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(54) Titre : COMPOSITIONS ET PROCEDES POUR LE TRAITEMENT DE MALADIE OCULAIRE
(54) Title: COMPOSITIONS AND METHODS FOR TREATING OCULAR DISEASE

(57) Abrégé/Abstract:
In various aspects and embodiments, the invention provides methods and pharmaceutical compositions for treating ocular disease, including ocular disease involving ocular vascular permeability or ocular inflammation. In various aspects and embodiments, the invention comprises administering about 1 µg to about 1 mg of collagen IV-derived biomimetic peptide or salt thereof to a patient by intraocular injection. Injections are provided at a frequency of from about monthly to about once every two years. In various embodiments, the methods and compositions provide for potent action and long duration of action, with infrequent intravitreal injections of a small volume.

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(54) Title: COMPOSITIONS AND METHODS FOR TREATING OCULAR DISEASE

(57) Abstract: In various aspects and embodiments, the invention provides methods and pharmaceutical compositions for treating ocular disease, including ocular disease involving ocular vascular permeability or ocular inflammation. In various aspects and embodiments, the invention comprises administering about 1 μg to about 1 mg of collagen IV-derived biomimetic peptide or salt thereof to a patient by intraocular injection. Injections are provided at a frequency of from about monthly to about once every two years. In various embodiments, the methods and compositions provide for potent action and long duration of action, with infrequent intravitreal injections of a small volume.

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COMPOSITIONS AND METHODS FOR TREATING OCULAR DISEASE

PRIORITY

This application claims priority to, and the benefit of, US Provisional Application No. 62/824,017, filed March 26, 2019, which is hereby incorporated by reference in its entirety.

BACKGROUND

Diabetic macular edema (DME) and wet age-related macular degeneration (AMD) are the leading causes of blindness among adults. Progression of AMD leads to erosion of central vision, which is necessary for day-to-day activities such as reading, driving and identifying faces. While dry AMD leads to a gradual loss of vision, wet AMD leads to faster vision loss and is the most advanced form of the disease.

The introduction of injectable vascular endothelial growth factor (anti-VEGF) inhibitors (anti-VEGF drugs) has substantially lowered the incidence of AMD-related blindness, and allows many patients to maintain vision. These anti-VEGF drugs include ranibizumab (LUCENTIS) and aflibercept (EYLEA). During treatment, the ophthalmologist places anesthetic and antiseptic drops on the eye, then administers the anti-VEGF drug by injection into the vitreous (e.g., near the retina at the back of the eye). The recommended frequency of these injections varies from every few weeks to every few months. Patients often require multiple doses over the course of a few months, and repeat treatments are needed for continued benefit. The cost per treatment can be very high, around $2000 per injection in the U.S. Further, potential complications of intravitreal injection include infection (such as that caused by *Streptococcus endophthalmitis*), retinal detachment, ocular hypertension, cataracts, inflammation, and others.

Accordingly, potent, safe, and patient-friendly therapies for eye disease, including retinal disease such as wet AMD and diabetic macular edema, are desirable.

SUMMARY OF ASPECTS OF THE INVENTION

In various aspects and embodiments, the invention provides methods and pharmaceutical compositions for treating ocular disease, including retinal diseases involving vascular permeability and/or inflammation. In various aspects and embodiments, the invention comprises administering about 1 μg to about 1 mg of a collagen IV-derived biomimetic peptide or salt thereof to a patient by intraocular injection. Injections are provided at a frequency of from about monthly to no more frequent than about once every two years. As disclosed herein, the peptides form a clear gel upon intraocular injection, and provide a sustained release over an extended period, with a surprisingly small amount of active agent. Accordingly, the peptide can provide for potent action and long duration of action, with infrequent intravitreal injections of a small volume.

An exemplary collagen-IV-derived biomimetic peptide comprises, consists of, or consists essentially of the amino acid sequence LRRFSTAPFAFIDINDVINF (SEQ ID NO:1). The collagen IV-derived biomimetic peptides promote the Tie2 agonist activities of Angiopoietin 2 (Ang2), thereby stabilizing vasculature. The peptides target and disrupt α5β1 and αVβ3 integrins, and inhibit signaling through multiple receptors, including vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGFR), insulin-like growth factor receptor (IGFR), and epidermal growth factor receptor (EGFR). The peptide of SEQ ID NO:1 is referred to herein as AXT107.

In some embodiments, the peptide or salt thereof is administered to a patient having a condition selected from diabetic macular edema, retinal vein occlusion, AMD (e.g., wet AMD), or background diabetic retinopathy. In some embodiments, the patient has acute or chronic inflammation of the eye. In some embodiments, the patient has uveitis or an autoimmune or inflammatory condition that manifests in the eye.

In various embodiments of the invention, about 1 mg or less of the collagen IV-derived biomimetic peptide, or salt thereof, is administered by intraocular injection. For example, the collagen IV-derived biomimetic peptide, or salt thereof, is administered at a dose of about 800 μg or less, or about 500 μg or less, or about 250 μg or less (e.g., from 50 to 150 μg) per intraocular injection. The small amount of active agent provides a surprisingly

long duration of action, which substantially reduces the frequency of required injections. For example, the peptide or salt thereof may be administered by intraocular injection no more frequently than about once every three months, or no more frequently than about once every four months, or no more frequently than about once every six months, or no more frequently than about once every eight months, or no more frequently than about once every year, or no more frequently than about once every 1.5 years, or no more frequently than about once every two years, or no more frequently than about once every three years.

Further, in accordance with the invention, the peptide is delivered without the use of advanced formulation technologies (e.g., particle encapsulation), such as nanoparticle or microparticle encapsulation, or liposome encapsulation. That is, the peptide is delivered without any encapsulation technology (e.g., the peptide is delivered as a "naked peptide" in aqueous solution). The physical properties of the peptide, which are observed to form a clear gel in the vitreous, are sufficient for potent and long duration of action.

In various embodiments, the peptide can be delivered for conditions (including macular edema, wet AMD) that are refractory or only partially-responsive to vascular endothelial growth factor (VEGF) blockade or inhibitor therapy.

In other aspects, the invention provides pharmaceutical compositions suitable for intravitreal injection. The pharmaceutical compositions comprise about 1 μg to about 1 mg of a collagen IV-derived biomimetic peptide or salt thereof (as disclosed herein) as a unit dose in a pre-filled syringe. For example, the unit dose may be about 700 μg or less of the peptide or salt thereof, or about 500 μg or less of the peptide or salt thereof, or about 250 μg or less of the peptide or salt thereof, or about 100 μg or less of the peptide or salt thereof. An exemplary composition comprises a dose of from 50 to 150 μg of peptide (e.g., about 100 μg).

Other aspects and embodiments of the invention will be apparent from the following detailed description.

DESCRIPTION OF THE FIGURES

FIGURE 1A and FIGURE 1B are graphs showing AXT107 inhibition of VEGF-induced vascular leakage by dosing of 100 μg of AXT107 (FIGURE 1A) and 500 μg of

AXT107 (FIGURE 1B) over 12 Months in Dutch-Belted Rabbits. The "VEGF" bar indicates the no AXT107 control and is used to indicate the leakage that occurs in the absence of treatment with AXT107.

FIGURE 2 are graphs showing the amounts of AXT107 expressed as nanograms per gram (ng/g) that are present in the retina of Dutch-Belted Rabbits at various time points after intravitreal administration. AXT107 is found at significant levels in the retina 225, 271, and 315 days after a single injection.

FIGURE 3 is an image showing that AXT107 forms a gel upon injection in the rabbit eye. The gel remains below the visual axis, and does not block either the visual axis or the optic nerve.

FIG. 4 shows images of the gel over 301 days for AXT107 doses of 100 μg, 250 μg, 500 μg, and 1000 μg after a single injection.

FIGURE 5 is a graph showing the release of AXT107 from gels at 100 μg, 250 μg, 500 μg, and 1000 μg over time. Dashed lines show an estimate of the AXT107 levels through 361 days.

FIGURE 6 is an image showing AXT107 gel formation in human vitreous of different ages.

FIGURE 7 are images showing gels formed by AXT107 in the rabbit eye from AXT107 PK toxicology study of different doses from Dutch-Belted necropsy rabbits at 6 Months after administration. Arrows point to isolated AXT107 gels.

