SUMMARY OF THE INVENTION

[0004] The present invention fulfills an unresolved need in the art by providing methods and compositions for inhibiting, suppressing, blocking and/or eliminating angiogenesis and/or tumor metastasis. In certain examplembodiments, the compositions and/or methods may concern ligands for placenta growth factor-2 (PlGF), and/or ligands binding to both Flt-1 and PlGF. Such ligands may include, but are not limited to, peptides, antibodies, antibody fragments, humanized antibodies, chimeric antibodies, antibody analogs, aptamers, organic compounds and/or any other molecules or compounds known in the art that are ligands for PlGF.

[0005] In various examplembodiments, the P1GF ligands may be peptides. Methods for identifying peptides that bind to particular targets are well known in the art, including for example phage display techniques as discussed below. In phage display, libraries of peptides expressed on the surface of phage, such as filamentous bacteriophage, are created and may be screened by selection against the target(s) of interest. After one or more rounds of screening (panning) against the target, phage containing display peptides that bind to the target may be isolated and the peptide sequences determined, for example by sequencing of the peptide-encoding DNA inserts in the phage nucleic acid.

[0005a] In a first aspect, the present invention refers to a composition comprising a peptide P1GF (placenta growth factor) ligand, wherein the peptide comprises the sequence of BP-1 (SEQ ID NO: 1), BP-2 (SEQ ID NO: 2). BP-3 (SEQ ID NO: 3) or BP-4 (SEQ ID NO:4).

[0005b] In a second aspect, the present invention refers to the use of a peptide ligand that binds to P1GF in the manufacture of a medicament for treating a condition relating to angiogenesis, wherein said medicament inhibits angiogenesis, wherein said peptide comprises the sequence of BP-1 (SEQ ID NO:1), BP-2 (SEQ ID NO:2), BP-3 (SEQ ID NO:3) or BP-4 (SEQ ID NO:4).

[0005c] In a third aspect, the present invention refers to the use of a peptide ligand that binds to P1GF in the manufacture of a medicament for the treatment of cancer, wherein said peptide comprises the sequence of BP-1 (SEQ ID NO:1), BP-2 (SEQ ID NO:2), BP-3 (SEQ ID NO:3) or BP-4 (SEQ ID NO:4).

[0006] Other examplembodiments concern methods and/or compositions for treating subjects, such as subjects with cancer and/or with a condition related to angiogenesis (*e.g.*, macular degeneration, *etc.*). Subjects may include, but are not limited to, humans, animals, cats, dogs, cows, sheep, goats, horses, alpacas and mammals. The methods and compositions may comprise one or more PlGF ligands to be administered to a subject. In preferred examplembodiments, peptides identified as ligands by phage display against P1GF may be administered. Administration may be by any route known in the art, such as oral, nasal, buccal, inhalational, rectal, vaginal or topical. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal, intraarterial, intrathecal or intravenous injection. In preferred examplembodiments, the P1GF ligand (inhibitor) is orally administered. In more preferred examplembodiments, the P1GF ligand may comprise the sequence of (binding protein) BP-1, BP-2, BP-3 or BP-4, as disclosed in the Examples below.

[0007] The administration of PlGF ligands may be effective to inhibit or eliminate tumor metastasis, angiogenesis in solid tumors, tumor cell survival and/or tumor cell mobility. In preferred examplembodiments, administration of one or more P1GF ligands may prevent tumors from metastasizing or may result in regression or growth inhibition of existing tumors. The

skilled artisan will realize that one or more PlGF ligands may be administered alone or alternatively in conjunction with other known therapeutic treatments for cancer and/or angiogenesis, such as chemotherapy, radiation therapy, immunotherapy, anti-VEGF agents and/or other known anti-angiogenesis agents and the like. In some examplembodiments, the P1GF ligands may be administered with a bispecific antibody, with one binding site for the PlGF ligand and a second binding site for a tumor antigen or other target. In other examplembodiments, PlGF ligands may be covalently attached to or provided as a fusion protein with an antibody, antibody fragment, monoclonal antibody, Fc fragment, Fc-binding protein or antibody binding protein.

