[0009] The formation of tumor's network of blood vessels, i.e. neovascularization, plays an essential role throughout tumor development by helping the tumor to grow and metastasize. Once a tumor lesion exceeds a few millimeters in diameter, hypoxia and nutrient deprivation triggers an "angiogenic switch." Tumor cells release vascular endothelial growth factor (VEGF), which stimulates the sprouting and proliferation of endothelial cells. Several anti-angiogenic therapies are now approved by the FDA for cancer, including the humanized functional-blocking antibody fragment against VEGF-A, Avastin (bevacizumab) and the tyrosine kinase inhibitors, sorafenib and sunitinib, which target several growth receptors. Thus, therapies controlling tumor-associated angiogenesis are a promising tactic in limiting cancer progression and metastasis.

[0010] Loss of the inner endothelial blood-retinal barrier and the resultant macular edema and damage are the major causes of eye disorder and blindness in the elderly population. At present, these conditions, also known as age-related macular degeneration (AMD), are incurable. In addition, the neovascular form of AMD is characterized by growth of the blood vessels from the choroid, which penetrate through Bruch's membrane into the subretinal area. Some effective therapies to stem the common underlying cause of neovascular AMD are limited with the objective of hindering the vision loss by destroying new vessels arising in the choroid. Although current treatments with intravitreal injection of corticosteroids and anti-VEGF agents are effective in delaying progression of eye disease, they do not completely eliminate the risk of blindness. Therefore, novel and more potent therapies or combinational therapy approaches for treating eye disorders and preventing vision loss are needed.

SUMMARY

[0011] Provided herein is an isolated peptide. The peptide may comprise KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3), a fragment thereof, or a variant thereof. The peptide may also consist of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3), a fragment thereof, or a variant thereof. The variant may comprise a conservative substitution. The variant may comprise any peptide sequence containing Ser/Thr-x-Ile-Pro sequence (SEQ ID NO: 5), minimal EB binding consensus motif sequence. The peptide may be conjugated to a fatty acid, i.e. myristoylated or linked to a carrier peptide. The carrier peptide may be antennapedia peptide (AP), antennapedia peptide, penetratin peptide, TAT, tranportan or polyarginine. The peptide may be part of a pharmaceutical formulation, which may include a pharmaceutically acceptable excipient.

[0011a] In one aspect, the present invention refers to the use of an isolated peptide for the preparation of a medicament for the inhibition of angiogenesis in a patient in need, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3).

[0011b] In another aspect, the present invention refers to the use of an isolated peptide for the preparation of a medicament for the inhibition of angiogenesis in a patient in need, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3), wherein the peptide, or a fragments thereof, reduces the interaction between End Binding Protein 3 (EB3) and Inositol 1,4,5-Trisphosphate Receptor Type 3 (IP3R3).

[0012] The disclosure provides for methods of inhibiting angiogenesis comprising administering to a patient in need thereof an isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof. The methods include administering a therapeutically effective amount of a peptide of the disclosure, such as an amount effective to inhibit angiogenesis. In addition, the methods include administering pharmaceutical compositions comprising a therapeutically effective amount of a peptide of the disclosure. The disclosure provides for a method of treatment in which the patient in need is suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0013] The disclosure also provides for methods of treating a disorder associated with VEGF-induced vascular permeability comprising administering to a patient in need thereof an isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof. The methods include administering a therapeutically effective amount of a peptide of the disclosure , such as an amount effective to inhibit VEGF-induced vascular permeability. In addition, the methods include administering pharmaceutical compositions comprising a therapeutically effective amount of a peptide of the disclosure. The disclosure provides for a method of treatment in which the patient in need is suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0014] In any of the foregoing methods, the peptide administered may be linked to a carrier peptide such as antennapedia peptide (AP), antennapedia peptide, penetratin peptide,

TAT, tranportan or polyarginine. In addition, in any of the foregoing methods, the peptide administered may be conjugated to a fatty acid, e.g. myristoylated.