DETAILED DESCRIPTION OF THE INVENTION

In various aspects and embodiments, the invention provides methods and pharmaceutical compositions for treating ocular disease, including retinal diseases involving vascular permeability and/or inflammation. In various aspects and embodiments, the invention comprises administering about 1 μg to about 1 mg of a collagen IV-derived biomimetic peptide or salt thereof to a patient by intraocular injection. Injections are provided at a frequency of from about monthly to no more than about once every two years. As disclosed herein, the peptides form a gel upon intraocular injection, and provide a

sustained release over an extended period, with a surprisingly small amount of active agent. Accordingly, the peptide can provide for potent action and long duration of action, with infrequent intravitreal injections of a small volume.

In accordance with aspects of the invention, the active agent is a collagen IV-derived biomimetic peptide that promotes the Tie2 agonist activities of Angiopoietin 2 (Ang2), thereby stabilizing vasculature and providing anti-inflammatory action. See WO 2018/067646, which is hereby incorporated by reference in its entirety.

The collagen IV-derived biomimetic peptides are derived from the α5 fibril of type IV collagen. Exemplary peptides comprise, consist of, or consist essentially of the amino acid sequence LRRFSTAPFAFIDINDVINF (SEQ ID NO:1), or derivatives thereof. The peptides target and disrupt α5β1 and αVβ3 integrins, and inhibit signaling through multiple receptors, including vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGFR), insulin-like growth factor receptor (IGFR), and epidermal growth factor receptor (EGFR). The peptide of SEQ ID NO:1 is referred to herein as AXT107.

Collagen IV-derived biomimetic peptides further include those described in US 9,056,923 and US 9,802,984, which are hereby incorporated by reference in their entireties. For example, peptides in accordance with the following disclosure include peptides comprising the amino acid sequence LRRFSTXPXXXXNINNVXNF (SEQ ID NO:2), where X is a standard amino acid or non-genetically encoded amino acid. In some embodiments, X at position 7 is M, A, or G; X at position 9 is F, A, Y, or G; X at position 10 is M, A, G, D-Alanine (dA), or norleucine (Nle); X at position 11 is F, A, Y, G, or 4-chlorophenylalanine (4-ClPhe); X at position 12 and position 18 are independently selected from 2-Aminobutyric acid (Abu), G, S, A, V, T, I, L, or Allylglycine (AllylGly). In various embodiments, the peptide contains about 30 amino acids or less, or about 25 amino acids of less, or about 24 amino acids, or about 23 amino acids, or about 22 amino acids, or about 21 amino acids, or about 20 amino acids. In still other embodiments, one, two, three, four, or five amino acids of SEQ ID NO:2 are deleted. In some embodiments, the peptide comprises or consists of the amino acid sequence LRRFSTAPFAFININNVINF (SEQ ID NO:3).

In some embodiments, the peptide comprises the amino acid sequence LRRFSTAPFAFIDINDVINF (SEQ ID NO:1), or derivative thereof. Derivatives of the peptide of SEQ ID NO:1 include peptides having from 1 to 5 amino acid substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acid substitutions, insertions, or deletions collectively) with respect to SEQ ID NO:1, although in some embodiments the Asp at positions 13 and 16 are maintained. In some embodiments, the sequence DINDV is maintained in the derivative. The peptide may have the amino acid sequence of LRRFSTXPXXXXDINDVXNF, where X is a standard amino acid or non-genetically encoded amino acid (SEQ ID NO:4). In some embodiments, X at position 7 is M, A, or G; X at position 9 is F, A, Y, or G; X at position 10 is M, A, G, D-Alanine (dA), or norleucine (Nle); X at position 11 is F, A, Y, G, or 4-chlorophenylalanine (4-ClPhe); X at position 12 and position 18 are independently selected from 2-Aminobutyric acid (Abu), G, S, A, V, T, I, L, or Allylglycine (AllylGly). In various embodiments, the peptide contains about 30 amino acids or less, or about 25 amino acids of less, or about 24 amino acids, or about 23 amino acids, or about 22 amino acids, or about 21 amino acids, or about 20 amino acids. In still other embodiments, one, two, three, four, or five amino acids of SEQ ID NO:4 or SEQ ID NO:1 are deleted.

In some embodiments, amino acid substitutions are made at any position of a peptide of SEQ ID NO:1 or 3, which can be independently selected from conservative or non-conservative substitutions. In these or other embodiments, the peptide includes from 1 to 10 amino acids added to one or both termini (collectively). The N- and/or C-termini may optionally be occupied by another chemical group (other than amine or carboxy, *e.g.*, amide or thiol).

Conservative substitutions may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 genetically encoded amino acids can be grouped into the following six standard amino acid groups:

(1) hydrophobic: Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro; and

(6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices. Some preferred conservative substitutions within the above six groups are exchanges within the following sub-groups: (i) Ala, Val, Leu and Ile; (ii) Ser and Thr; (iii) Asn and Gln; (iv) Lys and Arg; and (v) Tyr and Phe.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the biomimetic peptide or peptide agent is a peptide of from about 8 to about 30 amino acids, or from about 10 to about 20 amino acids, and has at least 4, at least 5, or at least 6 contiguous amino acids of SEQ ID NO: 1 or 3. In some embodiments, the peptide contains at least one, at least two, or at least three d-amino acids. In some embodiments, the peptide contains from one to about five (*e.g.*, 1, 2, or 3) non-genetically encoded amino acids, which are optionally selected from 2-Aminobutyric acid (Abu), norleucine (Nle), 4-chlorophenylalanine (4-ClPhe), and Allylglycine (AllylGly).

Exemplary biomimetic peptides in accordance with the disclosure include:

LRRFSTMPFMF(Abu)NINNV(Abu)NF (SEQ ID NO:5),

LRRFSTMPAMF(Abu)NINNV(Abu)NF (SEQ ID NO:6),

LRRFSTMPFAF(Abu)NINNV(Abu)NF (SEQ ID NO:7),

LRRFSTMPFMA(Abu)NINNV(Abu)NF (SEQ ID NO:8),

LRRFSTMPF(Nle)F(Abu)NINNV(Abu)NF (SEQ ID NO:9),

LRRFSTMPFM(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:10),

LRRFSTMPFMFSNINNVSNF (SEQ ID NO:11),

LRRFSTMPFMFANINNVANF (SEQ ID NO:12),

LRRFSTMPFMFININNVINF (SEQ ID NO:13),

LRRFSTMPFMFTNINNVTNF (SEQ ID NO:14),

LRRFSTMPFMF(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:15),

LRRFSTMPFMFVNINNVVNF (SEQ ID NO:16),

LRRFSTMPFdAFININNVINF (SEQ ID NO:17),

LRRFSTMPFAFININNVINF (SEQ ID NO:18),

LRRFSTAPFAFININNVINF (SEQ ID NO:19),

LRRFSTAPFdAFIDINDVINF (SEQ ID NO:20),

LRRFSTAPFAFIDINDVINW (SEQ ID NO:21),

dLRRdLRRFSTAPFAFIDINDVINF (SEQ ID NO:22),

LRRFSTAPFAFIDINDVINdF (SEQ ID NO:23),

dLRRFSTAPFAFIDINDVINdF (SEQ ID NO:24).

F(Abu)NINNV(Abu)N (SEQ ID NO:25),

FTNINNVTN (SEQ ID NO:26),

FININNVINF (SEQ ID NO:27),

FSNINNVSNF (SEQ ID NO:28),

FANINNVANF (SEQ ID NO:29),

F(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:30),

FVNINNVVNF (SEQ ID NO:31),

FIDINDVINF (SEQ ID NO:32),

FIDINDVINW (SEQ ID NO:33),

FTDINDVTN (SEQ ID NO:34),

A(Abu)NINNV(Abu)NF (SEQ ID NO:35), or

(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:36).

In various embodiments, the biomimetic peptide forms a gel in human vitreous.

In some embodiments, the peptide or salt thereof is administered to a patient having a condition selected from diabetic macular edema, retinal vein occlusion, AMD (e.g., wet AMD), or background diabetic retinopathy. In some embodiments, the patient has acute or chronic inflammation of the eye. In some embodiments, the patient has uveitis or an autoimmune or inflammatory condition that manifests in the eye.

In some embodiments, the patient has macular edema. Macular edema occurs when fluid and protein deposits collect on or under the macula of the eye (a yellow central area of the retina) and causes it to thicken and swell. The causes of macular edema include chronic or uncontrolled diabetes type 2 (*e.g.,* diabetic retinopathy), in which peripheral blood vessels including those of the retina leak fluid into the retina. Other causes and/or associated disorders include age-related macular degeneration (AMD), chronic uveitis, atherosclerosis, high blood pressure and glaucoma. In some embodiments, the patient has or is at risk of retinal vein occlusion, which can lead to severe damage to the retina and blindness, due to ischemia and edema.

In some embodiments, the patient has AMD, which is optionally wet AMD or in some embodiments dry AMD.