[0010] In alternative examplembodiments, P1GF ligands may be of use to treat angiogenesis related conditions besides cancer. Examples of conditions related to angiogenesis include, but are not limited to, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, sarcoidosis, asthma, edema, pulmonary hypertension, formation and development of tumors , psoriasis, diabetic retinopathy, macular degeneration, corneal graft rejection, neovascular glaucoma, myocardial angiogenesis, plaque neovascularization, restenosis, neointima formation after vascular trauma, telangiectasia, hemophiliac joints, angiofibroma, fibrosis associated with chronic inflammation, lung fibrosis, deep venous thrombosis and wound granulation.

[0011] In other alternative examplembodiments, the P1GF ligands disclosed herein may be used as targeting peptides, for example by conjugation with a complex or therapeutic agents. PlGF ligands, such as BP-1, BP-2, BP-3 and/or BP-4, may be covalently or non-covalently attached to various moieties by methods well known in the art, such as the use of covalent cross-linking reagents. Many such agents, such as carbodiimides, bisimidates, N-hydroxysuccinimide ester of suberic acid, dimethyl-3,3'-dithio-bispropionimidate, azidoglyoxal, 1,5-difluoro-2,4-(dinitrobenzene) and other cross-linkers of use for proteins and/or peptides are known and may be used. In various examplembodiments, P1GF ligands may be attached to antibodies, antibody fragments, chemotherapeutic agents, anti-angiogenic agents, pro-apoptosis agents, liposomes incorporating such agents or any other known therapeutic compound.

[0011a] In a fourth aspect, the present invention refers to a kit comprising a peptide P1GF ligand, wherein said peptide comprises the sequence of BP-1 (SEQ ID NO:1), BP-2 (SEQ ID NO:2), BP-3 (SEQ ID NO:3) or BP-4 (SEQ ID NO:4).

[0012] In still other examplembodiments, the P1GF ligands may be used as adjuncts for diagnosis and/or imaging purposes. For example, PlGF ligands may be tagged with any known contrast or detection agent or may be detected using any known methodologies, such as ELISA, etc. The PlGF ligands may be used *ex vivo*, for example by immunohistochemistry of tissue

CLAIMS

1. A composition comprising a peptide PlGF (placenta growth factor) ligand, wherein the peptide comprises the sequence of BP-1 (SEQ ID NO: 1), BP-2 (SEQ ID NO: 2), BP-3 (SEQ ID NO: 3) or BP-4 (SEQ ID NO:4).

2. The composition of claim 1, wherein the peptide comprises the sequence of BP-1 (SEQ ID NO: 1).

3. The composition of claim 1, wherein the peptide is in a linear or a cyclic conformation.

4. The composition of claim 3, wherein the peptide comprises a cysteine residue at each end of the peptide and the cysteine residues are bonded to each other to form a cyclic peptide.

5. The composition of claim 1, wherein the peptide binds to both PlGF and Flt-I (Fms-like tyrosine kinase receptor).

6. The composition of claim 5, wherein the peptide binds to the heparin binding sites on P1GF-2 and Flt-I.

7. The composition of claim 6, wherein the peptide inhibits heparin binding to PlGF and/or Flt-I.

8. The composition of claim 1, wherein the peptide is attached as a fusion protein to an Fc part of a monoclonal antibody or to a bispecific antibody which has a binding site for the tumour associated antigen VEGFR.

9. The composition of claim 8, wherein the PlGF ligand is a binding peptide and the binding peptide is covalently attached to an Fc fragment of an antibody, an Fc- binding protein or an antibody-binding fusion protein.

10. The composition of claim 9, wherein the PlGF ligand is attached to an Fc fragment of an antibody and the antibody is IgGl.