[0015] In any of the foregoing a methods, the isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof is administered in combination with one or more VEGF inhibitors, wherein "VEGF inhibitors" refer to anti-VEGF antibodies and fragments thereof, anti-VEGF receptor (anti-VEGFR) antibodies and fragments thereof, antagonistic peptides and small molecules which inhibit the activity or signaling pathway of VEGF and/or VEGFR. Exemplary VEGF inhibitors include Bevacizumab (Avastin), Ranibizumab (Lucentis), Pegaptanib (Macugen), Aflibercept (Eylea), Sorafenib (Nexvar), Sunitinib (Sutent), Pazopanib (Votrient), Axitinib (Inlyta), PTK787/ZK222584, ZD-6474, SU6668, PD-547,632, VEGF-Trap, CEP-7055, NM-3, or SU11248.

[0016] In any of the foregoing methods of the disclosure, the isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof may be administered in combination with laser treatment for eye disease, wherein "eye disease" refers to visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0017] In any of the foregoing methods of the disclosure, the isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof may be administered in combination with a steroid or any current method treatment for eye disease.

[0018] In addition, in any of the methods of the disclosure, the isolated peptide of the disclosure, VEGF inhibitor, steroid or any other treatment may be administered by intravitreal injection or topically such as in the form of an eye drop.

[0019] The disclosure also provides for an use of an isolated peptide for the preparation of a medicament for the inhibition of angiogenesis in a patient in need, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ

ID NO: 3) or a fragments thereof. The uses of the disclosure include use of the isolated peptide of the disclosure for the preparation of a medicament comprising a therapeutically effective amount of a peptide of the disclosure, such as an amount effective to inhibit angiogenesis. In addition, the disclosure provides for us of the isolated peptide of the disclosure for the preparation of a medicament comprising a composition comprising a therapeutically effective amount of a peptide of the disclosure. The disclosure provides use of the isolated peptide of the disclosure for the preparation of a medicament to administer to a suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0020] The disclosure also provides for the use of an isolated peptide for the preparation of a medicament for the treatment of a VEGF-induced vascular disorder, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof. The uses of the disclosure include use of the isolated peptide of the disclosure for the preparation of a medicament comprising a therapeutically effective amount of a peptide of the disclosure, such as an amount effective to inhibit VEGF-induced vascular permeability. In addition, the disclosure provides for us of the isolated peptide of the disclosure for the preparation of a medicament comprising a composition comprising a therapeutically effective amount of a peptide of the disclosure. The disclosure provides for use of the peptide of the disclosure for the preparation of a medicament to administer to a subject suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0021] In any of the foregoing uses of the disclosure, the isolated peptide administered may be linked to a carrier peptide such as antennapedia peptide (AP), antennapedia peptide, penetratin peptide, TAT, tranportan or polyarginine. In addition, in any of the foregoing methods, the isolated peptide administered may be conjugated to a fatty acid, e.g. myristoylated.

[0022] In any of the foregoing uses, the isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof is administered in combination with one or more VEGF inhibitors, wherein "VEGF inhibitors" refer to anti-VEGF antibodies and fragments thereof, anti-VEGFR antibodies and fragments thereof, antagonistic peptides and small molecules which inhibit the activity or signaling pathway of VEGF or VEGFR. Exemplary VEGF inhibitors include Bevacizumab (Avastin), Ranibizumab (Lucentis), Pegaptanib (Macugen), Aflibercept (Eylea), Sorafenib (Nexvar), Sunitinib (Sutent), Pazopanib (Votrient), Axitinib (Inlyta), PTK787/ZK222584, ZD-6474, SU6668, PD-547,632, VEGF-Trap, CEP-7055, NM-3, or SU11248.

[0023] In any of the foregoing uses of the disclosure, the medicament comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or fragments thereof may be administered in combination with laser treatment for eye disease, wherein "eye disease" refers to visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0024] In any of the foregoing uses of the disclosure, the medicament may be administered in combination with a steroid or any current method of treatment for eye disease.

[0025] In addition, in any of the uses of the disclosure, the medicament may be administered by intravitreal injection or topically such as in the form of an eye drop.