The present invention in various embodiments provides for treatment of retinal disease with intravitreal injections of a collagen IV-derived biomimetic peptide, which only requires a small amount of active agent to be administered with infrequent injections. Generally, an intravitreal injection is an injection into the eye, and in particular the vitreous which is a jelly-like fluid that fills the eye. During the procedure, for example as is used conventionally for administering anti-VEGF drugs, the health care provider injects medicine into the vitreous, near the retina at the back of the eye. The procedure often takes about 15 to 30 minutes. For example, the procedure generally involves placing drops in the eyes to dilate the pupils, numbing drops are placed in the eye, and drug is injected into the eye with a small needle. Antibiotic drops may also be used to prevent infection. While the procedure is routine, it does not come without risks and potential complications. These include endophthalmitis, intraocular inflammation, retinal detachment, intraocular pressure elevation, ocular hemorrhage, in addition to systemic side effects. See, Falavarjani KG and Nguyen QD, Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature, *Eye* 2013 Jul; 27(7): 787–794. Further, the procedure for administering conventional anti-VEGF drugs is costly and not convenient since frequent injections are generally required.

In various embodiments of the invention, about 1 mg or less of the collagen IV-derived biomimetic peptide, or salt thereof, is administered by intraocular injection. In various embodiments, the unit dose of peptide is administered at the bottom of the eye, such as between 5:00 and 7:00, so that gel forms at the bottom. For example, the collagen IV-derived biomimetic peptide, or salt thereof, is administered at a dose of from about 25 μg to about 1000 μg. For example, about 800 μg or less, or about 700 μg or less, or about 500 μg or less, or about 250 μg or less, or about 100 μg or less of the peptide or salt thereof is administered per intraocular injection. In such embodiments, at least about 25 μg or at least about 50 μg is administered per intraocular injection. In some embodiments, the unit dose is greater than 1 mg, such as from 1 mg to about 2 mg. The small amount of active agent provides a surprisingly long duration of action, which substantially reduces the frequency of required injections. For example, the peptide or salt thereof may be administered by intraocular injection no more frequently than about once every three months, or no more frequently than about once every four months, or no more frequently than about once every

six months, or no more frequently than about once every eight months, or no more frequently than about once every year, or no more frequently than about once every 1.5 years, or no more frequently than about once every two years, or no more frequently than about once every three years.

Further, in accordance with the invention, the peptide is delivered without the use of advanced formulation technologies (e.g., particle encapsulation), such as nanoparticle or microparticle encapsulation, or liposome encapsulation. That is, the peptide is delivered without any encapsulation technology (e.g., the peptide is delivered as a "naked peptide" in aqueous solution). The physical properties of the peptide, which are observed to form a gel in the vitreous, are sufficient for potent and long duration of action.

Unless specifically stated or obvious from context, as used herein, the term "about" includes values within plus or minus 10% of a stated value.

In various embodiments, about 10 μg to about 50 μg of the collagen IV-derived biomimetic peptide, or salt thereof, is administered per intraocular injection, and at a frequency of about once per month or about once every other month. For example, about 25 μg of the peptide or salt thereof may be administered by intraocular injection about monthly. Alternatively, about 50 μg to about 150 μg per intraocular injection is administered at a frequency of no more than about once every third month, or no more frequently than about once every fourth month, or no more frequently than about once every six months. For example, the peptide or salt thereof may be administered at about 50 μg and at a frequency of about once every three or four months. In some embodiments, the peptide or salt thereof is administered at about 100 μg to about 150 μg per injection, and at a frequency of about once every five to seven months, and optionally about once every six months. In some embodiments, the dose of 100 to 150 μg is administered about once every eight months or about once every nine months.

In other embodiments, the amount of active agent delivered per injection is increased, providing unexpected durations of action. For example, the collagen IV-derived biomimetic peptide or salt thereof may be administered at about 150 μg to about 250 μg per intraocular injection, and at a frequency of no more than about once every six months. For example, in these embodiments, the peptide or salt thereof may be administered no more frequently than

about once every eight months. In some embodiments, the peptide or salt thereof is administered no more frequently than about once every ten months or about once every twelve months. In some embodiments, the peptide or salt thereof is administered at about 200 μg and at a frequency of about once every six to eight months. In some embodiments, the peptide or salt thereof is administered at about 250 μg and at a frequency of about once every six to twelve months.

In still other embodiments, the peptide or salt thereof is administered at from about 250 μg to about 1 mg per intraocular injection, and at a frequency of no more than about once every six months. In these embodiments, the peptide or salt thereof is administered at about 300 μg to about 700 μg per injection, or is administered at about 400 μg to about 700 μg per injection, or is administered at about 500 μg to about 700 μg per injection, or is administered at about 600 μg to about 700 μg per injection. In some embodiments, the peptide or salt thereof is administered at a frequency of about once every six to twelve months. For example, the peptide or salt thereof is administered about once every seven months, about once every eight months, about once every nine months, about once every ten months, about once every eleven months, or about once every twelve months, or about once every 18 months.

In still further embodiments, the peptide or salt thereof is administered at from about 700 μg to about 1 mg per intraocular injection, and at a frequency of no more than once every twelve months or no more than once every 15 months. In some embodiments, the peptide or salt thereof is administered at about 800 μg to about 1 mg per injection, or is administered at about 900 μg to about 1 mg per injection, or is administered at a frequency of once every twelve to eighteen months. In some embodiments, the peptide or salt thereof is administered about once every two years or about once every three years.

In some embodiments, the peptide dosed as described above, is the peptide consisting of SEQ ID NO:1 (AXT107).

In various embodiments, the patient will receive a plurality of doses, and in some embodiments, therapy can be continuous at the recommended frequency of injections for disease control or management. In some embodiments, therapy need not be continuous, where symptoms or disease has been substantially alleviated. In various embodiments, the

patient receives at least two injections, or at least four injections, or at least six injections, or at least eight injections, or at least ten injections. In some embodiments, injections are provided in a regimen of from four to ten injections.

The collagen IV-derived peptide promotes the Tie2 agonist activities of Angiopoietin 2 (Ang2), thereby stabilizing vasculature. The peptides target and disrupt $\alpha 5\beta 1$ and $\alpha V\beta 3$ integrins, and inhibit signaling through multiple receptors, including vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGFR), insulin-like growth factor receptor (IGFR), and epidermal growth factor receptor (EGFR). Accordingly, the peptides disclosed herein provide a potent alternative to VEGF blockade or inhibitor therapy, or potent combination therapy.

In various embodiments, the peptide can be delivered for conditions (including macular edema, wet AMD) that are refractory or only partially-responsive to vascular endothelial growth factor (VEGF) blockade or inhibitor therapy. Pharmaceutical agents that block VEGF include aflibercept, bevacizumab, ranibizumab, and ramucirumab, and similar agents, which are administered to slow or block angiogenesis. Other agents that target VEGF-mediated biological activity include kinase inhibitors such as pazopanib, sorafenib, sunitinib, axitinib, ponatinib, lenvatinib, vandetanib, regorafenib, and cabozantinib.

Aflibercept is a biopharmaceutical drug for the treatment of wet macular degeneration (EYLEA). Aflibercept is an inhibitor of VEGF, and is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2, that are fused to the Fc portion of the human IgG1 immunoglobulin. Aflibercept binds to VEGFs and acts like a "VEGF trap", inhibiting the activity of the vascular endothelial growth factor subtypes VEGF-A and VEGF-B, as well as to placental growth factor (PGF).

Bevacizumab (AVASTIN) is an angiogenesis inhibitor, a drug that slows the growth of new blood vessels. Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. Bevacizumab is administered for treating certain metastatic cancers, including colon cancer, lung cancers (*e.g.,* NSCLC), renal cancers, ovarian cancers, breast cancer, and glioblastoma. Bevacizumab can also be used for treatment of eye diseases, including AMD and diabetic retinopathy.

Ranibizumab (LUCENTIS) is a monoclonal antibody fragment (Fab), and is administered for treatment of wet AMD. The drug is injected intravitreally (into the vitreous humour of the eye) about once a month. Ranibizumab is a monoclonal antibody that inhibits angiogenesis by inhibiting VEGF A, similar to Bevacizumab.

The biomimetic peptide may be administered after unsuccessful VEGF blockade therapy, that is, where reductions in angiogenesis, lymphangiogenesis, and/or edema were not observed. In some embodiments, the peptide is administered as an alternative to VEGF blockade therapy. In still further embodiments, the peptide is administered in combination with VEGF blockade therapy, either simultaneously with, before, or after a VEGF blockade regimen. By activating Tie2 signaling, the biomimetic peptides or peptide agents provide therapeutic benefits that may not be observed with VEGF blockage therapy, or VEGF blockade therapy alone.

