO: 20). In further ~~aspect~~examples, the isolated antibody comprises VH and VL domains identical to those of monoclonal antibody 9F8BO.

[0015] In still further ~~aspect~~examples, the isolated or recombinant antibody comprises a first VH, a second VH, a third VH, a first VL, a second VL, and a third VL CDR sequence at least

80%, 85%, 90%, or 95% identical to the corresponding CDR sequence of monoclonal antibody Z14A7, which are represented by SEQ ID NOs: 13, 14, 15, 16, 17, and 18, respectively. In one ~~aspect~~example, the isolated antibody comprises CDR sequences that are identical to the CDR sequences of monoclonal antibody Z14A7. In further ~~aspect~~examples, the antibody is an IgG2c antibody.

[0016] In another ~~aspect~~example, the isolated antibody comprises a VH domain at least about 80%, 85%, 90%, or 95% identical to the VH domain of Z14A7 (SEQ ID NO: 3) and a VL domain at least about 80%, 85%, 90%, or 95% identical to the VL domain of Z14A7 (SEQ ID NO: 4). In some ~~aspect~~examples, the isolated antibody comprises VH and VL domains identical to those of monoclonal antibody Z14A7.

[0017] In some ~~aspect~~examples, an antibody of the ~~embodiment~~examples may be an IgG (*e.g.*, IgG1, IgG2, IgG3 or IgG4), IgM, IgA, or an antigen binding fragment thereof. In further ~~aspect~~examples, the antibody may be a Fab', a F(ab')2 a F(ab')3, a monovalent scFv, a bivalent scFv, or a single domain antibody. In some cases, the antibody may be a human, humanized, or de-immunized antibody. In a further ~~aspect~~example, the isolated antibody is the Z14A7, 9F8BO or 46A9BO antibody.

[0018] In certain ~~aspect~~examples, an antibody (or fragment thereof) of the ~~embodiment~~examples is a glycosylated antibody (*e.g.*, having a mammalian glycosylation pattern). In some ~~aspect~~examples, the antibody is a deglycosylated antibody (*e.g.*, an enzymatically treated antibody or an antibody produced in bacteria) or has non-mammalian glycosylation (*e.g.*, an antibody produced in yeast or insect cells).

[0019] In some ~~embodiment~~examples, there is ~~provided~~described an isolated polynucleotide molecule comprising nucleic acid sequence encoding an antibody or a polypeptide comprising an antibody V_H or V_L domain disclosed herein.

[0020] In further ~~embodiment~~examples, a host cell is ~~provided~~described that produces a monoclonal antibody or recombinant polypeptide of the ~~embodiment~~examples. In some ~~aspect~~examples, the host cell is a mammalian cell, a yeast cell, a bacterial cell, a ciliate cell, or an insect cell. In certain ~~aspect~~examples, the host cell is a hybridoma cell.

[0021] In still further ~~embodiment~~examples, there is ~~provided~~described a method of manufacturing an antibody of the present ~~embodiment~~examples comprising expressing one or more polynucleotide

molecule(s) encoding a V_L or V_H chain of an antibody disclosed herein in a cell and purifying the antibody from the cell.

[0022] In additional ~~embodiment~~examples, there are ~~provided~~described pharmaceutical compositions comprising an antibody or antibody fragment as discussed herein. Such a composition further comprises a pharmaceutically acceptable carrier and may or may not contain additional active ingredients

[0023] Thus, in some ~~aspect~~examples (*e.g.,* for medical or clinical application), an antibody or fragment may be attached to an agent to be targeted to an Olfml-3-expressing cell. The agent may be a cytotoxic agent, a cytokine, an anti-angiogenic agent, a chemotherapeutic agent, a diagnostic agent, an imaging agent, a radioisotope, a pro-apoptosis agent, an enzyme, a hormone, a growth factor, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an imaging agent, an antigen, a survival factor, an anti-apoptotic agent, a hormone antagonist, a virus, a bacteriophage, a bacterium, a liposome, a microparticle, a magnetic bead, a microdevice, a cell, a nucleic acid or an expression vector.

[0024] There may also be ~~provided~~described a pharmaceutical composition comprising one or more of the antibodies or fragments described above in a pharmaceutically acceptable carrier, for example, a pharmaceutical composition comprising an antibody or fragment and a pharmaceutically acceptable carrier.