[0026] The disclosure provides for an isolated peptide for the inhibition of angiogenesis, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof.

[0027] The disclosure also provides for a composition comprising a therapeutically effective amount of a peptide of the disclosure for the inhibition of angiogenesis. The disclosure provides for an isolated peptide or a composition comprising a therapeutically effective amount of the peptide for inhibition of angiogenesis in a subject a suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0028] The disclosure also provides for an isolated peptide for use in inhibition of angiogenesis in a patient suffering from a disorder associated with VEGF-induced vascular permeability wherein the isolated peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO:1), FTEIPTI (SEQ ID NO: 3) or a fragments thereof.

[0029] The disclosure also provide for a composition comprising a therapeutically effective amount of an isolated peptide of the disclosure for the inhibition of VEGF-induced vascular permeability. The disclosure provides for an isolated peptide or a composition comprising a therapeutically effective amount of the peptide for inhibition of VEGF-induced permeability in a subject a suffering from cancer or a disorder associated with VEGF-induced permeability, such as visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0030] The disclosure also provides for an isolated peptide for the treatment for a disorder associated with VEGF-induced vascular permeability. For example, the VEGF associated vascular disorder is visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of

prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0031] Any of the peptides of the disclosure are used for inhibiting angiogenesis or for treating a disorder associated with VEGF-induced vascular permeability may be linked to a carrier peptide such as antennapedia peptide (AP), antennapedia peptide, penetratin peptide, TAT, tranportan or polyarginine. In addition, any of the isolated peptides of the disclosure for use in inhibiting angiogenesis or treating a disorder associated with VEGF-induced vascular permeability may be conjugated to a fatty acid, e.g. myristoylated.

[0032] Any of the isolated peptides or compositions of the disclosure may be administered in combination with one or more VEGF inhibitors, wherein "VEGF inhbitors" refer to s anti-VEGF antibodies and fragments thereof, anti-VEGFR antibodies and fragments thereof, antagonistic peptides and small molecules that inhibit the activity or signaling pathway of VEGF or VEGFR. Exemplary VEGF inhibitors include Bevacizumab (Avastin), Ranibizumab (Lucentis), Pegaptanib (Macugen), Aflibercept (Eylea), Sorafenib (Nexvar), Sunitinib (Sutent), Pazopanib (Votrient), Axitinib (Inlyta), PTK787/ZK222584, ZD-6474, SU6668, PD-547,632, VEGF-Trap, CEP-7055, NM-3, or SU11248. In addition, the peptide or the VEGFR is administered by intravitreal injection or topically such as in the form of an eye drop.

[0033] Any of the isolated peptides or compositions of the disclosure may be administered in combination with laser treatment for eye disease wherein "eye disease" refers to visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

[0034] The isolated peptides or compositions of the disclosure may be administered in combination with a steroid or any current method treatment for eye disease.

[0035] In addition, the isolated peptides or compositions of the disclosure may be administered by intravitreal injection or topically such as in the form of an eye drop.

BRIEF DESCRIPTION OF DRAWING

[0036] **Figure 1** shows the role of EB3 in inflammatory-induced hyper-permeability of endothelial barrier. EB3 establishes transient interactions of growing MT ends with the IP_3R_3, sensitizes the IP_3R_3 and positively regulates both Ca^{2+}release from stores and SOC-dependent Ca^{2+}entry during inflammation. This results in amplification of Ca^{2+}signaling and increased permeability through PKCα-mediated phosphorylation of p120-catenin and acto-myosin contractility.

[0037] **Figure 2** shows an alignment of human IP_3 receptors (794-814 aa of IP_3R_3 type 3) with EB binding motif (highlighted). The IP_3R_3 peptide (SEQ ID NO: 1) is shown below the alignment.

[0038] **Figure 3** shows a ribbon representation of EB3 structure (magenta) and IP_3R_3 derived peptide (SEQ ID NO: 1) docked into EB3 hydrophobic binding groove of EB3; 180° rotation is shown. The IP_3R_3 derivative peptide was docked using a Z-Dock program in conjunction with Discovery Studio 3.0 software. The binding energy between the peptide and EB3 was calculated to be -68.882 kcal/mol.