Therefore, in some embodiments, the peptide or salt thereof is administered after unsuccessful VEGF blockade or inhibitor therapy. In some embodiments, the patient has a condition that is refractory or only partially-responsive to VEGF blockade or inhibitor therapy.

In other aspects, the invention provides pharmaceutical compositions suitable for intravitreal injection. The pharmaceutical compositions comprise about 1 μg to about 1 mg or about 25 μg to about 800 μg of a collagen IV-derived biomimetic peptide or salt thereof (as disclosed herein) as a unit dose in a pre-filled syringe. For example, the unit dose may be about 700 μg or less of the peptide or salt thereof, or about 500 μg or less of the peptide or salt thereof, or about 250 μg or less of the peptide or salt thereof, or about 100 μg or less of the peptide or salt thereof. Exemplary unit doses include about 100 μg, about 250 μg, about 500 μg, and about 750 μg.

In some embodiments, the composition has a unit dose of from about 10 μg to about 50 μg of the peptide or salt thereof. In other embodiments, the composition has a unit dose of from about 50 μg to about 150 μg (e.g., about 100 μg) of the peptide or salt thereof. In some embodiments, the composition has a unit dose of from about 150 μg to about 250 μg of the peptide or salt thereof. In some embodiments, the composition has a unit dose of from about 250 μg to about 700 μg, or about 300 μg to about 700 μg, or about 400 μg to about

700 μg, or about 500 μg to about 700 μg, or about 600 μg to about 700 μg of the peptide or salt thereof.

In still other embodiments, the pharmaceutical composition has a unit dose of from about 700 μg to about 1 mg, or from about 800 μg to about 1 mg, of the peptide or salt thereof. In some embodiments, the unit dose is about 1 mg. In some embodiments, the unit dose is greater than 1 mg, such as from about 1 mg to about 2 mg.

The unit dose volume (in accordance with the compositions and methods described herein) may be in the range of about 1 μl to about 1 mL, or from about 10 μL to about 0.5 mL, or from about 10 μL to about 250 μL, or from about 10 μL to about 50 μL. In some embodiments, the pharmaceutical composition comprises a unit volume of from about 25 μL to about 0.5 mL, or a unit volume of from about 25 μL to about 200 μL, or a unit volume of from about 25 μL to about 100 μL. In some embodiments, the unit volume is less than about 100 μL, or less than about 50 μL, or less than about 25 μL. In various embodiments, the volume is about 50 μL.

The biomimetic peptides or peptide agents can be chemically synthesized and purified using well-known techniques, such as solid-phase synthesis. See US 9,051,349, which is hereby incorporated by reference in its entirety.

Peptides may be provided in the form of a pharmaceutically acceptable salt in some embodiments. Pharmaceutically acceptable peptide salts are generally well known to those of ordinary skill in the art.

The biomimetic peptide or peptide agent may be formulated for intraocular injection (i.e., intravitreal injection) using a variety of pharmaceutically acceptable carriers, including, but not limited to, water, saline, dextrose solutions, etc. The biomimetic peptides may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers.

In certain aspects, the invention provides a method for preventing or treating an eye disease or condition involving Tie-2-related vascular permeability in a patient. The method comprises administering the pharmaceutical composition described herein to the patient, at a dosing schedule (i.e., frequency) described herein. In accordance with embodiments of the invention, with only small amounts of active agent and infrequent injection of unit doses,

potent and long acting restoration of Tie2 activation can be achieved. In various embodiments, the method provides therapeutic benefit in conditions associated with edema or vascular permeability, including macular edema, diabetic macular edema (DME), and other conditions, including conditions characterized by acute or chronic ocular inflammation. Tie2-related conditions include diabetic macular edema, retinal vein occlusion, wet AMD, background diabetic retinopathy.

As used herein, the term "about" includes ±10% of the associated numerical value.

As used in this Specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive and covers both "or" and "and".

The invention will further be described in accordance with the following non-limiting examples.

EXAMPLES

The following examples demonstrate that AXT107 and its derivative peptides are potent, safe, and have a surprisingly long duration of action with infrequent intravitreal injections of a small volume. The invention thereby provides patient-friendly therapies for eye disease, including retinal disease such as wet AMD and diabetic macular edema.

In these experiments, Dutch Belted rabbits were anesthetized with an intramuscular injection of ketamine (25 mg/kg) and xylazine (2.5 mg/kg), and the pupils were dilated with 2.5% phenylephrine. The conjunctiva was cleaned with 5% povidone-iodine and an intravitreous injection of 100 µg or 500 µg of AXT107 was given in one eye. Twenty-three days after injection of AXT107, 10 µg of VEGF was injected into the vitreous and 7 days later, 30 days after the initial AXT107 injection, vitreous fluorophotometry (VFP) was performed with a Fluorotron Master™ ocular fluorophotometer fitted with an animal adapter (OcuMetrics, Mountain View, CA). For VFP, 15 mg of sodium fluorescein (AK-Fluor 10%, Akorn, Lake Forest, IL) was injected into an ear vein, and after one-hour fluorescence was measured along the visual axis from the retina to the cornea. The area under the fluorescein concentration curve between 5 and 7 mm was calculated in front of the retina to determine the extent of leakage. This protocol of VEGF injection and VFP measurement was done on day 23 and day 30 of every subsequent month for 12 months. The leakage each month in eyes administered AXT107 was normalized to animals injected with VEGF only, at the same time point. See FIGS. 1A and 1B.

The results of these experiments show that AXT107 potently inhibits VEGF-induced vascular leakage in the rabbit eye, which is a better surrogate of human eye than mouse eye because of its size. In addition, AXT107 potently inhibits VEGF-induced vascular leakage for at least 12 months in the rabbit eye.

In FIGURE 2, AXT107 was injected into the vitreous of Dutch-Belted rabbits. The rabbits were then sacrificed at various time points, and the various ocular tissues were separated. The drug levels in the retina were measured by Liquid chromatography–mass spectrometry (LC/MS/MS). The drug levels were plotted as ng/g. The Kd for binding of AXT107 to its integrin targets is 1-2 nM. AXT107 is present at 100 ng/g or greater resulting in concentrations significantly greater than the Kd in the retina 225, 271, and 315 day time points.

In FIGURE 3, AXT107 was injected into the vitreous of Dutch-Belted rabbits. One day later a gel was visible at the site of injection. The gel is marked by arrows in FIGURE 3. The retina with the optic nerve is visible in the back of the eye. The gel is compact and does not block the visual axis.

In FIGURE 4, AXT107 formed a gel in the vitreous at the site of injection. The gel stayed in place and released the peptide in a sustained manner. FIGURE 4 shows that the gel becomes smaller in place over time. At all time points, the back of the eye is clear, indicating that the peptide does not block the visual axis, and therefore, does not interfere with vision. The data of this experiment demonstrates that the peptide stays in place, and does not break apart or migrate for 15 months within the rabbit eye. FIGURE 4 shows images of the gel over 301 days for AXT107 doses of 100 μg, 250 μg, 500 μg, and 1000 μg. FIGURE 5 is a graph showing the release of AXT107 from gels over time. Dashed lines show an estimate of the AXT107 levels through 361 days.

In the tube in FIGURE 6, AXT107 was put into vitreous from a 5yr old person and an 89yr old person. These pictures show that the peptide forms a gel in human vitreous that is similar to the one seen in the rabbit vitreous.

In FIGURE 7, AXT107 was injected into the vitreous of Dutch-Belted rabbits in a PK toxicology study. When the animals were necropsied and the eyes examined, the gels formed by the peptide were visible in the vitreous at all doses. The size of the gels correlated with the dose as seen on the bottom of FIGURE 7 with the rulers (marked by arrows).

CLAIMS:

1. A method for preventing or treating a condition involving ocular vascular permeability or inflammation in a patient, comprising: administering a unit dose of a collagen IV-derived biomimetic peptide or salt thereof to said patient by intraocular injection at a frequency of no more than about once every month.

2. The method of claim 1, wherein the unit dose comprises about 10 μg to about 1 mg of the peptide.

3. The method of claim 2, wherein the unit dose is formulated as a naked peptide in aqueous solution without particle encapsulation.

4. The method of claim 1, wherein the patient has a condition selected from diabetic macular edema, retinal vein occlusion, wet age-related macular degeneration (wet AMD), or background diabetic retinopathy.