[0025] It is contemplated that the Olfml-3 antibodies or fragments or the composition of the present invention described above may be used in the treatment of any disease or disorder in which angiogenesis plays a role, which will be referred to generally as an angiogenesis-related condition. It is contemplated that the invention will find applicability in any such disorder in humans or animals. Exemplary angiogenesis-related conditions include cancer, ocular neovascularization, arterio-venous malformations, coronary restenosis, peripheral vessel restenosis, glomerulonephritis, rheumatoid arthritis, ischemic cardiovascular pathologies, chronic inflammatory diseases, *etc.*

[0026] In the case of cancer, exemplary angiogenic cancers include angiogenic breast cancer, lung cancer, prostate cancer, ovarian cancer, brain cancer, liver cancer, cervical cancer, colorectal cancer, renal cancer, skin cancer, head and neck cancer, bone cancer, esophageal cancer, bladder cancer, uterine cancer, lymphatic cancer, stomach cancer, pancreatic cancer, testicular cancer, lymphoma, or leukemia. Ocular neovascularization

disorders include macular degeneration (*e.g.*, age-related macular degeneration (AMD), corneal graft rejection, corneal neovascularization, retinopathy of prematurity (ROP) and diabetic retinopathy.

[0027] Certain ~~embodiment~~examples are directed to an antibody or recombinant polypeptide composition comprising an isolated and/or recombinant antibody or polypeptide that specifically binds Olfml-3. In certain ~~aspect~~examples the antibody or polypeptide has a sequence that is, is at least, or is at most 80, 85, 90, 95, 96, 97, 98, 99, or 100% identical (or any range derivable therein) to all or part of any monoclonal antibody provided herein. In still further ~~aspect~~examples the isolated and/ or recombinant antibody or polypeptide has, has at least, or has at most 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more contiguous amino acids from any of the sequences provided herein (*e.g.,* SEQ ID NO:s 1, 2, 3, 4, 19 or 20) or a combination of such sequences.

[0028] In still further ~~aspect~~examples, an antibody or polypeptide of the ~~embodiment~~examples comprises one or more amino acid segments of the any of the amino acid sequences disclosed herein. For example, the antibody or polypeptide can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid segments comprising about, at least or at most 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 to 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 amino acids in length, including all values and ranges there between, that are at least 80, 85, 90, 95, 96, 97, 98, 99, or 100% identical to any of the amino acid sequences disclosed herein. In certain ~~aspect~~examples the amino segment(s) are selected from one of the amino acid sequences of an Olfml-3-binding antibody as provided in Table 1 (*e.g.,* SEQ ID NO:s 1, 2, 3, 4, 19 or 20).

[0029] In yet further ~~aspect~~examples, an antibody or polypeptide of the ~~embodiment~~examples comprises an amino acid segment that is at least 80, 85, 90, 95, 96, 97, 98, 99, or 100% identical (or any range derivable therein) to a V, VJ, VDJ, D, DJ, J or CDR domain of a Olfml-3-binding antibody (as provided in Table 1). For example, a polypeptide may comprise 1, 2 or 3 amino acid segment that are at least 80, 85, 90, 95, 96, 97, 98, 99, or 100%

17. The antibody of any one of claims 1-12, wherein the antibody is conjugated to an imaging agent, a chemotherapeutic agent, a toxin or a radionuclide.

18. A composition comprising an antibody of any one of claims 1-17 in a pharmaceutically acceptable carrier.

19. An isolated polynucleotide molecule comprising a nucleic acid sequence encoding an antibody of any one of claims 1-16.

20. A recombinant polypeptide comprising an antibody VH domain comprising CDRs 1-3 of the VH domain of 46A9BO (SEQ ID NOs: 7, 8 and 9); CDRs 1-3 of the VH domain of 9F8BO (SEQ ID NOs: 21, 22 and 23); or CDRs 1-3 of the VH domain of Z14A7 (SEQ ID NOs: 13, 14 and 15).

21. A recombinant polypeptide comprising an antibody VL domain comprising CDRs 1-3 of the VL domain of 46A9BO (SEQ ID NOs: 10, 11 and 12); CDRs 1-3 of the VL domain of 9F8BO (SEQ ID NOs: 24, 25 and 26); or CDRs 1-3 of the VL domain of Z14A7 (SEQ ID NOs: 16, 5 and 6).