[0039] **Figure 4** shows IP_3R_3 peptide (SEQ ID NO: 1) inhibits Ca^{2+}release from ER in response to PAR-1 activation. A. HMVECs pre-treated with AP-attached IP_3R_3 peptide or control (AP) peptide were loaded with Fura 2-AM and 340/380 ratio was calculated after stimulation of cells with thrombin (50 nM) in the absence and in the presence of extracellular Ca^{2+}. Arrow, time of thrombin addition. B. Plot shows the mean ±SD for thrombin-induced Ca^{2+}release and entry calculated as a maximum increase over the basal value. The increase is normalized to control non-treated cells from the same experiment (n=4).

[0040] **Figure 5** shows a ribbon representation of EB3 in the complex with EBIN (SEQ ID NO: 3) and IP_3R_3 peptide (SEQ ID NO: 1). The computed binding energy is -68.882 and -60.251 for IPR and EBIN, respectively.

[0041] **Figure 6A-6B** Panel A shows subcuteanous vascular leakage of albumin-bound Evans Blue Dye, which was induced by intradermal injection of VEGF, and Panel B quantifies the vascular leakage as measured spectrophotometrically at 620nm.

What is Claimed:

1. Use of an isolated peptide for the preparation of a medicament for the inhibition of angiogenesis in a patient in need, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3).

2. The use of claim 1 where the patient is suffering from a disorder associated with VEGF-induced permeability or cancer.

3. The use of claim 1 wherein the patient is suffering from visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

4. The use of any one of claims 1-3 wherein the peptide is linked to a carrier peptide.

5. The use of claim 4 wherein the carrier peptide is antennapedia peptide (AP), antennapedia peptide, penetratin peptide, TAT, tranportan or polyarginine.

6. The use of claim any one of claims 1-5, wherein the peptide is conjugated to a fatty acid.

7. The use of claim 6, wherein the peptide is myristoylated.

8. The use of any one of claims 1-7, wherein the isolated peptide is to be administered in combination with one or more VEGF inhibitors.

9. The use of any one of claims 1-7, wherein the isolated peptide is to be administered in combination with laser treatment of eye disease.

10. The use of any one of claims 1-7, wherein the isolated peptide is to be administered in combination with a steroid.

11. The use of any one of claims 1-10, wherein the isolated peptide, VEGF inhibitor or steroid is to be delivered via intravitreal injection or topically.

12. Use of an isolated peptide for the preparation of a medicament for the inhibition of angiogenesis in a patient in need, wherein the peptide comprises the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1), FTEIPTI (SEQ ID NO: 3), wherein the peptide, or a fragments thereof, reduces the interaction between End Binding Protein 3 (EB3) and Inositol 1,4,5-Trisphosphate Receptor Type 3 (IP3R3).

13. The use of claim 12, where the patient is suffering from a disorder associated with VEGF-induced permeability or cancer.

14. The use of claim 12, wherein the patient is suffering from visual impairment or vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal venin occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis and corneal graft neovascularization.

15. The use of any one of claims 12-14 wherein the peptide is linked to a carrier peptide.

16. The use of claim 15 wherein the carrier peptide is antennapedia peptide (AP), antennapedia peptide, penetratin peptide, TAT, tranportan or polyarginine.

17. The use of claim any one of claims 12-16, wherein the peptide is conjugated to a fatty acid.

18. The use of claim 17, wherein the peptide is myristoylated.

19. The use of any one of claims 12-18, wherein the isolated peptide or a fragment thereof is to be administered in combination with one or more VEGF inhibitors.

20. The use of any one of claims 12-18, wherein the isolated peptide or fragment thereof is to be administered in combination with laser treatment of eye disease.

21. The use of any one of claims 12-18, wherein the isolated peptide or fragment thereof is to be administered in combination with a steroid.

22. The use of any one of claims 12-20, wherein the isolated peptide, VEGF inhibitor or steroid is to be delivered via intravitreal injection or topically.