5. The method of claim 1, wherein the patient has acute or chronic inflammation of the eye.

6. The method of claim 5, wherein the patient has uveitis.

7. The method of claim 5, wherein the inflammation is associated with an autoimmune condition.

8. The method of claim 7, wherein the unit dose comprises about 700 μg or less, or about 500 μg or less, of the peptide or salt thereof.

9. The method of claim 8, wherein the unit dose comprises about 250 μg or less of the peptide or salt thereof.

10. The method of claim 9, wherein the unit dose comprises about 100 μg or less of the peptide or salt thereof.

11. The method of any one of claims 1 to 10, wherein the unit dose is administered by intraocular injection no more frequently than once every three months.

12. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every four months.

13. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every six months.

14. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every eight months.

15. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every year.

16. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every 18 months.

17. The method of claim 11, wherein the unit dose is administered by intraocular injection no more frequently than once every 2 years.

18. The method of any one of claims 1 to 7, wherein the unit dose comprises about 10 μg to about 50 μg of the peptide or salt thereof, and is administered at a frequency of no more than about monthly.

19. The method of claim 18, wherein the unit dose comprises about 25 μg of the peptide or salt thereof, and the unit dose is administered by intraocular injection about monthly.

20. The method of any one of claims 1 to 7, wherein the unit dose comprises about 50 μg to about 150 μg of the peptide or salt thereof, and the unit dose is administered by intraocular injection at a frequency of no more than once every third month.

21. The method of claim 20, wherein the unit dose is administered no more frequently than once every fourth month.

22. The method of claim 20, wherein the unit dose is administered no more frequently than once every six months.

23. The method of claim 20, wherein the unit dose comprises about 50 μg of the peptide or salt thereof, and the unit dose is administered at a frequency of once every three or four months.

24. The method of claim 20, wherein the unit dose comprises about 100 μg to about 150 μg of the peptide or salt thereof, and the unit dose is administered at a frequency of once every five to seven months, and optionally once every six months.

25. The method of any one of claims 1 to 7, wherein the unit dose comprises about 150 μg to about 250 μg of the peptide or salt thereof, and is administered at a frequency of no more than once every six months.

26. The method of claim 25, wherein the unit dose is administered no more frequently than once every eight months.

27. The method of claim 25, wherein the unit dose is administered no more frequently than once every twelve months.

28. The method of claim 25, wherein the unit dose comprises from about 200 μg to about 250 of the peptide or salt thereof, and is administered at a frequency of once every six to twelve months.

29. The method of any one of claims 1 to 7, wherein the unit dose comprises from about 250 μg to about 700 μg of the peptide or salt thereof, and is administered at a frequency of no more than once every six months.

30. The method of claim 29, wherein the unit dose comprises about 300 μg to about 700 μg of the peptide or salt thereof.

31. The method of claim 29, wherein the unit dose comprises about 400 μg to about 700 μg of the peptide or salt thereof.

32. The method of claim 29, wherein the unit dose comprises about 500 μg to about 700 μg of the peptide of salt thereof.

33. The method of claim 29, wherein the unit dose comprises about 600 μg to about 700 μg of the peptide or salt thereof.

34. The method of any one of claims 29 to 33, wherein the unit dose is administered at a frequency of once every six to eighteen months.

35. The method of claim 34, wherein the unit dose is administered about once every seven months, about once every eight months, about once every nine months, about once every ten months, about once every eleven months, or about once every twelve months, or about one every eighteen months.

36. The method of any one of claims 1 to 7, wherein the unit dose comprises about 700 μg to about 1 mg of the peptide or salt thereof, and the unit dose is administered at a frequency of no more than once every twelve months.

37. The method of claim 36, wherein the unit dose comprises about 800 μg to about 1 mg of the peptide or salt thereof.

38. The method of claim 36, wherein the unit dose comprises about 900 μg to about 1 mg of the peptide or salt thereof.

39. The method of any one of claims 36 to 38, wherein the unit dose is administered at a frequency of once every twelve months to once every two years.

40. The method of claim 39, wherein the unit dose is administered about once every eighteen months to about once every two years.

41. The method of any one of claims 1 to 40, wherein the peptide or salt thereof is administered after unsuccessful VEGF blockade or inhibitor therapy.

42. The method of any one of claims 1 to 40, wherein the patient's condition is refractory or only partially-responsive to VEGF blockade or inhibitor therapy.

43. The method of any one of claims 1 to 40, wherein the peptide or salt thereof is administered as an alternative to VEGF blockade or inhibitor therapy.

44. The method of any one of claims 1 to 40, wherein the peptide or salt thereof is administered in combination with VEGF blockade therapy.

45. The method of any one of claims 1 to 44, wherein the peptide comprises the amino acid sequence of any one of SEQ ID NOs: 1 to 36.

46. The method of any one of claims 1 to 44, wherein the peptide is derived from the α5 fibril of collagen IV, or a biomimetic thereof.

47. The method of claim 45 or 46, wherein the peptide is:
LRRFSTMPFMF(Abu)NINNV(Abu)NF (SEQ ID NO:5),
LRRFSTMPAMF(Abu)NINNV(Abu)NF (SEQ ID NO:6),

LRRFSTMPFAF(Abu)NINNV(Abu)NF (SEQ ID NO:7),
LRRFSTMPFMA(Abu)NINNV(Abu)NF (SEQ ID NO:8),
LRRFSTMPF(Nle)F(Abu)NINNV(Abu)NF (SEQ ID NO:9),
LRRFSTMPFM(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:10),
LRRFSTMPFMFSNINNVSNF (SEQ ID NO:11),
LRRFSTMPFMFANINNVANF (SEQ ID NO:12),
LRRFSTMPFMFININNVINF (SEQ ID NO:13),
LRRFSTMPFMFTNINNVTNF (SEQ ID NO:14),
LRRFSTMPFMF(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:15),
LRRFSTMPFMFVNINNVVNF (SEQ ID NO:16),
LRRFSTMPFdAFININNVINF (SEQ ID NO:17),
LRRFSTMPFAFININNVINF (SEQ ID NO:18),
LRRFSTAPFAFININNVINF (SEQ ID NO:19),
LRRFSTAPFdAFIDINDVINF (SEQ ID NO:20),
LRRFSTAPFAFIDINDVINW (SEQ ID NO:21),
dLRRdLRRFSTAPFAFIDINDVINF (SEQ ID NO:22),
LRRFSTAPFAFIDINDVINdF (SEQ ID NO:23), or
dLRRFSTAPFAFIDINDVINdF (SEQ ID NO:24).

48. The method of claim 45 or 46, wherein the peptide is:
F(Abu)NINNV(Abu)N (SEQ ID NO:25),
FTNINNVTN (SEQ ID NO:26),
FININNVINF (SEQ ID NO:27),
FSNINNVSNF (SEQ ID NO:28),
FANINNVANF (SEQ ID NO:29),
F(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:30),
FVNINNVVNF (SEQ ID NO:31),
FIDINDVINF (SEQ ID NO:32),
FIDINDVINW (SEQ ID NO:33),
FTDINDVTN (SEQ ID NO:34),
A(Abu)NINNV(Abu)NF (SEQ ID NO:35), or

(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:36).

49. The method of claim 46, wherein the peptide has the amino acid sequence LRRFSTAPFAFIDINDVINF (SEQ ID NO:1).

50. The method of any one of claims 1 to 49, wherein the unit dose has a volume in the range of about 1 µl to about 1 mL, or a volume in the range of about 10 µL to about 0.5 mL, or a volume in the range of about 10 µL to about 250 µL, or a volume in the range of about 10 µL to about 50 µL.

51. The method of claim 50, wherein the unit dose has a volume in the range of about 25 µL to about 0.5 mL, or a volume in the range of about 25 µL to about 200 µL, or a volume in the range of about 25 µL to about 100 µL.

52. The method of claim 50, wherein the unit volume is less than about 100 µL, or less than about 50 µL, or less than about 25 µL.

53. A pharmaceutical composition suitable for intravitreal injection, comprising about 1 µg to about 1 mg of a collagen IV-derived biomimetic peptide or salt thereof as a unit dose in a pre-filled syringe, the peptide being formulated in an aqueous solution without particle encapsulation.

54. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 1 mg of the peptide of salt thereof.

55. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 700 µg of the peptide or salt thereof.

56. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 500 µg or less of the peptide or salt thereof.

57. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 250 μg or less of the peptide or salt thereof.

58. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 100 μg or less of the peptide or salt thereof.

59. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 10 μg to about 50 μg of the peptide or salt thereof.

60. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 50 μg to about 150 μg of the peptide or salt thereof.

61. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 150 μg to about 250 μg of the peptide or salt thereof.

62. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 250 μg to about 700 μg of the peptide or salt thereof.

63. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 300 μg to about 700 μg of the peptide or salt thereof.

64. The pharmaceutical composition of claim 53, wherein the unit dose comprises about 400 μg to about 700 μg of the peptide or salt thereof.

65. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 500 μg to about 700 μg of the peptide or salt thereof.

66. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 600 μg to about 700 μg of the peptide or salt thereof.

67. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 700 μg to about 1 mg of the peptide or salt thereof.

68. The pharmaceutical composition of claim 53, wherein the unit dose comprises from about 800 μg to about 1 mg of the peptide or salt thereof.

69. The pharmaceutical composition of any one of claims 53 to 68, wherein the unit dose has a volume in the range of about 1 μl to about 1 mL, or a volume in the range of about 10 μL to about 0.5 mL, or a volume in the range of about 10 μL to about 250 μL, or a volume in the range of about 10 μL to about 50 μL.

70. The pharmaceutical composition of claim 69, wherein the unit dose has a volume in the range of about 25 μL to about 0.5 mL, or a volume in the range of about 25 μL to about 200 μL, or a volume in the range of about 25 μL to about 100 μL.

71. The pharmaceutical composition of claim 70, wherein the unit dose has a volume of less than about 100 μL, or less than about 50 μL, or less than about 25 μL.

72. The pharmaceutical composition of any one of claims 53 to 71, wherein the peptide comprises the amino acid sequence of any one of SEQ ID NOs: 1 to 36 or a derivative thereof.

73. The pharmaceutical composition of claim 72, wherein the peptide has the amino acid sequence of SEQ ID NO:1.

74. The pharmaceutical composition of claim 72, wherein the peptide has an amino acid sequence selected from:

LRRFSTMPFMF(Abu)NINNV(Abu)NF (SEQ ID NO:5),
LRRFSTMPAMF(Abu)NINNV(Abu)NF (SEQ ID NO:6),
LRRFSTMPFAF(Abu)NINNV(Abu)NF (SEQ ID NO:7),
LRRFSTMPFMA(Abu)NINNV(Abu)NF (SEQ ID NO:8),

LRRFSTMPF(Nle)F(Abu)NINNV(Abu)NF (SEQ ID NO:9),
LRRFSTMPFM(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:10),
LRRFSTMPFMFSNINNVSNF (SEQ ID NO:11),
LRRFSTMPFMFANINNVANF (SEQ ID NO:12),
LRRFSTMPFMFININNVINF (SEQ ID NO:13),
LRRFSTMPFMFTNINNVTNF (SEQ ID NO:14),
LRRFSTMPFMF(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:15),
LRRFSTMPFMFVNINNVVNF (SEQ ID NO:16),
LRRFSTMPFdAFININNVINF (SEQ ID NO:17),
LRRFSTMPFAFININNVINF (SEQ ID NO:18),
LRRFSTAPFAFININNVINF (SEQ ID NO:19),
LRRFSTAPFdAFIDINDVINF (SEQ ID NO:20),
LRRFSTAPFAFIDINDVINW (SEQ ID NO:21),
dLRRdLRRFSTAPFAFIDINDVINF (SEQ ID NO:22),
LRRFSTAPFAFIDINDVINdF (SEQ ID NO:23), or
dLRRFSTAPFAFIDINDVINdF (SEQ ID NO:24).

75. The pharmaceutical composition of claim 72, wherein the amino acid sequence of the peptide is selected from:

F(Abu)NINNV(Abu)N (SEQ ID NO:25),
FTNINNVTN (SEQ ID NO:26),
FININNVINF (SEQ ID NO:27),
FSNINNVSNF (SEQ ID NO:28),
FANINNVANF (SEQ ID NO:29),
F(AllyGly)NINNV(AllyGly)NF (SEQ ID NO:30),
FVNINNVVNF (SEQ ID NO:31),
FIDINDVINF (SEQ ID NO:32),
FIDINDVINW (SEQ ID NO:33),
FTDINDVTN (SEQ ID NO:34),
A(Abu)NINNV(Abu)NF (SEQ ID NO:35), or
(4-ClPhe)(Abu)NINNV(Abu)NF (SEQ ID NO:36).

FIGURE 1A

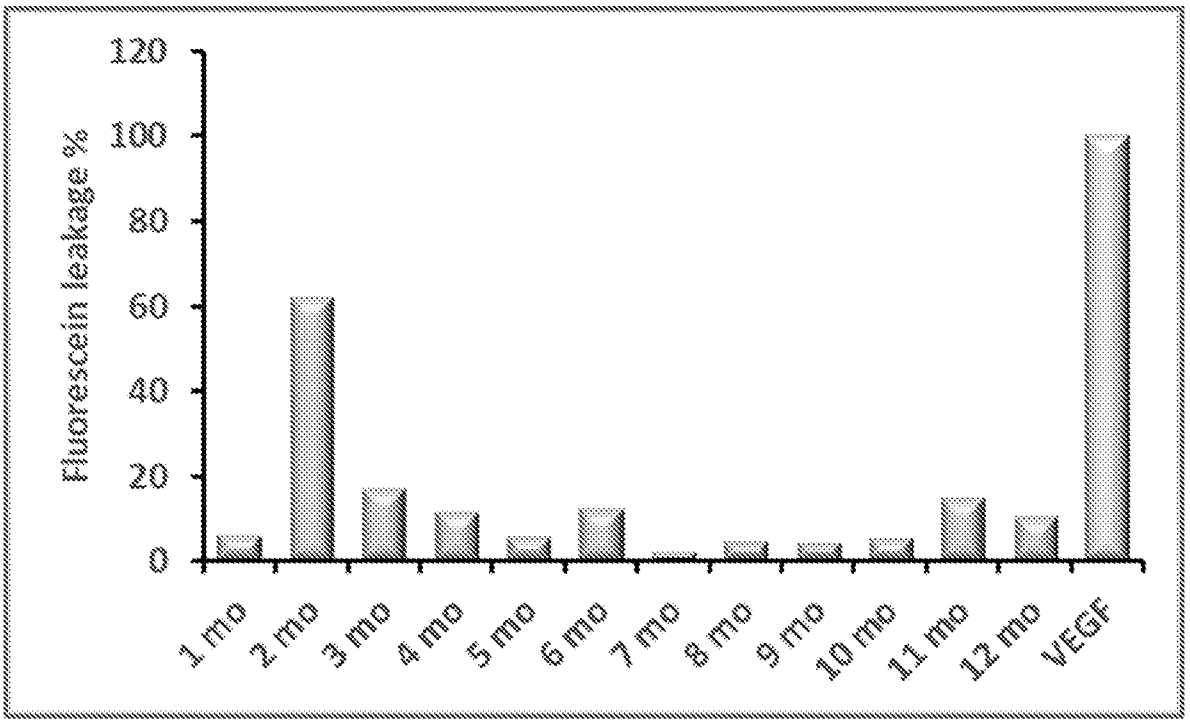

Fluorescein leakage %
120
100
80
60
40
20
0
1 mo
2 mo
3 mo
4 mo
5 mo
6 mo
7 mo
8 mo
9 mo
10 mo
11 mo
12 mo
VEGF