22. An isolated polynucleotide molecule comprising a nucleic acid sequence encoding a polypeptide of claim 20 or 21.

23. A host cell comprising one or more polynucleotide molecule(s) encoding an antibody of any one of claims 1-12 or a recombinant polypeptide of claim 20 or 21.

24. The host cell of claim 23, wherein the host cell is a mammalian cell, a yeast cell, a bacterial cell, a ciliate cell or an insect cell.

25. A method of manufacturing an antibody comprising:

(a) expressing one or more polynucleotide molecule(s) encoding a VL and VH chain of an antibody of any one of claims 1-12 in a cell; and

(b) purifying the antibody from the cell.

26. Use of an antibody in accordance with any one of claims 1-17 in the manufacture of a medicament for~~A method of~~ treating an angiogenesis-related condition in a subject~~ comprising administering to the subject an amount of an antibody in accordance with any one of claims 1-17 that is effective to treat the angiogenesis-related condition~~.

27. The ~~method~~ use of claim 26, wherein the angiogenesis-related condition comprises cancer.

28. The ~~method~~ use of claim 27, wherein the cancer is a solid tumor, a metastatic tumor, or a non-metastatic tumor.

29. The ~~method~~ use of claim 27, wherein the cancer is a breast cancer, lung cancer, head & neck cancer, prostate cancer, esophageal cancer, tracheal cancer, skin cancer brain cancer, liver cancer, bladder cancer, stomach cancer, pancreatic cancer, ovarian cancer, uterine cancer, cervical cancer, testicular cancer, colon cancer, rectal cancer or skin cancer.

30. The ~~method~~ use of claim 26, wherein the antibody is to be administered systemically.

31. The ~~method~~ use of claim 26, wherein the antibody is to be administered intravenously, intradermally, intratumorally, intramuscularly, intraperitoneally, subcutaneously, or locally.

32. The ~~method~~ use of claim 26, further comprising ~~administering~~ at least a second anticancer therapy to be administered to the subject.

33. The ~~method~~ use of claim 32, wherein the second anticancer therapy is a surgical therapy, chemotherapy, radiation therapy, cryotherapy, hormonal therapy, immunotherapy or cytokine therapy.

34. The ~~method~~ use of claim 26, wherein the angiogenesis-related conditions is ocular neovascularization, arterio-venous malformations, coronary restenosis, peripheral vessel restenosis, glomerulonephritis, rheumatoid arthritis, pancreatitis, bowel diseases, ischemic cardiovascular pathologies, or chronic inflammatory diseases.

35. The ~~method~~ use of claim 26, wherein the subject is a human subject.

36. A composition comprising an antibody in accordance with any one of claims 1-17 for use in treating an angiogenesis-related condition in a subject.

37. The composition of claim 36, wherein the angiogenesis-related condition comprises cancer.

38. The composition of claim 37, wherein the cancer is a solid tumor, a metastatic tumor, or a non-metastatic tumor.

39. The composition of claim 37, wherein the cancer is a breast cancer, lung cancer, head & neck cancer, prostate cancer, esophageal cancer, tracheal cancer, skin cancer brain cancer, liver cancer, bladder cancer, stomach cancer, pancreatic cancer, ovarian cancer, uterine cancer, cervical cancer, testicular cancer, colon cancer, rectal cancer or skin cancer.

40. The composition of claim 36, wherein the composition is ~~for systemic administration~~to be administered systemically.

41. The composition of claim 36, wherein the composition is formulated to be administered intravenously, intradermally, intratumorally, intramuscularly, intraperitoneally, subcutaneously, or locally.

42. The composition of claim 36, further comprising at least a second anticancer agent.

43. The composition of claim 36, wherein the angiogenesis-related conditions is ocular neovascularization, arterio-venous malformations, coronary restenosis, peripheral vessel restenosis, glomerulonephritis, rheumatoid arthritis, pancreatitis, bowel diseases, ischemic cardiovascular pathologies, or a chronic inflammatory disease.

44. The composition of claim 36, wherein the subject is a human subject.

~~45. The use of an antibody in accordance with any one of claims 1-17 in the manufacture of a medicament for treating an angiogenesis-related condition.~~