FIGURE 1B

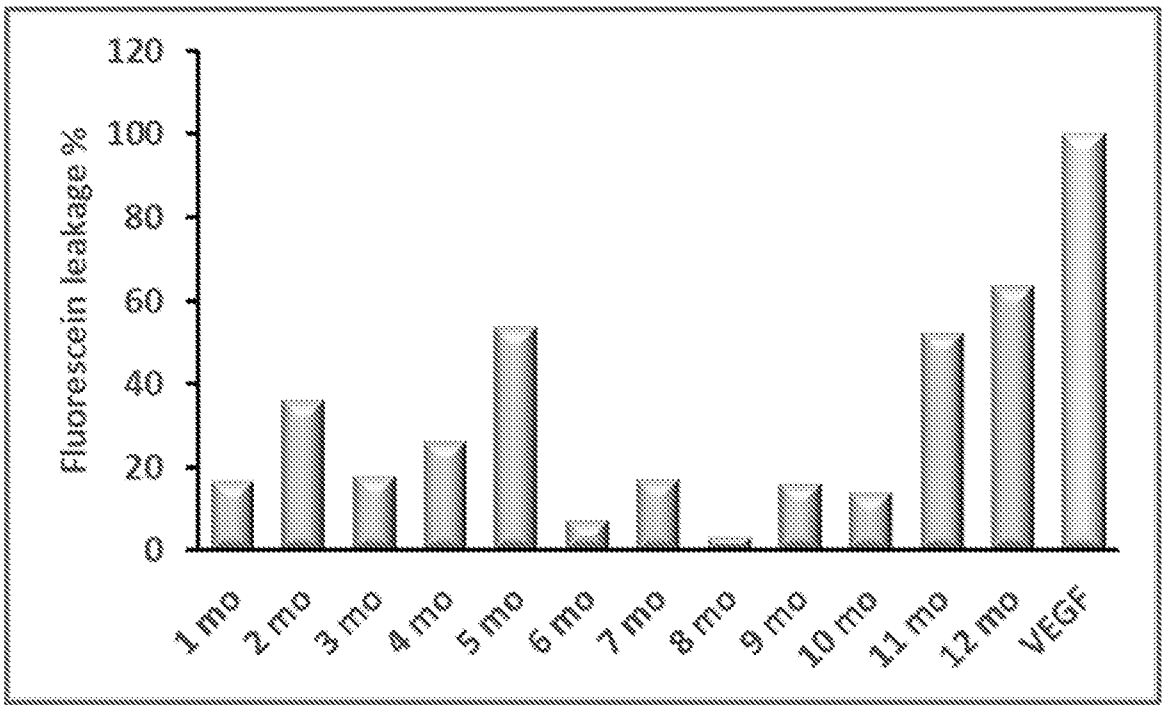
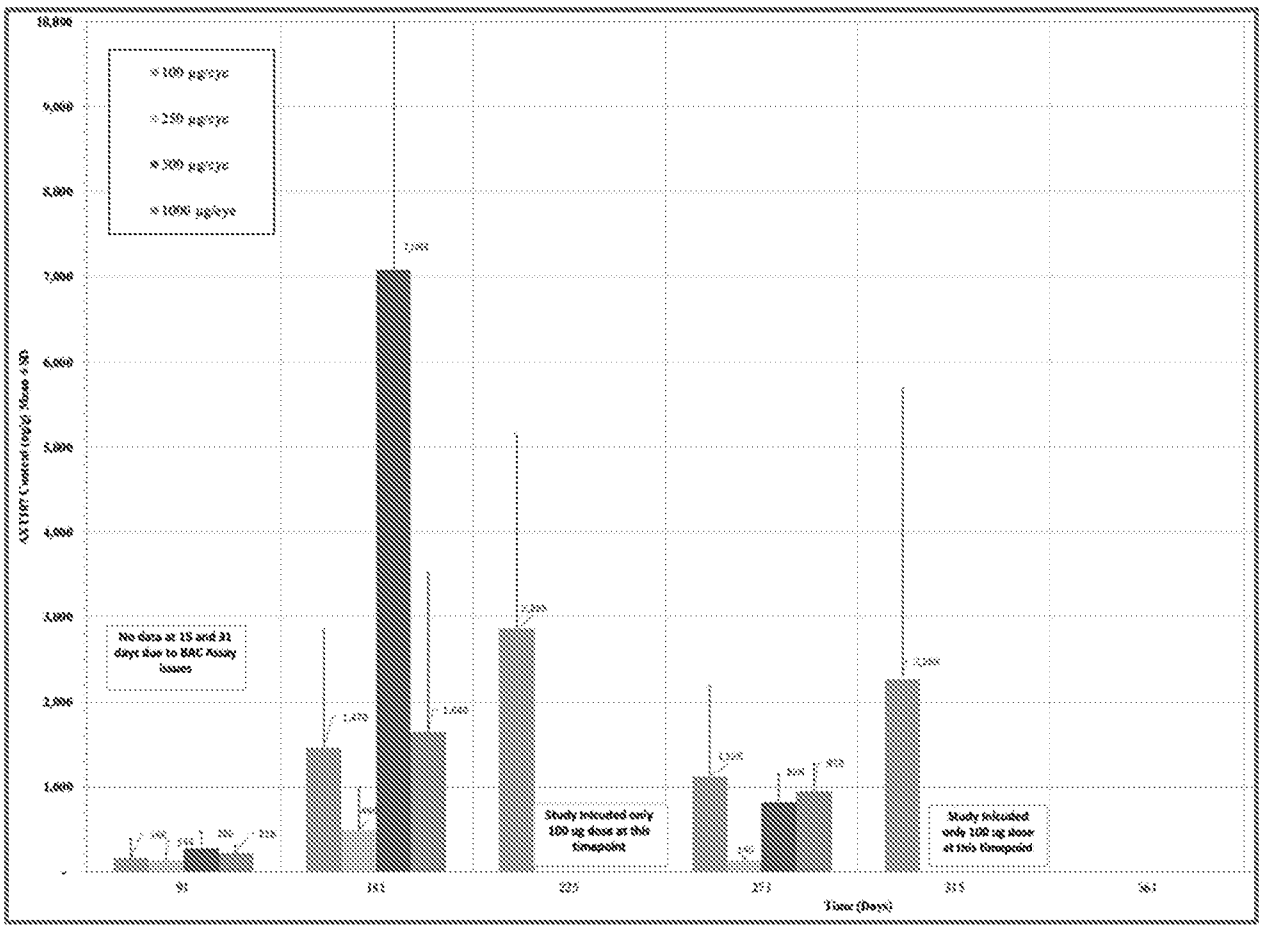

Fluorescein leakage %
120
100
80
60
40
20
0
1 mo
2 mo
3 mo
4 mo
5 mo
6 mo
7 mo
8 mo
9 mo
10 mo
11 mo
12 mo
VEGF

FIGURE 2


100 µg/eye
250 µg/eye
500 µg/eye
1000 µg/eye
No data at 15 and 31 days due to BAC Assay issues
Study included only 100 ug dose at this timepoint
Study included only 100 ug dose at this timepoint
Time (Days)

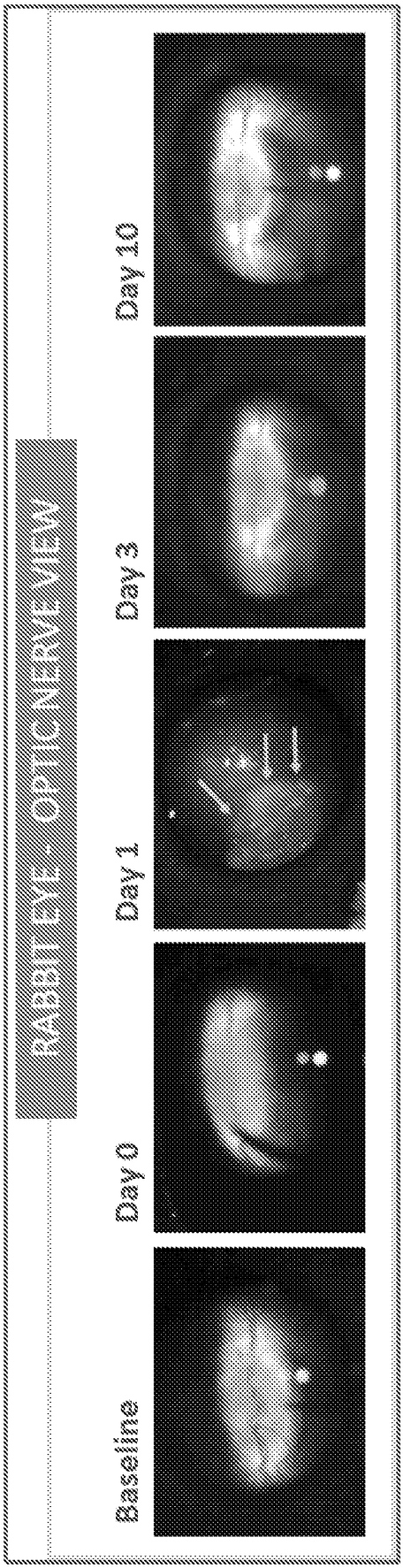
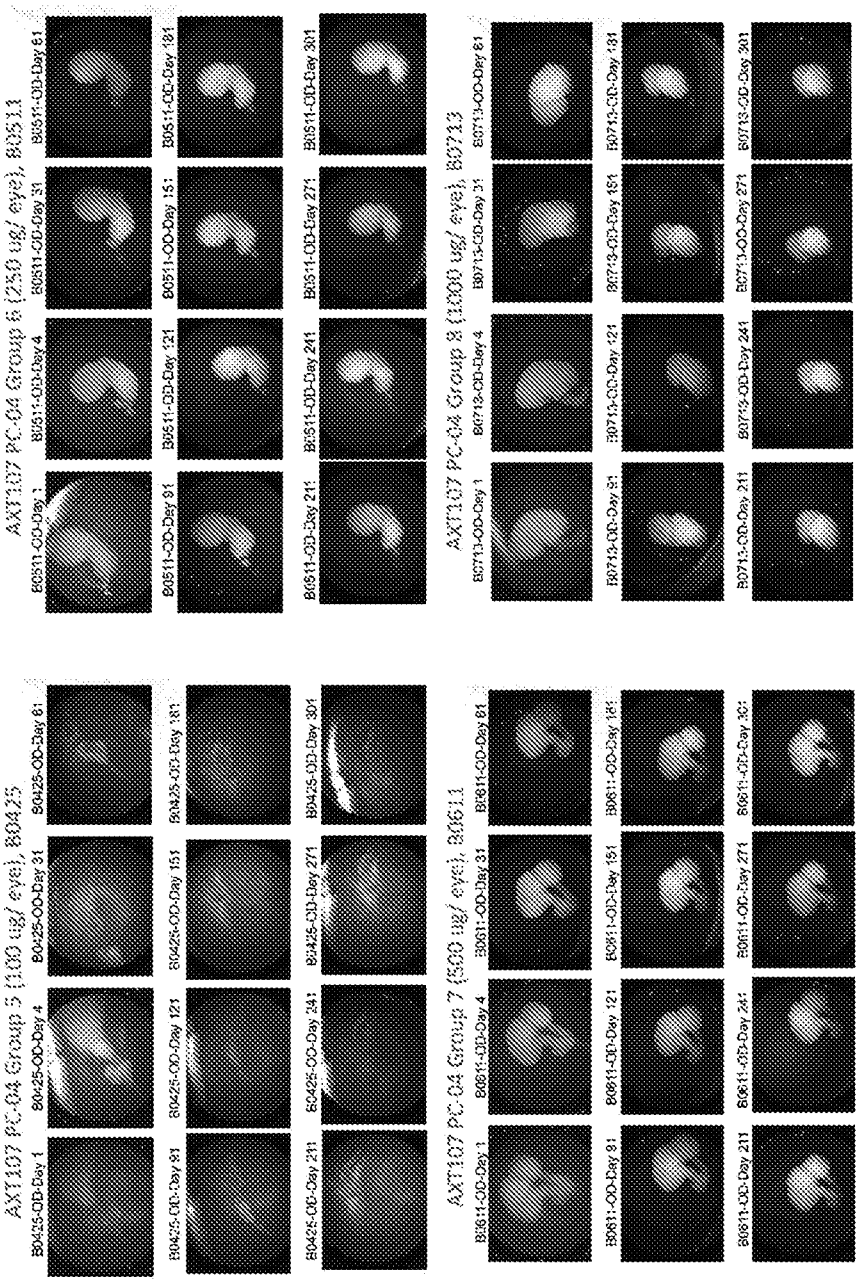


FIGURE 3

FIGURE 4


AXT107 PC-04 Group 6 (250 ug/ eye), B0511
B0511-OD-Day 1
B0511-OD-Day 4
B0511-OD-Day 31
B0511-OD-Day 61
B0511-OD-Day 91
B0511-OD-Day 121
B0511-OD-Day 151
B0511-OD-Day 181
B0511-OD-Day 211
B0511-OD-Day 241
B0511-OD-Day 271
B0511-OD-Day 301
AXT107 PC-04 Group 8 (1000 ug/ eye), B0713
B0713-OD-Day 1
B0713-OD-Day 4
B0713-OD-Day 31
B0713-OD-Day 61
B0713-OD-Day 91
B0713-OD-Day 121
B0713-OD-Day 151
B0713-OD-Day 181
B0713-OD-Day 211
B0713-OD-Day 241
B0713-OD-Day 271
B0713-OD-Day 301
AXT107 PC-04 Group 5 (100 ug/ eye), B0425
B0425-OD-Day 1
B0425-OD-Day 4
B0425-OD-Day 31
B0425-OD-Day 61
B0425-OD-Day 91
B0425-OD-Day 121
B0425-OD-Day 151
B0425-OD-Day 181
B0425-OD-Day 211
B0425-OD-Day 241
B0425-OD-Day 271
B0425-OD-Day 301
AXT107 PC-04 Group 7 (500 ug/ eye), B0611
B0611-OD-Day 1
B0611-OD-Day 4
B0611-OD-Day 31
B0611-OD-Day 61
B0611-OD-Day 91
B0611-OD-Day 121
B0611-OD-Day 151
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B0611-OD-Day 211
B0611-OD-Day 241
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B0611-OD-Day 301

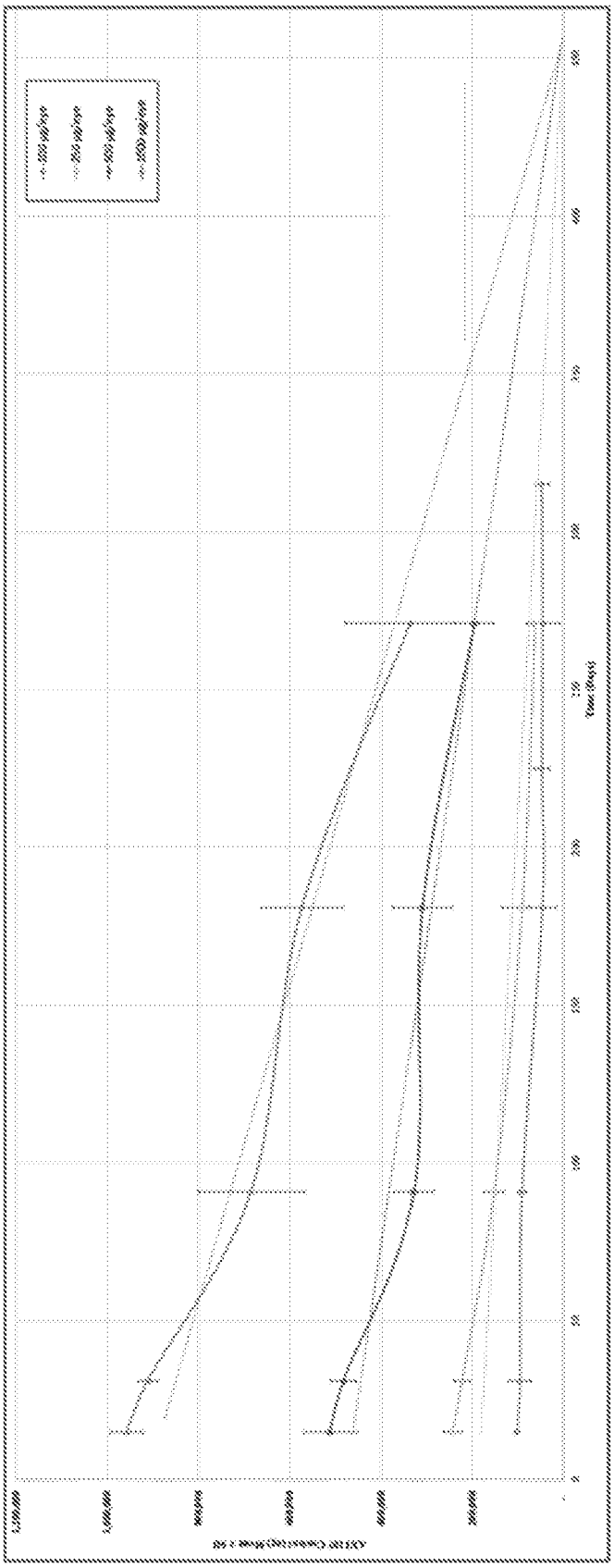
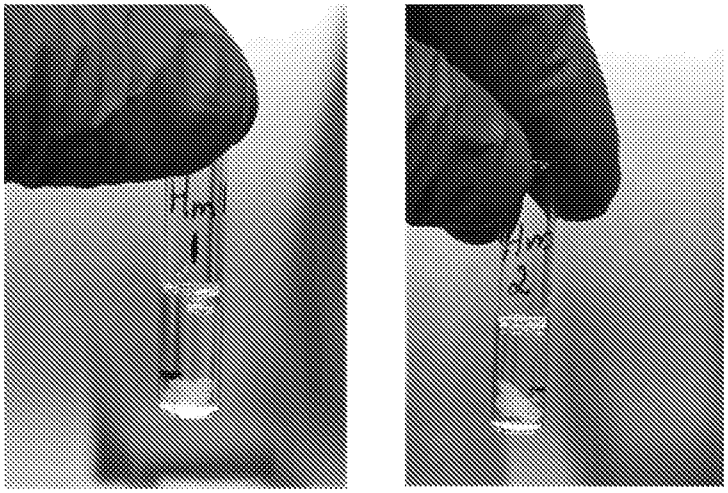


FIGURE 5

FIGURE 6



55 yr old Human

89 yr old Human

FIGURE 7

